# AN ABSTRACT OF THE CAPSTONE REPORT OF

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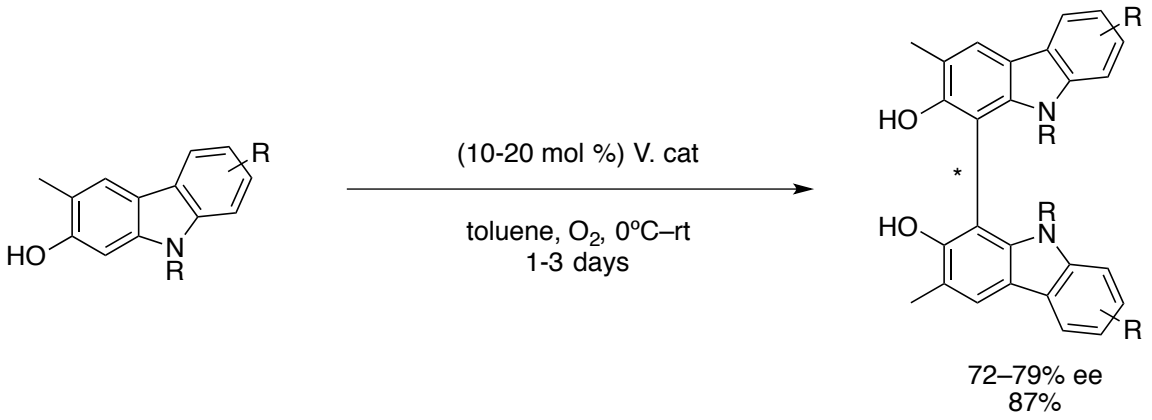


The biscarbazole skeleton is present in compounds produced by the plants of the *Rutaceae* family with over 20 naturally occurring molecules. Bishydroxycarbazoles, an important class of these alkaloids, are garnering increased interest for their potential antimalarial, cytotoxic, anti-HIV, and antimicrobial activity. Previous methods to form biscarbazoles are limited to racemic couplings to form the biaryl linkage. The goal of the project is to use a chiral vanadium catalyst and oxygen to achieve high enantioselectivity in a more efficient oxidative coupling. For a range of five substrates, enantioselectivies of 72-79% ee and yields up to 87% were obtained. This technique provides a potential route to various natural products, such as bismurrayfoline E. With the ability to synthesize these natural products, avenues are opened for further study of their biological activity.

*Asymmetric Oxidative Coupling of 2-Hydroxycarbazoles*

by

*Paul D. Sung*

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I understand that my Capstone Report will become part of the permanent collection of the University of Pennsylvania Master of Chemical Sciences Program. My signature below authorizes release of my final report to any reader upon request.

Paul Sung

*Paul D. Sung*, Author

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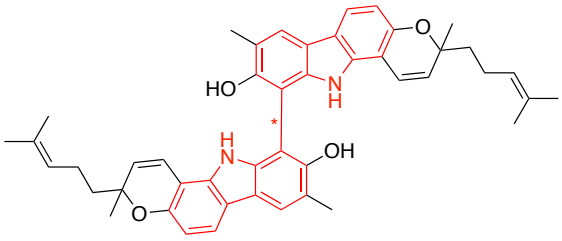
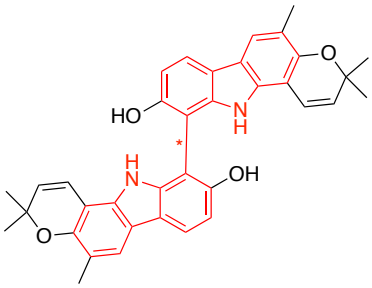
## Introduction

Biaryl compounds are commonly found in natural products as well as various chiral ligands. The biscarbazole skeleton, a biaryl derived from carbazoles, is seen in various alkaloid-based natural products. As highlighted in red in **Figure 1**, the biscarbazole carbon skeleton is a dimer of a carbazole, an indole like structure with an additional aromatic ring.

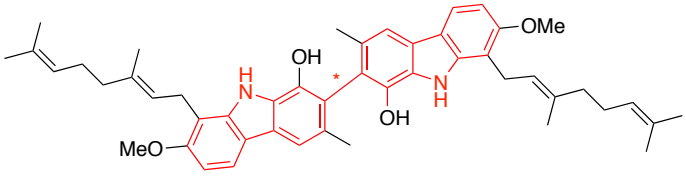
**Figure 1**. Natural Products with Biscarbazoles Skeletons




Bisisomahanine




Bis-7-hydroxygirinimbine-A



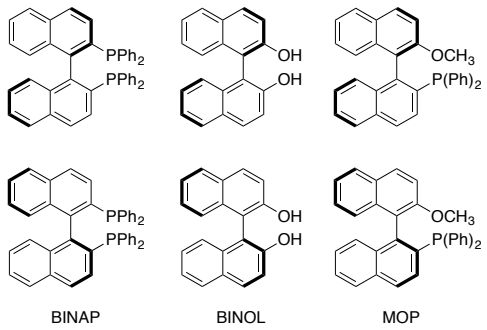

Bismurrayafoline E

Most of these natural products, including bismahanine, bis-7-hydroxygirinimbine-A and bismurrayfoline E (**Figure 1**), are obtained from the *Murraya koenigii* leaf.[1, 2, 3] This plant is from the family Rutaceae, which is native to India. Besides use as a flavoring and traditional medicine, the natural products from these leaves have cytotoxic, anti-HIV, and antiradical properties.

Most stereocenters in molecules arise from $sp^3$-hybridized carbons with four different substituents. The biscarbazoles possess a different form of chirality called, axial chirality. Due to the steric bulk of individual monomers, there is a high energy barrier to

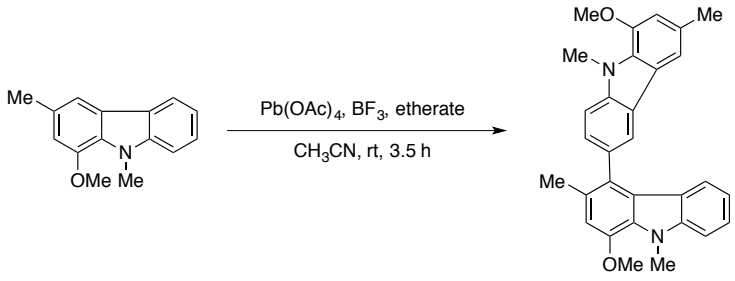
rotation around the biaryl bond via the planar conformation. Enantiopure biaryl molecules have proven useful because they make good targets for ligands. Examples of these include BINAP, BINOL, and MOP (**Figure 2**).[4] The natural products in Figure 1 also possess this axial chirality. Bisisomahanine is found to be axially racemic, while the other two natural products have unknown chirality.[5,6]

**Figure 2.** Possible Enantiopure Biaryl Molecules[4]




There are currently many syntheses of carbazoles monomers, but the corresponding dimerization is a challenging task. In addition, the reported methods to form these dimers do not allow generation of biscarbazoles with stereocontrol.[7] For example, the Bringmann group reported the first total synthesis of a biscarbazole, based on the Murraya alkaloid murrastifoline-F structure, in the year 2000 (**Figure 3**). In this study, it was noticed that protecting the nitrogen together with the use of lead tetraacetate, boron trifluoride etherate, and acetonitrile allowed C-C bonds to form between the carbazoles instead of C-N bonds. Problems with this method include the stoichiometric use of harmful reagents such as lead acetate. In 2013, the Knolker group developed a method to dimerize carbazoles to generate the biscarbazole alkaloids murrafoline A, murrafoline B, murrafoline C, and murrafoline D through the use of palladium and copper.[8] However, none of these products have a chiral biaryl bond.

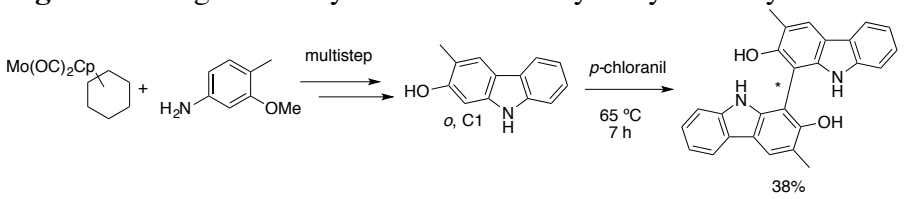
**Figure 3.** C,C-coupling Using an *N*-Protected Carbazole[7]




Other approaches to form chiral biaryl biscarbazoles have been reported, including common oxidants such as, di-*tert*-butyl peroxide, copper chloride, *para*-chloroanil, benzoyl peroxide, and copper sulfate.[9,10,11] For example, the dimerization of bis-2-hydroxy-3-methylcarbazole has been studied by Bringmann. As expected, the achiral

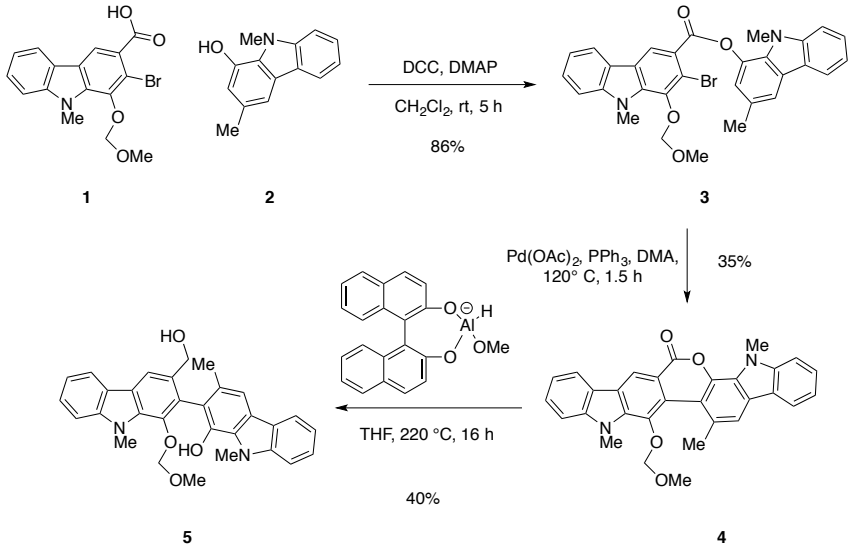
oxidant *para*-chloranil generated only racemic product. In fact, very few methods to provide enantiocontrol have been demonstrated in the formation of the chiral biaryl bonds.[12] In addition, there is no work showing the stereoselective coupling of *ortho-ortho*, C1-C1 bonds. (**Figure 4.**) Notably, a methyl group substituent prevents coupling at the aromatic carbon that is both *ortho* to the phenol and *para* to the carbazole nitrogen.

**Figure 4.** Bringmann's Synthesis of Bis-2-hydroxy-3-methylcarbazole[12]




Bringmann developed a route to an axially chiral biscarbazole in 2001.[13] His approach does not use an oxidative coupling to generate the biaryl bond, but uses a palladium catalyzed C-H insertion. Furthermore, the two substrates **1** and **2** are first united via an ester bond to generate **3** for a more facile intramolecular coupling to form **4**. The strained ester bridge causes facile isomerization of the chiral axis yielding an opportunity to use dynamic kinetic resolution. The chiral axis is significantly more stable once formed because of the strain caused by the bulk of the methyl group interfering with the ester. Thus, the stereochemistry of the biaryl bond was established after its formation by means of a dynamic kinetic resolution of **4** via reduction of the ester with BINAL to form **5** with 64% ee and 20% yield. While this strategy was ultimately successful for forming the targeted compound with enantiocontrol, the selectivity levels were only moderate and the method required several additional functional group maniupulations.

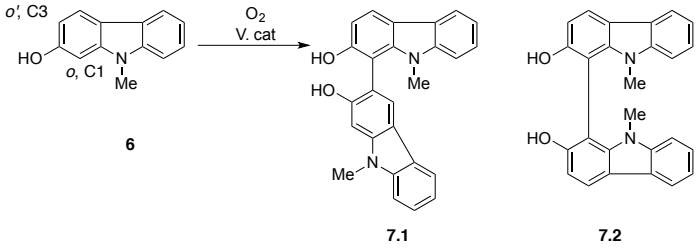
**Scheme 1.** Bringmann Enantioselective Carbazole Synthesis




Recently, the Kozlowski lab has developed a complementary coupling method to provide regioselective *ortho-ortho'*, C1-C3, coupling of unsubstituted carbazoles (**Figure**

**5**).[1] In Lei's work, the *ortho-ortho'*, C1-C3, coupling pattern was found to be favored over the *ortho-ortho*, C1-C1, pattern resulting in **7.1**. The *ortho-ortho* product, **7.2**, was initially expected to form because of the electron donation from the aniline. Together with electron donation from the alcohol, the C1-position is the most electron-rich, and the most readily oxidized; however, only one of the monomers reacts at the *ortho* position while the other monomer reacts at the *ortho'* position. This outcome is attributed to the increased steric hindrance between the two monomers during bond formation between the two *ortho*-sites. To override this inherent selectivity, methyl groups are installed at C3 to force the *ortho-ortho*, C1-C1, coupling as had been shown to be effective previously (**Figure 4**).

**Figure 5.** Oxidative Coupling Patterns of 1-Hydroxycarbazoles[1]



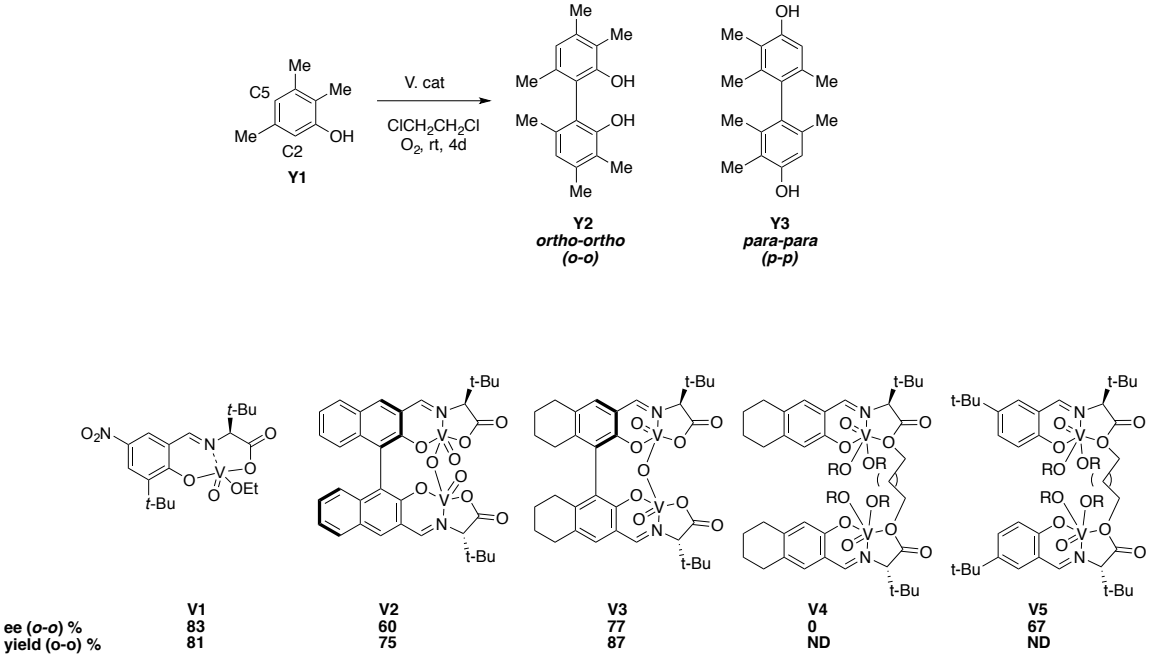

In the past, the Kozlowski group used copper-diaza-*cis*-decalin catalysts for asymmetric oxidative coupling of naphthols.[14] However, copper has proved ineffective in enantioselective phenol couplings. With electron-rich phenols, no enantioselectivity was seen although the copper catalysts were high reactive. Addition of a coordinating ester adjacent to the phenol, as was successful with the naphthols, led to low reactivity due to the electron-withdrawing character of the ester.[14]

As a result the Kozlowski group surveyed other catalysts for phenol coupling. The primary issue is that phenols are much less reactive than 2-naphthols, because of an intrinsically lower oxidation potential of phenols which do not have the same means of electron delocalization as is possible with 2-naphthols. Encouragingly, literature reports indicated that $VO(acac)_2$ is effective as a racemic catalyst for phenol couplings in 62-66% yield after 48-120 h.[15] In addition, chiral vanadium catalysts have been reported to form BINOL from 2-naphthol with a 90% ee.[16]

Using this starting point, the Kozlowski group developed a promising asymmetric couplings of phenols.[17] The optimal vanadium catalyst **V1** was determined after testing various other ligands as shown in **Figure 6**. Catalyst **V2** provided an initial result of 37% ee in Lee's phenol couplings, followed by an improved 60% ee after additive optimization. The ligands (**V3, V4, V5**) were also explored. **V3** resulted in a 77% ee, but modification to catalyst **V4** provided a drop in selectivity resulting from the loss of a sterically hindering group. **V5** provided a significant improvement in selectivity.

The dimeric scaffold was abandoned because the monomer was more easily tunable, while also maintaining a competitive enantiomeric excess. Interestingly, such vanadium Schiff base monomers are only moderately effective in naphthol coupling.[15] Catalyst **V1** was discovered by testing various R groups on the aromatic ring. Electron withdrawing groups destabilize the vanadium (V) oxidation state that forms during the redox reaction thereby forming a more reactive catalyst.

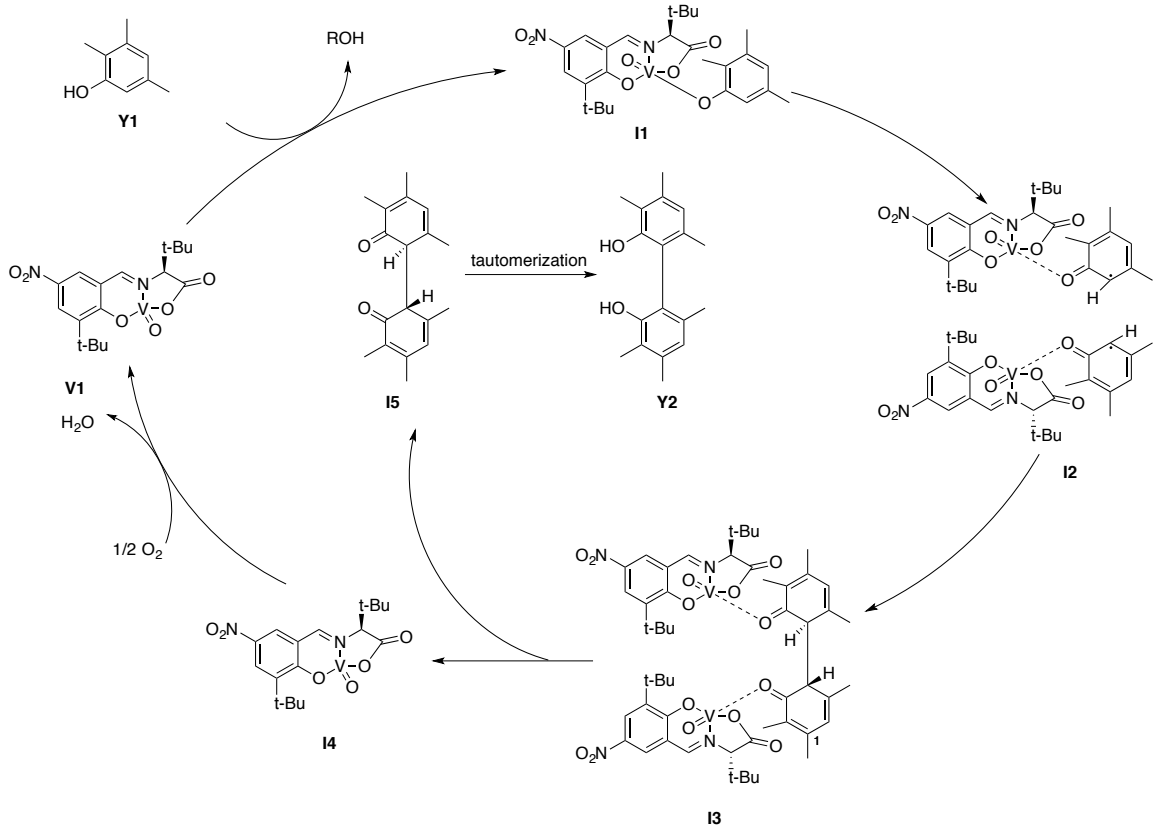
**Figure 6.** Asymmetric Phenol Coupling




Oxidative couplings can proceed via a range of different mechanisms, including radical-radical, radical anion, and cationic variants. There is evidence that vanadium catalyzed oxidative couplings of phenol substrates can proceed via a radical-radical pathway.[18] In addition, Gong and Sasai undertook extensive studies of a vanadium catalyzed asymmetric naphthol couplings and compiled compelling evidence of a metal bound radical-radical coupling.[18,19]

On the basis of this prior work, a catalytic cycle is proposed where phenol coordinates to the vanadium (**I1**) and becomes oxidized to keto radical equivalent **I2**. This coordination is followed by the radicals coupling to form **I3**. Afterwards, the vanadium catalyst is released and re-oxidized using oxygen gas, while the coupled product tautomerizes in order to form the final product (**Figure 7**). According to this mechanism, we proposed that carbazoles would be more reactive in an oxidative coupling reaction as they are more electron rich and, hence, more oxidizable.[17]

**Figure 7.** Proposed Mechanism of Oxidative Couplings




The goal of this research is to develop a process to form biscarbazoles with high yields, above 80%, and enantioselectivity, above 80%. The work in this thesis uses a very different approach to this type of structure where the axial chiral bond is established in an intermolecular oxidative asymmetric coupling rather than by a resolution after bond formation (see **Scheme 1**). Specifically, the *ortho-ortho*, C1-C1, coupling of the 3,9-dimethyl-9*H*-carbazol-2-ol (**Figure 8)** will be attempted.

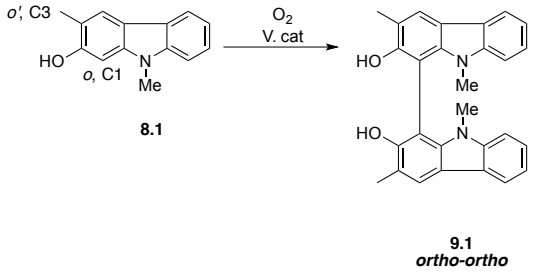
Chiral vanadium catalysts have been previously used by the Kozlowski group in the dimerization of phenols and indoles, and this work centers on expanding that reactivity to carbazoles. The monomeric units of the biscarbazole natural products contain a phenol group and an amine. Because of these two electron-donating groups, oxidation of the corresponding monomers is expected to be more facile than with phenol allowing generation of intermediates that can undergo dimerization.[20]

The vanadium catalyst **V1** works best with phenols having substitution at the C2 and C5 positions. The C5 substitution is necessary to create a chiral axis. The C2 methyl groups were found to be necessary to achieve high selectivity with the corresponding C2 hydro compound give very low selectivity. This same methyl substitution will be employed with 3,9-dimethyl-9*H*-carbazol-2-ol, **8.1**, the simplest and initial carbazole substrate used in the series. Other alterations to each individual step in carbazole formation will be indicated as structure **x.1-4**.

Also vanadium catalysts with similar ligands will be employed to couple the carbazoles. It is unclear if the carbazole nitrogen in either its free *N*-H or protected *N*-Me forms would allow similar selectivities to those seen with the phenols from **Figure 6**.

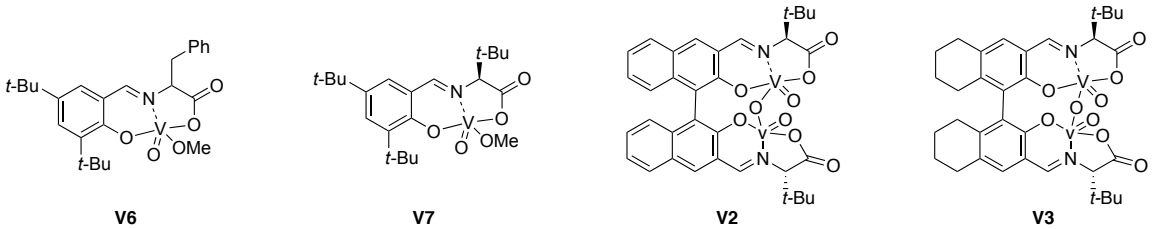
With the biscarbazole compounds, a high enantiomeric excess, above 90% ee (95:5 enantiomeric ratio) is the desired result.

**Figure 8.** Proposed Work




If the primary vanadium catalyst **V1**, does not provide adequate enantiomeric excess and yields, these other catalysts, as shown in **Figure 9**, will be used in hopes of improving the reactivity. These derivatives of **V1** are the next logical screening targets based on the fact that they provided some selectivity in the coupling of phenols. Once the biscarbazole is formed, with a yield above 80% and an enantiomeric excess above 80%, other substrates with the basic carbazole structure will be explored (**18.1**-**18.5**). The substituents will test how electronics affect the reactivity of carbazole with the vanadium catalysts. These substituents will include electron donating as well as electron withdrawing groups such as methyl and fluoro.

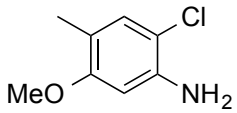
**Figure 9**. Supplementary Catalysts




**Materials and Method**

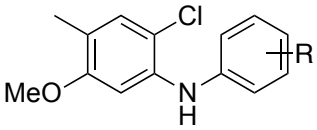
**General Consideration:** Unless otherwise noted, all non-aqueous reactions were carried out under an atmosphere of dry Argon in dried glassware. When necessary, solvents and reagents were dried prior to use. THF was distilled from sodium benzophenone ketyl. Toluene, dioxane, and methylene chloride were distilled from $CaH_2$. Analytical thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica0gel 254-F plages. Visualization was accomplished with UV light. Chromatography was performed using a forced flow of the indicated solvent system on EM Reagents Silica Gel 60 (230-400 mesh). $^1$H NMR Spectra were recorded on a Brüker AM -500 (500 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane (0 ppm) or from the solvent resonance ($CDCl_3$) 7.26 ppm, acetone-$d_6$ 2.05 ppm). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br= broad, m = multiplet) , coupling constants**.** IR spectra were taken on a Jaso FT/IR-480 Plus spectrometer or an Applied Systems React IR1000. Mass spectra were obtained on a

Waters LC-TOF mass spectrometer (model LCT-XE Premier) with ionization mode of either CI or ES. An analytical Chiralpak IA column (4.6 mm x 250 mm, 5 $\mu$ m) from Daicel was used with an Agilent 1100 series. Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) with UV detection at 254 nm. Optical rotations were taken on a Jasco polarimeter with a sodium lamp.



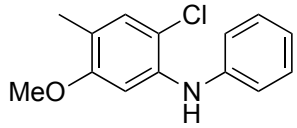

**2-Chloro-5-methoxy-4-methylaniline**

4-Amino-5-chloro-2-methoxybenzoic acid (3.05 g, 15.1 mmol) was suspended in chlorobenzene (30 mL) and cooled to 0 °C. Neat $BH_3 \bullet SMe_2$ (4.3 mL, 45.3 mmol) was added with vigorous stirring. When effervescence ceased, the mixture was heated for 3 h at 80 °C and then for 18 h at 130 °C. The reaction was quenched by addition of aqueous $Na_2CO_3$ (aq) (1 M, 50 mL). The mixture was extracted with $CH_2Cl_2$ (3 × 50 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give a yellow solid. The product was purified by column chromatography ($SiO_2$) to yield a white powder: (2.10 g 81%): $^1$H NMR (360 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.40 (s, 1H), 5.05 (s, 2H), 3.68 (s, 3H), 1.96 (s, 3H). Spectra are in accord with those previously reported.[21]

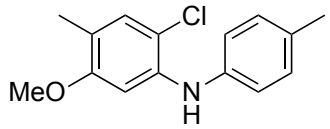



**General Procedure A**

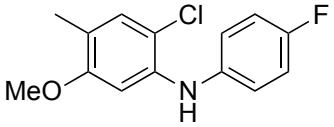
A mixture of NaO*t*-Bu (0.24 g, 2.5 mmol), $Pd(OAc)_2$ (0.004 g, 0.020 mmol), and HP(*t*-Bu)$_3$BF$_4$ (0.008 g, 0.025 mmol) was suspended in toluene (0.83 M). 2-Chloro-5-methoxy-4-methylaniline (0.086 g, 0.5 mmol) and an aryl bromide (0.51 mmol) were added, and the mixture was heated at reflux for 18 h. The mixture was quenched by addition of HCl (aq) (2 M). The mixture was extracted with dichloromethane, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The product mixture was subjected to column chromatography ($SiO_2$)



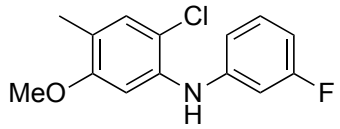

Following **General Procedure A**, Brown oil, 770 mg, 76%, $R_f$ = 0.6 (EtOAc/Hexanes = 1/4) $^1$H NMR (500 MHz, $d_6$-acetone) δ (ppm) 7.30 (t, J = 6.3, 2H), 7.13-7.10 (m, 3H), 6.99 (s, 1H), 6.8 (s, 1H), 5.94 (s, 1H), 3.71 (s, 3H), 2.13 (s, 3H); $^{13}$C NMR (125 MHz, $d_6$-acetone) δ 157.1, 143.3, 138.8, 130.7, 129.2, 120.9, 120.0, 118.2, 113.8, 101.3, 55.0, 14.5 IR (KBr) 3420, 1512, 1200, 605 cm$^{-1}$; HRMS calcd for $C_{14}H_{14}ClNO$ $[M+H]^+$ 248.0842, found 248.0842



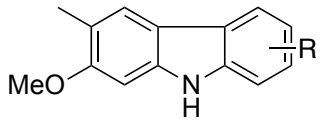

Following **General Procedure A**, Yellow oil, 440 mg, 22%, $R_f$ = 0.75 (EtOAc/Hexanes = 1/4) $^1$H NMR (500 MHz, $d_6$-acetone) 7.12 (d, J = 8.0, 2H), 7.08 (s, 1H), 7.04 (d, J = 8.5, 2H), 6.72 (s, 1H), 6.72 (s, 1H), 5.88 (br s, 1H), 3.96 (s, 3H), 2.32 (s, 3H), 2.12 (s, 3H); $^{13}$C NMR (500 MHz, $d_6$-acetone) 2 rotamers, IR (KBr) 3420, 2921, 1589, 606 cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{15}H_{17}ClNO$ $[M+H]^+$ 262.0999, found 262.1003.




Following **General Procedure A**, Brown oil, 1550 mg, 99%, $R_f$ = 0.55 (EtOAc/Hexanes = 1/4); $^1$H NMR (500 MHz, $d_6$-acetone) 7.20-7.17 (m, 2H), 7.12 (s, 1H), 7.07-7.04 (m, 2H), 6.83 (s, 1H), 6.78 (s, 1H), 3.72 (s, 3H), 2.09 (s, 3H); $^{13}$C NMR (500 MHz, $d_6$-acetone) 157.2 (d, J = 219), 156.9, 139.0, 130.7, 121.0 (d, J = 8.0), 119.6, 115.7 (d, J = 22), 112.2, 98.8, 97.7, 55.5, 15.2; IR (KBr) 3420, 1609, 1200, 602, cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{14}H_{14}ClFNO$ $[M+H]^+$ 266.0748, found 266.0743.

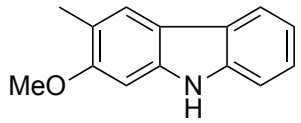



Following **General Procedure A**, Brown oil, 768 mg, 50%, $R_f$ = 0.45 (EtOAc/Hexanes = 1/4); $^1$H NMR (500 MHz, $d_6$-acetone) 7.24 (dd, J = 7.0, 15.0, 1H), 7.18 (s, 1H), 7.11 (s, 1H), 6.95 (s, 1H), 6.90 (dd, J = 2.0, 8.0, 1H), 6.79 (td, J = 2.5, 12.0), 6.58 (dt, J = 2.5, 8.0), 3.79 (s, 3H), 2.13 (s, 3H); $^{13}$C NMR (500 MHz, $d_6$-acetone) 163.8 (d, J = 243), 156.9, 144.6 (d, J = 10.0), 137.1, 131.0, 130.6 (d, J = 10.0), 121.3, 114.2, 113.6 (d, J = 2.5), 108.0 (d, J = 21.3), 104.7 (d, J = 25.0), 101.3, 55.7, 15.4 IR (KBr) 1604, 1582, 1518, 834, 815, 776, 767, 678, 615 cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{14}H_{14}NOFCl$ $[M+H]^+$ 266.0748, found 266.0740.

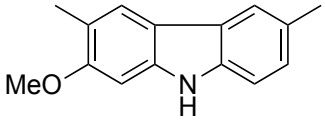



**General Procedure B**

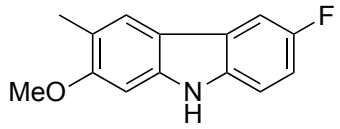
A mixture of NaO*t*-Bu (0.24, 2.5 mmol), $Pd(OAc)_2$ (0.004, 0.02 mmol), and HP(*t*-Bu)$_3BF_4$ (0.008, 0.025 mmol) was suspended in dioxane (0.328 mL, 1.25 M). The chlorobiphenylaniline (0.41 mmol) was added as a solution in dioxane (0.164 mL, 2.5 M). The mixture was heated at reflux for 18 h. After cooling, the mixture was quenched by addition of HCl (aq) (2 M, 3 mL). The organic phase was extracted with $CH_2Cl_2$ (2 × 20 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The product mixture was subjected to column chromatography ($SiO_2$)



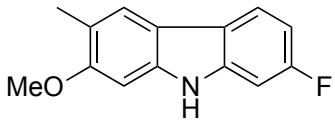

Prepared following **General Procedure B**. Spectral data were in agreement with those reported.[22]



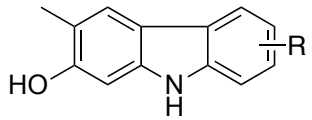

Following **General Procedure B**, Brown solid, 1.39 g, 83%, $R_f$ = 0.3 (EtOAc/Hexanes = 1/4); $^1$H NMR (500 MHz, $d_6$-acetone) 7.79 (s, 1H), 7.74 (s, 1H), 7.25 (d, J = 8.0, 1H), 7.12 (d, J = 7.0), 6.84 (s, 1H), 3.91 (s, 3H), 2.56 (s, 3H), 2.35 (s, 3H); $C^{13}$ NMR (500 MHz, $d_6$-acetone) 157.3, 140.3, 138.2, 127.5, 125.0, 123.5, 121.0, 118.9, 117.9, 115.8, 110.1, 92.6, 54.8, 20.6, 15.0; IR (KBr) 3390, 2920, 1634, 1615, 818, 746 cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{15}H_{16}NO$ $[M+H]^+$ 226.1232, found 226.1229.




Following **General Procedure B**, Yellow solid, 240 mg, 18%, $R_f$ = 0.2 (EtOAc/Hexanes = 1/4); $^1$H NMR (500 MHz, $d_6$-acetone) 10.08 (s, 1H), 7.81 (s, 1H), 7.69 (dd, J = 2.5, 9.3, 1H), 7.40 (dd, J = 4.4, 8.8, 1H), 7.04 (td, J = 2.6, 9.35, 1H), 7.01 (s, 1H), 3.89 (s, 3H), 2.30 (3H); $^{13}$C NMR (500 MHz, $d_6$-acetone) 157.9, 157.3 (d, J = 231), 141.2, 136.3, 123.9 (d, J = 9.7), 121.4, 118.5, 115.7 (d, J = 3.8), 111.1, 111.0 (d, J = 14.6), 104.4 (d, J = 23.8), 92.6, 54.9, 16.0; IR (KBr) 1486, 847, 822, 803, 783, cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{14}H_{13}NOF$ $[M+H]^+$ 230.0981, Found 230.0986.

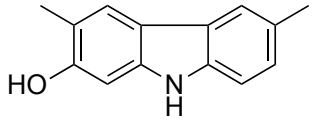



Following **General Procedure B**, Yellow solid, 60 mg 5%, $R_f$ = 0.5 (EtOAc/Hexanes = 1/4); $^1$H NMR (500 MHz, $d_6$-acetone) 10.18 (s, 1H), 7.92 (dd, J = 5.0, 5.0, 1H), 7.78 (s, 1H), 7.15 (dd, J = 2.4, 10.0, 1H), 7.03 (s, 1H), 6.90-6.86 (m, 1H), 3.89 (s, 3H), 2.30 (s, 3H); $^{13}$C NMR (500 MHz, $d_6$-acetone) 161.0 (d, J = 235), 157.2, 140.4 (d, J = 12.7), 140.4, 120.9, 120.0, 119.8 (d, J = 10.6), 118.6, 115.5, 106.2 (d, J = 24.3), 97.2 (d, J = 26.3), 92.8, 54.9, 15.9; IR (KBr) 3396, 2921, 1611, 841, 808, 742 cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{14}H_{11}NOF$ $[M-H]^-$ 228.0825, Found 228.0822.

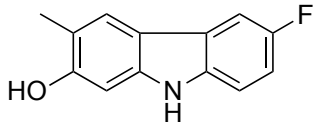



**General Procedure C**

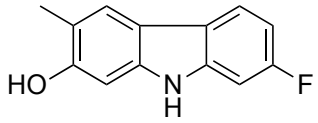
The methoxycarbazole (4.92 mmol) was dissolved in dichloromethane (49.2 mL, 0.1 M). After cooling to –78 ºC, a solution of boron tribromide (1 M in dichloromethane, 7.9 mmol) was added over a period of 11 min and the solution was allowed to warm to room temperature. The reaction mixture was stirred for 15.5 h at room temperature. The mixture was subsequently quenched with methanol under cooling, transferred to a separation funnel with ethyl acetate, and washed several times with water and brine. After extraction of the aqueous layer with ethyl acetate, the combined organic layers were dried over sodium sulfate, the solvent was evaporated, and the mixture was purified by chromatography ($SiO_2$) to provide the product.




Following **General Procedure C**, Brown solid, 510 mg, 94%; $R_f$ = 0.05 (EtOAc/Hexanes = 1/4); $^1$H NMR (500 MHz, $d_6$-acetone) 9.77 (s, 1H), 8.18 (s, 1H), 7.73 (s, 1H), 7.71 (d, J = 0.5, 1H), 7.24 (d, J = 8.0, 1H), 7.05 (dd, J = 1.2, 8.2, 1H), 6.92 (s, 1H), 2.44 (s, 3H), 2.33 (s, 3H); $^{13}$C NMR (500 MHz, $d_6$-acetone) 154.7, 140.5, 138.4, 127.4, 125.0, 123.9, 121.3, 118.9, 116.6, 116.1, 110.1, 96.2, 20.7, 15.9; IR (KBr) 3398, 1603, 826, 744, 719, 640 cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{14}H_{14}NO$ $[M+H]^+$ 212.1075, Found 212.1080.

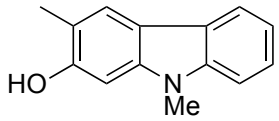



Following **General Procedure C**, Brown solid, 166 mg 90%; $R_f$ = 0.1 (EtOAc/Hexanes = 1/4); $^1$H NMR (500 MHz, $d_6$-acetone) 9.94 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.66 (dd, J = 2.6, 9.5, 1H), 7.35 (dd, J = 4.5, 8.8, 1H), 7.03-6.99 (dt, J = 2.6, 9.0, 1H), 6.97 (s, 1H), 2.35 (s, 3H); $^{13}$C NMR (500 MHz, $d_6$-acetone) 157.0 (d, J = 231), 155.3, 141.3, 136.3, 124.2 (d, J = 10.0), 121.6, 117.2, 115.8 (d, J = 3.8), 110.9, 110.7 (d, J = 14.8), 104.4 (d, J = 23.8), 96.2, 15.8; IR (KBr) 3406, 1485, 1406, 1257, 1146, 1013, 600 cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{13}H_9NOF$ $[M-H]^+$ 214.0668, Found 214.0672.

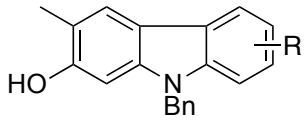



Following **General Procedure C**, Brown solid, 69 mg, 99%; $R_f$ = 0.1 (EtOAc/Hexanes = 1/4); $^1$H NMR (500 MHz, $d_6$-acetone) 10.06 (s, 1H), 8.26, (s, 1H), 7.89 (dd, J = 5.5, 8.5, 1H), 7.74 (s, 1H), 7.11 (dd, J = 2.5, 10.5), 6.96 (s, 1H), 6.86 (dt, J = 2.5, J = 8.5, 1H) 2.33

(s, 3H); $^{13}$C NMR (500 MHz, $d_6$-acetone) 161.0 (d, J = 235), 154.6, 140.6 (d, J = 14.8), 140.6, 121.2, 120.3, 119.7 (d, J = 10.5), 117.4, 115.7, 106.2 (d, J = 24.1), 97.0 (d, J = 26.3), 96.5, 15.9; IR (KBr) 3406, 1486, 1293, 834, 820, 810, 781, 600, cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{13}H_9NOF$ $[M-H]^+$ 214.0668, Found: 214.0669.

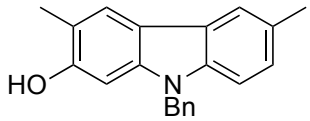



A solution of 2-hydroxycarbazole (0.092 g, 0.47 mmol) and DMF (0.07 mL) in dry THF (1 mL) was added drop-wise to NaH (0.028 g, 1.17 mmol) under a nitrogen atmosphere with stirring at room temperature. After 10 min, a 1 M solution of MeI (0.067 mL, 0.47 mmol) was added and stirring was continued for 2 h. The resulting mixture was cooled to 0 °C and quenched with water (0.4 mL). After removing the solvent under vacuum, the product was washed with acidic aqueous solution and purified by column chromatography ($SiO_2$) to provide the product. Brown solid, 10 mg 23%; $R_f$ = 0.4 (EtOAc/Hexanes = 1/4); $^1$H NMR (500 MHz, $d_6$-acetone) 8.29 (s, 1H), 7.94 (d, J = 7.5, 1H), 7.80 (s, 1H) 7.39 (d, J = 8.0, 1H), 7.30 (dt, J = 1.0, 7.5, 1H), 7.10 (dt, J = 0.5, 8.0, 1H), 6.89 (s, 1H), 3.76 (s, 3H), 2.35 (s, 3H); $^{13}$C NMR (500 MHz, $d_6$-acetone) 157.3, 139.8, 123.6, 123.2, 120.9, 118.8, 118.4, 118.0, 115.8, 110.3, 110.2, 92.4, 54.7,15.7; IR (KBr) 2922, 2853, 1634, 1604, 815, 740, 719, 621 cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{14}H_{12}NO$ $[M-H]^-$ 212.1075, Found 212.1083.

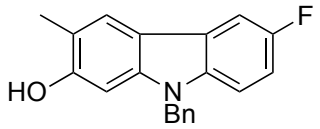



**General Procedure D**

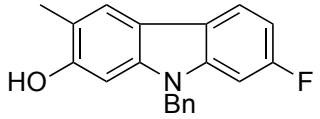
A solution of 2-hydroxycarbazole (0.092 g, 0.47 mmol) and DMF (0.07 mL) in dry THF (1 mL) was added drop-wise to NaH (0.028 g, 1.17 mmol) under a nitrogen atmosphere with stirring at room temperature. After 10 min, a 1 M solution of BnCl (0.067 mL, 0.47 mmol) was added and stirring was continued for 2 h. The resulting mixture was cooled to 0 °C and quenched with water (0.4 mL). After removing the solvent under vacuum, the product was washed with acidic aqueous solution and purified by column chromatography ($SiO_2$) to provide the product.



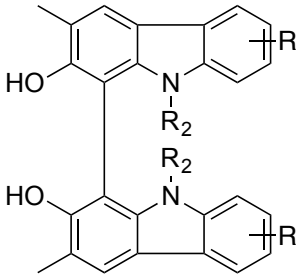

Following **General Procedure D**, Yellow solid, 81 mg, 53%; $R_f$ = 0.4 (EtOAc/Hexanes = 1/4); $^1$H NMR (500 MHz, $d_6$-acetone) 9.82 (s, 1H), 7.73 (s, 1H), 7.70 (s, 1H), 7.28-7.26 (m, 2H), 7.23 (d, J = 8.0, 1H), 7.19 (t, J = 7.5, 2H), 7.10 (t, J = 7.8, 1H), 7.03 (dd, J = 1.0, 8.0, 1H), 4.34 (s, 2H), 2.43 (s, 3H), 2.42 (s, 3H); $^{13}$C NMR (500 MHz, $d_6$-acetone) 151.7, 140.7, 139.8, 138.5, 128.3, 128.0, 127.4, 125.6, 125.0, 124.1, 119.3, 118.9, 116.8, 116.3, 110.1, 109.0, 30.5, 20.6, 16.5. IR (KBr) 3421, 2919, 2852, 1494, 863, 796, 735, 697 cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{21}H_{20}NO$ $[M+H]^+$ 302.1545, Found: 302.1545.




Following **General Procedure D**, Yellow solid, 193 mg, 81%; $R_f$ = 0.35 (EtOAc/Hexanes = 1/4); $^1$H NMR (500 MHz, $d_6$-acetone) 8.40 (s, 1H), 7.85 (s, 1H), 7.73 (dd, J = 5.0, 9.0, 1H), 7.41 (dd, J = 5.0, 10.0, 1H), 7.28-7.19 (m, 3H), 7.15-7.13 (m, 2H), 7.05 (td, J = 1.0, 10.0, 1H), 6.89 (s, 1H), 5.50 (s, 2H), 2.34 (s, 3H); $^{13}$C NMR (500 MHz, $d_6$-acetone) 157.4 (d, J = 231), 155.6, 141.7, 137.9, 137.0, 128.6, 127.2, 126.5, 123.9, (d, J = 10.0), 122.0, 117.5, 115.3, 110.9 (d, J = 25.0), 109.3 (d, J = 8.7), 104.6 (d, J = 23.8), 94.9, 46.1, 15.7; IR (KBr) 1633, 862, 828, 791, 729, 696, 626 cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{20}H_{17}FNO$ $[M+H]^+$ 306.1494 Found: 306.1497

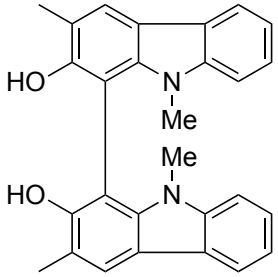



Following **General Procedure D**, Yellow solid, 57 mg, 83%; $R_f$ = 0.17 (EtOAc/Hexanes = 1/4); $^1$H NMR (500 MHz, $d_6$-acetone) 8.38 (s, 1H), 7.84 (s, 1H), 7.28-7.19 (m, 5H), 7.14 (d, J = 7.0, 2H), 6.91 (s, 1H), 6.84 (ddd, J = 1.5, J = 7.0, J = 8.5, 1H), 5.50 (s, 2H), 2.33 (s, 3H); $^{13}$C NMR (500 MHz, $d_6$-acetone) 157.6, 155.0, 143.0, 140.3, 137.5, 128.5, 127.2, 126.4, 124.5 (J = 8.25), 123.7 (J = 3.0), 117.9, 112.8, 111.0, (J = 21.0), 104.9, 104.4 (J = 19.3), 94.3, 46.2, 15.5; IR (KBr) 1470, 883, 776, 741, 715, 702, 693 cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{20}H_{15}FNO$ $[M-H]^-$ 304.0876 Found: 304.0875

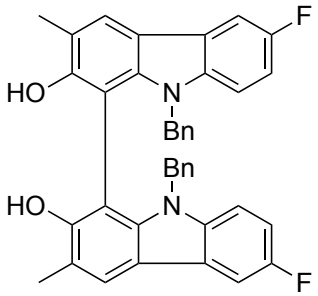



**General Procedure for Asymmetric Oxidative Hydroxycarbazole Coupling (E)**
To a 5 mL microwave vial was added hydroxycarbazole (0.10 mmol, 2.0 mg) and catalyst **11a** (0.020 mmol, 4.0 mg). The vial was sealed with a septum and solvent (0.20 mL) was added. Afterwards, AcOH (6.25 equiv, 20 μL). Oxygen was added *via* active purge. The septum was replaced with a crimping cap and the vessel was sealed and stirred for the indicated time at the indicated temperature. The reaction mixture was then directly chromatographed on silica gel using ethyl acetate/hexane to elute the product. The product was prepared for analysis by dissolving in pure methanol to provide a clear solution. Afterwards the product was filtered through a glass frit to filter off solids.

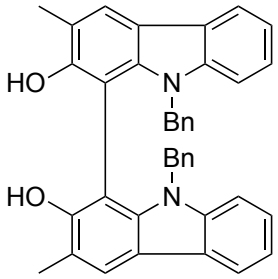
Analysis was done by Chiralpak IA 1.0 mL/min 90:10 hexanes:i-PrOH or Chiralpak IA 1.0 mL/min 95:5 hexanes:i-PrOH.



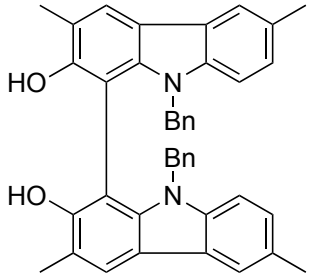

Following **General Procedure E**, Yellow solid, 4.1 mg, 83%; $R_f$ = 0.53 (EtOAc/Hexanes = 1/4); $^1$H NMR (500 MHz, $d_6$-acetone) 8.03 (dt, J = 0.8, 7.8, 2H), 8.00 (q, J = 1.0, 2H), 7.31-7.30 (m, 4H), 7.25 (s, 1H), 7.16 (ddd, J = 2.9, 5.2, 7.9, 2H), 3.45 (s, 6H), 2.45 (s, 6H); $^{13}$C NMR (500 MHz, $d_6$-acetone) 153.9, 141.7, 139.8, 123.9, 122.9, 122.1, 118.8, 118.6, 117.0, 116.3, 108.4, 101.7, 29.3, 16.3; IR (KBr) 3509, 2924, 2854, 1626, 1603, 882, 768, 737 cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{28}H_{25}N_2O_2$ $[M+H]^+$ 421.1916, found: 421.1928. $[\alpha]_D^{22}$ –31.80; CSP HPLC (Chiralpak AD, 1.0 mL/min, 90:10 hexanes:i-PrOH): $t_R$(*1*) = 16.6 min, $t_R$(*2*) = 20.9 min.



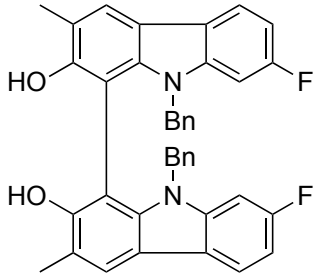

Following **General Procedure E**, Yellow solid, 4.8 mg 95%; $R_f$ = 0.47 (EtOAc/Hexanes = 1/4); $^1$H NMR (500 MHz, $d_6$-acetone) 7.94 (s, 2H), 7.78 (dd, J = 2.5, 9.0, 2H), 7.06 - 6.98 (m, 6H), 6.85-6.84 (m, 6H), 6.45-6.44 (m, 4H), 4.82 (d, J = 17.3, 2H), 4.69 (d, J = 17.3), 2.20 (s, 6H) $^{13}$C NMR (500 MHz, $d_6$-acetone) 157.6 (d, J = 231), 154.4, 140.0, 138.0, 137.9, 127.6, 126.2, 125.3, 123.7 (d, J = 10.0), 122.5, 117.8, 116.5, 111.1 (d, J = 2.5), 109.8 (d, J = 10.0), 104.2 (d, J = 25.0), 100.9, 46.8, 16.2; IR (KBr) 3515, 2923, 1627, 856, 796, 781, 703 cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{40}H_{31}F_2N_2O_2$ $[M+H]^+$ 609.2354, found 609.2368; $[\alpha]_D^{22}$ –24.167, CSP HPLC (Chiralpak IA, 1.0 mL/min, 90:10 hexanes:i-PrOH): tR(*1*) = 8.9 min, tR(*2*) = 9.7 min.



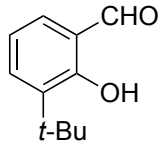

Following **General Procedure E**, Yellow solid, 17.2 mg, 86%; $R_f$ = 0.60 (EtOAc/Hexanes = 1/4) $^1$H NMR (500 MHz, $d_6$-acetone) 8.07, (d, J = 8.0, 2H), 7.96 (s, 2H), 7.33 (t, J = 7.5, 2H), 7.27 (t, J = 7.5, 2H), 7.11 (d, J = 8.0, 2H), 6.70 (t, J = 7.0, 2H), 6.83 (t, J = 7.0, 4H), 6.24 (d, J = 7.0, 4H), 4.73 (s, 2H), 4.71 (d, J = 17.5, 2H), 4.62 (d, J = 17.5, 2H), 2.17 (s, 6H); $^{13}$C NMR (125 MHz, $d_6$-acetone) 153.6, 141.7, 139.0, 138.0, 127.5, 126.0, 125.4, 123.9, 123.1, 122.0, 119.0, 118.6, 117.5, 116.8, 109.0, 101.0, 46.5, 16.2; IR (KBr) 3513, 2923, 1603, 736, 706 cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{40}H_{33}N_2O_2$ $[M-H]^+$ $C_{40}H_{32}N_2O_2$ 571.2386, found 571.2380 $[\alpha]_D^{22}$ –36.480; CSP HPLC (Chiralpak IA, 1.0 mL/min, 90:10 hexanes:i-PrOH): tR(*1*) = 7.8 min, tR(*2*) = 11.2 min.



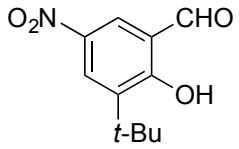

Following **General Procedure E**, Yellow solid, 16.9 mg, 83%; $R_f$ = 0.6 (EtOAc/Hexanes = 1/4) $^1$H NMR (500 MHz, $d_6$-acetone) 7.89 (s, 2H), 7.84 (s, 2H), 7.06 (dd, J = 1.8, 7.5, 2H), 6.97 (d, J = 8.0, 2H), 6.86-6.82 (m, 6H), 6.71 (s, 2H), 6.45 (s, 2H), 6.46-6.42 (m, 2H), 4.77 (d, J = 17.1, 2H), 4.58 (d, J = 17.1, 2H), 2.49 (s, 6H), 2.19 (s, 6H); $^{13}$C NMR (125 MHz, $d_6$-acetone) 140.0, 139.2, 138.3, 128.1, 127.3, 126.1, 125.4, 125.2, 123.3, 121.9, 118.6, 117.2, 116.7, 108.9, 108.8, 100.9, 46.6, 20.5, 16.2. IR (KBr) 2920, 1608, 793, 733, 701 cm$^{-1}$; HRMS(ES-TOF) calcd for $C_{42}H_{37}N_2O_2$ $[M+H]^+$ 601.2855, found 601.2849 $[\alpha]_D^{22}$ –146.593; CSP HPLC (Chiralpak IA, 1.0 mL/min, 90:10 hexanes:i-PrOH): tR(*1*) = 9.5 min, tR(*2*) = 14.1 min.



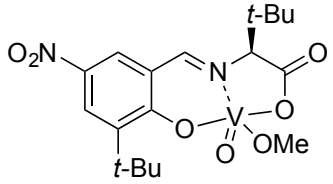

Following **General Procedure E**, Yellow solid, mg, 17.8 mg, 93%; $R_f$ = 0.6 (EtOAc/Hexanes = 1/4); $^1$H NMR (500 MHz, $d_6$-acetone) 7.95 (s, 2H), 7.21 (td, J = 5.5, 8.1, 2H), 7.06 (s, 2H), 6.91 (d, J = 8.1, 2H), 6.89 (d, J = 8.1, 2H), 6.84-6.82 (m, 6H), 6.45-6.43 (m, 4H), 4.85 (d, J = 17.9, 2H), 4.60 (d, J = 17.4, 2H), 2.21 (s, 6H); $^{13}$C NMR (125 MHz, $d_6$-acetone) 157.7 (J = 243), 153.9 144.1 (J = 10.6), 138.7.137.5, 127.5, 126.1, 125.2, 124.6 (J = 20.1), 124.4 (J = 20.1), 118.4, 114.1, 110.8, 105.3, 104.7 (J = 18.7), 101.0, 47.0, 16.2; IR (KBr) 3519, 1601, 965, 709 cm$^{-1}$; HRMS (ES-TOF) calcd for $C_{40}H_{29}F_2N_2O_2$ [M-H]$^-$ 607.2197, found 607.2191, [ $\alpha$ ]$_D^{22}$ –1.9753; CSP HPLC (Chiralpak IA, 1.0 mL/min, 95:5 hexanes:i-PrOH): tR(*1*) = 5.1 min, tR(*2*) = 5.6 min.




Dry formaldehyde (0.7 g, 23.3 mmol) was added in portions to a mixture of 4-*tert*-butylphenol (1.0 g, 6.66 mmol), triethylamine (2.6 mL, 18.8 mmol) and anhydrous $MgCl_2$ (2.0 g, 20.6 mmol) in 50 mL of THF. The mixture was refluxed for 8 h, cooled to room temperature, acidified with 3N HCl (70 mL), and extracted with diethyl ether (3 x 30 mL). The ether layer was washed with water (50 mL), and brine (50 mL), and dried using $MgSO_4$. Removal of solvent yielded a crude product and it was purified by column chromatography to yield a 3-(*tert-butyl*)-2-hydroxy-benzaldehyde as yellow oil (710 mg, 61% yield). Spectral data matched those reported in the literature.




In a 100 mL round-bottomed flask was placed 3-(*tert*-butyl)-2-hydroxybenzaldehyde (710 mg, 4.0 mmol) in HOAc (12 mL). Nitric acid (4.0 mL, 96 mmol) was added dropwise at 0 ºC and stirred for 1 hour at ambient temperature. The resulting mixture was poured into iced water (100 mL) with vigorous stirring. The orange precipitate formed was filtered through a sintered glass, then washed with water (10 mL). The crude product was recrystallized from ethanol to give 360 mg (65% yield) Spectral data matched those reported in the literature.

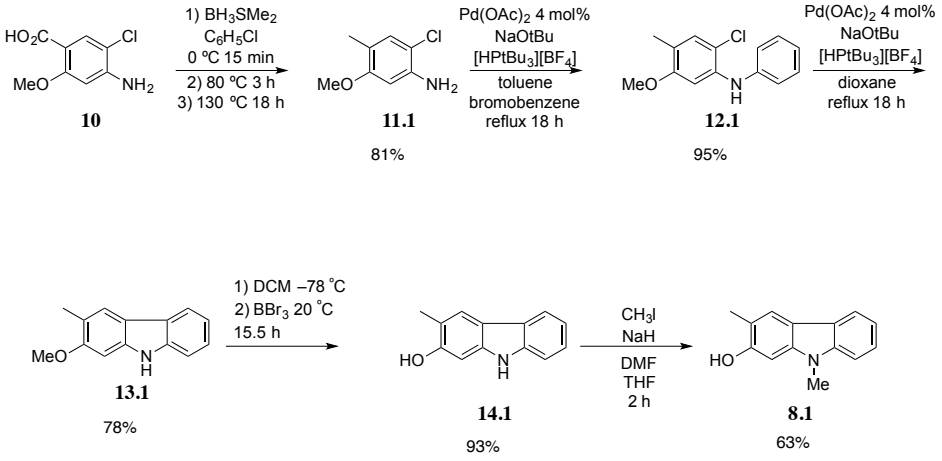



All glassware was flame dried. A mixture of L-*tert*-leucine (0.34) and 3-*tert*-butyl-5-nitro-2-hydroxybenzaldehyde (0.34 mmol) in MeOH:$CH_2Cl_2$ (2 mL, 1:1) was heated to reflux and monitored by TLC. The reaction mixture was cooled to room temperature and $VO(OEt)_3$ (0.34 mmol) was added. After 3 h under argon atmosphere, solvent was removed under reduced pressure to afford the catalyst.

**Results and Discussion**

The initial substrate is **8.1**, 2-hydroxy-3,9-dimethyl-9*H*-carbazole (**Scheme 2**) was prepared following literature reports as outlined in **Scheme 1**. Starting with 4-amino-5-chloro-2-methoxybenzoic acid **1**, reduction provided the methyl group needed in **2**.[21] The reduction is necessary to form the methyl group that will be block off the potential formation of *ortho-ortho'* biscarbazole during the oxidative coupling. Subsequent Buchwald Hartwig amination and concerted metallation deprotonation formed the carbazole moiety of **12**.[21] Demethylation with boron tribromide is used to form the known compound 3-hydroxycarbazole, **13**.[23] Based on past research from the Kozlowski group, it is necessary to have a hydroxyl group in order for the catalyst to bind to the substrate and to oxidize readily.[1] A methoxy group will not allow for a mild, selective coupling to occur. Finally, previous research revealed that the regioselective coupling would not occur in the presence of the free pyrrole,[1] which could also oxidize at the nitrogen. Thus, methylation of the pyrrole nitrogen is necessary to form the starting material for the project, **8.1**. Specifically, compound **14.1** was doubly deprotonated with sodium hydride, and the more nucleophilic functional group, nitrogen, was selectively methylated by adding one equivalent of methyl iodide.[24] Optimization of these routes was not performed as the primary goal was to probe the asymmetric oxidative coupling.

**Scheme 2.** Synthesis of Primary Substrate for Reaction Screening

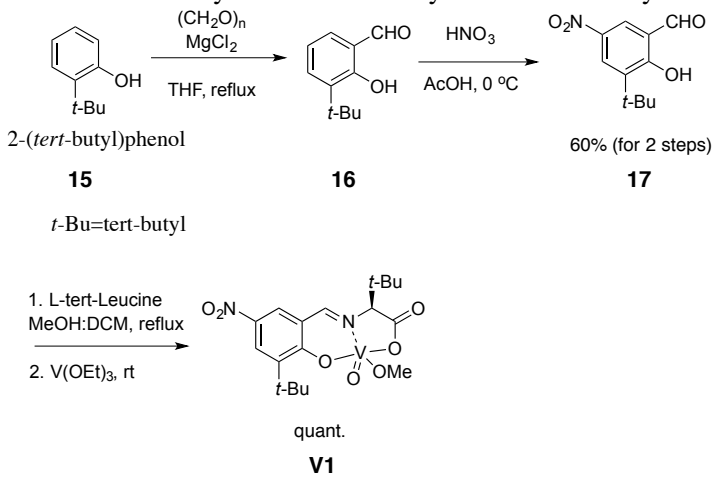



The first set of conditions that was examined in the asymmetric coupling of carbazoles, **14.1** and **8.1,** mirrored those used in asymmetric phenol couplings in our

group. Namely, vanadium catalyst **V1** was used (**Scheme 3**).[20] This catalyst was prepared by treatment of 2-(*tert*-butyl)phenol **15** with paraformaldehyde and magnesium chloride to generate the formylation product **16**.[17] Subsequent, nitric acid treatment yielded the nitrated product **17**. L-*tert*-Leucine was condensed with this aldehyde to yield a Schiff base that is treated with $VO(OEt)_3$ to generate catalyst **V1**.

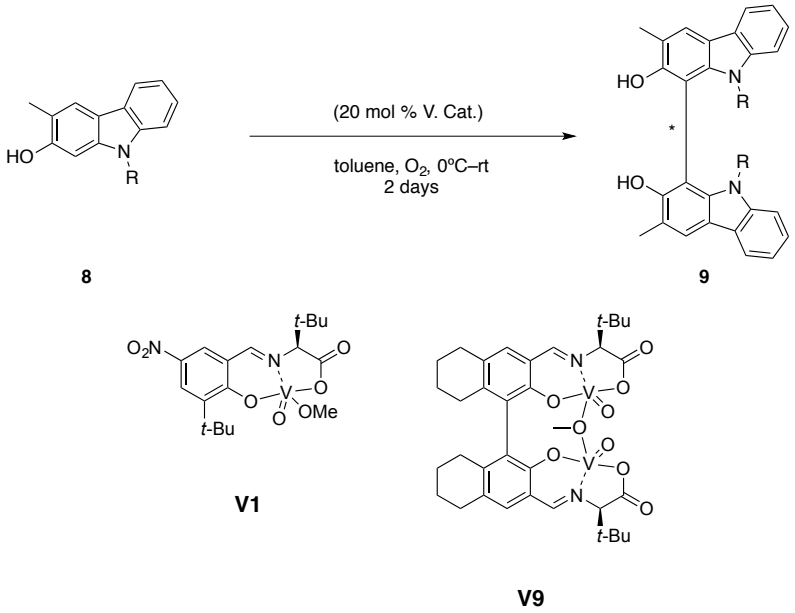
In order to properly evaluate the selectivity of the reaction through HPLC, a racemic standard was required. To make the racemic standard, the carbazoles were subjected to 50 mol % $VO(acac)_2$ under 1 atm oxygen in a 1 M solution of toluene. After purification, standards were obtained that gave two peaks of equal area upon passage through an analytical chiral stationary phase HPLC column.

**Scheme 3.** Synthesis of Primary Vanadium Catalyst




Carbazole couplings were examined using the same protocol as for the asymmetric phenol couplings except that 20 mol % catalyst **V1** was employed rather than 10 mol% catalyst. As expected from prior work, the substrate lacking a blocking group on nitrogen (**14**, R = H) did not undergo coupling due to oxidation of the nitrogen to other byproducts (**Table 1, entry 1**).[1] With **8.1** (R = Me), initial results were promising (**Table 1, entry 2**) providing the product in 58% ee with 100% conversion after 48 hours (half-life ~ 6 h).

**Table 1.** Oxidative Coupling Optimization[a]




[a]Conditions = 1 mmol carbazole, 0.2 mmol vanadium catalyst, toluene (0.5 M). [b] Conversions were estimated by TLC, yields were not taken before ee optimization

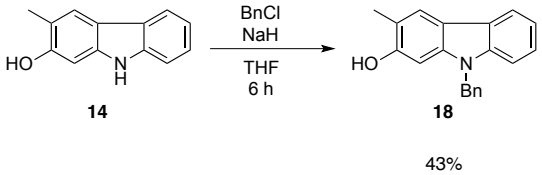
| Entry | R | V. Cat. | Additive | T (°C) | Conversion (%)[b] | ee (%) |
|---|---|---|---|---|---|---|
| 1 | H | **V1** | none | rt | 0 | n/a |
| 2 | Me | **V1** | none | rt | 100 | 58 |
| 3 | Me | **V1** | 0.2 LiCl | rt | 100 | 52 |
| 4 | Me | **V1** | 6.5 equiv AcOH | rt | 100 | 62 |
| 5 | Me | **V1** | 6.5 equiv AcOH | 0 | 85 | 72 |
| 6 | Me | **V9** | 6.5 equiv AcOH | 0 | 85 | 69 |
| 7 | Bn | **V1** | 6.5 equiv AcOH | 0 | 85 | 73 |
| 8 | Bn | **V9** | 6.5 equiv AcOH | 0 | 85 | 62 |

Other variables to improve the enantioselection were investigated. Lithium chloride, which was found to improve enantioselectivity in the asymmetric phenol coupling (see **Figure 6**), did not cause a significant change in this case (**Table 1, entry 3**).[17] However, the addition of another additive that had been successful in the phenol asymmetric coupling, acetic acid, was beneficial providing the product with 62% ee (**Table 1, entry 4**). Lowering the temperature to 0 °C improved the selectivity further to 72% ee (**Table 1, entry 5**). This result seemed reasonable because lowering the temperature decreases the possibility of reaching the higher energy transition state to the minor product. Use of the more complex catalyst that exhibited good enantioselectivity in naphthol and phenol coupling, **V9,** did not improve the enantioselectivity[17] (**Table 1, entry 6**).

At this juncture, we speculated that the low enantioselectivity might arise from insufficient steric interactions between the catalyst and substrate in the transition state leading to the minor product. To increase these steric interactions with the aims of further destabilizing the pathway to the minor enantiomer, a larger alkyl group was investigated

on the nitrogen center, which is directly adjacent to the axial chiral bond being formed. An *N*-benzyl group was thus surveyed which was obtained by treating compound **5** with 2.5 equivalents of sodium hydride to generate the dianion. Subsequent treatment with 1 equivalent of 1 M benzyl chloride in THF allowed for nucleophilic attack onto benzyl chloride by the more basic anilide vs phenoxide anion to generate **18.1** (**Figure 10**).

**Figure 10.** Benzylation of Carbazoles



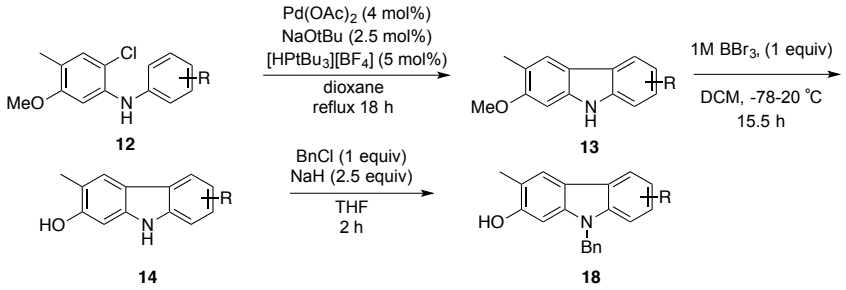

**14** **18**

43%

Initial trials with the *N*-benzyl analog **18** were very promising showing high selectivity (>95%ee). However, Houng Kang in our lab noted that some of the product did not fully dissolve in the 10% isopropanaol/hexane solution that was being analyzed by chiral phase HPLC. After fully dissolving the reaction product in 100% chloroform and analyzing, the *N*-benzyl analog **18** (**Table 1, entry 7**) was found to only give slightly higher selectivity (73% ee) relative to the *N*-methyl compound (**Table 1, entry 5**) under the same conditions. Again, the use of catalyst **V9** results in poorer enantiomeric excess with this compound (**Table 1, entry 8**). The differential solubility, however, indicates that the racemate can be removed by trituration to afford highly enantioenriched product. It should also be noted that during Lei Liu's work that *N*-benzyl protected carbazoles were one of the few substrates that decreased the selectivity for *ortho-ortho'* coupling and improved *ortho-ortho* coupling.[1] Normally, in Lei's work, the *ortho-ortho* coupling remained at 2-3% yield, but with a benzyl coupling, the yield went up to 8%, while simultaneously lowering the *ortho-ortho'* yield from 70% to 56%. This result could potentially arise from π-stacking interactions between the two benzyl groups from the separate monomers.

The optimal conditions, based off of enantiomeric excess, [20 mol % catalyst **V1**, 1 M toluene, 0º C, 6.5 equiv AcOH, $O_2$] were established. With these conditions in hand, a series of substrates was screened, **18.1-18.3**. To form each of these new carbazoles substrates, it is only necessary to change the bromobenzene used in the initial Buchwald Hartwig coupling step (**Table 2**). This change will result in various groups on carbons C*5* to C*8* of the final carbazoles.

**Table 2.** Additional Substrates for Asymmetric Oxidative Coupling

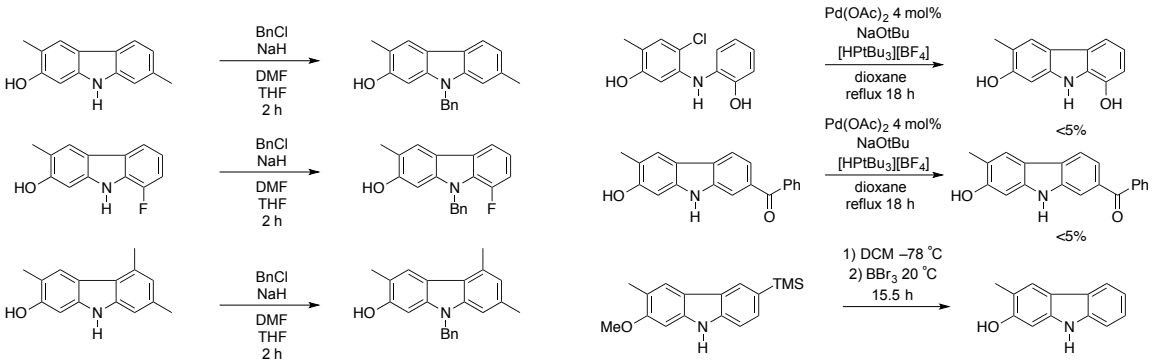



| Substitution | **12** | Yield (%) | **13** | Yield (%) | **14** | Yield (%) | **18** | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| 6-Fluoro | **12.2** | 33 | **13.2** | 27 | 5.3 | 81 | **18.2** | 82 |
| 6-Methyl | **12.3** | 61 | **13.3** | 20 | 5.4 | 98 | **18.3** | 67 |
| 7-Fluoro | **12.4** | 95 | **13.4** | 9 | 5.5 | 88 | **18.4** | 56 |

There was significant difficulty when attempting to make some of these substrates. The 6-phenyl, 7-methyl, 8-fluoro, 5,7-dimethyl, 8-hydroxy, 6-nitro, 7-phenacyl, and 6-trimethylsilyl, were attempted, but did not yield sufficient amounts of substrate for study in the asymmetric coupling. Specifically, these compounds decomposed during various steps of the synthesis step of the synthesis (**Figure 11**)**.** Most substrates had difficulty during the cyclization to form the carbazole, or during the benzylation process. The benzylation did not occur with the 7-methyl, 8 fluoro, nor the 5,7-dimethyl compounds. The 8-hydroxy and 7-phenacyl did not undergo cyclization in usable yield. Lastly, the TMS group on the 6-trimethylsilyl carbazole was cleaved after attempting to demethylate using $BBr_3$, resulting in the loss of the silyl group.

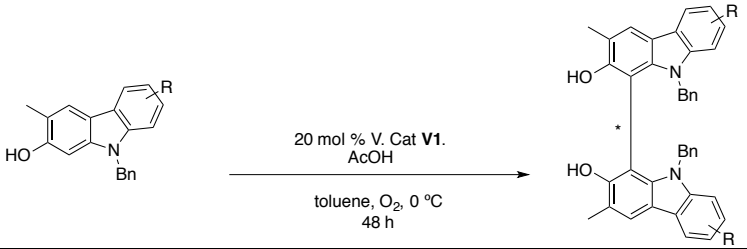
With three additional substrates in hand (**18.2-18.4**), the same conditions as from Table 1, entry 7 were applied. Overall, the addition of fluoro groups to the distal ring at C7 or C8 slightly enhanced the enantiomeric excess, whereas a methyl group did not indicating that electron withdrawing groups are benefical (**Table 3, entries 2-4**). The

**Figure 11.** Failed Carbazole Substrates




yield for some of the reactions was not as high, because of the significantly slower rates caused by the decrease in temperature from 25 to 0 ºC which resulted in significant amounts of starting material remaining even after 48 h.

**Table 3.** Substrate Scope




| Entry | R | Position | Substrate | Yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | H | n/a | **18.1** | 86 | 73 |
| 2 | F | 6 | **18.2** | 82 | 79 |
| 3 | F | 7 | **18.3** | 83 | 76 |
| 4 | Me | 6 | **18.4** | 67 | 73 |

**Conclusion**

In summary, an effective system to catalyze asymmetric coupling of carbazoles has been developed. This work describes the first enantioselective coupling of carbazoles using a chiral catalyst. Specifically, the coupling of 2-hydroxy-3-methylcarbazoles proceeds with moderate enantioselectivity under very mild reaction conditions. The original hypothesis that catalyst **V1** would be effective for carbazoles based upon its selectivity in the coupling of phenols is correct. It can be claimed that **V1** is an appropriate catalyst for a variety of carbazoles as well as aromatic phenol-based couplings.

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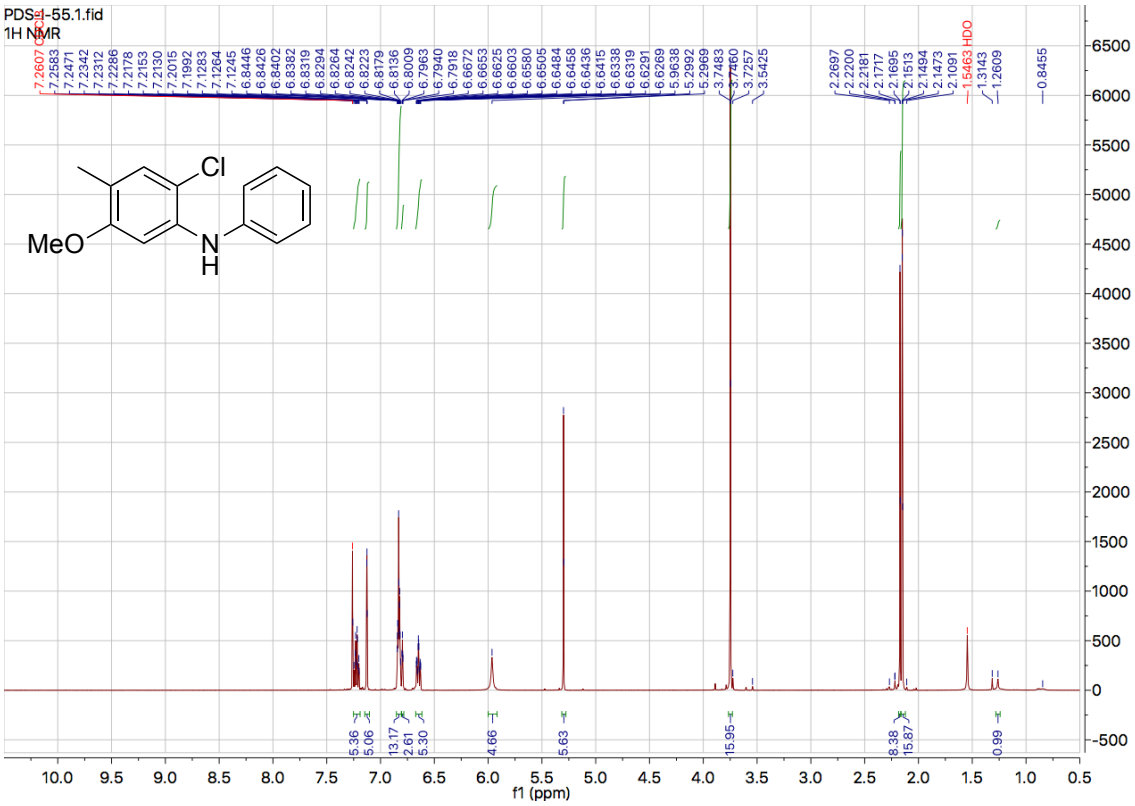
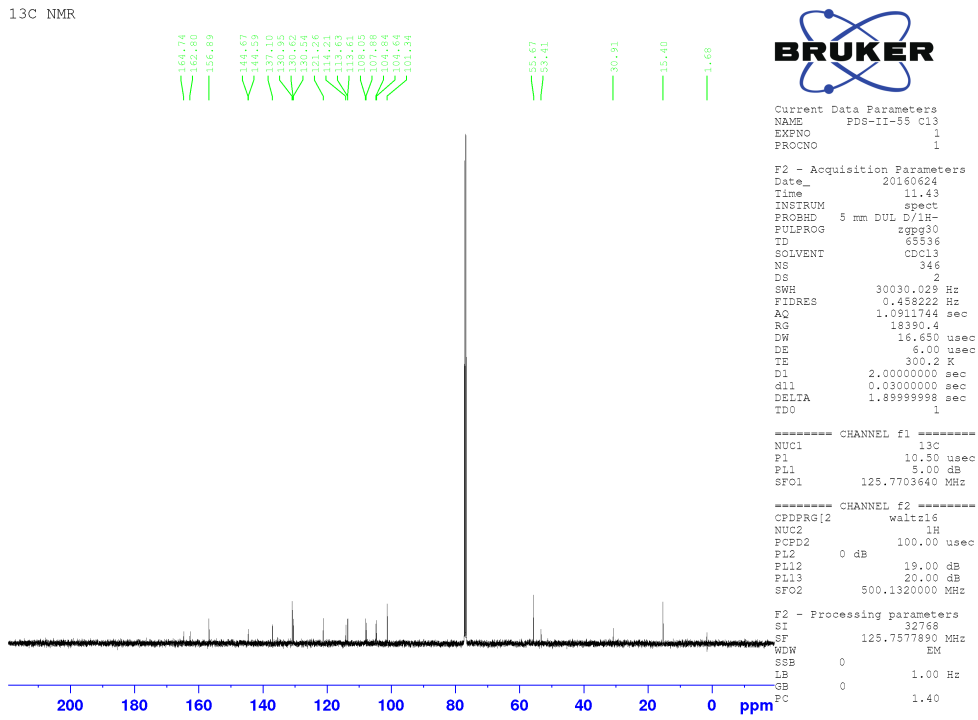
## Appendices




BRUKER

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PROCNO                  1

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INSTRUM             spect
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PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   346
DS                     2
SWH          30030.029 Hz
FIDRES        0.458222 Hz
AQ            1.0911744 sec
RG              18390.4
DW               16.650 usec
DE                6.00 usec
TE               300.2 K
D1           2.00000000 sec
d11          0.03000000 sec
DELTA        1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                10.50 usec
PL1                5.00 dB
SFO1        125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2        0 dB
PL12               19.00 dB
PL13               20.00 dB
SFO2        500.1320000 MHz

F2 - Processing parameters
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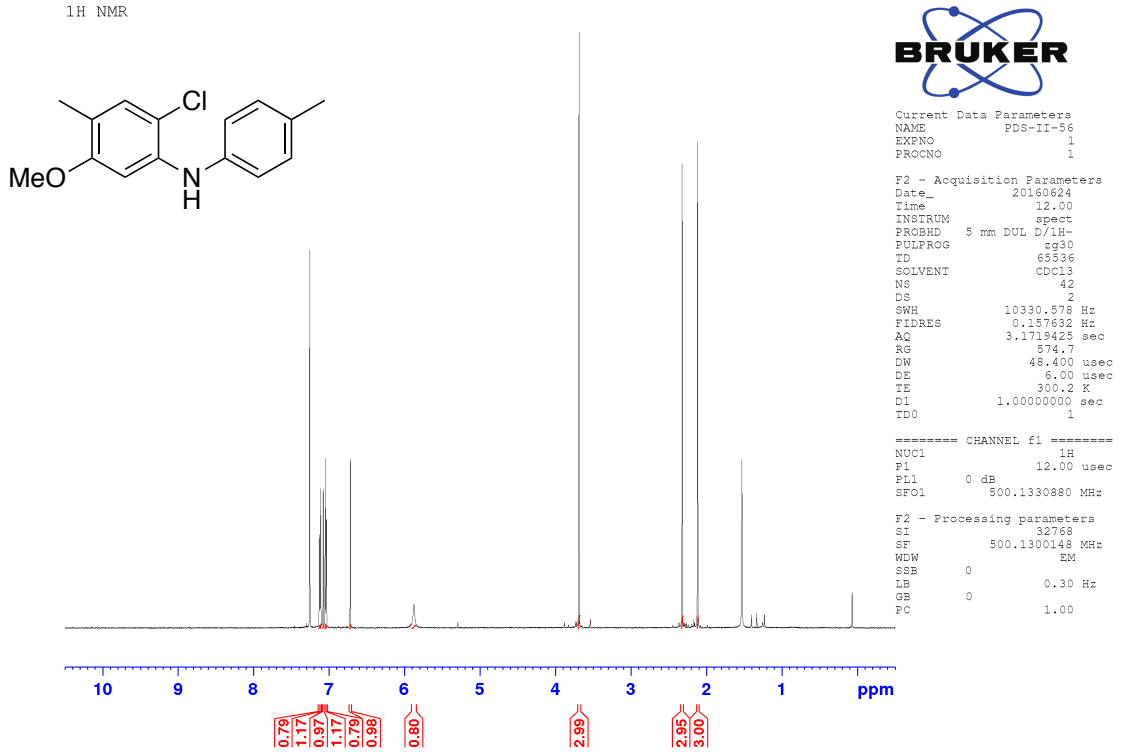
SF          125.7577890 MHz
WDW                    EM
SSB        0
LB                  1.00 Hz
GB         0
PC                  1.40
```


1H NMR
Cl
MeO
N
H
BRUKER
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PROCNO 1
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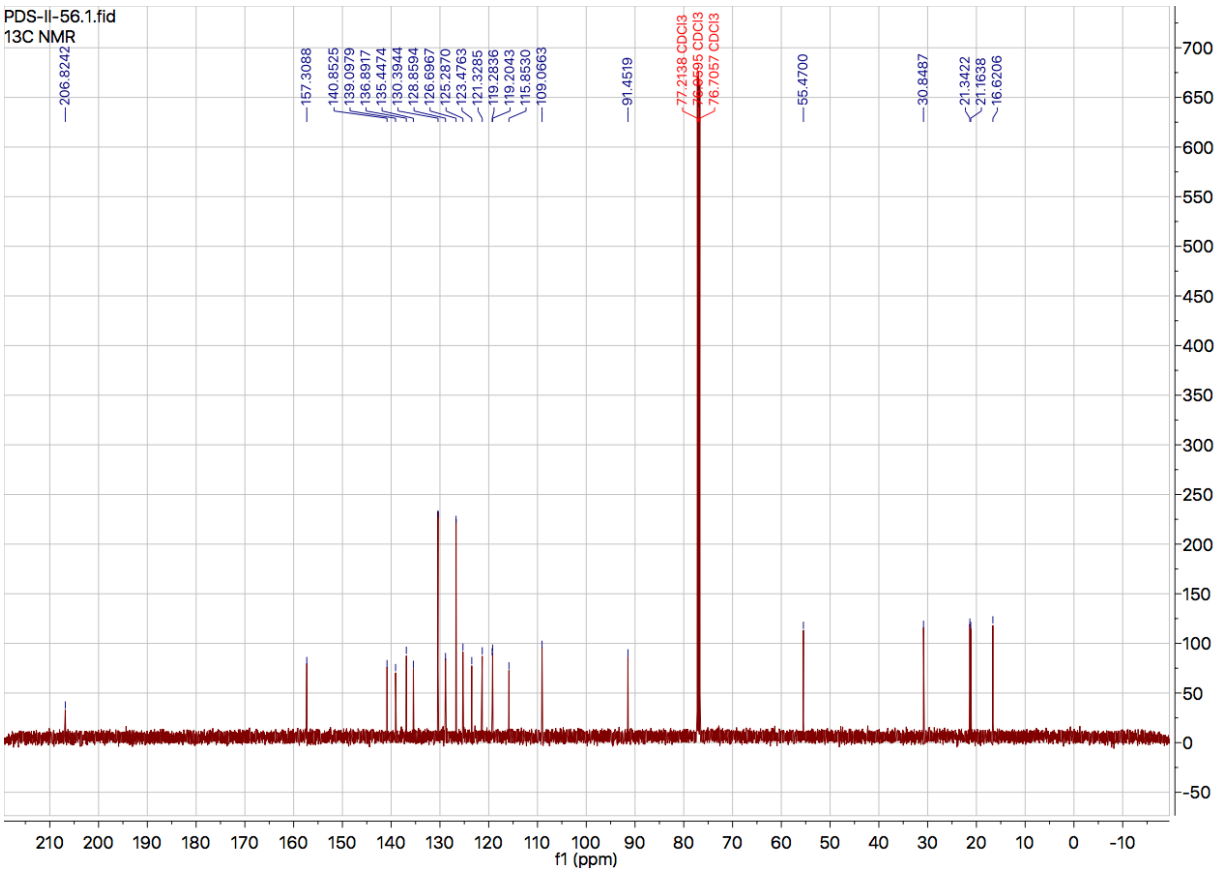
Time 12.00
INSTRUM spect
PROBHD 5 mm DUL D/1H-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 42
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 574.7
DW 48.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 0 dB
SFO1 500.1330880 MHz
F2 - Processing parameters
SI 32768
SF 500.1300148 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
10 9 8 7 6 5 4 3 2 1 ppm
0.79 1.17 0.97 1.17 0.79 0.98 0.80 2.99 2.95 3.00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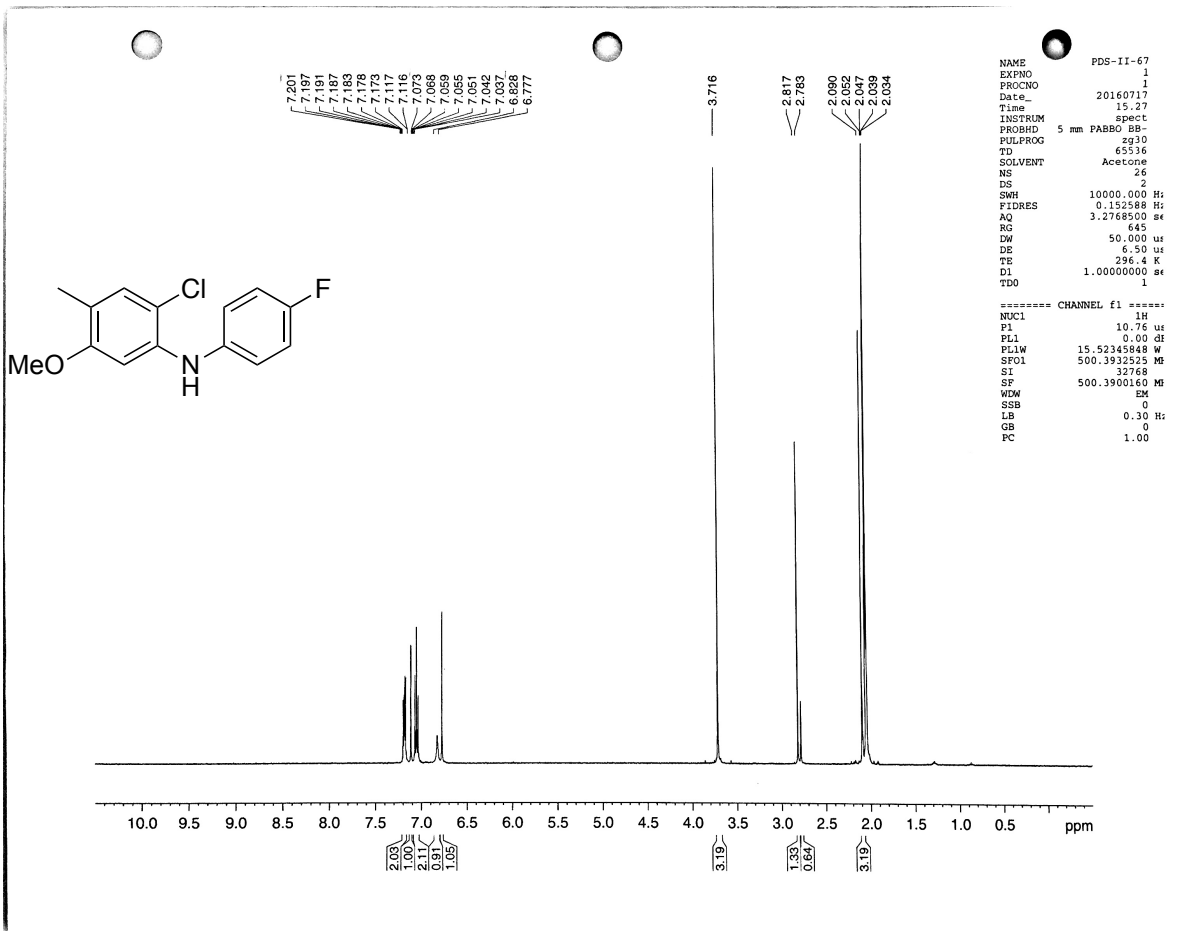
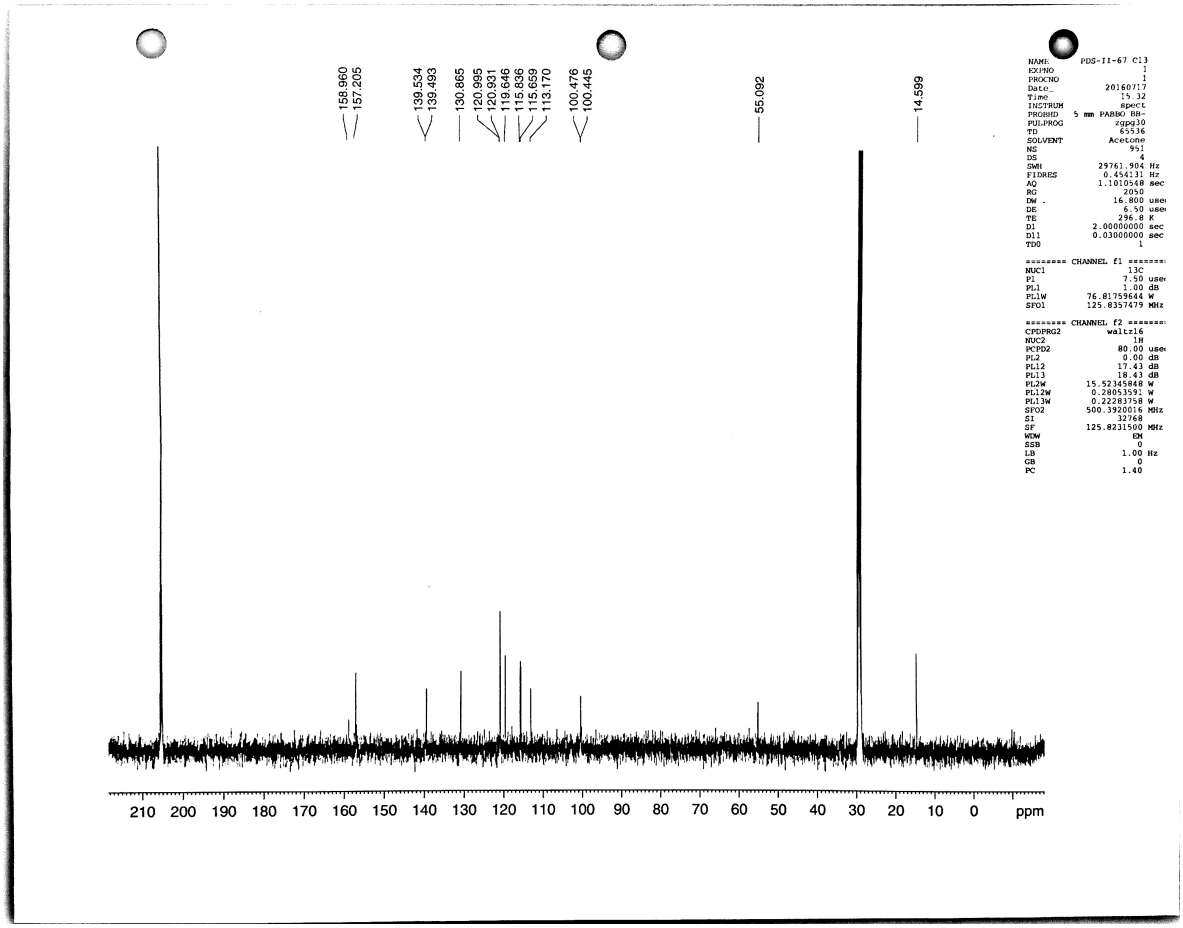
157.3088
140.8525
139.0979
136.8917
135.4474
130.3944
128.8594
126.6967
125.2870
123.4763
121.3285
119.2836
119.2043
115.8530
109.0663
91.4519
77.2138 CDCl3
76.7057 CDCl3
55.4700
30.8487
21.3422
21.1638
16.6206
f1 (ppm)


7.201
7.197
7.191
7.187
7.183
7.178
7.173
7.117
7.116
7.073
7.068
7.059
7.055
7.051
7.042
7.037
6.828
6.777
3.716
2.817
2.783
2.090
2.052
2.047
2.039
2.034
Cl
F
MeO
N
H
NAME PDS-II-67
EXPNO 1
PROCNO 1
Date_ 20160717
Time 15.27
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT Acetone
NS 26
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2768500 sec
RG 645
DW 50.000 us
DE 6.50 us
TE 296.4 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ======
NUC1 1H
P1 10.76 us
PL1 0.00 dB
PL1W 15.52345848 W
SFO1 500.3932525 MHz
SI 32768
SF 500.3900160 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.03
1.00
2.11
0.91
1.05
3.19
1.33
0.64
3.19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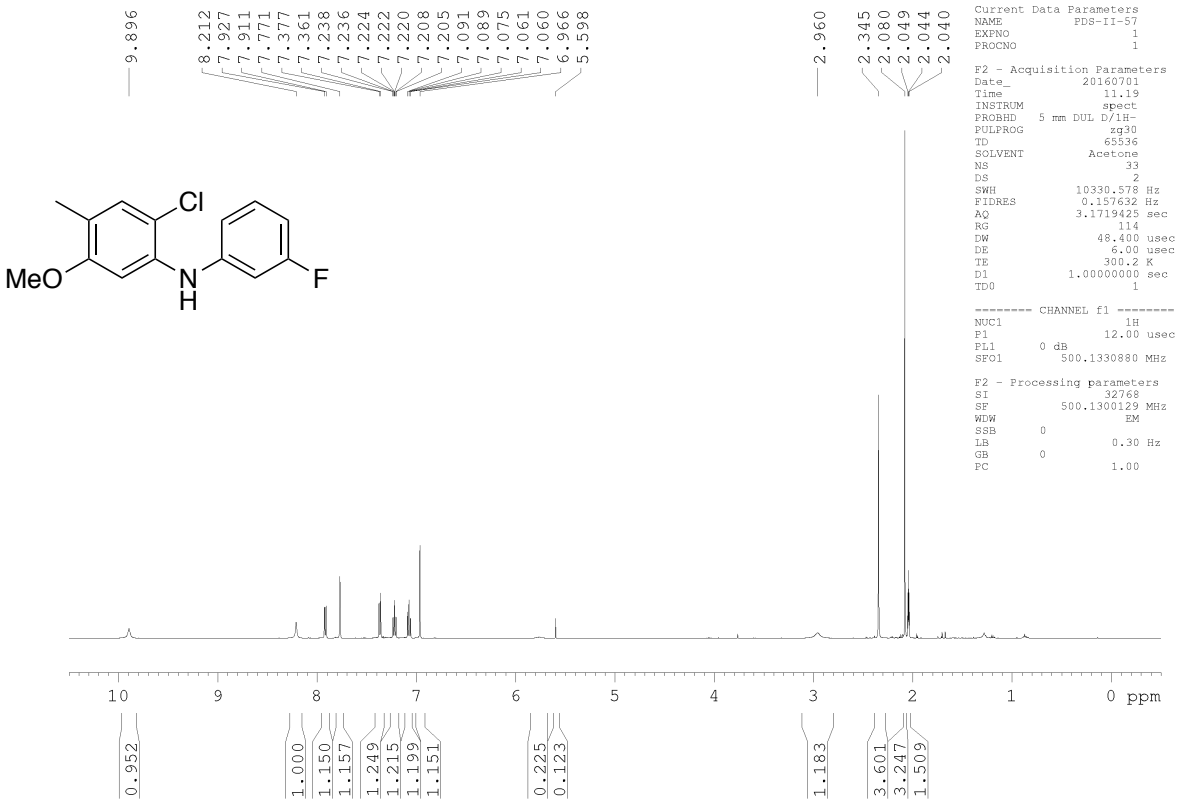
157.205
139.534
139.493
130.865
120.995
120.931
119.646
115.836
115.659
113.170
100.476
100.445
55.092
14.599
NAME PDS-II-67 C13
EXPNO 1
PROCNO 1
Date_ 20160717
Time 15.32
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT Acetone
NS 951
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010548 sec
RG 2050
DW 16.800 use
DE 6.50 use
TE 296.8 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ======
NUC1 13C
P1 7.50 use
PL1 1.00 dB
PL1W 76.81759644 W
SFO1 125.8357479 MHz
======== CHANNEL f2 ======
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 use
PL2 0.00 dB
PL12 17.43 dB
PL13 18.43 dB
PL2W 15.52345848 W
PL12W 0.28053591 W
PL13W 0.22283758 W
SFO2 500.3920016 MHz
SI 32768
SF 125.8231500 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


9.896
8.212
7.927
7.911
7.771
7.377
7.361
7.238
7.236
7.224
7.222
7.220
7.208
7.205
7.091
7.089
7.075
7.061
7.060
6.966
5.598
2.960
2.345
2.080
2.049
2.044
2.040
Cl
MeO
N
H
F
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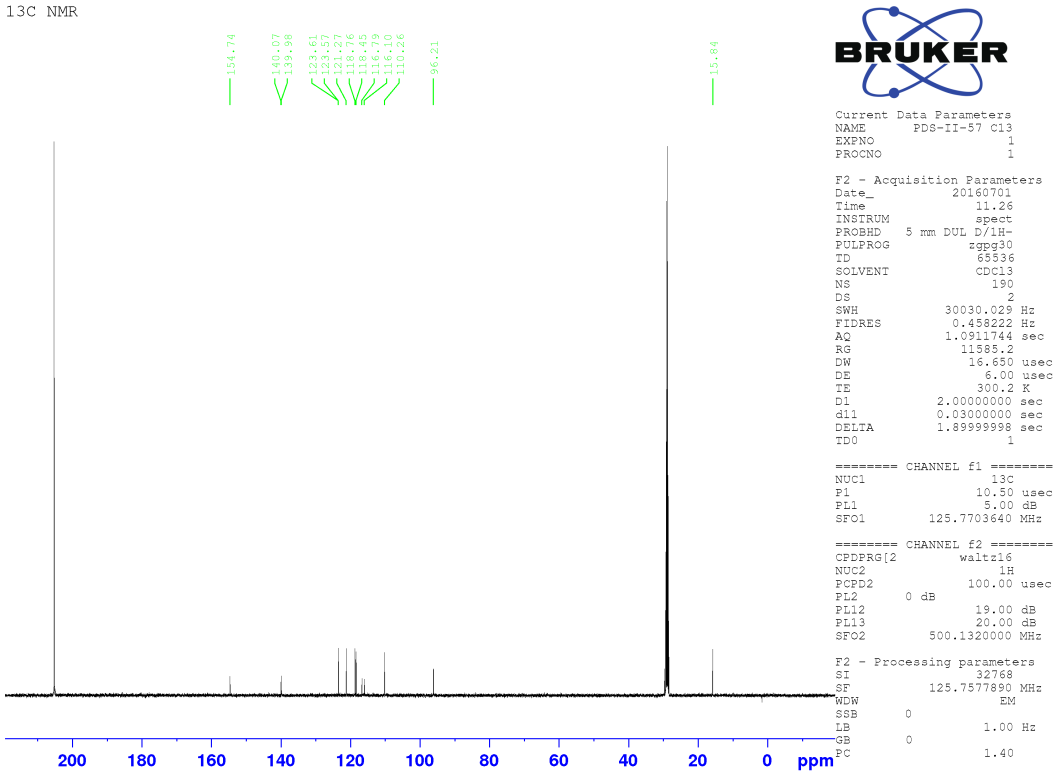
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160701
Time 11.19
INSTRUM spect
PROBHD 5 mm DUL D/1H-
PULPROG zg30
TD 65536
SOLVENT Acetone
NS 33
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 114
DW 48.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 0 dB
SFO1 500.1330880 MHz
F2 - Processing parameters
SI 32768
SF 500.1300129 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
10 9 8 7 6 5 4 3 2 1 0 ppm
0.952
1.000
1.150
1.157
1.249
1.215
1.199
1.151
0.225
0.123
1.183
3.601
3.247
1.509


13C NMR
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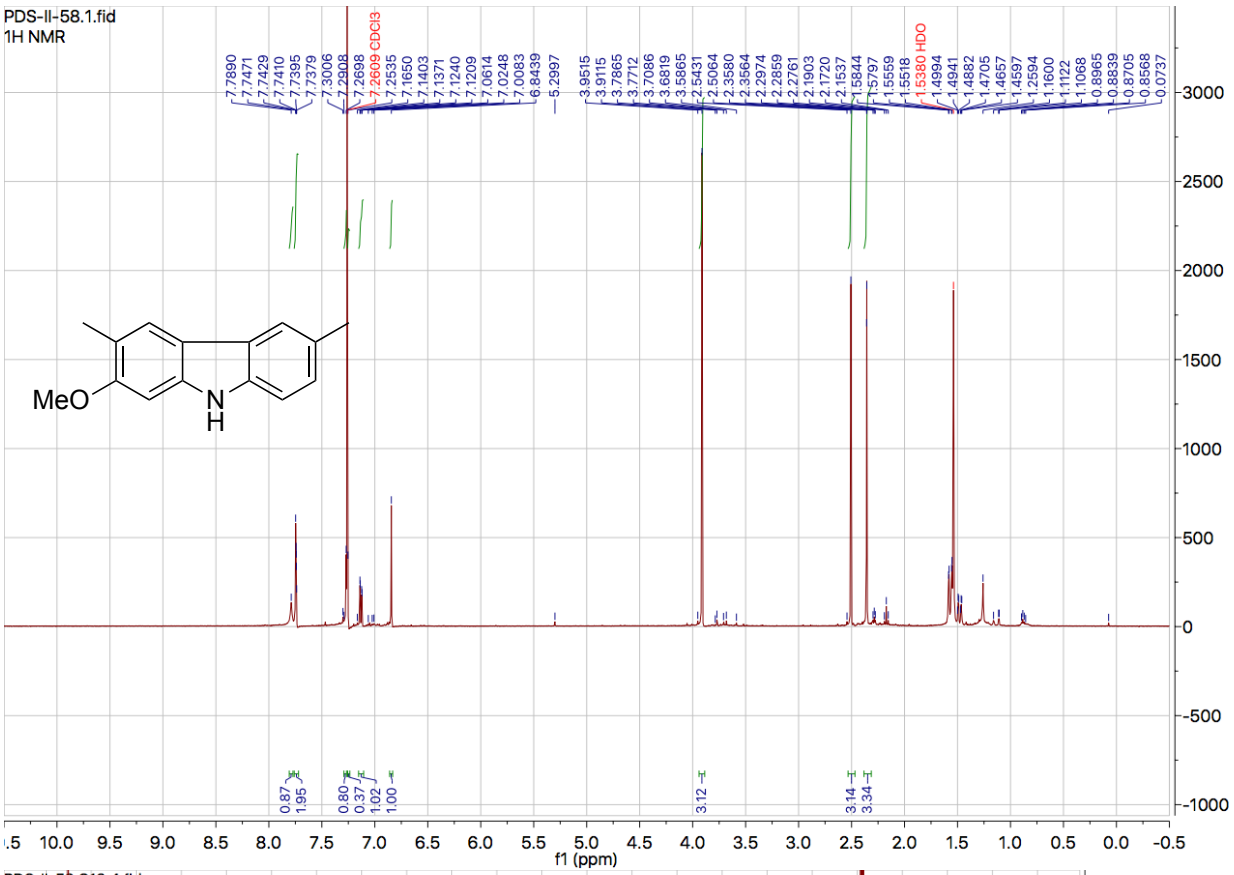
140.07
139.98
123.61
123.57
121.37
118.76
118.45
116.79
116.10
110.26
96.21
15.84
BRUKER
Current Data Parameters
NAME PDS-II-57 C13
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160701
Time 11.26
INSTRUM spect
PROBHD 5 mm DUL D/1H-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 190
DS 2
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0911744 sec
RG 11585.2
DW 16.650 usec
DE 6.00 usec
TE 300.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.50 usec
PL1 5.00 dB
SFO1 125.7703640 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0 dB
PL12 19.00 dB
PL13 20.00 dB
SFO2 500.1320000 MHz
F2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200 180 160 140 120 100 80 60 40 20 0 ppm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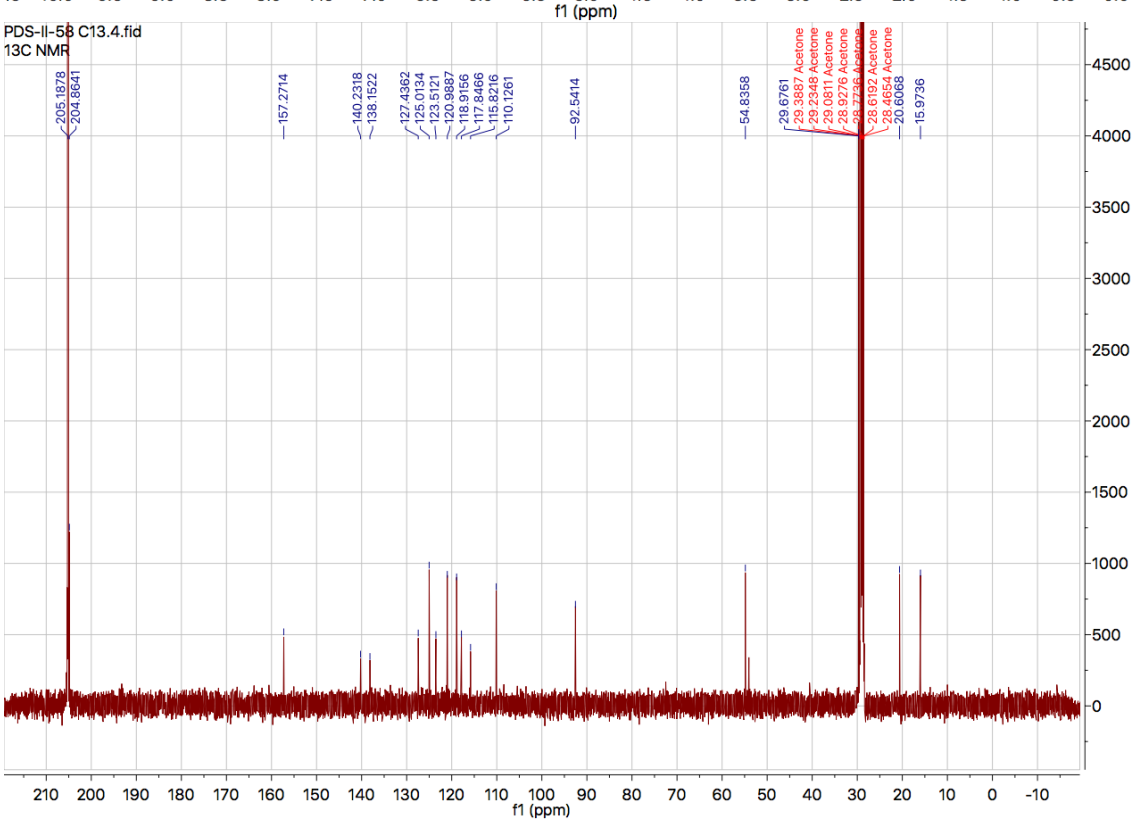
1H NMR
MeO
N
H
f1 (ppm)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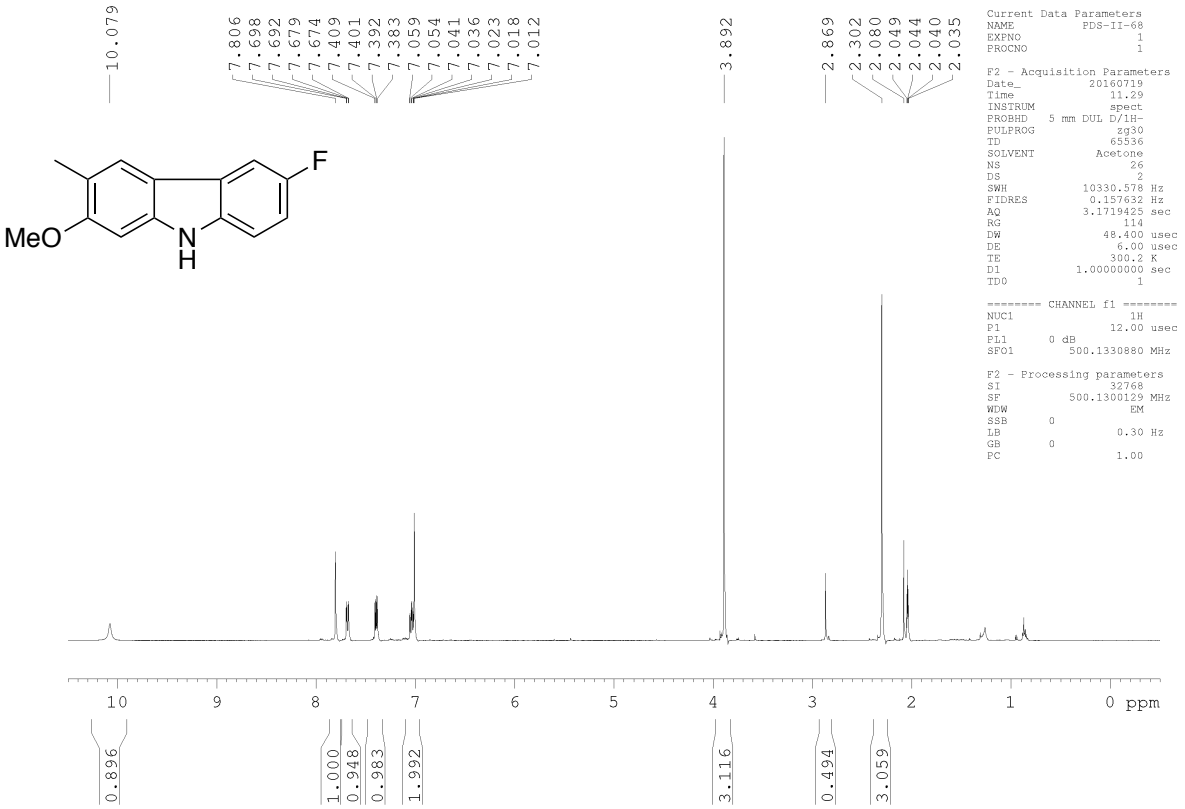
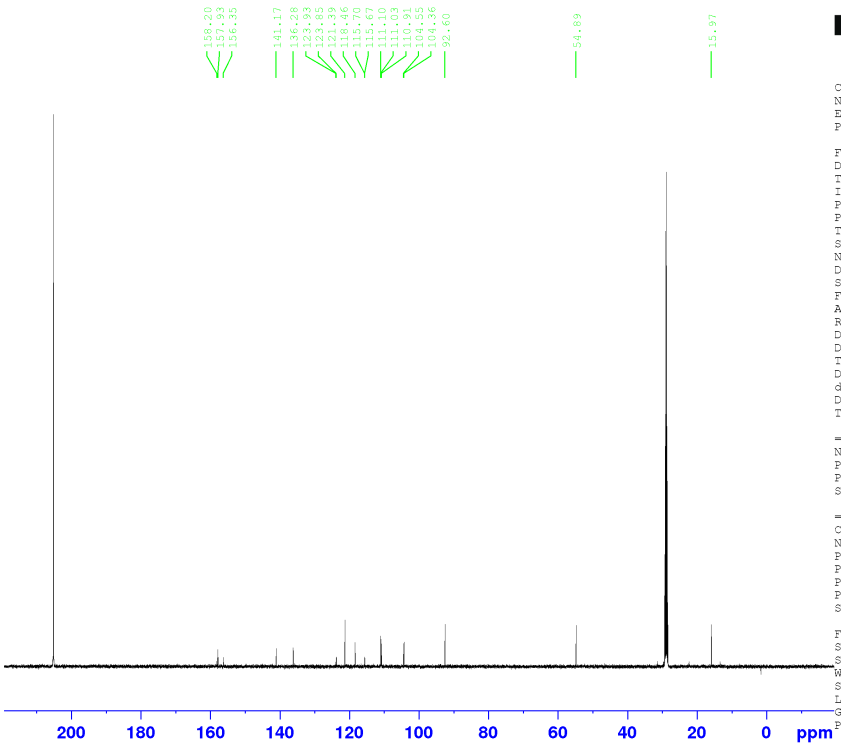
13C NMR
f1 (ppm)




13C NMR




BRUKER

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PROCNO 1

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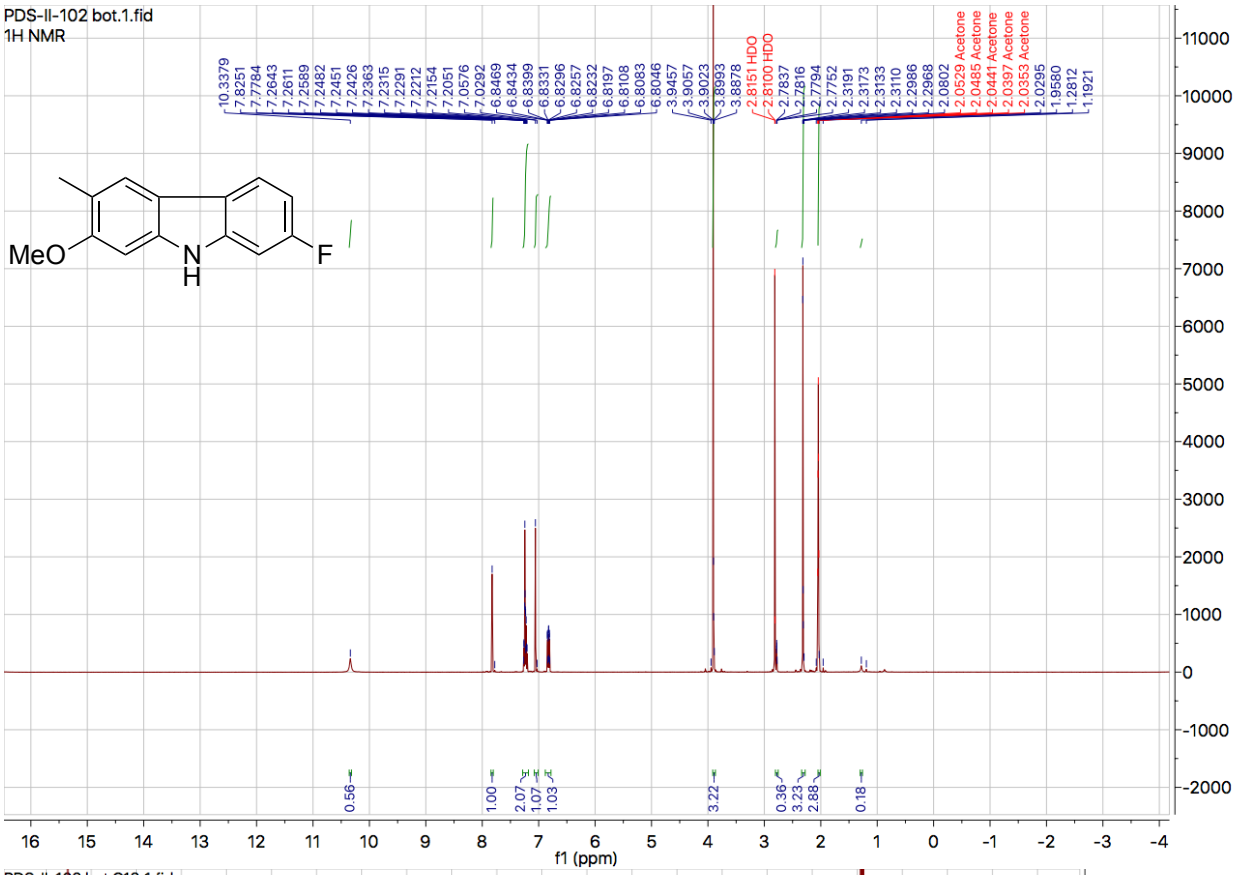
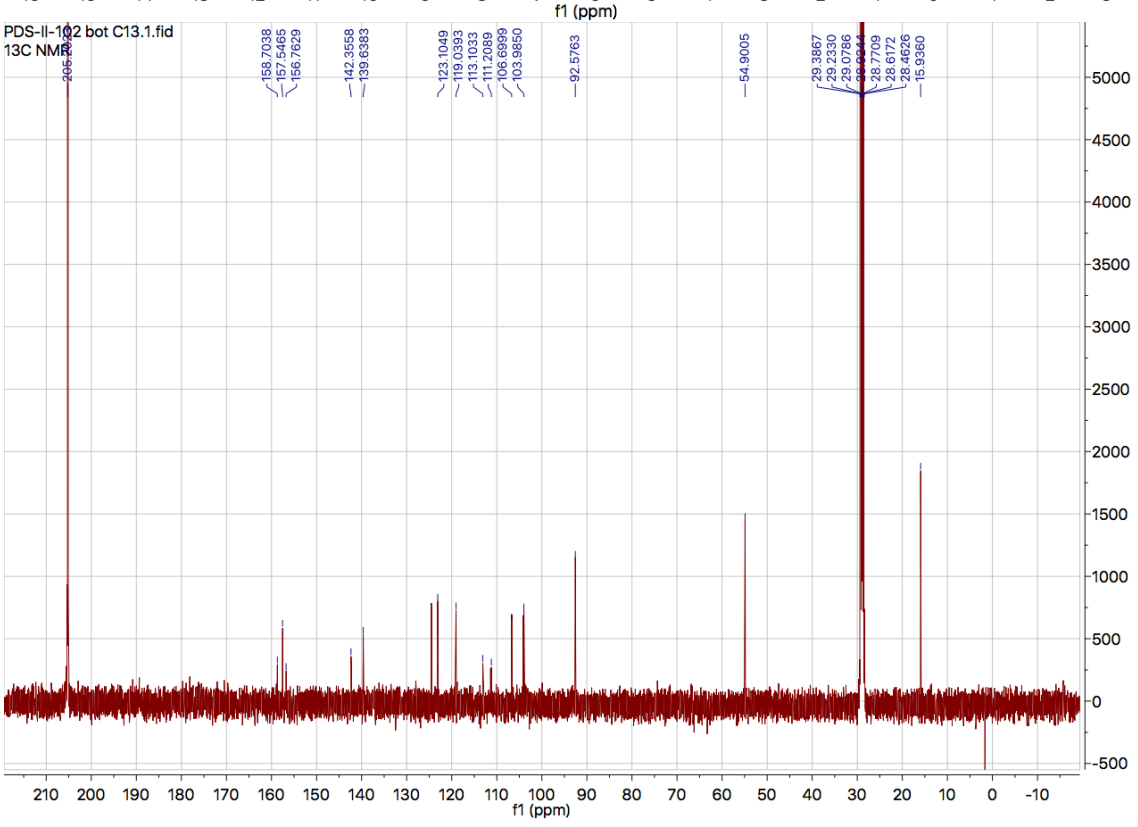
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 211
DS 2
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0911744 sec
RG 18390.4
DW 16.650 usec
DE 6.00 usec
TE 300.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 10.50 usec
PL1 5.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0 dB
PL12 19.00 dB
PL13 20.00 dB
SFO2 500.1320000 MHz

F2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


PDS-II-102 bot.1.fid
1H NMR
MeO
N
H
F
f1 (ppm)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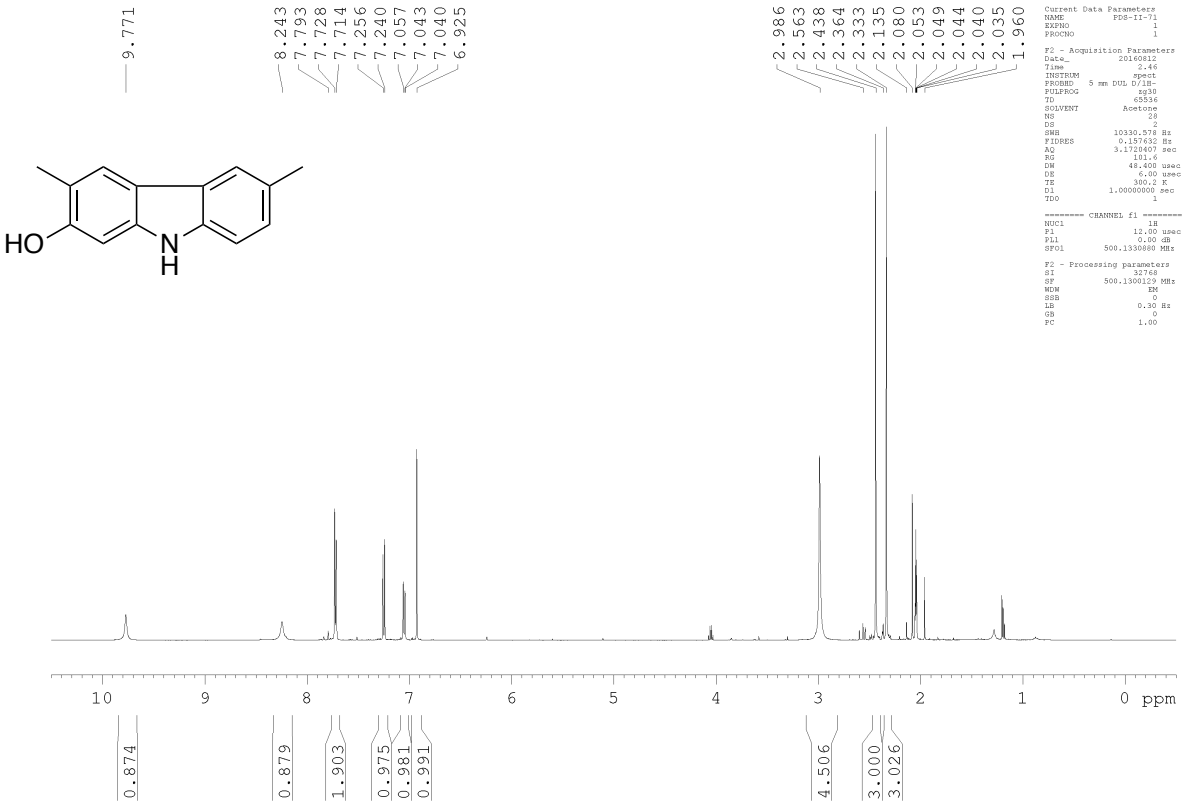
13C NMR
f1 (ppm)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7.714
7.256
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7.057
7.043
7.040
6.925
2.986
2.563
2.438
2.364
2.333
2.135
2.080
2.053
2.049
2.044
2.040
2.035
1.960
HO
N
H
10
9
8
7
6
5
4
3
2
1
0 ppm
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0.879
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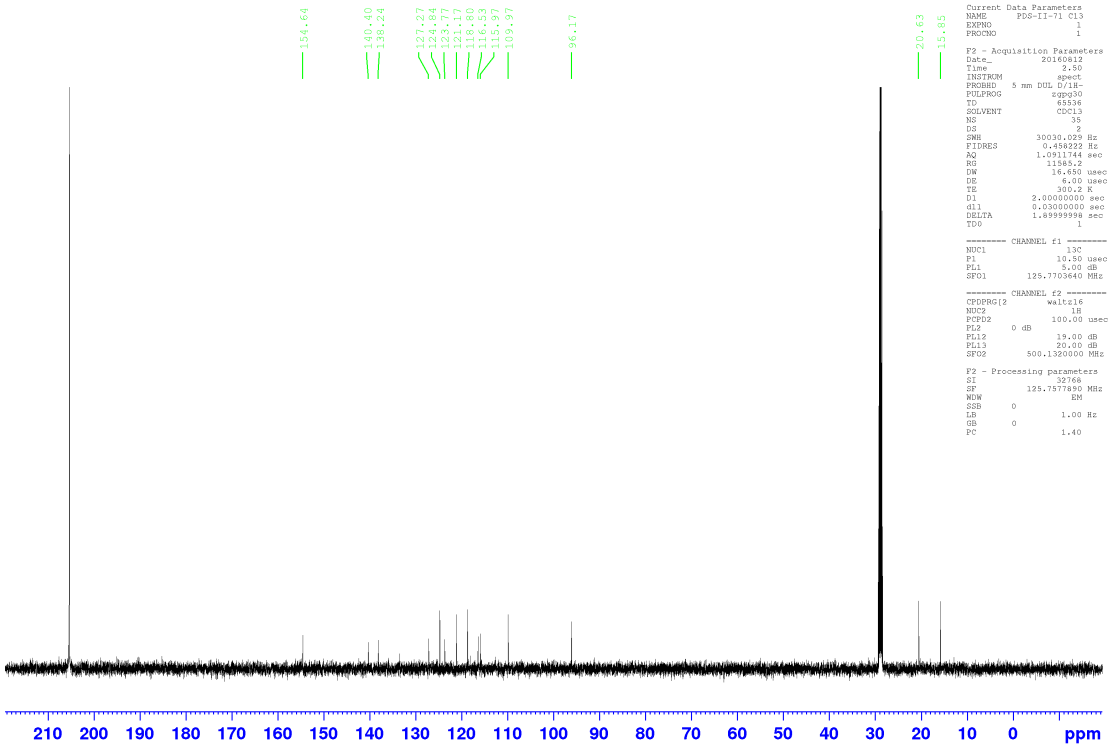
0.975
0.981
0.991
4.506
3.000
3.026

13C NMR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140.40
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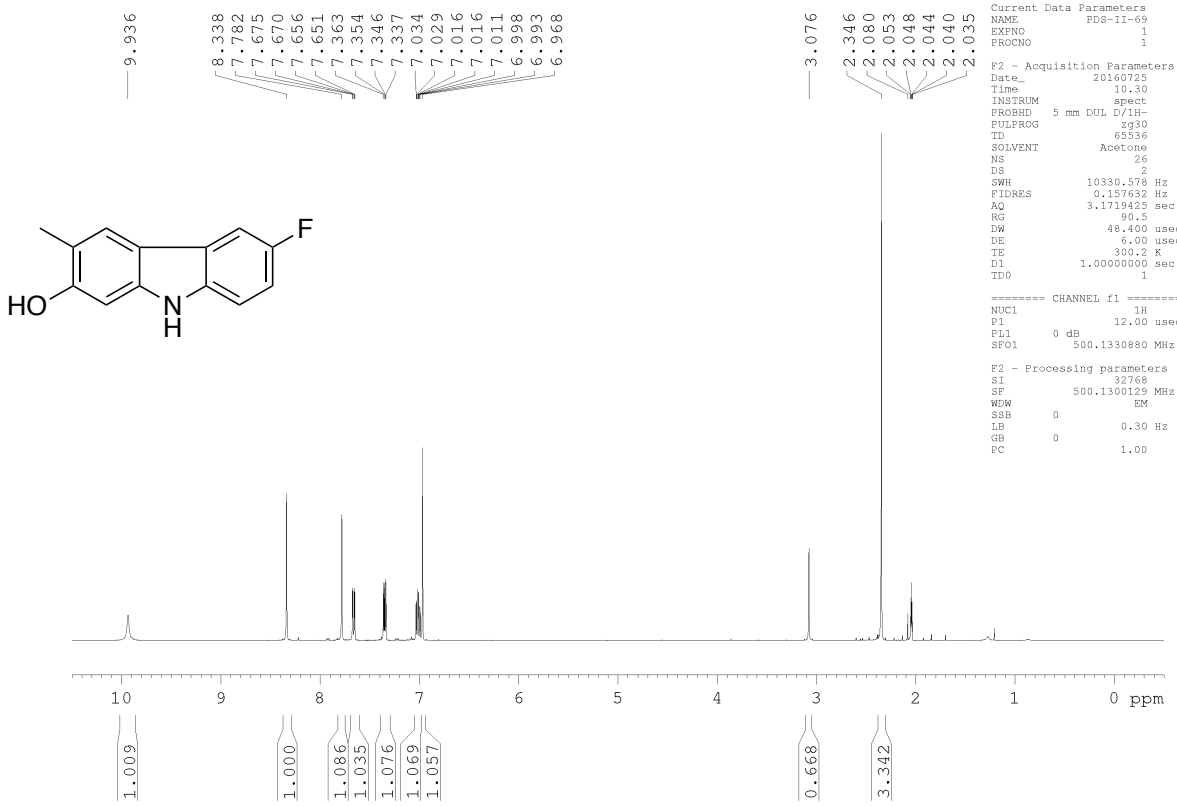
127.27
124.84
123.77
121.17
118.80
116.53
115.97
109.97
96.17
20.63
15.85
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

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PROCNO 1

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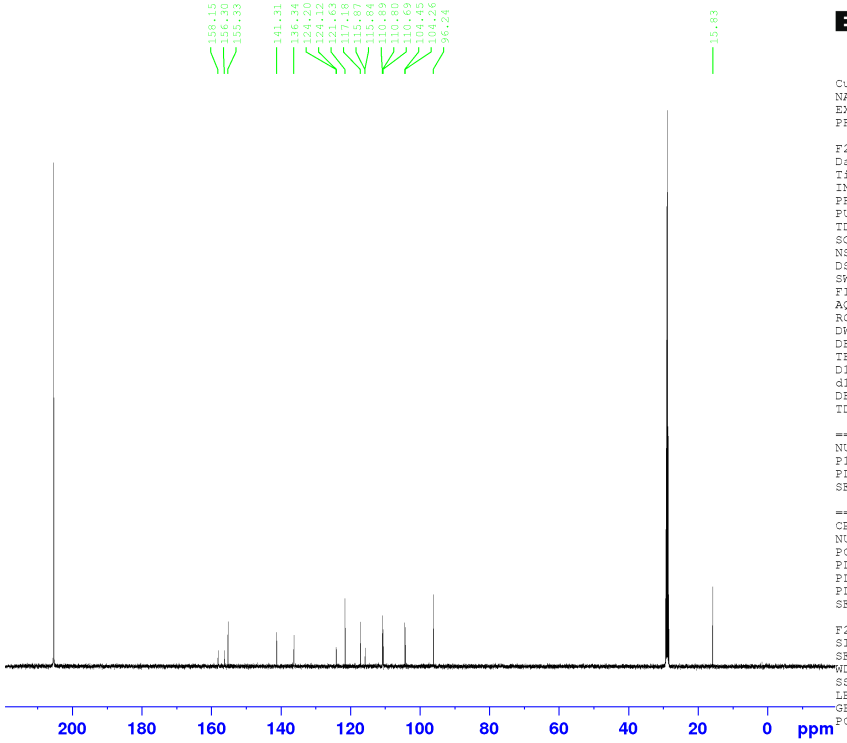
PROBHD 5 mm DUL D/1H-
PULPROG zg30
TD 65536
SOLVENT Acetone
NS 26
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 90.5
DW 48.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 0 dB
SFO1 500.1330880 MHz

F2 - Processing parameters
SI 32768
SF 500.1300129 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

13C NMR




Current Data Parameters
NAME PDS-II-69 C13
EXPNO 1
PROCNO 1

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Time 10.35
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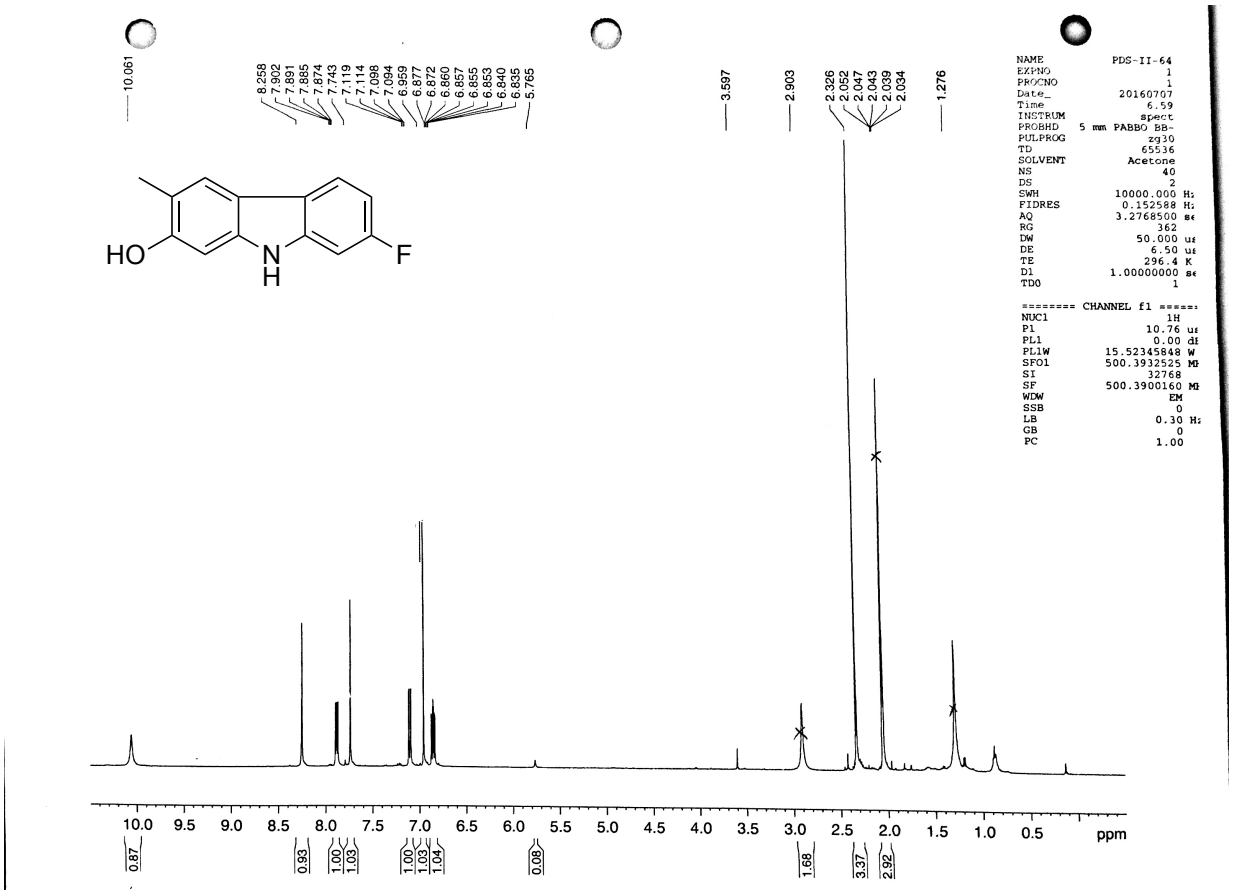
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 109
DS 2
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0911744 sec
RG 11585.2
DW 16.650 usec
DE 6.00 usec
TE 300.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 10.50 usec
PL1 5.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0 dB
PL12 19.00 dB
PL13 20.00 dB
SFO2 500.1320000 MHz

F2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40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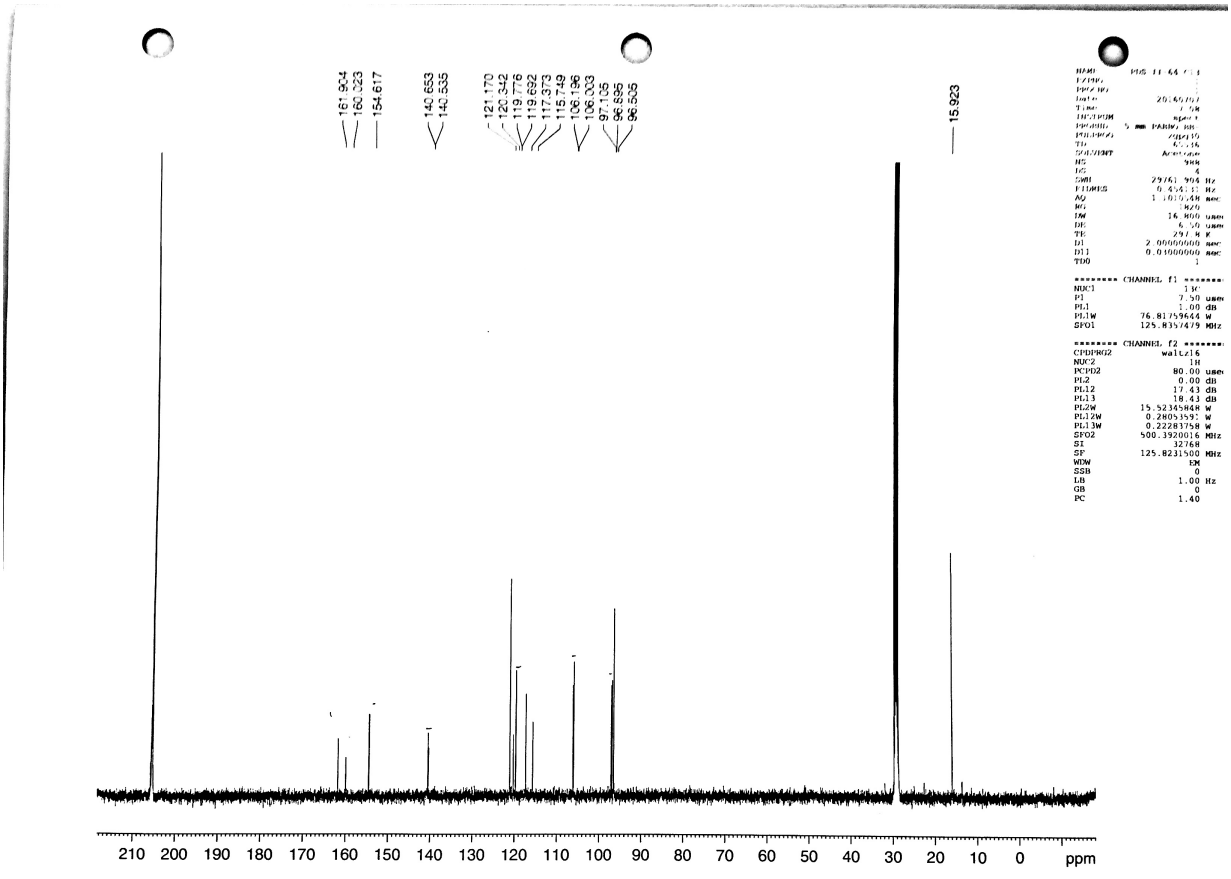
8.258
7.902
7.891
7.885
7.874
7.743
7.119
7.114
7.098
7.094
6.959
6.877
6.872
6.860
6.857
6.855
6.853
6.840
6.835
5.765
3.597
2.903
2.326
2.052
2.047
2.043
2.039
2.034
1.276
HO
N
H
F
NAME PDS-II-64
EXPNO 1
PROCNO 1
Date_ 20160707
Time 6.59
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT Acetone
NS 40
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2768500 se
RG 362
DW 50.000 us
DE 6.50 us
TE 296.4 K
D1 1.00000000 se
TD0 1
======== CHANNEL f1 ======
NUC1 1H
P1 10.76 us
PL1 0.00 dB
PL1W 15.52345848 W
SFO1 500.3932525 MH
SI 32768
SF 500.3900160 MH
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.87
0.93
1.00
1.03
1.00
1.03
1.04
0.08
1.68
3.37
2.92


161.904
160.323
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121.170
120.342
119.776
119.692
117.373
115.749
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97.135
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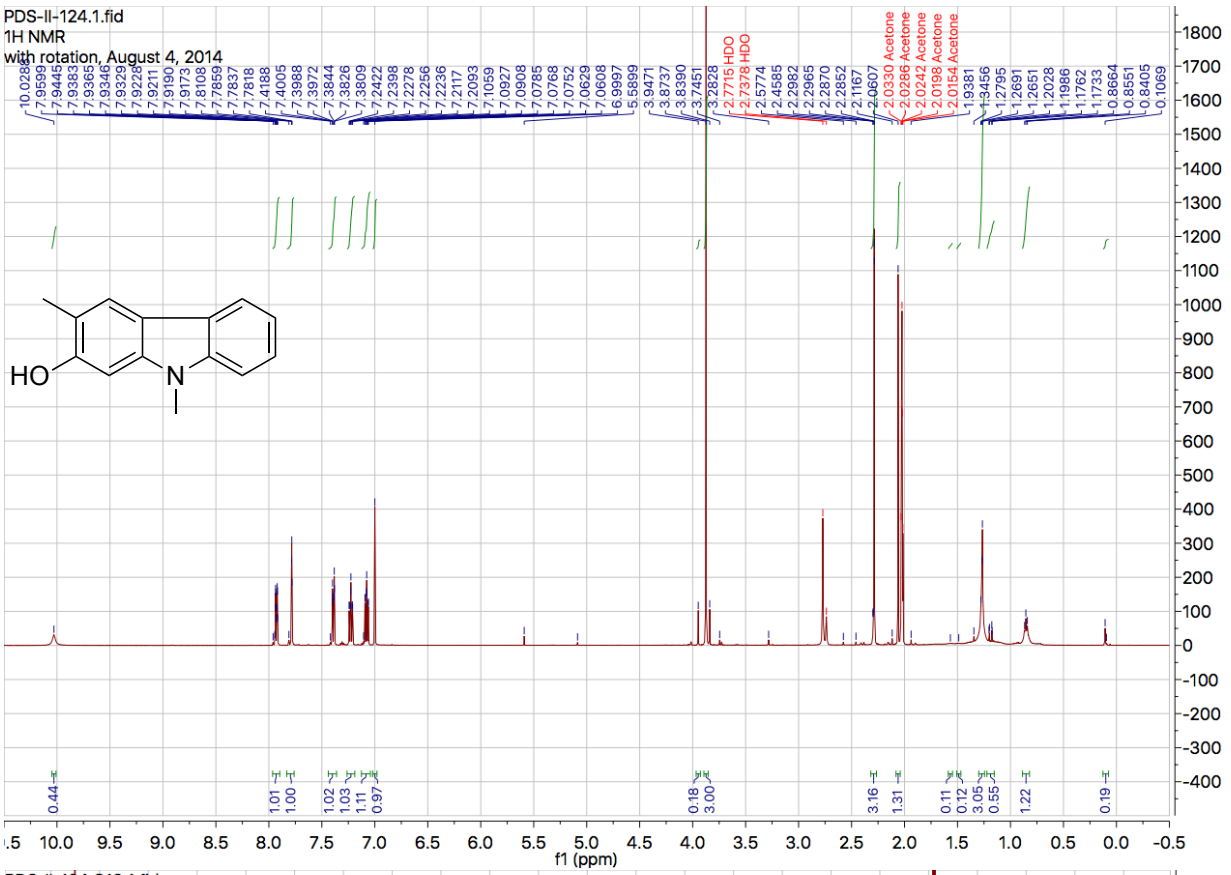
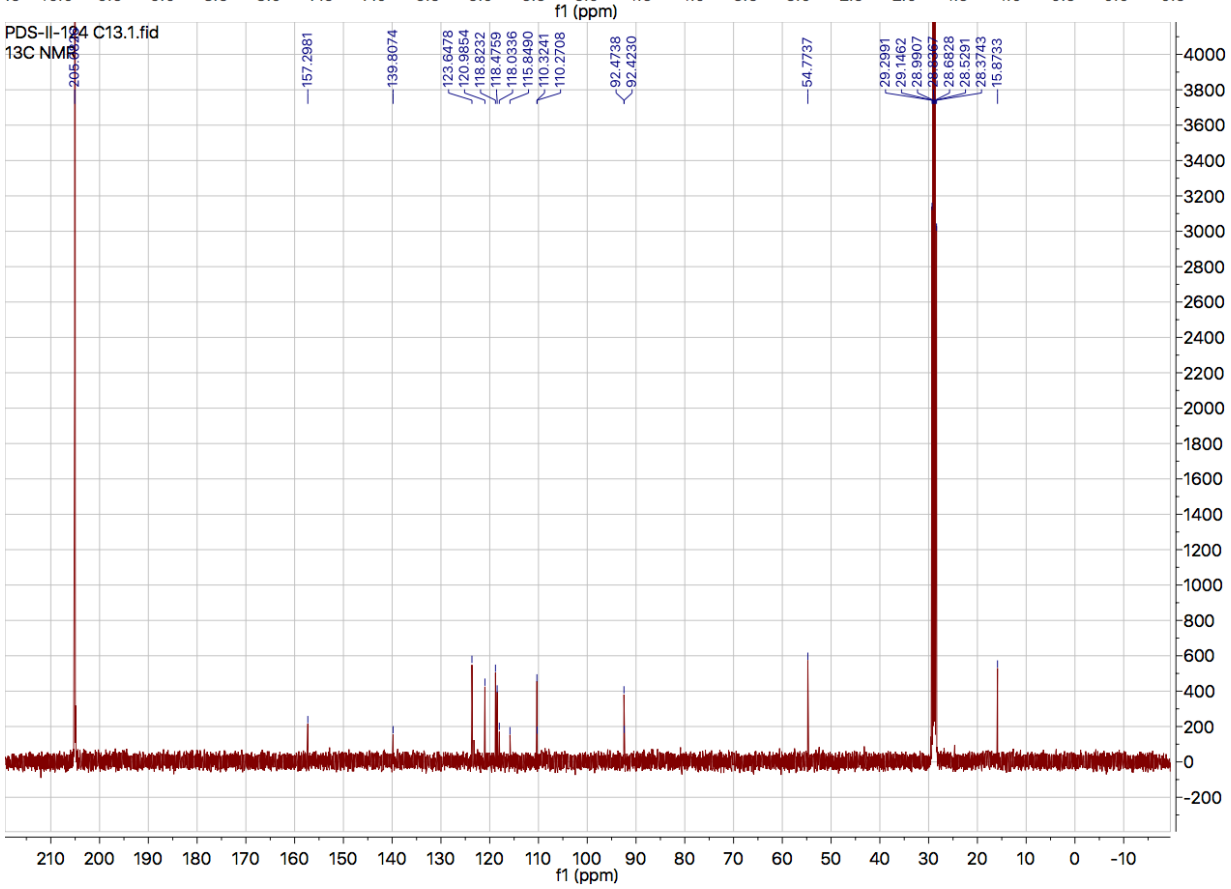
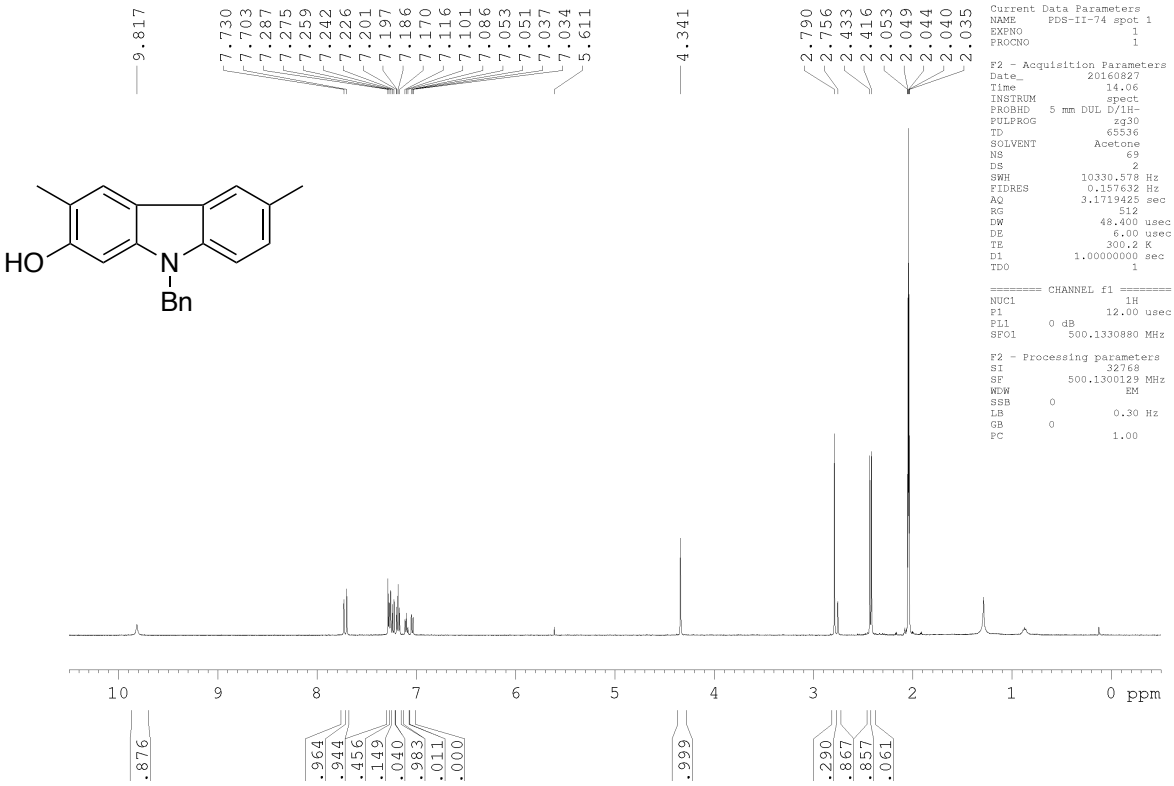
96.505
15.923
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


PDS-II-124.1.fid
1H NMR
with rotation, August 4, 2014
HO
N
f1 (ppm)


PDS-II-124 C13.1.fid
13C NMR
f1 (ppm)



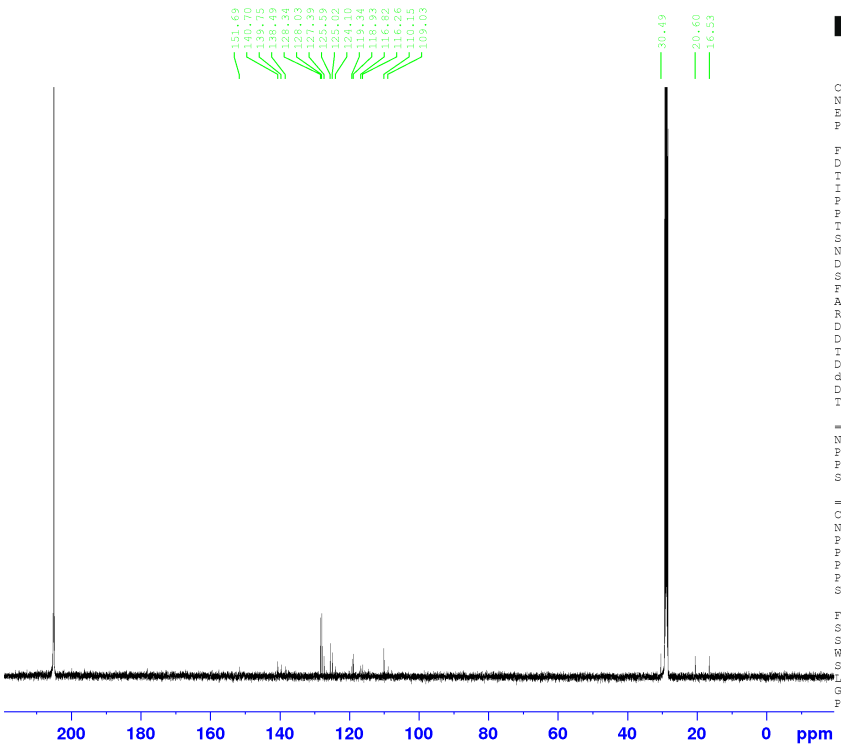

Current Data Parameters
NAME PDS-II-74 spot 1
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160827
Time 14.06
INSTRUM spect
PROBHD 5 mm DUL D/1H-
PULPROG zg30
TD 65536
SOLVENT Acetone
NS 69
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 512
DW 48.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 0 dB
SFO1 500.1330880 MHz

F2 - Processing parameters
SI 32768
SF 500.1300129 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

13C NMR




BRUKER

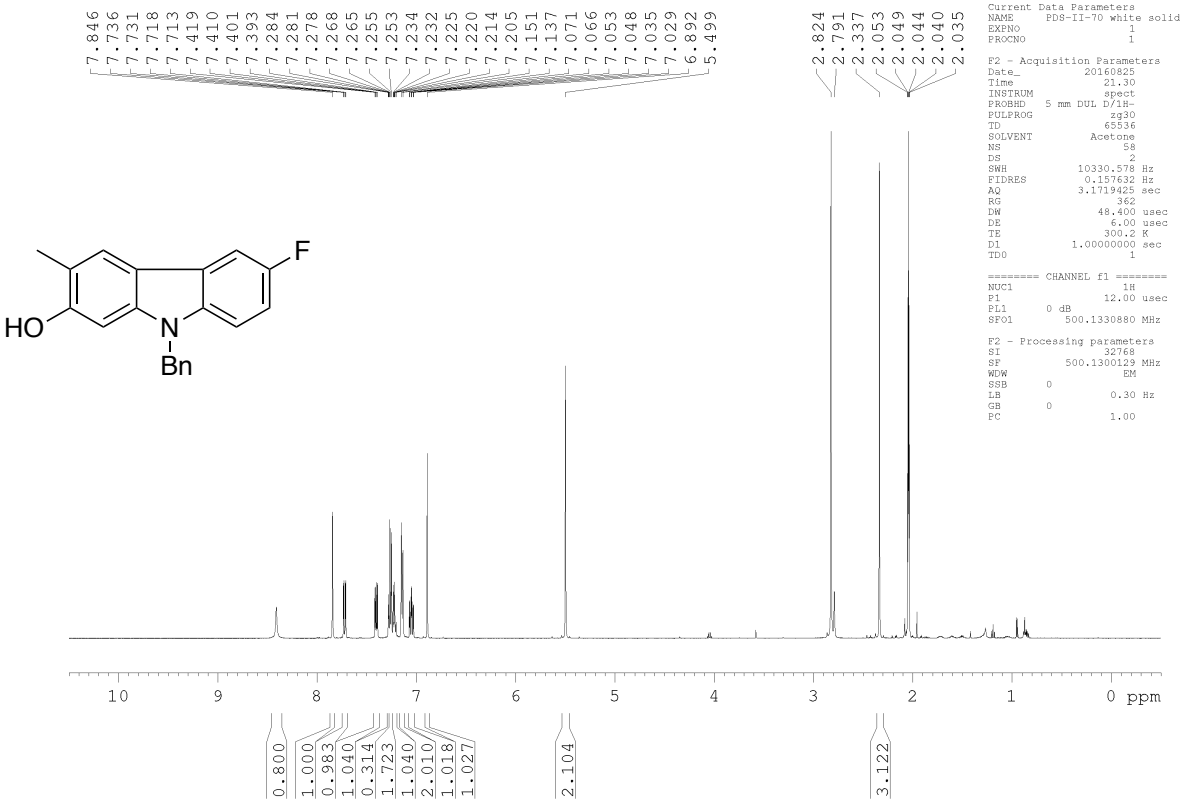
Current Data Parameters
NAME PDS-II-74 spot 1 C13
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160827
Time 14.16
INSTRUM spect
PROBHD 5 mm DUL D/1H-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1874
DS 2
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0911744 sec
RG 18390.4
DW 16.650 usec
DE 6.00 usec
TE 300.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 10.50 usec
PL1 5.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 0 dB
PL12 19.00 dB
PL13 20.00 dB
SFO2 500.1320000 MHz

F2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



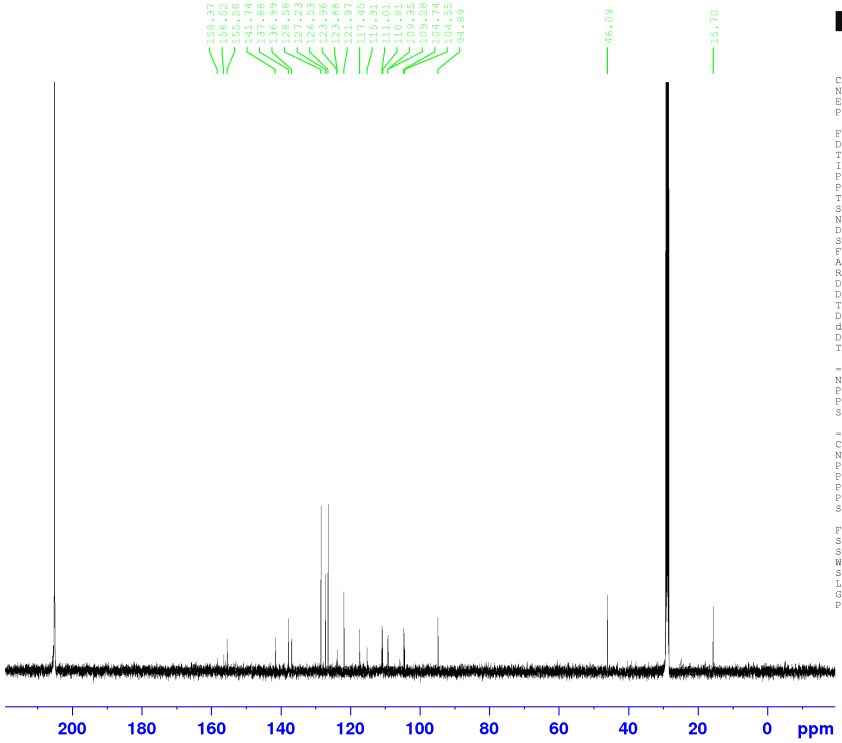

```
Current Data Parameters
NAME      PDS-II-70 white solid
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_           20160825
Time              21.30
INSTRUM           spect
PROBHD    5 mm DUL D/1H-
PULPROG           zg30
TD                65536
SOLVENT         Acetone
NS                   58
DS                    2
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ            3.1719425 sec
RG                  362
DW               48.400 usec
DE                6.00 usec
TE               300.2 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                12.00 usec
PL1        0 dB
SFO1          500.1330880 MHz

F2 - Processing parameters
SI                32768
SF          500.1300129 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

13C NMR



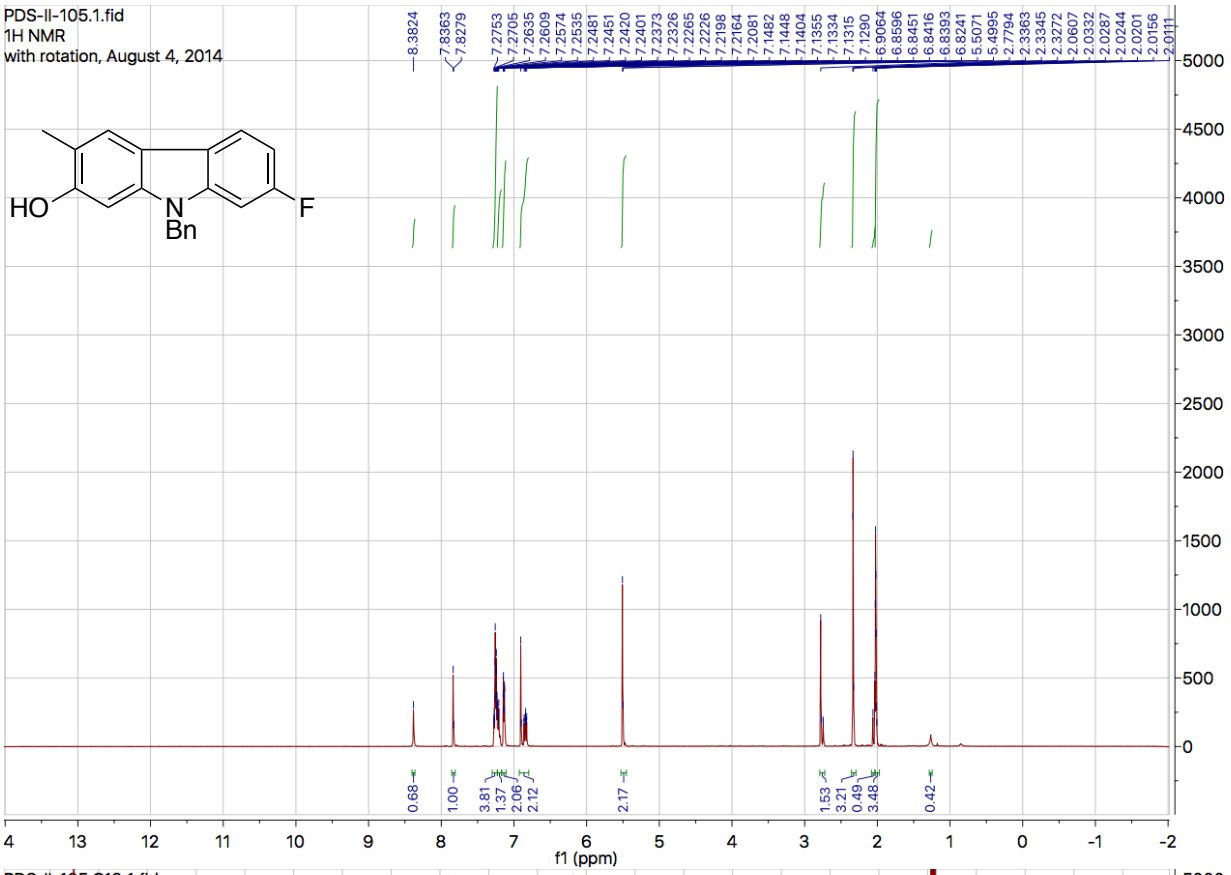

```
Current Data Parameters
NAME      PDS-II-70 white solid C13
EXPNO                 1
PROCNO                1

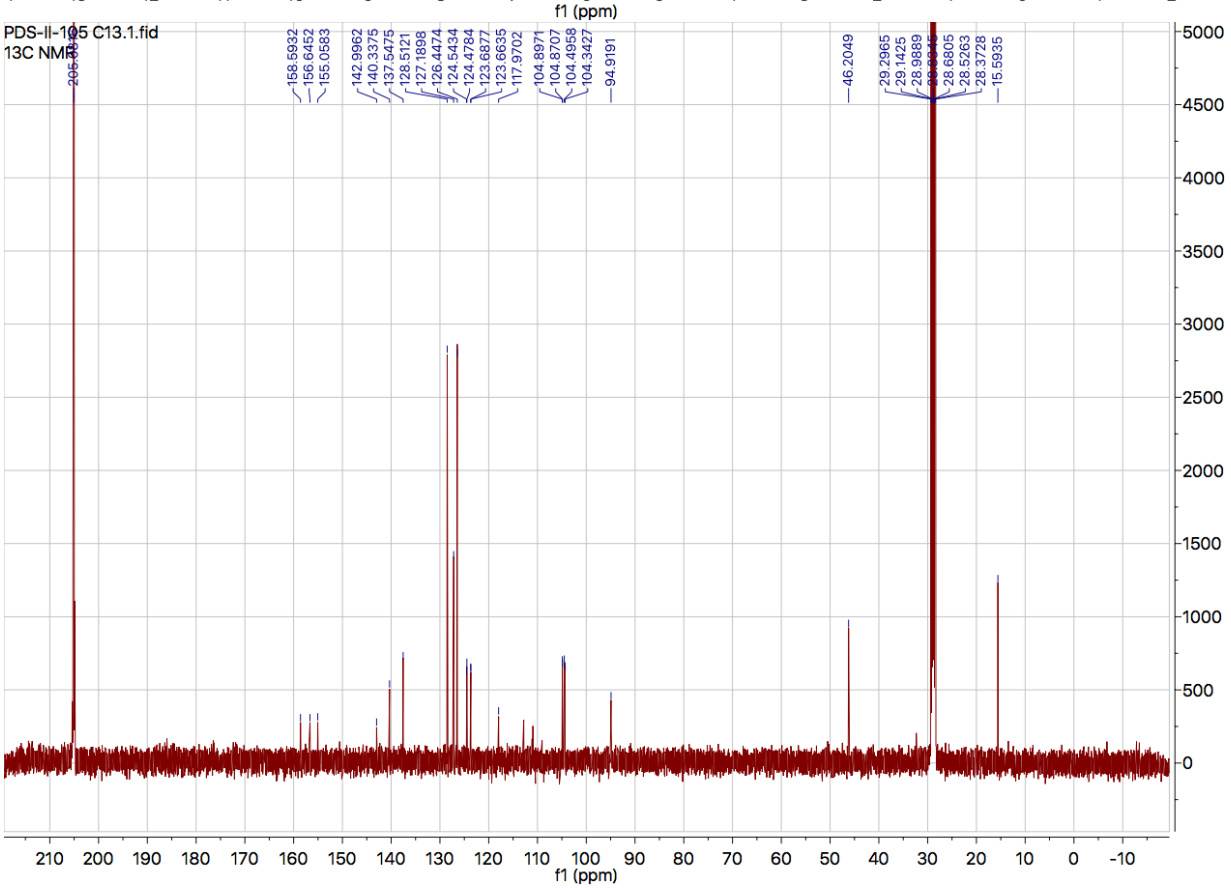
F2 - Acquisition Parameters
Date_           20160825
Time              21.34
INSTRUM           spect
PROBHD    5 mm DUL D/1H-
PULPROG           zgpg30
TD                65536
SOLVENT           CDCl3
NS                  866
DS                    2
SWH           30030.029 Hz
FIDRES         0.458222 Hz
AQ            1.0911744 sec
RG                18390.4
DW               16.650 usec
DE                6.00 usec
TE               300.2 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                   1

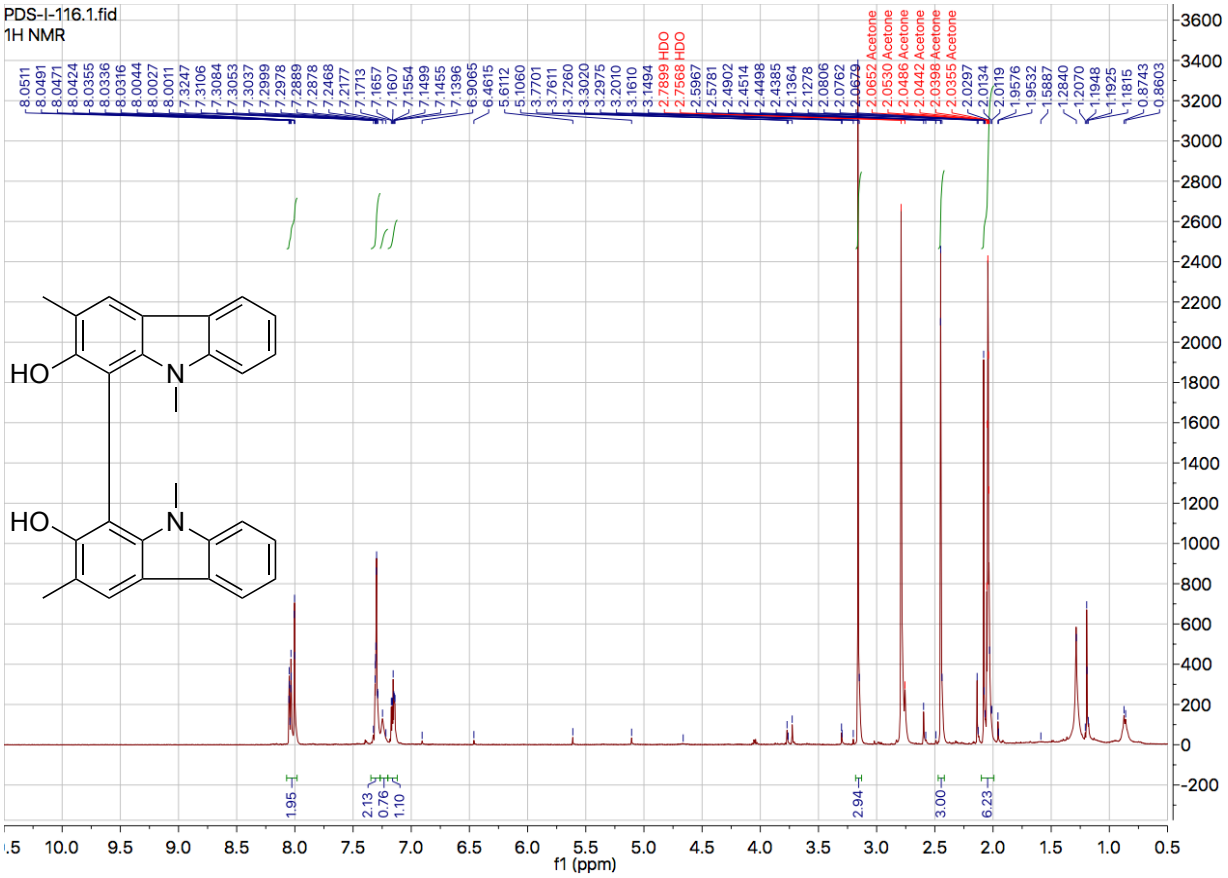
======== CHANNEL f1 ========
NUC1                 13C
P1                10.50 usec
PL1                5.00 dB
SFO1         125.7703640 MHz

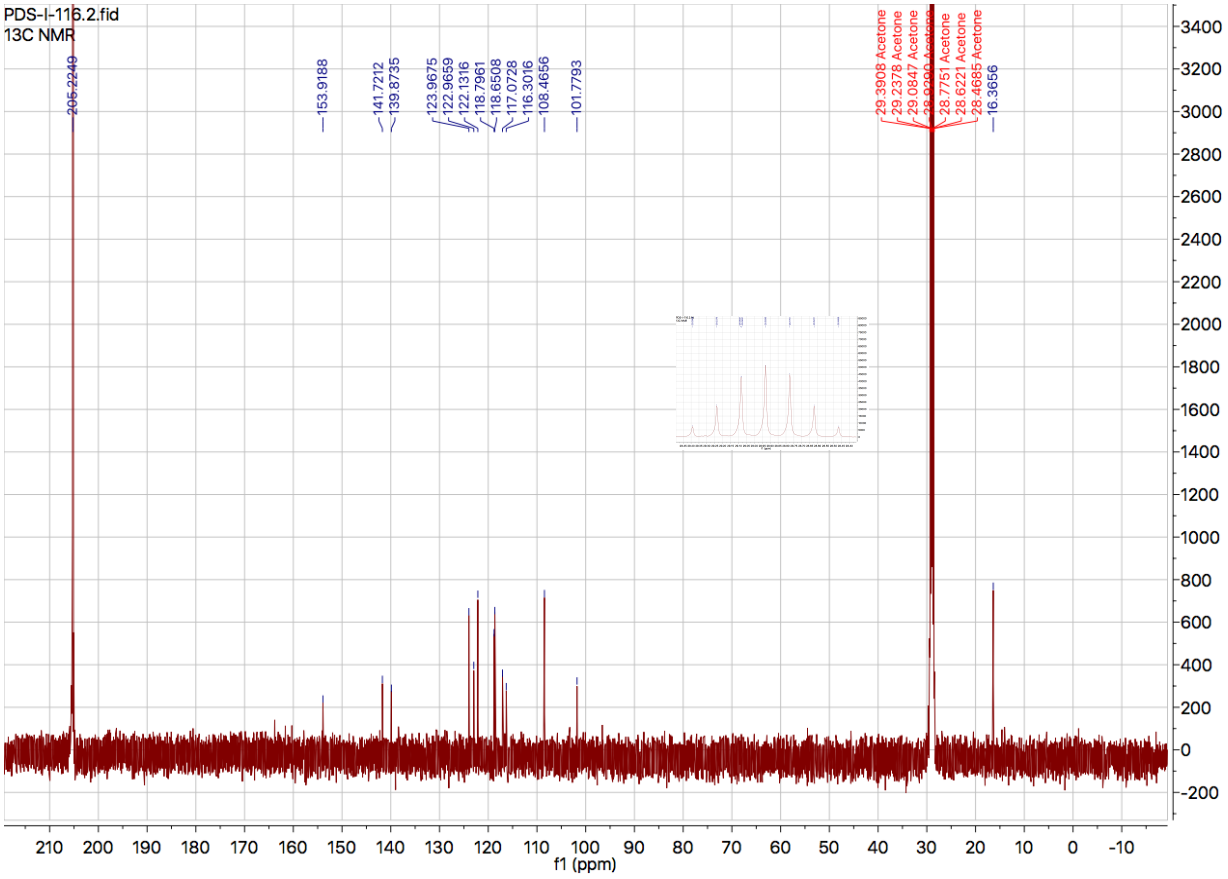
======== CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2        0 dB
PL12              19.00 dB
PL13              20.00 dB
SFO2         500.1320000 MHz

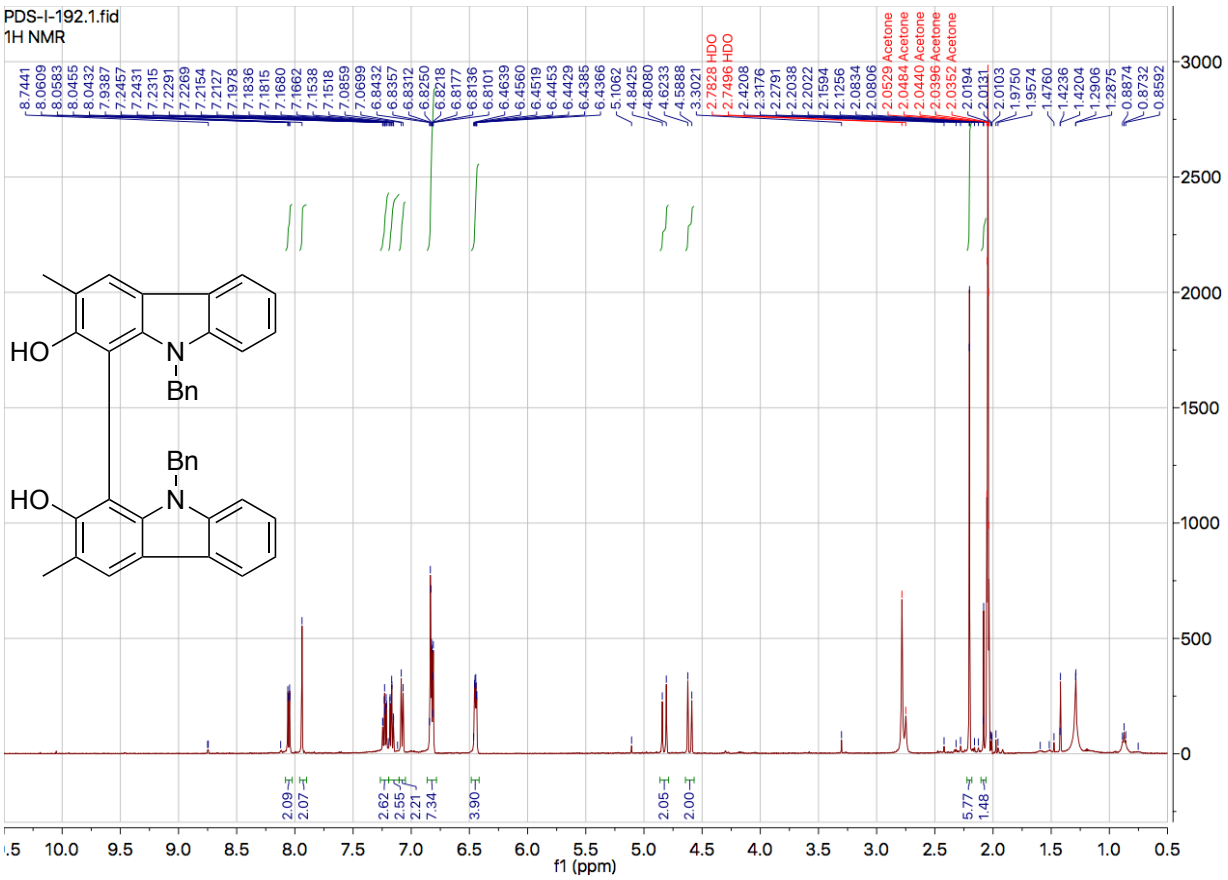
F2 - Processing parameters
SI                32768
SF          125.7577890 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

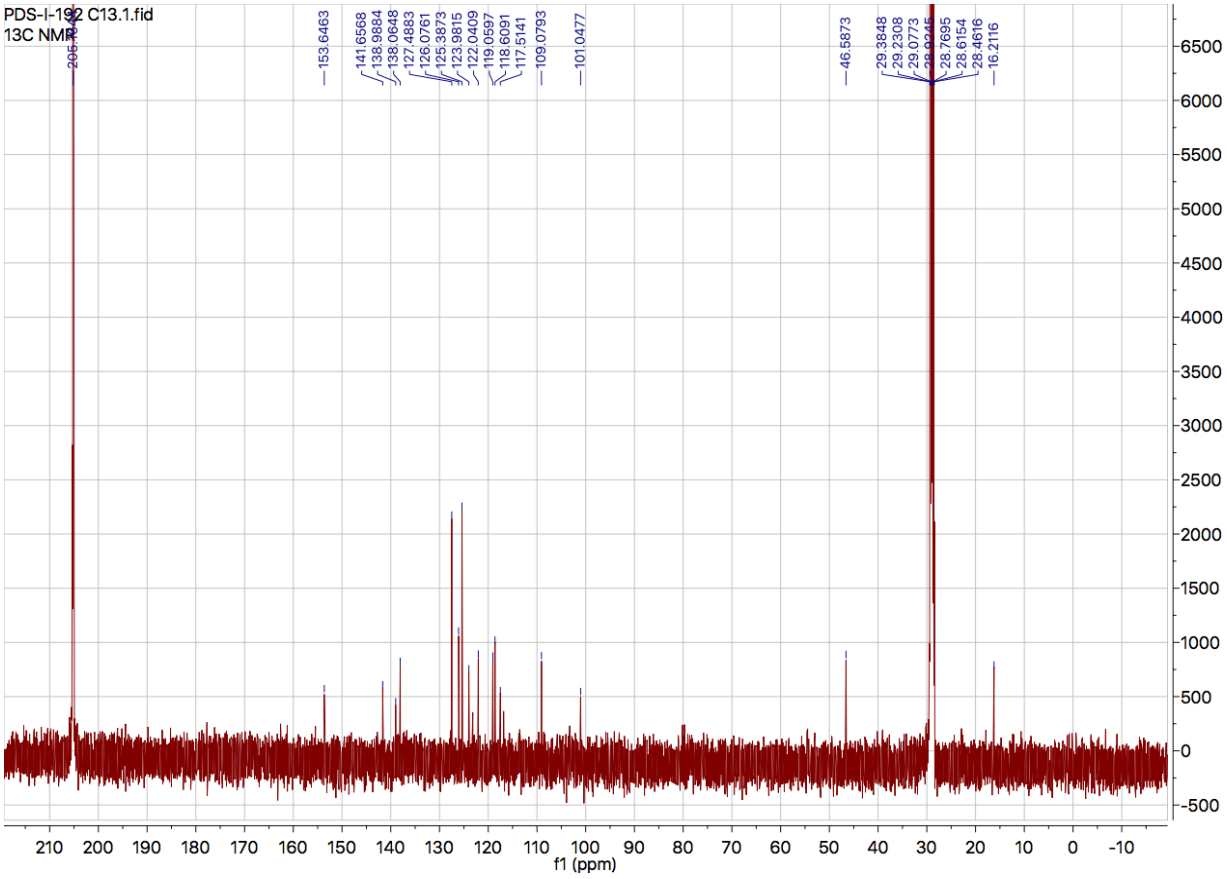

PDS-II-105.1.fid
1H NMR
with rotation, August 4, 2014
HO
N
Bn
F
f1 (ppm)

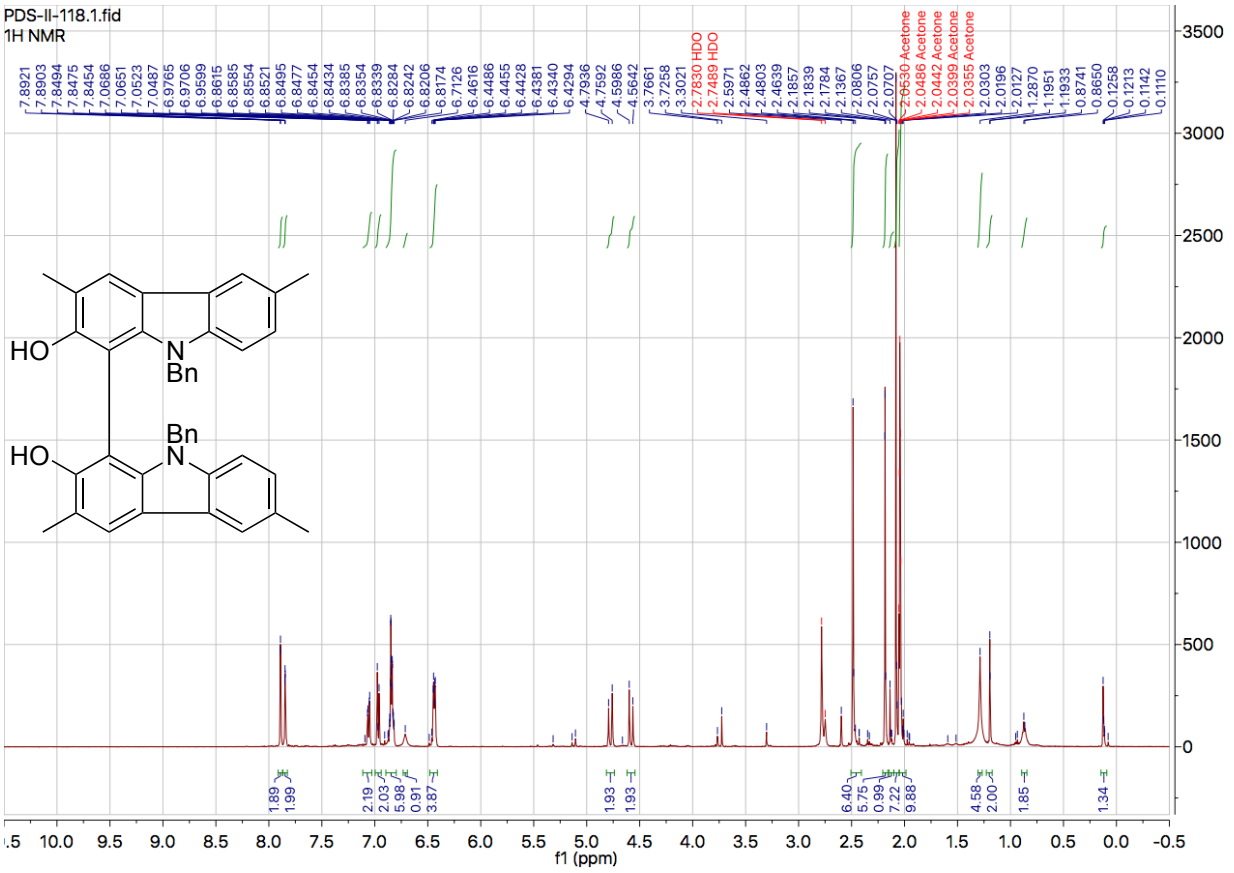

PDS-II-105 C13.1.fid
13C NMR
f1 (ppm)

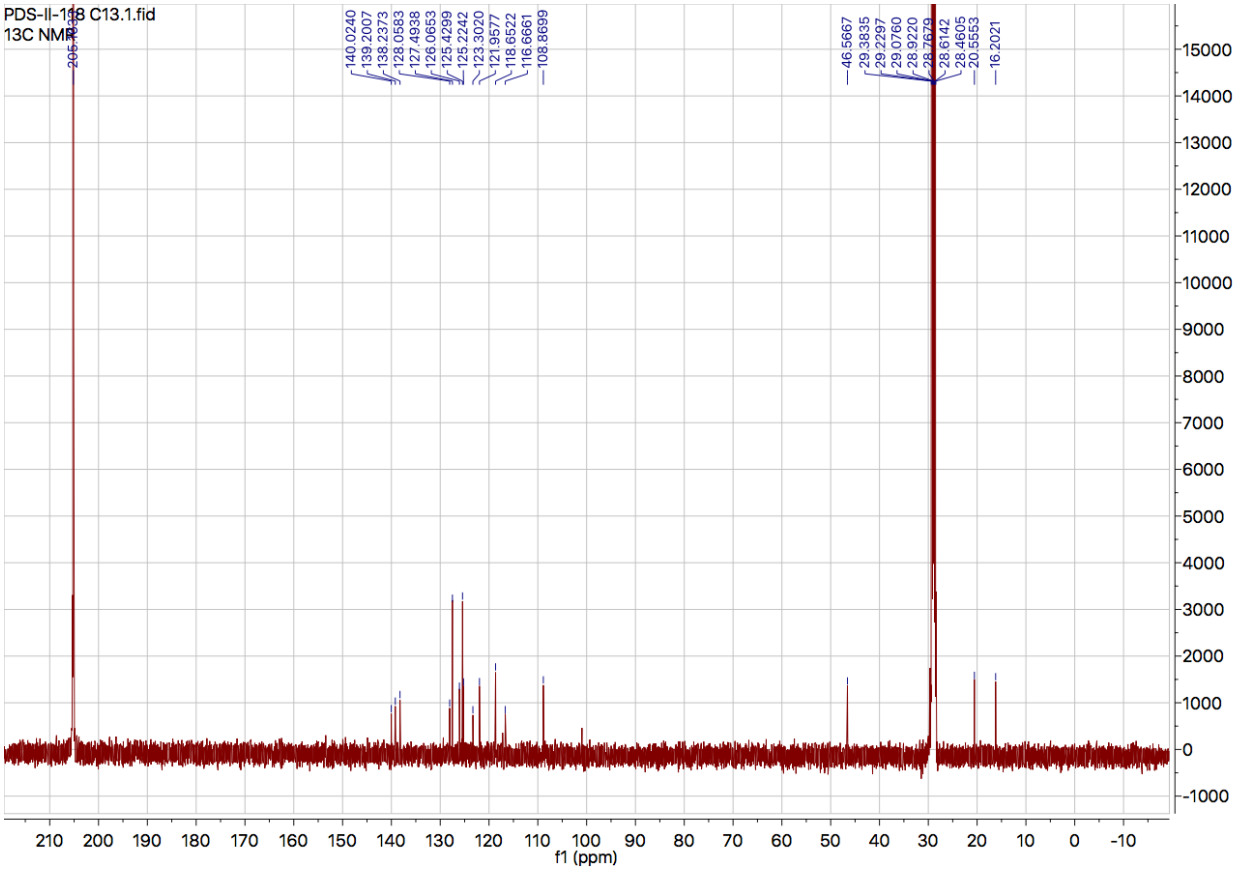

PDS-I-116.1.fid
1H NMR
HO
N
HO
N
f1 (ppm)

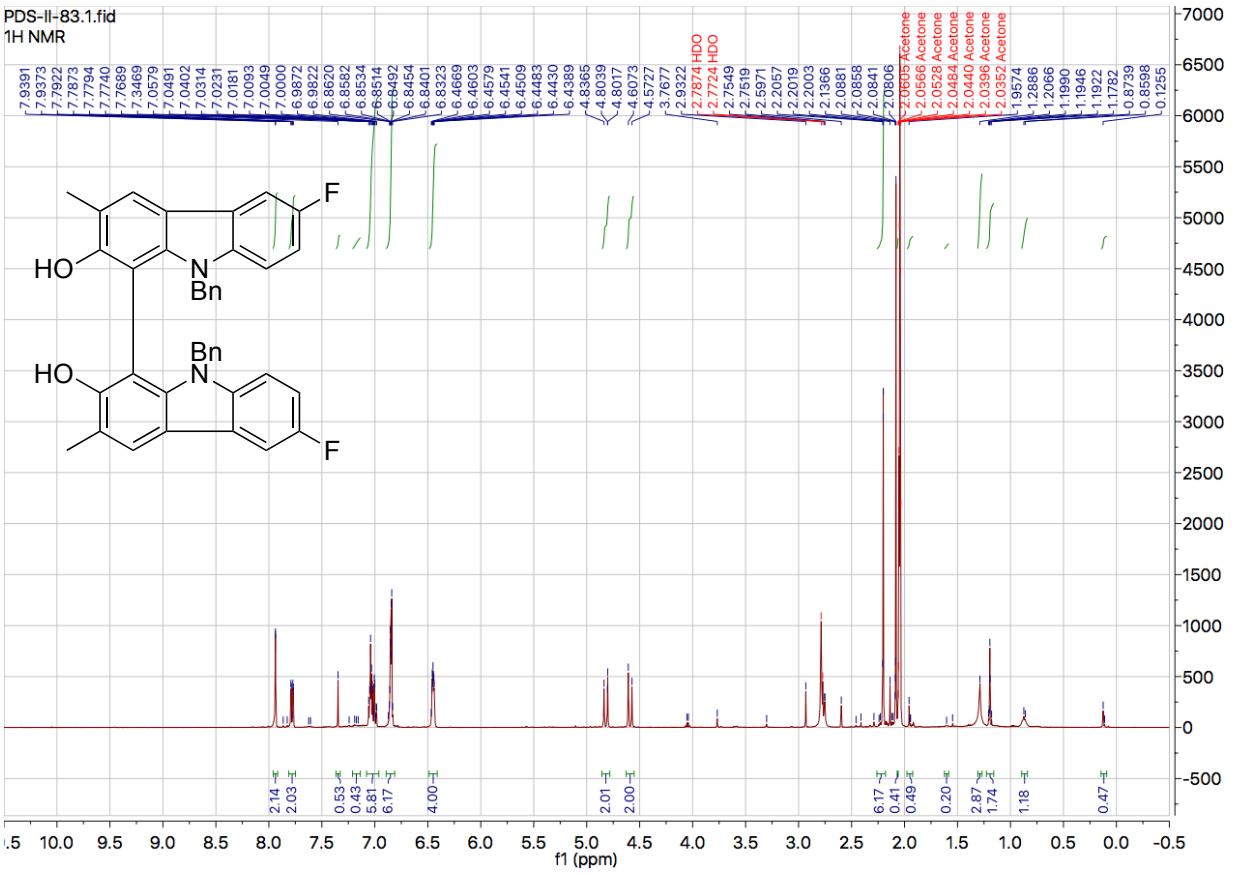

PDS-I-116.2.fid
13C NMR
206.2249
153.9188
141.7212
139.8735
123.9675
122.9659
122.1316
118.7961
118.6508
117.0728
116.3016
108.4656
101.7793
29.3908 Acetone
29.2378 Acetone
29.0847 Acetone
28.7751 Acetone
28.6221 Acetone
28.4685 Acetone
16.3656
f1 (ppm)

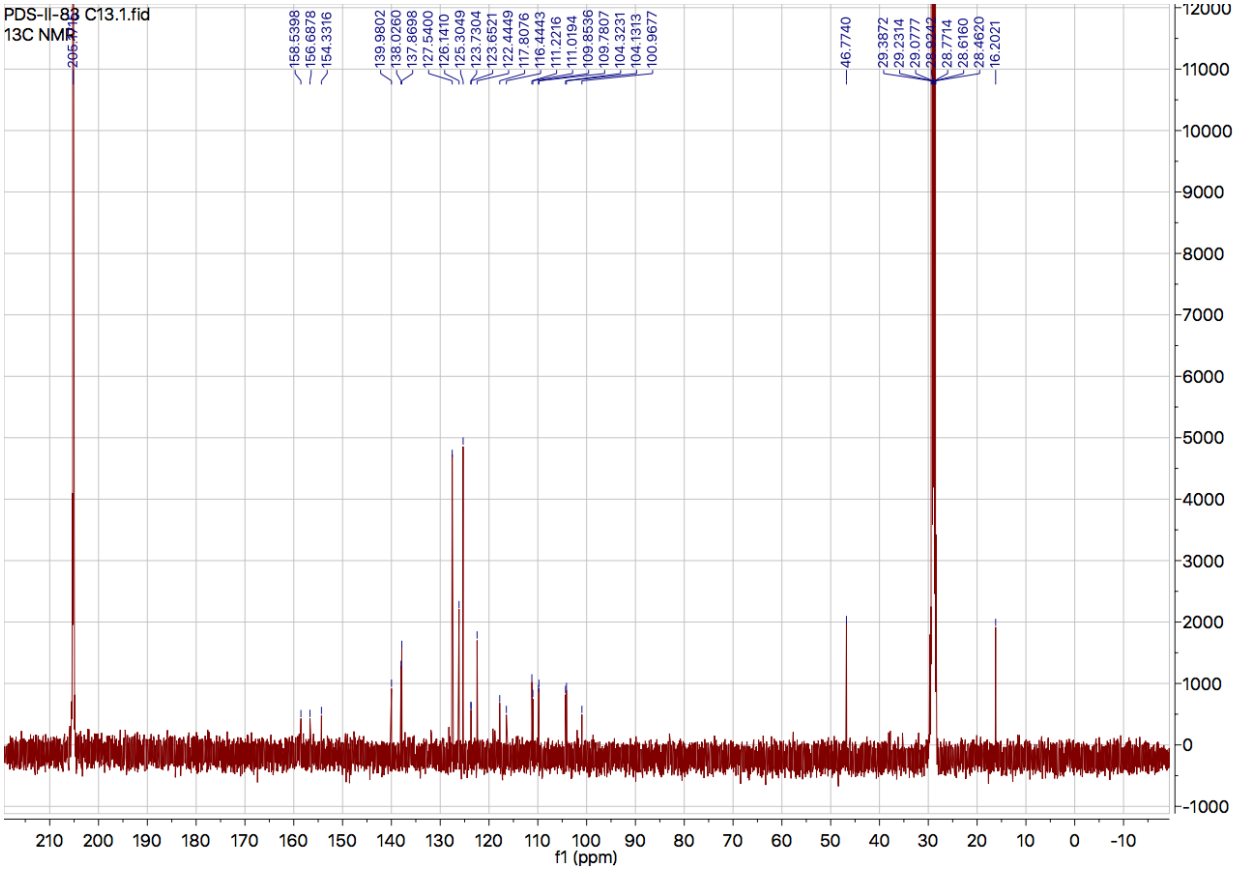

PDS-I-192.1.fid
1H NMR
HO
N
Bn
Bn
HO
N
f1 (ppm)

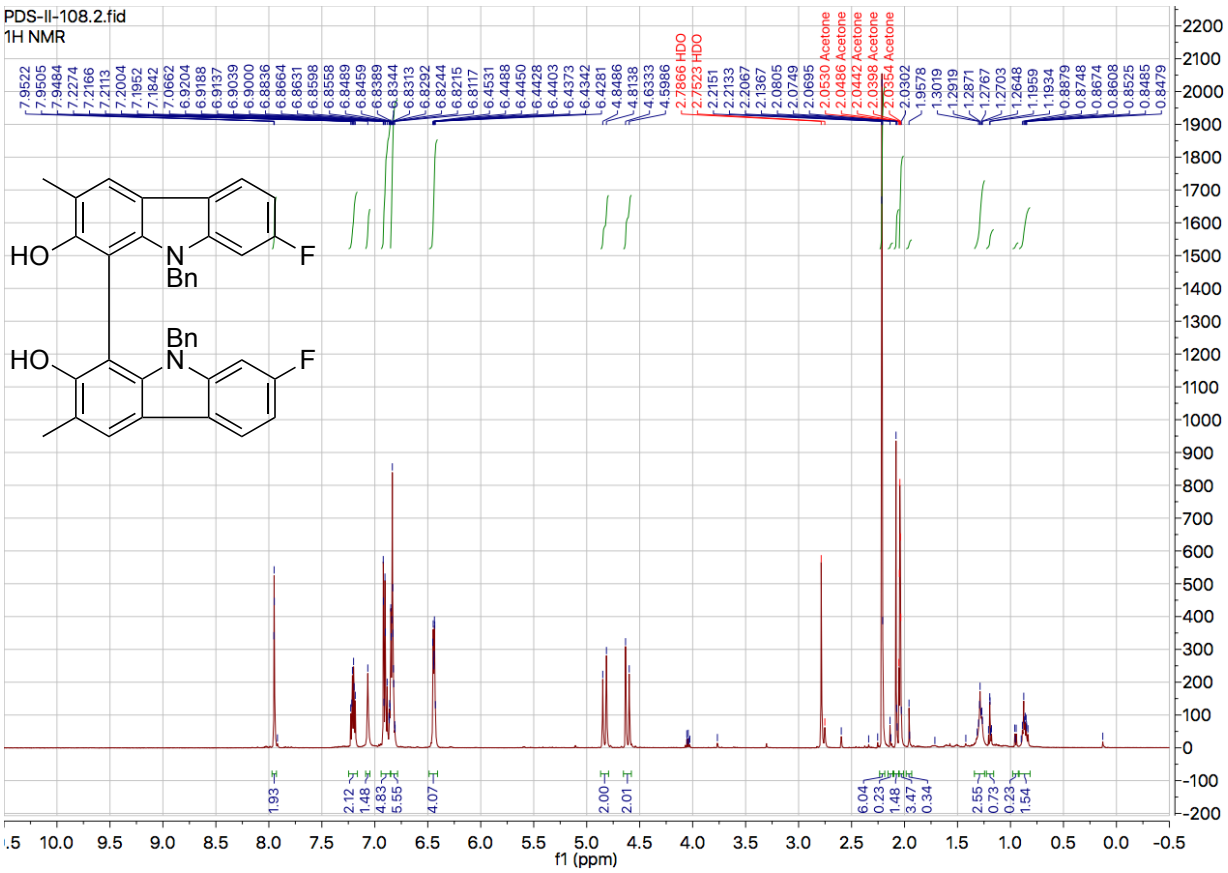

PDS-I-192 C13.1.fid
13C NMR
f1 (ppm)

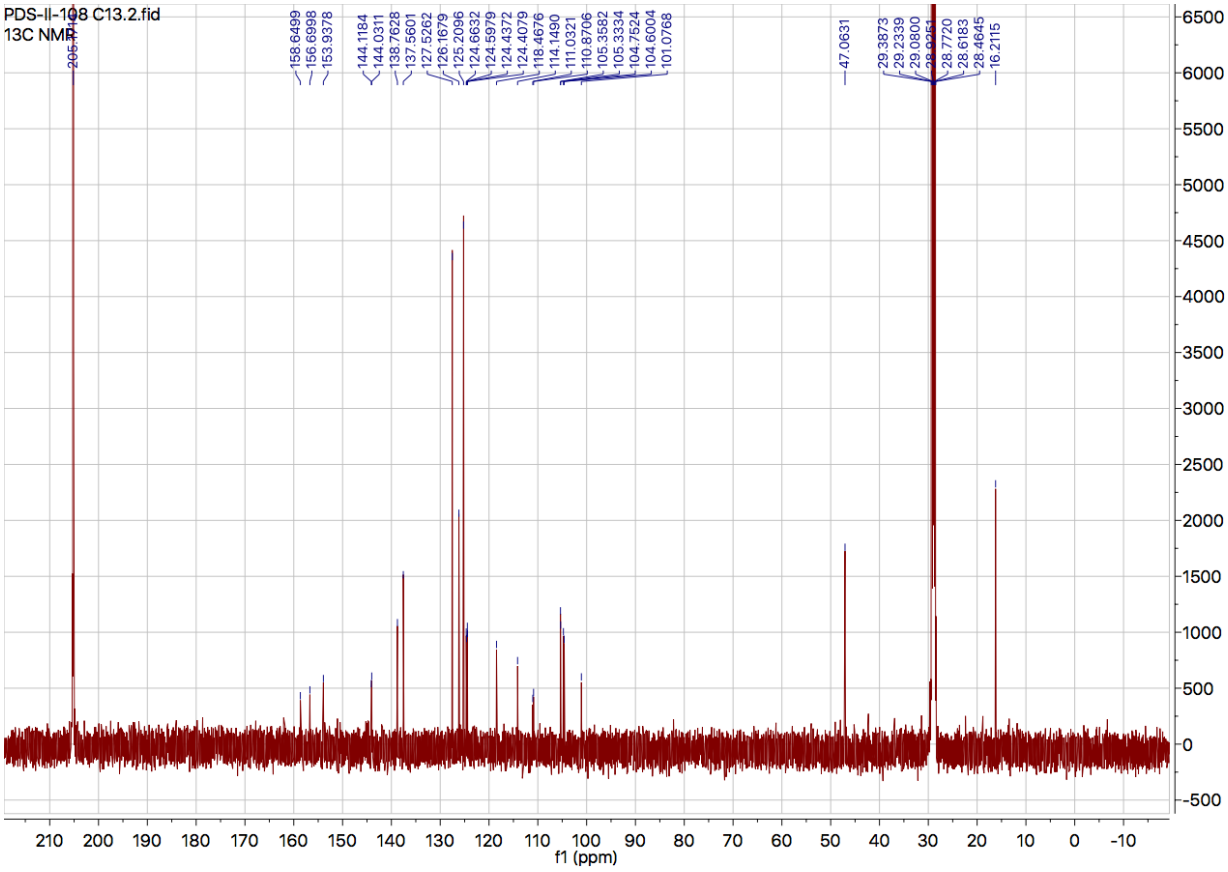

PDS-II-118.1.fid
1H NMR
HO
N
Bn
Bn
HO
N
f1 (ppm)

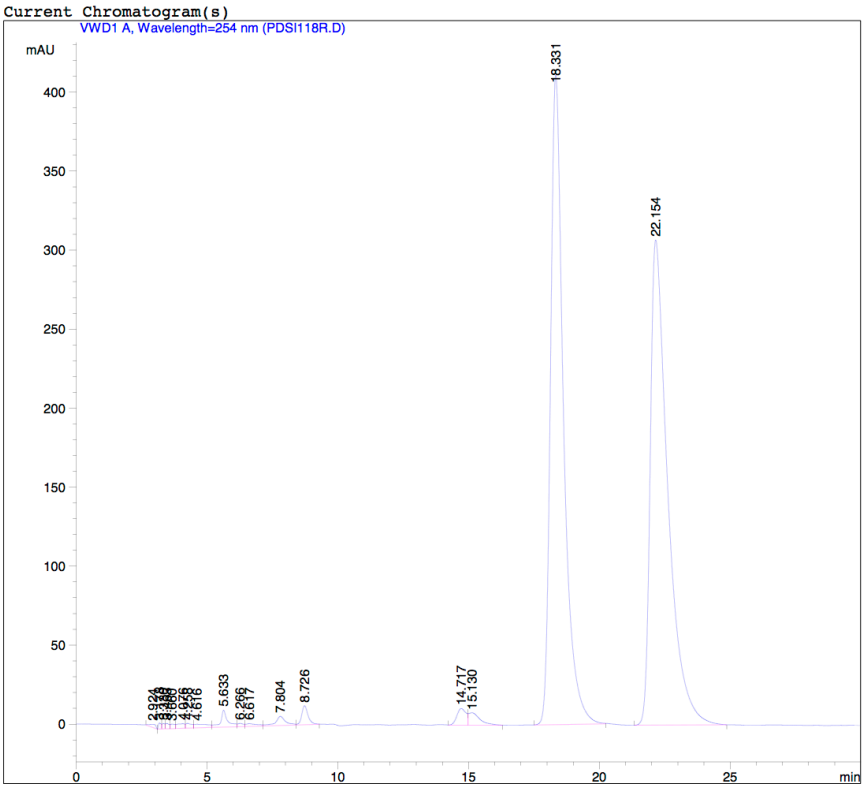

PDS-II-118 C13.1.fid
13C NMR
f1 (ppm)

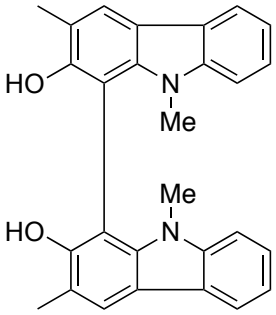

PDS-II-83.1.fid
1H NMR
HO
N
Bn
F
HO
Bn
N
F
f1 (ppm)

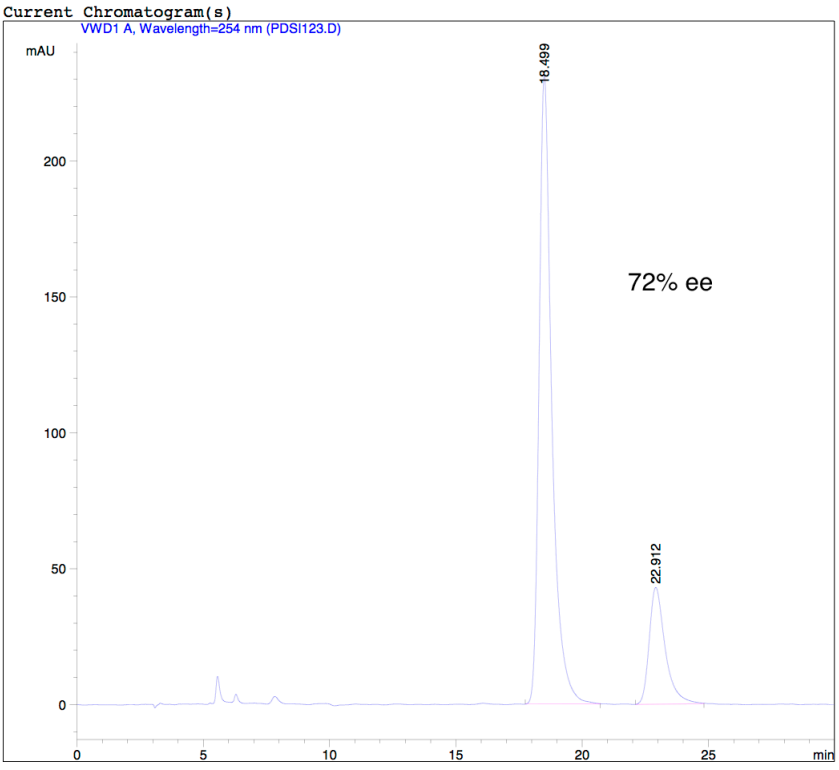

PDS-II-83 C13.1.fid
13C NMR
f1 (ppm)

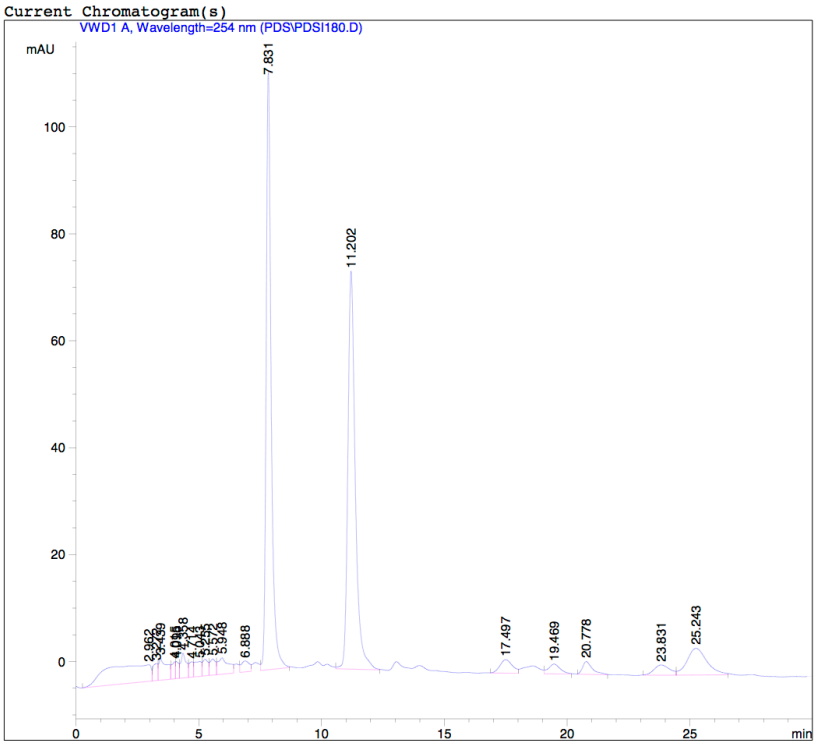

PDS-II-108.2.fid
1H NMR
HO
N
Bn
F
HO
Bn
N
F
f1 (ppm)

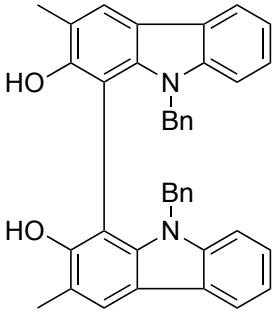

PDS-II-108 C13.2.fid
13C NMR
f1 (ppm)

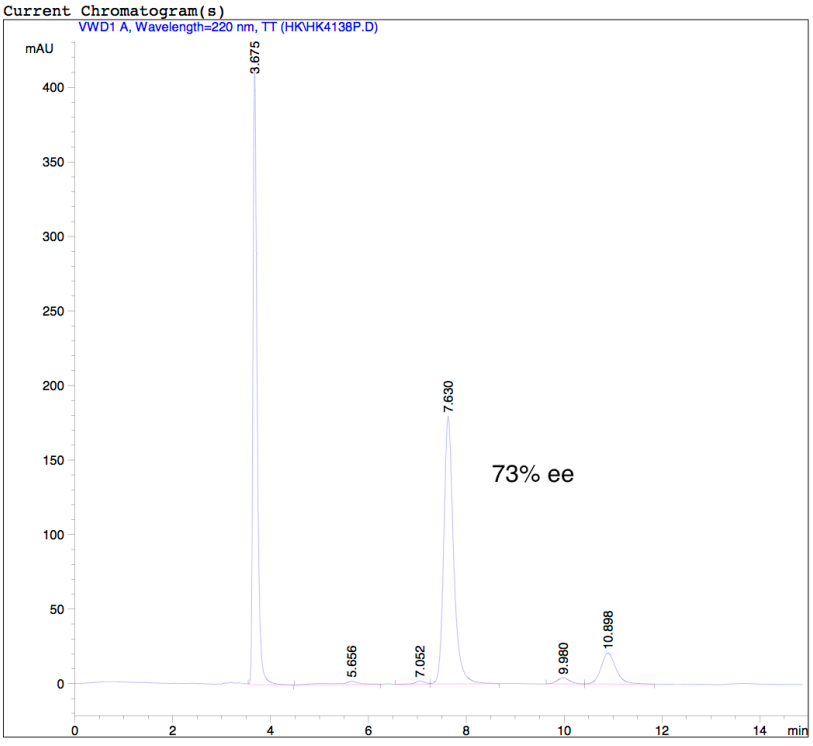

Current Chromatogram(s)
VWD1 A, Wavelength=254 nm (PDSI118R.D)
mAU
400
350
300
250
200
150
100
50
0
18.331
22.154
5.633
6.266
6.617
7.804
8.726
14.717
15.130
0
5
10
15
20
25
min

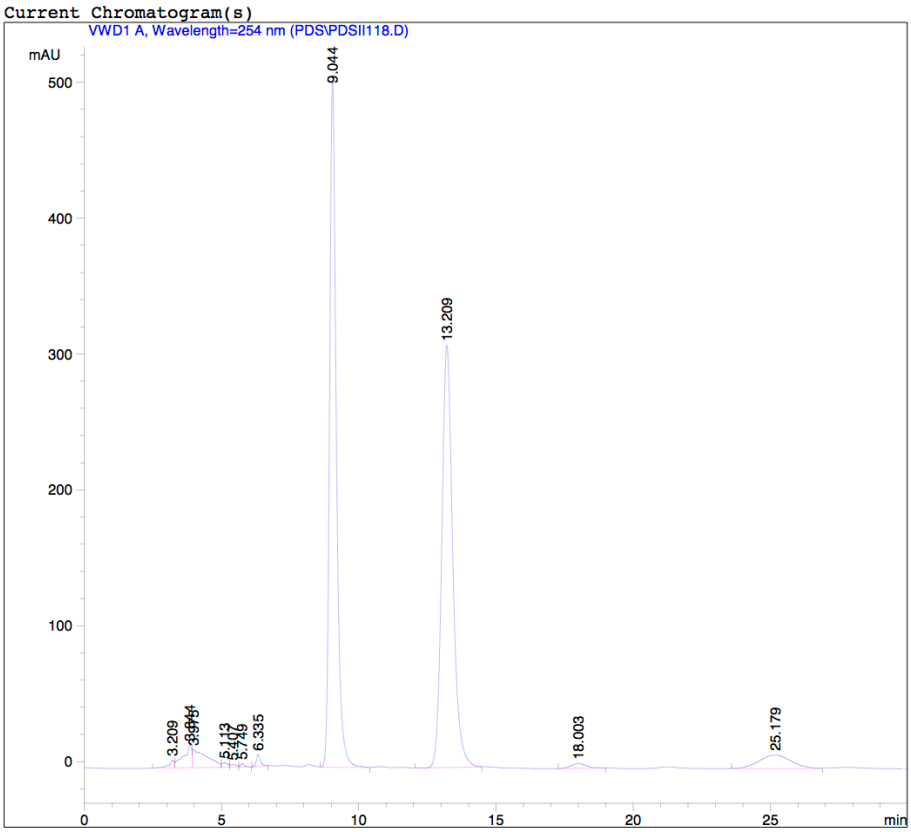

HO
N
Me
Me
HO
N

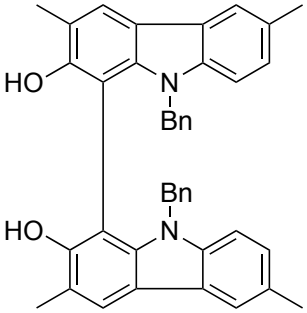

Current Chromatogram(s)
VWD1 A, Wavelength=254 nm (PDSI123.D)
mAU
200
150
100
50
0
18.499
22.912
72% ee
0
5
10
15
20
25
min

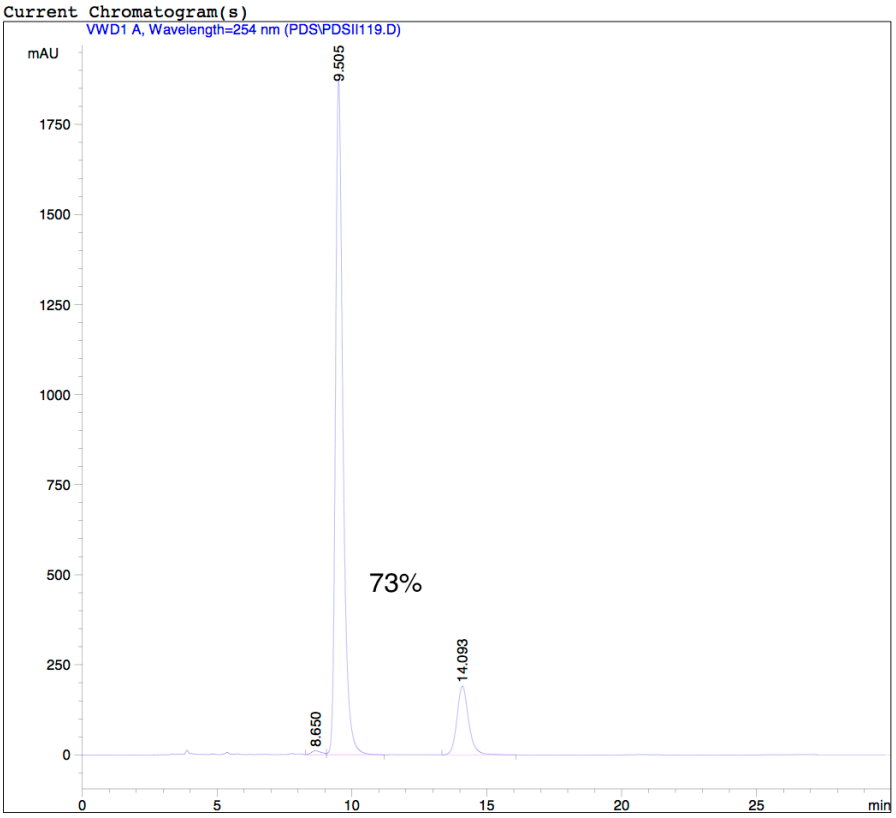

Current Chromatogram(s)
VWD1 A, Wavelength=254 nm (PDS\PDSI180.D)
mAU
7.831
11.202
17.497
19.469
20.778
23.831
25.243
6.888
min

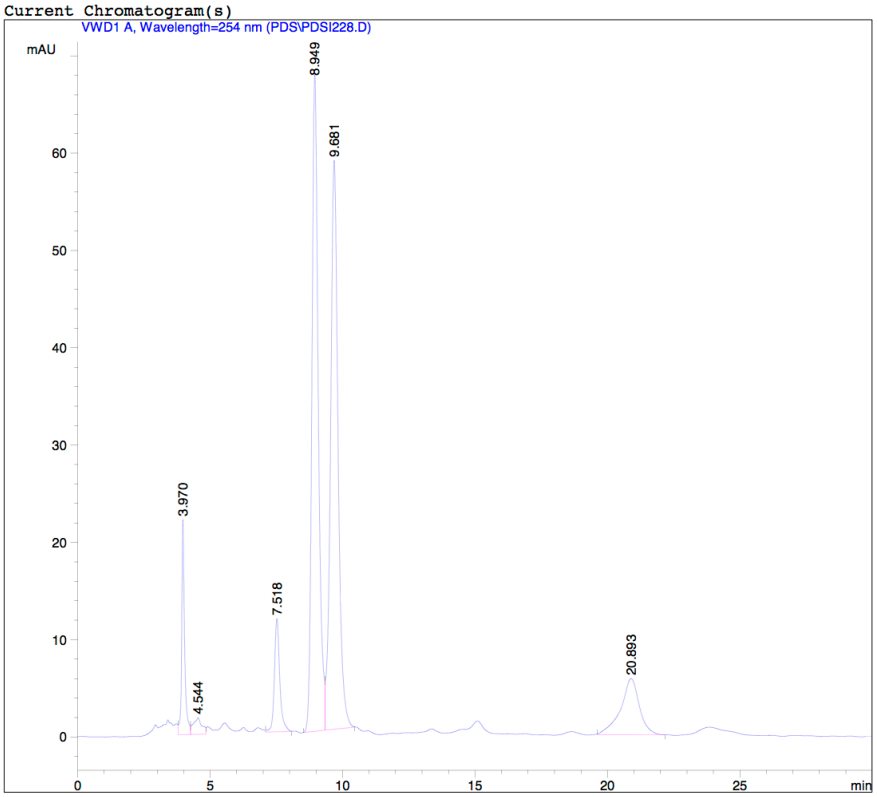

HO
N
Bn
Bn
HO
N

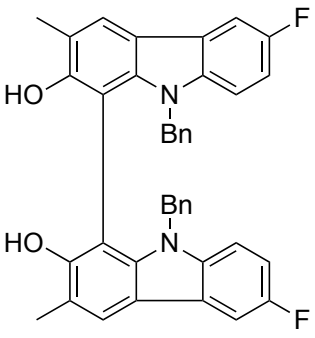

Current Chromatogram(s)
VWD1 A, Wavelength=220 nm, TT (HK\HK4138P.D)
mAU
3.675
7.630
73% ee
5.656
7.052
9.980
10.898
min

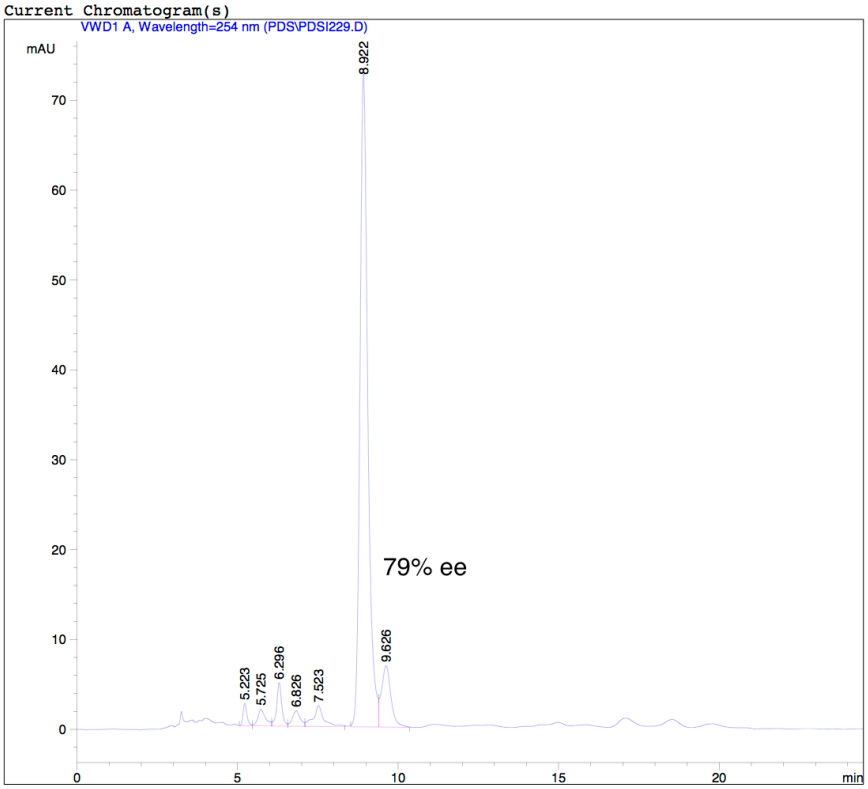

Current Chromatogram(s)
VWD1 A, Wavelength=254 nm (PDS\PDSII118.D)
mAU
9.044
13.209
3.209
6.335
18.003
25.179
min

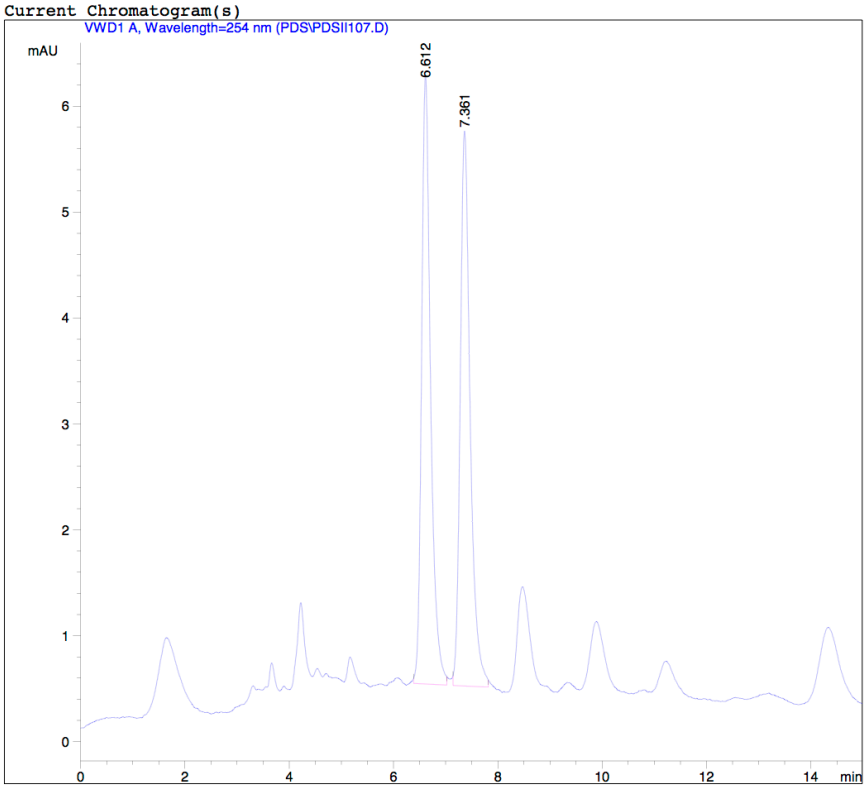

HO
N
Bn
Bn
HO
N

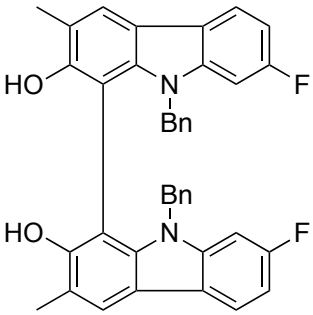

Current Chromatogram(s)
VWD1 A, Wavelength=254 nm (PDS\PDSII119.D)
mAU
9.505
73%
14.093
8.650
min

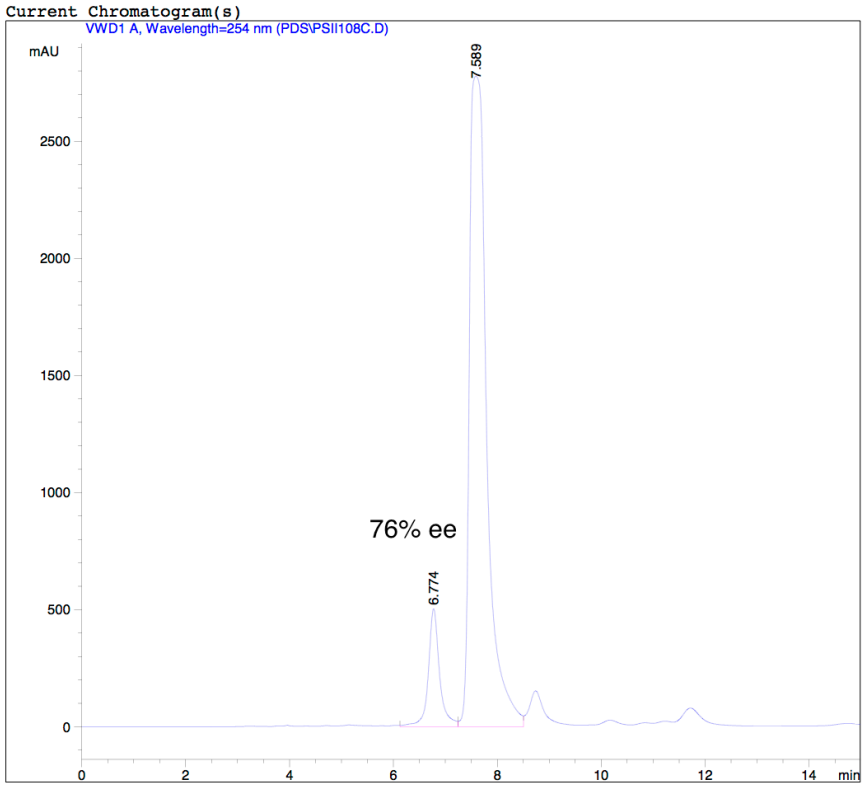

Current Chromatogram(s)
VWD1 A, Wavelength=254 nm (PDS\PDSI228.D)
mAU
8.949
9.681
3.970
7.518
20.893
4.544
min


F
HO
N
Bn
Bn
HO
N
F


Current Chromatogram(s)
VWD1 A, Wavelength=254 nm (PDS\PDSI229.D)
mAU
8.922
79% ee
9.626
5.223
5.725
6.296
6.826
7.523
min


Current Chromatogram(s)
VWD1 A, Wavelength=254 nm (PDS\PDSII107.D)
mAU
6.612
7.361
min


HO
N
Bn
F
Bn
HO
N
F

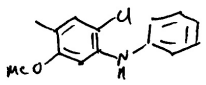

Current Chromatogram(s)
VWD1 A, Wavelength=254 nm (PDS\PSII108C.D)
mAU
7.589
76% ee
6.774
min

Director:
**Rakesh K. Kohli**

**Mass Spectrometry Center**

**Request for Analysis**

Department of Chemistry
University of Pennsylvania
Philadelphia, PA 19104
Phone: (215) 898-8164

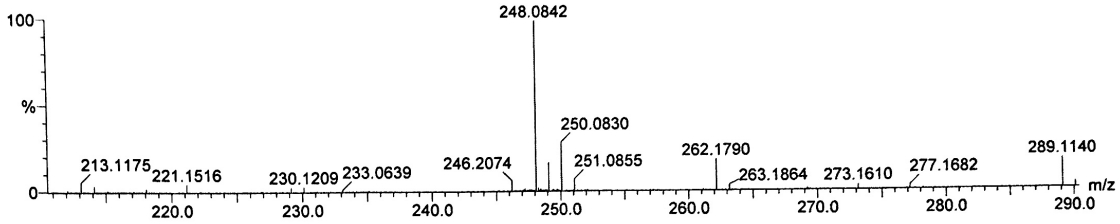
| | |
|---|---|
| Name: Paul Sung | Date: ~~7/25/16~~ 12/4/16 |
| Room: IAST 4070 | Sample Title: PDX-I-~~42~~ 55 |
| Phone: 3-4249 | Formula: $C_{14}H_{14}ClNO$ |
| Professor: Marisa Kozlowski | Purchase Order: |
| Info Required:<br>Low Res.: _____<br>High Res.: ___V___<br>Other: _____ | Molecular Weight ($^{12}C$ standard):<br>FW = 247.7220<br>(Exact Mass from ChemDraw)<br>247.0764 |
| Structure:  | Sample Location:<br>Hood #: ~~XX~~<br>Refrig. #: ~~29~~ 29<br>Freezer: _____<br>Call: _____ |
| Safety Information:<br><br>Harmful: Yes / No<br>If Yes, Specify:<br><br>90 | Solvents: Use / Don't Use<br>MeOH _____ _____<br>$CH_2Cl_2$ _____ _____<br>Hexane _____ _____<br>Acetonitrile _____ _____<br>Other Acetone V _____<br><br>*If in Solution*:<br>Solvent:<br>Approx. Concentration: |
| For MS Lab Use: | Calculated Value: 248.0842<br>Observed Value: 248.0842<br>Error (ppm):<br><br>$[M+H]^+$<br>Sung-Eun |

**Single Mass Analysis**
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
227 formula(e) evaluated with 3 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-200 H: 0-200 N: 0-10 O: 0-13 Cl: 1-1
06-Dec-2016

PDS-I-55 47 (2.333)

1: TOF MS ES+ 1.08e+004



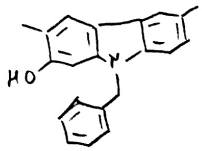

| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 10.0 | 50.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 248.0842 | 248.0842 | 0.0 | 0.0 | 7.5 | 42.0 | C14 H15 N O Cl |
| | 248.0802 | 4.0 | 16.1 | 3.5 | 151.9 | C9 H15 N3 O3 Cl |
| | 248.0874 | -3.2 | -12.9 | -0.5 | 393.8 | C3 H15 N7 O4 Cl |

Director:
**Rakesh K. Kohli**

**Mass Spectrometry Center**

**Request for Analysis**

Department of Chemistry
University of Pennsylvania
Philadelphia, PA 19104
Phone: (215) 898-8164

| | |
|---|---|
| Name: Paul Sung | Date: 7/25/16 |
| Room: IAST 4070 | Sample Title: PPS-II-74 |
| Phone: 3-4249 | Formula: $C_{21}H_{19}NO$ |
| Professor: Marisa Kozlowski | Purchase Order: |
| Info Required:<br>Low Res.: _____<br>High Res.: V<br>Other: _____ | Molecular Weight ($^{12}C$ standard):<br>FW = 301.3890<br>(Exact Mass from ChemDraw)<br>301.1467 |
| Structure:  | Sample Location:<br>Hood #: V<br>Refrig. #: 12<br>Freezer: _____<br>Call: _____ |
| Safety Information:<br>Harmful: Yes / No<br>If Yes, Specify:<br>113 | Solvents: Use / Don't Use<br>MeOH _____ / _____<br>$CH_2Cl_2$ _____ / _____<br>Hexane _____ / _____<br>Acetonitrile _____ / _____<br>Other Acetone V / _____<br>*If in Solution*:<br>Solvent:<br>Approx. Concentration: |
| For MS Lab Use: | Calculated Value: 302.1545<br>Observed Value: 302.1545<br>Error (ppm):<br>$[M+H]^+ < 5$ ppm |

## Elemental Composition Report



### Single Mass Analysis

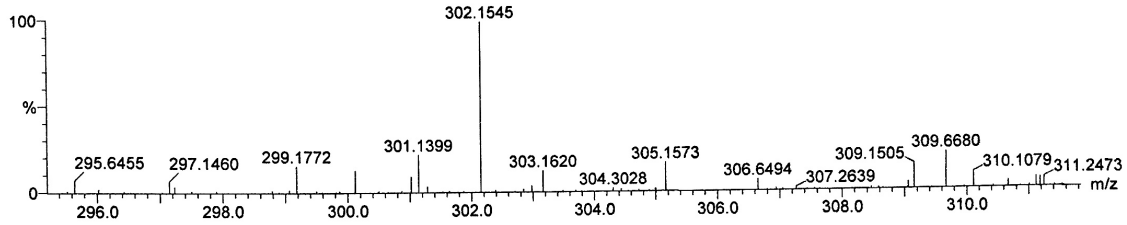
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 80.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
740 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-52 H: 0-70 B: 0-3 N: 0-4 O: 0-4 Cl: 0-1
01-Sep-2016

PaulS_2_74 57 (2.823)

1: TOF MS ES+

1.05e+003




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 5.0 | 80.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 302.1545 | 302.1545 | 0.0 | 0.0 | 12.5 | 40.3 | C21 H20 N O |