“New Methodologies for the Regio- and Stereoselective Electrophilic Cyanation of Alkynes”

Dissertation

zur Erlangung des mathematisch-naturwissenschaftlichen Doktorgrades

“Doctor rerum naturalium”

der Georg-August-Universität Göttingen

im Promotionsprogramm Chemie

der Georg-August University School of Science (GAUSS)

vorgelegt von

Alejandro García Barrado

aus Cáceres, Spanien

Göttingen, 2018

Betreuungsausschuss:
Prof. Dr. Manuel Alcarazo (Institut für Organische und Biomolekulare Chemie, Tammannstr. 2, 37077 Göttingen)
Prof. Dr. Prof. Dr. Dietmar Stalke (Institut für Anorganische Chemie, Tammannstr. 4, 37077 Göttingen)

Mitglieder der Prüfungskommission:
Referent: Prof. Dr. Manuel Alcarazo (Institut für Organische und Biomolekulare Chemie, Tammannstr. 2, 37077 Göttingen)
Korreferent: Prof. Dr. Dietmar Stalke (Institut für Anorganische Chemie, Tammannstr. 4, 37077 Göttingen)

Weitere Mitglieder der Prüfungskommission:

Prof. Dr. Inke Siewert (Institut für Anorganische Chemie, Tammannstr. 4, 37077 Göttingen)
Dr. Alexander Breder (Institut für Organische und Biomolekulare Chemie, Tammannstr. 2, 37077 Göttingen)
Dr. Shoubhik Das (Institut für Organische und Biomolekulare Chemie, Tammannstr. 2, 37077 Göttingen)
Dr. Max Hansmann (Institut für Organische und Biomolekulare Chemie, Tammannstr. 2, 37077 Göttingen)

Tag der mündlichen Prüfung: 26 November 2018

I hereby declare that this dissertation has been written independently and with no other sources and aids than quoted. I have indicated the parts which were performed
by project collaborators.
.....

Alejandro García Barrado

Acknowledgements

First of all, I would like to thank my supervisor Prof. Dr. Manuel Alcarazo for the opportunity of doing my PhD in his research group and his big patience at the beginning of it. Also I want to thank Prof. Dr. Alois Fürstner for the possibility of using his installations and for the knowledge I obtained from his advices. Special thanks to Elisa González Fernández who allowed the possibility for me to join this research group, and for her constant advices and corrections of the manuscript.

I want to warmly thank my committee members Prof. Dr. Dietmar Stalke, Prof. Dr. Inke Siewert, Dr. Alexander Breder, Dr. Shoubhik Das and Dr. Max Hansmann for taking part in the examination process and to Dr. Sergei Kozhushkov for the correction of my dissertation.

Many thanks to the technicians Gerlinde Mehler, Sigrid Lutz and Martina Pretor for their constant help and patience in the laboratory and thanks to secretaries Monika Lickfeld and Sabine Schacht for their enormous help with the paperwork.

Thanks to the NMR, chromatography, spectroscopy and crystallography departments in Max-Planck-Institut für Kohlenforschung and in Georg-August-Universiät Göttingen for the measurement of my analytical samples, and specially I want to acknowledge Dr. Richard Goddard from the X-Ray department in Mülheim and der Ruhr and to Dr. Michael John from the NMR department in Göttingen for their great work.

Thanks to all my co-workers who supported me at the beginning, during and end of my PhD with useful discussions and tips. Specially mention to my former colleagues and friends in Mülheim an der Ruhr Dr. Ágnes Kozma, Dr. Elisa González Fernández, Dr. Hendrik Tinnermann, Dr. Lianghu Gu, Dr. Estela Haldón Hermoso, Dr. Isaac Alonso, Dr. Jonathan Dube and Leo Nicholls for the good times in and outside the lab. And also thanks to my actual colleagues and friends from my laboratory in Göttingen Dr. Yin Zhang, Adam Zieliński, Kevin Kafuta, Nils Ostermann, Bernd Waldecker and Kai Averesch.

And one of the biggest thanks is for my parents, for the tremendous effort they made which allowed me to be where I am now and for the support I received in every moment of my PhD, and also I want to thank my family and friends for encouraging me to achieve this goal.

To my parents

“To be sure of hitting the target, shoot first, and call whatever you hit the target”

— Ashleigh Brilliant

Content

1. Introduction. General Overview of Cyanating Reagents in Organic Synthesis. 1

1.1. Cyanides. 1

1.1.1. Alkali metal cyanides. 1

1.1.2. Transition metal complexes with cyanides. 3

1.2. Nitriles. 3

1.2.1. Synthesis of nitriles. 6

1.2.1.1. Functional group derivatization. 7

1.2.1.2. Cyanations. 8

1.2.1.2.1. Cyanide-based reagents. 9

1.2.1.2.2. Recent developments. 13

1.2.1.2.2.1. *In situ* functionalization and derivatization. 14

1.2.1.2.2.2. *In situ* generation of cyanides. 17

1.2.1.2.2.3. Organonitriles as cyanating reagents. 19

1.2.1.2.2.3.1. Nucleophilic cyanations. 20

1.2.1.2.2.3.2. Electrophilic cyanations. 26

1.2.1.2.2.3.3. Radical cyanations. 33

2. Hypervalent Compounds Design and Electrophilic Cyanation. 35

2.1. Introduction. 35

2.2. Synthesis of hypervalent iodine reagents. 37

2.3. New cyanating reagents developed in our group. 41

2.4. Summary. 45

3. Regio- and Stereoselective Chlorocyanation of Alkynes. 47
3.1. Introduction. 47
3.2. Objective. 49
3.3. Results and discussion. 50
3.3.1. Reaction design. 50
3.3.2. Searching for appropriate reaction participants. 51
3.3.3. Chlorocyanation of alkynes. 54
3.3.3.1. Optimization. 54
3.3.3.2. Scope and limitations. 56
3.3.3.3. Structural studies. 63
3.3.3.4. Mechanistic studies. 68
3.3.3.4.1. Borylative cyclization. 68
3.3.3.4.2. Cycloisomerization. 69
3.3.3.4.3. By-products isolation from reaction mixtures. 71
3.3.3.4.4. Counterion effect. 72
3.3.3.4.5. Proposed mechanism. 73
3.3.3.5. Synthetic applications of chloroacrylonitriles. 74
3.3.3.5.1. Cross-couplings. 74
3.3.3.5.1.1. Suzuki-Miyaura couplings. 75
3.3.3.5.1.2. Sonogashira-Hagihara couplings. 76
3.3.3.5.2. Solvolytic experiments. 76
3.3.3.5.2.1. Alcoholysis of chloroacrylonitriles. 76
3.3.3.5.2.2. Aminolysis of chloroacrylonitriles. 77
3.3.3.5.2.3. Synthesis of heterocycles. 78
3.3.3.5.2.4. Natural products derivatization. 81

3.3.3.6. Summary. 82

4. Cyanative Cyclizations. 83

4.1. Intoduction. 83

4.2. Objective. 90

4.3. Results and discussion. 91

4.3.1. Synthesis and screening. 91

4.3.2. Optimization of reaction conditions. 94

4.3.3. Scope and limitations. 98

4.3.3.1. Synthesis of phenanthrenes. 98

4.3.3.2. Synthesis of heterocycles. 102

4.3.3.3. Synthesis of helicenes. 103

4.3.3.4. Synthesis of pyrenes. 109

4.3.3.5. Synthesis of non-aromatic cycles. 110

4.3.4. Proposed mechanism. 115

4.3.5. Summary. 116

5. Conclusion. 118

6. Experimental. 119

6.1. Instrumentation and chemicals. 119

6.2. Regio- and stereoselective chlorocyanation of alkynes. 120

6.2.1. Synthesis of starting materials. 120

6.2.2. Synthesis of new products. 121

6.2.2.1. Synthesis of chloroacrylonitriles. 121

6.2.2.2. Isolated by-products. 132

6.2.2.3. Bromocyanations. 132

6.2.2.4. Thiocyanations. 133

6.2.2.5. Cyanoarylations. 133

6.2.2.6. Derivatization of chloroacrylonitriles. 134

6.2.2.6.1. Suzuki-Miyaura couplings. 134

6.2.2.6.2. Solvolysis of chloroacrylonitriles. 136

6.2.2.6.3. Synthesis of heterocycles. 137

6.2.2.6.4. Attempted derivatization of natural products. 139

6.3. Cyanative cyclizations. 140

6.3.1. Synthesis of starting materials. 140

6.3.1.1. Terminal alkynes by Seyferth-Gilbert homologation. 140

6.3.1.2. Alkynes by Sonogashira-Hagihara coupling. 143

6.3.1.3. Alkynes by Suzuki-Miyaura coupling. 152

6.3.1.4. Bromination of terminal alkynes. 153

6.3.1.4. Thioalkynes. 154

6.3.2. Synthesis of new products. 154

6.3.2.1. Cyanative cyclizations. 154

6.3.2.2. Cycloisomerizations. 165

6.4. X-ray structures. 166

7. Appendix. 171

7.1. NMR spectra. 171

7.2. List of abbreviations. 289

7.3. References 292

7.4. Curriculum vitae 301

1. Introduction. General Overview of Cyanating Reagents in Organic Synthesis.

1.1. Cyanides.

The cyanide moiety is a functional group consisting of a carbon atom triple-bonded to a nitrogen, which contains an additional lone pair of electrons. In this situation two of the bonds are described as π-bonds and the remaining one as a σ-bond (**Figure 1**). Cyanide salts are available as free anions, which can serve as ligands in cyanide complexes, or as nitrile synthons after reaction with alkyl halides in the well-known Kolbe synthesis.[1] The preparation and properties of cyano-containing compounds are further detailed below in the next Chapters.[2]

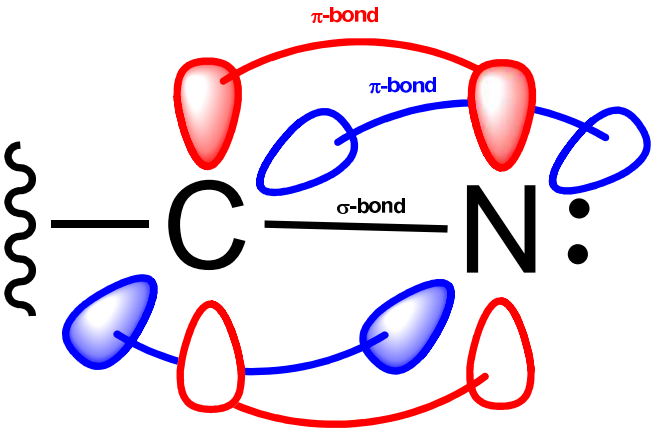
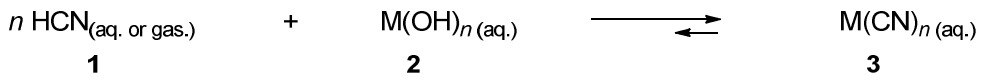


Figure 1. C–N bonds in a cyano group.

1.1.1. Alkali metal cyanides.

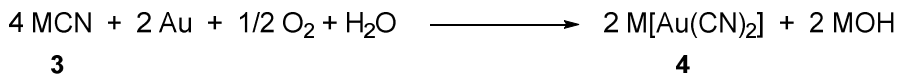
The common method for the synthesis of alkali cyanides consists of a neutralization process of an alkali hydroxide in aqueous solution with either gaseous or aqueous solution of hydrogen cyanide (**Scheme 1)**.[3] The latter is currently produced in great quantities by several industrial processes from methane and ammonia.



Scheme 1. Alkali cyanides synthesis.

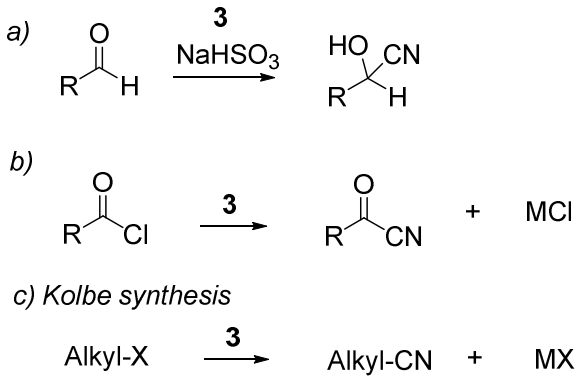
Following this methodology, the two most commonly used alkali metal cyanides — NaCN **3a** and KCN **3b** — can be prepared. Both are white crystalline solids of high toxicity.

These two salts have been used worldwide in gold mining.[4] Gold is a noble chemically inert metal that cannot easily be converted into water-soluble derivatives. Such transformation requires a strong oxidant in the presence of a complexing agent. The classical example is the use of *aqua regia* — 1/3 mixtures of $HNO_{3(conc.)}$/$HCl_{(conc.)}$ — where nitricic acid is the oxidant and the complexing agent is a chloride generated by $HCl_{(aq.)}$. As cyanides are even stronger coordinating agents, they can be used for the same purpose using oxygen as oxidant (**Scheme 2**).[4]



Scheme 2. Gold extraction with cyanides.

In organic synthesis their most common uses are in nucleophilic addition (for example, formation of cyanhydrines, **Scheme 3a**) or in nucleophilic substitution (cyanation of acyl chlorides or of (*pseudo*)halogen-substituted alkanes, **Scheme 3b,c**) reactions.[5]



Scheme 3. Common reactivity of alkali cyanides.

1.1.2. Transition metal complexes with cyanides.

When the lone electron pair localized on a carbon atom in the cyanide ion is employed for coordination to a metal, a very stable M–CN σ-bond is formed.[3] In such a case, a cyanide acts either as a σ-donating ligand, thus stabilizing high oxidation states of transition metals, or as a π-acid ligand, which accepts electron density in one of its empty π^*-antibonding orbitals from transition metals in low oxidation states (**Figure 2**). Different binding models, in which the nitrogen coordinates to the metal (isocyanide) or the cyanide acts as a bidentate or π-donor ligand are also possible.[6]

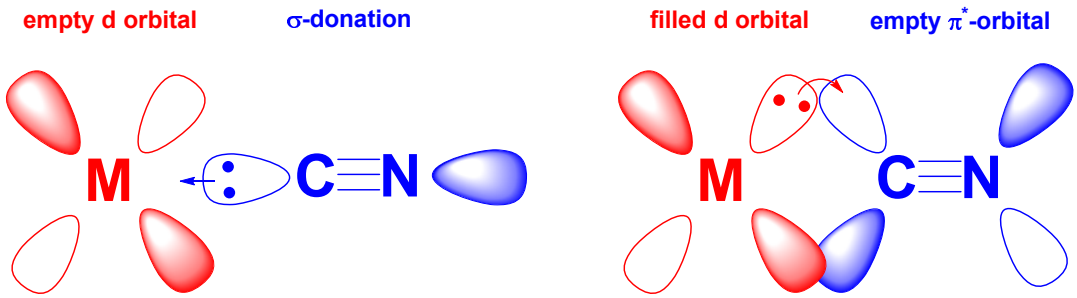


Figure 2. Cyanide anion as a ligand.

General procedures for their synthesis include ligand exchange with excess of a cyanide source or oxidative addition of cyanogens to metal centers in low oxidation states.

Hexacyanometallates of Fe(III) or Co(III) — $K_3[Fe(CN)_6]$ (**5**) and $K_3[Co(CN)_6]$ (**6**) — and tetracyanometallates of Pd(II) and Pt(II) — $K_2[Pd(CN)_4]$ (**7**) and $K_2[Pt(CN)_4]$ (**8**) — can be highlighted as representative examples of these complexes.

1.2. Nitriles.

A nitrile, which can also be more specifically designated as organonitrile, is every organic molecule containing a cyano group directly bonded to a C-atom.[7] In contrast to inorganic cyanides, the lone electron pair of a cyano moiety located on the carbon atom is used to form a covalent bond with an organic framework, thus modifying the polarity of the structure. The partial positive charge in nitriles is located on the carbon atom, whereas the partial negative charge – on the more electronegative nitrogen atom (**Figure 3**). Since the

carbon center has *sp* hybridization, the geometry of a molecule is expected to be linear.

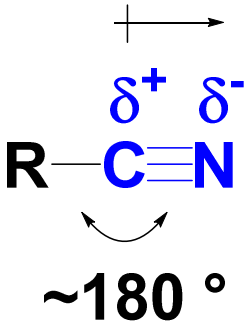
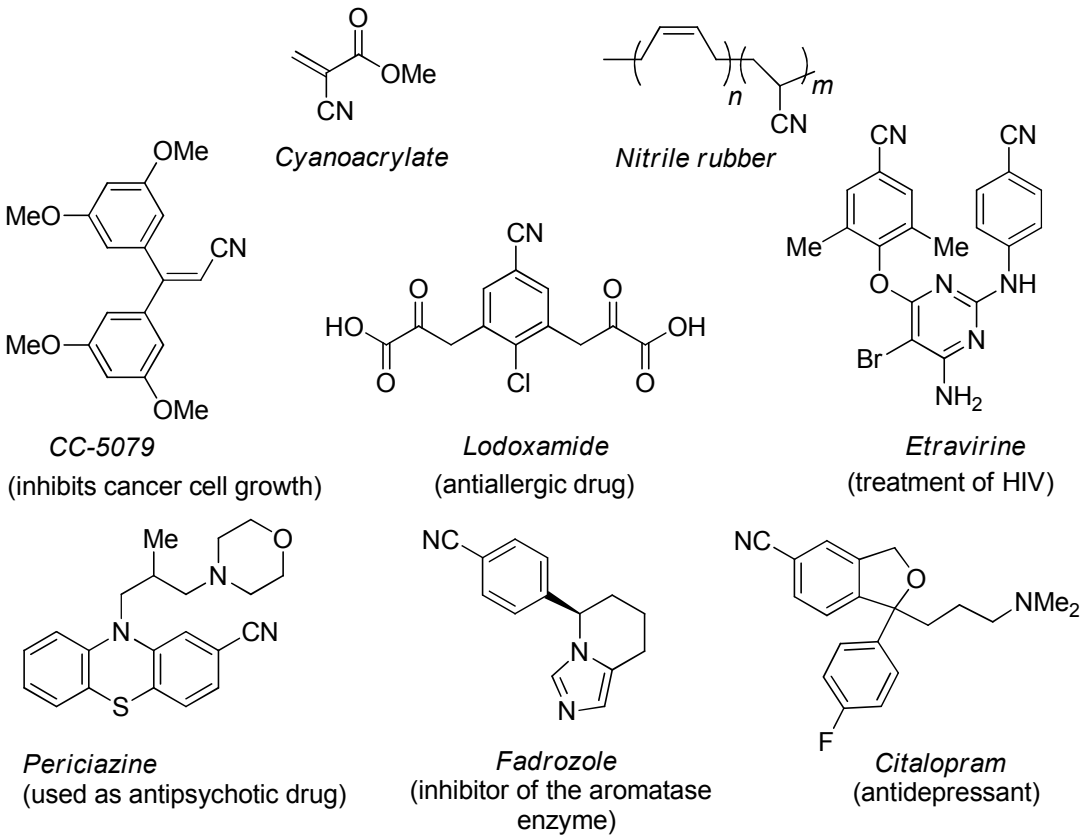


Figure 3. Polarity and molecular geometry in nitriles.

Organonitriles are undoubtedly very useful molecules playing an important role in everyday life of humans.[8] As representative examples, worth mentioning cyanoacrylate, which is used as an adhesive,[9a] — so-called nitrile rubber — acrylonitrile polymer derivatives employed as a resistant material for gloves or seals[9b] and a myriad of drugs featuring nitrile groups in their structures (**Scheme 4**).[10]

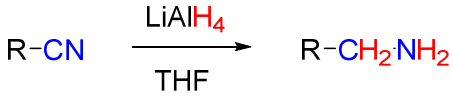


Scheme 4. Practically useful synthetic products possessing nitrile functionalities.

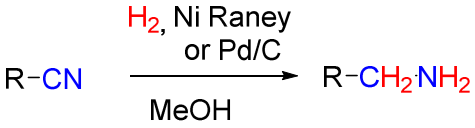
Regarding synthetic aspects, nitriles are extremely versatile groups in organic chemistry as they can easily be converted into different functional groups. Thus, they can be reduced to primary amines, aldehydes or ketones, hydrolyzed to carboxylic acids or amides, transformed into tetrazoles by "click chemistry" or be transformed into esters.[1][5][11] The most representative procedures to achieve these transformations through classical organic and organometallic chemistry are summarized in **Scheme 5** below.

a) Reduction of nitriles to primary amines:

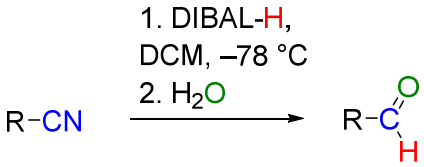
- With a reducing agent:



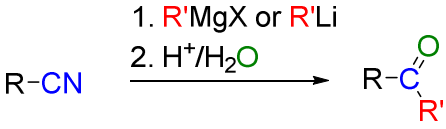
- Metal-catalyzed hydrogenation:



b) Reduction of nitriles to aldehydes:

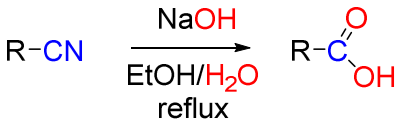


c) Reduction of nitriles to ketones:

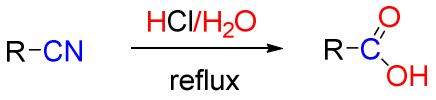


d) Hydrolysis of nitriles to carboxylic acids:

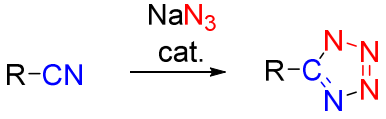
- Basic hydrolysis:



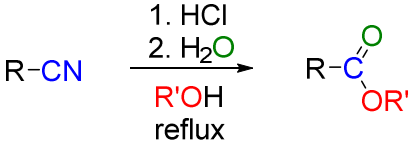
- Acidic hydrolysis:



e) Click chemistry:



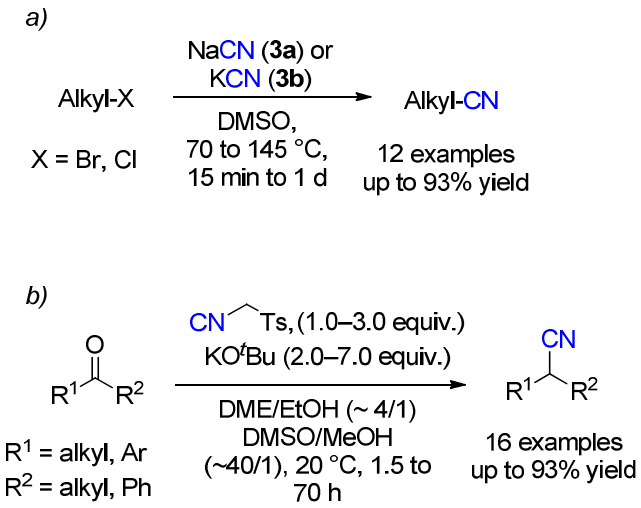
f) Pinner esterification:



Scheme 5. Chemical transformation of nitriles.

1.2.1. Synthesis of nitriles.

Alkyl nitriles are generally synthesized by nucleophilic substitution at alkyl halides using inorganic cyanide salts. Hence, the most classical approach to afford nitriles is the modified Kolbe synthesis,[12] where alkyl halides are converted into alkyl nitriles by treatment with sodium (**3a**) or potassium (**3b**) cyanides in DMSO (**Scheme 6a**). Alternatively, secondary nitriles can be accessed from ketones by reacting with sulfonylmethyl isocyanides according to Van Leusen protocol, which is also valid for the synthesis of arylnitriles (**Scheme 6b**).[13]



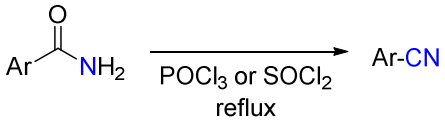
Scheme 6. Synthesis of alkyl nitriles.

Aryl nitriles represent important intermediates in organic synthesis and, as a consequence, a plethora of methodologies for their preparation have been established along the years.[14] As their synthesis is a main target of my dissertation, a detailed study of their formation will be discussed in the next sections.

Basically, there are two pathways to construct these frameworks: (1) by an indirect way performing a functional group derivatization or (2) by direct implantation of the cyano moiety into the molecule using a cyanating reagent.

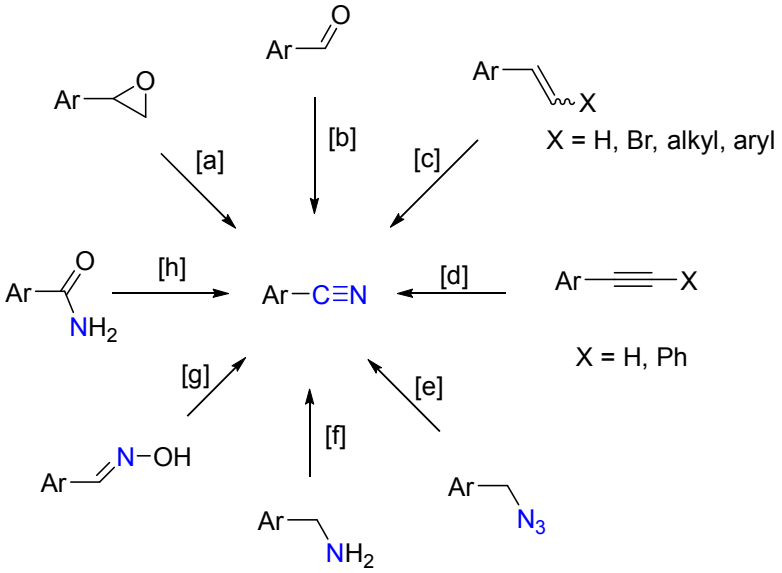
1.2.1.1. Functional group derivatization.

These methodologies are based on chemical transformations of functional groups and afford the nitrile group by forming the C≡N bonds *via* oxidation, reduction or elimination which take place on other functional groups. For example, aryl nitriles can be obtained upon refluxing primary amides with excess of $POCl_3$[15a] or $SOCl_2$[15b] (**Scheme 7**).[15]



Scheme 7. Traditional approach to access aryl nitriles.

Other more modern methods for their synthesis have been developed; some of them are summarized in **Scheme 8**.[14] In these preparations, aryl-substituted oxiranes ([a]),[16] benzaldehydes ([b]),[17] alkenes ([c]),[18] alkynes ([d])[19] and benzyl halides[20] were suitable starting materials when combined with different nitrogen sources to afford the formation of the corresponding aryl nitriles. Oxidation of benzylamines ([f])[21] as well as catalytic dehydration of aldoximes ([g])[22] and benzamides ([h])[23] also appeared to be suitable protocols for their synthesis.

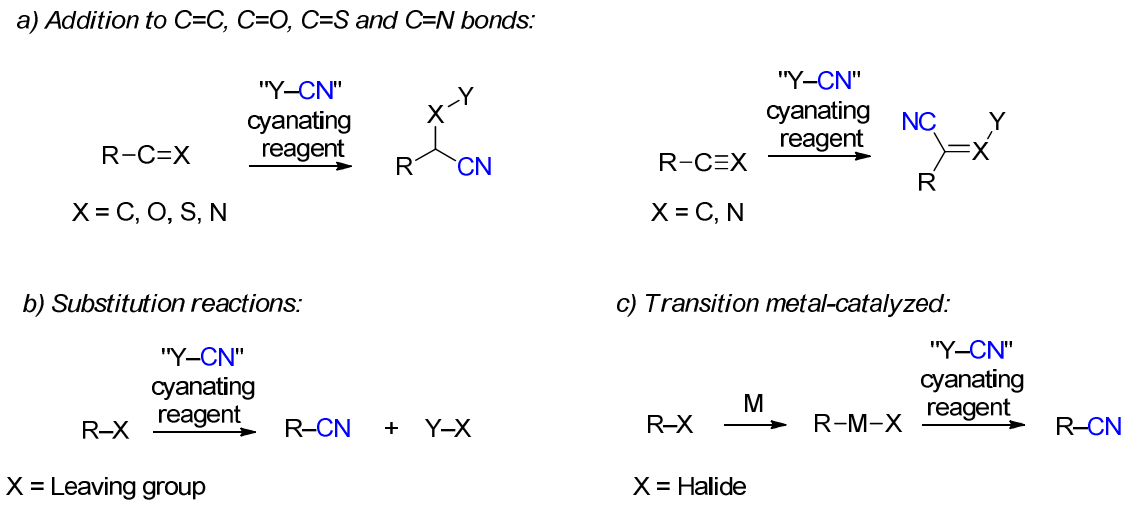


Scheme 8. Modern strategies for the synthesis of aryl nitriles. [a] DMP (2.0 equiv.), NH_3, 70 °C, 4 h. [b] NaN_3 (1.5 equiv.), TfOH (3.0 equiv.), MeCN, rt, 2 min. [c] $PhI(OAc)_2$ (5.5 equiv.), NH_4HCO_3 (6.0 equiv.), MeOH/H_2O, 36 °C, 12 h. [d] $TMSN_3$ (2.4 equiv.), NIS (2.4 equiv.), 1,2-DCE/MeCN, rt to 70 °C, 1–4 h. [e] TBAB (5.0 mol%), DDQ (1.3 equiv.), 1,2-DCE, rt to reflux, 24 h. [f] 4-(acetylamino)-2,2,6,6-tetramethyl-1-oxopiperidinium (4.0 equiv.), pyridine (4.0 equiv.), DCM, rt, 12–36 h. [g] $CuCl_2$ (5.0 mol%), MeCN, rt, ultrasound, 1 h. [h] TBAF (5.0 mol%), $PhSiH_3$ (1.0 equiv.) toluene, 100 °C, 30 min.

Most of these examples are based on the a) formation of a C≡N bond by utilizing different nitrogen sources (such as azides, ammonia or ammonium salts), b) an oxidation of a pre-installed C–N bond or c) by a dehydrative transformation. As a rule, an elimination step at some point is involved in all mechanistic rationalizations of these transformations. Even if the processes are simple and fast, they rely on the employment of excesses of oxidants, additives and may require a metal-based catalyst.

1.2.1.2. Cyanations.

In this group of reactions, the cyano functionality is inserted into the selected substrate in one step by employment of a cyanating reagent. Mechanistically this step can be accomplished *via* an addition or substitution stage, in the last case also as a transition metal-catalyzed process (**Scheme 9**).



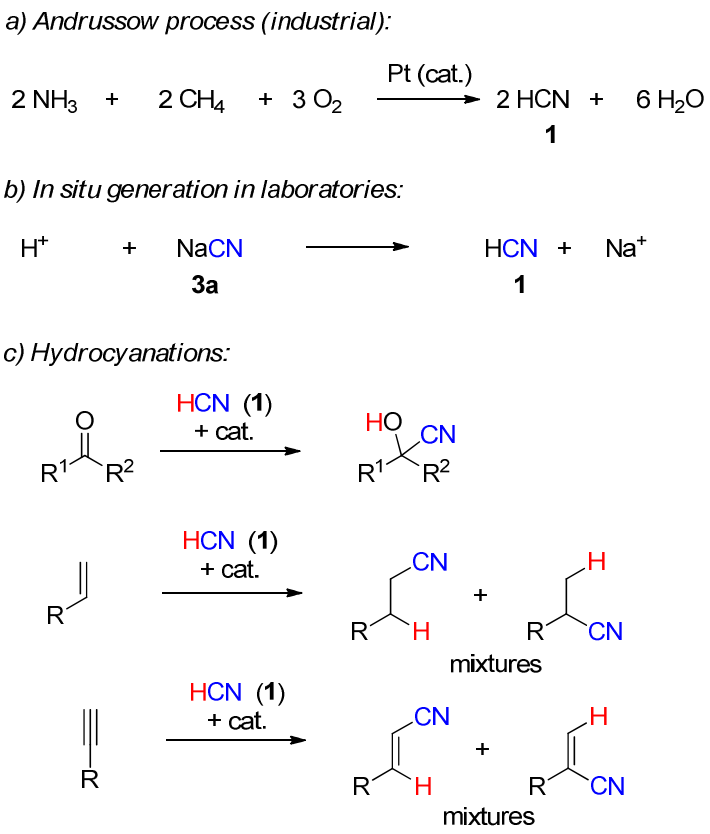
Scheme 9. Cyanation strategies.

The most representative and generally accepted cyanating reagents that have been used through the history of chemistry will be discussed in this Section, starting with the classical nucleophilic substitutions or additions and up to new environmentally friendly methodologies developed in the last decades.

1.2.1.2.1. Cyanide-based reagents.

Main commercially available inorganic cyanide sources are hydrogen cyanide (HCN, **1**), and its metal salts — NaCN (**3a**), KCN (**3b**), CuCN (**9**) or $K_4[Fe(CN)_6]$— (**10**).

Hydrogen cyanide (**1**) is a highly toxic low-boiling point liquid which is produced industrially by the so-called Andrussow process from methane and ammonia through oxidation with oxygen in the presence of platinum catalyst (**Scheme 10a**).[24] Due to its extreme toxicity, HCN in the laboratory is normally generated *in situ* from concentrated sulfuric acid and sodium cyanide (**Scheme 10b**).[25] As for applications, compound **1** is generally used for the addition onto alkenes, alkynes and carbonyl compounds to access alkyl nitriles (hydrocyanation), acrylonitriles or cyanohydrins, respectively (**Scheme 10c**).[26]

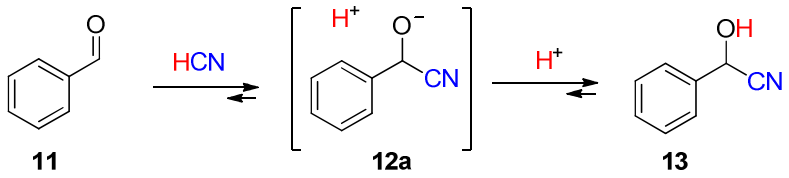


Scheme 10. Synthesis of hydrogen cyanide (**1**) and its general reactivity.

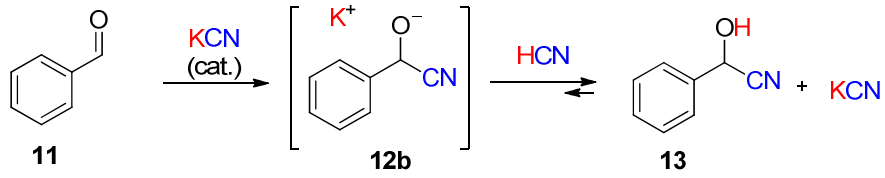
The synthesis of α-hydroxynitriles (**Scheme 10c**, top), most known as cyanohydrins, is the most important application of this reagent, as cyanohydrins are widely employed in

industry as precursors of carboxylic and amino acids.[27] The first example of the synthesis of these compounds was published by Winkler in 1832, consisting on the simple addition of hydrogen cyanide (**1**) to aldehydes **11** (**Scheme 11a**).[28] The reaction was then optimized in 1903 by Lapworth, who used catalytic amounts of cyanide (**Scheme 11b**).[29] Thus, hydrogen cyanide has been replaced by cyanating reagents **3a** and **3b** or TMSCN (**14**) (**Scheme 11c**).[30]

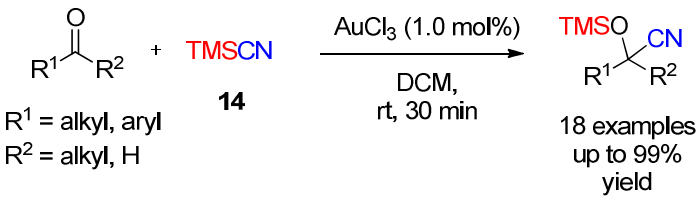
a) Winkler (1832):



b) Lapworth (1903):

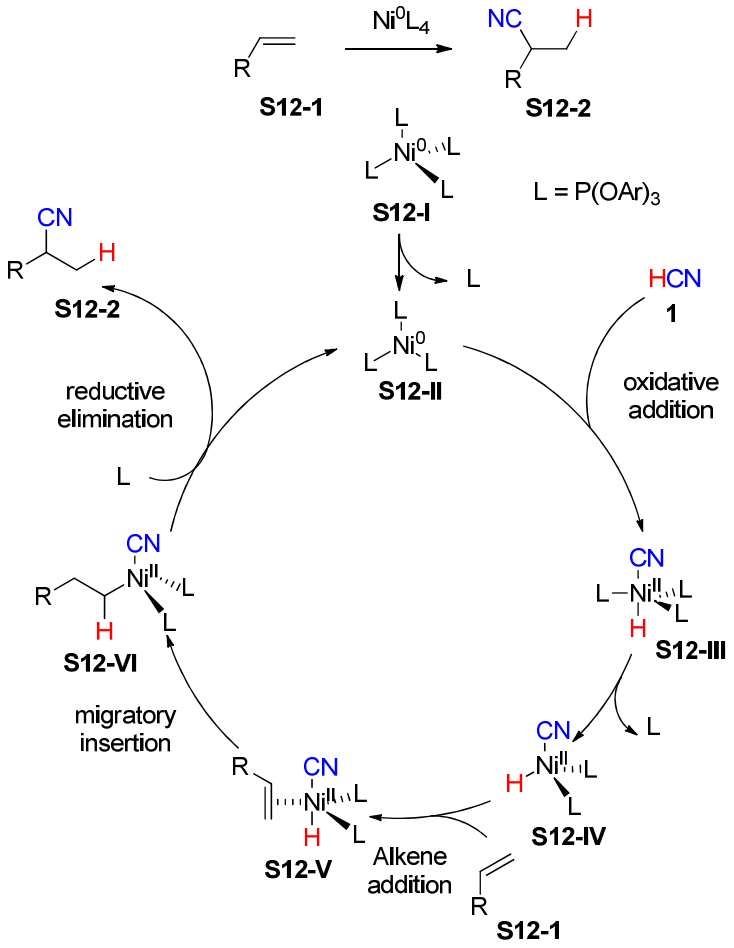


c) Lee (2008):



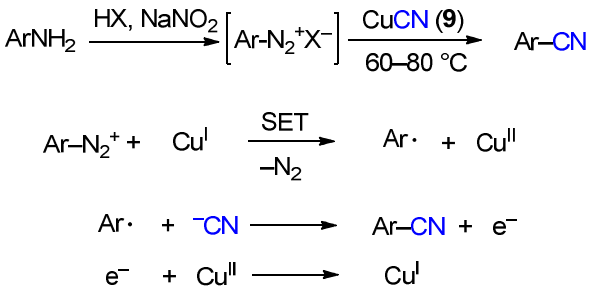
Scheme 11. Development of synthetic procedures towards cyanohydrines.

One widely employed application of HCN is in the hydrocyanation of alkenes, which can be selectively performed by using a Lewis acid-assisted [nickel(0)-triarylphosphite]-catalyzed process.[31] The proposed mechanism of the transformation is shown in **Scheme 12**. Initially the nickel complex NiL_4 (**S12-I**) dissociates into NiL_3 (**S12-II**). Oxidative addition of hydrogen cyanide to **S12-II** forms intermediate **S12-III** which dissociates again affording complex **S12-IV**. After this, the alkene **S12-1** is coordinated to the vacant coordination site of the metal center in **S12-IV** thus generating intermediate **S12-V** which, after migratory insertion and reductive elimination in **S12-VI**, furnishes the corresponding hydrocyanation product **S12-2**.



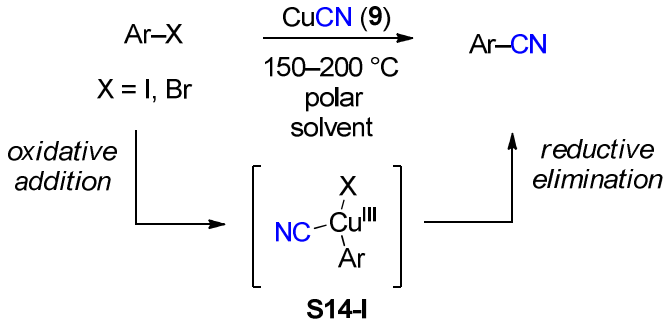
Scheme 12. Mechanism of nickel(0)-catalyzed hydrocyanation of alkenes.

Alkali metal cyanides have been extensively used for nucleophilic substitution reactions of alkyl halides.[12] Their main drawback arises from their high basicity that makes them prone to initiate side reactions like dehydrohalogenation or solvolysis.[1] These problems were overcome by replacing alkali metal cyanides with transition metal-based cyanides, more specifically copper(I) cyanide (**9**). CuCN was initially used in stoichiometric amounts for classical transformations like the Sandmeyer[32] or the Rosenmund-von Braun reaction.[33] Specifically, in the Sandmeyer reaction, an aryl diazonium salt is generated *in situ* and, after stoichiometric addition of copper(I) cyanide, the corresponding products are formed by a single electron transfer (SET)[33c] pathway (**Scheme 13**).



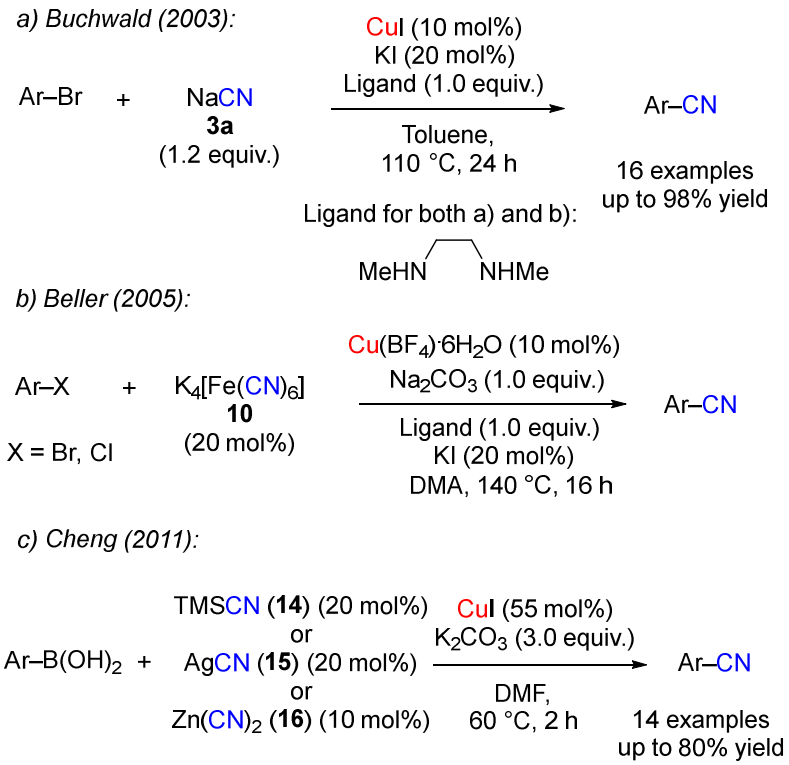
Scheme 13. Sandmeyer cyanation.

Another classical transformation performed with the salt **9** is the Rosenmund-von Braun reaction, where aryl halides undergo oxidative addition with the copper salt forming a copper(III) intermediates **S14-I**, which afford the corresponding aryl nitriles after reductive elimination (**Scheme 14**).



Scheme 14. Rosenmund-von Braun reaction.

Interestingly, in 2003 Buchwald and co-workers reported that these reactions could be performed by *in situ* generation of **9** from NaCN (**3a**) using catalytic amounts of copper halides (**Scheme 15a**).[34] This paved the way for the development of a wide scope of copper-catalyzed cyanations proceeding *via* catalytic formation of CuCN from different inorganic cyanide sources such as NaCN (**3a**), AgCN (**15**), $Zn(CN)_2$ (**16**) or $K_4[Fe(CN)_6]$ (**10**). Two years later, Beller and co-workers reported cyanoferrate **10** to be an efficient cyanating source for the copper-catalyzed cyanation of aryl bromides (**Scheme 15b**).[35] After this, in 2011 Cheng and co-workers established a copper-catalyzed cyanation of aryl boronic acids using different types of cyanating sources: TMSCN (**14**), AgCN (**15**) and $Zn(CN)_2$ (**16**) (**Scheme 15c**).[36]



Scheme 15. Cyanations *via in situ* generation of **9**.

However, despite all these achievements, all the reagents discussed above are far from ideal because of their toxicity. Indeed, generally the salts containing a cyanide anion represent a serious health risk, as they are capable to generate highly toxic hydrogen cyanide (**1**) in aqueous acidic media. Therefore, new methodologies to obtain organonitrile compounds without the employment of cyanides have become a stronger research field in the last decades.

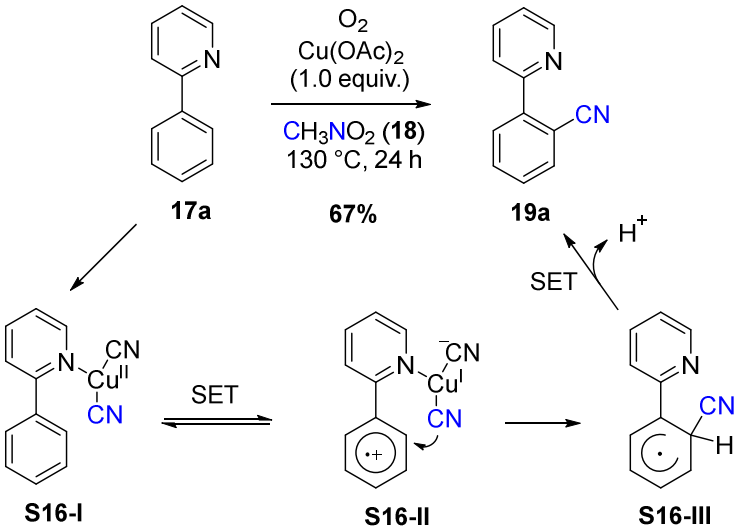
1.2.1.2.2. Recent developments.

All new procedures target the elaboration of efficient and non-toxic cyanation protocols as final goal. At the moment, two general strategies are employed: one of them based upon *in situ* formation of cyanides from non-cyanide sources, and the second one consists of using nitriles as cyano sources. The latter has an additional advantage of providing asymmetric variants when the selected nitrile is properly designed and conveniently activated, either by transition metals or Lewis acids.

1.2.1.2.2.1. *In situ* functionalization and derivatization.

In this cyanation procedure, the starting material can be *in situ* transformed into an activated species, which serves as aryl nitrile precursor and undergoes cyanation upon reacting with components of the reaction mixture. These procedures are formally cyanations performed without participation of any cyanating reagent.

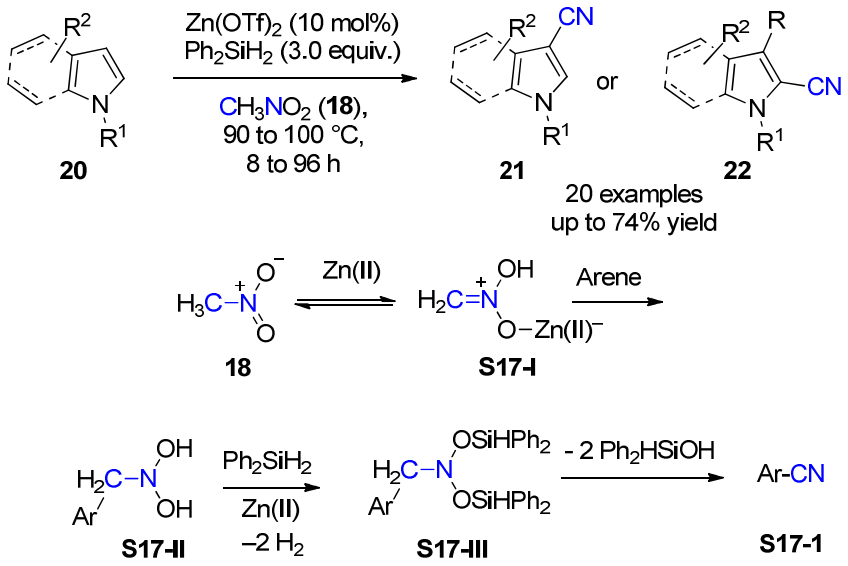
The first example of this type was published in 2006 by Yu and co-workers.[37] In this study 2-phenylpyridine (**17a**) was cyanated using nitromethane (**18**) as a cyanating solvent employing stoichiometric amounts of copper(II) acetate in the presence of oxygen. The proposed mechanism depicts the generation of copper(II) intermediate **S16-I** —whose CN moiety is speculated to be formed by a still unknown pathway from nitromethane— which leads to the generation of cation-radical intermediate **S16-II** *via* a SET process, intramolecular anion transfer (**S16-III**) and a following SET step that provides **19a** (**Scheme 16**).



Scheme 16. Nitromethane (**18**) as a cyanating reagent.

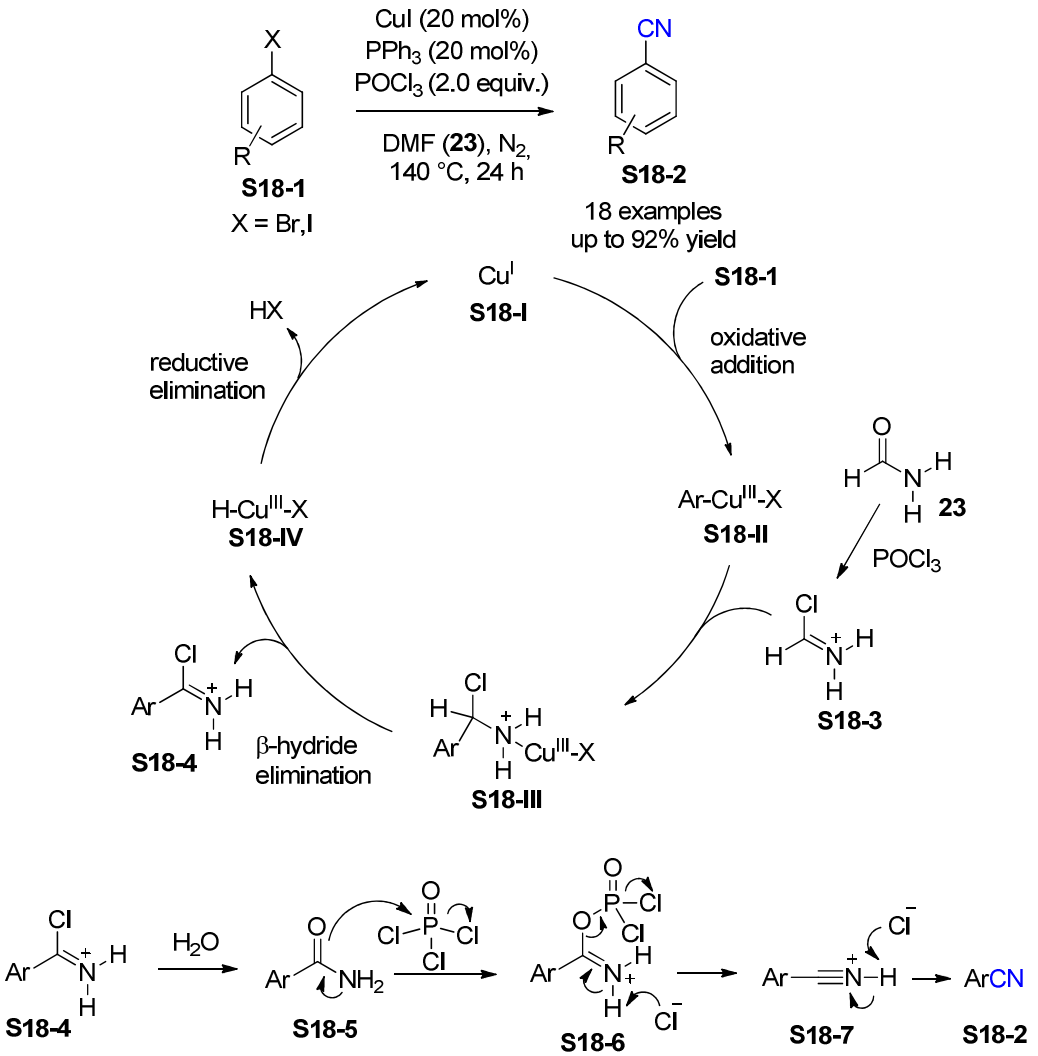
This concept was further developed by Tsuchimoto and co-workers, who reported in 2014 a zinc-catalyzed direct cyanation of indoles and pyrroles accelerated by Ph_2SiH_2 acting as Lewis acid (**Scheme 17**).[38] In the proposed mechanism, nitromethane (**18**) is initially activated by a zinc(II) center forming intermediate **S17-I**. The latter is attacked by electron-rich heteroarene substrate affording intermediate **S17-II**, zinc(II)-catalyzed

dehydrogenative silylation of which with Ph_2SiH_2 then furnishes intermediate **S17-III**. The corresponding aryl nitrile **S17-1** is generated from **S17-III** after two consecutive eliminations of Ph_2HSiOH moieties.



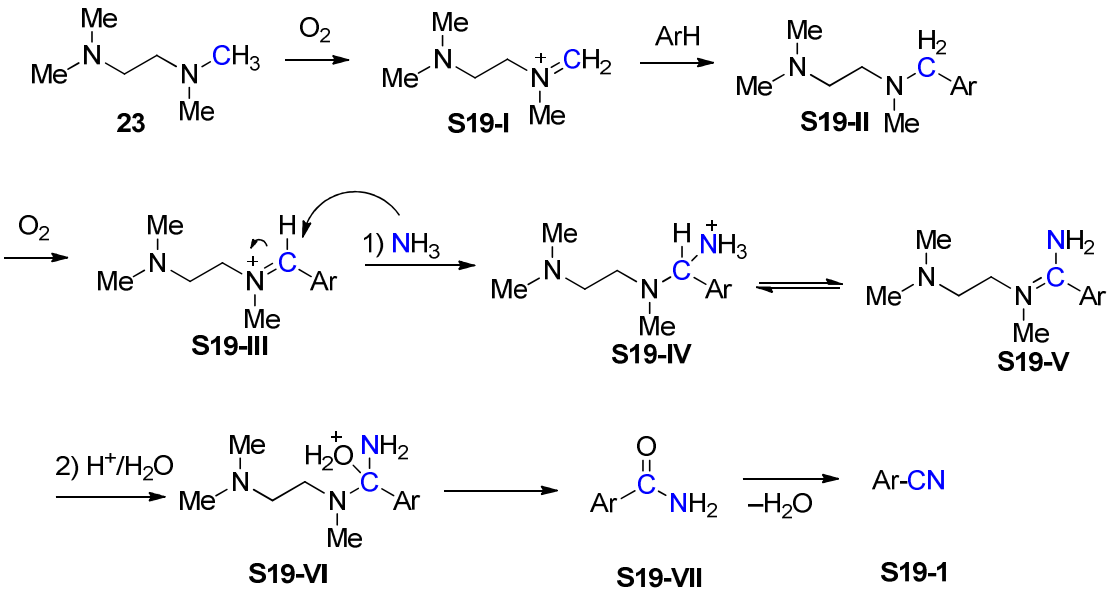
Scheme 17. Cyanation of indole derivatives**20** with nitromethane (**18**).

Alternative breakthrough was made in 2011 by Jiao and co-workers, who reported the cyanation of indoles and benzofuranes in an unprecedented manner using **DMF** (**23**) as a cyanating precursor.[39] Along the same year, the substrate scope was extended by Bhanage and co-workers, who reported the procedure to perform the cyanation of aryl halides using again DMF as a precursor in the presence of catalytic amounts of palladium(II) species.[40] Optimization of this reaction employing catalytic amounts of cuprous iodide was published in 2014 by the same research group.[41] Mechanistic details of this transformation are shown in **Scheme 18**. The process starts with an oxidative addition forming intermediate **S18-II**, which reacts with the *in situ* generated Vilsmeier-type reagent **S18-3** producing intermediate **S18-III**. After β-hydride elimination, the resulting iminium cation **S18-4** is further hydrolyzed (**18-5**), and oxidized with $POCl_3$ to the corresponding aryl nitrile **S18-2** (**Scheme 18, bottom**). The catalytic cycle continues with a reductive elimination step that regenerates initial copper(I) salt **S18-I**.



Scheme 18. Cyanations with dimethylformamide (**23**).

Further studies on this topic, this time using tetramethylethylenediamine (TMEDA, **24**) instead of **DMF** as a carbon source, and **$(NH_4)_2CO_3$** as a nitrogen source, were published by Cheng and co-workers in 2014.[42] The proposed mechanism is presented in **Scheme 19**. According to this, TMEDA (**24**) is oxidized to imine **S19-I** which, after nucleophilic attack of the substrate, oxidation of intermediate **S19-II** into **S19-III**, ammonolysis (**S19-IV to VI**) and dehydration of amide **S19-VII**, generates the corresponding aryl nitrile **S19-1**.

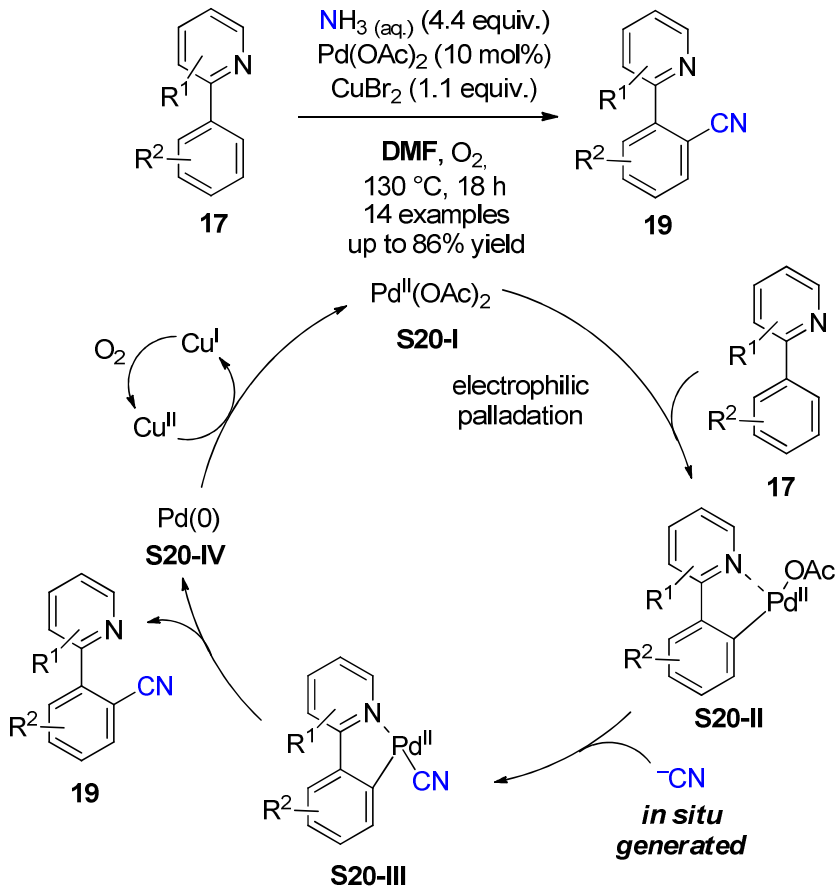


Scheme 19. Cyanations with TMEDA (**23**).

All these new methodologies represent efficient, atom-economy and safe ways to produce aryl nitriles from cheap and readily available reagents, the research of which is ongoing nowadays.

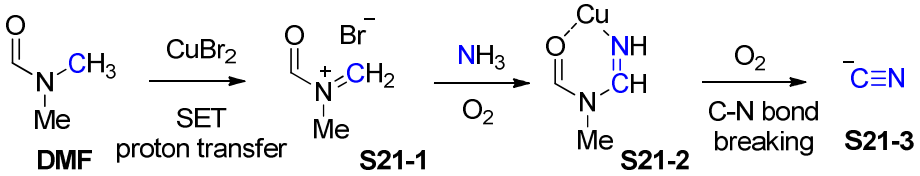
1.2.1.2.2.2. *In situ* generation of cyanides.

The *in situ* generation of cyanide ions in the reaction mixture allows the possibility of performing chemical transformations in a safer fashion regarding laboratory handling. Following this idea, in 2010 Chang and co-workers designed a novel strategy to cyanate 2-arylpyridines by an *in situ* cyanide formation directly from **NH_3** and **DMF**.[43] *Experiments with isotopically labeled* compounds demonstrated that the nitrogen atom came from the ammonia and the carbon atom from a methyl moiety in DMF. Once the cyanide is generated, the desired product is obtained by a C–H activation process[43b–e] promoted by the palladium catalyst (**Scheme 20**).



Scheme 20. Cyanation with a combination of **NH_3** and **DMF**.

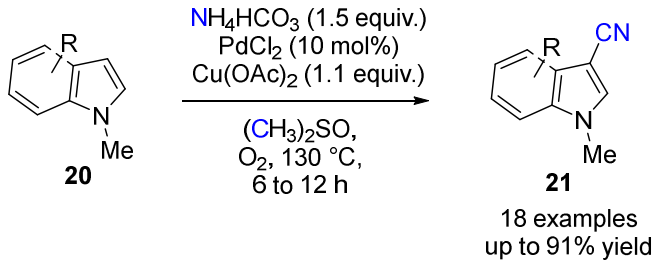
The proposed mechanism for the cyanide formation is detailed in **Scheme 21**. Presumably, imine specie **S21-1** is formed initially by a SET pathway[32c] initiated by $CuBr_2$. After this, ammonia attacks **S21-1** forming an amidine that coordinates to the copper center generating intermediate **S21-2**; aerobic conditions promote a C–N bond cleavage in **S21-2** affording cyanide anion **S21-3**.



Scheme 21. In situ generation of cyanides from **DMF**.

A similar approach was reported in 2011 by Cheng and co-workers.[44] In this case indoles **20** were cyanated with a cyanide anion formed from a combination of the nitrogen atom

contained in **NH_4HCO_3** salt and the carbon from the **DMSO** used as the solvent. The process was likewise catalyzed by a palladium(II) complex using stoichiometric amounts of a copper(II) salt (**Scheme 22**).



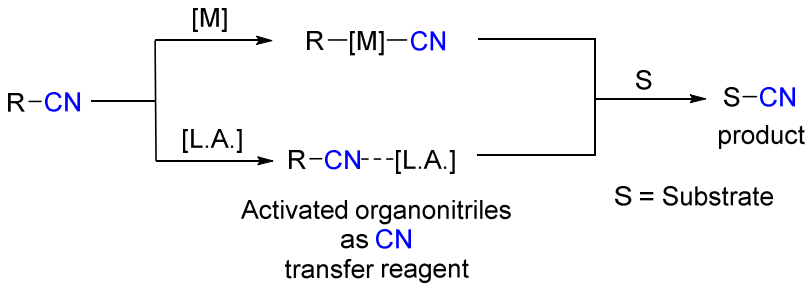
Scheme 22. Cyanation of indoles with **DMSO** and **NH_4HCO_3.**

Later reports are based on similar ideas using copper- or palladium-based catalysts combined with suitable oxidants.[45]

Another strategy to perform effective cyanations considers *in situ* breaking the carbon-carbon bond between a cyano group and an organic framework, thus generating in the reaction mixture a cyanide species that is ready to react with the selected substrate. As example of these procedures, I would like to mention the one that uses acetone cyanohydrine, to liberate hydrogen cyanide in solution, which can be directly used as a cyanide source.[46] Nonetheless even if hydrogen cyanide is liberated *in situ*, such a reaction is still a risky process that needed to be avoided.

1.2.1.2.2.3. Organonitriles as cyanating reagents.

In the recent years, several synthetic methodologies, in which the cyanating reagent is in fact a constituent of another nitrile molecule have been studied. All these new techniques are based on initial activation of the CN group by transition metals or Lewis acids, forming a so-called transfer reagent, followed by CN-transfer to the substrate molecule. (**Scheme 23**).

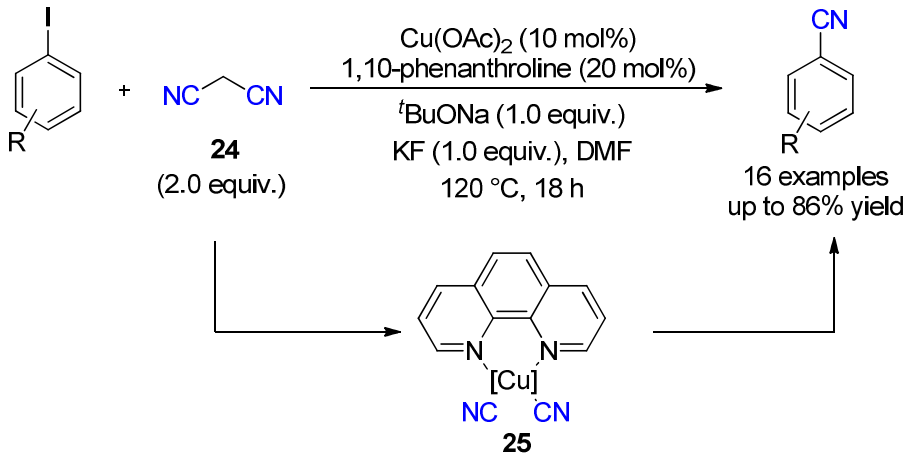


Scheme 23. Organonitriles as cyanating reagents.

All these novel protocols can be divided into three general groups based on the mechanism pathway that rules the reaction and the nature of the substrate, namely **a) nucleophilic cyanations**, **b) electrophilic cyanations** and **c) radical cyanations**.

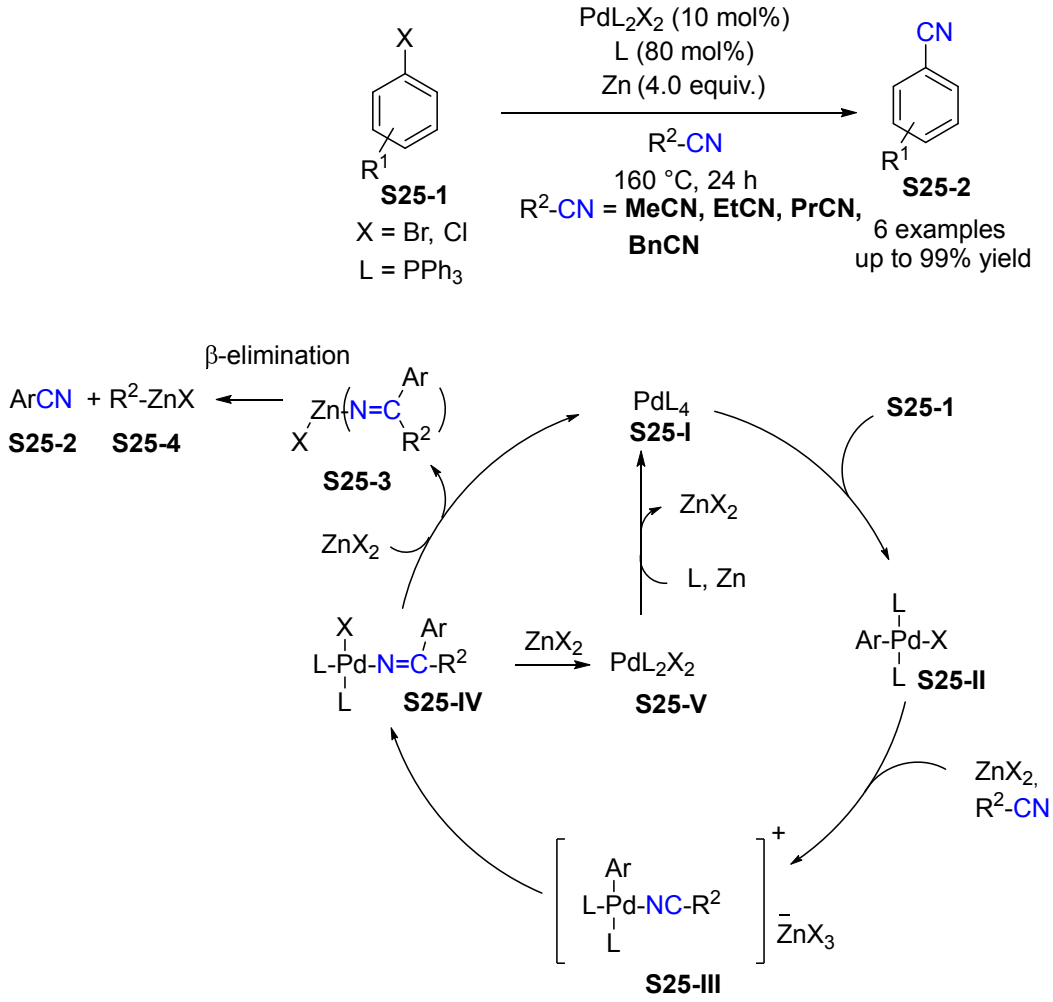
1.2.1.2.2.3.1. Nucleophilic cyanations.

Different protocols to achieve nucleophilic cyanations without the need of a cyanide source are discussed in this section. All the procedures require the activation of organonitrile molecules with transition metals, palladium and copper complexes in most of the cases. In 2012 Zhou and co-workers reported the copper-catalyzed cyanation of aryl iodides using malononitrile (**24**) as a nitrile source. Mechanistic studies of this transformation elucidated that the reaction was performed *via in situ* formation of a copper cyanide complex **25** which was the actual cyanating reagent (**Scheme 24**).[47]



Scheme 24. Cyanations with malononitrile (**24**).

One of the first examples in this field was reported by Cheng *et al.* in 1998. In this study, aryl halides **S25-1** were transformed into aryl nitriles **S25-2** in a metallic zinc-mediated Pd(0)-catalyzed cyanation using acetonitrile (**MeCN**), EtCN (**26**), PrCN (**27**) or BnCN (**28**) as cyanating reagents.[48] The catalytic cycle is shown in **Scheme 25**.

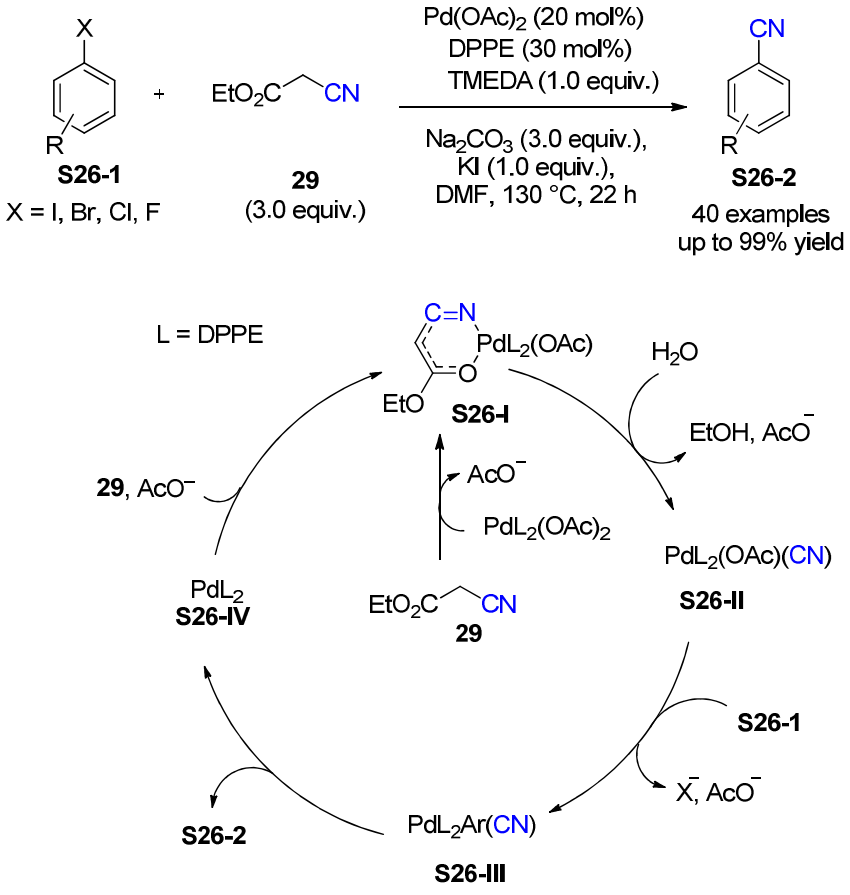


Scheme 25. Nitrile solvents **MeCN**, **EtCN**, **PrCN** and **BnCN** used as cyanating reagents.

In the proposed mechanism Pd halide **S25-I** is initially generated by employment of a Zn specie. Then the oxidative addition of aryl halides **S25-1** that generates palladium(II) complex **S25-II** occurs. In the next step the zinc halide salt extracts a halogen atom from the complex **S25-II** generating a coordination vacancy for the further coordination of the nitrile solvent. Afterwards the aryl group in **S25-III** is transferred to the carbon atom of a cyano group, thus generating imine intermediate specie **S25-IV**. Transmetallation with zinc

followed by a carbon-carbon bond cleavage in **S25-3** generates the corresponding aryl nitrile **S25-2** and an organozinc by-product **S25-4**.

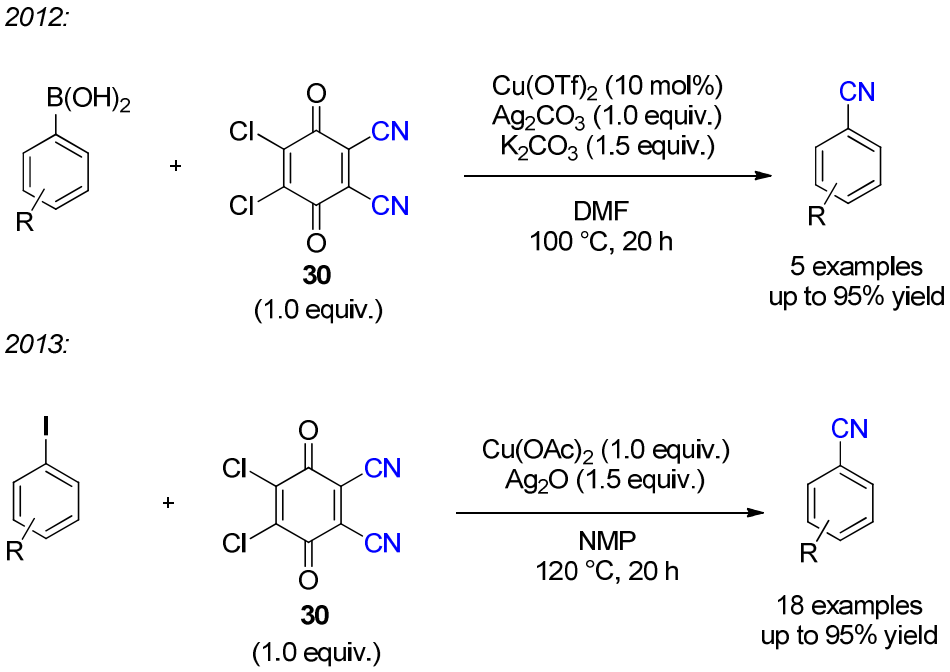
Shen and co-workers reported later a palladium-catalyzed cyanation of aryl halides using ethyl cyanoacetate (**29**) as a cyanide source.[49] Similar to the mechanism presented in **Scheme 25**, the actual cyanating reagent was in fact a cyanide palladium complex **S26-II**, formation of which is detailed in **Scheme 26**. Thus, cyanating proreagent **29** coordinates to the palladium(II) center forming complex **S26-I**, which generates after hydrolysis the actual cyanating complex **S26-II**. Addition of aryl halide **S26-1** forms intermediate **S26-III**, and subsequent reductive elimination in **S26-III** releases the desired organonitrile **S26-2** and restartes the catalytic cycle.



Scheme 26. Cyanations with ethyl cyanoacetate (**30**).

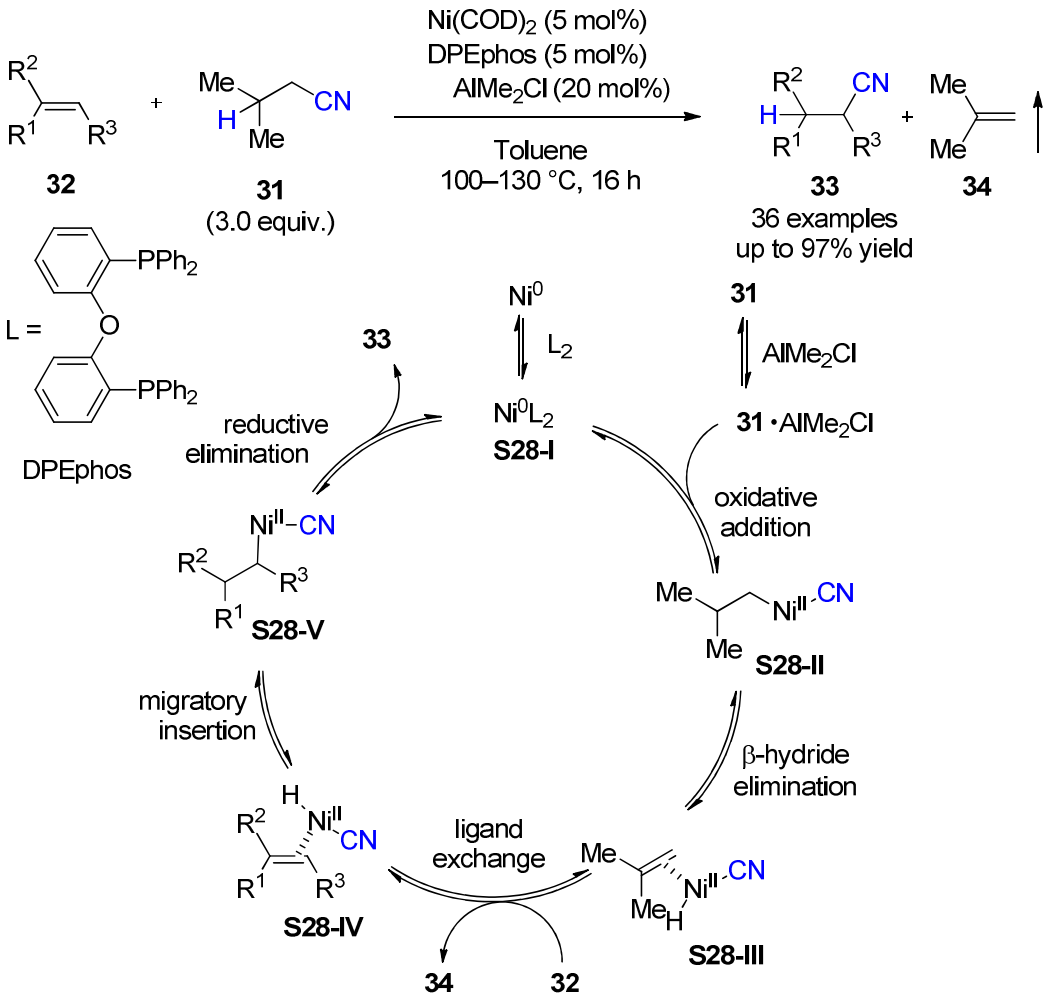
The following reports were published in 2012 and 2013 by J. Cheng and co-workers, including a new procedure in which aryl boronic acids and aryl halides were converted into aryl nitriles in the copper(I)-catalyzed process employing stoichiometric amounts of silver

salt as the oxidizing agent and 2,3-dichloro-5,6-dicyano-1,2-benzoquinone (DDQ, **30**) as a cyanide source (**Scheme 27**).[50] The mechanism of this transformation still remains unclear.



Scheme 27. Cyanations with **30**.

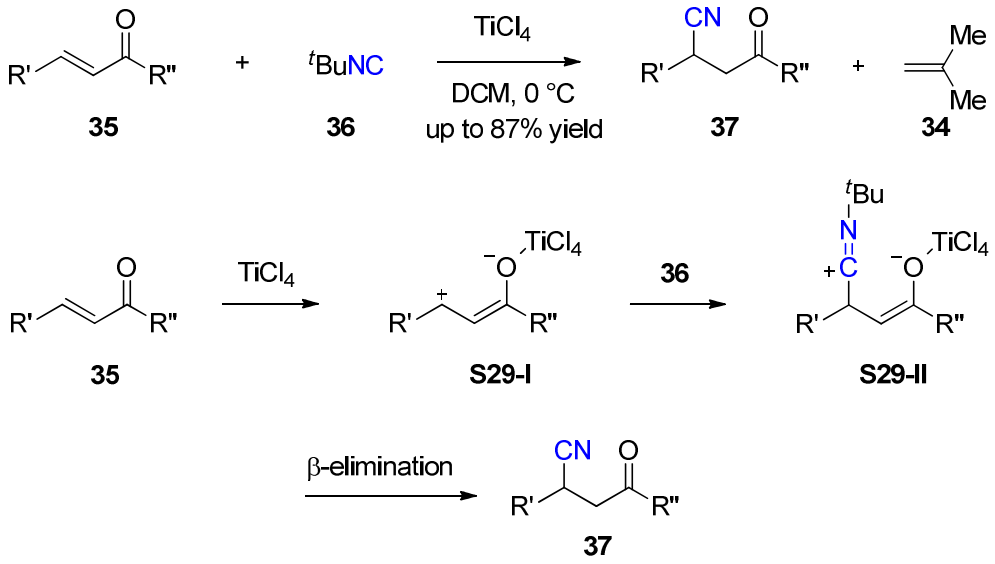
An indirectly but closely related protocol describing a novel hydrogen cyanide-free hydrocyanation with isovaleronitrile (**31**) consisting of a thermodynamically controlled reversible hydrofunctionalization of alkenes was recently published in 2016 by Morandi and co-workers. In this procedure, different alkenes are treated with alkyl nitriles as suitable hydrocyanating reagents using catalytic amounts of nickel(0) and an aluminum-based Lewis acid. The mechanism of this transformation is detailed in **Scheme 28**. The initial activation of the nitrile **31** with the aluminum-based Lewis acid promotes the oxidative addition of **31** to the Ni(0) catalyst **S28-I** forming complex **S28-II**. Subsequent β-hydride elimination and ligand exchange in the complex **S28-III** generates intermediate **S28-IV** with isobutene evolution. After migratory insertion and reductive elimination in **S28-V**, product **33** is generated.[51]



Scheme 28. Hydrogen cyanide-free hydrocyanations.

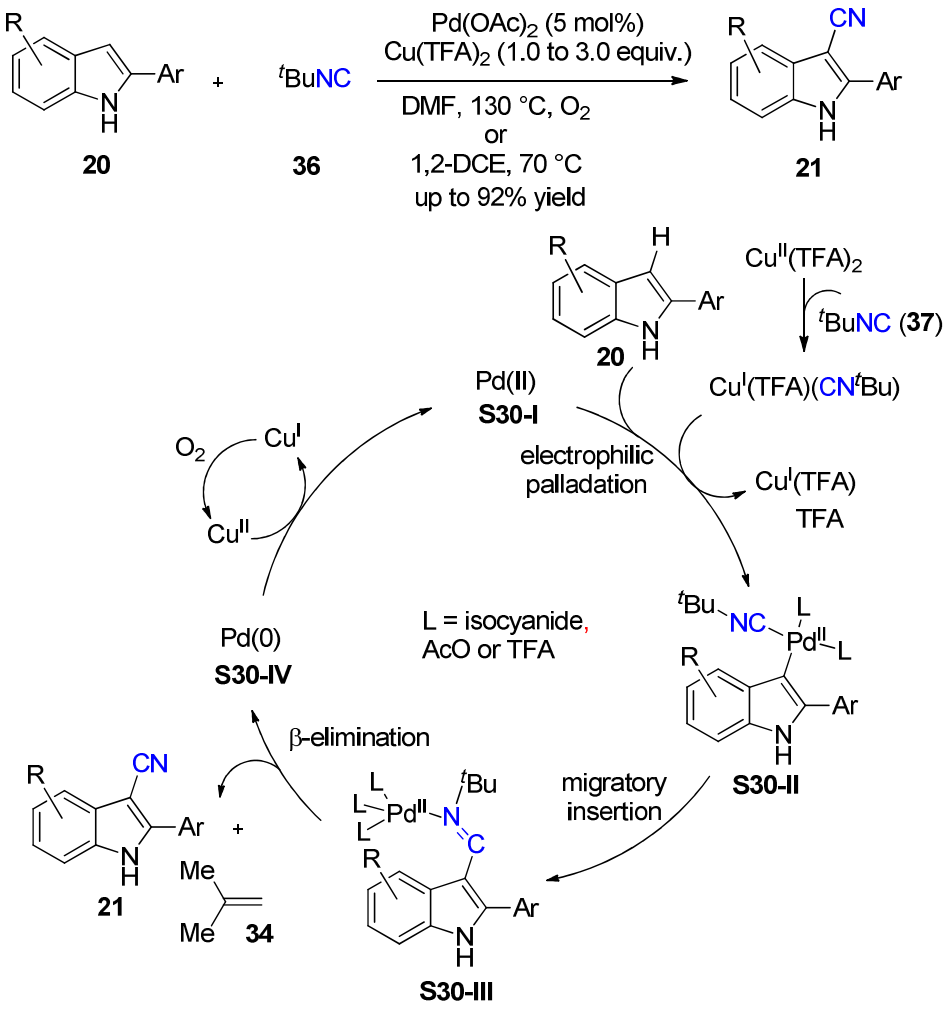
Isocyanides, more specifically defined as organo(iso)nitriles, are by definition isomers of cyanides featuring a zwitterionic species with two possible resonance structures. As the terminal carbon possesses high nucleophilicity, in theory isocyanides can be used for cyanations as well.

In 1982 Saegusa and co-workers reported a novel hydrocyanation of α,β-unsaturated carbonyl compounds using *tert*-butyl isocyanide (**36**) in combination with titanium tetrachloride. The mechanism, detailed in **Scheme 29**, is rationalized through an initial $TiCl_4$-promoted carbonyl activation which generates a carbocation in the γ-position of substrate **35**. The carbocationic center in **S29-I** then reacts with the isocyanide **36** furnishing intermediate **S29-II** which, after a β-elimination step followed by protolysis, forms the corresponding hydrocyanated product **37**.[52]



Scheme 29. Ti-promoted cyanations with *tert*-butyl isocyanide (**36**).

Recently the research groups of Xu[53a] and and Zhu[53b] reported a novel palladium-catalyzed, copper-assisted regioselective cyanation of different heteroarenes using *tert*-butyl isocyanide as a cyanating reagent. As detailed in **Scheme 30**,[53] this transformation proceeds through a C–H activation in the electrophilic position of the heteroarene (indole in **Scheme 30**) employing Pd(II) species (**S30-I**). Simultaneously, isocyanide **36** replaces one trifluoroacetate moiety in $Cu(TFA)_2$. Thus, activated isocyanide molecule is subsequently transferred to the palladium center forming the corresponding palladium complex **S30-II** and Cu(I) trifluoroacetate. The catalytic cycle continues with a migratory insertion of the isocyanide ligand generating intermediate **S30-III**. Finally, a β-*tert*-butyl elimination forms the cyanated product **21**, isobutene (**34**) as a gas waste and Pd(0) specie **S30-IV**. The latter is transformed to **S30-I** by copper-moderated oxidation using atmospheric oxygen. Xu and co-workers optimized further the reaction in 2014 using Rh(III) as a catalyst.[54]

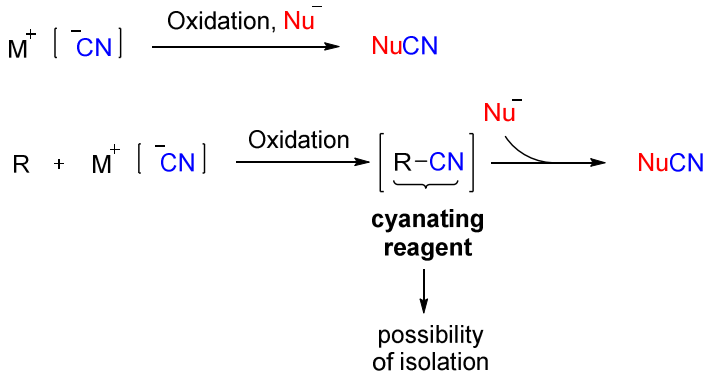


Scheme 30. Pd-catalyzed cyanations with *tert*-butyl isocyanide (**36**).

1.2.1.2.2.3.2. Electrophilic cyanations.

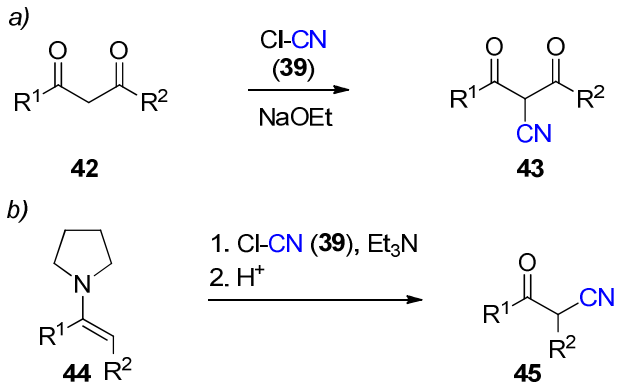
All the cyanations discussed above rely on the nucleophilic character of the cyano group. This implies that the substrates employed for these reactions are required to possess a certain electrophilic character, such as alkyl and aryl halides. Such a limitation of the the scope of cyanations can be overcome by development of electrophilic sources of the cyano group, which in principle can promote the electrophilic cyanation of any desired nucleophile. To achieve an electrophilic cyanation, two different approaches can be followed, consisting either in the *in situ* generation of [$^{+}$CN] species under oxidative conditions, or by the reversal of polarity in a molecule (*Umpolung)* via a proper design of the architecture of the cyanating reagent (**Scheme 31**). This last procedure requires a pre-

oxidation step to generate the corresponding cyanating reagent which can be either isolated and characterized or applied *in situ*. The major advantage of such cyanating reagents is that can be used for metal-free cyanations as a last step of a synthesis sequence, and furthermore, they open the route to asymmetric cyanations.



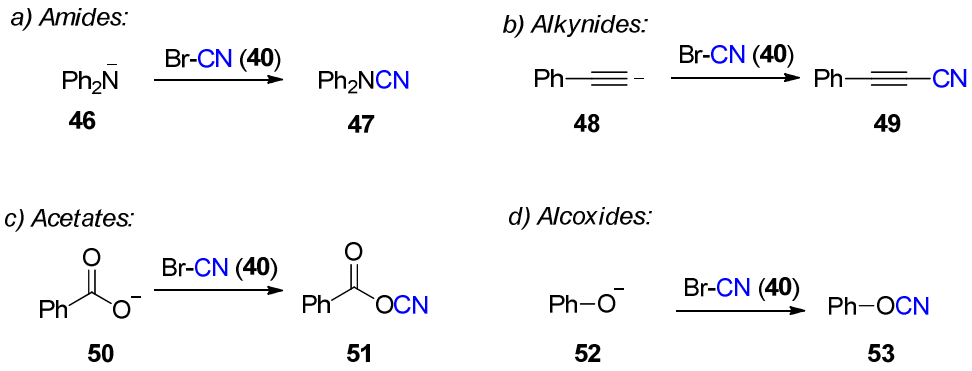
Scheme 31. Electrophilic cyanation strategies.

The first registered electrophilic cyanations were based on the employment of cyanogens such as cyanogen [$(CN)_2$, **38**], cyanogen chloride (ClCN, **39**), cyanogen bromide (BrCN, **40**) and cyanogen iodide (ICN, **41**). Compound **38** can be prepared from hydrogen cyanide (**1**) using chlorine as an oxidant,[55] and cyanogens **39**–**41** by oxidizing a metal cyanide salt with the corresponding halide.[56] One of the first examples of cyanations was the synthesis of diethyl cyanomalonate (**43**) using ClCN (**39**) (**Scheme 32a**),[57] which was promoted by cyanogens and employed enolates as a nucleophiles. Later, in 1959 the synthesis of β-ketonitriles by electrophilic cyanation of enamines was reported as well (**Scheme 32b**).[58]



Scheme 32. Cyanations with cyanogen chloride (**39**).

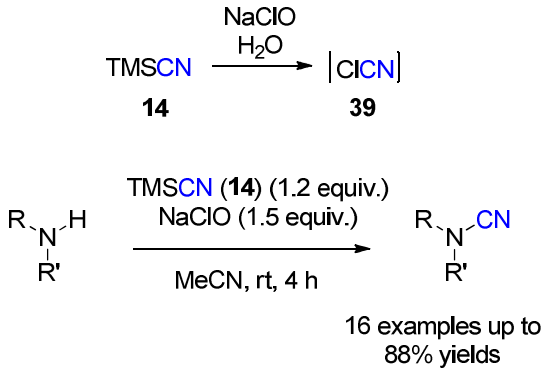
Cyanogen bromide (**40**) is a white solid at ambient temperature and therefore more convenient for laboratory preparations than ClCN. This compound has been also applied for the cyanation of amines,[59] alkynes,[60] esters[61] or alcohols[62] (**Scheme 33**). These reagents have the major disadvantage of possessing a high volatility, toxicity as well as high vapor pressure which becomes them in non-enviromentally friendly reagents.



Scheme 33. Cyanations with cyanogen bromide (**40**).

Further examples of cyanations with cyanogens were reported in 1967 by Dell and Boltze, who used thiocyanogen $(SCN)_2$ (**54**) for the electrophilic cyanation of aryl lithium derivatives. The limitation of this approach was the formation of undesired thiocyanated products.[63]

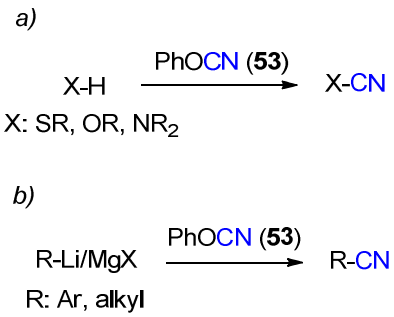
On the pursuit of finding a less toxic alternative for cyanogens, the idea of *in situ* generating "[$^+$CN]" species using cyanide anions under oxidative conditions arose. The first example, consisting in the cyanation or electron-rich aromatic rings through the electrolysis of sodium cyanide, was described in 1965.[64] Unfortunately, the reaction resulted in a formation of a complex mixture of cyanated products. However, half a century later, in 2014, Chen and co-workers published a cyanation protocol for secondary amines based on this idea. Thus, by *in situ* oxidation of TMSCN to ClCN a wide variety of *N*-cyanated tertiary amines were prepared (**Scheme 34**).[65]



Scheme 34. *In situ* generation of cyanogen chloride (**39**) for the cyanation of secondary amines.

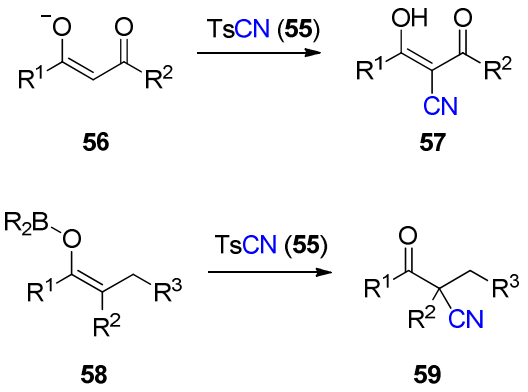
The most common result of these initial studies in the field of electrophilic cyanation was the formation of complex mixtures due to the high reactivity of the corresponding XCN reagents, whereas the target products were obtained in poor yields.

A new reagent was introduced in 1967 by Grigat and Pütter, who reported on electrophilic cyanations of different nucleophiles employing phenyl cyanate (**53**). Deprotonated alcohols, thiols or amines were also suitable substrates for these transformations (**Scheme 35a**).[66] Additionally, in the subsequent publications by Sato this reagent was applied for the cyanation of carbanionic organolithiums and organomagnesiums (**Scheme 35b**).[67]



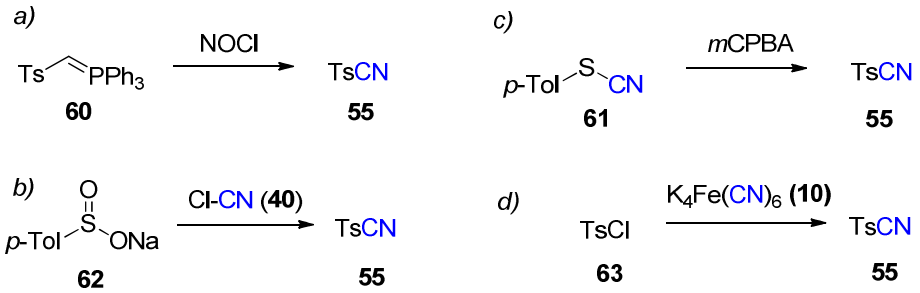
Scheme 35. Cyanations with phenyl cyanate (**53**).

Starting with the pioneering report by Leusen and Jagt in 1970 on application of tosyl cyanide (**55**) for electrophilic cyanation,[68] this reagent (or its derivatives) was successfully applied on the cyanation of enolate-type substrates such as malonates or boron enolates, as indicated in recent publications (**Scheme 36**).[69]



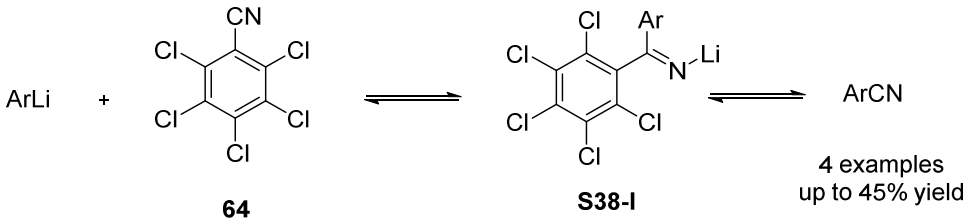
Scheme 36. Cyanations with tosyl cyanide (**55**).

Moreover, several syntheses of TsCN avoid the inconveniency of using toxic reagents or harsh conditions (**Scheme 37**).[70]



Scheme 37. Syntheses of tosyl cyanide (**55**).

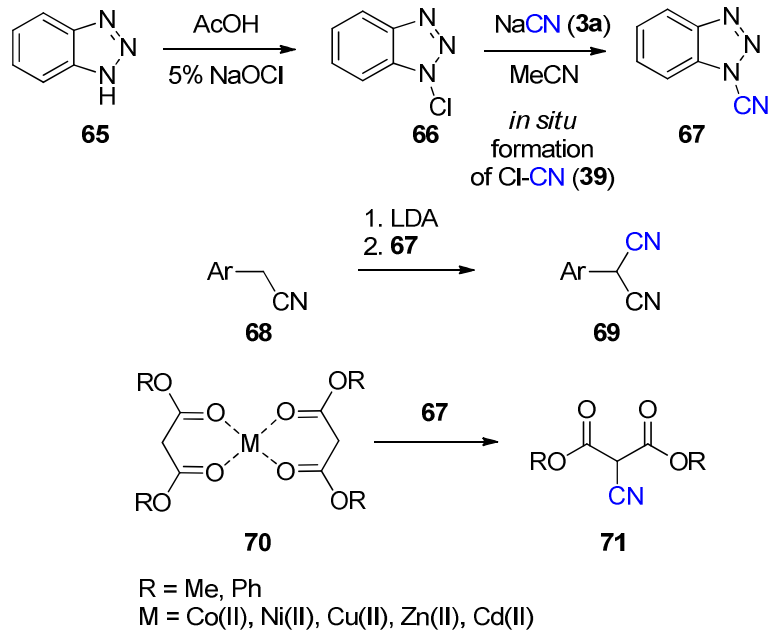
The electrophilic cyanation of aryllithium-compounds using pentachlorobenzonitrile (**64**) *via* a Li/CN exchange process, although with low yields and formation of undesired by-products, was reported in 1972 (**Scheme 38**).[71]



Scheme 38. Cyanations with pentachlorobenzonitrile **(64).**

Studies in the field were further extended in 1996 and 1998 after invention of 1-cyanobenzotriazole (BtCN, **67**), which was synthesized in two simple steps (**Scheme 38**). Its potential as a cyano-transfer reagent was probed using organolithium- and malonate-

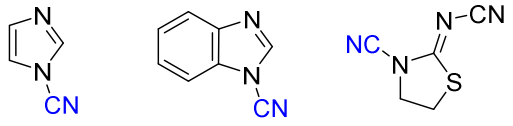
based substrates (**Scheme 39**).[72]



65 **66** **67** **68** **69** **70** **71**

Scheme 39. Synthesis of 1-cyanobenzotriazole (**67**) and examples of cyanations with **67**.

Following similar strategy, a variety of *N*-CN reagents were developed in the following years such as *N*-cyano imidazole (ImCN, **72**), *N*-cyano benzimidazole (BiCN, **73**) or 3-cyano-2-(*N*-cyanoimino)thiazolidine (3-cyano-NCT, **74**) (**Figure 4**). These reagents could be prepared avoiding a direct use of cyanides and represent an alternative for **67**, targeting a similar substrate scope.[73]

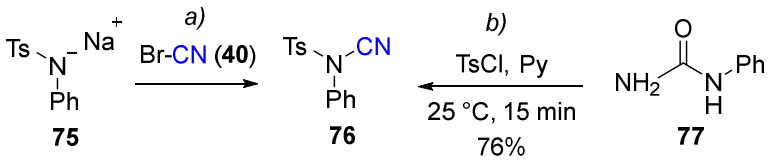


72 **73** **74**

Figure 4. Structures of *N*-CN reagents **72**, **73** and **74**.

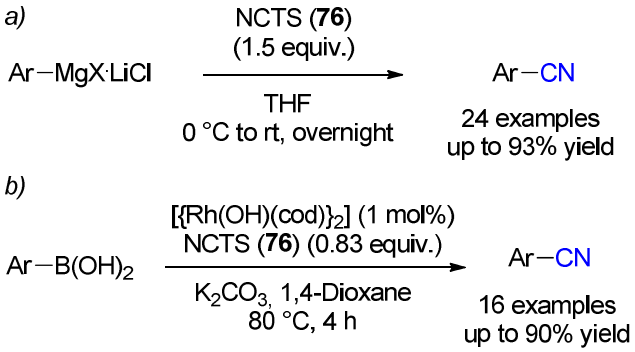
On the other hand, employment of all the reagents discussed above is in most cases limited to cyanation of strong nucleophiles of anionic character. This limitation was overcome with the design of novel *N*-cyano-tosylsulfonamide (NCTS, **76**) that constitutes nowadays one of the most employed electrophilic cyanating reagent in organic chemistry. Its synthesis by adding BrCN (**40**) to the corresponding sodium tosylanilide **75** was first described in 1949 by Kurzer (**Scheme 40a**),[74] but it was not until 2011 when this was prepared by the reaction of phenylurea with *p*-toluenesulfonyl chloride in pyridine by Beller

and co-workers (**Scheme 40b**), who tested reactivity of **76** as a cyanating reagent.[75]



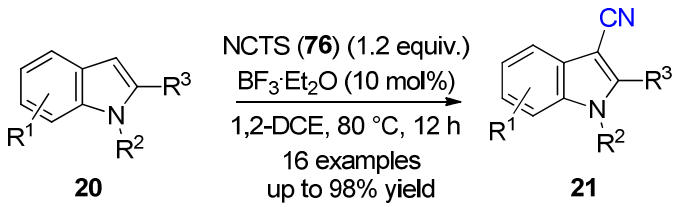
Scheme 40. Syntheses of NCTS (**76**).

As a proof of concept, they were able to carry out the cyanation of aryl Grignards (**Scheme 41a**), which were generated *in situ*. Most impressively, they performed the first rhodium-catalyzed cyanation of aryl boronic acids. (**Scheme 41b**).[76] Its noteworthy to mention that aryl boronic acids represent the first type of mild air- and moisture-stable nucleophiles in such transformations.



Scheme 41. Cyanations with NCTS (**76**).

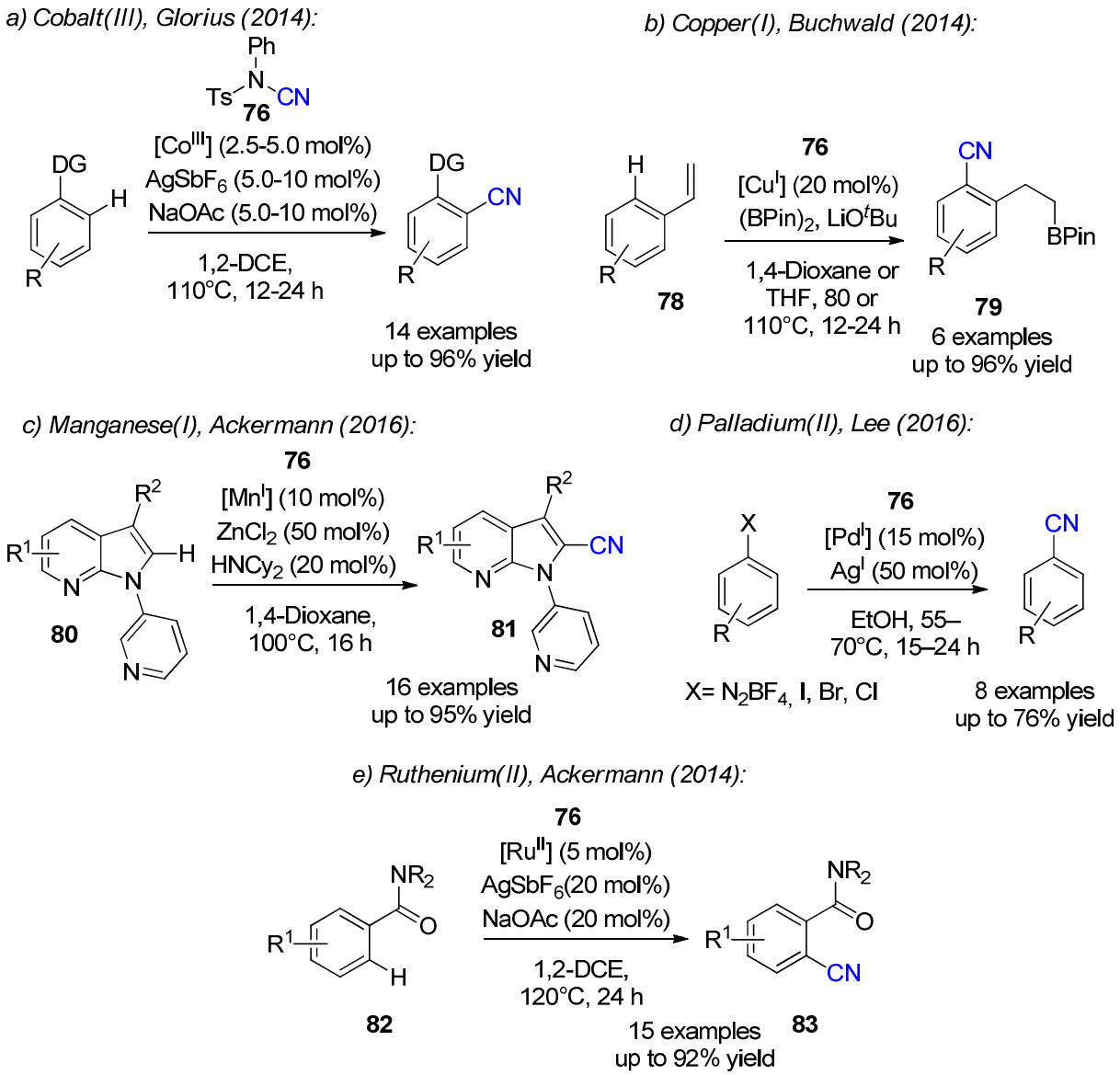
Another prominent example of electrophilic cyanations with **76** was published in the same year by Wang and co-workers. In this case, a selected set of indole derivatives **20** was successfully cyanated *via* a metal-free protocol using $BF_3{\cdot}Et_2O$ as Lewis acid catalyst (**Scheme 42**).[77]



Scheme 42. Lewis acid-promoted cyanation with NCTS (**76**).

In the recent years, a number of research groups have been focused on exploring further applications of **76** in metal-catalyzed cyanations, in most of the cases through a C–H activation, using cobalt,[78] copper,[79] manganese,[80] palladium[81] or ruthenium and

rhodium[82] complexes. Some recent examples are depicted in **Scheme 43**.

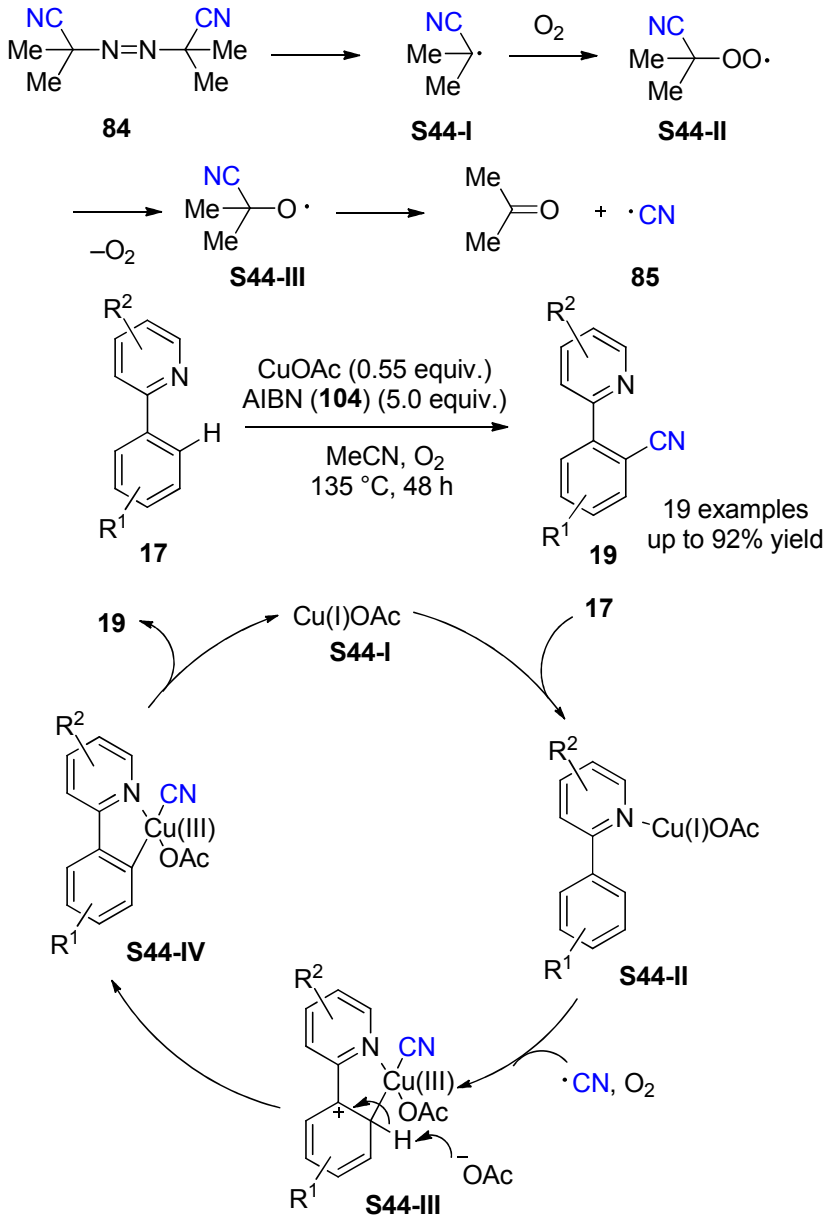


Scheme 43. Transition metal catalyzed cyanations with NCTS (**76**).

1.2.1.2.2.3.3. Radical cyanations.

An alternative strategy for cyanations can be based upon the *in situ* formation of cyano radicals. Han and co-workers reported in 2013 the first example on generating of this radical **85** initiated with decomposition of commercially available azabisisobutyronitrile (AIBN, **84**).[83] In this report, classical substrates 2-phenylpyridines **17** could be cyanated *via* C–H activation using a copper(I)-based catalyst. This novel procedure for the

generation of a cyano radical **85**, as well as the proposed mechanism are detailed in **Scheme 44**. Unfortunately, to the best of our knowledge, the transformations of this type were not further investigated.



Scheme 44. Radical cyanations initiated with AIBN (**84**).

2. Hypervalent Compounds: Design and Electrophilic Cyanation.

2.1. Introduction.

Hypervalency model was first introduced by Musher in 1969[84] and defined as molecules formed from atoms of Groups V–VIII of the periodic table in their higher valences, bearing more than 8 electrons in their valence shell and not obeying the general tendency of the octet rule. The excess of electrons is rationalized by the formation of a hypervalent bond between three atoms with participation of four electrons (three-center four-electron bond, or 3c-4e$^-$, proposed by Pimentel in 1951)[84b]. These bonds resemble to those formed between ligands and metals and can be refered to as weak covalent bonds and with longer interatomic distances. In the 3c-4e$^-$ model, three atomic orbitals are combined into three molecular orbitals: bonding, non-bonding and antibonding, where four electrons occupy the bonding and non-bonding orbitals. As can be seen, the HOMO orbital features a node in the central atom (A), so the entire electron density is localized in the ligands (L) (**Figure 5**).[85]

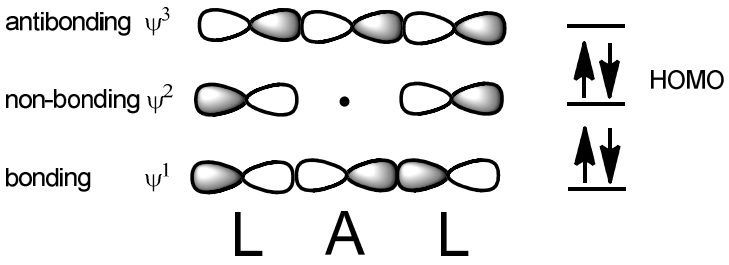


Figure 5. Three-center four-electrons model orbitals.

Regarding electrophilic cyanations, an elegant alternative metal-free approach to accomplish the *Umpolung* (change of polarity) of the cyano group has been successfully demonstrated by employing hypervalent iodine reagents. Most organic molecules with iodine, such as alkyl or aryl iodides, are monovalent iodine compounds with an oxidation state of 1. However, due to the large size of the iodine atom and its high polarizability

because of strategic position in the periodic table, the bonding in iodine compounds is different from that of the lighter main-group elements. Iodine in higher oxidation states is capable to form oligocoordinated structures; these molecules are also known under the common name of "hypervalent iodine (III) compounds".[86] As a consequence of the high electronegativity of the iodine atom, when a cyano group is directly connected to the iodine center, the electrophilicity of the nitrile moiety becomes higher, and can be transferred to a selected nucleophile.

It should be noticed, however, that the iodine atom is only slightly more electronegative than the carbon one and, therefore, the polarization is not pronounced.[87] Nevertheless, as iodine is one of the biggest and highly polarizable atoms, the electron density can be distributed in an easier manner by the formation of hypervalent bonds, thus affording hypervalent iodine(III) species.

In the specific case of compounds of hypervalent iodine (III), iodine atom contains 10 electrons in its valence shell, adopting the trigonal bipyramid geometry, where the most electronegative groups L occupy the *axial (a)* positions. Conversely, the less electronegative substituent R is linked in a covalent fashion to iodine, occupying an equatorial (*e*) position together with the two equatorial lone pairs of electrons in the same plane. Because of this, iodine(III) compounds adopt T-shaped structure (**Figure 6**).[88]

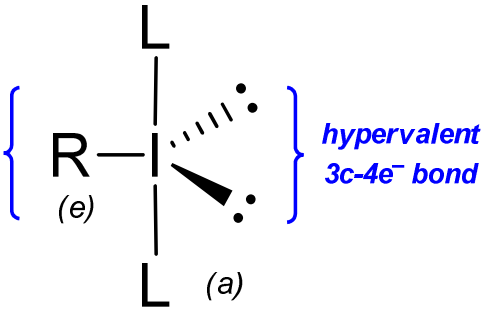
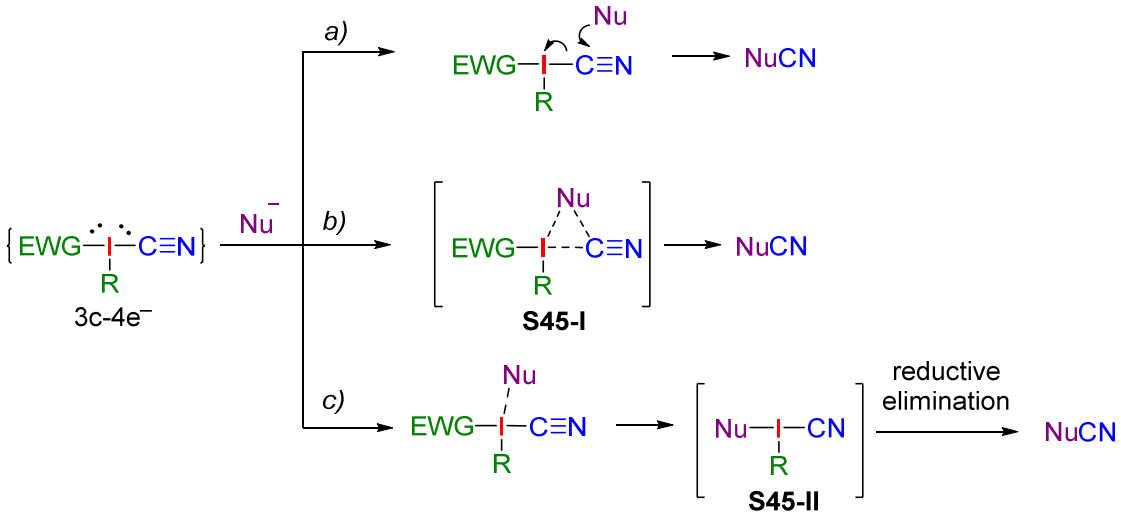


Figure 6. T-shape of hypervalent iodine(III) species.

When these compounds react with a given nucleophile three possible scenarios can explain the mechanism of the transformation; first situation involves a nucleophile attack directly on the cyanide moiety, which will generate the desired product and will release an iodane by-product **(Scheme 45a)**. A second possible pathway regards the generation of a three-membered-ring intermediate described by the carbon atom of the cyano group, the iodine atom and the nucleophile (**S45-I**),[86] due to the high electrophilicity of the iodine center, the latter constitutes an excellent leaving group, thus transferring the cyano group to the nucleophile and affording the subsequent nitrile (**Scheme 45b**). The third possible

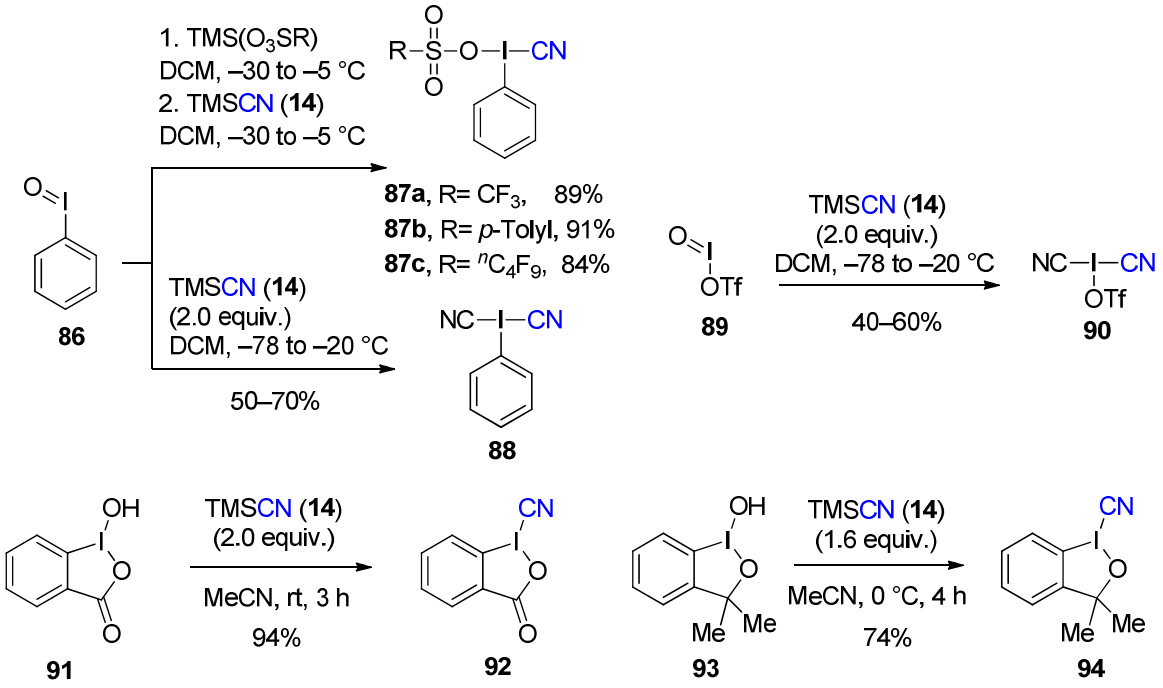
mechanism depicts a nucleophilic attack in the iodine center (**S45-II**), which will lead to the formation of the product by a reductive elimination step (**Scheme 45c**).



Scheme 45. Reactivity of hypervalent iodine(III).

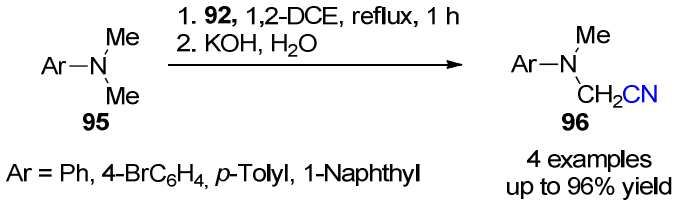
2.2. Synthesis of hypervalent iodine reagents.

Different hypervalent iodine compounds containing a CN group were synthesized in the early 90s, such as **87**, **87**, **90**, **92** and **94** (**Scheme 46**)[89], which could have potential as cyanating reagents.



Scheme 46. Synthesis of hypervalent iodine(III) species **87, 88, 90, 92** and **94.**

Reagent **92** was proved to be suitable to cyanate *N*-alkyl groups of *N*,*N*-dialkylanilines **95**; however, in this case the transformation was proposed to proceed rather through a radical than electrophilic pathway (**Scheme 47**).[90d]

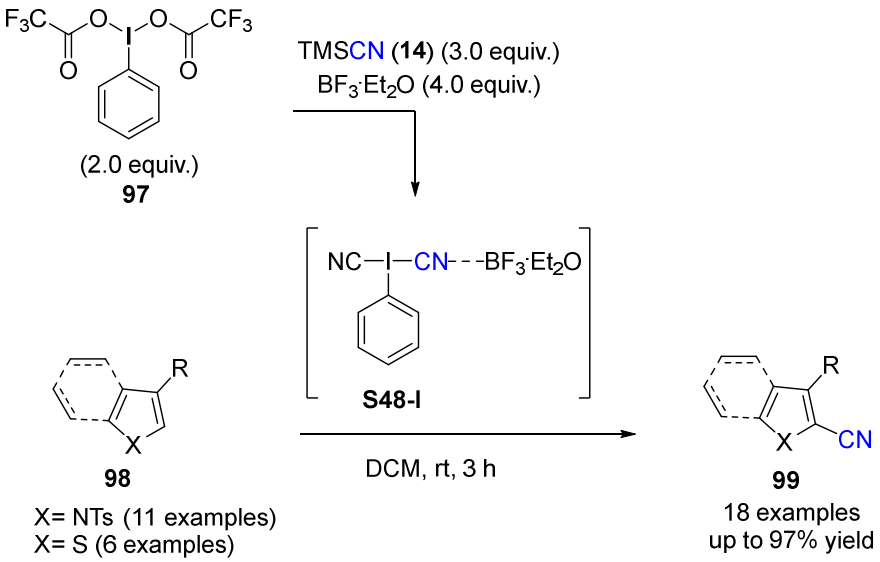


Scheme 47. Cyanation with **92**.

Very recently the latter transformation was extended to alkanes and ethers employing modified reaction conditions.[90e]

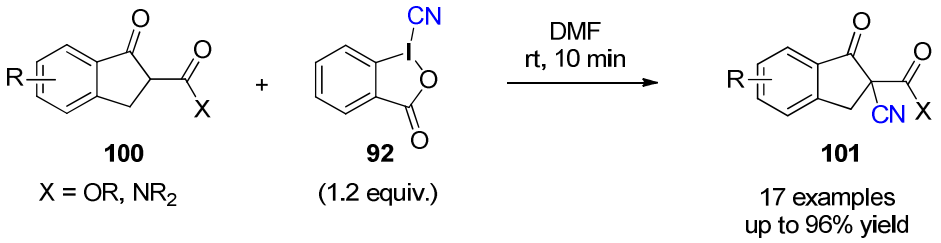
It should be mentioned that these iodanes are very unstable with respect to moisture and exhibit decomposition or violent explosions at elevated temperatures. This considerably limits their applicability.

The first example of electrophilic cyanation through a metal-free process using hypervalent iodine species and electron-rich heteroaromatics was reported in 2007 by Kita and co-workers.[90] Phenyliodine(III) dicyanide was generated *in situ* from phenyliodine(III) bis(trifluoroacetate) (PIFA) and TMSCN. Once generated, $BF_3{\cdot}Et_2O$ coordinates to the nitrile group enhancing electrophilicity in the intermediate **S48-I** and subsequently facilitating the nucleophilic attack. The reaction conditions and scope are detailed in **Scheme 48**.



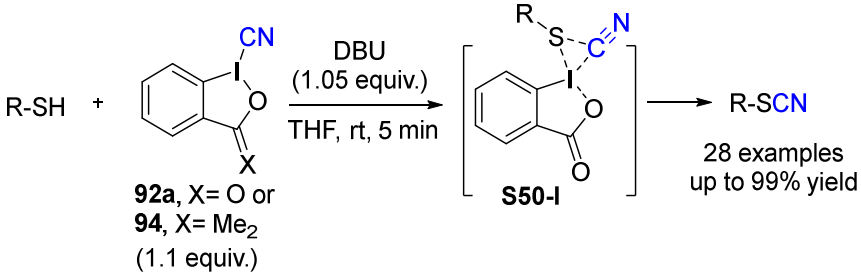
Scheme 48. Cyanation with phenyliodine(II) dicyanide-$BF_3{\cdot}Et_2O$ complex (**S47-I**).

The high potential of these reagents was realized only after 2015, when Chen and co-workers reported on cyanation of various cyclic β-dicarbonyl compounds **100** using hypervalent iodine reagent **92** (**Scheme 49**).[91]



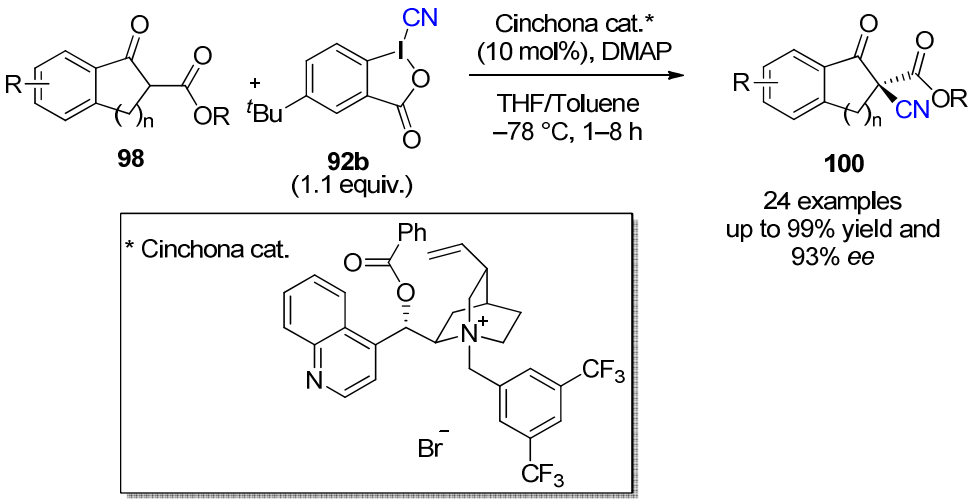
Scheme 49. Cyanation with hypervalent iodine reagent **92**.

In the same year, Waser and co-workers described the cyanation of deprotonated aryl and alkyl thioles with hypervalent iodine reagents **92** and **94**. The mechanism was rationalized as occurring *via* a concerted pathway through the formation of intermediate **S50-I** (**Scheme 50**).[92]



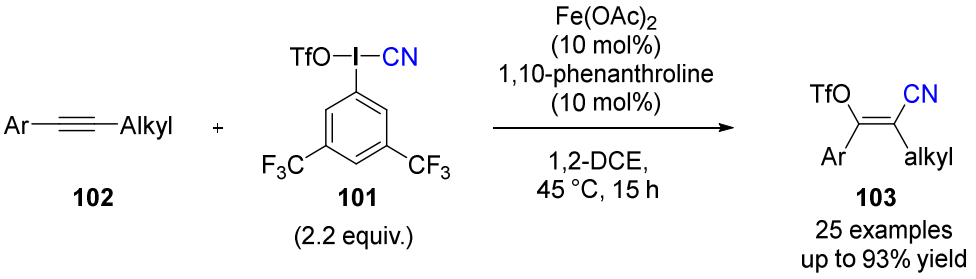
Scheme 50. Cyanations with hypervalent iodine reagents **92** and **94**.

The next breakthrough in this area was the development of a method allowing asymmetric cyanations. Hence, experimental protocols applying compound **92a** were tested in the same year by Waser and co-workers[93] and then improved by Zheng and co-workers by using the iodine reagent **92b**, which is essentially a ^{t}Bu-substituted analogue of **92a**. In combination with a cinchona-based chiral catalyst *ee*'s of up to 93% were obtained (**Scheme 51**).[94]



Scheme 51. Asymmetric cyanations with modified iodine reagent **92b**.

The most recent advances in this field were published in 2016 by Studer and Wang, who reported the first example of iron(II)-catalyzed electrophilic cyanation of intenal alkynes **102**. In this case, iodane **101** afforded the corresponding substituted 2-cyanopropenyl trifluormethylsulfonates **103** as final products (**Scheme 52**).[95]



Scheme 52. Cyanation with iodane **101**.

2.3. New cyanating reagents developed in our group.

The general trend used in literature for designing new cyanating reagents is based on the use of heteroatoms with high electronegativity directly attached to the cyano group. This decreases the electron density on the carbon atom in the nitrile group, thereby creating a certain electrophilic environment. To further enhance the electrophilicity of this center, a

proper selection of the substituents which will be liked to this heteroatom is crucial (generally electron-withdrawing groups) (**Figure 7**).

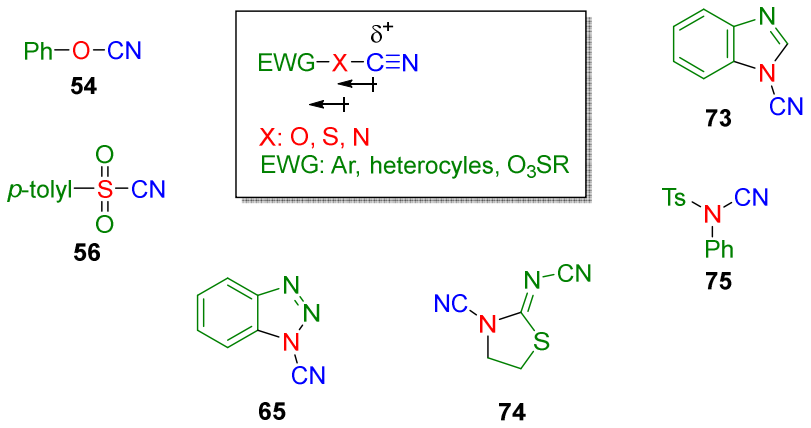
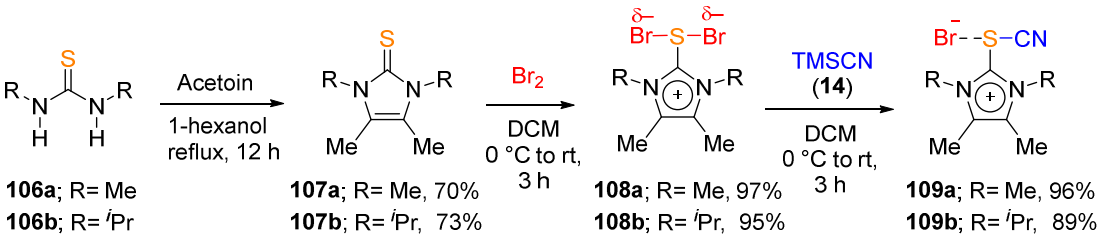


Figure 7. Design of electrophilic cyanating reagents.

As previously mentioned, hypervalent iodine (III) compounds can react violently when exposed to air, moisture or elevated temperatures. Therefore, our team focused the attention on developing analogues of these reagents which could be satisfactory employed in a safer manner. As first option, sulfur based compounds seemed to be the most appropriated molecules to start this new family of cyanating reagents, as sulfur atom possesses somewhat similar properties to iodine in terms of high electronegativity and polarizability. In addition, hypervalent sulfur species have already been described in the literature.[96,97] As explained afore, including an EWG in the reagent structucture will help to enhance the electrophilicity of the nitrile group, and based on previous experience of our research group, an imidazolium substituent was considered as first option.[98,99–101]

Imidazolium thiocyanates synthesis was already described by Burgess and Arduengo.[96] First, cyclic thioureas **107** were synthesized through condensation of thioureas **106** with acetoin, and further oxidized by bromine generating hypervalent species **108**. For the comparison, the general pathway to obtain hypervalent iodine(III) species is oxidation of phenyl iodide with chlorine.[102] As indicated above, preparation of every electrophilic cyanating reagent needs a cyanide source, and in this case trimethylsilyl cyanide **14** was added to hypervalent compounds **108**, thus affording the desired imidazolium thiocyanates **109** (**Scheme 53**).[103,104]



Scheme 53. Synthesis of cyanating reagents **109a** and **109b**.

The resulting products could be prepared in multigram scale from inexpensive and commercially available reagents through high yielding processes and could be stored under air for undefined time. As it is not trivial to assume that species **108** and **109** are in fact hypervalent molecules and not just simple cationic sulfides, both reagents **108b** and **109b** were recrystallized and analyzed by X-Ray diffractometry (**Figure 8**).[103]

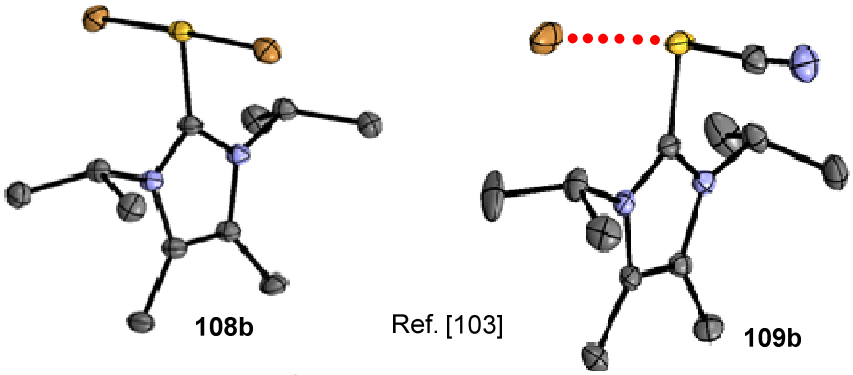


Figure 8. T-shaped hypervalent sulfur(II) species **108b**, **109b** and selected similar structures. Hydrogen atoms are removed for clarity.

Analogously to hypervalent iodine(III) species [90b], both structures are T-shaped, as do the similar hypervalent sulfur (II) compounds (**Figure 8**) [96,102]. The bromo and cyano substituents occupy the apical positions in respect to the plane of cyclic "thiouronium" moiety. In such a situation, the triads bromo-sulfur-bromo in **108b** as well as bromo-sulfur-cyano in **109b** are aligned in a hypervalent 3c-4e$^-$ bond (**Figure 9**). On the basis of this information it can be postulated that **108** are hypervalent sulfur(II) species, and possibly **109**.

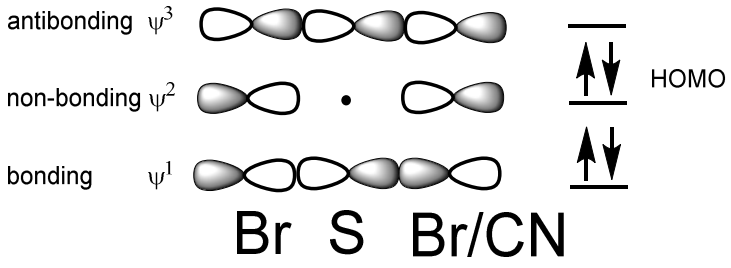
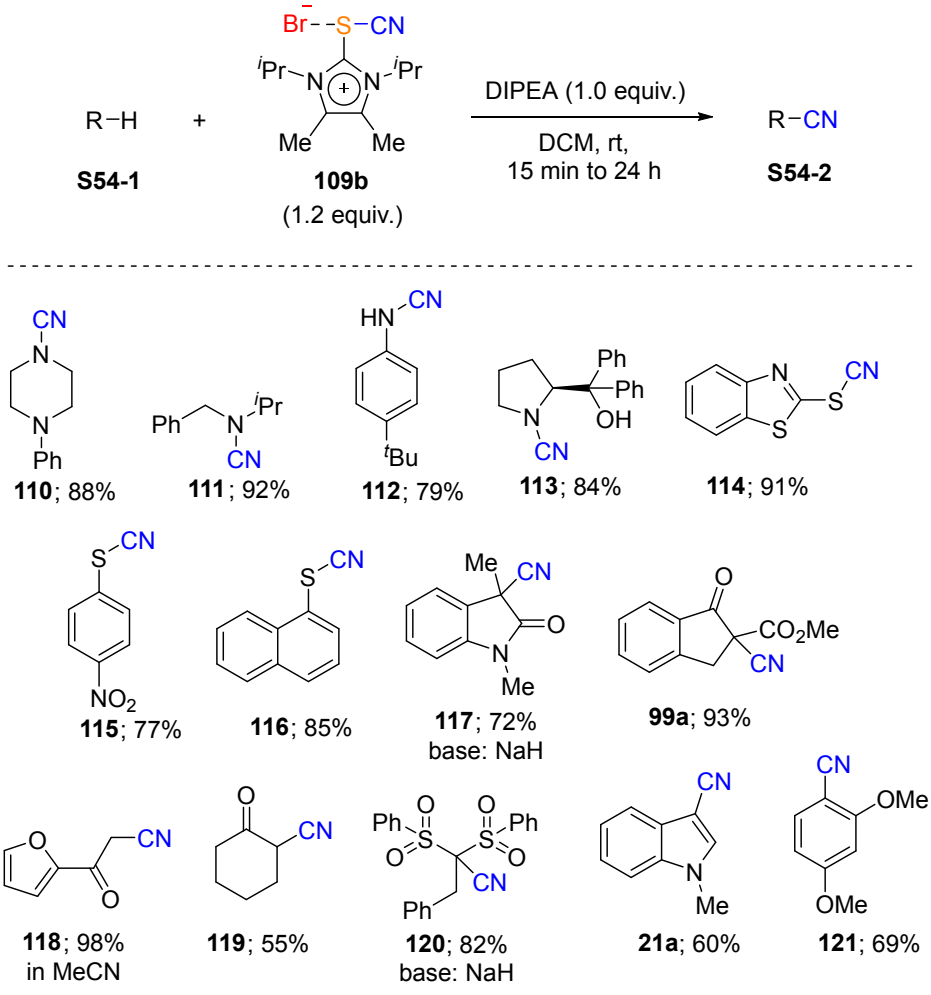


Figure 9. Hypervalent orbitals of **108b** and **109b**.

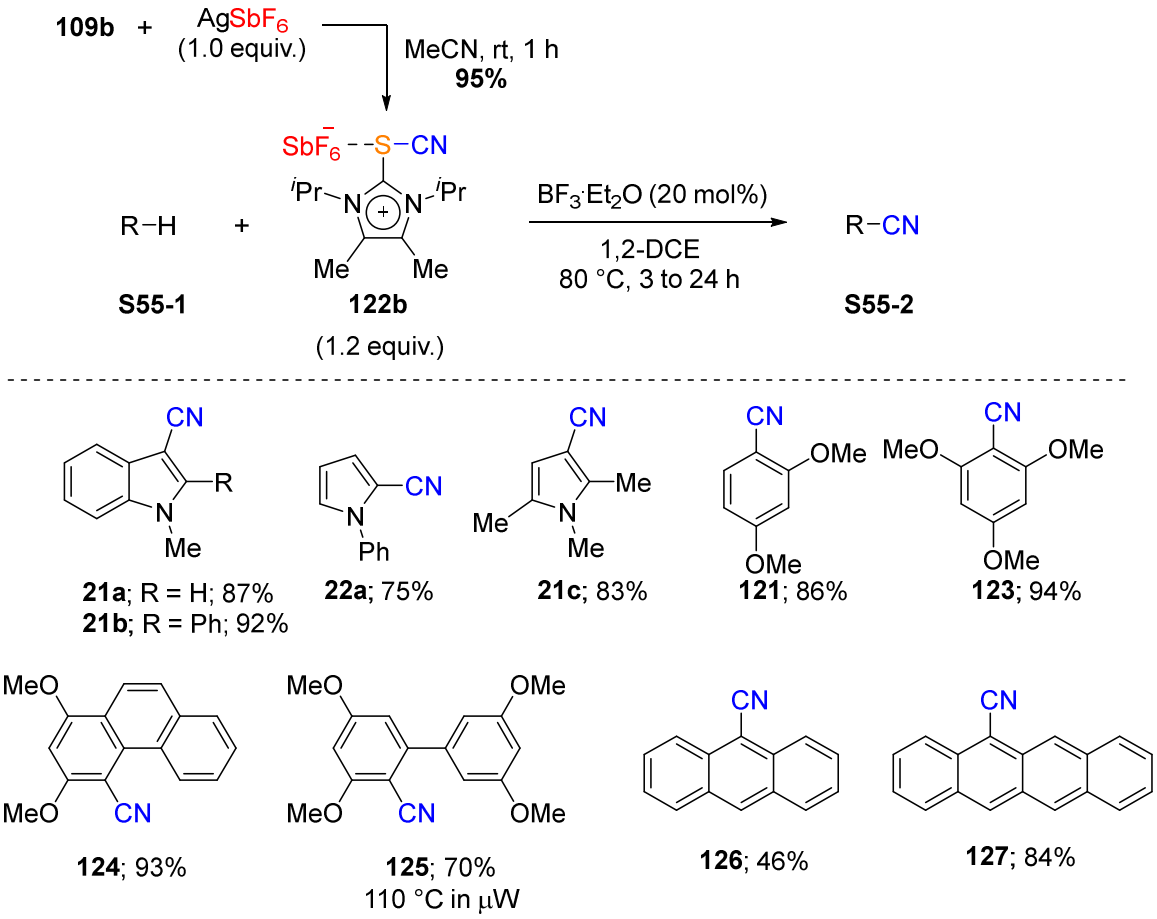


Scheme 54. Cyanation scope using reagent **109b**.

Interestingly, reagent **109b** demonstrated a remarkable ability to cyanate under basic conditions a wide variety of nucleophiles such as sulfur and nitrogen centers, enolate-type compounds and electron-rich aromatic rings (**Scheme 54**).[103]

Most reports on electrophilic cyanations require basic conditions due to the nature of the starting materials. Another approach to achieving successful electrophilic cyanations can

be accomplished under acidic conditions by activation of the cyanating reagent *via* Lewis adduct formation, as has been exemplified in previous reports employing boranes.[105] Following these studies, compound **122b**, which can successfully cyanate electron-rich aromatic rings when $BF_3{\cdot}Et_2O$ is used as catalyst, was designed in our group (**Scheme 55**).[103] It should be emphasized that a counterion exchange of bromine to the non-coordinating hexafluoroantimonate anion was necessary in order to avoid the quenching of the bromide anion by the Lewis acid catalyst.



Scheme 55. BF_3-catalyzed cyanation scope with the reagent **122b**.

These two protocols evidenced the potential benefits of compounds **109b** and **122b** in comparison to the cyanating reagents developed to date. As mentioned above, they are reactants that are stable towards air and moisture and be prepared in multigram scale from inexpensive starting materials under simple reaction conditions. Moreover, they do

not require metals for their activation and do not decompose violently under air or at elevated reaction temperatures.

The future goal of the group is to expand the scope of the nucleophiles that can be cyanated with these types of reagents.

2.4. Summary.

Up to day, a tremendous amount of protocols to perform cyanations have been reported. Classical methodologies employ highly toxic cyanating reagents such metal cyanides, hydrogen cyanide or cyanogens. To avoid direct contact with these cyanating reagents, some procedures were developed for their *in situ* generation, through construction of C≡N bonds from different sources of carbon and nitrogen, or more importantly through transfer of the C≡N group from another non-toxic molecule. This last approach of transferring a cyano group generally requires transition metal catalysts, most frequently copper and palladium. Last efforts were focused on the development of hypervalent iodine species, possessing metal-type behavior and capable to perform “oxidative addtions”- or “reductive eliminations”-type transformations. However, their disadvantage of possessing high air and moisture sensitivity as well as thermal instability up to violent explosions limits their application. The most important cyanating sources that have been employed successfully until our days, as well as their advantages and disadvantages, are summarized in **Figure 10**.

As organonitriles are very important intermediates in organic chemistry, performing cyanations applying a cheap, non-toxic and safe procedure is nowadays still an important research topic in the laboratories. Our research group has centered the attention on this problem since 2015 by developing new electrophilic cyanating reagents based on cationic sulfides.

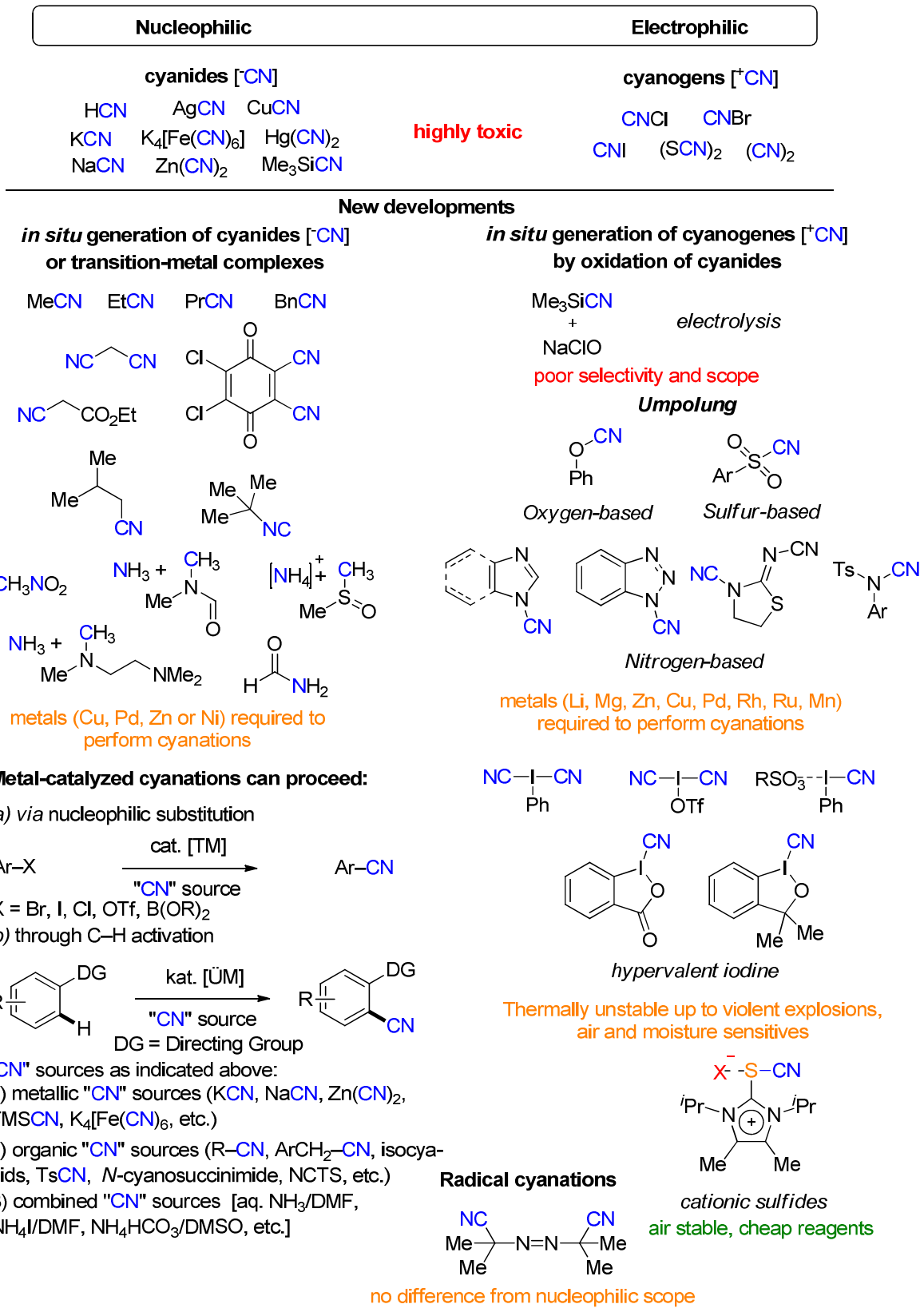
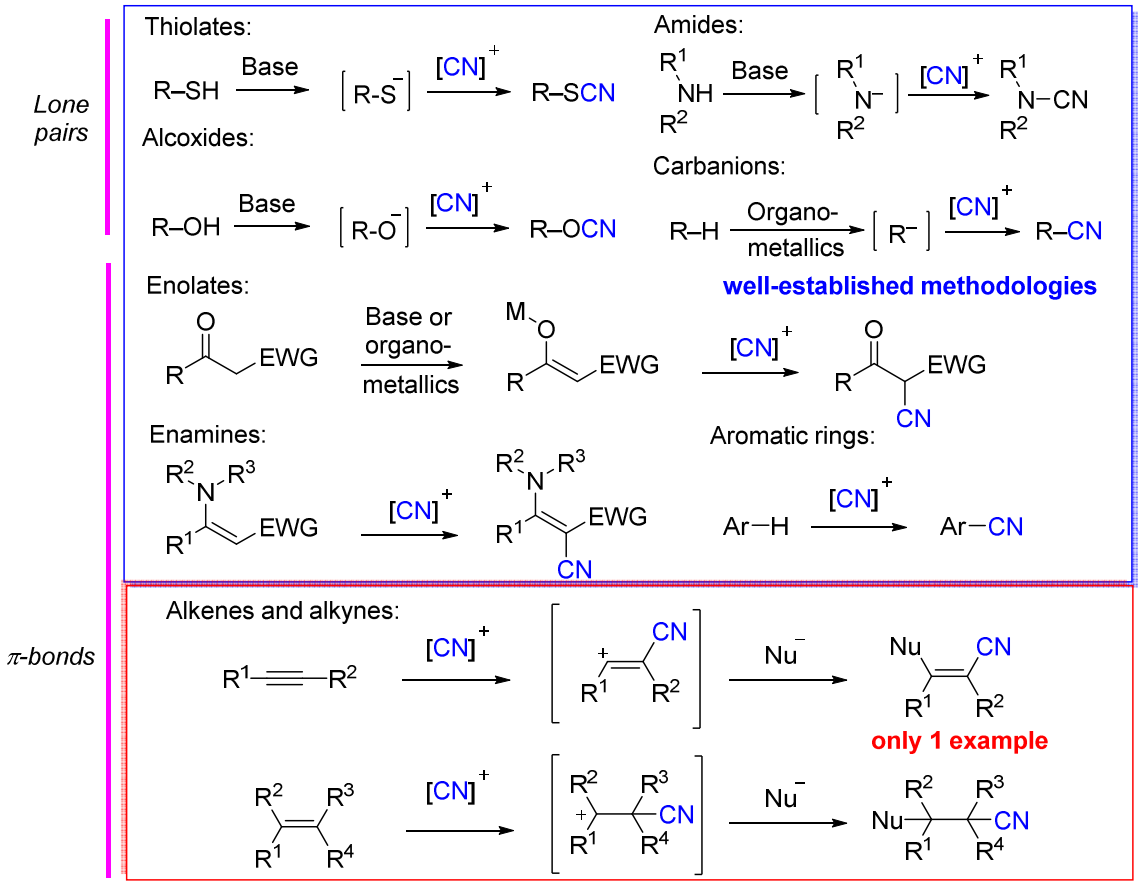


Figure 10. Summary of cyanation reagents, sources and selected strategies.

3. Regio- and Stereoselective Chlorocyanation of Alkynes.

3.1. Introduction.

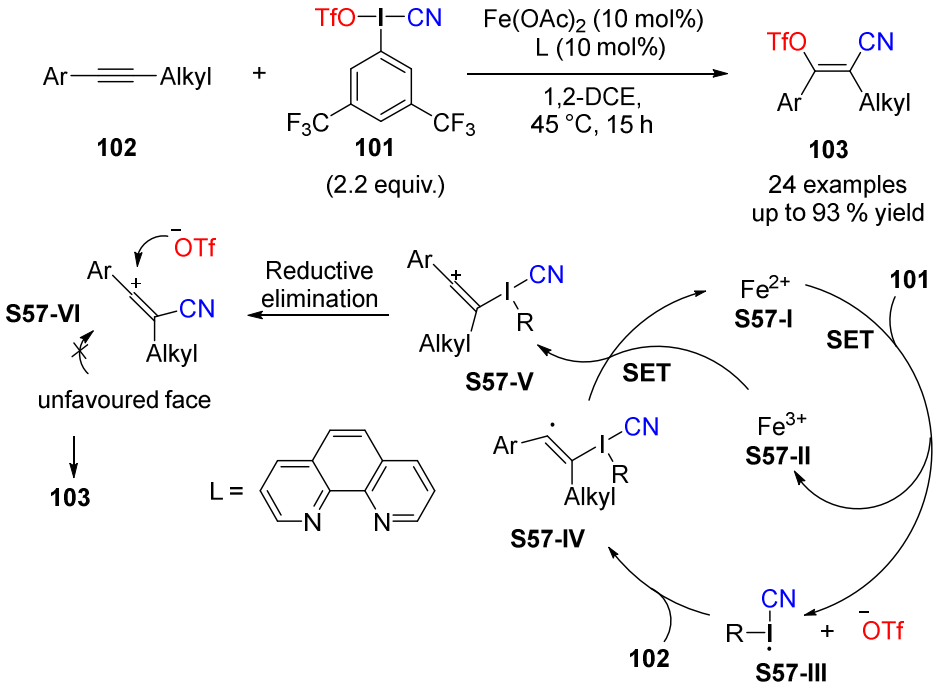
Nucleophiles are compounds with ability to donate a pair of electrons and can be sorted in three main categories depending on the origin of these two electrons: lone pairs-type, σ-bonds-type and π-bonds-type. Most of nucleophiles engaged in electrophilic cyanations belong to the lone pairs group, such thiolates, amides, alcoxides and carbanions. These species are usually generated *in situ* under basic conditions or by addition of organometallics. The second type, nucleophiles with participation of σ-bonds, is less common and occurs mostly in the cases of intramolecular reorganizations, such proton shifts or sigmatropic rearrangements. The third type, nucleophiles with π-bonds, includes enolates, enamines, aromatic rings, alkenes and alkynes. Electrophilic cyanations of nucleophiles of types I and III are summarized in **Scheme 56**.



Scheme 56. Cyanation of different types of nucleophiles.

The electrophilic cyanation of alkynes and alkenes still remains a challenge because alkynes and alkenes belong to the group of weak nucleophiles. Moreover, regio- and stereomeric mixtures of products are often formed when an electrophile is added. Finally, they require the addition of an external nucleophile to trap the generated carbocationic intermediate.

To the best of our knowledge, the first example of electrophilic cyanation of internal alkynes was reported by Studer and Wang in 2016.[95] This transformation is based upon employment of the hypervalent iodine(III) compound **101** with triflate as a suitable nucleophile to trap the cationic intermediate **S57-VI** which arises during the reaction. The conversion requires iron(II) catalyst **S57-I** that reduces **101** through a SET process,[32c] thus generating an iodanyl radical intermediate **S57-III**. The latter further reacts with alkyne **102** forming the iodonium radical **S57-IV**, which is then oxidized by the iron(III) complex to form the vinylic cation **S57-V**, simultaneously regenerating iron(II) catalyst **S57-I**. Finally, reductive elimination and triflate addition to vinylic cation **S57-VI** generates the desired products **103** (**Scheme 57**). Cooperative effect of stabilization in carbocation **S57-VI** provided by the aromatic substituent and of steric hindrance caused by an alkyl moiety justify the high regio- and stereoselectivity of the method.



Scheme 57. Cyanotriflation of internal alkynes with hypervalent iodine compound **101**.

Keeping in mind the excellent results obtained in our research team on the use of newly developed hypervalent sulfur reagents, we focused the attention on these underexplored transformations and envisioned the design of a protocol to perform effective and selective electrophilic cyanations of alkynes using imidazolium thiocyanates as cyanating reagents.

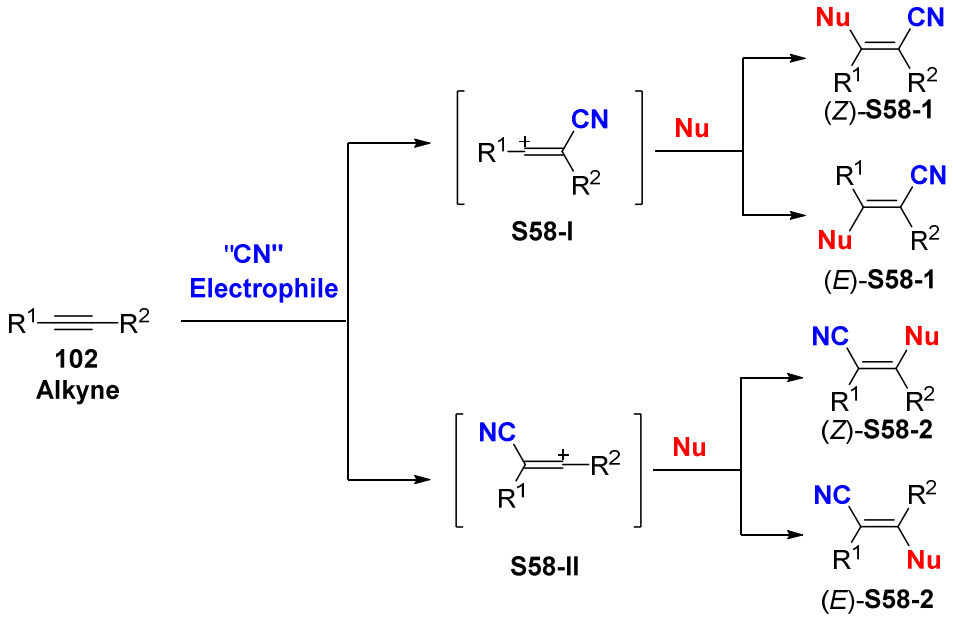
3.2. Objective.

The general objective of my dissertation is the development of metal-free methodologies for electrophilic cyanations of substrates with low nucleophilic character under mild conditions. More specific, developing an efficient methodology for performing electrophilic cyanations of alkynes, which will be attempted by using the novel imidazolium thiocyanate systems discussed in Section 2.[103] Hence. the main goal of my thesis is to study the chemical behavior of these imidazolium thiocyanate-based reagents from the viewpoint of efficient and selective electrophilic cyanations of alkynes.

3.3. Results and discussion.

3.3.1. Reaction design.

A general strategy for developing an efficient protocol of electrophilic cyanation of alkynes relies upon the initial generation of vinyl cation intermediates (**S58-I** or **S58-II**), which should be trapped with a specific nucleophile (**Scheme 58**). As a result of the substitution pattern of the alkyne **102** and the type of attack of the cyanating reagent, these transformations can produce four different diastereomers as main products: two pairs of regioisomers which differ on the direction of the initial electrophilic attack, and each consisting of a (*E*)- and (*Z*)-configurated stereoisomers, which depend on the favoured selectivity of the nucleophilic attack.



Scheme 58. Electrophilic additions to alkynes **102**.

Designing a process which favors the formation of only one product requires a careful analysis of each participant of the reaction —**Alkyne**, **Electrophile** and **Nucleophile** — and rigorous control of the reaction conditions:

Alkynes are by definition unsaturated hydrocarbons with a triple carbon-carbon bond.[106] As both carbon atoms possess similar electron density and hence reactivity, they need to be first differentiated in order to promote a proper regioselective cyanation. Desirable polarization of the triple bond can be accomplished by a reasonable selection of the substituents on this π-system, which can stabilize predominantly only one of the two possible carbocations **S58-I** or **S58-II**.[107] Thus, electron-rich groups directly linked to one

of the carbons polarize the triple bond making one of the carbons to exhibit an increased nucleophilicity as compared to the other one. One accessible alkyne, that fulfils all the above criteria is 1-methoxy-4-(phenylethynyl)benzene (**102a**), which was chosen as model substrate (**Figure 11**).[108]

Electrophile: In line with the subject of this study – extending the scope for the electrophilic cyanations using imidazolium thiocyanates – and based on the excellent results discussed above, reagent **109b** was employed (**Figure 11**).

Nucleophile: The most efficient and atom-economical approach would be the case if the nucleophile is actually the counterion in thiocyanate; therefore bromide anion in **109b** was initially tested as plausible nucleophilic source. (**Figure 11**).

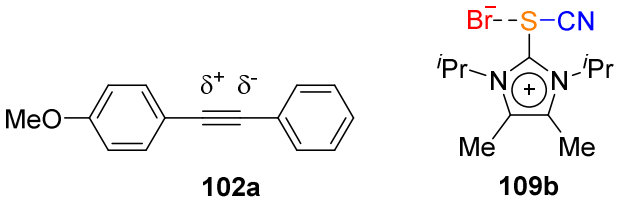
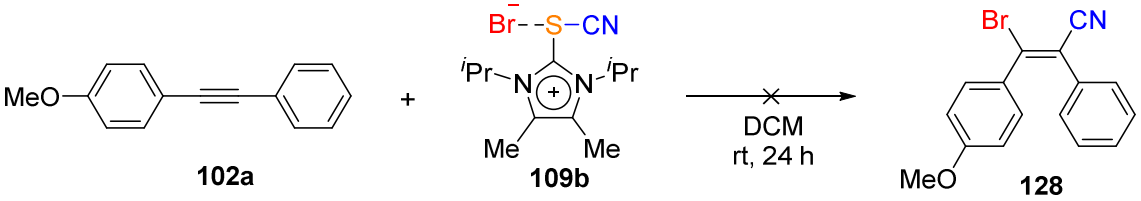


Figure 11. Selected alkyne, electrophile and nucleophile.

3.3.2. Searching for appropriate reaction participants.

With compounds **102a** and **109b** in hand, we started the investigation towards a regioselective bromocyanation of internal alkyne **102a**. In the first attempt, a solution of **102a** and **109b** (one equivalent each) in DCM was stirred at room temperature for 24 hours. Unfortunately, no conversion of **102a** was detected, and starting materials were recovered (**Scheme 59**).

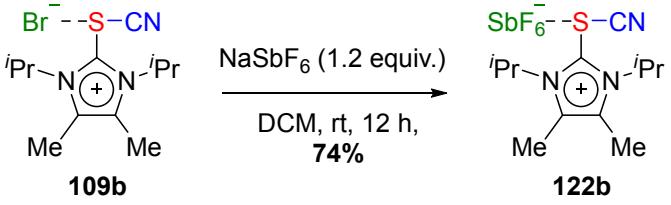


Scheme 59. Attempted bromocyanation of alkyne **102a** with **109b**.

This result can be rationalized based on two arguments. First, generally alkynes are known as compounds with moderate nucleophilicity and may not be reactive enough under the selected conditions. Secondly, the nitrile group is probably not electrophilic

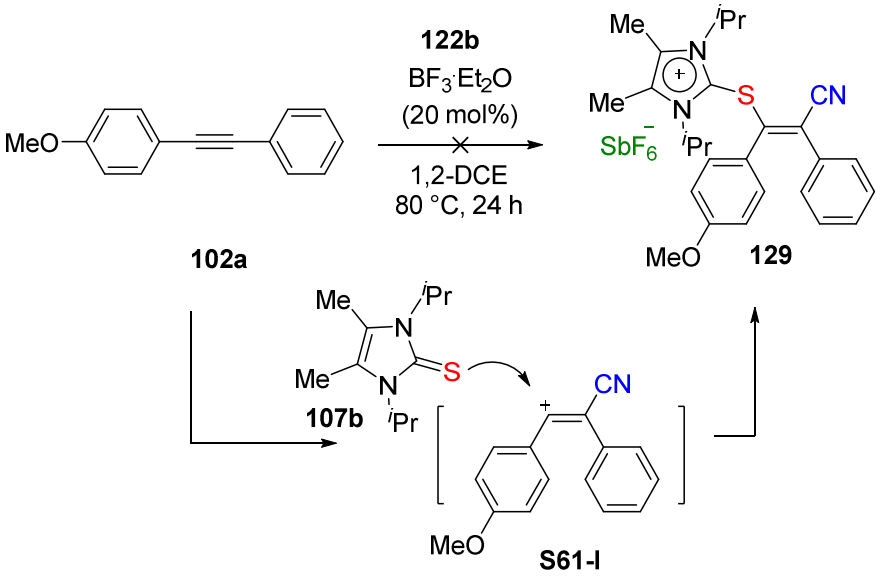
enough in the system. To enhance the electrophilicity of nitrile groups in similar situations, the employment of Lewis acids as activators has been investigated in great details. Lewis acids have the property of coordinating to the nitrogen center, thus enhancing electrophilicity of the carbon center.[77,109]

It is noteworthy that another problem may arise when salt **109b** is combined with a Lewis acid, as the formation of the corresponding adduct between the bromide anion and the added Lewis acid might occur. Thus, a non-coordinating hexafluoroantimonate counterion was included in the structure by performing a counterion exchange (**Scheme 60**).



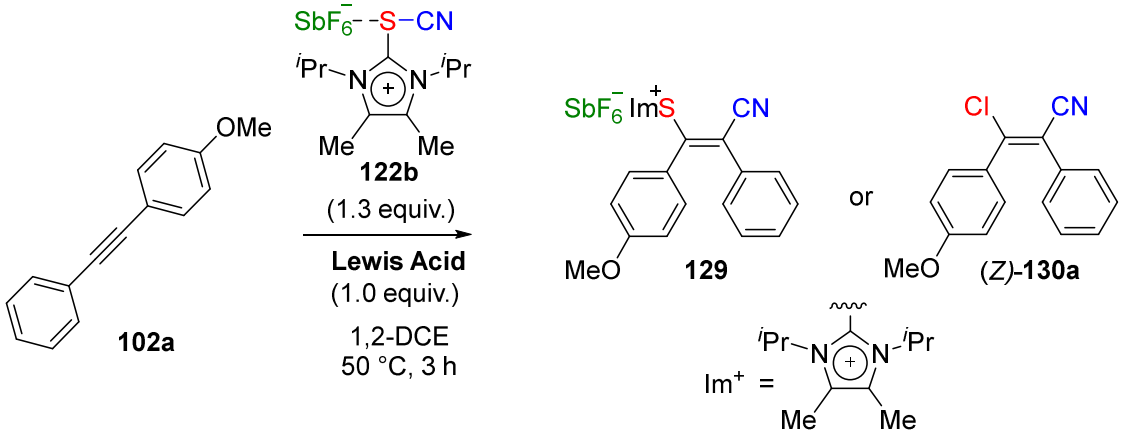
Scheme 60. Counterion exchange.

As **122b** is no source of bromide nucleophiles as was **109b**, we rationalized the following idea: if we assume that a cyanation is successfully performed, a carbocation intermediate like **S61-I** is generated forming a **107b** as main by-product, which indeed possesses a certain nucleophilic character and will quench **S61-I**. Unfortunately, no reactivity was observed again, and the starting materials were recovered (**Scheme 61**).



Scheme 61. Attempted thiocyanation of **102a** with **122b**.

In our previously reported cyanations with **122b**,[103] $BF_3{\cdot}Et_2O$ as a Lewis acid successively promoted the cyanation of electron-rich aryl or heteroaryl molecules. But for this new system it proved to be not acidic enough. As a consequence, different Lewis acids with stonger acidity than of $BF_3{\cdot}Et_2O$ were screened in the model reaction (**Scheme 55**). The results are summarized in **Table 1**.



Entry	Lewis acid	Isolated yield	*Z*/*E* ratio
1	$BF_3{\cdot}Et_2O$	n.r.	n.a.
2	$FeCl_3$	n.r.	n.a.
3	$AlCl_3$	n.r.	n.a.
4	TMSTfO	n.r.	n.a.
5	AgTfO	n.r.	n.a.
6	$B(C_6F_5)_3$	**90%** of **129**	**9/1**
7	$TiCl_4$	**14%** of (*Z*)-**130a**	**Only (*Z*)**

Table 1. Screening of Lewis acids.

$FeCl_3$ and $AlCl_3$ did not promote the transformation, and starting materials were recovered (**Table 1, entries 2** and **3**). Me_3Si^+ and Ag^+ cations also do not promote the product formation (**Table 1, entries 4** and **5**). Interestingly, when another boron-based Lewis acid, but of a higher Lewis acidity was employed, such as in $B(C_6F_5)_3$, the expected product **129** was formed and isolated in an excellent 90% yield as a 9/1 mixture of (*Z*)- and (*E*)-stereoisomers (**Table 1, entry 6**). This confirms our preliminary postulates. Even more interesting results were obtained when $TiCl_4$ was selected as a Lewis acid. In this case, small amounts of the corresponding chlorocyanated product **130a** were indeed formed and isolated. In this situation, the chlorine atoms embedded in the Lewis acid behave as

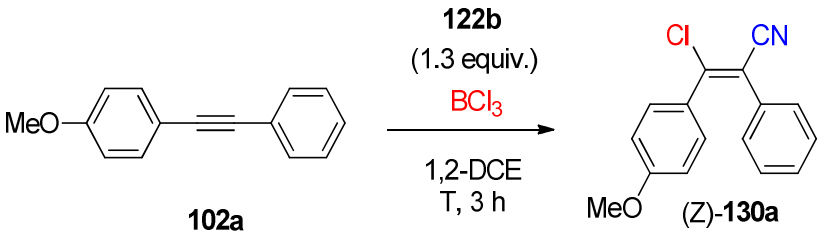
suitable nucleophiles under this reaction conditions. Even more fascinating is the fact that almost total regio- and high stereoselectivity in the formation of **130a** was accomplished (**Table 1, entry 7**).

3.3.3. Chlorocyanation of alkynes.

On the contrary to compound **129**, product **130** contains now a versatile chloro substituent that allows the possibility of further derivatizing **130** into more complex architectures. Accounting that, and due to the remarkable regio- and stereoselectivity of the transformation, we decided to focus our attention on the optimization of chlorocyanation of alkynes.

3.3.3.1. Optimization.

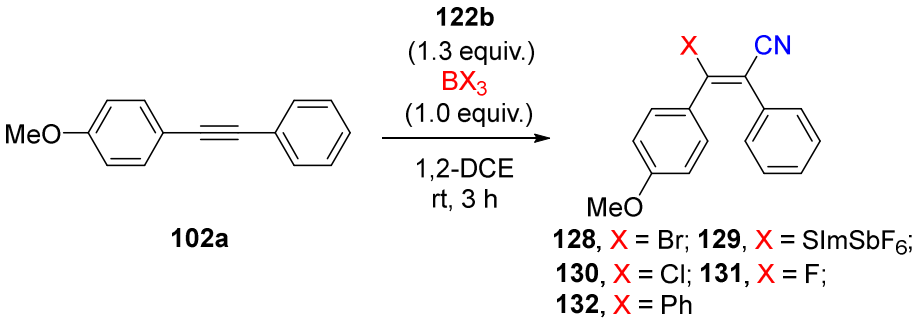
In accordance with the tendency of reactivity summarized in **Table 1**, it can be concluded that the presence of a boron-based Lewis acid is advantageous for the transformation and that the chloride ion should be an integral part of the Lewis acid structure. With these results and combining both ideas, we could speculate that BCl_3 would promote even more efficiently the desired transformation, with the additional advantage that it has a higher Lewis acidity than $B(C_6F_5)_3$. Following this rational, BCl_3 was tested under the reaction conditions described above. Indeed, the formation of the expected product (*Z*)-**130a** in a satisfactory 37% isolated yield, again with total regio- and stereoselectivity, was observed (**Table 2, entry 1**). Lowering the reaction temperature to ambient one and the employment of BCl_3 in excess resulted in the best conditions. The reaction time could also be reduced to one hour (**Table 2, entries 2**–**4**). The optimized conditions are indicated in **Table 2**, **entry 4**.



Entry	BCl_3 (equiv.)	T (°C)	Isolated yield (%)
1	1.0	50	**37**
2	1.5	rt	**65**
3	2.0	rt	**97**
4	**2.0**	**rt (1 h)**	**98**

Table 2. Optimization of reaction conditions.

The scope of this new transformation was next investigated. We were intrigued about whether the reaction was only limited to chlorocyanations with BCl_3, or could also be extended to other halocyanations (with BBr_3 and BF_3) or arylcyanations (with BAr_3) (**Table 3**). Thus, commercially available boranes were then tested in the transformation. In the case of $BF_3{\cdot}Et_2O$, no fluorocyanation product **131** was detected (**Table 3**, **entry 1**). Triphenylborane exhibited no reactivity as well (**Table 3**, **entry 2**). When BBr_3 was employed, the corresponding bromocyanation product **128** was obtained in only 9% isolated yield (**Table 3**, **entry 3**). Only traces of chlorocyanated product were detected when $BPhCl_2$ was employed as a Lewis acid (**Table 3**, **entry 4**).



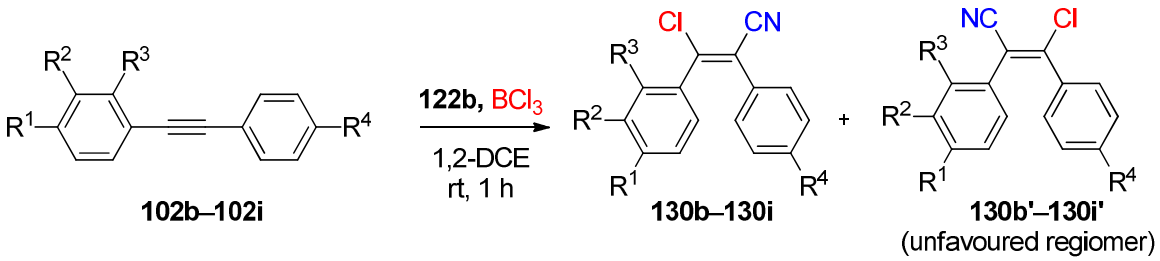
Entry	Lewis acid	Expected products	Isolated yield
1	BF_3-Et_2O	**129, 131**	**n.r.**
2	BPh_3	**129, 132**	**n.r.**
3	BBr_3	**128, 129**	**9%** of **128**
4	$BPhCl_2$	**129, 130, 132**	traces of **130**

Table 3. Boranes screening.

Once BCl_3 was identified as the most appropriate borane, we decided to focus our efforts on expanding the scope of the product and examining the limitations of the chlorocyanation methodology.

3.3.3.2. Scope and limitations.

Regioselectivity of the method. Due to the remarkable regioselectivity observed for the substrate **102a** in the course of optimization, we started our studies to enhance the reaction scope employing bisarylalkynes **102** bearing substituents with various electronic demands. These substrates **102b–102i** were synthesized following reported procedures[108,110–114] and used for the chlorocyanations under optimized conditions.The results are summarized in **Table 4**.



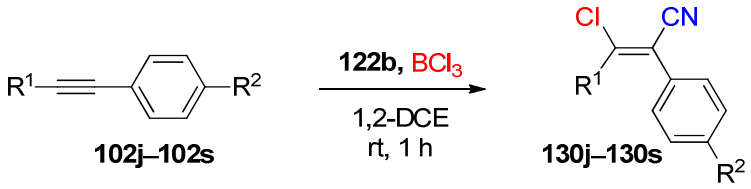
Entry	Alkyne	R^1	R^2	R^3	R^4	**130b-i/130b'-i'** ratio	Isolated yield (%)
1	**102b**	Me	H	H	H	**9/1**	**50**
2	**102c**	H	H	H	H	**n.a.**	**22**
3	**102d**	Me	H	H	Et	**1/1**	**68**
4	**102e**	Me	H	H	OMe	**96/4**	**81**
5	**102f**	H	OMe	H	H	**n.a.**	**n.a.**
6	**102g**	H	H	OMe	H	**98/2**	**93**
7	**102h**	Cl	H	H	H	traces of **130h'**	**n.a.**
8	**102i**	H	H	Br	H	**n.a.**	**n.a.**

Table 4. Scope for the chlorocyanation of **102b–i**.

In the case of **102b**, that depicts a reduced polarizability in comparison to **102a** (due to the

lower inductive effect that the methyl group creates in comparison with a methoxy group), it was reflected a lower nucleophilicity of the starting material, and as a consequence it was considerably reduced the conversion to the desired product **130b**, which could be isolated in moderate 50% yield. As a direct consequence of this low polarizability, a regiomeric ratio of 9:1 (*Z*)-**130b** *versus* (*Z*)-**130b'** was observed, and again the method showed an excellent stereoselectivity towards the formation of the *Z* isomers (**Table 4**, **entry 1**). Continuing the scope studies, a symmetric substrate without any polarizing substituent in the aromatic ring such tolane (**102c**) was tested in the reaction, where the corresponding chloroacrylate (*Z*)-**130c** could be formed again in a stereoselective manner, but in a modest yield of only 22% (**Table 4**, **entry 2**). On the contrary, alkyne **102d** also with a low polarized triple bond (but with a higher nucleophilicity derived from the alkyl substituents) underwent more readily the derived transformation, increasing the yield up to 68%. On the other hand, both products (*Z*)-**130d** and (*Z*)-**130d'** were isolated as an almost 1/1 regiomeric mixture as could be expected as methyl and ethyl groups are basically identicals regarding inductive effects. The stereoselectivity still remained excellent (**Table 4**, **entry 3**). Substrate **102e** was prepared for a direct comparison of the effect of including a methoxy and a methyl group in the *para* position, which can be directly evaluated by observation of the regioselectivity, as each substituent is responsible for the formation of a different regioisomer product (**130e** from methoxy and **130e'** from methyl). In this case, after performing the reaction, we observed a regioselectivity ratio of 96/4 in favour of the product that was consequence of including a methoxy substituent **130e**, and this compound was isolated with a very good yield (81%) and an excellent stereoselectivity (**Table 4**, **entry 4**). As might be expected, an electron-donating group in the *meta* position (R^2) of the phenyl group, as in **102f**, behaved as a deactivating substituent lowering the nucleophilicity of the triple bond and completely suppressing the reactivity (**Table 4**, **entry 5**). On the contrary, for *ortho* methoxy-substituted (R^3) alkyne **102g**, the group acts again as an activating substituent, favouring the formation of the desired product **130g**, which could be isolated in excellent yield (92%), with very high regioselectivity (98/2 ratio) and excellent stereoselectivity towards the *Z* isomer (**Table 4**, **entry 6**). Intrigued about if we could polarize the triple bond only with electron-withdrawing groups in the *para* (R^1) or in the *ortho* (R^3) positions, compounds **102h** and **102i** were prepared, but unfortunately it resulted in only some traces formation of **130h'** and no conversion of **102i** (**Table 4, entries 7–8**).

Analyzing the information discussed above, one can conclude that the methodology seems to be applicable to internal bisarylalkynes, in which at least one of the aryl groups must contain an electron-donating group either in the *ortho* or *para* position. To test this thesis, differently decorated internal alkynes **102** bearing various sterically- and electronically-demanding groups[92,93] were employed in the reaction (**Table 5**).



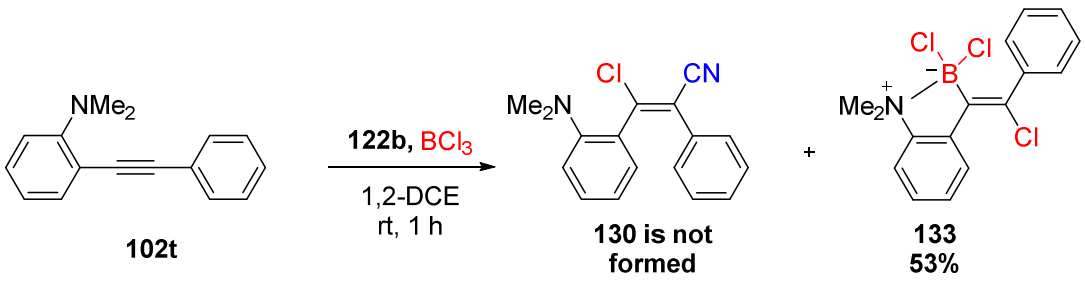
Entry	Alkyne	R^1	R^2	T (°C)	t (h)	Isolated yield (%)	*Z/E* ratio
1	**102j**	*p*-anisolyl	F	rt	1	**77**	**99/1**
2	**102k**	*p*-anisolyl	Cl	rt	1	**98**	**98/2**
3	**102l**	*p*-anisolyl	Br	rt	1	**78**	**98/2**
4	**102m**	*p*-anisolyl	I	rt	1	**67**	**93/7**
5	**102n**	*p*-anisolyl	NO_2	60	3	**44**	**96/4**
6	**102o**	*p*-anisolyl	CO_2Et	60	3	**37**	**95/5**
7	**102p**	*p*-anisolyl	CHO	60	3	**n.a.**	**n.a.**
8	**102q**	1-naphthyl	H	rt	1	**23**	*only* ***Z***
9	**102r**	2-(1,3)-benzodioxolyl	H	60	3	**n.a.**	**n.a.**
10	**102s**	*p*-anilinyl	H	60	3	**n.a.**	**n.a.**

Table 5. Scope for the chlorocyanation of **102j–s**.

Halogen-substituted methoxytolanes **102j–102m** reacted in all the cases with total regioselectivities producing (*Z*)-**130j**–(*Z*)-**130m** in very good to excellent yields. However, in each case the products were contaminated with small quantities of (*E*)-**130j**–(*E*)-**130m** stereomers (**Table 5**, **entries 1–4**). Methoxytolanes **102n** and **102o**, both decorated with electron-withdrawing groups, were converted into the corresponding chlorocyanated products (*Z*)-**130n** and (*Z*)-**130o** employing elevated temperature (60 °C, 3 h) and only in moderate yields. Both reactions are characterized by complete regioselectivity and high stereoselectivity, furnishing again the *Z*-stereomer in a remarkable excess *versus* the *E*

competitor (**Table 5**, **entries 5–6**). No conversion of formyl-substituted methoxytolane **102p** was observe mainly to two different reasons; one is that the aldehyde acts as a deactivating substituent due to its inductive effect, and second one is that the borane might have been inactivated by coordination to the carbonyl group of the aldehyde. In any case the starting material could be recovered (**Table 5**, **entry 7**). An attempt using a 1-naphthyl group as a potential electron-rich aryl group in alkyne **102q** was not successful: the reactivity decreased because of the low nucleophilicity of the triple bond in **102q**. Compound **130q** was formed stereospecifically, however, isolated in a moderate (23%) (**Table 5**, **entry 8**). Surprisingly, electron-rich alkynes **102r** and **102s** did not undergo chlorocyanation (**Table 5**, **entries 9** and **10**). In the latter case this can result from the deactivation of the boron center upon forming an adduct with the primary amine group, whereas the reasons of a failure in the former one can only be speculated about.

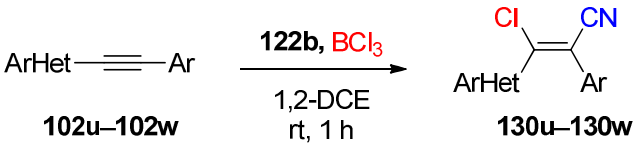
An unexpected reactivity was evidenced, when alkyne **102t** was used under the above indicated conditions. Instead of forming the corresponding chloroacrylonitrile **130t**, the chloroborylated product **133** was obtained in 53% yield. This compound was recently obtained and investigated using X-ray crystallography by Ingleson and co-workers, who used exactly the same conditions but without cyanating reagent **122b**.[115] Formation of this product could be rationalized in the way that BCl_3 preferentially coordinates to the tertiary amine center, subsequently reacting with the alkyne bond and afording the unusual chloroborylated product **133** as a zwitterionic specie (**Scheme 62**).



Scheme 62. Attempted chlorocyanation of alkyne **102t**.

The scope of the chlorocyanation was further investigated with heteroaryl-substituted alkynes **102u–102w**, which were synthesized applying the published protocols.[108,110–114] The results are summarized in **Table 6**. Thus, thiophene-substituted alkyne **102u** was successfully transformed into product (*Z*)-**130u** with total regio- and stereoselectivity in

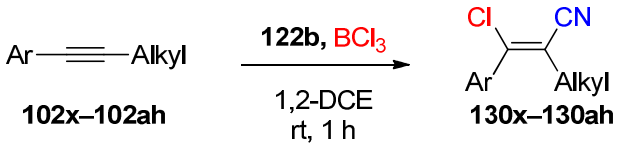
56% isolated yield (**Table 6**, **entry 1**). In contrast to this, no reaction occured with a donor-acceptor-substituted alkyne **102v**, probably due to basicity of a nitrogen atom in the substrate (**Table 6**, **entry 2**). Notable is the formation of indolyl-substituted product (*Z*)-**130w**, as with in this type of substrate the cyanation of the pyrrole subunit could be favoured (**Table 6**, **entry 3**).



Entry	Alkyne	HetAr	Ar	Isolated yield (%)
1	**102u**	2-thiophenyl	Ph	**56**
2	**102v**	*p*-pyridyl	*p*-anisolyl	**n.a.**
3	**102w**	2-(*N*Me)-indolyl	Ph	**15**

Table 6. Scope for the chlorocyanation of **102u**–**w**.

Subsequently, next studies were focused on the usage of internal alkynes containing alkyl groups as one of the substituents. As postulated above for this reaction, one of the carbons in a triple bond will be transformed into a carbocationic center, which needs to be stabilized by a neighboring electron-rich aromatic substituent. Due to the inability to perform such stabilization with aliphatic substituents, it is expected that only one of the two possible regiomers should be formed in all these transformations.[107] Hence, a wide variety of different alkylarylalkynes **102x**–**102ah** was further tested (**Table 7**).

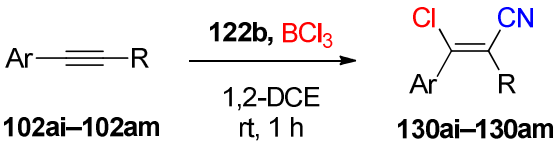


Entry	Alkyne	Ar	Alkyl	Isolated yield (%)	*Z/E* ratio
1	**102x**	Ph	Et	**64**	*only* ***Z***
2	**102y**	Ph	Pr	**71**	*only* ***Z***
3	**102z**	Ph	Bn	**63**	*only* ***Z***
4	**102aa**	Ph	Cyclohexyl	**80**	*only* ***Z***
5	**102ab**	Ph	Cyclopentyl	**76**	*only* ***Z***
6	**102ac**	*p*-(TMS)-C_6H_4	Bu	**57**	*only* ***Z***
7	**102ad**	Ph	3-(Cl)-C_3H_6	**62**	*only* ***Z***
8	**102ae**	Ph	4-(THPO)-C_4H_8	**n.a.**	**n.a.**
9	**102af**	Ph	2-(PMBO)-C_3H_6	**n.a.**	**n.a.**
10	**102ag**	2-thiophenyl	Cyclohexyl	**82**	*only* ***Z***
11	**102ah**	2-(*N*Me)-indolyl	Bu	**7**	*only* ***Z***

Table 7. Scope for the chlorocyanation of arylalkylalkynes **102x**–**ah**.

As anticipated, internal alkynes **102x** and **102y** with linear chains afforded the corresponding products (*Z*)-**130x** and (*Z*)-**130y** in 64 and 71% yield, respectively, with the expected complete regioselectivity and stereoselectivity in favor of (*Z*)-isomers (**Table 7, entries 1** and **2**). Benzyl (**102z**), cyclohexyl (**102 aa**) and cyclopentyl (**102ab**) substituents as well as silyl groups (**102ac**) or halogenated aliphatic chains (**102ad**) tolerated the chlorocyanation reaction, and successfully furnishing acrylonitriles (*Z*)-**130z**, (*Z*)-**130aa**, (*Z*)-**130ab**, (*Z*)-**130ac** and (*Z*)-**130ad**, respectively, again with a total regio- and stereoselectivity (**Table 7, entries 3**–7). Contrary to this, protected alcohols **102ae** and **102af** did not form the corresponding acrylonitriles. Only deprotection of substrate was observed under these conditions (**Table 7, entries 8** and **9**). Excellent conversion was observed for alkyne **102ag**, decorated with a thiophene group in combination with a cyclohexyl one. Once again, the reaction resulted in a total regio- and stereoselective formation of **130ag** (82% yield, **Table 7**, **entry 10**). Similar to **102w**, alkyne **102ah** with an indole moiety entered the transformation, however, affording **130ah** in very poor yield (Table 7, **entry 11**).

After an exhaustive study of the scope of internal alkynes, we further explored the reactivity of commercially available terminal alkynes **102ai**–**102am** (**Table 8**).



102ai–102am **130ai–130am**

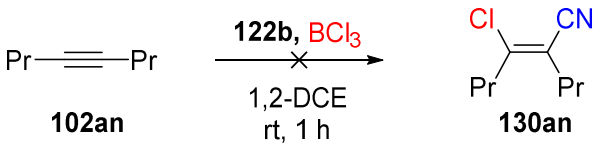
Entry	Alkyne	Ar	R	Isolated yield (%)	*Z/E* ratio
1	**102ai**	Ph	H	**58**	***Z***
2	**102aj**	*p*-anisolyl	H	**n.a.**	**n.a.**
3	**102ak**	*p*-tolyl	H	**21**	***Z***
4	**102al**	*p*-(Cl)-C_6H_4	H	**47**	***Z***
5	**102am**	Ph	TMS	**n.a.**	**n.a.**

Table 8. Scope for the chlorocyanation of terminal alkynes **102ai–am**.

As a carbocation on the terminal carbon cannot be stabilized, a regioselective transformation could also be expected in this case. Indeed, terminal alkyne **102ai** was efficiently converted to acrylonitrile (*Z*)-**130ai** in a stereoselective fashion in good yield (**Table 8, entry 1**). It should be emphasized that a complete conversion of the starting material **102ai** occurred and no by-products was formed in this case, although yields were not spectacular. Presumably, the Lewis acid promoted partial polymerization of the starting material. This assumption was further confirmed by testing electron-rich alkyne **102aj**, which led to a fast decomposition of starting material (**Table 8, entry 2**). Chlorocyanation of *para*-tolyl analogue **102ak** resulted in a single product formation along with decomposition of the starting material (**Table 8, entry 3**). Electron-deficient aromatic rings in alkyne **102al** could increase the yield to a moderate value of 47% (**Table 8, entry 4**). In addition, TMS-protected alkyne **102am** afforded product **130am**, but as a component of a complex non-separable mixture (**Table 8**, **entry 5**). Despite the low to moderate yields, the results discussed in this paragraph still constitute a remarkable total regio- and stereoselective transformations of inexpensive and commercially available starting materials.

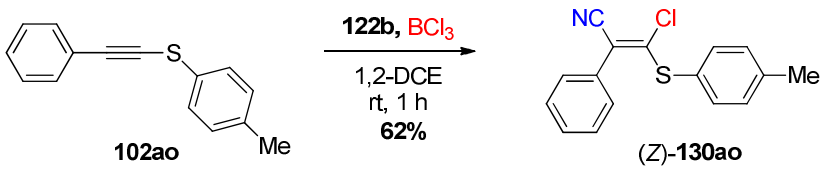
As aliphatic substituents on a triple bond cannot stabilize the carbocation proposed as intermediate on route to the derived products, dialkylalkynes were expected to be inert

towards chlorocyanation. Indeed, no conversion of commercially available 1,2-di-*n*-propylalkyne (**102an**) was detected under the optimized conditions. (**Scheme 63**).



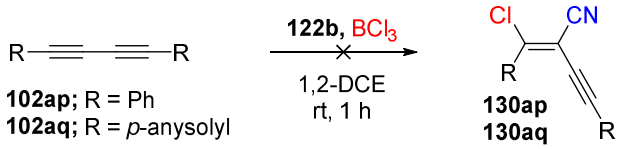
Scheme 63. Chlorocyanation of **102an**.

Alternatively, the intermediate carbocation could probably be stabilized by a neighboring heteroatom. To test this, compound **102ao** was synthesized according to the protocol developed in our laboratories[116] and subjected to chlorocyanation. Product (*Z*)-**130ao** was formed successfully, with a complete regio- and stereoselectivity, thus indicating the efficient stabilization of the carbocation with the sulfur atom (**Scheme 64**).



Scheme 64. Chlorocyanation of alkyne **102ao**.

Readily available 1,3-diynes **102**[117] represent another group of potentially suitable substrates to expand the scope of the chlorocyanation method developed. However, when **102ap** and **102aq** were subjected to the general cyanation conditions, both demonstrated lack of reactivity towards the desired product (**Scheme 65**).



Scheme 65. Attempted chlorocyanation of 1,3-diynes **102ap** and **102 aq**.

3.3.3.3. Structural studies.

Stereoselectivity of the method. As underlined throughout the study of the scope of chlorocyanation, only one of the possible regioisomers was preferentially formed in most cases by the correct choice of the starting alkynes. In fact, the regioselectivity of the

transformation could have been predicted with certain confidence. The truly unexpected result was the excellent stereoselectivity, which led to the formation of stereomers with a (*Z*)-configuration. The latter was proved by several analytic methods as described below.

NMR experiments. Unfortunately, the majority of the chlorocyanated products were not described in the literature before. Therefore, we had no opportunity for the direct comparison of the NMR in most cases. Only, in a single case all four possible chlorocyanated products derived from terminal alkyne **102ai** appeared to be synthesized and completely characterized. It was then easy to assure that our product was neither any of the unexpected regiomers (*Z*)-**130ai'**[118] and (*E*)-**130ai'**[118] nor (*E*)-**130ai**,[119] but only the *Z* stereomer (*Z*)-**130ai**.[120] This result allowed us to assume that the other chloroacrylonitriles **130** would probably also exhibit a *Z* configuration.

To corroborate the structure of (*Z*)-**130ai** and to be able to extend the analysis to other substrates, the interaction between the vinylic proton and C_2 *via* an HMBC experiment was performed by the NMR department of the Institute. The value of of ^3J {C-H} coupling constant of ~ 3 Hz undoubtedly indicates a *Z* stereoisomery (**Figure 12**).[121] Due to the structural similarity, every terminal alkyne could potentially be considered as forming the corresponding (*Z*)-3-chloroacrylonitrile.

HMBC ($CDCl_3$)

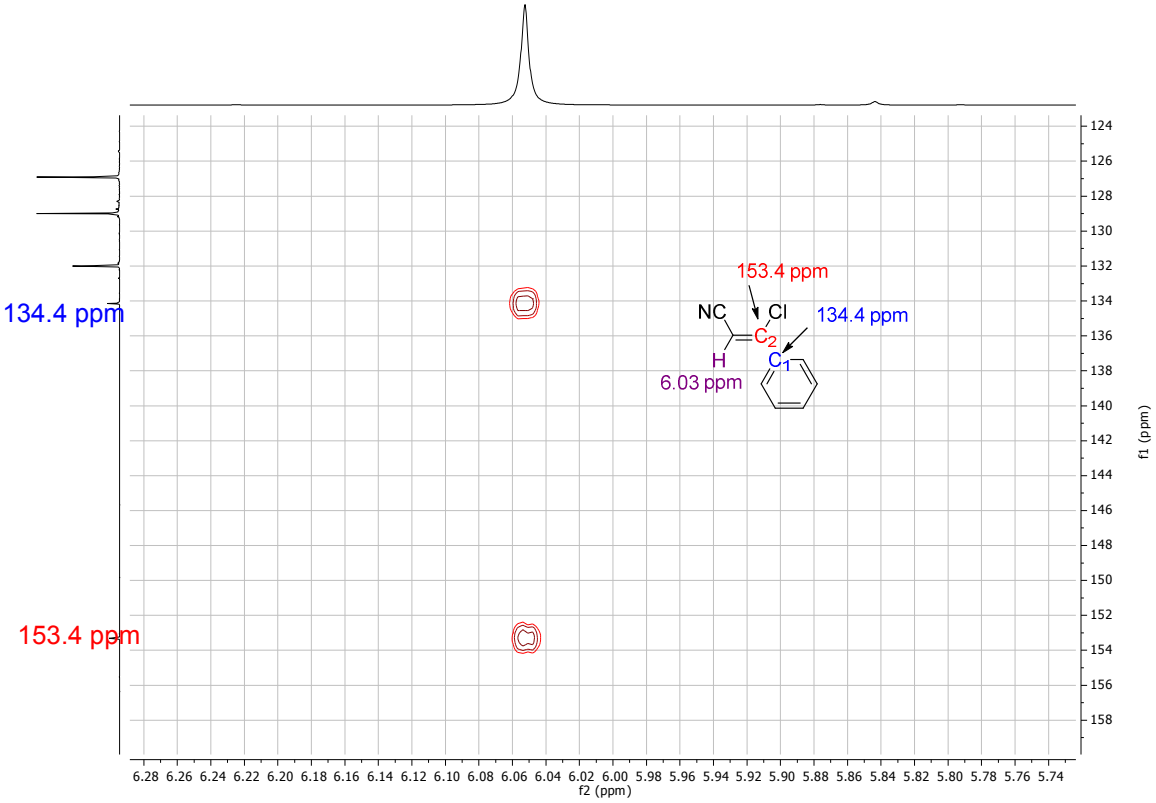


Figure 12. HMBC spectrum of **(*Z*)-130ai**.

X-Ray crystallography. Most of the products **130** were colorless solids at ambient temperature, and recrystallization of several compounds afforded suitable for X-ray diffractometry crystals. Thus, (*Z*)-configurations of compounds **130l**, **130u** and **130ao** as well as regioselectivity of their formation were confirmed in all the cases by X-ray crystal structure analysis after recrystallization from *n*-heptane (**Figure 13**).

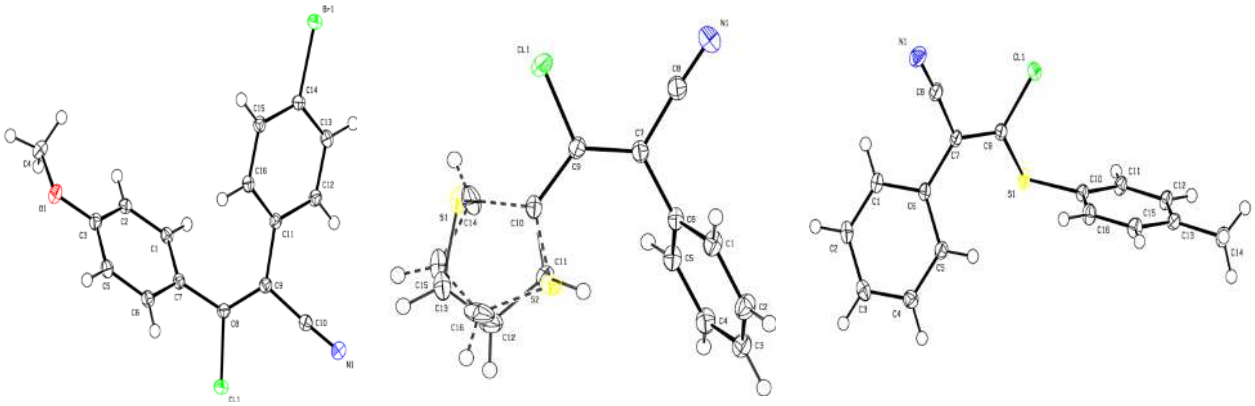


Figure 13. Structures of chloroacrylates (*Z*)-**130l**, (*Z*)-**130u** and (*Z*)-**130ao** in the crystals. Hydrogen atoms are removed for clarity.

Isomerization of chloroacrylates (*Z*)-130. A very interesting chemical behavior was detected for the compound **130m**. After the standard one hour reaction time, ^{1}H NMR spectrum of the crude reaction mixture undoubtedly indicated the formation of only the *Z* stereomer, together with a small quantity of still unreacted starting material **102m** (**Figure 14a**). Once the crude product was worked-up and isolated by column chromatography, the formation of a new product was observed. The latter was proved to be an isomer of (*Z*)-**130m** by HRMS analysis and could be no other than the corresponding stereomer (*E*)-**130m** formed by rotation of the double bond, as the formation of regiomer (*Z*)-**130m'** would involve a shift of both Cl and CN moieties which is not favoured (**Figure 14b**). NRM measurements were repited after 3 hours and showed the formation of the *E* isomer which was now majority (**Figure 14c**). Interestingly, the spectrum was then re-measured after one month, and no significant changes could be determined indicating that the equilibrium was achieved. This experiment confirms the complete stereoselectivity of the developed method, but also indicates the tendency of the products to isomerize upon standing.

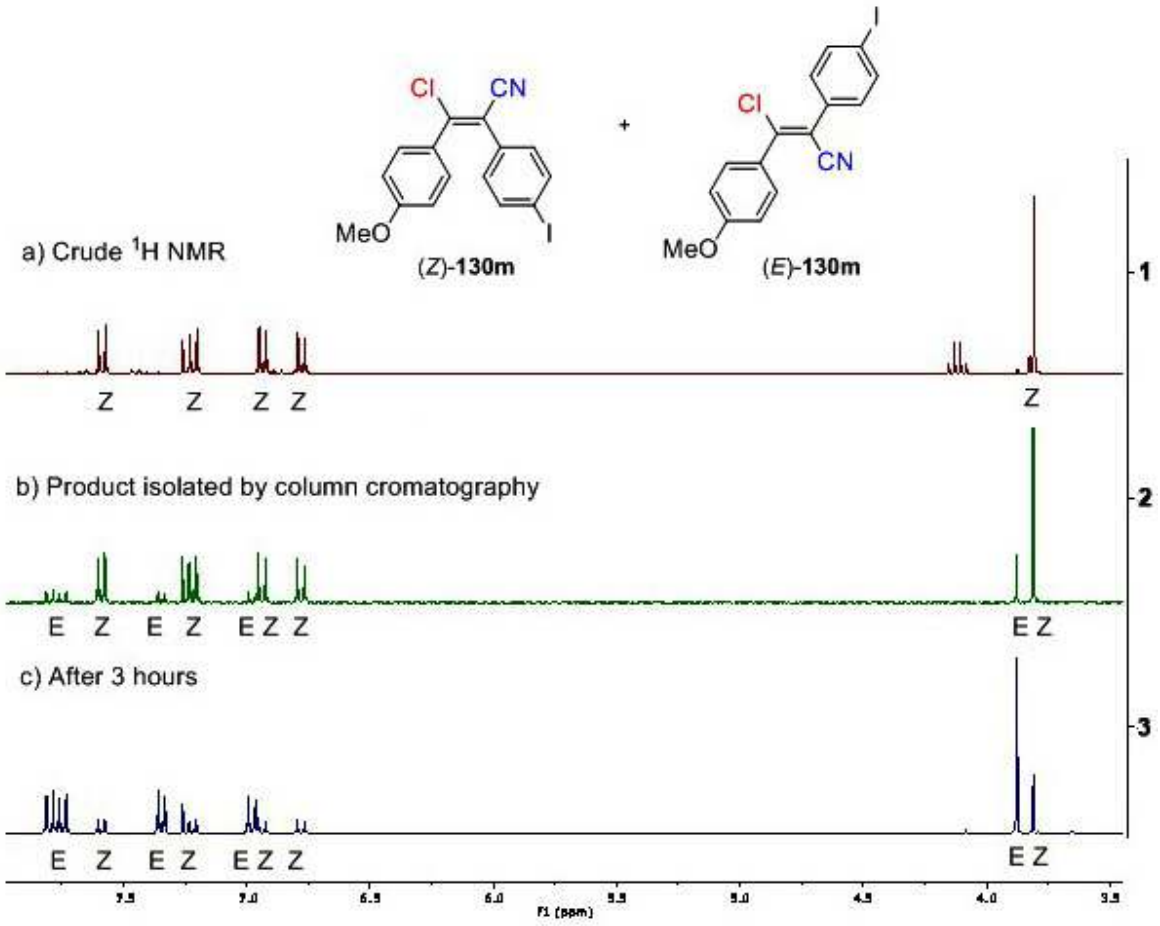


Figure 14. ^{1}H NMR spectra of **130m** after indicated time.

This phenomenon was observed for several other products. Thus, chloroacrylonitrile **130a** as reference was isolated in a pure form an identified as a single (*Z*)-isomer (**Figure 15**, compound **A**). After four weeks ^{1}H NMR measurement indicated the formation of a new isomer (**Figure 15**, compound **B**), as was observed in the case of **130m**. When the mixture of stereomers **130a** was analyzed by means of the NOESY technique, *ortho* aromatic protons of compound **B** were detected in two different areas (7.63 and 7.79 ppm), and no NOE interaction was observed between them. This identifies compound B as an (*E*)-isomer. Consequently, compound **A** should be identified as a (*Z*)-isomer.

^{1}H NMR (500 MHz, $CDCl_3$)

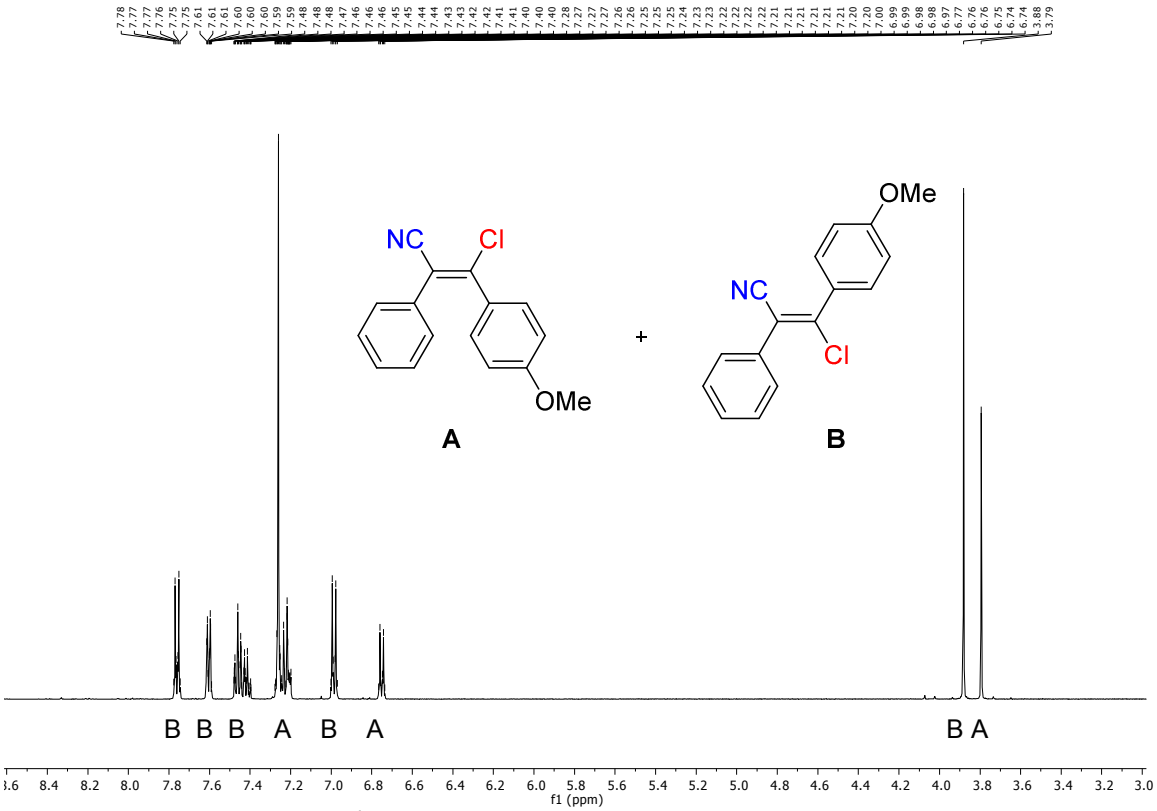


Figure 15. ^{1}H NMR spectrum for stereomeric mixture of 130a.

To investigate the origin of this isomerization, the reaction was performed using the same conditions with and without the presence of light, obtaining similar isomeric ratios in both cases thus indicating that the process was not ejected by a photochemical process, and was probably due to a thermal one. Unfortunately, thermal conditions we employed (warming the isolated products up to 60 ºC) did not provoke any sifnificant alteration in the

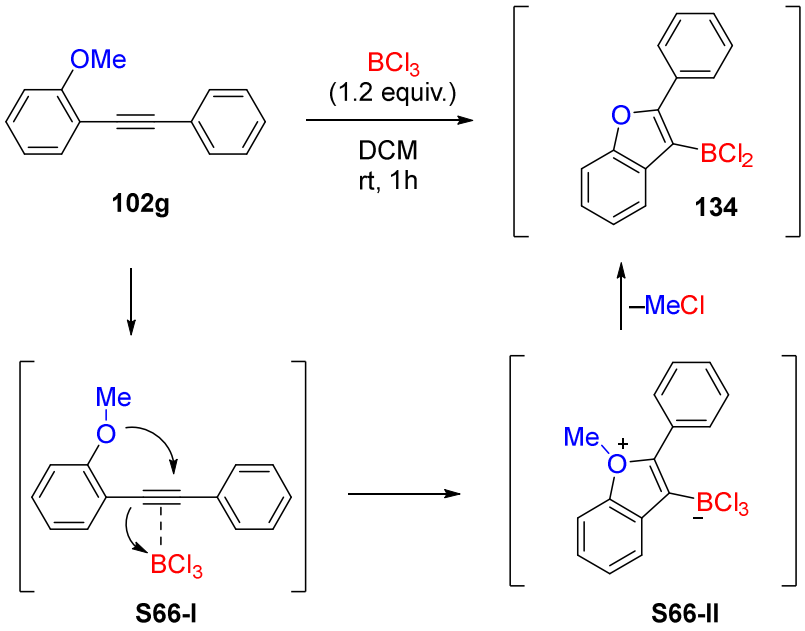
stereomer ratio.

3.3.3.4. Mechanistic studies.

For a complete understanding of the reaction mechanism and with a purpose to rationalize the possible pathways leading to such excellent stereoselectivities, various experiments were performed using internal alkyne (*Z*)-**130a** as a model substrate.

3.3.3.4.1. Borylative cyclization.

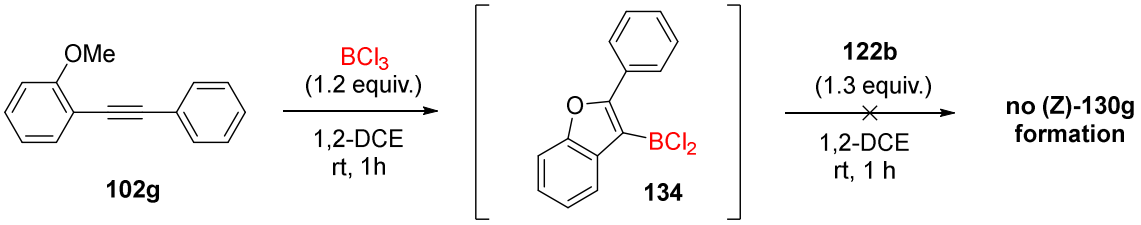
The recently reported results on borylative cyclization of compound **102g** can be helpful to enquire, whether the transformation occurred in a concerted or stepwise process. According to Ingleson and co-workers,[115] when internal alkyne **102g** is treated with one equivalent of BCl_3, the corresponding borylated benzofurane **134** is formed. Alkyne is initially activated by coordination of BCl_3 that promotes a borylative cyclization of **S66-I** by electrophilic attack of oxygen to the activated triple bond, forming zwitterionic specie **S66-II**, followed by further elimination of methylchloride (**Scheme 66**).



Scheme 66. Borylative cyclization of **102g**.

The conditions of this cyclization are almost identical to the optimized conditions used for

the chlorocyanation of alkynes **102**, with the exception of the employment of our cyanating reagent **122b**. To prove if benzofurane **134** was the precursor of the chlorocyanation product (*Z*)-**130g**, **134** was initially synthesized *in situ* as indicated above, and then it was treated with 1.3 equivalents of cyanating reagent **122b** in one portion. No formation of acrylonitrile (*Z*)-**130g** was observed in this case, thus excluding **134** as a possible intermediate (**Scheme 67**).



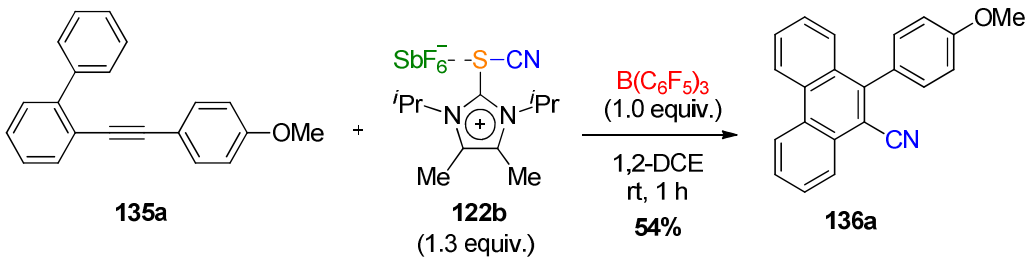
Scheme 67. Mechanistic experiment.

No reaction was observed mixing starting material **102g** with 1.3 equivalents of cyanating reagent **122b** in the absence of BCl_3.

3.3.3.4.2. Cycloisomerization.

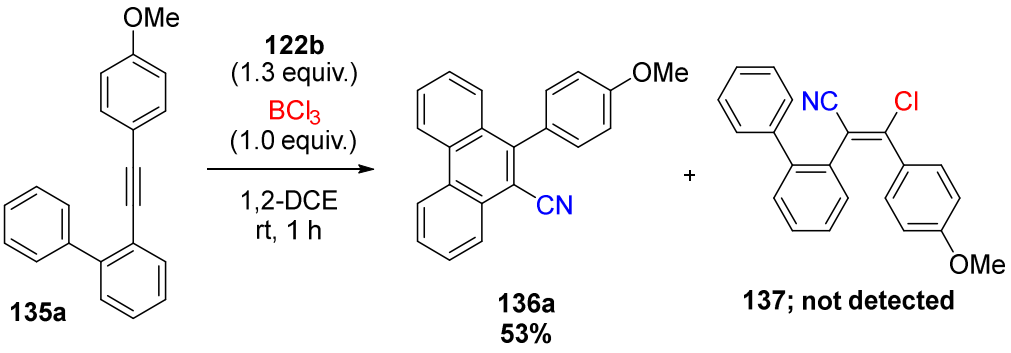
Another plausible mechanism for this process might be the *in situ* generation of cyanogen chloride (**39**) in stoichiometric amounts from BCl_3 and **122b**. Focusing the attention on the above discussed formation of **129**, it is observed that the cyanation also occurs when there are no chlorides present in the media. This excludes ClCN as cyanating reagent, and indicates that the alkyne is firstly cyanated, generating a carbocationic intermediate, which is further quenched by a selected nucleophile (such is the chloride in the chlorocyanation)

Employing substrates such **135a**, which include an extra phenyl ring, would result in a cyanative cyclization where the actual nucleophile is the new incorporated phenyl ring, when $B(C_6F_5)_3$ is employed. This idea was tested and, as a result, cyanated phenanthrene **136a** was obtained as the major product in a moderate isolated yield of 54% (**Scheme 68**).



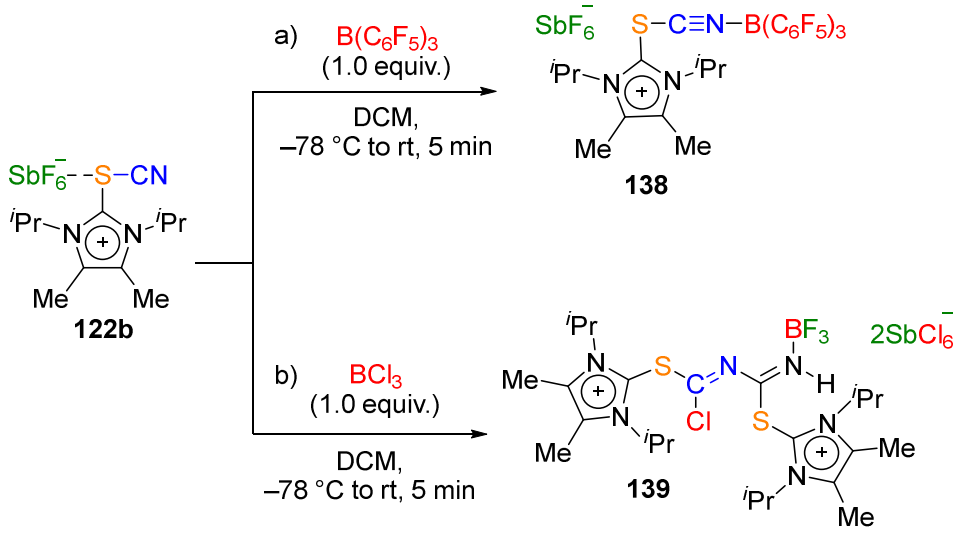
Scheme 68. Cyanative cyclization of **135a** with $B(C_6F_5)_3$.

Suprisingly, also employing BCl_3 produced only cyanated phenanthrene **136a** without any traces of the corresponding chlorocyanation product **137** (**Scheme 69**).



Scheme 69. Cyanative cyclization of **135a** with BCl_3.

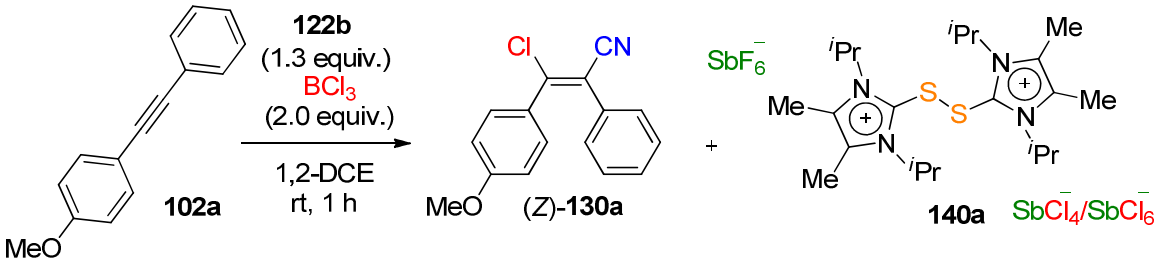
From these cyclization reactions it could be concluded, that (a) boranes activate the cyano group instead of the alkyne bond and (b) the cyanation occurs initially, forming a stabilized carbocation that is next trapped by a nucleophilic source. To obtain a tangible proof that the nitrile group interacts with the borane, two experiments were carried out. Cyanating reagent **122b** was reacted with one equivalent of $B(C_6F_5)_3$ (**Scheme 70a**) and separately with one equivalent of BCl_3 under otherwise identical conditions (**Scheme 70b**). After 5 minutes the resulting crude products were recrystallized. In the case of $B(C_6F_5)_3$, the formation of Lewis adduct **138** was confirmed by X-Ray crystal structure analysis. On the other hand, formation of a non-specific by-product **139** was observed with BCl_3, thus indicating the mechanistic complexity of this cyanation reaction.[122]



Scheme 70. Reactivity of **122b** towards BCl_3 and $B(C_6F_5)_3$. Formation of products **138** and **139**.

3.3.3.4.3. By-products isolation from reaction mixtures.

Gas evolution directly after addition of BCl_3 and formation of a big amount of almost insoluble orange solid were observed in each chlorocyanation experiment on larger scale. With the perspective of isolating the possible by-products, this solid was isolated and recrystallized under an inert atmosphere. The X-Ray crystal structure analysis disclosed an interesting bis(imidazolium)disulfide structure **140a** (**Scheme 71** and **Figure 16**) with a complex mixture of counterions. Hexafluoroantimonate and tetrachloroantimonate are observed in the X-ray-determined structure, and additional hexachloroantimonate in the HRMS analysis. This fact implies that an F^-/Cl^- exchange is taking place, presumably between BCl_3 and SbF_6^- species. It should be noted that the cyanation reagent **122b**, was completely converted to disulfide **140a**.



Scheme 71. Formation of the salt **140a** as a by-product.

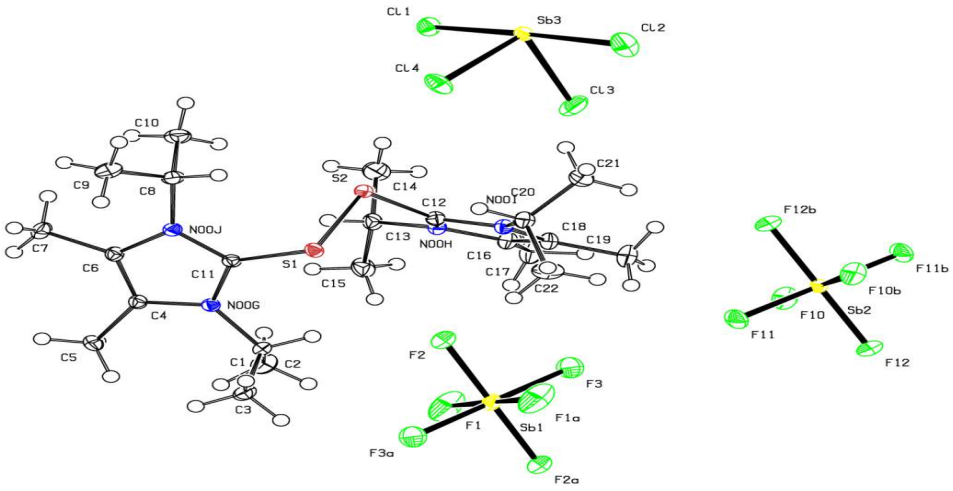
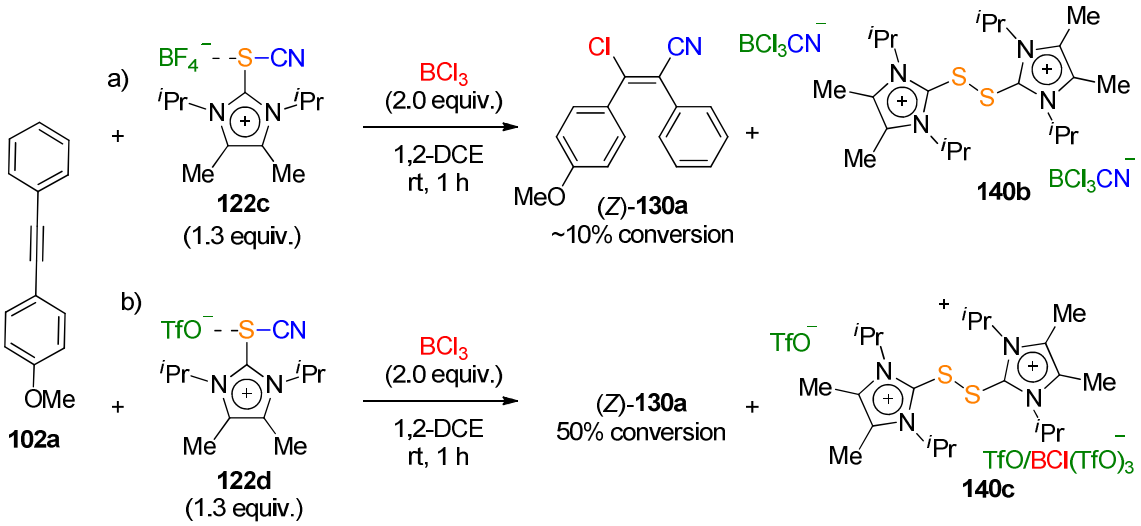


Figure 16. Structure of the salt **140a** in the crystal.

3.3.3.4.4. Counterion effect.

As indicated above, the counterion plays a crucial role in this transformation. Thus, various cyanating reagents with differently halogenated counterions, such **122c** possessing a tetrafluoroborate anion and **122d** with triflate counterion as a pseudohalide, were synthesized directly from **122b** *via* counterion exchange, and tested for **102a** in the chlorocyanation under optimized conditions (**Scheme 72**).

In the case of **122c**, ^{1}H NMR spectrum of the crude reaction mixture, measured after one hour of reaction time, indicated a formation of small amount of product (*Z*)-**130a** as a part of complex mixture (**Scheme 72a**). Interestingly, disulfide **140b**, but this time as the trichlorocyanoborate counterion, was also detected by Mass spectrometry. This trapping of the nitrile group by trichloroborane explains low formation of the product. The same experiment was conducted using the triflate-containing cyanating reagent **122d**. In this case, after one hour stirring, the reaction mixture consisted of the starting material **102a** and product (*Z*)-**130a** as approximately 1/1 mixture. ^{1}H NMR spectrum of the crude mixture was very clean, but disulfide **140c** was detected as a by-product as well (**Scheme 72b**).

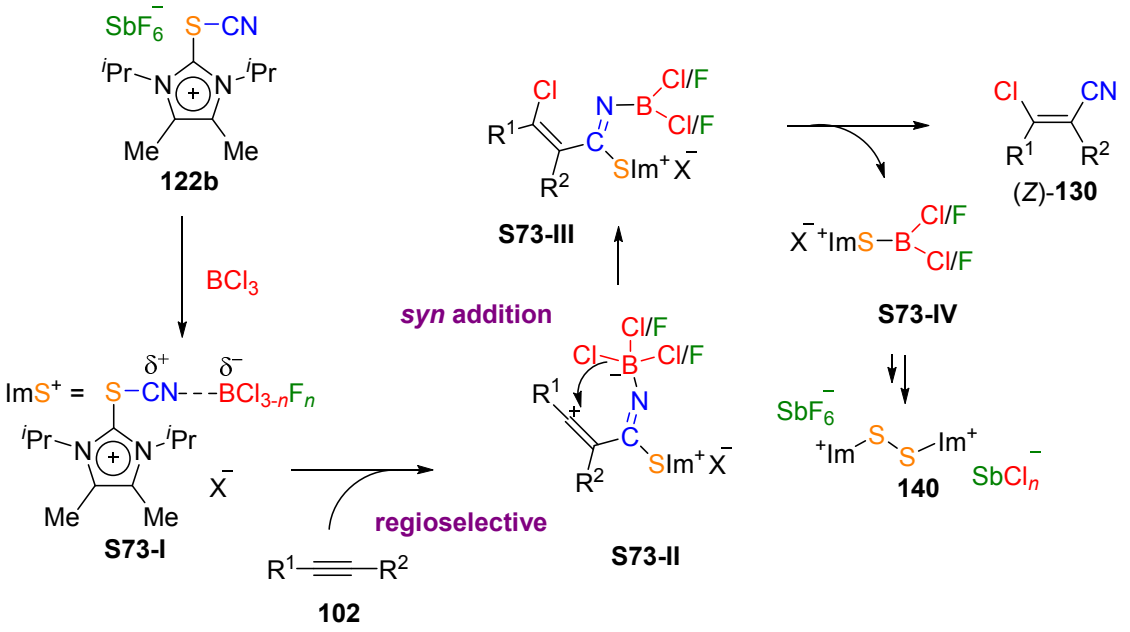


Scheme 72. Counterion effect experiments.

From both experiments one can conclude that he participation of hexafluoroantimonate as a counter ion is not critical, but it is very useful for the obtention of the chlorocyanated alkynes in good yields.

3.3.3.4.5. Proposed mechanism.

Analyzing the experimental material accumulated in our laboratory, a satisfactory mechanistic rationalization can be proposed for the chlorocyanation (**Scheme 73**). It would start with the nitrile activation in **122b**, thus generating Lewis Adduct **S73-I**. A F/Cl exchange in **S73-I** in some extent may occur as well. Next step would involve a regioselective addition of the corresponding alkyne **102** forming a stabilized carbocation **S73-II**. One of the chloride ions from BCl_3 moiety is then transferred in a *syn* fashion to this carbocation, forming selectively iminoborane intermediate **S73-III** in a pre-established (*Z*)-configuration, before forming the desired chloroacrylate (*Z*)-**130** by elimination of the imidazolium-thioborane moiety. As a side reaction, disulfide **140** can be formed. No evidence of fluoroacrylates formation was detected, as B–Cl bonds (~456 kJ/mol) are weaker that B–F bonds (~613 kJ/mol).



Scheme 73. Proposed mechanism.

3.3.3.5. Synthetic applications of chloroacrylonitriles.

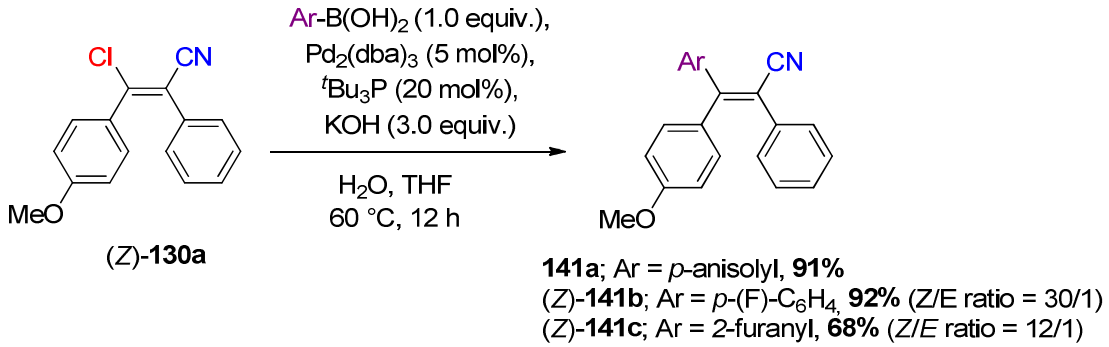
Once a family of products (*Z*)-**130** was prepared, their synthetic utility in organic synthesis was investigated as well. Therefore, various experiments have been conducted to derivatize (*Z*)-acrylonitriles into more complex architectures using product (*Z*)-**130a** as model a substrate.

3.3.3.5.1. Cross-couplings.

Among vinyl halides, vinyl chlorides represent substrates with a lowest reactivity towards cross-coupling reactions.[123] Nonetheless, they can be successfully converted into synthetically useful tetrakis-substituted alkenes with high stereoselectivities.

3.3.3.5.1.1. Suzuki-Miyaura couplings.

Following a standard procedure for the cross-coupling of vinyl chlorides,[124] products **141a–141c** were obtained in good to excellent yields with a remarkable stereoselectivity, thus affording an approach to synthetically useful tetrasubstituted alkenes bearing all-carbon substituents (**Scheme 74**). (*Z*)-Configuration of structure **141b** was confirmed by X-Ray crystal structure analysis (**Figure 17**).



(*Z*)-**130a**

141a; Ar = *p*-anisolyl, **91%**
(*Z*)-**141b**; Ar = *p*-(F)-C_6H_4, **92%** (*Z*/E ratio = 30/1)
(*Z*)-**141c**; Ar = 2-furanyl, **68%** (*Z*/*E* ratio = 12/1)

Scheme 74. Derivatization of chloroacrylonitroles (*Z*)-**130a** by Suzuki-Miyaura cross-coupling.

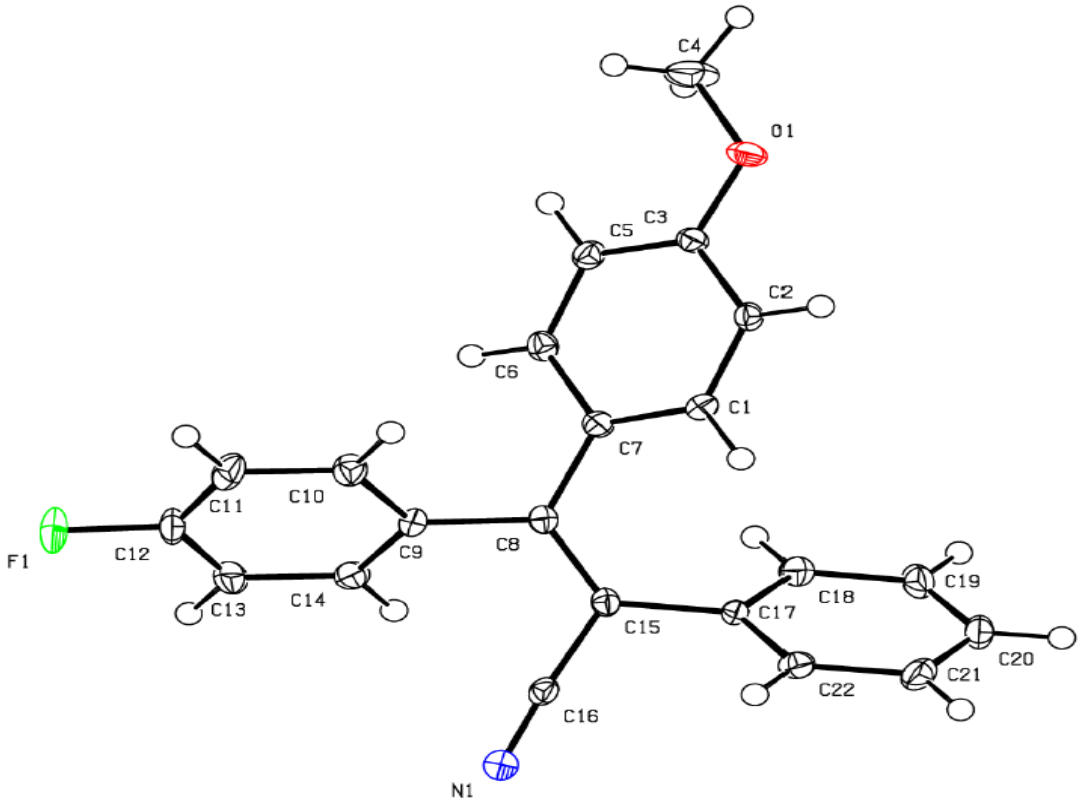
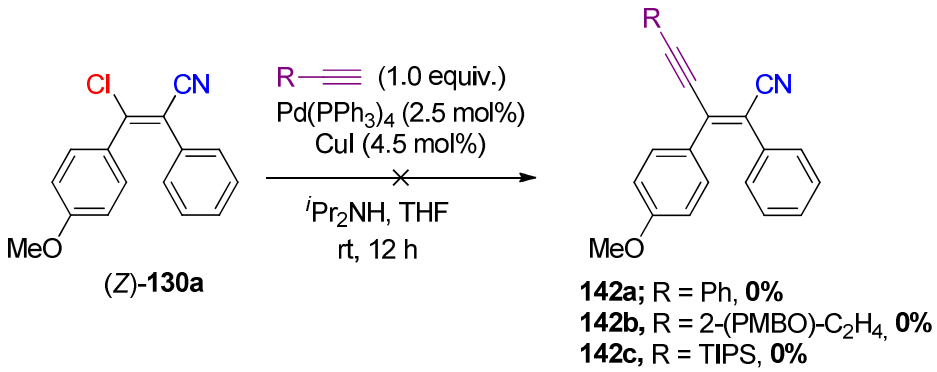


Figure 17. Structure of (*Z*)-**141b** in the crystal.

3.3.3.5.1.2. Sonogashira-Hagihara couplings.

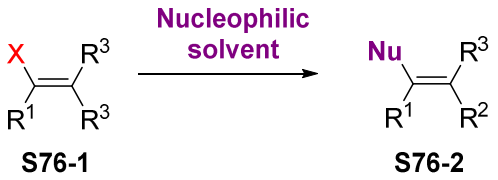
None from the published procedures[125] appeared to be appropriate for the Sonogashira-Hagihara couplings of 130, as formation of **142** was not detected in any case (**Scheme 75**).



Scheme 75. Attempted derivatization of (*Z*)-**130a** by a Sonogashira-Hagihara cross-coupling.

3.3.3.5.2. Solvolytic experiments.

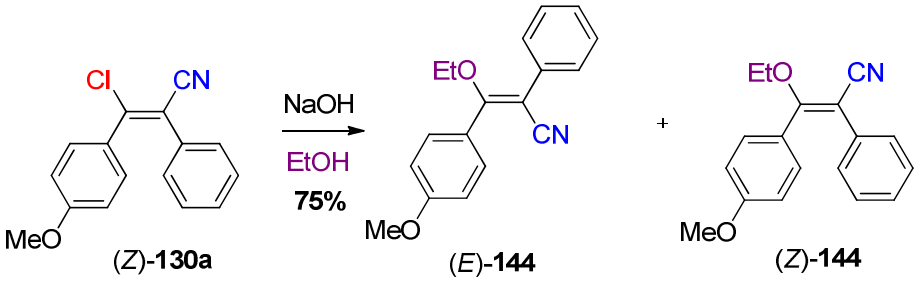
Vinyl chlorides **S76-1** can be functionalized by substitution reactions executed by solvents, also denominated as solvolysis, thus being alcoholysis and aminolysis the most common approaches (**Scheme 76**).[2]



Scheme 76. Solvolysis of chlorovinyl derivatives.

3.3.3.5.2.1. Alcoholysis of chloroacrylonitriles.

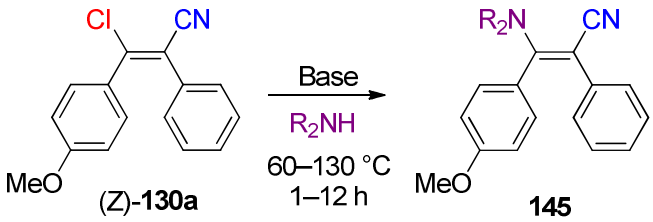
(*Z*)-Stereomerically pure acrylonitrile (*Z*)-**130a** was refluxed in ethanol for 12 hours in the presence of NaOH as a base according to the procedure reported in literature[126] affording the desired alcoholysis product **144** in good yield. Unfortunately, this transformation appeared to be not stereoselective affording a 2/1 stereomeric mixture of the alcoholysis products **144**. (**Scheme 77**).



Scheme 77. Alcoholysis of chloroacrylonitrile (*Z*)-**130a**.

3.3.3.5.2.2. Aminolysis of chloroacrylonitriles.

In an analogous way to alcoholysis, several aminolyses were examined for substrate (*Z*)-**130a** as summarizes **Table 9**.



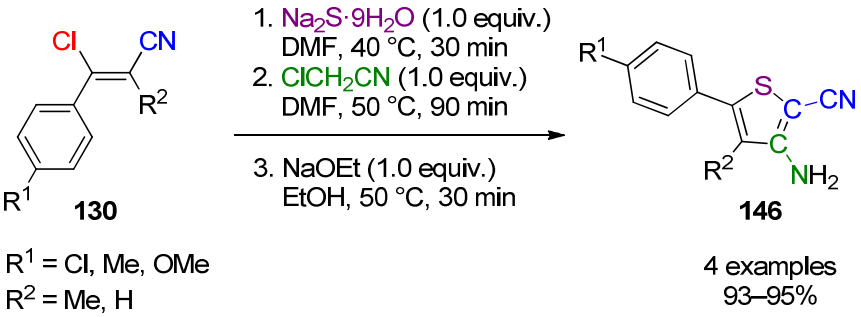
Entry	Amine	Base	T (°C)	t (h)	Product	Isolated yield (%)	*Z*/*E* ratio
1	$EtNH_2$	NaH	130	1	(*Z*)-**130a**	**n.a.**	**n.a.**
2	$NaNH_2$	n.a.	60	12	**decomp.**	**n.a.**	**n.a.**
3	piperidine	NaOH	100	1	**145c**	**95**	**1/1.2**
4	morpholine	NaOH	130	9	**145d**	**91**	**1/1.5**

Table 9. Aminolysis of chloroacrylonitrile (*Z*)-**130a**.

Neither primary amines in the presence of a strong base nor amides afforded the desired products (**Table 9, entries 1–2**). In the first case the starting material (*Z*)-**130a** was in part re-isolated, whereas in the second one it completely decomposed. More successful was the aminolysis using cyclic secondary amines such as piperidine and morpholine in the presence of a base. The first transformation was accomplished in excellent yields but without selectivity, as an almost 1/1 mixture of isomeric products (*E*)- and (*Z*)-**145c** was isolated (**Table 9**, **entry 3**). The same result was obtained in the case of morpholine (91% yield) with an 1.5:1 ratio of compounds in favor of compound (*E*)-**145d** (**Table 9**, **entry 4**).

3.3.3.5.2.3. Synthesis of heterocycles.

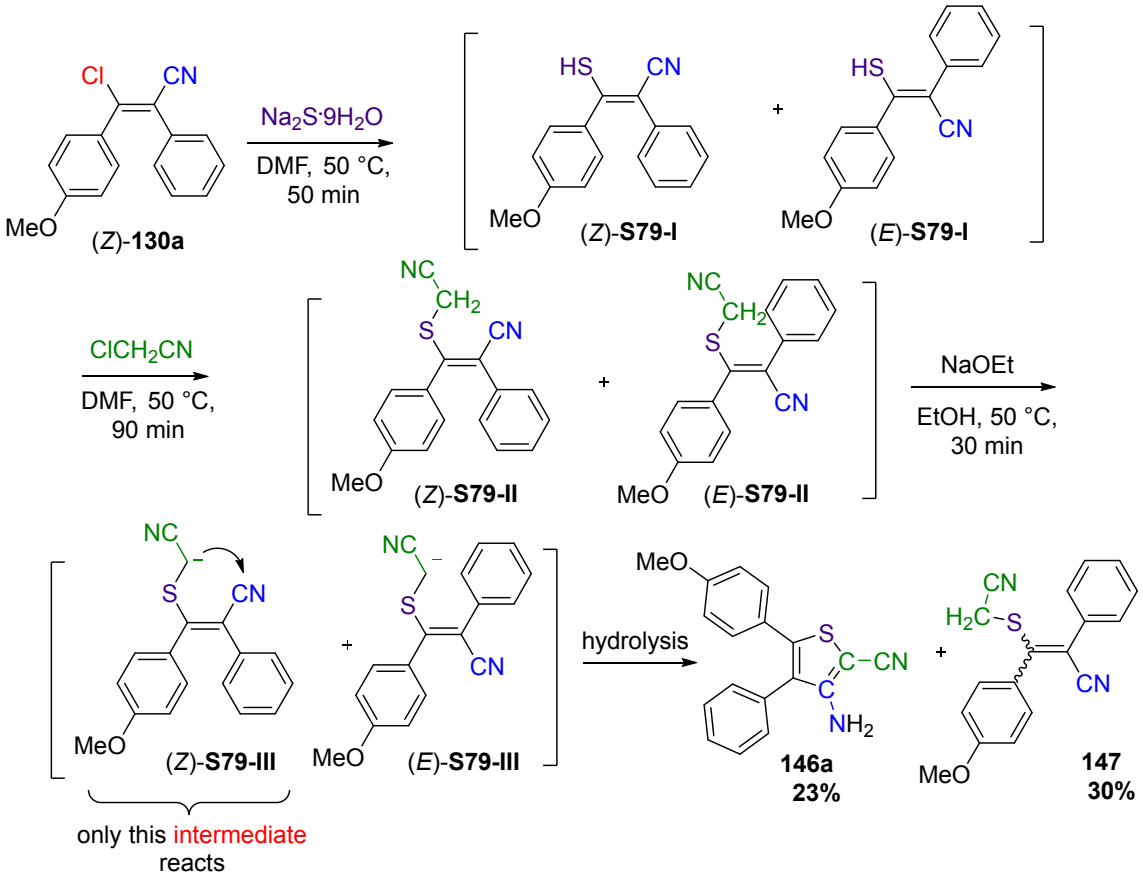
Thiophenes. Albeit the inconveniency of obtaining mixtures of stereomers, the products of these solvolyses discussed above had the definitive potential of being further employed for the synthesis of heterocycles. Following this principle, Thomae *et al.* reported the synthesis of thiophenes starting from chloroacrylonitriles (**Scheme 78**).[127]



Scheme 78. Thiophenes synthesis from chloroacrylonitriles **130**.

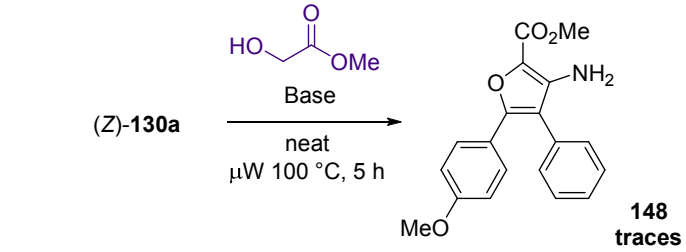
Model substrate (*Z*)-**130a** was then employed under the same conditions as in **Scheme 78**. The results including possible intermediates, generated in each step, are depicted in **Scheme 79**.

In the first step, the non-stereoselective addition/dehydrochlorination afforded thioles (*Z*)-**S79-I** and (*E*)-**S79-I**, which are directly condensed with one equivalent of chloroacetonitrile, forming intermediates (*Z*)-**S79-II** and (*E*)-**S79-II**. After deprotonation of the latter with a base, only anionic intermediate (*Z*)-**S79-III** is able to afford the corresponding thiophene **146a** *via* nucleophilic addition to the cyano group followed by hydrolysis, thus being reflected in a lower yield than expected. The intermediate (*E*)-**S79-III** generated compound **147**, which contaminated the final product. For the comparison, all the substrates employed by Thomae *et al.* contained sterically not demanding substituents R^2 such as H or Me. This increased the proportion of intermediate of the type (*Z*)-**S79-I**, which can additionally be stabilized by a S•••N through-space interaction, and thus the yield of final thiophene. In contrast to this, the intermediates **S79-I** contained bulkier aryl substituents. Nonetheless, the developed route for the synthesis of thiophenes from alkynes is shorted (5 steps) than the reported by Thomae *et al.* (7 steps).



Scheme 79. Synthesis of thiophene **146a** from (*Z*)-**130a**.

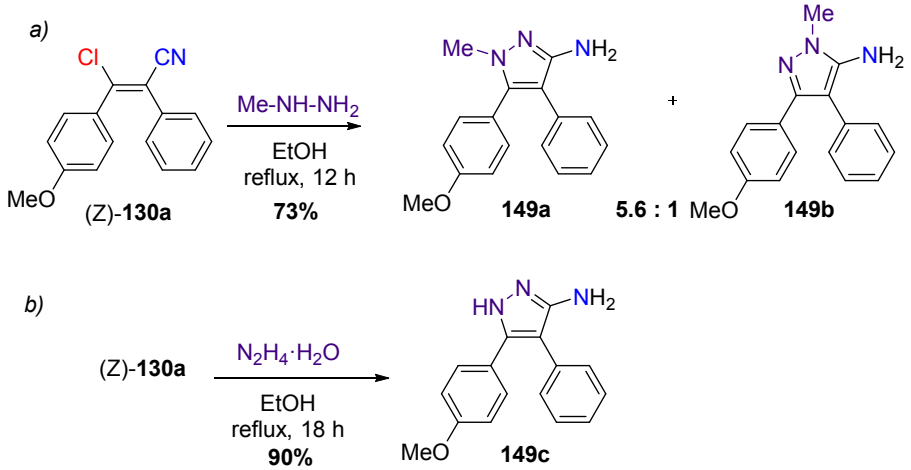
Furanes. Exploiting the same idea, it was envisioned to realize an equivalent synthesis of furanes using alcohol in combination with a base. Unfortunately, only traces of **148** could be detected and no product was isolated (**Scheme 80**).



Base = NaH, NaOH, K_2CO_3

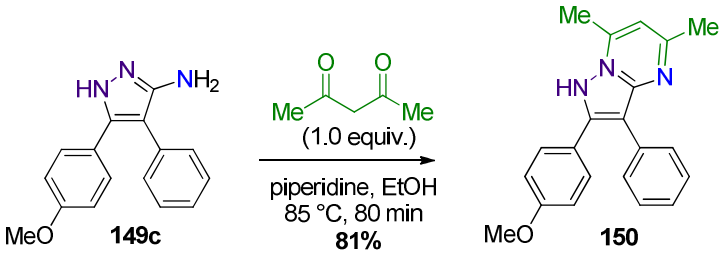
Scheme 80. Attempted synthesis of furane **148** from (*Z*)-**130a**.

Pyrazoles and pyrazolopyrimidines. Based on the work published by Almansa *et al.*,[128] pyrazole derivatives were prepared by reaction of (*Z*)-**130a** with hydrazines. In the case of the methylhydrazine, the isomeric mixture of the pyrazole **149a** and its regioisomer **149b** in a favorable 5.6:1 ratio was obtained in 73% yield (**Scheme 81a**). This inconveniency could be further avoided using a symmetric hydrazine, which afforded **149c** in excellent yields (**Scheme 81b**).



Scheme 81. Pyrazoles synthesis from (*Z*)-**130a.**

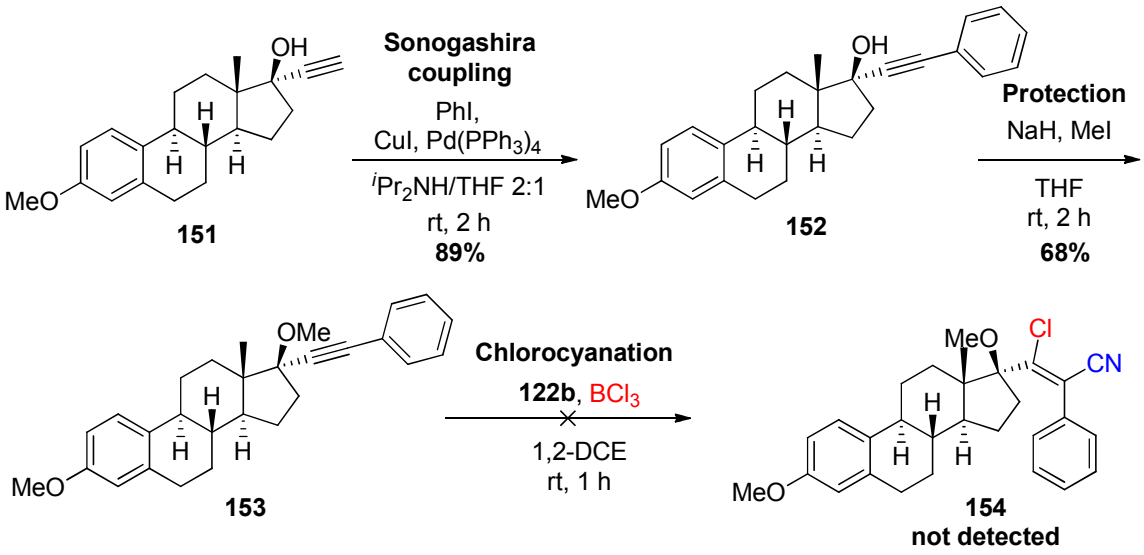
As a synthetic extension, it is possible to further derivatize **149c** by converting it into pyrazolopyrimidine **150** via condensation with acetylacetone following the procedure reported by Almansa *et al.*,[128] also in a very good yield (**Scheme 82**).



Scheme 82. Synthesis of **150** from **149c**.

3.3.3.5.2.4. Natural products derivatization.

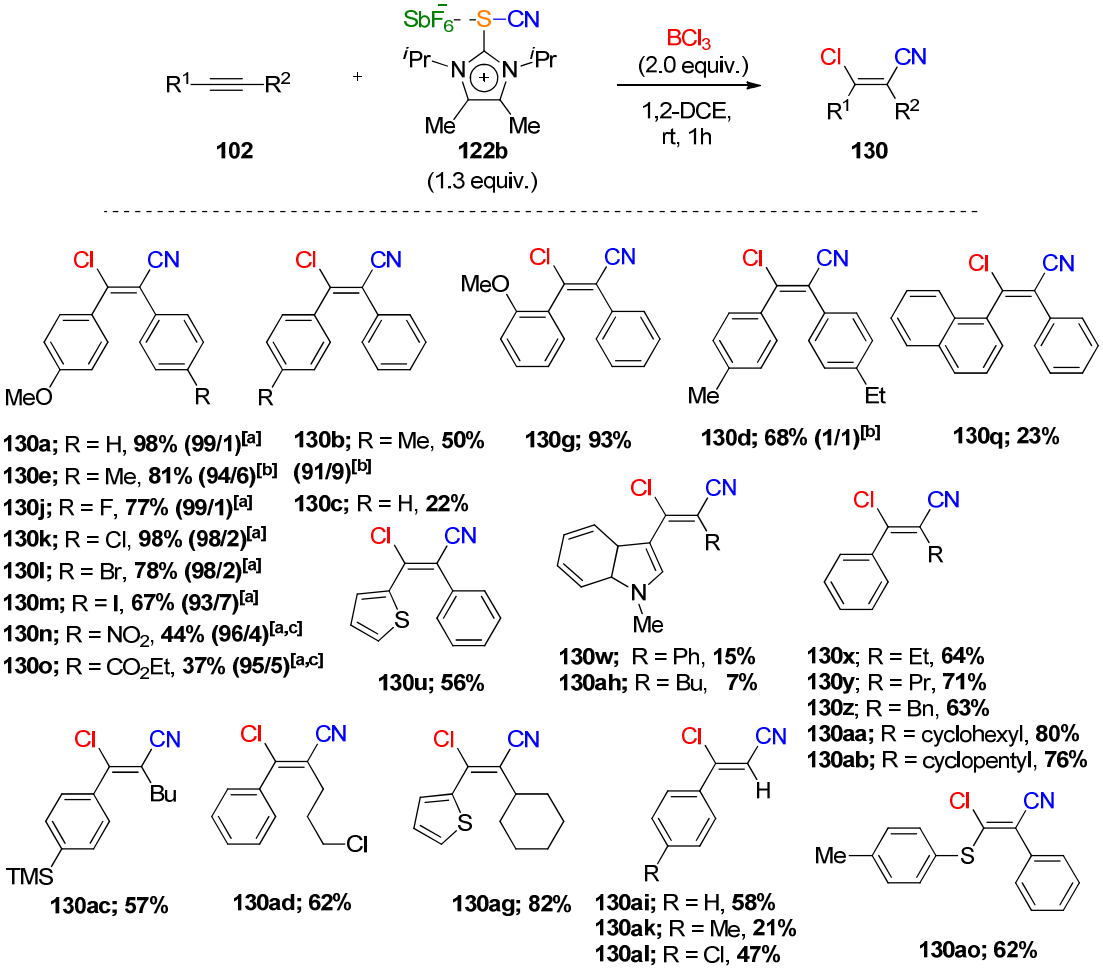
Another direct application of the newly developed methodology was by derivatization of a natural product containing an alkyne unit.[117d–c] For this purpose, mestranol (**151**), a commercially available and inexpensive alkyne derivative of estradiol, was chosen as a model substrate. After simple derivatization to **152** by a Sonogashira-Hagihara cross-coupling and alcohol protection affording **153**, this alkyne was further subjected to the optimized chlorocyanation conditions. Lamentably, but only decomposition of the starting material was observed, while product **154** was not detected (**Scheme 83**).



Scheme 83. Attempted chlorocyanation of estradiol derivative **153**.

3.3.3.6. Summary.

In summary, a new methodology for the chlorocyanation of alkynes, based on a combined action of BCl_3 and cyanating reagent **122b**, has been developed. Final products, the synthetically interesting 3-chloroacrylonitriles **130**, were formed with excellent regio- and stereoselectivities. The reaction tolerates a wide variety of functionally substituted alkynes, including terminal and internal ones, as summarized in **Scheme 84**. The newly described products could be successfully converted into more complex molecules, hence validating the synthetic interest to this process.



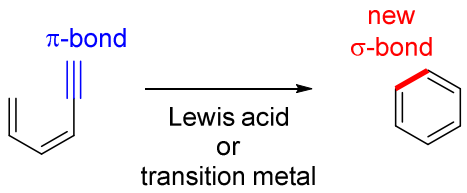
Scheme 84. Scope for the regio- and stereoselective chlorocyanation of alkynes. [a] Isolated as a mixture of stereomers (ratio expressed as *Z*/*E*), [b] Isolated as a mixture of regiomers. [c] Reaction performed at 60 °C during 3 h.

4. Cyanative Cyclizations.

4.1. Introduction.

Organic cycles represent, with no doubt, the most important type of molecules in organic chemistry as they are present in almost every natural product, reason why they are subject of study in important scientific fields such medicine, pharmacology, materials science, industry, *etc*… Due to their importance, a plethora of synthetic procedures have been developed to achieve their synthesis and its further derivatization. Among them, gain more power those new routes which lower the environmental impact and the atom economy of the process. As special interest worths mentioning the denomatinated as intramolecular cyclization, which can be defined as a type of reaction that implies the formation of one or more cycles by a rearrangement of the starting material.[129] One of the most attractive points which derives from them, comes from the excellent atom economy which they exhibit, as every atom present in the starting material is also present in the final product.

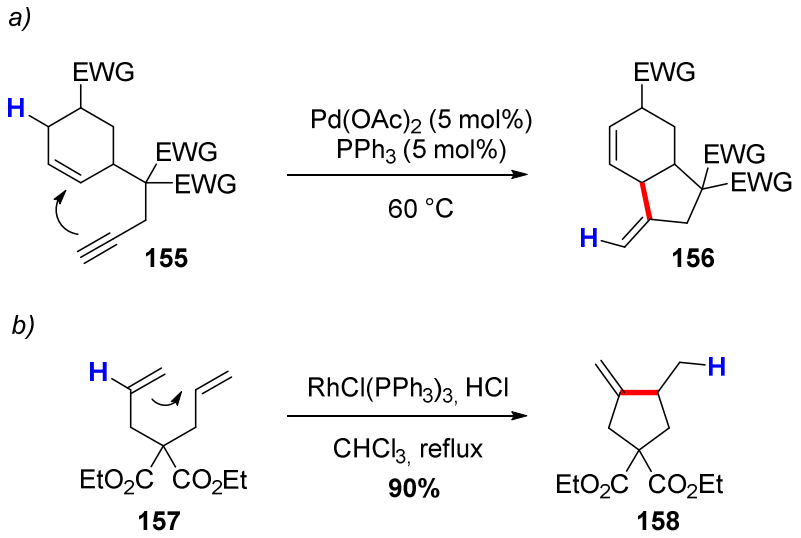
Intramolecular cyclizations (also denominated cycloisomerizations) can be accomplished by addition of catalytic amounts of Lewis acid or transition metal to the desired substrate, resulting as above indicated, in the generation of at least one new cycle. The transformation involves the generation of new σ-bonds at the expence of another π-bonds included in the substrate.[130] Of particular interest are those associated with the formation of a new C–C bond, as they are a simple tool to construct polycyclic compounds (**Scheme 85**).



Scheme 85. Cycloisomerization involving the generation of a new C-C bond.

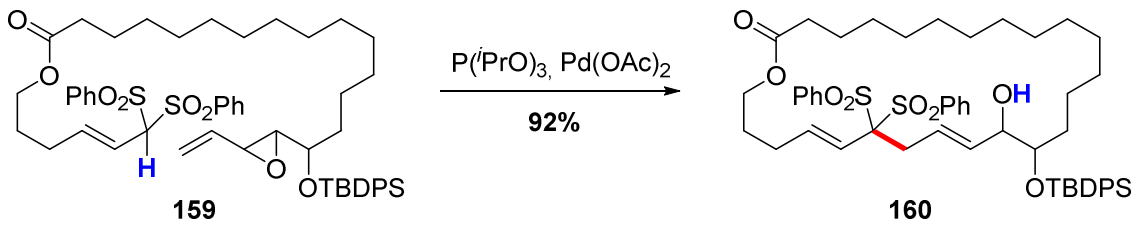
As a small summary, some of the most representative cycloisomerization cases reported in literature are detailed in the following page. One classical way is denominated as ene-

type cyclizations, where a π-bond nucleophile which usually is an alkyne (**Scheme 86a**) or an alkene (**Scheme 86b**) attacks another π-bond (electrophile) present in the molecule.[131]



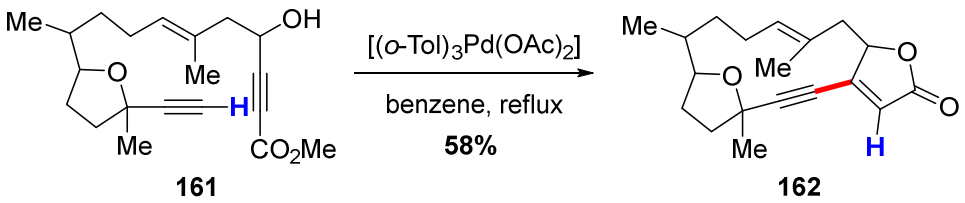
Scheme 86. Ene-type cyclization.

Alternatively, intramolecular cyclizations can be accomplished when a π-allyl group is initially activated by a transition metal, and subsequently acts as a nucleophile reacting with another double bond on the molecule (**Scheme 87**).[132]



Scheme 87. Cycloisomerization by π-allyl activation.

One of the other many ways to achieve cycloisomerizations is the situation in which, two alkynes from the same molecule react with each other forming a new cycle (**Scheme 88**).[133]



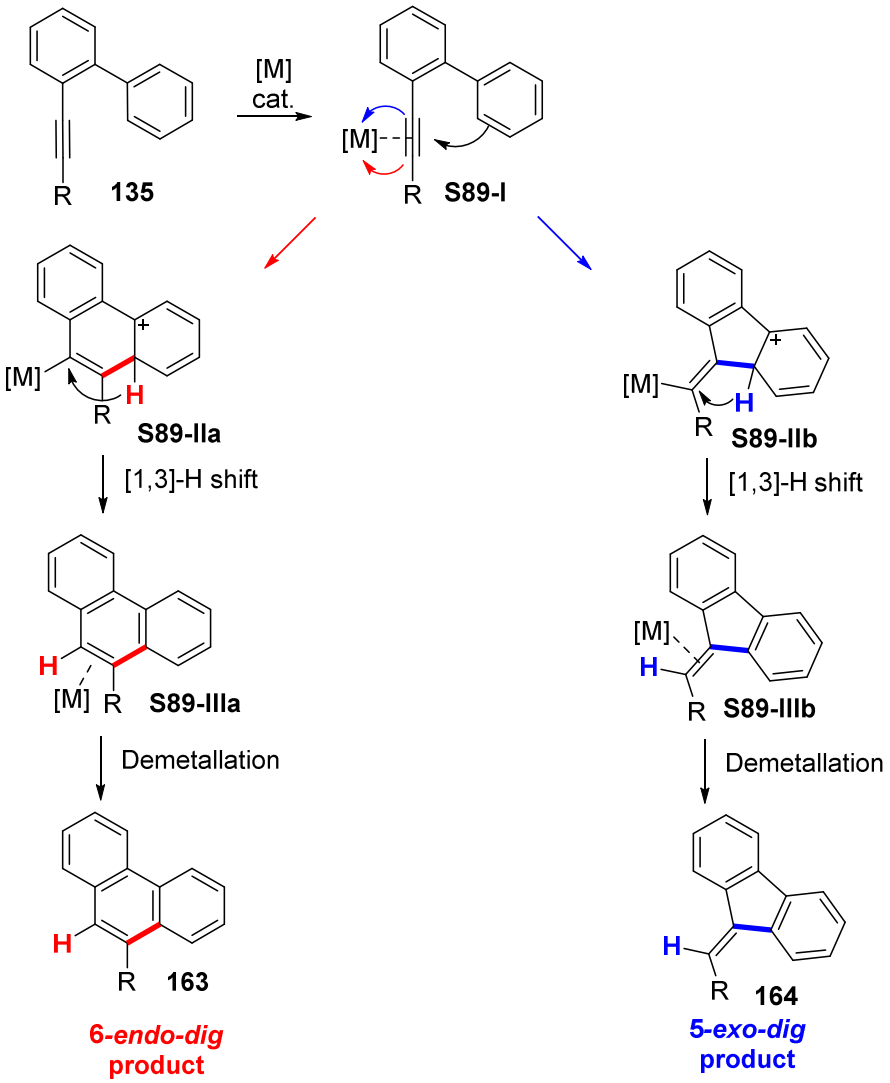
161 **162**

Scheme 88. Cycloisomerizations.

Internal alkynes seem to play an important role on this type of transformations, therefore we decided to investigate if could extend our developed methodology of cyanation of alkynes to processes which involve a cyclization step.

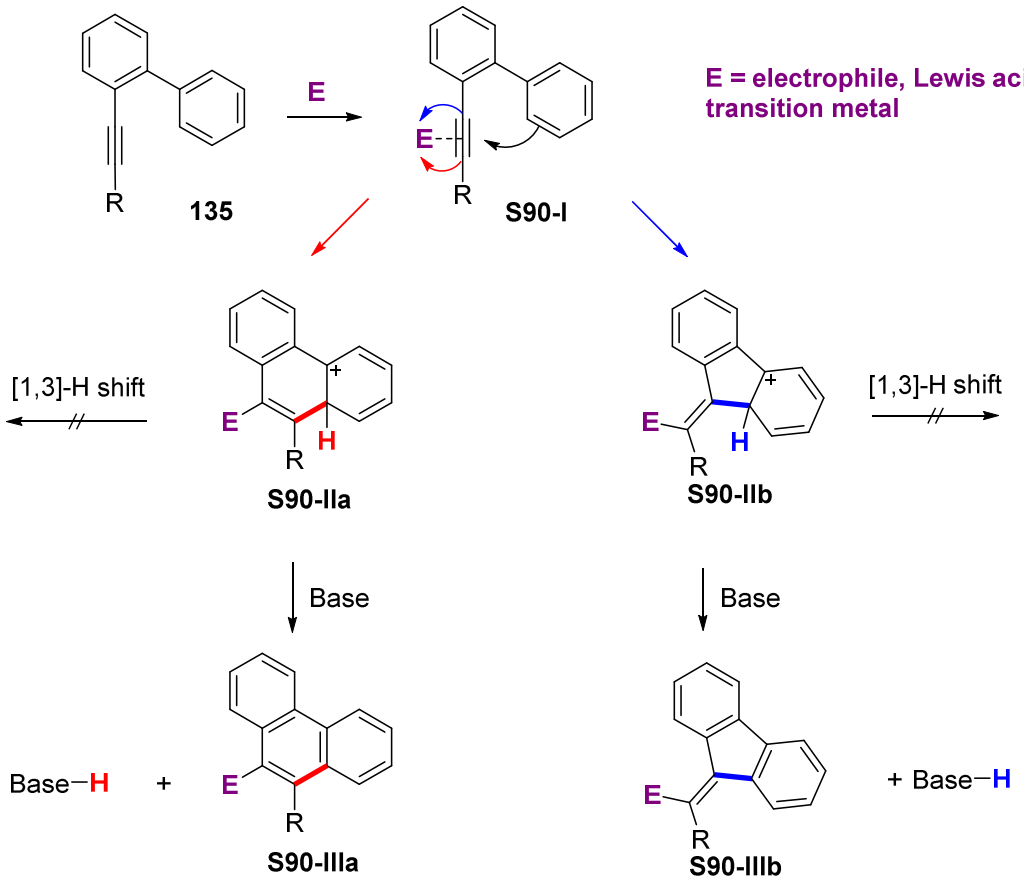
Internal alkynes such **135,** which represent one of the classical substrates used in cycloisomerizations brought our attention. The mechanism of the transformation is detailed in **Scheme 89**.[134]

First, the formation of metal-alkyne complex **S89-I** occurs, which increases the triple bond electrophilicity in **135**. Next step is the nucleophilic attack by the arene moiety, leading to the formation of intermediates **S89-IIa** or **S89-IIb** with a 6- or 5-membered ring, respectively. The regioselectivity of this step can be controlled by a proper selection of the substituents R, metals and/or ligands.[135] Both carbocationic intermediates **S89-IIa** and **S89-IIb** rearrange *via* a [1,3]-H shift step, which is strongly favored by a bencene ring formation process which leads to the corresponding metal-alkene complexes **S89-IIIa** and **S89-IIIb**, respectively. Finally, products 6-*endo*-*dig* **163** or 5-*exo*-*dig* **164** are generated after demetalation.



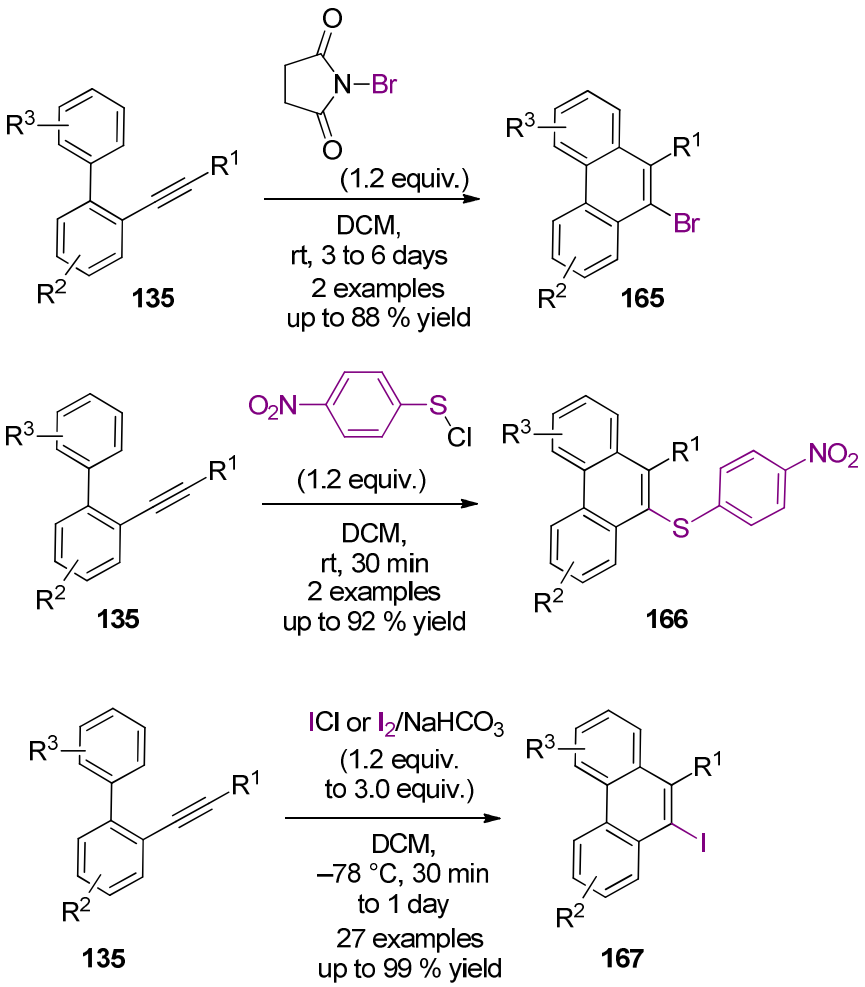
Scheme 89. The two possible pathways in the cycloisomerization of ene-yne type substrates like **135**.

Analyzing the generally accepted mechanism we came with interesting conclusions. We can observe that to proceed from **S89-IIa** and **S89-IIb** to **163** and **164** respectively, a proton needs to be shifted, and that if this proton is conveniently trapped by a suitable base, another electrophilic source could take its place and be incorporated in the final product.[136] In theory, when the reaction is performed with stoichiometric amounts of any suitable electrophile in combination with a proper base, products like **S90-IIIa** and **S90-IIIb** will be formed (**Scheme 90**).



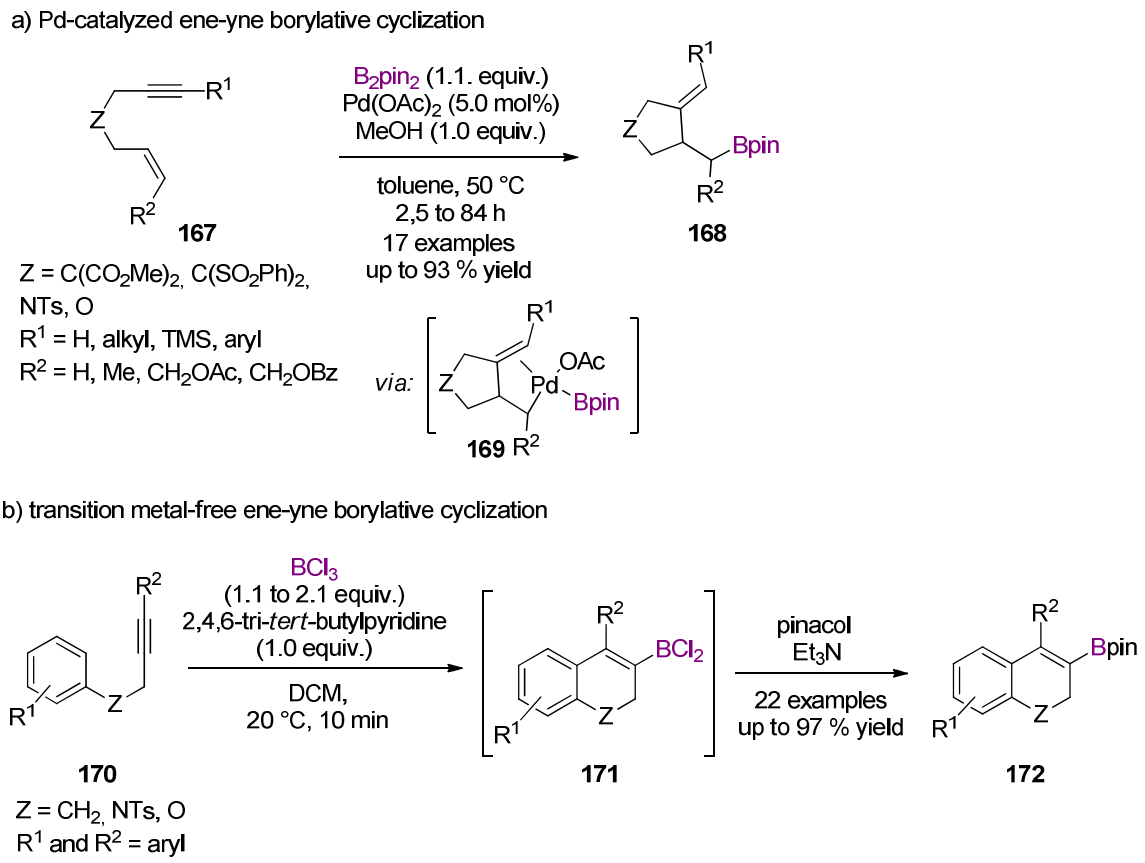
Scheme 90. Electrophile-promoted cyclization of ene-ynes **135**.

The latter methodology has an obvious advantage, since synthetic versatile halides, silanes or boranes substituents can be introduced in the final products, thus allowing their further functionalization by cross-coupling methodologies. In the most ideal case, the electrophile is reactive enough for the direct activation of the alkyne and for promoting the cyclization, such is the case of protic acids which can promote efficient cascade cyclizations.[137] This idea has been already exploited by Larock and co-workers in 2005, who have prepared regioselectively iodo-, bromo- and sulfur-substituted phenanthrenes **165**–**167** (**Scheme 91**).[138]



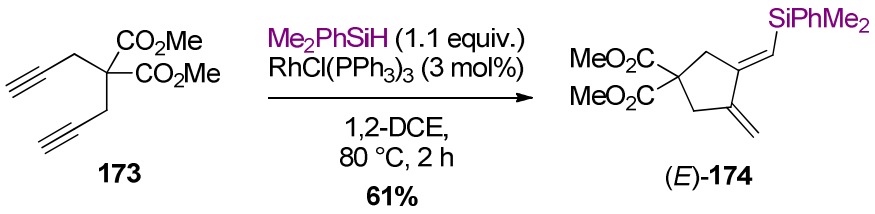
Scheme 91. Electrophile-promoted synthesis of phenanthrenes **165**–**167** *via* cyclization of ene-ynes **135**.

Another well-developed cyclization procedure is the so-called borylative cyclization, where borane electrophiles are incorporated in the final cyclic products. In most cases, the boron-based electrophile must be activated by a transition metal, as in the intermediate **169**, and then incorporated after the reductive elimination step (**Scheme 92a**).[139] Ingleson and co-workers reported on one of the first examples of metal-free borylative cyclizations by using trichloroborane as the selected electrophile (**Scheme 92b**).[140]



Scheme 92. Palladium-catalyzed and metal-free borylative cyclizations.

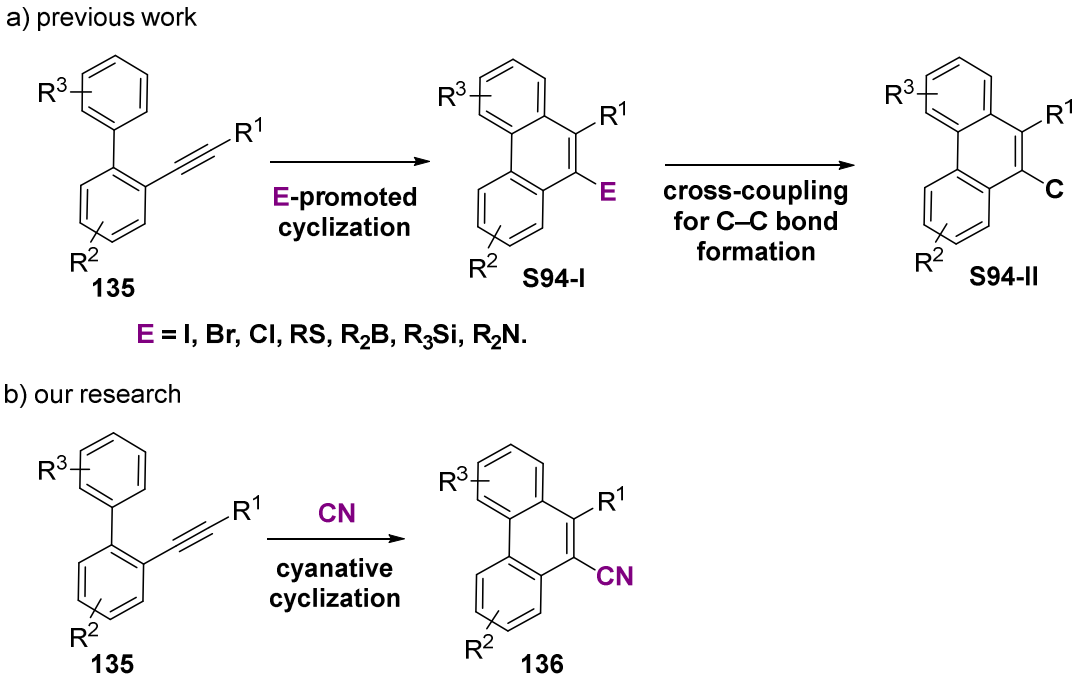
Analogous silylative cyclizations are still underexplored. A rare example is shown in **Scheme 93**, where the main product (*E*)-**174** is formed together with a complex mixture of its various regio- and stereomers.[141]



Scheme 93. Rhodium-catalyzed silylative cyclization of **173**.

As already mentioned, all these protocols described above have one general synthetic perspective, that the final products can be transformed into more complex structures, for example, when creating a new C–C bond by performing cross-coupling. The whole process requires a two steps sequence, namely initial electrophile-promoted cyclization followed by a cross-coupling process catalyzed by a transition metal complex (**Scheme 94a**). This transformation, however, can be optimized by direct employment of a carbon-

based electrophile which would promote both reactions – cyclization and C–C bond formation – in one step. The electrophilic cyano species would represent an ideal option for this purpose (**Scheme 94b**). So far, to the best of our knowledge, there are no examples of cyclizations promoted by electrophiles such [$^{+}$CN], and this question has become one of the main research topics in our laboratory.



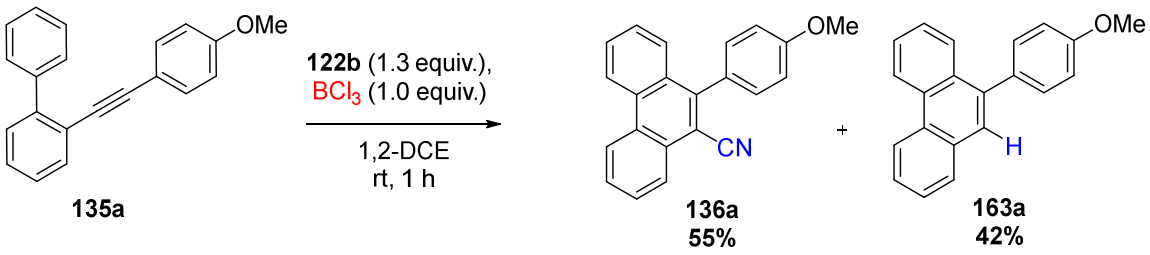
Scheme 94. Cyanative cyclization strategy.

4.2. Objective.

The topic of this Chapter is focused on the development of an efficient protocol for the metal-free cyanative cyclization of ene-yne-type substrates by employment of imidazolium thiocyanates as cyanating reagents.

4.3. Results and discussion.

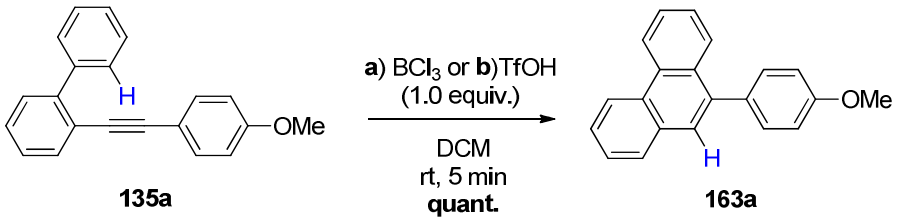
After efficiently developing a metal-free methodology for the regio- and stereoselective chlorocyanation of alkynes,[142] the possibility of extending the scope of transformations with cyanating reagent **122b** was further explored. As evidenced before in the course of mechanistic studies, substrate **135a** could successfully produce cyanated phenanthrene **136a** *via* a cyanative cyclization procedure. As no base participated in this process, the formation of undesired cycloisomerized product **163a** was observed as well (**Scheme 95**).



Scheme 95. Cyanative cyclization and cycloisomerization of **135a**.

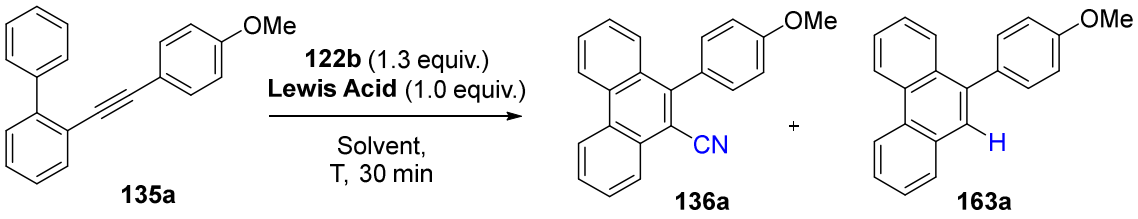
4.3.1. Synthesis and screening.

To further corroborate how **163a** can be formed, two test experiments were initially carried out. In the first experiment, the substrate **135a** was mixed with BCl_3 in a ratio of 1:1, and in the second one – with one equivalent of TfOH (**Scheme 96**). In both cases, a quantitative cycloisomerization of substrate **135a** was observed.



Scheme 96. BCl_3- and TfOH-promoted cyclosiomerizations of **135a**.

These types of cycloisomerizations are favored by an aromatization process, which allows the reaction to be terminated in a very short time under the action of an acid. Thus, different Lewis acids were screened for this transformation (**Table 10**). Unfortunately, none of the tested transition metal-based Lewis acids tested stimulated the formation of cyanated product **136a**.

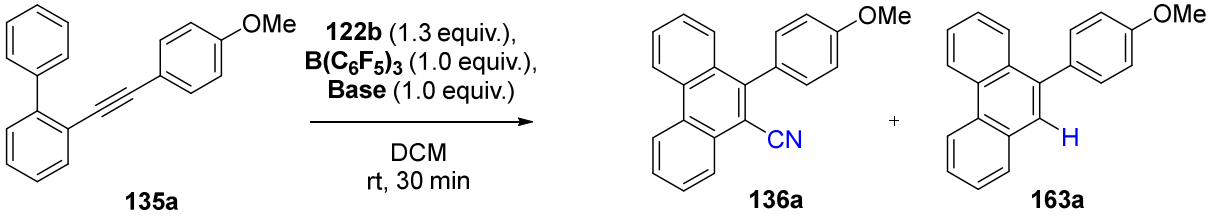


Entry	Lewis acid	Solvent	T (°C)	Conversion	Product[a]
1	**$AlCl_3$**	DCM	rt	**n.r.**	**n.a.**
2	**$AlCl_3$**	1,2-DCE	80	**n.r.**	**n.a.**
3	**$Al(TfO)_3$**	DCM	rt	**Full**	**163a**
4	**$TiCl_4$**	DCM	rt	**Full**	**n.a.**
5	**AuL[b]+ $AgSbF_6$**	DCM	rt	**Full**	**163a**
6	**$PdCl_2$**	1,2-DCE	80	**n.r.**	**n.a.**
7	**CuI**	DCM	rt	**n.r.**	**n.a.**
8	**CuI**	1,2-DCE	80	**Full**	**163a**
9	**$Y(TfO)_3$**	DCM	rt	**Full**	**163a**
10	**$BF_3{\cdot}Et_2O$**	DCM	rt	**Full**	**163a**
11	**$BF_3{\cdot}Et_2O$**	DCM	0	**Full**	**163a**
12	**$BF_3{\cdot}THF$**	DCM	rt	**Full**	**163a**
13	**$B(C_6F_5)_3$**	DCM	rt	**Full**	**136a/163a (~1/1)**
14	**BCl_3**	DCM	rt	**Full**	**136a/163a (~1/1)**

Table 10. Screening of Lewis acids for the cyanative cyclization of **135a**.[a] Determined by ^{1}H NMR. [b] L = phenyl-bis(di *iso*propylaminecycloproprenium)phosphine.

In the case of $AlCl_3$, only starting material was recovered (**Table 10**, **entries 1** and **2**), Lewis acids like $Al(TfO)_3$, AuL, CuI and $Y(TfO)_3$ resulted in the conversion to the undesired cycloisomerized product **163a** without any traces of **136a** (**Table 10**, **entries 3**, **5**, **8**, **9** and **13**). $TiCl_4$ produced decomposition of starting material (**Table 10**, **entry 4**). As already known from our previous study, borane-based Lewis acids like BF_3, BCl_3 or $B(C_6F_5)_3$ can efficiently activate **122b** to promote electrophilic cyanations. Thus, BF_3 was tested in the reaction, but only **163a** was detected again (**Table 10**, **entries 10**–**12**). Similar to the methodology for chlorocyanation of internal alkynes, only $B(C_6F_5)_3$ and BCl_3 appeared to be suitable for the formation of the cyanated product **136a**, however, in *circa* a 1:1 mixture with **163a** (**Table 10**, **entries 13**–**14**).

To further develop an efficient method for the cyanative cyclization of alkynes and in accordance with the mechanism shown in **Scheme 90**, the reaction was probed in the presence of an appropriate base which does not form adducts with a Lewis acid. As borane $B(C_6F_5)_3$ features a sterically surrounded boron atom, it was chosen as Lewis acid for this transformation in combination with different bases (**Table 11**). Unfortunately, neither inorganic (**Table 11**, **entries 1** and **2**) nor organic bases (**Table 11**, **entries 3**–**7**) appeared to be efficient, they all seem to deactivate the borane by formation of a Lewis adduct. DABCO base was not suitable also and the starting material **135** remained unchanged (**Table 11**, **entries 5**–**7)**.

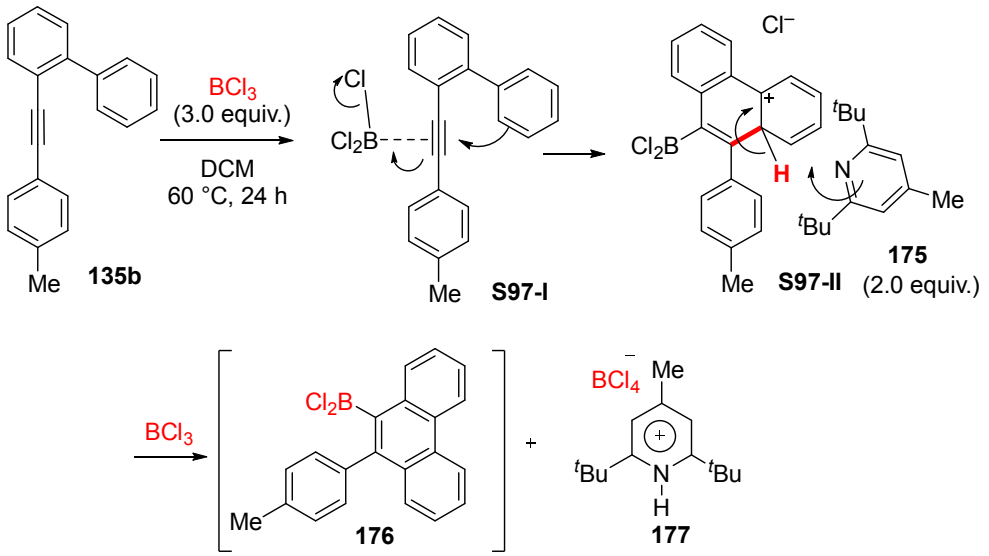


135a **136a** **163a**

Entry	Base	Conversion	Product
1	**K_2CO_3**	**n.r.**	**n.a.**
2	**NaAcO**	**n.r.**	**n.a.**
3	**Me^{i}Pr$_2$N**	**n.r.**	**n.a.**
4	**P(^{t}Bu)$_3$**	**n.r.**	**n.a.**
5	**DABCO**	**n.r.**	**n.a.**
6	**2,6-di*tert*butylpyridine**	**n.r.**	**n.a.**
7	**1,8-naphthalenediamine**	**n.r.**	**n.a.**

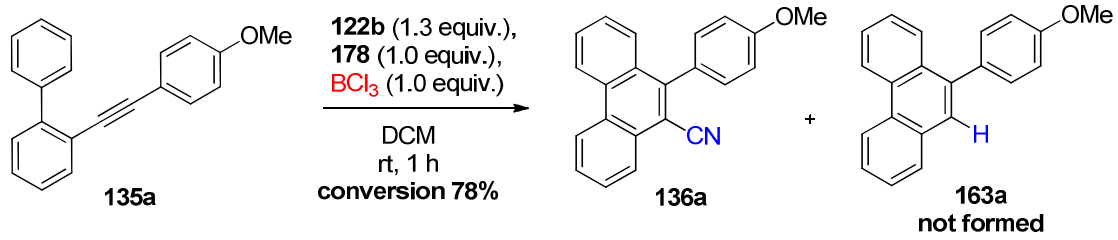
Table 11. Bases screeining for the cyanative cyclization of **135a.**

Ingleson and co-workers[140] reported 2,6-di-*tert*-butyl-4-methylpyridine (**175**) as an efficient base to avoid the cycloisomerization of substrates **135** into **163** in the presence of excess of BCl_3. In this borylative cyclization procedure, the hydrogen atom in intermediate **S97-II** which should undergo a [1,3]-H shift is trapped by the sterically hindered pyridine **175**, generating the corresponding product of the borylative cyclization **176** and pyridinium salt **177** (**Scheme 97**).



Scheme 97. Borylative cyclization of **135b**.

This type of base may be perfectly suitable for our reaction system as well, taking into account the similarity of the reaction conditions (*cf.* **Table 10**, **entry 14**). Indeed, employing slightly modified version of **175,** such is 2,6-di-*tert*-butylpyridine (**178**), we observed a remarkably high conversion of **135a** to the desired compound product **136a** as a single product and without any traces of cycloisomerized side-product **163a**. The unreacted starting material **135a** could be further recovered (**Scheme 98**).

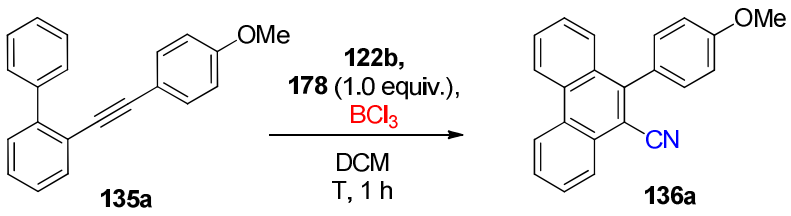


Scheme 98. Cyanative cyclization of alkyne **135a**.

4.3.2. Optimization of reaction conditions.

Once the formation of side product **163a** was successfully suppressed, the reaction was next optimized as shown in **Table 12**. By varying the reaction stoichiometry (**Table 12**, **entries 1–5**), it was concluded that an advantageous conversion is observed when the ratio of borane and cyanating reagent is close to 1:1, while the preferable temperature is 0 °C (**Table 12**, **entries 6–8**). The required quantities of **122b** and BCl_3 could be

successfully reduced to 1.2 equivalents (**Table 12**, **entries 6–8**). Therefore, conditions from **entry 8** in **Table 10** were chosen as optimal, providing **136a** in 95% isolated yield.

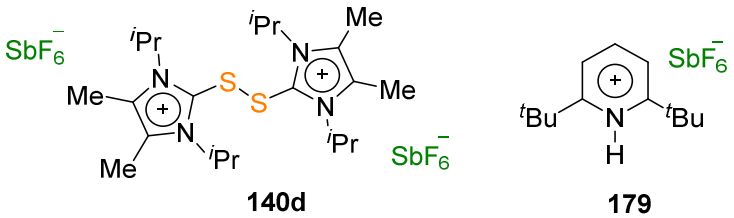


135a **136a**

Entry	BCl_3 equiv.	**122b** equiv.	Temperature	Conversion
1	1.0	1.0	rt	78%
2	1.1	1.1	rt	80%
3	1.5	1.1	rt	83%
4	3.0	1.1	rt	full
5	2.0	1.3	rt	full
6	2.0	1.3	0 °C	full
7	1.3	1.3	0 °C	full
8	**1.2**	**1.2**	**0 °C**	**full (95% yield)**

Table 12. Optimization of conditions for the cyclization of **135a.**

The bis(imidazolium)disulfide **140d** was again isolated as by-products of this transformation, however, this time with hexafluoroantimonate as a single counterion, instead of tetra- or hexachloroantimonate anions. The protonated pyridine hexafluoroantimonate **179** was detected as well (**Figure 18**). Both **140d** and **179** were confirmed by HRMS. Compound **136a** was recrystallized and analyzed by X-Ray analysis (**Figure 19**).



140d **179**

Figure 18. By-products **140d** and **179** in the cyanative cyclization of **135**.

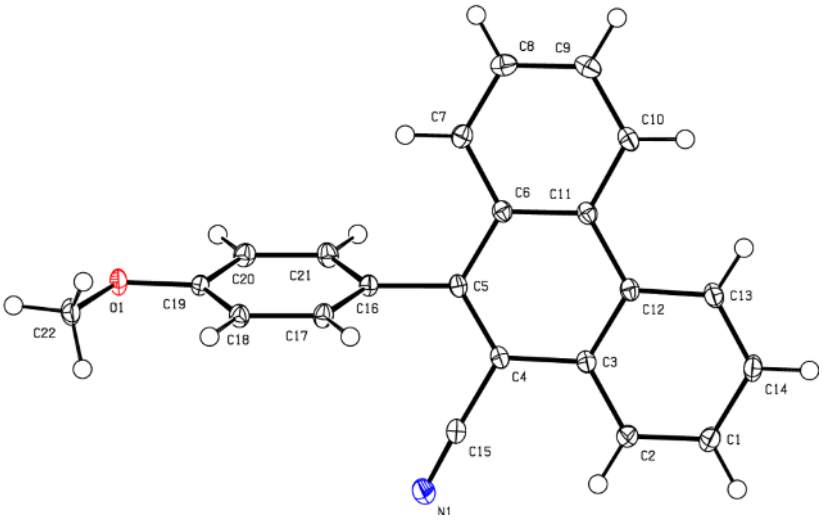
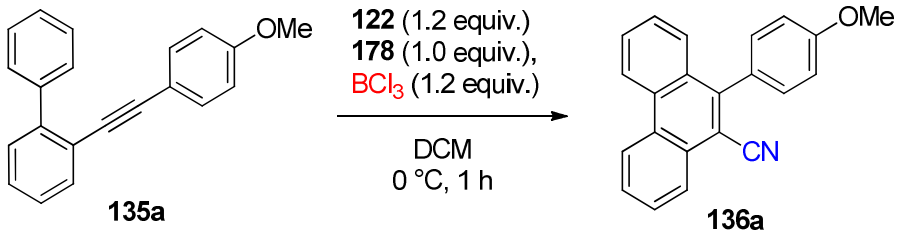


Figure 19. Structure of cyanophenanthrene **136a** in the crystal.

Counterion effect. To evaluate the effect of the counterion on the reactivity, various cyanidation reagents with different counterions were tested under optimized reaction conditions (**Table 13**).



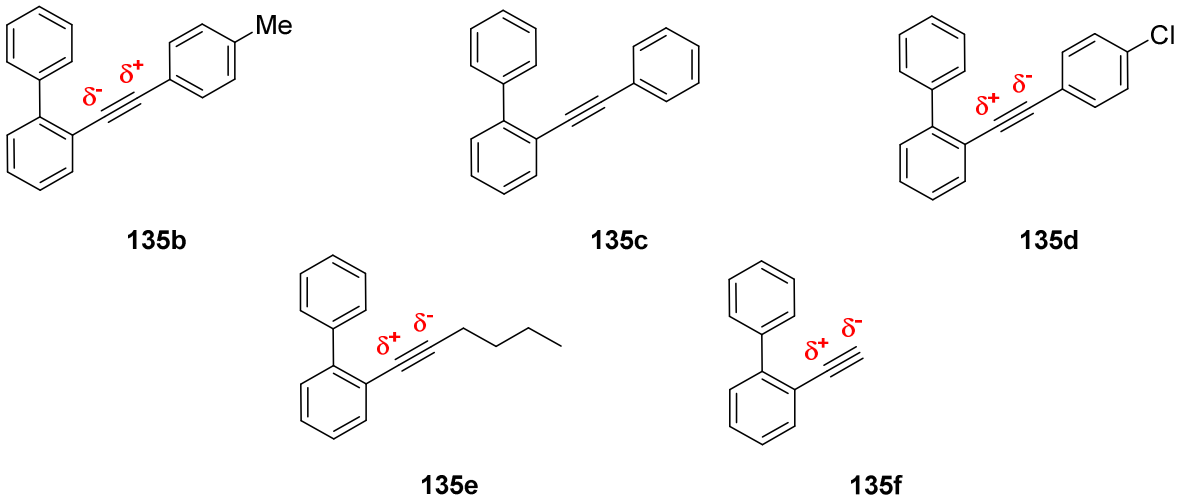
Entry	Reagent	Counterion	Conversion to **136a**[a]
1	**122b**	**SbF_6**	**Full**
2	**122c**	**BF_4**	**5%**
3	**122d**	**TfO**	**5%**
4	**122e**	**PF_6**	**20%**

Table 13. Counterion effect in the cyanative cyclization of **135a.** [a] Determined by ^{1}H NMR.

Using tetrafluoroborate (**122c**) or triflate (**122d**) as a counterion, only 5% of substrate was converted into the desired product **136a** in each reaction (**Table 13**, **entries 2** and **3**). In the former case (**entry 2**) dimer **140b** with two trichlorocyanoborates counterions was detected as a main product (*cf.* **Scheme 70**), but no electrophilic cyanation could be detected. At last, 20% conversion was obtained for **122e** with a hexafluorophosphate

counterion (**Table 13**, **entry 4**). As different counterions appeared not to be beneficial for the reaction, the hexafluoroantimonate system **122b** was used in the subsequent study of the scope of the reaction.

Selectivity of the method. Three possible products might be formed in this transformation; the two regiomers 6-*endo-dig* (**136**) and 5-*exo-dig* (**180**), and the corresponding chlorocyanated products (**130**). Taking into account the experience accumulated during the chlorocyanation of alkynes, five representative substrates with different degree of polarization in the alkyne bond **135b**–**135f** were synthesized to start the scope and limitations studies.[143] Compound **135b** possesses a slightly polarized triple bond, in **135c** the triple bond is not polarized, and **135d**–**f** have the opposite effects benefiting the formation of the *5-exo-dig* product (**Figure 20**).

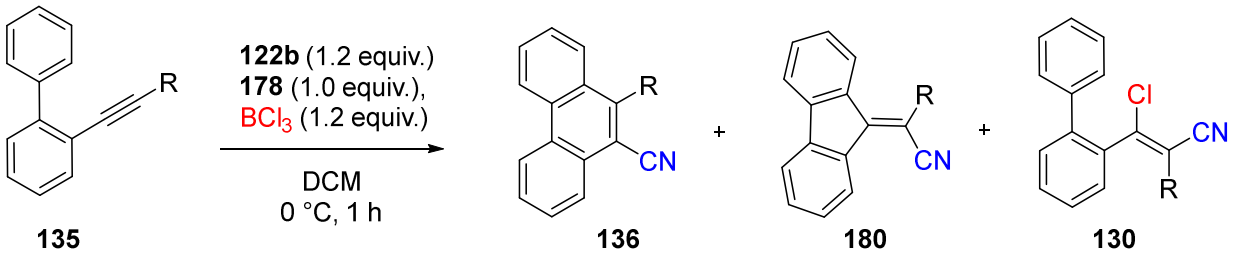


135b **135c** **135d**

135e **135f**

Figure 20. Polarization in substrates **135b**–**135f**.

Under the optimized cyanative cyclization conditions; substrate **135b** afforded the formation of product **136b** in a moderate yield of 51% with the opportunity of recovering unreacted starting material (**Table 14**, **entry 1**). Alkyne **135c** underwent low conversion to a 10:1 mixture of chlorocyanated product **130ar** and phenanthrene **136c** (**Table 14**, **entry 2**). In the case of **135d** only traces of **136d** were detected (**Table 14**, **entry 3**), as well as only traces of chlorocyanated product were observed with the closely related substrate **102h** (*cf.* **Table 4**, **entry 7**). Alkyne **135e** surprisingly afforded the chlorocyanated product **130as** in excellent yield (97%) (**Table 14, entry 4**), and in the case of terminal alkyne **135f** chloroacrylate **130at** in 44% yield and unreacted starting material **135f** were isolated (**Table 14**, **entry 5**).



Entry	Compound	R	**136**/**180**/**130** ratio	Isolated yield (%)
1	**135b**	*p*-tolyl	only **136b**	**51**
2	**135c**	Ph	**136c/0/130ar**	**25**
3	**135d**	*p*-(Cl)-C_6H_4	**n.a.**	**n.a.**
4	**135e**	^{n}Bu	only **130as**	**97**
5	**135f**	H	only **130at**	**44**

Table 14. Scope of the cyanative cyclization of **135b**–**f**.

4.3.3. Scope and limitations.

4.3.3.1. Synthesis of phenanthrenes.

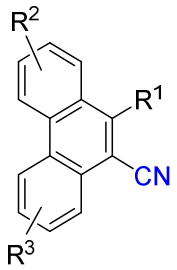
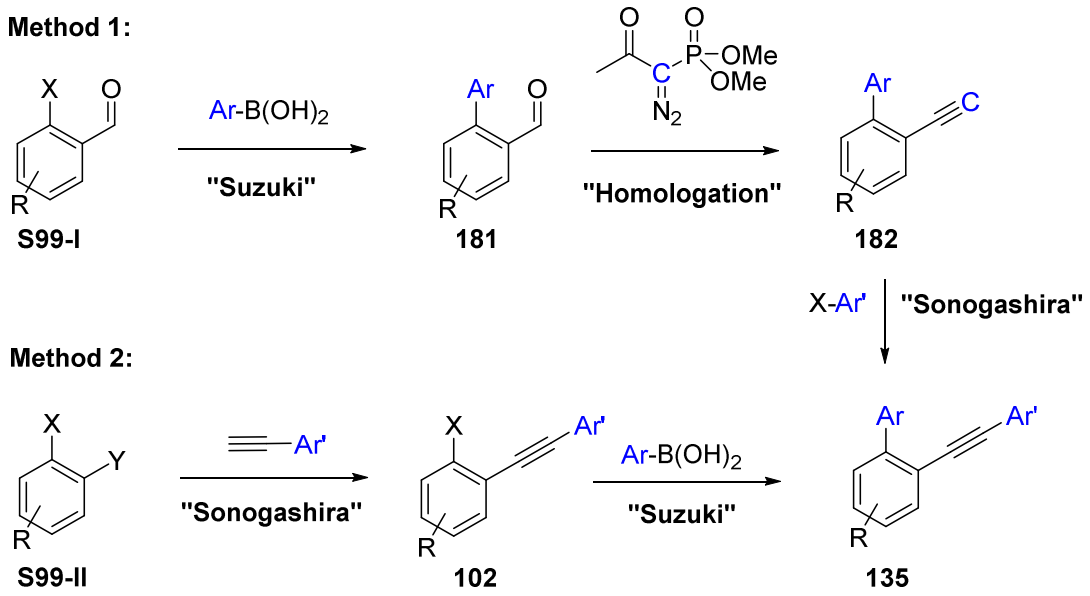


Figure 21. Cyanated phenanthrenes **136**.

The reaction scope appeared to be limited to internal alkynes decorated with a biphenyl moiety on one side and an electron rich system on the other side. As mentioned above, the closely related substrates **102** with similar polarization showed an almost similar reactivity in the chlorocyanation reactions. Taking this into account, the efforts were initially focused on the decoration of the biphenyl moiety in the starting material **135**.

Two main routes were followed for the substrate synthesis.[100,101,143] **Method 1** consisted in the initial Suzuki-Miyaura cross-coupling with aldehyde **S99-I** to produce biaryl products **181**, followed by homologation of the latter to generate **182** and final Sonogashira-

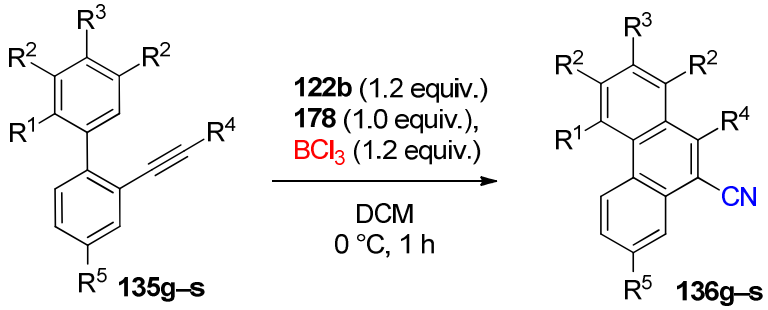
Hagihara cross-coupling providing substrates **135**. **Method 2** was started with a Sonogashira-Hagihara cross-coupling with **S99-II**; the resulting internal alkynes **102** were converted to compounds employing a Suzuki-Miyaura reaction (**Scheme 99**).



Scheme 99. Methods for the synthesis of substrates **135**.

Substrates **135g**–**s** were prepared as indicated in **Scheme 99** (see Experimental Section), and further tested in the cyanative cyclization transformation, whose details and results are summarized in **Table 15**. At including electron-withdrawing groups in substituent R_1, we were able to obtain the corresponding products in moderate to very good yields (**Table 15**, **entries 1**–**3**). However, in the case of including benzyloxy group as substituent, only deprotection of the benzyl group (**135k**) and decomposition was detected (**Table 15**, **entry 4**). It was also tolerated a TMS group in the position 4' of the biphenyl moiety, which formed product **136l** with an isolated yield of 56% (**Table 15**, **entry 5**). Regarding the reactivity of a bromomethyl-substituted biphenyl like **135m**, only resulted in the formation of product **135n** as a result from a Br/Cl exchange (**Table 15**, **entry 6**). Unfortunately, heteroaromatic-substituted alkynes such **135o** and **135p** appeared to be less efficient in this transformation, leading to a very low conversion to **136o** and **136p**, respectively, remaining a majority of unreactive starting material in the reaction mixture (**Table 15**, **entries 7** and **8**). Even more unproductive was including various electron-donating groups in the aromatic rings (**135q** and **135r**), where a quick decomposition of substrates was detected (**Table 15**, **entries 9** and **10**). On the other hand, employment of starting material

135s resulted in a complex mixture, from which product **136s** was isolated in a moderate 42% yield (**Table 15**, **entry 11**).

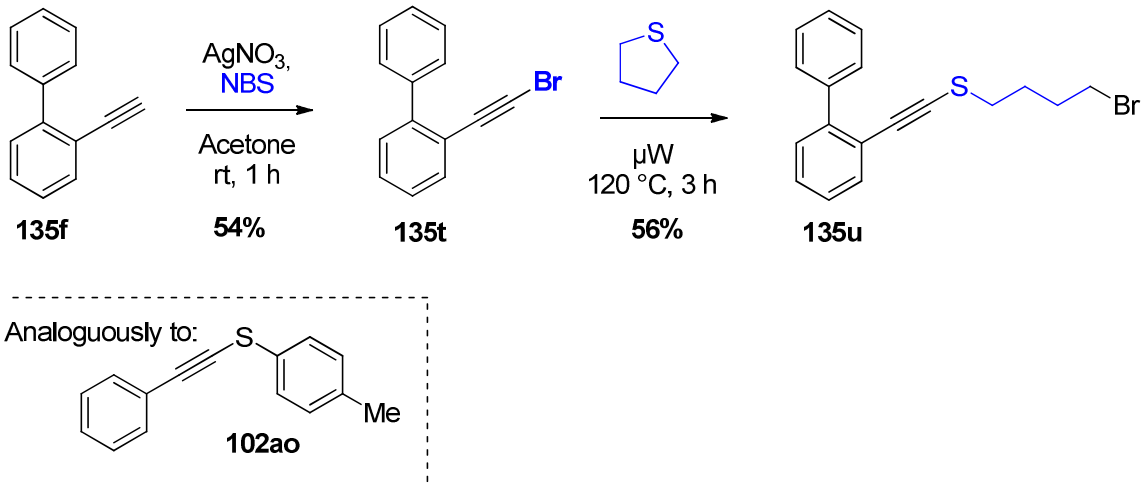


Entry	Alkyne	R^1	R^2	R^3	R^4	R^5	Product	Isolated yield (%)
1	**135g**	CF_3	H	H	*p*-tolyl	H	**136g**	**52**
2	**135h**	CF_3	H	H	*p*-anisolyl	H	**136h**	**67**
3	**135i**	Cl	H	H	*p*-anisolyl	H	**136i**	**86**
4	**135j**	H	H	H	*p*-(BnO)-C_6H_4	H	**135k**	**n.a.**
5	**135l**	H	H	TMS	*p*-anisolyl	H	**136l**	**56**
6	**135m**	H	H	CH_2Br	*p*-anisolyl	H	**135n**	**n.a.**
7	**135o**	H	H	H	2-thiophenyl	H	**136o**	**22**
8	**135p**	H	H	H	2-benzo-thiophenyl	H	**136p**	**15**
9	**135q**	CO_2Me	MeO	MeO	*p*-anisolyl	H	**n.a.**	**n.a.**
10	**135r**	H	MeO	H	*p*-anisolyl	CF_3	**n.a.**	**n.a.**
11	**135s**	H	MeO	H	Ph	H	**136s**	**42**

Table 15. Scope of the cyanative cyclization of alkynes **135g–s**

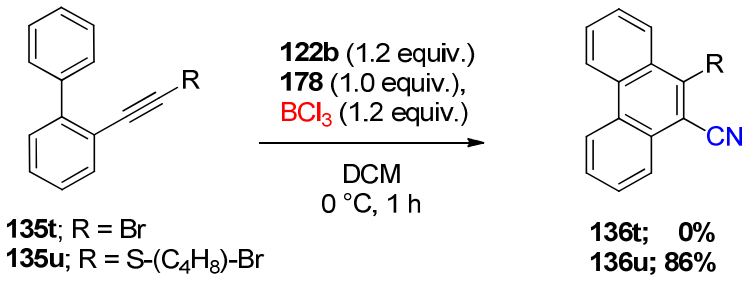
.

Aware of the limitations that the method seemed to show so far, we decided to slightly change the structure of the substrate. Thus, it was synthesized **135u** which included a heteroatom directly linked to the alkyne moiety. Terminal alkyne **135f** was brominated forming **135t**,[144] and further transformed into substrate **135u** after heating in tetrahydrothiophene (**Scheme 100**).[145]



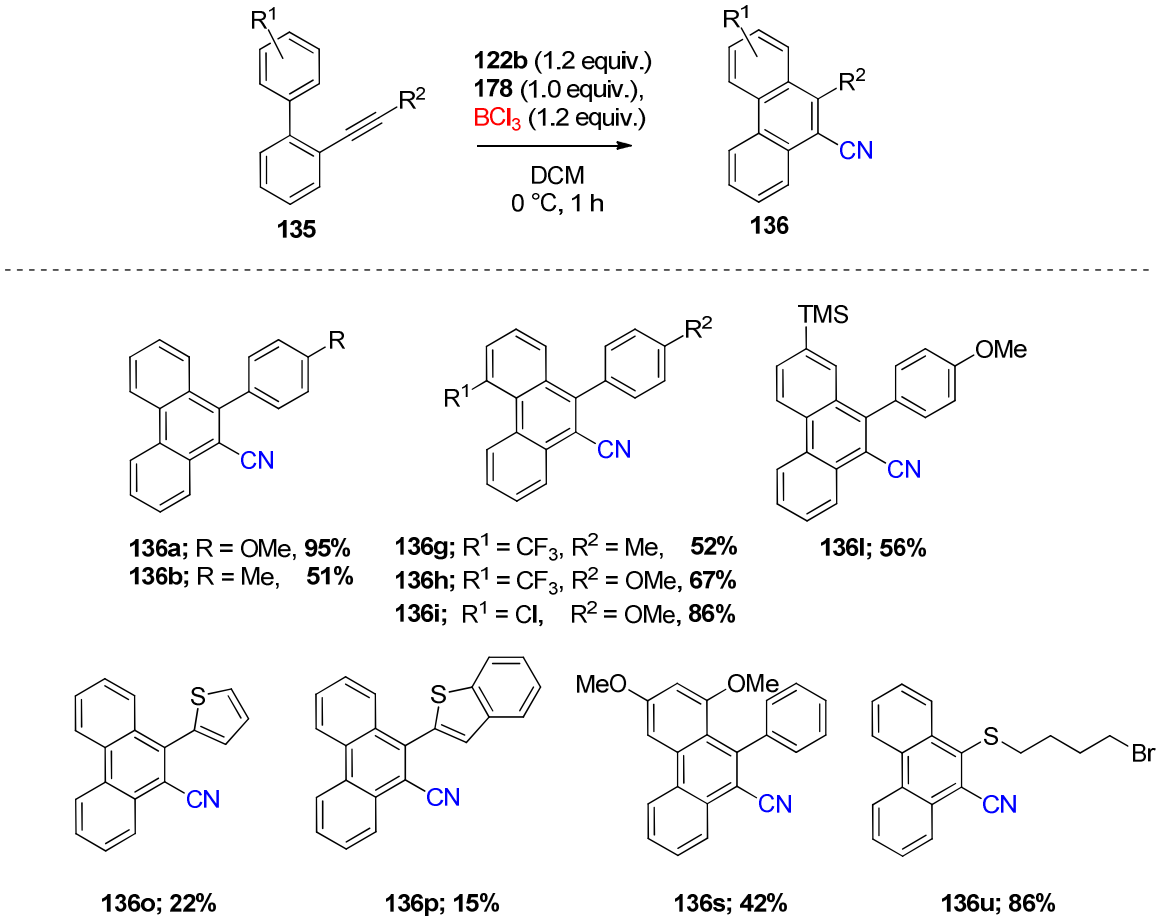
Scheme 100. Procedure for the synthesis of **135t** and **135u**.

Compounds **135t** and **135u** were tested under the optimized conditions obtaining the following results: **135t** was decomposed, while alkyne **135u** could be succesfully transformed into the desired product **136u** in very good yield (86%) (**Scheme 101**).



Scheme 101. Cyanative cyclization of alkynes **135t** and **135u**.

As a summary of the scope and limitations, a new metal-free method has been developed for the synthesis of 9-cyanophenanthrenes, where different electron-demanding groups could be incorporated in the biphenyl core. At this stage of the investigation, the reaction is only limited to the formation of *6-endo-dig* products, as when *5-exo-dig* cyclizations are favoured chlorocyanations occur in faster way avoiding their formation and forming the corresponding chlorocyanated product instead. The scope is summarized in **Scheme 102**.



Scheme 102. Scope for synthesis of cyanated phenantrenes **136**.

4.3.3.2. Synthesis of heterocycles.

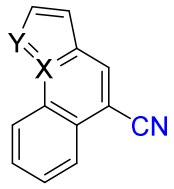
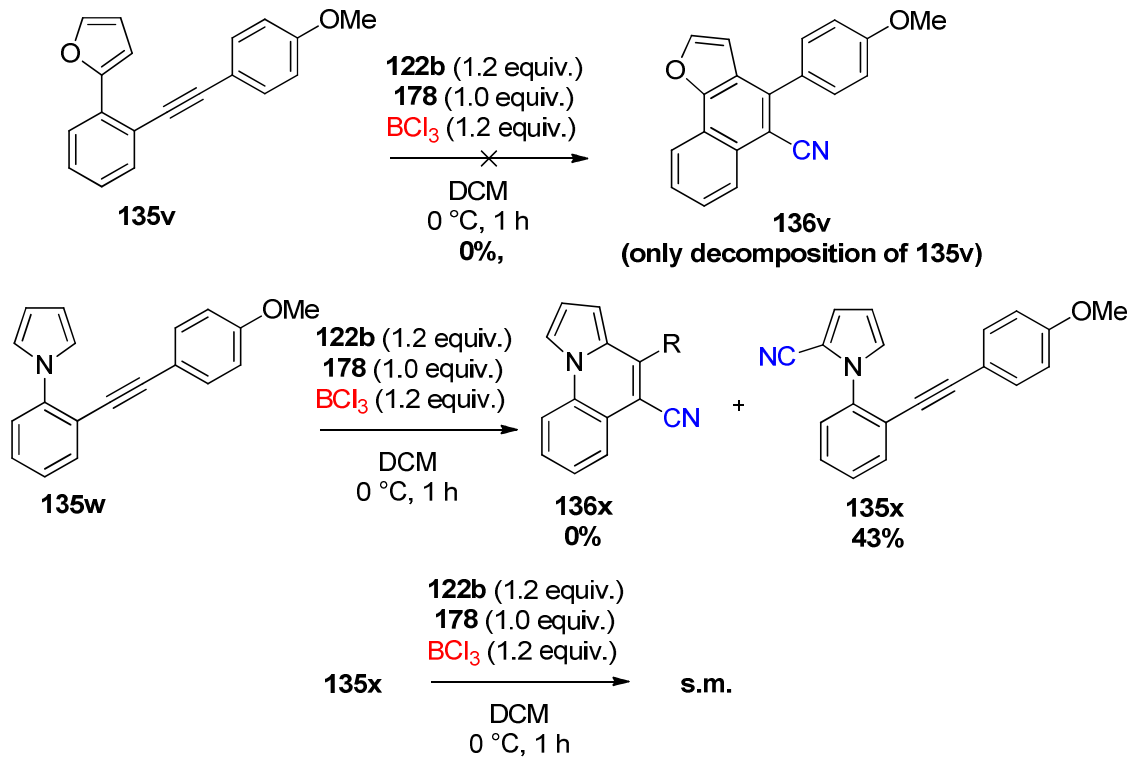


Figure 22. Cyanated heterocycles.

Similarly to the preparation of phenanthrenes already discussed, the synthesis of condensed heterocyclic structures showed in **Figure 22** could be envisaged by simply modifying the biphenyl framework used as starting material. Some attempts were then made to synthesize cyano-substituted naptho[1,2-*b*]furane (**136v**) and pyrrolo[1,2-

a]naphthalene(**136x**) from the corresponding substrates **135v** and **135w**, which were prepared following the reported procedures.[100,101] Unfortunately, in the first case no formation of naphtofurane product **136v** was observed, the starting material decomposed directly after the borane addition. In the second case, the only isolated product was compound **135x** resulted from cyanation of the pyrrole ring in position 2, in a similar way as previously reported in the group.[103] Re-submitting **135x** to the same reaction conditions again did not result in its further formation (**Scheme 103**).



Scheme 103. Attempted cyanative cyclization of heterocycle-substituted tolanes **135v** and **135w**.

4.3.3.3. Synthesis of helicenes.

Helicenes represent a group of poliaromatic helical systems that feature chiral axis. Their interesting electronic and optical properties make them unique for certain applications in material chemistry.[146] The scope of the cyanative cyclization could potentially be used for the metal-free synthesis of different types of substituted carbohelicenes.

Cyano-substituted [4]carbohelicenes (Figure 23).

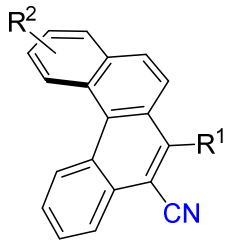
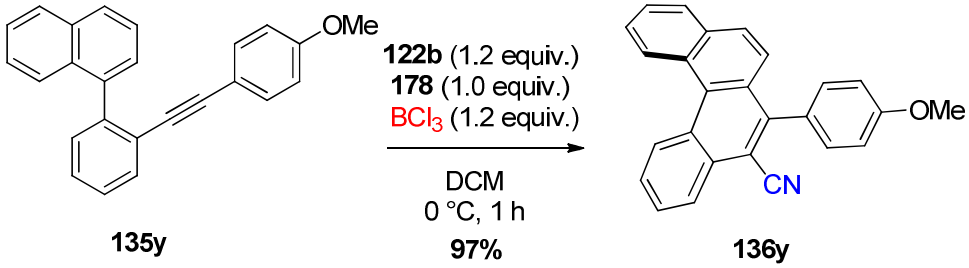


Figure 23. Cyanated [4]carbohelicenes.

To access cyano-substituted [4]carbohelicenes, the same approach as for the synthesis of phenanthrenes **135** was followed. Thus, acetylene **135y** was synthesized and then submitted to the cyanative cyclization conditions. The reaction successfully afforded product **136y** in an excellent isolated yield of 97% (**Scheme 104**). After recrystallization, its structure was verified by X-ray crystal structure analysis (**Figure 24**).



Scheme 104. Synthesis of **136y**.

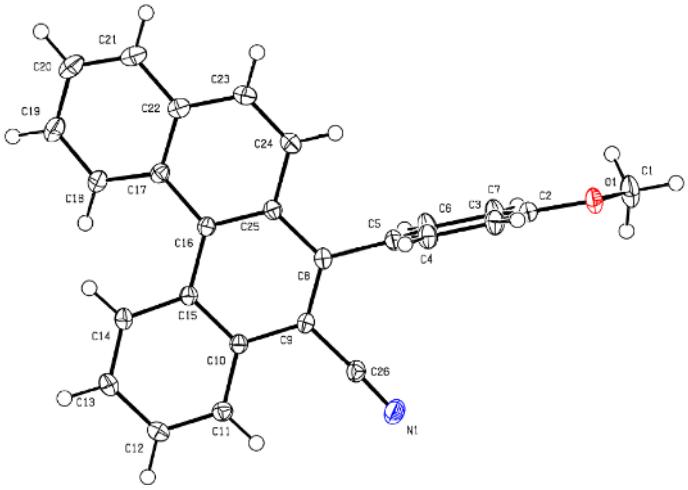


Figure 24. Structure of cyano-substituted [4]carbohelicene 136y in the crystal.

Cyano-substituted [5]carbohelicenes (Figure 25).

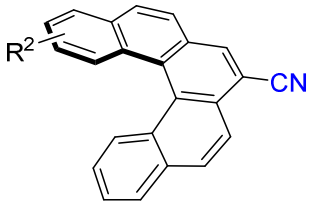
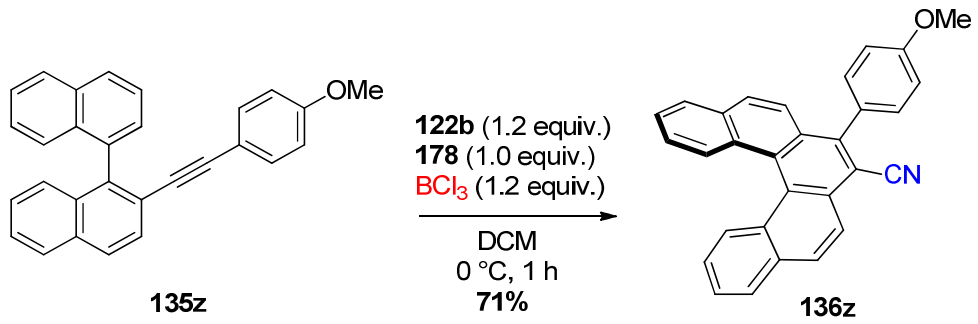


Figure 25. Cyanated [5]carbohelicene.

In a similar way, [5]carbohelicene **136z** was also synthetized from readily available substrate **135z** in a good yield as well (**Scheme 105**).



Scheme 105. Synthesis of cyanated [5]carbohelicene **136z**.

Cyano-substituted [6]carbohelicenes (Figure 26).

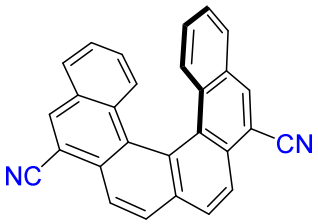
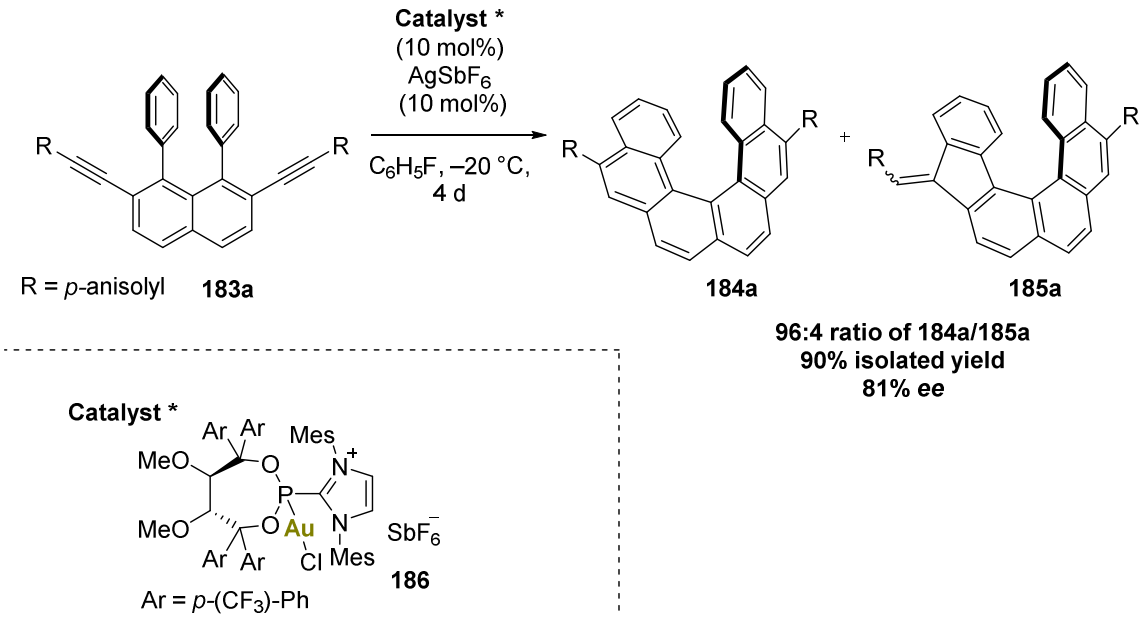


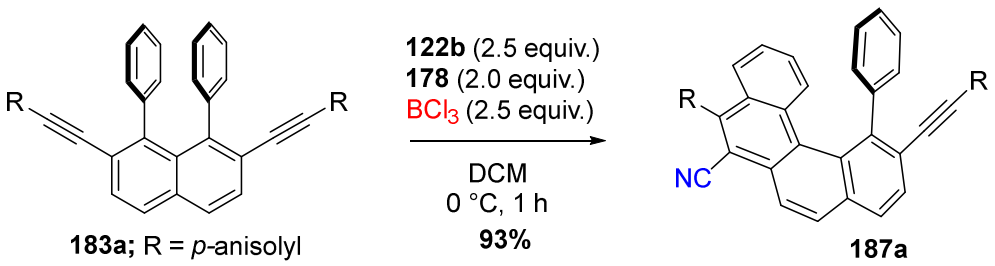
Figure 26. Cyanated [6]carbohelicene.

More synthetically interesting is the preparation of [6]carbohelicenes. Recently our research group published the enantioselective synthesis of [6]carbohelicenes **184** based on a double cycloisomerization of substrates **183** catalyzed by gold(I) catalyst coordinated to a chiral cationic phosphonite ligand **185** (**Scheme 106**).[99]



Scheme 106. Enantioselective synthesis of [6]carbohelicenes **184**.

Hence, substrate **183a** was prepared according to the published method[99] and tested in a double cyanative cyclization. Surprisingly, only monocyanated product **187a**, as confirmed by X-ray crystallography of the recrystallized compound, was formed in an excellent yield of 93% (**Scheme 107** and **Figure 27**).



Scheme 107. Synthesis of compound **187a**.

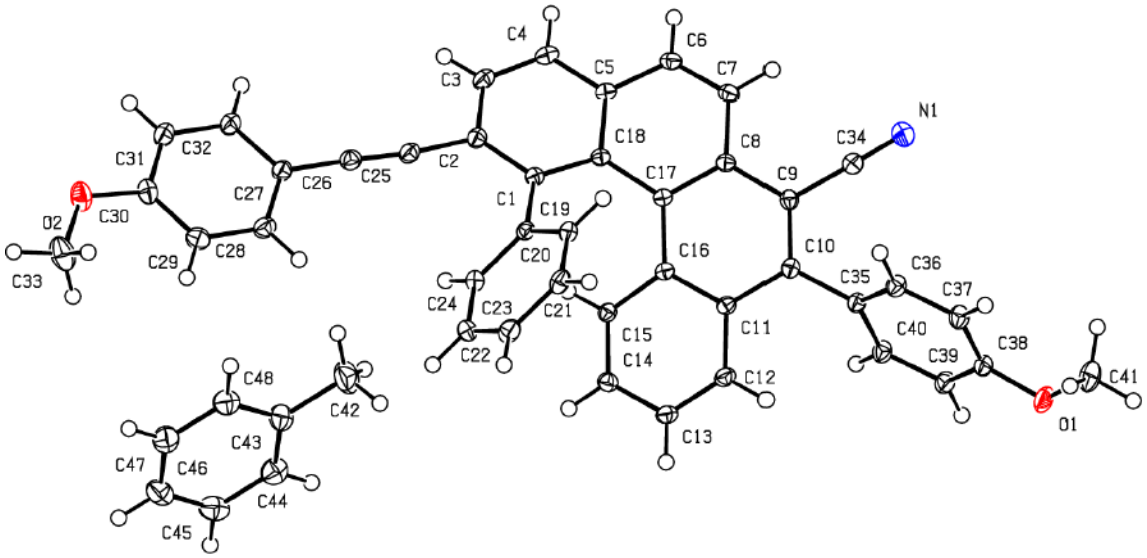
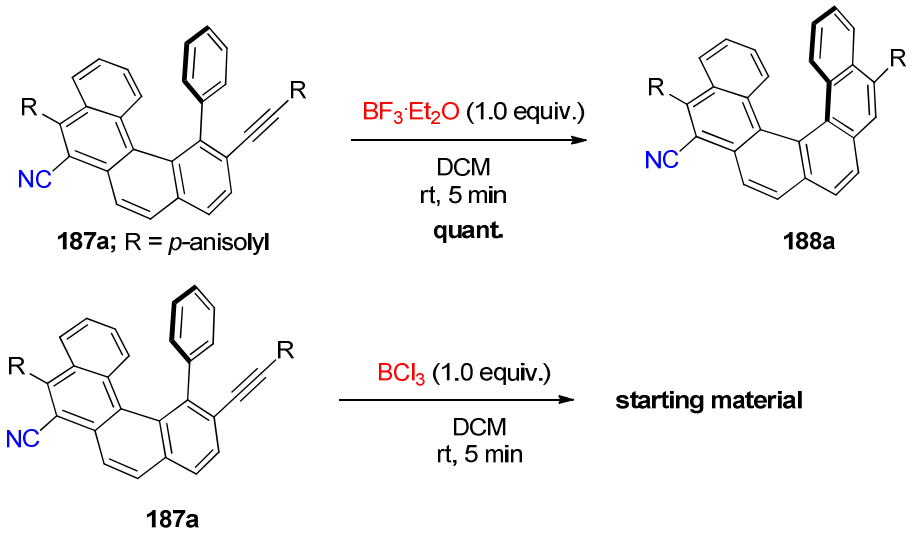


Figure 27. Structure of compound **187a** in the crystal.

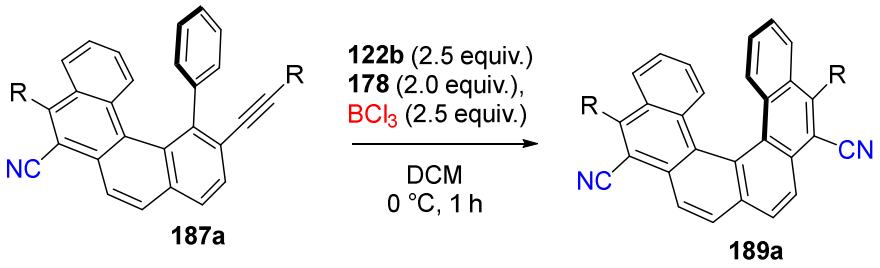
This unexpected result opened the door for the synthesis of [6]carbohelicenes, both in unsymmetric as well as asymmetric variants. To synthesize unsymmetric [6]carbohelicenes, **187a** needs to be reacted with a selected electrophile which is able to promote the second cyclization (H, Cl, Br, I, *etc*…). Moreover, as the second cyclization is the one that determines the enantioselectivity, using asymmetric methods can lead to the formation of [6]carbohelicenes in an enantioselective manner.[99]

As a proof of concept, employing stoichiometric amounts of $BF_3{\cdot}Et_2O$ as Lewis acid could successfully perform the cycloisomerization of intermediate **187a**, generating quantitative amounts of [6]carbohelicene **188a** (**Scheme 108**), thus implying that a chiral Lewis acid could successfully perform the same reaction in an enantioselective way.



Scheme 108. Synthesis of cyanated [6]carbohelicene **188a**.

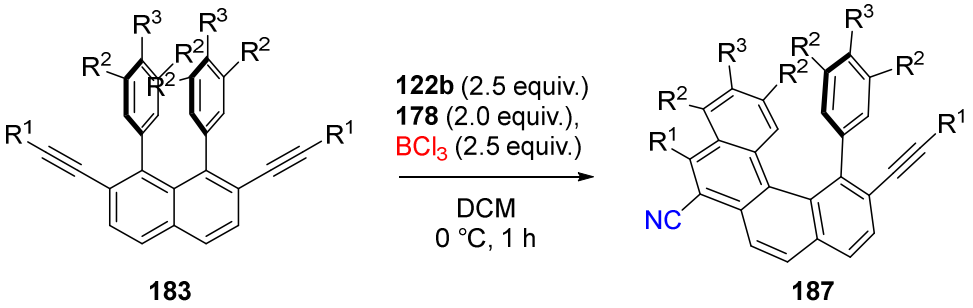
Interestingly the same transformation of **187a** could not be achieved using BCl_3 (**Scheme 108**); however, cyanative cyclization of **187a** appeared to be successful, resulting in the conversion of starting material to the dicyanated [6]carbohelicene **189a** (**Scheme 109**). Unfortunately, compound **189a** exhibited an extreme insolubility in all common solvents and could only be confirmed by High Resolution Mass Spectrometry.



R = *p*-anisolyl

Scheme 109. Synthesis of dicyanated [6]carbohelicene **189a**.

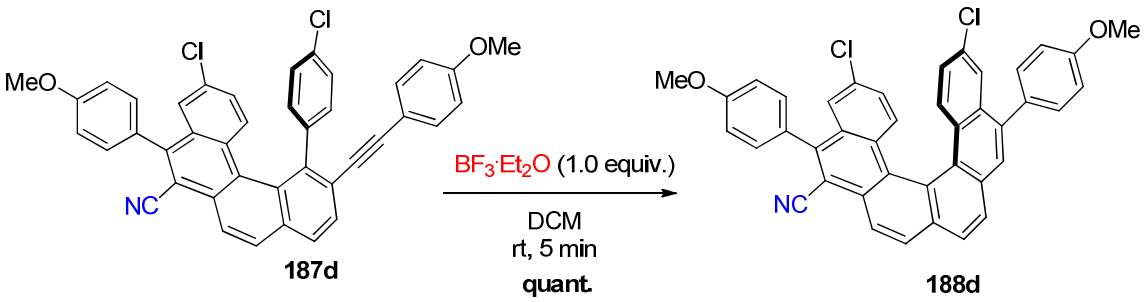
Continuing this study, differently substituted substrates were prepared and further tested under these conditions, affording in all the cases the corresponding cyclization products **187b–d** in poor to moderate yields (**Table 16, entries 1–3**). The re-isolation of unreacted starting materials **183** was possible as well.



Entry	Alkyne	R^1	R^2	R^3	Product	Isolated yield (%)
1	**183b**	*p*-anisolyl	Me	H	**187b**	**52**
2	**183c**	*p*-tolyl	H	Cl	**187c**	**18**
3	**183d**	*p*-anisolyl	H	Cl	**187d**	**47**

Table 16. Synthesis of [4]helicenes **187**.

Compound **187d** could be consequently virtually quantitative cycloisomerized upon treatment with $BF_3{\cdot}Et_2O$ using the same protocol as indicated above (**Scheme 110**).



Scheme 110. Synthesis of [6]carbohelicene **188d**.

4.3.3.4. Synthesis of pyrenes (Figure 28).

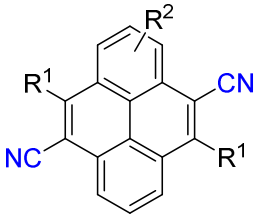
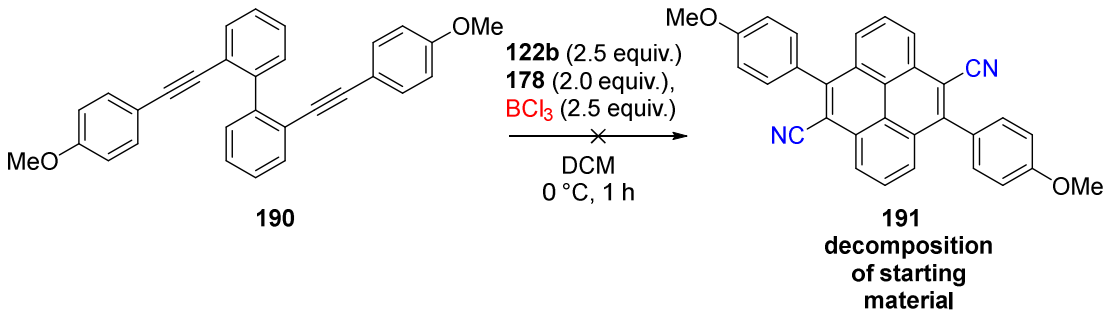


Figure 28. Cyanated pyrenes.

Diyne **190** was prepared with the idea of testing the double cyanation as for the synthesis of [6]carbohelicenes. In this case, however, decomposition of starting material was observed, and no formation of product **191** could be detected (**Scheme 111**).



Scheme 111. Attempted synthesis of dicyanated pyrene **191**.

4.3.3.5. Synthesis of non-aromatic cycles.

In all the cases shown so far, it was always involved an aromatization process, that probably makes the reaction to occur in such a fast fashion. Intrigued about whether this concept could be applied in a cyanative cyclization where no aromatization is involved, the following cycles were attempted to be synthesized:

5,6,7,8-Tetrahydro-2H-λ²-quinolines (Figure 29).

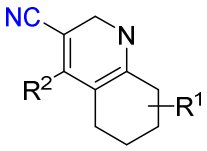
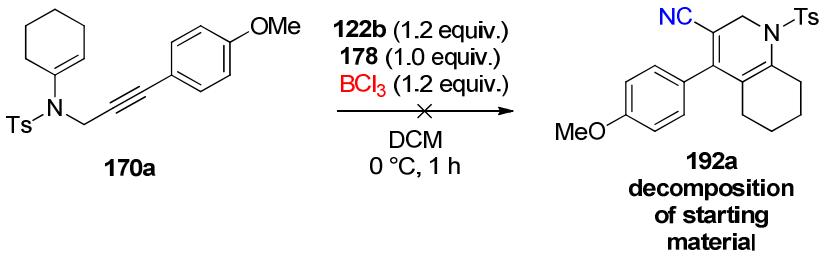


Figure 29. 5,6,7,8-Tetrahydro-2H-λ²-quinolines.

A number of cycloisomerizations are based on reorganization of ene-yne-type substrates, where a nucleophilic alkene fragment reacts with an activated triple bond which acts as the electrophile. To this family of substrates belongs also compound **170a**, which was prepared and then tested under the optimized conditions for cyanative cyclization. However, formation of the product **192a** was not indicated, as the starting material underwent decomposition (**Scheme 112**).



Scheme 112. Attempted synthesis of hexahydroquinoline **192a**.

2,3-Dihydro-1*H*-fluorenes (Figure 30).

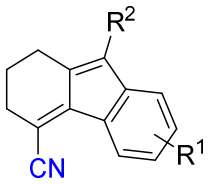
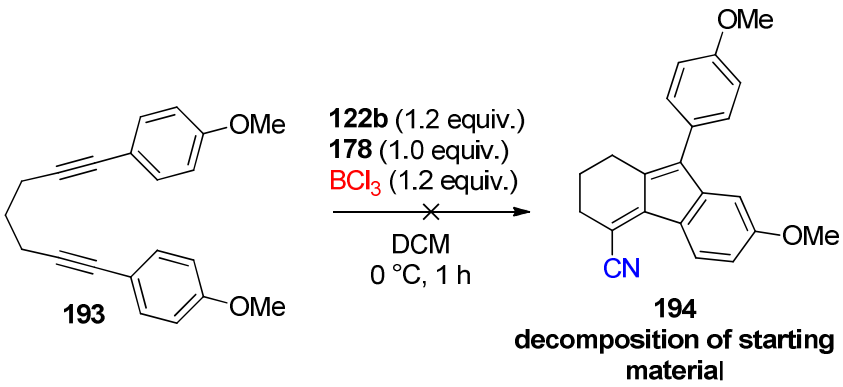


Figure 30. 2,3-dihydro-1H-fluorenes.

The next substrate investigated of the yne-yne type was dialkyne **193**. In this compound, one alkyne moiety can be activated with the Lewis acid, while the second triple bond may act as a nucleophile. Upon attempted cyanative cyclization of diyne **193**, complete decomposition of starting material was observed again (**Scheme 113**).



Scheme 113. Attempted synthesis of **194**.

1,2-Dihydronaphthalenes (Figure 31).

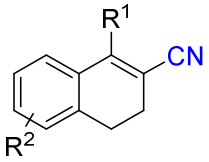
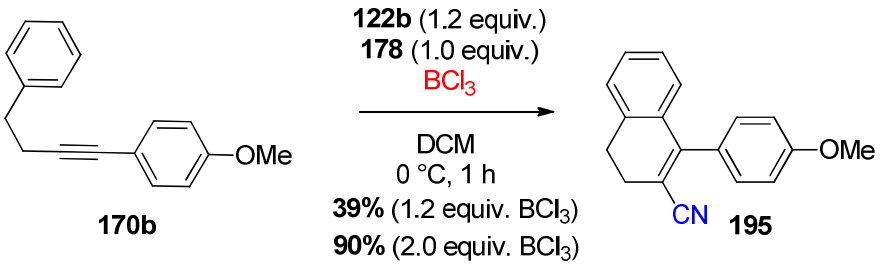


Figure 31. 1,2-Dihydronaphthalenes.

Since substrates of aryl-yne type proved to be more appropiate for the cyanative

cyclizations, alkyne **170b** was prepared and then used in cyanation under standard conditions. Product **195** was successfully isolated in poor yields (39%), and unreacted starting material was recovered. However, employment of borane in excess was enough to obtain the desired product in excellent yields (90%), as shown in **Scheme 114**. Structure of **195** was confirmed by X-ray crystal structure analysis (**Figure 32**).



Scheme 114. Synthesis of dihydronaphthalene **195**.

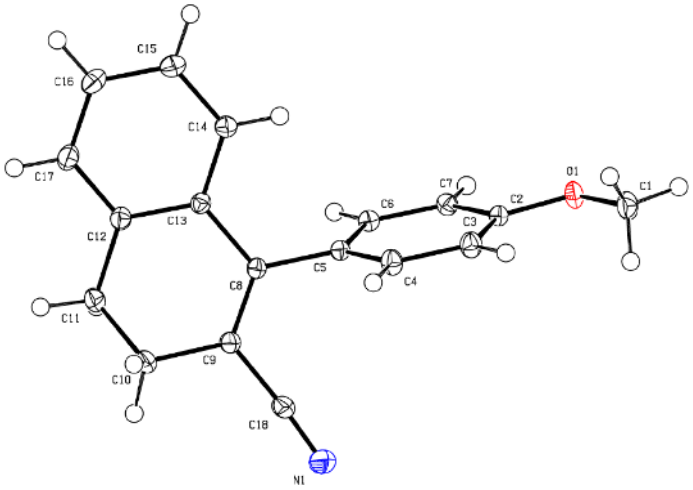


Figure 32. Structure of dihydronaphthalene **195** in the crystal.

2*H*-Chromenes (Figure 33).

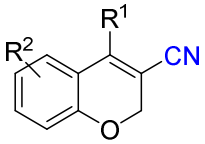
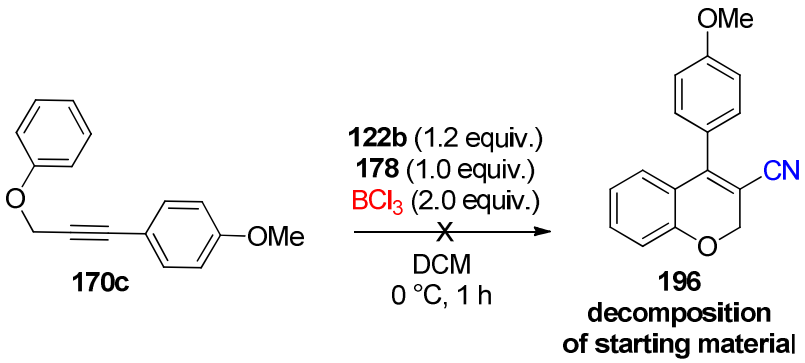


Figure 33. 2*H*-Chromenes.

Using the same idea as for the synthesis of 1,2-dihydronaphthalene **195**, the preparation of 2*H*-chromene **196** was attempted applying the starting material **170c** with an oxygen atom instead of methylene moiety. Unfortunately, this compound appeared ot to be

inappropriate for the transformation, as only decomposition of **170c** was detected (**Scheme 115**).



Scheme 115. Attempted synthesis of 2*H*-chromene **196**.

7-Dihydro-5*H*-benzo[7]annulene (Figure 34).

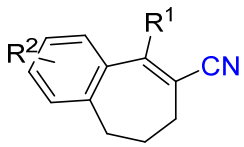
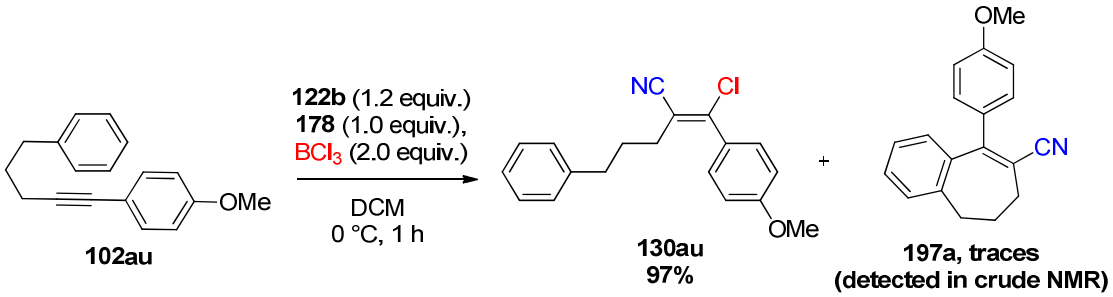


Figure 34. 7-Dihydro-5*H*-benzo[7]annulenes.

Mimicking the reaction for the 1,2-dihydronaphthalenes synthesis, one more methylene group was added to the framework of alkyne **170b**. When the reaction of this homologous compound **102au** was performed, only formation of chlorocyanated compound **130au** in an excellent isolated yield of 97% was observed predominantly, whereas the desired product **197a** was detected only as traces (**Scheme 116**).



Scheme 116. Attempted synthesis of dihydroannulene **197a**.

5*H*-Dibenzo[*a*,*d*][7]annulene (Figure 35).

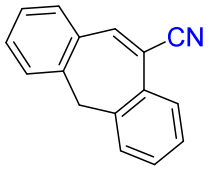
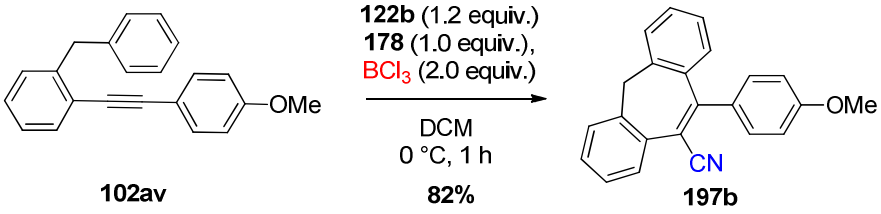


Figure 35. 5*H*-Dibenzo[*a*,*d*][7]annulene.

Attachment of a second aromatic ring in the propper position but separated by a methylene unit, as in substrate **102av**, promotes the formation of the desired 7-membered ring. Thus, cyanative cyclization of **102av** furnished the product **197b** in very good isolated yield (82%) (**Scheme 117**), which structure was confirmed by X-Ray crystallography (**Figure 36**).



Scheme 117. Synthesis of dibenzo[*a*,*d*][7]annulene **197b**.

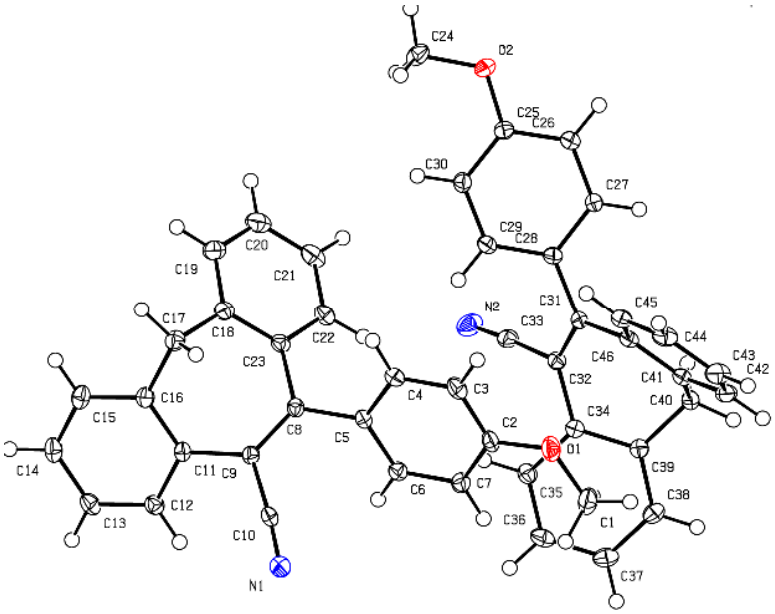
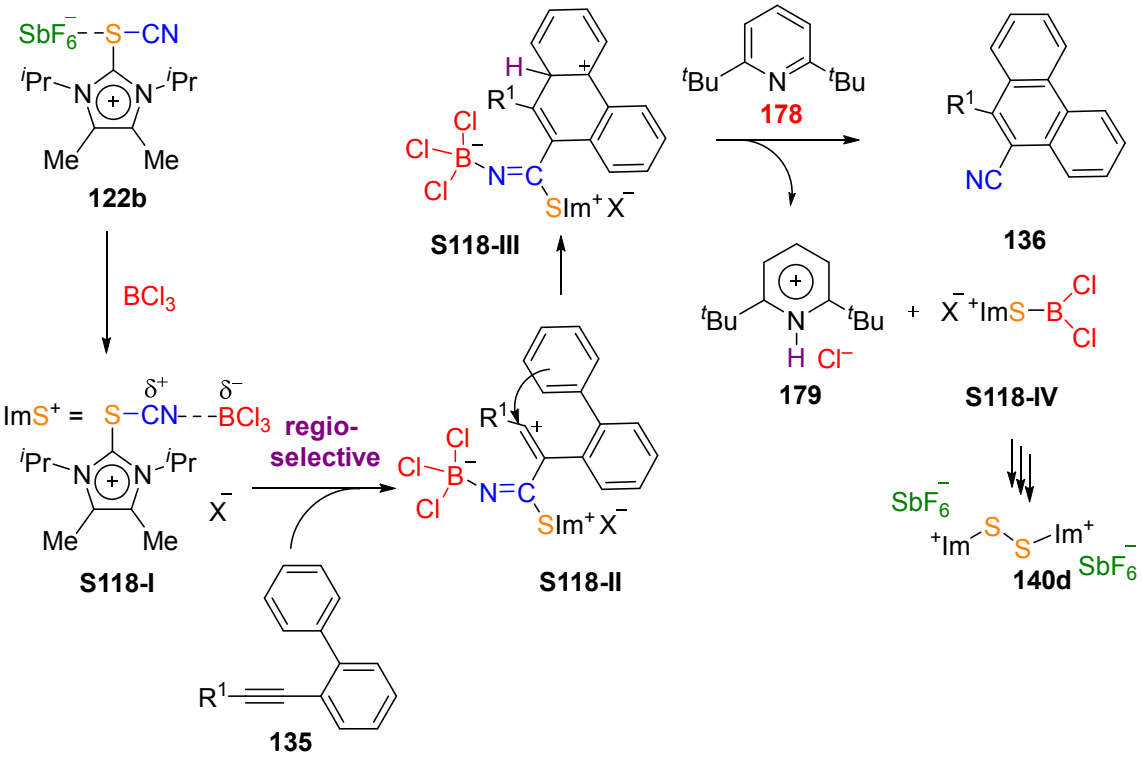


Figure 36. Structure of dibenzo[*a*,*d*][7]annulene **197b** in the crystal.

4.3.4. Proposed mechanism.

By analyzing the experience gained from all the experiments discussed above and taking into account the information on the chlorocyanation of alkynes, a plausible mechanistic rationalization for the cyanative cyclization of alkynes can be proposed. The transformation starts with activation of the cyanating reagent **122b** by Lewis acid affording a complex **S118-I**, which underwent a regioselective electrophilic addition to the triple bond forming intermediate **S118-II**. In the next step, an electrophilic Friedel-Crafts-type attack on the aromatic ring furnished intermediate **S118-III**. Aromatization of **S118-III**, which is facilitated by action of 2,6-di-*tert*-butylpyridine (**178**) as a base, afforded the corresponding cyanated products **136**. On this stage, pyridinium salt **179** and, probably, boreneylthioimidazolium **S118-IV** are formed. The latter is presumably a parent compound for the formation of isolated dithiouronium disulfide **140d** (**Scheme 118**).



Scheme 118. Proposed mechanic rationalization of the cyanative cyclization.

Some conclusions can be derived from the proposed mechanism. Upon direct comparison with the chlorocyanation reaction one can conclude, that both start in exactly the same

way, differentiating at the stage of nucleophilic addition. The latter, in fact, is a competition between trapping the cationic center with an aromatic moiety followed by aromatization and trapping with a chlorine atom associated with the BC_3 fragment (**Figure 37**).

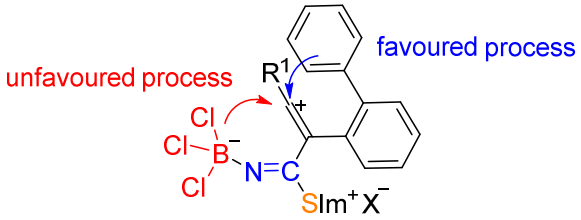
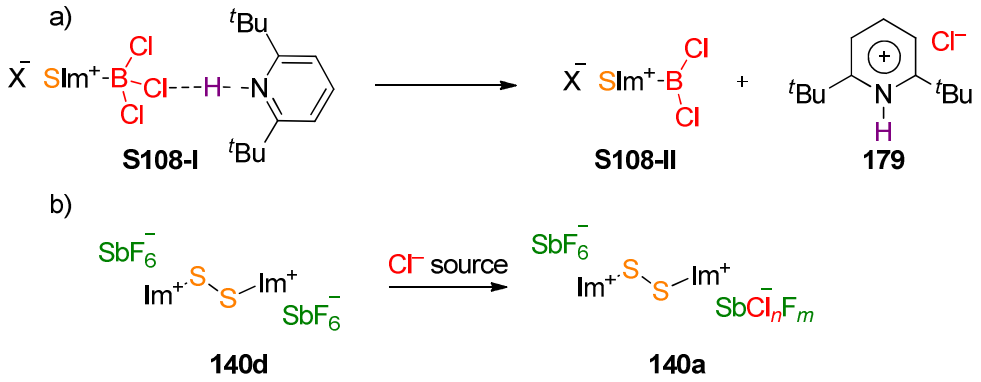


Figure 37. Selectivity of the process.

Extraction of a chlorine atom from the borane would impede the recovery of the Lewis acid in a catalytic process, explaining why stoichiometric amounts of Lewis acid are employed (**Scheme 119a**). It is also notable that no F^-/Cl^- counterion exchange was observed in this reaction. This might indicate that this process occurs in a late stage as a side reaction in already formed dithiouronium disulfide is (**Scheme 119b**).

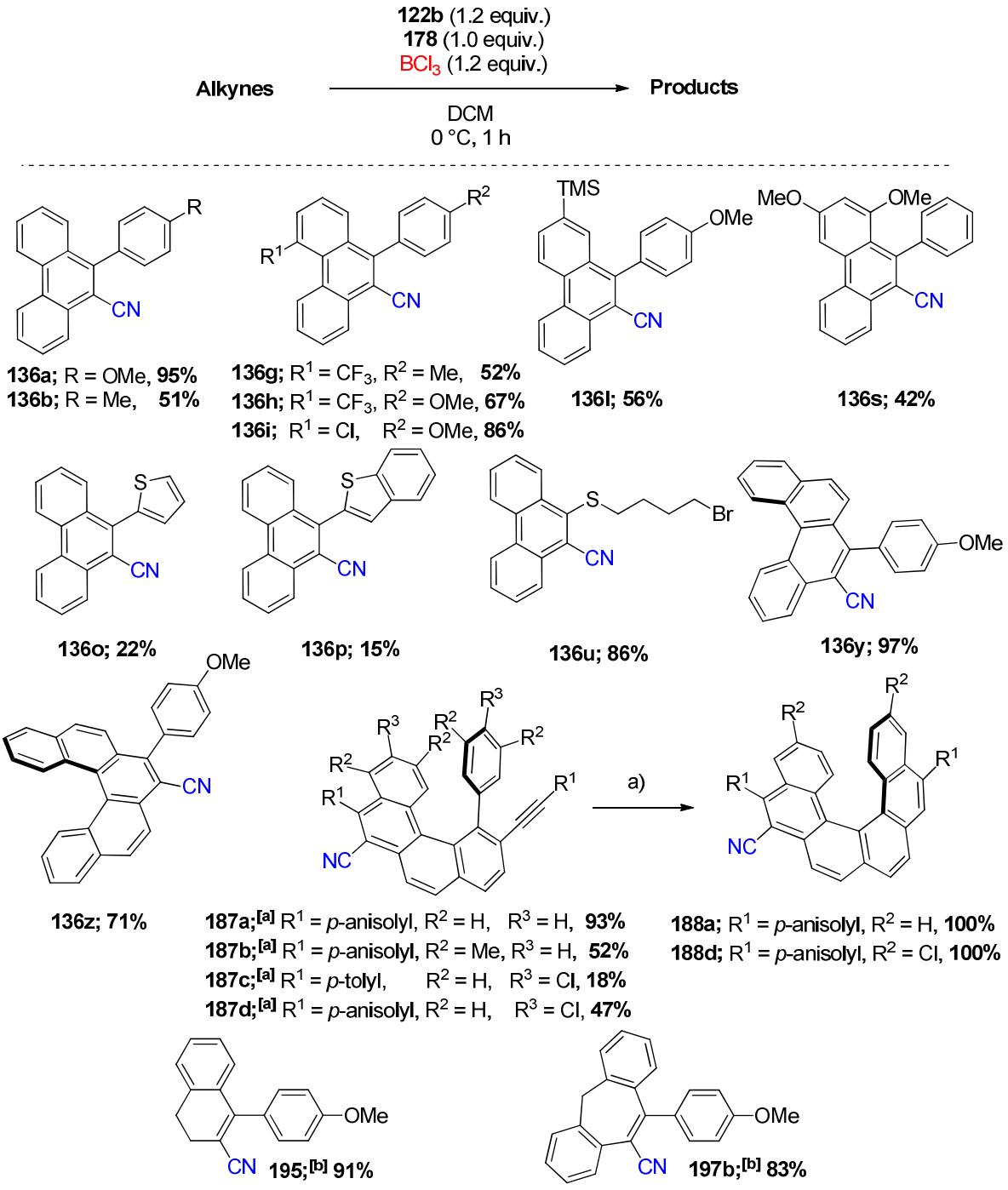


Scheme 119. Mechanistic aspects.

4.3.5. Summary.

As an extension of the twofold functionalization of alkynes using electrophilic cyanating reagents, a new methodology for the formation of various types of cyanated rings has been developed. The process is metal-free and proceeds with total regioselectivity when it is combined with stoichiometric amounts of Lewis acid. Thus, the transformation was successfully employed for the synthesis of phenanthrenes **136** with different substitution patterns, synthesis of [4]-, [5]- and [6]-carbohelicenes **136** and **188**, 1,2-dihydronaphthalenes **195** and 5*H*-dibenzo[*a*,*d*][7]annulenes **197b**, as summarized in **Scheme 120**. This process paves the way for the synthesis of plethora of organic cycles – constituents

of natural compounds and other practically useful products.



Scheme 120. Cyanative cyclization scope. [a] 2.5 equiv. of BCl_3 and 2.5 equiv. of **122b** were employed. [b] 2.0 equiv. of BCl_3 were employed. Reaction conditions of a) 1.0 equiv. of $BF_3{\cdot}Et_2$, DCM (1 mL), rt, 5 min.

5. Conclusion.

The ability of electrophilic sulfur imidazolium thiocyanates salts to serve as a remarkable source of cyano groups, thus promoting cyanations of internal and terminal alkynes. The methods described are performed under mild conditions in a metal-free environment, making these type of salts as interesting reagents for further investigations in the field.

6. Experimental.

6.1. Instrumentation and chemicals.

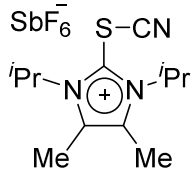
All solvents used in reactions with hydrolysis-sensitive substances (THF, dichloromethane, toluene) were purified with the MBraun Solvent Purification System (SPS) (or by distillation over the drying agents as indicated below) and stored under a protective gas atmosphere. Anhydrous ethanol was supplied by Fisher Chemicals and used without further purification. All reactions were carried out using pre-dried glassware under Ar atmosphere unless otherwise stated. IR: Nicolet FT-7199, JASCO FT-4100 spectrometers with an ATR measuring device, software OPUS 6, wavenumbers in cm^{-1}. Microwave: Biotage Initatior. MS (EI): Finnigan MAT 8200 (70 eV), ESIMS: Finnigan MAT 95; accurate mass determinations: Bruker APEX III FT-MS (7 T magnet). NMR: Spectra were recorded on a Bruker AV 500, 400 or DPX 300; ^{1}H and ^{13}C chemical shifts (δ) are given in ppm with TMS as a standard, coupling constants (*J*) in Hz. The residual solvent signals were used as references, and the chemical shifts converted to the TMS scale. Flash chromatography was performed on Merck 60 silica gel (40–63 µm). Thin-layer chromatography (TLC) analysis was performed using Merck silica gel 60 F254 TLC plates and visualized by UV irradiation and/or ceric ammonium molybdate, $KMnO_4$ or *p*-anysaldehyde dip.

Compounds **109b**,[103] and alkynes **102a**, **102b**, **102f**, **102u**, **102z**,[108] **102e**, **102l**,[110] **102g**, **102n**,[111] **102h**, **102j**, **102k**,[112] **102m**,[113] **102w**,[114] **102ao**,[116] **102d**,[147a] **102ab**,[147b] **102aa**,[147c] **102ad**,[147d] **102ag**,[147e] **102o**[147f] and **102p**[147i] were prepared accordingly to previously published procedures (see below). All commercially available compounds (Acros, ABCR, Alfa Aesar, Aldrich, Fluorochem) were used as received.

6.2. Regio- and stereoselective chlorocyanation of alkynes.

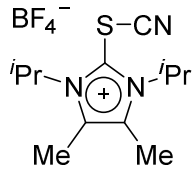
6.2.1. Synthesis of starting materials.

1,3-Diisopropyl-4,5-dimethyl-2-thiocyanato-1*H*-imidazol-3-ium Hexafluoroantimonate (122b)



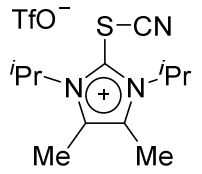
1,3-Diisopropyl-4,5-dimethyl-2-thiocyanato-1*H*-imidazol-3-ium bromide (**109b**) (9.115 g, 28.64 mmol) and sodium hexafluoroantimonate (8.899 g, 34.39 mmol, 1.2 equiv.) were charged into a round-bottomed flask and solved in 50 ml of DCM. The reaction mixture was stirred overnight at room temperature. The solid was filtered off; the mother liquor was concentrated under vacuum and the residue redissolved in acetonitrile. The solution was filtered and concentrated under vacuum again. The residue solid was washed with methanol affording product **122b** as a pale yellow solid (10.053 g, 21.20 mmol, **74%**). ^{1}H NMR (400 MHz, CD_3CN, ppm) δ = 1.64 (12H, d, *J* = 7.0 Hz), 2.40 (6H, s), 5.19 (2H, hept, *J* = 6.9 Hz). ^{13}C NMR (101 MHz, CD_3CN, ppm) δ =10.7, 20.9, 55.1, 106.8, 124.7, 133.7. ^{19}F NMR (282 MHz, CD_3CN) δ= –124.05 (sext, $J_{F-^{121}Sb}$ = 1947 Hz). IR (neat, cm^{-1}) = 905, 1114, 1139, 1217, 1381, 1397, 1460, 1600, 2173, 2999. HRMS: calcd. for $C_{12}H_{20}N_3S^+$ $[M–SbF_6]^+$ = 238.1372; found = 238.1372.
The spectral data are identical to those reported in the literature.[103]

1,3-Diisopropyl-4,5-dimethyl-2-thiocyanato-1*H*-imidazol-3-ium Tetrafluoroborate (122c)



Compound **109b** (1000 mg, 3.14 mmol) and sodium tetrafluoroborate (346 mg, 3.15 mmol, 1.0 equiv) and DCM (15 ml) were charged into a round-bottomed flask. The reaction mixture was stirred for 3 hours at room temperature. The solid was filtered off; the mother liquor was concentrated under vacuum and the residue solid was washed with diethyl ether affording product **122c** as a pale yellow solid (998 mg, 3.01 mmol, **98%**). ^{1}H NMR (500 MHz, CD_3CN, ppm) δ = 1.76 (12H, d, *J* = 7.1 Hz), 2.43 (6H, s), 5.41 (2H, hept, *J* = 7.0 Hz). ^{13}C NMR (101 MHz, CD_3CN, ppm) δ = 10.9, 21.0, 55.2, 107.7, 130.6. ^{11}B NMR (128 MHz, $CDCl_3$, ppm) δ = –1.5. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ = –153.0, –153.0.

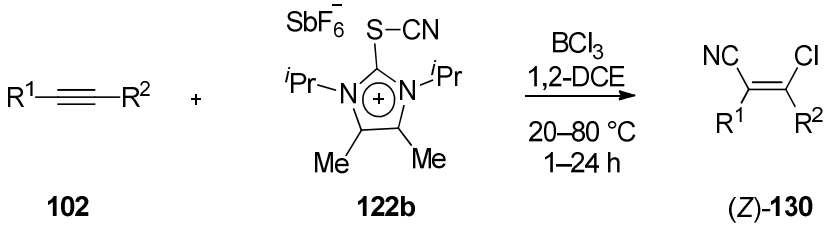
1,3-Diisopropyl-4,5-dimethyl-2-thiocyanato-1*H*-imidazol-3-ium Trifluoromethylsulfonate (122d)



Compound **109b** (1000 mg, 3.14 mmol) and potassium trifluoromethanesulfonate (592 mg, 3.16 mmol, 1.0 equiv) were charged in a round-bottomed flask and solved in 15 ml of DCM. The reaction mixture was stirred for 3 hours at room temperature. The solid was filtered off; the mother liquor was concentrated under vacuum and the residue solid was washed with diethyl ether affording product **122d** as a pale yellow solid (1.213 g, 3.13 mmol, **99%**). ^{1}H NMR (500 MHz, CD_3CN, ppm) δ = 1.63 (12H, d, *J* = 7.1 Hz), 2.39 (6H, s), 5.19 (2H, hept, *J* = 7.1 Hz). ^{13}C NMR (126 MHz, CD_3CN, ppm) δ = 10.8, 20.9, 55.2, 106.7, 122.1 (d, $J_{C\text{-}F}$ = 323 Hz), 133.8. ^{19}F NMR (470 MHz, $CDCl_3$, ppm) δ = –79.3. IR (neat, cm^{-1}): 660, 752, 908, 1027, 1116, 1141, 1222, 1251, 1277, 1380, 1397, 1463, 1602, 2106, 2297. HRMS: calcd. for $C_{12}H_{20}N_3S^+$ [M]$^+$ = 238.1372; found = 238.1376

6.2.2. Synthesis of new products.

6.2.2.1. Synthesis of chloroacrylonitriles 130.

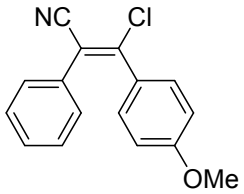


102 **122b** (*Z*)-**130**

Scheme 121. Chlorocyanation of alkynes (*Z*)-**102**.

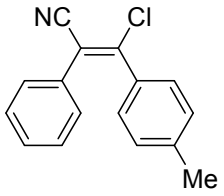
General procedure (GP1): A dry Schlenk flask was charged with the corresponding alkyne **102** (1.0 equiv.) and 1,3-diisopropyl-4,5-dimethyl-2-thiocyanato-1*H*-imidazol-3-ium Hexafluoroantimonate (**122b**) (1.3 equiv.). The mixture was suspended in 1,2-DCE (*ca*. 1 mL), and a 1 M solution of BCl_3 or BBr_3 in DCM (2.0 equiv.) was added dropwise. The reaction mixture was stirred at the corresponding temperature for the indicated time. All volatiles were removed under reduced pressure and finally under high vacuum, then the remaning solid was suspended in ethyl acetate, filtered through a Silica pad and concentrated *in vacuo*. The mixture was further purified by column chromatography (*n*-hexane /EtOAc) affording the corresponding products (*Z*)-**130**.

(*Z*)-3-Chloro-3-(4-methoxyphenyl)-2-phenylacrylonitrile [(*Z*)-130a]



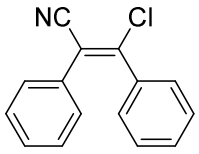
Using GP1, compound (*Z*)-**130a** was prepared from **102a** (115 mg, 0.55 mmol), **122b** (341 mg, 0.72 mmol) and trichloroborane (1.11 ml, 1 M in DCM, 1.11 mmol) in 1,2-DCE (1.11 ml) [rt, 1 h] as yellow crystals (147 mg, 0.54 mmol, **98%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 3.79 (3H, s), 6.72 – 6.77 (2H, m), 7.19 – 7.27 (7H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 55.5, 112.5, 113.9, 118.0, 127.4, 128.9, 129.0, 129.4, 131.5, 133.1, 147.0, 161.4. IR (neat, cm^{-1}): 587, 695, 759, 819, 839, 901, 1026, 1173, 1252, 1444, 1506, 1603, 2213, 2839, 3058. HRMS: calcd. for $C_{16}H_{12}ClNO^+$ $[M]^+$ = 269.0607; found = 269.0601.

(*Z*)-3-Chloro-2-phenyl-3-(*p*-tolyl)acrylonitrile [(*Z*)-130b]



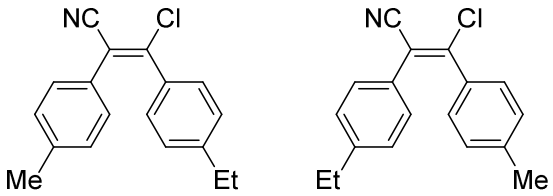
Using GP1, compound (*Z*)-**130b** was prepared from **102b** (100 mg, 0.52 mmol), **122b** (321 mg, 0.68 mmol) and trichloroborane (1.04 ml, 1 M in DCM, 1.04 mmol) in 1,2-DCE (1.04 ml) [60 °C, 3 h] as a pale yellow solid (66 mg, 0.26 mmol, **50%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 2.33 (3H, s), 7.05 – 7.08 (2H, m), 7.16 – 7.29 (7H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 21.5, 113.4, 117.6, 128.8, 129.0, 129.1, 129.2, 129.4, 132.3, 132.7, 141.1, 147.1. IR (neat, cm^{-1}): 511, 548, 652, 693, 757, 808, 902, 1020, 1183, 1444, 1507, 1588, 1606, 2213, 2919. HRMS: calcd. for $C_{16}H_{12}ClN^+$ $[M]^+$ = 253.0658; found = 253.0656.

(*Z*)-3-Chloro-2,3-diphenylacrylonitrile [(*Z*)-130c]



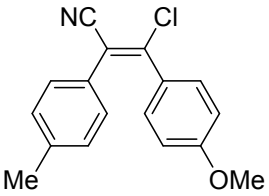
Using GP1, compound (*Z*)-**130c** was prepared from **102c** (200 mg, 1.12 mmol), **122b** (693 mg, 1.46 mmol) and trichloroborane (2.25 ml, 1 M in DCM, 2.25 mmol) in 1,2-DCE (2.25 ml) [rt, 1 h] as a a pale yellow solid (58 mg, 0.24 mmol, **22%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 7.16 – 7.37 (10H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 114.2, 117.4, 128.5, 128.8, 129.1, 129.3, 129.5, 130.5, 132.5, 135.3, 146.9. IR (neat, cm^{-1}): 507, 548, 658, 690, 752, 825, 898, 1157, 1203, 1271, 1443, 1488, 1588, 2213, 3066. HRMS: calcd. for $C_{15}H_{11}ClN^+$ $[M+H]^+$ = 240.0575; found = 240.0569. The spectral data correspond to those reported in the literature.[126]

(*Z*)-3-Chloro-3-(4-ethylphenyl)-2-(*p*-tolyl)acrylonitrile [(*Z*)-130d, left] and(*Z*)-3-chloro-2-(4-ethylphenyl)-3-(*p*-tolyl)acrylonitrile [(*Z*)-130d', right]



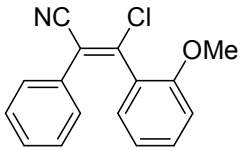
Using GP1, compounds (*Z*)-**130d** and (*Z*)-**130d'** were prepared from **102k** (87 mg, 0.40 mmol), **122b** (244 mg, 0.51 mmol) and trichloroborane (0.79 ml, 1 M in DCM, 0.79 mmol) in 1,2-DCE (0.79 ml) [rt, 1 h] as a pale yellow oil (77 mg of a 1/1 regioisomer mixture, 0.27 mmol, **68%**) after flash chromatography (*n*-hexane/EtOAc 9:1). (*Z*)-**130d:** ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 1.21 (3H, t, *J* = 7.6 Hz), 2.33 (3H, s), 2.61 (2H, m), 7.06 – 7.22 (6H, m), 7.31 – 7.36 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 15.6, 31.3, 28.7, 113.5, 117.8, 128.0, 129.2, 129.5, 129.6, 129.9, 132.8, 139.2, 146.4, 147.2. (*Z*)-**130d':** ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 1.20 (3H, t, *J* = 7.6 Hz), 2.30 (3H, s), 2.59 (2H, m), 7.06 – 7.22 (6H, m), 7.31 – 7.36 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 15.2, 21.5, 28.6, 113.5, 117.8, 128.3, 129.2, 129.2, 129.5, 130.0, 132.6, 141.0, 145.4, 146.3. IR (neat, cm^{-1}): 551, 759, 813, 903, 1019, 1058, 1185, 1273, 1413, 1455, 1510, 1587, 1607, 2216, 2966. HRMS: calcd. for $C_{18}H_{17}ClN^+$ $[M+H]^+$ = 282.1044; found = 282.1042.

(*Z*)-3-Chloro-3-(4-methoxyphenyl)-2-(*p*-tolyl)acrylonitrile [(*Z*)-130e]



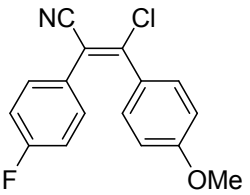
Using GP1, compound (*Z*)-**130e** was prepared from **102e** (59 mg, 0.27 mmol), **122b** (164 mg, 0.35 mmol) and trichloroborane (0.53 ml, 1 M in DCM, 0.53 mmol) in 1,2-DCE (0.53 ml) [rt, 1 h] as a pale yellow solid (62 mg, 0.22 mmol, **81%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 2.30 (3H, s), 3.19 (3H, s), 6.71 – 6.80 (2H, m), 7.02 – 7.13 (4H, m), 7.20 – 7.29 (2H, m).^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 21.3, 55.4, 112.5, 113.9, 118.0, 127.5, 129.2, 129.6, 130.1, 130.8, 131.4, 139.1, 146.1, 161.2. IR (neat, cm^{-1}): 587, 729, 768, 812, 829, 902, 1027, 1116, 1173, 1252, 1300,, 1504, 1601, 2213, 2922. HRMS: calcd. for $C_{17}H_{14}ClNO^+$ $[M]^+$ = 283.0764; found = 283.0774.

(*Z*)-3-Chloro-3-(2-methoxyphenyl)-2-phenylacrylonitrile [(*Z*)-130g]



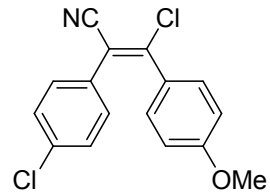
Using GP1, compound (*Z*)-**130g** was prepared from **102g** (63 mg, 0.30 mmol), **122b** (187 mg, 0.39 mmol) and trichloroborane (0.61 ml, 1 M in DCM, 0.61 mmol) in 1,2-DCE (0.61 ml) [rt, 1 h] as a pale yellow solid (75 mg, 0.28 mmol, **93%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 3.67 (3H, s), 6.90 (1H, dd, *J* = 8.3, 1.0. Hz), 7.02 (1H, td, *J* = 7.5, 1.0 Hz), 7.23 – 7.35 (6H, m), 7.45 (1H, ddd, *J* = 8.4, 7.4, 1.0 Hz). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 55.4, 111.5, 116.2, 117.3, 120.8, 124.8, 128.2, 128.9, 130.3, 132.1, 133.1, 144.1, 156.1. IR (neat, cm^{-1}): 655, 695, 754. 904, 1022, 1254, 1434, 1463, 1488, 1592, 1603, 2218, 2341, 2360, 2837. HRMS: calcd. for $C_{16}H_{13}ClNO^+$ $[M+H]^+$ = 270.0680; found = 270.0679.

(*Z*)-3-Chloro-2-(4-fluorophenyl)-3-(4-methoxyphenyl)acrylonitrile [(*Z*)-130j]



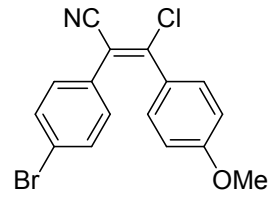
Using GP1, compound (*Z*)-**130j** was prepared from **102j** (120 mg, 0.53 mmol), **122b** (327 mg, 0.69 mmol) and trichloroborane (1.06 ml, 1 M in DCM, 1.06 mmol) in 1,2-DCE (1.06 ml) [rt, 1 h] as a pale yellow solid (117 mg, 0.41 mmol, **76%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 3.79 (1H, s), 6.74 – 6.79 (2H, m), 6.91 – 6.98 (2H, m), 7.15 – 7.24 (4H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 55.5, 111.3, 114.0, 116.1 (d, *J* = 22.0 Hz), 117.7, 127.0, 129.1 (d, *J* = 3.6 Hz), 131.3 (d, *J* = 8.4 Hz), 131.4, 147.2, 161.0, 161.4, 164.3. ^{19}F NMR (282 MHz, $CDCl_3$, ppm) δ = –110.9. IR (neat, cm^{-1}): 524, 587, 827, 902, 1026, 1160, 1174, 1231, 1253, 1301, 1461, 1504, 1599, 2214, 2962. HRMS: calcd. for $C_{16}H_{11}ClFNO^+$ $[M]^+$ = 287.0513; found = 287.0520.

(*Z*)-3-Chloro-2-(4-chlorophenyl)-3-(4-methoxyphenyl)acrylonitrile [(*Z*)-130k]



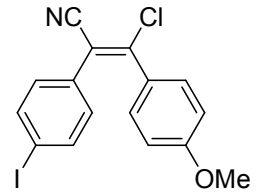
Using GP1, compound (*Z*)-**130k** was prepared from **102k** (42 mg, 0.17 mmol), **122b** (107 mg, 0.23 mmol) and trichloroborane (0.35 ml, 1 M in DCM, 0.35 mmol) in 1,2-DCE (0.35 ml) [rt, 1 h] as a pale yellow solid (52 mg, 0.17 mmol, **98%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 3.80 (3H, s), 6.75 – 6.81 (2H, m), 7.11 – 7.16 (2H, m), 7.19 – 7.25 (4H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 55.5, 111.3, 114.1, 117.5, 127.0, 129.2, 130.6, 131.4, 131.5, 135.0, 147.6, 161.5. (neat, cm^{-1}): 633, 721, 813, 909, 1012, 1026, 1089, 1176, 1254, 1302, 1508, 1582, 1603, 2209, 2957. HRMS: calcd. for $C_{16}H_{11}Cl_2NO^+$ $[M]^+$ = 303.0218; found = 303.0216.

(*Z*)-3-Chloro-2-(4-bromophenyl)-3-(4-methoxyphenyl)acrylonitrile [(*Z*)-130l]



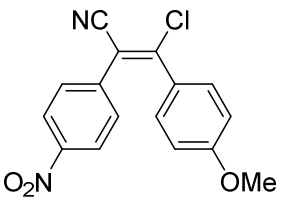
Using GP1, compound (*Z*)-**130l** was prepared from **102l** (91 mg, 0.32 mmol), **122b** (195 mg, 0.41 mmol) and trichloroborane (0.63 ml, 1 M in DCM, 0.63 mmol) in 1,2-DCE (0.30 ml) [rt, 1 h] as a white solid (88 mg, 0.25 mmol, **78%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 3.80 (3H, s), 6.76 – 6.79 (2H, m), 7.06 – 7.09 (2H, m), 7.20 – 7.23 (2H, m), 7.37 – 7.40 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 55.5, 111.3, 114.1, 117.5, 123.3, 126.9, 130.9, 131.4, 132.0, 132.2, 147.8, 161.6. IR (neat, cm^{-1}): 548, 804, 1007, 1027, 1074, 1173, 1248, 1458, 1485, 1507, 1604, 1729, 2209, 2922, 2922. HRMS: calcd. for $C_{16}H_{11}BrClNO^+$ $[M]^+$ = 346.9713; found = 346.9725.

(*Z*)-3-Chloro-2-(4-iodophenyl)-3-(4-methoxyphenyl)acrylonitrile [(*Z*)-130m]



Using GP1, compound (*Z*)-**130m** was prepared from **102m** (48 mg, 144 µmol), **122b** (89 mg, 0.19 mmol) and trichloroborane (0.29 ml, 1 M in DCM, 290 µmol) in 1,2-DCE (0.29 ml) [rt, 1 h] as a white solid (38 mg, 96 µmol, **67%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.81 (3H, s), 6.76 – 6.80 (2H, m), 6.92 – 6.95 (2H, m), 7.20 – 7.24 (2H, m), 7.57 – 7.60 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ = 55.5, 95.1, 111.5, 114.1, 117.5, 127.0, 131.0, 131.4, 132.6, 138.1, 147.7, 161.6. IR (neat, cm^{-1}): 571, 776, 809, 908, 1003, 1021, 1177, 1245, 1310, 1390, 1460, 1509, 1603, 2209, 2918. HRMS: calcd. for $C_{16}H_{11}ClINNaO^+$ $[M+Na]^+$ = 417.9466; found = 417.9452.

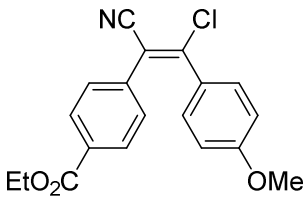
(*Z*)-3-chloro-3-(4-methoxyphenyl)-2-(4-nitrophenyl)acrylonitrile [(*Z*)-130n]



Using GP1, compound (*Z*)-**130n** was prepared from **102n** (106 mg, 419 µmol), **122b** (245 mg, 577 µmol) and trichloroborane (0.80 ml, 1 M in DCM, 0.80 mmol) in 1,2-DCE (8.80 ml) [60°C, 3 h] as a pale yellow solid (58 mg, 184 µmol, **44%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 3.83 (1H, s), 6.78 – 6.83 (2H, m), 7.21 – 7.28 (2H, m), 7.39 – 7.43 (2H, m), 8.10 – 8.15 (2H, m).^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 55.5, 110.3, 114.3, 117.0, 124.1, 126.4, 130.4, 130.5, 131.5, 139.5, 147.5, 150.6, 162.1. IR (neat, cm^{-1}): 701, 752, 821, 855, 915, 1022, 1183, 1236, 1270, 1306, 1346, 1520, 1603, 2210, 3074. HRMS:

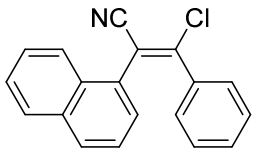
calcd. for $C_{16}H_{11}ClN_2NaO_3^+$ [M+Na]$^+$ = 337.0350; found = 337.0341.

Ethyl (*Z*)-4-[2-Chloro-1-cyano-2-(4-methoxyphenyl)vinyl]benzoate [(*Z*)-130o]



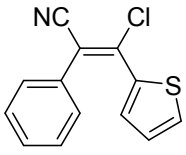
Using GP1, compound (*Z*)-**130o** was prepared from **102o** (74 mg, 264 µmol), **122b** (165 mg, 348 µmol) and trichloroborane (0.52 ml, 1 M in DCM, 0.52 mmol) in 1,2-DCE (0.52 ml) [60°C, 3 h] as a pale yellow solid (33 mg, 97 µmol, **37%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 1.38 (3H, t, *J* = 7.1 Hz), 3.80 (3H, s), 4.36 (2H, q, *J* = 7.2 Hz), 6.72 – 6.79 (2H, m), 7.18 – 7.24 (2H, m), 7.27 – 7.31 (2H, m), 7.88 – 7.95 (2H, m).^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 14.4, 55.5, 61.4, 111.6, 114.1, 117.5, 127.0, 129.4, 130.1, 130.8, 131.5, 137.4, 148.8, 161.7, 165.8. IR (neat, cm^{-1}): 547, 703, 764, 824, 907, 1018, 1102, 1184, 1265, 1279, 1513, 1604, 1723, 2208, 2917. HRMS: calcd. for $C_{19}H_{17}ClNO_3^+$ [M+H]$^+$ = 342.0891; found = 342.0886.

(*Z*)-3-Chloro-2-(naphthalen-1-yl)-3-phenylacrylonitrile [(*Z*)-130q]



Using GP1, compound (*Z*)-**130q** was prepared from **102q** (82 mg, 359 µmol), **122b** (222 mg, 468 µmol) and trichloroborane (0.72 ml, 1 M in DCM, 0.72 mmol) in 1,2-DCE (0.72 ml) [rt, 1 h] as a pale yellow solid (24 mg, 83 µmol, **23%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 7.22 – 7.35 (5H, m), 7.45 – 7.58 (2H, m), 7.71 – 7.80 (2H, m), 8.05 – 8.09 (2H, m), 8.14 – 8.18 (1H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 117.1, 117.6, 124.7, 125.3, 126.9, 127.4, 127.6, 128.4, 128.6, 128.9, 129.2, 130.0, 130.9, 132.0, 132.0, 133.2, 133.7. IR (neat, cm^{-1}): 552, 634, 693, 757, 769, 798, 901, 1087, 1231, 1257, 1339, 1445, 1589, 2220, 3056. HRMS: calcd. for $C_{19}H_{12}ClN^+$ [M]$^+$ = 289.0658; found = 289.0669.

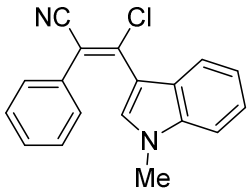
(*Z*)-3-Chloro-2-phenyl-3-(thiophen-2-yl)acrylonitrile [(*Z*)-130u]



Using GP1, compound (*Z*)-**130u** was prepared from **102u** (100 mg, 543 µmol), **122b** (335 mg, 707 µmol) and trichloroborane (1.09 ml, 1 M in DCM, 1.09 mmol) in 1,2-DCE (1.09 ml) [rt, 1 h] as a white solid (75 mg, 305 µmol, **56%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 6.92 (1H, dd, *J* = 5.1, 3.9 Hz), 7.27 (1H, dd, *J* = 3.9, 1.3 Hz), 7.35 – 7.47 (6H, m).^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 110.8, 117.8, 127.1, 129.7, 129.7, 130.2, 132.1, 132.5, 133.5, 137.1, 140.1. IR (neat, cm^{-1}): 655, 694, 713, 756, 814,

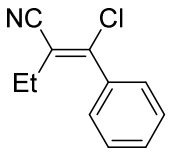
828, 1047, 1176, 1232, 1353, 1414, 1443, 1566, 2205, 3102. HRMS: calcd. for $C_{13}H_8ClNS^+$ $[M]^+$ = 245.0066; found = 245.0060.

(*Z*)-3-Chloro-3-(1-methyl-1*H*-indol-3-yl)-2-phenylacrylonitrile [(*Z*)-130w]



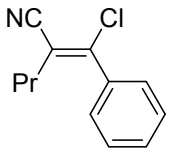
Using GP1, compound (*Z*)-**130w** was prepared from **102w** (122 mg, 527 µmol), **122b** (325 mg, 685 µmol) and trichloroborane (1.06 ml, 1 M in DCM, 1.06 mmol) in 1,2-DCE (1.06 ml) [rt, 1 h] as a yellow solid (23 mg, 79 µmol, **15%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, C_6D_6, ppm) δ = 2.53 (3H, s), 6.52 (1H, s), 6.69 (1H, dt, *J* = 8.2, 0.9 Hz), 6.75 – 6.80 (3H, m), 6.88 (1H, ddd, *J* = 8.1, 7.1, 1.0 Hz), 6.99 (1H, ddd, *J* = 8.3, 7.1, 1.2 Hz), 7.13 (1H, dt, *J* = 8.1, 1.0 Hz), 7.19 – 7.22 (2H, m). ^{13}C NMR (101 MHz, C_6D_6, ppm) δ = 32.1, 110.0, 110.1, 111.7, 118.8, 121.5, 121.7, 122.9, 125.3, 128.4, 128.8, 129.3, 133.5, 134.5, 137.2, 141.2. IR (neat, cm^{-1}): 564, 699, 741, 824, 1047, 1076, 1203, 1245, 1361, 1461, 1564, 1581, 2200, 2923, 3052. HRMS: calcd. for $C_{18}H_{13}ClN_2^+$ $[M]^+$ = 292.0767; found = 292.0756.

(*Z*)-2-[Chloro(phenyl)methylene]butanenitrile [(*Z*)-130x]



Using GP1, compound (*Z*)-**130x** was prepared from **102x** (93 mg, 714 µmol), **122b** (441 mg, 930 µmol) and trichloroborane (1.43 ml, 1 M in DCM, 1.43 mmol) in 1,2-DCE (1.43 ml) [rt, 1 h] as a yellow oil (88 mg, 459 µmol, **64%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 0.77 (3H, t, *J* = 7.3 Hz), 1.75 (2H, q, *J* = 7.3 Hz), 6.89 – 6.96 (5H, m).^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 13.3, 25.7, 116.0, 117.0, 128.3, 128.7, 130.3, 135.4, 144.7. IR (neat, cm^{-1}): 649, 695, 756, 797, 899, 1027, 1239, 1259, 1444, 1459, 1489, 1594, 1606, 2219, 2975. HRMS: calcd. for $C_{11}H_{10}ClN^+$ $[M]^+$ = 191.0502; found = 191.0505.

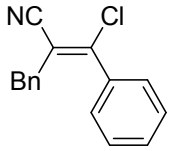
(*Z*)-2-[Chloro(phenyl)methylene]valeronitrile (*Z*)-130y



Using GP1, compound (*Z*)-**130y** was prepared from **102y** (75 mg, 520 µmol), **122b** (322 mg, 679 µmol) and trichloroborane (1.04 ml, 1 M in DCM, 1.04 mmol) in 1,2-DCE (1.04 ml) [rt, 1 h] as a yellow oil (76 mg, 369 µmol, **71%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 0.89 (3H, t, *J* = 7.4 Hz), 1.54 – 1.71 (2H, m), 2.28 – 2.32 (2H, m), 7.31 – 7.38 (2H, m), 7.40 – 7.46 (3H, m).^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 13.3, 21.8, 33.6, 114.7, 117.1, 128.4, 128.7, 130.3, 135.4, 145.1. IR (neat, cm^{-1}): 540, 648, 659,

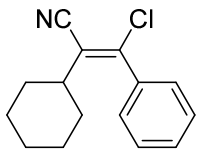
754, 807, 900, 914, 1075, 1130, 1236, 1445, 1489, 1591, 2217, 2963. HRMS: calcd. for $C_{12}H_{12}ClN^+$ $[M]^+$ = 205.0658; found = 205.0663.

(*Z*)-2-Benzyl-3-chloro-3-phenylacrylonitrile [(*Z*)-130z]



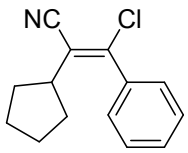
Using the GP1, compound (*Z*)-**130z** was prepared from **102z** (74 mg, 385 µmol), **122b** (237 mg, 500 µmol) and trichloroborane (0.76 ml, 1 M in DCM, 0.76 mmol) in 1,2-DCE (0.76 ml) [rt, 1 h] as an orange solid (58 mg, 229 µmol, **60%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (500 MHz, C_6D_6, ppm) δ = 3.10 (2H, s), 6.83 – 6.93 (7H, m), 6.99 – 7.07 (3H, m). ^{13}C NMR (126 MHz, C_6D_6, ppm) δ = 37.5, 114.1, 117.1, 127.5, 128.4, 128.5, 128.7, 129.1, 130.2, 135.4, 136.5, 145.6. IR (neat, cm^{-1}): 562, 650, 671, 695, 761, 909, 1029, 1073, 1237, 1453, 1494, 1604, 2219, 3029, 3061. HRMS: calcd. for $C_{16}H_{13}ClN^+$ $[M+H]^+$ = 254.0731; found = 254.0739.

(*Z*)-3-Chloro-2-cyclohexyl-3-phenylacrylonitrile [(*Z*)-130aa]



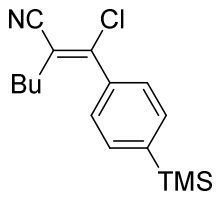
Using GP1, compound (*Z*)-**130aa** was prepared from **102aa** (58 mg, 315 µmol), **122b** (194 mg, 409 µmol) and trichloroborane (0.63 ml, 1 M in DCM, 0.63 mmol) in 1,2-DCE (0.63 ml) [rt, 1 h] as a pale yellow solid (62 mg, 252 µmol, **80%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 1.05 – 1.25 (3H, m), 1.53 – 1.78 (7H, m), 2.35 (1H, tt, *J* = 11.8, 13.6, 1.0 Hz), 7.30 – 7.37 (2H, m), 7.42 – 7.47 (3H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 25.2, 25.6, 31.7, 40.5, 116.2, 120.8, 128.1, 128.8, 130.3, 135.8, 144.0. IR (neat, cm^{-1}): 548, 646, 694, 706, 755, 896, 913, 996, 1130, 1236, 1445, 1489, 1591, 2217, 2926. HRMS: calcd. for $C_{15}H_{16}ClN^+$ $[M]^+$ = 245.0971; found = 253.0973.

(*Z*)-3-Chloro-2-cyclopentyl-3-phenylacrylonitrile [(*Z*)-130ab]



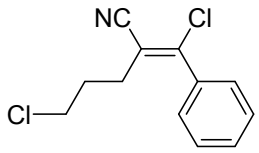
Using GP1, compound (*Z*)-**130ab** was prepared from **102ab** (69 mg, 405 µmol), **122b** (250 mg, 527 µmol) and trichloroborane (0.80 ml, 1 M in DCM, 0.80 mmol) in 1,2-DCE (0.80 ml) [rt, 1 h] as a white solid (71 mg, 306 µmol, **76%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 1.49 – 1.57 (2H, m), 1.64 – 1.87 (6H, m), 2.69 – 2.77 (1H, tt, *J* = 9.2, 7.6, 1.0 Hz), 7.33 – 7.38 (2H, m), 7.40 – 7.45 (3H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 25.5, 32.6, 41.6, 116.2, 119.7, 128.3, 128.7, 130.2, 135.6, 143.6. IR (neat, cm^{-1}): 547, 696, 695, 732, 754, 888, 914, 1239, 1444, 1489, 1592, 1607, 2218, 2869, 2953. HRMS: calcd. for $C_{14}H_{15}Cl^+$ $[M+H]^+$ = 232.0888; found = 232.0886.

(*Z*)-2-{Chloro[4-(trimethylsilyl)phenyl]methylene}capronitrile [(*Z*)-130ac]



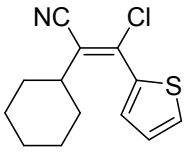
Using GP1 compound (*Z*)-**130ac** was prepared from **102ac** (138 mg, 599 µmol), **122b** (370 mg, 780 µmol) and trichloroborane (1.20 ml, 1 M in DCM, 1.20 mmol) in 1,2-DCE (1.20 ml) [rt, 1 h] as a colorless oil (99 mg, 339 µmol, **57%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, C_6D_6, ppm) δ = 0.14 (9H, s), 0.50 – 0.70 (3H, m), 0.90 (2H, dt, *J* = 15.7, 7.3 Hz), 1.23 – 1.41 (2H, m), 1.86 – 2.05 (2H, m), 7.02 (2H, m), 7.28 – 7.32 (2H, m). ^{13}C NMR (76 MHz, C_6D_6, ppm) δ = -1.3, 13.7, 22.0, 30.6, 31.7, 115.7, 117.1, 133.7, 133.8, 136.1, 143.5, 144.3. IR (neat, cm^{-1}): 546, 624, 702, 721, 756, 816, 836, 912, 1108, 1248, 1384, 1466, 1593, 2218, 2930, 2957. HRMS: calcd. For $C_{16}H_{22}ClNSi^{+}$ $[M]^{+}$ = 291.1210; found = 291.1217.

(*Z*)-5-Chloro-2-[chloro(phenyl)methylene]valeronitrile [(*Z*)-130ad]



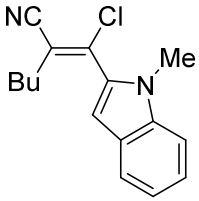
Using GP1, compound (*Z*)-**130ad** was prepared from **102ad** (104 mg, 582 µmol), **122b** (359 mg, 757 µmol) and trichloroborane (1.16 ml, 1 M in DCM, 1.16 mmol) in 1,2-DCE (1.16 ml) [rt, 1 h] as a colorless oil (87 mg, 362 µmol, **62%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 1.98 – 2.13 (2H, m), 2.39 – 2.55 (2H, m), 3.50 (2H, t, *J* = 6.2 Hz), 7.28 – 7.41 (2H, m), 7.41 – 7.50 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ = 29.0, 30.9, 43.3, 113.0, 116.7, 128.3, 128.8, 130.6, 135.0, 146.5. IR (neat, cm^{-1}): 696, 757, 796, 867, 909, 1016, 1076, 1258, 1444, 1489, 1594, 1612, 2218, 2853, 2962. HRMS: calcd. For $C_{12}H_{11}Cl_2N^{+}$ $[M]^{+}$ = 239.0269; found = 239.0266.

(*Z*)-3-Chloro-2-cyclohexyl-3-(thiophen-2-yl)acrylonitrile [(*Z*)-130ag]



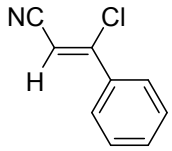
Using GP1, compound (*Z*)-**130ag** was prepared from **102ag** (88 mg, 462 µmol), **122b** (286 mg, 603 µmol) and trichloroborane (0.93 ml, 1 M in DCM, 0.93 mmol) in 1,2-DCE (0.93 ml) [rt, 1 h] as a yellow solid (95 mg, 377 µmol, **82%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, C_6D_6, ppm) δ = 0.82 – 0.97 (3H, m), 1.31 – 1.52 (7H, m), 2.62 (1H, dt, *J* = 9.8, 4.7 Hz), 6.49 (1H, q, *J* = 4.6, 3.6 Hz), 6.76 (1H, t, *J* = 4.1 Hz), 6.97 (1H, t, *J* = 3.2 Hz). ^{13}C NMR (100 MHz, C_6D_6, ppm) δ = 25.2, 25.7, 31.7, 40.9, 116.4, 120.4, 127.4, 129.9, 131.2, 136.1, 137.1. IR (neat, cm^{-1}): 628, 710, 724, 813, 899, 993, 1241, 1351, 1416, 1455, 1584, 2208, 2851, 2931, 3105. HRMS: calcd. For $C_{13}H_{14}ClNS^{+}$ $[M]^{+}$ = 251.0535; found = 251.0532.

(*Z*)-2-[Chloro(1-methyl-1*H*-indol-2-yl)methylene]capronitrile [(*Z*)-130ah]



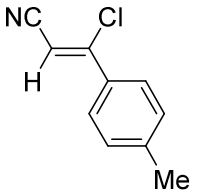
Using GP1, compound (*Z*)-**130ah** was prepared from **102ah** (75 mg, 355 µmol), **122b** (218 mg, 460 µmol) and trichloroborane (0.71 ml, 1 M in DCM, 0.17 mmol) in 1,2-DCE (0.71 ml) [rt, 1 h] as a brown oil (7 mg, 26 µmol, **7%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, C_6D_6, ppm) δ = 0.84 (3H, t, *J* = 7.3 Hz), 1.28 (2H, hept., *J* = 7.3 Hz), 1.58 (2H, pent., *J* = 7.5 Hz), 2.63 (3H, s), 2.41 (2H, t, *J* = 7.5 Hz), 6.82 (1H, d, *J* = 7.7 Hz), 7.24 – 7.14 (3H, m), 8.11 (1H, d, *J* = 7.9 Hz). ^{13}C NMR (125 MHz, C_6D_6, ppm) δ = 14.1, 22.6, 30.3, 32.2, 32.3, 108.7, 110.3, 111.6, 119.3, 121.3, 121.7, 123.0, 126.7, 131.4, 137.3, 143.8. IR (neat, cm^{-1}): 571, 739, 934, 1069, 1133, 1254, 1363, 1463, 1524, 1590, 2205, 2870, 2927, 2956, 3052, 3112. HRMS: calcd. For $C_{16}H_{17}ClN_2^+$ $[M]^+$ = 272.1080; found = 272.1079.

(*Z*)-3-Chloro-3-phenylacrylonitrile [(*Z*)-130ai]



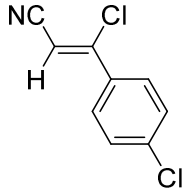
Using GP1, compound (*Z*)-**130ai** was prepared from **102ai** (31 mg, 304 µmol), **122b** (187 mg, 394 µmol) and trichloroborane (0.60 ml, 1 M in DCM, 0.60 mmol) in 1,2-DCE (0.60 ml) [rt, 1 h] as a yellow oil (29 mg, 177 µmol, **58%**) after flash chromatography (*n*-hexane/EtOAc 9:1) ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 6.03 (1H, s), 7.42 – 7.46 (1H, m), 7.47 – 7.55 (2H, m), 7.65 – 7.69 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 96.3, 115.5, 127.0, 129.1, 132.0, 134.4, 153.4. IR (neat, cm^{-1}): 575, 616, 651, 676, 753, 804, 902, 999, 1229, 1445, 1489, 1575, 1597, 2220, 3060. HRMS: calcd. For $C_9H_6ClN^+$ $[M]^+$ = 163.0189; found = 163.0185.

(*Z*)-3-Chloro-3-(*p*-tolyl)acrylonitrile [(*Z*)-130ak]



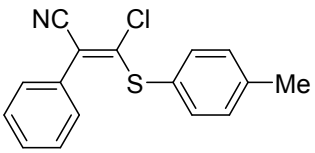
Using GP1, compound (*Z*)-**130ak** was prepared from **102ak** (79 mg, 680 µmol), **122b** (420 mg, 886 µmol) and trichloroborane (1.36 ml, 1 M in DCM, 1.36 mmol) in 1,2-DCE (1.36 ml) [rt, 1 h] as a yellow oil (26 mg, 0.14 µmol, **21%**) after flash chromatography (*n*-hexane/EtOAc 9:1) a yellow solid (26 mg, 146 µmol, **21%**). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 2.41 (3H, s), 5.98 (1H, s), 7.23 – 7.26 (2H, m), 7.54 – 7.57 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 21.5, 95.1, 115.7, 126.9, 129.7, 131.5, 142.8, 153.4. IR (neat, cm^{-1}): 673, 719, 730, 903, 1019, 1186, 1239, 1373, 1463, 1597, 1736, 2218, 2847, 2916, 2916. HRMS: calcd. For $C_{10}H_9ClN^+$ $[M+H]^+$ = 177.0418; found = 178.0417.

(*Z*)-3-Chloro-3-(4-chlorophenyl)acrylonitrile [(*Z*)-130al]



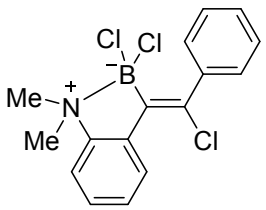
Using GP1, compound (*Z*)-**130al** was prepared from 1-chloro-4-ethynylbenzene (**102al**) (56 mg, 410 µmol), **122b** (252 mg, 532 µmol) and trichloroborane (0.82 ml, 1 M in DCM, 0.82 mmol) in 1,2-DCE (0.82 ml) [rt, 1 h] as a white solid (38 mg, 192 µmol, **47%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 6.01 (1H, s), 7.41 – 7.45 (2H, m), 7.59 – 7.62 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 96.8, 115.2, 128.2, 129.4, 132.7, 138.4, 152.1. IR (neat, cm^{-1}): 670, 721, 803, 833, 903, 1009, 1094, 1234, 1402, 1489, 1591, 2217, 2341, 2361, 3043. HRMS: calcd. For $C_9H_5Cl_2N^+$ $[M]^+$ = 196.9799; found = 196.9792.

(*Z*)-3-Chloro-2-phenyl-3-(*p*-tolylthio)acrylonitrile [(*Z*)-130ao]



Using GP1, compound (*Z*)-**130ao** was prepared from **102ao** (23 mg, 103 µmol), **122b** (63 mg, 133 µmol) and trichloroborane (0.20 ml, 1 M in DCM, 0.20 mmol) in 1,2-DCE (0.20 ml) [rt, 1 h] as a pale yellow solid (19 mg, 66 µmol, **64%**)obtaining after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 2.39 (3H, s), 7.18 – 7.23 (2H, m), 7.31 – 7.36 (2H, m), 7.42 – 7.50 (3H, m), 7.52 – 7.56 (2H, m).^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 21.6, 112.8, 117.0, 125.6, 128.9, 129.2, 129.6, 130.2, 132.2, 135.0, 146.8, 147.7. IR (neat, cm^{-1}): 511, 648, 691, 754, 803, 916, 1015, 1180, 1257, 1442, 1488, 1532, 1595, 2210, 2921. HRMS: calcd. For $C_{16}H_{12}ClNS^+$ $[M]^+$ = 285.0379; found = 285.0386.

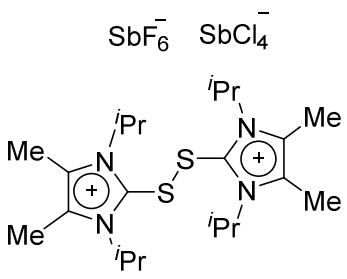
(*Z*)-2,2-Dichloro-3-[chloro(phenyl)methylene]-1,1-dimethyl-2,3-dihydro-1*H*-1λ^4,2λ^4-benzo[*d*][1,2]azaborole (133)



Using GP1, compound **133** was prepared from **102t** (79 mg, 357 µmol), **122b** (220 mg, 464 µmol) and trichloroborane (0.71 ml, 1 M in DCM, 0.71 mmol) in 1,2-DCE (0.71 ml) [rt, 1 h] as a pale yellow solid (64 mg, 189 µmol, **53%**) after flash chromatography (*n*-hexane/EtOAc 2:1) ^{1}H NMR (400 MHz, CD_2Cl_2, ppm) δ = 3.01 (6H, s), 7.37 – 7.49 (6H, m), 7.64 – 7.74 (2H, m), 8.48 (1H, dd, *J* = 7.9, 1.5 Hz). ^{13}C NMR (126 MHz, CD_2Cl_2, ppm) δ = 50.1, 117.6, 128.0, 128.1, 128.7, 195.5, 129.5, 129.6, 130.0, 136.6, 141.1, 149.7. ^{11}B NMR (128 MHz, CD_2Cl_2, ppm) δ = 10.5. The spectral data correspond to those reported in the literature.[115]

6.2.2.2. Isolated by-products.

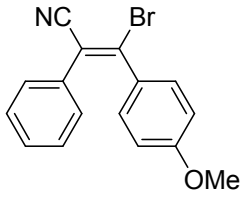
2,2'-Disulfanediylbis(1,3-diisopropyl-4,5-dimethyl-1*H*-imidazol-3-ium) Hexafluoroantimonate Tetrachloroantimonate (140a)



Using GP1, compound (*Z*)-**130a** was prepared from **102a** (1.000 g, 4.80 mmol), **122b** (2.963 g, 6.25 mmol) and trichloroborane (9.61 ml, 1 M in DCM, 9.61 mmol) in 1,2-DCE (9.61 ml) [rt, 1 h] as a yellow solid (1.055 g, 3.91 mmol, **81%**) after flash chromatography (*n*-hexane/EtOAc 9:1). The solid remaning after filtration of the ethyl acetate solution was stirred with DCM, filtered again, concentrated under reduced pressure and recrystallized from a 1/1 mixture of acetonitrile and diethyl ether affording **140a** as yellow crystals. ^{1}H NMR (300 MHz, CD_3CN, ppm) δ = 1.47 (24H, d, *J* = 7.0 Hz), 2.42 (12H, s), 5.02 (4H, hept, *J* = 7.0 Hz). ^{13}C NMR (126 MHz, CD_3CN, ppm) δ = 11.0, 21.1, 55.3, 133.6, 134.4. IR (neat, cm^{-1}): 651, 748, 804, 905, 979, 1116, 1147, 1216, 1264, 1377, 1395, 1414, 1457, 1592, 2987. HRMS: calcd. For $C_{22}H_{40}F_6N_4S_2Sb^+$ $[M–SbCl_4]^+$ = 659.1631; found = 659.1624.

6.2.2.3. Bromocyanations.

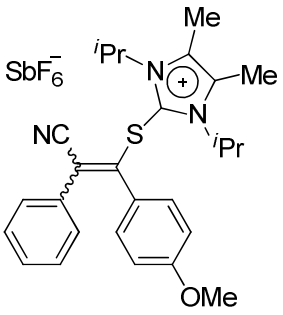
(*Z*)-3-Bromo-3-(4-methoxyphenyl)-2-phenylacrylonitrile [(*Z*)-128]



Using GP1, compound (*Z*)-**128** was prepared from **102a** (100 mg, 480 µmol) and **122b** (252 mg, 532 µmol) tribromoborane (0.48 ml, 1 M in DCM, 0.48 mmol) in 1,2-DCE (1.92 ml) at rt for 3 h. In this case was used as promoter. After flash chromatography (*n*-hexane/EtOAc 9:1) **6** was obtained as a yellow solid (14 mg, 45 µmol, **9%**). ^{1}H NMR (300 MHz, C_6D_6, ppm) δ = 3.03 (3H, s), 6.25 – 6.33 (2H, m), 6.75 – 6.81 (3H, m), 6.83 – 6.91 (2H, m), 6.95 – 7.01 (2H, m). ^{13}C NMR (126 MHz, C_6D_6, ppm) δ = 54.8, 113.9, 117.5, 119.3, 128.7, 128.8, 129.4, 129.7, 131.8, 134.4, 138.4, 161.1. IR (neat, cm^{-1}): 695, 753, 800, 1028, 1174, 1255, 1300, 1363, 1439, 1505, 1602, 1684, 2206, 2359, 2962. HRMS: calcd. for $C_{16}H_{12}BrNO^+$ $[M]^+$ = 313.0102; found = 313.0109.

6.2.2.4. Thiocyanations.

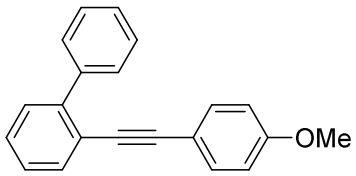
(*Z*/*E*)-2-{[2-Cyano-1-(4-methoxyphenyl)-2-phenylvinyl]thio}-1,3-diisopropyl-4,5-dimethyl-1*H*-imidazol-3-ium Hexafluoroantimonate (129)



Compound **129** was prepared from **102a** (35 mg, 168 µmol), **122b** (95 mg, 200 µmol) in 1,2-DCE (0.67 ml) according to GP1 [50 °C, 3 h], but employing tris(pentafluorophenyl)borane (88 mg, 172 µmol) as a Lewis acid. The reaction mixture was filtered through a pad of silica gel and concentrated *in vacuo*. Compound **129** (103 mg, 151 µmol, 90 %) was obtained as a *Z/E* mixture which could not be separated by chromatography. (*Z*)-**129**, content **80%**: ^{1}H NMR (400 MHz, CD_3CN, ppm) δ = 1.53 (12H, d, *J* = 7.0 Hz), 2.32 (6H, s), 3.73 (3H, s), 5.29 (2H, hept, *J* = 7.0 Hz), 6.77 – 6.88 (2H, m), 7.08 – 7.14 (2H, m), 7.14 – 7.19 (2H, m), 7.22 – 7.30 (3H, m). (*E*)-**129**, content **20%**: ^{1}H NMR (400 MHz, CD_3CN, ppm) δ = 1.35 (12H, d, *J* = 7.0 Hz), 2.22 (6H, s), 3.81 (3H, s), 4.92 (2H, hept, *J* = 7.0 Hz), 6.94 – 7.04 (2H, m), 7.34 – 7.37 (2H, m), 7.57 – 7.65 (3H, m), 7.65 – 7.70 (2H, m). IR (neat, cm^{-1}): 680, 763, 972, 1028, 1084, 1175, 1256, 1378, 1460, 1513, 1602, 1644, 2341, 2360, 2980. HRMS: calcd. for $C_{27}H_{32}N_3OS^+$ [M–SbF_6]$^+$ = 446.2261; found = 446.2261.

6.2.2.5. Cyanoarylations.

10-(4-Methoxyphenyl)phenanthrene-9-carbonitrile (135a)

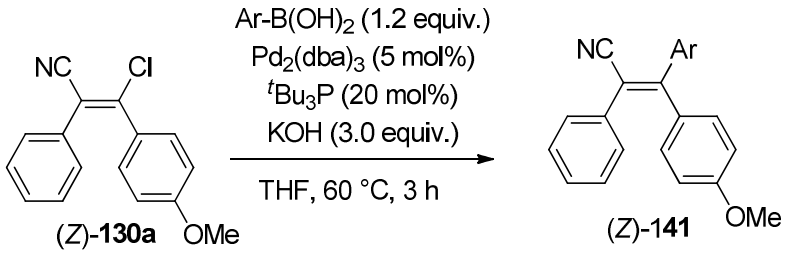


Alkyne **135a** (100 mg, 352 µmol, 1.0 equiv.) was treated with **122b** (217 mg, 458 µmol, 1.3 equiv.) and tris-(pentafluorophenyl)borane (179 mg, 350 µmol, 1.0 equiv.) in 1,2-DCE (1.4 ml) according to GP1. [rt, 1 h]. The reaction mixture was filtered through a pad of silica gel, filtrate was concentrated *in vacuo* and purified by flash chromatography (*n*-hexane/EtOAc 9:1) affording compound **136a** as colorless crystals (59 mg, 191 µmol, **54%**). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.93 (3H, s), 7.08 – 7.17 (2H, m), 7.40 – 7.49 (2H, m), 7.58 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz), 7.74 – 7.83 (4H, m), 8.35 – 8.42 (1H, m), 8.73 – 8.79 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.5, 109.8, 114.2, 117.6, 123.0, 126.5, 127.5, 128.1, 128.4, 128.9, 129.1, 129.2, 129.5, 129.7, 130.6, 131.4, 131.9, 147.2, 160.2. IR (neat, cm^{-1}): 538, 647,

669, 722, 756, 1028, 1034, 1066, 1173, 1247, 1508, 2341, 2360, 2900, 2972. HRMS: calcd. for $C_{22}H_{15}NO^+$ $[M]^+$ = 309.1154; found = 309.1162.

6.2.2.6. Derivatization of chloroacrylonitriles.

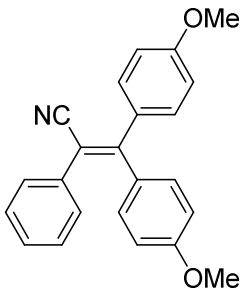
6.2.2.6.1. Suzuki-Miyaura couplings.



Scheme 122. Suzuki-Miyaura cross-coupling of (*Z*)-**130a**.

General procedure (GP2):[124] Under N_2 atmosphere, a Schlenk tube was charged with (*Z*)-**130a** (1.0 equiv.), the corresponding boronic acid (1.2 equiv.), $Pd_2(dba)_3$ (0.05 equiv.), $^tBu_3P$ (0.20 equiv.), 3 M KOH *aqueous* solution (3.0 equiv.) and THF (ca. 0.5 ml). The mixture was stirred at 60 °C for 3 hours. The reaction was quenched with an aqueous ammonium chloride solution and extracted with diethylether. The extract was washed with water, dried over $MgSO_4$ and concentrated in vacuum affording a brown solid crude product. The latter was purified by column chromatography (*n*-hexane/EtOAc 9:1) or recrystallized from a 1/1 mixture of DCM and *n*-pentane.

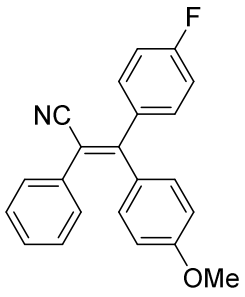
3,3-Bis(4-methoxyphenyl)-2-phenylacrylonitrile (141a)



Using GP2, compound **141a** was prepared from (*Z*)-**130a** (25 mg, 93 µmol), $Pd_2(dba)_3$ (4.3 mg, 4.6 µmol, 5 mol%), $^tBu_3P$ (4 mg, 20 µmol), KOH (16 mg, 95 µl, 3 M in H_2O, 285 µmol) and *para*-anisolylboronic acid (14 mg, 0.09 µmol) in THF (0.50 ml) as a yellow solid (29 mg, 85 µmol, **91%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^1H NMR (300 MHz, $CDCl_3$, ppm) δ = 3.77 (3H, s), 3.86 (3H, s), 6.66 – 6.72 (2H, m), 6.90 – 6.95 (4H, m), 7.18 – 7.26 (4H, m), 7.26 – 7.29 (2H, m), 7.37 – 7.43 (2H, m).^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 55.4, 55.5, 108.9,

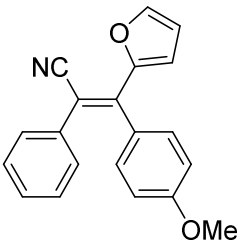
113.7, 113.9, 121.2, 128.0, 128.6, 129.8, 131.6, 132.0, 132.9, 133.1, 135.6, 157.4, 160.3, 161.1. HRMS: calcd. for $C_{23}H_{19}NO_2^+$ [M]$^+$ = 341.1416; found = 341.1423.

(*Z*)-3-(4-Fluorophenyl)-3-(4-methoxyphenyl)-2-phenylacrylonitrile [(*Z*)-141b]



Using GP2, compound (*Z*)-**141b** was prepared from (*Z*)-**130a** (100 mg, 371 µmol), $Pd_2(dba)_3$ (17 mg, 18.5 µmol, 5 mol%), $^tBu_3P$ (15 mg, 74 µmol), KOH (62 mg, 368 µl, 3 M in H_2O, 1.10 mmol) and 4-fluorophenylboronic acid (63 mg, 450 µmol) in THF (0.40 ml) as a white solid (113 mg, 343 µmol, **92%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 3.77 (3H, s), 6.63 – 6.77 (2H, m), 6.83 – 6.97 (2H, m), 7.04 – 7.17 (2H, m), 7.23 – 7.30 (5H, m), 7.42 – 7.48 (2H, m).^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 55.3, 55.5, 108.8, 113.6, 113.8, 121.1, 128.0, 128.6, 129.8, 131.5, 131.9, 132.8, 133.0, 153.6, 157.3, 160.3, 161.1. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ = –110.5. IR (neat, cm^{-1}): 701, 765, 831, 1030, 1159, 1183, 1226, 1252, 1275, 1297, 1457, 1505, 1601, 2200, 3069. HRMS: calcd. for $C_{22}H_{16}FNO^+$ [M]$^+$ = 329.1216; found = 329.1206.

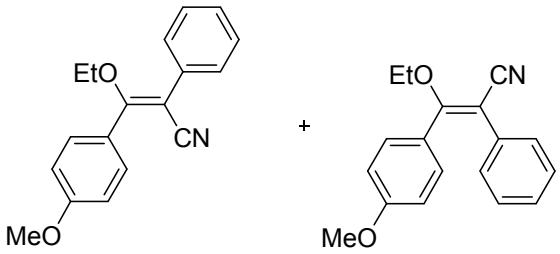
(*Z*)-3-(Furan-2-yl)-3-(4-methoxyphenyl)-2-phenylacrylonitrile [(*Z*)-141c]



Using GP2, compound (*Z*)-**141c** was prepared from (*Z*)-**130a** (33 mg, 122 µmol), $Pd_2(dba)_3$ (5.5 mg, 6 µmol, 4.9 mol%), $^tBu_3P$ (5 mg, 24.7 µmol), KOH (21 mg, 125 µl, 3 M in H_2O, 374 µmol) and 2-furylboronic acid (63 mg, 563 µmol) in THF (0.50 ml) as a yellow solid (25 mg, 0.08 µmol, **68%**) after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, C_6D_6, ppm) δ = 3.11 (3H, s), 6.00 (1H, dd, *J* = 3.5, 1.8 Hz), 6.41 – 6.49 (2H, m), 6.55 (1H, dd, *J* = 3.6, 0.8 Hz), 6.75 – 6.80 (2H, m), 6.80 – 6.89 (3H, m), 7.06 (1H, dd, *J* = 1.8, 0.8 Hz), 7.17 – 7.22 (2H, m).^{13}C NMR (101 MHz, C_6D_6, ppm) δ = 54.8, 107.3, 112.2, 113.9, 116.8, 120.3, 127.9, 128.5, 128.6, 130.2, 132.4, 135.8, 143.3, 144.7, 152.9, 160.4. IR (neat, cm^{-1}): 590, 696, 759, 838, 1017, 1028, 1175, 1250, 1293, 1462, 1509, 1605, 1783, 2360, 2958. HRMS: calcd. for $C_{20}H_{15}NO_2^+$ [M]$^+$ = 301.1103; found = 301.1104.

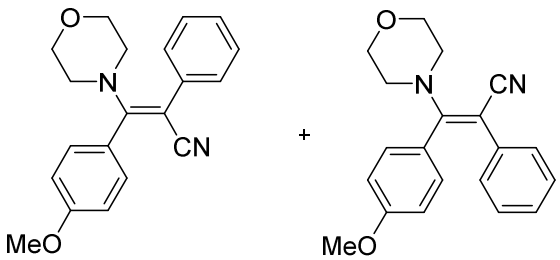
6.2.2.6.2. Solvolysis of chloroacrylonitriles.

(*E*)- and (*Z*)-3-Ethoxy-3-(4-methoxyphenyl)-2-phenylacrylonitriles [(*E*)-144 and (*Z*)-144]



Following the reported procedure,[126] substrate (*Z*)-**130a** (14 mg, 52 µmol) and NaOH (10 mg, 250 µmol, 5.0 equiv.) were refluxed in ethanol (1 ml) for 12 hours. The reaction mixture was filtered through a silica pad. After evaporation of volatiles, the crude product was washed with hexanes affording the desired product as a 2/1 mixture of (*E*)-**144** and (*Z*)-**144** as a yellow solid (11 mg, 39 µmol, **75%**). (*E*)-**144**: ^{1}H NMR (400 MHz, C_6D_6, ppm) δ = 0.80 (3H, t, *J* = 7.1 Hz), 3.21 (3H, s), 3.33 (2H, q, *J* = 7.1 Hz), 6.63 – 6.71 (2H, m), 7.17 – 7.24 (3H, m), 7.24 – 7.31 (2H, m), 7.95 – 8.02 (2H, m). (*Z*)-**144**: 1.06 (3H, t, J = 7.0 Hz), 3.10 (3H, s), 3.57 (2H, q, J = 7.1 Hz), 6.37 – 6.50 (2H, m), 6.83 – 6.92 (5H, m), 7.07 (2H, ddt, J = 8.6, 6.9, 1.3 Hz). ^{13}C NMR (126 MHz, C_6D_6, ppm) δ = 14.8, 15.0, 54.4, 54.5, 66.6, 66.9, 96.5, 113.9, 113.9, 118.3, 119.7, 123.6, 124.9, 127.0, 127.3, 127.9, 128.2, 128.4, 129.4, 130.6, 131.2, 133.1, 133.5, 160.9, 161.2, 167.3, 167.3.

(*E*)- and (*Z*)-3-(4-Methoxyphenyl)-3-morpholino-2-phenylacrylonitrile [(*E*)-145d and (*Z*)-145d]

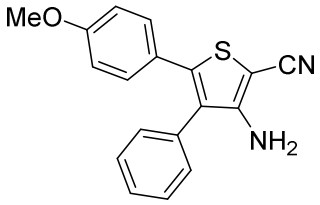


Substrate (*Z*)-**130a** (24 mg, 89 µmol) and NaOH (18 mg, 450 µmol, 5.0 equiv.) were solved in morpholine (1 ml) and heated by the microwave irradiation for 9 hours. After evaporation of volatiles, the residue was purified by flash chromatography (*n*-hexane/EtOAc 4:1) affording the desired products as a 1.5/1 mixture of (*E*)-**145d** and (*Z*)-**145d** as a yellow oil (26 mg, 81 µmol, **91%**). (*E*)-**145d**: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 2.85 (4H, dd, *J* = 5.4, 4.2 Hz), 3.58 – 3.65 (4H, m), 3.85 (3H, s), 6.94 – 7.01 (4H, m), 7.23 – 7.28 (3H, m), 7.51 – 7.58 (2H, m). (*Z*)-**145d**: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.42 – 3.47 (4H, m), 3.76 (3H, s), 3.77 – 3.81 (4H, m), 6.73 – 6.78 (2H, m), 7.02 – 7.07 (2H, m), 7.12 – 7.17 (2H, m), 7.32 – 7.39 (3H, m). ^{13}C NMR (101 MHz, C_6D_6, ppm) δ = 51.1, 51.3, 55.4, 55.5, 67.2, 67.5, 84.6, 86.6, 114.3, 114.5, 123.6, 125.4, 126.7, 126.8,

128.1, 128.1, 128.6, 128.8, 129.3, 132.1, 132.8, 136.1, 136.4, 161.2, 161.5, 162.0, 163.1.

6.2.2.6.3. Synthesis of heterocycles

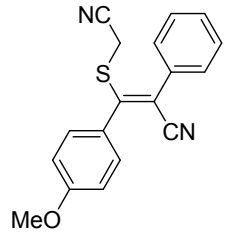
3-Amino-5-(4-methoxyphenyl)-4-phenylthiophene-2-carbonitrile (146a)



Following the reported procedure,[127] a suspension of $Na_2S·9H_2O$ (77 mg, 321 µmol, 1.0 equiv.) in DMF (4 mL) was heated at 40 °C for 30 min. A solution of (*Z*)-**130a** (86 mg, 319 µmol, 1.0 equiv.) in DMF (2 mL) was added to the former solution, and the reaction mixture was stirred at 50 °C for 50 min. Chloroacetonitrile (0.02 ml, 320 µmol, 1.0 equiv.) in DMF (1 mL) was then added, and the solution was stirred at 50 °C for 90 additional minutes. Subsequently, a solution of NaOEt (22 mg, 323 µmol, 1.0 equiv.) in absolute EtOH (2 mL) was added, and the mixture was stirred at 50 °C for 1 h. The reaction was then cooled to rt and poured into ice-cold water (10 mL). The precipitate was filtered off and washed with cold water and dried. Finally, the solid was purified by column chromatography (*n*-hexane/EtOAc 10:1 to 1:1) affording **146a** as a yellow solid (22 mg, 72 µmol, **23%**) and **147** as a yellow oil (29 mg, 95 µmol, **30%**).

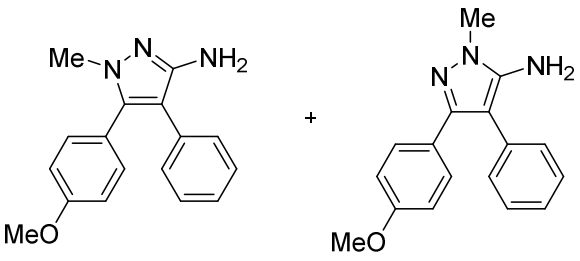
Compound **146a**: ^{1}H NMR (500 MHz, C_6D_6, ppm) δ = 3.11 (3H, s), 3.70 (2H, s), 6.37 – 6.47 (2H, m), 6.85 – 6.91 (2H, m), 6.93 – 7.04 (5H, m). ^{13}C NMR (126 MHz, C_6D_6, ppm) δ = 30.2, 54.7, 79.8, 114.3, 115.1, 125.5, 128.2, 129.4, 130.2, 130.3, 134.0, 145.7, 154.1, 160.4. IR (neat, cm^{-1}): 780, 833, 1035, 1049, 1066, 1175, 1252, 1417, 1514, 1603, 1630, 2341, 2360, 2987, 3471. HRMS: calcd. for $C_{18}H_{14}N_2OS^+$ $[M]^+$ = 306.0827; found = 306.0832.

(*E*)- and (*Z*)-3-[(Cyanomethyl)thio]-3-(4-methoxyphenyl)-2-phenylacrylonitrile [(*E*)-147 and (*Z*)-147]



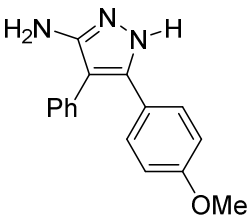
Compound **147** was isolated as a 10/1 *E*/*Z* diastereomeric mixture. ^{1}H NMR (600 MHz, C_6D_6, ppm) δ = 1.99 (2H, s), 3.20 (3H, s), 6.64 – 6.71 (2H, m), 6.99 – 7.05 (1H, m), 7.06 – 7.12 (2H, m), 7.27 – 7.32 (2H, m), 7.45 – 7.52 (2H, m). ^{13}C NMR (126 MHz, C_6D_6, ppm) δ = 18.0, 55.1, 114.7, 115.0, 115.5, 118.3, 126.8, 129.1, 129.4, 129.5, 131.2, 134.3, 153.1, 161.7.

Compounds 149a and 149b



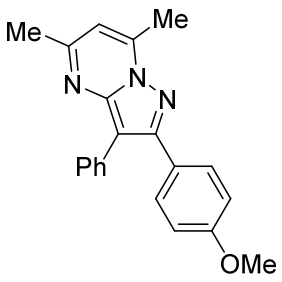
Following literature conditions,[128] Compound (*Z*)-**130a** (90 mg, 0.33 mmol, 1.0 equiv.) and methylhydrazine (77, 1.67 mmol, 5 equiv.) were refluxed in ethanol (2 ml) for 24 hours. After completition, the mixture was diluted in water and the product extracted with DCM, the organic phase was separated, dried with Na_2SO_4, filtered and concentrated *in vacuo*. The solid was purified by column chromatography (Et_2O/EtOAc 10/1 to 1/1) affording a mixture of regiomers **149a/149b** (86/14) as a yellow oil that solidifies on standing (68 mg, 0.24 mmol, **73%**). Washing the product with DCM allowed the isolation of pure **149a**: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.62 (3H, s), 3.81 (3H, s), 6.84 – 6.92 (2H, m), 7.07 – 7.19 (5H, m), 7.20 – 7.26 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 36.4, 55.4, 107.0, 114.2, 122.4, 126.0, 128.7, 128.9, 129.7, 131.3, 141.7, 151.1, 159.8. IR (neat, cm^{-1}): 596, 701, 768, 822, 1030, 1173, 1247, 1386, 1524, 1601, 2341, 2360, 2924, 2957, 3402. HRMS: calcd. for $C_{17}H_{17}N_3O$ $[M]^+$ = 279.1372; found = 279.1371.

Compound 149c



Following the reported procedure,[128] compound **(*Z*)-130a** (28 mg, 0.10 mmol, 1.0 equiv.) and hydrazine monohydrate (10 mg, 0.20 mmol, 2.0 equiv.) were refluxed in ethanol (1 ml) for 18 hours. After completition, the mixture was concentrated and solved in a water/ethylacetate mixture, the organic phase was separated, dried and concentrated *in vacuo*. The solid was purified by column chromatography (*n*-hexane/EtOAc 4/1 to 1/1) affording product **149c** as a white solid (25 mg, 0.93 mmol, **90%**). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.77 (3H, s), 5.83 (2H, bs), 6.72 – 6.88 (2H, m), 7.18 – 7.39 (7H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.3, 105.85 114.2, 122.8, 126.5, 128.9, 129.0, 129.6, 132.9, 141.6, 152.5, 159.7. IR (neat, cm^{-1}): 775, 832, 1030, 1244, 1507, 1604, 1915, 2115, 2281, 2343, 2372, 2579, 2924, 2958, 3197. HRMS: calcd. for $C_{16}H_{15}N_3O^+$ $[M]^+$ = 265.1215; found = 265.1222.

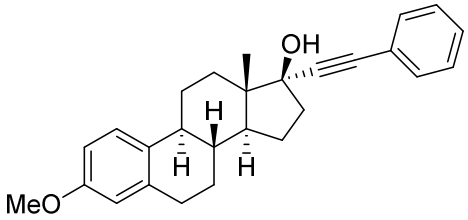
Compound 150



Follwing reported conditions,[128] compound **149c** (20 mg, 0.07 mmol, 1.0 equiv.), acetylacetone (23 mg, 0.22 mmol, 3.0 equiv.) and piperidine (6 mg, 0.07 mmol, 1.0 equiv.) were solved in ethanol (1 ml) and heated in the microwave for 80 minutes at 85 °C. The mixture was concentrated and purified by column chromatography (*n*-hexane/EtOAc 4/1 to 1/1) affording product **150** as a white solid (19 mg, 0.06 mmol, **81%**). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 2.54 (3H, s), 2.77 (3H, s), 3.80 (3H, s), 6.54 (1H, s), 6.76 – 6.94 (2H, m), 7,23 (1H, s), 7.34 (2H, t, *J* = *7.7 Hz*), 7.45 – 7.63 (4H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 17.1, 25.0, 55.3, 107.7, 108.8, 113.9, 126.2, 126.4, 128.4, 130.1, 130.4, 132.6, 144.9, 146.8, 153.4, 158.7, 159.9. IR (neat, cm^{-1}): 599, 697, 734, 777, 834, 961, 1028, 1091, 1179, 1248, 1433, 1556, 1613, 2924, 2960. HRMS: calcd. for $C_{21}H_{19}N_3O$ [M-H] = 328.1450; found = 328.1458.

6.2.2.6.4. Attempted derivatization of natural products.

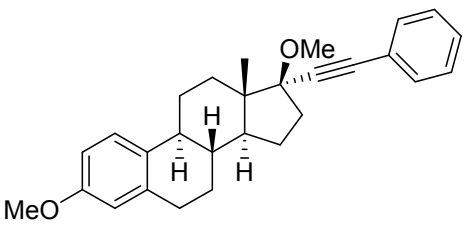
(8*R*,9*S*,13*S*,14*S*,17*S*)-3-Methoxy-13-methyl-17-(phenylethynyl)-7,8,9,11,12,13,14,15, 16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (152)



Commertially available mestranol **151** (200 mg, 644 µmol, 1.0 equiv.), $Pd(PPh_3)_4$ (19 mg, 16 µmol, 8 mol%), CuI (6 mg, 31 µmol, 15 mol%) and phenyl iodide (134 mg, 657 µmol, 1.0 equiv.) were solved in a previously degassed $^{i}Pr_2NH$/THF 2:1 mixture and stirred at rt for 3 h. The reaction mixture was filtered through a silica and Celite pad, filtrate was concentrated and purified by flash chromatography (*n*-hexane/EtOAc 9:1) affording 152 as a pale yellow solid (222 mg, 574 µmol, **89%**). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 0.94 (3H, d, *J* = 0.7 Hz), 1.34 – 1.58 (4H, m), 1.77 – 1.83 (2H, m), 1.92 (2H, s), 2.00 (1H, td, *J* = 13.1, 4.4 Hz), 2.11 (1H, td, *J* = 13.7, 12.6, 3.4 Hz), 2.25 (1H, t, *J* = 11.3 Hz), 2.35 – 2.47 (2H, m), 2.87 (2H, t, *J* = 8.2 Hz), 3.78 (3H, s), 6.64 (1H, d, *J* = 2.8 Hz), 6.72 (1H, dd, *J* = 8.6, 2.8 Hz), 7.20 – 7.25 (1H, m), 7.29 – 7.35 (3H, m), 7.43 – 7.48 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 13.1, 23.1, 26.7, 27.4, 30.0, 33.2, 39.2, 39.7, 43.8, 47.8, 49.9, 55.4, 80.5, 86.1, 92.9, 111.6, 113.9, 123.1, 126.5, 128.4, 128.4, 131.8,

132.7, 138.1, 157.6.

(8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-Dimethoxy-13-methyl-17-(phenylethynyl)-7,8,9,11,12,13,14, 15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene (153)

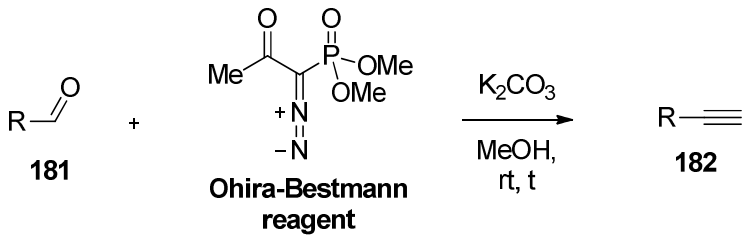


Compound **152** (43 mg, 111 µmol), methyl iodide (32 mg, 225 µmol, 2.0 equiv.) and sodium hydride (9 mg, 375 µmol, 3.4 equiv.) were solved in anhydrous THF (5 ml) and stirred at room temperature for 3 hours. After solvent evaporation, the residue was purified by column chromatography (*n*-hexane/EtOAc 9:1) affording product **153** as a white solid (30 mg, 75 µmol, **68%**). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 0.95 (3H, s), 1.35 – 1.61 (4H, m), 1.77 – 1.97 (4H, m), 2.10 (2H, tdd, *J* = 12.2, 7.1, 3.8 Hz), 2.25 (1H, td, *J* = 11.2, 4.1 Hz), 2.36 (2H, ddt, *J* = 14.1, 9.0, 4.2 Hz), 2.87 (2H, dd, *J* = 9.9, 6.4 Hz), 3.50 (3H, s), 3.79 (3H, s), 6.64 (1H, d, *J* = 2.9 Hz), 6.73 (1H, dd, *J* = 8.6, 2.8 Hz), 7.23 (1H, d, *J* = 8.6 Hz), 7.28 – 7.40 (3H, m), 7.49 (2H, dd, *J* = 6.7, 3.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 13.0, 23.0, 26.8, 27.4, 30.0, 34.6, 37.0, 39.4, 43.8, 48.1, 50.0, 53.6, 55.3, 86.3, 88.0, 90.4, 111.6, 113.9, 123.3, 126.5, 128.3, 128.4, 131.8, 132.7, 138.1, 157.5.

6.3. Cyanative cyclizations.

6.3.1. Synthesis of starting materials.

6.3.1.1. Terminal alkynes 182 by Seyferth-Gilbert homologation.

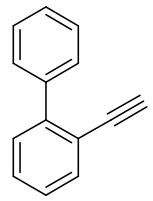


Scheme 123. Seyferth-Gilbert homologation of **181**.

General procedure (GP3): A round-bottomed flask was flushed with nitrogen and charged with the corresponding aldehyde **181** (1.0 equiv.), Ohira-Bestmann reagent (1.5 equiv.), potassium carbonate (2.0 equiv.), suspended in anhydrous methanol (ĉ ~ 0.1 M with

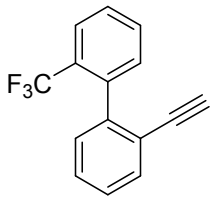
respect to **181**) and stirred at room temperature for the indicated time. All volatiles were removed; the remaining solid was taken up with DCM and washed with brine. The organic layer was dried with Na_2CO_3, evaporated and purified by flash chromatography.[100,101]

2-Ethynyl-1,1'-biphenyl (135f)



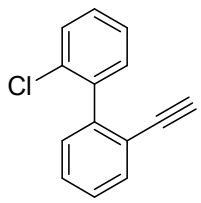
From [1,1'-biphenyl]-2-carbaldehyde (900 mg, 4.94 mmol, 1.0 equiv.), Ohira-Bestmann reagent (1.424 g, 7.44 mmol, 1.50 equiv.) and potassium carbonate (1.365 g, 9.88 mmol, 2.0 equiv.) in methanol (49 ml), **135f** (863 mg, 4.84 mmol, **98%**) was obtained according to GP3 [3 h] as a colorless oil after purification by column chromatography (*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.04 (1H, s), 7.31 (1H, ddd, *J* = 7.7, 6.9, 1.9 Hz), 7.34 – 7.48 (5H, m), 7.55 – 7.65 (3H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 80.3, 83.2, 120.6, 127.0, 127.6, 128.0, 129.0, 129.3, 129.7, 133.9, 140.3, 144.5. IR (neat, cm^{-1}): 505, 567, 615, 696, 735, 755, 1007, 1074, 1261, 1430, 1448, 1473, 2104, 3021, 3058, 3281. HRMS: calcd. for $C_{14}H_{10}^+$ $[M]^+$ = 178.0783; found = 178.0784.

2-Ethynyl-2'-(trifluoromethyl)-1,1'-biphenyl (182g)



Compound **182g** was cordially supplied by Dr. Javier Carreras. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 2.90 (1H, s), 7.24 – 7.32 (1H, m), 7.32 – 7.45 (3H, m), 7.51 (1H, tdq, *J* = 7.6, 1.7, 0.9 Hz), 7.54 – 7.67 (2H, m), 7.78 (1H, ddt, *J* = 7.8, 1.3, 0.6 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 80.8, 82.2, 122.0, 122.8, 125.5, 126.1 (q, *J* = 5.2 Hz), 127.9 (d, *J* = 2.2 Hz), 128.1, 129.7 (q, *J* = 1.8 Hz), 131.2, 132.1, 132.7, 139.6, 139.6, 142.4. IR (neat, cm^{-1}): 523, 632, 663, 758, 1033, 1070, 1107, 1177, 1312, 1366, 1471, 1738, 2361, 2969, 3273. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ = –58.2. HRMS: calcd. for $C_{15}H_9F_3^+$ $[M]^+$ = 246.0656; found = 246.0656.

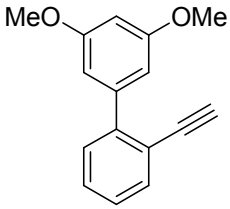
2-Chloro-2'-ethynyl-1,1'-biphenyl (182i)



From **181i** (157 mg, 725 µmol, 1.0 equiv.), Ohira-Bestmann reagent (209 mg, 1088 µmol, 1.5 equiv.) and potassium carbonate (200 mg, 145 µmol, 2.0 equiv.) in methanol (7.3 ml), compound **182i** (137 mg, 644 µmol, **89%**) was obtained according to GP3 [1 h] as a pale yellow oil

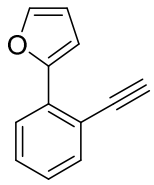
after purification by column chromatography (*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 2.95 (1H, s), 7.28 – 7.45 (6H, m), 7.45 – 7.53 (1H, m), 7.59 – 7.67 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 80.4, 82.3, 122.0, 126.5, 127.8, 128.6, 129.1, 129.6, 130.0, 131.5, 133.1, 133.4, 139.5, 142.5. IR (neat, cm^{-1}): 519, 618, 651, 733, 754, 1004, 1033, 1070, 1259, 1435, 1462, 1567, 2106, 3059, 3286. HRMS: calcd. for $C_{14}H_9Cl^+$ $[M]^+$ = 212.0393; found = 212.0398.

2-Ethynyl-3',5'-dimethoxy-1,1'-biphenyl (182s)



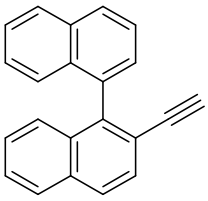
Compound **182s** (58 mg, 243 µmol, **41%**) was obtained from **181s** (143 mg, 590 µmol, 1.0 equiv.), Ohira-Bestmann reagent (170 mg, 885 µmol, 1.5 equiv.) and potassium carbonate (163 mg, 1.18 mmol, 2.0 equiv.) in methanol (5.9 ml) according to GP3 [1.5 h] as a colorless oil after purification by column chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.09 (1H, s), 3.84 (6H, s), 6.50 (1H, t, *J* = 2.3 Hz), 6.76 (2H, d, *J* = 2.3 Hz), 7.28 – 7.34 (1H, m), 7.37 – 7.42 (2H, m), 7.62 (1H, dt, *J* = 7.8, 1.0 Hz) ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.5, 80.6, 83.2, 100.1, 107.6, 120.5, 127.3, 129.1, 129.6, 134.1, 142.3, 144.5, 160.4. IR (DCM, cm^{-1}): 653, 695, 760, 837, 1027, 1063, 1154, 1204, 1349, 1418, 1457, 1591, 2835, 2937, 3279. HRMS: calcd. for $C_{16}H_{14}O_2^+$ $[M]^+$ = 238.0994; found = 238.0996. The spectral data correspond to those reported in the literature.[134]

2-(2-Ethynylphenyl)furan (182v)



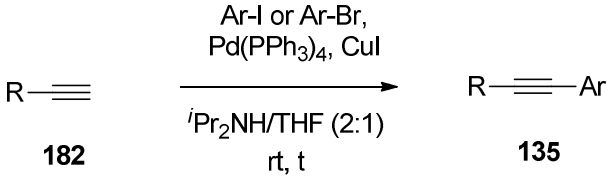
Compound **182v** (196 mg, 1.17 mmol, **63%**) was obtained from **181v** (320 mg, 1.86 mmol, 1.0 equiv.), Ohira-Bestmann reagent (536 mg, 2.79 mmol, 1.5 equiv.) and potassium carbonate (513 mg, 3.71 mmol, 2.0 equiv.) were suspended in methanol (18 ml) according to GP3 [1.5 h] as a pale yellow oil after purification by column chromatography (*n*-hexane) ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.40 (1H, s), 6.51 (1H, dd, *J* = 3.5, 1.8 Hz), 7.22 (1H, td, *J* = 7.6, 1.3 Hz), 7.36 – 7.44 (2H, m), 7.50 (1H, dd, *J* = 1.8, 0.8 Hz), 7.58 (1H, ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.85 (1H, ddd, *J* = 8.1, 1.3, 0.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 82.2, 83.7, 109.8, 111.7, 117.2, 125.6, 126.7, 129.2, 132.4, 134.7, 142.0, 151.7. IR (neat, cm^{-1}): 512, 530, 561, 597, 667, 757, 901, 1066, 1216, 1228, 1366, 1738, 2341, 2362, 2969.

2-Ethynyl-1,1'-binaphthalene (182z)



Compound **182z** (130 mg, 467 µmol, **88%**) was obtained from **181z** (150 mg, 531 µmol, 1.0 equiv.), Ohira-Bestmann reagent (153 mg, 796 µmol, 1.5 equiv.) and potassium carbonate (146 mg, 1.06 mmol, 2.0 equiv.) in methanol (5.3 ml) according to GP3 [40 min] as a white foam after purification by column chromatography (*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 2.81 (1H, s), 7.23 – 7.33 (4H, m), 7.46 – 7.52 (3H, m), 7.64 (1H, dd, *J* = 8.3, 7.0 Hz), 7.73 (1H, d, *J* = 8.6 Hz), 7.89 – 7.94 (2H, m), 7.64 (2H, ddq, *J* = 11.0, 8.4, 0.7 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 81.0, 83.3, 120.3, 125.5, 126.0, 126.2, 126.2, 126.8, 126.8, 127.1, 128.0, 128.0, 128.2, 128.3, 128.3, 129.1, 132.7, 133.0. 133.3, 133.7, 136.6, 142.2. IR (neat, cm^{-1}): 627, 746, 779, 817, 1028, 1174, 1243, 1284, 1508, 1590, 1603, 2205, 2535, 2833, 3052. HRMS: calcd. for $C_{22}H_{14}^{2+}$ $[M–2H]^{2+}$ = 276.0928; found = 276.0945.

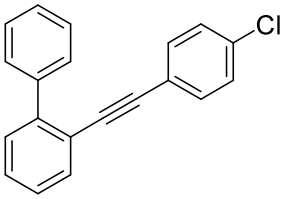
6.3.1.2. Alkynes 135 by Sonogashira-Hagihara coupling.



Scheme 124. Sonogashira-Hagihara coupling with alkyne **182**.

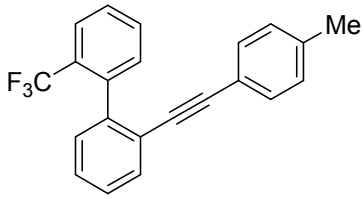
General procedure (GP4): A 2/1 mixture of diisopropylamine and THF (ĉ ~ 0.01 M with respect to **182**) was degassed in a round-bottomed flask for 10 min under a N_2 atmosphere. The corresponding Ar-I or Ar-Br (1.0 equiv.), $Pd(PPh_3)_4$ (2.5 mol%) and CuI (5 mol%) were added in one portion and stirred for 15 min. After addition of the corresponding alkyne (1.0 equiv.), the reaction mixture was stirred at rt for indicated time. Filtration through a silica and Celite pad afforded a clear solution that was concentrated and further purified by column chromatography.[143]

2-[(4-chlorophenyl)ethynyl]-1,1'-biphenyl (135d)



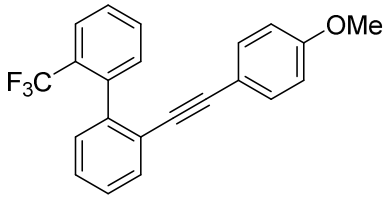
Following GP4, **135d** was prepared from 2-iodo-1,1'-biphenyl (308 mg, 1.10 mmol), $Pd(PPh_3)_4$ (32 mg, 28 µmol, 2.5 mol%), CuI (9 mg, 47 µmol, 4.3 mol%) and 1-chloro-4-ethynylbenzene (150 mg, 1.10 mmol) [rt, 3 h] as a pale yellow solid (201 mg, 0.70 mmol, **64%**) after flash chromatography (*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.24 – 7.27 (4H, m), 7.34 (1H, ddd, *J* = 7.7, 6.6, 2.3 Hz), 7.37 – 7.49 (5H, m), 7.61 – 7.67 (3H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 90.5, 91.2, 121.4, 122.1, 127.2, 127.7, 128.0, 128.8, 128.9, 129.5, 129.7, 132.7, 132.9, 134.2, 140.7, 144.2. IR (neat, cm^{-1}): 503, 697, 733, 753, 774, 824, 1012, 1088, 1431, 1487, 1591, 1738, 2216, 3021, 3056. HRMS: calcd. for $C_{20}H_{13}Cl^+$ $[M]^+$ = 288.0706; found = 288.0717. The spectral data correspond to those reported in the literature.[143]

Compound 135g



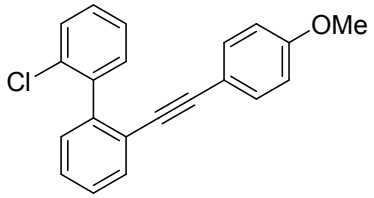
Following GP4, **135g** (91 mg, 271 µmol, **72%**) was prepared from 4-methyliodobenzene (104 mg, 477 µmol), $Pd(PPh_3)_4$ (12 mg, 10 µmol, 2.7 mol%), CuI (4 mg, 21 µmol, 5.6 mol%) and **182g** (92 mg, 374 µmol) [rt, 1 h] as a pale yellow solid after flash chromatography (*n*-hexanes/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 2.30 (3H, s), 6.94 – 6.98 (2H, m), 6.98 – 7.06 (2H, m), 7.31 (1H, dtd, *J* = 6.7, 1.6, 0.7 Hz), 7.33 – 7.46 (3H, m), 7.47 – 7.56 (1H, m), 7.56 – 7.63 (2H, m), 7.78 (1H, ddd, *J* = 7.5, 1.5, 0.8 Hz). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 21.6, 87.8, 93.6, 120.2, 123.4, 124.3 (q, *J* = 239.4 Hz), 126.0 (q, *J* = 5.1 Hz), 127.4, 127.7, 127.9, 128.9, 129.0, 129.4 – 129.4 (m), 131.1, 131.3, 131.5, 132.4, 138.4, 140.0 (q, *J* = 2.1 Hz), 142.0. ^{19}F NMR (471 MHz, $CDCl_3$, ppm) δ = –58.2. IR (neat, cm^{-1}): 509, 761, 810, 1030, 1068, 1101, 1170, 1313, 1366, 1436, 1738, 2212, 2360, 2920, 2969. HRMS: calcd. for $C_{22}H_{15}F_3^+$ $[M]^+$ = 336.1126; found = 336.1118.

2-[(4-Methoxyphenyl)ethynyl]-2'-(trifluoromethyl)-1,1'-biphenyl (135h)



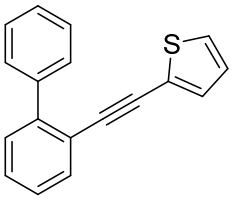
Following GP4, **135h** (104 mg, 295 µmol, **93%**) was prepared from 4-iodoanisole (75 mg, 317 µmol), $Pd(PPh_3)_4$ (9 mg, 8 µmol, 2.5 mol%), CuI (3 mg, 16 µmol, 5.0 mol%) and **182h** (78 mg, 317 µmol) [rt, 40 min] as a white solid after flash chromatography (*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.77 (3H, s), 6.70 – 6.78 (2H, m), 6.95 – 7.05 (2H, m), 7.27 – 7.38 (3H, m), 7.38 – 7.44 (1H, m), 7.47 – 7.55 (1H, m), 7.55 – 7.63 (2H, m), 7.75 – 7.81 (1H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 55.4, 87.2, 93.5, 113.9, 115.4, 123.5, 124,0 (q, (q, *J* = 289.9 Hz), 125.82 – 126.34 (m), 127.1, 127.6, 127.8, 128.9, 129.32 (q, *J* = 1.9 Hz), 131.0, 131.2, 132.4, 132.8, 140.1, 141.8, 159.5. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ = –58.2. IR (neat, cm^{-1}): 513, 533, 649, 766, 830, 1025, 1066, 1109, 1158, 1246, 1313, 1438, 1507, 1603, 2357. HRMS: calcd. for $C_{22}H_{15}F_3O^+$ $[M]^+$ = 352.1075; found = 352.1065.

2-Chloro-2'-[(4-methoxyphenyl)ethynyl]-1,1'-biphenyl (135i)



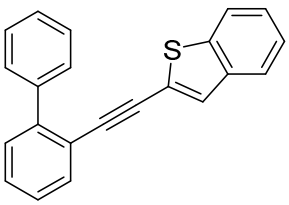
Following GP4, **135i** (146 mg, 458 µmol, **75%**) was prepared from 4-iodoanisole (158 mg, 675 µmol, 1.1 equiv.), $Pd(PPh_3)_4$ (29 mg, 25 µmol, 4.1 mol%), CuI (5 mg, 26 µmol, 4.3 mol%) and **182i** (130 mg, 611 µmol) [rt, 1 h] as a colorless oil after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.79 (3H, s), 6.77 – 6.84 (2H, m), 7.17 (2H, dd, *J* = 8.7, 1.6 Hz), 7.36 – 7.42 (5H, m), 7.43 – 7.47 (1H, m), 7.52 – 7.58 (1H, m), 7.63 – 7.69 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.3, 87.3, 92.9, 114.0, 115.5, 123.5, 126.3, 127.7, 127.8, 128.9, 129.4, 129.8, 131.7, 131.8, 132.9, 133.6, 139.9, 141.9, 159.6. IR (neat, cm^{-1}): 513, 682, 744, 829, 944, 1028, 1173, 1245, 1286, 1462, 1509, 1605, 2213, 2834, 3055. HRMS: calcd. for $C_{21}H_{15}ClO^+$ $[M]^+$ = 318.0811; found = 318.0815.

2-([1,1'-Biphenyl]-2-ylethynyl)thiophene (135o)



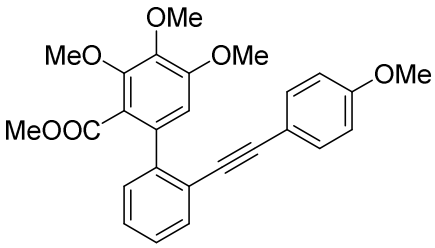
Following GP4, **135o** (75 mg, 288 µmol, **51%**) was prepared from 2-bromothiophene (92 mg, 564 µmol), $Pd(PPh_3)_4$ (16 mg, 14 µmol, 2.5 mol%), CuI (5 mg, 26 µmol, 4.6 mol%) and **135f** (100 mg, 561 µmol) [rt, 1 h] as a yellow oil after flash chromatography (*n*-hexane). NMR (400 MHz, $CDCl_3$, ppm) δ = 6.98 (1H, dd, *J* = 5.1, 3.6 Hz), 7.14 (1H, dd, *J* = 3.6, 1.2 Hz), 7.23 – 7.27 (1H, m), 7.35 (1H, ddd, *J* = 7.6, 7.2, 1.7 Hz), 7.39 – 7.52 (5H, m), 7.65 (1H, ddd, *J* = 7.6, 1.5, 0.6 Hz), 7.67 – 7.70 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 85.8, 93.3, 121.4, 123.6, 127.1, 127.2, 127.3, 127.6, 128.1, 128.8, 129.4, 129.6, 131.6, 132.6, 140.5, 143.8. IR (neat, cm^{-1}): 556, 693, 733, 753, 828, 852, 1007, 1034, 1074, 1212, 1419, 1473, 1520, 2203, 3057. HRMS: calcd. for $C_{18}H_{11}S^+$ $[M–H]^+$ = 259.0576; found = 259.0590.

2-([1,1'-Biphenyl]-2-ylethynyl)benzo[*b*]thiophene [135p]



Following GP4, **135p** (165 mg, 532 µmol, **83%**) was prepared from 2-bromobenzothiophene (150 mg, 704 µmol, 1.1 equiv.), $Pd(PPh_3)_4$ (19 mg, 16 µmol, 2.5 mol%), CuI (6 mg, 32 mmol, 5.0 mol%) and **135f** (114 mg, 640 µmol) [rt, 3 h] as a yellow oil after flash chromatography (*n*-hexane). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.36 – 7.44 (4H, m), 7.44 – 7.61 (5H, m), 7.72 – 7.83 (5H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 86.0, 95.2, 121.0, 122.0, 123.5, 123.8, 124.7, 125.4, 127.2, 127.7, 128.1, 128.3, 129.1, 129.4, 129.6, 132.8, 139.2, 140.4, 140.4, 144.1. IR (neat, cm^{-1}): 511, 560, 697, 723, 826, 856, 906, 1007, 1079, 1155, 1181, 1434, 1472, 2203, 3055.

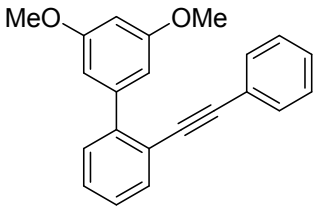
Methyl 3,4,5-Trimethoxy-2'-[(4-methoxyphenyl)ethynyl]-[1,1'-biphenyl]-2-carboxylate (135q)



Following GP4, **135q** (43 mg, 99 µmol, **49%**) was prepared from 4-iodoanisole (52 mg, 222 µmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5 µmol, 2.5 mol%), CuI (2 mg, 11 µmol, 5.4 mol%) and **182q** (66 mg, 202 µmol) [rt, 4 h] as a yellow oil after flash chromatography (*n*-hexane/EtOAc 9:1). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.55 (3H, s), 3.79 (3H, s), 3.84 (3H, s), 3.95 (3H, s), 3.98 (3H,

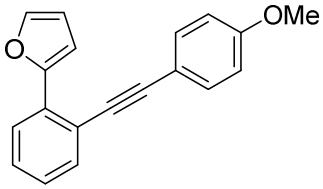
s), 6.77 – 6.82 (2H, m), 6.83 (1H, s), 7.20 – 7.25 (2H, m), 7.28 – 7.34 (3H, m), 7.54 – 7.59 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 52.0, 55.4, 56.3, 61.1, 62.2, 87.4, 93.2, 110.3, 114.0, 115.6, 121.7, 122.7, 127.5, 127.7, 129.2, 132.1, 132.9, 135.8, 141.6, 142.4, 151.8, 154.0, 159.7, 167.4. IR (neat, cm^{-1}): 756, 831, 1027, 1106, 1245, 1272, 1344, 1396, 1454, 1510, 1592, 1725, 2212, 2836, 2937. HRMS: calcd. for $C_{26}H_{24}O_6^+$ $[M]^+$ = 432.1573; found = 432.1577.

3',5'-Dimethoxy-2-(phenylethynyl)-1,1'-biphenyl (135s)



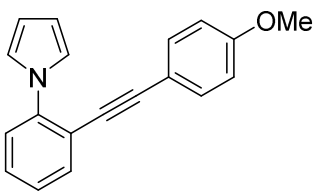
Following GP4, **135s** (42 mg, 134 µmol, **64%**) was prepared from iodobenzene (43 mg, 211 µmol), $Pd(PPh_3)_4$ (7 mg, 6 µmol, 2.9 mol%), CuI (2 mg, 10 µmol, 4.8 mol%) and **182s** (50 mg, 210 µmol) [rt, 2 h] as a white solid after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.83 (6H, s), 6.54 (1H, t, *J* = 2.3 Hz), 6.85 (2H, d, *J* = 2.3 Hz), 7.28 – 7.43 (7H, m), 7.43 – 7.48 (1H, m), 7.63 – 7.69 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.5, 89.5, 92.8, 100.2, 107.6, 121.7, 123.6, 127.3, 128.3, 128.4, 128.6, 129.5, 131.5, 133.1, 142.6, 143.9, 160.4. IR (neat, cm^{-1}): 690, 753, 773, 1027, 1060, 1154, 1202, 1260, 1348, 1417, 1587, 1737, 2362, 2960, 3015. HRMS: calcd. for $C_{22}H_{18}O_2^+$ $[M]^+$ = 314.1307; found = 314.1309.

2-{2-[(4-methoxyphenyl)ethynyl]phenyl}furan (135v)



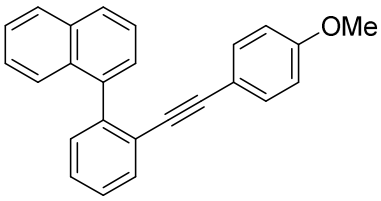
Following GP4, 1**35v** (119 mg, 434 µmol, **88%**) was prepared from 4-iodoanisole (167 mg, 714 µmmol, 1.45 equiv.), $Pd(PPh_3)_4$ (17 mg, 15 µmol, 3.0 mol%), CuI (5 mg, 26 µmol, 5.3 mol%) and **182v** (83 mg, 493 µmol) [rt, 1 h] as a pale yellow oil after flash chromatography (*n*-hexane/EtOAc 50/1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.84 (3H, s), 6.57 (1H, dd, *J* = 3.4, 1.8 Hz), 6.90 – 6.98 (2H, m), 7.23 – 7.29 (1H, m), 7.40 (1H, ddd, *J* = 7.9, 7.4, 1.4 Hz), 7.46 (1H, dd, *J* = 3.5, 0.8 Hz), 7.50 – 7.58 (3H, m), 7.63 (1H, ddd, *J* = 7.7, 1.5, 0.5 Hz), 7.88 – 7.96 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.4, 88.4, 94.1, 109.5, 111.8, 114.2, 115.5, 118.7, 125.6, 126.8, 128.4, 131.7, 133.0, 133.7, 141.9, 152.3, 159.9. IR (neat, cm^{-1}): 528, 733, 756, 828, 1004, 1027, 1173, 1245, 1287, 1462, 1508, 1604, 2210, 2834, 2932. HRMS: calcd. for $C_{19}H_{14}O_2^+$ $[M]^+$ = 274.0994; found = 274.0993.

1-{2-[(4-methoxyphenyl)ethynyl]phenyl}-1*H*-pyrrole (135w)



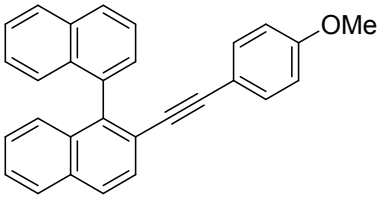
From 4-ethynylanisol (103 mg, 779 µmol, 1.05 equiv.), $PdCl_2(PPh_3)_2$ (26 mg, 37 µmol, 5.0 mol%), CuI (7 mg, 37 µmol, 5.0 mol%) and 1-(2-iodophenyl)-1*H*-pyrrole (200 mg, 743 µmol) in MeCN (40 ml) [60 °C, 12 h], **135w** (104 mg, 380 µmol, **51%**) was prepared as a colorless oil after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 3.82 (3H, s), 6.35 (2H, t, *J* = 2.2 Hz), 6.81 – 6.89 (2H, m), 7.16 – 7.19 (2H, m), 7.33 – 7.41 (4H, m), 7.61 (1H, ddd, *J* = 7.6, 1.6, 0.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 55.5, 85.4, 94.1, 109.2, 114.1, 115.2, 118.7, 121.9, 125.0, 126.3, 128.9, 133.0, 133.4, 141.9, 159.8. IR (neat, cm^{-1}): 729, 756, 800, 1024, 1078, 1172, 1247, 1451, 1511, 1603, 1710, 2342, 2361, 2923, 2961. HRMS: calcd. for $C_{19}H_{15}NO^+$ $[M]^+$ = 273.1154; found = 273.1162.

1-{2-[(4-Methoxyphenyl)ethynyl]phenyl}naphthalene (135y)



Following GP4, **135y** (215 mg, 643 µmol, **85%**) was prepared from 4-iodoanisole (178 mg, 761 µmol), $Pd(PPh_3)_4$ (22 mg, 19 µmol, 2.5 mol%), CuI (7 mg, 37 µmol, 4.9 mol%) and **182y** (173 mg, 758 µmol) [rt, 3 h] as a pale yellow oil after flash chromatography (*n*-hexanes/EtOAc 9:1). ^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ = 3.72 (3H, s), 6.59 – 6.67 (2H, m), 6.67 – 6.74 (2H, m), 7.37 – 7.52 (6H, m), 7.55 (1H, dd, *J* = 8.2, 7.0 Hz), 7.63 – 7.69 (1H, m), 7.71 (1H, dd, *J*=8.5, 1.0 Hz), 7.88 – 7.96 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 55.4, 87.9, 93.2, 113.7, 115.4, 124.1, 125.2, 125.7, 125.9, 126.6, 127.4, 127.5, 127.8, 127.9, 128.1, 130.6, 131.7, 132.0, 132.7, 133.6, 139.1, 143.0, 159.4. IR (neat, cm^{-1}): 524, 756, 776, 801, 830, 1027, 1173, 1243, 1286, 1508, 1604, 1733, 2213, 2834, 3054. HRMS: calcd. for $C_{25}H_{18}O^+$ $[M]^+$ = 334.1358; found = 334.1351.

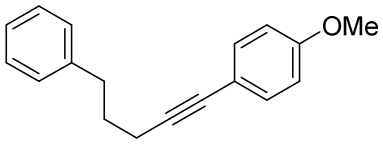
2-[(4-Methoxyphenyl)ethynyl]-1,1'-binaphthalene (135z)



Following GP4, **135z** (165 mg, 429 µmol, **96%**) was prepared from 4-iodoanisole (126 mg, 538 µmol, 1.2 equiv.), $Pd(PPh_3)_4$ (13 mg, 11 µmol, 2.4 mol%), CuI (4 mg, 21 µmol, 4.7 mol%) and **182z** (125 mg, 449 µmol) [rt, 12 h] as a white solid after flash chromatography (*n*-hexane/EtOAc 25:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.73 (3H, s), 6.64 – 6.70 (2H,

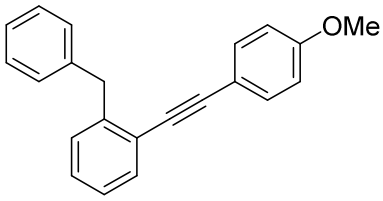
m), 6.74 – 6.79 (2H, m), 7.32 (2H, ddd, *J* = 8.4, 6.7, 1.3 Hz), 7.41 (2H, dddt, *J* = 8.5, 2.9, 1.4, 0.8 Hz), 7.50 (2H, dddd, *J* = 8.1, 6.7, 3.8, 1.3 Hz), 7.57 (1H, dd, *J* = 7.0, 1.3 Hz), 7.67 (1H, dd, *J* = 8.2, 7.0 Hz), 7.77 (1H, d, *J* = 8.5 Hz), 7.92 – 7.96 (2H, m), 7.99 – 8.06 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.3, 88.6, 94.0, 113.8, 115.4, 121.9, 125.5, 125.9, 126.1, 126.4, 126.5, 126.7, 126.9, 127.9, 128.1, 128.1, 128.2, 128.3, 128.5, 132.8, 132.8, 133.0, 133.1, 133.7, 137.2, 141.1, 159.5. IR (neat, cm^{-1}): 627, 746, 779, 817, 1028, 1174, 1243, 1284, 1508, 1590, 1603, 2205, 2535, 2833, 3052. HRMS: calcd. for $C_{29}H_{20}O^+$ $[M]^+$ = 384.1514; found = 384.1523.

1-Methoxy-4-(5-phenylpent-1-yn-1-yl)benzene (102au)



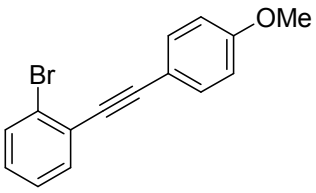
Following GP4, compound **102au** (289 mg, 1.15 mmol, **58%**) was prepared from 4-iodoanisole (509 mg, 2.17 mmol, 1.1 equiv.), $PdCl_2(PPh_3)_2$ (69 mg, 98 µmol, 4.9 mmol), CuI (190 mg, 100 µmol, 5.0 mol%) and 4-pentynylbenzene (285 mg, 1.98 mmol) [rt, 50 min] as a yellow oil after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 1.93 (2H, dt, *J* = 14.6, 7.1 Hz), 2.42 (2H, t, *J* = 7.0 Hz), 2.77 – 2.84 (2H, m), 3.81 (3H, s), 6.80 – 6.87 (2H, m), 7.20 – 7.26 (3H, m), 7.28 – 7.34 (2H, m), 7.34 – 7.39 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 19.0, 30.6, 35.0, 55.4, 81.0, 88.3, 114.0, 116.3, 126.0, 128.5, 128.7, 133.0, 141.9, 159.2. IR (neat, cm^{-1}): 535, 698, 743, 830, 1030, 1105, 1170, 1242, 1287, 1454, 1507, 1604, 1737, 2834, 2933. HRMS: calcd. for $C_{18}H_{18}O^+$ $[M]^+$ = 250.1358; found = 250.1357.

1-Benzyl-2-[(4-methoxyphenyl)ethynyl]benzene (102av)



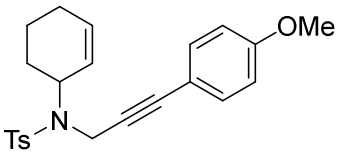
Following GP4, **102av** (104 mg, 349 µmol, **72%**) was prepared from 1-benzyl-2-iodobenzene (142 mg, 483 µmol), $Pd(PPh_3)_4$ (14 mg, 12 µmol, 2.5 mol%), CuI (4 mg, 21 µmol, 4.3 mol%) and 4-ethynylanisol (77 mg, 583 µmol, 1.21 equiv.) [rt, 3 h] as a white solid after flash chromatography (*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.80 (3H, s), 4.23 (2H, s), 6.81 – 6.89 (2H, m), 7.12 – 7.29 (8H, m), 7.35 – 7.44 (2H, m), 7.51 (1H, ddd, *J* = 7.0, 1.9, 0.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ = 40.5, 55.4, 87.2, 93.5, 114.1, 115.7, 123.4, 126.2, 126.3, 128.3, 128.5, 129.1, 129.5, 132.2, 133.1, 140.8, 143.0, 159.7. IR (neat, cm^{-1}): 529, 696, 728, 756, 829, 906, 1028, 1173, 1245, 1285, 1451, 1509, 1604, 2358, 2835. HRMS: calcd. for $C_{22}H_{18}O^+$ $[M]^+$ = 298.1358; found = 298.1357.

1-Bromo-2-[(4-methoxyphenyl)ethynyl]benzene (102aw)



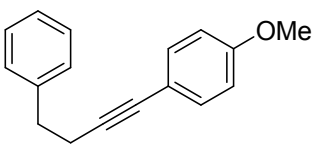
Following GP4, **102aw** (503 mg, 1.75 mmol, **99%**) was prepared from 1,2-bromoiodobenzene (500 mg, 1.77 mmol), $Pd(PPh_3)_4$ (51 mg, 44 µmol, 3.7 mol%), CuI (15 mg, 79 µmol, 6.7 mol%) and 4-ethynylanisol (233 mg, 1.76 mmol) [rt, 3 h]. A white solid was obtained after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.84 (3H, s), 6.85 – 6.93 (2H, m), 7.16 (1H, ddd, *J* = 8.1, 7.5, 1.7 Hz), 7.24 – 7.31 (1H, m), 7.48 – 7.56 (3H, m), 7.61 (1H, dd, *J* = 8.1, 1.2 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.5, 87.0, 94.2, 114.2, 115.2, 125.6, 125.9, 127.1, 129.1, 132.5, 133.2, 133.3, 160.1. IR (neat, cm^{-1}): 520, 533, 673, 756, 836, 1022, 1107, 1174, 1247, 1290, 1435, 1508, 1602, 2360, 2963. HRMS: calcd. for $C_{15}H_{11}BrO^+$ $[M]^+$ = 285.9993; found = 285.9992.

***N*-(Cyclohex-2-en-1-yl)-*N*-(3-(4-methoxyphenyl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide (170a)**



Following GP4, **170a** (166 mg, 420 µmol, **81%**) was prepared from 4-iodoanisole (146 mg, 624 µmol, 1.2 equiv.), $Pd(PPh_3)_4$ (15 mg, 13 µmol, 2.5 mol%), CuI (4 mg, 21 µmol, 4.1 mol%) and *N*-(2-cyclohexen-1-yl)-4-methyl-*N*-(2-propyn-1-yl)benzenesulfonamide (150 mg, 518 µmol) [rt, 90 min]. A white solid was obtained after flash chromatography (*n*-hexane/EtOAc 5:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 1.74 – 1.87 (3H, m), 1.93 – 2.07 (2H, m), 2.36 (3H, s), 3.80 (3H, d, *J* = 0.7 Hz), 4.08 – 4.40 (2H, m), 4.57 (1H, td, *J* = 5.5, 2.7 Hz), 5.42 (1H, dd, *J* = 10.2, 2.3 Hz), 5.77 – 5.99 (1H, m), 6.73 – 6.85 (2H, m), 7.09 – 7.24 (4H, m), 7.78 – 7.90 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 21.6, 21.6, 24.6, 28.1, 33.8, 55.2, 55.4, 84.0, 84.6, 113.9, 115.0, 127.6, 127.6, 129.5, 132.9, 133.0, 138.5, 143.1, 159.7. IR (neat, cm^{-1}): 542, 582, 647, 665, 726, 907, 1031, 1094, 1157, 1246, 1333, 1508, 1605, 2359, 2933. HRMS: calcd. for $C_{23}H_{25}NO_3S^+$ $[M]^+$ = 395.1555; found = 395.1560.

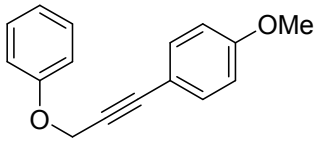
1-Methoxy-4-(4-phenylbut-1-yn-1-yl)benzene (170b)



Following GP4, **170b** (349 mg, 1.48 mmol, **96%**) was prepared from 4-iodoanisole (360 mg, 1.54 mmol), $PdCl_2(PPh_3)_2$ (49 mg, 70 µmol, 6.1 mol%), CuI (13 mg, 68

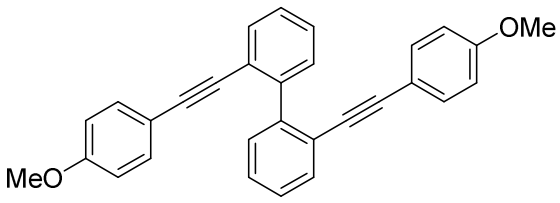
µmol, 5.9 mol%) and 3-butynylbenzene (200 mg, 1.54 mmol) [rt, 24 h] as a white solid after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 2.66 (2H, t, *J* = 7.5 Hz), 2.90 (2H, t, *J* = 7.6 Hz), 3.78 (3H, s), 6.77 – 6.82 (2H, m), 7.23 – 7.32 (7H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 21.8, 35.5, 55.4, 81.2, 88.0, 114.0, 116.2, 126.4, 128.5, 128.7, 133.0, 141.0, 159.2. IR (neat, cm^{-1}): 506, 697, 746, 830, 1030, 1172, 1241, 1287, 1453, 1485, 1508, 1605, 2833, 2930, 3025. HRMS: calcd. for $C_{17}H_{16}O^+$ $[M]^+$ = 236.1201; found = 236.1202.

1-Methoxy-4-(3-phenoxyprop-1-yn-1-yl)benzene (170c)



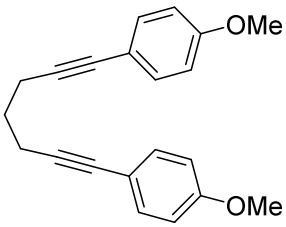
Following GP4, **170c** (475 mg, 1.99 mmol, **85%**) was prepared from 4-iodoanisole (602 mg, 2.57 mmol, 1.1 equiv.), $PdCl_2(PPh_3)_2$ (82 mg, 117 µmol, 5.0 mol%), CuI (22 mg, 116 µmol, 5.0 mol%) and (2-propynyloxy)benzene (309 mg, 2.34 mmol) [rt, 1 h] as white crystals after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.80 (3H, s), 4.96 (2H, s), 6.83 – 6.94 (2H, m), 7.03 – 7.18 (3H, m), 7.35 – 7.44 (2H, m), 7.44 – 7.51 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.1, 56.6, 82.7, 87.1, 113.9, 114.3, 114.9, 121.3, 129.4, 133.3, 157.9, 159.9. IR (neat, cm^{-1}): 533, 756, 837, 1023, 1107, 1176, 1247, 1290, 1440, 1462, 1507, 1602, 2217, 2837, 2965. HRMS: calcd. for $C_{16}H_{14}O_2^+$ $[M]^+$ = 238.0994; found = 238.0999.

2,2'-Bis[(4-methoxyphenyl)ethynyl]-1,1'-biphenyl (190)



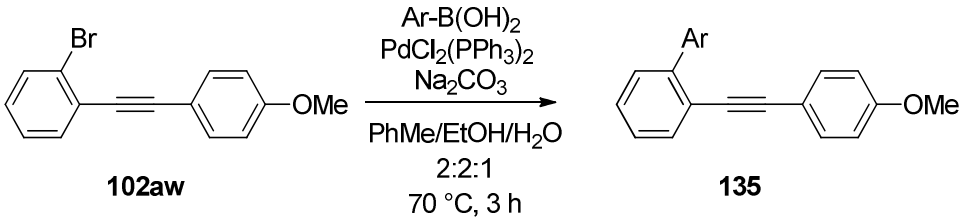
Following GP4, **190** (130 mg, 314 µmol, **65%**) was prepared from 4-iodoanisole (454 mg, 1.94 mmol, 4.0 equiv.), $Pd(PPh_3)_4$ (28 mg, 24 µmol, 2.5 mol%), CuI (8 mg, 42 µmol, 4.3 mol%) and 2,2'-diethynyl-1,1'-biphenyl (98 mg, 485 µmol) [rt, 12 h] as a yellow solid (130 mg, 0.31 mmol, **65%**) after flash chromatography (*n*-hexane/toluene 1/1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.77 (3H, s), 6.72 – 6.83 (2H, m), 7.11 – 7.21 (2H, m), 7.31 – 7.44 (2H, m), 7.51 – 7.60 (1H, m), 7.60 – 7.68 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.4, 88.0, 92.6, 114.0, 115.8, 123.3, 127.4, 127.4, 130.5, 131.9, 132.9, 143.1, 159.5. IR (neat, cm^{-1}): 756, 831, 1028, 1106, 1173, 1247, 1287, 1439, 1463, 1510, 1604, 1656, 2213, 2361, 2835. HRMS: calcd. for $C_{30}H_{22}O_2^+$ $[M]^+$ = 414.1620; found = 414.1619.

1,7-bis(4-methoxyphenyl)hepta-1,6-diyne (193)



Following GP4, **193** (912 mg, 3.00 mmol, **92%**) was prepared from 4-iodoanisole (1.679 g, 7.17 mmol, 2.2 equiv.), $Pd(PPh_3)_4$ (188 mg, 163 µmol, 2.5 mol%), CuI (56 mg, 294 µmol, 4.5 mol%) and hepta-1,6-diyne (300 mg, 3.26 mmol, 1.0 equiv.) [rt for 3 h] as a white solid after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 1.90 (2H, d, *J* = 7.1 Hz), 2.58 (4H, t, *J* = 7.0 Hz), 3.80 (6H, s), 6.75 – 6.91 (4H, m), 7.30 – 7.40 (4H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 18.8, 28.3, 55.3, 81.0, 87.7, 113.9, 116.1, 133.0, 159.2. IR (neat, cm^{-1}): 538, 823, 836, 1030, 1107, 1172, 1216, 1231, 1286, 1366, 1439, 1508, 1604, 1738, 2362.

6.3.1.3. Alkynes 135 by Suzuki-Miyaura coupling.

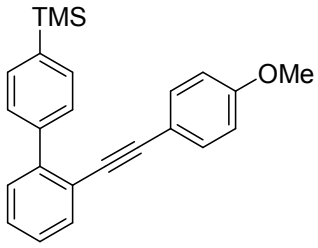


102aw **135**

Scheme 125. Suzuki-Miyaura cross-coupling with bromotolanes **102aw**.

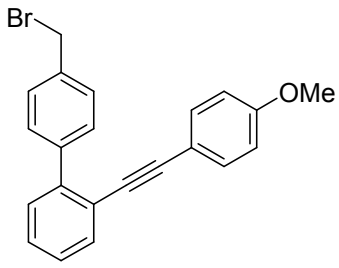
General procedure GP5: Following the reported procedure,[135] a round-bottomed flask was charged with $PdCl_2(PPh_3)_2$ (5 mol%), arylboronic acid (1.3 equiv.), arylbomide **102aw** (1.0 equiv.), Na_2CO_3 (2.0 equiv.) and previously degassed mixture of toluene/EtOH/H_2O (2:1:1) of (ĉ ~ 0.005 M with respect to **102aw**). The reaction mixture was placed into an oil bath preheated to 70 °C and stirred at this temperature for 3 h. The mixture was cooled down to room temperature, diluted with EtOAC and H_2O (10 ml each). The organic layer was dried (Na_2CO_3), the solvent evaporated and the residue purified by column chromatography.

{2'-[(4-Methoxyphenyl)ethynyl]-[1,1'-biphenyl]-4-yl}trimethylsilane (135l)



Following GP5, **135l** (58 mg, 163 µmol, **62%**) was prepared from **102aw** (76 mg, 265 µmol), 4-trimethylsilylphenylboronic acid (66 mg, 340 µmol), $PdCl_2(PPh_3)_2$ (9 mg, 12.8 µmol, 4.8 mol%) and Na_2CO_3 (56 mg, 528 µmol) as a colorless oil after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 0.35 (9H, s), 3.82 (3H, s), 6.80 – 6.86 (2H, m), 7.24 – 7.30 (2H, m), 7.33 (1H, td, *J* = 7.4, 1.6 Hz), 7.39 (1H, td, *J* = 7.5, 1.6 Hz), 7.45 (1H, ddd, *J* = 7.7, 1.6, 0.6 Hz), 7.61 – 7.66 (3H, m), 7.66 – 7.73 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.4, 88.3, 92.5, 114.0, 115.8, 122.1, 127.2, 128.3, 128.8, 129.5, 132.7, 132.9, 133.0, 139.5, 141.2, 143.7, 159.6. IR (neat, cm^{-1}): 534, 752, 822, 1028, 1116, 1173, 1244, 1286, 1439, 1463, 1509, 1604, 1738, 2213, 2952. HRMS: calcd. for $C_{24}H_{24}OSi^+$ $[M]^+$ = 356.1596; found = 356.1597.

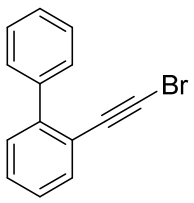
4'-(Bromomethyl)-2-[(4-methoxyphenyl)ethynyl]-1,1'-biphenyl (135m)



Following GP5, **135m** (29 mg, 77 µmol, **22%**) was prepared from **102aw** (100 mg, 348 µmol), 4-(bromomethyl)phenylboronic acid (97 mg, 451 µmol), $PdCl_2(PPh_3)_2$ (12 mg, 17 µmol, 4.9 mol%) and Na_2CO_3 (74 mg, 698 µmol) as a yellow oil after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.77 (3H, s), 4.56 (2H, s), 6.74 – 6.83 (2H, m), 7.16 – 7.47 (8H, m), 7.60 – 7.66 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 65.9, 72.7, 88.2, 92.4, 114.1, 115.8, 122.0, 127.1, 127.3, 128.3, 129.5, 129.6, 132.8, 132.9, 137.9, 140.1, 143.5, 159.7. IR (neat, cm^{-1}): 534, 731, 756, 829, 1027, 1094, 1173, 1245, 1285, 1508, 1604, 2212, 2853, 2927, 2970.

6.3.1.4. Bromination of terminal alkynes.

2-(Bromoethynyl)-1,1'-biphenyl (135t)

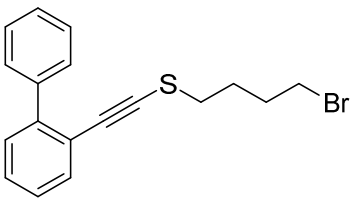


Following the published procedure,[144] to a solution of **135f** (100 mg, 561 µmol, 1.0 equiv.) in acetone (30 ml) were added NBS (120 mg, 674 µmol, 1.2 equiv.) and $AgNO_3$ (10 mg, 59 µmol, 0.11 equiv.) and the resulting mixture was stirred at room temperature for 1 h. After

completion of the reaction, the reaction mixture was filtered and the filtrate was concentrated in vacuum. The crude product was purified by column chromatography (*n*-hexane) affording **135t** as a colorless oil (79 mg, 307 µmol, **55%**). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.28 – 7.34 (1H, m), 7.37 – 7.43 (3H, m), 7.44 – 7.49 (2H, m), 7.57 – 7.62 (3H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 52.3, 79.7, 121.0, 127.0, 127.6, 128.1, 128.9, 129.1, 129.6, 133.7, 140.1, 144.4. IR (neat, cm^{-1}): 696, 734, 914, 1007, 1073, 1159, 1430, 1448, 1472, 1592, 1762, 2193, 2363, 3020, 3055. HRMS: calcd. for $C_{14}H_9Br^+$ $[M]^+$ = 255.9888; found = 255.9889.

6.3.1.5. Thioalkynes.

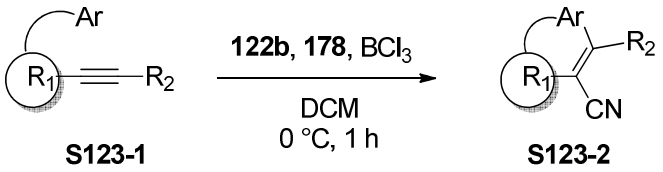
([1,1'-Biphenyl]-2-ylethynyl)(4-bromobutyl)sulfane (135u)



Following the literature procedure,[145] **135t** (58 mg, 226 µmol) was solved in tetrahydrothiophene (1 mL) and heated at 120 °C under microwave irradiation for 3 h. The reaction mixture was concentrated and purified by column chromatography (*n*-hexane/EtOAc 9:1) affording **135u** as a yellow oil (44 mg, 127 µmol, **56%**). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 1.62 – 1.74 (2H, m), 1.87 (2H, tt, *J* = 8.5, 6.5 Hz), 2.62 (2H, t, *J* = 7.0 Hz), 3.30 (2H, t, *J* = 6.7 Hz), 7.32 – 7.45 (6H, m), 7.47 – 7.51 (1H, m), 7.53 – 7.57 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 27.7, 31.0, 32.9, 34.5, 81.7, 93.2, 121.9, 127.1, 127.4, 127.9, 128.1, 129.2, 129.5, 132.3, 140.7, 143.5. IR (neat, cm^{-1}): 562, 697, 731, 753, 908, 1007, 1073, 1236, 1270, 1305, 1430, 1471, 2163, 2934, 3057. HRMS: calcd. for $C_{18}H_{17}BrS^+$ $[M]^+$ = 344.0234; found = 344.0227.

6.3.2. Synthesis of new products.

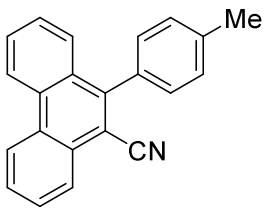
6.3.2.1. Cyanative cyclizations.



Scheme 126. Cyanative cyclization procedure.

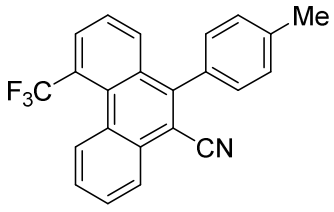
Method A: A dry Schlenk flask was charged with the corresponding alkyne (1.0 equiv.) and reagent **122b** (1.2 equiv.). The mixture was suspended in DCM (ĉ ~ 0.05 M with respect to alkyne) and a cooled down to 0 °C. Under stirring, 2,6-di-*tert*-butylpyridine (**178**) (1.0 equiv.) and a DCM solution of BCl_3 (1.0 M, 1.2 equiv.) were successively added to the suspension in one portion. The reaction mixture was stirred at 0 °C for 1 h. All volatiles were removed under reduced pressure and then in high vacuum, and the remaning solid was washed with ethylacetate, filtered through a Silica pad and concentrated *in vacuo*. The mixture was further purified by column chromatography (*n*-hexane/ethylacetate) affording the corresponding product.

10-(*p*-Tolyl)phenanthrene-9-carbonitrile (136b)



Following Method A, **136b** (43 mg, 147 µmmol, **51%**) was prepared from **135b** (77 mg, 287 µmol), **122b** (162 mg, 342 µmol), 2,6-di-*tert*-butylpyridine **178** (55 mg, 287 µmol) and trichloroborane (0.34 ml, 1 M in DCM, 340 µmol) in DCM (5.7 ml) as a a white solid after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 2.51 (3H, s), 7.40 (4H, s), 7.57 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz), 7.72 – 7.83 (4H, m), 8.38 (1H, dt, *J* = 8.0, 2.9 Hz), 8.77 (2H, dd, *J* = 8.7, 3.9 Hz). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 21.7, 109.7, 117.5, 123.0, 126.5, 127.4, 128.0, 128.3, 128.9, 129.0, 129.4, 129.7, 129.9, 130.4, 131.8, 134.1, 138.9, 147.6. IR (neat, cm^{-1}): 419, 525, 724, 757, 814, 856, 1018, 1372, 1446, 1948, 2054, 2148, 2217, 2381, 3789. HRMS: calcd. for $C_{22}H_{15}N^+$ $[M]^+$ = 293.1204; found = 293.1202.

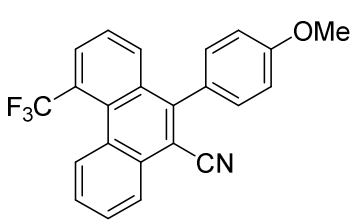
10-(*p*-Tolyl)-4-(trifluoromethyl)phenanthrene-9-carbonitrile (136g)



Following Method A, **136g** (29 mg, 80 µmol, **52%**) was prepared from **135g** (52 mg, 155 µmol), **122b** (88 mg, 0.19 mmol), 2,6-di-*tert*-butylpyridine **178** (30 mg, 157 µmol) and trichloroborane (0.19 ml, 1 M in DCM, 190 µmol) in DCM (3 ml) as a a pale yellow solid after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 2.51 (3H, s), 7.31 – 7.44 (4H, m), 7.62 (1H, t, *J* = 7.9 Hz), 7.71 – 7.79 (1H, m), 7.83 (1H, t, *J* = 7.5 Hz), 7.93 (1H, d, *J* = 8.2 Hz), 8.21 (1H, d, *J* = 7.5 Hz), 8.42 (1H, d, *J* = 7.9 Hz), 8.80 (1H, d, *J* = 8.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 21.6, 111.4, 117.0, 125.4 (q, *J* = 289.8 Hz), 126.0,

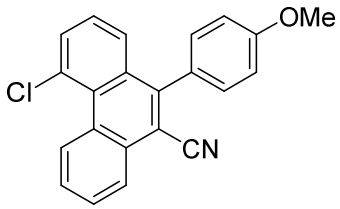
126.1, 127.4, 128.0, 128.85 (q, *J* = 8.1 Hz), 129.3, 129.7, 130.0, 130.0, 130.27 (q, *J* = 6.9 Hz), 130.7, 132.4, 133.0, 133.9, 139.3, 147.0.^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ = –54.0. IR (neat, cm^{-1}): 508, 723, 756, 815, 1033, 1104, 1120, 1165, 1284, 1314, 1438, 1511, 2221, 2920, 3060. HRMS: calcd. for $C_{23}H_{14}F_3N^+$ [M]$^+$ = 361.1078; found = 361.1088.

10-(4-Methoxyphenyl)-4-(trifluoromethyl)phenanthrene-9-carbonitrile (136h)



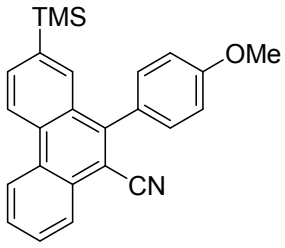
Following Method A, **136h** (58 mg, 154 µmol, **67%**) was prepared from **135h** (81 mg, 230 µmol), **122b** (131 mg, 276 µmol), 2,6-di-*tert*-butylpyridine (**178**) (44 mg, 230 µmol) and trichloroborane (0.28 ml, 1 M in DCM, 280 µmol) in DCM (3 ml) as a white solid after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.93 (3H, s), 7.07 – 7.18 (2H, m), 7.31 – 7.44 (2H, m), 7.63 (1H, t, *J* = 7.9 Hz), 7.74 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz), 7.78 – 7.90 (1H, m), 7.96 (1H, d, *J* = 8.1 Hz), 8.21 (1H, d, *J* = 7.4 Hz), 8.42 (1H, dd, *J* = 8.1, 1.4 Hz), 8.79 (1H, d, *J* = 8.5 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.5, 111.6, 114.5, 117.0, 125.3 (q, *J* = 315.0 Hz), 126.1, 126.5, 126.8, 126.9, 127.3, 128.0, 128.74 – 128.96 (m), 129.3, 130.03 – 130.37 (m), 130.7, 131.5, 132.6, 132.9, 146.7, 160.4. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ = –53.9. IR (neat, cm^{-1}): 562, 697, 731, 753, 908, 1007, 1236, 1270, 1430, 1471, 1591, 2163, 2933, 2959, 3057. HRMS: calcd. for $C_{23}H_{14}F_3NO^+$ [M]$^+$ = 377.1027; found = 377.1026.

4-Chloro-10-(4-methoxyphenyl)phenanthrene-9-carbonitrile (136i)



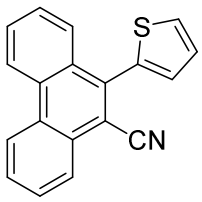
Following Method A, **136i** (75 mg, 218 µmol, **86%**) was prepared from **135i** (81 mg, 254 µmol), **122b** (145 mg, 305 µmol), 2,6-di-*tert*-butylpyridine (**178**) (49 mg, 256 µmol) and trichloroborane (0.31 ml, 1 M in DCM, 310 µmol) in DCM (5 ml) as white crystals after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.93 (3H, s), 7.11 (2H, d, *J* = 8.2 Hz), 7.41 (3H, dd, *J* = 23.2, 8.1 Hz), 7.65 – 7.89 (4H, m), 8.42 (1H, d, *J* = 8.5 Hz), 9.90 (1H, d, *J* = 8.3 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.5, 111.6, 114.4, 117.2, 126.3, 126.9, 127.2, 127.7, 128.5, 128.7, 129.0, 129.3, 129.3, 129.9, 131.3, 131.9, 133.5, 133.7, 147.0, 160.3. IR (neat, cm^{-1}): 545, 583, 717, 753, 767, 791, 810, 863, 1020, 1176, 1259, 1291, 1510, 1609, 2218. HRMS: calcd. for $C_{22}H_{14}ClNO^+$ [M]$^+$ = 343.0764; found = 343.0760.

10-(4-Methoxyphenyl)-2-(trimethylsilyl)phenanthrene-9-carbonitrile (136l)



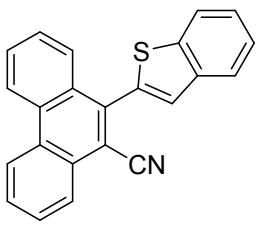
Following Method A, **136l** (17 mg, 45 µmol, **56%**) was prepared from **135l** (29 mg, 81 µmol), **122b** (46 mg, 97 µmol), 2,6-di-*tert*-butylpyridine (**178**) (16 mg, 84 µmol) and trichloroborane (0.10 ml, 1 M in DCM,100 µmol) in DCM (2 ml) as a white solid after flash chromatography (*n*-hexane/toluene 5:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 0.26 (9H, s), 3.95 (3H, s), 7.09 – 7.16 (2H, m), 7.42 – 7.49 (2H, m), 7.73 – 7.80 (2H, m), 7.89 – 7.96 (2H, m), 8.35 – 8.41 (1H, m), 8.71 – 8.79 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = -1.0, 55.5, 109.6, 114.1, 117.7, 122.0, 123.0, 126.5, 127.9, 128.4, 129.1, 129.2, 129.6, 129.7, 131.4, 132.1, 133.8, 134.2, 140.1, 147.5, 160.1. IR (neat, cm^{-1}): 722, 754, 791, 1020, 1088, 1172, 1247, 1288, 1369, 1448, 1511, 1606, 2217, 2922, 2960. HRMS: calcd. for $C_{25}H_{23}NOSi^{+}$ $[M]^{+}$ = 381.1549; found = 381.1553.

10-(Thiophen-2-yl)phenanthrene-9-carbonitrile (136o)



Following Method A, **136o** (16 mg, 56 µmol, **22%**) was prepared from **135o** (66 mg, 254 µmol), **122b** (145 mg, 306 µmol), 2,6-di-*tert*-butylpyridine (**178**) (49 mg, 256 µmol) and trichloroborane (0.30 ml, 1 M in DCM, 300 µmol) in DCM (5 ml) as a white solid after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.29 (1H, dd, *J* = 5.1, 3.5 Hz), 7.34 (1H, dd, *J* = 3.5, 1.2 Hz), 7.57 – 7.67 (2H, m), 7.72 – 7.85 (3H, m), 7.95 (1H, ddd, *J* = 8.3, 1.4, 0.6 Hz), 8.32 – 8.44 (1H, m), 8.68 – 8.78 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 111.9, 117.0, 122.9, 123.1, 126.8, 127.5, 127.8, 128.1, 128.5, 128.6, 128.6, 128.9, 129.8, 130.1, 130.1, 130.9, 131.7, 136.7, 140.0. IR (neat, cm^{-1}): 512, 615, 712, 753, 854, 1042, 1160, 1233, 1369, 1443, 2165, 2212, 2342, 2360, 2919. HRMS: calcd. for $C_{19}H_{11}NS^{+}$ $[M]^{+}$ = 285.0612; found = 258.0619.

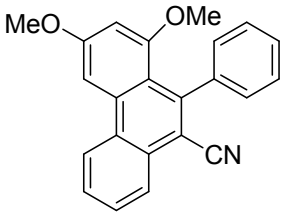
10-(Benzo[b]thiophen-2-yl)phenanthrene-9-carbonitrile (136p)



Following Method A, **136p** (16 mg, 48 µmol, **15%**) was prepared from **135p** (97 mg, 312 µmol), **122b** (178 mg, 375 µmol), 2,6-di-*tert*-butylpyridine (**178**) (60 mg, 314 µmol) and trichloroborane (0.38 ml, 1 M in DCM, 380 µmol) in DCM (6 ml) as a white solid after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 7.41 – 7.51 (2H, m), 7.57 (1H, d, *J* = 0.7 Hz), 7.62 (1H, ddd, *J* =

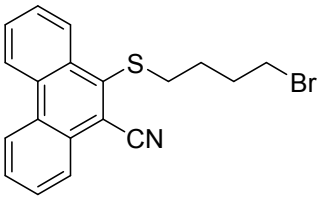
8.3, 7.0, 1.2 Hz), 7.76 – 7.87 (3H, m), 7.88 – 7.98 (2H, m), 8.02 (1H, ddd, *J* = 8.3, 1.4, 0.6 Hz), 8.37 – 8.46 (1H, m), 8.74 – 8.84 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 111.9, 116.9, 122.4, 123.0, 123.1, 124.4, 124.9, 125.3, 126.9, 127.0, 127.9, 128.7, 128.7, 128.8, 128.9, 129.9, 130.3, 130.6, 131.7, 137.3, 139.7, 139.9, 141.3. IR (neat, cm^{-1}): 698, 722, 756, 794, 864, 1012, 1076, 1258, 1446, 1509, 1603, 1729, 2220, 2922, 2961. HRMS: calcd. for $C_{23}H_{13}NS^+$ $[M]^+$ = 335.0769; found = 335.0768.

1,3-Dimethoxy-10-phenylphenanthrene-9-carbonitrile (136s)



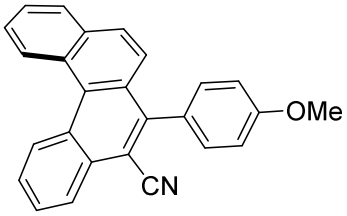
Following Method A, **136s** (16 mg, 47 µol, **42%**) was prepared from **135s** (35 mg, 111 µmol), **122b** (63 mg, 139 µmol), 2,6-di-*tert*-butylpyridine (**178**) (21 mg, 110 µmol) and trichloroborane (0.13 ml, 1 M in DCM, 130 µmol) in DCM (2 ml) as a white solid after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.82 (3H, s), 3.93 (3H, s), 6.49 (1H, d, *J* = 2.2 Hz), 6.70 (1H, d, *J* = 2.3 Hz), 7.26 (5H, s), 7.36 – 7.45 (3H, m), 7.62 – 7.67 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.9, 56.3, 88.3, 93.4, 95.2, 97.9, 107.9, 116.2, 122.5, 123.3, 128.4, 128.4, 128.5, 128.7, 129.6, 131.5, 132.8, 140.5, 147.6, 163.3, 163.4. IR (neat, cm^{-1}): 609, 796, 831, 1027, 1105, 1174, 1247, 1512, 1604, 2218, 2342, 2361, 2849, 2917, 2961. HRMS: calcd. for $C_{23}H_{17}NO_2^+$ $[M]^+$ = 339.1259; found = 339.1263.

10-[(4-Bromobutyl)thio]phenanthrene-9-carbonitrile (136u)



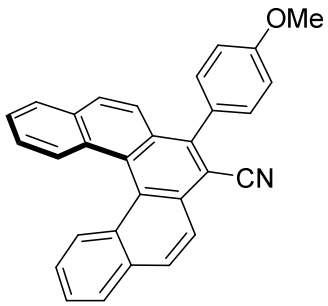
Following Method A, **136u** (40 mg, 108 µmol, **86%**) was prepared from **135u** (43 mg, 125 µmol), **122b** (71 mg, 150 µmol), 2,6-di-*tert*-butylpyridine (**178**) (24 mg, 125 µmol) and trichloroborane (0.15 ml, 1 M in DCM, 150 µmol) in DCM (2.5 ml) as a white solid after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 1.76 (2H, tt, *J* = 9.7, 6.2 Hz), 1.95 – 2.11 (2H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.38 (2H, t, *J* = 6.6 Hz), 7.66 – 7.90 (4H, m), 8.27 – 8.39 (1H, m), 8.63 – 8.74 (2H, m), 8.74 – 8.84 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 28.4, 31.5, 33.0, 36.6, 117.0, 118.1, 123.1, 123.4, 126.7, 128.2, 128.6, 128.9, 129.4, 130.0, 130.3, 131.4, 132.0, 140.6. IR (neat, cm^{-1}): 554, 721, 752, 801, 919, 974, 1021, 1095, 1233, 1276, 1443, 1484, 2220, 2927, 3074. HRMS: calcd. for $C_{19}H_{16}BrNS^+$ $[M]^+$ = 369.0187; found = 369.0187.

6-(4-Methoxyphenyl)benzo[*c*]phenanthrene-5-carbonitrile (136y)



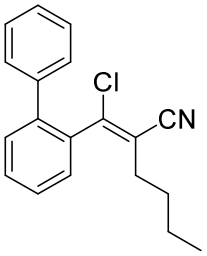
Following Method A, **136y** (61 mg, 170 µmol, **97%**) was prepared from **135y** (59 mg, 176 µmol), **122b** (101 mg, 213 µmol), 2,6-di-*tert*-butylpyridine (**178**) (33 mg, 172 µmol) and trichloroborane (0.21 ml, 1 M in DCM, 210 µmol) in DCM (3.5 ml) as white crystals after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.94 (3H, s), 7.08 – 7.19 (2H, m), 7.38 – 7.50 (2H, m), 7.66 (1H, d, *J* = 8.8 Hz), 7.69 – 7.89 (5H, m), 7.97 – 8.08 (1H, m), 8.44 – 8.55 (1H, m), 9.00 – 9.13 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.5, 109.7, 114.3, 117.8, 124.9, 126.2, 126.8, 127.3, 127.8, 128.0, 128.0, 128.5, 128.7, 129.1, 129.2, 129.4, 129.5, 129.6, 130.8, 130.9, 131.7, 134.4, 146.4, 160.2. IR (neat, cm^{-1}): 666, 754, 767, 798, 839, 1025, 1065, 1244, 1382, 1510, 1738, 2215, 2361, 2969, 3674. HRMS: calcd. for $C_{26}H_{17}NO^+$ $[M]^+$ = 359.1310; found = 359.1307.

4-(4-Methoxyphenyl)dibenzo[*c,g*]phenanthrene-3-carbonitrile (136z)



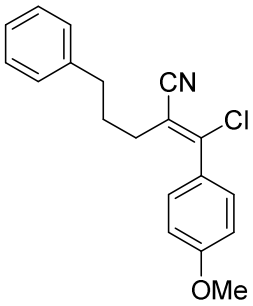
Following Method A, **136z** (42 mg, 103 µmol, **71%**) was prepared from **135z** (56 mg, 146 µmol), **122b** (83 mg, 175 µmol), 2,6-di-*tert*-butylpyridine (**178**) (28 mg, 146 µmol) and trichloroborane (0.18 ml, 1 M in DCM, 180 µmol) in DCM (3 ml) as a yellow solid after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.93 (3H, s), 7.12 (2H, td, *J* = 6.5, 3.3 Hz), 7.21 – 7.32 (2H, m), 7.38 – 7.49 (2H, m), 7.56 (2H, dddd, *J* = 8.0, 7.0, 6.0, 1.1 Hz), 7.71 (1H, d, *J* = 8.9 Hz), 7.85 (1H, d, *J* = 8.9 Hz), 7.89 – 7.95 (1H, m), 7.95 – 8.04 (1H, m), 8.09 (1H, d, *J* = 8.8 Hz), 8.29 – 8.42 (3H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.5, 109.9, 114.3, 114.3, 117.8, 123.1, 124.3, 125.2, 125.4, 126.7, 127.3, 127.8, 128.1, 128.2, 129.1, 129.1, 129.8, 130.0, 130.2, 130.2, 130.3, 130.4, 130.5, 131.4, 132.0, 132.7, 133.3, 145.8, 160.2. IR (neat, cm^{-1}): 740, 800, 940, 1006, 1123, 1173, 1241, 1289, 1329, 1416, 1509, 1548, 2219, 2359, 3047. HRMS: calcd. for $C_{30}H_{19}NO^+$ $[M]^+$ = 409.1467; found = 409.1459.

(*Z*)-2-([1,1'-Biphenyl]-2-ylchloromethylene)capronitrile (130as)



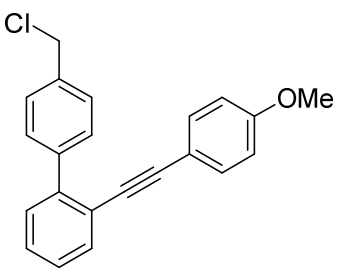
Following Method A, **130as** (119 mg, 402 µmol, **79%**) was prepared from **135e** (120 mg, 512 µmol), **122b** (292 mg, 616 µmol), 2,6-di-*tert*-butylpyridine (**178**) (98 mg, 512 µmol) and trichloroborane (0.62 ml, 1 M in DCM, 620 µmol) in DCM (10 ml) as a yellow solid after flash chromatography (*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 0.75 (3H, t, *J* = 7.3 Hz), 0.86 – 0.98 (1H, m), 1.00 – 1.21 (2H, m), 1.25 – 1.38 (1H, m), 1.66 (1H, td, *J* = 9.7, 5.0 Hz), 1.88 (1H, ddd, *J* = 14.3, 9.9, 6.6 Hz), 7.32 – 7.46 (8H, m), 7.47 – 7.53 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 13.7, 22.1, 29.3, 31.3, 116.1, 116.7, 127.7, 128.0, 128.7, 129.3, 130.4, 130.4, 134.0, 139.6, 140.9, 144.3. IR (neat, cm^{-1}): 510, 555, 647, 700, 740, 755, 906, 1431, 1449, 1474, 2213, 2339, 2360, 2928, 2958. HRMS: calcd. for $C_{19}H_{19}ClN^+$ $[M+H]^+$ = 296.1201; found = 296.1202.

(*Z*)-2-[Chloro(4-methoxyphenyl)methylene]-5-phenylvaleronitrile130au



Following slightly modified Method A, **130au** (115 mg, 369 µmol, **97%**) was prepared from **102au** (95 mg, 379 µmol), **122b** (216 mg, 456 µmol), 2,6-di-*tert*-butylpyridine (**178**) (73 mg, 382 µmol) and trichloroborane (0.76 ml, 1 M in DCM, 760 µmol, **2.0 equiv.**) in DCM (7.5 ml) as a yellow oil after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 1.88 – 2.02 (2H, m), 2.28 – 2.38 (2H, m), 2.59 (2H, t, *J* = 7.5 Hz), 3.85 (3H, s), 6.85 – 6.90 (2H, m), 7.07 – 7.11 (2H, m), 7.14 – 7.20 (1H, m), 7.21 – 7.27 (4H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 30.1, 31.2, 34.9, 55.6, 113.2, 114.1, 117.5, 126.2, 127.5, 128.5, 128.6, 130.2, 141.0, 145.5, 161.1. IR (neat, cm^{-1}): 587, 698, 748, 830, 906, 1027, 1174, 1253, 1299, 1454, 1507, 1603, 1738, 2213, 2932. HRMS: calcd. for $C_{19}H_{17}ClNO^+$ $[M–H]^+$ = 310.0999; found = 311.1073.

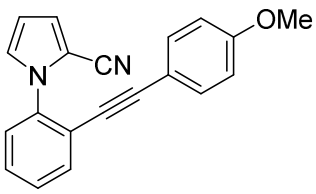
4'-(Chloromethyl)-2-[(4-methoxyphenyl)ethynyl]-1,1'-biphenyl (135n)



Compound **135n** was obtained upon attempted cyanative cyclization of **135m** (18 mg, 48 µmmol) by treatment with **122b** (27 mg, 57 µmol), 2,6-di-*tert*-butylpyridine (**178**) (9 mg, 47 µmol) and trichloroborane (0.06 ml, 1 M in DCM, 60 µmol) in DCM (1 ml) following Method A. **135n** was isolated as a white solid (12 mg, 37 µmol, **77%**) after flash

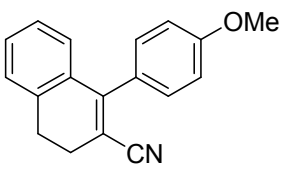
chromatography (*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.80 (3H, s), 4.67 (2H, s), 6.79 – 6.85 (2H, m), 7.23 – 7.28 (2H, m), 7.29 – 7.43 (3H, m), 7.47 (2H, d, *J* = 8.0 Hz), 7.62 (1H, dd, *J* = 7.3, 1.5 Hz), 7.64 – 7.69 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 46.4, 55.4, 88.0, 92.7, 114.1, 115.6, 122.1, 127.4, 128.3, 128.3, 129.5, 129.9, 132.8, 132.9, 136.7, 141.0, 143.0, 159.7. IR (neat, cm^{-1}): 533, 675, 732, 753, 829, 1027, 1173, 1244, 1509, 1604, 2212, 2341, 2360, 2923, 2957. HRMS: calcd. for $C_{22}H_{17}ClO^+$ $[M]^+$ = 332.0968; found = 332.0958.

1-{2-[(4-Methoxyphenyl)ethynyl]phenyl}-1*H*-pyrrole-2-carbonitrile (135x)



Upon attempted cyanative cyclization following Method A, **135x** (22 mg, 74 µmol, **43%**) was prepared from **135w** (47 mg, 172 µmol), **122b** (98 mg, 207 µmol), 2,6-di-*tert*-butylpyridine (**178**) (33 mg, 172 µmol) and trichloroborane (0.21 ml, 1 M in DCM, 210 µmol) in DCM (3.5 ml) as a white solid after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 3.81 (3H, s), 6.38 (1H, dd, *J* = 3.9, 2.8 Hz), 6.79 – 6.88 (2H, m), 7.02 (1H, dd, *J* = 3.9, 1.6 Hz), 7.18 (1H, dd, *J* = 2.8, 1.6 Hz), 7.24 – 7.31 (2H, m), 7.39 – 7.49 (3H, m), 7.65 (1H, ddd, *J* = 7.3, 3.6, 2.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ = 55.4, 83.7, 95.0, 105.5, 109.8, 113.8, 114.1, 114.7, 121.3, 121.7, 127.0, 128.6, 128.9, 129.0, 133.0, 133.2, 139.0, 160.1. IR (neat, cm^{-1}): 528, 746, 758, 800, 823, 1020, 1104, 1174, 1251, 1456, 1509, 1607, 2180, 2210, 2965. HRMS: calcd. for $C_{20}H_{14}N_2O^+$ $[M]^+$ = 298.1106; found = 298.1109.

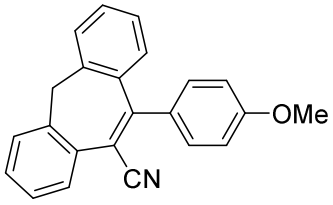
1-(4-Methoxyphenyl)-3,4-dihydronaphthalene-2-carbonitrile (195)



Following a slightly modified Method A, **195** (12 mg, 46 µmol, **90%**) was prepared from **170b** (12 mg, 51 µmol), **122b** (28 mg, 59 µmol), 2,6-di-*tert*-butylpyridine (**178**) (10 mg, 52 µmol) and trichloroborane (0.10 ml, 1 M in DCM, 100 µmol, **2.0 equiv.**) in DCM (1 ml), obtaining a white solid after flash chromatography (*n*-hexane/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 2.60 – 2.67 (2H, m), 2.93 (2H, dd, *J* = 9.1, 6.7 Hz), 3.85 (3H, s), 6.89 – 6.94 (1H, m), 6.95 – 7.00 (2H, m), 7.13 (1H, td, *J* = 7.6, 1.6 Hz), 7.18 – 7.23 (1H, m), 7.23 – 7.27 (1H, m), 7.27 – 7.32 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 26.1, 27.6, 55.4, 106.7, 114.1, 120.1, 126.9, 127.9, 128.2, 128.8, 129.9, 130.9, 133.9, 137.0, 152.8, 160.3. IR (neat, cm^{-1}): 535, 735, 771, 817, 845, 1030, 1178, 1244, 1287,

1511, 1603, 2200, 2832, 2905, 2958. HRMS: calcd. for $C_{18}H_{15}NO^+$ $[M]^+$ = 261.1154; found = 261.1554.

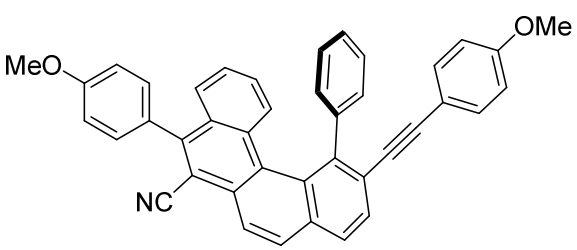
11-(4-Methoxyphenyl)-5*H*-dibenzo[*a*,*d*][7]annulene-10-carbonitrile (197b)



Following slightly modified Method A, **197b** (68 mg, 210 µmol, **82%**) was prepared from **102av** (76 mg, 255 µmol), **122b** (145 mg, 306 µmol), 2,6-di-*tert*-butylpyridine (**178**) (49 mg, 256 µmol) and trichloroborane (0.51 ml, 1 M in DCM, 510 µmol, **2.0 equiv.**) in DCM (5 ml) as white crystals after flash chromatography (*n*-hexane/EtOAc 20:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.80 (1H, s), 3.87 (1H, s), 3.89 (3H, s), 6.86 – 6.93 (1H, m), 6.96 – 7.05 (2H, m), 7.09 (1H, ddd, *J* = 8.4, 5.2, 3.6 Hz), 7.28 – 7.42 (5H, m), 7.42 – 7.49 (2H, m), 7.78 (1H, dd, *J* = 7.6, 1.3 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 41.0, 55.5, 111.7, 113.9, 120.2, 126.2, 126.7, 127.2, 127.2, 128.5, 129.8, 130.9, 131.3, 132.0, 133.1, 136.0, 140.9, 141.7, 156.1, 160.6. IR (neat, cm^{-1}): 539, 570, 614, 739, 758, 1029, 1174, 1251, 1439, 1508, 1603, 2202, 2852, 2921, 2959. HRMS: calcd. for $C_{23}H_{17}NO^+$ $[M]^+$ = 323.1310; found = 323.1303.

Method B: A dry Schlenk flask was charged with the corresponding alkyne (1.0 equiv.), reagent **122b** (2.5 equiv.), DCM (C ~ 0.05 M with respect to alkyne) and cooled down to 0 °C. Under stirring, 2,6-di-*tert*-butylpyridine (**178**) (2.0 equiv.) and a DCM solution of BCl_3 (1.0 M, 2.5 equiv.) were successively added to the suspension in one portion. The reaction mixture was stirred at 0 °C for 1 h. All volatiles were removed under reduced pressure and then by high vacuum, the remaning solid was washed with ethylacetate, filtered through a Silica pad and concentrated *in vacuo*. The mixture was further purified by column chromatography (*n*-hexane/toluene) affording the corresponding product.

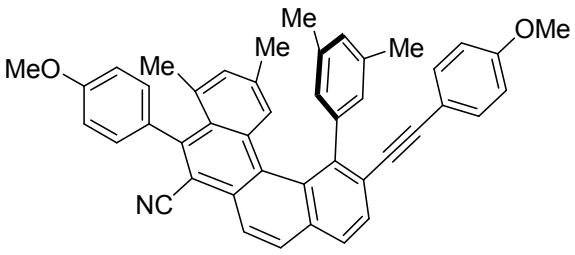
5-(4-Methoxyphenyl)-11-[(4-methoxyphenyl)ethynyl]-12-phenylbenzo[*c*]phenanthrene-6-carbonitrile (187a)



Following Method B, **187a** (100 mg, 177 µmol, **93%**) was prepared from **183a** (103 mg, 191 µmol), **122b** (226 mg, 477 µmol), 2,6-di-*tert*-butylpyridine (**178**) (76 mg, 397 µmol) and trichloroborane (0.48 ml, 1 M in DCM, 480 µmol) in DCM (3.8 ml) as orange crystals after flash chromatography (*n*-hexane/toluene 1:1). ^{1}H NMR (300 MHz,

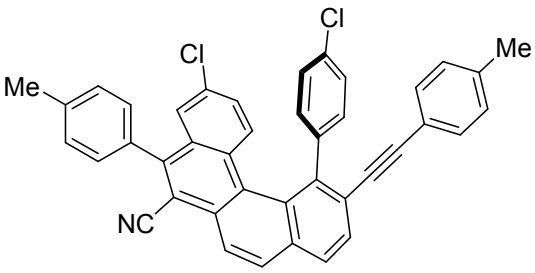
$CDCl_3$, ppm) δ = 3.82 (3H, s), 3.93 (3H, s), 6.05 (1H, s), 6.61 (1H, s), 6.81 – 6.89 (2H, m), 6.96 (1H, tt, *J* = 7.4, 1.2 Hz), 7.06 – 7.24 (4H, m), 7.28 – 7.64 (6H, m), 7.91 – 8.08 (4H, m), 8.29 (1H, d, *J* = 8.6 Hz), 8.46 (1H, s). ^{13}C NMR (101 MHz, CD_2Cl_2, ppm) δ = 53.5, 53.7, 54.0, 54.3, 54.5, 55.9, 55.9, 89.7, 94.7, 114.5, 114.6, 115.9, 118.3, 123.9, 124.4, 126.5, 126.5, 127.4, 127.7, 127.9, 128.0, 128.1, 128.8, 129.2, 129.5, 130.2, 130.4, 131.1, 131.4, 131.5, 132.0, 133.3, 135.0, 141.6, 142.9, 147.6, 160.5, 160.8. IR (neat, cm^{-1}): 538, 571, 605, 702, 744, 758, 829, 1026, 1175, 1248, 1288, 1511, 1604, 2362, 2923. HRMS: calcd. for $C_{41}H_{27}NNaO_2^+$ $[M+Na]^+$ = 588.1934; found = 588.1913.

12-(3,5-Dimethylphenyl)-5-(4-methoxyphenyl)-11-[(4-methoxyphenyl)ethynyl]-2,4-dimethylbenzo[*c*]phenanthrene-6-carbonitrile (187b)



Following Method B, **187b** (19 mg, 31 µmol, **52%**) was prepared from **183b** (36 mg, 60 µmol), **122b** (71 mg, 150 µmol), 2,6-di-*tert*-butylpyridine (**178**) (23 mg, 120 µmol) and trichloroborane (0.15 ml, 1 M in DCM, 150 µmol) in DCM (1 ml) as a yellow solid after flash chromatography (*n*-hexane/toluene 1:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 1.73 (3H, s), 1.89 (3H, s), 2.23 (3H, s), 2.45 (3H, s), 3.82 (3H, s), 3.91 (3H, s), 5.62 (1H, s), 6.59 (1H, s), 6.80 (1H, s), 6.82 – 6.89 (2H, m), 7.01 (1H, dd, *J* = 8.4, 2.7 Hz), 7.05 – 7.14 (2H, m), 7.30 – 7.35 (2H, m), 7.53 (1H, dd, *J* = 8.4, 2.3 Hz), 7.58 (1H, d, *J* = 1.7 Hz), 7.90 – 7.99 (3H, m), 8.01 (1H, s), 8.19 (1H, d, *J* = 8.5 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 21.6, 22.8, 24.9, 31.7, 55.5, 55.5, 89.6, 94.3, 113.8, 114.0, 114.1, 115.8, 118.3, 122.8, 123.5, 126.6, 127.3, 128.1, 128.4, 128.5, 128.6, 128.8, 129.2, 129.2, 130.0, 130.7, 130.8, 131.1, 132.3, 132.9, 133.0, 133.3, 134.4, 134.8, 136.7, 140.7, 142.6, 146.5, 159.8, 159.9. IR (neat, cm^{-1}): 803, 834, 1027, 1174, 1244 , 1439, 1511, 1604, 2182, 2211, 2326, 2342, 2357, 2918, 2958. HRMS: calcd. for $C_{45}H_{35}NO_2^+$ $[M]^+$ = 621.2668; found = 621.2666.

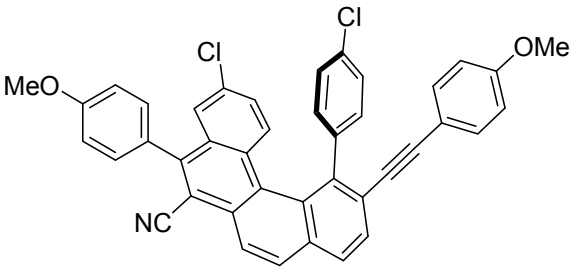
3-Chloro-12-(4-chlorophenyl)-5-(*p*-tolyl)-11-(*p*-tolylethynyl)benzo[*c*]phenanthrene-6-carbonitrile (187c)



Following Method B, **187c** (15 mg, 25 µmol, **18%**) was prepared from **183c** (82 mg, 142 µmol), **122b** (168 mg, 354 µmol), 2,6-di-*tert*-

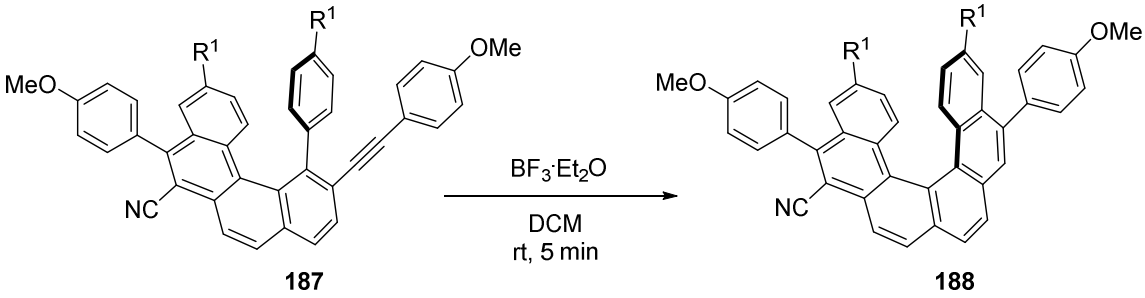
butylpyridine (**178**) (54 mg, 282 µmol) and trichloroborane (0.36 ml, 1 1 M in DCM, 360 µmol) in DCM (3 ml) as a yellow solid after flash chromatography (*n*-hexane/toluene 1:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 2.38 (3H, s), 2.52 (3H, s), 5.99 (1H, s), 6.63 (1H, s), 7.06 (1H, dd, *J* = 8.9, 2.2 Hz), 7.12 – 7.21 (2H, m), 7.27 – 7.32 (2H, m), 7.35 (1H, s), 7.39 – 7.54 (5H, m), 7.89 (1H, d, *J* = 8.9 Hz), 7.98 (1H, d, *J* = 8.3 Hz), 8.00 – 8.11 (2H, m), 8.30 (1H, d, *J* = 8.6 Hz), 8.38 (1H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 21.6, 21.7, 89.3, 95.3, 109.7, 117.5, 120.1, 123.7, 124.2, 125.4, 127.1, 127.7, 127.7, 128.0, 128.1, 129.2, 129.2, 129.4, 129.6, 129.8, 130.1, 130.2, 130.6, 131.4, 131.7, 132.0, 132.5, 133.0, 133.3, 134.7, 139.1, 139.2, 139.4, 141.0, 146.7. IR (neat, cm^{-1}): 537, 605, 728, 826, 1028, 1172, 1245, 1511, 1591, 1604, 2210, 2326, 2362, 2835, 2932. HRMS: calcd. for $C_{41}H_{25}Cl_2N^+$ $[M]^+$= 601.1364; found = 601.1340.

3-Chloro-12-(4-chlorophenyl)-5-(4-methoxyphenyl)-11-[(4-methoxyphenyl)ethynyl]-benzo[*c*]phenanthrene-6-carbonitrile (187d)



Following Method B, **187d** (29 mg, 46 µmol, **47%**) was prepared from **183d** (60 mg, 98 µmol), **122b** (117 mg, 247 µmol), 2,6-di-*tert*-butylpyridine (**178**) (38 mg, 199 µmol) and trichloroborane (0.25 ml, 1 M in DCM, 250 µmol) in DCM (2 ml) as a yellow solid after flash chromatography (*n*-hexane/toluene 1/1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.81 (3H, s), 3.93 (3H, s), 5.98 (1H, d, *J* = 15.2 Hz), 6.61 (1H, s), 6.81 – 6.92 (2H, m), 7.04 (1H, dd, *J* = 8.9, 2.2 Hz), 7.12 (2H, dt, *J* = 8.5, 1.2 Hz), 7.26 – 7.34 (2H, m), 7.34 – 7.56 (4H, m), 7.85 (1H, d, *J* = 8.9 Hz), 7.94 (1H, d, *J* = 8.3 Hz), 7.96 – 8.03 (2H, m), 8.26 (1H, d, *J* = 8.5 Hz), 8.35 (1H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.5, 55.6, 88.7, 95.2, 109.7, 114.3, 114.5, 115.2, 117.5, 123.8, 124.1, 125.4, 126.9, 127.7, 127.7, 128.0, 128.0, 128.1, 129.2, 129.3, 130.1, 130.7, 131.5, 131.8, 132.0, 132.5, 133.0, 133.3, 134.5, 139.3, 140.7, 146.3, 160.1, 160.5. IR (neat, cm^{-1}): 537, 605, 728, 826, 1028, 1172, 1245, 1511, 1591, 1604, 2045, 2210, 2326, 2362, 2835, 2932. HRMS: calcd. for $C_{41}H_{26}Cl_2NO_2^+$ $[M+H]^+$ = 634.1335; found = 634.1335.

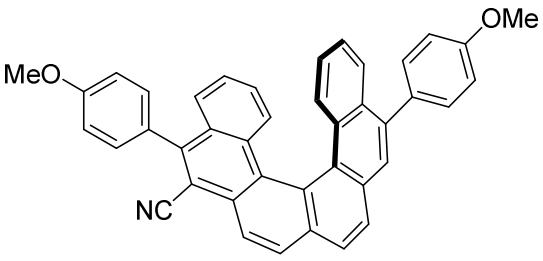
6.3.2.2. Cycloisomerizations.



Scheme 127. Cycloisomerization of [4]helicenes **187** to [6]helicenes **188**.

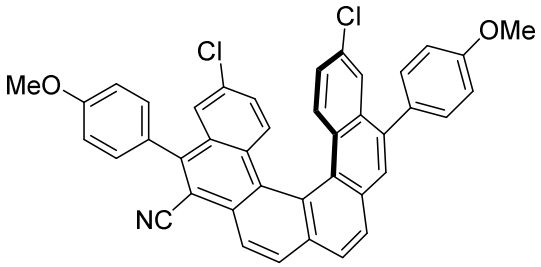
General procedure GP6: A dry Schlenk flask was charged with the corresponding alkyne (1.0 equiv.) and solved in DCM (1 ml) before $BF_3 \cdot Et_2O$ (1.0 equiv.) was added. The mixture was stirred at rt for 5 min. All volatiles were removed under reduced pressure and then by high vacuum, the remaining solid was solved in ethylacetate, filtered through a Silica pad and concentrated *in vacuo* affording the corresponding product.

1,8-bis(4-Methoxyphenyl)hexahelicene-2-carbonitrile (188a)



Following GP6, **188a** (12 mg, 21 µmol, **99%**) was prepared from **187a** (12 mg, 21.2 µmol) and $BF_3 \cdot Et_2O$ (3 mg, 21 µmol) as a yellow solid. ^{1}H NMR (400 MHz, CD_2Cl_2, ppm) δ = 3.94 (3H, s), 3.97 (3H, s), 6.74 (1H, t, *J* = 7.9 Hz), 6.83 (1H, t, *J* = 7.8 Hz), 7.06 – 7.30 (6H, m), 7.52 – 7.74 (6H, m), 7.77 (1H, d, *J* = 8.5 Hz), 7.85 – 7.99 (2H, m), 8.03 – 8.17 (2H, m), 8.24 (1H, d, *J* = 8.4 Hz), 8.46 (1H, d, *J* = 8.3 Hz). ^{13}C NMR (101 MHz, CD_2Cl_2, ppm) δ = 56.0, 106.8, 109.5, 114.4, 114.6, 118.4, 123.1, 124.1, 124.5, 125.2, 126.3, 126.6, 126.8, 126.9, 127.7, 127.7, 128.0, 128.2, 128.3, 128.6, 128.8, 129.2, 129.4, 129.7, 130.6, 130.7, 131.4, 131.7, 131.8, 132.0, 132.2, 133.0, 134.0, 140.4, 147.7, 159.9, 160.8. IR (neat, cm^{-1}): 610, 702, 765, 793, 864, 1013, 1084, 1175, 1257, 1444, 1511, 1606, 2853, 2923, 2961. HRMS: calcd. for $C_{41}H_{27}NO_2^+$ $[M]^+$= 565.2042; found = 565.2045.

10,15-Dichloro-1,8-bis(4-methoxyphenyl)hexahelicene-2-carbonitrile (188d)



Following GP6, **188d** (10 mg, 15.7 µmol, **99%**) was prepared from **187d** (10 mg, 15.7 µmol) and $BF_3{\cdot}Et_2O$ (2.2 mg, 15.7 µmol) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.96 (3H, s), 3.98 (3H, s), 6.75 (1H, dd, *J* = 9.0, 2.2 Hz), 6.83 (1H, dd, *J* = 9.0, 2.3 Hz), 7.12 – 7.17 (2H, m), 7.19 (2H, d, *J* = 8.2 Hz), 7.57 (1H, s), 7.58 – 7.63 (3H, m), 7.66 – 7.71 (2H, m), 7.87 (1H, d, *J* = 2.2 Hz), 7.93 (1H, s), 7.99 – 8.13 (2H, m), 8.20 (1H, d, *J* = 8.5 Hz), 8.48 (1H, d, *J* = 8.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 55.6, 55.6, 105.1, 110.4, 114.4, 114.7, 117.6, 123.3, 124.5, 125.5, 125.6, 126.7, 126.9, 127.4, 127.6, 127.7, 128.0, 128.3, 128.6, 128.9, 129.3, 129.4, 129.7, 129.9, 131.3, 131.3, 131.4, 131.7, 131.9, 132.2, 132.2, 132.2, 132.9, 133.9, 139.4, 146.4, 159.7, 160.6. IR (neat, cm^{-1}): 609, 796, 831, 1027, 1105, 1174, 1247, 1512, 1604, 2218, 2342, 2361, 2849, 2917, 2961. HRMS: calcd. for $C_{41}H_{26}Cl_2NO_2^+$ $[M+H]^+$ = 634.1335; found = 634.1344.

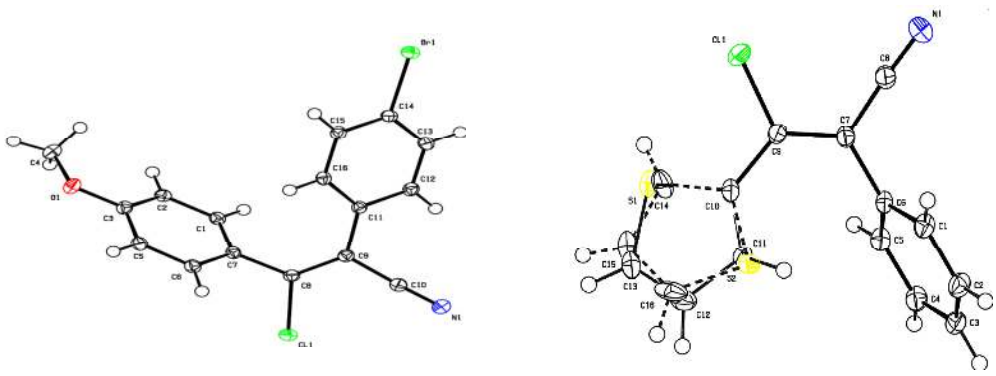
6.4. X-Ray structures.

Crystal Structure Analysis: Suitable for X-ray diffractometry crystals of compounds were obtained by recrystallization from *n*-heptane [(*Z*)-**130l**, (*Z*)-**130u** and **(*Z*)-130ao**], from a 1/1 mixture of DCM/*n*-pentane [(**136a**, **136y,** (*Z*)-**141b**, **187a**, **195** and **197b**] and from a 1/1 mixture of Acetonitrile/Diethylether [**140a**].

Data collections were done on a *Bruker D8 Venture* four-circle-diffractometer from *Bruker AXS GmbH*; used detector: *Photon II* from *Bruker AXS GmbH*; used X-ray sources: microfocus *IµS* Cu/Mo from *Incoatec GmbH* with mirror optics *HELIOS* and single-hole collimator from *Bruker AXS GmbH*. Radiation: MoKα (λ = 0.71073).

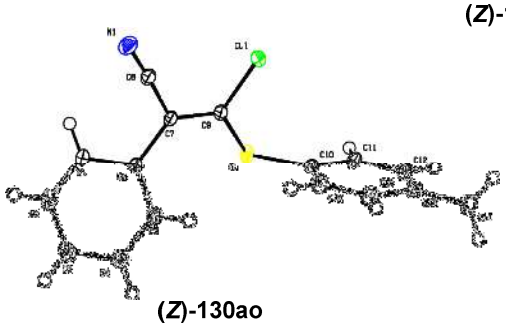
Used programs: *APEX3 Suite* (v2017.3-0) and therein integrated programs *SAINT* (Integration) und *SADABS* (Absorption correction) from *Bruker AXS GmbH*; structure solution was done with *SHELXT*, refinement with *SHELXS*;[149] OLEX^2 was used for data finalization.[150]

Special Utilities: *SMZ1270* stereomicroscope from *Nikon Metrology GmbH* was used for sample preparation; crystals were mounted on *MicroMounts* or *MicroLoops* from *MiTeGen*; for sensitive samples the *X-TEMP 2 System* was used for picking of crystals;[151] crystals were cooled to given temperature with *Cryostream 800* from *Oxford Cryosystems.*

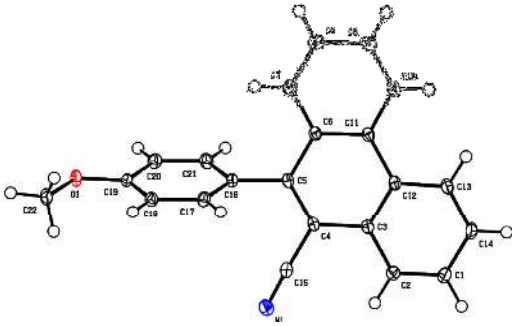


(*Z*)-130l

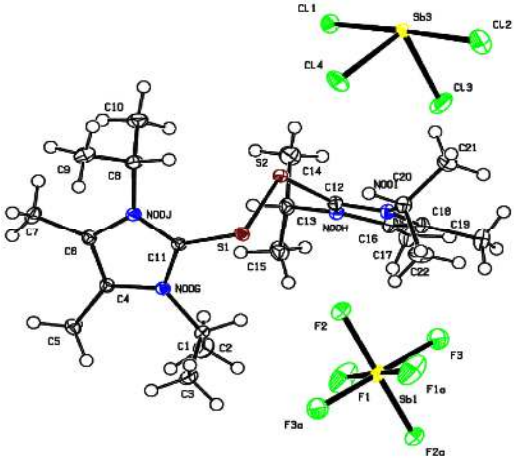
(*Z*)-130u



(*Z*)-130ao



136a

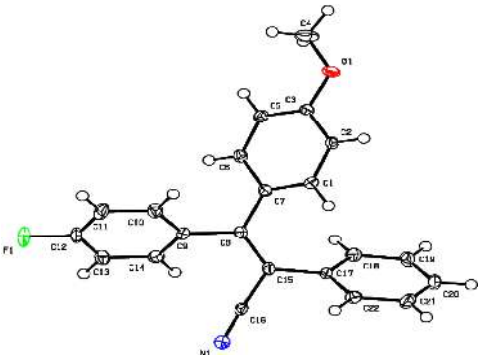


140a

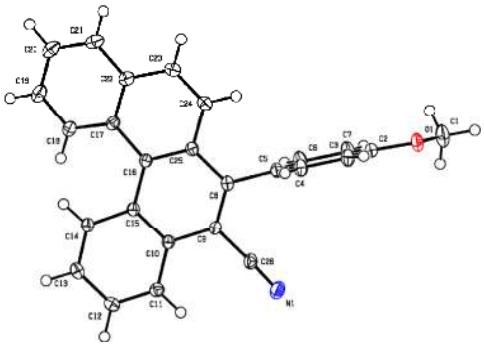
Table 17 Crystal and data collection parameters for compounds **(*Z*)-130l**, **(*Z*)-130u**, **(*Z*)-130ao**, **136a**, **140a**, **(*Z*)-141b**, **136y**, **187a**, **195 and 197b**. The numbering does not correspond to the IUPAC rules.

Compound	**(*Z*)-130l**	**(*Z*)-130u**	**(*Z*)-130ao**	**136a**	**140a**
Formula	$C_{16}H_{11}NOClBr$	$C_{13}H_8ClNS$		$C_{22}H_{15}NO$	$C_{22}H_{40}Cl_4F_6N_4S_2Sb_2$
Molecular mass	348.62	245.71		309.35	924.00
Temperature/K	100(2)	296.15		100(2)	100(2)
Crystal system	orthorhombic	monoclinic		triclinic	triclinic
Space group	$P2_12_12_1$	$P2_1/c$		*P*-1	*P*-1
Crystal size [mm]		0.2 × 0.169 × 0.12		0.10 x 0.10 x 0.03	0.07 × 0.067 × 0.029

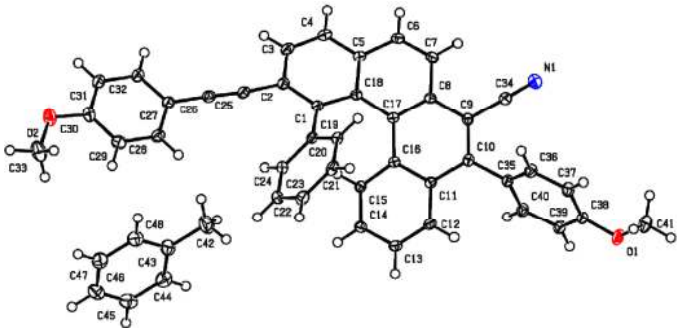
a [Å]	7.4816(3)	14.7305(17)	9.5671(14)	8.2494(11)
b [Å]	9.8397(6)	5.7754(7)	9.8579(15)	13.1492(18)
c [Å]	18.8362(7)	13.4004(16)	10.1130(15)	16.459(2)
α [°]	90	90	117.760(3)	96.967(2)
β [°]	90	94.853(2)	107.436(3)	101.713(3)
γ [°]	90	90	96.488(3)	102.793(3)
V [Å^3]	1386.66(11)	1135.9(2)	768.3(2)	1678.7(4)
Z	4	4	2	2
D [g cm^{-3}]	1.670	1.437	1.337	1.828
μ [mm^{-1}]	3.150	0.487	0.082	2.107
F(000)	696.0	504.0	324	912.0
$2\Theta_{max}$ [°]	66.322	72.632	61.990	72.784
Refl. collected	28409	42929	14058	66099
Refl. independent	5277	5513	4834	16073
R_{int}	0.0300	0.0227	0.0290	0.0497
R_{sigma}	0.0202	0.0120		0.0505
R_1 [I ≥ 2σ(I)]	0.0189	0.0291	0.0459	0.0337
wR_2(all data)	0.0453	0.0930	0.1355	0.0703
No. of parameters refined	182	182	218	376
GOOF	1.074	1.023	1.074	1.026
Largest diff. peak and hole, e·Å^{-3}	0.40/–0.29	0.55/–0.35	0.446/–0.249	1.77/–1.09



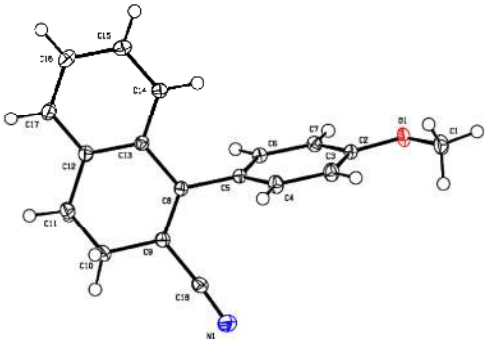
(*Z*)-141b



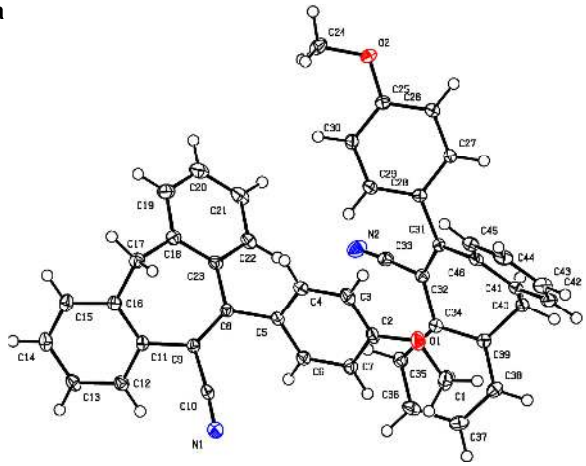
136y



187a



195



197b

Table 17 (Continued)

Compound	**(*Z*)-141b**	**136y**	**187a**	**195**	**197b**
Formula	$C_{22}H_{16}FNO$	$C_{26}H_{17}NO$	$C_{48}H_{35}NO_2$	$C_{18}H_{15}NO$	$C_{23}H_{17}NO$
Molecular mass	329.36	359.40	657.77	261.31	323.38
Temperature/K	100.(2)	101.93	100.0	100.01	100.01
Crystal system	triclinic	triclinic	monoclinic	monoclinic	triclinic
Space group	*P*-1	*P*-1	$P2_1/c$	$P2_1/c$	*P*1
Crystal size [mm]	0.340 × 0.172	0.563 × 0.383	0.216 × 0.134	0.335 × 0.117	0.448 × 0.202

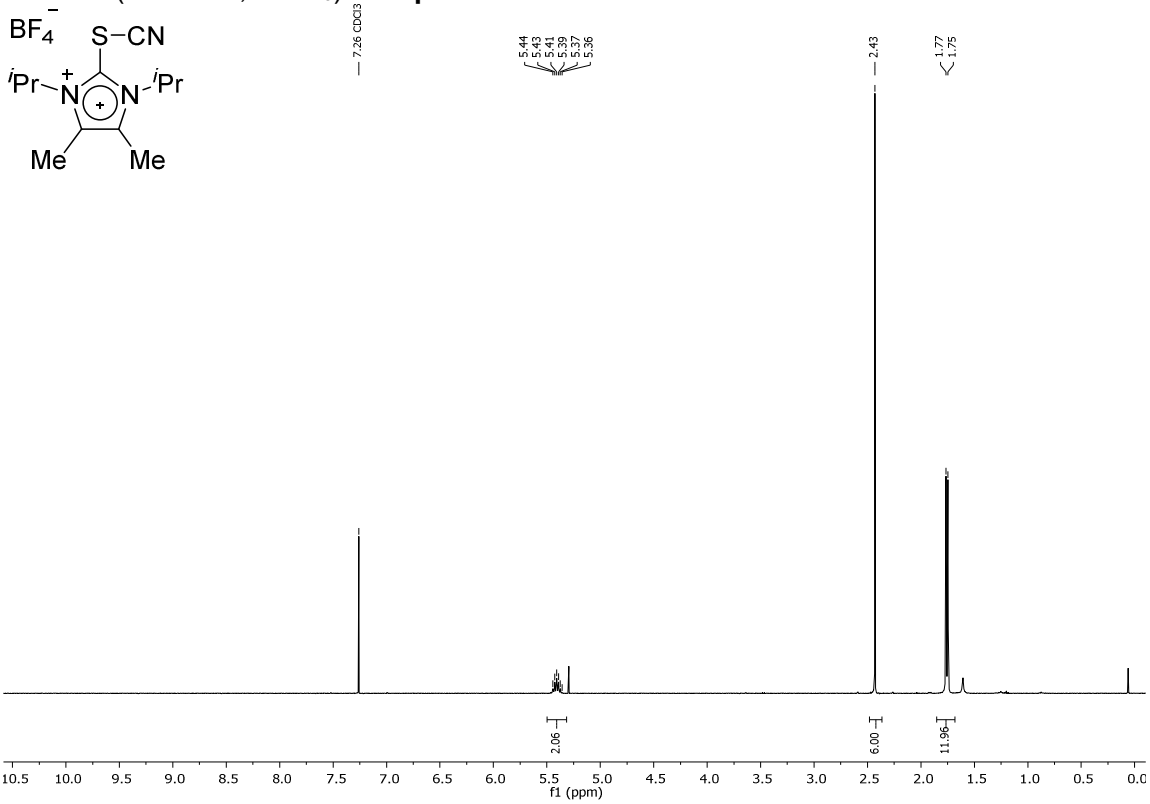
	× 0.169	× 0.314	× 0.066	× 0.105	× 0.038
a [Å]	8.9882(3)	9.0102(6)	9.4796(14)	5.6886(8)	8.7262(7)
b [Å]	10.1746(4)	10.1932(7)	36.328(6)	21.347(3)	9.7738(8)
c [Å]	10.7749(4)	11.6228(6)	10.6427(19)	11.2486(14)	9.8796(7)
α [°]	109.464(2)	67.190(2)	90	90	90.947(2)
β [°]	103.932(2)	76.502(2)	111.093(6)	96.637(5)	90.917(2)
γ [°]	99.489(2)	67.338(2)	90	90	103.584(3)
V [Å^3]	868.79(6)	903.58(10)	3419.5(10)	1356.8(3)	818.76(11)
Z	2	2	4	4	2
D [g cm^{-3}]	1.259	1.321	1.278	1.279	1.312
μ [mm^{-1}]	0.084	0.080	0.077	0.079	0.080
F(000)	344.0	376.0	1384.0	552.0	340.0
$2\Theta_{max}$ [°]	61.30	61.03	59.206	63.066	59.238
Refl. collected	54135	28914	64282	20204	8701
Refl. independent	5360	5519	9612	4529	8701
R_{int}	0.0801	0.0231	0.0229	0.0229	
R_{sigma}	0.0408	0.0169	0.0155	0.0192	0.0294
R_1 [I ≥ 2σ(I)]	0.0531	0.0420	0.0451	0.0389	0.0365
wR_2(all data)	0.1383	0.1226	0.1237	0.1114	0.0991
No. of parameters refined	227	254	463	182	454
GOOF	1.020	1.040	1.043	1.023	1.030
Largest diff. peak and hole, e·Å^{-3}	0.46/–0.38	0.46/–0.18	0.50/–0.23	0.43/–0.20	0.29/–0.20

CCDC 1545693, 1545694, 1545695, 1545696, 1545697, 1567971, and 1567989 contain (in part) the supplementary crystallographic data published in our paper.[142] These data can be obtained free of charge from The Cambridge Crystallographic Data Cent

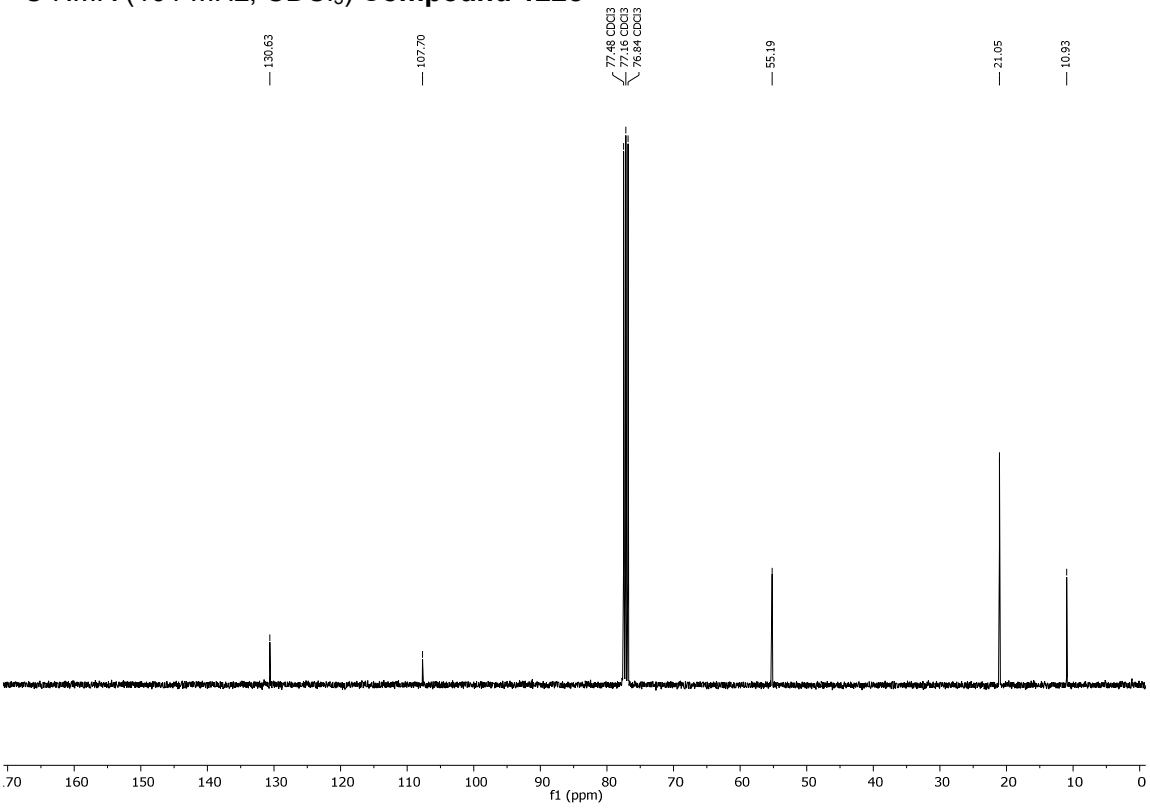
7. Appendix.

7.1. NMR spectra.

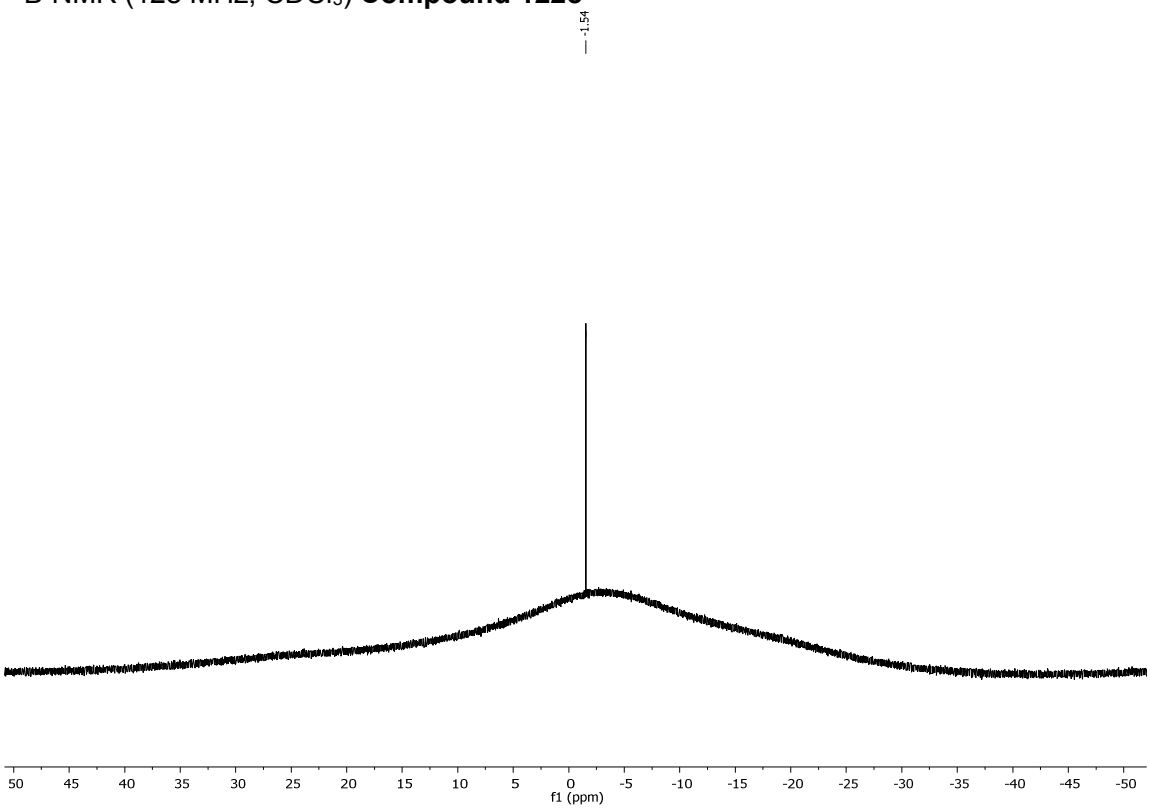
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 122c**



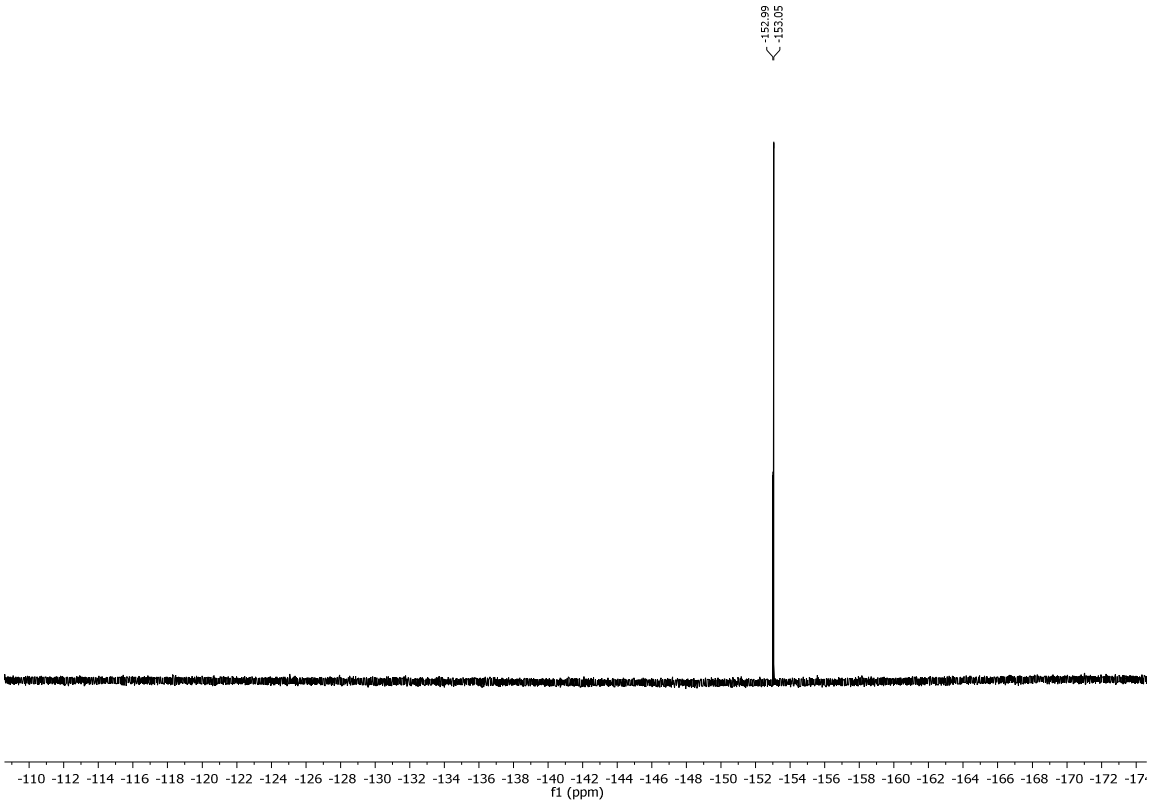
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 122c**



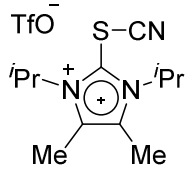
^{11}B NMR (128 MHz, $CDCl_3$) **Compound 122c**



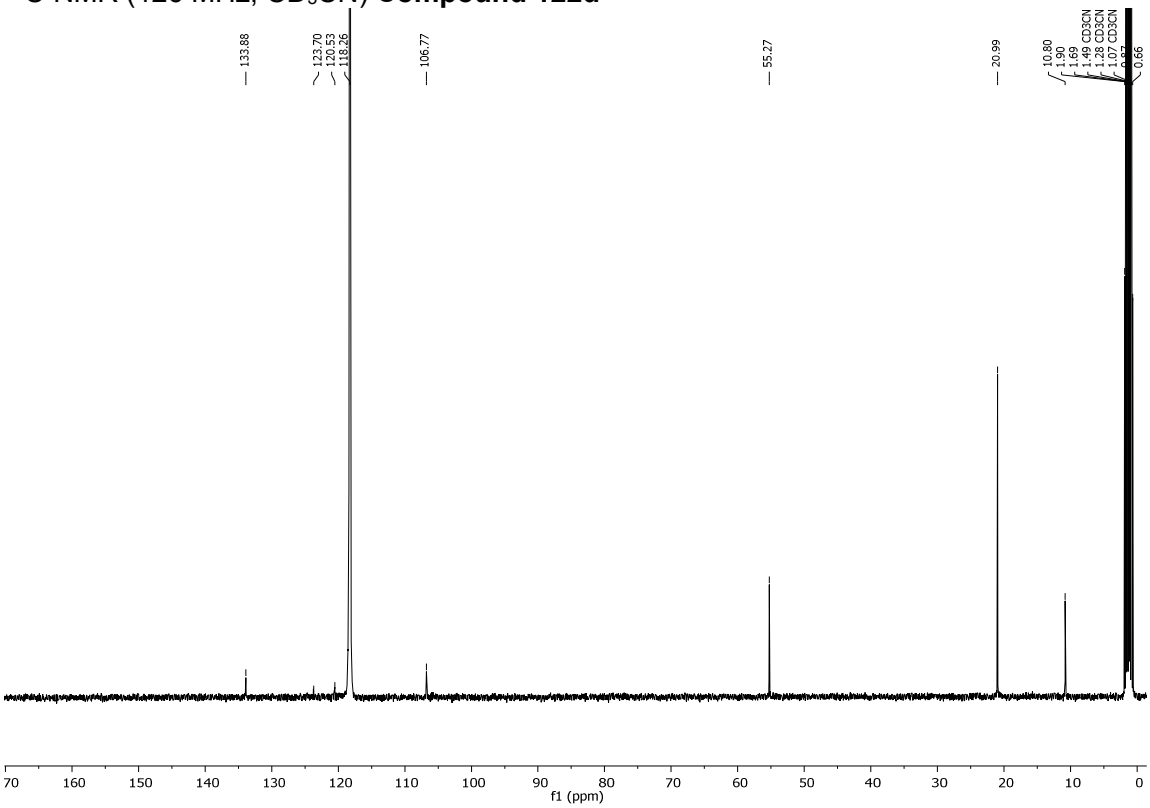
^{19}F NMR (376 MHz, $CDCl_3$) **Compound 122c**



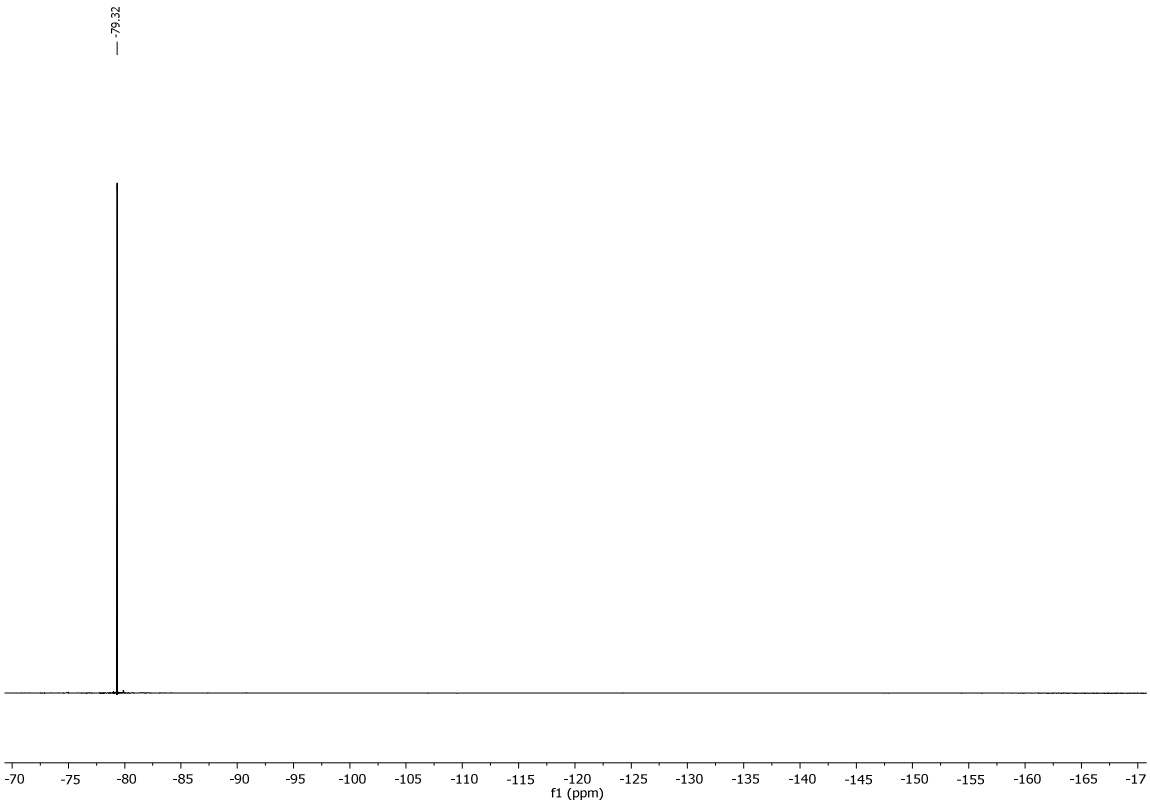
^{1}H NMR (500 MHz, CD_3CN) **Compound 122d**



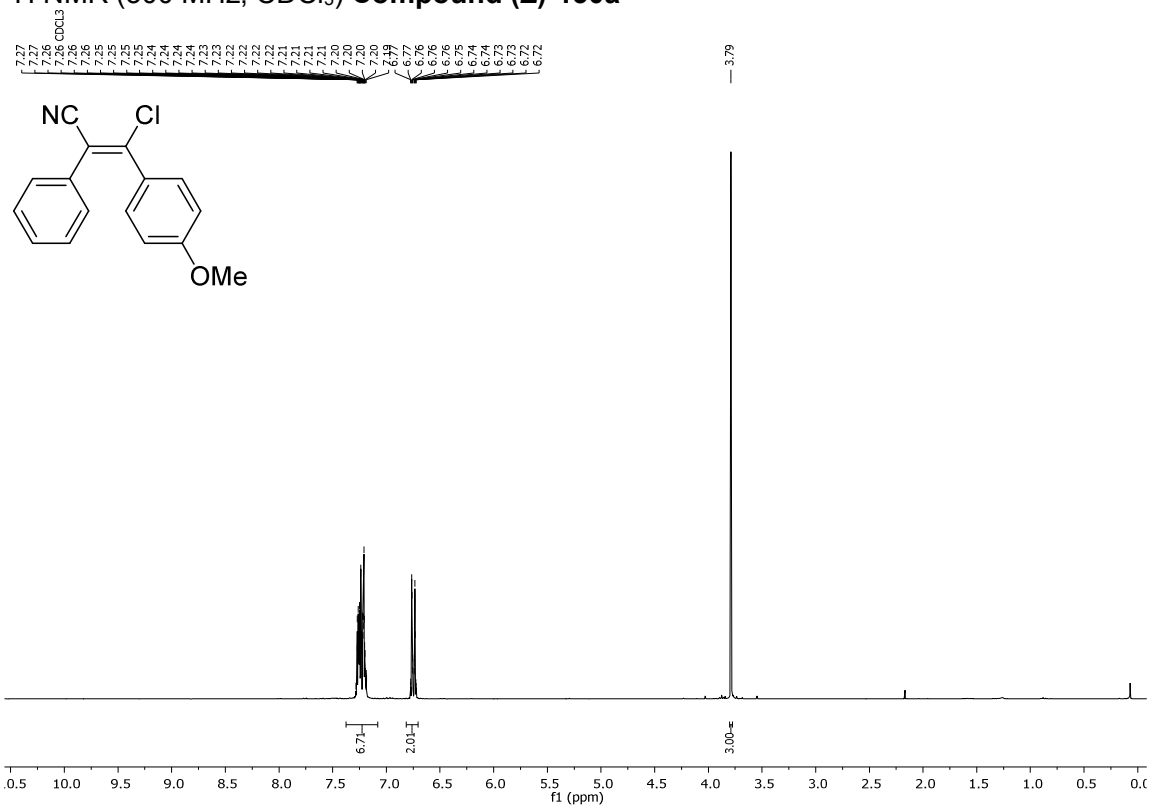
^{13}C NMR (126 MHz, CD_3CN) **Compound 122d**



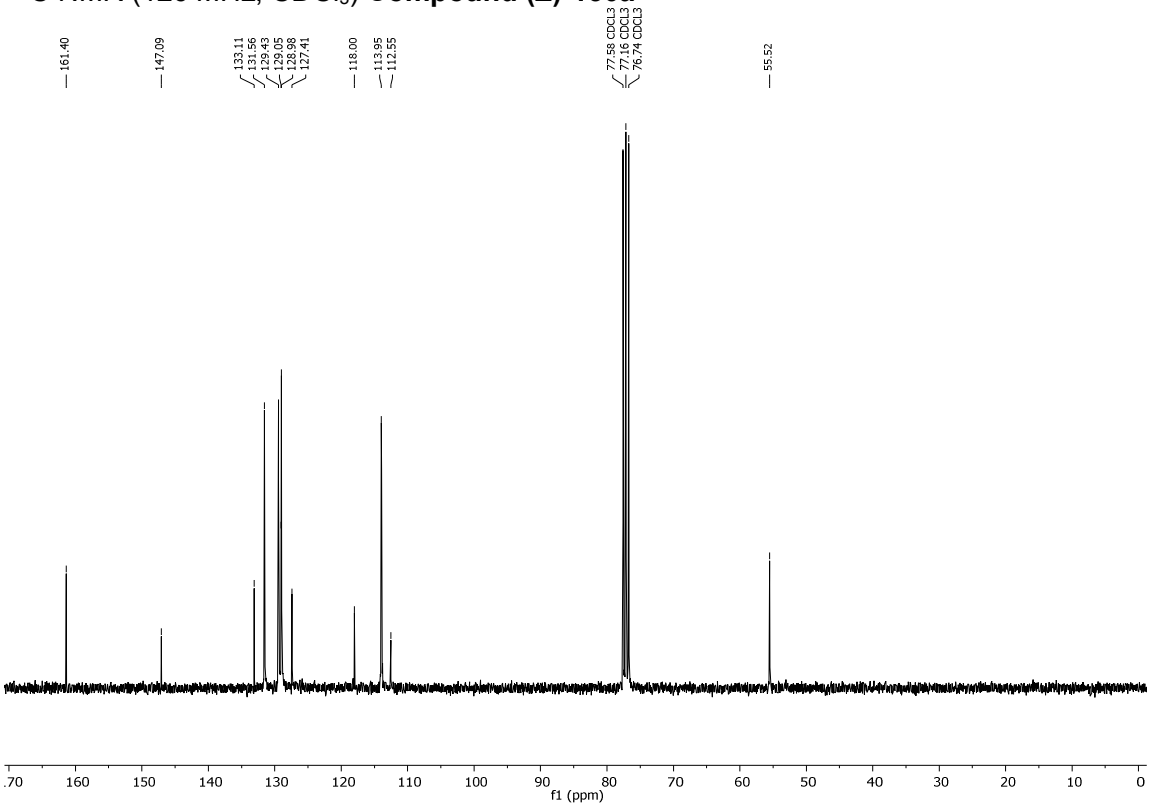
^{19}F NMR (470 MHz, CD_3CN) **Compound 122d**



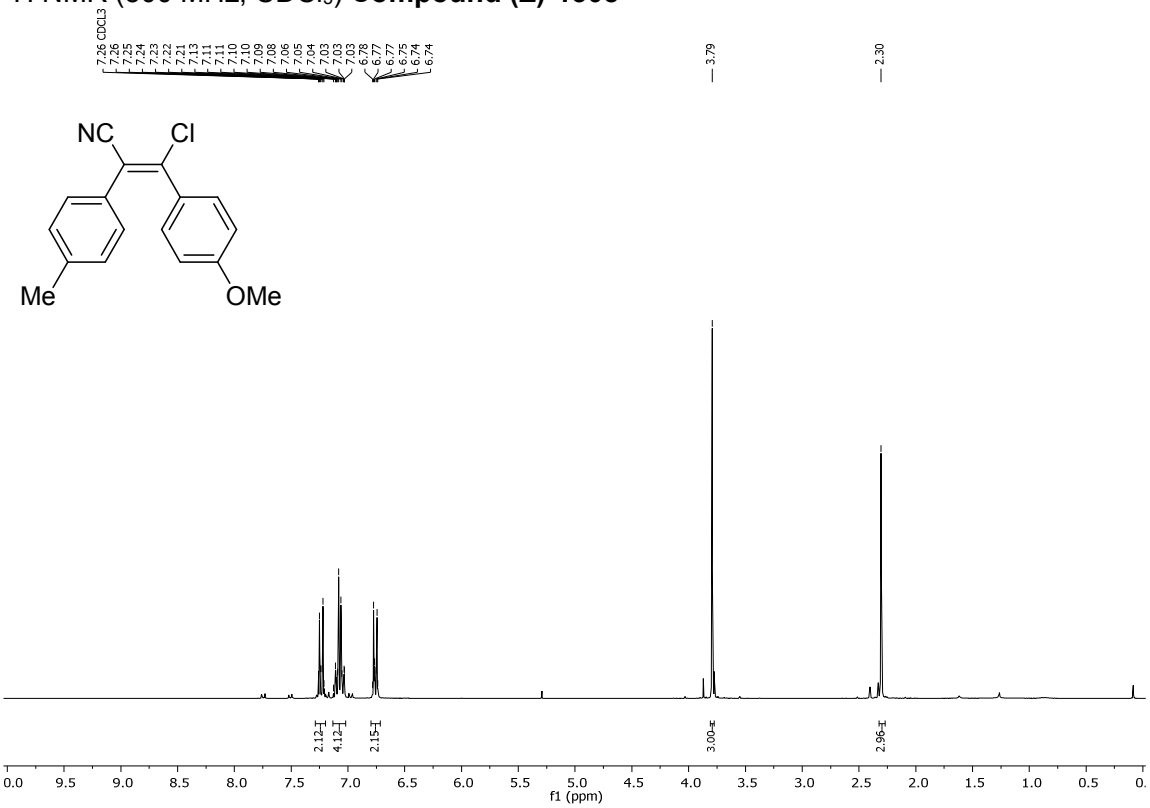
^{1}H NMR (300 MHz, $CDCl_3$) **Compound (*Z*)-130a**



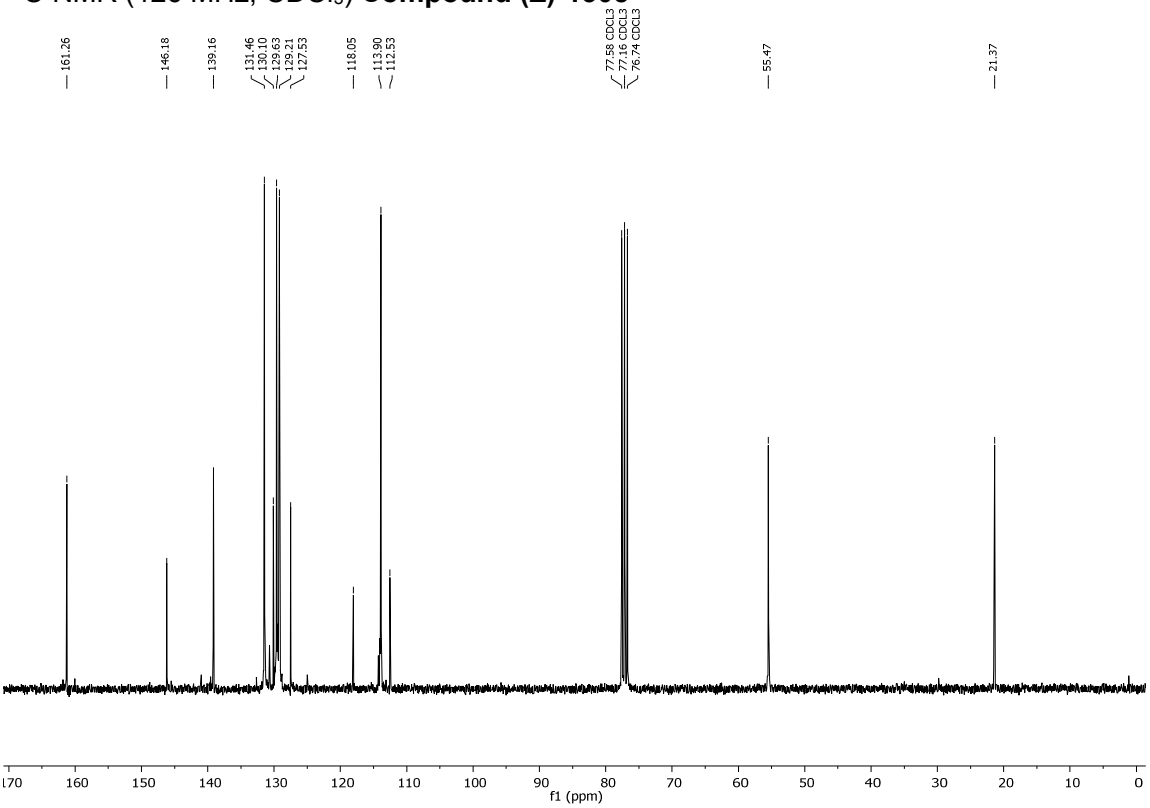
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130a**



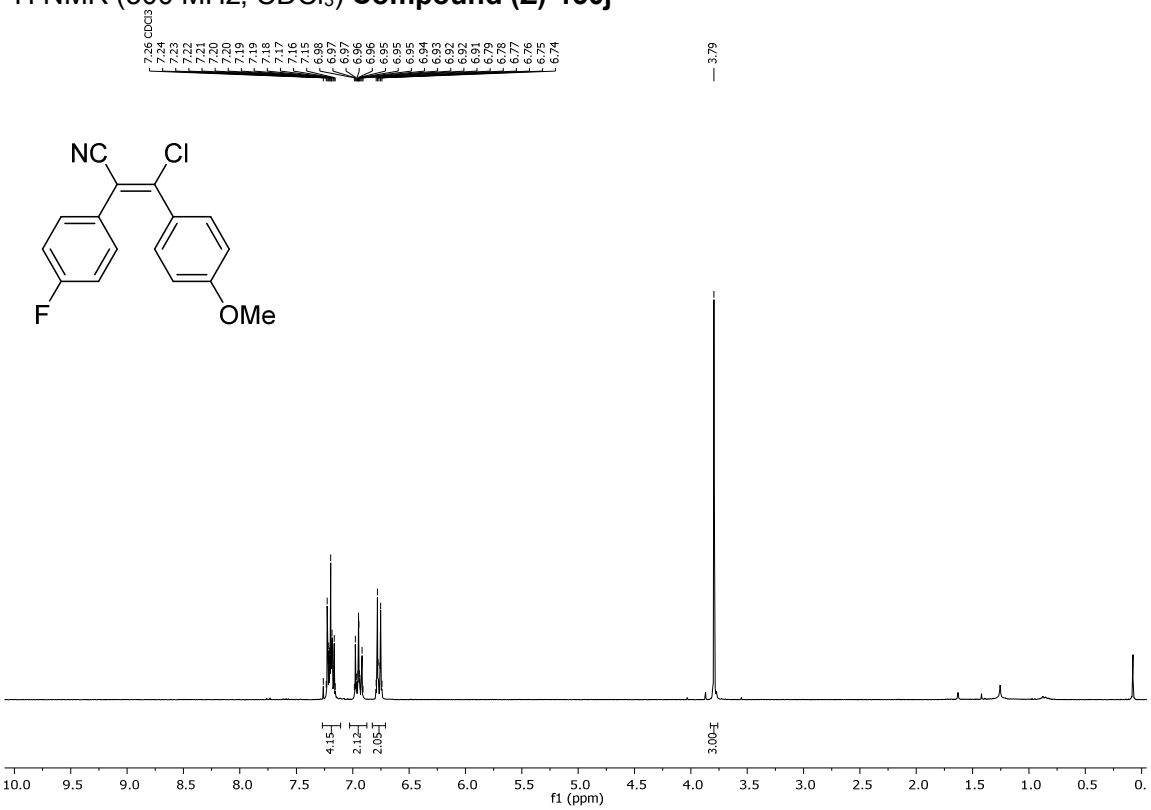
^{1}H NMR (500 MHz, $CDCl_3$) **Compound (*Z*)-130e**



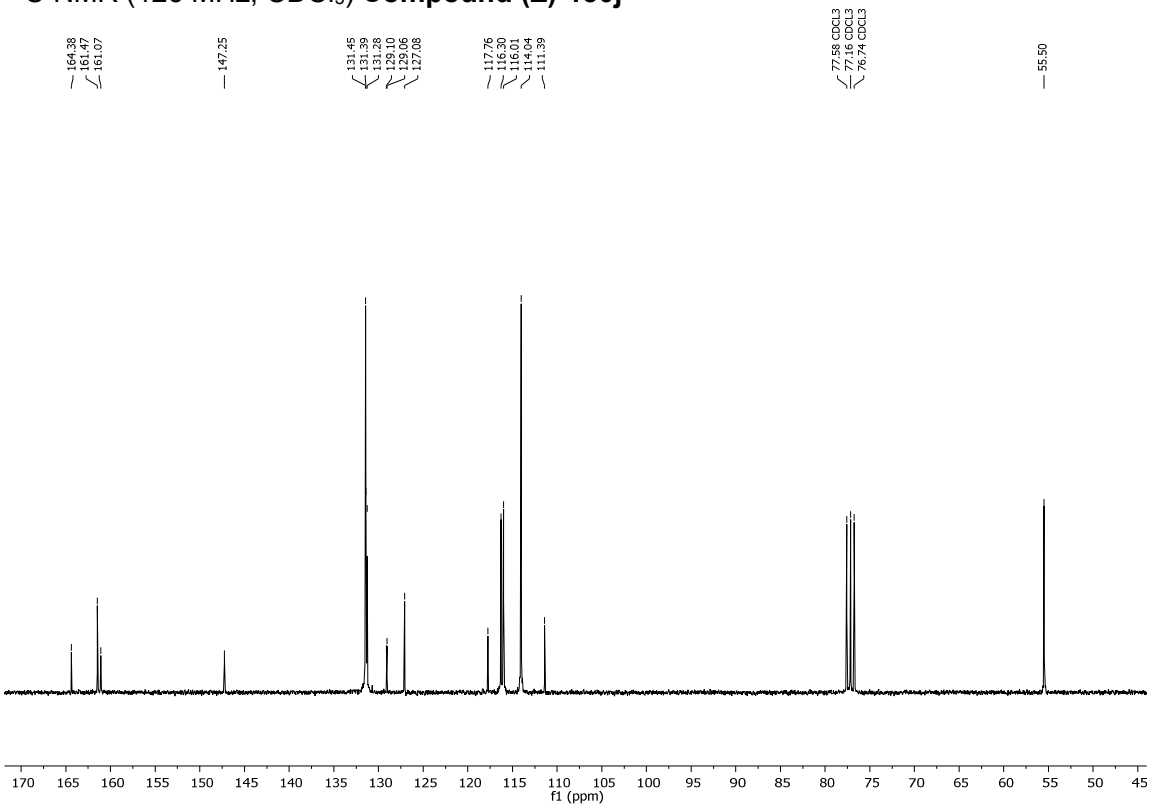
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130e**



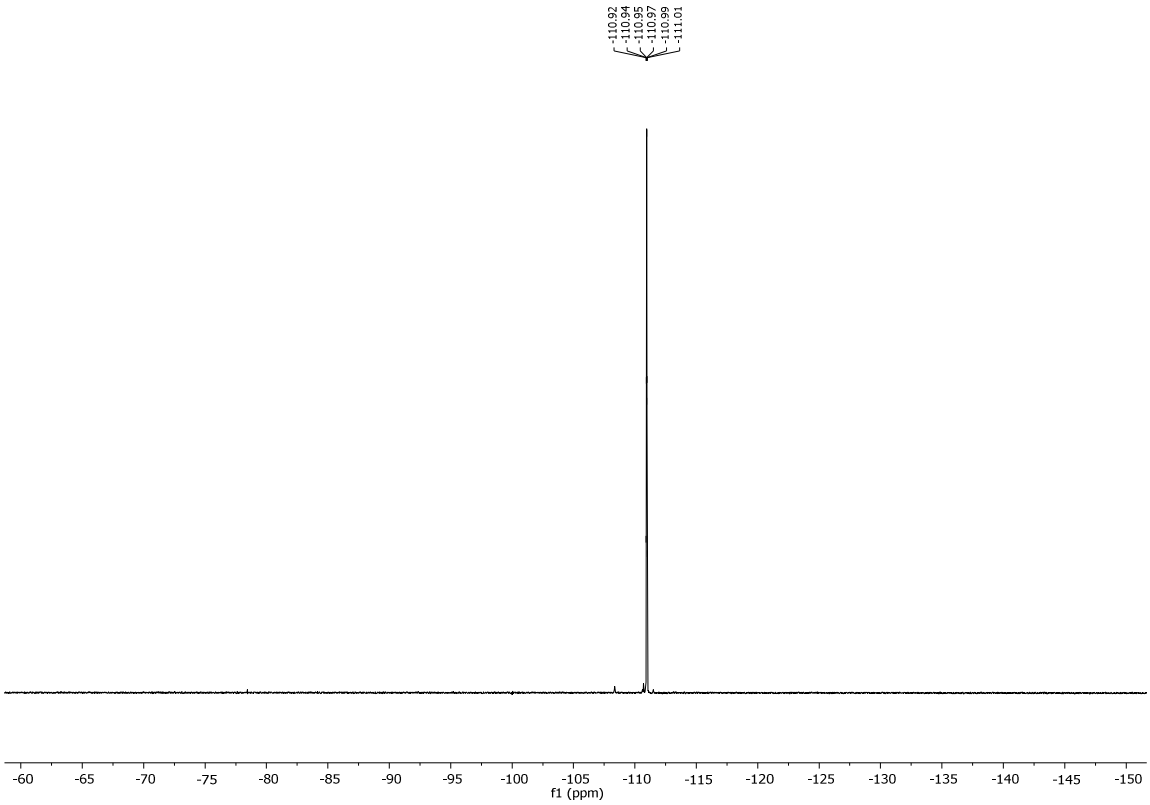
^{1}H NMR (300 MHz, $CDCl_3$) **Compound (*Z*)-130j**



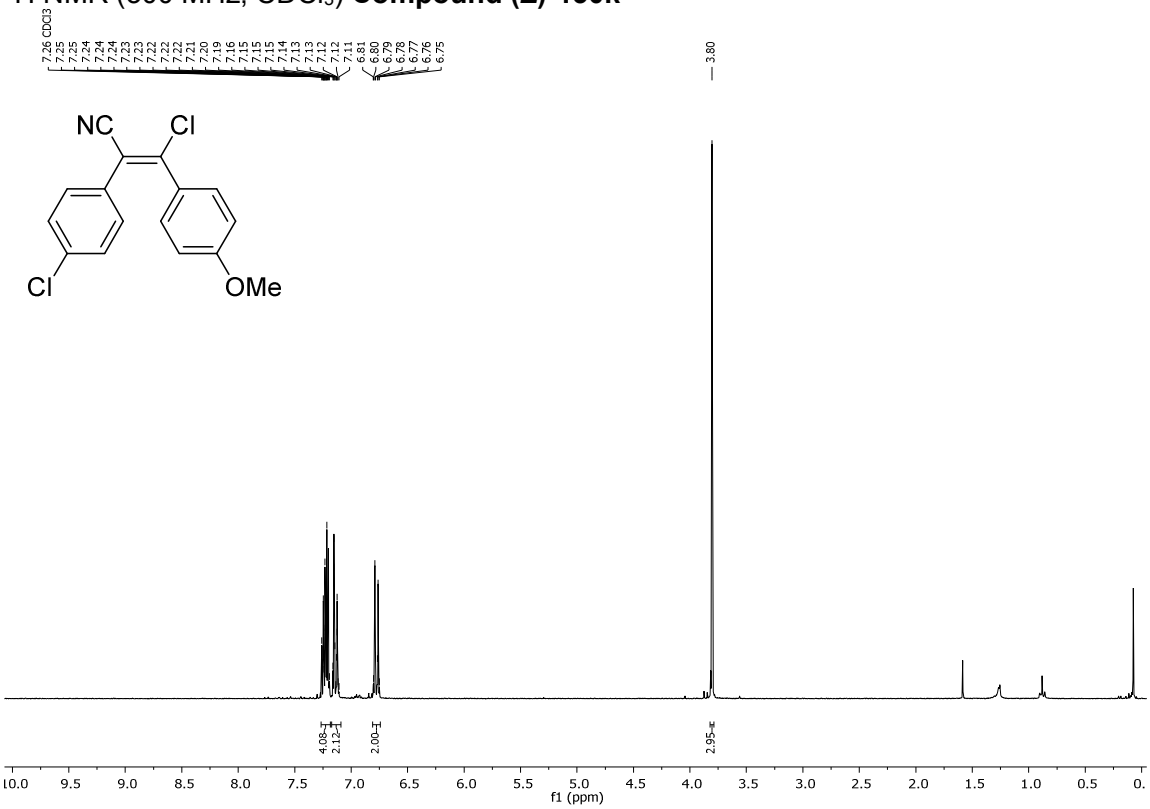
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130j**



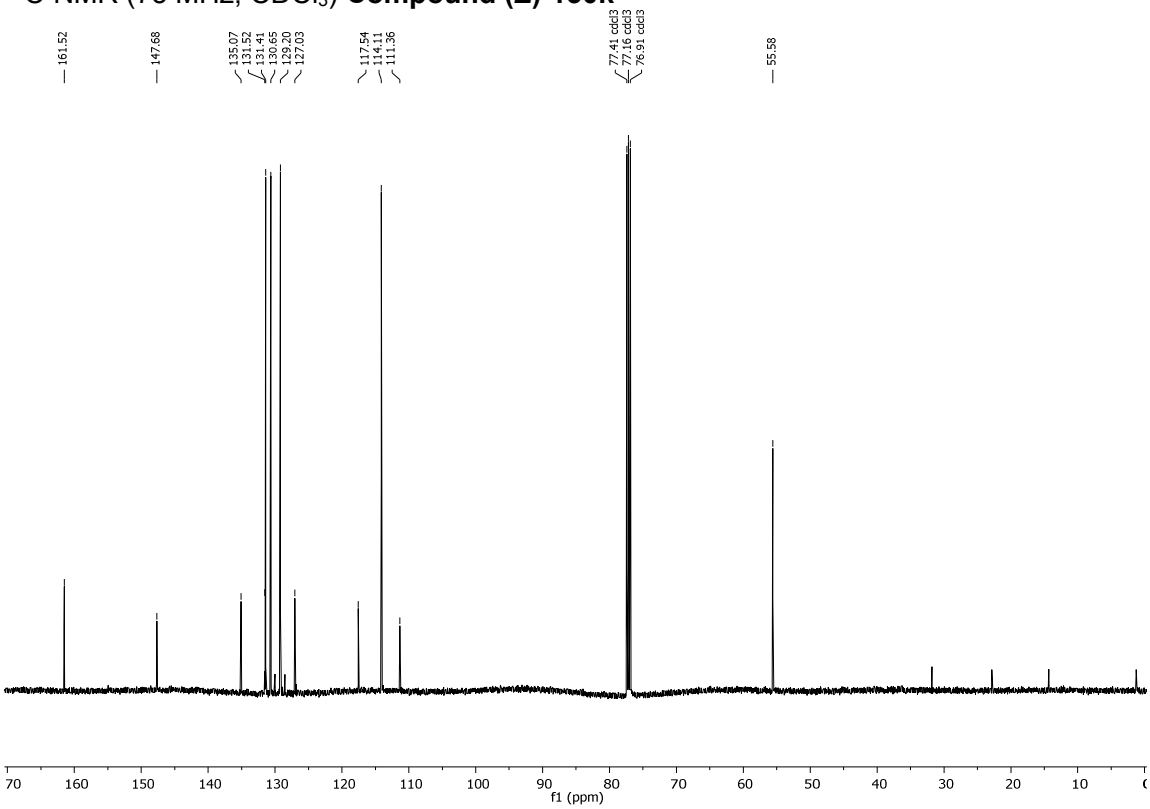
^{19}F NMR (282 MHz, $CDCl_3$) **Compound (*Z*)-130j**



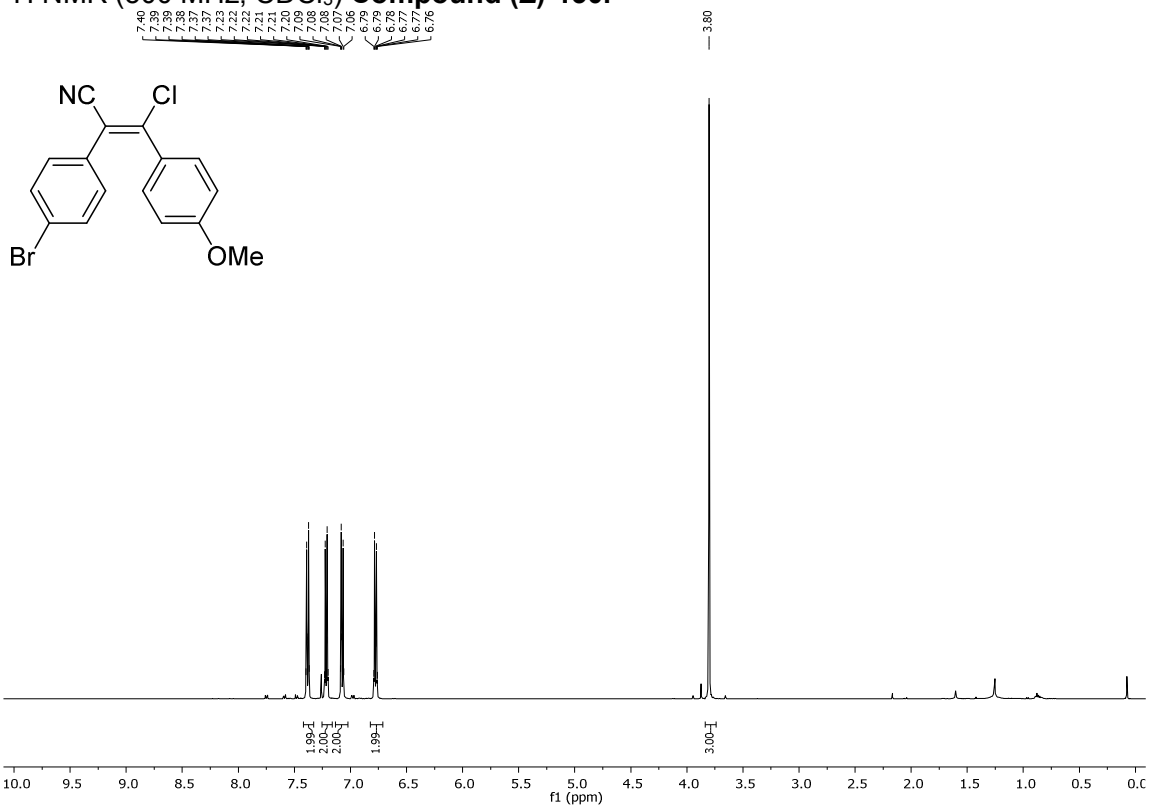
^{1}H NMR (300 MHz, $CDCl_3$) **Compound (*Z*)-130k**



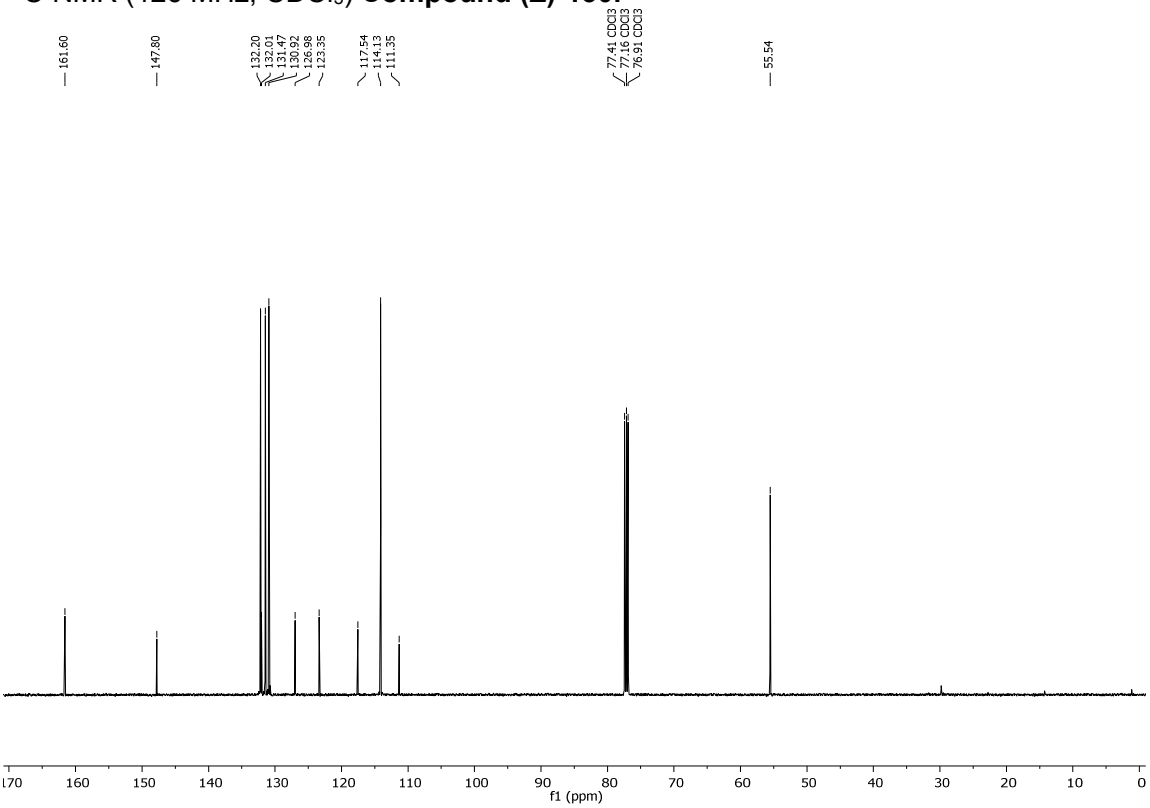
^{13}C NMR (75 MHz, $CDCl_3$) **Compound (*Z*)-130k**



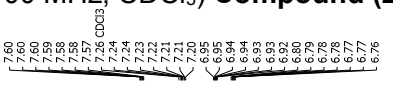
^{1}H NMR (500 MHz, $CDCl_3$) **Compound (*Z*)-130l**

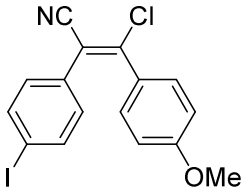


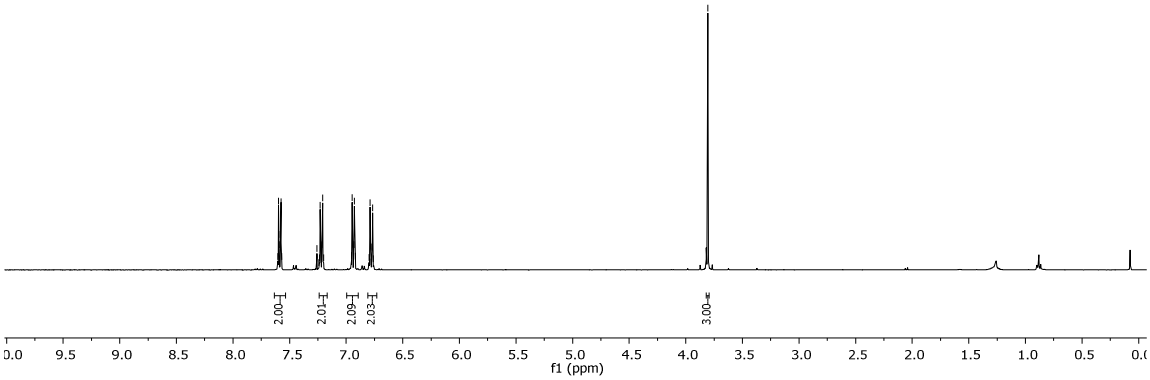
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130l**



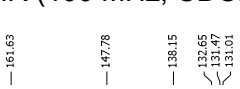
^{1}H NMR (400 MHz, $CDCl_3$) **Compound (*Z*)-130m**

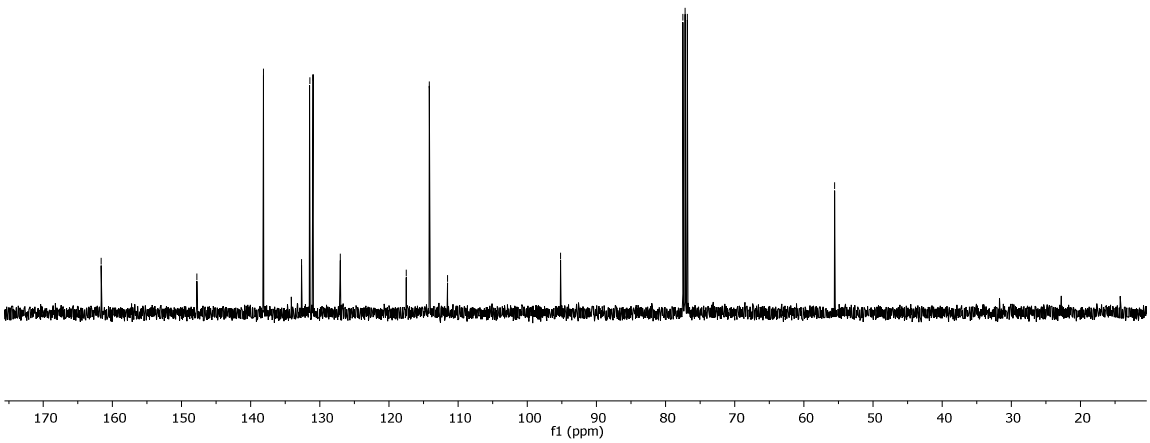




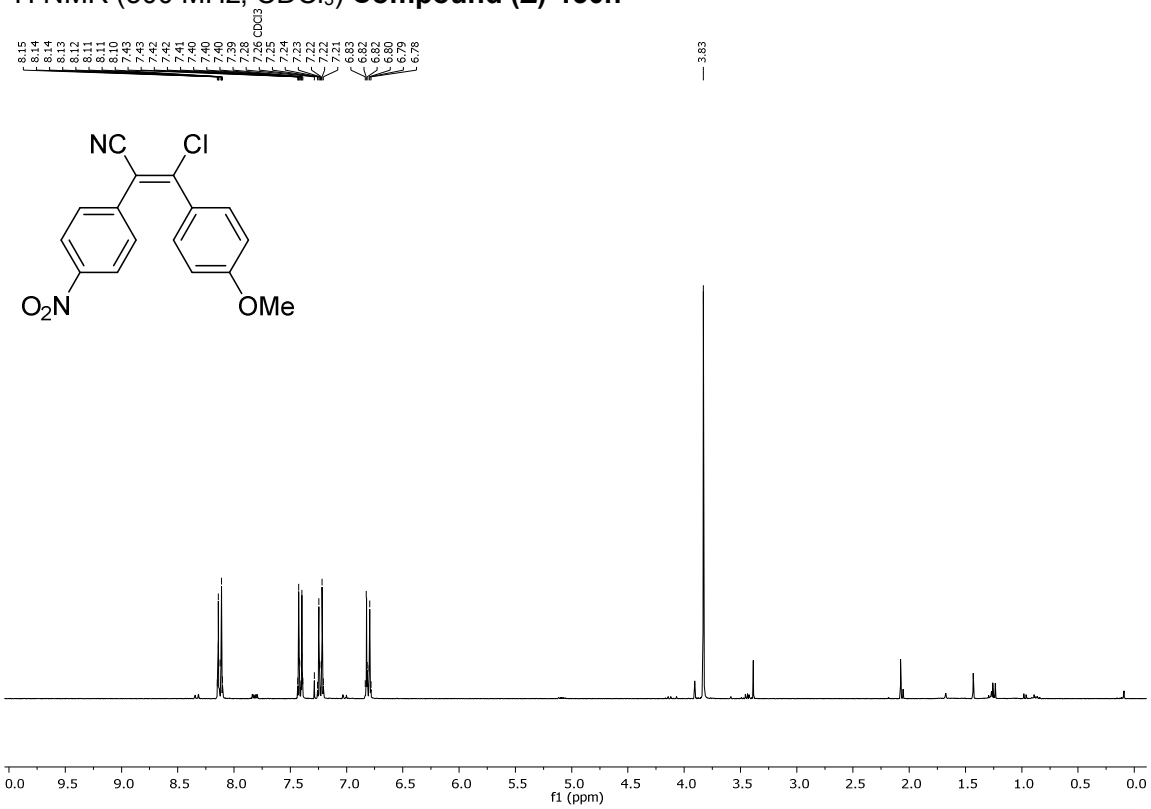


^{13}C NMR (100 MHz, $CDCl_3$) **Compound (*Z*)-130m**

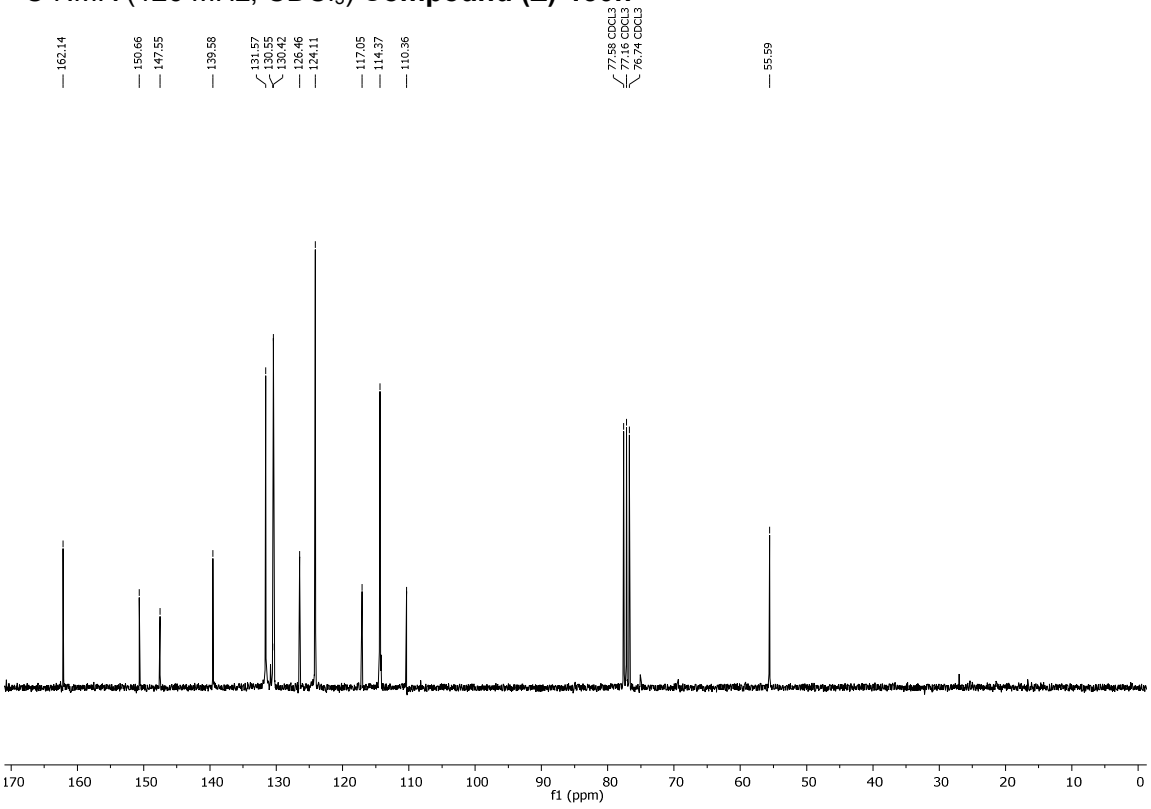




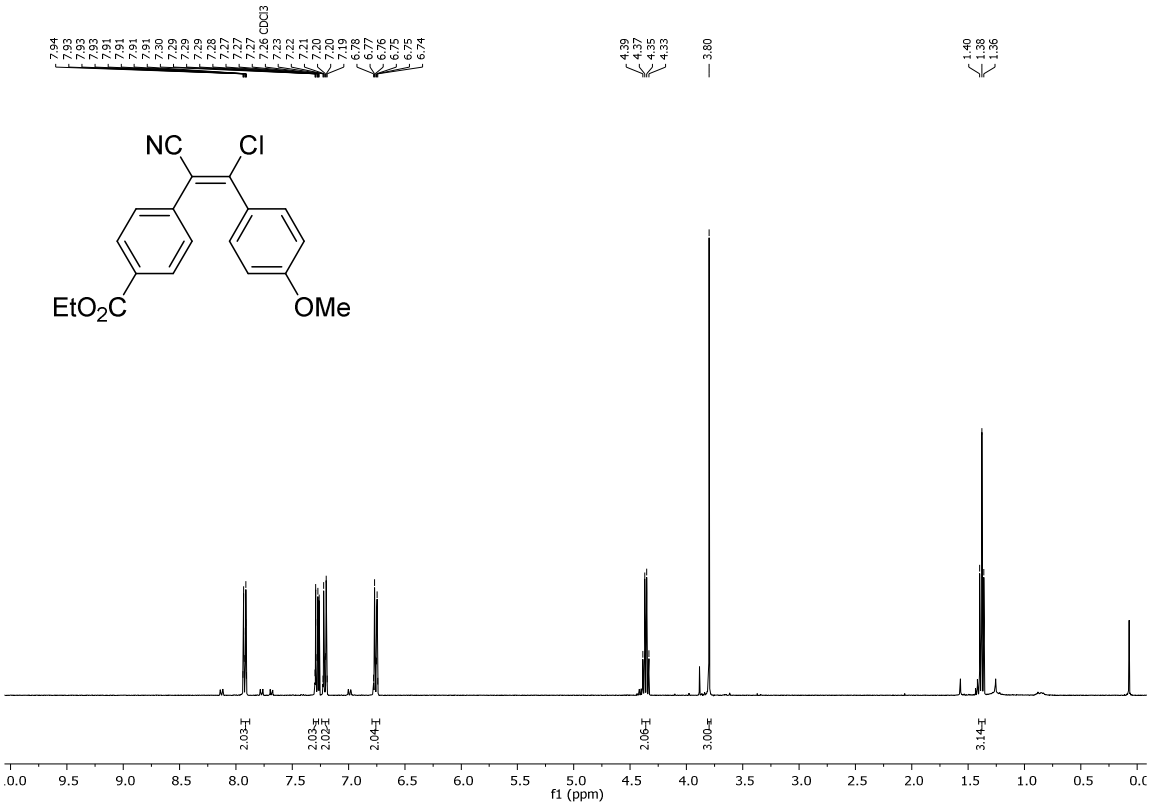
^{1}H NMR (300 MHz, $CDCl_3$) **Compound (*Z*)-130n**



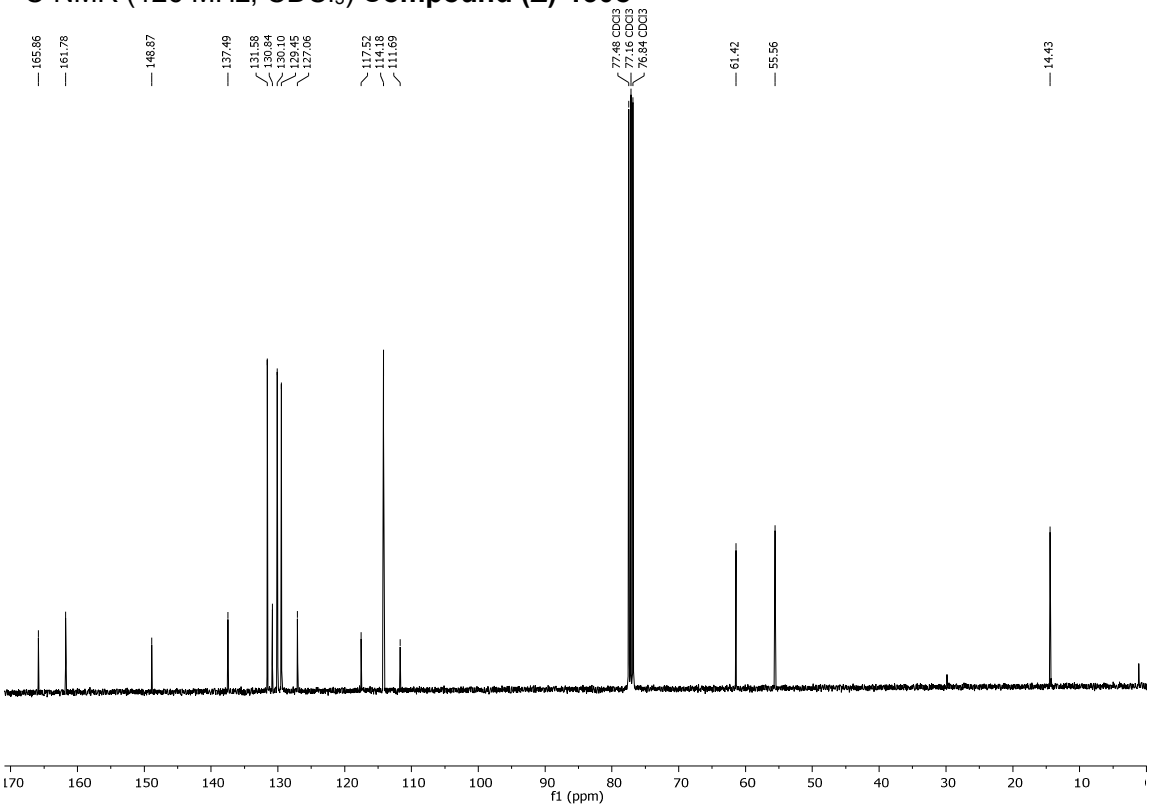
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130n**



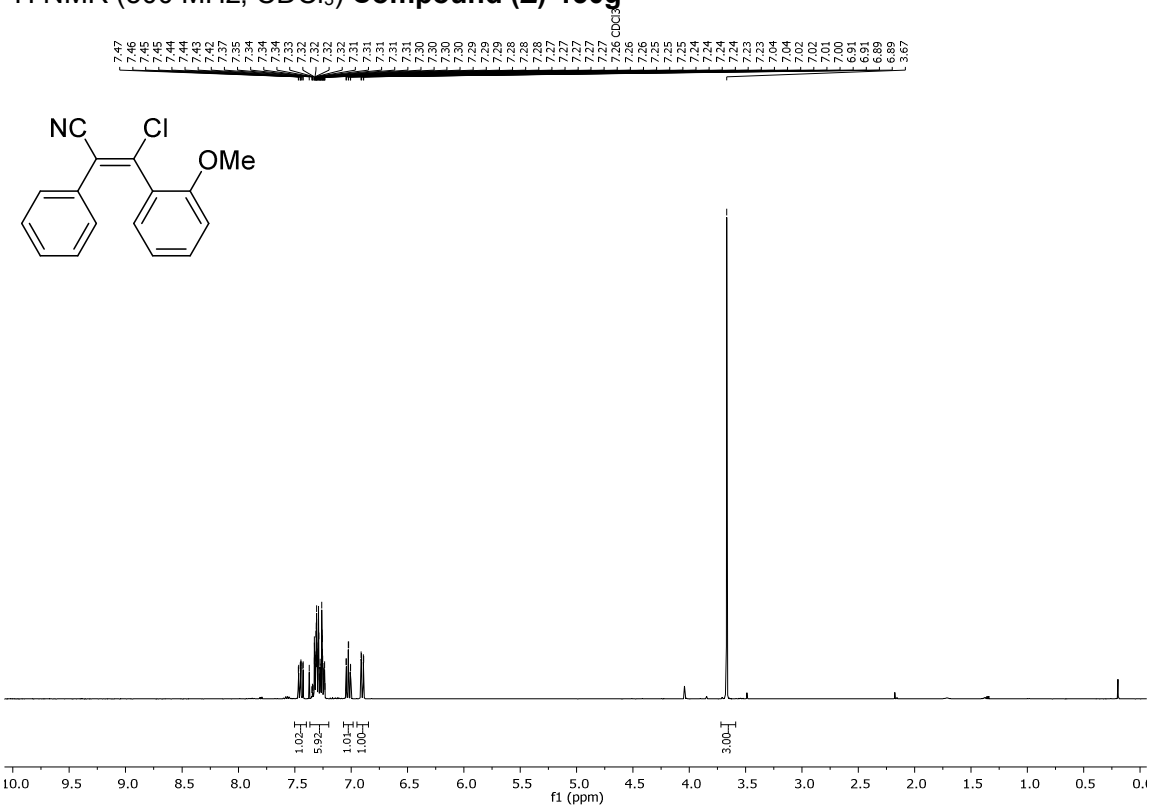
^{1}H NMR (300 MHz, $CDCl_3$) **Compound (*Z*)-130o**



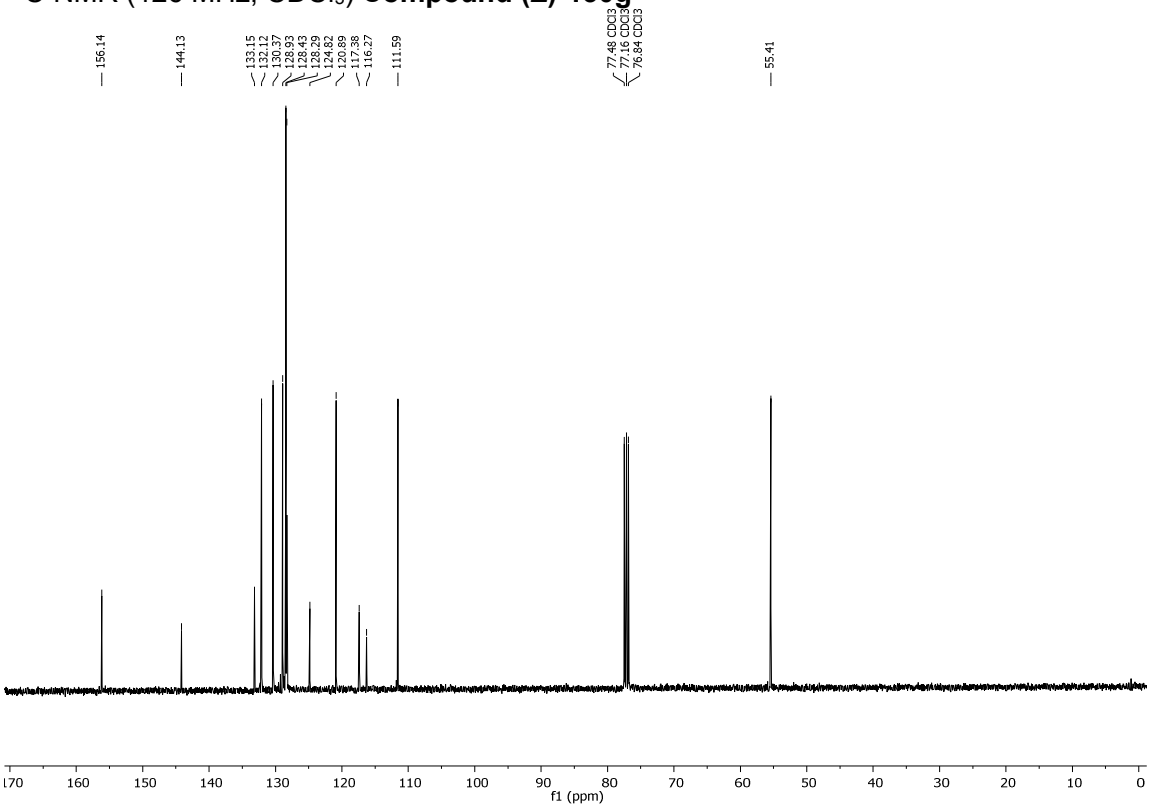
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130o**



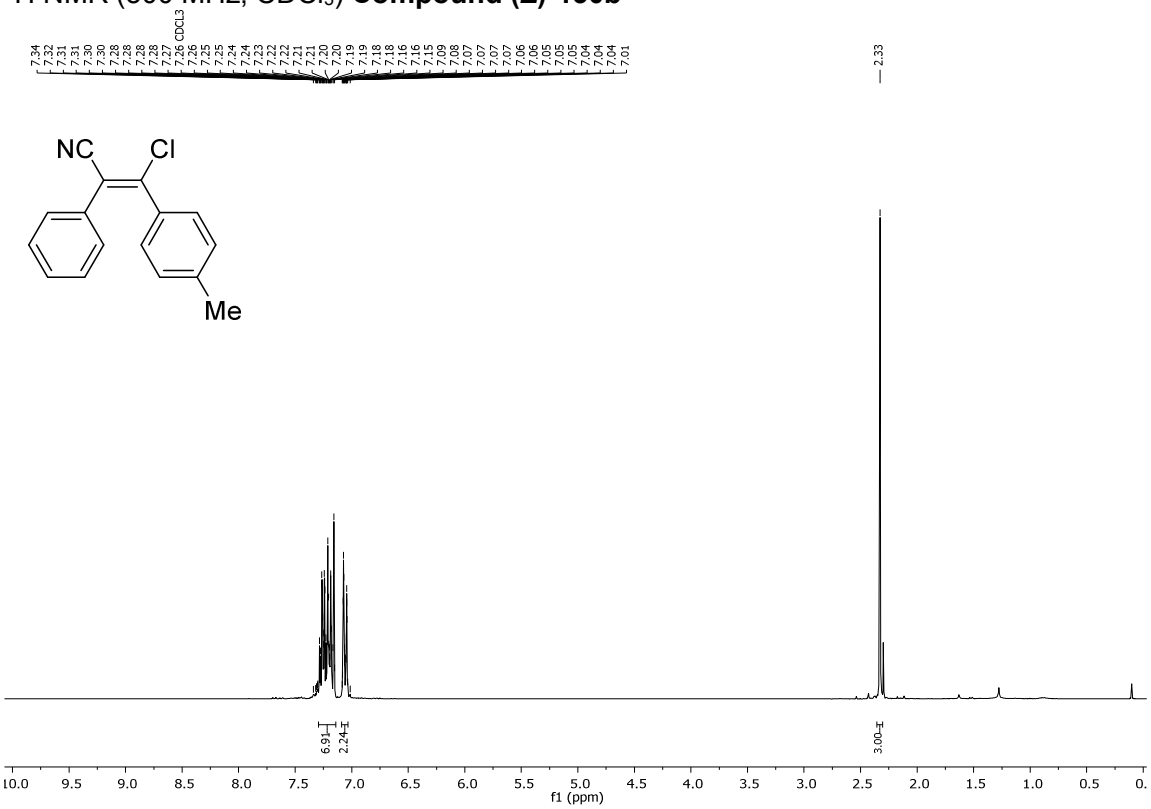
^{1}H NMR (500 MHz, $CDCl_3$) **Compound (*Z*)-130g**



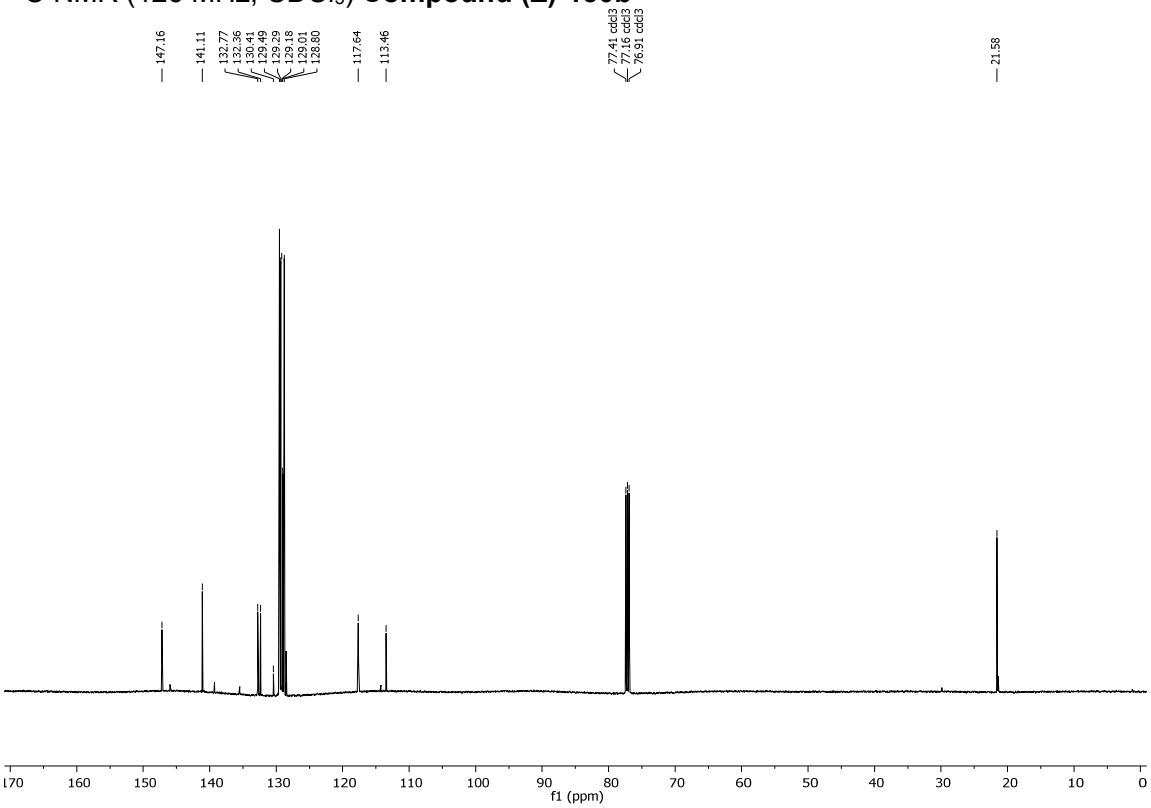
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130g**



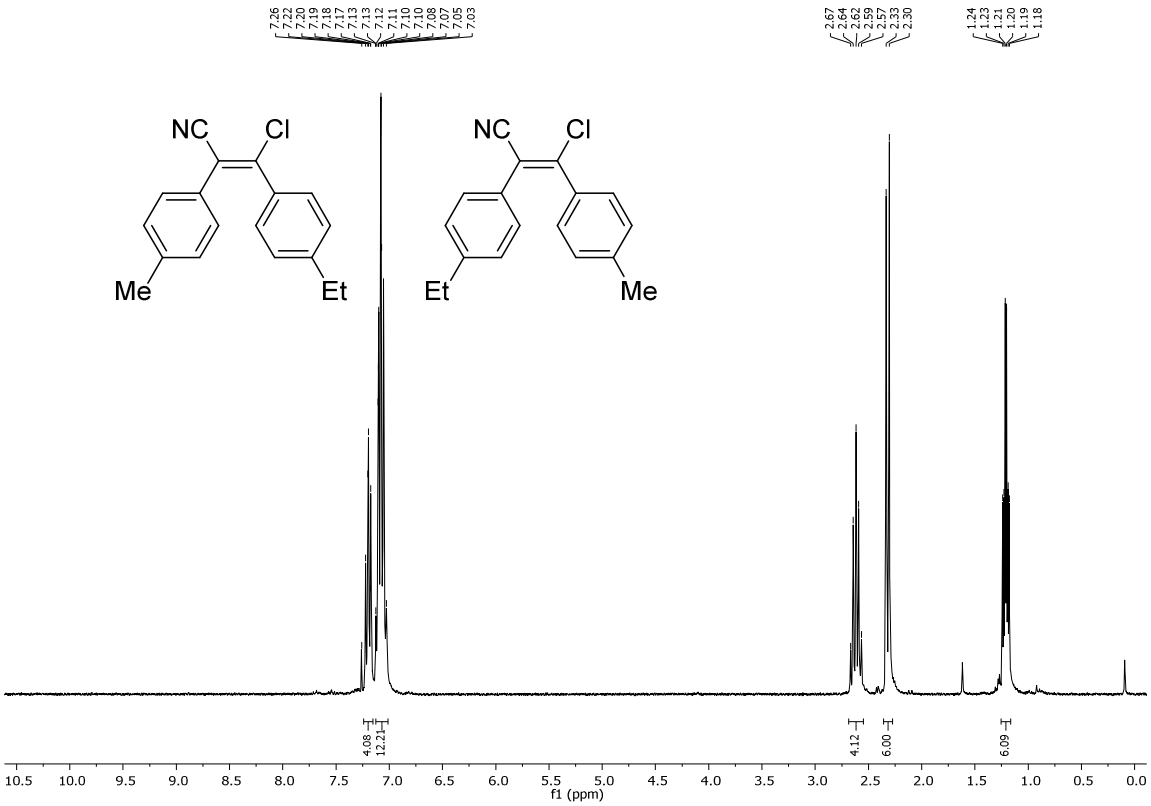
^{1}H NMR (500 MHz, $CDCl_3$) **Compound (*Z*)-130b**



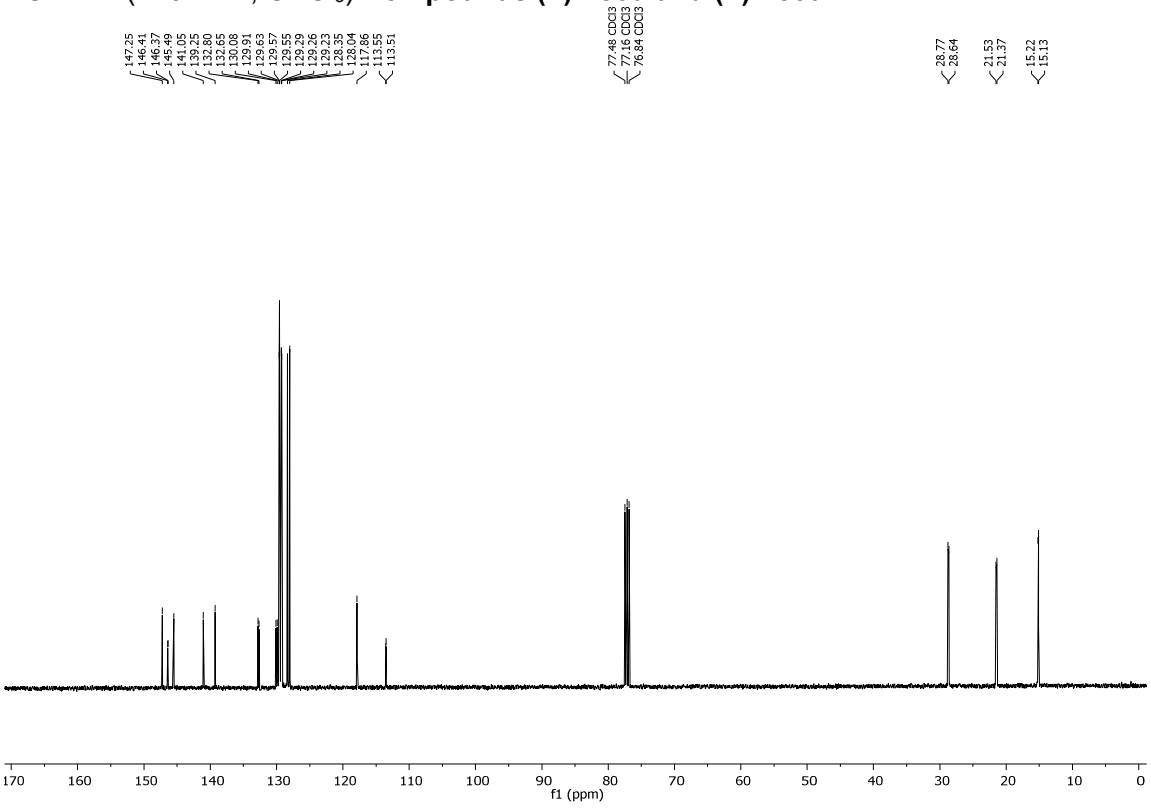
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130b**



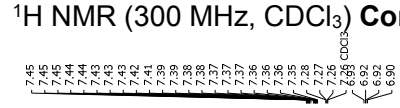
^{1}H NMR (300 MHz, $CDCl_3$) **Compounds (*Z*)-130d (left) and (*Z*)-130d' (right)**

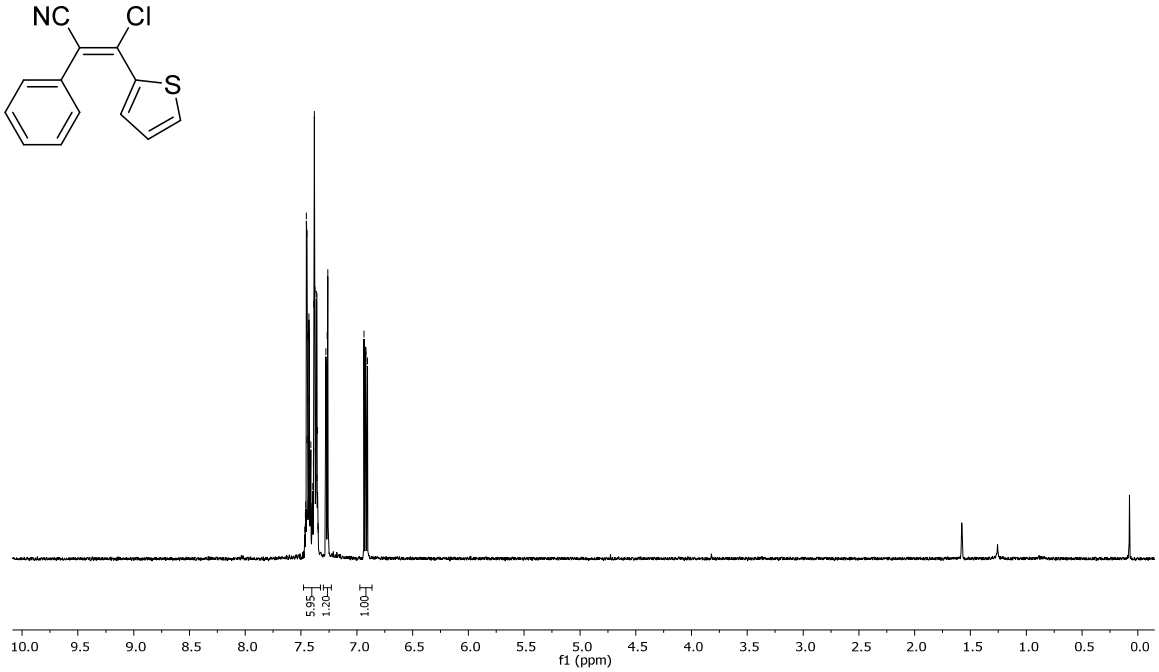


^{13}C NMR (126 MHz, $CDCl_3$) **Compounds (*Z*)-130d and (*Z*)-130d'**

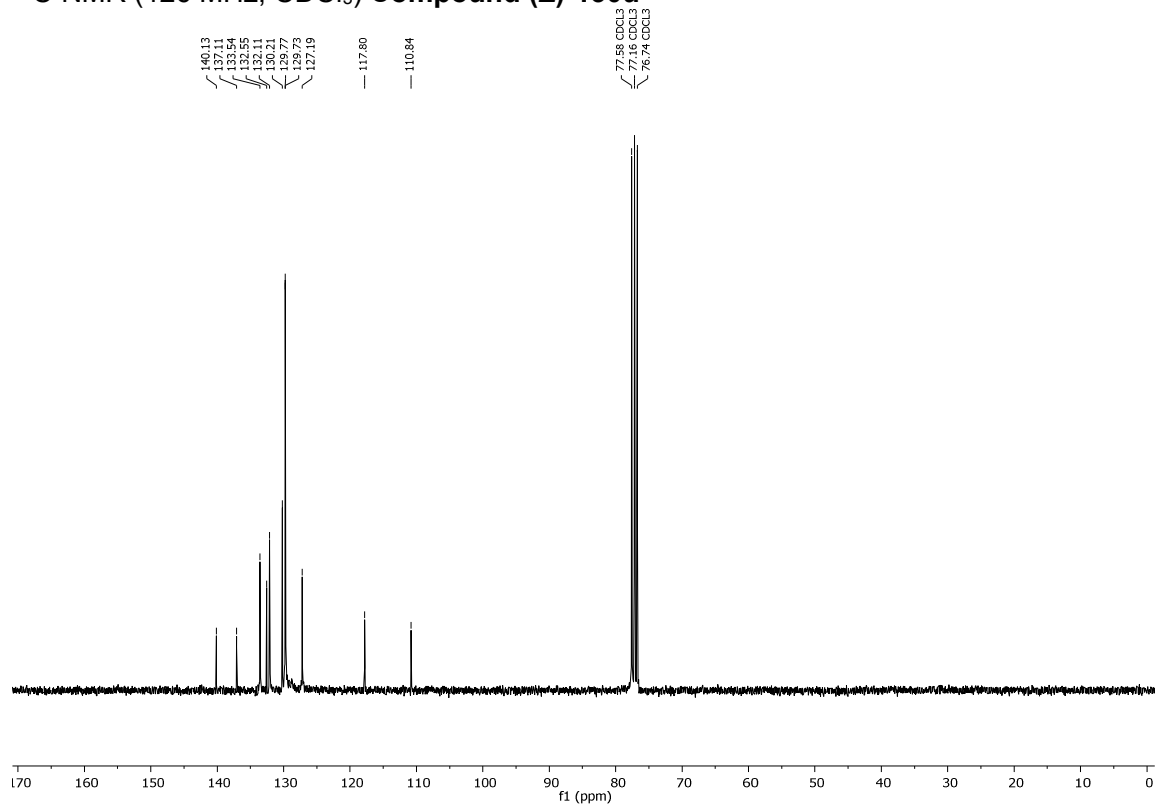


^{1}H NMR (300 MHz, $CDCl_3$) **Compound (*Z*)-130u**

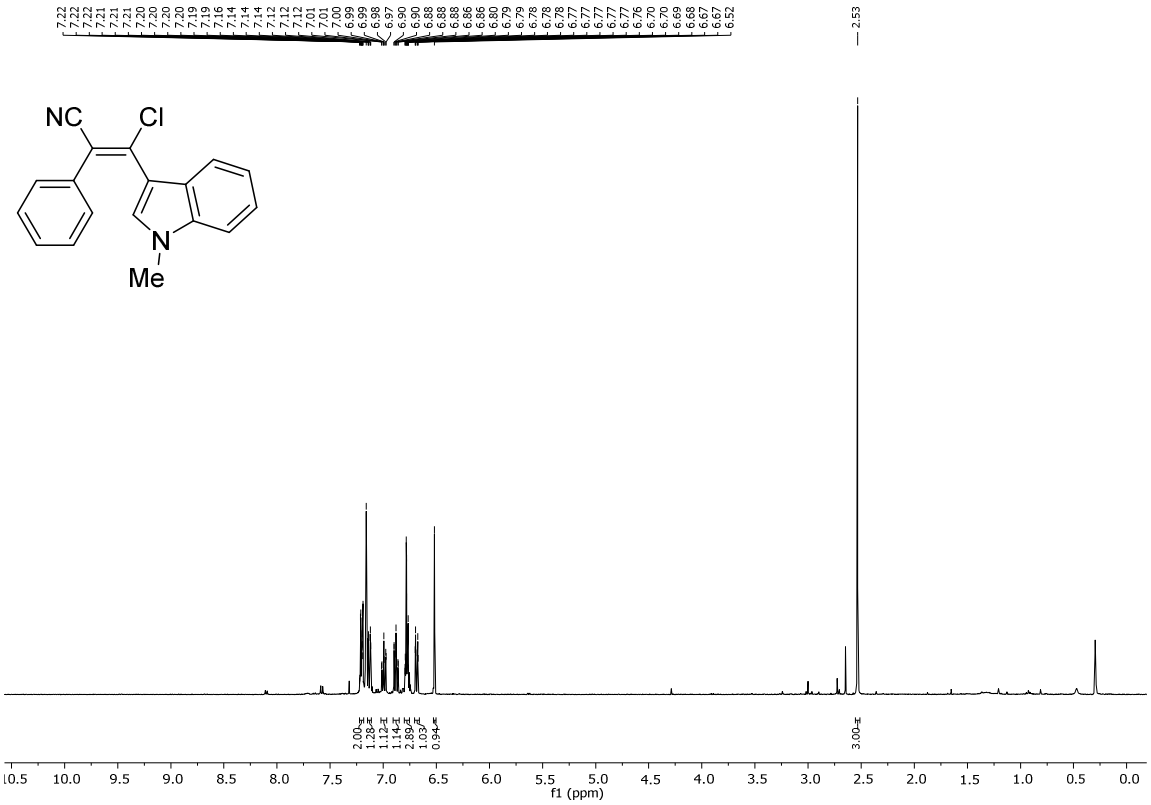




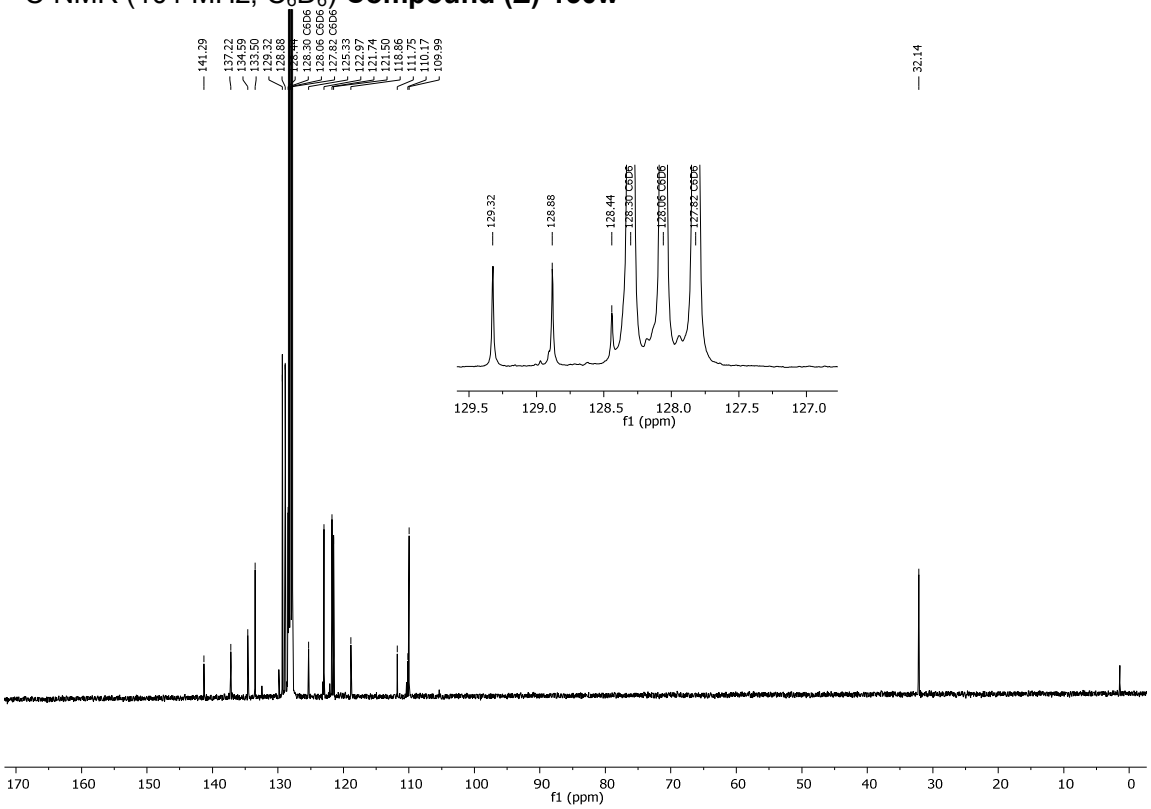
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130u**



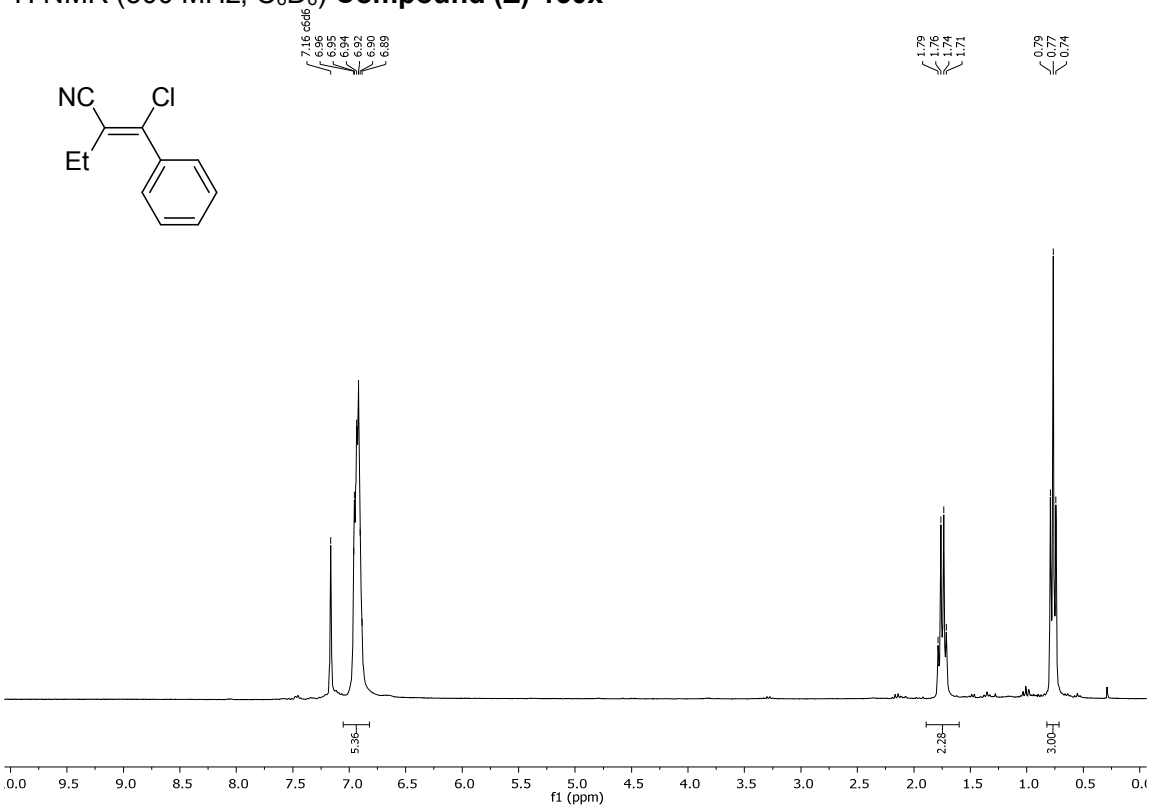
^{1}H NMR (400 MHz, C_6D_6) **Compound (*Z*)-130w**



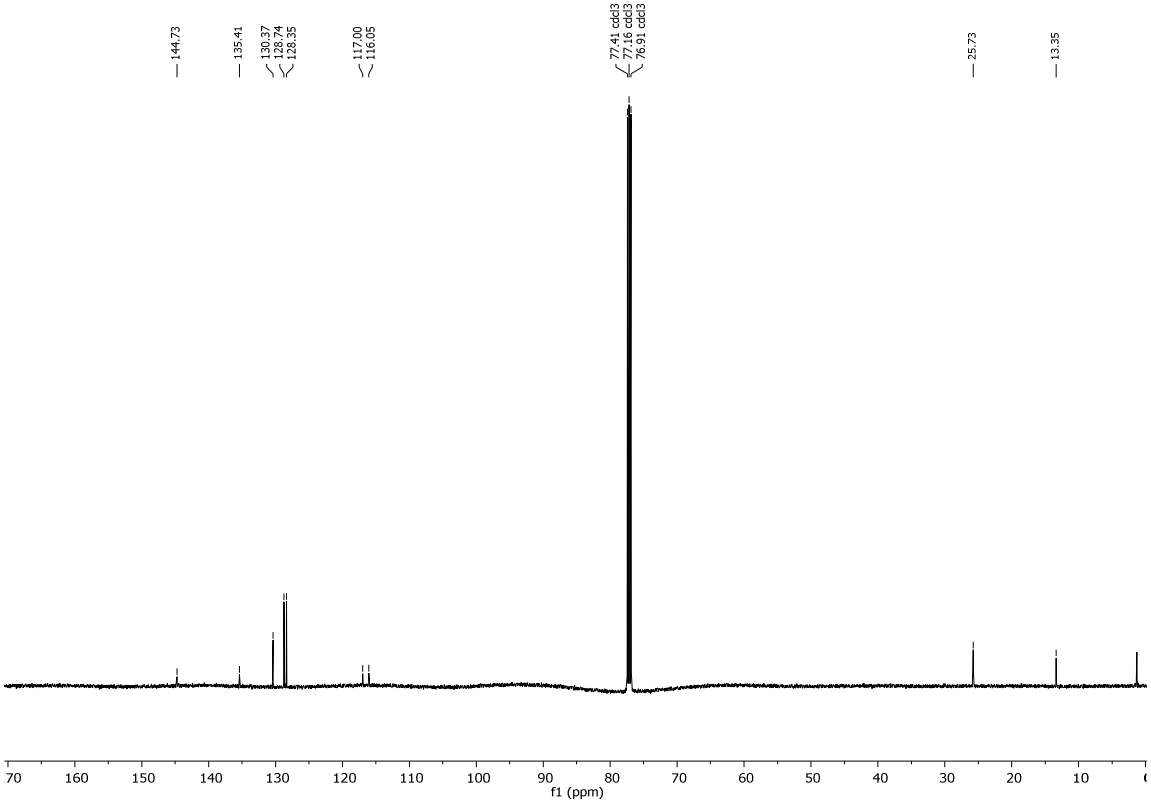
^{13}C NMR (101 MHz, C_6D_6) **Compound (*Z*)-130w**



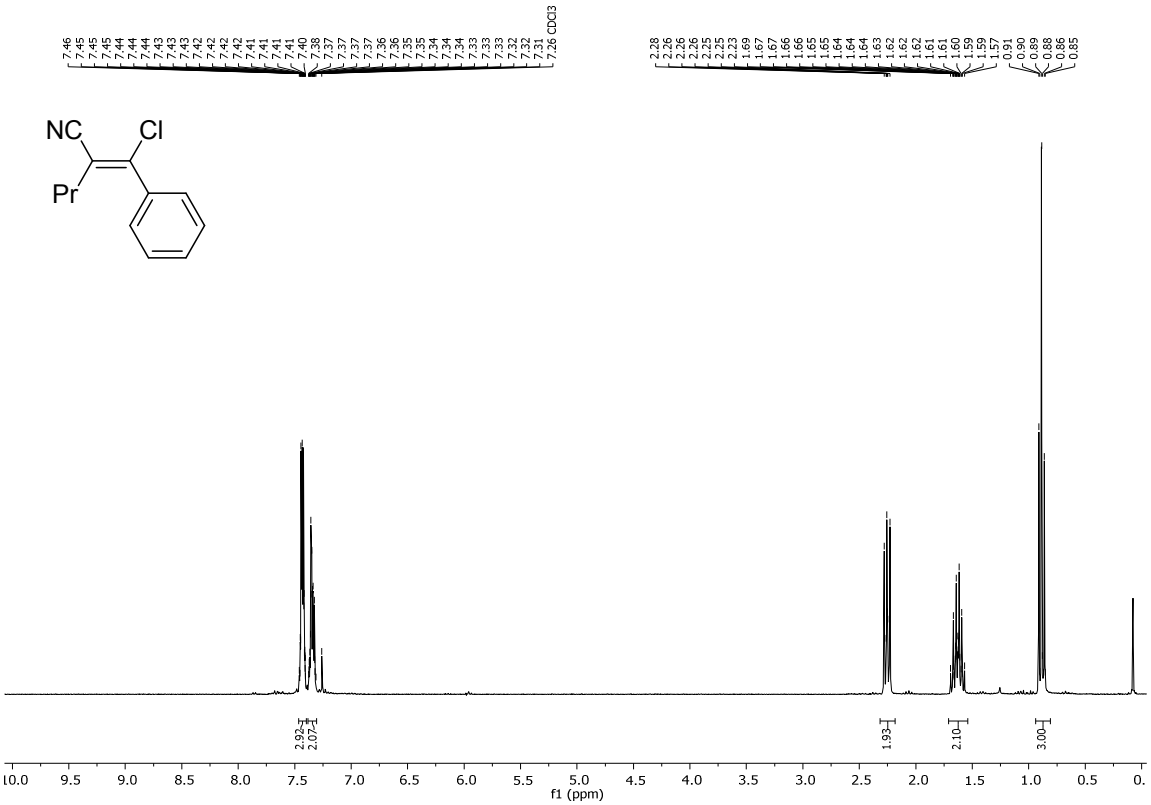
^{1}H NMR (500 MHz, C_6D_6) **Compound (*Z*)-130x**



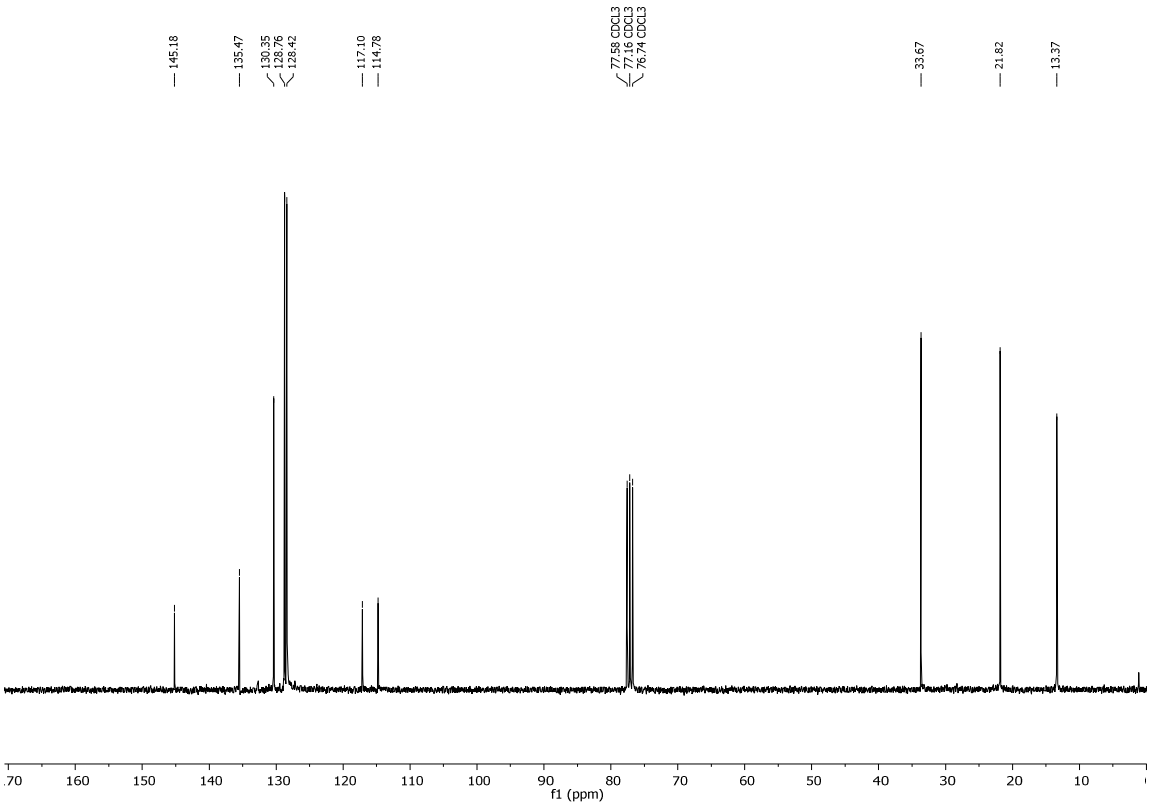
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130x**



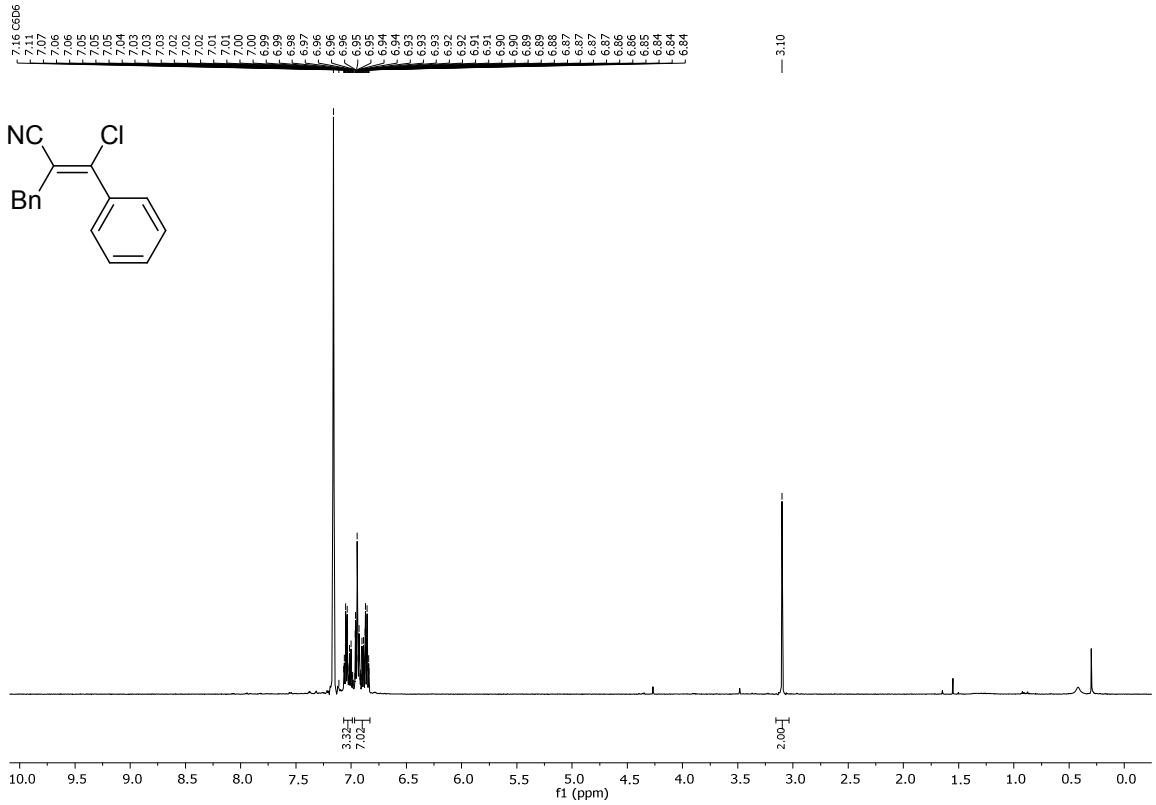
^{1}H NMR (300 MHz, $CDCl_3$) **Compound (*Z*)-130y**



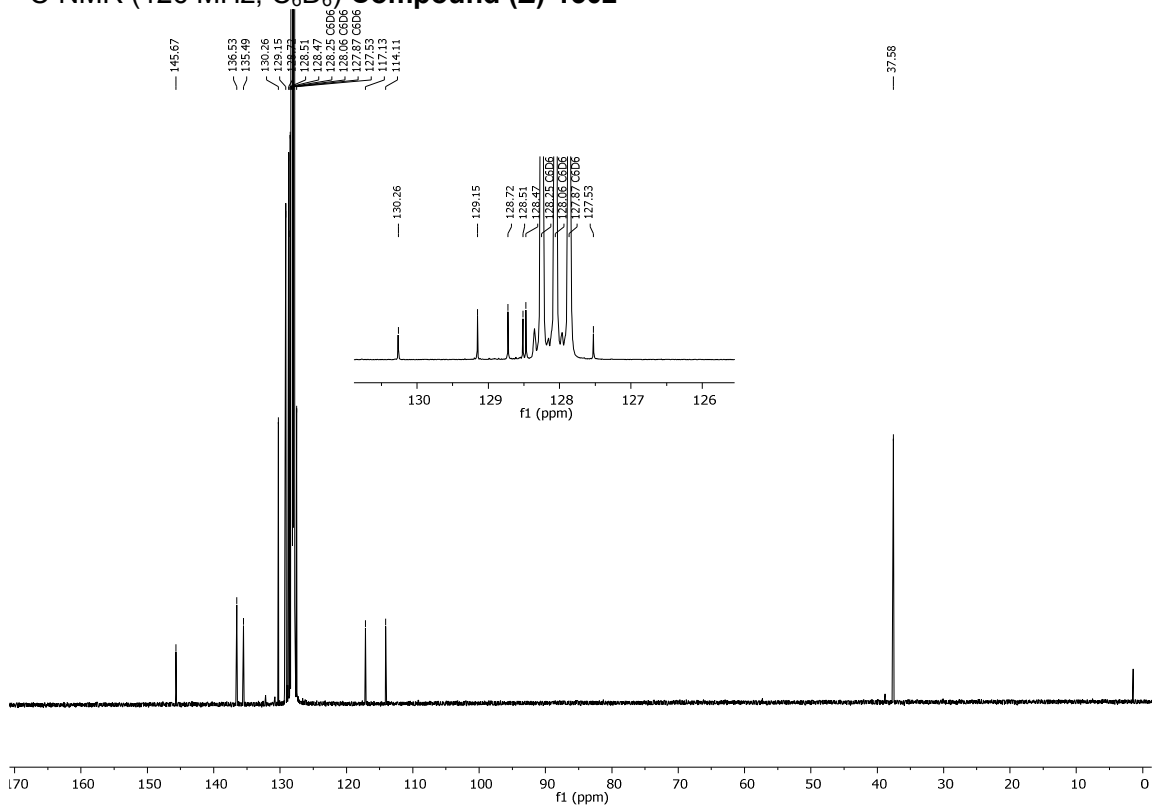
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130y**



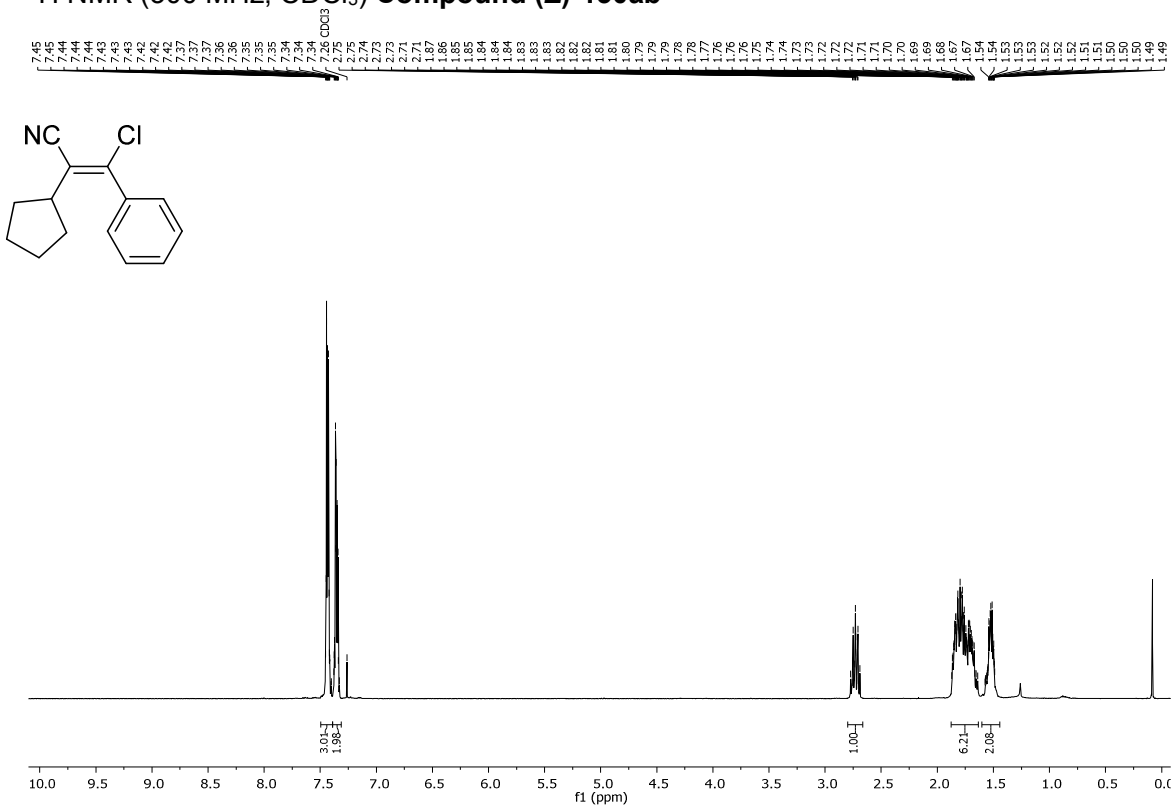
^{1}H NMR (500 MHz, C_6D_6) **Compound (*Z*)-130z**



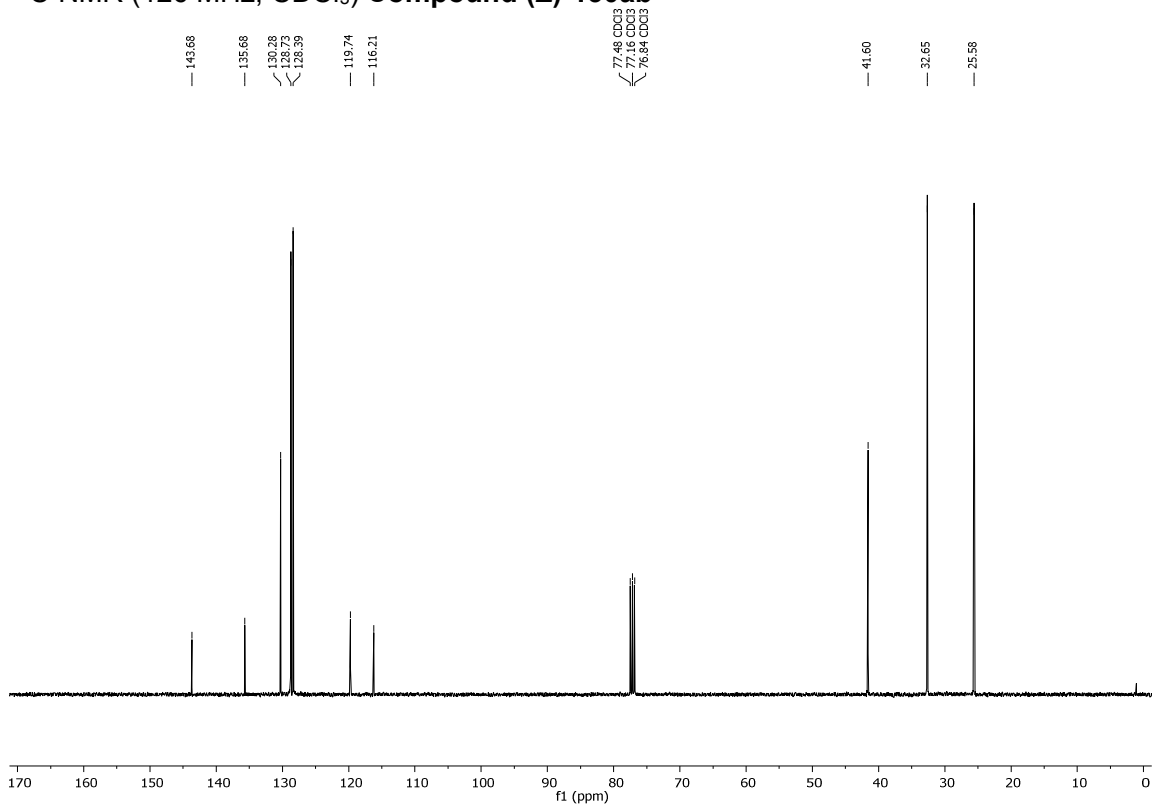
^{13}C NMR (126 MHz, C_6D_6) **Compound (*Z*)-130z**



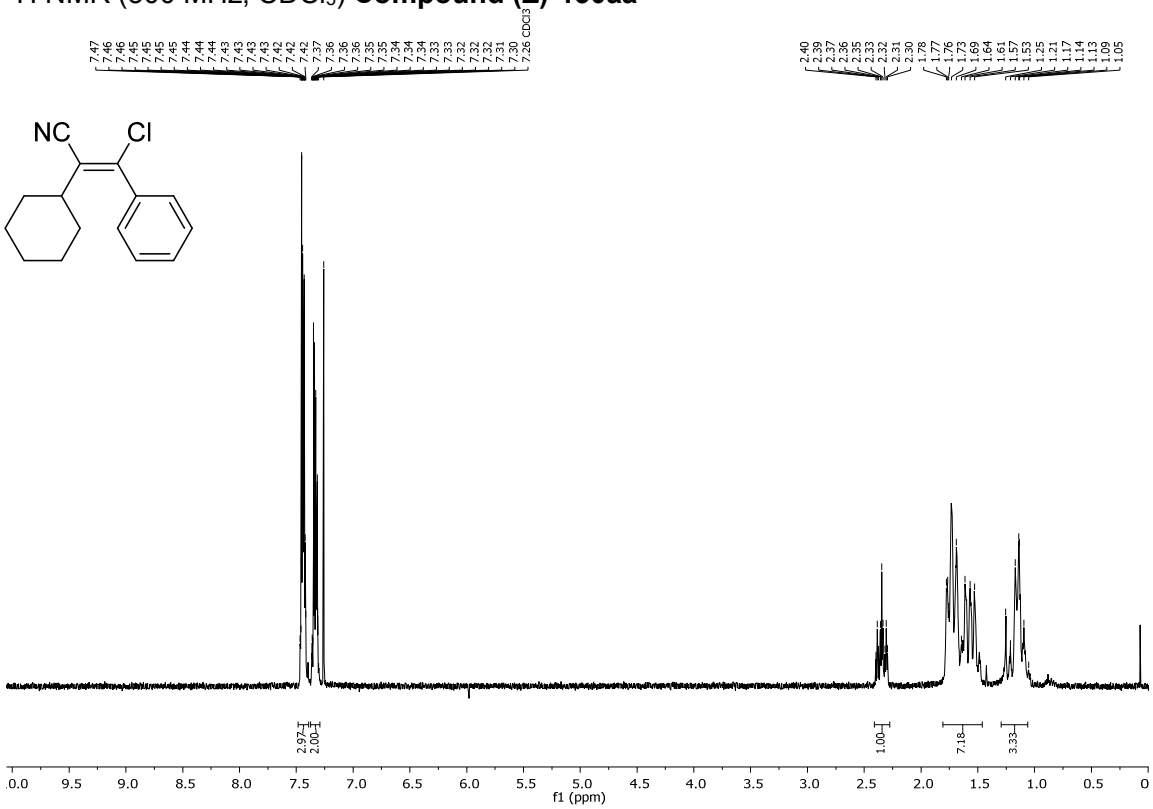
^{1}H NMR (300 MHz, $CDCl_3$) **Compound (*Z*)-130ab**



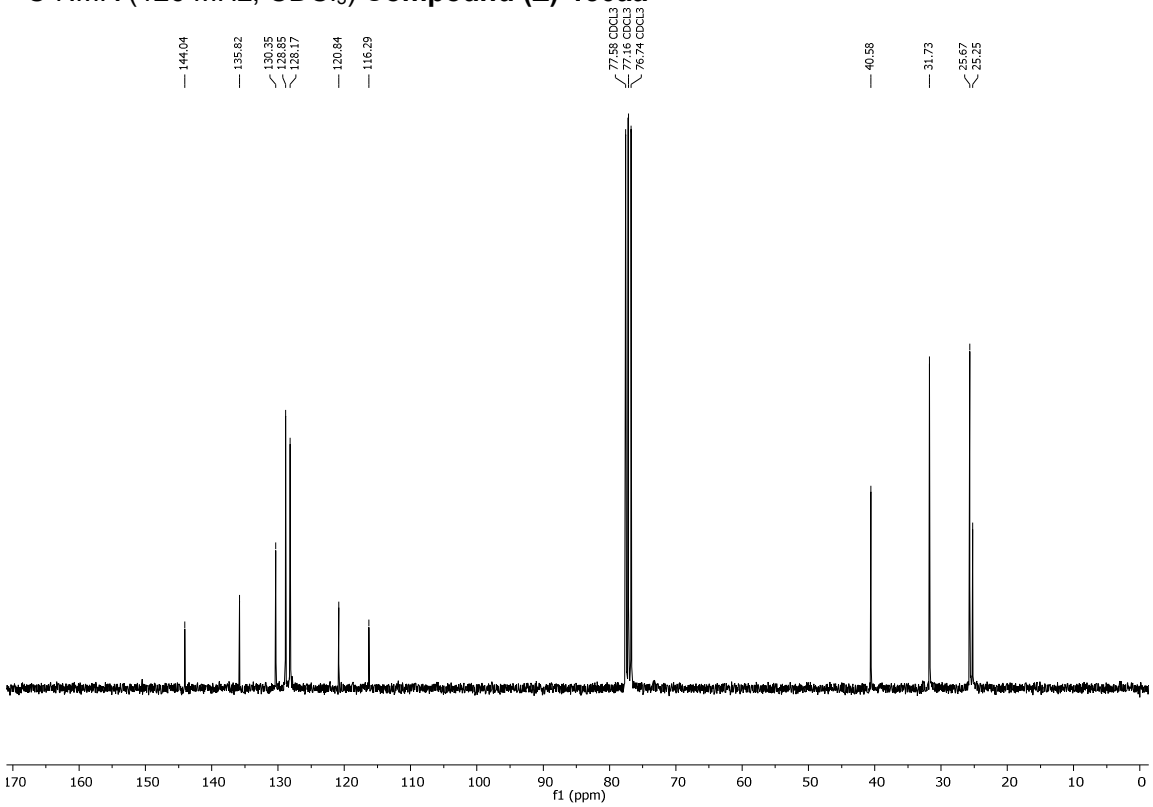
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130ab**



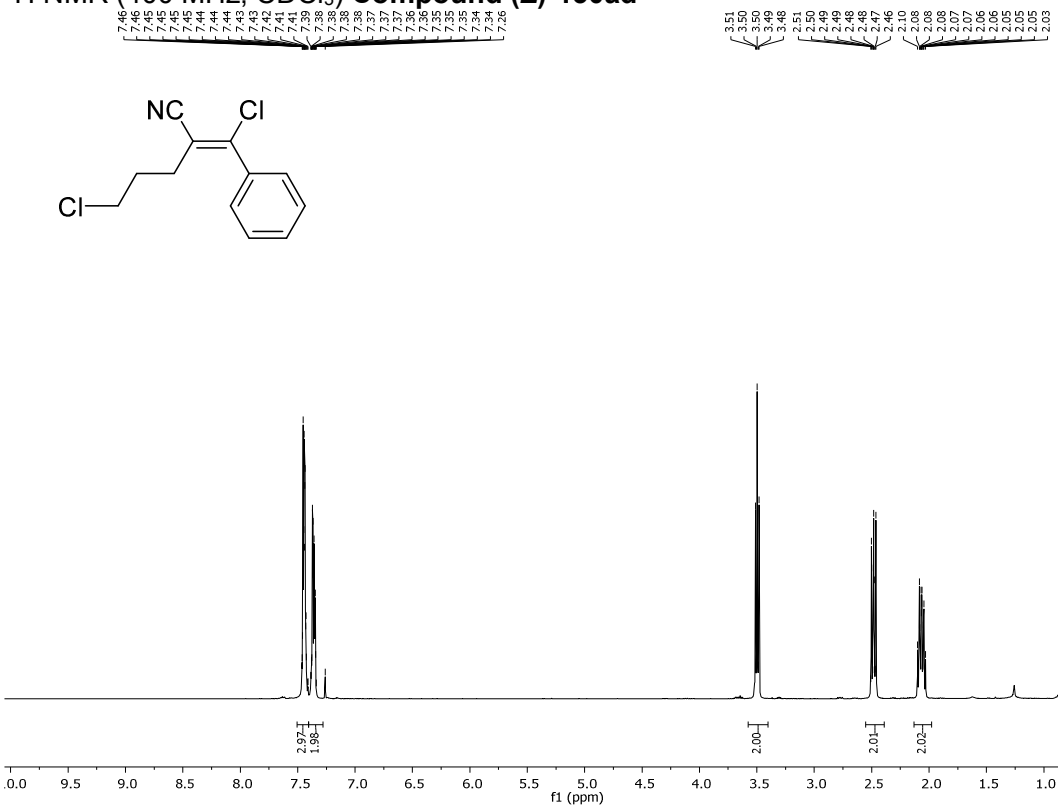
^{1}H NMR (300 MHz, $CDCl_3$) **Compound (*Z*)-130aa**



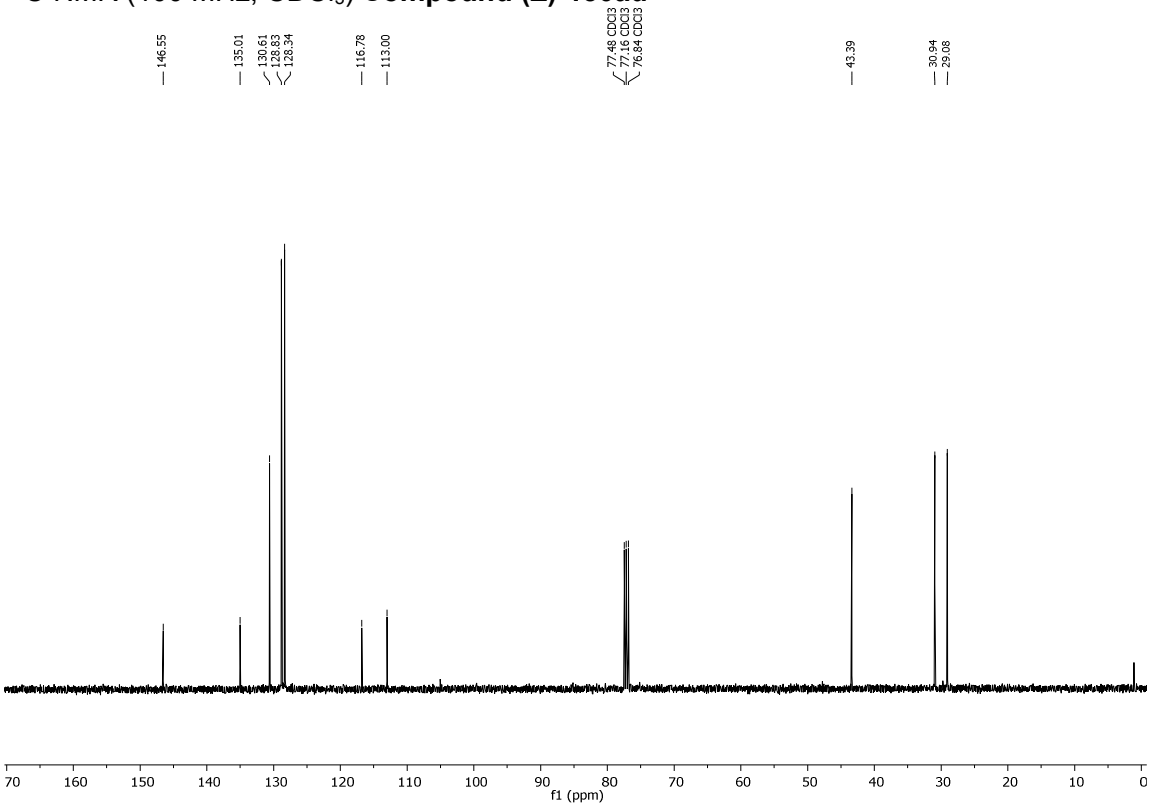
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130aa**



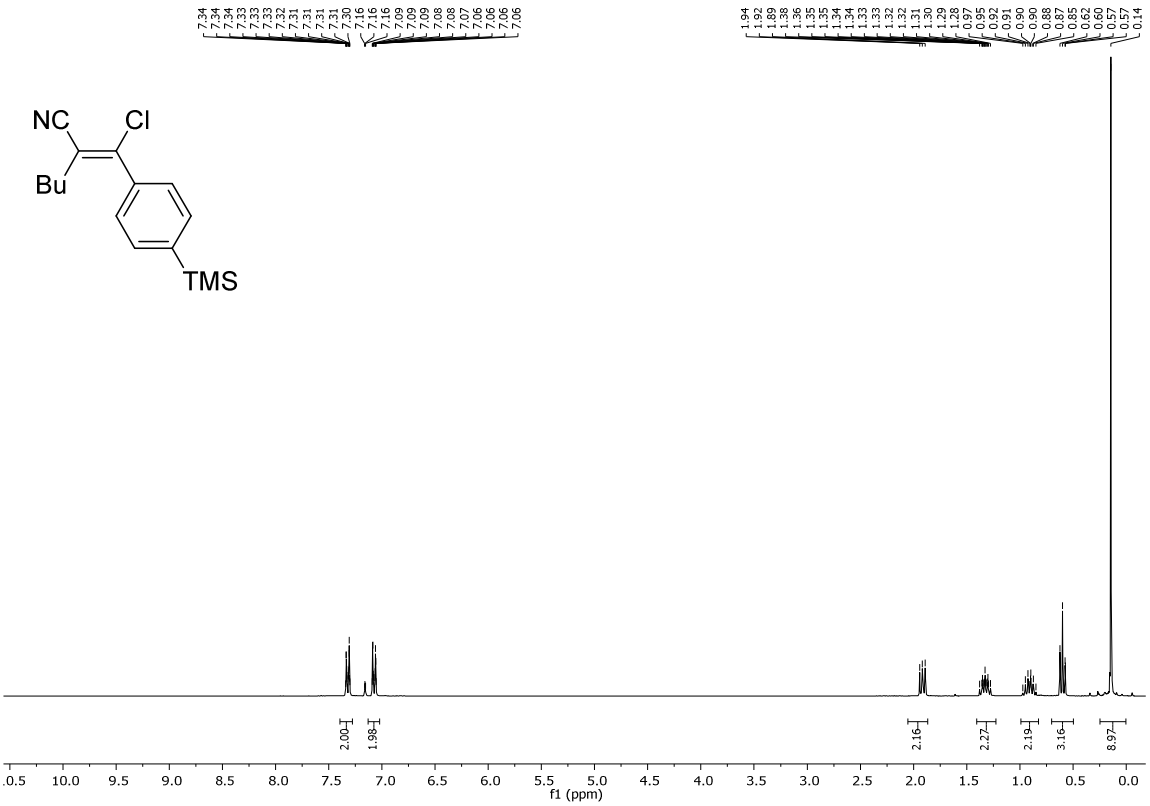
^{1}H NMR (400 MHz, $CDCl_3$) **Compound (*Z*)-130ad**



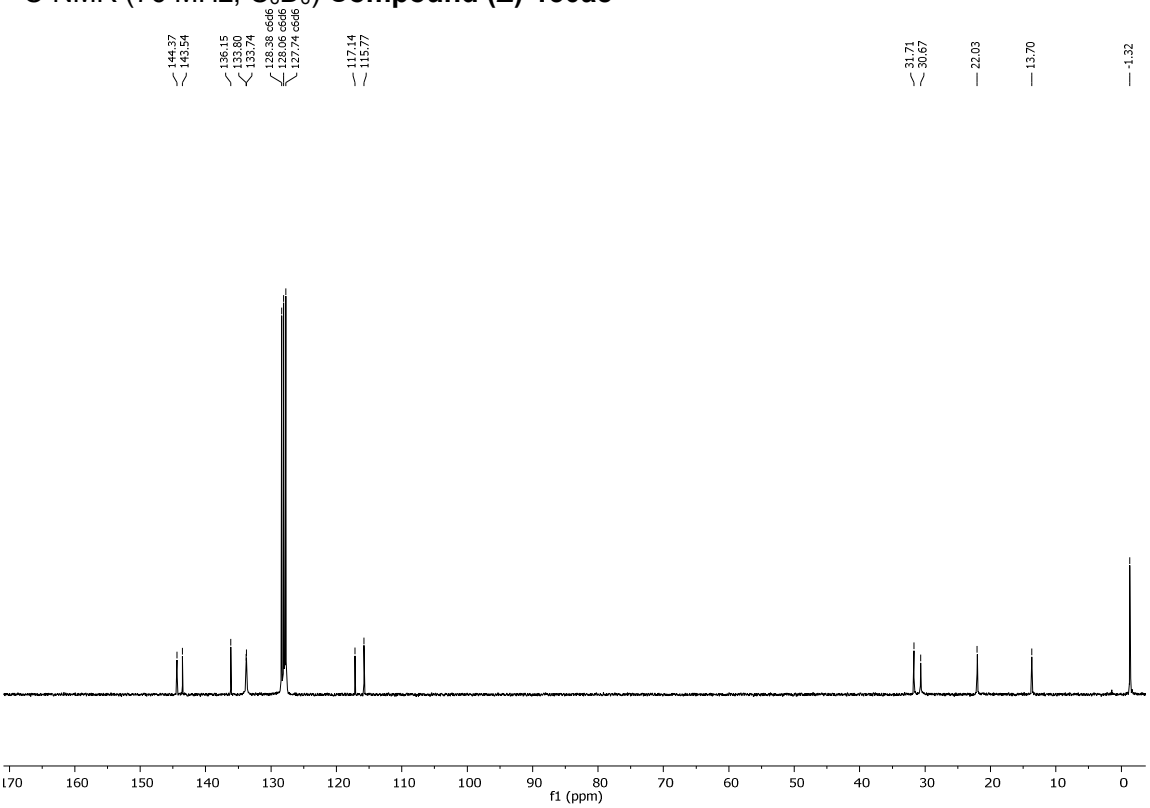
^{13}C NMR (100 MHz, $CDCl_3$) **Compound (*Z*)-130ad**



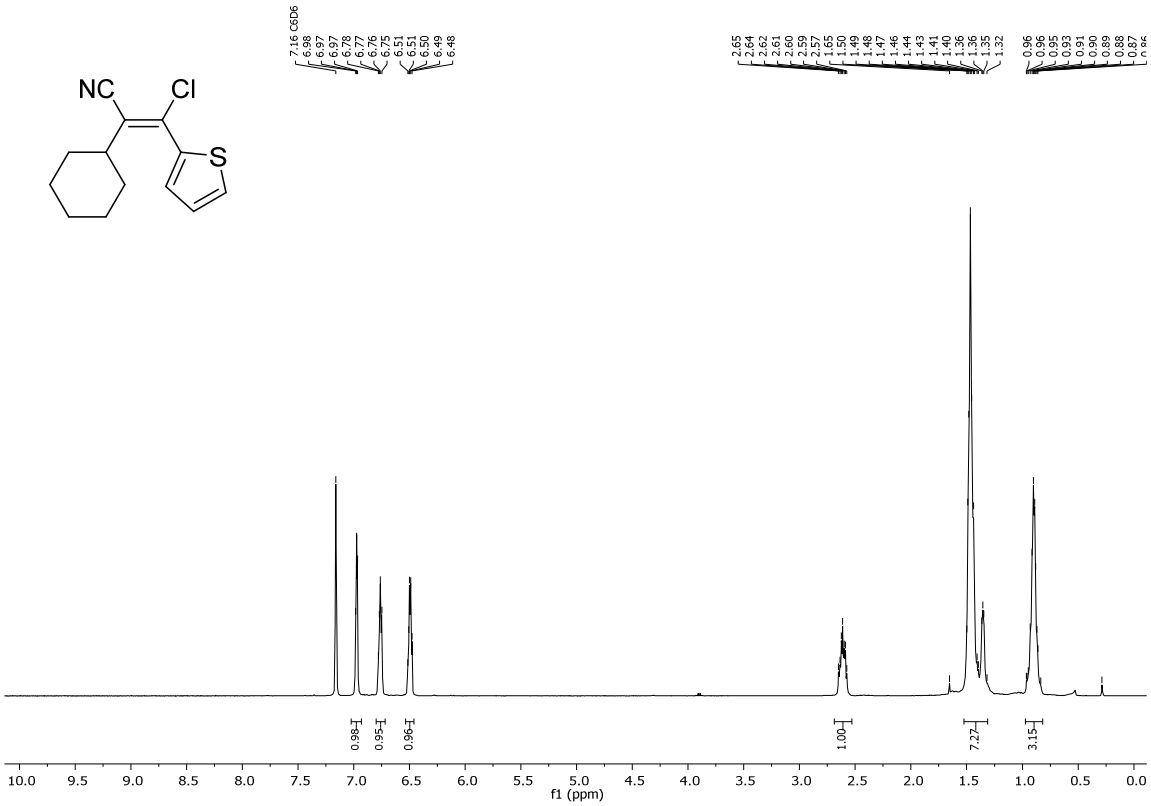
^{1}H NMR (400 MHz, C_6D_6) **Compound (*Z*)-130ac**



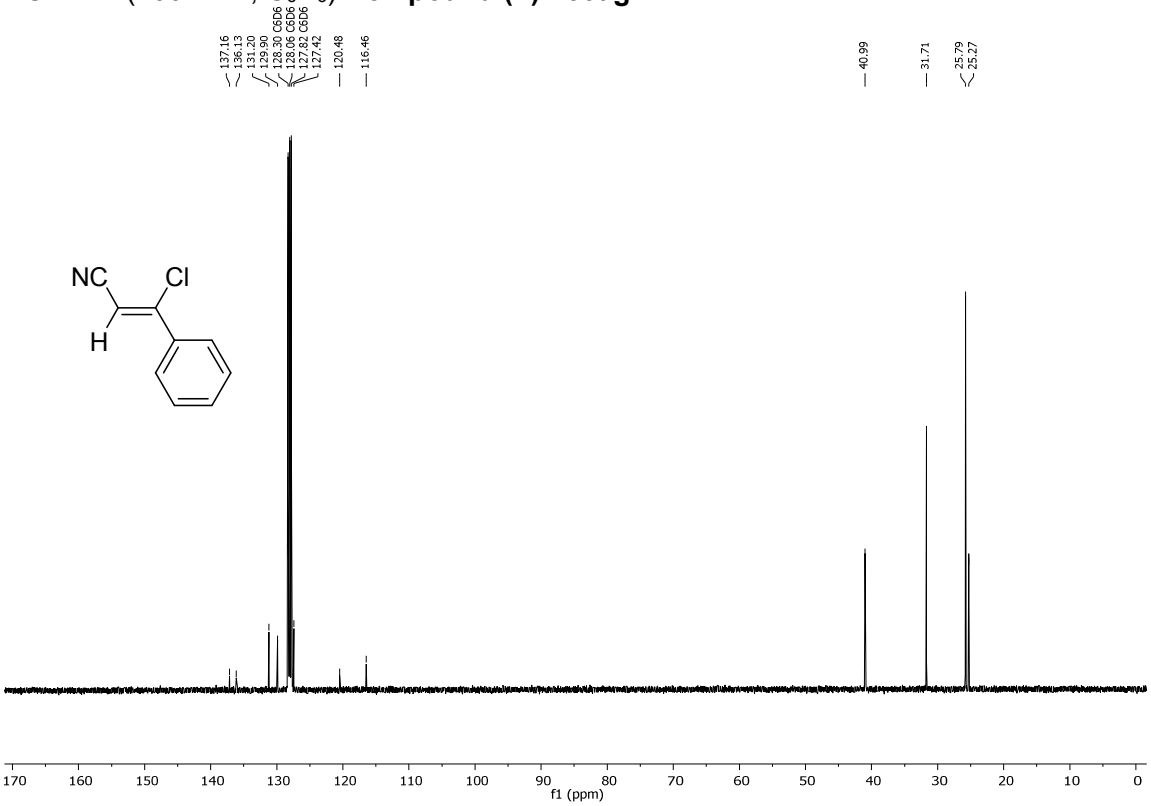
^{13}C NMR (76 MHz, C_6D_6) **Compound (*Z*)-130ac**



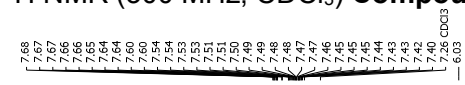
^{1}H NMR (400 MHz, C_6D_6) **Compound (*Z*)-130ag**

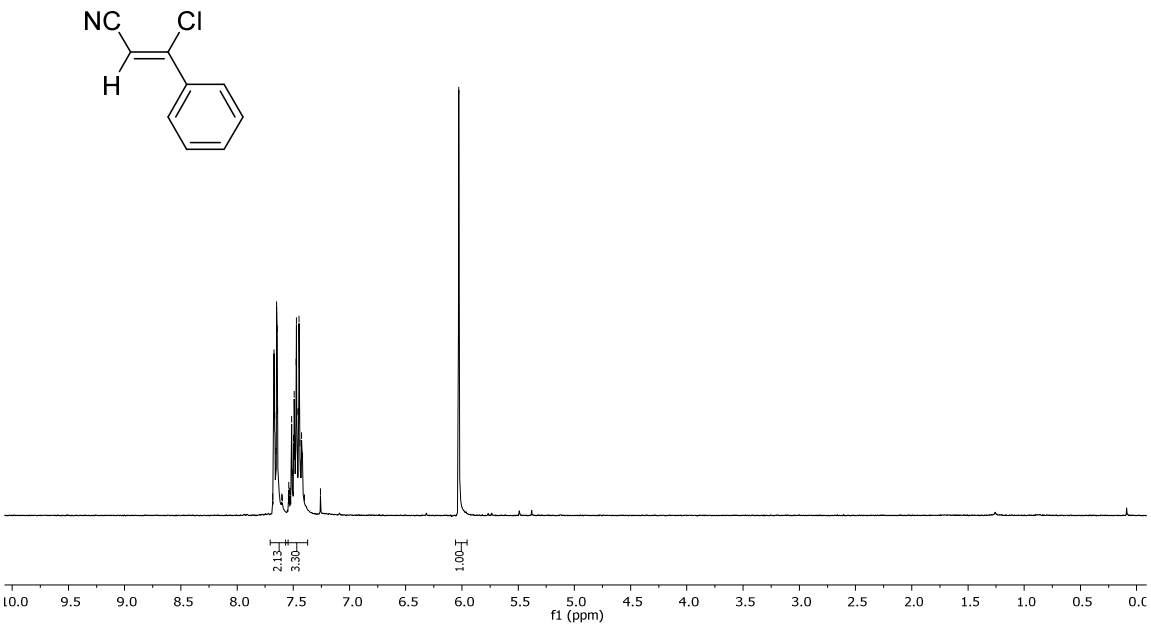


^{13}C NMR (100 MHz, C_6D_6) **Compound (*Z*)-130ag**

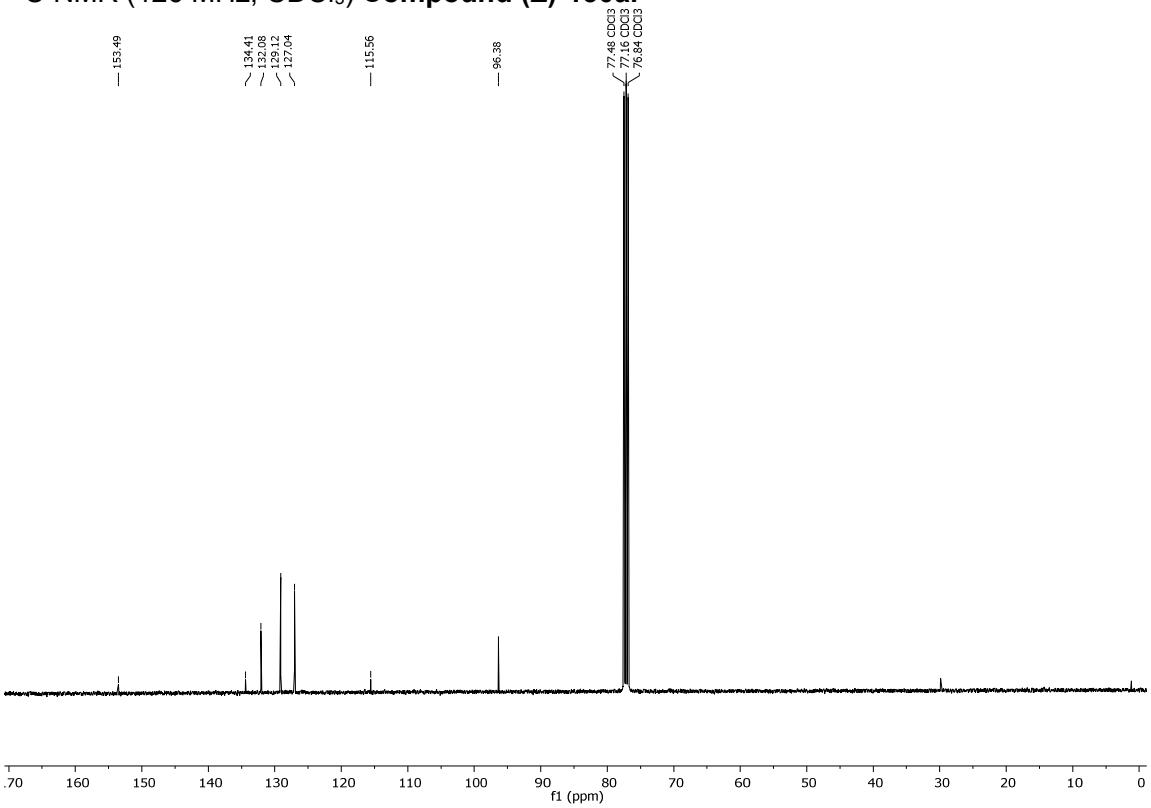


^{1}H NMR (300 MHz, $CDCl_3$) **Compound (*Z*)-130ai**

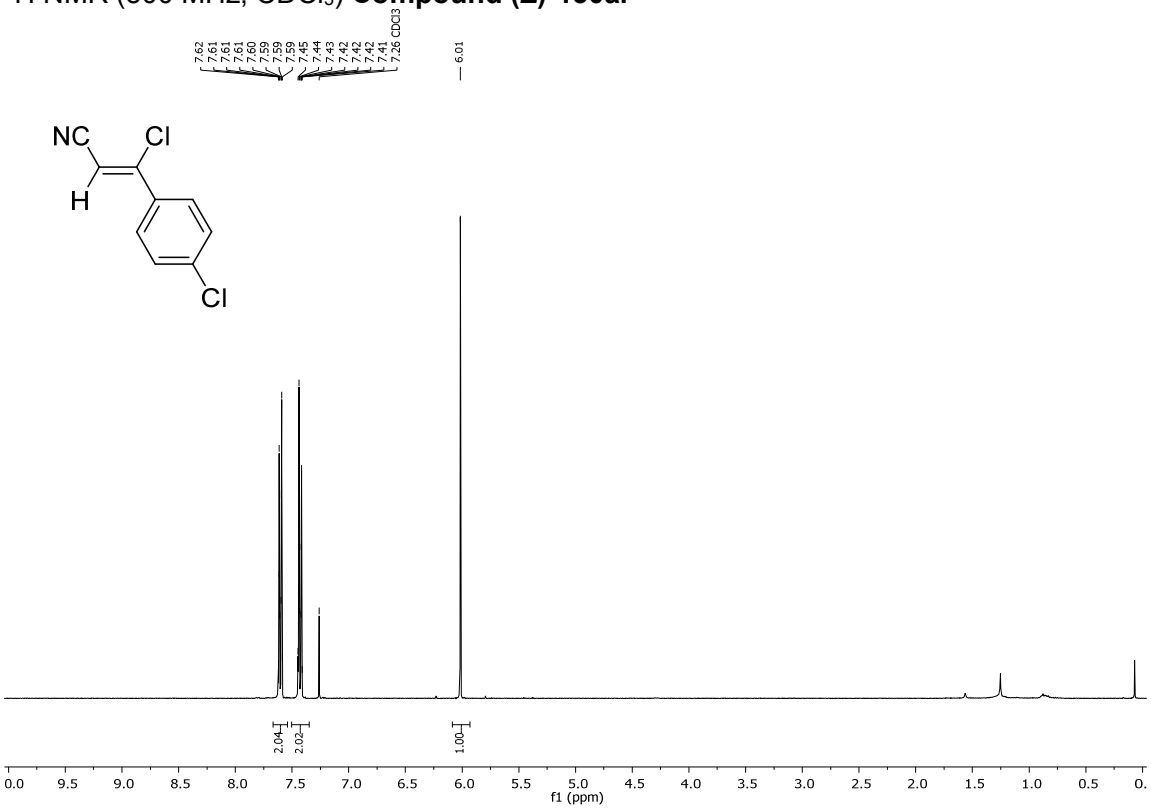




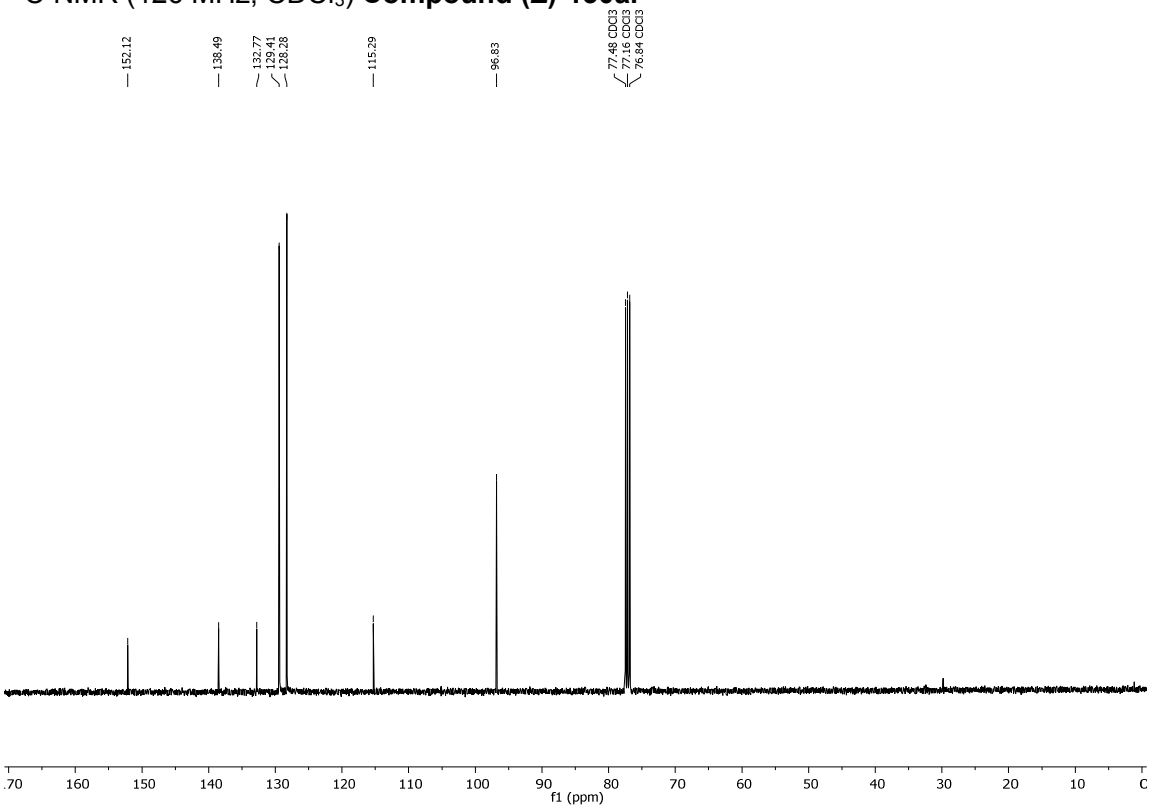
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130ai**



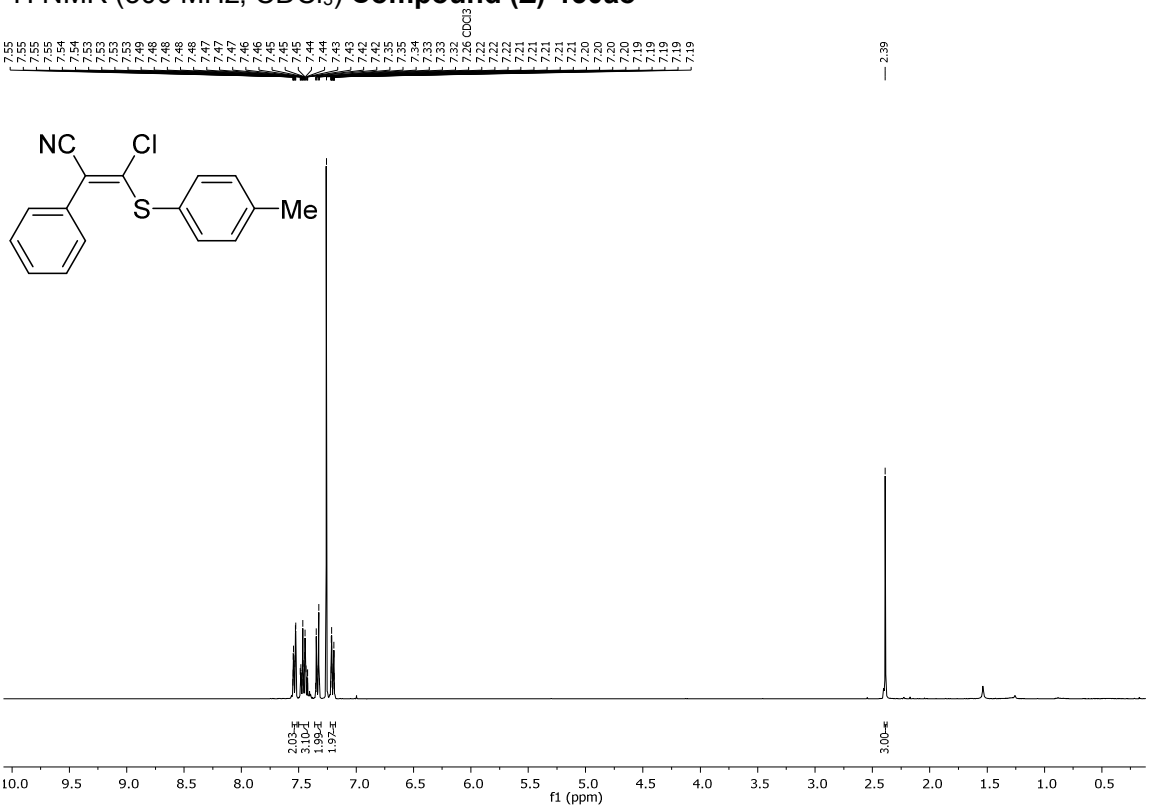
^{1}H NMR (500 MHz, $CDCl_3$) **Compound (*Z*)-130al**



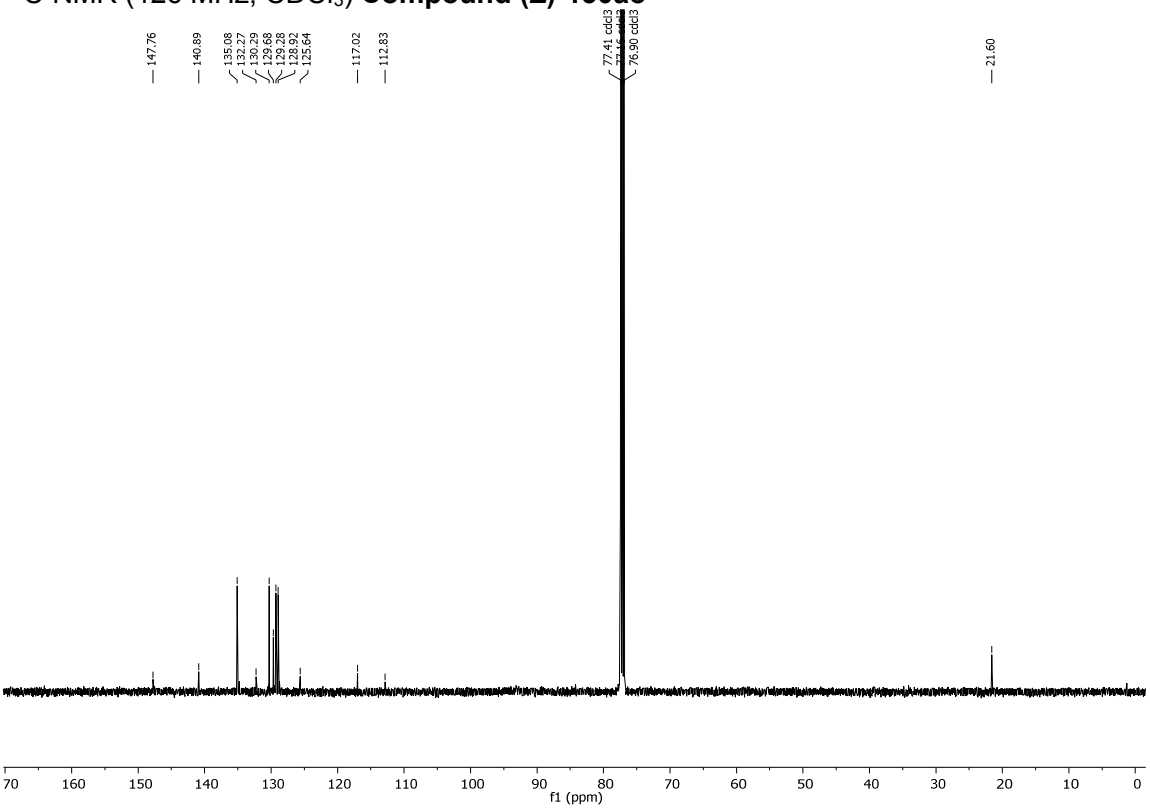
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130al**



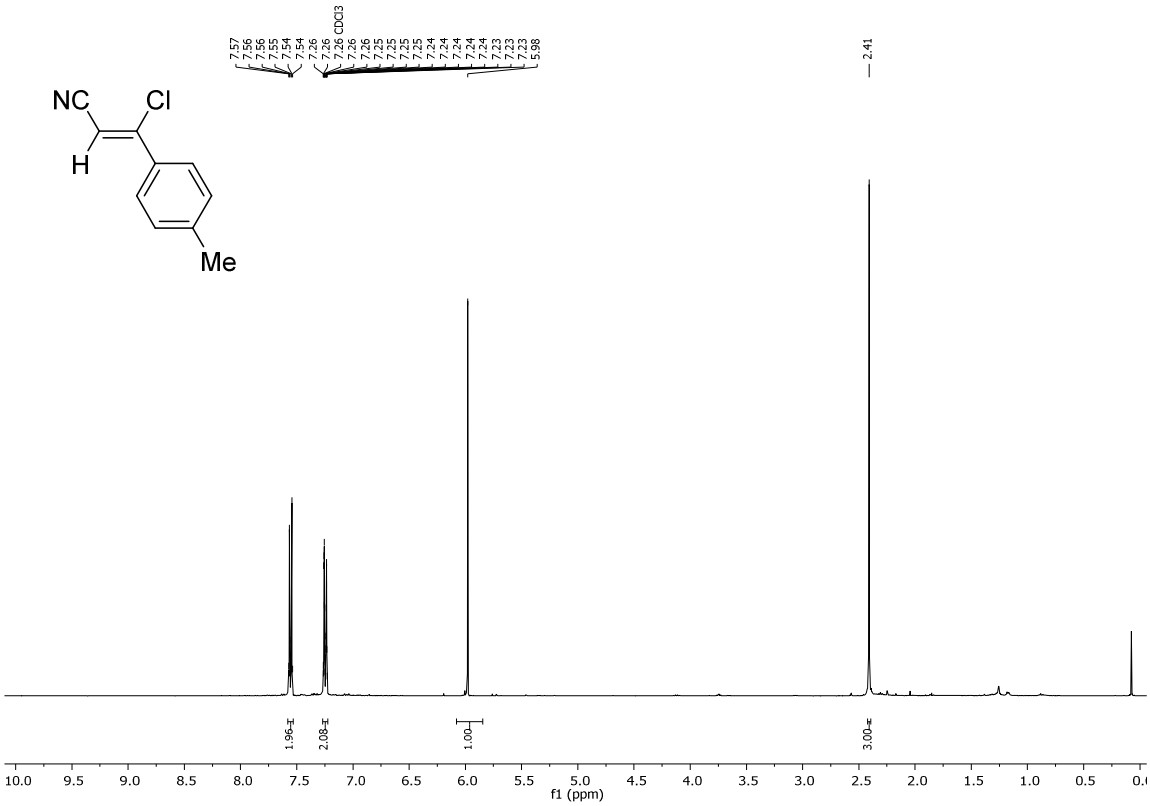
^{1}H NMR (300 MHz, $CDCl_3$) **Compound (*Z*)-130ao**



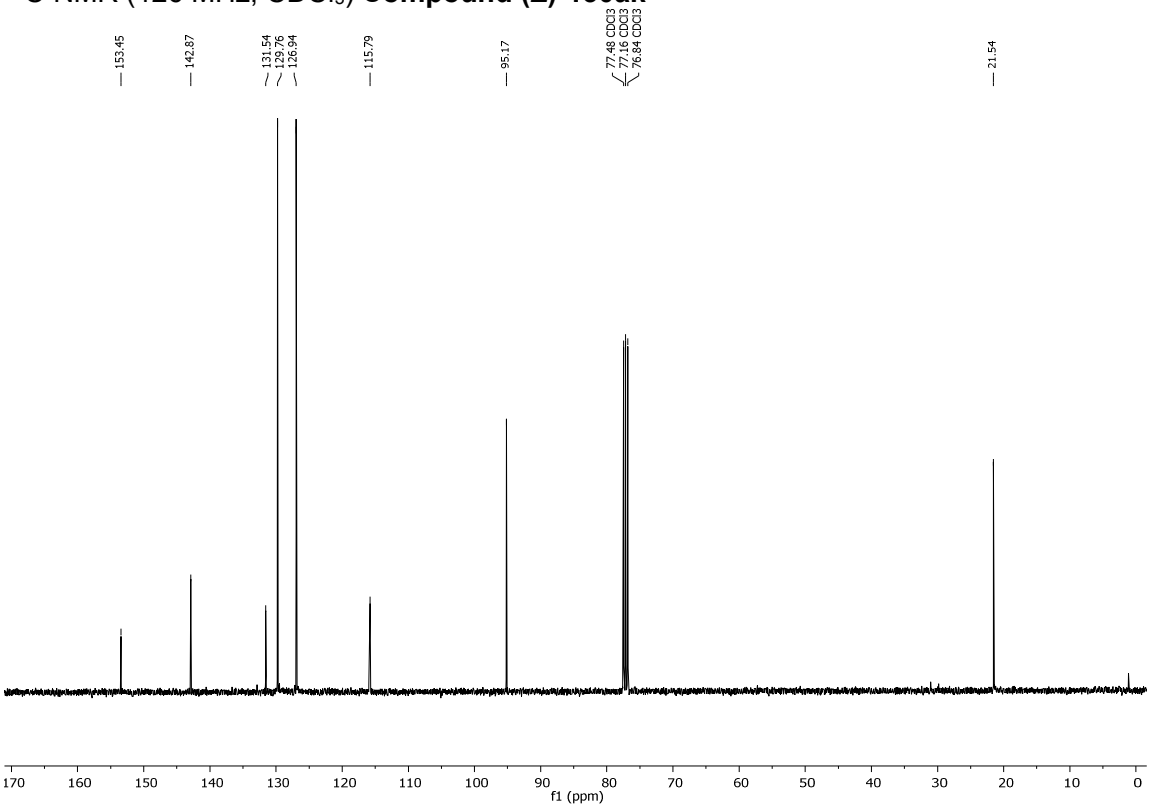
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130ao**



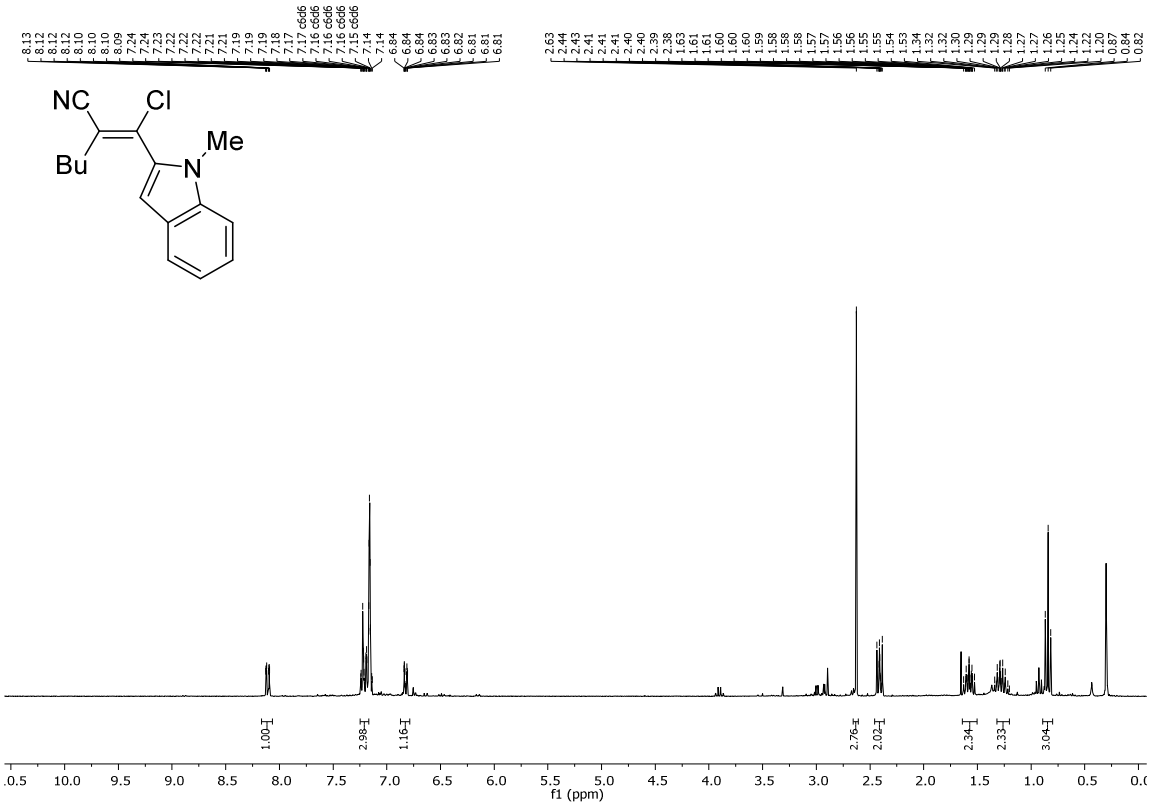
^{1}H NMR (300 MHz, $CDCl_3$) **Compound (*Z*)-130ak**



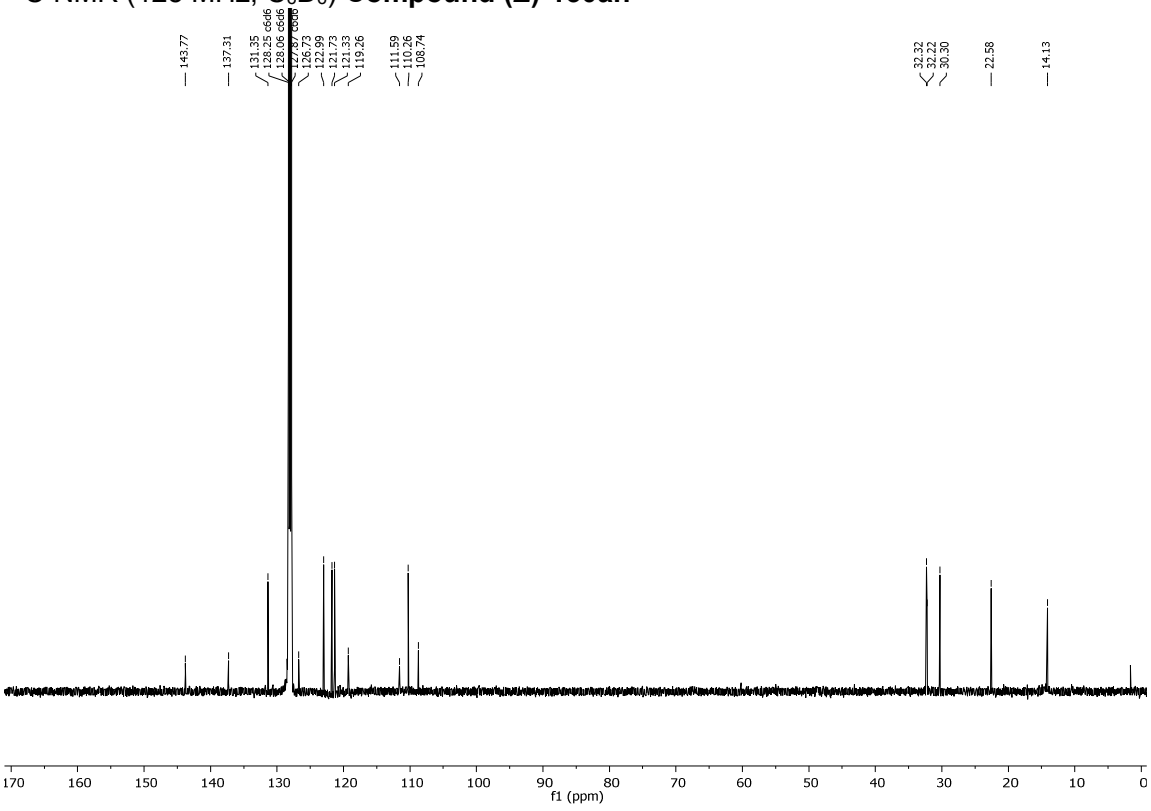
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130ak**



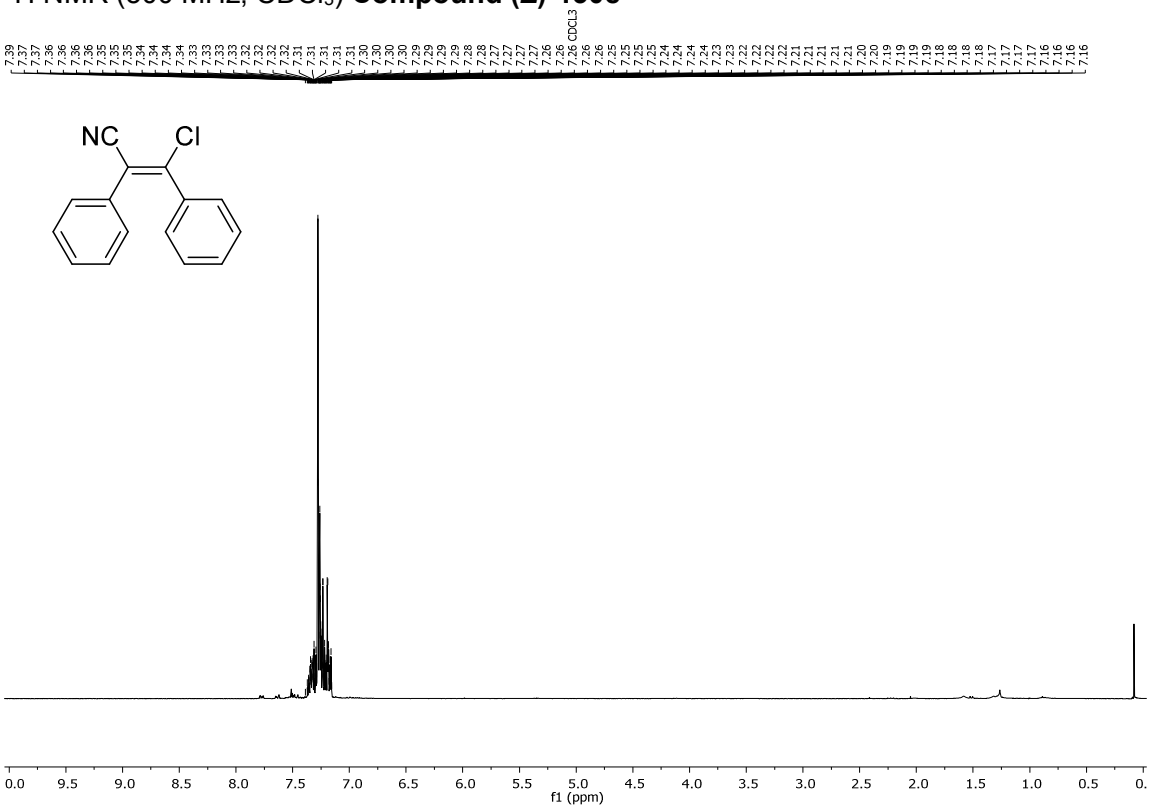
^{1}H NMR (300 MHz, C_6D_6) **Compound (*Z*)-130ah**



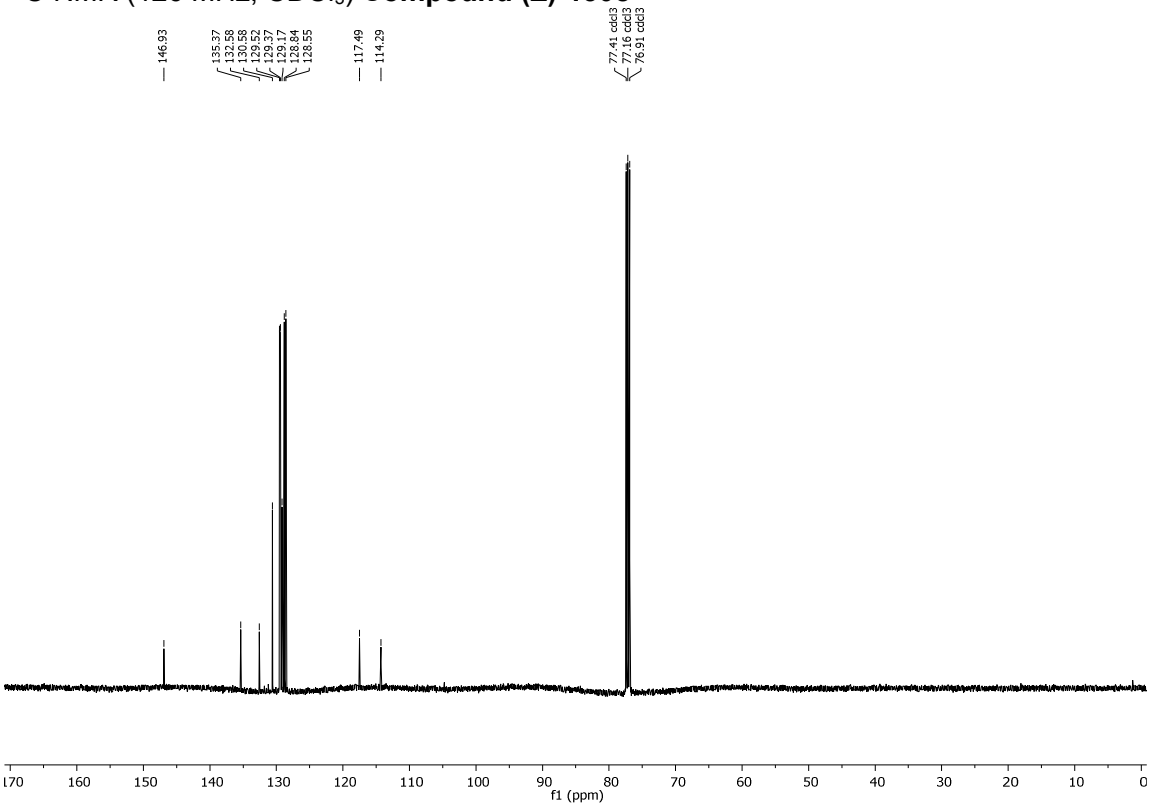
^{13}C NMR (125 MHz, C_6D_6) **Compound (*Z*)-130ah**



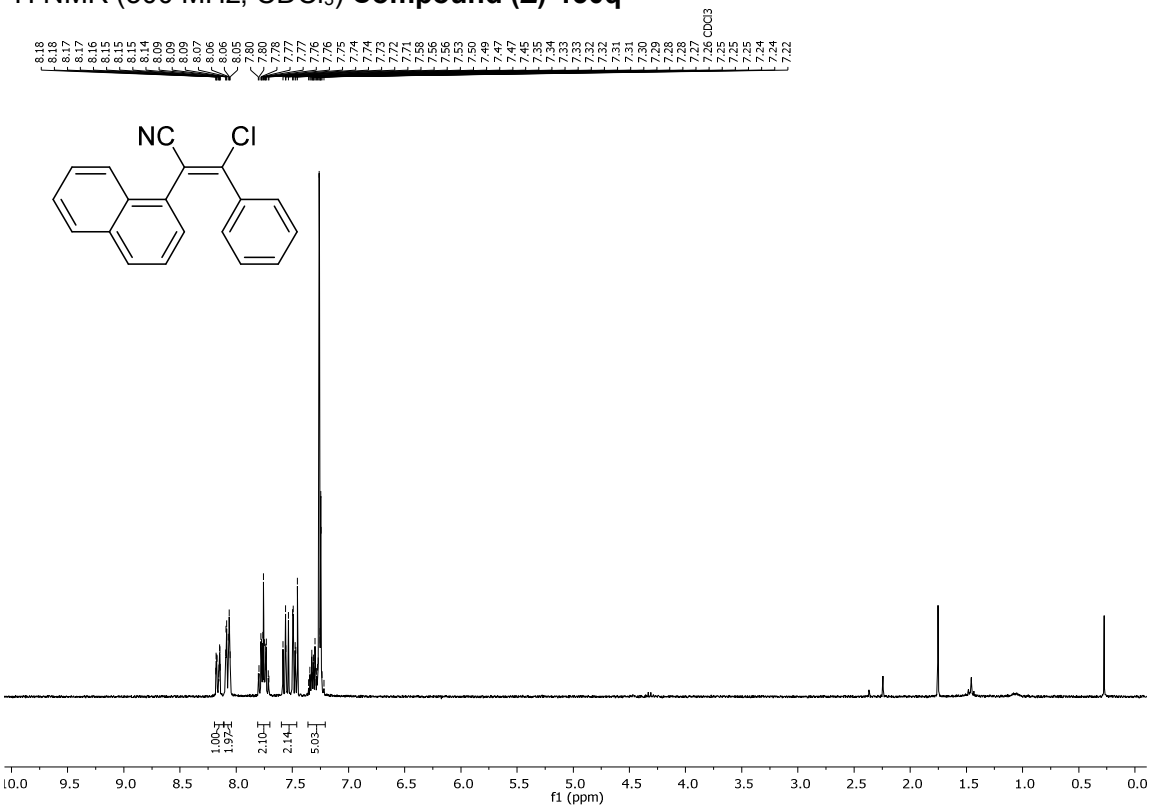
^{1}H NMR (500 MHz, $CDCl_3$) **Compound (*Z*)-130c**



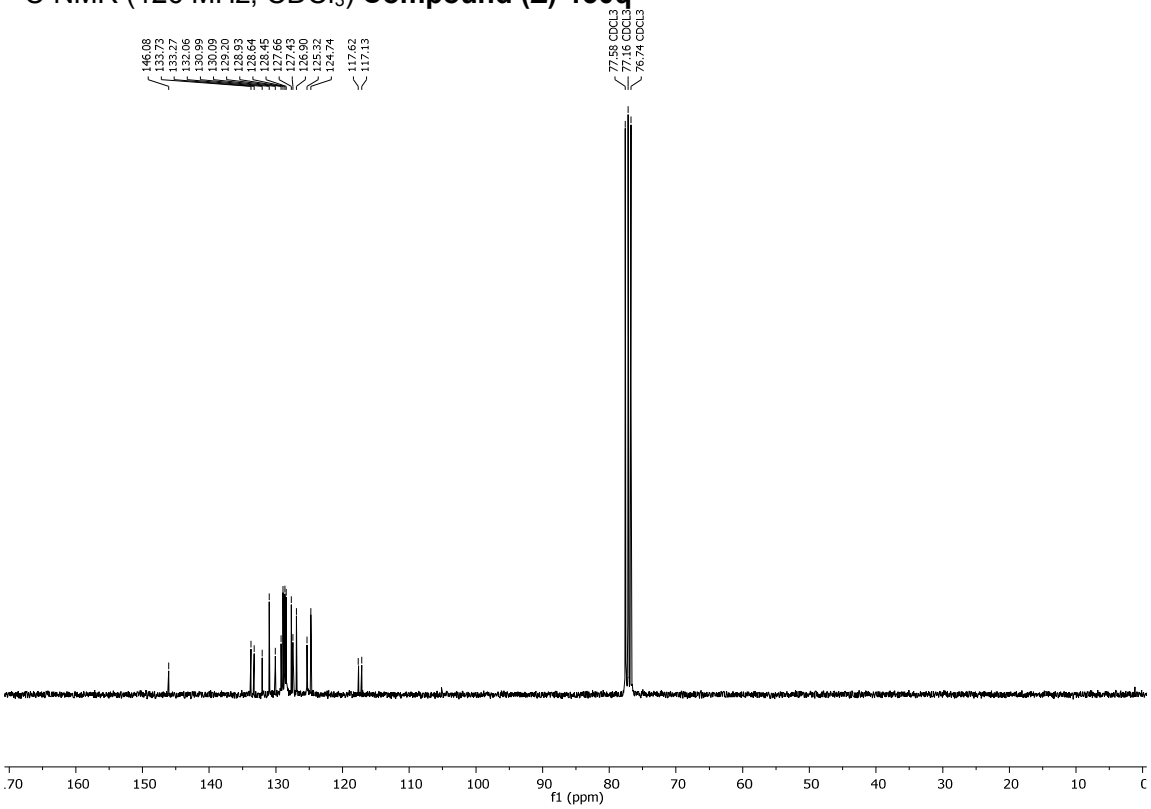
^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130c**



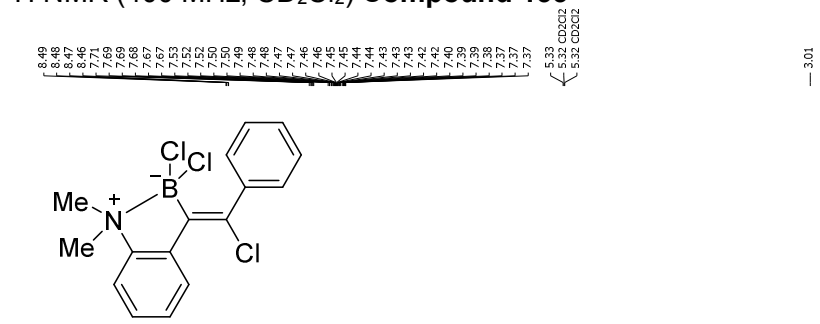
^{1}H NMR (300 MHz, $CDCl_3$) **Compound (*Z*)-130q**

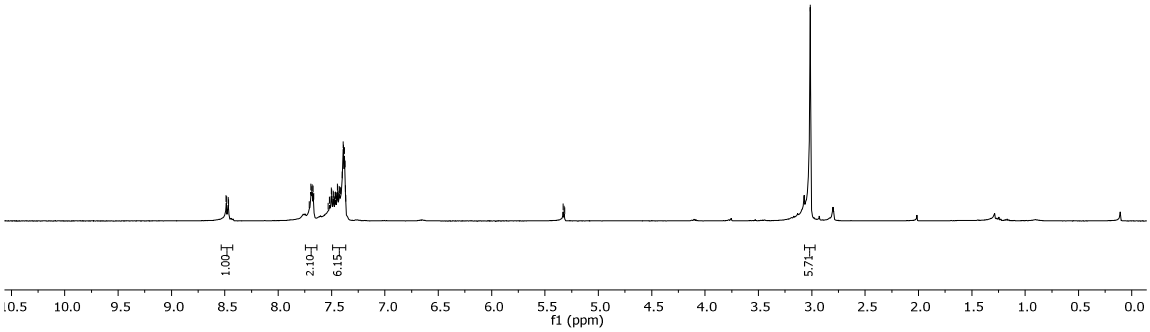


^{13}C NMR (126 MHz, $CDCl_3$) **Compound (*Z*)-130q**

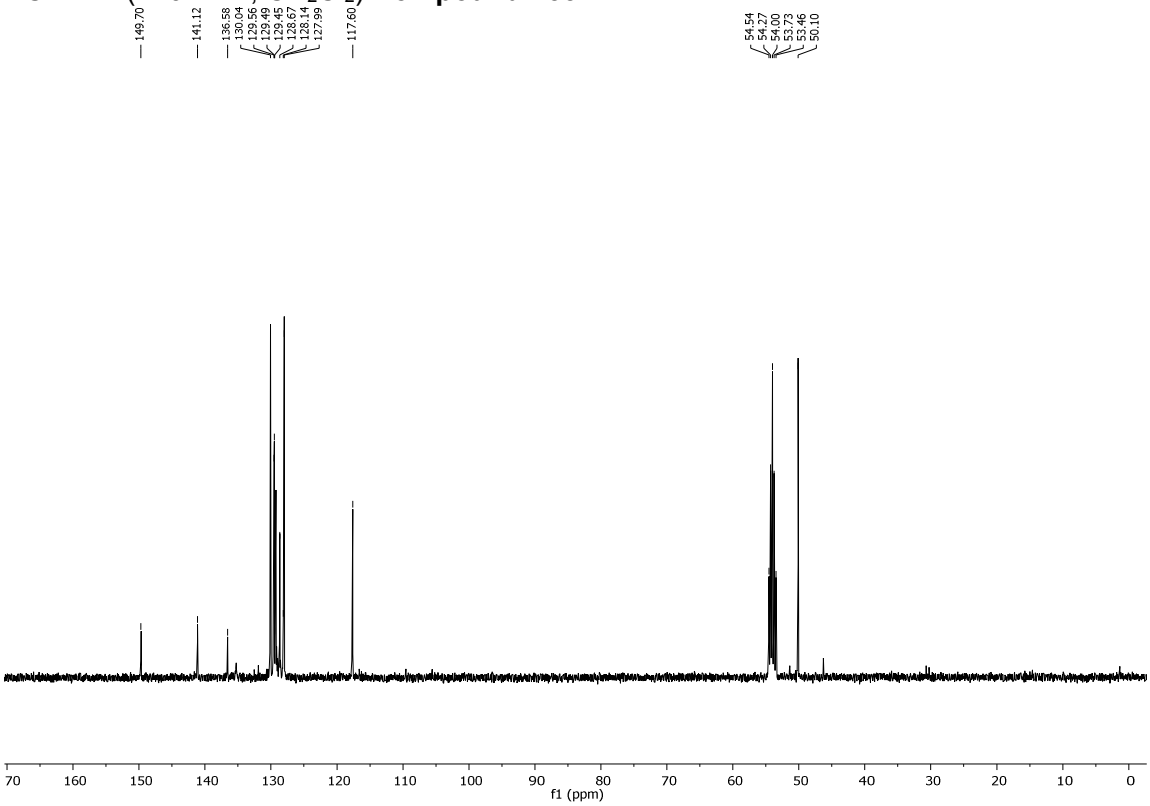


^{1}H NMR (400 MHz, CD_2Cl_2) **Compound 133**

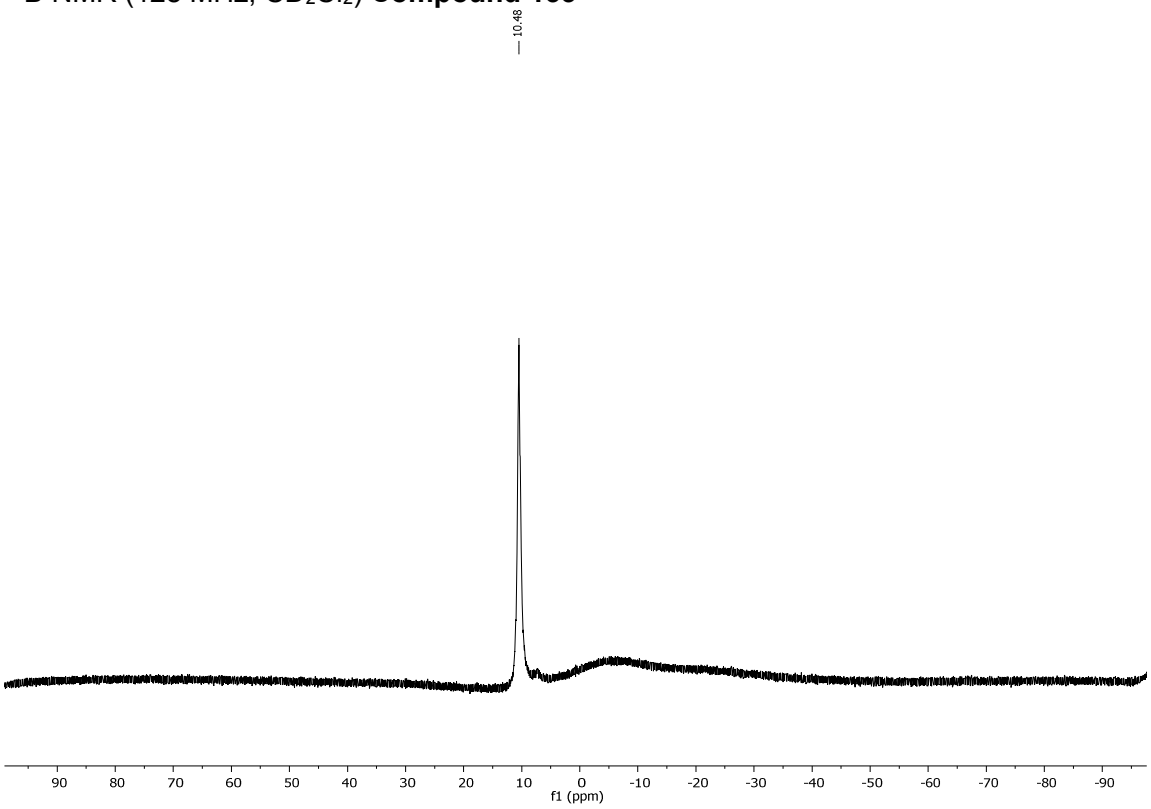




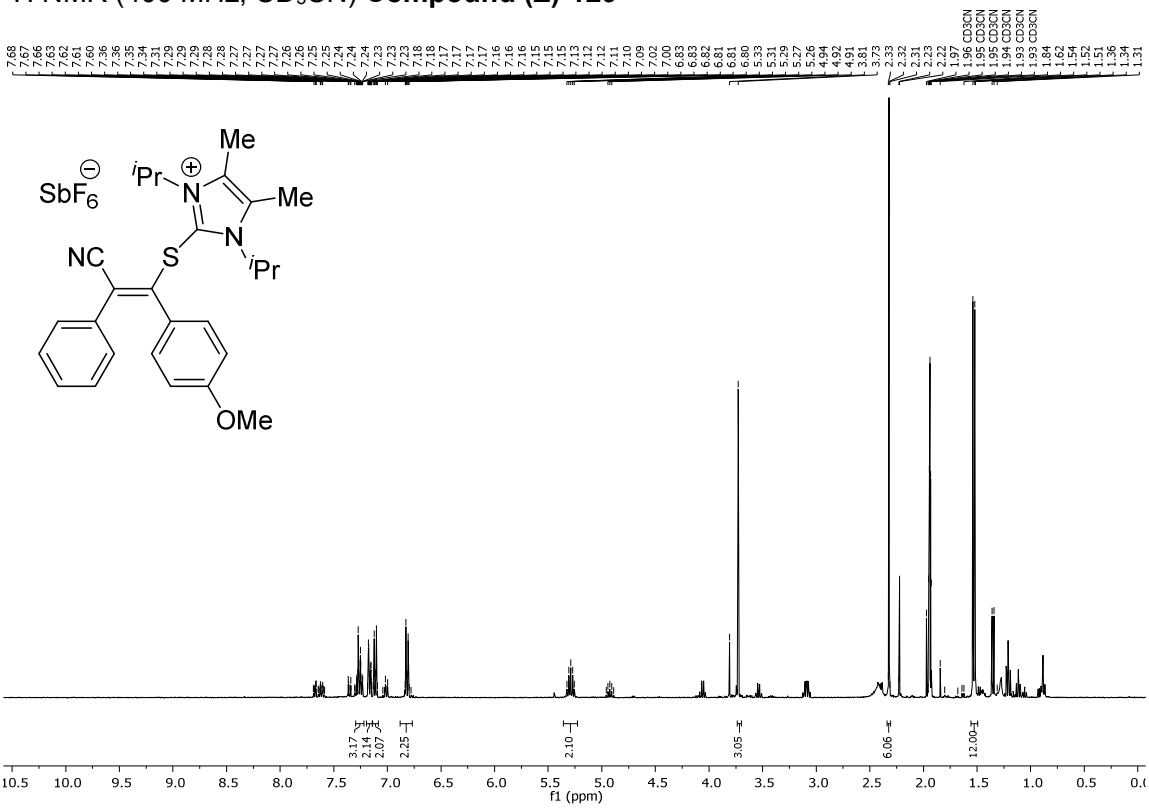
^{13}C NMR (126 MHz, CD_2Cl_2) **Compound 133**



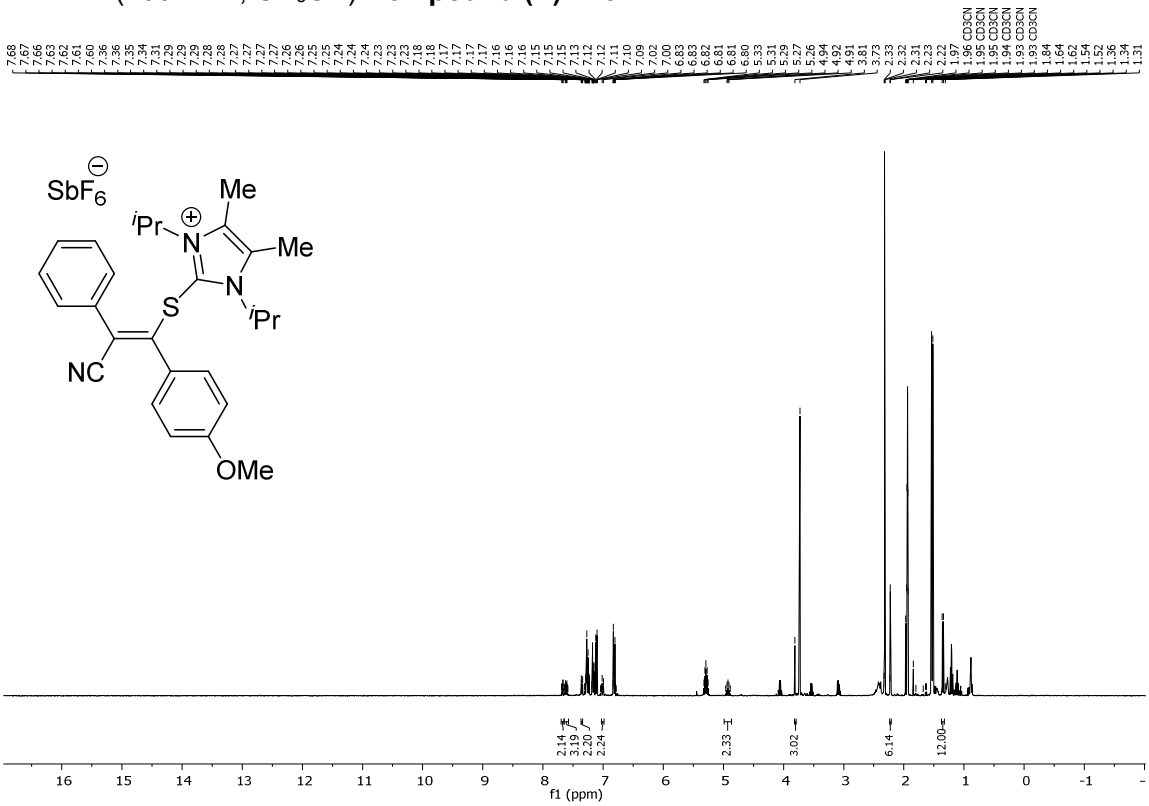
^{11}B NMR (128 MHz, CD_2Cl_2) **Compound 133**



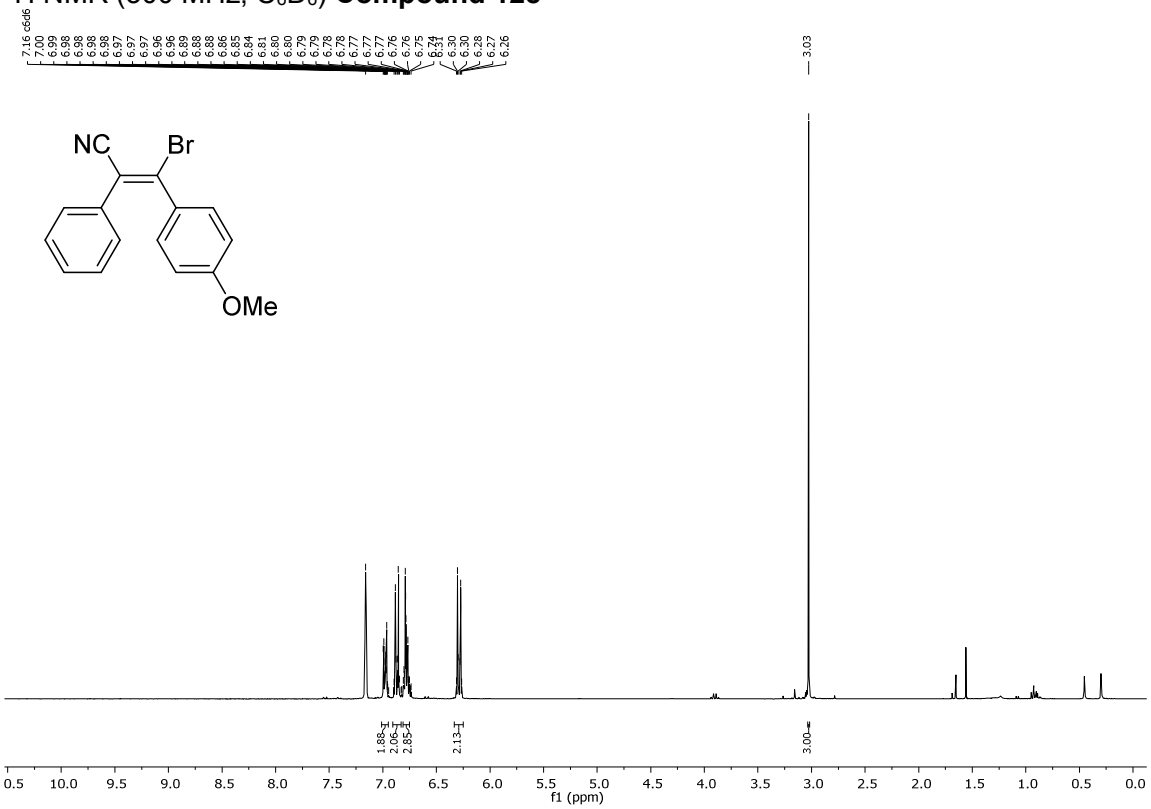
^{1}H NMR (400 MHz, CD_3CN) **Compound (*Z*)-129**



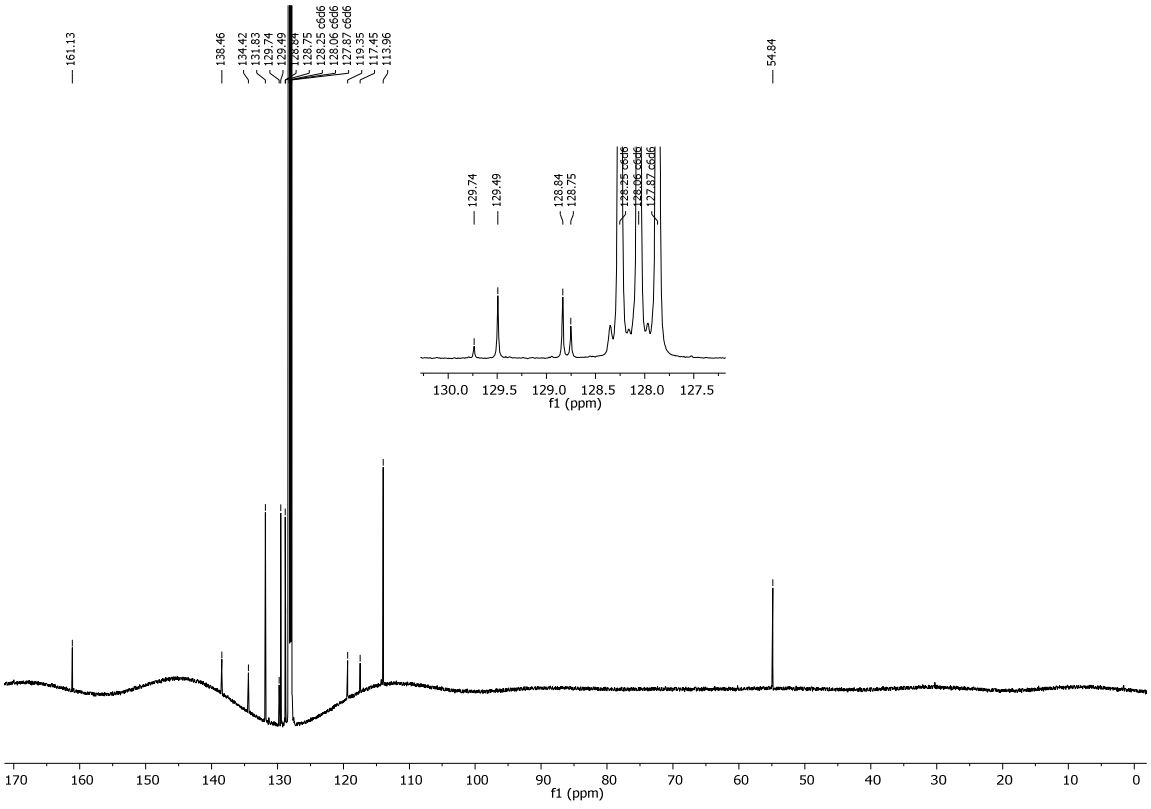
^{1}H NMR (400 MHz, CD_3CN) **Compound (*E*)-129**



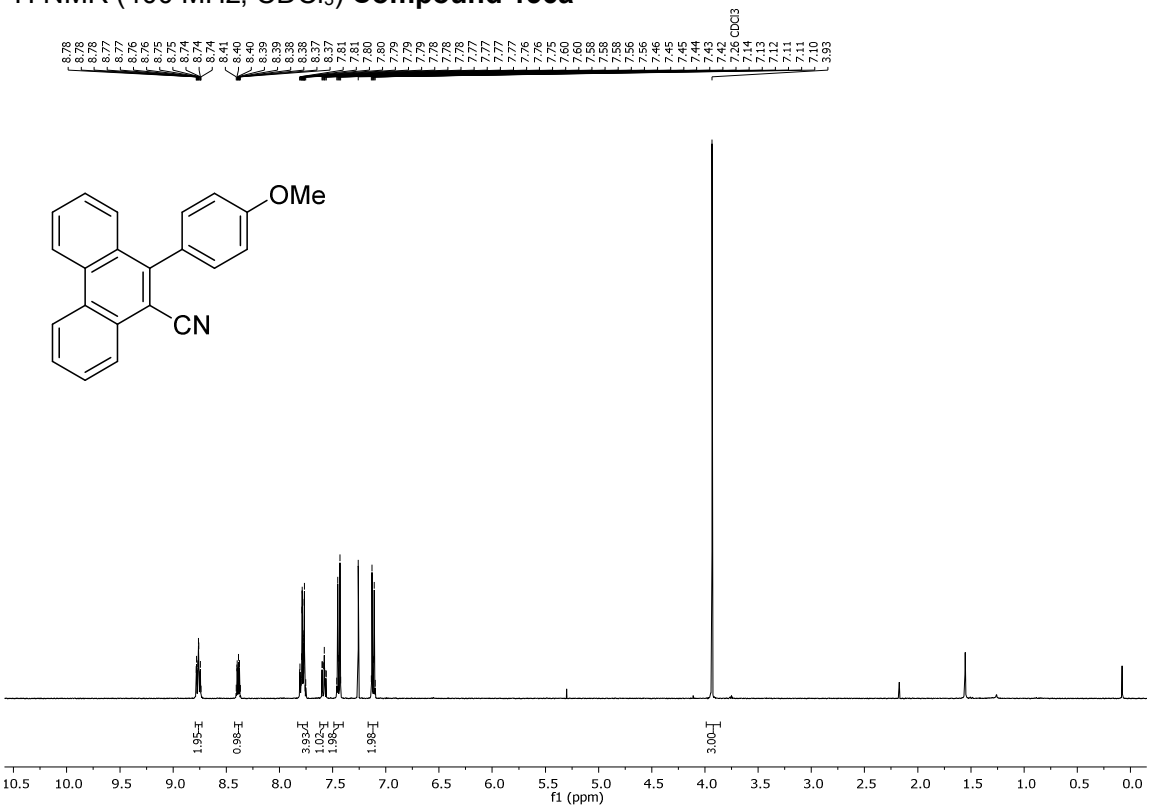
^{1}H NMR (300 MHz, C_6D_6) **Compound 128**



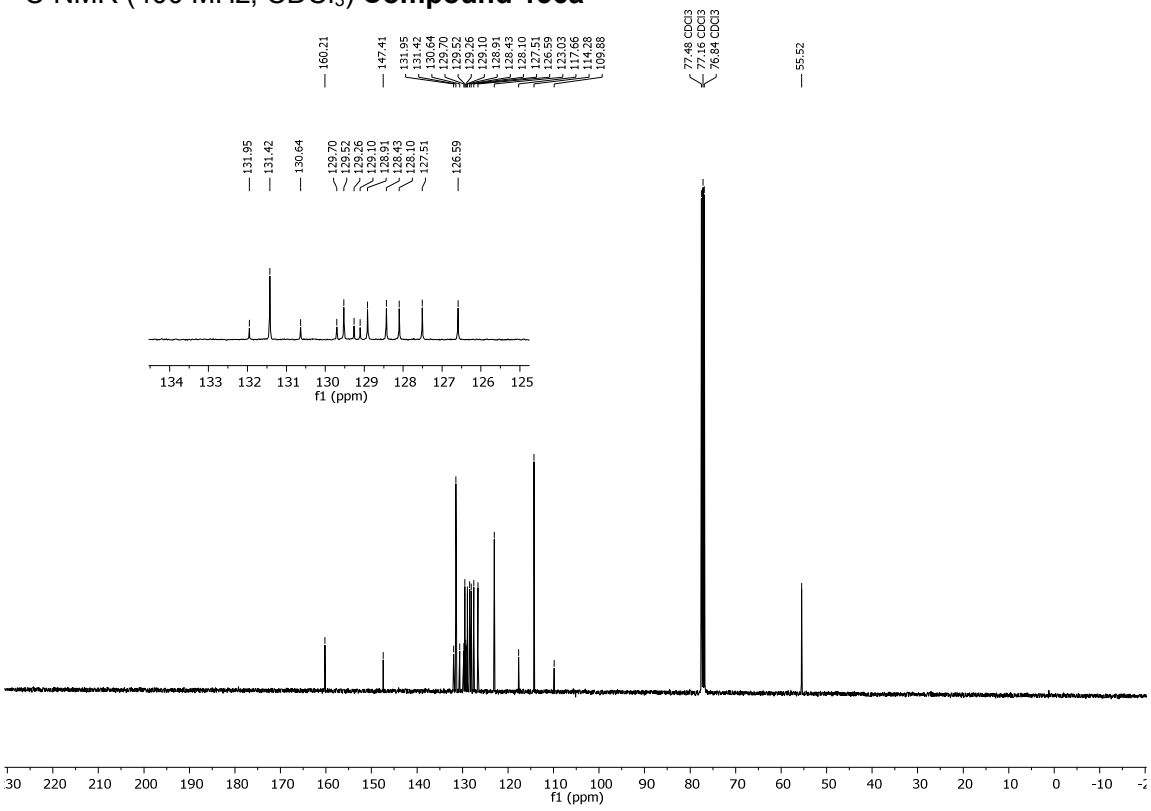
^{13}C NMR (126 MHz, C_6D_6) **Compound 128**



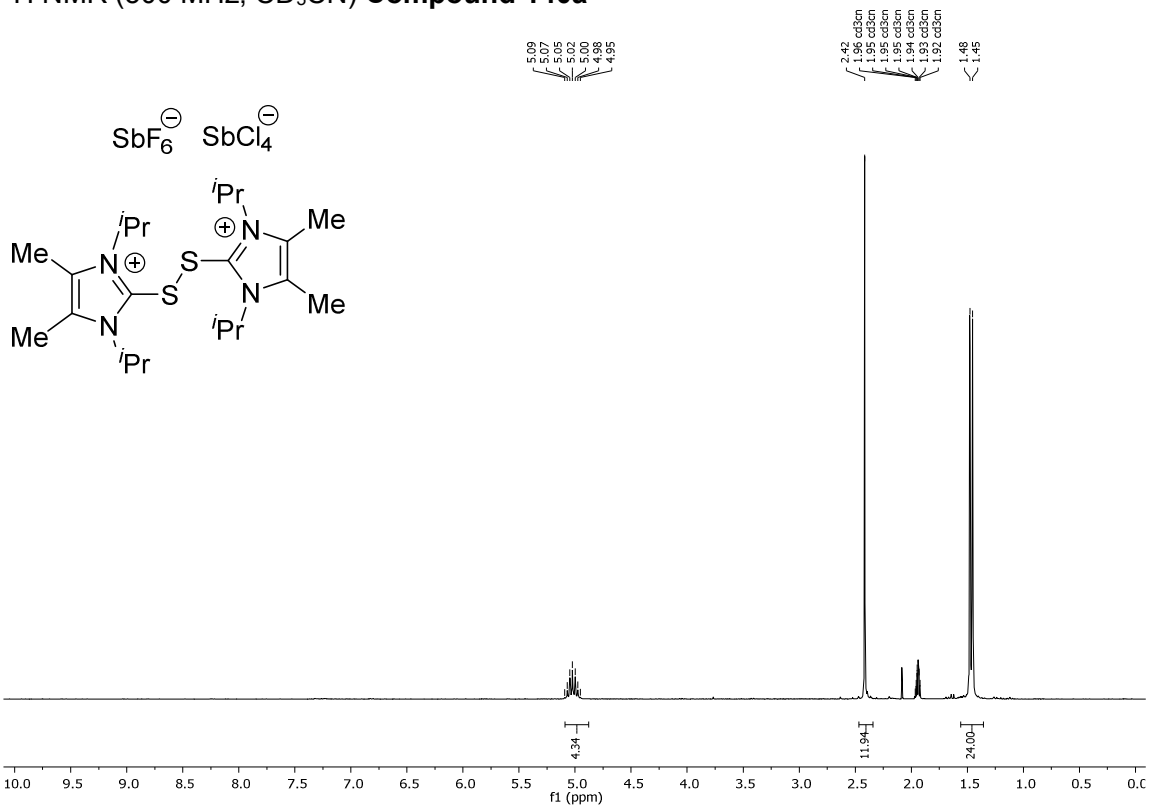
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 136a**



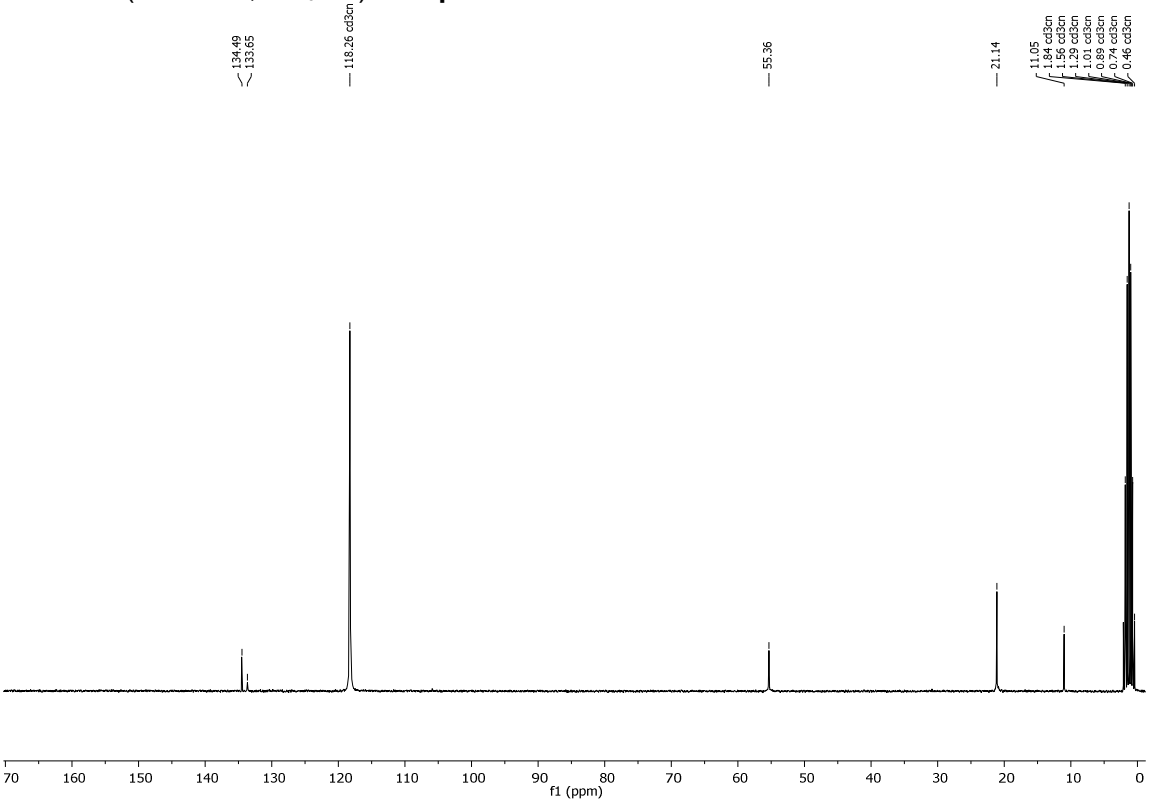
^{13}C NMR (400 MHz, $CDCl_3$) **Compound 136a**



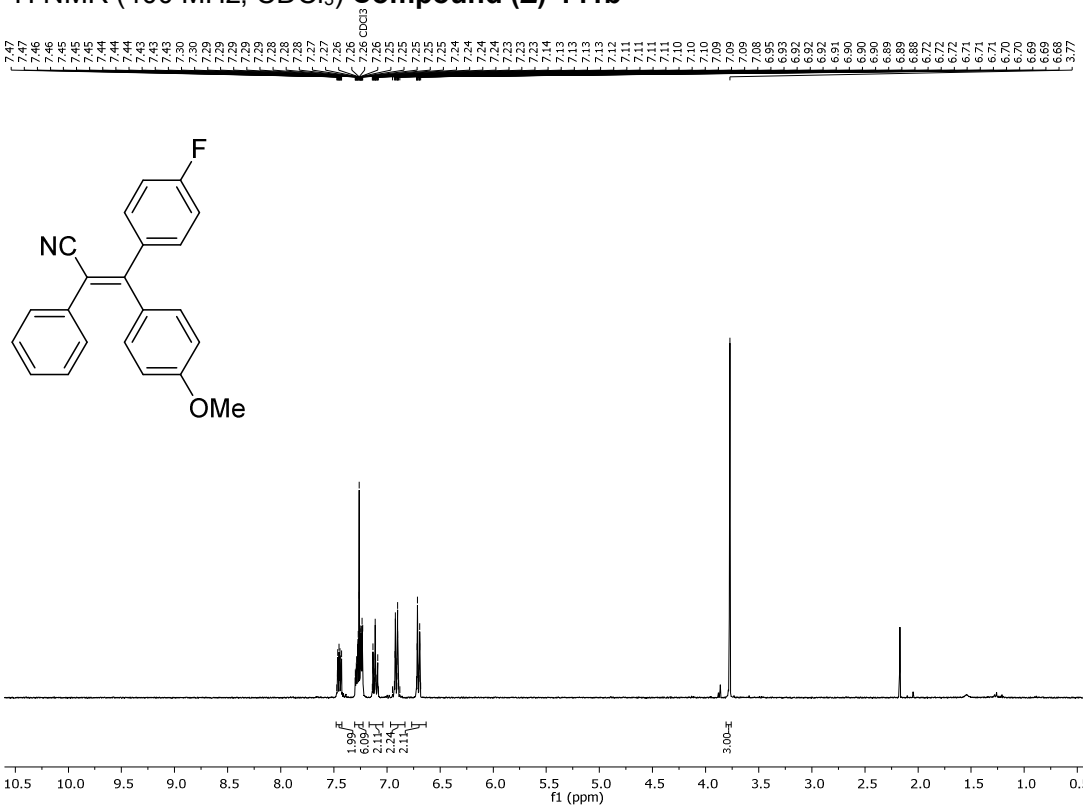
^{1}H NMR (500 MHz, CD_3CN) **Compound 140a**



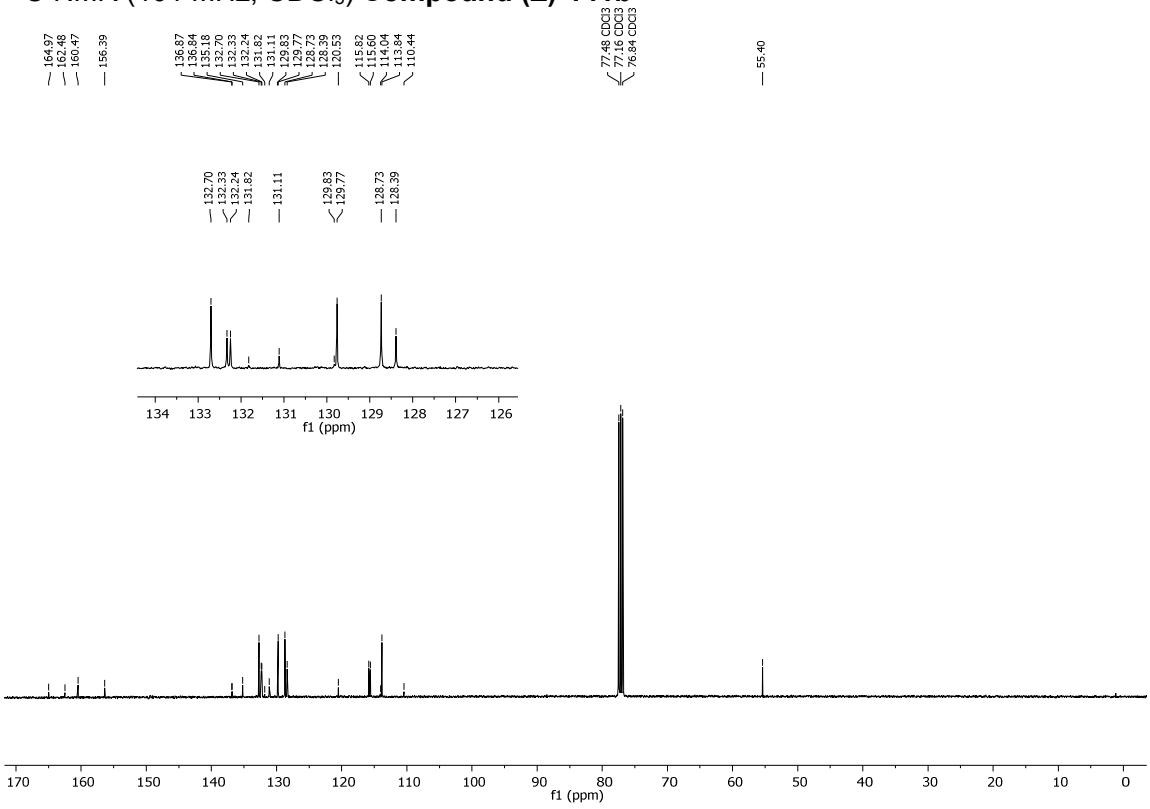
^{13}C NMR (126 MHz, CD_3CN) **Compound 140a**



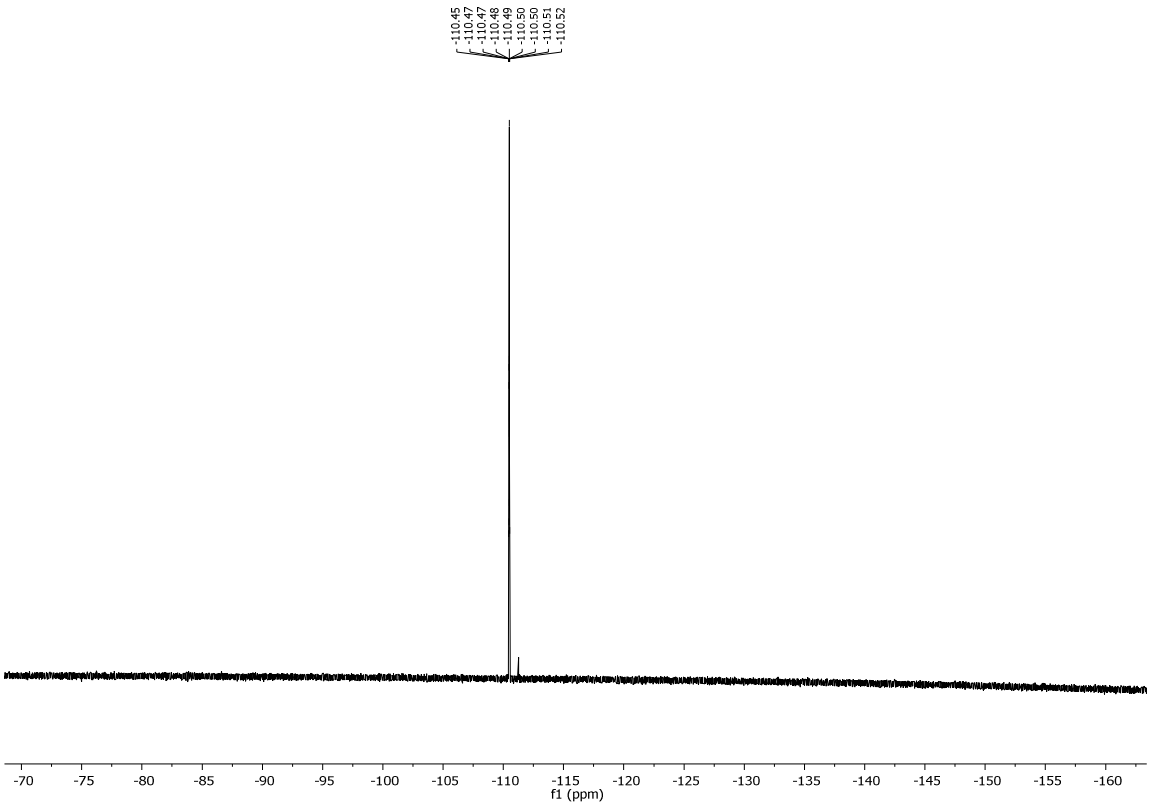
^{1}H NMR (400 MHz, $CDCl_3$) **Compound (*Z*)-141b**



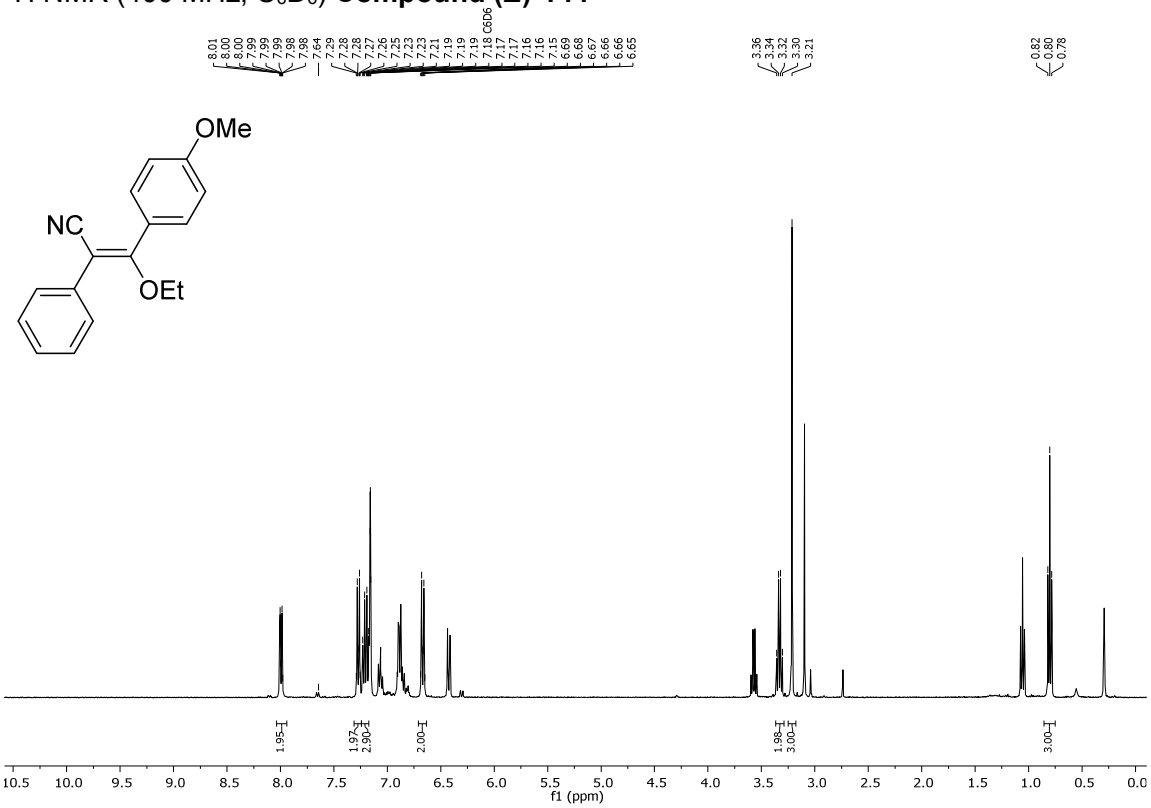
^{13}C NMR (101 MHz, $CDCl_3$) **Compound (*Z*)-141b**



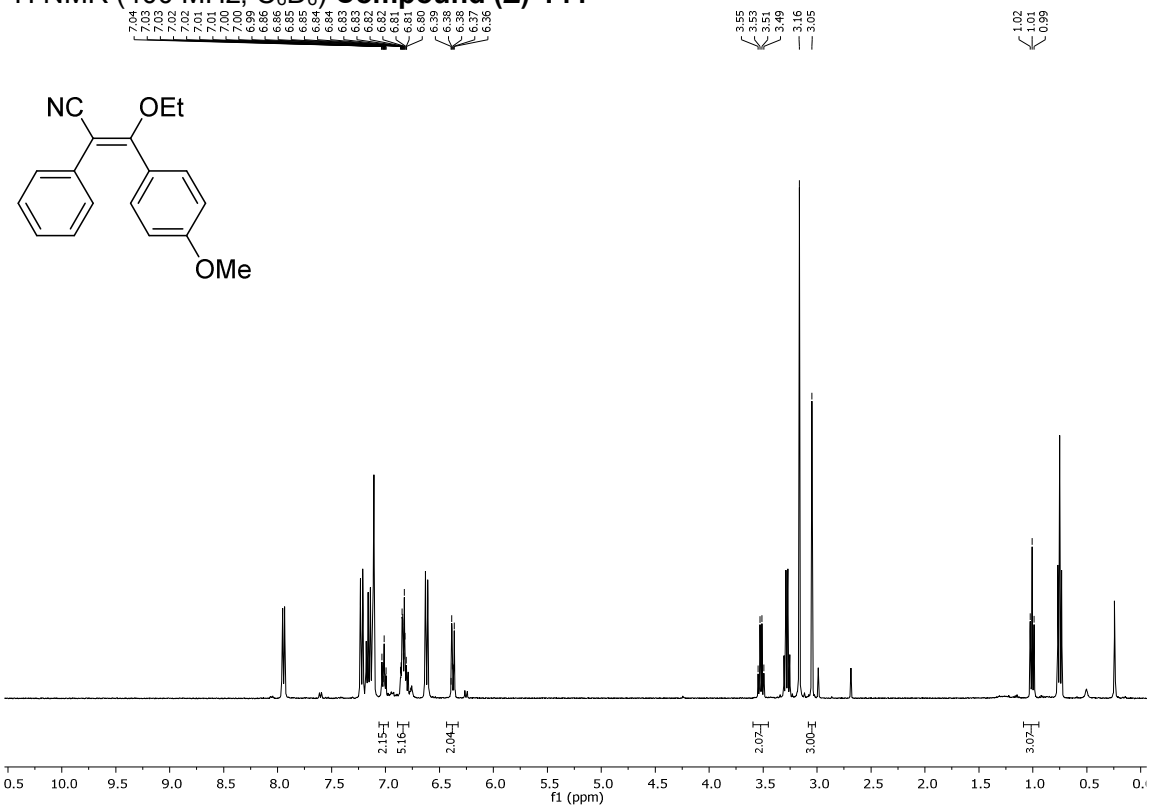
^{19}F NMR (376 MHz, $CDCl_3$) **Compound (*Z*)-141b**



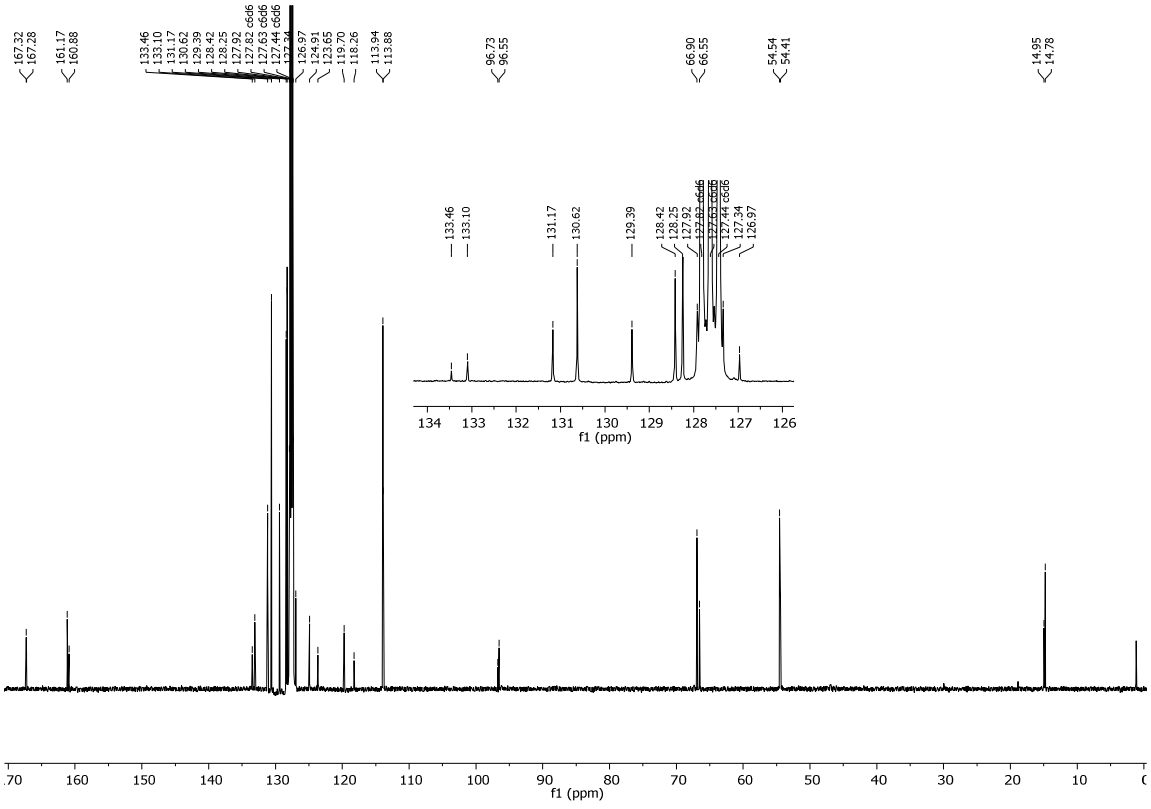
^{1}H NMR (400 MHz, C_6D_6) **Compound (*E*)-144**



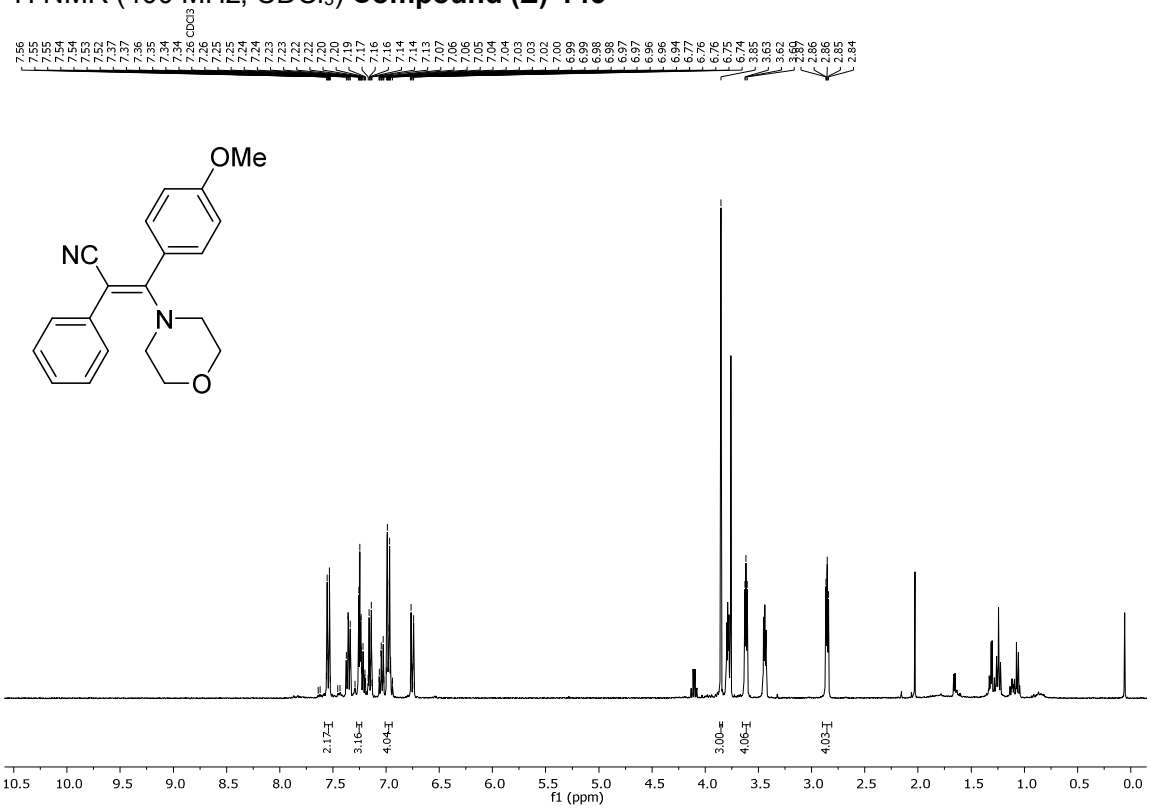
^{1}H NMR (400 MHz, C_6D_6) **Compound (*Z*)-144**



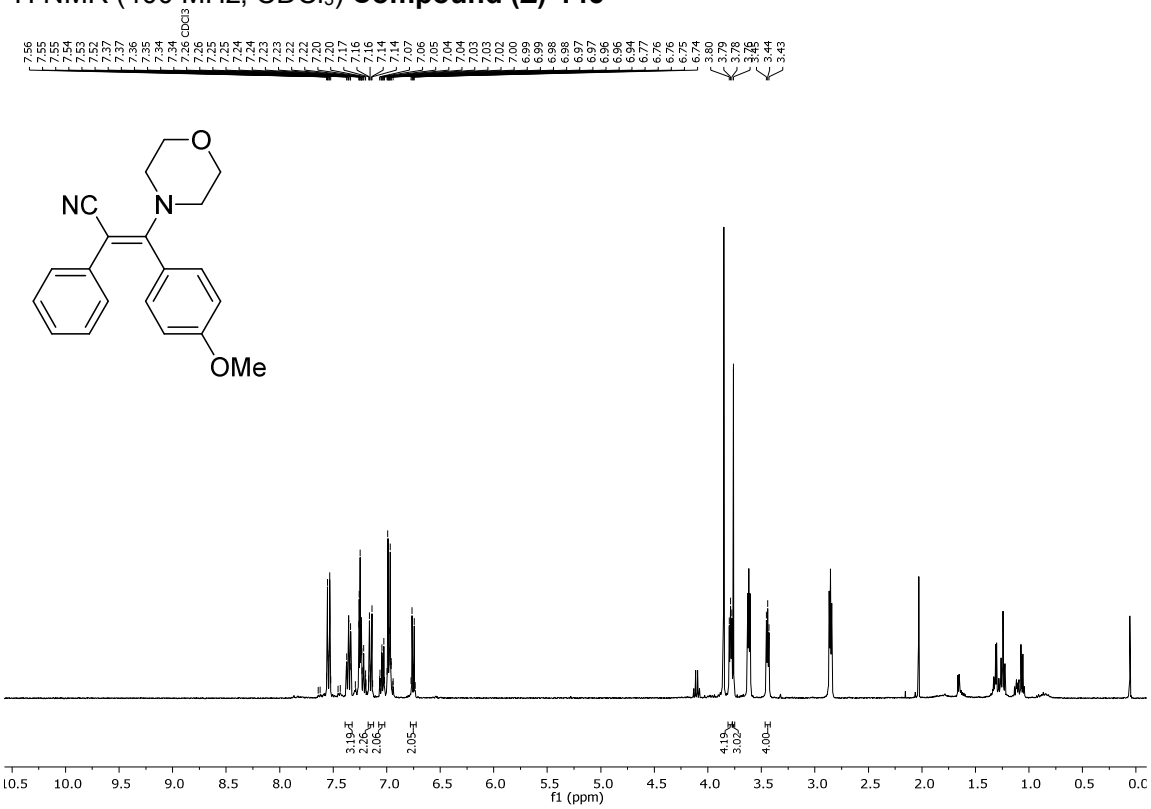
^{13}C NMR (126 MHz, C_6D_6) **Compound 144**



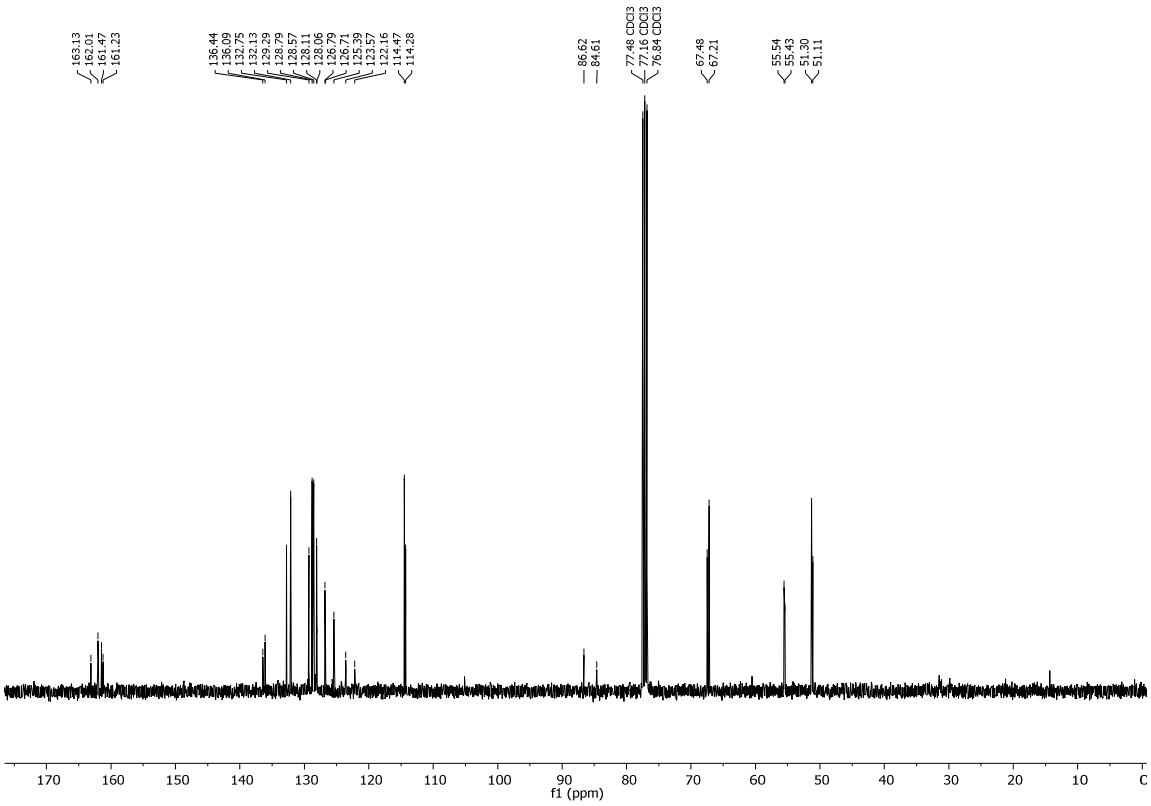
^{1}H NMR (400 MHz, $CDCl_3$) **Compound (*E*)-145**



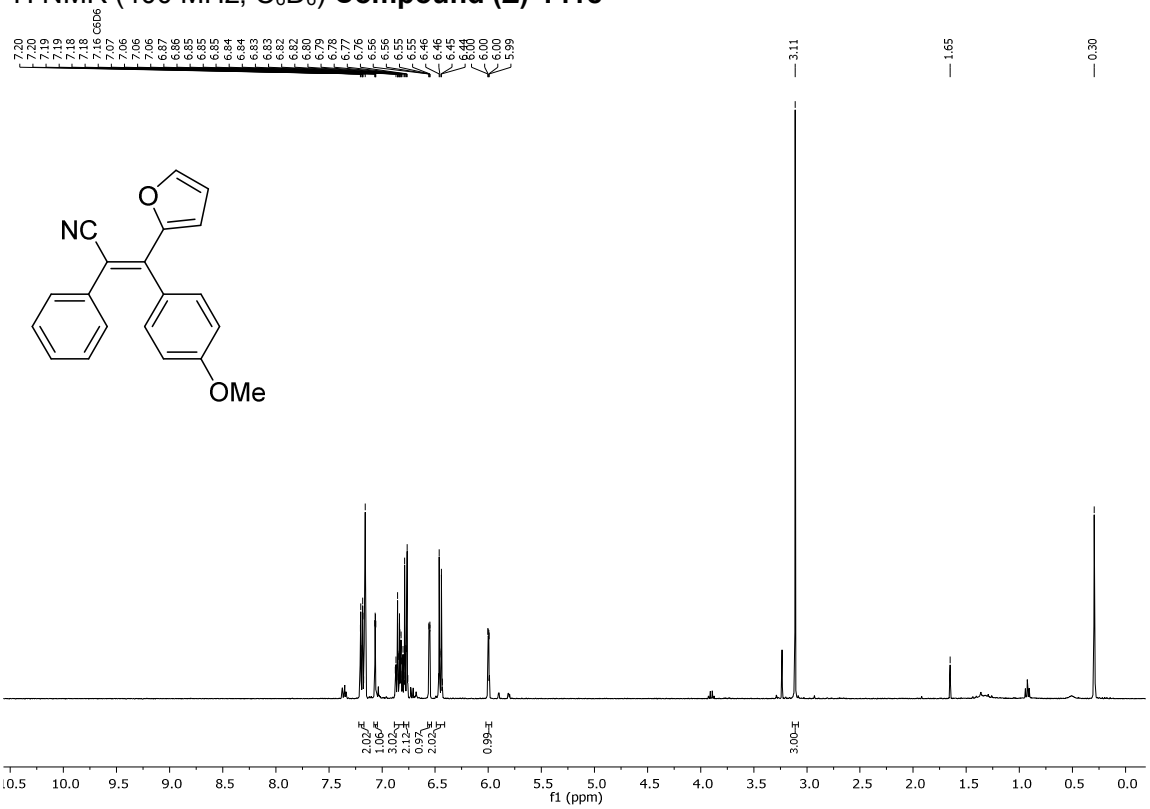
^{1}H NMR (400 MHz, $CDCl_3$) **Compound (*Z*)-145**



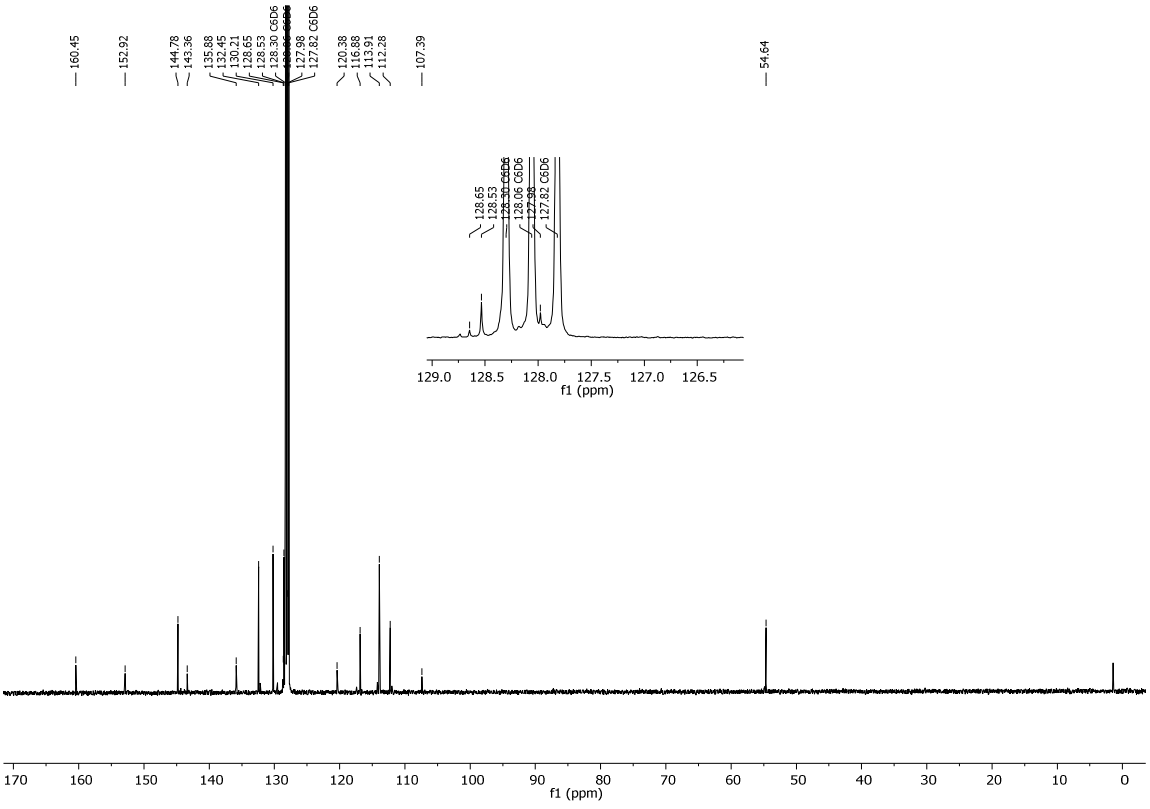
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 145**



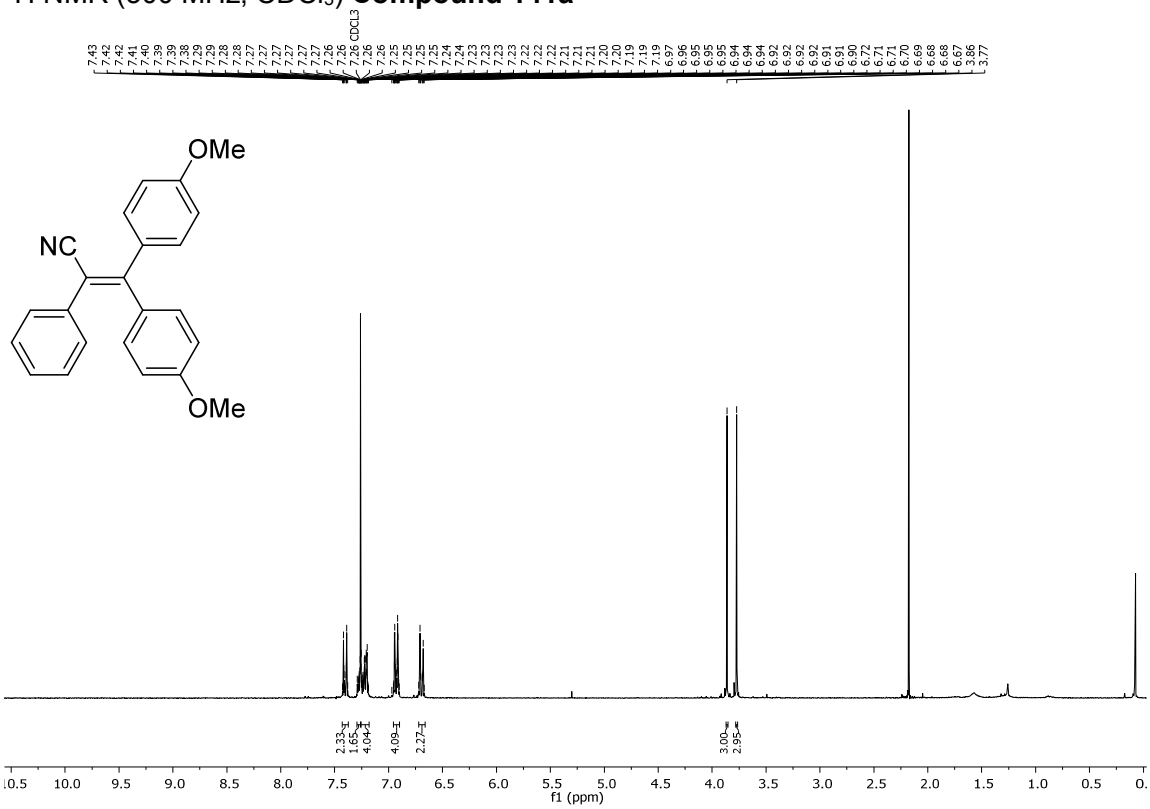
^{1}H NMR (400 MHz, C_6D_6) **Compound (*Z*)-141c**



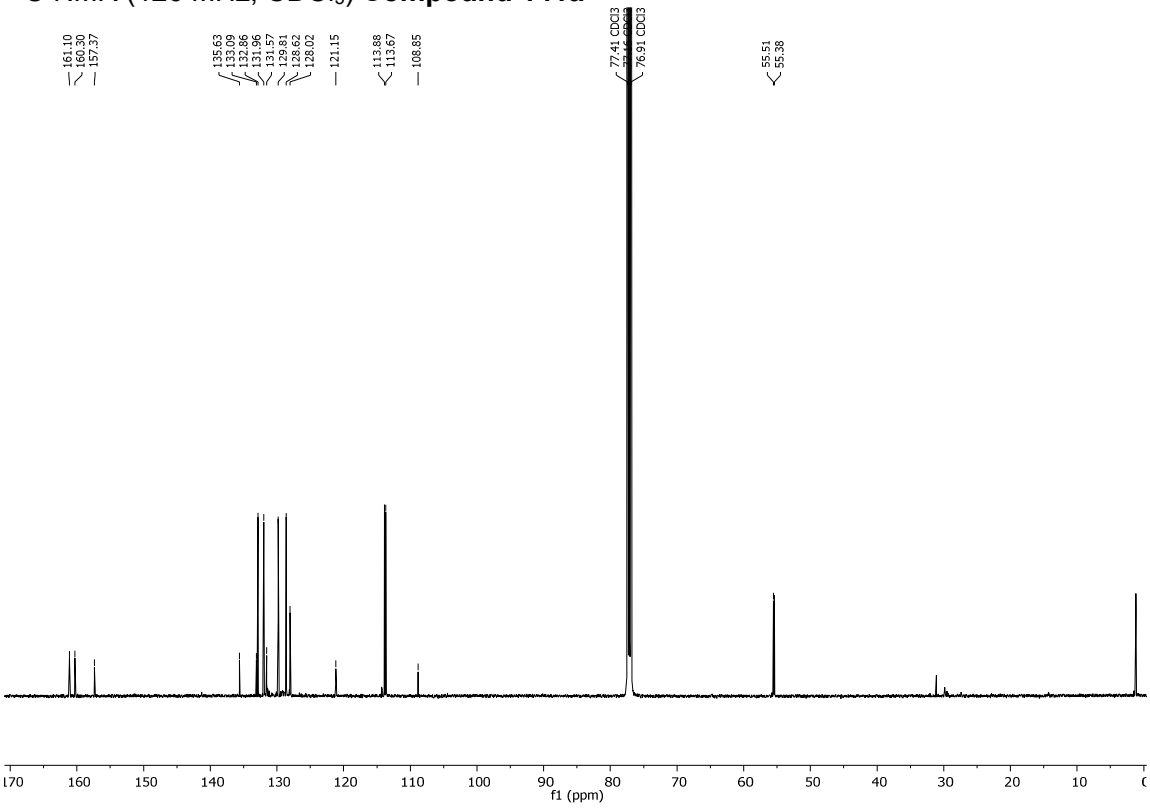
^{13}C NMR (101 MHz, C_6D_6) **Compound (*Z*)-141c**



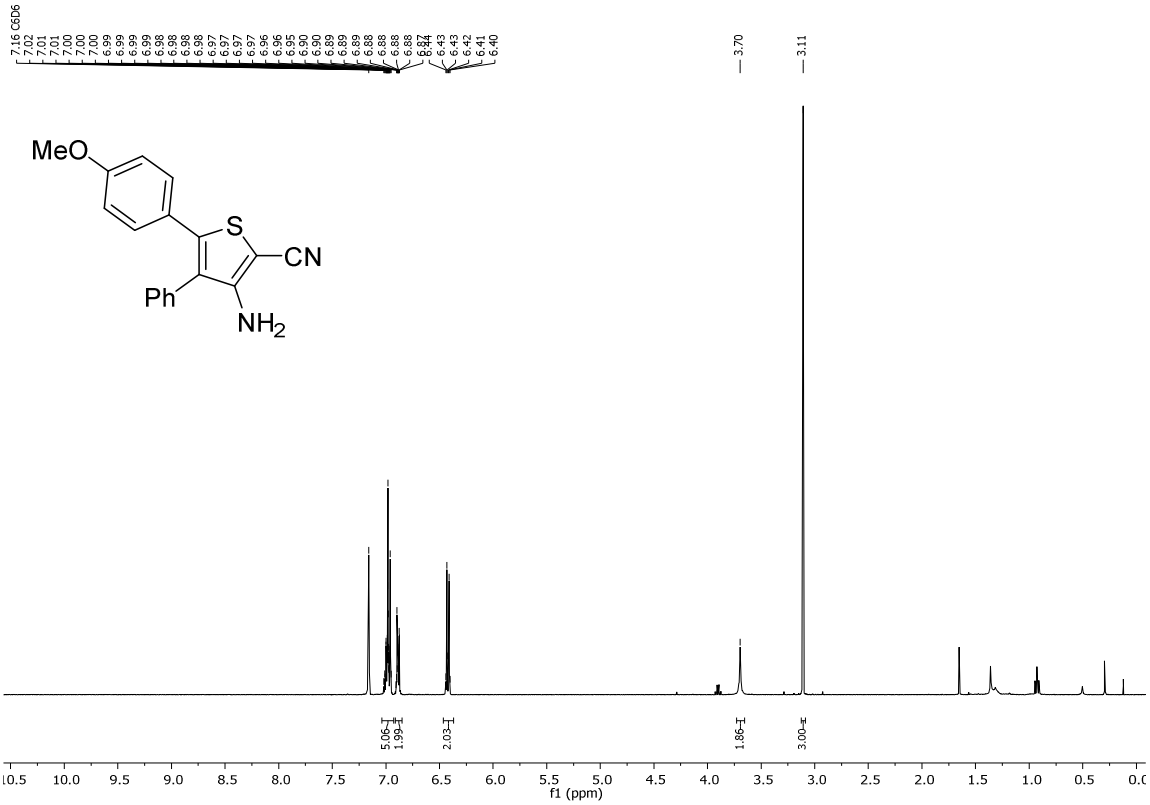
^{1}H NMR (300 MHz, $CDCl_3$) **Compound 141a**



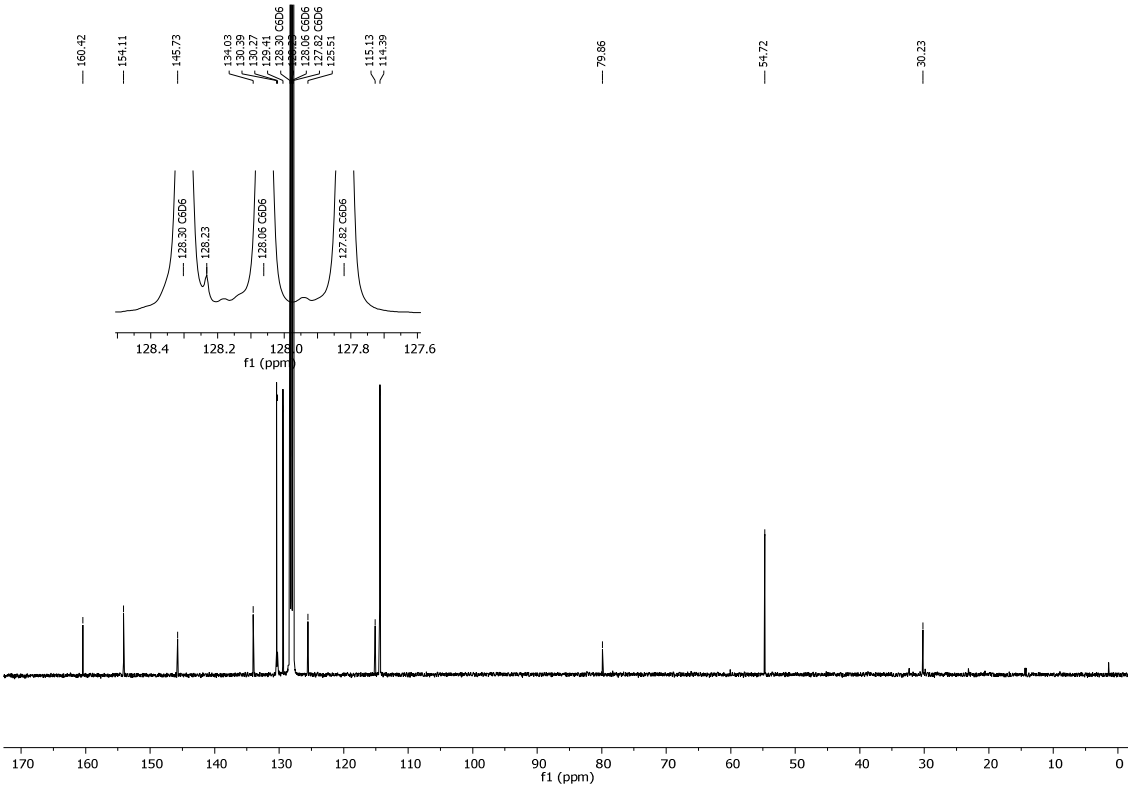
^{13}C NMR (126 MHz, $CDCl_3$) **Compound 141a**



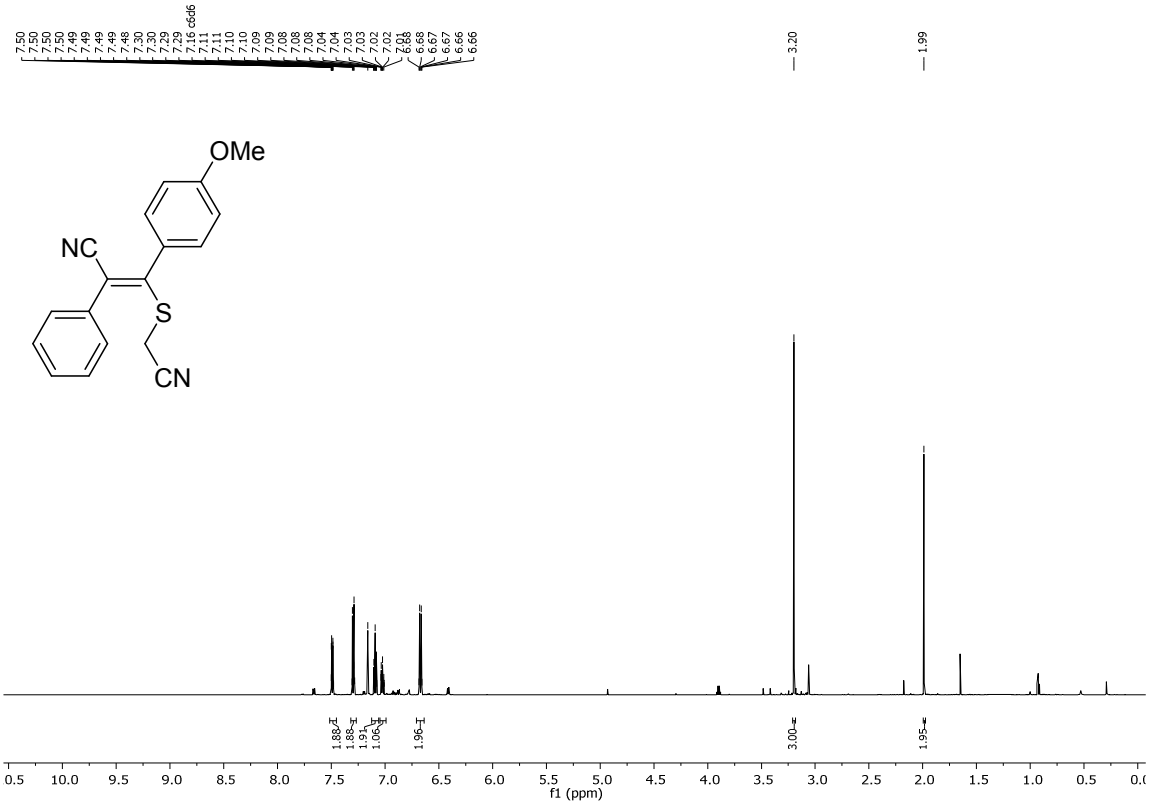
^{1}H NMR (500 MHz, C_6D_6) **Compound 146a**



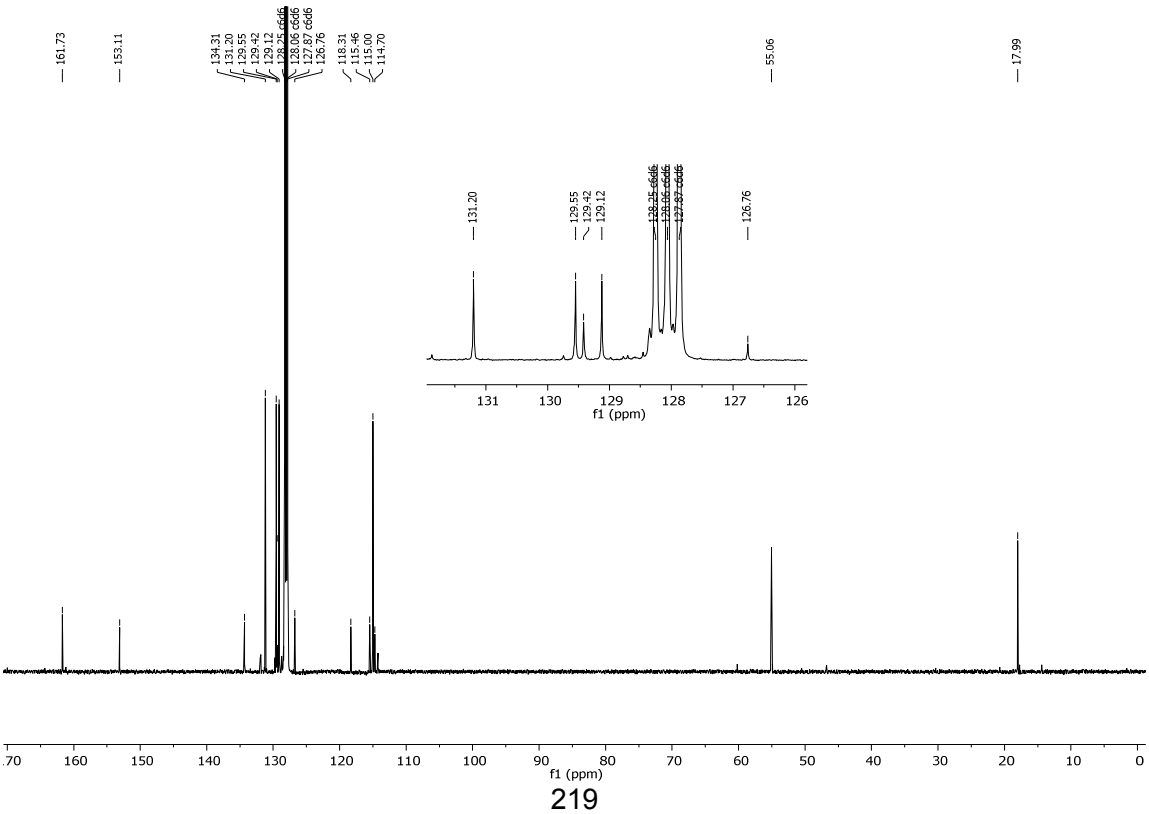
^{13}C NMR (126 MHz, C_6D_6) **Compound 146a**



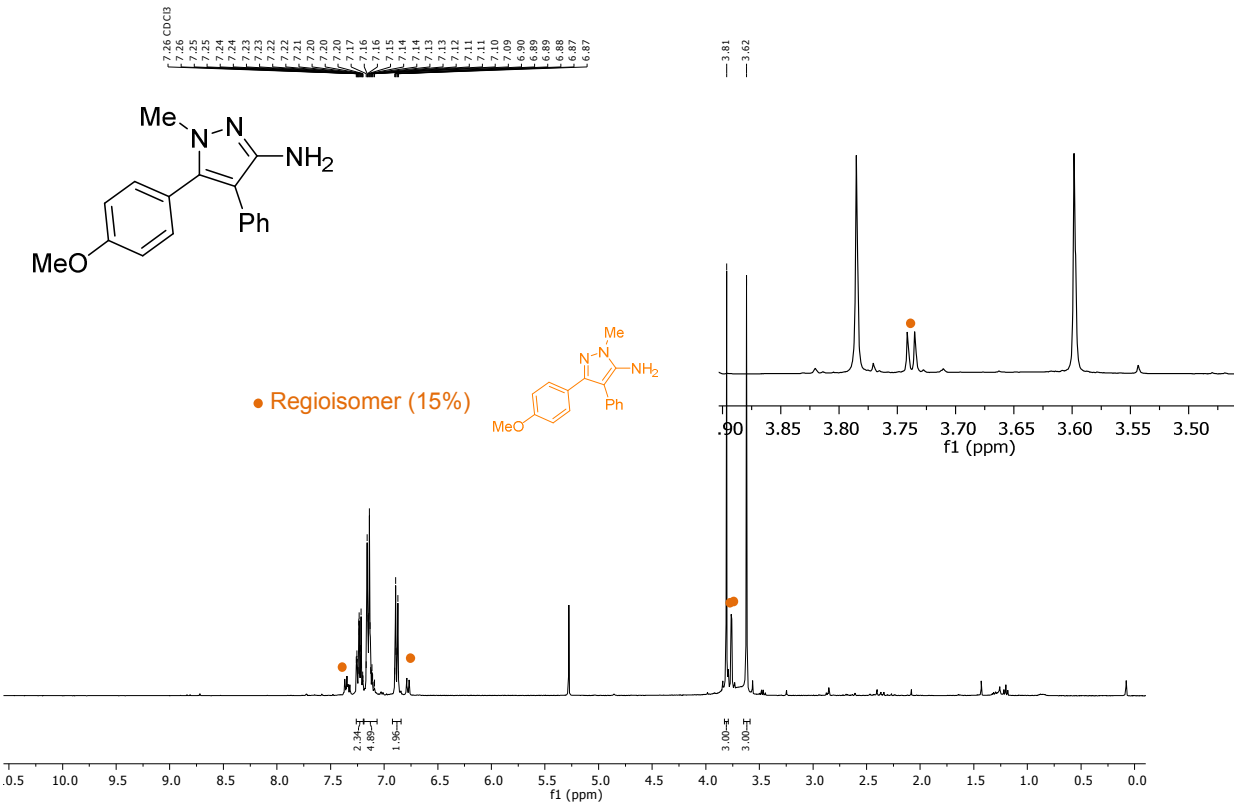
^{1}H NMR (600 MHz, C_6D_6) **Compound 147**



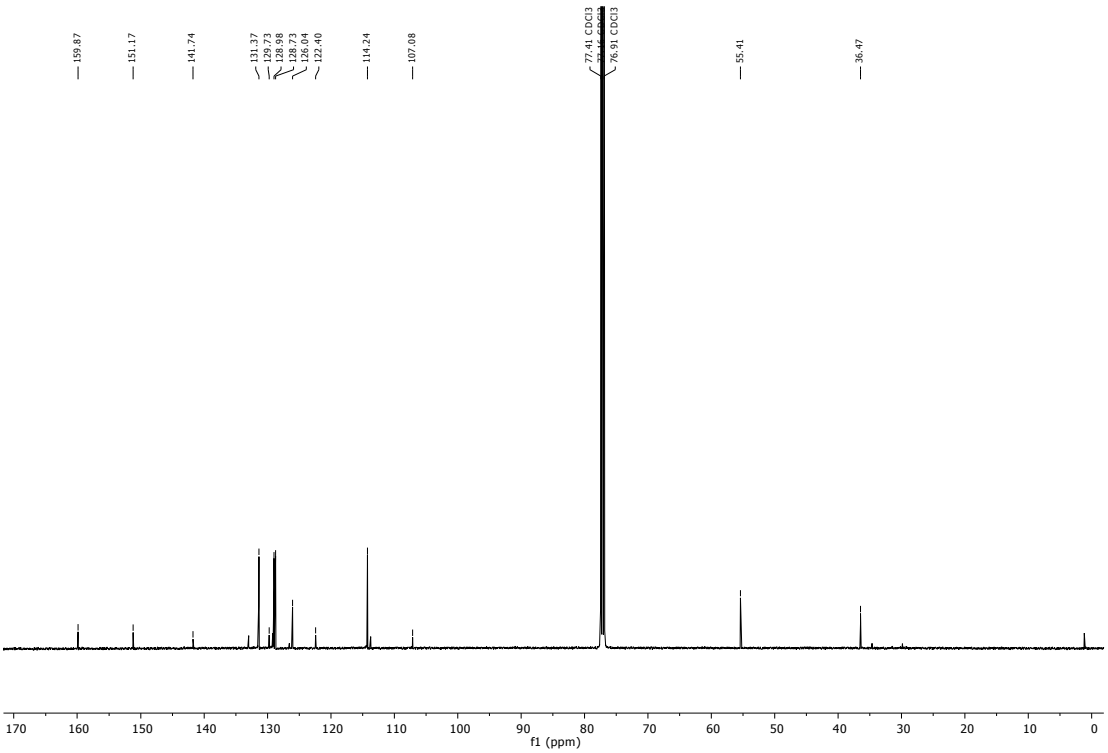
^{13}C NMR (126 MHz, C_6D_6) **Compound 147**



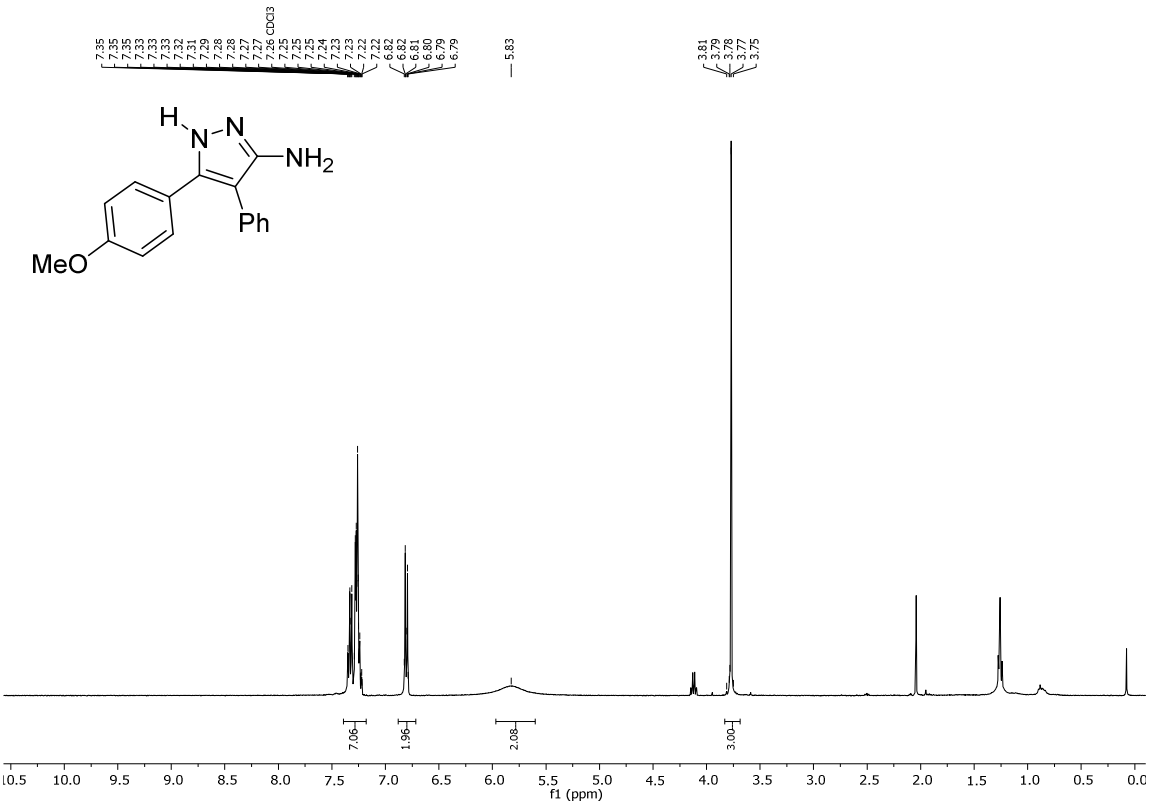
^{1}H NMR (400 MHz, $CDCl_3$) **Compounds 149a and 149b**



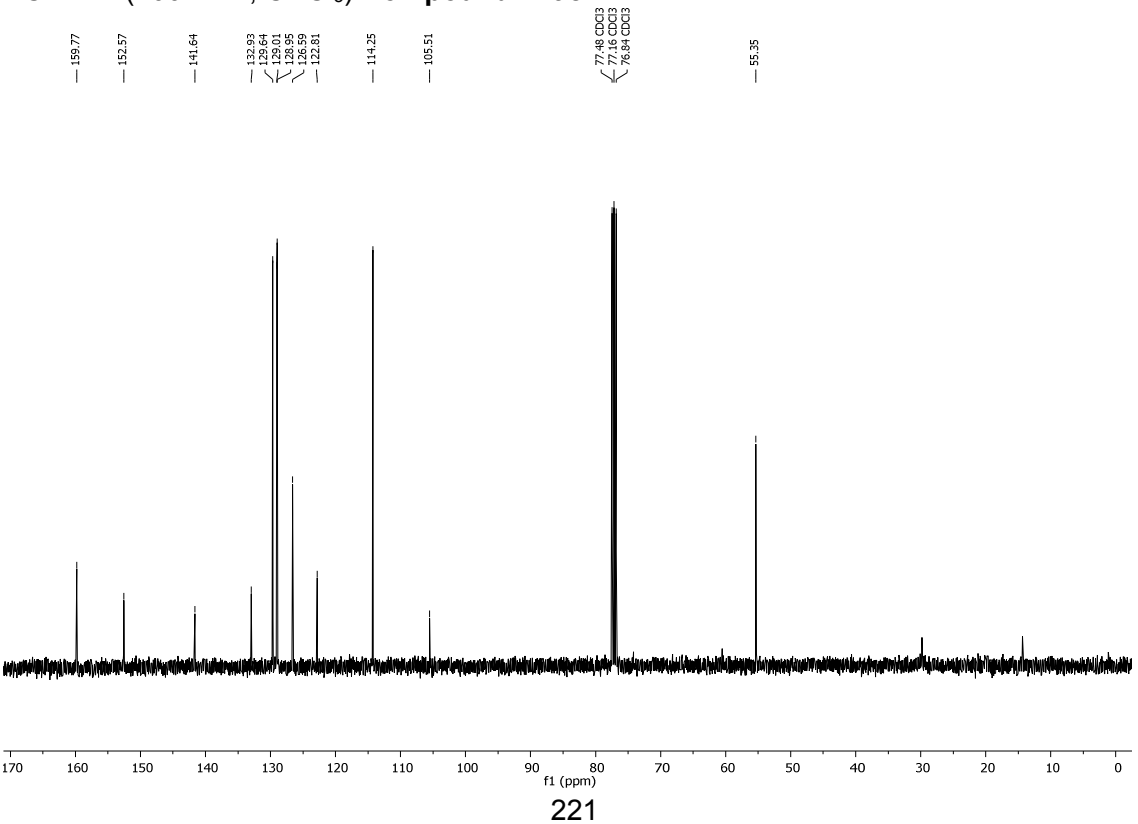
^{13}C NMR (100 MHz, $CDCl_3$) **Compounds 149a and 149b**



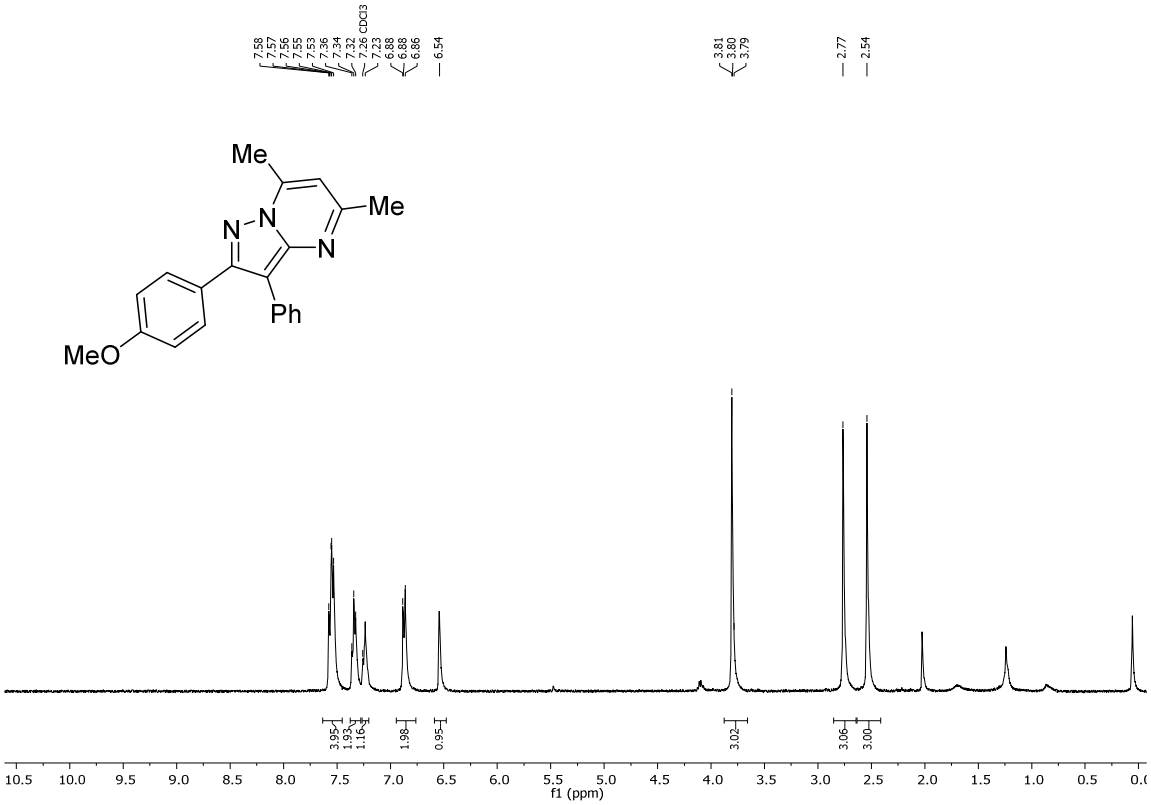
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 149c**



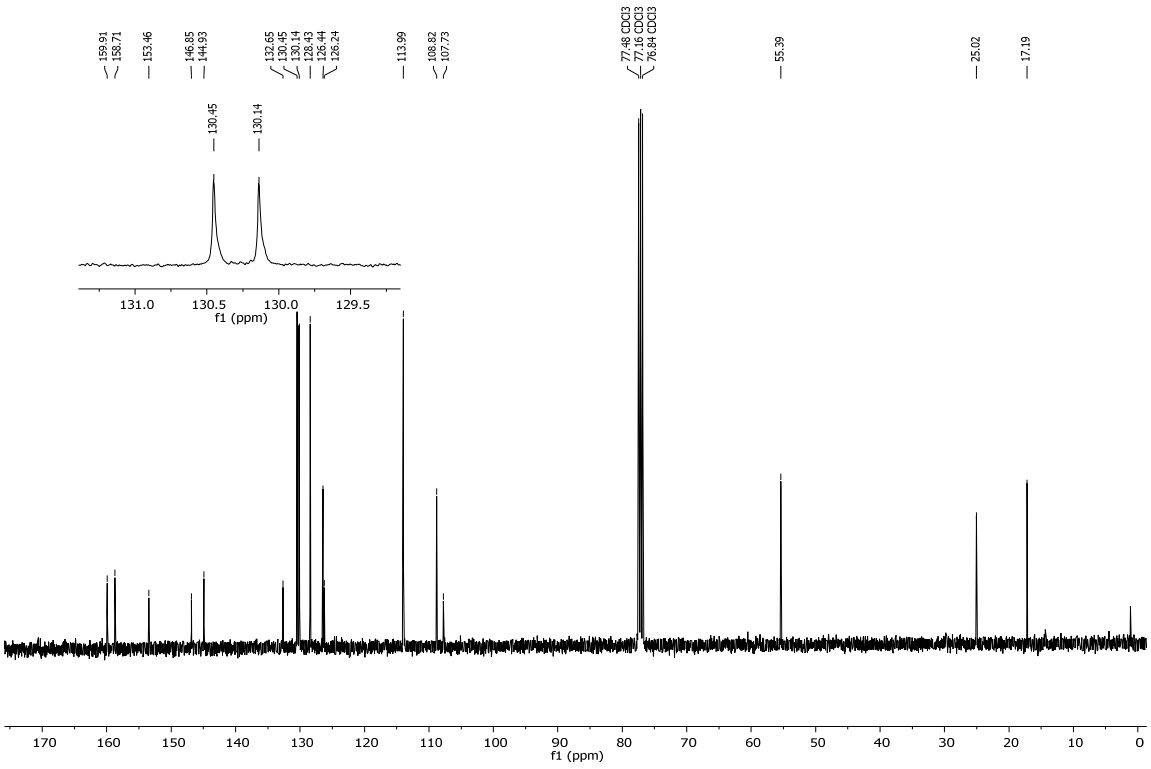
^{13}C NMR (100 MHz, $CDCl_3$) **Compound 149c**



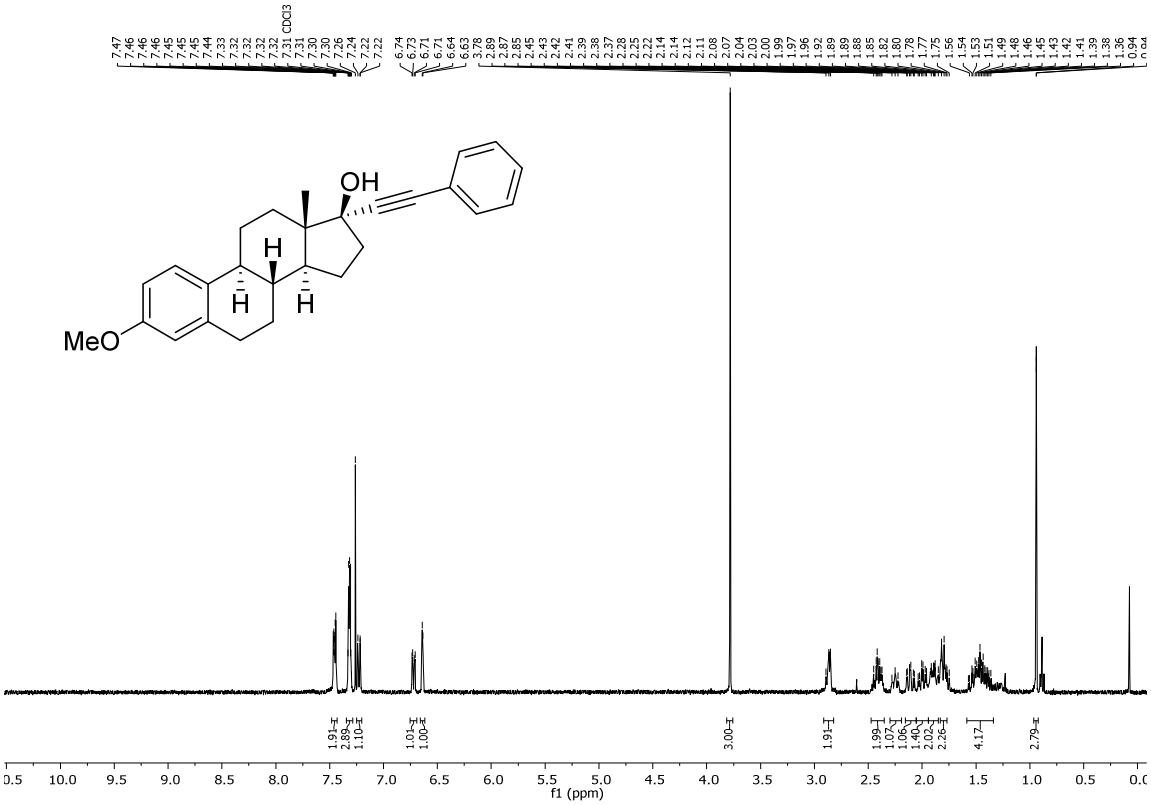
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 150**



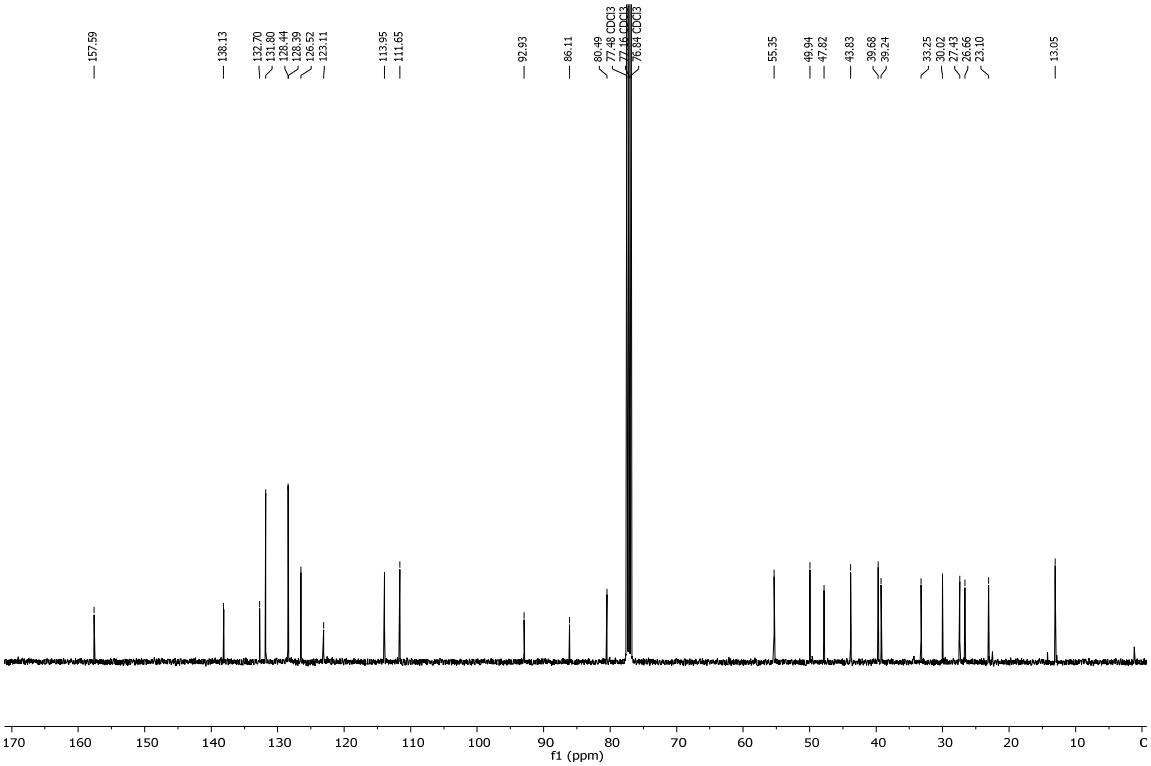
^{13}C NMR (100 MHz, $CDCl_3$) **Compound 150**



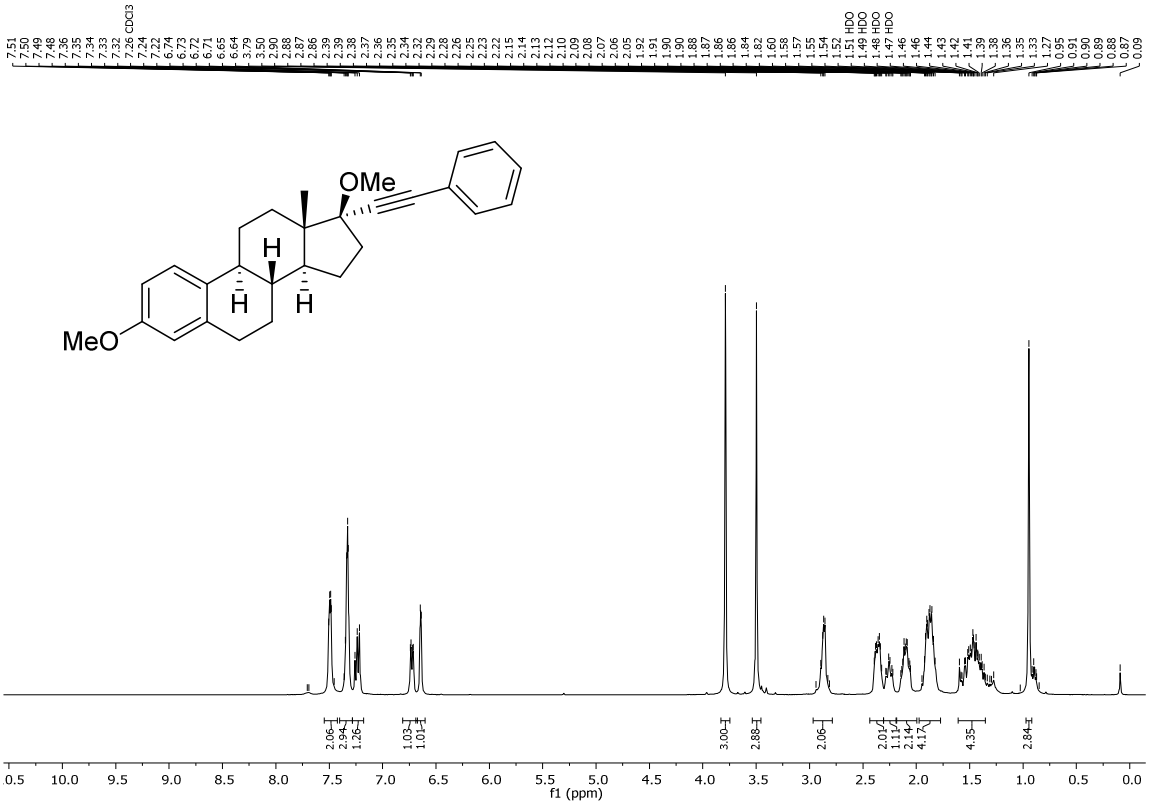
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 152**



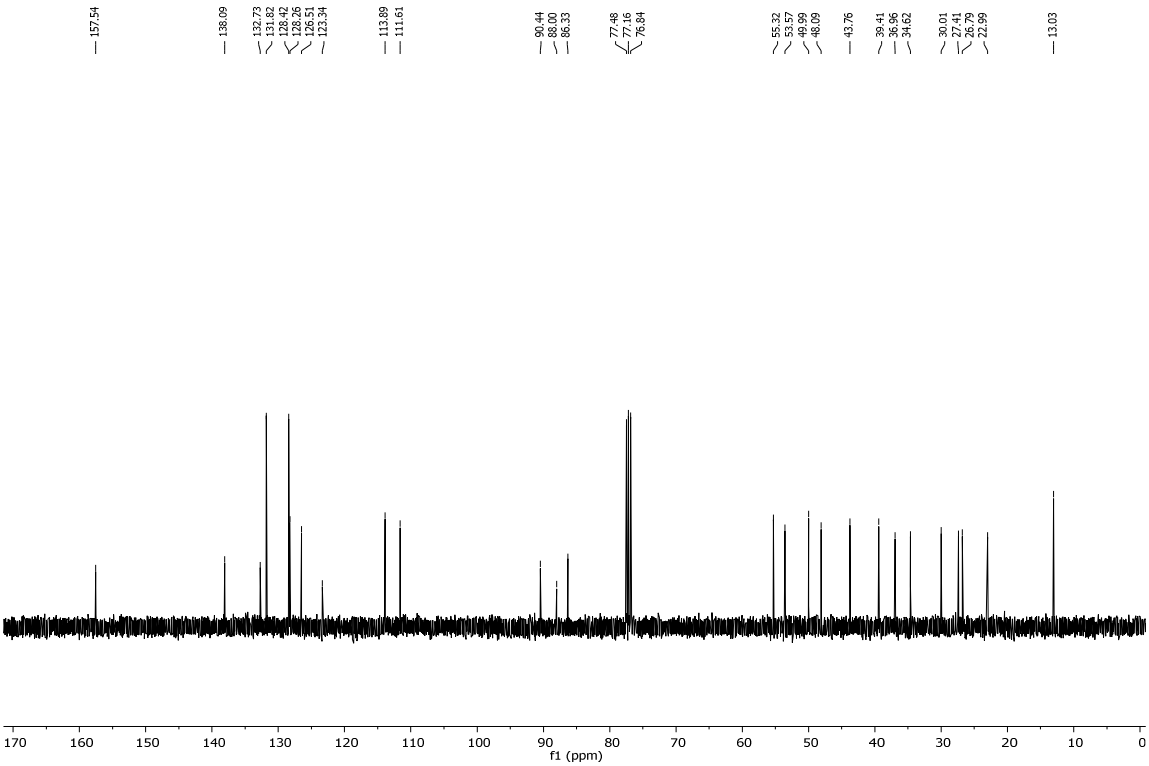
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 152**



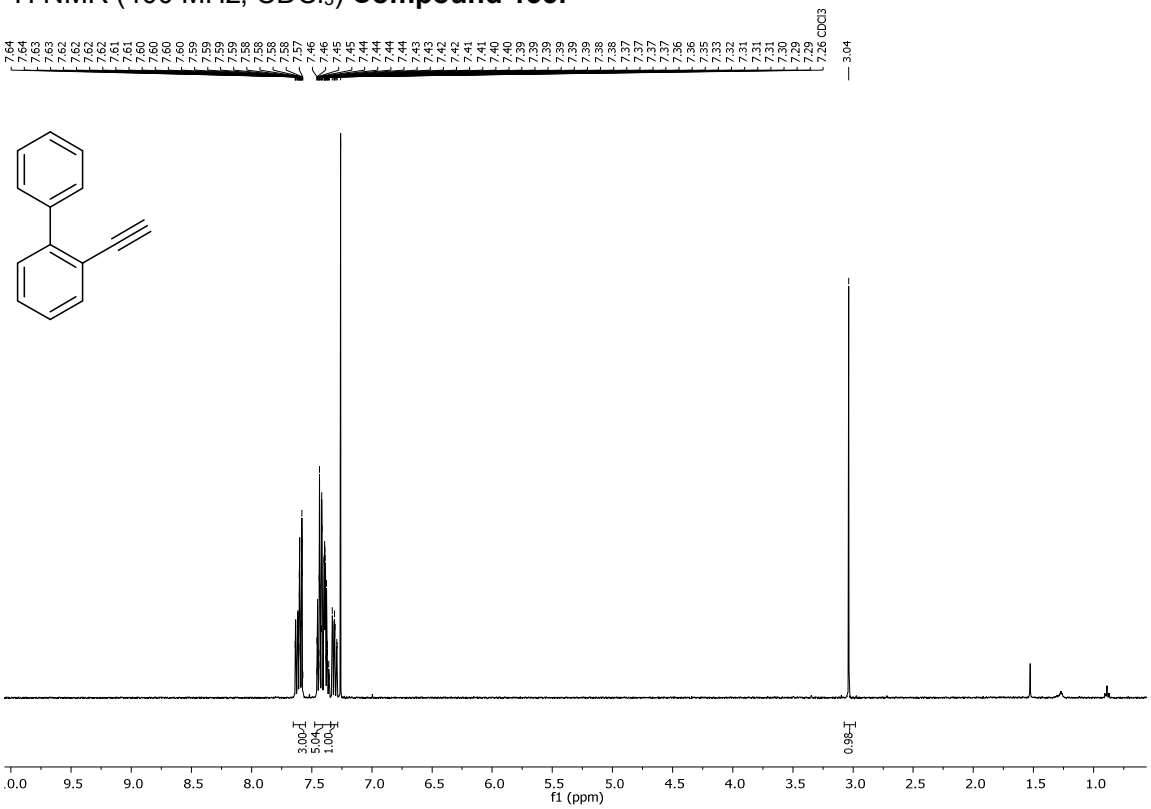
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 153**



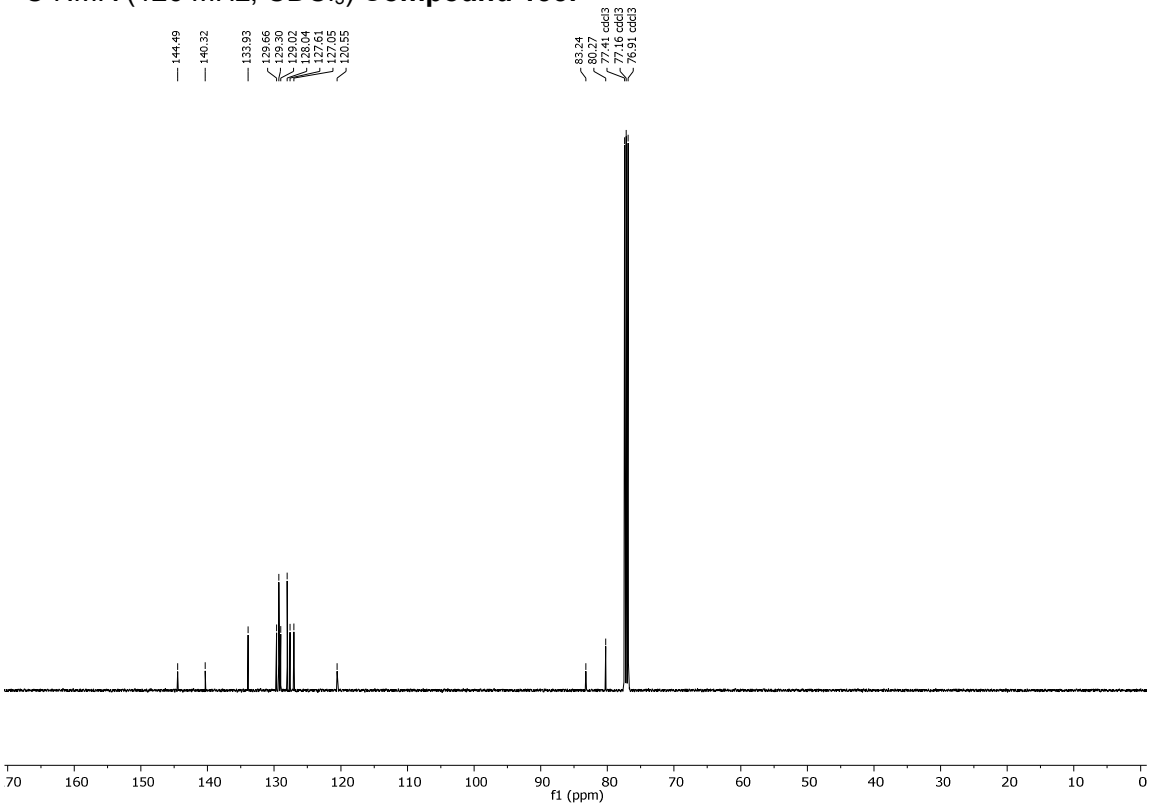
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 153**



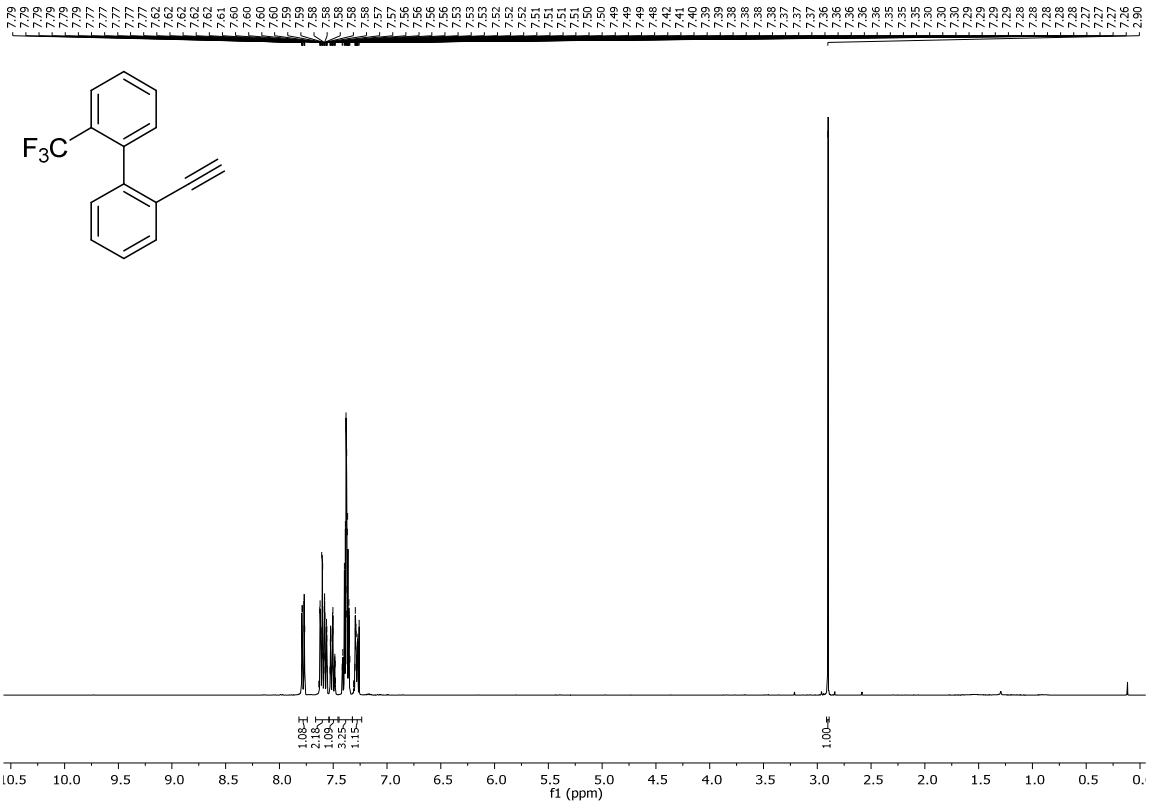
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135f**



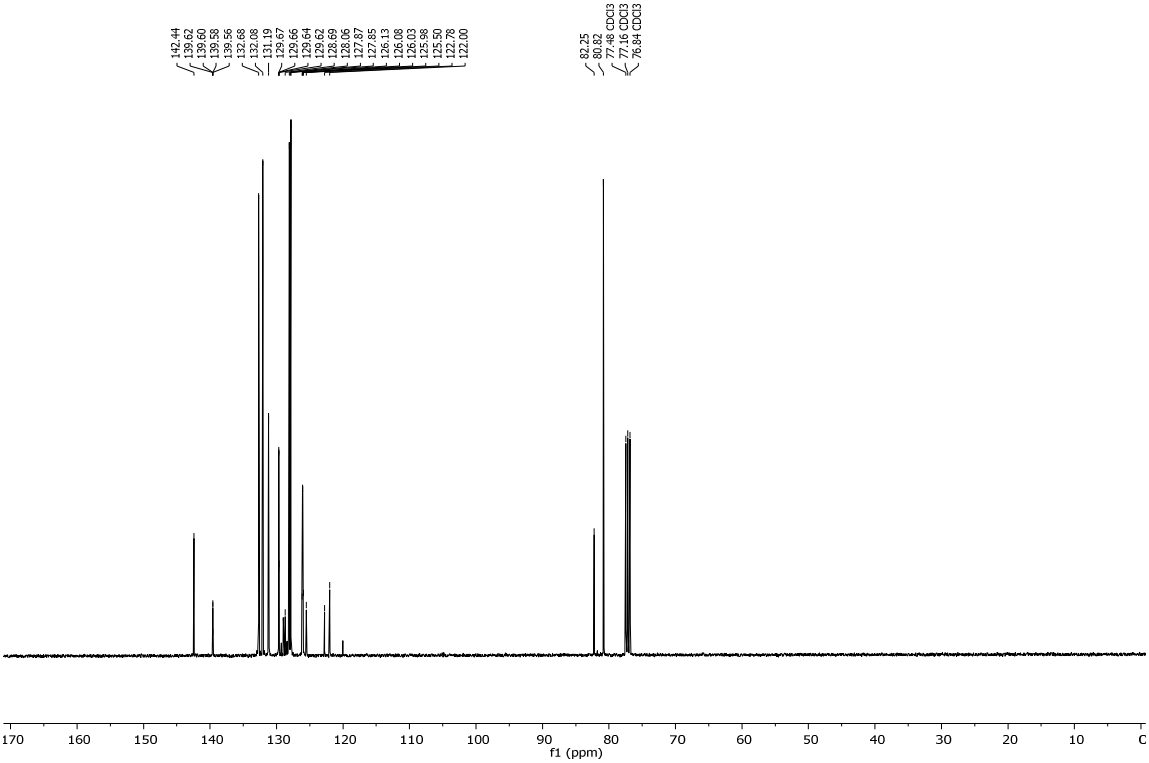
^{13}C NMR (126 MHz, $CDCl_3$) **Compound 135f**



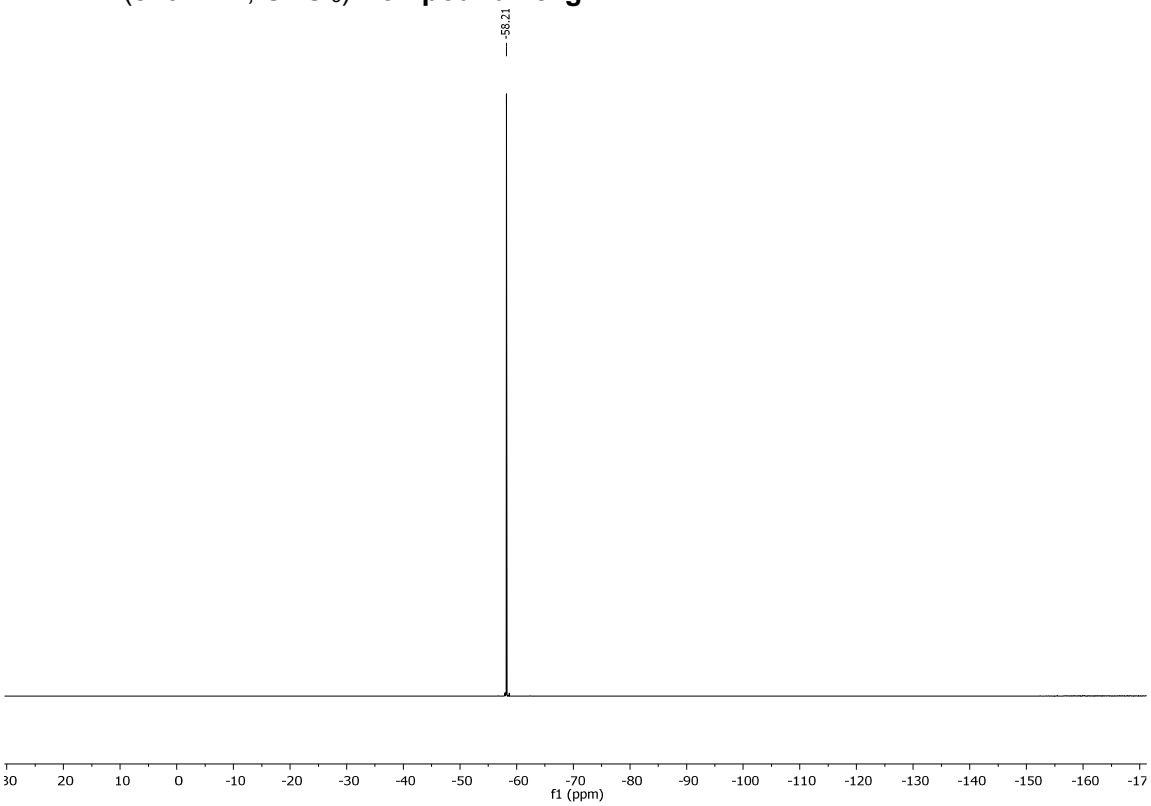
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 182g**



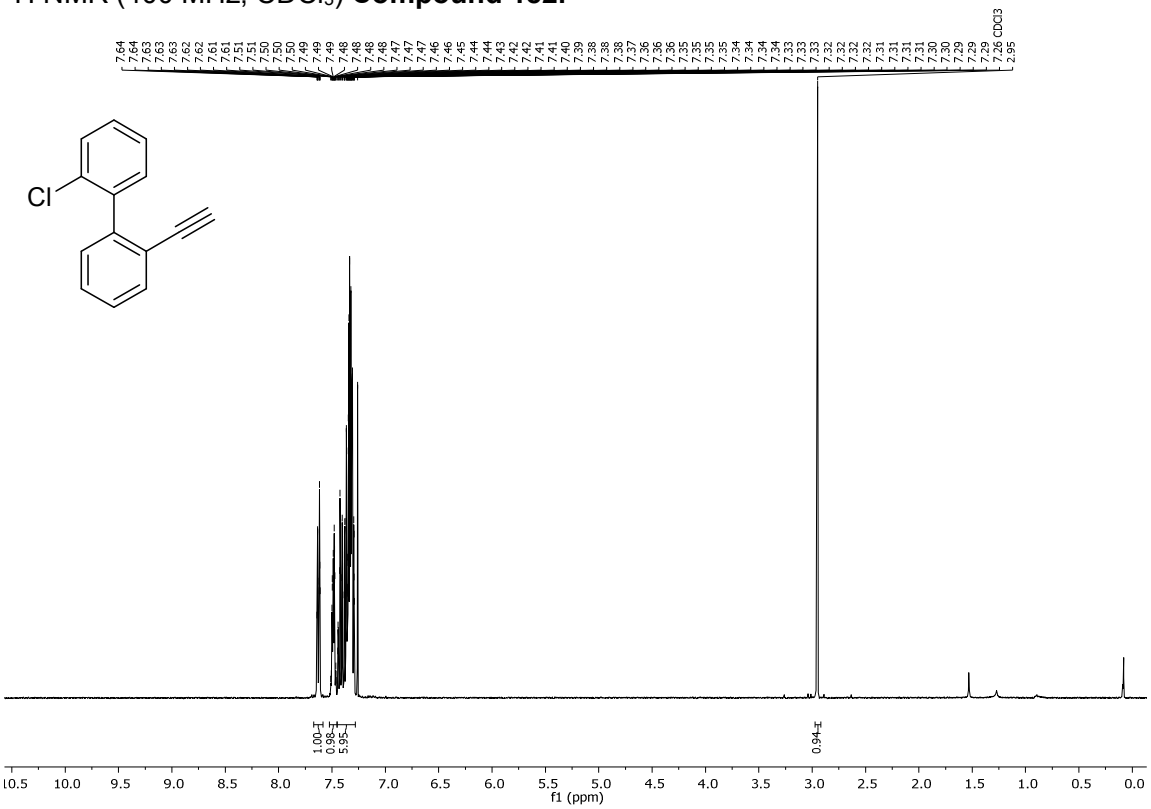
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 182g**



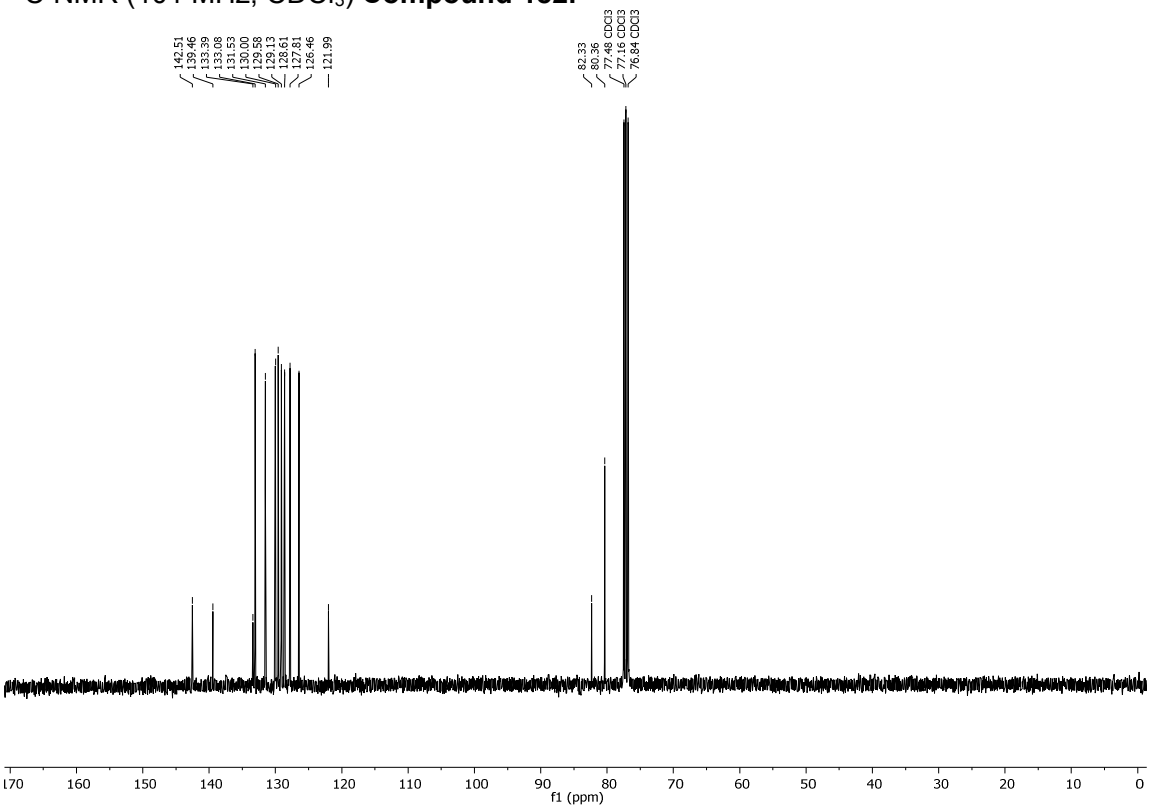
^{19}F NMR (376 MHz, $CDCl_3$) **Compound 182g**



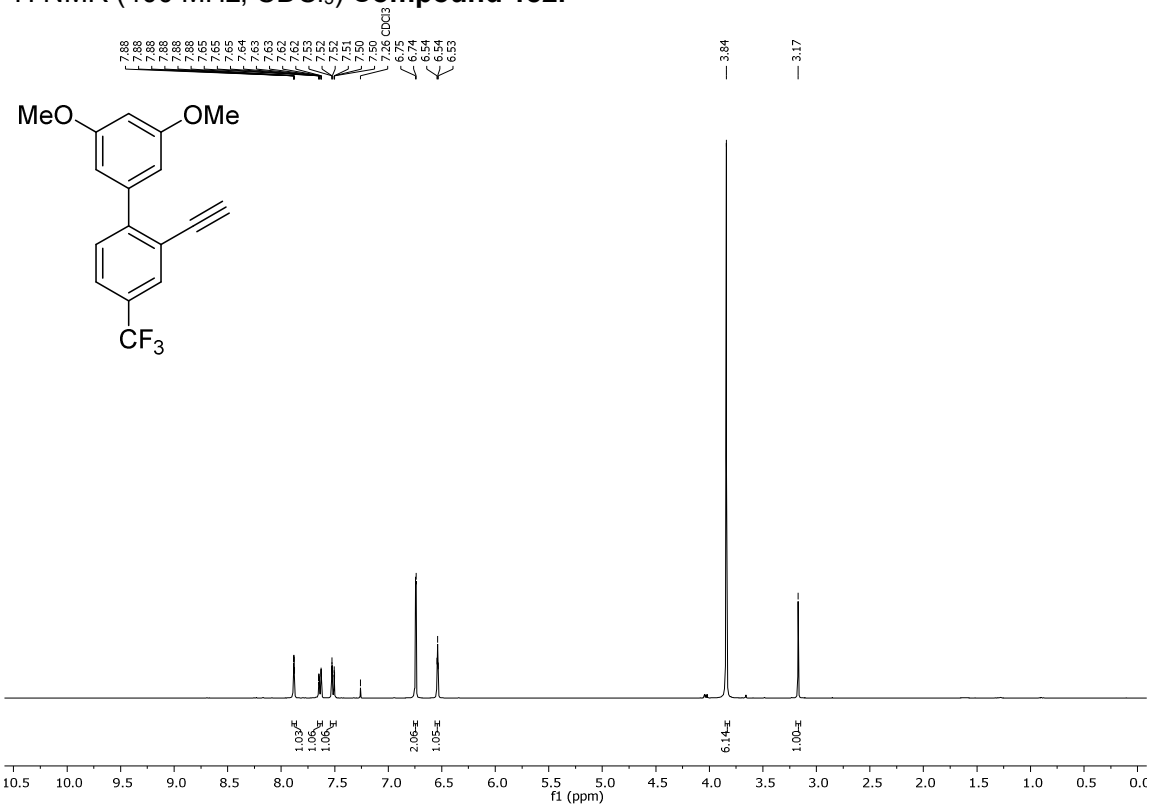
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 182i**



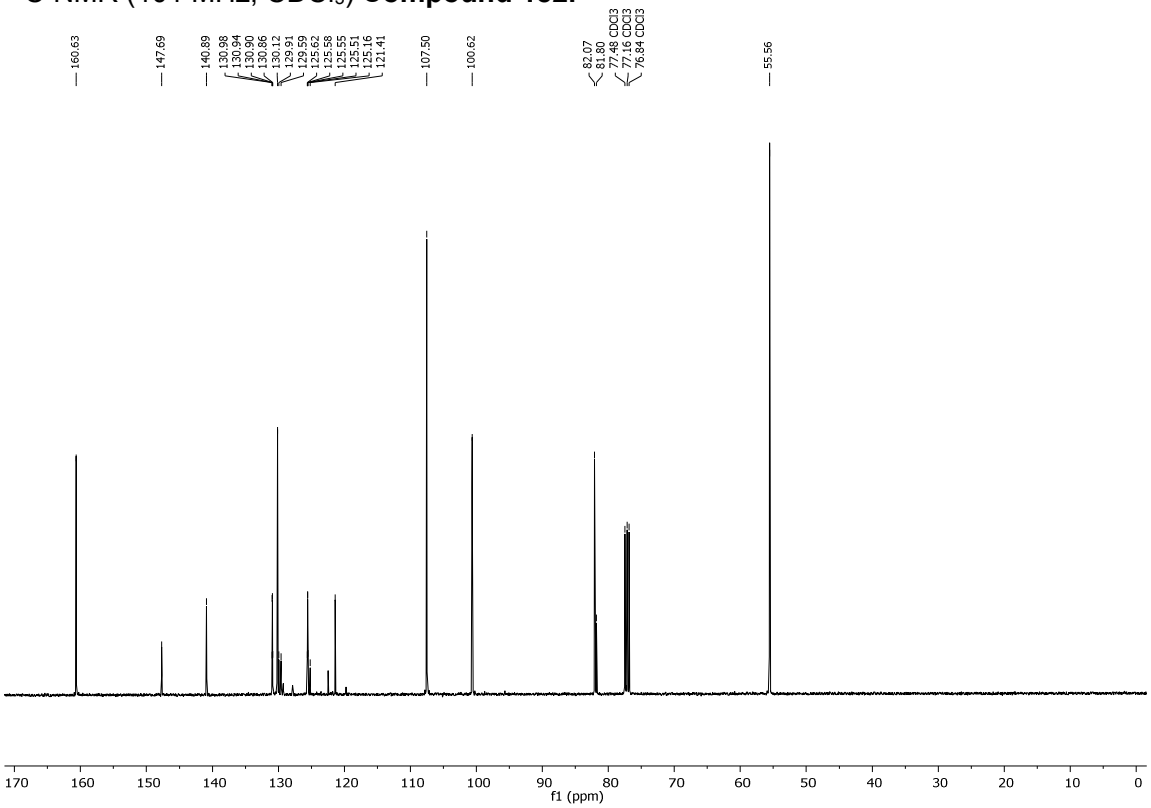
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 182i**



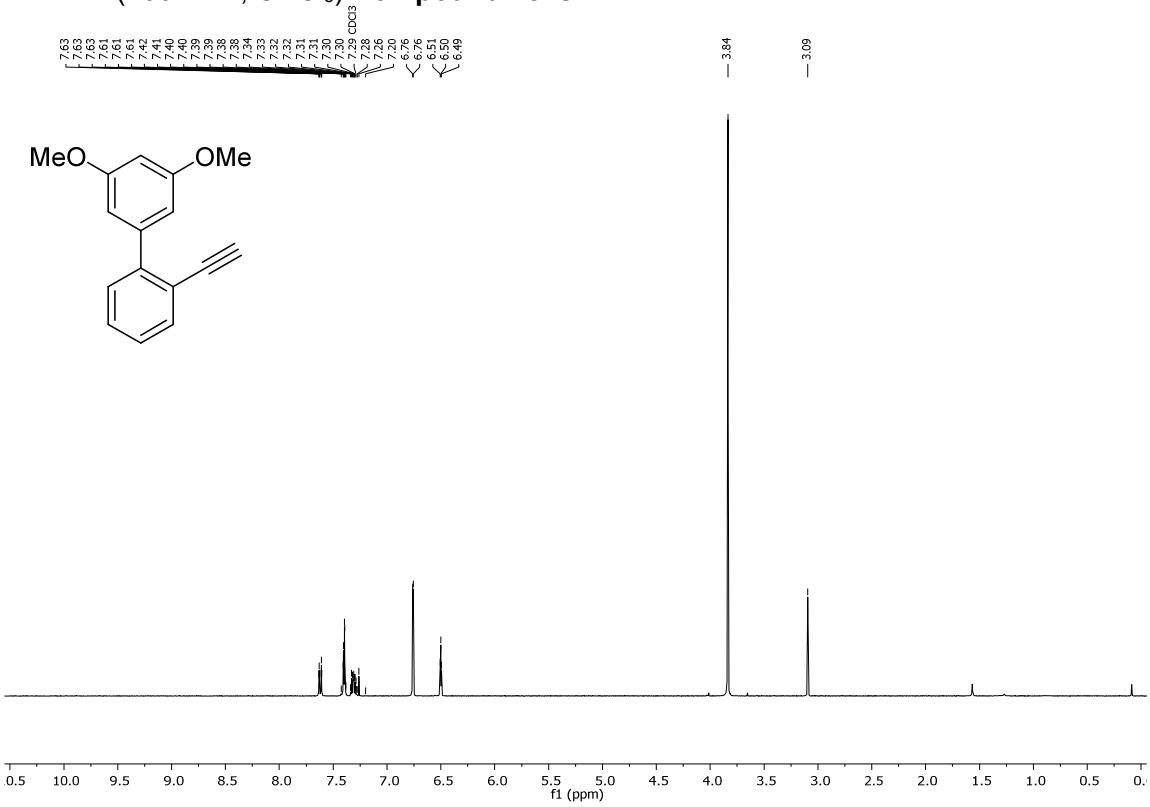
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 182r**



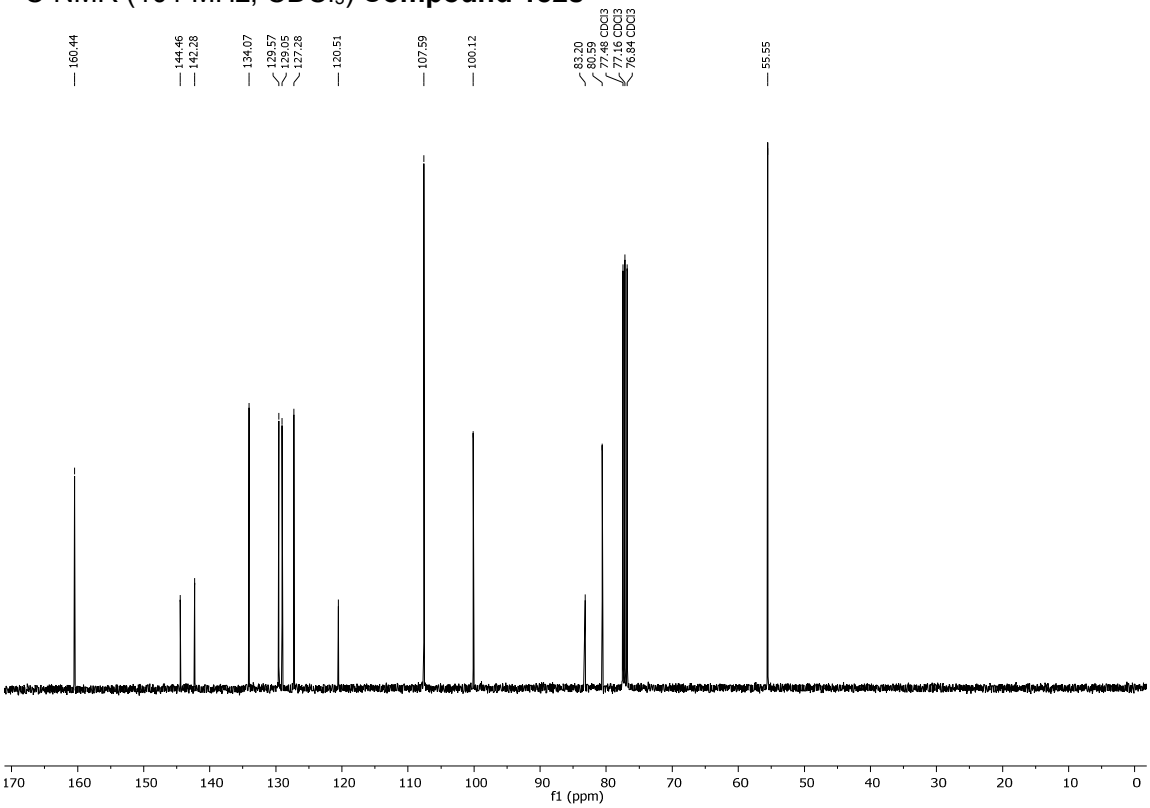
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 182r**



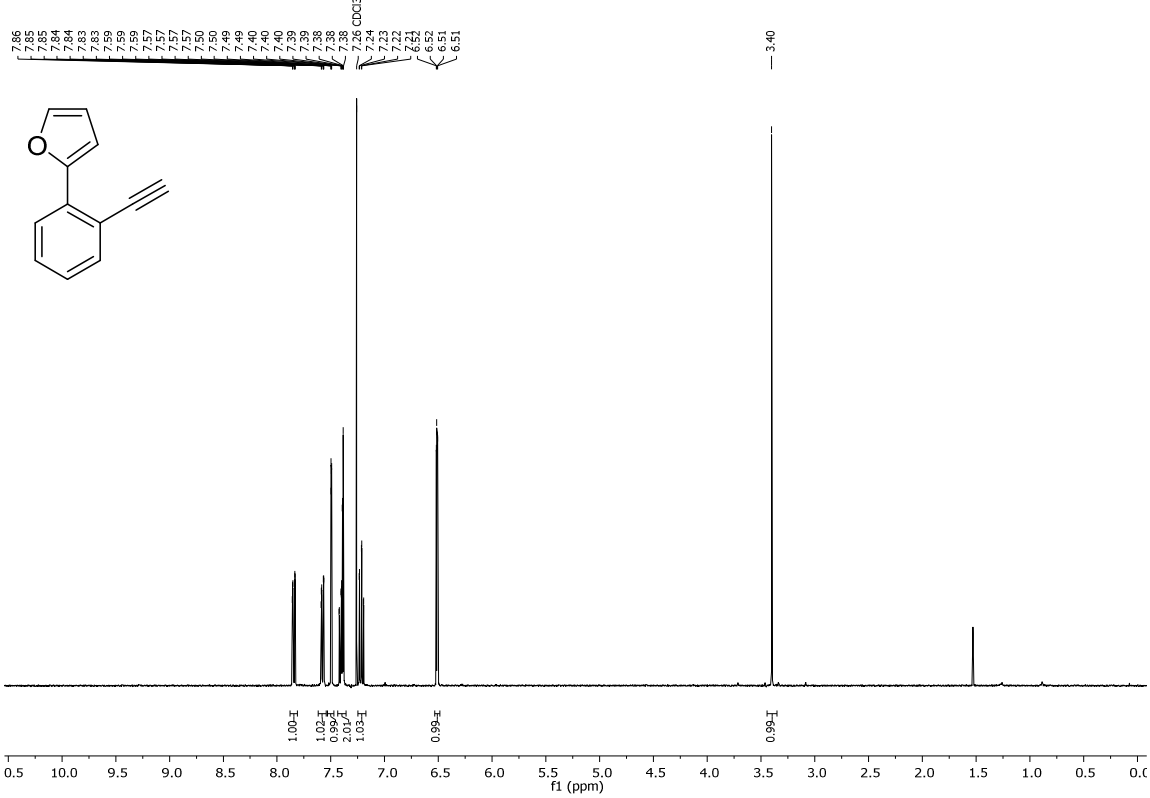
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 182s**



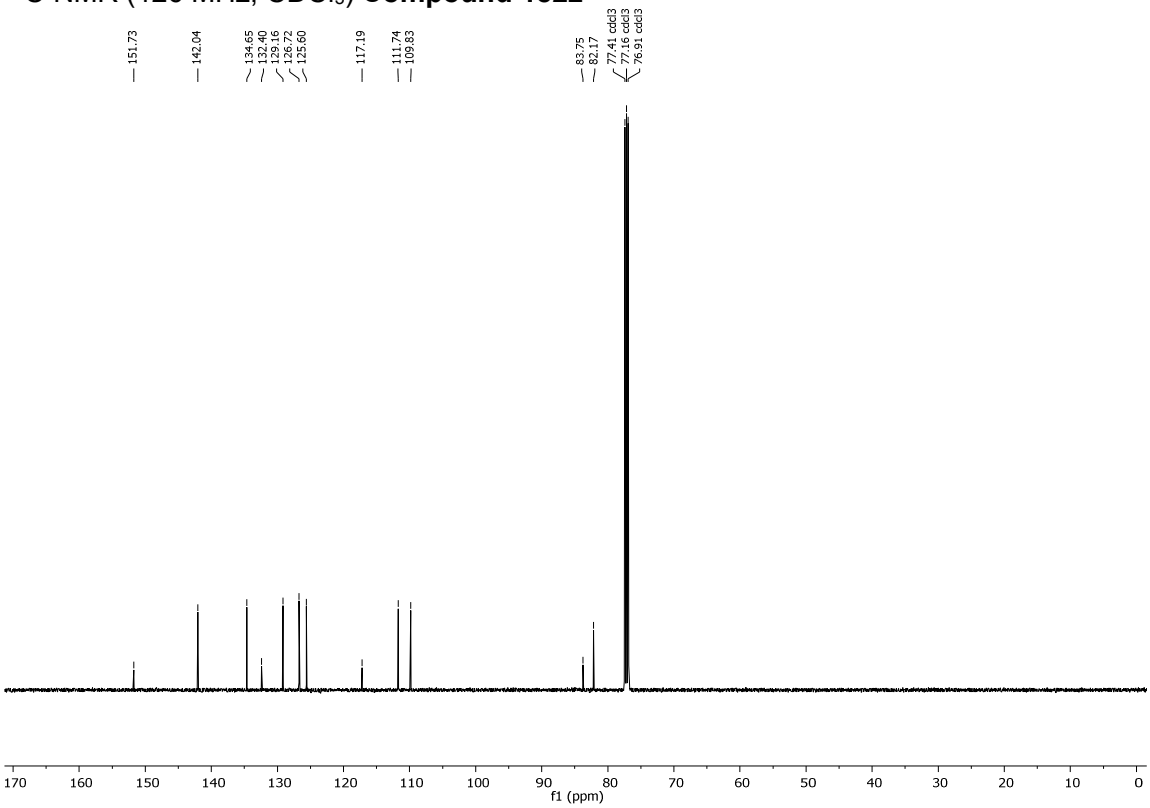
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 182s**



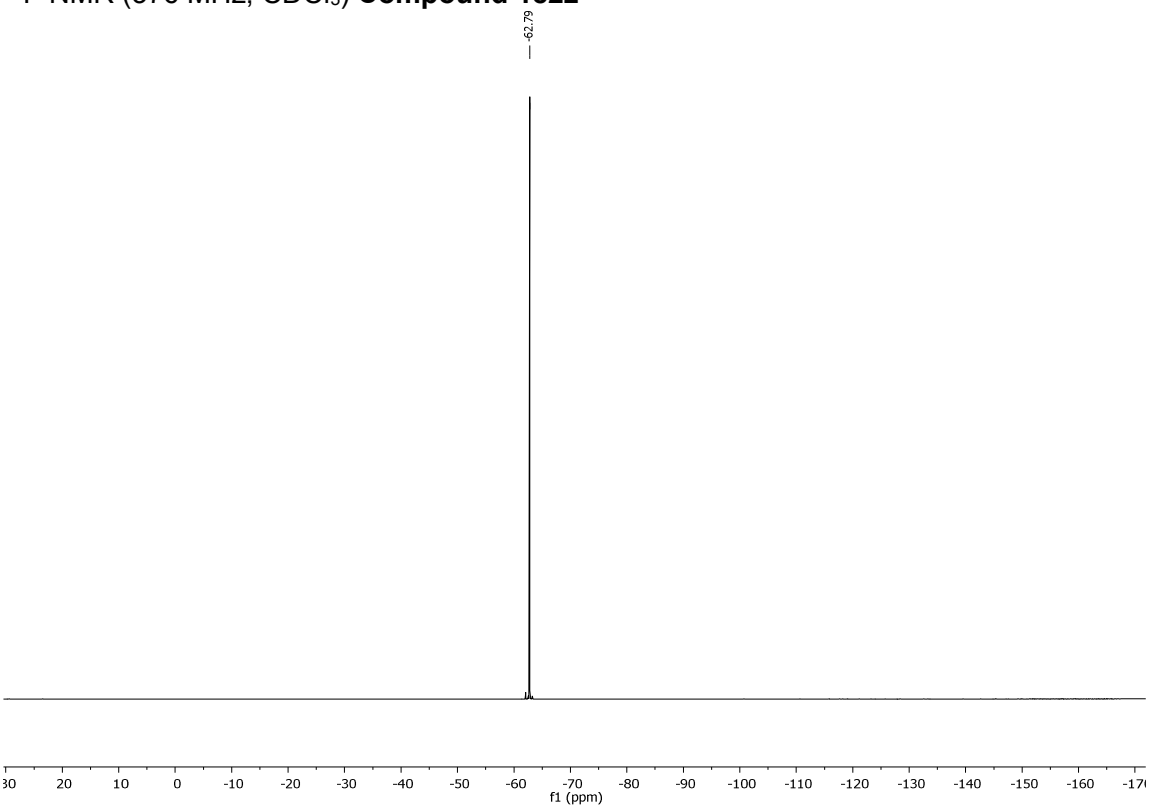
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 182v**



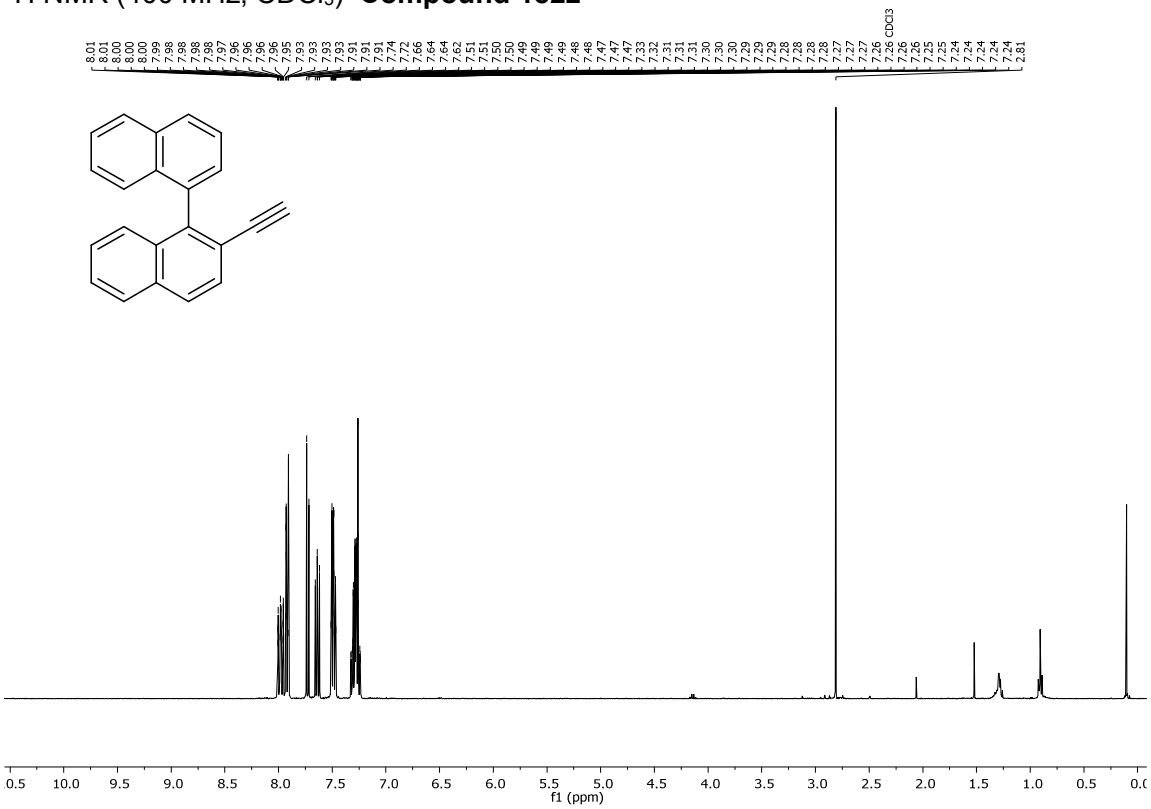
^{13}C NMR (126 MHz, $CDCl_3$) **Compound 182z**



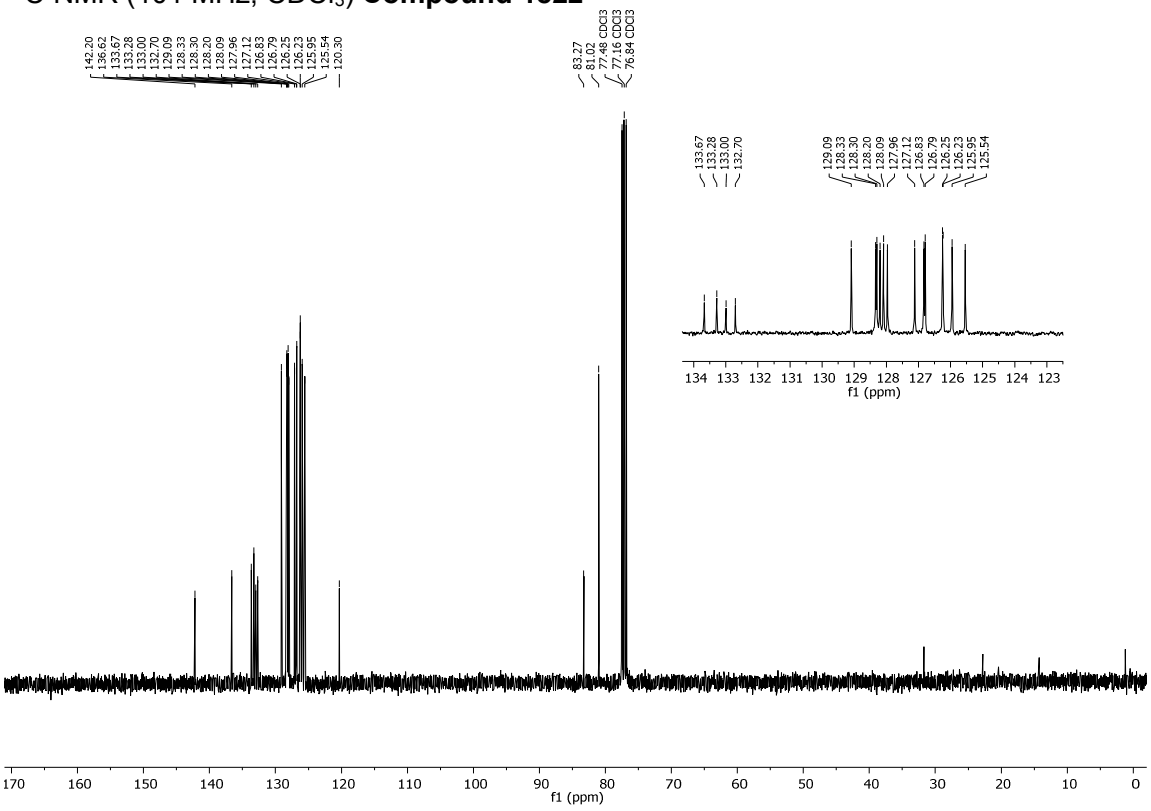
^{19}F NMR (376 MHz, $CDCl_3$) **Compound 182z**



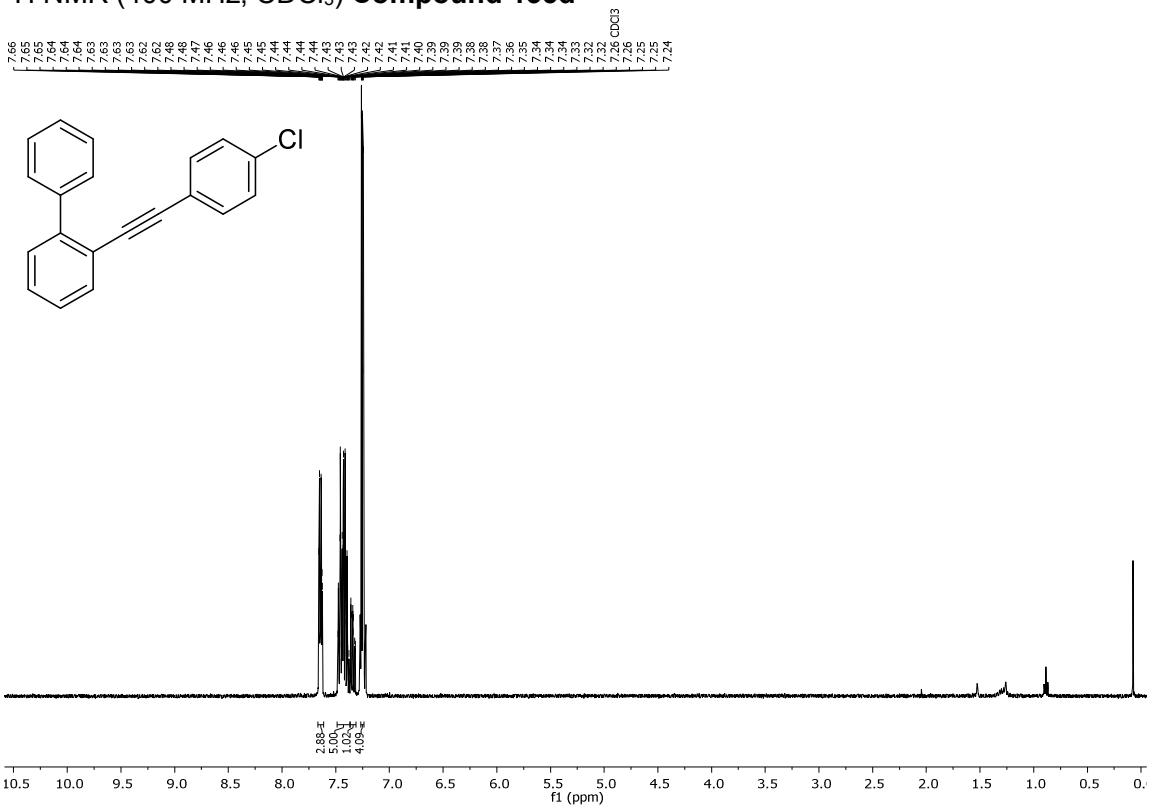
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 182z**



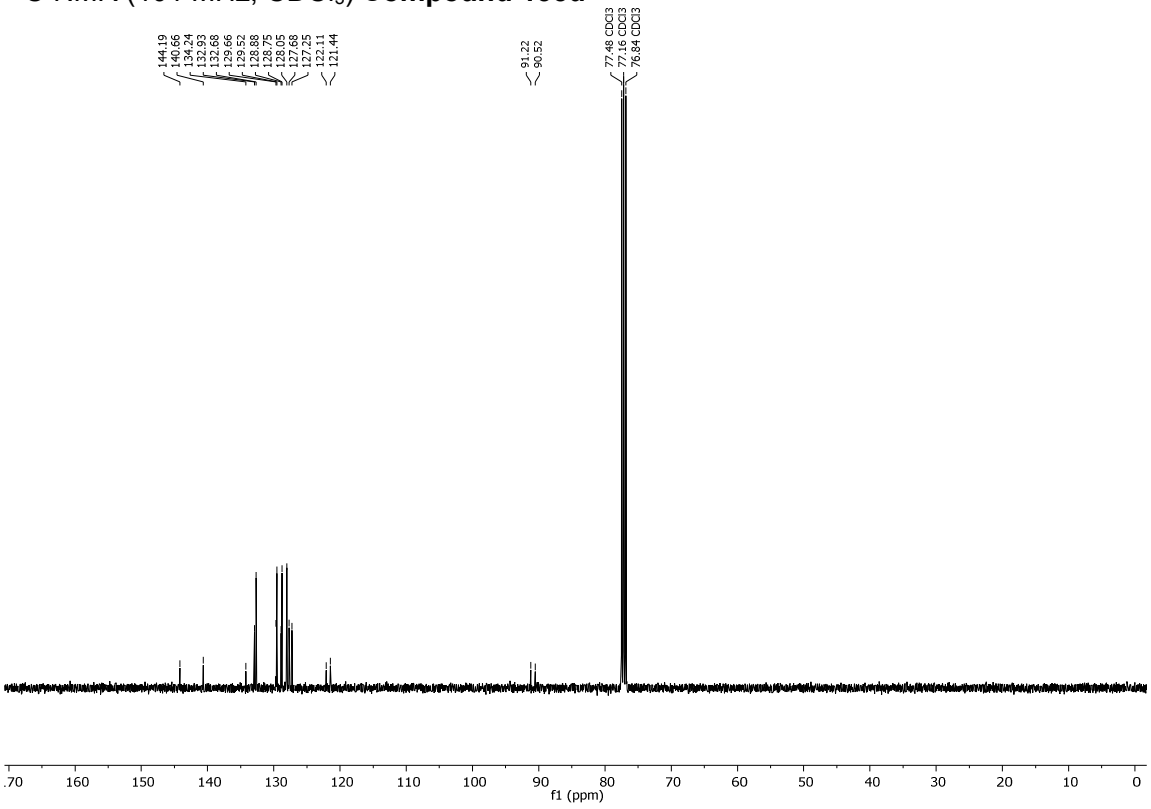
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 182z**



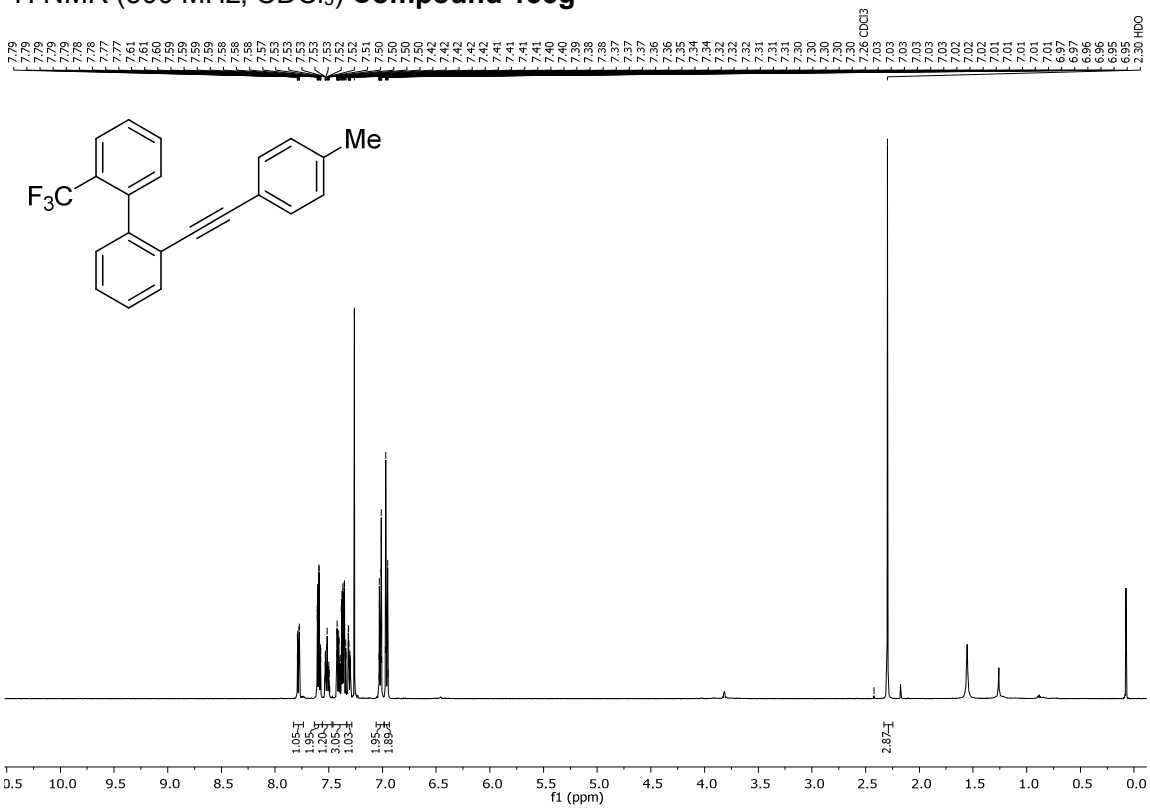
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135d**



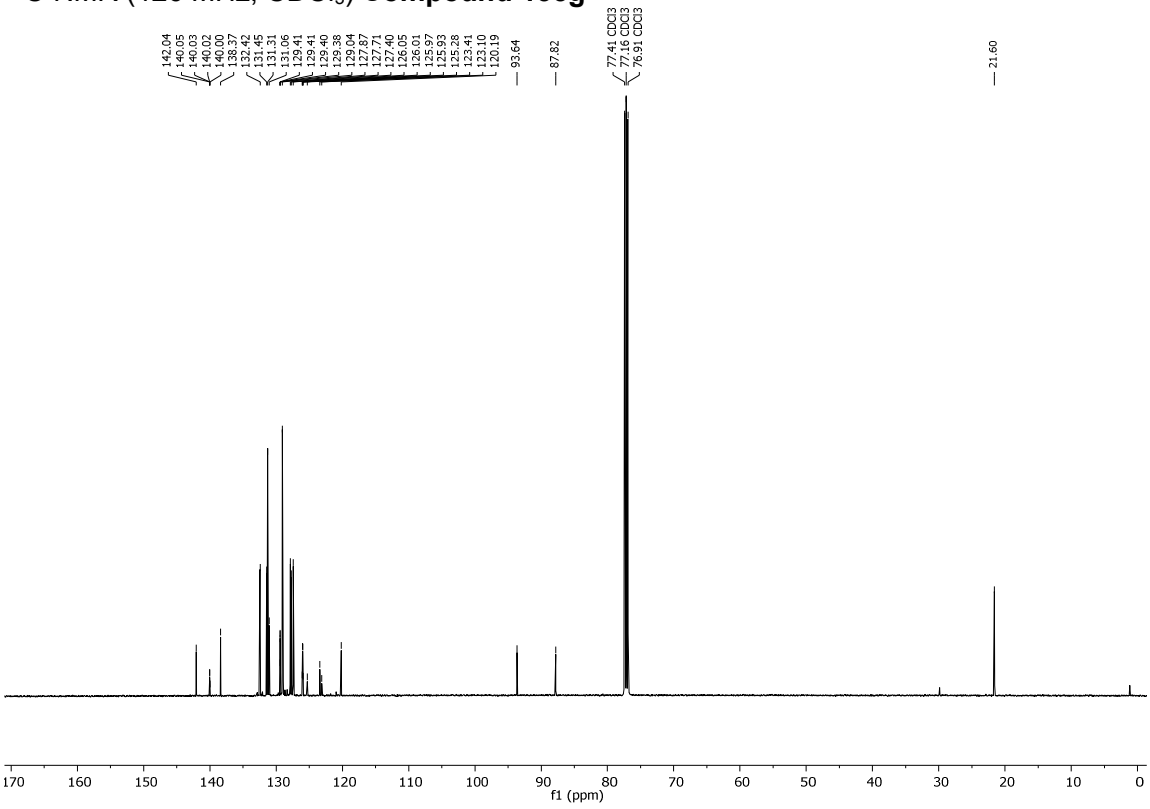
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 135d**



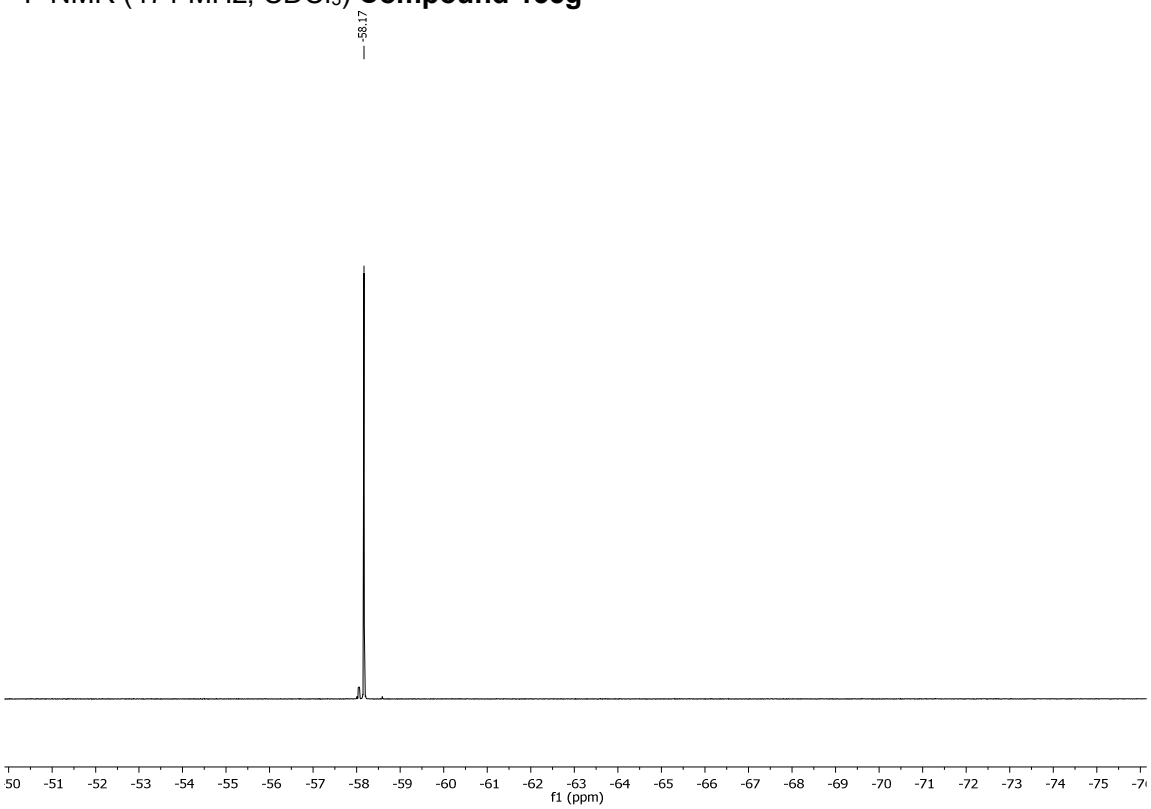
^{1}H NMR (500 MHz, $CDCl_3$) **Compound 135g**



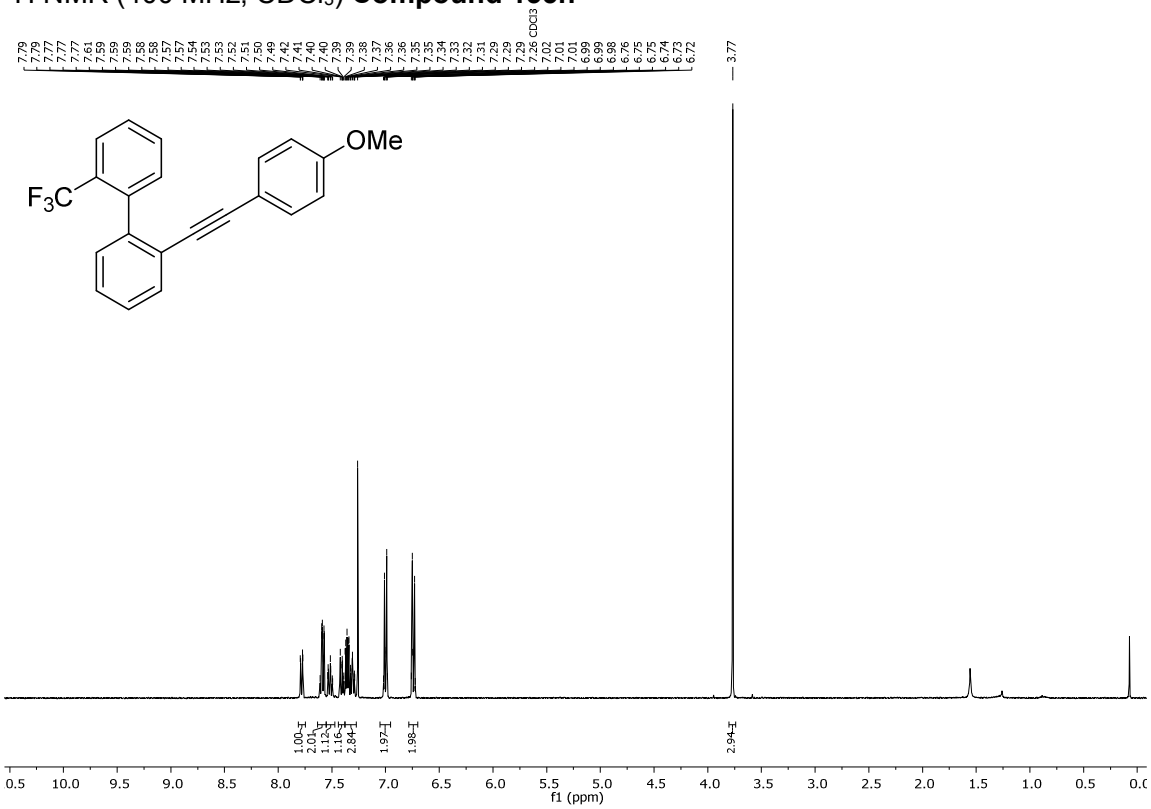
^{13}C NMR (126 MHz, $CDCl_3$) **Compound 135g**



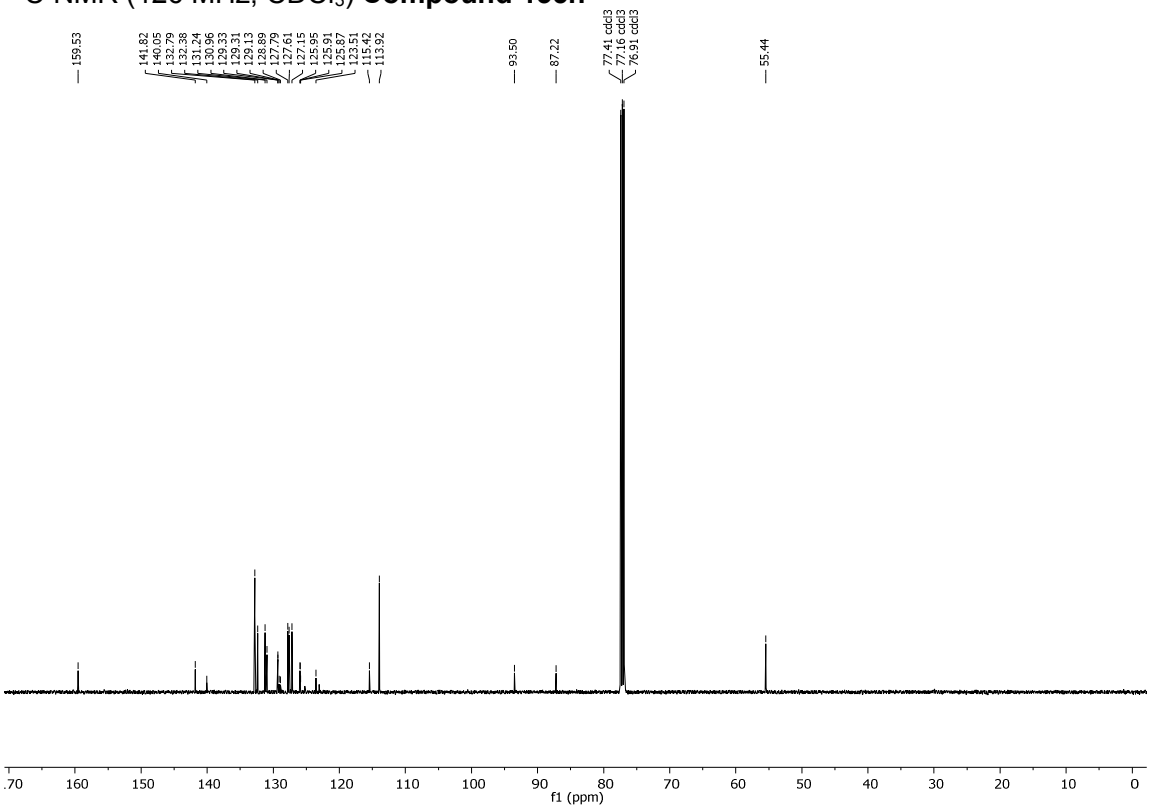
^{19}F NMR (471 MHz, $CDCl_3$) **Compound 135g**



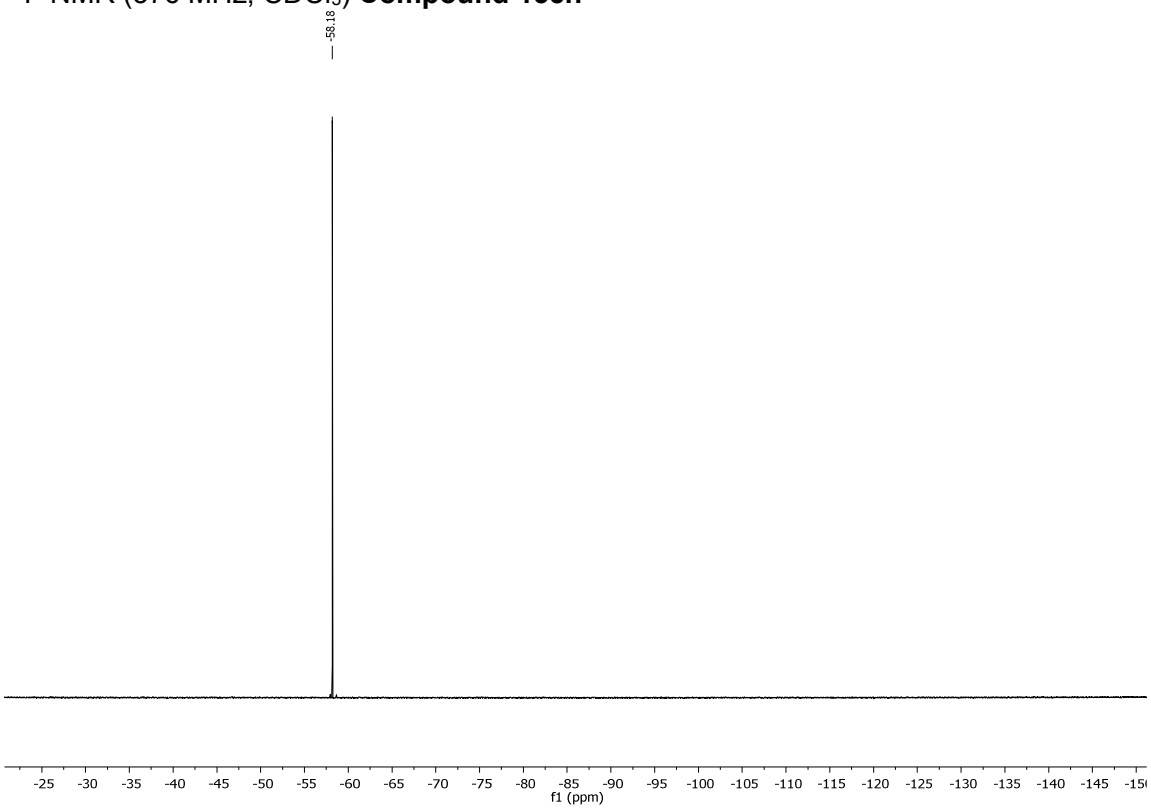
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135h**



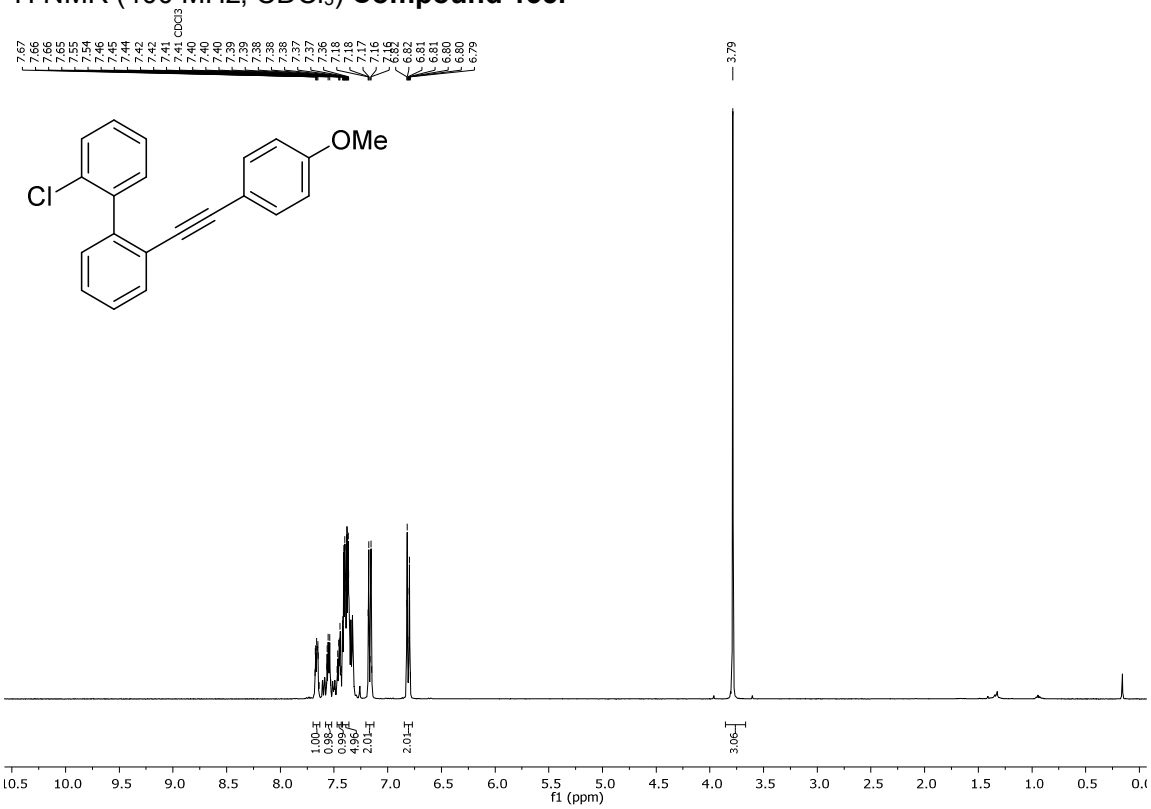
^{13}C NMR (126 MHz, $CDCl_3$) **Compound 135h**



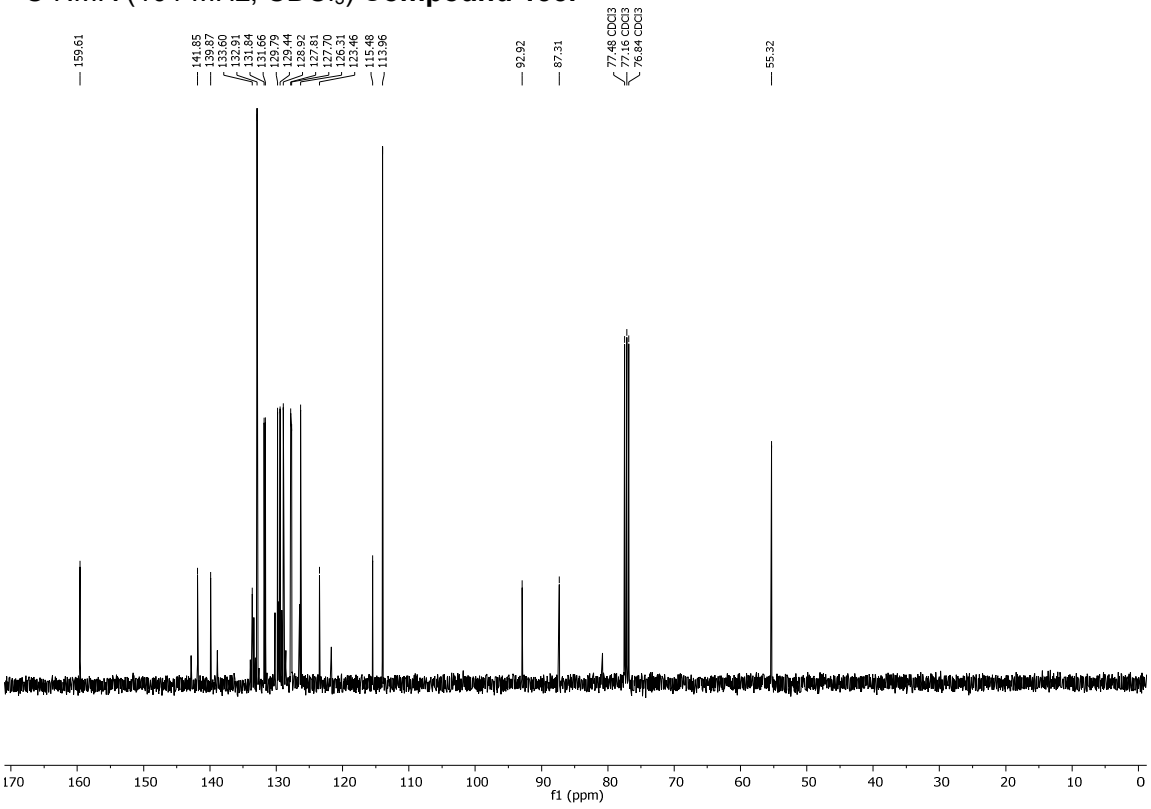
^{19}F NMR (376 MHz, $CDCl_3$) **Compound 135h**



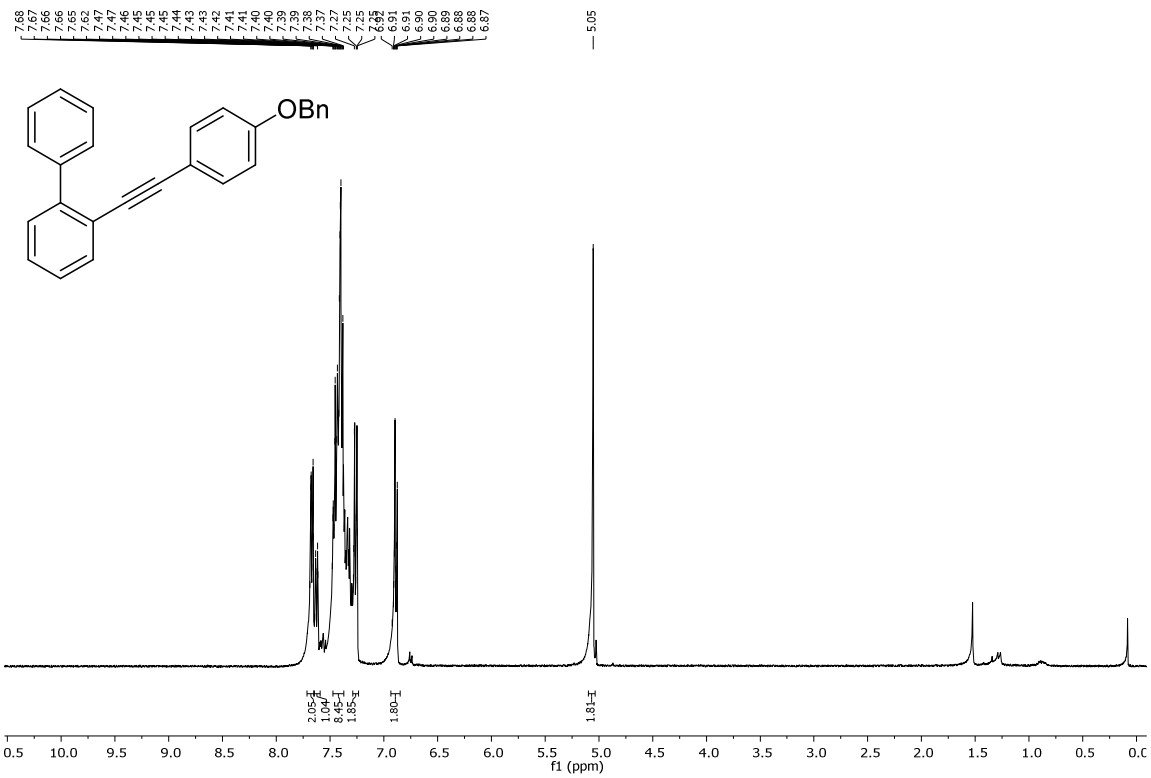
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135i**



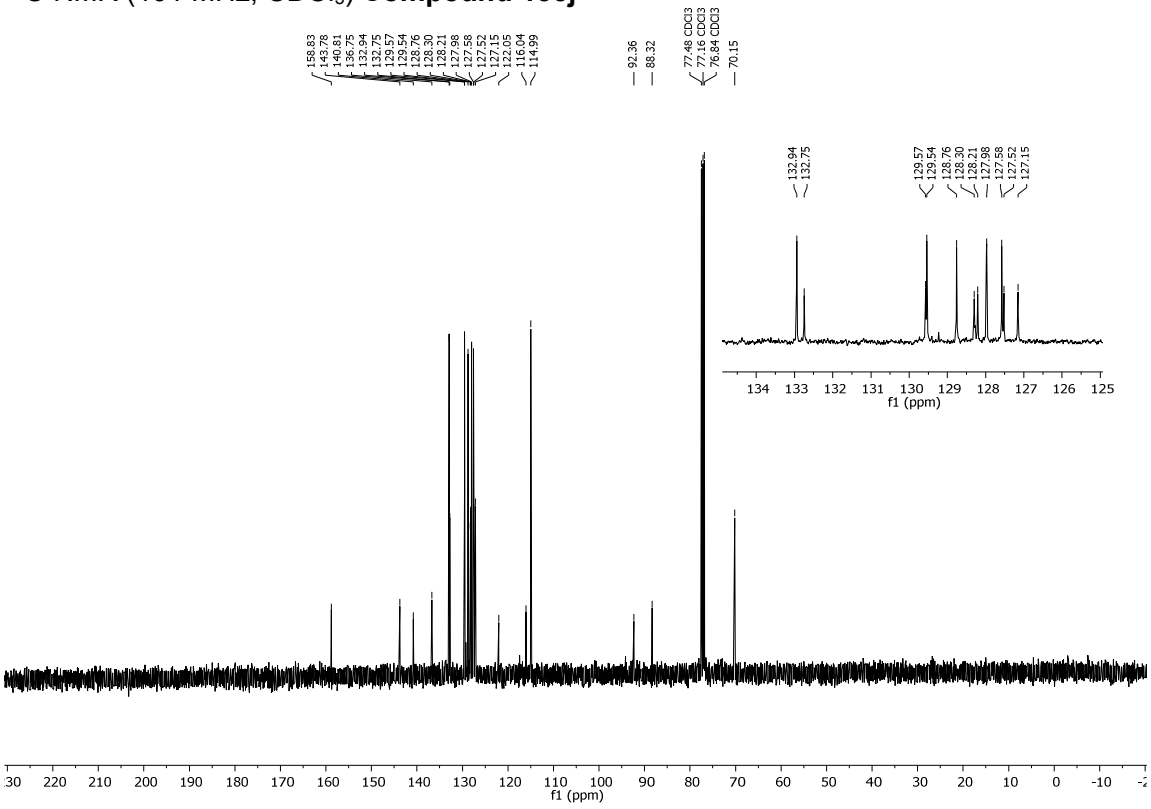
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 135i**



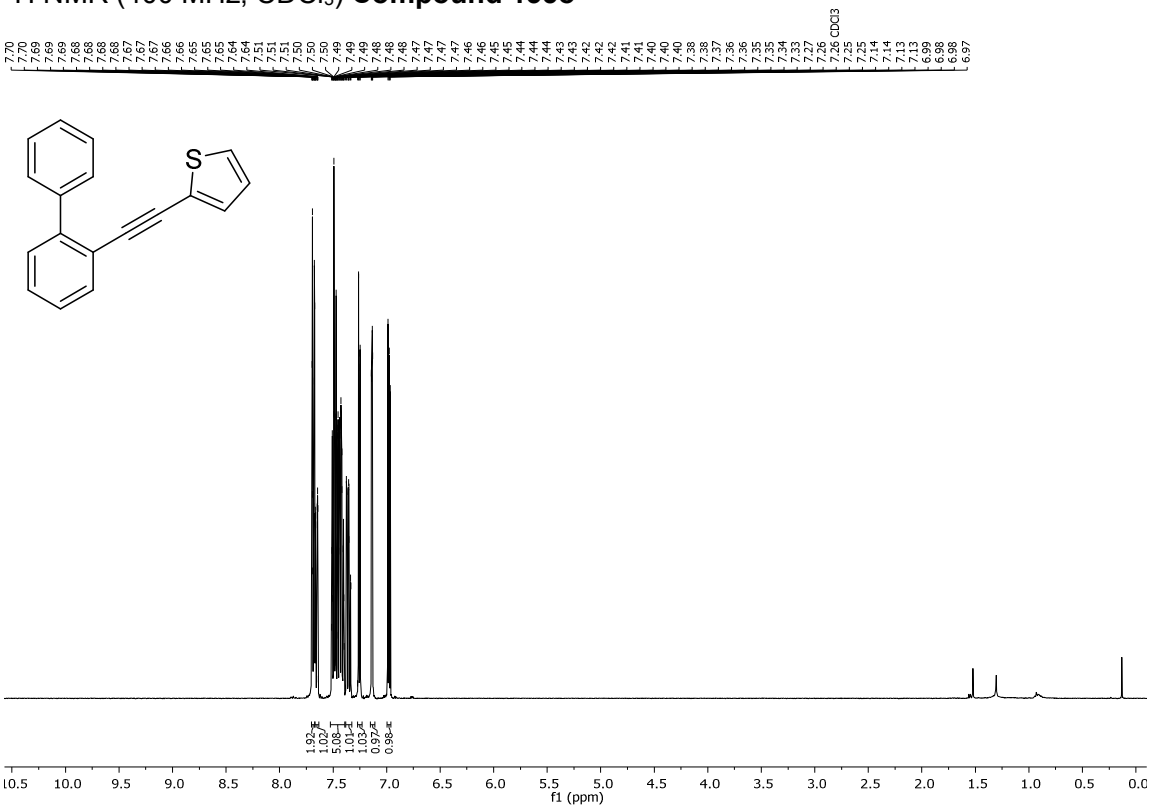
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135j**



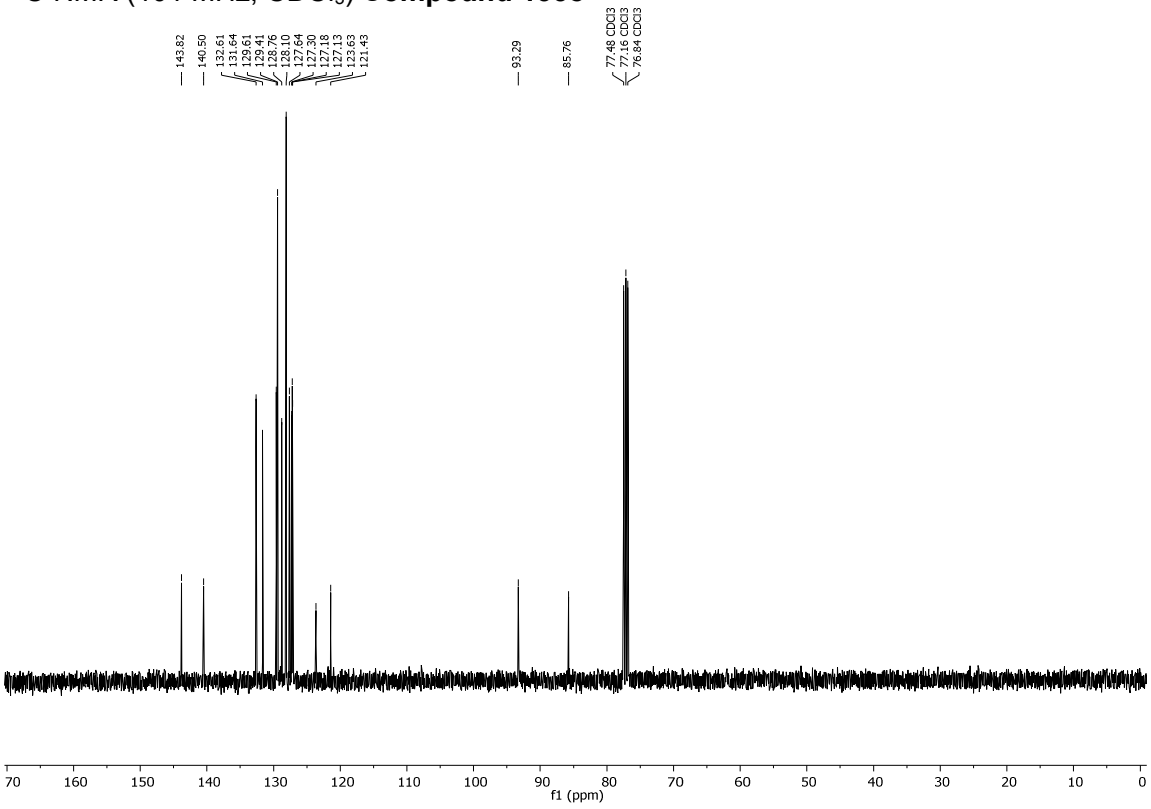
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 135j**



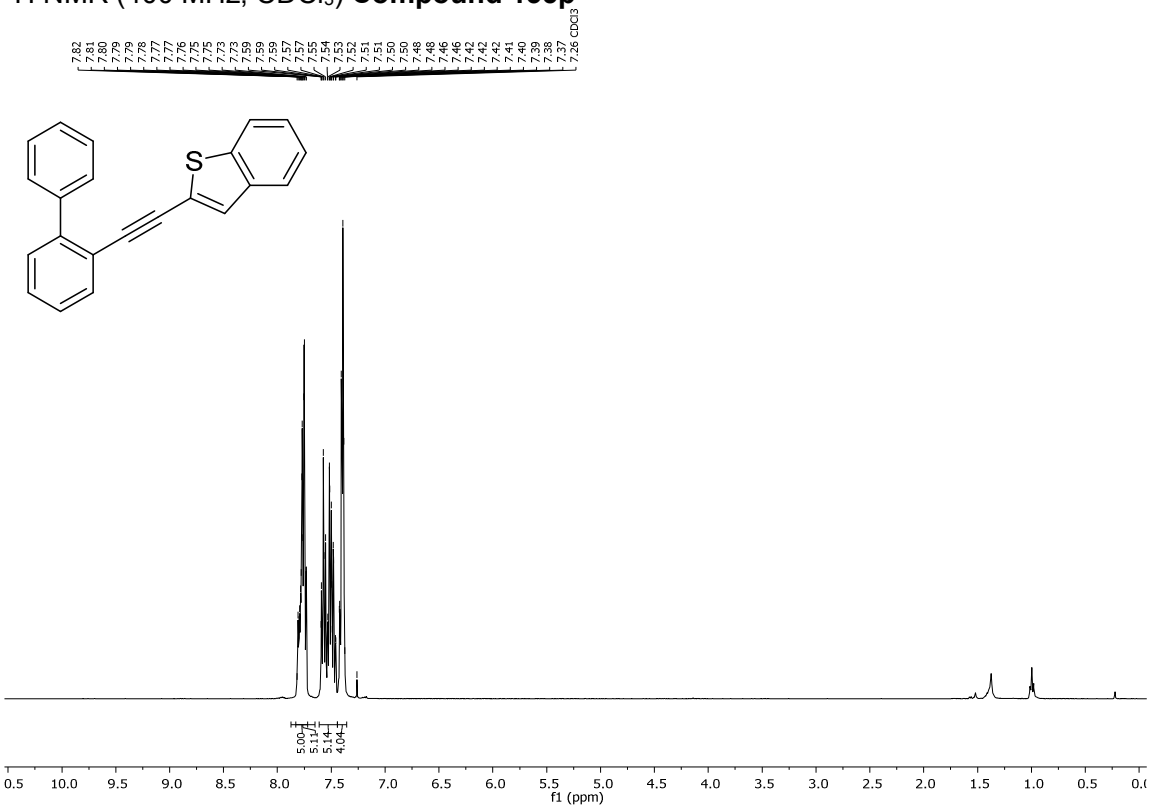
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135o**



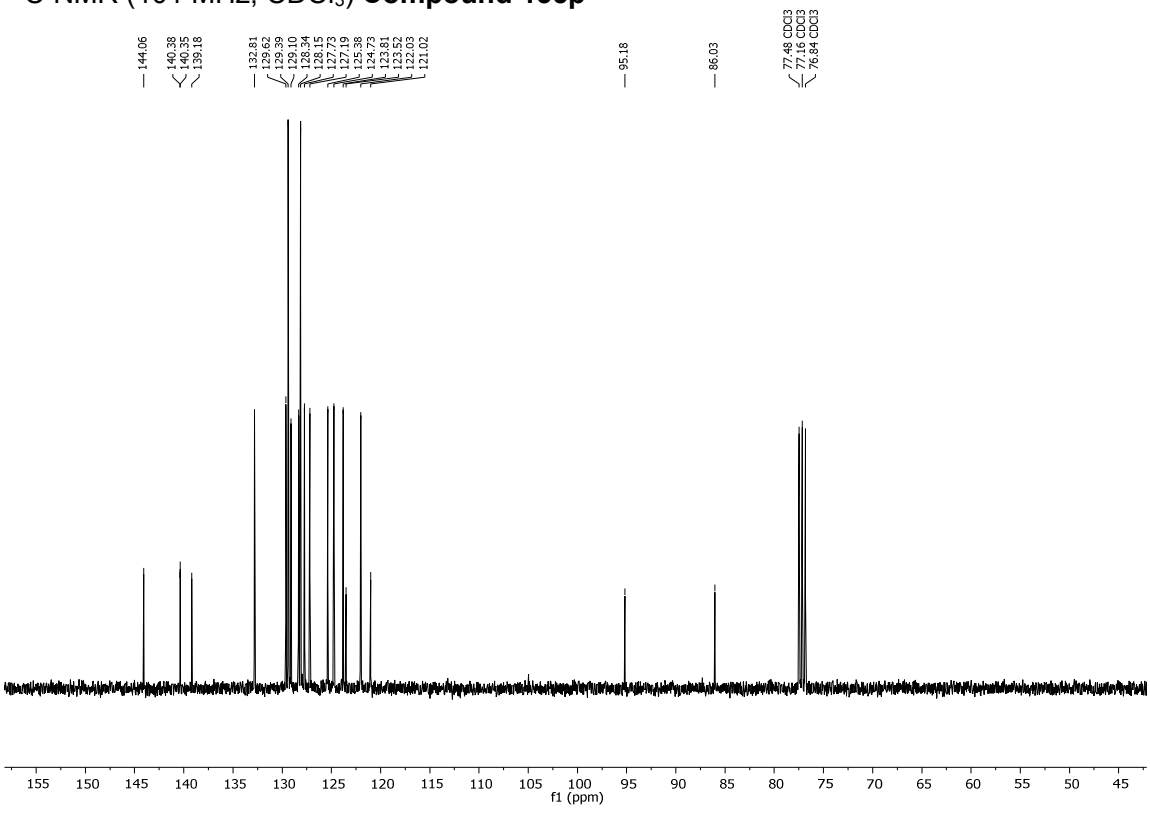
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 135o**



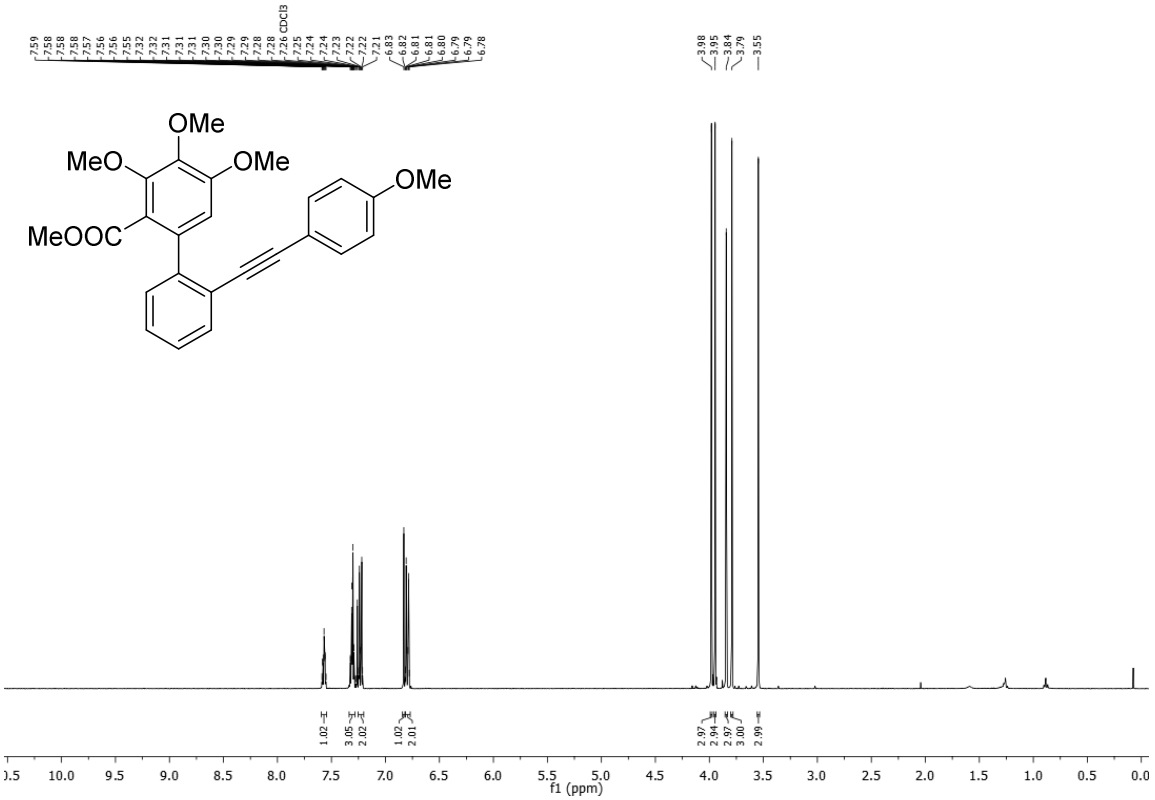
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135p**



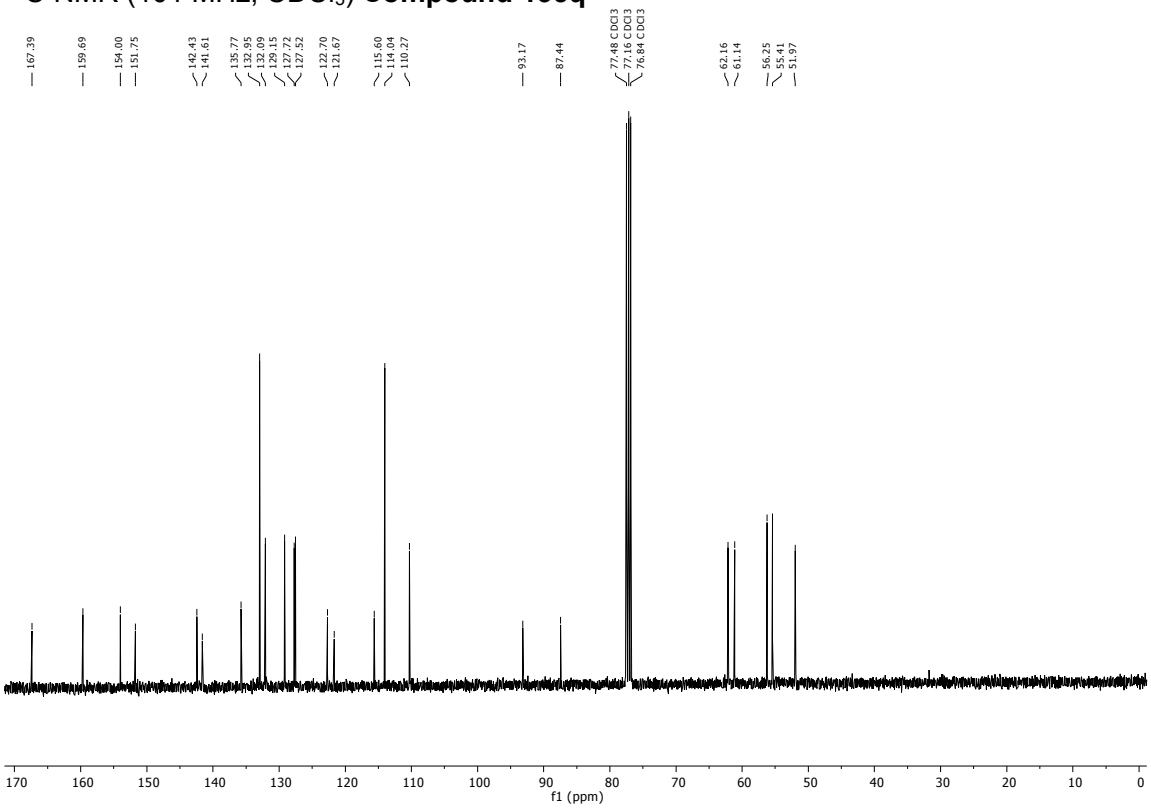
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 135p**



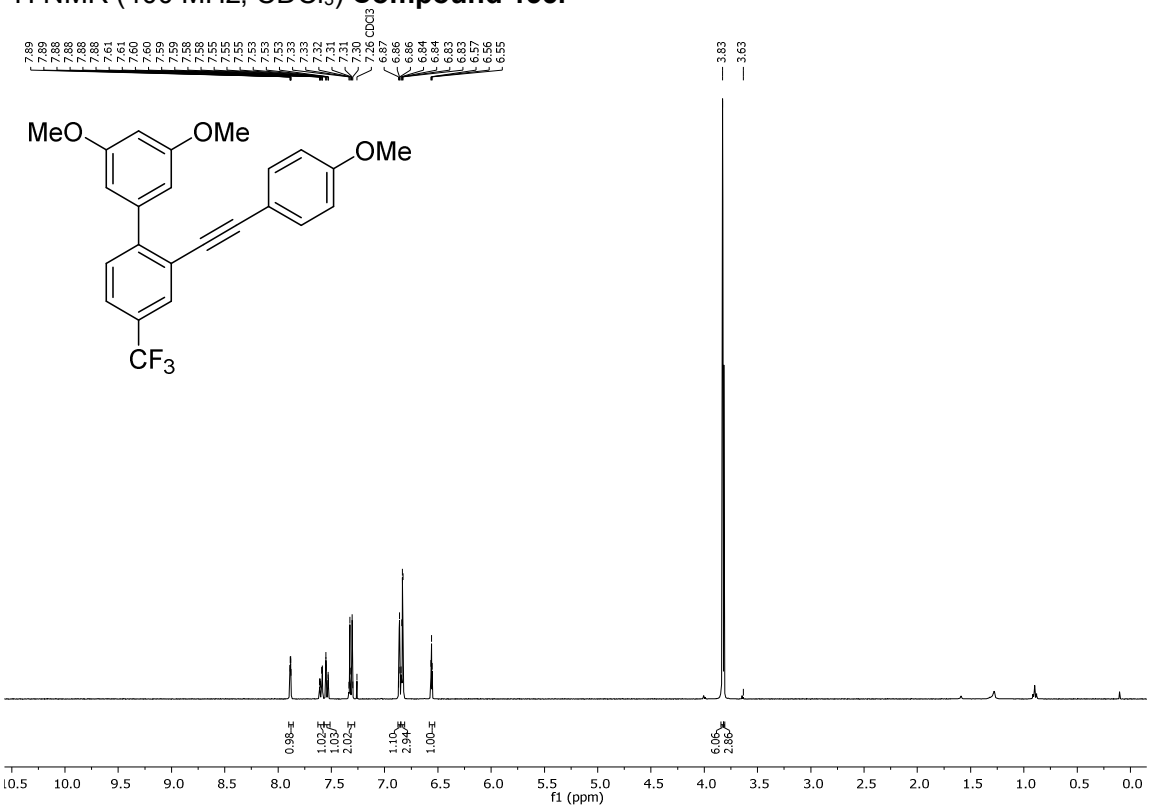
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135q**



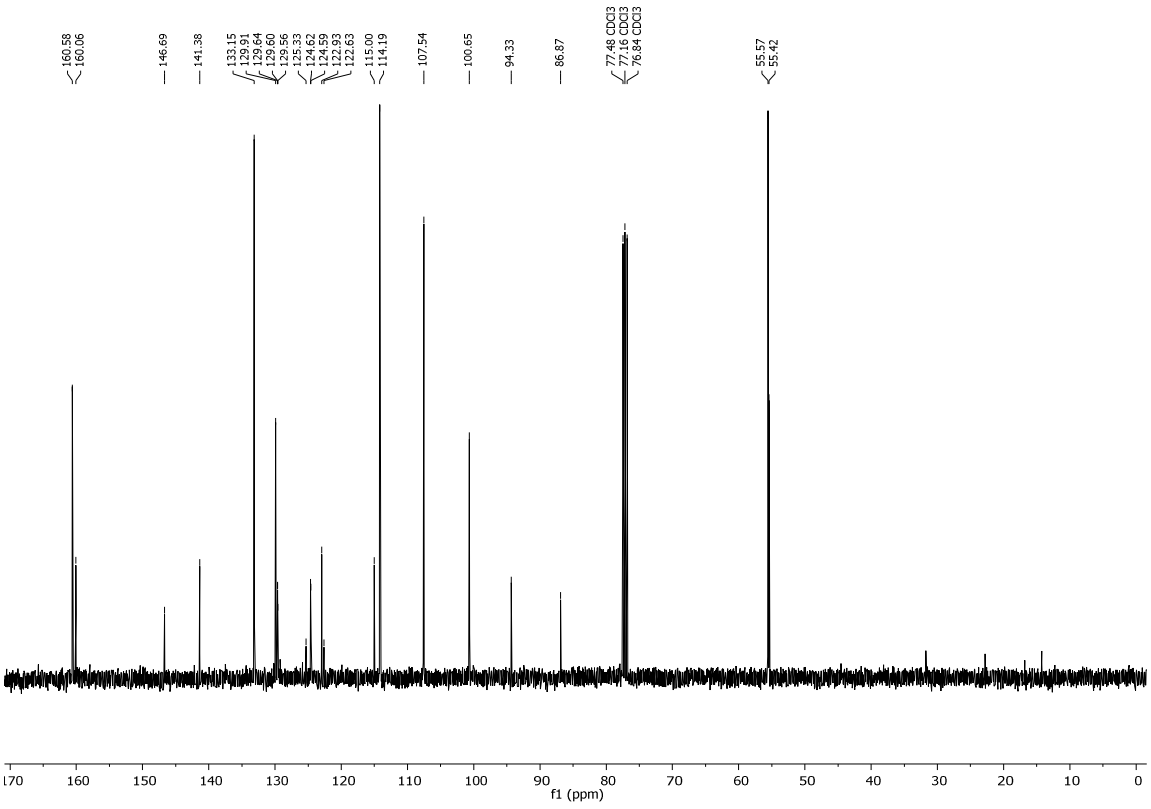
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 135q**



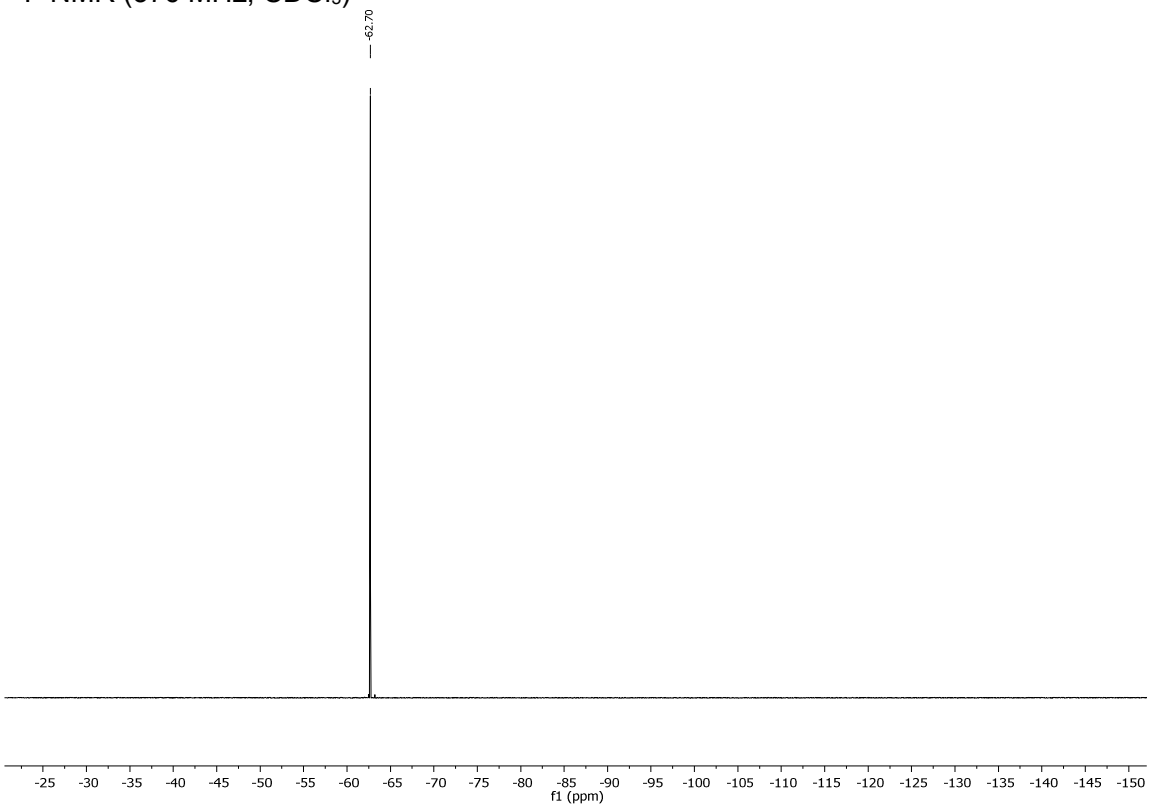
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135r**



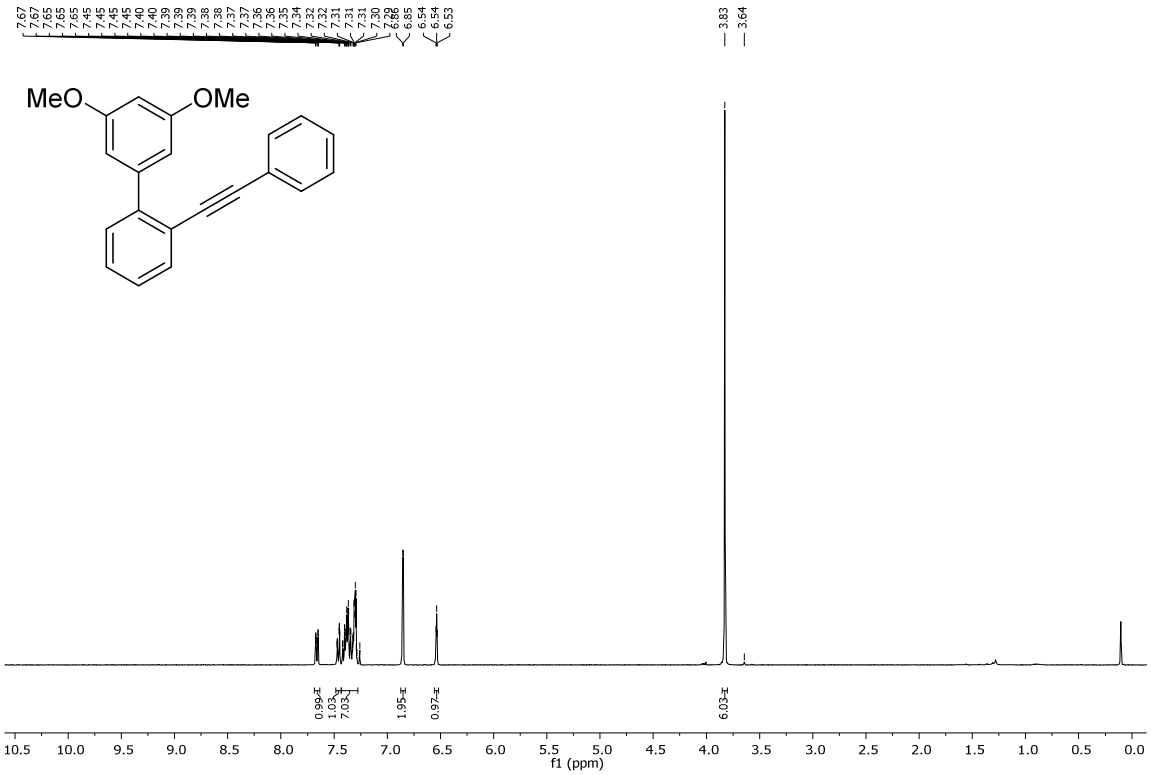
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 135r**



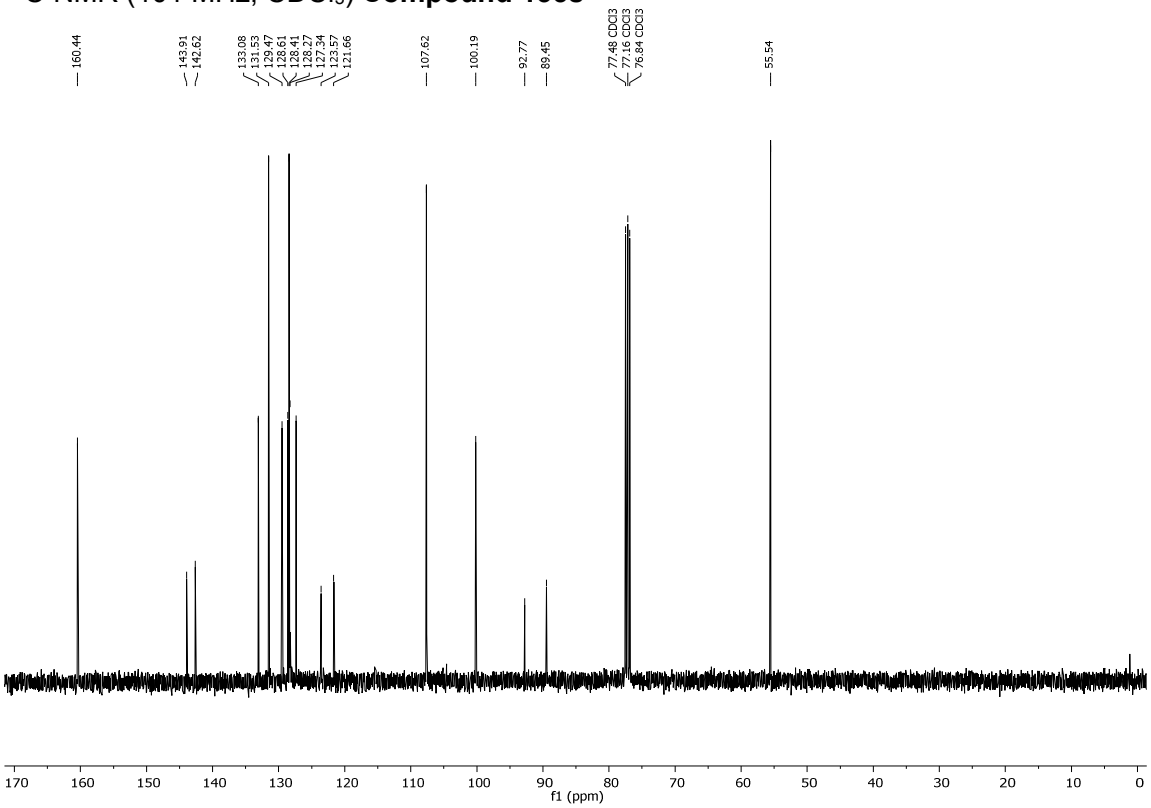
^{19}F NMR (376 MHz, $CDCl_3$)



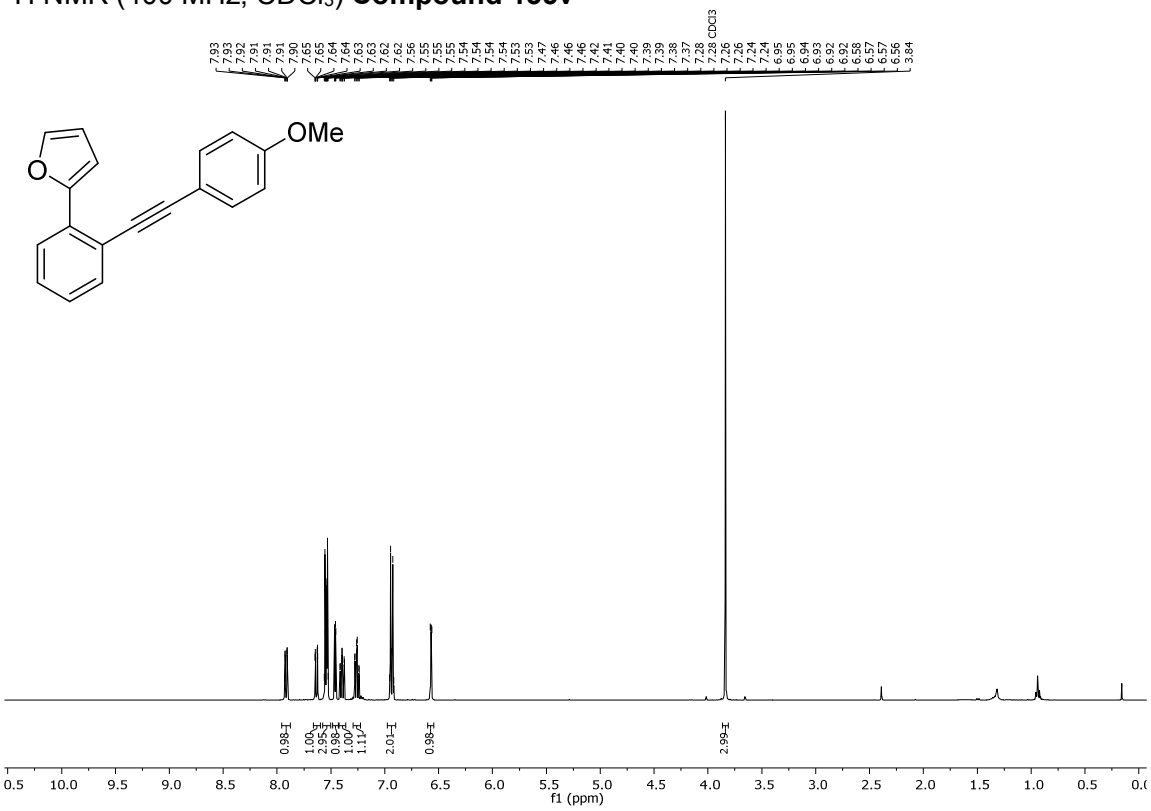
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135s**



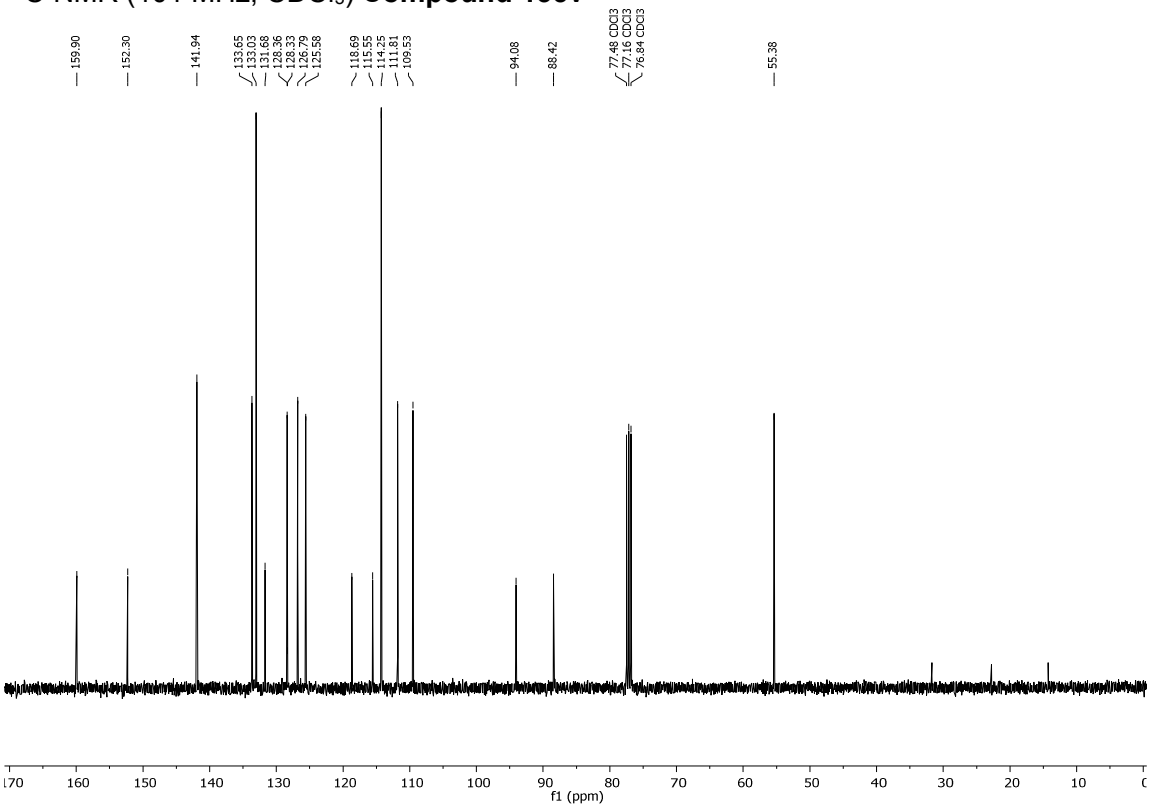
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 135s**



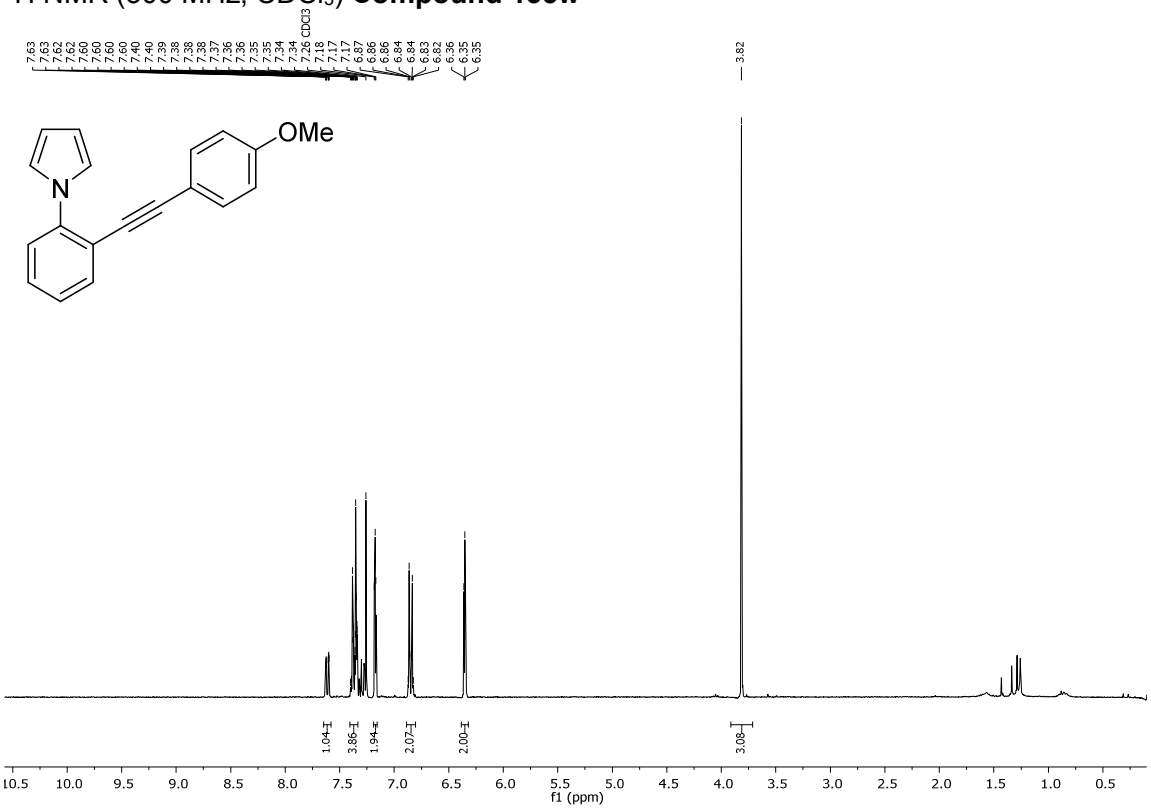
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135v**



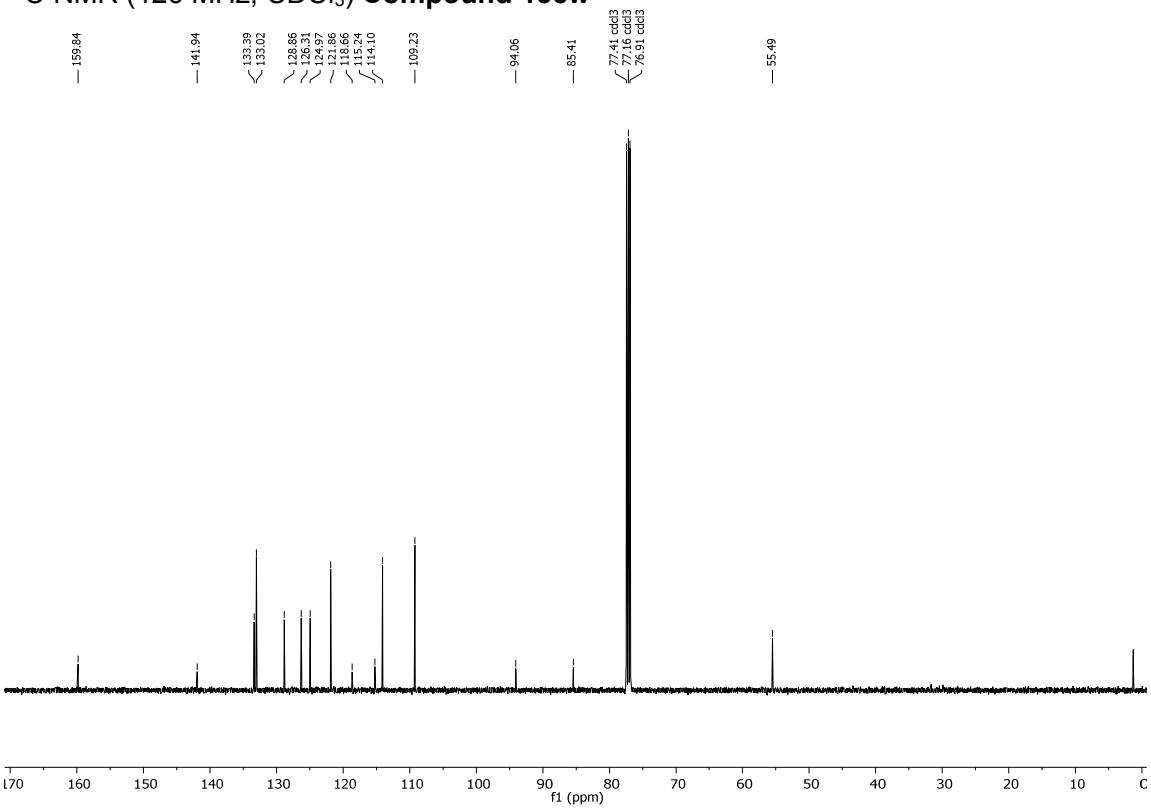
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 135v**



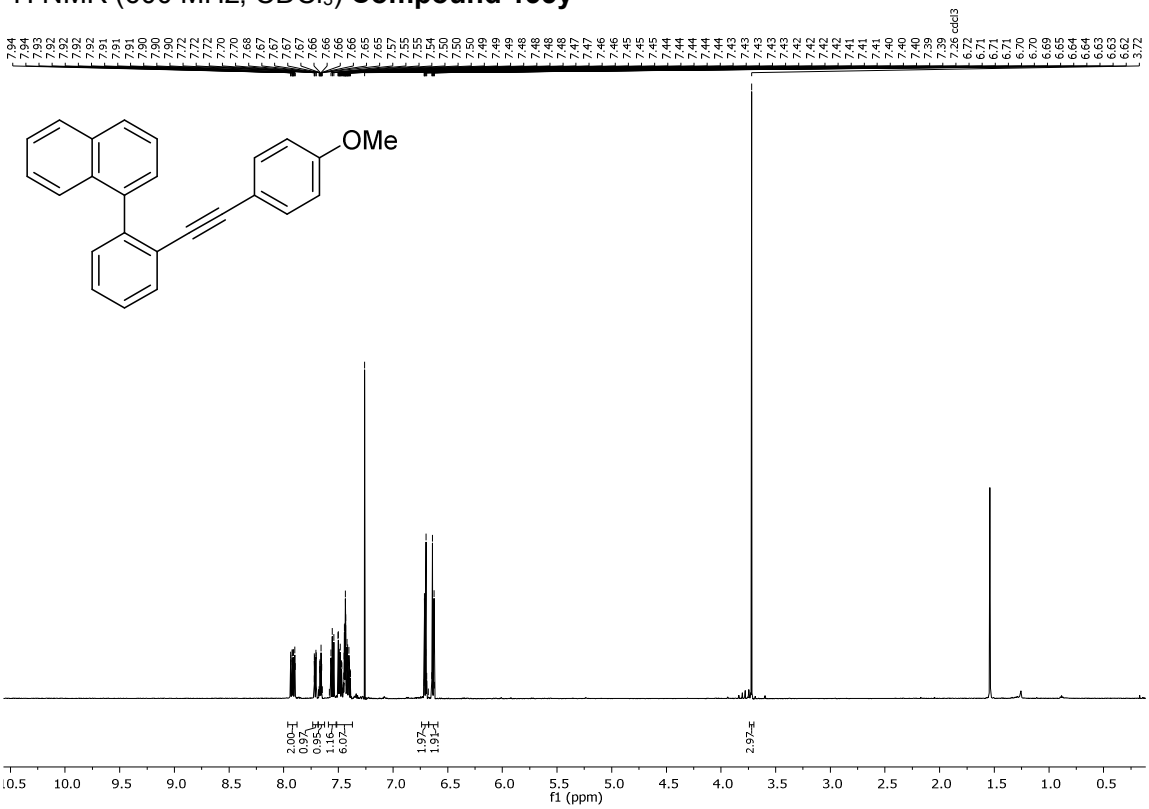
^{1}H NMR (300 MHz, $CDCl_3$) **Compound 135w**



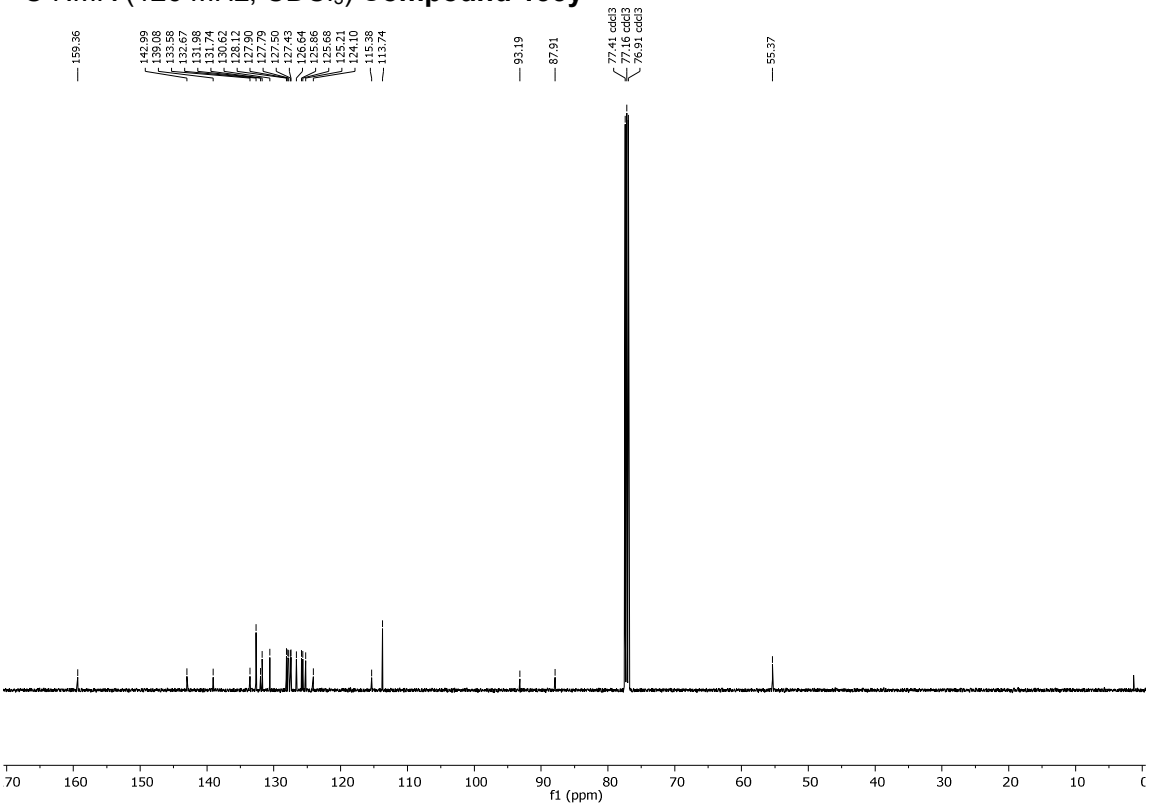
^{13}C NMR (126 MHz, $CDCl_3$) **Compound 135w**



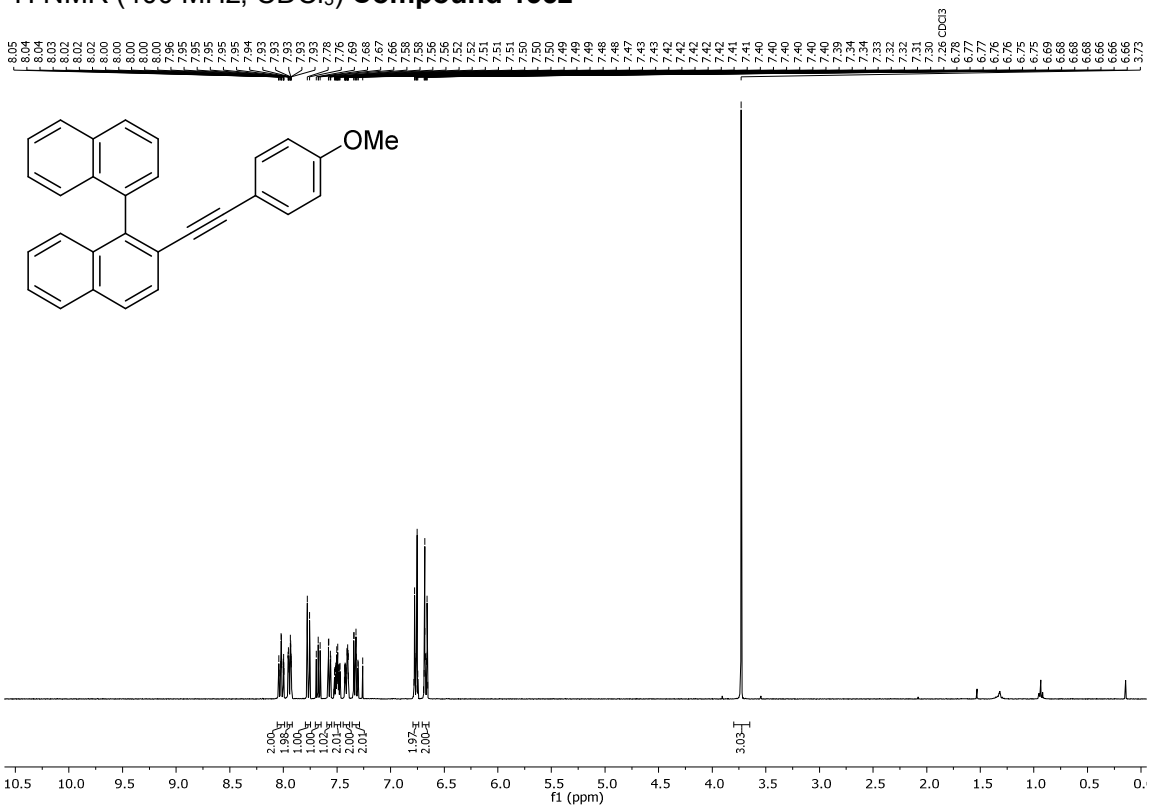
^{1}H NMR (600 MHz, $CDCl_3$) **Compound 135y**



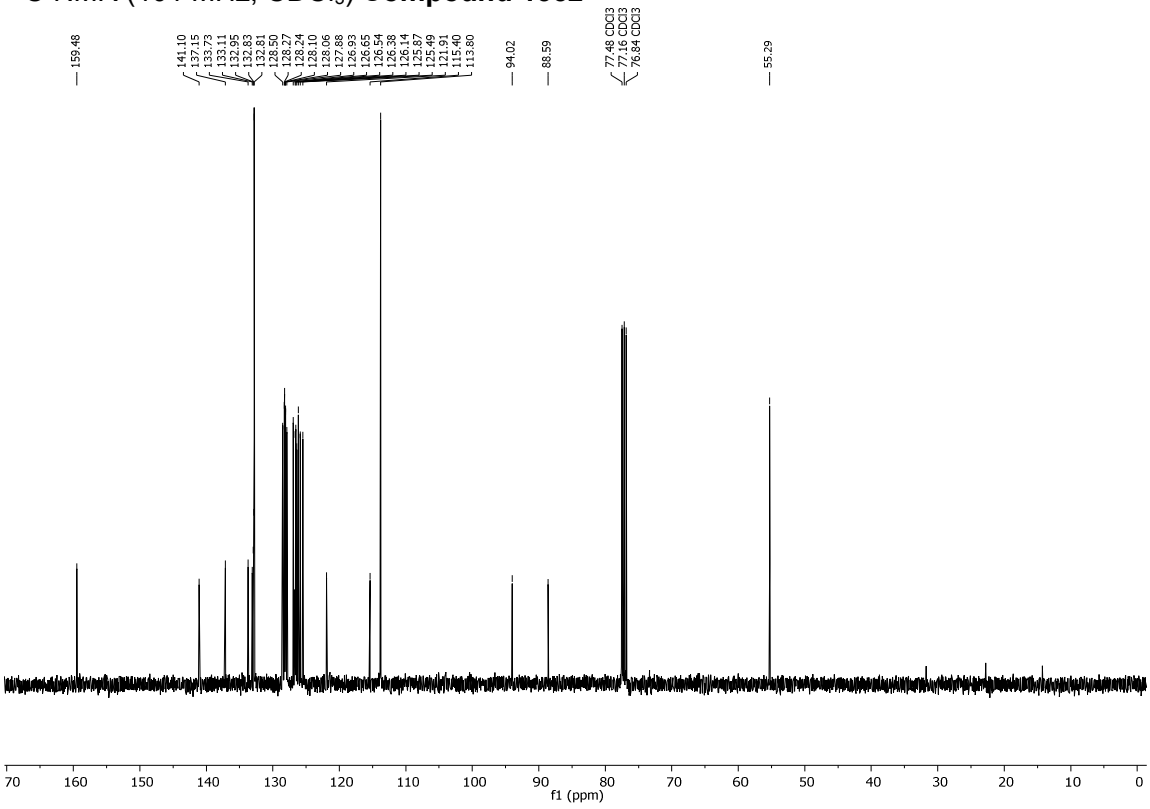
^{13}C NMR (126 MHz, $CDCl_3$) **Compound 135y**



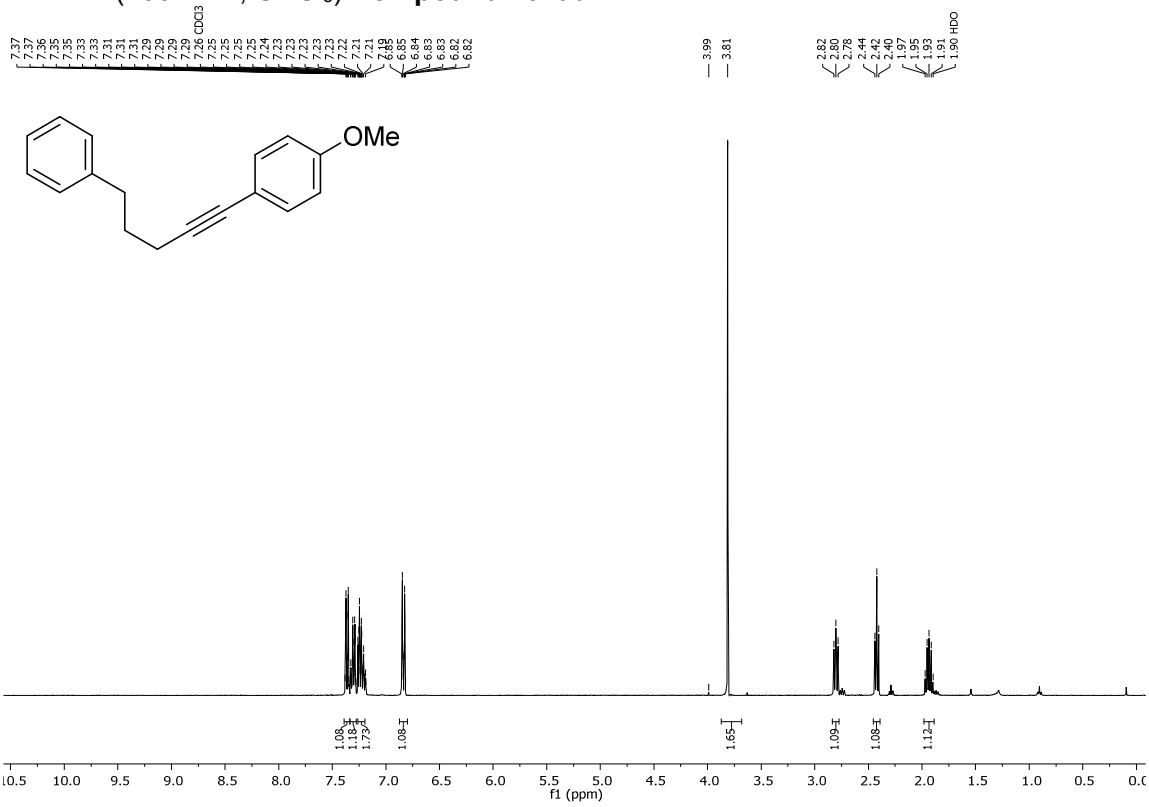
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135z**



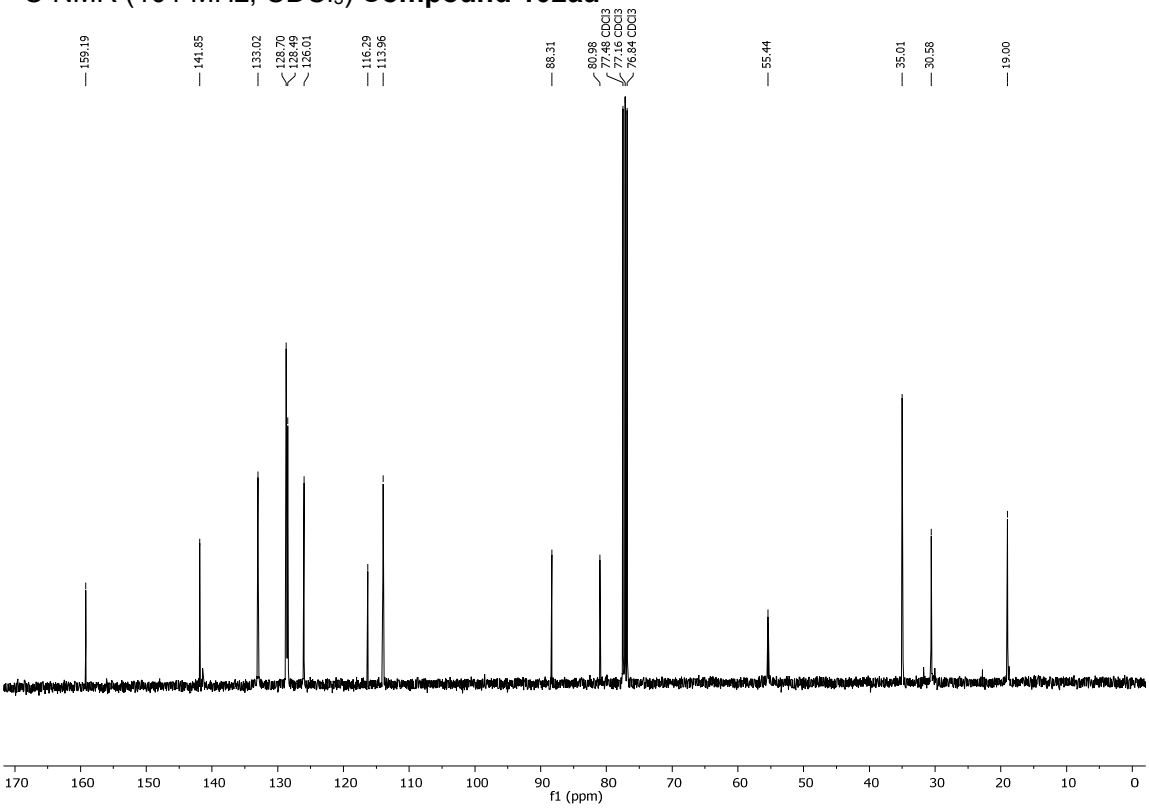
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 135z**



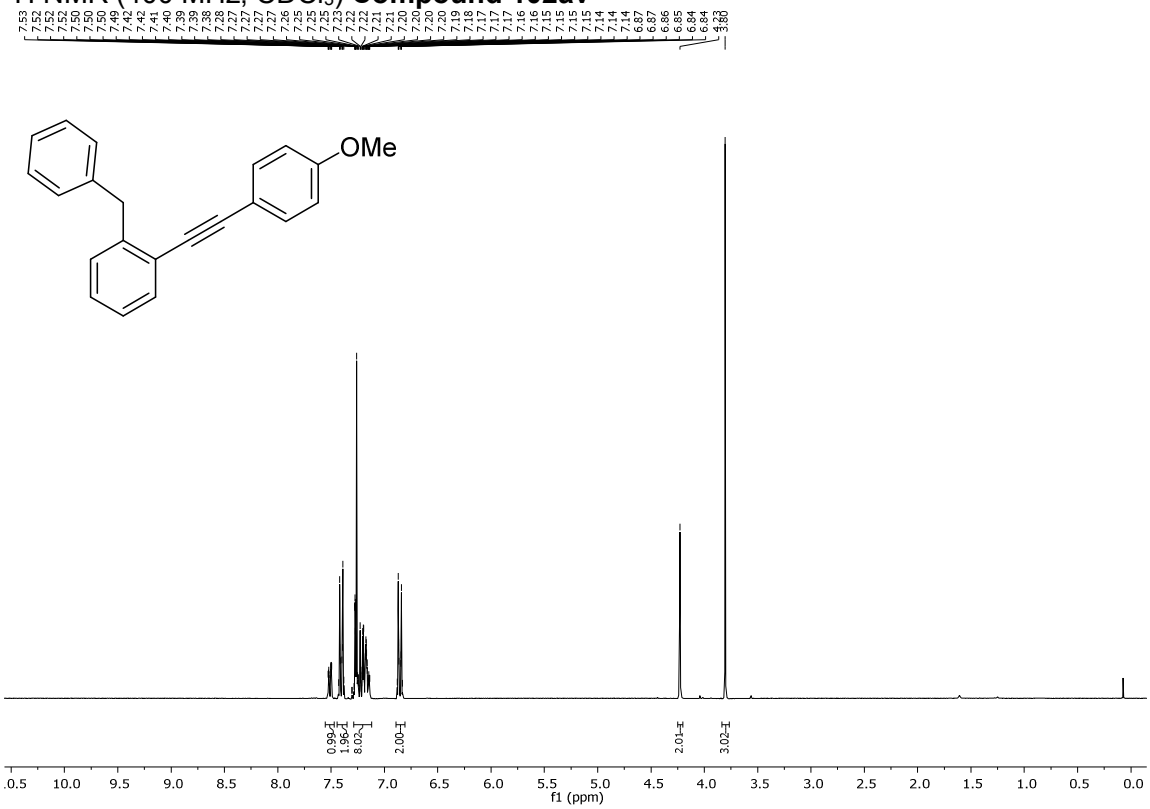
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 102au**



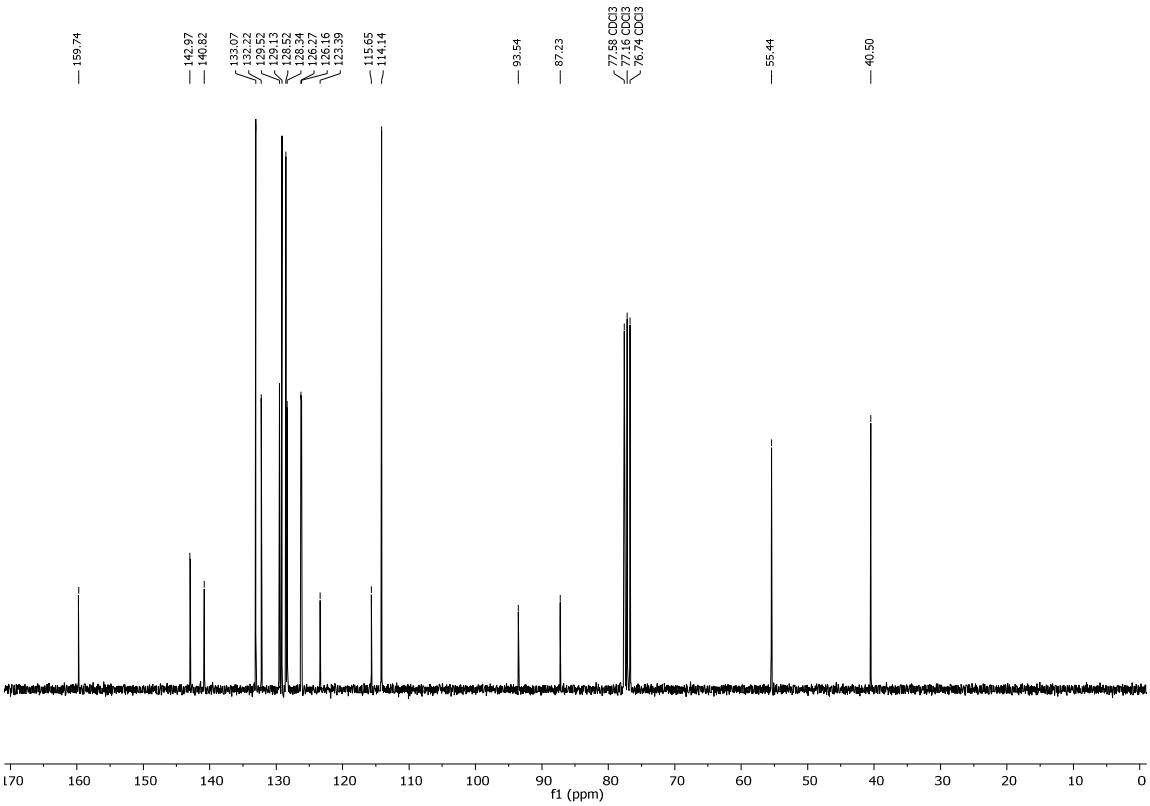
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 102au**



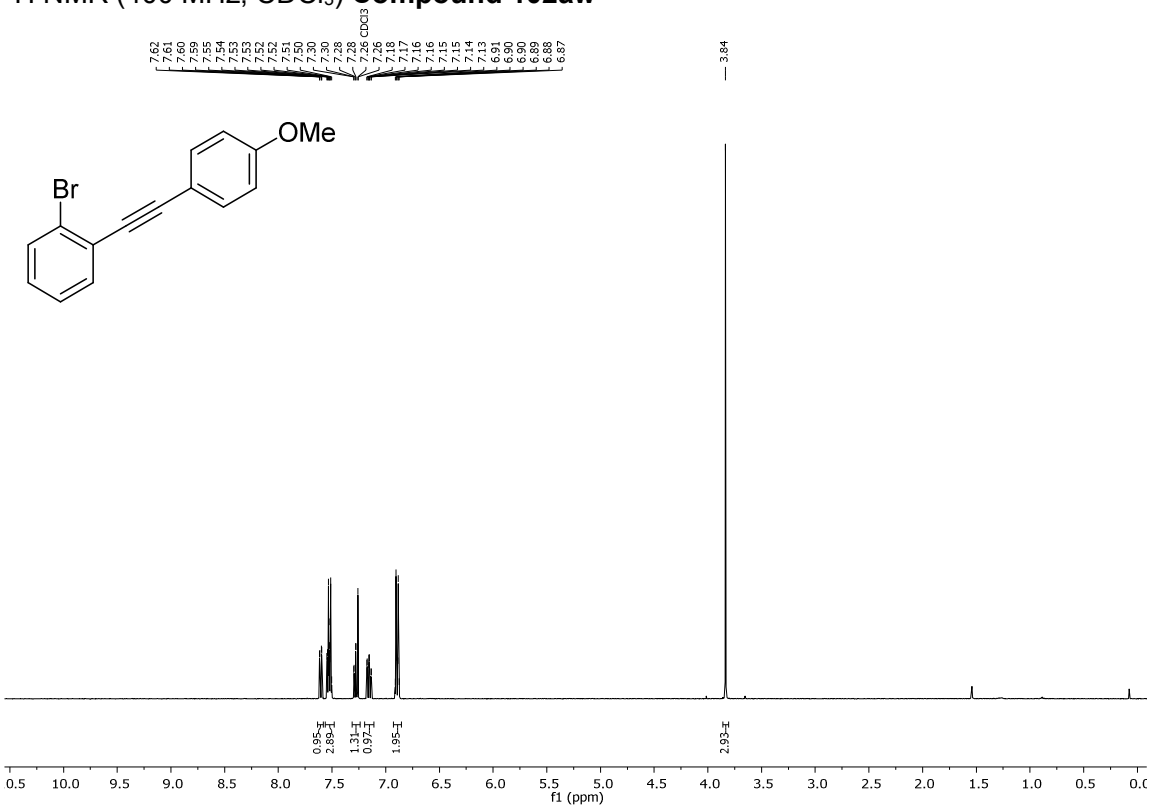
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 102av**



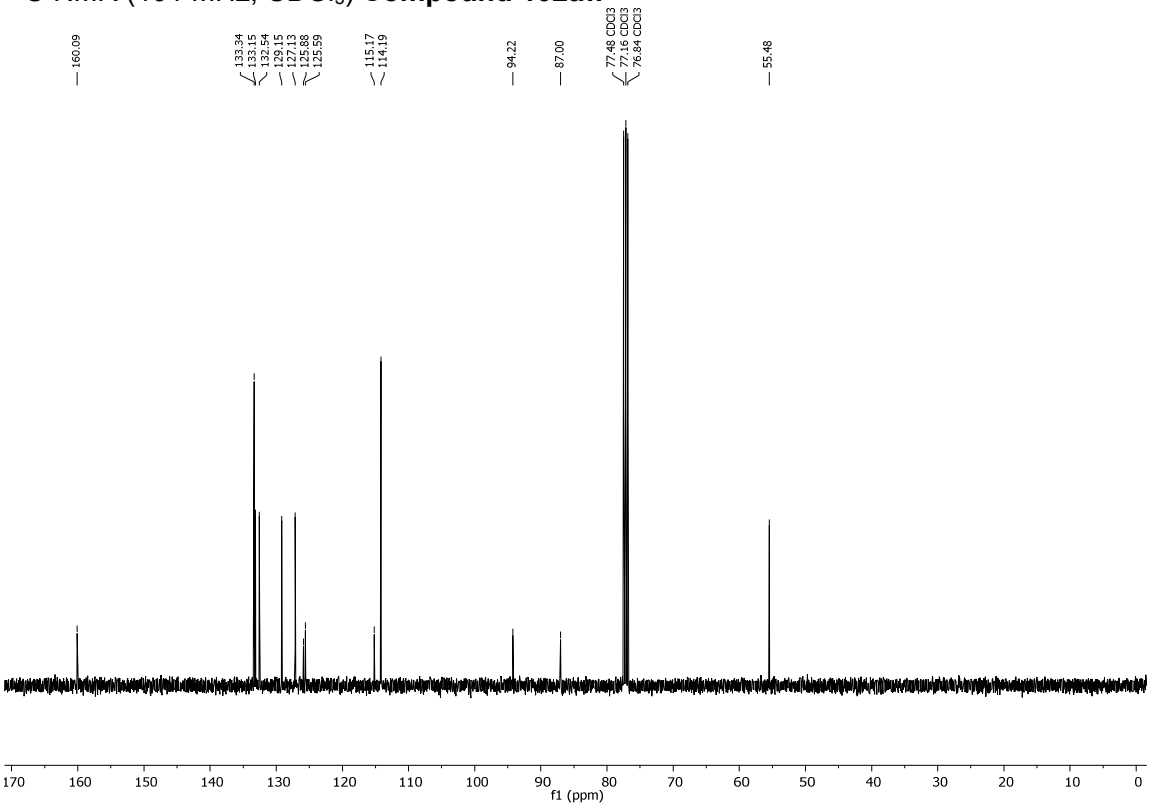
^{13}C NMR (75 MHz, $CDCl_3$) **Compound 102av**



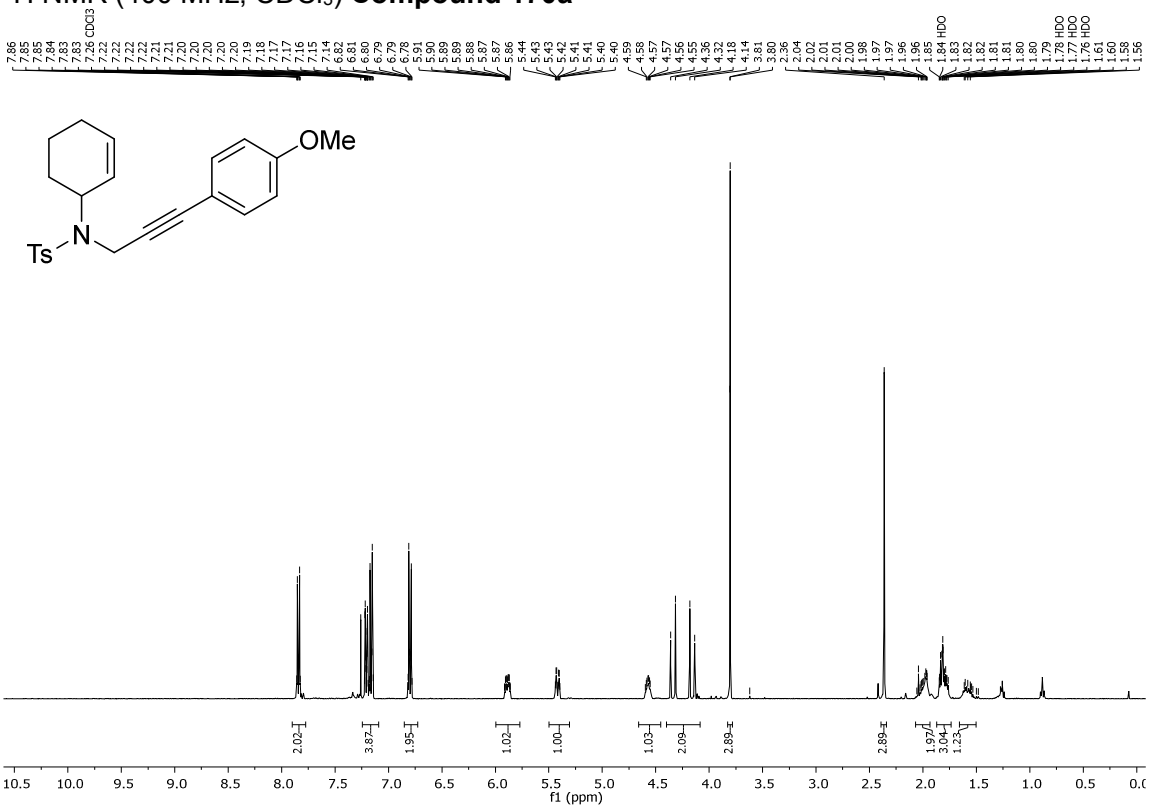
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 102aw**



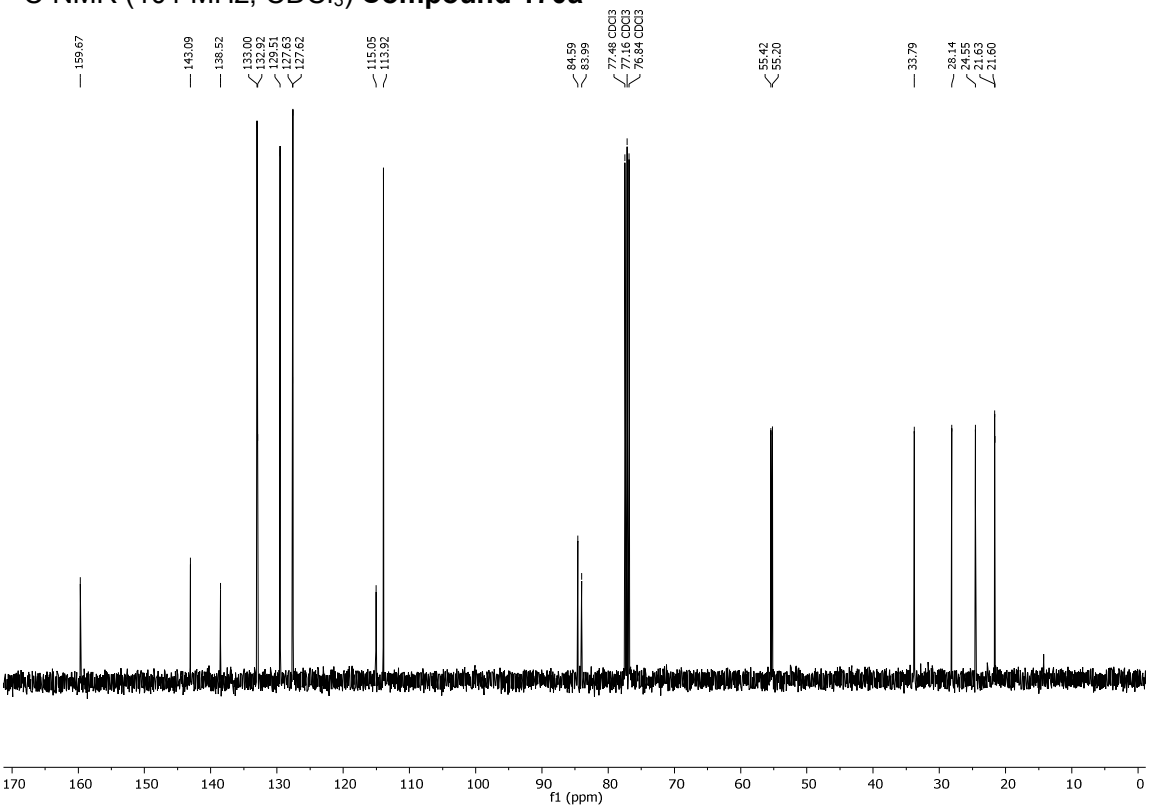
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 102aw**



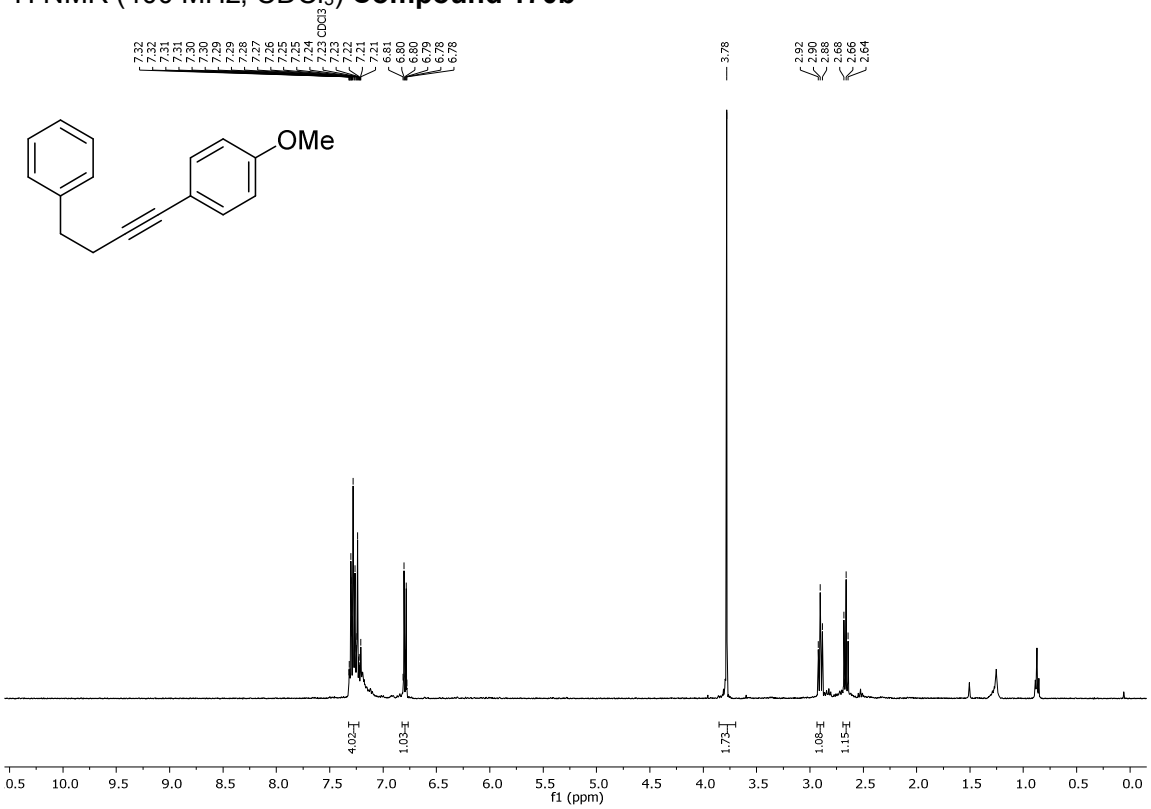
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 170a**



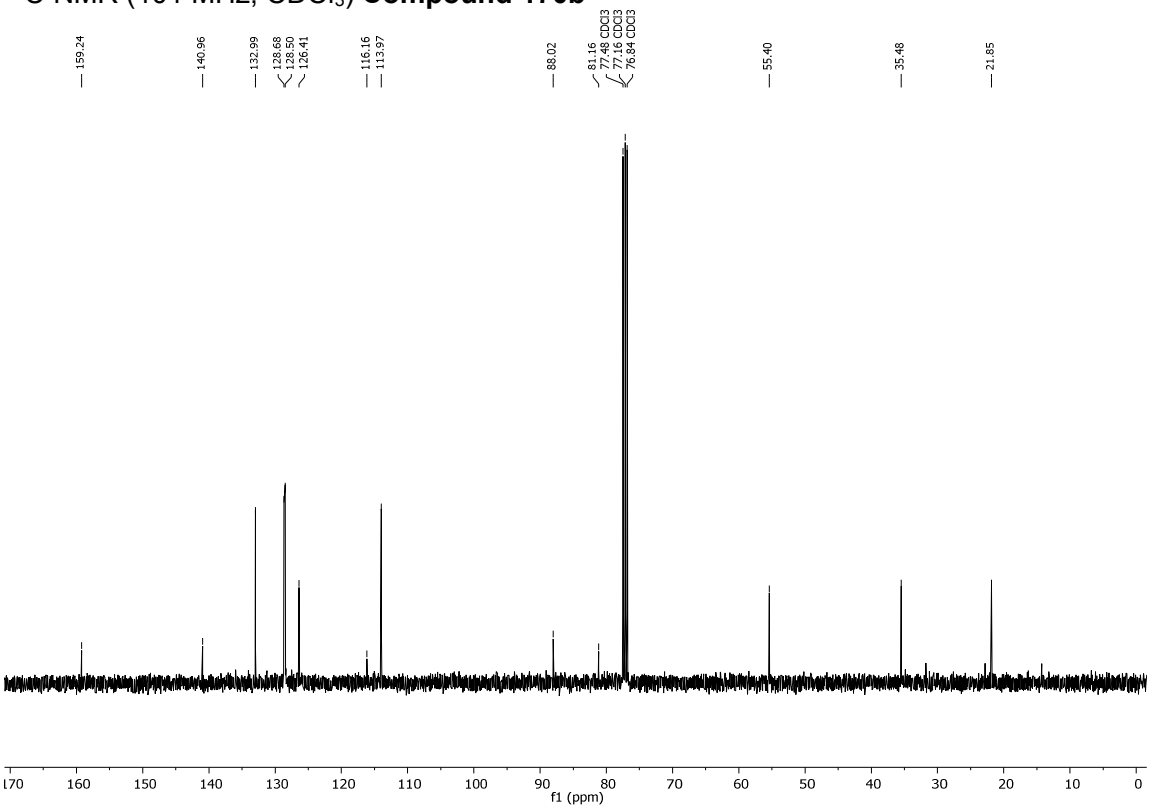
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 170a**



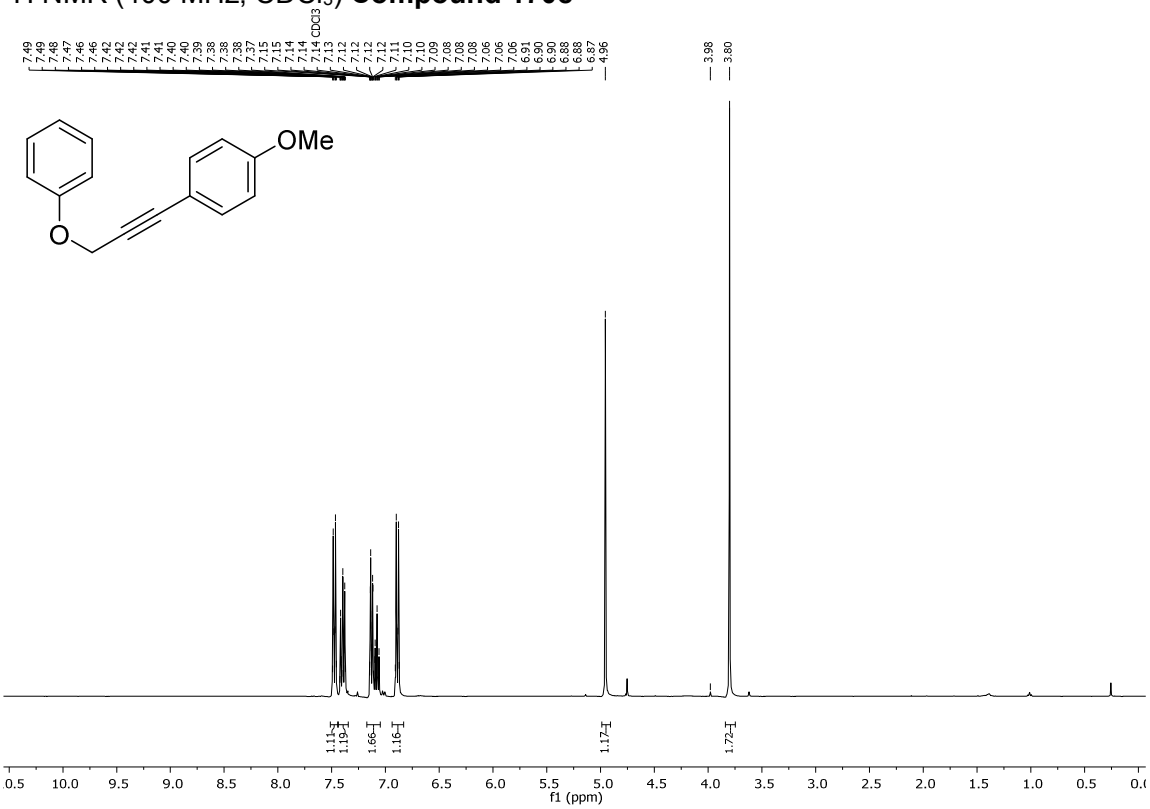
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 170b**



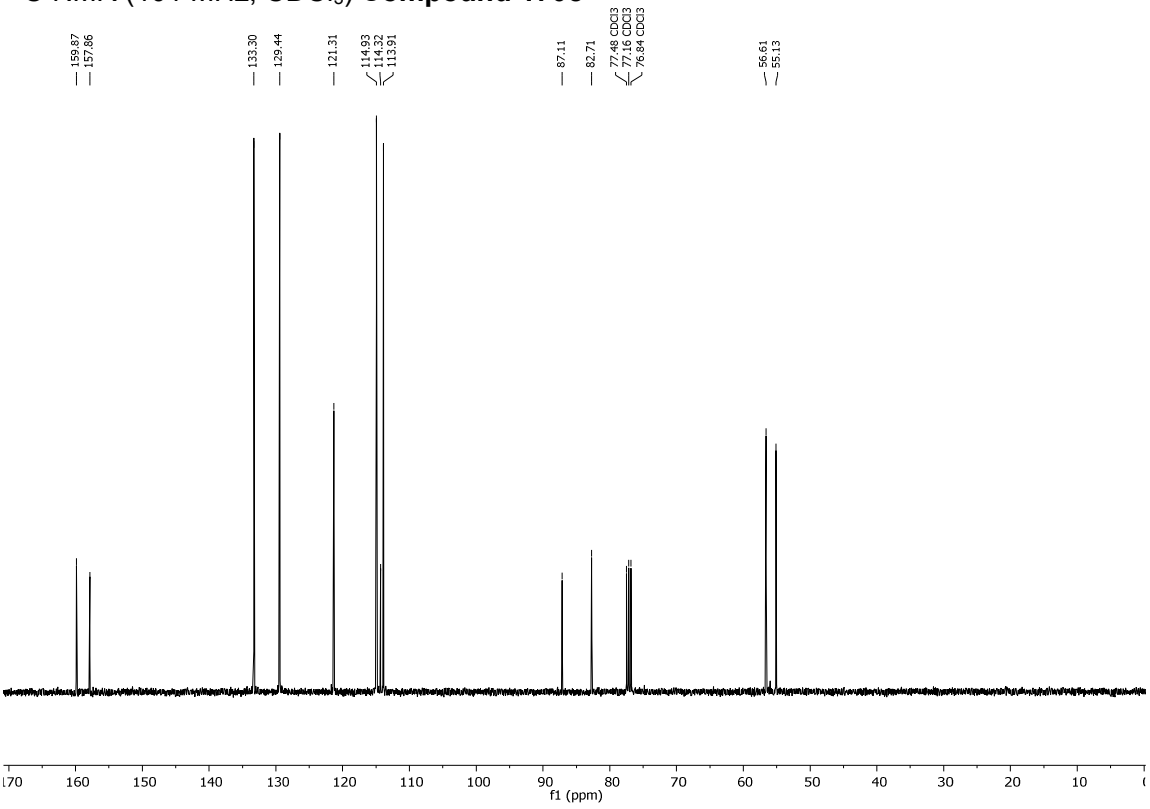
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 170b**



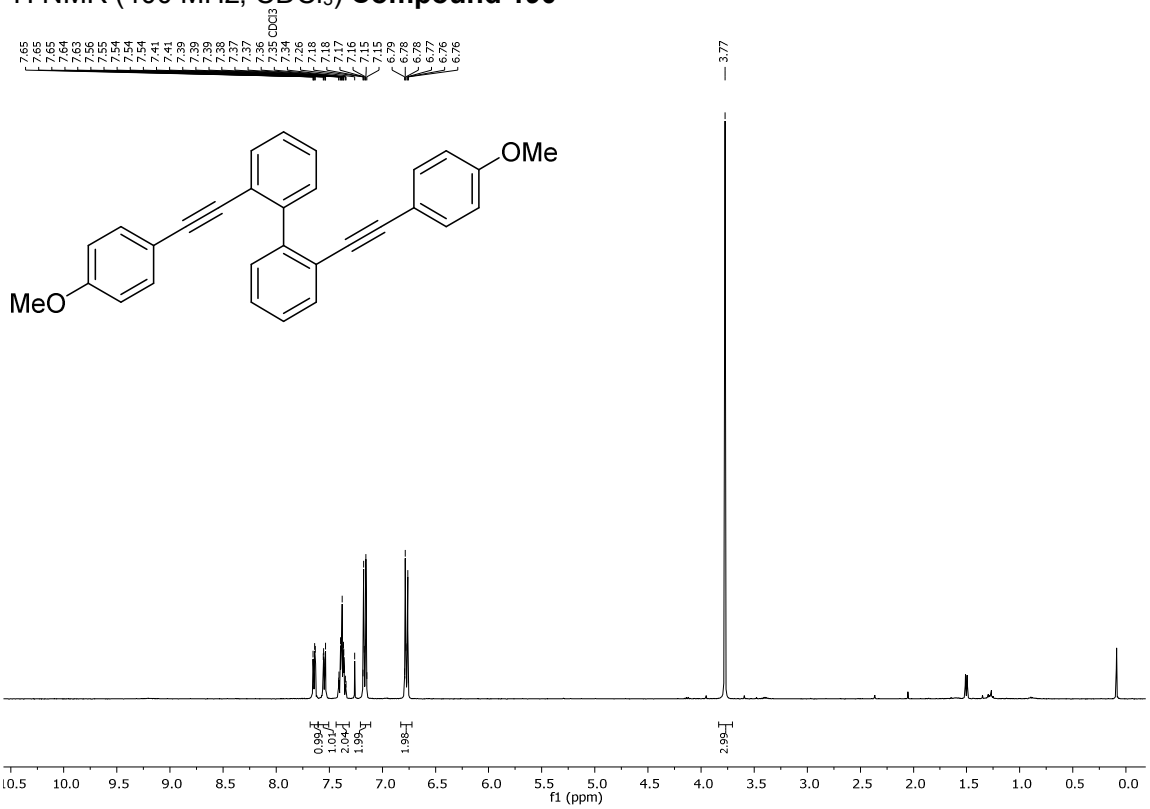
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 170c**



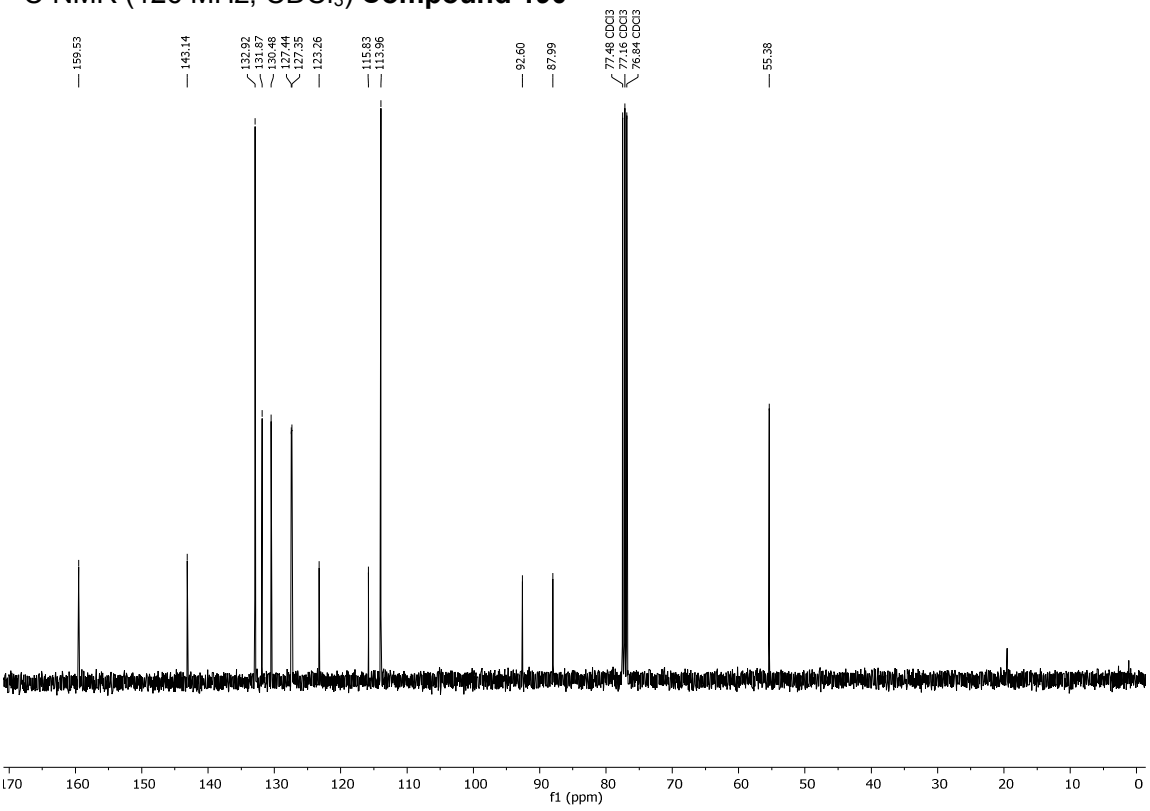
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 170c**



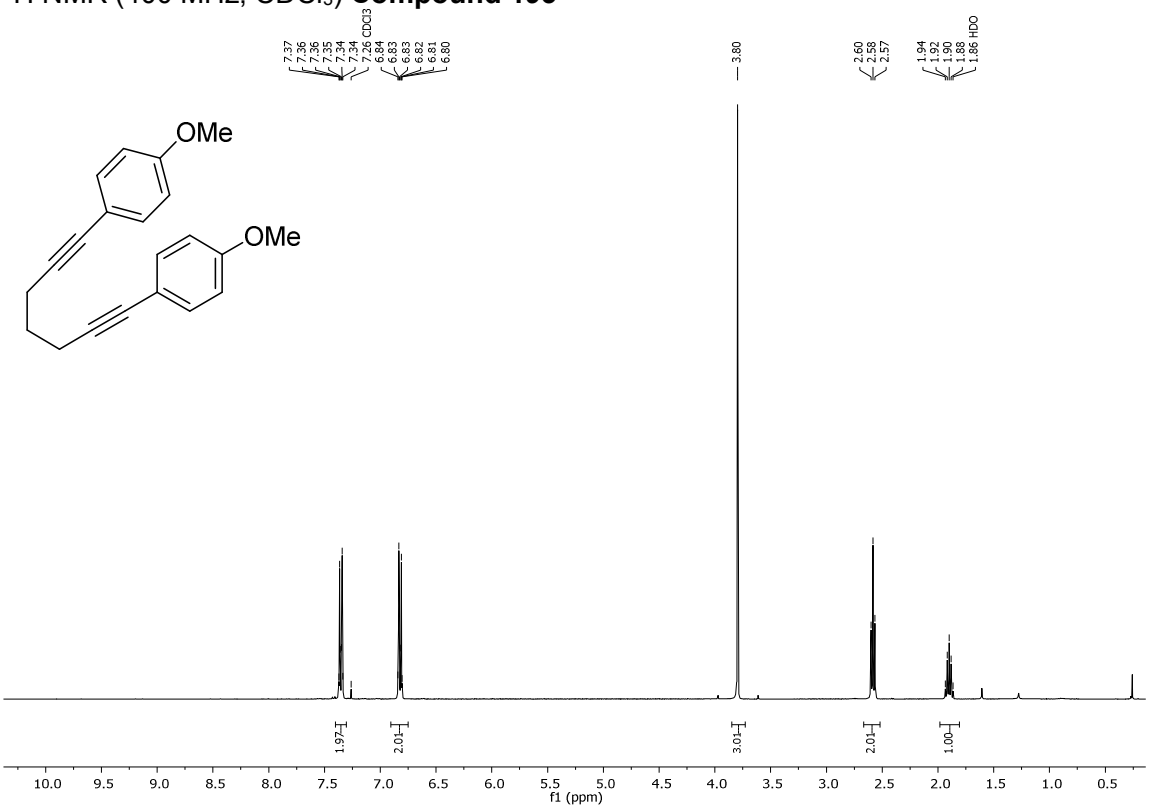
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 190**



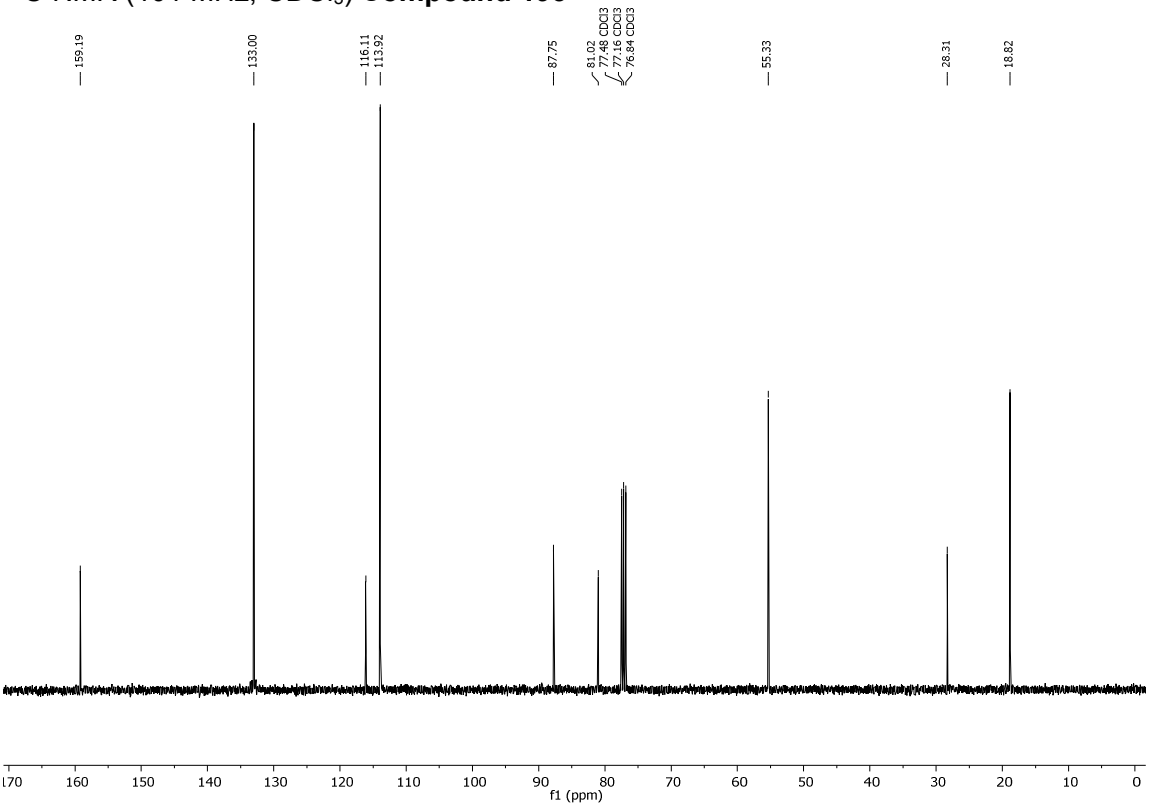
^{13}C NMR (126 MHz, $CDCl_3$) **Compound 190**



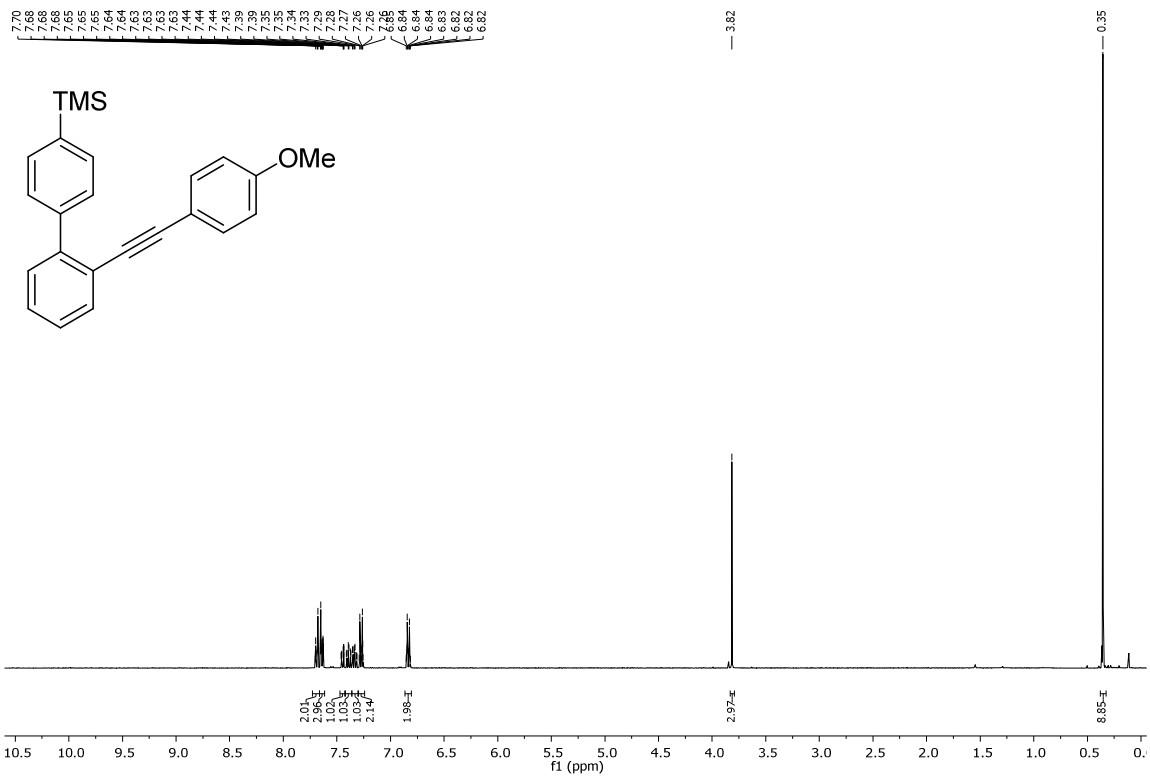
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 193**



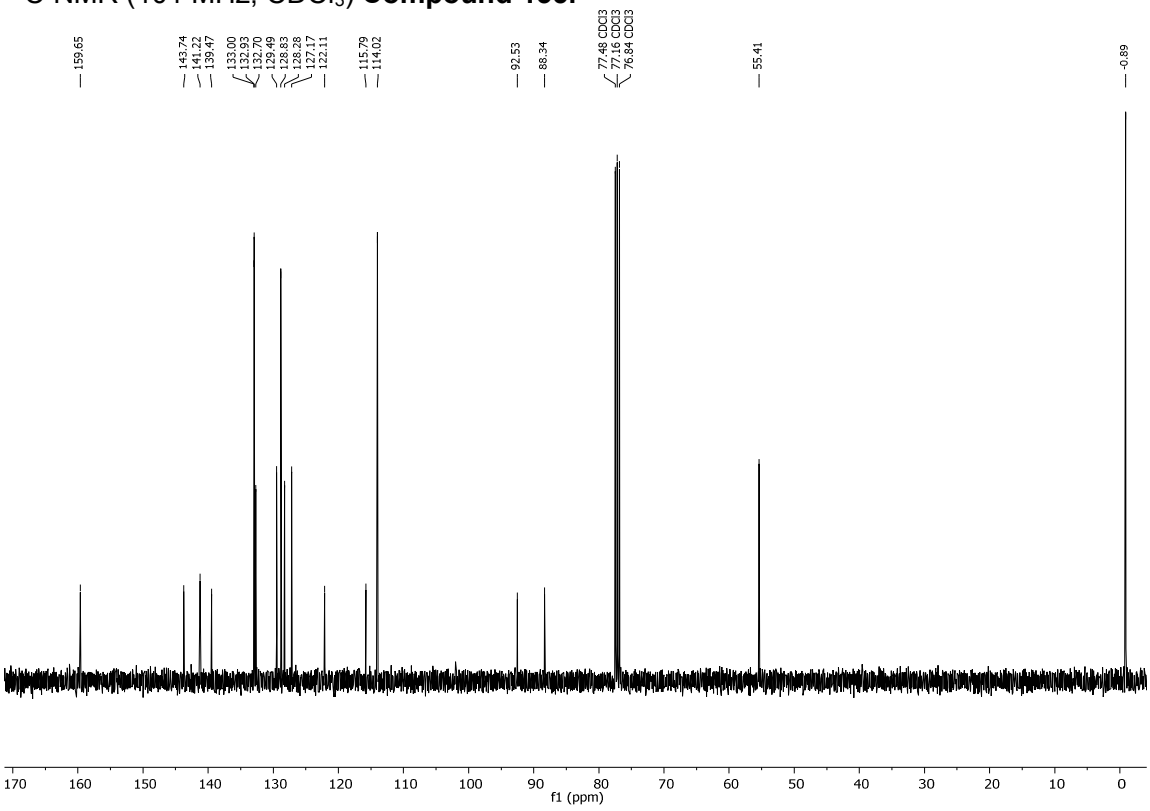
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 193**



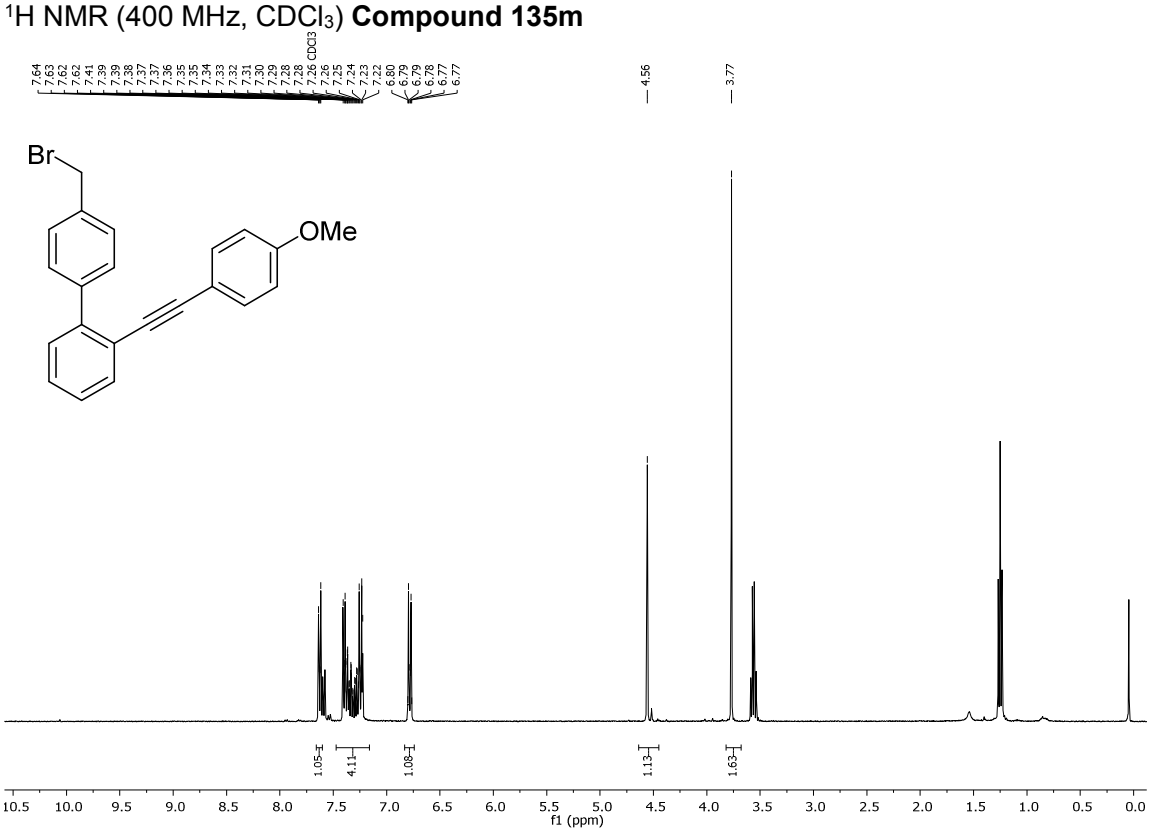
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135l**



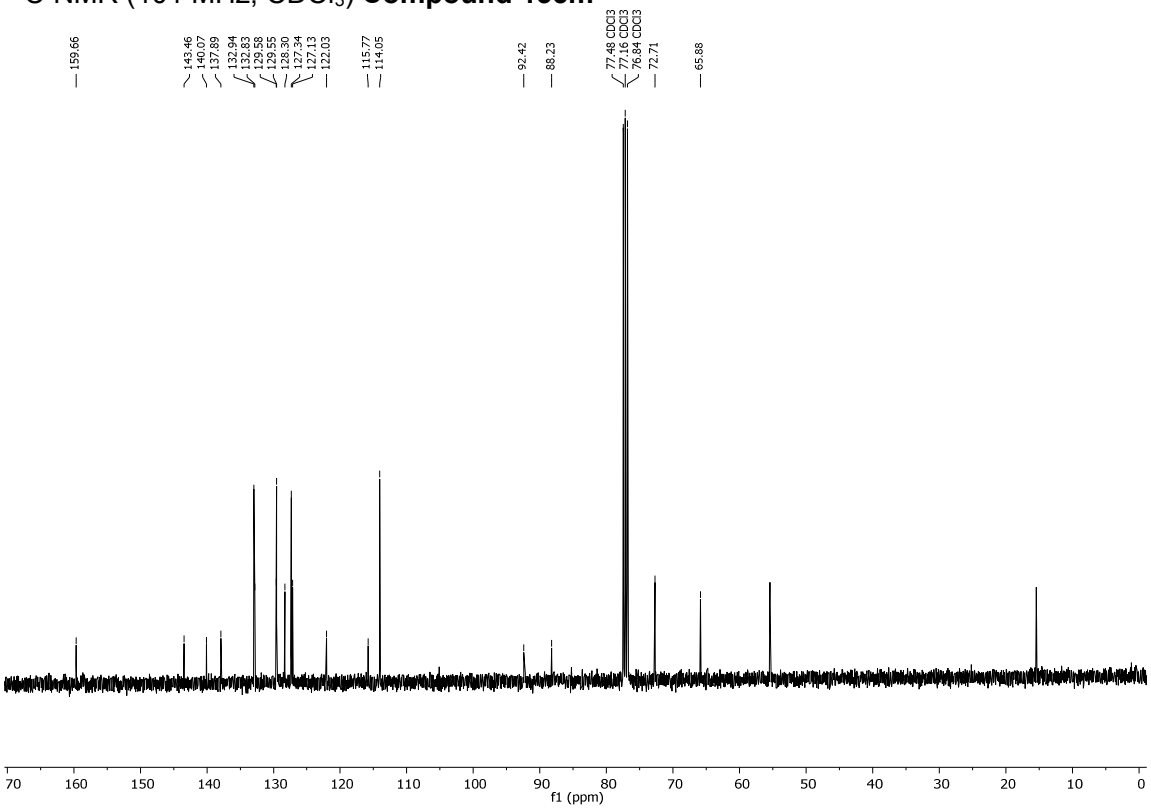
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 135l**



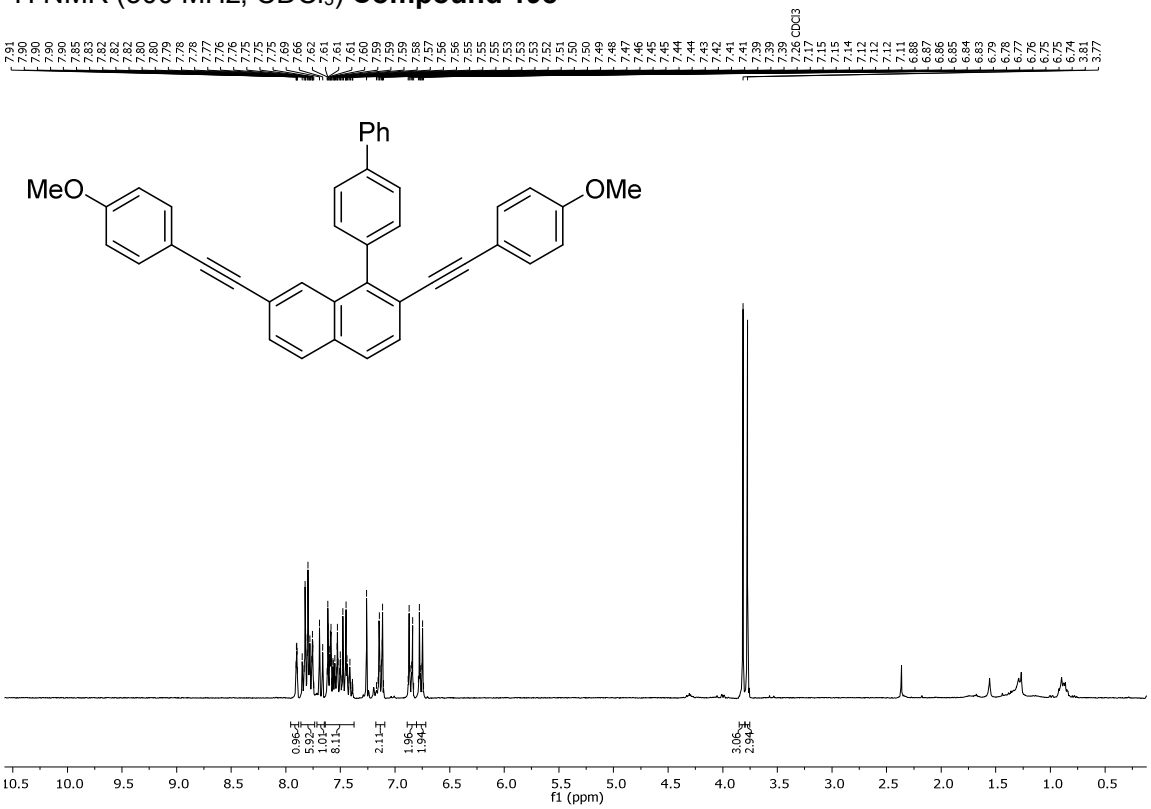
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135m**



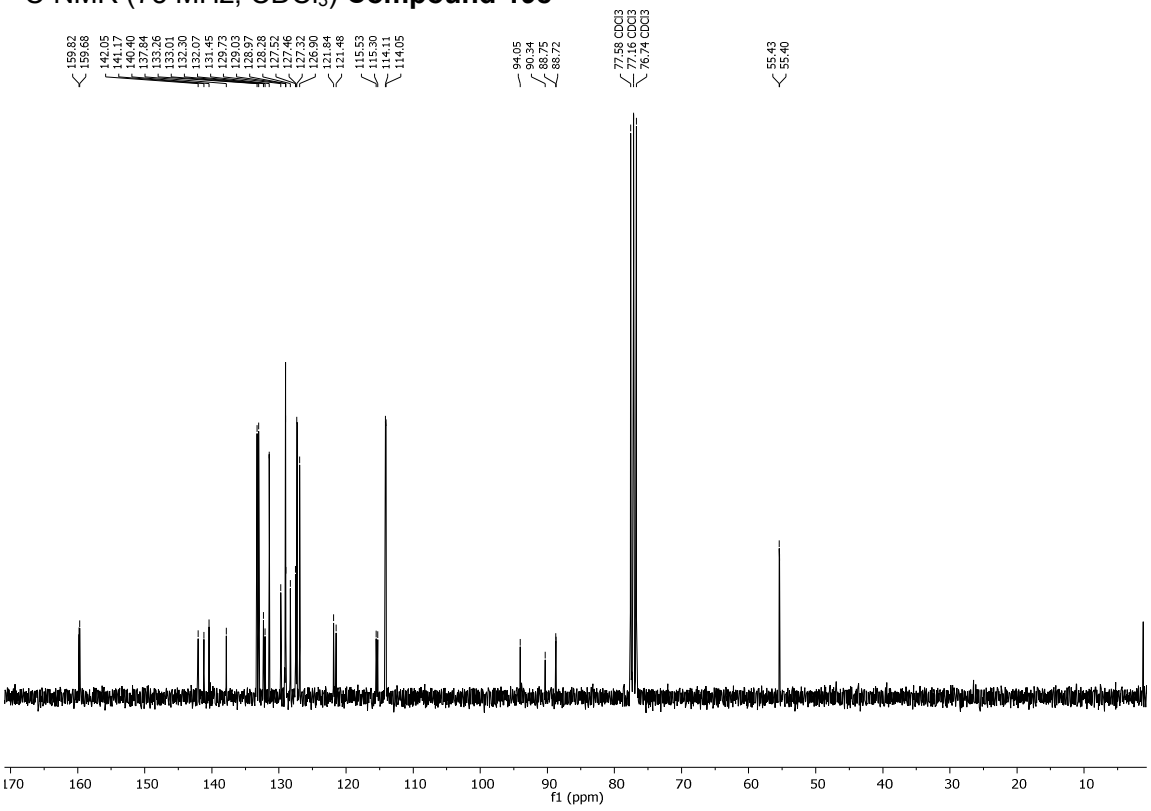
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 135m**



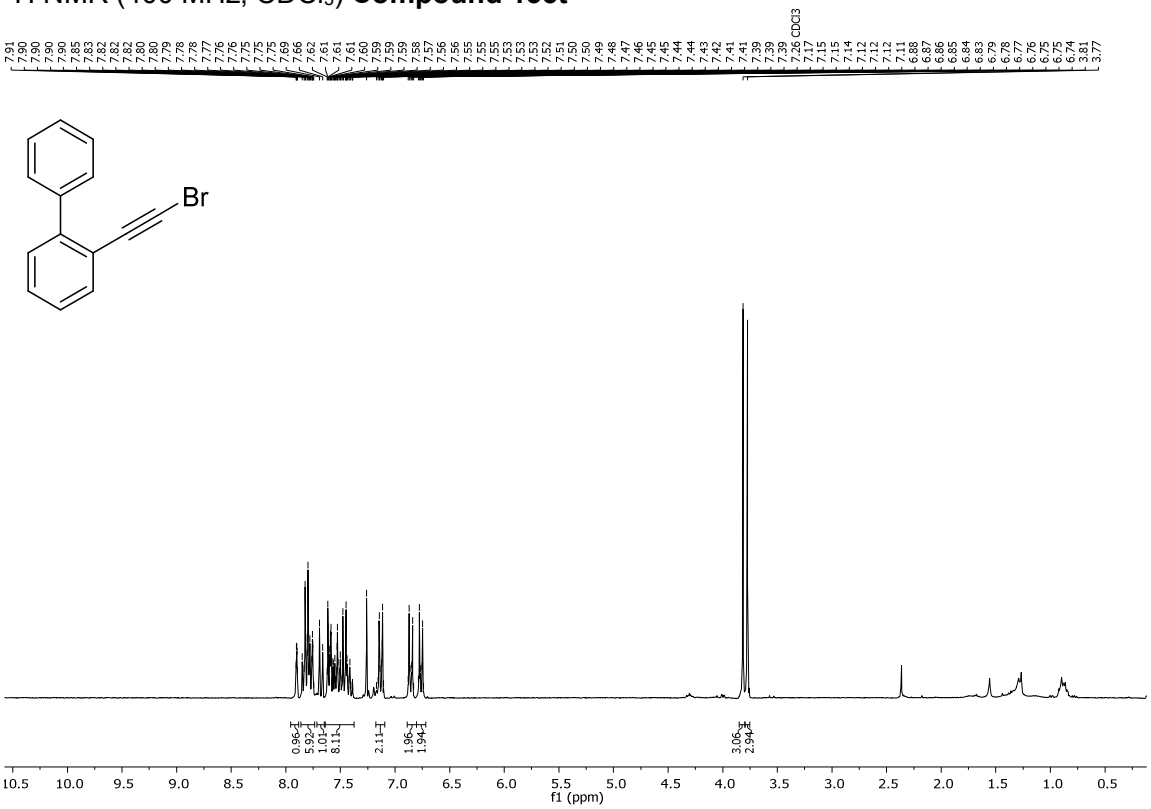
^{1}H NMR (300 MHz, $CDCl_3$) **Compound 198**



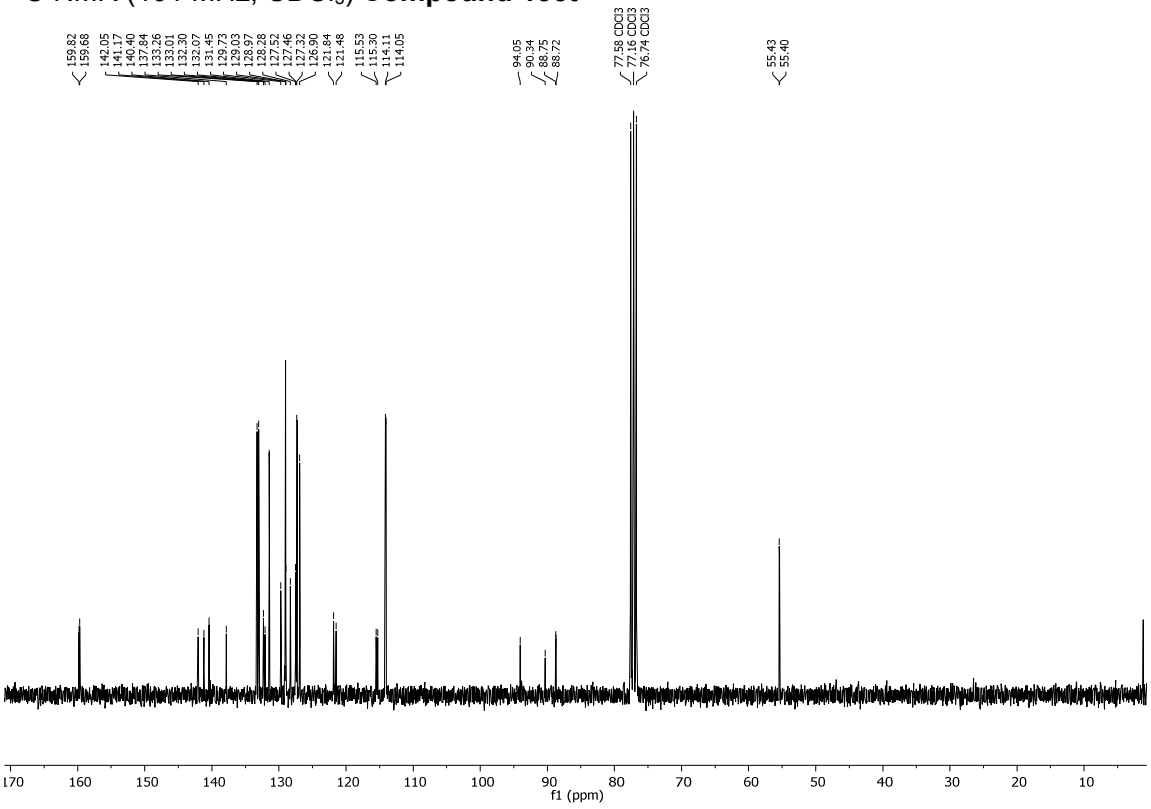
^{13}C NMR (75 MHz, $CDCl_3$) **Compound 198**



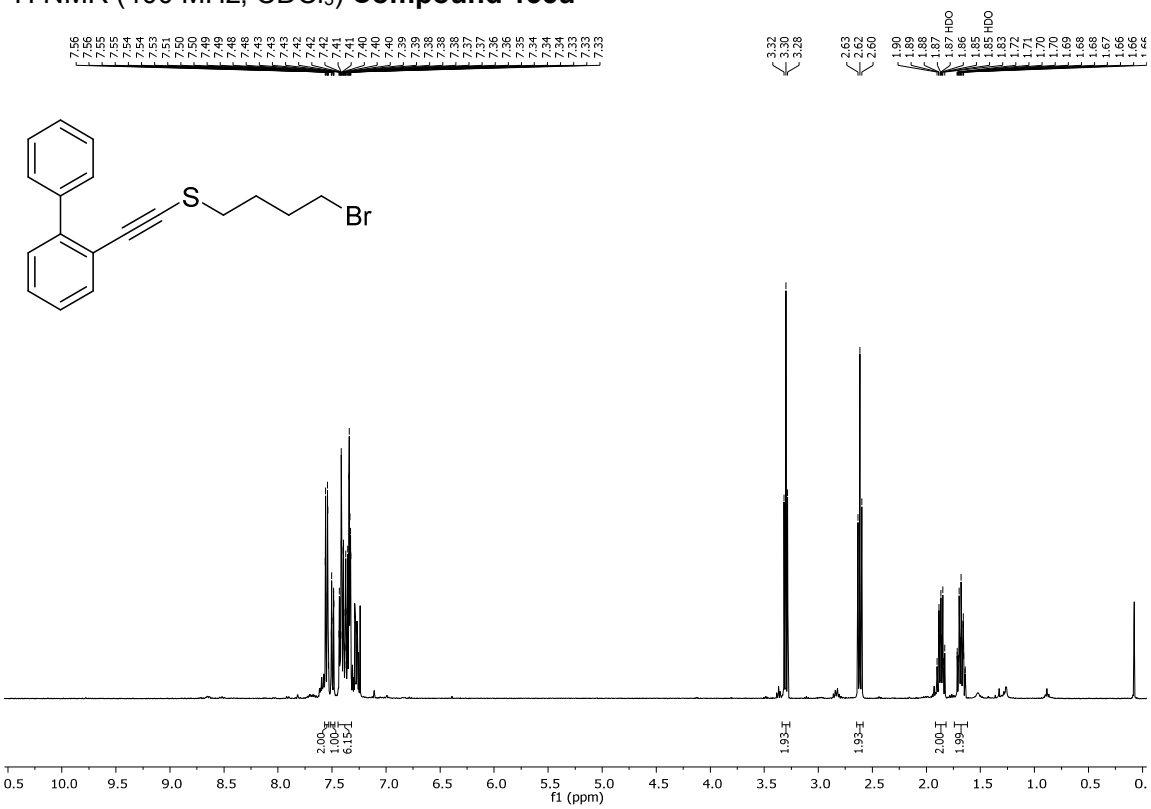
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135t**



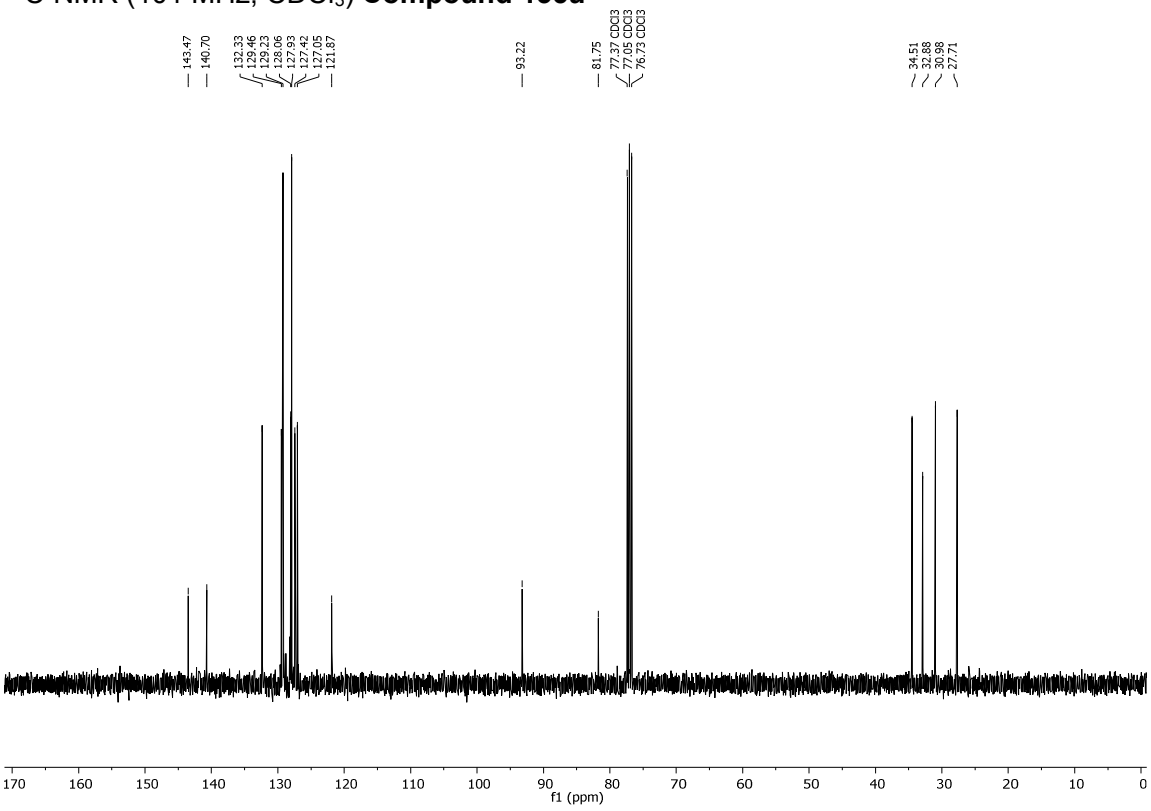
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 135t**



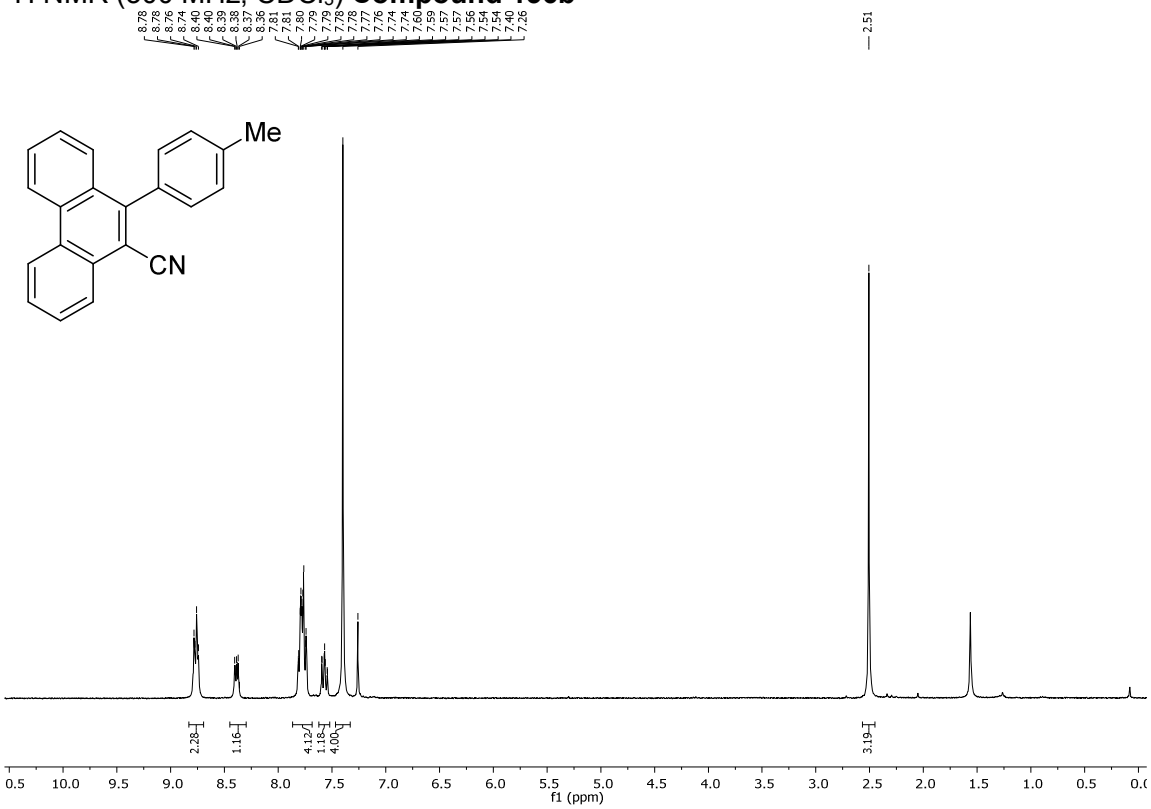
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135u**



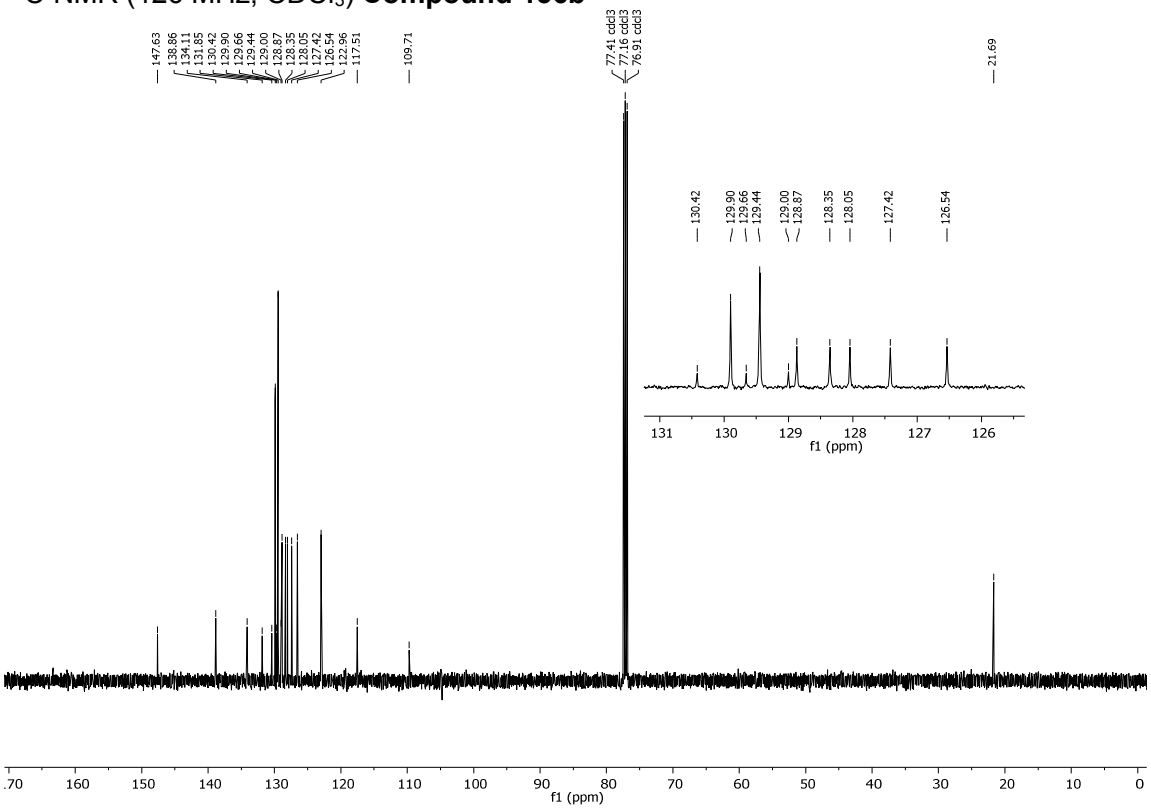
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 135u**



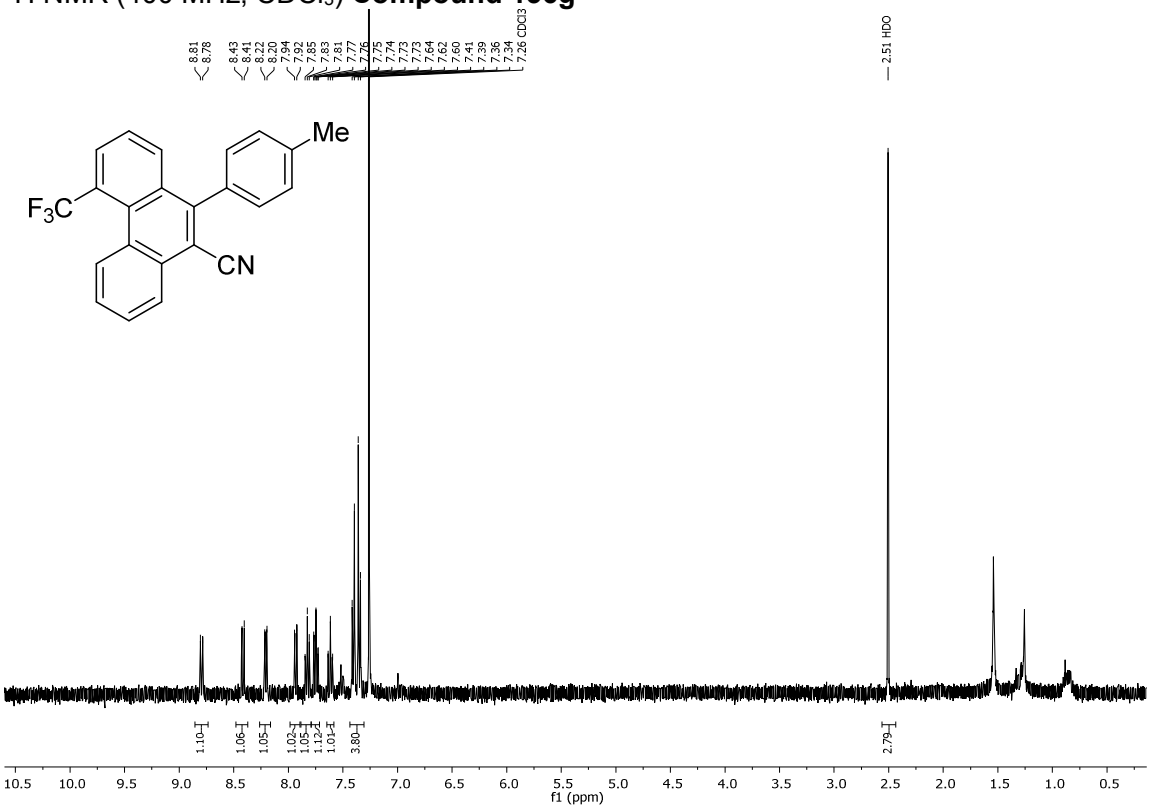
^{1}H NMR (300 MHz, $CDCl_3$) **Compound 136b**



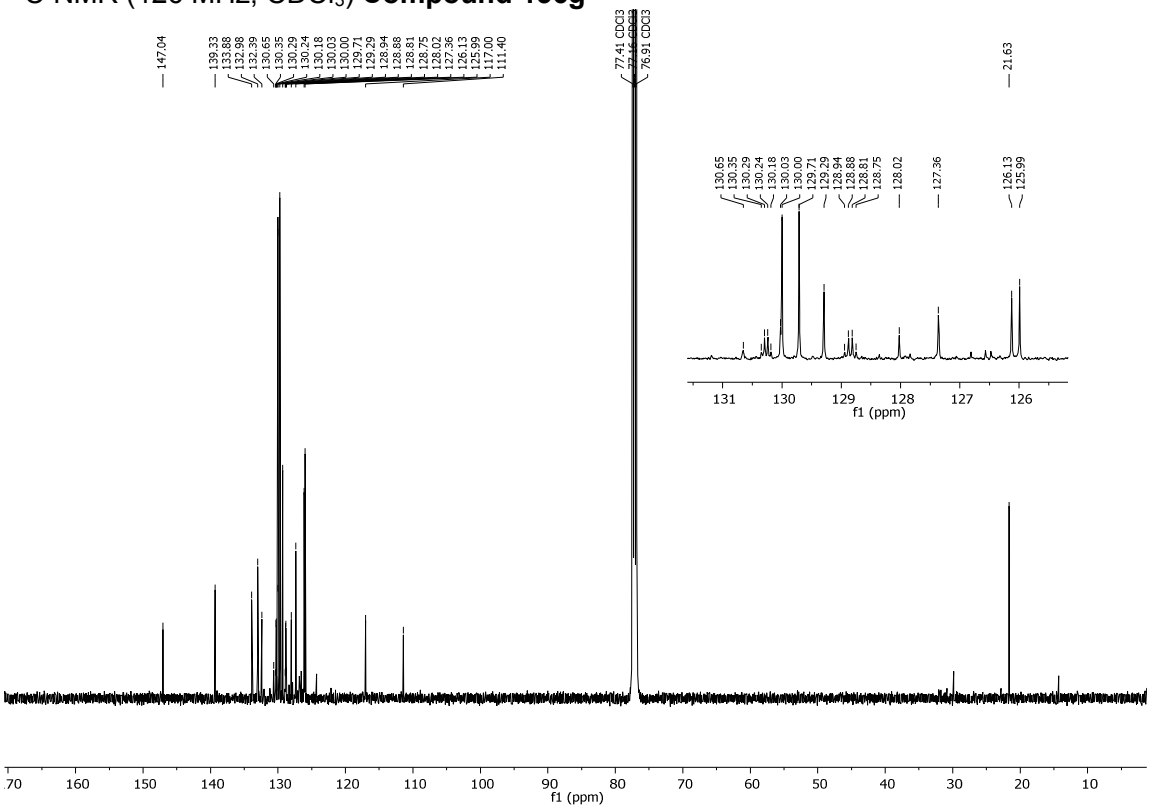
^{13}C NMR (126 MHz, $CDCl_3$) **Compound 136b**



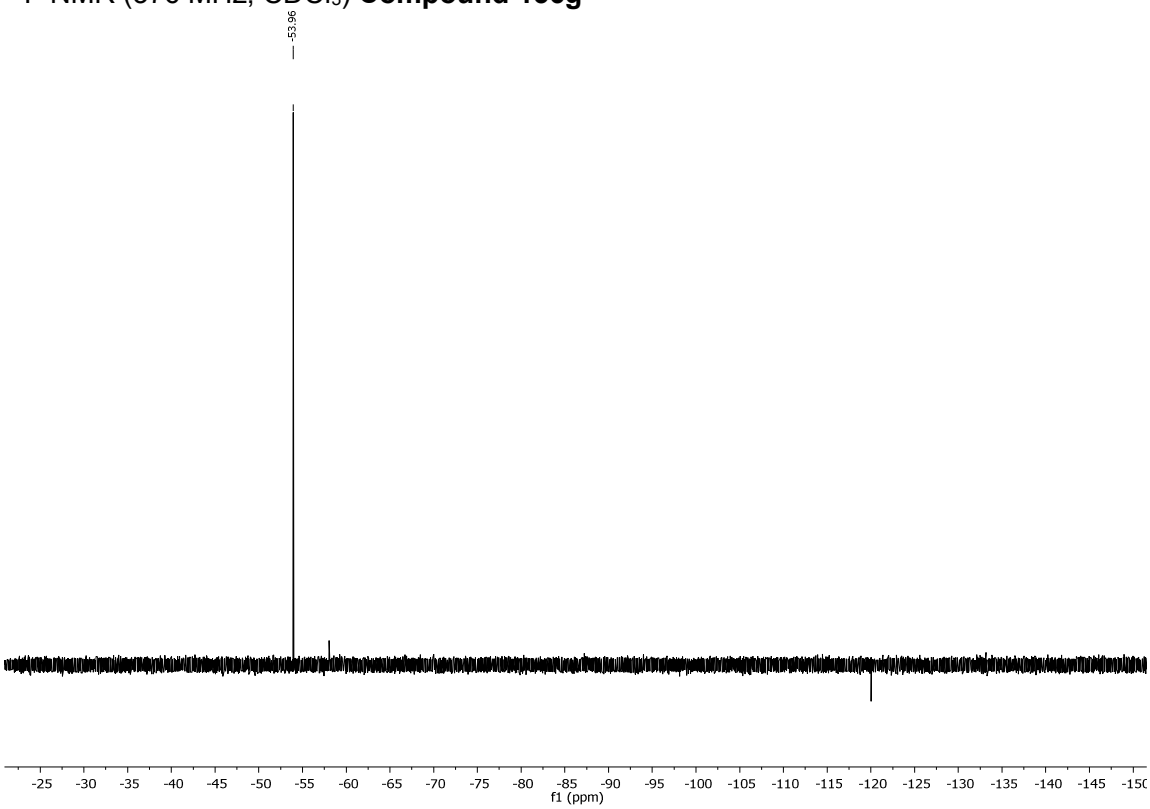
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 136g**



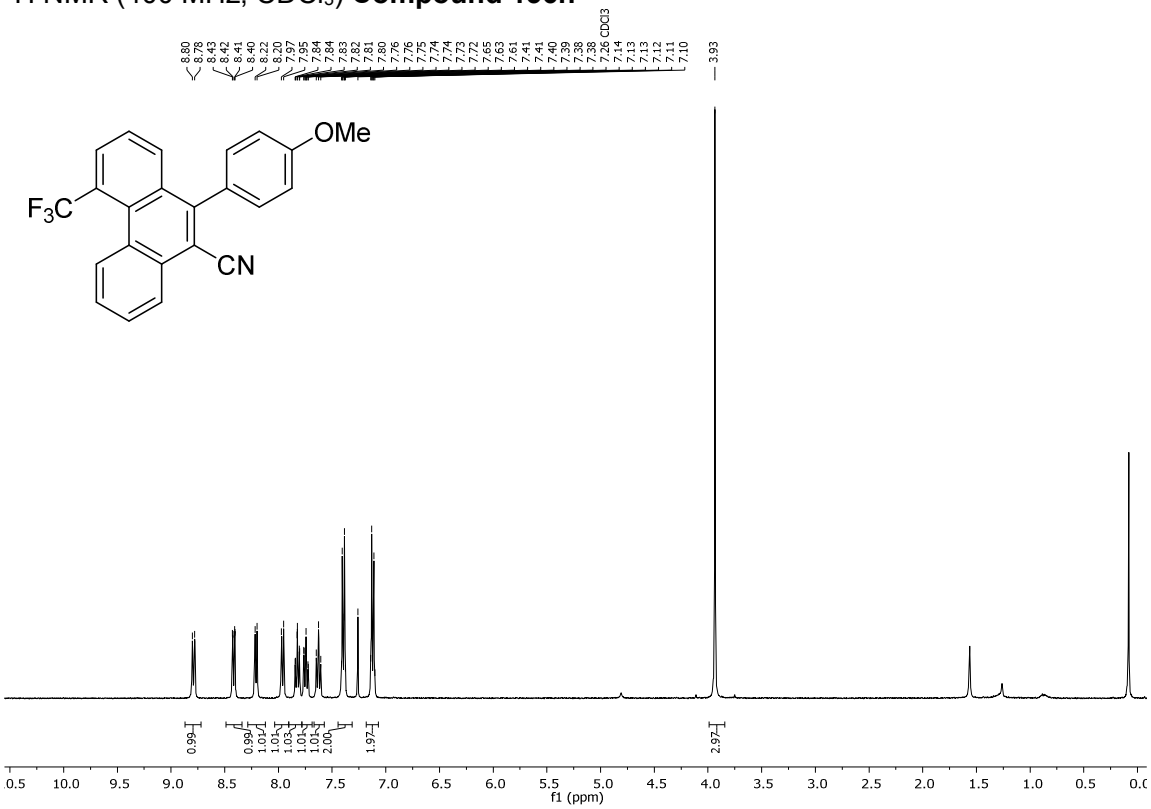
^{13}C NMR (126 MHz, $CDCl_3$) **Compound 136g**



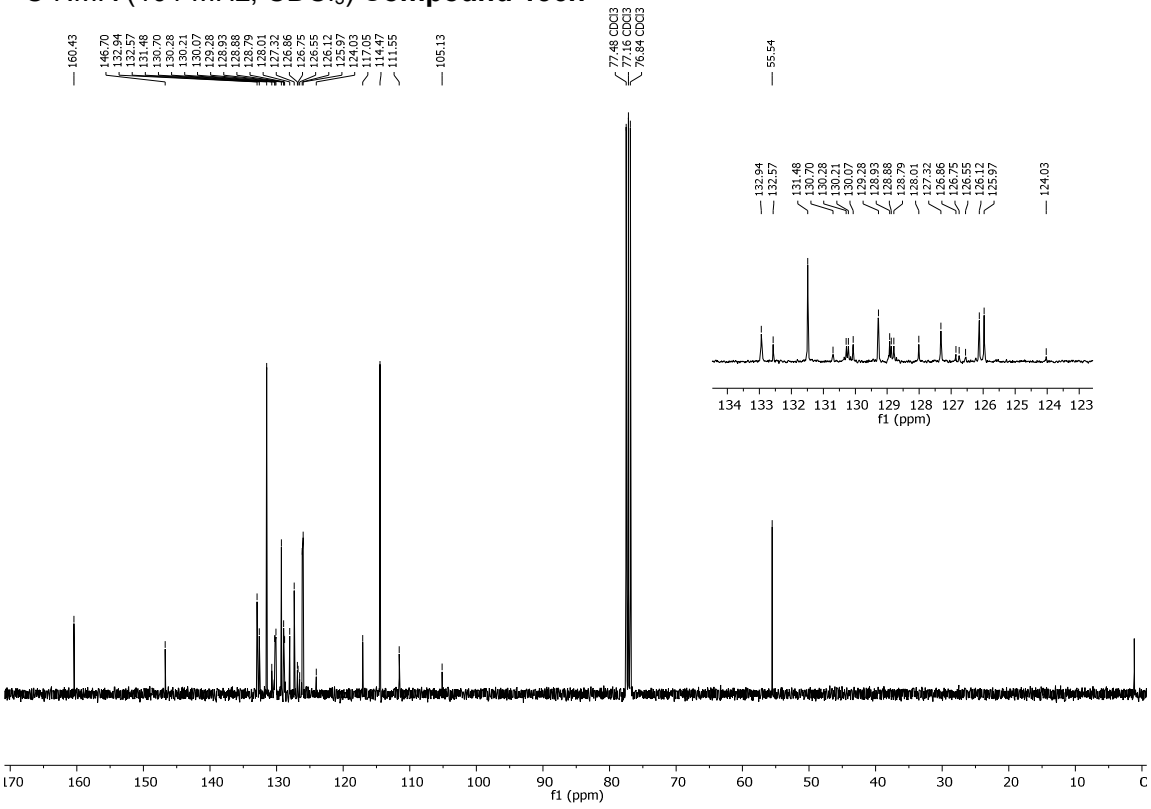
^{19}F NMR (376 MHz, $CDCl_3$) **Compound 136g**



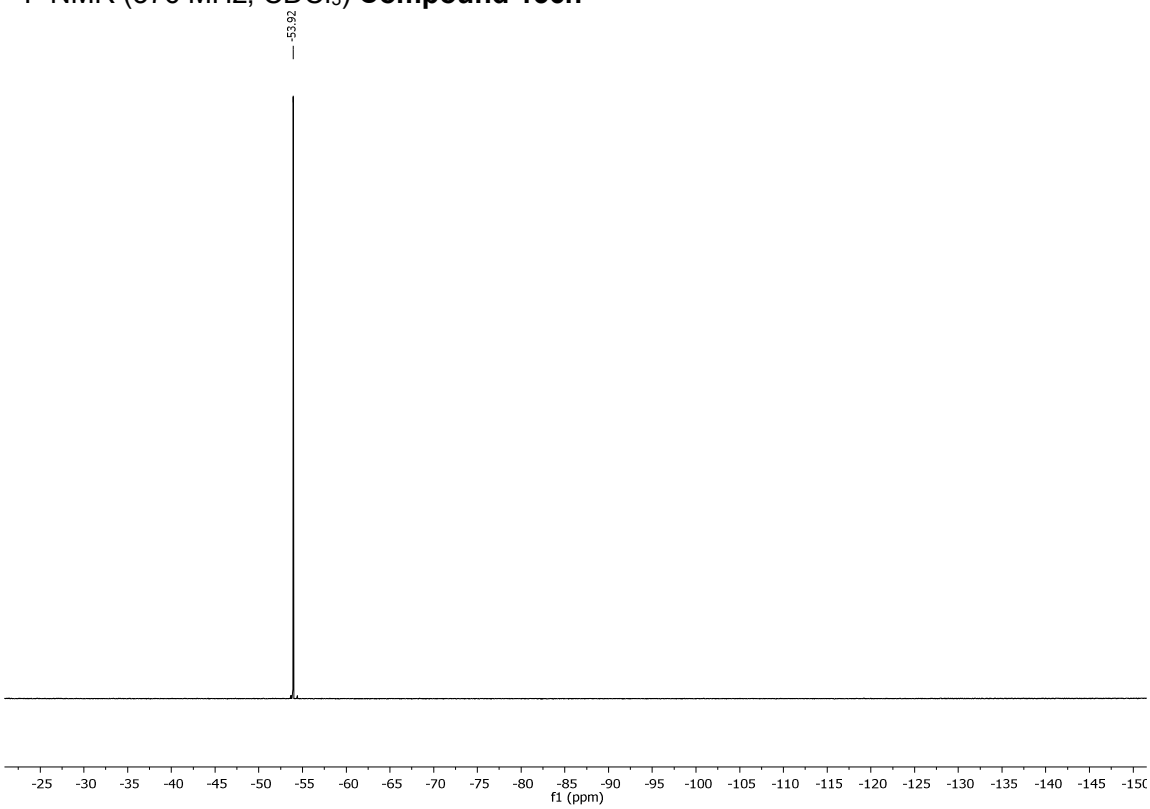
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 136h**



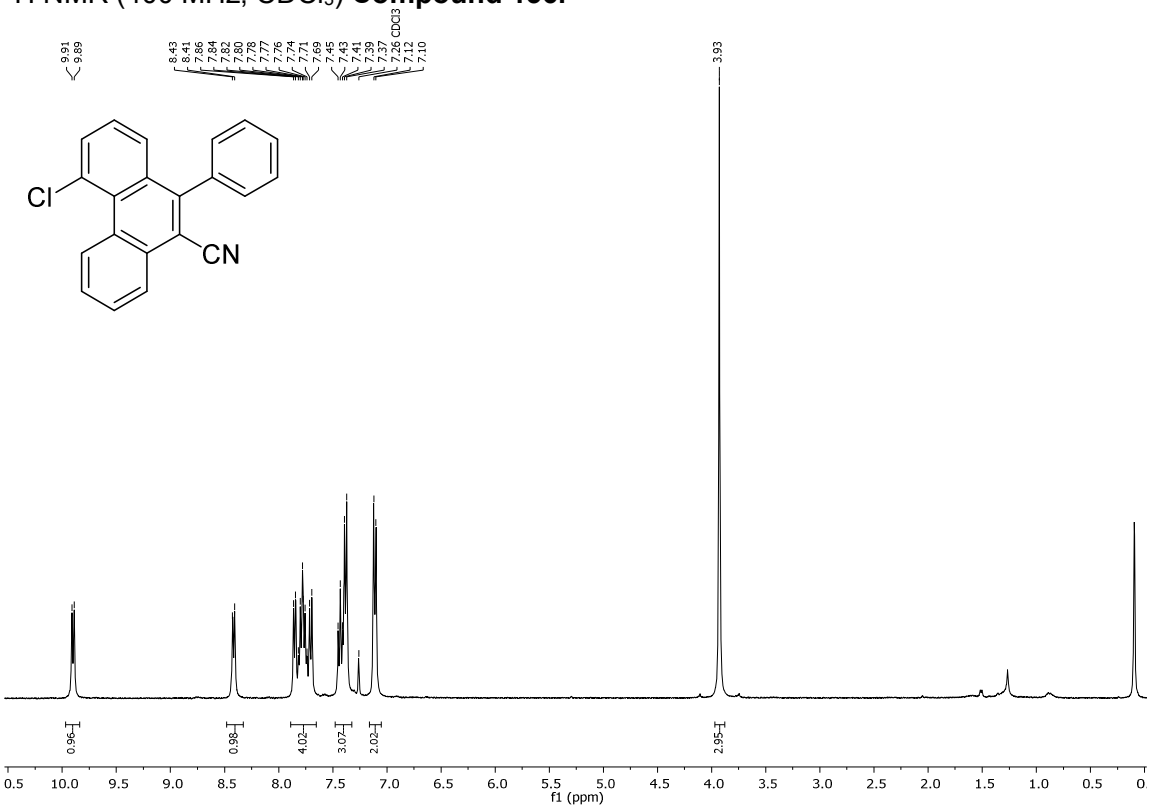
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 136h**



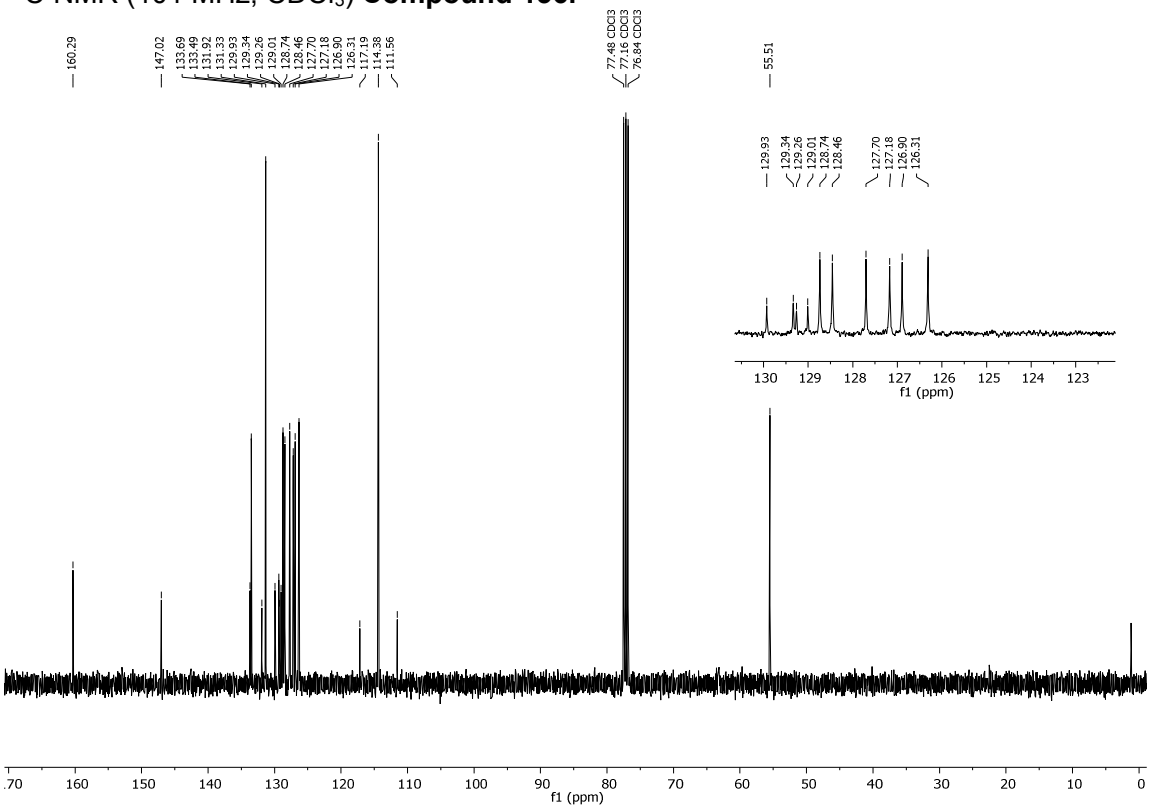
^{19}F NMR (376 MHz, $CDCl_3$) **Compound 136h**



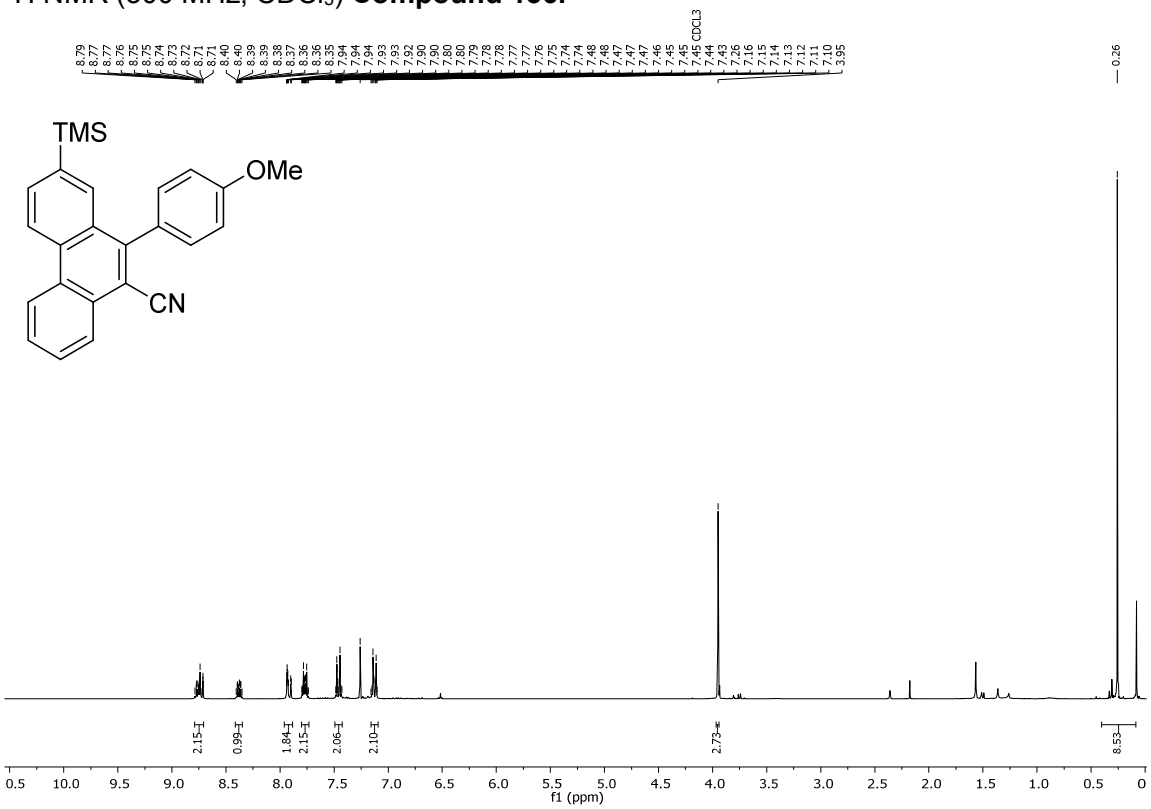
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 136i**



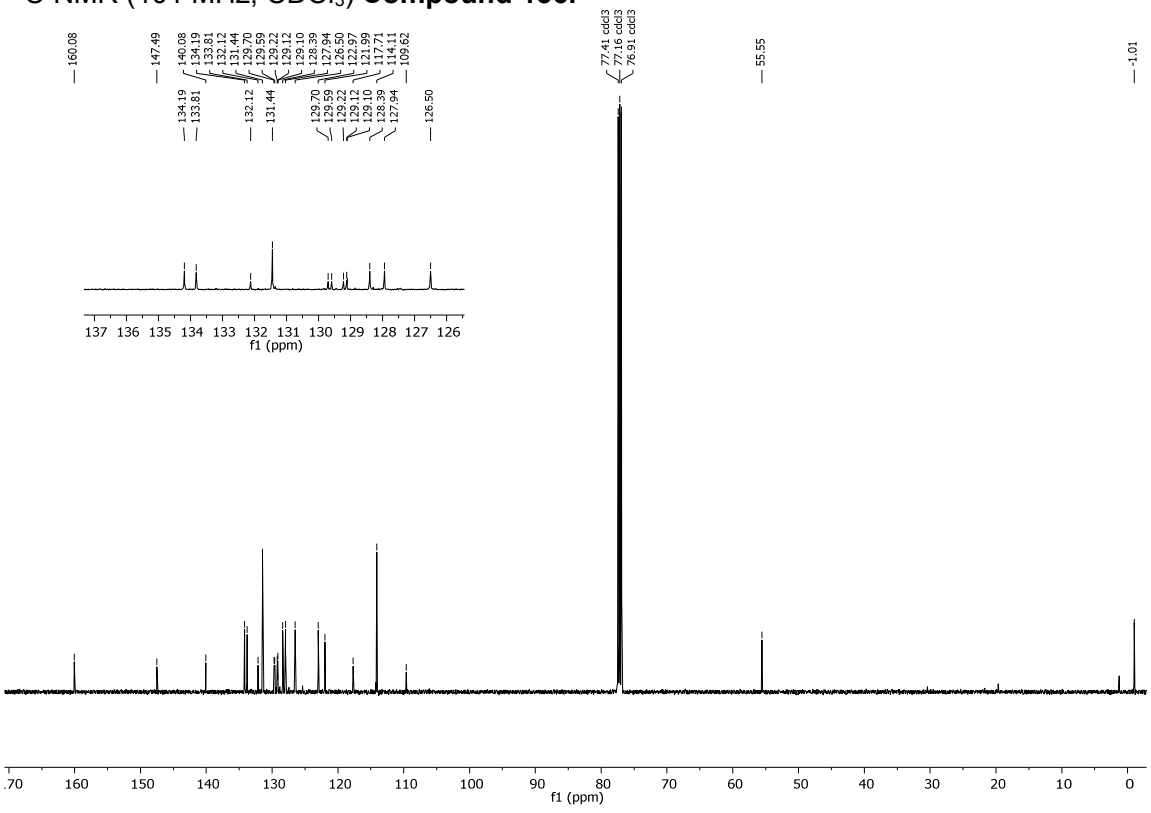
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 136i**



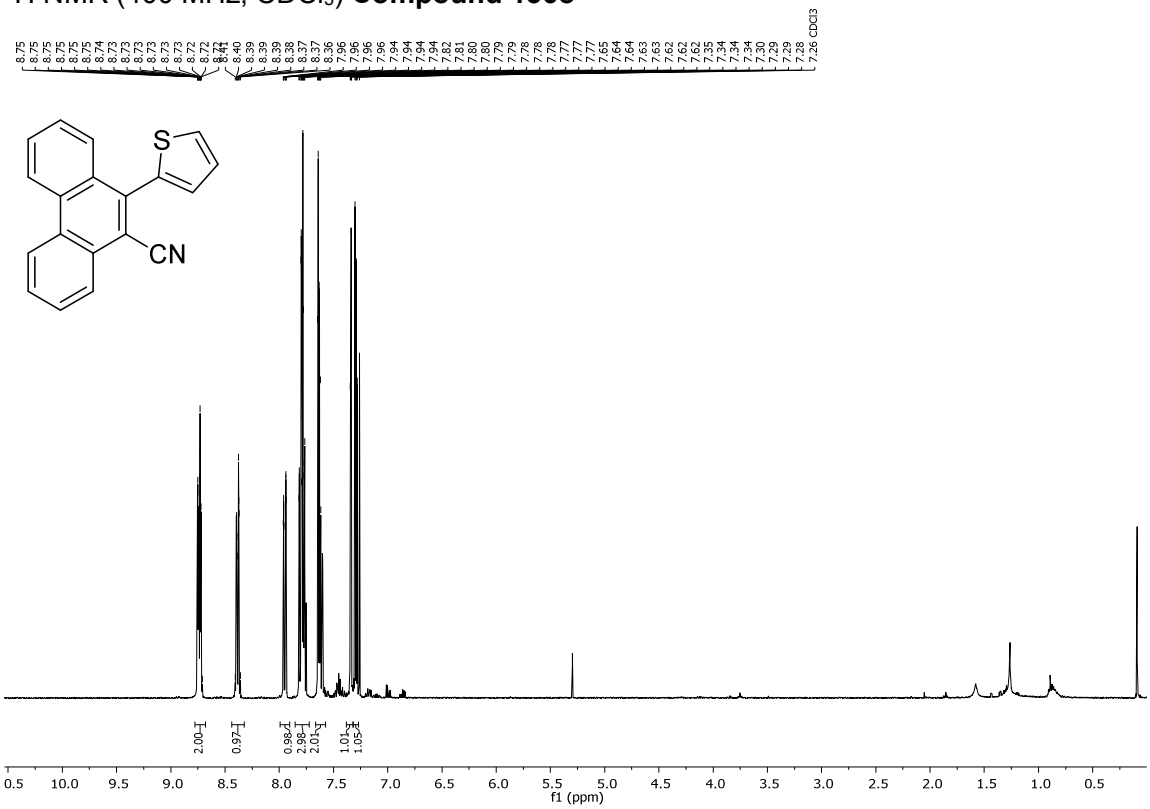
^{1}H NMR (300 MHz, $CDCl_3$) **Compound 136l**



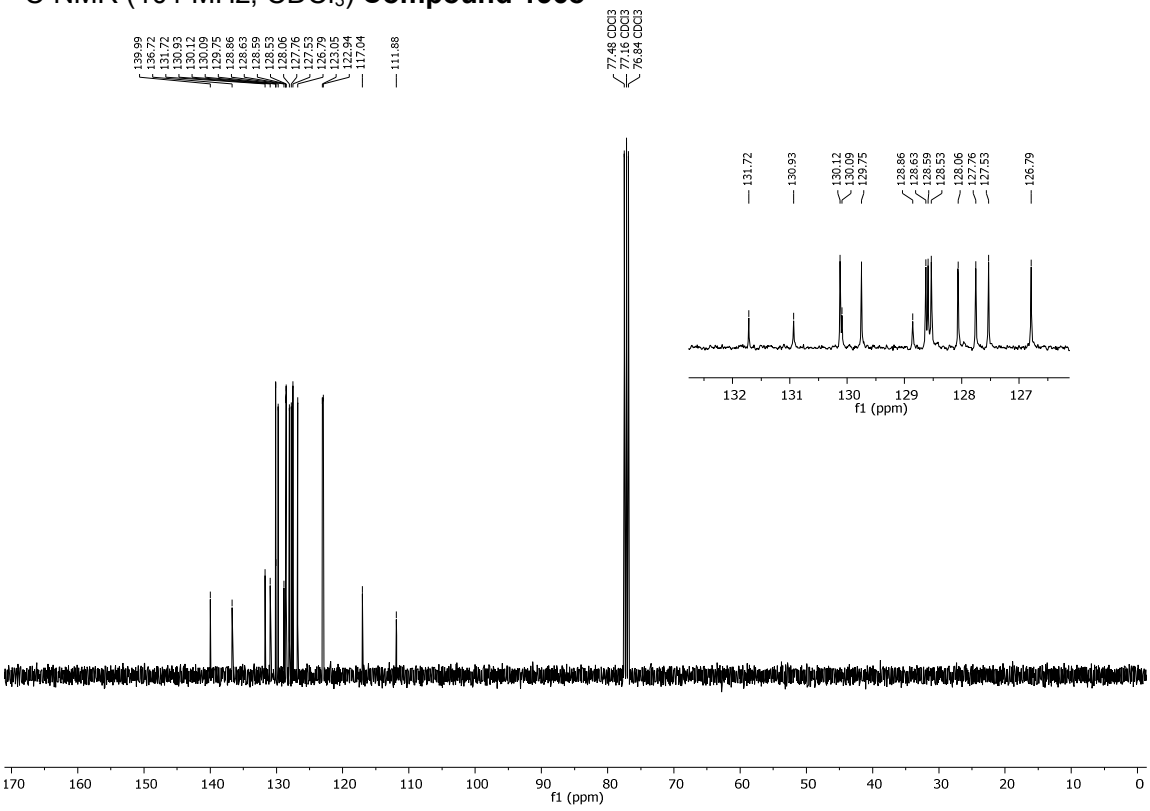
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 136l**



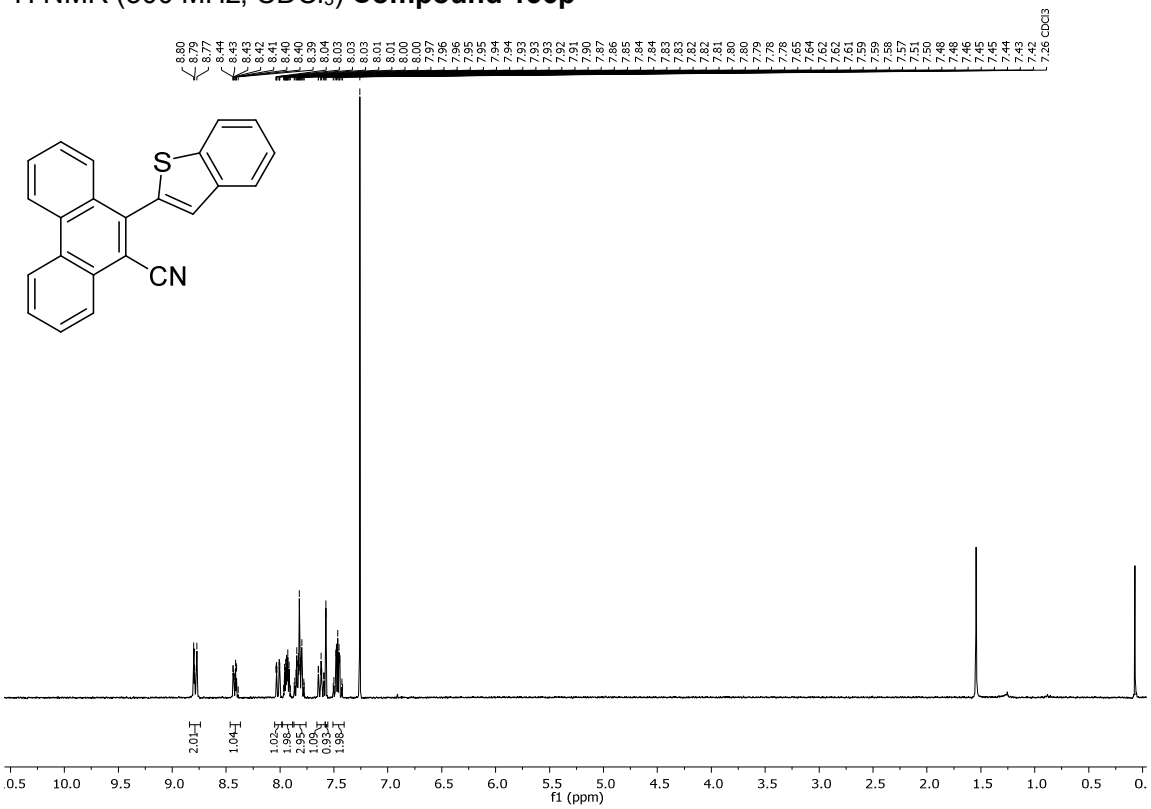
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 136o**



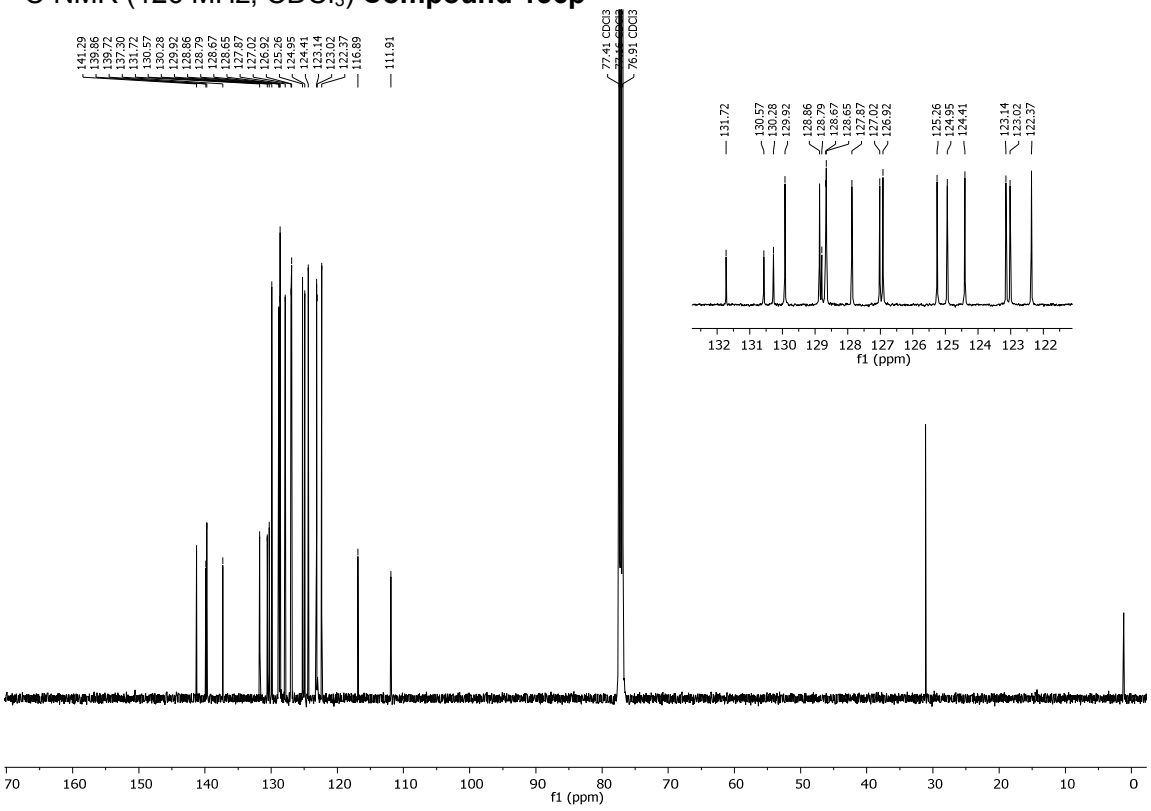
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 136o**



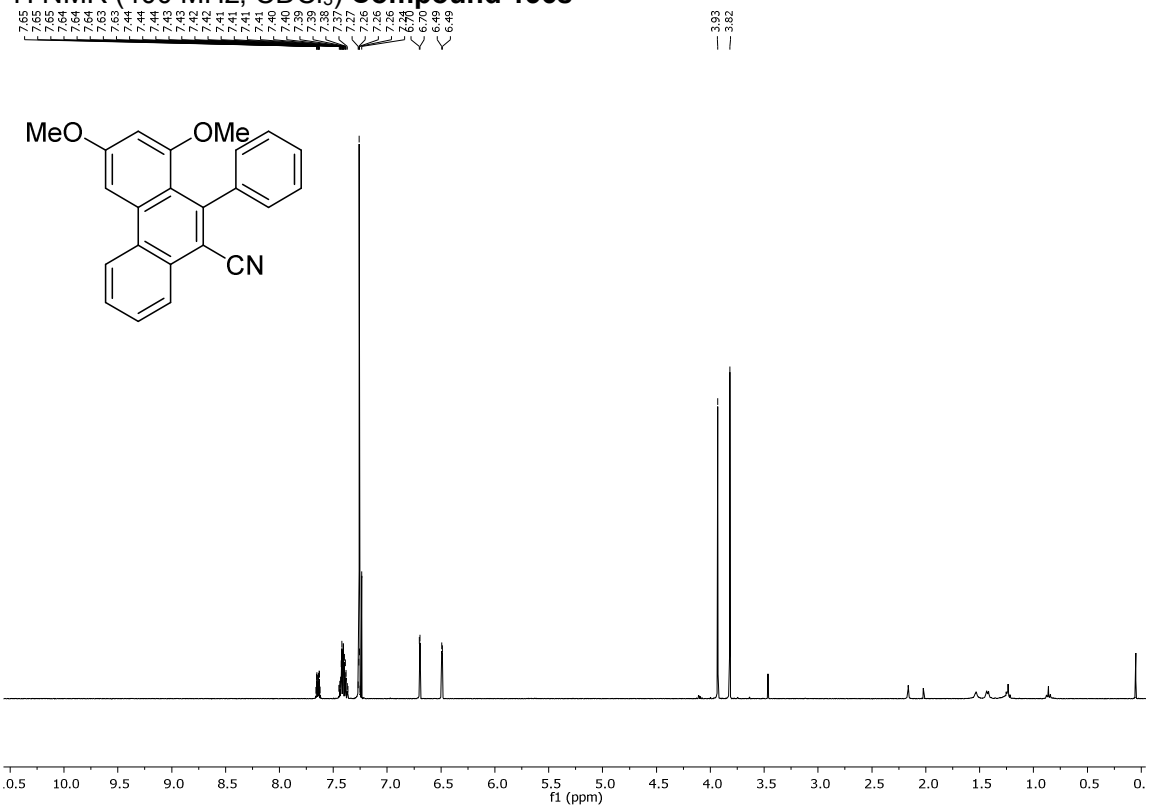
^{1}H NMR (300 MHz, $CDCl_3$) **Compound 136p**



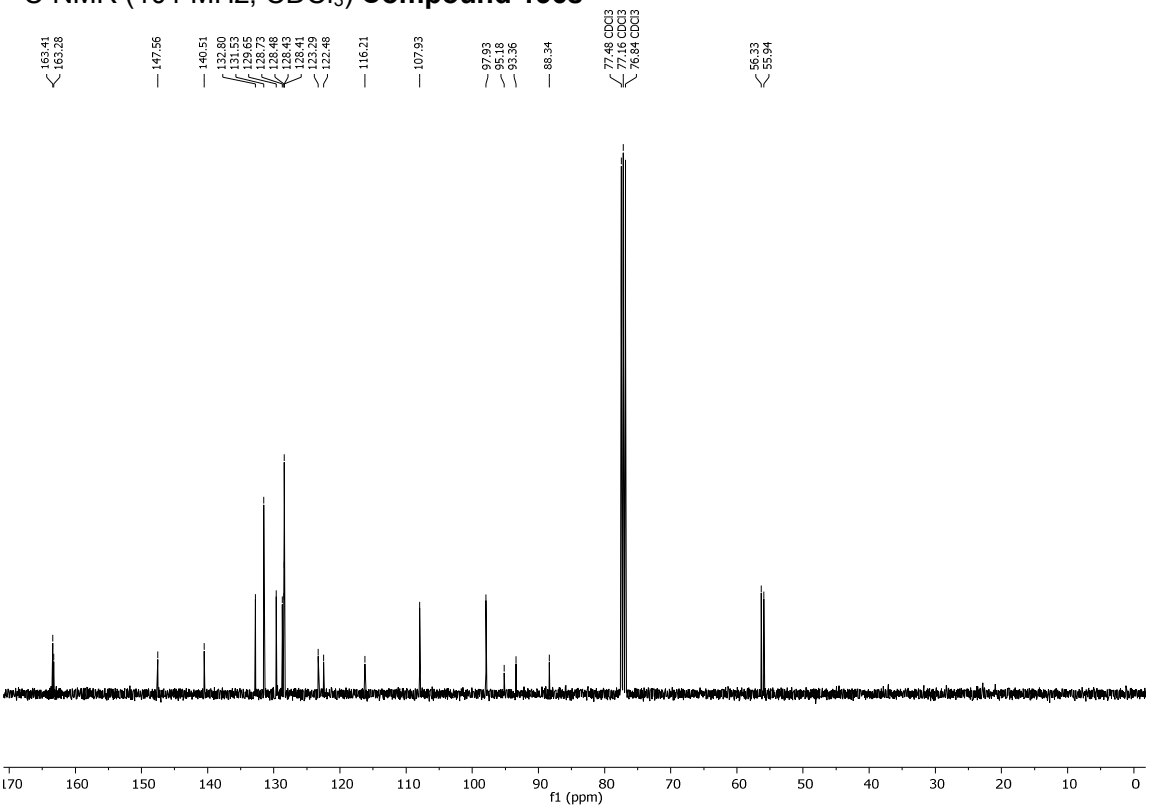
^{13}C NMR (126 MHz, $CDCl_3$) **Compound 136p**



^{1}H NMR (400 MHz, $CDCl_3$) **Compound 136s**

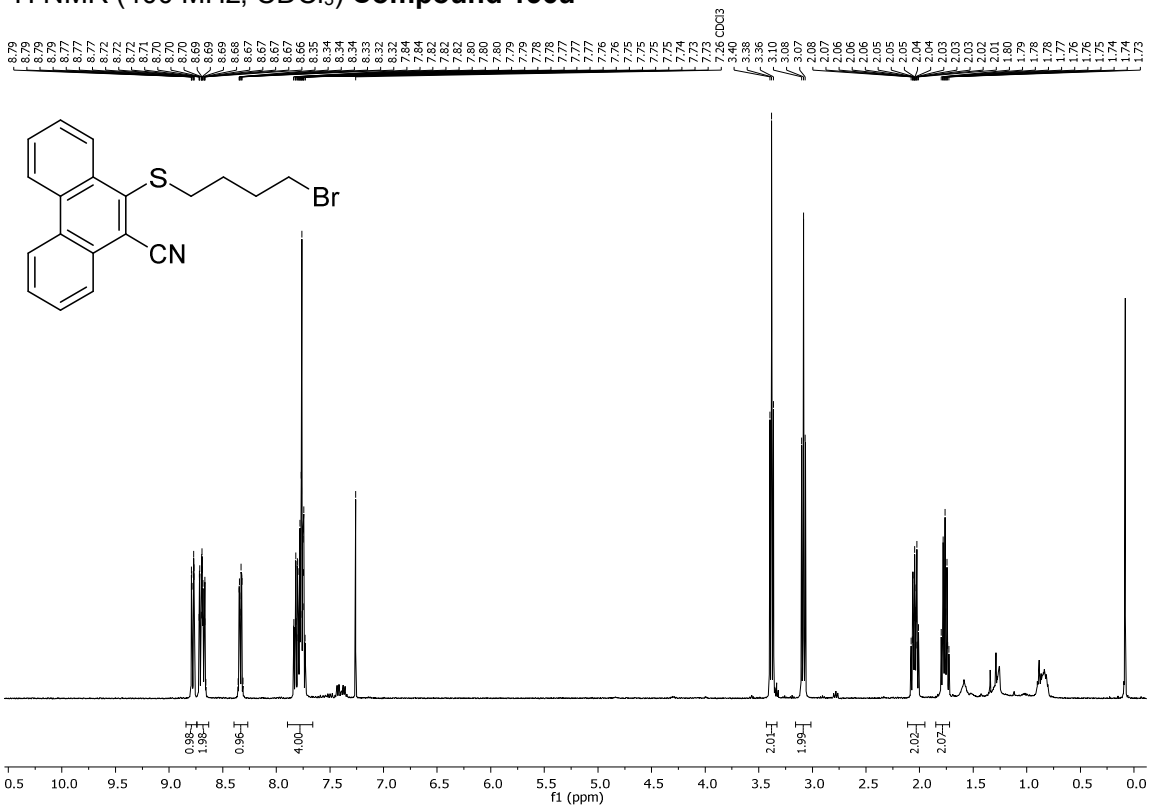


^{13}C NMR (101 MHz, $CDCl_3$) **Compound 136s**

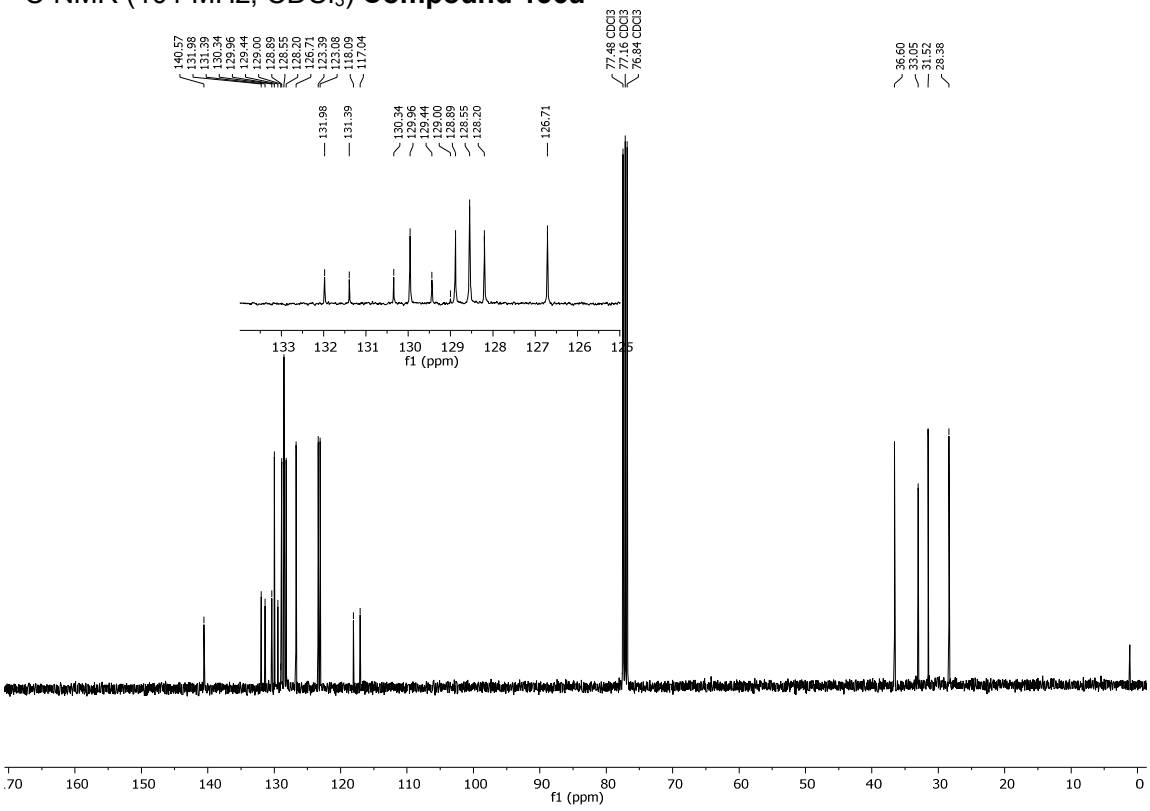


.

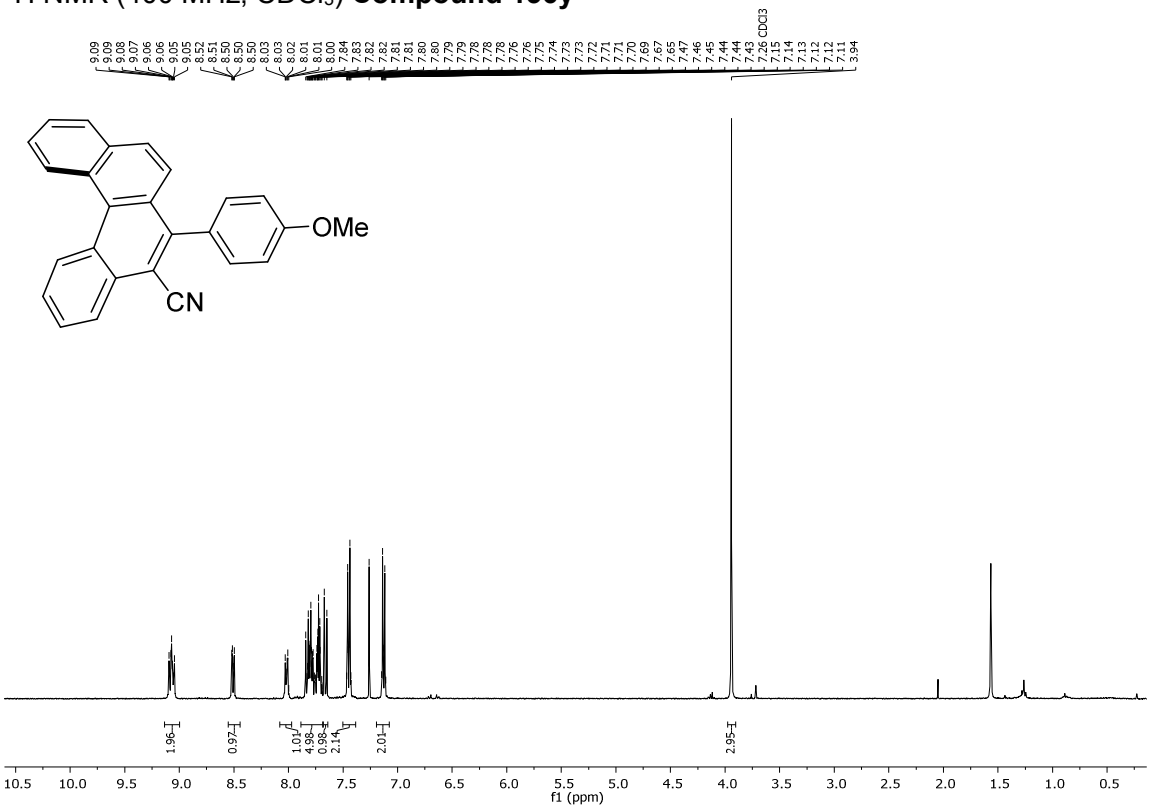
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 136u**



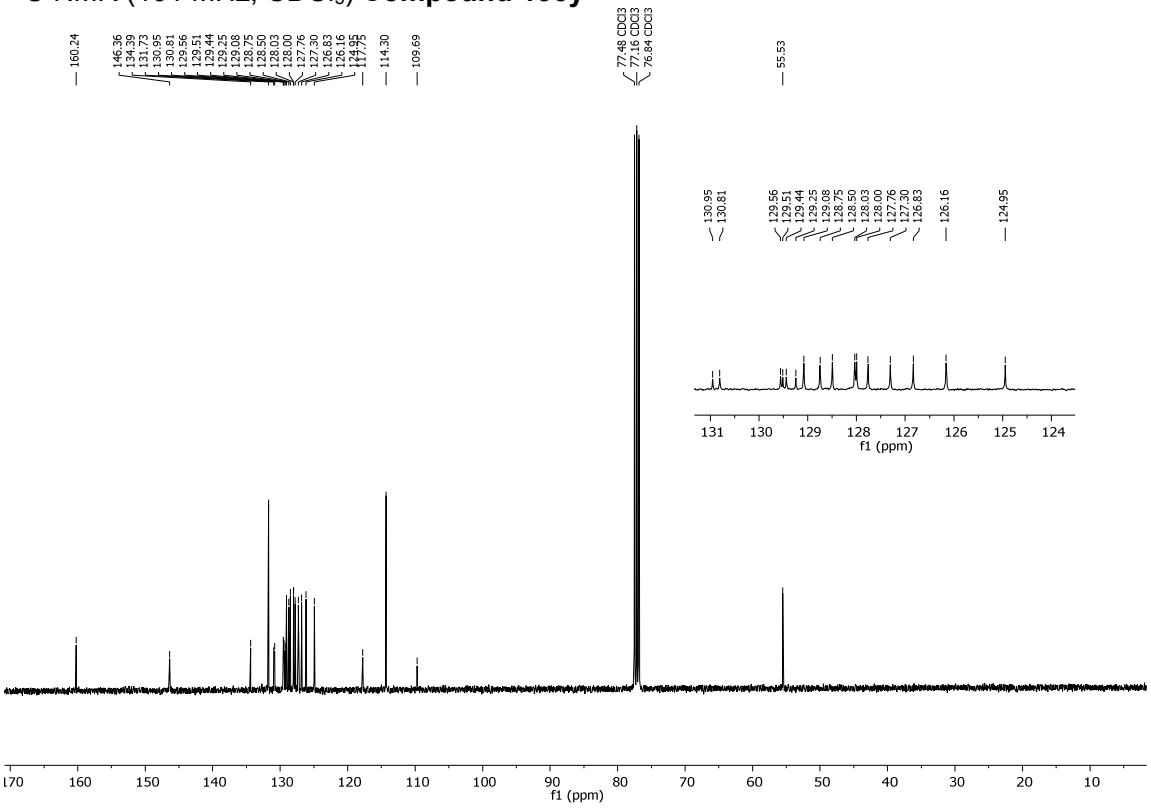
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 136u**



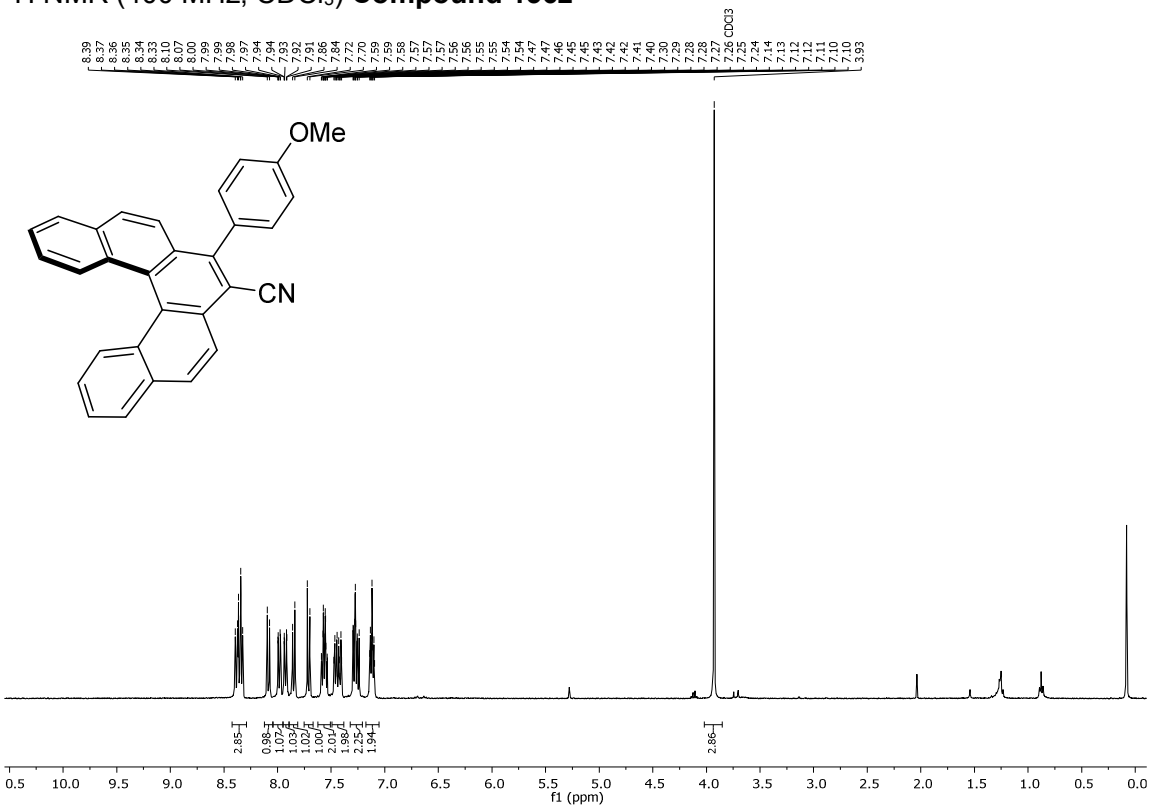
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 136y**



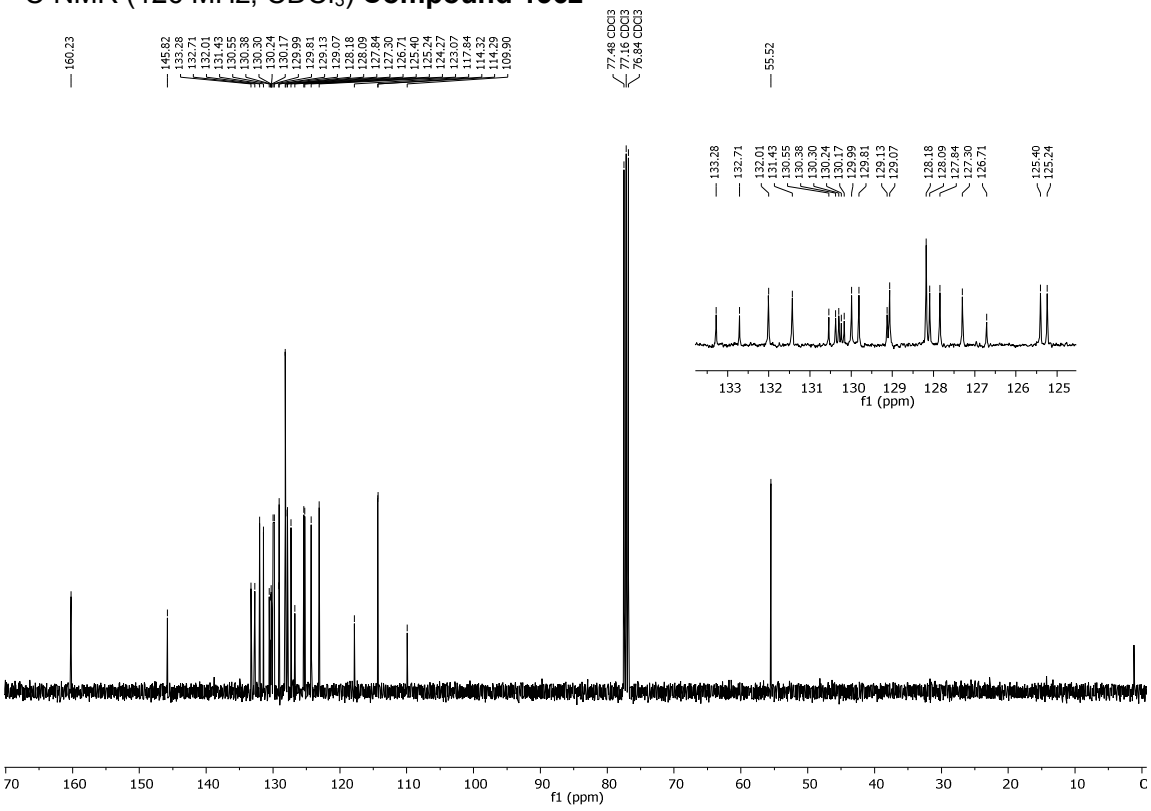
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 136y**



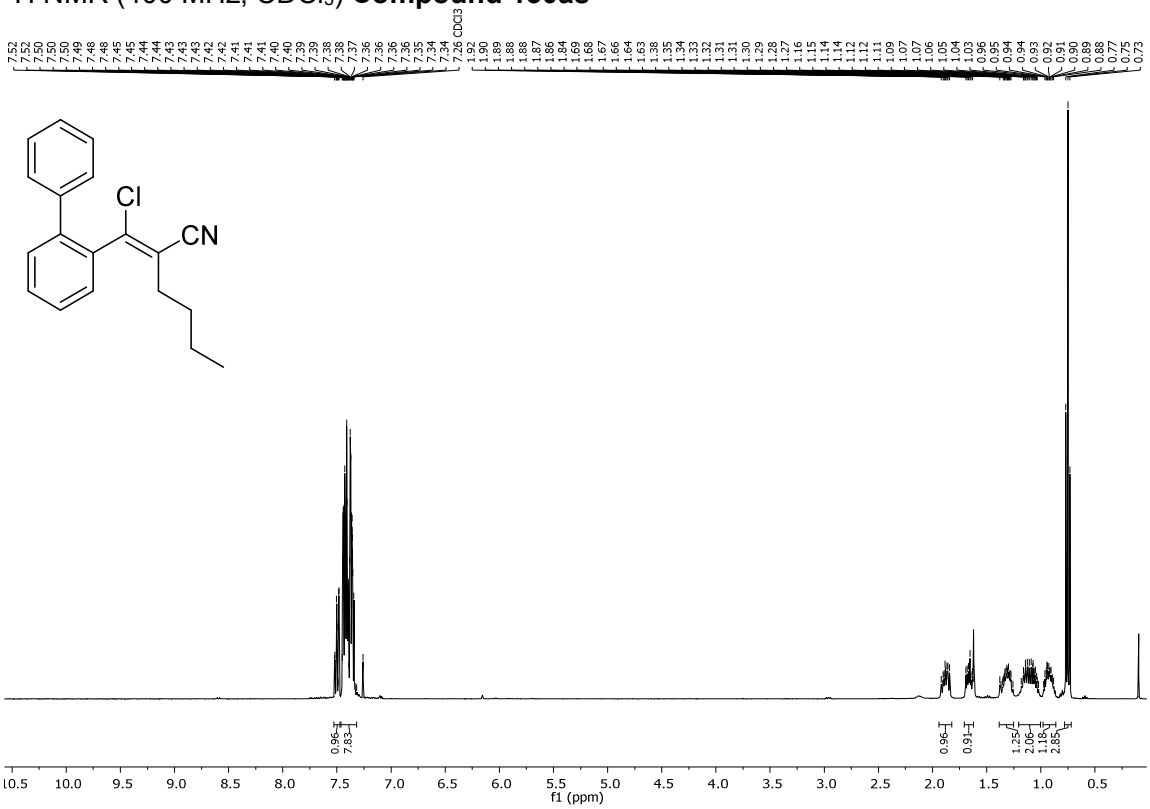
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 136z**



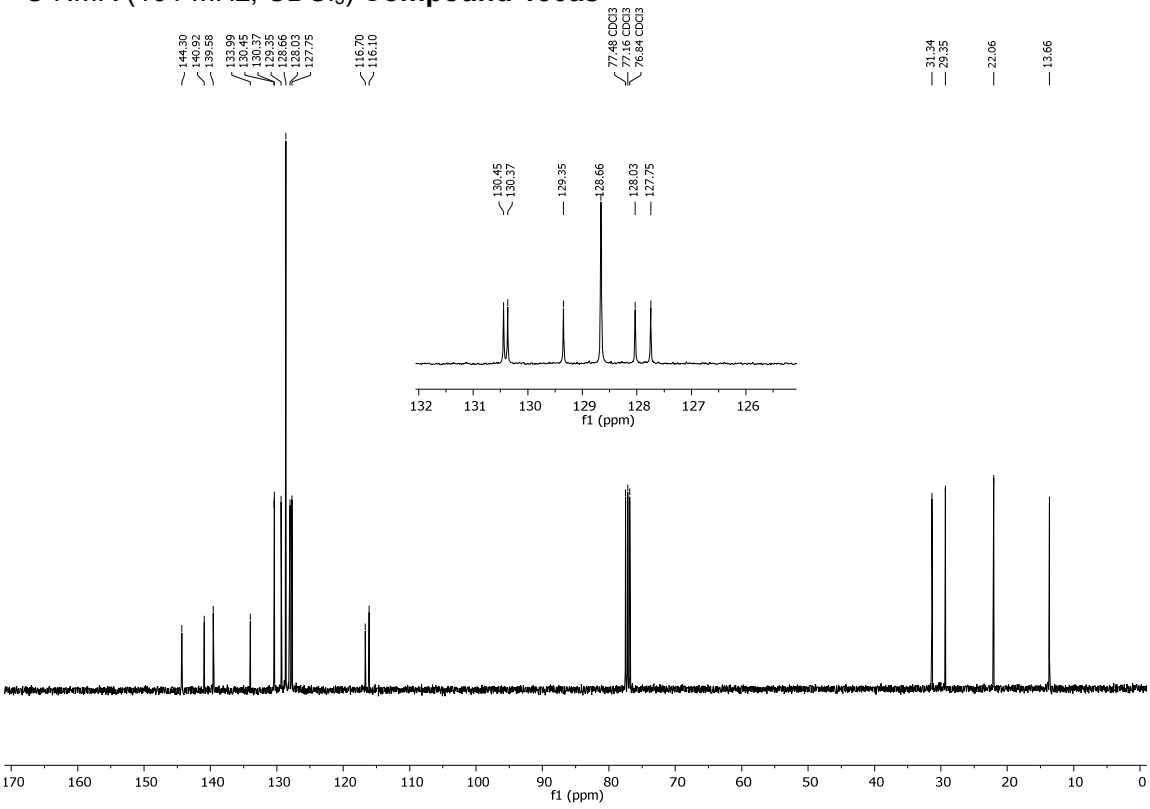
^{13}C NMR (126 MHz, $CDCl_3$) **Compound 136z**



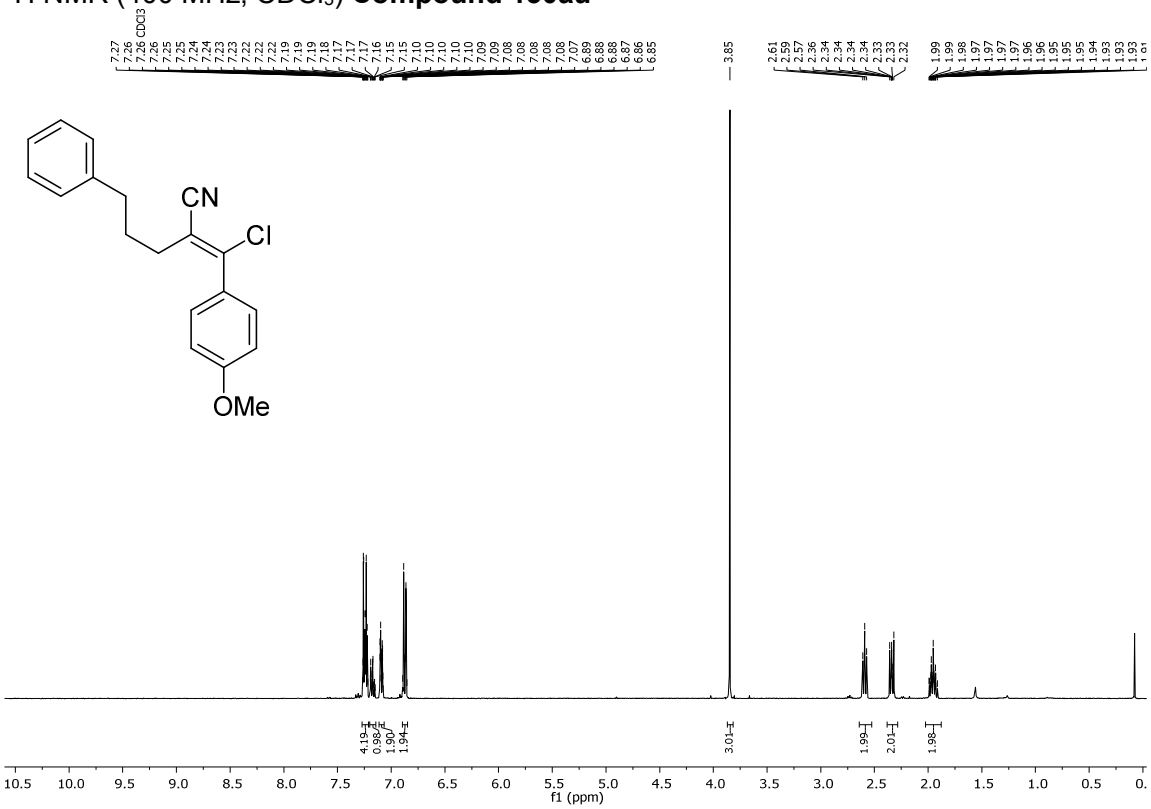
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 130as**



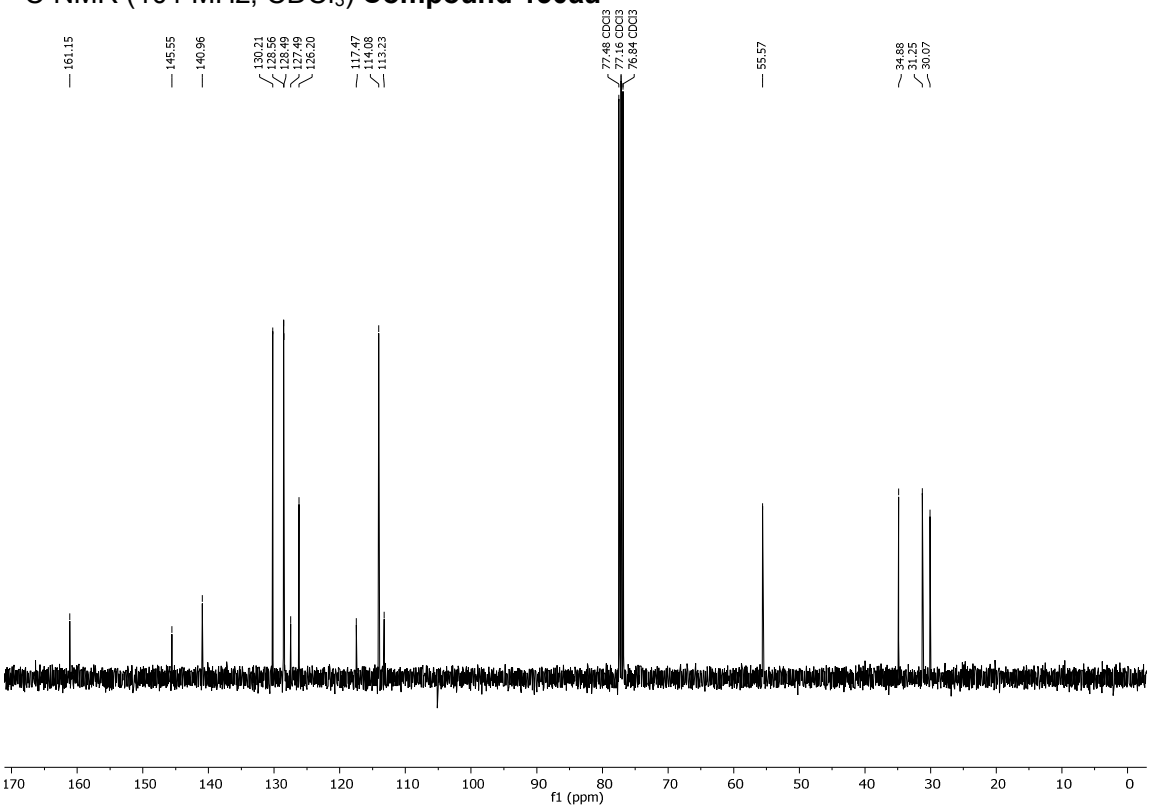
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 130as**



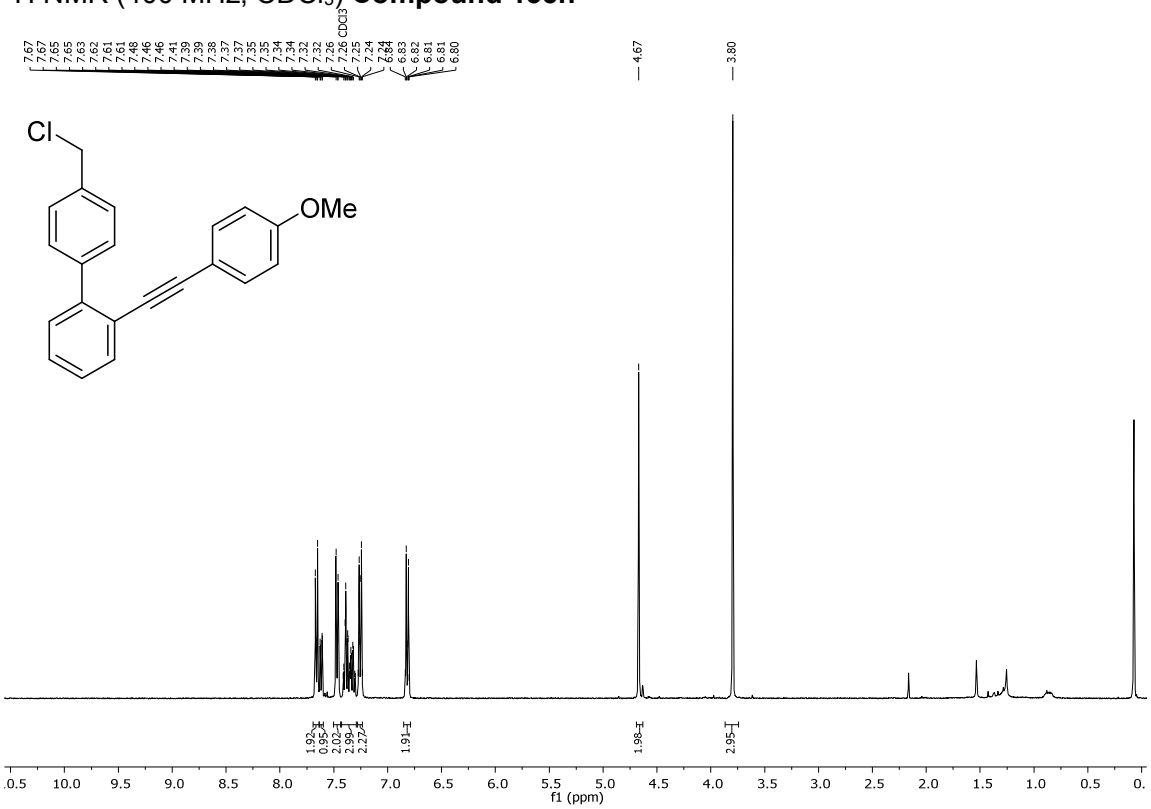
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 130au**



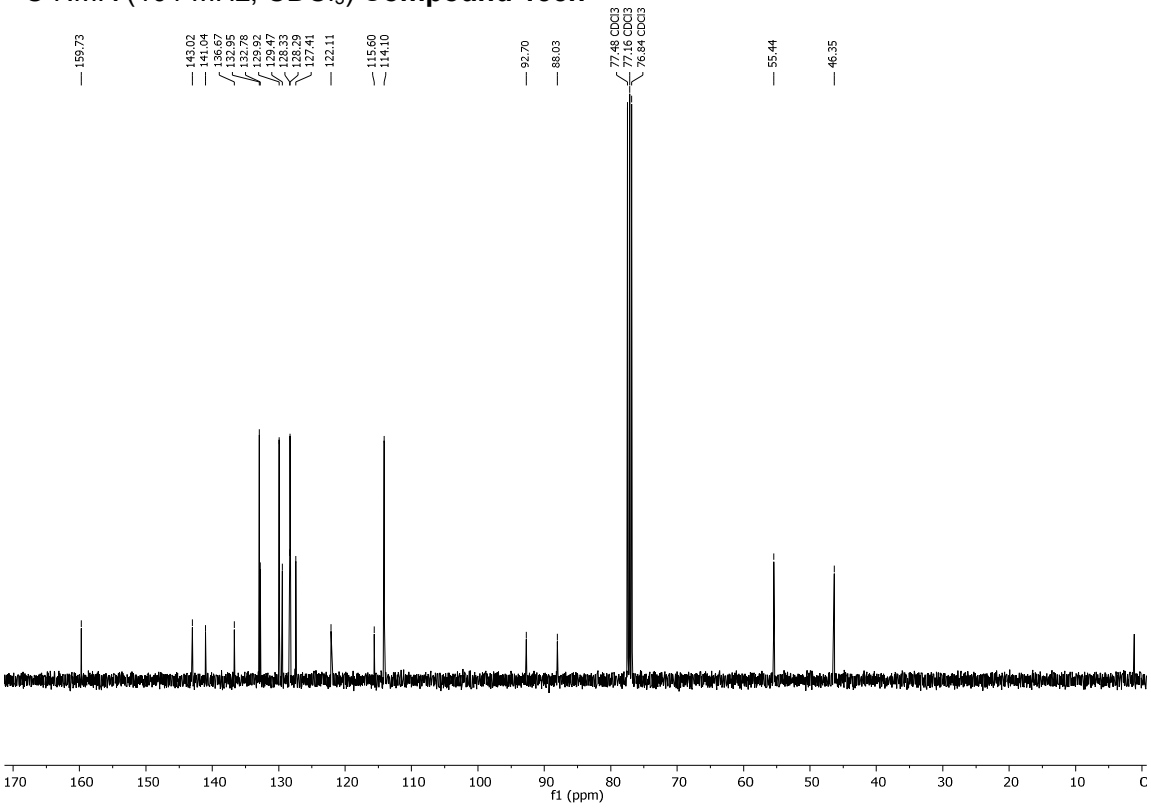
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 130au**



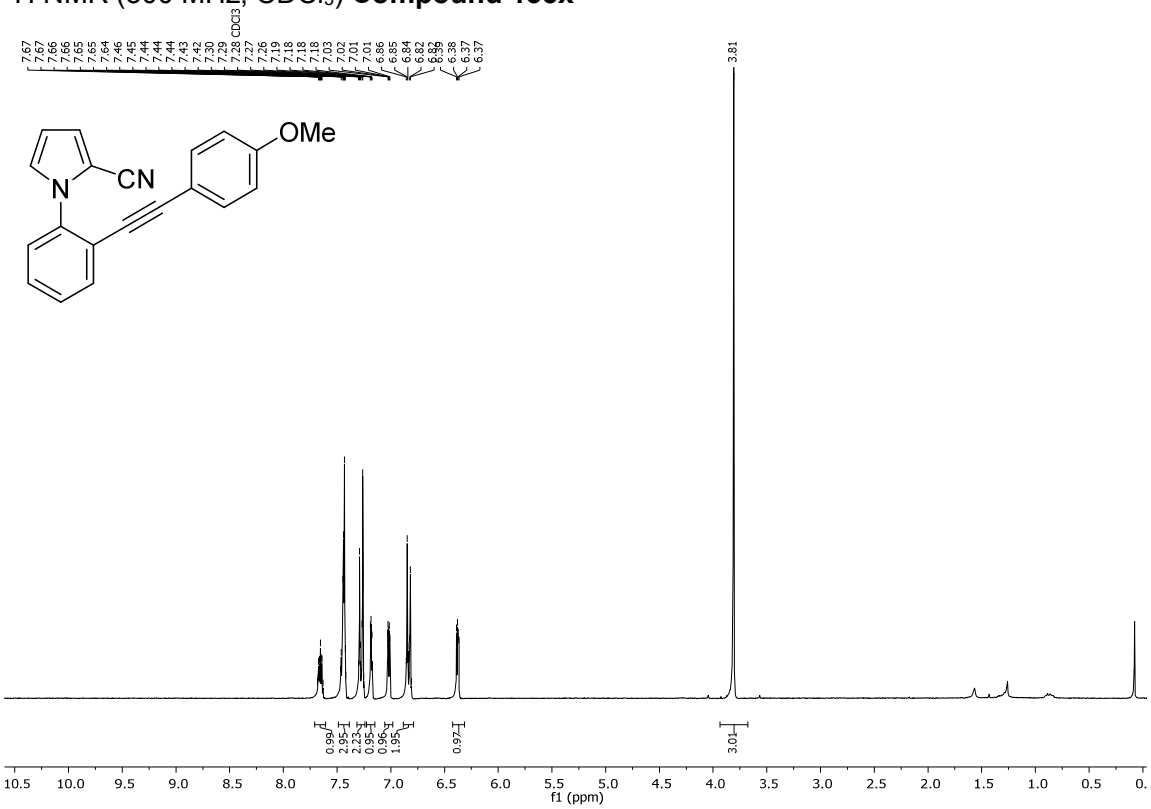
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 135n**



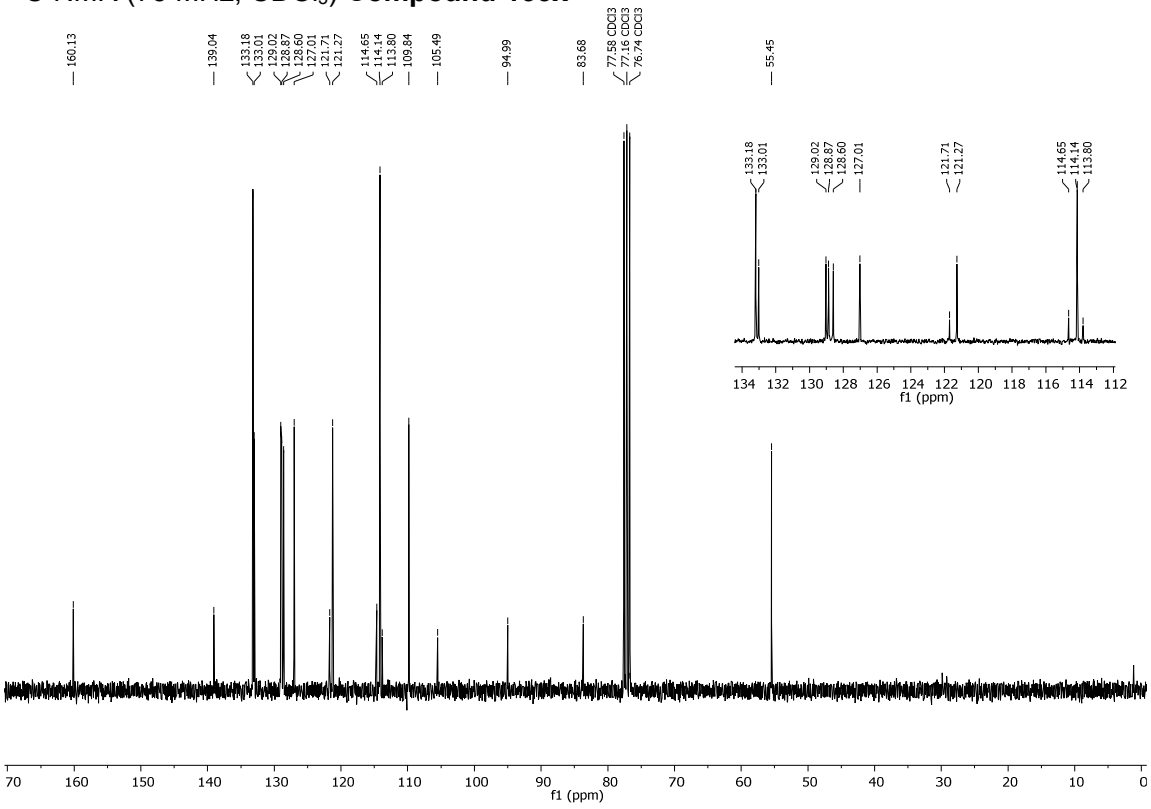
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 135n**



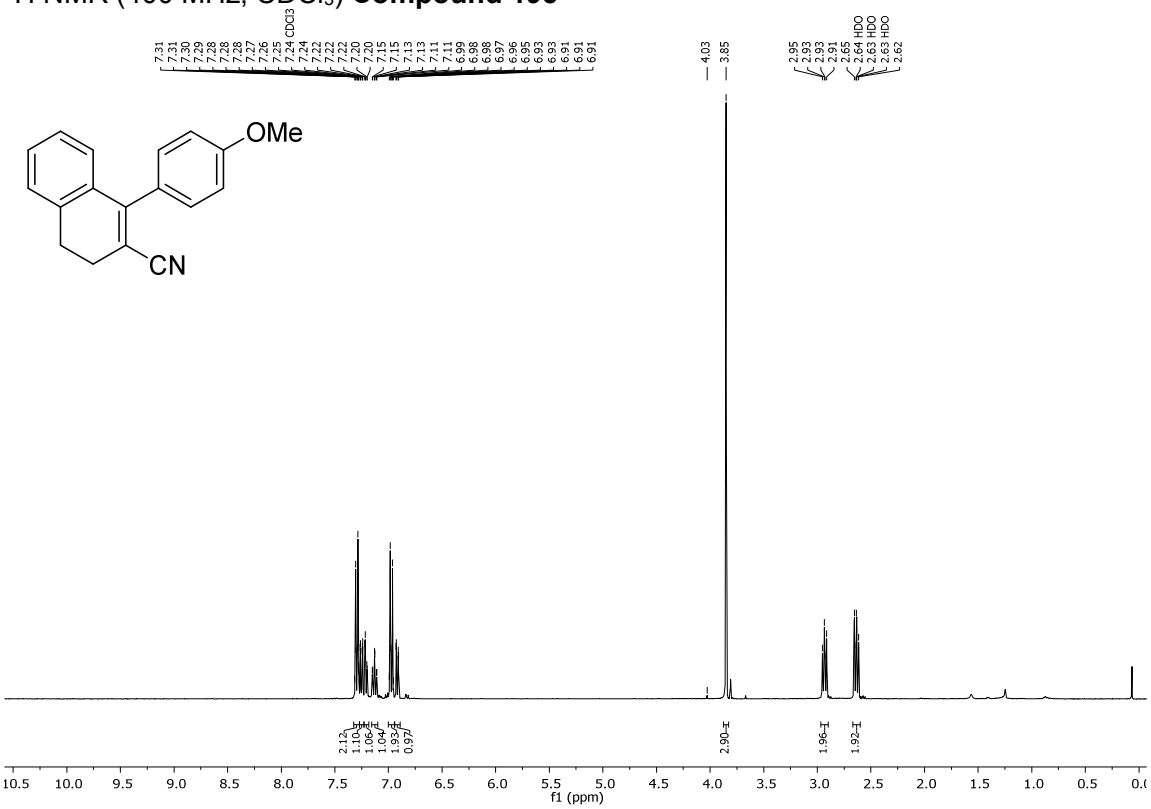
^{1}H NMR (300 MHz, $CDCl_3$) **Compound 135x**



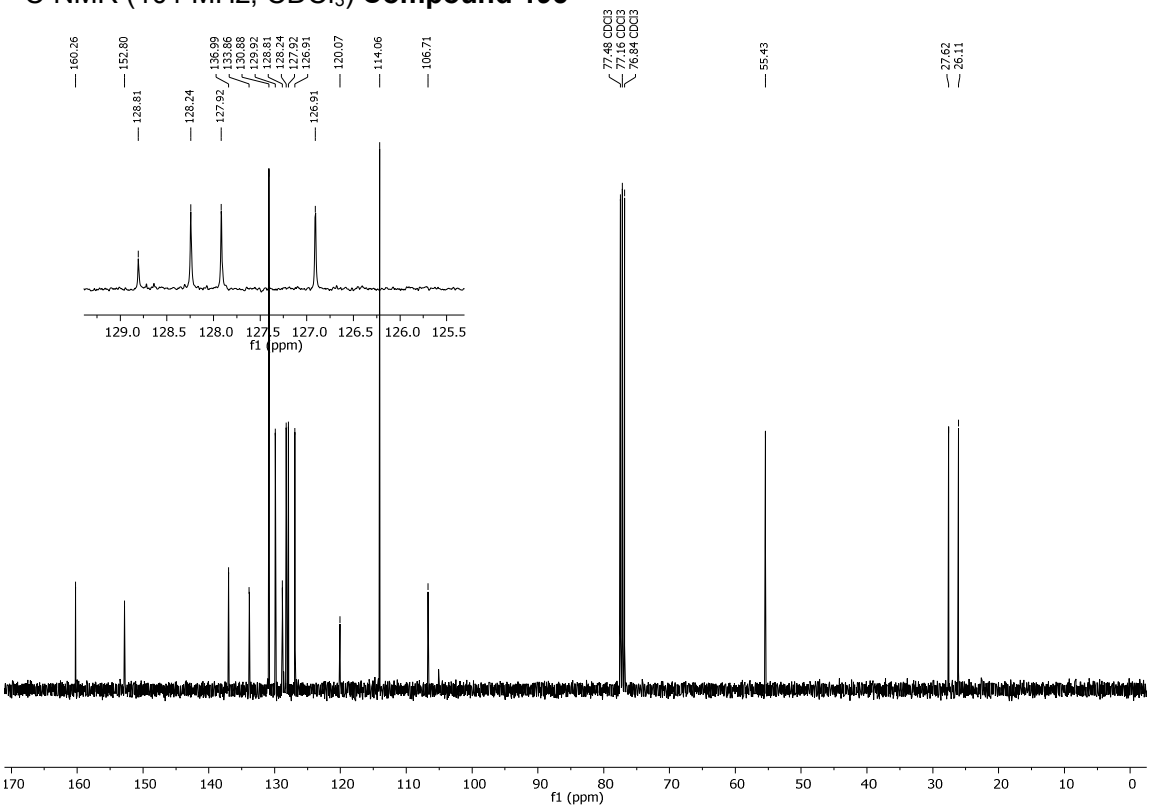
^{13}C NMR (75 MHz, $CDCl_3$) **Compound 135x**



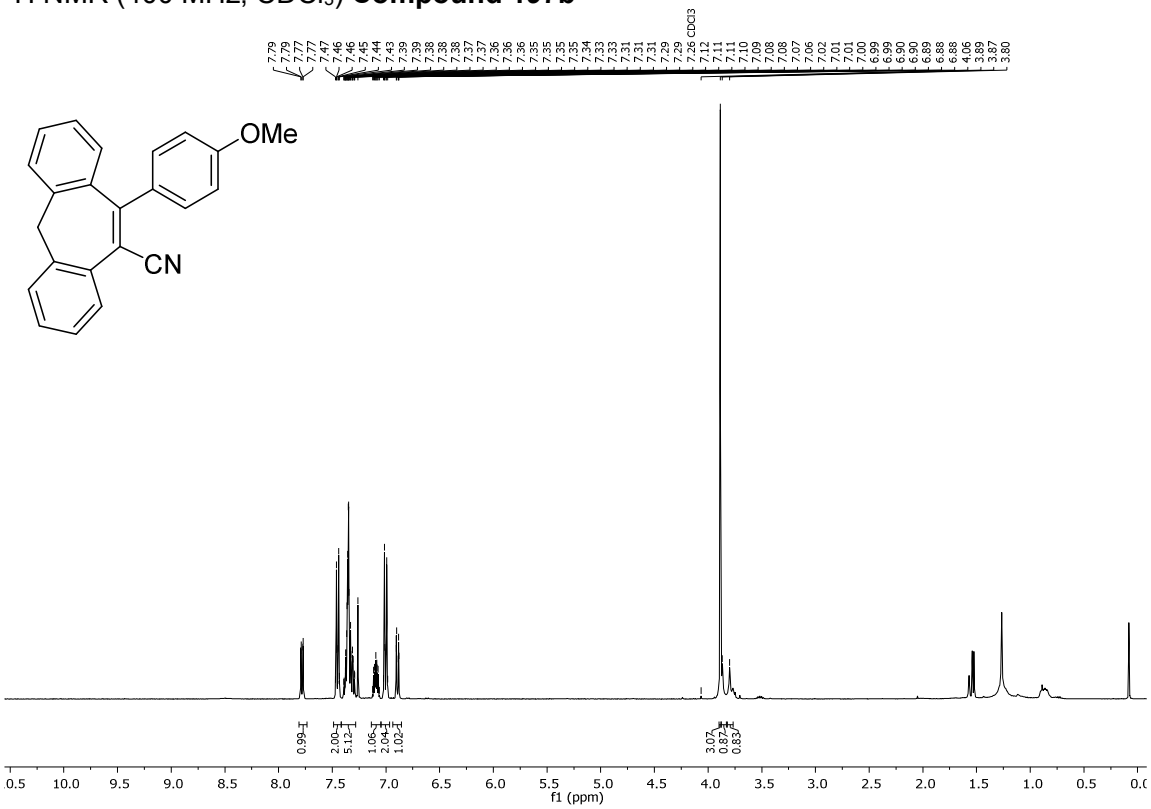
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 195**



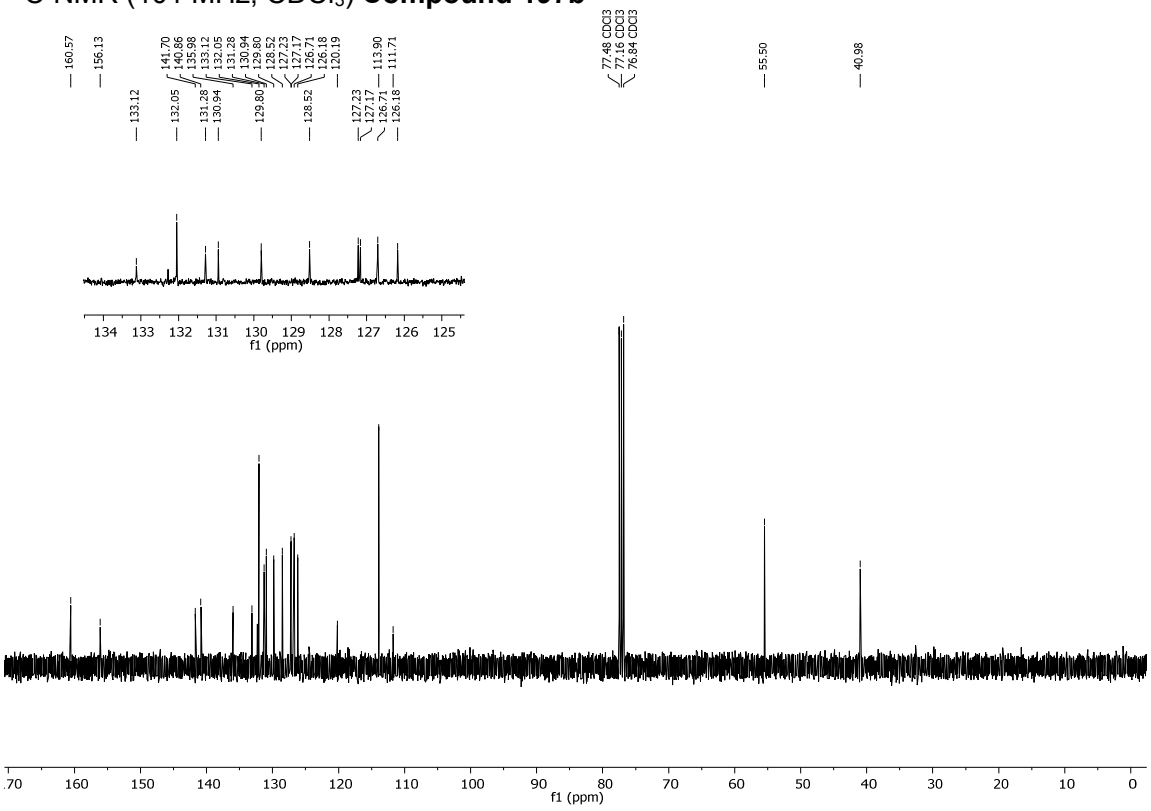
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 195**



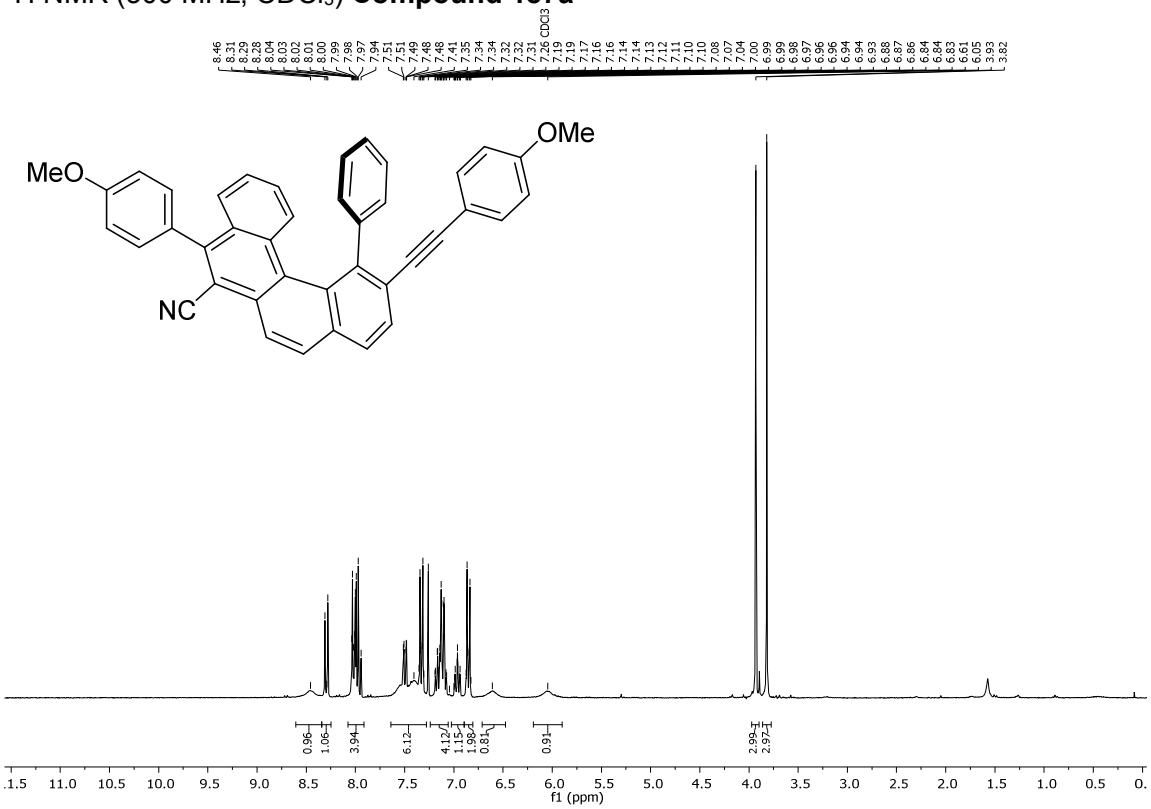
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 197b**



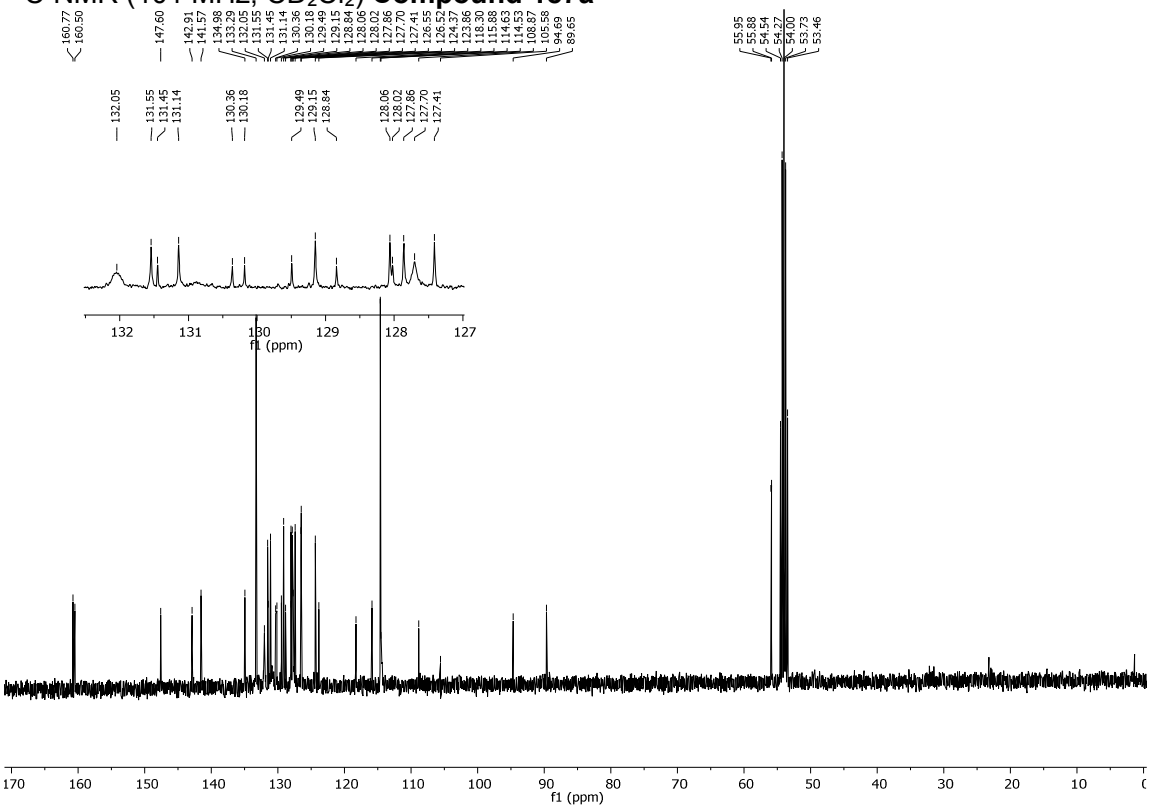
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 197b**



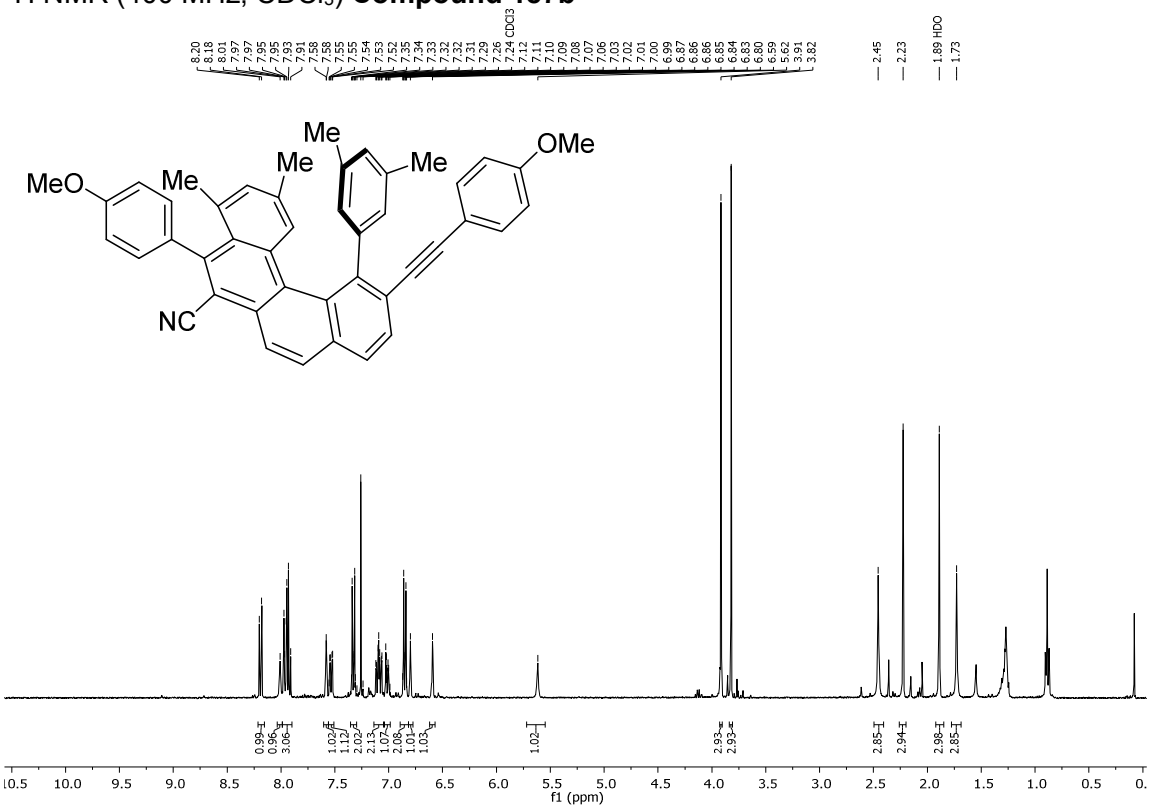
^{1}H NMR (300 MHz, $CDCl_3$) **Compound 187a**



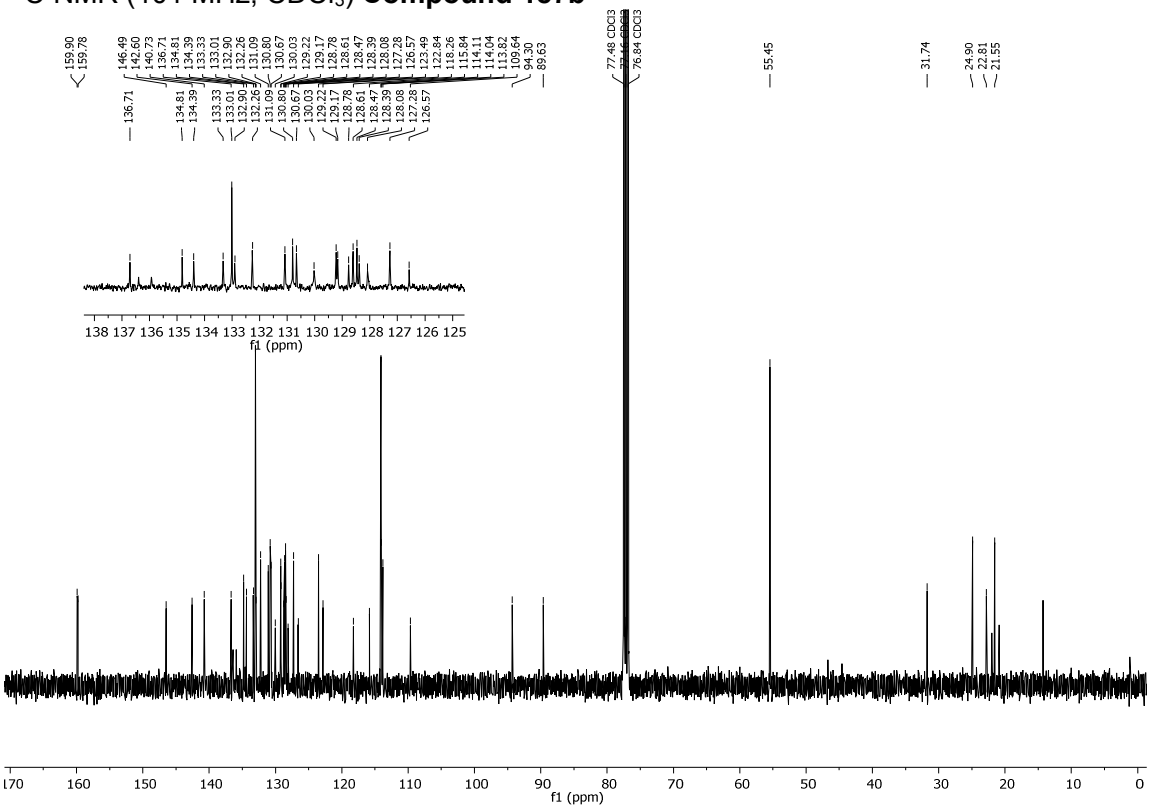
^{13}C NMR (101 MHz, CD_2Cl_2) **Compound 187a**



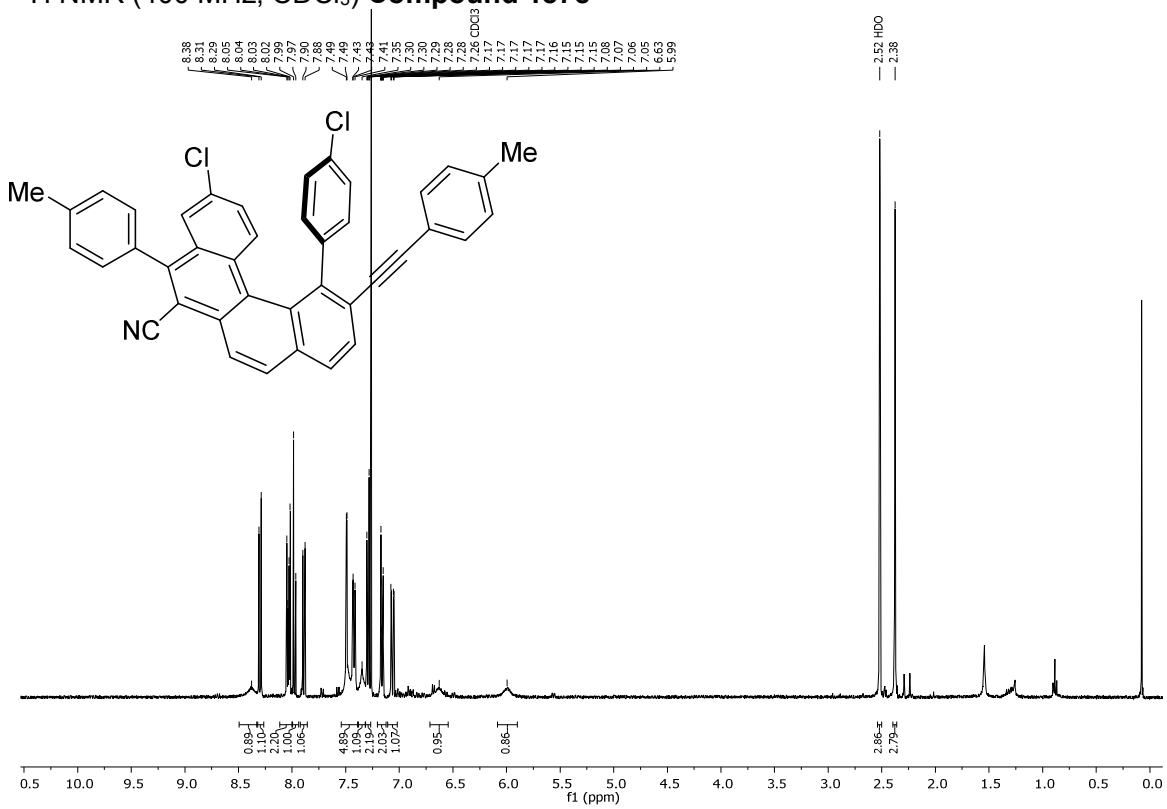
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 187b**



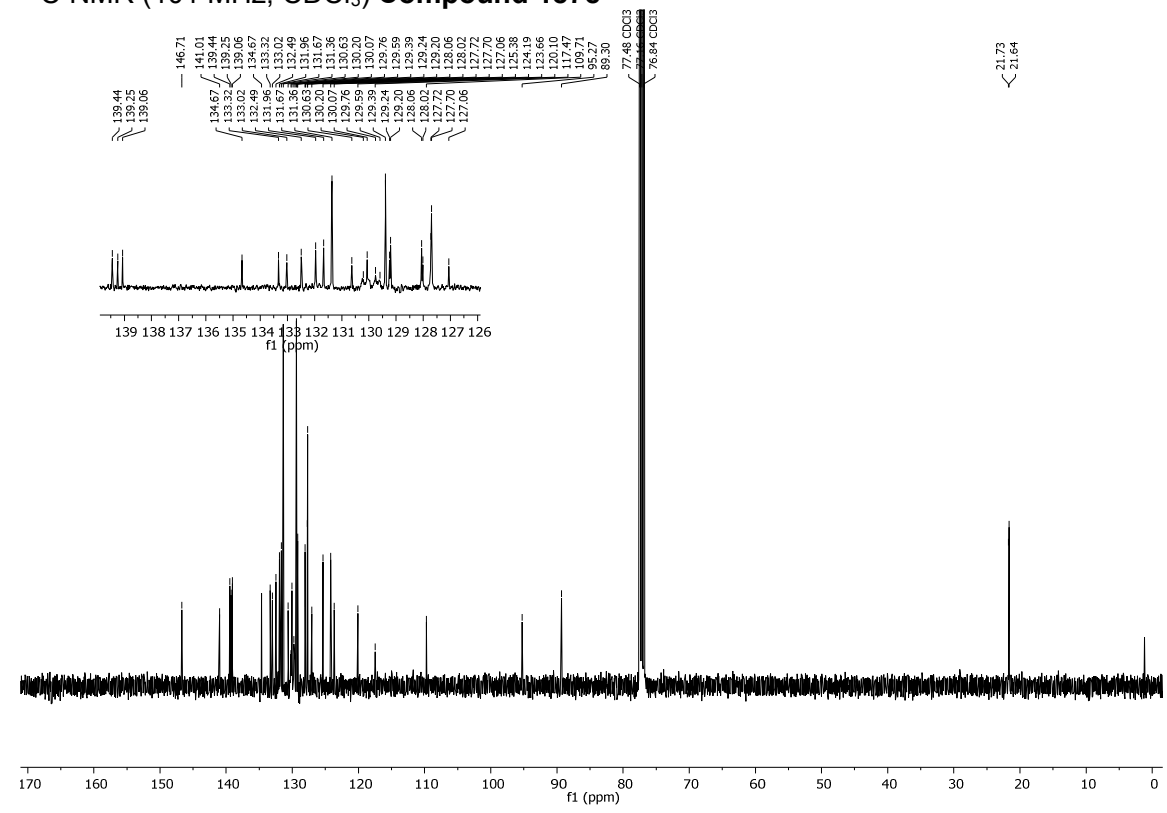
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 187b**



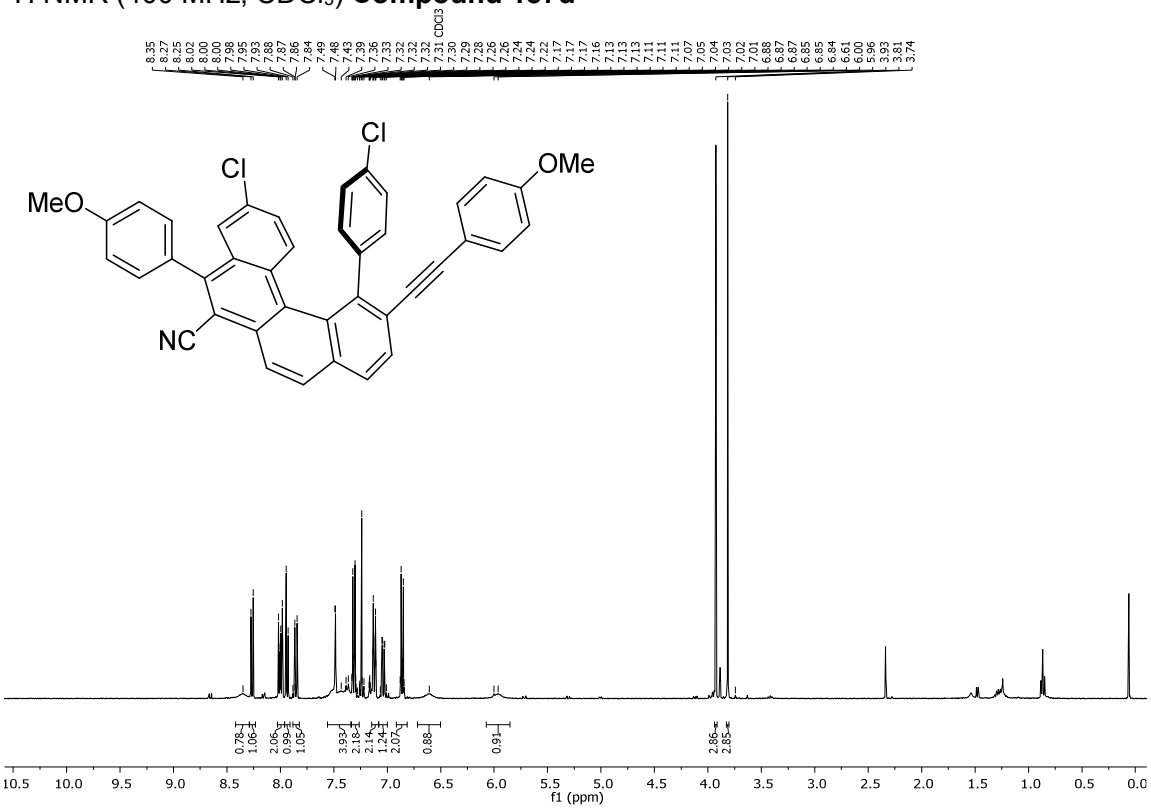
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 187c**



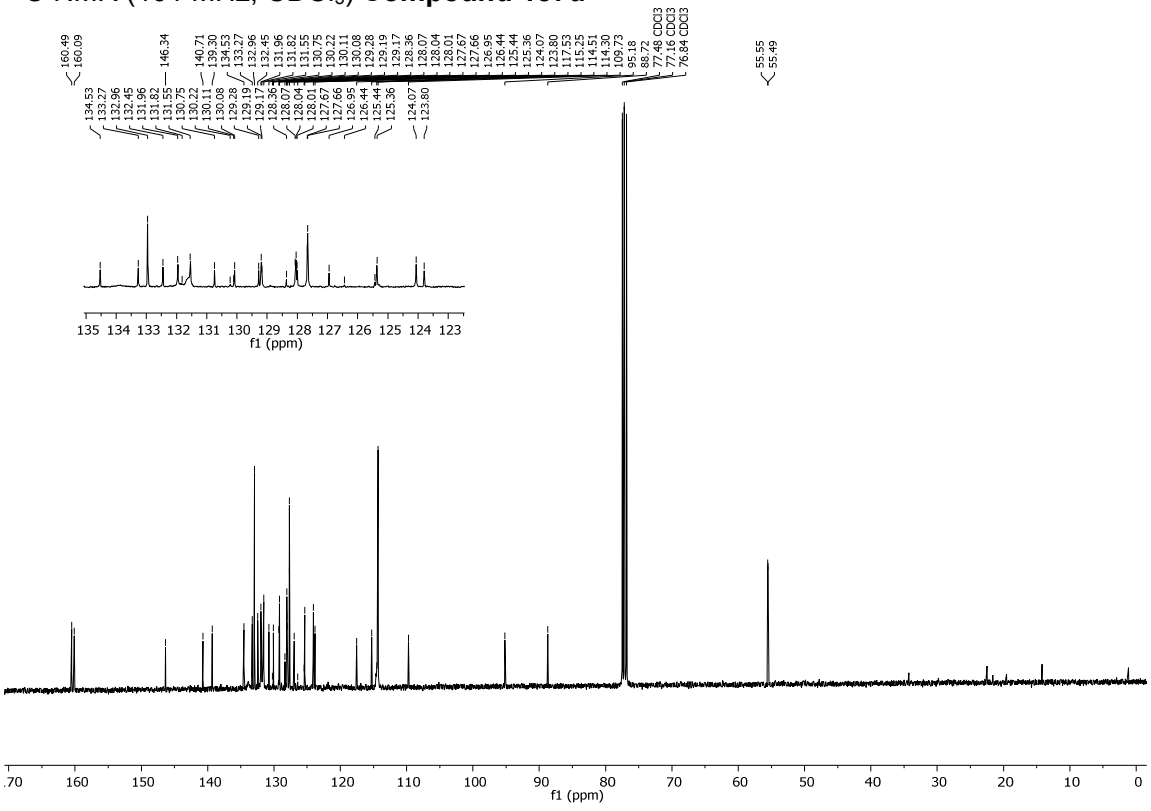
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 187c**



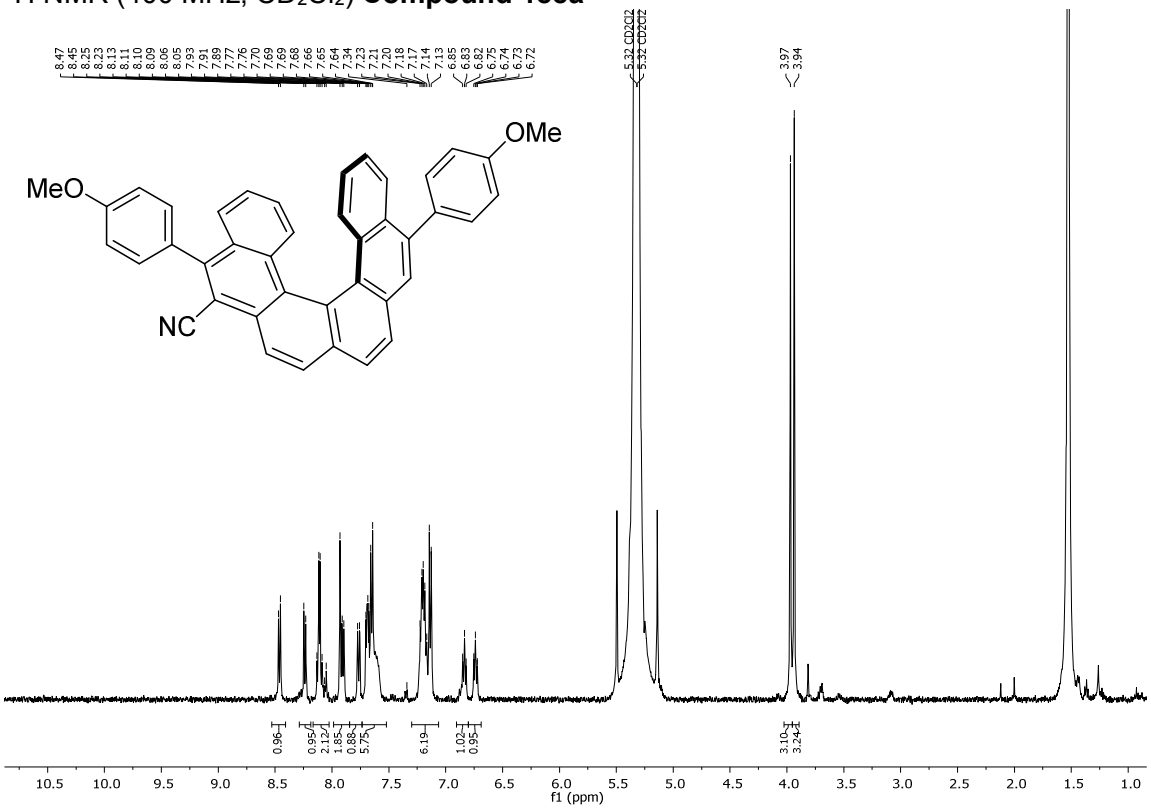
^{1}H NMR (400 MHz, $CDCl_3$) **Compound 187d**



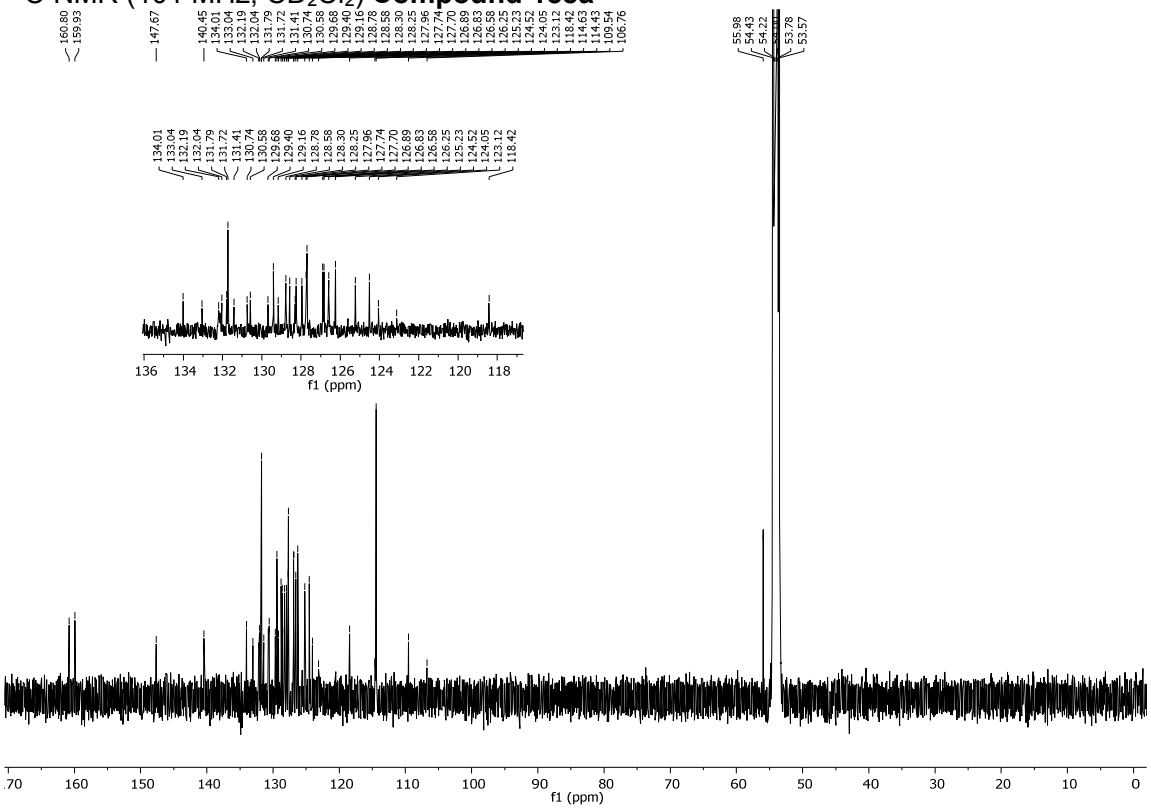
^{13}C NMR (101 MHz, $CDCl_3$) **Compound 187d**



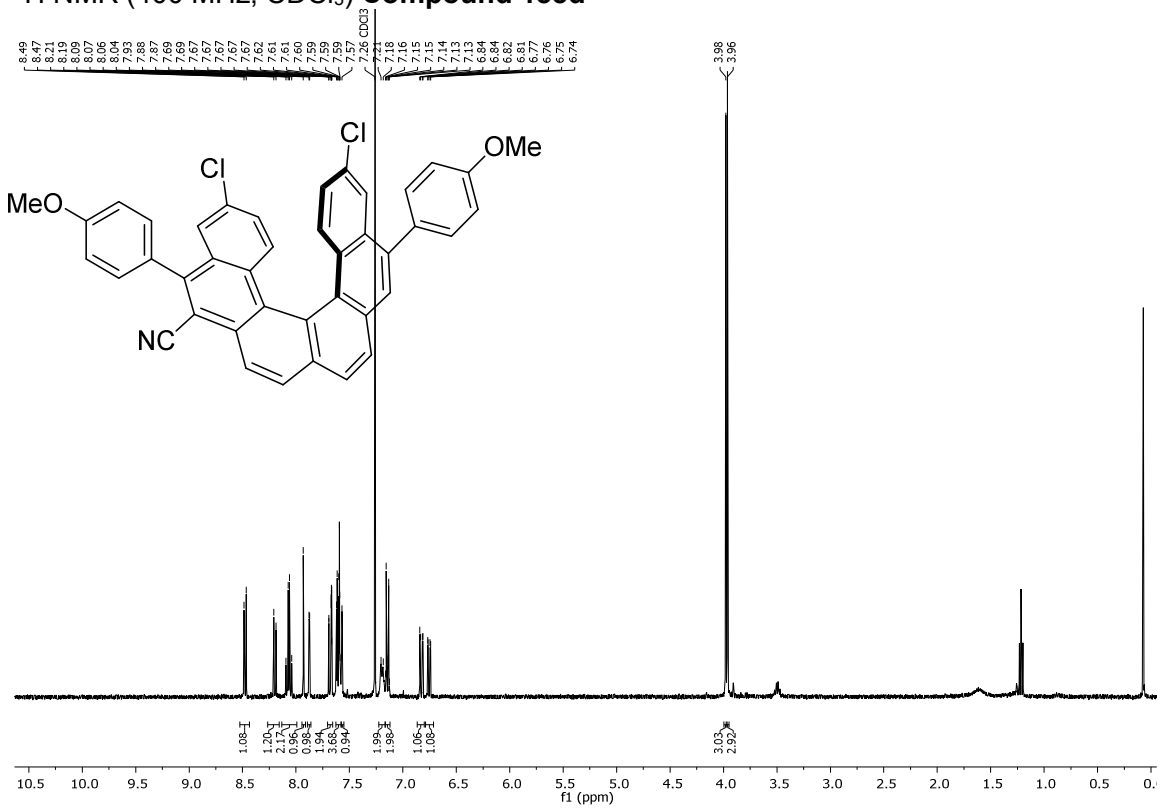
^{1}H NMR (400 MHz, CD_2Cl_2) **Compound 188a**



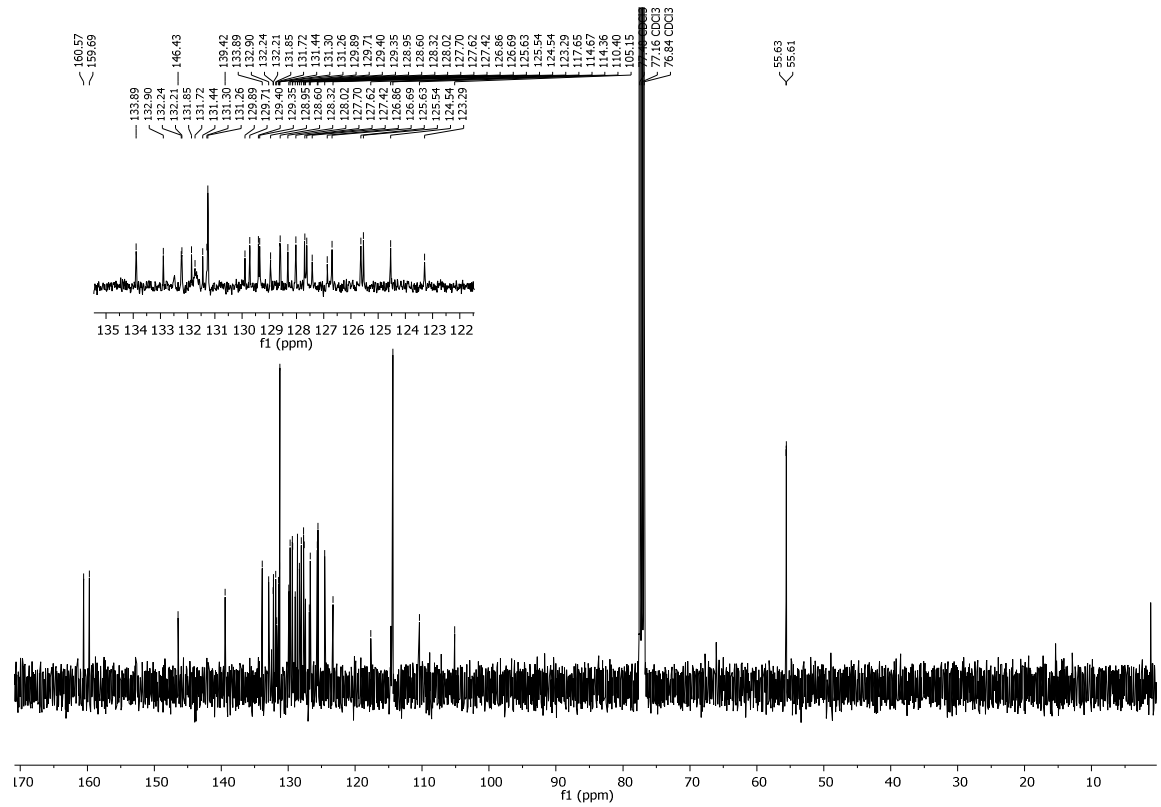
^{13}C NMR (101 MHz, CD_2Cl_2) **Compound 188a**



^{1}H NMR (400 MHz, $CDCl_3$) **Compound 188d**



^{13}C NMR (101 MHz, $CDCl_3$) **Compound 188d**



7.2. List of abbreviations.

Ac	acetyl
AIBN	2,2'-azobis(2-metilpropionitrilo)
aq.	aqueous media
Ar	aromatic substituent
B	base
bs	broad NMR singlet
Bu	butyl
Bn	benzyl
Bz	benzoyl
ºC	degree Celsius
ĉ	concentration
ca.	*circa*
calcd.	calculated
cat.	catalytic amount
cf.	*confer*
cm	centimetres
Cy	cyclohexyl
δ	chemical shift
d	doublet (NMR)
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
dd	doublet of doublets (NMR)
ddd	doublet of doublets of doublets (NMR)
DDQ	2,3-Dichloro-5,6-dicyano-*p*benzoquinone
decomp.	decomposition
DG	directing group
DIBAL-H	diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMA	dimethylacetamide
DMF	*N,N*-Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	dimethyl sulfoxide
DPEPhos	bis[(2-diphenylphosphino)phenyl] ether
DPPE	1,2-Bis(diphenylphosphino)ethane
dt	doublet of triplets (NMR)
e−	electron
ee	enantiomeric excess
EI	Electron Ionization
equiv.	equivalents
ESI	Electrospray Ionization
Et	ethyl
et al.	*et alii*
eV	electronvolt
EWG	electron-withdrawing group

g	gram
GC	Gas Chromatography
gas.	gaseous
h	hour
HMBC	Heteronuclear Multiple-Bond Correlation spectroscopy
HOMO	Highest Occupied Molecular Orbital
HRMS	High Resolution Mass Spectroscopy
Hz	Herz
i	*iso*-
IR	infrarred spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
K	Kelvin
kcal	kilocalorie
kJ	kilojoule
L	generic ligand
L	litre
LUMO	Lowest Unoccupied Molecular Orbital
m	*meta*-
m	multiplet (NMR)
m/z	mass-to-charge ratio
M	generic metal
M	molar
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
min	minute
MS	Mass Spectrometry
μW	microwave
n	linear
n.a.	not applicable
n.d.	not detected
n.r.	no reaction
NBS	*N*-bromosuccinimide
NCTS	*N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide
NIS	*N*-iodosuccinimide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
Nu	generic nucleophile
o	*ortho*-
p	*para*-
pent	pentet (NMR)
Ph	phenyl
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
pin	pinacol
PMB	4-methoxybenzyl ether
ppm	parts per million
Pr	propyl
q	quartet (NMR)
R	generic substituent

rt	room temperature
s	second
s	singlet
sept	septet (NMR)
SET	Single Electron Transfer
sext	sextuplet (NMR)
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	time
t	triplet
T	Temperature
t	*tert*-
TBAB	Tetra-*n*-butylammonium bromide
TBAF	Tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
td	triplet of doublets (NMR)
Tf	triflyl
THF	tetrahydrofurane
THP	tetrahydropyrane
TLC	Thin Layer Chromatography
TMS	trimethylsilyl
Tol	tolyl
Ts	tosyl
tt	triplet of triplets (NMR)
UV	Ultraviolet
vs	*versus*
X	generic halogen
Y	generic heteroatom

7.3. References.

[1] Z. Rappoport (Ed.), *Chemistry of the Cyano Group*, Wiley, Chichester, **1970**.

[2] A. D. McNaught, A. Wilkinson, *Compendium of chemical terminology*. *IUPAC recommendations*, Blackwell Science, Oxford, **1997**.

[3] E. Gail, S. Gos, R. Kulzer, J. Lorösch, A. Rubo, M. Sauer, in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, **2000**. Online: https://doi.org/10.1002/14356007.a08_159

[4] R. Eisler, S. N. Wiemeyer, in *Reviews of Environmental Contamination and Toxicology*, G. W. Ware (Ed.), Springer, NY, *Vol. 183*, **2004**, pp. 21–54.

[5] a) A. Rubo, R. Kellens, J. Reddy, N. Steier, W. Hasenpusch, *Alkali Metal Cyanides*, in Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH, Weinheim, **2006**. Online: https://doi.org/10.1002/14356007.i01_i01; b) A. J. Fatiadi, in *Preparation and synthetic applications of cyano compounds*, S. Patai, Z. Rappoport (Eds.), Wiley-VCH, NY, **1983**; c) R. C. Larock, in *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Wiley-VCH, Weinheim, **1989**, pp 819–955; d) C. Grundmann in: *Methoden der organischen Chemie (Houben-Weyl), Vol. E5*, *4th Ed.*, J. Falbe (Ed.), Thieme, Stuttgart, **1985**, pp. 1313 ff.

[6] R. A. Scott (Ed.), *Encyclopedia of inorganic and bioinorganic chemistry*, Wiley, Chichester, **2012**.

[7] In *IUPAC Compendium of Chemical Terminology*, M. Nič, J. Jirát, B. Košata, A. Jenkins, A. McNaught (Eds.), IUPAC, Research Triagle Park, NC, **2009**.

[8] a) J. S. Miller, J. L. Manson, *Acc. Chem. Res*. **2001**, *34*, 563; b) F. F. Fleming, *Nat. Prod. Rep.* **1999**, *16*, 597.

[9] a) A. E. Ardis, Pat. Appl. US 00002467926 A **1947**; b) E. Konrad, E. Tschunkur, US Pat. US 000001973000 A, **1934**.

[10] a) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *J. Med. Chem.* **2010**, *53*, 7902; b) A. Kleemann, J. Engel, B. Kutscher, D. Reichert, *Pharmaceutical Substances: Synthesis, Patents, Applications*. *4th Ed*., Thieme, Stuttgart, **2001**, pp. 241–242, 302, 488–489, 553, 542, 825–826, 1154, 1598–1599.

[11] F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry, Part B: Reactions and Synthesis, 5th Edition*, Springer, Heidelberg, **2007**.

[12] L. Friedman, H. Shechter, *J. Org. Chem.* **1960**, *25*, 877.

[13] O. H. Oldenziel, D. van Leusen, A. M. van Leusen, *J. Org. Chem.* **1977**, *42*, 3114.

[14] Review: G. Yan, Y. Zhang, J. Wang, *Adv. Synth. Catal.* **2017**, *359*, 4068.

[15] a) J. P. English, J. H. Clark, R. G. Shepherd, H. W. Marson, J. Krapcho, R. O. Roblin Jr., *J. Am. Chem. Soc.* **1946**, *68*, 1039; b) C. S. Marvel, M. M. Martin, *J. Am. Chem. Soc.* **1958**, *80*, 6600. For the modern protocols see ref. [14] and (c) *C.-W. Kuo, J.-L. Zhu, J.-D. Wu, C.-M. Chu, C.-F. Yao, K.-S. Shia, Chem. Commun.* ***2007****, 301.*

[16] S. S. Deshmukh, S. N. Huddar, R. R. Jadhav, K. G. Akamanchi, *Tetrahedron Lett.* **2011**, *52*, 4533.

[17] B. V. Rokade, K. R. Prabhu, *J. Org. Chem.* **2012**, *77*, 5364.

[18] J.-H. Xu, Q. Jiang, C.-C. Guo, *J. Org. Chem.* **2013**, *78*, 11881.

[19] N. Okamoto, M. Ishikura, R. Yanada, *Org. Lett.* **2013**, *15*, 2571.

[20] W. Zhou, J. Xu, L. Zhang, N. Jiao, *Org. Lett.* **2010**, *12*, 2888.

[21] K. M. Lambert, J. M. Bobbitt, S. A. Eldirany, K. B. Wiberg, W. F. Bailey, *Org. Lett.* **2014**, *16*, 6484.

[22] N. Jiang, A. J. Ragauskas, *Tetrahedron Lett.* **2010**, *51*, 4479.

[23] S. Zhou, K. Junge, D. Addis, S. Das, M. Beller, *Org. Lett.* **2009**, *11*, 2461.

[24] a) L. Andrussow, *Angew. Chem.* **1935**, *48*, 593; b) L. Andrussow, *Ber. dtsch. Chem. Ges. A/B* **1927**, *60*, 2005.

[25] R. Banavali, M. Y. Chang, S. J. Fitzwater, R. Mukkamala, *Ind. Eng. Chem. Res.* **2002**, *41*, 145.

[26] J. Podlech, *Science of Synthesis* **2004**, *19*, 325.

[27] a) A. Strecker, *Justus Liebigs Ann. Chem.* **1854**, *91*, 349; b) A. Strecker, *Justus Liebigs Ann. Chem.* **1850**, *75*, 27.

[28] F. Winkler, *Ann. Chem.* **1832**, *4*, 246.

[29] A. Lapworth, *J. Chem. Soc.* **1903**, *83*, 995.

[30] W. Cho, S. Kang, A. Medda, J. Lee, I. Choi, H.-S. Lee, *Synthesis* **2008**, , 507.

[31] R. J. McKinney, D. C. Roe, *J. Am. Chem. Soc.* **1986**, *108*, 5167.

[32] a) T. Sandmeyer, *Ber. dtsch. Chem. Ges.* **1884**, *17*, 2650; b) Review: C. Galli, *Chem. Rev*. **1988**, *88*, 765. For SET-processes see also: c) E. C. Ashby, *Acc. Chem. Res*. **1988**, *21*, 414.

[33] a) K. W. Rosenmund, E. Struck, *Ber. dtsch. Chem. Ges.* **1919**, *52*, 1749; b) Review: J. Lindley, *Tetrahedron* **1984**, *40*, 1433.

[34] J. Zanon, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 2890.

[35] T. Schareina, A. Zapf, M. Beller, *Tetrahedron Lett.* **2005**, *46*, 2585.

[36] G. Zhang, L. Zhang, M. Hu, J. Cheng, *Adv. Synth. Catal.* **2011**, *353*, 291.

[37] X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790.

[38] Y. Nagase, T. Sugiyama, S. Nomiyama, K. Yonekura, T. Tsuchimoto, *Adv. Synth. Catal.* **2014**, *356*, 347.

[39] S. Ding, N. Jiao, *J. Am. Chem. Soc.* **2011**, *133*, 12374.

[40] D. N. Sawant, Y. S. Wagh, P. J. Tambade, K. D. Bhatte, B. M. Bhanage, *Adv. Synth. Catal.* **2011**, *353*, 781.

[41] A. B. Khemnar, B. M. Bhanage, *RSC Adv.* **2014**, *4*, 13405.

[42] B. Liu, J. Wang, B. Zhang, Y. Sun, L. Wang, J. Chen, J. Cheng, *Chem. Commun.* **2014**, *50*, 2315.

[43] a) J. Kim, S. Chang, *J. Am. Chem. Soc.* **2010**, *132*, 10272. For the selected comprehensive Reviews on C–H activation see: b) *Catalytic Transformations via C–H Activation, Vol. 1–2*, J.-Q. Yu (Ed.), *Science of Synthesis*, Thieme, Stuttgart, **2016**, and references cited therein; c) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed*. **2009**, *48*, 9792; d) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev*. **2007**, *107*, 174; e) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev*. **2007**, *36*, 1173.

[44] X. Ren, J. Chen, F. Chen, J. Cheng, *Chem. Commun.* **2011**, *47*, 6725.

[45] a) C. Pan, H. Jin, P. Xu, X. Liu, Y. Cheng, C. Zhu, *J. Org. Chem.* **2013**, *78*, 9494; b) R.-J. Song, J.-C. Wu, Y. Liu, G.-B. Deng, C.-Y. Wu, W.-T. Wei, J.-H. Li, *Synlett* **2012**, *23*, 2491.

[46] F. Urech, *Justus Liebigs Ann. Chem.* **1872**, *164*, 255.

[47] Z. Jiang, Q. Huang, S. Chen, L. Long, X. Zhou, *Adv. Synth. Catal.* **2012**, *354*, 589.

[48] F.-H. Luo, C.-I. Chu, C.-H. Cheng, *Organometallics* **1998**, *17*, 1025.

[49] S. Zheng, C. Yu, Z. Shen, *Org. Lett.* **2012**, *14*, 3644.

[50] a) K. Zheng, P. Yu, S. Chen, F. Chen, J. Cheng, *Chin. J. Chem.* **2013**, *31*, 449; b) G. Zhang, S. Chen, H. Fei, J. Cheng, F. Chen, *Synlett* **2012**, *23*, 2247.

[51] X. Fang, P. Yu, B. Morandi, *Science* **2016**, *351*, 832.

[52] Y. Ito, H. Kato, H. Imai, T. Saegusa, *J. Am. Chem. Soc.* **1982**, *104*, 6449.

[53] a) S. Xu, X. Huang, X. Hong, B. Xu, *Org. Lett.* **2012**, *14*, 4614; b) J. Peng, J. Zhao, Z. Hu, D. Liang, J. Huang, Q. Zhu, *Org. Lett.* **2012**, *14*, 4966. For the Review on metal-catalyzed C–H functionalization involving isocyanides, see: c) B. Song, B. Xu, *Chem. Soc. Rev.* **2017**, *46***,** 1103.

[54] X. Hong, H. Wang, G. Qian, Q. Tan, B. Xu, *J. Org. Chem.* **2014**, *79*, 3228.

[55] A. A. Breneman, *J. Am. Chem. Soc.* **1889**, *11*, 2.

[56] W. C. Fernelius (Ed.), *Inorganic Syntheses*, *Vol. 2*, NY, McGraw-Hill Book, **1946**.

[57] A. Haller, *Compt. Rend*. **1882**, *95*, 142.

[58] M. E. Kuehne, *J. Am. Chem. Soc.* **1959**, *81*, 5400.

[59] C. Podesva, E. J. Tarlton, A. F. McKay, *Can. J. Chem.* **1962**, *40*, 1403.

[60] P.-L. Compagnon, B. Grosjean, *Synthesis* **1976**, *1976*, 448.

[61] T.-L. Ho, C. M. Wong, *Synth. Commun.* **1973**, *3*, 317.

[62] D. Martin, M. Bauer, *Org. Synth.* **1983**, *61*, 35.

[63] K.-H. Boltze, H.-D. Dell, H. Jansen, *Justus Liebigs Ann. Chem.* **1967**, *709*, 63.

[64] K. Koyama, T. Susuki, S. Tsutsumi, *Tetrahedron Lett.* **1965**, *6*, 627.

[65] C. Zhu, J.-B. Xia, C. Chen, *Org. Lett.* **2014**, *16*, 247.

[66] a) E. Grigat, R. Pütter, *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 206. For the recent Review on the construction of X–CN (X=N, S, O) bonds see: b) J.-T. Yu, F. Teng, J. Cheng, *Adv. Synth. Catal*. **2017**, *359*, 26.

[67] N. Sato, *Tetrahedron Lett.* **2002**, *43*, 6403.

[68] A. M. van Leusen, J. C. Jagt, *Tetrahedron Lett.* **1970**, *12*, 967.

[69] a) D. Kahne, D. B. Collum, *Tetrahedron Lett.* **1981**, *50*, 5011; b) R. Akula, H. Ibrahim, *RSC Adv.* **2013**, *3*, 25719; c) K. Kiyokawa, T. Nagata, S. Minakata, *Angew. Chem. Int. Ed.* **2016**, *55*, 10458.

[70] a) R. G. Pews, F. P. Corson, *J. Chem. Soc. D* **1969**, 1187b; b) Z. Li, J. Xu, *Phosphorus, Sulfur, and Silicon and the Related Elements* **2014**, *189*, 374; c) A. M. van Leusen, A. J. W. Iedema, J. Strating, *Chem. commun.* **1968**, 440; d) J. M. Cox, R. Ghosh, *Tetrahedron Lett.* **1969**, *10*, 3351.

[71] N. J. Foulger, B. J. Wakefield, *Tetrahedron Lett.* **1972**, *41*, 4169.

[72] a) T. V. Hughes, S. D. Hammond, M. P. Cava, *J. Org. Chem.* **1998**, *63*, 401; b) S. Thambidurai, K. Jeyasubramanian, S. K. Ramalingam, *Polyhedron* **1996**, *15*, 4011.

[73] a) Y.-q. Wu, D. C. Limburg, D. E. Wilkinson, G. S. Hamilton, *Org. Lett.* **2000**, *2*, 795; b) T. Tanaka, N. Maezaki, A. Furusawa, S. Uchida, *Heterocycles* **2003**, *59*, 161; c) P. Anbarasan, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 4725.

[74] F. Kurzer, *J. Chem. Soc.* **1949**, 1034.

[75] P. Anbarasan, H. Neumann, M. Beller, *Chem. Eur. J.* **2011**, *17*, 4217.

[76] P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2011**, *50*, 519.

[77] Y. Yang, Y. Zhang, J. Wang, *Org. Lett.* **2011**, *13*, 5608.

[78] a) D.-G. Yu, T. Gensch, F. de Azambuja, S. Vásquez-Céspedes, F. Glorius, *J. Am. Chem. Soc.* **2014**, *136*, 17722. See also: b) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 3635. For the review on advances in C–CN bond formation *via* C–H

bond activation, see: c) Y. Ping, Q. Ding, Y. Peng, *ACS Catal.* **2016**, *6*, 5989.

[79] Y. Yang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2014**, *53*, 8677.

[80] W. Liu, S. C. Richter, R. Mei, M. Feldt, L. Ackermann, *Chem. Eur. J.* **2016**, *22*, 17958.

[81] J. Li, W. Xu, J. Ding, K.-H. Lee, *Tetrahedron Lett.* **2016**, *57*, 1205.

[82] a) W. Liu, L. Ackermann, *Chem. Commun.* **2014**, *50*, 1878; b) A. Mishra, T. Kumari Vats, I. Deb, *J. Org. Chem*. **2016**, *81*, 6525. For Rh-catalyzed cyanations with NCTS see: c) X. Zhu, X.-J. Shen, Z.-Y. Tian, S. Lu, L.-L. Tian, W.-B. Liu, B. Song, X.-Q. Hao, *J. Org. Chem*. **2017**, *82*, 6022; d) N. Kumar Mishra, T. Jeong, S. Sharma, Y. Shin, S. Han, J. Park, J. S. Oh, J. H. Kwak, Y. H. Jung, I. S. Kim, *Adv. Synth. Cat*. **2015**, *357*, 1293; e) M. Chaitanya, P. Anbarasan, *J. Org. Chem*. **2015,** *80*, 3695; f) J. Dong, Z. Wu, Z. Liu, P. Liu, P. Sun, *J. Org. Chem*. **2015**, *80*, 12588; g) L.-J. Gu, C. Jin, R. Wang, H.-Y. Ding, *ChemCatChem* **2014**, *6*, 1225.

[83] H. Xu, P.-T. Liu, Y.-H. Li, F.-S. Han, *Org. Lett.* **2013**, *15*, 3354.

[84] a) J. I. Musher, *Angew. Chem. Int. Ed. Engl*. **1969**, *8*, 54; b) G. C. Pimentel, *J. Chem. Phys.* **1951**, *19*, 446**.**

[85] E. Vedejs, S. E. Denmark, *Lewis base catalysis in organic synthesis*, Wiley-VCH, Weinheim, **2016**.

[86] The first hypervalent iodine compound, $PhICl_2$, was prepared in 1886: a) Willgerodt, *J. Prakt. Chem.* **1886**, 33, 185; however, a renaissance in the chemistry of polyvalent iodine has occured only in the past 30 years. For Reviews see: b) A. Yoshimura, V. V. Zhdankin, *Chemical reviews* **2016**, *116*, 3328; c) V. V. Zhdankin, *Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds*, Wiley, Chichester, **2013**; d) Special Issue *Hypervalent Iodine Chemistry*, T. Wirth (Ed.), *Top. Curr. Chem*. **2016**, *373, 316 pp*; e) K. Aradi, B. L. Tóth, G. L. Tolnai, Z. Novák, *Synlett* **2016**, *27*, 1456.

[87] M. Nič, J. Jirát, B. Košata, A. Jenkins, A. McNaught (Eds.), *IUPAC Compendium of Chemical Terminology*, IUPAC, Research Triagle Park, NC, **2009**.

[88] P. J. Stang, V, V. Zhdankin, in *An Introduction to Lorentz Surfaces*, T. Weinstein (Ed.), DE GRUYTER, Berlin, New York, **1996**, pp. 1–3.

[89] Y.-F. Wang, J. Qiu, D. Kong, Y. Gao, F. Lu, P. G. Karmaker, F.-X. Chen, *Org. Biomol. Chem.* **2015**, *13*, 365.

[90] a) V. V. Zhdankin, C. M. Crittell, P. J. Stang, N. S. Zefirov, *Tetrahedron Lett.* **1990**, *31*, 4821; b) V. V. Zhdankin, R. Tykwinski, B. L. Williamson, P. J. Stang, N. S. Zefirov, *Tetrahedron Lett.* **1991**, *32*, 733; c) P. J. Stang, V. V. Zhdankin, R. Tykwinski, N. S.

Zefirov, *Tetrahedron Lett.* **1992**, *33*, 1419; d) V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, B. Mismash, J. K. Woodward, A. J. Simonsen, *Tetrahedron Lett.* **1995**, *36*, 7975; e) M.-X. Sun, Y.-F. Wang, B.-H. Xu, X.-Q, Ma, S.-J. Zhang, *Org. Biomol. Chem*. **2018**, *16*, 1971.

[91] T. Dohi, K. Morimoto, N. Takenaga, A. Goto, A. Maruyama, Y. Kiyono, H. Tohma, Y. Kita, *J. Org. Chem.* **2007**, *72*, 109.

[92] R. Frei, T. Courant, M. D. Wodrich, J. Waser, *Chem. Eur. J.* **2015**, *21*, 2662.

[93] R. Chowdhury, J. Schörgenhumer, J. Novacek, M. Waser, *Tetrahedron Lett.* **2015**, *56*, 1911.

[94] M. Chen, Z.-T. Huang, Q.-Y. Zheng, *Org. Biomol. Chem.* **2015**, *13*, 8812.

[95] X. Wang, A. Studer, *J. Am. Chem. Soc.* **2016**, *138*, 2977.

[96] A. J. Arduengo, E. M. Burgess, *J. Am. Chem. Soc.* **1977**, *99*, 2376.

[97] a) N. Kano, Y. Itoh, Y. Watanabe, S. Kusaka, T. Kawashima, *Angew. Chem. Int. Ed.* **2008**, *47*, 9430; b) B. K. Ackerman, K. K. Andersen, I. Karup-Nielsen, N. B. Peynircioglu, S. A. Yeager, *J. Org. Chem.* **1974**, *39*, 964.

[98] a) L. Gu, L. M. Wolf, A. Zieliński, W. Thiel, M. Alcarazo, *J. Am. Chem. Soc.* **2017**, *139*, 4948; b) H. Tinnermann, C. Wille, M. Alcarazo, *Angew. Chem. Int. Ed.* **2014**, *53*, 8732; c) J. Petuškova, M. Patil, S. Holle, C. W. Lehmann, W. Thiel, M. Alcarazo, *J. Am. Chem. Soc.* **2011**, *133*, 20758.

[99] E. González-Fernández, L. D. M. Nicholls, L. D. Schaaf, C. Farès, C. W. Lehmann, M. Alcarazo, *J. Am. Chem. Soc.* **2017**, *139*, 1428.

[100] J. Carreras, G. Gopakumar, L. Gu, L. Gu, A. Gimeno, P. Linowski, J. Petuškova, W. Thiel, M. Alcarazo, *J. Am. Chem. Soc.* **2013**, *135*, 18815.

[101] J. Carreras, M. Patil, W. Thiel, M. Alcarazo, *J. Am. Chem. Soc.* **2012**, *134*, 16753.

[102] H. J. Lucas, E. R. Kennedy, *Org. Synth.* **1942**, *22*, 69.

[103] G. Talavera, J. Peña, M. Alcarazo, *J. Am. Chem. Soc.* **2015**, *137*, 8704.

[104] a) N. Bricklebank, P. J. Skabara, D. E. Hibbs, M. B. Hursthouse, K. M. Abdul Malik, *J. Chem. Soc.*, *Dalton Trans*. **1999**, 3007; b) M. C. Aragoni, M. Arca, F. Demartin, F. A. Devillanova, A. Garau, F. Isaia, F. Lelj, V. Lippolis, G. Verani, *Chem. Eur. J*. **2001**, *7*, 3122, and references cited therein; c) b) M. C. Aragoni, M. Arca, F. A. Devillanova, P. Grimaldi, F. Isaia, F. Lelj, V. Lippolis, *Eur. J. Inorg. Chem.* **2006**, 2166, d) K. F. G. Averesch, forthcoming *Dissertation*, Universität Göttingen, **2019**, in preparation; e) M. Hinrichs, *Masterarbeit*, Universität Göttingen, **2017**. f) J. Esselborn, *Masterarbeit*, Universität Göttingen, **2017**.

[105] a) D. C. Koester, M. Kobayashi, D. B. Werz, Y. Nakao, *J. Am. Chem. Soc.* **2012**, *134*, 6544; b) Y. Nakao, *Bull. Chem. Soc. Jpn* **2012**, *85*, 731.

[106] A. Arora, *Hydrocarbons*. *Alkanes, alkenes, and alkynes*, Discovery Publishing, New Delhi, **2006**.

[107] R. R. Naredla, D. A. Klumpp, *Chem. Rev.* **2013**, *113*, 6905.

[108] K. L. Wilson, A. R. Kennedy, J. Murray, B. Greatrex, C. Jamieson, A. J. B. Watson, *Beilstein J. Org. Chem.* **2016**, *12*, 2005.

[109] a) N. M. Brunkan, D. M. Brestensky, W. D. Jones, *J. Am. Chem. Soc.* **2004**, *126*, 3627; b) C. A. Tolman, W. C. Seidel, J. D. Druliner, P. J. Domaille, *Organometallics* **1984**, *3*, 33.

[110] D. Pan, C. Zhang, S. Ding, N. Jiao, *Eur. J. Org. Chem.* **2011**, 4751.

[111] K. Tanaka, Y. Shigematsu, M. Sukekawa, Y. Hoshino, K. Honda, *Tetrahedron Lett.* **2016**, *57*, 5914.

[112] H. Wang, L. Li, X.-F. Bai, W.-H. Deng, Z.-J. Zheng, K.-F. Yang, L.-W. Xu, *Green Chem.* **2013**, *15*, 2349.

[113] L. Minuti, A. Taticchi, A. Marrocchi, S. Landi, E. Gacs-Baitz, *Tetrahedron Lett.* **2005**, *46*, 5735.

[114] E. Chatzopoulou, P. W. Davies, *Chem. Commun.* **2013**, *49*, 8617.

[115] A. J. Warner, A. Churn, J. S. McGough, M. J. Ingleson, *Angew. Chem. Int. Ed.* **2017**, *56*, 354.

[116] J. Peña, G. Talavera, B. Waldecker, M. Alcarazo, *Chem. Eur. J.* **2017**, *23*, 75.

[117] a) C. Glaser, *Ber. dtsch. Chem. Ges*. **1869**, *2*, 422; b) A. S. Hay, *J. Org. Chem*. **1960**, *25*, 1275. For the selected reviews on this topic, see: d) *Polyynes: Synthesis, Properties, and Applications,* F. Cataldo (Ed.),CRC Press/Taylor & Francis, Boca Raton, Florida, **2005**; e) F. Diederich, P. J. Stang, R. R. Tykwinski, *Acetylene Chemistry: Chemistry, Biology and Material Science*, Wiley-VCH, Weinheim, **2005**.

[118] Y. Echigo, T. Mukaiyama, *Chem. Lett.* **1978**, 465.

[119] K. v. Auwers, R. Hugel, *J. Prakt. Chem.* **1935**, *143*, 179.

[120] P. K. Sharma, S. Ram, N. Cahndak, *Adv. Synth. Catal.* **2016**, *358*, 894.

[121] P. S. Kalsi, *Spectroscopy of organic compounds*, New Age International, New Delhi, **2004**. We are grateful to Dr. Michael John for his kind help.

[122] *These two reactions were performed by Adam Zieliński*.

[123] A. de Meijere, F. Diederich (Eds.), *Metal-catalyzed cross-coupling reactions*, Wiley-VCH, Weinheim, **2004**.

[124] A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020.

[125] A. H. V. Ratovelomana, G. Linstrumelle, *Tetrahedron Lett.* **1987**, *28*, 1649.

[126] H. Yoshida, K. Yoshida, H. Totani, T. Ogata, K. Matsumoto, *Bull. Chem. Soc. Jpn* **1990**, *63*, 3579.

[127] D. Thomae, G. Kirsch, P. Seck, *Synthesis* **2007**, 1027.

[128] C. Almansa, A. F. de Arriba, F. L. Cavalcan, L. A. Gómez, Miralles A., M. Merlos, García, *J. Med. Chem.* **2001**, *44*, 350.

[129] S. Ma, *Handbook of cyclization reactions*, Wiley-VCH, Weinheim, **2010**.

[130] C. I. Stathakis, P. L. Gkizis, A. L. Zografos, *Natural product reports* **2016**, *33*, 1093.

[131] a) R. Grigg, T.R.B. Mitchell, A. Ramasubbu, *J. Chem. Soc., Chem. Commun.* **1980**, *27*; b) B. M. Trost, M. Lautens, *J. Am. Chem. Soc.* **1985**, *107*, 1781.

[132] B. M. Trost, J. T. Hane, P. Metz, *Tetrahedron Lett.* **1986**, *27*, 5695.

[133] Trost M. B., Krische J. M., *Synlett* **1998**.

[134] A. Fürstner, V. Mamane, *J. Org. Chem.* **2002**, *67*, 6264.

[135] N. Chernyak, V. Gevorgyan, *Adv. Synth. Catal.* **2009**, *351*, 1101.

[136] a) D. W. Stephan, *J. Am. Chem. Soc.* **2015**, *137*, 10018; b) G. Du, G. Wang, W. Ma, Q. Yang, W. Bao, X. Liang, L. Zhu, C.-S. *Synlett* **2017**, *28*, 1394, and references cited therein.

[137] W. S. Johnson, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 9.

[138] T. Yao, M. A. Campo, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 3511.

[139] J. Marco-Martínez, V. López-Carrillo, E. Buñuel, R. Simancas, D. J. Cardenas, *J. Am. Chem. Soc.* **2007**, *129*, 1874.

[140] A. J. Warner, J. R. Lawson, V. Fasano, M. J. Ingleson, *Angew. Chem. Int. Ed.* **2015**, *54*, 11245.

[141] a) T. Muraoka, I. Matsuda, K. Itoh, *Organometallics* **2002**, *21*, 3650; b) T. Muraoka, I. Matsuda, K. Itoh, *Tetrahedron Lett.* **1998**, *39*, 7325.

[142] A. G. Barrado, A. Zieliński, R. Goddard, M. Alcarazo, *Angew. Chem. Int. Ed.* **2017**, *56*, 13401.

[143] W. Liu, J. Chen, R. Jin, D. Xu, Y. Li, F. Ba, G. Gu, Y. Kuang, H. Guo, *Org. Chem. Front.* **2016**, *3*, 852.

[144] F. Beltran, I. Fabre, I. Ciofini, L. Miesch, *Org. Lett.* **2017**, *19*, 5042.

[145] Y. Yang, H. Huang, W. Liu, Y. Liang, *Synth. Commun.* **2014**, *45*, 86.

[146] a) N. Saito, K. Kanie, M. Matsubara, A. Muramatsu, M. Yamaguchi, *J. Am. Chem. Soc.* **2015**, *137*, 6594. For the selected reviews, see: b) M. Gingras, *Chem. Soc. Rev.*

2013, *42*, 968; c) M. Gingras, G. Félix, R. Peresutti, *Chem. Soc. Rev.* **2013**, *42*, 1007; d) M. Gingras, *Chem. Soc. Rev.* **2013**, *42*, 1051; d) Y. Shen, C.-F. Chen, *Chem. Rev.* 2012, *112*, 1463; e) K. Watanabe, K. Suda, K. Akagi, *J. Mater. Chem. C* **2013**, *1*, 2797.

[147] a) B.-Z. Liu, H.-L. Yang, Y.-P. Wang, Y.-Y. Wang, Z.-J. Wu, F.-X. Wei, *Key Engineering Materials* **2010**, *428-429*, 46; b) F. Roschangar, J. Liu, E. Estanove, M. Dufour, S. Rodríguez, V. Farina, E. Hickey, A. Hossain, P.-J.Jones, H.Lee, B. Z. Lu, R. Varsolona, J. Schröder, P. Beaulieu, J. Gillard, C. H. Senanayake, *Tetrahedron Lett.* **2008**, *49*, 363; c) A. Dewan, M. Sarmah, U. Bora, A. J. Thakur, *Tetrahedron Lett.* **2016**, *57*, 3760; d) F. Xue, J. Zhao, A. T. S. Hor, *Chem. Commun.* **2013**, *49*, 10121; e) J. Y. Back, Y. Kim, T. K. An, M. S. Kang, S. K. Kwon, C. E. Park Y. H. Kim, *Dyes Pigment.* **2015**, *112*, 220; f) H. He, Y.-J. Wu, *Tetrahedron Lett*. **2004**, *45*, 3237; g) O. Mongin, A. Gossauer, *Tetrahedron* **1997**, *53*, 6835; h) H. Kim, P. H. Lee, *Adv. Synth. Catal.* **2009**, *351*, 2827; i) M. M. Hansmann, A. Lopez-Andarias, E. Rettenmeier, C. Egler-Lucas, F. Rominger, A. S. K. Hashmi, C. Romero-Nieto, *Angew. Chem. Int. Ed*. **2016**, *55*, 1196.

[148] L. D. M. Nichols, forthcoming *Dissertation*, Universität Göttingen, **2018**, in preparation. Compound **201** was cordially supplied by Leo Nichols as well.

[149] G. M. Sheldrick, *Acta Cryst*. **2008,** *A64*, 112.

[150] O. V. Dolomanov, L.J. Bourhis, R. J Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Cryst*. **2009,** *42*, 339.

[151] T. Kottke, D. Stalke, *J. Appl. Cryst*. **1993**, *26*, 615-619.

7.4. Curriculum Vitae.

Personal data

Name:	Alejandro
Surnames:	García Barrado
Date of birth:	06.12.1988
Place of birth:	Cáceres, Spain
Nationality:	Spanish
Email:	abarrad@gwdg.de (work)
	alehandruhei@gmail.com (personal)
Current address:	Nikolaistrasse 8, Göttingen, 37073
Telephone:	+49 1577 1269427
	+34 644 768277

Academic education

2018	Georg-August-Universität Göttingen (Germany) Degree: Dr. rer. nat. Supervisor: Prof. Dr. Manuel Alcarazo Dissertation: "New Methodologies for the Selective Electrophilic Cyanation of Alkynes".
2015	Max-Planck-Institut für Kohlenforshung (Germany) Degree: Masterarbeit in Chemie Supervisor: Prof. Dr. Manuel Alcarazo Masterarbeit: "On the Lewis Acidity of Phosphonium Salts with Cationic Substituents: Synthesis and Applications".

2012 Salamanca University (Spain)
Degree: Chemistry Licenciatura (5 years)

Publications

- Dicationic phosphonium salts: Lewis acid initiators for the Mukaiyama-aldol reaction. **Alejandro G. Barrado**, Julia M. Bayne, Timothy C. Johnstone, Christian W. Lehmann, Douglas W. Stephan and Manuel Alcarazo. *Dalton Trans*., **2017**, *46* ,16216–16227.

- Regio- and Stereoselective Chlorocyanation of Alkynes. **Alejandro G. Barrado**, Adam Zieli*ński, Richard Goddard* and Manuel Alcarazo. *Angew. Chem. Int. Ed.*, **2017**, *56* ,13401–13405.