Université de Montréal

# Synthesis of Transition Metal N-Heterocyclic Carbene Complexes and Applications in Catalysis

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Thèse présentée à la Faculté des études supérieures et postdoctorales

en vue de l'obtention du grade de

philosophiæ doctor (Ph.D.) en chimie

Août, 2014

Université de Montréal

Faculté des études supérieures et postdoctorales

Cette thèse intitulée:

# Synthesis of Transition Metal N-Heterocyclic Carbene Complexes and Applications in Catalysis

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# Abstract

A new class of $C_1$-symmetric N-heterocyclic carbene (NHC) ligands has been developed. The new ligands exploit a biaryl methyne as a chiral relay, and an N-methyl group as a reactivity controlling element. The precursors for the new ligands were synthesized via a modular scheme that allows for facile diversification. Several of the new ligands were installed onto both copper and gold, generating mono N-heterocyclic carbene transition metal complexes.

The new $C_1$-symmetric copper complexes were tested as catalysts for the synthesis of binaphthols via the oxidative coupling of electron poor 2-naphthols. The new $C_1$-symmetric ligands afforded higher yields than their $C_2$-symmetric counterparts. During the course of the optimization, small molecule additives were found to modulate the reactivity of the copper catalyst. Pyridine additives, such as 2-picoline, were found to induce low to moderate enantioselectivity in the oxidative coupling reaction, while diethylmalonate was found to improve the reaction yield without affecting the selectivity.

The malonate additive was employed in the catalytic oxidative heterocoupling of electronically dissimilar 2-naphthols. The electron-rich coupling partner is normally added in a large excess due to its tendency to degrade. When the malonate additive is used, the coupling partners can be used in equimolar quantities. The discovery resulted in the development of a general protocol for the additive assisted aerobic oxidative heterocoupling of electronically dissimilar 2-naphthols.



**Keywords**: *N*-Heterocyclic Carbene, NHC, chiral relay, $C_1$-symmetric, alkylation, copper, gold, oxidative coupling, BINOL, binaphthyl

# Résumé

Les ligands de carbènes *N*-hétérocycliques (NHC) qui possèdent une symétrie $C_1$ attirent beaucoup l'attention dans la littérature. Le présent projet de recherche propose de synthétiser une nouvelle série de ligands NHC $C_1$-symétriques avec deux groupements *N*-alkyles qui exploitent un relais chiral. Un protocole modulaire et efficace pour la synthèse des sels d'imidazolium chiraux qui servent comme préligands pour les NHC a été développé. Quelques-uns de ces nouveaux ligands ont été installés sur le cuivre et de l'or, créant de nouveaux complexes chiraux.

Les nouveaux complexes à base de cuivre ont été évalués comme catalyseurs pour le couplage oxydatif de 2-naphthols. Les ligands $C_1$-symmétriques ont fourni des meilleurs rendements que les ligands $C_2$-symmétriques. Au cours de l'optimisation, des additifs ont été évalués; les additifs à base de pyridine ont fourni des énantiosélectivités modérées tandis que les additifs à base de malonate ont donné des meilleurs rendements de la réaction de couplage oxydatif.

Ultérieurement, les additifs à base de malonate ont été appliqués envers l'hétérocouplage de 2-naphthols. Le partenaire de couplage qui est riche en électrons est normalement en grand excès à cause de sa tendance à dégrader. Avec le bénéfice de l'additif, les deux partenaires de couplage peuvent être utilisés dans des quantités équivalentes. La découverte de l'effet des additifs a permis le développement d'un protocole général pour l'hétérocouplage de 2-naphthols.



**Mots Clés**: Carbène *N*-Hétérocyclic, NHC, relais chiral, $C_1$-symmétrique, alkylation, cuivre, or, couplage oxydatif, BINOL, binaphthyl

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# List of Abbreviations

| | |
|---|---|
| ° | Degrees |
| ACN | Acetonitrile |
| all | allyl |
| ARCM | Asymmetric Ring-Closing Metathesis |
| BINOL | 1,1'-Binaphthyl-2,2'-diol |
| C | Celsius |
| CAAC | Cyclic Alkyl-Amino Carbene |
| DBE | 1,2-Dibromoethane |
| DCE | 1,2-Dichloroethane |
| DCM | Dichloromethane |
| DEM | Diethylmalonate |
| DIAD | Di-isopropylcarbodiimide |
| DIPP | 2,6-Di-isopropylphenyl |
| DME | 1,2-Dimethoxyethane |
| DMF | N,N-Dimethylformamide |
| DMPU | 1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone |
| DMS | Dimethylsufide |
| h | Hour(s) |
| IAd | 1,3-bis-(1-adamantyl)imidazolin-2-ylidene |
| ItBu | 1,3-bis-(*t*-butyl)imidazolin-2-ylidene |
| ICy | 1,3-dicyclohexylimidazolin-2-ylidene |
| IMes | 1,3-bis-(mesityl)imidazolin-2-ylidene |
| IPr | 1,3-bis-(2,6-Di-isopropylphenyl)imidazolin-2-ylidene |
| IiPr | 1,3-bis-(isopropyl)imidazolin-2-ylidene |
| KHMDS | Potassium Hexamethyldisilylamide |
| LAH | Lithium Aluminum Hydride |
| LDA | Lithium Di-isopropylamide |
| Mes | Mesityl |
| min | Minutes |
| NHC | *N*-Heterocyclic Carbene |
| NMR | Nuclear Magnetic Resonance |
| NOBIN | 2'-amino-2-hydroxy-1,1'-binaphthalene |
| PEPPSI | Pyridine Enhanced Precatalyst Preparation, Stabilization and Initiation |
| pin | Pinacol |
| PMB | 4-Methoxybenzyl |
| RCM | Ring-Closing Metathesis |
| r.t. | Room Temperature |
| SIMes | 1,3-bis-(mesityl)imidazolidin-2-ylidene |

| | |
|---|---|
| SIPr | 1,3-bis-(2,6-Di-isopropylphenyl)imidazolidin-2-ylidene |
| THF | Tetrahydrofuran |
| TEP | Tolman Electronic Parameter |
| TES | Triethylsilyl |
| VBur | Buried Volume |

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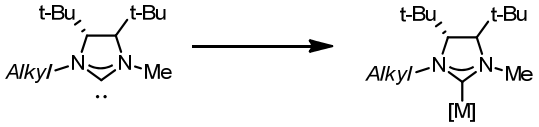
# Acknowledgements

It is difficult to compile a list of all the people I should thank. My original attempt was written in the hour preceding the printing of this thesis and was generally lacking. I would like to thank Shawn for accepting me into his group and giving me the opportunity to work on a variety of interesting projects, as well as Pat who was responsible for our introduction. I need to thank Mylène, who assisted with the substrate scope of the oxidative heterocoupling reaction and proofread the résumé section. Tatiana, Sandra, Alain and Marie-Êve laid the groundwork for the oxidative coupling chemistry. Antoine explored interesting new territory during an awesome summer as my stagiaire. The remaining members of the group: Anne-Cat, Tito, Mad-Dog, Jeff, Jr., Phil, and Brice for the productive discussions and friendship over the last few years.

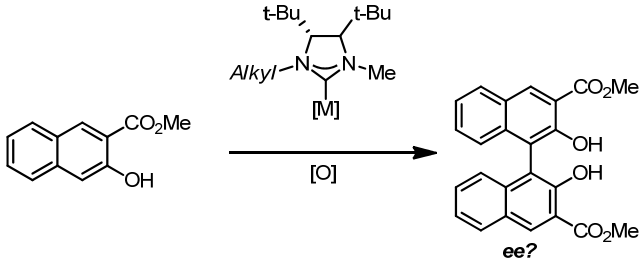
In addition to the members of the Collins group, I need to thank many others. The crystal structures found in chapters 4 and 6 were solved by Francine Bélanger and Benoît Deschênes-Simard. Members of the Charette (Éric, Daniella, Carolyn, Scott, Louis-Phillipe, Will, Guillaume, Jacob, Callum), Schmitzer (Julien, Vanessa, Vincent, Marc, Claude, Nadim, Dat, Salim, Matthieu, Julie), Hannessian (Rob, Étienne, Benoît, Stéphane) and Lebel (Nicholas, Carl, Laura, Henri, Johan) groups as well as Todd, Élodie, Simon, Boris and André. Lastly I would like to thank my family and friends for their unwavering support.

# Foreword

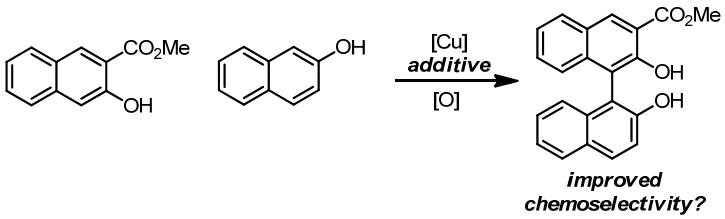
The research goals of the project to be presented are in two parts; firstly, to develop a new series of chiral dialkyl $C_1$-symmetric NHC ligands. Additionally, the ligand synthesis must be modular and robust. The new chiral ligands are to be installed onto transition metals so they can be employed as catalysts for reactions of organic compounds.




The second part of the project is to apply newly synthesized chiral copper complexes towards the asymmetric homocoupling of 2-naphthols. The goal of the second part of the project is to investigate the effect of varying steric bulk of the chiral NHC ligands on the selectivity and yield of the reaction. Focus will be put on the augmented reactivity of methyl-substituted $C_1$-symmetric NHC ligands.



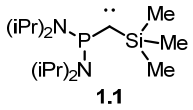

An additional goal in the oxidative coupling chemistry is to modulate the reactivity of the copper catalyst via the use of an additive. The ability of additives which resemble quinone-like structures to improve the chemoselectivity of the heterocoupling of electronically dissimilar 2-naphthols, will be tested.



# Chapter 1 - Introduction to N-Heterocyclic Carbenes

## 1.1 – Persistent Carbenes

Carbenes are carbon atoms that bear two covalent bonds and two unpaired electrons. Persistent carbenes are stabilized carbenes that have a much longer lifetime than other carbenes. Persistent carbenes are normally singlet, meaning that the two valence electrons are paired and there is an empty p orbital present. The empty p orbital can be stabilized by the lone pairs of adjacent heteroatoms; the resonance effect stabilizes the singlet state. The first example of a discreet persistent carbene is shown in Figure 1-1.[1] Carbene **1.1** is often referred to as a push-pull carbene. The lone pair on the carbon atom, in an $sp^2$ orbital, is stabilized by the low-lying empty d orbitals of the silicon atom, while the vacant p orbital of the carbon atom is stabilized by the lone pair on the phosphorous.




**1.1**

**Figure 1-1: Bertrand`s Push-Pull Carbene**

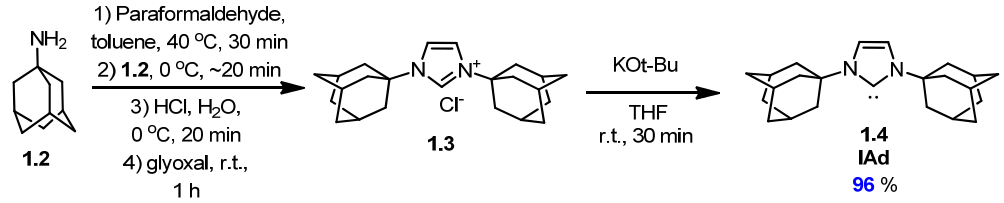
## 1.2 – N-Heterocyclic Carbenes

N-heterocyclic carbenes (NHCs) are persistent carbenes that are part of a nitrogen-containing heterocycle. The lone pairs of the nitrogen atoms provide the stabilization of the singlet state of the carbene. Most NHCs that are used in catalysis have two heteroatoms for improved stability. Although NHCs were under investigation as early as the 1960s,[2] isolation of the discrete carbene was not known until 1990.[3] Carbene **1.4**, whose synthesis is shown in Scheme 1-1, was the first NHC to be synthesized and isolated. It is based on the heterocycle imidazole and as such it has two nitrogen atoms stabilizing the singlet carbene.

The carbene precursor, imidazolium **1.3**, is synthesized in a 4-step one pot procedure (Scheme 1-1) from adamantyl amine (**1.2**), paraformaldehyde, glyoxal, and HCl. The precursor is deprotonated with potassium *t*-butoxide in dry THF at room temperature, affording nearly

[1] Igau, A.; Grutzmacher, H.; Baceirdo, A.; Bertrand, G. *J. Am. Chem. Soc.* **1988**, *110*, 6463.
[2] Wanzlick, I.H.W. *Angew. Chem., Int. Ed.* **1962**, *1*, 75.
[3] Arduengeo, A.J.III; Harlow, R.L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 363.

quantitative yield of carbene **1.4** which has been named IAd. The name derives from the structure, the I is for imidazole and Ad denotes the adamantyl groups bound to the nitrogen atoms. Although carbene **1.4** does not dimerize in solution, it is still strongly nucleophilic and unstable to both moisture and oxygen.




**Scheme 1-1: Arduengo`s Synthesis of IAd**

## 1.2.1 – N-Heterocyclic Carbenes of 5-Membered Rings

The earliest NHCs synthesized belong to the same imidazole family as IAd (**1.4**). By exchanging the amine used during the synthesis, they can all be synthesized in a method analogous to that developed for IAd (**1.4**).[4] Four examples are shown in Figure 1-2. Several alkyl groups of varying steric bulk are shown; IiPr (**1.5**) bears two N-isopropyl groups, ICy bears two N-cyclohexyl groups, ItBu (**1.7**) bears two N-t-butyl groups, and IAd (**1.4**) bears two N-adamantyl substituents.

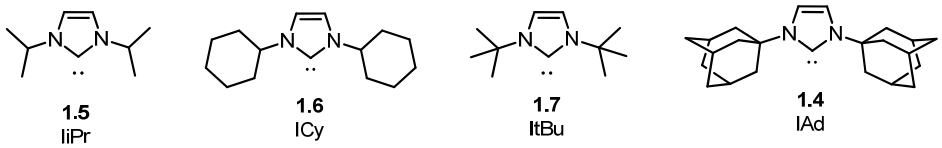



**Figure 1-2: Imidazole Based NHCs Bearing Two Alkyl Groups**

*N*-Aryl substituents were suspected to have more tuneable steric and electronic properties than their *N*-alkyl counterparts. The *N*-aryl groups of the carbenes commonly employed in catalysis have substituents at the ortho positions. The ortho substituents prevent the aryl groups from being in conjugation with the nitrogen atoms by forcing them to rotate out of plane. The first aryl group that was used for that purpose was mesityl (2,4,6-trimethylphenyl, or Mes). Shown in Figure 1-3 are the unsaturated version IMes[5] (**1.9**), and SIMes[6] (**1.8**) which has a fully

[4] Arduengo, A. J. III US 5077414, **1991.**
[5] Arduengo, A. J. III; Dias, H.V.R.; Harlow, R.L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530.

saturated backbone. Both can be prepared like IAd (**1.4**) by deprotonation of the corresponding azolium salt.[5,6] Bulky DIPP (2,6-di-isopropylphenyl) substituents were originally installed in order to increase the stability of the isolated carbene by providing more electron density to the nitrogen atoms, and more steric bulk about the carbene, which helps inhibit dimerization.[7] The unsaturated, aromatic IPr (**1.10**), and SIPr (**1.11**) having a saturated backbone have both been isolated.

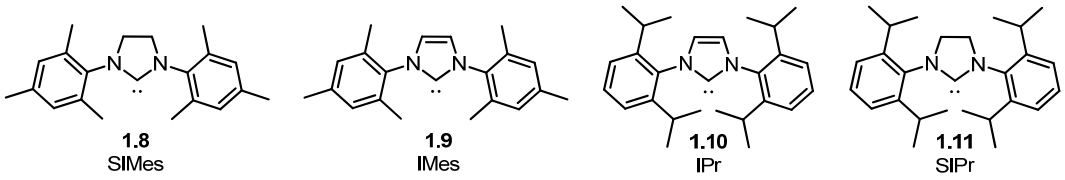



**Figure 1-3: Imidazole Based NHCs Bearing Two Aryl Groups**

The stability of NHCs extends to other nitrogen-containing heterocycles (Figure 1-4). Oxazole based carbene **1.12** has not been isolated as a free carbene, but has been installed onto transition metals for use in catalysis.[8] Although thiazole based carbene **1.13** has yet to be used as a transition metal ligand, the free carbene has been shown to be an effective organocatalyst.[9] In general, sterically unencumbered NHCs such as **1.12** and **1.13** are not isolable as they are prone to dimerization.[7] Bertrand has shown that a second heteroatom is not necessary, making a class of ligand referred to as cyclic alkyl-amino carbenes (CAACs).[10] Carbene **1.14** is a representative example. In place of a nitrogen in the 3-position, it has a bulky spiro-cyclohexane ring.

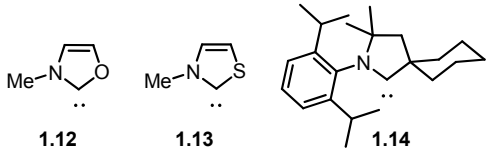



**Figure 1-4: Five Membered NHCs Containing only One Nitrogen**

## 1.2.2 – N-Heterocyclic Carbenes of Larger Ring-Sizes

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[6] Arduengo, A. J. III; Goerlich, J.R.; Marshall, W.J. *J. Am. Chem. Soc.* **1995**, *117*, 11027.
[7] Arduengo, A. J. III; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523.
[8] Tubaro, C.; Biffis, A.; Basato, M.; Benetollo, F.; Cavell, K. J.; Ooi, L. L. *Organometallics* **2005**, *24*, 4153.
[9] a) Miyashita, A.; Suzuki, Y.; Kobayashi, M.; Kuriyama, N.; Higashino, T. *Heterocycles* **1996**, *43*, 509. b) Diba, A. K.; Noll, C.; Richter, M.; Gieseler, M. T.; Kalesse, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8367.
[10] Lavallo, V.; Canac, Y.; Prasang, C.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 5705

Most NHCs are based on 5-membered rings; increasing the ring size can have a significant impact on the steric and electronic properties. While six membered precursors will have a wider angle between the substituents, meaning more steric bulk pushed towards a metal centre, they cannot be aromatic. An aromatic six-membered precursor would be a dication, and would not generate a neutral carbene. Carbene **1,15** is built upon a scaffold of tetrahydropyrimidine.[11] The seven-membered scaffold of carbene **1.16** is spread even wider than that of carbene **1.15**.[12]

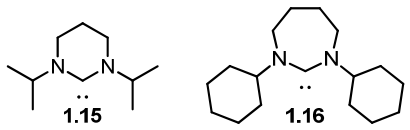



**Figure 1-5: NHCs of Different Ring Sizes**

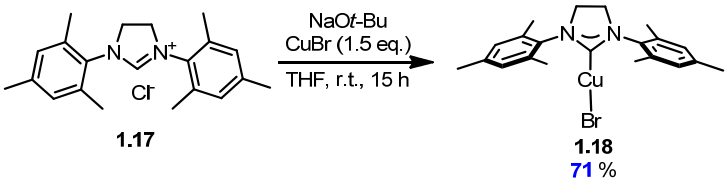
## 1.3 – Installation of N-Heterocyclic Carbenes onto Transition Metals

Several methods exist for the installation of NHCs onto transition metals. The methods can be classified into 3 categories: deprotonation, transmetallation, and employment of a masked carbene.

### 1.3.1 – Carbene Generation via Deprotonation

The most common method for the installation of an NHC onto a metal centre is via *in-situ* generation of the free carbene with a base. A strong base such as sodium *t*-butoxide can be used at room temperature to generate the free carbene. As shown in Scheme 1-2, sodium *t*-butoxide reacts with SIMes•HCl (**1.17**) and a small excess of CuBr affording Cu(SIMes)Br (**1.18**) in 71 % yield.[13] While sodium *t*-butoxide is considered a strong base, its reaction with imidazolium **1.17** is only formally a deprotonation; it has a stronger tendency to act as a nucleophile.

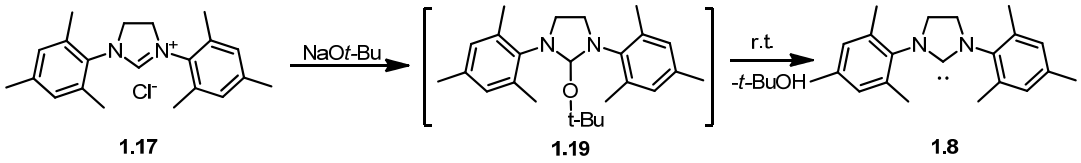
[11] Alder, R. W.; Blake, M. E.; Bortolotti, C.; Bufali, S.; Butts, C. P.; Linehan, E.; Oliva, J. M.; Orpen, G.; Quayle, M. J. *Chem. Commun.* **1999**, 241.
[12] Iglesias, M.; Beetstra, D.J.; Stasch, A.; Horton, P.N.; Hursthouse, M.B.; Coles, S.J.; Cavell, K.J.; Dervisi, A.; Fallis, I. A. *Organometallics* **2007**, *26*, 4800.
[13] Diez-Gonzalez, S.; Correa, A.; Cavallo, L. Nolan, S. P. *Chem.-Eur. J.* **2006**, *12*, 7558.




**1.17** **1.18** **71** %

**Scheme 1-2: Synthesis of Cu(SIMes)Br Employing NaO*t*-Bu as a Base**

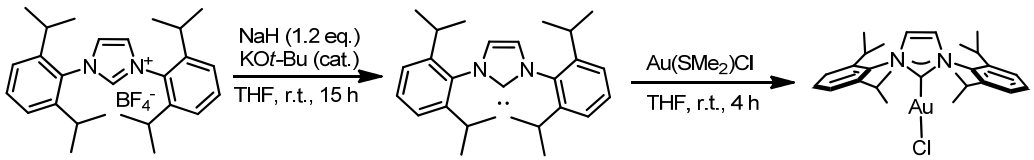
Figure 1-6 shows the mechanism of carbene formation with sodium *t*-butoxide. The alkoxide adds to the imidazolium as a nucleophile, transiently forming a neutral adduct (**1.19**), which then decomposes in solution at room temperature to form the free carbene (**1.8**).[14] The *t*-butoxide adduct **1.19** is considered to be short-lived, and the decomposition to the carbene is quantitative.




**1.17** **1.19** **1.8**

**Figure 1-6: Mechanism of Carbene Formation with Sodium t-Butoxide**

A demonstration of the necessity of the nucleophilic addition is the synthesis of Au(IPr)Cl (**1.21**), shown in Scheme 1-3. Imidazolium salt **1.20** reacts with a catalytic amount of potassium *t*-butoxide in the presence of sodium hydride, affording carbene **1.10** in 84 % yield.[15] The process is not as efficient without the potassium *t*-butoxide. The free carbene is then exposed to Au(DMS)Cl, affording gold complex **1.21** in 75 % yield.[16]

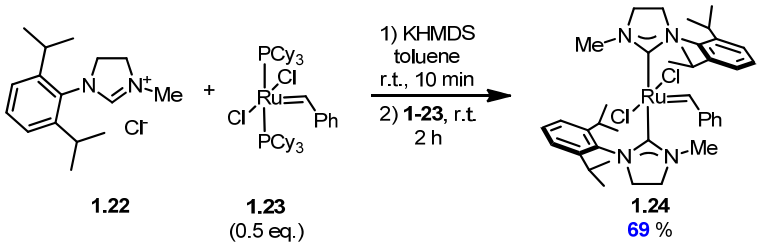



**1.20** **1.10** **84** % **1.21** **75** %

**Scheme 1-3: Isolation of IPr and Synthesis of Au(IPr)Cl**

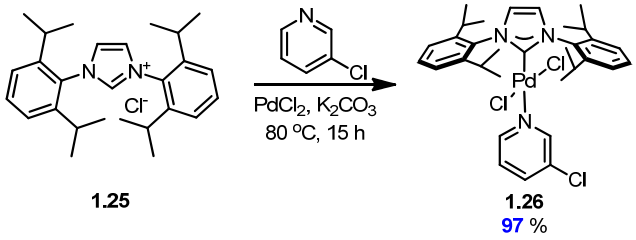
[14] Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T. L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546.
[15] Bantreil, X.; Nolan, S. P. *Nat. Prot.* **2011**, *6*, 69.
[16] De Fremont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2006**, *24*, 2411.

The other most commonly employed strong base for carbene formation is hexamethyldisilazide, generally the potassium salt (KHMDS). Unlike sodium *t*-butoxide, KHMDS is a poor nucleophile and thus acts as a base. The unsymmetrical precursor imidazolinium **1.22** is readily deprotonated at room temperature to form free the carbene (Scheme 1-4). Addition of half an equivalent of Grubbs I (**1.23**) affords complex **1.24** in 69 % yield following recrystallization.[17]




**Scheme 1-4: Carbene Formation with KHMDS**

Milder bases can also be employed, although they require heating in order to generate the free carbene. Palladium complex **1.26,** shown in Scheme 1-5, is afforded in 97 % yield when IPr•HCl (**1.25**) is heated overnight with potassium carbonate and palladium(II) chloride in 3-chloropyridine.[18] The pyridine acts as an additional ligand in order to form a stable and monomeric mono NHC palladium complex **1.26**. The use of potassium carbonate has also been extended to the synthesis of gold,[19] and copper complexes.[20]

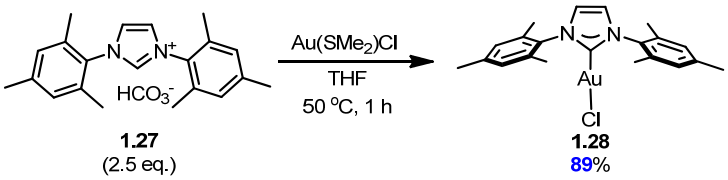



**Scheme 1-5: Synthesis of a Palladium NHC Complex with Potassium Carbonate**

A weak base can also be used as the counterion for the imidazolium salt (Scheme 1-6). When an excess of IMes•$H_2CO_3$ (**1.27**) and (dimethylsulfide)gold(I) chloride are heated at 50 °C

[17] Ledoux, N.; Allaert, B.; Linden, A.; Van der Voort, P.; Verpoort, F. *Organometallics* **2007**, *26*, 1052.
[18] O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem.-Eur. J.* **2006**, *12*, 4743.
[19] Collado, A.; Gomez-Suarez, A.; Martin, A. R.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Commun.* **2013**, *49*, 5541.
[20] Santoro, O.; Collado, A.; Slawin, A. M. Z.; Nolan, S. P.; Cazin, C. S. J. *Chem. Commun.* **2013**, *49*, 10483.

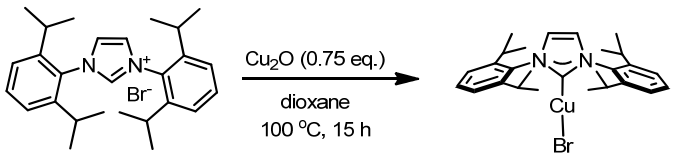
in THF for 1 h, complex **1.28** is afforded in 89 % yield.[21] The aryl substituted imidazolium salts exist as the bicarbonate salts while dialkyl imidazolium salts exhibit equilibrium between the bicarbonate salt and the corresponding carboxylate adduct.




**1.27** (2.5 eq.) **1.28** 89%

**Scheme 1-6: Synthesis of Au(IMes)Cl from IMes•$H_2CO_3$**

More recently, copper(I) oxide has been employed as a reactant for the direct synthesis of mono NHC copper complexes.[22] Unlike the above methods, the counterion of the imidazolium precursor ends up bound to the copper atom, and the only by-product is water. Heating IPr•HBr (**1.29**) with copper(I) oxide in dioxane affords Cu(IPr)Br (**1.30**) in 92 % yield. The method has been shown to work in water,[23] and has also been adapted to work in continuous flow.[24]




**1.29** **1.30** 92 %

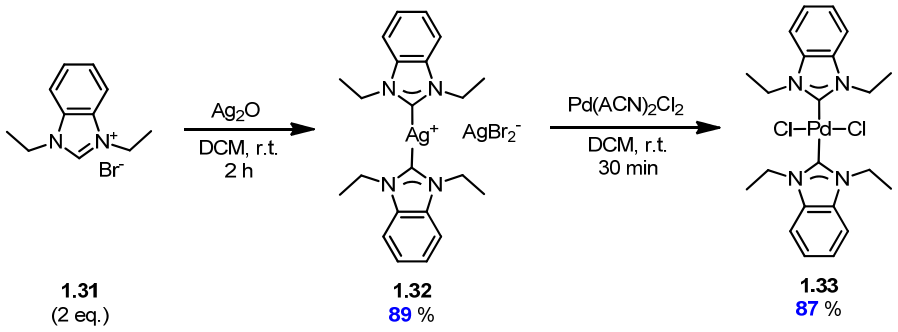
**Scheme 1-7: Direct Synthesis of Cu(IPr)Br from $Cu_2O$**

## 1.3.2 – Transmetallation

Transition metal NHC complexes can be synthesized via transmetallation from a more labile transition metal. The transition metal most often employed in the literature is silver.[25] Silver NHC complexes can be generated directly using silver oxide, in a method analogous to the one shown in Scheme 1-7. Unlike the corresponding copper(I) complexes, silver(I) NHC

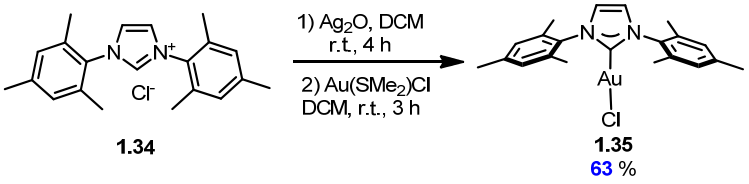
[21] Fevre, M.; Pinaud, J.; Leteneur, A.; Gnanou, Y.; Vignolle, J.; Taton, D.; Miqueu, K.; Sotiropouplos. J. M. *J. Am. Chem. Soc.* **2012**, *134*, 6776.
[22] Chun, J.; Lee, H. S.; Jung, I. G.; Lee, S. W.; Kim, H. J.; Son, S. U. *Organometallics* **2010**, *29*, 1518.
[23] Citadelle, C. A.; Le Nouy, E.; Bisaro, F.; Slawin, A. M. Z.; Cazin, C. S. J. *Dalton Trans.* **2010**, *39*, 4489.
[24] Opalka, S. M.; Park, J. K.; Longstreet, A. R.; McQuade, D. T. *Org. Lett.* **2013**, *15*, 996.
[25] Lin, I. J. B.; Vasam, C. S. *Coord. Chem. Rev.* **2007**, *251*, 642.

complexes are labile and can be used to transfer the NHC to another transition metal. Silver NHC complexes can be isolated, but are often generated *in-situ* and used without purification.




**Scheme 1-8: Synthesis of a Bis NHC Palladium Complex via Transmetallation from Silver**

The first example of a silver NHC complex being used a carbene transfer reagent is shown in Scheme 1-8.[26] Imidazolium **1.31** is treated with silver oxide, affording silver complex **1.32** in 89 % yield, with dibromoargentate(I) as a counterion. When the complex is mixed with bis(acetonitrile)palladium(II) chloride, NHC transfer occurs within 30 min, affording palladium complex **1.33** 87 % yield.




**Scheme 1-9: Use of an *in-situ* Generated Silver Complex to Synthesize Au(IMes)Cl**

*In-situ* generation of the silver complex is also effective. When IMes•HCl (**1.34**) is treated with silver(I) oxide, the corresponding silver complex is formed *in-situ*. Au(DMS)Cl is then added to the mixture, affording Au(IMes)Cl (**1.35**) in 63 % yield.[16] Performing both steps in one pot simplifies the reaction setup and saves a workup step.

## 1.3.3 – Masked Carbenes

NHCs can also be generated in solution by thermal decomposition of a masked carbene. The majority of masked carbenes consist of an HX adduct of the carbene where X is an electron

[26] Wang, H. M; Lin, I. J. B. *Organometallics* **1998**, *17*, 972.

withdrawing group. The electron withdrawing group can be an alkoxide, a haloalkane, or an arene. An exception to the rule is the carbon dioxide adduct which exists as a zwitterionic compound.

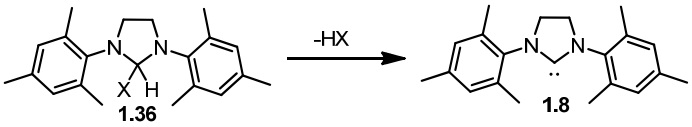
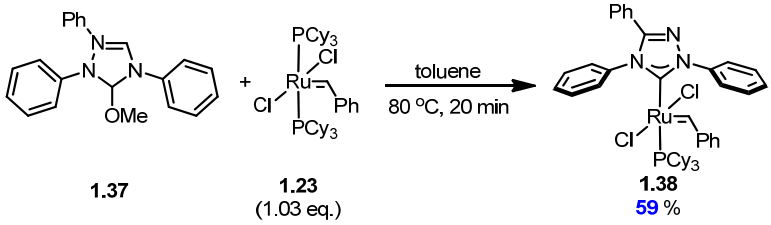



**Figure 1-7: Decomposition of a Masked Carbene**

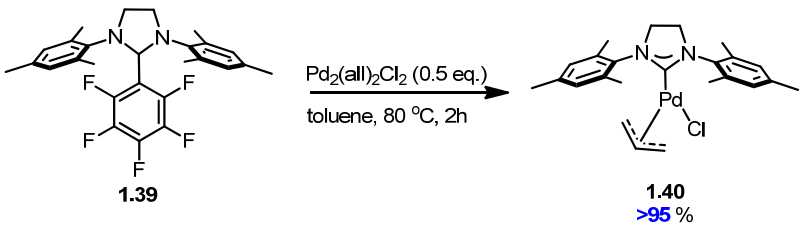
Enders first isolated methoxy adduct **1.37** shown in Scheme 1-10.[27] The compound was shown to quantitatively generate the carbene when heated under vacuum. The use of the methoxy adduct as a stable carbene precursor was exploited by Grubbs in order to install a carbene onto ruthenium.[14] When methoxy adduct **1.37** is heated to 80 °C in toluene in the presence of ruthenium complex **1.23**, the ruthenium NHC complex **1.38** is afforded in 59 % yield.




**Scheme 1-10: Extrusion of Methanol to Form a Ruthenium NHC Complex**

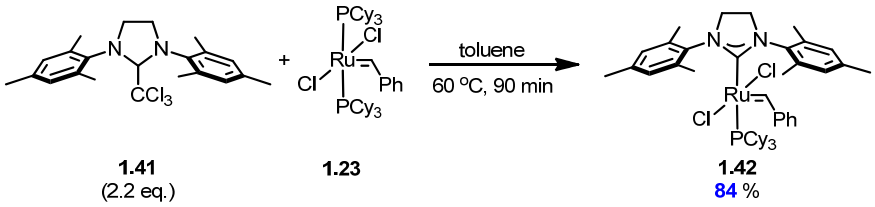
The pentafluorophenylimidazolidine **1.39** shown in Scheme 1-11 also decomposes upon heating to generate the free carbene. In the case of imidazolidine **1.39**, pentafluorobenzene is generated as a byproduct. When imidazolidine **1.39** is heated in the presence of allylpalladium chloride dimer, the mono NHC palladium complex **1.40** is afforded in quantitative yield.[28]

[27] Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J. P.; Ebel, K.; Brode, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1021.
[28] Nyce, G. W.; Csihony, S.; Waymouth, R. M.; Hedrick, J. L. *Chem.-Eur. J.* **2004**, *10*, 4073.




**Scheme 1-11: Extrusion of Pentafluorobenzene to Form Pd(SIMes)(all)Cl**

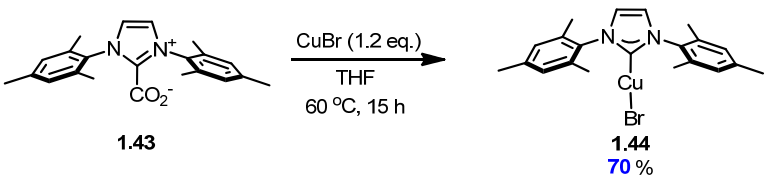
Chloroform adducts have also been shown to decompose to form the corresponding free carbenes. Early experiments with less sterically hindered carbenes led to rapid homodimerization of the carbene.[29] The strategy was later exploited for the installation of an NHC onto ruthenium (Scheme 1-12).[14] An excess of imidazolidine **1.41** forms the free carbene *in-situ* when heated in toluene. In the presence of ruthenium complex **1.23**, the second generation Grubbs catalyst (**1.42**) is afforded in 84 % yield.




**Scheme 1-12: Extrusion of Chloroform to Make Grubbs II**

Zwitterionic carboxylate adducts as NHC precursors were first reported by Crabtree in 2006.[30] The charge separation makes the carbon dioxide adducts very different from other masked carbenes. Although formally neutral, imidazolium carboxylates have decreased solubility in organic solvents. Carboxylate adducts have the advantage of being air and moisture stable. The loss of carbon dioxide to the gas phase upon heating helps ensure irreversible conversion to the carbene.

[29] Cardin, D. J.; Cetinkaya, B.; Cetinkaya, E.; Lappert, M. F. *J. Chem. Soc., Dalton Trans.* **1973**, 514.
[30] Voutchkova, A. M.; Appelhans, L. N.; Chianese, A. R.; Crabtree, R. H. *J. Am. Chem. Soc.* **2006**, *127*, 17624.




**1.43** **1.44** 70 %

**Scheme 1-13: Decarboxylative Synthesis of Cu(IMes)Br**

The Collins group has recently exploited imidazolium carboxylates for the synthesis of copper(I) NHC complexes.[31] The method is particularly advantageous for the synthesis of copper(I) complexes of unsaturated NHCs. Unsaturated NHCs have a strong tendency to form the corresponding bis NHC copper complexes, which precipitate out of solution. The two strategies normally employed to improve yields of the mono NHC complex are the use of a pre-ligated copper species such as $Cu(SMe_2)Br$ or to use an excess of the copper salt.[32] The carboxylate method shown in Scheme 1-13 generates 70 % of Cu(IMes)Br (**1.44**) when carboxylate **1.43** is heated in the presence of a slight excess of CuBr.

[31] Le Gall, T.; Baltatu, S.; Collins, S. K. *Synthesis* **2011**, 3687.
[32] Diez-Ganzalez, S.; Escudero-Adan, E. C.; Benet-Buchholz, J.; Stevens, E. D.; Slawin, A. M. Z.; Nolan, S. P. *Dalton Trans.* **2010**, *39*, 7595.

## 1.4 – Electronic and Steric Parameters of N-Heterocyclic Carbenes

### 1.4.1 – Electronic Properties

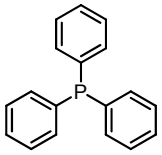
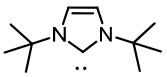
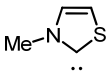
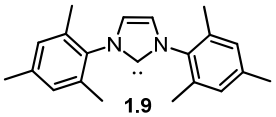
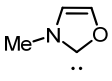
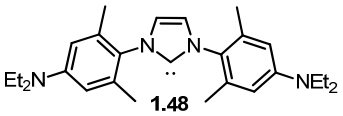
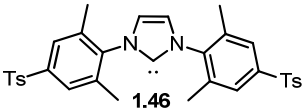
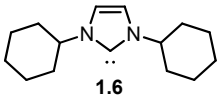
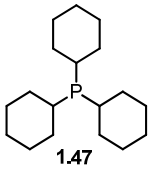
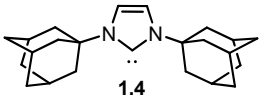
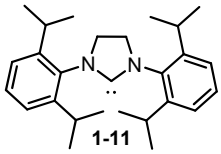
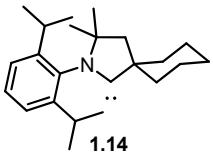
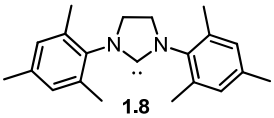
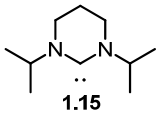
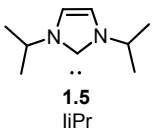
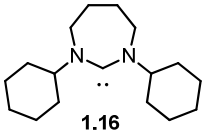
NHCs are some of the strongest σ donors currently known.[33] Due to the high amount of electron density being donated from the nitrogen atoms, there is minimal π back-bonding to the unoccupied p orbital, although it can become significant in some cases.[34] The standard method for the comparison of the electronic properties of ligands is to measure the stretching frequency of carbon monoxide ligands in a metal carbonyl complex. The stretching frequency of the $LNi(CO)_3$ complex is the standard for comparison,[35] and is referred to as the Tolman electronic parameter (TEP). The measurement does not have to be taken from the nickel complex; the correction can be done computationally.[36] The relationship between the electronic character and the TEP is inversely proportional, stronger σ donors resulting in a lower carbonyl stretching frequency.

The electronic parameters for several NHC and phosphine ligands are shown in Table 1-1, and have been arranged in order of increasing electron density.[33] Triphenylphosphine is the least donating of the group (entry 1). The most donating are the NHCs of non-standard ring size (entries 15, 16), with carbene **1.16** being the most donating. Very close to the 6 membered NHC **1.15** (entry 15), is Bertrand's CAAC ligand **1.14** (entry 14). When comparing oxazole NHC **1.12** and thiazole NHC **1.13** (entries 2, 3), the 2 p mixing ability of oxygen proves to have a slightly larger effect than sulphur's larger electron density. It can also be seen from the data that alkyl substituted NHCs are more donating than aryl substituted NHCs. The higher electron density of unsaturated imidazole type ligands makes them more donating than the saturated imidazoline framework. For a direct comparison, SIMes (**1.8**) (entry 6) has a higher TEP than IMes (**1.9**) (entry 10). Aryl substituted NHCs have tuneable electronic character. Entries 4 and 11 are structurally analogous to IMes (entry 10), but NHC **1.46** bears an electron withdrawing substituent at the 4 position of the aryl group while NHC **1.48** bears an electron-donating

[33] Droge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6940.
[34] Khramov, D.M.; Lynch, V.M.; Bielawski, C.W. *Organometallics* **2007**, *27*, 6042.
[35] Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.
[36] Kelly, R. A. III; Clavier, H.; Giudice, S.; Scott, N. M.; Stevens, E. D.; Bordner, J.; Samardjiev, I.; Hoff, C. D.; Cavallo, L.; Nolan, S. P. *Organometallics* **2008**, *27*, 202.

substituent. As expected, the TEP of NHC **1.46** (entry 11) is lower than SIMes (**1.8**) (entry 10), and the TEP of NHC **1.48** (entry 4) is higher.

**Table 1-1: TEP for Assorted Ligands**

| Entry | Ligand | TEP ($cm^{-1}$) | Entry | Ligand | TEP ($cm^{-1}$) |
|---|---|---|---|---|---|
| 1 |  **1.45** | **2068.9** | 9 |  **1.7** ItBu | **2050.1** |
| 2 |  **1.13** | **2061.5** | 10 |  **1.9** IMes | **2050.7** |
| 3 |  **1.12** | **2060** | 11 |  **1.48** | **2049.8** |
| 4 |  **1.46** | **2057** | 12 |  **1.6** ICy | **2049.6** |
| 5 |  **1.47** | **2056.3** | 13 |  **1.4** IAd | **2049.5** |
| 6 |  **1-11** SIPr | **2052.3** | 14 |  **1.14** | **2048.5** |
| 7 |  **1.8** SIMes | **2051.5** | 15 |  **1.15** | **2048.3** |
| 8 |  **1.5** IiPr | **2051.5** | 16 |  **1.16** | **2044.3** |

## 1.4.2 – Buried Volume

*N*-Heterocyclic carbenes represent a highly diverse class of ligands. While their electronic character can be evaluated using the standard techniques, the traditional method for comparing steric bulk among ligands falls short of an accurate description. The Tolman cone angle was originally designed to be able to compare the steric bulk of different phosphine ligands.[37] Phosphines have a relatively conical distribution when bound to a metal centre (Figure 1-9a); NHCs on the other hand vary widely depending upon which angle the viewer is looking from (Figure 1-8, b and c). Looking into the plane of the imidazolium ring (b), the NHC appears to have a very wide cone angle. Viewing the complex along the plane (c) shows a much narrower angle. Buried volume (Figure 1-9d) provides a much more apt description.[38] For a sphere of a given radius, the buried volume represents the percentage of the volume occupied by the ligand. No longer constrained by the symmetry of the ligand, a much more accurate comparison of the steric parameters is possible.

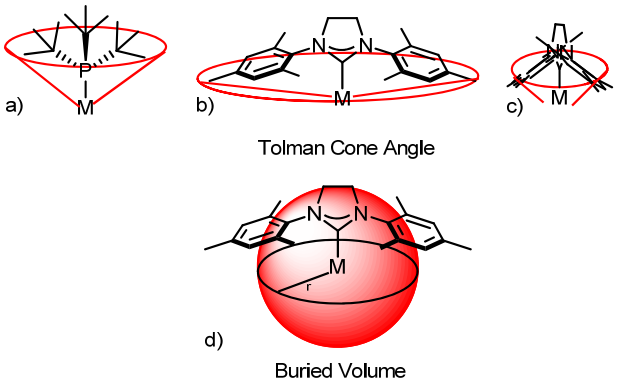


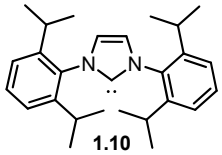
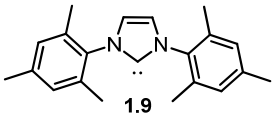
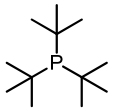
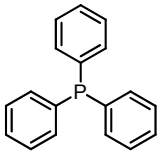
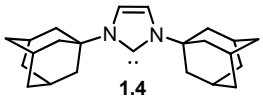
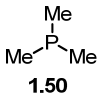
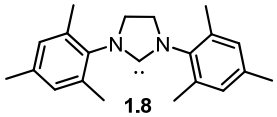

**Figure 1-8: Calculation of the Steric Parameters of Ligands in Transition Metal Complexes**

Nolan and Clavier summarized the buried volumes of the ligands most commonly employed in catalysis (Table 1-2), they have been arranged in order of increasing steric bulk.[39] Of note is the minimal difference between the saturated and unsaturated versions of the ligand (entries 2 and 3). The differences are intuitive, many of the examples have groups which extend far away from the metal centre and as such have little impact on the buried volume. The

[37] Tolman, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 2956.
[38] Poater, A.; Cosenza, B.; Correa, A.; Giudice, S.; Ragone, F.; Scarano, V.; Cavallo, L. *Eur. J. Inorg. Chem.* **2009**, 1759.
[39] Clavier, H.; Nolan, S. P. *Chem. Commun.* **2010**, *46*, 841.

isopropyl groups on IPr (**1.10**) (entry 1) penetrate into the coordination sphere of the metal, giving it a much higher buried volume, even higher than tri(*t*-butyl)phosphine (**1.49**) (entry 5).

**Table 1-2: Buried Volumes of Commonly Screened Ligands**

| Entry | Ligand | Buried Volume (%)[a] | Entry | Ligand | Buried Volume (%)[a] |
|---|---|---|---|---|---|
| 1 |  **1.10** IPr | **44.5** | 5 |  **1.9** IMes | **36.5** |
| 2 |  **1.49** | **43.9** | 6 |  **1.45** | **34.8** |
| 3 |  **1.4** IAd | **39.8** | 7 |  **1.50** | **27.3** |
| 4 |  **1.8** SIMes | **36.9** | | | |

a) Based on the Au(NHC)Cl complex

## 1.5 – N-Heterocyclic Carbenes as Ligands in Transition Metal Catalysis

*N*-Heterocyclic carbenes have been getting increased attention as ligands in transition metal catalysis.[40] As outlined in the preceding sections, NHCs have many advantages, including tuneable steric and electronic properties. Most transition metal NHC complexes have high stability to air and moisture, negating the need for specialized equipment in their handling. Transition metal NHC complexes can also be generated *in-situ* from stable precursors.

### 1.5.1 – Olefin Metathesis

*N*-Heterocyclic carbenes have been shown to be very effective ligands for ruthenium catalyzed olefin metathesis reactions.[40c] NHC containing catalysts react faster and are more stable than those containing other ligands.[40a] The wide variety of NHCs available has created a large diversity of catalysts with different reactivity.[40c] The selectivity of olefin metathesis catalysts is sterically controlled.[41] Having ligands with very different steric properties allows for effective control of reaction selectivity as more sterically hindered catalysts will have higher selectivity towards unhindered olefins.

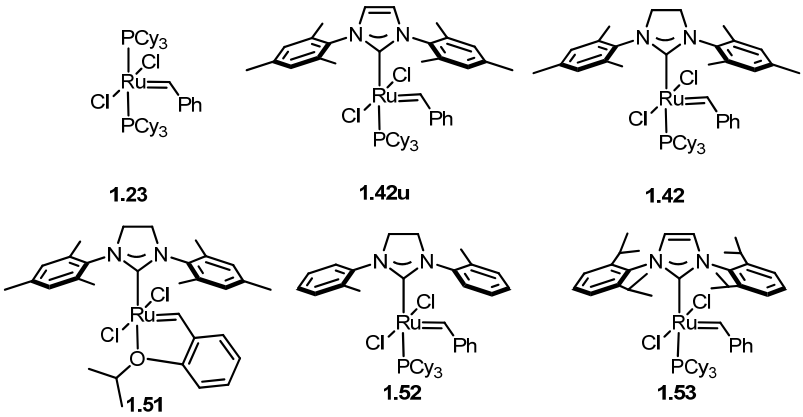



**Figure 1-9: NHC Containing Olefin Metathesis Catalysts**

[40] a) Diez-Gonzalez, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612. b) Lin, J. C. Y.; Huang, R. T. W.; Lee, C. S.; Bhattacharyya, A.; Hwang, W. S.; Lin, I. J. B. *Chem. Rev.* **2009**, *109*, 3561. c) Samojlowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009**, *109*, 3708.
[41] Nolan, S. P.; Clavier, H. *Chem. Soc. Rev.* **2010**, *39*, 3305.

The first well-defined ruthenium based olefin metathesis catalyst **1.23**, commonly referred to as Grubbs I contains no NHC (Figure 1-9). It was the starting point for the development of the NHC containing catalysts. The first NHC containing catalyst in the literature was reported by Nolan in 1999 when his group installed IMes onto ruthenium complex **1.23**, generating ruthenium catalyst **1.42u**.[42] Shortly thereafter, Grubbs reported the installation of SIMes onto complex **1.23**, yielding the second generation Grubbs catalyst **1.42**.[43] The NHC containing catalysts were found to have enhanced reactivity and stability. The stability was further increased by the group of Hoveyda who installed the pendant ether on the alkylidene, resulting in catalyst **1.51**.[44] Altering the steric bulk of the NHC changes the catalyst reactivity.[41] Substituting the bulky mesityl group for sterically less-encumbered *ortho*-tolyl groups in complex **1.52** makes the metal coordination sphere less hindered.[45] The decrease in bulk allows for the reaction of more sterically encumbered substrates. The NHC IPr (**1.10**) has also been installed onto a ruthenium olefin metathesis catalyst (**1.53**).[46] The increased steric bulk affords a faster initiating catalyst, and hence shorter reaction times for sterically unencumbered substrates.

**Table 1-3: RCM to Form Disubstituted Olefins**


**1.54** **1.55**

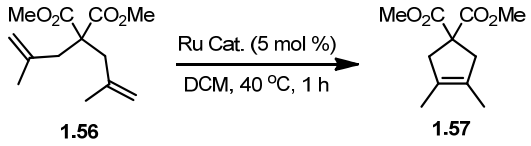
| Entry | Catalyst | Temperature | Time (min) | Conversion (%) | Ref. |
|---|---|---|---|---|---|
| 1 | **1.23** | r.t. | 15 | **85** | 46 |
| 2 | **1.42** | 30 °C | 30 | **95** | 47 |
| 3 | **1.51** | 30 °C | 20 | **95** | 47 |
| 4 | **1.53** | r.t. | 15 | **100** | 46 |

Table 1-3 shows a comparison of the reactivity of several ruthenium olefin metathesis catalysts for one of the benchmark ring-closing reactions, ring-closing metathesis (RCM) of malonate **1.54**. Catalyst **1.23** converts 85 % of the substrate in 15 min at room temperature. Catalyst **1.42**, takes 30 min at a slightly higher temperature to achieve near quantitative

[42] Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674.
[43] Scholl, M.; Ding, A.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
[44] Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
[45] Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589.
[46] Jafarpour, L.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2000**, *606*, 49.

conversion. Catalyst **1.51** is faster, achieving quantitative conversion in only 20 min.[47] Catalyst **1.53** initiates much faster, converting diene **1.54** quantitatively at room temperature in only 15 min. All of the catalysts show high reactivity towards terminal olefins. The differences are more apparent with more sterically encumbered substrates.

**Table 1-4: RCM to Form Tetrasubstituted Olefins**




**1.56** **1.57**

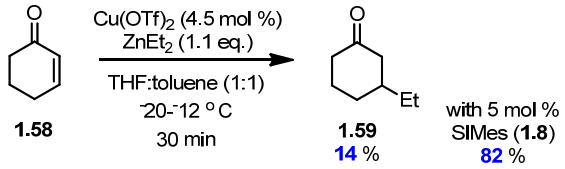
| Entry | Catalyst | Conversion (%) |
|---|---|---|
| 1 | **1.42** | **4** |
| 2 | **1.51** | **0** |
| 3 | **1.52** | **86** |

The *ortho*-tolyl substituted Stewart-Grubbs catalyst **1.52** shows enhanced activity for the formation of tetrasubstituted olefins via RCM.[45] After 24 h in refluxing dichloromethane, catalyst **1.42** has only converted 4 % of diene **1.56**, catalyst **1.51** converts none of diene **1.56**, while catalyst **1.52** has converted 86 % of diene **1.56** to cyclopentene **1.57**. The less sterically encumbered ligand is more effective for the ring-closing of more sterically hindered substrates.

## 1.5.2 – Conjugate Addition

The use of organocuprates for conjugate addition is not a new concept in organic chemistry.[48] The development of new ligands allows for acceleration of the process.[49] In addition, the reaction can be made catalytic in copper.[50] The reaction passes through a transient copper(III) intermediate, which is formed via formal oxidative addition of the copper(I) catalyst to the olefin.[51] As such, strongly σ donating ligands facilitate the reaction by stabilizing the high oxidation state intermediate.

[47] Anderson, D. R.; Lavallo, V.; O`Leary, D. J.; Bertrand, G.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7262.
[48] Alexakis, A.; Chuit, C.; Commercon, Bourgain, M.; Foulon, J. P.; Jabri, N.; Mengeney, P.; Normant, J. F. *Pure Appl. Chem.* **1984**, *56*, 91.
[49] Alexakis, A.; Frutos, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2427.
[50] Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.
[51] Woodward, S. *Chem. Soc. Rev.* **2000**, *29*, 393.

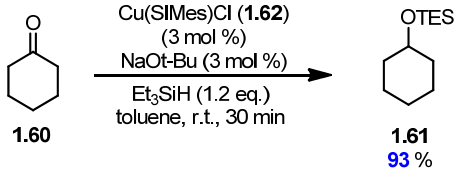



**Scheme 1-14: Copper Catalyzed 1,4-Addition with SIMes**

An unligated copper salt is not an effective catalyst for conjugate addition to enones. When diethylzinc is mixed with a catalytic amount of copper(II) triflate at low temperature, followed by addition of cyclohexenone **1.58**, only 14 % of cyclohexanone **1.59** is generated after 30 min (Scheme 1-14). In contrast, adding a catalytic amount of SIMes (**1.8**), generated *in-situ* prior to introduction of the substrate, affords 82 % of ketone **1.59**.[52]

## 1.5.3 – Hydrosilylation

Hydrosilylation is an important reduction method in organic synthesis.[53] It allows for the direct conversion of a ketone into a silyl protected alcohol. The reaction is normally carried out with silane and a transition metal catalyst.[53] While a wide array of transition metals can catalyze the reaction, investigations with transition metal NHC complexes have primarily focused on copper[32] and rhodium.[54]



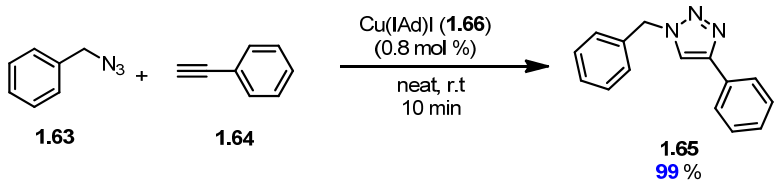

**Scheme 1-15: Hydrosilylation of Cyclohexanone with a Cu(NHC) Catalyst**

An example with a copper NHC catalyst is shown in Scheme 1-15. In the presence of t-butoxide, Cu(SIMes)Cl (**1.62**) undergoes anion exchange to form the copper alkoxide, which is an effective catalyst for the hydrosilylation of ketones.[32] The new complex formed *in-situ* catalyzes the hydrosilylation of cyclohexanone (**1.60**) with triethylsilane. The reaction proceeds at room temperature in toluene, affording 93 % of silyl ether **1.61** in 30 min.

[52] Fraser, P. K.; Woodward, S. *Tetrahedron Lett.* **2001**, *42*, 2747.
[53] Diez-Gonzalez, S.; Nolan, S. P. *Org. Prep. Proc. Int.* **2007**, *39*, 523.
[54] Hill, J. E.; Nile, T. A. *J. Organomet. Chem.* **1977**, *137*, 293.

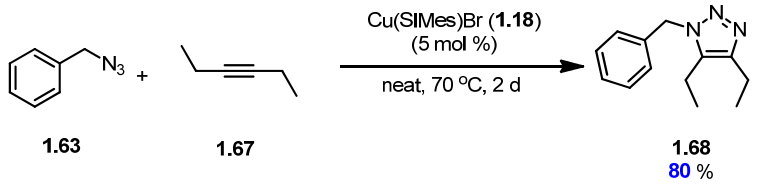
## 1.5.4 – Huisgen 1,3-Dipolar Cycloaddition

Copper catalyzed azide-alkyne cycloaddition has been getting increased attention in organic synthesis, due to its high yields and simple reaction setup.[55] Cu(IAd)I (**1.66**) has been shown to be a highly effective catalyst for the 1,3-dipolar cycloaddition of terminal alkynes with alkyl azides.[32] The reaction can be performed neat at room temperature. When phenylacetylene (**1.63**) and benzyl azide (**1.64**) are exposed to catalyst **1.66**, the reaction affords triazole **1.65** in quantitative yield after only 10 min. If an unligated copper salt is added to the reaction in place of copper complex **1.66**, no reaction is observed after one hour. If the halide is replaced with a phosphine, it has been shown that the NHC acts as a base and deprotonates the acetylene.[56]




**Scheme 1-16: 1,3-Dipolar Cycloaddition Between an Azide and a Terminal Alkyne with a Copper Catalyst**

Huisgen 1,3 dipolar cycloadditions of internal alkynes such as alkyne **1.67** cannot form the reactive acetylide intermediate,[57] and are thus more challenging. Cu(SIMes)Br (**1.18**) catalyzes the 1,3-dipolar cycloaddition between benzyl azide (**1.63**) and 3-hexyne (**1.67**), the reaction requires heating and takes 2 days, affording triazole **1.68** in 80 % yield (Scheme 1-17).[58]

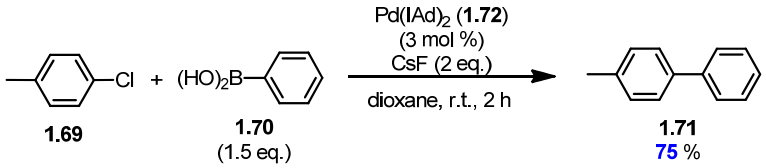



**Scheme 1-17: Cu(SIMes)Br Catalyzed Cycloaddition Between Benzyl Azide and 3-Hexyne**

[55] Meldal, M.; Tornoe, C. W. *Chem. Rev.* **2008**, *108*, 2952.
[56] Lazreg, F.; Slawin, A. M. Z.; Cazin, C. S. J. *Organometallics* **2012**, *31*, 7969.
[57] Himo, F. Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2006**, *127*, 210.
[58] Diez-Gonzalez, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem.-Eur. J.* **2006**, *12*, 7558.

## 1.5.5 – Palladium Catalyzed Cross-Coupling

In palladium catalyzed cross-coupling chemistry, one of the early challenges was slow oxidative addition into less reactive aryl halides.[59] Having a strongly donating ligand such as an NHC increases the electron density at palladium and allows for insertion into less reactive bonds.[60] The earliest example is the employment of $Pd(IAd)_2$ (**1.72**) as a catalyst (Scheme 1-18).[61] Palladium complex **1.72** inserts into aryl chlorides at room temperature. When 4-chlorotoluene and phenylboronic acid are stirred with a catalytic amount of palladium complex **1.72** and cesium fluoride, 75 % of biaryl **1.71** is afforded after 2 hours.




**Scheme 1-18: Suzuki Coupling of 4-Chlorotoluene with Phenylboronic Acid Catalyzed by $Pd(IAd)_2$**

More recently, mono NHC palladium(II) complexes have been getting increased attention as stable catalyst precursors for cross-coupling reactions.[62] Complex **1.26** whose synthesis is shown in Scheme 1-5 is member of a new class of palladium precatalysts. The new catalysts are referred to as PEPPSI (pyridine enhanced precatalyst preparation, stabilization and initiation) complexes and have the general structure of an NHC trans to a pyridine ligand. The new catalysts are characterized by high stability and fast initiation. Catalyst **1.26** catalyzes the coupling of 4-chloroanisole and 4-methylphenylboronic acid in dioxane at room temperature affording biaryl product **1-75** in 86 % yield after 2 h.[18] To achieve the same level of reactivity for the same coupling reaction in the same solvent, a phosphine coordinated precatalyst needs to be refluxed for over 9 h.[63] In addition to Suzuki coupling, PEPPSI complexes have been directed towards Negishi[64] and Kumada[65] coupling reactions.

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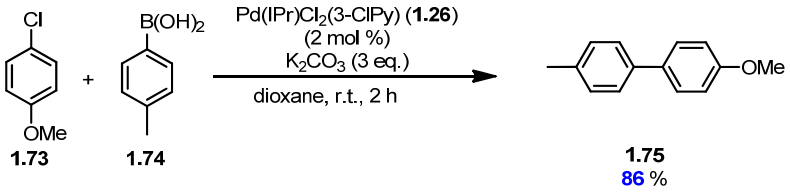
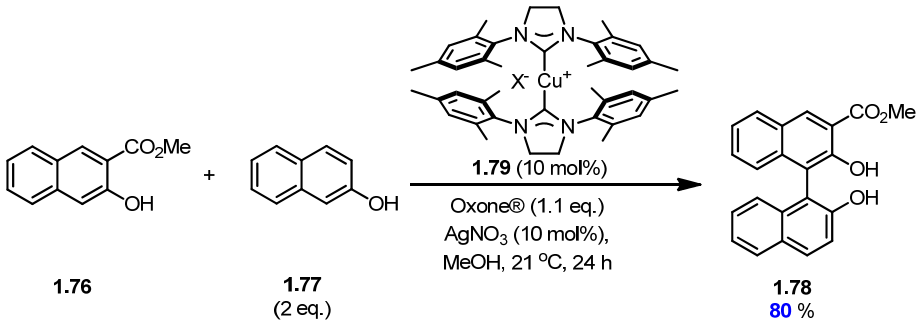
[59] Sturmer, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 3307.
[60] Crabtree, R. H.; *The Organometallic Chemistry of the Transition Metals*, Wiley: Hoboken, 2005, p 161.
[61] Gstottmayr, C. W. K.; Bohm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363.
[62] Valente, C.; Calimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314.
[63] Lu, B.; Fu, C.; Ma, S. *Tetrahedron Lett.* **2010**, *51*, 1284.
[64] Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O`Brien, C. J.; Valente, C. *Chem.-Eur. J.* **2006**, *12*, 4749.




**Scheme 1-19: Suzuki Coupling of an Aryl Chloride using a PEPPSI Complex**

## 1.5.6 – Oxidative Coupling of 2-Naphthols

Copper complex **1.79** catalyzes the oxidative coupling of 2-naphthols.[66] The catalyst was synthesized from the chloroform adduct of SIMes (**1.41**); however, the counterion of the complex is not known. An excess of the electron-rich coupling partner is necessary to achieve high yields as the substrate has a tendency to degrade in non-productive side reactions. When naphthol carboxylate **1.76** and 2 equivalents of naphthol **1.77** are mixed with 10 mol % of copper catalyst **1.79**, silver nitrate as an activator and oxone as an oxidant, cross-coupling product **1.78** is afforded in 80 % yield.




**Scheme 1-20: Oxidative Coupling of 2-Naphthols Employing a bis NHC Copper Catalyst**

[65] Organ, M. G.; Abel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O`Brien, A. J.; Valente, C. *Chem.-Eur. J.* **2007**, *13*, 150.
[66] Grandbois, A.; Mayer, M.-E.; Bedard, M.; Collins, S. K.; Michel, T. *Chem.-Eur. J.* **2009**, *15*, 9655.

# Chapter 2 – Introduction to Chiral *N*-Heterocyclic Carbenes

The preceding chapter showed the development of *N*-heterocyclic carbenes and their application in transition metal catalyzed transformations. The following sections will discuss the development of chiral imidazole based *N*-heterocyclic carbenes and their applications in asymmetric catalysis. There are two strategies that can be employed to make a chiral NHC. An exocyclic chiral group can be bound to one of the nitrogen atoms, or a chiral element can be built into the NHC backbone, enforcing a preferential conformation of the exocyclic groups bound to the nitrogen atoms. The reactivity of $C_1$ and $C_2$-symmetric NHCs will be compared in several asymmetric transformations.

## 2.1 – NHCs Containing Chiral Groups on Nitrogen

The earliest examples of chiral NHCs are derived from chiral amines and thus have exocyclic chiral groups bound to the nitrogen atoms.[40a] Several examples based on the imidazole scaffold are shown in Figure 5-1. Carbene **2.1** has two planar-chiral cyclophane units bound to the two nitrogen atoms.[67] Carbene **2.2** is based on (+)-isopinocampheylamine.[68] Carbene **2.3** is based on the chiral bisoxazoline structure.[69] The simplest, carbene **2.4**, is based on (R)-phenylethylamine.[70]

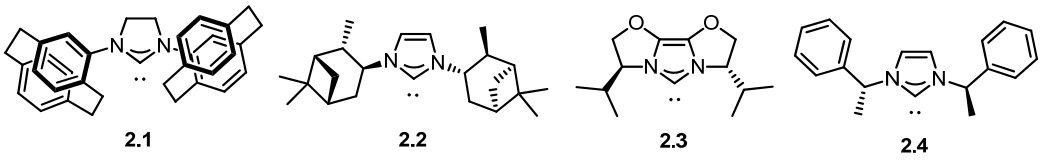



**Figure 2-1: NHCs Bearing Chiral Groups on Nitrogen**

## 2.2 – NHCs that Exploit a Chiral Relay

NHCs that exploit a preferred conformation of a bulky group in order to create a chiral environment in the metal's coordination sphere are said to possess a chiral relay. In general, the stereogenic unit that enforces the preferred conformation is found in the NHC backbone. In the

[67] Song, C.; Ma, C.; Ma, Y.; Feng, W.; Ma, S.; Chai, Q.; Andrus, M. B. *Tetrahedron Lett.* **2005**, *46*, 3241.
[68] Huang, J.; Jafarpour, L.; Hillier, A. C.; Stevens, E. D.; Nolan, S. P. *Organometallics*, **2001**, *20*, 2878.
[69] Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. *Chem. Commun.* **2002**, 2704.
[70] Herrmann, W. A.; Goossen, L. J.; Kocher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2805.

case of imidazole based NHCs, the ligand is often based off of a chiral diamine. Several NHCs that exploit a chiral relay are shown in Figure 2-2. Grubbs reported carbene **2.5** as a ligand for asymmetric olefin metathesis reactions.[71] Other aryl groups such as naphthyl as in carbene **2.6** can be installed.[72] Carbene **2.7** with two trimethylbenzyl substituents shows that the chiral relay bound to nitrogen does not have to be an aryl group and can also be alkyl.[73] Dialkyl substituted carbene **2.8** provides a more sterically demanding and more conformationally rigid environment than carbene **2.7**.[74]

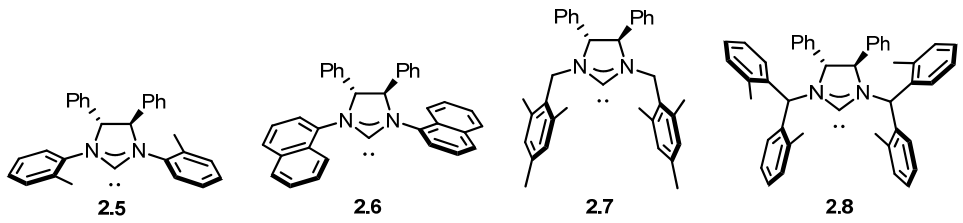



**Figure 2-2: NHC Ligands that Exploit a Chiral Relay Effect**

The X-ray structure of a rhodium complex **2.9** of carbene **2.5**, showing the conformational bias of its chiral relay is shown in Figure 2-3.[75] The *ortho*-tolyl group in the foreground is noticeably twisted compared to the plane of the imidazolidinylidene. Indeed the angle between them is only 58 $^{o}$. The direction that the *ortho*-tolyl is oriented is controlled by the adjacent phenyl group on the chiral imidazolidinylidene backbone, creating a highly dissymmetric environment about the metal centre.

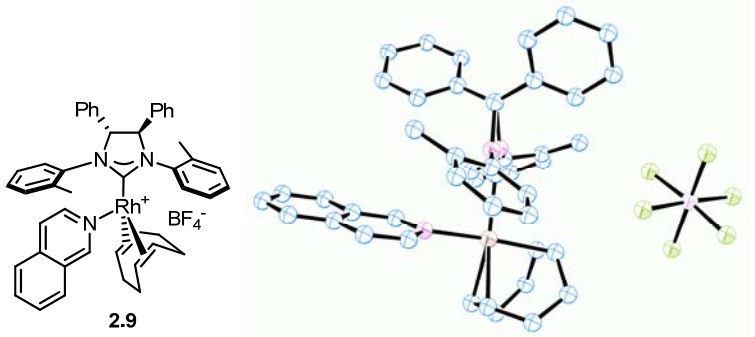
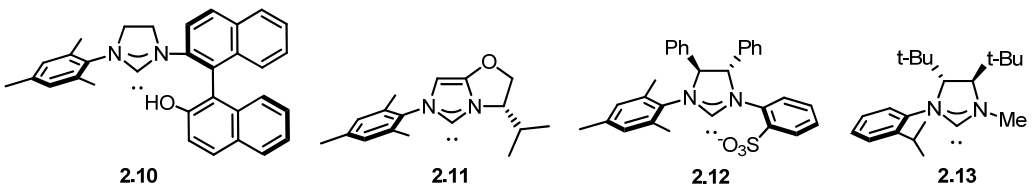



**Figure 2-3: Chiral Relay in a Rhodium NHC Complex**

[71] Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225.
[72] Kehrli, S.; Martin, D.; Rix, D.; Mauduit, M.; Alexakis, A. *Chem.-Eur. J.* **2010**, *16*, 9890.
[73] Matsumoto, Y.; Yamada, K.-I.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 4578.
[74] Selim, K. B.; Matsumoto, Y.; Yamada, K.; Tomioka, K., *Angew. Chem., Int. Ed.* **2009**, *48*, 8733.
[75] Faller, J. W.; Fontaine, P. P. *Organometallics* **2006**, *25*, 5887.

## 2.3 – $C_2$-Symmetric vs. $C_1$-Symmetric Ligands

All of the *N*-heterocyclic carbenes shown in the preceding section are $C_2$-symmetric. $C_1$-symmetric NHCs possess a higher level of asymmetry. Two different approaches to $C_1$-symmetric NHC ligands are shown in Figure 2-4. Examples **2.10** and **2.11** have chiral groups attached to one of the nitrogen atoms while examples **2.12** and **2.13** exploit a chiral relay effect. Examples **2.10** and **2.12** are also bidentate. Carbene **2.10** is based on an axially chiral NOBIN motif; the pendant naphthol makes the ligand bidentate.[76] Carbene **2.11** is a $C_1$-symmetric version of oxazole-based $C_2$-symmetric carbene **2.3**.[76] Carbene **2.12** bearing an *ortho*-sulfonate is bidentate, the chiral backbone of the imidazolidinylidene influences conformation of the aryl groups and hence the binding of the sulfonate to any transition metal.[77] Methyl-substituted carbene **2.13** provides a less sterically demanding environment than its $C_2$-symmetric counterparts.[78]




**2.10** **2.11** **2.12** **2.13**

**Figure 2-4: $C_1$-Symmetric NHCs**

$C_1$-symmetric NHCs generally provide a more asymmetric environment compared to $C_2$-symmetric NHCs. Hoveyda has described the high asymmetry of metal complexes bearing $C_1$-symmetric NHCs using a quadrant system (Figure 2-5).[79] Figure 2-5a shows the quadrant system applied to a metal complex bearing a $C_2$-symmetric NHC ligand. Among the 4 quadrants, **A** and **C**, and **B** and **D** provide the same environment for substrate binding; hence there are only 2 unique approaches. Figure 2-5b shows the quadrant system applied to a metal complex bearing a $C_1$-symmetric NHC ligand. In the case of the $C_1$-symmetric NHC, none of the quadrants provide the same approach for substrate binding.

[76] Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954.
[77] Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097.
[78] Fournier, P.-A.; Collins, S. K. *Organometallics*, **2007**, *26*, 2945.
[79] Lee, K.-S.; Hoveyda, A. H. *J. Org. Chem*. **2009**, *74*, 4455.

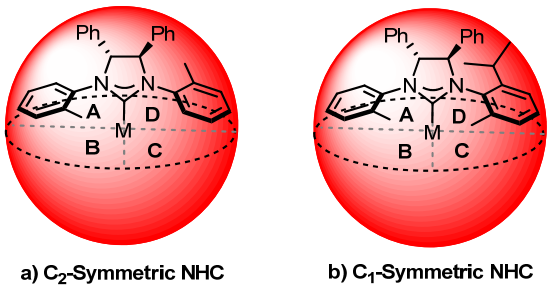
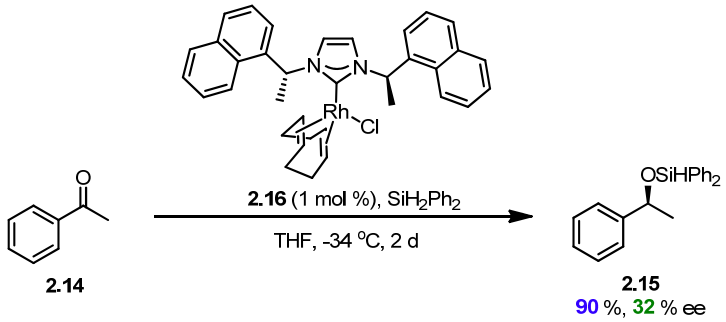



**Figure 2-5: Steric Environment of $C_1$-Symmetric vs. $C_2$-Symmetric NHCs**

## 2.4 – Chiral NHCs in Asymmetric Catalysis, Comparison of Reactivity between $C_1$ and $C_2$-Symmetric Ligands

The earliest example of the application of a chiral NHC in asymmetric catalysis is that of the rhodium NHC catalyzed hydrosilylation of ketones (Scheme 2-1).[40a] Chiral rhodium complex **2.16** catalyzes the asymmetric hydrosilylation of acetophenone **2.14**, converting 90 % of ketone **2.14** to silyl protected alcohol **2.15** in 32 % ee.[70] It should be noted that the silyl ether products are normally hydrolyzed and it is the corresponding alcohols that are evaluated for enantiomeric excess.




**Scheme 2-1: Rhodium Catalyzed Asymmetric Hydrosilylation of Acetophenone 2.14**

Since then, chiral *N*-heterocyclic carbenes have received increased attention in asymmetric catalysis.[80] The number of transformations is diverse and the structures of the ligands increasingly specialized. The following section will show the benefit that $C_1$-symmetric NHCs have brought to three asymmetric transformations: ring-closing olefin metathesis, conjugate addition and allylic substitution.

[80] Wang, F.; Liu, L.-J.; Wang, W.; Li, S.; Shi, M. *Coord. Chem. Rev.* **2012**, *256*, 804.

## 2.4.1 – Olefin Metathesis

With the advent of chiral *N*-heterocyclic carbenes, chiral ruthenium catalysts for olefin metathesis have been synthesized.[81] Several examples of chiral ruthenium catalysts are shown in Figure 2-6. Among the $C_2$-symmetric catalysts, complex **2.17** was the first to show important enantioselectivity in desymmetrization reactions.[71] Complexes **2.18** and **2.19** were synthesized in order to provide higher levels of steric bulk within the ruthenium atom's coordination sphere.[82] Methyl substituted catalysts **2.20** and **2.21** were designed to retain the enantioselectivity of the $C_2$-symmetric catalysts while having augmented reactivity.[78,83] Catalysts **2.20** and **2.21** although reactive, have poor solution stability; benzyl catalyst **2.22** was designed to have a longer lifetime in solution.[84]

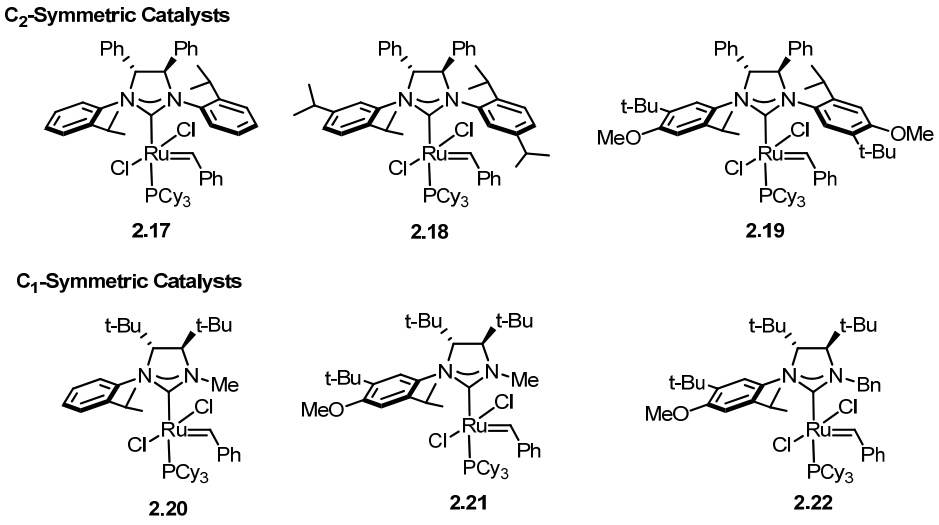
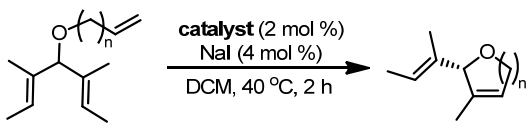



**Figure 2-6: Chiral Ruthenium-Based Olefin Metathesis Catalysts**

[81] Kress, S.; Blechert, S. *Chem. Soc. Rev.* **2012**, *41*, 4389.
[82] Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840.
[83] Fournier, P.-A.; Savoie, J.; Stenne, B.; Bedard, M.; Grandbois, A.; Collins, S. K. *Chem.-Eur. J.* **2008**, *14*, 8690.
[84] Savoie, J.; Stenne, B.; Collins, S. K. *Adv. Synth. Catal.* **2009**, *351*, 1826.

The first desymmetrization reaction conceived employing chiral ruthenium based olefin metathesis catalysts is the asymmetric ring-closing metathesis (ARCM) of prochiral trienes. The ARCM of prochiral trienes necessitates a substrate that has one olefin that is less sterically encumbered than the other two which are bound to the prochiral centre. The reactivities and selectivities of several chiral ruthenium olefin metathesis catalysts are compared in Table 2-1.[83] Complex **2.18** catalyzes the ring closing of triene **2.23a**, converting it quantitatively to dihydrofuran **2.24a** in 46 % ee (entry 1). When sodium iodide is added to replace the chlorine atoms on the catalyst, the ee improves to 90 % (entry 2). Catalyst **2.19** also converts triene **2.23a** quantitatively to dihydrofuran **2.24a** in 30 % ee (entry 3) and 87 % ee when sodium iodide is employed (entry 4). Methyl substituted catalyst **2.20** affords the same quantitative conversion of triene **2.23a** while affording heterocycle **2.24a** in 82 % ee (entry 5) without the need for sodium iodide. The more sterically demanding catalyst **2.21** converts triene **2.23a** quantitatively in 81 % ee (entry 6). Catalyst **2.17** quantitatively converts triene **2.23b** to six-membered **2.24b** in 90 % ee in the presence of sodium iodide (entry 7). While catalyst **2.20** converts triene **2.23b** quantitatively, it affords heterocycle **2.24b** in only 28 % ee (entry 8). The more sterically demanding catalyst **2.21** converts **2.23b** quantitatively to heterocycle **2.24b** in 92 % ee (entry 9). Complex **2.17** converts 5 % of triene **2.23c** to seven-membered **2.24c** in 85 % ee (entry 10). Methyl substituted catalyst **2.20** converts triene **2.23c** quantitatively to heterocycle **2.24c** in 60 % ee (entry 11). Complex **2.21** converts triene **2.23c** quantitatively to heterocycle **2.24c** in 88 % ee (entry 12). The methyl substituted $C_1$-symmetric catalysts provide high enantioselectivities without the need of sodium iodide as an additive. They also achieve much higher yields in the formation of seven-membered ring **2.24c**.

**Table 2-1: Asymmetric Ring-Closing Olefin Metathesis Forming Trisubstituted Olefins**



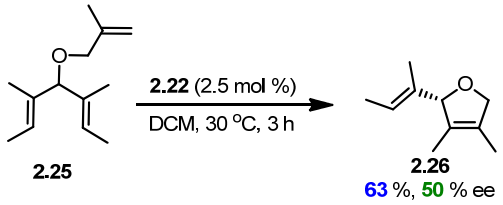

**2.23** n = 1: a; n = 2: b; n = 3: c

**2.24**

| Entry | Catalyst | n | Product | NaI | Conversion (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **2.18** | 1 | **2.24a** | no | >98 | 46 |
| 2 | **2.18** | 1 | **2.24a** | yes[c] | >98 | 90 |
| 3 | **2.19** | 1 | **2.24a** | no | >98 | 30 |
| 4 | **2.19** | 1 | **2.24a** | yes[c] | >98 | 87 |
| 5 | **2.20** | 1 | **2.24a** | no | >98 | 82 |
| 6 | **2.21** | 1 | **2.24a** | no | >98 | 81 |
| 7 | **2.17** | 2 | **2.24b** | yes[c] | >98 | 90 |
| 8 | **2.20** | 2 | **2.24b** | no | >98 | 28 |
| 9 | **2.21** | 2 | **2.24b** | no | >98 | 92 |
| 10 | **2.17** | 3 | **2.24c** | no | 5 | 85 |
| 11 | **2.20** | 3 | **2.24c** | no | >98 | 60 |
| 12 | **2.21** | 3 | **2.24c** | no | >98 | 88 |

a) Conversion determined by $^1$HNMR. b) Enantiomeric excess determined by HPLC
c) Reaction performed in THF.

Due to the low solution stability of the methyl-substituted catalysts **2.20** and **2.21**, they provide only poor conversions in ARCM reactions forming tetrasubstituted olefins.[85] Benzyl substituted catalyst **2.22** catalyzes the ARCM of triene **2.25**, affording dihydrofuran in **2.26** in 63 % yield and 50 % ee (Scheme 2-2). To date catalyst **2.22** is the only catalyst reported to perform ARCM forming tetrasubstituted olefins.




**2.25**

**2.26**
63 %, 50 % ee

**Scheme 2-2: ARCM of Triene 2.24 Catalyzed by Ruthenium Complex 2.22**

[85] Stenne, B.; Timperio, J.; Savoie, J.; Dudding, T.; Collins, S. K. *Org. Lett.* **2010**, *12*, 2032.

The preceding sections showed the augmented reactivity of ruthenium catalysts bearing methyl-substituted $C_1$-symmetric NHC ligands. Kinetic data for the ARCM of triene **2.22a** is shown in Figure 2-7.[78] The graph compares $C_2$-symmetric catalyst **2.17** with its methyl-substituted $C_1$-symmetric counterpart, catalyst **2.20**. The difference in reaction rate is clearly visible. While methyl-substituted catalyst **2.20** has reached near-quantitative conversion in only 9 min, its $C_2$-symmetric counterpart, catalyst **2.17** has yet to reach 10 %.

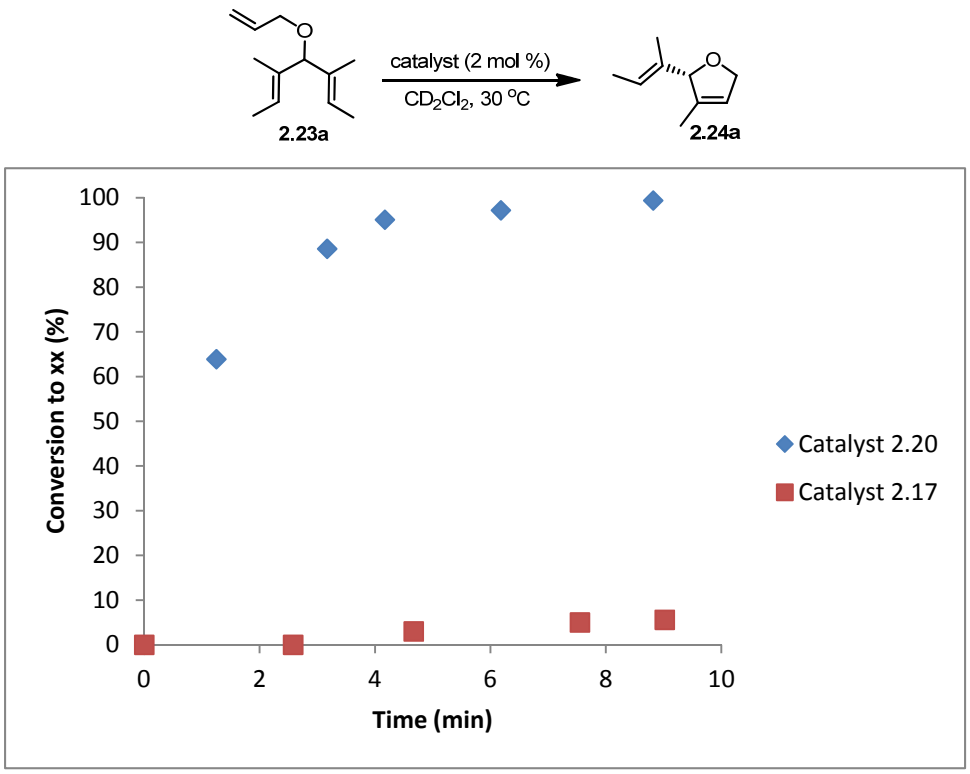
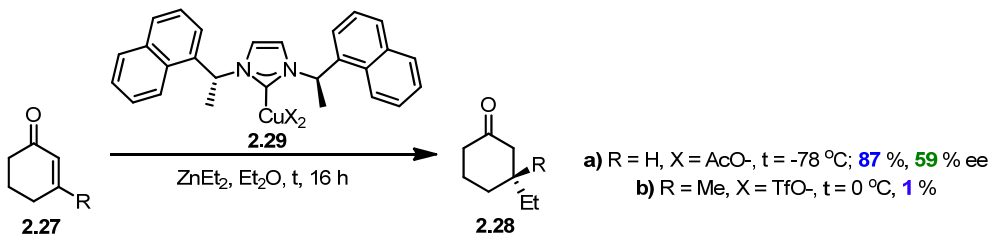



**Figure 2-7: Kinetic Plot of Catalysts 2.20 and 2.17 in the ARCM of Triene 2.23a**

## 2.4.2 – Conjugate Addition

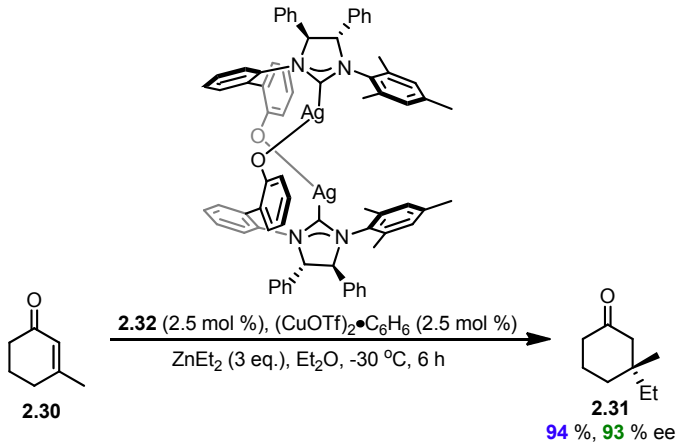
Asymmetric conjugate addition is an important reaction in organic synthesis.[86] Many chiral transition metal NHC complexes have been applied towards asymmetric conjugate addition reactions.[80] A comparison of the reactivity of different NHC ligands in copper catalyzed asymmetric conjugate addition follows.

[86] Harutyunyan, S. R.; den Hertog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824.




**Scheme 2-3: Copper Catalyzed Asymmetric Conjugate Addition Forming Tertiary vs. Quaternary Stereocenters**

Scheme 2-3 shows the addition of diethylzinc to cyclic enones catalyzed by *in-situ* generated copper catalysts. Both examples employ the same chiral $C_2$-symmetric NHC ligand bound to a copper(II) salt. When cyclohexenone **2.27a** and diethylzinc are mixed in the presence of catalyst **2.29a** at low temperature, ketone **2.28a** is afforded in 87 % yield and 59 % ee.[87] However, when methylcyclohexenone **2.27b** and diethylzinc are mixed in the presence of catalyst **2.29b**, even at higher temperature only 1 % of the enone starting material **2.27b** is converted after 16 h.[88]

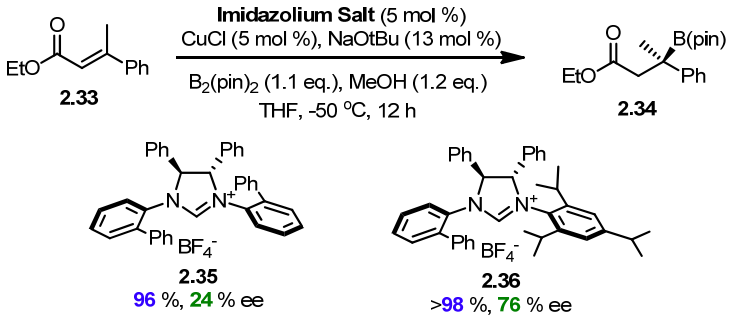



**Scheme 2-4: Copper Catalyzed β-Alkylation of Cyclohexenone 2.30 with Diethyl Zinc**

In contrast to the difficulty in constructing quaternary stereocenters with a copper catalyst bearing a $C_2$-symmetric ligand, Hoveyda reported the generation of quaternary stereocenters via addition of dialkylzinc reagents to enones catalyzed by an *in-situ* generated chiral $C_1$-symmetric copper complex (Scheme 2-4).[89] When silver complex **2.32** is mixed with an equimolar quantity

[87] Alexakis, A.; Winn, C. L.; Guillen, F.; Pytkowicz, J.; Roland, S.; Mangeney, P. *Adv. Synth. Catal.* **2003**, *345*, 345.
[88] Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416.
[89] Lee, K.-S.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182.

of a copper(I) salt, the corresponding copper NHC complex is formed via transmetallation. The resultant complex catalyzes the asymmetric conjugate addition of diethylzinc to enone **2.30**, converting 94 % of enone **2.30** and affording ketone **2.31** in 93 % ee.



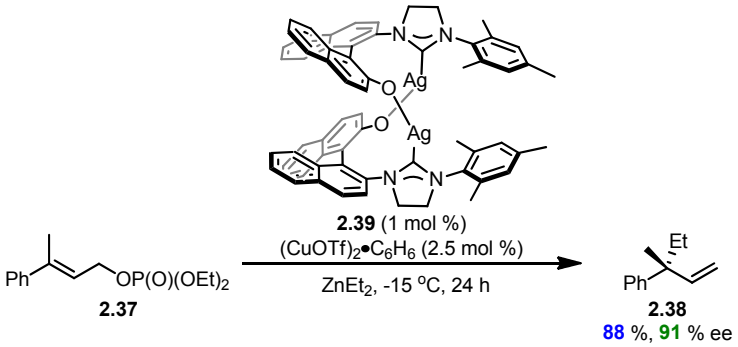

**Scheme 2-5: Cu-NHC Catalyzed β-Borylation of Cinnamate 2.33**

Chiral copper NHC complexes can also catalyze the asymmetric β-borylation of enones (Scheme 2-5).[90] Imidazolinium salts **2.35** and **2.36** react with copper(I) chloride and sodium *t*-butoxide *in-situ* to form chiral copper NHC complexes. The resultant copper complexes catalyze the asymmetric conjugate addition of bis(pinacolato)diboron to enone **2.33**, affording alkyl boronate **2.34**. $C_2$-symmetric salt **2.35** converts 96 % of enone **2.33** in 24 % ee. Bidentate $C_1$-symmetric salt **2.36** converts enone **2.33** quantitatively in 76 % ee. When the temperature is lowered to -78 °C, the ee increases to 93 % while retaining full conversion.

## 2.4.3 – Allylic Substitution

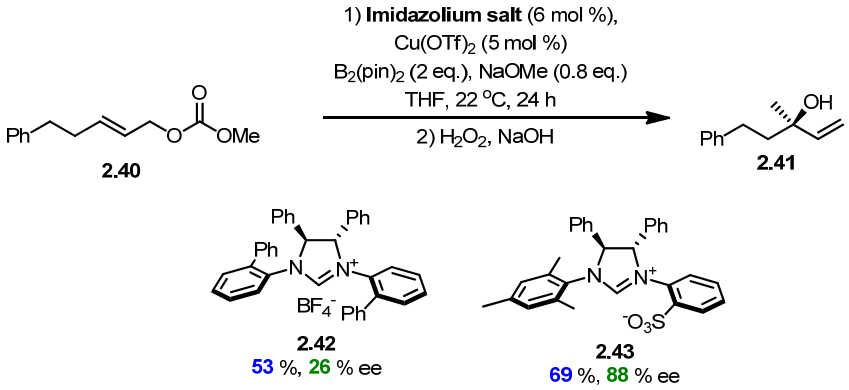
Asymmetric allylic substitution is an important transformation in organic chemistry, finding many applications in total synthesis.[91] $C_1$-symmetric NHCs enable the construction of quaternary stereocenters via copper catalyzed allylic substitution. An *in-situ* generated chiral copper NHC complex catalyzes the addition of dialkylzinc reagents to allylic phosphonate esters (Scheme 2-6).[92] Chiral silver complex **2.39** and a copper(I) salt undergo transmetallation in solution, generating a chiral copper NHC catalyst *in-situ*. The *in-situ* generated copper complex catalyzes the allylic substitution of phosphonate ester **2.37** with diethylzinc, affording quaternary compound **2.38** in 88 % yield and 91 % ee.

[90] O'Brien, J. M.; Lee, K.-S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630.
[91] Tros, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.
[92] Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130.




**Scheme 2-6: Copper Catalyzed Asymmetric Allylic Alkylation of Allyl Phosphonate 2.37**

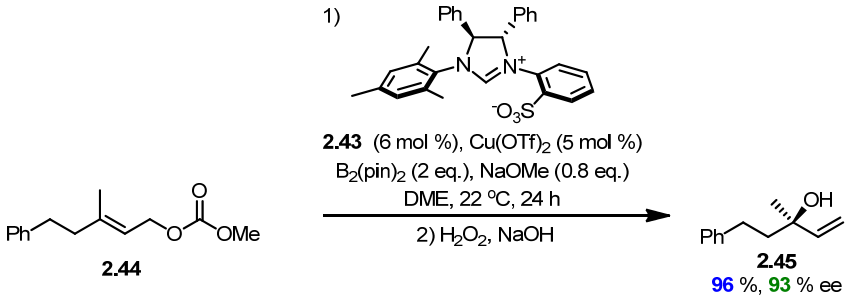
Chiral allylic alcohols can be generated following oxidative cleavage of an organoboron compound generated by substitution of an allyl carbonate (Scheme 2-7).[93] Imidazolinium salts **2.42** and **2.43** react with sodium methoxide, generating the free carbene and forming a copper catalyst *in-situ* with copper(II) triflate. The *in-situ* generated chiral copper NHC complexes catalyze the allylic substitution of allyl carbonate **2.40** with bis(pinacolato)diboron, following oxidative workup, alcohol **2.41** is afforded. $C_2$-symmetric NHC precursor **2.42** affords alcohol **2.41** in 53 % yield and 26 % ee. $C_1$-symmetric NHC precursor **2.43** affords alcohol **2.41** in 69 % yield and 88 % ee.




**Scheme 2-7: Synthesis of Chiral Allylic Alcohol 2.41 via Asymmetric Allylic Borylation**

[93] Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634.

$C_1$-symmetric NHCs allow for the construction of chiral quaternary allylic alcohols (Scheme 2-8).[94] Imidazolinium salt **2.43** reacts with sodium methoxide, forming free carbene which forms a copper catalyst *in-situ* with copper(II) triflate. The *in-situ* generated chiral copper NHC complex catalyzes the allylic substitution of allyl carbonate **2.44** with bis(pinacolato)diboron; following oxidative workup, alcohol **2.45** is afforded in 96 % yield and 93 % ee.




**Scheme 2-8: Synthesis of Chiral Allylic Alcohol 2.45 via Asymmetric Allylic Borylation**

[94] Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634.

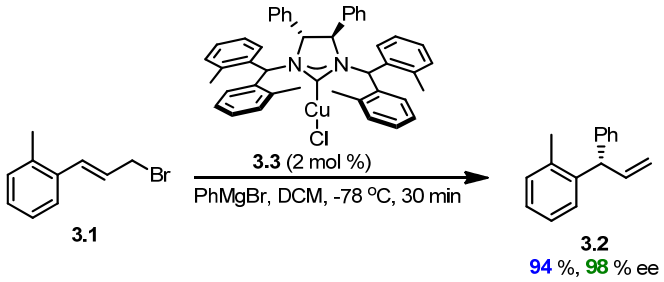
# Chapter 3 - Synthesis of Novel Chiral $C_1$-Symmetric NHCs

## 3.1 – Ligand Design

The preceding chapter showed the utility of chiral NHCs as ligands for asymmetric transition metal catalysis. Emphasis was placed on the utility of $C_1$-symmetric ligands in transformations involving sterically encumbered substrates. Copper catalyzed allylic substitution forming quaternary stereocenters was shown to benefit from the employment of $C_1$-symmetric NHC ligands.

Many $C_1$-symmetric NHCs exploit aryl groups as the chiral relay element bound to nitrogen,[80] and there has yet to be an example in the literature of a chiral $C_1$-symmetric NHC which exploits an alkyl group as a chiral relay. Alkyl substituents are sterically and electronically different from the standard aryl groups found on most chiral NHC ligands,[33,39] and are thus of great interest to expand the diversity of chiral NHCs.

Chiral $C_2$-symmetric copper complex **3.3** bearing dialkyl NHC ligand **2.8** catalyzes the allylic substitution of allyl bromides with aryl Grignard reagents (Scheme 3-1).[74] Allyl bromide **3.1** reacts with phenylmagnesium bromide in the presence of catalyst **3.3**, affording substitution product **3.2** in 94 % yield and 98 % ee.




**Scheme 3-1: Copper Catalyzed Asymmetric Allylic Arylation of Allyl Bromides**

The project goal is to synthesize a series of chiral dialkyl $C_1$-symmetric NHCs which exploit a chiral relay. Criteria of modular synthesis and simplified purification were stipulated for the synthetic protocols. The model substrate, carbene **3.4**, is shown in Figure 3-1. The chiral relay element chosen is the biaryl methyl group inspired by ligand **2.8**.[74] The group provides more bulk than the standard aryl groups and can penetrate deeper into a metal's coordination

sphere. Since methyl substituted NHCs show enhanced reactivity, a methyl group was chosen as the second alkyl substituent.[78] As with prior work in the Collins group,[78,83,84] the backbone of the NHC is based on di-*t*-butylethylenediamine. The larger *t*-butyl groups help to push the relay element closer to the metal.

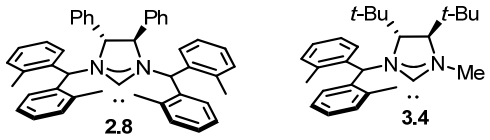
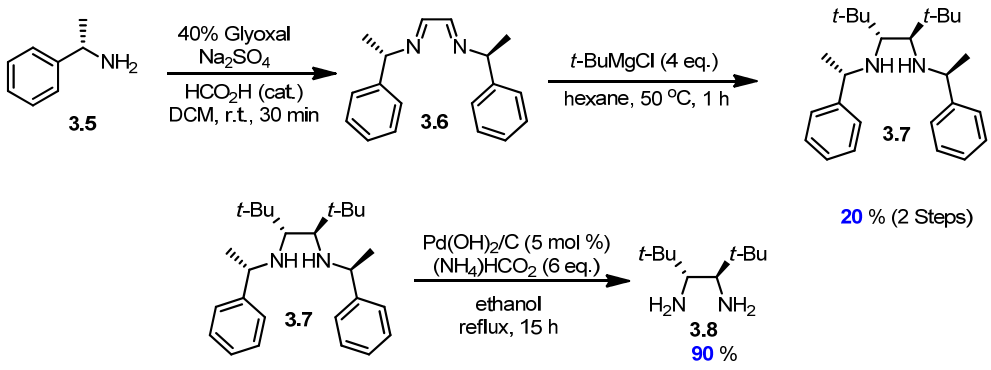



**Figure 3-1: $C_2$-Symmetric Precursor and Model Substrate**

## 3.2 – Synthesis of Precursors

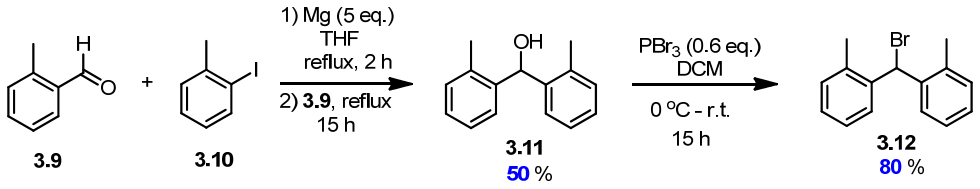
The existing syntheses of dialkyl NHC ligands that exploit a chiral relay effect rely on the alkylation of a chiral diamine.[74] The diamine required to synthesize the model ligand scaffold is chiral diamine **3.8**. (1R, 2R)-Di-*t*-butylethylenediamine (**3.8**) is not readily available from commercial sources. It can be synthesized on large scale in 3 steps from commercially available starting materials (Scheme 3-2),[95] begining with the formation of diimine **3.6**. Diimine **3.6** is formed by stirring (S)-phenylethylamine and glyoxal under dehydrating conditions, and following evaporation of solvent is added to a suspension of *t*-butylmagnesium chloride. The addition of the Grignard reagent to diimine **3.6** is diastereoselective, affording only diamine **3.7** in 20 % yield[96] over two steps. The phenylethyl groups are then removed via transfer hydrogenation using Pearlman's catalyst, affording diamine **3.8** in 90 % yield.

[95] Roland, S.; Mangeney, P.; Alexakis, A. *Synthesis* **1999**, 228.
[96] The reported yield in the literature is 95 %. In our hands the figure in the text represents the average isolated yield.




**Scheme 3-2: Synthesis of (1R, 2R)-1,2-Di-*t*-butylethylenediamine 3.8**

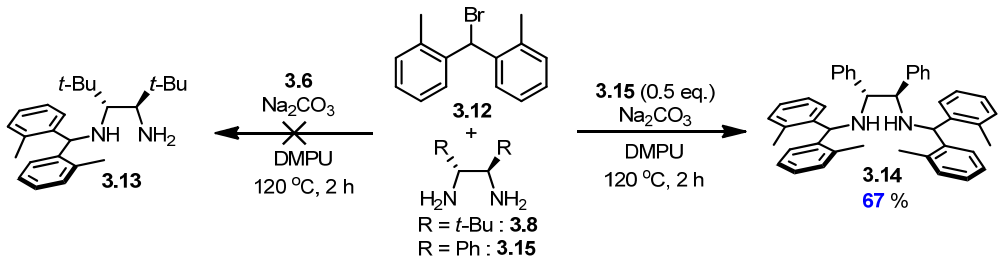
The biaryl methyne is installed via $S_N2$ substitution on the corresponding alkyl bromide. Alkyl halide **3.12** is synthesized from alcohol **3.11**, which is formed via Grignard reaction between 2-iodotoluene (**3.10**) and *ortho*-salicylaldehyde (**3.9**) (Scheme 3-3). *Ortho*-tolylmagnesium iodide is formed *in-situ* from iodide **3.10** and magnesium in refluxing THF. The aldehyde is then added, and following quench and recrystallization alcohol **3.11** is afforded in 50 % yield. Alcohol **3.11** is then brominated using phosphorous tribromide in DCM to afford bromide **3.12** in 80 % yield.




**Scheme 3-3: Synthesis of Bis(*ortho*-tolyl)methyl Bromide**

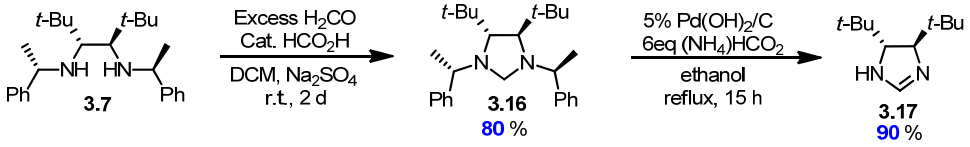
## 3.3 – Preliminary Experiments

With the precursors prepared, the previously reported alkylation conditions[74] were applied to di-*t*-butylethylenediamine (**3.8**). While the alkylation of diphenylethylenediamine (**3.15**) affords 67 % of alkylated diamine **3.14**, the *t*-butyl diamine **3.8** proved to be problematic (Scheme 3-4). The standard conditions did not result in formation of diamine **3.13**. But, when the reaction time was increased to 24 hours, trace amounts of diamine **3.13** were formed. However, isolating the product from the DMPU solvent proved troublesome. Since satisfactory yields of diamine **3.13** could not be obtained, it was decided to move forward instead with imidazoline **3.17** in place of diamine **3.8**.




**Scheme 3-4: Alkylation of Chiral Diamines with Bromide 3.12**

Imidazoline **3.17** is prepared from diamine **3.7** in two steps (Scheme 3-5).[97] Diamine **3.7** is treated with formaldehyde under dehydrating conditions, affording imidazolidine **3.16** in 80 % yield. The phenylethyl groups of imidazolidine **3.16** are then cleaved via transfer hydrogenation. During the reaction, an oxidation at the amine occurs, resulting in the formation of imidazoline **3.17** in 90 % yield.



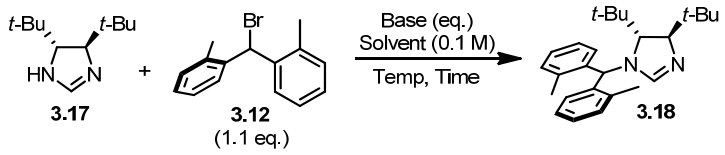

**Scheme 3-5: Synthesis of Imidazoline 3.17**

## 3.4 – Optimization of Alkylation Conditions

Table 3-1 shows the optimization of the conditions for the alkylation of imidazoline **3.17** with bromide **3.12** (Table 3-1). Initial experiments involved deprotonation of imidazoline **3.17** with a strong base, followed by addition of bromide **3.12**. Reactions employing either n-butyl lithium (entry 1) or sodium hydride (entry 2) as a base did not generate any alkylation products. Employing a milder base in potassium carbonate with dichloromethane as a solvent (entry 3) afforded imidazoline **3.18** in 20 % yield after 3 days. Changing the solvent to acetone and bringing the reaction to reflux (entry 4) improved the yield to 30 % in 24 hours. Performing the reaction in refluxing DMF (entry 5) afforded imidazoline **3.18** in only 17 % yield. The best yield was obtained by heating the reaction in acetone at 100 °C in a sealed tube for two days, affording imidazoline **3.18** in 45 % yield. Use of additives such as sodium iodide (entry 7) or silver carbonate (entry 8) did not have a significant effect on the yield of imidazoline **3.18**.

[97] Pytkovicz, J.; Roland, S.; Mangeney, P. *J. Organomet. Chem.* **2001**, *631*, 157.

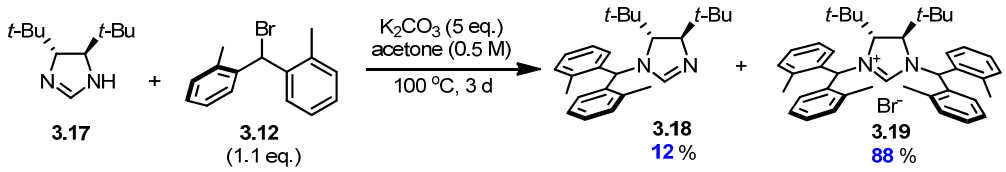
**Table 3-1: Alkylation of Imidazoline 3.17 with Bromide 3.12**




| Entry | Base (eq.) | Solvent | Temperature (°C) | Time | Additive (eq.) | Yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | n-BuLi (1) | THF | 0[b] | 2 h | N/A | 0 |
| 2 | NaH (1) | THF | 0[b] | 2 h | N/A | 0 |
| 3 | $K_2CO_3$ (5) | DCM | 20 | 72 h | N/A | **20** |
| 4 | $K_2CO_3$ (5) | Acetone | 60 | 24 h | N/A | **30** |
| 5 | $K_2CO_3$ (5) | DMF | 120 | 24 h | N/A | **17** |
| 6 | $K_2CO_3$ (5) | Acetone | 100 | 48 h | N/A | **45** |
| 7 | $K_2CO_3$ (5) | Acetone | 100 | 48 h | NaI (1) | **45** |
| 8 | $K_2CO_3$ (5) | Acetone | 100 | 48 h | $Ag_2CO_3$ (1) | **39** |

a) Yields following column chromatography, b) Reagent was added at 0 °C, and the reaction was allowed warm to room temperature

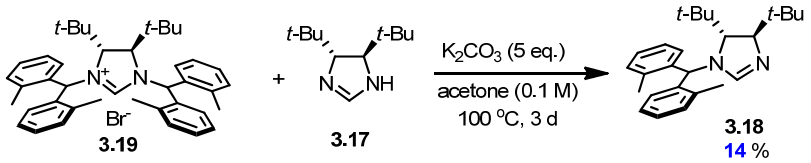
The yield of the reaction was found to be dependent on the concentration. Increasing the concentration of the reaction from 0.1 M to 0.5 M led to a drop in yield, affording only 12 % of imidazoline **3.18**. In addition, alkyl halide **3.12** was found to have formed the double addition product, imidazolinium salt **3.19**, which precipitated out of solution in 88 % yield (Scheme 3-6).




**Scheme 3-6: Isolation of Imidazolinium Salt 3-19**

The poor yield of imidazoline **3.18** in the alkylation of imidazolium **3.17** at 0.5 M (Scheme 3-6) suggests that the insolubility of imidazolinium **3.9** has a negative impact on the reaction yield. Furthermore, it suggests that the addition of the second alkyl group, resulting in imidazolinium **3.19**, is reversible. To test the reversibility of the second alkylation, imidazolinium **3.19** was resubmitted to the reaction conditions (Scheme 3-7), affording imidazoline **3.18** in only 14 % yield. The result indicates that the formation of imidazolinium salt **3.19** is poorly reversible and suggests that at higher concentration all of bromide **3.12** in

solution is converted to imidazolinium **3.19** before equilibrium shifts back towards formation of imidazoline **3.8**. At lower concentration, formation of imidazoline **3.18** is favoured.

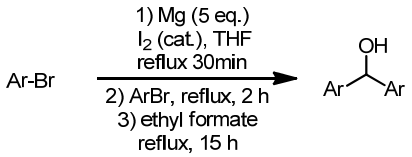


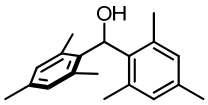
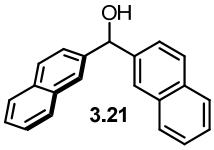
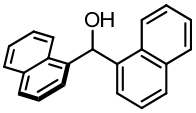
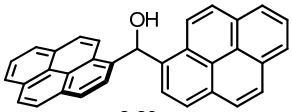

**Scheme 3-7: Reversibility of Formation of Imidazolinium Salt 3.19**

## 3.5 – Scope of the First Alkylation

With the conditions for the alkylation of imidazoline **3.7** optimized, attention was turned to the scope of the alkylation reaction. To that end, a series of biarylmethyl halides were synthesized in order to provide varying levels of steric bulk. All of the alkyl halides were prepared from biarylmethanol precursors. The alcohols were synthesized by reaction of 2 equivalents of the Grignard reagent formed from the corresponding alkyl bromide with ethyl formate (Table 3-2). Mesityl substituted alcohol **3.20** and 2-naphthyl substituted alcohol **3.21** were both synthesized in high yields, affording 90 and 94 % yields respectively. Alcohol **3.22** bearing 1-naphthyl substituents was afforded in good although somewhat lower 68 % yield. Alcohol **3.23** bearing 1-pyrenyl substituents was afforded in moderate 46 % yield.

**Table 3-2: Synthesis of Biarylmethanols via Grignard Reaction**



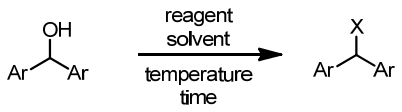

| Entry | Product | Yield (%)[a] |
|---|---|---|
| 1 |  **3.20** | **90** |
| 2 |  **3.21** | **94** |
| 3 |  **3.22** | **68** |
| 4 |  **3.23** | **46**[b] |

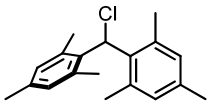
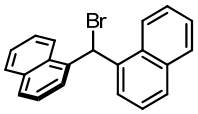
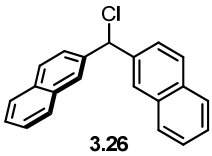
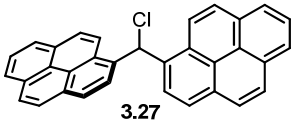
a) Isolated yields following recrystallization, b) Represents a crude yield

Not all of the alcohols shown in Table 3-2 could be halogenated in the same fashion as alcohol **3.11** with phosphorous tribromide. The halogenation conditions of the alcohols are summarized in Table 3-3. The halogenation of alcohol **3.20**, which has been described previously,[98] was carried out under biphasic conditions between a benzene solution of alcohol **3.20** and concentrated HCl, affording 85 % of alkyl chloride **3.24**. Alcohol **3.22** was brominated with phosphorous tribromide, affording alkyl bromide **3.25** in 90 % yield. Alkyl chloride **3.26** was afforded in 79 % yield by treating alcohol **3.21** with 2 equivalents of thionyl chloride at room temperature. Pyrene substituted alcohol **3.23** was chlorinated with 2 equivalents of thionyl chloride at reflux, affording alkyl chloride **3.27** in 95 % yield.

[98] Nauta, W. T.; Wuis, P. J. *Rec. trav. chim.* **1937**, *56*, 535.

**Table 3-3: Halogenation of Biarylmethanols**

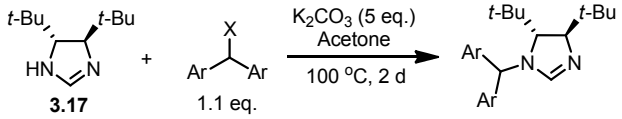


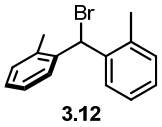
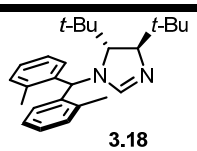
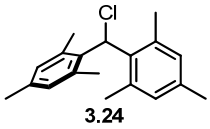
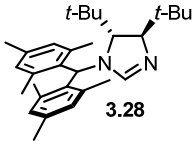
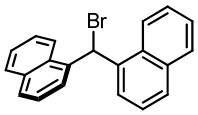
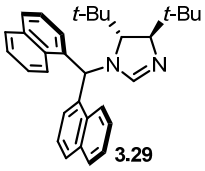
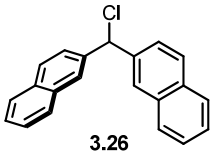
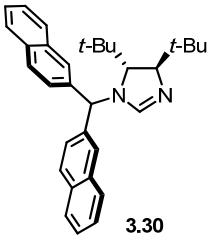
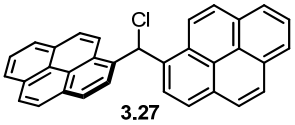
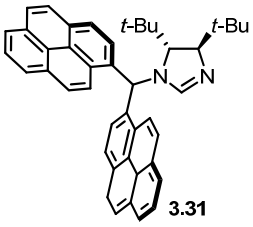

| Entry | Product | Reagent (eq.) | Solvent | Temperature | Time | Yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 |  **3.24** | HCl (xs) | $H_2O$/Benzene | r.t. | 2 d | **85** |
| 2 |  **3.25** | $PBr_3$ (0.6) | DCM | 0 °C[b] | 15 h | **90** |
| 3 |  **3.26** | $SOCl_2$ (2) | Benzene | 0 °C[b] | 15 h | **79** |
| 4 |  **3.27** | $SOCl_2$ (2) | Benzene | reflux | 15 h | **95**[c] |

a) Yields following filtration on basic alumina, b) Reagent was added at 0 °C, and the reaction was allowed to warm to room temperature overnight, c) Represents a crude yield

The alkyl halides shown in Table 3-3 were submitted to the optimized conditions for the alkylation of imidazoline **3.17**. The results of the alkylation reactions are summarized in Table 3-4. Mesityl substituted alkyl halide **3.24** resulted in a higher yield than the model system, affording imidazoline **3.19** in 60 % yield. Alkylation with bromide **3.25** resulted in the lowest yield, affording imidazoline **3.29** in 20 % yield. Imidazoline **3.30** was synthesized in 46 % yield from alkyl chloride **3.26**. Pyrene substituted alkyl halide **3.27** resulted in the highest yield, affording imidazoline **3.31** in 68 % yield.

**Table 3-4: Scope of Alkylation of Imidazoline 3.17**




| Entry | Alkyl Halide | Product | Yield (%) |
|---|---|---|---|
| 1 |  3.12 |  3.18 | 45 |
| 2 |  3.24 |  3.28 | 60 |
| 3 |  3.25 |  3.29 | 20 |
| 4 |  3.26 |  3.30 | 46 |
| 5 |  3.27 |  3.31 | 68 |

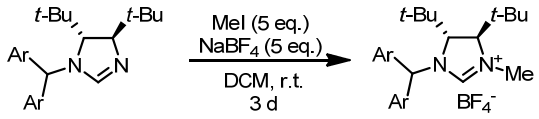
a) Yields following column chromatography

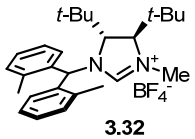
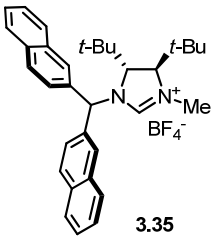
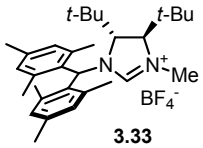
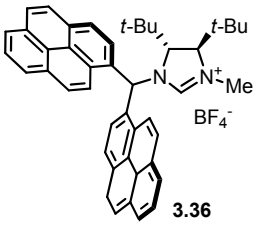
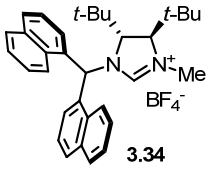
## 3.6 – Synthesis of Imidazolinium Salts

The main series of $C_1$-symmetric NHC precursors synthesized bears an *N*-methyl group for enhanced reactivity. The methyl group can be installed quantitatively on imidazoline **3.18** with an excess of methyl iodide (Table 3-5, entry 1). Since many procedures for the installation

of an NHC onto a transition metal centre necessitate a non-coordinating counterion, the imidazolinium salts were prepared with tetrafluoroborate counterions. The exchange was performed *in-situ* with sodium tetrafluoroborate in a one-pot, two-step process. Imidazolines **3.18**, **3.29**, and **3.30** reacted quantitatively, affording exclusively imidazolinium salts **3.32**, **3.34**, and **3.35** respectively. While the mesityl substituted imidazoline **3.30** was also found to react quantitatively, imidazolinium salt **3.33** was found to be much less stable than the other derivatives. Attempted purification on silica gel resulted in decomposition of the compound. As such, it was deemed inappropriate for further investigation, since it would decompose when exposed to reagents for forming a transition metal complex. The synthesis 1-pyenenyl derivative **3.31** was more challenging, affording imidazolinium salt **3.36** in a moderate 60 % yield and requiring more rigorous purification.

**Table 3-5: Methylation and Counterion Exchange**

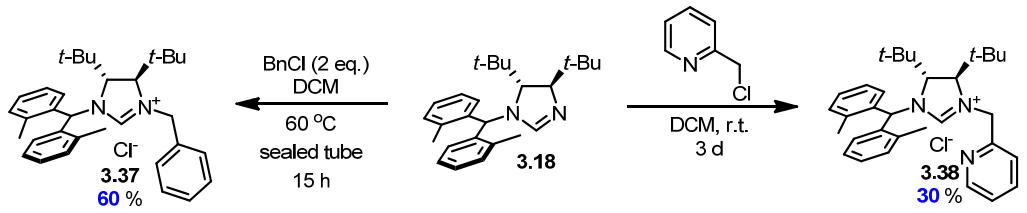



| Entry | Product | Yield (%)[a] | Entry | Product | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 |  **3.32** | >99 | 4 |  **3.35** | >99 |
| 2 |  **3.33** | >99[b] | 5 |  **3.36** | 60 |
| 3 |  **3.34** | >99 | | | |

a) Yields following purification, b) Compound is unstable

Reactivity controlling groups other than methyl were also investigated. To such an end, *N*-benzyl and *N*-(2-picolyl) substituents were installed on imidazoline **3.17** (Scheme 3-8). The

benzyl substituent was installed by heating imidazoline **3.17** with 2 equivalents of benzyl chloride in a sealed tube, affording imidazolinium salt **3.37** in 60 % yield following recrystallization. While the 2-picolyl group could also be installed using a similar protocol, imidazolinium salt **3.38** could not be adequately purified for installation onto a transition metal. Stirring imidazoline **3.18** with 2-picolyl chloride at room temperature for 3 days afforded imidazolinium salt **3.38** in a crude 30 % yield.




**Scheme 3-8: Variation of the Reactivity Controlling Substituent**

A convergent and modular protocol was created which allows for the efficient synthesis of chiral $C_1$-symmetric dialkyl NHC ligands in 2 steps from a chiral imidazoline precursor.[99] The protocol is based on chiral imidazoline **3.17** which is more stable than diamine **3.8** and has the added advantage of not requiring a high temperature distillation to purify. Biaryl methyne substituents of varying steric bulk could be installed as a chiral relay, in synthetically relevant yields. Reactivity controlling elements can be installed in moderate to excellent yields, and most imidazolinium salts could be used without the need for rigorous purification.

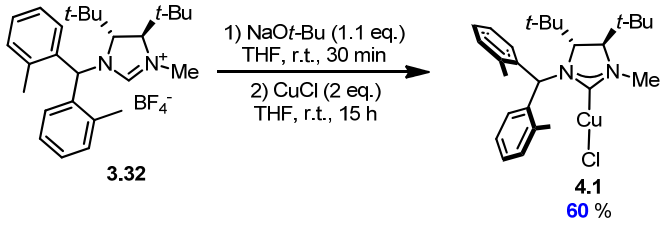
[99] Holtz-Mulholland, M.; Collins, S. K. *Synthesis* **2014**, *46*, 375.

# Chapter 4 – Synthesis New Chiral of Transition Metal NHC Complexes

The utility of NHC ligands in transition metal catalysis was shown in Chapter 1. The increasing interest in chiral $C_1$-symmetric NHC ligands in asymmetric catalysis was shown in Chapter 2. Since transition metal NHC complexes make good catalysts, the chiral $C_1$-symmetric NHC precursors whose synthesis was shown in the preceding chapter were submitted to metalation conditions for installation onto catalytically relevant transition metals. The target metals were copper, gold, palladium, ruthenium and iridium.

## 4.1 – Synthesis of Chiral Copper NHC Complexes

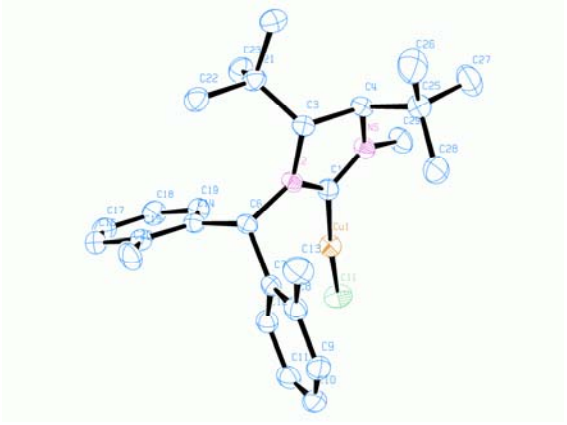
Chiral copper NHC complexes have found many uses in asymmetric catalysis.[80] As such, the copper NHC complexes of the new NHC ligands were synthesized. NHC precursor **3.32**, which is the $C_1$-symmetric analog of the previously reported $C_2$-symmetric ligand **2.8**,[74] was submitted to conditions developed by Nolan[32] for the synthesis of mono NHC copper complexes. Imidazolium salt **3.32** was stirred for 30 min in THF with a slight excess of sodium *t*-butoxide, generating the free carbene *in-situ*. Stirring the resultant solution overnight with a large excess of copper(I) chloride afforded chiral NHC complex **4.1** in 60 % yield (Scheme 4-1). Employing KHMDS or silver(I) oxide as carbene generating reagents did not result in higher yields of complex **4.1**.



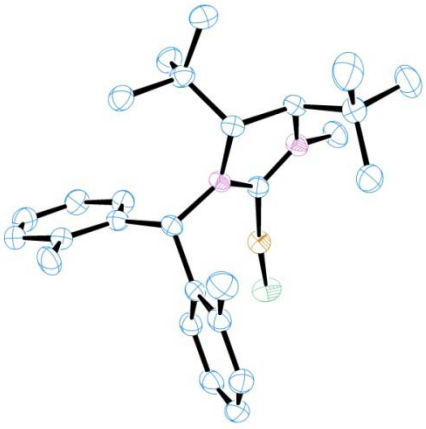

**Scheme 4-1: Synthesis of Chiral Copper NHC Complex 4-1**

Diffraction quality crystals of complex **4.1** were grown by vapour diffusion of pentane into a DCM solution of the complex. The X-ray structure of complex **4.1** is shown in Figure 4-1 and selected structural parameters are shown in Table 4-1. Figure 4-1b shows the staggered view of complex **4.1**, the area adjacent the sterically unencumbered methyl group is sterically accessible whereas the area surrounding the biaryl methyne is blocked by the aryl groups. Figure

4-1c shows the complex through the plane of the NHC from the side of the methyl group. The different conformations of the two aryl groups on biaryl methyne create a highly dissymmetric environment about the metal centre. The structural parameters of the complex are very similar to the values for Cu(SIPr)Cl (Table 4-2).[100] The copper-carbon bond of complex **4.1** is 1.893(2) Å long and the copper-chlorine bond is 2.1066(7) Å long. For Cu(SIPr)Cl the copper-carbon bond is 1.896(7) Å long and the copper-chlorine bond is 2.114(2) Å long. The carbon-copper-chlorine angle in complex **4.1** is slightly bent from the linear configuration at an angle of 171.51(7)°, the carbon-copper-chlorine angle of Cu(SIPr)Cl is also slightly bent, being 174.4(2)°. The buried volume of complex **4.1** is 44.5 %, slightly smaller than Cu(SIPr)Cl which has a buried volume of 46.4 %.



a)



b)

c)

**Figure 4-1: Crystal Structure of Complex 4-1**

[100] (a) Diez-Gonzalez, S.; Escudero-Adan, E. C.; Benet-Buchholz, J.; Stevens, E. D.; Slawin, M. Z. A.; Nolan, S. P. *Dalton Trans* **2010**, *39*, 7595. (b) Diez-Gonzalez, S.; Stevens, E. D.; Nolan, S. P. *Chem. Commun.* **2008**, 4747. (c) Buried volumes were computed using the MoLNaC SambVca web application using a fixed bond length of 2 Å, a sphere radius of 3.5 Å, and scaled bond radii. For examples see: Poater, A.; Cosenza, B.; Correa, A.; Giudice, S.; Ragone, F.; Scarano, V.; Cavallo, L. *Eur. J. Inorg. Chem.* **2009**, 1759.

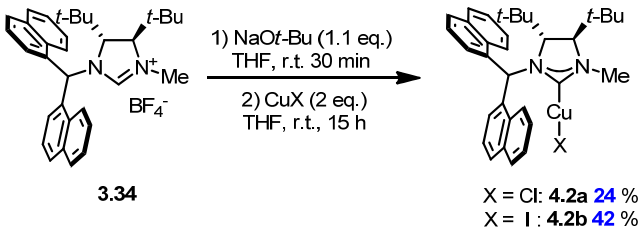
**Table 4-1: Selected Structural Parameters of Complex 4.1**

| Entry | Parameter | Value |
|---|---|---|
| 1 | Cu-C | 1.893(2) Å |
| 2 | Cu-Cl | 2.1066(7) Å |
| 3 | C-Cu-Cl | 171.51(7)° |
| 4 | Vbur | 44.5 % |

**Table 4-2: Selected Structural Parameters of Cu(SIPr)Cl**

| Entry | Parameter | Value |
|---|---|---|
| 1 | Cu-C | 1.896(7) Å |
| 2 | Cu-Cl | 2.114(2) Å |
| 3 | C-Cu-Cl | 174.4(2)° |
| 4 | Vbur | 46.4 % |

Naphthyl substituted ligand **3.34** was also installed onto copper(I) using sodium *t*-butoxide (Scheme 4-2). When copper(I) chloride was employed as the copper source, complex **4.2a** was isolated in 24 % yield. Changing the copper source to copper(I) iodide afforded complex **4.2b** in 42 % yield. As with the synthesis of complex **4.1** the use of KHMDS or silver(I) oxide as a carbene generating reagent did not result in higher yields of the desired copper NHC complex.




**Scheme 4-2: Synthesis of Chiral Naphthyl Copper Complexes 4.2**

Diffraction quality crystals of complex **4.2b** were grown by vapour diffusion of pentane into a saturated DCM solution of the complex. The X-ray structure of complex **4.2b**, which crystallized as a DCM solvate, is shown in Figure 4-2. Figure 4-2b shows the staggered view of complex **4.2b**. As with complex **4.1** the area adjacent the *N*-methyl group is sterically accessible, while the area surrounding the biaryl methyne is sterically encumbered. A look down the *N*-methyl bond, in Figure 4-2c, shows a highly dissymmetric environment about the metal centre. Selected structural parameters for complex **4.2b** are shown in Table 4-3. The complex

has a copper-carbon bond length of 1.894(3) Å, nearly identical to that of complex **4.1**. The copper-iodine bond length of complex **4.2b** is 2.3967(3) Å and the copper-carbon-iodine angle is again slightly bent at 173.22(9)°. The buried volume of complex **4.2b** is 43.9 %, slightly smaller than complex **4.1**. The slight difference is likely due to the increased steric repulsion of the larger naphthyl groups, pushing them further from the metal centre.

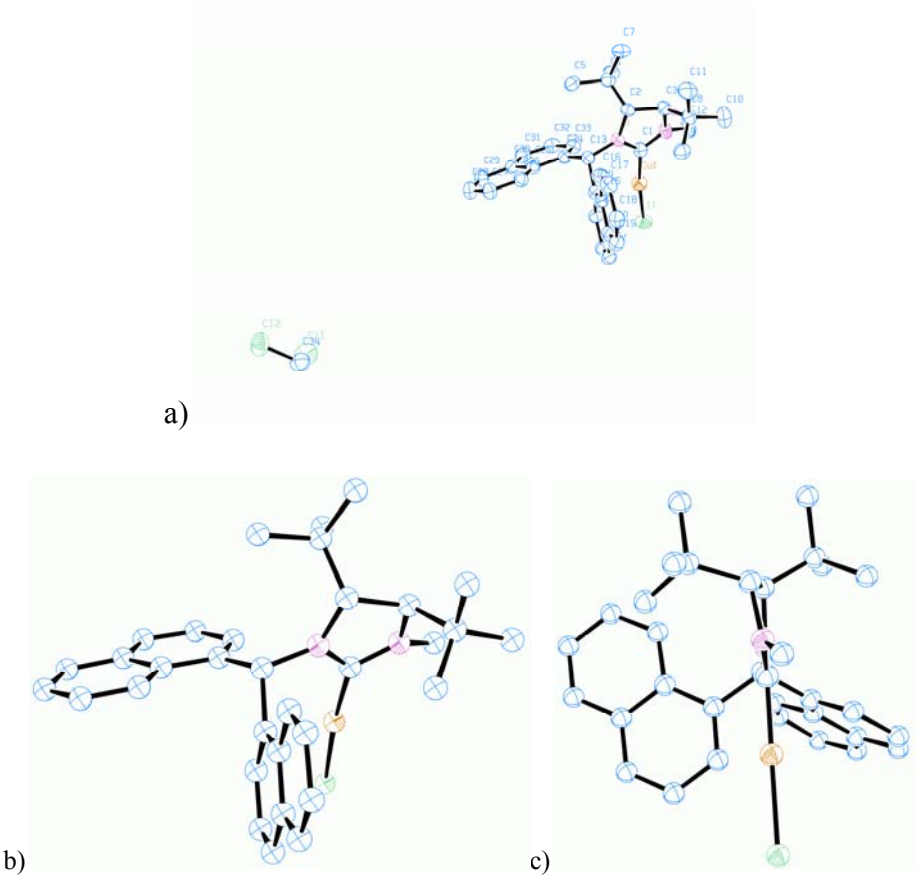


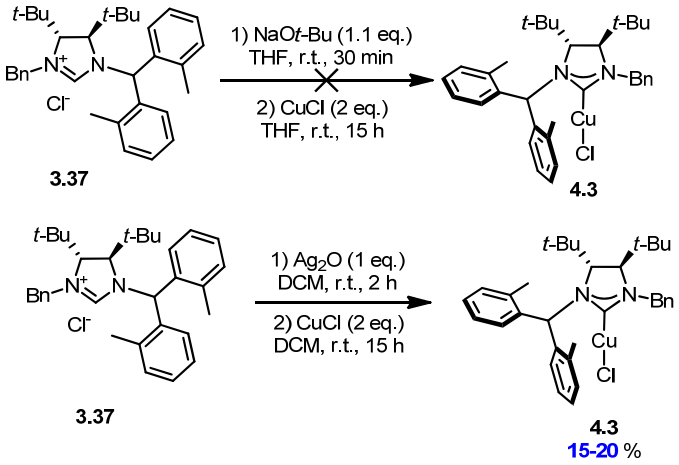

**Figure 4-2: Crystal Structure of Complex 4.2b**

**Table 4-3: Selected Structural Parameters of Complex 4.2b**

| Entry | Parameter | Value |
|---|---|---|
| 1 | Cu-C | 1.894(3) Å |
| 2 | Cu-I | 2.3967(3) Å |
| 3 | C-Cu-I | 173.22(9)° |
| 4 | Vbur | 43.9 % |

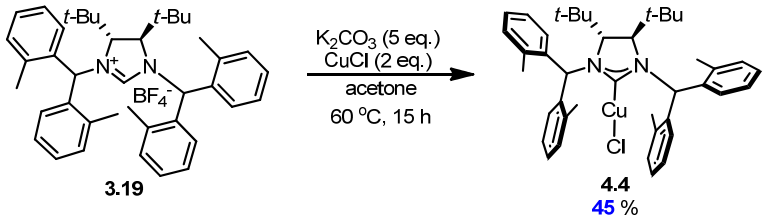
Benzyl substituted ligand **3.37** decomposes in the presence of strong bases, likely due to competitive reactions such as deprotonation at the benzylic position. Exposure of imidazolium

**3.37** to either KHMDS or sodium *t*-butoxide at room temperature results in complete decomposition of the ligand. Generation of a silver complex *in-situ* with silver(I) oxide followed by transmetallation with an excess of copper(I) chloride affords chiral copper complex **4.3** in 20 % yield.




**Scheme 4-3: Synthesis of Benzyl Complex 4.3**

The *t*-butyl substituted analog of ligand **2.8**, imidazolium **3.19** did not generate mono NHC copper complexes when treated with KHMDS, sodium t-butoxide, or silver oxide. Heating with potassium carbonate as in the recently reported procedure,[20] afforded $C_2$-symmetric complex **4.4** in 45 % yield. It should be noted that the reaction must be performed in degassed acetone otherwise only trace quantities of complex **4.4** are obtained.




**Scheme 4-4: Synthesis of $C_2$-Symmetric Copper Complex 4.4**

Imidazolinium salts **3.35** and **3.36** bearing 2-naphthyl and 1-pyrenyl groups respectively could not be installed successfully onto copper(I) (Figure 4-3). Use of strong bases such as KHMDS or sodium *t*-butoxide resulted in decomposition of the ligand, while use of milder reagents such as silver(I) oxide failed to convert the starting material to the desired products.

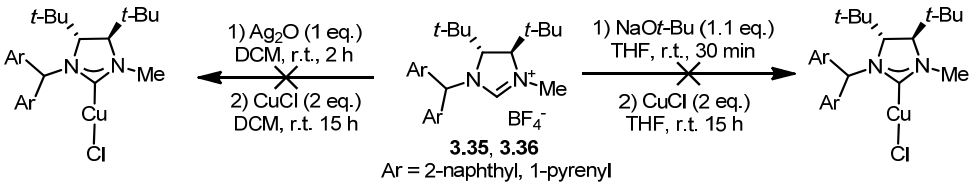



**Figure 4-3: Ligands that Could not be Installed onto a Transition Metal**

Bidentate picolyl substituted imidazolinium salt **3.38** could not be installed onto copper by any means. All efforts to install the ligand onto copper met with failure, generally with decomposition of the ligand into unidentifiable products. It should be noted that the starting material was never recovered.

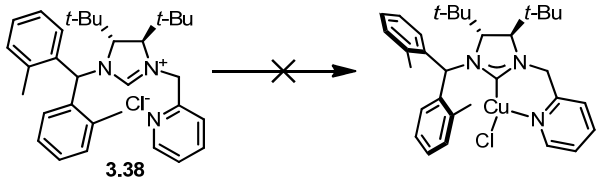
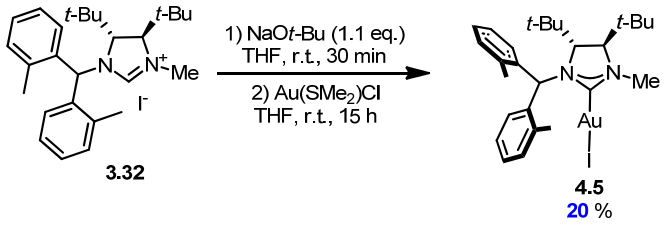



**Figure 4-4: Failure to Install Picolyl Ligand 3.38 onto Copper**

## 4.2 – Synthesis of a Chiral Gold NHC Complex

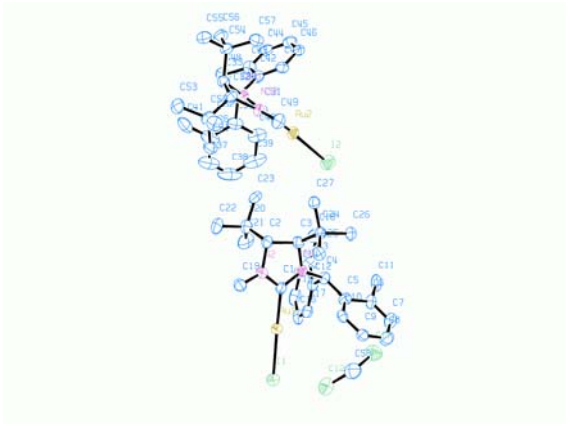
Due to the prevalence of gold NHC complexes in catalysis,[40a,b] the gold NHC complexes of the new ligands were targeted for synthesis. Imidazolinium salt **3.32** generates free carbene in the presence of sodium *t*-butoxide; addition of (dimethylsulfide)gold(I) chloride forms the corresponding gold NHC complex, which undergoes counterion exchange with iodide affording complex **4.5** in 20 % yield.



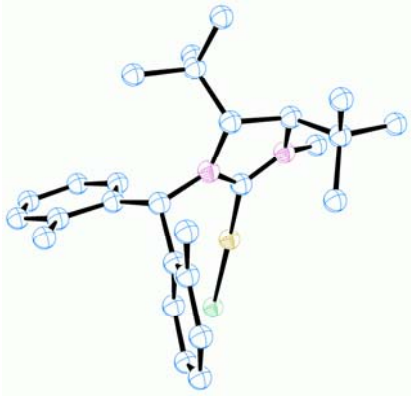

**Scheme 4-5: Synthesis of Chiral $C_1$-Symmetric Gold Complex 4.5**

Diffraction quality crystals of complex **4.5** were obtained by slow diffusion of diethyl ether into a saturated solution of complex **4.5** in dichloromethane. The X-ray structure of complex **4.5** is shown in Figure 4-5 and selected structural parameters are shown in Table 4-4.

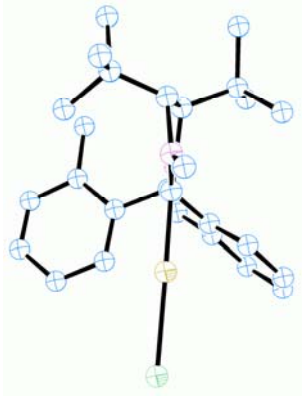
Figure 4-5b shows the staggered view of the complex, the area adjacent to the *N*-methyl group is sterically accessible. Figure 4-5b shows the complex from the angle of the *N*-methyl bond, two different steric environments are visible due to the aryl groups in the background. The gold-carbon bond of complex **4.5** is 2.00(1) Å long and the gold-iodine bond is 2.544(1) Å long. The carbon-gold-iodine angle of complex **4.5** is closer to linearity than the other examples, being 177.4(3)°. The buried volume of complex **4.5** is 42.3 %, slightly smaller than the corresponding copper complex **4.1**, likely due to increased steric repulsion between the chiral relay and the larger metal centre.



a)



b)



c)

**Figure 4-5: Crystal Structure of Complex 4.5**

**Table 4-4: Selected Structural Parameters of Complex 4-5**

| Entry | Parameter | Value |
|---|---|---|
| 1 | Au-C | 2.00(1) Å |
| 2 | Au-I | 2.544(1) Å |
| 3 | C-Au-I | 177.4(3)° |
| 4 | Vbur | 42.3 % |

Attempting to form a chiral $C_2$-symmetric gold(I) complex from imidazolium salt **3.19** in a method analogous to the formation of copper complex **4.4**, by heating imidazolium salt **3.19** with potassium carbonate in the presence of (dimethylsulfide)gold(I) chloride, resulted in failure. No new gold-containing products were formed in the reaction conditions and the majority of the imidazolium salt starting material was recovered.

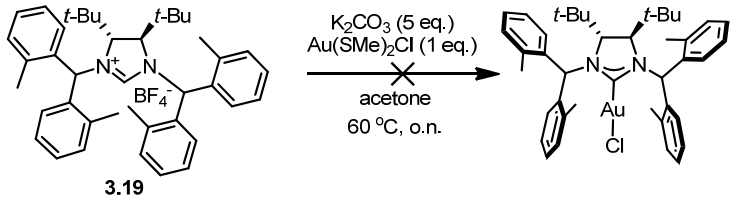
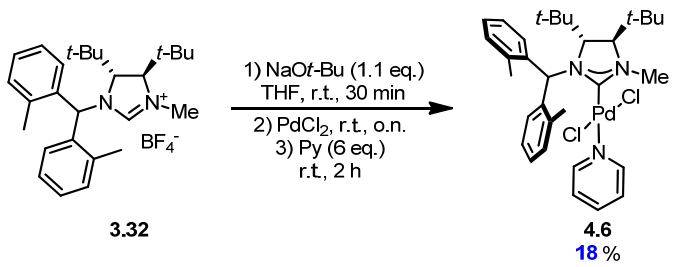



**Figure 4-6: Attempted Synthesis of a Chiral $C_2$-Symmetric Gold Complex**

## 4.3 – Towards the Synthesis of a Chiral Palladium NHC Complex

Due to the increased usage of NHC ligands in palladium catalyzed transformations,[40a] attempts were made to install ligand **3.32** onto palladium. Reactions, with any base, that did not include an additional L ligand for palladium did not result in the formation of isolable palladium NHC products. Neither acetonitrile nor triphenylphosphine formed stable and isolable heteroleptic mono NHC palladium complexes with ligand **3.32**. The method for generating palladium PEPPSI complexes[18] with potassium carbonate did not generate palladium complex **4.6**. Only *in-situ* carbene generation with sodium *t*-butoxide followed by complexation to palladium(II) chloride and addition of pyridine afforded what appears to be chiral palladium complex **4.6** in 18 % yield (Scheme 4-6). The results are highly preliminary as full characterization of the complex is not yet complete. Efforts are underway to obtain diffraction quality crystals of the complex. The pyridine and the NHC ligand are visible in a 1:1 ratio by $^1$H NMR spectroscopy. Mass spectrometric analysis of the crude product reveals a product containing one chlorine atom and one palladium atom, and a mass value high enough to imply the presence of the NHC ligand.




**Scheme 4-6: Synthesis of Chiral $C_1$-Symmetric Palladium NHC Complex 4.6**

## 4.4 – Towards the Synthesis of New Chiral Ruthenium Catalysts

Due to recent successes in asymmetric olefin metathesis reactions with ruthenium catalysts bearing chiral NHC ligands,[81] imidazolinium salt **3.32** was subjected to the standard conditions for the synthesis of ruthenium NHC complexes. Heating imidazolinium salt **3.32** with potassium hexafluoro-*t*-butoxide in the presence of Grubbs I (**1.23**) did not result in the formation of a new ruthenium catalyst. The bulky tricyclohexylphosphine likely did not leave sufficient space for the NHC to approach the ruthenium centre.

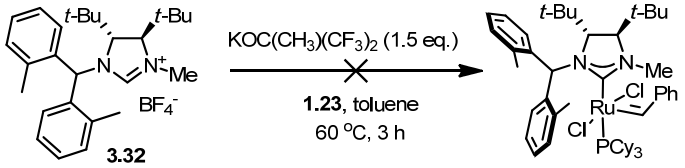



**Figure 4-7: Failed Installation of Ligand 3.32 onto Ruthenium Complex 1.23**

Attempts to install a chiral $C_1$-symmetric dialkyl NHC onto ruthenium(II)(*para*-cymene) dimer were also unsuccessful. When the free carbene was generated followed by addition of ruthenium and pyridine as a ligand, no ruthenium NHC products were observed.

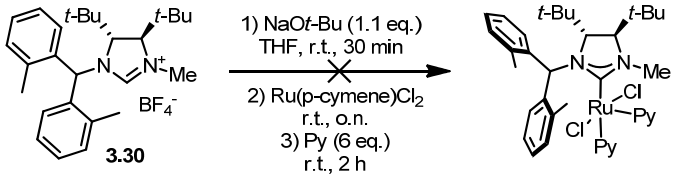



**Figure 4-8: Attempted Synthesis of a Chiral Ruthenium Complex**

## 4.5 – Towards the Synthesis of a New Chiral Iridium Complex

Iridium NHC complexes have shown their utility in catalytic transformations.[40a] Attempts to install a chiral NHC onto iridium were not successful (Figure 4-9). All attempts to form carbene complexes using methoxy iridium species met with failure. While using silver oxide as a carbene generating reagent did generate interesting new products, they were not found to correspond to an iridium NHC complex.

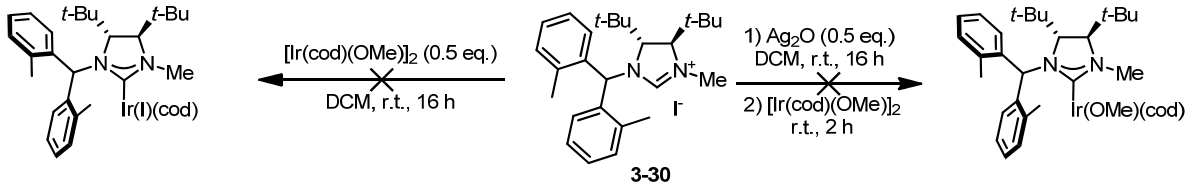



**Figure 4-9: Failed Synthesis of a Chiral Iridium Complex**

# Chapter 5 - Oxidative Coupling of 2-Naphthols

## 5.1 – Introduction to BINOLs

Biaryl compounds such as 1,1'-binaphthyl-2,2'-diol (BINOL) **5.1** represent a privileged ligand scaffold in organic chemistry. While all of the carbon atoms in the biaryl are $sp^2$, there is restricted rotation about the bond between the two aryl groups leading to two atropisomers. Figure 5-1 shows the atropisomers of BINOL **5.1** as well as their structures in the solid state.[101] The atropisomers are configurationally stable at room temperature; the temperature at which BINOL **5.1** racemizes varies from solvent to solvent but averages ~200 $^oC$.[102]

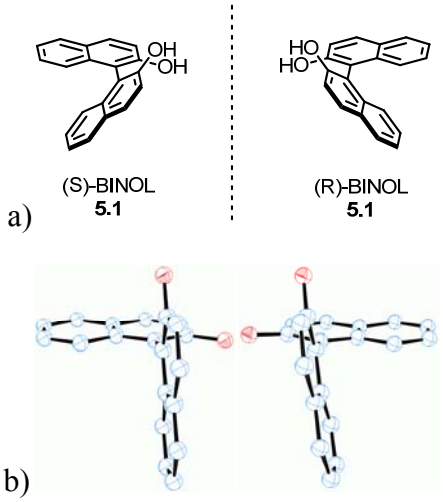



**Figure 5-1: The Atropisomers of BINOL 5.1**

Due to the axial chirality of the binaphthyl scaffold, BINOL **5.1** and BINOL derivatives have seen widespread use for asymmetric induction in chiral transformations.[103] BINOL **5.1** as well as 3 common derivatives are shown in Figure 5-2. In order to diversify the reactivity and steric environment of binaphthyls, BINOLs such as **5.2** bearing substituents at the 3 position of the naphthyl ring-system have been developed.[104] Functional groups can be chosen for steric bulk or to modify the electronic character of the aromatic system. Chiral phosphoric acid **5.3**

[101] Lee, T.; Peng, J. F. *Crystal Growth and Design* **2010**, *10*, 3547.
[102] Meca, L.; Reha, D.; Havlas, Z. *J. Org. Chem.* **2003**, *68*, 5677.
[103] a) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155. b) Brunel, J. M. *Chem. Rev.* **2007**, *107*, PR1.
[104] a) Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L. H.; Moreau, P.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 1930 b) Liu, G.-H.; Xue, Y.-N.; Yao, M.; Fang, H.-B.; Yu, H.; Yang, S.-P. *J. Mol. Struct.* **2008**, *875*, 50.

was developed as a chiral Brønsted acid for use in acid-catalyzed transformations.[105] More recently, phosphoramidite ligands such as phosphoramidite **5.4** based on BINOL have become popular for use in asymmetric transition metal catalysis.[106]

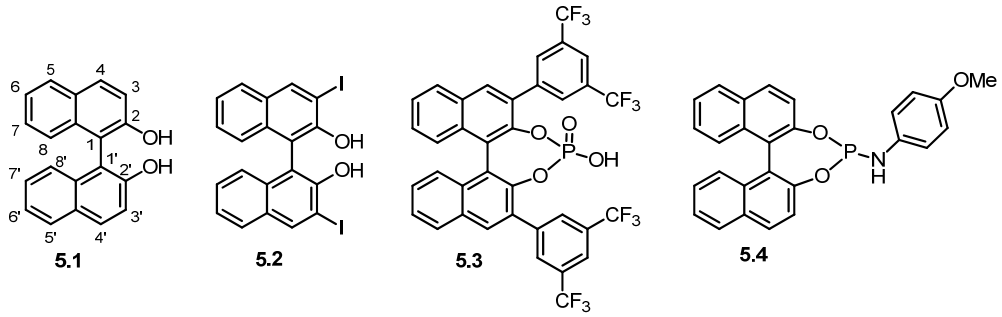



**Figure 5-2: BINOL Containing Structures Employed in Asymmetric Synthesis**

In addition to being an important structure for enantioinduction in organic chemistry, the axially chiral binaphthyl structure is found in many natural products. Three biologically relevant natural products containing an axially chiral BINOL skeleton are shown in Figure 5-3. Nigerone **5.5**, which can be synthesized via oxidative biaryl coupling,[107] displays both antibacterial[108] and antitumor[109] activity. Hypocrellin **5.6** has been shown to be a potent antifungal,[110] as well as displaying antitumor activity.[111] Cercosporin **5.7**, in which the BINOL hydroxyl groups are tethered, displays antiviral activity.[112]

[105] Koy, C.; Michalik, M.; Oehme, G.; Tillack, A.; Baudisch, H.; Kempe, R. *Phosporous, Sulfur and Silicon and the Related Elements* **1999**, *152*, 203.
[106] Teichert, J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486.
[107] DiVirgilio, E. S.; Dugan, E. C.; Mulrooney, C. A.; Kozlowski, M. K. *Org. Lett.* **2007**, *9*, 385.
[108] Boutibonnes, P.; Malherbe, C.; Kogbo, W.; Marais, C. *Microbiol., Aliments, Nutr.* **1983**, *1*, 259.
[109] Koyama, K.; Ominato, K.; Natori, S.; Tashiro, T.; Tsuruo, T. *J. Pharmacobio. Dynamics* **1988**, *11*, 630.
[110] Xing, M.-Z.; Zhang, X.-Z.; Sun, Z.-L.; Zhang, H.-Y. *J. Agric. Food. Chem.* **2003**, *51*, 7722.
[111] Morgan, B. J.; Dey, S.; Johnson, S. W.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 9413.
[112] Hudson, J. B.; Imperial, V.; Haughland, R. P.; Diwu, Z. *Photochem. Photobiol.* **1997**, *65*, 352.

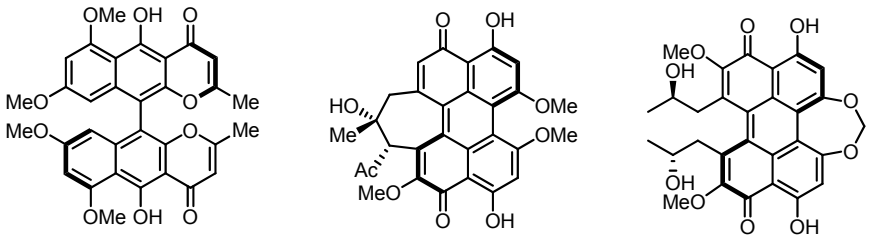


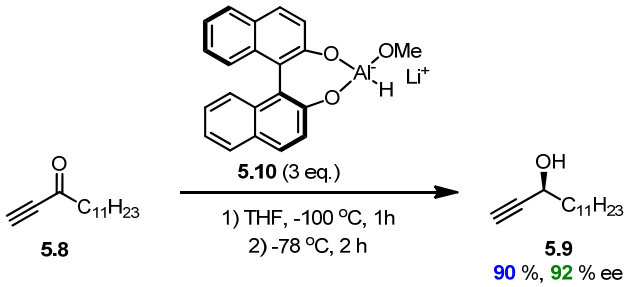

**Figure 5-3: Biologically Active Natural Products Containing the BINOL Scaffold**

## 5.2 – BINOLs in Enantioselective Transformations

BINOL and its derivatives have been employed in many asymmetric transformations.[103] BINOL containing compounds have been employed both as catalysts and as stoichiometric chiral reagents. Several examples that demonstrate good enantioselectivity follow.

### 5.2.1 – BINAL-H

Aluminum hydride **5.10**, commonly referred to as BINAL-H, is a stoichiometric chiral reducing agent that is synthesized from BINOL and lithium aluminum hydride.[113] The third alkoxy substituent on aluminum was found to be necessary to promote asymmetry in the reduction process, as having two hydrides bound to aluminum led to poor enantioselectivity. BINAL-H **5.10** reduces propargylic ketone **5.8**, at low temperature, affording propargylic alcohol **5.9** in 90 % yield and 92 % ee (Scheme 5-1). [114]

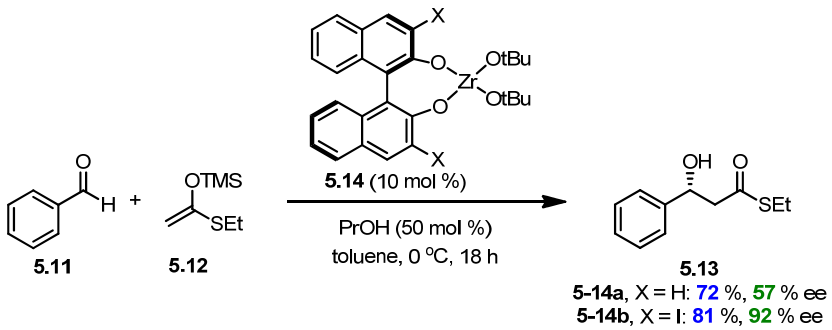



**Scheme 5-1: Asymmetric Reduction of a Propargylic Ketone with BINAL-H**

[113] Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.
[114] Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.

## 5.2.2 – Asymmetric Aldol Reaction

Chiral zirconium complexes **5.14** catalyze the aldol addition of silyl enol ether **5.12** to benzaldehyde **5.11** (Scheme 5-2).[115] The zirconium centre acts as a Lewis acid for the aldehyde oxygen atom. The unsubstituted versus 3,3'-disubstituted BINOL variants of the catalyst show large changes in selectivity. The unfunctionalized catalyst **5.14a** affords alcohol **5.13** in 72 % yield and 57 % ee. The iodo substituted catalyst **5.14b** affords only a slight increase in terms of yield, affording alcohol **5.13** in 81 % yield. However, the selectivity is greatly improved, affording alcohol **5.13** in 92 % ee.

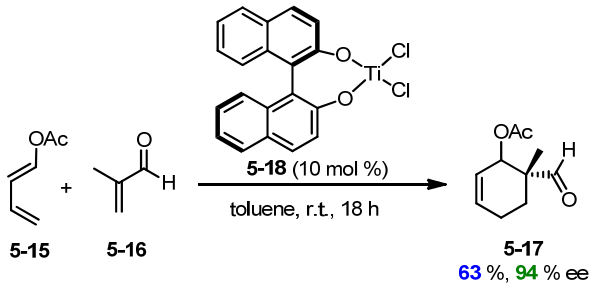



**Scheme 5-2: Asymmetric Aldol Reaction Catalyzed by a Zirconium-BINOL Complex**

## 5.2.3 – Asymmetric Diels-Alder Cycloaddition

The Diels-Alder cycloaddition is one of the most popular tools for the construction of 6-membered rings, and has found widespread application in total synthesis.[116] Chiral titanium-BINOL complex **5.18**, catalyzes the asymmetric cycloaddition of diene **5.15** and acrylaldehyde **5.16** (Scheme 5-3).[117] Titanium catalyst **5.18** is generated *in-situ* from BINOL **5.1** and $Ti(OiPr)_2Cl_2$. When diene **5.15** and aldehyde **5.16** are exposed to a catalytic amount of *in-situ* generated titanium catalyst **5.18**, cyclohexenol **5.17** is afforded in 63 % yield and 94 % ee.

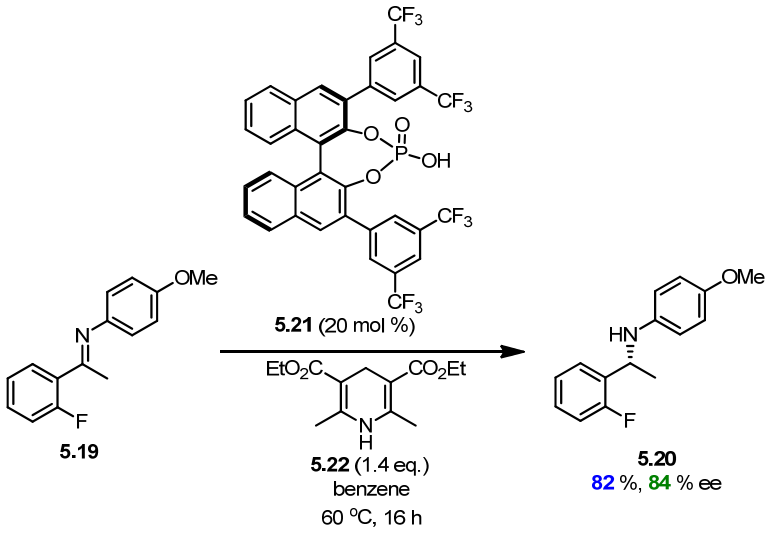
[115] Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 5403.
[116] Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668.
[117] Mikami, K.; Motoyama, Y.; Tereda, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812.




**Scheme 5-3: Asymmetric Diels-Alder Reaction Catalyzed by an *in-situ* Generated Titanium-BINOL Complex**

## 5.2.4 – Asymmetric Transfer Hydrogenation

BINOL derived chiral phosphoric acid **5.21** catalyzes the asymmetric transfer hydrogenation of imine **5.19** with the Hantzsch ester **5.22** (Scheme 5-4).[118] Chiral Brønsted acids induce chirality by forming a tight ion pair with the protonated intermediate. Imine **5.19** is reduced by the Hantzsch ester **5.22** in the presence of 20 mol % of phosphoric acid **5.21**, affording chiral amine **5.20** in 82 % yield and 84 % ee.



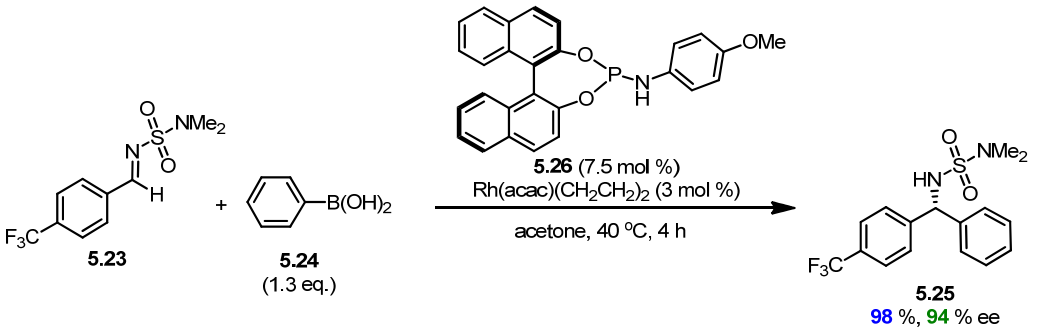

**Scheme 5-4: Asymmetric Transfer Hydrogenation of an Imine Catalyzed by a Chiral Brønsted Acid**

## 5.2.5 – Asymmetric Arylation of Imines

BINOL containing phosphoramidite ligands have become increasingly popular in asymmetric transition metal catalysis.[106] Phosphoramidite **5.26** acts as a ligand for the rhodium-

[118] Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781.

catalyzed arylation of imine **5.23** with phenylboronic acid **5.24** (Scheme 5-5).[119] Imine **5.23** reacts with a slight excess of phenylboronic acid **5.24** in the presence of an *in-situ* generated rhodium phosphoramidite catalyst, affording chiral amine **5.25** in 98 % yield and 94 % ee.

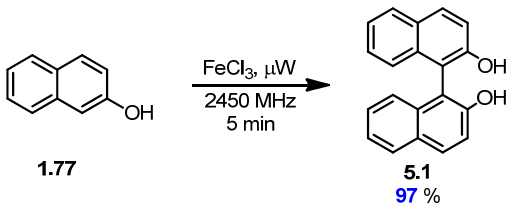



**Scheme 5-5: Asymmetric Arylation of an Imine with a Chiral Phosphoramidite Ligand**

## 5.3 – Synthesis of BINOLS Employing Stoichiometric Amounts of Transition Metal

### 5.3.1 – Homocoupling of 2-Naphthols

First reported in 1926, the synthesis of BINOL **5.1** is achieved via oxidative coupling of 2-naphthol with iron(III) chloride.[120] While the original BINOL synthesis was aqueous, the coupling reaction can also be performed in the solid state (Scheme 5-6).[121] The coupling reaction is anaerobic, the iron(III) acts as the oxidant. When a finely ground mixture of 2-naphthol **1.77** and iron(III) chloride is irradiated in the microwave for 5 min, BINOL **5.1** is afforded in 97 % yield.

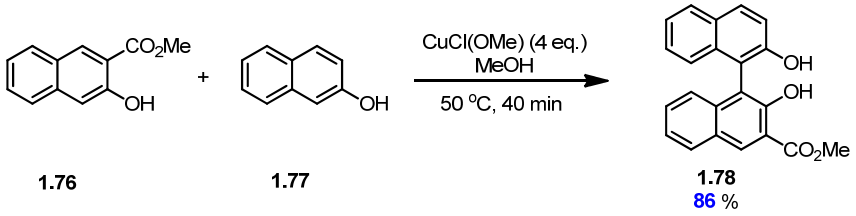



**Scheme 5-6: Microwave Assisted, Iron Mediated BINOL Synthesis**

[119] Jagt, R. B.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2789.
[120] Pummerer, R.; Prell, E.; Rieche, A. *Chem. Ber.* **1926**, *59*, 2159.
[121] Li, S.-J.; Lu, J.; Zhhu, X.; Yang, J.; Lang, J.-P.; Wu, L. *Synth. Commun.* **2002**, *32*, 3069.

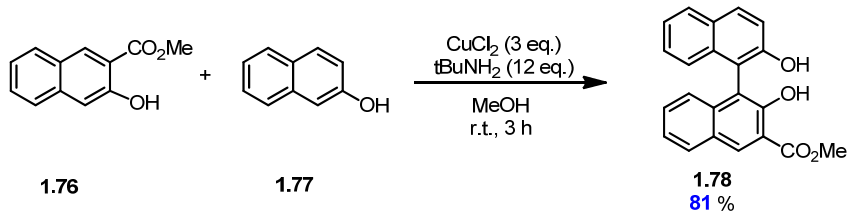
## 5.3.2 – Heterocoupling of Electronically Dissimilar 2-Naphthols

Stoichiometric amounts of copper(II) salts mediate the oxidative coupling of electronically dissimilar 2-naphthols.[122] As in the homocoupling of 2-naphthols, the transition metal is the oxidant, and the reaction is carried out under anaerobic conditions. Ester **1.76** and naphthol **1.77** undergo heterocoupling in the presence of a large excess of a copper(II) salt, affording binaphthyl **1.78** in 86 % yield (Scheme 5-7).[122a]




**Scheme 5-7: Copper(II) Mediated Oxidative Heterocoupling of Electronically Dissimilar 2-Naphthols**

Amines have been found to help tune the reactivity of the copper reagent.[122b] When t-butylamine is employed as a ligand, the reaction requires a smaller excess of the copper(II) oxidant. The coupling of ester **1.76** and naphthol **1.77** is mediated by an excess of copper(II) chloride and t-butylamine, affording binaphthyl **1.78** in 81 % yield (Scheme 5-8).



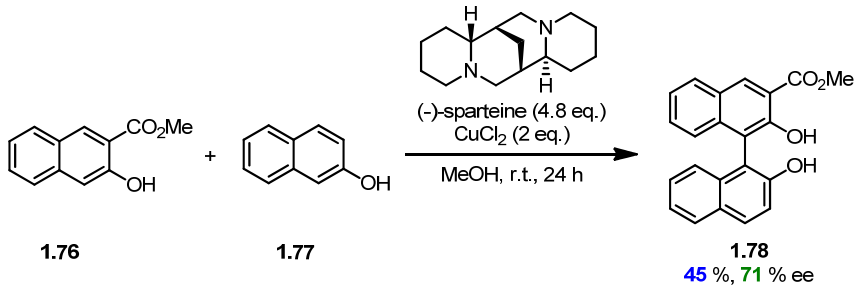

**Scheme 5-8: Amine Assisted Oxidative Heterocoupling of Electronically Dissimilar 2-Naphthols**

## 5.3.3 – Asymmetric Induction

The copper mediated oxidative coupling of 2-naphthols can be performed asymmetrically with the right choice of ligand.[123] Moderate to high selectivity can be achieved for both homocoupling and heterocoupling reactions, a representative example of the latter is shown in Scheme 5-9. Ester **1.76** and naphthol **1.77** undergo cross-coupling in the presence of 2

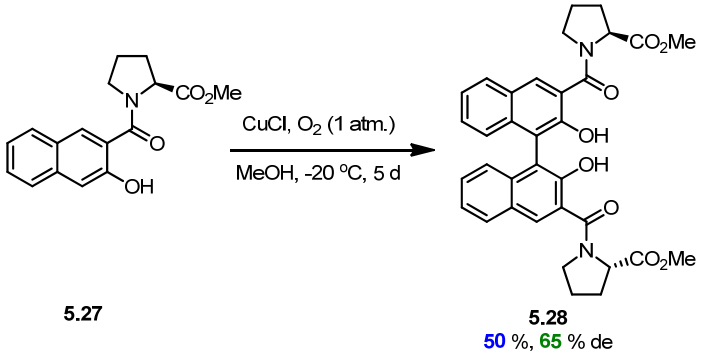
[122] a) Hovorka, M.; Scigel, R.; Gunterova, J.; Tichy, M.; Zavada, J. *Tetrahedron*, **1992**, *48*, 9503. b) Smrcina, M.; Vyskocil, S.; Maca, B.; Polakova, J.; Claxton, T. A.; Abbot, A. P.; Kocovsky, P. *J. Org. Chem.* **1994**, *59,* 2156.
[123] Smrcina, M.; Polakova, J.; Vyskocil, S.; Kocovsky, P. *J. Org. Chem.*, **1993**, *58*, 4534.

equivalents of a bis(sparteine)copper(II) complex, affording binaphthyl **1.78** in 45 % yield and 71 % ee.




**Scheme 5-9: Asymmetric Heterocoupling of 2-naphthols with a Cu(II)-(-)-Sparteine Complex**

Proline substituted naphthyl amide **5.27** undergoes oxidative coupling diastereoselectively (Scheme 5-10).[124] Amide **5.27** undergoes homocoupling in the presence of a stoichiometric amount of copper(I) chloride under an oxygen atmosphere, affording binaphthyl **5.28** in 50 % yield and 65 % de. The diastereomers are separable on silica gel, allowing for facile resolution of the two enantiomers of BINOL. The proline groups can then be cleaved with aqueous hydrochloric acid.



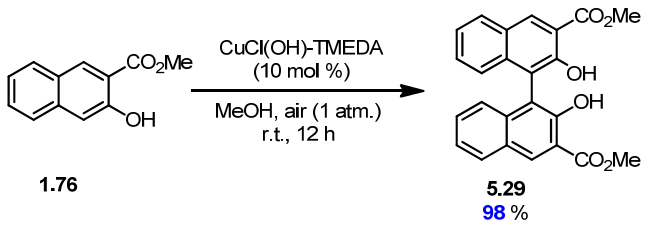

**Scheme 5-10: Diastereoselective Oxidative Coupling of Proline Amide 5-27**

[124] Xin, Z.-Q.; Da, C.-S.; Dong, S.-L.; Liu, D.-X.; Wei, J.; Wang, R. *Tetrahedron: Asymmetry* **2002**, *13*, 1937.

## 5.4 – Mechanism of the Catalytic Oxidative Coupling of 2-Naphthols

### 5.4.1 – Catalytic Oxidative Coupling of 2-Naphthols

The amine assisted oxidative coupling of 2-naphthols can be made catalytic in copper.[125] Ester **1.76** undergoes homocoupling in the presence of a catalytic amount of CuCl(OH)-TMEDA under aerobic conditions, affording binaphthyl **5.29** in 98 % yield (Scheme 5-11).




**Scheme 5-11: Copper Catalyzed Aerobic Oxidative Coupling of Ester 1-76**

### 5.4.2 – Catalytic Cycle

The mechanism of the oxidative coupling of 2-naphthols is proposed to proceed via a single electron transfer.[126] The reaction pathway has been explored both computationally and experimentally with both infrared spectroscopy and mass spectrometry. A representative example for the heterocoupling of electronically dissimilar 2-naphthols is shown in Figure 5-4. First the copper(I) precatalyst must be oxidized to copper(II). The copper(II) intermediate represents the catalyst resting state. Each substrate is then bound by one equivalent of copper(II). The homocoupling of ester **1.76** with copper-TMEDA has been shown to pass through a bridged bimetallic intermediate.[127] While the reaction is proposed to proceed via single electron transfer, the copper(II)-naphthol complex does not behave as a discrete radical.[126] Each copper atom transfers an electron to the naphthol to which it is bound during the bond forming event. The resulting species is a copper(I) bound ketone tautomer of the binaphthyl coupling product. Tautomerization in solution leads to the coupling product, while reoxidation of the catalyst restarts the catalytic cycle. The catalytic and stoichiometric versions of the oxidative coupling mechanism vary only in that the catalytic variant has the additional step of re-oxidation of the catalyst.

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[125] Nakajime, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.-I. *J. Org. Chem.* **1999**, *64*, 2264.
[126] Roithova, J.; Milko, P. *J. Am. Chem. Soc.* **2010**, *132*, 281.
[127] Roithova, J.; Schroder, D. *Chem.-Eur. J.* **2008**, *14*, 2180.

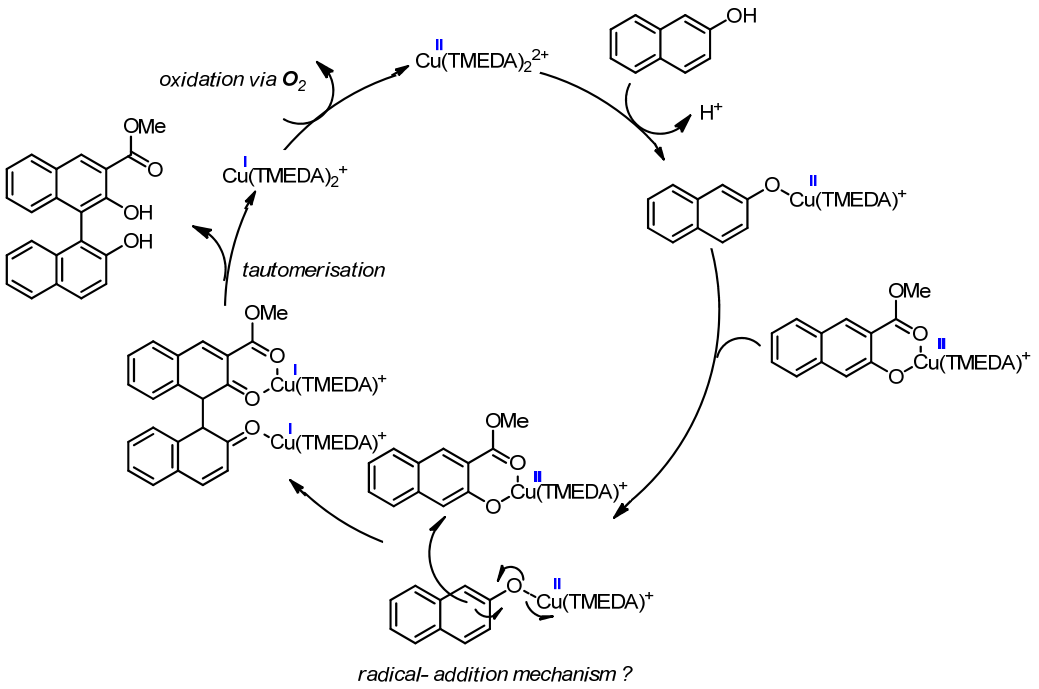
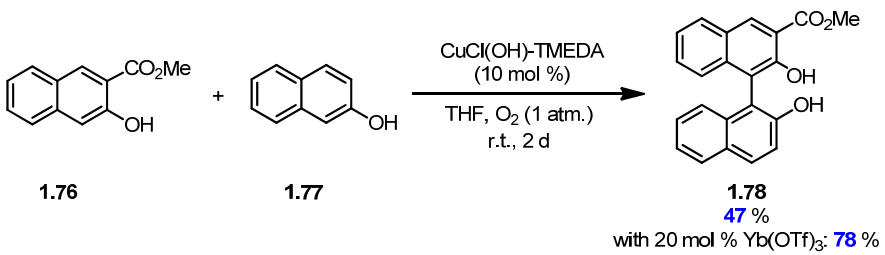



**Figure 5-4: Mechanism of the Oxidative Coupling of 2-Naphthols**

In the case of homocoupling reactions of 2-naphthols, the electron transfer is considered to be simultaneous between the two coupling partners.[127] For the heterocoupling of electronically dissimilar 2-naphthols, the employment of a Lewis acid has been found to be beneficial (Scheme 5-12).[128] The benefit of the Lewis acid additive suggests an added subtlety to the heterocoupling mechanism. The electron rich coupling partner donates its electron to the bond forming event before the electron poor coupling partner in a radical addition mechanism. The aerobic oxidative coupling of ester **1.76** and naphthol **1.77** is catalyzed by CuCl(OH)-TMEDA, affording binaphthyl **1.78** in 47 % yield. Addition of 20 mol % of ytterbium(III) triflate, affords coupling product **1.78** in 78 % yield.

[128] a) Yan, P.; Sugiyama, Y.; Takahashi, Y.; Kinemuchi, H.; Temma, T.; Habaue, S. *Tetrahedron* **2008**, *64*, 4325. b) Habaue, S.; Temma, T.; Sugiyama, Y.; Yan, P. *Tetrahedron Lett*. **2007**, *48*, 8595. c) Temma, T.; Hatano, B.; Habaue, S. *Tetrahedron* **2006**, *62*, 8559.




**Scheme 5-12: Effect of Ytterbium(III) Triflate on the Oxidative Heterocoupling of 2-Naphthols**

## 5.4.3 – Non-productive Oxidation Products

The major challenge in the catalytic oxidative coupling of 2-naphthols and especially in the heterocoupling of electronically dissimilar 2-naphthols, is the tendency to form new carbon-oxygen as opposed to new carbon-carbon bonds.[129] Figure 5-5 illustrates the two competing mechanisms that the activated naphthol can undergo. Electron rich 2-naphthols have a higher tendency to competitively incorporate oxygen. As such, the electron rich coupling partner is generally employed in large excess when heterocoupling of electronically dissimilar 2-naphthols is conducted.

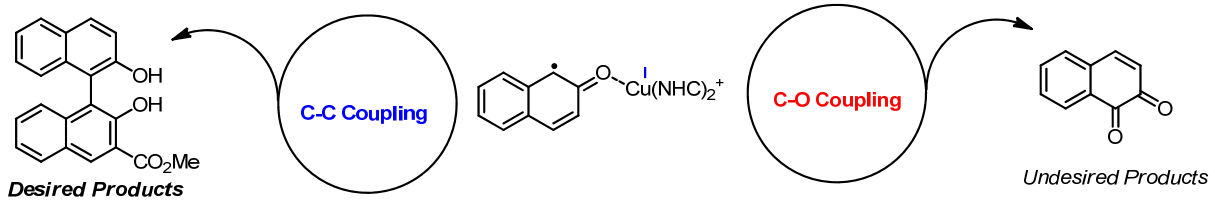



**Figure 5-5: Competing Mechanisms in Aerobic Oxidative Coupling**

From the asymmetric oxidative coupling of naphthol **1.76** catalyzed by a chiral copper diamine complex, Kozlowski and Stahl isolated C-O coupling products (Figure 5-6).[130] The chiral copper complex catalyzes the aerobic oxidative coupling of naphthol **1.76**, affording binaphthyl **5.29** in 85 % yield and 93 % ee. Quinone **5.30** and oxidized coupling product **5.31** were both isolated from the reaction mixture. The reaction kinetics show that that reaction has a short induction period during which there is a burst of non-productive oxidation. A small quantity of quinone **5.30** is generated before any C-C coupling products are formed. The authors suggest that the small quatity of quinone **5.30** that is generated may be acting as a ligand for the

[129] Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1137.
[130] Hewgley, J. B.; Stahl, S. S.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *132,* 12232.

catalyst. Naphthol **1.77** has been found to degrade to similar oxygen conatining products when subjected to conditions for aerobic oxidative coupling.[131]

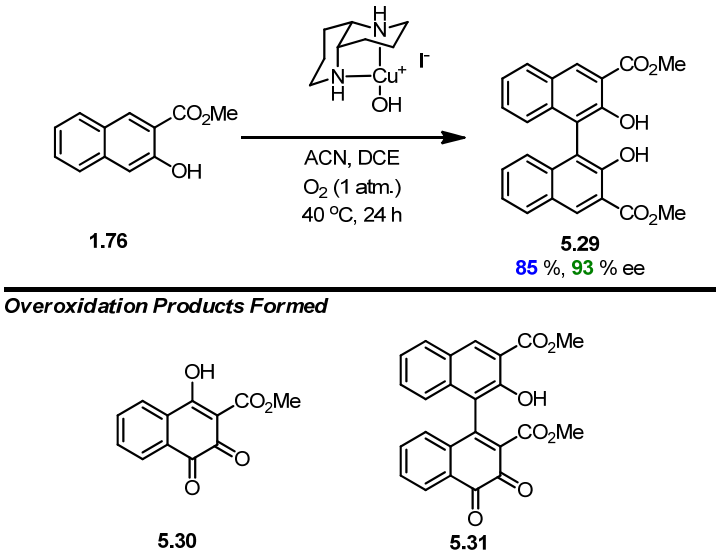


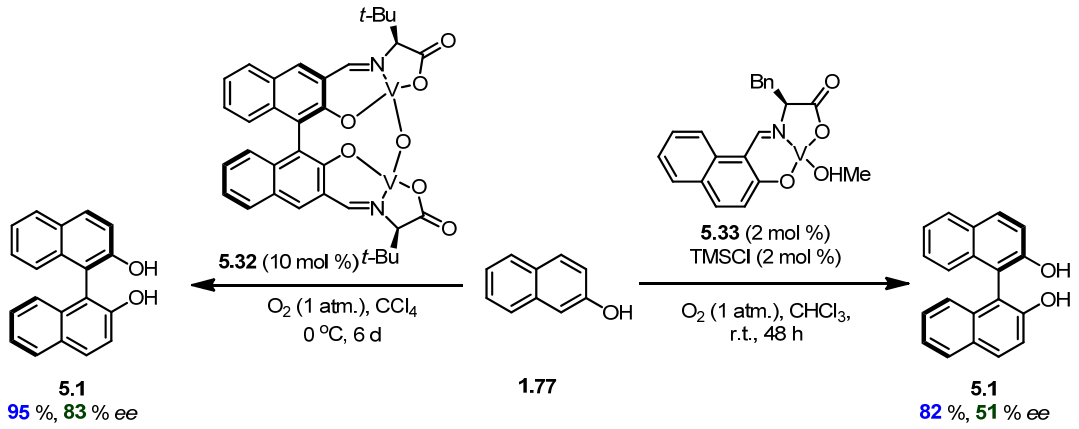

**Figure 5-6: Formation of Undesired C-O Coupling Products**

## 5.5 – Catalytic Asymmetric Oxidative Coupling

### 5.5.1 – Asymmetric Homocoupling of 2-Naphthols

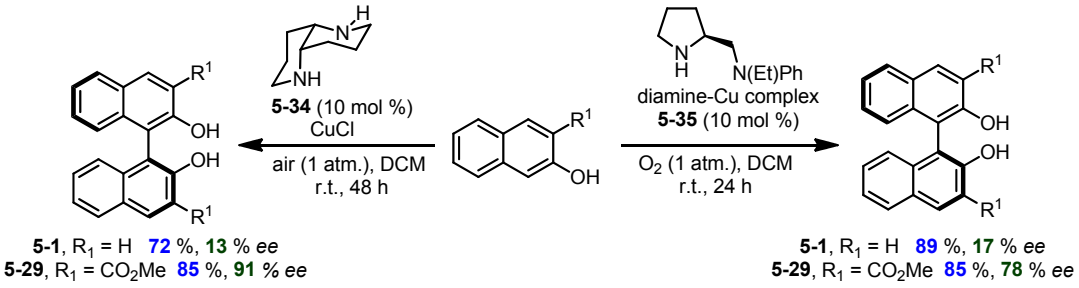
While many methods exist for the catalytic homocoupling of electron rich 2-naphthols, the best asymmetric methods are vanadium catalyzed (Scheme 5-13).[103a] Mono vanadium complex **5.33** catalyzes the homocoupling of 2-naphthol **1.77** under aerobic conditions, affording BINOL **5.1** in 82 % yield and 51 % ee.[132] Bis vanadium complex **5.32** provides much higher enantioselectivity, affording BINOL **5.1** in 95 % yield and 83 % ee. It should be noted that the catalysts are inactive towards 2-naphthols bearing substituents at the 3 position.

[131] Illesinghe, J.; Ebeling, R.; Ferguson, B.; Patel, J.; Campi, E. M.; Jackson, W. R.; Robinson, A. J. *Aust. J. Chem.* **2004**, *57*, 167.
[132] Guo, Q.-X.; Wu, Z.-J.; Luo, Z.-B.; Liu, Q.-Z.; Ye, J.-L.; Luo, S.-W.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 13927.




**Scheme 5-13: Catalytic Asymmetric Oxidative Coupling of Electron Rich 2-Naphthols**

In contrast, the most efficient methods for the asymmetric homocoupling of electron poor 2-naphthols are copper catalyzed (Scheme 5-14).[133] Proline derivative **5.35** affords good yields and enantioselectivity in the asymmetric homocoupling of ester **1.76**.[125] When a complex of proline derivative **5.35** and copper(I) is exposed to a naphthol under aerobic conditions, the results depend on the substitution of the naphthol. Unsubstituted 2-naphthol **1.77** affords BINOL **5.1** in 89 % yield and 17 % ee, while 3-substituted naphthol ester **1.76** affords binaphthyl **5.29** in 85 % yield and 78 % ee. Diazadecalin **5.34** affords even higher selectivity while still requiring the substituent at the 3 position to induce chirality.[134] Naphthol **1.76** affords higher enantioselectivities due to bidentate coordination of the ester in the 3 position, which prevents the substrate from rotating freely when bound to the catalyst.[129] When unsubstituted 2-naphthol **1.77** is exposed to diazadecalin **5.34** and copper(I) chloride under aerobic conditions, BINOL **5.1** is afforded in 72 % yield and 13 % ee. Naphthol ester **1.76** on the other hand, affords binaphthyl **5.29** in 85 % yield and 91 % ee.

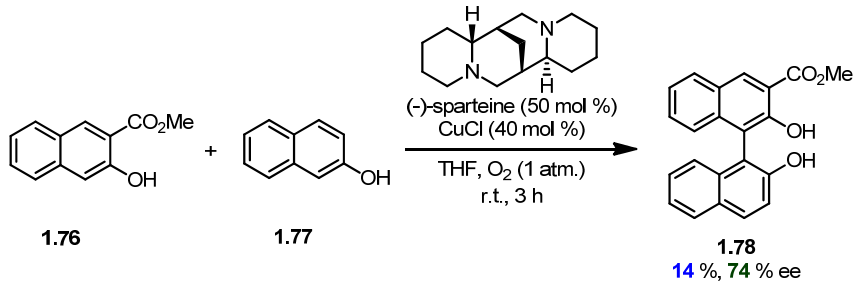



**Scheme 5-14: Catalytic Asymmetric Oxidative Coupling of Electron Poor 2-Naphthols**

[133] Li, X.; Hewgley, J. B.; Mulrooney, C. A.; Yang, J.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 5500.
[134] Mulrooney, C. A.; Li, X.; DiVirgilio, E. S.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2003**, *125*, 6856.

## 5.5.2 – Asymmetric Heterocoupling of Electronically Dissimilar 2-Naphthols

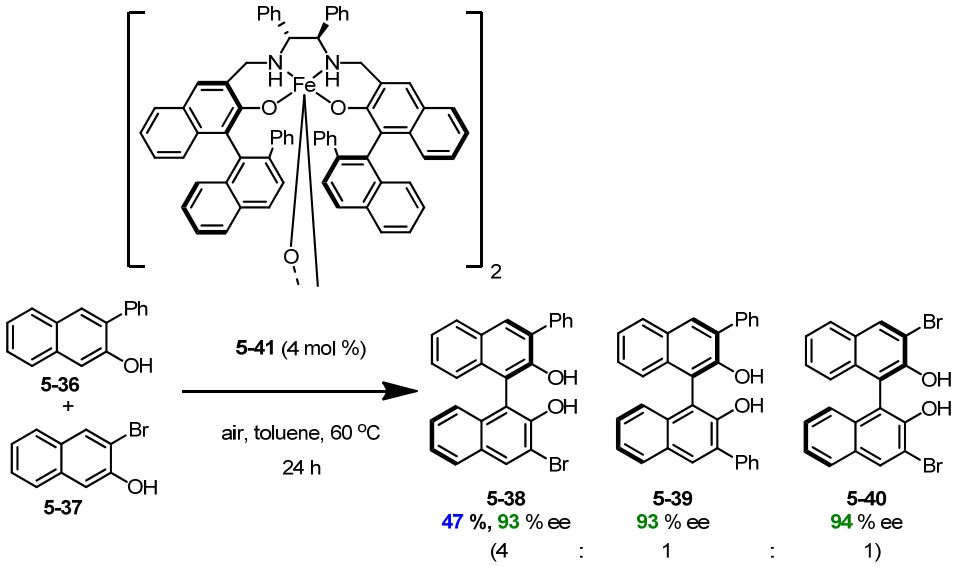
While there exist high-yielding, highly selective methods for the asymmetric homocoupling of 2-naphthols, comparable methods for the asymmetric heterocoupling of electronically dissimilar 2-naphthols are still under development.[103] The asymmetric heterocoupling of electronically dissimilar 2-napthols that is achieved with a stoichiometric amount of copper and sparteine[123] can be adapted for catalytic aerobic conditions (Scheme 5-15).[135] A bidentate copper complex formed *in-situ* from copper(I) chloride and (-)-sparteine catalyzes the oxidative heterocoupling of ester **1.76** and naphthol **1.77**, affording binaphthyl **1.78** in 14 % yield and 74 % ee. It should be noted that the actual amount of binaphthyl **1.78** formed is higher than reported and that the ee has been enhanced via partial crystallization. Other chiral ligands such as bisoxazolines afforded higher yields while affording only poor enantioselectivity.




**Scheme 5-15: Copper Catalyzed Asymmetric Heterocoupling of 2-Naphthols**

[135] Temma, T.; Habaue, S. *Tetrahedron Lett.* **2006**, *46*, 5655.

The iron-catalyzed asymmetric heterocoupling of electronically dissimilar 2-naphthols shown in Scheme 5-16 represents the state of the art in the field. [136] While the ratio of coupling partners **5.36** and **5.37** shown in the example is 1:1, most of the examples require an excess of the electron rich coupling partner due to its tendency to rapidly degrade to undesired oxygen containing products. It should also be noted that the electron rich coupling partner is added slowly via syringe pump in order to slow formation of undesired oxygen containing products. Chiral iron catalyst **5.41** catalyzes the heterocoupling of naphthols **5.36** and **5.37** in moderate yield and excellent enantioselectivity, affording binaphthyl **5.38** in 47 % yield and 93 % ee in a 4:1:1 ratio with the homocoupling products **5.39** and **5.40**.




**Scheme 5-16: Iron Catalyzed Asymmetric Heterocoupling of 2-Naphthols**

[136] Egami, H.; Matsumoto, K.; Oguma, T.; Kunisu, T.; Katsuki, T. *J. Am. Chem. Soc*. **2010**, *132*, 13633.

# Chapter 6 – Towards the Enantioselective Oxidative Coupling of 2-Naphthols

## 6.1 – Preface and Preliminary Experiments

The preceding chapter showed the high yields and enantioselectivities afforded by chiral copper catalysts in the asymmetric homocoupling of electron deficient 2-naphthols. Since copper NHC complexes have been shown to be active catalysts for the oxidative coupling of 2-naphthols,[66] the new chiral $C_1$-symmetric copper NHC complexes synthesized in chapter 4 were tested as catalysts for the asymmetric oxidative homocoupling of electron deficient 2-naphthols. Figure 6-1a shows the interaction between naphthol **1.76** and a copper diazadecalin catalyst proposed by Kozlowski.[129] The coordination geometry of the copper is tetrahedral. While the copper centre is formally copper(II) the intermediate is considered to behave as a radical bound to copper(I). Figure 6-1b shows the potential interaction between chiral copper catalyst **4.1** and naphthol **1.76**, with the methyl group of the *ortho*-tolyl substituent helping to orient the substrate. Since copper NHC catalyzed oxidative coupling of 2-naphthols requires silver nitrate as an additive,[66] the proposed intermediate is cationic. The coordination geometry of the copper atom is tetrahedral with the fourth coordination site being occupied by solvent, although the proximity of the coordination site to the aryl group of the biaryl methyne increases the chances of a 3-coordinate intermediate.

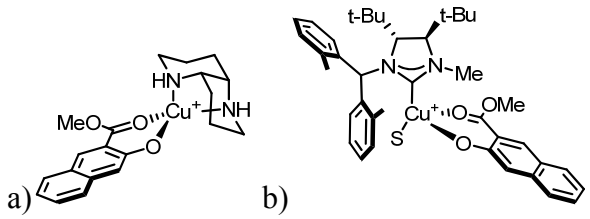
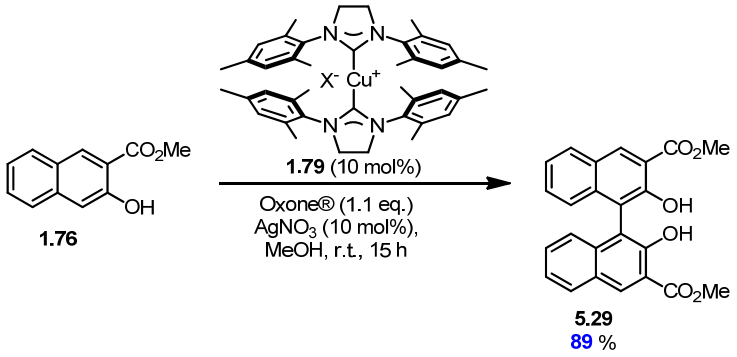


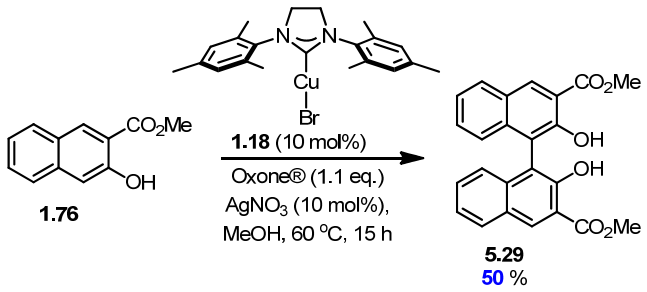

**Figure 6-1: Potential Interaction of Naphthol 1.76 with Copper Catalyst 4.1**

The ill-defined bis NHC copper complex **1.79**, introduced in Scheme 1-20, not only catalyzes the heterocoupling of electronically dissimilar 2-naphthols, but also the homocoupling of electron poor 2-naphthols.[66] When 10 mol % of complex **1.79** is employed to catalyze the homocoupling of naphthol **1.76**, binaphthyl **5.29** is afforded in 89 % yield (Scheme 6-1).




**Scheme 6-1: Homocoupling of Naphthol 1-76 with an Ill-defined Cu(NHC) Catalyst 1.79**

Since catalyst **1.79** is ill-defined and has problematic solubility properties, it was decided to test the reaction with a well-defined and homogenous mono copper NHC complex. To that end, Cu(SIMes)Br (**1.18**) was employed as a catalyst. Catalyst **1.18** was found to be much less reactive than catalyst **1.79** in the oxidative homocoupling of naphthol **1.76**, the reaction required heating, affording binaphthyl **5.29** in 50 % yield (Scheme 6-2).




**Scheme 6-2: Homocoupling of Naphthol 1.76 with a Mono NHC Copper Catalyst**

## 6.2 – Optimization of the Reaction Conditions

For the oxidative coupling of 2-naphthols catalyzed by chiral copper NHC complexes, the enhanced reactivity of methyl substituted $C_1$-symmetric NHCs was of prime interest. As such, several catalysts of varying steric bulk were tested (Figure 6-2). Methyl-substituted catalyst **4.1** is the least sterically demanding of the group. Naphthyl catalyst **4.2b** provides the second least encumbered environment, as it still bears one methyl group. Benzyl-substituted catalyst **4.3** is slightly larger still. Catalysts **3.3** and **4.4** being $C_2$-symmetric are the bulkiest, **4.4** being the most encumbered due to the influence of the bulky t-butyl substituents on the imidazolidinylidene backbone.

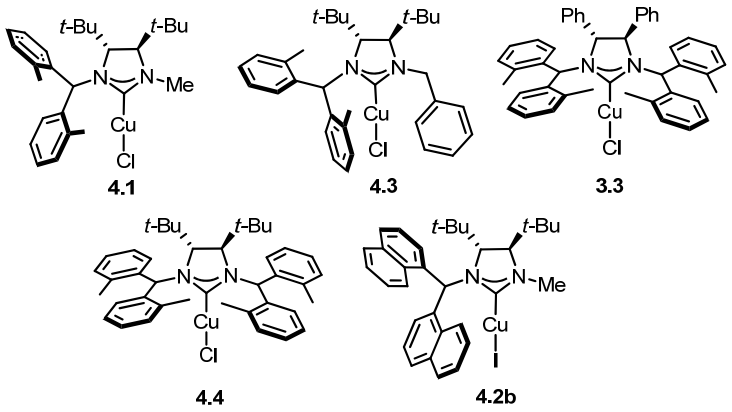
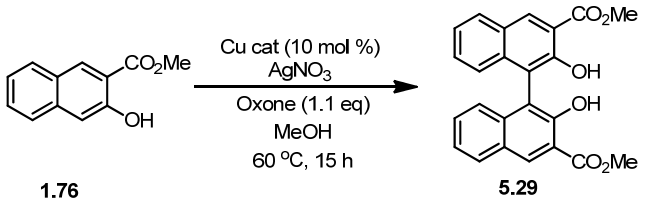



**Figure 6-2: Catalysts Used for Optimization**

The catalysts shown in Figure 6-2 were tested in the oxidative homocoupling of ester **1.76**; the results of the catalyst screen are summarized in Table 6-1. Methyl substituted catalyst **4.1** provided the best yield in the oxidative coupling of naphthol **1.76**, affording binaphthyl **5.29** in 76 % yield, while affording <5 % ee. Benzyl substituted catalyst **4.3** afforded coupling product **5.29** in a significantly lower yield of 22 % with no change in selectivity. $C_2$-symmetric catalyst **3.3** also afforded coupling product **5.29** in 22 % yield without any enantioinduction. Catalyst **4.4**, bearing *t*-butyl groups on the imidazolidinylidene backbone, provided the lowest yield, affording coupling product **5.29** in 14 % yield as a racemic mixture. Methyl substituted catalyst **4.2b**, being bulkier than catalyst **4.1**, afforded slightly lower yield, affording coupling product **5.29** in 31 % yield as a racemic mixture. It should be noted that lowering the reaction temperature did not induce any enantioselectivity in the product. The results show that copper catalysts bearing methyl substituted ligands afford higher yields in the oxidative homocoupling of naphthol **1-76** than catalysts bearing more sterically encumbered ligands.

**Table 6-1: Catalyst Screen**



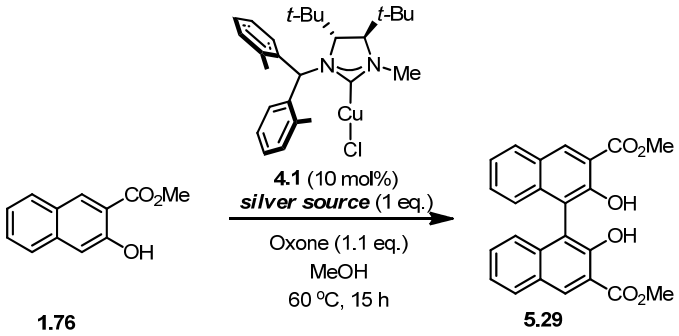

1.76 5.29

| Entry | Catalyst | Yield (%)[a,b] | Entry | Catalyst | Yield (%)[a,b] |
|---|---|---|---|---|---|
| 1 | **4.1** | **76** | 4 | **4.4** | **14**[c] |
| 2 | **4.3** | **22** | 5 | **4.2b** | **31** |
| 3 | **3.3** | **22** | | | |

a) Yields following column chromatography. b) Isolated products were racemic.
c) Reaction was performed in THF.

In order to improve the yield of the oxidative coupling of naphthol **1.76** catalyzed by complex **4.1**, several silver(I) additives were screened (Table 6-2). Silver is necessary for the reaction to proceed, when no silver salt is added to the reaction (entry 1), only trace amounts of coupling product **5.29** are formed. Silver nitrate (entry 2) affords coupling product **5.29** in 76 % yield. Silver chloride (entry 3) affords coupling product **5.29** in 73 % yield. Silver carbonate (entry 4) affords coupling product **5.29** in 64 % yield. Weakly coordinating silver triflate and non-coordinating silver hexafluoroantimonate (entries 5 and 6) surprisingly afford coupling product **5.29** in 13 % and 14 % yield respectively. Silver oxide (entry 7) affords coupling product **5.29** in 52 % yield. It should be noted that all of the coupling products isolated during the silver screen were isolated as racemic mixtures.

**Table 6-2: Optimization of the Silver Source**

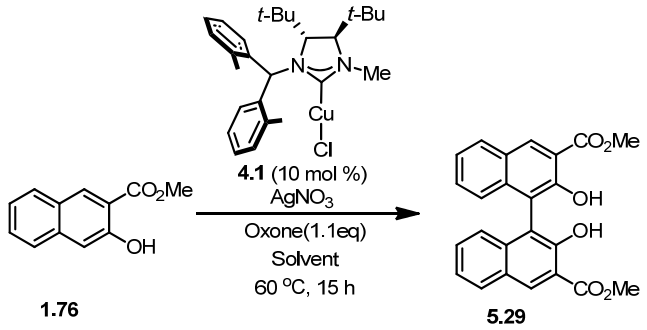



| Entry | Silver Salt | Yield (%)[a,b] | Entry | Silver Salt | Yield (%)[a,b] |
|---|---|---|---|---|---|
| 1 | none | trace | 5 | AgOTf | **13** |
| 2 | $AgNO_3$ | **76** | 6 | $AgSbF_6$ | **14** |
| 3 | AgCl | **73** | 7 | $Ag_2O$ | **52** |
| 4 | $Ag_2CO_3$ | **64** | | | |

a) Yields following column chromatography. b) Isolated products were racemic.

While silver nitrate remained the best silver source, solvent effects were also investigated. Several solvents were chosen, both for polarity and potential π stacking effects. The benchmark for the optimization in methanol affords binaphthyl **5.29** in 76 % yield. Performing the oxidative coupling of naphthol **1.76** in benzene was intended to induce potential π-π interactions. While several of the starting materials including the silver additive and oxone oxidant displayed diminished solubility in benzene, coupling product **5.29** was still isolated in 74 % yield, albeit still as a racemic mixture. Although more polar than benzene, THF afforded binaphthyl **5.29** in 48 % yield. The copper NHC catalyzed oxidative coupling of 2-napthols produces trace amounts of an unidentified yellow side-product. When the oxidative coupling of naphthol **1.76** catalyzed by complex **4.1** is performed in acetone, the only product isolated is an unidentified bright yellow compound.

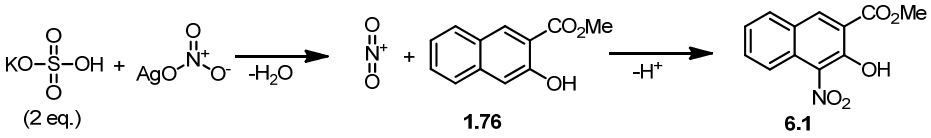
**Table 6-3: Optimization of the Solvent**




| Entry | Solvent | Yield (%)[a,b] | Entry | Solvent | Yield (%)[a,b] |
|---|---|---|---|---|---|
| 1 | MeOH | **76** | 3 | THF | **48** |
| 2 | Benzene | **74** | 4 | Acetone | **62**[c] |

a) Yields following column chromatography. b) Isolated products were racemic.
c) The isolated compound is not the desired product.

Isolation of the undesired yellow side-product followed by $^{1}$H NMR analysis strongly suggested substitution of naphthol **1.76** at the 1 position as in coupling product **5.29**. Large needle-like crystals of the compound were grown by slow evaporation of an acetone solution. X-ray crystallographic analysis of the crystals showed the presence of a nitro group at the 1 position, identifying the product as naphthol **6.1** (Figure 6-3). The identity of naphthol **6.1** was confirmed by HRMS. The nitration of naphthol **1.76** is likely due to the formation of a nitronium ion when silver nitrate and strongly acidic oxone are heated together.



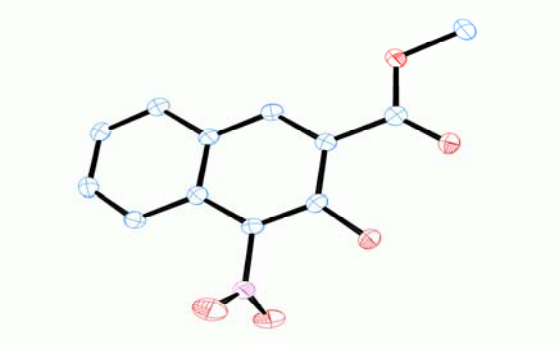



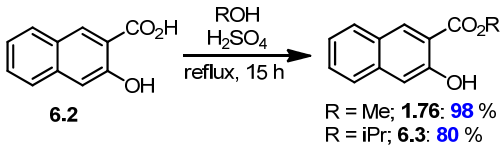
**Figure 6-3: X-Ray Structure of Naphthyl Impurity 6.1**

## 6.3 – Altering the Steric Bulk of Substrates for the Homocoupling of 2-Naphthols

Bulky $C_2$-symmetric catalysts **3.3** and **4.4** afforded poor yields of binaphthyl **5.29** compared to less-hindered methyl-substituted $C_1$-symmetric catalysts **4.1** and **4.2b** without affording any enantioselectivity. As such, further investigations were continued with methyl substituted catalyst **4.1** which afforded the highest yields. Several substrates of varying steric bulk were investigated in order to determine if increasing the bulk of the substrate might lead to enantioinduction in the coupling product. Since the proposed mechanism shows a chelate between the ester substrate and copper,[126] several groups were attached to the ester in order to vary the steric bulk in close proximity to the metal centre.

### 6.3.1 – Synthesis of Substrates

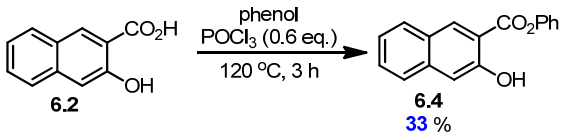
Methyl ester **1.76** has been previously reported in the literature.[137] Ester **1.76** is prepared via Fischer esterification of carboxylic acid **6.2** (Scheme 6-3). When acid **6.2** is refluxed overnight in methanol with a catalytic amount of sulphuric acid, ester **1.76** is afforded in 98 % yield; the isopropyl ester **6.3** is synthesized in an analogous method, when acid **6.2** is refluxed in 2-propanol with a catalytic amount of sulphuric acid, ester **6.3** is afforded in 80 % yield.




**Scheme 6-3: Fischer Esterification of 3-Hydroxy-2-naphthoic Acid**

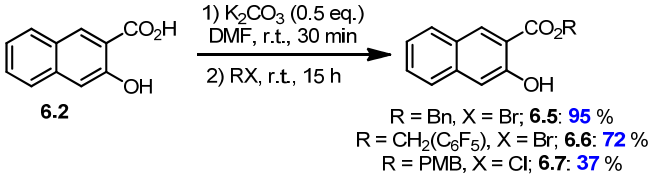
Phenyl ester **6.4** was synthesized in order to provide more steric bulk, but also an aromatic surface for potential π stacking. Phenyl ester **6.4** is not synthesized by Fischer esterification.[138] When carboxylic acid **6.2** and phenol are heated with phosphorous oxychloride, phenyl ester **6.4** is generated in 33 % yield (Scheme 6-4).

[137] AlHujran, T. A.; Dawe, L. N.; Collins, J.; Georghiou, P. E. *J. Org. Chem.* **2011**, *76*, 971.
[138] Strohbach, E. *Chem. Ber.* **1901**, *34*, 4146.




**Scheme 6-4: Synthesis of Naphthol Ester 6.4**

Benzyl esters **6.5**, **6.6**, and **6.7** were also synthesized in an attempt to exploit potential π-π interactions. The different electronic character between the perfluoro and methoxy substituted phenyl groups is intended to probe any potential π interactions. The synthesis of benzyl ester **6.5** was reported previously.[133] Deprotonation of carboxylic acid **6.2** with potassium carbonate is followed by addition of benzyl bromide, affording benzyl ester **6.5** in 95 % yield. Perfluorophenyl **6.6** and para-methoxy **6.7** can be synthesized using the same method, affording ester **6.6** and ester **6.7** in 72 and 37 % yield respectively.

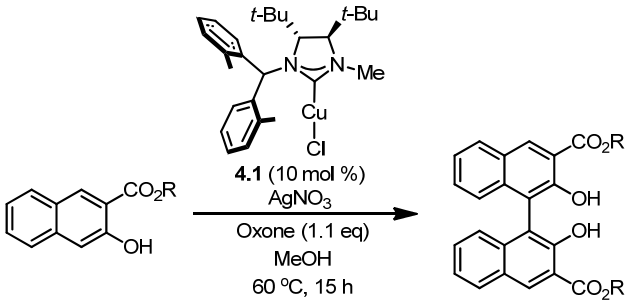


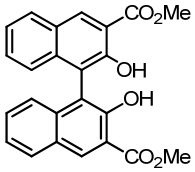
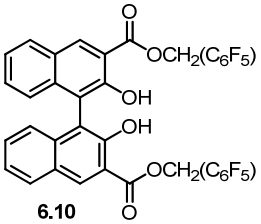
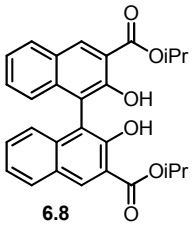
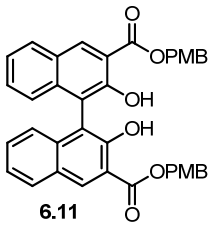
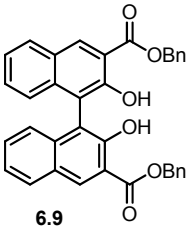
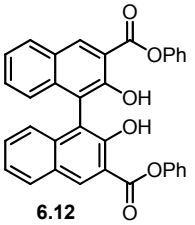

**Scheme 6-5: Synthesis of Benzylic Naphthol Esters**

## 6.3.2 – Coupling Results

The synthesized naphthol esters were submitted to the oxidative coupling conditions of heating in methanol with catalyst **4.1**, silver nitrate and oxone (Table 6-4). The benchmark of the methyl ester affords coupling product **5.29** in 76 % yield (entry 1). Ester **6.3** undergoes homocoupling under the optimized conditions, affording binaphthyl **6.8** in 32 % yield (entry 2). Oxidative coupling of benzyl ester **6.5** affords binaphthyl **6.9** in 50 % yield (entry 3). Perflourophenyl substituted **6.6** is considerably less reactive, affording binaphthyl **6.10** in only 13 % yield (entry 4). Para-methoxy substituted ester **6.7** also displays diminished reactivity compared to ester **1.76**, affording binaphthyl **6.11** in 17 % yield. Phenyl ester **6.4**, which is sterically very similar to isopropyl ester **6.3** affords binaphthyl **6.12** in 31 % yield. It should be noted that all of the coupling products were isolated as racemic mixtures.

**Table 6-4: Oxidative Coupling of Various Naphthol Esters**




| Entry | Product | Yield (%)[a,b] | Entry | Product | Yield (%)[a,b] |
|---|---|---|---|---|---|
| 1 |  **5.29** | **76** | 4 |  **6.10** | **13** |
| 2 |  **6.8** | **32** | 5 |  **6.11** | **17** |
| 3 |  **6.9** | **50** | 6 |  **6.12** | **31** |

a) Yields following column chromatography. b) Products were racemic.

## 6.4 – Additive Effects in the Oxidative Coupling of 2-Naphthols

### 6.4.1 – Additive Concept

The oxidative coupling of 2-naphthols has been shown to produce undesired C-O coupling products before C-C bond formation occurs.[130] The reaction has a short induction period before productive coupling begins, during which oxygen containing products such as quinone **5.30** are produced. The formation of undesired C-O coupling products is discussed in further detail in section 5.4.3. Since the quinone product **5.30** is suggested to act as ligand for the copper catalyst, it was decided to employ a small molecule additive in an attempt to mimic its effect.

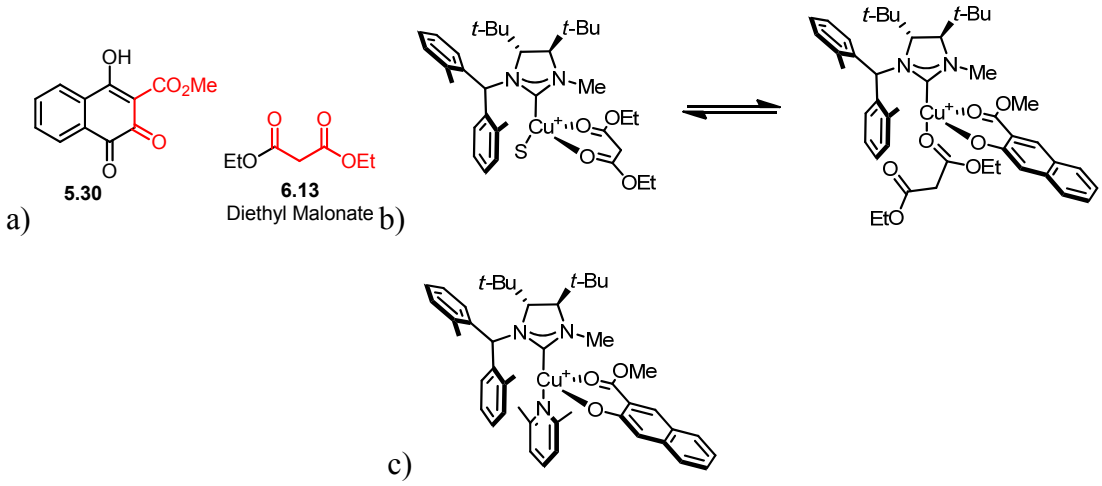


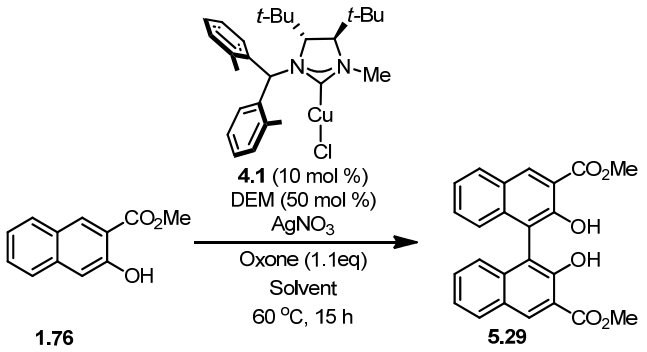

**Figure 6-4: Resemblance of an Quinone 5.30 to a Small Molecule Additive**

Figure 6-4a shows the similarity between quinone **5.30** and a common commercially available small molecule diethylmalonate (DEM) **6.13**. Figure 6-4b shows the potential interaction between catalyst **4.1** and DEM. Shown is an equilibrium between the catalyst resting state, which would be stabilized by the presence of DEM, and an intermediate where naphthol **1.76** is bound to the catalyst in a bidentate fashion. By occupying the fourth coordination site, DEM would make a better defined active species. Figure 6-4c shows the potential interaction between a monodentate pyridine additive and the catalyst with the substrate bound. The preferential conformation adopted by the pyridine ligand would force naphthol **1.76** to adopt a more rigid conformation and potentially induce enantioselectivity.

## 6.4.2 – Additive Screen

Due to its structural similarity to the overoxidation products which are proposed to modify the reactivity of copper catalysts in the oxidative coupling of ester **1.76**, DEM **6.13** was the model additive tested in the oxidative coupling of ester **1.76**. Since the additive is expected to act as a ligand for the catalyst, it modifies the active catalytic species. As such, the solvent was re-optimized in the presence of the additive (Table 6-5). In the presence of 50 mol % of DEM, the oxidative coupling of ester **1.76** in methanol affords binaphthyl **5.29** in 67 % yield. While the yield of coupling product **5.29** is somewhat lower than the reaction preformed without additive, more of ester **1.76** was recovered and fewer impurities were visible by TLC. Employing DEM as an additive in benzene did not result in a large impact on the reactivity, affording binaphthyl **5.29** in 44 % yield. THF proved to be the best solvent for the DEM additive, affording binaphthyl **5.29** in 91 % yield. It should be noted that when the reaction is performed in THF without the additive, that binaphthyl **5.29** is afforded in lower 48 % yield.

**Table 6-5: Effect of Solvent on Additive Effectiveness**

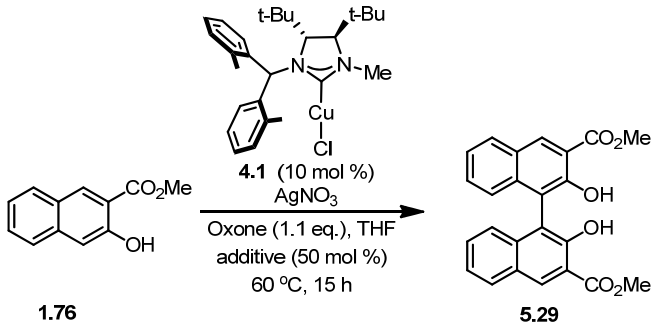



| Entry | Solvent | Yield (%)[a,b] | Entry | Solvent | Yield (%)[a,b] |
|---|---|---|---|---|---|
| 1 | MeOH | **67**[c] | 3 | THF | **91**[c] |
| 2 | Benzene | **44** | 4 | THF | **48**[d] |

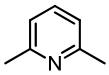
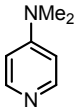
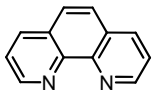
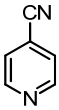
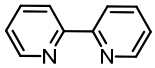
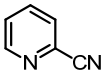
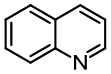
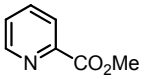
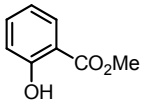
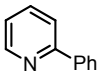
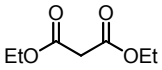
a) Yields following column chromatography. b) Isolated products were racemic.
c) Suppression of impurities was observed. d) Performed without additive.

With DEM showing an impact on the reactivity of catalyst **4.1** in THF, several other small molecule additives were assayed for effects on both reactivity and enantioselectivity (Table 6-6). In an attempt to influence the enantioselectivity of the reaction, several pyridine containing additives were surveyed as well as methyl salicylate, which is structurally similar to quinone **5.30**. Employing 50 mol % of pyridine **6.14** as an additive was found to completely shut the reaction down, resulting in no coupling product being formed and near quantitative recovery of the starting material. DMAP **6.15** formed an almost as unreactive system, forming only trace amounts of coupling product **5.29** with negligible enantioselectivity. Additive 4-cyanopyridine **6.16** provided the first observed enantioselectivity, affording binaphthyl **5.29** in 10 % yield and 15 % ee. Additive 2-cyanopyridine **6.17**, afforded coupling product **5.29** in 31 % yield with negligible ee. Methyl 2-picolinate **6.18** afforded binaphthyl **5.29** in 22 % yield and 10 % ee. Additive 2-phenylpyrdine **6.19** afforded coupling product **5.29** in 72 % yield as a racemic mixture. Additive 2-picoline **6.20** on the other hand, afforded coupling product **5.29** in 21 % yield and 41 % ee. Additive 2,6-lutidine **6.21** afforded binaphthyl **5.29** in 63 % yield and 24 % ee. Bidentate additive 1,10-phenanthroline **6.22** afforded only trace amounts of coupling product **5-29** and no measurable enantioselectivity. Additive 2,2'-bipyridine **6.23** afforded binaphthyl **5.29** in 14 % yield and 12 % ee. Additive quinoline **6.24** afforded coupling product **5.29** in 12 % yield and 9 % ee. Methyl salicylate **6.25** afforded coupling product **5.29** in 31 % yield and 12 % ee. DEM **6.13** afforded the highest yield of 91 % without affording any ee. Without any additive the reaction affords binaphthyl **5.29** in 48 % yield. While 2-picoline **6.14** was able to afford binaphthyl **5.29** in low yield and moderate enantioselectivity, diethyl malonate affords the coupling product in high yield. In the testing, DEM **6.13** showed a clear ability to suppress the formation of highly coloured over-oxidation products in the homocoupling of ester **1.76**.

**Table 6-6: Additive Effects in the Homocoupling of 2-Naphthols**




1.76 5.29

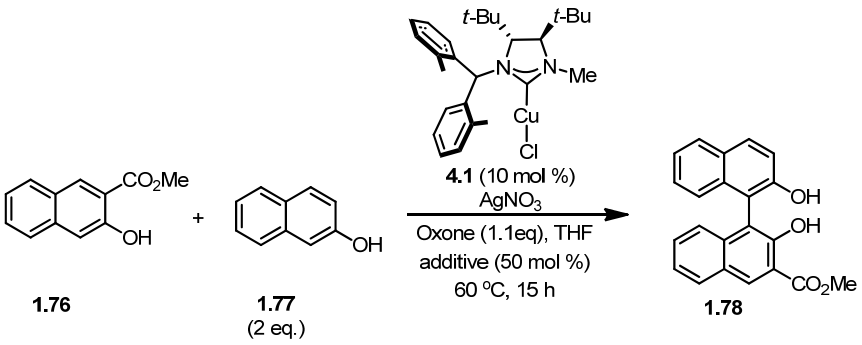
| Entry | Additive | Yield (%)[a] | ee (%)[b] | Entry | Additive | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 |  **6.14** | 0 | N/A | 8 |  **6.21** | **63** | **24** |
| 2 |  **6.15** | <5 | **7** | 9 |  **6.22** | <5 | <5 |
| 3 |  **6.16** | **10** | **15** | 10 |  **6.23** | **14** | **12** |
| 4 |  **6.17** | **31** | **5** | 11 |  **6.24** | **12** | **9** |
| 5 |  **6.18** | **22** | **10** | 12 |  **6.25** | **31** | **12** |
| 6 |  **6.19** | **72** | <5 | 13 |  **6.13** | **91** | <5 |
| 7 |  **6.20** | **21** | **41** | 14 | none | **48** | <5 |

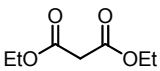
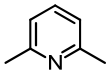
a) Yields following column chromatography. b) Ee measurements were made by HPLC with a chiralpak AD-H column.

## 6.5 – Application of Chiral Catalysts towards the Heterocoupling of Electronically Dissimilar 2-Naphthols

Based on the success of DEM **6.13** at suppressing the formation of undesired C-O coupling products in the oxidative coupling of naphthol **1.76**, the additive was applied towards the oxidative coupling of electronically dissimilar 2-naphthols (Table 6-7). Naphthol **1.77** is more prone to the formation of undesired oxidation products than naphthol **1.76**.[130] When 2 equivalents of **1.77** and 1 equivalent of **1.76** are heated with catalyst **4.1**, silver nitrate and oxone in THF, binaphthyl **1.78** is afforded in 50 % yield. When 50 mol % of DEM is employed as an additive, binaphthyl **1.78** is afforded in 79 % yield. Additive 2-picoline **6.20** affords binaphthyl **1.78** in 51 % yield. Additive 2,6-luitidine **6.21** affords coupling product **1.78** in 63 % yield. It should be noted that all of the coupling products were isolated as racemic mixtures, unlike the homocoupling reaction which afforded binaphthyl **1.78** in 41 % ee with the 2-picoline additive.

**Table 6-7: Additive Effects in the Oxidative Heterocoupling of 2-Naphthols Catalyzed by Complex 4.1**




| Entry | Additive | Yield (%)[a,b] | Entry | Additive | Yield (%)[a,b] |
|---|---|---|---|---|---|
| 1 | none | **50** | 3 |  **6.20** | **51** |
| 2 |  **6.13** | **79** | 4 |  **6.21** | **63** |

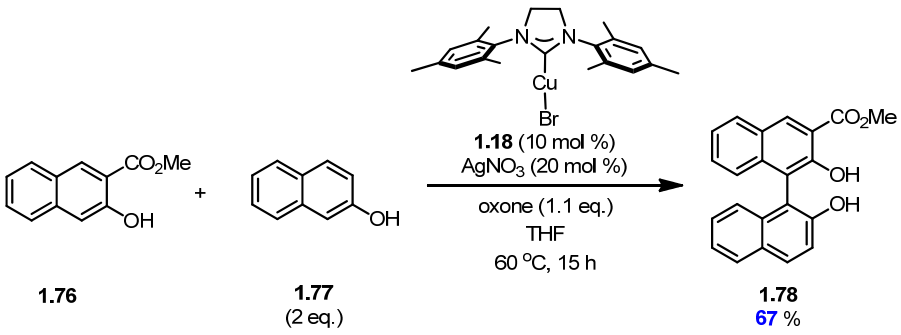
a) Yields following column chromatography. b) Products were racemic.

In the copper NHC catalyzed oxidative coupling of 2-naphthols, two important concepts were proven. Firstly, the augmented reactivity of methyl-substituted $C_1$-symmetric NHCs over $C_2$-symmetric NHCs in the copper catalyzed oxidative coupling of electron poor 2-naphthols was demonstrated. Catalysts **4.1** and **4.2b** bearing methyl-substituted NHCs provided higher yields than catalysts bearing more sterically demanding NHCs such as $C_2$-symmetric catalyst **3.3**. Secondly, the introduction of a small molecule additive was shown to modulate the reactivity of copper catalysts in the oxidative coupling of 2-naphthols. Additive 2-picoline **6.20** was found to induce enantioselectivity in the oxidative homocoupling of ester **1.76** affording binaphthyl **5.29** in 21 % yield and 41 % ee. Additive DEM **6.13** was found to suppress the formation of undesired oxidation products both in the oxidative homocoupling of ester **1.76** and in the oxidative heterocoupling of ester **1.76** and naphthol **1.77**. DEM shows much promise in improving the chemoselectivity of the oxidative heterocoupling of electronically dissimilar 2-naphthols.

# Chapter 7 – Additive Effects in the Oxidative Heterocoupling of 2-Naphthols

In the preceding chapter, the use of a small molecule additive, diethylmalonate (DEM) was found to suppress the formation of undesired C-O coupling products in the oxidative heterocoupling of naphthol ester **1.76** and naphthol **1.77**. Recent advances in the oxidative heterocoupling of electronically dissimilar 2-naphthols have focused on improving the enantioselectivity of the reaction.[136] While the chiral copper NHC complexes did not provide high enantioselectivity for the oxidative coupling of 2-naphthols, the combination of a copper NHC catalyst and a small molecule additive could be used to improve the chemoselectivity of the reaction.

In the heterocoupling of electronically dissimilar 2-naphthols, the electron rich coupling partner reacts much faster than the electron poor coupling partner.[126] As such, homocoupling and degradation products of the electron rich coupling partner are often observed.[129] The principal goal of the project is to improve the chemoselectivity of the coupling reaction so that the electron rich coupling partner does not have to be used in large excess. Additionally, slow addition techniques, which can be employed to prevent premature degradation of the substrate, will not be used. Finally, a "greener alternative" to the harsh oxidant oxone will be evaluated.




**Scheme 7-1: Preliminary Experiment**

In a preliminary experiment, the achiral copper complex Cu(SIMes)Br (**1.18**) was tested for activity in the oxidative heterocoupling of ester **1.76** and naphthol **1.77**; the reaction was performed in THF, since the effects of the additives were found to be much more pronounced in that solvent. With 20 mol % of silver(I) nitrate and a slight excess of oxone, copper complex

**1.18** catalyzes the heterocoupling of naphthol **1.76** and 2 equivalents of naphthol **1.77**, affording binaphthyl **1.78** in 67 % yield (Scheme 7-1).

## 7.1 – Optimization of the Reaction Conditions

Since achiral copper complex **1.18** was found to catalyze the oxidative coupling between naphthol ester **1.76** and naphthol **1.77**, a selection of common mono-NHC copper catalysts were surveyed in the reaction (Figure 7-1). The catalysts were chosen to evaluate steric differences between the mesityl and di-isopropylphenyl aryl groups, as well as electronic differences between saturated and unsaturated ligands. Since the lability of the counterion of the copper atom can have a large impact on the reactivity,[79] both chloro and bromo complexes were tested for activity.

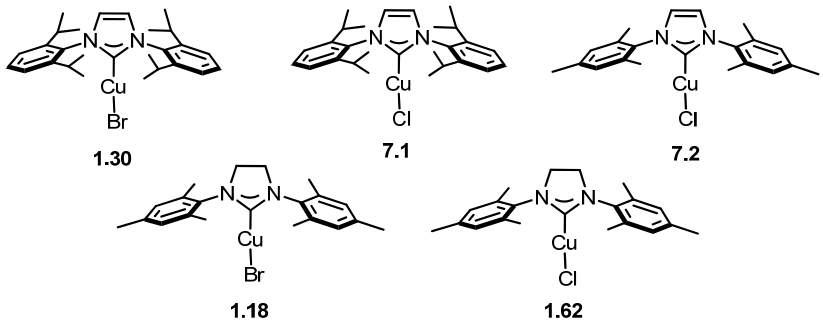
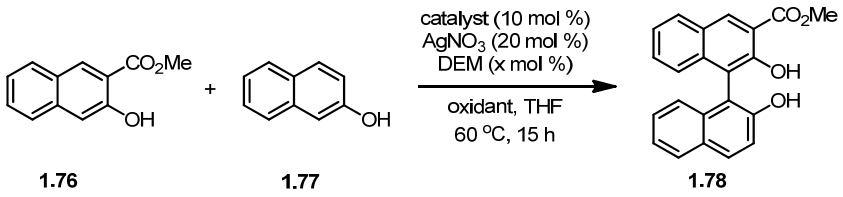



**Figure 7-1: Copper Catalysts Used for Optimization**

Initial experiments with oxone as the oxidant (Table 7-1) showed that catalyst **1.18** (entry 1) afforded a slightly higher yield than catalyst **1.30** (entry 2), affording binaphthyl **1.78** in 67 % and 63 % yield respectively. If one equivalent of naphthol **1.77** is used in the coupling reaction with catalyst **1.18** and oxone as the oxidant, the reaction affords only 8 % yield of binaphthyl **1.78** (entry 3). It should be noted that no homocoupling products were observed in the reaction mixture. Changing oxidant from oxone to oxygen gas with catalyst **1.18** and an excess of naphthol **1.77**, afforded binaphthyl **1.78** in 77 % yield (entry 4). Adding 50 mol % of diethyl malonate (DEM) afforded nearly quantitative amounts of binaphthyl **1.78** (entry 5). Catalyst **1.62** bearing a less labile chlorine atom, was much less reactive than catalyst **1.18** (entry 5), affording binaphthyl **1.78** in 64 % yield (entry 6). The unsaturated IMesCuCl (**7.2**, entry 7) and IPrCuCl (**7.1**, entry 8) catalysts both showed levels of reactivity comparable to catalyst **1.18** (entry 5), both affording near quantitative yields of binaphthyl **1.78**. It was decided to remain

with complex **1.18** as the optimal catalyst due to the simplicity of its synthesis.[32] With catalyst **1.18** and the diethylmalonate additive, it was possible to decrease the amount of naphthol **1.77** to one equivalent and still obtain binaphthyl **1.78** in 69 % yield (entry 9). When the loading of the diethylmalonate additive was decreased to 10 mol % (entry 10), the yield of binaphthyl **1.78** further improved to 79 %.

**Table 7-1: Optimization of the Reaction Conditions**




**1.76** **1.77** **1.78**

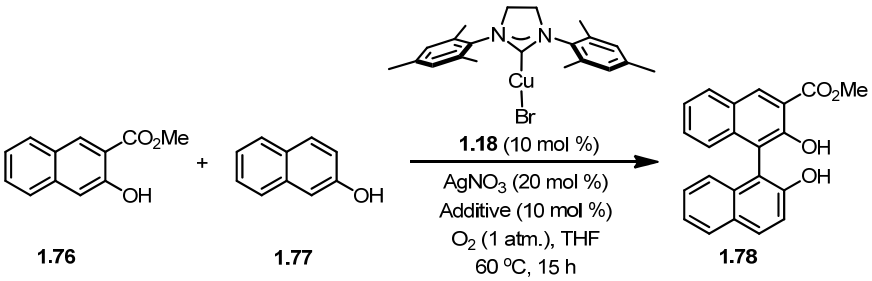
| Entry | Eq **1.77** | Catalyst | mol % DEM | oxidant[a] | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 2 | **1.18** | none | oxone | **67**[c] |
| 2 | 2 | **1.30** | none | oxone | **63**[c] |
| 3 | 1 | **1.18** | none | oxone | **8**[c] |
| 4 | 2 | **1.18** | none | oxygen | **77**[c] |
| 5 | 2 | **1.18** | 50 | oxygen | **98** |
| 6 | 2 | **1.62** | 50 | oxygen | **64** |
| 7 | 2 | **7.2** | 50 | oxygen | **98** |
| 8 | 2 | **7.1** | 50 | oxygen | **98** |
| 9 | 1 | **1.18** | 50 | oxygen | **69** |
| 10 | 1 | **1.18** | 10 | oxygen | **79** |

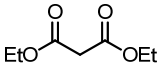
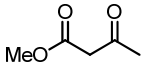
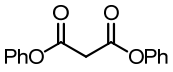
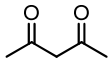
DEM: Diethylmalonate. a) Oxone (1.1 eq.), oxygen (1 atm.). b) Yields following column chromatography. c) 1 eq. $AgNO_3$.

## 7.2 – Additive Screen

Having shown that the use of an additive increased the yield of the oxidative heterocoupling of ester **1.76** and naphthol **1.77**, the effect of additive structure on the reaction was investigated. In addition to diethylmalonate (**6.13**), 3 additives based on the 1,3-dicarbonyl scaffold were tested. Diphenylmalonate **7.3** provides a variation of steric bulk. Additive **7.4** and additive **7.5** with one and two ketones respectively were chosen to investigate the effect of the electronic character of the 1,3-dicarbonyl scaffold on the oxidative coupling reaction.

**Table 7-2: Optimization of Additive Structure**




| Entry | Additive | Yield (%)[a] | Entry | Additive | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 |  **6.13** | 79 | 3 |  **7.4** | 69 |
| 2 |  **7.3** | 79 | 4 |  **7.5** | 14 |

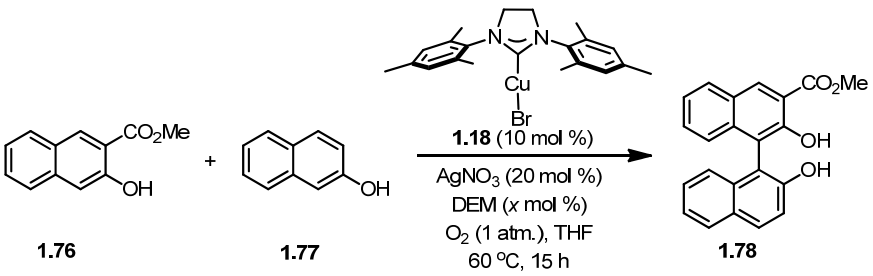
a) Yields following column chromatography.

The additives were tested in the oxidative heterocoupling of naphthol **1.76** and naphthol **1.77**. The coupling partners were used in equimolar quantities with catalytic amounts of complex **1.18**, silver(I) nitrate and additive. The results of the additive screen are summarized in Table 7-2. Diphenylmalonate **7.3** was found to provide identical results to diethylmalonate **6.13**, both affording binaphthyl **1.78** in 79 % yield. Employing acetylacetate **7.4** afforded binaphthyl **1.78** in 69 % yield. Acetylacetone **7.5**, when employed as an additive leads to only 14 % of binaphthyl **1.78**. Due to its commercial availability, diethylmalonate **6.13** was retained as the optimal additive.

## 7.3 – Role of the Additive

With the additive providing a significant increase in the yield of the oxidative heterocoupling of ester **1.76** and naphthol **1.77**, it was left to determine the role of the additive in the reaction. Since the additive was proposed to act as a ligand for the copper catalyst,[139] the effect of the additive loading on the yield of the oxidative coupling reaction was investigated. If the additive is acting as a ligand for the catalyst, the reaction yield will plateau.

[139] For more details see section 5.4.3



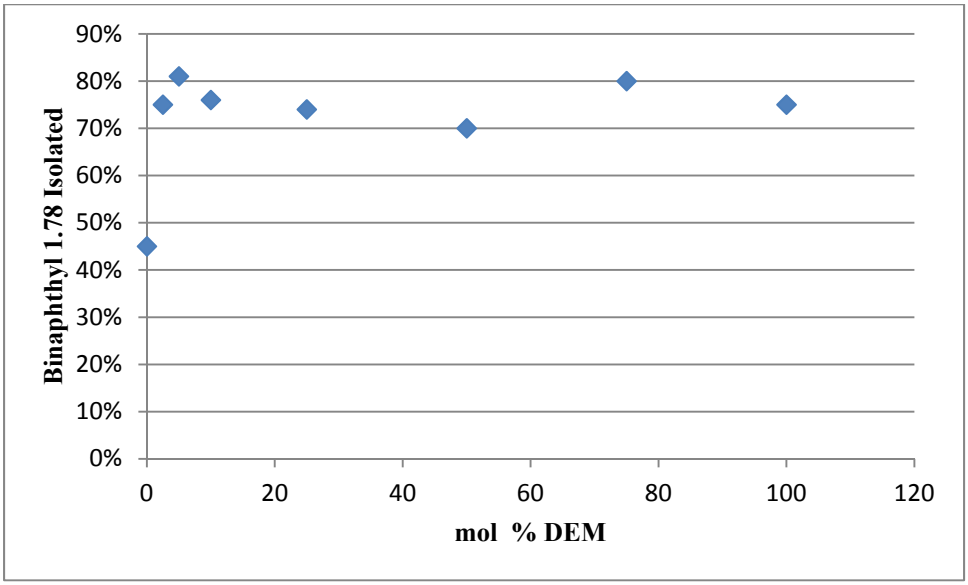




**Figure 7-2: Effect of Additive Loading on the Yield of Binaphthyl 1.78**

The graph in Figure 7-2 shows the effect of the additive loading on the yield of the oxidative heterocoupling of ester **1.76** and naphthol **1.77**. The graph shows that the oxidative coupling requires only a catalytic amount of malonate **6.13** in order to achieve maximum yield, with a plateau at 10 mol %. That only 10 mol % of additive is necessary suggests that the additive is acting as a ligand for the metal, and that only one equivalent of malonate binds to the catalyst. Furthermore, there is no inhibition of the catalyst at high loadings of DEM.

While the additive has been shown to improve isolated yield of binaphthyl **1.78**, the observed effect could still be due to inhibition of the decomposition of coupling product **1.78**. To that end, the effect of the additive on the recovery of binaphthyl **1.78** when resubmitted to the optimized oxidative coupling conditions was investigated. Figure 7-3 shows the effect of additive loading on the stability of binaphthyl **1.78** to the oxidative coupling conditions. No significant difference is observed in the amount of binaphthyl **1.78** recovered, even at high loadings of DEM **6-13**. The results together suggest strongly that the additive is acting as a

ligand that modulates the reactivity of the copper catalyst, promoting C-C bond formation over C-O bond formation.

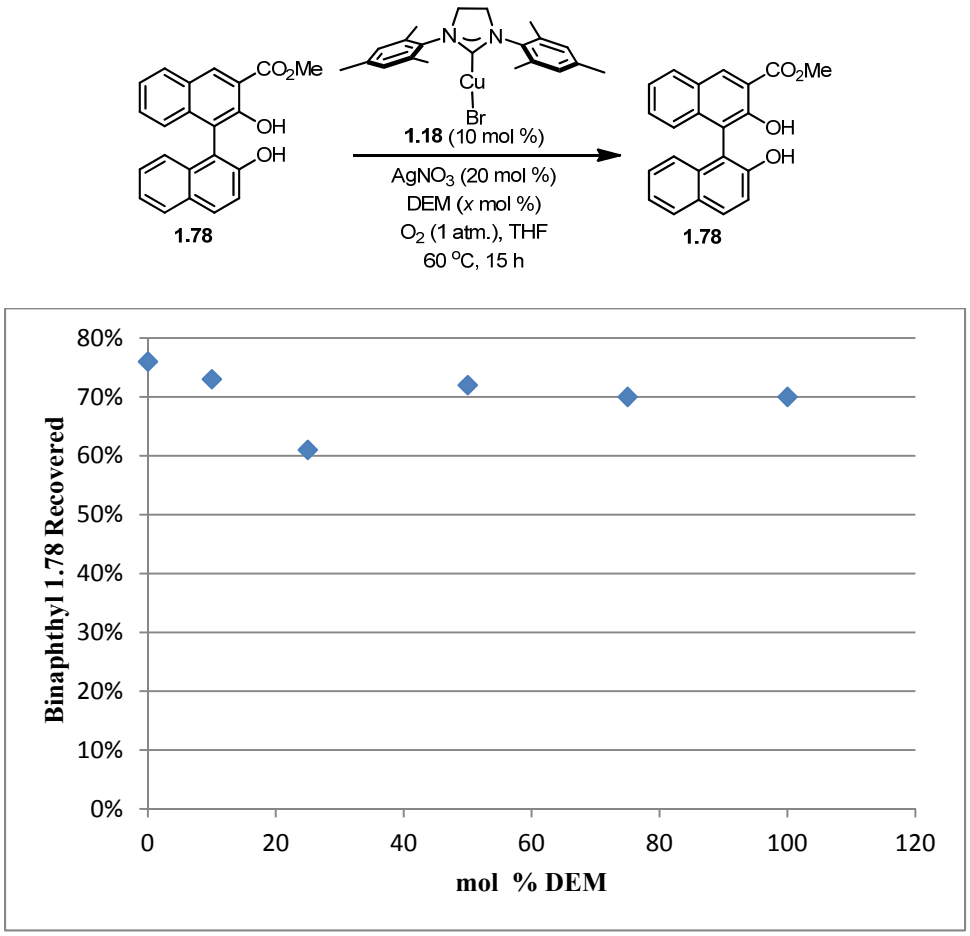



**Figure 7-3: Stability of Binaphthyl 1.78 to the Oxidative Coupling Conditions in the Presence of the Additive**

## 7.4 – Substrate Scope

### 7.4.1 – Synthesis of Substrates

With optimized conditions for the additive assisted heterocoupling of electronically dissimilar 2-naphthols in hand, attention was turned towards the scope of the reaction. Substrates were selected in order to evaluate steric bulk as well as electronic effects (Figure 7-4). Naphthol **1.77** as well as substituted naphthols **7.6** – **7.9** and aminonaphthalene **7.10** were targeted as electron rich coupling partners. Ester **1.76** as well as naphthols **7.12** – **7.20** were targeted as electron deficient coupling partners. The synthesis of ester **1.76** was shown in the

preceding chapter. Naphthols **1.77**, **7.6** and **7.7** are commercially available, the syntheses of the remaining compounds follow.

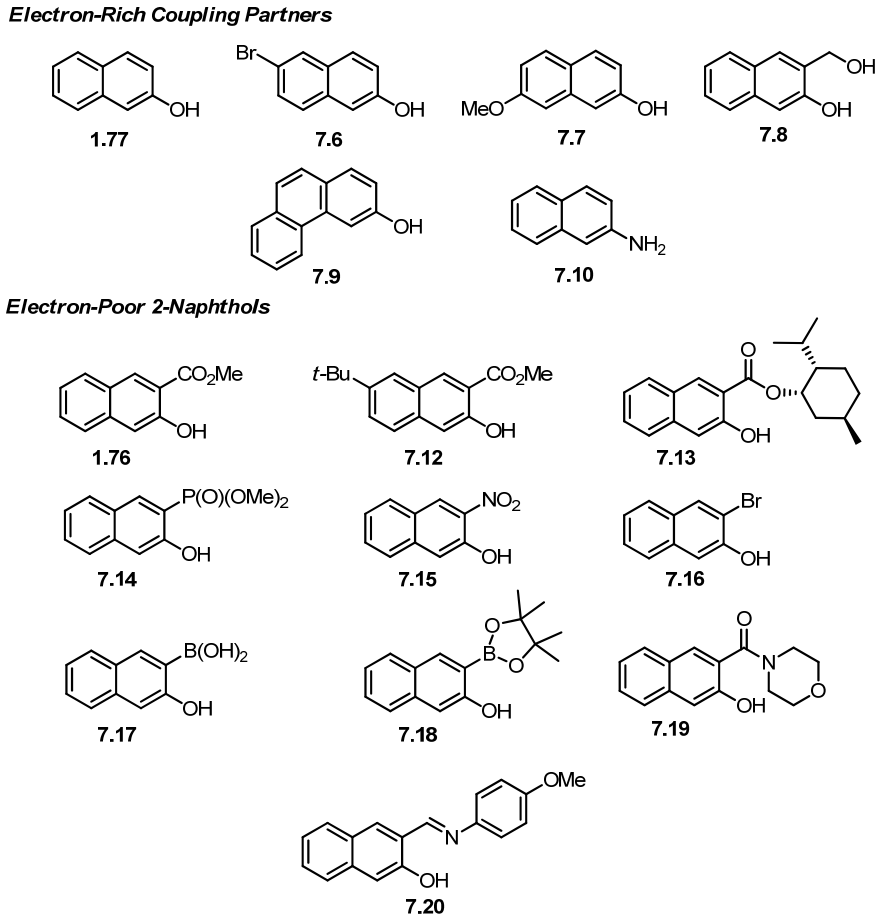
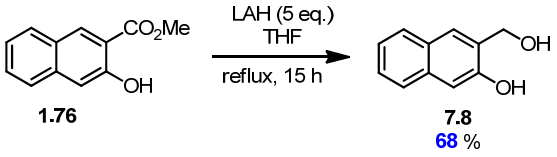


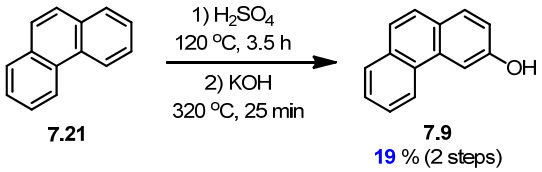

**Figure 7-4: Glossary of Substrates for the Oxidative Heterocoupling Reaction**

Naphthol **7.8** bearing a pendant alcohol is synthesized by reduction of ester **1.76**. When ester **1.76** is heated with an excess of LAH overnight, alcohol **7.6** is isolated in 68 % yield.



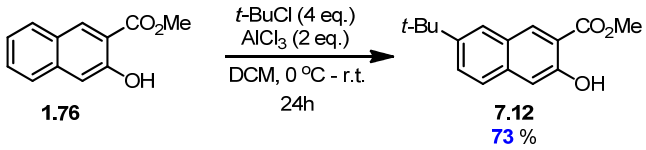

**Scheme 7-2: Synthesis of Substrate Bearing Pendant Alcohol**

Phenanthrol **7.9** is synthesized from phenanthroline in 2 steps.[140] First phenanthrene **7.21** is sulfonated, followed by separation of the regioisomers. The 3-phenanthryl sulfonate is then submitted to fusion conditions in liquid potassium hydroxide, affording 3-phenanthrol **7.9** in 19 % yield over the 2 steps.



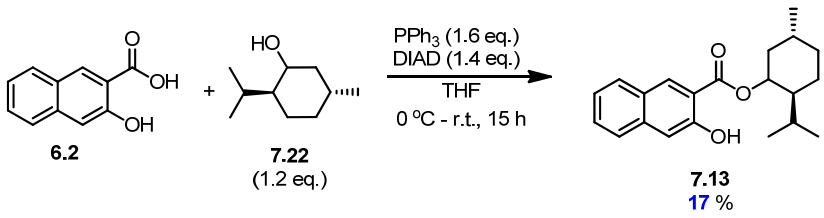

**Scheme 7-3: Synthesis of 3-Phenanthrol 7.9**

Ester **7.12** bearing a *t*-butyl substituent is synthesized from ester **1.76** via Friedel-Crafts alkylation (Scheme 7-4).[137] Ester **1.76** is alkylated with a large excess of *t*-butyl chloride and aluminum chloride in dichloromethane, affording *t*-butyl substituted naphthol **7.12** in 86 % yield.




**Scheme 7-4: Synthesis of t-Butyl Substituted Naphthol 7.12**

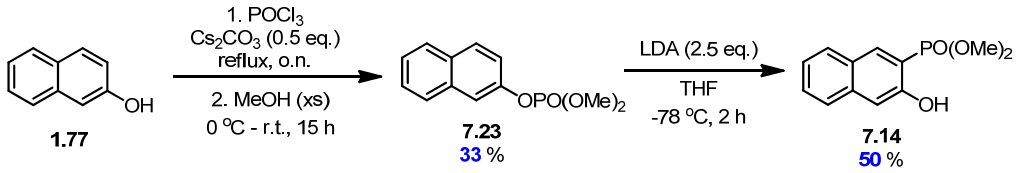
Menthol ester **7.13** was synthesized via Mitsunobu reaction following a previously reported procedure (Scheme 7-5).[66] Carboxylic acid **6.2** and menthol **7.22** are treated with triphenylphosphine and di-isopropylcarbodiimide, affording menthol ester **7.13** in 17 % yield following column chromatography.




**Scheme 7-5: Synthesis of Menthol Ester 7.13**

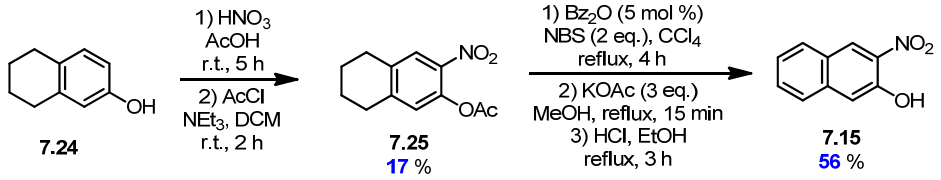
[140] Suzumura, H. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 1822.

Phosphonate **7.14** is synthesized by what is formally a Fries rearrangement (Scheme 7-6).[129] First 2-napthol **1.77** is refluxed with $POCl_3$ and cesium carbonate, followed by quenching with methanol to form phosphonate **7.23** in 33 % yield. The rearrangement is performed by directed ortho metalation of the ring with *in-situ* generated LDA. If the LDA is poorly formed and the *n*-BuLi performs the metalation, the phosphonate will migrate to the 1 position. Metalation at the 3 position provides the rearranged product **7-14** in 50 % yield.




**Scheme 7-6: Synthesis of the Phosphonate Ester 7.14**

Nitronaphthol **7.15** is synthesized in 5 steps from tetrahydronaphthol **7.24** (Scheme 7-7).[141] Tetrahydronaphthol **7.24** is nitrated with nitric acid in acetic acid for 5 h, followed by acetylation with acetyl chloride, affording nitro compound **7.25** in 17 % yield over the 2 steps. Intermediate **7.25** is then subjected to radical bromination with NBS and a catalytic amount of benzoyl peroxide as an initiator. The product is carried forward to elimination with potassium acetate, followed by cleavage of the acetate with HCl in refluxing ethanol. The overall yield for the 3 steps is 56 % of nitronaphthol **7.15**.

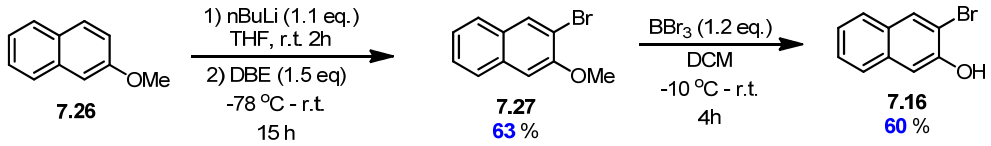



**Scheme 7-7: Synthesis of Nitro Precursor**

The synthesis of bromide **7.16** has been described previously (Scheme 7-8).[142] Directed ortho metalation of methoxynaphthalene **7.26** by *n*-BuLi, followed by quenching with a brominating agent leads to methoxynaphthalene **7.27**. When NBS or bromine is employed as a bromine source, only poor yields are obtained. Dibromoethane on the other hand, affords

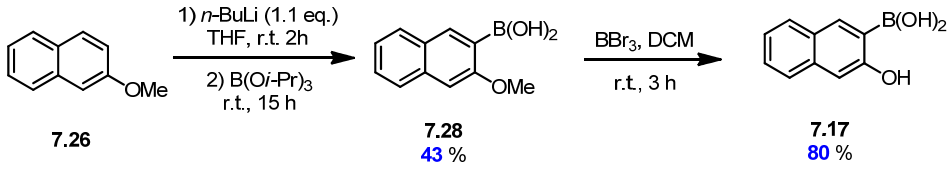
[141] Woodcock, D.; Clifford, D. R. *J. Chem. Soc.* **1957**, 4139.
[142] Biehl, E. R.; Deshmukh, A. R.; Dutt, M. *Synthesis* **1993**, 885.

bromonaphthalene **7.27** in 63 % yield. Methoxynaphthalene **7.27** is de-methylated using boron tribromide, affording naphthol **7.16** in 60 % yield.



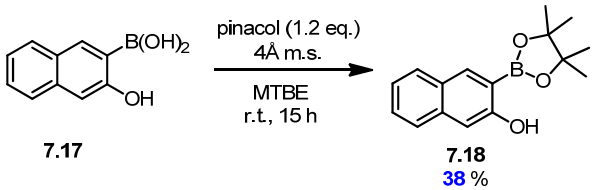

**Scheme 7-8: Synthesis of 3-Bromo-2-naphthol 7-16**

Due to the prevalence of aryl boronic acids in palladium cross-coupling, boronic acid **7.17** was synthesized (Scheme 7-9).[143] Boronic acid **7.17** is prepared in a similar fashion to bromide **7.16**.[144] Directed ortho metalation of naphthalene **7.26** is followed by quenching with a trialkyl borate. Quenching with trimethylborate did not lead to isolation of the desired product. However, quenching with tri-isopropyl borate affords boronic acid **7.28** in 43 % yield following acid workup. Methoxynaphthalene **7.28** is de-methylated with boron tribromide, affording boronic acid **7.17** in 80 % yield.




**Scheme 7-9: Synthesis of 2-Naphthol-3-boronic Acid 7.17**

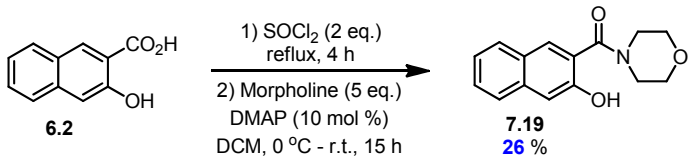
Pinacol esters are also common substrates in palladium cross-coupling chemistry.[145] Pinacol ester **7.18** was synthesized in 38 % yield by stirring boronic acid **7.17** in ether at room temperature with a slight excess of pinacol under dehydrating conditions (Scheme 7-10).




**Scheme 7-10: Synthesis of Borate Esters 7-18**

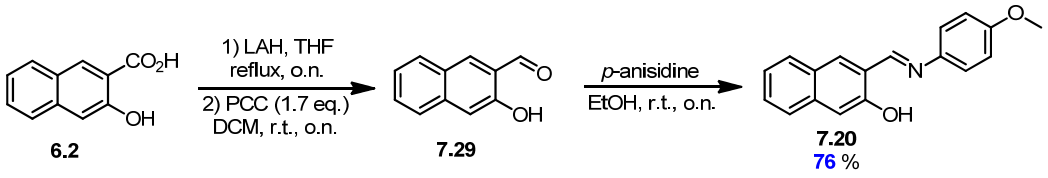
[143] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
[144] Routier, S.; Peixoto, P.; Merour, J. Y.; Coudert, G.; Dias, N.; Bailly, C.; Pierre, A.; Leonce, S.; Caignard, D. H. *J. Med. Chem.* **2005**, *48*, 1401.
[145] Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

Amide **7.19** was synthesized from the transiently generated acyl halide of carboxylic acid **6.2** following a previously reported procedure (Scheme 7-11).[133] Carboxylic acid **6.2** is refluxed with thionyl chloride until gas evolution ceases. The excess thionyl chloride is then distilled off and the resultant oil is dissolved in dichloromethane. DMAP and then morpholine are added at low temperature, the solution is then allowed to return to room temperature, affording amide **7.19** in 26 % yield.




**Scheme 7-11: Synthesis of Amide 7.19**

Imine **7.20** is synthesized via condensation of *para*-anisidine with aldehyde **7.29** (Scheme 7-12. Aldehyde **7.29** is prepared by sequential LAH reduction and PCC oxidation of carboxylic acid **6.2**. When aldehyde **7.29** and *para*-anisidine are stirred in ethanol at room temperature, imine **7.20** precipitates out of solution in 76 % yield.

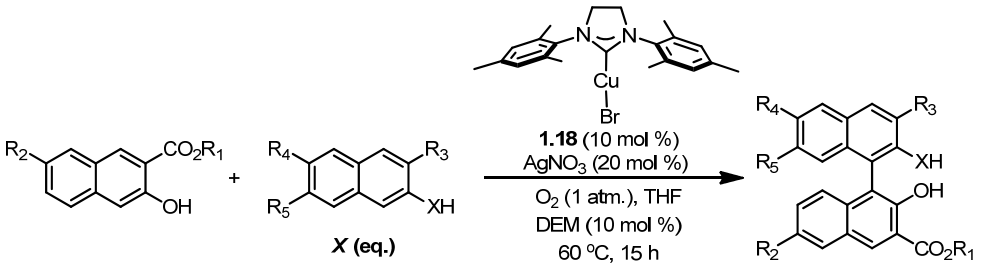


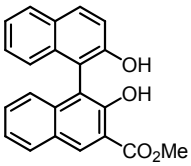
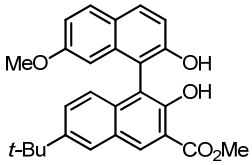
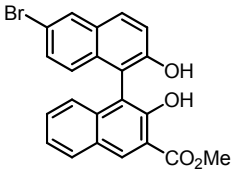
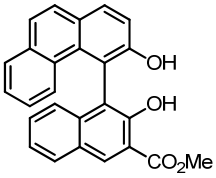
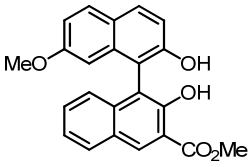
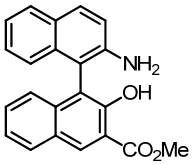
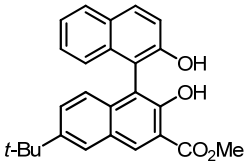
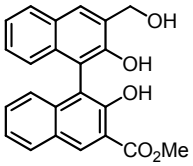
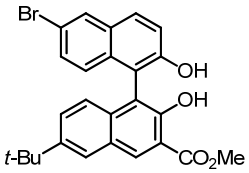
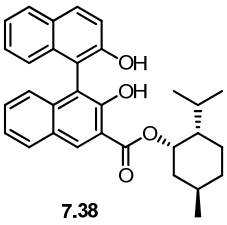

**Scheme 7-12: Synthesis of Imine 7.20**

## 7.4.2 – Results of Coupling Reactions

The substrates shown in Figure 7-4 were assayed for reactivity in the additive assisted heterocoupling of electronically dissimilar 2-naphthols. The results are summarized in Tables 7-3 – 7-5. Bromo substituted naphthol **7.6** when used in excess, couples nearly quantitatively with ester **1.76**, affording binaphthyl **7.30** in 95 % yield. However, when the loading naphthol **7.6** was decreased to one equivalent, the yield of binaphthyl **7.30** dropped to 58 %. When two equivalents of methoxy naphthol **7.7** are coupled with ester **1-76**, a slightly lower yield of 86 % of binaphthyl **7.31** is obtained; however, when 1 equivalent of methoxy naphthol **7.7** is employed, the yield remains quite good, affording naphthalene **7.31** in 76 % yield. The same coupling reactions were performed with *t*-butyl substituted ester **7.12**. Coupling of ester **7.12** with naphthol **1.77** afforded binaphthyl **7.32** in 72 % yield with one equivalent of naphthol **1.77** and 86 % yield with 2 equivalents of naphthol **1.77**. The number of equivalents of bromide **7.6** again showed a large impact on the yield, affording 82 % of binaphthyl **7.26** with 1.5 equivalents of naphthol **7.6** and 46 % with 1 equivalent. The difference in yield suggests an instability of naphthol **7.6** to the reaction conditions, similar to the instability of 2-naphthol **1.77** without the benefit of the additive. Methoxy naphthalene **7.7** coupled with ester **7.12** in good yields, affording 60 % of coupling product **7.34** with 1 equivalent of the electron-rich coupling partner and near quantitative yield with 2 equivalents. 3-phenanthrol **7.9**, a product known to be quite sensitive[66] still yields 49 % of biaryl **7.35** with only 1.3 equivalents of the electron rich coupling partner. Most surprising was the synthesis of NOBIN derivative **7.36** which was afforded in 67 % yield when employing 1.3 equivalents of 2-aminonaphthalene **7.10** and 47 % yield with 1 equivalent. Pendant alcohol **7.8** was found to have a very negative impact on the reaction yield; even when 2 equivalents of alcohol **7.8** are used, it affords only 14 % of coupling product **7.37**. The diminished reactivity is likely due to the formation of a stable chelate between alcohol **7.8** and catalyst **1.18**. Menthol derivative **7.13** also afforded lower yields, affording only 31 % of coupling product **7.38** when coupled with 2 equivalents of 2-naphthol **1.77**. The chelate with the ester is known to be reactive;[128] however, the bulk of the menthol is likely the cause of the diminished reactivity.

**Table 7-3: Variation of Naphthyl Substituents**



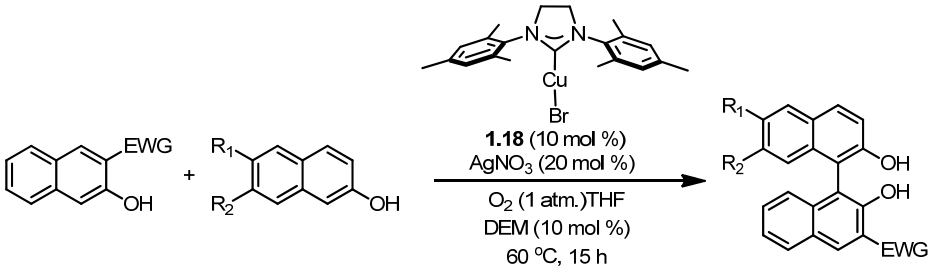

| Entry | Product | Eq. X | Yield (%)[a] | Entry | Product | Eq. X | Yield (%)[a] |
|---|---|---|---|---|---|---|---|
| 1 |  **1.78** | 1 | **79**[b] | 11 |  **7.34** | 1 | **60** |
| 2 | | 2 | **98**[c] | 12 | | 2 | **98** |
| 3 |  **7.30** | 1 | **58**[c] | 13 |  **7.35** | 1 | **35**[c] |
| 4 | | 2 | **95**[c] | 14 | | 1.3 | **49** |
| 5 |  **7.31** | 1 | **75**[c] | 15 |  **7.36** | 1 | **47** |
| 6 | | 2 | **86**[c] | 16 | | 1.3 | **67** |
| 7 |  **7.32** | 1 | **72**[c] | 17 |  **7.37** | 1 | <5 |
| 8 | | 2 | **86**[c] | 18 | | 2 | **14** |
| 9 |  **7.33** | 1 | **46** | 19 |  **7.38** | 1 | **15** |
| 10 | | 1.5 | **82** | 20 | | 2 | **31** |

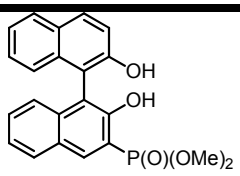
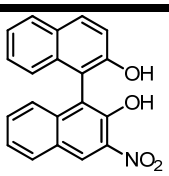
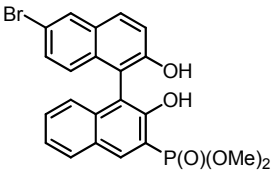
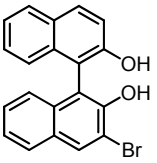
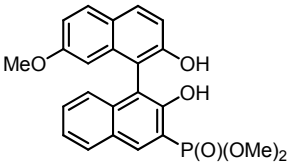
a) Yields following column chromatography. b) For 1 mmol scale yield is 77 %. c) 50 mol % additive.

After investigating the effect of substitution patterns the next step was to investigate the effect of variation of the electron withdrawing group (Table 7-4). Phosphonate **7.14** coupled successfully with one equivalent of 2-naphthol **1.77**, affording coupling product **7.39** in 77 %

yield. The bromo and methoxy derivatives could also be synthesized, affording binaphthyl **7.40** and binaphthyl **7.41** in 50 % and 62 % yield respectively. Nitronaphthol **7.15** coupled with 1 equivalent of naphthol **1.77**, affording binaphthyl **7.42** in 71 % yield. Bromide **7.16** reacted surprisingly well, considering that the bromo substituent is only inductively withdrawing, affording coupling product **7.43** in 61 % yield when 1.3 equivalents of 2-naphthol **1.77** were employed.

**Table 7-4: Variation of the Electron Withdrawing Group**



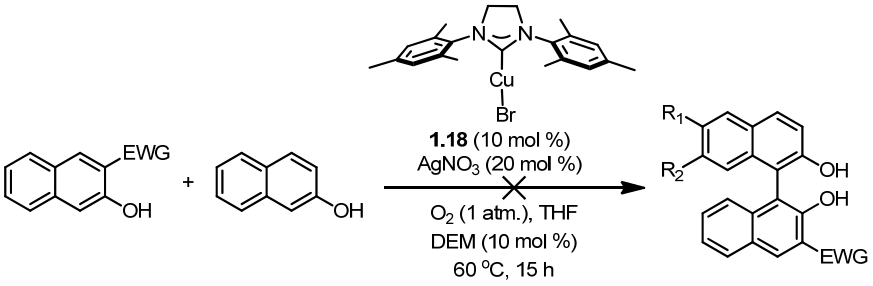

| Entry | Product | Yield (%)[a] | Entry | Product | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 |  **7.39** | **77**[b] | 4 |  **7.42** | **71**[c] |
| 2 |  **7.40** | **50** | 5 |  **7.43** | **62**[d] |
| 3 |  **7.41** | **62** | | | |

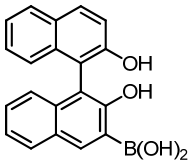
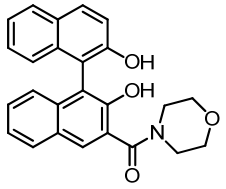
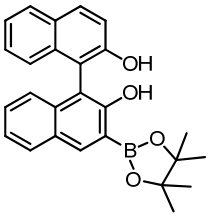
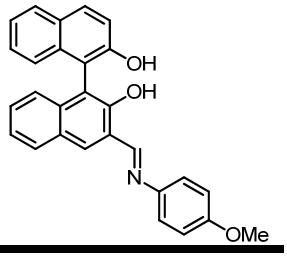
a) Yields following column chromatography. b) For 1 mmol scale yield is 66 %. c) 50 mol % additive.
d) 1.3 eq. 2-naphthol.

Some of the derivatives synthesized did not generate coupling products when submitted to the optimized reaction conditions (Table 7-5). Boronic acid derivatives (entries 1-2) failed to provide coupling products of the boron containing compounds, even with an excess of 2-naphthol **1.77**. Amide substrate **7.19** was found to decompose in the reaction conditions as

opposed to forming any recognizable coupling products. Imine **7.20** also failed to generate coupling products under the reaction conditions. New products were formed; unfortunately none of them corresponded to the desired oxidative coupling product.

**Table 7-5: Ineffective Electron-Withdrawing Groups**



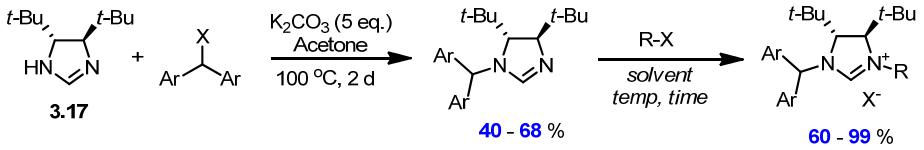

| Entry | Product | Entry | Product |
|---|---|---|---|
| 1 |  | 4 |  |
| 2 |  | 5 |  |

The effectiveness of copper NHC complexes as catalysts for the oxidative coupling of 2-naphthols has been demonstrated.[66,146] In addition, the use of a small molecule additive diethylmalonate, has been shown to improve the chemoselectivity of the cross-coupling reaction, allowing the electron-rich coupling partner to be employed in stoichiometric quantities while still providing synthetically relevant yields of the $C_1$-symmetric BINOL products.[145] The purification of the binaphthyl products has been simplified by the suppression of the formation of C-O coupling products. The reaction is performed with the environmentally benign oxidant, molecular oxygen, and does not require slow addition of the electron rich coupling partner to achieve the reported yields.

[146] Holtz-Mulholland, M.; De Léséleuc, M.; Collins, S. K. *Chem. Commun.* **2013**, *49*, 1835.

# 8 - Conclusions and Perspectives

A new protocol for the synthesis of chiral $C_1$-symmetric, dialkyl substituted NHC precursors was developed (Scheme 8-1). The protocol is modular and efficient, derived from sequential alkylations of chiral imidazoline **3.17**. A series of biaryl methynes of varying steric bulk were installed by heating imidazoline **3.17** with the corresponding alkyl halide, affording mono-alkylated chiral imidazolines in 40 - 68 % yield. The newly generated chiral imidazolines were then alkylated to generate chiral imidazolinium salts which serve as NHC precursors. Methyl, benzyl and picolyl substituents could be installed, affording chiral imidazolinium salts in 60 - 99 % yield.




**Scheme 8-1: Modular Synthesis of Chiral Dialkyl Substituted $C_1$-Symmetric NHC Precursors**

The new NHC precursors were submitted to conditions for the formation of transition metal NHC complexes. Four new chiral copper complexes **4.1**, **4.2b**, **4.3** and **4.4** and a new chiral gold complex **4.5** were synthesized (Figure 8-1). Crystal structures of copper complexes **4.1** and **4.2b** as well as gold complex **4.5** were obtained.

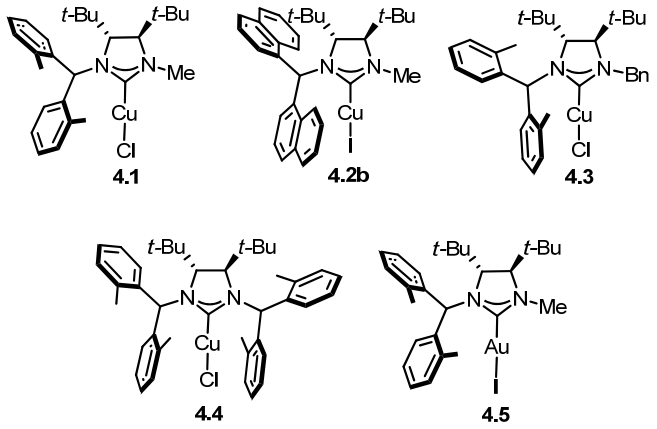
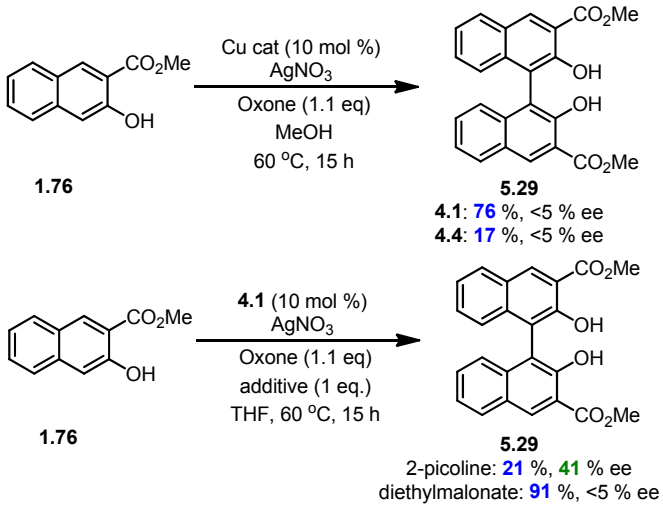



**Figure 8-1: New Chiral Transition Metal NHC Complexes**

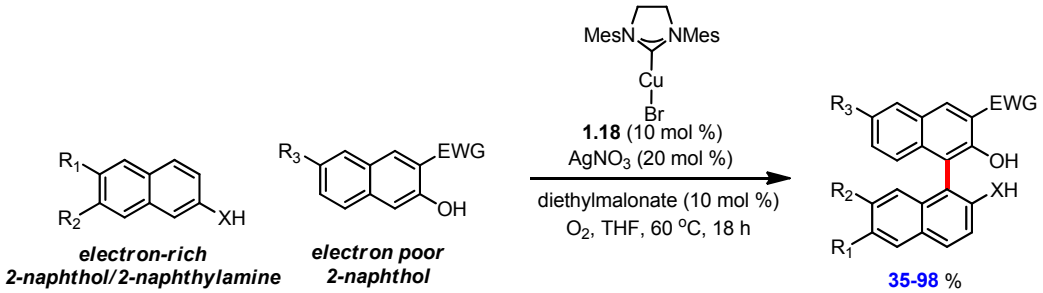
The new chiral copper complexes were tested in the oxidative homocoupling of naphthol **1.76**. Catalysts bearing methyl-substituted $C_1$-symmetric NHCs were found to provide higher

yields than their bulkier $C_2$-symmetric counterparts, without showing any change in selectivity (Scheme 8-2). Catalyst **4.1** affords binaphthyl **5.29** in 76 % yield while catalyst **4.4** affords binaphthyl **5.29** in 17 % yield. The use of a small molecule additive was found to modulate the catalyst reactivity. When the oxidative coupling of naphthol **1.76** catalyzed by complex **4.1** was carried out in the presence of 2-picoline, binaphthyl **5.29** was afforded in 21 % yield and 41 % ee. When diethyl malonate was employed as an additive, binaphthyl **5.29** was afforded in 91 % yield and a suppression of impurities was observed.



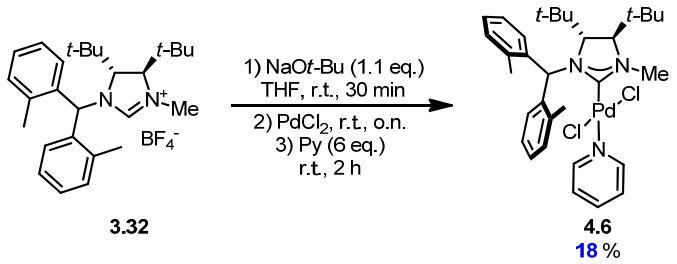

**Scheme 8-2: Copper NHC Catalyzed Oxidative Coupling of Naphthol 1.76**

The malonate additive was applied to the symmetric oxidative heterocoupling of electronically dissimilar 2-naphthols (Scheme 8-3). The additive was able to improve the chemoselectivity so that the coupling partners can now be used in equimolar quantities. A series of $C_1$-symmetric BINOLs and one NOBIN derivative were synthesized following the general protocol in 35 – 98 % yield.



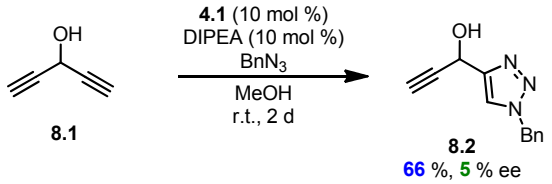

**Scheme 8-3: Additive Assisted Oxidative Heterocoupling of 2-Naphthols**

Future work may include the characterization of palladium complex **4.6** (Scheme 8-4). The complex could be tested as a catalyst for asymmetric transformations such as allylic alkylation and biaryl synthesis via Suzuki coupling.




**Scheme 8-4: Ongoing Work Towards a New Chiral Palladium Complex**

The copper and gold complexes could also find new uses in catalytic asymmetric transformations. Sterically unencumbered $C_1$-symmetric NHCs allow for the construction of sterically hindered products such as quaternary stereocenters via reactions such as conjugate addition, allylic substitution and potentially hydroamination in the case of the gold complex. Scheme 5 shows a preliminary result in the desymmetrization of diyne **8.1** via Huisgen 1,3-dipolar cycloaddition catalyzed by complex **4-1**, affording triazole **8.2** in 66 % yield and 5 % ee.[147]




**Scheme 5: Preliminary Result in the Desymmetrization of Diyne 1**

[147] The ee is an average of 2 experiments.

The additive chemistry could be adapted towards a general protocol for the catalytic aerobic synthesis of NOBIN derivatives via oxidative coupling. The additive would slow the degradation and homocoupling of 2-aminonaphthalene (Figure 8-2).

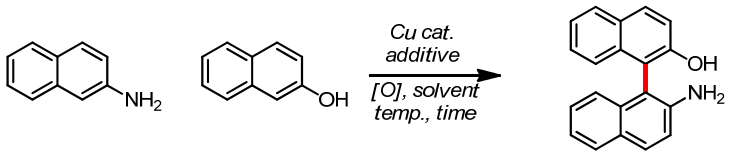



**Figure 8-2: General NOBIN Synthesis**

# 9 - Experimental Section

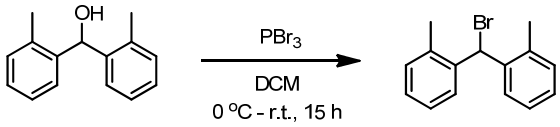
## 9.1 - General Considerations

All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 $^{o}$C or had been flame dried and cooled under a stream of argon or nitrogen.[148] All chemical products were obtained from Sigma-Aldrich Chemical Company or Strem Chemicals and were reagent quality. Technical solvents were obtained from VWR International Co. Anhydrous solvents ($CH_2Cl_2$, $Et_2O$, THF, DMF, Toluene, and *n*-hexane) were dried and deoxygenated using a GlassContour system (Irvine, CA). Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by W. C. Still[149] and using silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescence indicator (Silicycle Chemical division, 0.25 mm, $F_{254}$.). Visualization of TLC plate was performed by UV (254 nm), $KMnO_4$ or *p*-anisaldehyde stains. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported compounds were homogeneous by thin layer chromatography (TLC) and by $^{1}$H NMR. NMR spectra were taken in deuterated $CDCl_3$ using Bruker AV-300, AV-400, AV-500, AV-700 and DRX-400 instruments unless otherwise noted. Signals due to the solvent served as the internal standard ($CHCl_3$: δ 7.27 for $^{1}$H, δ 77.0 for $^{13}$C)(acetone: δ 2.05 for $^{1}$H, δ 29.84 for $^{13}$C). The acquisition parameters are shown on all spectra. The $^{1}$H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), sept(septet), m (multiplet), br (broad); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. High resolution mass spectroscopy (HRMS) was done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université de Montréal from an Agilent LC-MSD TOF system using ESI mode of ionization unless otherwise noted.

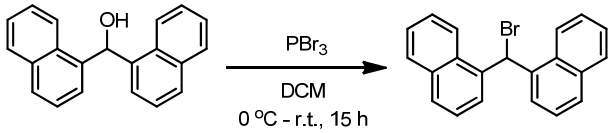
[148] Shriver, D. F.; Drezdon, M. A. in *The Manipulation of Air-Sensitive Compounds*; Wiley-VCH: New York, 1986.
[149] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923-2925.

## 9.2 - Synthetic Procedures

### 9.2.1 - Synthesis of Alkyl Halides

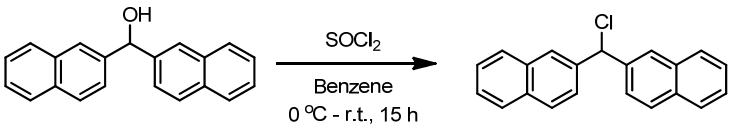



**Bis(2-methylphenyl)methyl bromide (3.12):** Bis(2-methylphenyl)methanol[150] (6.30 g, 29.7 mmol) was dissolved in dichloromethane (300 mL). Phosphorous tribromide (1.40 mL, 14.7 mmol) was added slowly at 0 °C and the solution was allowed to warm to room temperature. The reaction was stirred at room temperature overnight after which water was added. The aqueous layer was extracted twice with dichloromethane. The combined organic fractions were dried over sodium sulfate and filtered on basic alumina. The solvent was removed *in vacuo* to afford the product as a beige solid (7.0 g, 86 %). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.54 (m, 2H), 7.27 – 7.22 (m, 4H), 7.19 (dd, $J$ = 5.6, 3.5 Hz, 2H), 6.63 (s, 1H), 2.36 (s, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 138.42, 135.08, 130.46, 129.57, 128.07, 126.41, 50.78, 19.12; HRMS (ESI +) for $C_{15}H_{15}$ $[M - Br]^+$ calculated: 195.1168 found: 195.1176.

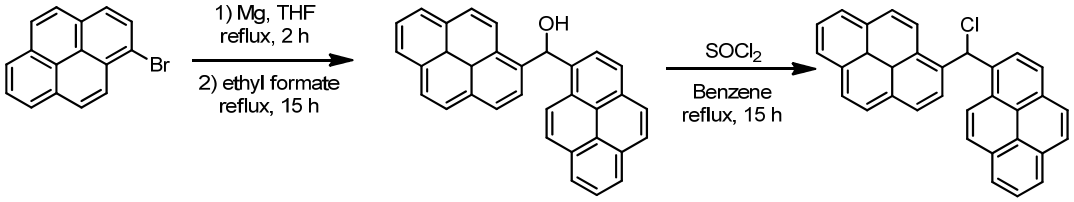



**Bis(1-naphthyl)methyl bromide (3.25):** Bis(1-naphthyl)methanol[151] (1.7 g, 6 mmol) was dissolved in dichloromethane (60 mL). Phosphorous tribromide (0.28 mL, 3 mmol) was added slowly at 0 °C and the solution was allowed to warm to room temperature. The reaction was stirred at room temperature overnight after which water was added. The aqueous layer was extracted twice with dichloromethane. The combined organic fractions were dried over sodium sulfate and filtered on basic alumina. The solvent was removed *in vacuo* to afford the product as a white solid (1.87 g, 90 %). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.06 (m, 2H), 7.98 – 7.90 (m, 2H), 7.91 – 7.82 (m, $J$ = 9.5 Hz, 3H), 7.77 (d, $J$ = 7.2 Hz, 2H), 7.60 – 7.49 (m, 4H), 7.45 (t, $J$ = 7.7 Hz, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 135.86, 133.83, 130.14, 129.16, 128.94, 128.22, 126.74, 125.92, 125.47, 123.15, 50.00; HRMS (ESI +) for $C_{21}H_{15}$ $[M - Br]^+$ calculated: 267.11683 found: 267.11745.

[150] Bis(2-methylphenyl)methanol was prepared *via* Grignard reaction, see: Griffin, G.; Manmade, A. *J. Org. Chem.* **1972**, *37*, 2589.
[151] Bis(1-naphthyl)methanol was prepared *via* Grignard reaction, see: Bassas, O.; Huuskonen, J.; Rissanen, K.; Koskinen, A. M. P. *Eur. J. Org. Chem.* **2009**, 1340-1351.



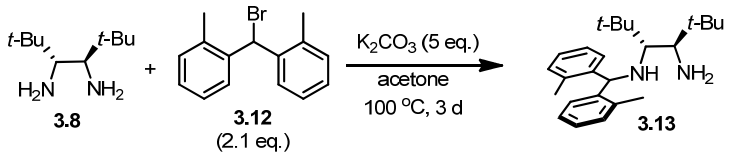

**Bis(2-naphthyl)methyl chloride (3.26):** Bis(2-naphthyl)methanol[152] (1.94 g, 7 mmol) was dissolved in benzene (20 mL). Thionyl chloride (0.75 mL, 10 mmol) was added slowly at room temperature and the solution was heated to reflux. The reaction was stirred at reflux overnight after which the reaction mixture was cooled and water was added. The aqueous layer was extracted twice with dichloromethane. The combined organic fractions were dried over sodium sulfate and filtered on basic alumina. The solvent was removed *in vacuo* to afford the product as a beige solid (1.64 g, 79 %). $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 7.94 (s, 2 H), 7.90 - 7.79 (m, 6 H), 7.61 - 7.47 (m, 6 H), 6.49 (s, 1 H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 138.1, 133.0, 132.9, 128.5, 128.2, 127.6, 126.7, 126.5, 126.5, 125.7, 64.8; HRMS (ESI +) for $C_{21}H_{15}$ $[M - Cl]^+$ calculated: 267.11683 found: 267.11699.




**Bis(1-pyenyl)methyl chloride (3.27):** In a flame dried flask under nitrogen, magnesium turnings (0.225 g, 9.3 mmol) were suspended in THF (15 mL) and a crystal of iodine was added. The suspension was refluxed until the colour dissipated, approximately 30 min. To the activated magnesium was added 1-bromopyrene (1.5 g, 5.3 mmol). The solution was refluxed for 2 h at which point ethyl formate (0.2 mL, 2.5 mmol) was added. The mixture was left at reflux for an additional 15 h. The reaction was removed from heat and allowed to cool to room temperature. The reaction was slowly quenched with saturated aqueous ammonium chloride. The mixture was filtered to remove excess magnesium and the product was extracted with 3 portions of dichloromethane. The combined organic fractions were dried over sodium sulfate and the solvent was removed *in vacuo* to give the crude product. The crude product was dissolved in toluene, addition of hexane yielded white crystals (0.53 g, 50 %). The product was carried on to the next step without further purification as degradation was observed over short periods of time (days). Bis(1-pyrenyl)methanol (2 g, 4.6 mmol) was dissolved in benzene (20 mL). Thionyl chloride (0.75 mL, 10 mmol) was added slowly at room temperature and the solution was heated to reflux. The reaction was stirred at reflux overnight after which the reaction mixture was cooled and water was added. The aqueous layer was extracted twice with dichloromethane. The combined organic fractions were dried over sodium sulfate and filtered on basic alumina. The solvent was removed *in vacuo* to afford the product as a brown solid (2.1 g, > 95 %). The product could not be sufficiently purified for characterization purposes and was typically used crude in the following alkylation step without additional purification. $^{1}$H NMR (400 MHz, $C_6D_6$) δ 8.75 – 8.22 (m, 5H), 8.20 – 7.62 (m, 14H).

[152] Bis(2-naphthyl)methanol was prepared *via* Grignard reaction, see: Park, B. S.; Lee, S. W.; Kim, I. T.; Tae, J. S.; Lee, S. H. *Heteroatom Chemistry* **2012**, *23*, 66-73.

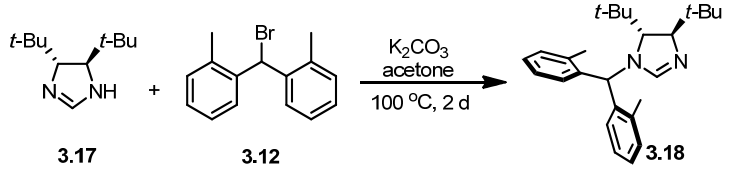
## 9.2.2 - Synthesis of Alkyl Diamine



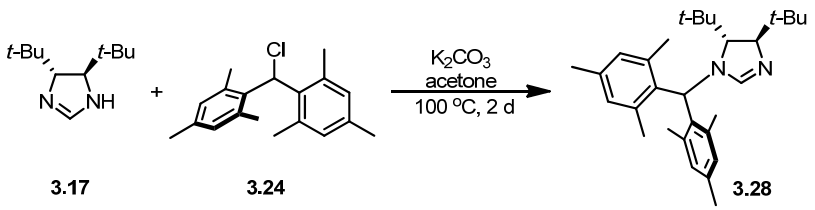

**(1R,2R)- 1,2-Di-*tert*-butyl-N-(bis(2-methylphenyl)methyl)ethylenediamine (3-13):** In a sealed tube was placed alkyl halide **3-10** (150 mg, 0.55 mmol), diamine **3-6** (45 mg, 0.26 mmol), and potassium carbonate (345 mg, 2.5 mmol). To the starting materials was added acetone (1.8 mL). The tube was sealed and placed in a 100 $^{o}$C oil bath for 2 days. The sealed tube was removed from the bath and allowed to return to room temperature. The solids were filtered off on Celite and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (4:1, Hexanes:EtOAc) to yield **3.11** (43 mg, 45 %) as a white solid. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 7.58 (d, *J* = 7.5 Hz, 1H), 7.31 (s, 1H), 7.25 - 7.18 (m, 2H), 7.18 - 7.03 (m, 4H), 6.96 (d, *J* = 6.4 Hz, 1H), 5.91 (s, 1H), 3.49 (dd, *J* = 4.5, 1.4 Hz, 1H), 3.33 (d, *J* = 4.5 Hz, 1H), 2.53 (s, 3H), 2.04 (s, 3H), 0.84 (s, 9H), 0.75 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.48, 140.14, 139.49, 135.20, 134.85, 130.83, 130.67, 128.55, 127.14, 126.31, 126.05, 76.93, 71.13, 59.16, 35.93, 34.00, 26.15, 20.51, 19.54; HRMS (ESI+) for $C_{25}H_{39}N_2$ [M+H$^+$] calculated: 367.3108 found: 367.3109.

## 9.2.3 - Synthesis of Alkyl Imidazolines

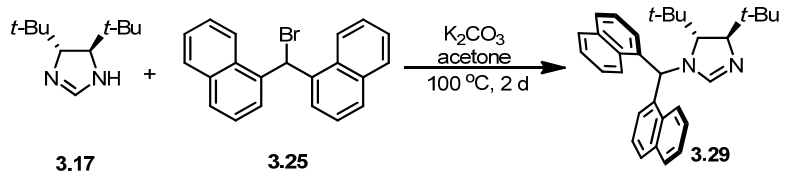
**General Procedure for the Mono-Alkylation of Imidazoline 3.17**



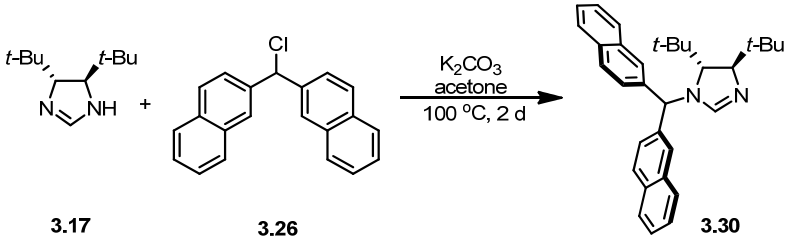

**(4*R*,5*R*)-4,5-Di-*tert*-butyl-1-(bis(2-methylphenyl)methyl)imidazoline (3.18):** In a sealed tube was placed imidazoline precursor **3.17** (1.0 g, 5.5 mmol), alkyl halide **3.12** (1.66 g, 6 mmol) and potassium carbonate (3.75 g, 27.1 mmol). To the mixture was added acetone (100 mL) and the tube was sealed and placed in a 100 $^{o}$C oil bath for 2 days. The tube was removed from the oil bath and cooled to room temperature. The solution was then diluted with ethyl acetate and filtered on Celite®. The solvent was removed *in vacuo* to yield a crude oil. The crude product was purified by column chromatography on silica gel (2:98, $NEt_3$: $Et_2O$) yielding compound **3.16** (0.93 g, 45 %) as a white solid. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 7.58 (d, *J* = 7.5 Hz, 1H), 7.31 (s, 1H), 7.25 - 7.18 (m, 2H), 7.18 - 7.03 (m, 4H), 6.96 (d, *J* = 6.4 Hz, 1H), 5.91 (s, 1H), 3.49 (dd, *J* = 4.5, 1.4 Hz, 1H), 3.33 (d, *J* = 4.5 Hz, 1H), 2.53 (s, 3H), 2.04 (s, 3H), 0.84 (s, 9H), 0.75 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.48, 140.14, 139.49, 135.20, 134.85, 130.83, 130.67, 128.55, 127.14, 126.31, 126.05, 76.93, 71.13, 59.16, 35.93, 34.00, 26.15, 20.51, 19.54; HRMS (ESI+) for $C_{26}H_{37}N_2$ [M+H$^+$] calculated: 377.2951 found: 377.2954.




**(4*R*,5*R*)-4,5-Di-*tert*-butyl-1-(bis(2,4,6-trimethylphenyl)methyl)imidazoline (3.28):** Was prepared from **3.15** using the general procedure. Dimesitylmethyl chloride **3.24** was synthesized following a procedure found in the literature.[153] The crude product was purified by column chromatography on silica gel (1:99, $NEt_3$: $Et_2O$) yielding compound **3.28** (71 mg, 62 %) as a beige solid. $^1$H NMR (400 MHz, $CDCl_3$) δ = 6.83 (d, *J* = 9.5 Hz, 2 H), 6.69 (s, 1 H), 6.73 (s, 1 H), 5.96 (s, 1 H), 3.62 - 3.57 (m, 1 H), 3.57 - 3.52 (m, 1 H), 2.70 (s, 3 H), 2.63 (s, 3 H), 2.24 (s, 3 H), 2.19 (s, 3 H), 1.99 (s, 3 H), 1.95 (s, 3 H), 1.44 (s, 1 H), 0.87 (s, 9 H), 0.78 (s, 9 H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 157.2, 136.7, 136.4, 136.3, 136.2, 136.0, 135.8, 132.6, 132.4, 130.5, 130.2, 76.0, 73.6, 61.5, 53.8, 35.6, 34.3, 29.3, 27.2, 26.6, 23.4, 23.4, 21.6, 21.3, 20.5, 20.5; HRMS (ESI+) for $C_{19}H_{23}$ [M-Imid$^+$] calculated: 251.17943 found: 251.18007.



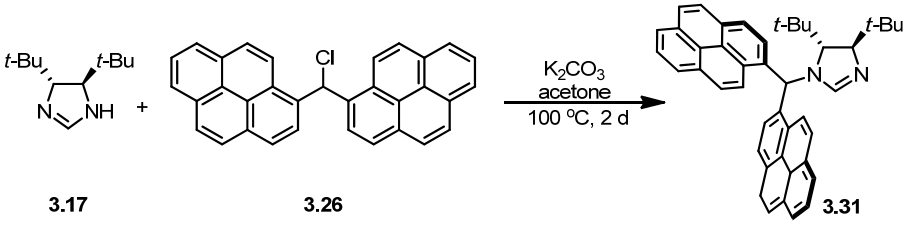

**(4*R*,5*R*)-4,5-Di-*tert*-butyl-1-(bis(1-naphthyl)methyl)imidazoline (3.29):** Was prepared from **3.17** using the general procedure. The crude product was purified by column chromatography on silica gel (2:98, $NEt_3$: $Et_2O$) yielding compound **3.29** (0.47 g, 40 %) as a beige solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 7.2 Hz, 1H), 7.88 (dd, *J* = 17.2, 8.4 Hz, 3H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.71 – 7.49 (m, 4H), 7.41 – 7.34 (m, *J* = 6.3, 5.2 Hz, 2H), 7.26 – 7.13 (m, 3H), 7.09 (d, *J* = 7.0 Hz, 1H), 3.56 (d, *J* = 4.4 Hz, 1H), 3.48 (d, *J* = 4.3 Hz, 1H), 0.91 (s, 9H), 0.42 (s, 9H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 153.79, 138.91, 137.68, 134.30, 133.97, 130.82, 130.72, 129.52, 128.87, 128.36, 128.15, 126.99, 126.45, 126.35, 125.82, 125.61, 125.58, 125.14, 125.11, 123.27, 122.72, 77.00, 71.27, 36.20, 33.77, 26.28, 25.78; HRMS (ESI+) for $C_{32}H_{37}N_2$ [M+H$^+$] calculated: 449.29513 found: 449.2958.




**(4*R*,5*R*)-4,5-Di-*tert*-butyl-1-(bis(2-naphthyl)methyl)imidazoline (3.30):** Was prepared from **3.17** using the general procedure. The crude product was purified by column chromatography on silica gel (2:98, $NEt_3$: $Et_2O$) yielding compound **3.28** (0.57 g, 46 %) as a beige solid. $^1$H NMR (400 MHz, $CDCl_3$) δ = 7.88 - 7.74 (m, 8 H), 7.56 - 7.47 (m, 5 H), 7.33 - 7.27 (m, 2 H), 5.94 (s, 1

[153] Nauta, W. T.; Wuis, P. J. *Rec. trav. chim.* **1937**, *56*, 535-540.

H), 3.54 (d, *J* = 3.2 Hz, 1 H), 3.19 (d, *J* = 4.6 Hz, 1 H), 1.08 (s, 9 H), 0.48 (s, 9 H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 152.6, 138.2, 137.7, 133.2, 133.1, 132.9, 132.5, 128.9, 128.6, 128.3, 128.1, 127.9, 127.7, 127.5, 126.7, 126.6, 126.4, 126.3, 126.2, 126.2, 125.8, 77.4, 68.6, 67.0, 36.5, 34.0, 26.6, 26.1; HRMS (ESI+) for $C_{32}H_{37}N_2$ [M+H$^+$] calculated: 449.29513 found: 449.29572.

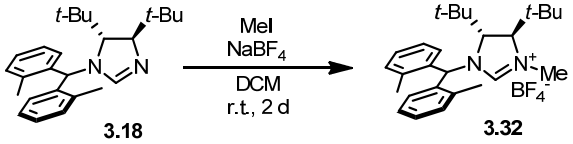



3.17 3.26 3.31

**(4*R*,5*R*)-4,5-Di-*tert*-butyl-1-(bis(1-pyrenyl)methyl)imidazoline (3.31):** Was prepared from **3.17** using the general procedure. The crude product was purified by column chromatography on silica gel (4:96, $NEt_3$: $Et_2O$) yielding compound **3.29** (0.41 g, 68 %) as a beige solid. $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.93 (d, *J* = 9.2 Hz, 1 H), 8.71 (d, *J* = 8.1 Hz, 1 H), 8.44 (d, *J* = 8.1 Hz, 2 H), 8.32 (d, *J* = 7.8 Hz, 1 H), 8.23 (d, *J* = 7.4 Hz, 1 H), 8.15 (d, *J* = 8.8 Hz, 2 H), 8.11 - 8.02 (m, 3 H), 8.00 - 7.88 (m, 5 H), 7.79 (s, 1 H), 7.73 (d, *J* = 9.2 Hz, 1 H), 7.69 - 7.62 (m, 2 H), 3.79 (d, *J* = 4.2 Hz, 1 H), 3.60 (d, *J* = 3.9 Hz, 1 H), 1.01 (s, 9 H), 0.50 (s, 9 H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 153.8, 136.9, 135.7, 131.4, 131.2, 130.9, 130.6, 130.5, 130.3, 129.0, 128.2, 127.9, 127.9, 127.6, 127.4, 127.4, 126.7, 126.1, 126.0, 125.8, 125.5, 125.3, 125.2, 125.2, 125.2, 125.1, 125.0, 124.7, 124.6, 122.3, 122.3, 77.2, 77.1, 71.7, 36.2, 33.9, 26.4, 25.9; HRMS (ESI+) for $C_{44}H_{41}N_2$ [M+H$^+$] calculated: 597.32643 found: 597.32594.

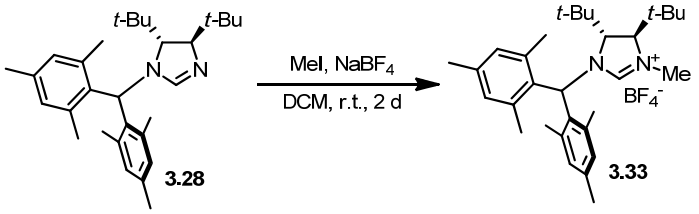
## 9.2.4 - Synthesis of Imidazolidinium Salts

### General Procedure for the Synthesis of Methyl Substituted Imidazolidinium Salts

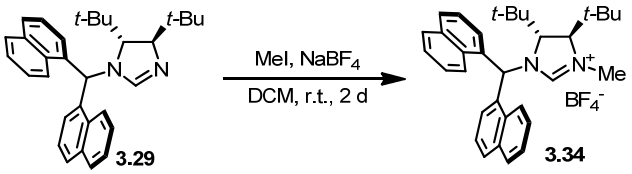



3.18 3.32

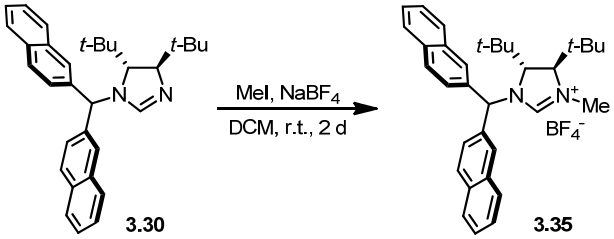
**(4*R*,5*R*)-4,5-Di-*tert*-butyl-3-methyl-1-(bis(2-methylphenyl)methyl)imidazolidinium fluoborate (3.32):** To a solution of imidazolinium salt **3.18** (430 mg, 1.14 mmol) in dichloromethane (10 mL) was added methyl iodide (0.21 mL, 3.42 mmol) and sodium tetrafluoroborate (625 mg, 5.7 mmol). The resulting suspension was stirred at room temperature for 2 days. The reaction mixture was filtered. Solvent and excess methyl iodide were removed *in vacuo* giving imidazolidinium salt **3.30** (543 mg, >95 %) as a yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ = 9.82 (s, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.64 - 7.54 (m, 2H), 7.34 (t, *J* = 6.7 Hz, 2H), 7.26 - 7.18 (m, 3H), 6.13 (s, 1H), 3.91 (d, *J* = 3.2 Hz, 1H), 3.79 (s, 3H), 3.66 (d, *J* = 3.9 Hz, 1H), 2.65 (s, 3H), 2.15 (s, 3H), 0.99 (s, 9H), 0.97 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 158.8, 136.7, 134.8, 134.2, 133.8, 131.3, 130.8, 129.3, 128.9, 128.5, 128.4, 127.7, 127.1, 75.7, 73.5, 61.6, 38.8, 35.8, 35.2, 26.3, 25.4, 20.3, 19.6; HRMS (ESI+) for $C_{27}H_{39}N_2$ [M$^+$] calculated: 391.3108 found: 391.3112.




**(4*R*,5*R*)-4,5-Di-*tert*-butyl-3-methyl-1-(bis(mesityl)methyl)imidazolidinium fluoborate (3.33):** Imidazolinium salt **3.33** was prepared following the general procedure. $^{1}$HNMR analysis of the reaction mixture showed **3.33** as the only identifiable product. Loading the product onto silica gel for purification resulted in decomposition of the product, with **3.28** as well as several unidentifiable products being isolated. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9 H), 1.14 (s, 9 H), 1.55 (s, 3 H), 2.23 (s, 3 H), 2.25 (s, 3 H), 2.46 (s, 3 H), 2.52 (s, 3 H), 2.92 (s, 3 H), 2.98 (s, 3 H), 3.80 (d, *J* = 5.65 Hz, 1 H), 3.83 (d, *J* = 5.65 Hz, 1 H), 6.22 (s, 1 H), 6.95 (s, 1 H), 7.01 (s, 1 H), 7.10 (s, 1 H), 7.12 (s, 1 H), 7.38 (s, 1 H).

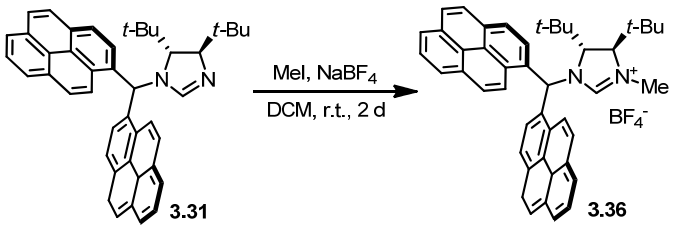



**(4*R*,5*R*)-4,5-Di-*tert*-butyl-3-methyl-1-(bis(1-naphthyl)methyl)imidazolidinium fluoborate (3.34):** Imidazolinium salt **3.34** was prepared following the general procedure. The product can be recrystallized from a mixture of dichloromethane and hexanes to yield a yellow solid (0.58 g, >95 %). $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 10.17 (s, 1 H), 8.49 (d, *J* = 7.4 Hz, 2 H), 7.96 - 7.81 (m, 5 H), 7.76 (t, *J* = 7.6 Hz, 2 H), 7.65 - 7.59 (m, 1 H), 7.48 - 7.41 (m, 2 H), 7.37 (t, *J* = 7.6 Hz, 1 H), 7.32 (s, 1 H), 7.23 - 7.16 (m, 1 H), 4.09 (d, *J* = 3.2 Hz, 1 H), 3.68 (s, 3 H), 3.50 (d, *J* = 3.2 Hz, 1 H), 0.95 (s, 9 H), 0.58 (s, 9 H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 159.8, 136.0, 134.0, 131.5, 130.1, 129.7, 129.6, 129.4, 129.2, 128.2, 127.8, 127.2, 127.0, 126.2, 126.0, 125.8, 121.8, 121.1, 77.9, 75.7, 73.9, 38.7, 36.0, 34.9, 25.9, 25.5; HRMS (ESI+) for $C_{33}H_{39}N_2$ [$M^+$] calculated: 463.31078 found: 463.30906.



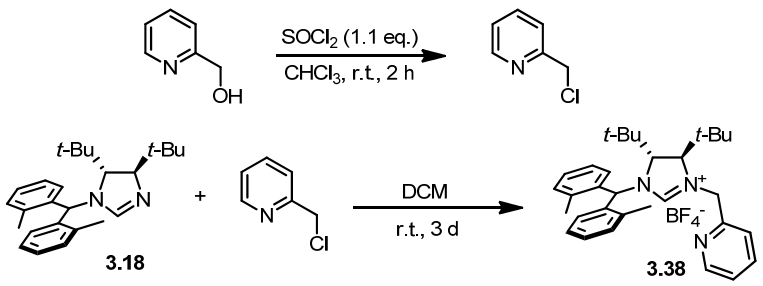

**(4*R*,5*R*)-4,5-Di-*tert*-butyl-3-methyl-1-(bis(2-naphthyl)methyl)imidazolidinium fluoborate (3.35):** Imidazolinium salt **3.35** was prepared following the general procedure. The product can be recrystallized from a mixture of dichloromethane and hexanes to yield **3.35** as a yellow solid (0.6 g, >95 %). $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 9.83 (s, 1 H), 8.24 (s, 2 H), 8.17 - 8.11 (m, 1 H), 8.04 - 7.97 (m, 1 H), 7.90 - 7.82 (m, 2 H), 7.81 - 7.74 (m, 3 H), 7.54 - 7.41 (m, 5 H), 6.28 (s, 1 H), 4.06 (d, *J* = 3.1 Hz, 1 H), 3.59 (s, 3 H), 3.50 (d, *J* = 3.1 Hz, 1 H), 1.07 (s, 9 H), 0.74 (s, 9 H);

$^{13}$C NMR (101 MHz, $CDCl_3$) δ = 158.2, 133.2, 133.1, 133.0, 132.8, 129.7, 129.3, 129.0, 128.5, 127.5, 127.3, 127.0, 126.7, 126.6, 126.0, 125.0, 105.5, 73.9, 73.7, 38.7, 36.0, 35.6, 26.2, 25.9; HRMS (ESI+) for $C_{33}H_{39}N_2$ [$M^+$] calculated: 463.31078 found: 463.31117.



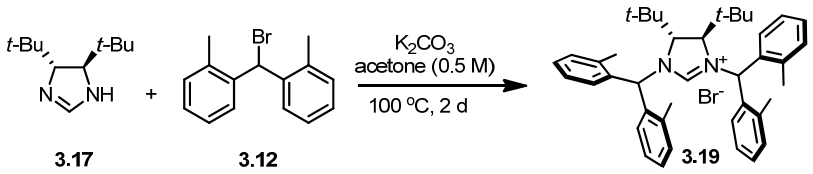

**(4*R*,5*R*)-4,5-Di-*tert*-butyl-3-methyl-1-(bis(1-pyrenyl)methyl)imidazolidinium fluoborate (3.36):** Imidazolinium salt **3.36** was prepared following the general procedure. The product can be recrystallized from a mixture of dichloromethane and hexanes to yield **3-36** as a yellow solid (0.35 g, 72 %). $^1$H NMR (400 MHz, $CDCl_3$) δ = 10.36 (s, 1 H), 9.20 (d, *J* = 8.1 Hz, 1 H), 9.12 (d, *J* = 9.2 Hz, 1 H), 8.66 - 8.56 (m, 2 H), 8.37 (d, *J* = 8.1 Hz, 1 H), 8.25 (d, *J* = 7.4 Hz, 1 H), 8.12 (d, *J* = 7.8 Hz, 1 H), 8.06 (d, *J* = 8.1 Hz, 1 H), 8.02 - 7.87 (m, 5 H), 7.85 - 7.79 (m, 1 H), 7.78 - 7.69 (m, 4 H), 7.64 (d, *J* = 9.2 Hz, 1 H), 4.47 (d, *J* = 2.8 Hz, 1 H), 3.67 (s, 3 H), 3.54 (d, *J* = 2.8 Hz, 1 H), 0.98 (s, 9 H), 0.58 (s, 9 H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 159.6, 133.4, 131.3, 131.1, 131.1, 130.8, 130.3, 130.2, 130.0, 129.8, 128.7, 128.2, 127.4, 127.2, 127.1, 127.1, 127.0, 126.6, 126.2, 126.2, 125.9, 125.7, 125.6, 125.6, 125.1, 125.0, 124.9, 124.7, 124.6, 124.0, 121.3, 120.8, 77.2, 76.0, 73.7, 38.5, 35.9, 35.1, 25.9, 25.5; HRMS (ESI+) for $C_{45}H_{43}N_2$ [$M^+$] calculated: 611.34208 found: 611.34397.


**(4*R*,5*R*)-3-Benzyl-4,5-di-*tert*-butyl-1-(bis(2-methylphenyl)methyl)imidazolidinium chloride (3.37):** In a sealed tube, imidazoline **3.18** (140 mg, 0.37 mmol) was dissolved in dichloromethane (6 mL), and benzyl chloride (0.3 mL, 2.6 mmol) was added. The tube was sealed, and was put in a 60 °C oil bath overnight. After cooling to room temperature, the reaction mixture was concentrated (~1 mL) and diethyl ether was added to precipitate the product **3.37** as an off-white solid (112 mg, 60 %). $^1$H NMR (400 MHz, $CDCl_3$) δ = 11.01 (d, *J* = 6.7 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.76 - 7.69 (m, 3H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.44 - 7.32 (m, 4H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.22 - 7.16 (m, 1H), 7.15 - 7.08 (m, 2H), 6.41 (dd, *J* = 14.1, 3.9 Hz, 1H), 5.98 (s, 1H), 4.45 (d, *J* = 14.1 Hz, 1H), 3.76 (d, *J* = 3.5 Hz, 1H), 3.45 (d, *J* = 3.5 Hz, 1H), 2.59 (s, 3H), 2.03 (s, 3H), 0.96 (s, 9H), 0.52 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 161.2, 136.9, 135.4, 133.1, 133.1, 131.0, 130.4, 130.4, 130.3, 130.3, 130.3, 129.1, 129.0, 128.8, 128.3, 127.7, 127.7, 126.8, 126.8, 76.0, 68.0, 61.4, 53.0, 35.7, 35.5, 26.9, 25.3, 20.3, 19.6; HRMS (ESI+) for $C_{33}H_{43}N_2$ [$M^+$] calculated: 467.3421 found: 467.3425.




**(4*R*,5*R*)-3-(2-Picolyl)-4,5-di-*tert*-butyl-1-(bis(2-methylphenyl)methyl)imidazolidinium chloride (3.38):** To a solution of 2-pyridinemethanol (1.1 mL, 104 mmol) in chloroform (500 mL), was added thionyl chloride (15 mL, 208 mmol). The solution was allowed to stir at room temperature for 2 h. Full consumption of the starting material was confirmed by thin layer chromatography. The solution was washed with aqueous sodium bicarbonate, dried over sodium sulfate and filtered on basic alumina. The solvent was removed *in vacuo* to yield 2-picolylchloride as a red oil (1 g, 75 %). In a round-bottom flask was added **3.18** (1 g, 2.6 mmol) and picolyl chloride (1 g, 7.8 mmol). 26 mL of anhydrous dichloromethane was added and the mixture was allowed to stir at room temperature for 3 days. Ether was added to precipitate the product which was collected via vacuum filtration to yield **3.38** as a red solid (400 mg, 30 %). Despite repeated attempts, silica gel chromatography (9:1; DCM:MeOH) could not fully remove trace impurities from the product. $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 10.24 (s, 1 H), 8.57 (d, *J* = 6.0 Hz, 1 H), 8.20 (d, *J* = 7.9 Hz, 1 H), 7.94 (d, *J* = 7.5 Hz, 1 H), 7.83 - 7.75 (m, 1 H), 7.57 - 7.48 (m, 2 H), 7.36 (s, 1 H), 7.29 (br. s., 2 H), 7.25 - 7.13 (m, 3 H), 6.05 (s, 1 H), 6.03 (d, *J* = 14.8 Hz, 1 H), 4.87 (d, *J* = 14.5 Hz, 1 H), 4.18 (d, *J* = 3.5 Hz, 1 H), 3.80 (d, *J* = 3.5 Hz, 1 H), 2.57 (s, 3 H), 2.08 (s, 3 H), 0.99 (s, 9 H), 0.62 (s, 9 H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 160.8, 153.8, 148.8, 138.0, 136.8, 135.4, 134.5, 133.8, 131.3, 130.8, 129.5, 129.0, 128.6, 128.5, 127.5, 126.8, 125.3, 123.6, 77.2, 75.8, 69.7, 61.4, 53.8, 35.8, 35.7, 26.6, 25.5, 20.2, 19.6; HRMS (ESI+) for $C_{32}H_{42}N_3$ [$M^+$] calculated: 468.3373 found: 468.3393.

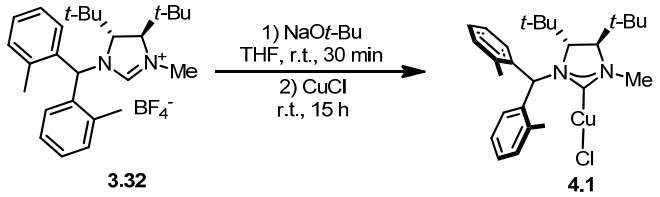
## 9.2.5 - Synthesis of $C_2$-Symmetric NHC Precursor




**(4*R*,5*R*)-4,5-Di-*tert*-butyl-bis-1,3-(bis(2-methylphenyl)methyl)imidazoline (3.19):** In an open sealed tube vessel was placed imidazoline precursor **3.17** (365 mg, 2 mmol), alkyl halide **3.12** (600 mg, 2.2 mmol) and potassium carbonate (1.8 g, 13 mmol). To the mixture was added acetone (5 mL) and the tube was sealed and placed in a 100 °C oil bath for 2 days. The tube was removed from the oil bath and cooled to room temperature. The tube was opened and the solution was then diluted with ethyl acetate and filtered on Celite®. The Celite was then flushed with an excess of dichloromethane. The DCM filtrate was treated with diethyl ether to precipitate the product **3.19** (700 mg, 88 %) as a white solid. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 7.05 - 6.99 (m, 4 H), 6.98 - 6.91 (m, 4 H), 6.91 - 6.85 (m, 4 H), 6.82 (d, *J* = 7.3 Hz, 2 H), 6.43 (d, *J* = 7.7 Hz, 2 H), 5.94 (s, 2 H), 3.99 (br. s., 2 H), 2.03 (br. s., 6 H), 1.76 (s, 6 H), 0.68 (s, 18 H);

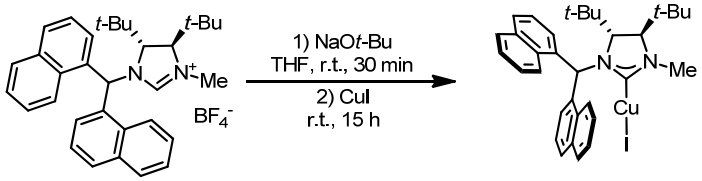
$^{13}$C NMR (101 MHz, $CDCl_3$) δ = 158.3, 135.0, 134.5, 134.0, 132.4, 131.4, 131.1, 128.7, 128.4, 126.3, 126.0, 125.5, 73.9, 34.8, 25.8, 19.2, 18.6; HRMS (ESI+) for $C_{41}H_{51}N_2$ [$M^+$] calculated: 571.4047 found: 571.4060.

## 9.2.6 - Synthesis of Transition Metal Complexes



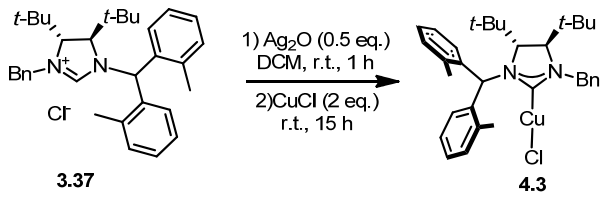

3.32 4.1

**(4*R*,5*R*)-4,5-Di-*tert*-butyl-1-(bis(2-methylphenyl)methyl)-3-methylimidazolidin-2-ylidene copper(I) chloride (4.1):** In a flame dried flask under nitrogen, imidazolidinium salt **3.32** (400 mg, 0.84 mmol) and sodium *tert*-butoxide (90 mg, 0.93 mmol) were suspended in THF (8.4 mL) and stirred at room temperature for 30 minutes. Copper (I) chloride (164 mg, 1.64 mmol) was then added and the reaction mixture stirred overnight. The crude mixture was filtered on Celite® and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography on silica gel (2:98, MeOH:$CH_2Cl_2$) to yield the product **4.1** as a white solid (250 mg, 60 %). Diffraction quality crystals were grown *via* vapour diffusion of pentane into a saturated solution in DCM. $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.26 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 7.4 Hz, 1H), 7.48 (m, 1H), 7.40 - 7.18 (m, 5 H), 6.11 (s, 1H), 3.74 (d, *J* = 3.2 Hz, 1H), 3.54 (s, 3H), 3.31 (d, *J* = 3.2 Hz, 1H), 2.63 (s, 3H), 2.16 (s, 3H), 1.02 (s, 9H), 0.98 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 139.6, 138.2, 134.2, 131.4, 130.4, 128.8, 128.1, 127.9, 127.9, 127.6, 126.6, 76.4, 73.8, 61.2, 40.7, 35.3, 34.7, 27.3, 26.1, 20.4, 19.6; HRMS (ESI+) for $C_{27}H_{38}CuN_2$ [M-Cl]$^+$ calculated: 453.2325 found: 453.2334.

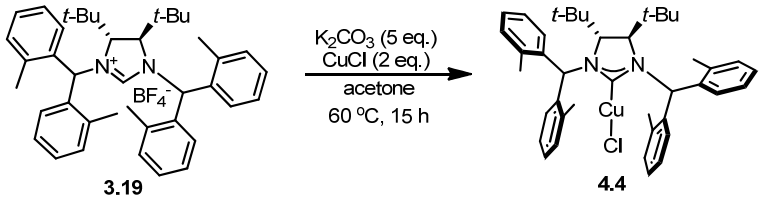



3.34 4.2b

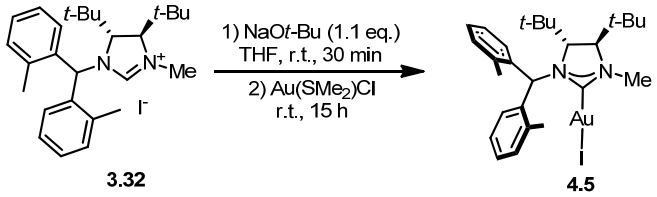
**(4*R*,5*R*)-4,5-Di-*tert*-butyl-3-methyl-1-(bis(1-naphthyl)methyl)imidazolidin-2-ylidene copper(I) chloride (4.2b):** Complex **4.2b** was prepared from imidazolium **3.34** using the same procedure as for **4.1**. The resulting residue was purified by column chromatography on silica gel (2:98, MeOH:$CH_2Cl_2$) to yield the product **4.2b** as a white solid (15 mg, 42 %). Diffraction quality crystals were grown *via* vapour diffusion of pentane into a saturated solution in DCM. $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.71 (d, *J* = 7.2 Hz, 1 H), 8.47 (d, *J* = 8.6 Hz, 1 H), 7.95 - 7.89 (m, 4 H), 7.86 (d, *J* = 7.9 Hz, 1 H), 7.72 (m, 3 H), 7.62 - 7.55 (m, 1 H), 7.45 (d, *J* = 8.6 Hz, 1 H), 7.37 (t, *J* = 7.7 Hz, 2 H), 7.22 - 7.14 (m, 2 H), 3.91 (d, *J* = 3.1 Hz, 1 H), 3.36 (s, 3 H), 3.17 (d, *J* = 3.1 Hz, 1 H), 0.88 (s, 9 H), 0.58 (s, 9 H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 139.1, 135.5, 134.1, 134.1, 130.6, 130.2, 129.9, 129.1, 129.0, 128.8, 127.5, 127.5, 127.0, 126.6, 125.9, 125.8, 125.6, 125.2, 122.6, 122.4, 76.6, 74.0, 60.1, 40.6, 35.6, 34.4, 26.9, 26.1; HRMS (ESI+) for $C_{33}H_{38}CuN_2$ [M-Cl]$^+$ calculated: 525.2326 found: 525.2339.



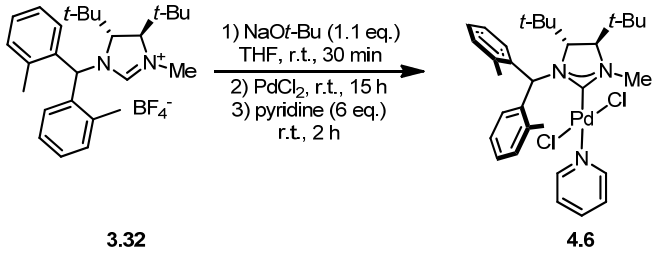

**(4*R*,5*R*)-3-Benzyl-4,5-di-*tert*-butyl-1-(bis(2-methylphenyl)methyl)imidazolidin-2-ylidene copper(I) chloride (4.3):** In a flame dried flask under nitrogen, imidazolidinium **3.37** (200 mg, 0.4 mmol) and silver oxide (47 mg, 0.2 mmol) were suspended in dichloromethane (4 mL). The mixture was stirred at room temperature for 1 h. Copper (I) chloride (56 mg, 0.8 mmol) was added and the reaction was stirred at room temperature overnight. The solution was then filtered on Celite® and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel (2:98, MeOH:$CH_2Cl_2$) to yield the product **4.3** as an off-white solid (22.3 mg, 60 %). $^1$H NMR (300 MHz, $CDCl_3$) δ = 8.02 (d, *J* = 7.3 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.53 - 7.47 (m, 2H), 7.41 - 7.29 (m, 4H), 7.29 - 7.10 (m, 5H), 5.97 (s, 1H), 5.59 (d, *J* = 14.3 Hz, 1H), 4.56 (d, *J* = 14.7 Hz, 1H), 3.64 (d, *J* = 3.5 Hz, 1H), 3.27 (d, *J* = 3.5 Hz, 1H), 2.47 (s, 3H), 2.05 (s, 3H), 1.00 (s, 9H), 0.54 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 139.19, 137.96, 135.32, 134.31, 133.72, 131.35, 130.54, 129.44, 129.40, 129.30, 128.68, 128.34, 128.30, 128.17, 127.98, 127.88, 127.72, 126.67, 69.22, 63.11, 61.29, 56.77, 28.24, 27.27, 26.29, 25.82, 20.38, 19.69; HRMS (ESI+) for $C_{33}H_{42}CuN_2$ $[M\text{-}Cl]^+$ calculated: 529.2638 found: 529.2638.




**(4*R*,5*R*)-4,5-Di-*tert*-butyl-1,3-bis(bis(2-methylphenyl)methyl)imidazolidin-2-ylidene copper(I) chloride (4.4):** In an open oven-dried sealed tube vessel under nitrogen, imidazolidinium salt **3.19** (150 mg, 0.23 mmol), copper (I) chloride (45 mg, 0.46 mmol), and potassium carbonate (138 mg, 1.1 mmol) were suspended in degassed acetone (3 mL). The tube was then sealed and the mixture was stirred at 60 °C overnight. The tube was removed from oil bath and allowed to cool. The vessel was opened and the crude mixture was then filtered on Celite® and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography on silica gel (5:95, MeOH:$CH_2Cl_2$) to yield the product **4.1** as a white solid (76 mg, 49 %). $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.11 (br. s., 2 H), 7.97 (d, *J* = 4.0 Hz, 2 H), 7.33 - 7.28 (m, 2 H), 7.25 - 7.11 (m, 8 H), 7.09 - 7.02 (m, 2 H), 6.05 (s, 2 H), 3.64 (s, 2 H), 2.60 (s, 6 H), 1.85 (s, 6 H), 0.81 (s, 18 H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 139.7, 137.6, 135.0, 134.1, 131.1, 130.4, 130.2, 128.1, 127.9, 127.8, 126.1, 75.3, 62.6, 35.6, 26.7, 20.9, 19.8; HRMS (ESI+) for $C_{41}H_{50}ClCuN_2Na$ $[M+Na]^+$ calculated: 691.2851 found: 691.2854.

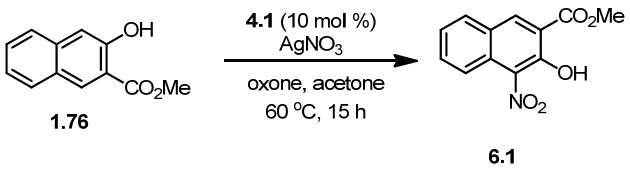



**(4*R*,5*R*)-4,5-Di-*tert*-butyl-1-(bis(2-methylphenyl)methyl)-3-methylimidazolidin-2-ylidene gold(I) iodide (4.1):** In a flame dried flask under nitrogen, imidazolidinium salt **3.32** (81 mg, 0.16 mmol) and sodium *tert*-butoxide (18 mg, 0.19 mmol) were suspended in THF (1.6 mL) and stirred at room temperature for 30 minutes. (Dimethylsulfide)gold(I) chloride (50 mg, 0.16 mmol) was then added and the reaction mixture stirred overnight. The crude mixture was filtered on Celite® and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography on silica gel ($CH_2Cl_2$) to yield the product **4.5** as a white solid (14 mg, 20 %). $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.46 (d, *J* = 7.7 Hz, 1 H), 7.93 (d, *J* = 7.3 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.27 - 7.21 (m, 1 H), 7.18 - 7.04 (m, 4 H), 5.93 (s, 1 H), 3.69 (d, *J* = 2.9 Hz, 1 H), 3.44 (s, 3 H), 3.22 (d, *J* = 2.9 Hz, 1 H), 2.58 (s, 3 H), 1.87 (s, 3 H), 0.90 (s, 8 H), 0.87 (s, 8 H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 204.2, 138.4, 138.3, 135.0, 131.7, 131.0, 129.9, 128.3, 128.2, 127.7, 127.6, 126.0, 77.2, 73.3, 40.9, 35.5, 34.8, 27.2, 25.9, 21.0, 19.6; HRMS (ESI+) for $C_{27}H_{38}AuN_2\,C_2H_3N$ $[M\text{-}Cl+ACN]^+$ calculated: 628.2961 found: 628.2953.



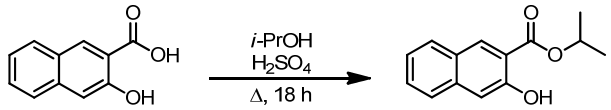

**Pyridine(4*R*,5*R*)-4,5-di-*tert*-butyl-1-(bis(2-methylphenyl)methyl)-3-methylimidazolidin-2-ylidene palladium(II) chloride (4.6):** In a flame dried flask under nitrogen, imidazolidinium salt **3.30** (50 mg, 0.1 mmol) and sodium *tert*-butoxide (12 mg, 0.11 mmol) were suspended in THF (2 mL) and stirred at room temperature for 30 minutes. Palladium(II) chloride (18.4 mg, 0.1 mmol) was then added and the reaction mixture stirred overnight. Then pyridine (48 μL, 0.6 mmol) was added, and the reaction mixture was stirred a further 2 hours. Ether was added to precipitate left over starting material, the crude mixture was filtered on Celite®, and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography on silica gel ($CH_2Cl_2$) to yield the product **4.6** as a yellow solid (12 mg, 18 %). $^1$H NMR (400 MHz, $CDCl_3$) δ = 8.42 (d, *J* = 4.8 Hz, 2 H), 8.36 (d, *J* = 7.5 Hz, 1 H), 7.75 (d, *J* = 8.1 Hz, 1 H), 7.60 - 7.53 (m, 1 H), 7.42 - 7.34 (m, 1 H), 7.26 - 7.17 (m, 3 H), 7.15 - 6.99 (m, 4 H), 6.58 (s, 1 H), 3.84 (s, 3 H), 3.44 - 3.38 (m, 2 H), 2.82 (s, 3 H), 2.00 (s, 3 H), 1.15 (d, *J* = 7.7 Hz, 18 H); MS (ESI+) for $C_{31}H_{50}ClN_2O_2Pd$ $[M\text{-}Cl + H_2O + OtBu]^+$ calculated: 623.26 found: 623.29.

## 9.2.7 - Isolation of Naphthyl Impurity

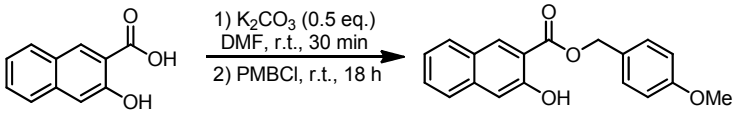



**Methyl 2-Hydroxy-1-nitro-3-naphthoate (6.1):** In an open sealed-tube vessel equipped with a stir bar, methyl 3-hydroxy-2-naphthoate (21 mg, 0.1 mmol), copper catalyst **4.1** (5 mg, 0.01 mmol), silver nitrate (17 mg, 0.1 mmol) and oxone (35 mg, 0.11 mmol) were suspended in acetone (1 mL). The tube was sealed and the mixture was stirred at 60 °C overnight. The reaction mixture was then cooled to room temperature, the vessel was opened, silica gel was added and the residual solvent was removed *in vacuo*. The resulting solid was purified by column chromatography on silica gel (20 % EtOAc: Hexanes) affording the product **6.1** as a bright yellow solid (13 mg, 53 %). Diffraction quality crystals were obtained by slow evaporation of an acetone solution of naphthol **6.1**. $^{1}$H NMR (500 MHz ,$CDCl_3$) δ = 11.26 (s, 1 H), 8.63 (s, 1 H), 7.90 (d, *J* = 8.3 Hz, 1 H), 7.77 - 7.69 (m, 2 H), 7.49 (ddd, *J* = 1.5, 6.6, 8.2 Hz, 1 H), 4.09 (s, 3 H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 169.2, 149.0, 135.0, 132.0, 129.7, 128.8, 126.1, 125.6, 120.6, 114.2, 53.3; HRMS (ESI+) for $C_{12}H_{10}NO_5$ $[M+H]^+$ calculated: 248.0554 found: 248.0335.

## 9.2.8 - Synthesis of Substituted 2-Napthols



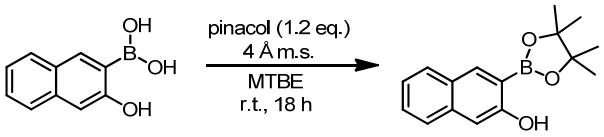

**Isopropyl 3-Hydroxy-2-naphthoate (6.3):** In a 250 mL round-bottom flask equipped with a stir bar, 3-hydroxy-2-naphthoic acid (2.0 g, 10.6 mmol) was dissolved in 2-propanol (100 mL). A few drops of sulfuric acid were added after which a reflux condenser was fitted and the flask was put in a hot oil bath to reflux overnight. The reaction mixture was then cooled to room temperature and silica gel was added and the residual solvent was removed *in vacuo*. The resulting solid was purified by column chromatography on silica gel (10 % EtOAc: Hexanes) to give the product **6.3** as a yellow solid (1.35 g, 55 %). $^{1}$H NMR (400 MHz ,$CDCl_3$) δ = 10.64 (s, 1H), 8.49 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.50 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.37 - 7.29 (m, 2H), 5.38 (spt, *J* = 6.3 Hz, 1H), 1.47 (d, *J* = 6.2 Hz, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ = 169.5, 156.5, 137.8, 132.2, 129.2, 129.0, 127.0, 126.3, 123.8, 114.8, 111.6, 69.7, 21.9; HRMS (ESI+) for $C_{14}H_{15}O_3$ $[M+H]^+$ calculated: 231.1016 found: 231.1022.




**4-Methoxyphenylmethyl 3-Hydroxy-2-naphthoate (6.7):** In a 250 mL round-bottom flask equipped with a stir bar, 3-hydroxy-2-naphthoic acid (0.5 g, 2.7 mmol) and potassium carbonate (184 mg, 1.3 mmol) were dissolved in DMF (25 mL). The resultant solution was stirred at room

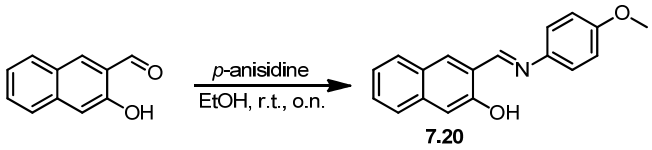
temperature for 30 minutes. To the flask was added 4-methoxybenzyl choride (0.36 mL, 2.7 mmol), and the solution was stirred at room temperature overnight. Water was added and the mixture was extracted 3x with ethyl acetate. The organic fractions were dried over sodium sulfate and the solvent removed *in-vacuo*. The resultant oil was purified by column chromatography on silica gel (10 % EtOAc: Hexanes) to give the product **6.7** as a yellow solid (308 mg, 37 %). $^{1}$H NMR (400 MHz, Acetone) δ 11.29 (s, 1H), 8.60 (s, 1H), 8.05 – 7.86 (m, 3H), 7.57 – 7.44 (m, 1H), 7.35 (ddd, *J* = 8.0, 6.8, 0.9 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 3H), 6.77 (d, *J* = 8.7 Hz, 3H), 4.42 (s, 3H), 3.69 (s, 6H); $^{13}$C NMR (75 MHz, Acetone) δ 172.93, 158.82, 155.15, 137.47, 133.66, 132.58, 131.08, 130.08, 128.14, 124.40, 124.27, 121.77, 114.63, 114.47, 55.34; Unfortunately mass-spec data does not closely agree with the calculated values (diff = 35 ppm), HRMS (ESI+) for $C_{19}H_{17}O_4Na$ $[M+Na]^+$ calculated: 331.0941 found: 331.0824.


**Pentafluorophenylmethyl 3-Hydroxy-2-naphthoate (6.6):** In a 250 mL round-bottom flask equipped with a stir bar, 3-hydroxy-2-naphthoic acid (0.5 g, 2.7 mmol) and potassium carbonate (184 mg, 1.3 mmol) were dissolved in DMF (25 mL). The resultant solution was stirred at room temperature for 30 minutes. To the flask was added pentafluorobenzyl bromide (0.4 mL, 2.7 mmol), and the solution was stirred at room temperature overnight. Water was added and the mixture was extracted 3x with ethyl acetate. The organic fractions were dried over sodium sulfate and the solvent removed *in-vacuo*. The resultant oil was purified by column chromatography on silica gel (10 % EtOAc: Hexanes) to give the product **6.6** as a yellow solid (715 mg, 72 %). $^{1}$H NMR (400 MHz ,$CDCl_3$) δ = 10.15 (s, 1 H), 8.43 (s, 1 H), 7.79 (d, *J* = 8.1 Hz, 1 H), 7.69 (d, *J* = 8.6 Hz, 1 H), 7.51 (ddd, *J* = 1.3, 6.9, 8.3 Hz, 1 H), 7.35 - 7.30 (m, 2 H), 5.59 - 5.51 (m, 2 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ = 169.1, 156.2, 138.1, 132.6, 129.5, 129.2, 127.0, 126.3, 124.1, 113.3, 111.9, 54.2; $^{19}$F NMR (471 MHz, $CDCl_3$) δ -141.35 (dd, *J* = 21.3, 7.8 Hz), -151.51 (t, *J* = 20.8 Hz), -160.43 – -161.47 (m); HRMS (ESI+) for $C_{14}H_{15}O_3$ $[M+H]^+$ calculated: 369.0545 found: 369.0556.




**(3-Hydroxy-2-naphthyl)pincolatoboronate (7.18):** In a round-bottom flask equipped with a stir bar boronic acid **7.17** (200 mg, 1.1 mmol) and pinacol (151 mg, 1.3 mmol) were suspended in methyl t-butyl ether. Activated 4 Å molecular sieves were added and the suspension was stirred at room temperature overnight. The mixture was filtered, silica gel was added and the residual solvent was removed *in vacuo*. The resulting solid was purified by column chromatography on silica gel (20 % EtOAc: Hexanes) to give the product **7.18** as a yellow solid (113 mg, 38 %). Spectral data agreed with those found in the literature.[154]

[154] Sumida, Y.; Kato, T.; Hosoya, T. *Org. Lett.* **2013**, *15*, 2806.

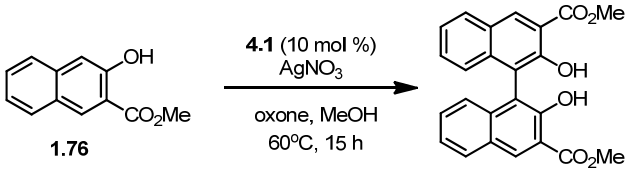



7.20

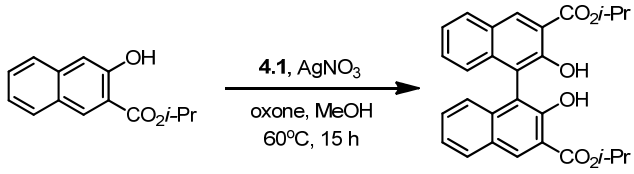
**4-Methoxyphenyl 2-Hydroxynaphthalene-3-carboxyimine (7.20):** In a round-bottom flask equipped with a stir bar, 2-naphthol-3-carboxaldehyde (50 mg, 0.3 mmol) and p-anisidine (36 mg, 0.3 mmol) were dissolved in ethanol (0.7 mL). The solution was allowed to stir overnight at room temperature after which the product **7.20** precipitated as a bright yellow solid (61 mg, 76 %). $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ = 8.88 (s, 1 H), 8.06 (br. s., 1 H), 7.80 (d, $J$ = 8.6 Hz, 1 H), 7.67 (d, $J$ = 8.2 Hz, 1 H), 7.47 (t, $J$ = 7.5 Hz, 1 H), 7.43 - 7.35 (m, 3 H), 7.31 (t, $J$ = 7.4 Hz, 1 H), 6.98 (d, $J$ = 8.8 Hz, 2 H), 3.88 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ = 160.1, 159.1, 156.7, 141.2, 136.1, 133.8, 128.4, 128.3, 127.5, 126.4, 123.5, 122.4, 121.7, 114.7, 111.1, 55.5; HRMS (ESI+) for $C_{18}H_{16}NO_2$ $[M+H]^+$ calculated: 278.1176 found: 278.1175.

## 9.2.9 - Synthesis of $C_2$-Symmetric BINOLs

### General Procedure for the Homocoupling of 2-Naphthols



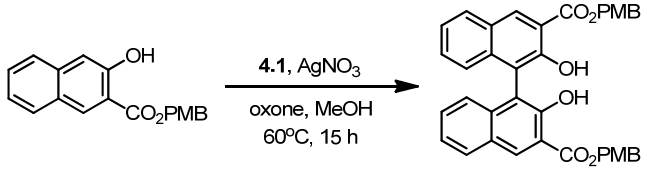

In a sealed tube, naphthol ester **1.76** (20.8 mg, 0.1 mmol), catalyst **4.1** (5 mg, 0.01 mmol), silver (I) nitrate (17.4 mg, 0.1 mmol) and Oxone® (34.6 mg, 0.11 mg) were added to methanol (1 mL). The tube was placed in a 60 °C oil bath and stirred overnight. The tube was removed from the bath and allowed to cool to room temperature. After cooling, silica gel was added and the solvent was removed in vacuo. The crude solid was purified by flash chromatography on silica gel (1:9, EtOAc:Hexanes) to give the product **5.29** as a yellow solid (15.7 mg, 76 %). Spectral data for the compound agreed with that found in the literature.[155]



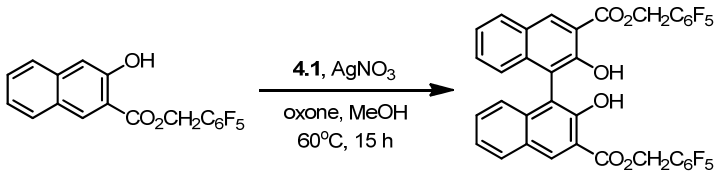

**Diisopropyl 2,2'-Dihydroxy-1,1'-binaphthyl-3,3'-dicarboxylate (6.8):** Prepared following the general procedure for the oxidative coupling. The product was purified by flash chromatography on silica gel (1:9, EtOAc:Hexanes) to yield **6.8** as an off-white solid (8 mg, 32 %). $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ = 10.92 (s, 2H), 8.68 (s, 2H), 7.97 - 7.90 (m, 2H), 7.39 - 7.30 (m, 4H), 7.20 - 7.13 (m, 2H), 5.40 (spt, $J$ = 6.2 Hz, 2H), 1.49 (dd, $J$ = 8.3, 6.3 Hz, 12H); $^{13}$C NMR (101 MHz

[155] Wang, K.; Hu, Y.; Li, Z.; Wu, M.; Liu, Z.; Su, B.; Yu, A.; Liu, Y.; Wang, Q. *Synthesis*, **2010**, 1083.

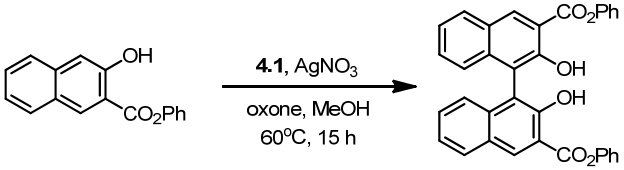
,$CDCl_3$) δ = 169.7, 154.2, 137.1, 132.6, 129.7, 129.3, 127.1, 124.7, 123.8, 116.9, 114.7, 69.8, 21.9; HRMS (ESI+) for $C_{28}H_{27}O_6$ $[M+H]^+$ calculated: 459.1802 found: 459.1817.




**Bis(4-methyoxybenzyl) 2,2'-Dihydroxy-1,1'-binaphthyl-3,3'-dicarboxylate (6.11):** Prepared following the general procedure for the oxidative coupling. The product was purified by flash chromatography on silica gel (2:8, EtOAc:Hexanes) to yield **6.11** as a yellow solid (5 mg, 17 %). $^1$H NMR (400 MHz, $CDCl_3$) δ = 10.73 (s, 2 H), 8.69 (s, 2 H), 7.98 - 7.86 (m, 2 H), 7.51 - 7.43 (m, 4 H), 7.37 - 7.30 (m, 4 H), 7.17 - 7.11 (m, 2 H), 7.02 - 6.95 (m, 4 H), 5.43 (s, 4 H), 3.86 (s, 6 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.99, 154.08, 137.86, 132.91, 130.50, 129.76, 129.41, 127.28, 127.15, 124.66, 123.91, 114.27, 114.14, 67.34, 55.35; HRMS (ESI+) for $C_{38}H_{30}AgO_8$ $[M+Ag]^+$ calculated: 721.0986 found: 721.0952.



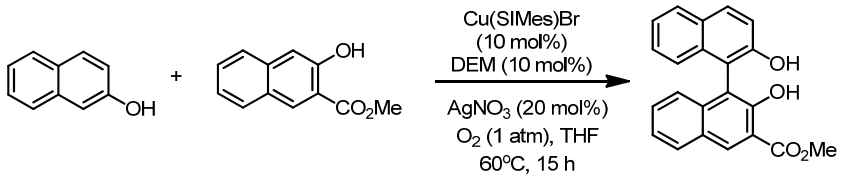

**Bis(pentafluorobenzyl) 2,2'-Dihydroxy-1,1'-binaphthyl-3,3'-dicarboxylate (6.10):** Prepared following the general procedure for the oxidative coupling. The product was purified by flash chromatography on silica gel (1:9, EtOAc:Hexanes) to yield **6.10** as a yellow solid (5 mg, 13 %). $^1$H NMR (400 MHz, $CDCl_3$) δ = 10.40 (s, 2 H), 8.62 (s, 2 H), 7.95 - 7.86 (m, 2 H), 7.39 - 7.31 (m, 4 H), 7.19 - 7.10 (m, 2 H), 5.58 (s, 4 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.31, 153.88, 137.40, 133.12, 129.85, 129.81, 127.14, 124.65, 124.17, 117.07, 113.35, 54.39; $^{19}$F NMR (471 MHz, $CDCl_3$) δ -141.25 (d, *J* = 14.2 Hz), -151.48 (t, *J* = 21.6 Hz), -160.96 (dd, *J* = 20.6, 13.0 Hz); HRMS (ESI+) for $C_{36}H_{17}F_{10}O_6$ $[M+H]^+$ calculated: 735.0860 found: 735.0843.



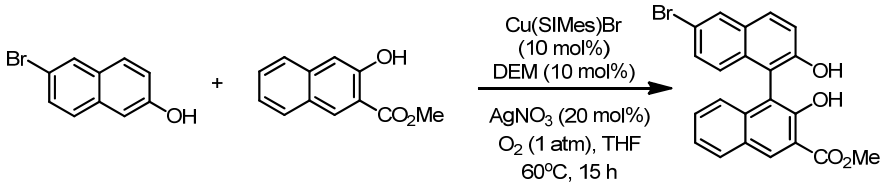

**Diphenyl 2,2'-Dihydroxy-1,1'-binaphthyl-3,3'-dicarboxylate (6.12):** Prepared following the general procedure for the oxidative coupling. The product was purified by flash chromatography on silica gel (1:9, EtOAc:Hexanes) to yield **6.12** as an off-white solid (8 mg, 31 %). $^1$H NMR (400 MHz, $CDCl_3$) δ = 10.45 (s, 2 H), 8.97 (s, 2 H), 8.04 - 7.97 (m, 2 H), 7.56 - 7.46 (m, 4 H), 7.44 - 7.39 (m, 4 H), 7.39 - 7.33 (m, 2 H), 7.31 (d, *J* = 7.5 Hz, 4 H), 7.24 (d, *J* = 9.5 Hz, 2 H); $^{13}$C NMR (101 MHz ,$CDCl_3$) δ = 168.9, 154.2, 150.2, 137.6, 133.7, 130.0, 129.9, 129.8, 127.3, 126.5, 124.7, 124.3, 121.7, 117.2, 113.6; HRMS (ESI+) for $C_{34}H_{23}O_6$ $[M+H]^+$ calculated: 527.1489 found: 527.1489.

## 9.2.10 - Synthesis of $C_1$-Symmetric BINOLs

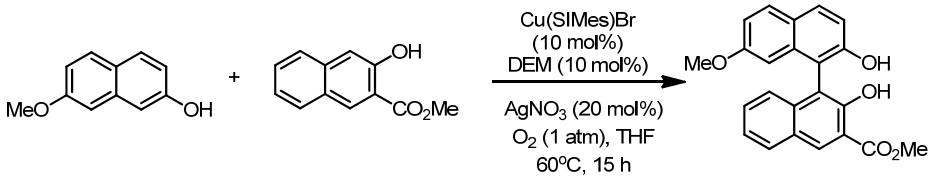
**General Procedure for Oxidative Heterocoupling of 2-Naphthols**:



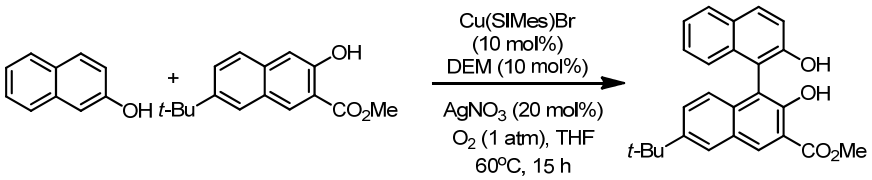

In a sealed-tube was added the 2-naphthol **1.77** (16.1 mg, 0.111 mmol), methyl-2-hydroxy-3-naphthoate **1.76** (22.5 mg, 0.111 mmol), silver nitrate (4.0 mg, 0.022 mmol), diethylmalonate (0.1 mL of 0.1 M solution in THF, 0.011 mmol), and Cu(SIMes)Br (5.0 mg, 0.011 mmol) and dissolved in THF (1.1 mL). Upon dissolution, the solution had oxygen bubbled through it under sonication for 5 min. The reaction was then capped and stirred for 15 h in a 60 $^{o}$C oil bath. The reaction was removed from the oil bath and allowed to cool to room temperature. The tube was opened, the cap rinsed with ethyl acetate and the stir-bar removed. Silica gel was added to the crude reaction mixture and the solvent was then removed *in vacuo*. The resulting solid is purified by flash chromatography on silica gel (20 % EtOAc/Hexanes) to give the product **1.78** (30.2 mg, 79%) as a yellow solid. NMR data of this compound matched that previously reported in the literature.[122]



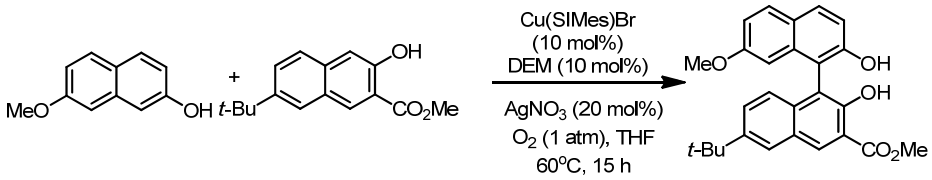

**Methyl 6'-Bromo-2,2'-dihydroxy-1,1'-binaphthyl-3-carboxylate (7.30):** Prepared following the general procedure for the oxidative coupling. The product was purified by flash chromatography on silica gel (20% EtOAc/Hexanes) to afford the product **7.30** (27.4 mg, 58 %) as a yellow solid. NMR data for this compound matched that found in the literature.[66]



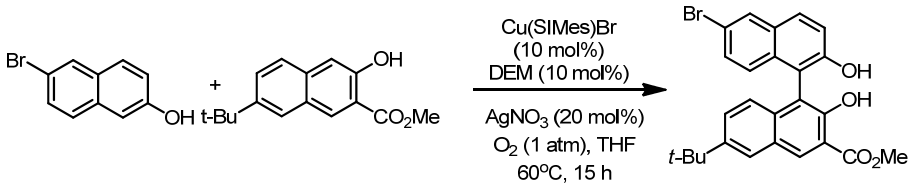

**Methyl 6'-Bromo-2,2'-dihydroxy-1,1'-binaphthyl-3-carboxylate (7.31):** Prepared following the general procedure for the oxidative coupling. The product was purified by flash chromatography on silica gel (20% EtOAc/Hexanes) to afford the product **7.31** (31.3 mg, 75 %) as a yellow solid. NMR data for this compound matched that found in the literature.[66]




**Methyl 6-*tert*-Butyl-2,2'-dihydroxy-1,1'-binaphthyl-3-carboxylate (7.32):** Prepared following the general procedure for the oxidative coupling. The product was purified by flash chromatography on silica gel (20% EtOAc/Hexanes) to afford the product **7.32** (32.2 mg, 72 %) as a yellow solid. $^{1}$H NMR (400MHz ,$CDCl_3$) δ = 10.79 (s, 1H), 8.73 (s, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 7.90 - 7.84 (m, 2H), 7.49 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.34 (ddd, *J* = 8.0, 6.9, 1.3 Hz, 1H), 7.26 (td, *J* = 7.6, 1.3 Hz, 1H), 7.14 (m, 2H), 4.98 (s, 1H), 4.08 (s, 3H), 1.39 (s, 9H); $^{13}$C NMR (101MHz, $CDCl_3$): δ = 170.4, 154.6, 151.3, 147.2, 135.6, 133.8, 133.5, 130.2, 129.4, 129.2, 128.2, 127.3, 126.6, 124.6, 124.6, 124.5, 123.4, 117.6, 114.1, 114.1, 114.0, 52.8, 34.6, 31.0 ppm; HRMS (ESI+) for $C_{26}H_{25}O_4$ $[M + H]^+$ calculated: 401.1747, found: 401.1728.

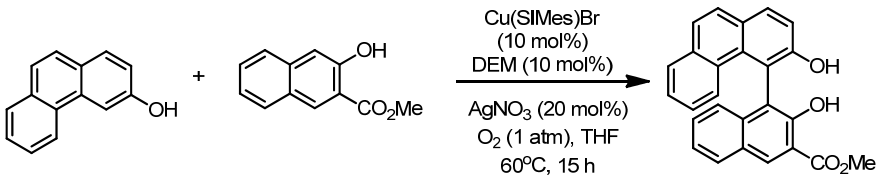



**Methyl 6-*tert*-Butyl-7'-methoxy-2,2'-dihydroxy-1,1'-binaphthyl-3-carboxylate (7.34):** Prepared following the general procedure for the oxidative coupling. The product was purified by silica gel column chromatography (20 % EtOAc/Hexanes) to afford the product **7.34** as a yellow solid (22.1 mg, 46 %). $^{1}$H NMR (400MHz ,$CDCl_3$) δ = 10.79 (s, 1 H), 8.72 (s, 1 H), 7.88 - 7.82 (m, 2 H), 7.78 (d, *J* = 9.0 Hz, 1 H), 7.50 (dd, *J* = 2.0, 9.0 Hz, 1 H), 7.22 (d, *J* = 8.8 Hz, 1 H), 7.17 (d, *J* = 9.0 Hz, 1 H), 7.00 (dd, *J* = 2.5, 8.9 Hz, 1 H), 6.41 (d, *J* = 2.4 Hz, 1 H), 4.95 (s, 1 H), 4.08 (s, 3 H), 3.54 (s, 3 H), 1.39 (s, 9 H); $^{13}$C NMR (101MHz ,$CDCl_3$) δ = 170.4, 158.3, 154.5, 152.0, 147.2, 135.5, 134.8, 133.8, 129.9, 129.8, 129.4, 127.4, 124.7, 124.6, 124.6, 115.1, 115.0, 114.1, 114.1, 113.3, 104.3, 55.0, 52.8, 34.6, 31.0; HRMS (ESI+) for $C_{27}H_{27}O_5$ $[M + H]^+$ calculated: 431.1853, found: 431.18596.

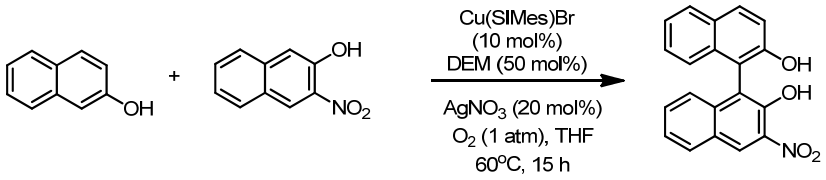



**Methyl 6'-Bromo-6-*tert*-butyl-2,2'-dihydroxy-1,1'-binaphthyl-3-carboxylate (7.33):** Prepared following the general procedure for the oxidative coupling. The product was purified by silica gel column chromatography (20 % EtOAc/Hexanes) to afford the product **7.33** as a yellow solid (31.9 mg, 60 %). $^{1}$H NMR (400MHz , $CDCl_3$) δ = 10.83 (s, 1 H), 8.73 (s, 1 H), 8.02 (d, *J* = 2.0 Hz, 1 H), 7.85 - 7.81 (m, 1 H), 7.66 (d, *J* = 9.7 Hz, 1 H), 7.39 (d, *J* = 9.0 Hz, 1 H), 7.31 (dd, *J* = 2.0, 9.0 Hz, 1 H), 7.13-7.09 (m, 2H), 6.99 (d, *J* = 9.0 Hz, 1 H), 5.07 (s, 1 H),

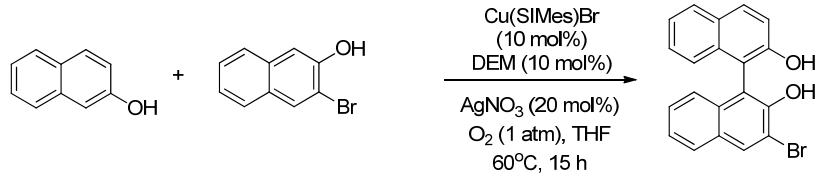
4.08 (s, 3 H), 1.39 (s, 9 H); $^{13}$C NMR (101MHz ,$CDCl_3$) δ = 170.4, 154.5, 153.7, 151.7, 134.1, 133.0, 130.1, 129.8, 129.7, 129.7, 129.5, 129.2, 128.9, 128.0, 126.6, 124.7, 124.2, 118.8, 117.0, 114.1, 109.5, 52.9, 34.6, 31.0; HRMS (ESI+) for $C_{26}H_{24}BrO_4$ $[M + H]^+$ calculated: 479.08525, found: 479.08574.




**Methyl 2-Hydroxy-1-(3-hydroxyphenanthren-4-yl)naphthalene-3-carboxylate (7.35):** Prepared following the general procedure for the oxidative coupling except the quantity of 3-phenanthrol (29.1 mg, 0.144 mmol) was increased. The product was purified by flash chromatography on silica gel (20% EtOAc/Hexanes) to afford the product **7.35** (21.4 mg, 49%) as a yellow solid. NMR data for this compound matched that found in the literature.[66]

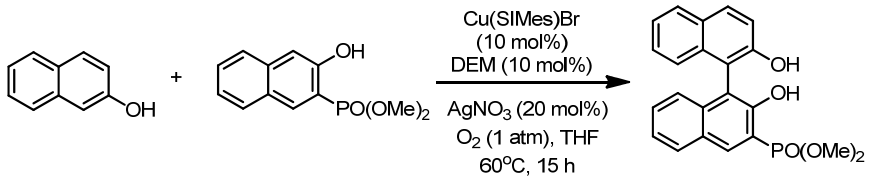



**3-Nitro-1,1'-binapthalene-2,2'-diol (7.42):** Prepared following the general procedure for the oxidative coupling except the quantity of diethylmalonate was increased (0.5 mL of a 0.1M solution in THF, 0.056 mmol). The product was purified by flash chromatography on silica gel (15% EtOAc/Hexanes) to afford the product **7.42** (26.1 mg, 71%) as a red solid. $^1$H NMR (400MHz , $CDCl_3$) δ ppm 10.27 (s, 1H), 9.01 (s, 1H), 8.03 (m, 1H), 7.97 (d, $J$ = 9.2 Hz, 1H), 7.91 (d, $J$ = 8.4 Hz, 1H), 7.49 (m, 2H), 7.36 (m, 2H), 7.30 (m, 1H), 7.25 (m, 1H), 7.05 (d, $J$ = 8.4Hz, 1H) 4.90 (s, 1H) $^{13}$C NMR ($CDCl_3$, 75MHz) δ ppm 151.3, 148.0, 138.1, 134.6, 133.2, 131.8, 130.8, 130.5, 129.3, 128.4, 128.2, 127.0, 126.8, 126.0, 125.08, 124.1, 123.7, 118.2, 117.8, 112.9 HRMS (ESI+) for $C_{20}H_{14}NO_4$ $[M+H^+]$ calculated: 332.0917, found: 332.0928.

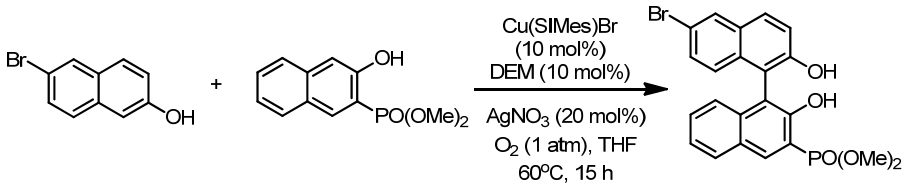



**3-Bromo-1,1'-binaphthalene-2,2'-diol (7.43):** Prepared following the general procedure for the oxidative coupling except the quantity of 2-naphthol was increased (20.7 mg, 0.144 mmol). The product was purified by flash chromatography on silica gel (15% EtOAc/Hexanes) to afford the product **7.43** (25 mg, 62 %) as a yellow solid. NMR data for this compound matched that found in the literature.[156]

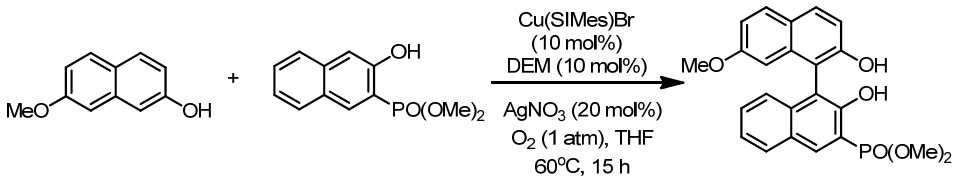
[156] Harada, T., Kanda, K. *Org. Lett.* **2006**, *8*, 3817.




**Dimethyl 2,2'-Dihydroxy-1,1'-binaphthyl-3-phosphate (7.39):** Prepared following the general procedure for the oxidative coupling. The product was purified by silica gel column chromatography (1 % MeOH/DCM) to afford the product **7.39** as a yellow solid (34.5 mg, 77 %). $^{1}$H NMR (400MHz , $CDCl_3$) δ = 9.87 (d, *J* = 0.9 Hz, 1H), 8.30 (s, 1H), 7.99 - 7.85 (m, 3H), 7.44 - 7.31 (m, 4H), 7.26 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.21 (m, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 5.04 (s, 1H), 3.92 (d, *J* = 4.0 Hz, 3H), 3.89 (d, *J* = 4.0 Hz, 3H); $^{13}$C NMR (176MHz ,$CDCl_3$) δ = 155.0 (d, J = 7.8 Hz), 151.4, 137.1, 136.0 (d, J = 5.2 Hz), 133.3, 130.4, 129.8, 129.2 (d, J = 9.8 Hz), 128.3, 127.8, 126.7, 124.9, 124.6, 124.5, 123.4, 117.7, 114.4 (d, J = 11.7 Hz), 113.8 (d, J = 1.9 Hz), 112.1, 111.1, 53.5 (d, J = 5.9 Hz), 53.4 (d, J = 5.2 Hz); HRMS (ESI+) for $C_{22}H_{20}O_5P$ [M+H$^+$] calculated: 395.1043, found: 395.1048.

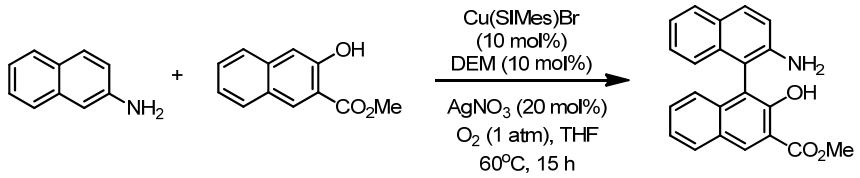



**Dimethyl 6'-Bromo-2,2'-dihydroxy-1,1'-binaphthyl-3-phosphate (7.40):** Prepared following the general procedure for the oxidative coupling. The product was purified by silica gel column chromatography (2.5 % MeOH/DCM) to afford the product **7.40** as a brown solid (25 mg, 48 %). $^{1}$H NMR (400MHz ,$CDCl_3$) δ = 10.03 (s, 1H), 8.27 (d, *J* = 16.1 Hz, 1H), 8.03 (s, 1H), 7.97 - 7.89 (m, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.47 - 7.35 (m, 3H), 7.31 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.21 - 7.11 (m, 1H), 6.96 (d, *J* = 9.0 Hz, 1H), 5.05 (s, 1H), 3.93 (d, *J* = 4.0 Hz, 3H), 3.90 (d, *J* = 4.0 Hz, 3H); $^{13}$C NMR (176MHz ,$CDCl_3$) δ = 155.1 (d, J = 7.8 Hz), 151.7, 137.0 (d, J = 2.6 Hz), 136.2 (d, J = 5.9 Hz), 131.9, 130.3, 130.0, 129.9, 129.4, 129.3, 127.7, 127.7, 126.4, 124.7, 118.9, 117.2, 114.2 (d, J = 1.3 Hz), 113.8 (d, J = 11.7 Hz), 112.1, 111.1, 53.5 (d, J = 5.2 Hz), 53.5 (d, J = 5.2 Hz); HRMS (ESI+) for $C_{22}H_{19}BrO_5P$ [M+H$^+$] calculated: 473.0148, found: 473.0169.

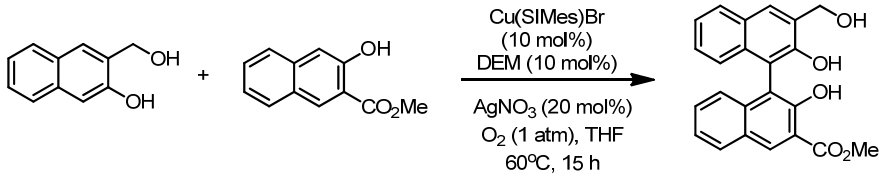



**Dimethyl 7'-Methoxy-2,2'-dihydroxy-1,1'-binaphthyl-3-phosphate (7.41):** Prepared following the general procedure for the oxidative coupling. The product was purified by silica gel column chromatography (2.5 % MeOH/DCM) to afford the product **7.41** as a red solid (29.2

mg, 62 %). $^{1}$H NMR (400MHz ,$CDCl_3$) δ = 9.66 (s, 1H), 8.28 (d, *J* = 16.3 Hz, 1H), 7.95 - 7.89 (m, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.44 - 7.36 (m, 2H), 7.22 (d, *J* = 9.0 Hz, 1H), 7.01 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 6.45 - 6.38 (m, 1H), 5.10 (s, 1H), 3.91 (d, *J* = 5.3 Hz, 3H), 3.88 (d, *J* = 5.5 Hz, 3H), 3.54 (s, 3H); $^{13}$C NMR (176 MHz, $CDCl_3$) δ 158.4, 154.9(d, J = 7.2 Hz), 152.1, 136.9 (d, J = 2.6 Hz), 136.1 (d, J = 5.9 Hz), 134.7, 130.1, 129.9 (d, J = 11.1 Hz), 129.2, 127.8 (d, J = 15.6 Hz), 125.0, 124.7, 124.6, 115.2, 115.0, 114.5, 112.8, 112.2, 111.2, 104.2, 55.0, 53.5 (d, J = 5.2 Hz), 53.3(d, J = 5.2 Hz); HRMS (ESI+) for $C_{23}H_{22}O_6P$ [$M+H^+$] calculated: 425.1148, found: 425.1163.

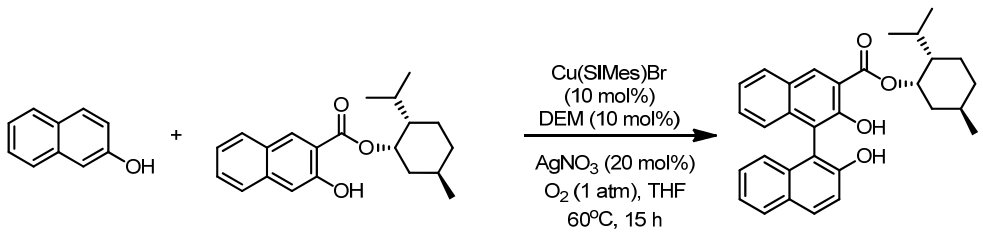



**Methyl 2'-Amino-2-hydroxy-1,1'-binaphthalene-3-carboxylate (7.36):** Prepared following the general procedure for the oxidative coupling except 2-naphthylamine (20.6 mg, 0.144 mmol) was used. The product was purified by flash chromatography on silica gel (10% EtOAc/Hexanes) to afford the product **7.36** (25 mg, 67 %) as a yellow solid. NMR data for this compound matched that found in the literature.[157]




**Methyl 3'-Hydroxymethyl-2,2'-dihydroxy-1,1'-binaphthalene-3-carboxylate (7.37):** Prepared following the general procedure with the exception that 3-hydroxymethyl-2-naphthol (39 mg, 0.22 mmol) was used. The product was purified by flash chromatography on silica gel (2:8, EtOAc:Hexanes) to afford biaryl **7.37** (6 mg, 14 %). NMR data for compound **7.37** agreed with those found in the literature.[66]

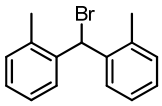
[157] Smrcina, M., Vykskocil, S., Maca, B., Polasek, M., Claxton, T. A., Abbott, A. P., Kocovsky, P. *J. Org. Chem.* **1994**, *59*, 2156-2163.

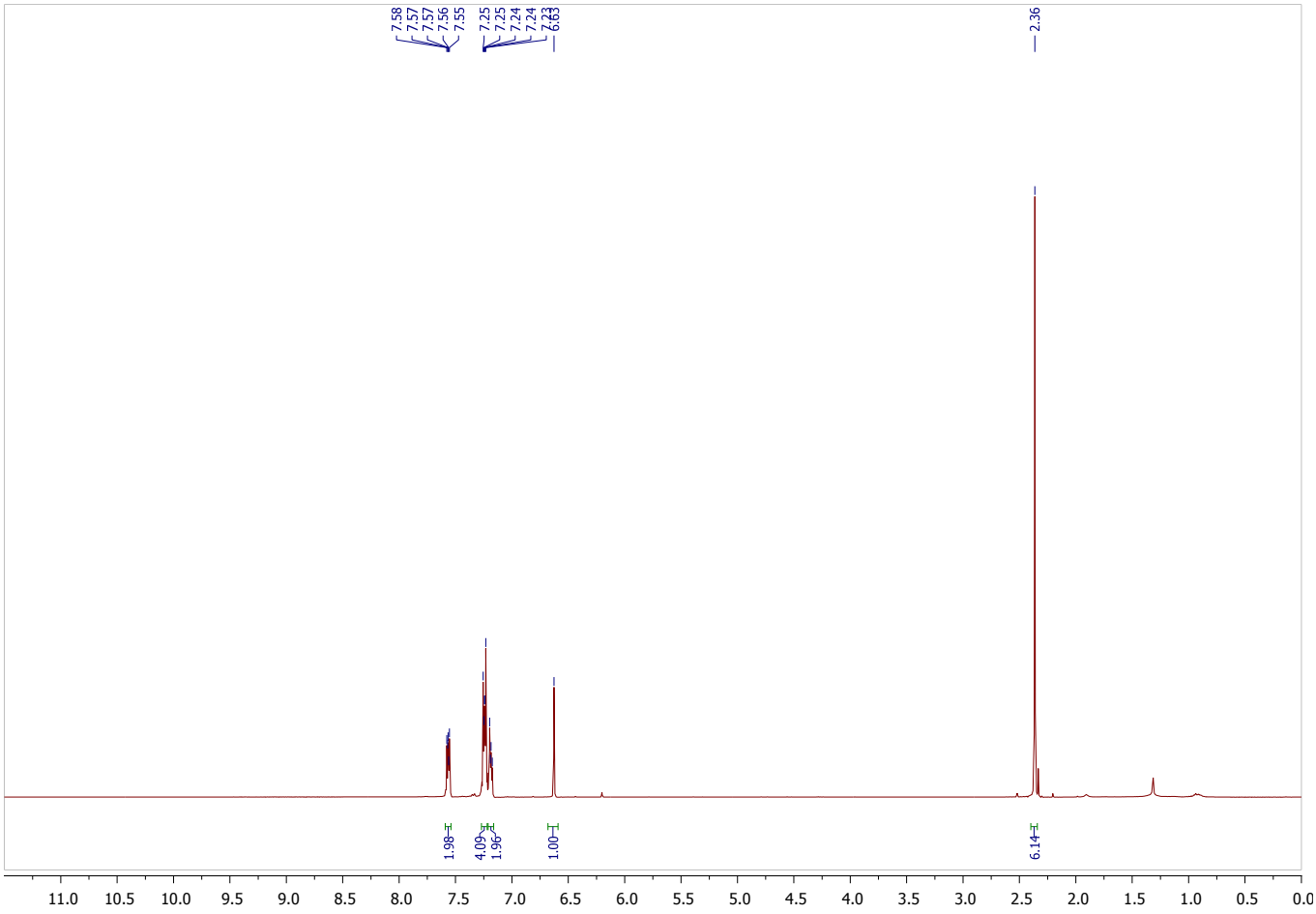


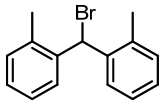

**Menthyl 2,2'-Dihydroxy-1,1'-binaphthalene-3-carboxylate (7.38):** Prepared following the general procedure except that menthol ester **7.38** (36 mg, 0.11 mmol) and an excess of 2-naphthol (32 mg, 0.22 mmol) were used. The product was purified by column chromatography on silica gel (2:8; EtOAc:Hexanes) to afford coupling product **7.38** (16 mg, 31 %). NMR data for compound **7.38** agreed with those found in the literature.[66]

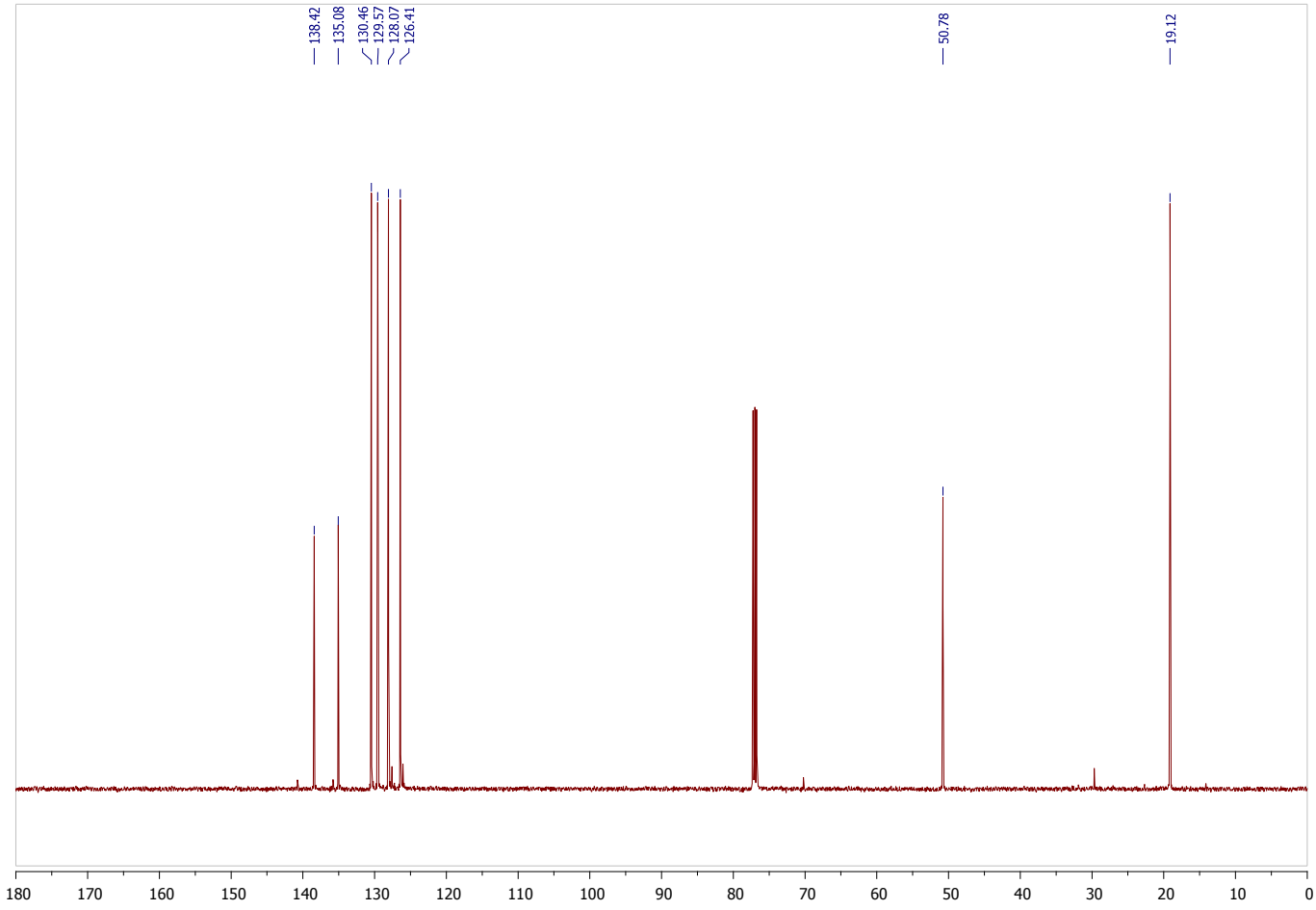
# Appendix I: NMR Data

## Alkyl Halides

$^{1}$H NMR spectrum of **3.12**: 

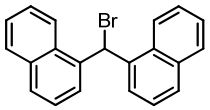



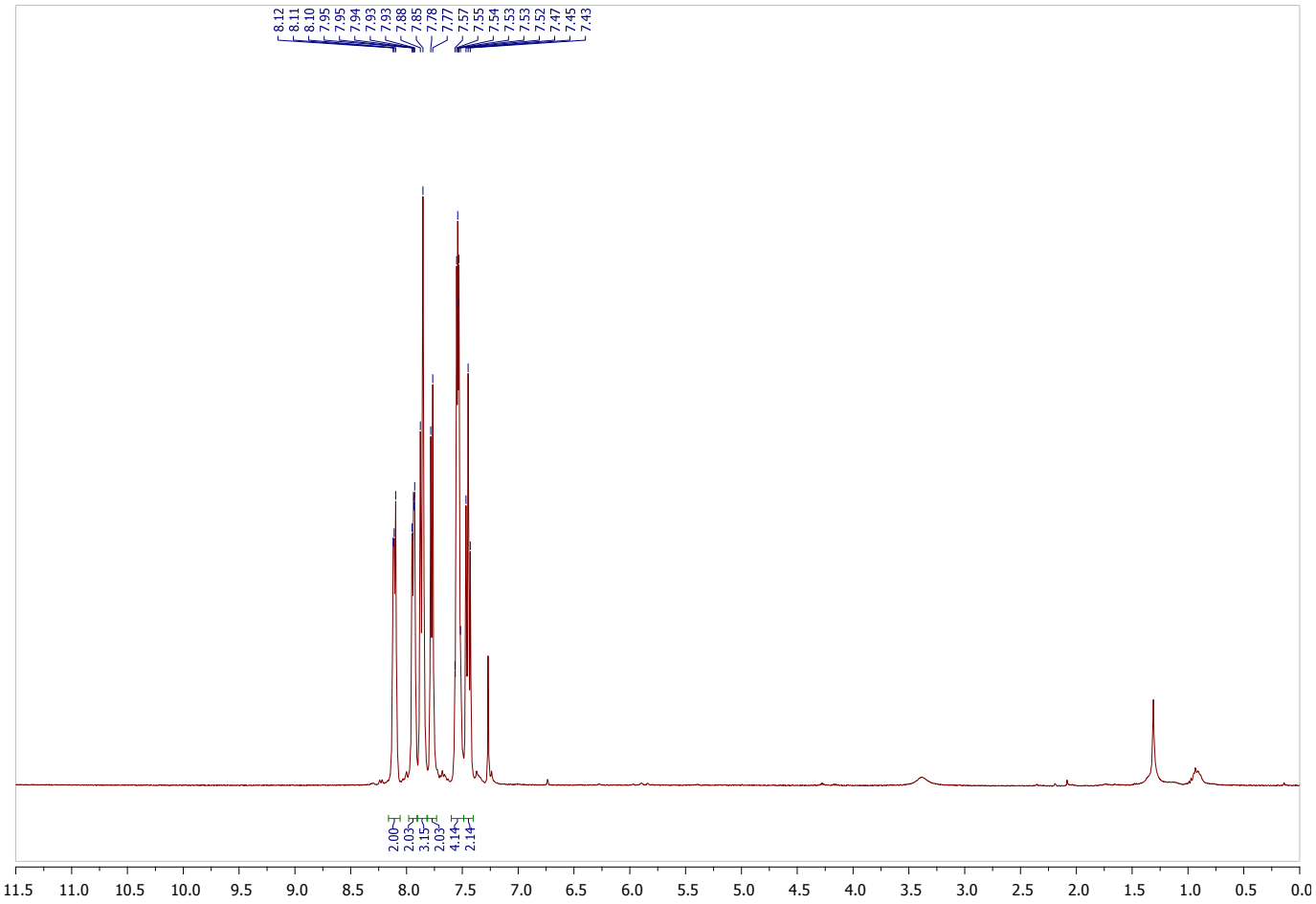
$^{13}$C NMR spectrum of **3.12**: 

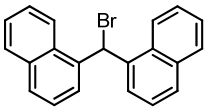

B

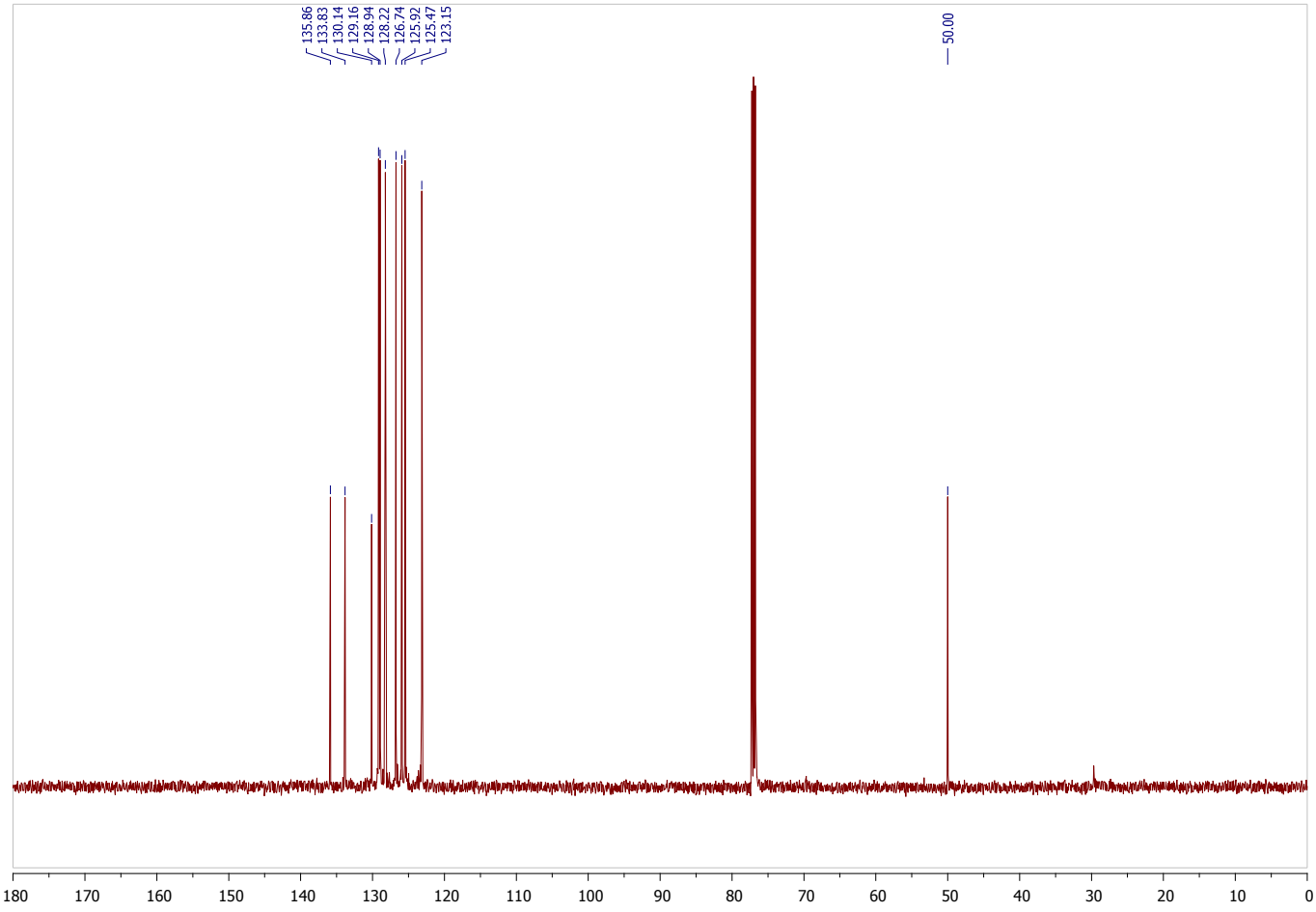
$^{1}$H NMR spectrum of **3.25**:

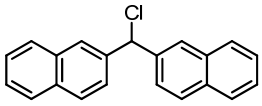


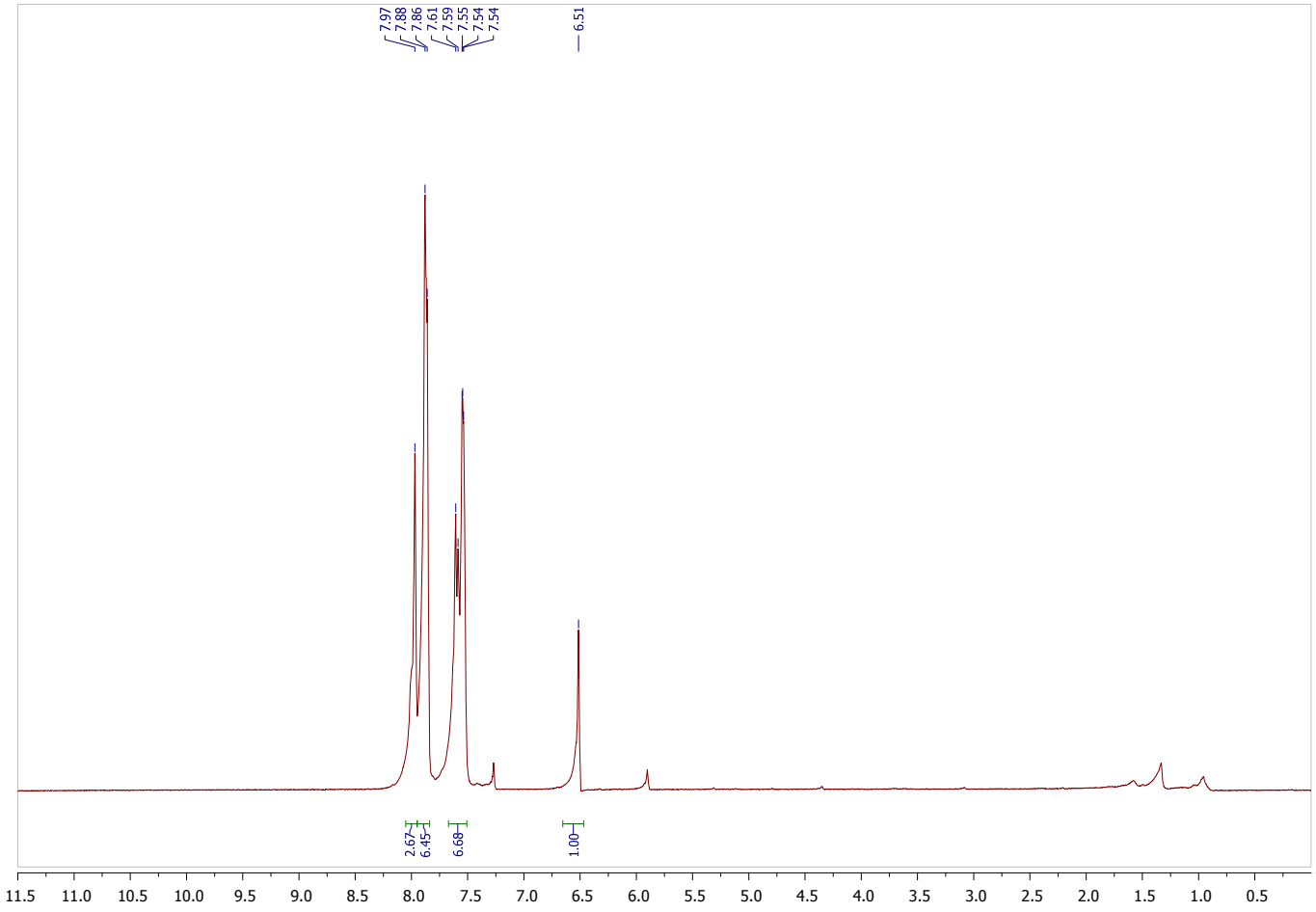



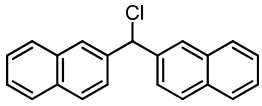
$^{13}$C NMR spectrum of **3.25**:

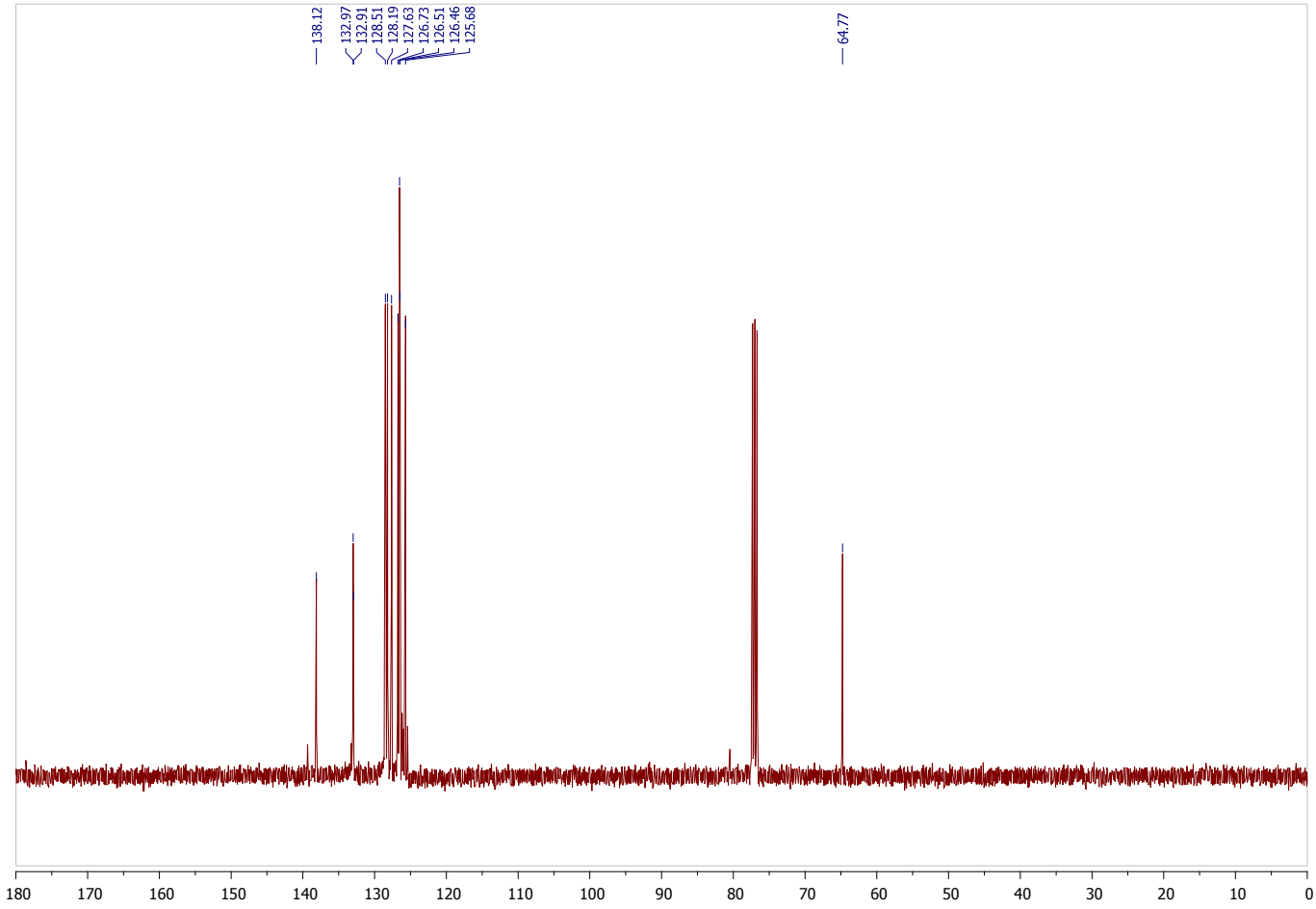


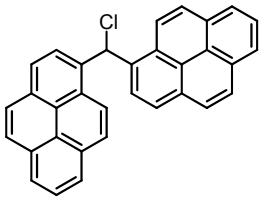



$^{1}$H NMR spectrum of **3.26**: 

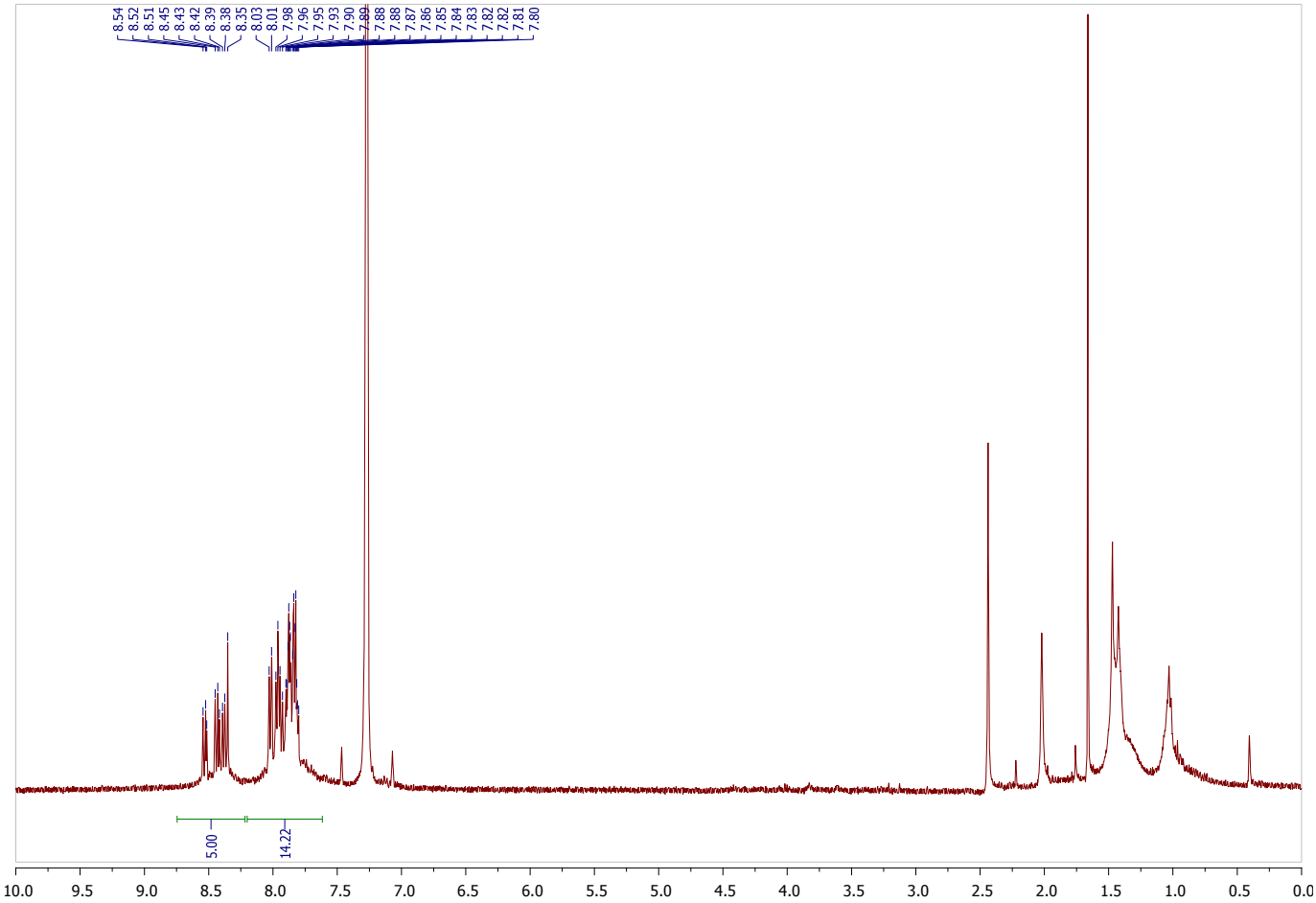



$^{13}$C NMR spectrum of **3.26**: 

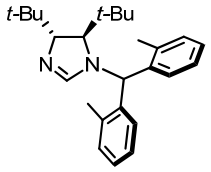





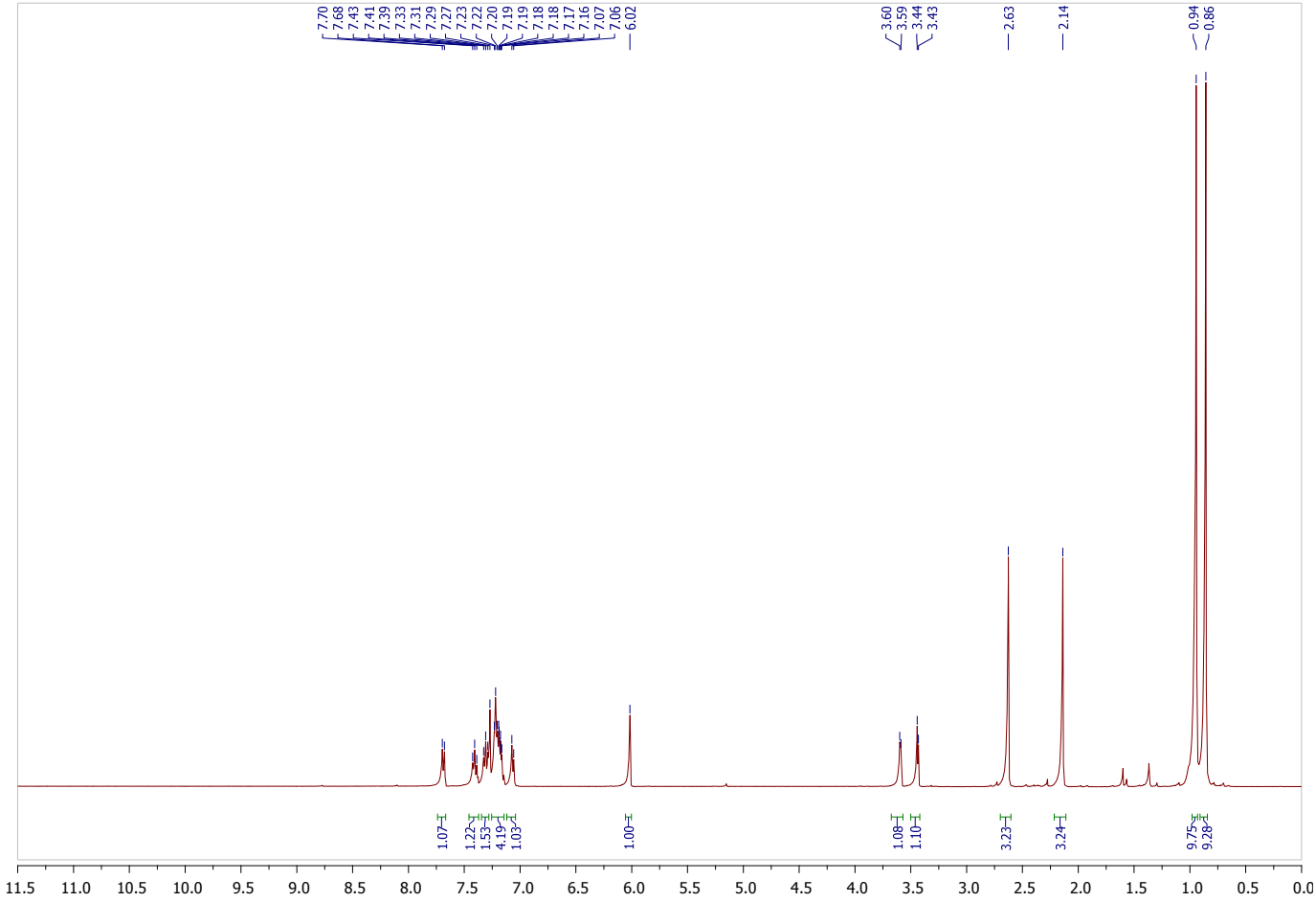

$^{1}$H NMR spectrum of **3.27**:

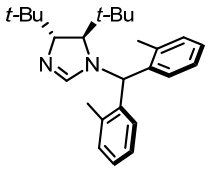


## Imidazolines

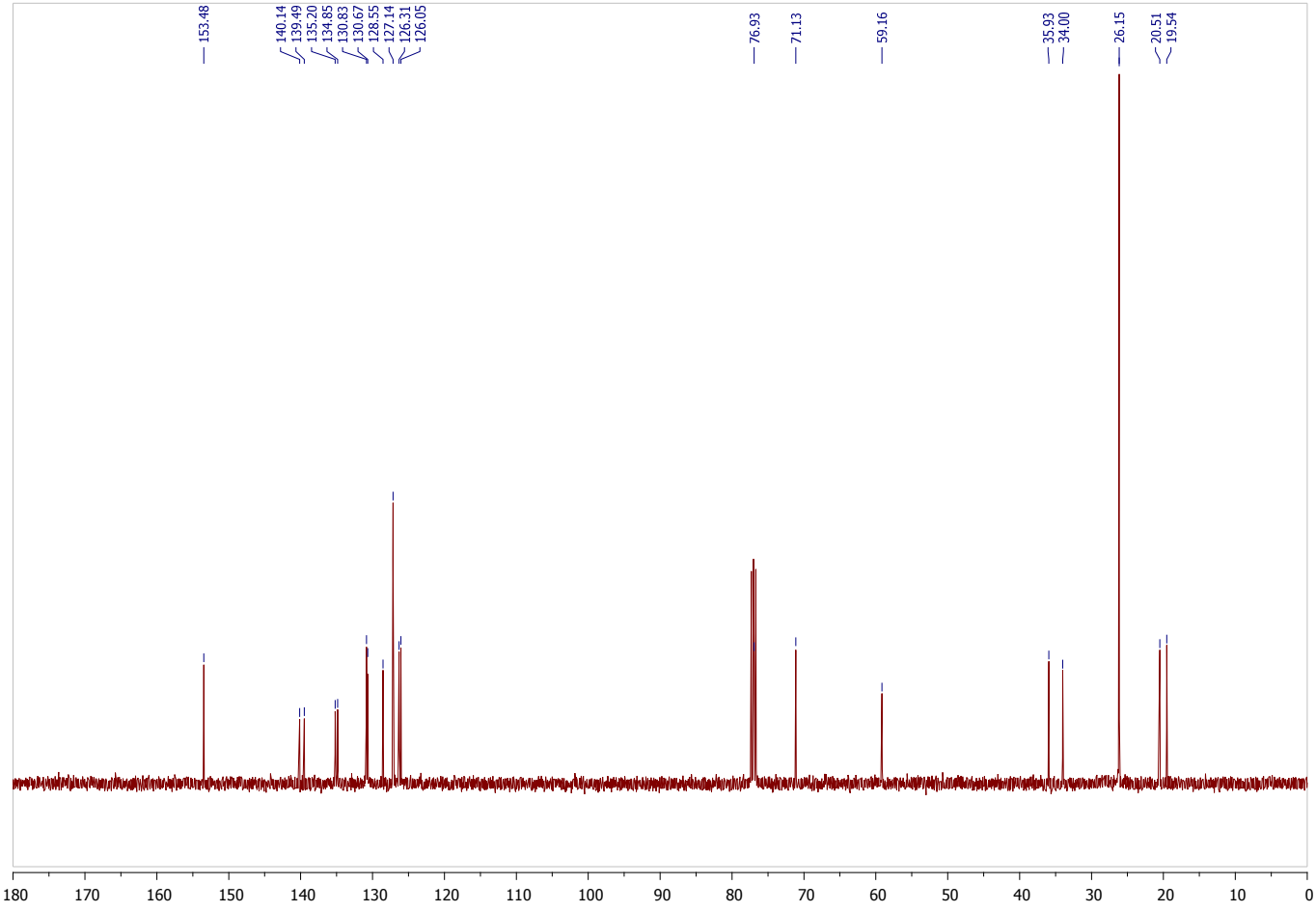


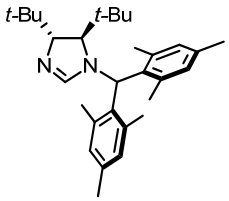

$^{1}$H NMR spectrum of **3.18**:






$^{13}$C NMR spectrum of **3.18**:



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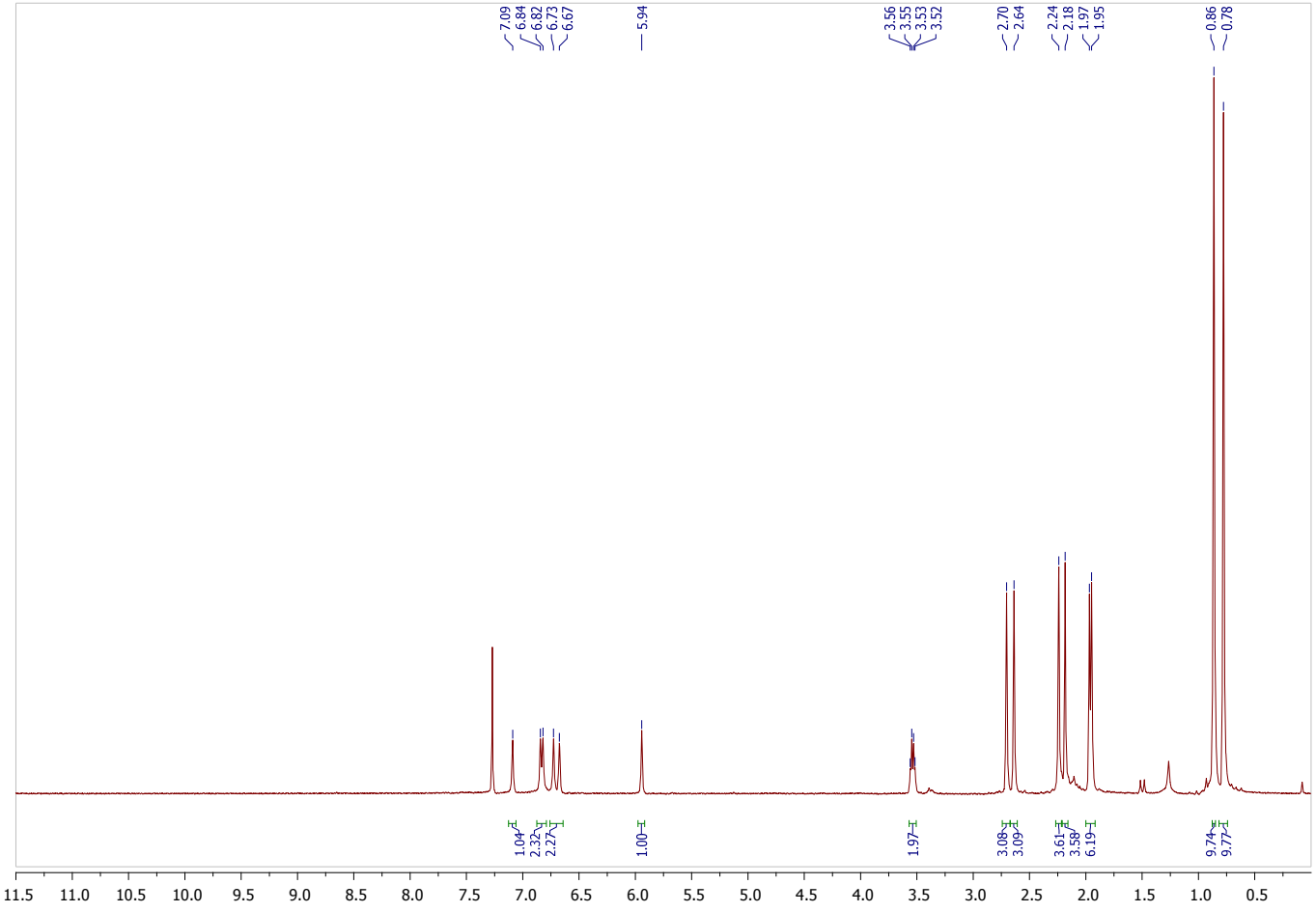

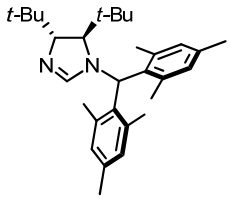


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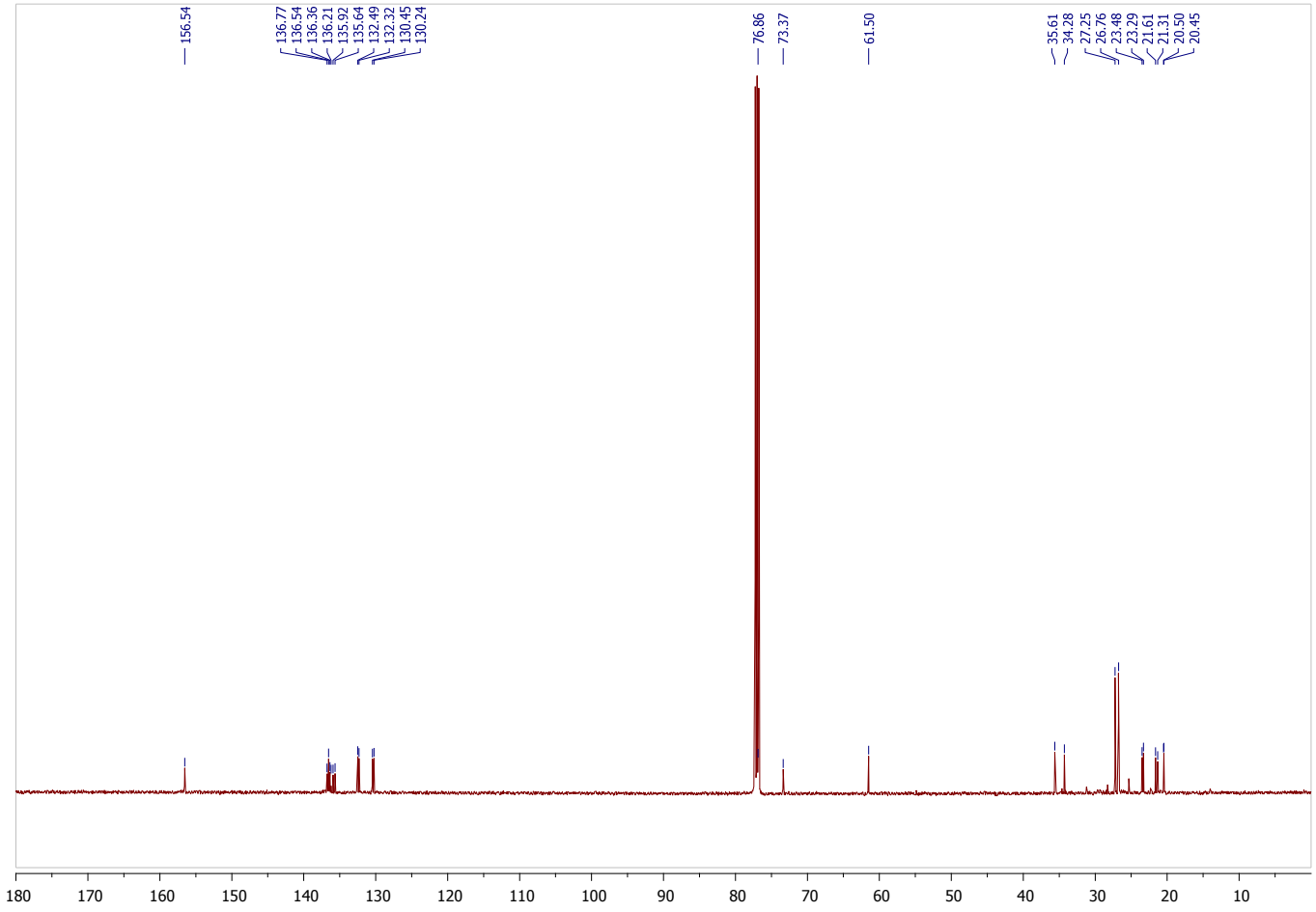
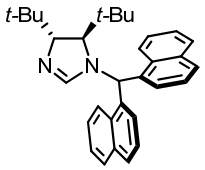
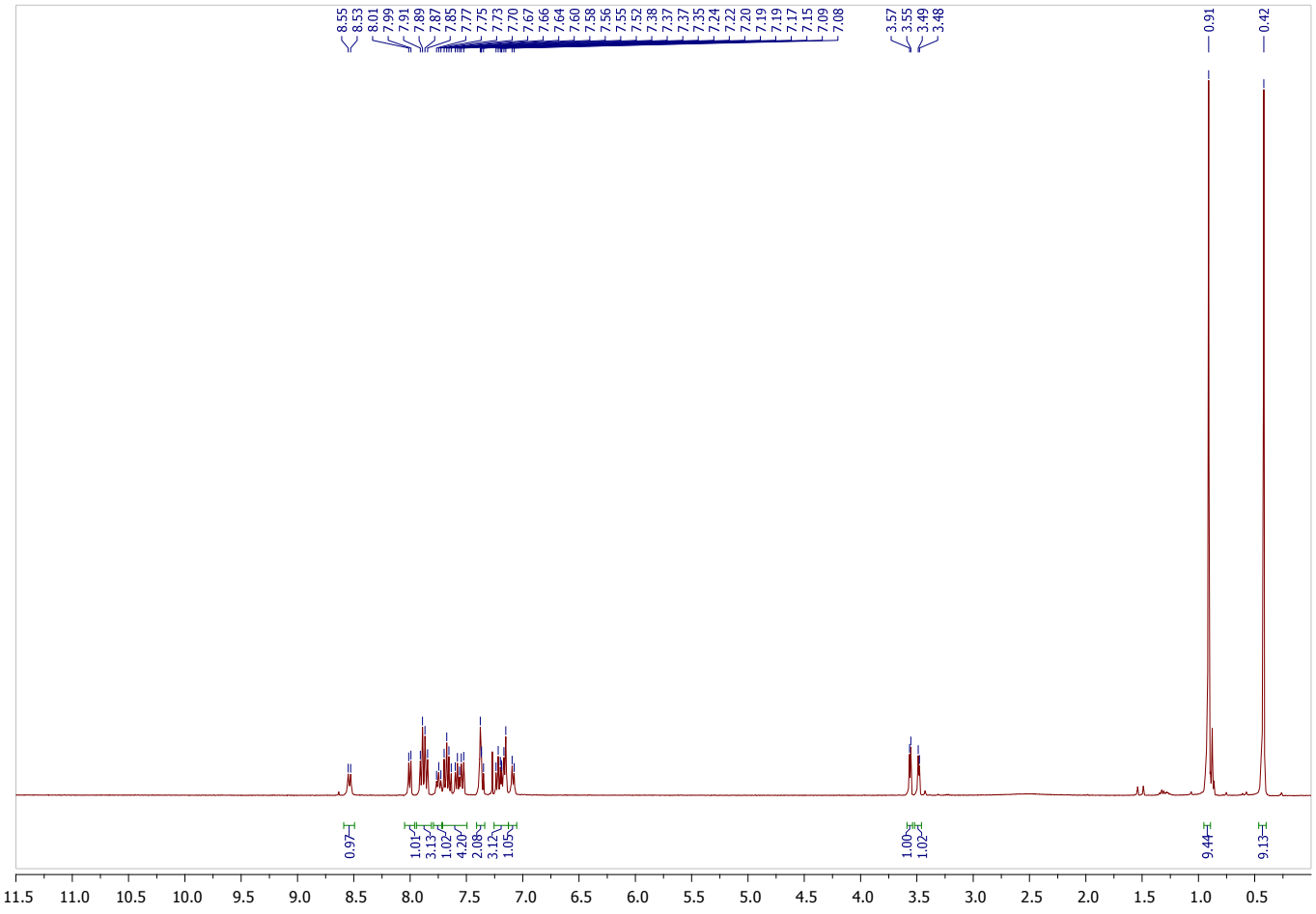
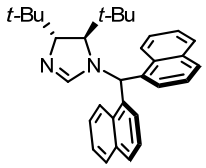





$^1$H NMR spectrum of **3.29**:



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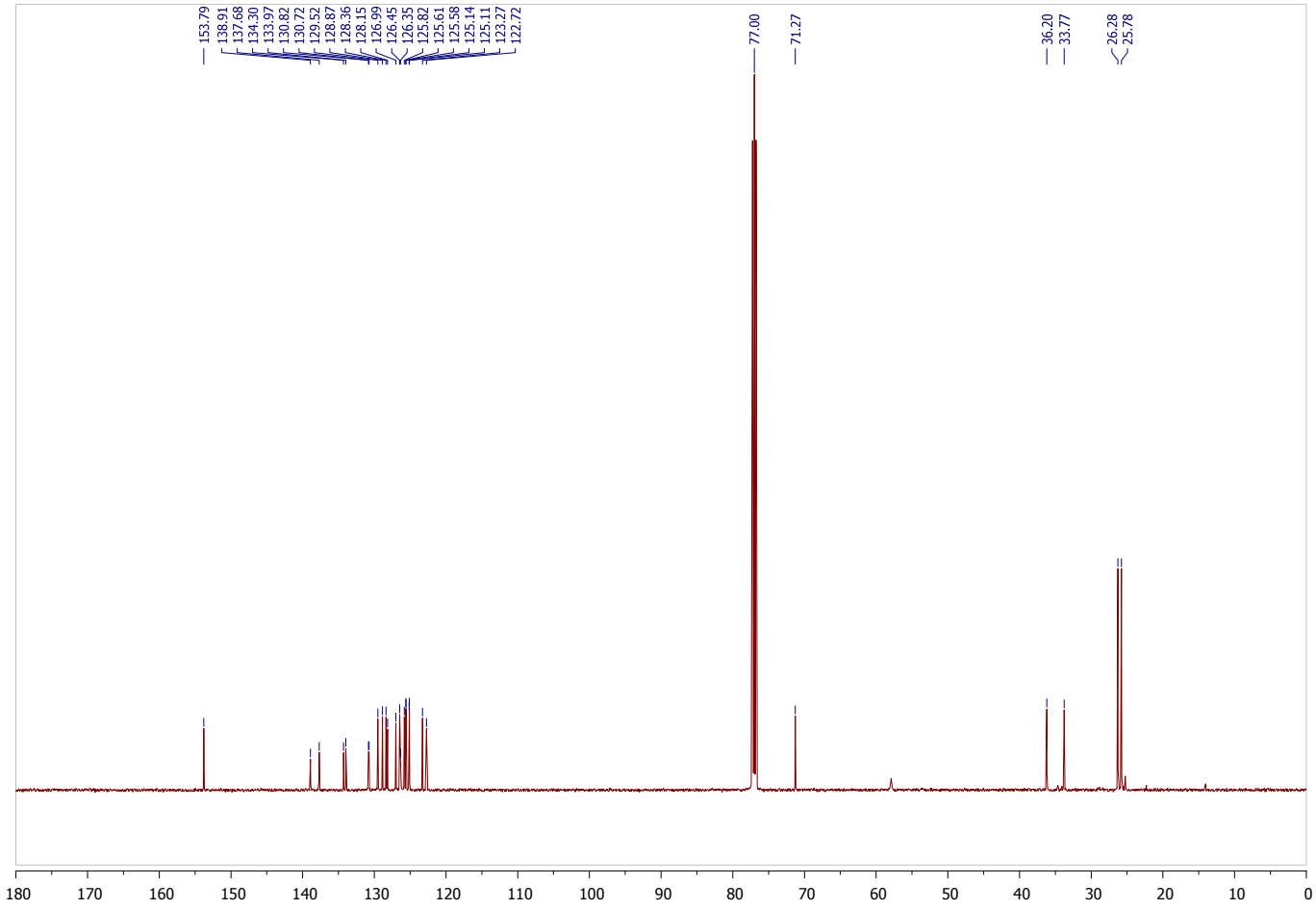
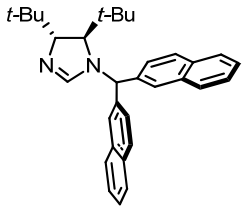
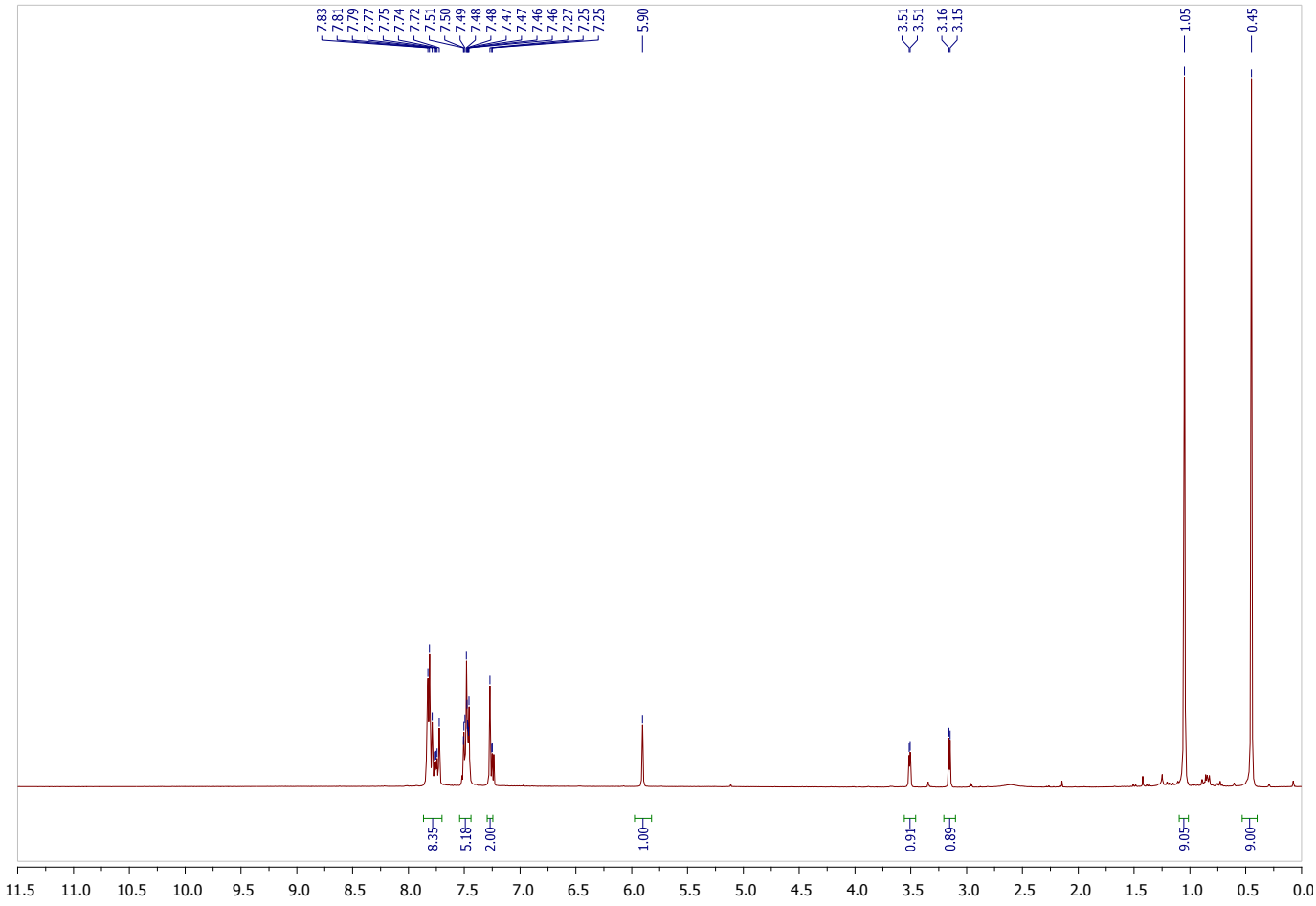


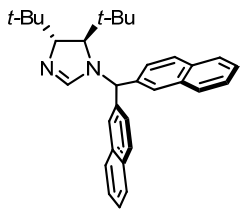

M




$^{1}$H NMR spectrum of **3.30**:




N

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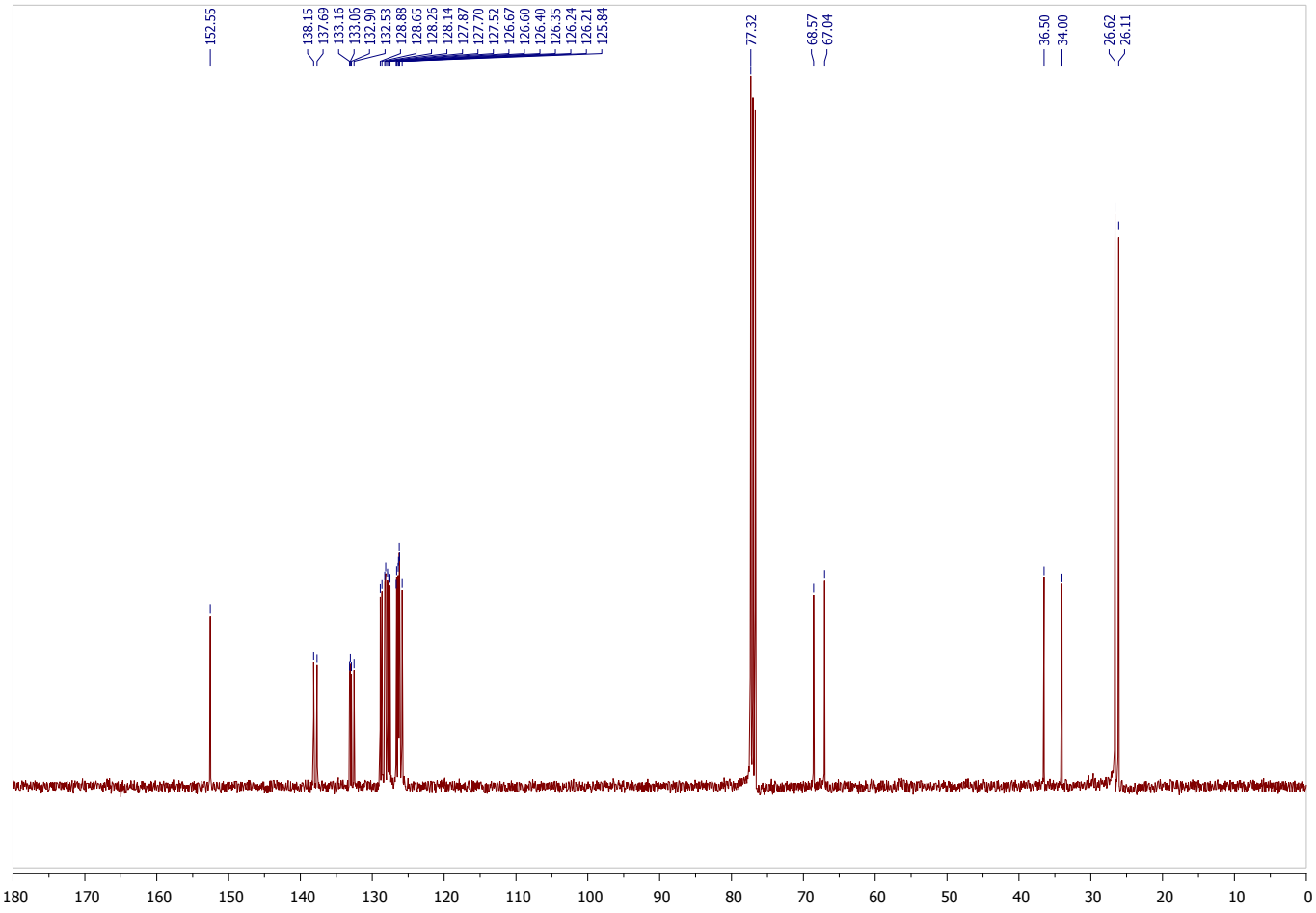
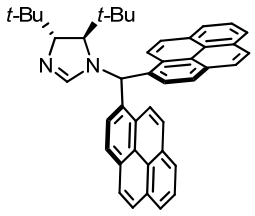
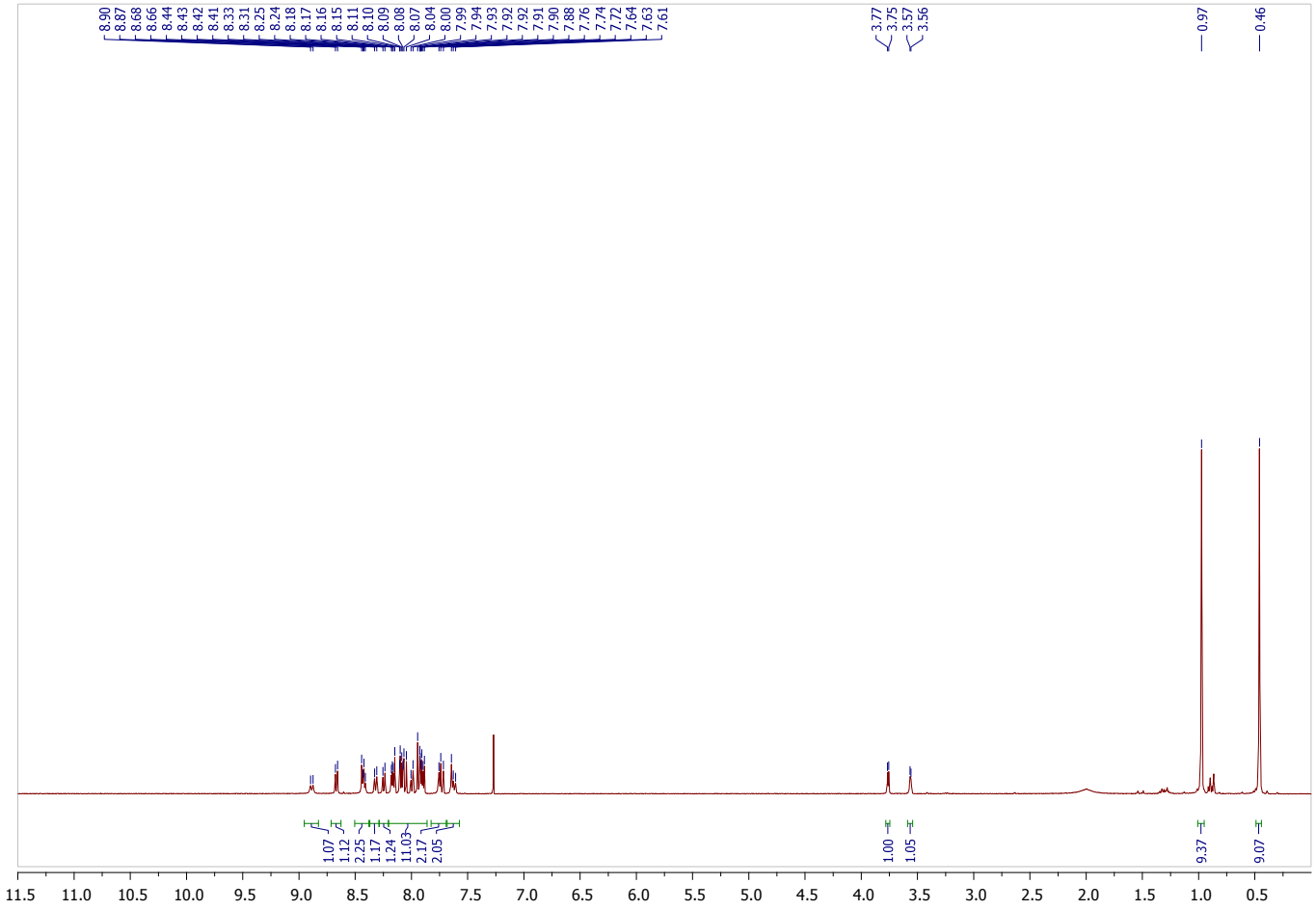


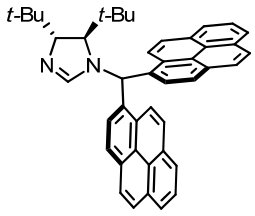

O



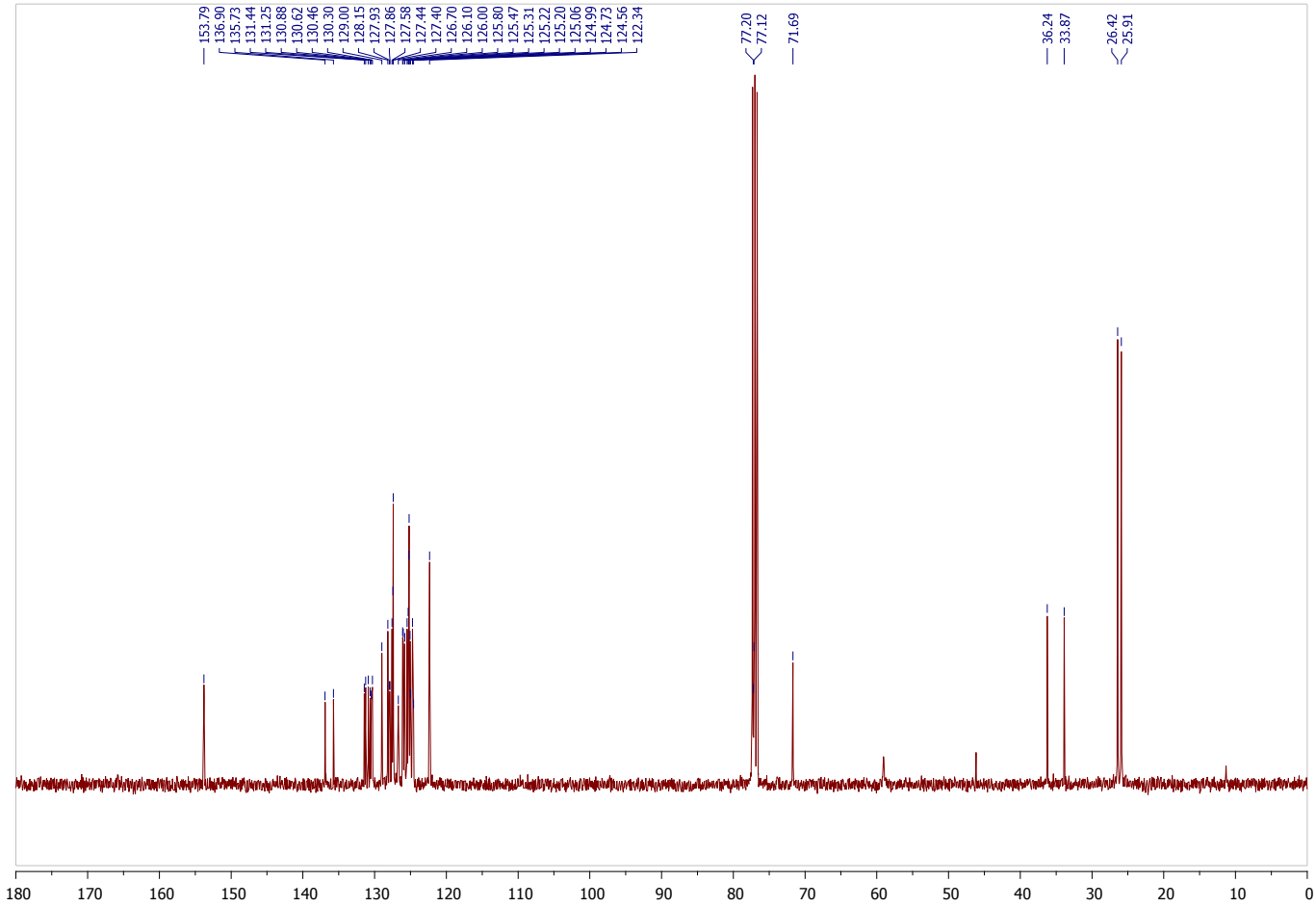

$^{1}$H NMR spectrum of **3.31**:




P

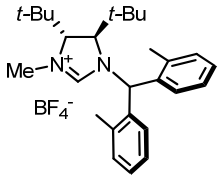



$^{13}$C NMR spectrum of **3.31**:

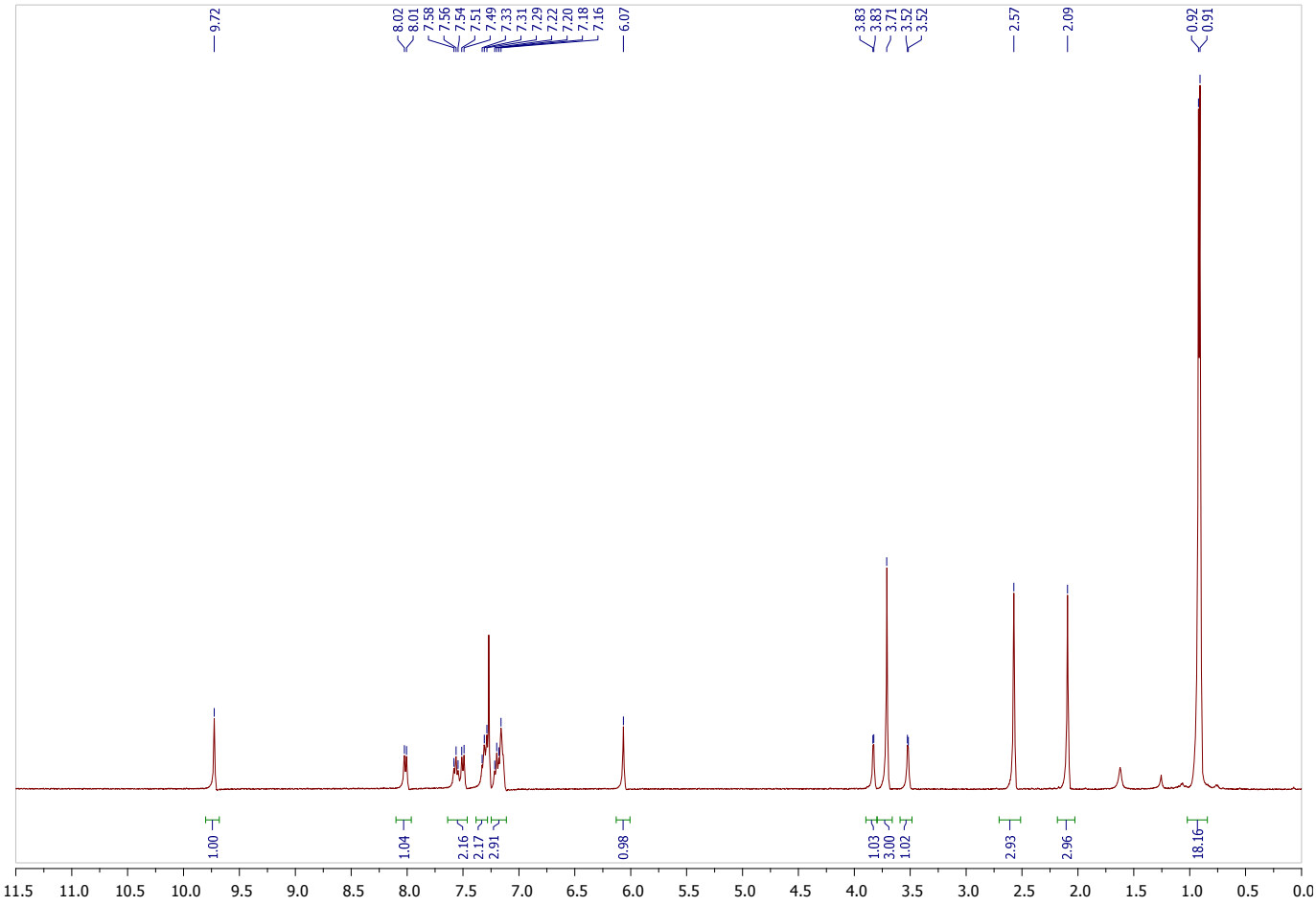



Q

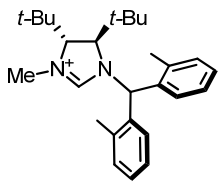
## Imidazolinium Salts



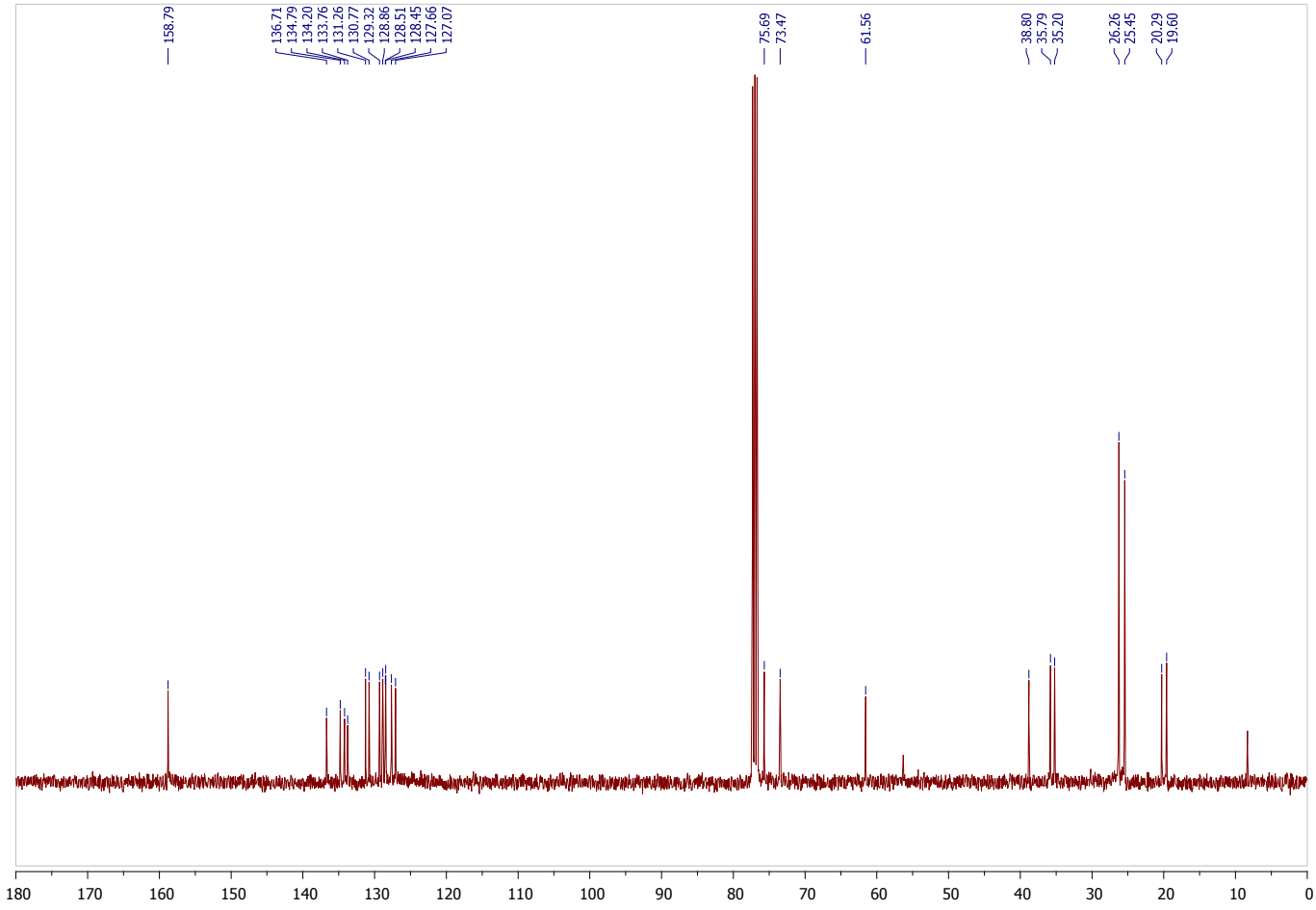

$^1$H NMR spectrum of **3.32**:

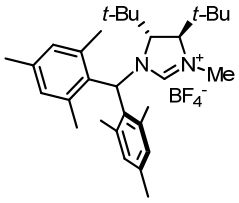



R

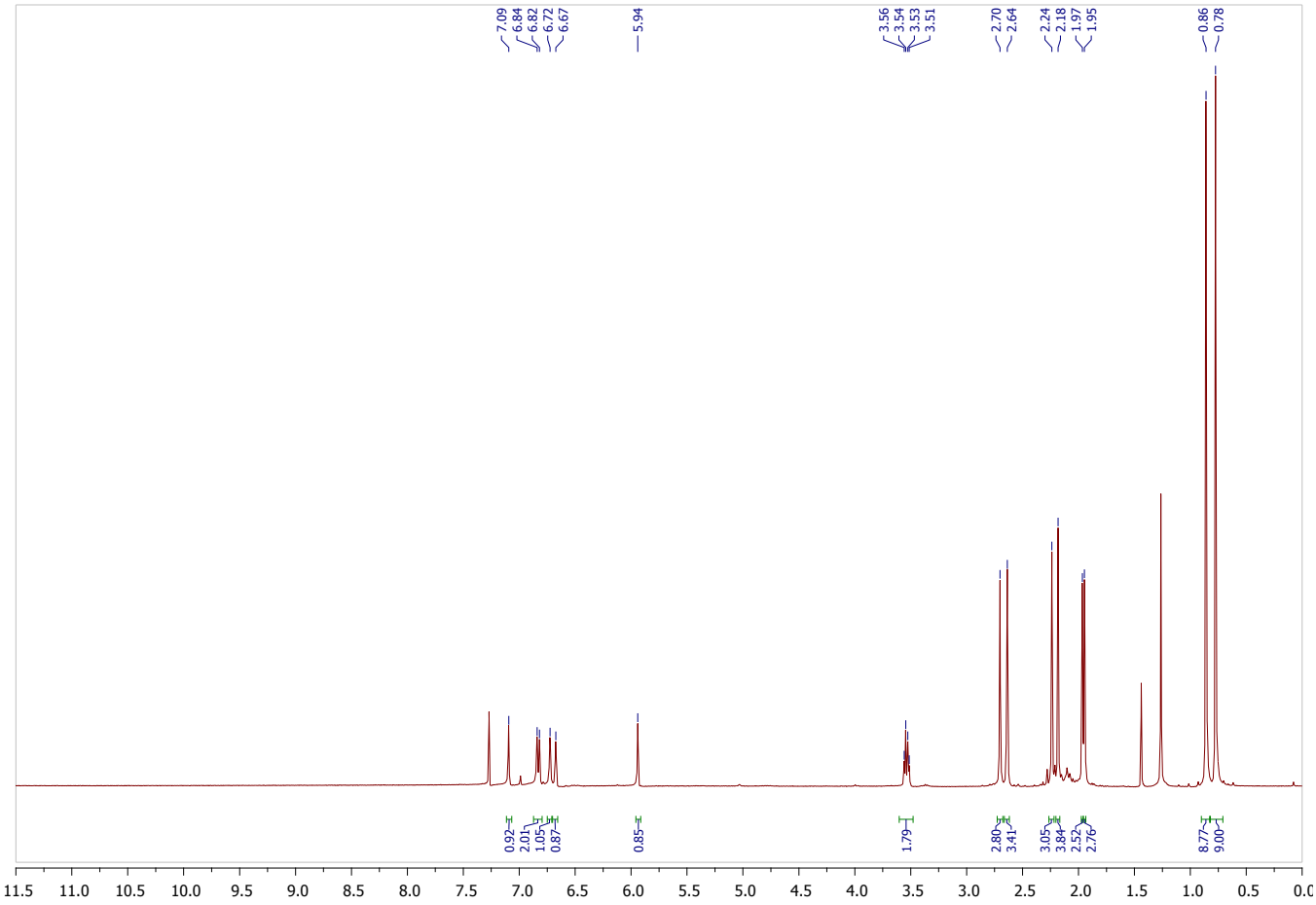



$^{13}$C NMR spectrum of **3.32**:

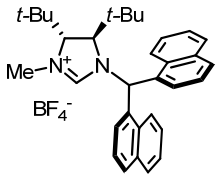




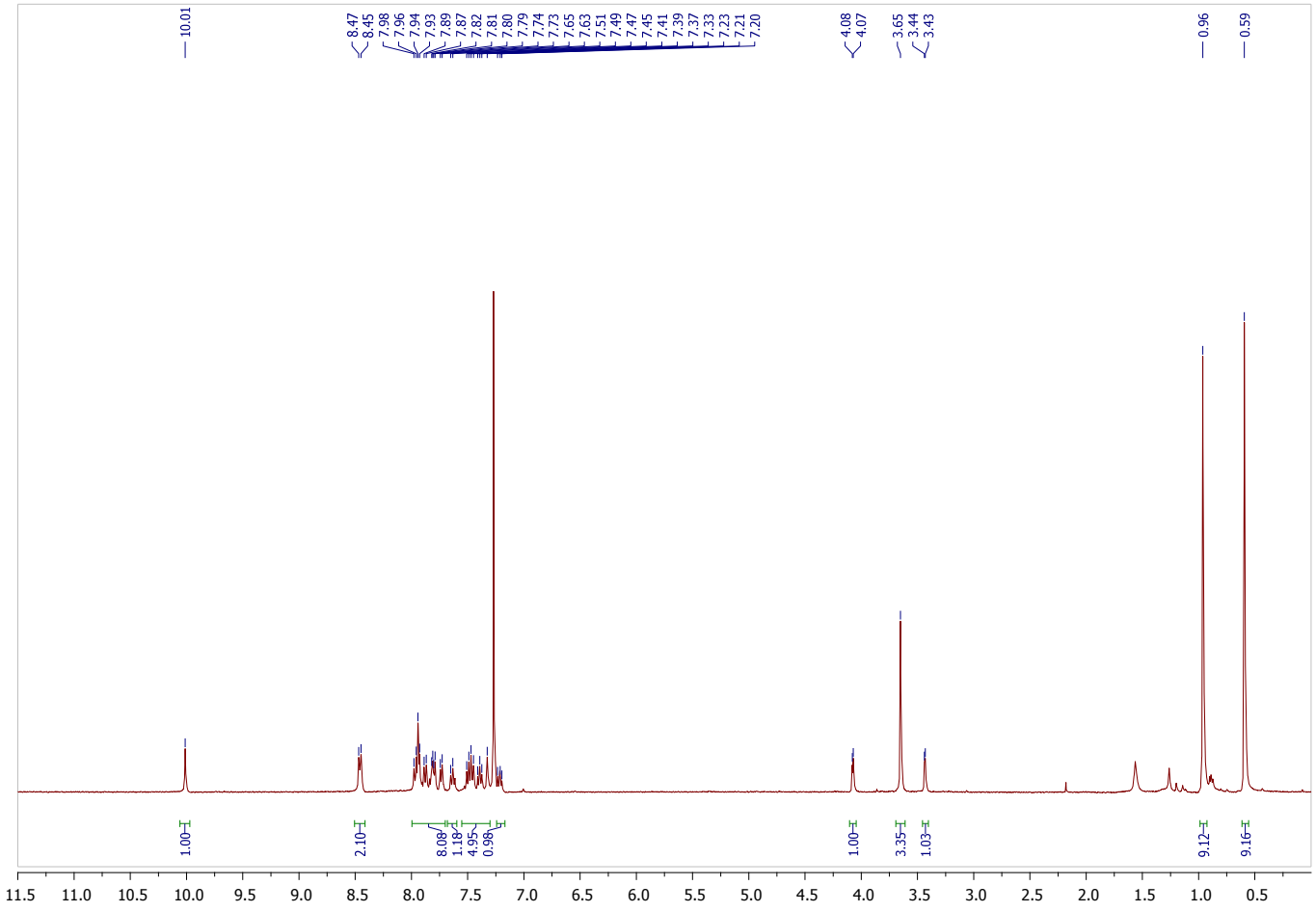

[1]HNMR Spectrum of **3.33**:



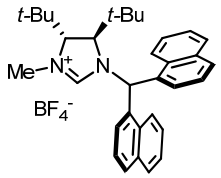

T



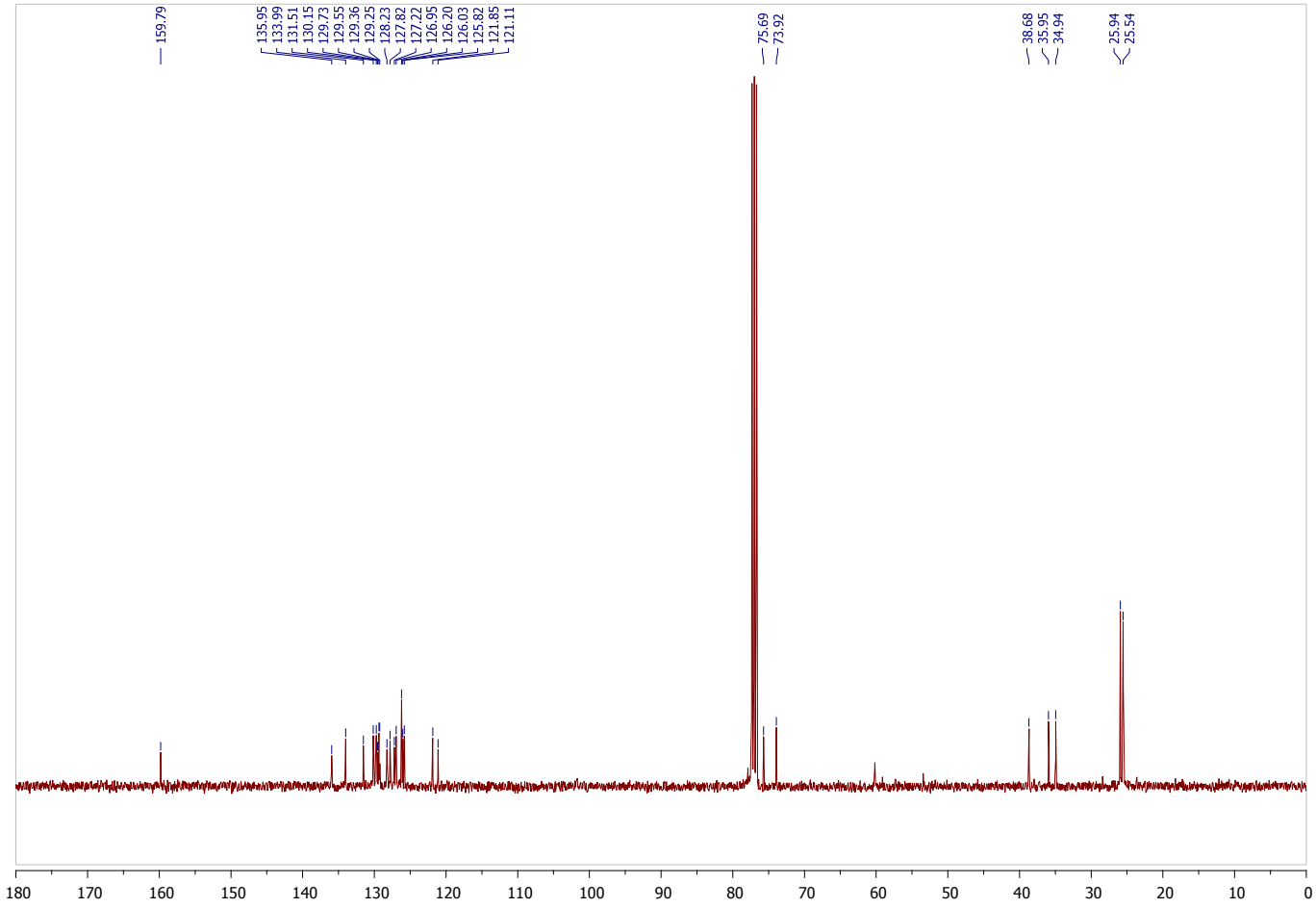

$^{1}$H NMR spectrum of **3.34**:

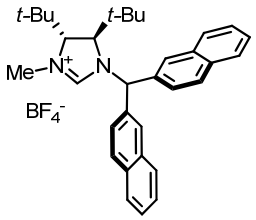



U

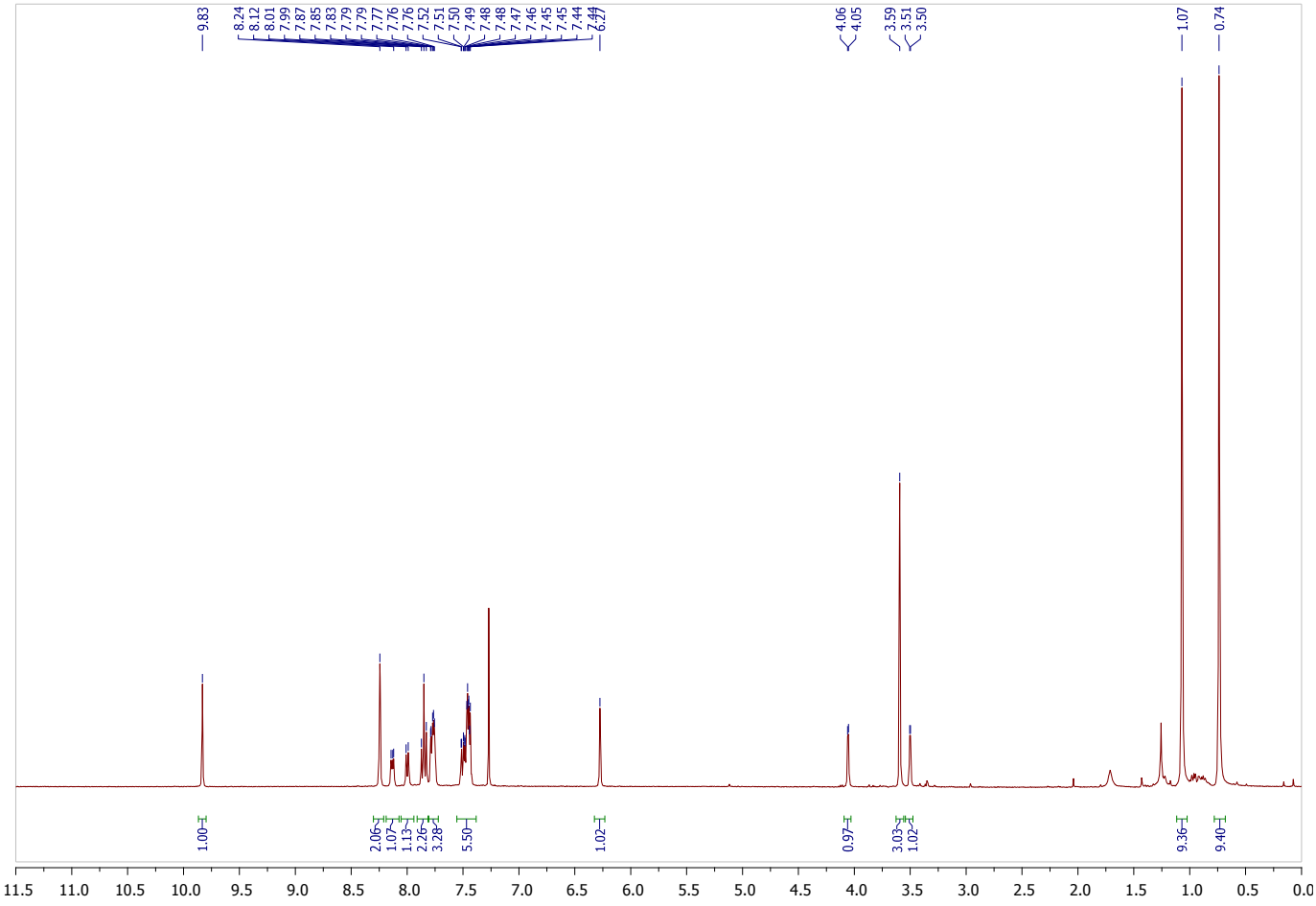



$^{13}$C NMR spectrum of **3.34**:

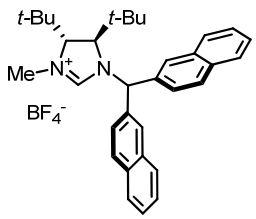




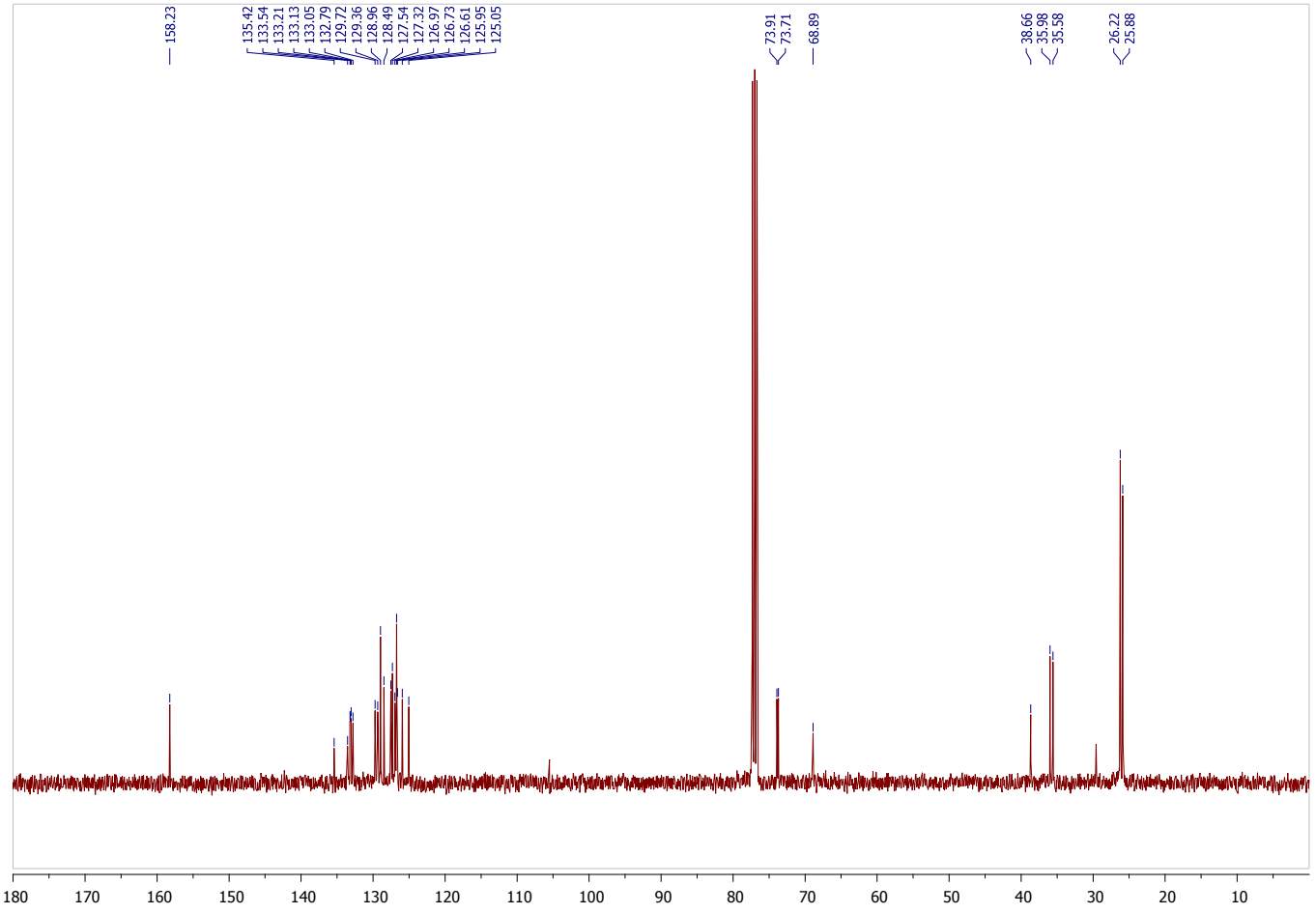

$^{1}$H NMR spectrum of **3.35**:

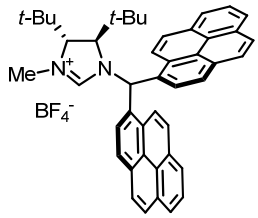



W

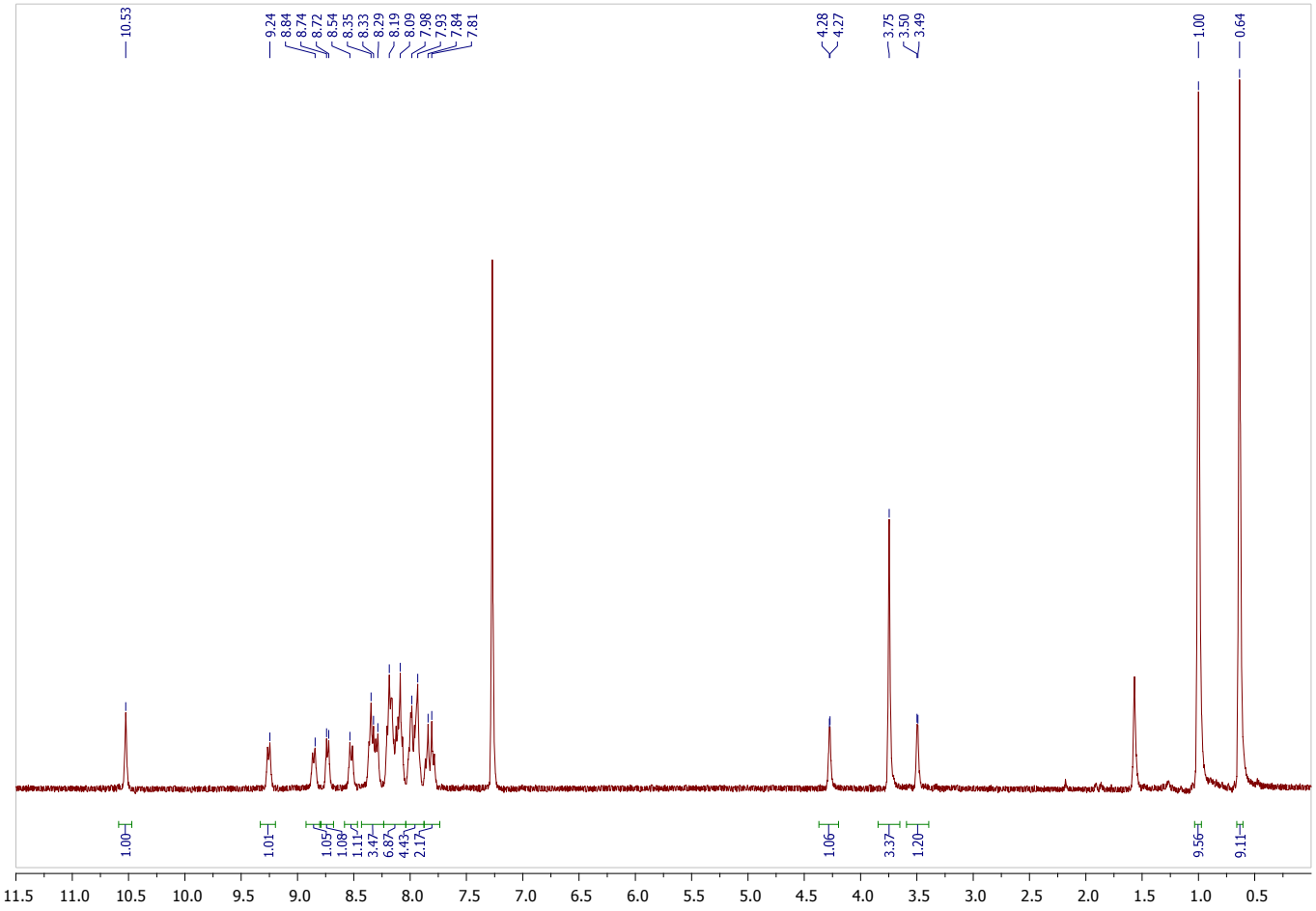



$^{13}$C NMR spectrum of **3.35**:

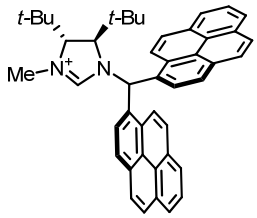




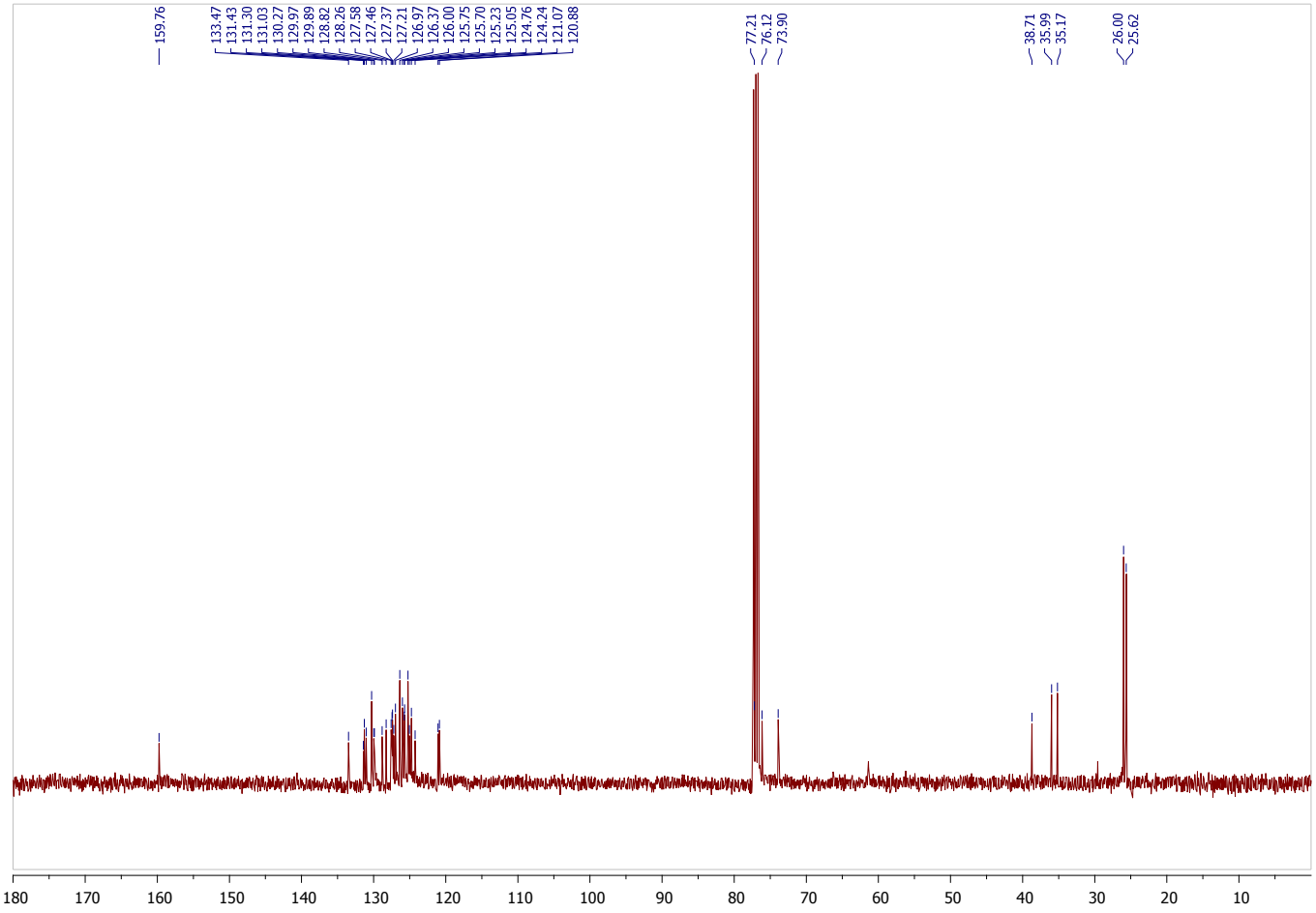

$^{1}$H NMR spectrum of **3.36**:



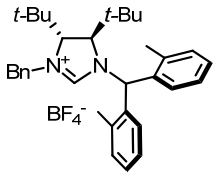

Y



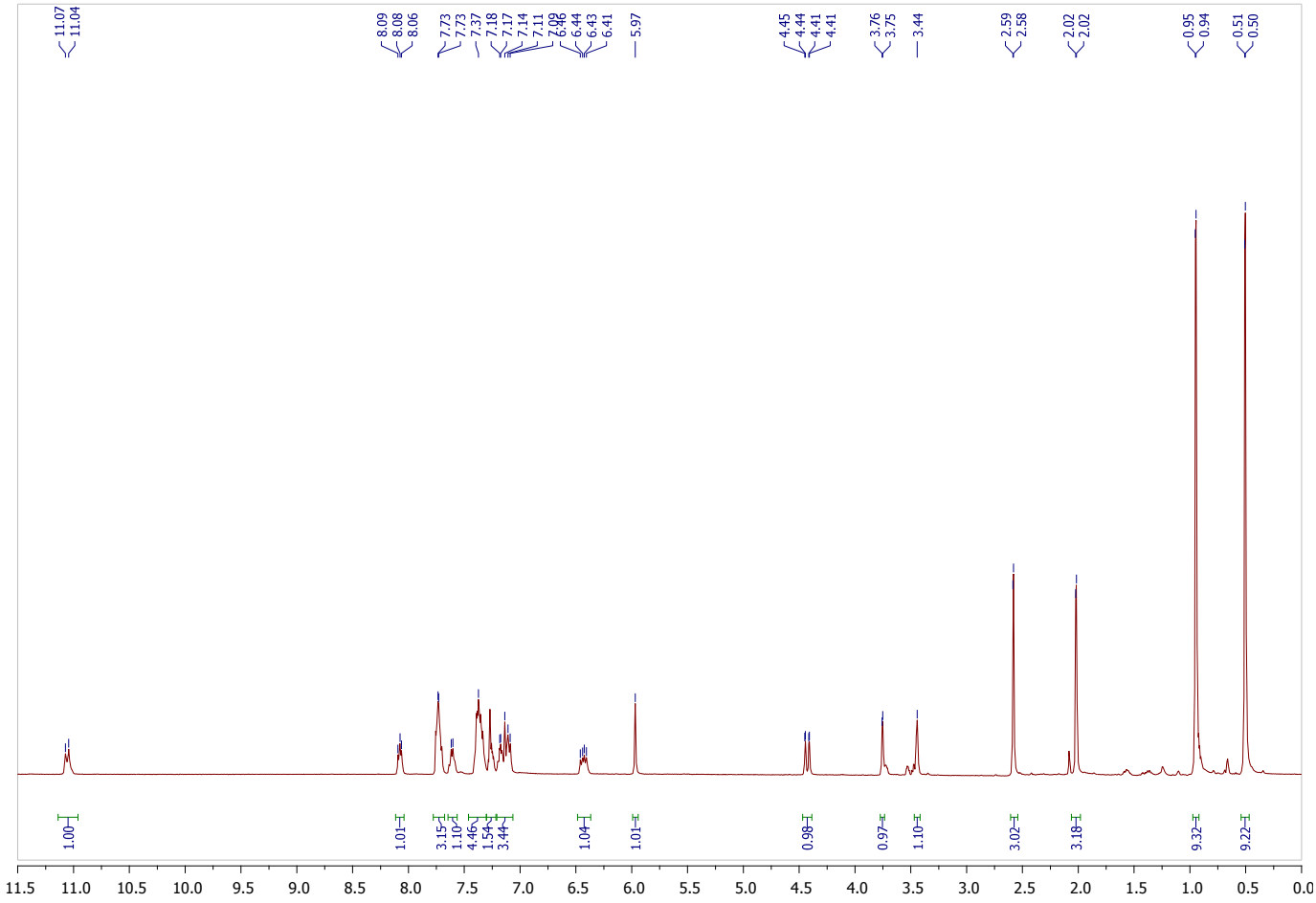

$^{13}$C NMR spectrum of **3.36**:



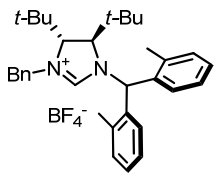

Z



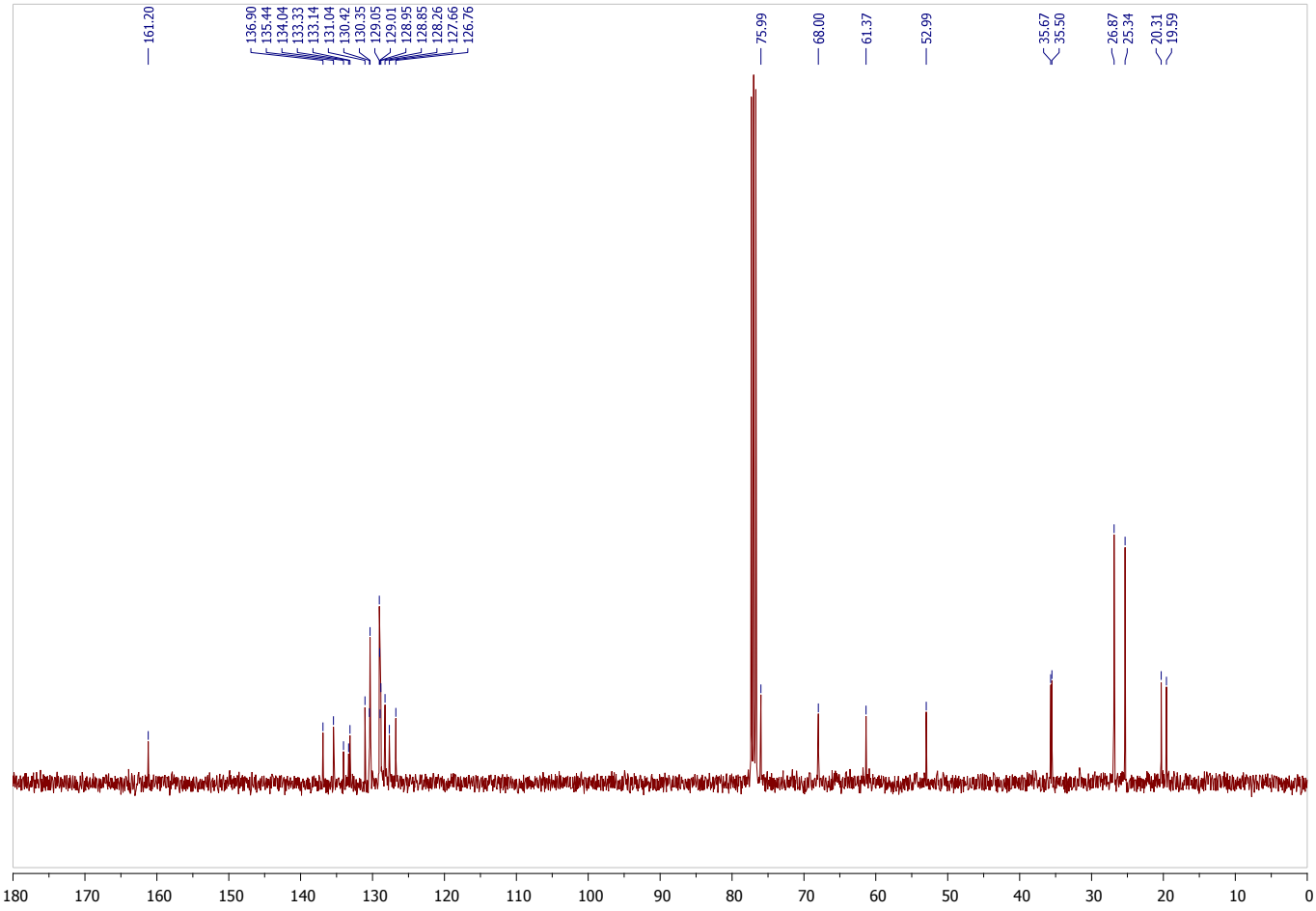

$^{1}$H NMR spectrum of **3.37**:



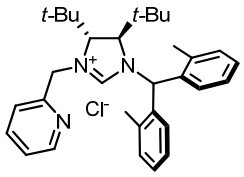

AA



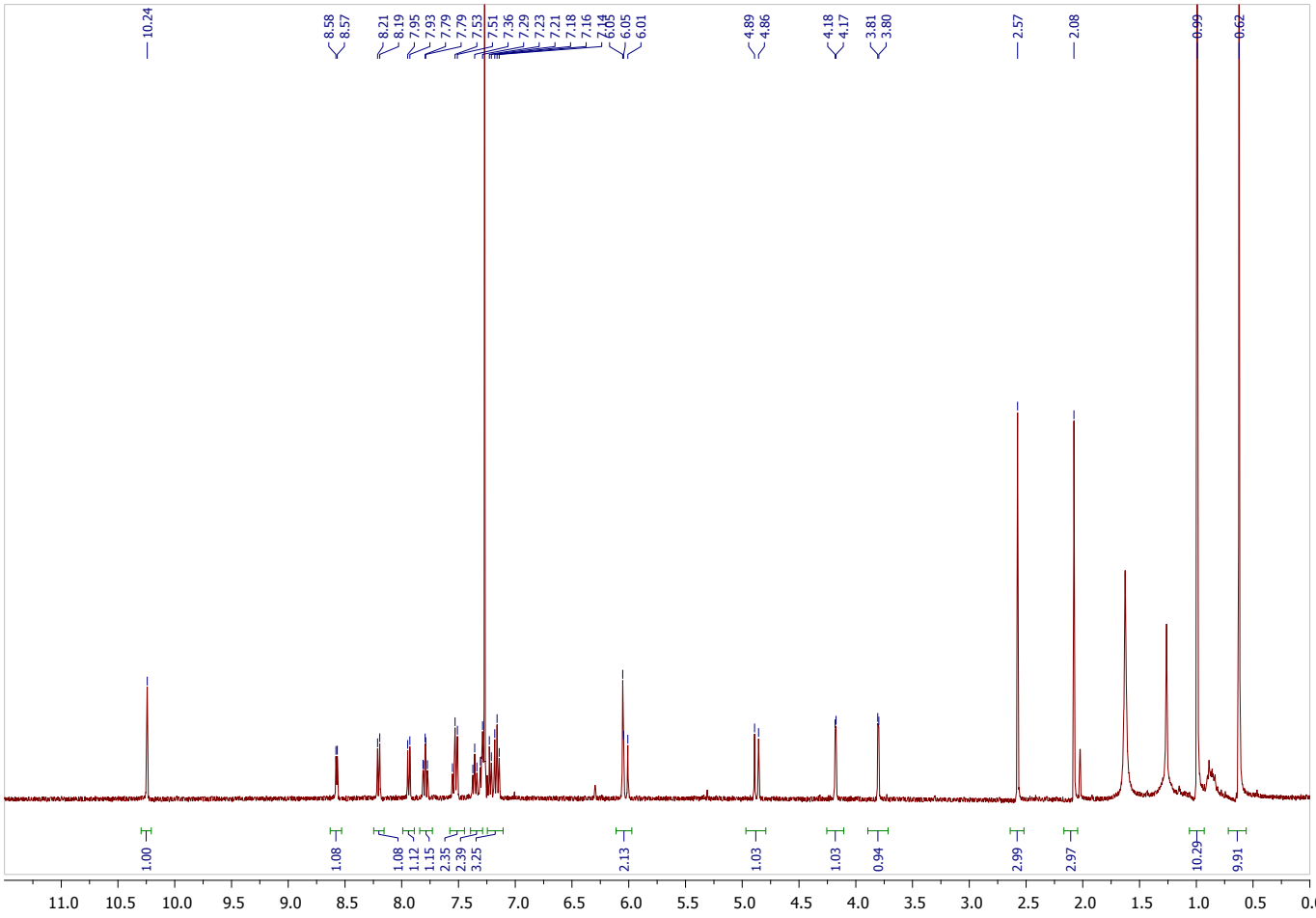

$^{13}$C NMR spectrum of **3.37**:



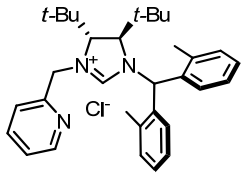

BB



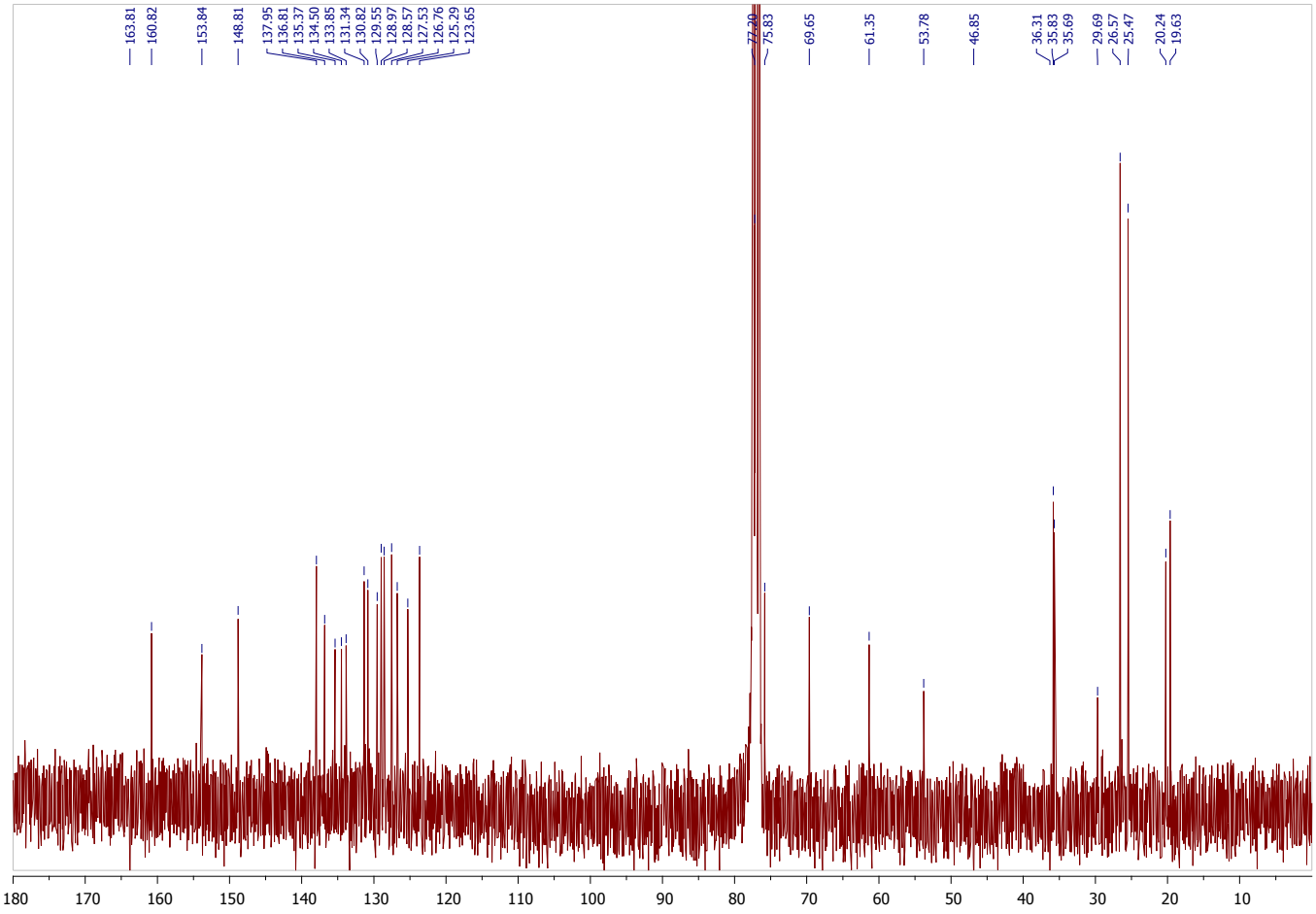

$^1$H NMR spectrum of **3.38**:




CC



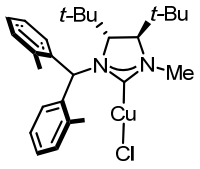

$^{13}$C NMR spectrum of **3.38**:

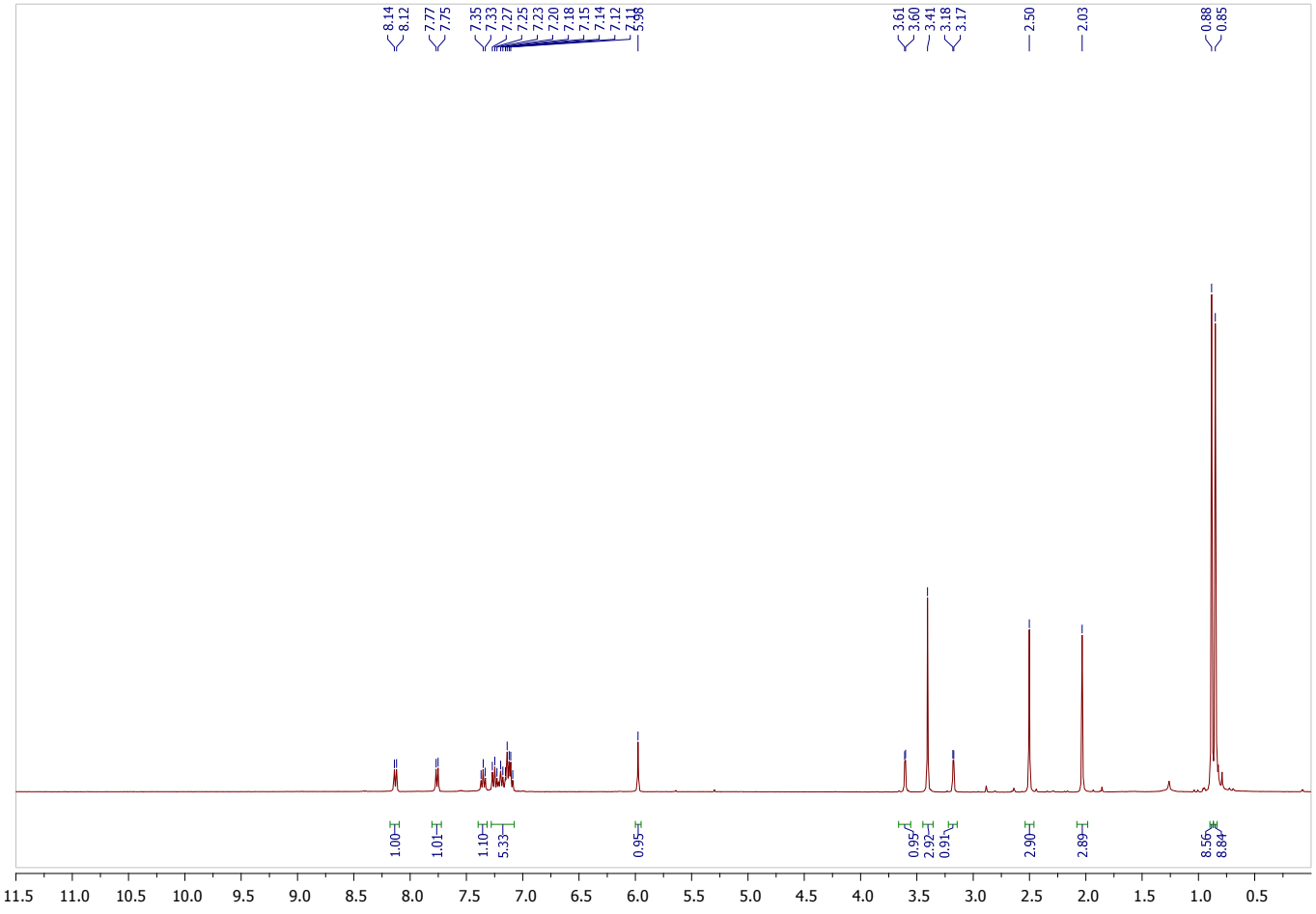



DD

## Metal Complexes

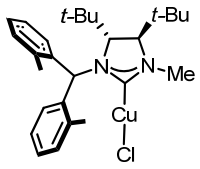
$^1$H NMR spectrum of **4.1**:

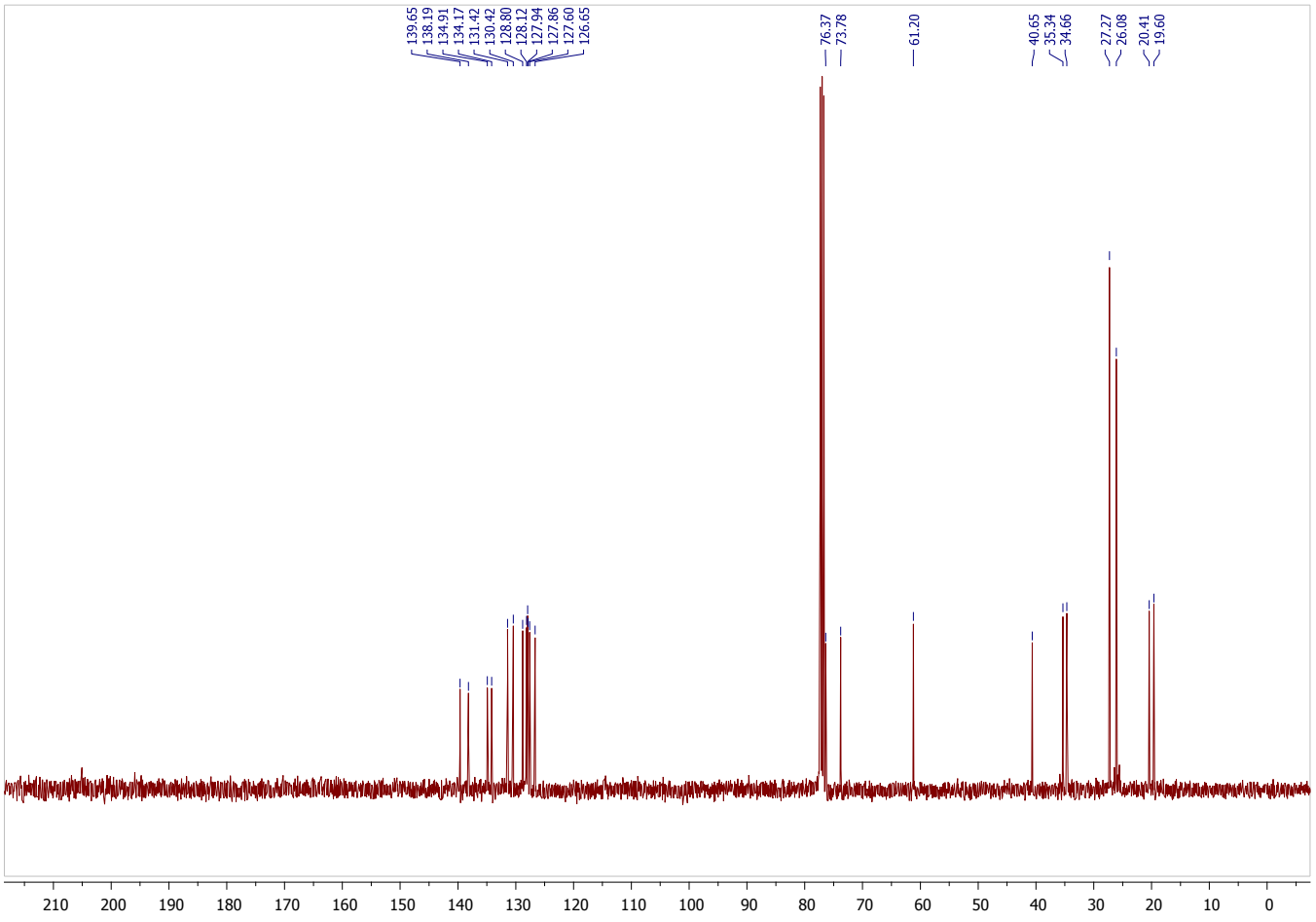



EE

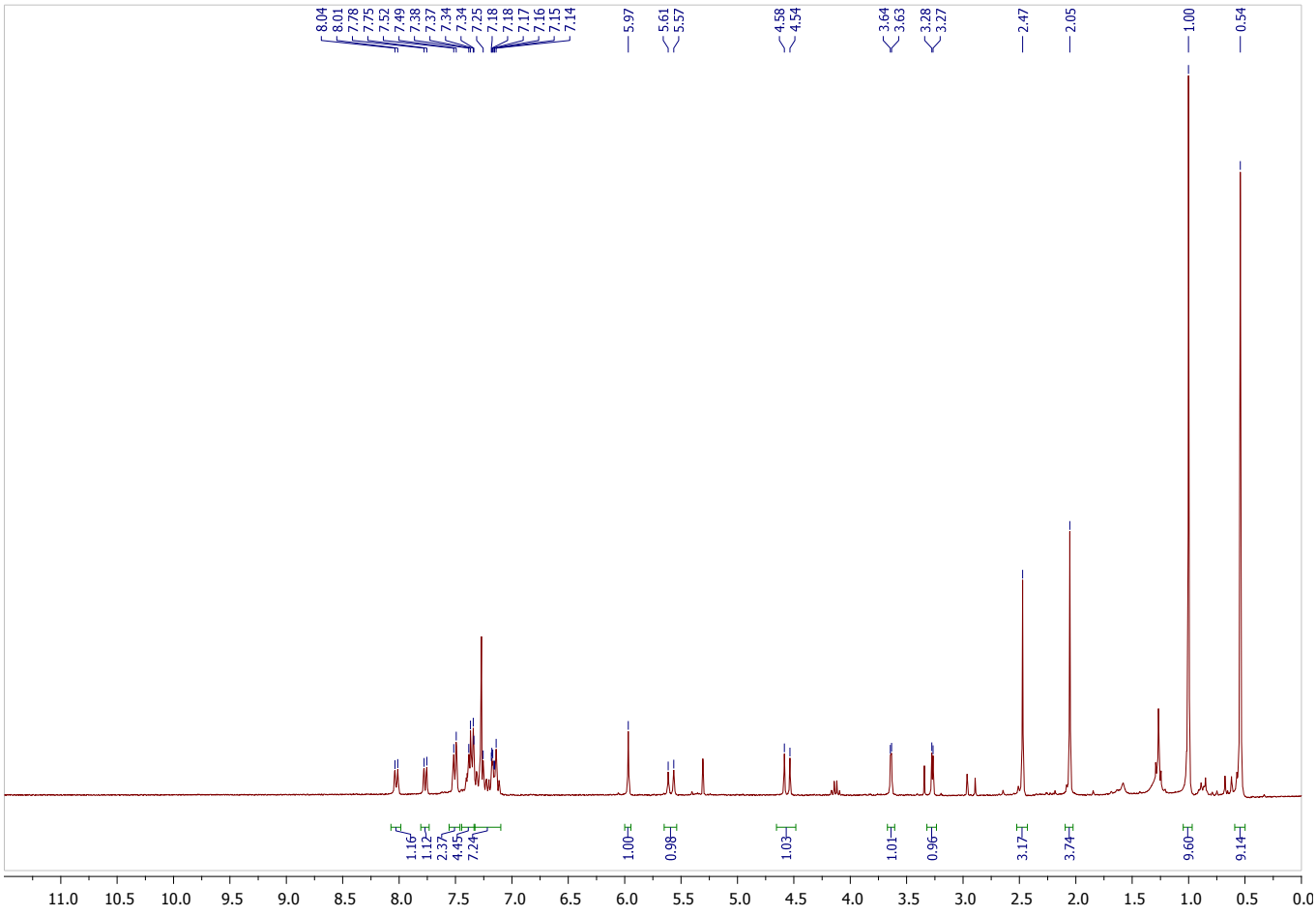
$^{13}$C NMR spectrum of **4.1**:



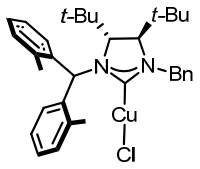

FF

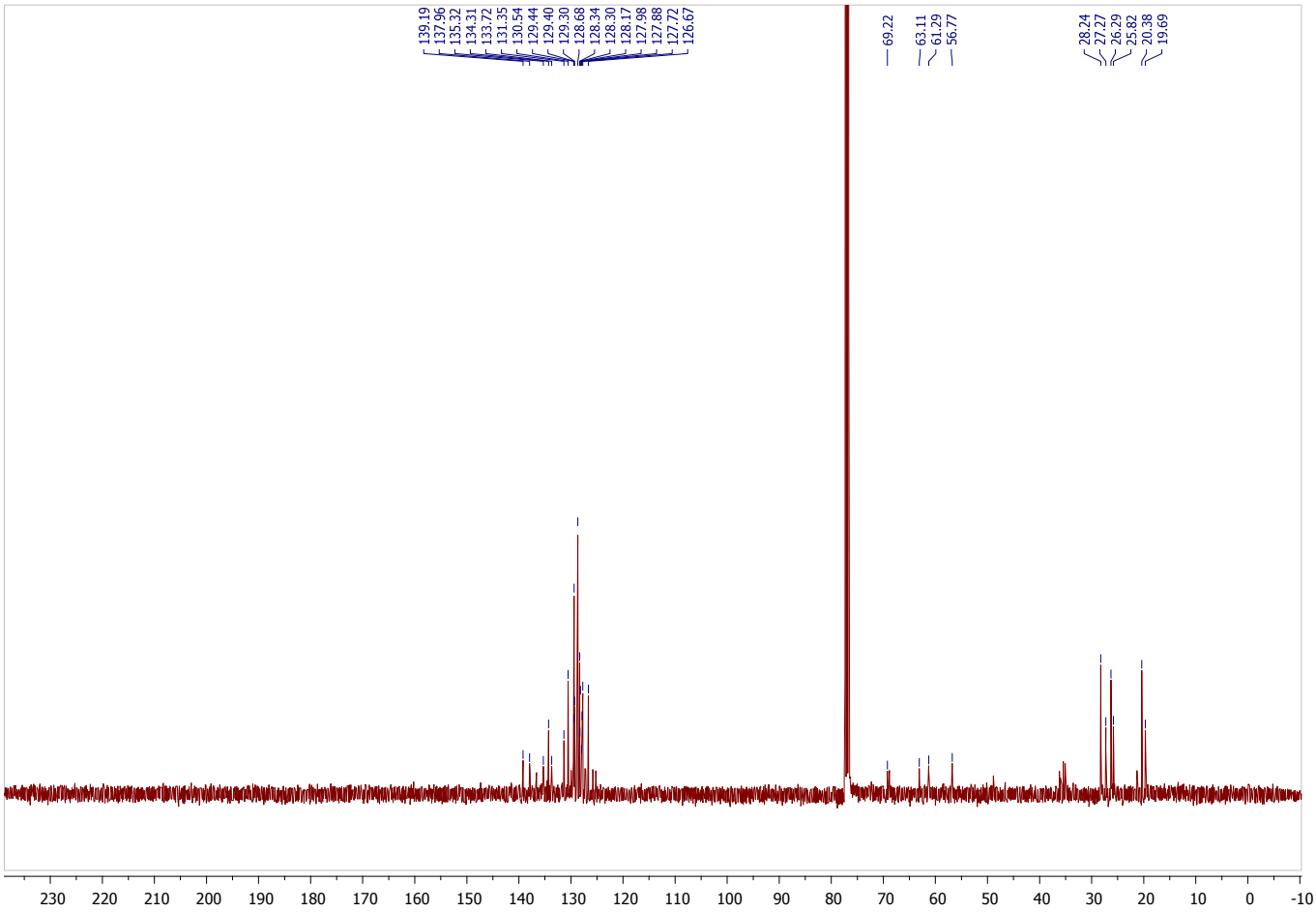
$^{1}$H NMR spectrum of **4.3**:



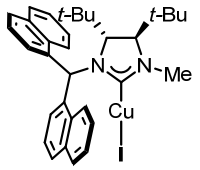

GG

$^{13}$C NMR spectrum of **4.3**:

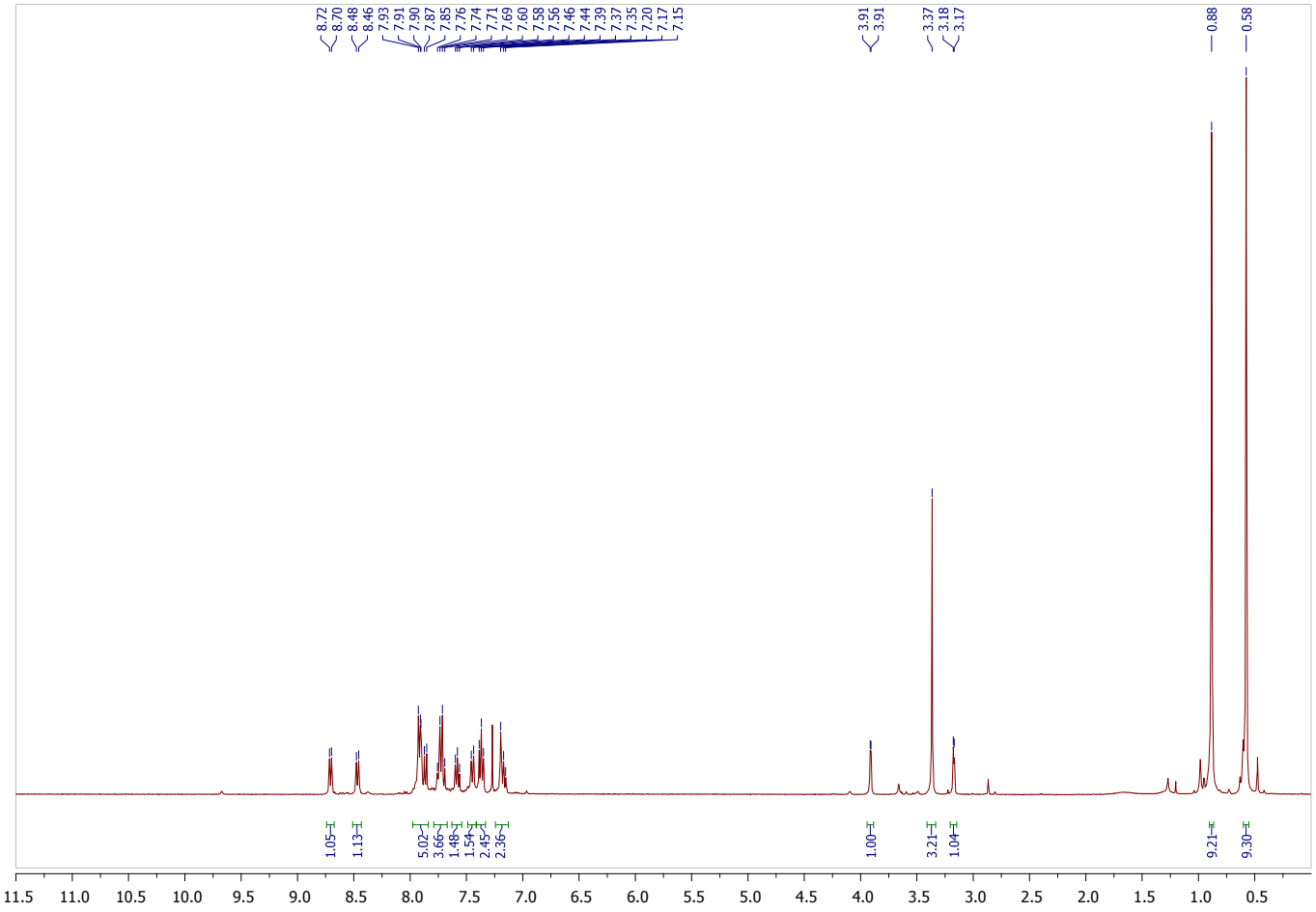


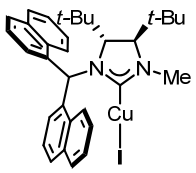

HH

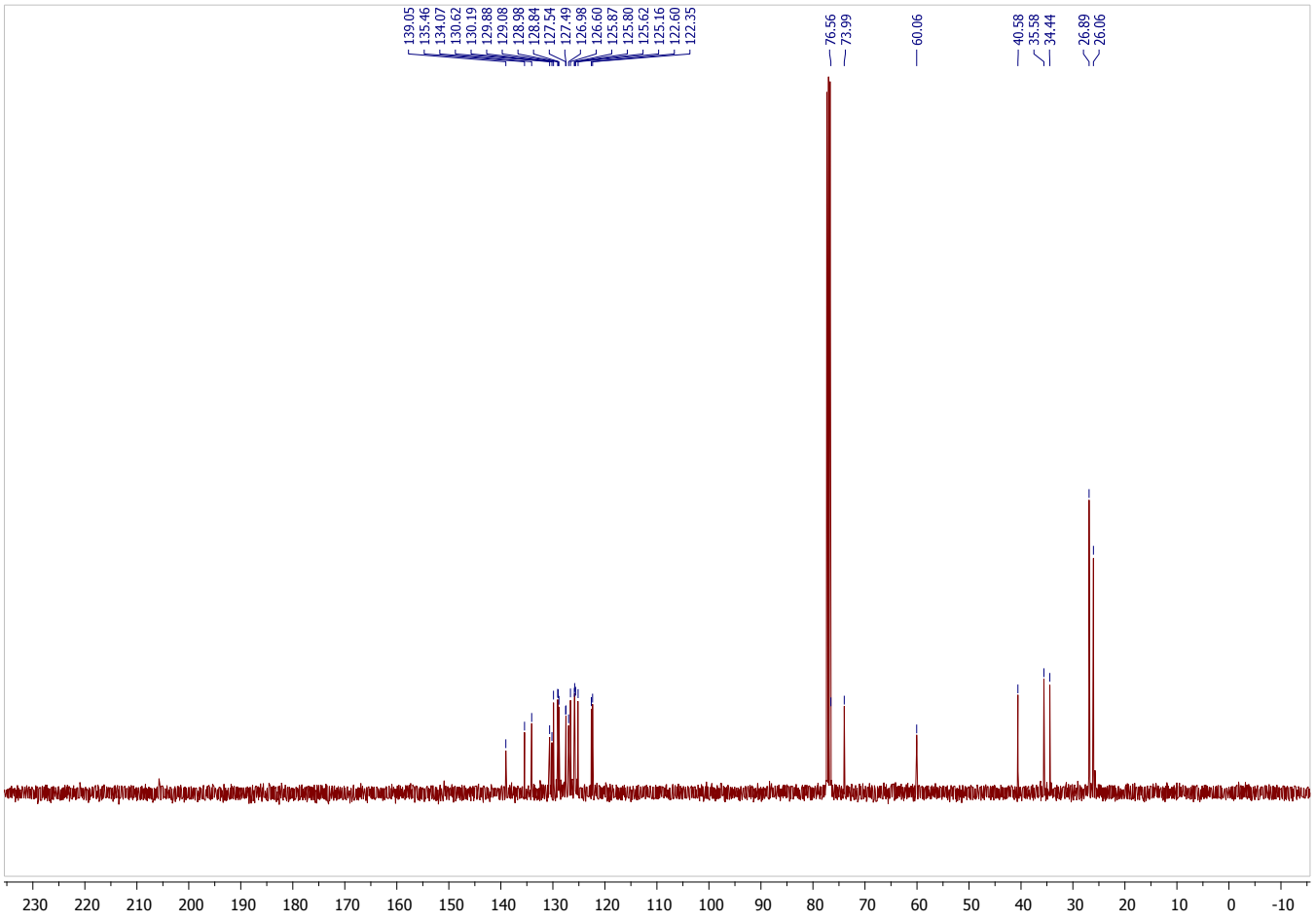



$^{1}$H NMR spectrum of **4.2b**:

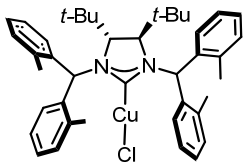


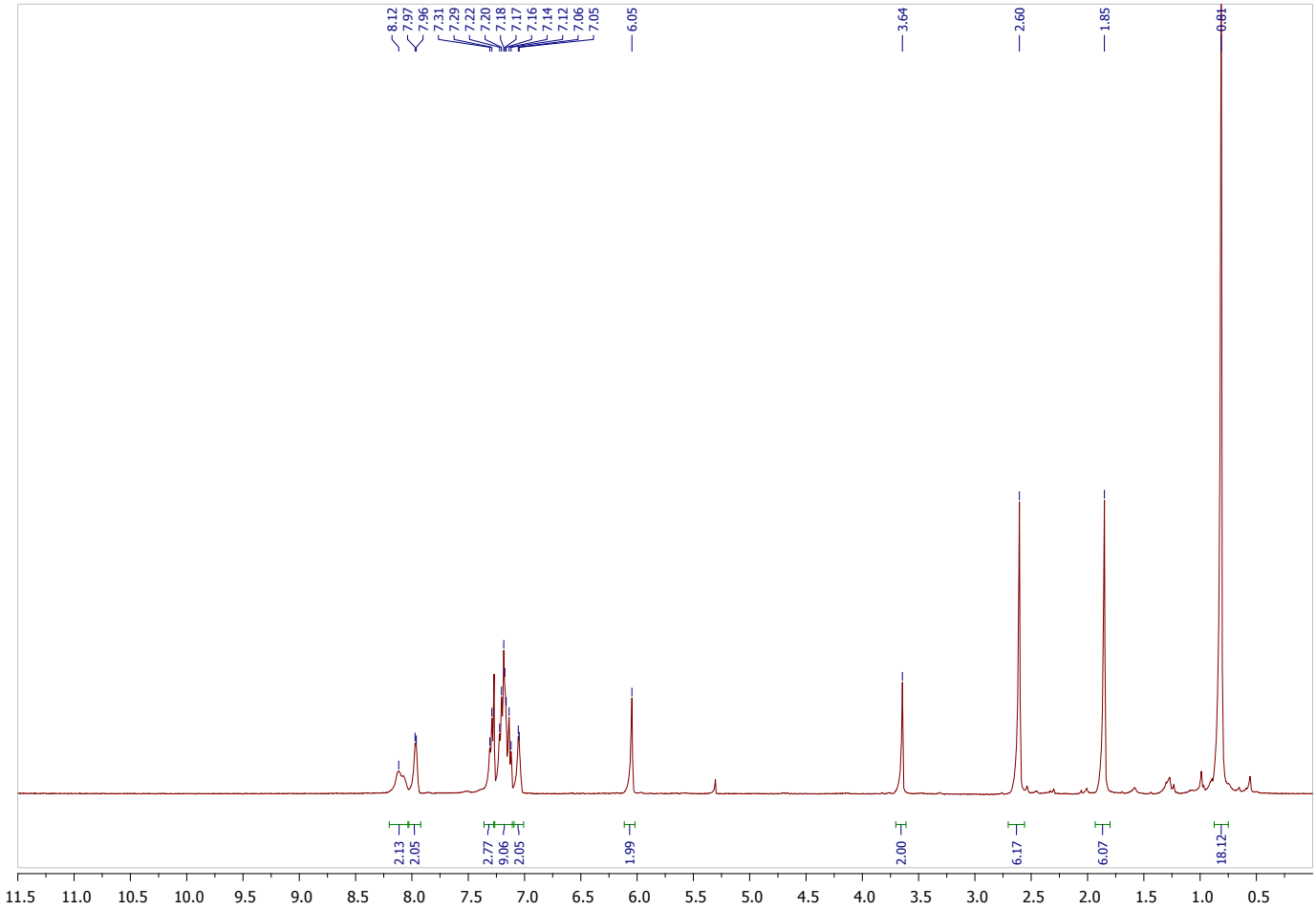
$^{13}$C NMR spectrum of **4.2b**:



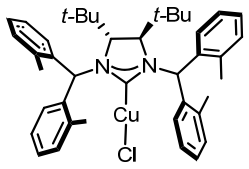
$^{1}$H NMR spectrum of **4.4**:

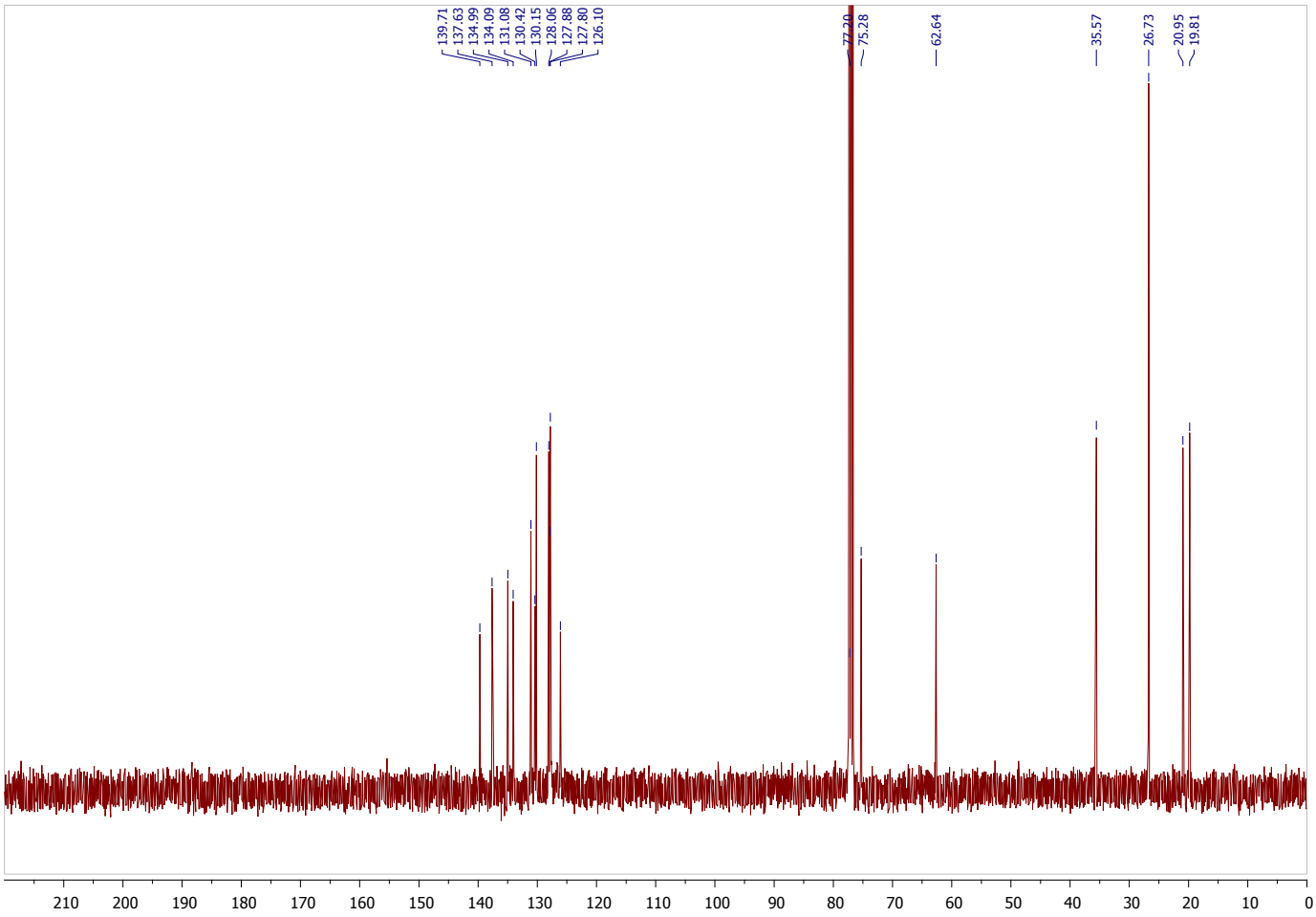



KK

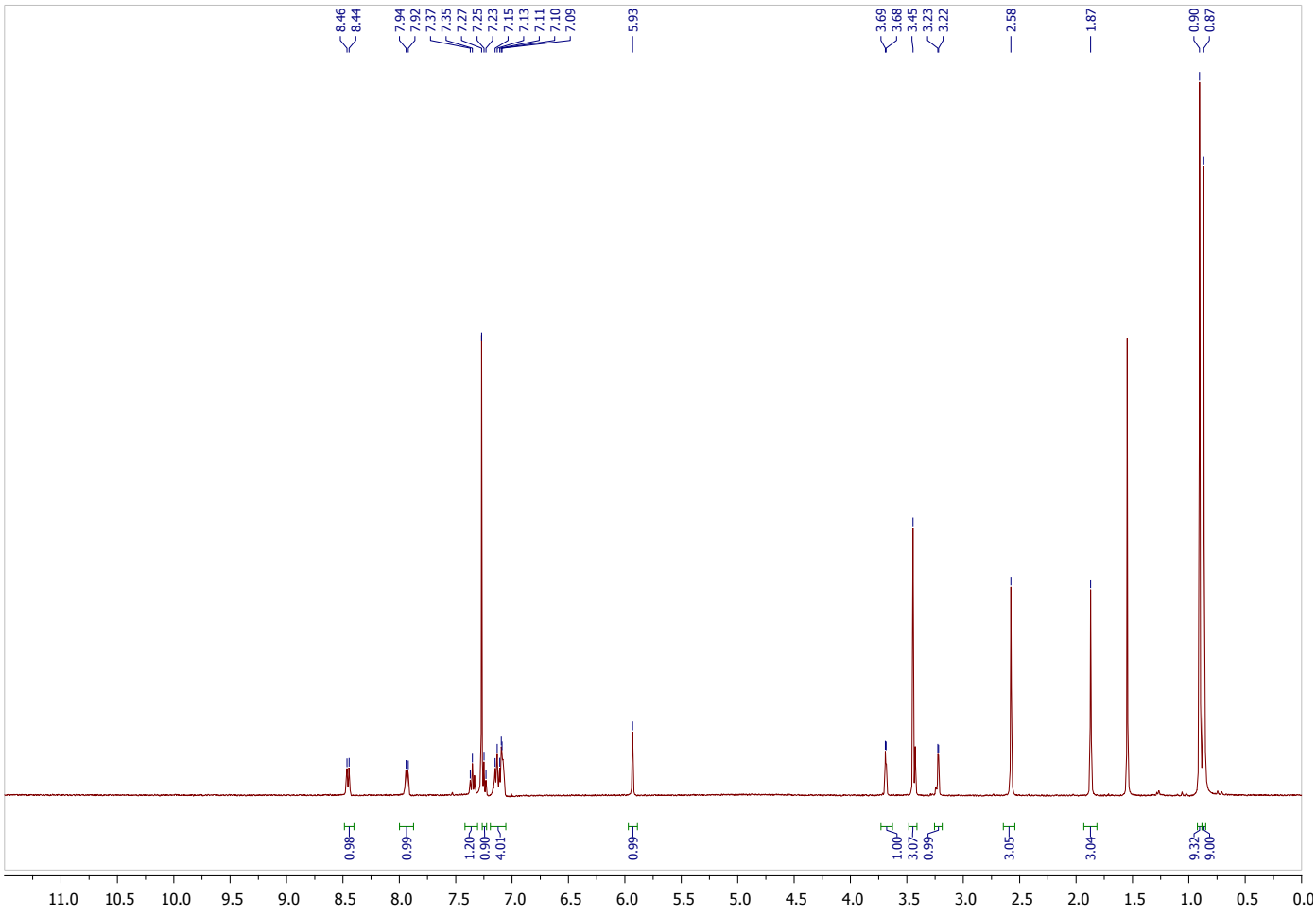
$^{13}$C NMR spectrum of **4.4**:



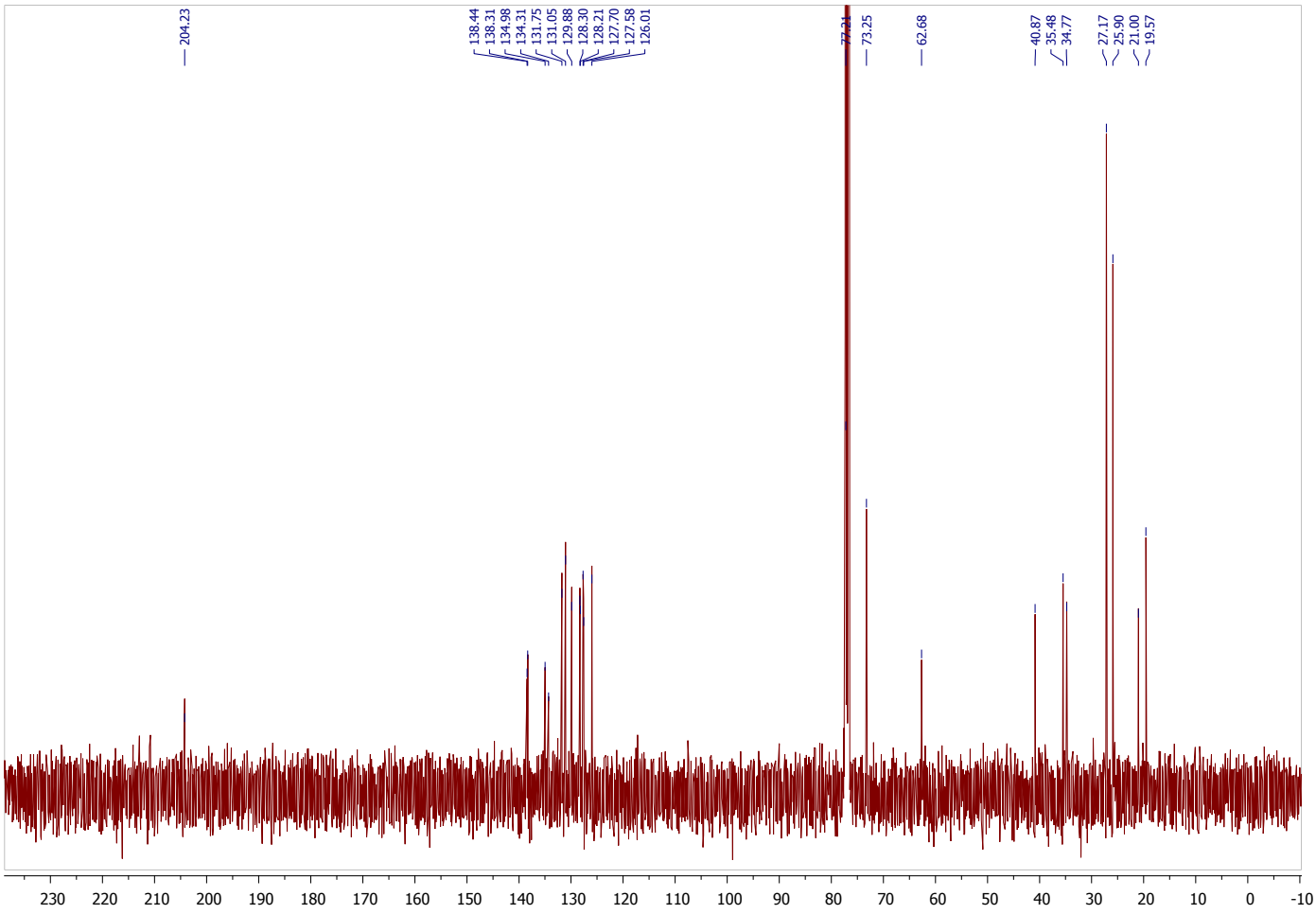

LL

$^{1}$H NMR spectrum of **4.5**:

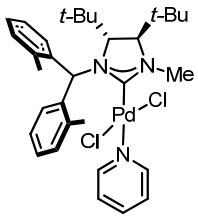



MM

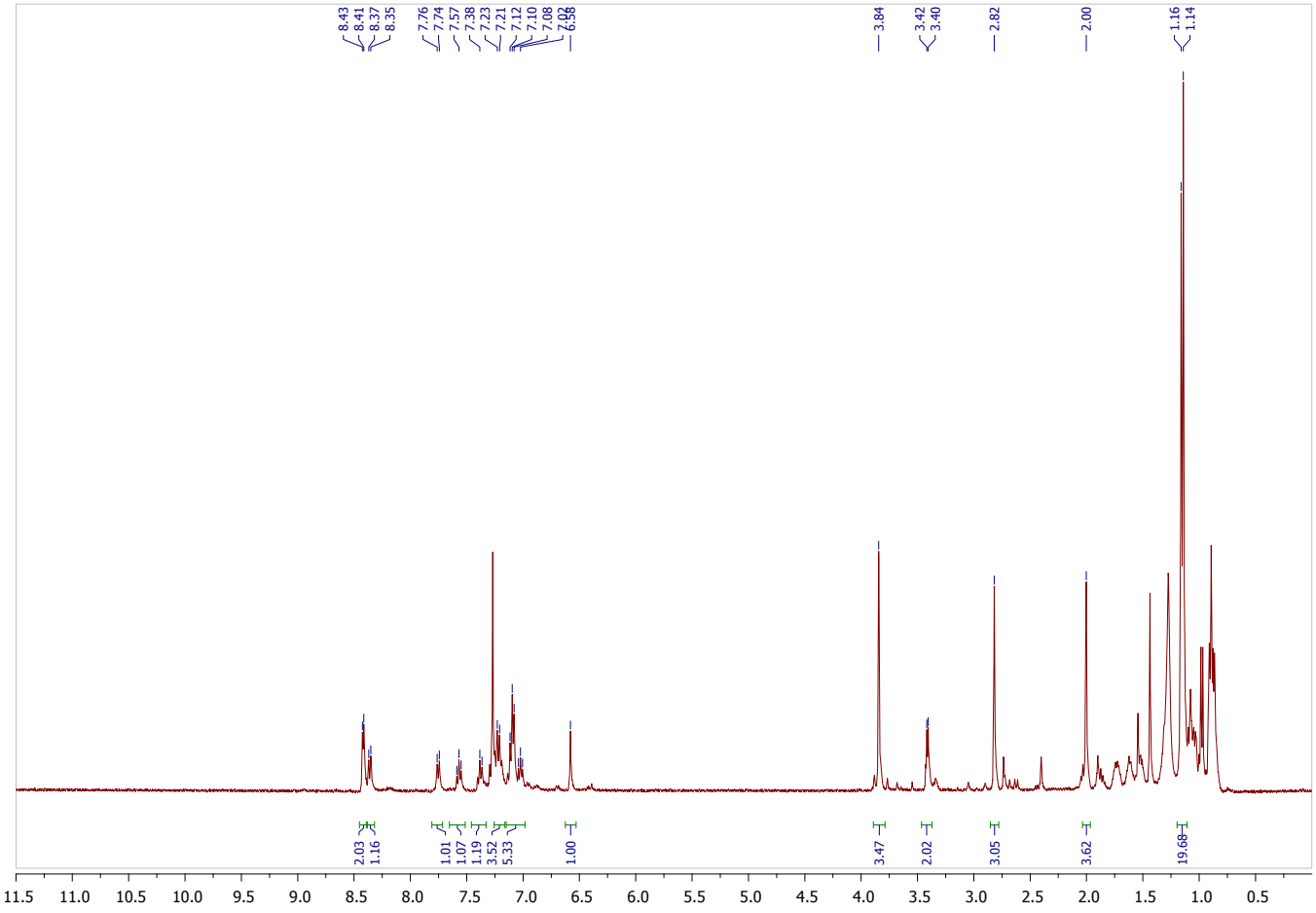
$^{13}$C NMR spectrum of **4.5**:




NN

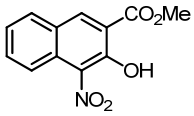



$^{1}$H NMR spectrum of **4.6**:

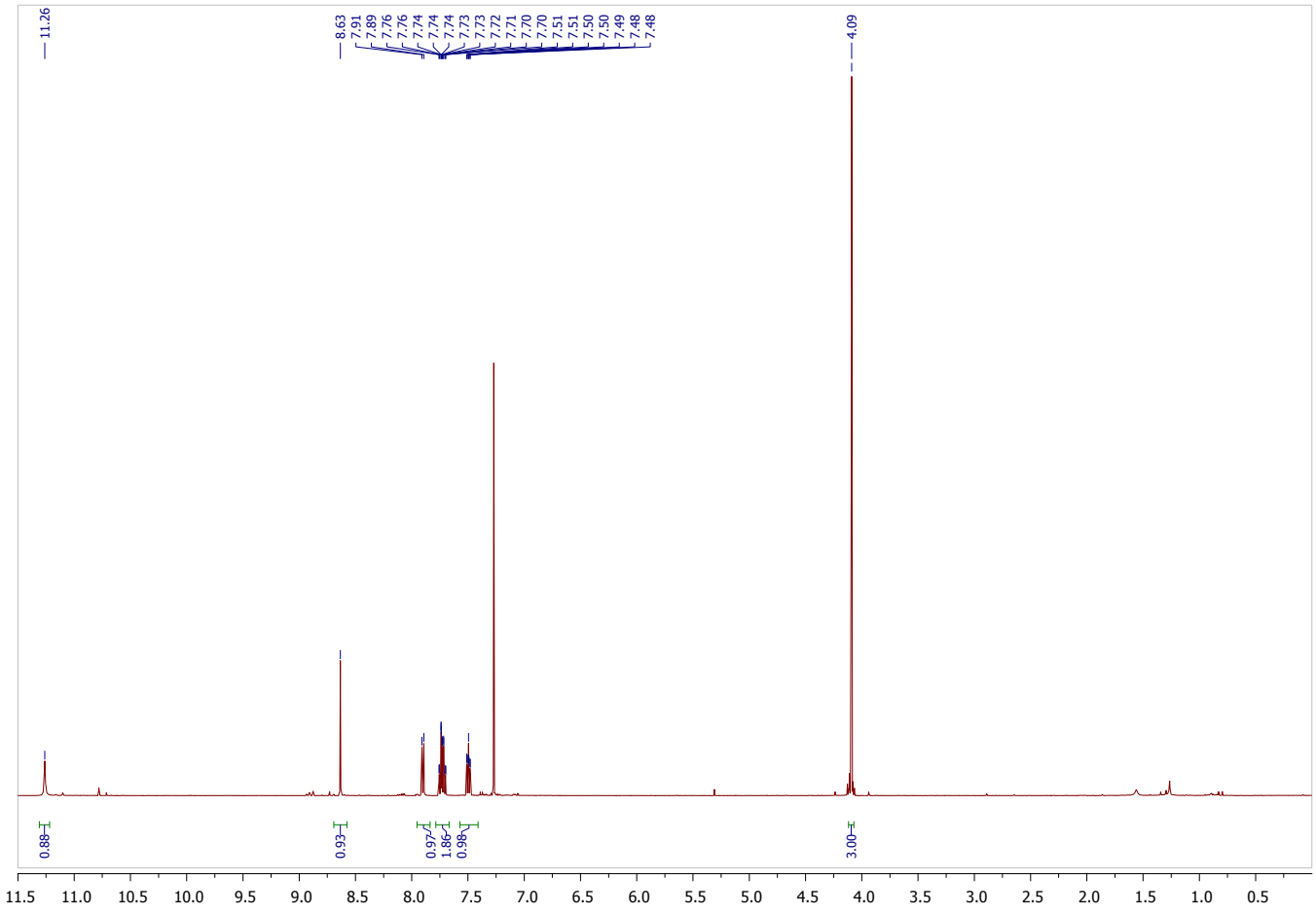



OO

## 2-Naphthols

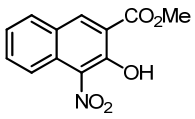


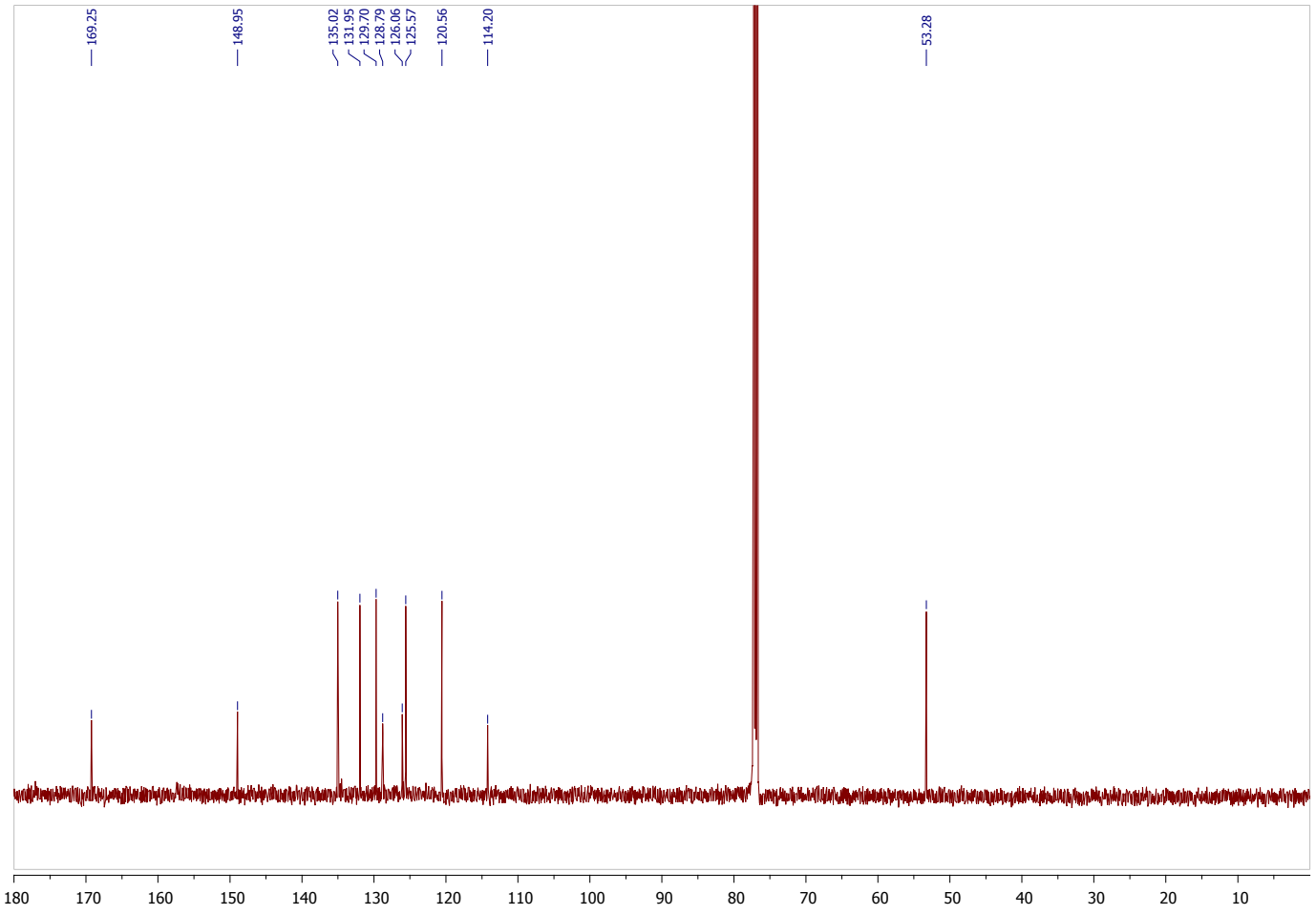

$^1$H NMR Spectrum of **6.1**:




PP

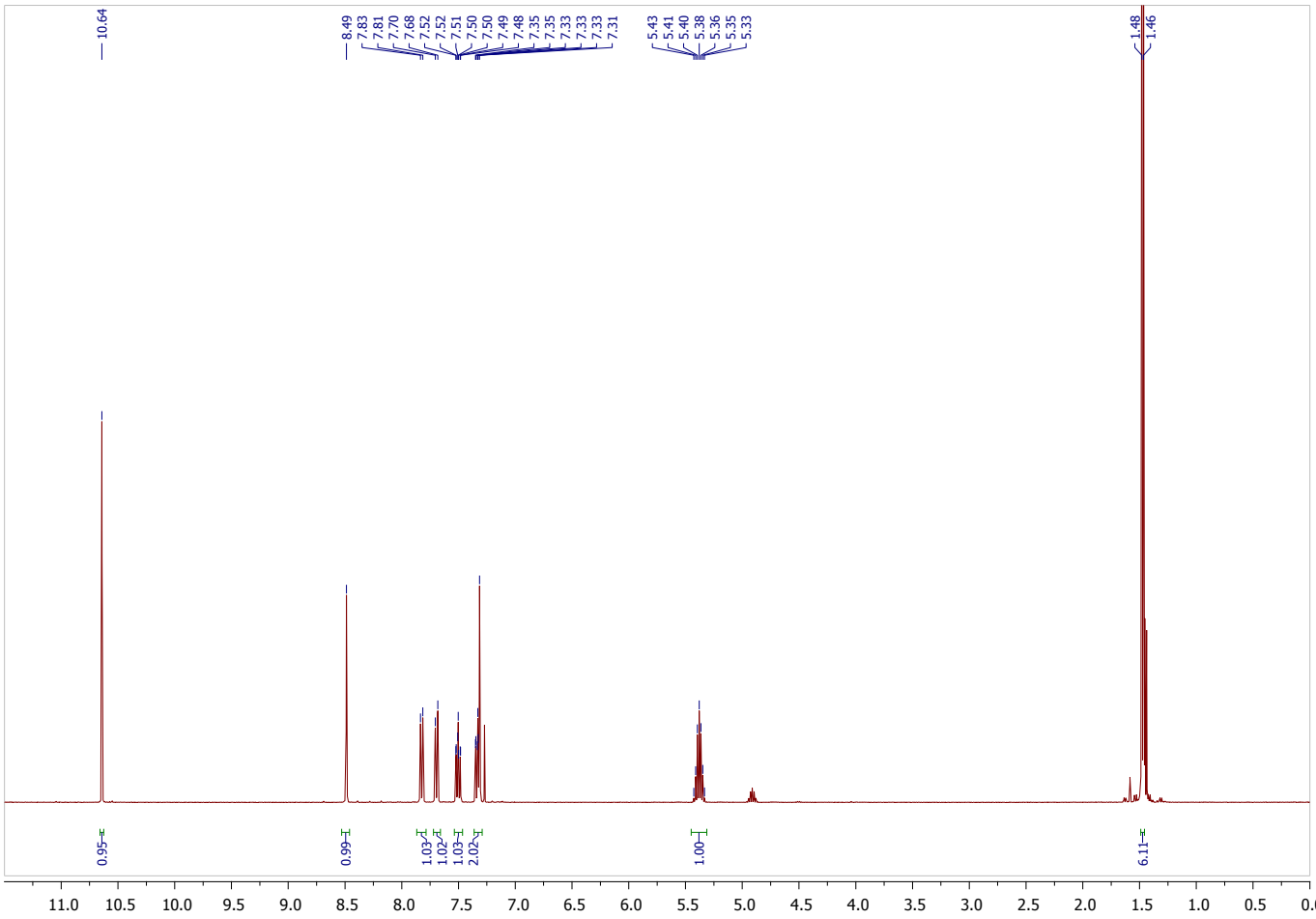
$^{13}$C NMR Spectrum of **6.1**:



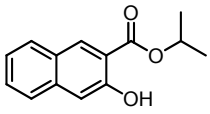

QQ

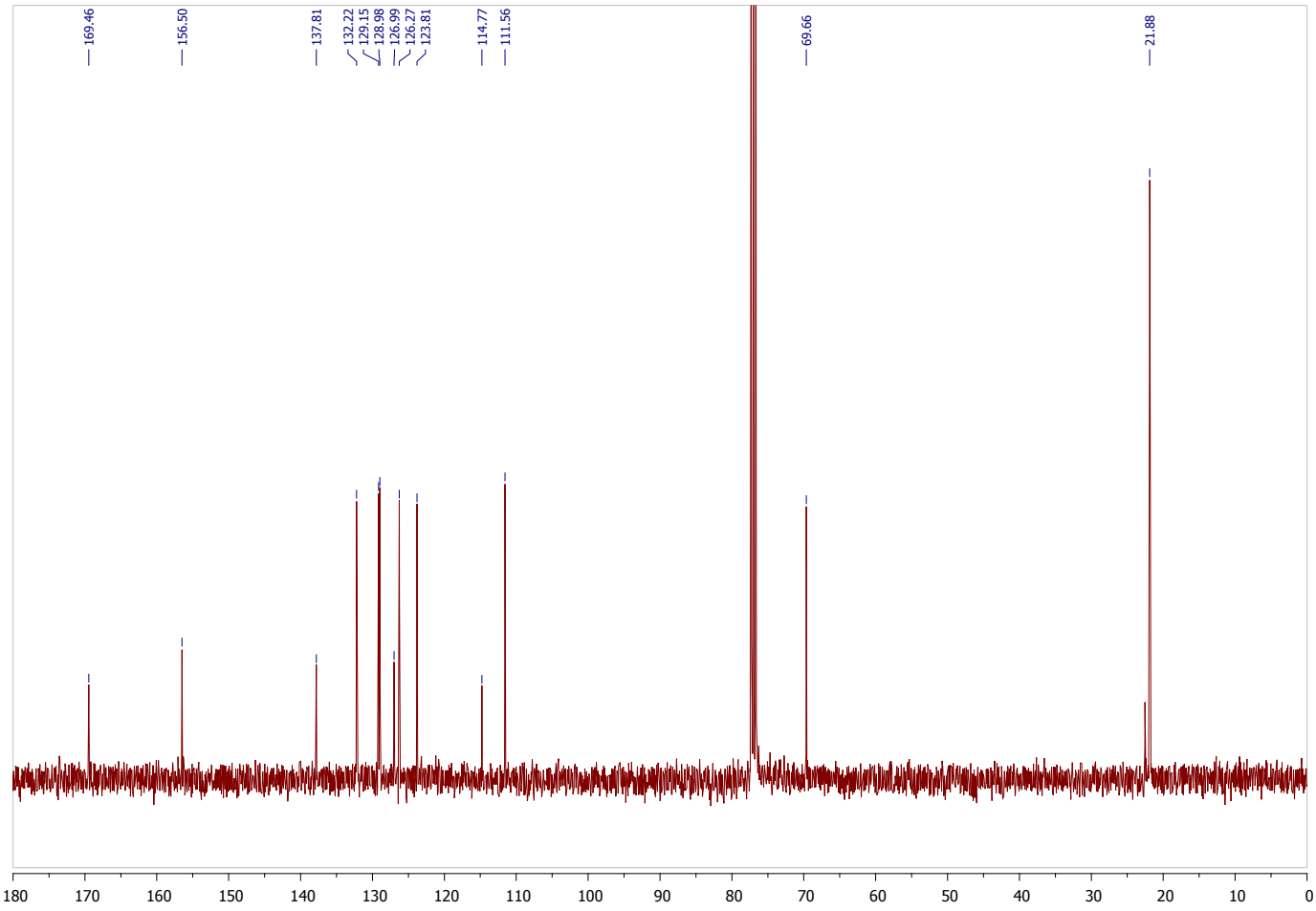
$^{1}$H NMR Spectrum of **6.3**:



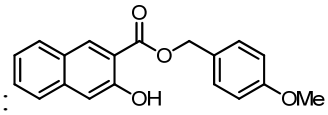

RR

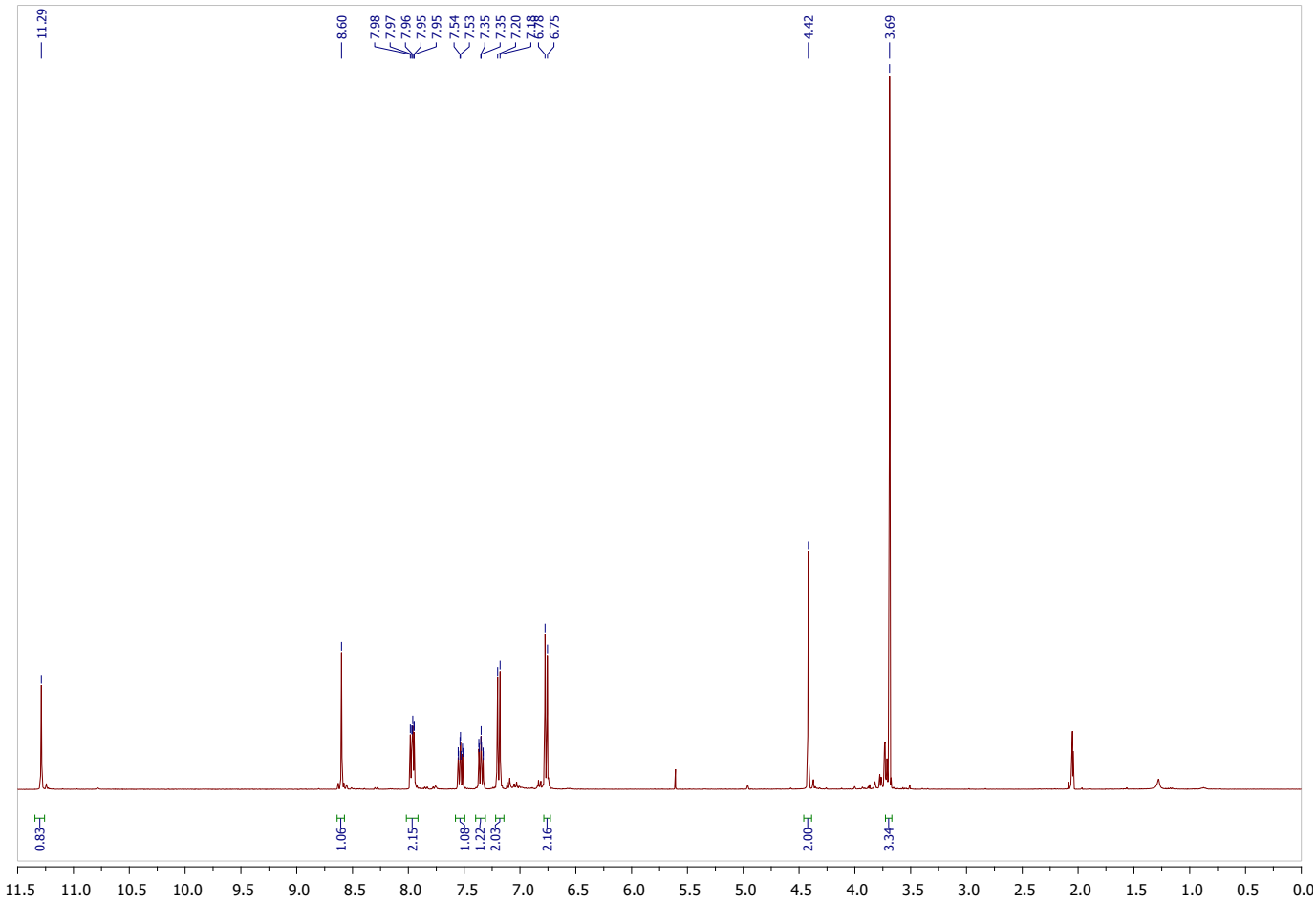
$^{13}$C NMR Spectrum of **6.3**:



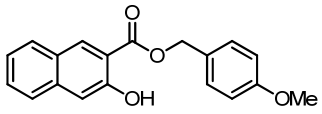
$^{1}$HNMR Spectrum of **6.7**:

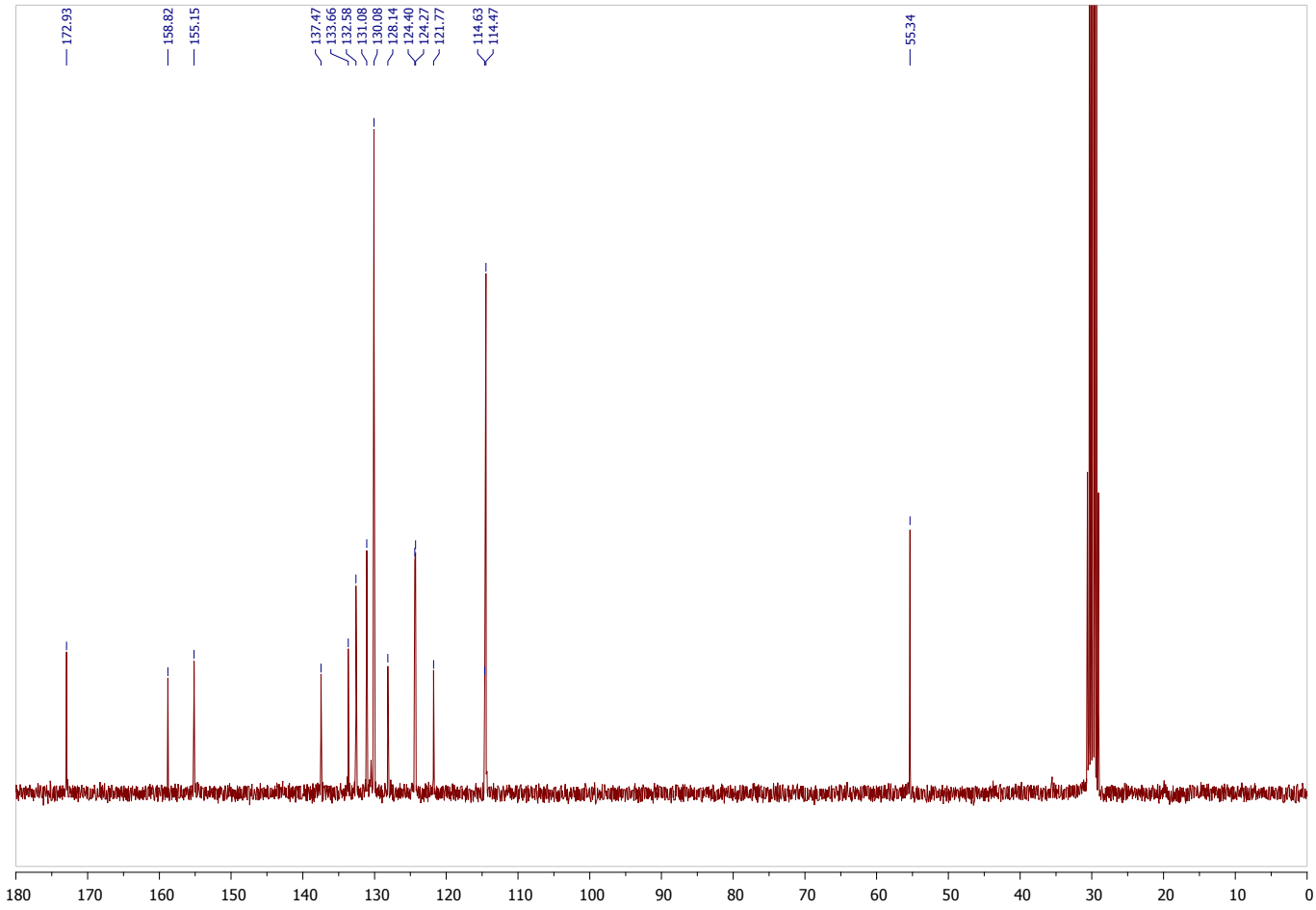



TT

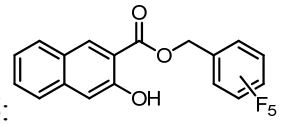
$^{13}$C NMR Spectrum of **6.7**:

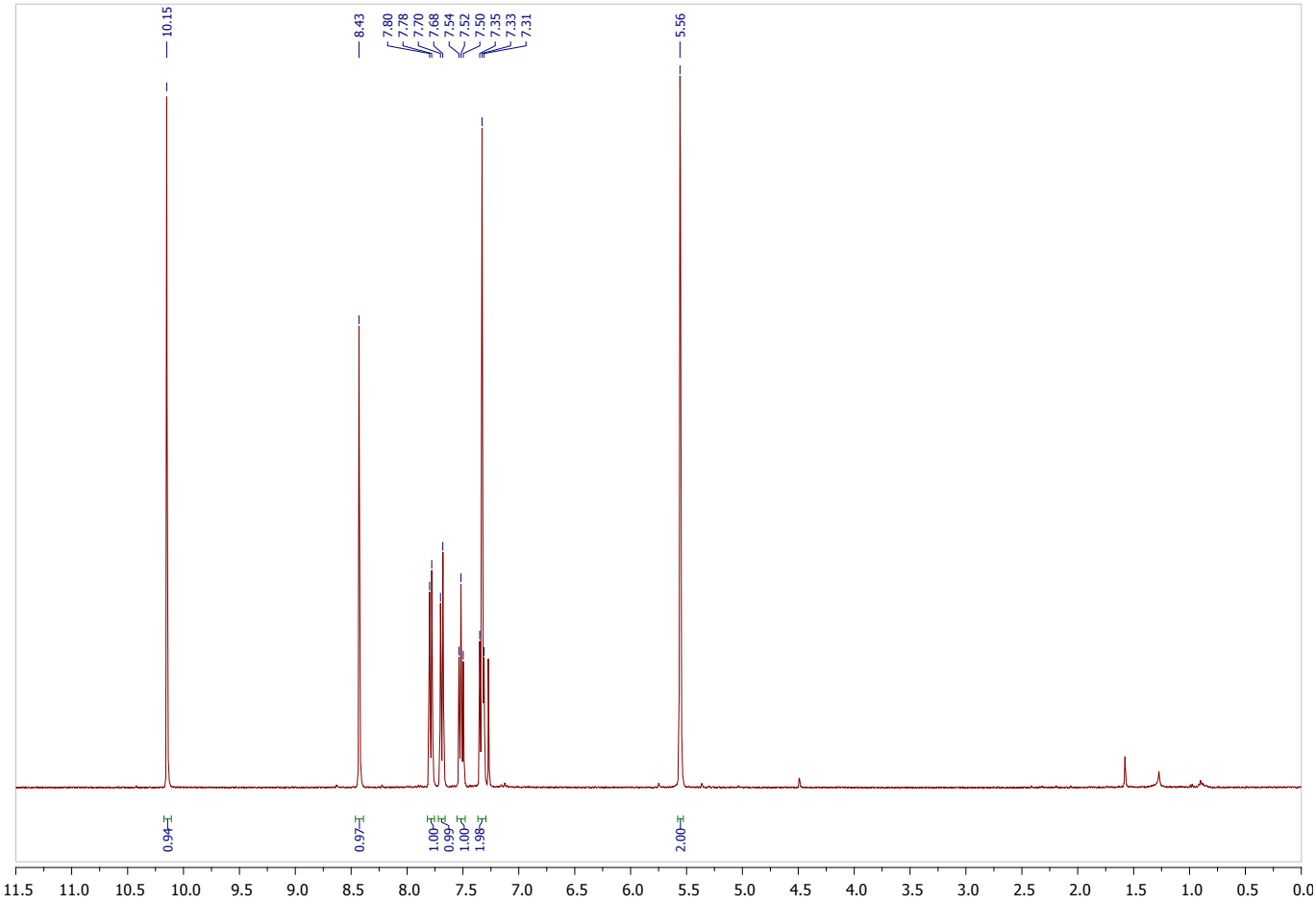


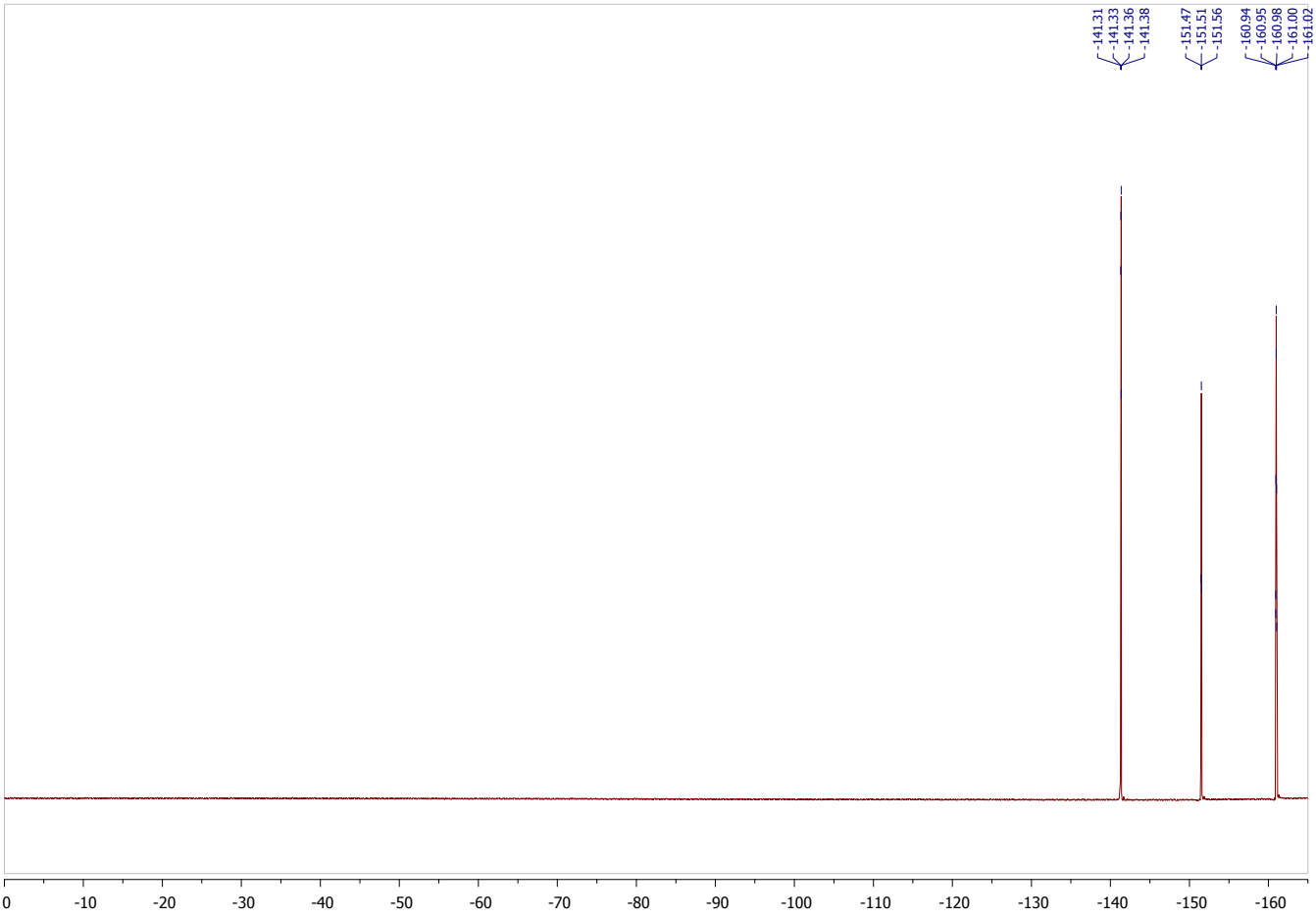

UU

$^{1}$H NMR Spectrum of **6.6**:



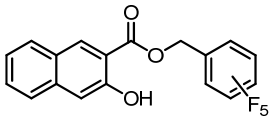



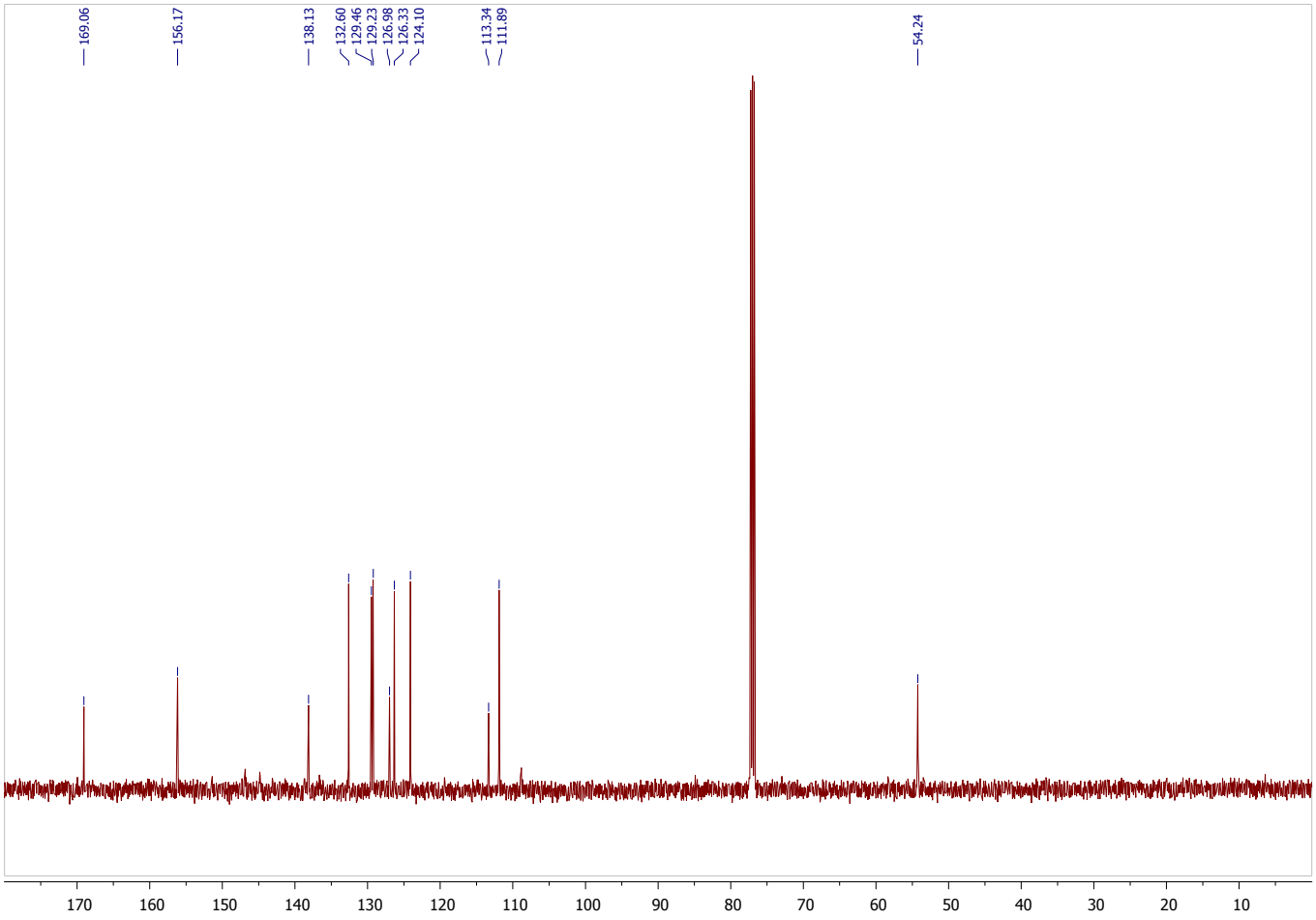
$^{19}$F NMR Spectrum of **6.6**:



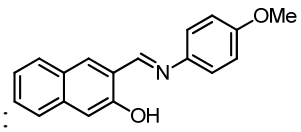

WW

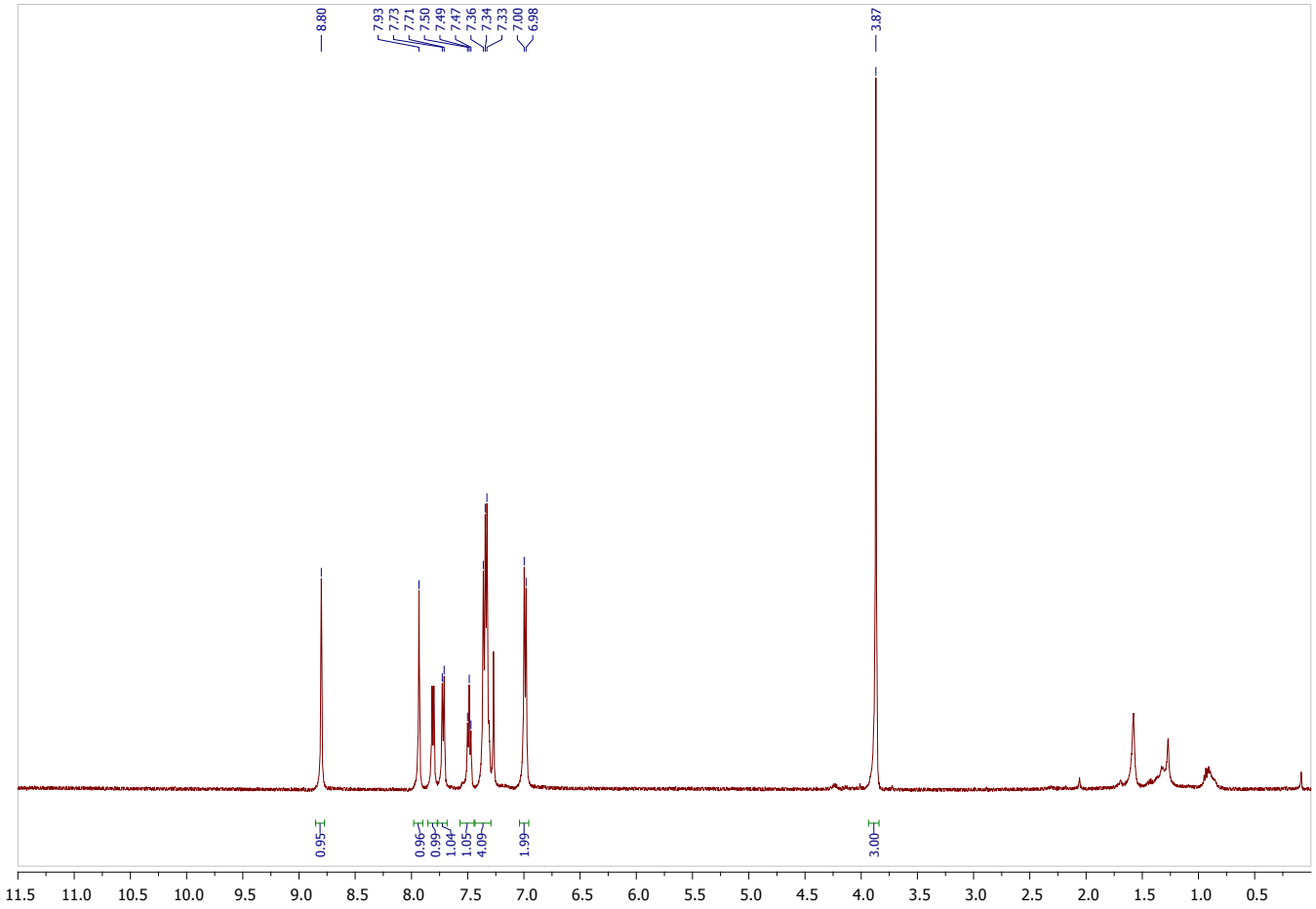
$^{13}$C NMR Spectrum of **6.6**:



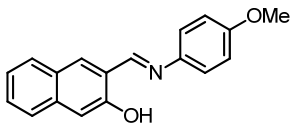
$^{1}$H NMR Spectrum of **7.20**:

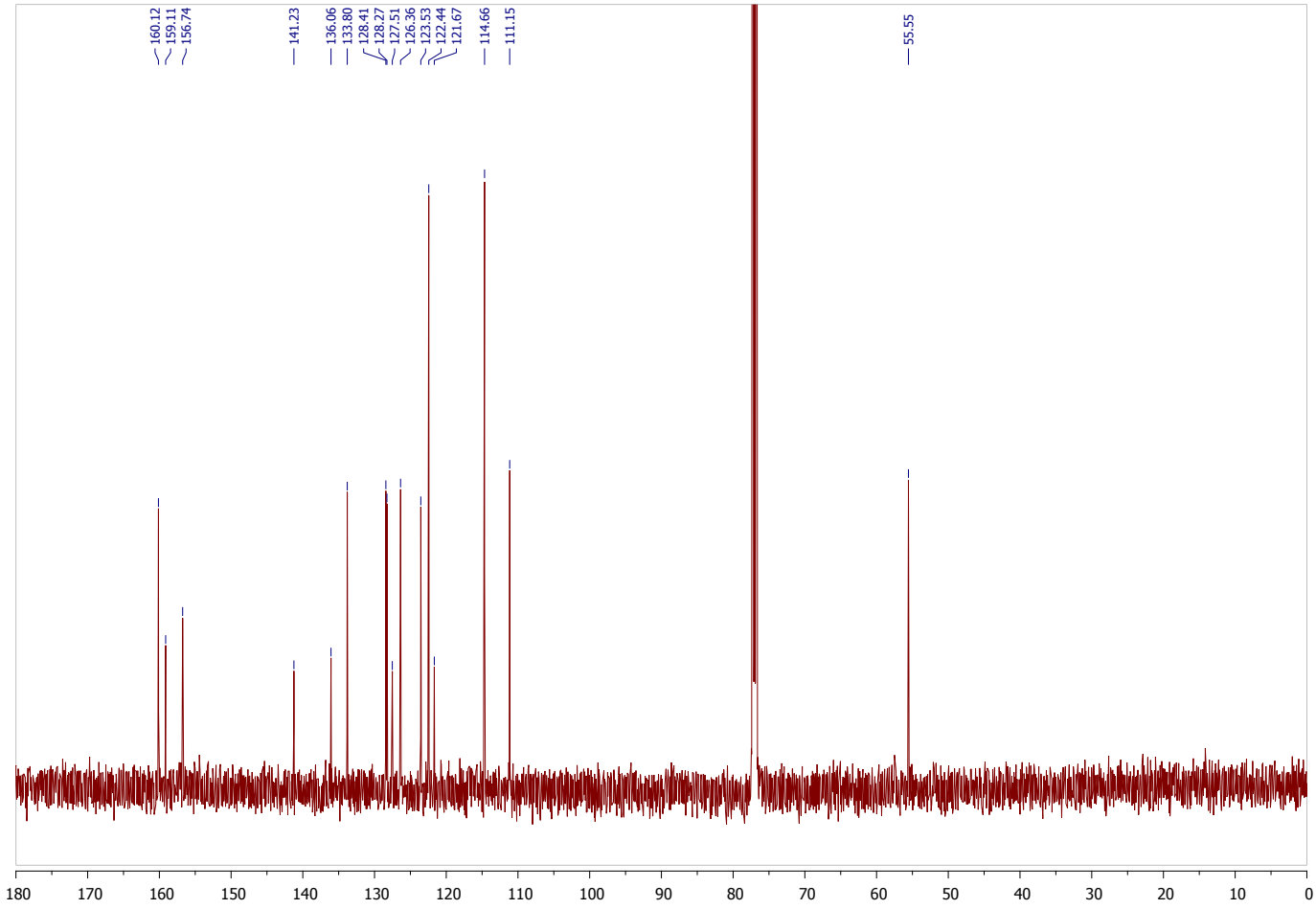



YY

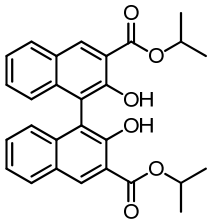
$^{13}$C NMR Spectrum of **7.20**:



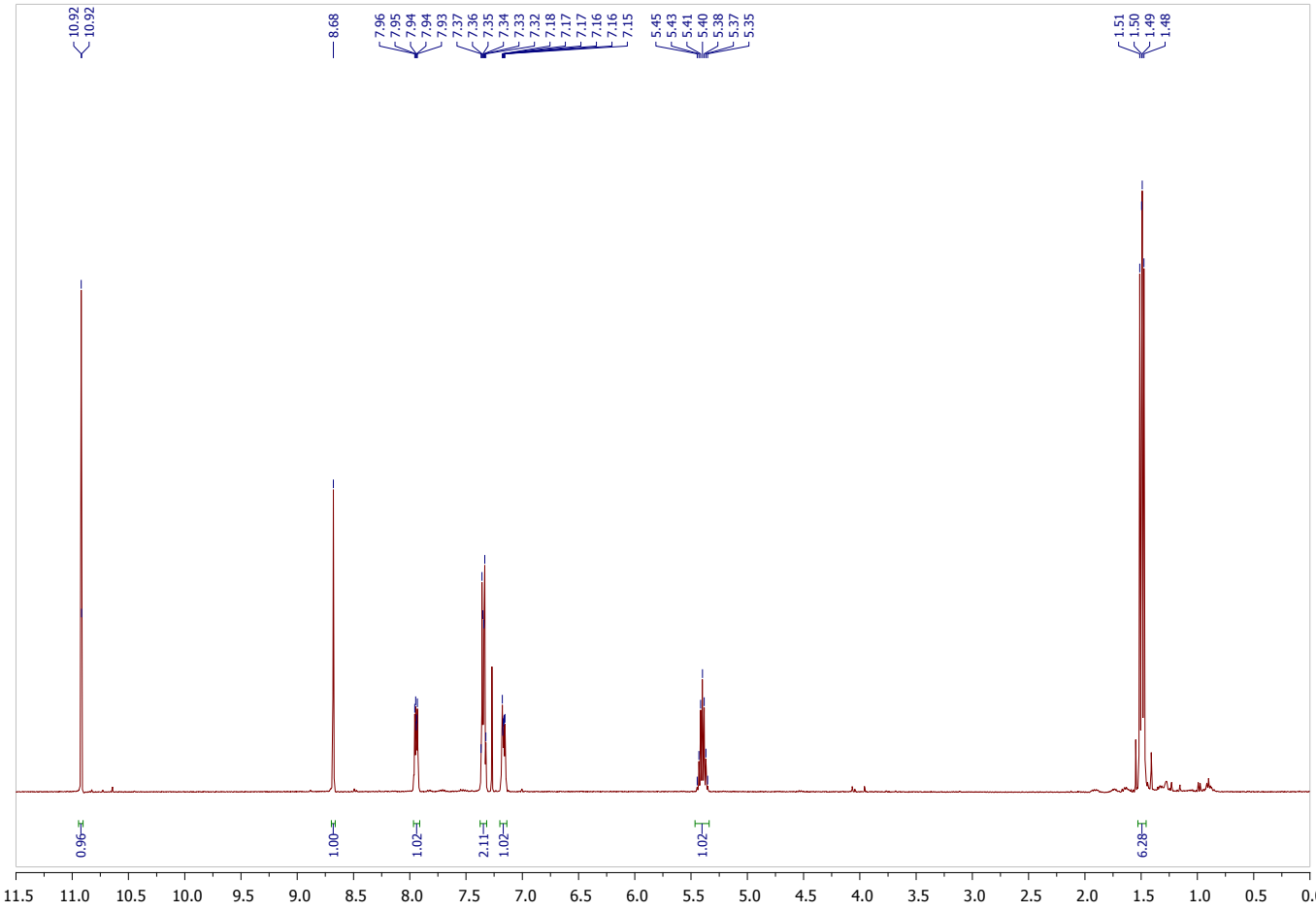




ZZ

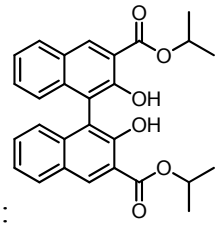
## $C_2$-Symmetric BINOLS



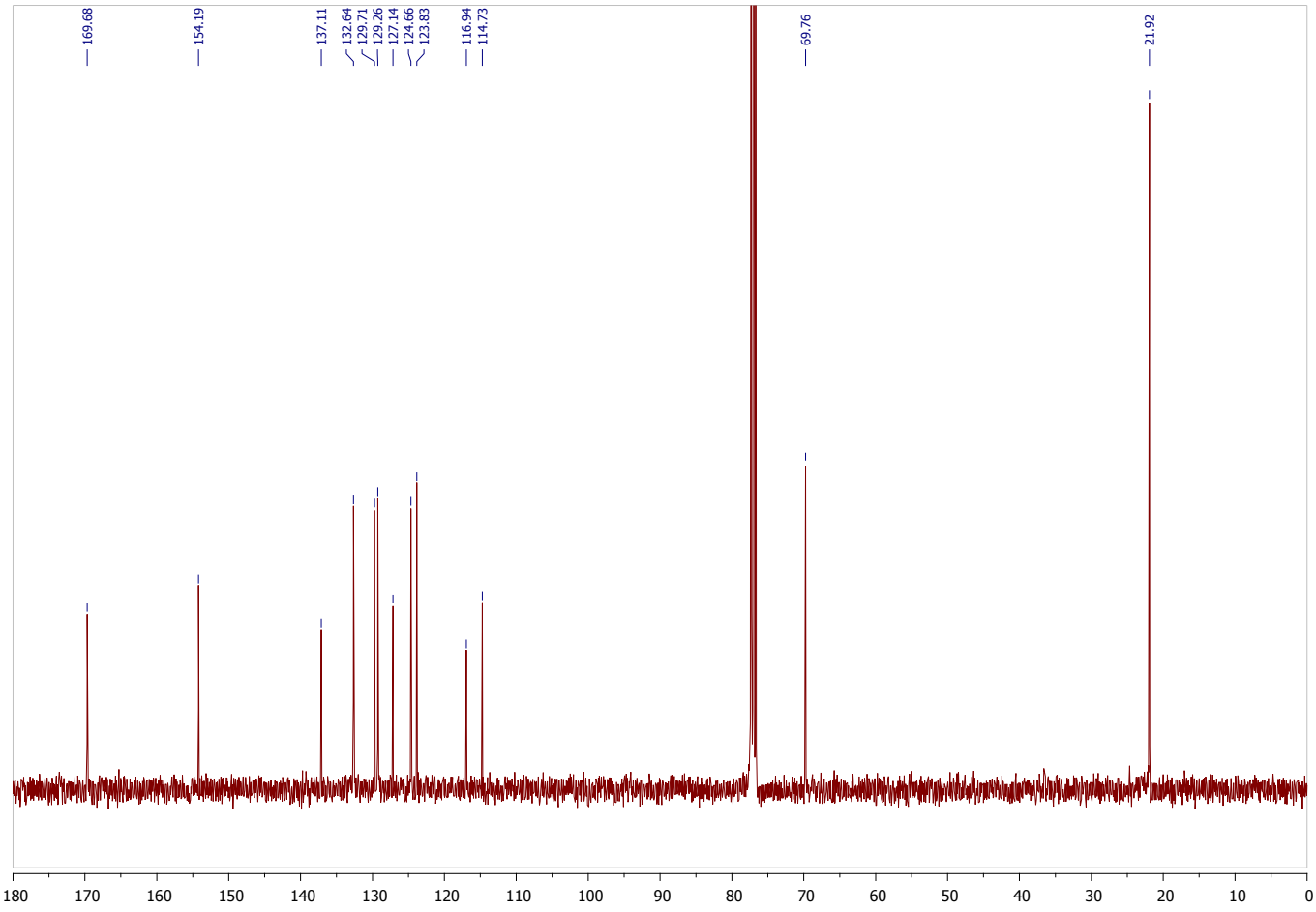

$^1$H NMR Spectrum of **6.8**:



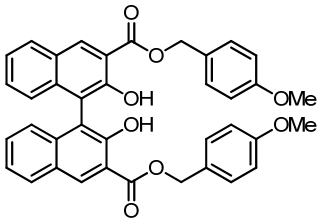

AAA



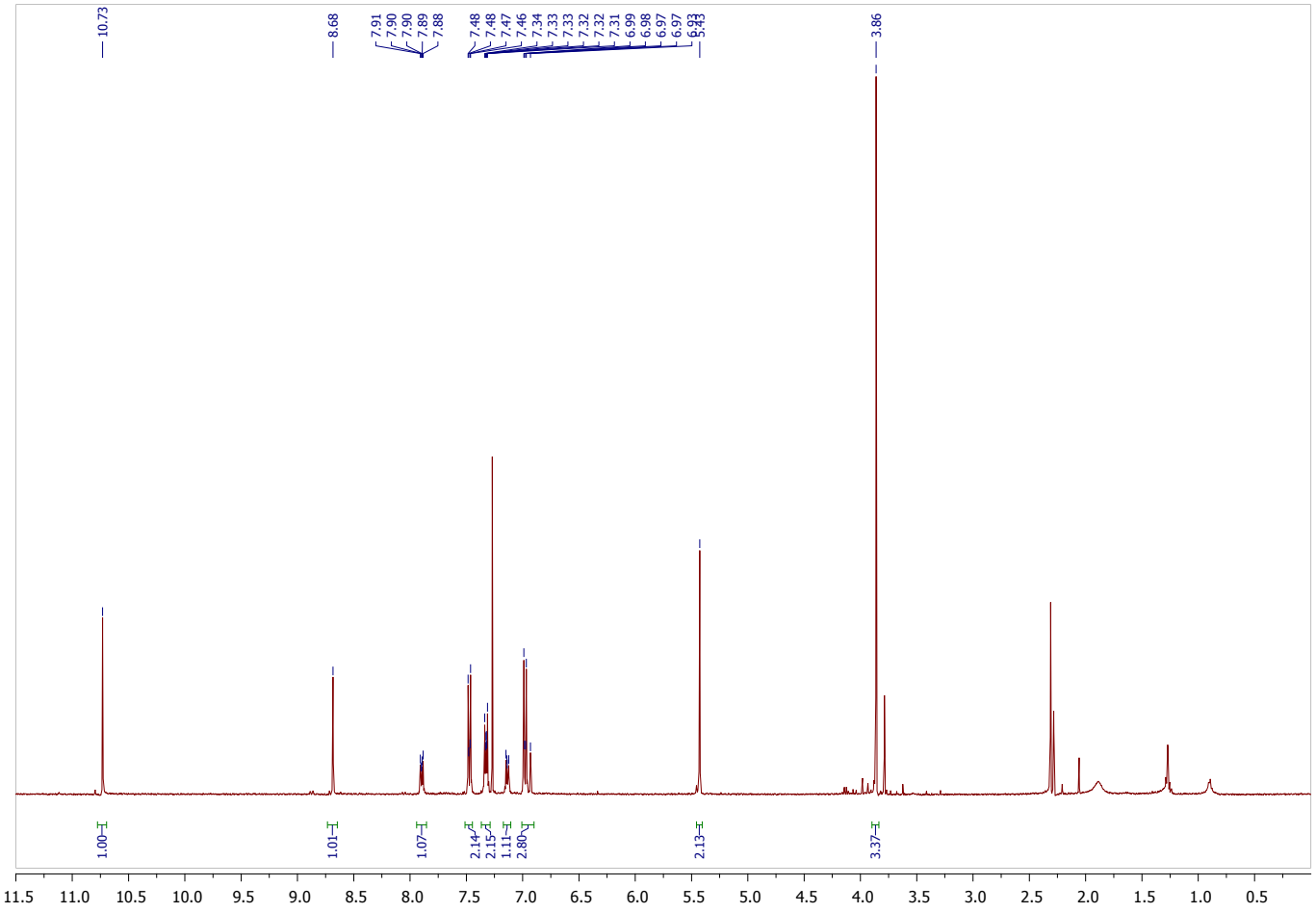

$^{13}$C NMR Spectrum of **6.8**:



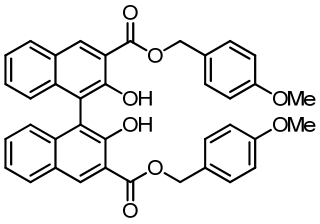

BBB



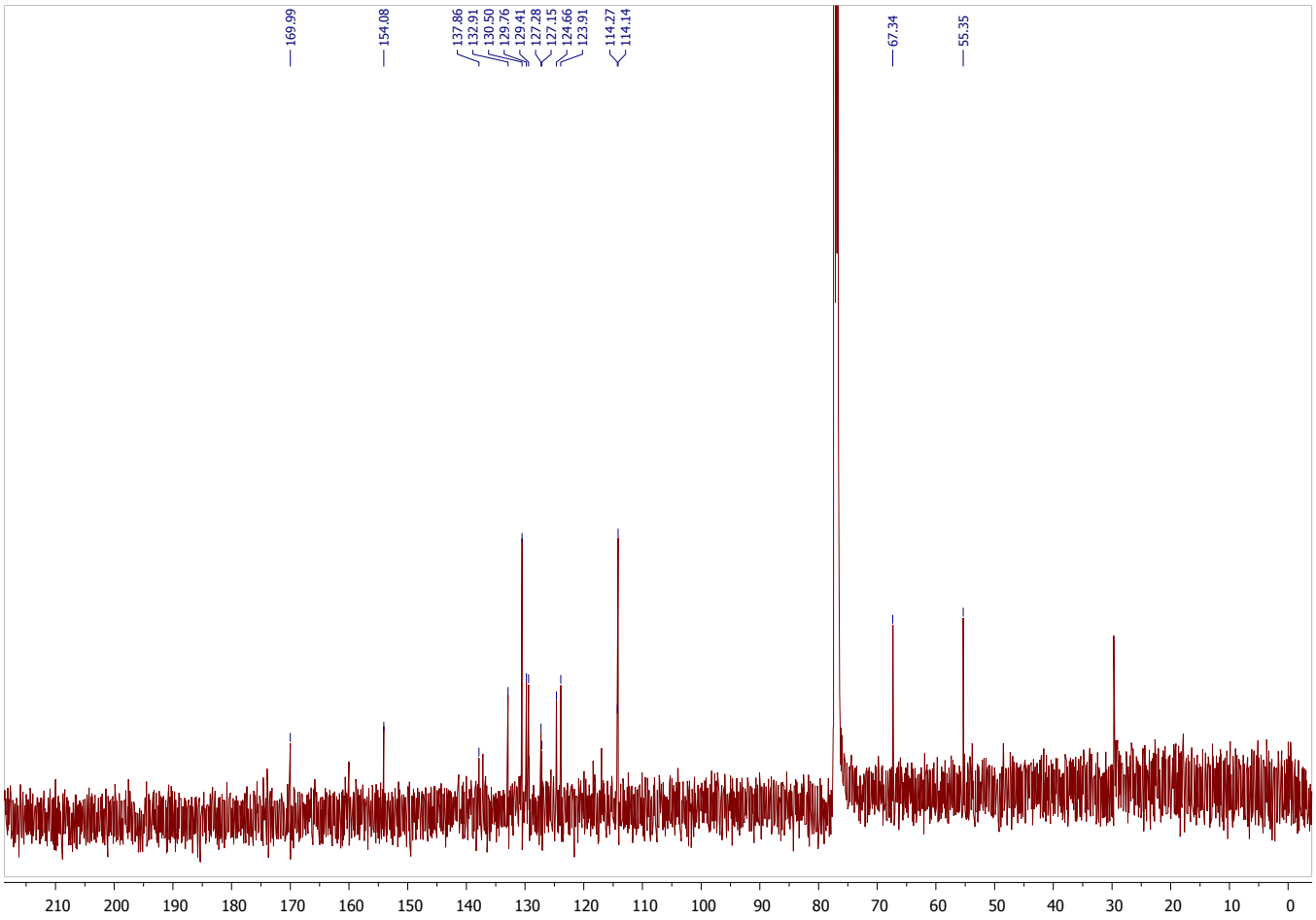

$^{1}$H NMR Spectrum of **6.11**:



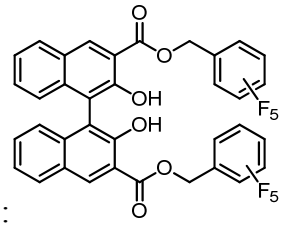

CCC



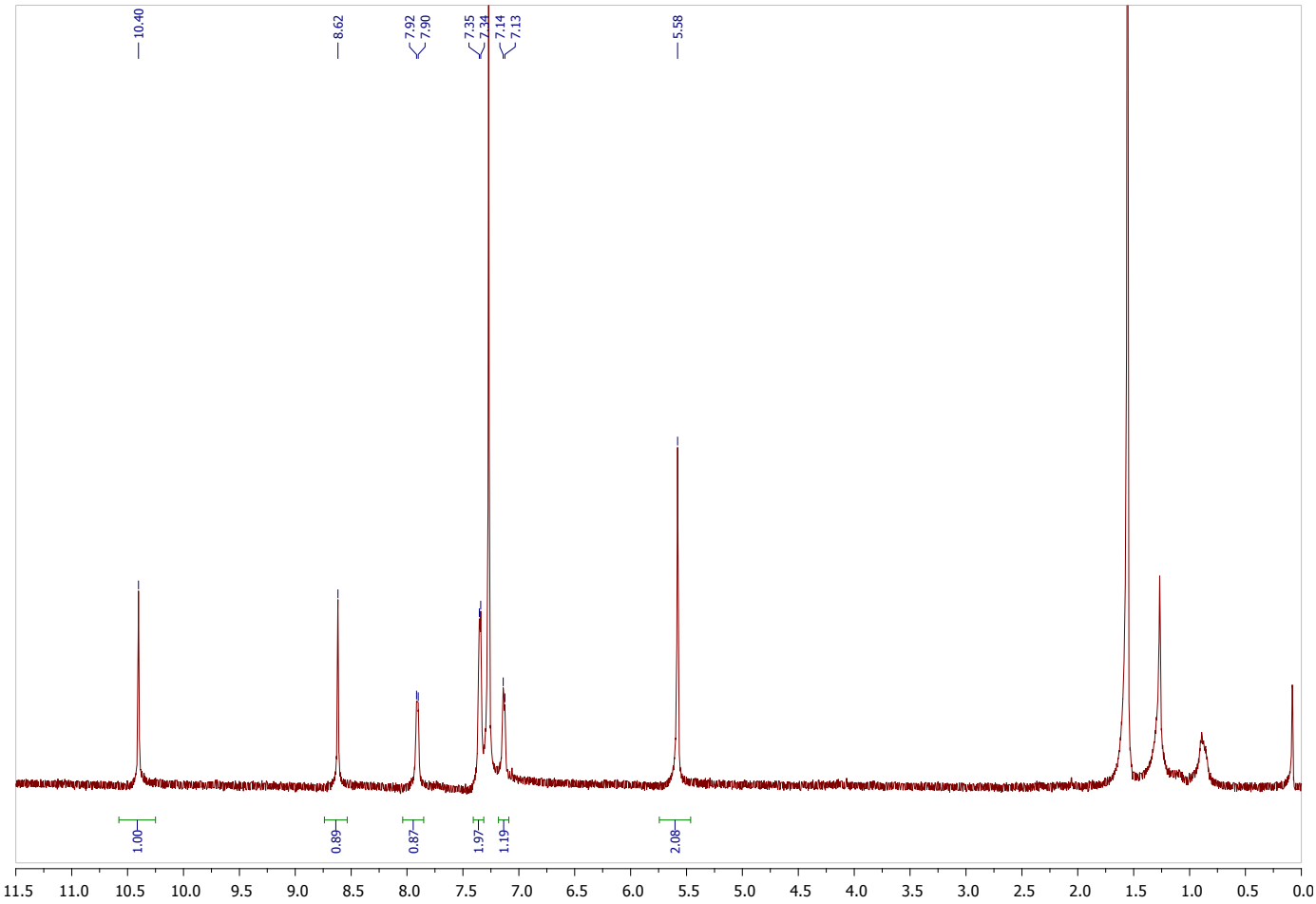

$^{13}$C NMR Spectrum of **6.11**:



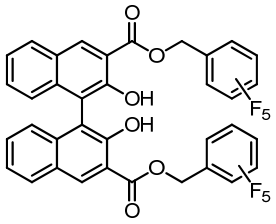

DDD



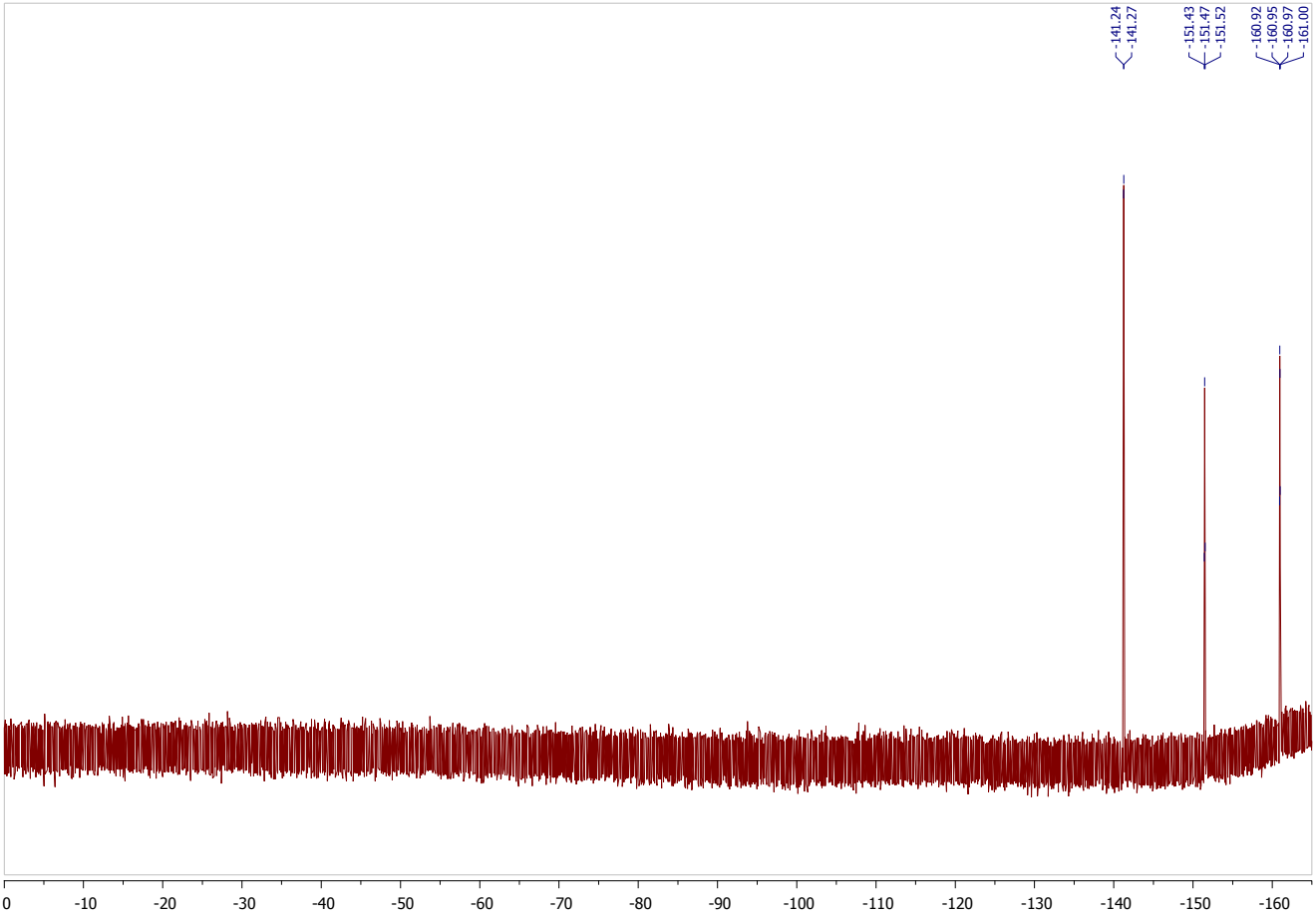

$^{1}$H NMR Spectrum of **6.10**:



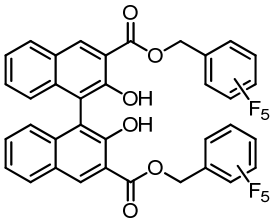

EEE



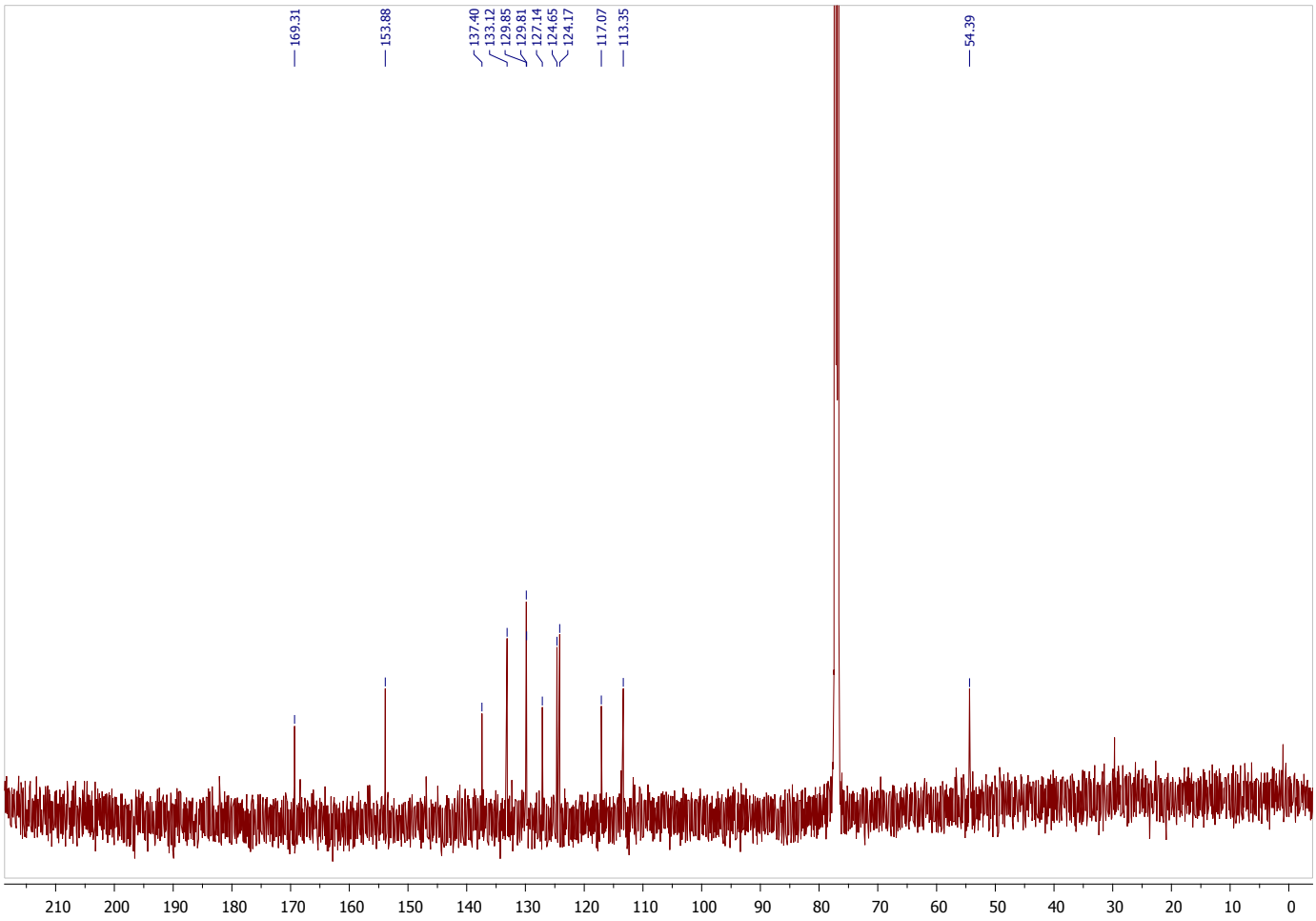

$^{19}$F NMR Spectrum of **6.10**:



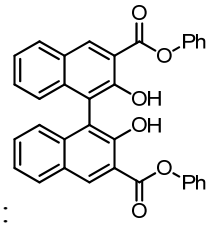

FFF



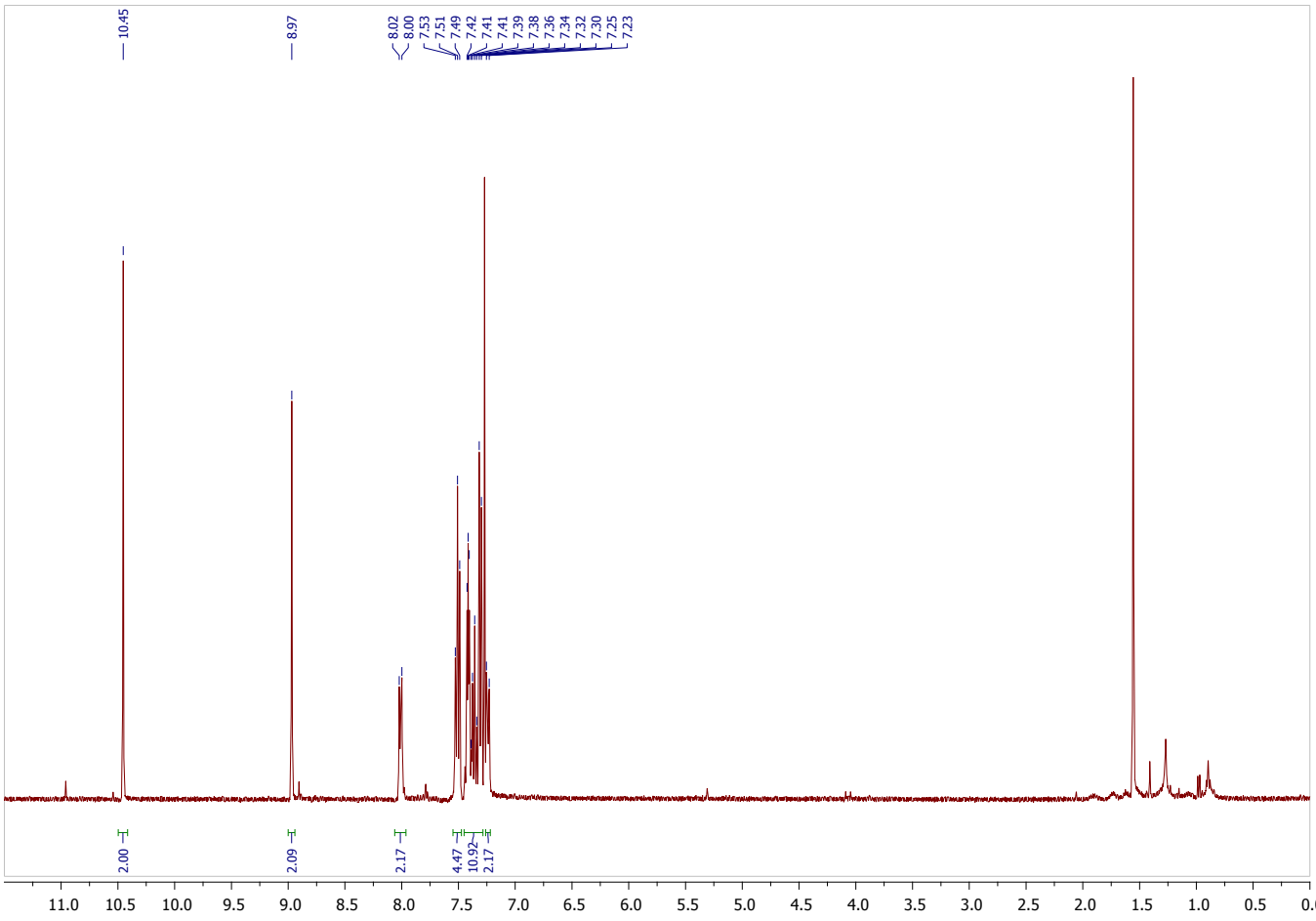

$^{13}$C NMR Spectrum of **6.10**:



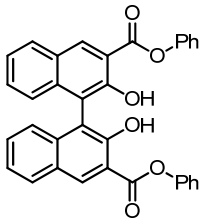

GGG



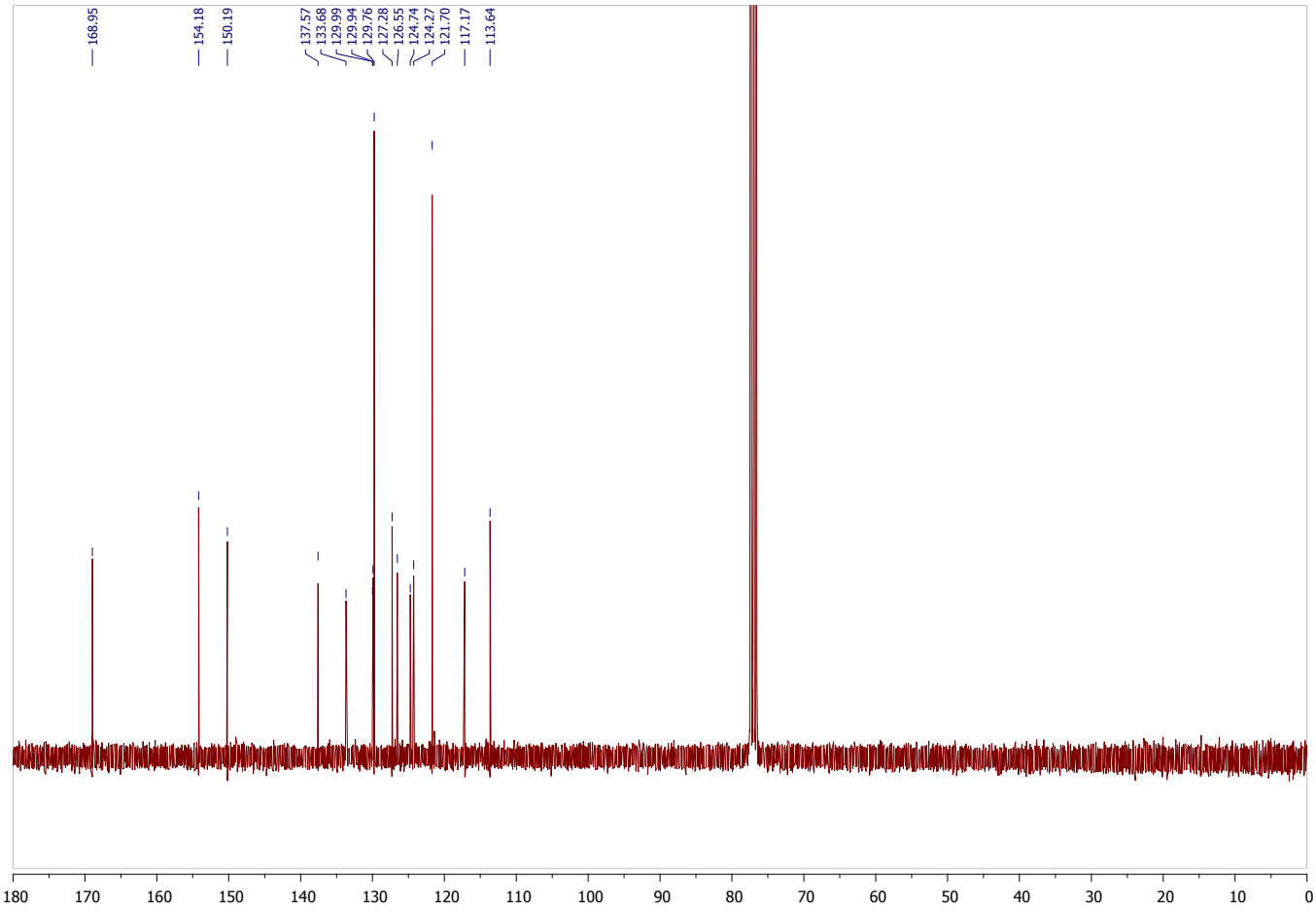

$^{1}$H NMR Spectrum of **6.12**:




HHH

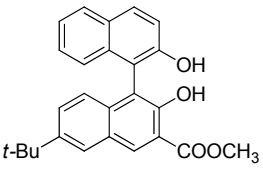


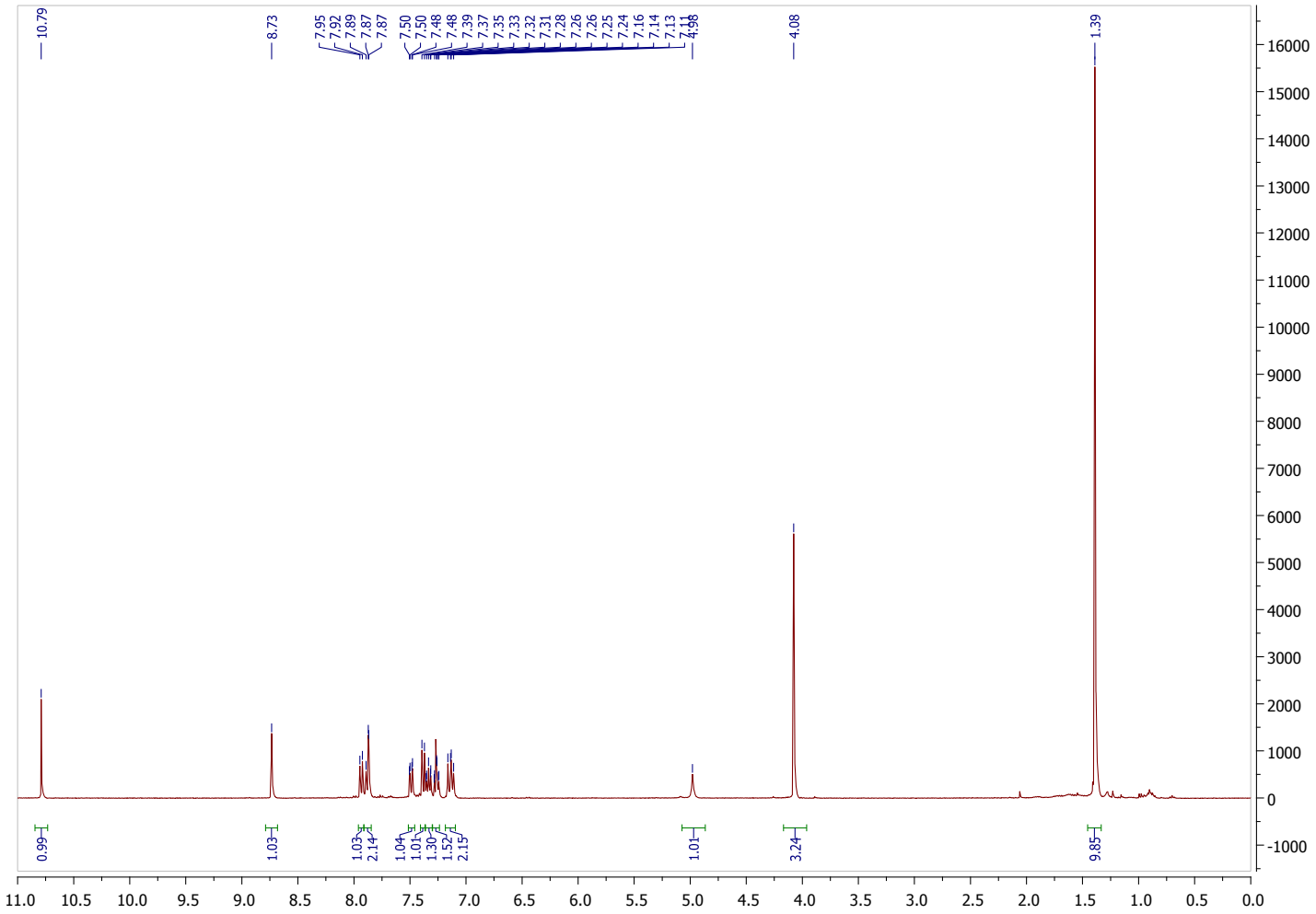

$^{13}$C NMR Spectrum of **6.12**:

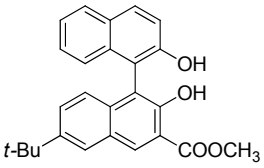


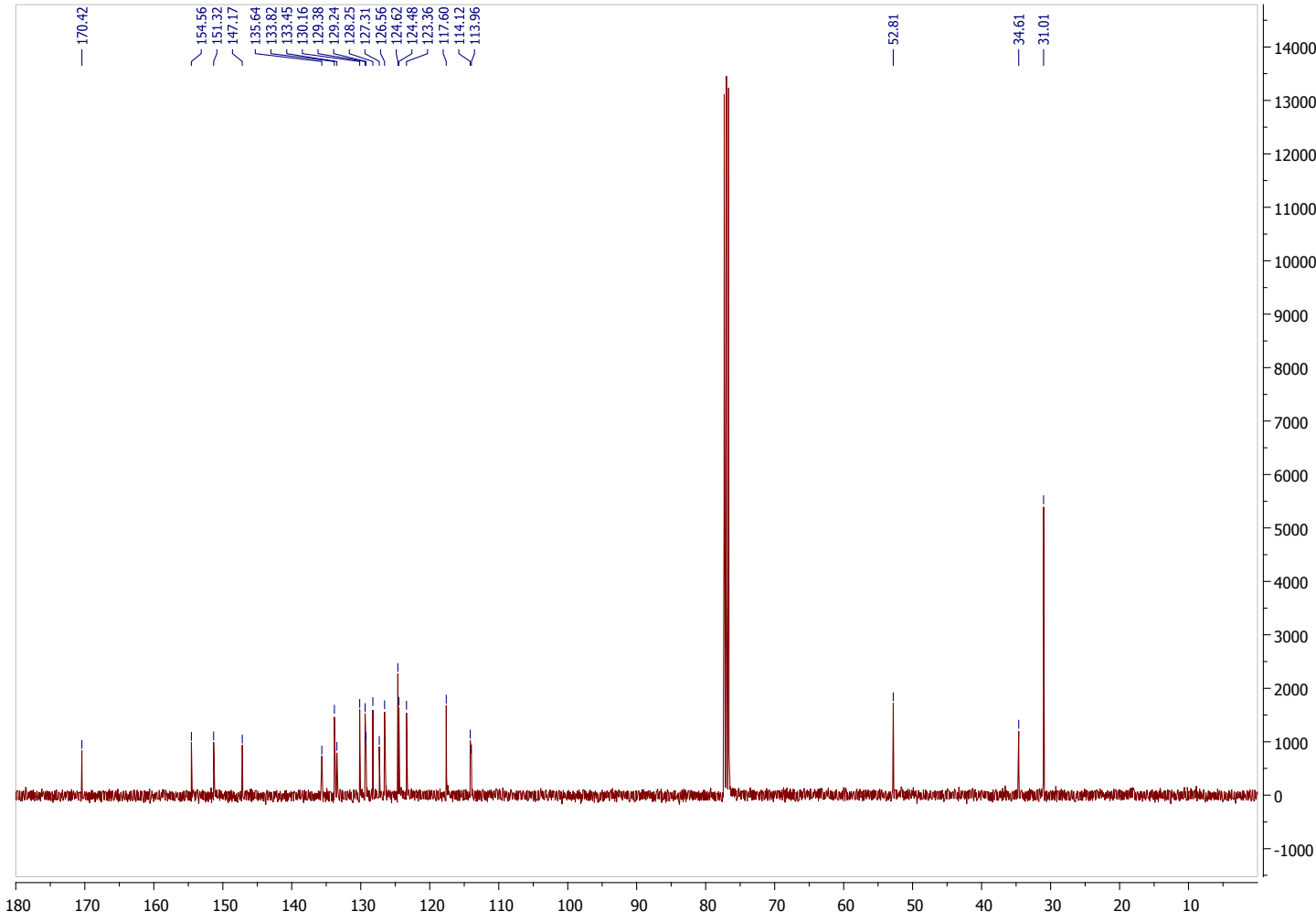
# $C_1$-Symmetric BINOLS

$^1$H NMR spectrum of **7.32**:



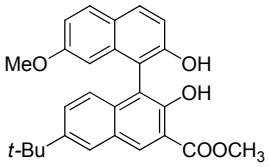



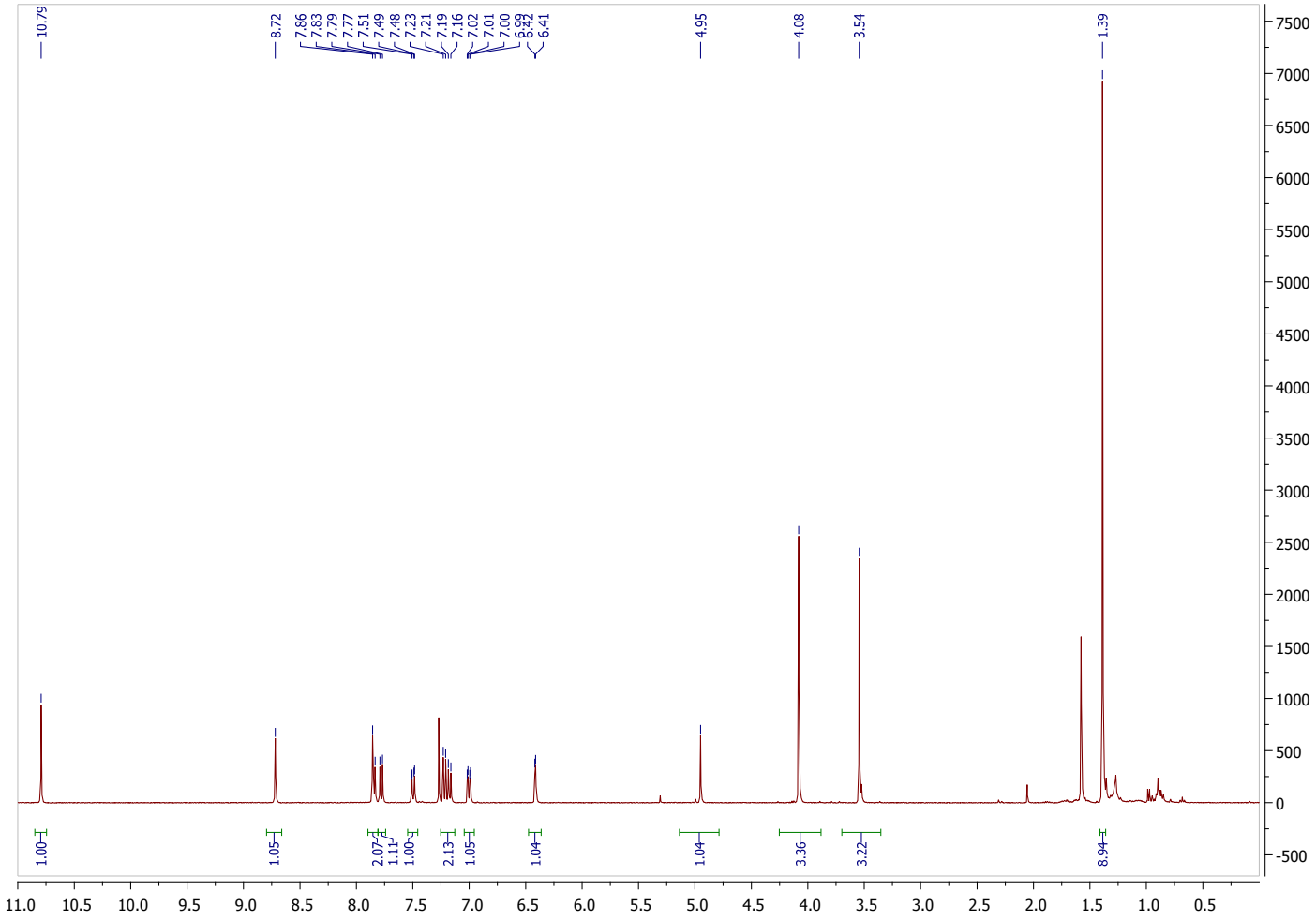
$^{13}$C NMR spectrum of **7.32**: 


KKK

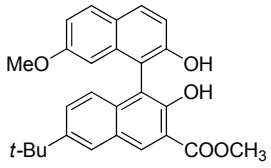
$^1$H NMR spectrum of **7.34**:

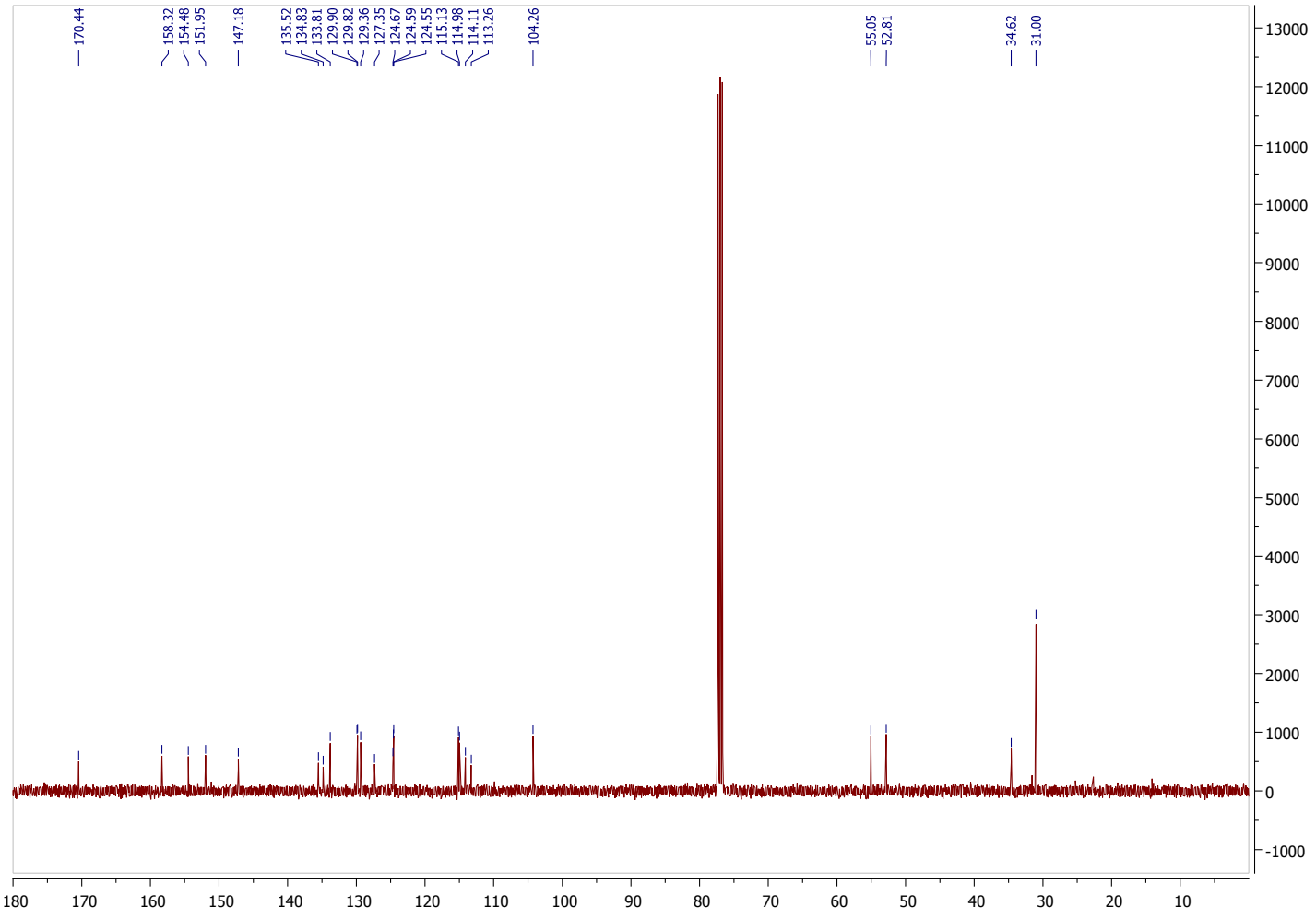


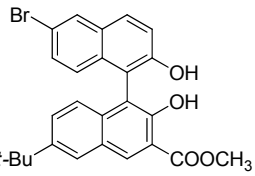

LLL

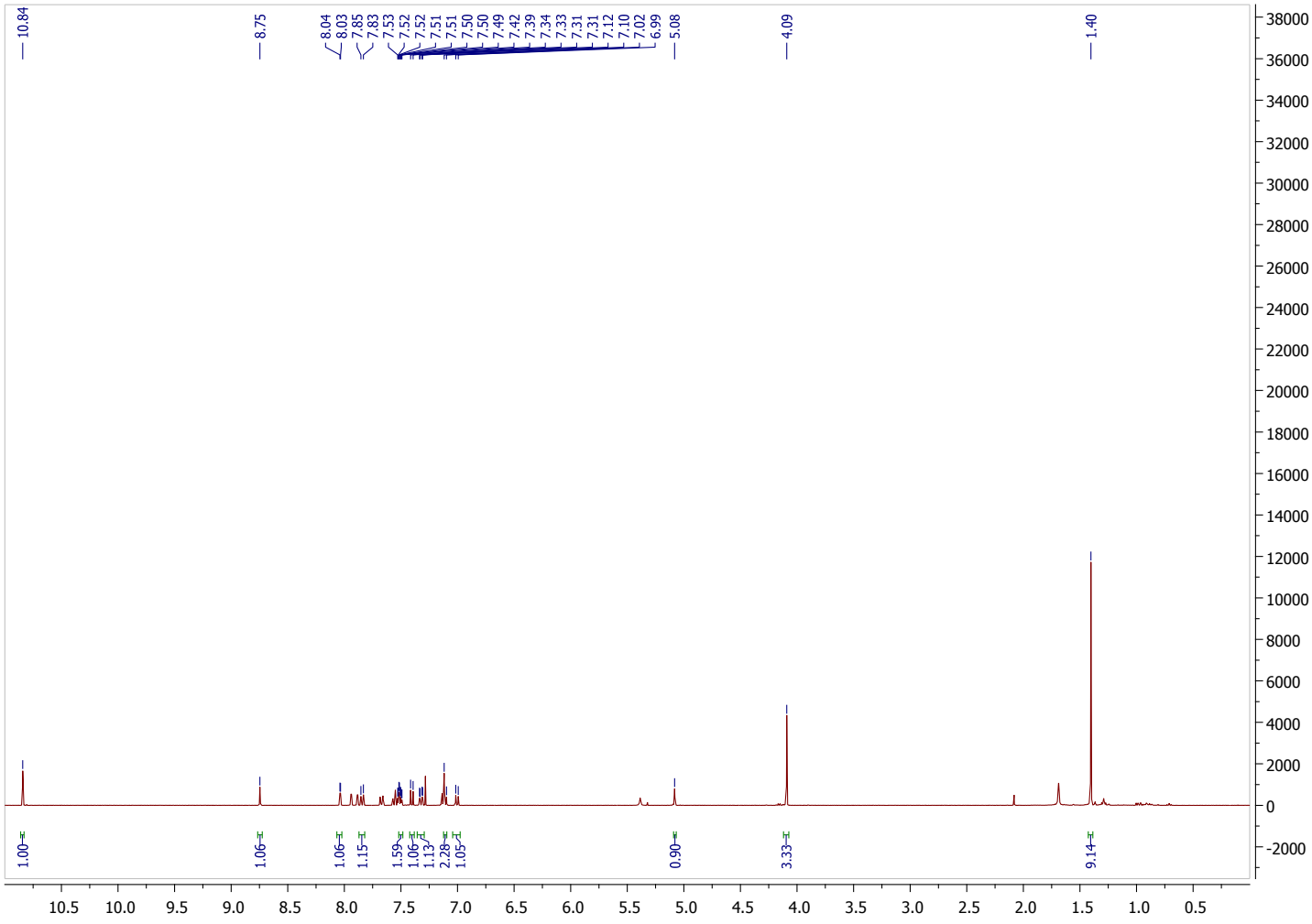
$^{13}$C NMR spectrum of **7.34**:



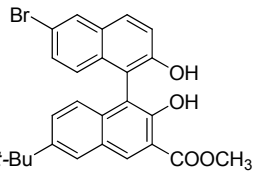

MMM

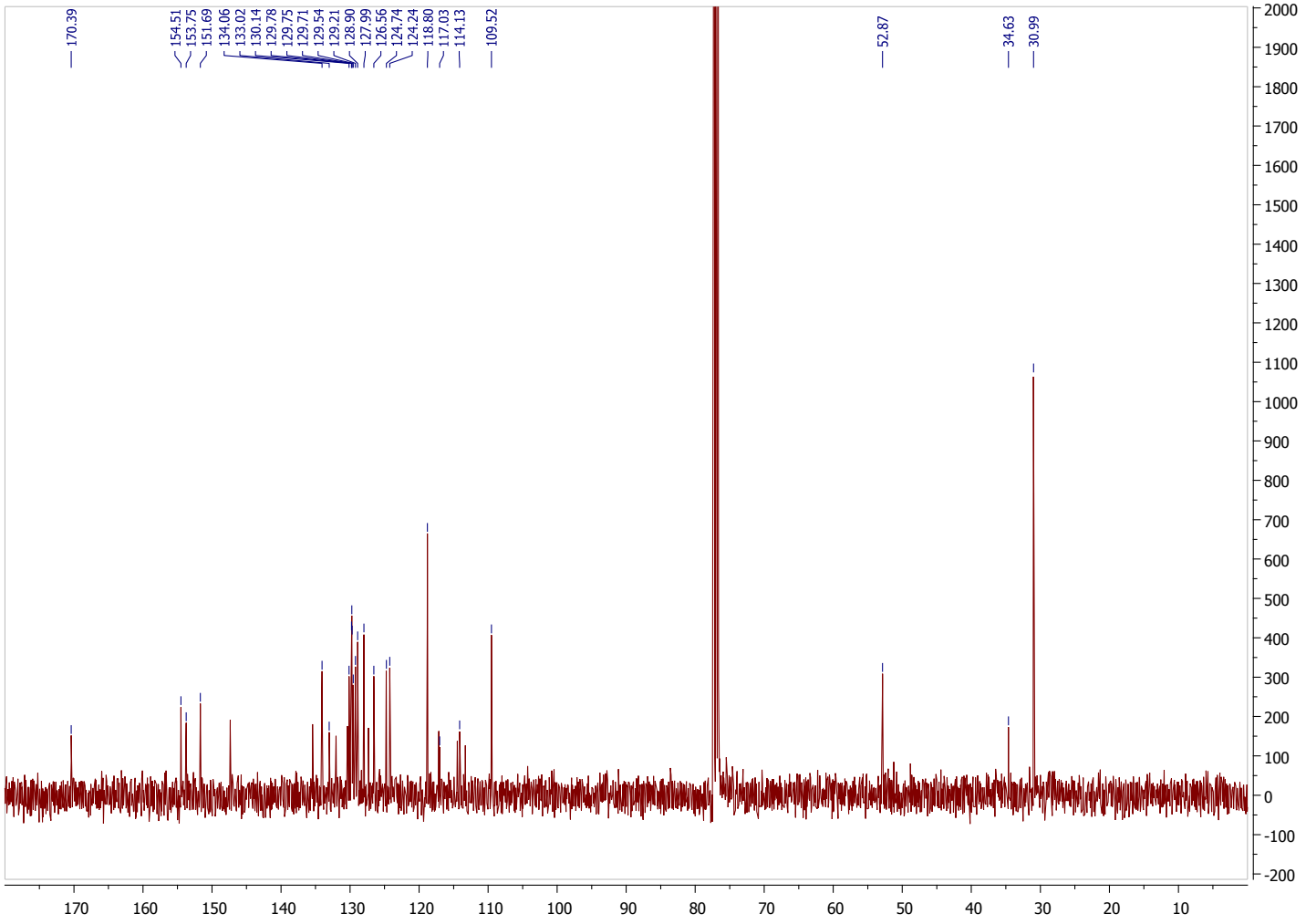
$^1$H NMR spectrum of **7.33**: 

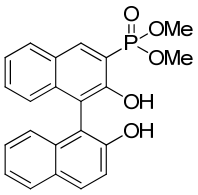

NNN

$^{13}$C NMR spectrum of **7.33**:

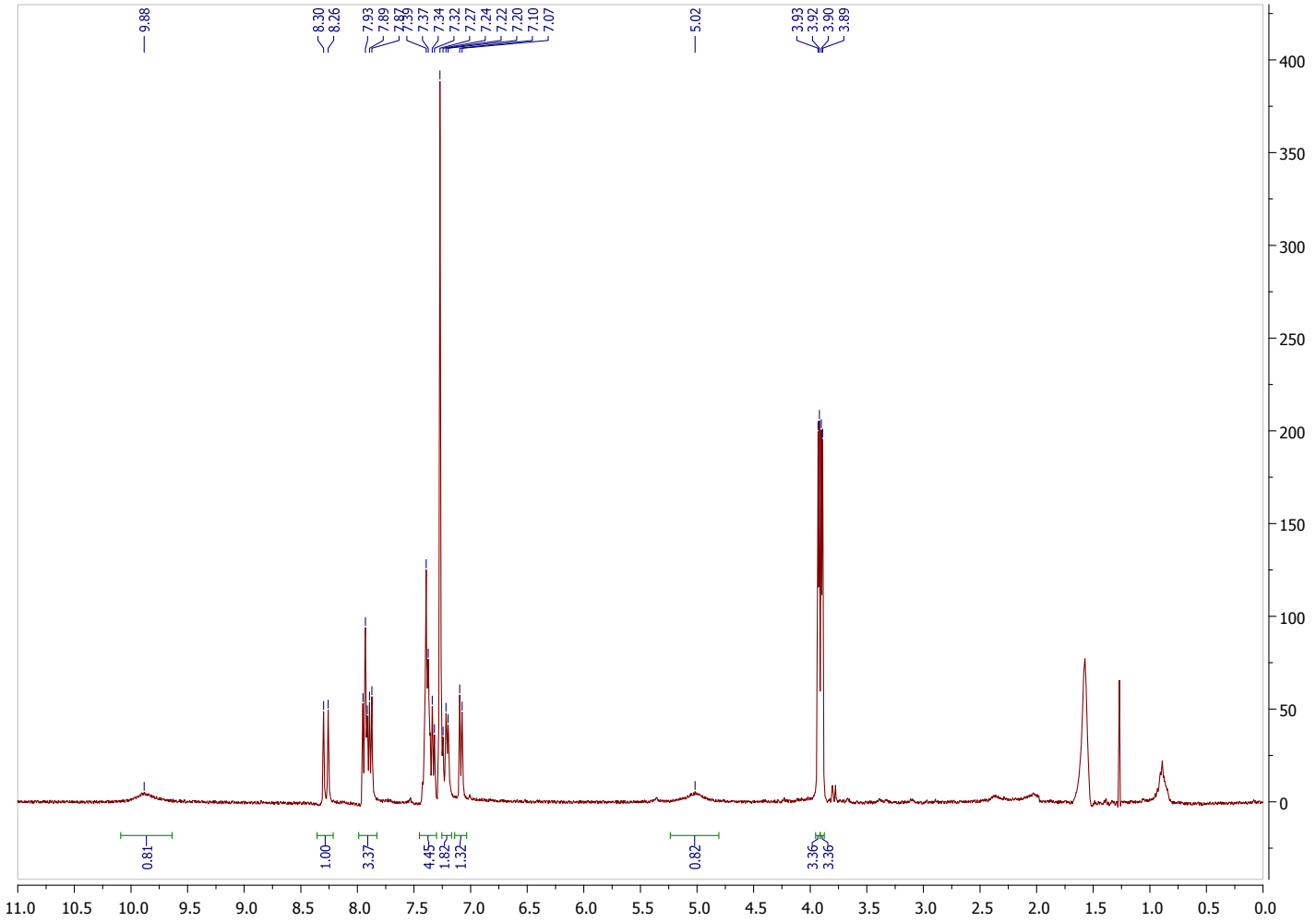


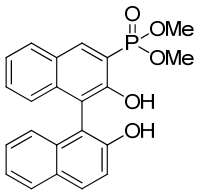

OOO



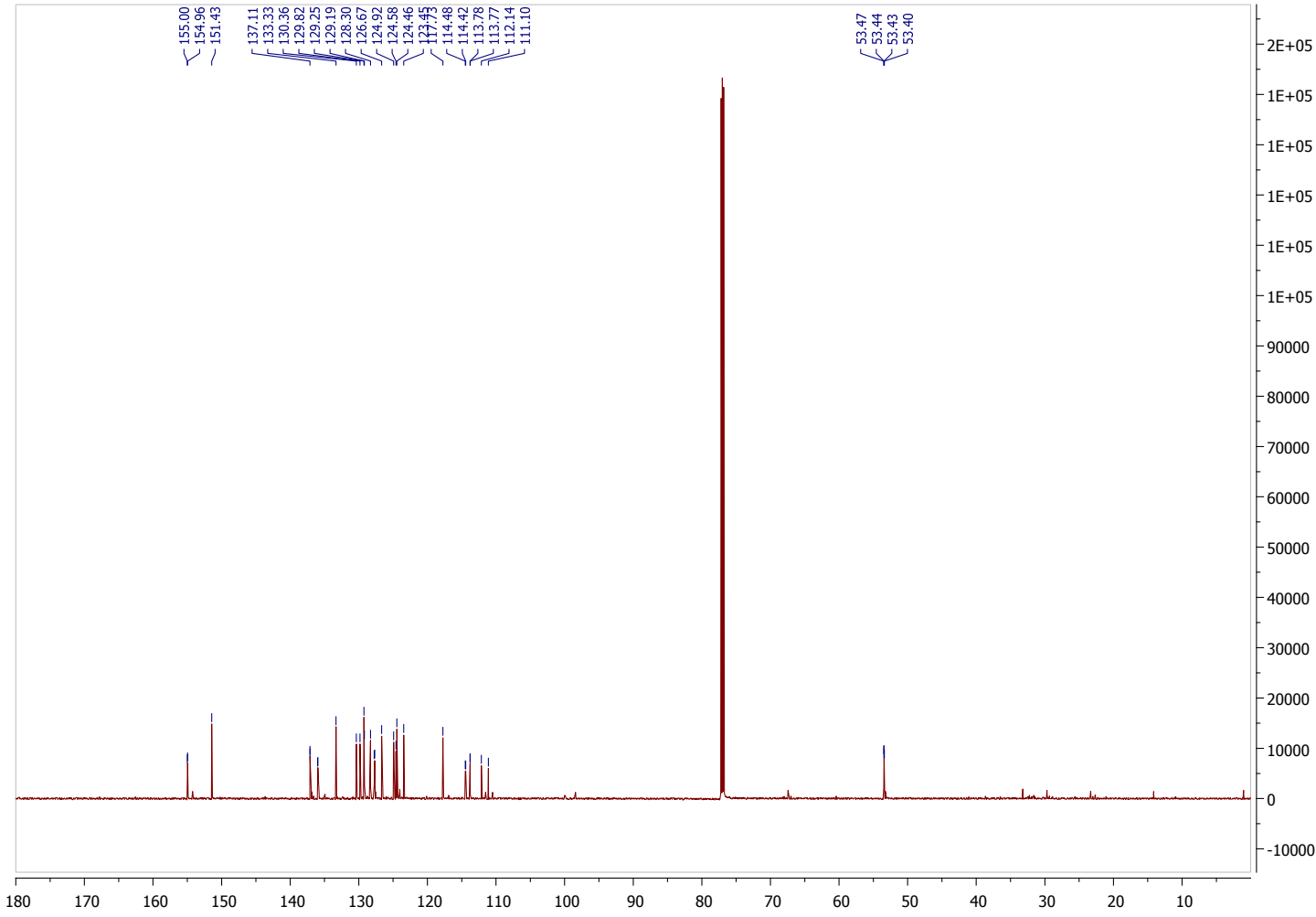

$^{1}$H NMR spectrum of **7.39**:




PPP

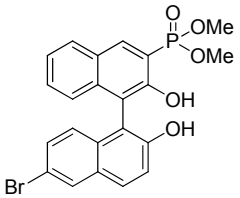


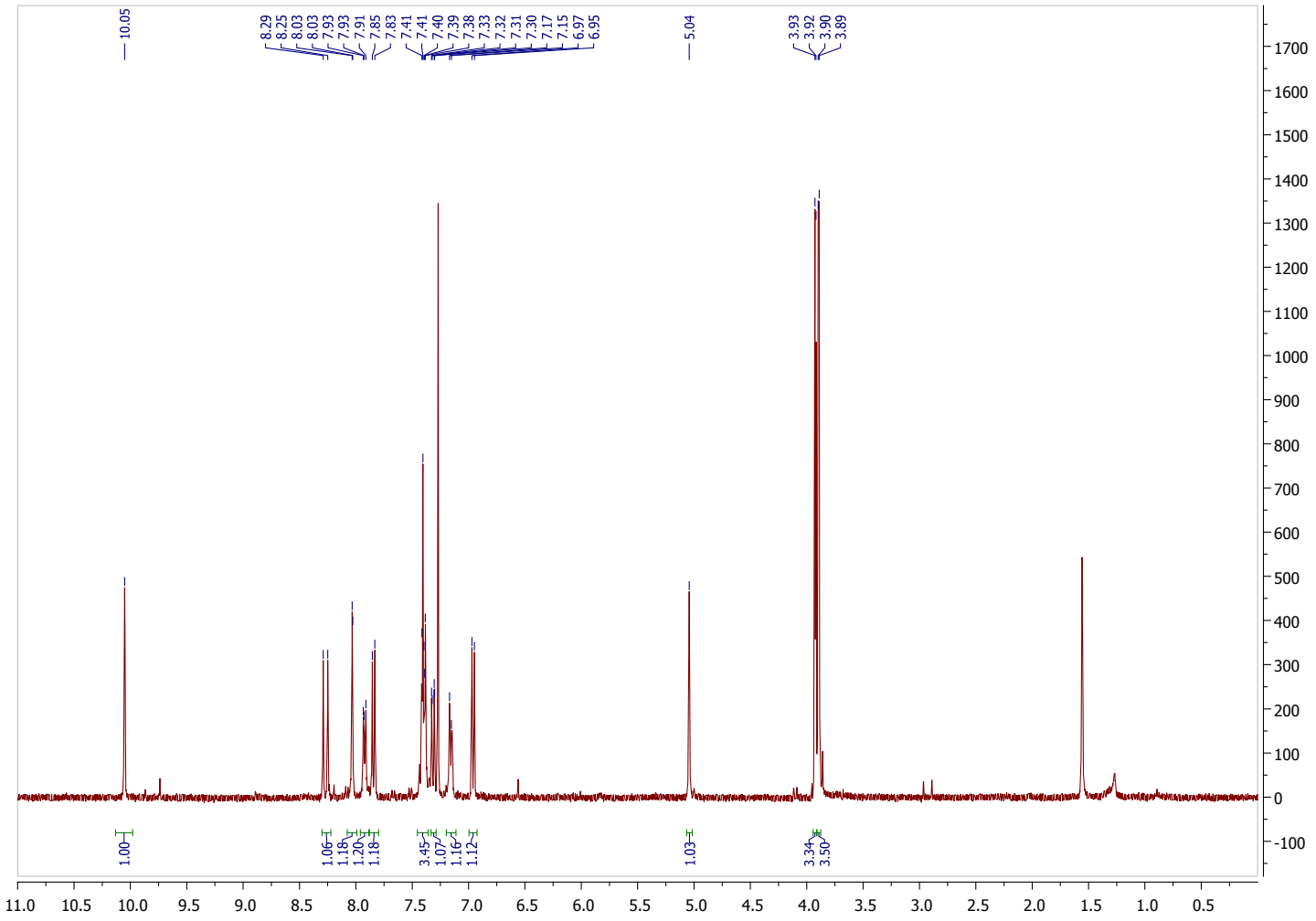

$^{13}$C NMR spectrum of **7.39:**




QQQ

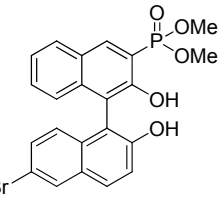
$^{1}$H NMR spectrum of **7.40**:

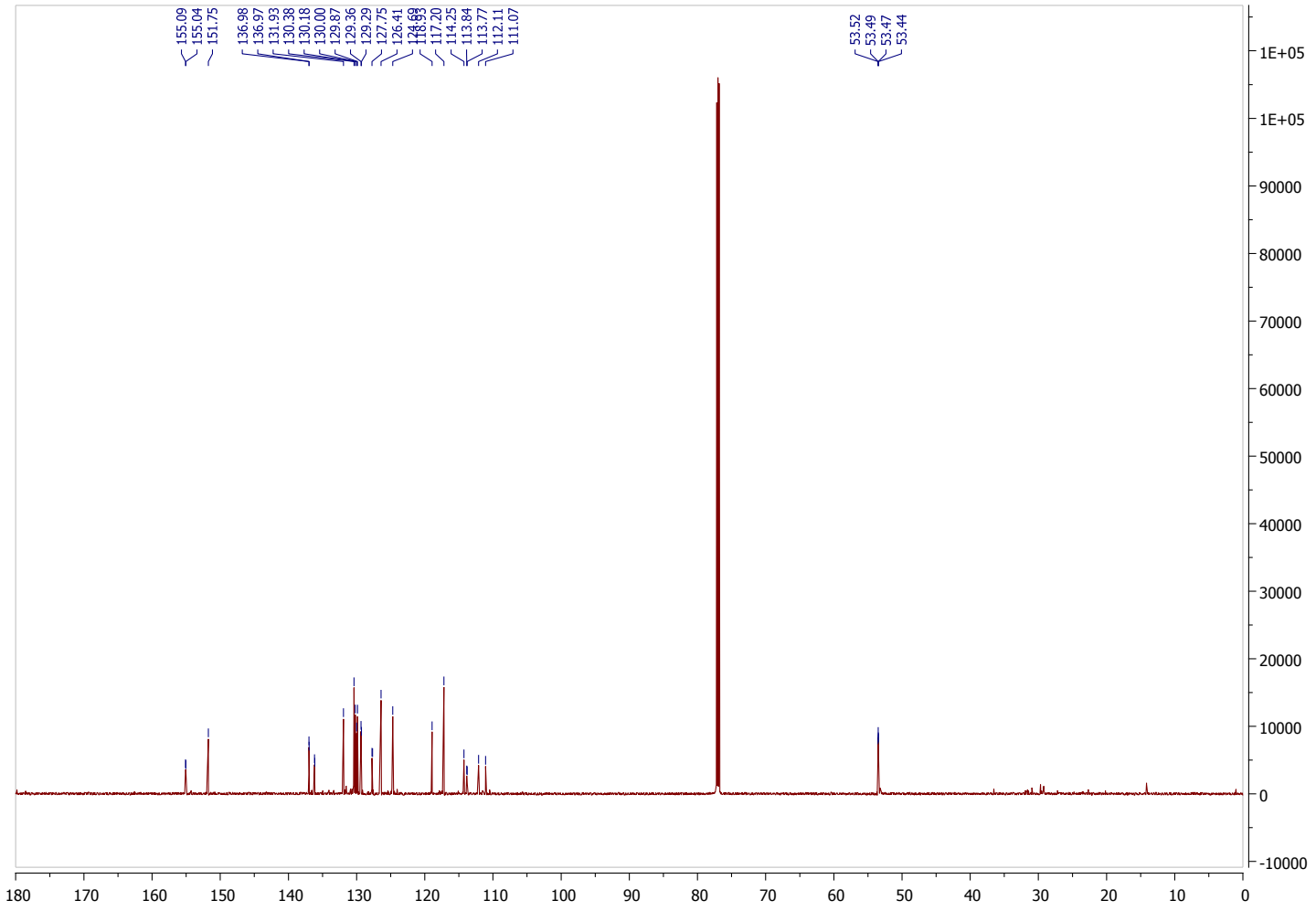


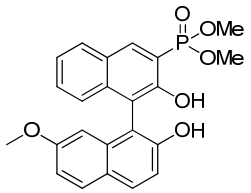

RRR

$^{13}$C NMR spectrum of **7.40:**

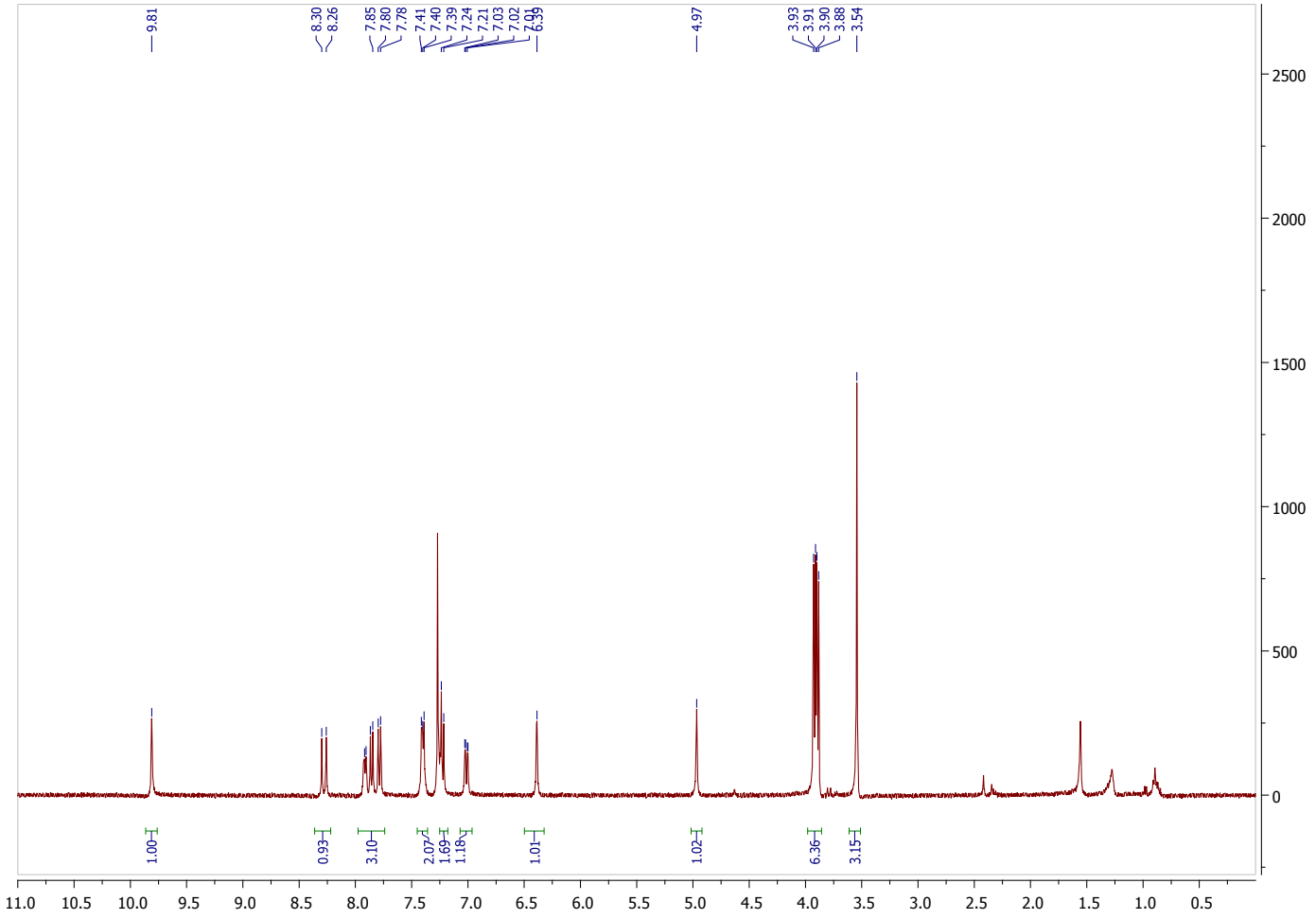


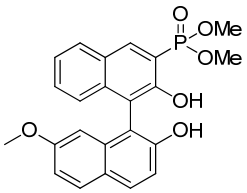

SSS



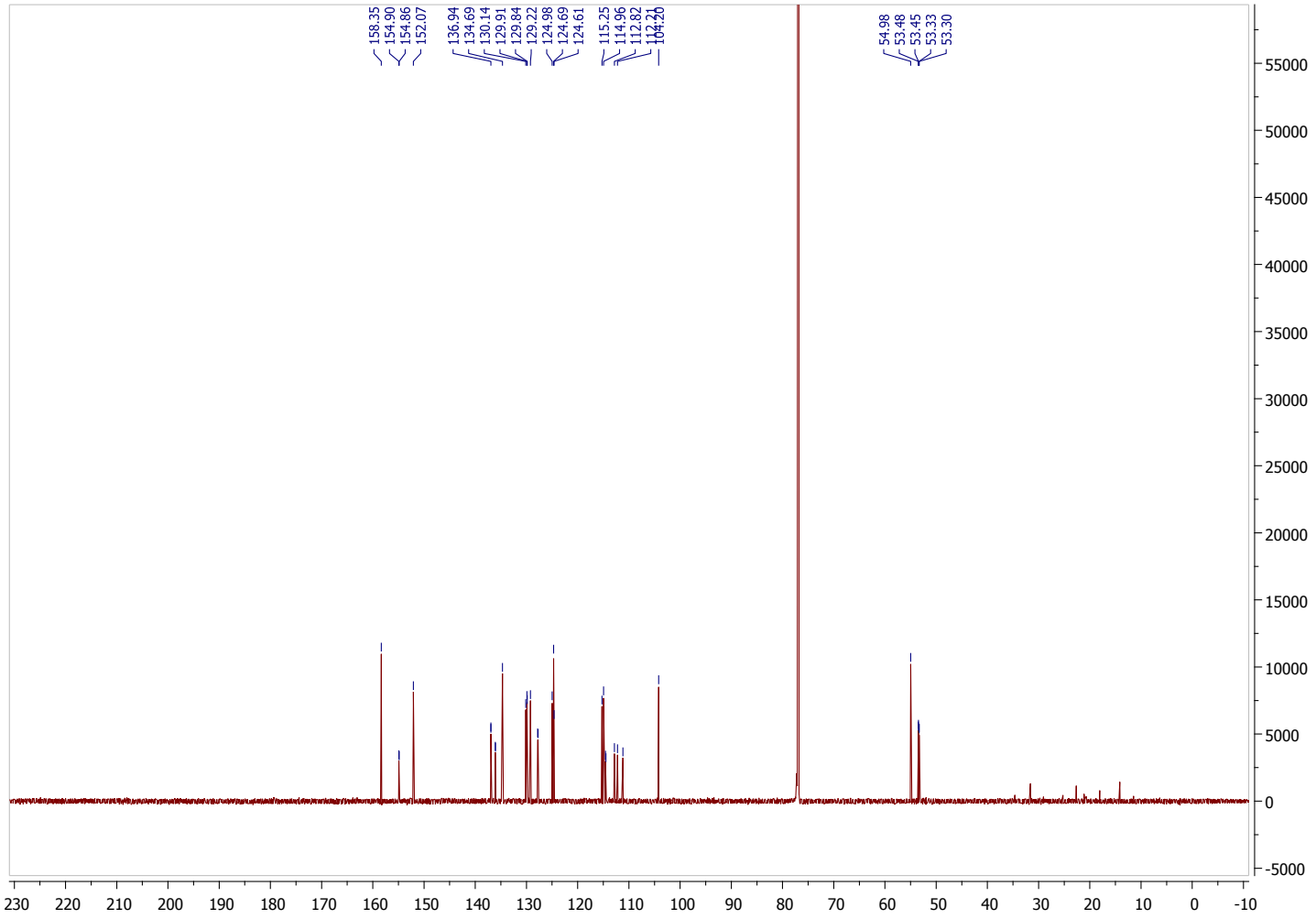

$^{1}$H NMR spectrum of **7.41**:




TTT

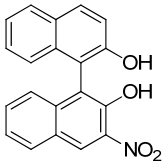


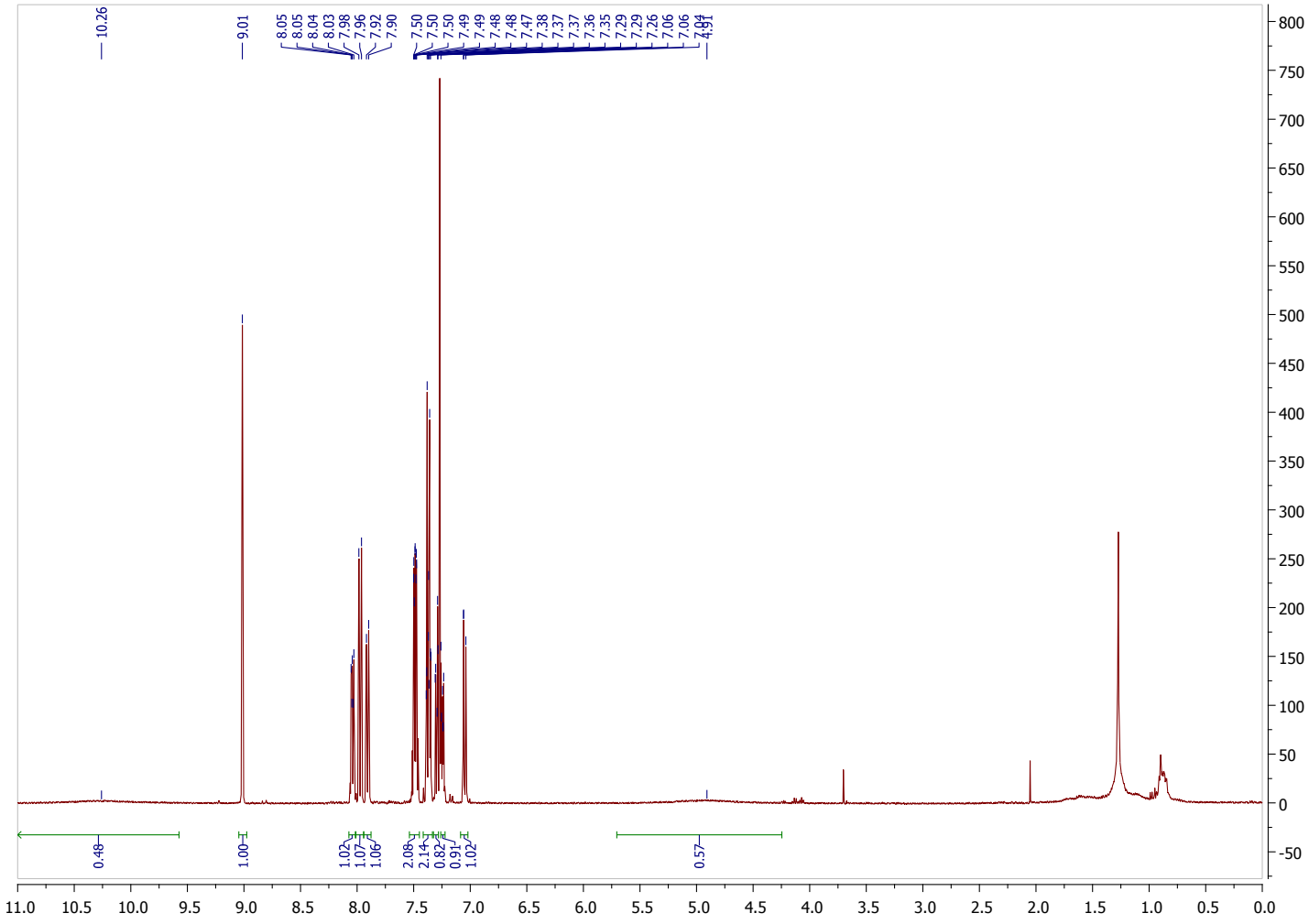

$^{13}$C NMR spectrum of **7.41:**




UUU

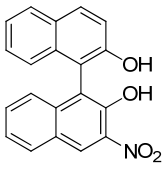
$^{1}$H NMR spectrum of **7.42**:

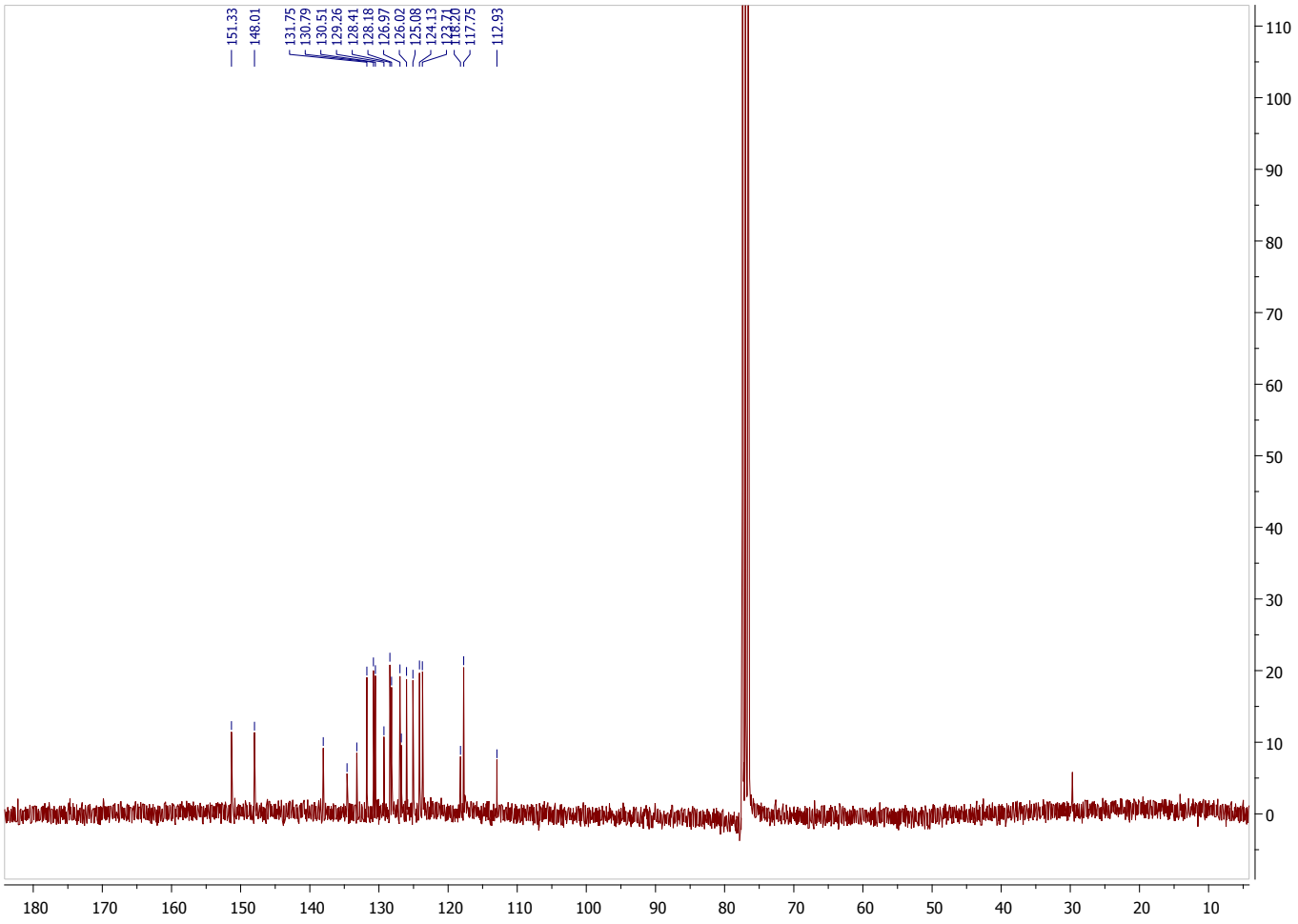



VVV

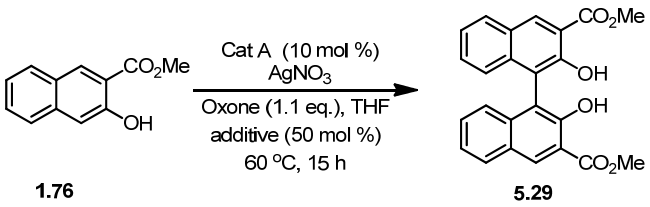
$^{13}$C NMR spectrum of **7.42**:



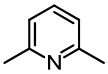
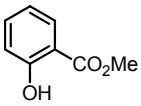
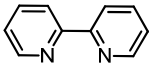
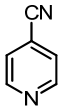
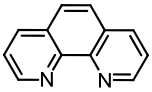
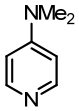
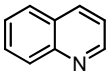




WWW

# Appendix II: HPLC Data

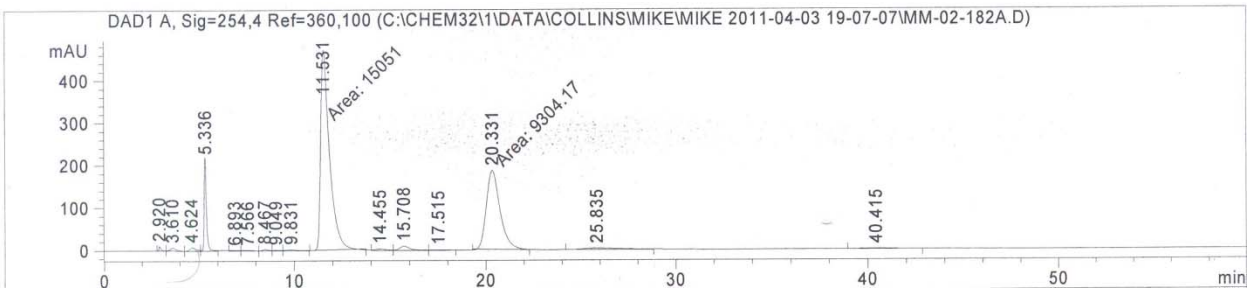



1.76 5.29

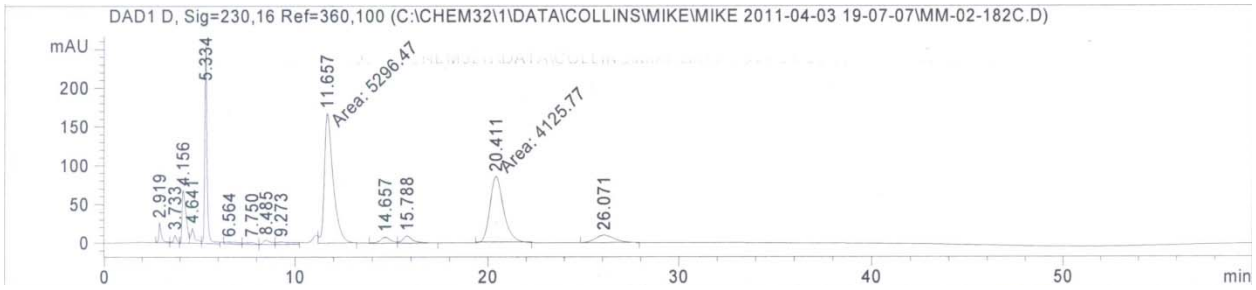
| Entry | Additive | Filename | ee (%) | Entry | Additive | Filename | ee (%) |
|---|---|---|---|---|---|---|---|
| 1 |  6.21 | mm-02-182a | 24 | 5 |  6.25 | mm-02-183b | 12 |
| 2 |  6.23 | mm-02-182c | 12 | 6 |  6.16 | mm-02-183c | 15 |
| 3 |  6.22 | mm-02-182d | <5 | 7 |  6.15 | mm-02-183d | 7 |
| 4 |  6.20 | mm-02-183a | 41 | 8 |  6.24 | mm-02-184a | 9 |

Method: 1 mL/min 10 % *i*-PrOH, 90 % Hexane; chiralpak AD-H

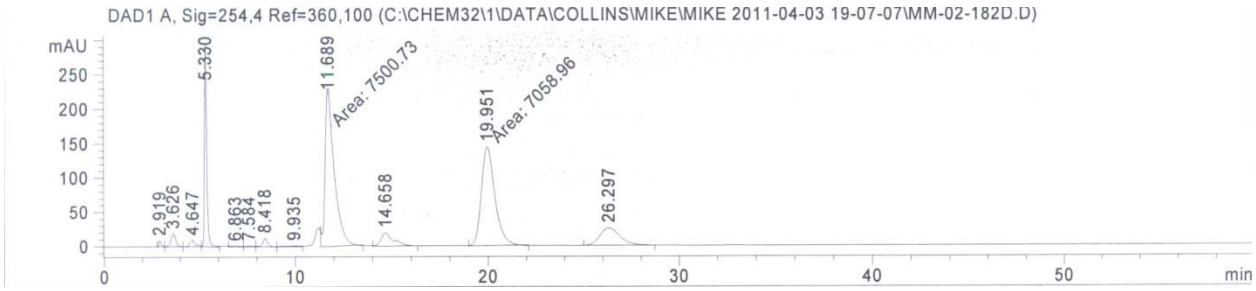
Entry 1



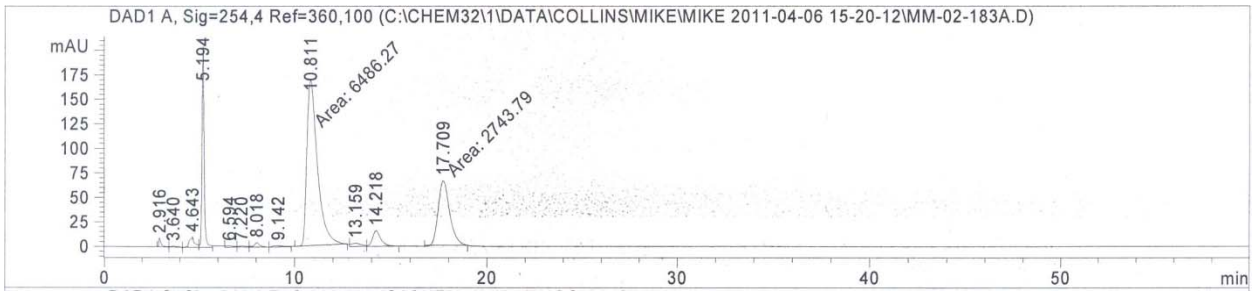
Entry 2



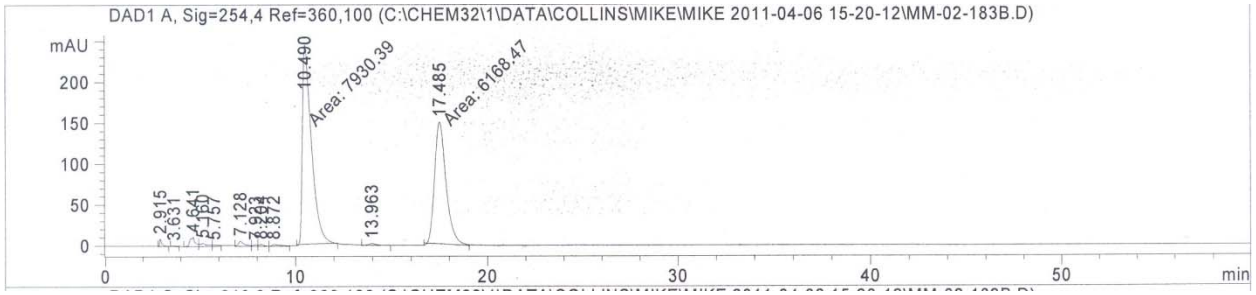

Entry 3




Entry 4

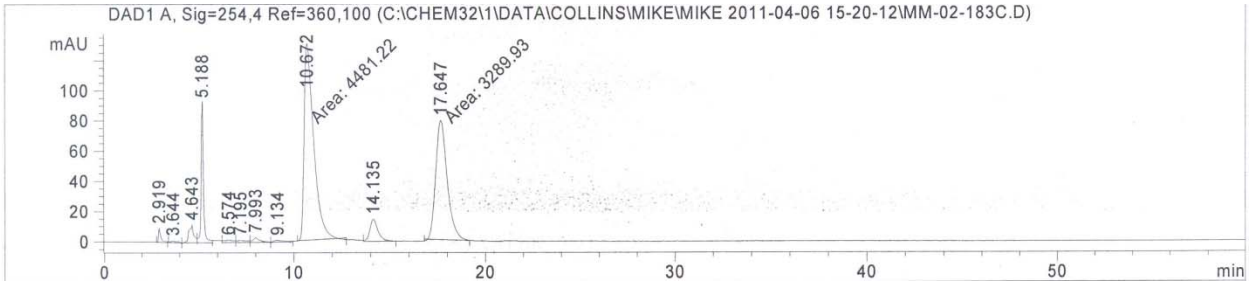



Entry 5

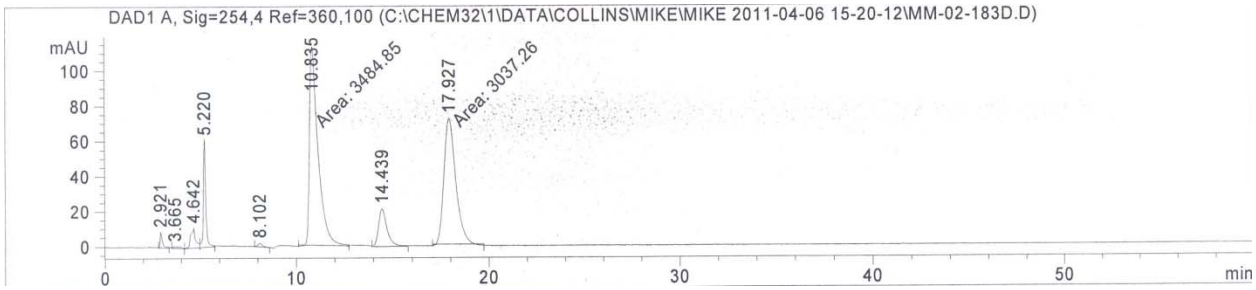



YYY

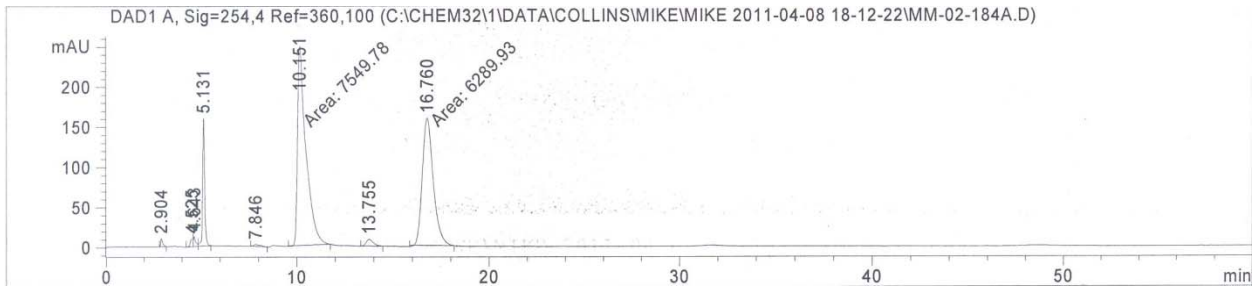
Entry 6




Entry 7



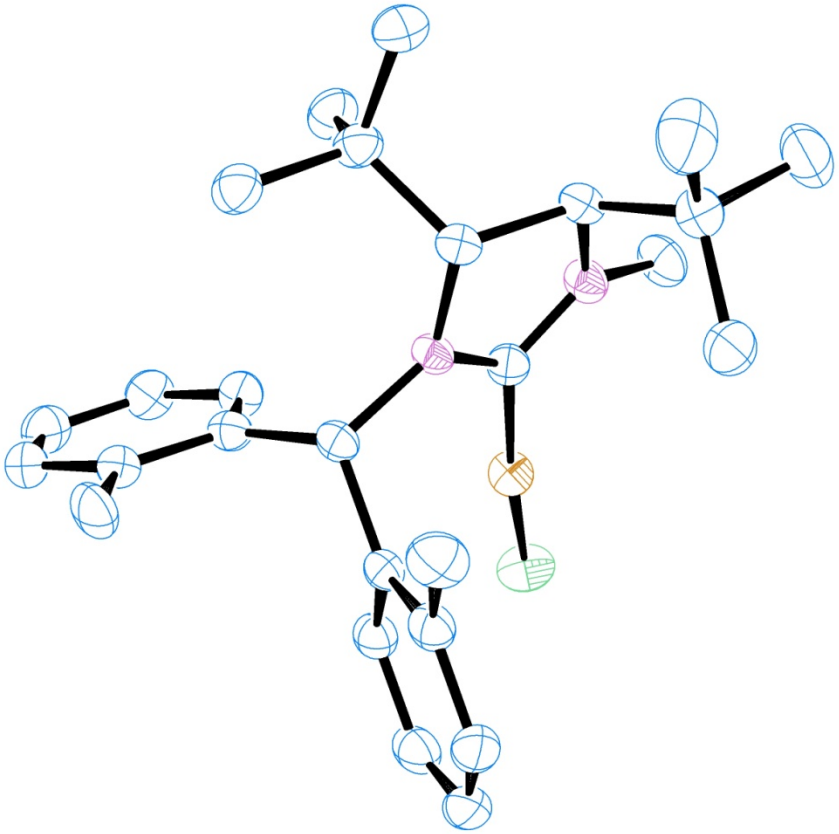

Entry 8




ZZZ

# Appendix III: X-Ray Data

## Crystallographic Parameters for Complex 4.1 (CCDC-913107)

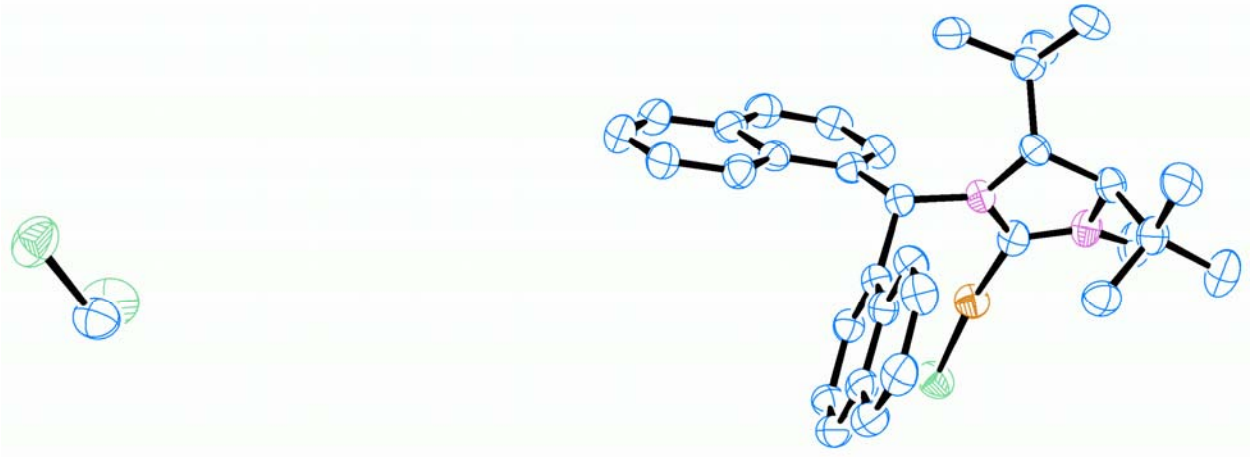


| | | |
|---|---|---|
| Empirical formula | C27 H38 Cl Cu N2 | |
| Formula weight | 489.58 | |
| Temperature | 150K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Orthorhombic | |
| Space group | P212121 | |
| Unit cell dimensions | a = 11.1388(6) Å | $\alpha$ = 90° |
| | b = 13.8447(8) Å | $\beta$ = 90° |
| | c = 16.1733(8) Å | $\gamma$ = 90° |
| Volume | 2494.1(2)Å$^3$ | |
| Z | 4 | |
| Density (calculated) | 1.304 g/cm$^3$ | |
| Absorption coefficient | 2.327 mm$^{-1}$ | |

AAAA

| | |
|---|---|
| F(000) | 1040 |
| Crystal size | 0.13 x 0.10 x 0.03 mm |
| Theta range for data collection | 4.20 to 69.35° |
| Index ranges | $-13 \leq h \leq 13$, $-16 \leq k \leq 12$, $-19 \leq \ell \leq 19$ |
| Reflections collected | 49781 |
| Independent reflections | 4644 [$R_{int}$ = 0.052] |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9326 and 0.7088 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 4644 / 0 / 290 |
| Goodness-of-fit on $F^2$ | 1.056 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0306, $wR_2$ = 0.0818 |
| R indices (all data) | $R_1$ = 0.0322, $wR_2$ = 0.0833 |
| Absolute structure parameter | 0.004(14) |
| Largest diff. peak and hole | 0.524 and -0.289 e/Å$^3$ |

**Crystallographic Parameters for Complex 4.2 (DCM solvate) (CCDC-947160)**



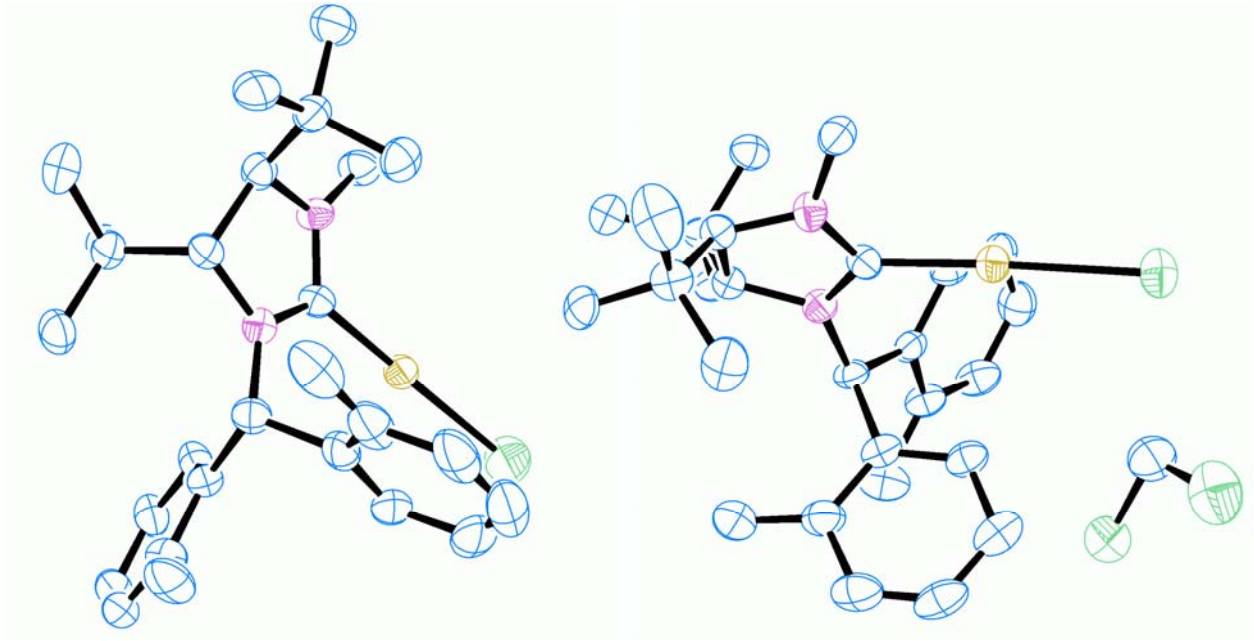
| | |
|---|---|
| Empirical formula (solvent) | C33 H38 Cu I N2 • C H2 Cl2 |
| Empirical formula | C34 H40 Cl2 Cu I N2 |
| Formula weight | 738.02 |
| Temperature | 150K |
| Wavelength | 1.54178 Å |
| Crystal system | Orthorhombic |
| Space group | P212121 |
| Unit cell dimensions | a = 12.4293(3) Å  α = 90°<br>b = 15.5759(3) Å  β = 90°<br>c = 16.8950(4) Å  γ = 90° |
| Volume | 3270.83(13)Å$^3$ |
| Z | 4 |
| Density (calculated) | 1.499 g/cm$^3$ |
| Absorption coefficient | 10.038 mm$^{-1}$ |
| F(000) | 1496 |
| Crystal size | 0.13 x 0.09 x 0.05 mm |
| Theta range for data collection | 3.86 to 69.36° |
| Index ranges | $-15 \leq h \leq 12$, $-18 \leq k \leq 18$, $-20 \leq \ell \leq 20$ |
| Reflections collected | 56989 |

CCCC

| | |
|---|---|
| Independent reflections | 5888 [$R_{int}$ = 0.044] |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.6054 and 0.4197 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 5888 / 0 / 369 |
| Goodness-of-fit on $F^2$ | 1.077 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0276, $wR_2$ = 0.0779 |
| R indices (all data) | $R_1$ = 0.0281, $wR_2$ = 0.0783 |
| Absolute structure parameter | 0.018(4) |
| Extinction coefficient | 0.00065(7) |
| Largest diff. peak and hole | 0.489 and -0.534 e/Å$^3$ |

DDDD

**Crystallographic Information for Complex 4.5:**



Bond precision: C-C = 0.0188 A Wavelength=1.54178

Cell: a=9.8081(2) b=15.4816(3) c=37.0741(7)
alpha=90 beta=90 gamma=90

Temperature: 100 K

| | Calculated | Reported |
|---|---|---|
| Volume | 5629.52(19) | 5629.52(19) |
| Space group | P 21 21 21 | P 21 21 21 |
| Hall group | P 2ac 2ab | P 2ac 2ab |
| Moiety formula | 2(C27 H38 Au I N2), C H2 Cl2 | 2(C27 H38 Au I N2), C H2 Cl2 |
| Sum formula | C55 H78 Au2 Cl2 I2 N4 | C55 H78 Au2 Cl2 I2 N4 |
| Mr | 1513.85 | 1513.84 |
| Dx,g cm-3 | 1.786 | 1.786 |
| Z | 4 | 4 |
| Mu (mm-1) | 19.424 | 19.424 |
| F000 | 2936.0 | 2936.0 |
| F000' | 2907.34 | |
| h,k,lmax | 12,19,45 | 12,18,45 |
| Nref | 10991[ 6125] | 10664 |
| Tmin,Tmax | 0.659,0.823 | 0.084,0.233 |
| Tmin' | 0.043 | |

Correction method= MULTI-SCAN

Data completeness= 1.74/0.97 Theta(max)= 71.681

R(reflections)= 0.0422( 10179) wR2(reflections)= 0.1171( 10664)

S = 1.075 Npar= Npar = 604

EEEE

**Table 1: List of Atoms**

| Label | Xfrac + ESD | Yfrac + ESD | Zfrac + ESD |
|---|---|---|---|
| Au1 | 0.29446(5) | 0.35688(3) | 0.54002(2) |
| I1 | 0.36785(10) | 0.36685(6) | 0.60570(2) |
| N1 | 0.2229(10) | 0.4220(6) | 0.4658(2) |
| N2 | 0.2156(11) | 0.2807(6) | 0.4699(2) |
| C1 | 0.2403(11) | 0.3544(7) | 0.4879(3) |
| C2 | 0.1992(12) | 0.2942(7) | 0.4306(3) |
| H2 | 0.1149 | 0.2638 | 0.4223 |
| C3 | 0.1736(11) | 0.3932(8) | 0.4298(3) |
| H3 | 0.2337 | 0.4192 | 0.4109 |
| C4 | 0.2591(11) | 0.5133(7) | 0.4732(3) |
| H4 | 0.2392 | 0.5447 | 0.4502 |
| C5 | 0.1717(11) | 0.5567(8) | 0.5010(3) |
| C6 | 0.1753(11) | 0.6508(7) | 0.5033(3) |
| C7 | 0.0988(14) | 0.6921(9) | 0.5292(4) |
| H7 | 0.1029 | 0.7533 | 0.5311 |
| C8 | 0.0139(15) | 0.6452(11) | 0.5533(4) |
| H8 | -0.0369 | 0.674 | 0.5715 |
| C9 | 0.0073(12) | 0.5574(8) | 0.5495(3) |
| H9 | -0.0515 | 0.5254 | 0.5649 |
| C10 | 0.0820(12) | 0.5148(7) | 0.5245(3) |
| H10 | 0.0731 | 0.4539 | 0.5228 |
| C11 | 0.2619(15) | 0.7036(8) | 0.4777(4) |
| H11A | 0.3559 | 0.7057 | 0.4867 |
| H11B | 0.2254 | 0.7624 | 0.4762 |
| H11C | 0.2606 | 0.6769 | 0.4538 |
| C12 | 0.4127(12) | 0.5247(7) | 0.4791(3) |
| C13 | 0.4993(14) | 0.5440(10) | 0.4491(4) |
| C14 | 0.6416(14) | 0.5562(9) | 0.4571(4) |
| H14 | 0.7024 | 0.5682 | 0.4378 |
| C15 | 0.6922(13) | 0.5513(9) | 0.4908(4) |
| H15 | 0.7872 | 0.559 | 0.4947 |
| C16 | 0.6071(14) | 0.5353(8) | 0.5198(4) |
| H16 | 0.643 | 0.5336 | 0.5436 |
| C17 | 0.4663(13) | 0.5215(8) | 0.5138(4) |
| H17 | 0.4079 | 0.5099 | 0.5337 |
| C18 | 0.4551(18) | 0.5555(13) | 0.4115(4) |
| H18A | 0.3746 | 0.593 | 0.4109 |
| H18B | 0.4323 | 0.4992 | 0.4011 |
| H18C | 0.5289 | 0.5821 | 0.3976 |
| C19 | 0.1869(13) | 0.1988(7) | 0.4870(3) |

FFFF

| | | | |
|---|---|---|---|
| H19A | 0.1033 | 0.1743 | 0.4767 |
| H19B | 0.175 | 0.2074 | 0.513 |
| H19C | 0.263 | 0.159 | 0.4827 |
| C20 | 0.3218(13) | 0.2608(8) | 0.4088(3) |
| C21 | 0.4581(14) | 0.3000(12) | 0.4235(4) |
| H21A | 0.4587 | 0.3625 | 0.4193 |
| H21B | 0.5354 | 0.2735 | 0.4109 |
| H21C | 0.4654 | 0.2886 | 0.4494 |
| C22 | 0.327(2) | 0.1626(10) | 0.4097(4) |
| H22A | 0.3503 | 0.1433 | 0.4341 |
| H22B | 0.396 | 0.1421 | 0.3927 |
| H22C | 0.2376 | 0.1393 | 0.4029 |
| C23 | 0.3055(14) | 0.2869(8) | 0.3695(3) |
| H23A | 0.2158 | 0.2685 | 0.3608 |
| H23B | 0.3768 | 0.2592 | 0.355 |
| H23C | 0.3134 | 0.3498 | 0.3674 |
| C24 | 0.0223(11) | 0.4183(7) | 0.4213(3) |
| C25 | -0.0752(12) | 0.3795(8) | 0.4490(3) |
| H25A | -0.0691 | 0.3164 | 0.4482 |
| H25B | -0.1687 | 0.3974 | 0.4434 |
| H25C | -0.0504 | 0.3999 | 0.4731 |
| C26 | 0.0044(12) | 0.5181(7) | 0.4206(3) |
| H26A | -0.0879 | 0.5324 | 0.4124 |
| H26B | 0.0712 | 0.5436 | 0.4041 |
| H26C | 0.0186 | 0.5413 | 0.4449 |
| C27 | -0.0135(12) | 0.3858(8) | 0.3832(3) |
| H27A | -0.0032 | 0.3229 | 0.3822 |
| H27B | 0.0478 | 0.4126 | 0.3655 |
| H27C | -0.108 | 0.4013 | 0.3775 |
| Au2 | 0.22064(5) | 0.39202(3) | 0.28475(2) |
| I2 | 0.26762(13) | 0.53230(6) | 0.31838(3) |
| N31 | 0.2762(10) | 0.2371(6) | 0.2381(2) |
| N32 | 0.0804(10) | 0.2283(6) | 0.2661(3) |
| C31 | 0.1936(11) | 0.2767(7) | 0.2599(3) |
| C32 | 0.0949(11) | 0.1405(8) | 0.2510(3) |
| H32 | 0.0128 | 0.1281 | 0.2358 |
| C33 | 0.2197(12) | 0.1521(7) | 0.2254(3) |
| H33 | 0.2877 | 0.1054 | 0.2302 |
| C34 | 0.4185(11) | 0.2620(8) | 0.2299(3) |
| H34 | 0.4599 | 0.2102 | 0.2181 |
| C35 | 0.5038(13) | 0.2769(10) | 0.2645(3) |
| C36 | 0.5595(13) | 0.2051(13) | 0.2829(4) |
| C37 | 0.6295(15) | 0.2207(17) | 0.3145(4) |

GGGG

| | | | |
|---|---|---|---|
| H37 | 0.6663 | 0.1729 | 0.3273 |
| C38 | 0.6481(16) | 0.3002(19) | 0.3279(4) |
| H38 | 0.6948 | 0.3075 | 0.3501 |
| C39 | 0.5973(16) | 0.3757(17) | 0.3086(5) |
| H39 | 0.6126 | 0.4324 | 0.3174 |
| C40 | 0.5260(13) | 0.3618(12) | 0.2770(4) |
| H40 | 0.4919 | 0.4095 | 0.2636 |
| C41 | 0.5499(16) | 0.1150(12) | 0.2697(4) |
| H41A | 0.4547 | 0.0959 | 0.2705 |
| H41B | 0.6056 | 0.0773 | 0.285 |
| H41C | 0.5831 | 0.1121 | 0.2448 |
| C42 | 0.4320(13) | 0.3355(7) | 0.2019(3) |
| C43 | 0.5558(13) | 0.3436(9) | 0.1831(3) |
| C44 | 0.5651(14) | 0.4062(9) | 0.1560(3) |
| H44 | 0.6483 | 0.4126 | 0.1431 |
| C45 | 0.4559(15) | 0.4590(9) | 0.1476(3) |
| H45 | 0.4641 | 0.5007 | 0.1289 |
| C46 | 0.3344(15) | 0.4509(8) | 0.1664(3) |
| H46 | 0.2596 | 0.4877 | 0.1611 |
| C47 | 0.3234(13) | 0.3878(8) | 0.1933(3) |
| H47 | 0.2396 | 0.381 | 0.2058 |
| C48 | 0.6750(13) | 0.2844(11) | 0.1900(4) |
| H48A | 0.6998 | 0.2869 | 0.2156 |
| H48B | 0.7529 | 0.3028 | 0.1753 |
| H48C | 0.6499 | 0.2251 | 0.1836 |
| C49 | -0.0406(12) | 0.2570(8) | 0.2847(4) |
| H49A | -0.0403 | 0.2343 | 0.3094 |
| H49B | -0.1216 | 0.236 | 0.272 |
| H49C | -0.0421 | 0.3203 | 0.2854 |
| C50 | 0.1055(12) | 0.0688(8) | 0.2806(3) |
| C51 | 0.1922(13) | 0.1004(8) | 0.3127(3) |
| H51A | 0.1515 | 0.1529 | 0.3228 |
| H51B | 0.285 | 0.1129 | 0.3044 |
| H51C | 0.1951 | 0.0553 | 0.3313 |
| C52 | -0.0395(15) | 0.0480(10) | 0.2941(4) |
| H52A | -0.0343 | 0.006 | 0.3138 |
| H52B | -0.0932 | 0.0237 | 0.2742 |
| H52C | -0.0831 | 0.101 | 0.3028 |
| C53 | 0.1640(17) | -0.0150(8) | 0.2656(4) |
| H53A | 0.1532 | -0.0612 | 0.2834 |
| H53B | 0.2611 | -0.0071 | 0.2602 |
| H53C | 0.1155 | -0.0306 | 0.2434 |
| C54 | 0.1779(12) | 0.1502(8) | 0.1848(3) |

HHHH

| | | | |
|---|---|---|---|
| C55 | 0.1246(16) | 0.0596(10) | 0.1766(4) |
| H55A | 0.2004 | 0.0183 | 0.1772 |
| H55B | 0.0829 | 0.059 | 0.1525 |
| H55C | 0.0563 | 0.0433 | 0.1946 |
| C56 | 0.3014(14) | 0.1660(9) | 0.1604(3) |
| H56A | 0.3398 | 0.2232 | 0.1655 |
| H56B | 0.273 | 0.1633 | 0.1351 |
| H56C | 0.3706 | 0.1217 | 0.165 |
| C57 | 0.0684(13) | 0.2175(9) | 0.1762(3) |
| H57A | -0.0192 | 0.1984 | 0.1861 |
| H57B | 0.0605 | 0.2241 | 0.15 |
| H57C | 0.0937 | 0.2729 | 0.1871 |
| Cl1 | 0.4210(5) | 0.7490(3) | 0.56991(12) |
| Cl2 | 0.5270(6) | 0.6105(3) | 0.61495(14) |
| C58 | 0.381(2) | 0.6569(11) | 0.5945(5) |
| H58A | 0.338 | 0.6138 | 0.5783 |
| H58B | 0.3138 | 0.672 | 0.6135 |

**Table 2: List of Bonds**

| Atom1 | Atom2 | Length |
|---|---|---|
| Au1 | I1 | 2.544(1) |
| Au1 | C1 | 2.00(1) |
| N1 | C1 | 1.34(1) |
| N1 | C3 | 1.49(1) |
| N1 | C4 | 1.48(1) |
| N2 | C1 | 1.34(1) |
| N2 | C2 | 1.48(1) |
| N2 | C19 | 1.45(1) |
| C2 | H2 | 1.00(1) |
| C2 | C3 | 1.55(2) |
| C2 | C20 | 1.54(2) |
| C3 | H3 | 1.00(1) |
| C3 | C24 | 1.57(2) |
| C4 | H4 | 1.00(1) |
| C4 | C5 | 1.50(2) |
| C4 | C12 | 1.53(2) |
| C5 | C6 | 1.46(2) |
| C5 | C10 | 1.40(2) |
| C6 | C7 | 1.38(2) |
| C6 | C11 | 1.51(2) |
| C7 | H7 | 0.95(1) |

| | | |
|---|---|---|
| C7 | C8 | 1.42(2) |
| C8 | H8 | 0.95(2) |
| C8 | C9 | 1.37(2) |
| C9 | H9 | 0.95(1) |
| C9 | C10 | 1.35(2) |
| C10 | H10 | 0.95(1) |
| C11 | H11A | 0.98(1) |
| C11 | H11B | 0.98(1) |
| C11 | H11C | 0.98(1) |
| C12 | C13 | 1.43(2) |
| C12 | C17 | 1.39(2) |
| C13 | C14 | 1.44(2) |
| C13 | C18 | 1.47(2) |
| C14 | H14 | 0.95(1) |
| C14 | C15 | 1.35(2) |
| C15 | H15 | 0.95(1) |
| C15 | C16 | 1.38(2) |
| C16 | H16 | 0.95(1) |
| C16 | C17 | 1.42(2) |
| C17 | H17 | 0.95(1) |
| C18 | H18A | 0.98(2) |
| C18 | H18B | 0.98(2) |
| C18 | H18C | 0.98(2) |
| C19 | H19A | 0.98(1) |
| C19 | H19B | 0.98(1) |
| C19 | H19C | 0.98(1) |
| C20 | C21 | 1.57(2) |
| C20 | C22 | 1.52(2) |
| C20 | C23 | 1.52(2) |
| C21 | H21A | 0.98(2) |
| C21 | H21B | 0.98(1) |
| C21 | H21C | 0.98(1) |
| C22 | H22A | 0.98(2) |
| C22 | H22B | 0.98(2) |
| C22 | H22C | 0.98(2) |
| C23 | H23A | 0.98(1) |
| C23 | H23B | 0.98(1) |
| C23 | H23C | 0.98(1) |
| C24 | C25 | 1.53(2) |
| C24 | C26 | 1.56(2) |
| C24 | C27 | 1.54(2) |
| C25 | H25A | 0.98(1) |
| C25 | H25B | 0.98(1) |

JJJJ

| | | |
|---|---|---|
| C25 | H25C | 0.98(1) |
| C26 | H26A | 0.98(1) |
| C26 | H26B | 0.98(1) |
| C26 | H26C | 0.98(1) |
| C27 | H27A | 0.98(1) |
| C27 | H27B | 0.98(1) |
| C27 | H27C | 0.98(1) |
| Au2 | I2 | 2.546(1) |
| Au2 | C31 | 2.03(1) |
| N31 | C31 | 1.30(1) |
| N31 | C33 | 1.50(1) |
| N31 | C34 | 1.48(1) |
| N32 | C31 | 1.36(1) |
| N32 | C32 | 1.48(2) |
| N32 | C49 | 1.44(2) |
| C32 | H32 | 1.00(1) |
| C32 | C33 | 1.56(2) |
| C32 | C50 | 1.56(2) |
| C33 | H33 | 1.00(1) |
| C33 | C54 | 1.56(2) |
| C34 | H34 | 1.00(1) |
| C34 | C35 | 1.55(2) |
| C34 | C42 | 1.55(2) |
| C35 | C36 | 1.41(2) |
| C35 | C40 | 1.41(2) |
| C36 | C37 | 1.38(2) |
| C36 | C41 | 1.48(3) |
| C37 | H37 | 0.95(2) |
| C37 | C38 | 1.34(4) |
| C38 | H38 | 0.95(2) |
| C38 | C39 | 1.46(3) |
| C39 | H39 | 0.95(3) |
| C39 | C40 | 1.38(2) |
| C40 | H40 | 0.95(2) |
| C41 | H41A | 0.98(2) |
| C41 | H41B | 0.98(2) |
| C41 | H41C | 0.98(1) |
| C42 | C43 | 1.41(2) |
| C42 | C47 | 1.38(2) |
| C43 | C44 | 1.40(2) |
| C43 | C48 | 1.51(2) |
| C44 | H44 | 0.95(1) |
| C44 | C45 | 1.38(2) |

KKKK

| | | |
|---|---|---|
| C45 | H45 | 0.95(1) |
| C45 | C46 | 1.39(2) |
| C46 | H46 | 0.95(1) |
| C46 | C47 | 1.40(2) |
| C47 | H47 | 0.95(1) |
| C48 | H48A | 0.98(1) |
| C48 | H48B | 0.98(1) |
| C48 | H48C | 0.98(2) |
| C49 | H49A | 0.98(1) |
| C49 | H49B | 0.98(1) |
| C49 | H49C | 0.98(1) |
| C50 | C51 | 1.54(2) |
| C50 | C52 | 1.54(2) |
| C50 | C53 | 1.52(2) |
| C51 | H51A | 0.98(1) |
| C51 | H51B | 0.98(1) |
| C51 | H51C | 0.98(1) |
| C52 | H52A | 0.98(2) |
| C52 | H52B | 0.98(1) |
| C52 | H52C | 0.98(2) |
| C53 | H53A | 0.98(1) |
| C53 | H53B | 0.98(2) |
| C53 | H53C | 0.98(2) |
| C54 | C55 | 1.53(2) |
| C54 | C56 | 1.53(2) |
| C54 | C57 | 1.53(2) |
| C55 | H55A | 0.98(2) |
| C55 | H55B | 0.98(1) |
| C55 | H55C | 0.98(2) |
| C56 | H56A | 0.98(1) |
| C56 | H56B | 0.98(1) |
| C56 | H56C | 0.98(1) |
| C57 | H57A | 0.98(1) |
| C57 | H57B | 0.98(1) |
| C57 | H57C | 0.98(1) |
| Cl1 | C58 | 1.74(2) |
| Cl2 | C58 | 1.77(2) |
| C58 | H58A | 0.99(2) |
| C58 | H58B | 0.99(2) |

LLLL

**Table 3: List of Angles**

| Atom1 | Atom2 | Atom3 | Angle |
|---|---|---|---|
| I1 | Au1 | C1 | 177.4(3) |
| C1 | N1 | C3 | 110.8(9) |
| C1 | N1 | C4 | 126.9(9) |
| C3 | N1 | C4 | 122.0(9) |
| C1 | N2 | C2 | 112.9(9) |
| C1 | N2 | C19 | 124.2(9) |
| C2 | N2 | C19 | 122.3(9) |
| Au1 | C1 | N1 | 127.5(8) |
| Au1 | C1 | N2 | 122.9(8) |
| N1 | C1 | N2 | 109.7(9) |
| N2 | C2 | H2 | 109(1) |
| N2 | C2 | C3 | 100.1(9) |
| N2 | C2 | C20 | 112.6(9) |
| H2 | C2 | C3 | 109(1) |
| H2 | C2 | C20 | 109(1) |
| C3 | C2 | C20 | 116.6(9) |
| N1 | C3 | C2 | 103.1(9) |
| N1 | C3 | H3 | 108(1) |
| N1 | C3 | C24 | 114.5(9) |
| C2 | C3 | H3 | 108(1) |
| C2 | C3 | C24 | 113.7(9) |
| H3 | C3 | C24 | 109(1) |
| N1 | C4 | H4 | 105.0(9) |
| N1 | C4 | C5 | 114.7(9) |
| N1 | C4 | C12 | 111.8(9) |
| H4 | C4 | C5 | 104.9(9) |
| H4 | C4 | C12 | 104.9(9) |
| C5 | C4 | C12 | 114.3(9) |
| C4 | C5 | C6 | 118(1) |
| C4 | C5 | C10 | 125(1) |
| C6 | C5 | C10 | 116(1) |
| C5 | C6 | C7 | 119(1) |
| C5 | C6 | C11 | 121(1) |
| C7 | C6 | C11 | 120(1) |
| C6 | C7 | H7 | 119(1) |
| C6 | C7 | C8 | 121(1) |
| H7 | C7 | C8 | 119(1) |
| C7 | C8 | H8 | 121(1) |
| C7 | C8 | C9 | 118(1) |
| H8 | C8 | C9 | 121(1) |

MMMM

| | | | |
|---|---|---|---|
| C8 | C9 | H9 | 119(1) |
| C8 | C9 | C10 | 122(1) |
| H9 | C9 | C10 | 119(1) |
| C5 | C10 | C9 | 123(1) |
| C5 | C10 | H10 | 119(1) |
| C9 | C10 | H10 | 119(1) |
| C6 | C11 | H11A | 109(1) |
| C6 | C11 | H11B | 109(1) |
| C6 | C11 | H11C | 109(1) |
| H11A | C11 | H11B | 109(1) |
| H11A | C11 | H11C | 110(1) |
| H11B | C11 | H11C | 110(1) |
| C4 | C12 | C13 | 120(1) |
| C4 | C12 | C17 | 120(1) |
| C13 | C12 | C17 | 120(1) |
| C12 | C13 | C14 | 116(1) |
| C12 | C13 | C18 | 126(1) |
| C14 | C13 | C18 | 118(1) |
| C13 | C14 | H14 | 119(1) |
| C13 | C14 | C15 | 123(1) |
| H14 | C14 | C15 | 119(1) |
| C14 | C15 | H15 | 120(1) |
| C14 | C15 | C16 | 121(1) |
| H15 | C15 | C16 | 120(1) |
| C15 | C16 | H16 | 120(1) |
| C15 | C16 | C17 | 120(1) |
| H16 | C16 | C17 | 120(1) |
| C12 | C17 | C16 | 121(1) |
| C12 | C17 | H17 | 120(1) |
| C16 | C17 | H17 | 120(1) |
| C13 | C18 | H18A | 109(2) |
| C13 | C18 | H18B | 109(2) |
| C13 | C18 | H18C | 109(2) |
| H18A | C18 | H18B | 110(2) |
| H18A | C18 | H18C | 110(2) |
| H18B | C18 | H18C | 110(2) |
| N2 | C19 | H19A | 109(1) |
| N2 | C19 | H19B | 110(1) |
| N2 | C19 | H19C | 109(1) |
| H19A | C19 | H19B | 110(1) |
| H19A | C19 | H19C | 109(1) |
| H19B | C19 | H19C | 110(1) |
| C2 | C20 | C21 | 111(1) |

NNNN

| | | | |
|---|---|---|---|
| C2 | C20 | C22 | 111(1) |
| C2 | C20 | C23 | 109(1) |
| C21 | C20 | C22 | 111(1) |
| C21 | C20 | C23 | 109(1) |
| C22 | C20 | C23 | 107(1) |
| C20 | C21 | H21A | 109(1) |
| C20 | C21 | H21B | 109(1) |
| C20 | C21 | H21C | 110(1) |
| H21A | C21 | H21B | 109(1) |
| H21A | C21 | H21C | 109(2) |
| H21B | C21 | H21C | 110(2) |
| C20 | C22 | H22A | 109(1) |
| C20 | C22 | H22B | 109(1) |
| C20 | C22 | H22C | 109(1) |
| H22A | C22 | H22B | 110(2) |
| H22A | C22 | H22C | 109(2) |
| H22B | C22 | H22C | 109(2) |
| C20 | C23 | H23A | 109(1) |
| C20 | C23 | H23B | 110(1) |
| C20 | C23 | H23C | 109(1) |
| H23A | C23 | H23B | 109(1) |
| H23A | C23 | H23C | 110(1) |
| H23B | C23 | H23C | 110(1) |
| C3 | C24 | C25 | 111.1(9) |
| C3 | C24 | C26 | 110.9(9) |
| C3 | C24 | C27 | 108.6(9) |
| C25 | C24 | C26 | 109.4(9) |
| C25 | C24 | C27 | 110.2(9) |
| C26 | C24 | C27 | 106.5(9) |
| C24 | C25 | H25A | 110(1) |
| C24 | C25 | H25B | 109(1) |
| C24 | C25 | H25C | 109(1) |
| H25A | C25 | H25B | 109(1) |
| H25A | C25 | H25C | 110(1) |
| H25B | C25 | H25C | 110(1) |
| C24 | C26 | H26A | 109(1) |
| C24 | C26 | H26B | 110(1) |
| C24 | C26 | H26C | 109(1) |
| H26A | C26 | H26B | 109(1) |
| H26A | C26 | H26C | 109(1) |
| H26B | C26 | H26C | 109(1) |
| C24 | C27 | H27A | 110(1) |
| C24 | C27 | H27B | 110(1) |

OOOO

| | | | |
|---|---|---|---|
| C24 | C27 | H27C | 109(1) |
| H27A | C27 | H27B | 109(1) |
| H27A | C27 | H27C | 109(1) |
| H27B | C27 | H27C | 109(1) |
| I2 | Au2 | C31 | 176.1(3) |
| C31 | N31 | C33 | 112.2(9) |
| C31 | N31 | C34 | 126.4(9) |
| C33 | N31 | C34 | 120.8(9) |
| C31 | N32 | C32 | 111.4(9) |
| C31 | N32 | C49 | 126(1) |
| C32 | N32 | C49 | 123(1) |
| Au2 | C31 | N31 | 128.1(8) |
| Au2 | C31 | N32 | 121.0(8) |
| N31 | C31 | N32 | 111(1) |
| N32 | C32 | H32 | 108(1) |
| N32 | C32 | C33 | 101.6(9) |
| N32 | C32 | C50 | 113.2(9) |
| H32 | C32 | C33 | 108(1) |
| H32 | C32 | C50 | 108(1) |
| C33 | C32 | C50 | 117.2(9) |
| N31 | C33 | C32 | 101.5(8) |
| N31 | C33 | H33 | 109.4(9) |
| N31 | C33 | C54 | 114.5(9) |
| C32 | C33 | H33 | 109(1) |
| C32 | C33 | C54 | 112.3(9) |
| H33 | C33 | C54 | 109(1) |
| N31 | C34 | H34 | 105.3(9) |
| N31 | C34 | C35 | 112.2(9) |
| N31 | C34 | C42 | 114.2(9) |
| H34 | C34 | C35 | 105(1) |
| H34 | C34 | C42 | 105(1) |
| C35 | C34 | C42 | 114(1) |
| C34 | C35 | C36 | 119(1) |
| C34 | C35 | C40 | 120(1) |
| C36 | C35 | C40 | 121(1) |
| C35 | C36 | C37 | 118(1) |
| C35 | C36 | C41 | 124(1) |
| C37 | C36 | C41 | 119(1) |
| C36 | C37 | H37 | 118(2) |
| C36 | C37 | C38 | 123(2) |
| H37 | C37 | C38 | 119(2) |
| C37 | C38 | H38 | 120(2) |
| C37 | C38 | C39 | 121(2) |

| | | | |
|---|---|---|---|
| H38 | C38 | C39 | 120(2) |
| C38 | C39 | H39 | 121(2) |
| C38 | C39 | C40 | 118(2) |
| H39 | C39 | C40 | 121(2) |
| C35 | C40 | C39 | 120(1) |
| C35 | C40 | H40 | 120(1) |
| C39 | C40 | H40 | 120(2) |
| C36 | C41 | H41A | 110(1) |
| C36 | C41 | H41B | 110(1) |
| C36 | C41 | H41C | 109(1) |
| H41A | C41 | H41B | 110(2) |
| H41A | C41 | H41C | 109(2) |
| H41B | C41 | H41C | 109(2) |
| C34 | C42 | C43 | 118(1) |
| C34 | C42 | C47 | 122(1) |
| C43 | C42 | C47 | 120(1) |
| C42 | C43 | C44 | 118(1) |
| C42 | C43 | C48 | 122(1) |
| C44 | C43 | C48 | 120(1) |
| C43 | C44 | H44 | 119(1) |
| C43 | C44 | C45 | 121(1) |
| H44 | C44 | C45 | 119(1) |
| C44 | C45 | H45 | 120(1) |
| C44 | C45 | C46 | 120(1) |
| H45 | C45 | C46 | 120(1) |
| C45 | C46 | H46 | 120(1) |
| C45 | C46 | C47 | 119(1) |
| H46 | C46 | C47 | 120(1) |
| C42 | C47 | C46 | 121(1) |
| C42 | C47 | H47 | 119(1) |
| C46 | C47 | H47 | 119(1) |
| C43 | C48 | H48A | 109(1) |
| C43 | C48 | H48B | 109(1) |
| C43 | C48 | H48C | 109(1) |
| H48A | C48 | H48B | 109(1) |
| H48A | C48 | H48C | 109(1) |
| H48B | C48 | H48C | 109(1) |
| N32 | C49 | H49A | 109(1) |
| N32 | C49 | H49B | 110(1) |
| N32 | C49 | H49C | 109(1) |
| H49A | C49 | H49B | 109(1) |
| H49A | C49 | H49C | 109(1) |
| H49B | C49 | H49C | 109(1) |

QQQQ

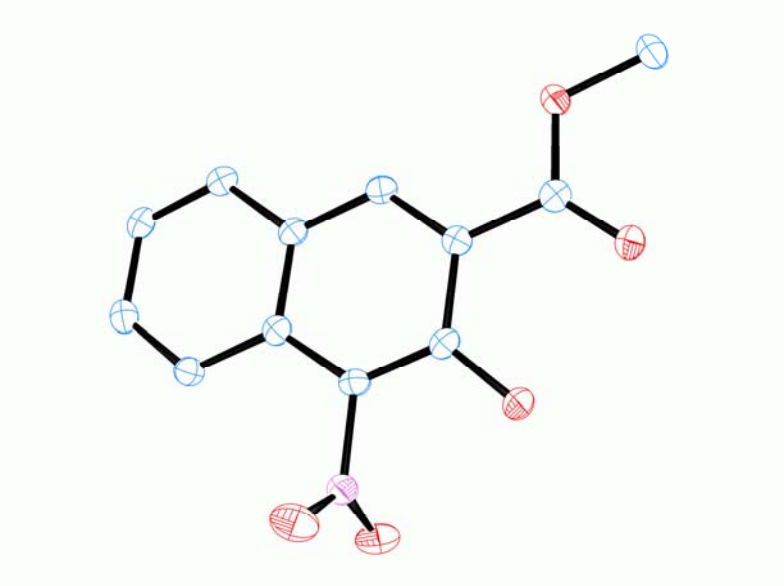
| | | | |
|---|---|---|---|
| C32 | C50 | C51 | 110.7(9) |
| C32 | C50 | C52 | 108(1) |
| C32 | C50 | C53 | 112(1) |
| C51 | C50 | C52 | 109(1) |
| C51 | C50 | C53 | 110(1) |
| C52 | C50 | C53 | 107(1) |
| C50 | C51 | H51A | 109(1) |
| C50 | C51 | H51B | 109(1) |
| C50 | C51 | H51C | 109(1) |
| H51A | C51 | H51B | 110(1) |
| H51A | C51 | H51C | 109(1) |
| H51B | C51 | H51C | 110(1) |
| C50 | C52 | H52A | 109(1) |
| C50 | C52 | H52B | 109(1) |
| C50 | C52 | H52C | 110(1) |
| H52A | C52 | H52B | 110(1) |
| H52A | C52 | H52C | 109(1) |
| H52B | C52 | H52C | 110(1) |
| C50 | C53 | H53A | 110(1) |
| C50 | C53 | H53B | 110(1) |
| C50 | C53 | H53C | 109(1) |
| H53A | C53 | H53B | 109(1) |
| H53A | C53 | H53C | 109(1) |
| H53B | C53 | H53C | 109(1) |
| C33 | C54 | C55 | 107(1) |
| C33 | C54 | C56 | 111(1) |
| C33 | C54 | C57 | 112(1) |
| C55 | C54 | C56 | 107(1) |
| C55 | C54 | C57 | 110(1) |
| C56 | C54 | C57 | 109(1) |
| C54 | C55 | H55A | 110(1) |
| C54 | C55 | H55B | 109(1) |
| C54 | C55 | H55C | 110(1) |
| H55A | C55 | H55B | 109(1) |
| H55A | C55 | H55C | 110(1) |
| H55B | C55 | H55C | 109(1) |
| C54 | C56 | H56A | 110(1) |
| C54 | C56 | H56B | 110(1) |
| C54 | C56 | H56C | 109(1) |
| H56A | C56 | H56B | 109(1) |
| H56A | C56 | H56C | 109(1) |
| H56B | C56 | H56C | 110(1) |
| C54 | C57 | H57A | 109(1) |

RRRR

| | | | |
|---|---|---|---|
| C54 | C57 | H57B | 109(1) |
| C54 | C57 | H57C | 109(1) |
| H57A | C57 | H57B | 109(1) |
| H57A | C57 | H57C | 109(1) |
| H57B | C57 | H57C | 110(1) |
| Cl1 | C58 | Cl2 | 112(1) |
| Cl1 | C58 | H58A | 109(1) |
| Cl1 | C58 | H58B | 109(1) |
| Cl2 | C58 | H58A | 109(1) |
| Cl2 | C58 | H58B | 109(1) |
| H58A | C58 | H58B | 108(2) |

SSSS

## Crystallographic Information for Compound 6.1



| | |
|---|---|
| Empirical formula | C24 H18 N2 O10 |
| Formula weight | 494.40 |
| Temperature | 100K |
| Wavelength | 1.54178 Å |
| Crystal system | Monoclinic |
| Space group | P21/c |
| Unit cell dimensions | a = 10.2650(2) Å  α = 90°<br>b = 30.2487(5) Å  β = 106.173(1)°<br>c = 7.2124(1) Å  γ = 90° |
| Volume | 2150.84(6)Å$^3$ |
| Z | 4 |
| Density (calculated) | 1.527 g/cm$^3$ |
| Absorption coefficient | 1.033 mm$^{-1}$ |
| F(000) | 1024 |
| Crystal size | 0.08 x 0.03 x 0.02 mm |
| Theta range for data collection | 2.92 to 70.95° |
| Index ranges | $-12 \le h \le 12$, $-36 \le k \le 36$, $-6 \le \ell \le 8$ |

TTTT

| | |
|---|---|
| Reflections collected | 38170 |
| Independent reflections | 4071 [$R_{int}$ = 0.024] |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9796 and 0.8489 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 4071 / 0 / 335 |
| Goodness-of-fit on $F^2$ | 1.037 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0346, $wR_2$ = 0.0991 |
| R indices (all data) | $R_1$ = 0.0397, $wR_2$ = 0.1044 |
| Largest diff. peak and hole | 0.280 and -0.206 e/Å$^3$ |

**Table 1: List of Atoms**

| Label | Xfrac + ESD | Yfrac + ESD | Zfrac + ESD |
|---|---|---|---|
| O12 | 0.28807(9) | 0.92420(3) | 0.03078(13) |
| H12 | 0.220(2) | 0.9402(7) | -0.032(3) |
| O13 | 0.47413(12) | 0.86730(3) | 0.36427(17) |
| O14 | 0.57518(12) | 0.86895(3) | 0.13981(18) |
| N13 | 0.51860(10) | 0.88681(3) | 0.24697(16) |
| O21 | 0.14269(8) | 0.99526(3) | -0.08337(12) |
| O22 | 0.23102(8) | 1.06150(3) | 0.02395(12) |
| C11 | 0.36782(11) | 0.99919(4) | 0.12516(17) |
| C12 | 0.38468(12) | 0.95218(4) | 0.12950(17) |
| C13 | 0.50494(12) | 0.93527(4) | 0.23926(17) |
| C14 | 0.61542(12) | 0.96092(4) | 0.34699(17) |
| C15 | 0.73945(12) | 0.94293(4) | 0.46051(18) |
| H15 | 0.7522 | 0.9118 | 0.4678 |
| C16 | 0.84113(12) | 0.97049(4) | 0.55981(18) |
| H16 | 0.924 | 0.9582 | 0.6359 |
| C17 | 0.82443(12) | 1.01677(4) | 0.55062(18) |
| H17 | 0.8962 | 1.0354 | 0.6194 |
| C18 | 0.70517(12) | 1.03505(4) | 0.44296(17) |
| H18 | 0.6946 | 1.0663 | 0.4385 |
| C19 | 0.59742(11) | 1.00775(4) | 0.33818(17) |
| C20 | 0.47276(12) | 1.02551(4) | 0.22711(17) |
| H20 | 0.461 | 1.0567 | 0.2227 |
| C21 | 0.23627(11) | 1.01778(4) | 0.01121(17) |
| C22 | 0.10515(13) | 1.08185(4) | -0.0857(2) |

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|---|---|---|---|
| H22A | 0.092 | 1.0765 | -0.2237 |
| H22B | 0.1091 | 1.1137 | -0.0611 |
| H22C | 0.0293 | 1.069 | -0.0464 |
| O32 | -0.17411(9) | 0.82338(3) | 0.40544(13) |
| H32 | -0.239(2) | 0.8072(6) | 0.336(3) |
| O33 | 0.03791(11) | 0.88151(3) | 0.76437(16) |
| O34 | 0.08122(11) | 0.87955(3) | 0.48800(15) |
| N33 | 0.05379(10) | 0.86188(3) | 0.62467(16) |
| O41 | -0.30690(8) | 0.75107(3) | 0.26846(13) |
| O42 | -0.22118(8) | 0.68569(3) | 0.39097(13) |
| C31 | -0.08951(11) | 0.74872(4) | 0.49910(17) |
| C32 | -0.07631(11) | 0.79583(4) | 0.50577(17) |
| C33 | 0.04143(12) | 0.81341(4) | 0.62122(17) |
| C34 | 0.15221(12) | 0.78838(4) | 0.73129(17) |
| C35 | 0.27405(12) | 0.80709(4) | 0.84875(17) |
| H35 | 0.2837 | 0.8383 | 0.8601 |
| C36 | 0.37763(12) | 0.78005(4) | 0.94568(18) |
| H36 | 0.4588 | 0.7927 | 1.0247 |
| C37 | 0.36582(12) | 0.73367(4) | 0.93015(17) |
| H37 | 0.4396 | 0.7155 | 0.9966 |
| C38 | 0.24884(12) | 0.71466(4) | 0.82002(17) |
| H38 | 0.2414 | 0.6834 | 0.8119 |
| C39 | 0.13863(11) | 0.74143(4) | 0.71783(17) |
| C40 | 0.01682(11) | 0.72294(4) | 0.60242(17) |
| H40 | 0.0077 | 0.6917 | 0.5956 |
| C41 | -0.21669(12) | 0.72933(4) | 0.37530(17) |
| C42 | -0.33902(12) | 0.66433(4) | 0.26319(19) |
| H42A | -0.4214 | 0.6753 | 0.2909 |
| H42B | -0.3323 | 0.6323 | 0.2836 |
| H42C | -0.3429 | 0.671 | 0.1288 |

**Table 2: List of Bonds**

| Atom1 | Atom2 | Length |
|---|---|---|
| O12 | H12 | 0.87(2) |
| O12 | C12 | 1.347(1) |
| O13 | N13 | 1.220(2) |
| O14 | N13 | 1.215(2) |
| N13 | C13 | 1.472(2) |
| O21 | C21 | 1.219(1) |
| O22 | C21 | 1.328(2) |
| O22 | C22 | 1.451(1) |

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|---|---|---|
| C11 | C12 | 1.432(2) |
| C11 | C20 | 1.376(2) |
| C11 | C21 | 1.482(1) |
| C12 | C13 | 1.367(2) |
| C13 | C14 | 1.415(2) |
| C14 | C15 | 1.417(2) |
| C14 | C19 | 1.428(2) |
| C15 | H15 | 0.950(1) |
| C15 | C16 | 1.371(2) |
| C16 | H16 | 0.950(1) |
| C16 | C17 | 1.410(2) |
| C17 | H17 | 0.950(1) |
| C17 | C18 | 1.370(2) |
| C18 | H18 | 0.951(1) |
| C18 | C19 | 1.418(2) |
| C19 | C20 | 1.413(2) |
| C20 | H20 | 0.951(1) |
| C22 | H22A | 0.980(1) |
| C22 | H22B | 0.978(1) |
| C22 | H22C | 0.980(1) |
| O32 | H32 | 0.86(2) |
| O32 | C32 | 1.350(1) |
| O33 | N33 | 1.219(2) |
| O34 | N33 | 1.221(2) |
| N33 | C33 | 1.471(2) |
| O41 | C41 | 1.219(1) |
| O42 | C41 | 1.327(2) |
| O42 | C42 | 1.452(1) |
| C31 | C32 | 1.431(2) |
| C31 | C40 | 1.379(2) |
| C31 | C41 | 1.482(2) |
| C32 | C33 | 1.370(2) |
| C33 | C34 | 1.412(2) |
| C34 | C35 | 1.418(2) |
| C34 | C39 | 1.428(2) |
| C35 | H35 | 0.950(1) |
| C35 | C36 | 1.369(2) |
| C36 | H36 | 0.949(1) |
| C36 | C37 | 1.410(2) |
| C37 | H37 | 0.950(1) |
| C37 | C38 | 1.368(2) |
| C38 | H38 | 0.949(1) |
| C38 | C39 | 1.419(2) |

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|---|---|---|
| C39 | C40 | 1.410(1) |
| C40 | H40 | 0.950(1) |
| C42 | H42A | 0.979(1) |
| C42 | H42B | 0.980(1) |
| C42 | H42C | 0.980(1) |

**Table 3: List of Angles**

| Number | Atom1 | Atom2 | Atom3 | Angle |
|---|---|---|---|---|
| 1 | H12 | O12 | C12 | 107(1) |
| 2 | O13 | N13 | O14 | 124.3(1) |
| 3 | O13 | N13 | C13 | 117.3(1) |
| 4 | O14 | N13 | C13 | 118.4(1) |
| 5 | C21 | O22 | C22 | 115.6(1) |
| 6 | C12 | C11 | C20 | 119.4(1) |
| 7 | C12 | C11 | C21 | 118.3(1) |
| 8 | C20 | C11 | C21 | 122.2(1) |
| 9 | O12 | C12 | C11 | 123.1(1) |
| 10 | O12 | C12 | C13 | 119.0(1) |
| 11 | C11 | C12 | C13 | 117.9(1) |
| 12 | N13 | C13 | C12 | 117.1(1) |
| 13 | N13 | C13 | C14 | 118.2(1) |
| 14 | C12 | C13 | C14 | 124.7(1) |
| 15 | C13 | C14 | C15 | 124.1(1) |
| 16 | C13 | C14 | C19 | 116.5(1) |
| 17 | C15 | C14 | C19 | 119.4(1) |
| 18 | C14 | C15 | H15 | 120.0(1) |
| 19 | C14 | C15 | C16 | 119.9(1) |
| 20 | H15 | C15 | C16 | 120.0(1) |
| 21 | C15 | C16 | H16 | 119.5(1) |
| 22 | C15 | C16 | C17 | 120.9(1) |
| 23 | H16 | C16 | C17 | 119.6(1) |
| 24 | C16 | C17 | H17 | 119.9(1) |
| 25 | C16 | C17 | C18 | 120.3(1) |
| 26 | H17 | C17 | C18 | 119.8(1) |
| 27 | C17 | C18 | H18 | 119.7(1) |
| 28 | C17 | C18 | C19 | 120.5(1) |
| 29 | H18 | C18 | C19 | 119.7(1) |
| 30 | C14 | C19 | C18 | 118.8(1) |
| 31 | C14 | C19 | C20 | 119.2(1) |
| 32 | C18 | C19 | C20 | 122.0(1) |
| 33 | C11 | C20 | C19 | 122.2(1) |

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|---|---|---|---|---|
| 34 | C11 | C20 | H20 | 118.9(1) |
| 35 | C19 | C20 | H20 | 118.9(1) |
| 36 | O21 | C21 | O22 | 123.7(1) |
| 37 | O21 | C21 | C11 | 123.5(1) |
| 38 | O22 | C21 | C11 | 112.8(1) |
| 39 | O22 | C22 | H22A | 109.5(1) |
| 40 | O22 | C22 | H22B | 109.5(1) |
| 41 | O22 | C22 | H22C | 109.4(1) |
| 42 | H22A | C22 | H22B | 109.5(1) |
| 43 | H22A | C22 | H22C | 109.4(1) |
| 44 | H22B | C22 | H22C | 109.5(1) |
| 45 | H32 | O32 | C32 | 107(1) |
| 46 | O33 | N33 | O34 | 124.6(1) |
| 47 | O33 | N33 | C33 | 117.9(1) |
| 48 | O34 | N33 | C33 | 117.4(1) |
| 49 | C41 | O42 | C42 | 115.5(1) |
| 50 | C32 | C31 | C40 | 119.5(1) |
| 51 | C32 | C31 | C41 | 118.3(1) |
| 52 | C40 | C31 | C41 | 122.2(1) |
| 53 | O32 | C32 | C31 | 123.2(1) |
| 54 | O32 | C32 | C33 | 119.0(1) |
| 55 | C31 | C32 | C33 | 117.8(1) |
| 56 | N33 | C33 | C32 | 117.0(1) |
| 57 | N33 | C33 | C34 | 118.2(1) |
| 58 | C32 | C33 | C34 | 124.7(1) |
| 59 | C33 | C34 | C35 | 124.0(1) |
| 60 | C33 | C34 | C39 | 116.6(1) |
| 61 | C35 | C34 | C39 | 119.4(1) |
| 62 | C34 | C35 | H35 | 120.1(1) |
| 63 | C34 | C35 | C36 | 119.8(1) |
| 64 | H35 | C35 | C36 | 120.1(1) |
| 65 | C35 | C36 | H36 | 119.5(1) |
| 66 | C35 | C36 | C37 | 121.1(1) |
| 67 | H36 | C36 | C37 | 119.4(1) |
| 68 | C36 | C37 | H37 | 119.8(1) |
| 69 | C36 | C37 | C38 | 120.4(1) |
| 70 | H37 | C37 | C38 | 119.8(1) |
| 71 | C37 | C38 | H38 | 119.8(1) |
| 72 | C37 | C38 | C39 | 120.4(1) |
| 73 | H38 | C38 | C39 | 119.8(1) |
| 74 | C34 | C39 | C38 | 118.9(1) |
| 75 | C34 | C39 | C40 | 119.2(1) |
| 76 | C38 | C39 | C40 | 121.8(1) |

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| | | | | |
|---|---|---|---|---|
| 77 | C31 | C40 | C39 | 122.2(1) |
| 78 | C31 | C40 | H40 | 118.9(1) |
| 79 | C39 | C40 | H40 | 118.9(1) |
| 80 | O41 | C41 | O42 | 123.5(1) |
| 81 | O41 | C41 | C31 | 123.6(1) |
| 82 | O42 | C41 | C31 | 112.8(1) |
| 83 | O42 | C42 | H42A | 109.5(1) |
| 84 | O42 | C42 | H42B | 109.5(1) |
| 85 | O42 | C42 | H42C | 109.5(1) |
| 86 | H42A | C42 | H42B | 109.5(1) |
| 87 | H42A | C42 | H42C | 109.4(1) |
| 88 | H42B | C42 | H42C | 109.5(1) |

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