NICKEL CATALYZED BORYLATION AND CROSS-COUPLING OF REPRESENTATIVE C-O BASED ELECTROPHILES

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Dedicated to My Family

ACKNOWLEDGMENT

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ABSTRACT

NICKEL CATALYZED BORYLATION AND CROSS-COUPLING OF REPRESENTATIVE C-O BASED ELECTROPHILES

Na Zhang

Virgil Percec

The Suzuki-Miyaura cross-coupling is widely used in the synthesis of pharmaceuticals, agrochemicals, and organic light-emitting materials. Utilization of phenol derivatives in Suzuki-Miyaura coupling is economically, environmentally and synthetically desired. Nickel is less expensive, and more reactive than Pd in activation of inert C-Cl and C-O bonds. Replacing Pd catalysts with Ni in the borylation and cross-coupling of aryl halides and representative C-O based electrophiles provides inexpensive and efficient access to biaryl moieties.

In Chapter 2, the nickel catalyzed neopentylglycolborylation of *ortho*-substituted aryl halides was achieved by zero-valent metals accelerated $NiCl_2$(dppp)/dppf mixed-ligand system. As a result of the fast borylation reaction, an enhancement of the yield of *ortho*- and *para*-substituted aryl halides catalyzed by nickel was achieved.

In Chapter 3, $Ni(COD)_2/PCy_3$ catalyzed cross-coupling of aryl and heteroaryl mesylates and sulfamates with aryl and heteroaryl neopentylglycolboronates in THF at room temperature was discussed. Meanwhile, the efficiencies of six different phenol derivatives, namely mesylates, sulfamates, pivalates, carbamates, carbonates and methyl ethers were compared in four different nickel-based cross-coupling reaction conditions. Aryl mesylates and sulfamates were the most reactive under $Ni(COD)_2/PCy_3/K_3PO_4$/THF catalytic condition, producing quantitative yields. The conditions developed for cross-coupling of aryl pivalates, sulfamates, carbamates and carbonates with arylboronic acids are not efficient for cross-coupling with aryl neopentylglycolboronates. The

efficiencies of four aryl-boron nucleophiles in the Ni-catalyzed coupling of aryl halides, mesylates and sulfamates were compared. Aryl-boronic acids are much more reactive than aryl neopentylglycolboronates in nickel-catalyzed Suzuki-Miyaura cross-coupling in THF. Aryl neopentylglycolboronates were demonstrated to be more reactive and less expensive than currently used pinacol boronates and cross-couple quantitatively.

In Chapter 4, a bench stable and inexpensive $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2/PCy_3$ mixed-ligand catalytic system was developed as a more accessible alternative to the air-sensitive $Ni(COD)_2/PCy_3$ catalytic system. Further development of a library containing ten air-stable $Ni^{II}X(Aryl)(PCy_3)_2$ precatalysts (X = Cl, Br, OTs, OMs, Aryl = 1-naphthyl, 2-naphthyl; X = Cl, Aryl = 1-acenaphthenyl, 1-(2-methoxynaphthyl), 9-phenanthrenyl, 9-anthracyl) has enabled quantitative cross-coupling of aryl sulfamates with aryl neopentylglycolboronates at 23 °C in less than 60 min.

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1.1 Nickel Catalyzed Suzuki-Miyaura Cross-Coupling of Phenol Derivatives

Biaryl structures are important building moiety in material science, as they can be applied in functional macromolecule and supramolecular structures.[1-6] Methods to synthesize biaryl structures include Ullmann type homocoupling[6-13] and cross-coupling methods.[1,6,14-17] We selected Suzuki-Miyaura cross-coupling reaction to construct biaryl structures[6,18] because of the bench-stability, commercial availability, functional group tolerance and low toxicity of boron reagents.[18-20] Traditional Suzuki-Miyaura cross-coupling applies Pd catalysts, aryl halides or triflates and boronic acids.[1,6,21-24] Unlike aryl halides, phenol derivatives show both *ortho* selectivity by directed *ortho* metalation and a *para* directing effect by electronic aromatic substitution.[25] Moreover, phenols and enols are naturally abundant.[6] The reactivity difference of C-O leaving groups with halides provides the potential for orthogonal reaction conditions.[26] However, expensive ligands are needed to cross-couple aryl tosylates, mesylates and sulfamates using Pd catalysts.[27] Nickel, not only less expensive than Pd, but less electronegative than Pd, is more reactive toward C-O bonds. Since our first report on $NiCl_2$(dppf) catalyzed cross-coupling of aryl sulfonates with arylboronic acids in the presence of Zn in 1995, great advances has been made on nickel catalyzed Suzuki-Miyaura cross-coupling reactions of phenol derivatives.[28] The advancement can be divided into two parts, Ni^{II} as a catalyst precursor and Ni^0 as a catalyst source.

1.1.1 Ni^{II} Catalysts in Suzuki-Miyaura Cross-Coupling of Phenol Derivatives

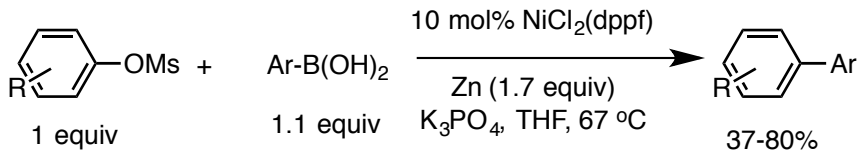
Ni^{II} catalysts are bench-stable but their activation generally requires reducing reagents.[29] The first attempt of nickel catalyzed Suzuki-Miyaura cross-coupling reactions of phenol derivatives applied $Ni^{II}Cl_2$(dppf). Inspired by the successful homocoupling of aryl mesylates with Ni^{II} catalysts,[28] Percec proposed the oxidative addition of aryl mesylates with Ni^0 was feasible.[28] Applying $Ni^{II}Cl_2$(dppf), similarly to $Pd^{II}Cl_2$(dppf), which was the most reactive Pd catalyst at that moment, aryl sulfonates were cross-coupled efficiently in the presence of Zn.[28] The use of Zn was crucial,

as no cross-coupling product was observed when the reaction was carried out in the absence of Zn.[28] Powdered K_3PO_4 was selected instead of aqueous K_2CO_3 to avoid the hydrolysis of sulfonates by aqueous base (Scheme 1.1).[28]

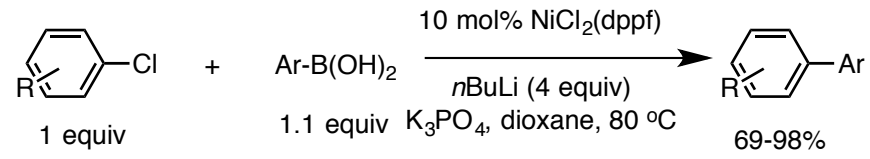
Similarly to our approach, Miyaura group reported the cross-coupling reaction of aryl chlorides with arylboronic acids catalyzed by Ni^0 *in situ* generated from reduction of $Ni^{II}Cl_2L$ by *n*-butyllithium prior to use.[30,31] This strategy was also applied to the synthesis of biaryls from aryl mesylates and arylboronic acids in toluene at 100 °C.[32] A range of $Ni^{II}Cl_2L$ (L = dppf, dppp, PCy_3, PPh_3, dppe) complexes were examined. $Ni^{II}Cl_2$(dppf) was found to be the most reactive. Electron-rich mesylates are less reactive compared to electron-deficient aryl mesylates, presumably due to the higher oxidative addition activation energy for electron-rich mesylates (Scheme 1.1).[32,33] Cross-coupling reactions catalyzed by Ni^0 supported on active charcoal, which was reduced from Ni^{II} by *n*- butyllithium, were also reported.[34]

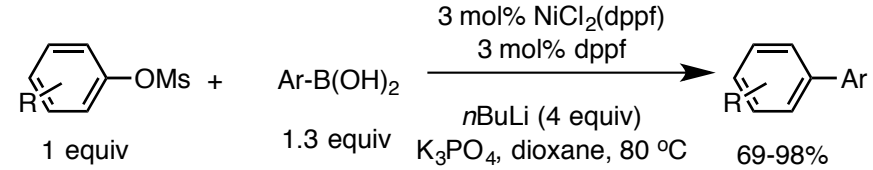
Scheme 1.1. $NiCl_2$(dppf) Catalyzed Suzuki-Miyaura Cross-Coupling of Aryl Chlorides and Mesylates with Arylboronic Acids in the Presence of External Reducing Reagents

With Zn Powder



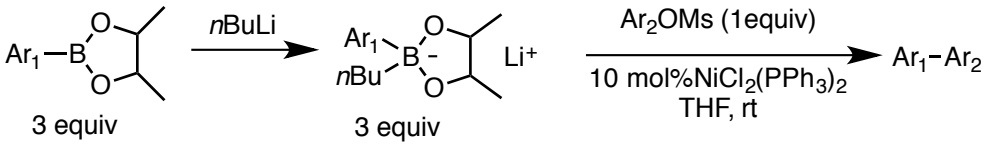
With *n*BuLi





While Percec believes the oxidative addition of C_{Ar}-OMs bond is the rate-determining step, Kobayashi proposed transmetalation as the sluggish step.[35,36] In transmetalation, a base binds to boron atom to form a borate intermediate.[1] To promote the transmetalation, Kobayashi prepared the borate from arylboronic ester and alkyllithium reagents. Methyl, *n*-butyl and CH_2TMS lithium reagents were investigated. *n*-Butyllithium was found to promote transmetalation. Since borate is prepared in a separate step, no base is needed for the coupling step. $NiCl_2(PPh_3)_2$ was found to be more reactive than $NiCl_2$(dppf) (Scheme 1.2).[35,36] It is important to note that recent studies showed that the base in cross-coupling reaction not only participates in the formation of borates but also binds with nickel intermediates.[37] Thus, the mechanism for cross-coupling of aryl mesylates in Percec's and Kobayashi's work is different.

Scheme 1.2. Nickel Catalyzed Suzuki-Miyaura Cross-Coupling of Aryl Lithium Borates with Aryl Mesylates in THF at Room Temperature



These preliminary studies either require extra steps to activate Ni^{II} or provide only moderate yields for a limited substrate scope.[28,30,31,35] High catalyst loadings (larger than 5 mol%) are required. In 1997, Indolese reported 1 mol% $NiCl_2$(dppf) catalyzed coupling reaction of aryl chlorides with arylboronic acids.[38] No external reducing reagent was required for these coupling reactions.[38] Importantly, it was observed that addition of Zn did not increase the yield, contradicting the observation Percec made on coupling of aryl mesylates. This work indicates that boronic acid reduces Ni^{II} effectively at high temperature and the rate determine step in cross-coupling of aryl chlorides is different than that of cross-coupling of aryl sulfonates.[38] Later, Miyaura observed that with additional PPh_3, inexpensive $NiCl_2(PPh_3)_2$ is capable of catalyzing the cross-coupling of aryl chlorides with arylboronic acids with $K_3PO_4(H_2O)_n$ suspension in toluene at 80 -100 ^oC.[39] Electron-deficient aryl chlorides react faster than electron-rich aryl chlorides,

generating excellent yields. Only moderate yields were obtained for electron-rich aryl chlorides.[39] Low yields were obtained for 2-chloropyridine and methyl 2-chlorobenzoate. Miyaura suspected the retarding effect of *ortho*-substituted pyridine and benzoate is due to the chelating of nickel by *ortho* groups (Figure 1.1).

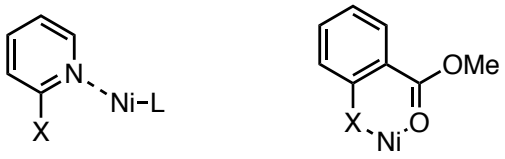
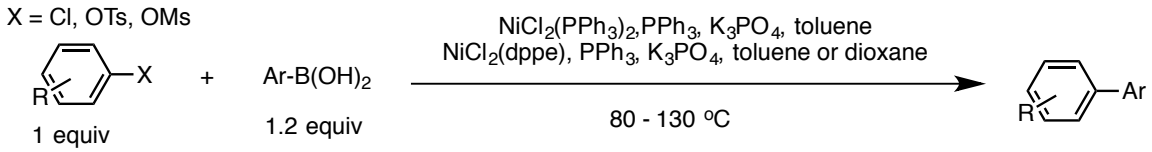


Figure 1.1. Chelating Effects of *Ortho*-Substituted Aryl Halides

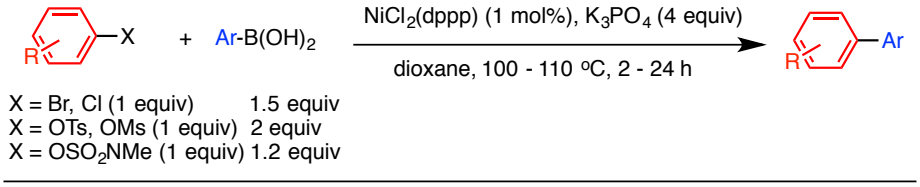
As can be seen from the discussion above, minor changes itn reaction conditions, such as the addition of Zn, the hygroscopy of the base, the nature of the substrates, impact the yields significantly. However, for the preparation of a library of compounds, such as in medicinal chemistry or in the modular synthesis of supramolecular structures,[40,41] it is impossible to optimize conditions for each compound. A universal catalytic system for aryl halides, tosylates and mesylates is highly desired. Driven by the aim of identifying the most applicable catalytic system to a wide range of aryl chlorides and sulfonates, our laboratory surveyed a range of Ni^{II} complexes, including $NiCl_2(PCy_3)_2$, $NiCl_2$(dppp), $NiCl_2$(dppe), $NiCl_2$(dppf) and $NiCl_2$(dppb).[42] $NiCl_2$(dppe) (5 mol%) was found to be active for cross-coupling of aryl chlorides, mesylates and tosylates in both toluene and dioxane.[42] Although the single ligand system $NiCl_2$(dppe)/dppe only showed good activity to electron deficient aryl sulfonates, mixed-ligand system $NiCl_2$(dppe)/PPh_3 showed excellent reactivity to both electron-rich and electron-deficient aryl halides and mesylates.[42] This work demonstrated the concept of a mixed-ligand effect, which will be discussed in the following chapters. Most importantly, a universal catalytic system was reported.[42]

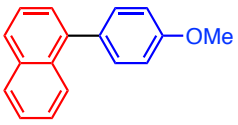
Scheme 1.3. Ni^{II} Complex Catalyzed Cross-Coupling of Aryl Chlorides, Mesylates and Tosylates with Arylboronic Acids in the Absence of External Reducing Reagents



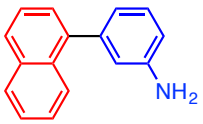
Later it was found $NiCl_2$(dppp) is highly efficient in cross-coupling of aryl tosylates, mesylates,[43] sulfamates[44] and halides[43] with arylboronic acids at only 1 mol% catalyst loading in dioxane at 100 – 110 °C. Interestingly, when unprotected boronic acids bearing free $–NH_2$ group was used, C-C bond formation was completely selective over C-N bond formation. Naphthyl tosylates, mesylates and sulfamates were found to be of similar reactivity under $NiCl_2$(dppp) (1 mol%)/K_3PO_4/dioxane/100-110 °C catalytic conditions. The scope of this catalytic system is shown in Scheme 1.4.

Scheme 1.4. $NiCl_2$(dppp) (1 mol%) Catalyzed Cross-Coupling of Aryl/HeteroAryl Halides, Sulfonates and Sulfamates with Arylboronic Acids

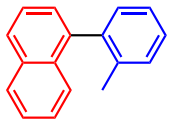




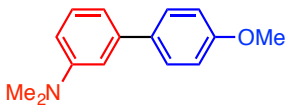
X = Br, 90%
X = Cl, 96%
X = OTs, 91%
X = OMs, 99%
X = OSO_2NMe_2, 84%



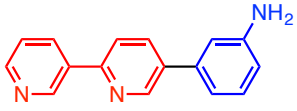
X = Br, 92%
X = Cl, 98%
X = OTs, 98%
X = OMs, 90%



X = Br, 94%
X = Cl, 80%
X = OTs, 92%
X = OMs, 75%
X = OSO_2NMe_2, 76%



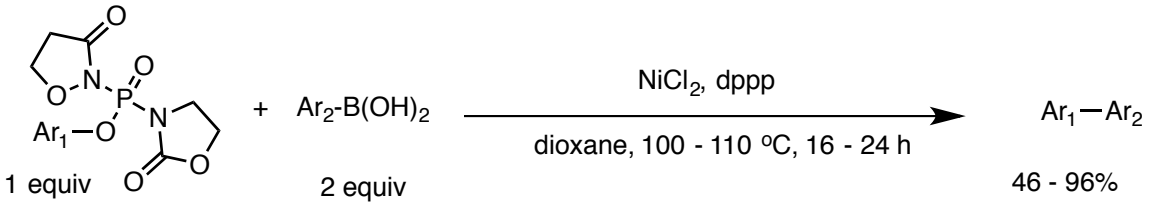
X = Cl, 71%
X = OTs, 57%
X = OMs, 80%



X = Br, 83%

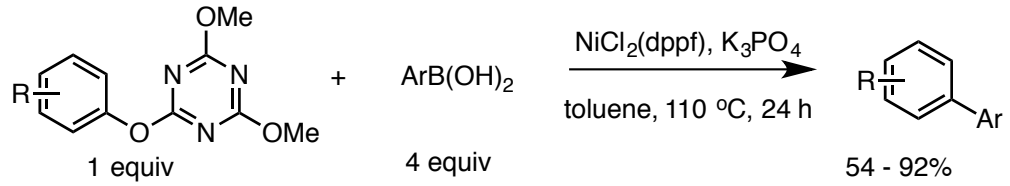
Following these studies, other novel C-O electrophiles including phosphoramides[45] (Scheme 1.5), phosphonium salts,[46] DMT ethers[47] (Scheme 1.6) were applied in $NiCl_2$(dppp) or $NiCl_2$(dppf) catalyzed Suzuki-Miyaura cross-coupling with arylboronic acids at elevated temperatures. Phosphoramides were found to be the most active aryl phosphate derivatives. [45] Later, the *in situ* formed phosphonium salts were reported to participate in Suzuki-Miyaura cross-coupling.[46]

Scheme 1.5. $NiCl_2$/dppp Catalyzed Suzuki-Miyaura Cross-Coupling of Aryl Phosphoramides with Arylboronic Acids[45]



Ar_1 = 1-naphthyl, 2-naphthyl, 4-tolyl, 4-fluorophenyl, 3-pyridinyl, 4-pyridinyl
Ar_2 = phenyl, 4-methoxylphenyl, 4-tolyl

Scheme 1.6. $NiCl_2$(dppf) Catalyzed Suzuki-Miyaura Cross-Coupling of Aryl 2,4-Dimethoxy-1,3,5-triazine-6-yl Ethers with Arylboronic Acids[47]



R = 4-OMe, 2-OMe, 4-Me, 3-Me, 2-Me, 1-naphthyl, 2-naphthyl, 4-*t*Bu, 4-F, 4-CF_3

Ar = Ph, 2-tolyl, 4-tolyl, 1-naphthyl, 4-methoxyphenyl

The one-pot tosylation of phenol with *N,N*-ditosylaniline followed by Suzuki-Miyaura cross-coupling of tosylates with arylboronic acids catalyzed by $NiCl_2$(dppp) generates good to excellent yields for a wide range of phenols.[48] The one-pot tosylation strategy avoids the synthesis and purification of tosylates, thus was considered greener.

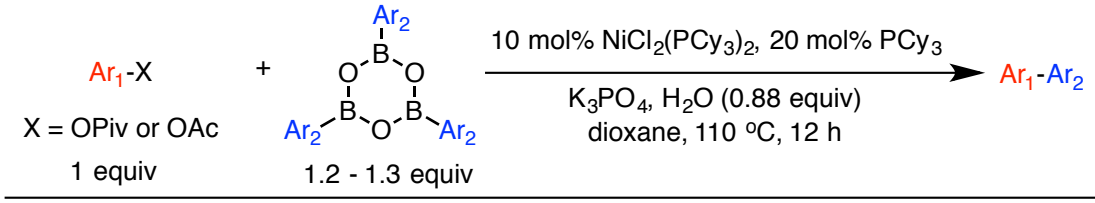
While $NiCl_2$(dppp) is efficient for coupling of aryl tosylates, for less reactive aryl carboxylates, a more electron-rich ligand, PCy_3 is needed. The application of PCy_3 in nickel catalysis started when Monteiro found that coupling of aryl tosylates without reducing reagents processed readily with electron-rich and sterically hindered PCy_3.[49] With excess PCy_3, 1.5 – 3 mol% of $NiCl_2(PCy_3)_2$ efficiently catalyzes the cross-coupling of aryl tosylates with arylboronic acids in dioxane with K_3PO_4 at 130 ^oC. Cross-coupling of aryl tosylates is less sensitive to the electronic property of tosylates compared to the cross-coupling of aryl chlorides under similar catalytic conditions,[39] but does not tolerate *ortho* substituents well.[49] From these examples, Monteiro proposed the rate-determining step for coupling of tosylates is not the oxidative addition step, which is dependent on the electronic properties of aryl tosylates, but the transmetalation step, which is impacted by the steric hindrance of aryl tosylates.[49]

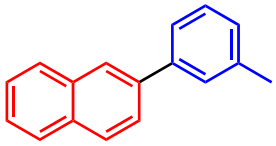
In 2008, Shi[50] and Garg[51] independently applied $NiCl_2(PCy_3)_2$ in the cross-coupling of phenolic esters with aryl boroxines and boronic acids.

Inspired by the Kumada coupling of methyl enol ether catalyzed by $NiCl_2(PPh_3)_2$ three decades ago,[52,53] Shi selected Ni instead of Pd to activate aryl C-O bonds.[50] Other transition metals including Co, Cu, Pd and Fe did not show activity in Suzuki coupling of naphthyl acetates.[50] PCy_3 was found to be the most efficient ligand while more electron-rich $P(^tBu)_3$, bidentate dppf, inexpensive PPh_3, as well as phosphite ligand $P(OMe)_3$ showed lower or no activity in the cross-coupling of naphthyl acetates with aryl boroxines in the presence of K_3PO_4 in dioxane at 110 ^oC.[50] Since the bond energy of C-O bond in phenyl acetate is higher than that of naphthyl acetate,[50] phenyl acetate does not participate in the coupling reaction readily. Instead, hydrolysis of phenyl acetates occurs. Replacing the acetate group with the bulkier pivalate group, the cross-coupling of phenyl pivalate was achieved in moderate to good yields. Ketones, esters, methyl ethers and free hydroxyl groups are tolerated on the aryl pivalate electrophiles while –OMe, -COOMe, -$COCH_3$, -F and -CF_3 are tolerated on the aryl boroxines (Scheme 1.7).[50] Electron-withdrawing groups activate the pivalates while electron-donating groups slow down the cross-coupling

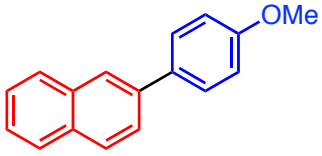
(Scheme 1.7). Similar to our observation in $NiCl_2$(dppe) catalyzed cross-coupling of aryl mesylates with arylboronic acids, both toluene and dioxane are beneficial to promote the coupling reaction.[42]

Scheme 1.7. $NiCl_2(PCy_3)_2$ Catalyzed Suzuki-Miyaura Cross-Coupling of Phenol Carboxylates with Aryl Boroxines in Dioxane at 110 °C

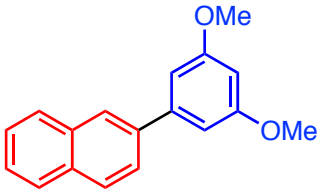




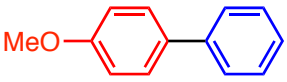
X = OAc, 81%



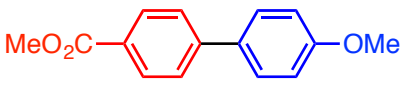
X = OAc, 75%



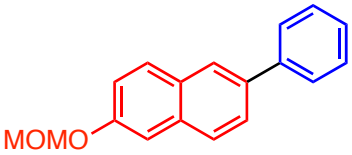
X = OAc, 64%



X = OPIv, 47%



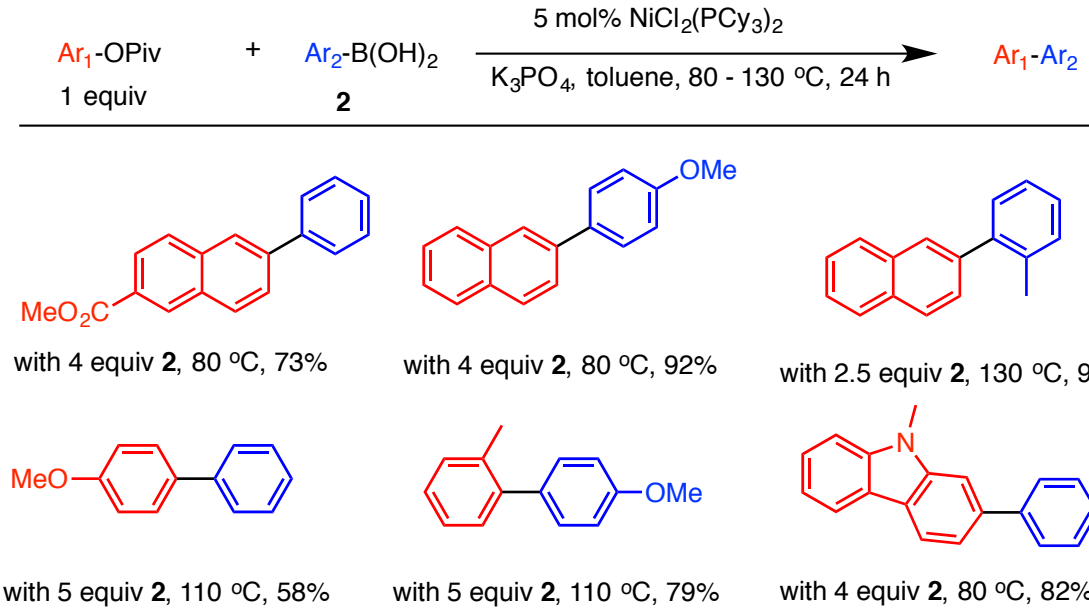
X = OPiv, 80%



X = OAc, 73%

Meanwhile, Garg[51] used boronic acids as coupling reagents and applied toluene instead of dioxane. For coupling of naphthyl pivalates, 80 °C is sufficient. For phenyl pivalates, the reaction temperature has to be elevated to 110 - 130 °C. This reactivity difference comes from the lower oxidative addition energy of C_{Ar}-O bonds in fused aromatic ring compared to that of phenyl C-O bonds. A one-pot pivaloylation, cross-coupling strategy was achieved as well. (**Scheme 1.8**) The reaction is highly sensitive to steric hindrance on both electrophiles and nucleophiles, with decreased yields even at elevated temperature for *ortho* substituted substrates.[51]

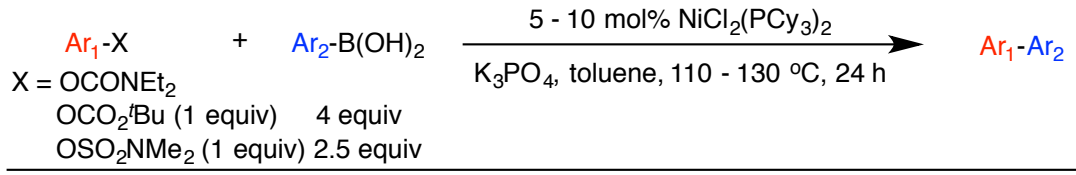
Scheme 1.8. $NiCl_2(PCy_3)_2$ Catalyzed Suzuki-Miyaura Cross-Coupling of Aryl Pivalates with Arylboronic Acids in Toluene at 110 °C[51]

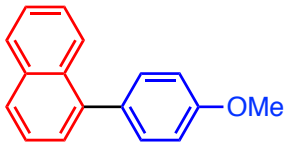


After the cross-coupling of aryl pivalates was demonstrated, soon the $NiCl_2(PCy_3)_2$ catalyzed cross-coupling of aryl carbamates,[25,26,54-56] sulfamates,[25,55,56] carbonates[25,56] and phosphates[45] with aryl and heteroarylboronic acids was demonstrated. Compared to pivalates and sulfonates, carbamates, sulfamates and carbonates enable the directed *ortho* metalation and provide orthogonal strategy.[57-60] Phosphates are present in biological systems.[61]

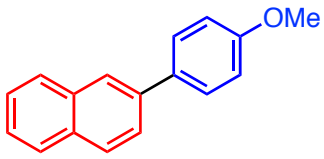
Garg successfully achieved the cross-coupling of boronic acids with naphthyl carbamates, carbonates and sulfamates with arylboronic acids in the presence of anhydrous K_3PO_4 in toluene at 110 °C to 130 °C. While the cross-coupling of aryl sulfamates gives excellent yields, the cross-coupling of phenyl carbamates was shown to be more challenging with only moderate yield. Impressively, 2,6-dimethylphenyl sulfamate was cross-coupled with 4-methoxyphenylboronic acid in 63% isolated yield.[25]

Scheme 1.9. $NiCl_2(PCy_3)_2$ Catalyzed Suzuki-Miyaura Cross-Coupling of Aryl Carbamates, Sulfamates and Carbonates with Arylboronic Acids in Toluene

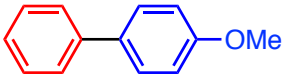




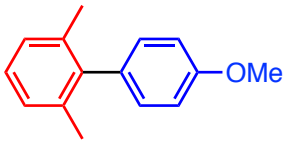
X = $OCONEt_2$, 130 °C, 86%
X = $OCO_2{}^t$Bu, 130 °C, 72%
X = OSO_2NMe_2, 110 °C, 95%



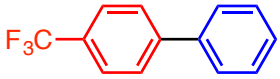
X = $OCONEt_2$, 130 °C, 47%
X = $OCO_2{}^t$Bu, 130 °C, 85%



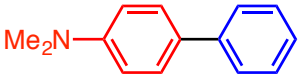
X = $OCONEt_2$, 130 °C, 52%
X = OSO_2NMe_2, 110 °C, 87%



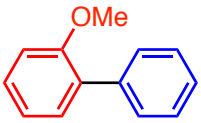
X = OSO_2NMe_2, 110 °C, 63%



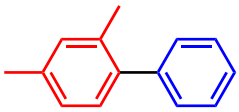
X = OSO_2NMe_2, 110 °C, 81%



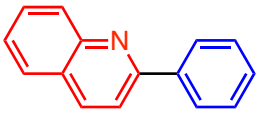
X = OSO_2NMe_2, 110 °C, 76%



X = $OCONEt_2$, 130 °C, 36%
X = OSO_2NMe_2, 110 °C, 90%



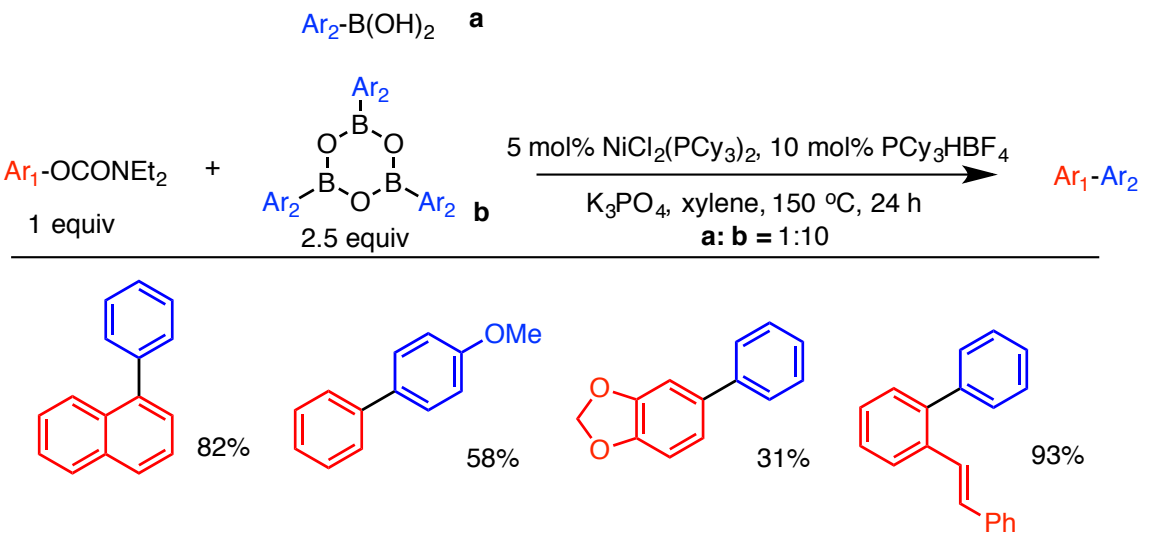
X = $OCONEt_2$, 130 °C, 8%



X = $OCONEt_2$, 130 °C, 51%

The Snieckus[26] group approached the cross-coupling of aryl carbamates in a similar manner but with different nucleophiles. Similar to the observations made by Shi[50], Snieckus found the amount of water is crucial to the reactivity of $NiCl_2(PCy_3)_2$. While Shi approached the water problem by using anhydrous boroxines and additional water, the Snieckus group heated the boronic acids in vacuum to achieve a mixture of boroxines and boronic acids in 10:1 ratio (**b:a** in Scheme 1.10), which is further confirmed by ^{1}H NMR.

Scheme 1.10. $NiCl_2(PCy_3)_2$ Catalyzed Suzuki-Miyaura Cross-Coupling of Aryl Carbamates with Aryl Boroxines/Boronic Acids = 10:1 in *o*-Xylene



With a mixture of boronic acids and boroxines, the cross-coupling of naphthyl carbamates gives good yields in xylene at 150 °C. However, cross-coupling of electron-rich phenyl carbamates gives only moderated yields. [26]

Shi[54] also reported the Suzuki-Miyaura cross-coupling of alkenyl and aryl carbamates with aryl boroxines in dioxane at 120 °C. To avoid the use of the hygroscopic base K_3PO_4, K_2CO_3 was used. Additional water was needed to promote the formation of borate in the transmetalation. Green solvents including *t*-amyl alcohol, 2-methyl-tetrahydrofuran, and ethyl acetate were used for the cross-coupling of aryl sulfamates and carbamates as well.[62] Microwave assisted rapid cross-coupling of aryl sulfamates and carbamates cut down the reaction time from 24 h to 10 min at 180 °C.[55]

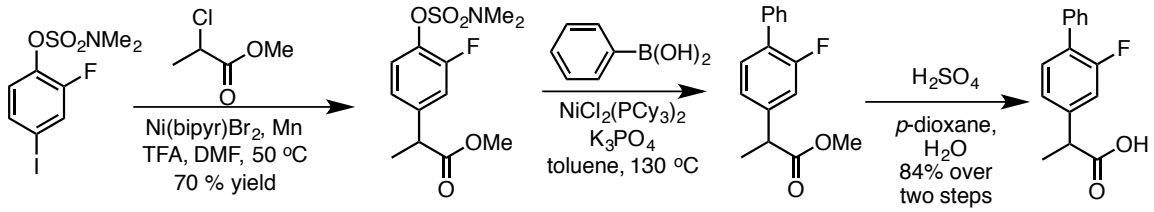
The mechanism of $NiCl_2(PCy_3)_2$ catalyzed cross-coupling of aryl sulfamates and carbamates was studied by DFT method.[56] It was found that nickel first binds with sulfamates and carbamates to form a five-membered ring. The oxidative addition step happens readily, followed by ligand exchange and transmetalation. The transmetalation step is rate determining for both sulfamates and carbamates. The different reactivity of aryl sulfamates and carbamates lies in the effect of

water in the transmetalation step. Water slows down the transmetalation step for cross-coupling of aryl carbamates, while it accelerates the transmetalation for reactions of aryl sulfamates.[56]

The applications of nickel catalyzed cross-coupling of C-O electrophiles in pharmaceuticals and material science have been demonstrated.

Flurbiprofen, an anti-inflammatory drug, was prepared *via* directed *ortho* metalation followed by orthogonal cross-coupling of the iodo group and sulfamate group method (Scheme 1.11) from phenol.[56]

Scheme 1.11. Synthesis of Flurbiprofen with Orthogonal Coupling Strategy[56]

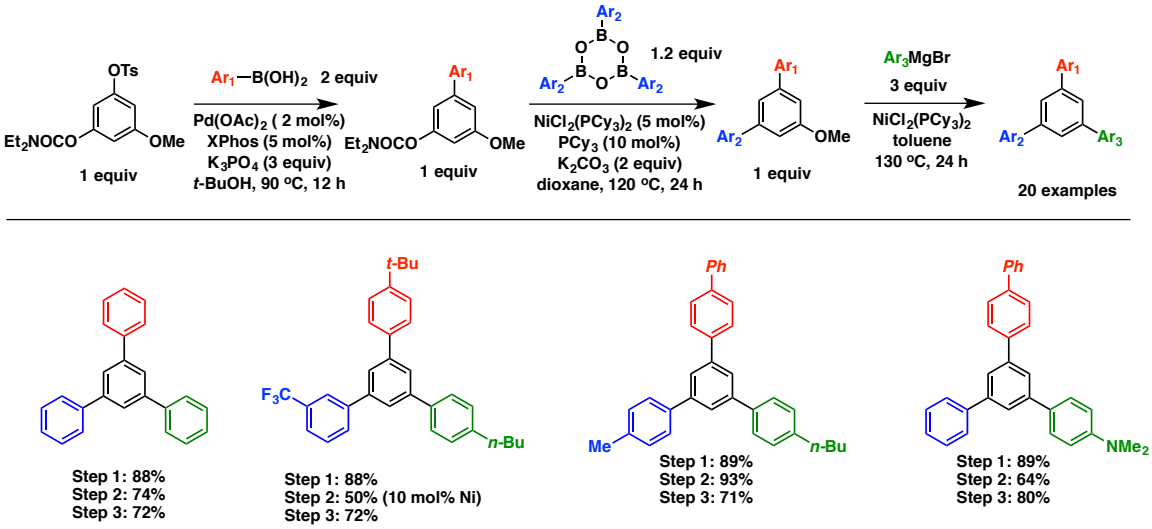


ortho-Lithiation of phenyl sulfamate generates (2-((*N*,*N*-dimethylsulfamoyl)oxy)phenyl)lithium, which was trapped by trimethyl borate to produce the (2-((*N*,*N*-dimethylsulfamoyl)oxy)phenyl)boronic acid after acidic workup. Fluorination of (2-((*N*,*N*-dimethylsulfamoyl)oxy)phenyl)boronic acid with Selectfluor® provides *ortho*-fluoro phenyl sulfamate. Electrophilic aromatic substitution of *ortho*-fluoro phenyl sulfamate at the *para* position of the sulfamate group installs the iodo group. The selective enolate coupling of the iodide group catalyzed by nickel complex installs a propionate chain. Cross-coupling of the sulfamate followed by hydrolysis of the ester produced flurbiprofen in 7 steps from readily available, inexpensive phenol.[56]

Nickel catalyzed cross-coupling of phenol derivatives can not only be applied in the inexpensive synthesis of pharmaceuticals, it can also be applied in the orthogonal synthesis of building blocks for functional organic molecules. Utilizing the reactivity differences of aryl C-O derivatives,

programmed selective C-O bond activation from phloroglucinol derivatives (Scheme 1.12) has been used to synthesize multiarenes.[63]

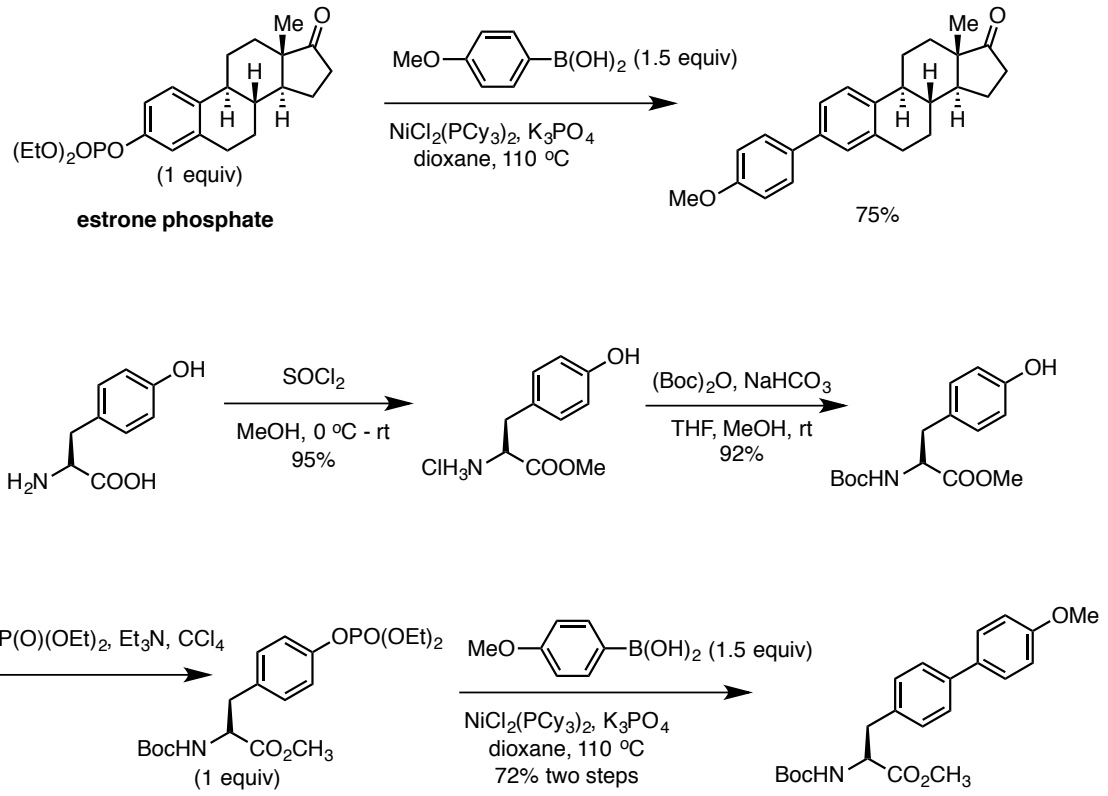
Scheme 1.12. Synthesis of Multiarylated Benzene via Orthogonal Activation of C-O Bonds



The first step is the Pd catalyzed cross-coupling of aryl tosylates. Carbamates are totally inert under this condition.[63] The biaryl carbamates were isolated, applied in $NiCl_2(PCy_3)_2$ catalyzed cross-coupling of aryl carbamates with aryl boroxines. Finally, the methyl ether group is transferred to another aryl group by a nickel-catalyzed Kumada coupling reaction. In total, 20 multiarenes were prepared in three orthogonal cross-coupling steps. Good to excellent yields were obtained for each step. The harsh condition of Kumada coupling of aryl methyl ethers limits the scope of substituents on the multiarenes to alkyl, tertiary amine and trifluoromethyl groups (Scheme 1.12).

Due to the wide existence of phosphate groups in biological systems, cross-coupling of aryl phosphates on biologically active molecules as well as amino acid derivatives are interesting,[61] because it has potential application in the formation of a nonlabile linkage at a residue functional group orthogonal to amino acids (Scheme 1.13).[64]

Scheme 1.13. Potential Application of $NiCl_2(PCy_3)_2$ Catalyzed Suzuki-Miyaura Cross-Coupling in Biologically Active Molecules

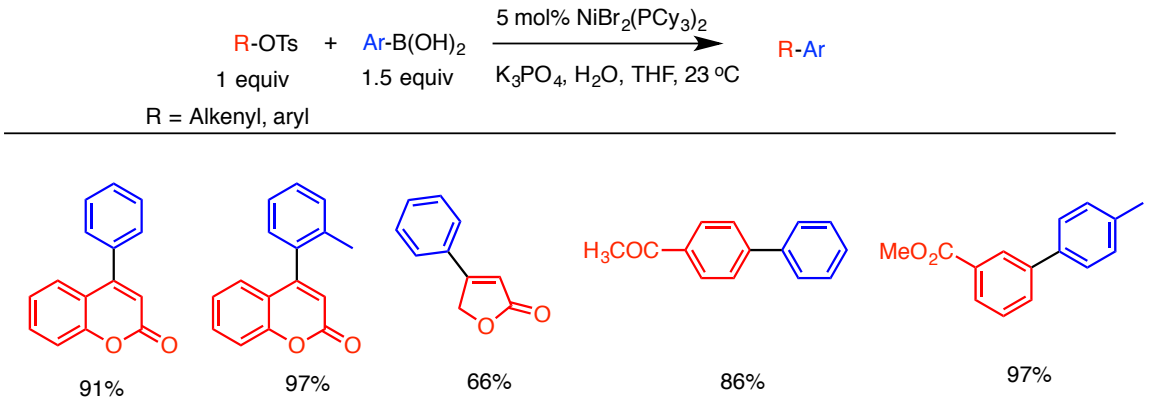


Estrone is a naturally produced hormone. It can be converted to the phosphate then cross-coupled with a 4-methoxyphenylboronic acid in 75% yields while maintaining the rest of the functional group of the molecule. (Scheme 1.13)

D-Tyrosine was first methylated in 95% yield, followed by protection of the free amino group with Boc under mild conditions. Then the phenol group was transformed to the phosphate, and cross-coupled without racemization of the stereocenter in good yields. (Scheme 1.13)

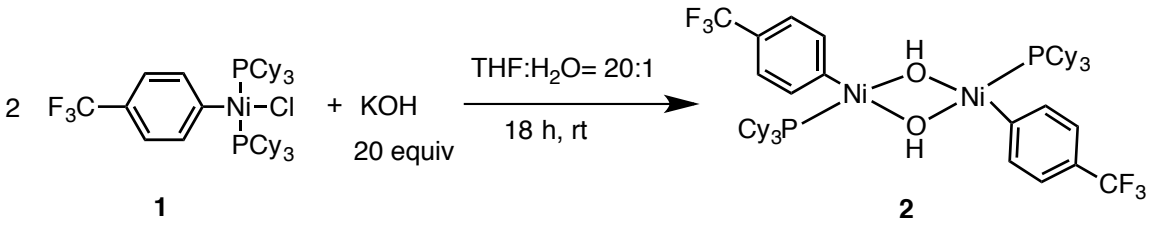
Interestingly, changing Cl to Br, $NiBr_2(PCy_3)_2$ is capable of mediating room temperature cross-coupling of alkenyl tosylates with arylboronic acids in THF.[65] Addition of water (2 equiv) was found to promote the coupling reaction. It was proposed that water stabilizes Ni^0 as a ligand.

Scheme 1.14. Cross-Coupling of Aryl and Alkenyl Tosylates with Arylboronic Acids Catalyzed by $NiBr_2(PCy_3)_2$ in THF at Room Temperature



However, another mechanism on the promoting effect of water in cross-coupling reactions was proposed by Christian[66]. It is stated that nickel hydroxyl complex (**2,** Scheme 1.15) was the true catalytically active species. By preparing nickel hydroxyl complex (**2,** Scheme 1.15) from nickel precatalysts (**1,** Scheme 1.15), Christian observed the coupling reaction catalyzed by nickel hydroxyl complex (**2,** Scheme 1.15) obtained from ligand exchange is much faster (complete conversion in 2 min) compared to the reaction catalyzed by precatalysts (**1,** Scheme 1.15) (complete conversion in 6 h).

Scheme 1.15. Formation of Nickel Hydroxyl Complex in Suzuki-Miyaura Cross-Coupling Reactions



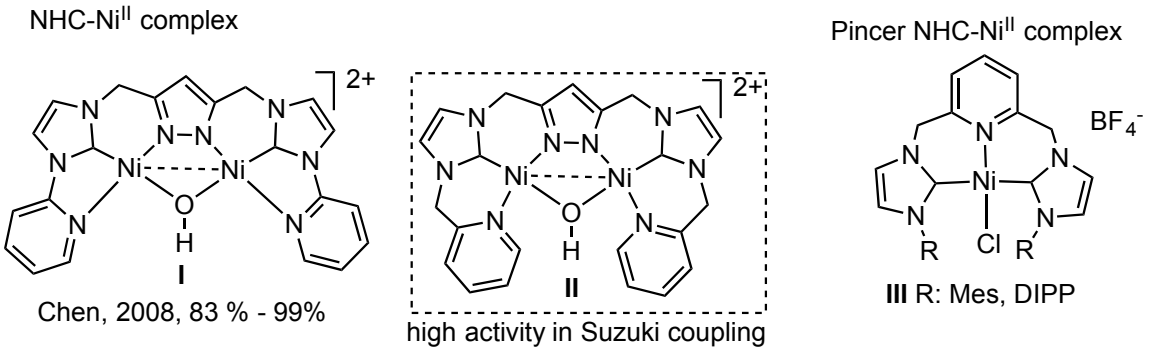
1 **2**

However, as can be seen in Scheme 1.15, the formation of nickel hydroxyl complex requires excess of base in aqueous solution in 18 h, a much longer time compared to the actual cross-

coupling reaction. The pathway of cross-coupling with oxidative addition intermediate **1** cannot be excluded.

Besides Ni^{II}-phosphine catalysts, Ni^{II}-NHC catalysts have also been applied to the cross-coupling of aryl tosylates, mesylates[67] and anthracenyl[68] carboxylates due to the ease of handling of NHC ligands.

Scheme 1.16. Selected Nickel NHC Complex in Suzuki-Miyaura Cross-Coupling Reactions

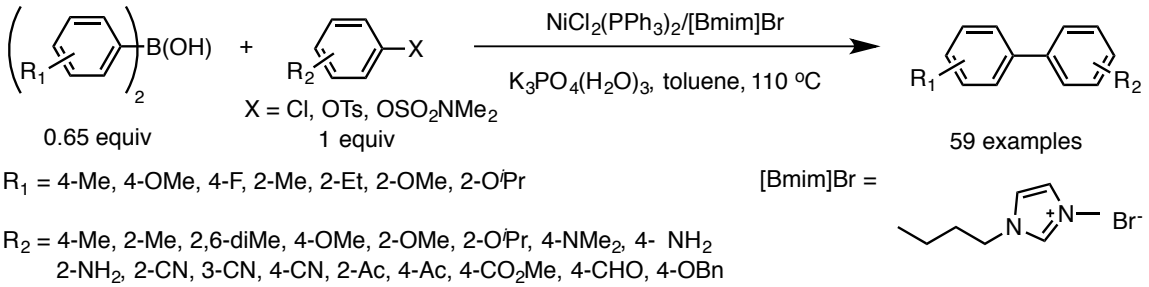


I and II were found to be highly reactive in the cross-coupling of aryl chlorides with boronic acids (78% -98% yield).[69] Complex III (Scheme 1.16) was demonstrated active in cross-coupling of aryl and alkenyl tosylates and mesylates as well as bromides and chlorides with arylboronic acids.[67] Medium to good isolated yields were obtained with improved reactivity for electron-deficient aryl tosylates.[67] Electron-rich and sterically hindered tosylates provided lower yields.[67]

Besides boronic acids, diarylborinic acids have emerged to be a new class of boron reagents used for Suzuki-Miyaura cross-coupling reactions because they have higher atom economy than arylboronic acids and can be prepared less expensively than arylboronic aicds.[70,71] After demonstrating the capability of diarylborinic acids in the cross-coupling of aryl chlorides catalyzed by $Ni[P(4\text{-}MeOC_6H_4)_3]_2Cl_2/P(4\text{-}MeOC_6H_4)_3$,[70] Zou and colleagues turned to NHC ligands instead of phosphine ligands since NHC ligands are bench-stable and thermally stable. After surveying four different kinds of NHC ligands and a wide range of Ni^{II} sources, including $NiCl_2$, $NiCl_2(PPh_3)_2$, $NiCl_2[P(4\text{-}MeOC_6H_4)_3]_2$, $NiCl_2(PCy_3)_2$, $NiCl_2$(dppm), $NiCl_2$(dppe), $NiCl_2$(dppp), $NiCl_2$(dppb) and

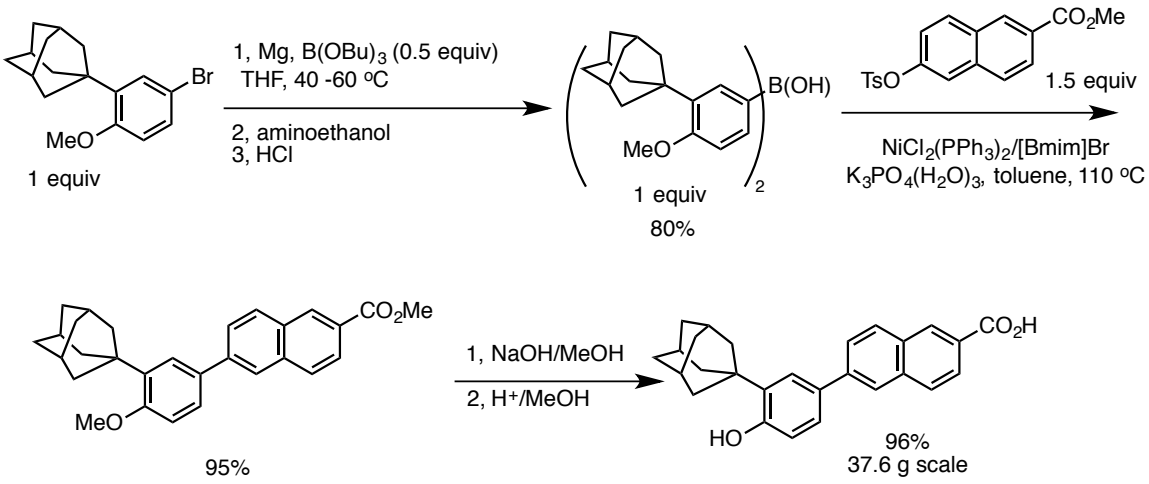
$NiCl_2$(dppf), the combination of $NiCl_2(PPh_3)_2$/[Bmin]Br/$K_3PO_4(H_2O)_3$/toluene/110 ^oC was found to be the most effective in promoting the cross-coupling of aryl halides, tosylates and sulfamates (Scheme 1.17).

Scheme 1.17. $NiCl_2(PPh_3)_2$ Catalyzed Suzuki-Miyaura Cross-Coupling of Diarylborinic Acids with Aryl Chlorides, Tosylates and Sulfamates



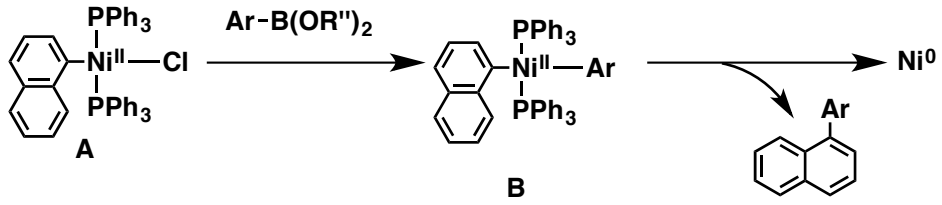
The newly developed method was applied in the laboratory synthesis of a topical retinoid Adapalene (Scheme 1.18) *via* a cost-effective, environmentally friendly Suzuki-Miyaura cross-coupling.

Scheme 1.18. Cost-Effective Synthesis of Adapalene *via* Suzuki-Miyaura Cross-Coupilng of Diarylborinic Acids



The last category of Ni^{II} catalysts involve Ni^{II} precatalysts. They will be discussed in detail in the precatalyst chapter. Compared to $NiCl_2(PPh_3)_2$, $NiCl_2$(dppf), $NiCl_2(PCy_3)_2$ and $NiCl_2$(dppe), nickel precatalysts are bench-stable and generate the active Ni^0 species readily under mild conditions. First reported by Shaw,[72] $Ni^{II}X$(aryl)(PR_3) (X = Cl, Br; aryl = naphthyl, phenyl; R = PPh_3, PCy_3) catalysts were shown to mediate the cross-coupling of aryl halides, sulfonates and sulfamates with arylboronic acids and esters. Ni^{II}Cl(1-naphthyl)$(PPh_3)_2$ was demonstrated to catalyze the cross-coupling of aryl halides and tosylates with arylboronic acids in THF at room temperature[73,74] *via* an activation mechanism by transmetalation and reductive elimination (**Scheme 1.19**).

Scheme 1.19. Activation of Ni^{II}Cl(1-naphthyl)$(PPh_3)_2$



A PCy_3 derivative - $Ni^{II}OTs(4\text{-}OMeC_6H_4)(PCy_3)_2$ was reported for the cross-coupling of aryl tosylates with arylboronic acids.[65] Water accelerates the reaction, and 2 equiv of water to aryl tosylates is the optimum amount. We applied Ni^{II}Cl(1-naphthyl)$(PPh_3)_2/PCy_3$ in the cross-coupling of aryl and heteroaryl mesylations and sulfamates with aryl and heteroaryl neopentylglycolboronates.[29] The cross-coupling proceeds readily at room temperature in THF. A variety of functional groups, including ester, ether, cyano group, imide and ketone are tolerated.[29] A library of $Ni^{II}X(aryl)(PCy_3)_2$ (X = Cl; aryl = 1-naphthyl, 2-naphthyl, 9-phenanthrenyl, 9-anthracyl, 2-methoxy naphthyl; X = OMs, OTs; aryl = 1-naphthyl, 2-naphthyl) precatalysts was prepared and studied by us.[75] These precatalysts catalyze Suzuki-Miyaura cross-coupling of sterically hindered aryl sulfamates with aryl neopentylglycolboronates in less than 60 min at room temperature.[75] This will be discussed in more detail in the following chapters. The Hartwig group applied a single-component Ni^{II}Cl(cinnamyl)(dppf) precatalyst to a broad scope cross-coupling of heteroaryl bromides and chlorides with heteroarylboronic acids. Only 0.5% catalyst loading was sufficient. [76]

1.1.2 Ni^0 Catalysts in Suzuki-Miyaura Cross-Coupling of Phenol Derivatives

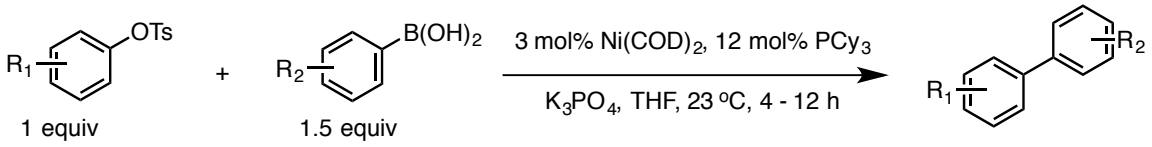
The first example of Ni^0 catalyst directly used in Suzuki-Miyaura cross-coupling reaction is the supported nickel on charcoal (Ni/C catalyst) developed by Lipshutz in 2000.[34] Similar to the reduction of $Ni^{II}Cl_2$(dppf) with *n*BuLi *in situ*,[30,31] nickel nitrate impregnated on charcoal was reduced by *n*BuLi (4 equiv) in the presence of triphenylphosphine prior to the cross-coupling reaction. Aryl and heteroaryl chlorides were effectively coupled with arylboronic acids in refluxing dioxane catalyzed by 5-10 mol% Ni^0/C, PPh_3, K_3PO_4 and LiBr as an additive. Aldehyde, ketone, nitrile and quinoline were tolerated. Bidentate ligands such as BINAP, dppf, dppe inhibit the coupling while the monodentate phosphine ligand PPh_3 promotes the coupling. To understand the nature of the supported catalyst, the Ni^0/C catalyst was exposed to 4 equiv of PPh_3 in THF at room temperature in the absence of the aryl chloride substrate and boronic acid.[34] Only half of the initial quantity of PPh_3 ligand was detected after filtration of the solution. This indicates that only two phosphine ligands bind with the Ni^0/C catalyst. The heterogeneous form of the Ni^0/C enables the easy recovery of Ni and also provides a greener analog to the homogeneous counterpart. Only trace amounts of Ni leached from the charcoal during the reaction period according to inductively coupled plasma atomic emission spectroscopy (ICP-AES), which indicates the reaction is surface mediated.[77,78]

The homogeneous Ni^0 source $Ni(COD)_2$ was used by Semmelhack in the homocoupling of aryl halides.[79,80] The application of $Ni(COD)_2$ in Suzuki-Miyaura cross-coupling reactions led to the discoveries of room-temperature cross-coupling of aryl and heteroaryl sulfonates,[6,81,82] halides[81] and sulfamates[6] with aryl and heterarylboronic acids and esters.

Inspired by using Pd^0 and bulky ligands in cross-coupling reactions, Hu first examined $NiCl_2(PCy_3)_2$/Zn mixture at room temperature for cross-coupling of *p*-substituted phenyl tosylate with phenylboronic acids.[82] Only low yields were obtained. Hu concluded that reduction of Ni^{II} by Zn or boronic acid at room temperature is not efficient. Applying $Ni(COD)_2$ as a zero valent nickel source, with PCy_3, near complete conversion was observed. Electron deficient ligands such as

PPh_3, P(*o*-tosyl)$_3$, dppe and dppf provide low yields (0-17 %). Electron-rich, bulky ligands such as Buchwald ligands also inhibit the reaction. Only PCy_3 provides the right combination of electronic as well as steric properties. The ratio between PCy_3 and $Ni(COD)_2$ is also important. The most efficient ligand/metal ratio is 3 or 4 [$PCy_3/Ni(COD)_2$].[82] Electron-rich and electron-deficient tosylates were cross-coupled with sterically hindered arylboronic acids in good to excellent yields.(Scheme 1.20)

Scheme 1.20. $Ni(COD)_2/PCy_3$ Catalyzed Room Temperature Cross-Coupling of Aryl Tosylates with Arylboronic Acids



1 equiv 1.5 equiv

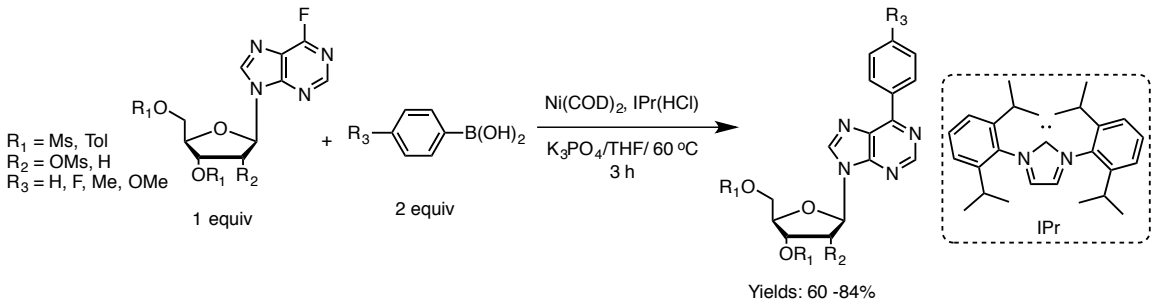
R_1 = 4-OMe, 4-Me, 2-Me, 4-$COCH_3$, 3-CF_3
R_2 = 2-Me, 4-OMe, 4-Me

86 - 99%

Later, Hu found bench stable ferrocenylmethylphosphine is also effective for coupling of aryl sulfonates and chlorides with arylboronic acids in THF at room temperature.[81] More importantly, the polymer bond ferrocenyl ligands are also effective for the coupling of aryl chlorides, though inefficient for coupling of aryl tosylates, which enables the quick removal and recovery of catalysts and ligands.[81]

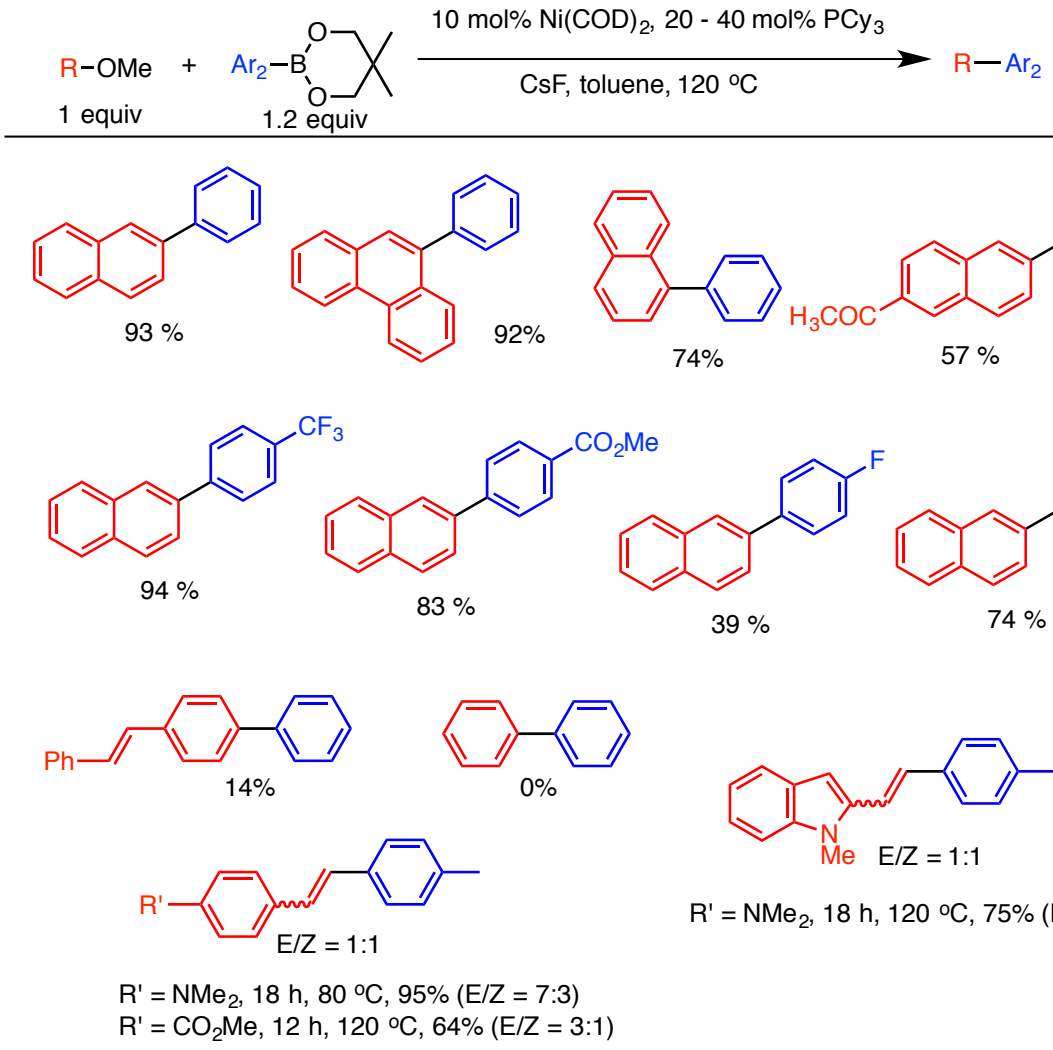
Since $Ni(COD)_2$ provides Ni^0 species that enter catalytic cycles directly, the $Ni(COD)_2$/ligand system provides superior reactivity. For example, with $Ni(COD)_2$ and NHC ligand, cross-coupling of 6-fluoropurine nucleosides at the C-F bond was achieved with the $Ni(COD)_2$/IPr/K_3PO_4/THF system at 60 ^oC (Scheme 1.21).[83]

Scheme 1.21. $Ni(COD)_2$/IPr Catalyzed Cross-Coupling of Fluorinated Nucleosides



Chatani reported the cross-coupling of aryl methyl ether with aryl neopentylglycolboronates catalyzed by $Ni(COD)_2/PCy_3/CsF$ in toluene at 120 ^oC.[84] Compared to the catalytic system reported by Shi and Garg [$NiCl_2(PCy_3)_2/K_3PO_4$],[50,51] acetates are not reactive under this condition. This highlights the delicacy of nickel catalyzed Suzuki-Miyaura cross-coupling. Small modifications of the base (from K_3PO_4 to CsF) or boron reagents (from boronic acids or boroxines to boronic esters) lead to changes in the reactivity of leaving groups (acetate and methyl ethers). The transformation proceeded efficiently with fused aromatic substrates or activated aromatic methyl ethers (lines 1 and 2, Scheme 1.22). A variety of boronic esters could be utilized. Anisole is inactive in this coupling (line 3, Scheme 1.22). The scope of the reaction was later expanded to facilitate the Suzuki coupling of vinyl methyl ethers (Scheme 1.22).[85] When Z alkenyl methyl ether was used, a mixture of E and Z product formed. The mechanism for isomerization was studied. With Z alkenyl methyl ether, in the presence of $Ni(COD)_2/PCy_3/CsF$, no isomerization was detected. So the isomerization step was proposed to happen at the product formation step rather than oxidative addition of the alkenyl methyl ether step.[85]

Scheme 1.22. $Ni(COD)_2/PCy_3$ Catalyzed Cross-Coupling of Aryl and Alkenyl Methyl Ethers with Aryl Neopentylglycolboronates in Toluene at 120 °C

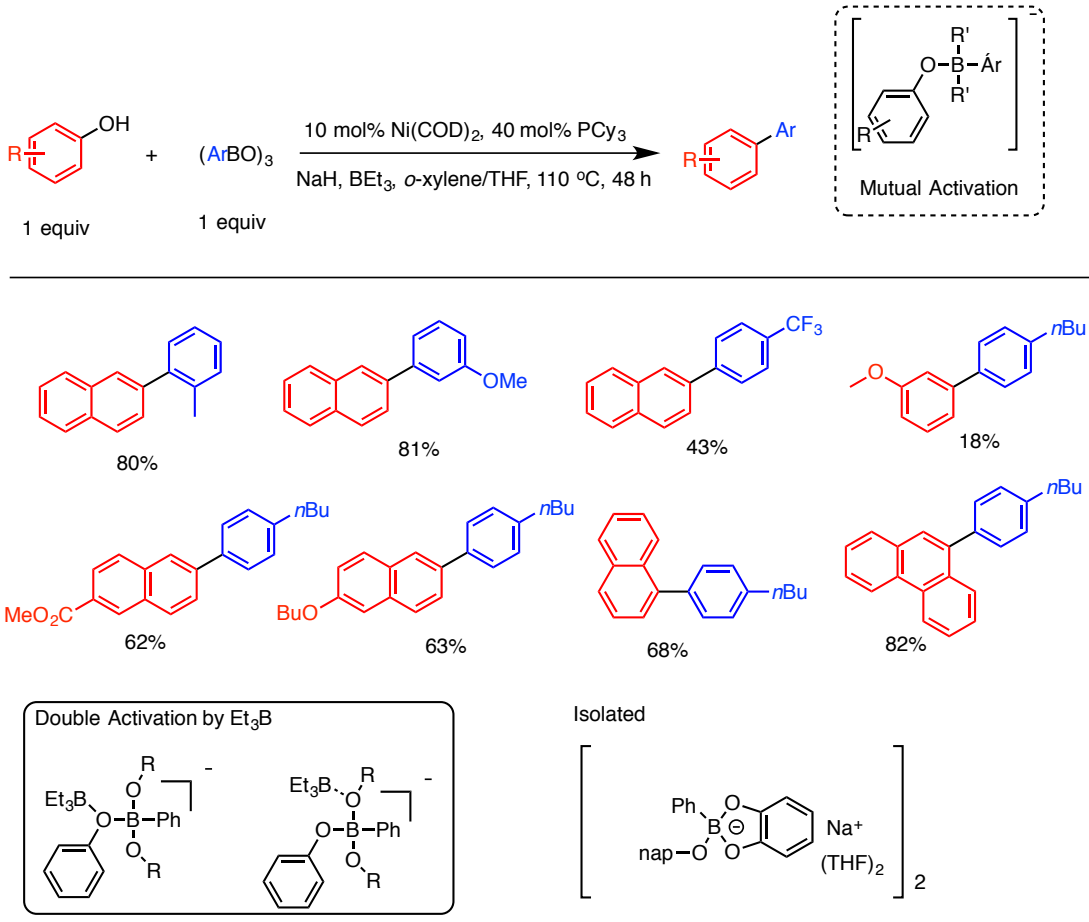


Using $Ni(COD)_2$ accompanied with ferrocenyl bisphosphine ligands, Kuwano was able to improve the yield of cross-coupling of arylboronic acids with aryl carbonates from low to moderate. However, only moderate yields were obtained with significant hydrolysis product.[86] Thus, the method of cross-coupling of carbonates is yet to be developed.

Recently, Shi[87] reported a new strategy in nickel catalyzed Suzuki-Miyaura cross-coupling of naphtholates, namely the mutual activation method. The rationale is to activate naphtholates with boronic acids to form activated naphtholate-boron derivatives, and mutually activate boronic acids

with naphtholates to form active borates (Scheme 1.23). Sodium hydride was used to generate naphtholates. Triethylborane is essential to obtain a good yield, probably *via* a double activation mechanism as depicted in Scheme 1.23. To confirm the mutual activation mechanism, the proposed borate intermediated was isolated and characterized by crystal structure. A dimer was isolated with sodium ion bridging a THF molecule and a borate molecule. The bridging effect of Na ion and THF showed the stabilization effect of THF to the borate intermediates. Direct application of the isolated intermediate to cross-coupling condition gives 60% isolated yield.[87] The concept of mutual activation and direct cross-coupling of naphtholates is interesting because it avoids the necessity of preparation of phenol derivatives. However, the use of sodium hydride limits the scope of the functional group tolerated in this mutual activated cross-coupling reaction. Only fused aromatic rings such as naphtholates were cross-coupled efficiently. Only 18% yield was isolated for cross-coupling of 3-methoxyphenol with para-*n*-butyl phenyl boroxine. The scope of aryl boroxines is also limited to alkyl, tertiary amine, and trifluoromethyl-substituted phenyl boroxines.

Scheme 1.23. Direct Cross-Coupling of Naphtholates via Mutual Activation Strategy



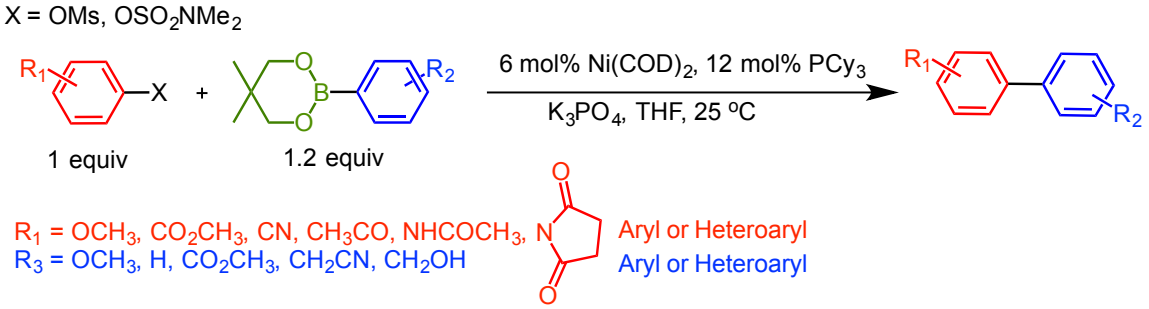
Besides the development of electrophiles in $Ni(COD)_2/PCy_3$ catalyzed Suzuki-Miyaura cross-coupling reactions, the nucleophiles have also been extended to aryl and heteroaryl trifluoroborates[27,88] and boronic esters.[6] MIDA boronates have yet to be applied in nickel catalyzed Suzuki-Miyaura cross-coupling.[89,90]

Molander[88] reported the scope of cross-coupling of aryl and heteroaryl mesylates and pivalates with aryl and heteroaryltrifluoroborates catalyzed by $Ni(COD)_2/PCy_3$ in *t*BuOH/H_2O = 1/1 mixture at 110 °C. Due to the instability of heteroarylboronic acids in basic conditions, heteroarylboronic acids are challenging cross-coupling partners. Heteroaryltrifluoroborates are a protected form of heteroarylboronic acids and release boronic acids by hydrolysis in reaction. With *t*BuOH/H_2O = 1/1 mixture, a wide variety of aryl and heteroaryl mesylates were cross-coupled with various aryl

and heteroaryl trifluoroborates with good to excellent yields. Aryl and heteroaryl pivalates were cross-coupled in moderate yields. Pyridinyl, quinolyl, iso-quinolyl, indolyl, cyano, methyl ether, acetyl and ester groups were tolerated on the electrophile. Thienyl, pyridinyl, furanyl and iso-quinolyl groups were tolerated on the nucleophile side.

Besides the cross-coupling of aryltrifluoroborates, arylboronic esters are also cross-coupled.[6,29,91] Arylboronic esters are less reactive compared to arylboronic acids and trifluoroborates in nickel catalyzed cross-coupling reactions.[91] However, they are important cross-coupling partners due to the precise control of stoichiometry in reaction.[91] After a preliminary study on $Ni(COD)_2/PCy_3$ catalyzed cross-coupling of aryl neopentylglycol with aryl sulfonates,[92] we reported the full scope of $Ni(COD)_2/PCy_3$ catalyzed cross-coupling of aryl and heteroaryl sulfonates with aryl and heteroaryl neopentylglycolboronates (Scheme 1.24), which will be discussed in later chapters. Sterically hindered *ortho*-substituents as well as electron-donating substituents were tolerated. Heteroaryl groups including pyridinyl, quinolyl and isoquinolyl groups were tolerated. [6]

Scheme 1.24. $Ni(COD)_2/PCy_3$ Catalyzed Cross-Coupling of Aryl/HeteroAryl Mesylates and Sulfamates with Aryl/HeteroAryl Neopentylglycolboronates

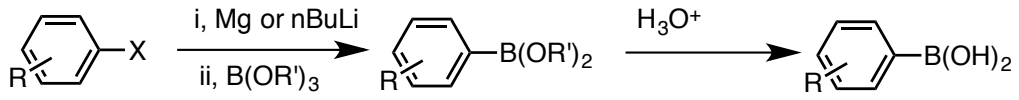


1.2 Nickel Catalyzed Borylation Reactions

Accessing inexpensive, selective, and functionalized arylboron reagents is the key to construct complicated structures *via* Suzuki-Miyaura cross-coupling.[1,6,24,93-96] We decided to develop an inexpensive nickel catalyzed borylation method to access boron reagents with base and nucleophile sensitive functional groups.

The first report on C-B bond formation uses boron trichloride to trap diarylmercury compounds.[97] The chemistry showed limited substrate scope, safety and environmental concerns. A modification by trapping Grignard or aryllithium reagents derived from aryl halides with electrophilic borates at low temperatures emerged as one of the most common methods to access large amounts of arylboronic acids in both academic and industrial settings (**Scheme 1.25**).[98] Only aryl bromides and iodides are reactive. Base or nucleophile sensitive functional groups are not tolerated.[99] A recent development, namely the "*in-situ quench method*" was reported to improve the functional group tolerance problem.[100] For instance, *n*-BuLi was added to a mixture of 3-bromopyridine and triisopropyl borate to quench the 3-pyridinyllithium intermediate rapidly and prevent the decomposition of pyridinyl group. The yield remained inadequate for arylboronic acids with base-sensitive functional groups such as esters.[100]

Scheme 1.25. Preparation of Arylboronic Acid by Trapping Electrophiles

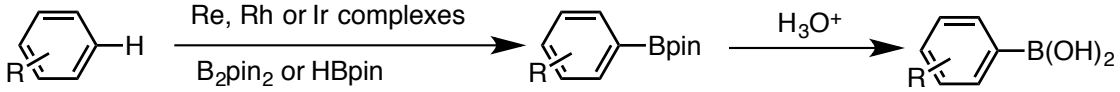


X = Br, I

Transition metal mediated direct borylation of C-H bond is quite attractive from an atom economic view (**Scheme 1.26**).[101-104] An expensive transition metal catalyst, such as Ir or Ru, is usually applied. Both B_2pin_2 and HBpin can be applied as the boron source, although B_2Pin_2 sometimes provides multi-borylation. The selectivity of this reaction is mostly sterically driven. In the

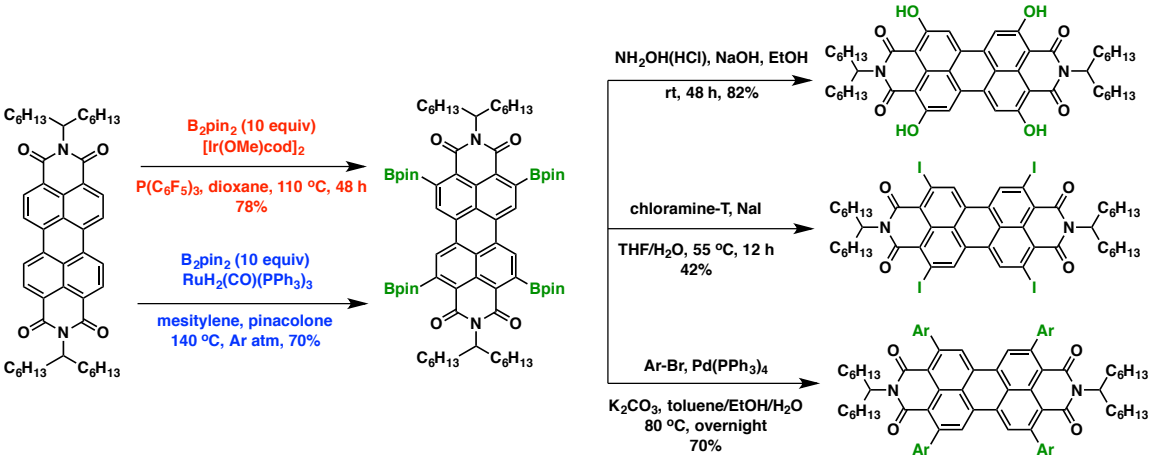
presence of a directing group, *ortho* borylation is favored.[105] Monoborylation as well as multiborylation were achieved.[105]

Scheme 1.26. Direct Borylation by C-H Activation



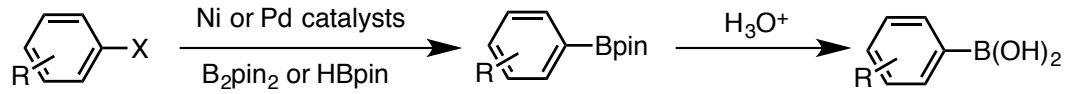
Recently, $RuH_2(CO)(PPh_3)_3$ and $[Ir(OMe)(COD)]_2$ catalyzed tetraborylation of the *ortho* positions of perylene bisimide were reported by Müllen and Shinokubo groups, respectively (**Scheme 1.27**).[106,107] The C-B bond was further transformed to other functional groups. Despite the atom-economy of transition metal catalyzed C-H borylation, the method is limited in its regioselectivity.[105]

Scheme 1.27. $RuH_2(CO)(PPh_3)_3$ and $[Ir(OMe)(COD)]_2$ Catalyzed C-H Borylation of Perylene Bisimide



The third method of C_{Ar}-B bond formation is the Ni or Pd catalyzed borylation of aryl halides and pseudo halides (**Scheme 1.27**). This method provides regioselectivity. However, it is limited to the accessibility of aryl halides. Due to the loss of a halide, the atom-economy is also lower compared to direct C-H borylation.

Scheme 1.28. Ni or Pd Catalyzed Borylation of Aryl Halides



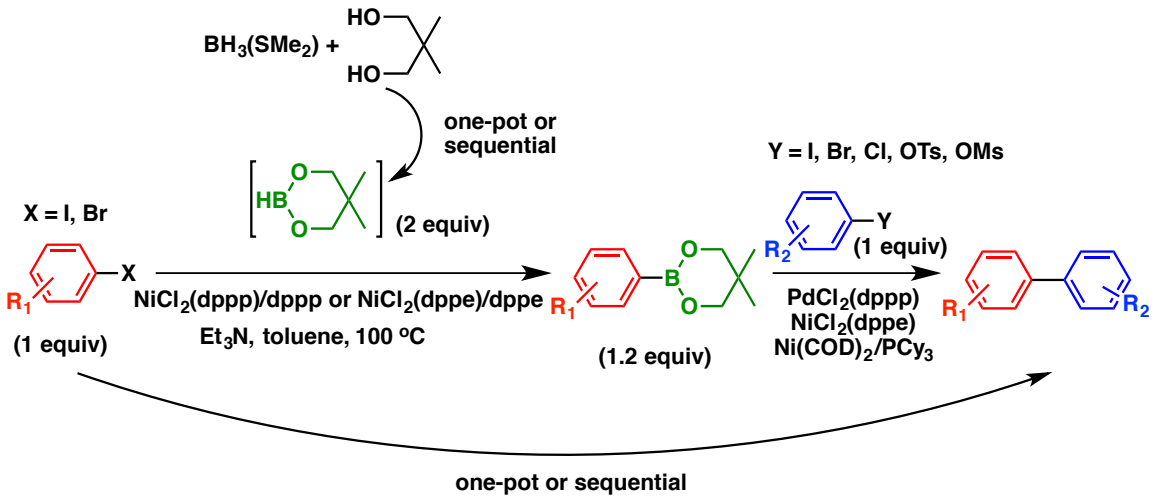
X = Cl, Br, I, OTf, OMs, OTs

Firstly reported in 1995 by Miyaura,[108] $PdCl_2$(dppf) catalyzes the transformation of aryl halides to aryl pinacol boronic esters in 60-98% yields in the presence of a weak base KOAc in DMSO at 80 ^oC. Nucleophile sensitive groups including nitro, cyano, ester and carbonyl groups are tolerated. Soon, Pd catalyzed borylations of aryl triflates were also achieved.[109] The method soon attracted great attention from the synthetic community due to the mild reaction conditions, high functional group tolerance as well as the accessibility of aryl halides and triflates.[110] However, the high cost of Pd catalysts, diboronyl reagents, and aryl halides or triflates were obstacles to the implementation of Pd catalyzed Miyaura borylation.

In 2000, in search of polyborylated flame-retardent materials, Tour reported the first example of Ni-catalyzed borylation of 1,4-dibromobenzene and 1,3,5-tribromobenzene.[111] Inspired by Miyaura's work on Pd^0 catalysts,[108] Tour surveyed an array of bidentate phosphine ligands (namely dppm, dppe, dppp, and dppb) and found that $Ni^{II}Cl_2$(dppp) was the most effective catalyst for the diborylation and triborylation of 1,4-dibromobenzene and 1,3,5-tribromobenzene.

In our effort to cut short synthetic steps for biphenyl AB_n dendrons and dendrimers,[18] we reported the $NiCl_2$(dppp)/dppp catalyzed borylation with *in situ* formed pinacol boronates as well as neopentylglycloboranes (**Scheme 1.29**).[112]

Scheme 1.29. Biaryl Construction *via* Nickel Catalyzed Borylation of Aryl Halides and Cross-Coupling of Aryl Halides and Sulfonates[92,112]

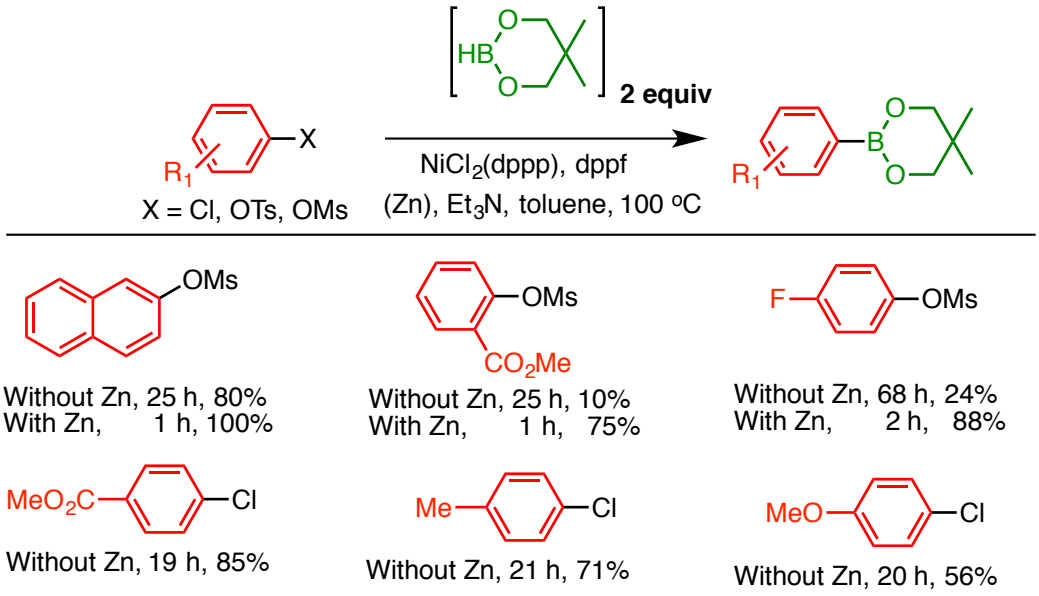


Using *in situ* formed boranes from BH_3•DMS,[113] we were able to avoid the use of expensive diboron reagents and the difficult purification of pinacol borane.[112] Replacing expensive pinacol with less expensive neopentylglycol is beneficial, not only cost wise. Aryl neopentylglycolboronates gives a crystalline compound while the corresponding pinacol boronate is a liquid.[6] Moreover, the hydrolysis of aryl neopentylglycolboronate is faster compared to the pinacol boronate.[6] $NiCl_2$(dppp) and $NiCl_2$(dppe) were the most effective catalysts in neopentylglycolborylation.[112] Addition of external ligand dppp or dppe inhibits the formation of byproducts.[112] We also developed $NiCl_2$(dppe)/dppe catalyzed Suzuki-Miyaura cross-coupling of aryl neopentylglycolboronates with aryl iodides and bromides.[112] A two-step, one-pot borylation and cross-coupling method was also developed (**Scheme 1.29**).[92]

Recalling the mixed-ligand method in cross-coupling of aryl mesylates,[42] we surveyed a mixed-ligand system for the neopentylglycolborylation of more challenging aryl chlorides.[114] 5 mol% $NiCl_2$(dppp)/10 mol% dppf was found to be the most efficient in borylation of aryl chlorides, significantly decreasing the formation of side product.[114] Both electron-rich and electron-deficient aryl chlorides were borylated. Nucleophile sensitive functional groups including esters, imides,

and cyano groups were tolerated. Selective borylation of the C-Br bond over the C-Cl bond was achieved.[114] Applying the same catalytic system with Zn as an external reducing reagent, aryl mesylates and tosylates was borylated in 1 to 6 h.[92] In the absence of Zn, borylation is slow with unfunctionalized mesylates. For mesylates bearing *ortho* or electron-withdrawing substituents, the borylation without Zn is not efficient, producing only low yields even after 60 h. These results highlight the importance of mixed-ligand concept and accelerating effect of reducing agent in nickel catalyzed borylation reactions.[92]

Scheme 1.30. Nickel Catalyzed Neopentylglycolborylation of Aryl Chlorides and Mesylates[92,114]



ortho-Substituted aryl halides and mesylates are difficult to borylate due to steric hindrance.[115] Applying $NiCl_2$(dppp)/dppf mixed-ligand system, protodeborylation and hydrodehalogenation resulting from oxygen and moisture are the side reactions that competes with borylation. To accelerate borylation of *ortho*-substituted aryl halides, zero-valent metals were added. Zero-valent metals accelerate the borylation reaction by reducing Ni^{II} generated in the catalytic cycle. With faster borylation, a shorter reaction time was needed for complete conversion of aryl halides.

Thus, reduction and homocoupling were inhibited.[116] This will be discussed in more detail in following chapters.

Recent advances in nickel catalyzed borylation reactions include applying aryl sulfamates and carbamates as substrates. Inspired by the effective cross-coupling of aryl sulfamates and carbamates with $NiCl_2(PCy_3)_2$, [50] Shi applied the same catalyst for borylation of aryl sulfamates and carbamates. With careful selection of base and solvent, cross-coupling was inhibited and aryl neopentylglycolboronates were prepared in moderate to good yield.[117] A more synthetically attractive method is the use of tetrahydroxydiboron to access boronic acid directly from aryl and heteroaryl halides, sulfonates and sulfamates at room temperature.[118] Following the initial report on Pd catalyzed borylation of aryl chlorides with tetrahydroxydiboron,[119] Molander reported 1 mol% $NiCl_2$(dppp) catalyzed borylation of aryl and heteroaryl halides, sulfonates and sulfamates. The boronic acids can be transformed to a range of boron reagents, such as trifluoroborates, boronic esters and MIDA boronates.[118] Notably, di-*ortho* substituted aryl chlorides were borylated with $NiCl_2(PMe_3)_2$ and and Pd catalysts.[120,121]

The development of transition metal mediated borylation reactions continues to provide important boron reagents, not only as cross-coupling partners for Suzuki-Miyaura reaction, but as drugs, sensors and catalysts.[97,122]

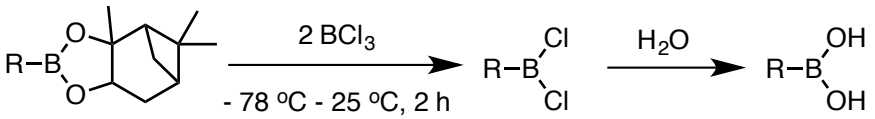
1.2.1.1 Hydrolysis of Boronic Esters

The hydrolysis of acyclic boronic esters such as diisopropyl arylboronic acid and small unhindered cyclic ones such as aryl ethyleneglycolboronic esters is very rapid under acidic conditions.[123] The hindered cyclic boronic esters such as aryl pinacol boronic esters and aryl neopentylglycolboronic esters are resistant to hydrolysis in simple acidic or basic conditions.[123,124] As a result, these hindered boronic esters are stable to acidic workup and silica gel column chromatography.[123] On the other hand, hydrolysis of pinacol boronic ester or neopentylglycolboronic ester in water even at extreme pH is ineffective.[123] So far, only the

following methods are effective to prepare aryl boronic acids from aryl pinacol boronic esters or aryl neopentylglycolboronic esters.

The first method is the transborylation with boron trichloride (Scheme 1.31).[125-128] However, the gaseous feature, reactivity and toxicity of boron trichloride limit the use of this method.

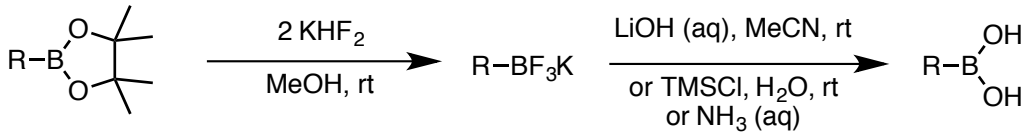
Scheme 1.31. Hydrolysis of Boronic Esters by Transborylation with BCl_3



R = *n*-C_4H_9, Ph, Cy

The second method transforms boronic esters to potassium trifluoroborates (Scheme 1.32), which are hydrolyzed in the presence of lithium hydroxide, trimethylsilyl chloride or aqueous ammonia. [129,130]

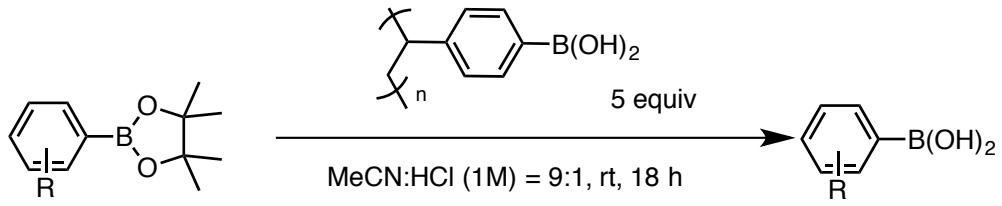
Scheme 1.32. Hydrolysis of Boronic Esters *via* Potassium Trifluoroborate



R = aryl or alkyl

The third method is the transesterification with a large excess amount of phenyl boronic acid (**Scheme 1.33**). The Hutton laboratory applied a polystyrene-boronic acid to deprotect pinacol boronic esters.[131] The use of large excess of polystyrene bounded boronic acids are not practical due to the need to regeneration of polystyrene-boronic acid.

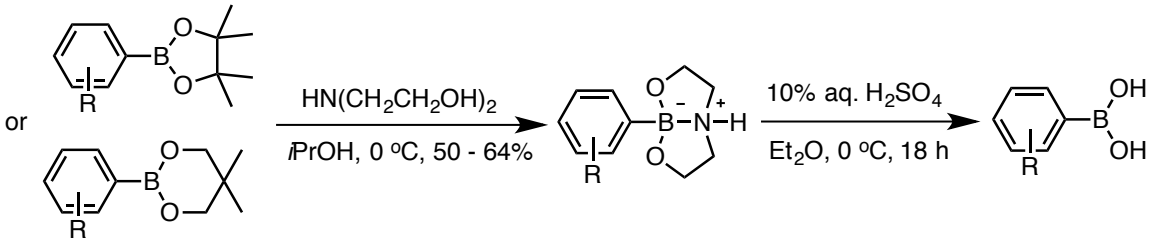
Scheme 1.33. Hydrolysis of Boronic Esters *via* Tranesterification



R = 2-Me, 3-Me, 4-Me, 2-OMe, 3-OMe, 4-OMe, 3,4-OMe, 2-OH, 2-COMe, 3-NO_2, 4-NHBoc, 2-OBn

The fourth method is a mild and practical method and selected by our laboratory to prepare arylboronic acids from aryl neopentylglycolboronic esters (Scheme 1.34).[132] The arylboronic esters react with diethanolamine to produce a borate salt, which crystalize out of the solution.[132] The crystallization is essential to the hydrolysis process as it drives the equilibrium of the transesterification reaction to completion.[132,18] The diethanolamine salts of arylboronate are hydrolyzed by 10% aqueous sulfuric acid at 0 ^{o}C to room temperature.[132] For alkylboronic esters, which the corresponding diethanolamine esters are soluble, this method is not applicable.

Scheme 1.34. Hydrolysis of Aryl Pinacolboronic Esters and Neopentylglycolboronic Esters *via* Diethanolamine Esters



1.3 Precatalyst Concept In Ni or Pd Catalyzed Cross-Coupling Reactions

Precatalyst refers to any compound that can be converted to active catalyst during a reaction. From a broad point of view, most commercially available catalysts are actually precatalysts. For example, $Ni(COD)_2$ is not efficient in Suzuki-Miyaura cross-coupling reactions without the addition of an external ligand.[29,75] $Pd(OAc)_2$ is another commercially available precatalyst widely used as a stable Pd source.[133] However, the concept of single-component, highly reactive, discrete precatalysts is only developed recently. We intend to use bench-stable, inexpensive, and highly reactive nickel precatalysts for the synthesis of biphenyl AB_n dendritic building blocks.[18,19,134-136 137,138]

Pd^{II} and Ni^{II} are bench stable.[29,139] Common Pd^{II} sources such as $Pd(OAc)_2$ and $PdCl_2$ are activated *in situ* by mild reducing reagents, such as a ligand or a base. The reduction of Ni^{II} to Ni^0 requires an external reducing reagent such as Zn,[12,28,140] BuLi,[141] or NaH.[142,143] Excess boronic acid can also reduce Ni^{II} to Ni^0, but only at elevated temperature (80 ^oC to 130 ^oC).[42,50,56,144,145] The deficiencies of generating Ni^0 *in situ* from Ni^{II} sources are the relatively low functional group tolerance (in the cases of *n*-BuLi, NaH), high temperature, and unknown amount of active Ni species generated in the reaction. Since some boronic acids are prone to protodeborylate at high temperature in the presence of bases, elevated temperature limits the scope of heteroaryl or electron deficient boronic acids in Suzuki-Miyaura cross-coupling reactions.[146]

A second class of Pd or Ni catalyst is the zero-valent metal species, such as $Pd_2(dba)_3$, $Pd(PPh_3)_4$ and $Ni(COD)_2$. They are commercially available and enter the catalytic cycle by ligand exchange. The deficiencies include the stability of these zero-valent metal complexes. For example, commercially available $Pd_2(dba)_3$ contains varying contaminates as Pd nanoparticles and free dba.[147] $Ni(COD)_2$ needs to be kept under nitrogen at low temperature.[148] The quality of commercially available $Ni(COD)_2$ varies from batch to batch. [149] Last but not least, the PPh_3, dba and COD in these precursors inhibits the cross-coupling reactions.[75,139,150] Due to the deficiencies

of commercially available Pd^0 and Ni^0 catalysts, an increasing amount of research was focused on the development of highly reactive, single component precatalysts.

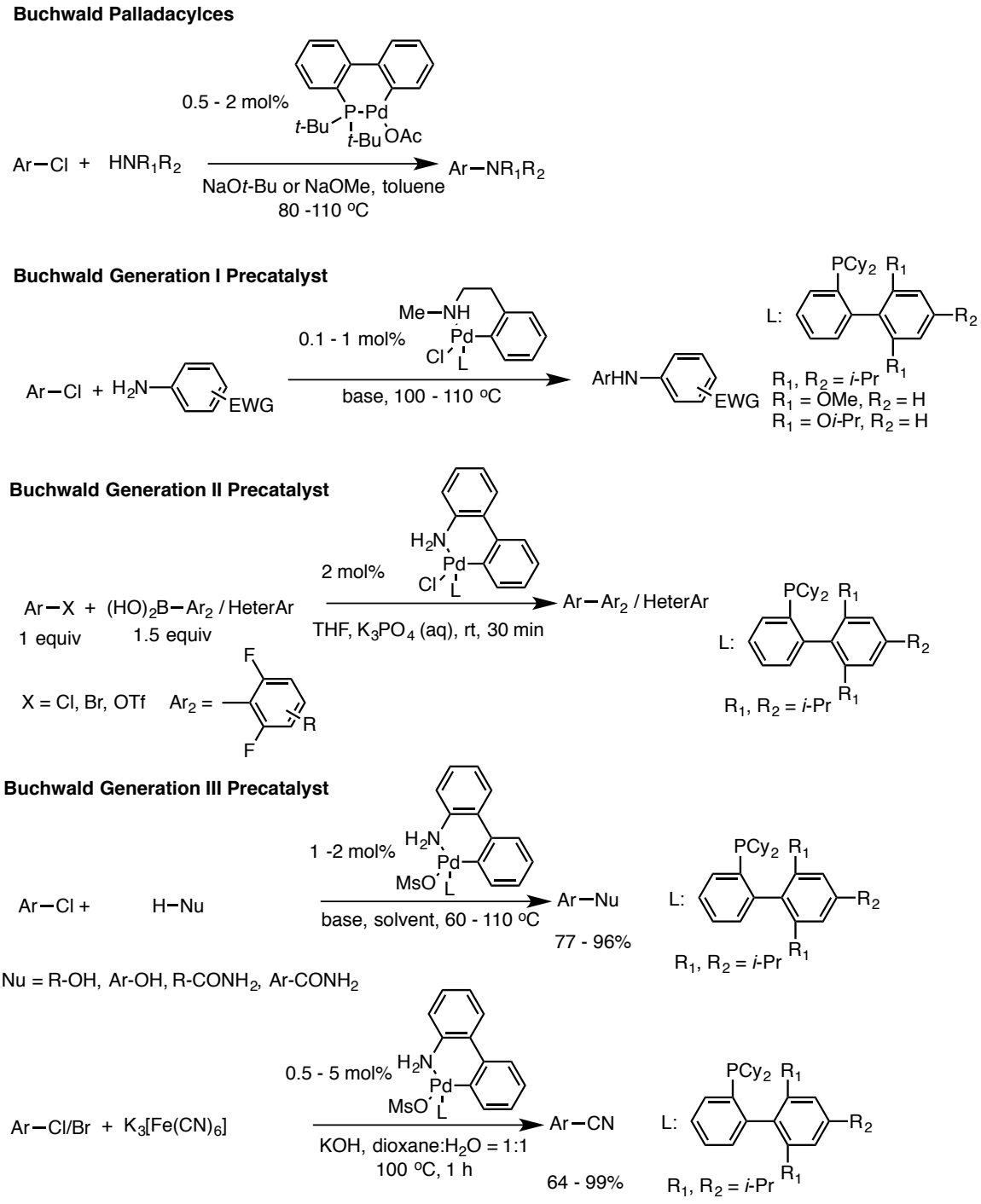
To qualify as a desired precatalyst, it has to be a) easily activated *in situ*; b) generating side products that do not interfere with reaction; c) bench-stable for easy handling and d) low cost or easily synthesized.

1.3.1 Pd Precatalysts in Cross-Coupling Reactions

Several classes of palladium precatalysts have been designed and tested based on the above principles. One class of palladium complexes that was extensively investigated is the palladacyles. [151-155] They were first prepared and noted by Beller and Herrmann in 1995 for the Suzuki-Miyaura cross-coupling of aryl chlorides,[156] then modified further due to the high turn-over number reported for these precatalysts in cross-coupling reactions.[154] Buchwald soon reported an air, moisture and thermally stable palladacyclic precatalyst based on JohnPhos as an *in situ* precursor to Pd^0(JohnPhos).[157] The precatalyst showed superior reactivity in the amination of aryl chlorides compared to the simple mixture of $Pd(OAc)_2$ and JohnPhos (**Scheme 1.35**).[157] Five years later, a new generation of amine based precatalyst was reported.[158] These precatalysts are synthesized in three steps in multi-gram scales. They are able to achieve C-N bond formation between electron-deficient aniline and unactivated aryl chloride even at 0.1 mol% catalyst loading (**Scheme 1.35**). In contrast, amination of unactivated aryl chlorides catalyzed by $Pd_2(dba)_3$ or Pd^{II} sources stops at 25% conversion.[158] Moreover, C-N bond formation at -10 ^oC was also achieved with the first generation Buchwald precatalysts (**Scheme 1.35**).[158] Cutting down the synthesis of three step to one step, a second generation Buchwald precatalyt were developed. The second generation Buchwald precatalysts promotes the facile cross-coupling of electron-deficient or heteroaromatic boronic acids with aryl bromide, chlorides and triflates.[159] These electron-deficient or heteroaromatic boronic acids have short half-lives in the basic conditions used for Suzuki-Miyaura cross-coupling due to protodeborylation.[159] By using a highly reactive precatalyst, the rate of cross-coupling competes with protodeborylation and enabled the challenging coupling

reactions. Later, it was reported that replacement of –Cl in the second-generation Buchwald precatalysts with –OMs group (Buchwald third generation precatalysts) improved the solubility of the third generation Buchwald precatalysts.[150] This replacement also simplified the synthesis of the precatalysts series from three steps to two steps. Moreover, sterically hindered ligands are tolerated on the third generation precatalysts. Improved reactivity in C-N, C-O and C-C bond formation reactions was observed as well.[150]

Scheme 1.35. Buchwald Precatalyst for C-N and C-C Bond Formation



One last class of Pd precatalysts is the Pd-NHC (N-heterocarbene) complexes.[148,160-162] The NHC based Pd precatalysts showed extraordinary activity toward sterically hindered substrates, including the formation of tetra-*ortho* substituted biaryl compounds.

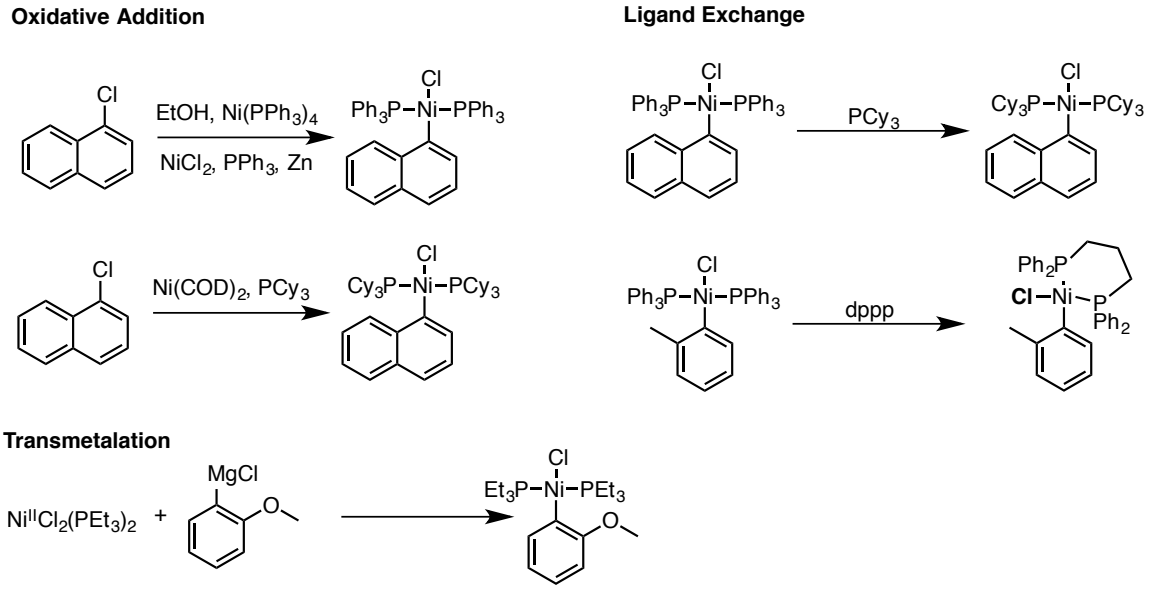
To summarize, the development of Pd precatalysts provides access to fast cross-coupling of boronic acids prone to deborylation,[139,150,157-159] steric hindered coupling reactions[162] and higher TON.[156]

1.3.2 Nickel Precatalysts in Cross-Coupling Reactions

Inspired by the development of Pd precatalysts, we decided to design inexpensive, single-component, and highly reactive nickel precatalysts for the fast and quantitative cross-coupling of phenol derivatives with aryl neopentylglycolboronates.

The preparation of nickel precatalysts started in the 1960s by Shaw. [72] A series of $Ni^{II}X(aryl)(PR_3)$ (X = Cl, Br; aryl = naphthyl, phenyl; R = aryl, alkyl) was prepared by transmetalation reaction. Later, the precatalysts were also prepared from oxidative addition to Ni^0 complexes[163] and ligand exchange method.[164]

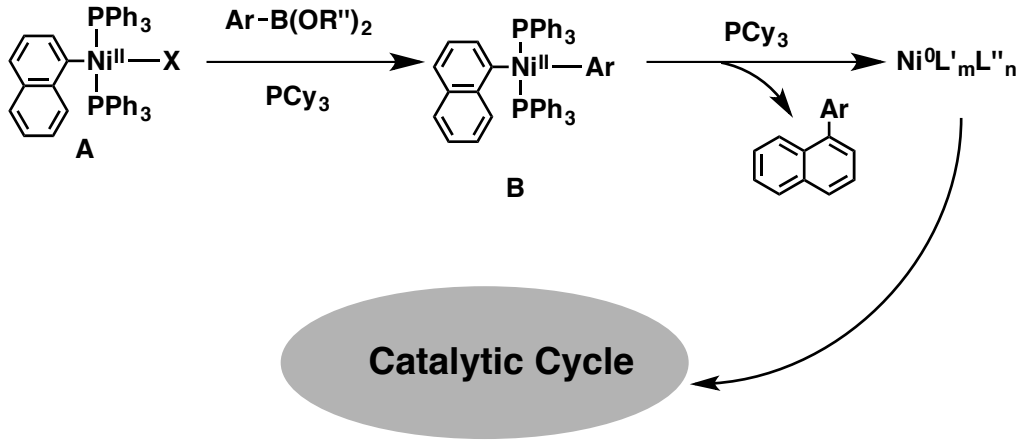
Scheme 1.36. Synthesis of Nickel Precatalysts



Oxidative addition method is the most applicable to all substrates and ligands. However, Ni^0 complexes are air and moisture sensitive. When the ligand is bidentate, oxidative addition is slow or unsuccessful. The ligand exchange method is preferred for bidentate ligands. Transmetalation is limited to substrates without base sensitive groups such as halides.

Despite the work on preparation of the nickel precatalysts, their application in catalytic reactions is only reported quite recently. A single case of cyanation of bromothiophene was reported in 1990.[165] 17 years later, the Yang group reported $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$ catalyzed cross-coupling of aryl halides and tosylates with arylboronic acids in THF at room temperature. [73,74] The $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$ activates by transmetalation and reductive elimination in the presence of boronic acid at room temperature (**Scheme 1.37**).

Scheme 1.37. Activation of $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$



The same precatalyst was also applied in amination of aryl tosylates in the presence of NHC ligands.[74] The Hu laboratory applied $Ni^{II}OTs(4\text{-}OMeC_6H_4)(PCy_3)_2$ for the cross-coupling of aryl tosylates with arylboronic acids.[65] It was observed 2 equiv of water accelerated the reaction. Water was suspected to be an additional ligand in stabilizing Ni^0 in this case. Inspired by Yang and Hu's work, we also applied $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2/PCy_3$ in the cross-coupling of aryl and heteroaryl mesylations and sulfamates with aryl and heteroaryl neopentylglycolboronates.[29] The

cross-coupling proceeds readily at room temperature in THF. A variety of functional groups, including esters, ethers, cyano groups, imides and ketones are tolerated.[29]

However $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2/PCy_3$ is not as reactive as $Ni(COD)_2/PCy_3$ mixed-ligand system.[29] Moreover, a single component precatalysts is preferred.[29] We decided to develop a single component, reactive and stable nickel precatalyst for sterically hindered substrates. After a careful study on mixed-ligand effects, as well as the amount of water in the reaction, we found a library of $Ni^{II}X(aryl)(PCy_3)_2$ (X = Cl; aryl = 1-naphthyl, 2-naphthyl, 9-phenanthrenyl, 9-anthracyl, 2-methoxy naphthyl; X = OMs, OTs; aryl = 1-naphthyl, 2-naphthyl) precatalysts.[75] These precatalysts catalyze Suzuki-Miyaura cross-coupling of sterically hindered aryl sulfamates with aryl neopentylglycolboronates in less than 60 min at room temperature.[75] This will be discussed in more detail in the following chapters.

At the same time as we were developing our precatalysts, the Hartwig group reported a reactive, single-component $Ni^{II}Cl(cinnamyl)(dppf)$ precatalyst which provides a broad scope of cross-coupling of heteroaryl bromides and chlorides with heteroarylboronic acids in acetonitrile at 50 °C or dioxane at 80 °C. Most importantly, only 0.5% catalyst loading was applied (Figure 1.2). Pyridinyl boronates were not cross-coupled though.[76]

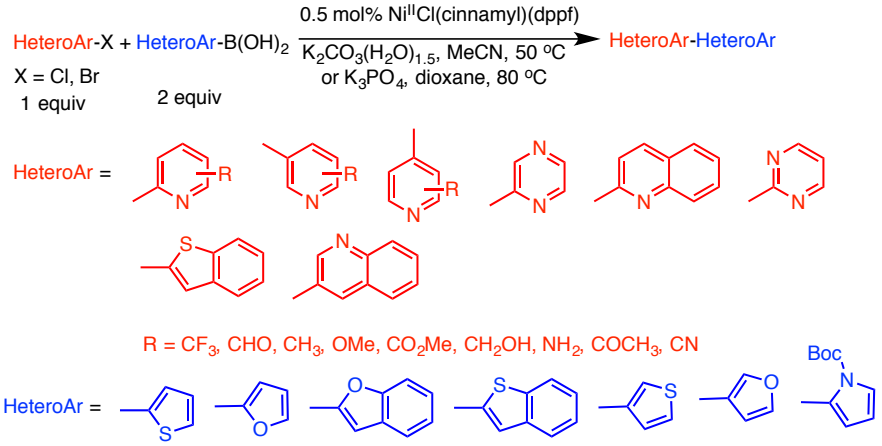


Figure 1.2. Single-component $Ni^{II}Cl(cinnamyl)(dppf)$ catalyzes Suzuki-Miyaura cross-coupling of heteroaryl bromides and chlorides with heteroarylboronic acids at 0.5 mol% loading.

The Jamison laboratory applied $Ni^{II}Cl(2\text{-tosyl})(PCy_2Ph)_2$ for benzylation of terminal alkenes.[166] The cyclooctadiene released from $Ni(COD)_2$ not only inhibits the Ni catalyzed Heck reaction, but also benzylates faster than terminal alkenes in some cases.[166] By employing $Ni^{II}Cl(2\text{-tosyl})(PCy_2Ph)$, the reaction can be carried out on the bench top without exclusion of air or water. Over 95:5 regioselectivity and high yield were obtained in nearly all cases. [166] The Buchwald group developed $Ni^{II}Cl(2\text{-tosyl})(dppf)$ for the amination of aryl chlorides, sulfamates, mesylates and triflates with primary, secondary amines and anilines.[149]

Nickel precatalysts have been demonstrated as air stable nickel complexes for a broad reaction scope.[133,146] It is expected to show more application in broader field including polymerization and supramolecular chemistry.

1.4 Mixed-Ligand Concept in Borylation and Cross-Coupling Reactions

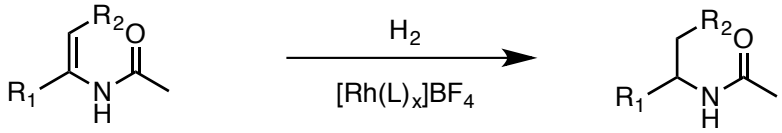
As has been shown in previous chapters, ligands are important to transition metal catalyzed homogeneous reactions.[167-169] A lot of work in optimizing reaction conditions are involved in the selection of ligands.[170] Ligands stabilize the metal center, mediate the electronic and steric properties of the metal center as well as provide chemo-, regio- and stereoselectivity to chemical reactions.[171] The proper selection of ligands is of crucial importance in Suzuki-Miyaura cross-coupling reactions as well as in borylation reactions. However, development of new ligands can be tedious and costly. To fully exploit the potential of existing ligands, we applied mixed-ligand strategy to develop nickel based catalytic systems for neopentyglycolborylations and Suzuki-Miyaura cross-coupling reactions.[6,116,172]

In this chapter, only mixed-ligand systems showing improved reactivity or selectivity compared to mono-ligand systems will be discussed. Tandem reactions applying mixed-ligands will not be discussed because essentially these reactions involve two sequential reactions utilizing two different ligands instead of applying mixed-ligand concept in a one-step reaction.[173,174]

In 2002-2003, the concept of mixed-ligand or ligand combination was developed.[175-178] Reetz[176] proposed to exploit the potential of existing ligands by combining different ligands in one reaction ($ML_nL'_m$) instead of inventing new ligands. Considering in most cases, multiple ligands bind to one reactive metal center (ML_n, n=3-6).[179] By mixing the ligands bound to the metal center, heterocombination metal ligand complexes ($ML_nL'_m$) can be formed. During reaction, ligands dissociate, exchange and associate.[179,180] The mixed-ligand method greatly increases the amount of available catalytic systems. For example, given a library of 10 ligands, there are 45 heterocombinations, a five fold increase in the number of catalytic systems.

The Reetz group applied the idea on Rh catalyzed asymmetric hydrogenation of actamidoacrylate.[176] With monodentate BINOL-based modular phosphonite ligand, the *ee* of hydrogenation of acetamidoacrylate ranges from 7.4 to 95.4. With combined phosphonite ligands, the *ee* of hydrogenation of acetamidoarylate increases to 98.0. (**Scheme 1.38**)

Scheme 1.38. Increase of *ee* of Rh Catalyzed Asymmetric Hydrogenation of Actamidoacrylate by Mixed-Ligand System[176]



R_1 = CO_2CH_3, Ph, *p*-Cl-C_6H_4, 2-naphthyl
R_2 = H, Ph

Homocombination of ligand: *ee* 75.6 - 94.4
Mixed-ligand system: *ee* 96.4 - 98

The Feringa group demonstrated that improved *ee* and yield could be obtained for Rh catalyzed asymmetric C-C bond formation using the mixed ligand approach.

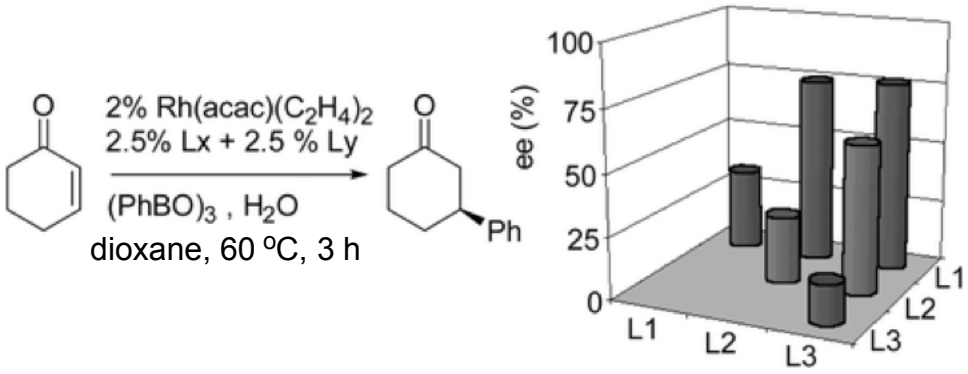


Figure 1.3. Improved *ee* was obtained for Rh catalyzed asymmetric C-C bond formation by mixed-ligand approach.

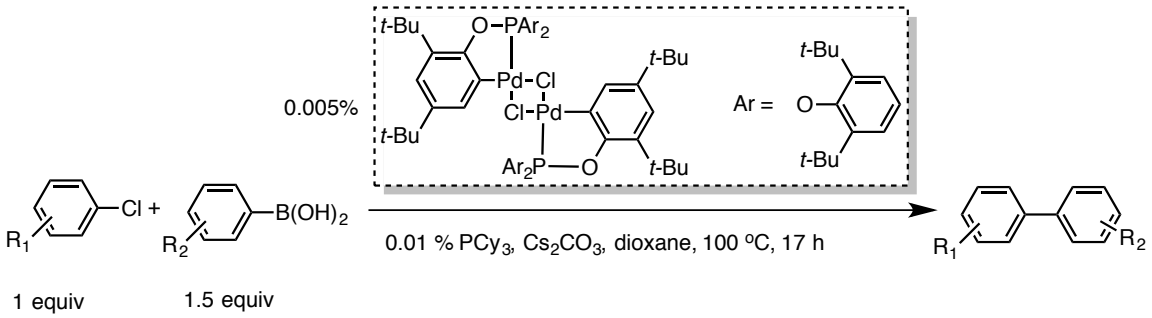
(Reprinted with permission from reference [177] . Copyright (2003) American Chemical Society.[177])

Both Reetz's and Feringa's systems are built upon two basic features: 1) a metal center is bonded to multiple ligands; 2) ligand exchange happens easily in reaction. Thus with a mixed ligand, several catalytically active species, ML_n, $ML_{n-m}L'_m$, ML'_n coexist in reaction mixture. Due to the different binding affinity of ligands to the metal center, the ratio of each species in the mixture does not necessarily follow a statistical distribution. During the reaction, the most reactive and selective species will react fastest, hence increase the conversion and selectivity of the system. It is important to notice that mixed-ligand systems might not be necessarily more reactive or selective than monoligand systems. Thus, an optimization process is needed. For chiral systems, generally a combination of chiral ligands or a chiral ligand with an achiral ligand is applied. Achiral ligands can be used to improve the conversion or regioselectivity of an achiral reaction.[170]

The scenario is different for Ni or Pd based mixed-ligand catalyzed cross-coupling and borylation systems. In 2002, the Bedford[178] group observed that using a mixture of PCy_3 and triarylphosphite ligand, a turnover number (TON) of up to 1,000,000 was reported for palladium catalyzed Suzuki-Miyaura cross-coupling of aryl chlorides with arylboronic acids (**Scheme 1.39**).[178] For comparison, the TON of a single ligand system generally ranges from 3000 to 6000.[178] The increase of TON comes from the increased longevity of catalyst life rather than higher reaction rate according to kinetic studies.[178] The coligand (PCy_3) decreases the reactivity

of Pd triarylphosphite complex but stabilizes the resting state of Pd by preventing the aggregation of Pd^0.

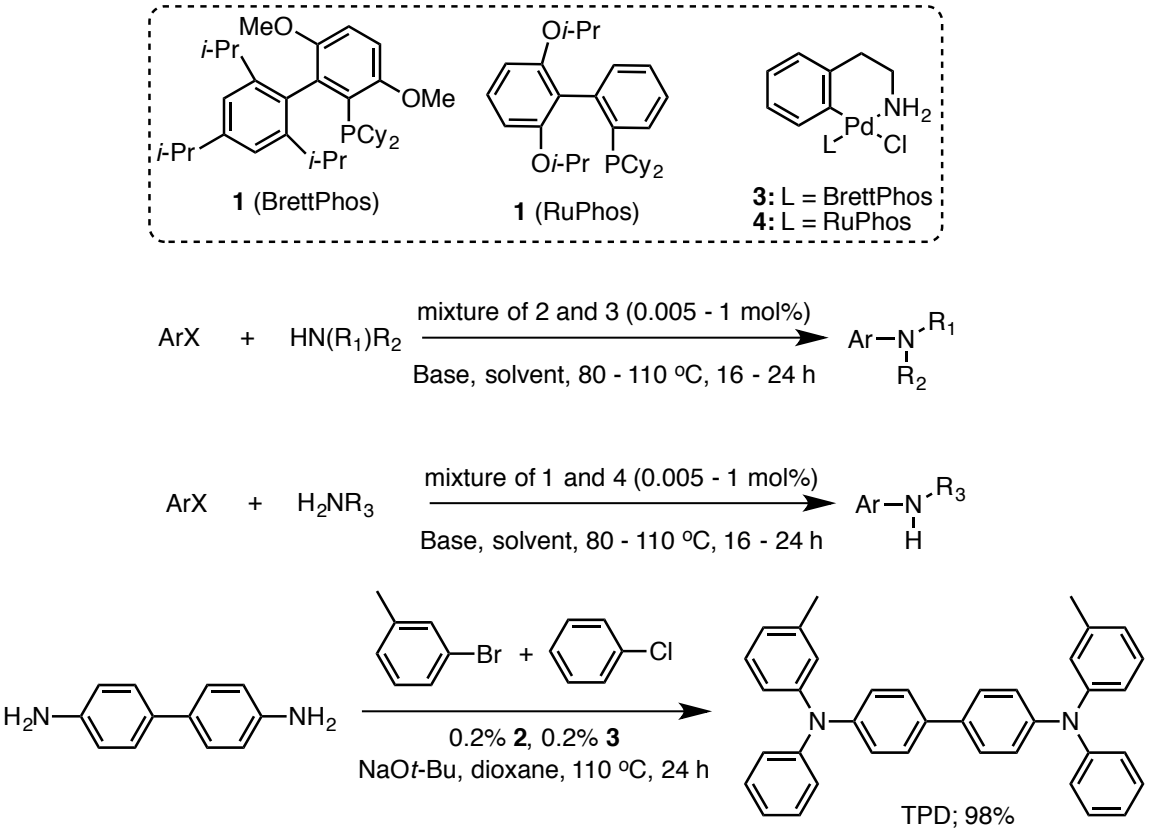
Scheme 1.39. Suzuki-Miyaura Cross-Coupling of Aryl Chlorides with Mixed-Ligand Pd Catalytic System[178]



In the case of Buchwald precatalysts, due to the high steric hindrance of the Buchwald ligand, the metal center is only bonded to one ligand.[167,174,181] The feature of a combination of ligands on one metal center does not apply. However, an increase of activity and selectivity of mixed-ligands in Pd catalyzed amination[181] reactions was observed. The mixed-ligand system not only showed the merits of each mono ligand system but enabled the synthesis of asymmetric triarylamines. The catalysts based on BrettPhos (**1** and **3**, **Scheme 1.40**) are only efficient for monoarylation of primary amines but inefficient in amination reactions of secondary amines.[181] On the other hand, the catalysts based on RuPhos (**2** and **4**, **Scheme 1.40**) are efficient for the arylation of secondary amines but produce low conversion for amination of primary amines due to the formation of significant quantities of undesired diarylation byproduct.[174,181] Upon mixing the precatalysts based on BrettPhos (**3, Scheme 1.40)** with RuPhos (**2**, **Scheme 1.40**), the arylation of secondary amine was accomplished with comparable yields compared to precatalysts based on RuPhos alone (**4**, **Scheme 1.40**).[181] When mixing the precatalysts based on RuPhos (**2, Scheme 1.40)** with BrettPhos (**1**, **Scheme 1.40**), the arylation of primary amines was accomplished with comparable yields compared to precatalysts based on RuPhos alone (**4**, **Scheme 1.40**) without undesired biarylation reaction.[181] Most importantly, the synthesis of an

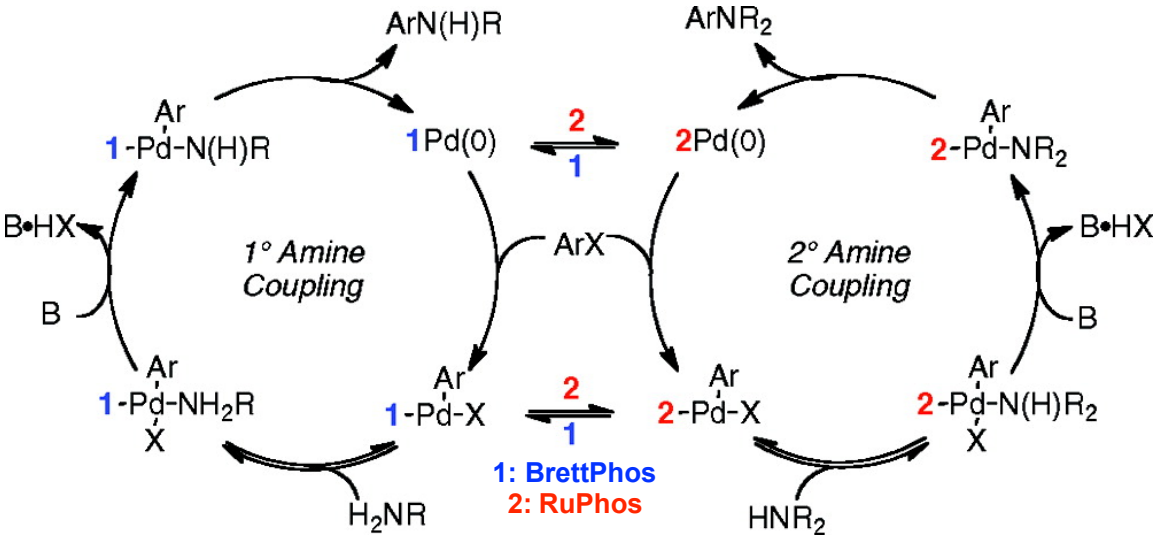
asymmetric triarylamine TPD was accomplished using this mixed-ligand system. (**Scheme 1.40**)[181]

Scheme 1.40. Mixed-Ligand Pd-Catalyzed C-N Cross-Coupling Reactions for Both Primary Amines and Secondary Amines[181]



Using crossover experiments, the mechanism of this enhanced reactivity of mixed-ligand Pd system was proposed. (Scheme 1.41)

Scheme 1.41. Proposed Mechanism of the Mixed-Ligand Pd Catalytic System for Arylation of Amines[181] (Reprinted with permission from reference [181]. Copyright (2010) American Chemical Society)

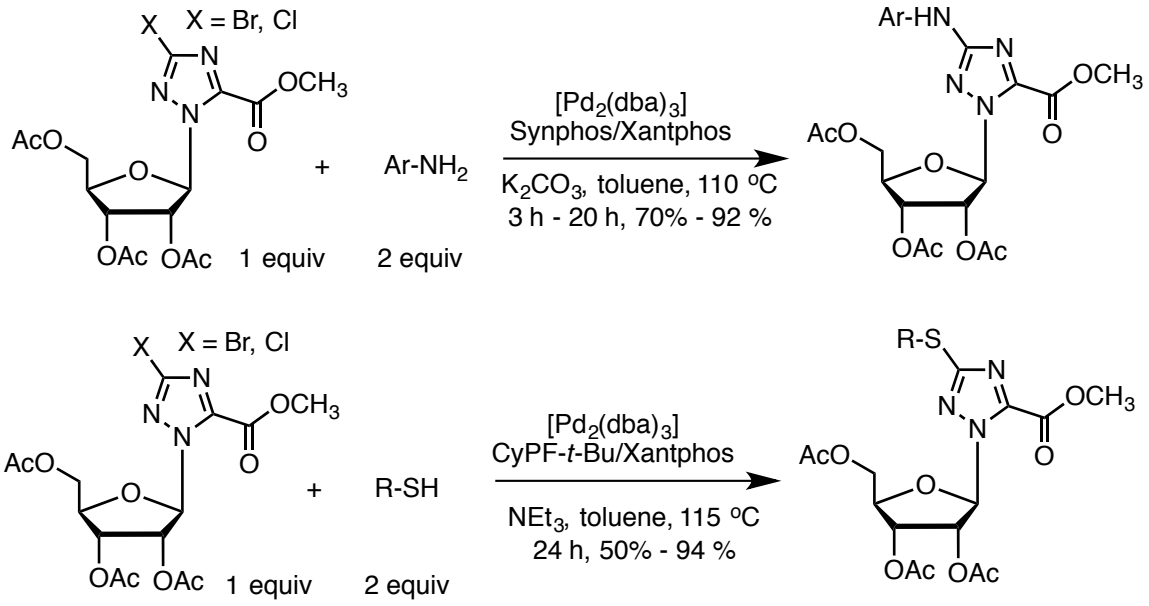


For the arylation of primary amines, the left catalytic cycle dominates. The right hand cycle proceeds for arylation of secondary amines. It indicates Pd preferably binds with BrettPhos, thus only small amount of RuPhos-Pd complex exists in the reaction mixture. Therefore, no biarylation of primary amine was observed. For secondary amines, since BrettPhos cannot catalyze the amination, a small amount of RuPhos-Pd complex from ligand exchange at Pd^{II} or Pd^{0} oxidation state catalyzes the amination. In the synthesis of asymmetric triarylamines, the Pd undergoes facile ligand exchange between the two cycles at both Pd^{0} and Pd^{II} state. The success of this mixed-ligand system is based on the rapid ligand exchange process on Pd as well as the higher rate of the desired reaction compared to undesired side reactions.[181]

The Peng group also observed the enhanced reactivity of mixed-ligand Pd catalyzed C-N and C-S coupling of *N*-arylaminotriazole nucleosides with anilines and thiols (**Scheme 1.42**), which is otherwise not achievable with single ligand systems.[182,183] Both triazole and purine chlorides and bromides are aminated with a broad scope of anilines. Selective amination of bromo-triazole

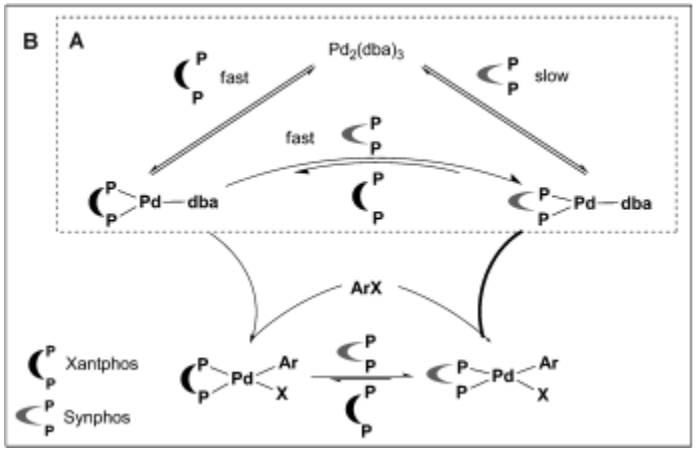
processes smoothly with 4-chloroaniline with 73% yield. Heteroaryl chlorides and bromides were thiolated with aromatic and aliphatic thiols. [182,183]

Scheme 1.42. Pd Mixed-Ligand Catalyzed Amination and Thiolation of *N*-arylaminotriazole Nucleosides[182,183]



To study the mechanism underlining the mixed-ligand system, cyclic voltammetry and ^{31}P NMR experiments were carried out. Peng concluded that the enhanced reactivity comes from the faster formation of desired (Synphos)Pd(dba)[183] and [(CyPF-*t*Bu)Pd(dba)][182] in the presence of Xantphos. While (Xantphos)Pd(dba) is not reactive for amination or thiolation, it is formed quickly in the reaction and exchanges rapidly with Synphos and CyPF-*t*Bu. [182,183] During reaction, the Pd^0 and Pd^{II} are stabilized by Xantphos, and facile ligand exchange happens on Pd^0 and Pd^{II} states. Later, the Peng group concluded that $Pd(dba)_2$ and $Pd_2(dba)_3$ offered equivalent catalytic efficiency in the reported Pd-catalyzed C-N and C-S cross-coupling reactions involving mixed ligand systems.[184] (**Scheme 1.43**)

Scheme 1.43. Proposed Mechanism of Mixed-Bidentate-Ligand Pd Catalytic System (Reprinted with Permission from Reference [183] Copyright © 2012 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim)

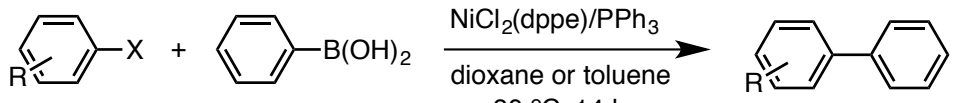


A similar explanation was provided *via* DFT studies on the increased reactivity of mixed ligand systems in the Pd^{II}-Bronsted acid catalyzed migratory ring expansion reaction of an indenyl cyclobutanol to a spirocyclic indene compounds. The DFT studies showed that ligand exchange stabilizes the intermediate species, thus lowering the activation energy of the ring expansion reaction, [185] which is similar to the effect of a supporting ligand in Pd mixed-ligand catalyzed amination of halogenated nucleosides.[183]

Our group first noticed the mixed-ligand effects in both nickel catalyzed borylation and Suzuki-Miyaura cross-coupling reactions.

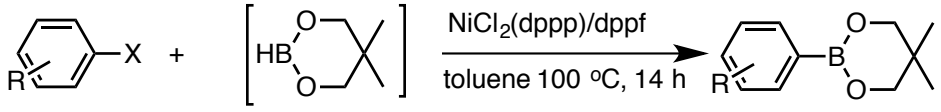
In 2004, we observed that a mixed-ligand $NiCl_2$(dppe)/PPh_3 system[42] showed solvent-independent reactivity in nickel catalyzed Suzuki-Miyaura cross-coupling reactions of aryl mesylates, arenesulfonates and halides with arylboronic acids. Both electron-rich (-OMe substituted) or electron-deficient (COOMe substituted) aryl mesylates and chlorides are cross-coupled in good to excellent yields in toluene and dioxanes. As-received ACS reagent grade solvents were applied successfully as well (**Scheme 1.44**).[42]

Scheme 1.44. $NiCl_2(dppe)/PPh_3$ Mixed Ligand System Catalyzed Suzuki-Miyaura Cross-Coupling of Aryl Halides and Sulfonates



Later, we observed similar mixed-ligand effects in nickel catalyzed borylation of aryl sulfonates and halides (**Scheme 1.45**).[114-116] With $NiCl_2$(dppp)/dppf, the rate of borylation increased while side reactions such as dehalogenation and homocoupling were inhibited. A variety of functional groups including esters, ethers, imides and cyanides were tolerated. Halogenated thiophene was borylated but not pyridine derivatives. Zero valent metals accelerate the borylation reaction, which competes with side dehalogenation reactions.[114-116]

Scheme 1.45. $NiCl_2$(dppp)/dppf Mixed-Ligand System Catalyzed Neopentylglycolborylation of Aryl Halides and Sulfonates[114-116]

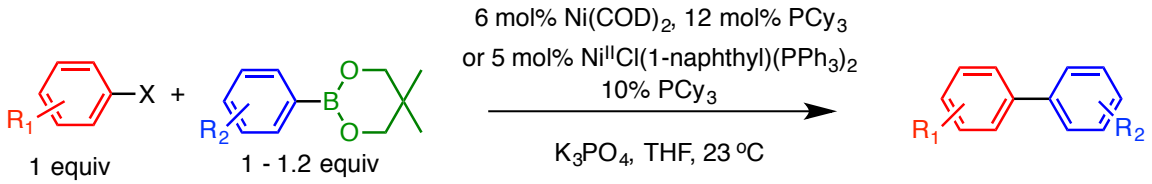


R = *o, m, p* -F, OMe, COOMe
CN, CH_2CN
X = I, Br, Cl, OMs, OTs

Later, we applied mixed ligand[6,172] $Ni(COD)_2/PCy_3$ and $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2/PCy_3$ system in the cross-coupling of aryl/heteraryl mesylates and sulfamates with aryl/heteroaryl neopentylglycolboronates in THF at room temperature.[6,172] The reaction showed a great tolerance to functional groups. Without PCy_3, neither $Ni(COD)_2$ nor $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$ is capable of catalyzing the coupling reaction. We suspect the more electron rich PCy_3 replaces

COD and PPh_3 in the catalyst activation step. Further study showed COD and PPh_3 are deleterious to the reaction.

Scheme 1.46. $Ni(COD)_2/PCy_3$ and $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2/PCy_3$ Catalyzed Cross-Coupling of Aryl/Heteraryl Mesylates and Sulfamates with Aryl/Heteroaryl Neopentylglycolboronates[6,172]



$R_1 = OCH_3, CO_2CH_3, COCH_3,, CN; R_2 = OCH_3, CO_2CH_3$

The Lei group reported that the $Ni(PPh_3)_4$/dppp mixed-ligand system catalyzed the Heck reaction of terminal alkenes with secondary and tertiary α-carbonyl alkyl bromides.[186] The reaction proceed by a SET mechanism in which $Ni^0(PPh_3)_4$ serves as the electron donor. Reactions carried out with mixed-ligand $Ni(PPh_3)_4$/dppp showed higher activity compared to the $Ni(PPh_3)_4/PPh_3$ system.

The difference in Ni mixed-ligand catalyzed reactions and Pd mixed-ligand catalyzed reactions lies in the rate of ligand exchange. While the ligand exchange in palladium mixed-ligand catalyzed reactions is facile,[181] in nickel mixed-ligand catalyzed reactions, the exchange is relatively slow.[115]

To conclude, the mixed-ligand strategy has provided a powerful method in transition metal catalyzed reactions, including hydrogenation,[176] asymmetric C-C bond formation,[177] amination,[183,187] thiolation,[182] Suzuki-Miyaura cross-coupling,[42] borylation[114-116] and Heck reactions.[186] Mixed-ligand systems provide superior activity by providing stable intermediates in the catalytic cycle,[185] extending the lifetime of the zero oxidation state metal and facilitate the formation of active species. The mixed-ligand effect is expected to influence other transition metal

catalytic systems with the development of high throughput technology. However, there is no guideline yet to predict the behavior of mixed-ligand systems.

1.5 Nickel Mediated Single-Electron Transfer Reactions

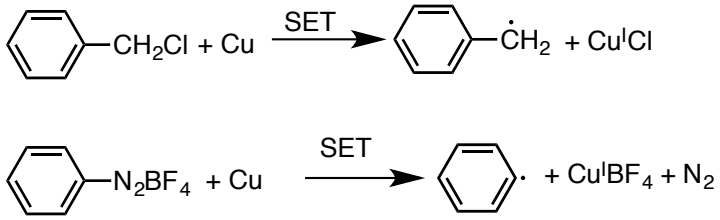
(Adapted with permission from reference [20]. Copyright (2014) American Chemical Society)

Due to our interest in Single-Electron-Transfer Living Radical Polymerization (SET-LRP), single-electron-transfer (SET) reactions involving nickel will be discussed briefly. Three categories of SET involving nickel are of interest to us, nickel mediated radical polymerization reactions, nickel mediated Ullmann-like homocoupling reactions, and nickel mediated cross-coupling reactions *via* SET mechanism.

1.5.1 Single-Electron-Transfer Reaction of Ni^0 Species in Radical Polymerization

Zero-valent nickel is prone to oxidation similar to zero-valent copper. Early work on radical polymerization adopted zero-valent metal powder to generate radical initiators via *SET* reaction. The Furukawa laboratory[188] reported the first application of metal^0 powder in polymerization, using Cu^0 powder and benzyl chloride to polymerize styrene (Sty), methyl methacrylate (MMA) and vinyl acetate (VAc) in 1954. The reaction was carried out in a sealed glass tube heated to 70 ^oC. The conversion, the degree of polymerization (the number of monomer repeat units in a polymer chain, DP) and the rate constant of polymerization increased linearly with reaction time, indicating some potential living polymerization character.[188] A living polymerization is a chain polymerization accompanied by negligible extent of termination (bimolecular termination in the case of radical polymerization), disproportionation, and chain transfer reactions. The amount of copper as well as benzyl chloride did not impact the conversion or DP of the resulting polymer. The mechanism of initiation was proposed to be a SET by Cu^0 to benzyl chloride (**Scheme 1.47**).

Scheme 1.47. Mechanism of Polymerization Initiation by Cu^0



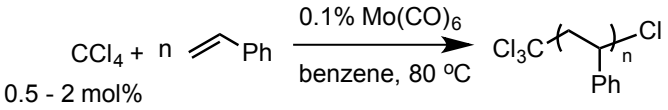
In 1965, other transition metal colloids including V, Cr and Co were found effective in catalyzing the radical polymerization of vinyl monomers in the presence of CCl_4.[189] Soon, Raney Ni was applied with a variety of organic halides including: CCl_4, BnCl, *n*-$C_4H_9NCl_2$, *t*-C_4H_9OCl, C_6H_5SCl and CH_3SiCl_3 to generate radical initiators to polymerize methyl methacrylate and styrene.[190] Diamines, diols and organic halides increase the polymerization rate.[191] Commercially available zero-valent metals were found to be inefficient compared with activated metals in initiating radical polymerization of methyl methacrylate and styrene in benzene with alkyl halides.[192] This indicates the importance of an active $metal^0$ surface in polymerization, and metal oxides are not sufficient to generate radicals with organic halides.

When Raney nickel was used as catalyst,[193] CCl_4 is more effective than $CHCl_3$, while CHI_3 is more effective than $CHBr_3$ in initiating radical polymerization. The rate-determining step of the polymerization was proposed to be a SET step (**Scheme 1.47**).[193] Nitrobenzene and hydroquinone inhibit the polymerization, indicating a radical mechanism. Nickel chloride was isolated after polymerization with Raney nickel was carried out, indicating the generation of radical initiator *via* SET mechanism by Ni^o rather than by Ni chloride.[193]

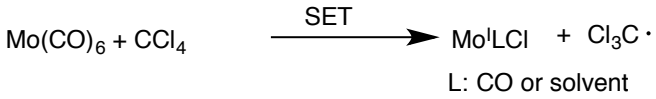
Solvents also show an impact on the radical polymerization. The radical polymerization of MMA in DMF and DMSO was faster than reactions carried out in benzene. Moreover, commercially available metals, which were inactive in benzene, efficiently initiate polymerization in DMF and DMSO. Use of MeCN resulted in no polymerization.[194] These results can be explained by the stabilization of radical or radical anion species in DMF and DMSO.

Not only metal powders, but zero-valent and low-valent metal complexes also catalyzed the polymerization of vinyl monomers. The Bamford laboratory reported the polymerization of methyl methacrylate catalyzed by a variety of metal carbonyl complexes with CCl_4 as the initiator.[195] The metal complexes used include: $Cr(CO)_6$,[195] $Mo(CO)_6$, $W(CO)_6$,[196] $Mn_2(CO)_{10}$, $CpMn(CO)_3$, $Cp^*Mn(CO)_3$,[197] $Ni(CO)_4$,[198] and $Co_4(CO)_{12}$.[199] The polymerization was proposed to proceed *via* a SET initiated radical mechanism and was strongly inhibited by CO.[200] The reaction rate was independent of the concentration of CCl_4 once the concentration of CCl_4 increased to a certain amount. Incorporation of ^{14}C in the polymer chain when $^{14}CCl_4$ was used indicates that $Cl_3{}^{14}C\bullet$ radical was generated as an initiator for the polymerization (step i, **Scheme 1.48**).[200] The isotope incorporation experiment confirmed 100% rate of $^{14}CCl_3$ chain end incorporation. A chain-transfer reaction of the propagating radical to CCl_4 led to –Cl polymer end group (step iii, **Scheme 1.48**). A chain-transfer reaction of propagating radical to another chain or solvent led to –H polymer chain end group (steps v and vi, **Scheme 1.48**).

Scheme 1.48. The Mechanism of Zero-Valent Metal Complex Catalyzed Radical Polymerization

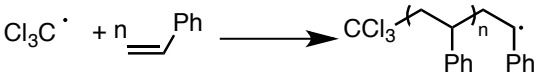


Initiation:

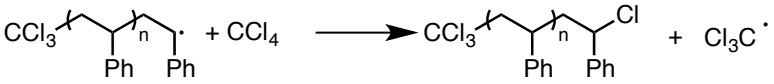


(i)

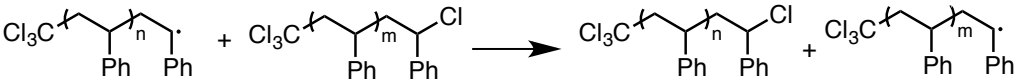
Propagation:



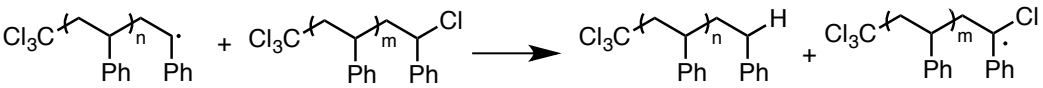
(ii)



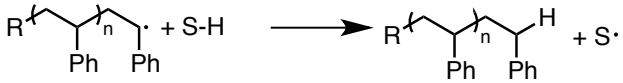
(iii)



(iv)



(v)



(vi)

S: solvent

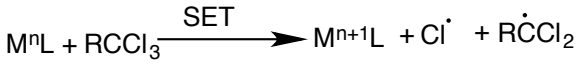
Termination:

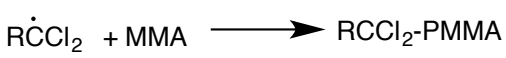
Radical-radical combination, disproportion reactions.

Moreover, when polyvinyl trichloracetate was used as initiator, a grafted polymer or graft copolymer (a branched polymer with side chains having different features, constitutionally or configurationally, from the main chain) was generated instead of a homopolymer. These results support the mechanism of radical polymerization initiated by SET from metal complex to perhaloalkane (**Scheme 1.49**).[200] Polymerization initiated by $Mo(CO)_6$ and CCl_4 carried out in different solvents showed different characters. In inert solvents such as benzene and cyclohexane, the solvent only shows a dilution effect. However, when the solvent is capable of

coordinating with the metal, such as ethyl acetate, dioxane, acetic anhydride, and benzonitrile, the solvent replaces CO and shows an assisting effect in the activation of CCl_4.[201-203] Light was shown to increase the rate of the polymerization.[204]

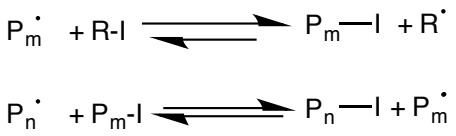
Scheme 1.49. Metal Complexes-Haloalkanes Initiated Polymerizations[205]





Not only metal carbonyl ligand complexes could be used as catalysts. The generation of free radicals from CCl_4 with $Mo(CNPh)_6$ and $W(CNPh)_6$ was also reported.[206,207] Rapid polymerization of methyl methacrylate was observed even at room temperature when $Ni(PPh_3)_4$ or $Ni(CO)_4$ and CCl_4 mixtures were used to initiate the polymerization.[208] Moreover, PPh_3 did not show an inhibiting effect to the radical polymerization as CO did. Hence, the polymerization of MMA at room temperature is faster when $Ni(PPh_3)_4$ was used compared to the rate of polymerization when $Ni(CO)_4$ was used.[208] For dinuclear metal carbonyl complexs, such as $Mn_2(CO)_{10}$, photolysis[209] or thermolysis[205] produces [•$Mn(CO)_5$], which abstracts a halogen atom from an initiator. In 2008, the well-known $Mn_2(CO)_{10}$ mediated polymerization of vinyl monomers was reexamined. Living radical polymerization of vinyl acetate, methacrylate (MA) and styrene catalyzed by $Mn_2(CO)_{10}$ under photolysis conditions was reported. [210] Polymers with M_w up to 10^5 were synthesized in a controlled manner by degenerative iodine transfer mechanism (**Scheme 1.50**) at 40 ^oC in a reaction time of 2 h.

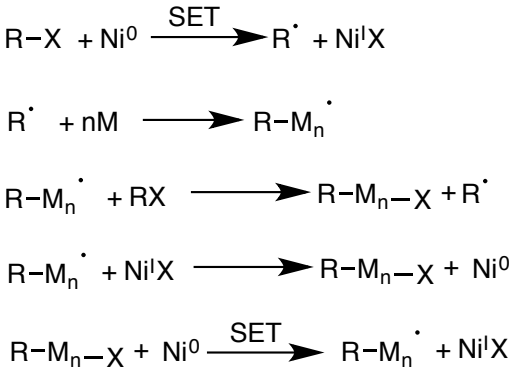
Scheme 1.50. Degenerative Iodine Transfer Mechanism



The polymerization only proceeds in the presence of light and stops with light shielding. This work inspired a very comprehensive investigation of $Mn_2(CO)_{10}$-photomediated LRP of vinylidene fluoride *via* iodine degenerative transfer with up to 43 initiators and 41 solvents. [211] The reaction conditions were mild, 40 ^{o}C, and various solvents including water and alkyl carbonates were used. Iodine degenerative transfer dramatically suppressed head-to-head defects common to conventional vinylidene difluoride free radical polymerization. The total iodine functionality was higher than 95% and enabled the synthesis of block copolymers with styrene, butadiene, vinyl chloride, vinyl acetate, methacrylate and acrylonitrile (AN). [211]

In 1990, after the proposal of initiator-transfer agent-terminator (iniferter) concept by Otsu for living radical polymerization[212], reduced nickel/halide systems were used as redox iniferters. The mechanism for the polymerization was proposed as in **Scheme 1.51**.[213]

Scheme 1.51. Mechanism of Nickel Mediated LRP



The termination of the monomer chain with X is of essential importance to the living character of the polymerization. Ni^0 generated from chain transfer reinitiates the terminated polymer.

Polymerization of styrene by reduced Ni and benzyl chloride were carried out to test the concept, which is a monofunctional redox system. The bifunctional redox system can be achieved by using reduced nickel and *p*-xylene dichloride. The polymerization showed a linear relationship between conversion and reaction time regardless of the initiator system used. Moreover, block copolymers of methyl methacrylate and styrene were synthesized in 91.4% yield.[213] Otsu discussed the iniferter concept in great details in a more recent highlight.[214] The catalysts, initiators as well as monomers used in zero-valence metal mediated LRP prior to 1995 are summarized in **Table 1.2**. A list of radical polymerizations using metal complexes as well as low-valence metal salts is provided in **Table 1.2**.

Table 1.1.Summary of Metal^0, Initiators and Monomers Used in Metal-Catalyzed Radical Polymerization Prior to 1995[a]

Metal^0	Initiator	Monomer	Year	Ref
Cu^0, Fe^0, Zn^0	BnCl, *p*-nitrobenzyl chloride, chloromethyl ether	MMA, Sty, MA, VAc	1954	188
Cu^0 with $Na_2S_2O_3$	$ArN_2^+X^-$	MMA, MA, Sty, VAc	1954	215
V^0, Cr^0, Co^0 colloids	CCl_4	MMA	1965	189
Raney Ni^0, Fe^0, Co^0; Urushibara Ni^0, Co^0; Ullmann Cu^0	CCl_4	MMA	1967	191
Raney Ni^0, Fe^0, Co^0; Urushibara Ni^0, Co^0; Ullmann Cu^0	CH_2Cl_2, $CHCl_3$, CCl_4, $CHBr_3$, CHI_3, *n*-BuCl, *t*-BuCl, BnCl, $CH_2=CHCH_2Cl$	MMA, Sty	1967	192,193
Reduced Ni^0	CCl_4, BnCl, PhCOCl, *n*-$BuNCl_2$, NBS, PhSCl, $PhSO_2Cl$, $PhPCl_2$, $PhSiCl_3$, *n*-BuCl, *t*-BuCl	MMA, Sty, VAc	1967	190
Ni^0	$SiCl_4$	MMA, Sty, *i*-Butyl Vinyl Ether	1969	216
Sn^0	BnCl	MMA	1969	217
Ni^0	CCl_4, CBr_4, CHX_3, BnBr, $CH_2=CHCH_2Br$	CH_2=CH-CH=CH_2	1969	218
Fe^0	BnCl	MMA	1970	194
Ni^0	BnCl	MMA, Sty	1990	213

[a]X=Cl, Br, I

Table 1.2. Summary of Metal Complexes, Initiators and Monomers Used in Metal-Catalyzed Radical Polymerization Prior to 1995[a]

Metal Complexes	Initiator	Monomer	Year	Ref
[b]$Mo(CO)_6$	CCl_4	MMA, Sty	1962	196,200,201,219-221
[b]$W(CO)_6$	CCl_4	MMA	1962	196
[b]$Ni(CO)_4$	CCl_4, CBr_4	MMA	1962	198
$Co_4(CO)_6$	CCl_4	MMA	1963	199
[b,d]$Mn_2(CO)_{10}$, $CpMn(CO)_3$, $Cp^*Mn(CO)_3$	CCl_4	MMA	1963	197,202,207
[b]$Cr(CO)_6$	CCl_4, poly(vinyl trichloroacetate)	MMA	1964	200
[b]$Mo(CNPh)_6$	CCl_4, poly(vinyl trichloroacetate)	MMA	1965	206
[b]$W(CNPh)_6$	CCl_4, poly(vinyl trichloroacetate)	MMA	1965	206
[b]NiO_2		Sty	1965	222
[b]$Ni(PPh_3)_4$	CCl_4, poly(vinyl trichloroacetate)	MMA	1966	208,223
[b]$Na_3[C_6H_5CH_2Co(CN)_5]$		MMA, Sty, VAc, AN	1969	224
[b]$VO(acac)_2Cl$, VO(8-quinolyloxyo)$_2OCH_3$		MMA	1974, 1975	225,226
[c]$Re_2(CO)_{10}$, $Mn_2(CO)_{10}$, $Os_3(CO)_{12}$		MMA, TFE	1975, 1976	227,228
[c]Pt^{II}(dimethyl-(2,2'-bipyridyl))		TFE	1976	229
[c]$Mn(CO)_5Cl$, [c]$CH_3Mn(CO)_5$, [c]$CH_3COMn(CO)_5$		TFE, MMA	1976, 1978	230,231
[c]$BzCr(CO)_3$ and $TolCr(CO)_3$		MMA, Sty	1977, 1984	232,233

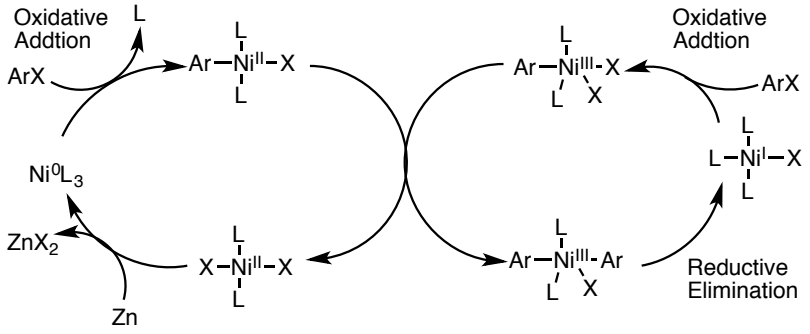
[a]X=Cl, Br, I; TFE: tetrafluoroethylene. [b]Thermally initiated. [c]Photoinitiated. [d]Reaction was carried out at 25 ^oC with inactive sodium light.

Ever since 1995, the development of atom-transfer radical polymerization (ATRP)[234-237] as well as single-electron-transfer living radical polymerization (SET-LRP)[238,239] greatly improves the scope of metal, including nickel, mediated precise synthesis of polymers.

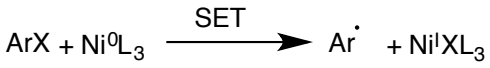
1.5.2 Nickel Catalyzed Ullmann-Type Homocoupling and Polymerization

The Ullmann reaction refers to the homocoupling of aryl and alkyl halides mediated by Cu.[10] Saito and Yamamoto reported the first nickel mediated Ullmann-like reaction in 1966. They observed the formation of butane during the decomposition of $Et_2Ni^{II}(bpy)$.[240] In 1971, Semmelhack reported the first homocoupling reaction of aryl halides by stoichiometric $Ni(COD)_2$ in DMF at 25 – 45 ^{o}C.[241] It was not until 1977 that Kumada and coworkers achieved the first case of homocoupling of aryl halides mediated by a catalytic amount of nickel in the presence of Zn.[242] Aryl sulfonates are also applied in homocoupling.[12] Although quite a number of studies were carried out on nickel catalyzed Ullmann-like reactions, the mechanism for homocoupling is under debate. Initially, Semmelhack proposed the 2 ArX + Ni^0 -> ArX + $ArNi^{II}X$ -> $Ar_2Ni^{IV}X_2$ mechanism to account for the generation of biaryl.[241] However, Kochi proposed a different mechanism involving Ni^{I} and Ni^{III} radical chain mechanism (**Scheme 1.52**).[243] In this mechanism, one ArX reacts with Ni^0 to form Ni^{II}, while another ArX molecule reacts with Ni^{I} to generate Ni^{III}. Aryl-halide exchange followed by reductive elimination generates the biaryl products. However, the origin of the Ni^{I} species was not understood. One possibility proposed by Kochi involves an SET process (**Scheme 1.53**).

Scheme 1.52. The Mechanism of Nickel Catalyzed Homocoupling

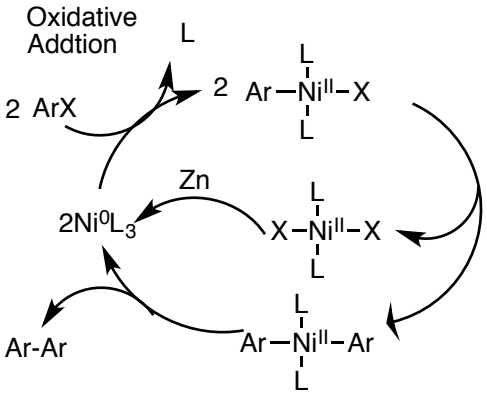


Scheme 1.53. The Generation of Ni^{I}



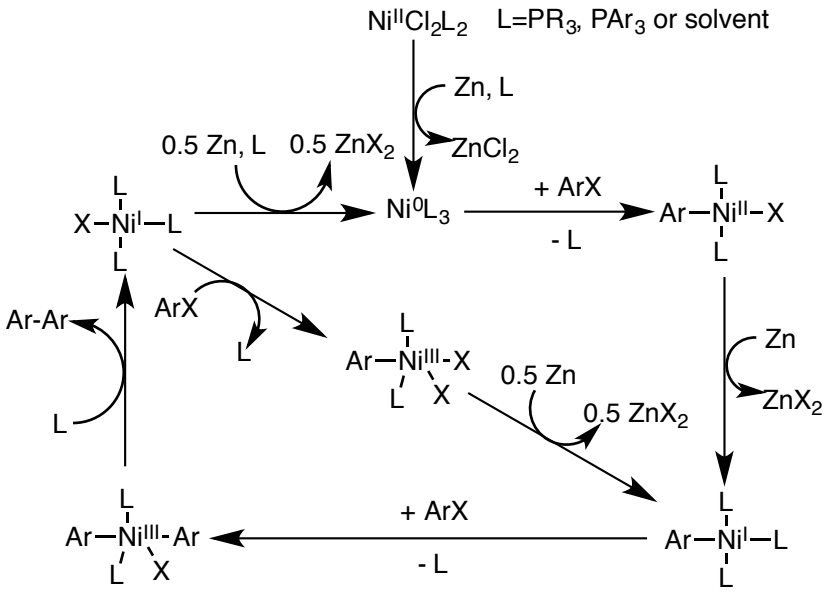
Rieke proposed a different mechanism involving a Ni^{II} complex metathesis as a key step (**Scheme 1.54**).[244] The metathesis or disproportion step is supported by the generation of biaryl in the thermal decomposition of $ArNi^{II}XL$.

Scheme 1.54. Mechanism of Nickel Catalyzed Homocoupling



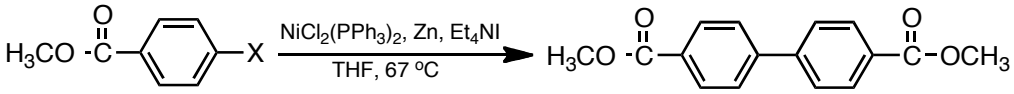
Colon proposed the generation of Ni^{I} *via* SET from Zn to Ni^{II} (**Scheme 1.55**).

Scheme 1.55. The Mechanism of Homocoupling Catalyzed by Ni in the Presence of Zn[245]



It is possible that both Kochi and Colon mechanisms are operating. With excess Zn, the Colon mechanism is more likely to occur. However, with limited Zn, the Kochi mechanism is more plausible.[11] For a more detailed discussion on mechanism and structures synthesized from Ni mediated Ullmann like reaction, the readers are referred to a recent review.[245] Although no unified mechanism was proposed for the Ni mediated Ullmann-like reaction, great progress has been made over the years such as the development on C-O substrates and the application of this reaction in poly(*p*-phenylene) (PPP) synthesis.[245] In attempts to synthesize oligomers and polymers from Ni catalyzed Ullmann like reactions,[11] aryl sulfonates instead of aryl halides were used to avoid the dehalogenation of aryl halides. Further study showed a wide range of sulfonate leaving groups is active in Ni catalyzed homocoupling reactions (**Table 1.3**).[12] In the case of the 4-chlorophenylsulfonyl leaving group, the low yield was obtained due to the participation of Cl in *para*-chlorophenyl sulfonyl group (**Table 1.3**, entry 3).

Table 1.3. Ni^0-Catalyzed Homocoupling of Various *p*-Carbomethoxyphenyl Sulfonates[a,12]

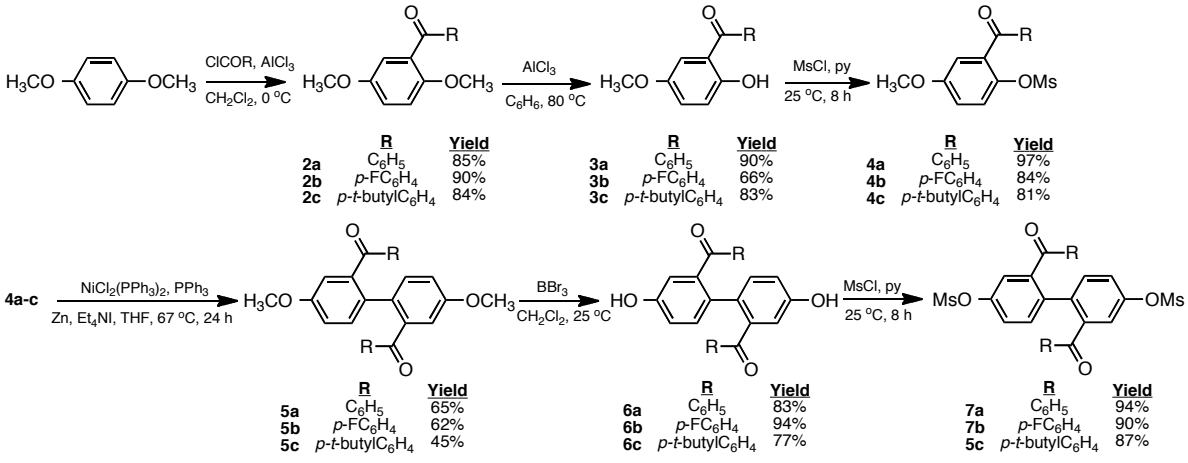


entry	leaving group X	reaction time (h)	GC yield[b] (%)
1	CF_3SO_2O	5	>99
2	*p*-$FPhSO_2O$	5	>99 (85)
3	*p*-$ClPhSO_2O$	10	(79)[c]
4	$PhSO_2O$	5	97 (83)
5	*p*-CH_3PhSO_2O	10	>99
6	CH_3SO_2O	10	>99

[a] Reaction conditions: 10 mol% of $NiCl_2(PPh_3)_2$, 1.7 equiv of Zn, 1.5 equiv of Et_4NI, refluxing THF, N_2. [b] Isolated yields in parentheses, [c] Chlorine of 4-chlorobenzenesulfonate moiety was also homocoupled and cross-coupled to give complicated byproducts.

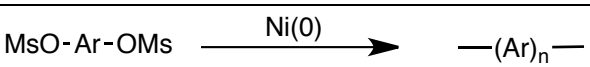
Applying the nickel catalyzed homocoupling reaction, bismesylates can be synthesized and applied in the polymerization of polyarenes.

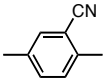
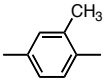
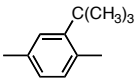
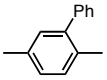
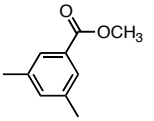
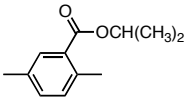
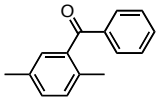
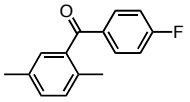
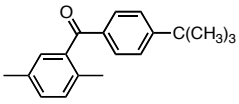
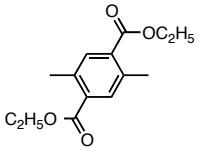
Scheme 1.56. The Synthesis of Bismesylates of 2,2'-Diaroyl-4,4'-dihydroxybiphenyls (7a-c)[246]



Friedel-Crafts acylation of 1,4-dimethoxybenzene produces a mono-functionalized hydroquinone derivative, which is deprotected by aluminum chloride selectively on one side. The phenols were transformed to aryl mesylates, which further underwent homocoupling reaction mediated by Ni^{II} and Zn.[246] Deprotection of the methoxy group and mesylation gives the monomer in 67-85% yields in two steps. The biaryl monomers were applied in synthesis of HH-TT regioregular polymers (**Table 1.4**).[247]

Table 1.4. Ni^0-Catalyzed Homocoupling Polymerization of Various Aryl Bismesylates MsOArOMs[a,247]

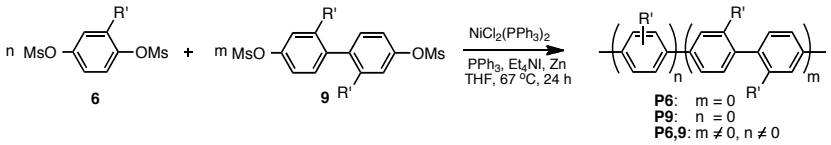


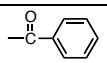
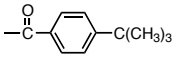
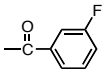
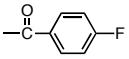
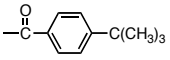
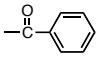
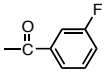
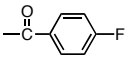
entry	Ar	yield (%)	M_n
1		68	-
2		87	2150
3		85	690
4		82	1410
5		85	1150
6		88	4920
7		95	7370
8		68	20030
9		82	7170
10		81	2630

[a] Conditions: $NiCl_2(PPh_3)_2/PPh_3/Et_4NI/Zn/THF$.

The presence of alkyl side-chains increases the solubility of the polymer hence increases the yield of the polymerization. The copolymerization of substituted MsOArArOMs was also studied in detail (**Table 1.5**).

Table 1.5. Ni^0-Catalyzed Homo- and Copolymerization of 2-Substituted 1,4-Bis[(methylsulfonyl)oxy]benzene (6) and 2,2'-Disubstituted 4,4'-Bis[(methylsulfonyl) oxy]biphenyl (9)[13]



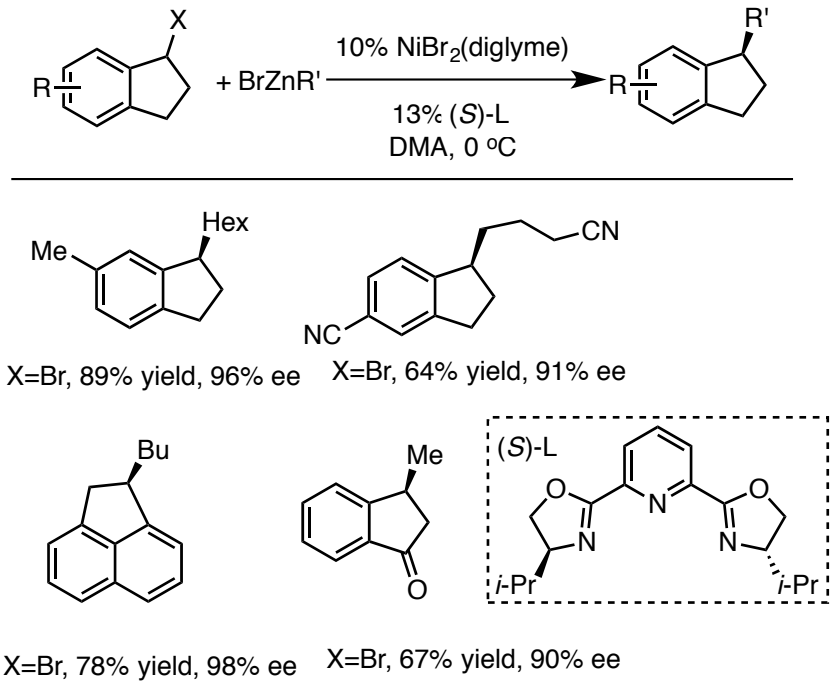
entry	monomer(s)[a]	R'	polymer (yield, %)	M_n[b]
1	**6a**		**P6a** (95)	7370
2	**6b**		**P6b** (82)	7170
3	**6d**		**P6d** (69)	3490
4	**6e**		**P6e** (68)	20030
5	**6f**		**P6f** (87)	2150
6	**9b**		**P9b** (68)	11120
7	**6a, 9a**		**P6a, 9a** (94)	11090
8	**6d, 9d**		**P6d, 9d** (74)	2540
9	**6e, 9e**		**P6e, 9e** (79)	34790
10	**6f, 9f**		**P6f, 9f** (76)	3580

[a] Mole ratio of monomers is 1:1 when comonomers are listed. [b] Determine by GPC versus polystyrene standards.

1.5.3 Single-Electron-Transfer of Nickel Catalysts in Cross-Coupling Reactions

With hints of SET reaction in nickel-catalyzed homocoupling reactions, it is obvious that nickel catalyzed cross-coupling reactions will undergo radical pathway in conditions similar to homocoupling reactions. Fu observed a radical pathway in the nickel-catalyzed enatioselective Negishi coupling of unactivated secondary alkyl halides.[248] The reaction conditions and selected products are listed in **Scheme 1.57**.

Scheme 1.57. Enatioselective Negishi Reactions of Benzyl Halides[248]



X=Br, 89% yield, 96% ee

X=Br, 64% yield, 91% ee

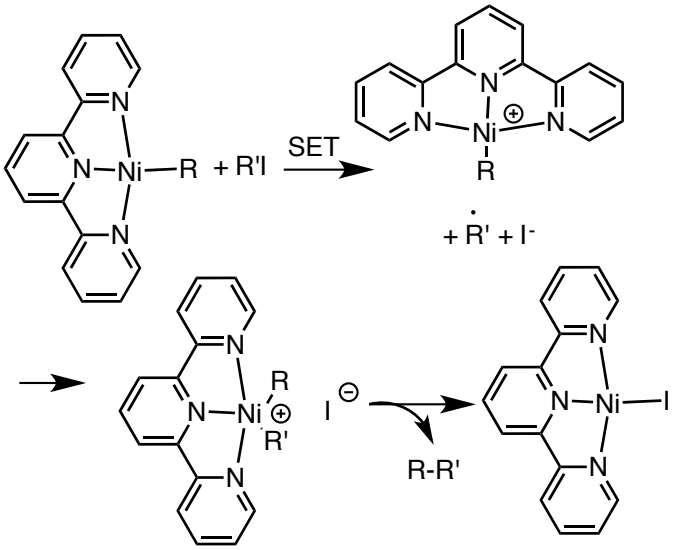
X=Br, 78% yield, 98% ee

X=Br, 67% yield, 90% ee

Since the process is stereoconvergent, the racemic starting material being converted to the enantiopure product, the authors made the assumption that radical species are generated in this reaction.[248] Later, mechanistic studies were carried out to understand the effects of ligand structure to the electronic structure, and the reactivity of nickel catalysts in alkyl-alkyl coupling reactions.[249] No isotope scrambling was observed in the labeling experiments, while ESR provided evidence for the radical anion of the π system single electron species.[249] To clarify this discrepancy, DFT calculations were also carried out to study the Negishi alkyl-alkyl coupling

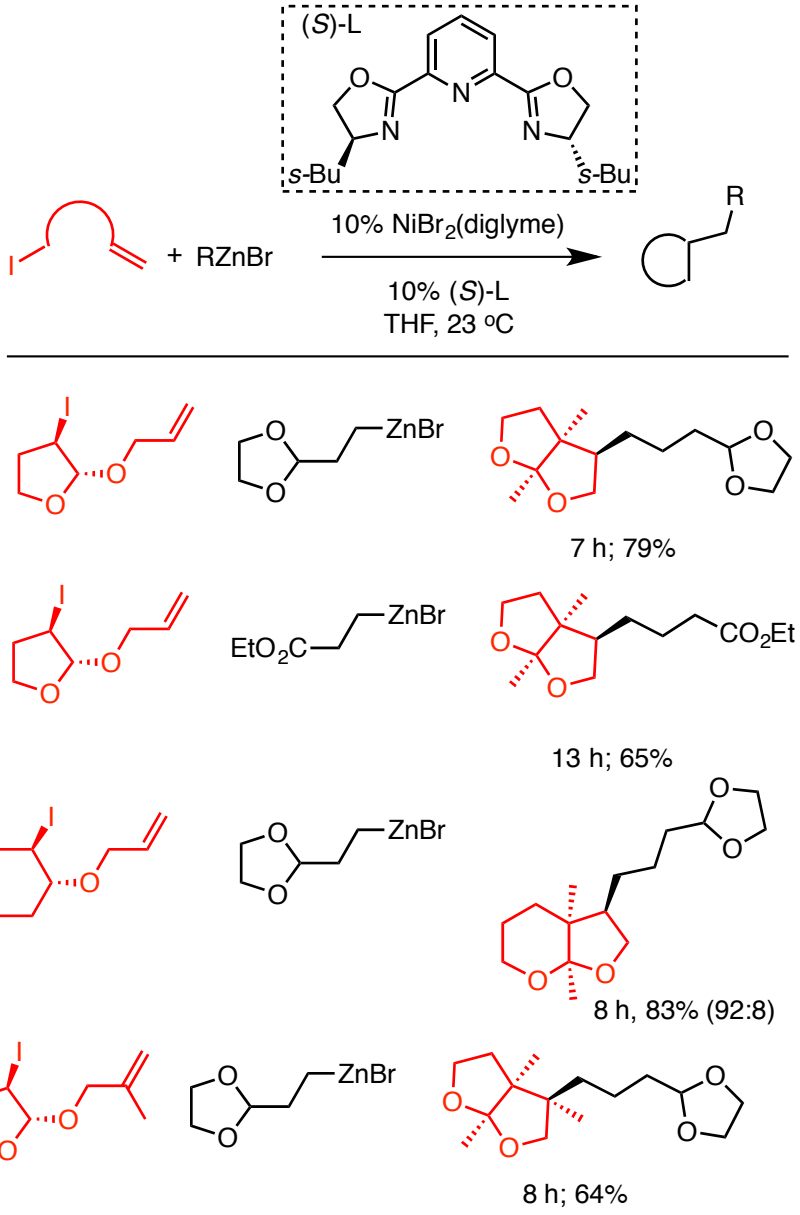
reactions.[250] The DFT study showed that the reaction includes four steps. In the first step iodine transfers *via* a SET mechanism occurs, followed by radical addition, reductive elimination, and transmetalation (**Scheme 1.58**) thus confirming the ESR experiments.[250]

Scheme 1.58. Mechanism for Nickel Catalyzed Alkyl Alkyl Coupling[250]



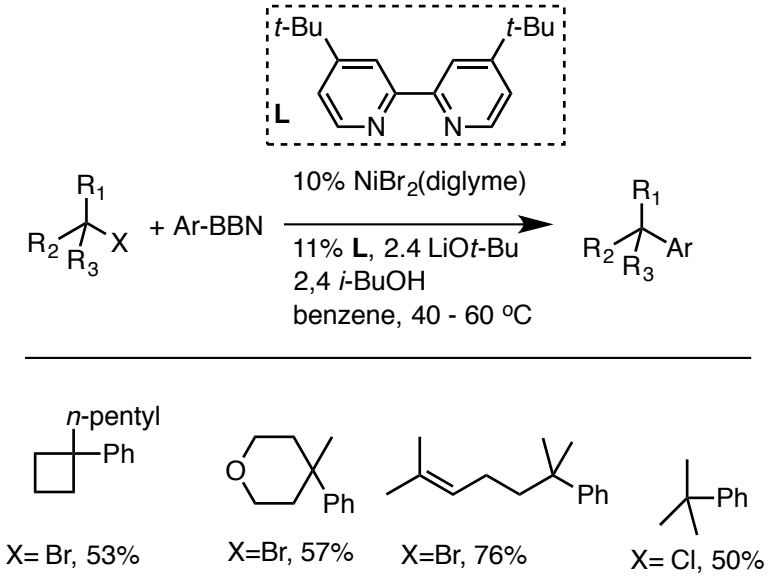
The cross-coupling reaction was also applied for cascade cyclization and cross-coupling of iodoalkenes with alkyl zinc halides (**Scheme 1.59**).[251] Kinetic studies and DFT calculations[251] indicate the reaction is a radical process.[251]

Scheme 1.59. Nickel Catalyzed Cyclization and Cross-Coupling of Alkyl Halides[251]



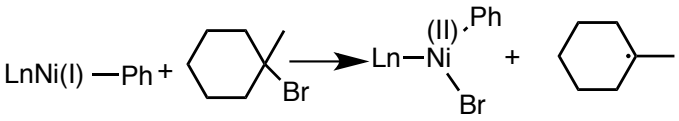
Recently, the Fu laboratory also investigated the Suzuki coupling of unactivated tertiary alkyl halides with aryl-BBN catalyzed by nickel.[252]

Scheme 1.60. Suzuki Cross-Coupling of Tertiary Halides with Aryl BBN[252]



To account for the formation of diastereomeric cross-coupling products from a single diastereomer of a tertiary alkyl halide, a radical mechanism was proposed.[252] An ISET pathway was proposed by Fu as the intermediate step for oxidative addition of alkyl halides to Ni^{I} species (**Scheme 1.61**).[252]

Scheme 1.61. ISET Generation of Alkyl Radicals



Following the similar ISET mechanism, reductive cyclization of alkyl dihalides catalyzed by nickel diiodide and Zn was reported.[253] Three to seven membered rings were readily synthesized at moderate to good yields. Utilizing the Ni^{0}-Ni^{I} redox cycle, bimetallic photoredox/nickel catalyzed Suzuki-Miyaura cross-couplings of benzylic potassium trifluoroborates with a wide range of aryl halides were reported by the Molander group.[254] Notably, the single-electron transmetalation is faster compared to two-electron process, highlighting the merits of SET reactions.

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2 Chapter 2

2.1 Zero-Valent Metals Accelerate the Neopentylglycolborylation of Aryl Halides Catalyzed by $NiCl_2$-Based Mixed-Ligand Systems

2.1.1 Introduction

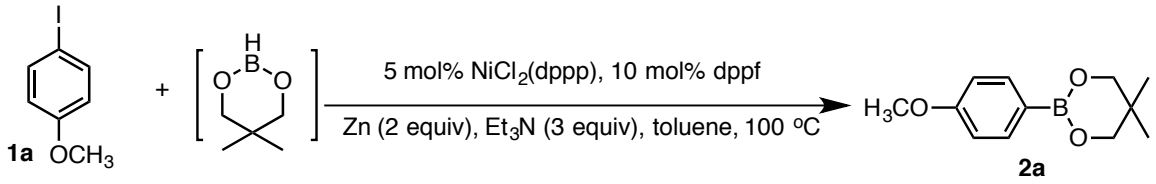
For our long term pursuit of functional macromolecules and organic functional materials, we are interested in the construction of biaryl structures *via* inexpensive methods.[1] Suzuki-Miyaura cross-coupling,[2,3] with its high functional group tolerance on both aryl electrophiles and boron containing nucleophiles, great versatility, and low toxicity of boron compounds is certainly the method of choice to construct biaryl motifs. The accessibility of the aryl and heteroarylboronic acids, boronic esters and trifluoroborates, which is crucial to Suzuki-Miyaura coupling, is limited compared to aryl halides. The method for preparing arylboron reagents has been discussed in chapter 1. To be brief, transition-metal catalyzed regioselective borylation reactions that completely obviate the use for highly reactive organolithium or Grignard reagents have been selected to synthesize arylboron reagents. The current method involves C-H activation *via* Re,[2] Rh,[3,4] or Ir[5-10] catalysis. Pd-catalyzed Miyaura borylation[11-16] of aryl halides and triflates has proven to be an effective regiospecific strategy. Often, relatively expensive tetraalkoxydiborons such as bis- (pinacolato)diboron are needed.[17,18] Recent research has extended the scope of boron sources to more practical dialkoxyboranes, such as pinacolborane.[8,19-22] Less expensive metals such as Cu has been used for the borylation of aryl halides.[23,24] Nickel, a d^{10} metal as Pd, shows the ability to employ less reactive electrophiles at a lower catalyst cost.[25-29] In 2000, the possibility of Ni-catalyzed borylation was demonstrated.[30] Meanwhile, a novel borylating reagent, neopentylglycolborane, which can be prepared *in situ* from neopentylglycol and borane-dimethyl sulfide complex was developed by our group.[31,32] This reagent facilitated the development of Ni-catalyzed neopentylglycolborylation as an effective strategy for the preparation of arylboronic esters. The resulting aryl neopentylglycolboronic esters have been harnessed in the sequential[31] or one-pot cross-coupling[32] with aryl halides[31-33] and aryl sulfonates[34] to form a diversity of

substituted biaryls. The first catalyst for this neopentylglycolborylation was the single ligand 1:1 complex of $NiCl_2$(dppp)/dppp, which was effective for aryl iodide and bromide substrates.[31,32] However, it was later discovered that mixed-ligand systems, in particular $NiCl_2$(dppp)/dppf, were significantly more efficient for the catalytic neopentylglycolborylation of aryl chlorides[33] and of the less reactive aryl sulfonates.[34] While some aryl mesylates and tosylates were successfully neopentylglycolborylated in high yield with $NiCl_2$(dppp)/dppf without any additives, the addition of zerovalent Zn metal provided for very broad substrate compatibility and greatly accelerated the reaction, typically generating excellent yields within 1-2 h.[34] Recently, it was shown that $NiCl_2$(dppp)/dppf, as well as other mixed-ligand Ni complexes, are also superior catalysts for the neopentylglycolborylation of *ortho*-substituted aryl halides.[35] Borylation of *ortho*-substituted aryl iodide typically reached maximum yields within a few hours. However, aryl bromides and chlorides usually require extended reaction times, often exceeding 24 h. In some cases, this longer reaction time allows competitive protodeborylation that diminishes the yield of the reaction and generates mixtures of products. Herein, we explore the application of zerovalent metal activation to the acceleration of neopentylglycolborylation of aryl halides, including of the less reactive ortho-substituted aryl iodides, bromides, and chlorides.

2.1.2 Results and Discussion

Previous work in our laboratory showed that addition of Zn^0 can accelerate the rate of the borylation reactions of aryl mesylates by producing the active catalyst Ni^0 species *in situ.*[34] However, the effect of Zn along with other zero-valent metal reducing reagents in aryl halides systems has yet to be investigated. In this paper, we explored the utility of zero-valent metals such as Al, Ca, Fe, Mg, Mn, and Zn in $NiCl_2$-based mixed ligand systems. 4-Methoxy phenyl halides were selected as electrophiles. The results are shown in Tables 2.1 to 2.3. It is noteworthy to mention that although $NiCl_2$(dppp)/dppf appears to be the best mixed-ligand system for Zn, the reaction conditions for other metals were not optimized.

Table 2.1. Neopentylglycolborylation of 4-Iodo Anisole Catalyzed by $NiCl_2$(dppp)/dppf Activated with Different Metals

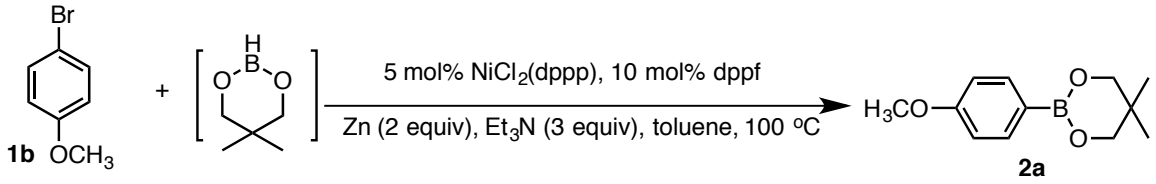


entry	X	metal[a]	time (h)	convn[b] / yield[c](%)
1	I	none	1.0	100/100 (85)
2	I	none	0.5	66/66 (40)
3	I	Zn	0.5	100/100 (95)
4	I	Mn	0.5	100/100 (92)
5	I	Fe	1	100/100 (95)
6	I	Al	0.5	100/100 (78)
7	I	Mg	0.7	100/97 (82)
8	I	Ca	0.5	92/86 (76)[d]

[a]Metals are all 325 mesh. [b]Conversion determined by GC. [c]Yield determined by GC. Isolated yield in parentheses. [d]Isolated yield for potassium trifluoroborate.

From Table 2.1, addition of zero-valent metal increases the rate of the reaction for all aryl halides that were investigated (entries 1 and 2 compared to entries 3-8). Active aryl iodides coupled with neopentylglycolborane in less than 1 h. Mn and Mg are comparable to Zn in accelerating the reaction. The accelerating effect of zero-valent metals is more clearly expressed in the less reactive aryl bromide and chloride systems (Table 2.2 and Table 2.3).

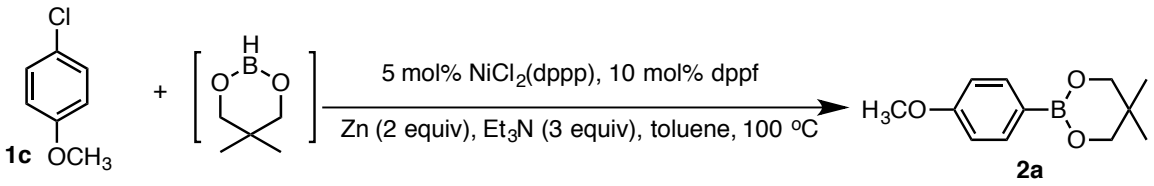
Table 2.2. Neopentylglycolborylation of 4-Bromo Anisole Catalyzed by $NiCl_2$(dppp)/dppf Activated with Different Metals



entry	X	metal[a]	time (h)	convn[b] / yield[c](%)
1	Br	none	1.0	26/26 (22)
2	Br	Zn	0.7	100/98 (68)
3	Br	Mn	1.0	74/70
4	Br	Mn	2.0	100/97 (76)
5	Br	Fe	24	88/86 (73)
6	Br	Al	1.0	100/75 (58)
7	Br	Mg	1.0	84/84
8	Br	Mg	1.5	100/93 (67)
9	Br	Ca	14	73/73 (46)

[a]Metals are all 325 mesh. [b]Conversion determined by GC. [c]Yield determined by GC. Isolated yield in parentheses.

Table 2.3. Neopentylglycolborylation of 4-Chloro Anisole Catalyzed by $NiCl_2$(dppp)/dppf Activated with Different Metals



entry	X	metal[a]	time (h)	convn[b] / yield[c](%)
1	Cl	none	1.0	7/7
2	Cl	Zn	1.0	100/98 (70)
3	Cl	Mn	2.0	100/98 (85)
4	Cl	Fe	2.0	11/11
5	Cl	Fe	22	100/100 (73)
6	Cl	Al	1.0	100/76 (49)
7	Cl	Mg	1.0	57/55
8	Cl	Mg	1.7	100/95 (84)
9	Cl	Ca	24	54/54 (30)[d]

[a]Metals are all 325 mesh. [b]Conversion determined by GC. [c]Yield determined by GC. Isolated yield in parentheses. [d]Isolated yield for potassium trifluoroborate.

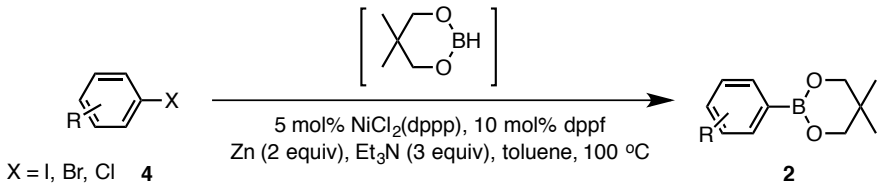
In the case of 4-methoxyphenyl bromide and chloride, adding reducing reagents increased the reaction yields by three times (Table 2.2, entry 3) and ten times (Table 2.3, entry 2), respectively. Mild reducing reagents such as Zn are favored. For more active reducing reagents such as Ca, the isolated yields were lower compared to those obtained from the reactions using Zn as the reducing reagent. This might be attributed to dehalogenation reactions caused by highly reactive metals. The borylation reactions using Fe as reducing agents showed similar rates to systems without external reducing agents. This is likely due to the tight attachment of Fe powder to the stirring bar, leading to decreased surface area.

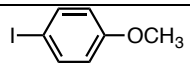
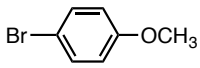
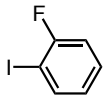
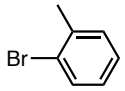
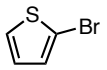
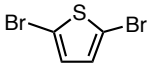
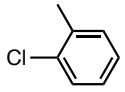
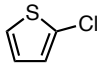
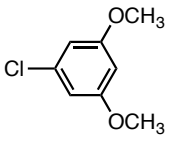
The acceleration of $NiCl_2$(dppp)/dppf catalyzed neopentylglycolborylation of 4-methoxyphenyl halides by various zero-valent metals demonstrated the universality of the activation concept by zerovalent metals. Zn appears to be effectively accelerating the reaction rate as well as

suppressing side reactions. In some cases, Mn (Table 2.1, entry 4; Table 2.2, entry 4 and Table 2.3, entry 3) or Mg (Table 2.1, entry 7;Table 2.2, entry 8 and Table 2.3, entry 8) showed comparable accelerating effect compared to Zn powder in similar or slightly longer reaction time. Since Zn was already used in zero-valent metal promoted homocoupling, cross-coupling and borylation reactions, it would be advantageous to develop a single universal catalytic system. We selected Zn as the reducing metal for the rest of the study.

Zn metal is commercially available in various forms, including chips, powders, sheets and wires. Zn powders provide the largest surface area while bulk zinc provides an easier form of removal and recover. The polymerization rate of Cu^0 catalyzed single-electron-transfer living radical polymerization was demonstrated to be dependent on copper surface area via a Langmuir-Hinshelwood mechanism.[36] Thus, Zn chips and powders (325 mesh) were employed to study the dependence of nickel catalyzed neopentylglycolborylation reaction to the surface area of Zn as in Table 2.4. Both Zn powder and chips accelerate the neopentylglycolborylation reaction (Table 2.4).

Table 2.4. Neopentylglycolborylation of Aryl Halides Catalyzed by $NiCl_2$(dppp)/dppf Activated with Zn Powder and Zn Chips



entry	substrate	2	Zn Chips		Zn Powder	
			Time (h)	Convn/Yield (%)	Time (h)	Convn/Yield (%)
1		**2a**	0.5	100/89	0.5	100/95
2		**2a**	5	100/77[c]	2	100/80[c]
3		**2b**	8	90/51	1	100/91
4		**2c**	12	100/72[c]	1	100/85[c]
5		**2d**	1	95/90	1	100/95
6		**2e**	5	100/53[d], 36	7	100/76[d], 20[e]
7		**2c**	7	100/87[c]	3	100/71[c]
8		**2d**	6	100/79	1	100/92
9		**2f**	12	33/13[c]	3	81/53

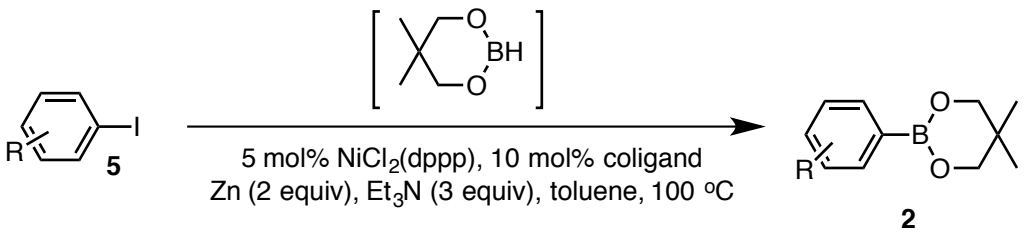
[a]Conversion determined by GC. [b]Isolated yield. [c]Isolated as potassium trifluoroborate.
[d]Monoborylated product. [e]Diborylated product.

In general higher yields at shorter reaction were obtained when Zn powder was used compared to reactions run with Zn chips. Zn powder also promotes diborylation (Table 2.4, entry 6). This is expected because Zn powder has a larger surface area compared to Zn chips.

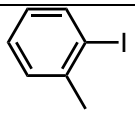
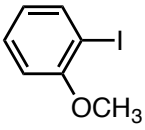
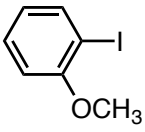
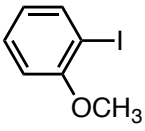
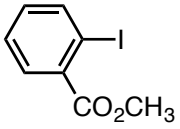
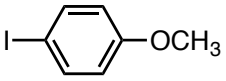
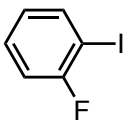
2.1.2.1 Ni-Catalyzed Neopentylglycolborylation of Aryl Iodides

The Zn-activated neopentylglycolborylation catalyzed by $NiCl_2$-based systems was compared using several mixed-ligand and single-ligand catalysts for a diversity of aryl iodide substrates. The neopentylglycolborylation of 4-iodoanisole using the mixed-ligand catalyst $NiCl_2$(dppp)/dppf was extremely efficient and rapid in the presence of 2 equiv of Zn, leading to 95% yield after only 30 min (entry 1 in Table 2.4). An extensive array of *ortho*- and *para*-substituted aryl iodides, bromides, and chlorides has been tested in the Ni-catalyzed neopentylglycolborylation. In this report, the borylation of *ortho*-substituted aryl halides will be used as the benchmark for reaction efficiency, as *para*- and *meta*-substituted aryl halides are generally more reactive. Similarly, electron-rich *ortho*-substituted aryl iodides 2-iodotoluene and 2-iodoanisole were previously borylated using $NiCl_2$(dppp)/dppf in the absence of Zn, providing 78% yield (24 h) and 80% yield (1 h), respectively.[35] Here, it is found that the presence of 2 equiv of Zn accelerates the reaction, increasing the yield to 85% for 2-iodotoluene (1 h, Table 2.4 entry 1) and 96% for 2-iodoanisole (1 h, Table 2.4 entry 2). It should be noted that these yields correspond to a two-step process of neopentylglycolborylation followed by conversion of the boronate ester to the more readily isolated potassium trifluoroborate. Therefore, the yields of the first step of this process may in fact be higher than reported as potassium trifluoroborates. The Ni-catalyzed and Zn-activated neopentylglycolborylation of 2-iodoanisole was explored without coligand, and single-ligand catalysts such as $NiCl_2$(dppp)/dppp, but in all cases in significantly diminished yield, highlighting the merit of mixed-ligand concept.[33]

Table 2.5. Neopentylglycolborylation of Aryl Iodides Catalyzed by $NiCl_2$-Based Mixed-Ligand Systems Activated with Zn Powder



5 **2**

entry	substrate	coligand	**2**	time (h)	Convn[a]/yield[b] (%)
1		dppf	**2c**	1	100/85[c]
2		dppf	**2g**	1	100/96[c]
3		NA	**2g**	1	100/67
4		dppp	**2g**	24	11/6
5		dppf	**2h**	0.5	100/81[c]
6		dppf	**2a**	0.5	100/95
7		dppf	**2b**	0.5	100/80[c]

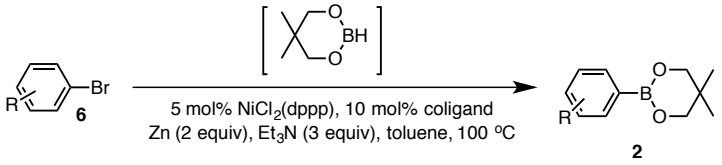
[a]Conversion determined by GC. [b]Isolated yield. [c]Isolated as potassium trifluoroborate.

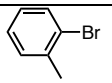
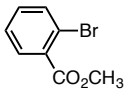
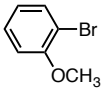
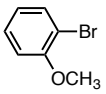
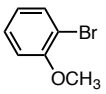
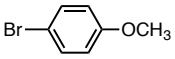
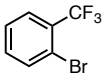
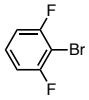
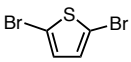
The electron-deficient aryl iodides methyl 2-iodobenzoate and 2-fluoro-1-iodobenenze were also investigated. Methyl 2-iodobenzoate was also neopentylglycolborylated in the absence of Zn using the mixed-ligand catalysts $NiCl_2$(dppp)/dppf (97% yield, 5 h) and $NiCl_2$(dppp)/PPh_3 (81% yield, 5 h).[35] However, in the presence of Zn^0 the reaction reaches high yields in a very short reaction time using either $NiCl_2$(dppp)/dppf (81% yield, 0.5 h) (Table 2.5, entry 5). For 2-fluoro-1-iodobenzene, an 89% yield was achieved in 1 h using $NiCl_2$(dppp)/dppf alone, whereas 80% yield was obtained in only 30 min in the presence of Zn (Table 2.5, entry 7). The Ni-catalyzed neopentylglycolborylation of aryl iodides, including less reactive *ortho*-substituted aryl iodides, was generally efficient even without the use of Zn as an additive. However, more sluggish reactions were observed for aryl bromides and aryl chlorides in the absence of Zn.

2.1.2.2 Ni-Catalyzed Neopentylglycolborylation of Aryl Bromides

In an earlier report, $NiCl_2$(dppp)/dppp-catalyzed neopentylglycolborylation of 4-bromoanisole provided 90% yield in 18 h.[32] Using the mixed-ligand $NiCl_2$(dppp)/dppf catalyst in the presence of Zn activator, 91% yield could be obtained in only 1 h (Table 2.4 entry 7). Using $NiCl_2$(dppp)/dppf and Zn activator, a similar yield could be obtained for 2-bromoanisole [95% of the trifluoroborate salt, after 1 h (Table 2.4 entry 3)]. However, the use of single-ligand catalytic systems (Table 2.4 entry 4) or without coligand (Table 2.4 entries 5) in the presence of Zn or the mixed-ligand $NiCl_2$(dppp)/dppf catalyst in the absence of Zn[35] provided significantly lower yields.

Table 2.6. Neopentylglycolborylation of Aryl Bromides Catalyzed by $NiCl_2$-Based Mixed-Ligand Systems Activated with Zn Powder



entry	substrate	coligand	**2**	time (h)	Convn[a]/yield[b] (%)
1		dppf	**2c**	1	100/85[c]
2		dppf	**2h**	1	100/87[c]
3		NA	**2g**	1	100/95[c]
4		dppp	**2g**	16	72/50[c]
5		dppf	**2g**	36	71/53[c]
6		dppf	**2i**	2	100/83[f]
7		dppf	**2a**	1	100/91
8		dppf	**2j**	6	100/85
9		dppf	**2k**	1	100/73
10		dppf	**2d**	1	100/95
11		dppf	**2d, 2e**	1	100/76[d], 20[e]

[a]Conversion determined by GC, [b]Isolated yield, [c]Isolated yield for potassium trifluoroborate, [d]Yield for diborylated product, [e]Yield for monoborylated product and deborylated product, [f]4 equiv of neopentylglycolborane was used.

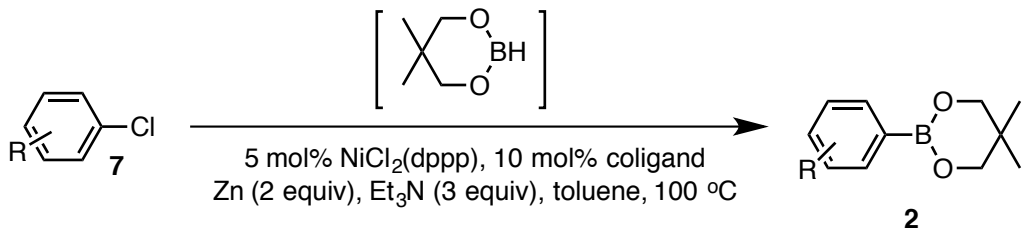
. Similarly high yields could be obtained in 1 h for 2-bromotoluene and 2-bromothiophene (Table 2.6, entries 1 and 10). The true advantage of the Zn-activated system is, however, exemplified by the neopentylglycolborylation of methyl 2-bromobenzoate (Table 2.6, entry 2), *o*-dibromobenzene (Table 2.6, entry 6), 1-bromo-2-trifluoromethylbenzene (Table 2.6, entry 8), and 1-bromo-2,6-difluorobenzene (Table 2.6, entry 9). In previous work the $NiCl_2$(dppp)/dppf-catalyzed neopentylglycolborylation of methyl 2-bromobenzoate was plagued by very high levels of protodeborylation, resulting in a diminished yield (11% in 20 h).[35] Through the use of Zn additive, the borylation process was significantly accelerated, allowing complete conversion in 1 h and obviating the need to run the reaction for longer times, where protodeborylation begins to dominate. Furthermore, the doubly *ortho*-substituted 1-bromo-2,6-difluorobenzene and the *ortho*-substituted 1-bromo-2-trifluoromethylbenzene were isolated in poor-to fair yield after only very long reaction times (44 h) in the absence of Zn.[35] Here, in the presence of Zn, good yields could be achieved in only 1−6 h (Table 2.6, entries 8, 9). 1,2-Dibromobenzene could be efficiently diborylated (Table 2.6, entry 6), whereas in previous efforts without Zn additive only a low yield of a mixture of mono- and diborylated adducts was obtained.[35] Nevertheless, attempts to prepare diborylated 2,5-dibromothiophene were not as successful, as protodeborylation seemed to be more rapid for this system, resulting in a mixture of 2,5-diborylated thiophene and 2-borylated-thiophene (Table 2.6, entry 11).

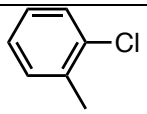
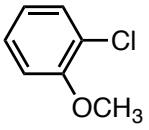
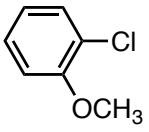
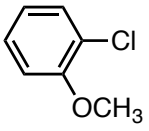
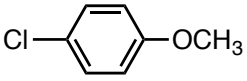
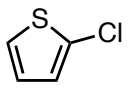
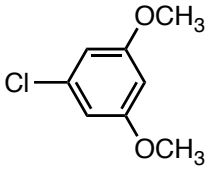
2.1.2.3 Ni-Catalyzed Neopentylglycolborylation of Aryl Chlorides

The mixed-ligand $NiCl_2$(dppp)/dppf catalytic system was discovered while pursuing the neopentylglycolborylation of relatively unreactive aryl chloride electrophiles.[33] Despite the higher activity of the mixed-ligand $NiCl_2$(dppp)/dppf catalytic system, electron-rich aryl chlorides did not provide particularly high yields. For example, in the absence of Zn, 4-chloroanisole achieved only 56% yield after 20 h[33] and 7% in 1 h (Table 2.3, entry 1). Here, it is shown that using Zn as an additive provides 91% yield in only 1 h (Table 2.7, entry 5). Even 1-chloro-3,5-dimethoxybenzene could be neopentylglycolborylated in 53% yield after only 3 h (Table 2.7, entry 7).

Electron-rich *ortho*-substituted aryl chlorides are among the most challenging substrates for Ni-catalyzed neopentylglycolborylation.[35] Nevertheless, $NiCl_2$(dppp)/dppf in the presence of Zn provides good yields of 2-chlorotoluene (71%) and 2-chloroanisole (90%) in only 1 h (Table 2.7, entries 1 and 2). The results from Table 2.7 demonstrate that both the mixed-ligand $NiCl_2$(dppp)/dppf catalyst and the Zn activator were needed for high catalytic performance. The single-ligand catalyst (Table 2.7, entry 4) was less effective. In the presence of Zn, electron-deficient *para*-substituted aryl chlorides (Table 2.8, entries 4-6) could be borylated in comparable yield, but in a fraction of the time required in the absence of Zn.[33] The contrast between Ni-catalyzed borylation with and without Zn is clearer for *ortho*-substituted electron-deficient aryl chlorides. For example, using $NiCl_2$(dppp)/dppf alone, only 26% yield was obtained after 24 h.[33] The use of this catalyst in conjunction with Zn provided 95% yield after conversion to the trifluoroborate salt in only 1 h (Table 2.8, entry 1).

Table 2.7. Neopentylglycolborylation of Electron-Rich Aryl Chlorides Catalyzed by $NiCl_2$-Based Mixed-Ligand Systems Activated with Zinc Powder

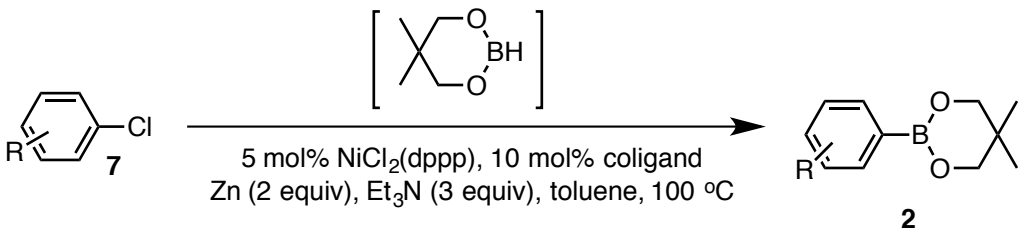


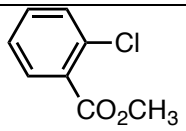
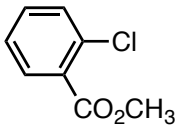
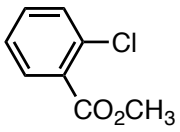
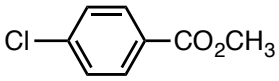
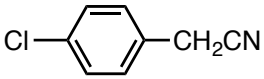
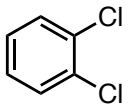
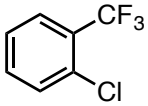
entry	substrate	coligand	**2**	time (h)	Convn[a]/yield[b] (%)
1		dppf	**2c**	1	100/71[c]
2		dppf	**2g**	1	100/90[c]
3		NA	**2g**	24	10/10[c]
4		dppp	**2g**	24	0/0[c]
5		dppf	**2a**	1	100/91
6		dppf	**2d**	1	100/92
7		dppf	**2f**	3	81/53

[a]Conversion determined by GC. [b]Isolated yield. [c]Isolated as potassium trifluoroborate.

As has been shown repeatedly, this effect requires both the very efficient $NiCl_2$(dppp)/dppf mixed-ligand catalyst as well as the Zn activator. Significantly lower yields were obtained for a single-ligand (Table 2.8, entry 3) even in the presence of Zn. Impressively, a 76% yield of *o*-diborylated benzene was obtained in 3 h from *o*-dichlorobenzene (Table 2.8, entry 7), and a 91% borylation yield was obtained from 1-chloro-2-trifluoromethylbenzene in 4 h (Table 2.8, entry 8), despite worse yields under extended reaction times (24−65 h) using $NiCl_2$(dppp)/dppf without Zn as an additive.

Table 2.8. Neopentylglycolborylation of Electron-Rich Aryl Chlorides Catalyzed by $NiCl_2$-Based Mixed-Ligand Systems Activated with Zinc Powder



entry	substrate	coligand	**2**	time (h)	Convn[a]/yield[b] (%)
1		dppf	**2h**	1	100/95[c]
2		NA	**2h**	22	67/36[c]
3		dppp	**2h**	19	12/7[c]
4		dppf	**2l**	1	100/79
5		dppf	**2m**	1	100/79
6		dppf	**2n**	1	100/77
7		dppf	**2i**	3	100/76[d]
8		dppf	**2j**	4	100/91

[a]Conversion determined by GC. [b]Isolated yield. [c]Isolated as potassium trifluoroborate.

2.1.3 Conclusions

In two recent reports from our laboratory the power of the mixed-ligand systems for the Ni-catalyzed borylation of less reactive aryl chlorides[33] and *ortho*-substituted aryl halides[35] was established. Using the particularly efficient mixed-ligand catalyst $NiCl_2$(dppp)/dppf, similar borylations of phenol-derived aryl mesylates and tosylates were shown to be feasible, and in fact the catalyst significantly accelerated the reaction in the presence of Zn additive.[35] Unlike aryl sulfonates, aryl halides suffer from both protodeborylation and hydrodehalogenation side reactions, and therefore the ability to accelerate productive borylation and limit overall reaction time is of particular value. By combining the highly active mixed-ligand $NiCl_2$(dppp)/dppf catalyst with zero-valent metal activation, the neopentylglycolborylation of aryl iodides, bromides, and chlorides, including *ortho*-substituted derivatives, proceeds extremely quickly, typically achieving complete conversion and high yield in 1 h or less. Zn was found to be a universal reducing reagent for Ni^{II} catalyzed cross-coupling and borylation reactions. The rate of borylation was found to be dependent on the surface area of Zn metal. Although the use of superstoichiometric Zn powder may be disadvantageous for some applications, easier product isolation due to increased yield and decreased byproduct contamination, as well as a significantly reduced reaction time, is quite compelling. Furthermore, similar efficacy with easily recoverable and recyclable Zn chips and the extension to other zerovalent metal additives has been demonstrated.

2.1.4 Experiments

Materials

Borane dimethyl sulfide complex, 1,3-bis(diphenylphosophino)propane (dppp), 2-iodotoluene, 2-iodoanisole, methyl 2-iodobenzoate, 1-iodo-4-methoxybenzene, 1-fluoro-2-iodobenzene, 2-bromotoluene, 2-bromothiophene, 1-bromo-2,6-difluorobenzene, 2-bromobenzotrifluoride, 2,5-dibromothiophene, benzyl bromide, 2-bromobenzoic acid, 1-bromo-4-methoxybenzene, 2-bromoanisole, *ortho*-dibromobenzene, 2-chlorothiophene, *ortho*dichlorobenzene, 2-chlorotoluene, methyl 2-chlorobenzoate, 2-chloroanisole, 2-

chlorobenzotrifluoride, 2-(4-chlorophenyl)acetonitrile, 4-chlorobenzonitrile, methyl 4-chlorobenzoate, 1-chloro-4-methoxybenzene, 1-chloro-3,5-dimethoxybenzene, KHF_2, 1,1'-bis(diphenylphosphino)ferrocene (dppf), $NiCl_2$•6H2O, ethanol, $MgSO_4$, NH_4Cl, NaCl, $NaHCO_3$, zinc (powder 325 mesh and chips), manganese (powder 325 mesh), iron (powder 325 mesh), aluminum (powder 325 mesh), magnesium (powder 325 mesh), calcium (powder granular ~200 mesh), dichloromethane, acetone, ethyl acetate, hexanes, and methanol were all used as received. Neopentylglycol was recrystallized from dichloromethane prior to use. Triphenylphosphine was recrystallized from hexane prior to use. Toluene and triethylamine (ACS reagent grade), were distilled over CaH_2 and stored under nitrogen prior to use. Ni-based catalysts $NiCl_2$(dppp), $NiCl_2(PPh_3)_2$ were synthesized according to literature procedures.[37] The methyl ester of 2-bromobenzoic acid,[31] and 1-chloro-2-benzyloxybenzene[38] were synthesized according to literature procedures.

Instrumentation

^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded using TMS as internal standard. High-resolution mass spectra of new compounds were obtained on a high-resolution double focusing chemical ionization mass spectrometer. A GC coupled with an FID detector and column HP 19091J-413 (5%-phenyl)-methylpolysiloxane 30m Length 0.32mm internal diameter was used to follow the reaction conversions and to assess purity of final compounds complementary to the NMR technique.

The crude reaction mixtures were diluted with THF and analyzed by GC. BHT is used as a stabilizer in THF at a percentage of 0.025%. We used the retention time and peak area of the BHT to monitor GC performance for rapid determination of abnormalities in the GC performance. Calibration curves of each compound were used to calculate the response factors (Rf) from the FID detector where GC shows multiple signals due to incomplete reactions and the presence of side products resulted from protodeborylation, hydrodehalogenation or homocoupling. The starting materials, products and by-products have a different response factor from the FID detector that affect the calculation of the conversion and yield. The response factors (Rf) corresponding to starting material, product and byproducts separated by column chromatography

were obtained from the slope of the linear or quadratic least squares fit of the calibration curve. The % molar composition is obtained by dividing the corrected area determined from the area of each compound corrected by the response factor giving the corrected area to the molar mass.

Preparation of Neopentylglycolborane

To a cooled solution (0 °C) of neopentylglycol (0.625 g, 6.0 mmol, 2.0 equiv) dissolved in toluene (3 mL) was slowly added $(CH_3)_2S{\cdot}BH_3$ (0.57 mL, 6.0 mmol, 2.0 equiv) via a syringe under nitrogen. After 30 min of stirring at 0 °C, the reaction mixture was allowed to warm to 23 °C and was left stirring until the gas evolution ceased (60−90 min). Neopentylglycolborane was used directly without further purification.

General Procedure for Neopentylglycolborylation

To an oven-dried 25 mL Schlenk tube were added Zn powder or chips (0.390 g, 6×10^{-3} mol), Ni-based catalyst (1.5×10^{-4} mol), and ligand (3×10^{-4} mol) along with the appropriate aryl halide (if it is solid) (3×10^{-3} mol). The *ortho*-substituted aryl halide, catalyst, and ligand were degassed by pumping and backfilling with nitrogen three times. Toluene was added to the reaction mixture (3 mL) along with the appropiate aryl halide (if it is liquid) and Et_3N (1.26 mL, 9×10^{-3} mol). Neopentylglycol borane was added dropwise to the reaction mixture. The reaction was placed into a preheated oil bath at 100 °C with stirring under an inert atmosphere. Samples were taken in time through the septum under nitrogen, and the conversion was followed by GC. After complete consumption of the starting material, the reaction was then quenched with a saturated NH_4Cl solution (50 mL) and extracted with ethyl acetate (3 × 25 mL). No difference between the crude GC and the last recorded GC prior quenching except for the disappearance of the *in situ* prepared neopentylglycolborane peak was observed. The organic fractions were combined and dried over $MgSO_4$. Following filtration the solvent was removed under reduced pressure and the crude reaction mixture was immediately purified on a silica gel column with the appropriate eluent.

2-(4-Methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (2a)

Purified by silica gel column chromatography with gradient dichloromethane : hexanes = 7 : 3 to dichloromethane. White solid, mp 54−56 °C (lit.[35] 59 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 3.82 (s, 3H), 3.75 (s, 4H), 1.01 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 135.4, 113.0, 72.1, 55.0, 31.8, 21.8.

2-(2-Fluorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (2b)[35]

Purified by silica gel column chromatography with gradient dichloromethane : hexanes = 1 : 9 to dichloromethane. Yellowish solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 22.9, 7.3 Hz, 2H), 7.56−7.37 (m, *J* = 12.6, 7.3 Hz, 2H), 3.79 (s, 4H), 1.07 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.8, 130.6, 129.2, 121.0, 120.3, 72.6, 33.3, 21.8.

5,5-Dimethyl-2-(*o*-tolyl)-1,3,2-dioxaborinane (2c)[35]

Purified by silica gel column chromatography with gradient hexanes to ethyl acetate in hexanes (10% by volumn).Colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.4 Hz, 1H), 7.27 (td, *J* = 7.5, 1.3 Hz, 1H), 7.14 (t, *J* = 7.7 Hz, 2H), 3.76 (s, 4H), 2.51 (s, 3H), 1.02 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.1, 135.0, 130.2, 130.1, 124.8, 72.4, 31.8, 22.5, 22.0.

5,5-Dimethyl-2-(thiophen-2-yl)-1,3,2-dioxaborinane (2d)

Purified by silica gel column chromatography with dichloromethane. White solid, mp 90−91 °C (lit. 91−92 °C);[35] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61−7.54 (m, 2H), 7.19−7.15 (m, 1H), 3.76 (s, 4H), 1.03 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.8, 131.5, 128.2, 72.6, 32.2, 22.1.

2,5-Bis(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)thiophene (2e)

Purified by silica gel column chromatography with dichloromethane. White solid, mp 155−156 °C (lit.[35] 156−157 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 2H), 3.75 (s, 8H), 1.02 (s, 12H); ^{13}C

NMR (126 MHz, $CDCl_3$) δ 136.2, 72.3, 31.9, 21.8.

2-(3,5-Dimethoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (2f)

Purified by silica gel column with gradient dichloromethane to ethyl acetate in dichloromethane (20% by volumn). White solid, mp 112 °C (lit.[35] 115 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, *J* = 2.4 Hz, 2H), 6.55 (t, *J* = 2.4 Hz, 1H), 3.82 (s, 6H), 3.77 (s, 4H), 1.04 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3, 110.7, 103.8, 72.2, 55.2, 31.8, 21.8.

2-(2-Methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (2g)

Purified by silica gel column with gradient dichloromethane: hexanes = 3 : 7 to dichloromethane. White solid, mp 40 °C (lit.[35] 39−40 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.39−7.33 (m, 1H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 4H), 1.04 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.8, 135.9, 131.8, 120.4, 110.6, 72.6, 55.9, 31.9, 22.0.

Methyl 2-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (2h)[35]

Purified by silica gel column with gradient dichloromethane to ethyl acetate: dichloromethane = 1 : 9. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.9 Hz, 1H), 7.55−7.46 (m, 2H), 7.38 (dd, *J* = 8.0, 2.5 Hz, 1H), 3.92 (s, 3H), 3.80 (s, 4H), 1.12 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 132.7, 131.9, 131.3, 128.6, 128.3, 72.5, 52.3, 31.7, 22.0.

1,2-Bis(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzene (2i)[35]

Purified by siliga gel column chromatography with dichloromethane. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 5.4, 3.3 Hz, 2H), 7.33 (dd, *J* = 5.5, 3.3 Hz, 2H), 3.76 (s, 8H), 1.07 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.3, 128.7, 72.7, 32.0, 22.1.

5,5-Dimethyl-2-(2-(trifluoromethyl)phenyl)-1,3,2-dioxaborinane (2j)[35]

Purified by silica gel column chromatography with hexanes : ethyl acetate = 9 : 1. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.2 Hz, 1H), 7.66−7.60 (m, 1H), 7.52−7.41 (m, 2H), 3.78 (s, 4H), 1.05 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.7, 133.8, 130.8, 129.3, 125.44, 125.40, 72.4, 31.8, 21.9.

2-(2,6-Difluorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (2k)

Purified by silica gel column chromatography with gradient hexanes and dichloromethane mixture. Yellowish solid, mp 42−44 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.15 (m, 1H), 6.82 (t, *J* = 7.5 Hz, 2H), 3.81 (s, 4H), 1.07 (d, *J* = 0.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0 (dd, *J* = 247.5, 13.5 Hz), 131.9, 111.1, 72.8, 32.0, 21.8; HRMS (CI+) calcd for $C_{11}H_{14}BF_2O_2$ (M^+ + H) 227.1055, found 227.1055.

Methyl 4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (2l)

Purified by silica gel column chromatography with gradient dichloromethane to dichloromethane : ethyl acetate = 4:1. White solid, mp 111−113 °C (lit.[35] 114 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.3 Hz, 2H), 7.86 (d, *J* = 8.1 Hz, 2H), 3.92 (s, 3H), 3.79 (s, 4H), 1.03 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4, 133.9, 131.9, 128.6, 72.5, 52.2, 32.0, 22.0.

4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)benzonitrile (2m)

Purified by silica gel column chromatography with gradient dichloromethane to dichloromethane : ethyl acetate = 2:1. White solid; mp 122 °C (lit.[35] 124−125 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 7.9 Hz, 2H), 3.78 (s, 4H), 1.02 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.4, 131.1, 119.2, 114.0, 72.5, 32.0, 21.9.

2-(4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)acetonitrile (2n):[33]

Purified by silica gel column chromatography with gradient dichloromethane to dichloromethane :

ethyl acetate = 3:1. White solid, mp 77−78 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 7.7 Hz, 2H), 3.77 (s, 4H), 3.75 (s, 2H), 1.02 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.8, 132.3, 127.2, 117.9, 72.5, 32.0, 23.9, 22.0.

General Procedure for Aryl Trifluoroborate Synthesis

The trifluoroborates were prepared from the corresponding crude boronic esters according to the following procedure. In a Nalgene bottle were added a stirr bar and the crude boronic ester (5 mmol, 1 equiv) dissolved in 12 mL of MeOH/H_2O (2:1). KHF_2 (15 mmol, 3 equiv) was added in one portion over the reaction mixture, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was transferred to a round-bottom flask and concentrated by rotary evaporation. The crude product was recrystallized from acetone to yield the corresponding trifluoroborate.

Potassium Trifluoro(4-methoxyphenyl)borate (3a)[33]

White solid, mp >250 °C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 7.21 (d, *J* = 8.0 Hz, 2H), 6.65 (d, *J* = 8.2 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.5, 132.6, 112.2, 54.9.

Potassium Trifluoro(2-fluorophenyl)borate (3b)

White solid, mp >250 °C (lit.[39] 304−305 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.34 (s, 1H), 7.16−6.99 (m, 1H), 6.91 (t, *J* = 6.9 Hz, 1H), 6.78 (t, *J* = 8.5 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.7 (d, *J* = 239.1 Hz), 134.2, 125.8, 122.5, 113.7 (d, *J* = 26.1).

Potassium Trifluoro(*o*-tolyl)borate (3c)

White solid, mp 229 °C (lit.[40] 232 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.31 (d, *J* = 5.7 Hz, 1H), 6.87 (dd, *J* = 15.4, 5.9 Hz, 3H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 140.5, 131.6, 128.2, 125.1, 123.3, 21.7.

Potassium Trifluoro(2-methoxyphenyl)borate (3g)

White solid, mp >250 °C (lit.[35] >250 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.29 (dd, J = 6.9, 1.4 Hz, 1H), 7.02 (td, J = 7.9, 1.9 Hz, 1H), 6.73−6.65 (m, 2H), 3.62 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.5, 133.2, 126.6, 119.1, 109.6, 54.7.

Potassium Trifluoro(2-(methoxycarbonyl)phenyl)borate (3h)

White solid, mp >260 °C (lit.[35] >250 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.45 (d, J = 7.3 Hz, 1H), 7.20 (t, J = 7.3 Hz, 1H), 7.16 (d, J = 7.3 Hz, 1H), 7.09 (t, J = 7.3 Hz, 1H), 3.65 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.2, 136.5, 132.7, 128.3, 125.8, 124.9, 51.3.

2.1.5 Characterization of Reaction Products

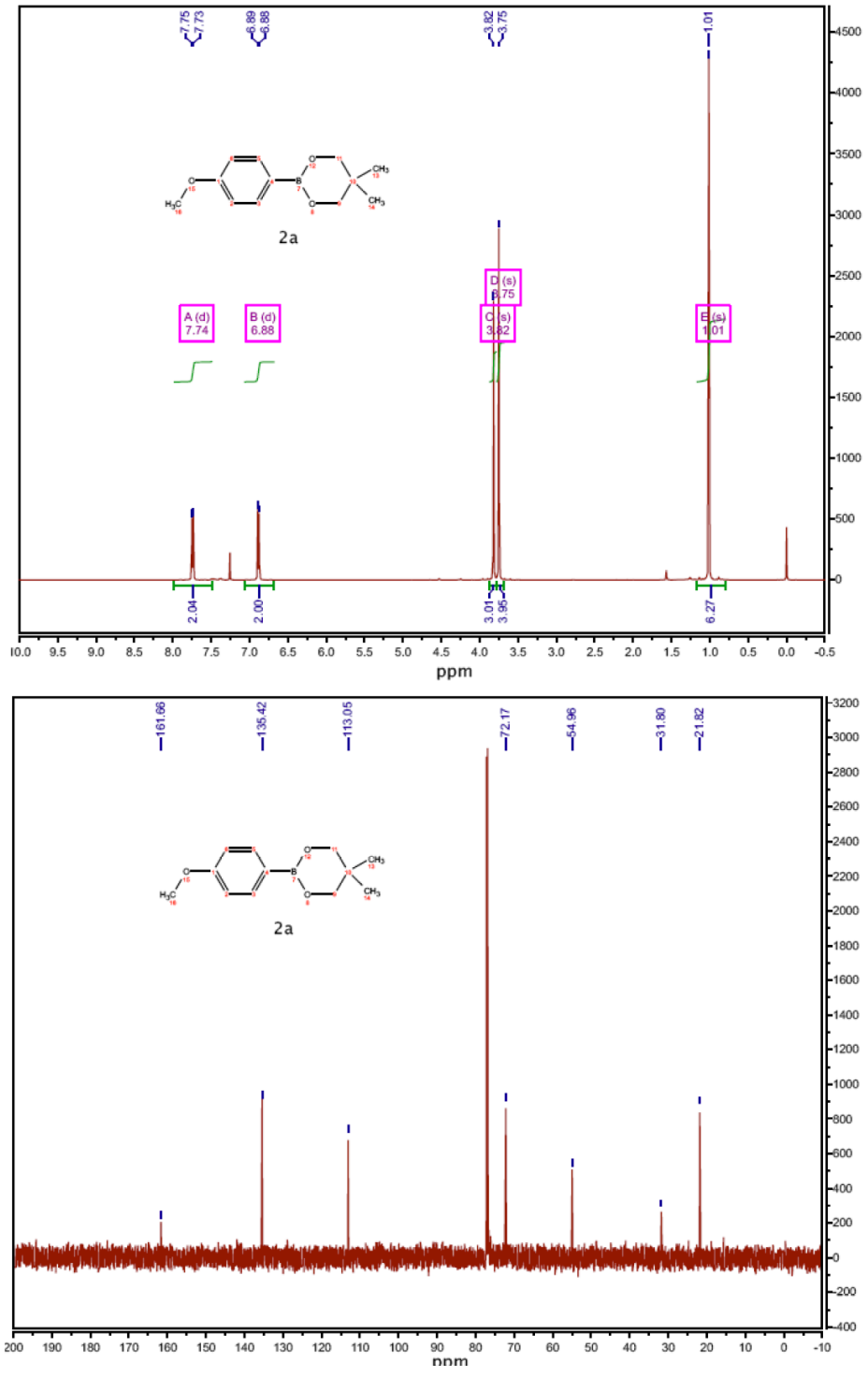


Figure SF 2.1. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 2-(4-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane in $CDCl_3$

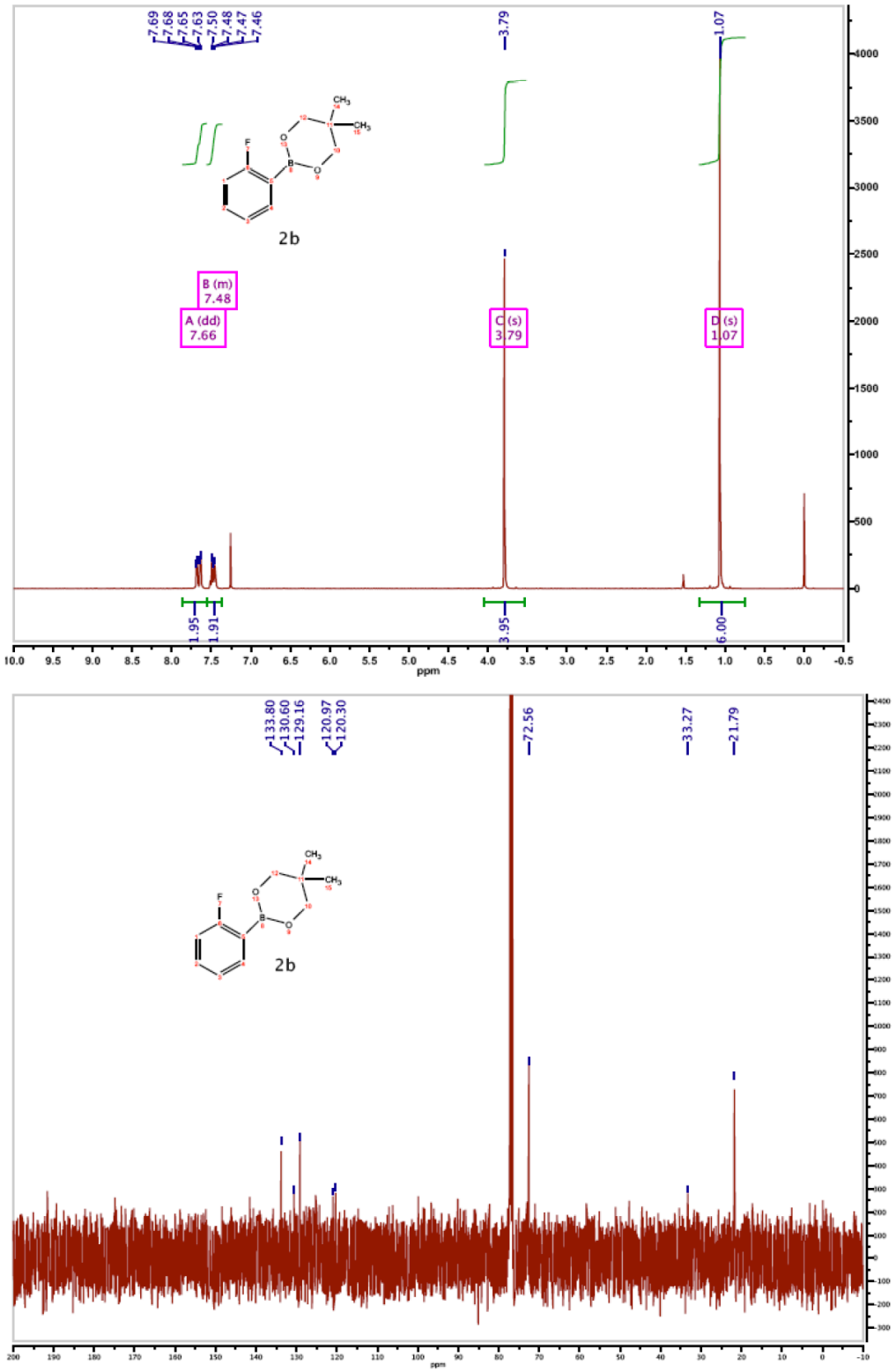


Figure SF 2.2. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 2-(2-fluorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane in $CDCl_3$

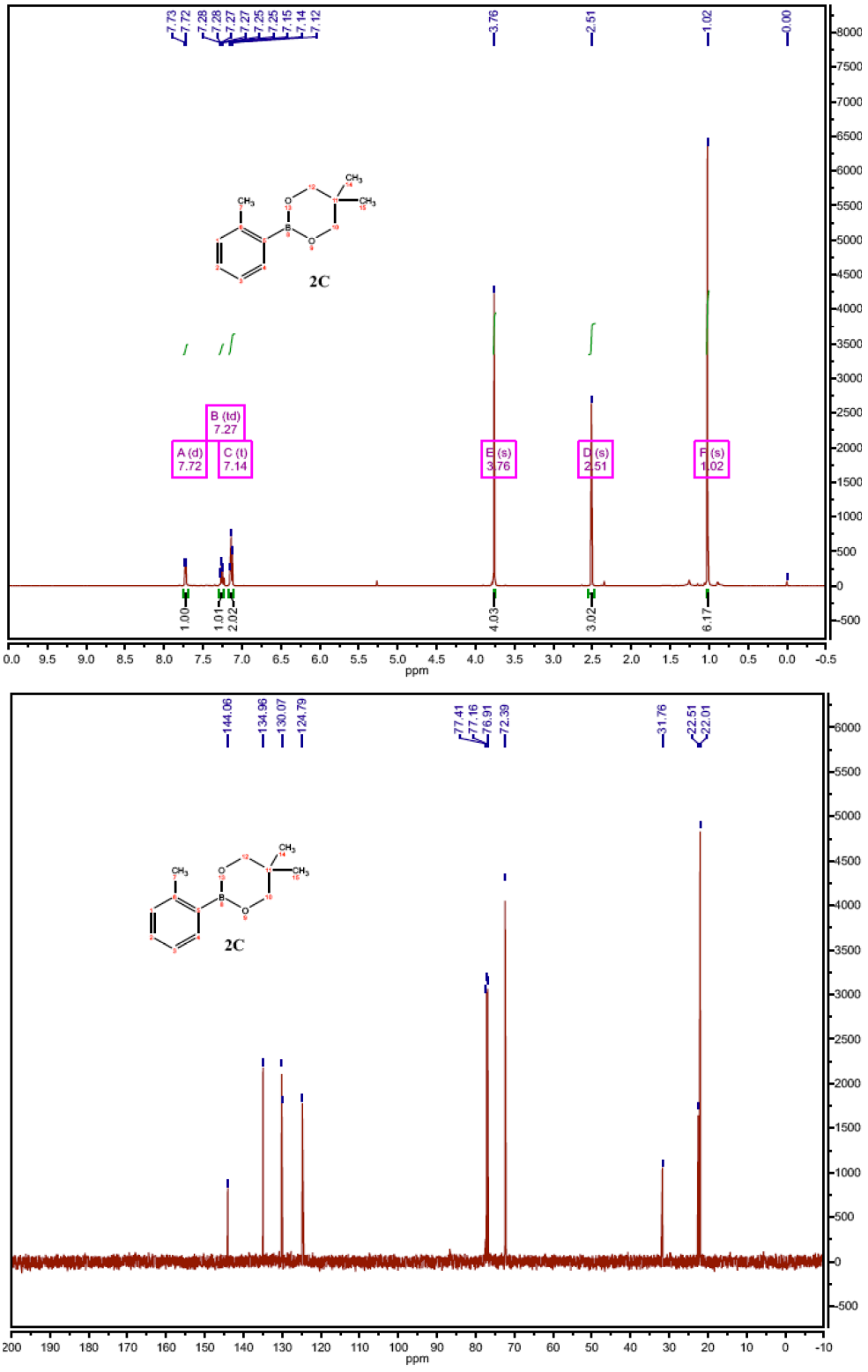


Figure SF 2.3. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 5,5-dimethyl-2-(*o*-tolyl)-1,3,2-dioxaborinane in $CDCl_3$.

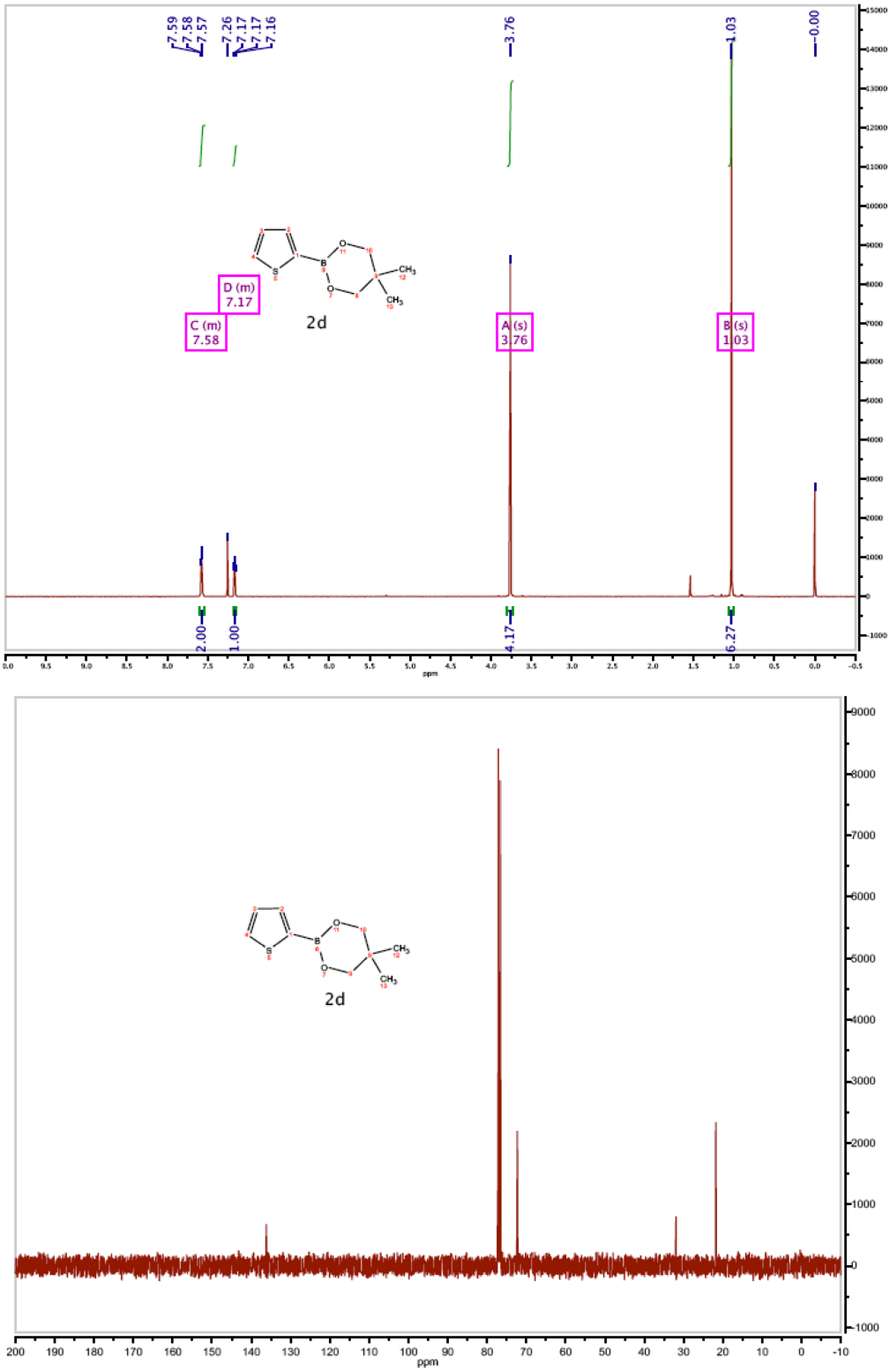


Figure SF 2.4. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 5,5-dimethyl-2-(thiophen-2-yl)-1,3,2-dioxaborinane in $CDCl_3$.

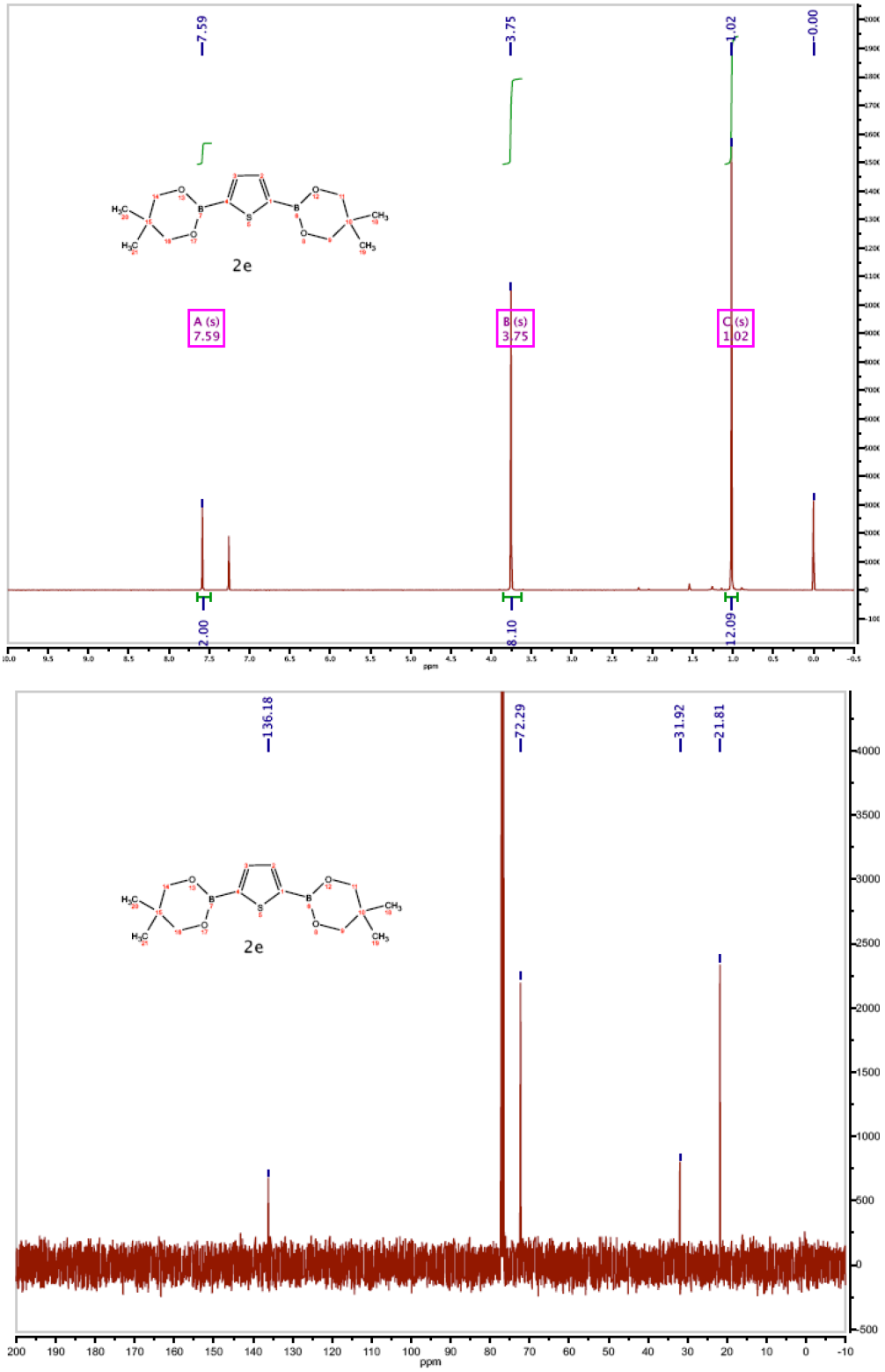


Figure SF 2.5. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 2,5-bis(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)thiophene in $CDCl_3$.

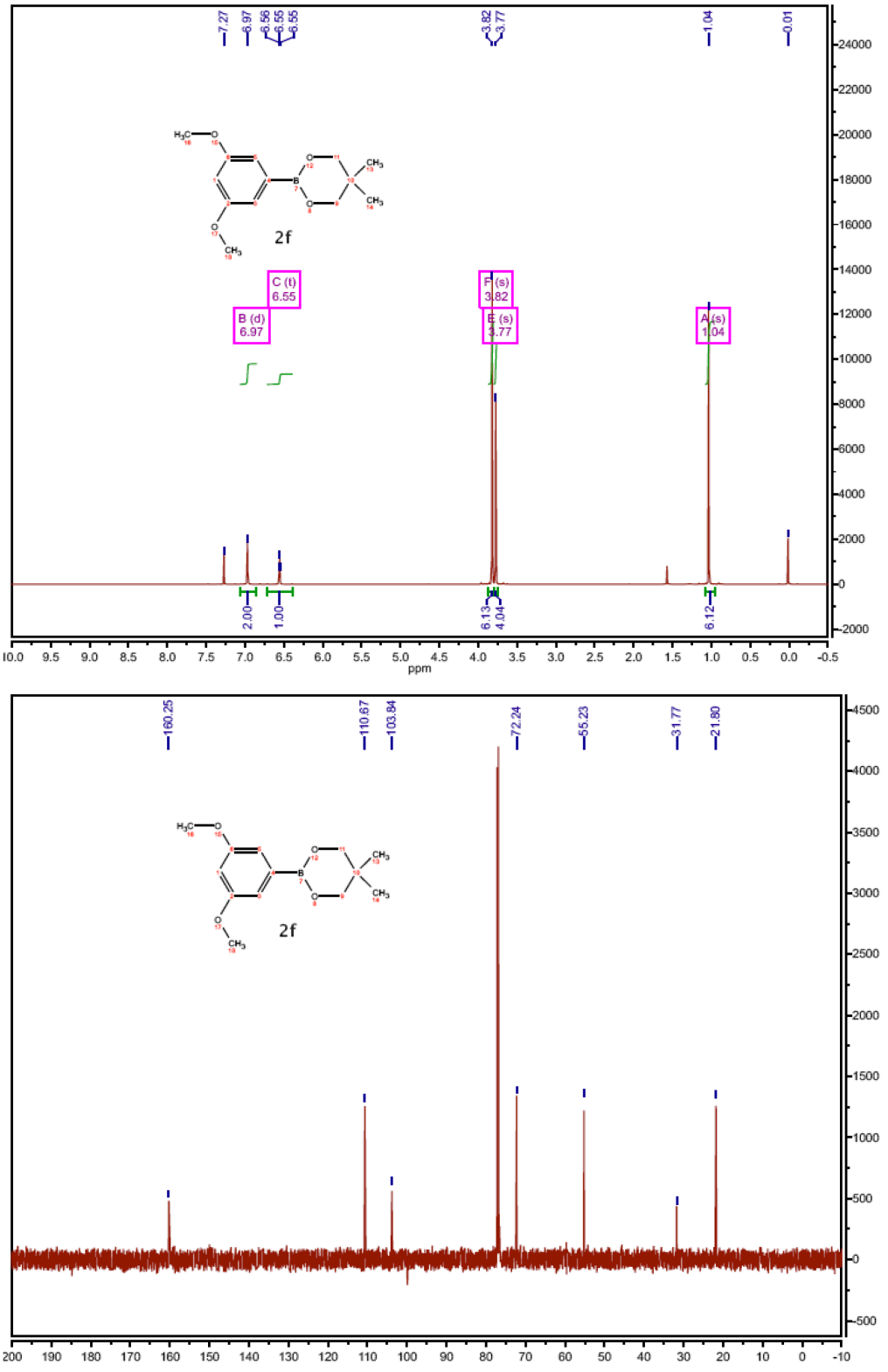


Figure SF 2.6. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 2-(3,5-dimethoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane in $CDCl_3$.

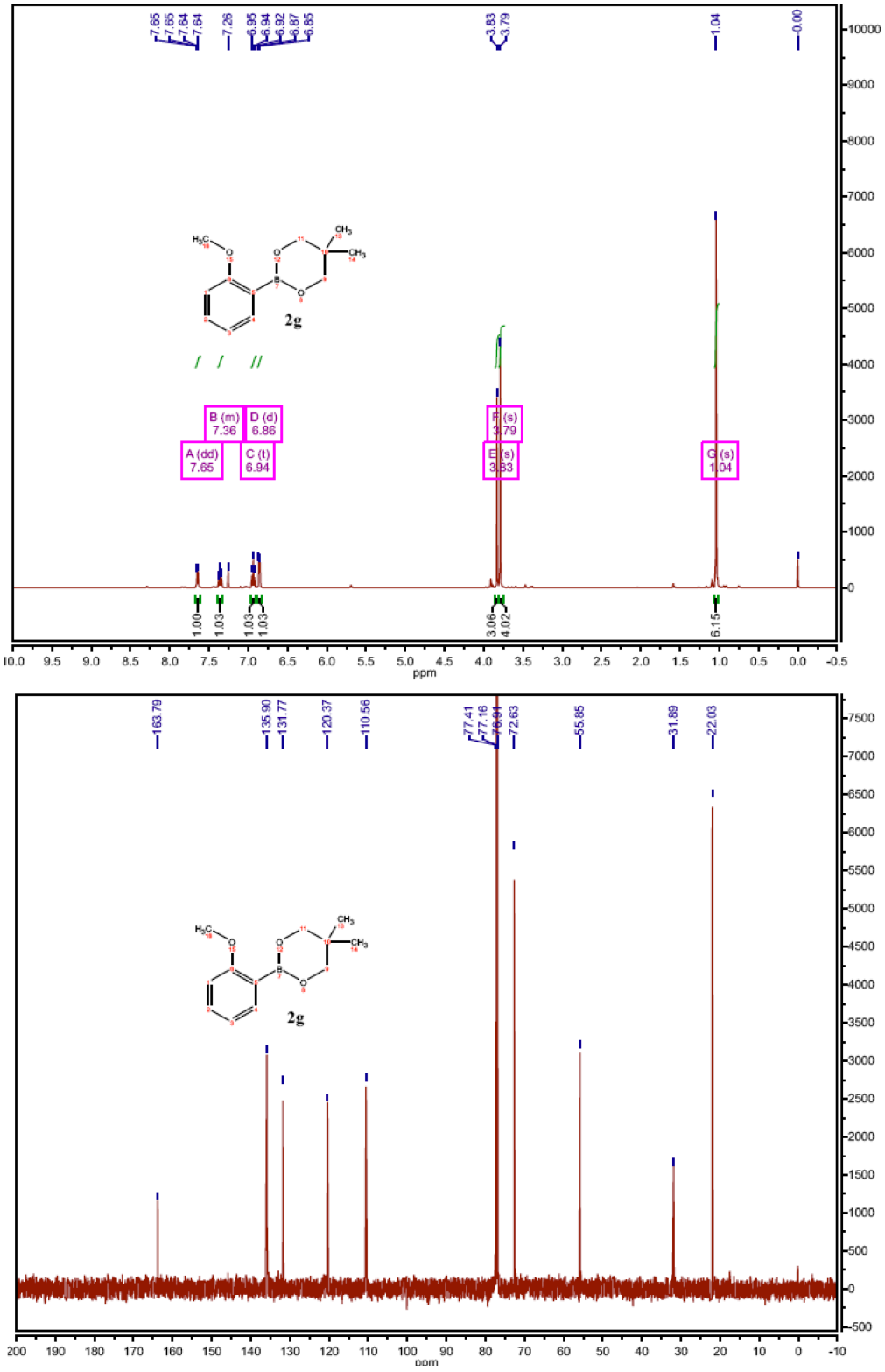


Figure SF 2.7. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 2-(2-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane in $CDCl_3$.

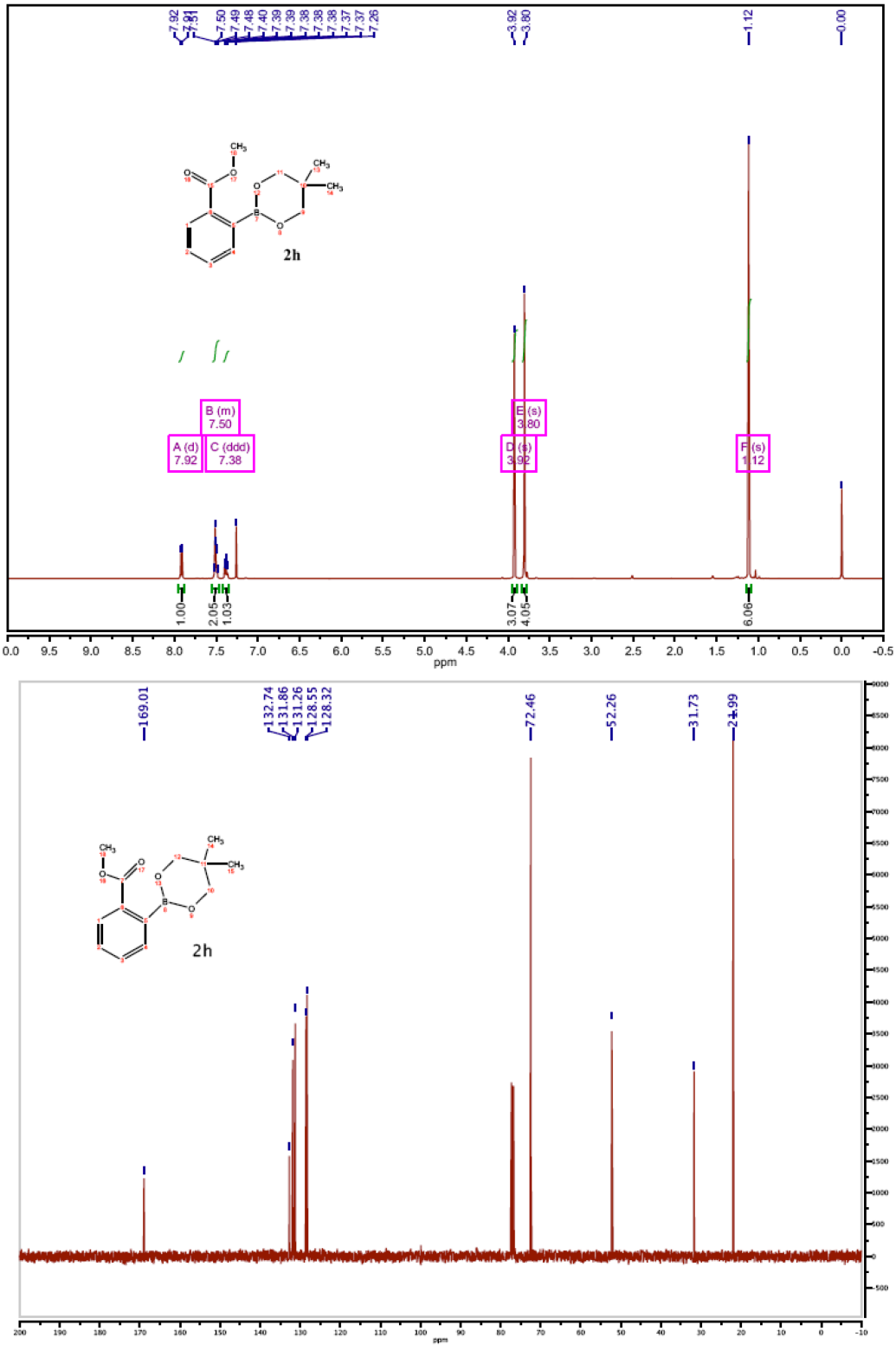


Figure SF 2.8. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate in $CDCl_3$.

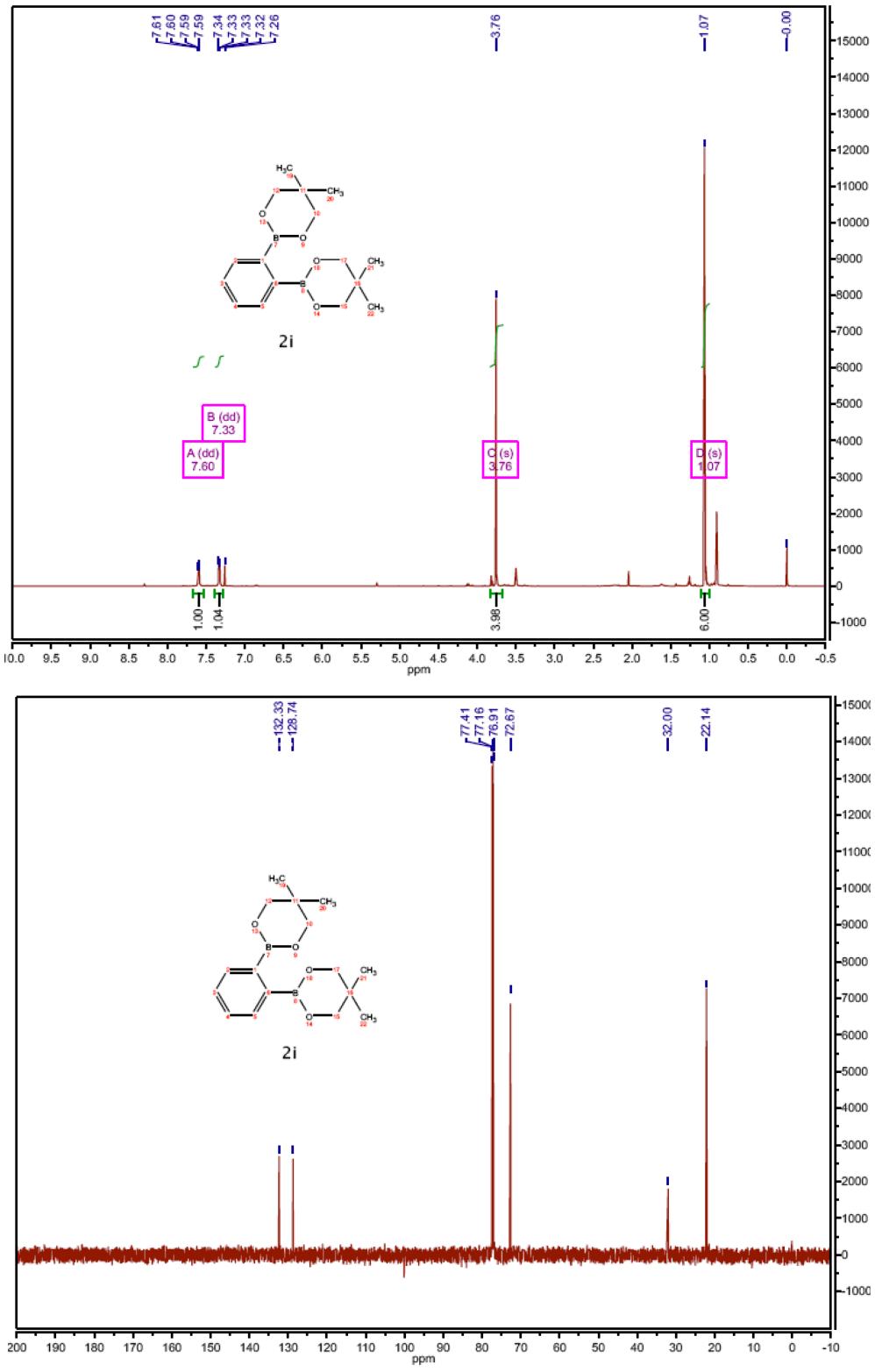


Figure SF 2.9. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 1,2-bis(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzene in $CDCl_3$.

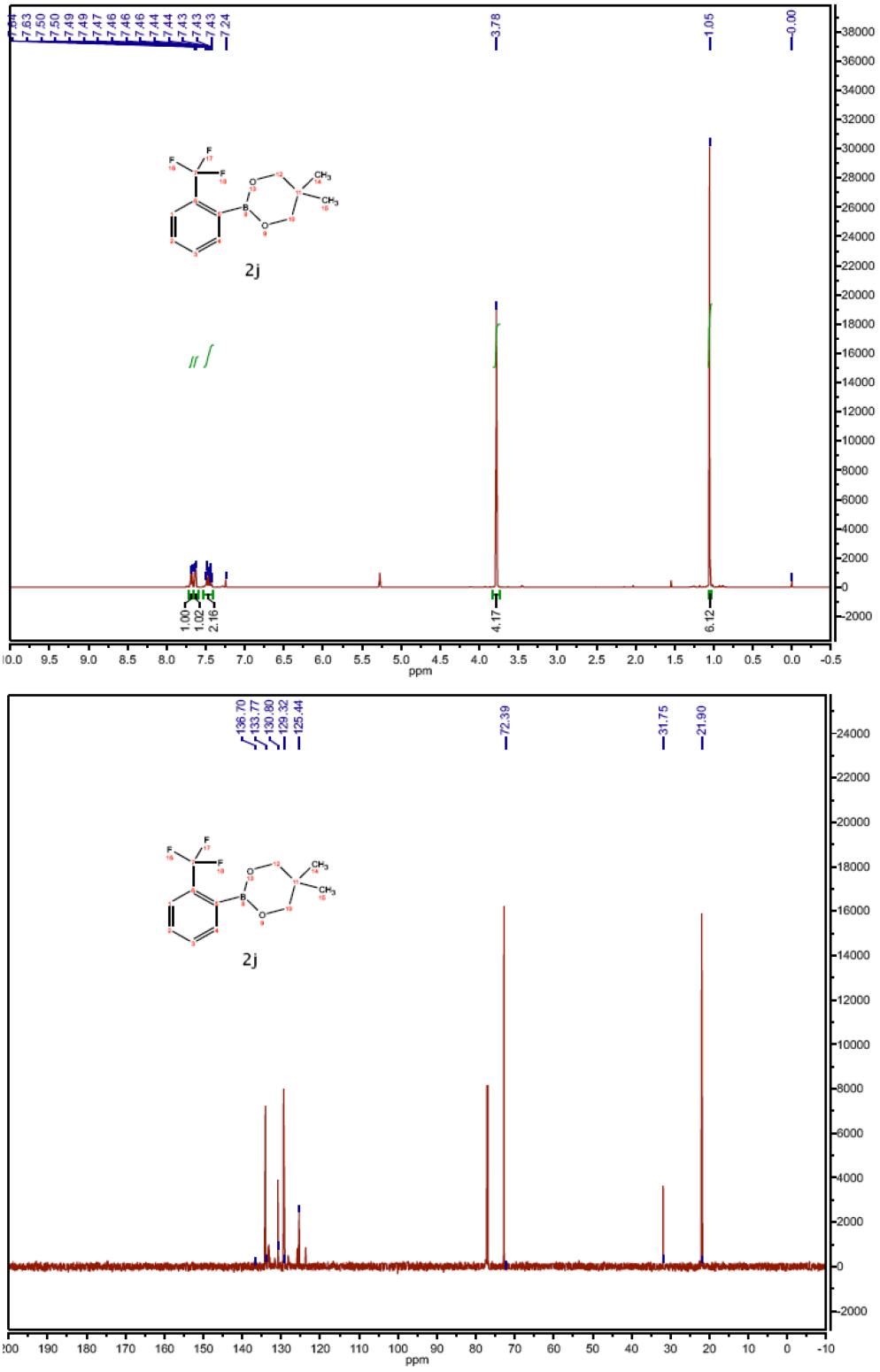


Figure SF 2.10. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 5,5-dimethyl-2-(2-(trifluoromethyl)phenyl)-1,3,2-dioxaborinane in $CDCl_3$.

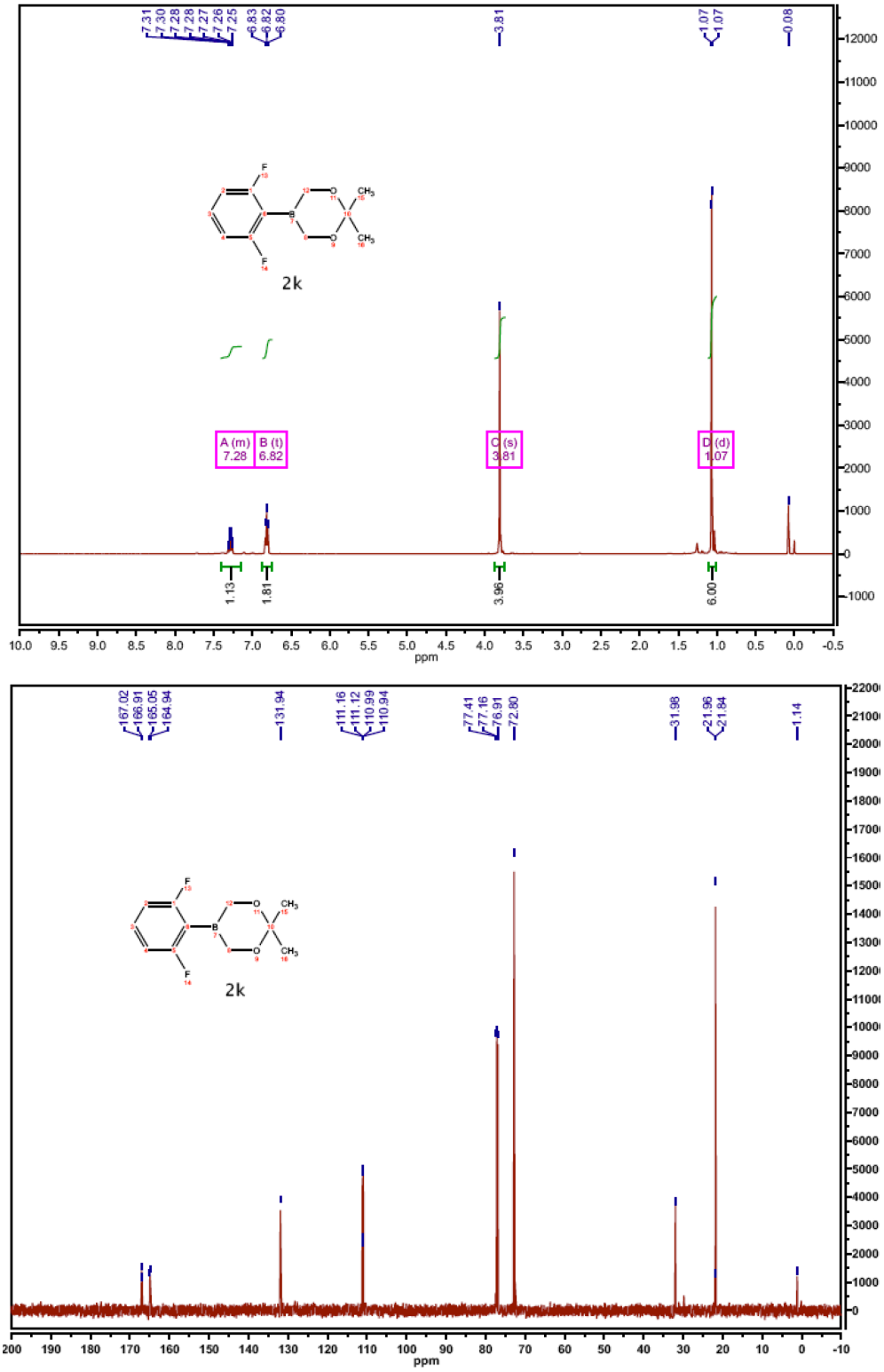


Figure SF 2.11. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 2-(2,6-difluorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane in $CDCl_3$.

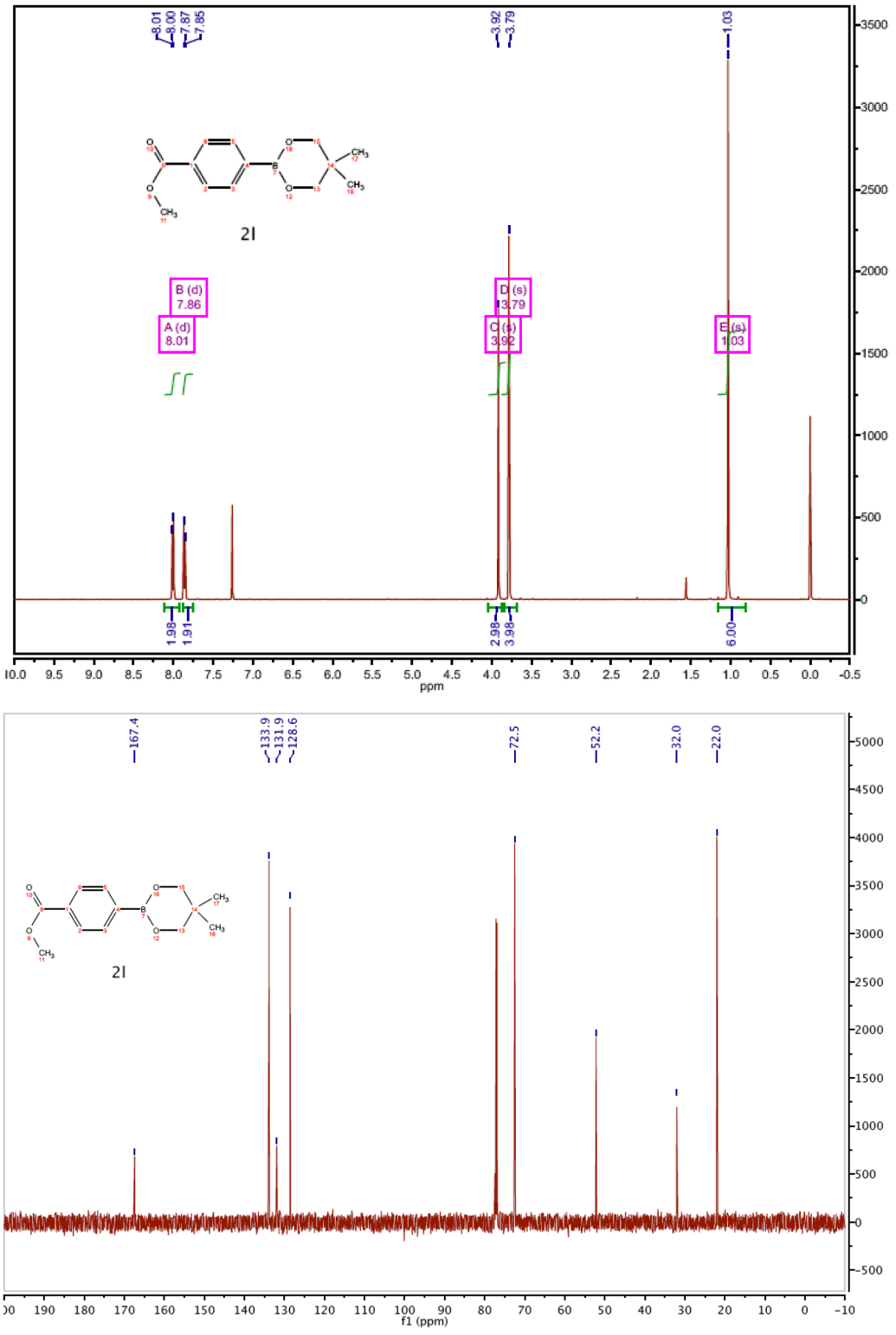


Figure SF 2.12. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate in $CDCl_3$.

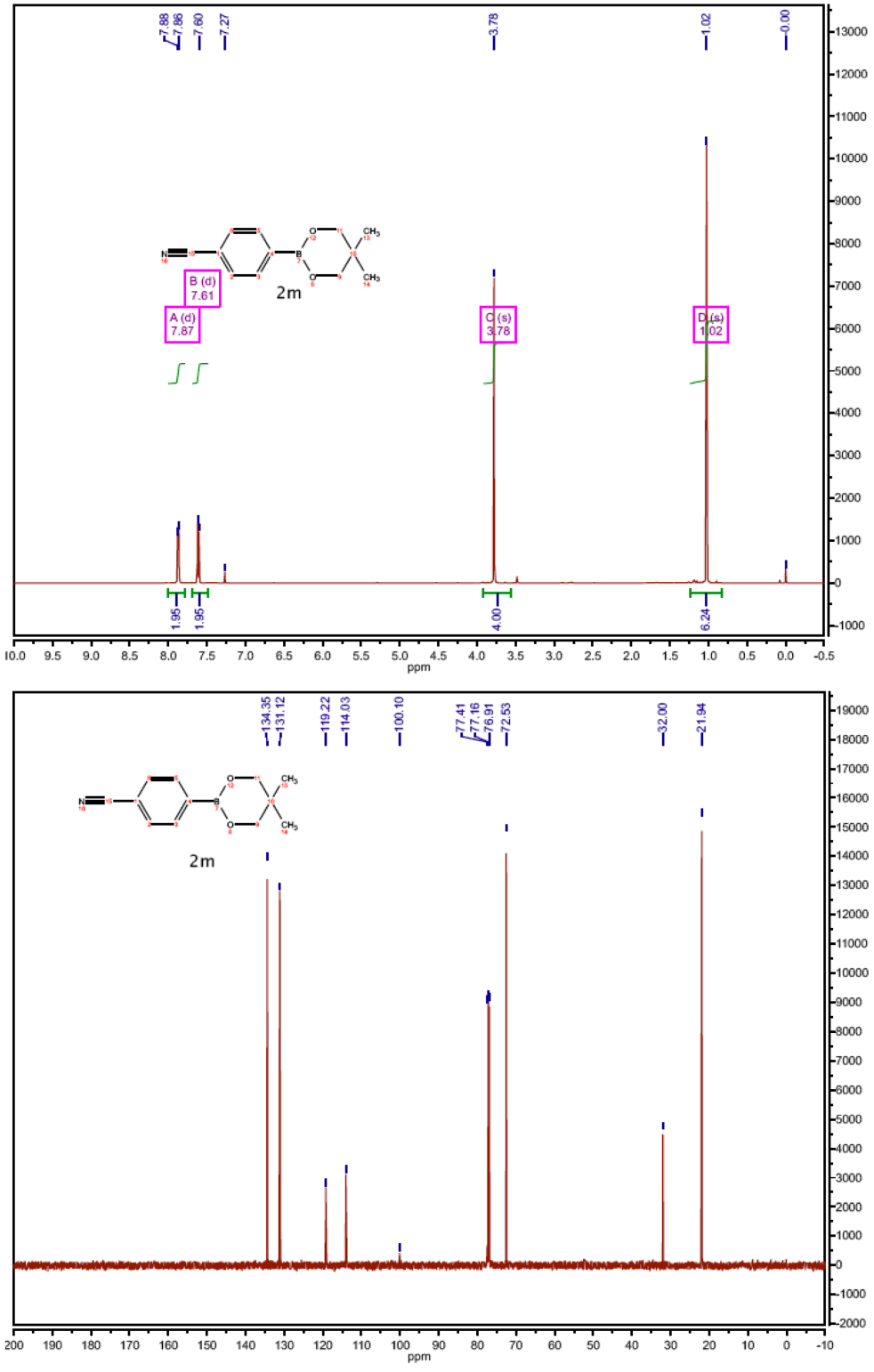


Figure SF 2.13. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzonitrile in $CDCl_3$.

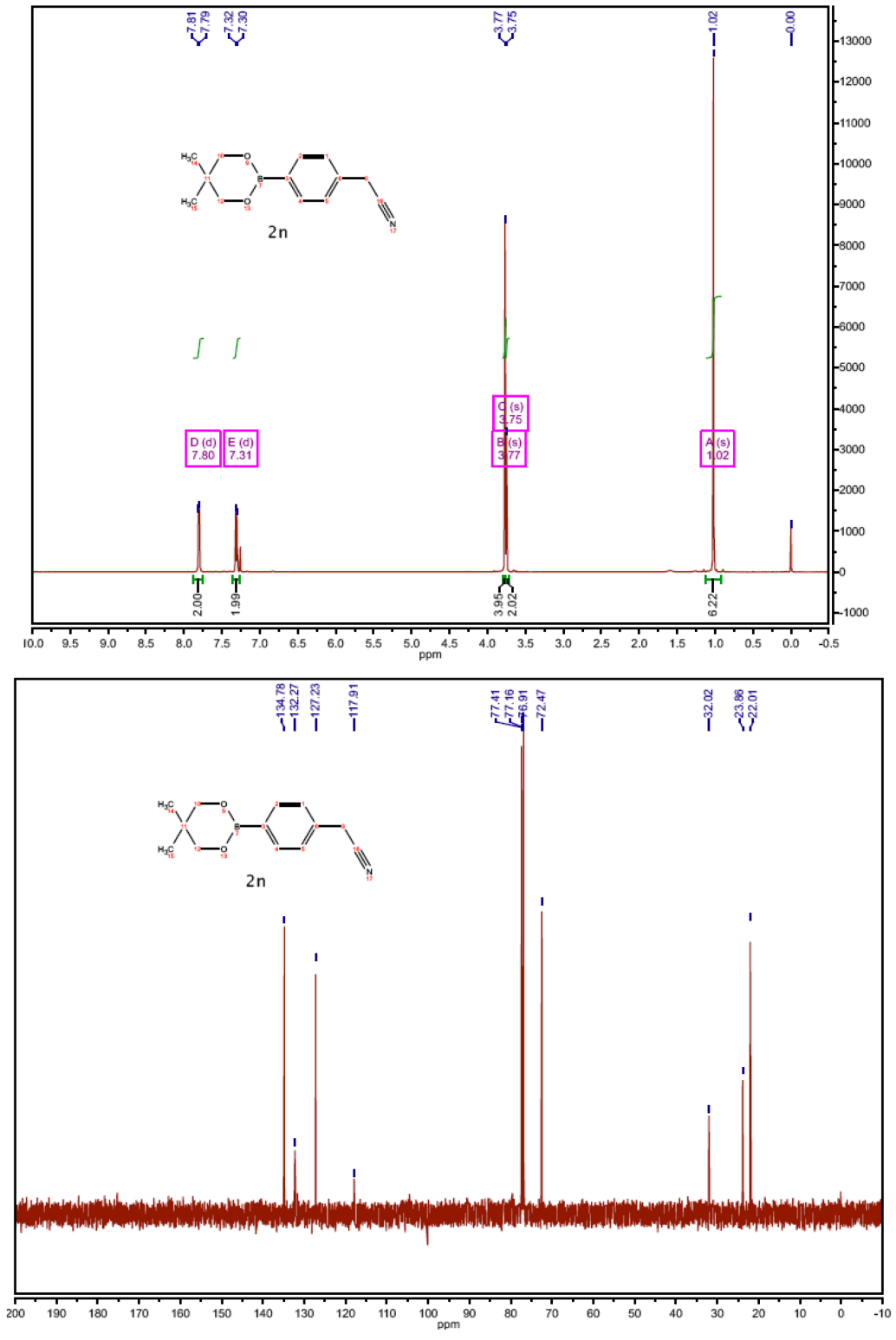


Figure SF 2.14. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 2-(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)acetonitrile in $CDCl_3$.

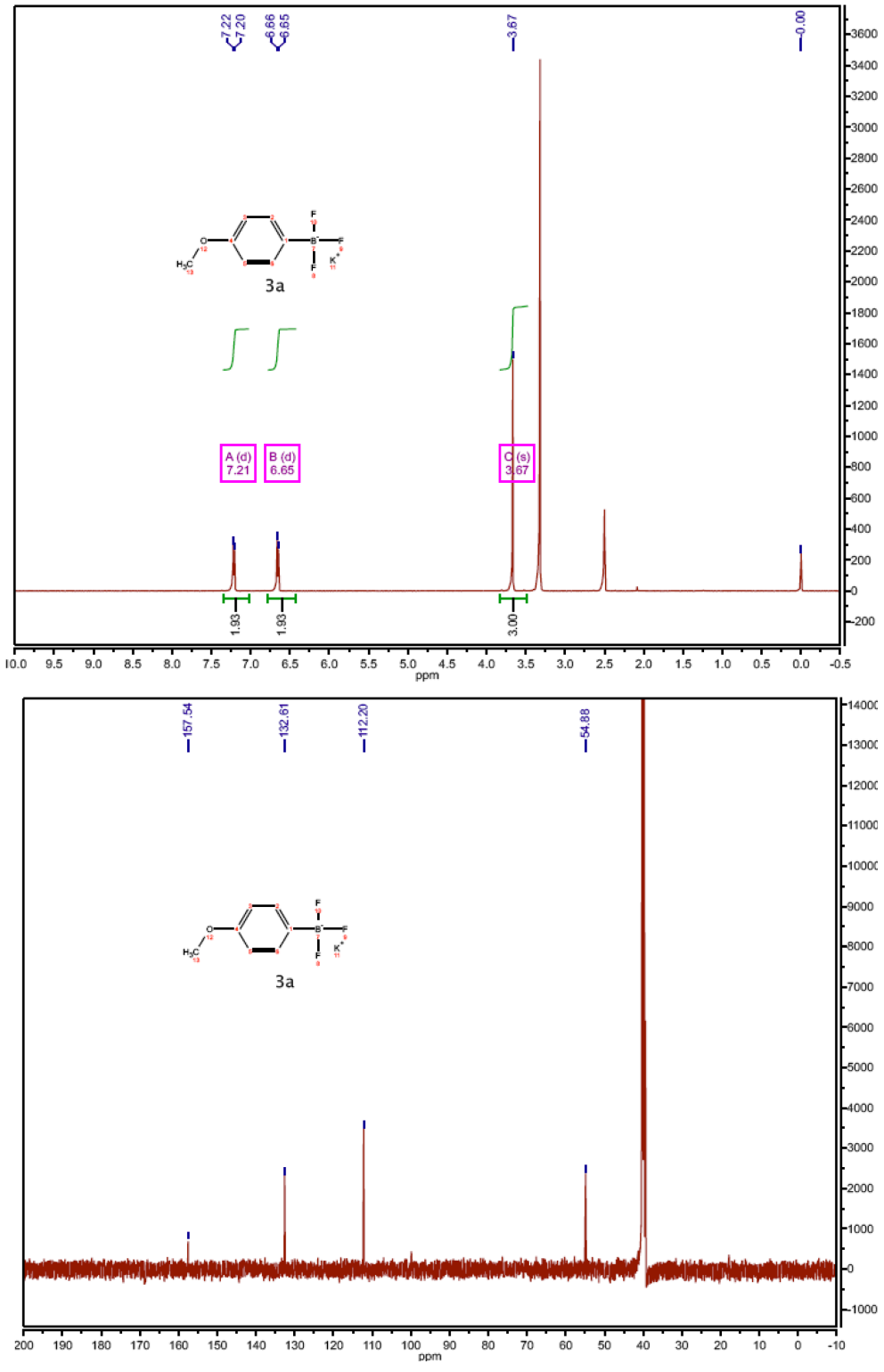


Figure SF 2.15. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of potassiumtrifluoro(4-methoxyphenyl)borate in DMSO-d_6.

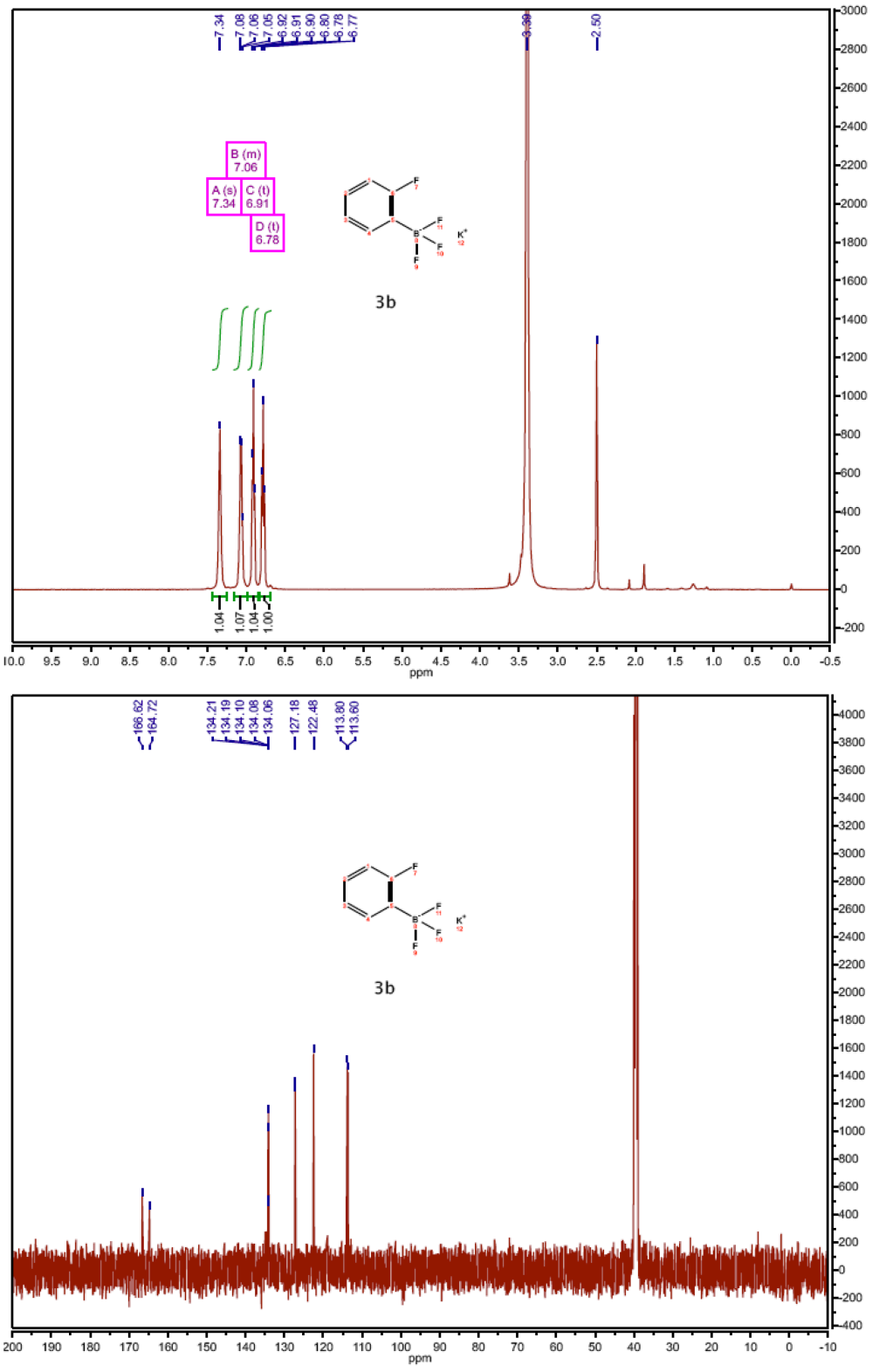


Figure SF 2.16. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of potassiumtrifluoro(2-fluorophenyl)borate in DMSO-d_6.

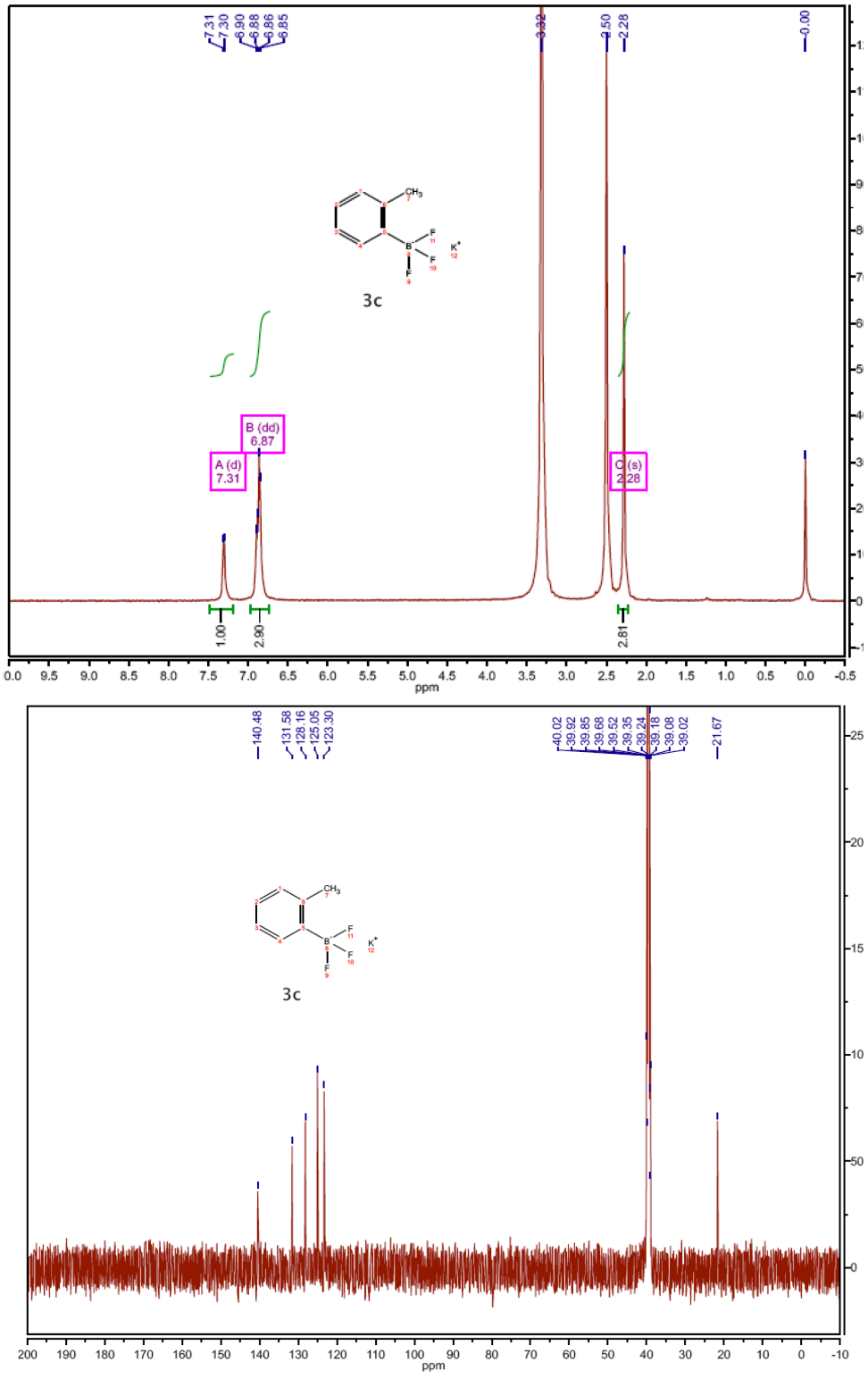


Figure SF 2.17. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of potassiumtrifluoro(*o*-tolyl)borate in DMSO-d_6.

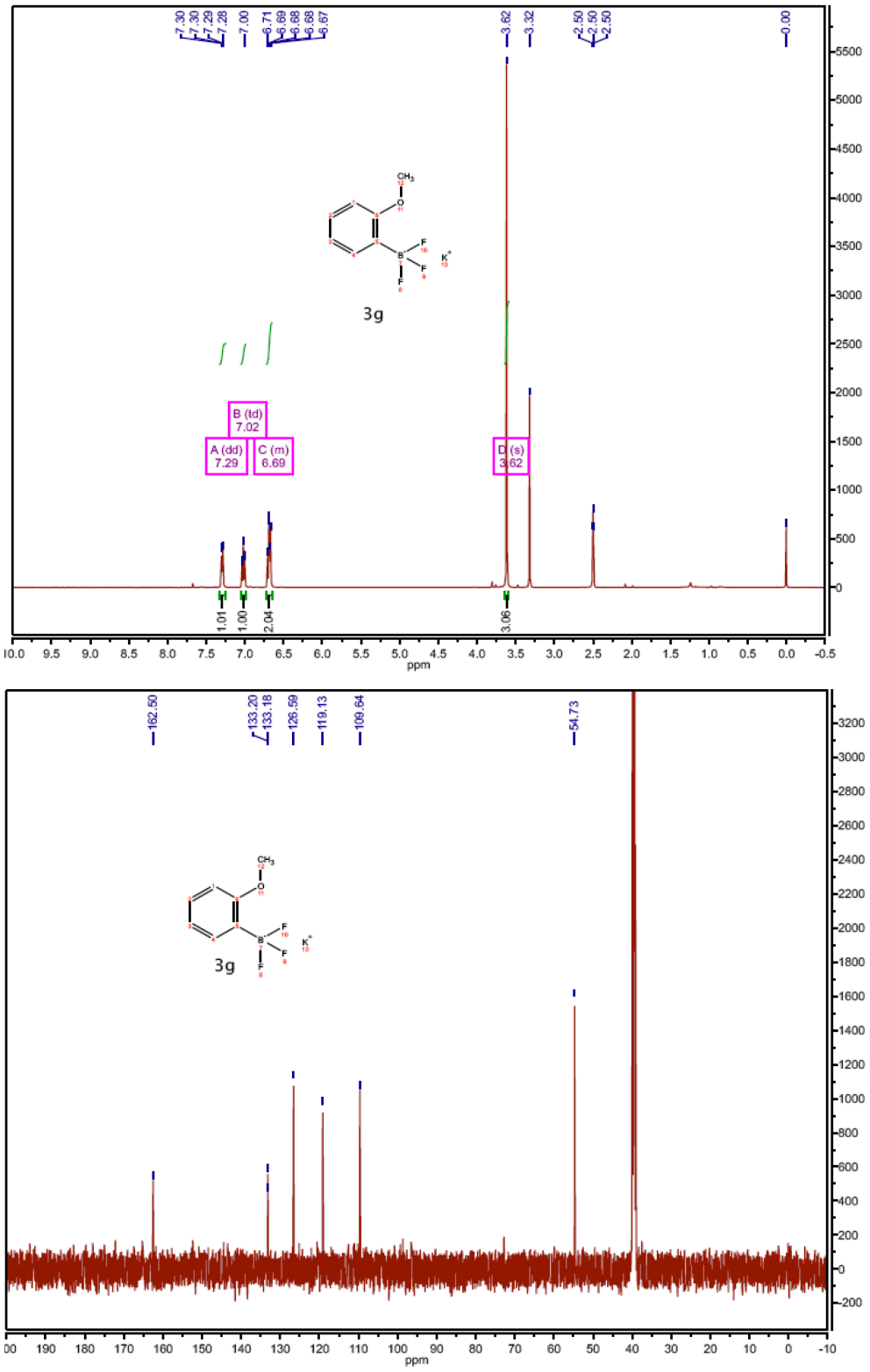


Figure SF 2.18. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of potassiumtrifluoro(2-methoxyphenyl)borate in DMSO-d^{6}.

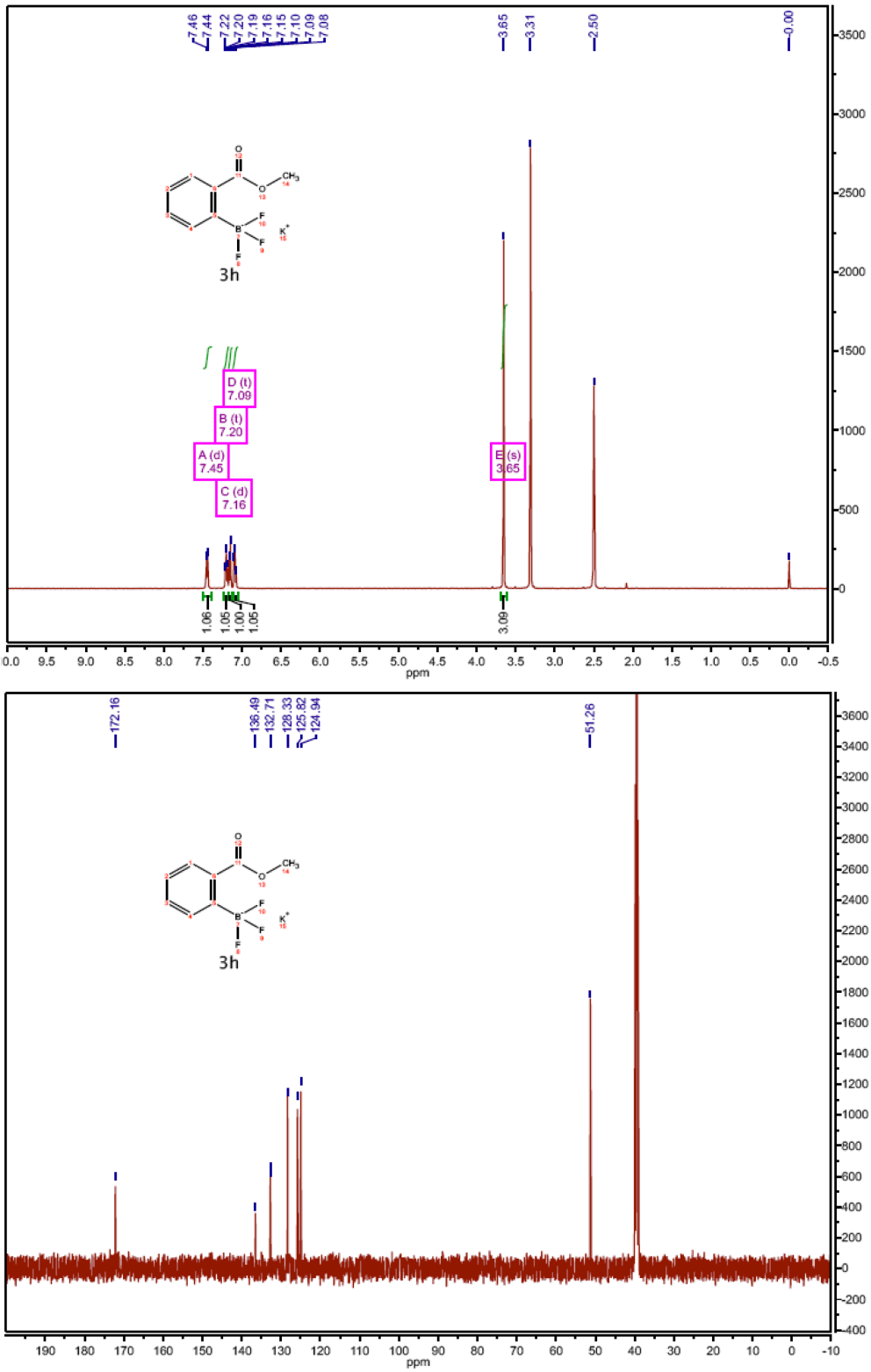


Figure SF 2.19. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of potassiumtrifluoro(2-(methoxycarbonyl)phenyl)borate in DMSO-d_6.

2.1.6 Account of Contribution

In this work, I contributed to data in Tables 2.1-2.3. I also contributed to the data organization of this manuscript.

2.1.7 References

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3 CHAPTER 3

Nickel Mixed-Ligand Systems Catalyzed Cross-Coupling Reactions of Aryl C-O Electrophiles with Aryl Neopentylglycolboronates

3.1 $Ni(COD)_2/PCy_3$ Catalyzed Cross-Coupling of Aryl and Heteroaryl Neopentylglycolboronates with Aryl and Heteroaryl Mesylates and Sulfamates in THF at Room Temperature

3.1.1 Introduction

In Chapter 1, we discussed our laboratorys interest in aryl-aryl and aryl-heteroaryl coupling for the purpose of supramolecular and polymer chemistry.[2] We developed $NiCl_2$(dppe)/PPh_3 mixed-ligand system for cross-coupling of aryl mesylates with arylboronic acids.[3] Garg reported the first examples of $NiCl_2(PCy_3)_2$ catalyzed cross-coupling of aryl sulfamates with arylboronic acids at 110 ^oC.[4] $Ni(COD)_2$ have also been proven efficient for the cross-coupling of aryl sulfonates[5] and other C-O[6] derived electrophiles with arylboronic acids and potassium aryltrifluoroborates.[7] We reported $NiCl_2(PPh_3)_2$ cross couples aryl chlorides, mesylates and tosylates with arylboronic acids.[3,8] In previous chapters, the method of preparing aryl neopentylglycolboronic esters with electron-withdrawing groups as well as *ortho* functional groups from aryl halides and sulfonates *via* $NiCl_2$(dppp)/dppf mixed-ligand system in the presence of zero-valent metal was demonstrated.[9-12] We are able to prepare aryl neopentylglycolboronates bearing nucleophile-sensitive groups in one step by nickel catalyzed borylation reactions.[5,9-13] To avoid deprotection of the boronic ester,[2] a nickel catalyzed Suzuki-Miyaura cross-coupling of phenol derivatives with aryl neopentylglycolboronates is desired. Moreover, for purposes such as building up a complex system, strict stoichiometry is desired. A classic example is provided by step polymerization reactions where perfect stoichiometry is required for the synthesis of high molar mass polymers and of polymers with well defined chain ends.[14] Boronic acids are

undesirable reagents in these cases because of concerns of reaction stoichiometry derived from inconsistent concentrations of boronic acid anhydrides.[15,16]

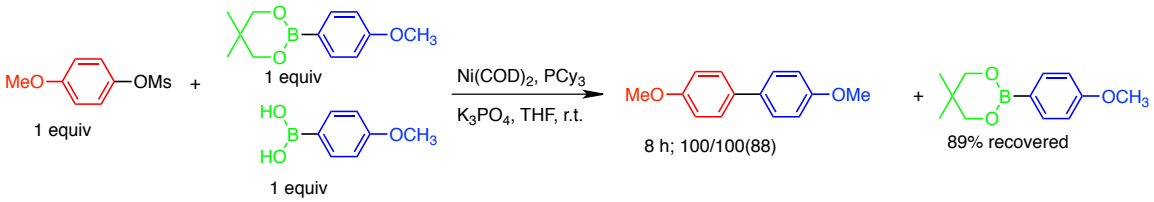
However, there are few reports on the Ni-catalyzed cross-coupling of aryl neopentylglycolboronates and of other boronic esters with aryl C-O derived electrophiles and with aryl halides.[5,13] In a preliminary communication on this Ni-catalyzed borylation, we reported that indeed several aryl neopentylglycolboronates could be effectively cross-coupled with aryl bromides and iodides using $Ni(dppe)Cl_2$ as catalyst.[13] To our knowledge these experiments represented the first examples of Ni-catalyzed cross-coupling of aryl halides with arylboronic esters. Shortly thereafter, Chatani found that $Ni(COD)_2/PCy_3$ provides efficient cross-coupling of highly activated aryl methyl ethers with arylboronic esters in the presence of CsF as base.[6] Later, we demonstrated with two preliminary examples of aryl mesylates, two aryl sulfonates, and one aryl chloride that $Ni(COD)_2/PCy_3$ in the presence of K_3PO_4 as base could expand the Ni-catalyzed cross-coupling of aryl neopentylglycolboronates to aryl chlorides, mesylates and tosylates.[5] To date, no comprehensive investigation of the cross-coupling of aryl boronate esters with any class of electrophiles has been undertaken for any Ni-catalytic system. Herein, we demonstrate robust catalytic conditions for $Ni(COD)_2/PCy_3$ catalyzed cross-coupling of aryl neopentylglycolboronates with both aryl and heteroaryl mesylates and sulfamates in THF at room temperature.

3.1.2 Results and Discussion

Competitive Cross-Coupling of Aryl Neopentylglycolboronates and Arylboronic Acids with Aryl Mesylates. It is often improperly assumed that the reactivity of arylboronic esters in cross-coupling reactions is identical to that of boronic acids. This is both mechanistically and empirically incorrect. Arylboronic esters tend to react slower and in some cases can require more active catalytic systems to mediate their cross-coupling efficiently. A simple experiment was devised to determine the relative rate of arylboronic acid and arylboronic ester cross-coupling catalyzed by the $Ni(COD)_2/PCy_3$ system, wherein 1 equiv 4-methoxyphenyl methanesulfonate was subjected to $Ni(COD)_2/PCy_3$ catalytic system in the presence of 1 equiv of *para*-methoxyphenylboronic acid and 1 equiv of its aryl neopentylglycolboronate analog (Scheme 3.1).

At the point that 100% conversion of 4-methoxyphenyl methanesulfonate was achieved, 89% percent of the boronic ester remained unreacted. This result demonstrates that the rate of cross-coupling with aryl neopentylglycolboronate esters is at least 8 times slower than for the boronic acids. As there is no evidence of *in situ* hydrolysis under the catalytic conditions, this suggests that transmetalation of the ArOMs-Ni^{II}/L complex with arylboronate esters is slower than for arylboronic acid.

Scheme 3.1. Competitive Cross-Coupling of an Aryl Mesylate with Both an Arylboronic Acid and an Aryl Neopentylglycolboronate

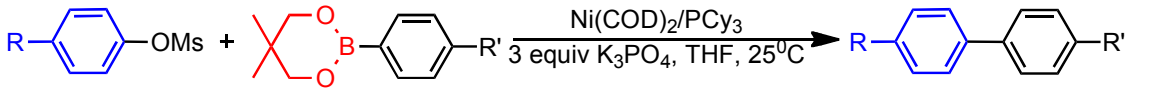


Having established that aryl neopentylglycolboronates are less reactive than arylboronic acids, we started from the condition for cross-coupling of aryl sulfonates with arylboronic acids but with higher catalyst loading to optimize the reaction conditions.[17]

Optimization of Cross-Coupling Reaction Conditions of Aryl Neopentylglycolboronates with Aryl Mesylates. In a preliminary communication it was reported that 2-(4-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane **2a** could be efficiently cross-coupled with aryl chlorides (one example), mesylates (two examples) and tosylates (two examples) using 6 mol % $Ni(COD)_2$ as a zero-valent Ni source in the presence of 18 mol% PCy_3 in THF at 25 °C.[5] To develop the most efficient room-temperature Ni-catalyzed cross-coupling conditions for aryl neopentylglycolboronates, the reaction parameters were investigated in detail (Table 3.1). Methyl 4-(methylsulfonyloxy)benzoate was chosen as a representative aryl mesylate bearing an electron-deficient group. It was determined that 4 mol% $Ni(COD)_2$ in conjunction with 8 mol% PCy_3 did not provide complete conversion (80%, Table 3.1, entry 1). Maintaining the same Ni/ligand ratio, but increasing $Ni(COD)_2$ loading to 6 mol% provided quantitative conversion within 12 h (Table 3.1, entry 2). Increasing the PCy_3 level to 18 mol% while maintaining the Ni loading at

6 mol% led to complete conversion in only 8 h (Table 3.1, entry 3). Higher PCy_3 vs $Ni(COD)_2$ ratio either stabilized the catalyst or provided a more reactive tricoordinate complex. The same trend was observed when using 4-methoxyphenyl methanesulfonate as a representative electron-rich aryl mesylate electrophile. To minimize the loading levels of catalyst and ligand, the reagents' concentration was increased to accelerate the reactions. Here, doubling the reagents' concentration (Table 3.1, entries 4-7) allowed for complete conversion and excellent recovered yield for as low as 5 mol% $Ni(COD)_2$ and 10 mol% PCy_3.

Table 3.1. Cross-Coupling of *para*-Substituted Aryl Mesylates with *para*-Substituted Aryl Neopentylglycolboronates Catalyzed by $Ni(COD)_2/PCy_3$ in THF at 25 ^oC



1a: R = CO_2CH_3
1b: R = OCH_3

2a: R' = OCH_3

3a: R = CO_2CH_3,R' = OCH_3
3b: R = OCH_3, R' = OCH_3

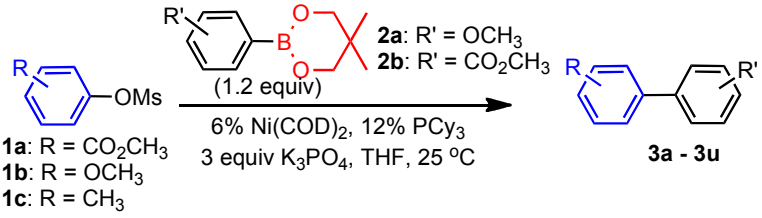
entry	substrate	$Ni(COD)_2$ (%)	PCy_3(%)	THF (mL)	time (h)	**3**	convn[a]/yield[b] (%)
1	**1a**	4	8	2	12	**3a**	80 / 80
2	**1a**	6	12	2	12	**3a**	100 / 100
3	**1a**	6	18	2	8	**3a**	100 / 100
4	**1a**	6	12	1	4	**3a**	100 / 100 (94)
5	**1a**	6	18	1	4	**3a**	100 / 100 (96)
6	**1a**	5	10	1	4	**3a**	100 / 100 (99)
7	**1a**	5	15	1	4	**3a**	100 / 100 (84)
8	**1b**	6	18	1	8	**3b**	100 / 100 (95)
9	**1b**	6	12	1	12	**3b**	100 / 100 (93)

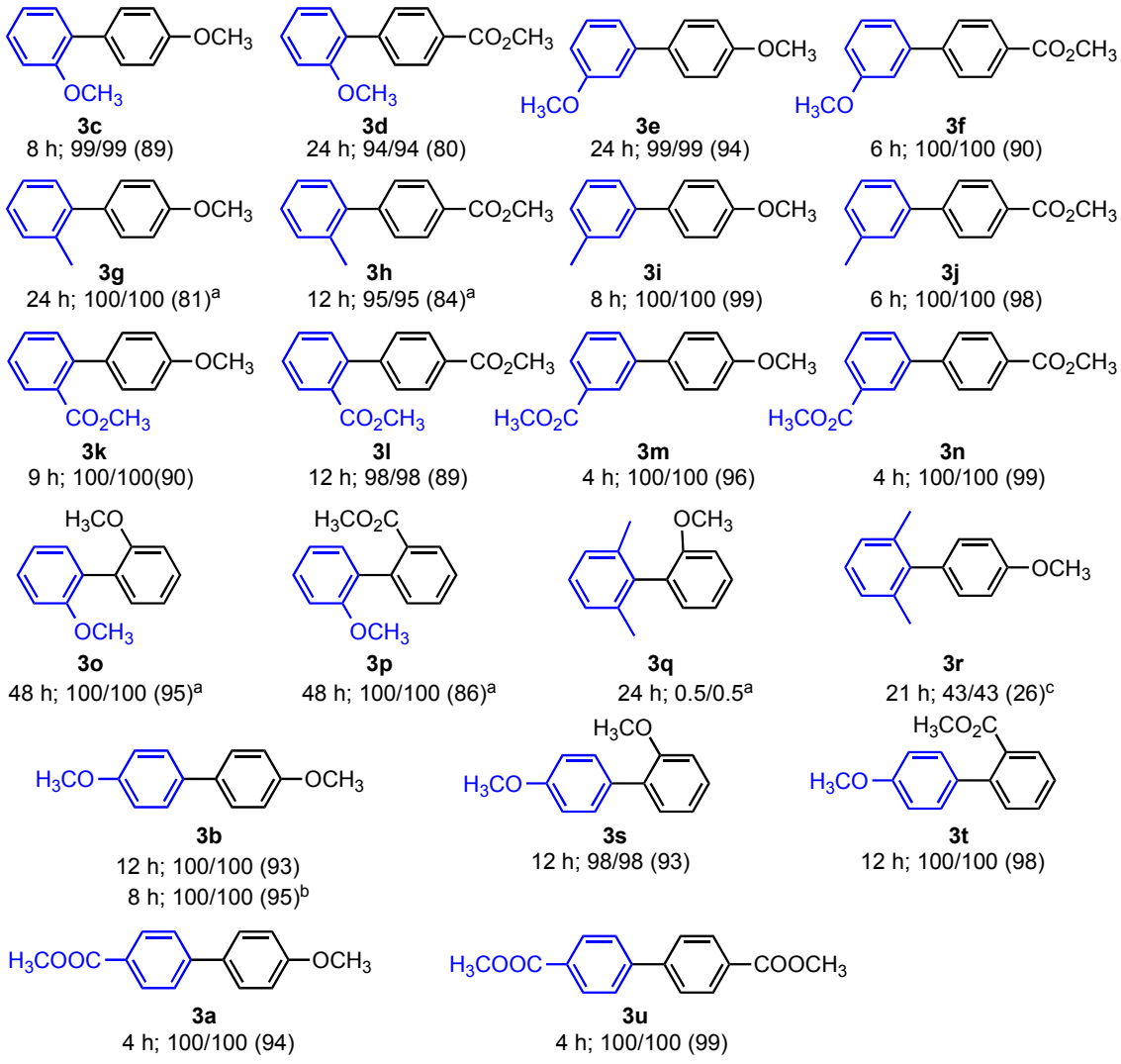
[a]Conversion determined by GC. [b]Yield determined by GC. Isolated yield in parentheses.

Scope of the Cross-Coupling of Aryl Neopentylglycolboronates with Aryl Mesylates. A variety of electron-rich and electron-deficient aryl mesylates were cross-coupled with electron-rich and electron-deficient aryl neopentylglycol boronates with 6 mol% $Ni(COD)_2$ and 12 mol% PCy_3 in

1 mL of THF in quantitative or nearly quantitative GC coupling yield and excellent isolated yield (Table 3.2). The cross-coupling of mono-*ortho* substituted aryl mesylates and/or mono-*ortho* substituted aryl neopentylglycolboronic esters requires a higher catalyst loading of 10 mol% $Ni(COD)_2$ and 20 mol% PCy_3 to achieve excellent conversion and yield. The cross-coupling of doubly *ortho*-substituted 2,6-dimethylphenyl methanesulfonate to form **3q** or **3r** was not successful.

Table 3.2. Cross-Coupling of Aryl Mesylates with Aryl Neopentylglycolboronates Catalyzed by $Ni(COD)_2/PCy_3$ in THF at 25 °C

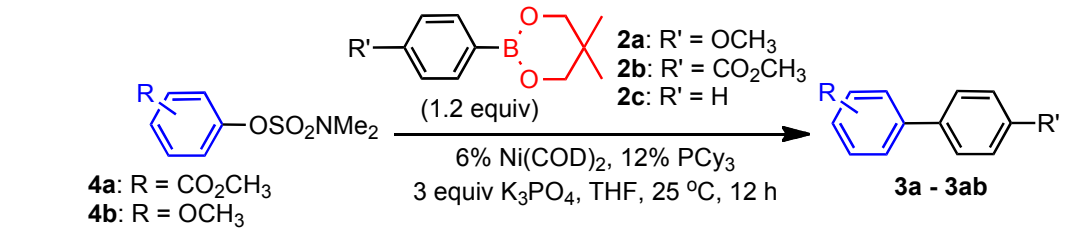


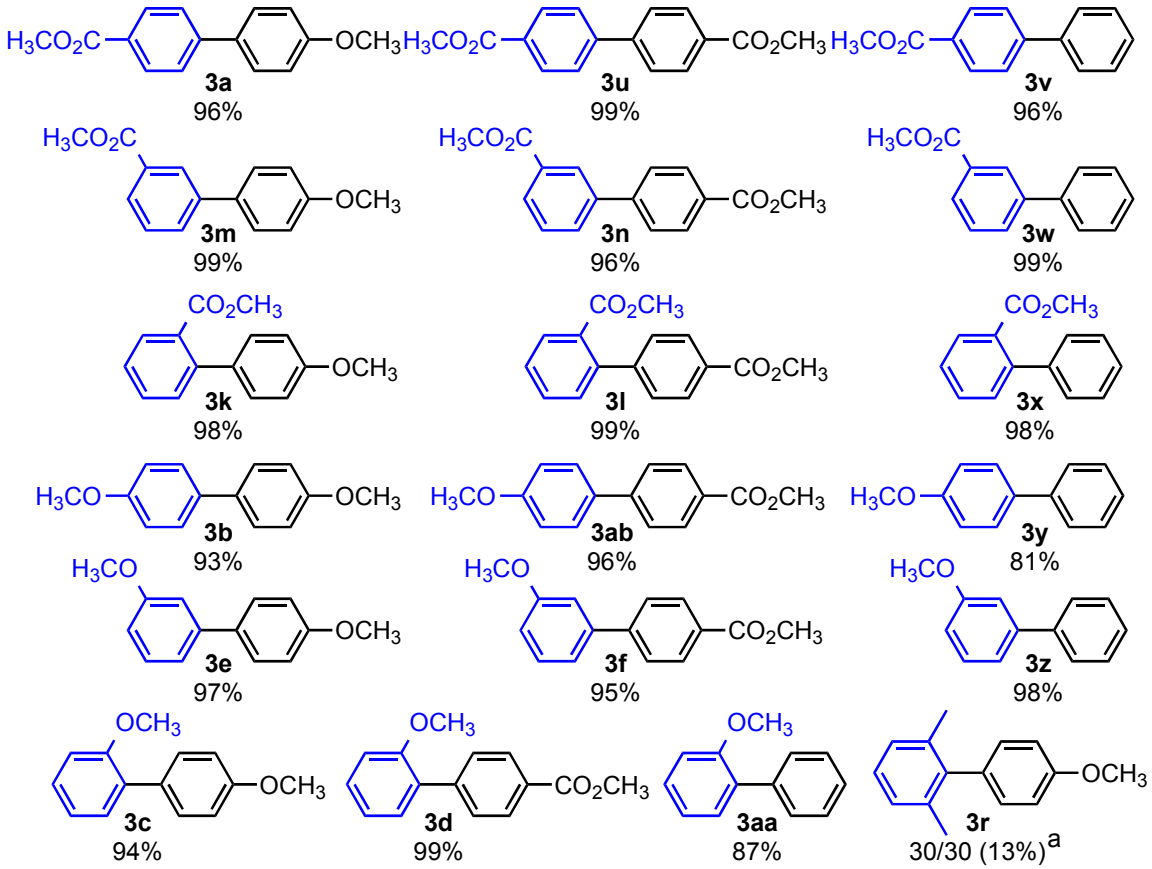


Conversion / GC yield (Isolated yield in parenthesis).[a]10% $Ni(COD)_2$ and 20% PCy_3. [b]6% $Ni(COD)_2$ and 18% PCy_3. [c]10% $Ni(COD)_2$, 20% PCy_3 in 0.5 mL THF.

Scope of the Cross-Coupling of Aryl Neopentylglycolboronates with Aryl Sulfamates. *N*, *N*-Dimethyl sulfamates can be used for directed-*ortho*-metalation to functionalize further the aryl before cross-coupling.[18] Thus, we surveyed the scope of cross-coupling of aryl neopentylglycolboronates with aryl *N*, *N*-dimethyl sulfamates. It was discovered that 6 mol% $Ni(COD)_2$ and 12 mol% PCy_3 developed for the cross-coupling of arylmesylates with aryl neopentylglycolboronic esters, effectively cross-couples aryl sulfamates without any modification (Table 3.3). Various substituted aryl sulfamates and aryl neopentylglycolboronic esters were cross-coupled in generally excellent isolated yields despite the electronic and steric properties of *N*, *N*-dimethyl sulfamates and aryl neopentylglycolboronic esters. Di-ortho substituted sulfamate is not successfully employed as in the case of mesylate, with only 13% isolated yield (Table 3.3, **3r**).

Table 3.3. Cross-Coupling of Aryl Sulfamates with Aryl Neopentylglycolboronates Catalyzed by $Ni(COD)_2/PCy_3/K_3PO_4$ in THF at 25 °C



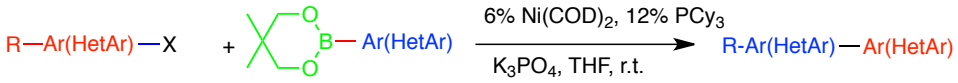


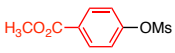
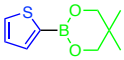
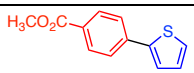
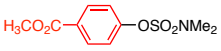
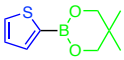
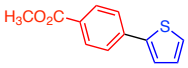
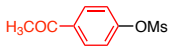
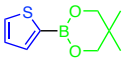
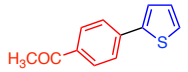
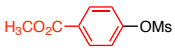
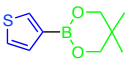
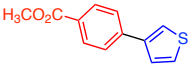
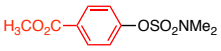
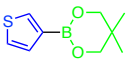
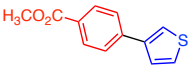
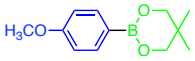
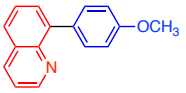
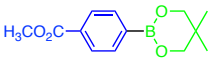
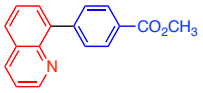
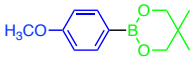
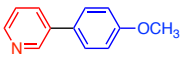
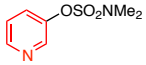
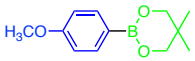
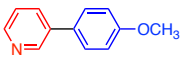
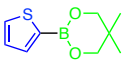
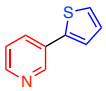
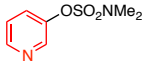
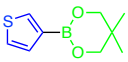
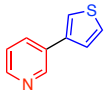
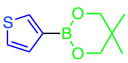
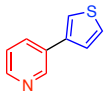
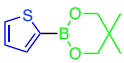
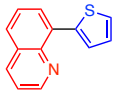
Conversion / GC yield (Isolated yield in parenthesis).[a]10% $Ni(COD)_2$ and 20% PCy_3, 60 °C, 48 h.

Scope of the Cross-Coupling of Aryl and Heteroaryl Neopentylglycolboronates with Aryl and Heteroaryl Mesylates and Sulfamates. Heteroaromatic structures are important building blocks in pharmaceuticals and organic functional materials. To date, Ni-catalyzed cross-coupling

to form heterobiaryl compounds has not been well explored. Using $Ni(COD)_2/PCy_3$ as a catalyst in THF at 25 ^{o}C with K_3PO_4, the cross-coupling of aryl mesylates and aryl sulfamates, thienyl boronate esters (Table 3.4, entries 1-5), aryl boronate esters with N-heterocyclic mesylates and sulfamates (Table 3.4, entries 6-9, 14-16), N-heterocyclic mesylates and sulfamates with thienyl boronate esters (Table 3.4, 10-13). Nearly all examples achieved quantitative conversion and excellent recovered yield. Only 2-(4-methoxyphenyl)thiophene proved difficult to recover (Table 3.4, entry 3) and the cross-coupling of 8-quinonyl methanesulfonate with thienyl boronates proved inefficient (Table 3.4, entries 13-14).

Table 3.4. Cross-Coupling of Aryl and Heteroaryl Mesylates with Aryl and Heteroaryl Neopentylglycolboronates Catalyzed by $Ni(COD)_2/PCy_3/K_3PO_4$ in THF at 25 °C

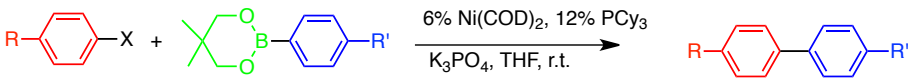


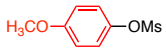
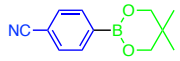
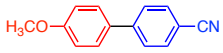
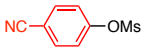
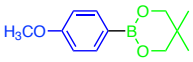
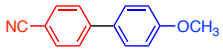
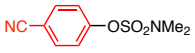
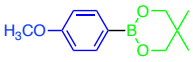
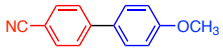
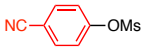
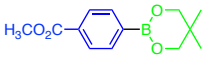
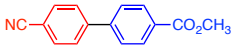
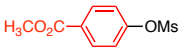
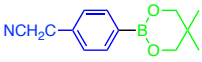
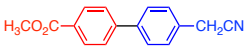
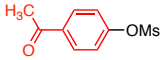
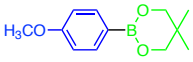
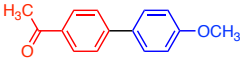
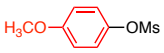
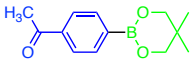
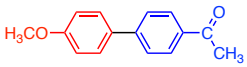
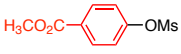
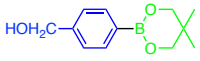
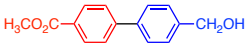
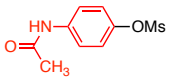
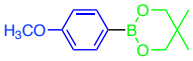
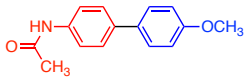
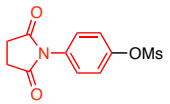
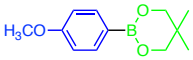
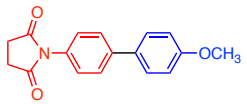
entry	electrophile		Time (h)	product	convn[a]/yield (%)
1			12		100/100(99)
2			12		100/100(95)
3			16		100/100(64)
4			12		100/100(97)
5			12		100/100(99)
6			12		100/100(99)
7			12		100/100(85)
8			12		100/100(96)
9			12		100/100(99)
10			12		100/100(99)
11			14		100/100(88)
12			14		100/100(91)
13			47		8
14			21		44
15			17		100/100(96)
16			18		99/99(99)

[a]Conversion determined by GC. [b]Yield determined by GC. Isolated yield in parenthesis.

Cross-Coupling in the Presence of Sensitive Functional Groups. While the cross-coupling of heteroaryls provides access to a structurally diverse class of heterobiaryl compounds, the cross-coupling of arenes bearing sensitive functional group can prove more challenging. Cyano, keto, hydroxyl, and amido functional group are not trivial coupling partners. In the cross-coupling of aryl mesylates and sulfamates with aryl boronate esters, it is apparent that some functional groups are less readily cross-coupled than others and there is often a preference for delivering the sensitive functional group through the electrophile or the boronate ester (Table 3.5). Benzonitrile neopentylglycolboronates (Table 3.5, entry 1) do not undergo cross-coupling, though benzyl nitrile boronate esters do so readily (Table 3.5, entry 5). Cross-coupling of cyano mesylates is more tractable. 4-Cyanophenyl methanesulfonate is cross-coupled with an electron-rich aryl boronate ester in good yield (Table 3.5, entry 2) and sluggishly in fair yield with an electron-deficient aryl boronate ester (Table 3.5, entry 4). Cross-coupling of cyano aryl sulfamates appear slower and less effective than for mesylates (Table 3.5, entry 3). The *para*-keto functional group is highly compatible if found on the mesylate electrophile (Table 3.5, entry 6), but not tolerated at all on the aryl boronate ester (Table 3.5, entry 7). Likewise, free hydroxyl group (Table 3.5, entry 8) result in very low yields, while amides (Table 3.5, entry 9) and imides (Table 3.5, entry 10) can be cross-coupled in excellent yield.

Table 3.5. Cross-Coupling of in the Presence of Sensitive Functional Groups



entry	electrophile	Ar(HetAr)	time (h)	product	convn[a]/yield[b](%)
1			12		0/0
2			12		100/100(64)
3			40		27
4			60		53
5			16		100/100(77)
6			12		100/100(99)
7			36		0/0
8			40		10/10
9			12		100/100(85)
10			12		100/100(97)

[a]Conversion determined by GC. [b]Yield determined by GC. Isolated yield in parenthesis.

3.1.3 Conclusions

$Ni(COD)_2/PCy_3$ in the presence of K_3PO_4 as base provides extremely effective cross-coupling of aryl mesylates and sulfamates with aryl neopentylglycolboronate esters both containing electron-rich and electron-deficient substituents in their *para*, *ortho* and *meta* positions, in THF at room temperature. This Ni-catalyzed cross-coupling of aryl neopentylglycolboronates is effective for the synthesis of diverse heterobiaryls and biaryls containing select sensitive electrophillic functional group. In conjunction with recently developed techniques for Ni-catalyzed neopentylglycolborylation, particularly the combination of mixed-ligand catalyst with zero-valent metal accelerators, rapid and efficient all-Ni catalyzed routes to functional biaryls, polyaryls, heterobiaryls and heteropolyaryls are readily accessible.

3.1.4 Experiments

General Experimental Methods. 4-Methoxyphenol, 3-methoxyphenol, 2-methoxyphenol, *o*-cresol, *m*-cresol, *p*-cresol, 2,6-dimethylphenol, methyl 4-hydroxybenzoate, methyl 2-hydroxybenzoate, methyl 3-hydroxybenzoate, 3-hydroxypyridine, 8-hydroxyquinoline, 4-aminophenol, 4-hydroxybenzonitrile, $Ni(COD)_2$ (98+%), PCy_3, methanesulfonyl chloride, and dimethylsulfamoyl chloride were used as received from commercial sources. THF from a commercial source was distilled over sodium and benzophenone and stored under nitrogen prior to use. K_3PO_4 from a commercial source was dried at 40 °C under vacuum overnight prior to use. Methyl 4-((methylsulfonyl)-oxy)benzoate, 4-methoxyphenyl methanesulfonate, *p*-tolyl methanesulfonate, methyl 3-((methylsulfonyl)oxy)benzoate, *m*-tolyl methanesulfonate, methyl 2-((methylsulfonyl)oxy)benzoate, 2-methoxyphenyl methanesulfonate, *o*-tolyl methanesulfonate, 4-acetylphenyl methanesulfonate (**1e**), quinolin-6-yl methanesulfonate (**1h**), isoquinolin-5-yl methanesulfonate (**1i**), 4-cyanophenyl methanesulfonate (**1j**), and 4- acetamidophenyl methanesulfonate (**1k**) were synthesized according to literature procedures.[3,11,14] 4-Methoxyphenyl dimethylsulfamate and 2,6-dimethylphenyl dimethylsulfamate were prepared according to literature methods.[4] Methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2- yl)benzoate (**2aa**),

methyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)- benzoate (**2ab**), 2-(4-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (**2ba**), 2-(2-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (**2bb**), 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane (**2c**), 1-(4-(5,5- dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)ethanone, (4-(5,5-dimethyl- 1,3,2-dioxaborinan-2-yl)phenyl)methanol, 5,5-dimethyl-2-(thiophen- 2-yl)-1,3,2-dioxaborinane, 5,5-dimethyl-2-(thiophen-3-yl)-1,3,2-dioxaborinane, 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzonitrile, and 2- (4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)acetonitrile were synthesized according to the literature procedures.[9-12] ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded using TMS as internal standard. High-resolution mass spectra of new compounds were obtained on a high-resolution double focusing chemical ionization mass spectrometer. A GC coupled with an FID detector and column HP 19091J-413 (5%-phenyl)-methylpolysiloxane 30 m length, 0.32 mm internal diameter was used to follow the reaction conversions and to assess purity of final compounds complementary to the NMR technique. The crude reaction mixtures were diluted with THF and analyzed by GC as reported in previous related publications from our laboratory.[9-12]

General Procedure for the Synthesis of Aryl Mesylates. The aryl mesylates were prepared according to literature procedures.[11] To an oven dried round bottom flask equipped with a stirring bar under nitrogen atmosphere was added phenol (38 mmol) and freshly distilled dichloromethane (31 mL) followed by anhydrous pyridine (15 g, 0.19 mol). The reaction mixture was cooled to 0 ^{o}C before methanesulfonyl chloride (3.5 mL, 45.6 mmol) was added dropwise. The reaction was allowed to stir at 0 ^{o}C for 4 h and at room temperature until TLC observed the completion of the starting material. The reaction was quenched by addition of water (50 mL). The aqueous phase was extracted with dichloromethane (50 mL) and the organic layers were washed with 15 % HCl (50 mL) three times. The combined aqueous phase was washed with dichloromethane (25 mL) three times. The combined organic phase was extracted with brine (25 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography or crystallization.

3-Methoxyphenyl methanesulfonate[11] (1bb). Purified by silica gel column chromatography with dichloromethane to produce a colorless liquid. 84%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, J = 8.2, 1H), 6.94 – 6.85 (m, 2H), 6.85 (t, J = 2.3, 1H), 3.82 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9, 150.3, 130.5, 114.0, 113.3, 108.2, 37.5.

2,6-Dimethylphenyl methanesulfonate[19] (1d). Purified by silica gel column chromatography with 10% ethyl acetate in hexanes by volumn to produce a colorless liquid. 78%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (s, 1H), 3.30 (s, 1H), 2.39 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.1, 129.5, 129.5, 127.0, 39.4, 17.7.

Quinolin-8-yl methanesulfonate (1f). Purified by silica gel column chromatography with dichloromethane to produce yellow solid. 99%, mp 73-74 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (dd, J = 4.2, 1.6, 1H), 8.23 (dd, J = 8.3, 1.6, 1H), 7.81 (dd, J = 8.2, 1.0, 1H), 7.73 (dd, J = 7.6, 1.2, 1H), 7.58 (t, J = 7.9, 1H), 7.50 (dd, J = 8.3, 4.2, 1H), 3.47 (d, J = 4.7, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.1, 145.7, 141.6, 136.3, 130.0, 127.4, 126.6, 123.9, 122.3, 39.3. The ^{1}H NMR and ^{13}C NMR are comparable to the literature.[7]

Pyridin-3-yl methanesulfonate (1g). Purified by silica gel column chromatography with dichloromethane to produce a white solid, mp 58-59 ^{o}C (lit.[20] 57-58 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 2H), 7.72 – 7.63 (m, 1H), 7.39 (dd, J = 8.3, 4.6, 1H), 3.22 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.6, 146.1, 143.7, 129.9, 124.6, 37.9.

1-(4-hydroxyphenyl)pyrrolidine-2,5-dione (1la). Purified by silica gel column chromatography with dichloromethane and ethyl acetate mixture to produce a light grey solid, 45%, mp > 225 ^{o}C; 1H NMR (500 MHz, Acetone-D6) δ 7.12 – 7.04 (m, 1H), 6.92 – 6.83 (m, 1H), 2.81 (s, 2H); 13C NMR (126 MHz, Acetone-D6) δ 177.92, 158.40, 129.56, 126.24, 116.57, 29.57. HRMS (CI+) calcd for $C_{10}H_{9.}NO_3$ (M^{+}+H) 192.0582, found 192.0665.

4-(2,5-Dioxopyrrolidin-1-yl)phenyl methanesulfonate (1l). Recrystalized from ethanol, 91%, white solid, mp 196-197 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 4H), 3.16 (s, 3H), 2.91 (s, 4H).;

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 148.8, 131.0, 128.2, 122.9, 37.6, 28.5; HRMS (CI+) calcd for $C_{11}H_{12}NO_5S$ (M^++Na) 270.0436, found 270.0442.

General Procedure for the Synthesis of Aryl Sulfamates. The aryl sulfamates were prepared according to literature procedures.[4] To an oven dried round bottom flask equipped with a stirring bar under nitrogen atmosphere was added NaH (15.6 mmol, 0.37 g) and the flask was cooled to 0 ^oC. A solution of the corresponding phenol (13 mmol) in dried DME (16 mL) was added dropwise at 0 ^oC into the flask. The reaction mixture was allowed to stir at room temperature for 10 min then cooled to 0 ^oC. The dimethyl sulfamoyl chloride (15.6 mmol, 2.24 g) in DME (4 mL) was added dropwise and the reaction was allowed to stir at room temperature for 12 h. The reaction was quenched by addition of water (5 mL, dropwise) followed by the evaporation of the solvent. The solid was dissolved in Et_2O (25 mL) and the ether solution was washed with 1 M KOH (25 mL) and water (25 mL). The combined aqueous layers were extracted with Et_2O (25 mL), washed with brine (25 mL), and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by column chromatography.

Methyl 2-((*N*, *N*-dimethylsulfamoyl)oxy)benzoate (4aa). Purified by silica gel column chromatography with dichloromethane to ethyl acetate in dichloromethane 1: 9 mixture. 80%, white solid, mp 68-69 ^oC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (dd, J = 7.8, 1.7, 1H), 7.58 – 7.52 (m, 1H), 7.49 (dd, J = 8.2, 1.1, 1H), 7.36 – 7.30 (m, 1H), 3.91 (s, 3H), 3.04 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 148.9, 133.5, 131.9, 126.5, 124.7, 123.3, 52.4, 38.9; HRMS (CI+) calcd for $C_{10}H_{13}NNaO_5S$ (M^++Na) 282.0412, found 282.0404.

Methyl 3-((*N*, *N*-dimethylsulfamoyl)oxy)benzoate (4ab). Purified by silica gel column chromatography with dichloromethane to ethyl acetate in dichloromethane 1: 9 mixture. 75%, white solid, mp 71-74 ^oC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 7.4, 1H), 7.95 – 7.82 (m, 1H), 7.60 – 7.42 (m, 2H), 3.93 (s, 3H), 3.01 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 149.4, 131.2, 129.0, 127.0, 125.5, 122.0, 51.6, 37.9; HRMS (CI+) calcd for $C_{10}H_{13}NNaO_5S$ (M^++Na) 282.0412, found 282.0411.

Methyl 4-((*N*, *N*-dimethylsulfamoyl)oxy)benzoate (4ac). Purified by silica gel column chromatography with dichloromethane to ethyl acetate in dichloromethane 1: 9 mixture. 84%, white solid, mp 67-68 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 8.2, 2H), 7.36 (d, J = 8.2, 2H), 3.93 (s, 3H), 3.01 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 152.9, 130.6, 127.6, 120.6, 51.4, 37.9. HRMS (CI+) calcd for $C_{10}H_{14}NO_5S$ (M^++H) 260.0593, found 260.0600.

2-Methoxyphenyl dimethylsulfamate (4ba). Purified by silica gel column chromatography with hexanes and ethyl ether mixture from 4:1 to 3:2. 80%, white solid, mp 40-42 ^{o}C (lit.[21] 38-42 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, J = 8.0, 1.0, 1H), 7.22 (td, J = 8.3, 1.6, 1H), 7.00 – 6.92 (m, 2H), 3.89 (s, 3H), 2.967 (s, 3H), 2.966 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.7, 139.5, 127.7, 123.9, 121.0, 113.0, 56.1, 38.8.

3-Methoxyphenyl dimethylsulfamate (4bb). Purified by silica gel column chromatography with hexanes and ethyl ether mixture from 4:1 to 3:2. 80%, colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 8.5, 1H), 6.90 – 6.86 (m, 1H), 6.83 (dd, J = 7.9, 5.4, 2H), 3.81 (s, 3H), 2.97 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 150.2, 129.2, 112.8, 111.7, 106.8, 54.7, 37.9; HRMS (CI+) calcd for $C_9H_{14}NO_4S$ (M^++H) 232.0644, found 232.0650.

Pyridin-3-yl dimethylsulfamate (4c). Purified by silica gel column chromatography with dichloromethane and ethyl acetate 4:1 mixture. 67%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, J = 2.6, 1H), 8.54 (d, J = 4.7, 1H), 7.67 (ddd, J = 8.4, 2.7, 1.4, 1H), 7.35 (dd, J = 8.4, 4.7, 1H), 3.02 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.0, 146.3, 142.8, 128.5, 123.4, 37.9. HRMS (CI+) calcd for $C_7H_{11}N_2O_3S$ (M^++H) 203.0490, found 203.0490.

4-Cyanophenyl dimethylsulfamate (4d). Purified by silica gel column chromatography with gradient dichloromethane to dichloromethane : ethyl acetate = 4:1. 89%, white solid, mp 69-70 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.8, 2H), 7.40 (d, J = 8.8, 2H), 3.02 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 133.2, 121.6, 117.1, 109.7, 37.9. HRMS (CI+) calcd for $C_9H_{10}N_2O_3S$ (M^++H) 227.0490, found 227.0482.

Preparation of Neopentylglycolborane. A procedure elaborated in our laboratory was used.[13] To a cooled solution (0 ^{o}C) of neopentylglycol (0.625 g, 6.0 mmol, 2.0 equiv) in toluene (3 mL) was slowly added $(CH_3)_2S{\bullet}BH_3$ (0.57 mL, 6 mmol, 2.0 equiv) under nitrogen. The reaction was allow to stir at 0 ^{o}C for 30 min, then at room temperature for 90 min. The neopentylglycolborane was used directly without further purification.

General Procedure for Neopentylglycolborylation. The arylboronic esters were prepared according to literature procedures.[5,9-13] To an oven-dried 25 mL Schlenk tube were added Zn powder (0.390 g, 6.0 mmol), $NiCl_2$(dppp) (81.3 mg, 0.15 mmol), and PPh_3 (78 mg, 0.3 mmol) along with the appropriate aryl halide (if it is solid) (3.0 mmol). The aryl halide, catalyst, and PPh_3 were degassed by pumping and backfilling with nitrogen three times. Dry toluene (3 mL) was added to the reaction mixture along with the appropriate aryl halide (if it is liquid) and Et_3N (1.3 mL, 9.0 mmol). The neopentylglycolborane was added dropwise to the reaction mixture. The reaction was placed into an oil bath at 100 ^{o}C with stirring under nitrogen. After the starting material was consumed, the reaction was quenched by addition of saturated NH_4Cl solution (25 mL) and extracted with EtOAc (25 mL) for 3 times. The organic fractions were combined and dried over $MgSO_4$, followed by filtration and evaporation of the solvent. The crude product was purified by column chromatography.

General Procedure for Cross-Coupling. To an oven-dried test tube (15 x 85 mm) were added aryl mesylate or aryl sulfamate (0.3 mmol), neopentylglycol boronic ester (0.36 mmol), K_3PO_4 (191 mg, 0.9 mmol). The tube was taken into a glove box and PCy_3 (10.1 mg, 0.036 mmol) and $Ni(COD)_2$ (5.0 mg, 0.018 mmol) were added. Dried THF (1.0 mL) was then added and the tube was capped with rubber septum. The reaction was stirred at room temperature under nitrogen for 4-24 h inside the glove box (see Table 3.2 and Table 3.3). The crude mixture was filtered through a short column of silica gel (1 cm length). The solvent was evaporated and the product was purified by column chromatography with dichloromethane/hexane or dichloromethane as eluent.

Methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (3a). Purified by silica gel column chromatography with ethyl acetate and hexanes mixture (15%). White solid, mp 172-173 ^{o}C (lit.[13] 173-174 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 – 8.00 (m, 2H), 7.69 – 7.51 (m, 4H), 7.05 – 6.88 (m, 2H), 3.93 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 159.8, 145.1, 132.3, 130.0, 128.3, 128.15, 126.4, 114.3, 55.3, 52.0.

4,4'-Dimethoxy-1,1'-biphenyl (3b). Purified by silica gel column chromatography with ethyl acetate (10%) in hexanes. White solid, mp 171-172 ^{o}C (lit.[22] 172-174 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 8.8, 4H), 6.95 (d, J = 8.8, 4H), 3.84 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 133.6, 127.9, 114.3, 55.5.

2,4'-Dimethoxy-1,1'-biphenyl (3c). Purified by silica gel column chromatography with ethyl acetate (10%) in hexanes. White solid, mp 64-66 ^{o}C (lit.[23] 69.7-70.4 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 8.8, 2H), 7.34 – 7.26 (m, 2H), 7.00 (td, J = 7.4, 1.0, 1H), 6.99 – 6.88 (m, 3H), 3.83 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 156.6, 131.0, 130.8, 130.7, 130.5, 128.3, 121.0, 113.6, 111.3, 55.7, 55.4.

Methyl 2'-methoxy-[1,1'-biphenyl]-4-carboxylate (3d). Purified by silica gel column chromatography with ethyl acetate (10%) in hexanes. White solid, mp 80 ^{o}C (lit.[24] 79 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.2, 2H), 7.60 (d, J = 8.3, 2H), 7.38 – 7.27 (m, 2H), 7.02 (tt, J = 3.9, 1.9, 1H), 6.98 (d, J = 8.2, 1H), 3.91 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 156.6, 143.5, 130.8, 129.7, 129.6, 129.5, 129.4, 128.6, 121.0, 111.4, 55.6, 52.1.

3,4'-Dimethoxy-1,1'-biphenyl (3e). Purified by silica gel column chromatography with ethyl acetate (10%) in hexanes. White solid, mp 56-58 ^{o}C (lit.[25] 60-61 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 8.7, 2H), 7.32 (t, J = 7.9, 1H), 7.14 (d, J = 7.7, 1H), 7.12 – 7.06 (m, 1H), 6.96 (d, J = 8.7, 2H), 6.85 (dd, J = 8.2, 2.4, 1H), 3.85 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 159.4, 142.5, 133.8, 129.8, 128.3, 119.4, 114.3, 112.7, 112.2, 55.5, 55.4.

Methyl 3'-methoxy-[1,1'-biphenyl]-4-carboxylate (3f). Purified by silica gel column chromatography with ethyl acetate (10%) in hexanes. White solid, mp 52-54 ^{o}C (lit.[26] 55 ^{o}C); ^{1}H

NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 8.6, 2H), 7.65 (d, J = 8.6, 2H), 7.38 (t, J = 7.9, 1H), 7.21 (ddd, J = 7.7, 1.6, 0.9, 1H), 7.17 – 7.13 (m, 1H), 6.94 (dd, J = 8.2, 1.7, 1H), 3.94 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 159.2, 144.7, 140.7, 130.2, 129.2, 129.1, 128.2, 126.3, 118.9, 112.7, 112.2, 54.5, 51.3.

4'-Methoxy-2-methyl-1,1'-biphenyl[27] (3g). Purified by silica gel column chromatography with ethyl acetate (10%) in hexanes. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 8.7, 2H), 7.32 (t, J = 7.9, 1H), 7.14 (d, J = 7.7, 1H), 7.12 – 7.06 (m, 1H), 6.96 (d, J = 8.7, 2H), 6.85 (dd, J = 8.2, 2.4, 1H), 3.85 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 141.7, 135.6, 134.5, 130.4, 130.4, 130.0, 127.1, 125.9, 113.6, 55.4, 20.7.

Methyl 2'-methyl-[1,1'-biphenyl]-4-carboxylate[28] (3h). Purified by silica gel column chromatography with ethyl acetate (10%) in hexanes. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.5, 2H), 7.40 (d, J = 8.5, 2H), 7.32 – 7.19 (m, 4H), 3.94 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 146.9, 141.0, 135.3, 130.6, 129.7, 129.6, 129.4, 128.8, 128.0, 126.0, 52.3, 20.5.

4'-Methoxy-3-methyl-1,1'-biphenyl (3i). Purified by silica gel column chromatography with ethyl acetate (10%) in hexanes. White solid, mp 50 ^oC (lit.[29] 51-52 ^oC); ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 8.7, 2H), 7.34 (d, J = 12.0, 2H), 7.28 (t, J = 7.5, 1H), 7.10 (d, J = 7.4, 1H), 6.94 (d, J = 8.7, 2H), 3.81 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 140.9, 138.4, 134.0, 128.8, 128.3, 127.7, 127.5, 124.0, 114.3, 55.4, 21.7.

Methyl 3'-methyl-[1,1'-biphenyl]-4-carboxylate (3j). Purified by silica gel column chromatography with ethyl acetate (10%) in hexanes. White solid, mp 58-59 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 8.1, 2H), 7.66 (d, J = 8.1, 2H), 7.43 (d, J = 8.9, 2H), 7.36 (t, J = 7.6, 1H), 7.21 (d, J = 7.4, 1H), 3.94 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 145.0, 139.2, 137.7, 129.2, 128.0, 127.98, 127.96, 127.2, 126.2, 123.5, 51.3, 20.7; HRMS (CI+) calcd for $C_{15}H_{15}O_2$ (M^++H) 227.1072, found 227.1073.

Methyl 4'-methoxy-[1,1'-biphenyl]-2-carboxylate[30] (3k). Purified by silica gel column chromatography with ethyl acetate (10%) in hexanes. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 7.7, 1H), 7.50 (td, J = 7.6, 1.4, 1H), 7.37 (t, J = 7.9, 2H), 7.24 (d, J = 8.7, 2H), 6.93 (d, J = 8.8, 2H), 3.84 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 159.1, 142.1, 133.8, 131.3, 131.0, 130.9, 129.9, 129.6, 126.9, 113.7, 55.4, 52.1.

Dimethyl [1,1'-biphenyl]-2,4'-dicarboxylate[31] (3l). Purified by silica gel column chromatography with dichloromethane. White solid, mp 56-58 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 – 8.04 (m, 2H), 7.88 (dd, J = 7.8, 1.1, 1H), 7.55 (td, J = 7.6, 1.4, 1H), 7.45 (td, J = 7.6, 1.3, 1H), 7.37 (td, J = 8.1, 1.4, 3H), 3.94 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 167.1, 146.4, 141.8, 131.6, 130.70, 130.68, 130.3, 129.5, 129.0, 128.6, 128.0, 52.3, 52.1.

Methyl 4'-methoxy-[1,1'-biphenyl]-3-carboxylate (3m). Purified by silica gel column chromatography with ethyl acetate (10%) in hexanes. White solid, mp 68-70 ^{o}C (lit.[32] 71-73 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 1.7, 1H), 7.97 (d, J = 7.7, 1H), 7.75 (d, J = 7.7, 1H), 7.57 (d, J = 8.7, 2H), 7.49 (t, J = 7.7, 1H), 7.00 (d, J = 8.7, 2H), 3.95 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 158.7, 140.2, 131.8, 130.2, 129.8, 128.0, 127.4, 127.0, 126.9, 113.5, 54.5, 51.3.

Dimethyl [1,1'-biphenyl]-3,4'-dicarboxylate (3n). Purified by silica gel column chromatography with dichloromethane. White solid, mp 95 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (t, J = 1.7, 1H), 8.16 – 8.10 (m, 2H), 8.09 – 8.03 (m, 1H), 7.86 – 7.77 (m, 1H), 7.71 – 7.65 (m, 2H), 7.54 (t, J = 7.8, 1H), 3.96 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.01, 166.98, 144.6, 140.4, 131.8, 131.0, 130.4, 129.5, 129.3, 129.2, 128.5, 127.3, 52.4, 52.3; HRMS (CI+) calcd for $C_{16}H_{15}O_4$ (M^++H) 271.0970, found 271.0974.

2,2'-Dimethoxy-1,1'-biphenyl (3o). Purified by silica gel column chromatography with ethyl acetate (10%) in hexanes. White solid, mp 152-154 ^{o}C (lit.[33] 154-155 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (td, J = 8.2, 1.7, 2H), 7.31 (dd, J = 7.4, 1.6, 2H), 7.06 (t, J = 7.4, 2H), 7.03 (d, J =

8.3, 2H), 3.82 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.2, 131.6, 128.7, 128.0, 120.5, 111.2, 55.8.

Methyl 2'-methoxy-[1,1'-biphenyl]-2-carboxylate[34] (3p). Purified by silica gel column chromatography with ethyl acetate (10%) in hexanes. Colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.8, 1.3, 1H), 7.54 (td, J = 7.6, 1.4, 1H), 7.39 (td, J = 7.6, 1.3, 1H), 7.33 (tdd, J = 6.0, 4.3, 1.7, 2H), 7.27 – 7.22 (m, 1H), 7.03 (td, J = 7.4, 1.0, 1H), 6.90 (d, J = 8.2, 1H), 3.71 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 156.2, 138.9, 131.74, 131.68, 131.5, 130.7, 130.1, 129.5, 129.0, 127.2, 120.9, 110.3, 55.4, 51.8.

2'-Methoxy-2,6-dimethyl-1,1'-biphenyl (3q). Not isolated.

4'-Methoxy-2,6-dimethyl-1,1'-biphenyl (3r). Purified by silica gel column chromatography with hexanes. White solid, mp 46-48 °C (lit.[35] 50.3-50.9 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.02 (m, 5H), 6.96 (d, J = 8.7, 2H), 3.85 (s, 3H), 2.04 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 141.7, 136.7, 133.5, 130.2, 127.4, 127.0, 114.0, 55.4, 21.0.

Dimethyl [1,1'-biphenyl]-4,4'-dicarboxylate (3u). Purified by silica gel column chromatography with dichloromethane. White solid, mp 212-214 °C (lit.[33] 215.5-216.5 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 8.2, 4H), 7.69 (d, J = 8.2, 4H), 3.95 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 144.5, 130.3, 129.9, 127.4, 52.3.

Methyl [1,1'-biphenyl]-4-carboxylate (3v). Purified by silica gel column chromatography with dichloromethane. White solid, mp 110 °C (lit.[36] 110-112 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 8.1, 2H), 7.67 (d, J = 8.2, 2H), 7.63 (d, J = 7.4, 2H), 7.47 (t, J = 7.7, 2H), 7.40 (t, J = 7.1, 1H), 3.95 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 144.8, 139.2, 129.2, 128.1, 127.3, 126.4 126.2, 51.3.

Methyl [1,1'-biphenyl]-3-carboxylate[37] (3w). Purified by silica gel column chromatography with dichloromethane. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (t, J = 1.5, 1H), 8.01 (d, J = 7.8, 1H), 7.77 (d, J = 7.8, 1H), 7.65 – 7.58 (m, 2H), 7.49 (t, J = 7.7, 1H), 7.45 (t, J = 7.6, 2H), 7.36 (t, J

= 7.4, 1H), 3.93 (s, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 141.6, 140.2, 131.6, 130.8, 129.01, 128.97, 128.5, 128.4, 127.9, 127.3, 52.3.

Methyl [1,1'-biphenyl]-2-carboxylate[38] (3x). Purified by silica gel column chromatography with dichloromethane. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 7.8, 1H), 7.52 (td, J = 7.6, 1.4, 1H), 7.43 – 7.33 (m, 5H), 7.33 – 7.28 (m, 2H), 3.63 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 142.6 141.5, 131.4, 131.0, 130.8, 129.9, 128.5, 128.2 127.4, 127.3, 52.1.

4-Methoxy-1,1'-biphenyl (3y). Purified by silica gel column chromatography with dichloromethane. White solid, mp 85 ^{o}C (lit.[3] 85-87 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.50 (m, 4H), 7.41 (t, J = 7.7, 2H), 7.30 (t, J = 7.4, 1H), 7.01 – 6.95 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 141.0, 133.9, 128.9, 128.3, 126.9, 126.8, 114.4, 55.5.

3-Methoxy-1,1'-biphenyl[39] (3z). Purified by silica gel column chromatography with dichloromethane. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, J = 5.2, 3.3, 2H), 7.41 (dd, J = 10.4, 4.9, 2H), 7.33 (td, J = 7.6, 3.5, 2H), 7.15 (dt, J = 4.1, 2.9, 2H), 6.88 (dd, J = 8.2, 2.5, 1H), 3.83 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 142.9, 141.2, 129.9, 128.9, 127.5, 127.3, 119.8, 113.0, 112.8, 100.0, 55.4.

2-Methoxy-1,1'-biphenyl[39] (3aa). Purified by silica gel column chromatography with dichloromethane. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 7.8, 2H), 7.39 (t, J = 7.6, 2H), 7.33 – 7.28 (m, J = 7.2, 3H), 7.02 (t, J = 7.4, 1H), 6.97 (d, J = 8.6, 1H), 3.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 138.7, 131.0, 130.9, 129.7, 128.7, 128.1, 127.0, 121.0, 111.4, 55.7.

Methyl 4-(thiophen-2-yl)benzoate (3ac). Purified by silica gel column chromatography with dichloromethane. Pale yellow solid, mp 138-139 ^{o}C (lit.[40] 139-140 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.5, 2H), 7.66 (d, J = 8.5, 2H), 7.57 (dd, J = 2.7, 1.5, 1H), 7.45 – 7.39 (m, 2H), 3.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 140.4, 139.2, 129.4, 127.8, 125.8, 125.4, 125.3, 121.0, 51.2.

1-(4-(Thien-2-yl)phenyl)ethanone (3ad). Purified by silica gel column chromatography with 50% ethyl acetate in hexanes. Pale yellow solid, mp 121 ^{o}C (lit.[41] 124-126 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4, 2H), 7.70 (d, J = 8.4, 2H), 7.44 (dd, J = 3.6, 1.0, 1H), 7.37 (dd, J = 5.1, 1.0, 1H), 7.12 (dd, J = 5.0, 3.7, 1H), 2.62 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0, 134.9, 128.3, 127.5, 125.6, 124.8, 123.8, 25.7.

Methyl 4-(Thien-3-yl)benzoate (3ae). Purified by silica gel column chromatography with dichloromethane. Pale yellow solid, mp 160-161 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.3, 2H), 7.67 (d, J = 8.2, 2H), 7.57 (dd, J = 2.7, 1.5, 1H), 7.46 – 7.40 (m, 2H), 3.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 140.4, 139.2, 129.4, 127.8, 125.8, 125.4, 125.3, 121.0, 51.3; HRMS (CI+) calcd for $C_{12}H_{11}O_2S$ (M^++H) 219.0480, found 219.0480.

8-(4-Methoxyphenyl)quinoline (3af). Purified by silica gel column chromatography with 50% ethyl acetate in hexanes. White solid, mp 113-114 ^{o}C (lit.[42] 117-118 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (dd, J = 4.1, 1.7, 1H), 8.18 (dd, J = 8.2, 1.5, 1H), 7.78 (d, J = 8.1, 1H), 7.71 (dd, J = 7.1, 1.2, 1H), 7.66 (d, J = 8.7, 2H), 7.58 (t, J = 7.6, 1H), 7.39 (dd, J = 8.2, 4.1, 1H), 7.04 (d, J = 8.7, 2H), 3.87 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 150.3, 146.3, 140.7, 136.4, 132.1, 131.9, 130.1, 128.9, 127.2, 126.4, 121.0, 113.7, 55.5.

Methyl 4-(quinolin-8-yl)benzoate (3ag). Purified by silica gel column chromatography with 50% ethyl acetate in hexanes. White solid, mp 92-93 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (dd, J = 4.1, 1.7, 1H), 8.21 (dd, J = 8.3, 1.6, 1H), 8.17 (d, J = 8.4, 2H), 7.86 (d, J = 8.1, 1H), 7.78 (d, J = 8.4, 2H), 7.74 (dd, J = 7.1, 1.3, 1H), 7.62 (t, J = 7.6, 1H), 7.43 (dd, J = 8.2, 4.1, 1H), 3.95 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 150.6, 146.0, 144.5, 140.0, 136.5, 130.8, 130.5, 129.4, 129.1, 128.9, 128.4, 126.4, 121.4, 52.2; HRMS (CI+) calcd for $C_{17}H_{14}NO_2$ (M^++H) 264.1025, found 264.1030.

3-(4-Methoxyphenyl)pyridine (3ah). Purified by silica gel column chromatography with 30% hexanes in dichloromethane. White solid, mp 60-61 ^{o}C (lit.[43] 62-63 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.54 (d, J = 4.7, 1H), 7.83 (ddd, J = 7.9, 2.3, 1.7, 1H), 7.52 (d, J = 8.8, 2H),

7.33 (dd, J = 7.9, 4.8, 1H), 7.01 (d, J = 8.8, 2H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 147.1, 147.0, 135.4, 133.0, 129.4, 127.4, 122.6, 113.7, 54.5.

3-(Thien-2-yl)pyridine (3ai). Purified by silica gel column chromatography with 50% ethyl acetate in hexanes. Light brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.52 (s, 1H), 7.87 (d, J = 7.4, 1H), 7.36 (d, J = 4.3, 2H), 7.31 (s, 1H), 7.14 – 7.10 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 147.1, 140.6, 133.1, 130.6, 128.4, 126.2, 124.4, 123.8. The ^{1}H NMR and ^{13}C NMR are comparable to the literature.[44]

3-(Thien-3-yl)pyridine (3aj). Purified by silica gel column chromatography with 50% ethyl acetate in hexanes. White solid, mp 76-77 ^{o}C (lit.[45] 75-77 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.54 (d, J = 3.7, 1H), 7.86 (d, J = 7.9, 1H), 7.52 (d, J = 1.8, 1H), 7.45 (dd, J = 4.8, 3.1, 1H), 7.40 (d, J = 5.0, 1H), 7.32 (dd, J = 7.8, 4.8, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 147.9, 139.0, 133.6, 131.7, 127.1, 126.1, 123.8, 121.6.

8-(Thiophen-2-yl)quinoline[46] (3ak). Purified by silica gel column chromatography with gradient 50% - 60% ethyl acetate in hexanes. Pale yellow oil. ^{1}H NMR (500 MHz, CDCl3) δ 9.02 (dd, J = 4.1, 1.8, 1H), 8.19 (dd, J = 8.2, 1.7, 1H), 8.08 (dd, J = 7.3, 1.3, 1H), 7.79 (dd, J = 3.7, 1.1, 1H), 7.76 (dd, J = 8.1, 1.1, 1H), 7.57 (t, J = 7.7, 1H), 7.49 (dd, J = 5.1, 1.1, 1H), 7.45 (dd, J = 8.3, 4.1, 1H), 7.18 (dd, J = 5.1, 3.7, 1H). ^{13}C NMR (126 MHz, CDCl3) δ 148.7, 143.9, 138.9, 135.5, 132.3, 128.0, 127.2, 127.1, 126.3, 125.9, 125.8, 125.6, 120.4.

8-(Thiophen-3-yl)quinoline[46] (3al). Purified by silica gel column chromatography with 50% ethyl acetate in hexanes. Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.19 (d, J = 5.9, 1H), 7.90 (s, 1H), 7.87 (d, J = 7.1, 1H), 7.78 (d, J = 5.7, 1H), 7.67 (d, J = 5.0, 1H), 7.58 (t, J = 6.0, 1H), 7.47 – 7.39 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.0, 145.9, 139.5, 136.3, 135.1, 129.7, 129.4, 128.8, 127.3, 126.3, 124.6, 124.5, 120.9.

6-(4-Methoxyphenyl)quinoline (3am). Purified by silica gel column chromatography with 40% ethyl acetate in hexanes. White solid, mp 108-109 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (d, J = 2.7, 1H), 8.17 (dd, J = 18.0, 8.4, 2H), 7.98 – 7.91 (m, 2H), 7.66 (d, J = 8.8, 2H), 7.41 (dd, J = 8.3,

4.2, 1H), 7.07 – 7.01 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 149.2, 146.6, 138.1, 135.3, 131.9, 128.9, 128.2, 127.7, 127.7, 123.8, 120.6, 113.6, 54.5. The ^{1}H NMR and ^{13}C NMR are comparable to the literature.[47]

5-(4-Methoxyphenyl)isoquinoline (3an). Purified by silica gel column chromatography with 50% ethyl acetate in hexanes. White solid, mp 63-65 ^{o}C (lit.[48] 68-69 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.48 (d, J = 5.9, 1H), 7.95 (dd, J = 6.0, 3.3, 1H), 7.74 (d, J = 5.9, 1H), 7.64 (dd, J = 8.0, 5.2, 2H), 7.41 (d, J = 8.6, 2H), 7.05 (d, J = 8.6, 2H), 3.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 153.0, 143.4, 139.1, 134.5, 131.5, 131.1, 131.0, 129.2, 127.0, 126.9, 118.8, 114.2, 55.5.

4'-Methoxy-[1,1'-biphenyl]-4-carbonitrile (3ao). Purified by silica gel column chromatography with 50% ethyl acetate in hexanes. White solid, mp 102-103 ^{o}C (lit.[49] 102-103 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.4, 2H), 7.64 (d, J = 8.1, 2H), 7.54 (d, J = 8.8, 2H), 7.01 (d, J = 8.8, 2H), 3.87 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 144.4, 131.7, 130.5, 127.5, 126.3, 118.2, 113.7, 109.3, 54.6.

Methyl 4'-cyano-[1,1'-biphenyl]-4-carboxylate (3ap). Purified by silica gel column chromatography with 50% ethyl acetate in hexanes. White solid, mp 141-142 ^{o}C (lit.[30] 144-145 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 8.3, 1H), 7.76 (d, J = 8.2, 1H), 7.72 (d, J = 8.4, 1H), 7.66 (d, J = 8.3, 1H), 3.96 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 144.6, 143.6, 132.9, 130.5, 130.4, 128.1, 127.4, 118.8, 112.0, 52.5.

Methyl 4'-(cyanomethyl)-[1,1'-biphenyl]-4-carboxylate (3aq). Purified by silica gel column chromatography with 50% ethyl acetate in hexanes. White solid, mp 150-151 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.12 (d, J = 8.5, 2H), 7.69 – 7.61 (m, 4H), 7.44 (d, J = 8.4, 2H), 3.95 (s, 3H), 3.81 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 143.7, 139.1, 129.3, 129.0, 128.4, 127.7, 127.1, 126.1, 116.8, 51.3, 22.5. HRMS (CI+) calcd for $C_7H_{11}N_2O_3S$ (M^++Na) 274.0844, found 274.0834.

1-(4'-Methoxy-[1,1'-biphenyl]-4-yl)ethanone (3ar). Purified by silica gel column chromatography with 50% ethyl acetate in hexanes. White solid, mp 154-155 ^{o}C (lit.[50] 157^{o}C). ^{1}H NMR (500 MHz,

$CDCl_3$) δ 8.01 (d, J = 8.6, 1H), 7.65 (d, J = 8.6, 1H), 7.58 (d, J = 8.8, 1H), 7.00 (d, J = 8.8, 1H), 3.87 (s, 2H), 2.63 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.9, 159.1, 144.5, 134.5, 131.4, 128.1, 127.5, 125.8, 113.6, 54.5, 25.8.

N-(4'-methoxy-[1,1'-biphenyl]-4-yl)acetamide (3at). Purified by silica gel column chromatography with 50% ethyl acetate in hexanes. White solid, mp 203-205 ^oC (lit.[47] 207-208 ^oC). ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.40 (m, 6H), 6.96 (d, J = 8.4, 2H), 3.84 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 159.2, 137.1, 136.7, 133.2, 128.0, 127.3, 120.4, 114.4, 55.5, 24.8.

1-(4'-Methoxy-[1,1'-biphenyl]-4-yl)pyrrolidine-2,5-dione (3au). Purified by silica gel column chromatography with 50% ethyl acetate in hexanes. White solid, mp 212-213 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 8.5, 2H), 7.52 (d, J = 8.8, 2H), 7.33 (d, J = 8.5, 2H), 6.98 (d, J = 8.8, 2H), 3.85 (s, 3H), 2.92 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 159.6, 141.5, 132.9, 130.5, 128.4, 127.7, 126.8, 114.5, 55.5, 28.6. HRMS (CI+) calcd for $C_{17}H_{15}NO_3$ (M^++H) 282.1130, found 282.1122.

3.1.5 Characterization of Reaction Products

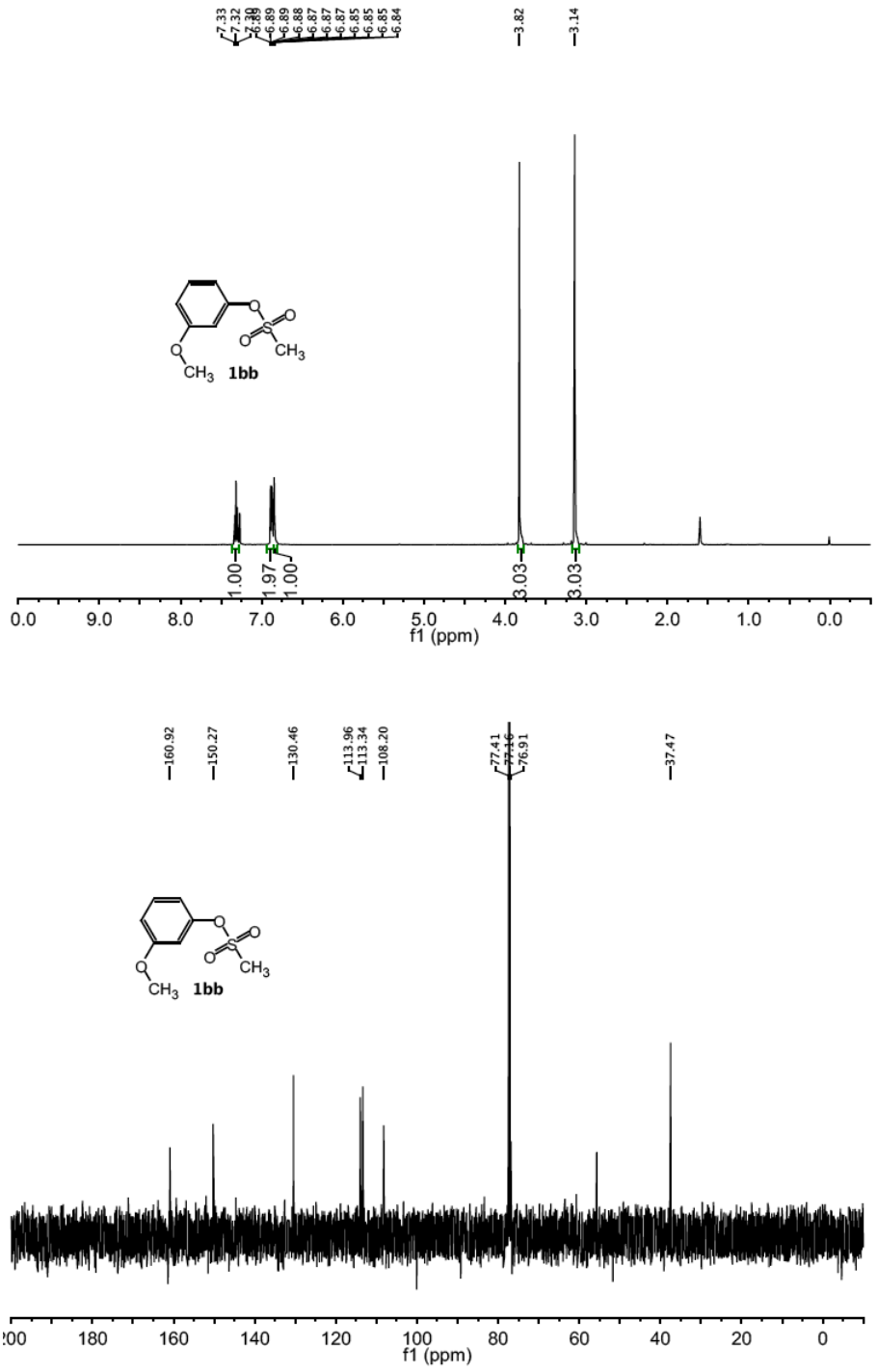


Figure SF 3.1. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 3-methoxyphenyl methanesulfonate in $CDCl_3$.

Figure SF 3.2. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 2,6-dimethylphenyl methanesulfonate in $CDCl_3$.

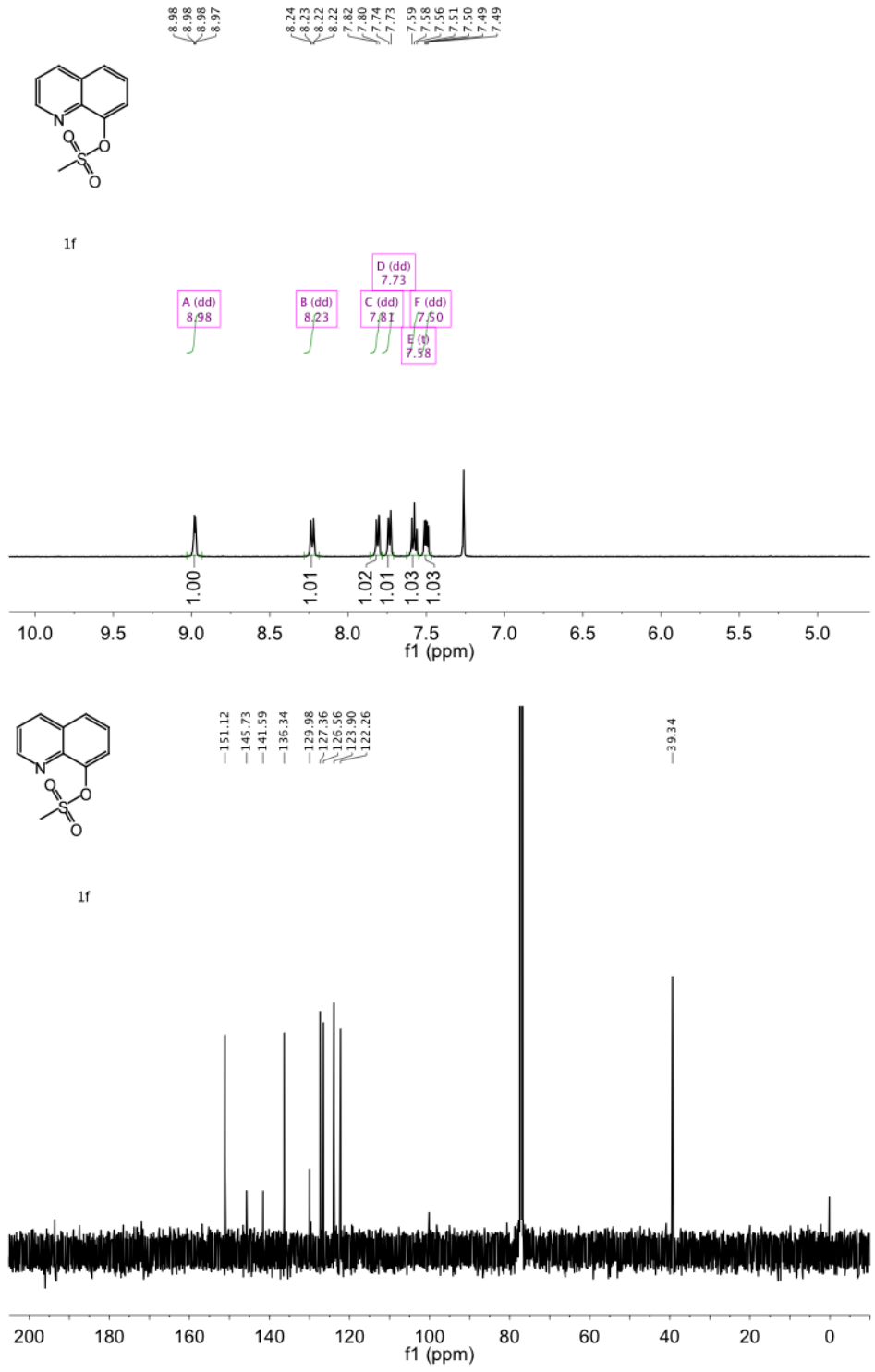


Figure SF 3.3. ^{1}H-NMR (top, 500 MHz) and 13C-NMR (bottom, 125 MHz) spectra of quinolin-8-yl methanesulfonate in $CDCl_3$.

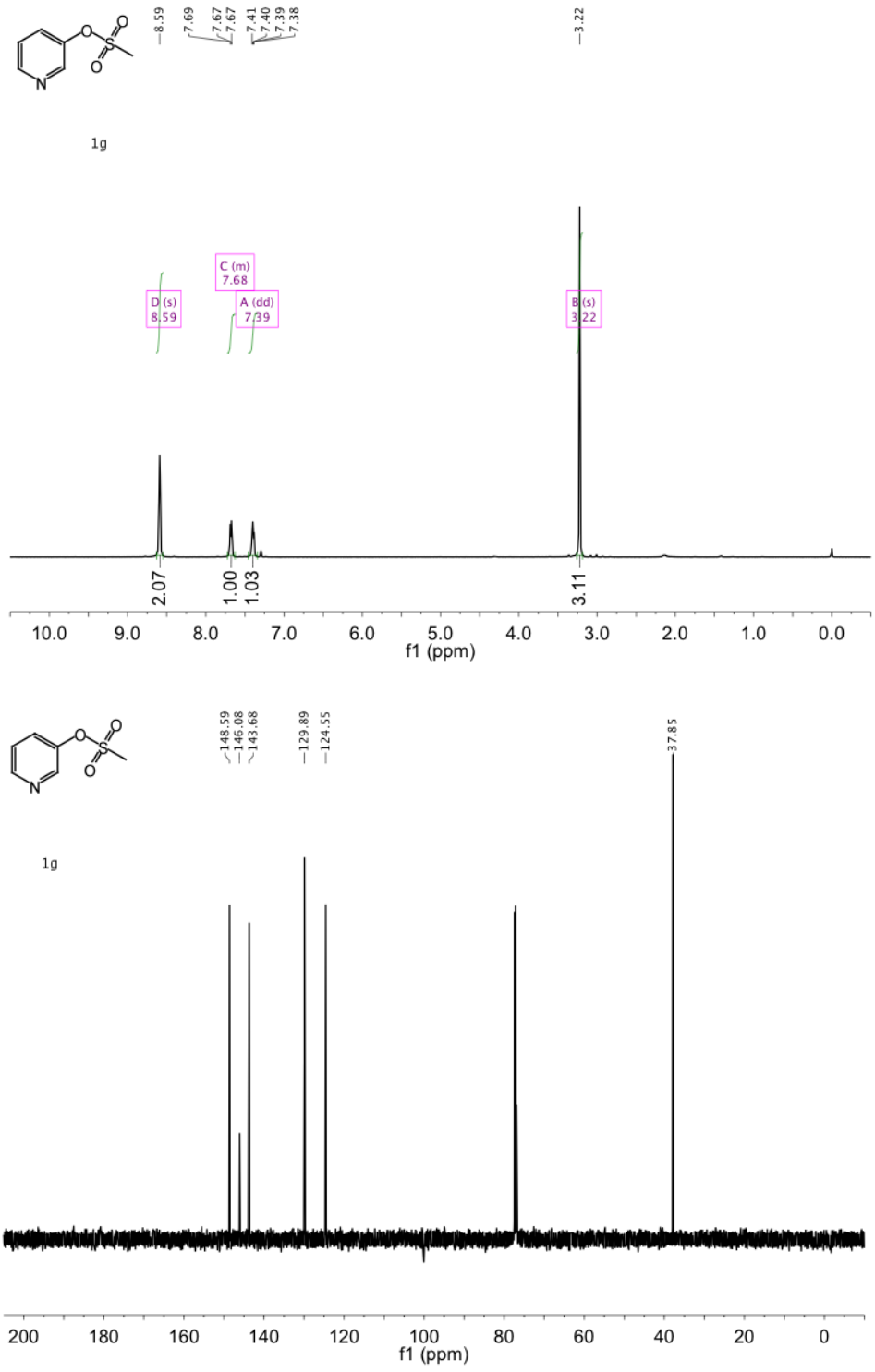


Figure SF 3.4. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of pyridin-3-yl methanesulfonate in $CDCl_3$.

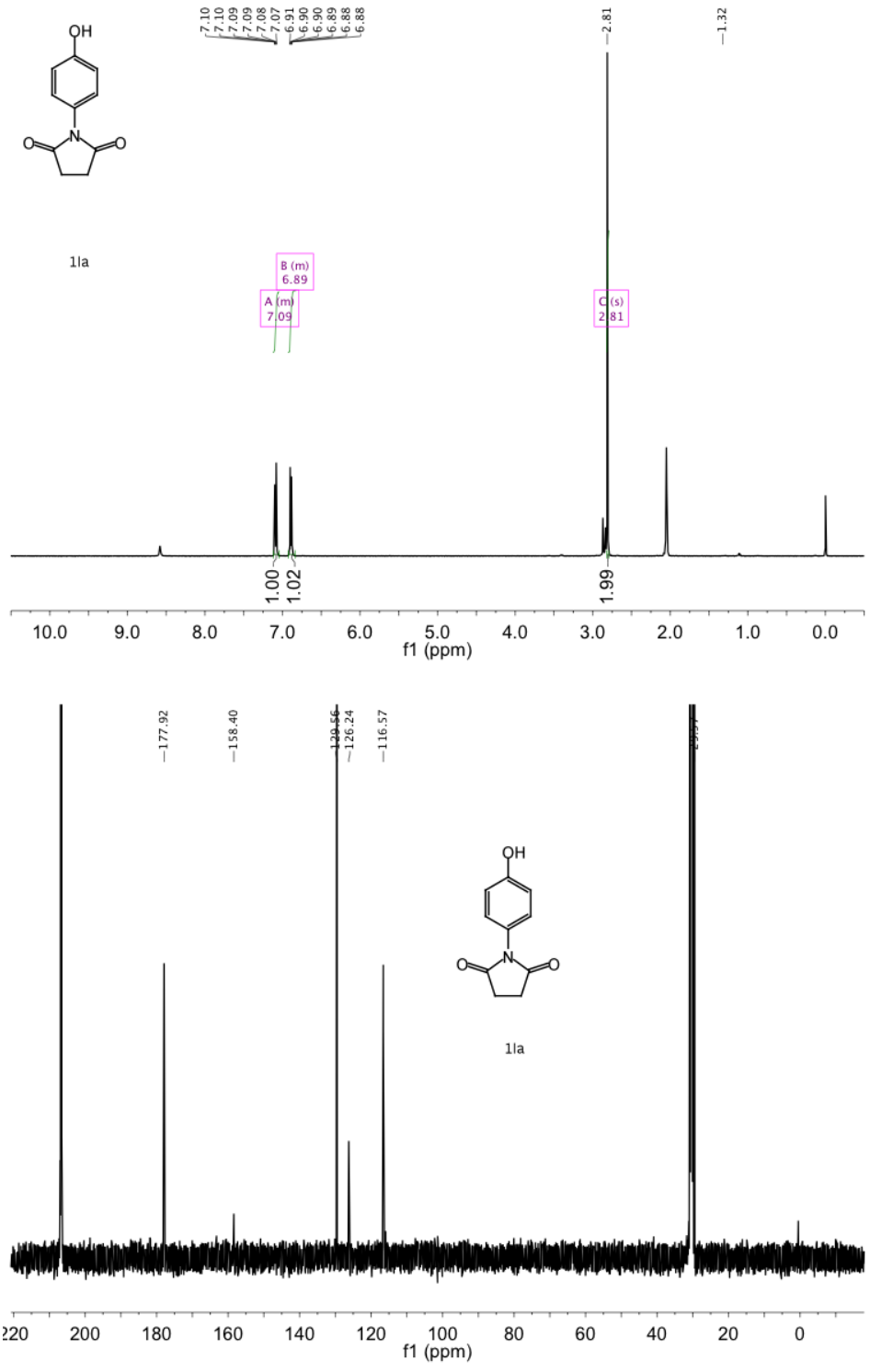


Figure SF 3.5. ^{1}H-NMR (top, 500 MHz) and 13C-NMR (bottom, 125 MHz) spectra of 2-(4-hydroxyphenyl)cyclopentane-1,3-dione in acetone-D^{6}.

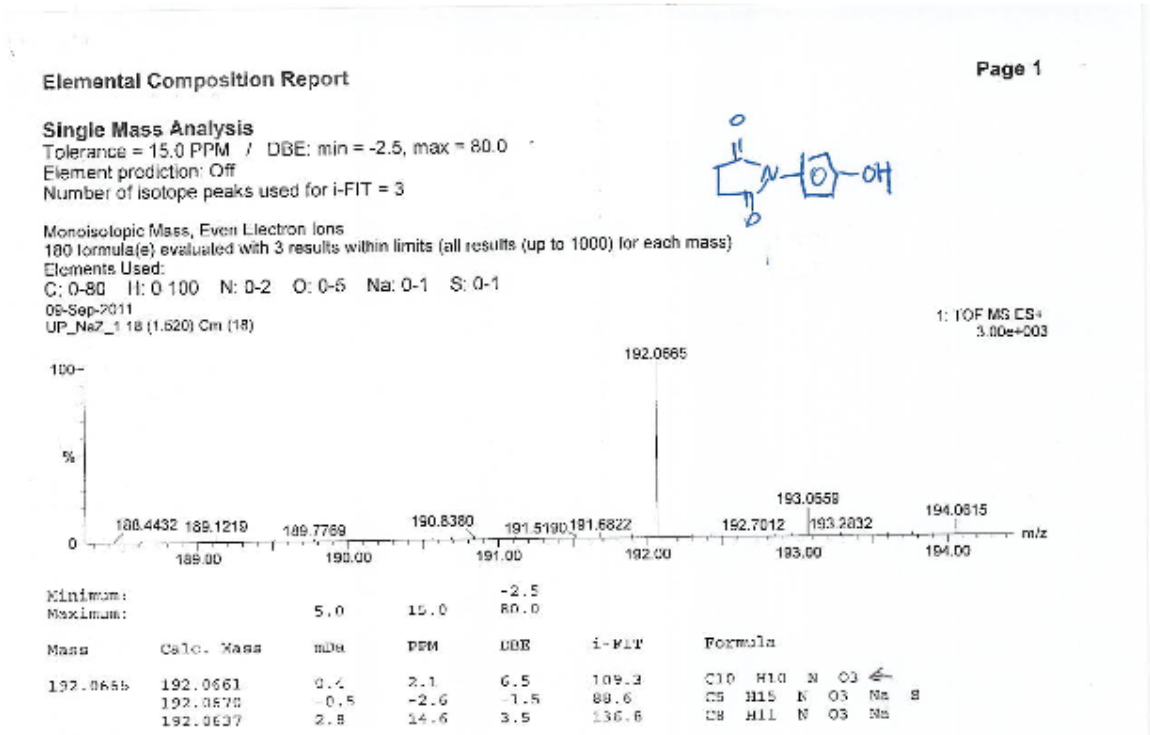


Figure SF 3.6. HRMS of 2-(4-hydroxyphenyl)cyclopentane-1,3-dione.

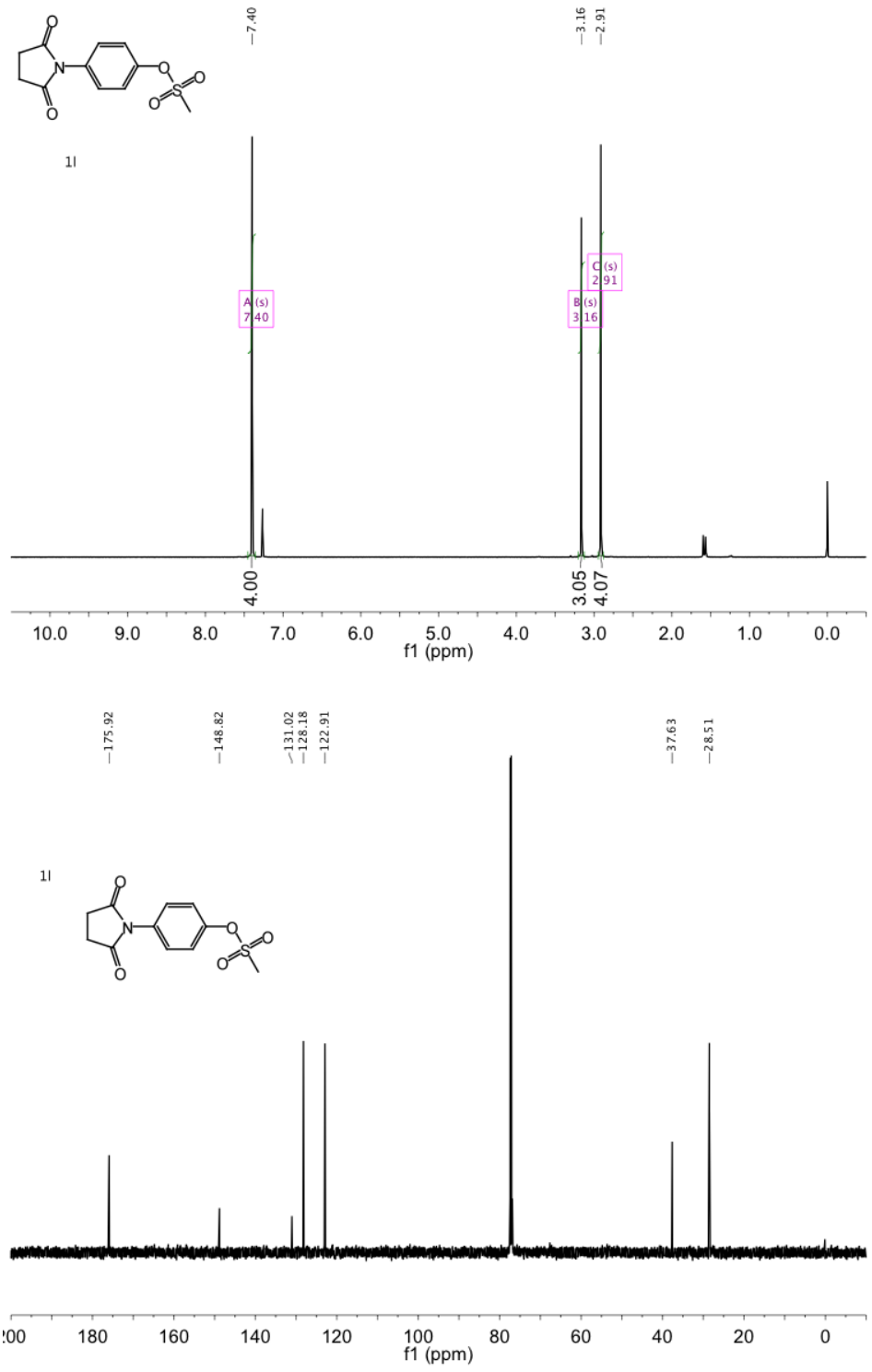


Figure SF 3.7. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 4-(2,5-dioxocyclopentyl)phenyl methanesulfonate in $CDCl_3$.

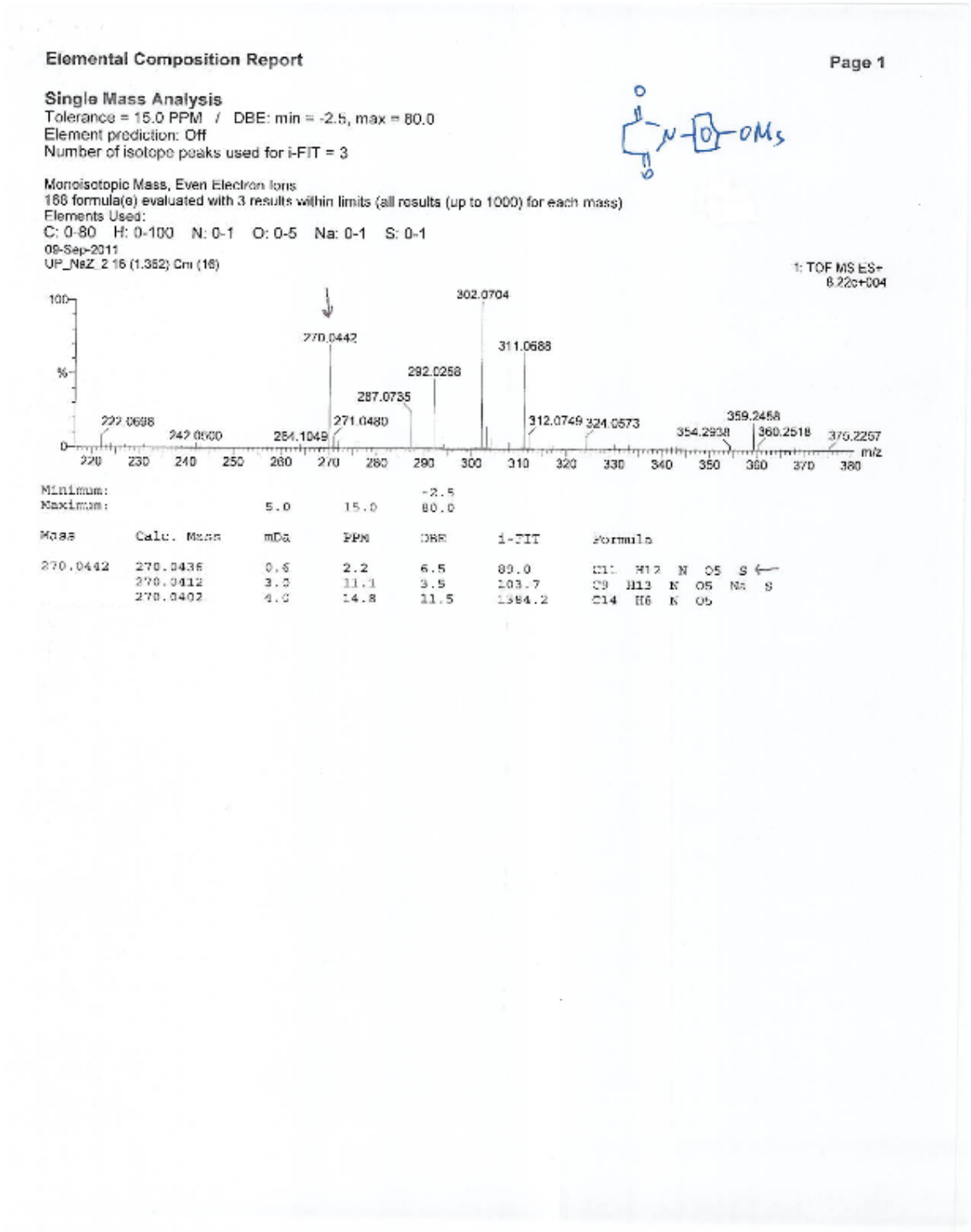


Figure SF 3.8. HRMS of 4-(2,5-dioxocyclopentyl)phenyl methanesulfonate.

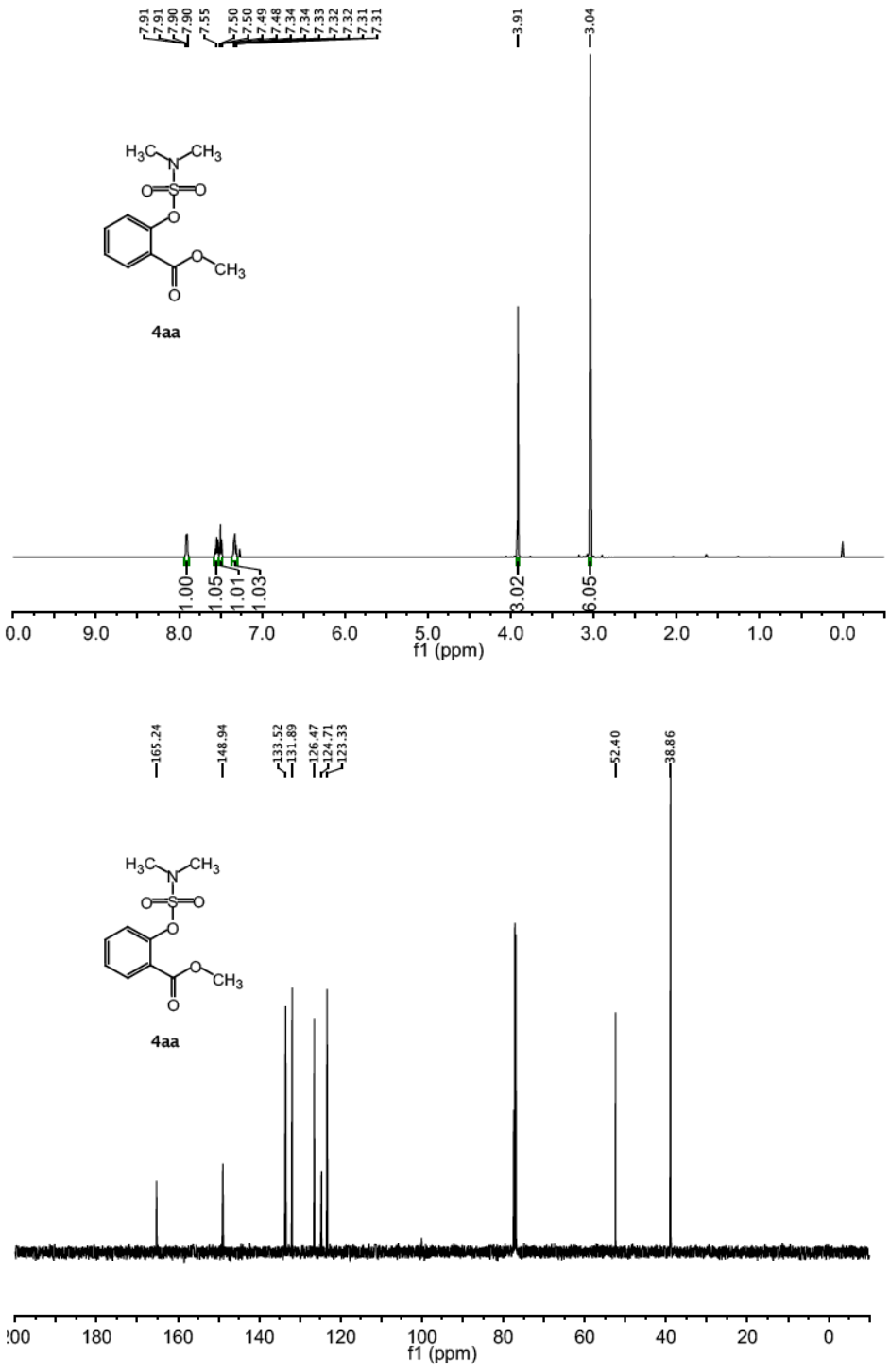


Figure SF 3.9. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 2-((*N*,*N*-dimethylsulfamoyl)oxy)benzoate in $CDCl_3$.

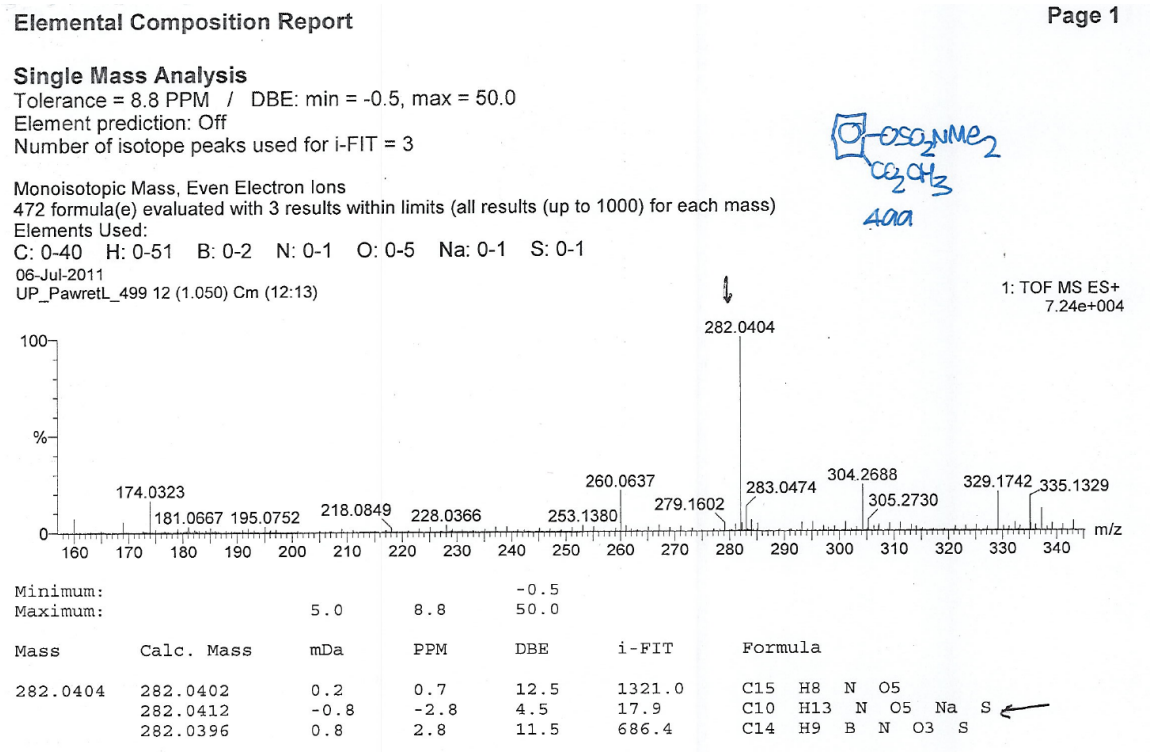


Figure SF 3.10. HRMS of methyl 2-((*N*,*N*-dimethylsulfamoyl)oxy)benzoate.

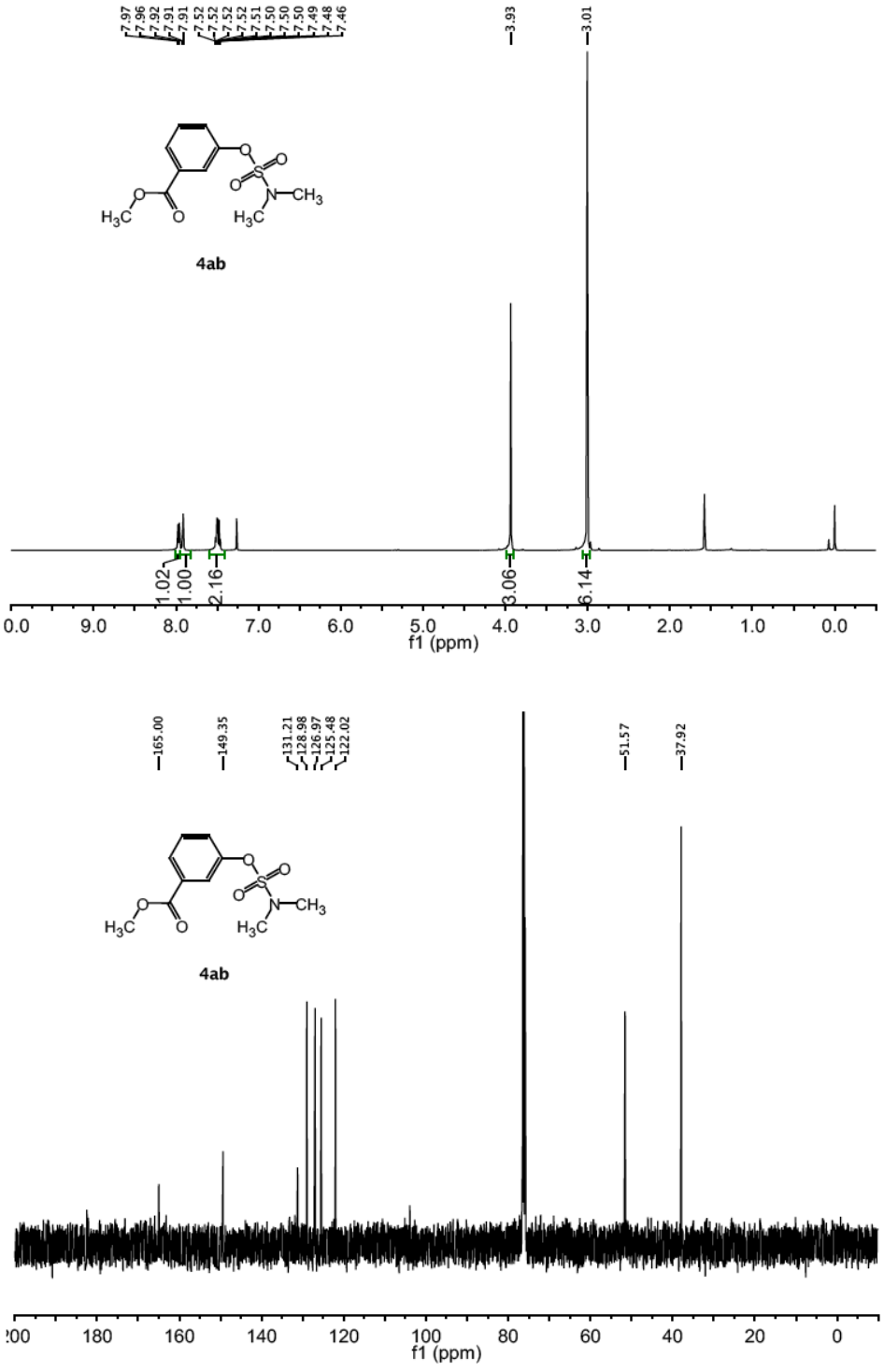


Figure SF 3.11. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 3-((*N*,*N*-dimethylsulfamoyl)oxy)benzoate in $CDCl_3$.

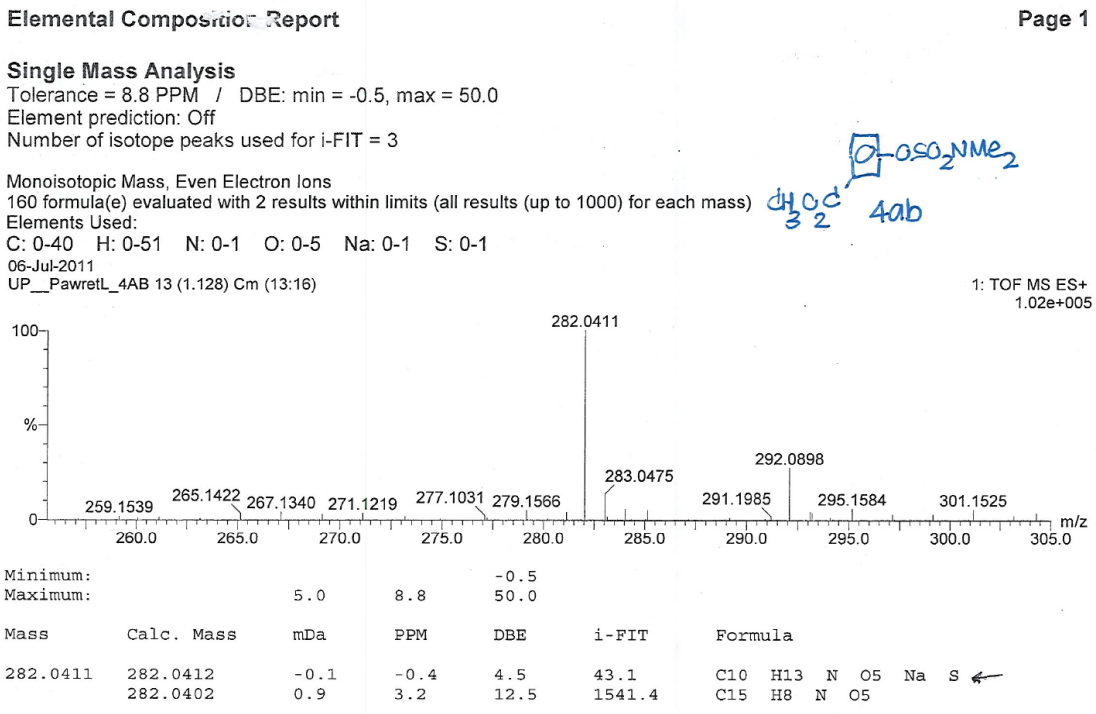


Figure SF 3.12. HRMS of methyl 3-((*N*,*N*-dimethylsulfamoyl)oxy)benzoate.

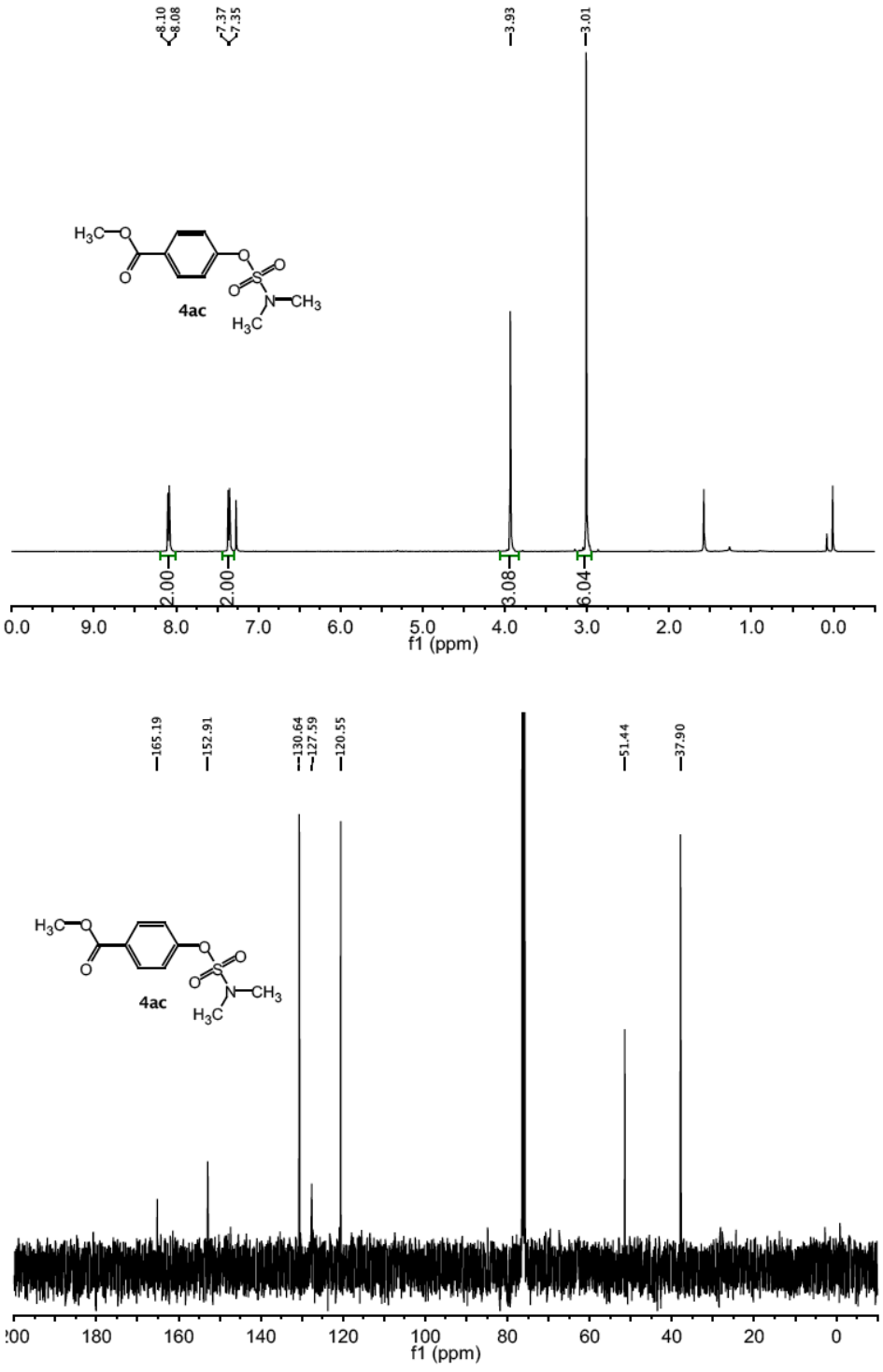


Figure SF 3.13. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 4-((*N*,*N*-dimethylsulfamoyl)oxy)benzoate in $CDCl_3$.

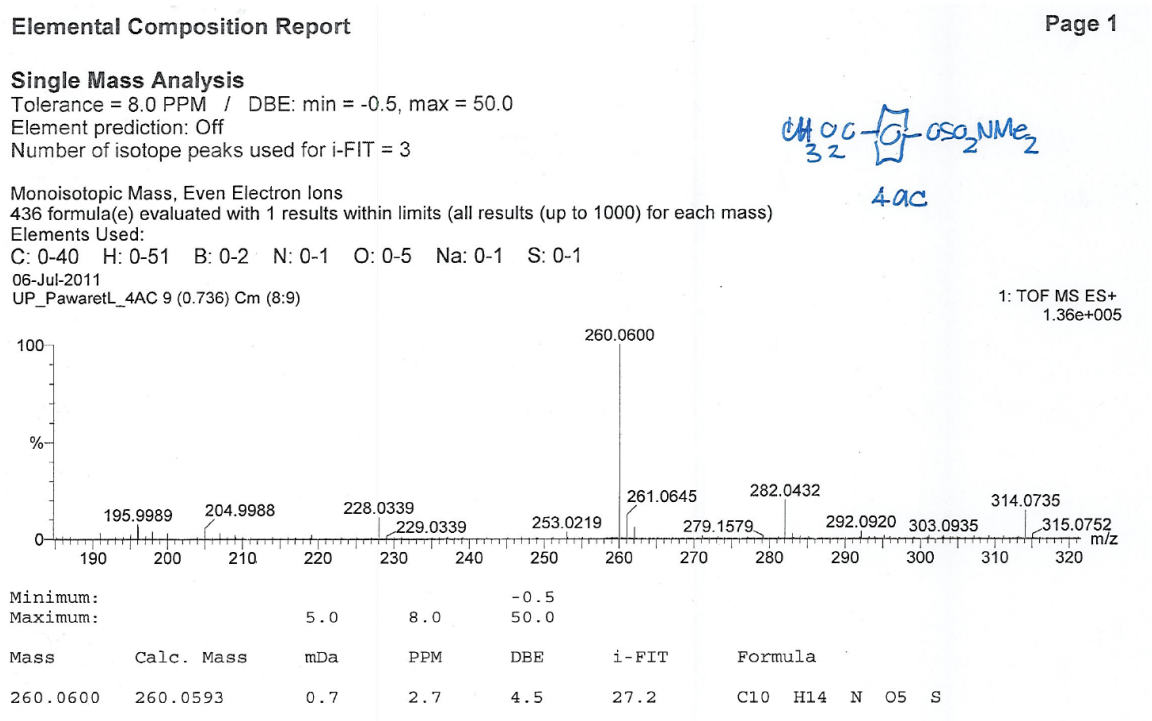


Figure SF 3.14. HRMS of methyl 4-((*N*,*N*-dimethylsulfamoyl)oxy)benzoate.

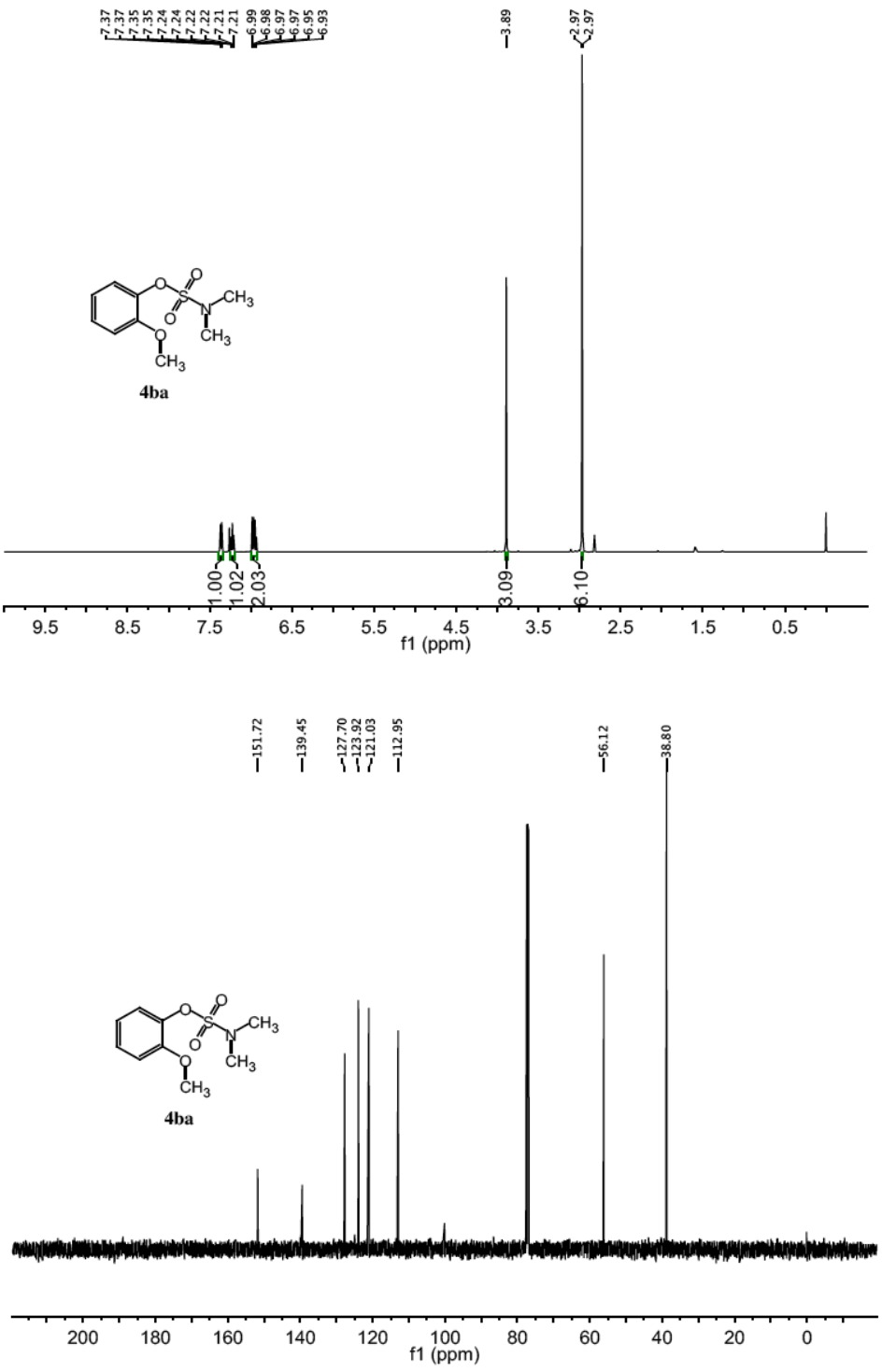


Figure SF 3.15. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 2-methoxyphenyl dimethylsulfamate in $CDCl_3$.

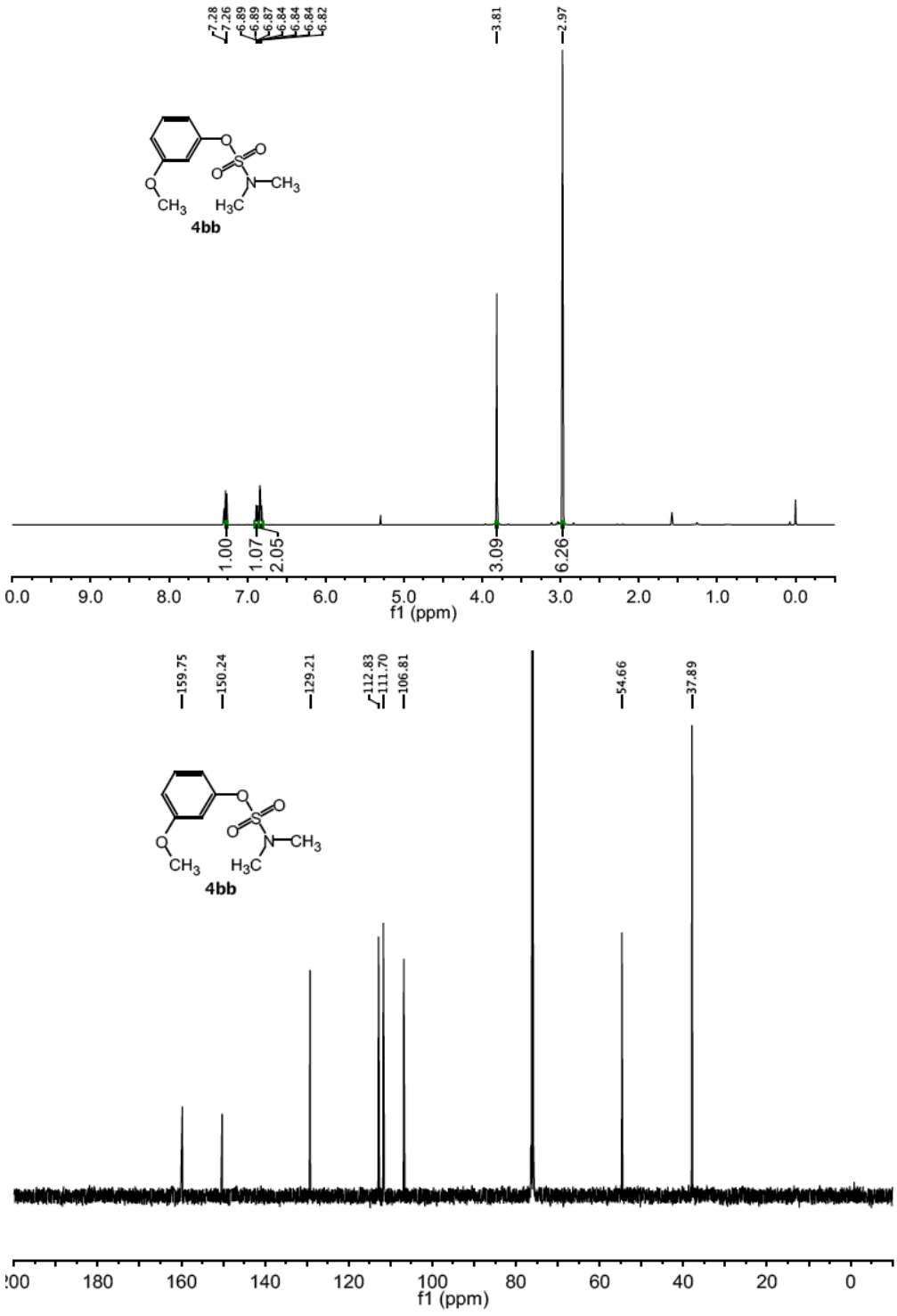


Figure SF 3.16. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 3-methoxyphenyl dimethylsulfamate in $CDCl_3$.

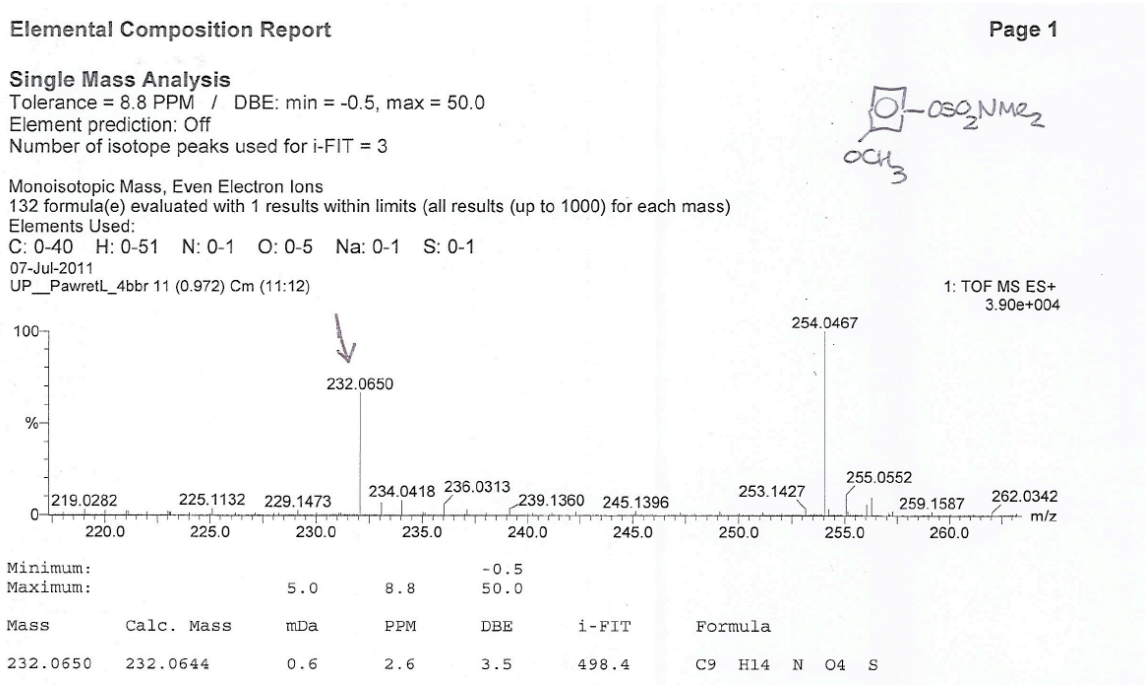


Figure SF 3.17. HRMS of 3-methoxyphenyl dimethylsulfamate in $CDCl_3$.

Figure SF 3.18. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of pyridin-3-yl dimethylsulfamate in $CDCl_3$.

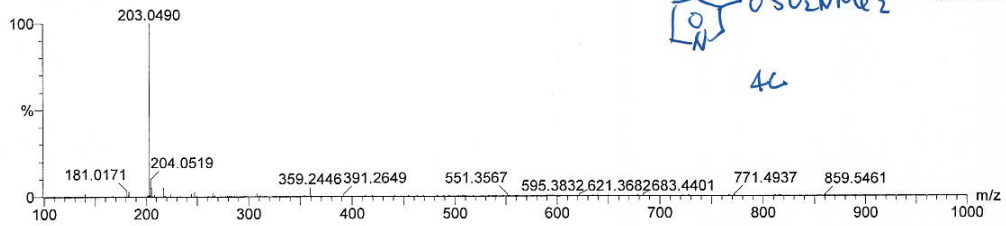
Elemental Composition Report Page 1

Single Mass Analysis
Tolerance = 15.0 PPM / DBE: min = -2.5, max = 80.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
191 formula(e) evaluated with 5 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-80 H: 0-100 N: 0-2 O: 0-5 Na: 0-1 S: 0-1

09-Sep-2011
UP_NaZ_3 21 (1.835) Cm (21:22)

1: TOF MS ES+
5.85e+005



Minimum:				-2.5		
Maximum:		5.0	15.0	80.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
203.0490	203.0490	0.0	0.0	3.5	9.3	C7 H11 N2 O3 S ←
	203.0497	-0.7	-3.4	12.5	20723.5	C15 H7 O
	203.0473	1.7	8.4	9.5	16103.1	C13 H8 O Na
	203.0507	-1.7	-8.4	4.5	1636.8	C10 H12 O Na S
	203.0466	2.4	11.8	0.5	1903.4	C5 H12 N2 O3 Na S

Figure SF 3.19. HRMS of pyridin-3-yl dimethylsulfamate.

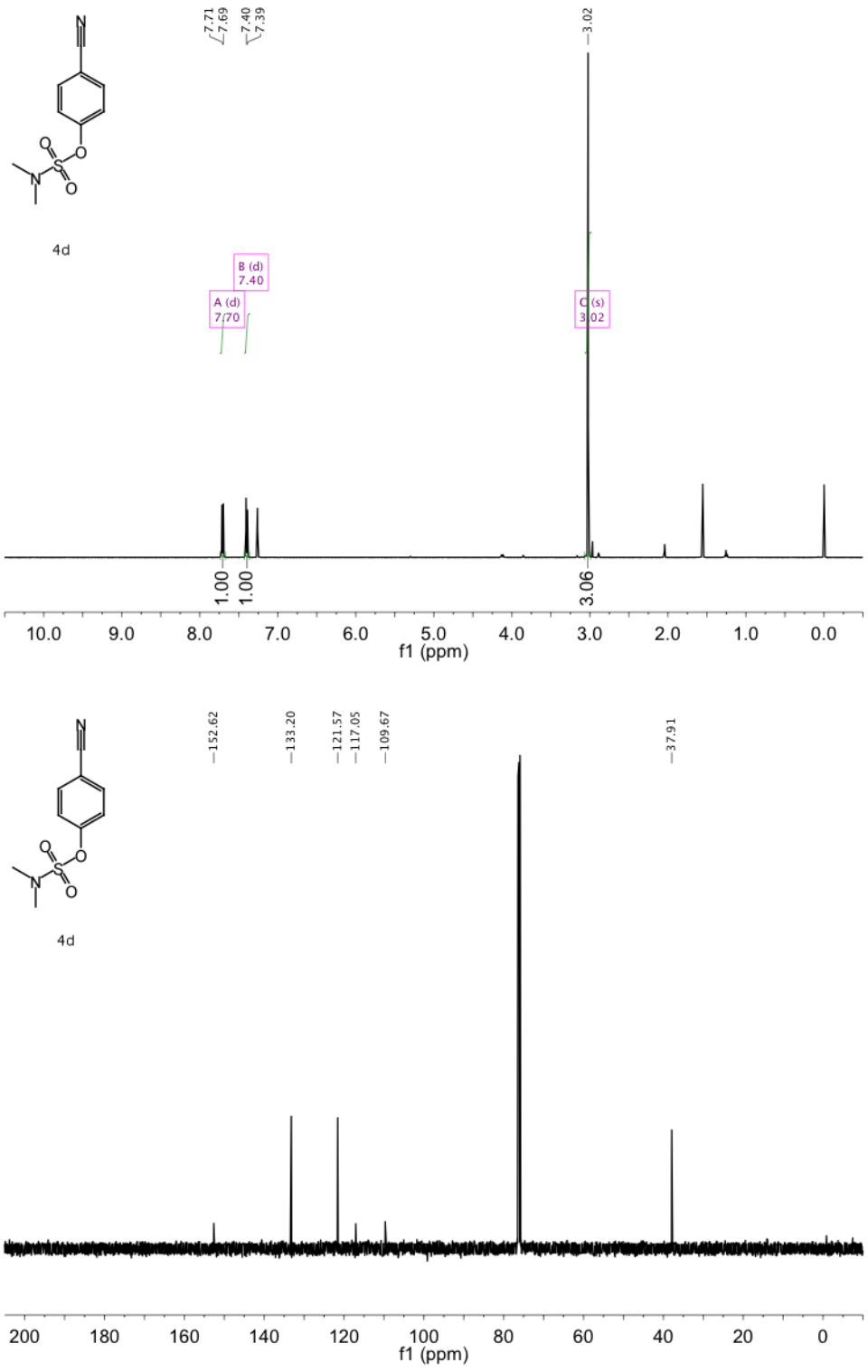
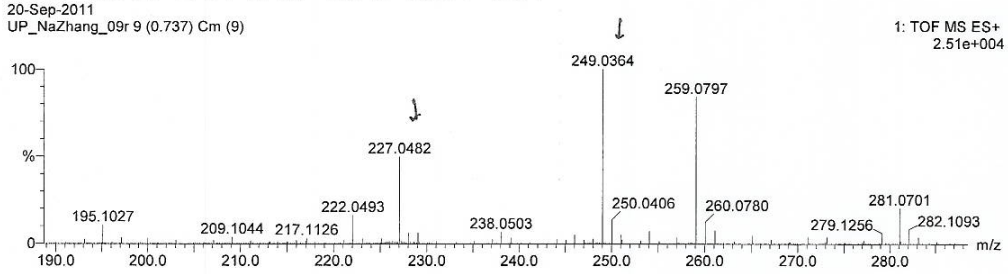


Figure SF 3.20. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 4-cyanophenyl dimethylsulfamate in $CDCl_3$.

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 8.8 PPM / DBE: min = -2.5, max = 80.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
630 formula(e) evaluated with 8 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-80 H: 0-100 B: 0-1 N: 0-2 O: 0-10 Na: 0-1 S: 0-1
20-Sep-2011
UP_NaZhang_09r 9 (0.737) Cm (9)



Minimum:				-2.5		
Maximum:		5.0	8.8	80.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
227.0482	227.0485	-0.3	-1.3	-2.5	424.8	C2 H13 B N2 O6 Na S
	227.0475	0.7	3.1	5.5	621.8	C7 H8 B N2 O6
	227.0490	-0.8	-3.5	5.5	216.3	C9 H11 N2 O3 S ←
	227.0473	0.9	4.0	11.5	679.4	C15 H8 O Na
	227.0491	-0.9	-4.0	-1.5	850.1	C3 H12 N2 O8 Na
	227.0492	-1.0	-4.4	6.5	599.4	C10 H9 B O4 Na
	227.0497	-1.5	-6.6	14.5	742.8	C17 H7 O
	227.0466	1.6	7.0	2.5	261.8	C7 H12 N2 O3 Na S

Figure SF 3.21. HRMS of 4-cyanophenyl dimethylsulfamate.

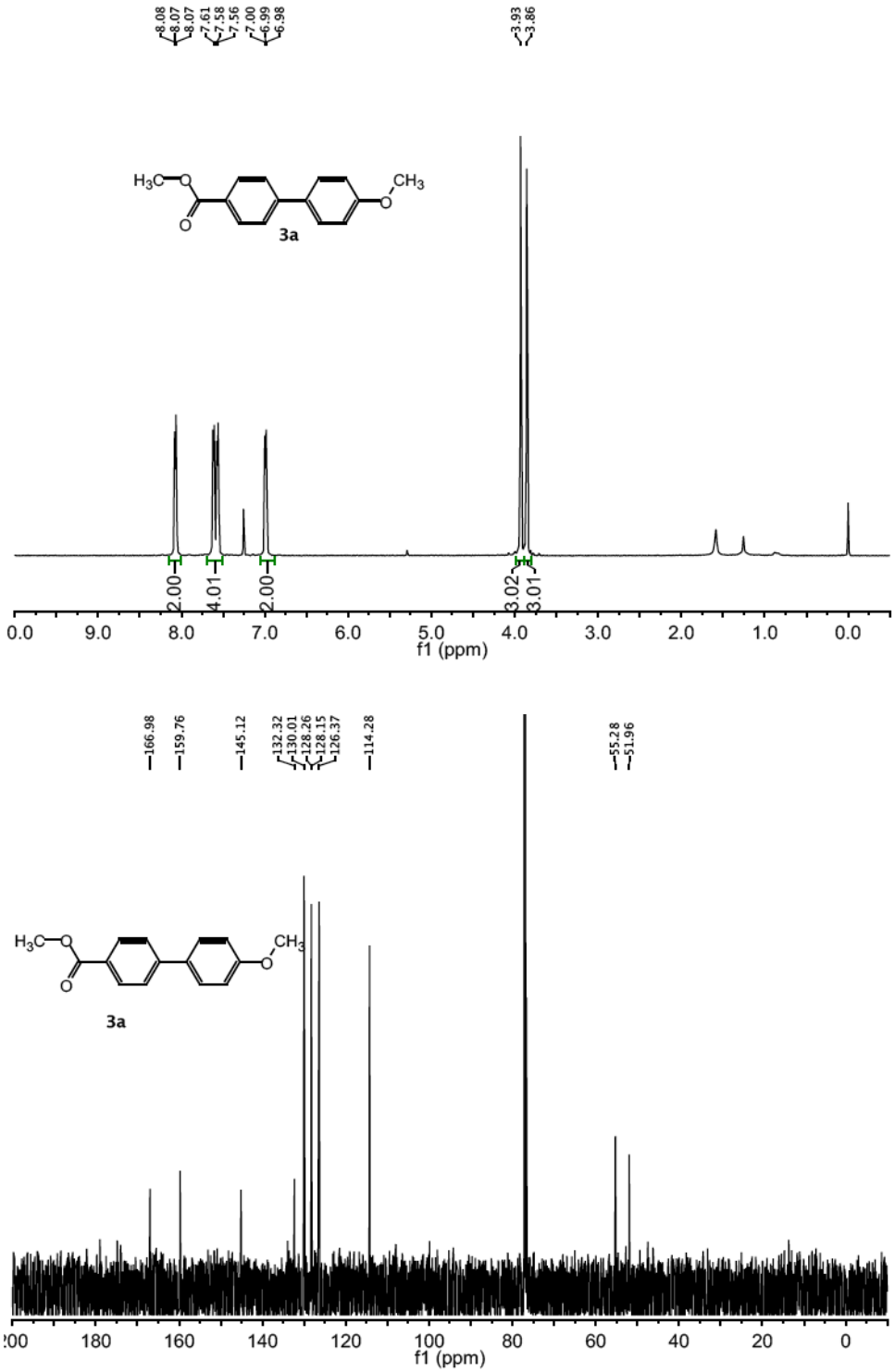


Figure SF 3.22. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate in $CDCl_3$.

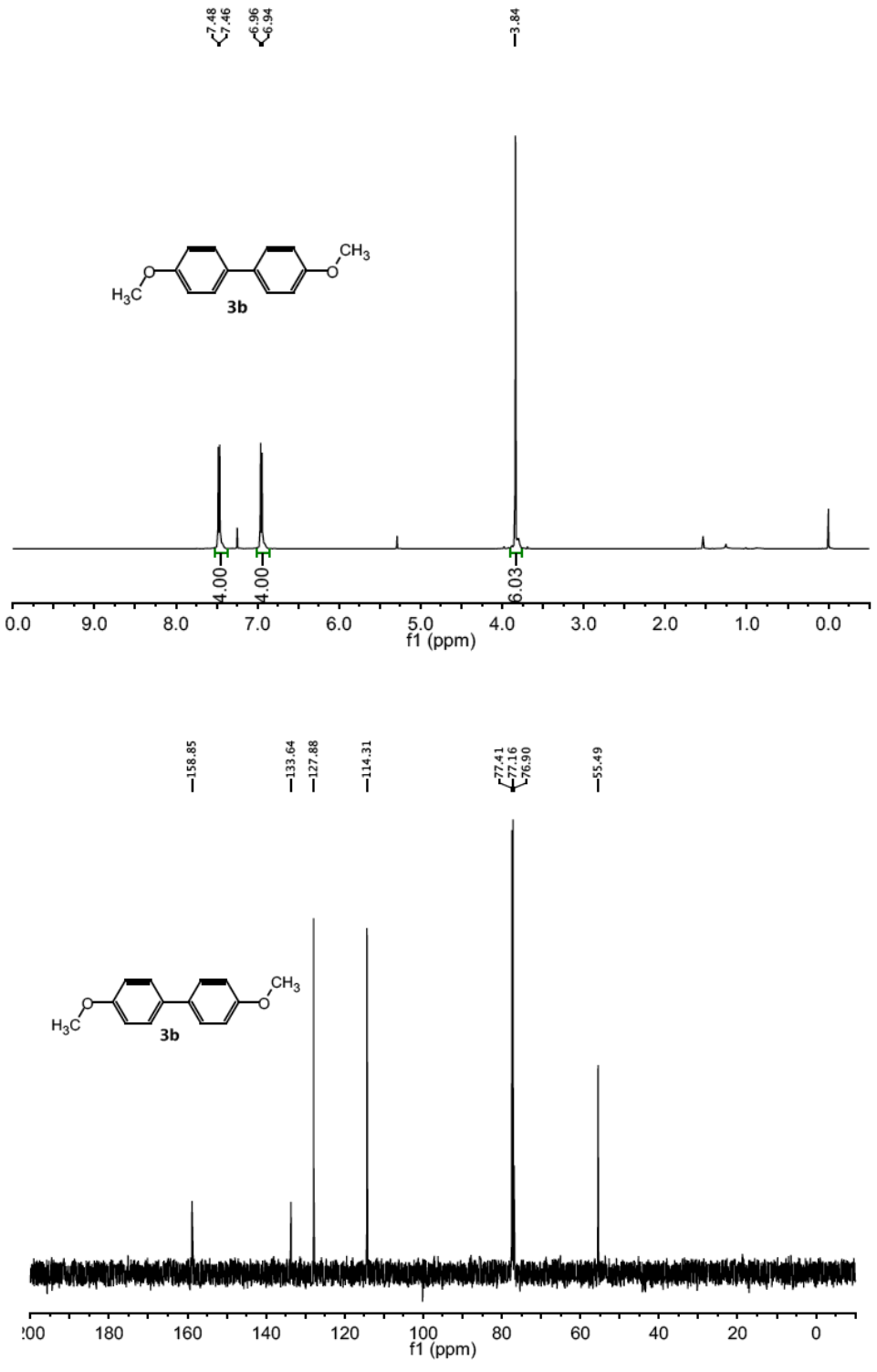


Figure SF 3.23. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 4,4'-dimethoxy-1,1'-biphenyl in $CDCl_3$.

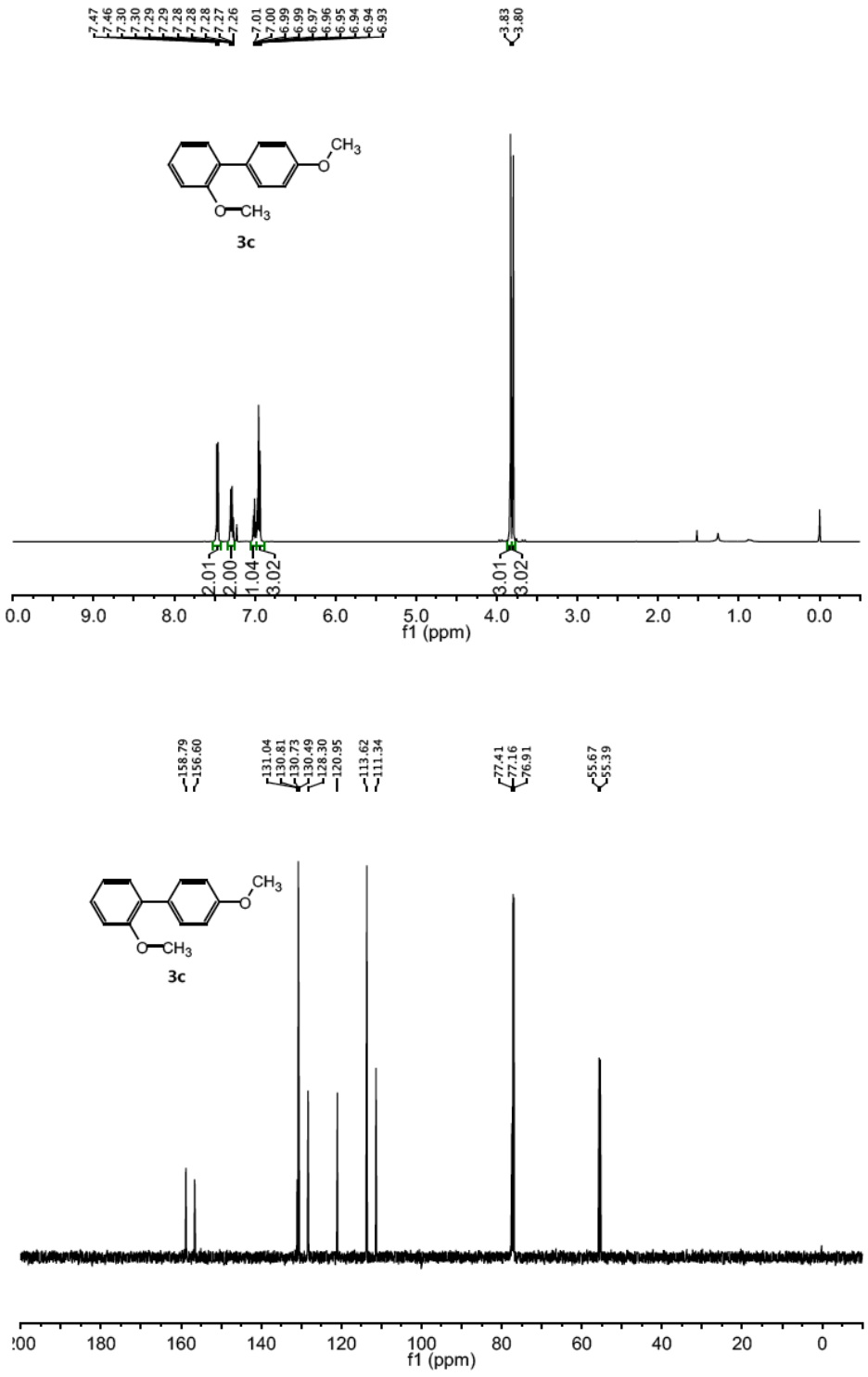


Figure SF 3.24. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 2,4'-dimethoxy-1,1'-biphenyl in $CDCl_3$.

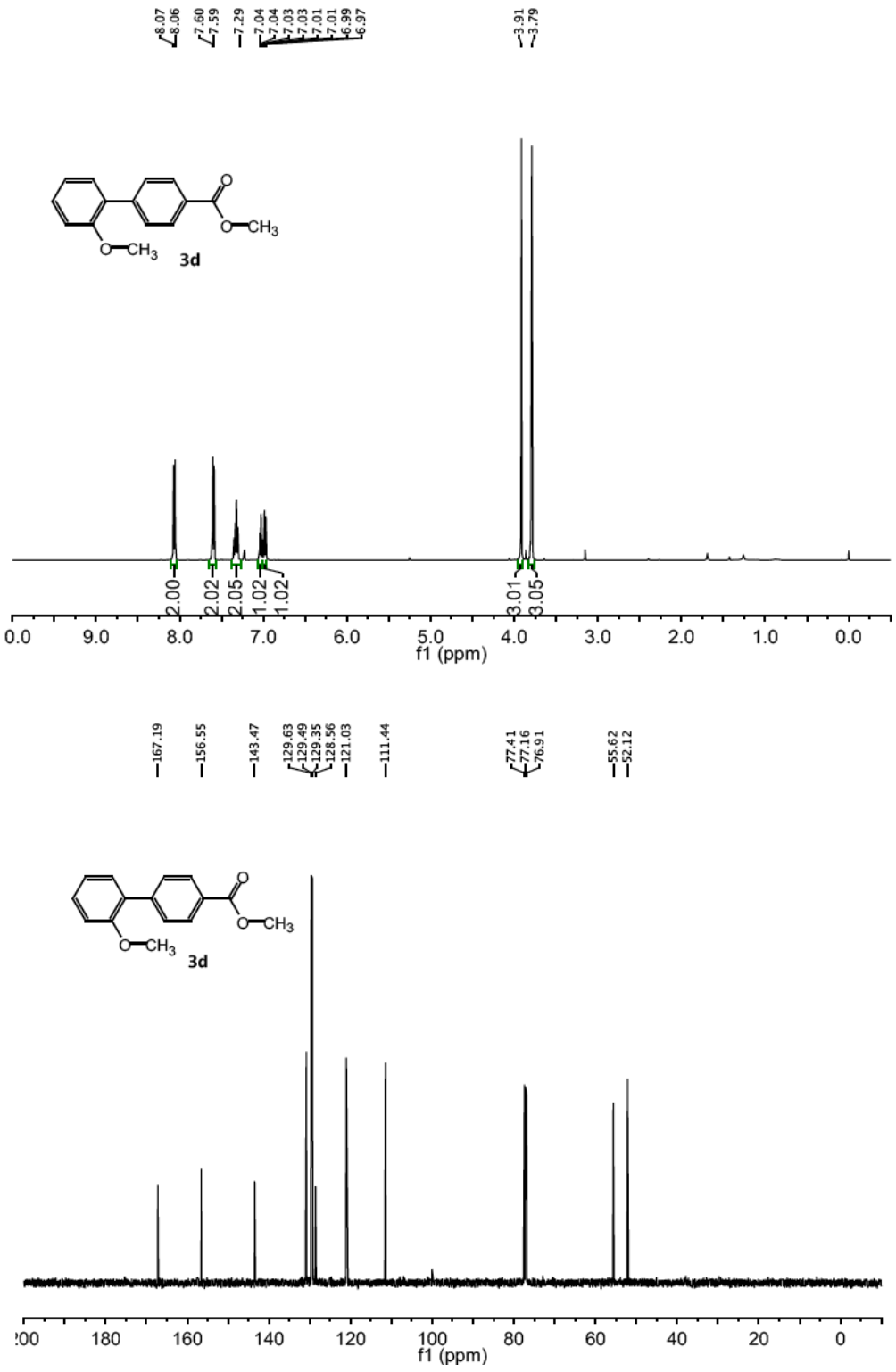


Figure SF 3.25. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 2'-methoxy-[1,1'-biphenyl]-4-carboxylate in $CDCl_3$.

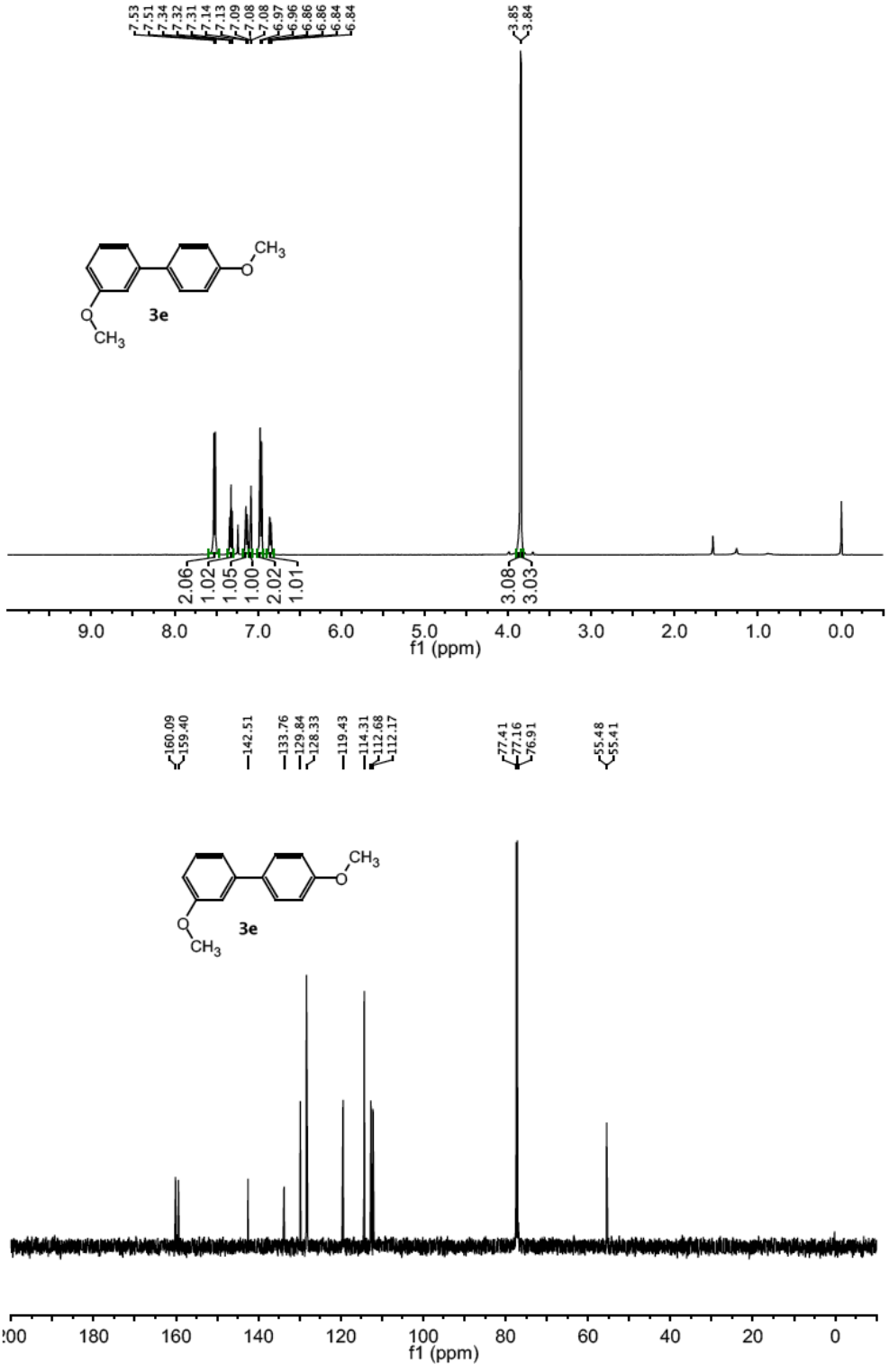


Figure SF 3.26. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 3,4'-dimethoxy-1,1'-biphenyl in $CDCl_3$.

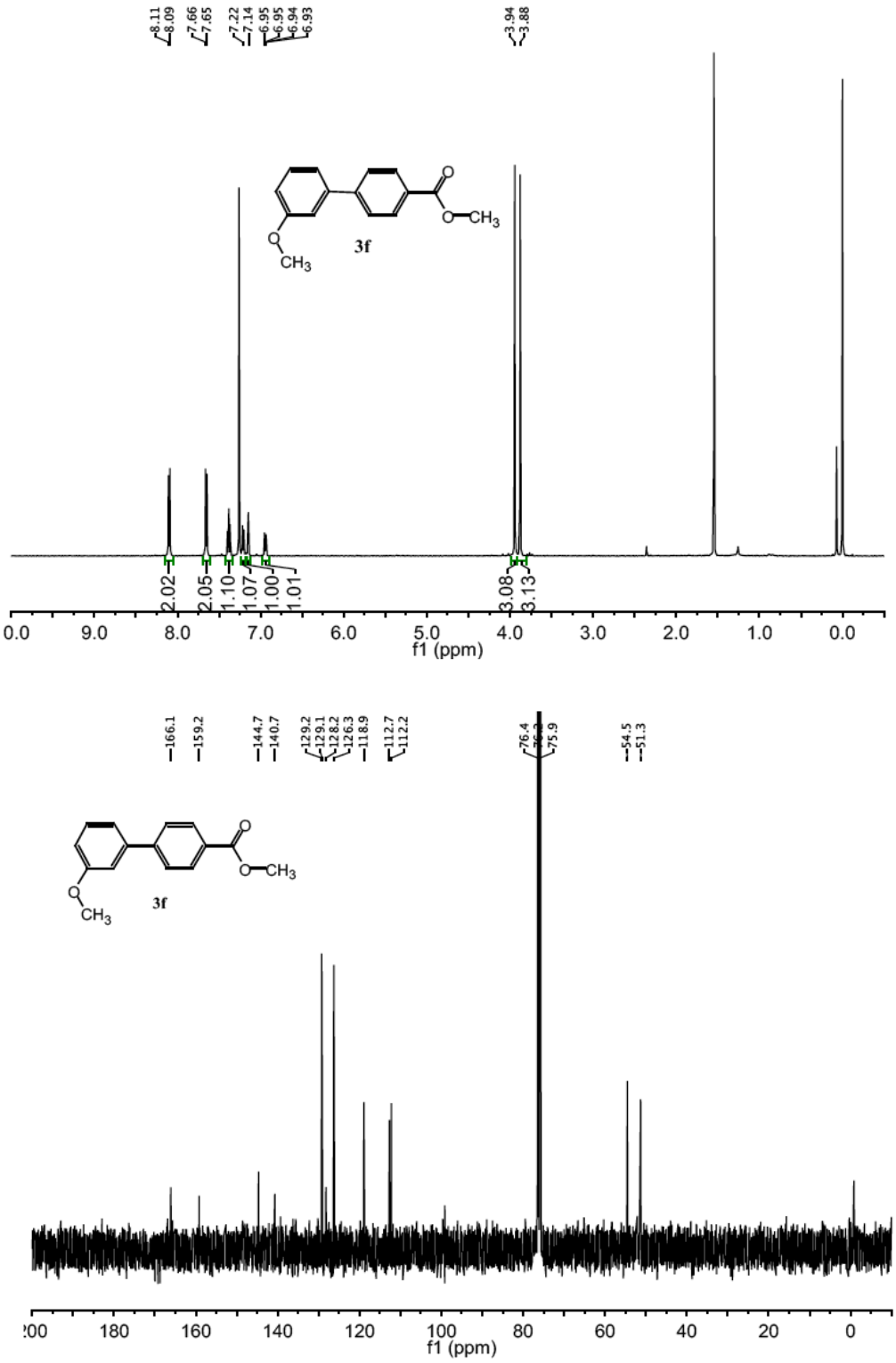


Figure SF 3.27. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 3'-methoxy-[1,1'-biphenyl]-4-carboxylate in $CDCl_3$.

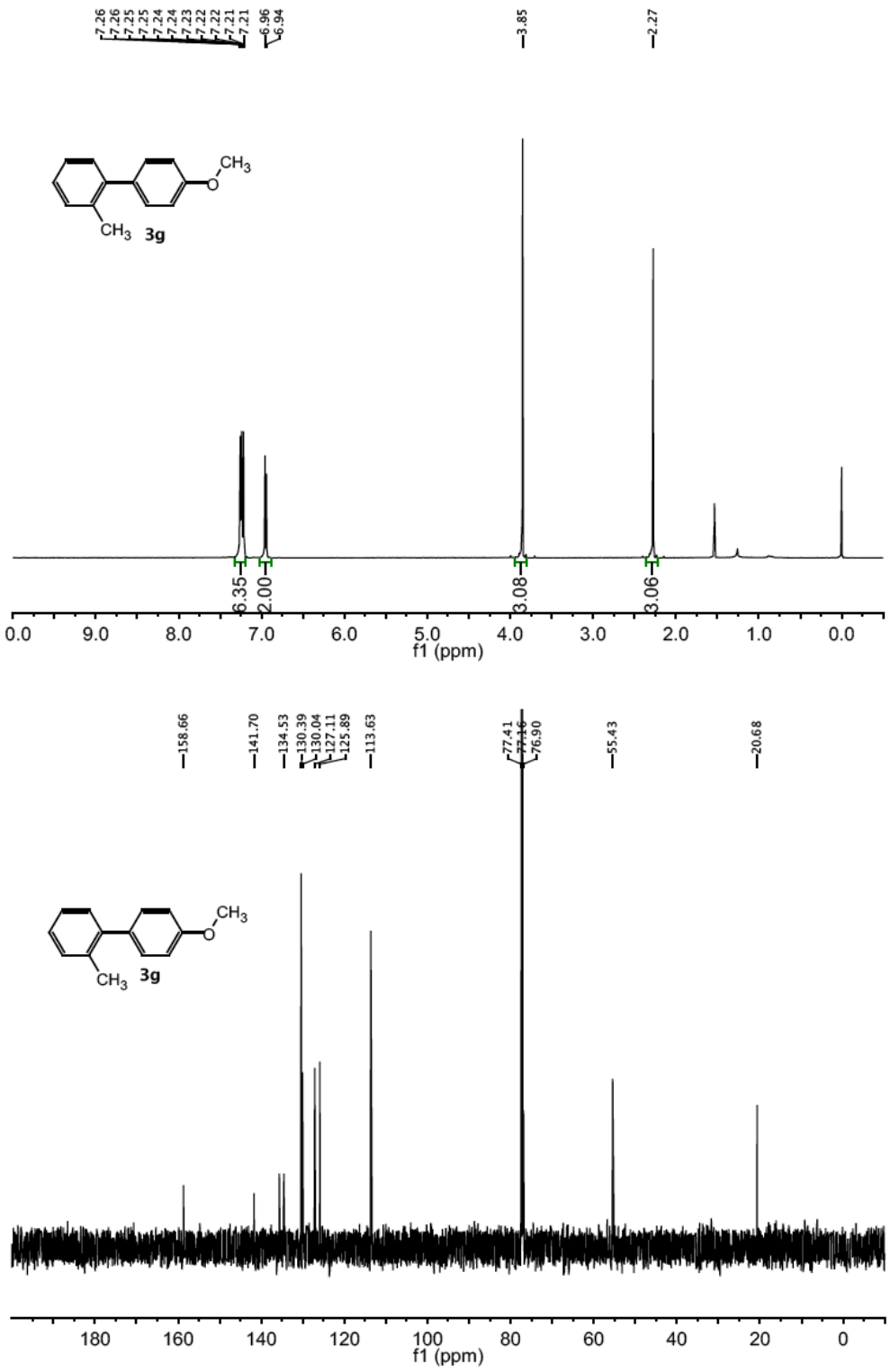


Figure SF 3.28. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 4'-methoxy-2-methyl-1,1'-biphenyl in $CDCl_3$.

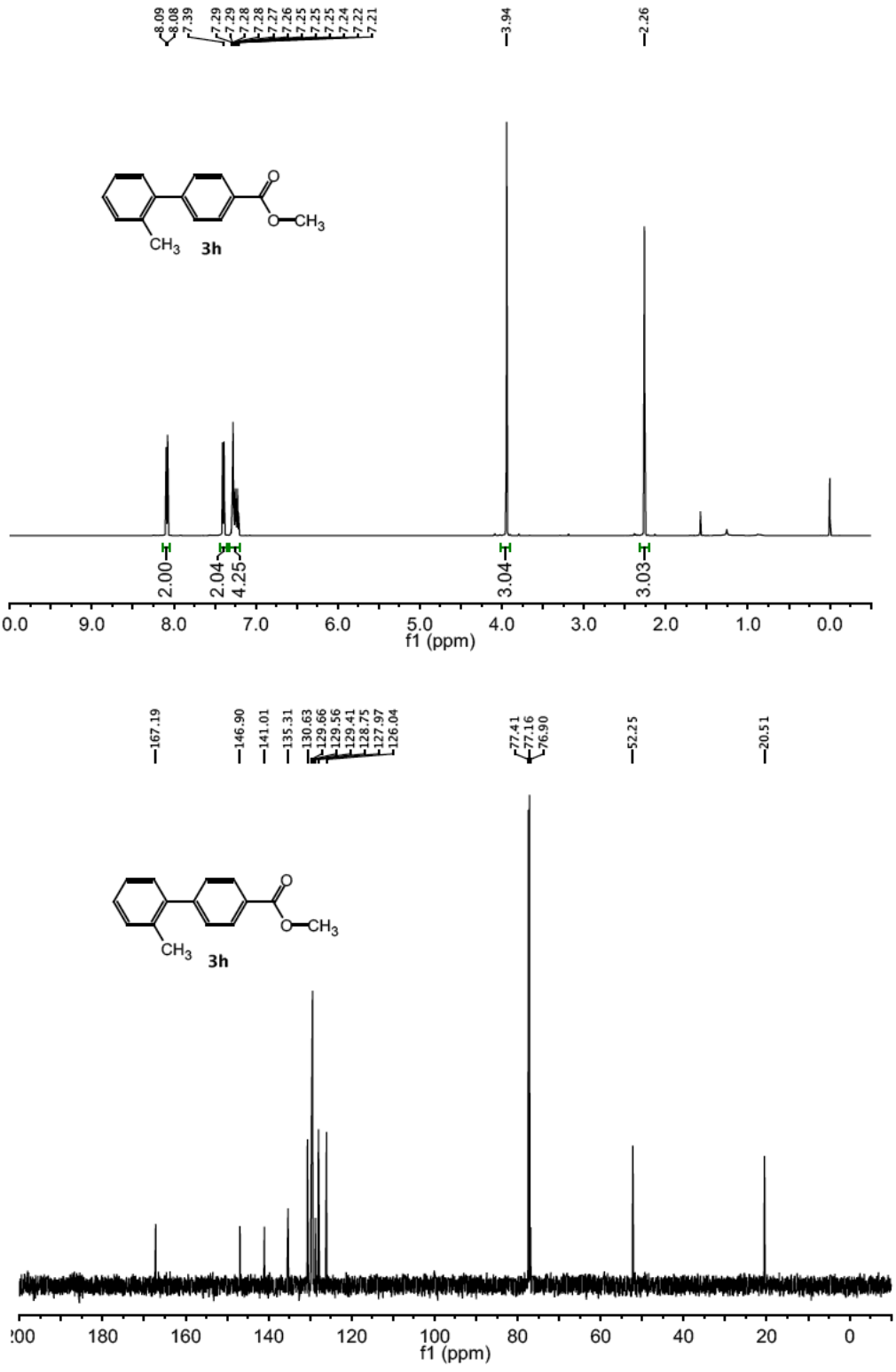


Figure SF 3.29. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 2'-methyl-[1,1'-biphenyl]-4-carboxylate in $CDCl_3$.

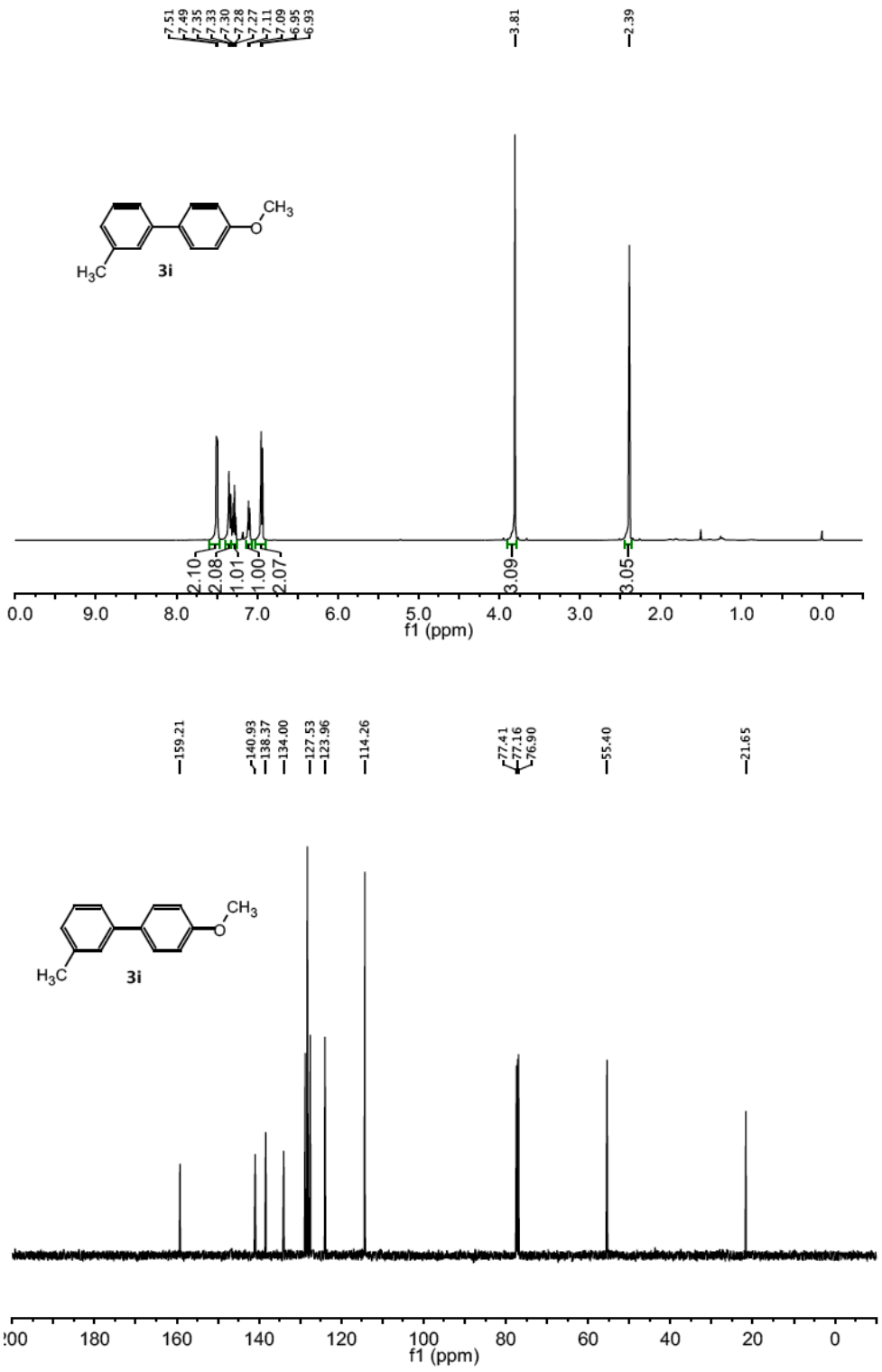


Figure SF 3.30. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 4'-methoxy-3-methyl-1,1'-biphenyl in $CDCl_3$.

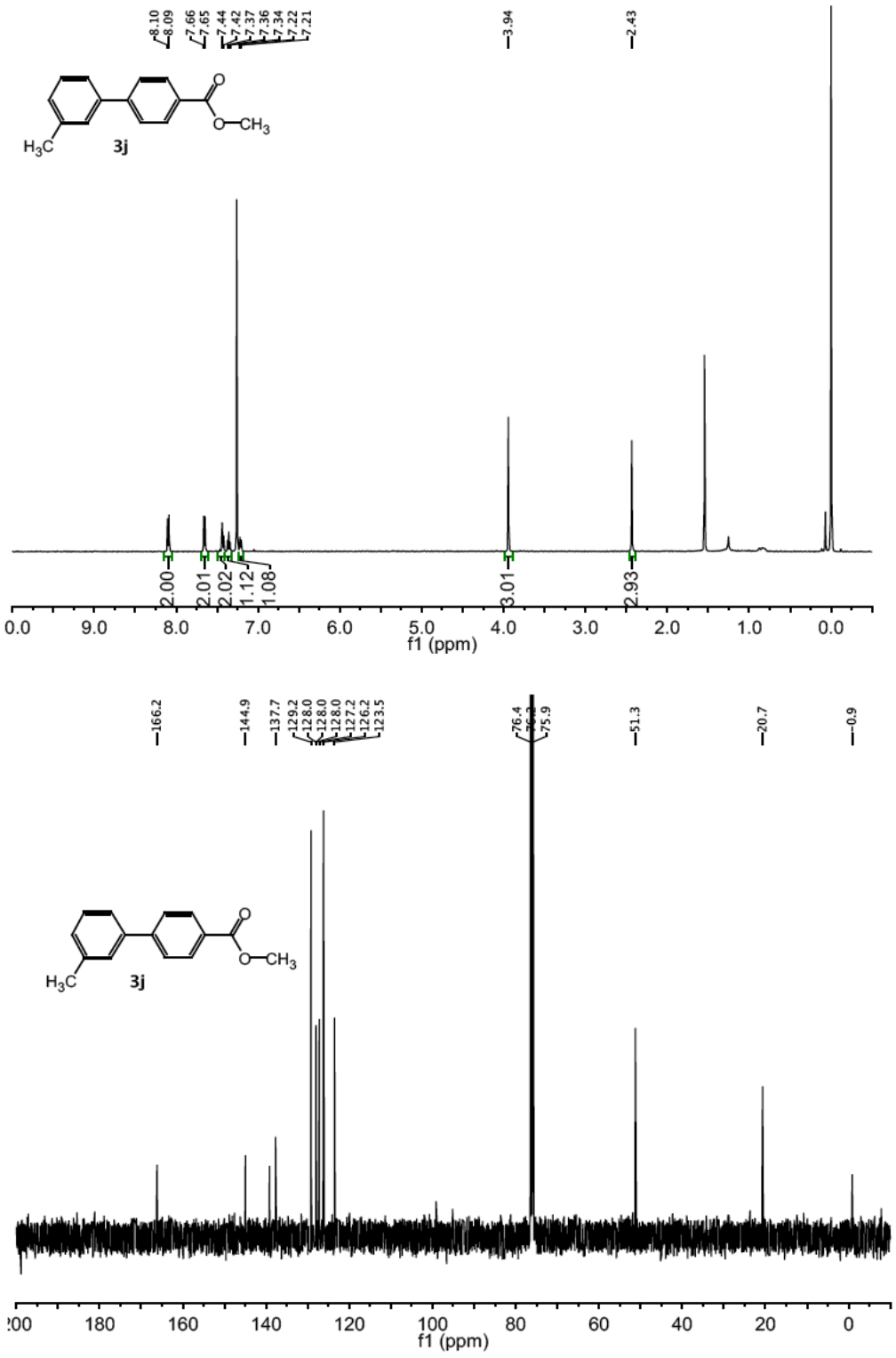


Figure SF 3.31. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 3'-methyl-[1,1'-biphenyl]-4-carboxylate in $CDCl_3$.

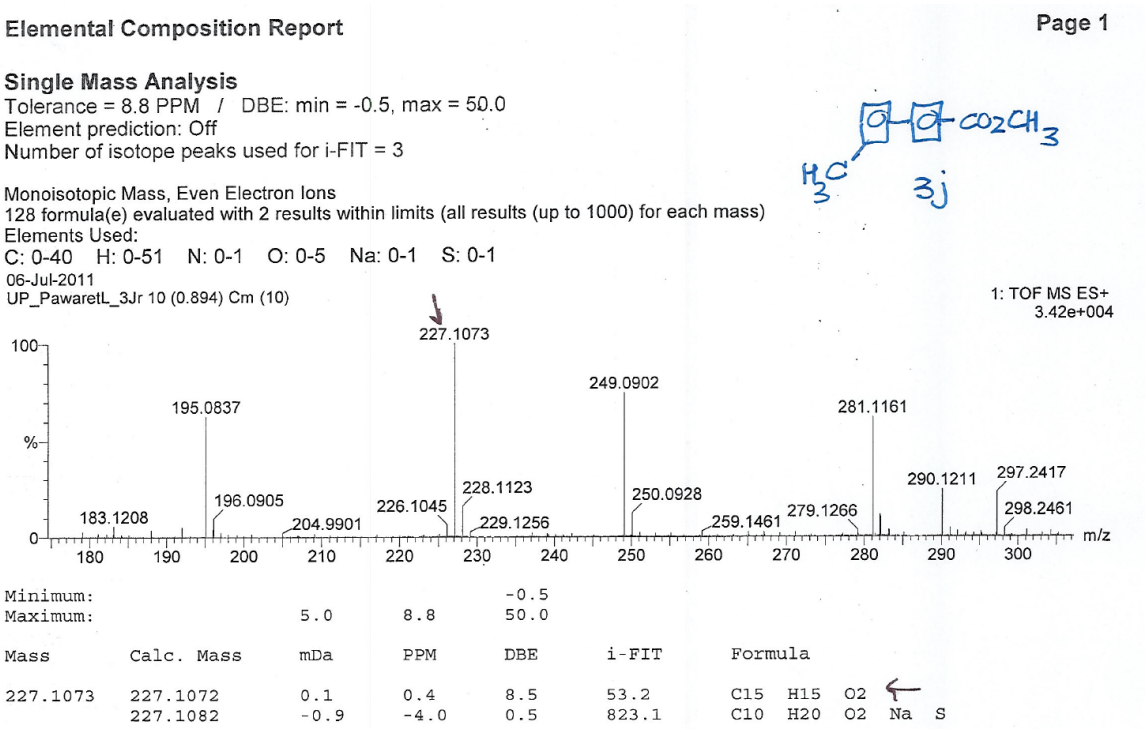


Figure SF 3.32. HRMS of methyl 3'-methyl-[1,1'-biphenyl]-4-carboxylate.

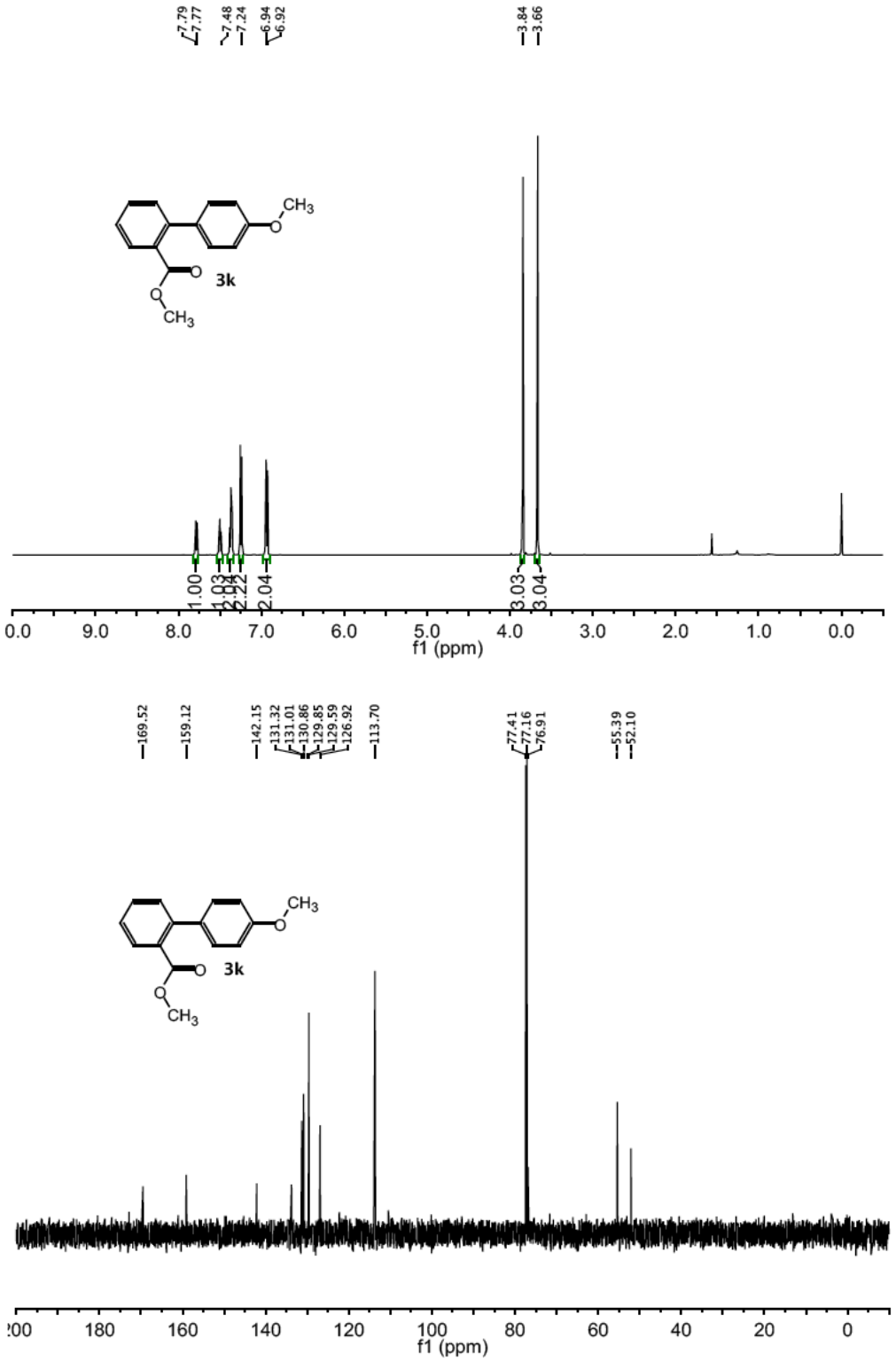


Figure SF 3.33. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 4'-methoxy-[1,1'-biphenyl]-2-carboxylate in $CDCl_3$.

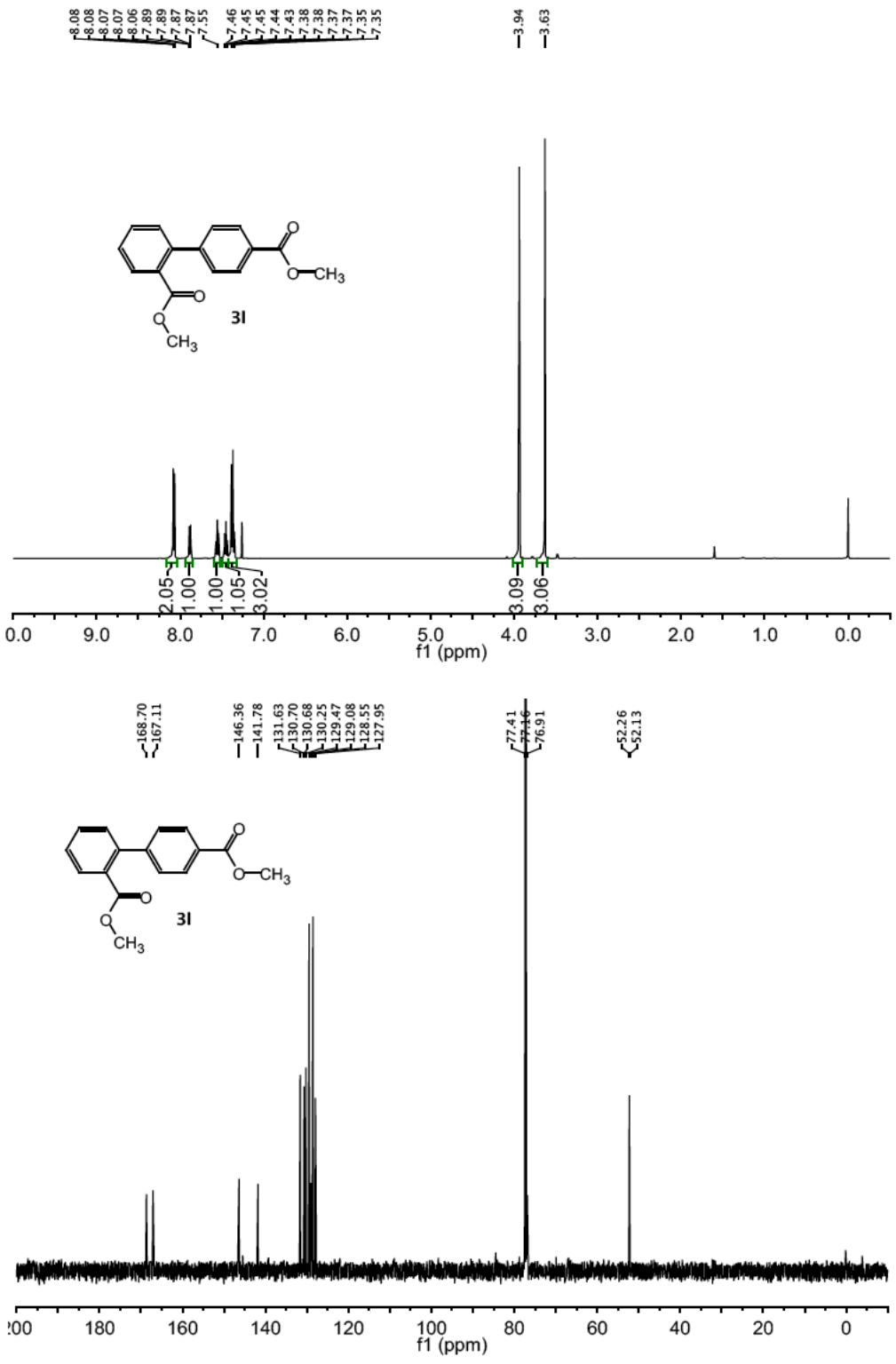


Figure SF 3.34. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra dimethyl [1,1'-biphenyl]-2,4'-dicarboxylate in $CDCl_3$.

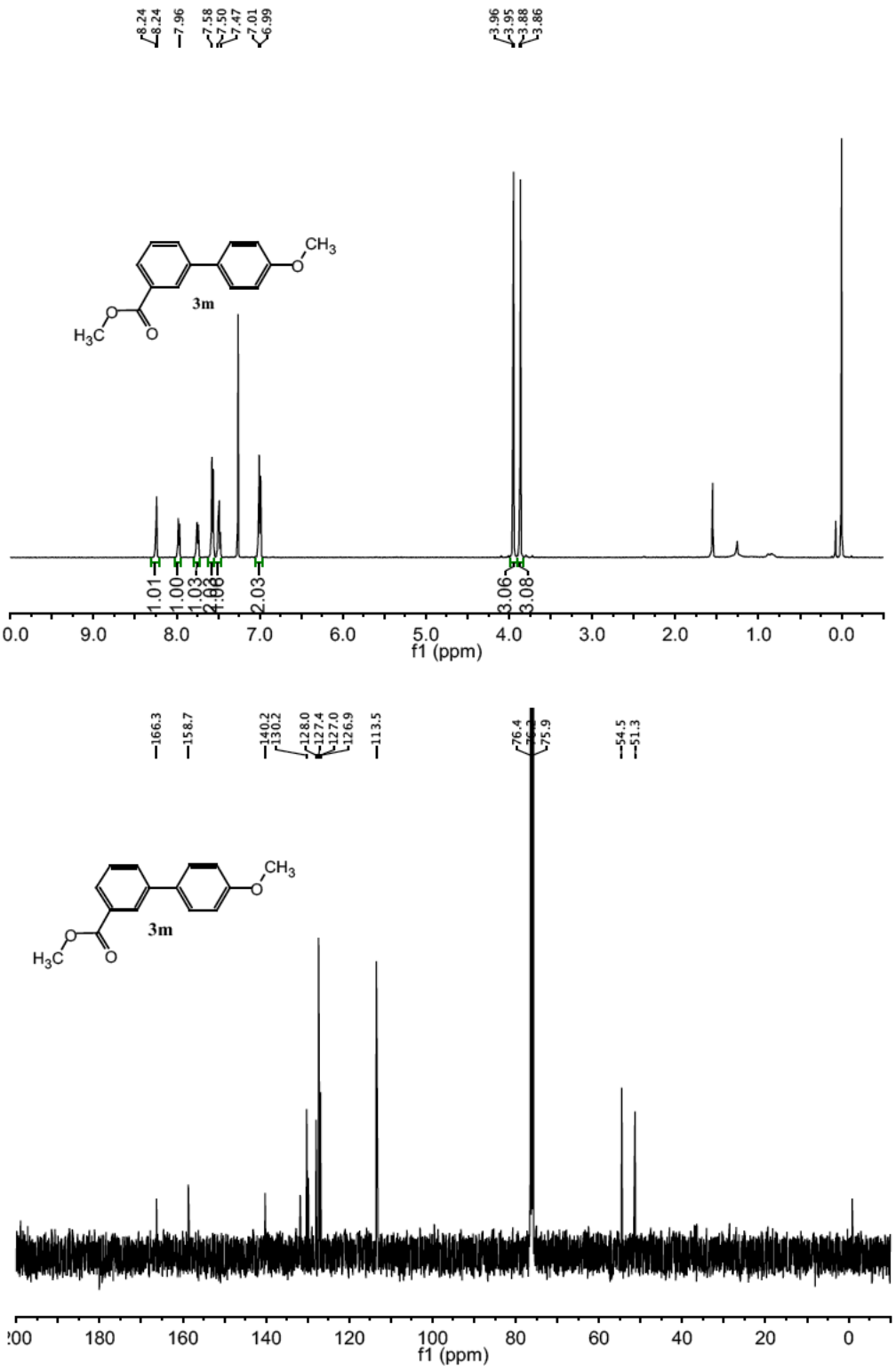


Figure SF 3.35. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 4'-methoxy-[1,1'-biphenyl]-3-carboxylate in $CDCl_3$.

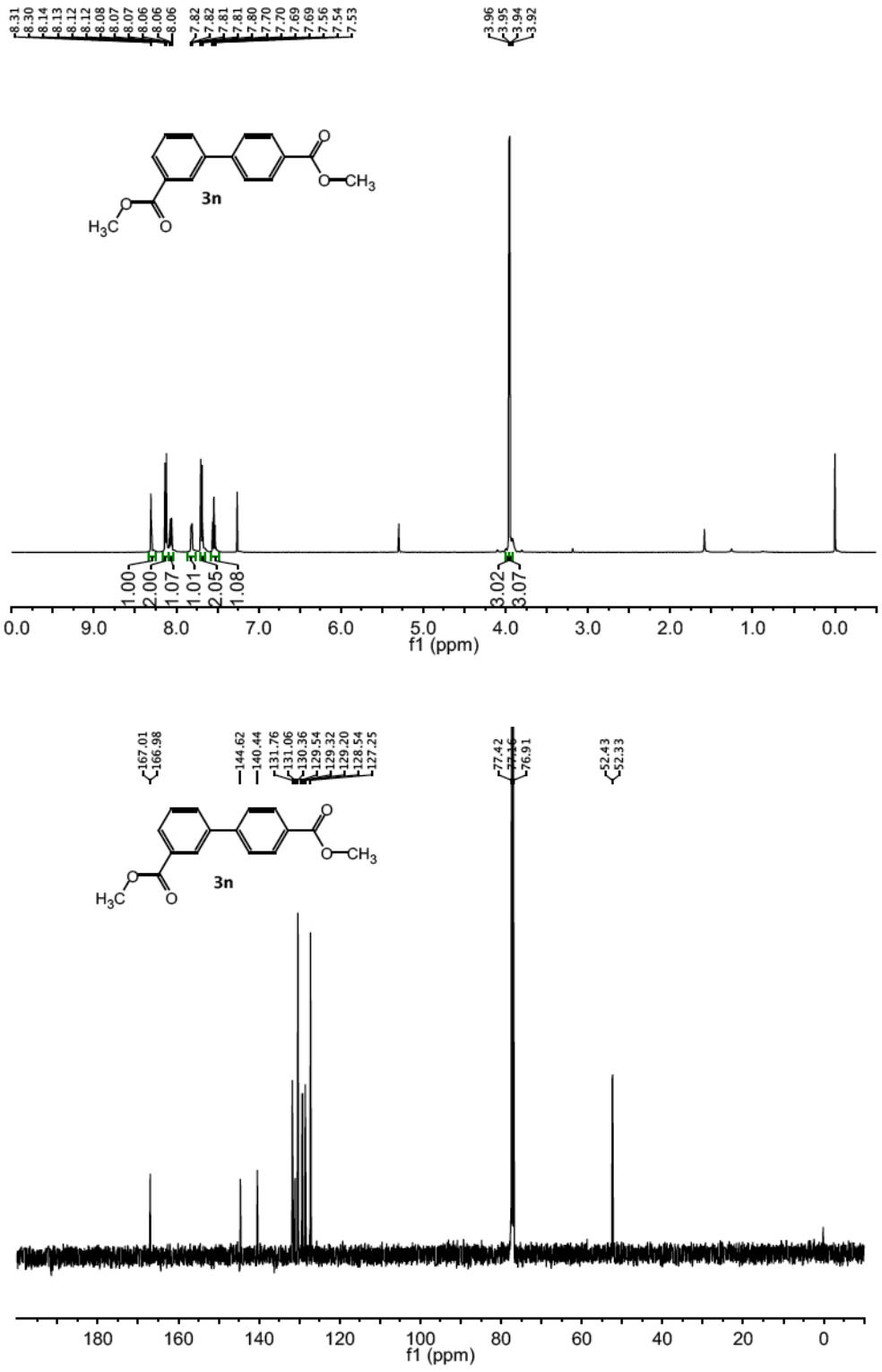
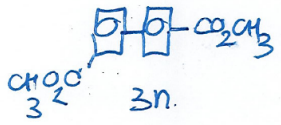


Figure SF 3.36. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of dimethyl [1,1'-biphenyl]-3,4'-dicarboxylate in $CDCl_3$.

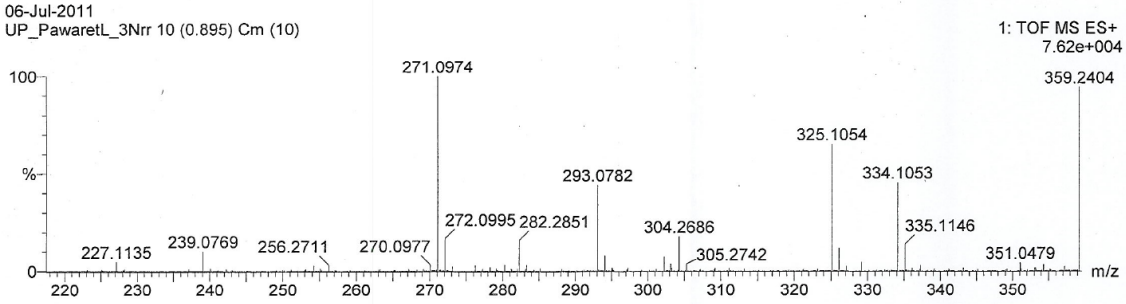
Elemental Composition Report Page 1

Single Mass Analysis
Tolerance = 8.0 PPM / DBE: min = -0.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3



Monoisotopic Mass, Even Electron Ions
88 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-40 H: 0-51 N: 0-1 O: 0-5 Na: 0-1

06-Jul-2011
UP_PawaretL_3Nrr 10 (0.895) Cm (10)



Minimum:				-0.5		
Maximum:		5.0	8.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
293.0782	293.0790	-0.8	-2.7	9.5	58.0	C16 H14 O4 Na

Figure SF 3.37. HRMS of dimethyl [1,1'-biphenyl]-3,4'-dicarboxylate.

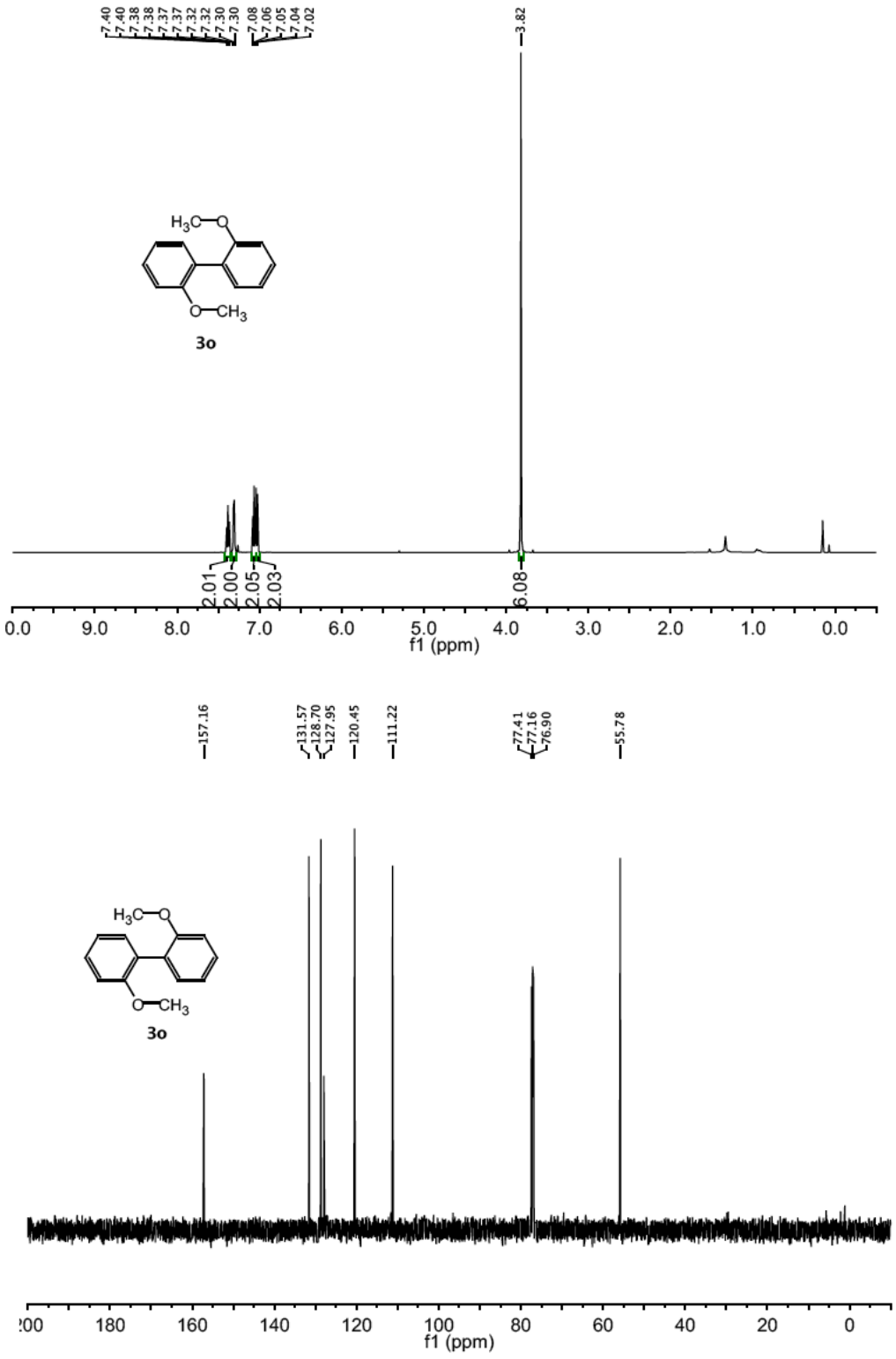


Figure SF 3.38. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 2,2'-dimethoxy-1,1'-biphenyl in $CDCl_3$.

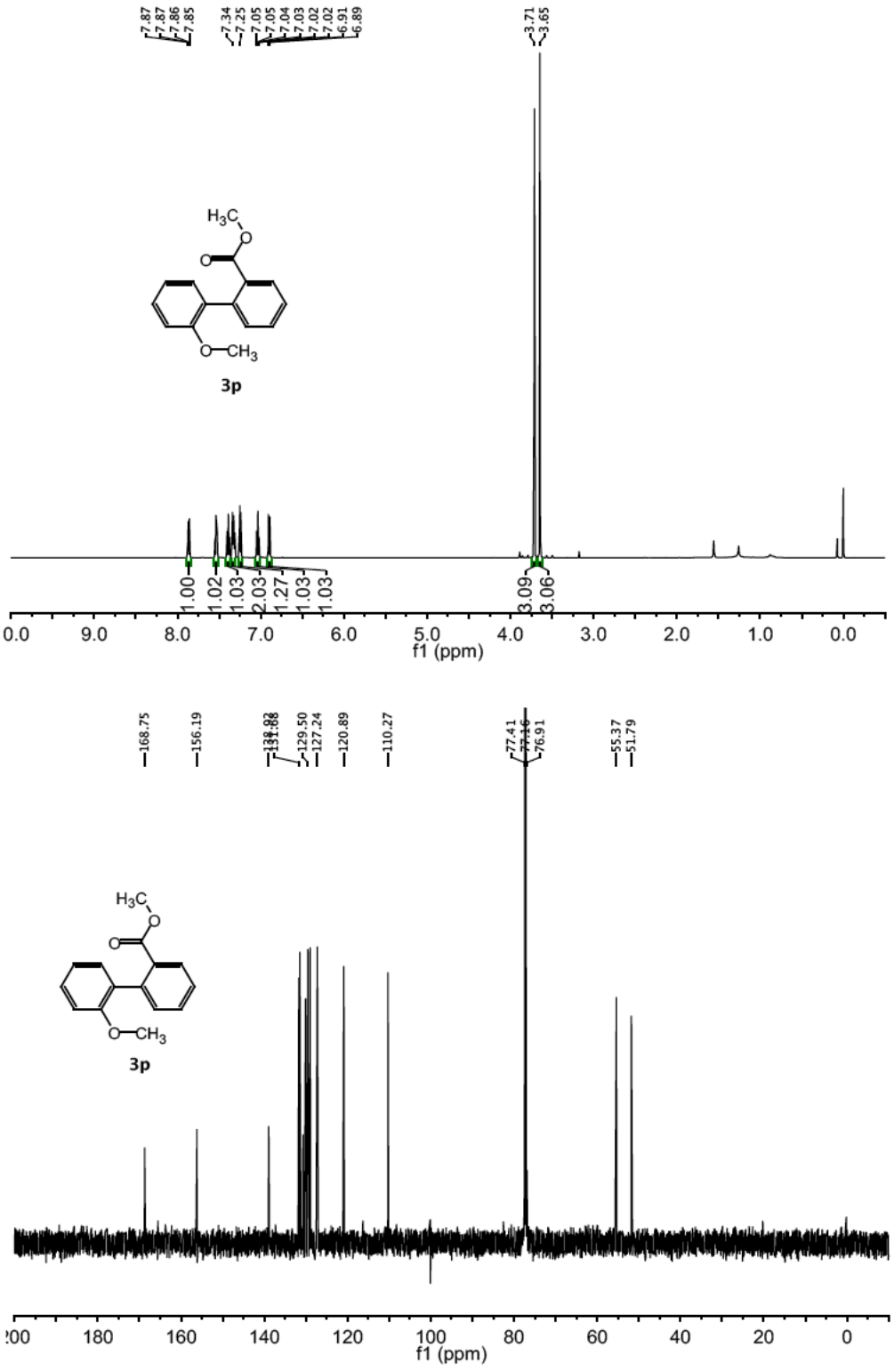


Figure SF 3.39. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 2'-methoxy-[1,1'-biphenyl]-2-carboxylate in $CDCl_3$.

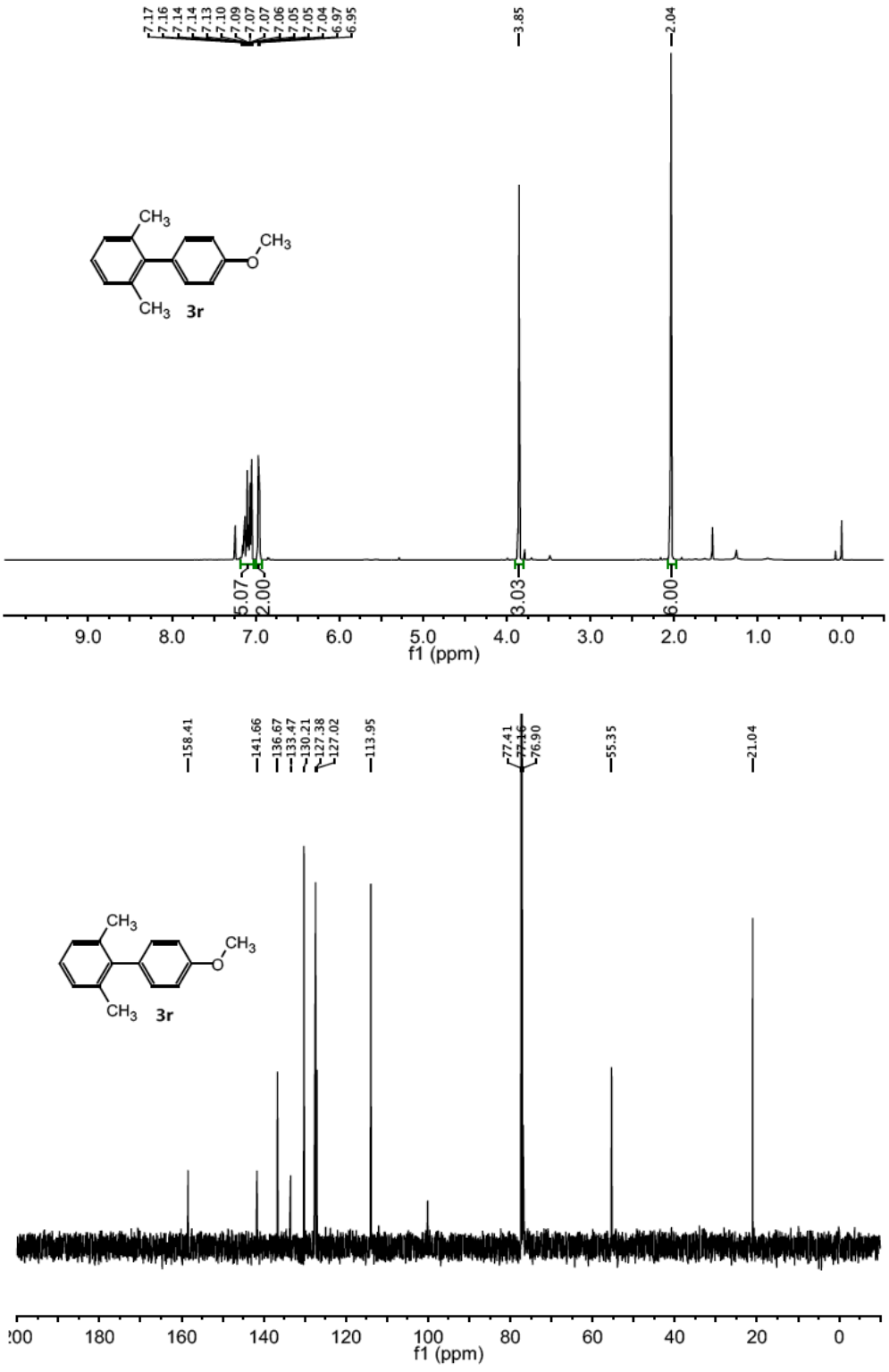


Figure SF 3.40. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 4'-methoxy-2,6-dimethyl-1,1'-biphenyl in $CDCl_3$.

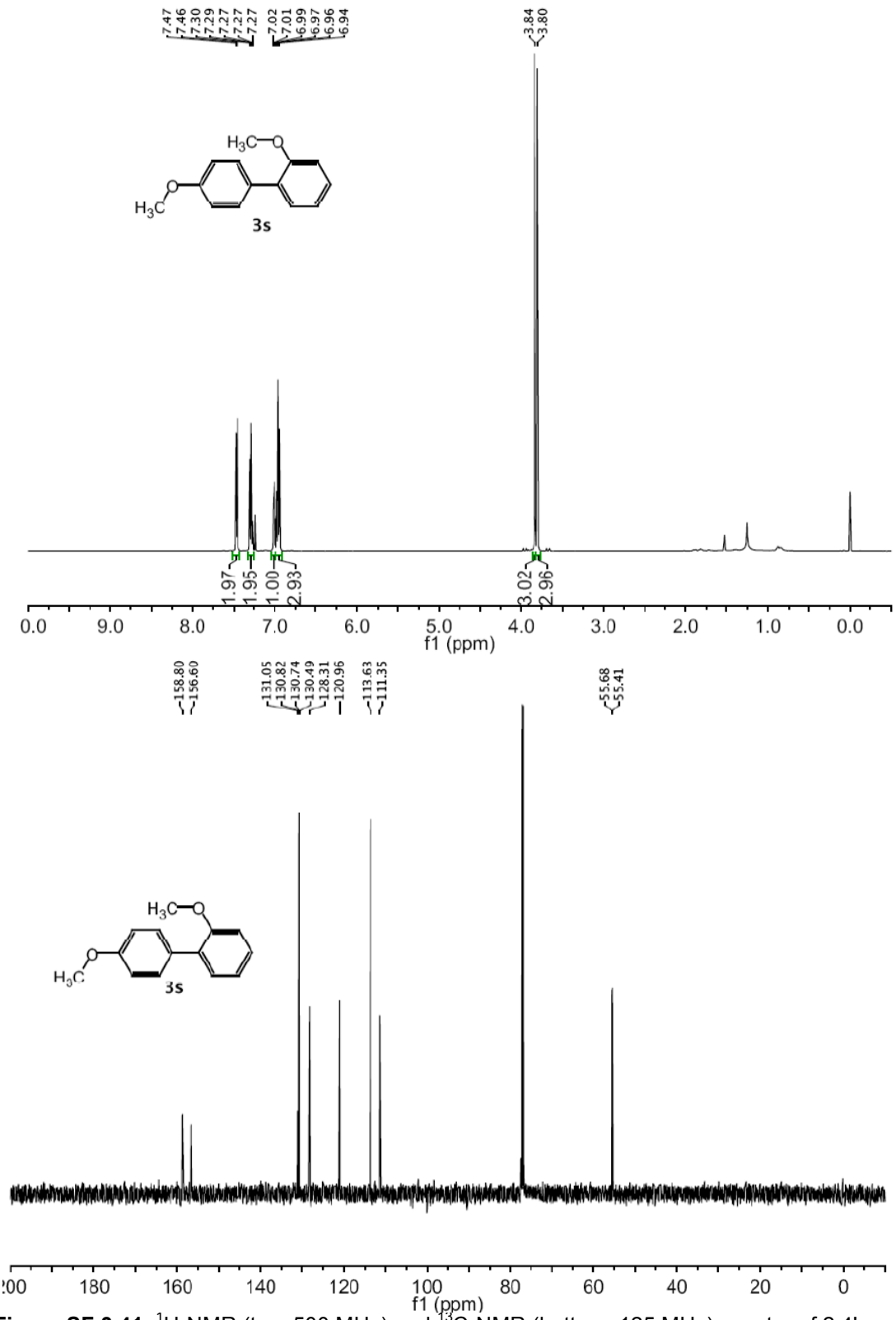


Figure SF 3.41. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 2,4'-dimethoxy-1,1'-biphenyl in $CDCl_3$.

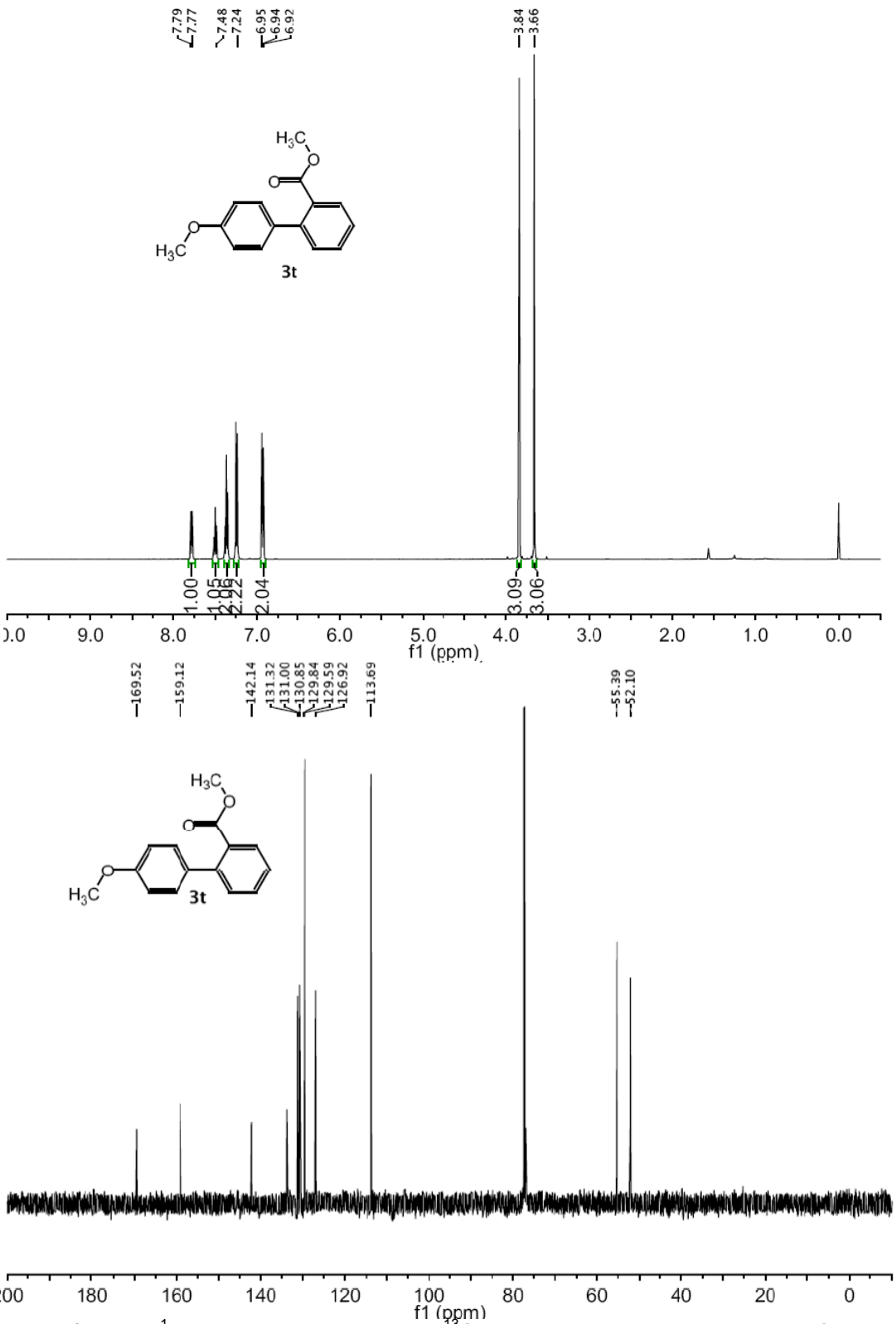


Figure SF 3.42. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 4'-methoxy-[1,1'-biphenyl]-2-carboxylate in $CDCl_3$.

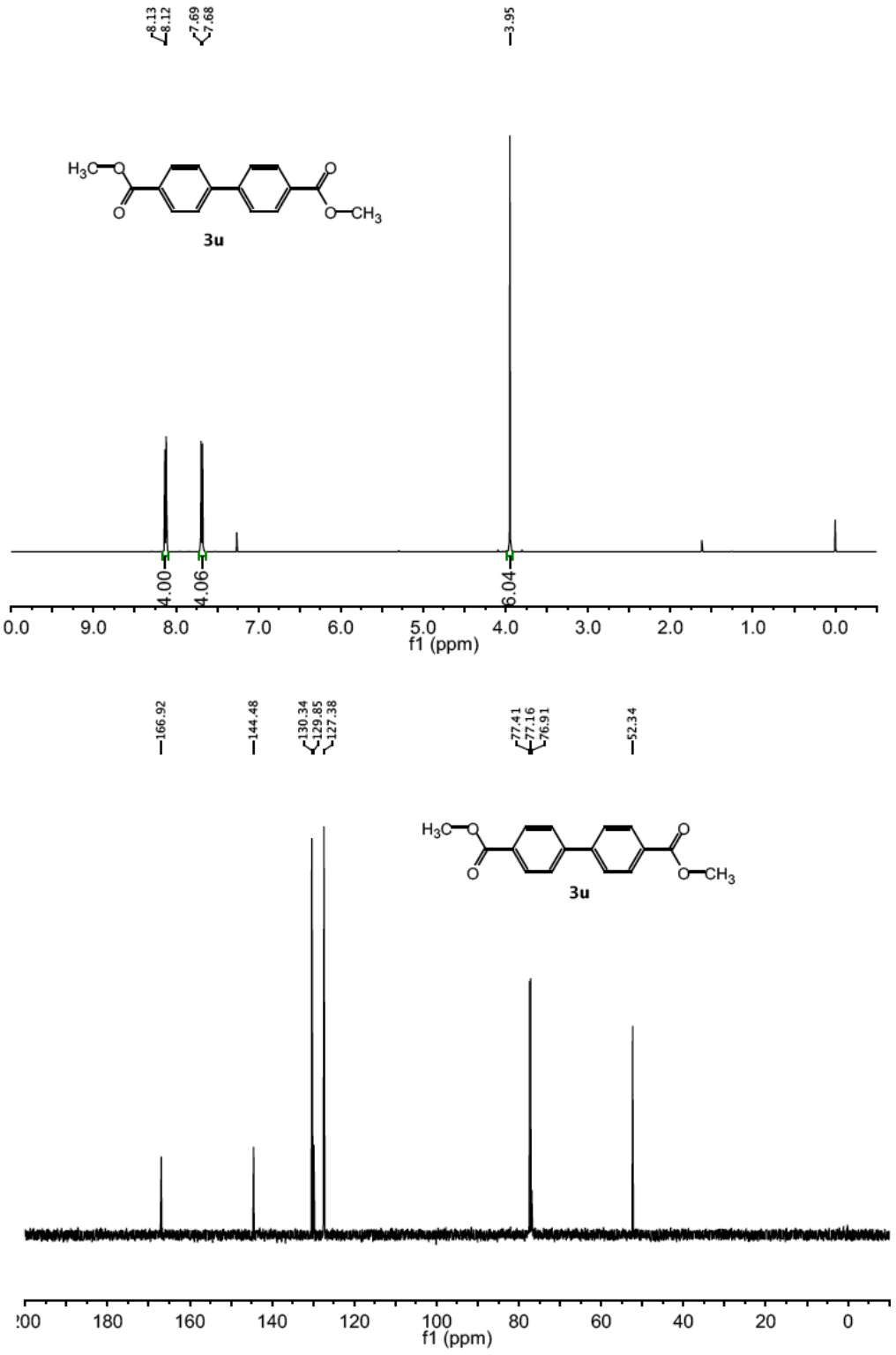


Figure SF 3.43. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of dimethyl [1,1'-biphenyl]-4,4'-dicarboxylate in $CDCl_3$.

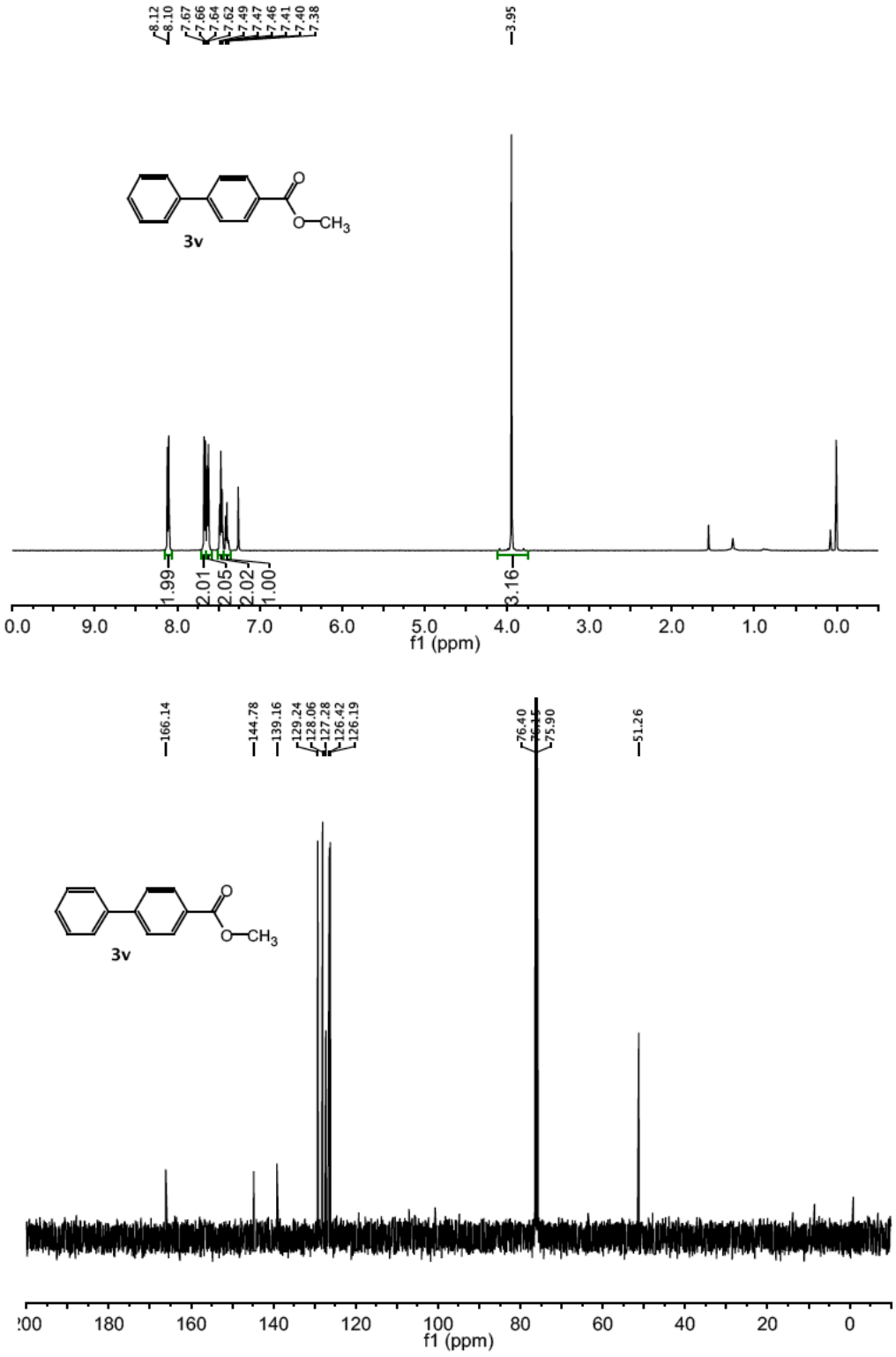


Figure SF 3.44. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra methyl [1,1'-biphenyl]-4-carboxylate in $CDCl_3$.

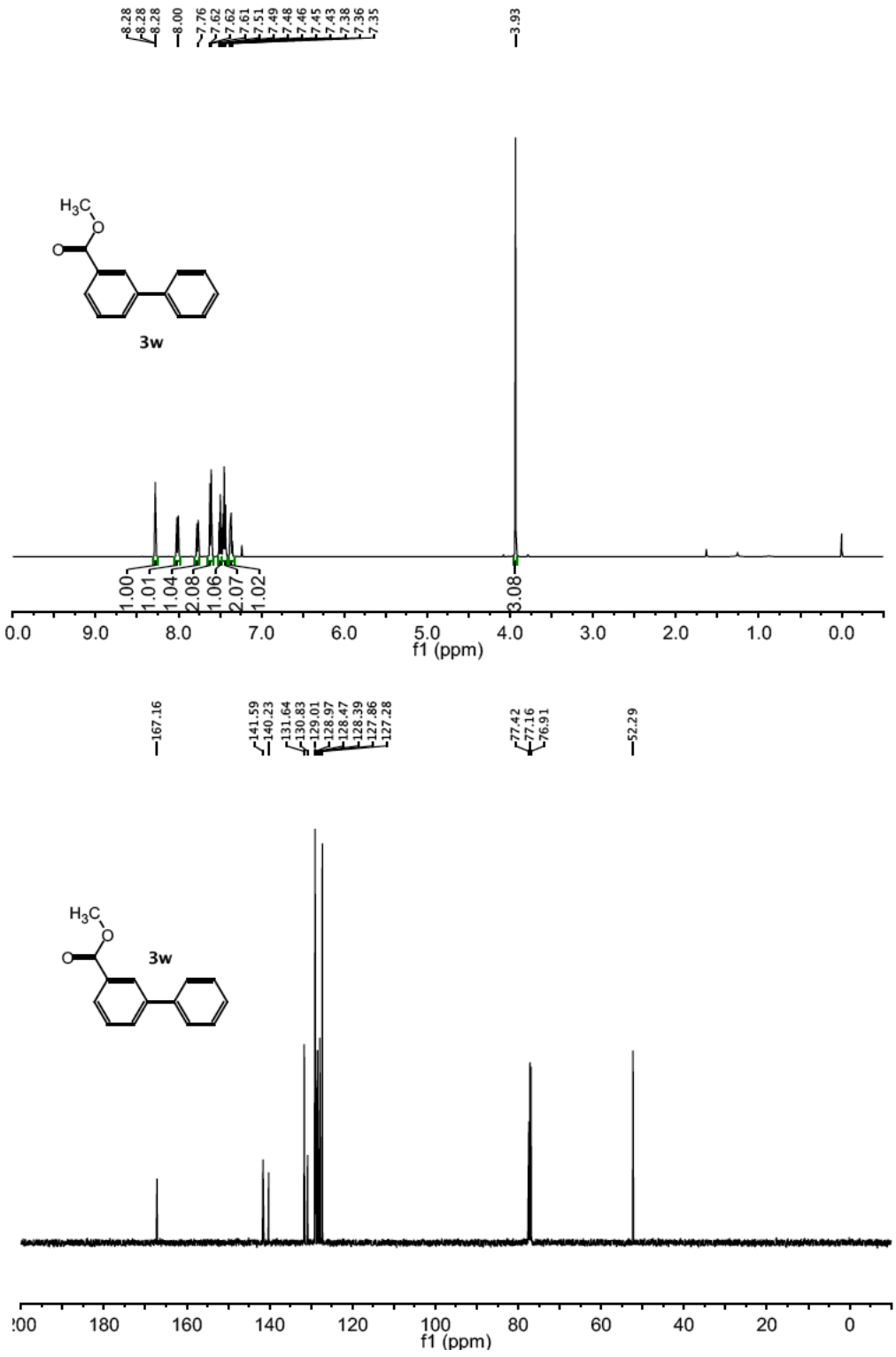


Figure SF 3.45. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl [1,1'-biphenyl]-3-carboxylate in $CDCl_3$.

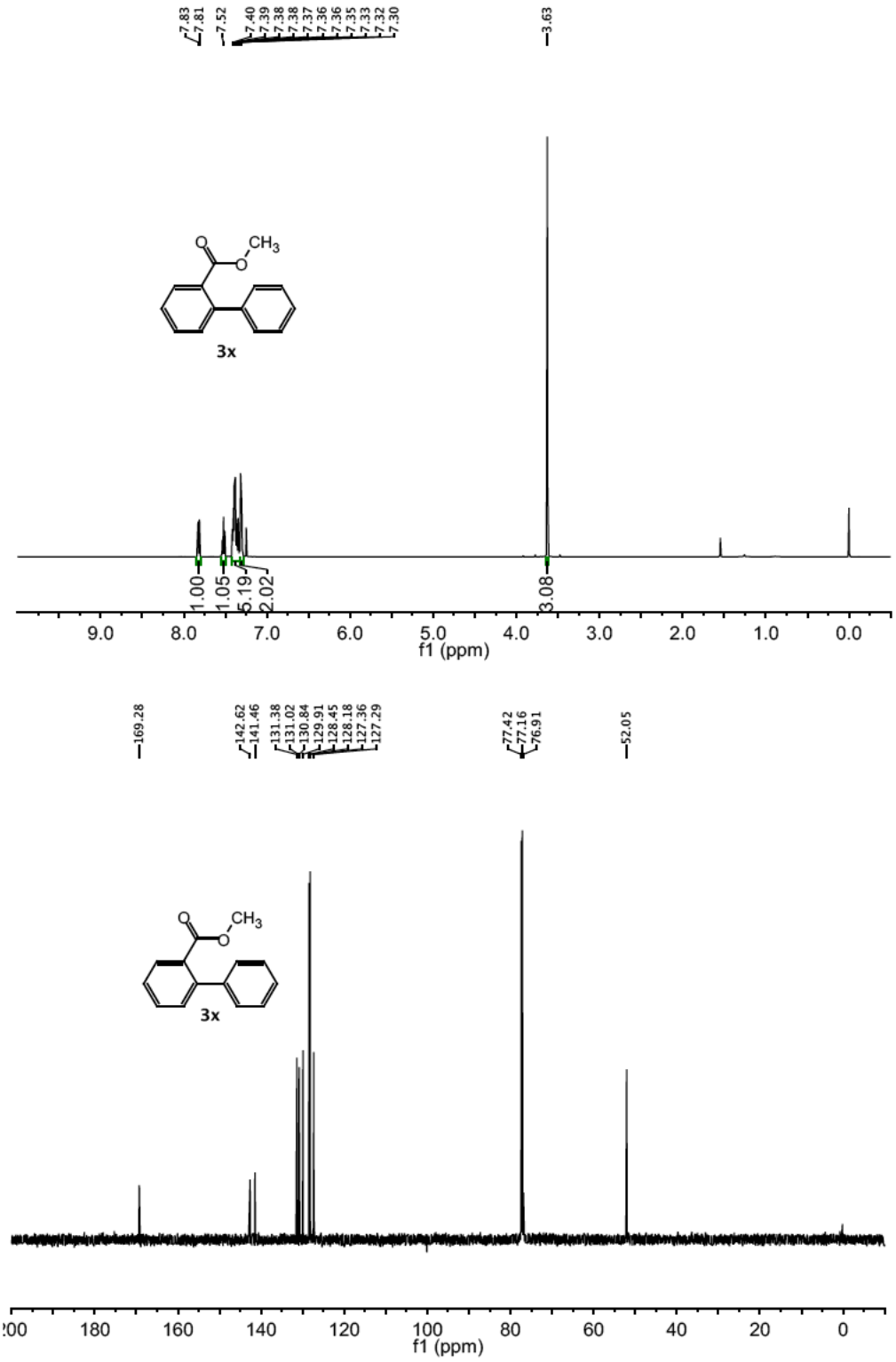


Figure SF 3.46. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl [1,1'-biphenyl]-2-carboxylate in $CDCl_3$.

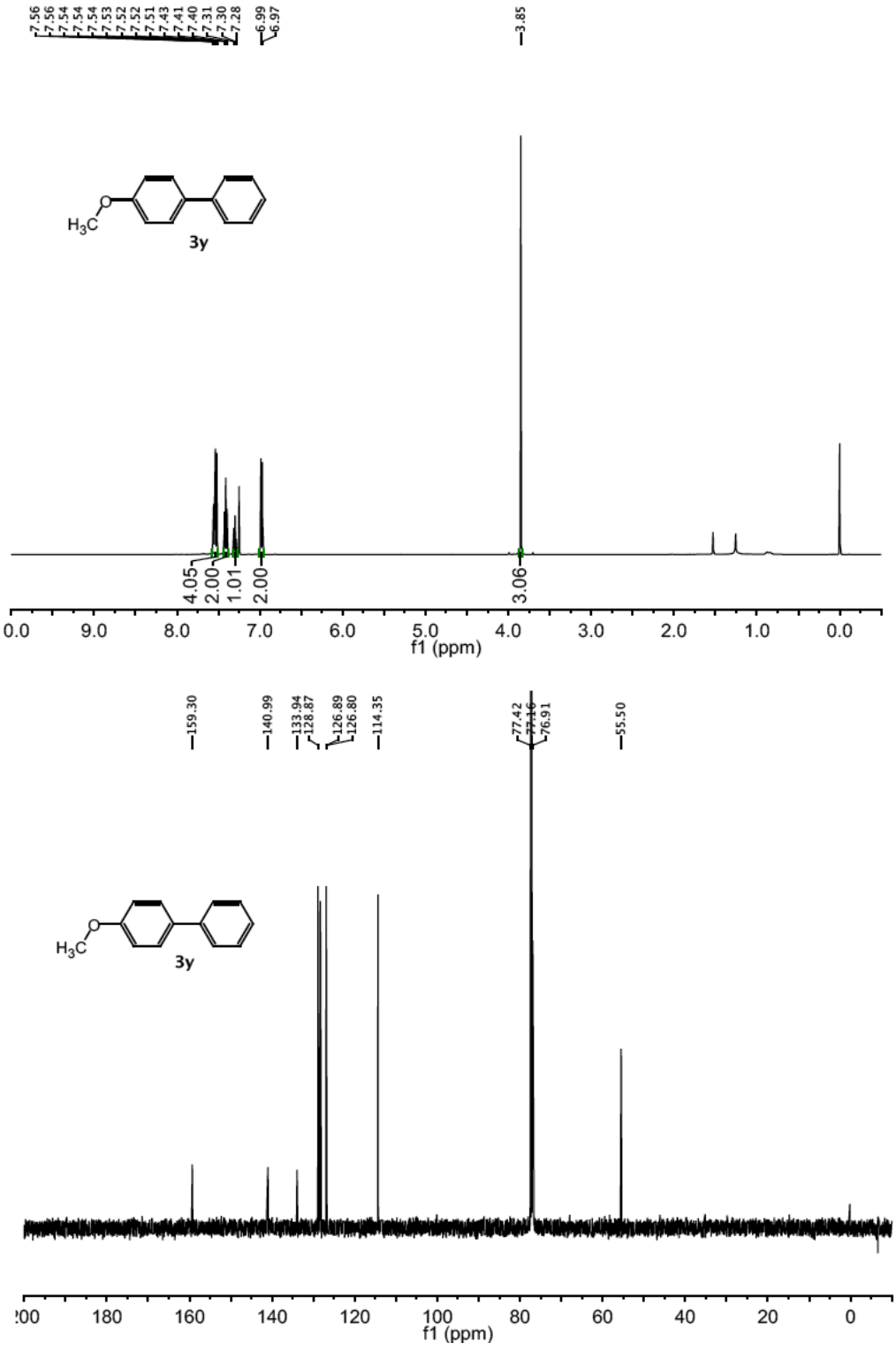


Figure SF 3.47. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra 4-methoxy-1,1'-biphenyl in $CDCl_3$.

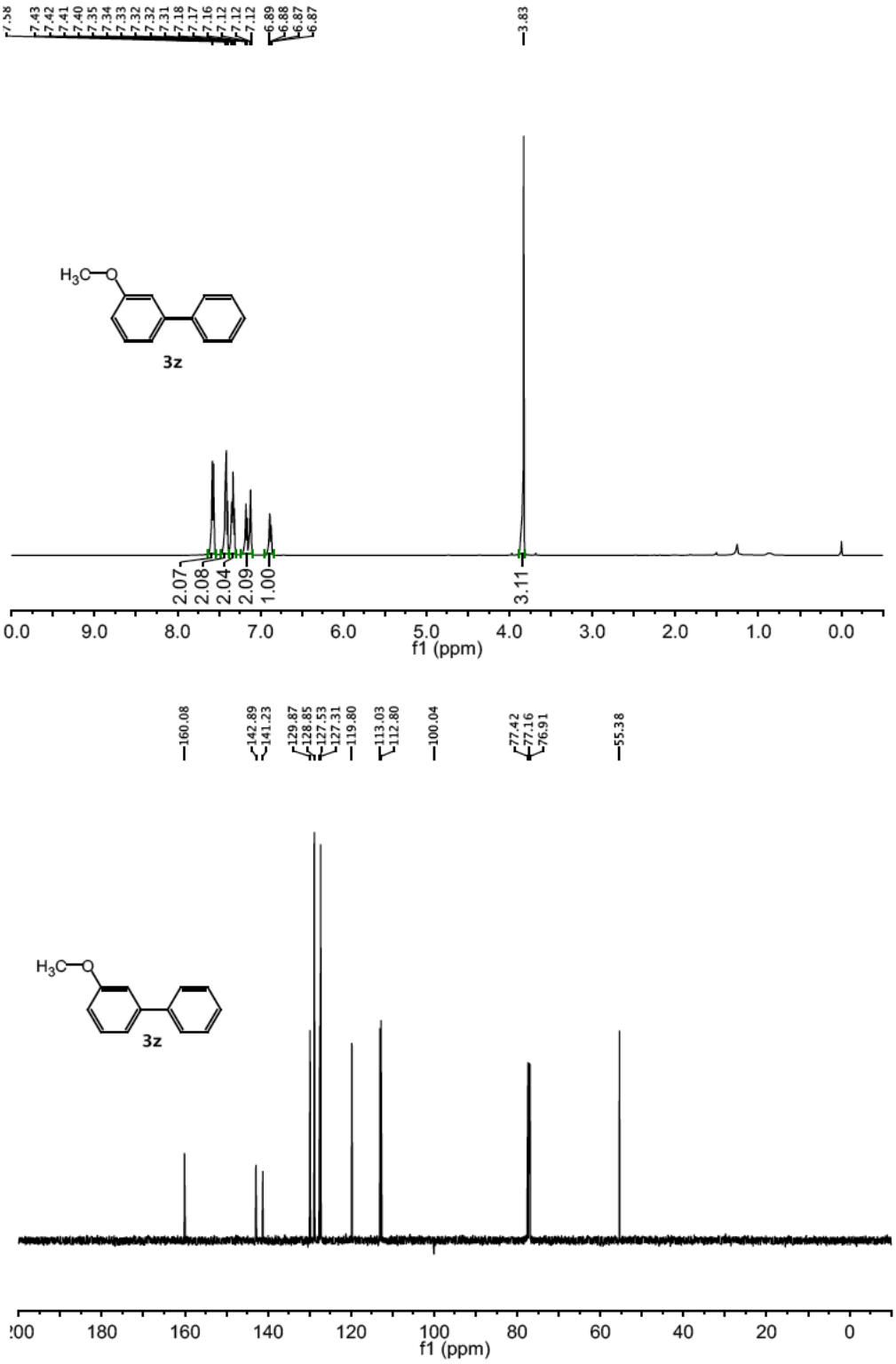


Figure SF 3.48. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 3-methoxy-1,1'-biphenyl in $CDCl_3$.

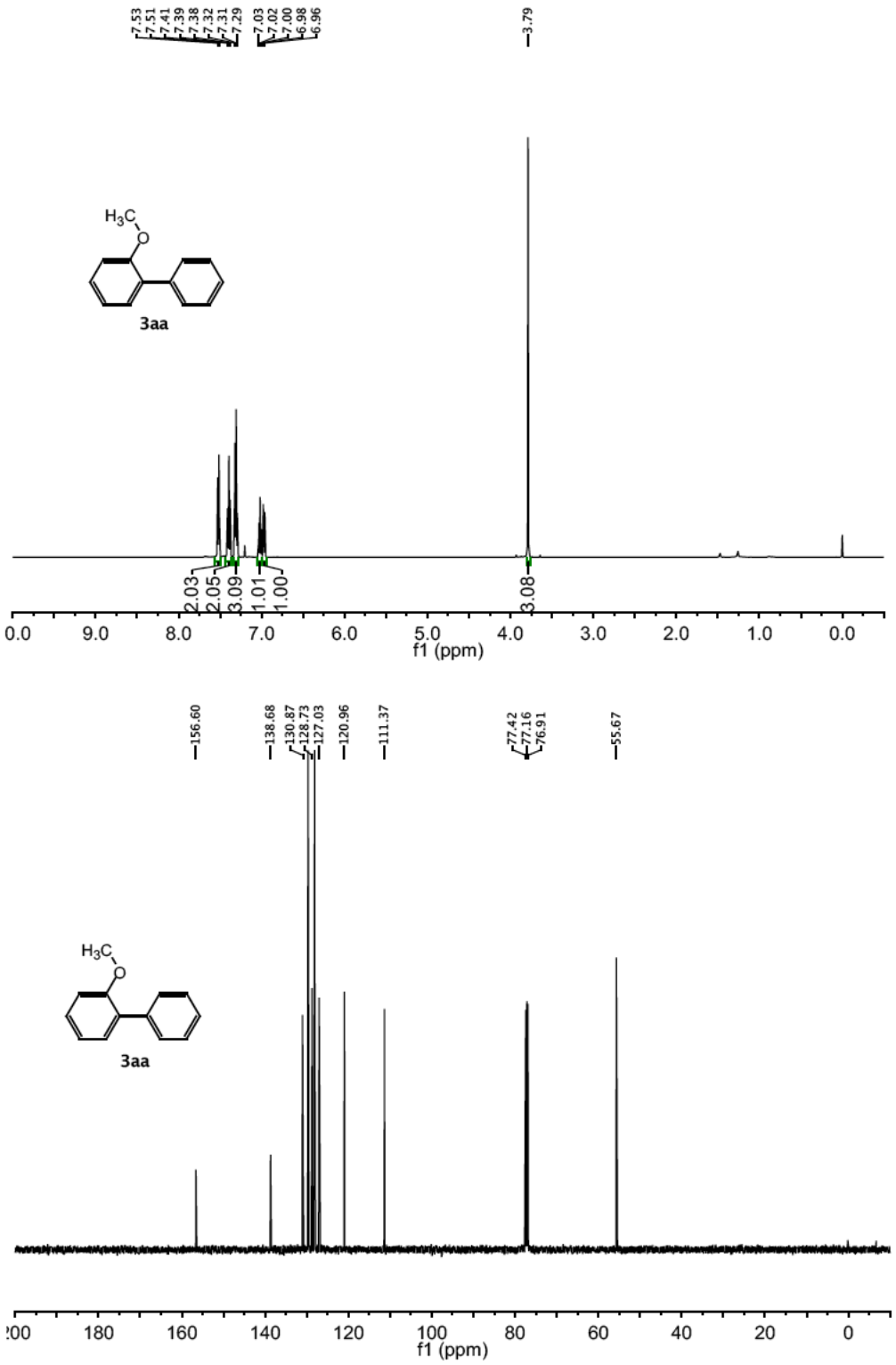


Figure SF 3.49. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 2-methoxy-1,1'-biphenyl in $CDCl_3$.

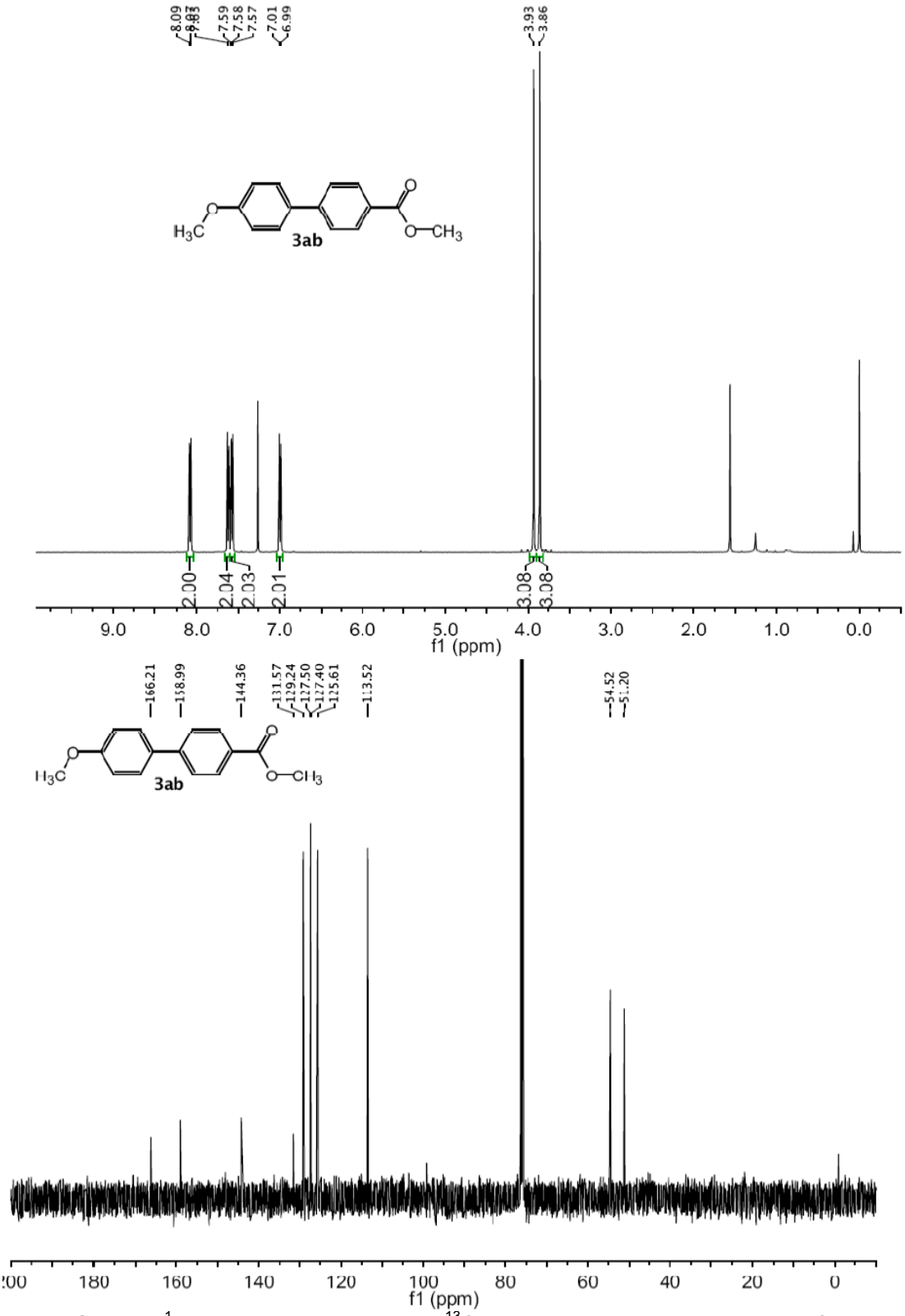


Figure SF 3.50. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate in $CDCl_3$.

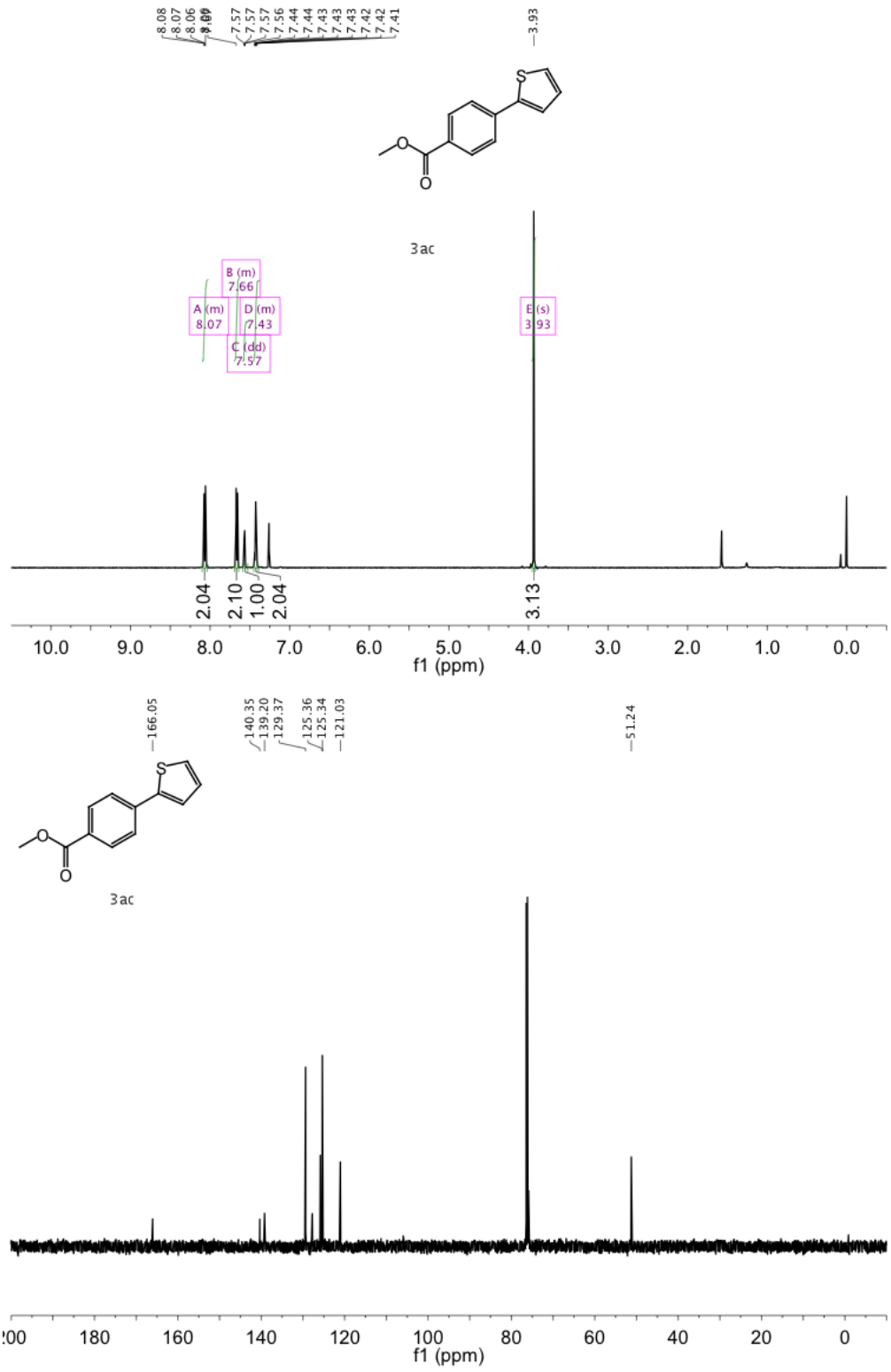


Figure SF 3.51. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 4-(thiophen-2-yl)benzoate in $CDCl_3$.

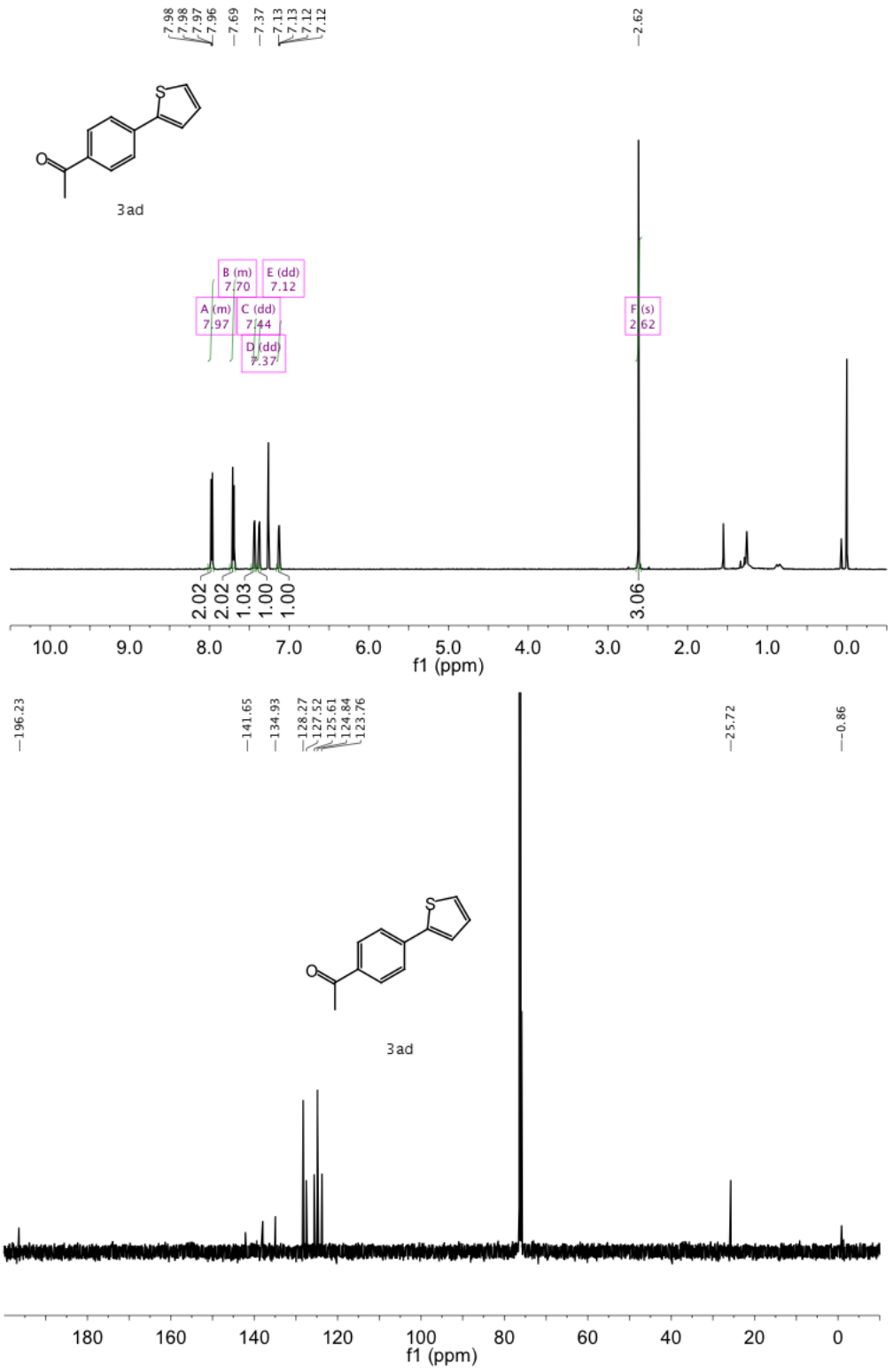


Figure SF 3.52. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 1-(4-(thiophen-2-yl)phenyl)ethanone in $CDCl_3$.

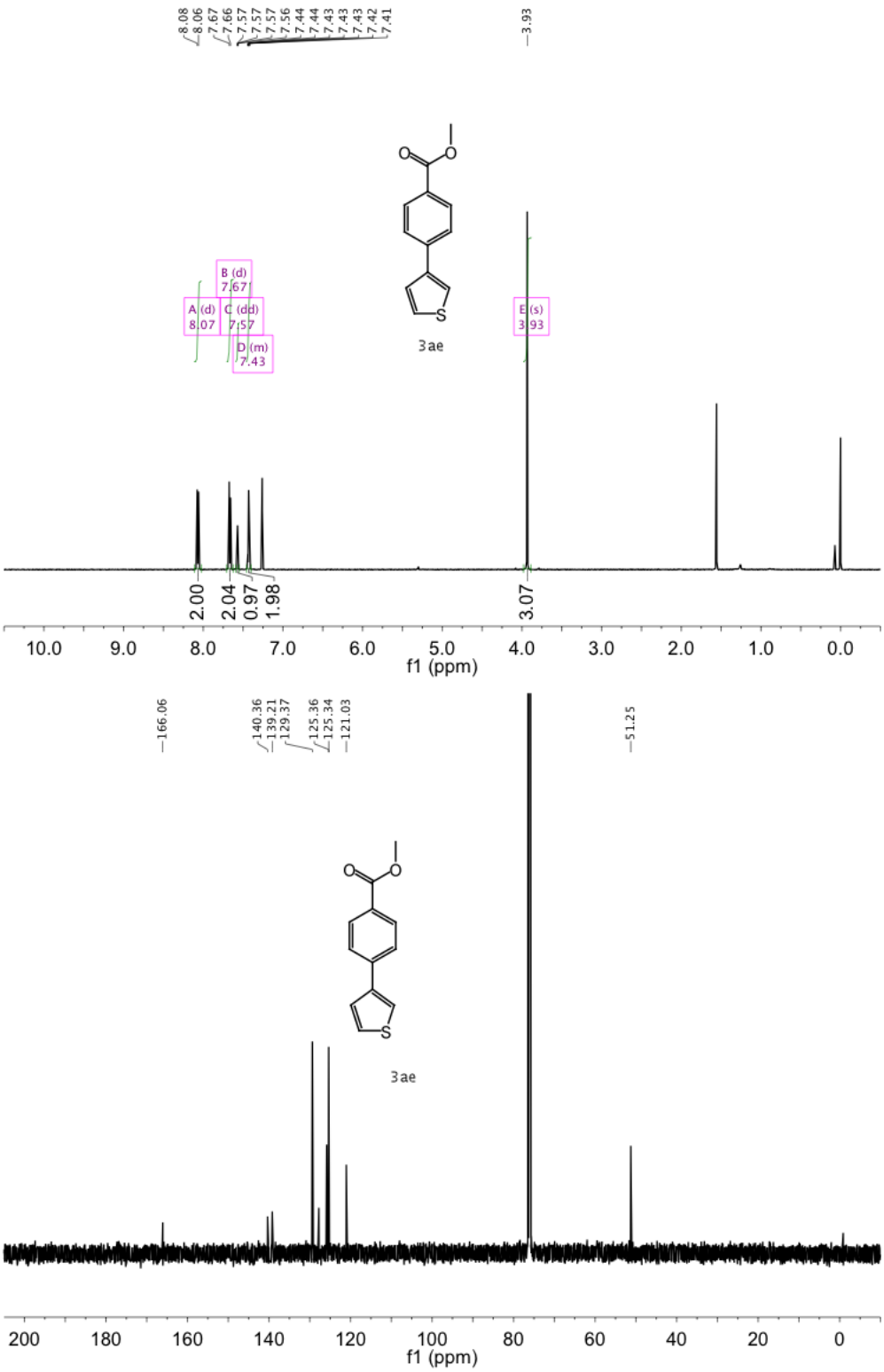


Figure SF 3.53. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 4-(thiophen-3-yl)benzoate in $CDCl_3$.

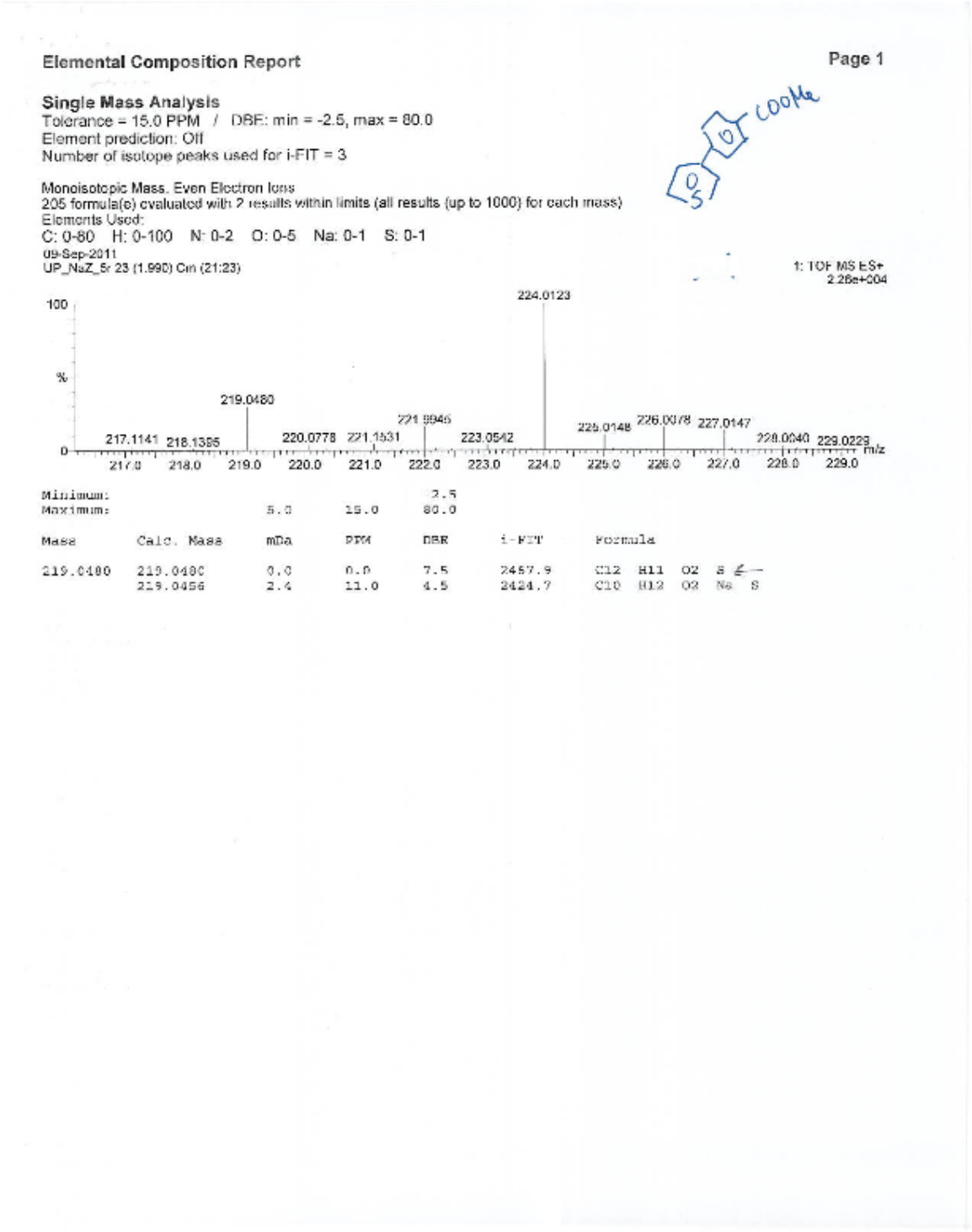


Figure SF 3.54. HRMS of methyl 4-(thiophen-3-yl)benzoate.

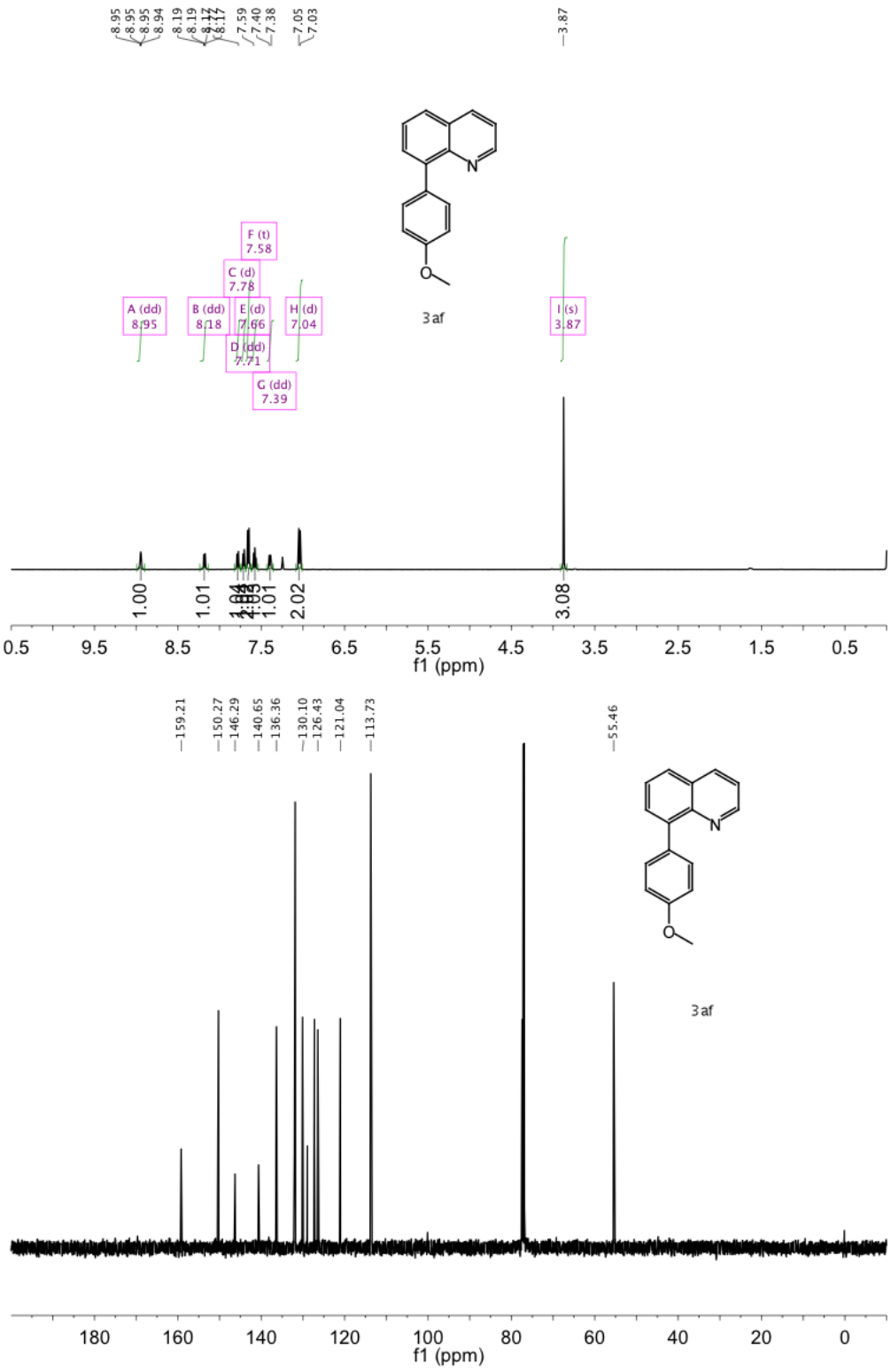


Figure SF 3.55. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 8-(4-methoxyphenyl)quinoline in $CDCl_3$.

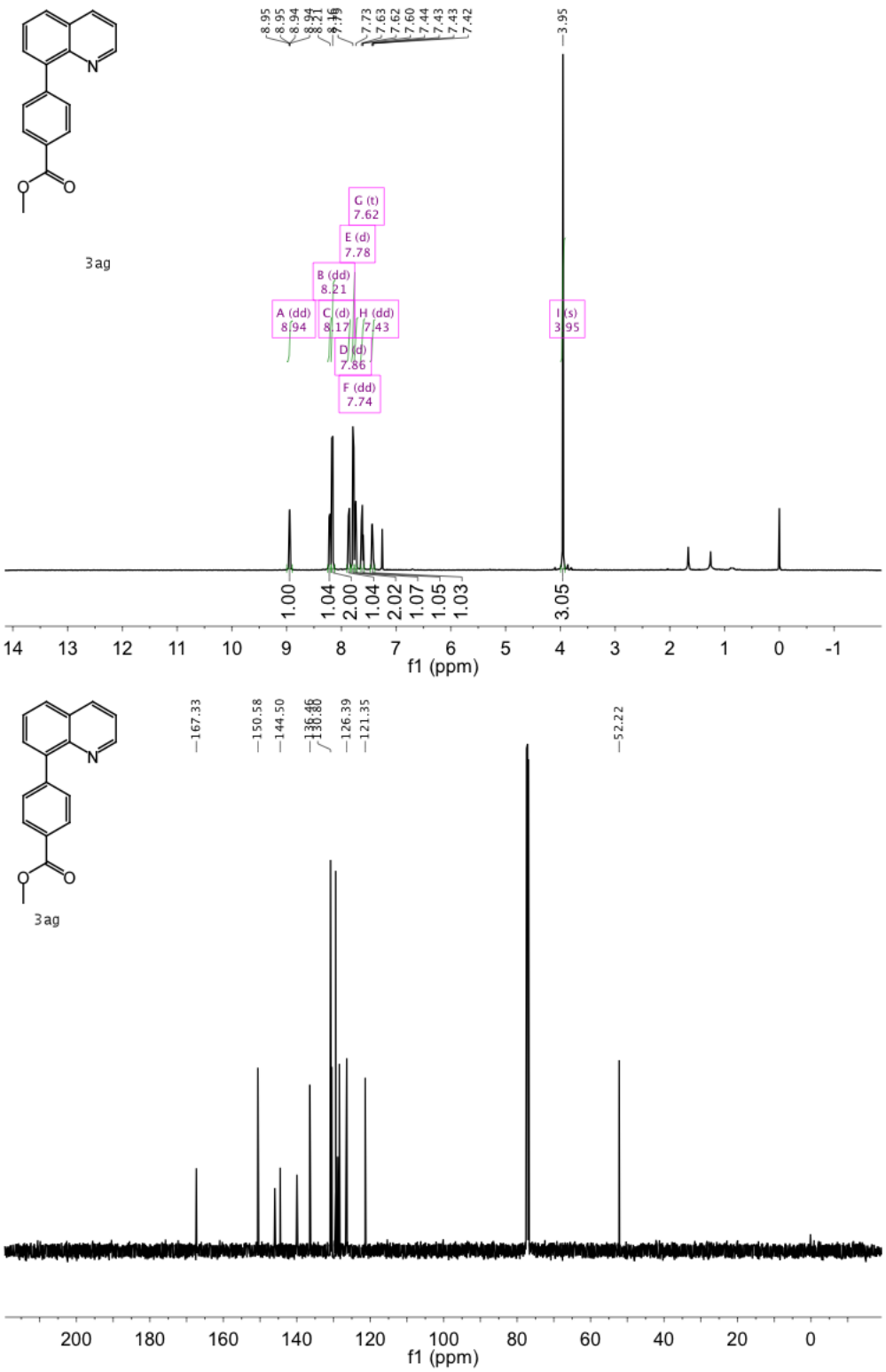


Figure SF 3.56. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 4-(quinolin-8-yl)benzoate in $CDCl_3$.

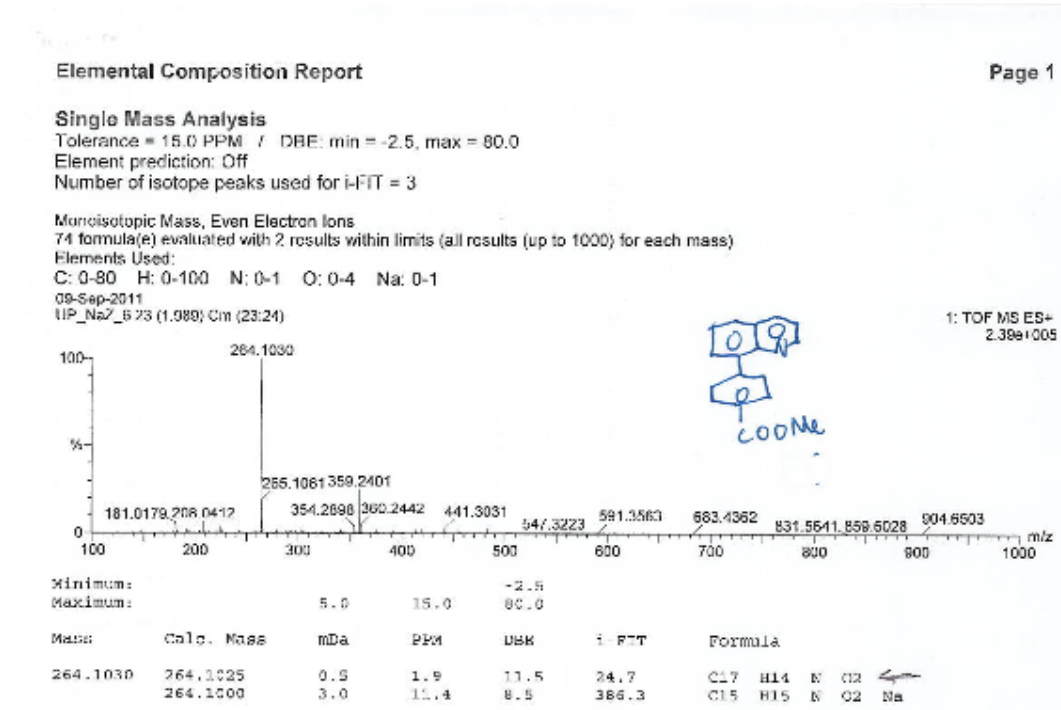


Figure SF 3.57. HRMS of methyl 4-(quinolin-8-yl)benzoate.

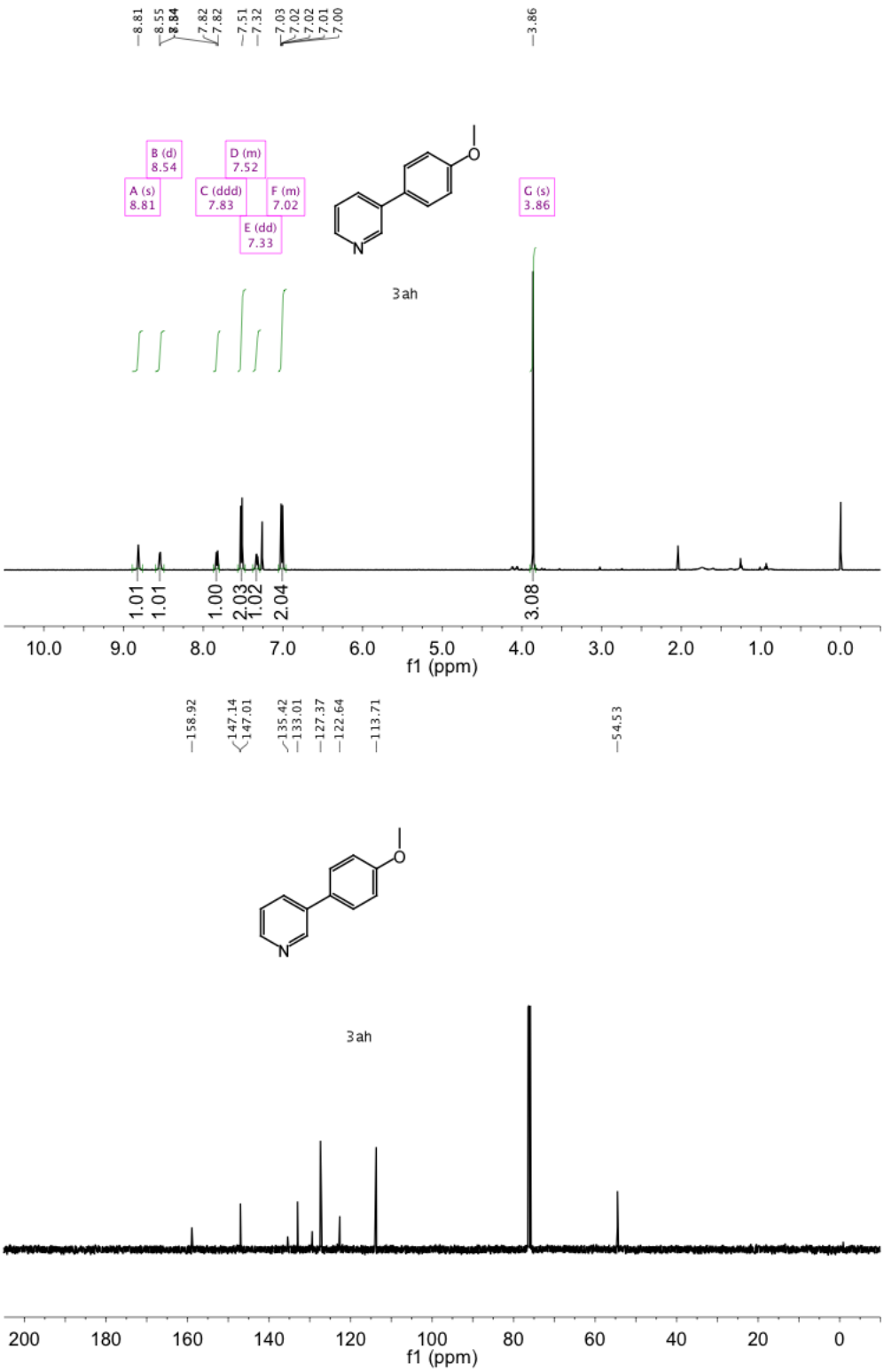


Figure SF 3.58. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 3-(4-methoxyphenyl)pyridine in $CDCl_3$.

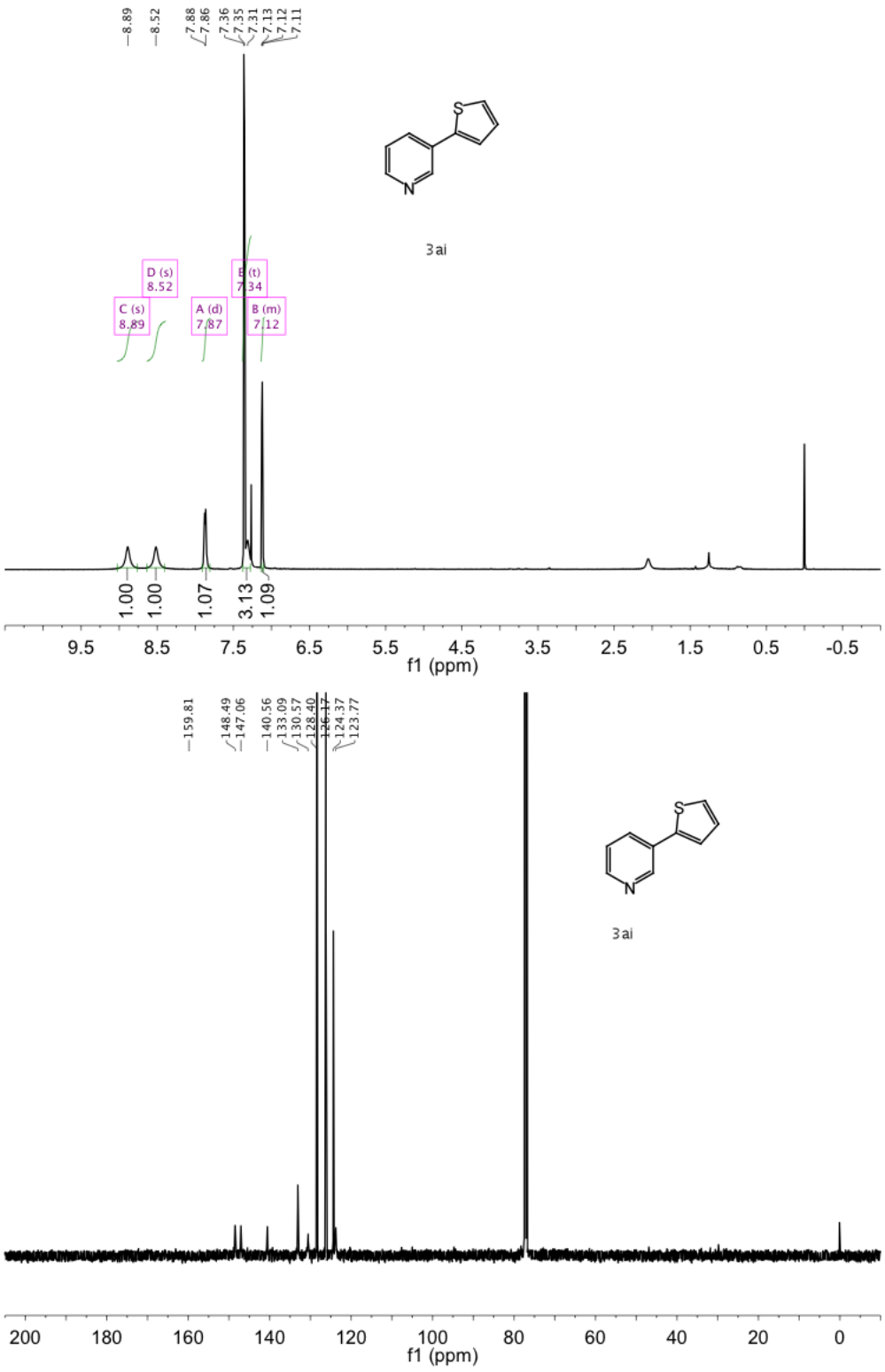


Figure SF 3.59. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 3-(thiophen-2-yl)pyridine in $CDCl_3$.

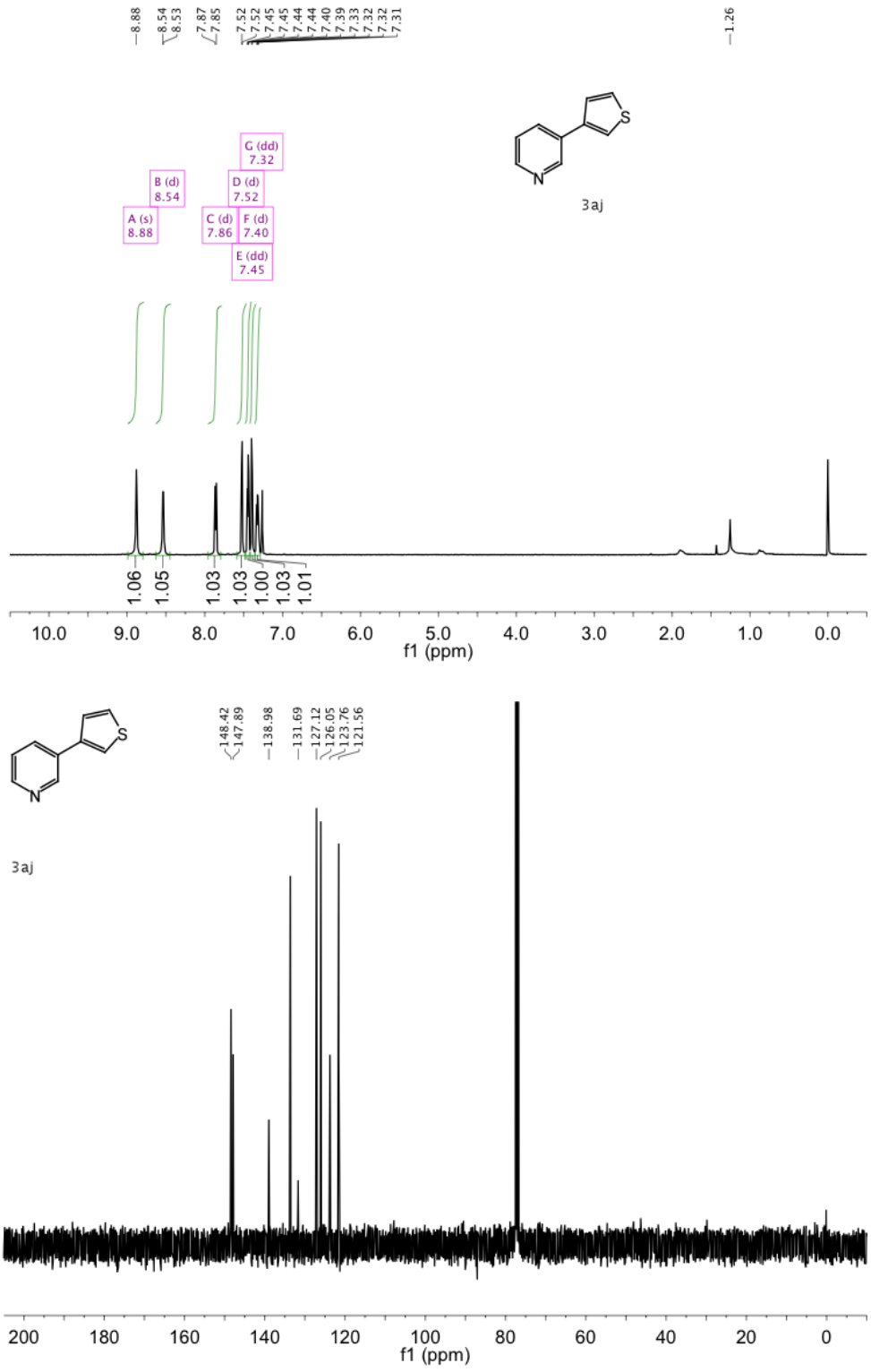


Figure SF 3.60. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 3-(thiophen-3-yl)pyridine in $CDCl_3$.

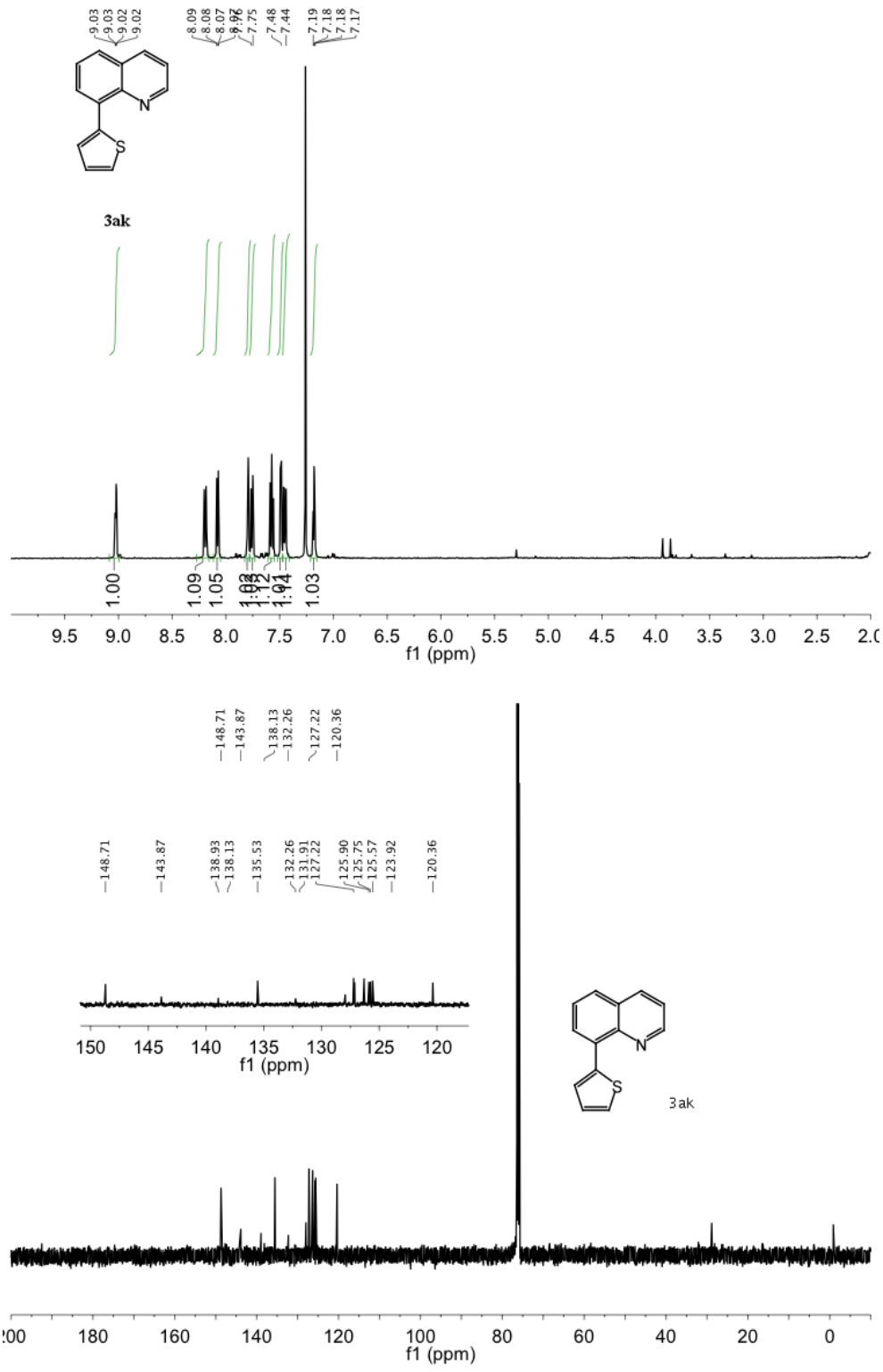


Figure SF 3.61. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 8-(thiophen-2-yl)quinoline in $CDCl_3$.

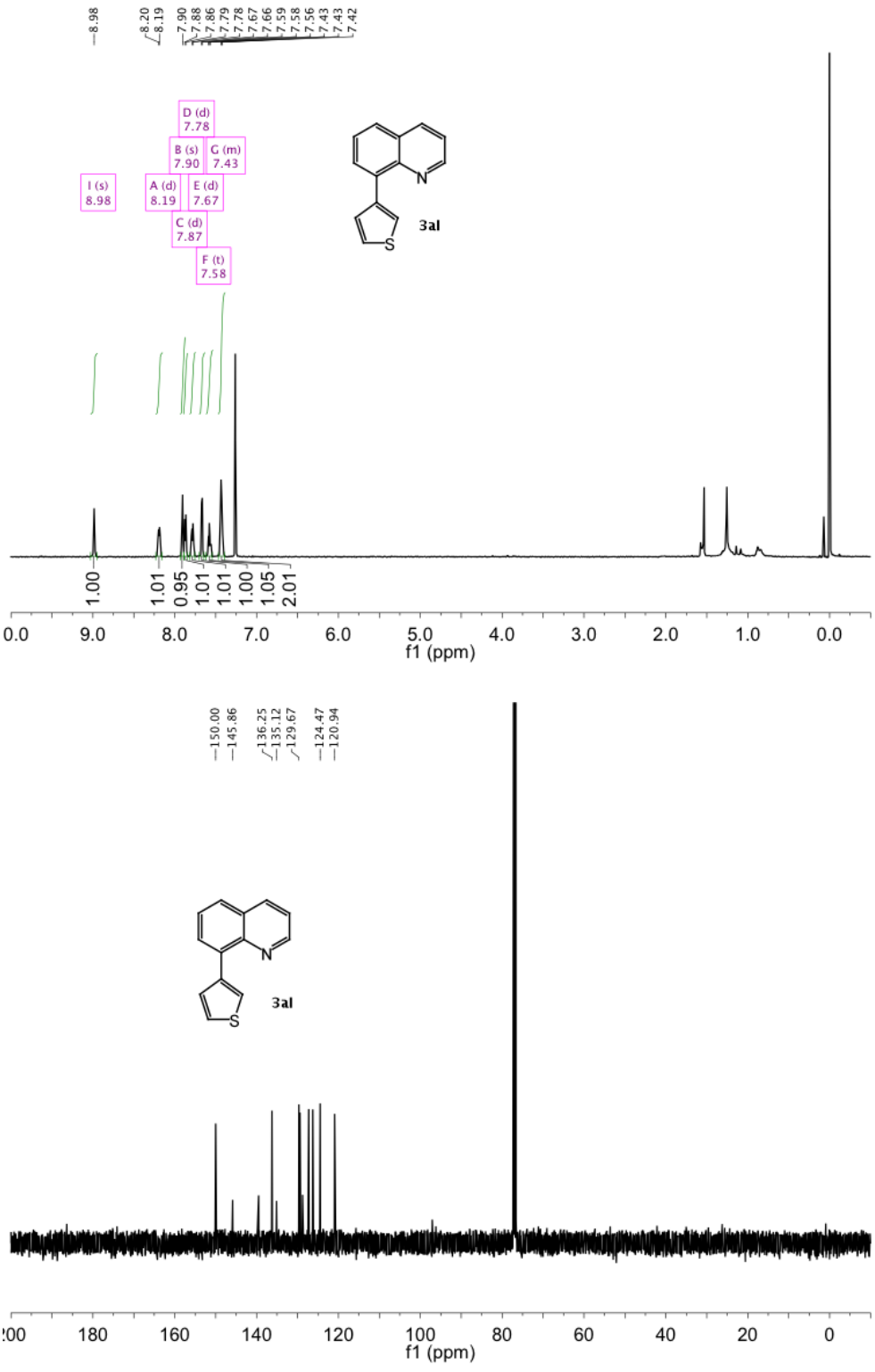


Figure SF 3.62. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 8-(thiophen-3-yl)quinoline in $CDCl_3$.

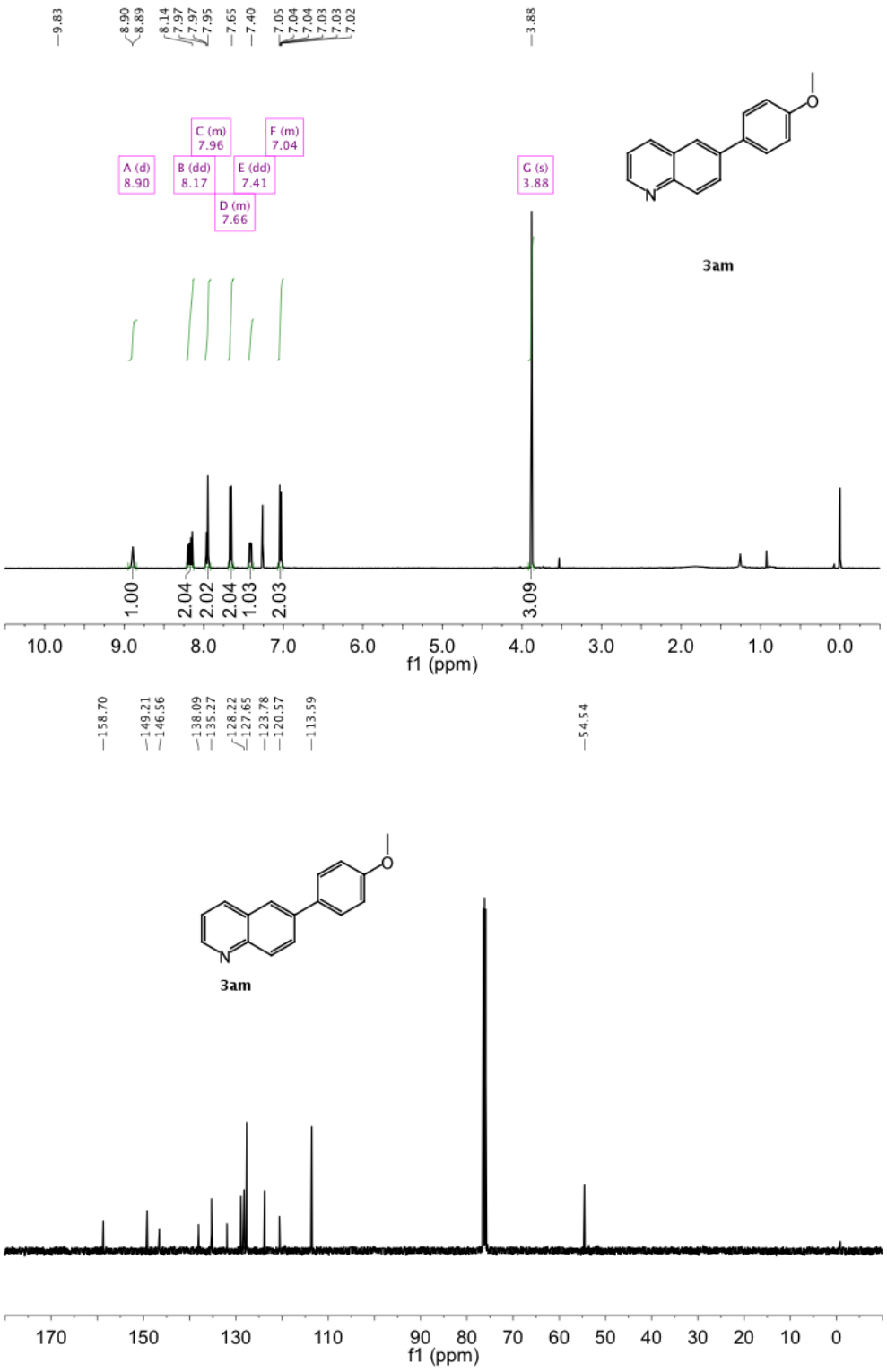


Figure SF 3.63. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 6-(4-methoxyphenyl)quinoline in $CDCl_3$.

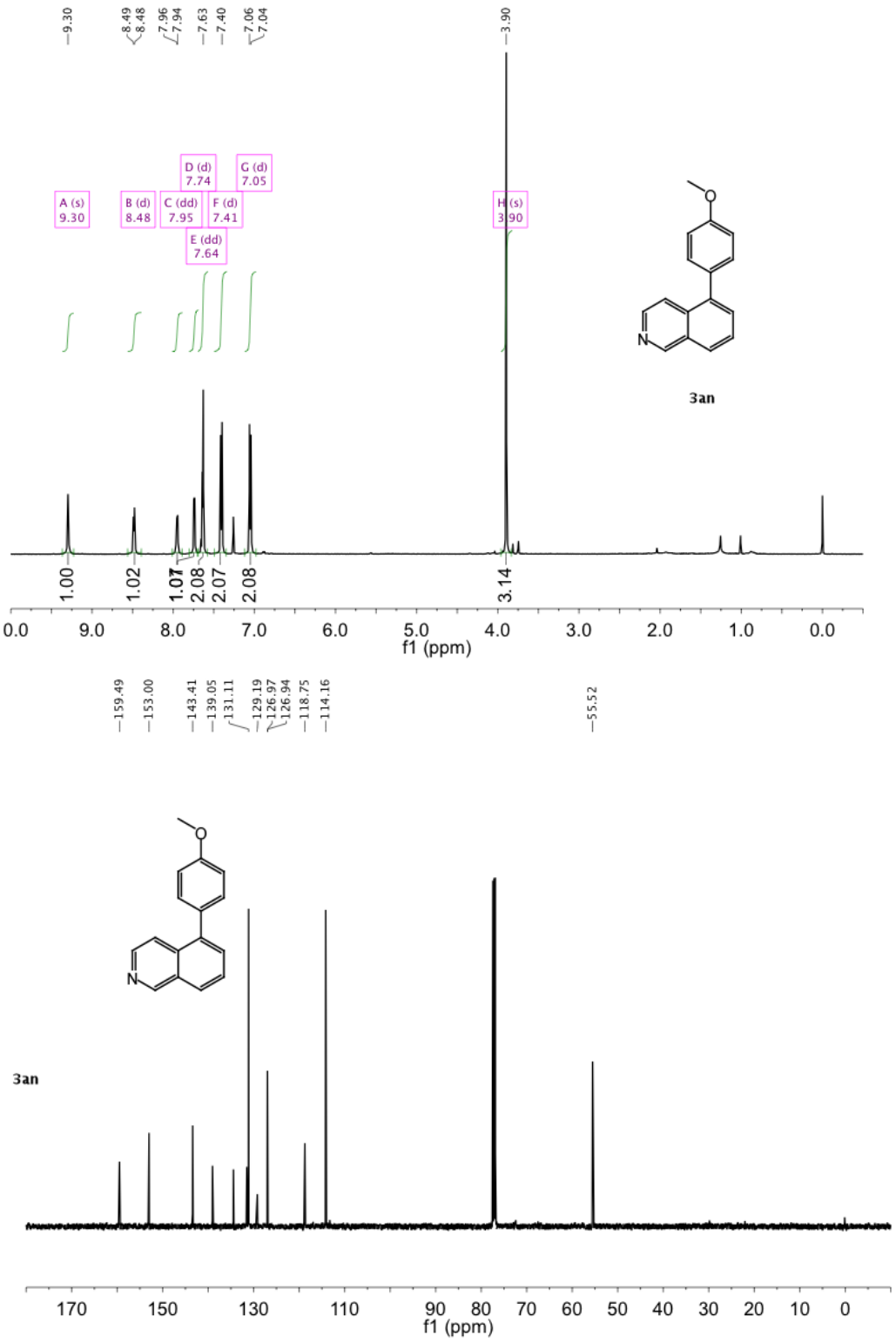


Figure SF 3.64. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 5-(4-methoxyphenyl)isoquinoline in $CDCl_3$.

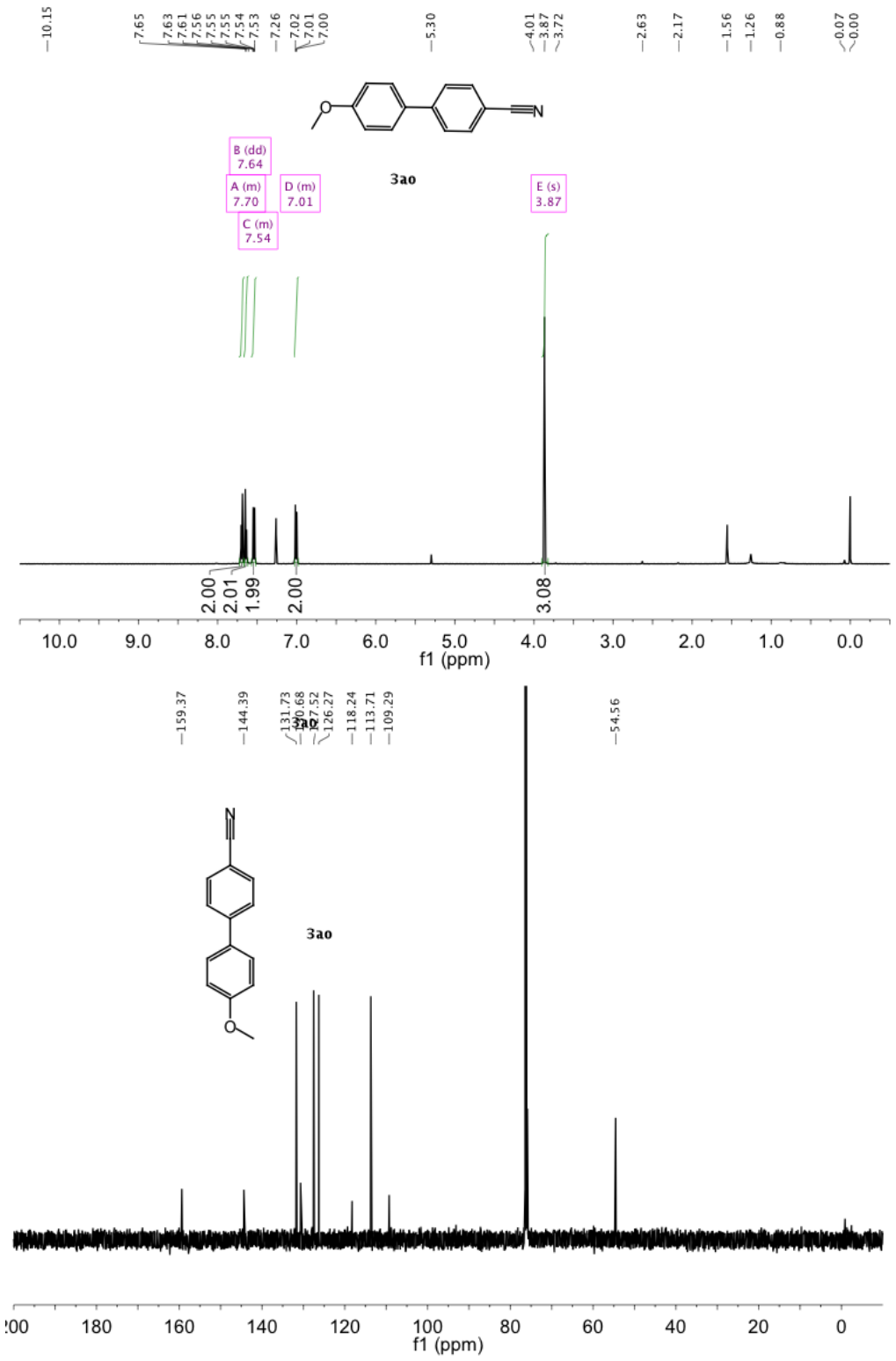


Figure SF 3.65. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 4'-methoxy-[1,1'-biphenyl]-4-carbonitrile in $CDCl_3$.

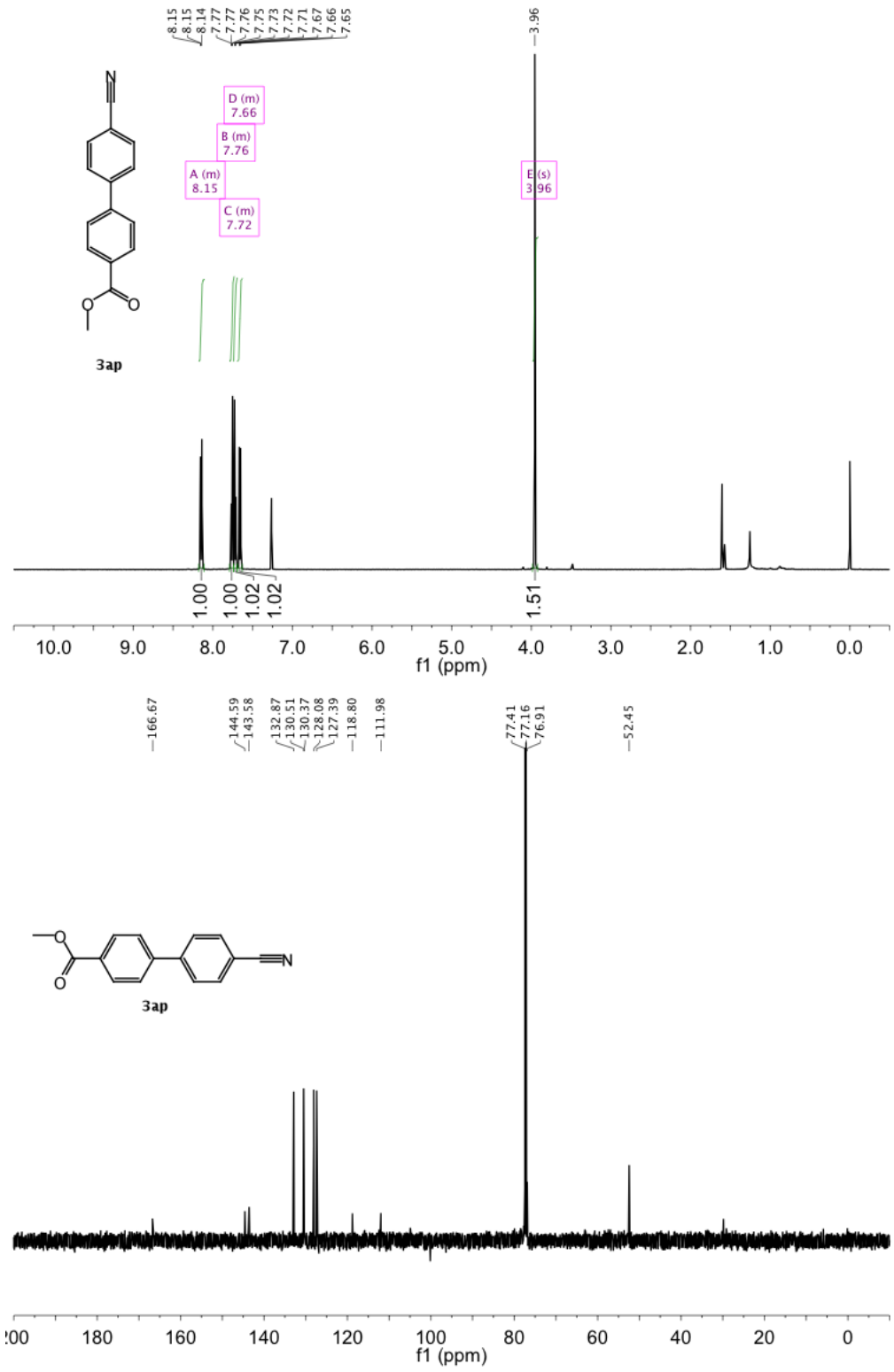


Figure SF 3.66. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 4'-cyano-[1,1'-biphenyl]-4-carboxylate in $CDCl_3$.

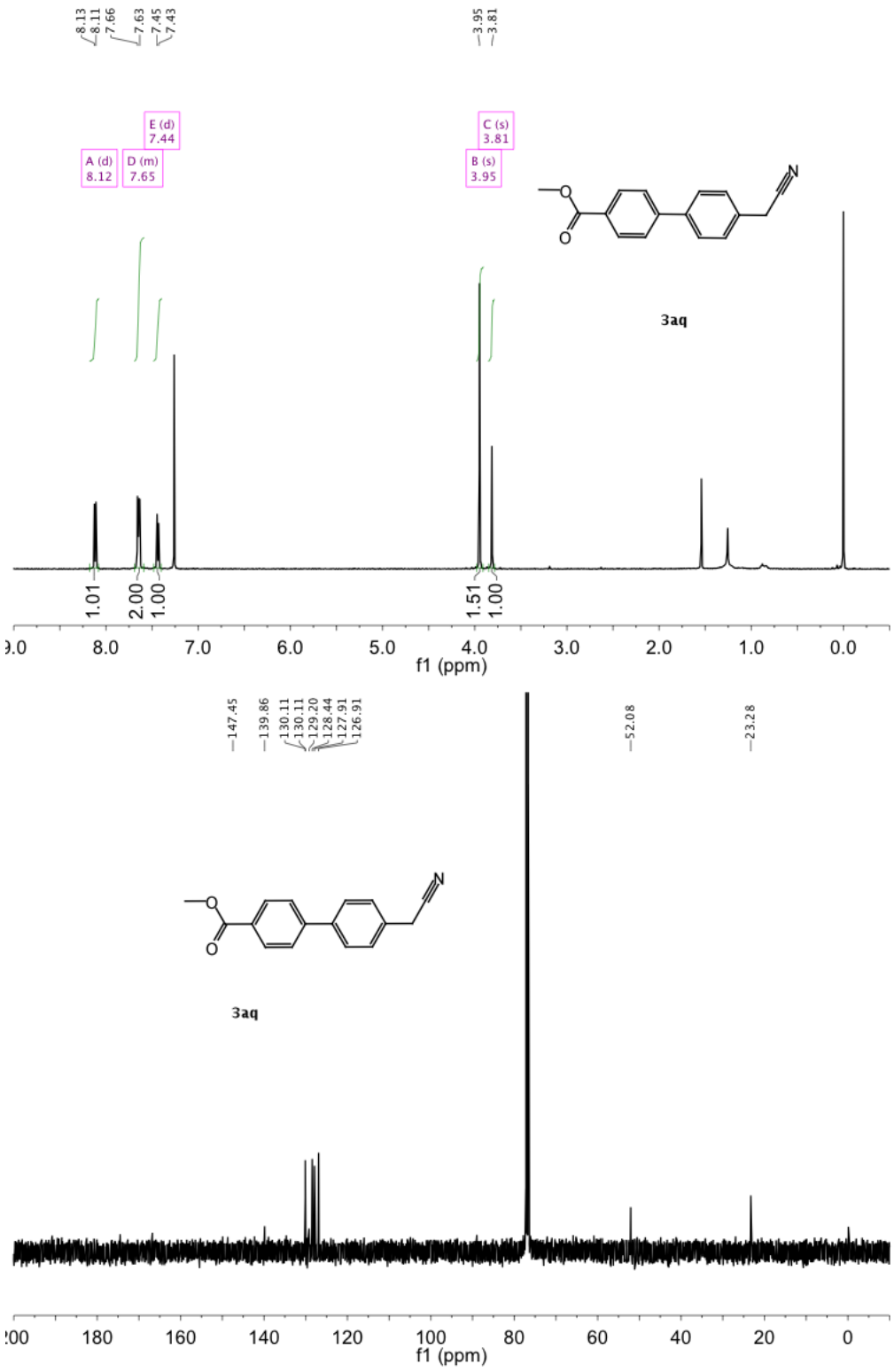
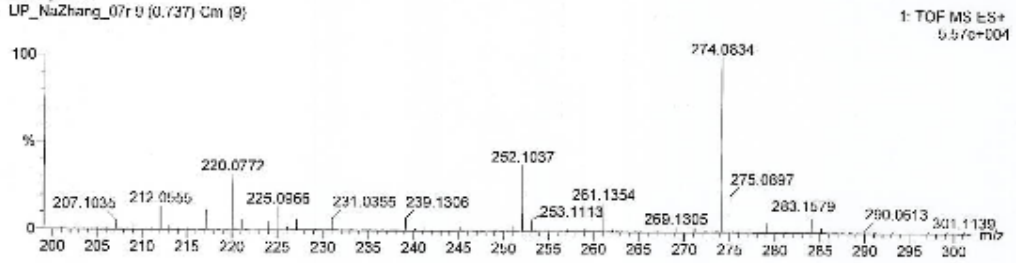


Figure SF 3.67. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of methyl 4'-(cyanomethyl)-[1,1'-biphenyl]-4-carboxylate in $CDCl_3$.

Elemental Composition Report Page 1

Single Mass Analysis
Tolerance = 8.8 PPM / DBE: min = -2.5, max = 80.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
420 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-80 H: 0-100 B: 0-1 N: 0-2 O: 0-10 Na: 0-1
20 Sep-2011
UP_NaZhang_07r 9 (0.737) Cm (9)



Minimum:				-2.5		
Maximum:		5.0	8.8	80.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
274.0834	274.0828	0.6	2.2	17.5	97.2	C20 H9 B N
	274.0844	-1.0	-2.6	10.5	91.2	C16 H13 N O2 Na

Figure SF 3.68. HRMS of methyl 4'-(cyanomethyl)-[1,1'-biphenyl]-4-carboxylate.

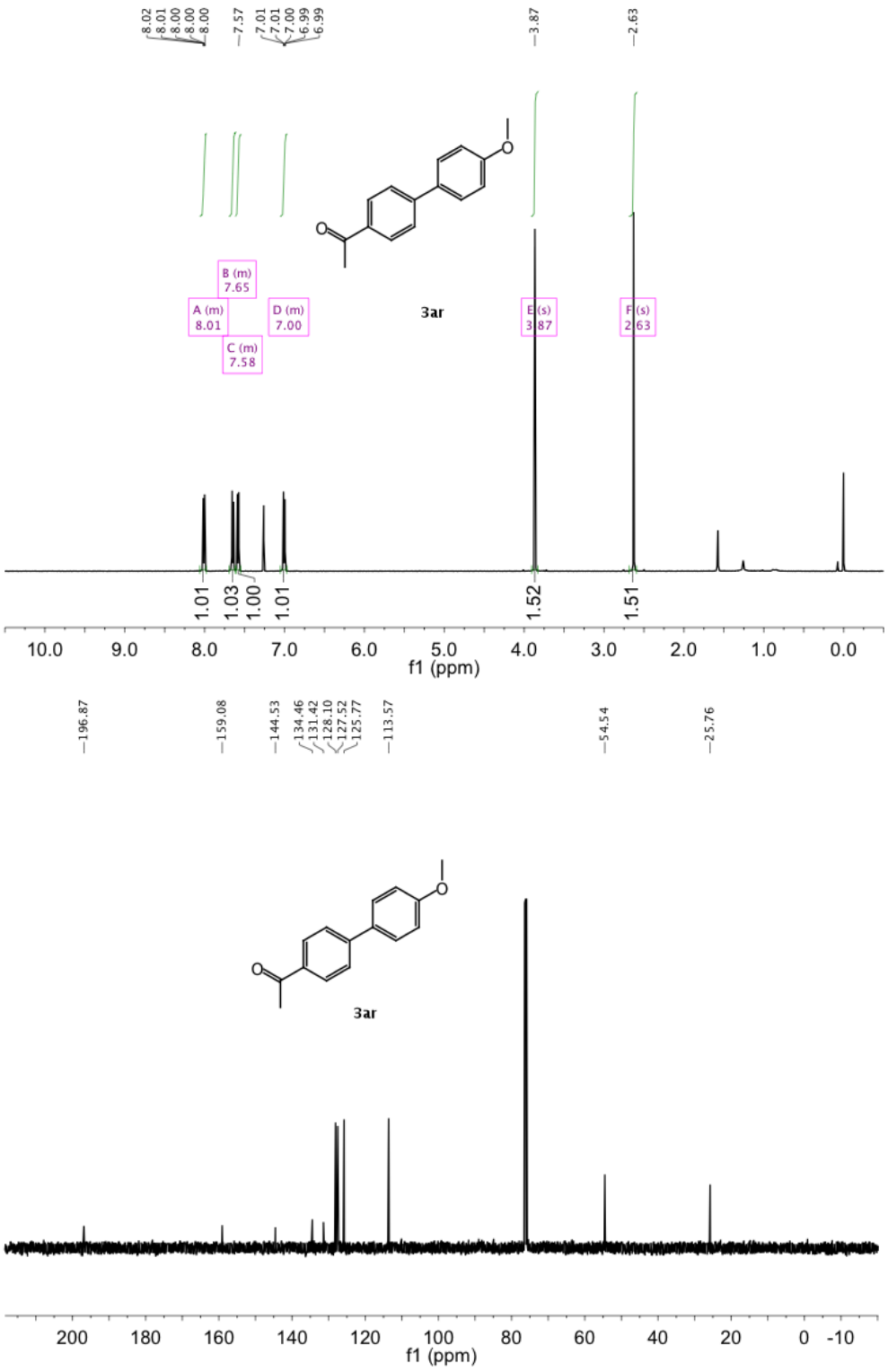


Figure SF 3.69. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 1-(4'-methoxy-[1,1'-biphenyl]-4-yl)ethanone in $CDCl_3$.

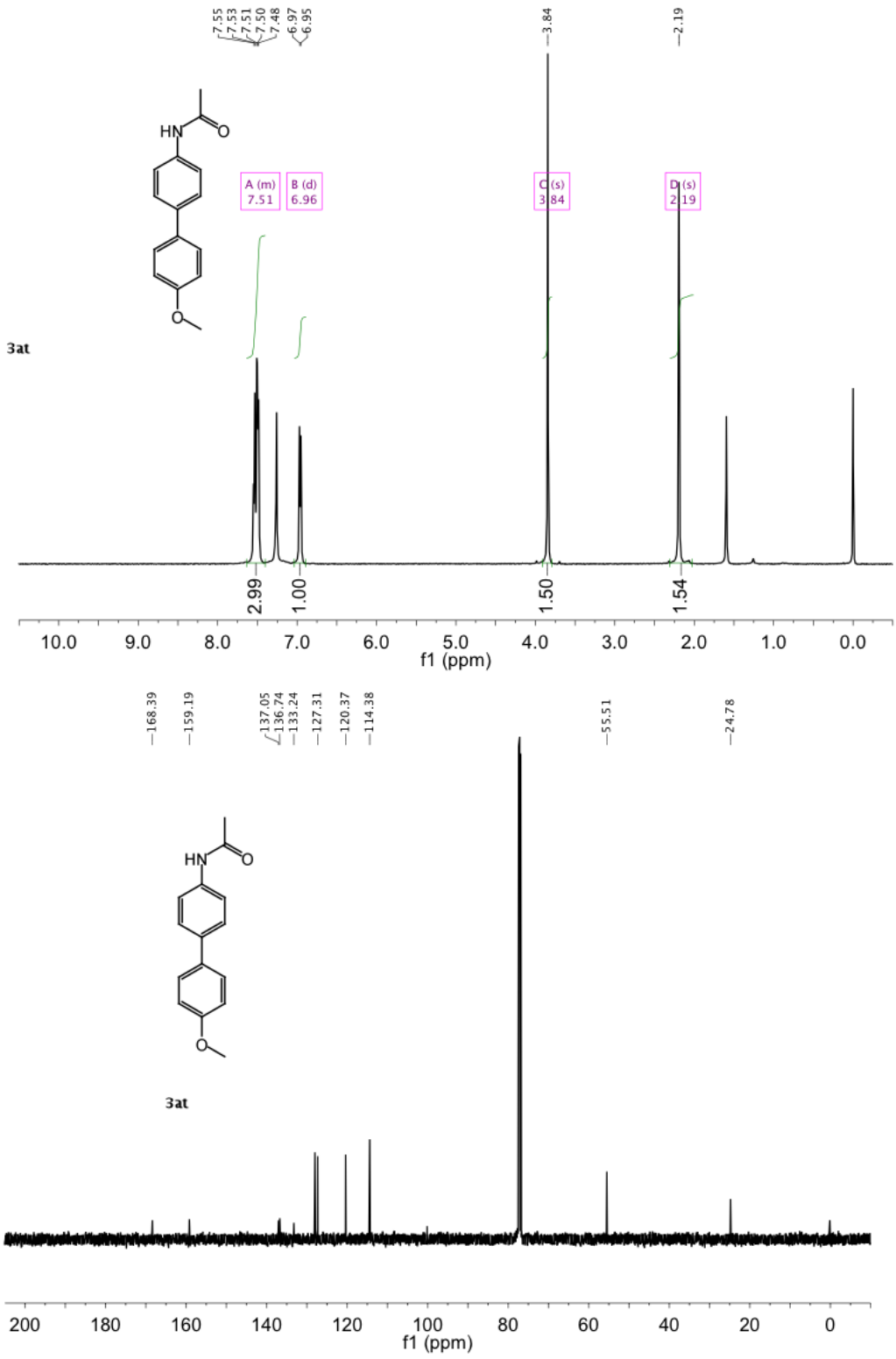


Figure SF 3.70. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of N-(4'-methoxy-[1,1'-biphenyl]-4-yl)acetamide in $CDCl_3$.

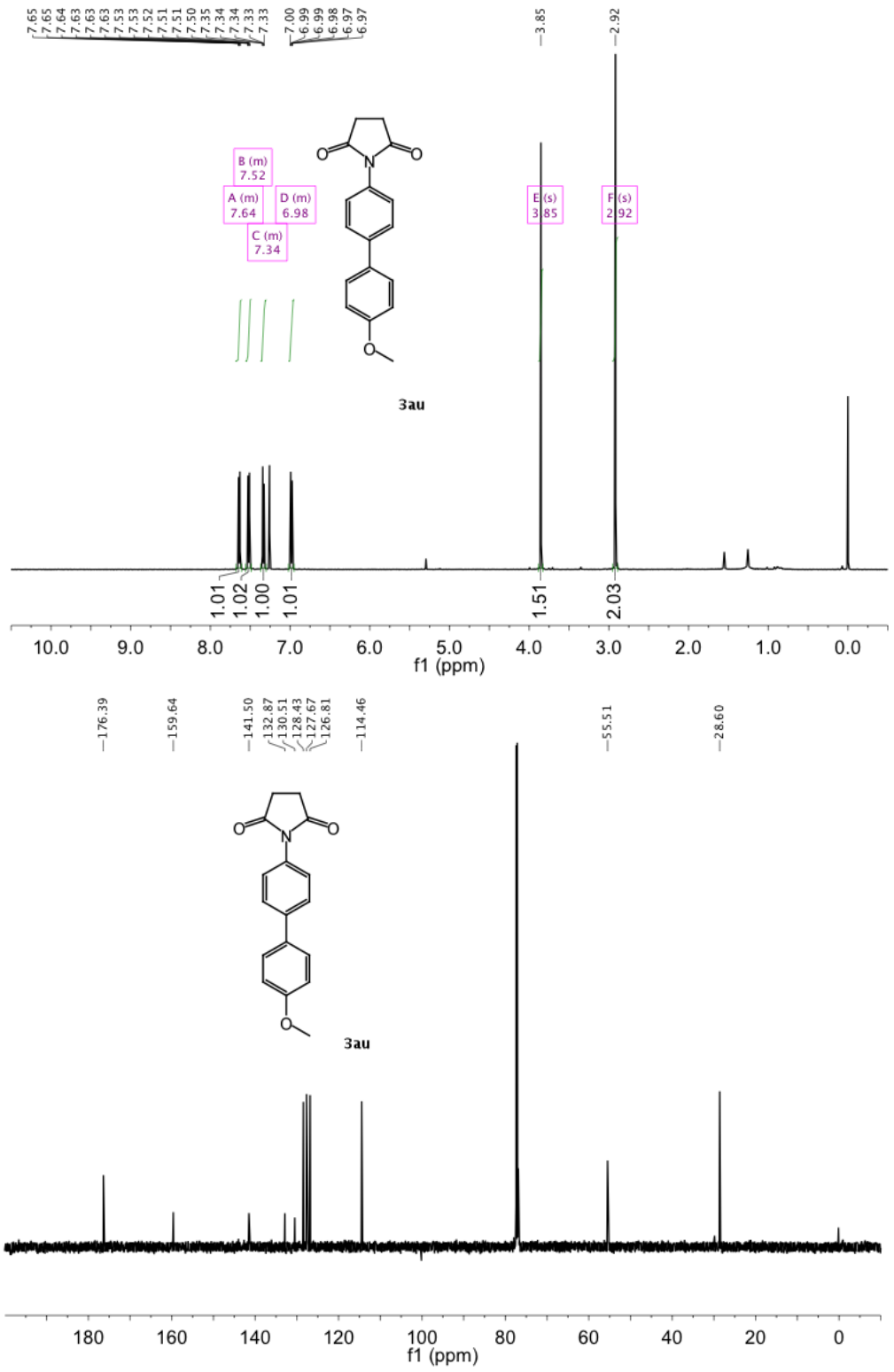


Figure SF 3.71. ^{1}H-NMR (top, 500 MHz) and ^{13}C-NMR (bottom, 125 MHz) spectra of 1-(4'-methoxy-[1,1'-biphenyl]-4-yl)pyrrolidine-2,5-dione in $CDCl_3$.

3.1.6 Account of Contribution

I contributed to half the experimental work as well as participated in manuscript organization and revising.

3.1.7 References

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3.2 Comparison of Efficiencies of Six Aryl Phenol Derivatives in Nickel Catalyzed Suzuki-Miyaura Cross-Coupling of Aryl Neopentylglycolboronates

3.2.1 Introduction

In the introduction, it has been established that Ni is less expensive and more reactive toward C-O based electrophiles[2] than Pd. So far nickel has been employed as an alternative catalyst in Suzuki-Miyaura cross-coupling[3-11] for a variety of aryl C-O based electrophiles such as aryl sulfonates,[12-21] ethers,[22] esters, carbonates,[23] carbamates,[23-26] sulfamates, [23,25,26] and phosphates[27] with arylboronic acids, and for the case of aryl methyl ethers,[22] with aryl neopentylglycolboronates. However, the reaction conditions for nickel catalyzed cross-coupling of aryl phenol derivatives and arylboronic acids or neopentylglycolboronates are delicate.[2] A slight change of base, temperature or water amount leads to dramatically different results.[2]

For our group, boronic esters are more favored than boronic acids in Suzuki-Miyaura cross-coupling reactions for several reasons. First, boronic esters can be used in stoichiometric amounts because they are monomeric under anhydrous conditions whereas boronic acids form anhydrides.[4] Thus, for purposes such as stepwise polymerization, boronic esters are needed to achieve high molecular mass polymers.[28] Second, while boronic esters can be purified by column chromatography, boronic acids are waxy solids, difficult to purify. Last but not least, boronic esters are less sensitive than boronic acids in basic conditions to side reactions such as protodeborylation.[4]

Two methods are applied to prepare boronic esters: the esterification of boronic acids[29] and transition metal-catalyzed borylation of aryl halides.[2,29] Transition metal-catalyzed borylation provides a one-step synthesis of boronic esters.[2] In previous chapters, a method of inexpensive Ni-catalyzed borylation reactions of aryl halides[12,30,31] and sulfonates[32] was discussed. Aryl neopentylglycolboronates are less expensive and more atom economical than the currently more commonly used pinacolboronates.[30] The versatile Ni^{II} catalyzed borylation of aryl halides and

sulfonates with neopentylglycolborane generated *in situ* from neopentylglycol and $BH_3 \bullet S(CH_3)_2$ tolerates a variety of *ortho-, meta-* and *para*-electrophilic functional groups and provides excellent yields.[31,33] Some preliminary data suggested that $NiCl_2$(dppe) catalysts can cross-couple aryl halides with aryl neopentylglycolboronates in moderate to good yields.[12,30] Encouraged by these results, preliminary cross-coupling reactions between aryl neopentylglycolboronates and aryl sulfonates were also reported.[12] A more comprehensive study on the cross-coupling of aryl sulfonates and sulfamates was recently reported.[34] So far, only aryl sulfonates,[12,34] sulfamates,[34] and methyl ethers[22] have been shown to be active in the cross-coupling reaction with aryl neopentylglycolboronates. However, other electrophiles such as aryl pivalates, carbonates and carbamates have not been investigated in cross-coupling with aryl neopentylglycolboronates.

After a survey of the literature on C-O based electrophiles in cross-coupling reactions, we found that the reaction conditions employed Ni^{II}- or Ni^0-based catalysts, ligands, boron sources, bases, solvents, and temperatures, differed from one group of C-O electrophile to another. The only comparative study on the reactivity of different C-O electrophiles was recently reported for cross-coupling with potassium aryl and heteroaryl trifluoroborates.[4]

In search for other C-O based electrophiles for nickel catalyzed Suzuki-Miyaura cross-coupling reactions, we compared the reactivity of six different aryl containing C-O based electrophiles in Ni-catalyzed Suzuki-Miyaura cross-coupling with aryl neopentylglycolboronates under four different catalytic systems. These four catalytic conditions were developed specifically for the cross-coupling of aryl methyl ethers[22] with aryl neopentylglycolboronates, aryl mesylates[34] with aryl neopentylglycolboronates, and respectively of aryl esters, carbamates and carbonates with arylboronic acids[23,26] and aryl boroxines.[35] The results are discussed in this Chapter.

Selection of the Ni-Based Catalysts. Nickel-catalysis was used for the cross-coupling of aryl containing C-O based electrophiles with arylboronic acids, anhydrides and boronic esters.[2] Different reaction conditions and catalysts are required for the cross-coupling of aryl containing C-O based electrophiles with arylboronic acids, anhydrides and boronic esters.[2] From the entire

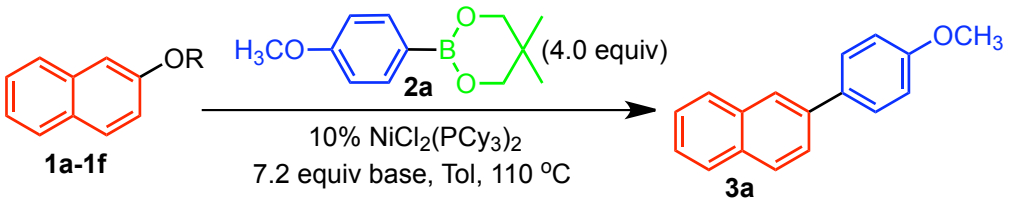
group of C-O based electrophiles only aryl mesylates and tosylates were investigated in cross-coupling with both boronic acids and boronic esters.[2] Cross-coupling of aryl sulfonates with boronic acids proceeds in the presence of Ni^{II}-based catalysts at high temperature and in the presence of Ni^{0}-based catalysts at low temperature. The Ni^{II}-based catalysts of choice for this reaction are $NiCl_2(PCy_3)_2/K_3PO_4$/dioxane at 130 °C,[16] and $NiCl_2$(dppe) or $NiCl_2$(dppp), both in toluene and in dioxane at temperatures between 80 °C and 100 °C.[15,19] A Ni^{0} system that is found active in cross-coupling of aryl sulfonates with arylboronic acids at room temperature is $Ni(COD)_2/PCy_3/K_3PO_4$/THF.[14] Preliminary results on the cross-coupling of aryl neopentylglycolboronates demonstrated that they can cross-couple with aryl chlorides, bromides and iodides with $NiCl_2$(dppe)/dppe/K_3PO_4 or NaOH in dioxane at 110 °C.[30] However, the same catalyst is completely inactive in the cross-coupling of aryl neopentylglycolboronates with aryl sulfonates.[30] Nevertheless, preliminary results demonstrated that $Ni(COD)_2/PCy_3/K_3PO_4$ in THF at room temperature is an excellent catalyst for the cross-coupling of aryl mesylates and tosylates with aryl neopentylglycolboronates.[12] The only other C-O based electrophile that was cross-coupled with aryl neopentylglycolboronates is the aryl methyl ether.[22] The catalyst of choice for this cross-coupling is $Ni(COD)_2/PCy_3$/CsF in toluene at 120 °C.[22] All other C-O based electrophiles, including esters, carbonates, carbamates and sulfamates were cross-coupled only with arylboronic acids by using $NiCl_2(PCy_3)_2/K_3PO_4$ in toluene, dioxane or xylene at temperatures ranging from 80 ºC to 150 ºC.[23-26,35-38] Reaction conditions specific for individual classes of C-O electrophiles namely for aryl mesylates ($Ni(COD)_2/PCy_3/K_3PO_4$/THF/23 ^{o}C), aryl methyl ethers ($Ni(COD)_2/PCy_3$/CsF/toluene/120 ^{o}C), for aryl esters, carbonates, carbamates and sulfamates ($Ni(COD)_2/PCy_3/K_3PO_4$/toluene/120 ^{o}C), and a modified catalyst specific for aryl methyl ethers were investigated.

3.2.2 Results and Discussion

The Reactivity of Aryl C-O Based Electrophiles in Cross-Coupling with Aryl Neopentylglycolboronates Catalyzed by $NiCl_2(PCy_3)_2/K_3PO_4$ in Toluene at 110 ºC. The reaction conditions employed by Garg's laboratory [23,26,36] for the cross-coupling of a diversity of

aryl C-O based electrophiles including aryl-OPiv, -OCO_2NEt_2, -OBoc, and -OSO_2NMe_2 with arylboronic acids, were used to investigate the cross-coupling of all aryl C-O electrophiles with aryl neopentylglycolboronates. These conditions employ $NiCl_2(PCy_3)_2$ as catalyst, and flame-dried K_3PO_4 as base in toluene at 110 ºC. The results from Table 3.6 showed that under these conditions aryl–OMs, -OSO_2NMe_2 and -OCO_2NEt_2 gave cross-coupling products in moderate yields (25%, 54% and 34%, Table 3.6, entries 1, 2 and 5). However, no reaction was observed for aryl-OBoc and -OMe electrophiles, and only a low yield was obtained for -OPiv (6%, Table 3.6, entry 3). Table 3.6 reports also the same cross-coupling experiments in which the K_3PO_4 base was replaced with CsF. With the exception of the experiments from entries 7 and 8, which showed very low efficiency, all other experiments demonstrated that CsF is not an active base for cross-couplings performed under the reaction conditions reported in Table 3.6.

Table 3.6. Cross-Coupling of 2-Naphthyl Containing C-O Electrophiles with *para*-Methoxyphenyl Neopentylglycolboronate Catalyzed by $NiCl_2(PCy_3)_2$/ K_3PO_4 or CsF in Toluene at 110 °C



entry	OR	base	Time (h)	Yield (%)[a]
1	OMs	K_3PO_4	12	25
2	OSO_2NMe_2	K_3PO_4	12	54
3	OPiv	K_3PO_4	12	6
4	OBoc	K_3PO_4	24	0
5	$OCONEt_2$	K_3PO_4	24	34
6	OMe	K_3PO_4	24	13
7	OMs	CsF	12	7
8	OSO_2NMe_2	CsF	12	1
9	OPiv	CsF	12	0
10	OBoc	CsF	24	0
11	$OCONEt_2$	CsF	24	0
12	OMe	CsF	24	0

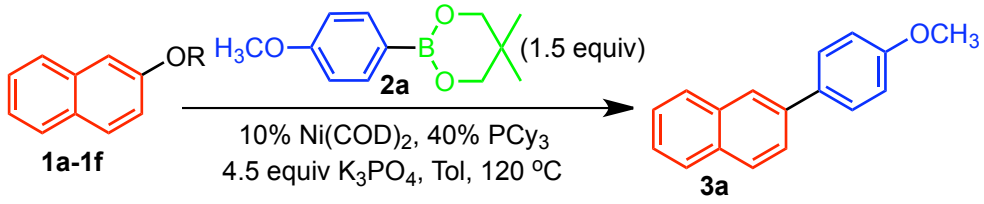
[a]Isolated yield.

The yields of the biaryl products using aryl neopentylboronates were generally lower than those obtained for the cross-coupling of the same C-O electrophiles with arylboronic acids.[23,26,36] It was reported that a certain amount of water facilitated the transmetalation step of the cross-coupling reaction with arylboronic acids.[24,26] However, in contrast to the reaction with arylboronic acid, no water is generated during the cross-coupling of aryl neopentylglycolboronates. Therefore, the Ni-catalysis conditions previously employed for arylboronic acids might not be the most suitable for aryl boronates.

The Reactivity of Aryl C-O Based Electrophiles in Cross-Coupling with Aryl Neopentylglycolboronates Catalyzed by $Ni(COD)_2/K_3PO_4$ in Toluene at 120 °C.

Since CsF did not show activity for coupling of aryl neopentylglycolboronates with most aryl C-O electrophiles, the catalytic system employed by Chatani laboratory for the cross-coupling of aryl methyl ethers with aryl neopentylglycolboronates[22] involving $Ni(COD)_2/PCy_3$/CsF/toluene/120 °C was modified by changing its base from CsF to $K_3PO_4 \cdot xH_2O$ while maintaining toluene as solvent at 120 °C. All aryl C-O based electrophiles from Table 3.7 were cross-coupled to a certain extent under these conditions in low to moderate yield. However, the aryl -OBoc and –OMe, which were previously inert under the $NiCl_2(PCy_3)_2$ catalysis (Table 3.6, entries 4 and 6), reacted under these conditions (Table 3.7, entries 4 and 6).

Table 3.7. Cross-Coupling of 2-Naphthyl Containing C-O Electrophiles with *para*-Methoxyphenyl Neopentylglycolboronate Catalyzed by $Ni(COD)_2/PCy_3/K_3PO_4$ in Toluene at 120 °C



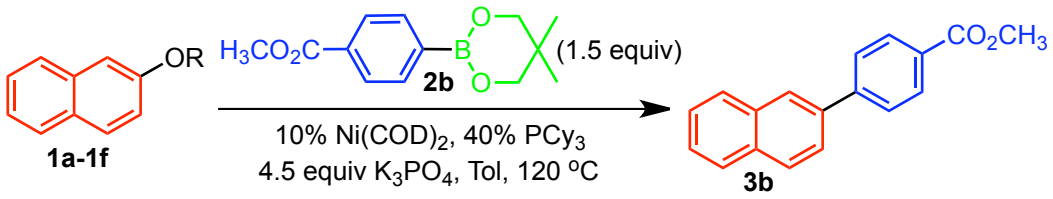
Entry	OR	Time (h)	Yield (%)[a]
1	OMs	18	59
2	OSO_2NMe_2	18	44
3	OPiv	36	33
4	OBoc	36	17
5	$OCONEt_2$	36	23
6	OMe	36	17

[a]Isolated yield.

To explore the electronic effect of the aryl neopentylglycolboronates, both electron-rich (Table 3.7) and electron-deficient (Table 3.8) aryl neopentylglycolboronates were studied. Under identical conditions, the electron-deficient arylboronic ester gave higher yields than the electron-

rich arylboronic ester with all types of C-O based electrophiles. This observation suggested that transmetalation step might be the rate-determining step in this reaction. Significant improvement was observed for -$OCONEt_2$ (40%) compared to 23% in the reaction with electron-rich aryl neopentylglycolboronates. The trend of the reactivity of aryl C-O based electrophiles was found to be: -OMs (52%) > -OSO_2NMe_2 (49%) > -OPiv (45%) > -OBoc (24%) > -OMe (22%) (Table 3.3). A similar reactivity was also found for Ni-catalyzed cross-coupling of C-O based electrophiles with potassium aryl and heteroaryl trifluoroborates.[21]

Table 3.8. Cross-Coupling of 2-Naphthyl Containing C-O Electrophiles with *para*-Methylcarboxylate Phenyl Neopentylglycolboronate Catalyzed by $Ni(COD)_2/PCy_3/K_3PO_4$ in Toluene at 120 °C



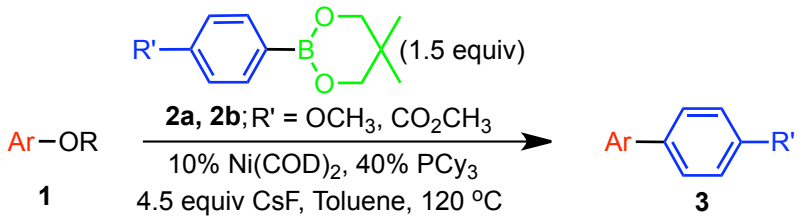
entry	OR	Time (h)	Yield (%)[a]
1	OMs	18	52
2	OSO_2NMe_2	18	49
3	OPiv	36	45
4	OBoc	36	24
5	$OCONEt_2$	12	40
6	OMe	36	22

[a]Isolated yield.

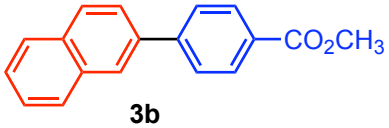
The Reactivity of Aryl C-O Based Electrophiles in Cross-Coupling with Aryl Neopentylglycolboronates Catalyzed by $Ni(COD)_2/PCy_3$/CsF in Toluene at 120 °C. By using CsF as base at 120 °C, the C-O bond of naphthyl methyl ethers was successfully cross-coupled with aryl neopentylglycolboronates in moderate to good yields with $Ni(COD)_2/PCy_3$ in toluene.[22] Inspired by this work, we applied these unmodified reaction conditions to all C-O based electrophiles. The optimized conditions for the methoxy leaving group were found to be very

specific and not applicable to other leaving groups. Aryl mesylates and sulfamates were cross-coupled with moderate yields (36% to 61%) (Table 3.9, **3b** and **3d**; OR = OMs, OSO_2NMe_2). This result is in agreement with the results obtained when $NiCl_2(PCy_3)_2/K_3PO_4$ was used in toluene at 110 °C (Table 3.6, entries 1 and 2) and also $Ni(COD)_2/PCy_3/K_3PO_4$ in toluene at 120 °C (Table 3.7, entries 1 and 2). In addition, cross-coupling of aryl carbamates gave poor yields (13%-14%, Table 3.9, **3b** and **3d**; OR = $OCONEt_2$) while -OPiv was almost inert (<3%) (Table 3.9, **3b** and **3d**; OR = OPiv). This low reactivity of the aryl ester leaving group (-OPiv) was also reported from Chatani laboratory in cross-coupling using the same catalytic system employed for –OAc leaving group.[22] Furthermore, the reactivity of cross-coupling of -OBoc was found to be highly dependent on the electronic character of the aryl neopentylglycolboronates. With electron-deficient aryl neopentylglycolboronates, a moderate yield (51%) was isolated (Table 3.9, **3b**; OR = OBoc).

Table 3.9. Cross-Coupling of Aryl Containing C-O Electrophiles with *para*-Substituted Aryl Neopentylglycolboronates Catalyzed by $Ni(COD)_2/PCy_3/CsF$ in Toluene at 120 °C

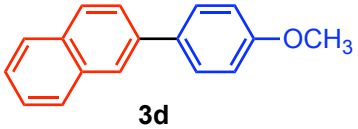


1 → 3



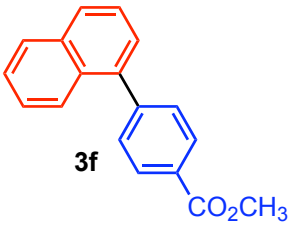
3b

OR = OMs : 12 h; 36%
OR = OSO_2NMe_2: 12 h; 42%
OR = OPiv : 12 h; 1%
OR = OBoc : 19 h; 51%
OR = $OCONEt_2$: 19 h; 14%
OR = OCH_3 : 18 h; 71%



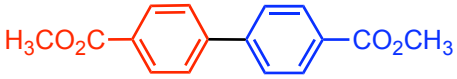
3d

OR = OMs : 12 h; 49%
OR = OSO_2NMe_2: 12 h; 61%
OR = OPiv : 20 h; <3%
OR = OBoc : 19 h; 3%
OR = $OCONEt_2$: 20 h; 13%
OR = OCH_3 : 18 h; 50%



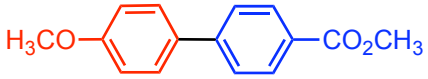
3f

OR = OMs : 12 h; 36%
OR = OBoc: 19 h; 21%



3i

OR = OMs : 24 h; 20%
OR = OSO_2NMe_2: 24 h; 38%
OR = OPiv : 24 h; 0%
OR = OBoc : 24 h; 0%
OR = $OCONEt_2$: 24 h; 0%
OR = OCH_3 : 24 h; 0%



3j

OR = OMs : 24 h; 23%
OR = OBoc : 24 h; 0%
OR = $OCONEt_2$: 24 h; 0%

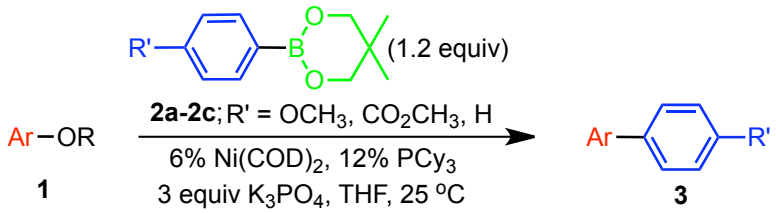
Isolated yield in all cases

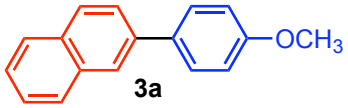
However, with electron-rich aryl neopentylglycolboronates, almost no product was separated (3 %) (Table 3.9, **3d**; OR = OBoc). Cross-coupling of *ortho*-substituted aryl carbonate substrate gave a diminished yield (21%) (Table 3.9, **3f**; OR = OBoc). Aryl methyl ether substrates cross-coupled with aryl neopentylglycolboronate with the highest yields compared to other C-O electrophiles (50% and 71%) (Table 3.9, **3b** and **3d**; OR = OMe). These results contrast with reactions carried out with the same Ni-catalyst but K_3PO_4 as base (Table 3.7, entry 6 and Table 3.8, entry 6). Thus, by changing the base from K_3PO_4 to CsF, the reactivity of electrophiles was completely different. This observation may have significant implications for synthetic applications such as the orthogonal cross-coupling of aryl derivatives containing the methoxy group as an

electrophile and the less reactive electrophiles -OPiv, -OBoc, and -$OCONEt_2$ as inert functional groups. Phenol derivatives generally were less reactive than naphthol derivatives due to the higher activation energy of C-O bond in the oxidative addition step.[22] Only substituted phenyl mesylates and sulfamates were coupled with poor yield (Table 3.9, **3i** and **3j**; OR = OMs, OSO_2NMe_2).

The Reactivity of Aryl C-O Based Electrophiles in Cross-Coupling with Aryl Neopentylglycolboronates Catalyzed by $Ni(COD)_2/PCy_3/K_3PO_4$ in THF at 25 °C. First introduced by the Hu laboratory[14] for cross-coupling of aryl tosylates with arylboronic acids, the catalytic system $Ni(COD)_2/PCy_3/K_3PO_4$ in THF, has been subsequently employed for the cross-coupling of aryl mesylates and sulfamates with aryl neopentylglycolboronates.[34] This catalytic system is very efficient for the cross-coupling of aryl sulfonates and sulfamates at room temperature regardless of the electronic properties and steric hinderance of both substrates.[34] Therefore, we applied these reaction conditions to all six aryl C-O based electrophiles. Among the C-O based eletrophiles investigated, mesylates and sulfamates were cross-coupled with excellent yields (92% - 99%) (Table 3.10, **3a-f**; OR = OMs, OSO_2NMe_2). The reactivity of naphthyl pivalates and carbamates is determined by the electronic properties of the aryl neopentylglycolboronate used in the reaction. The -OPiv was more reactive toward eletron-rich aryl neopentylglycolboronates (70% and 72%) (Table 3.10, **3a** and **3d**; OR = OPiv) than electron-deficient derivatives (11%) (Table 3.10, **3b**; OR = OPiv).

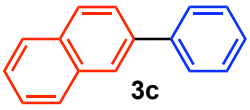
Table 3.10. Cross-Coupling of Aryl Containing C-O Electrophiles with *para*-Substituted Aryl Neopentylglycolboronates Catalyzed by $Ni(COD)_2/PCy_3/K_3PO_4$ in THF at 25 °C





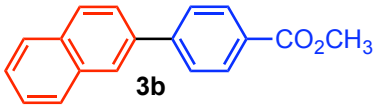
3a

OR = OMs : 12 h; 98%
OR = OSO_2NMe_2: 12 h; 99%
OR = OPiv : 48 h; 70%
OR = OBoc : 48 h; 0%
OR = OCO_2NEt_2 : 48 h; 10%
OR = OCH_3 : 48 h; 0%



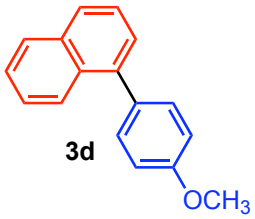
3c

OR = OMs : 12 h; 99%
OR = OSO_2NMe_2: 12 h; 98%
OR = OPiv : 48 h; 11%
OR = OBoc : 48 h; 10%
OR = OCO_2NEt_2 : 48 h; 60%
OR = OCH_3 : 48 h; 0%



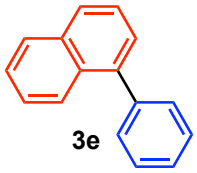
3b

OR = OMs : 12 h; 98%
OR = OSO_2NMe_2: 12 h; 98%
OR = OPiv: 48 h; 11%



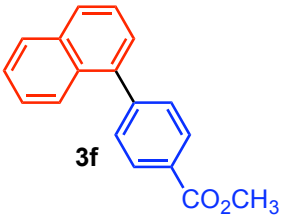
3d

OR = OMs : 12 h; 92%
OR = OSO_2NMe_2: 12 h; 97%
OR = OPiv: 48 h; 72%



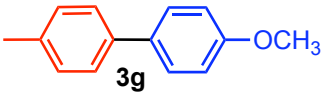
3e

OR = OMs : 12 h; 95%
OR = OSO_2NMe_2: 12 h; 93%
OR = $OCONEt_2$: 48 h; 16%



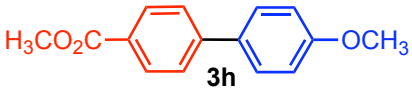
3f

OR = OMs : 12 h; 97%
OR = OSO_2NMe_2: 12 h; 99%



3g

OR = OMs: 12 h; 99%
OR = OPiv: 48 h; 0%



3h

OR = OMs: 12 h; 94%
OR = OPiv: 48 h; 0%

Isolated yield in all cases

No reaction was observed for substituted phenyl pivalates (Table 3.10, **3g** and **3h**; OR= OPiv). At room temperature, aryl methyl ethers remained unreactive while carbonates gave diminished yields (<10%) (Table 3.10, **3a**, **3c**; OR = OBoc).

The Comparison of the Reactivity of Different Electrophiles in Cross-Coupling Reaction with 4-Methoxyphenyl Neopentylglycolboronates. As observed from previous series of experiments (Table 3.6, 2, 3, 4, and 5) and by their summary from Figure 3.1 (conditions 1, 2, 3

and 4) aryl mesylates and sulfamates are more reactive than the other C-O based electrophiles regardless of the catalyst used. $Ni(COD)_2/PCy_3/K_3PO_4$ in THF at room temperature provides the best conditions for the cross-coupling of aryl mesylates, sulfamates and pivalates with aryl neopentylglycolboronates. This catalyst is completely unreactive for carbonates and methyl ethers and exhibits poor reactivity for carbamates.

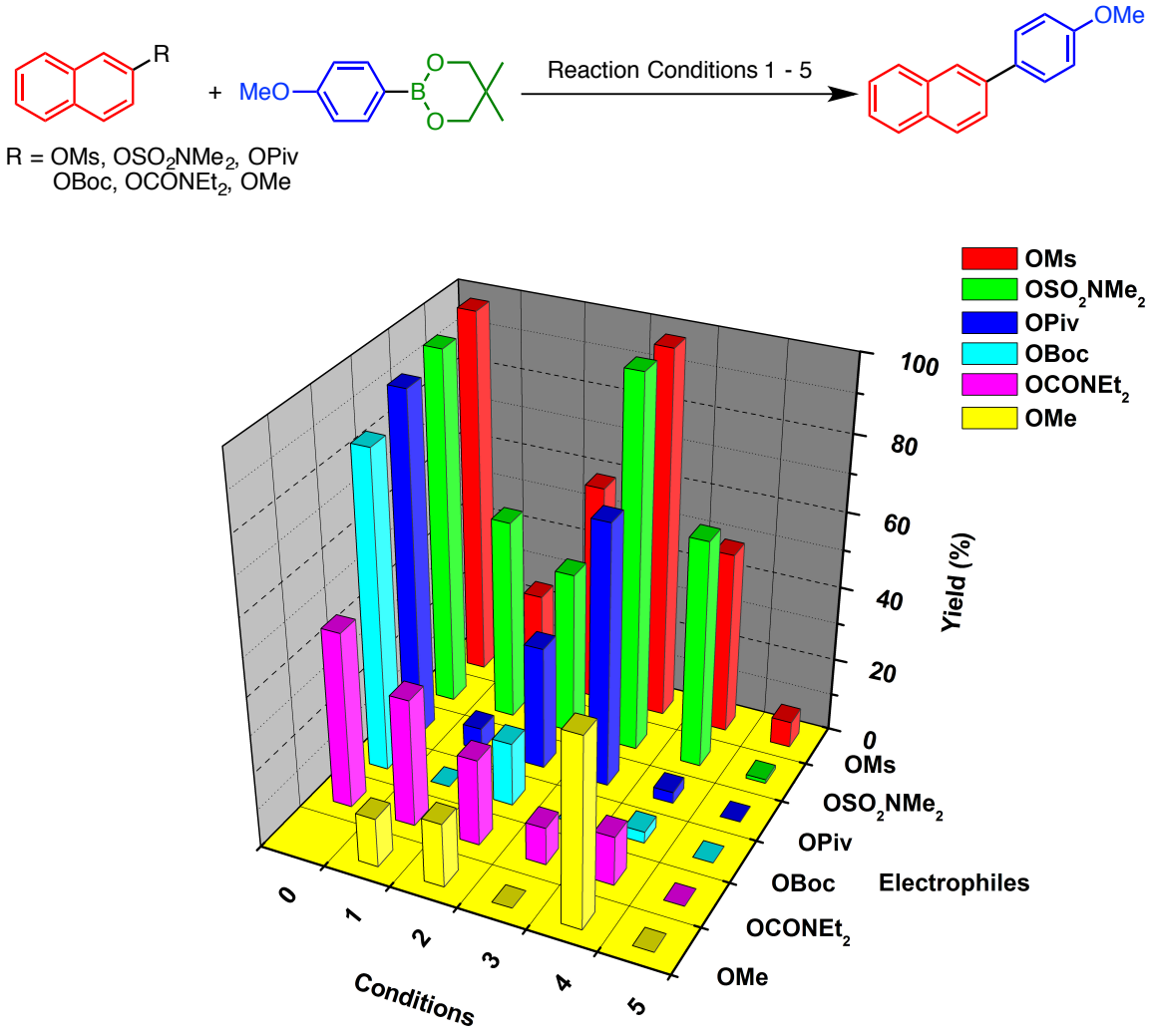


Figure 3.1. Comparison of the reactivity of 2-naphthyl C-O electrophiles in the cross-coupling reaction with 4-methoxyphenylboronic acid (0) and 4-methoxyphenyl neopentylglycolboronate (1 to 5). (0) 5% (pivalate), 10% (for the rest) $NiCl_2(PCy_3)_2/K_3PO_4$/toluene/130 °C[23,36] except for OMs where 1% $NiCl_2$(dppp)/K_3PO_4/dioxane/100 °C[19] was used; (1) 10% $NiCl_2(PCy_3)_2/K_3PO_4$/toluene/110 °C; (2) 10% $Ni(COD)_2$/40% PCy_3/K_3PO_4/toluene/120 °C; (3) 6% $Ni(COD)_2$/12% PCy_3/K_3PO_4/ THF/23 °C; (4) 10% $Ni(COD)_2$/40% PCy_3/CsF/toluene/120 °C; (5) 10% $NiCl_2(PCy_3)_2$/CsF/toluene/110 °C.

By contrast, $Ni(COD)_2/PCy_3/CsF$ in toluene at 120 °C is the best catalyst for the cross-coupling of aryl methyl ethers, although this catalyst is also active for aryl mesylates and sulfamates (Figure 3.1). This catalytic system is unreactive toward aryl pivalates and carbonates but shows low reactivity toward aryl carbamates. $Ni(COD)_2/PCy_3/K_3PO_4$/toluene at 120 °C catalytic system was found to be active but less efficient and at the same time less selective for all substrates. $NiCl_2(PCy_3)_2/K_3PO_4$/toluene at 110 ^oC is the less reactive of all catalysts but exhibitSSD selectivity that is complementary to $Ni(COD)_2$-based catalytic systems. Column (0) of Figure 3.1 compares also literature data for the cross-coupling of the same C-O electrophiles in cross-coupling with 4-methoxyphenylboronic acid with $NiCl_2(PCy_3)_2/K_3PO_4$/toluene at 130 ^oC. [23,36] This is the catalyst of choice employed in Garg laboratory[23,36] for the cross-coupling of aryl C-O electrophiles with arylboronic acids. Only the cross-coupling of 2-naphthyl mesylate with 4-methoxyphenylboronic acid was selected from experiments catalyzed with $NiCl_2$(dppp)/K_3PO_4/dioxane/100°C was used.[19] These results are self-explanatory. Arylboronic acids are more reactive than aryl neopentylglycolboronates when $NiCl_2(PCy_3)_2/K_3PO_4$ in toluene at high temperature is used (compare columns 0 and 1 in Figure 3.1). Nevertheless the efficiency of the cross-coupling of 2-naphthyl mesylates and sulfamates with aryl neopentylglycolboronate catalyzed with $Ni(COD)_2$/ PCy_3/K_3PO_4/THF at 23 ^oC is comparable with that of the same electrophiles cross-coupled with arylboronic acids when catalyzed with $NiCl_2(PCy_3)_2/K_3PO_4$/toluene at 130 ^oC (Figure 3.1). This result is remarkable. The electronic properties of aryl neopentylglycolboronates also influence on the reactivity of C-O electrophiles.

3.2.3 Conclusions

The reactivity of aryl mesylates, sulfamates, pivalates, carbonates, carbamates and methyl ethers was investigated for the first time in Ni-catalyzed cross-coupling with aryl neopentylglycolboronates. Four different catalytic systems and reaction conditions that are specific for aryl mesylates with aryl neopentylglycolboronates, aryl methyl ethers with aryl neopentylglycolboronates, aryl sulfamates, pivalates, carbonates and carbamates with arylboronic acids were applied to all six aryl C-O based electrophiles. A catalytic system based on

modified conditions for aryl methyl ethers was also investigated. It was shown that the optimum catalyst for aryl mesylates, $Ni(COD)_2/PCy_3/K_3PO_4$/THF/23 ºC, is the most efficient not only for mesylates but also for aryl sulfamates and pivalates and the least efficient for carbonates, carbamates and methyl ethers. Therefore, this catalytic system is very selective and may be able to provide for the first time orthogonal reaction conditions for the cross-coupling of aryl mesylates, sulfamates and pivalates in the presence of aryl carbonates, carbamates and methyl ethers. The reaction conditions $Ni(COD)_2/PCy_3$/CsF/toluene/120 ºC are the most efficient for the cross-coupling of aryl methyl ethers and provide moderate yields for aryl mesylates and sulfamates, but display little reactivity for aryl pivalates, carbonates, and carbamates. Therefore, these are orthogonal reaction conditions for the cross-coupling of aryl methyl ethers, mesylates and sulfamates in the presence of aryl pivalates, carbonates and carbamates. The catalytic system $Ni(COD)_2/PCy_3/K_3PO_4$/toluene/120 ºC is the least selective, generating comparable yield with all C-O electrophiles. $NiCl_2(PCy_3)_2/K_3PO_4$/toluene/110 ºC is most efficient for sulfamates, carbamates and mesylates in all cases with moderate yields and is inefficient for pivalates, carbonates and methyl ethers. Therefore, this catalyst provides also chemical orthogonality although with much lower efficiency. The reactivity of 2-naphthyl containing C-O electrophiles was also compared with literature data for cross-coupling with $NiCl_2(PCy_3)_2/K_3PO_4$/toluene/130 ^oC. This comparison showed that with the exception of aryl mesylates and sulfamates cross-coupled with aryl neopentylglycolboronates in the presence of $Ni(COD)_2/PCy_3/K_3PO_4$/THF/23 ^oC, aryl containing C-O electrophiles are more reactive in cross-coupling with arylboronic acids than the corresponding aryl neopentylglycolboronate. At the same time catalytic systems based on Ni^{II} are non-selective toward C-O electrophiles regardless if they are cross-coupled with arylboronic acids or with aryl neopentylglycolboronates, while all catalytic systems based on Ni^0 exhibit high selectivity for the cross-coupling of aryl C-O based electrophiles with aryl neopentylglycolboronates. The selectivity of Ni^0 based catalysts for aryl neopentylglycolboronates toward C-O based electrophiles contrasts the lack of selectivity observed for the same electrophiles in cross-coupling with potassium aryltrifluoroborates.[21]

3.2.4 Experiments

General Experimental Methods. 1-Naphthol, 2-naphthol, *p*-cresol, methyl 4-hydroxybenzoate, *N,N*-dimethylsulfamoyl chloride, methanesulfonyl chloride, pivaloyl chloride, di-*tert*-butyl dicarbonate, *N,N*-diethylcarbamic chloride, iodomethane, DMAP, NaH, $Ni(COD)_2$ (98+%), PCy_3, and CsF were used as received from commercial sources. Toluene, triethylamine, pyridine, DMF, DME, and dichloromethane were distilled over CaH_2, and stored under nitrogen prior to use. THF from commercial source was distilled over sodium and benzophenone and stored under nitrogen prior to use. K_3PO_4 from commercial source was dried at 40 °C under vacuum overnight and kept in a desiccator prior to use. $NiCl_2(PCy_3)_2$, naphthalen-1-yl pivalate, (**1i**), *p*-Tolyl pivalate (**1v**) and naphthalen-2-yl pivalate (**1c**) were synthesized according to literature procedure.[36] 2-Methanesulfonyloxynaphthalene (**1a**) 4-methoxyphenyl methanesulfonate (**1r**), *p*-tolyl methanesulfonate (**1u**), Naphthalen-1-yl dimethylsulfamate (**1h**), [31] *tert*-butyl naphthalen-1-yl carbonate (**1j**), *tert*-butyl naphthalen-2-yl carbonate (**1d**), naphthalen-1-yl diethylcarbamate (**1k**), and naphthalen-2-yl diethylcarbamate (**1e**) were synthesized according to literature procedure.[23] Methyl 4-methoxybenzoate (**1q**)[39] and 4-methoxyphenyl dimethylsulfamate (**1m**)[34] were prepared by following the literature procedure. 2-(4-Methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (**2a**), methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (**2b**), and 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane (**2c**) were prepared according to the literature procedures.[12,31-33,40] ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded using TMS as internal standard. High-resolution mass spectra of new compounds were obtained on a high-resolution double focusing chemical ionization mass spectrometer. A GC coupled with an FID detector and column HP 19091J-413 (5%-phenyl)-methylpolysiloxane 30m length 0.32 mm internal diameter was used to follow the reaction conversions and to assess purity of final compounds complementary to the NMR technique. The crude reaction mixtures were diluted with THF and analyzed by GC as reported in previous related publications from our laboratory.

Typical Procedure for the Synthesis of Aryl Sulfamates.

The aryl sulfamates were prepared according to a literature procedure.[23]

Naphthalen-2-yl dimethylsulfamate(1b). To an oven dried round bottom flask equipped with a stirring bar was added under nitrogen atmosphere NaH (25.0 mmol, 0.58 g). The flask was cooled to 0 ^{o}C and 2-naphthol (20.8 mmol, 3.0 g) in dried DME (25 mL) was added dropwise at 0 ^{o}C. The reaction mixture was allowed to stir at room temperature for 10 min then was cooled to 0 ^{o}C. Dimethyl sulfamoyl chloride (25.0 mmol, 3.74 g) in DME (4 mL) was added dropwise and the reaction was allowed to stir at room temperature for 12 h. The reaction was quenched by addition of water (5 mL, dropwise) followed by the evaporation of the solvent. The solid was dissolved by Et_2O (25 mL) and washed with 1 M KOH (25 mL) and water (25 mL). The combined aqueous layers were extracted with Et_2O (25 mL), washed with brine (25 mL), and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by column chromatography with dichloromethane/hexane (3/7) as eluent to give a white solid (4.49 g, 86%), mp = 74-75 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.82 (m, 3H), 7.77 (d, J = 2.3, 1H), 7.52 (m, 2H), 7.43 (dd, J = 8.9, 2.4, 1H), 3.03 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.9, 133.8, 131.9, 130.1, 127.93, 127.91, 127.0, 126.3, 120.9, 119.1, 38.9; HRMS (CI+) calcd for $C_{12}H_{13}NNaO_3S$ (M^++Na) 274.0514, found 274.0526.

Typical Procedure for the Synthesis of Aryl Ethers

2-Methoxynaphthalene (1f). To an oven dried round bottom flask equipped with a stirring bar was added under nitrogen atmosphere NaH (30.0 mmol, 0.72 g). The flask was cooled to 0 ^{o}C and anhydrous DMF (25 mL) was added. 2-Naphthol (30.0 mmol, 4.32 g) was added slowly during stirring at 0 ^{o}C. The resulting clear solution was stirred during the rapid addition of iodomethane (37.0 mmol, 5.25 g). The reaction mixture was allowed to stir at room temperature for 3 h. The reaction was quenched with water (5 mL, dropwise) and extracted with EtOAc (25 mL). The combined organic phase was washed with 10% NaOH (25 mL), water (25 mL), and brine (25 mL), then dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography with CH_2Cl_2 as an eluent to give a white solid (4.0 g, 84 %), mp = 73-75 ^{o}C (lit.[41] 73-74 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 – 7.70 (m, 3H), 7.43 (t, J = 7.5, 1H), 7.33

(dd, J = 11.0, 3.9, 1H), 7.19 – 7.11 (m, 2H), 3.92 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.8, 134.7, 129.5, 129.1, 127.8, 126.9, 126.5, 123.7, 118.9, 105.9, 55.4.

Typical Procedure for the Synthesis of Aryl Mesylates.

The aryl mesylates were prepared according to a literature procedure.[32]

1-Methanesulfonyloxynaphthalene (**1g**).[42] To an oven dried round bottom flask equipped with a stirring bar was added under nitrogen atmosphere 1-naphthol (20 mmol, 2.88 g) and freshly distilled dichloromethane (20 mL) followed by anhydrous pyridine (8.0 mL). The reaction mixture was cooled to 0 ^{o}C before methanesulfonyl chloride (24.0 mmol, 2.80 g) was added dropwise. The reaction was allowed to stir at 0 ^{o}C for 4 h at room temperature until TLC demonstrated the consumption of the starting material. The reaction was quenched by addition of water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (20 mL) three times and all the combined organic layers were washed with 15% HCl (50 mL), brine (20 mL), and dried over $MgSO_4$. After the filtration, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography to give a pale yellow oil (3.98 g, 89%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.3, 1H), 7.90 (d, J = 7.5, 1H), 7.82 (d, J = 8.1, 1H), 7.64 – 7.52 (m, 3H), 7.48 (t, J = 7.9, 1H), 3.22 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 134.1, 127.2, 126.5, 126.4, 126.14, 126.13, 124.5, 120.6, 117.54, 37.1.

Typical Procedure for the Synthesis of Aryl Pivalates. The aryl pivalates were prepared according to a literature procedure.[36]

Methyl 4-(pivaloyloxy)benzoate (**1n**) Dry triethylamine (36.1 mmol, 5 mL) and DMAP (3.0 mmol, 0.39 g) were added at room temperature into a solution of methyl 4-hydroxybenzoate (30.0 mmol, 4.56 g) and dry CH_2Cl_2 (25 mL). Pivaloyl chloride (36.2 mmol, 4.5 mL) was added slowly during stirring and the reaction mixture was allowed to stir at room temperature for 12 h. The organic phase was washed with saturated ammonium chloride solution (25 mL) and brine (25 mL). The aqueous phase was extracted with EtOAc (25 mL). The organic phase was combined, dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (SiO_2, CH_2Cl_2) to give a white solid (6.95 g, 98%), mp =

58.5 - 60 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.8, 2H), 7.14 (d, J = 8.8, 2H), 3.91 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.7, 166.5, 155.0, 131.3, 121.7, 90.6, 52.3, 39.4, 27.2; HRMS (CI+) calcd for $C_{13}H_{17}O_4$ (M^++H) 237.1127, found 237.1118.

Typical Procedure for Synthesis of Aryl Carbonates. The aryl carbonates were prepared according to a literature procedure.[23]

Methyl 4-[(*tert*-Butoxycarbonyl)oxy]benzoate[43] (1o). To an oven dried round bottom flask equipped with stirring bar under nitrogen was added methyl 4-hydroxybenzoate (8.0 mmol, 1.22 g), 4-*N,N*-dimethylaminopyridine (0.80 mmol, 0.098 g) and freshly distilled CH_2Cl_2 (20 mL). Triethylamine (8.8 mmol, 0.89 g) and di-*tert*-butyl dicarbonate (8.8 mmol, 1.87 g) were added at room temperature. The reaction mixture was allowed to stir until the bubbling subsided. The solution was washed with 0.5 M $NaHSO_4$ (30 mL) and the aqueous layer was extracted with CH_2Cl_2. The organic phase was combined, dried over $MgSO_4$ and filtered. The solution was evaporated under reduced pressure and the crude product was purified by column chromatography (SiO_2, CH_2Cl_2) to give the product as a white solid (2.00 g, 99%), mp = 83 – 84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.6, 2H), 7.25 (d, J = 8.7, 2H), 3.91 (s, 3H), 1.56 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 154.8, 151.2, 131.2, 127.7, 121.3, 84.2, 52.3, 27.8, HRMS (CI+) calcd for $C_{13}H_{17}O_5$ (M^++H) 253.1076, found 253.1067.

***tert*-Butyl (4-methoxyphenyl) carbonate (1s)**. Following the typical procedure for the synthesis of aryl carbonates. Purified by silica gel column chromatography with dichloromethane. White solid (90%), mp = 65 - 66.5 °C (lit[44] 66 - 67 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, J = 9.0, 2H), 6.88 (d, J = 9.1, 2H), 3.79 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.2, 156.4, 151.5, 143.9, 121.2, 113.5, 82.5, 54.8, 26.9.

Typical Procedure for the Synthesis of Aryl Carbamates.

The aryl carbamates were prepared according to a literature procedure.[23]

Methyl 4-[(Diethylcarbamoyl)oxy]benzoate[45] (1p). To an oven dried round bottom flask equipped with a stirring bar was added under nitrogen atmosphere NaH (15.6 mmol, 0.37 g). The

flask was cooled to 0 ^{o}C and methyl 4-hydroxybenzoate (13.0 mmol, 1.98 g) in dried DME (5 mL) was added dropwise at 0 ^{o}C. The reaction mixture was allowed to stir at room temperature for 10 min then was cooled to 0 ^{o}C. Diethylcarbamoyl chloride (15.6 mmol, 2.12 g) in DME (5 mL) was added dropwise and the reaction was allowed to stir at room temperature for 12 h. The reaction was quenched by addition of water (5 mL, dropwise) followed by the evaporation of the solvent. The solid was dissolved in Et_2O (25 mL) and washed with 1 M KOH (25 mL) and water (25 mL). The combined aqueous layers were extracted with Et_2O (30 mL), washed with brine (20 mL), and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by column chromatography with gradient 0 – 4% EtOAc/CH_2Cl_2 as eluent to give a colorless oil (0.89 g, 27%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 8.5, 2H), 7.20 (d, J = 8.6, 2H), 3.90 (s, 3H), 3.47 – 3.36 (m, 4H), 1.26 (t, J = 6.9, 3H), 1.21 (t, J = 6.9, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 155.4, 153.5, 131.1, 127.0, 121.7, 52.2, 42.5, 42.1, 14.4, 13.4.

4-Methoxyphenyl diethylcarbamate[24] **(1t)**. Following the typical procedure of the synthesis of aryl carbamates. Column chromatography (SiO_2; 0 -20 % EtOAc/CH_2Cl_2), colorless oil (73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, J = 9.0, 2H), 6.87 (d, J = 9.0, 2H), 3.79 (s, 3H), 3.48 – 3.31 (m, 4H), 1.26 – 1.17 (m, J = 23.5, 6H), ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 155.8, 153.8, 144.3, 121.7, 113.4, 54.8, 41.4, 41.0, 13.4, 12.5.

Preparation of Neopentylglycolborane. A procedure elaborated previously in our laboratory was used.[33,40] To a cooled solution (0 ^{o}C) of neopentylglycol (0.625 g, 6.0 mmol, 2.0 equiv) in toluene (3 mL) was slowly added $(CH_3)_2S{\bullet}BH_3$ (0.57 mL, 6.0 mmol, 2.0 equiv) under nitrogen. The reaction was allowed to stir at 0 ^{o}C for 30 min, then at room temperature for 90 min. The neopentylglycolborane was used directly without further purification.

General Procedure for Neopentylglycolborylation. The arylboronic esters were prepared according to literature procedures.[12,30,31,33,40] To an oven-dried 25 mL Schlenk tube were added Zn powder (0.390 g, 6.0 mmol), $NiCl_2$(dppp) (81.3 mg, 0.15 mmol), and PPh_3 (78 mg, 0.3 mmol) along with appropriate aryl halides (if it is solid) (3.0 mmol). The aryl halide, catalyst, and PPh_3

were degassed by evacuation and backfilling with nitrogen three times. Dry toluene (3 mL) was added to the reaction mixture along with the appropriate aryl halide (if it is liquid) and Et_3N (1.25 mL, 9.0 mmol). Neopentylglycolborane was added dropwise to the reaction mixture. The reaction was placed into an oil bath at 100 ^oC with stirring under nitrogen. After completion of the starting material, the reaction was quenched by the addition of a saturated NH_4Cl solution (25 mL) and extracted with EtOAc 3 times (25 mL). The combined organic fractions were dried over $MgSO_4$, followed by filtration and evaporation of the solvent. The crude product was purified by column chromatography.

General procedure for Cross-coupling

Method A (in Table 3.6).[23,35,36] Entry 3: to an oven-dried test tube (15 x 85 mm) were added the 2-naphthyl pivalate (68.4 mg, 0.3 mmol), neopentylglycol boronic ester (264 mg, 1.2 mmol, 4 equiv), $NiCl_2(PCy_3)_2$ (20.7 mg, 0.03 mmol, 0.10 equiv). The tube was taken into the glove box and anhydrous K_3PO_4 (458.5 mg, 2.16 mmol, 7.2 equiv) which was obtained by flame drying and kept in the glove box, was added. Dried toluene (1.0 mL) was then added and the tube was capped with a rubber septum, which was wrapped with copper wire. The tube was taken outside the glove box and stirred at 110 ^oC for 12 h (see Table 3.6). The crude mixture was filtered through a short column of silica gel and washed with THF. The solvent was evaporated and the product was purified by column chromatography with 5% ethyl acetate in hexanes.

Method B (in Table 3.7 and Table 3.8). Table 3.8, entry 2: to an oven-dried test tube (15 x 85 mm) were added the 2-naphthyl sulfamate (75.4 mg, 0.3 mmol), neopentylglycol boronic ester (112 mg, 0.45 mmol, 1.5 equiv), and K_3PO_4 (287 mg, 1.35 mmol, 4.5 equiv). The tube was taken into the glove box, and $Ni(COD)_2$ (8.3 mg, 0.03 mmol) and PCy_3 (33.7 mg, 0.12 mmol, 0.40 equiv) were added. Dried THF (1.0 mL) was then added and the tube was capped with a rubber septum, which was wrapped with copper wire. The tube was taken outside the glove box and stirred at 120 ^oC for 18 h (see Table 3.7 and Table 3.8). The crude mixture was filtered through a short

column of silica gel and washed with THF. The solvent was evaporated and the product was purified by column chromatography with dichloromethane/hexane = 7:3.

Method C (in Table 3.9).[22] Table 3.9, **3f**, for OBoc, to an oven-dried test tube (15 x 85 mm) were added the 1-naphthyl carbonate (73.0 mg, 0.3 mmol), and the aryl neopentylglycol boronic ester (112 mg, 0.45 mmol, 1.5 equiv). The tube was taken into the glove box and CsF (205 mg, 1.35 mmol, 4.5 equiv), PCy_3 (33.7 mg, 0.12 mmol, 0.40 equiv) and $Ni(COD)_2$ (8.3 mg, 0.03 mmol, 0,10 equiv) were added. Dried toluene (1.0 mL) was then added and the tube was capped with a rubber septum, which was wrapped with copper wire. The tube was taken outside the glove box and stirred at 120 ^oC for 19 h (see Table 3.9). The crude mixture was filtered through a short column of silica gel and washed with THF (25 mL). The solvent was evaporated and the product was purified by column chromatography with dichloromethane/hexane = 7/3.

Method D (in Table 3.10).[12] Table 3.10, **3a**, OR = OPiv: to an oven-dried test tube (15 x 85 mm) were added the 2-naphthyl pivalate (68.0 mg, 0.3 mmol), the aryl neopentylglycol boronic ester (79.0 mg, 0.36 mmol, 1.2 equiv), and K_3PO_4 (191 mg, 0.9 mmol, 3 equiv). The tube was taken into the glove box and PCy_3 (10 mg, 0.036 mmol, 0.12 equiv) and $Ni(COD)_2$ (5 mg, 0.018 mmol, 0.06 equiv) were added. Dried THF (1.0 mL) was then added and the tube was capped with a rubber septum. Inside the glove box, the reaction was stirred at room temperature under nitrogen for 12-48 h (see Table 3.10). The crude mixture was filtered through a short column of silica gel and washed with THF. The solvent was evaporated and the product was purified by column chromatography with dichloromethane in hexanes (0 – 30%).

2-(4-Methoxyphenyl)naphthalene (3a). Purified by silica gel column chromatography with dichloromethane in hexanes (0 – 30%). White solid, mp = 130-131 ^oC (lit.[46] 131-133 ^oC); ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2, 1H), 7.72 (d, J = 8.5, 2H), 7.47 – 7.40 (m, 1H), 7.37 – 7.29 (m, 1H), 7.18 – 7.09 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 137.3, 132.9, 132.8, 131.5, 127.6, 127.5, 127.2, 126.8, 125.4, 124.8, 124.6, 124.2, 113.5, 54.5.

Methyl 4-(naphthalen-2-yl)benzoate[27] (3b). Purified by silica gel column chromatography with dichloromethane in hexanes (50 – 70%). White solid, mp = 149-150 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.5, 2H), 8.07 (d, J = 1.3, 1H), 7.96 – 7.84 (m, 3H), 7.77 (d, J = 8.5, 2H), 7.74 (dd, J = 8.5, 1.8, 1H), 7.54 – 7.47 (m, 2H), 3.94 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 145.6, 137.4, 133.7, 133.1, 130.3, 129.0, 128.8, 128.5, 127.8, 127.4, 126.6, 126.5, 126.5, 125.3, 52.3.

2-Phenylnaphthalene (3c). Purified by silica gel column chromatography with hexanes. White solid, mp = 98-99 ^{o}C (lit.[19] 100-101 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.93 – 7.84 (m, 3H), 7.77 – 7.70 (m, 3H), 7.53 – 7.45 (m, 4H), 7.38 (dd, J = 10.6, 4.2, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.3, 138.7, 133.8, 132.8, 129.0, 128.6, 128.4, 127.8, 127.6, 127.5, 126.4, 126.07, 125.95, 125.8.

1-(4-Methoxyphenyl)naphthalene (3d). Purified by silica gel column chromatography with dichloromethane in hexanes (0 – 30%). White solid, mp = 110-111 ^{o}C (lit.[21] 112-113 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.92 – 7.83 (m, 3H), 7.72 (dd, J = 8.5, 1.8, 1H), 7.67 (d, J = 8.8, 2H), 7.52 – 7.44 (m, 2H), 7.03 (d, J = 8.8, 2H), 3.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 139.1, 133.0, 132.3, 131.0, 130.3, 127.4, 126.5, 126.1, 125.2, 125.1, 124.9, 124.6, 112.9, 54.5.

1-Phenylnaphthalene[46] (3e). Purified by silica gel column chromatography with hexanes Colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 7.6, 2H), 7.83 (d, J = 8.1, 1H), 7.52 – 7.43 (m, 6H), 7.43 – 7.37 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.9, 140.4, 133.9, 131.7, 130.2, 128.4, 127.8, 127.4, 127.0, 126.2, 125.9, 125.5.

Methyl 4-(naphthalen-1-yl)benzoate (3f). Purified by silica gel column chromatography with dichloromethane in hexanes (30%). White solid, mp = 62-63 ^{o}C (lit.[47] 65.5-66.5 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 8.3, 2H), 7.91 (dd, J = 13.6, 8.2, 2H), 7.84 (d, J = 8.5, 1H), 7.58 (d, J = 8.3, 2H), 7.56 – 7.49 (m, 2H), 7.47 – 7.41 (m, 2H), 3.97 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 145.8, 139.3, 133.9, 131.4, 130.3, 129.7, 129.2, 128.6, 128.4, 127.1, 126.5, 126.1, 125.8, 125.5, 52.3.

4-Methoxy-4'-methyl-1,1'-biphenyl (3g). Purified by silica gel column chromatography with dichloromethane in hexanes (50%). White solid, mp = 103-104 ^{o}C (lit.[48] 103-104 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 8.8, 2H), 7.45 (d, J = 8.1, 2H), 7.23 (d, J = 7.8, 2H), 6.97 (d, J = 8.8, 2H), 3.85 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 137.9, 136.3, 133.7, 129.3, 127.9, 126.5, 114.1, 55.3, 21.0.

Methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (3h). Purified by silica gel column chromatography with dichloromethane in hexanes (70%). White solid, mp = 172-173 ^{o}C (lit.[30] 173-174 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.3, 2H), 7.62 (d, J = 8.3, 2H), 7.57 (d, J = 8.7, 2H), 6.99 (d, J = 8.7, 2H), 3.93 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 159.8, 145.1, 132.3, 130.0, 128.3, 128.2, 126.4, 114.3, 55.3, 52.0.

Dimethyl [1,1'-biphenyl]-4,4'-dicarboxylate (3i). Purified by silica gel column chromatography with dichloromethane. White solid, mp = 212-214 ^{o}C (lit.[49] 215.5-216.5 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 8.2, 4H), 7.69 (d, J = 8.2, 4H), 3.95 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 144.5, 130.3, 129.9, 127.4, 52.3.

3.2.5 Characterization of Reaction Products

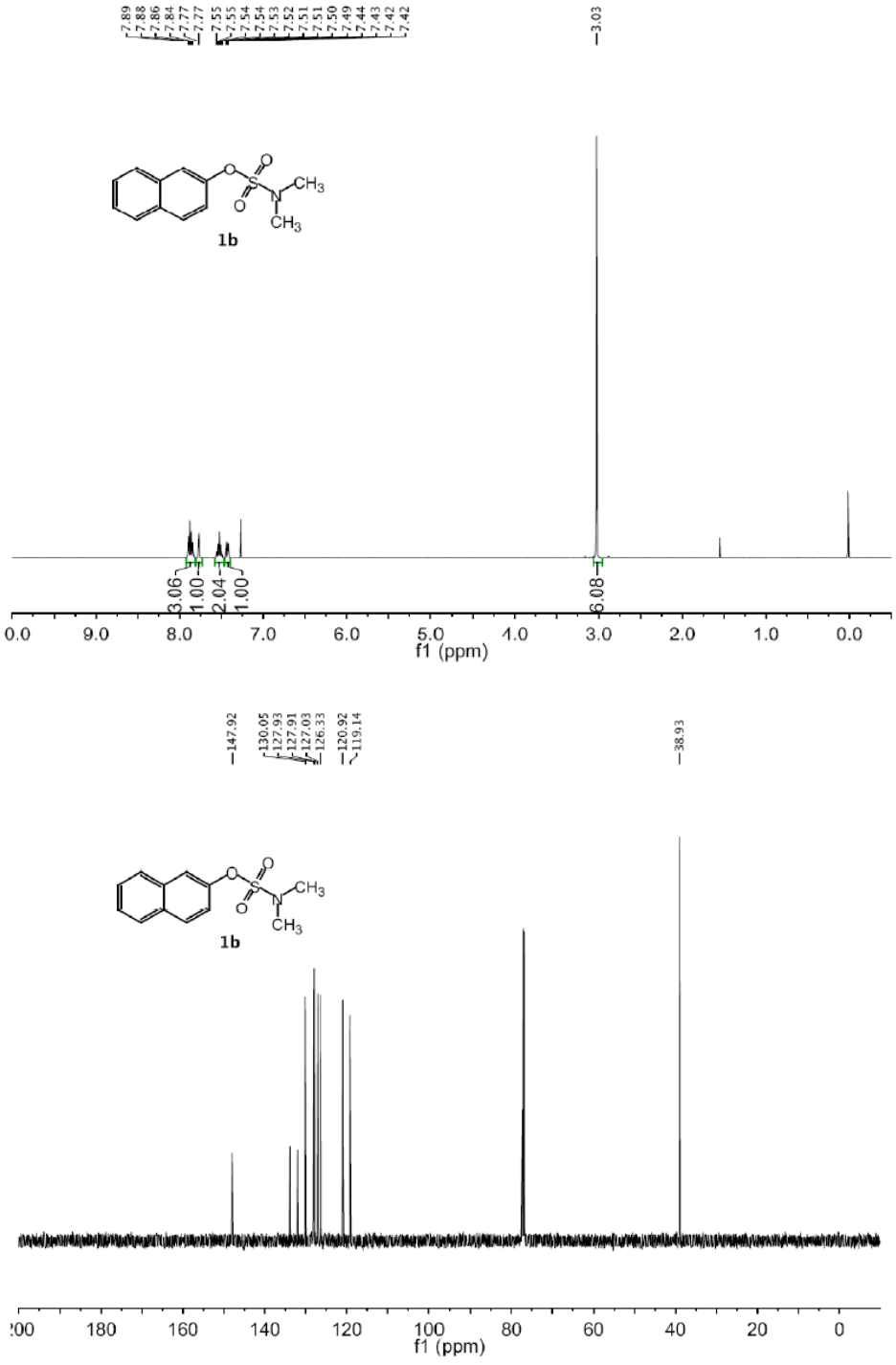


Figure SF1. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of naphthalen-2-yl dimethylsulfamate (**1b**) in $CDCl_3$

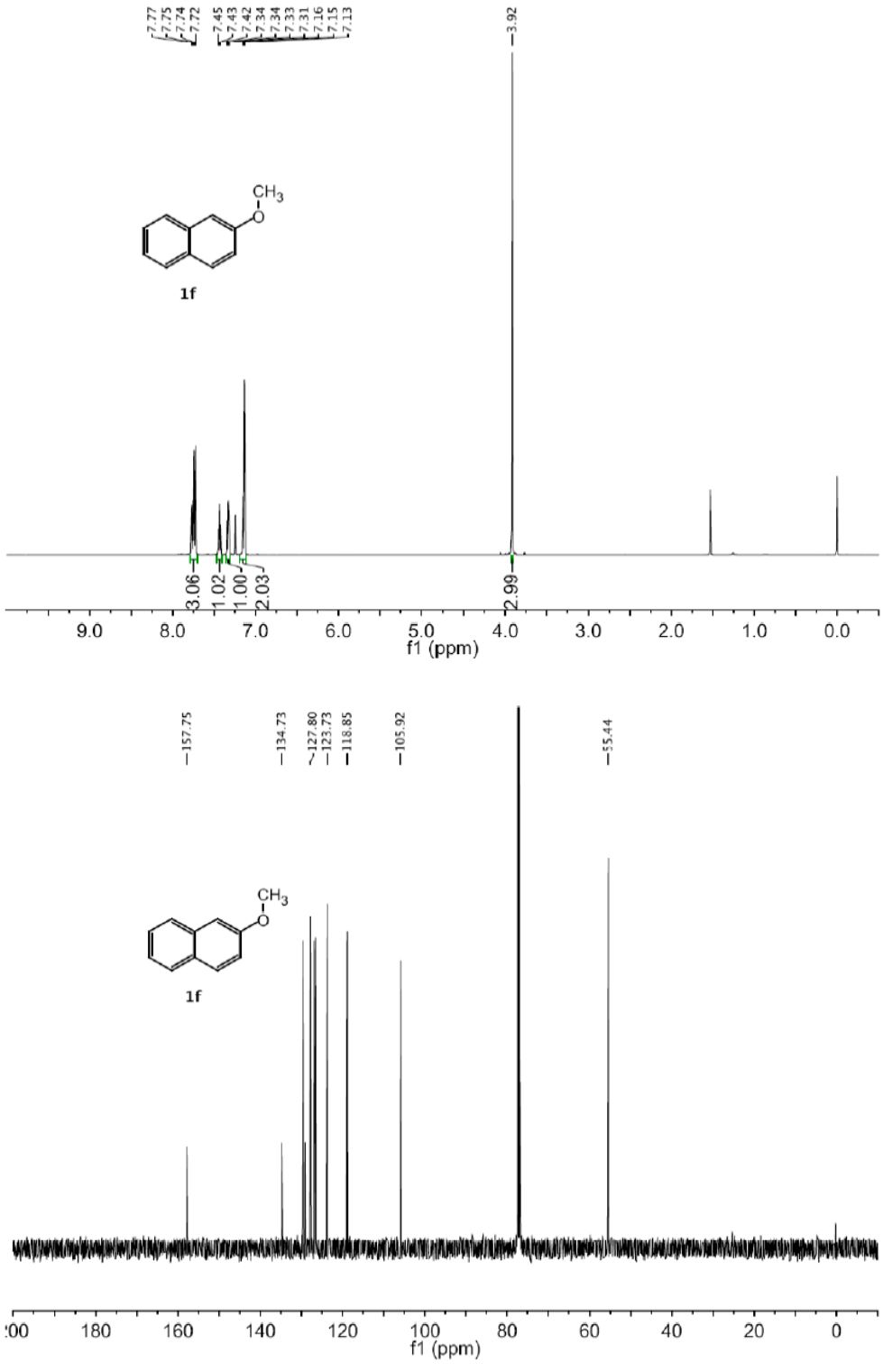


Figure SF2. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 2-methoxynaphthalene (**1f**) in $CDCl_3$

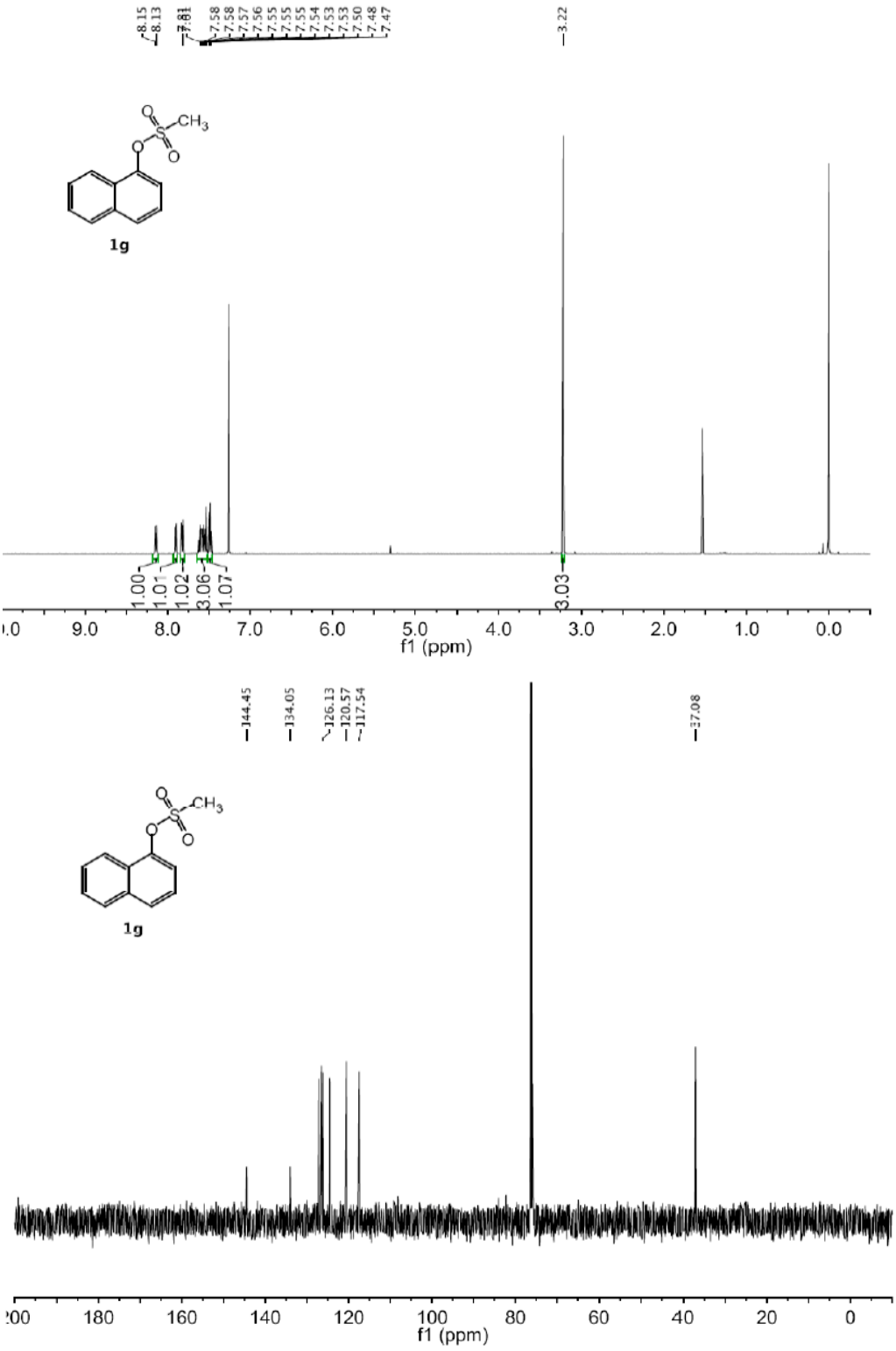


Figure SF3. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of naphthalen-1-yl methanesulfonate (**1g**) in $CDCl_3$

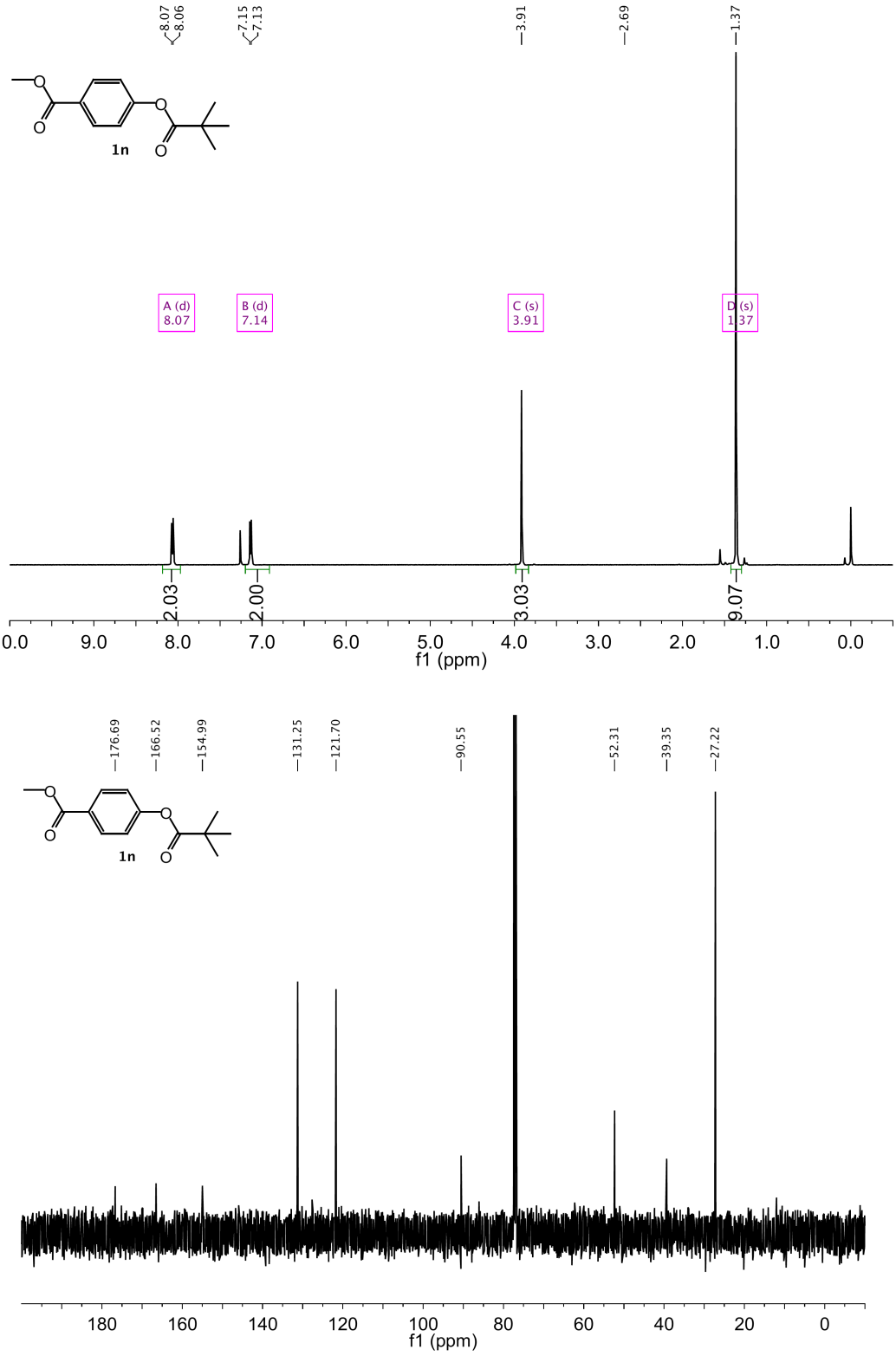


Figure SF4. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4-(pivaloyloxy)benzoate (**1n**) in $CDCl_3$

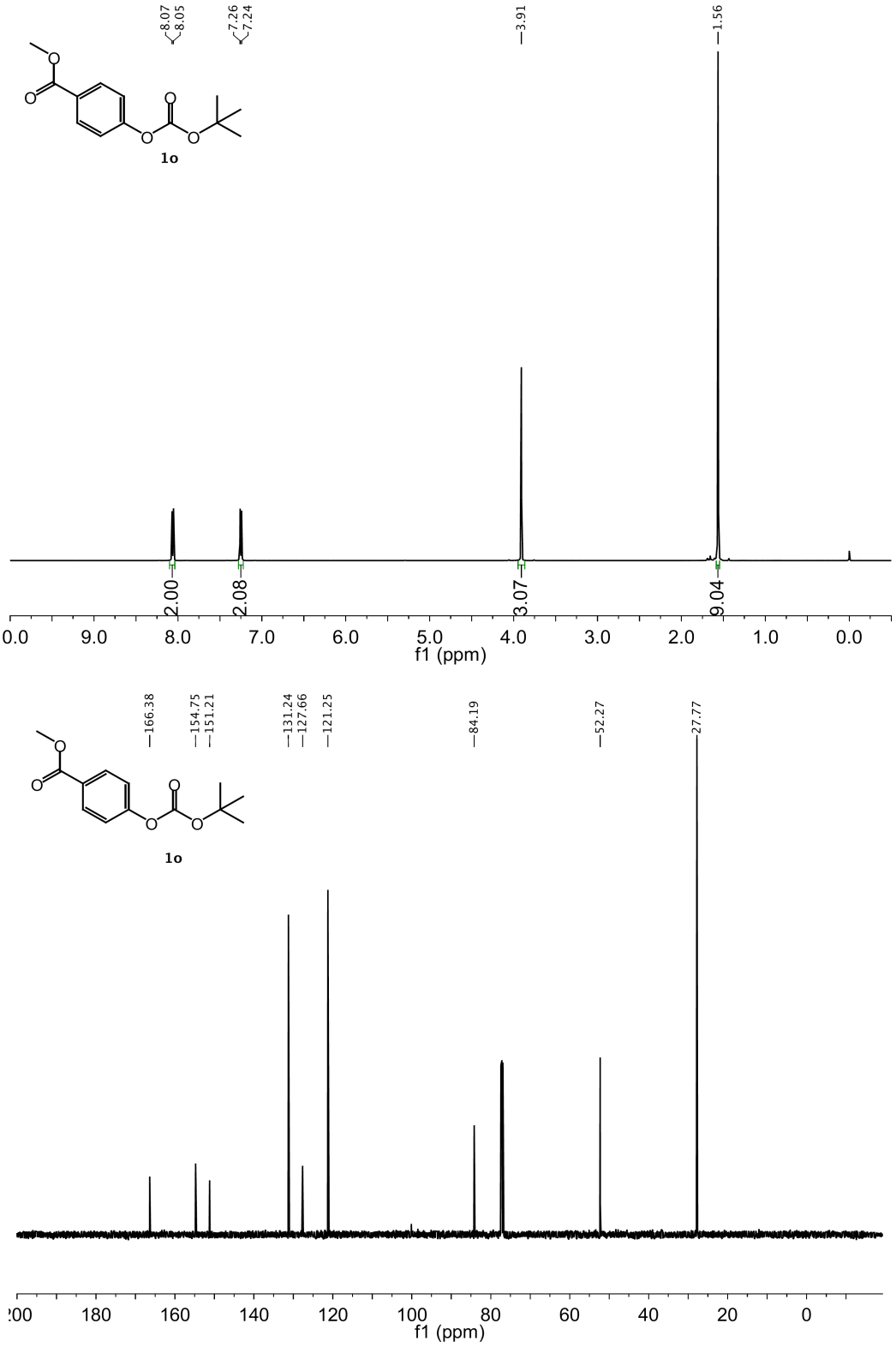


Figure SF5. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4-((*tert*-butoxycarbonyl)oxy)benzoate (**1o**) in $CDCl_3$

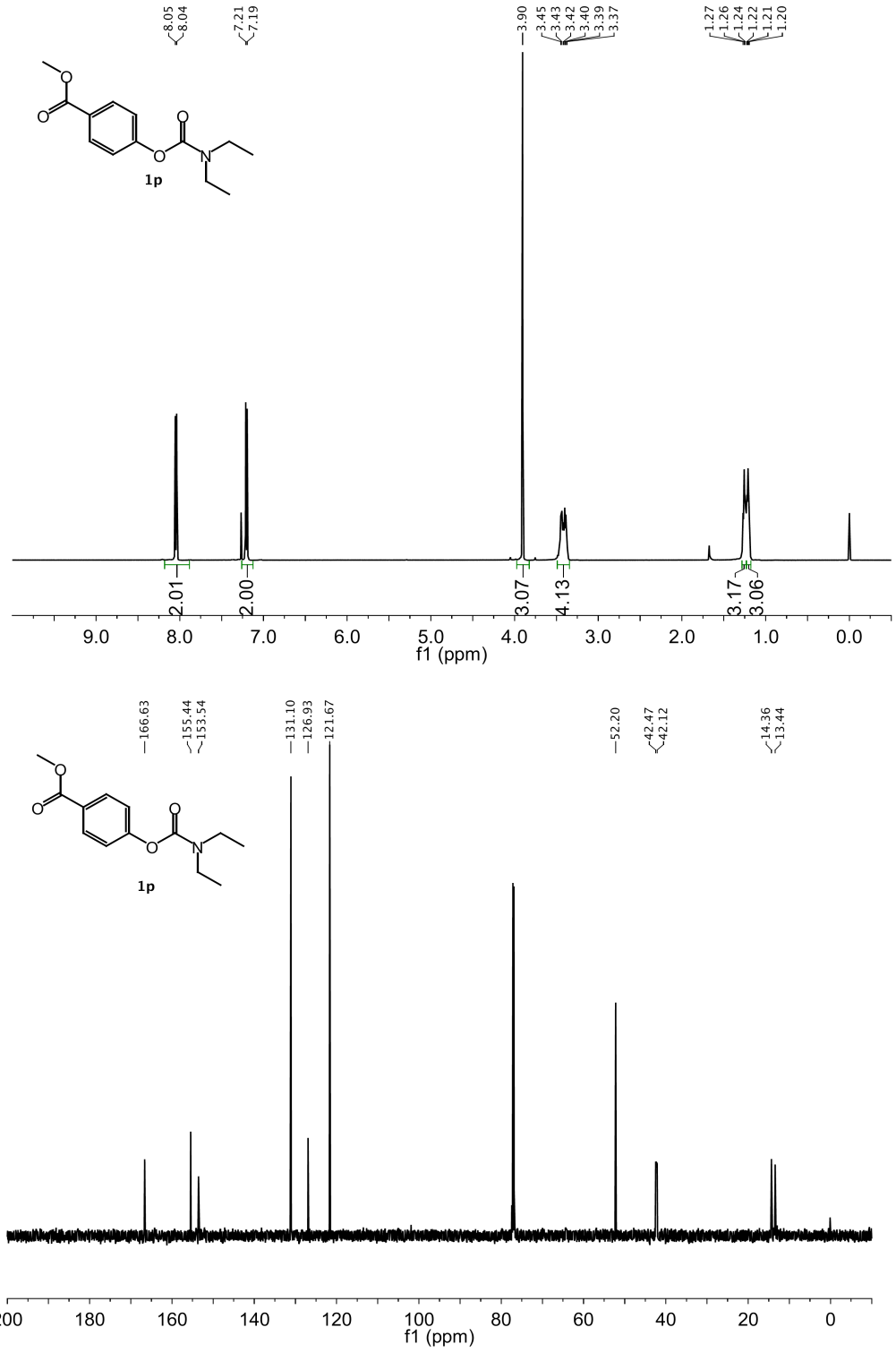


Figure SF6. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4-((diethylcarbamoyl)oxy)benzoate (**1p**) in $CDCl_3$

Figure SF7. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of *tert*-butyl (4-methoxyphenyl) carbonate (**1s**) in $CDCl_3$

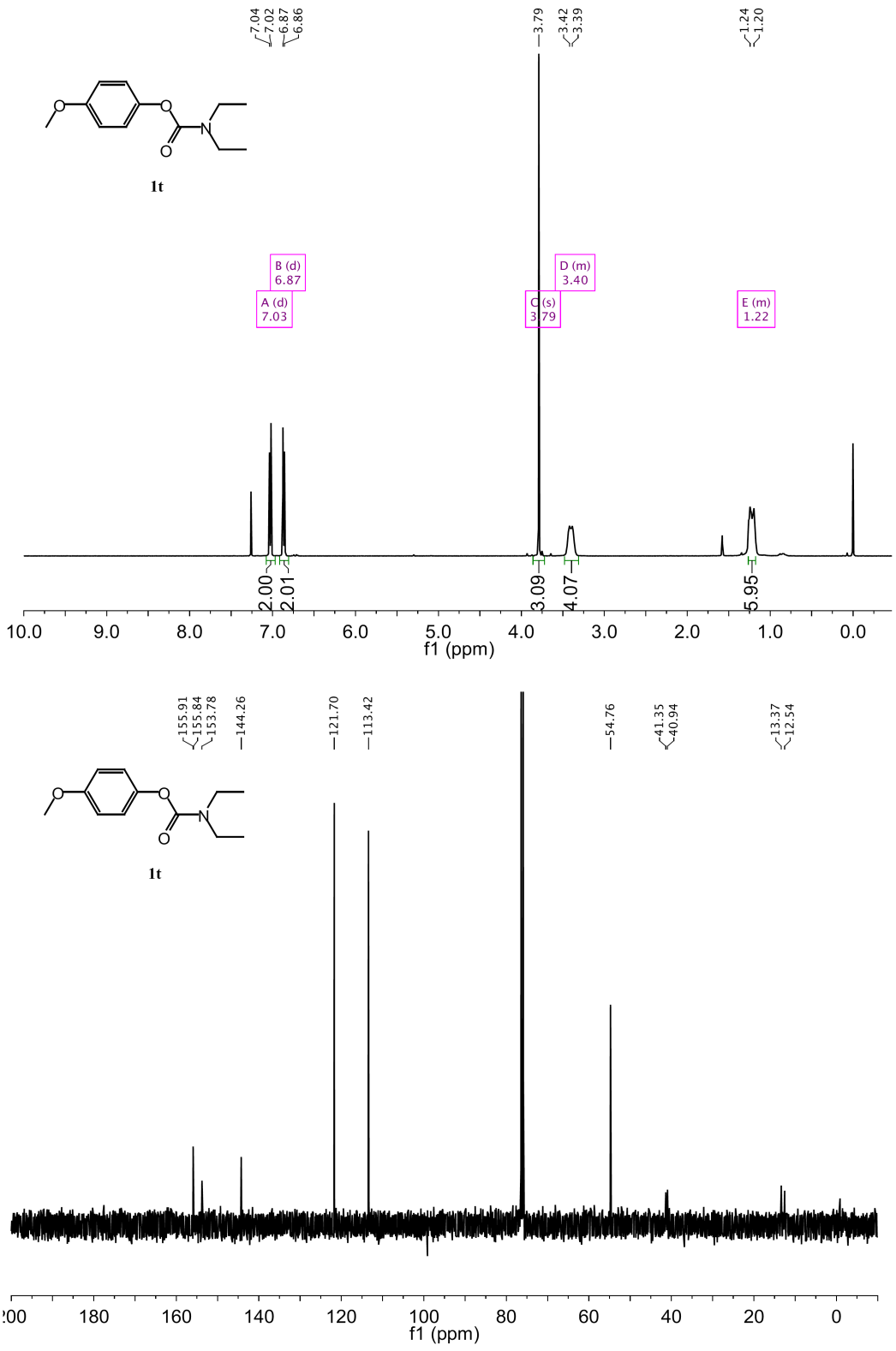


Figure SF8. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 4-methoxyphenyl diethylcarbamate (**1t**) in $CDCl_3$

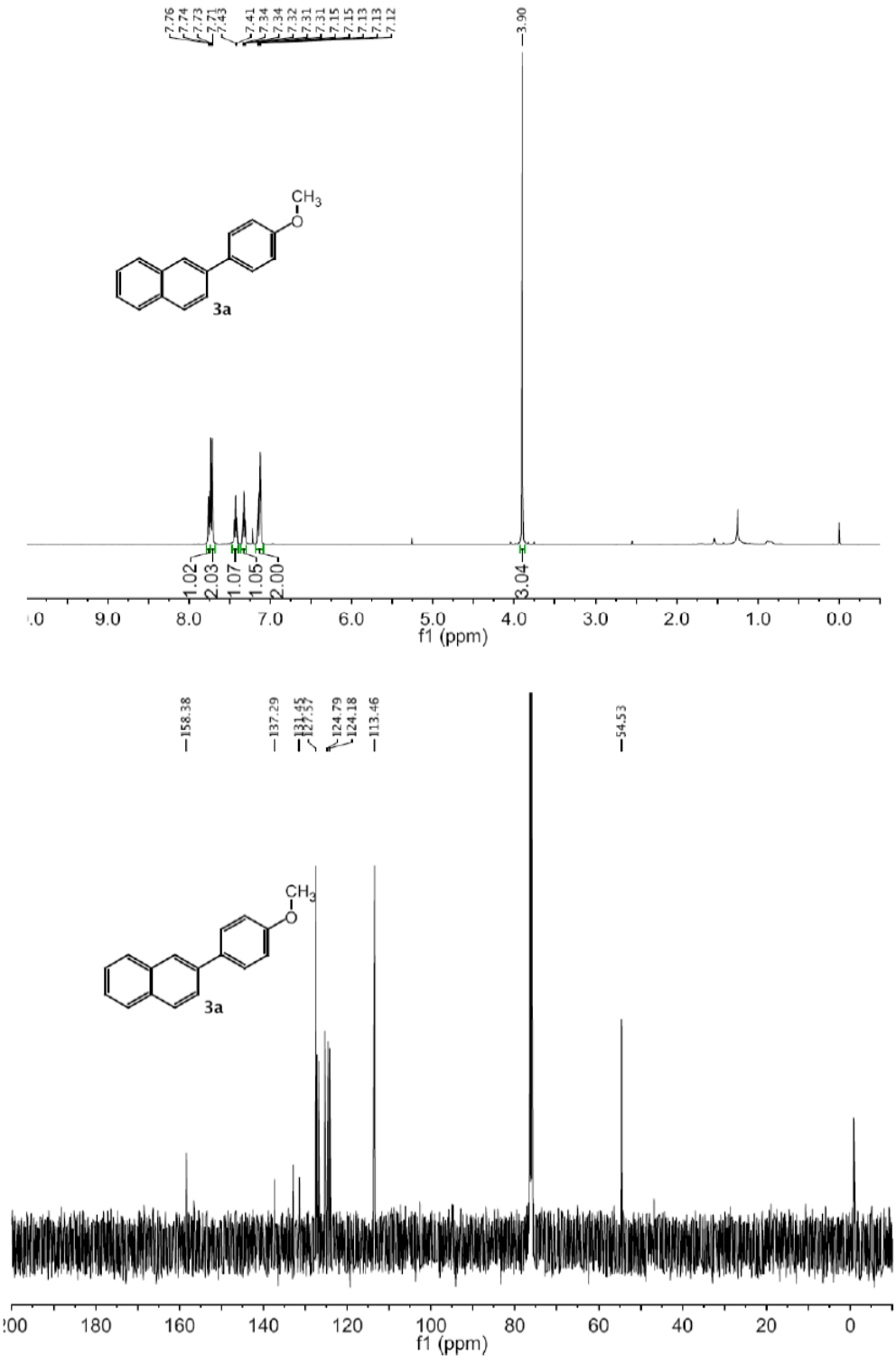


Figure SF9. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 2-(4-methoxyphenyl)naphthalene (**3a**) in $CDCl_3$

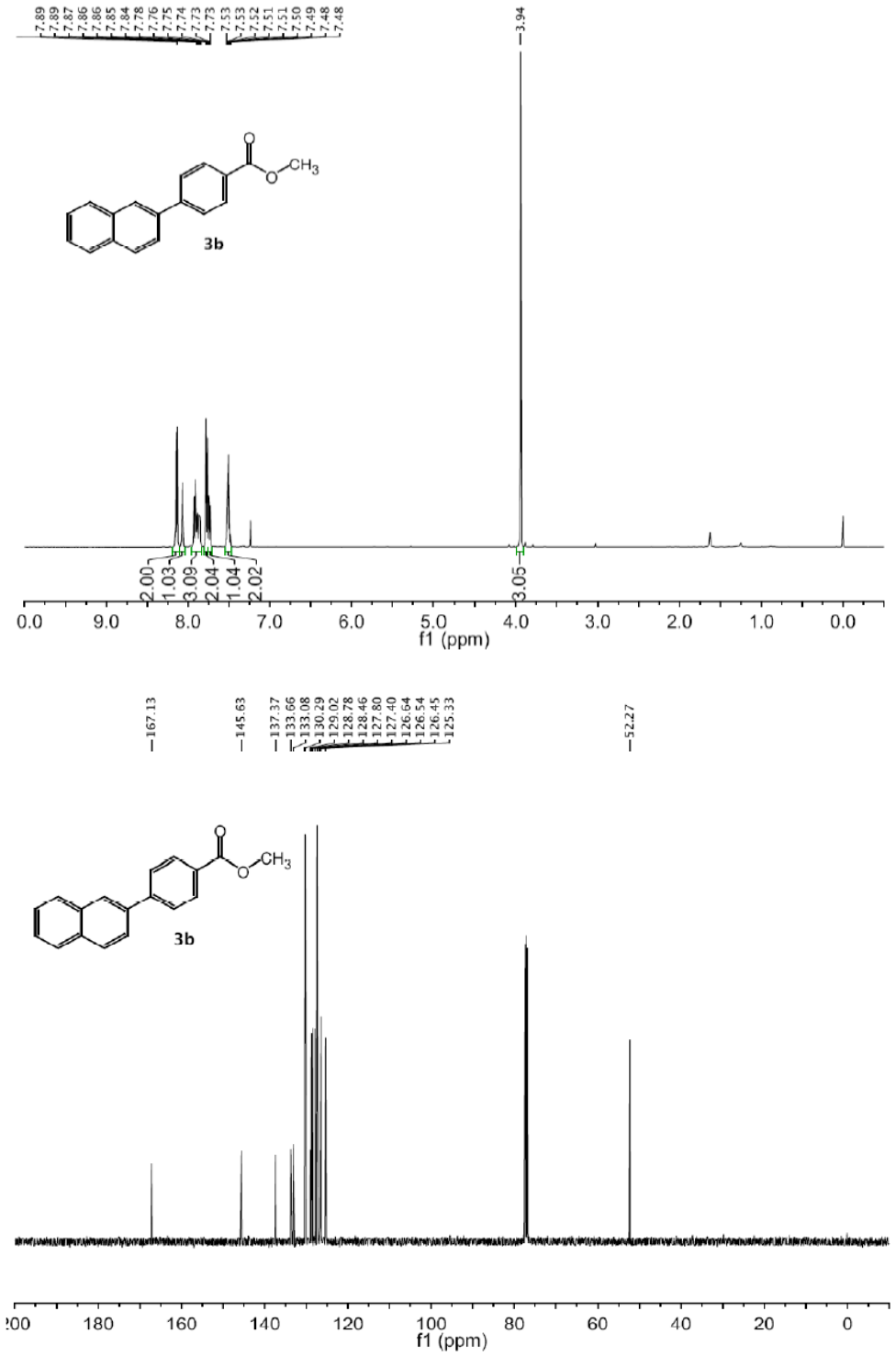


Figure SF10. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4-(naphthalen-2-yl)benzoate (**3b**) in $CDCl_3$

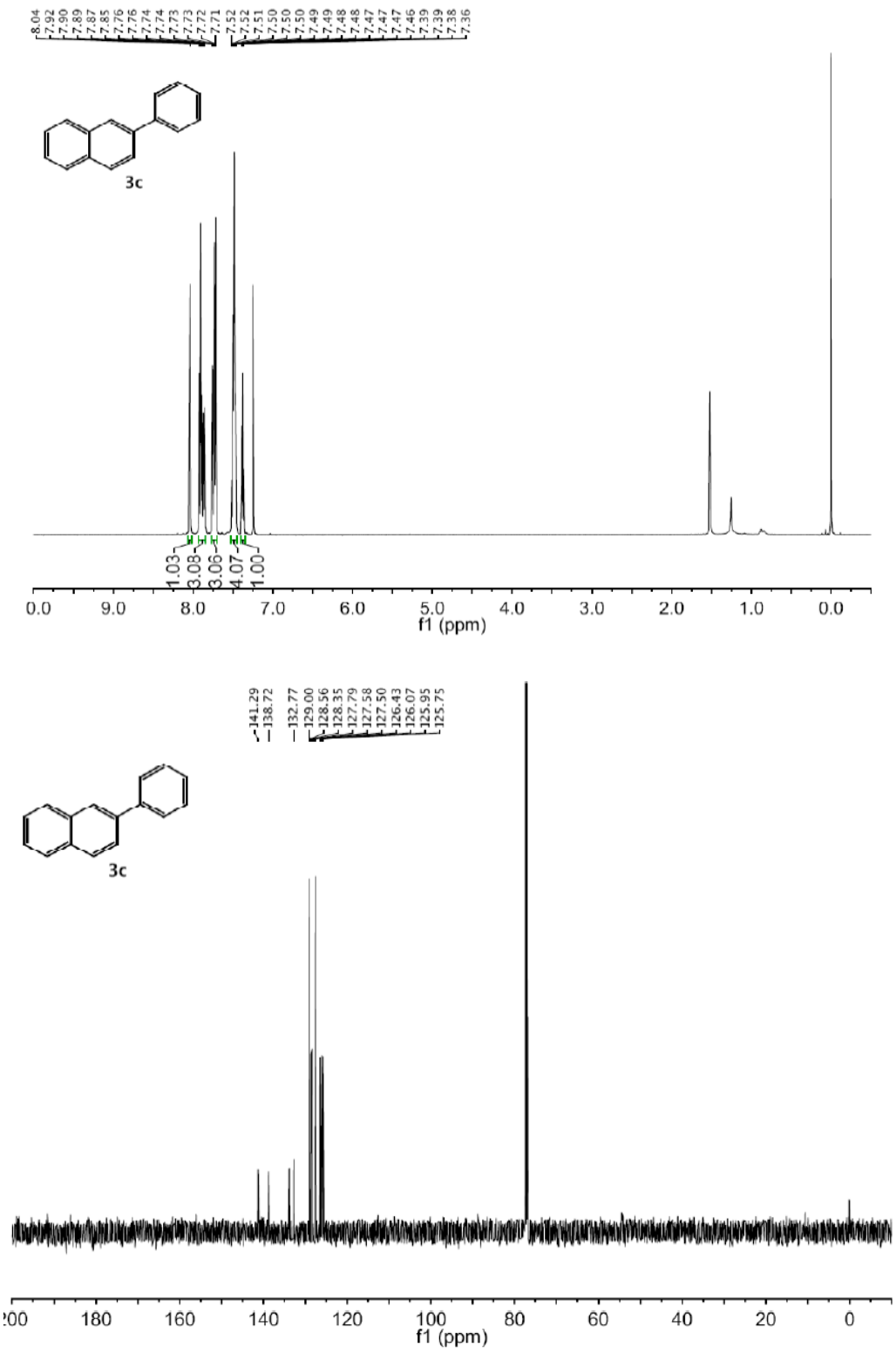


Figure SF11. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 2-phenylnaphthalene (**3c**) in $CDCl_3$

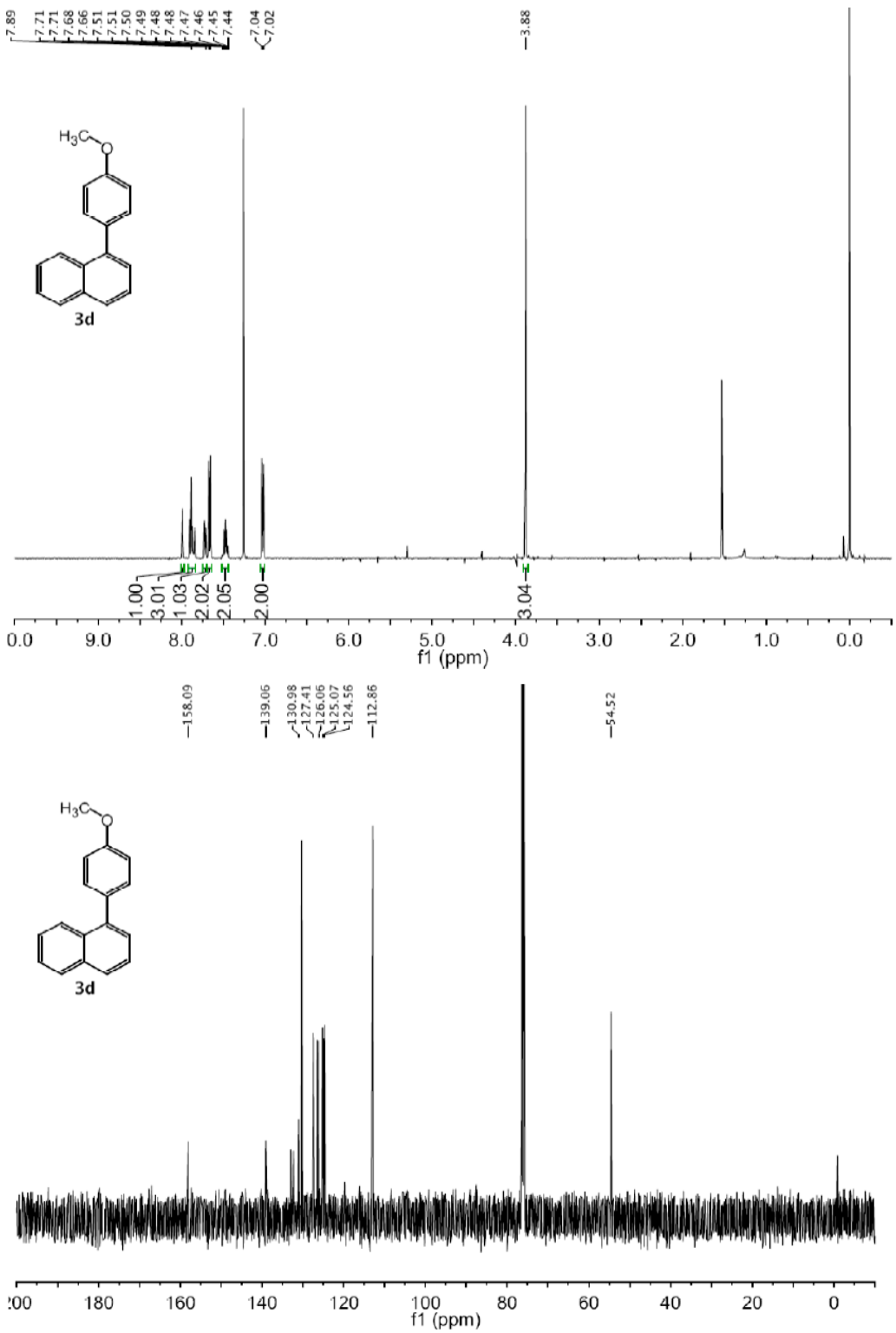


Figure SF12. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 1-(4-methoxyphenyl)naphthalene (**3d**) in $CDCl_3$

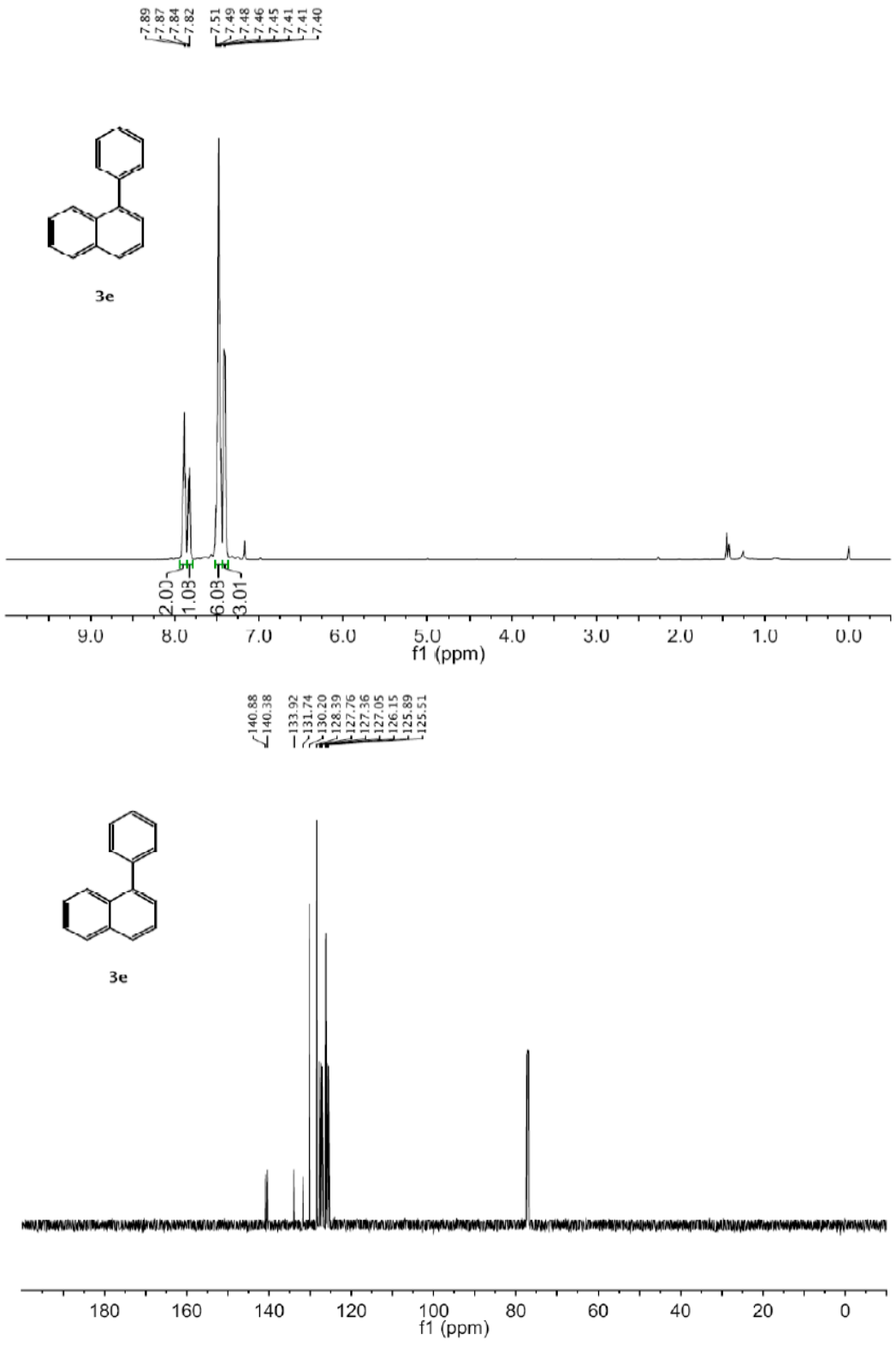


Figure SF13. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 1-phenylnaphthalene (**3e**) in $CDCl_3$

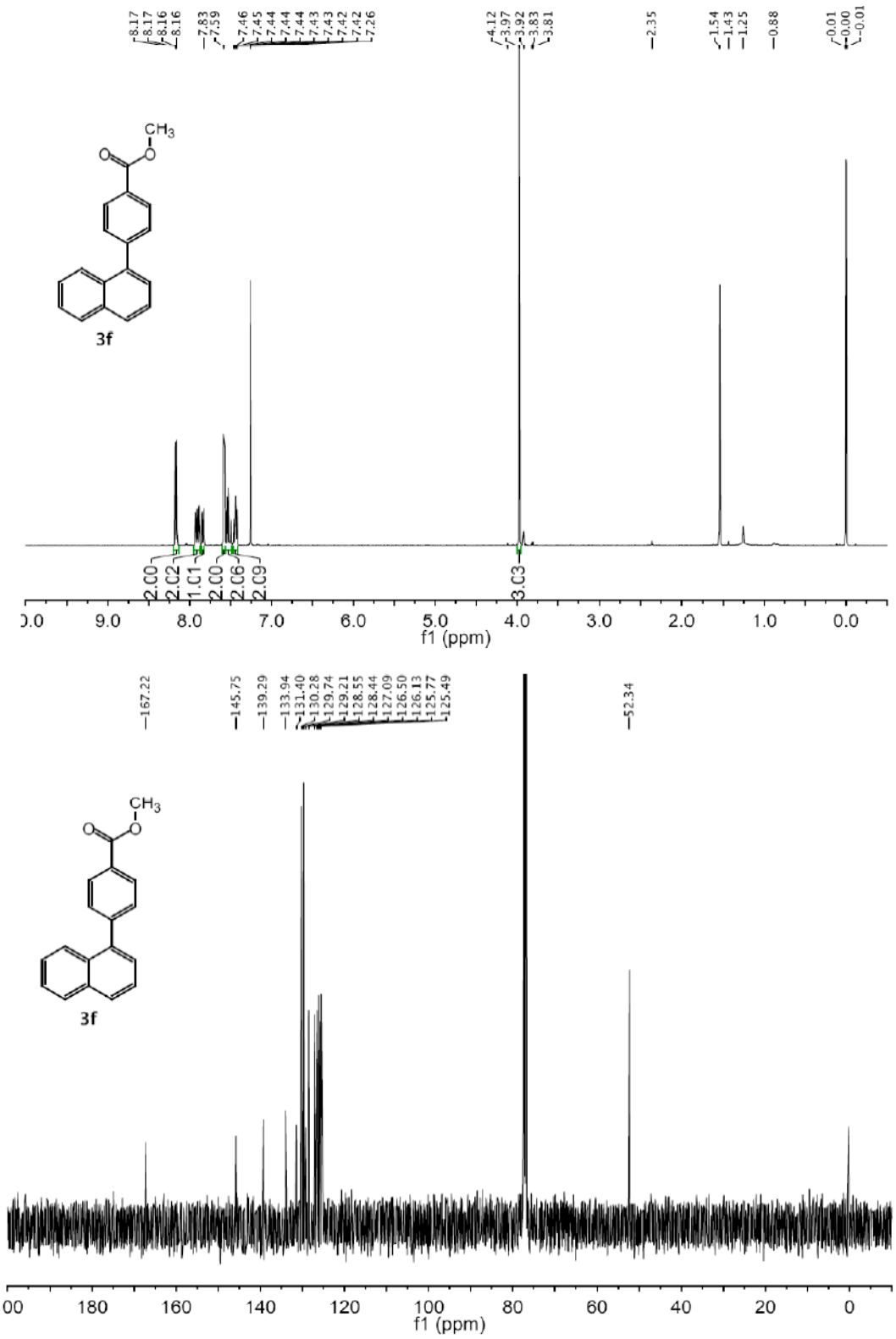


Figure SF14. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4-(naphthalen-1-yl)benzoate (**3f**) in $CDCl_3$

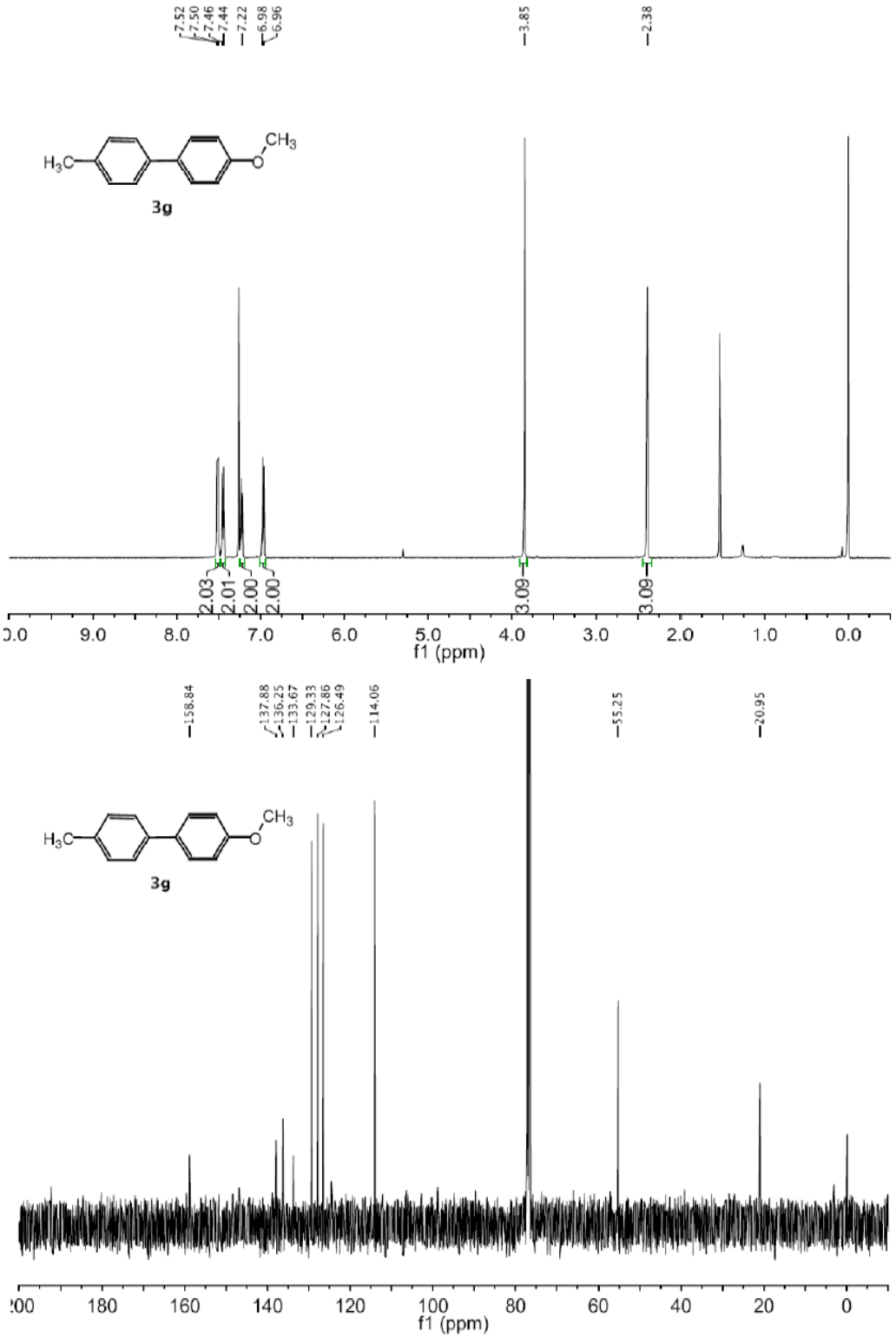


Figure SF15. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 4-methoxy-4'-methyl-1,1'-biphenyl (**3g**) in $CDCl_3$

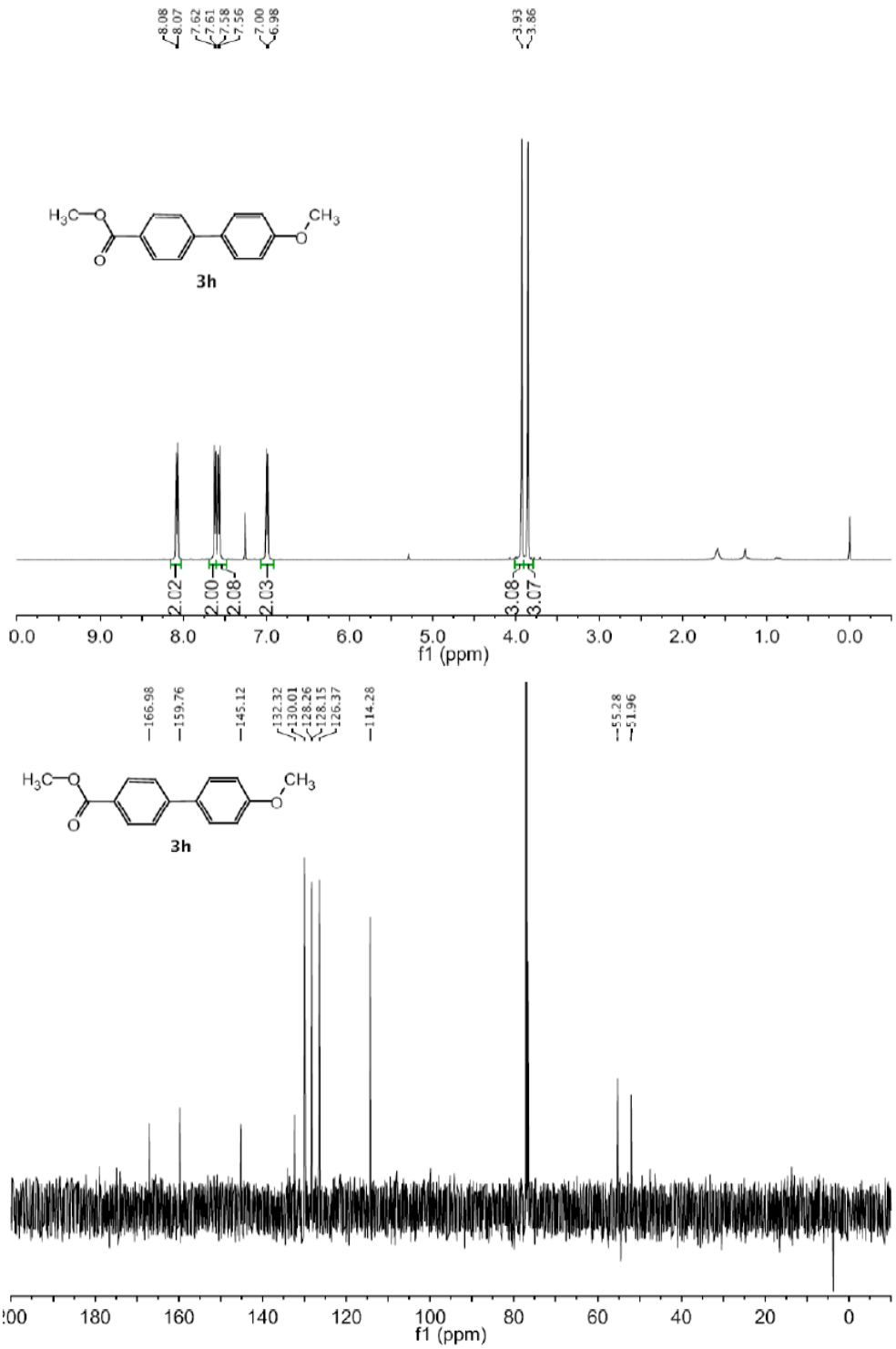


Figure SF16. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (**3h**) in $CDCl_3$

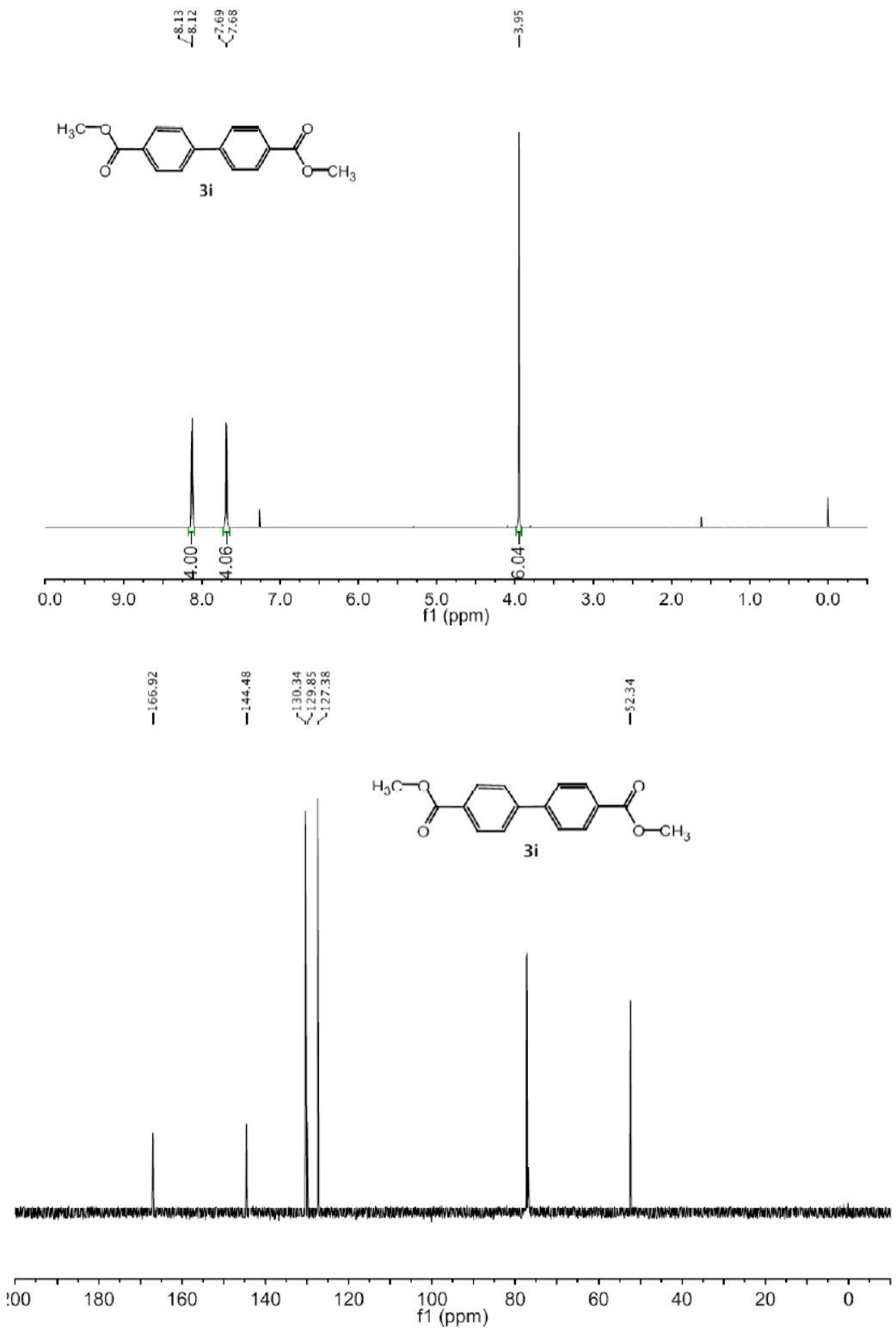


Figure SF17. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of dimethyl [1,1'-biphenyl]-4,4'-dicarboxylate (**3i**) in $CDCl_3$

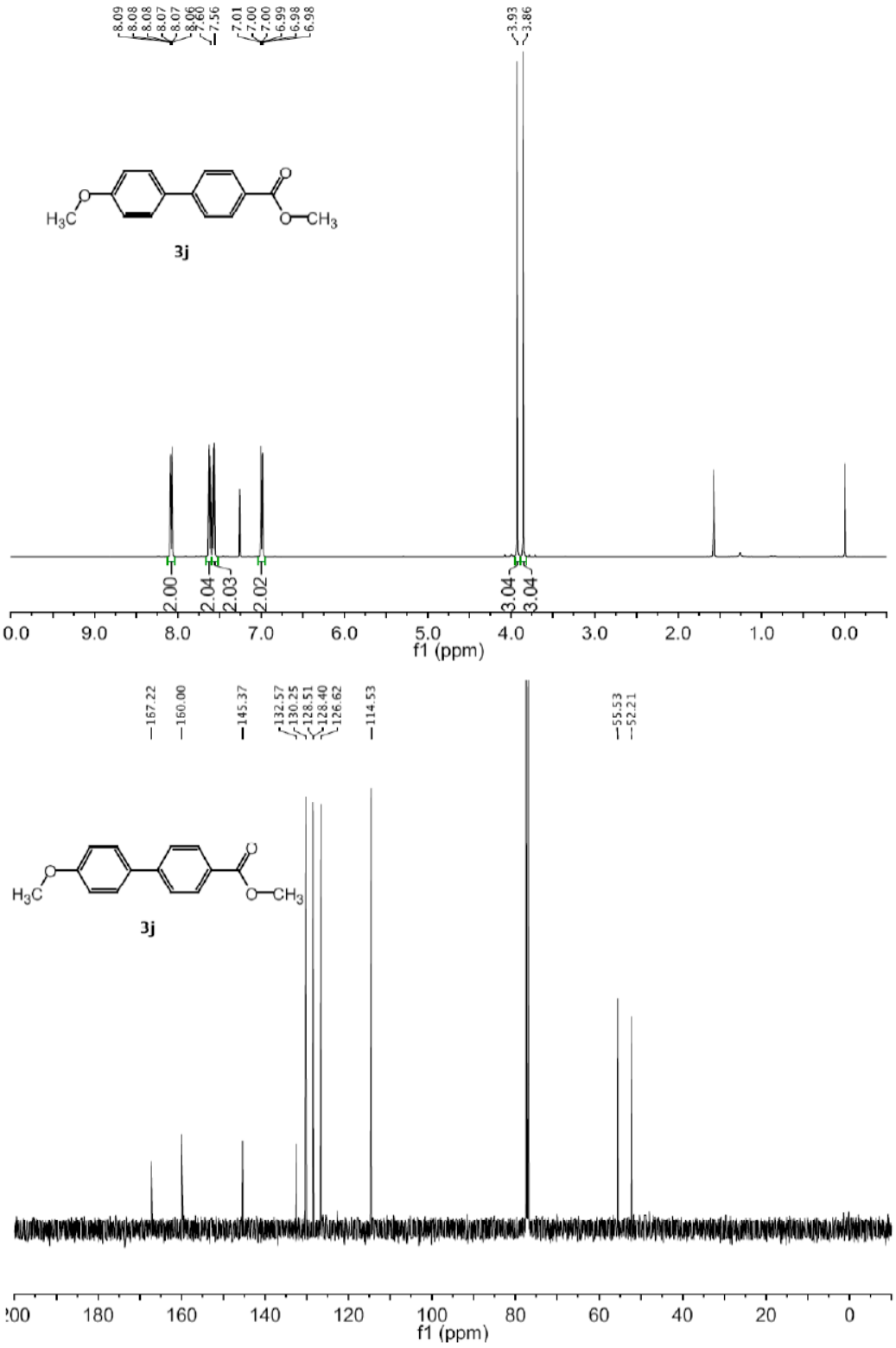


Figure SF18. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (**3j**) in $CDCl_3$

3.2.6 Account of Contribution

In this work, I contributed to half the experimental work as well as the data organization. I also participated in manuscript writing and revising.

3.2.7 References

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3.3 Comparison of Arylboron Based Nucleophiles in Ni Catalyzed Suzuki–Miyaura Cross-Coupling with Aryl Mesylates, Sulfamates and Halides

3.3.1 Introduction

As discussed in Chapter 1, both industry and academia use Suzuki-Miyaura cross-coupling to construct biaryl structures in organic, polymer and supermolecular chemistry.[2-12] Replacing Pd with less expensive metals, such as Ni,[10,12] developing new electrophiles including C-O based electrophiles,[10,12] targeting sterically hindered substrates,[13] and developing new nucleophiles other than boronic acids are the most recent developments.[4,8,9] With the development of arylboron reagents, currently, arylboronic acids,[4] aryltrifluoroborates,[8,9] aryl neopentylglycolboronates[14,15] and aryl pinacolboronates[5] are the four major classes of boron nucleophiles employed in Suzuki-Miyaura cross-coupling reaction. Great progress has been recently made in employing C-O based electrophiles[10,12] in nickel catalyzed cross-coupling reactions with arylboronic acids, boronates, and trifluoroborates.

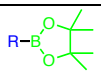
To choose the most desired coupling reagent in nickel catalyzed Suzuki-Miyaura cross-coupling, we compared the four boron nucleophiles in Suzuki-Miyaura cross-coupling reactions. Progress on developing boron-based nucleophiles has mainly focused on applying aryltrifluoroborates and boronates in the cross-coupling reactions. The reactivity, stability, and economy of boron-based nucleophiles in the cross-coupling reactions differ from each other.[2,4,9,16] The reaction conditions optimized for arylboronic acids are not necessary applicable to aryl trifluoroborates and boronates. The cross-coupling reactions involving aryltrifluoroborates require different conditions due to the low solubility of aryltrifluoroborates in solvents used for the cross-coupling of arylboronic acids.[2,9] Moreover, it is necessary to cleave trifluoroborates *in situ*.[2,9] Catalytic systems for the cross-coupling of aryl methyl ethers with aryl neopentylglycolboronates have been developed.[15] Recently, we reported two efficient catalytic systems for the cross-coupling aryl neopentylglycolboronates with aryl sulfonates and sulfamates at room

temperature.[17,18] We recently detected the reactivity difference between arylboronic acid and aryl neopentylglycolboronate in the cross-coupling reactions with aryl mesylates catalyzed by $Ni(COD)_2/PCy_3/K_3PO_4$ in THF.[17] Cross-coupling of aryl neopentylglycolboronates with aryl esters, carbamates, and carbonates is less efficient but more selective than reactions carried out with arylboronic acids.[18] Other groups also observed the difference of the reactivity between arylboronic acids, aryl boronates and trifluoroborates in the cross-coupling reactions.[19,20] When applying aryl boronates in the cross-coupling reactions, pinacolboronates[5] and neopentylglycolboronates[15] are the most commonly employed nucleophiles. However, the difference between the efficiency of these two aryl boronates in Suzuki-Miyaura cross-coupling reactions is not well understood. Here, we report a study of the efficiency of arylboron based nucleophiles, boronic acid, potassium trifluoroborate, neopentylglycolboronate and pinacolboronate in Ni-catalyzed cross-coupling with two aryl C-O based electrophiles, mesylates and sulfamates.

A Brief Discussion of Atom Economy and the Synthesis of Arylboronic Acids, Aryltrifluoroborates, Aryl Neopentylglycolboronates, and Aryl Pinacolboroantes. Due to their high reactivity, commercial and preparative availability, arylboronic acids are the most widely investigated arylboron-based nucleophiles in Suzuki-Miyaura cross-coupling reaction. Arylboronic acids are also the most atom economic[16] of all arylboron-based nucleophiles (Table 3.11).

The most common preparation of arylboronic acid is through electrophilic trapping of organolithium or Grignard reagents followed by cleavage of the ester bonds in an aqueous acid.[21] The metal and alkyl groups are lost during this reaction. This method cannot tolerate electrophilic functional groups sensitive to organolithium or Grignard reagents and sometimes suffers from regioselectivity problems.[21] (Scheme 3.2, a)

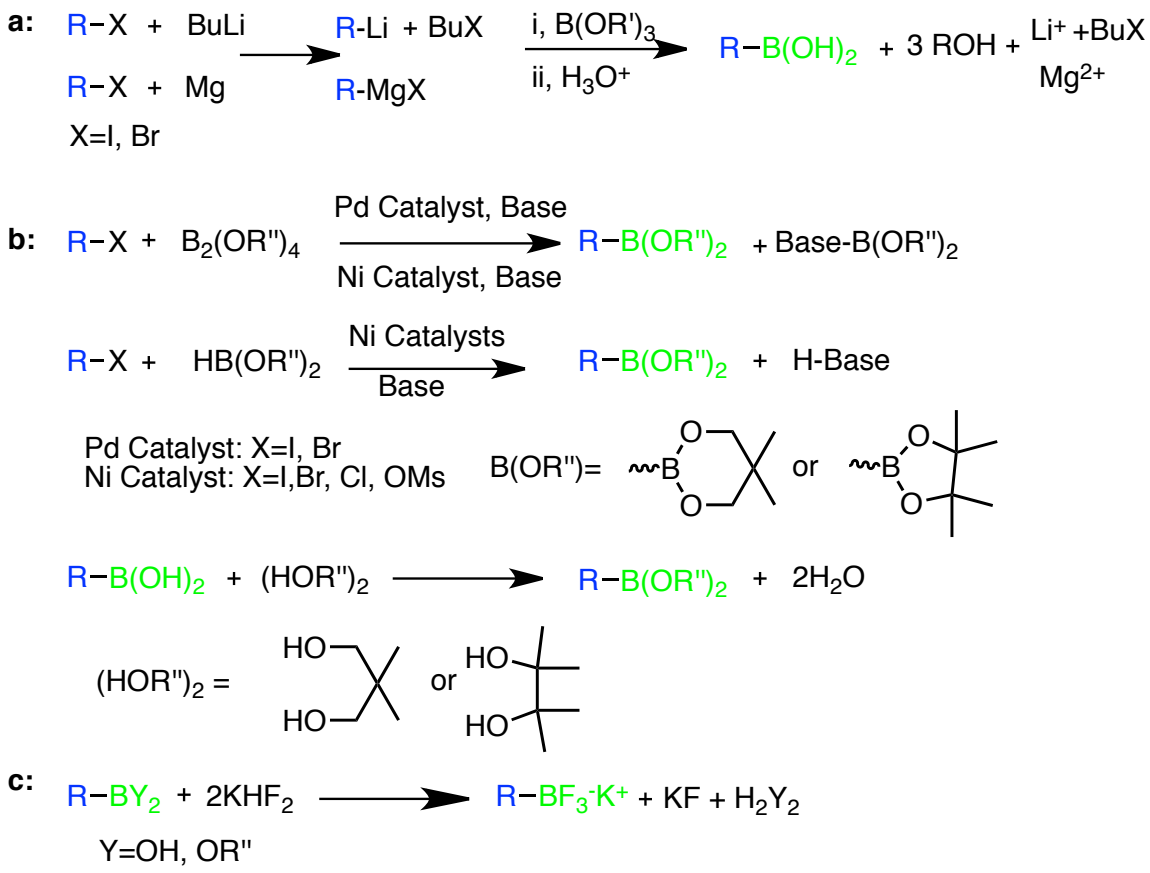
Table 3.11. The Economy of Boron Based Nucleophiles in Suzuki-Miyaura Cross-Coupling Reactions

	R–$B(OH)_2$	R–$BF_3^-K^+$		
Formula	BH_2O_2	BF_3K	$C_5H_{10}BO_2$	$C_6H_{12}BO_2$
M.W.	44.8257	106.9045	112.9427	126.9693
Price in $ per mole[a]		7.63[b]	2.62	85.20

[a]Commercial source. [b]Two equivalents of KHF_2 are consumed per boronic acid.

However, arylboronic acids decompose readily by protodeborylation and oxidation both during the storage and during the cross-coupling process.[8,9] For instance, Buchwald studied the half-life of polyfluorinated and 2-heteroarylboronic acids.[23] They found the half life of 2,3,6-trifluorophenyl boronic acid was only 2 min in THF and K_3PO_4 (0.5 M) solution. The fast decomposition of boronic acids decrease the efficiency of boronic acids leading to the requirement of large excess of boronic acid for coupling reactions and difficulty to carry though multiple reaction steps. [8,9,23] Moreover, most arylboronic acids are waxy solids, increasing the difficulty of purification.[8,9] The presence of dimeric or trimeric species of arylboronic acids makes it difficult to calculate their reaction stoichiometry.[8,9]

Scheme 3.2. The Synthesis of Arylboron-Based Nucleophiles



An alternative way to introduce the boron-containing group is through transition metal catalyzed borylation.[4] Miyaura discovered the Pd catalyzed borylation with tetraalkoxy-diboron reagents.[6] Recently, Ni has been applied as an inexpensive catalyst for borylation reactions of aryl iodides, bromides, chlorides, sulfonates,[14,24-26] and carbamates.[27] Borylation of sterically hindered aryl halides using tetraalkoxydiboron was reported in good to excellent yields using both nickel[28] and palladium catalysts.[29] Moreover, applying nickel catalysts can replace the need of expensive and non-atom economic tetraalkoxy-diboron reagents by the easily prepared, even *in situ* formed borane reagents (Scheme 3.2, b).[14,24-26] Aryl boronates can also be synthesized *via* esterification of arylboronic acids with corresponding diols.[4] Most of the aryl boronates are crystalline solids and can be purified by column chromatography. The transition metal catalyzed borylation reaction tolerates sensitive functional groups. Aryl boronates exist in monomeric form and have a higher molecular weight than the corresponding arylboronic acids hence lower atom economy. However,

for some applications such as stepwise polymerization,[11] it is important to have a perfect control of the reaction stoichiometry. Therefore, aryl boronates are also important cross-coupling partners. Two aryl boronates are frequently employed in cross-coupling reactions, namely pinacolboronatess[6] and neopentylglycolboronates.[10,15,18,30,31] Neopentyglycolboronates are more atom-economic than pinacolboronates and less expensive (Table 3.11). Pinacol is about six times more expensive than potassium hydrofluoride, while the price of neopentylglycol is only one sixth of the price of potassium hydrofluoride (Table 3.11, column 3 and 4). However, in previous chapters, we have demonstrated aryl boronates are less reactivie in the nickel catalyzed Suzuki-Miyaura cross-coupling of phenol derivatives, despite the nickel sources, base, solvent and temperature.[18,24]

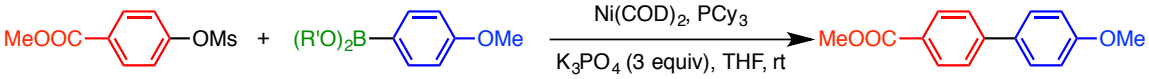
Aryltrifluoroborates are also synthesized as a protecting form of arylboronic acids. They are synthesized via reacting other boron based nucleophiles with KHF_2.[32] They are stable on shelf for several years.[8,9] Aryltrifluoroborates exist in monomeric form hence reaction stoichiometry can be calculated. The molecular weight of aryltrifluoroborate is higher than that of arylboronic acid but lower than that of aryl boronates (Table 3.11). Therefore, the atom economy of aryltrifluoroborates is lower than that of arylboronic acids but higher than that of aryl boronates (Table 3.11, column 3). Considering the price of the protecting group, aryltrifluoroborate is about six times less expensive than aryl pinacolboronate but about six times more expensive than neopentylglycolboronates (Table 3.11).

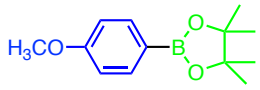
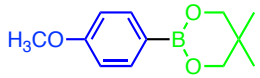
3.3.2 Results and Discussion

A Comparison of the Competitive and Kinetic Experiments of Arylboron-Based Nucleophiles. The turnover number (TON) and the turnover frequency (TOF) are two important characters for catalytic reactions. The efficiency of catalysts are best represented by TON or TOF of the reaction.[33,34] The TON of nickel catalyzed coupling reactions[3,35] is generally lower than that of palladium catalyzed coupling reactions. The TON of $Ni(COD)_2/PCy_3$ catalyzed cross-coupling of 4-methoxyphenyl neopentylglycolboronate and 4-methoxyphenyl pinacolboronate with methyl

4-[(methylsulfonyl)oxy]benzoate were determined (Table 3.12) to compare the efficiency of the cross-coupling of these two boronates.

Table 3.12. The Turnover Number (TON) and Turnover Frequency (TOF) for the Cross-Coupling of Methyl 4-((Methylsulfonyl)oxy)benzoate with 4-Methoxyphenyl Neopentylglycolboronate and 4-Methoxyphenyl Pinacolboronate[a]



Boronate[a]	$Ni(COD)_2$ (%)	PCy_3 (%)	Time (h)	Yield[b] (%)	TON ($mol_{mesylate}$ /mol_{nickel})	TOF ($mol_{mesylate}$/ (mol_{nickel}•h))
	1	2	60	60	60	1
	1	2	60	96	96	1.6

[a]Reaction Conditions: Ar-X (0.3 mmol), aryl boronate (0.3 mmol), $Ni(COD)_2$ (0.003 mmol), PCy_3 (0.006 mmol), K_3PO_4 (0.9 mmol), THF (1 mL). [b]Reaction yield determined by NMR.

The TON and TOF of cross-coupling using 4-methoxyphenyl neopentylglycolboronate is higher than those of cross-coupling using 4-methoxyphenyl pinacolboronate. This shows that 4-methoxyphenyl neopentylglycolboronate is more effective than 4-methoxyphenyl pinacolboronate.

We designed competitive experiments that can be used to determine the efficiency difference of two boron-based nucleophiles in cross-coupling reactions rapidly. To validate the results obtained from competitive experiments, kinetic experiments were also carried out since kinetic experiments are direct sources of reactivity data. Competitive experiments are valid only when the rate of diol exchange is much smaller than the rate of the competitive cross-coupling reaction. Two sets of kinetic experiments were performed. The first one was used to compare the reactivity of two aryl boronates and the second one to compare the rate of competitive experiments with the rate of diol exchange experiments. To slow down the reaction and decease the impact of

sampling process to reaction progress, these kinetic experiments were carried out at half of the concentration of the rest of the experiments to be discussed in this report (Figure 3.2).

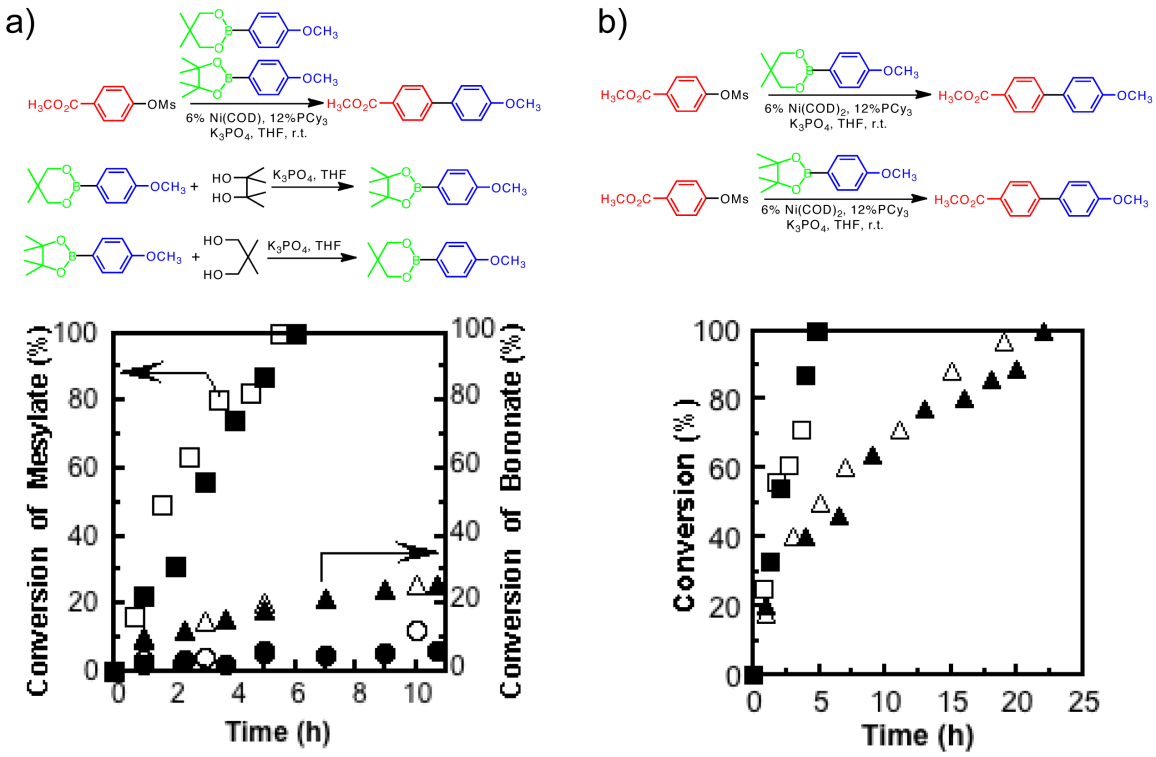


Figure 3.2. a) Comparison of the rate of the competitive cross-coupling of 4-methoxyphenyl pinacolboronate and 4-methoxyphenyl neopentylglycolboronate (■, □), diol exchange rate of 4-methoxyphenyl neopentylglycolboronate with pinacol (▲, △), and diol exchange rate of 4-methoxyphenyl pinacolboronate with neopentylglycol (●, ○). b) comparison of the rate of the cross-coupling of 4-methoxyphenyl neopentylglycolboronate (■, □) and 4-methoxyphenyl pinacolboronate (▲, △) with methyl 4-((methylsulfonyl)oxy)benzoate. In all kinetic experiments, two sets of experimental data, plotted in solid and open symbols, were used.

As can be seen clearly from Scheme 3.2 a, the overall rate of the competitive experiments is 8 times faster than the rate of diol exchange of 4-methoxyphenyl neopentylglycolboronate with pinacol, and 10 times faster than the rate of diol exchange of 4-methoxyphenyl pinacolboronate with neopentylglycol when the concentration of boronates are the same. Therefore, the diol

exchange reaction will not impact significantly the conclusion obtained from competitive experiments. The overall reactivity of 4-methoxyphenyl neopentylglycolboronate is 5 times higher than that of 4-methoxyphenyl pinacolboronate in cross-coupling with methyl 4-((methylsulfonyl)oxy) benzoate (Figure 3.2, b). This is in agreement with the results obtained from the competitive experiments. Based on this set of experiments the rest of the reactivity studies will be carried out by competitive experiments.

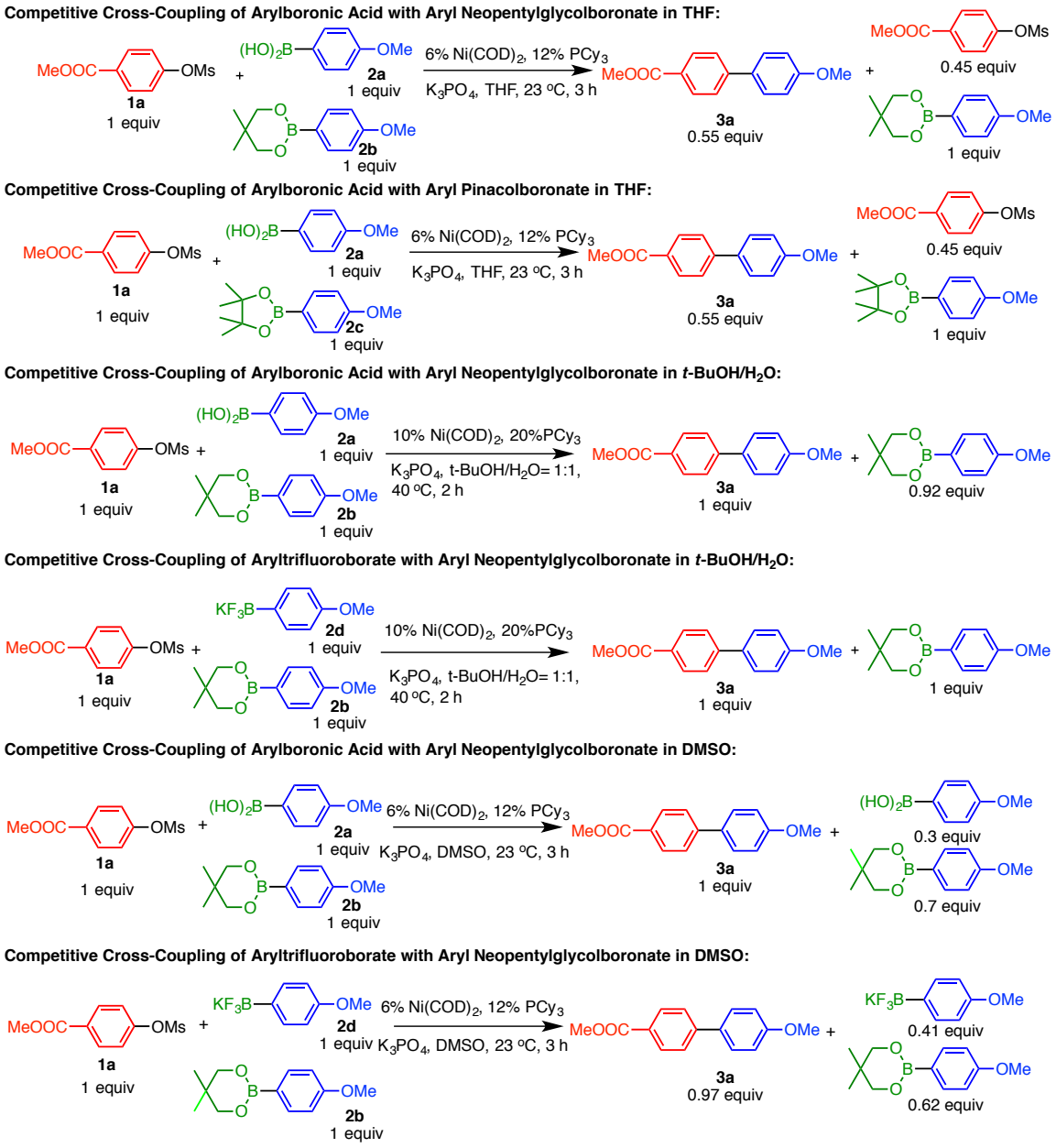
Competitive Experiments of Arylboron-Based Nucleophiles. The comparison of the reactivity of different boron nucleophiles should be carried out under conditions optimized for different boron nucleophiles. To compare the efficiency of arylboron-based nucleophiles, several competitive experiments were carried with different catalytic systems. For the comparison of 4-methoxyphenylboronic acid with 4-methoxyphenyl boronate, reaction conditions developed for room temperature nickel catalyzed cross-coupling reactions of boronic acids[36,37] and boronic esters[31,38] with aryl sulfonates were applied. A mixture of equal equivalence of aryl mesylate, 4-methoxyphenyl boronic acid and 4-methoxyphenyl boronates were added at the beginning of the reaction. After 3 h, the reaction was worked-up and the crude mixture was examined by 500 MHz, ^{1}H-NMR. The mesylate (0.45 equiv), the product (0.55 equiv) and the 4-methoxyphenyl boronate (1 equiv) were detected by ^{1}H NMR (Scheme 3.3, part a). It is reasonable to conclude that the product was produced solely from 4-methoxyphenylboronic acids. Neither aryl neopentylglycolboronate nor aryl pinacolboronate were consumed in the reaction.

Comparison of aryltrifluoroborates with other boron nucleophiles cannot be carried out in THF because aryl potassium trifluoroborates are not soluble in dry THF. To compare aryltrifluoroborates with aryl boronates, the catalytic system developed by the Molander laboratory for cross-coupling of aryl mesylates and pivalates with aryl and heteroaryltrifluroborates[39] was applied with the only modification that a lower reaction temperature was used. In 2 h, Arylboronic acid and aryltrifluoroborate were fully consumed while the aryl boronates remained almost unconsumed, as determined by ^{1}H NMR from the composition of the crude mixture. 4-Methoxyphenylboronic acid was compared with 4-methoxyphenyl neopentylglycolboronate under identical condition. Protodeborylation was

detected by ^{1}H NMR and 0.08 equiv boronic ester was consumed to compensate the difference. In the presence of water and base, potassium trifluoroborate hydrolyzed and was completely consumed, while 4-methoxyphenyl neopentylglycolboronate remained unconsumed (Scheme 3.3, part b).

To study the impact of the amount of water to the efficiency of arylboron-based nucleophiles, anhydrous DMSO and K_3PO_4 dried at 40 ^{o}C under vacuum overnight were employed. Interestingly, the efficiency difference of arylboron-based nucleophiles decreases dramatically when DMSO was used as solvent. Taking the amount of boron species consumed in a reaction as the efficiency, an arylboronic acid was only 2.3 times more efficient than an neopentylglycolboronate and aryltrifluoroborate was only 1.55 times more efficient than neopentylglycolboronate, respectively (Scheme 3.3, part c). It is noteworthy that the efficiency difference of aryltrifluoroborates and aryl boronates is highly dependent on the amount of water involved in the reaction. When the reaction was carried out in the absence of water (flame dried K_3PO_4), no cross-coupling product was observed when aryltrifluoroborate was employed.

Scheme 3.3. Competitive Cross-Coupling of Arylboron-Based Nucleophiles

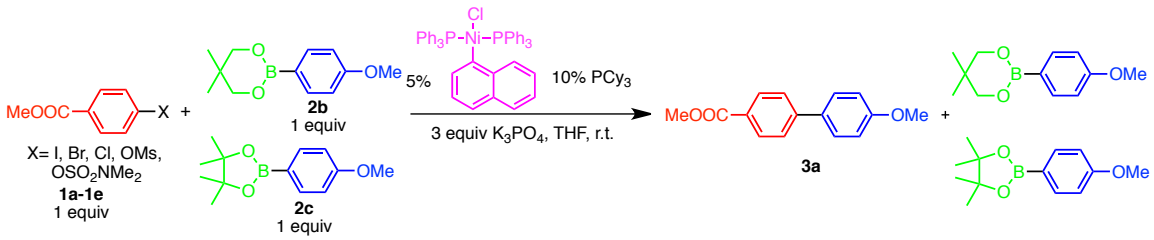


Above all, the efficiency of arylboronic acid is the highest of the four arylboron-based nucleophiles studied. Aryltrifluoroborates are more efficient than aryl boronates when sufficient water for cleavage of C-F bond is present in the reaction. When reactions are carried out in the absence of water, aryltrifluoroborates are inefficient. The difference between the efficiency of aryl

neopentylglycolboronates and pinacolboronates will be discussed in more detail in the following subchapter.

Comparison of Aryl Neopentylglycolboronates and Aryl Pinacolboronates. Aryl boronates are important cross-coupling partners for the Suzuki-Miyaura cross-coupling reactions. For stepwise polymerizations,[11] aryl boronates are preferable to arylboronic acids because boronates exist only in monomeric form. Pinacolboronates are presently widely used.[11] However, pinacol is a relatively expensive diol and has a higher molecular weight than neopentylglycol (Table 3.11). It is reasonable to replace aryl pinacolboronates with aryl neopentylglycolboronates if the reactivities of both boronates are similar. However, the reactivity difference of neopentylglycolboronate and pinacolboronate in nickel catalyzed Suzuki-Miyaura cross-coupling reactions of C-O electrophiles are not well understood. Competitive cross-coupling experiments of aryl neopentylglycolboronates and pinacolboronates catalyzed by $Ni(COD)_2/PCy_3/K_3PO_4$[30] and $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2/PCy_3/K_3PO_4$[31] in THF were carried out to study the efficiency difference of these two aryl boronates. These reaction conditions were optimized by our group for cross-coupling of aryl and heteroaryl mesylates and sulfamates with aryl and heteroaryl neopentylglycolboronates. Aryl iodides, bromides, chlorides, mesylates and sulfamates were employed as electrophiles. Equal equivalents of electrophile and the two boronates were added at the beginning of the reaction, and the crude reactions were examined by ^1H NMR. Blank experiments were carried out to exclude the possibility of consumption of boronates by protodeborylation. It was observed that less 4-methoxyphenyl neopentylglycolboronate than pinacolboronates was left unconsumed in the crude reaction mixture in all cases, indicating that more neopentylglycolboronate than pinacolboronates was consumed in this reaction (Table 3.13 and Table 3.14).

Table 3.13. Competitive Cross-Coupling of 4-Methoxyphenyl Pinacolboronate and 4-Methoxyphenyl Neopentylglycolboronate in Reaction Catalyzed by $Ni^{II}Cl(1\text{-Naphthyl})(PPh_3)_2/PCy_3/K_3PO_4$ in THF[a]

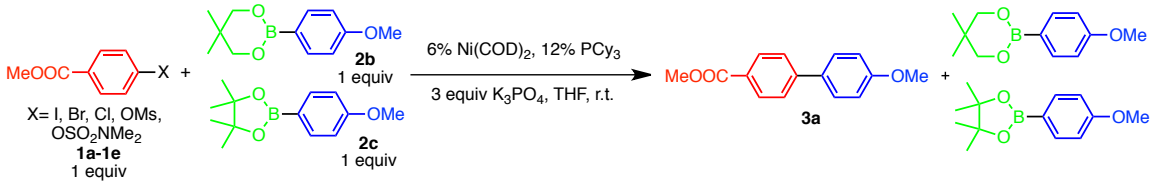


entry	X	time (h)	**3a** equiv[b]	**2b** equiv[b]	**2c** equiv[b]	**2b/2c**[c]
1	I (**1b**)	1.7	1	0.26	0.74	2.8
2	Br (**1c**)	3	0.64	0.45	0.86	3.9
3	Cl (**1d**)	4	0.79	0.28	0.64	2.0
4	OMs (**1a**)	3	1	0.15	0.85	5.7
5	OSO_2NMe_2 (**1e**)	12	1	0.28	0.72	2.6

[a]Reaction Conditions: Ar-X (0.3 mmol), arylboronic ester (0.3 mmol) each, $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$ (0.015 mmol), PCy_3 (0.03 mmol), K_3PO_4 (0.9 mmol), THF (1 mL). [b]Equivalence determined by NMR. [c]Ratio refers to consumption of **2b** to **2c** in reaction.

The equivalents of product and boronates left in the crude reaction mixture was calculated from the NMR spectrum of the crude mixture. The ratios between the consumption of 4-methoxyphenyl neopentylglycolboronates to pinacolboronates were calculated and listed in Table 3.13 and Table 3.14. The efficiency difference was best presented when aryl mesylate was used as an electrophile. The efficiency of neopentylglycolboronate is nearly six times higher than that of aryl pinacolboronate when cross-coupled with aryl mesylates (Table 3.13, entry 4 and Table 3.14, entry 4). Competitive experiments of electron-deficient aryl boronates were also carried out. The efficiency trend was similar (Supporting Information).

Table 3.14. Competitive Cross-Coupling of 4-Methoxyphenyl Pinacolboronate and 4-Methoxyphenyl Neopentylglycolboronate Catalyzed by $Ni(COD)_2/PCy_3/K_3PO_4$ in THF[a]

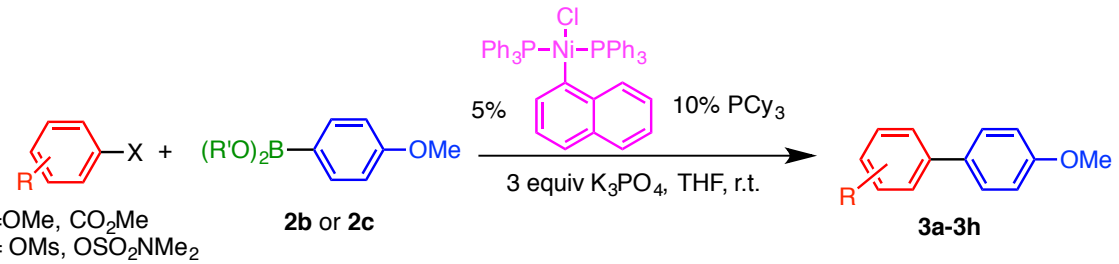


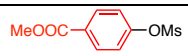
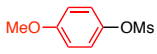
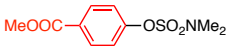
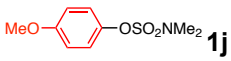
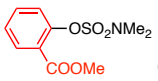
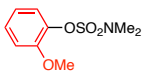
entry	X	time (h)	**3a** equiv[b]	**2b** equiv[b]	**2c** equiv[b]	**2b/2c**[c]
1	I (**1b**)	1	1	0.23	0.77	3.3
2	Br (**1c**)	3	0.44	0.61	0.98	4.8
3	Cl (**1d**)	3	0.34	0.74	0.98	3.3
4	OMs (**1a**)	2.5	1	0.15	0.85	5.7
5	OSO_2NMe_2 (**1e**)	12	1	0.33	0.67	2.0

[a]Reaction Conditions: Ar-X (0.3 mmol), arylboronic ester (0.3 mmol) each, $Ni(COD)_2$ (0.018 mmol), PCy_3 (0.036 mmol), K_3PO_4 (0.9 mmol), THF (1 mL). [b]Ratio determined by NMR.[c]Ratio refers to consumption of **2b** to **2c** in reaction.

Competitive experiments showed the reactivity difference of these two boronates. However, it also might be possible that one boronate was deactivating the other one. Hence, $Ni(COD)_2/PCy_3/K_3PO_4$[17] and $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2/PCy_3/K_3PO_4$[31] catalyzed cross-coupling reactions of aryl mesylates and sulfamates bearing electron-withdrawing and electron-rich substituents were carried out in THF. After the same reaction time, lower GC yields and isolated yields were observed for the cross-coupling reactions carried out with 4-methoxylphenyl pinacolboronates than with neopentylglycolboronates in both catalytic systems. The reactivity difference was best observed for electron rich substrates. For example, after 4 h, methyl 4-[(methylsulfonyl)oxy]benzoate was completely consumed when cross-coupled with 4-methoxyphenyl neopentylglycolboronate, while only 75% of the mesylate was consumed when cross-coupled with 4-methoxylphenyl neopentylglycolboronate (Table 3.15, entry 1).

Table 3.15. Comparison of the Efficiency of 4-Methoxyphenyl Neopentylglycolboronate and 4-Methoxyphenyl Pinacolboronate in the Cross-Coupling with Aryl Mesylates and Sulfamates Catalyzed by $Ni^{II}Cl(1\text{-Naphthyl})(PPh_3)_2/PCy_3/K_3PO_4$ in THF[a]

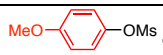
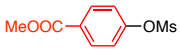
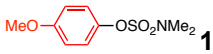
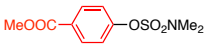
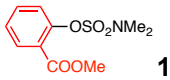
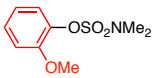


1a, 1f-1l	2b		2c	
	Time (h)	Convn[b]/Yield[c](%)	Time (h)	Convn[b]/Yield[c] (%)
 **1a**	4	100/99	4	75/57
 **1f**	12	100/94	12	50/50
 **1g**	14	100/89	14	100/77
 **1h**	14	100/87	14	70/44
 **1i**	10	100/81	20	97/86
 **1j**	24	83/80	24	51/46
 **1k**	14	100/93	14	95/90
 **1l**	60	100/94	74	96/88

[a]Reaction Conditions: Ar-X (0.3 mmol), aryl boronate (0.3 mmol) each, $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$ (0.015 mmol), PCy_3 (0.03 mmol), K_3PO_4 (0.9 mmol), THF (1 mL). [b]Conversion determined by GC. The GC yield has always the same value as the conversion. [c]Isolated yield.

The efficiency difference was even larger when the $Ni(COD)_2/PCy_3/K_3PO_4$ catalytic system was employed. Only 31% of methyl 4-[(methylsulfonyl)oxy]benzoate was cross-coupled after 4 h when 4-methoxyphenylboronate was used (Table 3.16, entry 1). With results from both competitive and comparison experiments, it is reasonable to conclude that aryl neopentylglycolboronate is more efficient, less expensive, more atom economic than aryl pinacolboronate in nickel catalyzed cross-couplng reactions with aryl C-O based electrophiles.

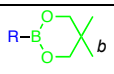
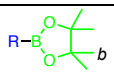
Table 3.16. Comparison of the Efficiency of 4-Methoxyphenyl Neopentylglycolboronate and 4-Methoxyphenyl Pinacolboronate in the Cross-Coupling with Aryl Mesylates and Sulfamates Catalyzed by $Ni(COD)_2/PCy_3/K_3PO_4$ in THF[a]

1a, 1f-1l	2b		2c	
	time (h)	Convn[b]/Yield[c] (%)	time (h)	Convn[b]/Yield[c] (%)
 **1f**	4	90/89	4	31/30
 **1a**	4	100/94	4	75/56
 **1g**	9	100/90	9	96/81
 **1h**	8	99/89	12	88/86
 **1j**	12	100/93	12	58/63
 **1i**	8	100/92	8	91/88
 **1k**	12	100/98	12	100/98
 **1l**	12	100/99	12	45/38

[a]Reaction Conditions: Ar-X (0.3 mmol), aryl boronate (0.36 mmol), $Ni(COD)_2$ (0.018 mmol), PCy_3 (0.036 mmol), K_3PO_4 (0.9 mmol), THF (1 mL). [b]Conversion determined by GC. The GC yield is always the same as the conversion. [c]Isolated yield.

The Comparison of Efficiency of Different Boron-Based Nucleophiles in Nickel Catalyzed Cross-Coupling Reactions in Different Solvents. A summary of the efficiency trend for boron based nucleophiles in nickel catalyzed Suzuki-Miyaura cross-coupling reactions with C-O electrophiles are presented in Table 3.17. The consumption of boron based nucleophiles in the cross-coupling with methyl 4-[(methylsulfonyl)oxy]benzoate was considered as the measurement of efficiency. Arylboronic acid is the most reactive of all boron-based nucleophiles. In the presence of water, aryltrifluoroborates will cleave and form *in-situ* the corresponding arylboronic acid. Hence, aryltrifluoroborates were much more efficient in cross-coupling with aryl C-O electrophiles than aryl boronates in *t*-BuOH/water mixture. However in DMSO, all boron-based nucleophiles showed a comparable reactivity. The efficiency of arylboronic acid and boronate decreased when DMSO was used as solvent. Nevertherless, the reactivity trend remains arylboronic acid > aryltrifluoroborates > aryl boronates. Aryl neopentylglycolboronates were more efficient than aryl pinacolboronates in THF by a factor of 6 (Table 3.17, entry 3).

Table 3.17. Efficiency Trend for Boron Based Nucleophiles For the Cross-Coupling Reactions[a]

Solvent	R–B(OH)$_2$ [b]	R–BF$_3^-$K$^+$ [b]	 [b]	 [b]
t-BuOH /H$_2$O=1:1[c]	>>1	>>1	1	NA
DMSO[d]	2.3	1.55	1	NA
THF[d]	>>1	N.R. (insoluble)	6	1

[a]Comparison was made based on the cross-coupling with methyl 4-[(methylsulfonyl)oxy]benzoate. The least reactive species under each condition was arbitrary set as one. The data was calculated according to the consumption of boron-based nucleophiles. The trend for both aryl boronate is consistent for all electrophiles. [b]R was 4-methoxyphenyl group. [c]10% Ni(COD)$_2$, 20% PCy$_3$, K$_3$PO$_4$ (3 equiv), 40 ^{o}C. [d]6% Ni(COD)$_2$, 12% PCy$_3$, K$_3$PO$_4$ (3 equiv), 23 ^{o}C.

3.3.3 Conclusions

The efficiency and atom economy of arylboron-based nucleophiles in nickel catalyzed cross-coupling reactions with aryl C-O based electrophiles were investigated. Arylboronic acids have both the highest atom economy and reactivity in cross-coupling reactions. However, the decomposition and the presence of dimers and trimers of boronic acids limit their applicability. In the presence of water, aryltrifluoroborates are more efficient in the cross-coupling reactions than aryl boronates. Aryltrifluoroborates are also shelf stable, less expensive than pinacolboronates and easily prepared from other boron nucleophiles. However, the extra step in the preparation and the requirement of polar solvents and water for their cross-coupling reactions limits the use of aryltrifluoroborates in synthetic organic chemistry, material and polymer chemistry. Aryl neopentylglycolboronates, with higher atom-economy, lower price, higher efficiency than aryl pinacolboronates, accompanied with two-step, one-pot nickel catalyzed neopentylglycolborylation, are expected to play a more important role in Suzuki-Miyaura cross-coupling reactions with aryl C-O electrophiles. Moreover, the reactivity difference of arylboronic acids in THF and trifluoroborates in *t*-BuOH/H_2O mixture with aryl boronates made it possible to apply orthogonal cross-coupling of arylboronic acids or trifluoroboratess with aryl boronates in organic synthesis.

3.3.4 Experiments

General Experimental Methods. $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$[37] and (4-methoxyphenyl)boronic acid were prepared according to literature methods.[40] 2-(4-Methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane and 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane were synthesized by the esterification of (4-methoxyphenyl)boronic acid with the corresponding diol. (4-Methoxyphenyl)trifluoroborate was synthesized according to a literature procedure.[25] K_3PO_4 from a commercial source was dried at 40 ^oC under vacuum overnight prior to use. THF was distilled over sodium/benzophenone. *t*-BuOH and water were degassed by bubbling with N_2 overnight. DMSO was distilled from calcium hydride. Aryl mesylates and aryl sulfamates were synthesized according to literature procedures.[26,41] All other reagents were used as received from commercial

sources. General procedure for the cross-coupling reactions were carried out according to a literature procedure elaborated in our laboratory.[17,31] ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded using TMS as internal standard. High-resolution mass spectra of new compounds were obtained on a high-resolution double focusing chemical ionization mass spectrometer. A GC coupled with an FID detector and column HP 19091J-413 (5%-phenyl)-methylpolysiloxane 30 m length 0.32 mm internal diameter was used to follow the reaction conversions and to assess the purity of the final compounds. This method is complementary to the NMR technique. The crude reaction mixtures were dissolved in THF and analyzed by GC as reported in the previous publications from our laboratory. [17,31]

General Procedure for Competitive Experiments in THF. To an oven-dried test tube (15 x 85 mm) were added the aryl mesylate (69 mg, 0.3 mmol), the two arylboron-based nucleophiles (0.30 mmol each), $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$ (11mg, 0.015 mmol) when indicated, and K_3PO_4 (191 mg, 0.9 mmol). The tube was taken into a glove box. $Ni(COD)_2$ when indicated and PCy_3 (0.030 mmol) was added. Dried THF (1.0 mL) was then added and the tube was capped with a rubber septum. The reaction was stirred at room temperature under nitrogen in the glove box for 1-12 h (see Scheme 3.2, part a;). A sample was taken *via* syringe inside the glove box. The sample was dissolved in distilled THF and was filtered through a short column of silica gel. The solvent was evaporated and the NMR spectrum of the crude was examined.

General Procedure for Competitive Experiments in *t*-BuOH/H_2O=1:1. To an oven-dried test tube (15 x 85 mm) were added the aryl mesylate (69 mg, 0.3 mmol), the two arylboron-based nucleophiles (0.30 mmol each), $Ni(COD)_2$ (8.3 mg, 0.03 mmol), and K_3PO_4 (191 mg, 0.9 mmol). The tube was taken into a glove box and PCy_3 (16.7 mg, 0.060 mmol) was added. The tube was capped and taken out of the glove box. Degassed *t*-BuOH (0.5 mL) and degassed deionized water (0.5 mL) were added *via* a syringe. The reaction was stirred at 40 ^{o}C for 2 h (see Scheme 3.2, part b). The mixture was extracted with ethyl acetate three times and dried over anhydrous magnesium sulfate. The solvent was evaporated *via* rotary evaporator and characterized by NMR.

General Procedure for Competitive Experiments in DMSO. To an oven-dried test tube (15 x 85 mm) were added the aryl mesylate (69 mg, 0.3 mmol), the two arylboron-based nucleophiles (0.30 mmol each), and K_3PO_4 (191 mg, 0.9 mmol). The tube was taken into a glove box. $Ni(COD)_2$ (8.3 mg, 0.03 mmol) and PCy_3 (16.7 mg, 0.060 mmol) was added. Dry DMSO (1 mL) was added inside the glove box. The tube was capped and left for stirring at room temperature. After 3 h, the tube was taken out of the glove box and the crude reaction mixture was washed with water then extracted with ethyl acetate three times. The organic phase was collected and dried over anhydrous magnesium sulfate. The solvent was evaporated in a rotary evaporator and characterized by NMR.

Procedure for Blank Experiments of Comparison of 4-Methoxyphenyl Neopentylglycolboronate with 4-Methoxylphenyl Pinacolboronate in THF. To an oven-dried test tube (15 x 85 mm) were added two arylboron-based nucleophiles (0.30 mmol each), $Ni^{II}Cl$(1-naphthyl)$(PPh_3)_2$ (11mg, 0.015 mmol), and K_3PO_4 (191 mg, 0.9 mmol). The tube was taken into a glove box. PCy_3 (0.030 mmol) was added. Dried THF (1.0 mL) was then added and the tube was capped with a rubber septum. The reaction was stirred at room temperature under nitrogen in the glove box for 3 h. A sample was taken *via* syringe inside the glove box. The sample was dissolved in distilled THF and was filtered through a short column of silica gel. The solvent was evaporated and the NMR spectrum of the crude reaction mixture was examined.

2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2c): colorless oil (3.48 g, 96%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.71 (m, 2H), 6.93 – 6.84 (m, 2H), 3.83 (s, 3H), 1.33 (s, 12H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.4, 113.2, 83.5, 55.0, 24.8. NMR spectrum is identical with literature data.[25]

Methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (3a): white solid (Table 3.15: from 4-methoxyphenyl neopentylglycolboronate: 72 mg; 99%; from 4-methoxyphenyl pinacolboronate: 41.0 mg, 57%; Table 3.16: from 4-methoxyphenyl neopentylglycolboronate: 64.0 mg; 89%; from 4-methoxyphenyl pinacolboronate: 22.0 mg, 30%;), mp 173 ^{o}C (lit.[25] 173-174 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.2, 11H), 7.60 (dd, J = 22.7, 8.3, 23H), 7.26 (s, 17H), 7.00 (d, J = 8.5,

11H), 3.90 (d, J = 35.1, 34H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 145.1, 132.3, 130.9, 130.0, 128.3, 128.2, 126.4, 114.3, 55.3, 52.0.

4,4'-Dimethoxy-1,1'-biphenyl (3b): white solid (Table 3.15: from 4-methoxyphenyl neopentylglycolboronate: 60.0 mg; 94%; from 4-methoxyphenyl pinacolboronate: 32.3 mg, 50%;Table 3.16: from 4-methoxyphenyl neopentylglycolboronate: 60.2 mg; 94%; from 4-methoxyphenyl pinacolboronate: 36.0 mg, 56%;), mp 173 ^{o}C (lit.[25] 171-172 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 8.5, 1H), 6.96 (d, J = 8.6, 1H), 3.85 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 133.6, 127.9, 114.3, 55.6.

Methyl 4'-methoxy-[1,1'-biphenyl]-2-carboxylate (3c): Colorless oil (Table 3.15: from 4-methoxyphenyl neopentylglycolboronate: 64.0 mg; 89%; from 4-methoxyphenyl pinacolboronate: 56.0 mg, 77%; Table 3.16: from 4-methoxyphenyl neopentylglycolboronate: 65.0 mg; 90%; from 4-methoxyphenyl pinacolboronate: 58.0 mg, 81%;). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.70 (m, 1H), 7.51 (td, J = 7.6, 1.4, 1H), 7.41 – 7.31 (m, 2H), 7.28 – 7.20 (m, 4H), 6.99 – 6.88 (m, 2H), 3.85 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 169.5, 159.1, 142.2, 133.8, 131.3, 131.0, 130.9, 129.9, 129.6, 126.9, 113.7, 100.1, 55.4, 52.1. NMR spectrum is identical with the literature data.[25]

2,4'-Dimethoxy-1,1'-biphenyl (3d). White solid (Table 3.15: from 4-methoxyphenyl neopentylglycolboronate: 56.0 mg; 87%; from 4-methoxyphenyl pinacolboronate: 28.0 mg, 44%; Table 3.16: from 4-methoxyphenyl neopentylglycolboronate: 57.0 mg; 89%; from 4-methoxyphenyl pinacolboronate: 55.2 mg, 86%;), mp 69 ^{o}C (lit.[25] 64-66 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.43 (m, 1H), 7.30 (td, J = 7.4, 1.6, 1H), 7.04 – 6.92 (m, 2H), 3.85 (s, 2H), 3.81 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 156.4, 130.8, 130.6, 130.5, 130.2, 128.1, 120.7, 113.4, 111.1, 55.5, 55.2.

Methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (3e): white solid (Table 3.15: from 4-methoxyphenyl neopentylglycolboronate: 58.3 mg; 81%; from 4-methoxyphenyl pinacolboronate: 66 mg, 92%; Table 3.16: from 4-methoxyphenyl neopentylglycolboronate: 62.0 mg; 86%; from 4-methoxyphenyl pinacolboronate: 63.0 mg, 88%;), mp 175 ^{o}C (lit.[25] 173-174 ^{o}C). ^{1}H NMR (500

MHz, $CDCl_3$) δ 8.09 (d, J = 8.2, 1H), 7.63 (d, J = 8.2, 1H), 7.59 (d, J = 8.8, 1H), 7.01 (d, J = 8.8, 1H), 3.95 (s, 2H), 3.87 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 160.0, 145.4, 132.6, 130.3, 128.5, 128.4, 126.6, 114.5, 55.5, 52.2.

4,4'-Dimethoxy-1,1'-biphenyl (3f): white solid (Table 3.15: from 4-methoxyphenyl neopentylglycolboronate: 51.0 mg; 80%; from 4-methoxyphenyl pinacolboronate: 29.5 mg, 46%; Table 3.16: from 4-methoxyphenyl neopentylglycolboronate: 53.5 mg; 93%; from 4-methoxyphenyl pinacolboronate: 40.5 mg, 63%;), mp 174 ^oC (lit.[25] 171-172 ^oC). ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.44 (m, 1H), 7.01 – 6.91 (m, 1H), 3.84 (s, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6, 133.4, 127.6, 114.1, 55.3.

Methyl 4'-methoxy-[1,1'-biphenyl]-2-carboxylate (3g): Colorless oil (Table 3.15: from 4-methoxyphenyl neopentylglycolboronate: 67.0 mg; 93%; from 4-methoxyphenyl pinacolboronate: 65.0 mg, 90%; Table 3.16: from 4-methoxyphenyl neopentylglycolboronate: 70 mg; 98%; from 4-methoxyphenyl pinacolboronate: 70 mg, 98%;). ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 – 7.73 (m, 1H), 7.50 (tt, J = 13.6, 6.8, 1H), 7.43 – 7.31 (m, 2H), 7.31 – 7.19 (m, 4H), 6.99 – 6.89 (m, 2H), 3.85 (s, 3H), 3.67 (s, 3H). ^{13}C (126 MHz, $CDCl_3$) δ 169.3, 158.9, 141.9, 133.6, 131.1, 130.8, 130.6, 129.6, 129.4, 126.7, 113.5, 55.2, 51.9. NMR spectrum matches with literature data.[25]

2,4'-Dimethoxy-1,1'-biphenyl (3h). White solid (Table 3.15: from 4-methoxyphenyl neopentylglycolboronate: 60.0 mg; 94%; from 4-methoxyphenyl pinacolboronate: 56.0 mg, 88%; Table 3.16: from 4-methoxyphenyl neopentylglycolboronate: 64 mg; 99%; from 4-methoxyphenyl pinacolboronate: 24.5 mg, 38%;), mp 68 ^oC (lit.[25] 64-66 ^oC). ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H), 7.29 (td, J = 7.4, 1.6, 2H), 7.02 (td, J = 7.4, 1.1, 1H), 7.00 – 6.93 (m, 3H), 3.85 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.8, 155.7, 130.0, 129.8, 129.7, 129.5, 127.3, 120.0, 112.6, 110.3, 54.7, 54.4.

3.3.5 NMR Spectrum of Crude Reaction Mixture of Competitive Experiments

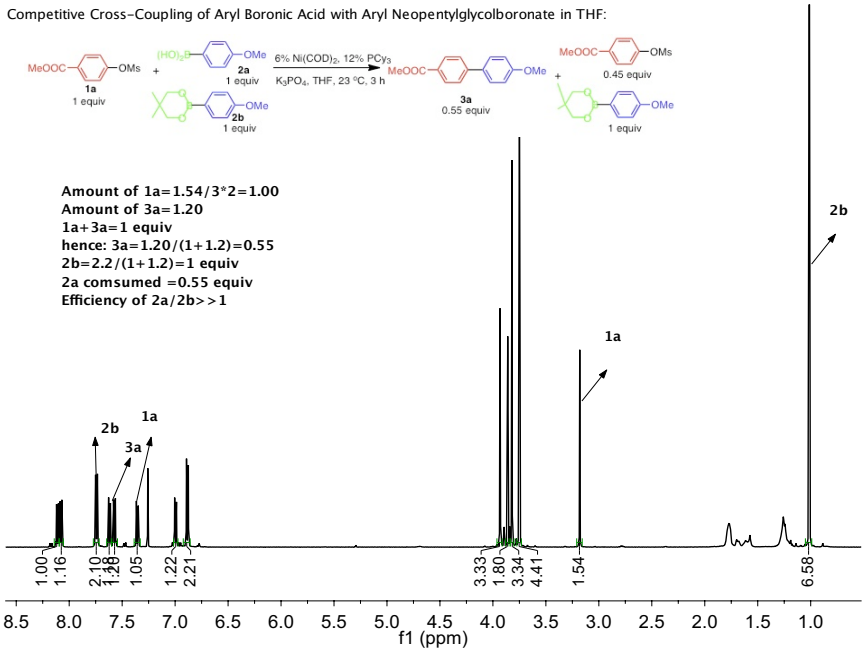


Figure SF 3.72. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of the competitive cross-coupling of arylboronic acid with aryl neopentylglycolboronate in THF.

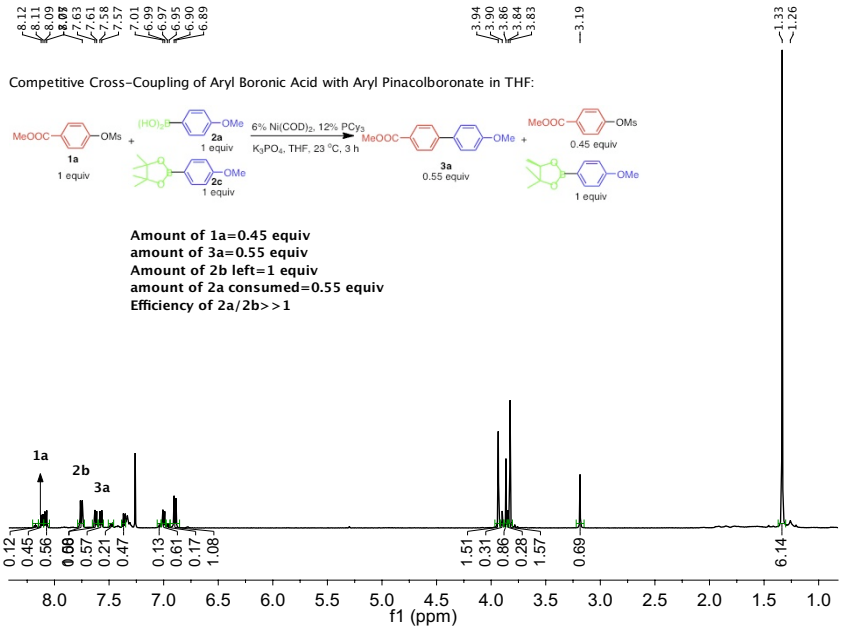


Figure SF 3.73. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of the competitive cross-coupling of arylboronic acid with aryl pinacolboronate in THF.

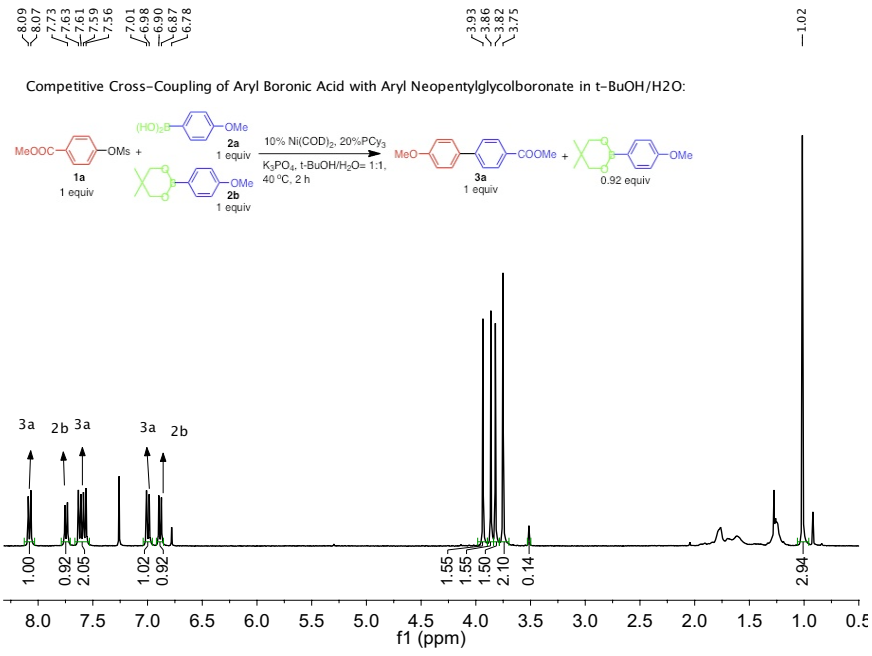


Figure SF 3.74. ^{1}H NMR (500 MHz) spectrum of crude reaction mixture of competitive cross-coupling of arylboronic acid with aryl neopentylglycolboronate in *t*-BuOH/H_2O=1:1 mixture.

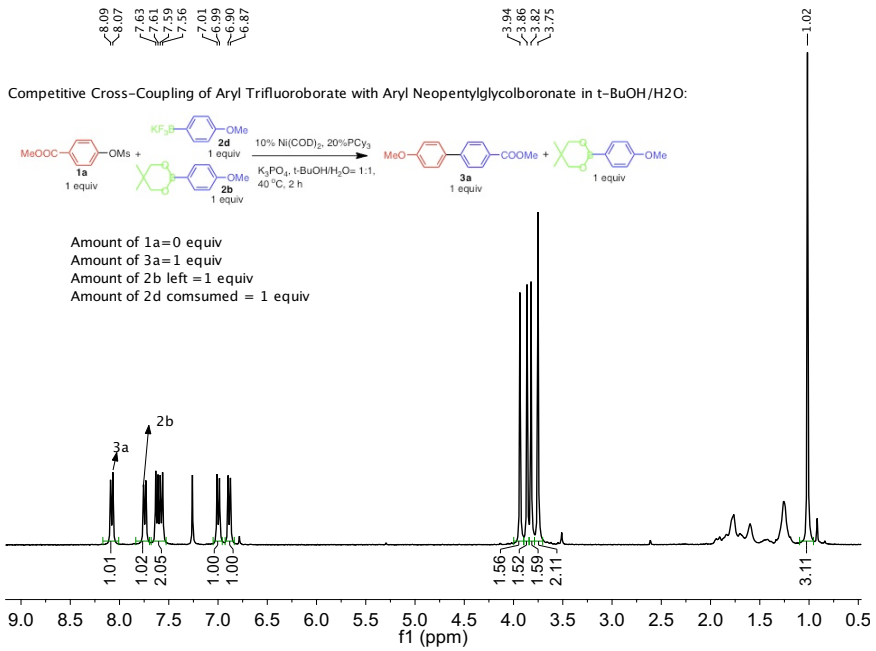


Figure SF 3.75. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of the competitive cross-coupling of aryl trifluoroborate with aryl neopentylglycolboronate in *t*-BuOH/H_2O=1:1 mixture.

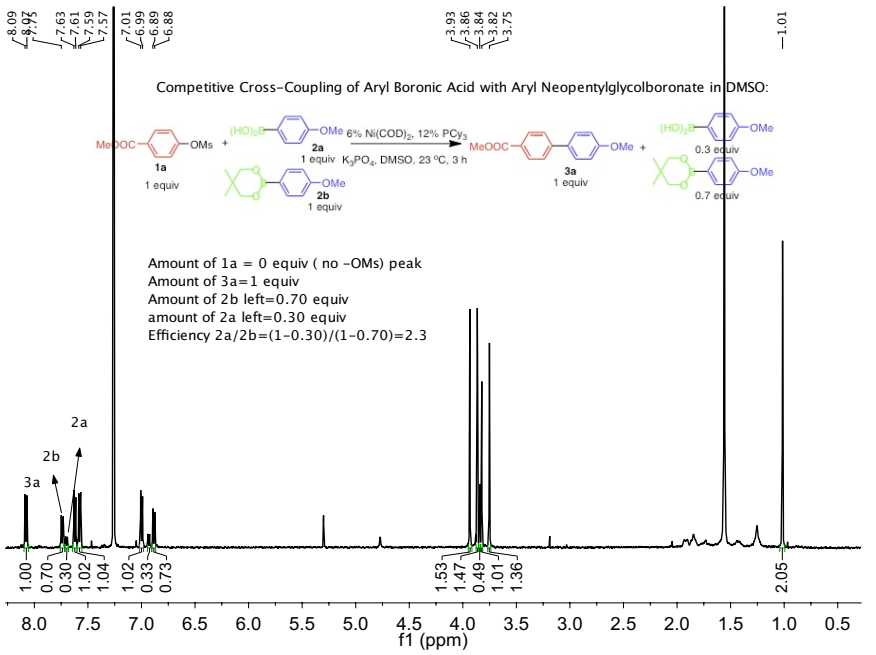


Figure SF 3.76. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of the competitive cross-coupling of arylboronic acid with aryl neopentylglycolboronate in DMSO.

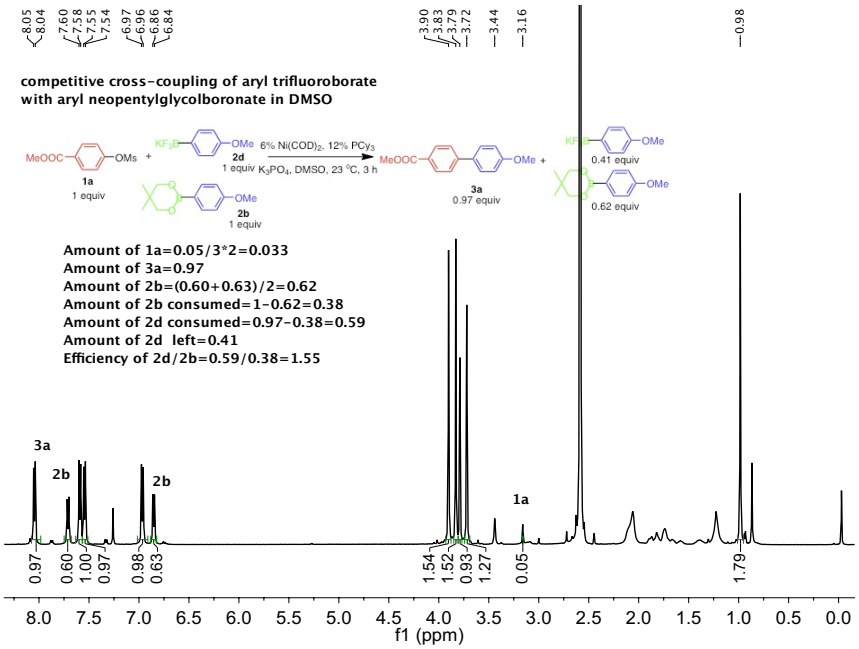


Figure SF 3.77. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of the competitive cross-coupling of aryl trifluoroborate with aryl neopentylglycolboronate in DMSO.

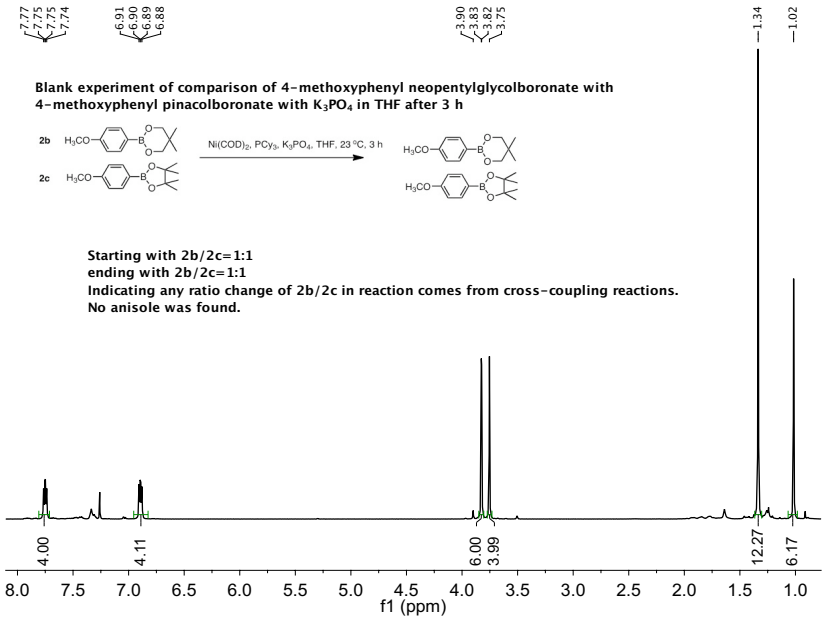


Figure SF 3.78. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of the blank experiment of the comparison of 4-methoxyphenyl neopentylglycolboronate and 4-methoxylphenyl pinacolboronate in THF after 3 h.

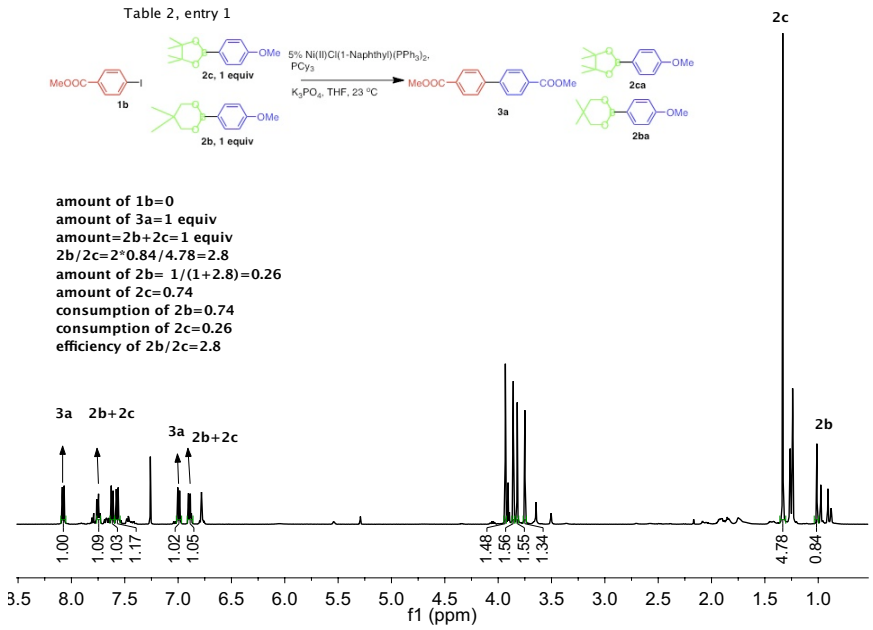


Figure SF 3.79. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of **Table 3.13**, entry 1.

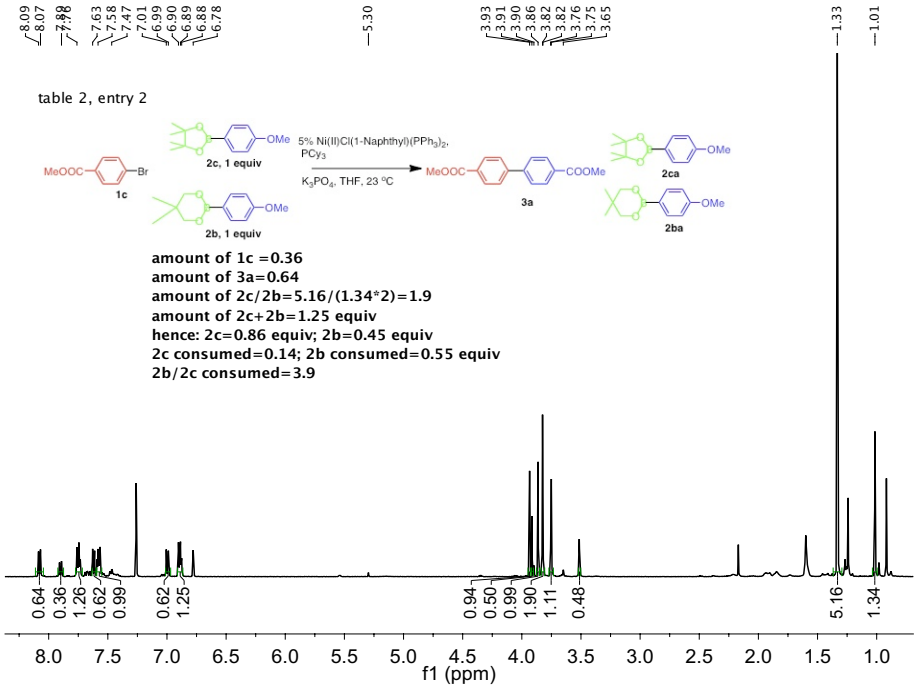


Figure SF 3.80. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of **Table 3.13**, entry 2.

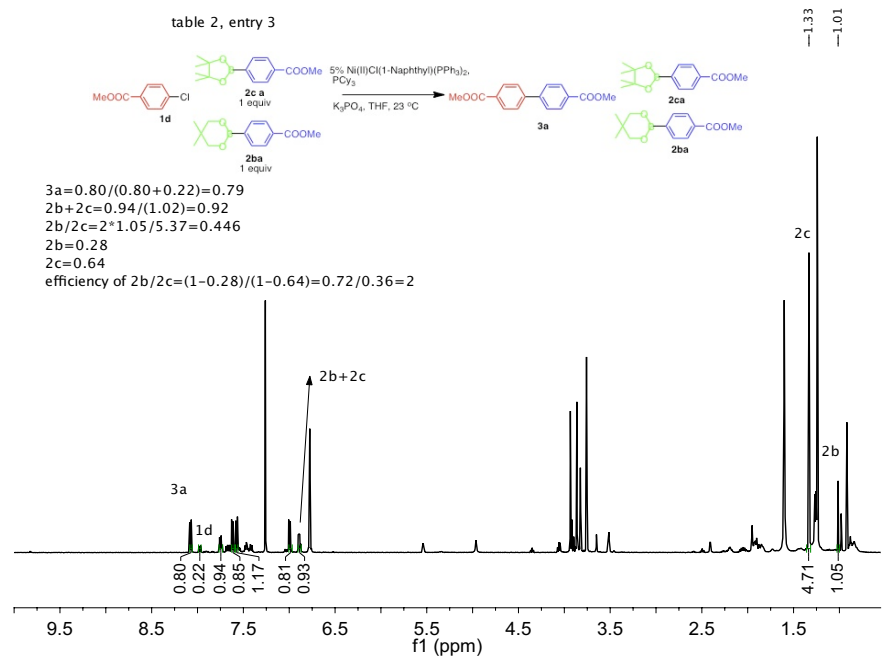


Figure SF 3.81. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of **Table 3.13**, entry 3.

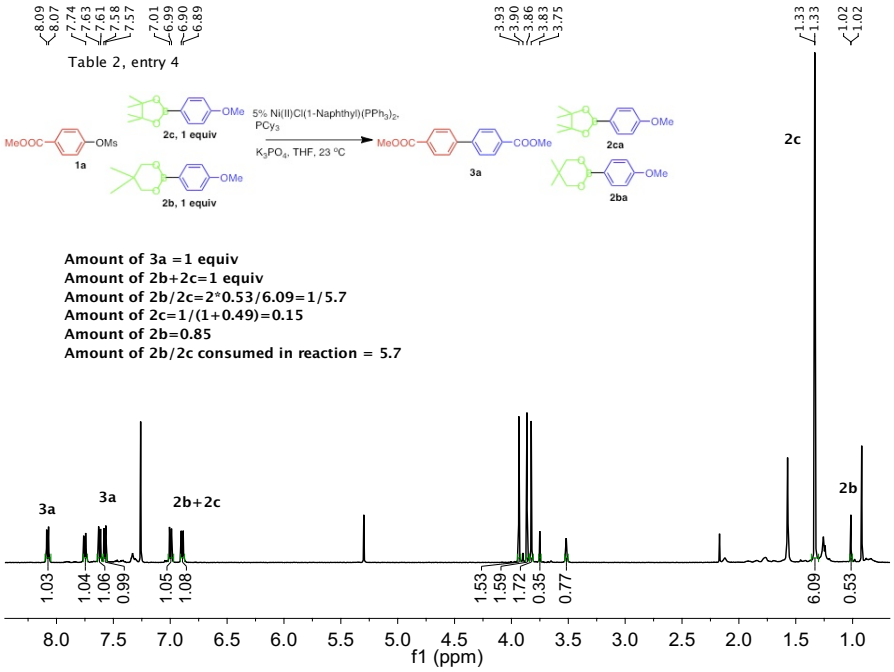


Figure SF 3.82. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of **Table 3.13**, entry 4.

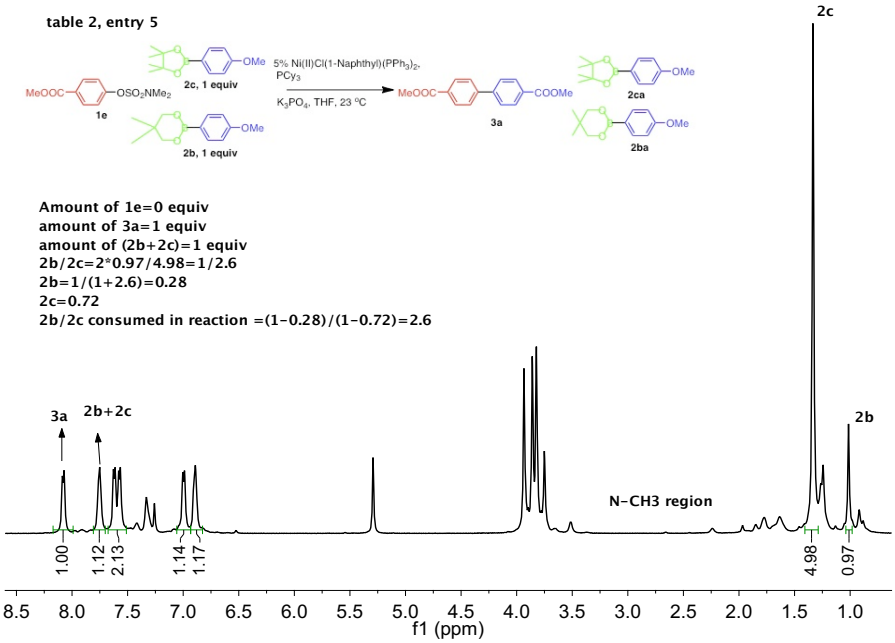


Figure SF 3.83. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of **Table 3.13**, entry 5.

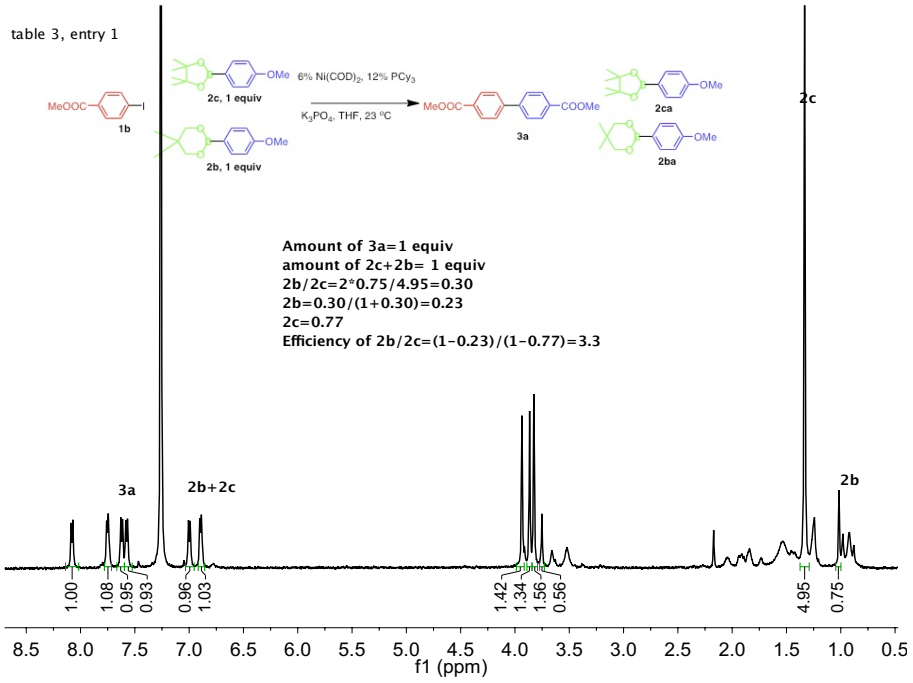


Figure SF 3.84. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of **Table 3.14**, entry 1.

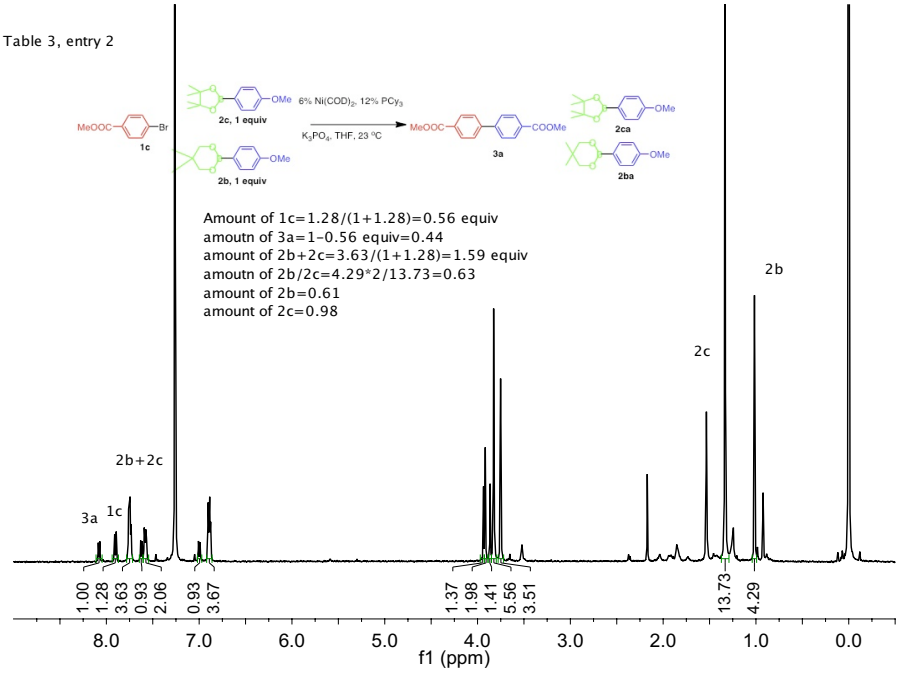


Figure SF 3.85. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of **Table 3.14**, entry 2.

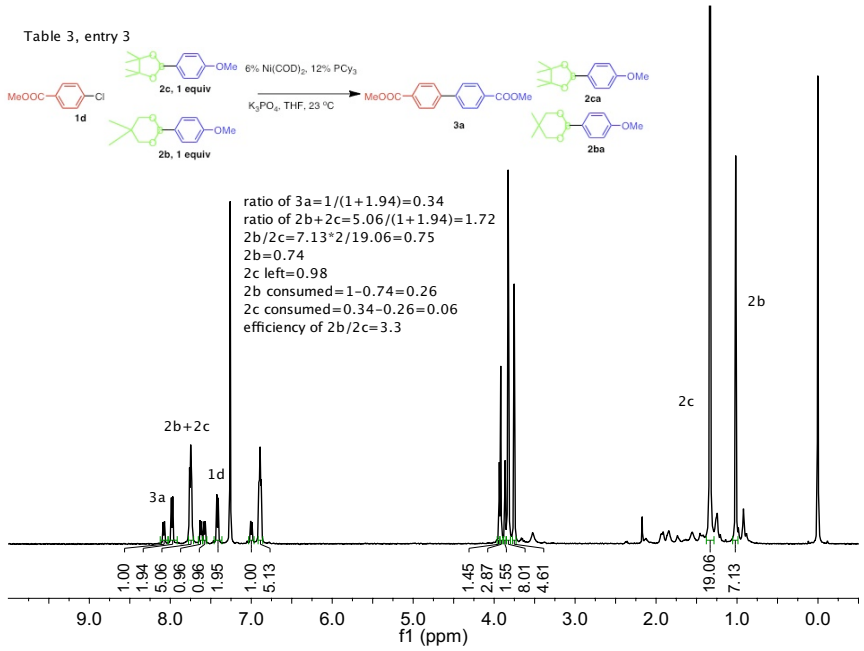


Figure SF 3.86. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of **Table 3.14**, entry 3.

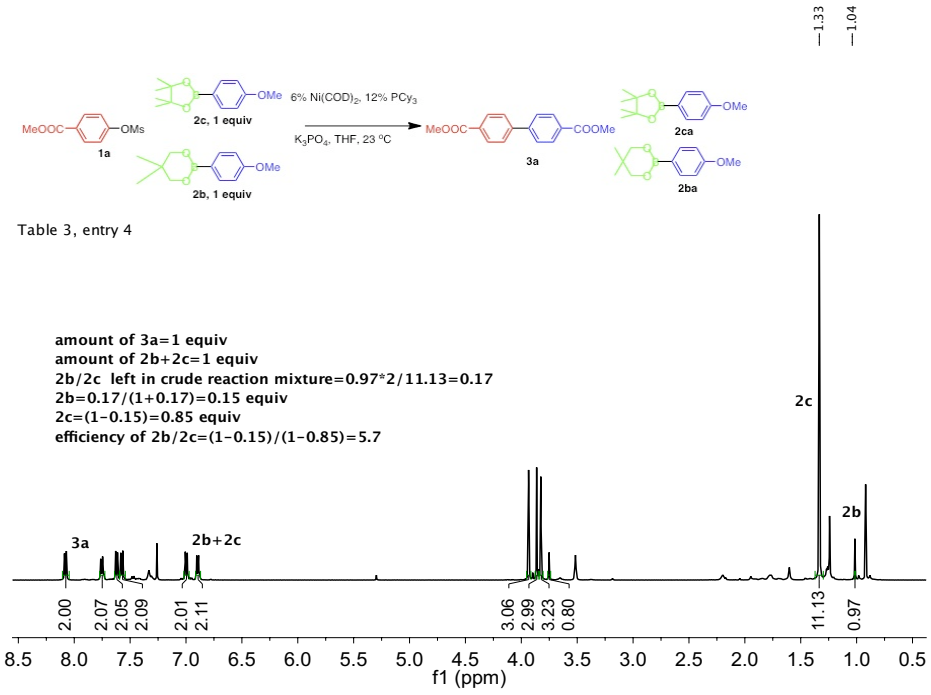


Figure SF 3.87. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of **Table 3.14**, entry 4.

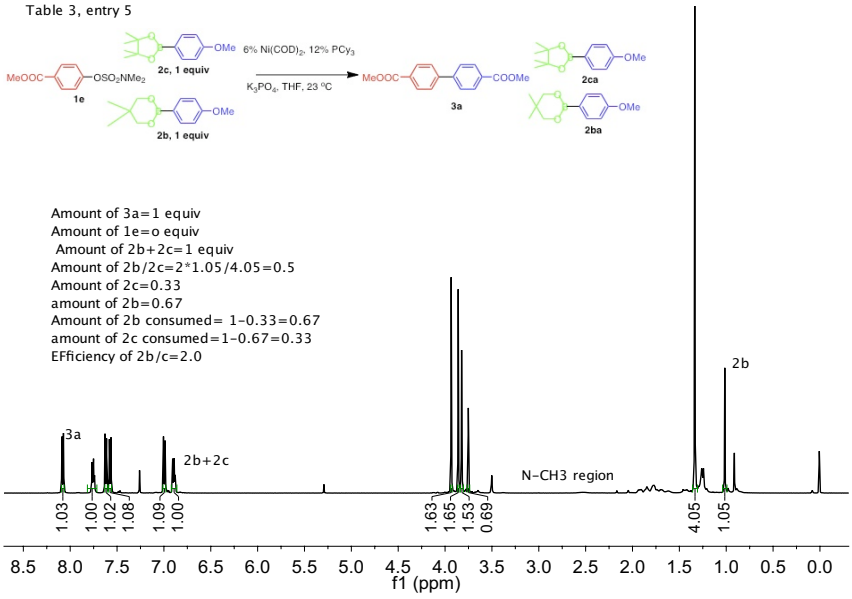


Figure SF 3.88. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of **Table 3.14**, entry 5.

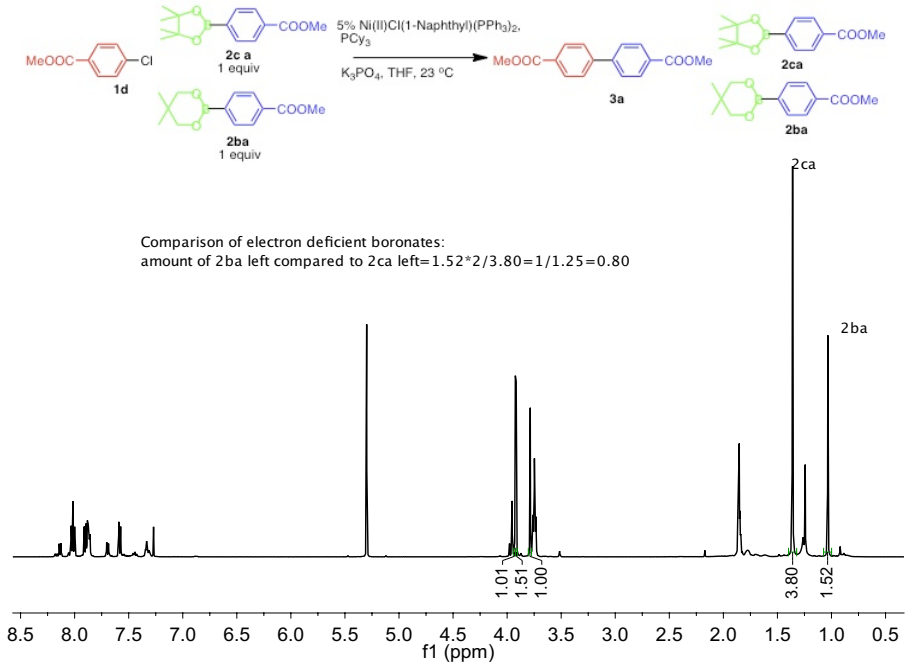


Figure SF 3.89. ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture of the comparison cross-coupling of electron deficient aryl boronates in THF.

3.3.6 Representative of NMR Spectrum of Kinetic Experiments

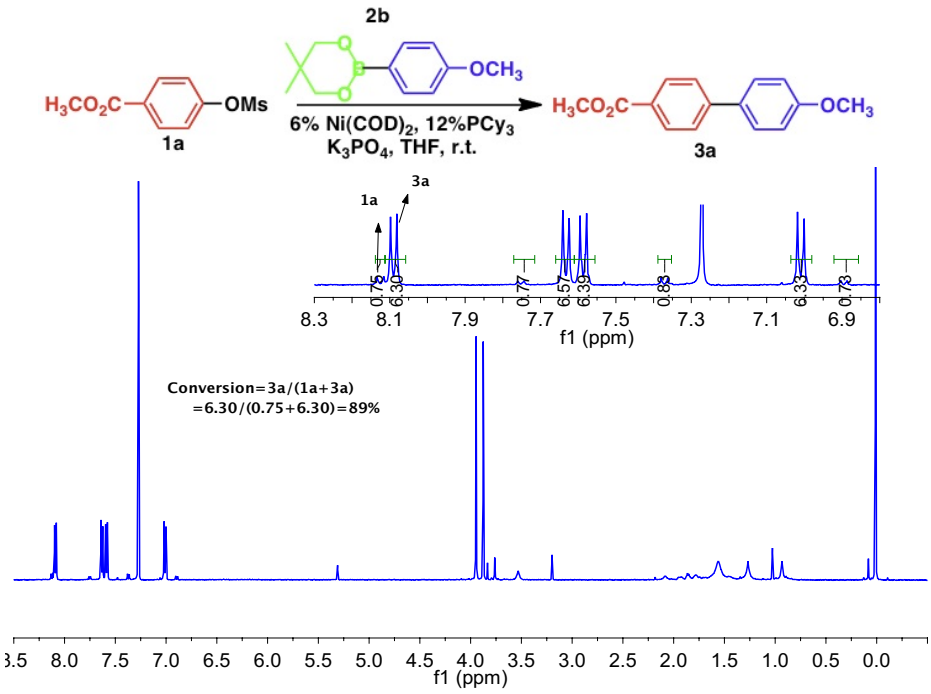


Figure SF 3.90. Determination of Conversion of $Ni(COD)_2/PCy_3/K_3PO_4$ Catalyzed Cross-Coupling of Methyl 4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)Benzoate with 4-Methoxyphenyl Neopentylglycolboronate by ^1H NMR

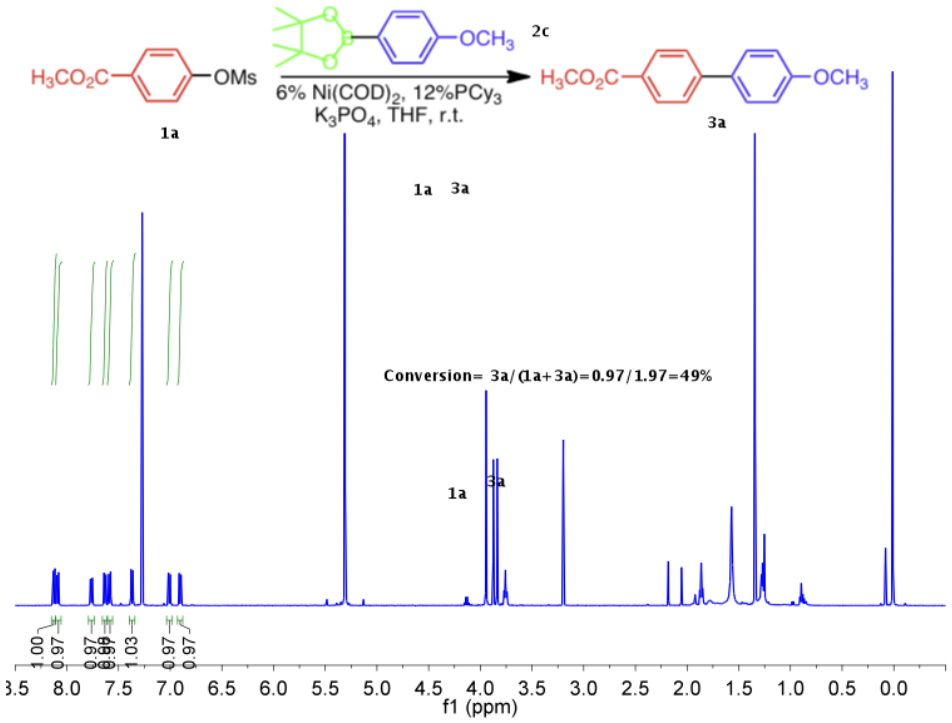


Figure SF 3.91. Determination of Conversion of $Ni(COD)_2/PCy_3/K_3PO_4$ Catalyzed Cross-Coupling of Methyl 4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)Benzoate with 4-Methoxyphenyl Pinacol Boronate by ^1H NMR

3.3.7 Characterization of Reaction Products

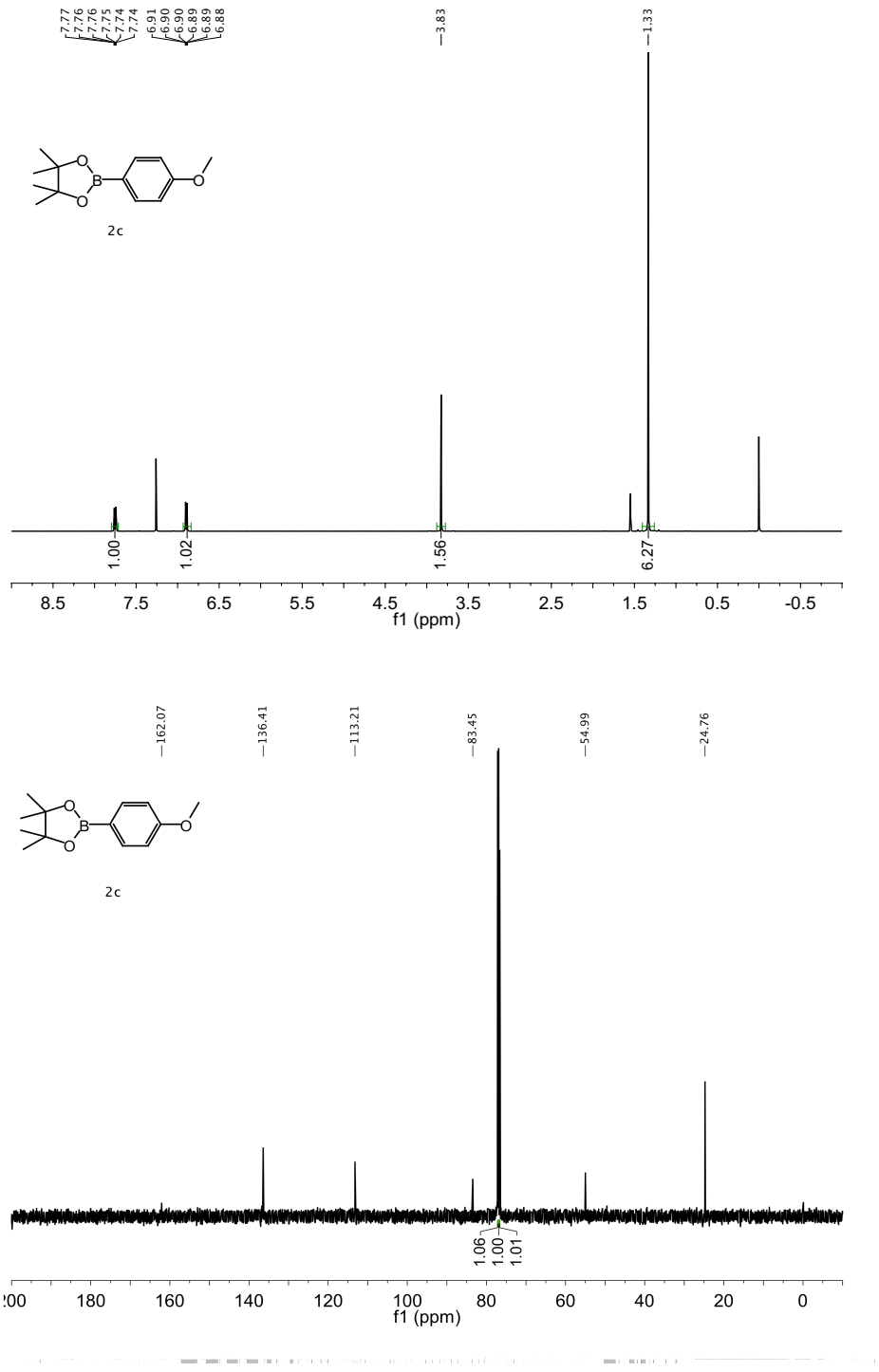


Figure SF 3.92. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in $CDCl_3$.

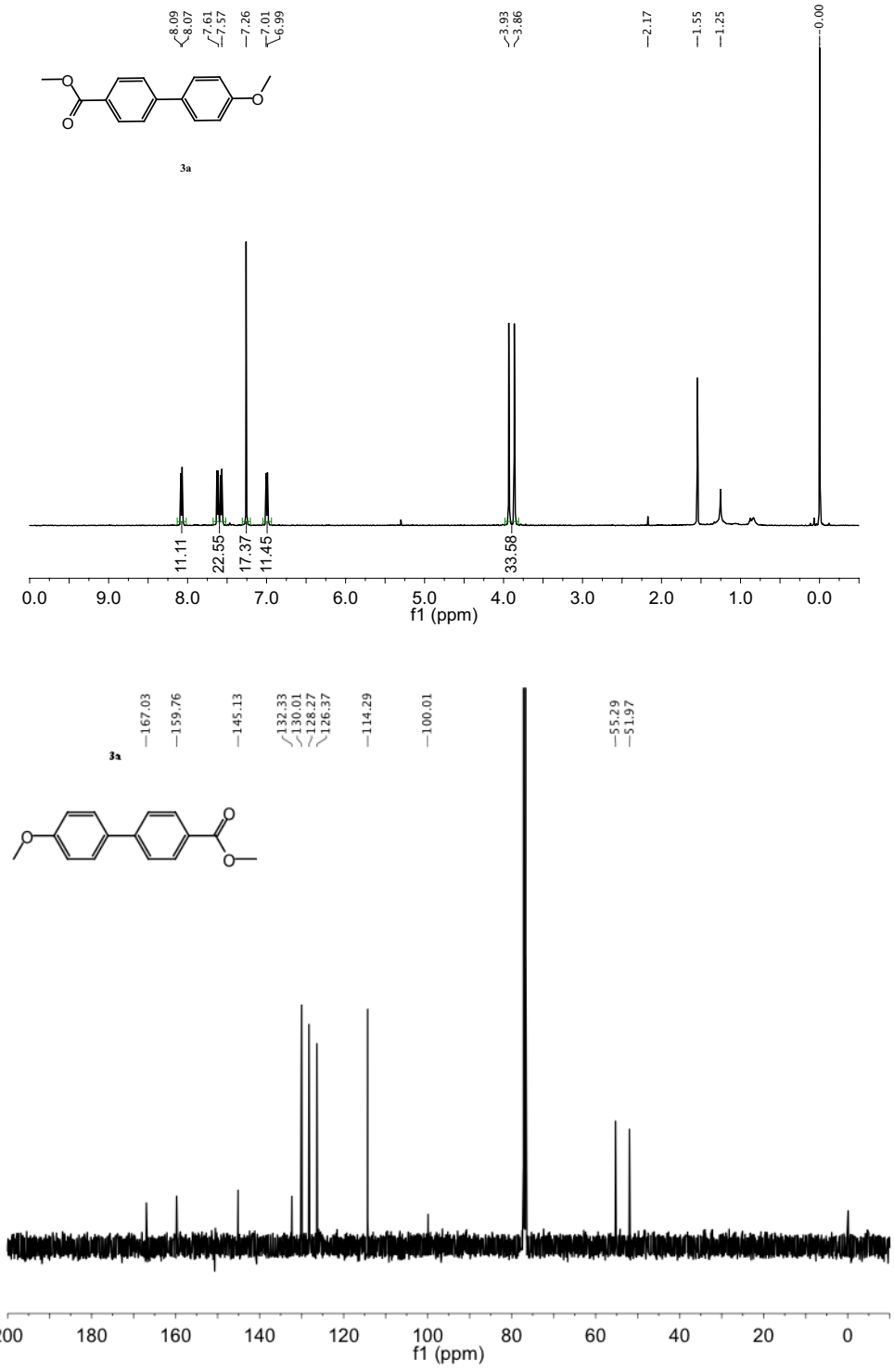


Figure SF 3.93. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate in $CDCl_3$.

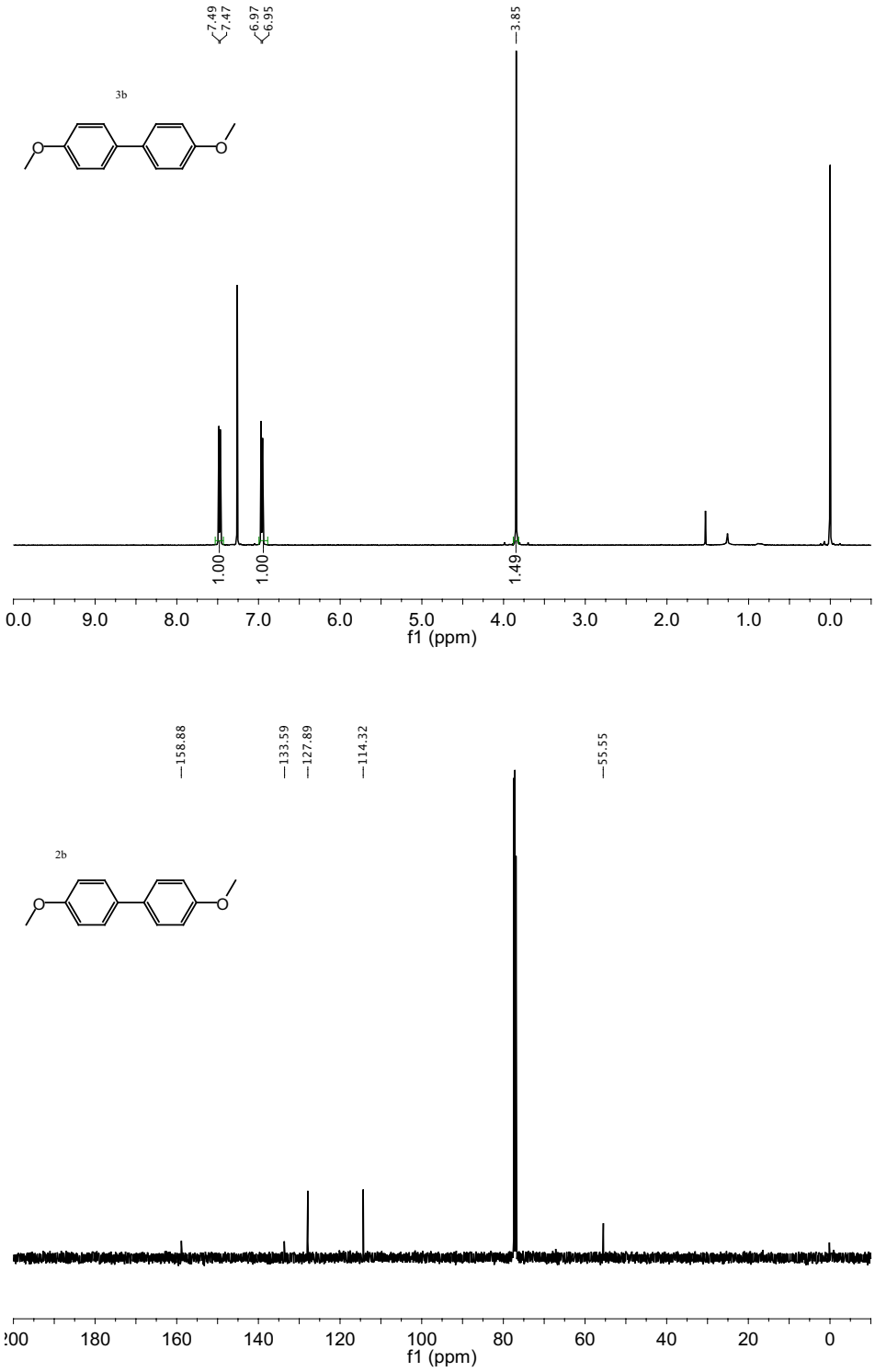


Figure SF 3.94. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 4,4'-dimethoxy-1,1'-biphenyl in $CDCl_3$.

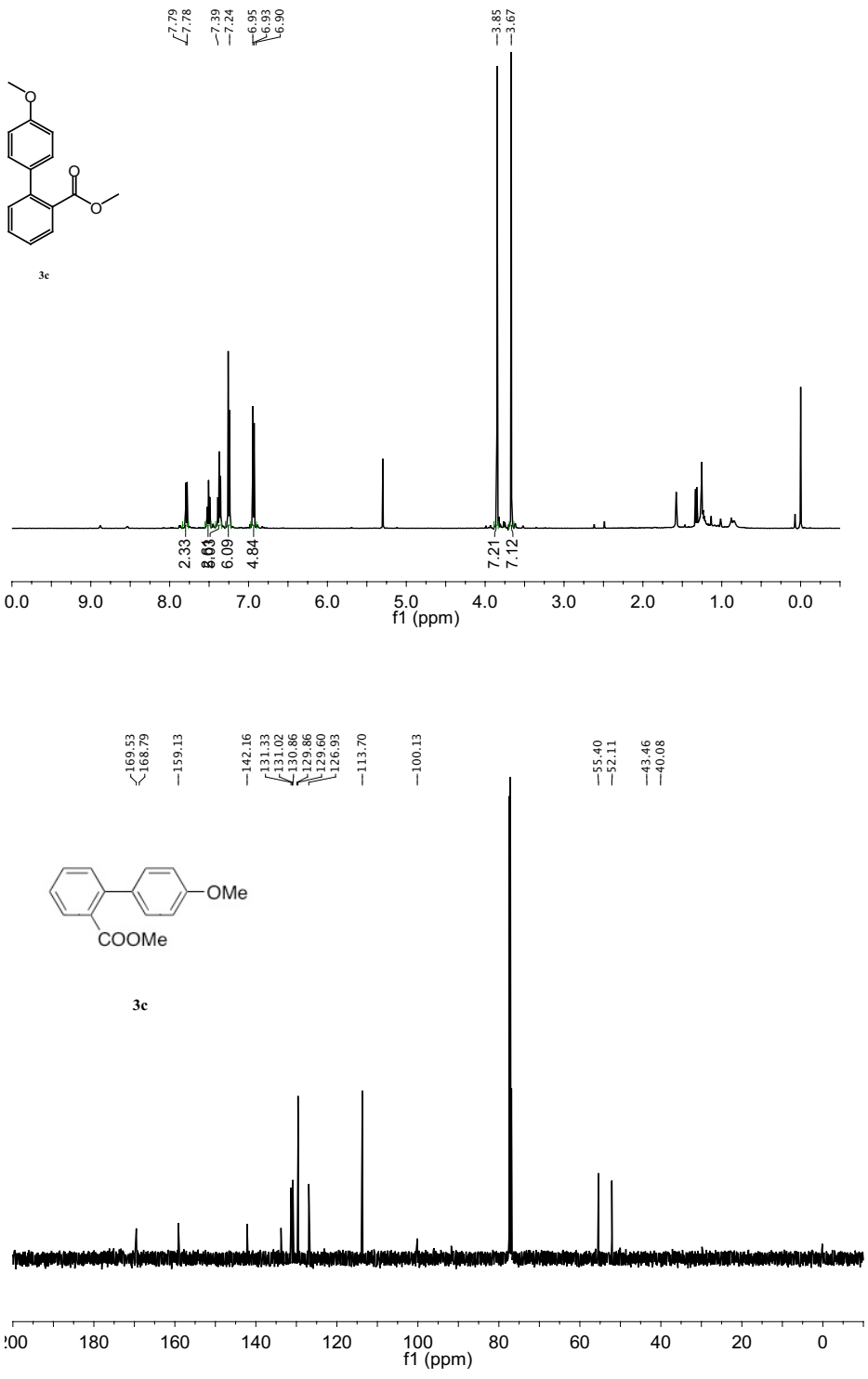


Figure SF 3.95. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4'-methoxy-[1,1'-biphenyl]-2-carboxylate in $CDCl_3$.

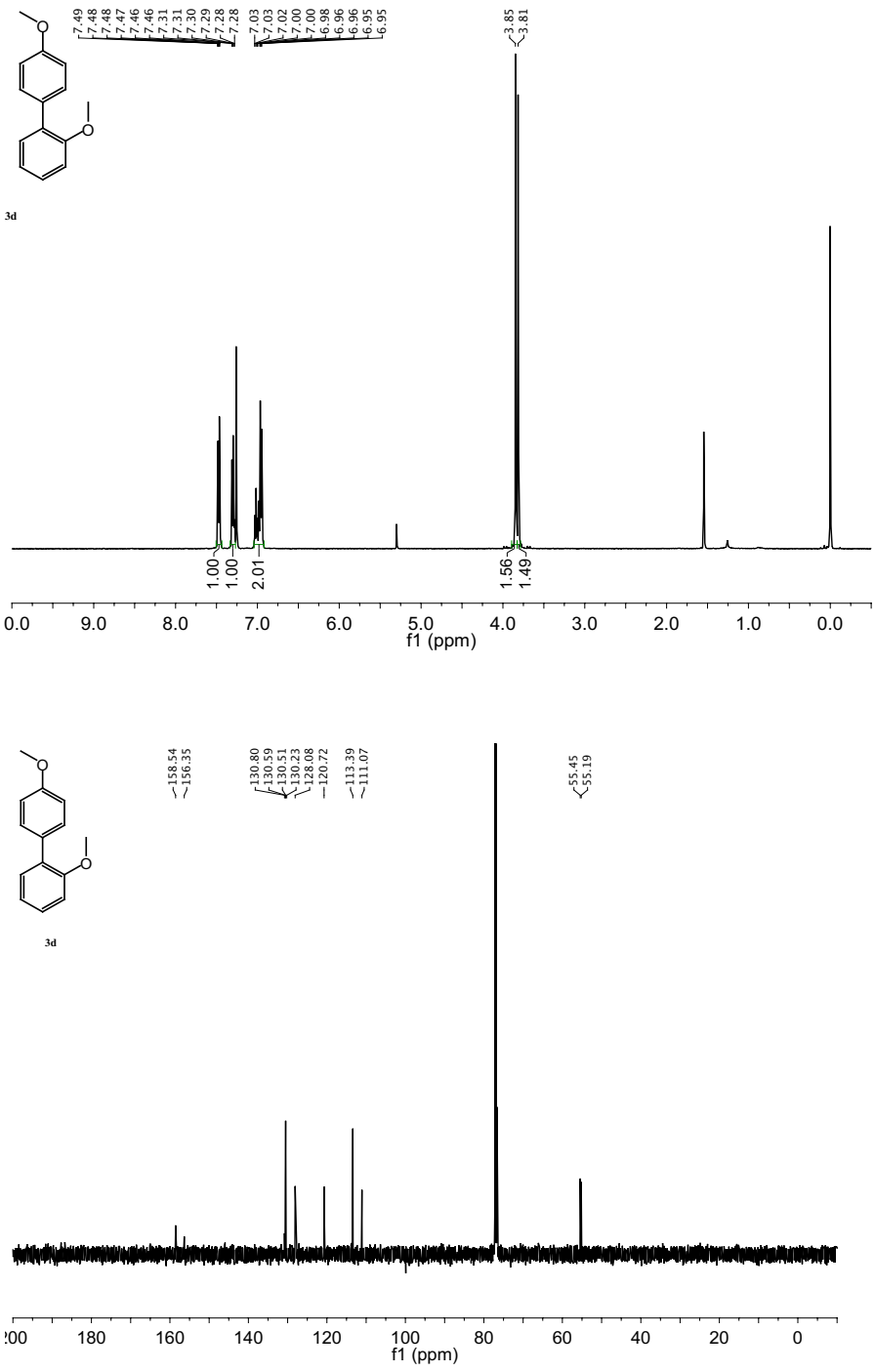


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Figure SF 3.96. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 2,4'-dimethoxy-1,1'-biphenyl in $CDCl_3$.

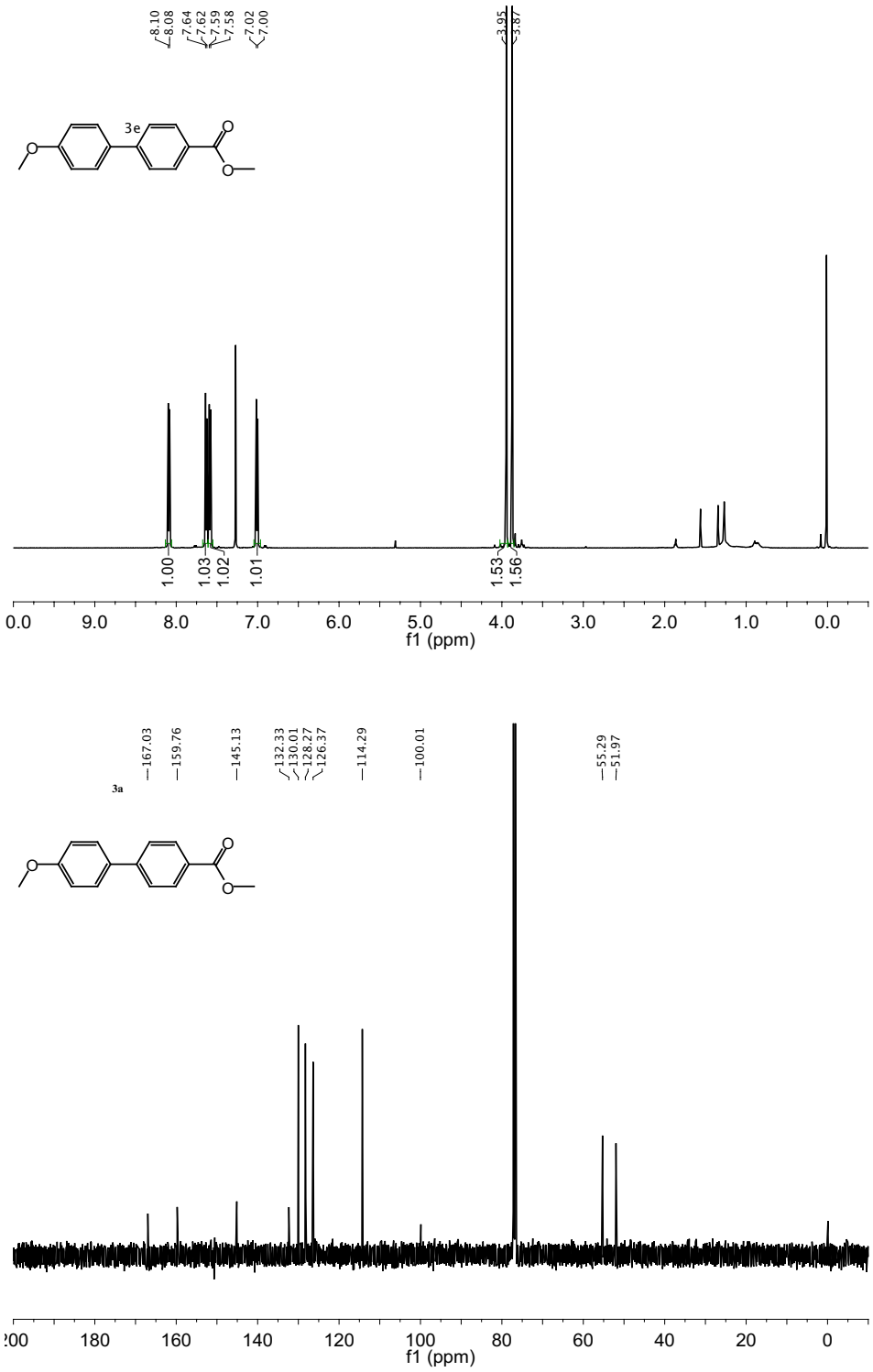

Figure SF 3.97. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate in $CDCl_3$.

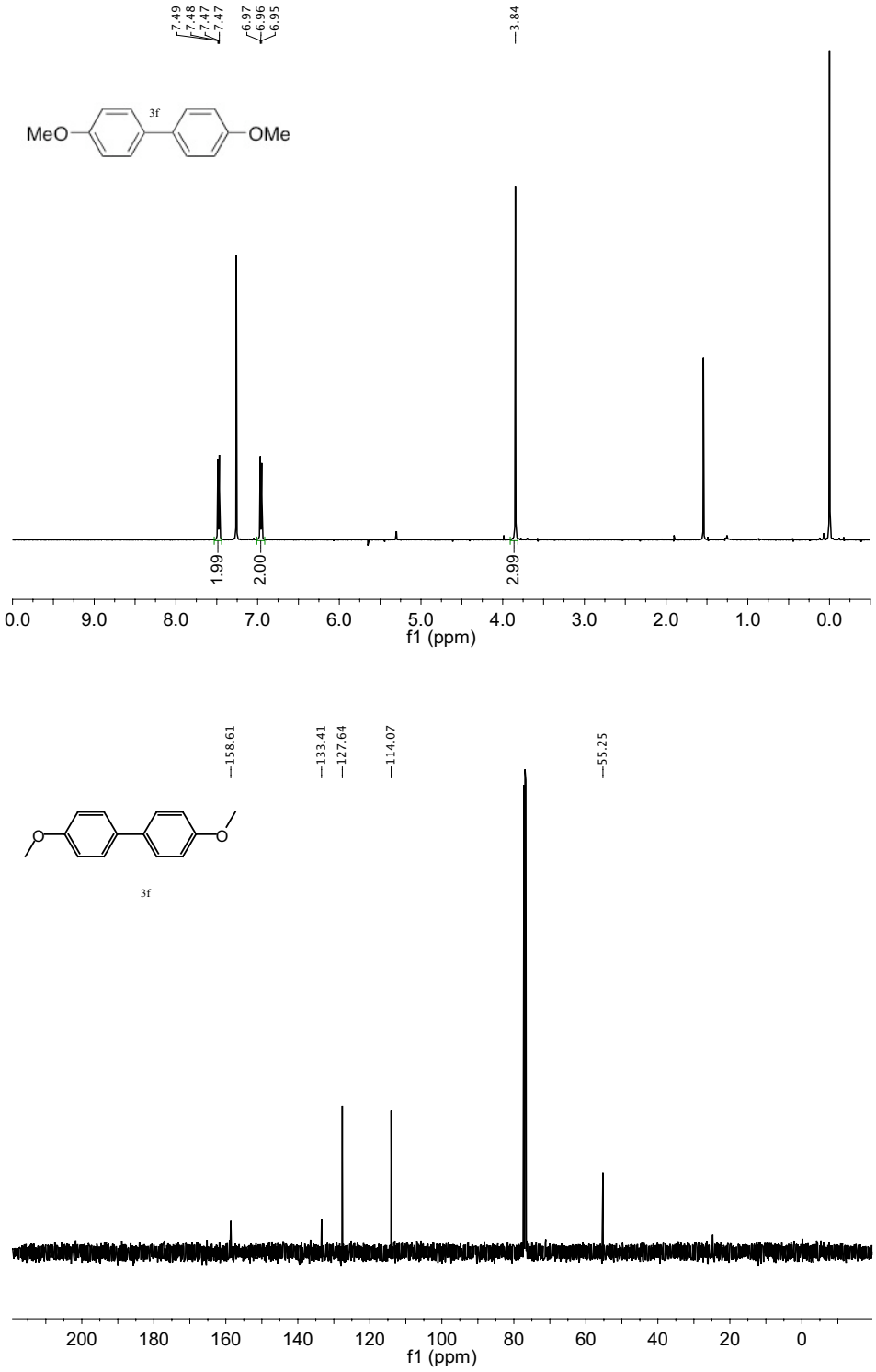

Figure SF 3.98. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 4,4'-dimethoxy-1,1'-biphenyl in $CDCl_3$.

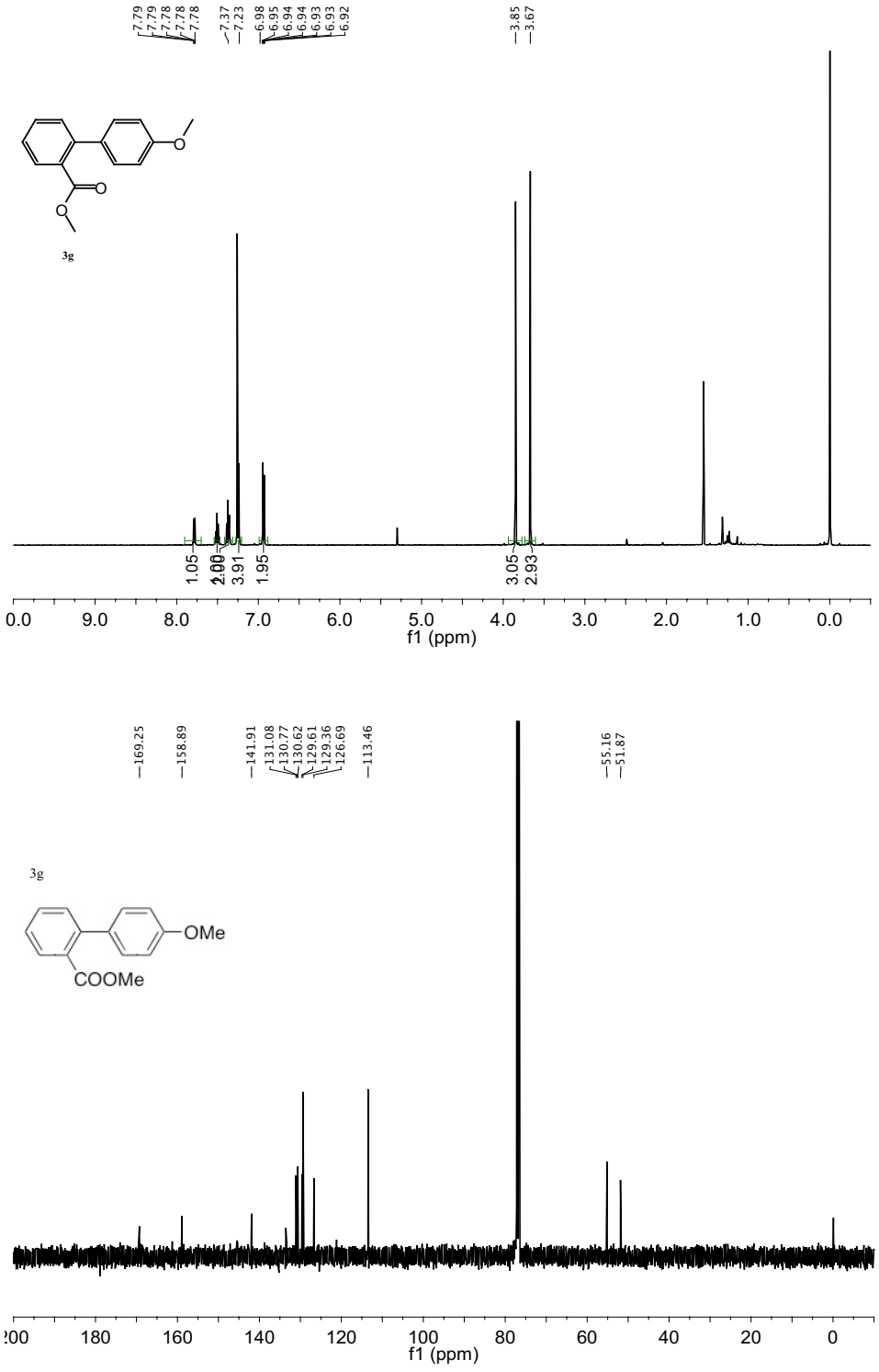

Figure SF 3.99. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4'-methoxy-[1,1'-biphenyl]-2-carboxylate in $CDCl_3$.

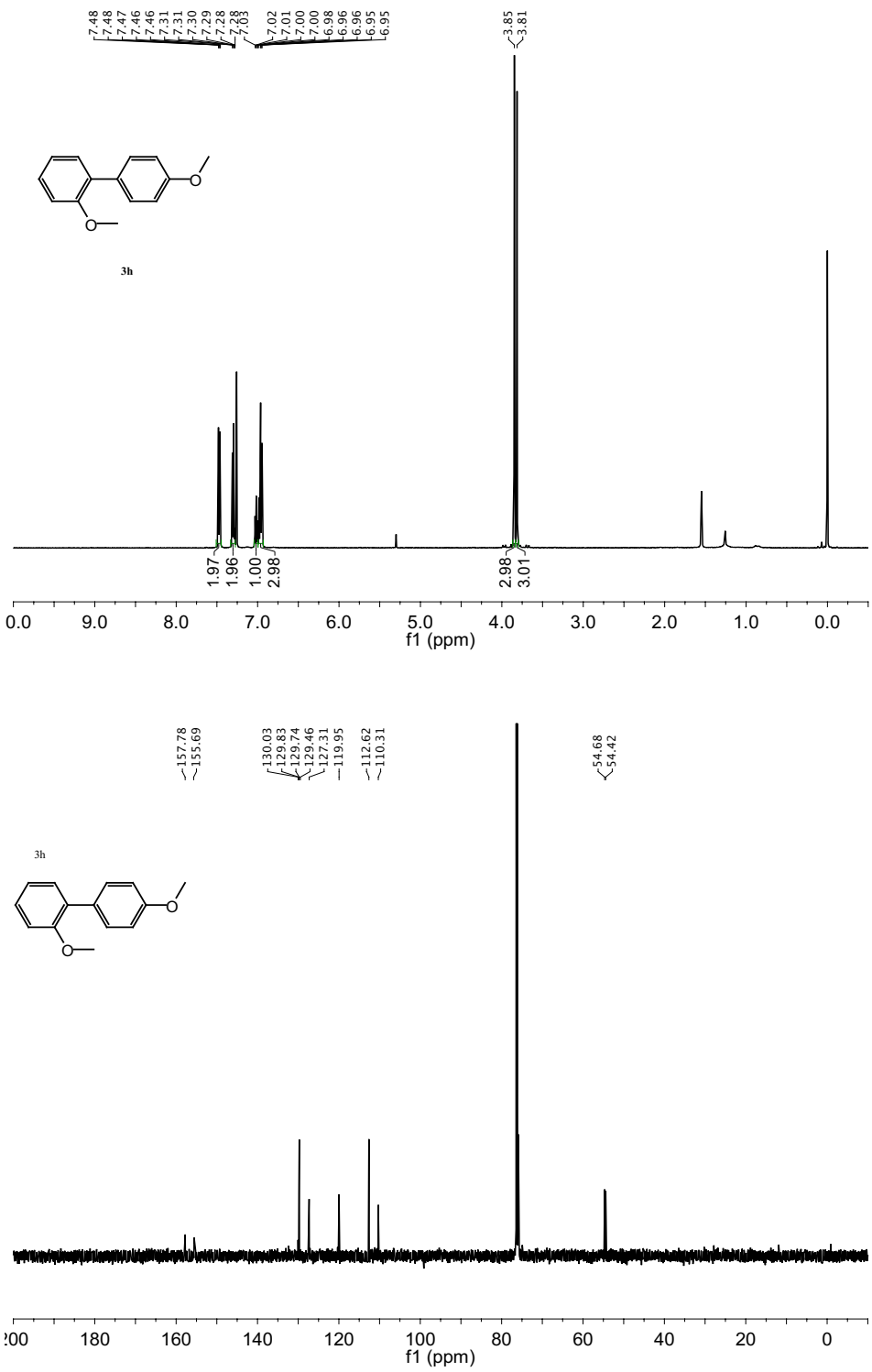

Figure SF 3.100. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 2,4'-dimethoxy-1,1'-biphenyl in $CDCl_3$.

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4 Chapter 4

Development of Bench-Stable Ni^{II} Precatalysts for Suzuki-Miyaura Cross-Coupling of Aryl C-O Electrophiles and Aryl Neopentylglycolboronates

4.1 trans-Chloro(1-Naphthyl)Bis(Triphenylphosphine)Nickel(II)/PCy_3 Catalyzed Cross-Coupling of Aryl and Heteroaryl Neopentylglycolboronates with Aryl and Heteroaryl Mesylates and Sulfamates at Room Temperature

4.1.1 Introduction

In the previous chapter, we discussed $Ni(COD)_2/PCy_3/K_3PO_4$/THF catalyzed cross-coupling of aryl and heteroaryl mesylates with aryl and heteroaryl neopentylglycolboronic esters at room temperature.[2] However, $Ni(COD)_2$ is expensive. The price advantage of using nickel catalysis is negligible considering the relatively high catalyst loading of $Ni(COD)_2$ (3-6 mol%) compared to that of Pd catalyst (0.5 – 1 mol%).[2,3] Moreover, the storage and handling of $Ni(COD)_2$ requires glove box and low-temperature. Commercially available $Ni(COD)_2$ shows varying quality, leading to unrepeatable results.[4] Although methods for the laboratory synthesis of $Ni(COD)_2$ are available,[5] the process involves strict air-free conditions, thus not applicable to every laboratory. Moreover, the toxicity of $Ni(COD)_2$ is a concern. To apply the nickel catalyzed cross-coupling strategy in the synthesis of AB_n dendritic building blocks, an affordable, easily handled and inexpensive catalytic system is desired.

We surveyed the literature of Ni catalyzed Suzuki-Miyaura cross-coupling reactions. To be brief, the bench-stable $NiCl_2$(dppf) catalyzes Suzuki-Miyaura cross-coupling of aryl sulfonates with boronic acids at elevated temperatures in the presence of Zn.[6] Other external reducing reagents such as n-BuLi[7] have also been used. The Monteiro laboratory reported that

$NiCl_2(PCy_3)_2$ is active for the cross-coupling of aryl tosylates with arylboronic acids.[8] Subsequently, $NiCl_2(PCy_3)_2$ was also used for the successful cross-coupling of aryl carboxylates,[9,10] aryl carbonates,[11] aryl carbamates,[4,11] aryl sulfamates,[2,11-13] and aryl phosphates.[14] In these reactions, boronic acids reduce $NiCl_2(PCy_3)_2$ at elevated temperature (80 – 130 ^oC). We have attempted to use $NiCl_2(PCy_3)_2$ for the cross-coupling of six aryl phenol derivatives, namely mesylates, sulfamates, carbamates, pivalates, carbonates and methyl ethers, with aryl neopentylglycolboronates.[1] However, low-yields or no conversion were observed using either K_3PO_4 or CsF.[1]

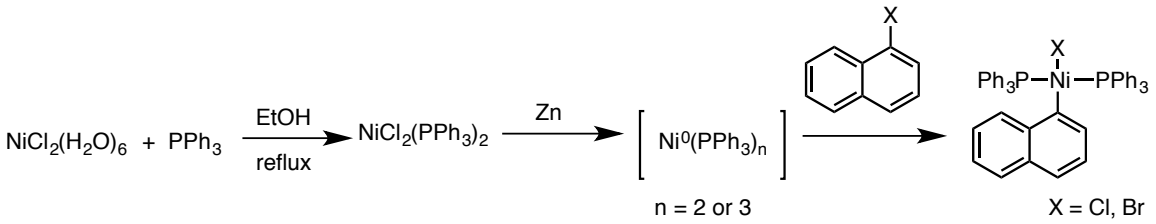
Recently, an alternative, easily prepared, and air-stable *trans*-chloro(aryl)bis(triphenylphosphine)Ni^{II} complex and related compounds from the same class of $Ni^{II}X(\sigma\text{-Aryl})(PR_3)_2$ complexes have drawn research interest. First reported by Cassar in 1960,[15,16] *trans*-chloro(aryl)bis(triphenylphosphine)Ni^{II} complex was found to be active for the cyanation[17] of aryl halides and recently for the amination[18] and Suzuki-Miyaura cross-coupling of aryl halides and sulfonates with arylboronic acids.[19-21] The room-temperature Suzuki-Miyaura cross-coupling reaction of aryl halides[19] and aryl sulfonates[20,21] with arylboronic acids has been reported with $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$ and $Ni^{II}Cl(4\text{-methoxyphenyl})(PCy_3)_2$ complexes. However, the activation and activity of this catalyst in the cross-coupling with aryl boronates is unknown. In this chapter, we disclose the scope of the air and moisture stable as well as readily accessible *trans*-chloro(aryl)bis(triphenylphosphine)Ni^{II} complex in Suzuki-Miyaura cross-coupling of aryl neopentylglycolboronates with both aryl and heteroaryl mesylates and sulfamates at room temperature.

4.1.2 Results and Discussion

A Brief Discussion of the Preparation of $Ni^{II}X(\sigma\text{-Aryl})(PR_3)_2$ Complexes. After surveying the literature, two methods of forming $Ni^{II}X(\sigma\text{-Aryl})(PR_3)_2$ complexes were found. The first method involves the transmetalation of NiL_2X_2 with aryl Grignard or organolithium reagents.[15] The second method involves the oxidative addition of aryl halides[16,17,22] or aryl sulfonates[21] to Ni^0 complexes such as $Ni(COD)_2$ or $Ni(PPh_3)_4$ by in situ formed Ni^0, which is generated from the

reduction of $Ni^{II}Cl_2(PPh_3)_2$ with Zn[22] or other reducing reagents such as manganese/iron alloy.[17] We decided to employ the *in situ* reduction method for the preparation of the catalyst to avoid the need of using the air sensitive and/or expensive reagents. The synthesis of $Ni^{II}X(\sigma\text{-Aryl})(PR_3)_2$ complexes is shown in Scheme 4.1.

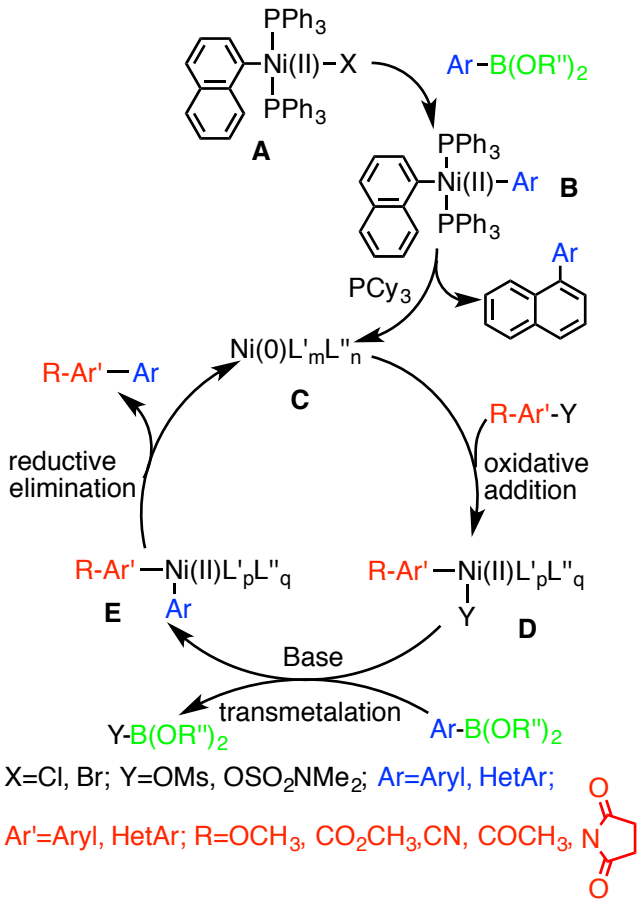
Scheme 4.1. Preparation of $Ni^{II}X(\sigma\text{-Aryl})(PR_3)_2$ Complexes



By stirring $NiCl_2 \cdot 6H_2O$ and PPh_3 in refluxing ethanol, $NiCl_2(PPh_3)_2$ was formed without isolation. After its *in situ* reduction with Zn to Ni^0 followed by oxidative addition to 1-chloronaphthalene, $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$ (Scheme 4.1) was obtained. The same approach can be applied to the synthesis of $Ni^{II}Br(1\text{-naphthyl})(PPh_3)_2$. These precatalysts can be prepared on gram scale from inexpensive starting materials and kept on the bench for several months with no decrease of its catalytic activity.

A Brief Discussion of the Preparation of $Ni^{II}X(\sigma\text{-Aryl})(PR_3)_2$ Complexes. In the presence of a base, solvent and arylboronic ester, the $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$ (Scheme 4.2, compound **A**) catalyst precursor activates before entering the catalytic cycle in a similar way as in the case of arylboronic acids.[19,20] Transmetalation facilitated by base produces a naphthyl-$Ni^{II}(PPh_3)_2$-Ar (Scheme 4.2, compound **B**) complex followed by reductive elimination to yield the naphthyl-aryl product and mixed-ligand species $Ni^0L'_mL''_n$. The naphthyl-aryl product generated in small amount can be detected by its fluorescence in TLC and removed from the desired product by column chromatography. Then the $Ni^0L'_mL''_n$ (Scheme 4.2, compound **C**) generated will enter the general catalytic cycle of Ni^0/Ni^{II} mechanism by following the sequence of oxidative addition, transmetalation with aryl neopentylglycolboronates followed by reductive elimination to give the desired biaryl product. This process is facile enough to occur at room temperature.

Scheme 4.2. The Synthesis of *trans*-Chloro(Aryl)Bis-(Triphenylphosphine)Ni(II) Complex and the Proposed Mechanism for the Cross-Coupling Reaction

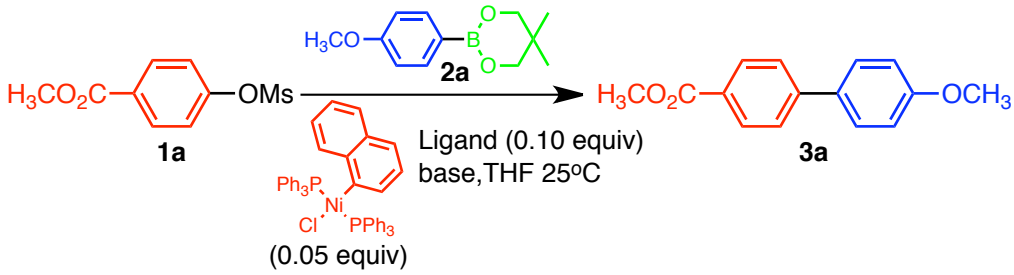


Optimization of Cross-Coupling Reaction Conditions of Aryl Neopentylglycolboronates with Aryl Mesylates. To provide the optimum reaction conditions for the cross-coupling reaction of aryl mesylates with aryl neopentylglycolboronates, various bases, solvents and catalyst loadings were investigated. The amount of boronic ester used in the reaction was also examined to reduce the amount of aryl boronate used in the cross-coupling, since sometimes boronic esters is the most expensive reagent for Suzuki coupling.

K_3PO_4 proved to be more effective than K_2CO_3 (Table 4.1, entries 3, 4 and entries 1, 2). This is in agreement with our study in 1995 for the $NiCl_2$(dppf) catalyzed cross-coupling of aryl mesylates

with arylboronic acids.[6] Using dry THF and K_2CO_3 gave the lowest yields for all combinations (Table 4.1, entries 1 and 9), indicating water is essential for this reaction. Both PCy_3 and PPh_3 were efficient ligands in the cross-coupling of methy 4-methanesulfonyloxy benzoate with *para*-methoxyphenyl neopentylglycol boronate in the presence of K_3PO_4. Decreasing the amount of boronate to 1 equivalent with respect to mesylate maintained excellent reaction yield (Table 4.1, entry 7). Although dried THF worked as well as wet as received THF, in this reaction we used dry THF as solvent throughout the rest of the study to avoid the inconsistent water amount in THF from commercial sources.

Table 4.1. Cross-Coupling of Methyl 4-(Methanesulfonyloxy)benzoate with *para*-Methoxyphenyl Neopentylglycolboronate Catalyzed by $Ni^{II}Cl(1\text{-Naphthyl})(PPh_3)_2$/Phosphine Ligand at 25 °C



entry	**2a**	ligand	base	THF	time (h)	convn[a]/yield[b] (%)
1	1.5	PPh_3	K_2CO_3	dry	37	89/57
2	1.5	PPh_3	K_2CO_3	wet	36	97/85
3	1.5	PPh_3	K_3PO_4	dry	12	100/94
4	1.5	PPh_3	K_3PO_4	wet	18	99/93
5	1.5	PCy_3	K_3PO_4	dry	12	100/90
6	1.2	PCy_3	K_3PO_4	dry	5	100/99
7	1.0	PCy_3	K_3PO_4	dry	4	100/99
8	1.5	PCy_3	K_3PO_4	wet	12	100/96
9	1.5	PCy_3	K_2CO_3	dry	37	64/17

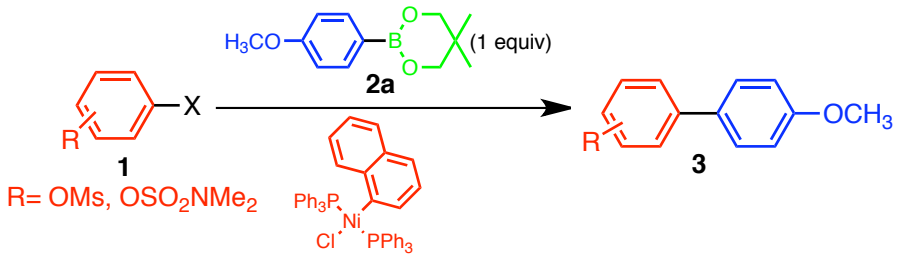
[a]Conversion determined by GC. The GC yield has always the same value as the conversion.

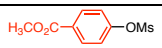
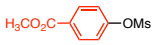
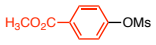
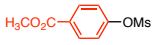
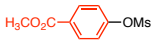
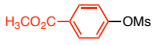
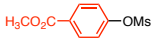
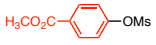
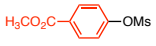
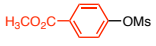
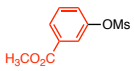
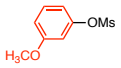
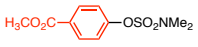
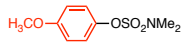
[b]Isolated yield.

To compare PCy_3 and PPh_3 ligands, we further decreased the catalyst and ligand loading for both ligands and screened several more challenging substrates using PPh_3 as the ligand. Decreasing the catalyst loading to as low as 2% did not reduce the yield. However, a further decrease of the catalyst loading to 1% significantly decreased the reaction yield. PCy_3 was shown to be more efficient than PPh_3 at low catalyst loading (Table 4.2, entries 5 and 10). With PCy_3 as the ligand and 5% catalyst loading, the reaction was complete in 3 h. Although PCy_3 was more efficient, the less expensive and oxidatively more stable PPh_3 is preferable. Hence we further screened several substrates utilizing PPh_3 as the ligand.

To our disappointment, with extended reaction time, *meta*-methoxy phenyl mesylate was shown to be challenging when using PPh_3 as the ligand (Table 4.2, entries 12 and 14) even at 5 mol% catalyst loading while electron deficient aryl mesylates and sulfamates were cross-coupled in moderate yields (Table 4.2, entries 11 and 13). To develop a universal catalytic system, we chose 5% Ni catalyst/10% PCy_3/K_3PO_4, dry THF as general reaction conditions.

Table 4.2. Cross-Coupling of Aryl Mesylates and Sulfamates with *para*-Methoxyphenyl Neopentylglycolboronates. Screening for Optimum Combinations of Catalyst and Ligand Loadings

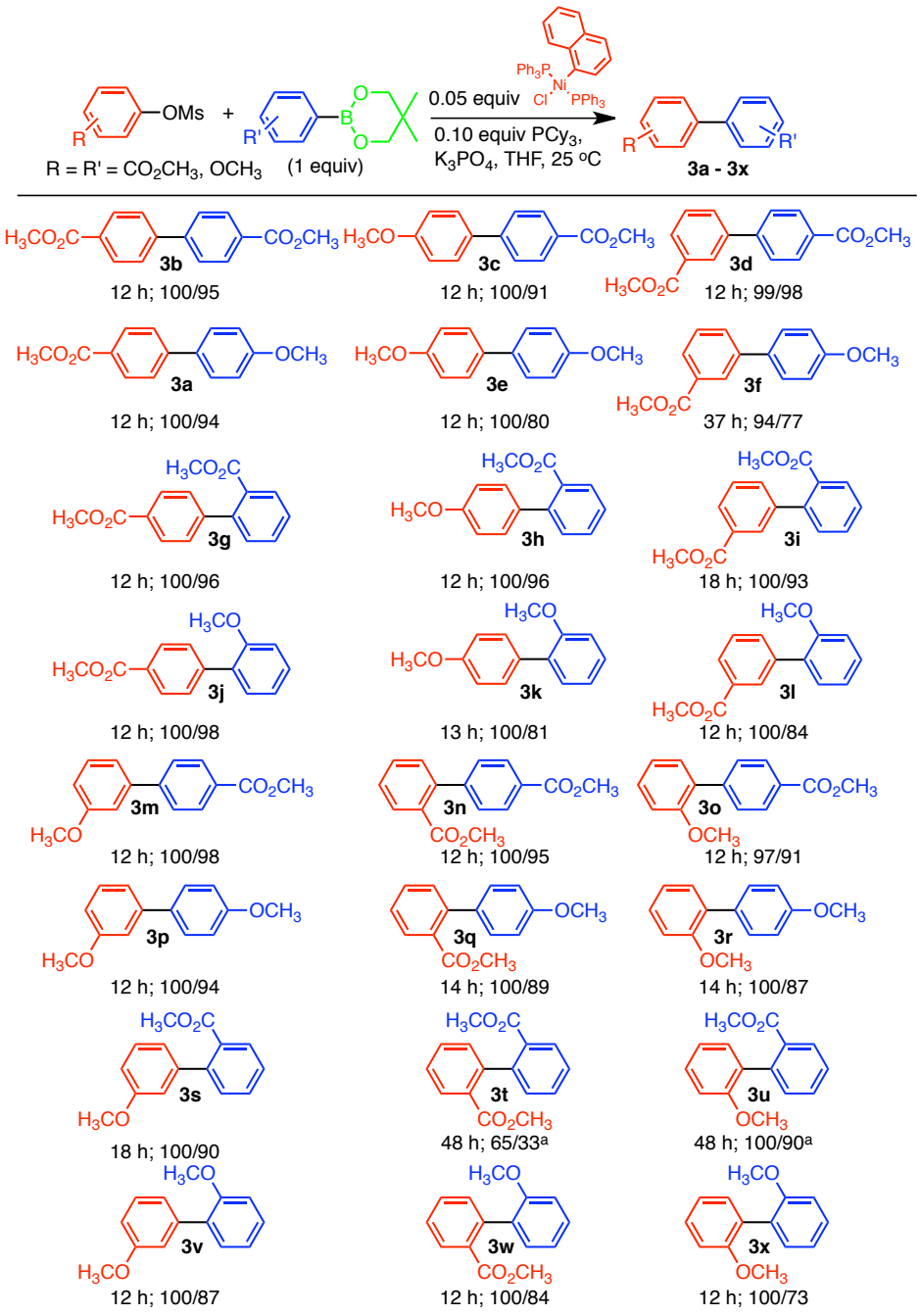


entry	1	Catalyst (%)	Ligand (%)	Time (h)	convn[a]/yield[b] (%)
1		5	PPh_3(10)	12	100/94
2		5	PPh_3(10)	6	100/86
3		2.5	PPh_3(5)	12	100/85
4		2	PPh_3(4)	12	100/86
5		1	PPh_3(2)	28	79/42
6		5	PCy_3(10)	12	100/90[c]
7		5	PCy_3(10)	3	100/84[c]
8		2.5	PCy_3(5)	12	100/89[c]
9		2	PCy_3(4)	12	100/89[c]
10		1	PCy_3(2)	23	84/78[c]
11		5	PPh_3(10)	37	94/77
12		5	PPh_3(10)	48	60/53
13		5	PPh_3(10)	48	81/68
14		5	PPh_3(10)	48	28/23

[a]Conversion determined by GC, the GC yield is always the same as the conversion. [b]Isolated yield. [c]Aryl boronate 1.5 equiv.

Cross-Coupling Reaction of Aryl Neopentylglycolboronates with Aryl Mesylates. The cross-coupling reaction of aryl mesylates with aryl neopentylglycolboronates bearing both electron-withdrawing and electron-donating functional groups was studied to survey the scope and limitations of this catalytic system. We chose the methoxy group and the carboxylate group as representatives of electron donating and electron withdrawing substituents. The steric factor on both mesylate and aryl neopentylglycolboronates were also studied by using *ortho*, *meta* and *para* substituents. In general, cross-coupling reactions were complete within 14 h and gave good to excellent yields despite steric hindrance or the presence of deactivating electron-donating substituent on both electrophiles and nucleophiles. *ortho*-*ortho* Coupling was shown to be more challenging due to steric hindrance, which requires 10 mol% catalyst loading and 48 h reaction time. Nevertheless, *ortho*-*ortho* coupling (Table 4.3, **3u, 3w, 3x**) was accomplished in good to excellent yields with the exception of *ortho*-methyl benzoate with *ortho*-methyl benzoate (Table 4.3, **3t**).

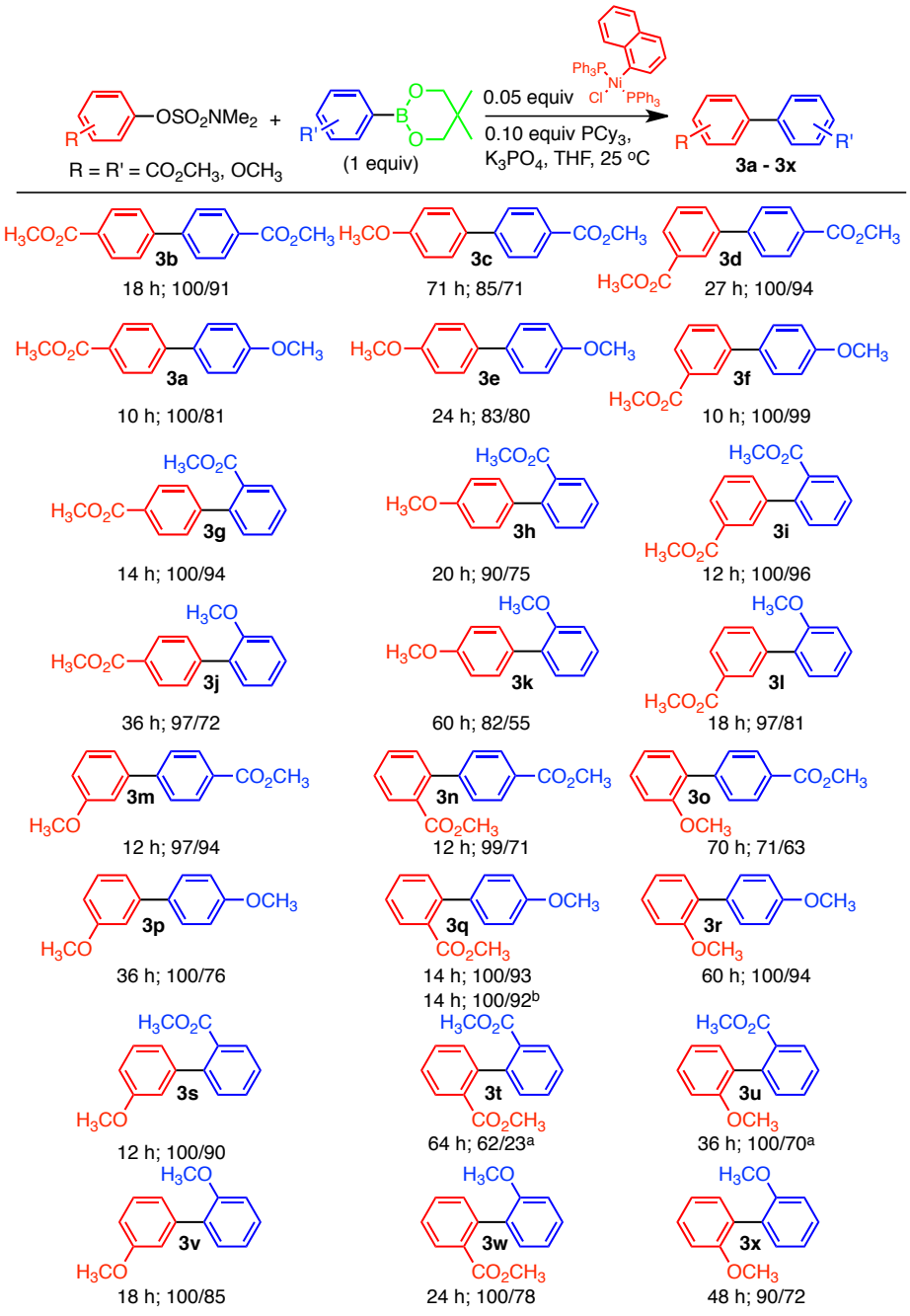
Table 4.3. Cross-Coupling of Aryl Mesylates with Aryl Neopentylglycolboronates Catalyzed by $Ni^{II}Cl(1\text{-Naphthyl})(PPh_3)_2/PCy_3$ in THF at 25 °C



Reaction conditions: ArOMs (0.3 mmol), aryl neopentylglycolboronate (0.3 mmol), Ni(II)Cl(1-naphthyl)$(PPh_3)_2$ (0.015 mmol), PCy_3 (0.03 mmol), K_3PO_4 (0.9 mmol), THF (1.0 mL). Conversion / Isolated yield, the GC yield has the same value as the conversion. [a]10 % Catalyst and 20 % PCy_3.

Cross-Coupling Reaction of Aryl Neopentylglycolboronates with Aryl Sulfamates. In recent studies,[2] it has been shown that aryl mesylates and sulfamates behave similar in their Suzuki-Miyaura cross-coupling reactions with aryl neopentylglycolboronates. With $Ni(COD)_2/PCy_3/K_3PO_4$ catalytic system at room temperature, both mesylates and sulfamates were cross-coupled efficiently. Although mesylates are important C-O electrophiles, the cross-coupling reaction of sulfamates is also important due to their reactivity in *ortho*-metalation reactions.[4] It was expected that the $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$ precatalyst would provide similar reaction results with $Ni(COD)_2$, and therefore, the cross-coupling of aryl neopentylglycolboronates with aryl sulfamates was also investigated. Aryl sulfamates were less reactive than aryl mesylates when $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2/PCy_3$ was used as a catalyst, generating lower yields at longer reaction time compared to the results obtained from $Ni(COD)_2/PCy_3/K_3PO_4$ system.[2] However, good yields were still obtained with a longer reaction time. Electron rich sulfamates, namely 4-methoxy phenyl and 2-methoxy phenyl sulfamates were found to be challenging, require 20 to 71 h to go to near complete or complete conversion. The reason is still under investigation. Steric hindrance was tolerated as well. (Table 4.4, **3i, 3g**) *ortho*-*ortho* Coupling was again more challenging as in the case of aryl mesylates. Cross-coupling of substrates with *ortho*-electron withdrawing groups and aryl boronates with *ortho*-withdrawing groups (Table 4.4, **3t** and Table 4.3, **3t**) did not give good yields even with higher catalyst loading and reaction times as long as 64 h. An increased reaction time did not result in an increased reaction yield. Instead, methyl benzoate was detected by GC in the reaction mixture after 90 h.

Table 4.4. Cross-Coupling of Aryl Sulfamates with Aryl Neopentylglycolboronates Catalyzed by Ni(II)Cl(1-Naphthyl)(PPh_3)$_2$/PCy_3 in THF at 25 ^oC

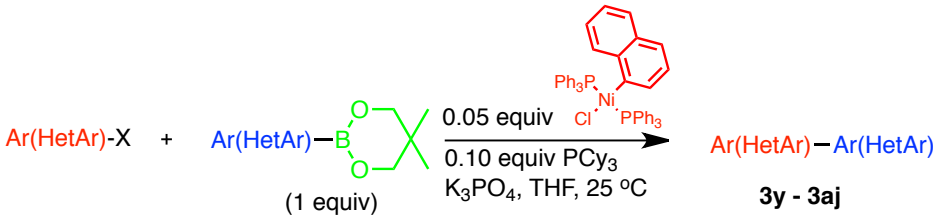


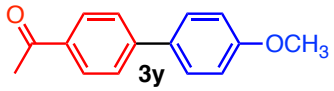
Reaction conditions: $ArOSO_2NMe_2$ (0.3 mmol), aryl neopentylglycol boronate (0.3 mmol), Ni(II)Cl(1-naphthyl)(PPh_3)$_2$ (0.015 mmol), PCy_3 (0.03 mmol), K_3PO_4 (0.9 mmol), THF (1.0 mL). Conversion / Isolated yield, the GC yield has the same value as the conversion except for **3t** (48%). [a]10 % Catalyst and 20 % PCy_3.

Scope of Cross-Coupling Reaction of Aryl and Heteroaryl Neopentylglycolboronates with Aryl and Heteroaryl Mesylates and Sulfamates. Various functional groups including keto-, cyano-, and imido- were tested for these reaction conditions (Table 4.5). It was found that these reaction conditions tolerated these sensitive functional groups with good isolated yields when cross-coupling electron-rich aryl neopentylglycol boronate with aryl mesylates bearing keto group (81%, Table 4.5, **3y**), cyano group (93%, Table 4.5, **3z**; X = OMs), and imido group (94%, Table 4.5, **3af**). However, the isolated yields were lower with longer reaction time when these aryl mesylates were coupled with electron-deficient aryl neopentylglycolboronates [keto group (57%, Table 4.5, **3ab**), cyano group (85%, Table 4.5, **3ac**), and imido group (49%, Table 4.5, **3ai**)]. The functionalized aryl sulfamates also gave the coupled product but in diminished yield (45%, Table 4.5, **3z**).

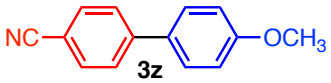
The cross-coupling reaction of heteroaryl mesylates and heteroaryl sulfamates with aryl or heteroarylneopentylglycol boronates was also investigated. Generally, the isolated yields for both heteroaryl mesylates and sulfamates were excellent (81-99%) regardless of the electronic properties of aryl neopentylglycolboronates (**3ae, 3ah, 3aa, 3ad, 2ag**). Only the cross-coupling of 3-pyridinyl mesylate with 2-thienyl neopentylglycolboronates showed diminished isolated yield (67%, Table 4.5, **3aj**).

Table 4.5. Cross-Coupling of Aryl and Heteroaryl Mesylates and Sulfamates with Aryl and Heteroaryl Neopentylglycolboronates Catalyzed by Ni(II)Cl(1-Naphthyl)(PPh_3)$_2$/PCy_3 in THF at 25 °C

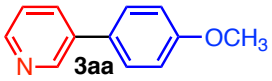




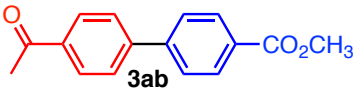
X = OMs: 12 h; 81%



X = OMs: 72 h; 93%
X = OSO_2NMe_2: 26 h; 45%

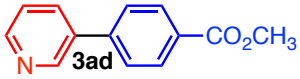


X = OMs: 50 h; 95%
X = OSO_2NMe_2: 26 h; 99%

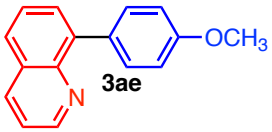


X = OMs: 72 h; 57%

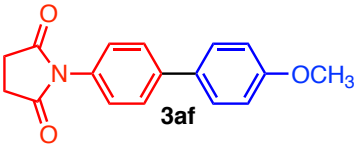
X = OMs: 48 h; 85%



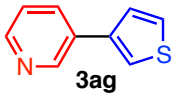
X = OMs: 24 h; 90%
X = OSO_2NMe_2: 24 h; 87%



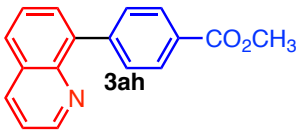
X = OMs: 12 h; 87%



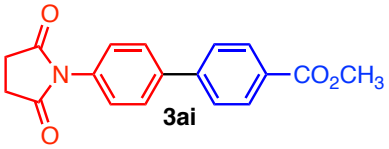
X = OMs: 12 h; 94%



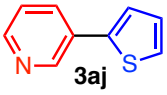
X = OMs: 12 h; 81%



X = OMs: 24 h; 99%



X = OMs: 48 h; 49%



X = OMs: 37 h; 48%

Reaction conditions: Ar(HetAr)-OMs or Ar(HetAr)-OSO_2NMe_2 (0.3 mmol), aryl neopentylglycolboronate (0.3 mmol), Ni(II)Cl(1-naphthyl)(PPh_3)$_2$ (0.015 mmol), PCy_3 (0.03 mmol), K_3PO_4 (0.9 mmol), THF (1.0 mL). All yields are isolated.

4.1.3 Conclusions

The bench-stable, inexpensive and readily available *trans*-chloro(1-naphthyl)-bis-(triphenylphosphine) Ni^{II} complex was demonstrated to be an efficient catalyst of the cross-coupling of electron-rich and electron-deficient aryl and heteroaryl mesylates and sulfamates with aryl and heteroaryl neopentylglycolboronates. The reaction is carried out in THF at room temperature without external reducing reagent and tolerates a variety of functional groups. The ability of *trans*-chloro(1-naphthyl)-bis-(triphenylphosphine)Ni^{II} complex to catalyze the Suzuki-Miyaura cross-coupling of aryl and heteroaryl neopentylglycolboronates provides support for the Ni^0/Ni^{II} catalytic cycle mechanism for this nickel catalyzed cross-coupling reaction. Now, room temperature Suzuki-Miyaura cross-coupling reactions can be achieved without the use of air sensitive and expensive $Ni(COD)_2$. With this development, large-scale syntheses of complex building blocks and macromolecules can be achieved at lower cost and in fewer steps.

4.1.4 Experiments

General Experimental Methods. $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$ was prepared according to a literature method.[18-20] 2-(4-Methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (**2a**) was synthesized by the esterification of the boronic acid with neopenthyl glycol. K_3PO_4 from a commercial source was dried at 40 ^oC under vacuum overnight prior to use. PPh_3 was recrystalized from hexane. THF was distilled over sodium/benzophenone. Aryl mesylates and aryl sulfamates were synthesized according to literature procedures.[11,23] All other reagents were used as received from commercial sources. ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded using TMS as an internal standard. High-resolution mass spectra of new compounds were obtained on a high-resolution double focusing chemical ionization mass spectrometer. A GC coupled with an FID detector and column HP 19091J-413 (5%-phenyl)-methylpolysiloxane 30 m length 0.32 mm internal diameter was used to follow the reaction conversions and to assess the purity of the final compounds. This method is complementary to the NMR technique. The crude

reaction mixtures were diluted with THF and analyzed by GC as reported in the previous publications from our laboratory.[23-28]

Preparation of Neopentylglycolborane. A procedure elaborated in our laboratory was used.[27,28] To a cooled solution (0 ^{o}C) of neopentylglycol (6.0 mmol, 2.0 equiv) in toluene (3 mL) was slowly added $(CH_3)_2S{\bullet}BH_3$ (6 mmol, 2.0 equiv) under nitrogen. The reaction was allow to stir at 0 ^{o}C for 30 min, then at room temperature for 90 min. The neopentylglycolborane was used directly without further purification.

General Procedure for Neopentylglycolborylation. The arylboronic esters (except 2-(4-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (**2a**)) were prepared according to literature procedures.[24,26] To an oven-dried 25 mL Schlenk tube were added Zn powder (6.0 mmol), $NiCl_2$(dppp) (1.5 mmol), and PPh_3 (3.0 mmol) along with the appropriate aryl halide (if it is solid) (3.0 mmol). The aryl halide, catalyst, and PPh_3 were degassed by pumping and backfilling with nitrogen three times. Dry toluene (3 mL) was added to the reaction mixture along with the appropriate aryl halide (if it is liquid) and Et_3N (9.0 mmol). The neopentylglycolborane was added dropwise to the reaction mixture. The reaction was placed into an oil bath at 100 ^{o}C with stirring under nitrogen. After the starting material was consumed, the reaction was quenched by addition of saturated NH_4Cl solution (25 mL) and extracted with EtOAc (25 mL) for 3 times. The organic fractions were combined and dried over $MgSO_4$, followed by filtration and evaporation of the solvent. The crude product was purified by column chromatography with dichloromethane.

General Procedure for Cross-Coupling Reaction. To an oven-dried test tube (15 x 85 mm) were added aryl mesylate or aryl sulfamate (0.3 mmol), neopentylglycol boronic ester (0.30 mmol), $Ni^{II}Cl$(1-naphthyl)$(PPh_3)_2$ (12 mg, 0.015 mmol), and K_3PO_4 (191 mg, 0.9 mmol). The tube was taken into a glove box and PCy_3 (8.4 mg, 0.030 mmol) was added. Dried THF (1.0 mL) was then added and the tube was capped with rubber septum. The reaction was stirred at room temperature under nitrogen in the glove box for 10 – 72 h. The crude mixture was filtered through

a short column of silica gel. The solvent was evaporated and the product was purified by column chromatography with dichloromethane/hexane or EtOAc/hexane as eluent.

Methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (3a). Purified by silica gel column chromatography with 30% hexanes in dichloromethane mixture. White solid (from mesylate: 68 mg, 94%; from sulfamate: 59 mg, 81%), mp 173-174 ^{o}C (lit.[2] 172-173 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.3, 2H), 7.62 (d, J = 8.3, 2H), 7.57 (d, J = 8.7, 2H), 6.99 (d, J = 8.7, 2H), 3.93 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.22, 160.00, 145.37, 132.57, 130.25, 128.51, 128.41, 126.62, 114.53, 55.53, 52.21.

Dimethyl [1,1'-biphenyl]-4,4'-dicarboxylate (3b). Purified by silica gel column chromatography with dichloromethane. White solid (from mesylate: 77 mg, 95%; from sulfamate: 74 mg, 91%), mp 213-214 ^{o}C (lit.[2] 212-214 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 8.4, 4H), 7.69 (d, J = 8.4, 4H), 3.95 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 144.5, 130.4, 129.9, 127.4, 52.4.

Dimethyl [1,1'-biphenyl]-3,4'-dicarboxylate (3d). Purified by silica gel column chromatography with dichloromethane. White solid (from mesylate: 79 mg, 98%; from sulfamate: 76 mg, 94%), mp 95-96 ^{o}C (lit.[2] 95 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.11 (d, J = 7.7, 2H), 8.05 (d, J = 7.3, 1H), 7.78 (d, J = 7.2, 1H), 7.67 (d, J = 7.7, 2H), 7.52 (t, J = 7.5, 1H), 3.94 (s, 3H), 3.93 (s,3H)). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 166.8, 144.5, 140.3, 131.6, 131.0, 130.3, 129.4, 129.2, 129.1, 128.4, 127.1, 52.3, 52.2.

4,4'-Dimethoxy-1,1'-biphenyl (3e). Purified by silica gel column chromatography with 50% hexanes in dichloromethane. White solid (from mesylate: 51 mg, 80%; from sulfamate: 51 mg, 80%), mp 172-173 ^{o}C (lit.[2] 171-172 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 8.8, 4H), 6.96 (d, J = 8.8, 4H), 3.84 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 132.7, 126.9, 113.3, 54.5.

Methyl 4'-methoxy-[1,1'-biphenyl]-3-carboxylate (3f). Purified by silica gel column chromatography with 30% hexanes in dichloromethane. White solid (from mesylate: 56 mg, 77%; from sulfamate: 72 mg, 99%), mp 69-70 ^{o}C (lit.[2] 68-70 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.96 (d, J = 7.7, 1H), 7.72 (d, J = 7.7, 1H), 7.55 (d, J = 8.7, 2H), 7.46 (t, J = 7.7, 1H), 6.98 (d,

J = 8.7, 2H), 3.93 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 159.6, 141.2, 132.7, 131.2, 130.8, 128.9, 128.3, 127.9, 127.8, 114.4, 55.4, 52.2.

Dimethyl [1,1'-biphenyl]-2,4'-dicarboxylate (3g). Purified by silica gel column chromatography with dichloromethane. White solid (from mesylate: 78 mg, 96%; from sulfamate: 76 mg, 94%), mp 58-59 °C (lit.[2] 56-58 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.2, 2H), 7.88 (d, J = 7.6, 1H), 7.54 (t, J = 7.1, 1H), 7.44 (t, J = 7.3, 1H), 7.41 – 7.31 (m, J = 8.8, 3H), 3.93 (s, 3H), 3.63 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 167.0, 146.3, 141.7, 131.6, 130.7, 130.6, 130.2, 129.4, 129.0, 128.5, 127.9, 52.2, 52.1.

Methyl 4'-methoxy-[1,1'-biphenyl]-2-carboxylate[2] (3h). Purified by silica gel column chromatography with 30% hexanes in dichloromethane. Colorless oil (from mesylate: 68 mg, 94%; from sulfamate: 55 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 7.8, 1H), 7.49 (td, J = 7.6, 1.4, 1H), 7.40 – 7.31 (m, J = 12.0, 4.5, 2H), 7.24 (d, J = 8.7, 2H), 6.93 (d, J = 8.7, 2H), 3.84 (s, 3H), 3.66 (s, 3H). 52.08. ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 159.1, 142.1, 133.8, 131.3, 131.0, 130.8, 129.8, 129.6, 126.9, 113.7, 55.4, 52.1.

Dimethyl [1,1'-biphenyl]-2,3'-dicarboxylate[29] (3i). Purified by silica gel column chromatography with dichloromethane. Colorless oil (from mesylate: 75 mg, 93%; from sulfamate: 78 mg, 96%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dt, J = 7.2, 1.7, 1H), 8.01 (s, 1H), 7.90 (d, J = 7.8, 1H), 7.56 (td, J = 7.5, 1.3, 1H), 7.52 – 7.42 (m, 3H), 7.37 (d, J = 7.6, 1H), 3.92 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 167.1, 141.9, 133.1, 131.7, 131.0, 130.6, 130.3, 130.2, 129.6, 128.6, 128.2, 127.8, 52.3, 52.1.

Methyl 2'-methoxy-[1,1'-biphenyl]-4-carboxylate (3j). Purified by silica gel column chromatography with 30% hexanes in dichloromethane. White solid (from mesylate: 71 mg, 98%; from sulfamate: 52 mg, 72%), mp 78-80 °C (lit.[2] 80 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.3, 2H), 7.60 (d, J = 8.3, 2H), 7.38 – 7.28 (m, J = 15.1, 7.5, 2H), 7.03 (t, J = 7.5, 1H), 6.98 (d, J = 8.2, 1H), 3.92 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 156.6, 143.5, 130.9, 129.7, 129.7, 129.5, 129.4, 128.6, 121.0, 111.5, 55.6, 52.1.

2,4'-Dimethoxy-1,1'-biphenyl (3k). Purified by silica gel column chromatography with 30% hexanes in dichloromethane. White solid (from mesylate: 52 mg, 81%; from sulfamate: 35 mg, 55%), mp 69-70 ^{o}C (lit.[2] 64-66 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 8.5, 2H), 7.33 – 7.25 (m, 2H), 7.01 (t, J = 7.4, 1H), 6.98 – 6.91 (m, 3H), 3.84 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 156.6, 131.1, 130.8, 130.7, 130.5, 128.3, 121.0, 113.6, 111.4, 55.7, 55.4.

Methyl 2'-methoxy-[1,1'-biphenyl]-3-carboxylate (3l). Purified by silica gel column chromatography with 30% hexanes in dichloromethane (from mesylate: 61 mg, 84%; from sulfamate: 59 mg, 81%). White solid, mp 96-97 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (t, J = 1.5, 1H), 8.03 – 7.97 (m, 1H), 7.73 (ddd, J = 7.7, 1.7, 1.3, 1H), 7.47 (t, J = 7.7, 1H), 7.38 – 7.30 (m, 2H), 7.04 (td, J = 7.5, 1.0, 1H), 6.99 (d, J = 8.2, 1H), 3.92 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4, 156.6, 139.0, 134.3, 131.0, 130.9, 130.1, 129.8, 129.2, 128.2, 128.1, 121.1, 111.4, 100.1, 55.7, 52.2. HRMS (CI+) calcd for $C_{15}H_{14}O_3Na$ (M^++Na) 265.0841, found 265.0842.

Methyl 3'-methoxy-[1,1'-biphenyl]-4-carboxylate (3m). Purified by silica gel column chromatography with 30% hexanes in dichloromethane. White solid (from mesylate: 71 mg, 98%; from sulfamate: 68 mg, 94%), mp 54-55 ^{o}C (lit[2] 52-54 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4, 2H), 7.63 (d, J = 8.4, 2H), 7.35 (t, J = 7.9, 1H), 7.18 (d, J = 7.6, 1H), 7.15 – 7.10 (m, 1H), 6.92 (dd, J = 8.2, 1.9, 1H), 3.92 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 160.1, 145.6, 141.5, 130.1, 130.0, 129.1, 127.2, 119.8, 113.6, 113.1, 55.4, 52.2.

3,4'-Dimethoxy-1,1'-biphenyl (3p). Purified by silica gel column chromatography with 30% hexanes in dichloromethane. White solid (from mesylate: 60 mg, 94%; from sulfamate: 49 mg, 76%), mp 53-54 ^{o}C (lit.[2] 56-58 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 7.3, 2H), 7.33 (t, J = 7.9, 1H), 7.14 (d, J = 8.5, 1H), 7.09 (s, 1H), 6.97 (d, J = 7.3, 2H), 6.89 – 6.81 (m, 1H), 3.86 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 158.4, 141.5, 132.8, 128.8, 127.3, 118.4, 113.3, 111.7, 111.2, 54.5, 54.4.

Methyl 3'-methoxy-[1,1'-biphenyl]-2-carboxylate (3s). Purified by silica gel column chromatography with 30% hexanes in dichloromethane. Colorless oil (from mesylate: 65 mg,

90%; from sulfamate: 65 mg, 90%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.7, 1.0, 1H), 7.52 (td, J = 7.5, 1.4, 1H), 7.44 – 7.37 (m, 2H), 7.30 (t, J = 7.9, 1H), 6.94 – 6.84 (m, 3H), 3.83 (s, 3H), 3.65 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 158.5, 141.9, 141.4, 130.3, 130.2, 129.7, 128.8, 128.2, 126.4, 120.0, 113.0, 112.0, 54.4, 51.1. HRMS (CI+) calcd for $C_{15}H_{14}O_3Na$ (M^++Na) 265.0841, found 265.0834.

Dimethyl [1,1'-biphenyl]-2,2'-dicarboxylate (3t). Purified by silica gel column chromatography with dichloromethane. White solid (from mesylate: 27 mg, 33%; from sulfamate: 19 mg, 23%), mp 72-73 ^{o}C (lit.[30] 74 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 7.7, 2H), 7.53 (t, J = 7.5, 2H), 7.43 (t, J = 7.6, 2H), 7.21 (d, J = 7.5, 2H), 3.61 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 143.4, 131.6, 130.3, 130.0, 129.5, 127.3, 51.9.

Methyl 2'-methoxy-[1,1'-biphenyl]-2-carboxylate[2] (3u). Purified by silica gel column chromatography with 30% hexanes in dichloromethane. Colorless oil (from mesylate: 64 mg, 90%; from sulfamate: 51 mg, 70%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.7, 1.1, 1H), 7.52 (td, J = 7.6, 1.3, 1H), 7.37 (td, J = 7.6, 1.1, 1H), 7.34 – 7.28 (m, 2H), 7.23 (dt, J = 6.2, 3.1, 1H), 7.02 (t, J = 7.4, 1H), 6.88 (d, J = 8.2, 1H), 3.69 (s, 3H), 3.63 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 156.1, 138.9, 131.7, 131.6, 131.4, 130.6, 130.0, 129.4, 128.9, 127.2, 120.8, 110.2, 55.3, 51.7.

2,3'-Dimethoxy-1,1'-biphenyl[29] (3v). Purified by silica gel column chromatography with 30% hexanes in dichloromethane. Colorless oil (from mesylate: 62 mg, 97%; from sulfamate: 55 mg, 85%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, J = 7.3, 3H), 7.12 – 7.06 (m, 2H), 7.01 (td, J = 7.5, 1.0, 1H), 6.97 (d, J = 7.8, 1H), 6.87 (ddd, J = 8.2, 2.6, 0.9, 1H), 3.83 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 156.6, 140.1, 131.0, 130.7, 129.0, 128.8, 122.2, 120.9, 115.5, 112.6, 111.4, 55.7, 55.4.

2,2'-Dimethoxy-1,1'-biphenyl (3x). Purified by silica gel column chromatography with 30% hexanes in dichloromethane. White solid (from mesylate: 47 mg, 73%; from sulfamate: 46 mg, 72%), mp 153-155 ^{o}C (lit.[2] 152-154 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, J = 7.8, 2H), 7.24

(d, J = 7.4, 2H), 6.99 (t, J = 7.5, 2H), 6.96 (d, J = 8.3, 2H), 3.75 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.2, 131.6, 128.7, 128.0, 120.5, 111.2, 55.8.

1-(4'-Methoxy-[1,1'-biphenyl]-4-yl)ethanone[2] (3y). Purified by silica gel column chromatography with dichloromethane. White solid (from mesylate: 55 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4, 2H), 7.64 (d, J = 8.4, 2H), 7.58 (d, J = 8.8, 2H), 7.00 (d, J = 8.8, 2H), 3.86 (s, 3H), 2.63 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.9, 160.1, 145.5, 135.5, 132.4, 129.1, 128.5, 126.8, 114.6, 55.5, 26.8. ^{1}H NMR matches with literature data.

4'-Methoxy-[1,1'-biphenyl]-4-carbonitrile (3z). Purified by silica gel column chromatography with dichloromethane. White solid (from mesylate: 58 mg, 93%; from sulfamate: 28 mg, 45%), mp 102-103 ^{o}C (lit.[2] 102-103 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.3, 2H), 7.64 (d, J = 8.1, 2H), 7.54 (d, J = 8.7, 2H), 7.01 (d, J = 8.7, 2H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 145.4, 132.7, 131.7, 128.5, 127.3, 119.2, 114.7, 110.3, 55.6.

3-(4-Methoxyphenyl)pyridine[2] (3aa). Purified by silica gel column chromatography with dichloromethane . White solid (from mesylate: 53 mg, 95%; from sulfamate: 55 mg, 99%), mp 62-64 ^{o}C (lit.[2] 60-61 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.55 (d, J = 4.4, 1H), 7.83 (d, J = 7.9, 1H), 7.53 (dd, J = 6.9, 4.8, 2H), 7.33 (dd, J = 7.8, 4.8, 1H), 7.01 (d, J = 8.7, 2H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9, 148.1, 148.0, 136.4, 134.0, 130.4, 128.4, 123.7, 114.7, 55.5.

Methyl 4'-acetyl-[1,1'-biphenyl]-4-carboxylate[31] (3ab). Purified by silica gel column chromatography with 30% hexanes in dichloromethane. White solid (from mesylate: 43 mg, 57%), mp 164-165 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 8.2, 2H), 8.05 (d, J = 8.2, 2H), 7.72 (d, J = 8.3, 2H), 7.69 (d, J = 8.3, 2H), 3.95 (s, 3H), 2.65 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 166.9, 144.6, 144.4, 136.7, 130.4, 129.9, 129.1, 127.6, 127.4, 52.4, 26.8.

Methyl 4'-cyano-[1,1'-biphenyl]-4-carboxylate (3ac). Purified by silica gel column chromatography with dichloromethane. White solid (from mesylate: 61 mg, 85%), mp 141-142 ^{o}C (lit.[2] 141-142 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 8.5, 2H), 7.76 (d, J = 8.5, 2H), 7.72 (d,

J = 8.6, 2H), 7.66 (d, J = 8.5, 2H), 3.96 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 144.5, 143.5, 132.8, 130.5, 130.3, 128.1, 127.4, 118.8, 112.0, 52.4.

Methyl 4-(pyridin-3-yl)benzoate (3ad). Purified by silica gel column chromatography with dichloromethane. White solid (from mesylate: 58 mg, 90%; from sulfamate: 56 mg, 87%), mp 103-104 °C (lit.[32] 105-107 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.64 (d, J = 4.7, 1H), 8.15 (d, J = 8.2, 2H), 7.91 (dd, J = 7.9, 1.5, 1H), 7.66 (d, J = 8.2, 2H), 7.40 (dd, J = 7.8, 4.8, 1H), 3.95 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 149.4, 148.5, 142.4, 135.7, 134.6, 130.5, 129.9, 127.2, 123.8, 52.4.

8-(4-Methoxyphenyl)quinoline (3ae). Purified by silica gel column chromatography with dichloromethane. White solid (from mesylate: 62 mg, 87%), mp 111-112 °C (lit.[2] 113-114 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (dd, J = 4.1, 1.8, 1H), 8.19 (dd, J = 8.3, 1.8, 1H), 7.79 (dd, J = 8.1, 1.3, 1H), 7.71 (dd, J = 7.1, 1.4, 1H), 7.66 (d, J = 8.7, 2H), 7.62 – 7.56 (m, 1H), 7.40 (dd, J = 8.2, 4.1, 1H), 7.04 (d, J = 8.7, 2H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 150.3, 146.3, 140.7, 136.4, 132.1, 131.9, 130.1, 129.0, 127.2, 126.4, 121.1, 113.7, 55.5.

1-(4'-Methoxy-[1,1'-biphenyl]-4-yl)pyrrolidine-2,5-dione (3af). Purified by silica gel column chromatography with dichloromethane. White solid (from mesylate: 79 mg, 94%), mp 212-213 °C (lit.[2] 212-213 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 8.5, 2H), 7.52 (d, J = 8.7, 2H), 7.33 (d, J = 8.5, 2H), 6.98 (d, J = 8.7, 2H), 3.85 (s, 3H), 2.92 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 159.6, 141.4, 132.8, 130.5, 128.4, 127.6, 126.8, 114.4, 55.5, 28.6.

3-(Thiophen-3-yl)pyridine (3ag). Purified by silica gel column chromatography with dichloromethane. White solid (from mesylate: 39 mg, 81%), mp 75-76 °C (lit.[2] 76-77 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.54 (s, 1H), 7.90 – 7.83 (m, 1H), 7.52 (dd, J = 2.9, 1.3, 1H), 7.45 (dd, J = 5.0, 3.0, 1H), 7.40 (dd, J = 5.0, 1.3, 1H), 7.33 (dd, J = 7.8, 4.8, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 147.9, 139.0, 133.7, 131.7, 127.1, 126.1, 123.8, 121.6.

Methyl 4-(quinolin-8-yl)benzoate (3ah). Purified by silica gel column chromatography with dichloromethane. White solid (from mesylate: 78 mg, 99%), mp 91-92 °C (lit.[2] 92-93 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (dd, J = 4.1, 1.6, 1H), 8.22 (dd, J = 8.3, 1.6, 1H), 8.17 (d, J = 8.2, 2H),

7.86 (d, J = 8.1, 1H), 7.78 (d, J = 8.1, 2H), 7.75 (d, J = 7.1, 1H), 7.62 (t, J = 7.6, 1H), 7.43 (dd, J = 8.3, 4.1, 1H), 3.95 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 150.6, 146.0, 144.5, 140.0, 136.5, 130.8, 130.5, 129.4, 129.1, 128.9, 128.4, 126.4, 121.4, 52.2.

Methyl 4'-(2,5-dioxopyrrolidin-1-yl)-[1,1'-biphenyl]-4-carboxylate (3ai). Purified by silica gel column chromatography with dichloromethane. White solid (from mesylate: 46 mg, 49%), mp 217-219 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, J = 8.2, 2H), 7.72 (d, J = 8.4, 2H), 7.65 (d, J = 8.2, 2H), 7.41 (d, J = 8.3, 2H), 3.94 (s, 3H), 2.93 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 167.0, 144.7, 140.6, 131.9, 130.3, 129.5, 128.2, 127.3, 127.0, 52.3, 28.6. HRMS (CI^+) calcd for $C_{18}H_{10}NO_4$ (M^++H) 310.1079, found 310.1075.

3-(Thiophen-2-yl)pyridine[2] (3aj). Purified by silica gel column chromatography with dichloromethane. Light brown oil (from mesylate: 32 mg, 67%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.51 (d, J = 4.2, 1H), 7.90 – 7.81 (m, 1H), 7.40 – 7.33 (m, 2H), 7.33 – 7.28 (m, 1H), 7.16 – 7.06 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.6, 147.1, 140.5, 133.1, 130.5, 128.4, 126.2, 124.3, 123.7.

4.1.5 Characterization of Reaction Products

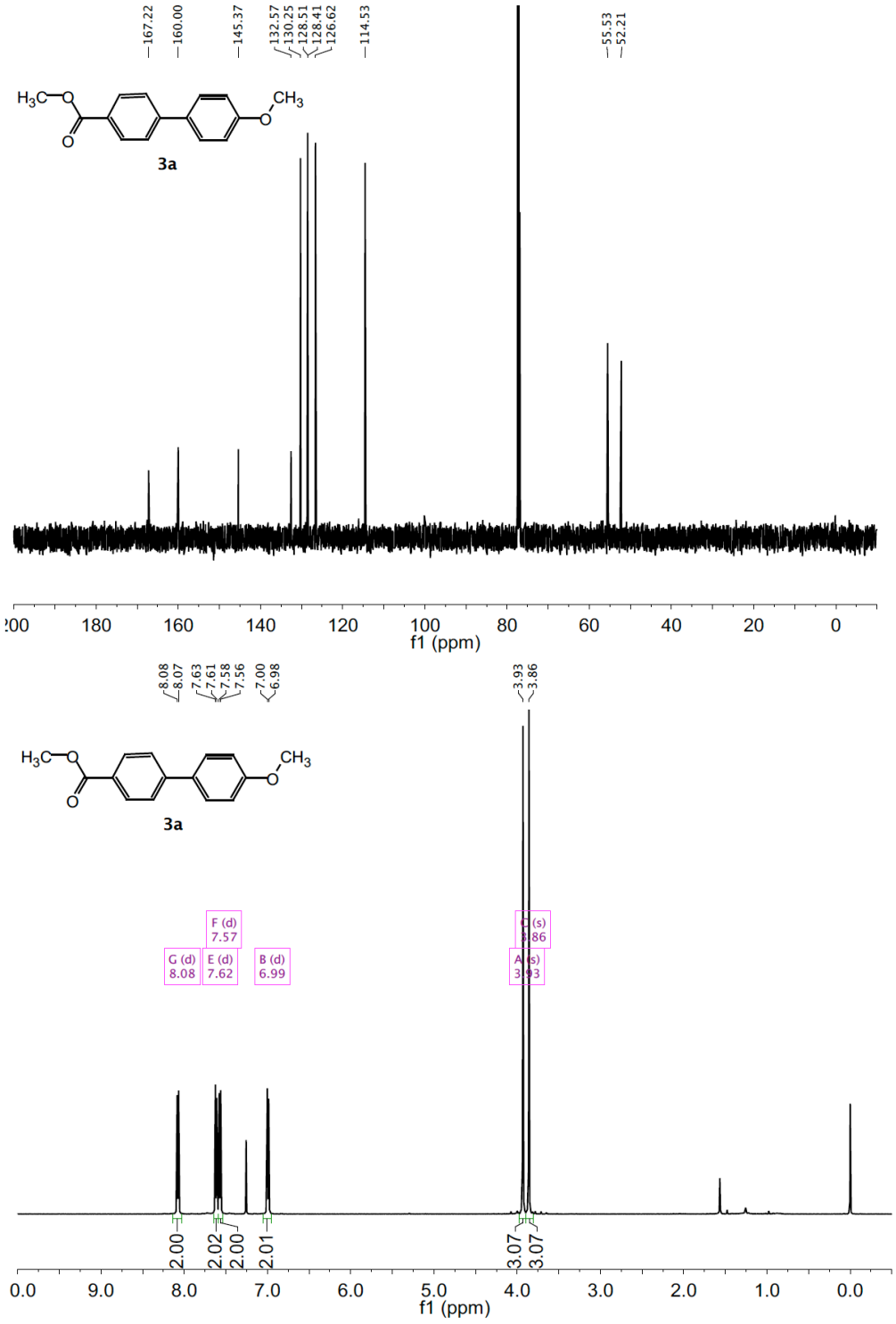


Figure SF 4.1. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (**3a**) in $CDCl_3$.

Figure SF 4.2. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of dimethyl [1,1'-biphenyl]-4,4'-dicarboxylate (**3b**) in $CDCl_3$.

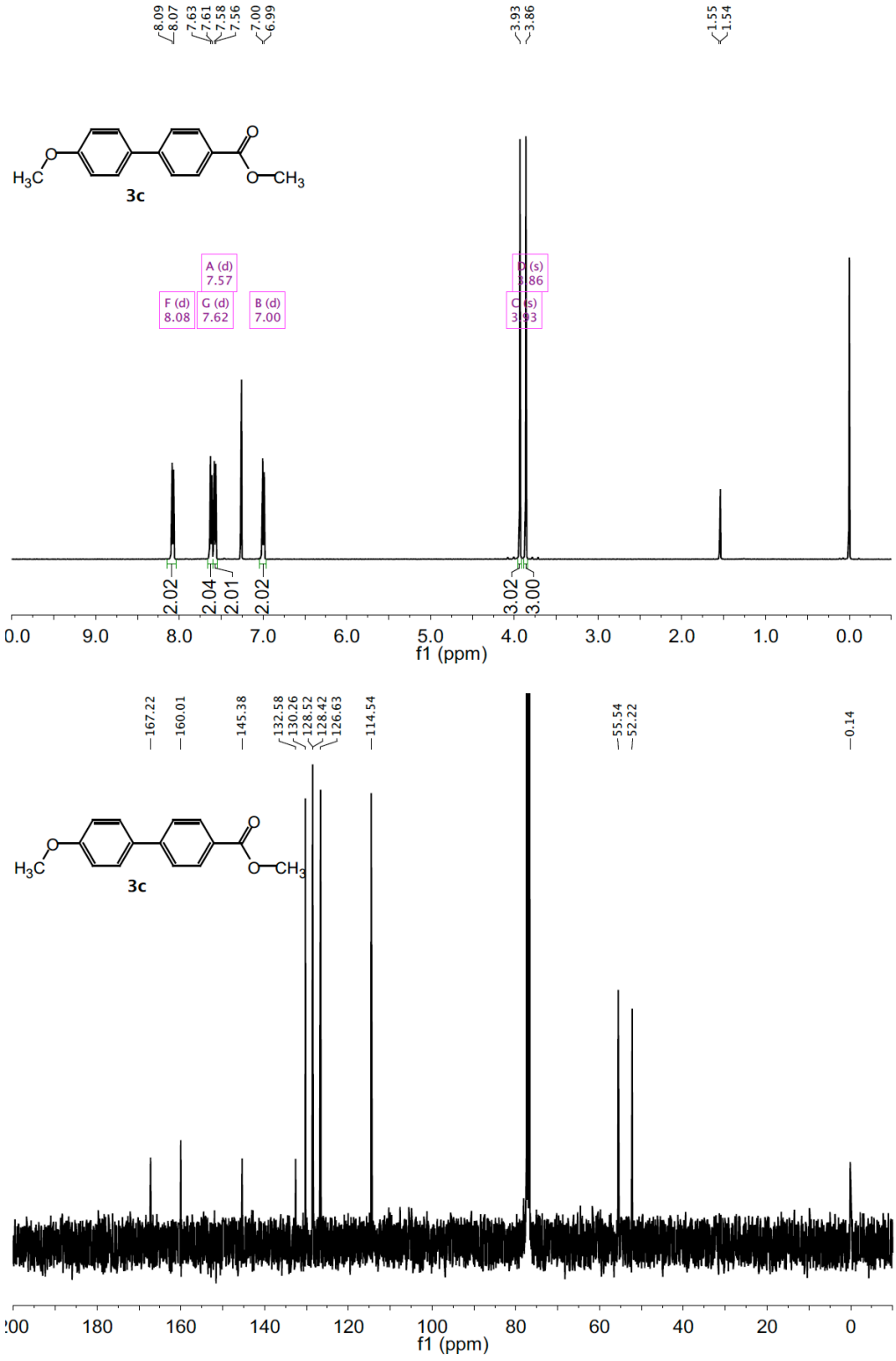


Figure SF 4.3. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (**3c**) in $CDCl_3$.

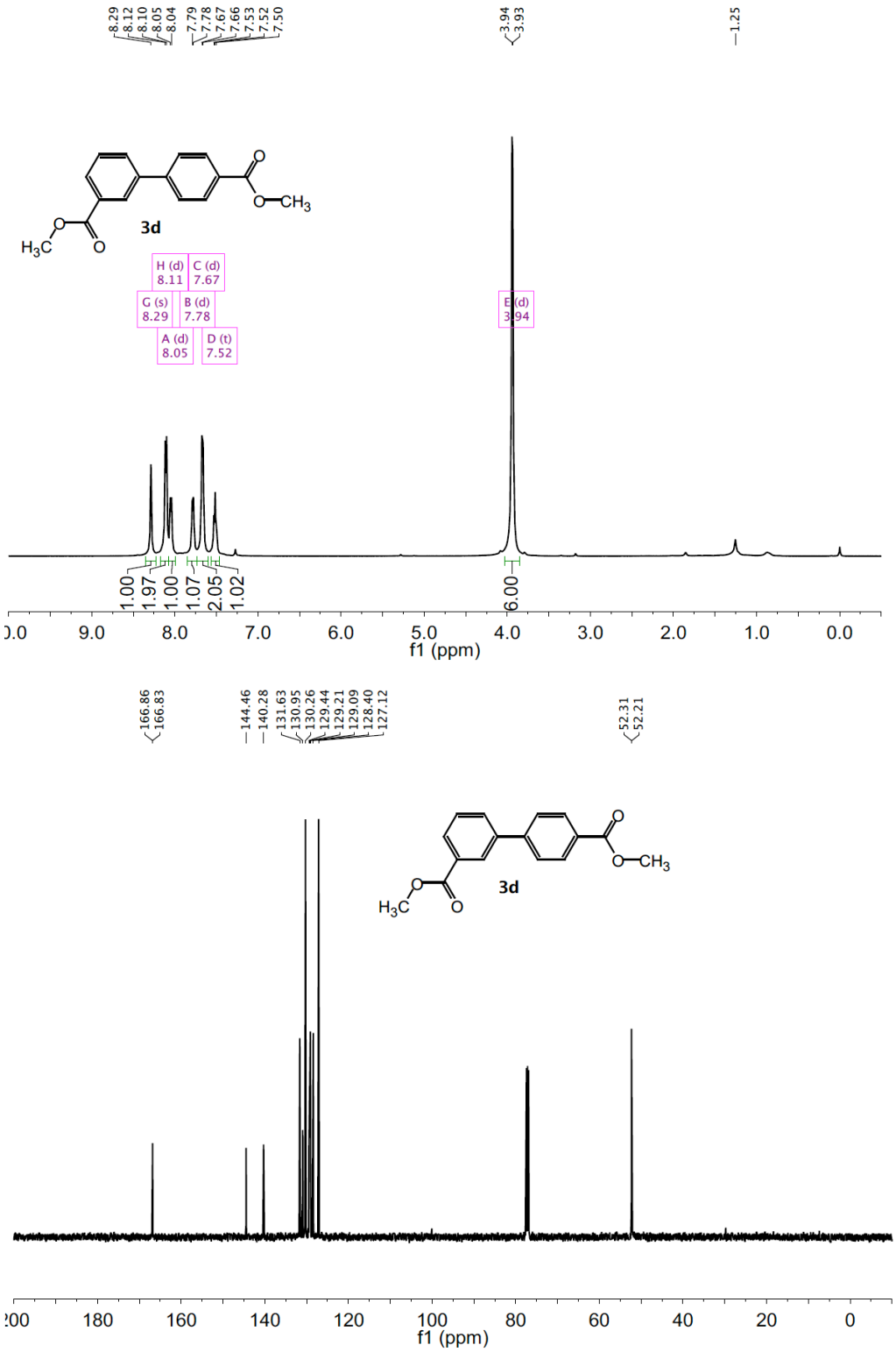


Figure SF 4.4. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of dimethyl [1,1'-biphenyl]-3,4'-dicarboxylate (**3d**) in $CDCl_3$.

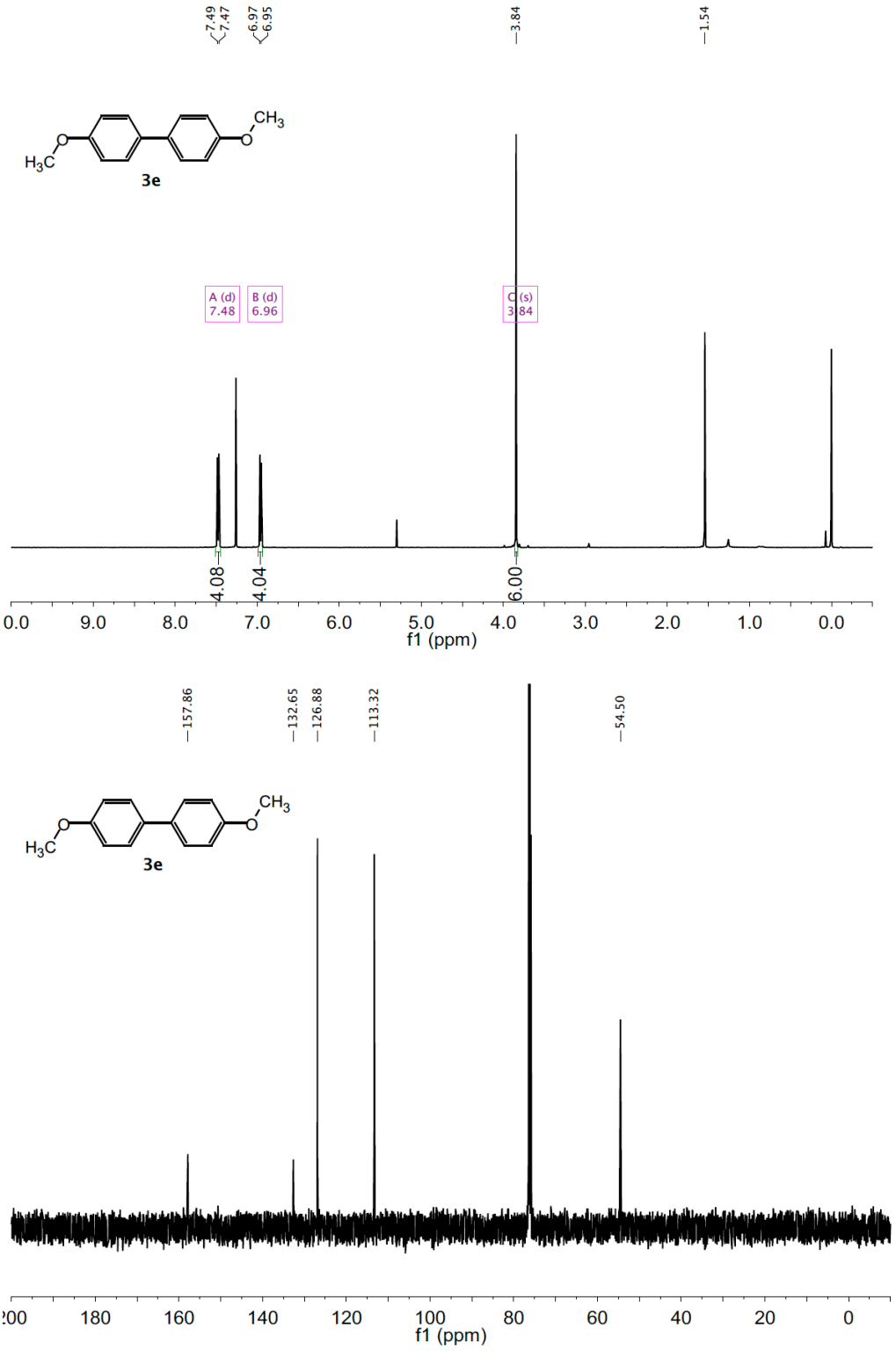


Figure SF 4.5. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 4,4'-dimethoxy-1,1'-biphenyl (**3e**) in $CDCl_3$.

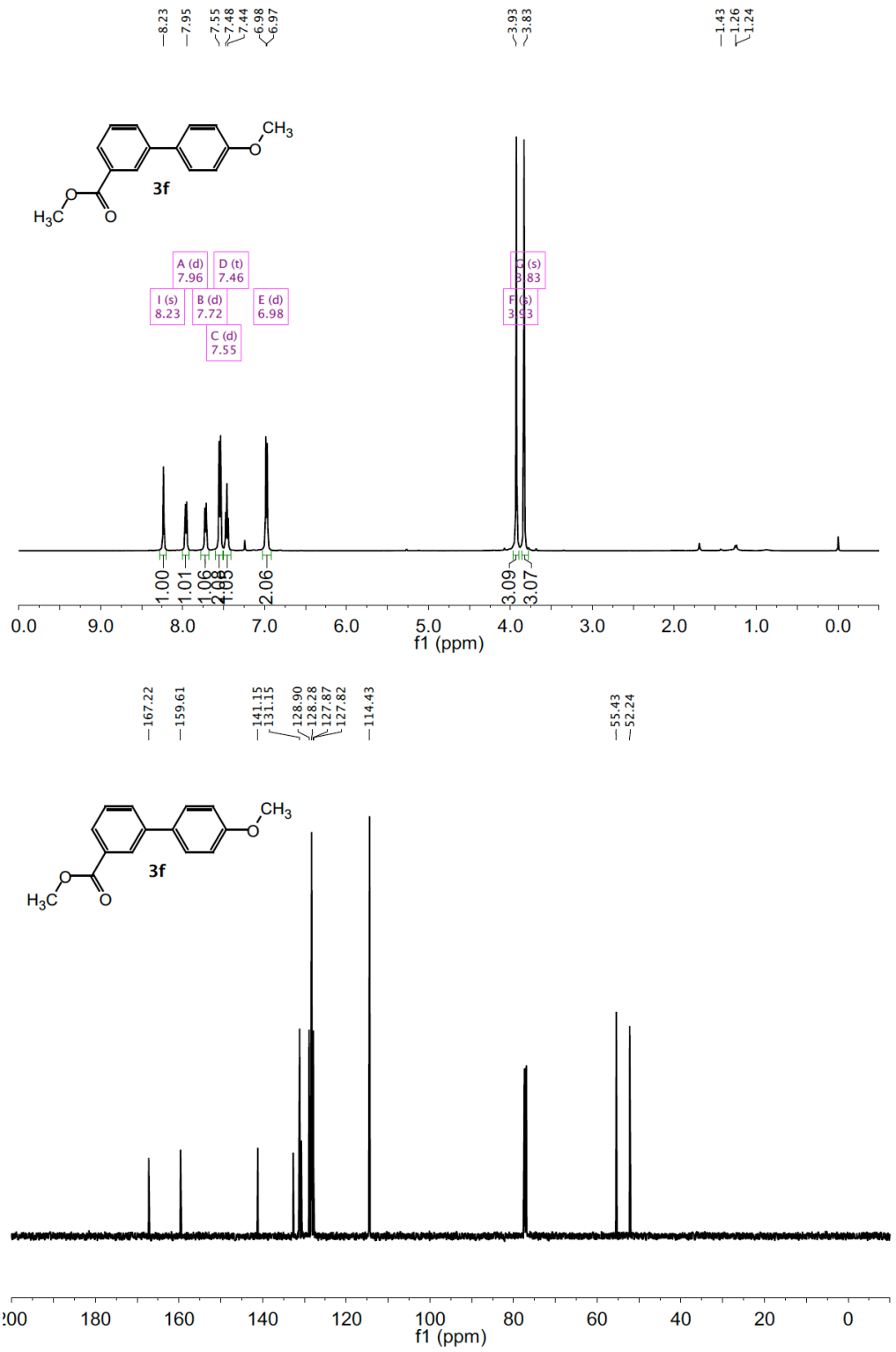


Figure SF 4.6. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4'-methoxy-[1,1'-biphenyl]-3-carboxylate (**3f**) in $CDCl_3$.

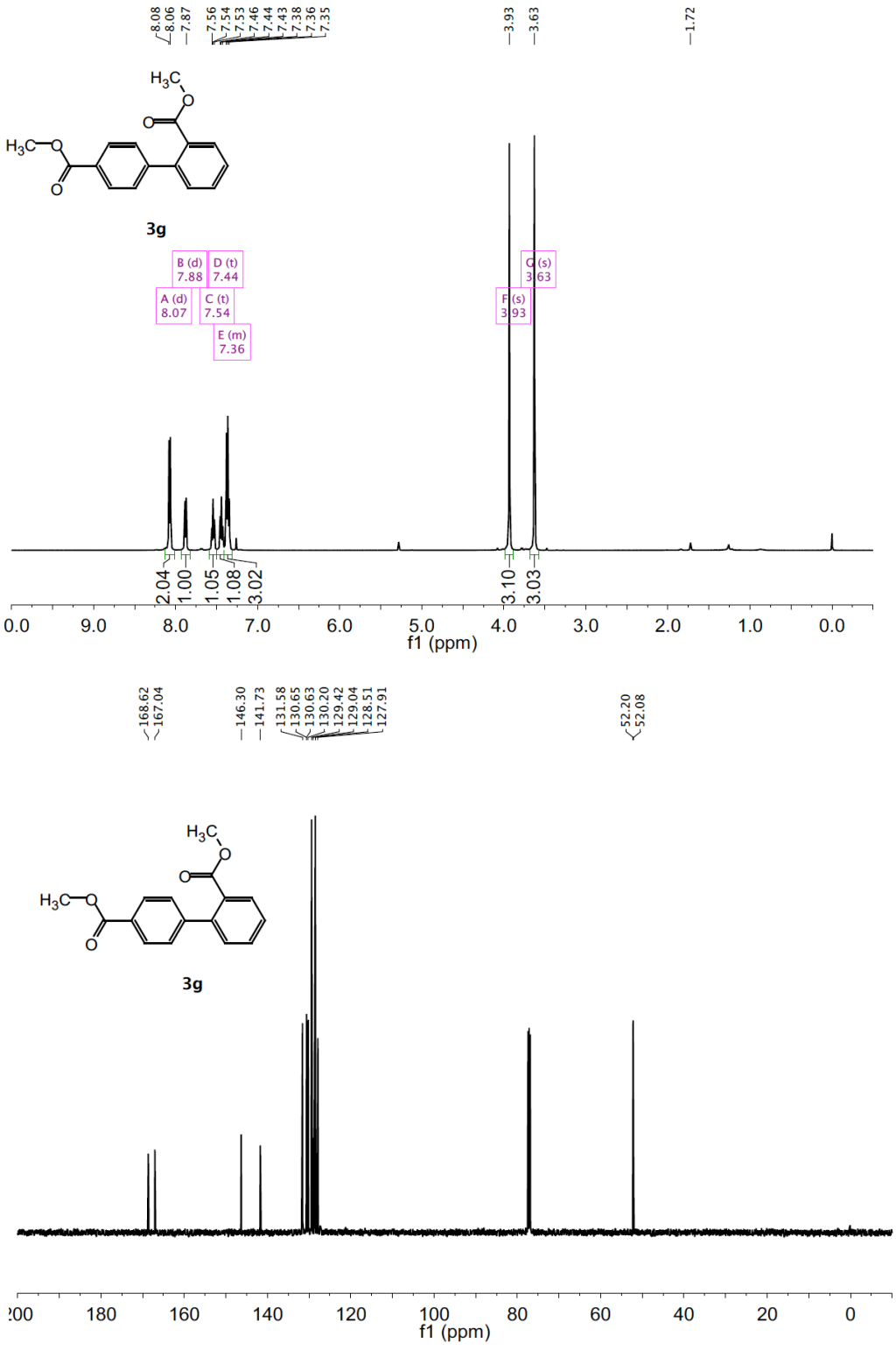


Figure SF 4.7. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of dimethyl [1,1'-biphenyl]-2,4'-dicarboxylate (**3g**) in $CDCl_3$.

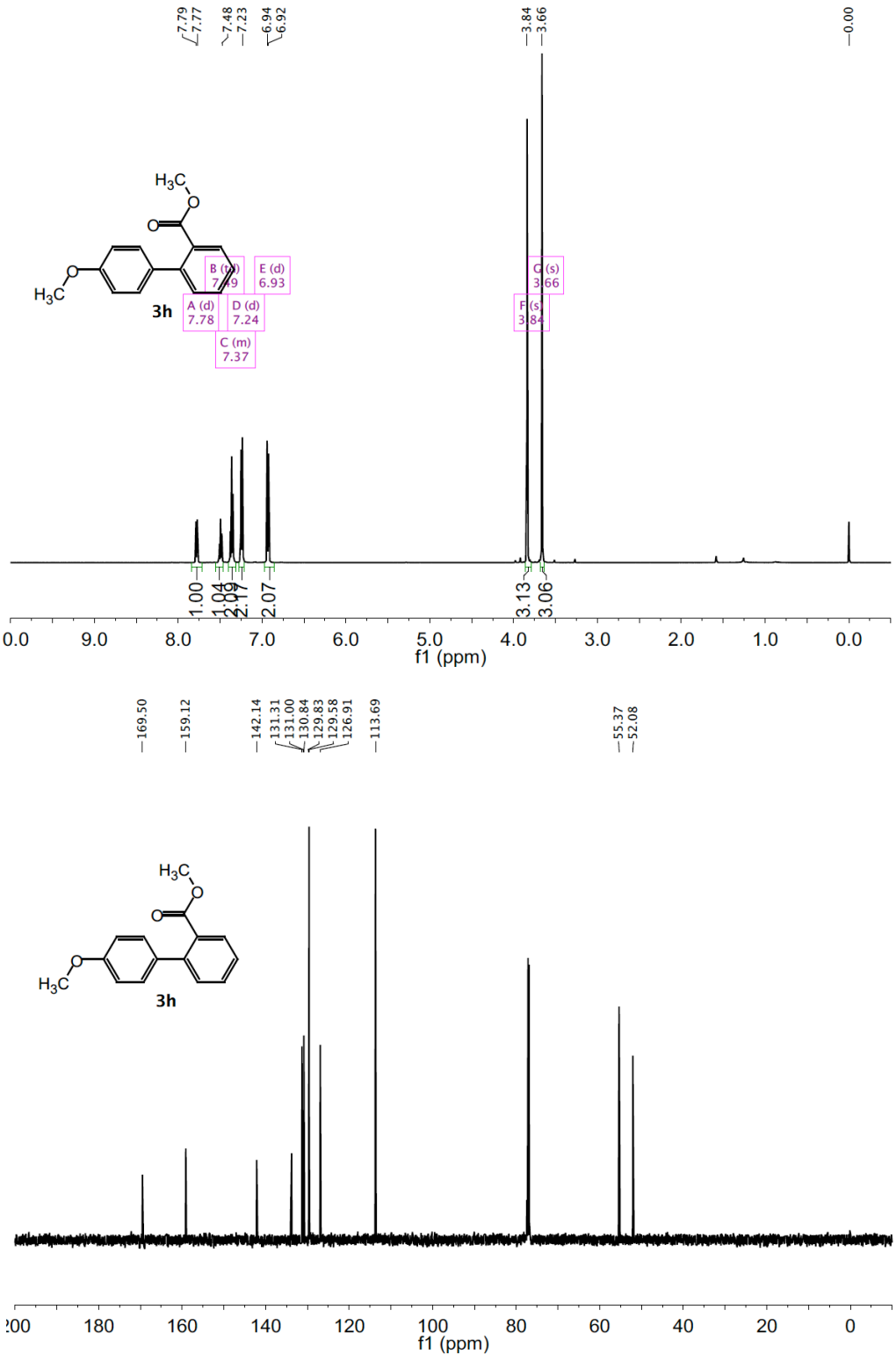


Figure SF 4.8. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4'-methoxy-[1,1'-biphenyl]-2-carboxylate (**3h**) in $CDCl_3$.

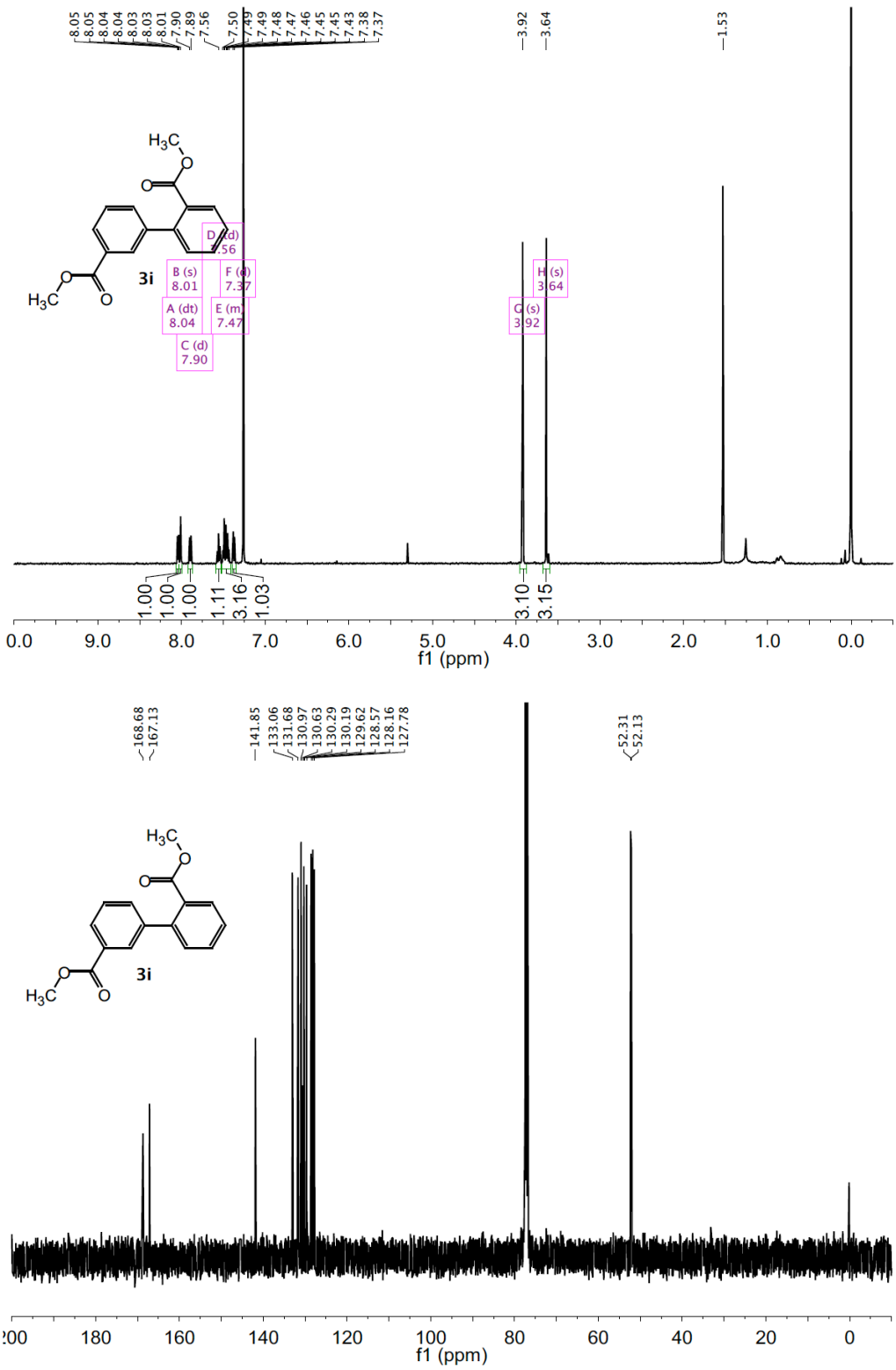


Figure SF 4.9. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of dimethyl [1,1'-biphenyl]-2,3'-dicarboxylate (**3i**) in $CDCl_3$

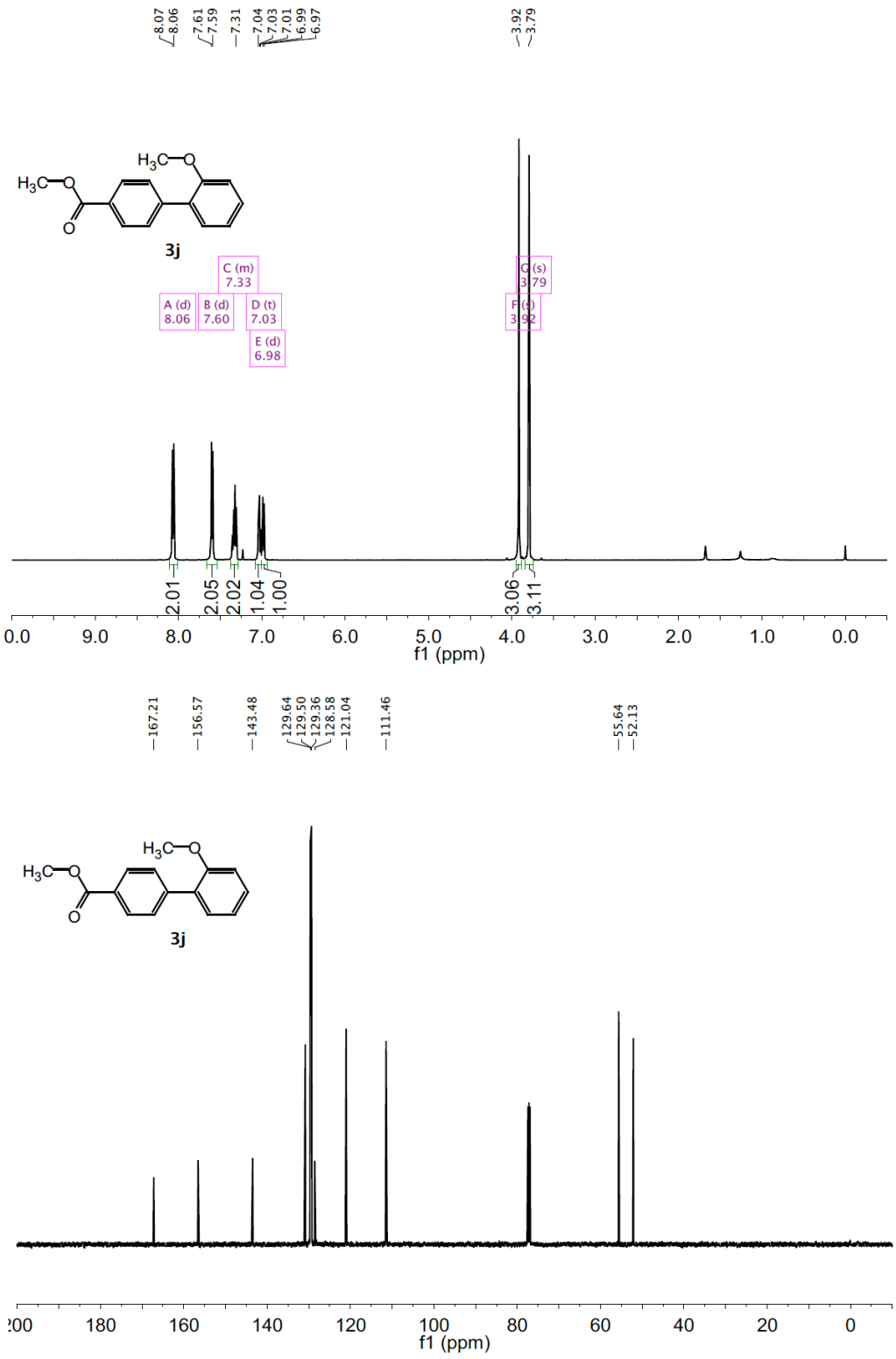


Figure SF 4.10. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 2'-methoxy-[1,1'-biphenyl]-4-carboxylate (**3j**) in $CDCl_3$.

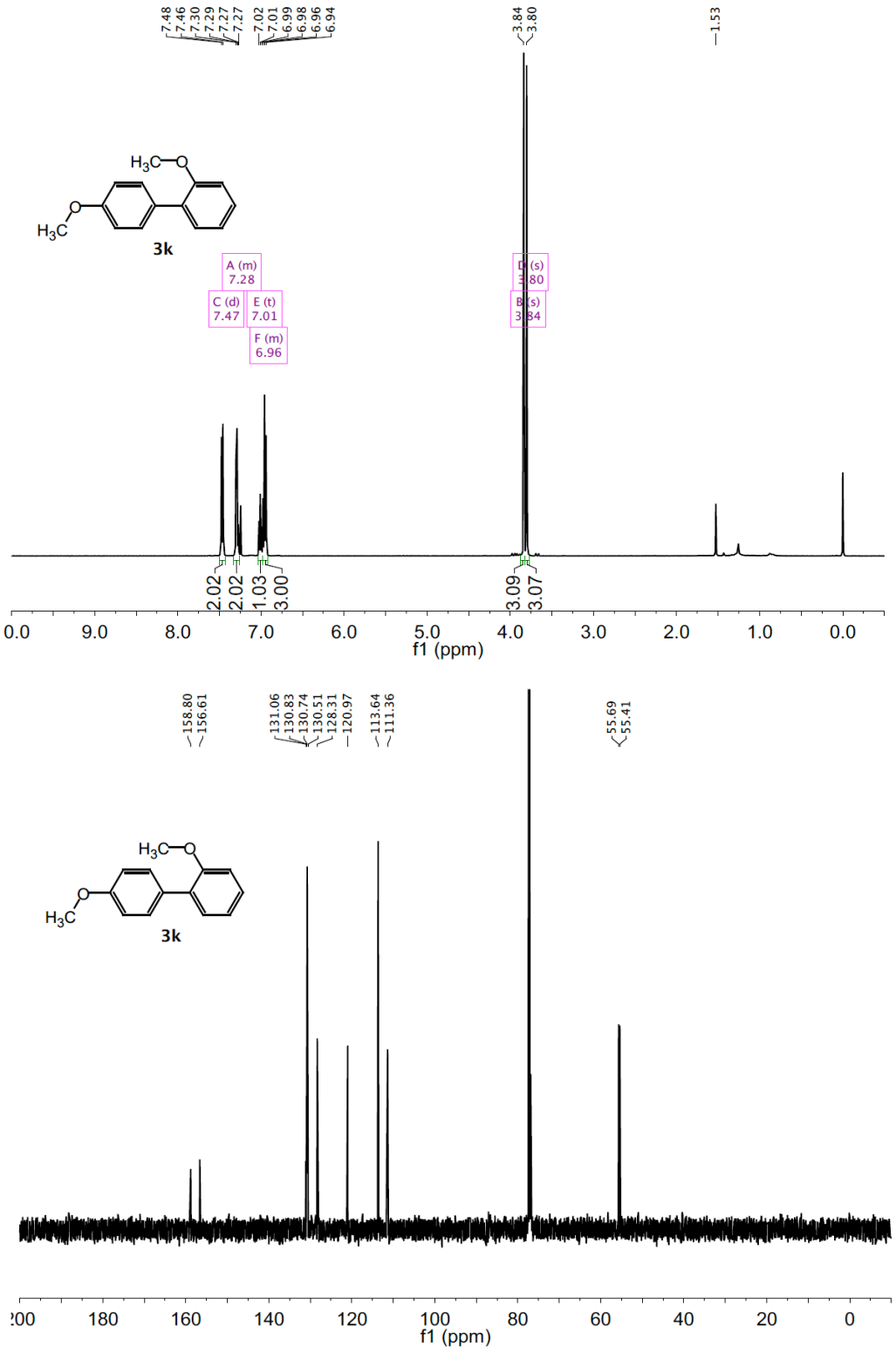


Figure SF 4.11. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 2,4'-dimethoxy-1,1'-biphenyl (**3k**) in $CDCl_3$.

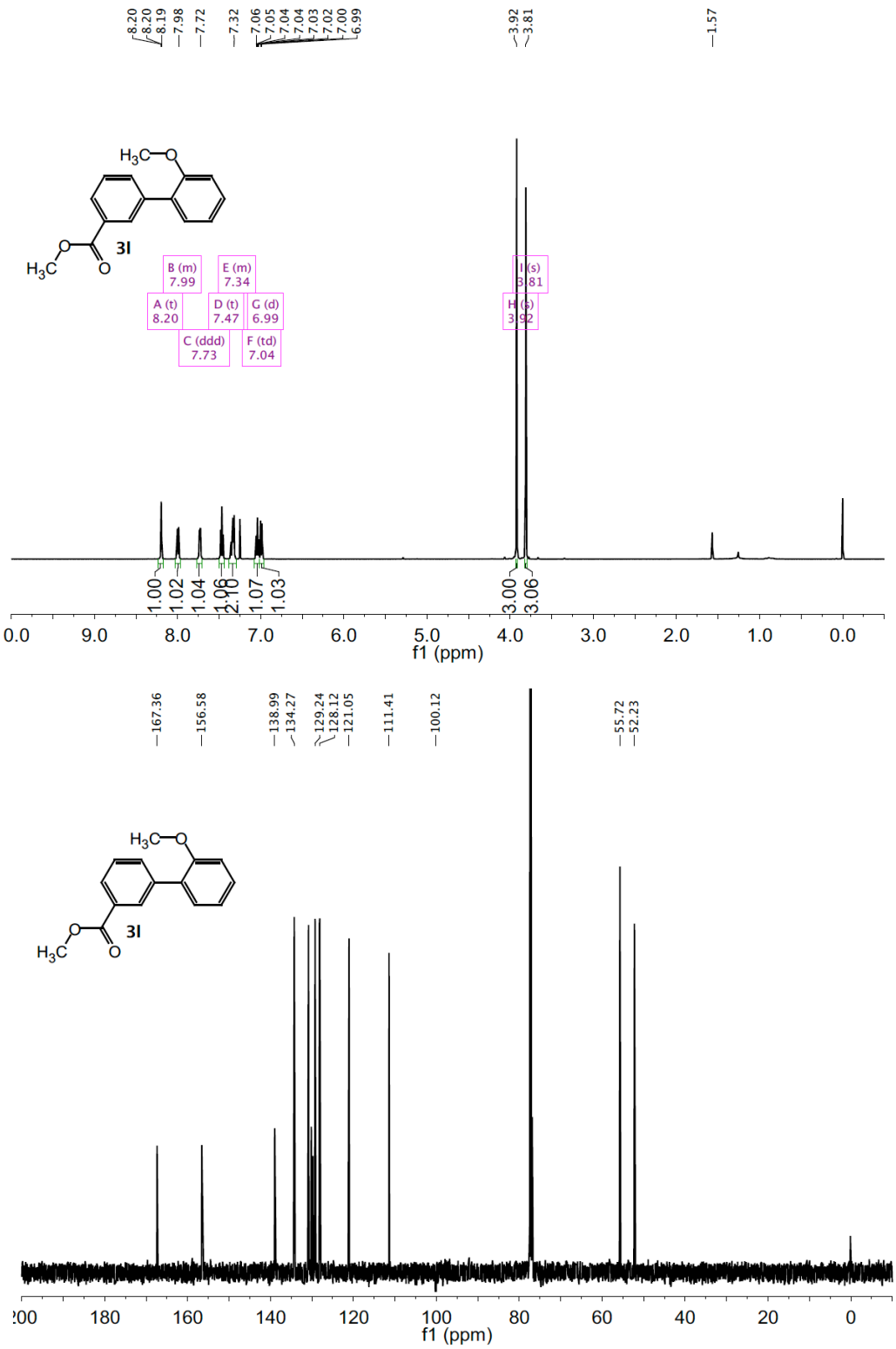


Figure SF 4.12. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 2'-methoxy-[1,1'-biphenyl]-3-carboxylate (**3l**) in $CDCl_3$.

Figure SF 4.13. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 3'-methoxy-[1,1'-biphenyl]-4-carboxylate (**3m**) in $CDCl_3$.

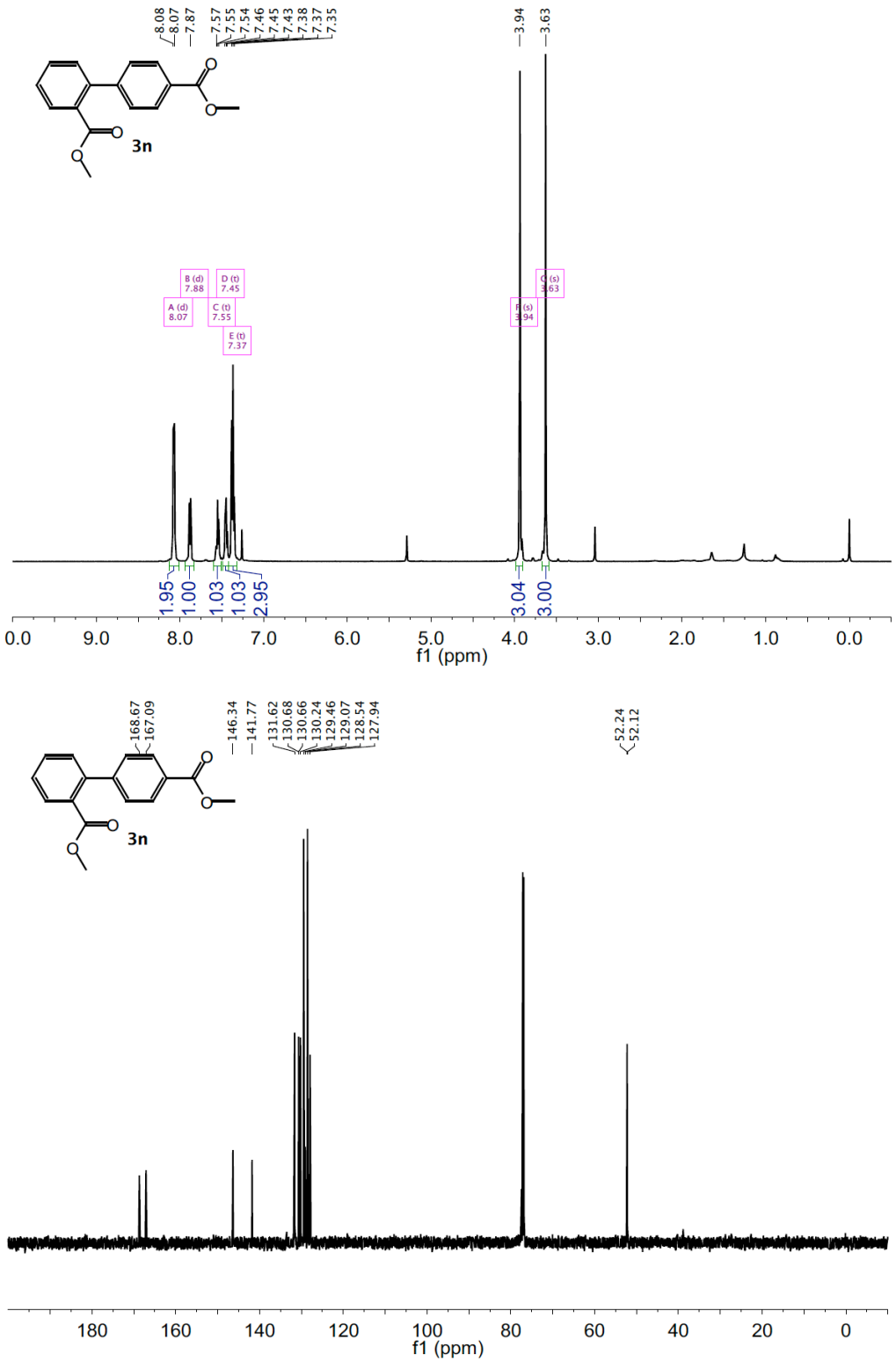


Figure SF 4.14. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of dimethyl [1,1'-biphenyl]-2,4'-dicarboxylate (**3n**) in $CDCl_3$.

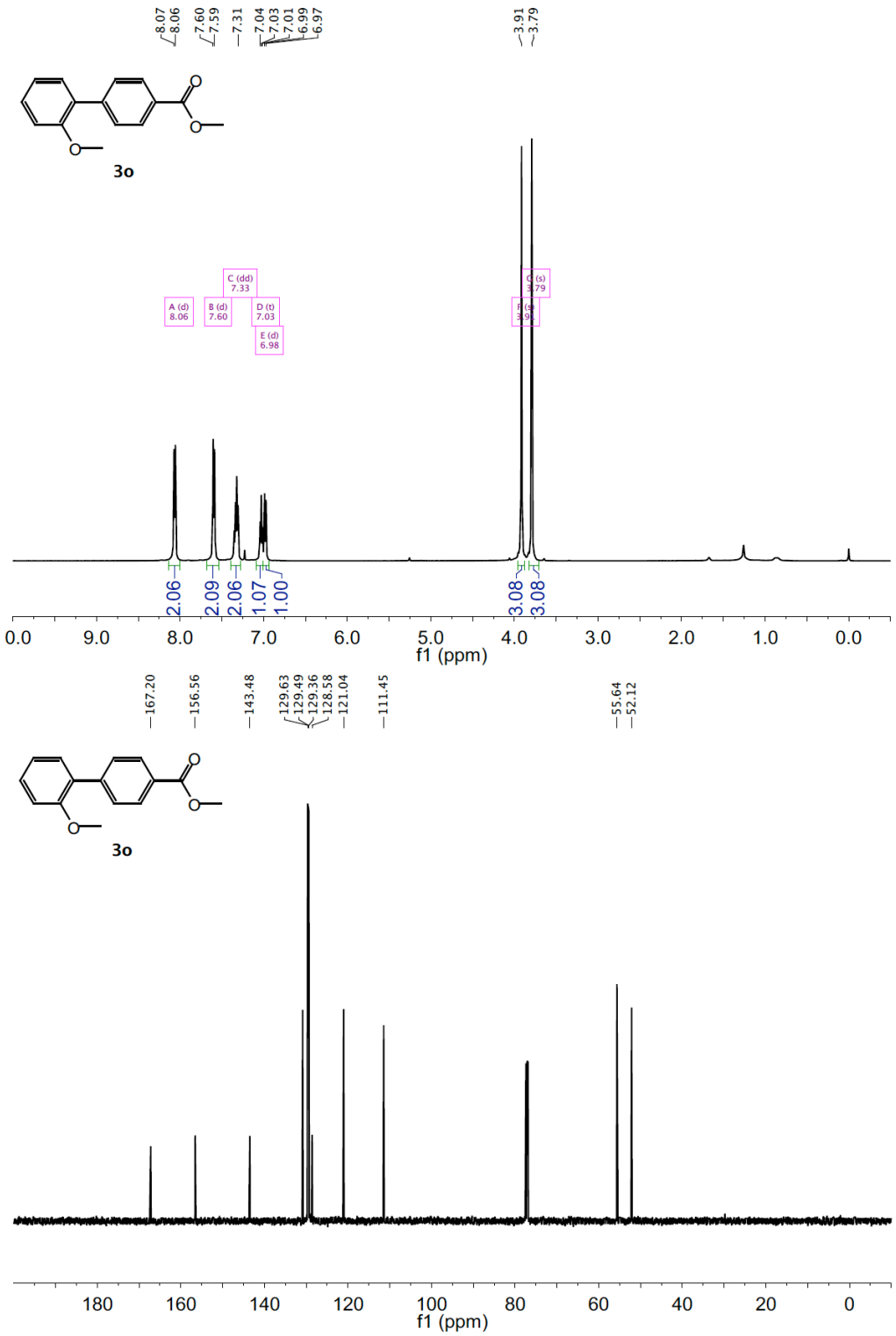


Figure SF 4.15. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 2'-methoxy-[1,1'-biphenyl]-4-carboxylate (**3o**) in $CDCl_3$.

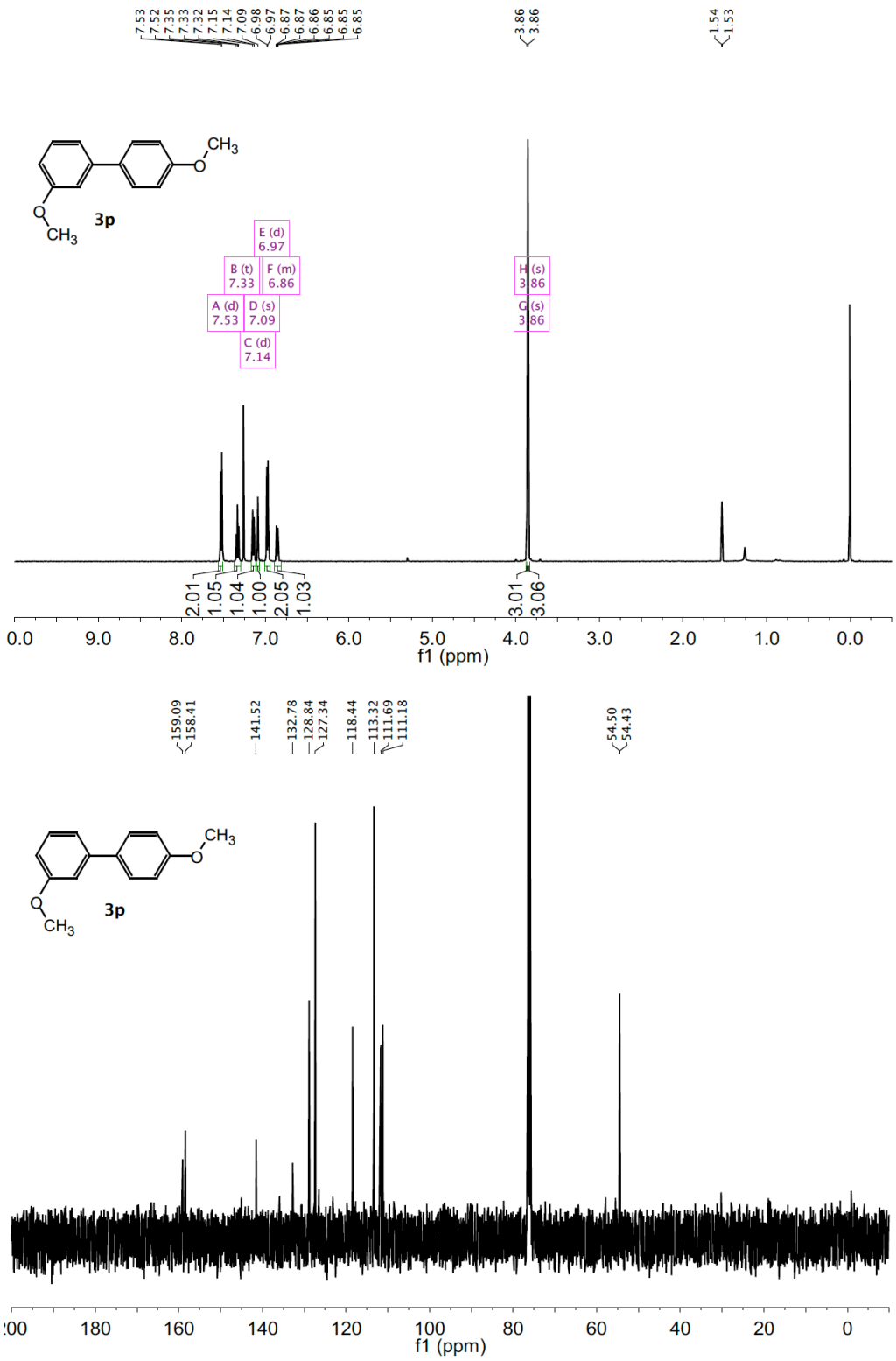


Figure SF 4.16. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 3,4'-dimethoxy-1,1'-biphenyl (**3p**) in $CDCl_3$.

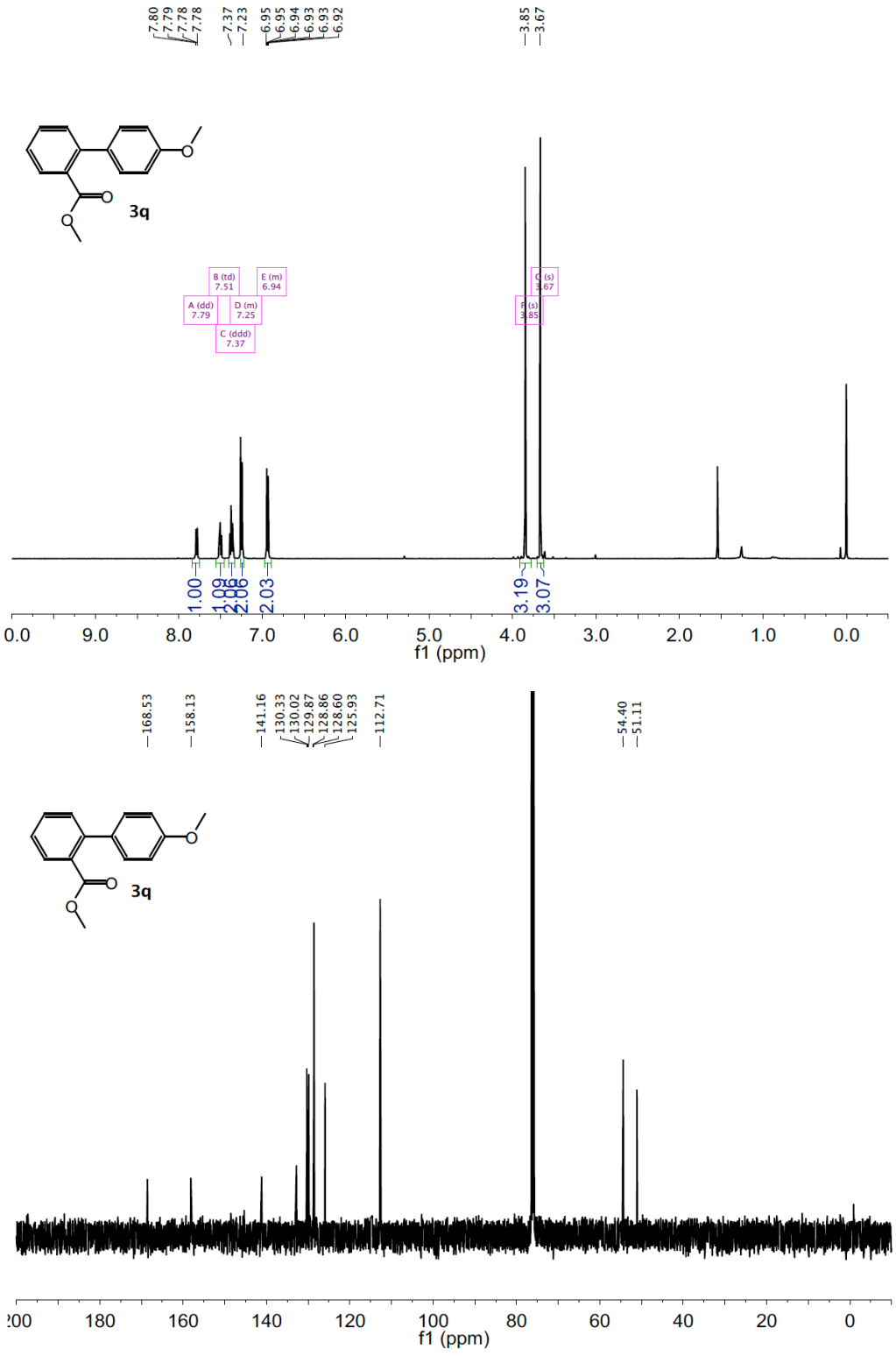


Figure SF 4.17. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4'-methoxy-[1,1'-biphenyl]-2-carboxylate (**3q**) in $CDCl_3$.

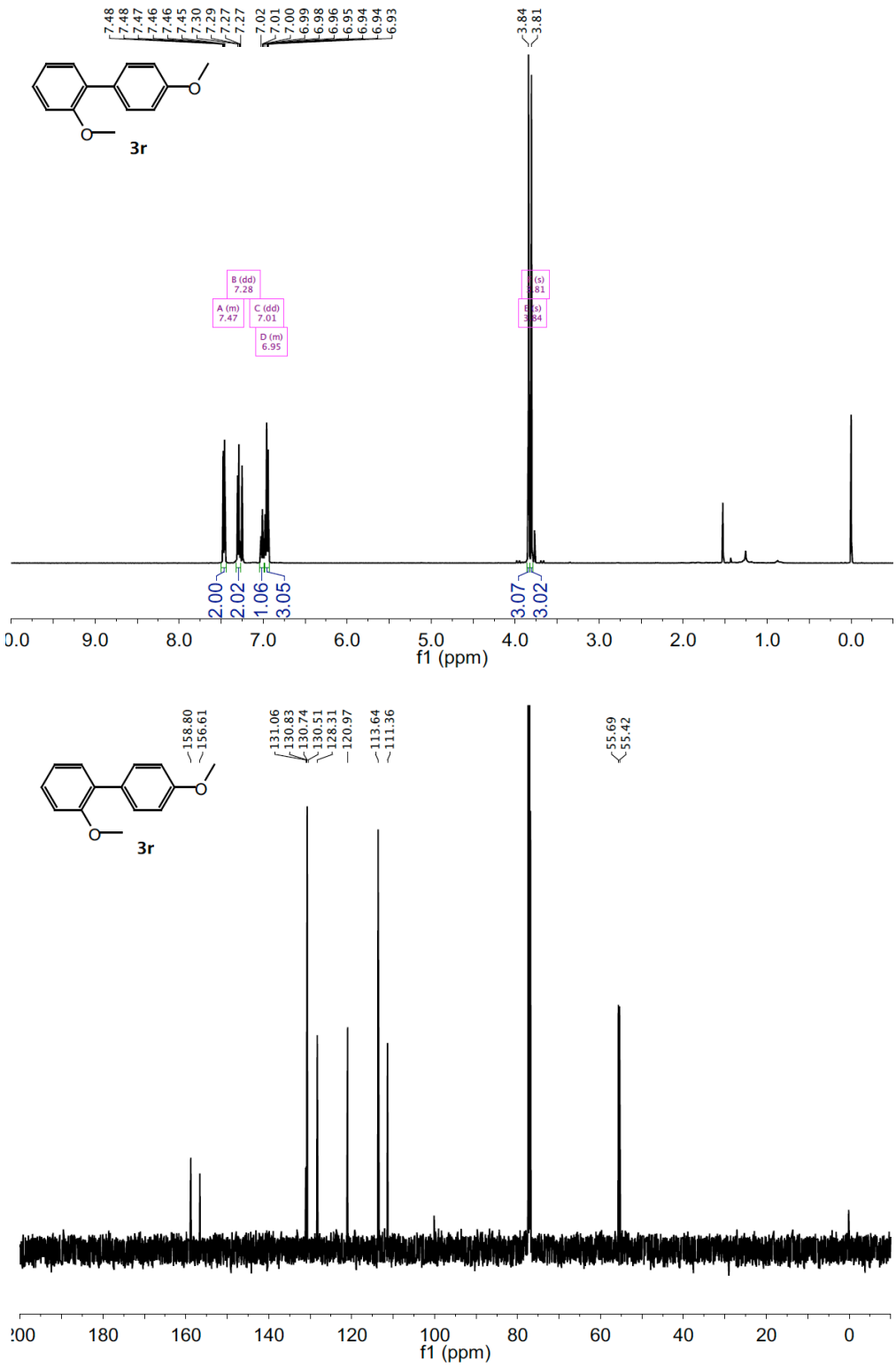


Figure SF 4.18. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 2,4'-dimethoxy-1,1'-biphenyl (**3r**) in $CDCl_3$

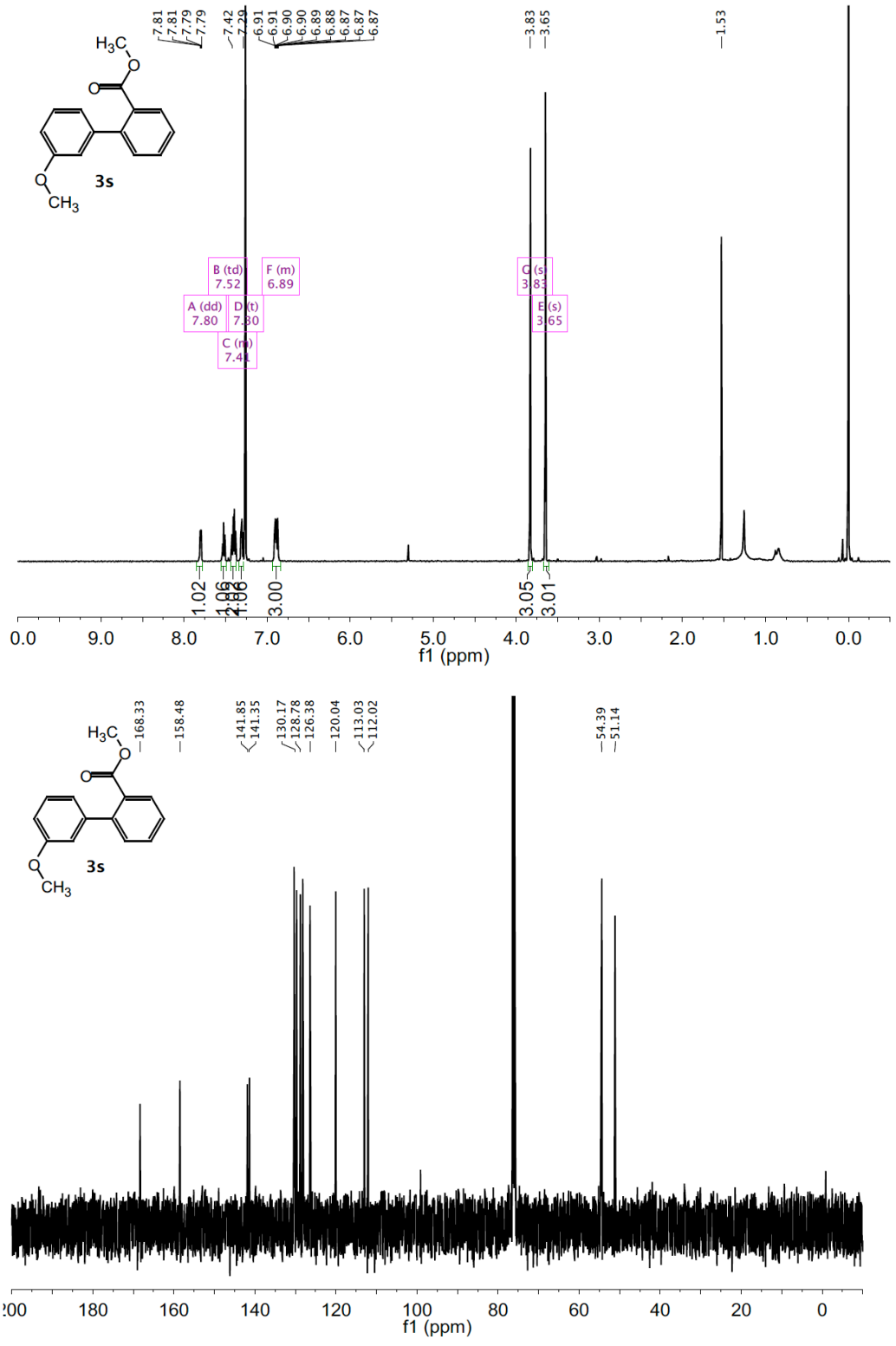


Figure SF 4.19. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 3'-methoxy-[1,1'-biphenyl]-2-carboxylate (**3s**) in $CDCl_3$

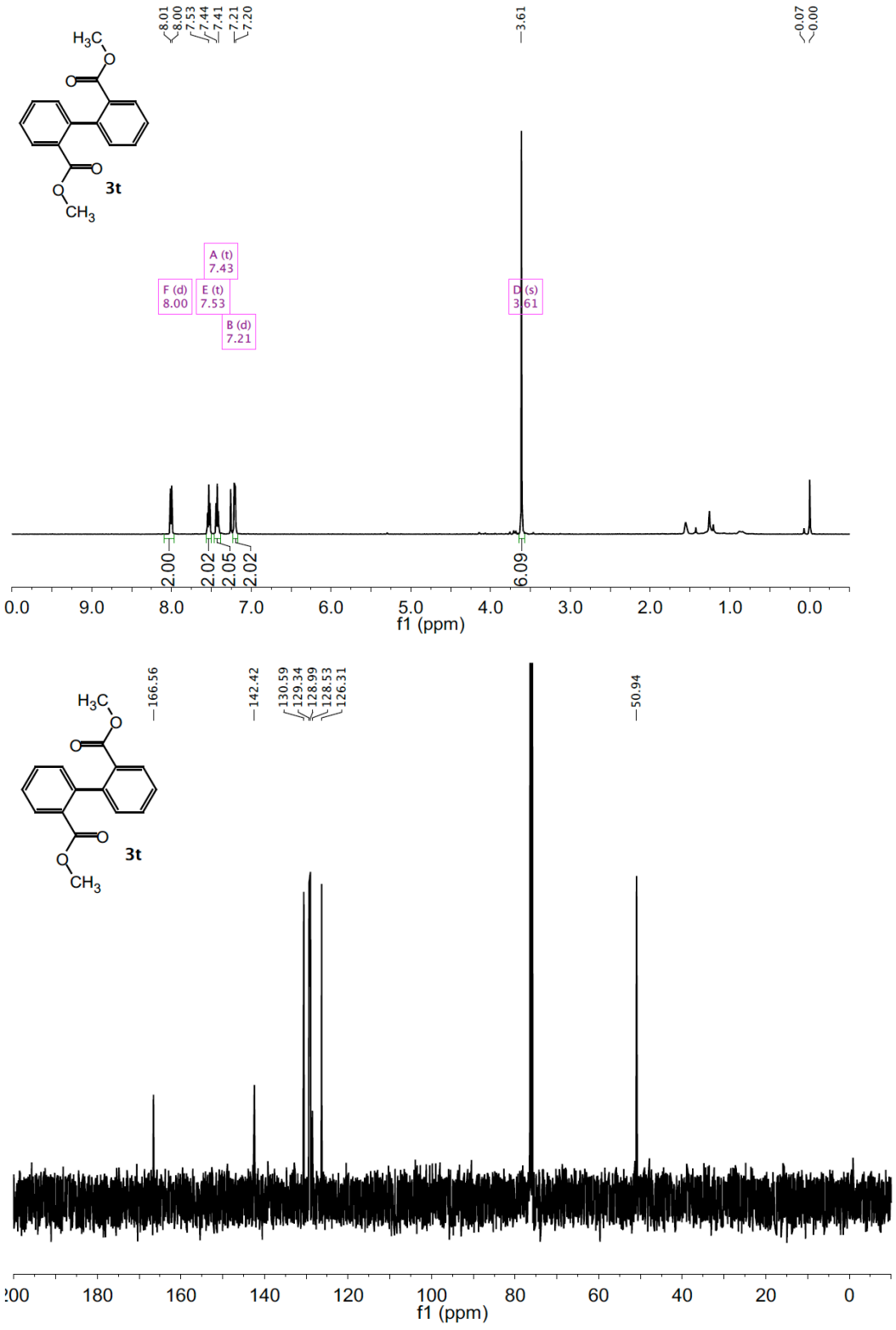


Figure SF 4.20. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of dimethyl [1,1'-biphenyl]-2,2'-dicarboxylate (**3t**) in $CDCl_3$

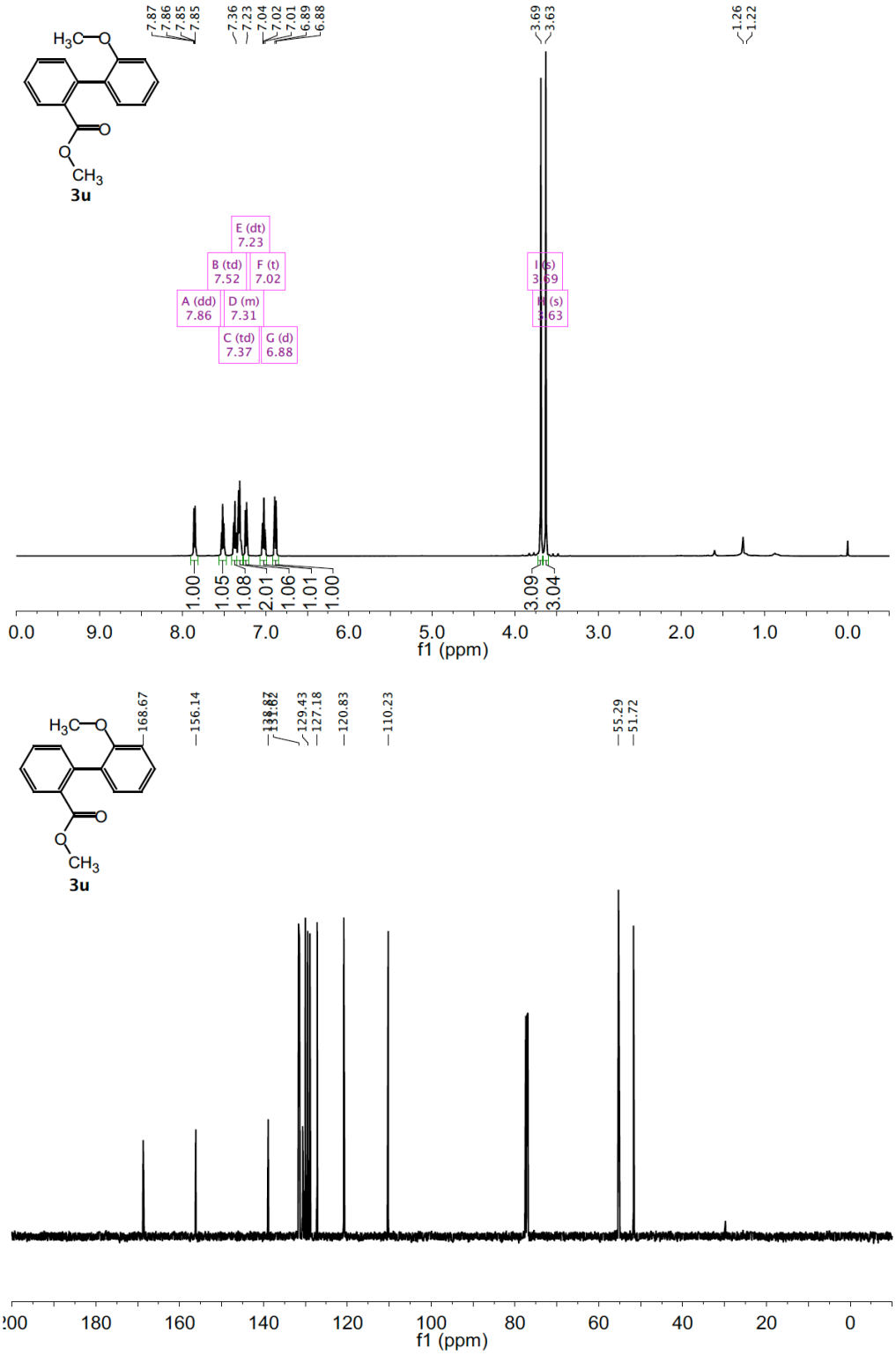


Figure SF 4.21. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 2'-methoxy-[1,1'-biphenyl]-2-carboxylate (**3u**) in $CDCl_3$

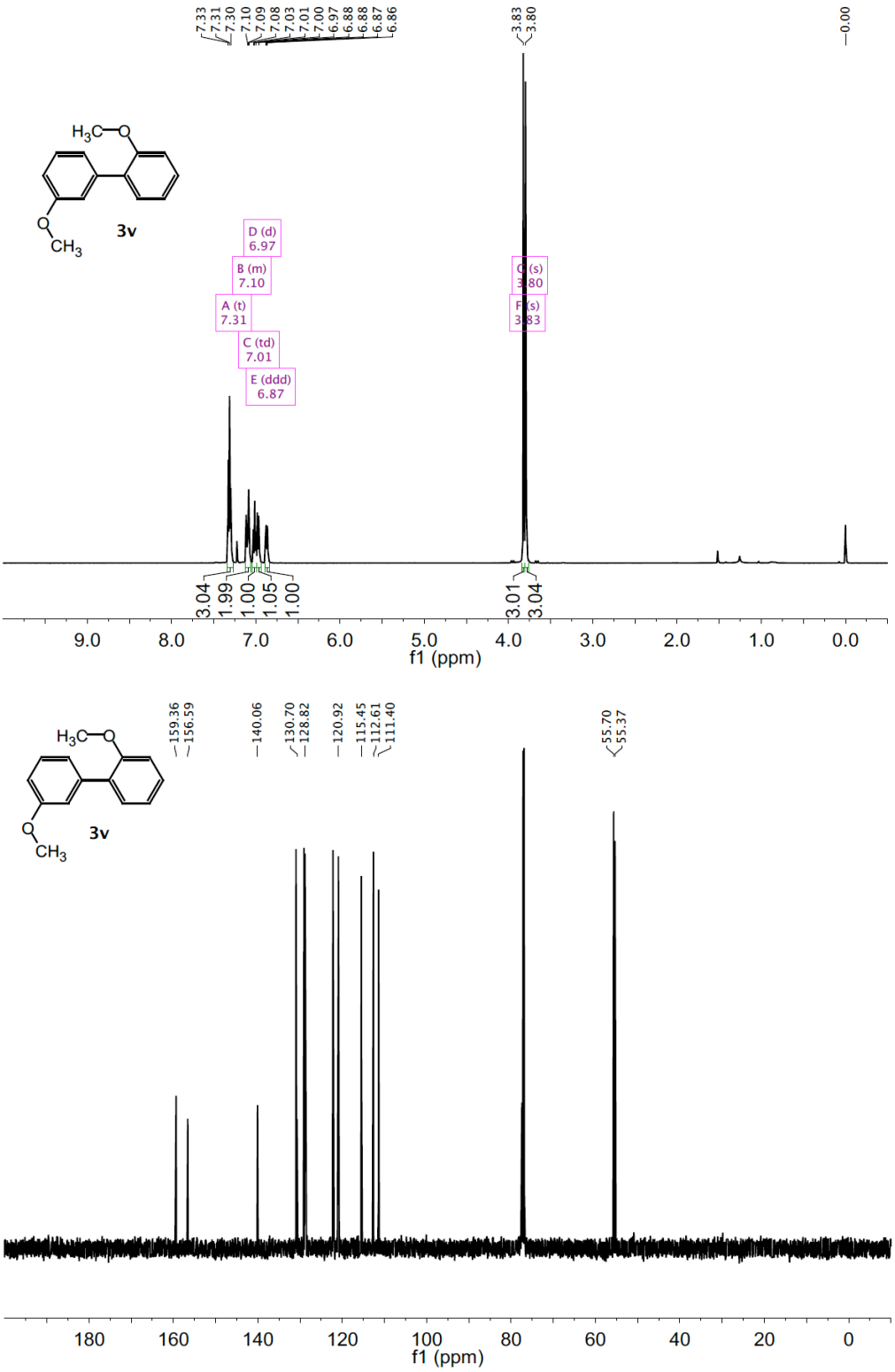


Figure SF 4.22. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 2,3'-dimethoxy-1,1'-biphenyl (**3v**) in $CDCl_3$

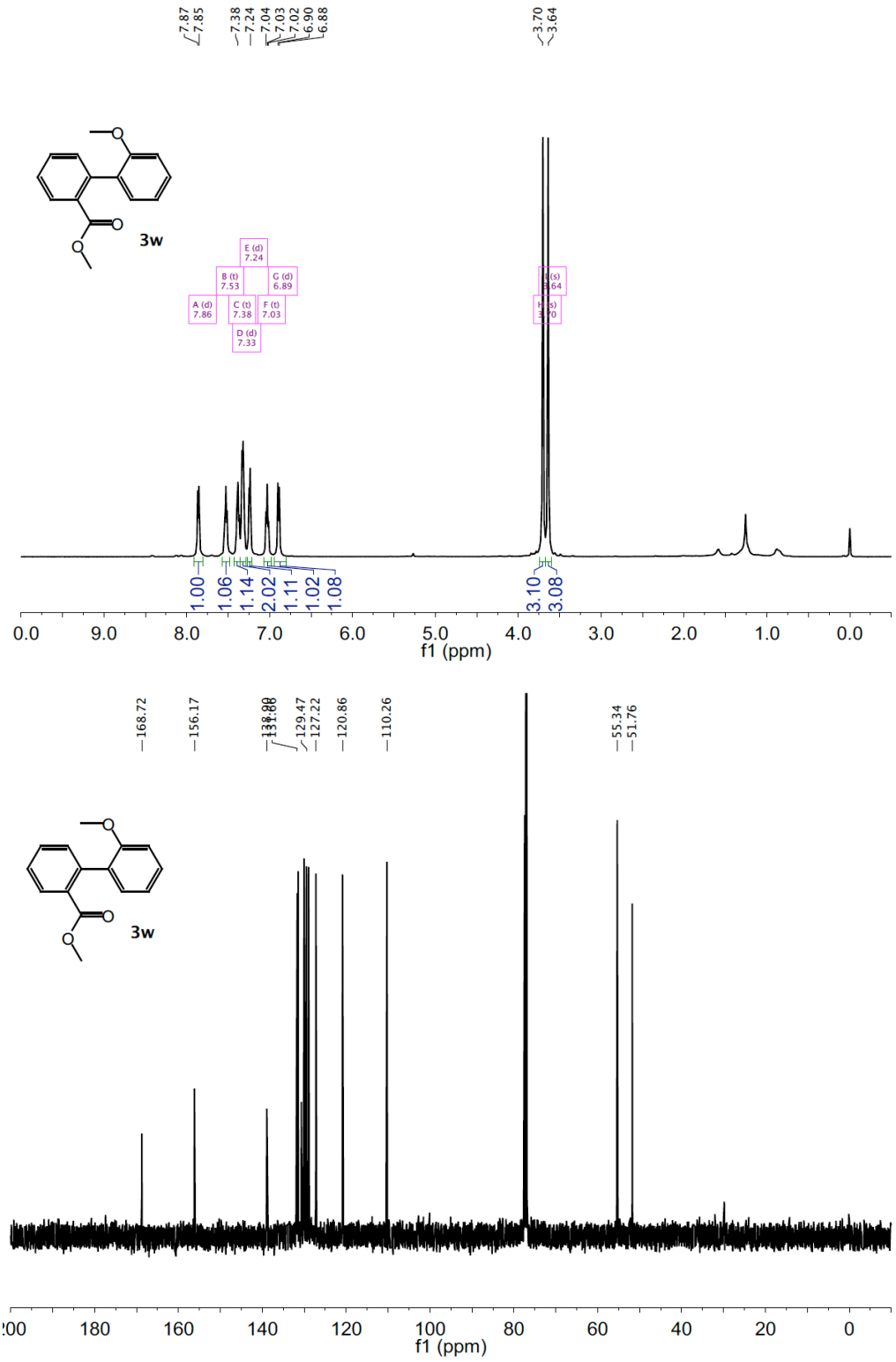


Figure SF 4.23. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 2'-methoxy-[1,1'-biphenyl]-2-carboxylate (**3w**) in $CDCl_3$

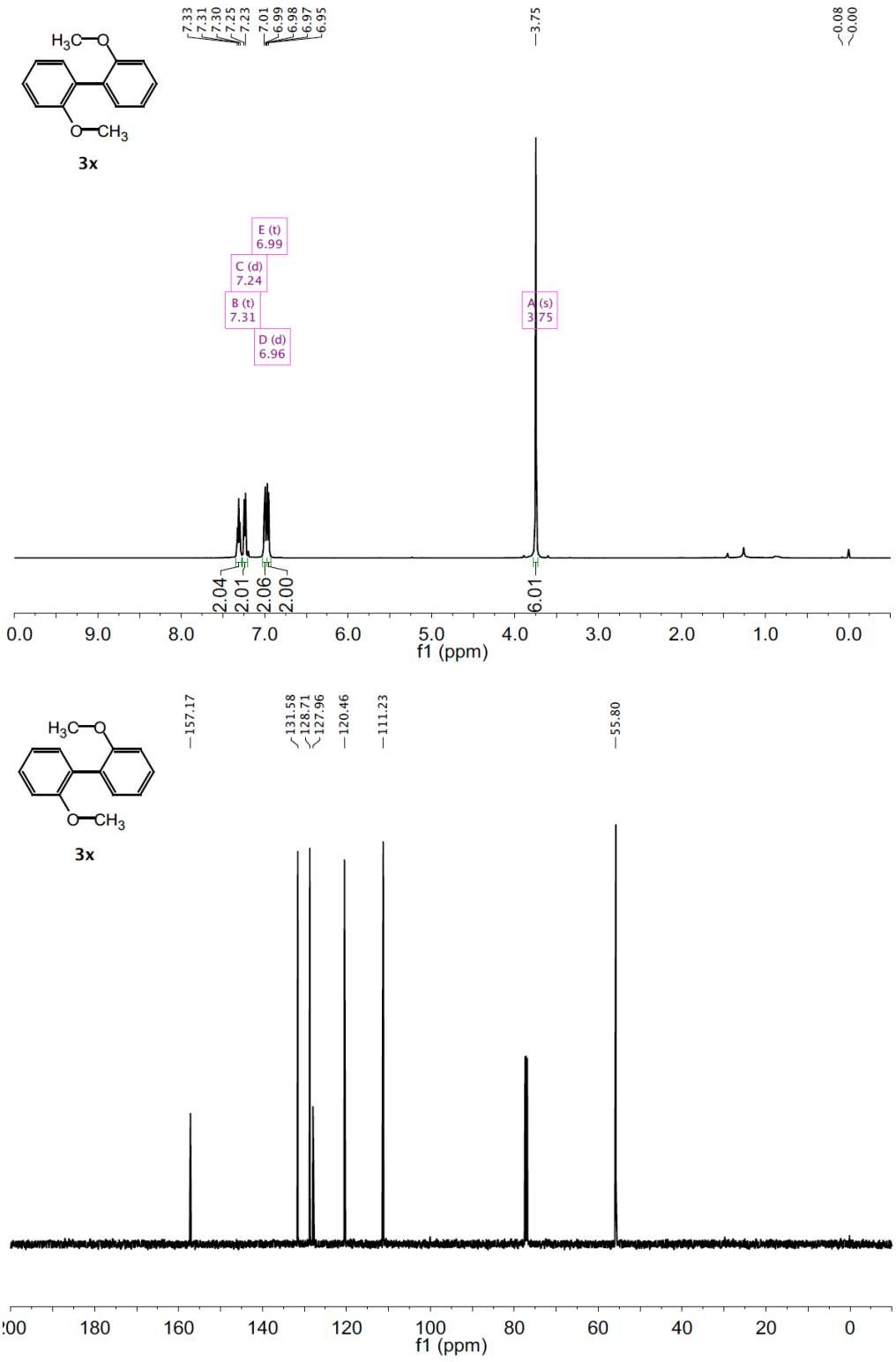


Figure SF 4.24. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 2,2'-dimethoxy-1,1'-biphenyl (**3x**) in $CDCl_3$

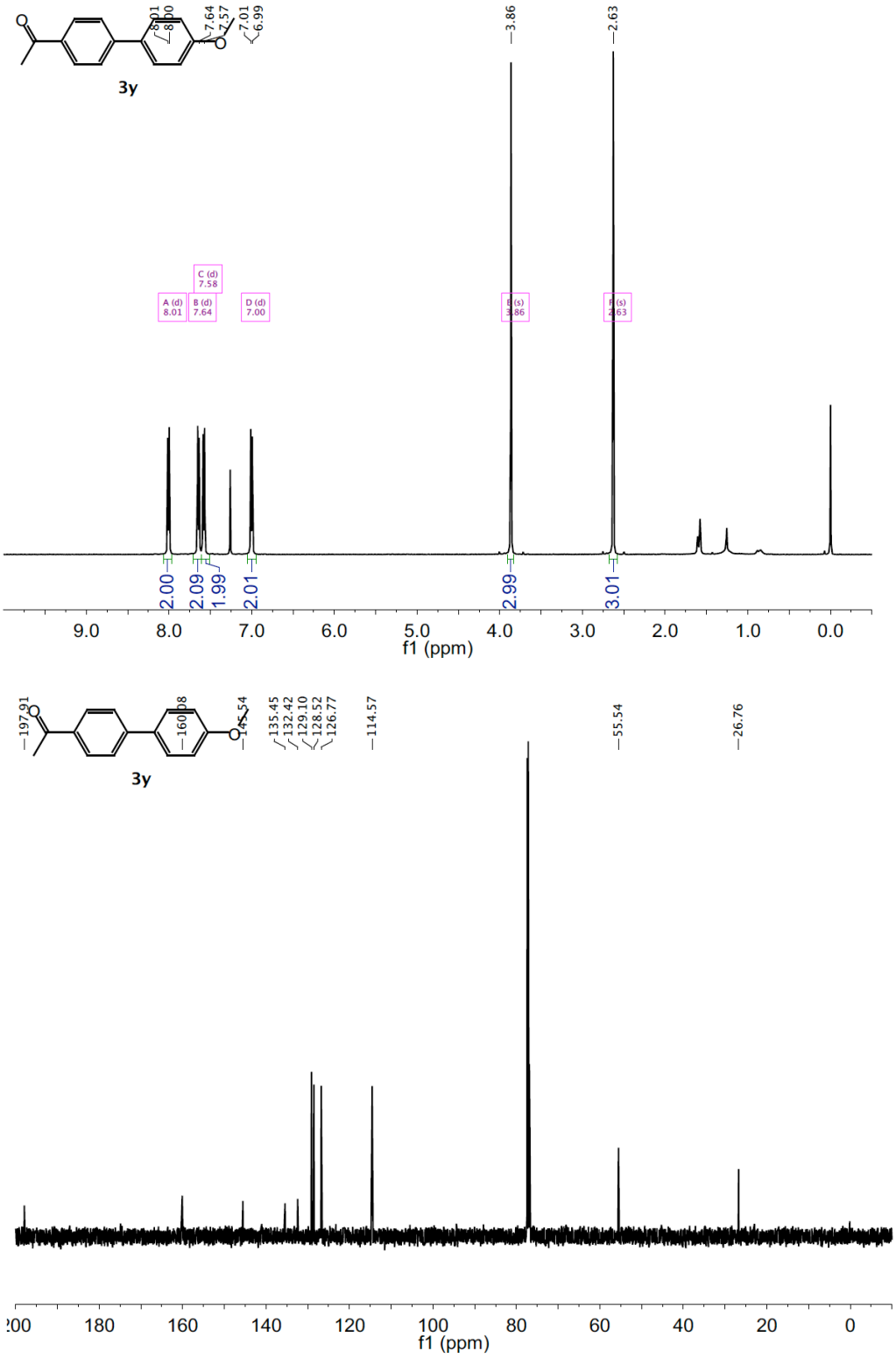


Figure SF 4.25. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 1-(4'-methoxy-[1,1'-biphenyl]-4-yl)ethanone (**3y**) in $CDCl_3$

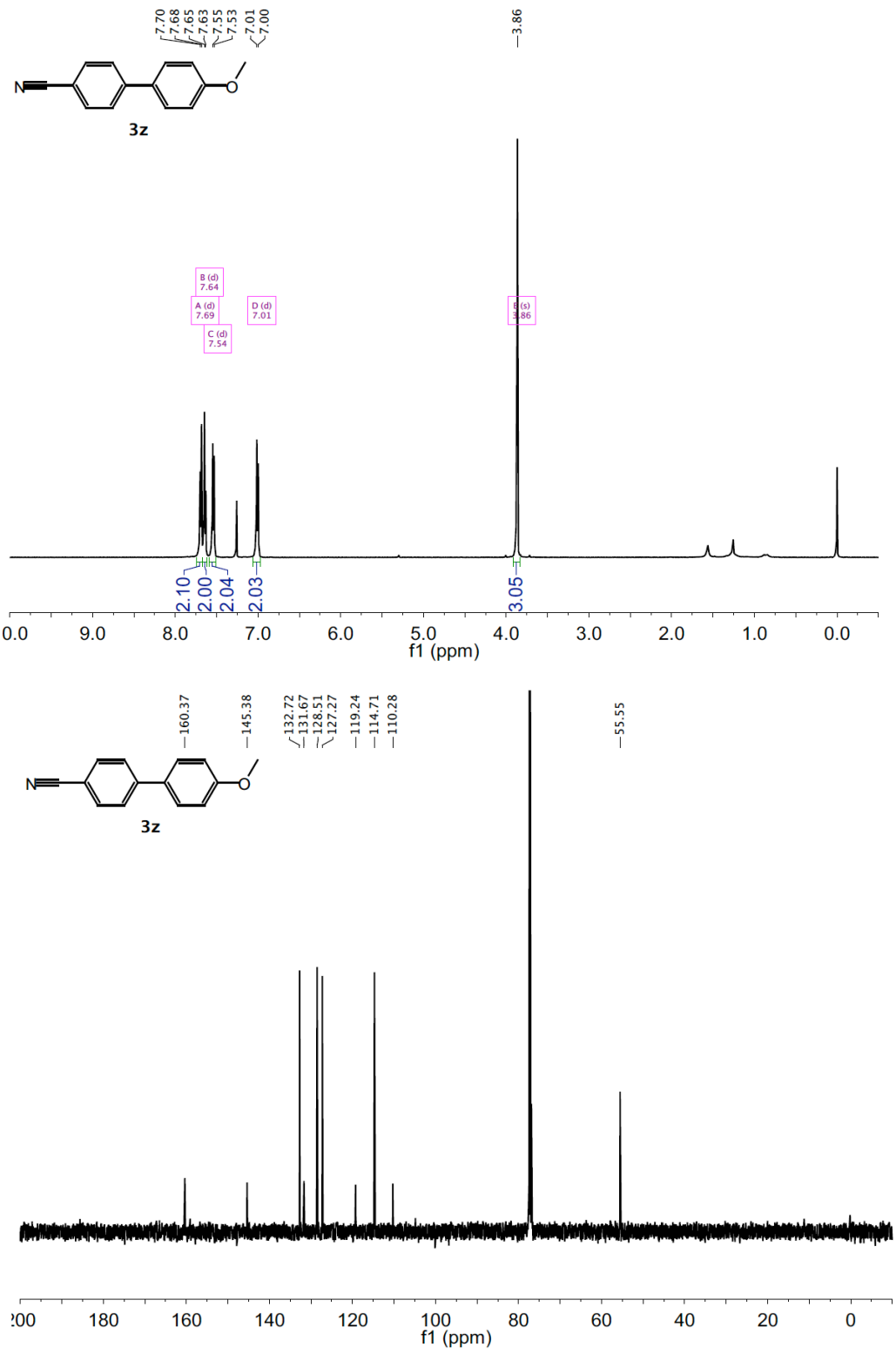


Figure SF 4.26. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 4'-methoxy-[1,1'-biphenyl]-4-carbonitrile (**3z**) in $CDCl_3$

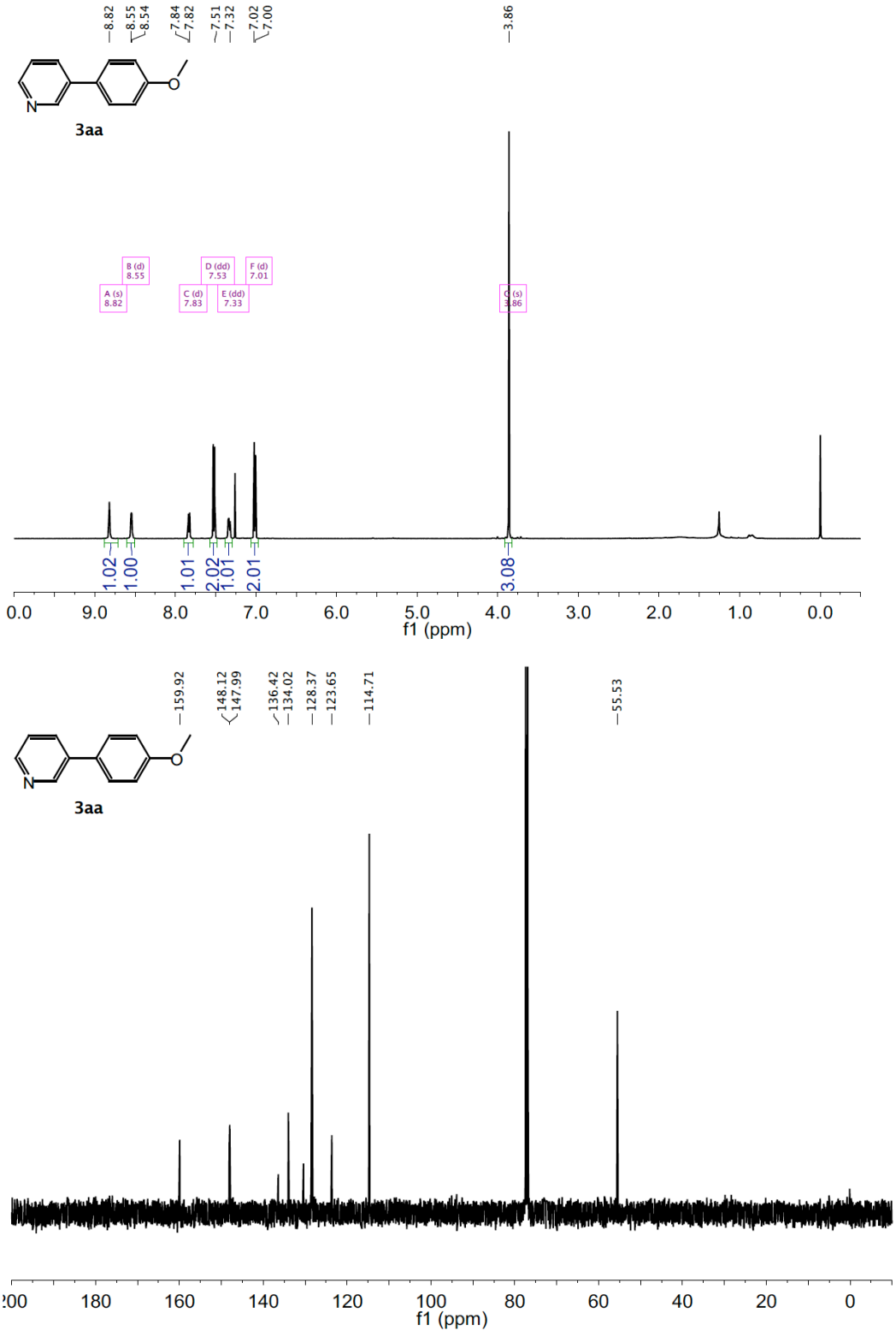


Figure SF 4.27. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 3-(4-methoxyphenyl)pyridine (**3aa**) in $CDCl_3$

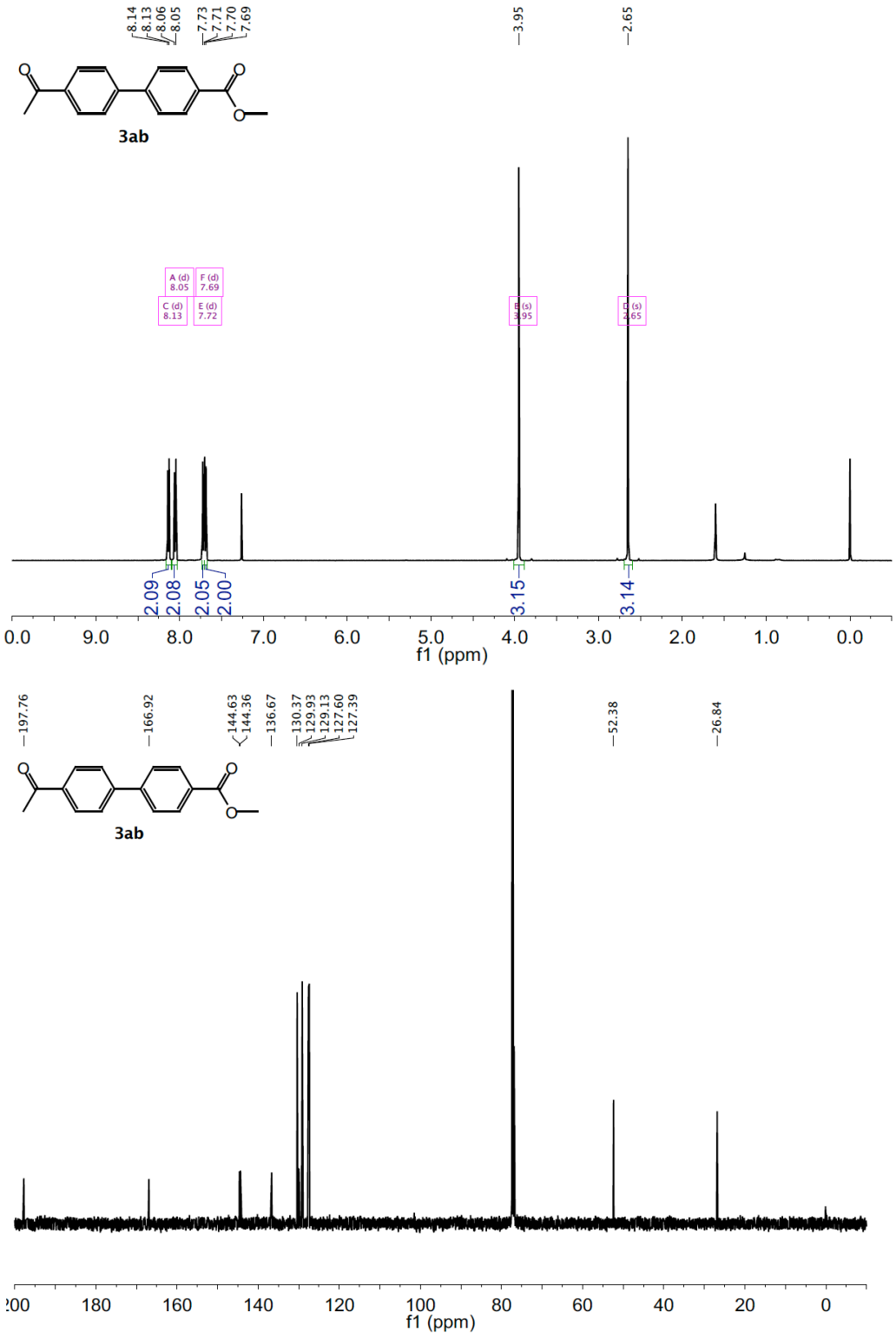


Figure SF 4.28. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4'-acetyl-[1,1'-biphenyl]-4-carboxylate (**3ab**) in $CDCl_3$

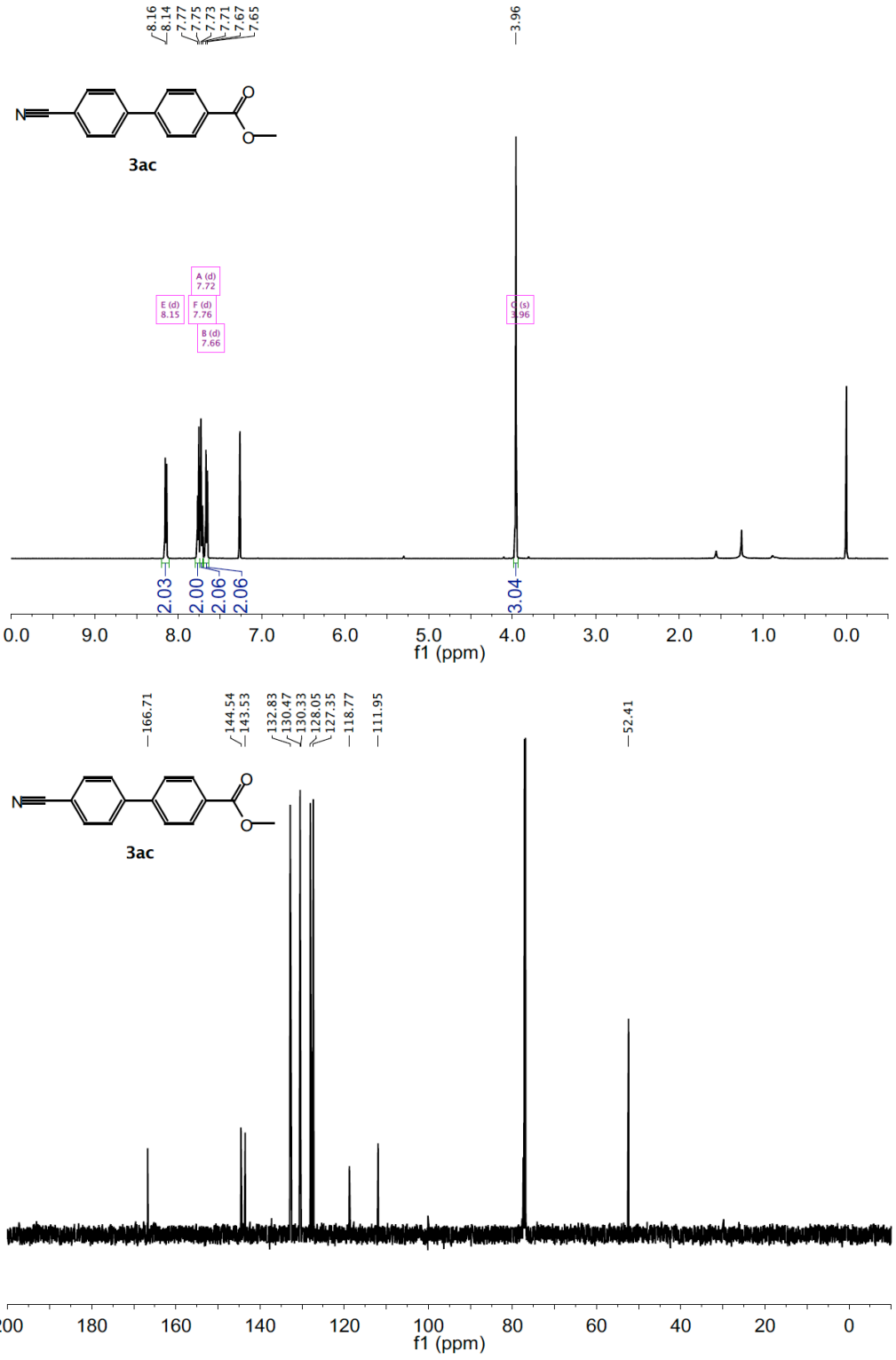


Figure SF 4.29. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4'-cyano-[1,1'-biphenyl]-4-carboxylate (**3ac**) in $CDCl_3$

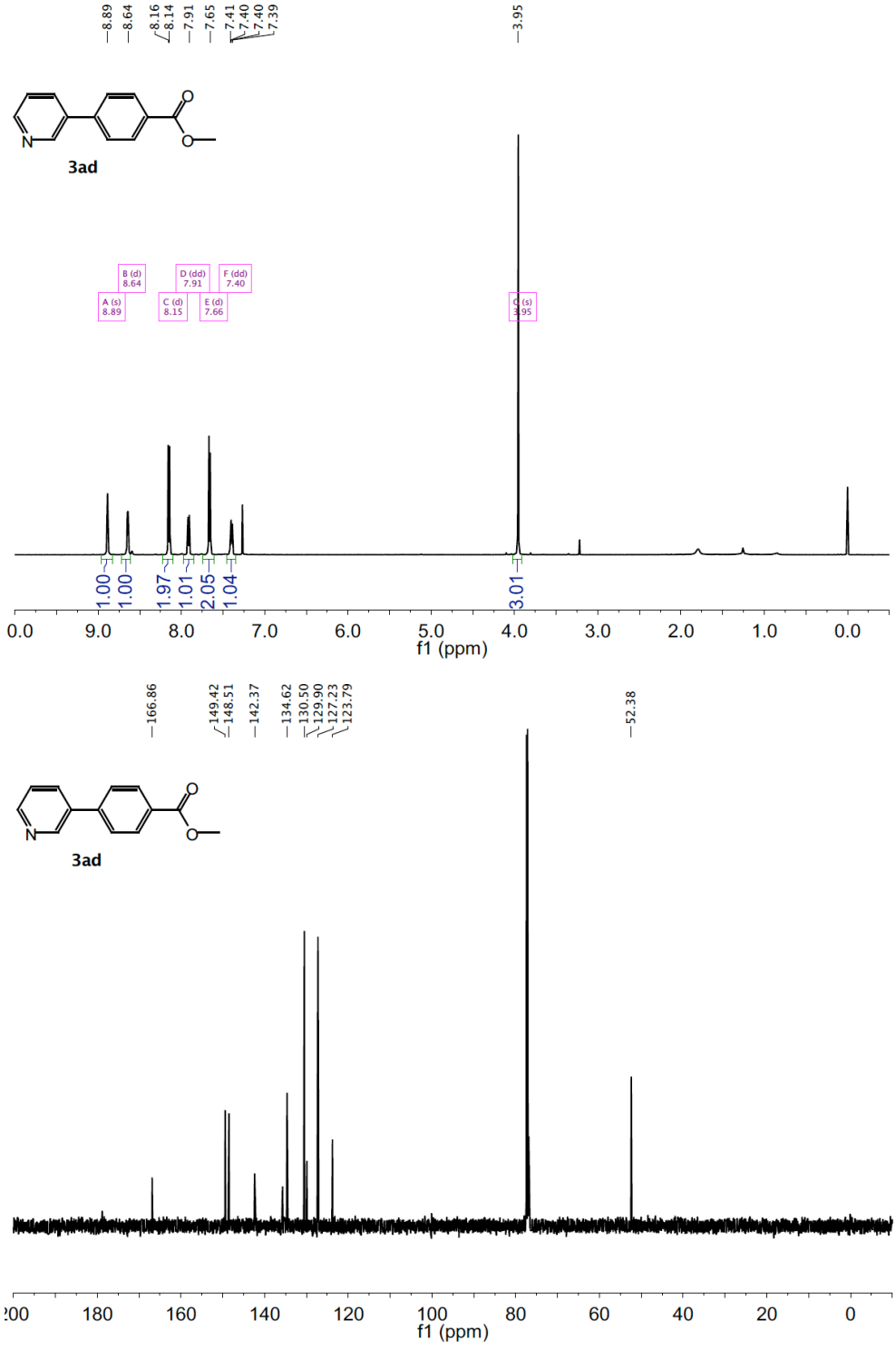


Figure SF 4.30. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4-(pyridin-3-yl)benzoate (**3ad**) in $CDCl_3$

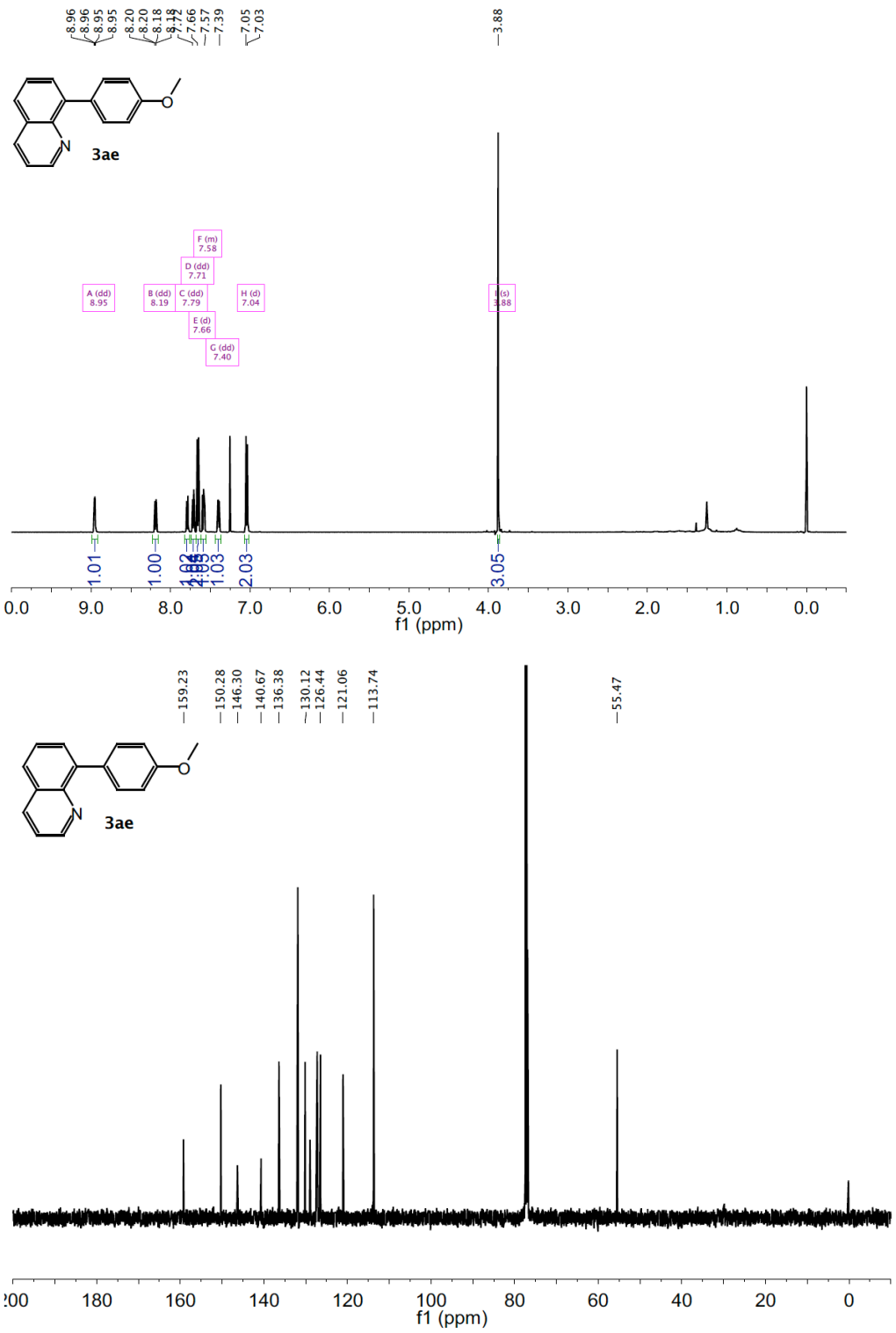


Figure SF 4.31. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 8-(4-methoxyphenyl)quinoline (**3ae**) in $CDCl_3$

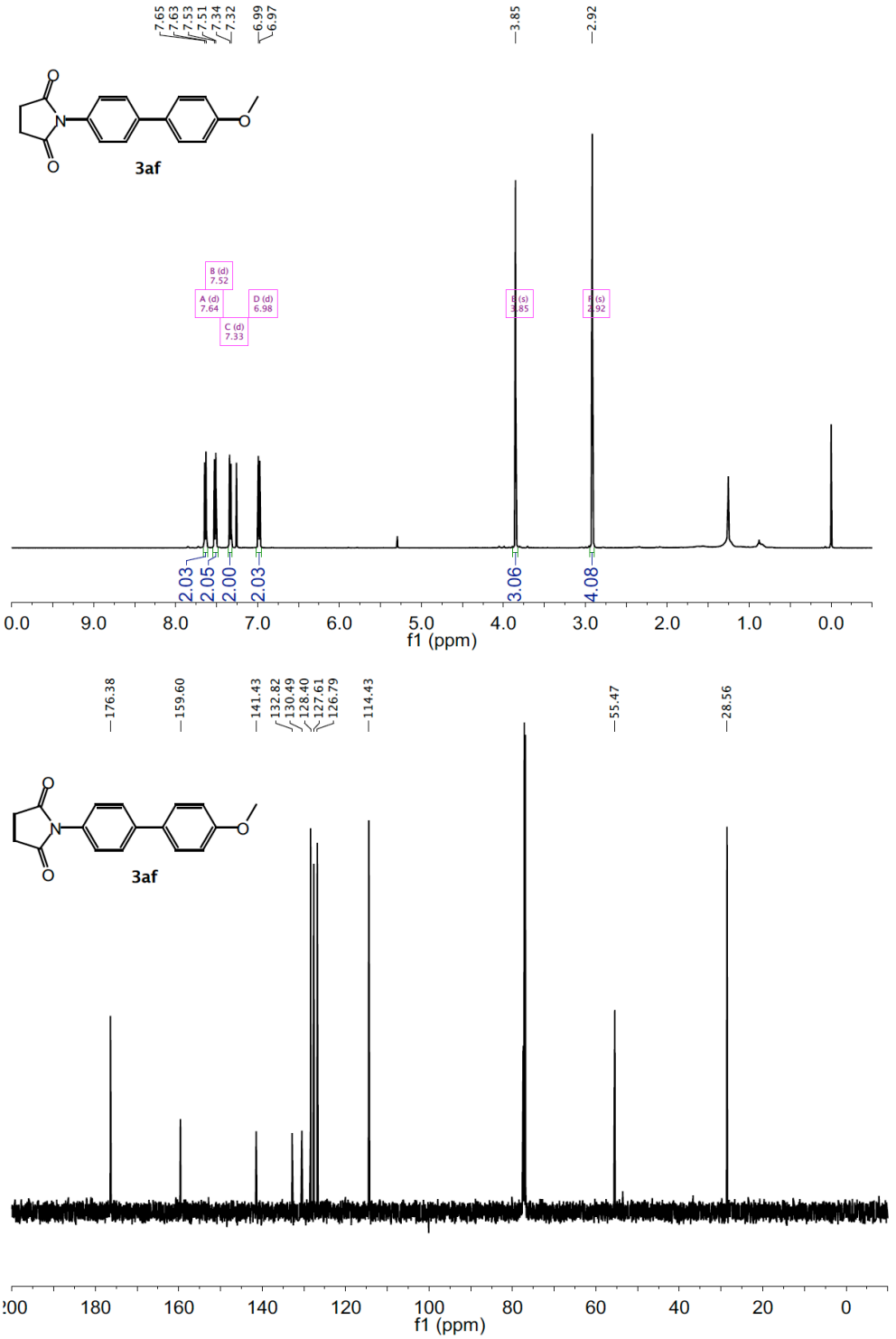


Figure SF 4.32. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 1-(4'-methoxy-[1,1'-biphenyl]-4-yl)pyrrolidine-2,5-dione (**3af**) in $CDCl_3$

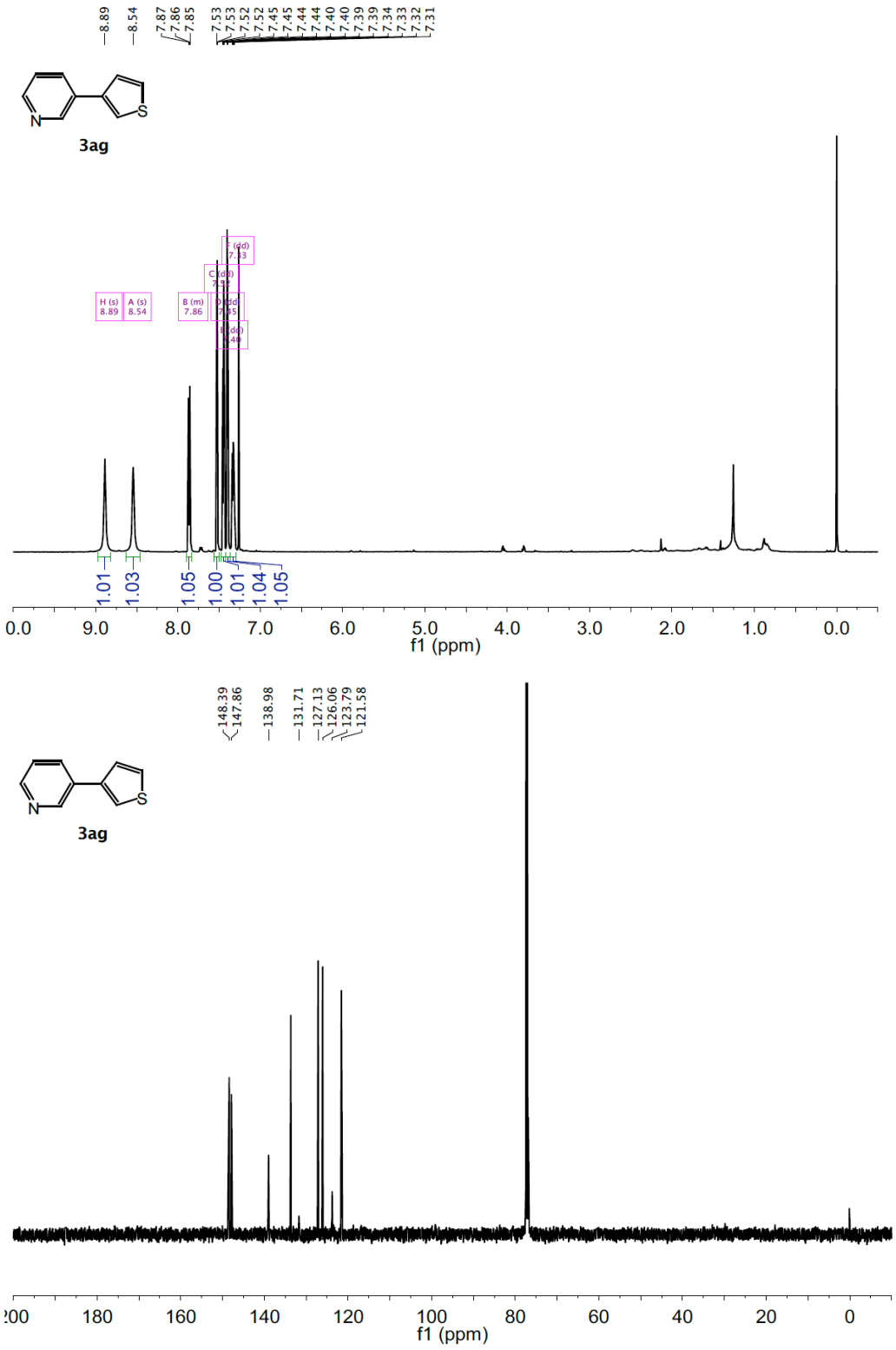


Figure SF 4.33. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 3-(thiophen-3-yl)pyridine (**3ag**) in $CDCl_3$

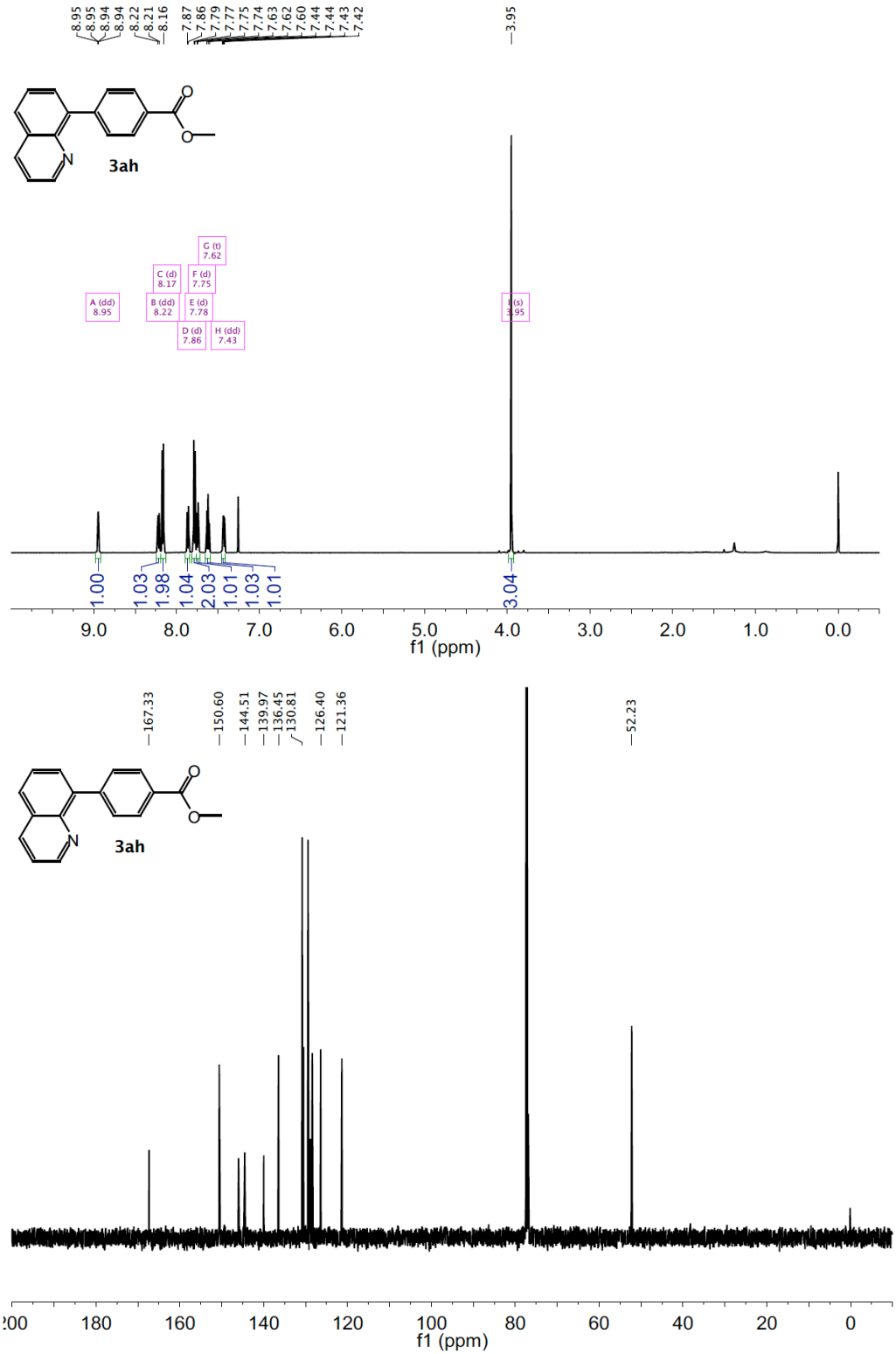


Figure SF 4.34. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4-(quinolin-8-yl)benzoate (**3ah**) in $CDCl_3$

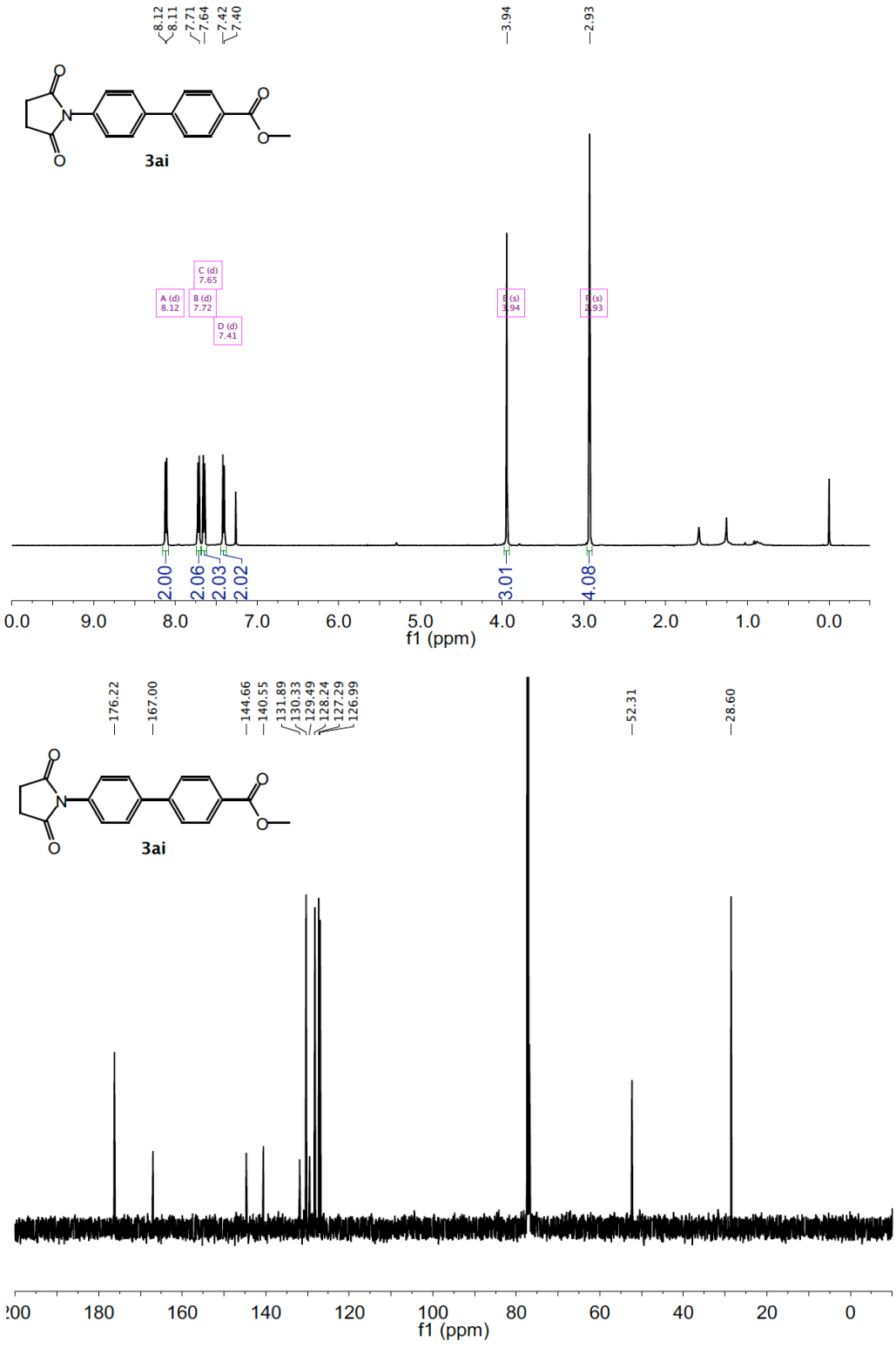


Figure SF 4.35. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4'-(2,5-dioxopyrrolidin-1-yl)-[1,1'-biphenyl]-4-carboxylate (**3ai**) in $CDCl_3$

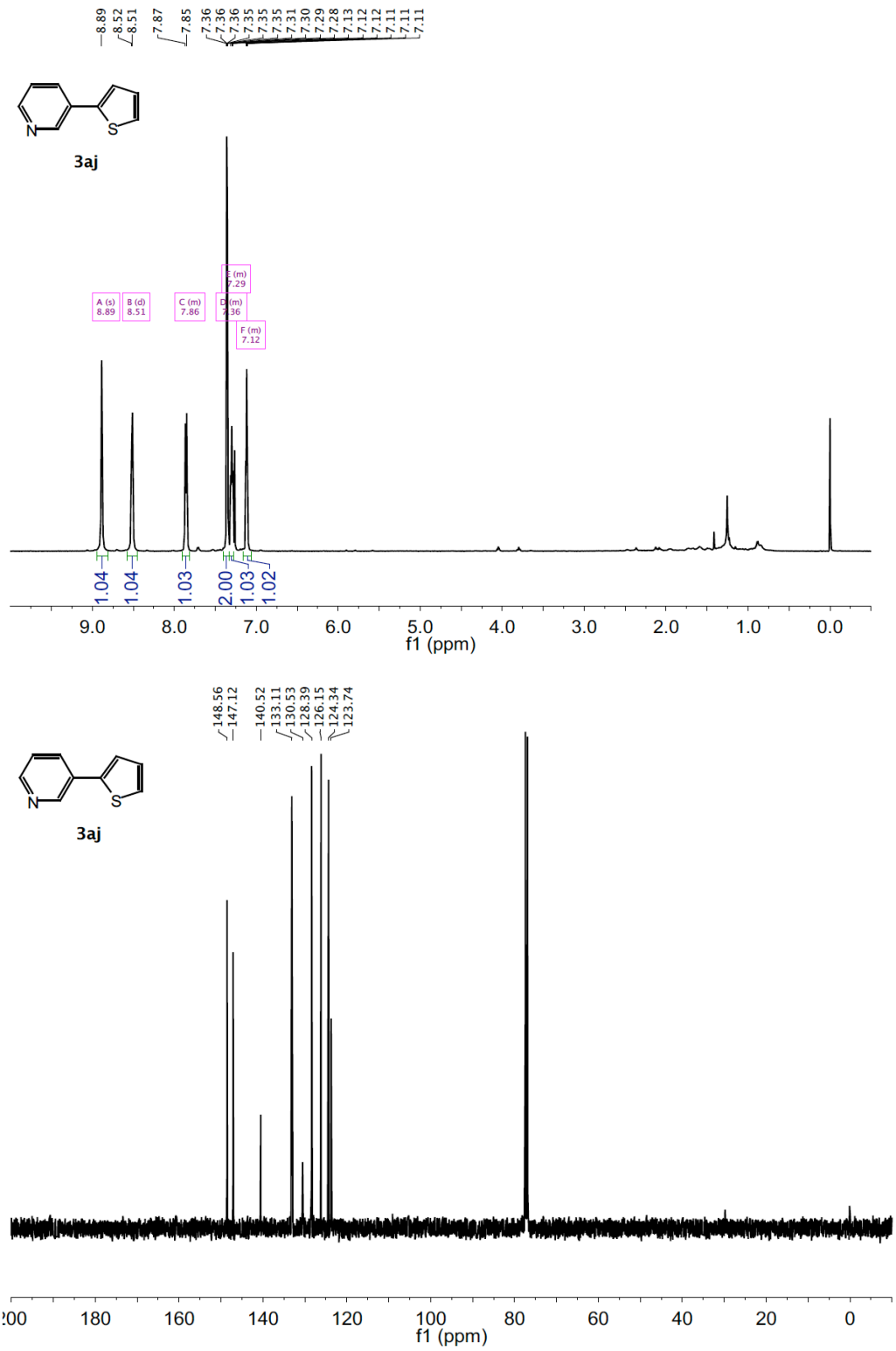


Figure SF 4.36. ^{1}H NMR (top, 500 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of 3-(thiophen-2-yl)pyridine (**3aj**) in $CDCl_3$

4.1.6 Account of Contribution

I contributed to experiments in Table 4.1 and Table 4.2, half the experiments in Table 4.3 and Table 4.4 and selected examples in Table 4.5. I also participated in data organization as well as manuscript writing and revising.

4.1.7 References

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4.2 Air-Stable Nickel Precatalysts for Fast and Quantitative Cross-Coupling of Aryl Sulfamates with Aryl Neopentylglycolboronates at Room Temperature

4.2.1 Introduction

Ni catalysts have been applied to borylation,[2-5] homocoupling[6] and cross-coupling of a variety of unreactive electrophiles based on carbon-oxygen bonds[7-19] and even aryl fluorides.[20-22] Ni-catalysis provides both a less expensive and a more reactive variant than Pd-catalysis toward activation of C-O bonds.[8] However, the commonly used Ni^0 source $Ni(COD)_2$ is air-sensitive and Ni^{II} catalysts need harsh conditions to activate.[8] Recently $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2/PCy_3$ was used for Suzuki-Miyaura cross-coupling of aryl and heteroaryl neopentylglycolboronates with aryl and heteroaryl mesylates and sulfamates in THF at room temperature.[23] $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$ is also applied in cyanation,[5] amination[6] and coupling of aryl halides, and C-O electrophiles.[7] The Hartwig laboratory recently reported the $Ni^{II}Cl(cinnamyl)(dppf)$ catalyzed coupling of heteroaryl halides with arylboronic acids.[24] Enantioenriched 2-aryl- and 2-heteroaryl-1,2-dihydroquinolines were prepared from a nickel precatalyst mediated asymmetric Suzuki-Miyaura cross-coupling of quinolinium ions. A Ni^{II} precatalyst that activates without the need for strong reductants or high temperatures is the key to this successful cross-coupling.[10] $Ni^{II}Cl(o\text{-Tol})(PCy_3)_2$ also catalyzed coupling of benzyl chlorides with terminal alkenes.[11] So far, all Ni precatalysts were used as stable or COD free alternative for $Ni(COD)_2$. No report is available on the reactivity and structural relationship of Ni precatalysts.

The mixed-ligand[25] $Ni(COD)_2/PCy_3$[26] and the precatalyst[27-32] based on the σ-complex[33-35] *trans*-chloro(1-naphthyl) bis(triphenylphosphine)Ni^{II}, $[Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2]/PCy_3$ (precatalyst **4**)

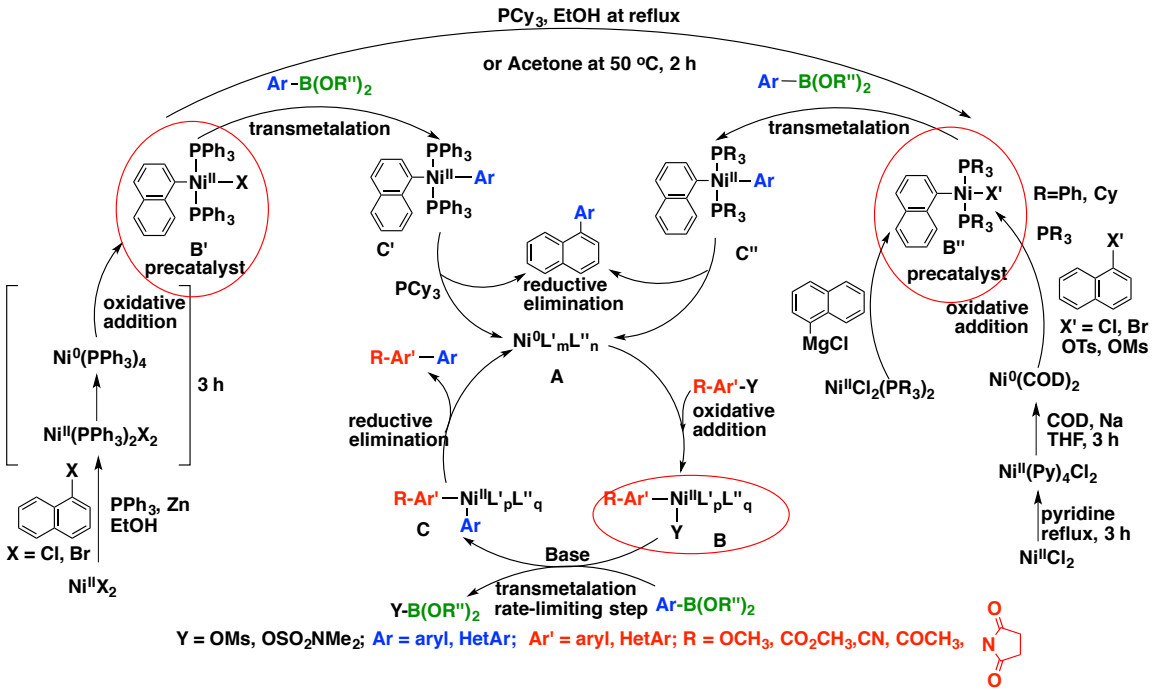
together with PCy_3 mixed-ligand facilitated entries into room temperature cross-coupling reactions of carbon-oxygen based electrophiles[23] with a diversity of boron-based nucleophiles.[23] Since Ni^0 catalysts including $Ni(COD)_2$ are air sensitive, σ-complexes obtained by oxidative addition of aryl electrophiles to Ni^0 species generated an attractive approach to reactive and air stable nickel precatalysts. During our investigation of 5 mol% $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$/10 mol% PCy_3 catalyzed cross-coupling of aryl mesylates and sulfamates,[23] it was found the reactivity of electron-rich aryl sulfamates reacted slower compared to that of 6 mol% $Ni(COD)_2$/12 mol% PCy_3 catalytic system.[26] For instance, 2-methoxy phenyl sulfamate was consumed completely in 12 h when 6 mol% $Ni(COD)_2$/12 mol% PCy_3 was used,[26] but only 71% conversion was detected even after 70 h when 5 mol% $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$/10 mol% PCy_3 was used.[23] The reactivity difference of these two catalytic systems indicates that COD and PPh_3 are not innocent in the cross-coupling.

Inspired by the $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2/PCy_3$ precatalyst/mixed-ligand system, a library of air stable $Ni^{II}X(Aryl)(PCy_3)_2$ (X = Cl, Br, OTs, OMs, Aryl = 1-naphthyl, 2-napththyl; X = Cl, Aryl = 1-acenaphthenyl, 1-(2-methoxynaphthyl), 9-phenanthrenyl, 9-anthracenyl) precatalysts was designed. These catalysts were shown to mediate the quantitative cross-coupling of 2-methoxy phenyl sulfamates with aryl neopentylglycolboronates in less than 1 h at room temperature (23 ^oC) in dry THF. The *ortho*-substituted aryl sulfamate electrophile was selected due to its synthetic versatility[9] and lower reactivity compared with aryl mesylates[4a,l] and aryl halides.[4l] The aryl neopentylglycolboronate nucleophile, synthesized from the *in situ* prepared neopentylglycolborane by a method inspired by the procedure reported for pinacolborane,[36] was used due to its lower reactivity when compared with other arylboron nucleophiles.[18] This selection will allow the preliminary results reported here to be used to estimate the reactivity of these precatalysts in cross-couplings of other electrophiles[4a] and nucleophiles.[4l]

4.2.2 Results and Discussion

Synthesis of Ni precatalysts. The Ni precatalysts can be synthesized by oxidative addition from in situ generated Ni^0 species or $Ni(COD)_2$. Ligand exchange also produces Ni precatalysts from complexes with lower coordination constant to higher coordination constant. $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$ was synthesized by the left-hand route depicted in Scheme 4.3. A mixture of $NiCl_2(H_2O)_6$ and PPh_3 was heated in refluxing ethanol to generate $NiCl_2(PPh_3)_2$, which was reduced to Ni^0 species by Zn in the presence of aryl halides. The facile oxidative addition happens immediately to produce $Ni^{II}Cl_2(1\text{-naphthyl})(PPh_3)_2$. $Ni^{II}Cl(1\text{-naphthyl})(PCy_3)_2$ was obtained both by the top and right routes. The top route is the ligand exchange of more electron rich PCy_3 with PPh_3 in $Ni^{II}Cl_2(1\text{-naphthyl})(PPh_3)_2$. The right route is the oxidative addition of $Ni(COD)_2$, which was prepared in our laboratory. All other precatalysts were synthesized by the right-hand route from $Ni(COD)_2$.

Scheme 4.3. Synthesis of *trans*-$Ni^{II}X(1\text{-Naphthyl})(PR_3)_2$ σ-Complexes (X=Br, Cl, OMs, OTs) and the Proposed Mechanism of Nickel-Catalyzed Suzuki-Miyaura Cross-Coupling

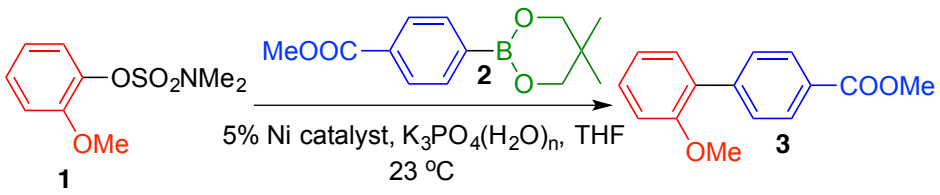


In situ oxidative addition from $NiCl_2$ is inexpensive. However, it is limited to aryl chlorides and bromides and PPh_3 ligand, while oxidative addition from $Ni(COD)_2$ applies an expensive, air-sensitive reagent, but it is universal for a range of $Ni^{II}X(aryl)(PR_3)_2$ complexes. The ligand exchange method is limited to the availability of $Ni^{II}X(aryl)(PPh_3)_2$ and only effective from PPh_3 to PCy_3.

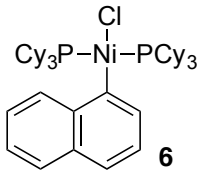
In the reaction, in the presence of excess ligand, ligand exchange might occur during the activation or catalyst resting state. Thus, the amount of excess coligand impacts the reaction.

Water is known to be involved in the cross-coupling catalytic process, either stabilizing Ni complexes in transmetalation, facilitating the formation of aryl borates or providing the active catalytic intermediate.[11,37-41] Since K_3PO_4 is a hygroscopic base, a series of samples of K_3PO_4 with various amounts of water of hydration were used to optimize Ni-catalyzed cross-coupling experiments with both dry and as received, wet and inhibited THF (Scheme 4.4).

Scheme 4.4. Effect of Water on Ni-Catalyzed Cross-Coupling of 2-Methoxyphenyl Dimethylsulfamate with Methyl 4-(5,5-Dimethyl-1,3,2-dioxaborinane-2-yl)benzoate at 23 °C in THF[a]



Dry THF

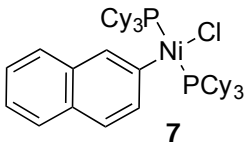


6

$K_3PO_4(H_2O)_n$

n = 1.0	70 min,	16%
	27 h,	100%
n = 3.0	60 min,	100%
n = 3.1	60 min,	98%
n = 3.2	62 min,	100%
n = 3.7	60 min,	98%
n = 4.7	60 min,	95%
n = 7.0	168 min,	99%

Dry THF

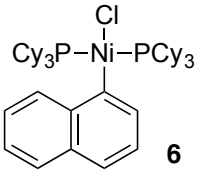


7

$K_3PO_4(H_2O)_n$

n = 2.8	58 min,	85%
n = 3.2	60 min,	100%

As Received THF



6

$K_3PO_4(H_2O)_n$

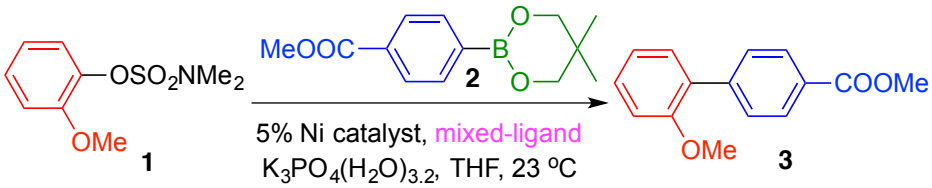
n = 1.0	70 min,	95%
	120 min,	99%
	160 min,	100%
n = 3.2	70 min,	96%
	120 min,	99%
	160 min,	100%
n = 7.0	60 min,	93%
	120 min,	98%
	180 min,	99%

[a]Reaction conditions: aryl sulfamates (0.30 mmol), aryl neo-pentylglycolboronates (0.32 mmol), Ni precatalyst (0.015 mmol), $K_3PO_4(H_2O)_n$ (191 mg), THF (1.0 mL). Conversion by GC.

Best results are obtained when a $K_3PO_4(H_2O)_{3.2}$ sample was used with dry THF, producing 100% conversion in about 1 h. When the K_3PO_4 is too dry (n = 1.0), the reaction takes 27 h to achieve 100% conversion. Too much water also shows a deleterious effect to the reaction. As received THF stabilized by BHT from commercial source was used without further purification. Longer reaction time was required for complete conversion. However, when as received THF was applied, the amount of water in the base sample does not show a significant impact on the efficiency of the reaction.

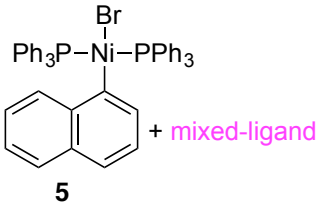
Furthermore, with the optimized $K_3PO_4(H_2O)_{3.2}$ base, dry THF, cross-coupling with $Ni(COD)_2$/mixed-ligand, **4**/mixed-ligand, **5**/mixed-ligand, and **6**/mixed-ligand was carried out (Scheme 4.5).

Scheme 4.5. Cross-Coupling of 2-Methoxyphenyl Dimethylsulfamate with Methyl 4-(5,5-Dimethyl-1,3,2-dioxaborinane-2-yl)benzoate at 23 °C in THF Catalyzed by Ni Precatalysts and Mixed-Ligand Systems[a]

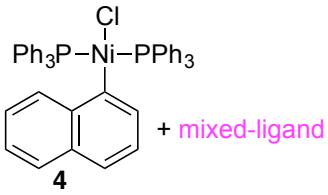


$Ni(COD)_2$ + mixed-ligand

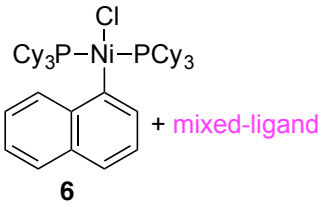
10% PPh_3 : 90 h, 7%
10% PCy_3 : 1 h, 71% (71%)
20% PCy_3 : 1 h, 92% (89%)



10% PCy_3 : 68 h, 97% (94%)
15% PCy_3 : 56 h, 100%



10% PCy_3 : 67 - 70 h, 100% (96%)
15% PCy_3 : 56 h, 100%
20% PCy_3 : 47 h, 100% (95%)



No mixed-ligand: 62 min, 100%
10% COD : 2 h, 57% (50%)
10% PPh_3: 2 h, 60% (48%)

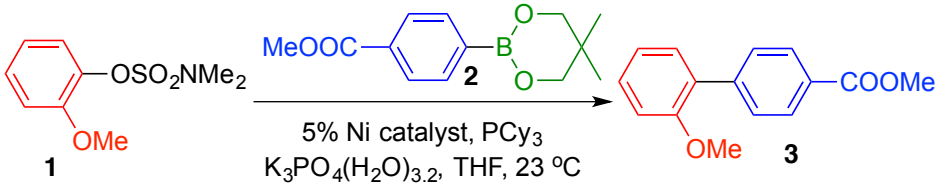
[a]Reaction conditions: aryl sulfamates (0.30 mmol), aryl neopentylglycolboronates (0.32 mmol), Ni precatalyst (0.015 mmol), mixed-ligand (10 to 20 mol %) *vs* aryl sulfamate, $K_3PO_4(H_2O)_{3.2}$ (191 mg), THF (1.0 mL). Conversion by GC, isolated yield in parentheses.

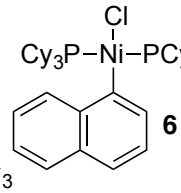
$Ni(COD)_2$ and PPh_3 is not sufficient to cross-couple 2-methoxyphenyl sulfamate with aryl neopentylglycolboronate. Addition of PCy_3 to $Ni(COD)_2$ or $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$ significantly increase the rate of the catalytic system. Changing anion from Br to Cl does not impact the efficiency of the reaction. The synthesis of **6** demonstrated that indeed, in the absence of the

mixed-ligands PPh_3 and COD, this precatalyst is more reactive than $Ni(COD)_2$, 4 and 5 with PCy_3 as mixed-ligand. COD and PPh_3 both inhibits the reactivity of $Ni^{II}Cl(1\text{-naphthyl})(PCy_3)_2$.

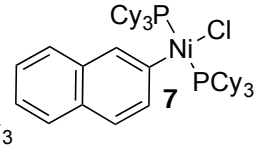
Buchwald reported increased reactivity of Pd precatalysts in Suzuki-Miyaura cross-coupling and amination when Cl was replaced to OMs. To compare the role of X (Cl, OTs, OMs), a library of nickel precatalysts was synthesized. (Scheme 4.6) The amount of excess PCy_3 in cross-coupling reactions was also studied by monitoring by GC to quantitative conversion. It was observed that precatalysts **6** to **11** yield quantitative conversions in 50 to 60 min regardless of the nature of X when no excess of PCy_3 was used, or even in 30 to 50 min when excess PCy_3 was used. The amount of excess PCy_3 impacts the reactivity of all precatalysts. It was found that 1 to 2 equiv of PCy_3 to nickel precatalyts provide the best condition for cross-coupling reactions, presumably by stabilization of coordinatively unsaturated Ni^0 generated *in situ*.

Scheme 4.6. Activity of $Ni^{II}X(Naphthyl)(PCy_3)_2$ Precatalysts in Cross-Coupling of 2-Methoxyphenyl Dimethylsulfamate with Methyl 4-(5,5-Dimethyl-1,3,2-dioxaborinane-2-yl)benzoate at 23 °C in THF[a]

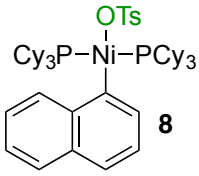




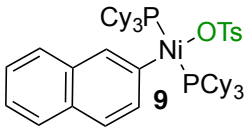
PCy3
0%: 52-60 min, 100%
5%: 35-40 min, 99-100%
10%: 48-50 min, 100%
15%: 40 min, 100%
20%: 40 min, 97% (97%)



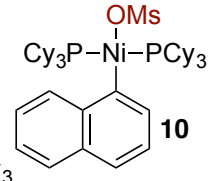
PCy3
0%: 50-70 min, 99-100% (95)
0%: 60 min, 99%[b]
5%: 47 min, 100%
10%: 32-60 min, 99-100%
15%: 44 min, 100%
20%: 60 min, 99-100%



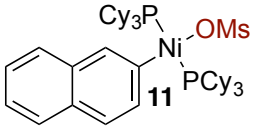
PCy3
0%: 50-60 min, 100%
5%: 53 min, 100%
10%: 40-60 min, 100%
15%: 67 min, 100%
20%: 40 - 60 min, 100% (93-99%)



PCy3
0%: 50 - 60 min, 99 - 100% (100%)
5%: 40 min, 99%
10%: 40 - 53 min, 100%
15%: 65 min, 100%
20%: 60 min, 100%



PCy3
0%: 60 - 70 min, 99- 100% (86-91%)
5%: 50 min, 99%
10%: 40-50 min, 100% (98%)
20%: 30-50 min, 100% (98%)



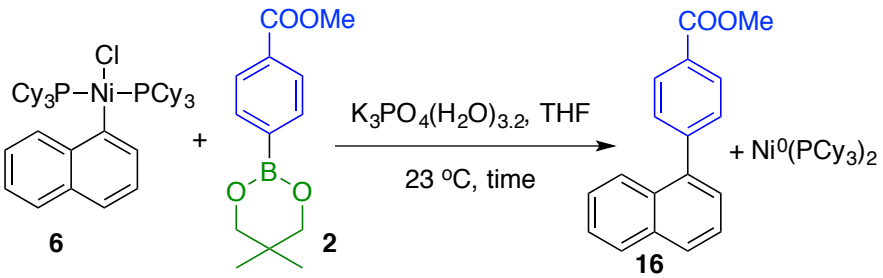
PCy3
0%: 50 min, 100% (95%)
5%: 60 min, 99%
10%: 40-50 min, 100% (98%)
20%: 30-40 min, 100%

[a]Reaction conditions: aryl sulfamates (0.30 mmol), aryl neopentylglycolboronates (0.32 mmol), Ni precatalyst (0.015 mmol), $K_3PO_4(H_2O)_{3.2}$ (191 mg), THF (1.0 mL). Conversion by GC, isolated yield in parentheses. [b]Precatalyst was recrystallized from toluene/hexanes (1:10).

Additional recrystallization of precatalyst **7**, isolated by precipitation in hexane when prepared by the left or right route from Scheme 4.3, does not change its activity (Scheme 4.6). Exchange of

Cl from **6** and **7** for tosylate in **8** and **9** and mesylate in **10** and **11** maintain the same catalytic activity despite the increased solubility. Changing the 1-naphthyl group (precatalysts **6**, **8**, **10**, Scheme 4.6) to a 2-naphthyl group (precatalysts **7**, **9**, **11**, Scheme 4.6) also does not impact the reactivity, indicating that catalyst activation is not rate-determining. To understand the activation of the precatalysts, model reactions on the activation step were carried out. The results are depicted in Scheme 4.7.

Scheme 4.7. Activation of Precatalyst 6



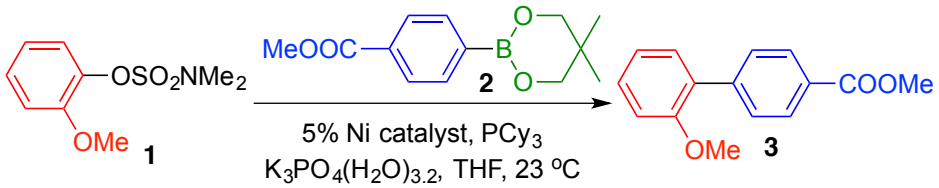
Condition 1: **6** (0.10 mmol), **2** (0.20 mmol) $K_3PO_4(H_2O)_{3.2}$ (0.30 mmol), dry THF (1.0 mL). **16** was isolated in 0.088 mmol in 12 h.
Condition 2: **6** (0.015 mmol), **2** (0.32 mmol) $K_3PO_4(H_2O)_{3.2}$ (191 mg), dry THF (1.0 mL). 100% conversion was obtained in 5 min as determined by ^{1}H NMR.

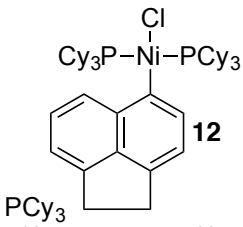
Precatalyst **6** was selected as an example for model reactions. First, precatalyst **6** was mixed with dioxaborinane **2** quantitatively, producing cross-coupling product **16** in 88% isolated yield (Condition 1, Scheme 4.7). This confirms the activation mechanism proposed.[7,35] Then the activation of precatalyst **6** was studied under the precise reaction conditions. Upon mixing with dioxaborinane **2**, precatalyst **6** generated quantitatively the active species $Ni^0(PCy_3)_2$ in less than 5 min (Scheme 4.7) according to ^{1}H NMR. This coordinatively unsaturated Ni^0 species, in contrast with the coordinatively saturated $Ni^0(PCy_3)_3$[42], may act as the active catalyst in the subsequent cross-coupling reaction (Scheme 4.3). Additional mechanistic investigations are required to support this hypothesis.

Lei[43] reported that $Ni^{II}Cl$(9-phenathranyl)$(PPh_3)_2$ is more reactive than $Ni^{II}Cl$(1-naphthyl)$(PPh_3)_2$. To elucidate the role of substitution of the naphthyl groups of these precatalysts, several electron

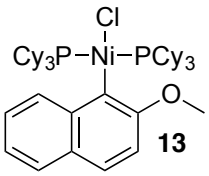
rich substituents and extra fused aromatic rings were incorporated in the structure of **6**. Therefore, precatalysts **12**, **13**, **14**, **15** were prepared and tested in the same cross-coupling reaction (Scheme 4.8). Additional *ortho*-substitution on the 1-naphthyl group of precatalyst **13** leads to slightly lower reactivity, while *para*-substitution (precatalyst **12**) has no effect. An additional fused aromatic ring as in precatalysts **14** and **15** does not significantly change the reactivity but does decrease the atom economy of the catalytic system (Scheme 4.8).

Scheme 4.8. Activity of $Ni^{II}X(R\text{-Naphthyl})(PCy_3)_2$ Precatalysts in Cross-Coupling of 2-Methoxyphenyl Dimethylsulfamate with Methyl 4-(5,5-Dimethyl-1,3,2-dioxaborinane-2-yl)benzoate at 23 °C in THF[a]

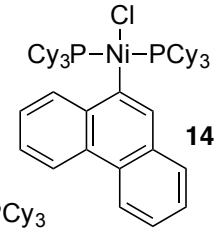




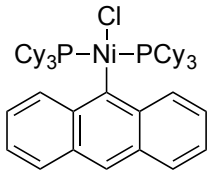
PCy3
0%: 50 min, 99%
10%: 70 min, 99%
20%: 50 min, 100%



PCy3
0%: 70 min, 97%



PCy3
0%: 80 min, 99%
10%: 60 min, 99%
20%: 70 min, 99%



PCy3
0%: 60 min, 100%
10%: 60 min, 100%
20%: 60 min, 99%

[a]Reaction conditions: aryl sulfamates (0.30 mmol), aryl neopentylglycolboronates (0.32 mmol), Ni precatalyst (0.015 mmol), $K_3PO_4(H_2O)_{3.2}$ (191 mg), THF (1.0 mL). Conversion by GC.

In summary, a library of 10 Ni precatalysts which mediate quantitative cross-coupling of *ortho*-substituted aryl sulfamates with aryl neopentylglycolboronates in the presence of $K_3PO_4(H_2O)_{3.2}$

in less than 60 min at room temperature was reported. Precatalyst **6** was prepared by both the left and right routes from Scheme 4.3, while the other synthetic pathway by the right route that is recommended for aryl tosylates, aryl mesylates and for more reactive aryl chlorides such as 9-chloroanthracene. It is remarkable that precatalysts **6** to **15** maintain their reactivity after being stored for one year at room temperature in air, despite the sensitivity of free PCy_3 to oxygen. Furthermore, precatalyst **4** has not changed reactivity even after 4 years in air. Previously reported Ni precatalysts were stable in air for at least two weeks at 0 ^{o}C.[29] The simple synthesis of the precatalysts reported here, their air-stability and ability to achieve complete conversion at room temperature in dry and in as received THF will most probably make them valuable for cross-coupling reactions in medicinal, materials, supramolecular and macromolecular synthesis. Additional Ni precatalysts, electrophilic and nucleophilic substrates are under investigation.

4.2.3 Experiments

4.2.3.1 Materials

Tricyclohexylphosphine, $NiCl_2 \cdot 6H_2O$, 1,5-cyclooctadiene, sodium, pyridine, 4-iodobenzoic acid, borane-dimethyl sulfide complex, 2-methoxyphenol, anthracene, potassium phosphate tribasic trihydrate, potassium phosphate anhydrous, and Mg turnings were used as received from commercial sources. THF, and toluene were distilled from sodium and benzophenone. Hexanes were distilled from sodium. Triethylamine was distilled from calcium hydride. Methanol was distilled from Mg turnings. Triphenylphosphine was recrystallized from hexanes. 9-Chloroanthracene,[44] 9-chlorophenanthrene, 5-chloro-dihydroacenaphthene,[45] methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate,[46] 1-naphthyl 4-methylbenzenesulfonate, 2-naphthyl 4-methylbenzenesulfonate, 1-naphthyl methanesulfonate, 1-naphthyl methanesulfonate and 2-methoxyphenyl dimethyl sulfamate were synthesized according to literature procedures.[47] $Ni^{II}Cl(1\text{-Naphthyl})(PPh_3)_2$, and $Ni^{II}Br(1\text{-Naphthyl})(PPh_3)_2$ were synthesized according to a literature procedure.[33] C_6D_6 was distilled from sodium and benzophenone and kept inside a nitrogen filled glove box. Chlorobenzene was dried over P_2O_5 for 4 h and then distilled from molecular sieves (0.3 nm) under N_2. Phenanthrene and acenaphthene were recrystallized from ethanol. Solvents for column chromatography were used as received from commercial sources. 1-Naphthol and 2-naphthol were sublimed prior use in the synthesis of their mesylates and tosylates.

4.2.3.2 Instrumentation

^1H NMR and ^{13}C NMR spectra were recorded at 500 or 360 MHz on a Bruker DRX (500 MHz) or Bruker DMX (360 MHz). All NMR spectra were measured at 25°C in the indicated deuterated solvents. Proton and carbon chemical shifts (δ) are reported in ppm and coupling constants (J) are reported in Hertz (Hz). The resonance multiplicities in the ^1H NMR spectra are described as “s” (singlet), “d” (doublet), “t” (triplet) and “m” (multiplet) and broad resonances are indicated by “br”. Residual protic solvent of $CDCl_3$ (^1H, 7.27 ppm; ^{13}C, 77.16 ppm (central resonance of the

triplet)), and tetramethylsilane (TMS) were used as the internal reference. ^{31}P NMR (203 MHz) spectra were recorded using H_3PO_4 in D_2O as external standard. A GC coupled with an FID detector and column HP 19091J-413 (5%-phenyl)-methylpolysiloxane 30m length 0.32mm internal diameter was used to follow the reaction conversions and to assess purity of final compounds complementary to the NMR technique. The crude reaction mixtures were diluted with distilled THF. Evolution of the reaction, when indicated, was monitored by analytical thin-layer chromatography using silica gel 60 F254 pre-coated plates (E. Merck). Compounds were visualized by 254 nm light. Purifications by flash column chromatography were performed using flash silica gel from Silicycle (60 Å, 40-63 µm) with the indicated eluent. The purity of the products was determined by a combination of thin-layer chromatography (TLC) on silica gel coated aluminum plates (with F253 indicator; layer thickness, 200 µm; particle size, 2-25 µm; pore size, 60 Å). Detection was done by UV absorbance at 254 nm. Accurate mass measurements (HRMS) were performed on a high-resolution double focusing chemical ionization mass spectrometer (Mass Spectrometry Facility, University of Pennsylvania). Dechlorinated $[M\text{-}Cl]^+$, protonated molecular ions $[M+nH]^{n+}$ or sodium adducts $[M+Na]^+$ were used for empirical formula confirmation. LC/MS were performed with a Waters LCT Premier XE LC/MS system and a Waters GC-TOF Premier. The LCT Premier was equipped with a high-resolution orthogonal time-of-flight (oa-TOF) analyzer using ESI^+ ionization condition. Dechlorinated $[M\text{-}Cl]^+$, $[M\text{-}OTs]^+$, protonated molecular ions $[M+nH]^{n+}$ or sodium adducts $[M+Na]^+$ were used for empirical formula confirmation. Elemental analyses were performed at M-H-W Laboratories in Phoenix, AZ.

4.2.3.3 List of Abbreviations

COD	1, 5-cyclooctadiene
dppe	1, 2-bis(diphenylphosphino)ethane
dppf	1, 1'-bis(diphenylphosphino)ferrocene
dppp	1, 3-dis(diphenylphosphino)propane

PCy_3	tricyclohexylphosphine
PPh_3	triphenylphosphine
THF	tetrahydrofuran
Tol	toluene

4.2.3.4 Syntheses of Coupling Reagents

Synthesis of 2-Methoxyphenyl dimethylsulfamate (1). 2-Methoxyphenyl dimethyl sulfamate was synthesized according to a literature procedure.[48] A flame-dried round bottom flask was charged with a stirring bar and sodium hydride (0.864 g, 36 mmol, 1.2 equiv). The flask was degassed by evacuation for 5 min, backfilled with nitrogen for 1 min for three cycles. 2-Methoxyphenol (3.724 g, 30 mmol, 1 equiv) in dry THF (20 mL) was added dropwise *via* syringe. The flask was cooled in an ice bath for 10 min. *N,N*-Dimethyl sulfamoyl chloride (3.54 mL, 33 mol, 1.1 equiv) in dry THF (20 mL) was added dropwise to the solution. The solution was warmed to room temperature and reacted for 1 h. The crude was quenched by addition of deionized water (20 mL). Ethyl acetate (30 mL) was added to extract the organic phase. The aqueous phase was back extracted with DCM (20 mL) twice. The organic phases were combined, dried over $MgSO_4$ and then filtered. The filtrate was concentrated on a rotary evaporator and purified by silica gel column chromatography with 40% ethyl ether in hexanes as eluent. The off-white solid was recrystallized from methanol to give a white solid. Yield (5.49 g, 23.73 mmol, 79%), m. p. 47-48.5 ^{o}C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.23 (t, *J* = 7.9 Hz, 1H, Ar*H*), 6.96 (dd, *J* = 13.5, 6.0 Hz, 2H, 2Ar*H*), 3.90 (s, 3H, OCH_3), 2.97 (d, *J* = 1.3 Hz, 6H, N(CH_3)$_2$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.7(Ar*C*), 139.5(Ar*C*), 127.7(Ar*C*), 123.9(Ar*C*), 121.0(Ar*C*), 113.0(Ar*C*), 56.1(O*C*H$_3$), 38.8 (N(*C*H$_3$)$_2$). ^{1}H and ^{13}C NMR spectra match with literature data.[26,49]

Synthesis of Methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (2). Methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate was synthesized according to a literature procedure.[4]

Preparation of Neopentylglycolborane

Neopentylglycol (recrystallized from DCM, 1. 25 g, 12 mmol) and a stirring bar were added to a 50 mL round bottom flask. The flask was evacuated for 5 min and then refilled with N_2 three times. Toluene (distilled, 6 mL) was added *via* syringe. The flask was cooled to 0 ^{o}C in an ice/water bath for 10 min. Borane dimethyl sulfide complex (1.14 mL, 12 mmol) was added dropwise *via* a syringe. The reaction was kept at 0 ^{o}C for 0. 5 h then 23 ^{o}C for 1.5 h until the bubbling ceased.

Neopentylglycolborylation of Methyl 4-Iodobenzoate

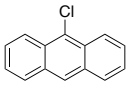
A 50 mL round bottom flask was charged with a stirring bar, methyl 4-iodobenzoate (1. 572 g, 6 mmol), $NiCl_2$(dppp) (163 mg, 0. 3 mmol, 0.05 equiv), PPh_3 (157 mg, 0.6 mmol, 0.1 equiv). The flask was degassed for 10 min and refilled with nitrogen. The process was repeated two more times. Then, toluene (distilled, 6 mL) was added *via* syringe. The reaction was left stirring for 5 min. Et_3N (dry, 2.5 mL, 18 mmol, 3 equiv) was added *via* a syringe. The neopentylglycolborane prepared in step 1 was transferred to the flask *via* a syringe right after the addition of Et_3N. The flask was heated to 100 ^{o}C for 1 h. Then the reaction mixture was cooled to 23 ^{o}C, quenched by addition of saturated ammonium chloride solution (20 mL) and ethyl acetate (20 mL). The organic phase was washed with saturated ammonium chloride solution (20 mL) twice. The aqueous phase was combined and extracted with ethyl acetate (25 mL) three times. The organic phase was collected, combined, washed with brine and then dried over anhydrous $MgSO_4$. The solution was filtered and the filtrate was concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/hexanes mixture, gradient from DCM/hexanes = 7:3 to DCM to DCM/ethyl acetate = 17:3 to obtain a white solid. The white solid was recrystallized from methanol to give a colorless flat crystal, m.p. 113-115.5 ^{o}C, 1.35 g, 91%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 8.4 Hz, 2Ar*H*), 7.87 (d, *J* = 8.3 Hz, 2Ar*H*), 3.93 (s, 3COOCH_3), 3.79 (s, 4H, 2(OCH_2)), 1.04 (s, 6H, 2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2(*C*OOCH$_3$), 133.7(Ar*C*),

131.7(Ar*C*), 128.4(Ar*C*), 72.3(O*C*H_2), 52.0(COO*C*H_3), 31.8(*C*($CH_2O)_2$($CH_3)_2$), 21.8(*C*H_3). ^{1}H and ^{13}C NMR spectra match with literature data.[23]

4.2.3.5 Syntheses of Precatalysts

Syntheses of Precursors for Precatalysts

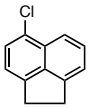
Synthesis of 9-Chloroanthracene. 9-Chloroanthracene was synthesized according to a literature procedure.[44] A 250 mL round bottom flask was charged with a stirring bar, anthracene (3.56 g, 20 mmol, 1 equiv), $CuCl_2$ (anhydrous, dried in a 180 ^{o}C oven for 24 h prior to use, 5.44 g, 40 mmol, 2 equiv) and chlorobenzene (100 mL). The reaction mixture was heated in a silicone oil bath from 23 ^{o}C to 150 ^{o}C in 30 min and was allowed to cool in the oil bath to 23 ^{o}C in approximately 1 h. The solid cuprous chloride was removed by filtration. The filtrate was passed through 40 g basic alumina column to remove the copper residue. The column was eluted with chlorobenzene (50 mL), hexanes (100 mL) and dichloromethane (100 mL). The solution was collected and concentrated first in a rotary evaporator. Subsequently the chlorobenzene was removed by vacuum distillation. The solid was purified by silica gel column chromatography with hexanes. The first portion (R_f = 0.7) was 9,10-dichloroanthracene, the second portion (R_f = 0.6) was 9-chloroanthracene and the last portion was anthracene (R_f = 0.5). 9-Chloroanthracene was recrystallized from ethanol prior to being used.



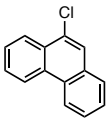
9-Chloroanthracene. Lemon yellow needle crystals (1.465 g, 70%) were obtained by recrystallization from ethanol. m.p. 108-109 ^{o}C, lit.[44] 104-106 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, J = 8.8, 2H, 2Ar*H*-1), 8.41 (s, 1H, Ar*H*-10), 8.02 (d, J = 8.4, 2H, 2Ar*H*-4), 7.74 – 7.59 (m, 2H, 2Ar*H*-2), 7.59 – 7.50 (m, 2H, 2Ar*H*-3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 128.7 (2Ar*C*CCl), 127.0 (Ar*C*Cl), 126.2 (2Ar*C*), 125.8 (Ar*C*H), 124.9 (Ar*C*H). M. p. matches with literature data.[44]

Chlorination of Phenanthrene and 1, 2-Dihydroacenaphthene.

9-Chlorophenanthrene and 5-chloro-dihydroacenaphthene were synthesized according to a literature procedure.[45] $CuCl_2$ on basic alumina was prepared by dissolving $CuCl_2$ (10 g) in water and adding it to basic alumina (20 g). The solid was dried in a rotary evaporator and then at 180 ^oC for 24 h prior to use. A round bottom flask was charged with a stirring bar, 1,2-dihydroacenaphthene (1.386 g, 9 mmol), $CuCl_2/Al_2O_3$ (22 g) and chlorobenzene (90 mL). The mixture was heated to 130 ^oC for 2 h. The mixture was filtered, washed with 10 mL chlorobenzene, and concentrated by vacuum distillation. An orange solid (972.6 mg, 57%) was obtained after purification by silica gel column chromatography with hexanes.



5-Chloro-dihydroacenaphthene. An orange solid (972.6 mg, 57%) was obtained after purification by silica gel column chromatography with hexanes. m. p. 71 ^oC, lit.[50] 70. 5 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.3, 1H, Ar*H*-6), 7.66 – 7.54 (m, 1H, Ar*H*-7), 7.49 (d, J = 7.3, 1H, Ar*H*-8), 7.35 (d, J = 6.8, 1H, Ar*H*-4), 7.18 (d, J = 7.3, 1H, Ar*H*-3), 3.56 – 3.40 (m, 2H, ArCH_2-2), 3.40 – 3.26 (m, 2H, ArCH_2-1). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6 (Ar*C*-CH_2), 146.2 (Ar*C*-CH_2), 145.2 (Ar*C*), 140.3 (Ar*C*), 129.5 (Ar*C*Cl), 128.9 (Ar*C*H), 127.4 (Ar*C*H), 126.9 (Ar*C*H), 120.2 (Ar*C*H), 119.6 (Ar*C*H), 119.4 (Ar*C*H), 30.8 (Ar*C*H_2), 29.9 (Ar*C*H_2). m. p. matches with literature data.[50]

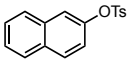


9-Chlorophenanthrene.[45] A round bottom flask was charged with a stirring bar, phenanthrene (1.604 g, 9 mmol), $CuCl_2/Al_2O_3$ (22 g) and chlorobenzene (90 mL). The reaction mixture was heated to 130 ^oC for 2 h. The mixture was lifted out of the oil bath, cooled to 23 ^oC, filtered,

washed with 10 mL chlorobenzene, and concentrated by vacuum distillation. An off-white solid (1.3844 g, 72.3%) was obtained after purification by silica gel column chromatography with hexanes. m. p. 49 ^{o}C. The solid was recrystallized from aqueous ethanol (95% ethanol in water) two times to give white needle-like crystals (0.374 g, 27.6%) with m. p. 51-52 ^{o}C. lit. 51-52 ^{o}C.[45] ^{1}H NMR matches with literature data.[45] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, J = 8.0, 1H, Ar*H*-5), 8.67 (d, J = 8.4, 1H Ar*H*-4), 8.41 (d, J = 8.6, 1H, Ar*H*-8), 7.89 (s, 1H, Ar*H*-10), 7.82 (d, J = 7.7, 1H, Ar*H*-1), 7.79 – 7.70 (m, 2H, 2Ar*H*-3, 6), 7.67 (t, J = 7.5, 1H, Ar*H*-7), 7.62 (t, J = 7.4, 1H, Ar*H*-2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.7 (Ar*C*), 131.3 (Ar*C*), 130.5 (Ar*C*-Cl), 129.4 (Ar*C*), 129.3 (Ar*C*), 127.8 (Ar*C*H), 127.3 (Ar*C*H), 127.2 (Ar*C*H), 127.2 (Ar*C*H), 126.8 (Ar*C*H), 126.4 (Ar*C*H), 125.2 (Ar*C*H), 122.8 (Ar*C*H), 122.6 (Ar*C*H).

1-Naphthyl 4-methylbenzenesulfonate. Under nitrogen, to an oven dried round bottom flask charged with a stirring bar was added the sublimed 1-naphthol (3.0 g, 2.08 x 10^{-2} mol), toluenesulfonyl chloride (5.95 g, 3.12 x10^{-2} mol) and freshly distilled dichloromethane (20 mL). The flask was cooled for 10 min in an ice water bath. Anhydrous pyridine (25 mL, 0.31 mol) was added. The reaction was allowed to proceed with stirring in the ice water bath for 4 h, after which the ice water bath was removed and the reaction was allowed to warm to room temperature, and stirring was continued until complete consumption of the starting material was observed by TLC. The reaction was quenched by addition of water (40 mL), and the organic phase was separated. The aqueous phase was further extracted with dichloromethane (3 x 20 mL), and all the organic layers were combined and washed successively with 15% HCl (2 x 20 mL) and brine (3 x 20 mL) then dried over anhydrous $MgSO_4$. Following filtration the solvent was removed under reduced pressure and purified by silica gel column chromatography with dichloromethane to yield a pale yellow crystal (4.37 g, 70%). Recrystallization from methanol gives white crystals, m.p. 87 ^{o}C. lit.[51] 89-91 ^{o}C. If 1-naphthol used in this synthesis is not sublimed, the resulting tosylate crystals are

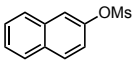
pale yellow. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.81 (dd, *J* = 12.5, 8.0 Hz, 3H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.46 (dt, *J* = 21.4, 6.9 Hz, 2H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.23 (dd, *J* = 7.6, 1.1 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.7, 145.3, 134.6, 132.7, 129.7, 128.4, 127.6, 127.2, 127.0, 126.6, 126.6, 125.0, 121.7, 118.3, 21.6.



2-Naphthyl 4-methylbenzenesulfonate. Under nitrogen, to an oven dried round bottom flask charged with a stirring bar was added the sublimed 2-naphthol (5.48 g, 3.8 x 10-^{2} mol), toluenesulfonyl chloride (8.68 g, 4.56 x10^{-2} mol) and freshly distilled dichloromethane (31 mL). The flask was cooled for 10 min in an ice water bath. Anhydrous pyridine (15 g, 0.19 mol) was added. The reaction was allowed to proceed with stirring in the ice water bath for 4 h after which the ice water bath was removed and the reaction was allowed to warm to room temperature and stirring was continued until complete consumption of the starting material was observed by TLC. The reaction was quenched by addition of water (40 mL), and the organic phase was separated. The aqueous phase was further extracted with dichloromethane (3 x 20 mL), and all organic layers were combined and washed successively with 15% HCl (2 x 20 mL), and brine (3 x 20 mL) then dried over anhydrous $MgSO_4$. Following filtration the solvent was removed under reduced pressure and purified by silica gel column chromatography with dichloromethane to yield pale yellow crystals (5.6 g, 80%). Recrystalization from methanol gives white crystals, m.p. 125 ^{o}C. lit.[51] 119-120 ^{o}C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 9.0 Hz, 1H), 7.75 (t, *J* = 8.8 Hz, 4H), 7.54 - 7.44 (m, 3H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.11 (dd, *J* = 8.9, 2.1 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.1, 145.3, 133.4, 132.4, 131. 8, 129.7, 129.6, 128.5, 127.8, 127.6, 126.7, 126.3, 121.1, 119.9, 21.6.

1-Naphthyl methanesulfonate. A flame-dried 50 mL round bottom flask was charged with a stirring bar, sublimed 1-naphthol (2.88 g, 20 mmol, 1 equiv), and DMAP (244 mg, 2 mmol, 0.1

equiv). The flask was sealed with a rubber septum and then purged with nitrogen for 10 min. Dichloromethane (20 mL) was added *via* syringe followed by pyridine (8 mL, 100 mmol, 5 equiv). The flask was placed in a 0°C ice bath and stirred for 10 min. Methanesulfonyl chloride (2.4 mL, 30 mmol, 1.5 equiv) was added dropwise *via* syringe. The reaction was allowed to run for 1 h and then the ice bath was removed. After 10 hours, the reaction was quenched by addition of 10 mL of 1 M HCl. The contents of the flask were transferred to a 125 mL separatory funnel and then washed three times with 10 mL of 1 M HCl. The organic layer was dried by washing two times with 15 mL brine solution and then stirred over anhydrous $MgSO_4$. The solution was filtered and then the solvent was removed on a rotary evaporator. Column chromatography on silica gel with dichloromethane yielded a solid that was recrystallized from methanol to obtain colorless crystals. Yield (4.08 g, 92%), m.p. 36.5°C, lit.[51] 35-36 °C.^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.16 - 8.11 (m, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.81 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.62 - 7.51 (m, 3H), 7.47 (td, *J* = 7.9, 1.0 Hz, 1H), 3.20 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.4, 135.0, 128.2, 127.5, 127.4, 127.1, 125.5, 121.5, 118.5, 38.1.



2-Naphthyl methanesulfonate. A flame-dried 50 mL round bottom flask was charged with a stirring bar, sublimed 2-naphthol (2.88 g, 20 mmol, 1 equiv), and DMAP (244 mg, 2 mmol, 0.1 equiv). The flask was sealed with a rubber septum and then purged with nitrogen for 10 minutes. Dichloromethane (20 mL) was added *via* syringe followed by pyridine (8 mL, 100 mmol, 5 equiv). The flask was placed in a 0°C ice bath and stirred for 10 min. Methanesulfonyl chloride (2.4 mL, 30 mmol, 1.5 equiv) was added dropwise *via* syringe. The reaction was allowed to run for 1 h and then the ice bath was removed. After 10 h, the reaction was quenched by addition of 10 mL of 1 M HCl. The contents of the flask were transferred to a 125 mL separatory funnel and then washed three times with 10 mL of 1 M HCl. The organic layer was dried by washing two times with 15 mL brine solution and then stirred over anhydrous $MgSO_4$. The solution was filtered, and then the solvent was removed on a rotary evaporator. Column chromatography on silica gel with

dichloromethane yielded a solid that was recrystallized from MeOH to obtain colorless crystals. Yield (3.20g, 72%) m. p. 105-106.5 ^{o}C, lit.[51] 101-102 ^{o}C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 - 7.83 (m, 3H), 7.78 (s, 1H), 7.55 (p, *J* = 6.8 Hz, 2H), 7.42 (d, *J* = 9.0 Hz, 1H), 3.19 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.8, 133.5, 132.0, 130.2, 127.8, 127.8, 127.1, 126.5, 120.7, 119.3, 37.3.

Ni(COD)$_2$. Ni(COD)$_2$ was synthesized *via* a modified literature procedure.[52] $NiCl_2$(pyridine)$_4$ (20.58 g) was prepared by refluxing of $NiCl_2(H_2O)_6$ (10.8 g) in pyridine (125 mL) for 3 h. The bright blue solid was collected by vacuum filtration and then allowed to air dry. A 250 mL round bottom flask was charged with a stirring bar and $NiCl_2$(pyridine)$_4$ (8.92 g, 20 mmol). The flask was evacuated (10 min) and refilled with nitrogen three times. 1,5-Cyclooctadiene (7.4 mL, 60 mmol) and THF (12 mL, distilled immediately before addition) were introduced *via* syringes. The mixture was left stirring for 5 min. Na (in small pieces, 0.92 g) was added quickly. The solution was cooled to – 78 ^{o}C for 10 min. The flask was evacuated (15 s), refilled with nitrogen (1 min) and the procedure was repeated two more times. The mixture was warmed to 23 ^{o}C and kept stirring vigorously at 23 ^{o}C for 3 h. MeOH (24 mL, distilled from Mg turnings under nitrogen immediately before addition) was added to induce the precipitation of Ni(COD)$_2$. Stirring was halted, and the yellow precipitate was allowed to settle. After all the sodium was consumed, the black upper layer was removed by syringe. MeOH (12 mL) was added again to rinse the crystals, and the upper layer was removed by syringe. The procedure was repeated 4 more times until the upper layer was clear. The Ni(COD)$_2$ (3.3 g, 70%, yellow solid) was dried overnight under vacuum for 12 h. Ni(COD)$_2$ (1 g) was dissolved in toluene (distilled within 1 day of use) at 23 ^{o}C inside the glove box, and then the solution was filtered through Celite inside the glove box. The filtrate was kept in a screw cap vial (20 mL) at – 78 ^{o}C for 12 h until a bright yellow solid formed in the bottom of the vial. The bright yellow crystals (350 mg) were washed with ethyl ether (distilled right before use) two times, hexanes (distilled right before use) two times and dried under vacuum for 2 h. The NMR tube was prepared inside a nitrogen filled glove box with C_6D_6. ^{1}H NMR (500 MHz, C_6D_6) δ

4.40 (s, 4H, 4C*H*), 2.17 (s, 8H, 4CH_2). ^{13}C NMR (126 MHz, C_6D_6) δ 89.7 (4*C*H), 30.9 (4*C*H_2). ^{1}H NMR matches with literature data.[52]

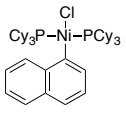
Syntheses of Precatalysts

General Procedure for the Synthesis of $Ni^{II}X(Aryl)(PCy_3)_2$. Nickel sigma complexes used as precatalysts were synthesized according to a literature procedure.[41] All nickel sigma complexes were synthesized and purified in a nitrogen filled glove box.

General Procedure for the Synthesis of $Ni^{II}Cl(Aryl)(PCy_3)_2$.

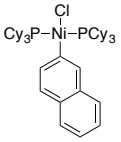
Oxidative Addition of Aryl Chlorides to $Ni(COD)_2$. In a nitrogen filled glove box, a stirring bar, $Ni(COD)_2$ (100 mg, 0.36 mmol), PCy_3 (300 mg, 1.07 mmol), and THF (1 mL) were added to a 20 mL vial. The solution was left stirring for 1 min, and then 9-chloroanthracene (76 mg, 0.36 mmol) was added. The reaction was left stirring inside a glove box with inert atmosphere for 6 h. At this time the oxidative addition reaction was complete as demonstrated by NMR. The reaction mixture was filtered through a membrane (0.22 μm) inside the glovebox, the solid was collected, washed 5 times with distilled hexanes (2 mL), then dried for 12 h under vacuum. Yield: 200 mg, 70%.

Ligand exchange. $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$ (0.2 mmol, 149 mg), PCy_3 (0.6 mmol, 148 mg) and 10 mL EtOH (anhydrous) were added to a Schlenk tube inside the glovebox with a stirring bar. The tube was sealed, brought outside the glovebox, and then heated to 80 ^{o}C for 2 h. The reaction mixture was then cooled to 23 ^{o}C. The Schlenk tube was brought inside the glove box. After filtration, the solid was washed with ethyl ether three times inside the glovebox. The solid was recrystallized from a DCM/hexanes = 2:8 mixture to yield a yellow solid (106 mg, 68%).

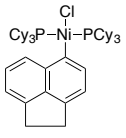


(**6)** The reaction was carried out following the general procedure from 1-chloronaphthalene (50 μL, 0.36 mmol). Yield: by oxidative addition, from 1-chloronaphthalene (50 μL, 0.36 mmol), $Ni(COD)_2$ (100 mg, 0.36 mmol), 200mg, 70%; by ligand exchange method, from $Ni^{II}Cl(1\text{-naphthyl})(PPh_3)_2$ (0.2 mmol, 149 mg), PCy_3 (0.6 mmol, 148 mg), yield 106 mg, 68%.

Yellow solid, m.p. 190.4 °C (decompose). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.18 (d, J = 8.6, 1H), 7.50 (d, J = 8.4, 1H), 7.47 – 7.42 (m, 1H), 7.40 (s, 1H), 7.23 (d, J = 7.6, 2H), 7.05 – 6.97 (m, 1H), 2.10-0.72 (br, 76H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8, 141.6, 136.7, 135.1, 132.5, 127.8, 124.5, 124.3, 122.4, 121.4, 33.4, 30.2, 29.4, 28.1, 28.0, 27.7, 26.6. ^{31}P NMR (203 MHz, $CDCl_3$) δ 10.66. $[M\text{-}Cl]^+$ calcd for $C_{46}H_{73}NiP_2$, 745.4541, HRMS found 745. 4360.

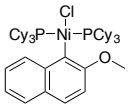


(**7**) The reaction was carried out following the general procedure from 2-naphthyl chloride (59 mg, 0.36 mmol, 1 equiv), with $Ni(COD)_2$ (100 mg, 0.36 mmol, 1 equiv). Yield: 147 mg, 52%. Yellow solid, m.p. 147-148 °C (decompose). ^{1}H NMR (500 MHz, C_6D_6) δ 8.22 (d, J = 7.8, 1H), 8.18 (s, 1H), 7.77 (d, J = 7.4, 2H), 7.71 (d, J = 7.9, 1H), 7.52 (d, J = 7.8, 1H), 7.46 – 7.36 (m, 2H), 7.31 (s, 1H), 1.07-2.26 (br, 66 H). ^{31}P NMR (203 MHz, C_6D_6) δ 12.36. ^{13}C NMR (126 MHz, C_6D_6) δ 137.8, 137.6, 132.6, 130.3, 128.5, 128.2, 125.2, 125.0, 123.2, 122.9, 33.9, 30.1, 27.8, 26.6. ^{1}H and ^{31}P NMR spectra match literature data.[53] The catalyst was also recrystallized from toluene/hexanes = 1:10 mixture. In an oven dried screw cap vial were added $Ni^{II}Cl(2\text{-Naphthyl})(PCy_3)_2$ (100.1 mg), the catalyst was dissolved in 4 mL boiling toluene/hexanes = 1:10 mixture. The dark red solution was filtered through a 0.22 μm membrane filter and cooled in -10 °C freezer for 4 h. The solid was collected, washed with cold hexanes and dried in vacuum. Yield: 77.8 mg. The ^{1}H, ^{31}P NMR spectra as well as kinetic results are identical with that of the non-recrystalized precatalyst.



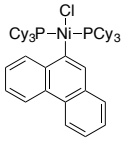
(**12**) The reaction was carried out following the general procedure from 5-chloro-1,2-dihydroacenaphthene (68.6 mg, 0.36 mmol). Yield: 110mg, 39%. Yellow-brown solid, m.p. 151-153 °C (decompose). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92 (d, J = 7.0, 1H), 7.75 (d, J = 6.5, 2H), 7.32 (d, J = 6.4, 2H), 3.33 (s, 2H), 3.31 (s, 2H), 2.48-0.91 (br, 66H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.1, 141.0, 139.4, 138.4, 137.6, 129.9, 129.2, 125.4, 119.1, 118.5, 34.0, 30.8, 30.0, 28.4, 28.1,

27.1. ^{31}P NMR (203 MHz, $CDCl_3$) δ 11.69. $[M\text{-}Cl]^+$ calcd for $C_{48}H_{75}NiP_2$, 771.470, LC/MS found 771.500. Anal. calcd for $C_{48}H_{75}ClNiP_2$: C, 71.33; H, 9.35. Found: C 71.63 H, 8.97.

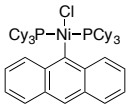


(**13**) In a nitrogen filled glove box, 1-chloro-2methoxynaphthalene (154 mg, 0.8 mmol, 1.1 equiv), $Ni(COD)_2$ (200 mg, 0.72 mmol, 1 equiv) and PCy_3 (610 mg, 2.16 mmol, 3 equiv) were added to a 20 mL vial charged with a stirring bar. THF (distilled, 1 mL) was added via syringe. The solution was left stirring for 18 h, transferred to a Schlenk flask and brought outside the glove box. The dark red solution was concentrated under reduced pressure and brought inside the glove box. Distilled hexanes (1 mL) were added to induce precipitation. The precipitate was collected and washed with distilled hexanes (0.5 mL) five times. The pink solid was collected and dried under vacuum for 6 h. Then, the pink solid (150 mg) was transferred to a 4 mL vial. Dichloromethane/hexanes 1:7 solution was heated until boiling and added to the solid until the solid was fully dissolved. (In the case of slow solvation, a maximum of 4 mL of mixed solvent was added and the vial was sealed and heated until homogeneous.) The solution was filtered while still hot to generate a red solution. The red solution was left in a -10 ^{o}C freezer for 12 h to produce a pink solid. The pink solid was collected, washed with distilled hexanes (0.5 mL) three times and dried under vacuum to give the COD free catalyst. (57.8 mg, yield: 10%) m.p. 193 ^{o}C.

^{1}H NMR (500 MHz, Benzene-d_6) δ 10.70 (d, J = 8.4 Hz, 1H), 7.81-7.68 (m, 2H), 7.51 (d, J = 8.7 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 3.72 (s, 3H), 2.38 (s, 6H), 2.06 (s, 6H), 1.86 (m, 18H), 1.75-1.59 (m, 18H), 1.26 (s, 12H), 1.07 - 0.90 (m, 12H). ^{31}P NMR (203 MHz, C_6D_6) δ 11.76. ^{13}C NMR (126 MHz, C_6D_6) δ 159. 7, 143.7, 134.2, 128.8, 128.2, 124.3, 123.2, 122.5, 109.1, 53.2, 36.0, 34.6, 34.0, 30.4, 28.2, 28.0, 26.7, 25.3, 20.5, 11.3. $[M\text{-}Cl]^+$ calcd for $C_{47}H_{75}ONiP_2$, 775.4647, HRMS found 775.4639.



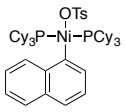
(**14**) In a nitrogen filled glove box, 9-chlorophenanthrene (61 mg, 0.29 mmol, 1.1 equiv), $Ni(COD)_2$ (70 mg, 0.26 mmol, 1 equiv) and PCy_3 (280 mg, 0.78 mmol, 3 equiv) were added to a 20 mL vial charged with a stirring bar. THF (distilled, 0.5 mL) was added via a syringe. The solution was left stirring for 6 h. The solid was collected, washed with hexanes (1 mL) five times. The yellow solid was dried under vacuum for 6 h to remove the solvent. Then, the yellow solid (97 mg) was transferred to a 4 mL vial. A dichloromethane/hexanes 1:5 solution was heated until boiling and added to the solid until the solid was fully dissolved. (In the case of slow solvation, a maximum of 4 mL of mixed solvent was added and the vial was sealed and heated till homogeneous.) The solution was filtered while still hot to generate a red solution. The red solution was concentrated under reduced pressure to produce a yellow solid. The yellow solid was washed 3 times with distilled hexanes to remove the COD. The yellow solid was collected and dried under vacuum for 12 h. (59.2 mg, yield: 27.4%) Yellow solid, m.p. 158 ^{o}C (decompose). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.13 (d, *J* = 8.0 Hz, 1H), 8.61 (dd, *J* = 31.5, 8.3 Hz, 2H), 7.99 (s, 1H), 7.91 (t, *J* = 7.4 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.46-7.38 (m, 1H), 4.38 (s, 1.2 H, C*H*$_2$Cl$_2$), 2.55-0.72 (m, 80H). ^{13}C NMR (91 MHz, $CDCl_3$) δ 141.2, 137.4, 136.1, 135.1, 132.2, 128.5, 127.1, 126.3, 125.6, 125.4, 123.9, 122.6, 122.5, 34.7, 33.8, 30.5, 29.7, 28.1, 27.8, 26.7. ^{31}P NMR (203 MHz, $CDCl_3$) δ 9.75. $[M\text{-}Cl]^+$ calcd for $C_{50}H_{75}NiP_2$, 795.470, LC-MS found 795.509. Anal. calcd for $C_{50}H_{75}NiClP_2(CH_2Cl_2)_{0.55}$: C, 69.08; H, 8.73. Found: C 68.69 H, 8.48. The ratio between CH_2Cl_2 and the nickel complex was determined by ^{1}H NMR.



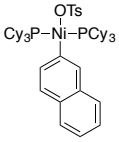
(**15**) The reaction was carried out following the general procedure, from 9-chloroanthracene (77 mg, 0.36 mmol). Yield: 248 mg, 82%. Orange solid, m.p. 170 ^{o}C (decompose). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.21 (d, J = 7.6, 2H), 7.79 (s, 1H), 7.73 (d, J = 7.2, 2H), 7.48 – 7.39 (m, 2H), 7.39 – 7.31 (m, 2H), 1.92 – 0.50 (br, 68H). ^{13}C NMR (126 MHz, $CDCl_3$)

δ 140.0, 136.3, 130.6, 128.6, 124.6, 121.4, 121.4, 121.0, 77.4, 77.2, 76.9, 34.1, 34.0, 34.0, 30.1, 28.1, 26.6. ^{31}P NMR (146 MHz, $CDCl_3$) δ 8.82. $[M\text{-}Cl]^+$ calcd for $C_{50}H_{75}NiP_2$, 795.4697, HRMS found 795.4698.

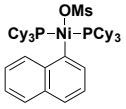
General Procedure for the Synthesis of $Ni^{II}OTs(Aryl)(PCy_3)_2$ or $Ni^{II}OMs(Aryl)(PCy_3)_2$. A stirring bar, $Ni(COD)_2$ (100 mg, 0.36 mmol), PCy_3 (300 mg, 1.07 mmol), and 1 mL THF were added to a 20 mL vial. The solution was left stirring for 1 min, and then 1-naphthyl 4-methylbenzenesulfonate (107 mg, 0.36 mmol) was added. The reaction was left stirring inside a glove box under an inert atmosphere for 6 h - until the oxidative addition reaction was complete as demonstrated by NMR. The reaction mixture was dissolved in THF, filtered through a 22 μm membrane and collected. The filtrate was collected in a 50 mL Schlenk flask and dried under vacuum outside the glove box. The side arm of the flask was degassed prior to application of the vacuum. Once the filtrate had dried, the flask was brought inside the glove box and the residue was washed with hexanes 5 times. The solid was collected and dried under vacuum overnight.



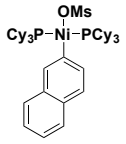
(**8**) The reaction was carried out following the general procedure from 1-naphthyl 4-methylbenzenesulfonate (108.5 mg, 0. 36 mmol), $Ni(COD)_2$ (100 mg, 0.36 mmol). Yield: 212 mg, 64%. The catalyst contained a small amount of $Ni^{II}OTs(2\text{-}Naphthyl)(PCy_3)_2$, as indicated by a small peak in ^{31}P NMR. Yellow solid, m.p. 149 ^{o}C. ^{1}H NMR (500 MHz, C_6D_6) δ 10.86 (d, J = 15.3, 1H), 8.18 (d, J = 7.9, 2H), 7.77 (d, J = 6.9, 2H), 7.56 (d, J = 8.0, 1H), 7.48 – 7.35 (m, 2H), 7.31 (d, J = 7.6, 1H), 7.11 (t, J = 7.5, 1H), 7.02 (d, J = 7.8, 2H), 2.51-2.13 (br, 6H), 2.13 (s, 3H), 2.13 – 0.80 (br, 60H). ^{31}P NMR (203 MHz, C_6D_6) δ 11.04. ^{13}C NMR (126 MHz, C_6D_6) δ 143.4, 141.3, 139.4, 136.5, 135.4, 132.5, 128.3, 128.2, 128.0, 127.1, 125.3, 123.7, 123.5, 122.2, 34.0, 31.6, 30.6, 30.0, 27.7, 26.5, 22.7, 20.7. $[M+H]^+$ calcd for $C_{53}H_{81}NiO_3P_2S$, 917.473, LC/MS found 917.057. $[M\text{-}OTs]^+$ calcd for $C_{46}H_{73}NiP_2$, 745.4541, HRMS found 745.4539, $[M\text{-}OTs + MeCN]^+$ calcd for $C_{48}H_{76}NNiP_2$, 786.4806, HRMS found 786.4839.



(**9**) The reaction was carried out following the general procedure from 2-naphthyl 4-methylbenzenesulfonate (108. 5 mg, 0. 36 mmol), with $Ni(COD)_2$ (100 mg, 0.36 mmol). Yield: 182 mg, 55%. Yellow solid, m.p. 112-113 ^{o}C. ^{1}H NMR (500 MHz, C_6D_6) δ 8.40 (d, J = 7.0, 1H), 8.07 (d, J = 6.5, 2H), 7.79 (s, 1H), 7.59 (dd, J = 21.9, 7.6, 2H), 7.32 (d, J = 4.7, 1H), 7.26 (t, J = 7.3, 1H), 6.92 (d, J = 6.9, 2H), 2.35-1.99 (br, 11H), 1.99 (s, 3H), 1.99-0.83 (br, 63H). ^{31}P NMR (203 MHz, C_6D_6) δ 10.99. ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.4, 139.5, 137.1, 136.9, 132.4, 130.6, 128.4, 128.0, 127.0, 125.3, 125.0, 123.6, 122.7, 34.1, 31.6, 30.2, 29.9, 27.5, 26.5, 20.7. $[M\text{-}OTs]^+$ calcd for $C_{46}H_{73}NiP_2$, 745.454, LC/MS found 745. 611. $[M+MeCN+Na]^+$ calcd for $C_{55}H_{83}NNaNiO_3P_2S$, 980.482, LC/MS found 980.470. $[M\text{-}OTs]^+$ calcd for $C_{46}H_{73}NiP_2$, 745.4541, HRMS found 745.4555.



(**10**) The reaction was carried out following the general procedure from 1-naphthyl methanesulfonate (163 mg, 0. 72 mmol), with $Ni(COD)_2$ (200 mg, 0.72 mmol). Yield: 482 mg, 79%. Yellow solid, m.p. 139-143 ^{o}C. The catalyst had small amount of impurity after 24 h of drying under vacuum by ^{31}P NMR. The crude was used for reactivity tests. ^{1}H NMR (500 MHz, Benzene-d_6) δ 10.96 (d, J = 8.7 Hz, 1H), 7.74 (s, 1H), 7.64 (s, 1H), 7.54 (s, 1H), 7.39 (d, J = 9.3 Hz, 1H), 7.10 (s, 1H), 3.67 (s, 2.8H), 2.87 (s, 3H), 1.10 (s, 77H). ^{31}P NMR (203 MHz, Benzene-d_6) δ 10.01, 9.67. ^{13}C NMR (126 MHz, C_6D6) δ 141.27, 136.29, 135.12, 132.30, 128.19, 127.17, 125.24, 123.85, 123.60, 122.16, 67.46, 40.34, 33.84, 31.40, 31.30, 30.53, 29.84, 27.80, 27.68, 26.55, 25.46. Anal. calcd for $C_{47}H_{76}NiO_3P_2S(C_4H_8O)_{0.7}(C_6H_{14})_{0.5}$: C, 67.85; H, 9.48. Found: C 67.67; H, 9.16. The ratio of THF and hexanes to the nickel complex was determined by ^{1}H NMR spectroscopy.



(**11**) The reaction was carried out following the general procedure from 2-naphthyl methanesulfonate (163 mg, 0. 72 mmol), with $Ni(COD)_2$ (200 mg, 0.72 mmol). Yield: 458 mg, 75%. Yellow solid, m. p. 123 ^{o}C. ^{1}H NMR (500 MHz, Benzene-d_6) δ 8.41 (s, 1H), 7.74 (s, 1H), 7.66 – 7.44 (m, 2H), 7.26 (m, 2H), 3.57 (s, 3H, THF), 2.74 (s, 3H), 1.73-1.13 (m, 74H). ^{31}P NMR (203 MHz, Benzene-d_6) δ 9.84. ^{13}C NMR (126 MHz, Benzene-d_6) δ 136.6, 136.5, 132.5, 128.2, 128.0, 126.3, 125.9, 125.3, 125.0, 123.6, 122.7, 34.6, 33.8, 30.2, 30.0, 29.8, 27.6, 26.5, 25.5. Anal. calcd for $C_{47}H_{76}NiO_3P_2S(C_4H_8O)_{0.7}$: C, 67.09; H, 9.15. Found: C 66.99; H, 8.90. The ratio of THF to the nickel complex was determined by ^{1}H NMR spectroscopy.

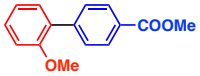
4.2.3.6 General Procedure for Kinetic Experiments

Sampling Kinetic Experiment Without Additional PCy_3. In an oven dried test tube (15 mm x 85 mm) charged with a stirring bar (5/8'' x 5/16'') were added 2-methoxyphenyl dimethyl sulfamate (69.40 ± 0.10 mg, 0. 3 mmol, 1 equiv), methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (78.15 + 0.10 mg, 0.315 mmol, 1.05 equiv), $Ni^{II}Cl(1\text{-Naphthyl})(PCy_3)_2$ (11.73 ± 0.0510 mg, 0.015 mmol, 5% catalyst loading) and $K_3PO_4(H_2O)_n$ (191.00 ± 1.00 mg, ~ 9 mmol, ~ 3 equiv). The test tube was brought into a nitrogen filled glove box (moisture level < 10 ppm) through three degassing cycles. Distilled THF (1 mL) was added inside the glove box and the test tube was sealed by a rubber septum and left stirring for 60 min. A sample was taken by syringe and transferred outside the glove box. The sample was diluted by distilled THF (0.2 mL) and filtered through a short column of silica gel. The filtrate was concentrated and the GC analysis was carried out.

Sampling Kinetic Experiment with Additional PCy_3 (10%). Inside a nitrogen filled glove box, a 20 mL vial was charged with a stirring bar, PCy_3 (37.1 mg) and distilled THF (4.5 mL). The vial was screw closed and kept stirring. The solution was prepared prior to the kinetic experiments and kept inside the glove box for less than 4 h to prevent the oxidation of PCy_3 and evaporation of

THF. Outside the glove box, in an oven dried test tube (15 mm x 85 mm) charged with a stirring bar (5/8'' x 5/16'') were added 2-methoxyphenyl dimethyl sulfamate (69.40 ± 0.10 mg, 0. 3 mmol, 1 equiv), methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (78.15 + 0.10 mg, 0.315 mmol, 1.05 equiv), $Ni^{II}Cl(1\text{-Naphthyl})(PCy_3)_2$ (11.73 ± 0.050 mg, 0.015 mmol, 5% catalyst loading) and $K_3PO_4(H_2O)_n$ (191.00 ± 1.00 mg, ~ 9 mmol, ~ 3 equiv). The test tube was brought into a nitrogen filled glove box (moisture level < 10 ppm) through three degassing cycles. PCy_3 in THF (1 mL) was added inside the glove box. The test tube was sealed by a rubber septum and left stirring for 60 min. A sample was taken by syringe and transferred outside the glove box. The sample was diluted by distilled THF (0.2 mL) and filtered through a short column of silica gel. The filtrate was concentrated and the GC analysis was carried out. The results are summarized in Table SI 1-8. The product was isolated by silica gel column chromatography with 10% ethyl acetate in hexanes.

Sampling Kinetic Experiments with as Received THF. As received, wet THF was used from a commercial source (Fisher certified grade), containing ~0.025% butylated hydroxytoluene, about five months after opening and purged by N_2 for 30 min prior to use. In an oven dried test tube (15 mm x 85 mm) charged with a stirring bar (5/8'' x 5/16'') were added 2-methoxyphenyl dimethyl sulfamate (69.40 ± 0.10 mg, 0. 3 mmol, 1 equiv), methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (78.15 + 0.10 mg, 0.315 mmol, 1.05 equiv), $Ni^{II}Cl(1\text{-Naphthyl})(PCy_3)_2$ (11.73± 0.10 mg, 0.015 mmol, 5% catalyst loading) and $K_3PO_4(H_2O)_n$ (191.00 ± 1.00 mg, ~ 9 mmol, ~ 3 equiv). The test tube was brought into a nitrogen filled glove box (moisture level < 10 ppm) through three degassing cycles. Wet THF (1 mL) was added inside the glove box and the test tube was sealed by a rubber septum and left stirring for 60 min. A sample was taken by syringe and transferred outside the glove box. The sample was diluted by distilled THF (0.2 mL) and filtered through a short column of silica gel. The filtrate was concentrated and the GC analysis was carried out.



3: Isolated after kinetics experiments. Purified by silica gel column chromatography with hexanes to 10% ethyl acetate in hexanes gradient. White solid, m.p. 47.5-49 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 7.6, 1H), 7.50 (t, J = 7.5, 1H), 7.37 (t, J = 8.3, 2H), 7.25 (d, J = 8.6, 2H), 6.94 (d, J = 8.5, 2H), 3.85 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 159.1, 131.3, 131.0, 130.9, 129.9, 129.6, 127.0, 113.7. Spectroscopy data matches with literature data.[23]

Isolated yields are listed in Table SI 9. ^{1}H and ^{13}C NMR spectra are listed in section 4.2.4.

Sample Procedures for Drying $K_3PO_4(H_2O)_n$ and Measuring Water Content:

Measuring Water Content in $K_3PO_4(H_2O)_n$ by Weight Loss:

In a tared round bottom flask (47.6791 g, average of three measurements within instrumental error) fitted with an adapter were added $K_3PO_4(H_2O)_n$ (48.9636 g for flask and base). The round bottom flask was heated by a Fischer burner until the visible water was evaporated. The flask was then connected to vacuum and flame dried until constant mass (flask + base: 48.6924 g, average of three measurements within instrumental error). The value of n is determined by the following equation:

$$n = \frac{mole\ (H_2O)}{mole\ (K_3PO_4)} = \frac{m(H_2O)/M_w(H_2O)}{m(K_3PO_4)/M_w(K_3PO_4)} = \frac{\frac{(48.9636-48.6924)g}{18.02g/mol}}{\frac{(48.6924-47.6791)g}{212.27g/mol}} = 3.2$$

The water content determination is more accurate with large amount of base. To minimize error induced by dehydration of glassware, water content determination with smaller round bottom flask (25 mL) are more accurate compared to large ones (250 mL) when the water content of base is determined.

Drying $K_3PO_4(H_2O)_n$ to Predetermined n:

The amount of weight loss desired is calculated from following equation:

$$m(mass\ loss) = m_1 \frac{18.02(n_1 - n_2)}{(212.27 + 18.02 \times n_1)}$$

where: m_1 is the mass of the $K_3PO_4(H_2O)n_1$ from commercial source;

n_1 is the water content determined by weight loss in commercial source

n_2 is the desired water content.

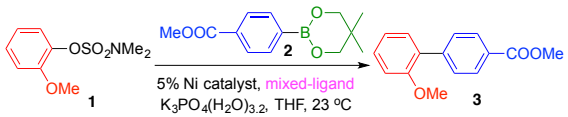
Drying procedure for base with n = 3.2:

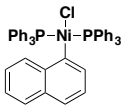
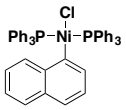
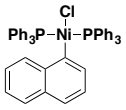
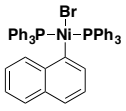
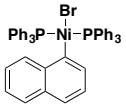
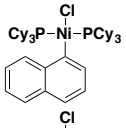
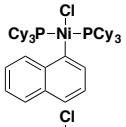
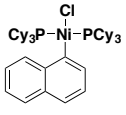
From the equation above, for 23.8093 g of $K_3PO_4(H_2O)_7$, the desired weight loss was calculated to be 4.9 g. In a tared round bottom flask (250 mL) fitted with an adapter were added a stirring bar, $K_3PO_4(H_2O)_7$ (23.8093 g, hydrous, tribasic from commercial source) were added and dried at 40 ^oC under vacuum. After 6 h, the mass of the flask with the base was weighed and 4.8841 g water was lost. The base was ground and the exact amount of water was then verified to be 3.2 by the method above.

Kinetics experiments were carried out with bases dried by these procedures and the results are provided in Table SI 2.

4.2.3.7 Supporting Data for Kinetic Experiments

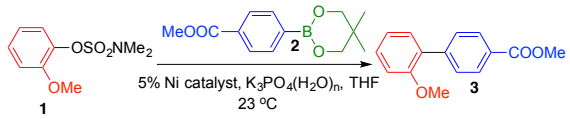
Table SI 1. Supporting Data for Scheme 4.5[a]

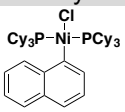
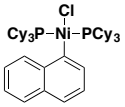
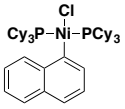
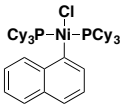
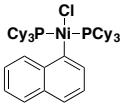
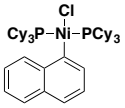
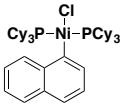
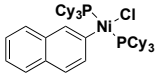
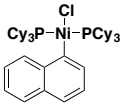
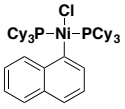
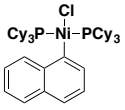


entry	catalyst	mixed-ligand (%)	time (h)	convn/yield (%)	compound number
1	$Ni(COD)_2$	PPh_3 (10)	90	6.9	
2	$Ni(COD)_2$	PCy_3 (10)	1	71/71	**3a**
3	$Ni(COD)_2$	PCy_3 (20)	1	92/89	**3b**
4		PCy_3 (10)	1 24 48 70	61 95 96 100/96	**3c**
5		PCy_3 (15)	48 56	99 100	
6		PCy_3 (20)	24	100/95	**3d**
7		PCy_3 (10)	48 70	96 100/94	**3e**
8		PCy_3 (15)	48 57	99 100	
9*			0.7 0.9	98 100	
10		COD (10)	1 2	44 57/50	**3f**
11		PPh_3 (10)	1 2	53 60/48	**3g**

[a]Conversion by GC, isolated yield, both as percentages.

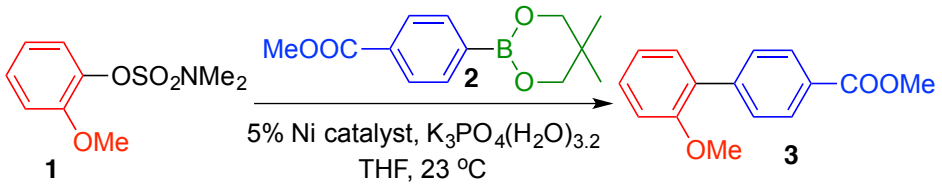
Table SI 2. Supporting Data for Scheme 4.4

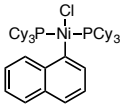
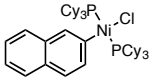
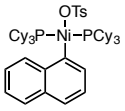
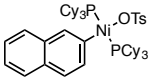
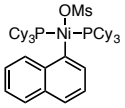
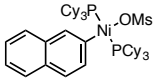


entry	catalyst	THF	n	time (min)	convn (%)
1*		dry	1.0	70 270 990 1620	16 45 92 100
2		dry	3.0	60	100
3		dry	3.1	50 60 70	97 98 99
4		dry	3.2	42 52	97 100
5		dry	3.7	40 50 60	92 95 98
6*		dry	4.7	52 70 80 90	100 97 99 99
7*		dry	7.0	60 90 168	94 97 99
8		dry	2.8	38 58 78 116	75 85 95 98
9		dry	3.2	50 60	99 100/95 (**3h**)
10*		As received	1.0	58 78 116	85 95 98
11*		As received	3.2	50 70 120 160	94 96 99 100
12*		As received	7.0	60 120 180	93 98 99

[a]Conversion by GC, isolated yield, both as percentages.

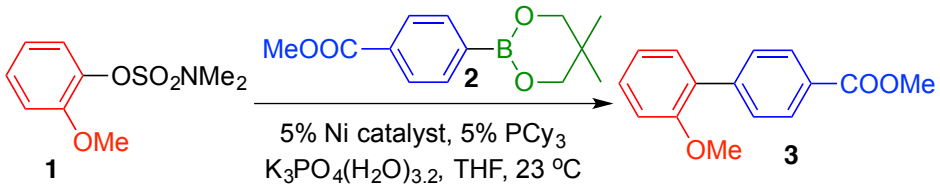
Table SI 3. Supporting Data for Scheme 4.6 **with 0% PCy_3**

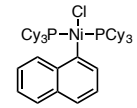
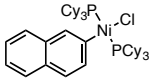
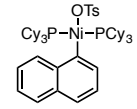
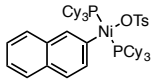
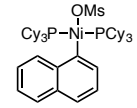
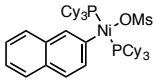


entry	catalyst	time (min)	convn/ yield (%)	time (min)	convn/ yield (%)	time (min)	convn/ yield (%)
1		42	98	50	94	50	97*
		52	100	60	100	60	98*
		-	-	70	100	70	99*
2		50	99	40	98	50	98*
		60	100	50	99	60	99*
		70	100/95 (**3h**)	60	100	70	99*
3		47	97	50	100	50	100*
		57	100	60	100	60	100*
		-	-	70	100	70	100*
4		47	98.0	50	99	50	98*
		57	100	60	100	60	99*
		-	-	70	100	70	100*
5		50	99	50	98	50	97*
		60	99	60	99	60	98*
		70	100/91 (**3i**)	70	99	70	99*
6		42	99	40	95	40	96*
		52	100/95 (**3j**)	50	96	50	99*
		62	100	60	98	60	100*

[a]Conversion by GC as percentages. Reactions were duplicated by three different chemists.

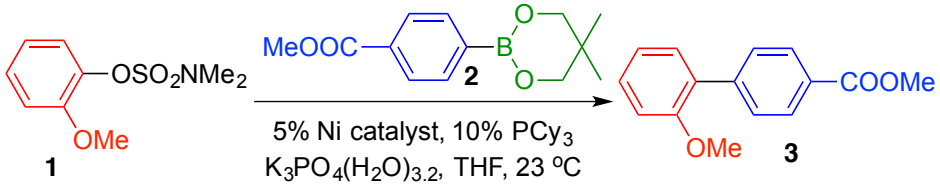
Table SI 4. Supporting Data for Scheme 4.6 **with 5% PCy_3**

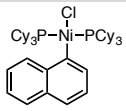
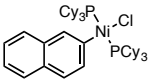
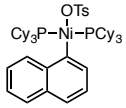
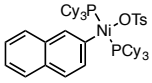
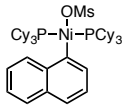
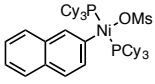


entry	catalyst	time(min)	convn(%)	time(min)	convn(%)
1		30	97	40	96*
		40	99	50	97*
		-	-	60	99*
2		37	99	40	99*
		47	100	50	99*
		-	-	60	100*
3		43	98	40	100*
		53	100	50	100*
		-	-	60	100*
4		-	-	40	99*
		-	-	50	100*
		-	-	60	100*
5		-	-	40	96*
		-	-	50	97*
		-	-	60	99*
6		-	-	40	99*
		-	-	50	99*
		-	-	60	100*

[a]Conversion by GC as percentages. Reactions were duplicated by two different chemists.

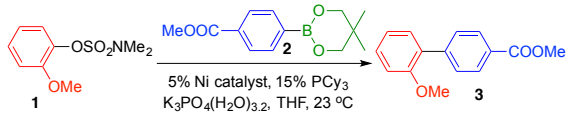
Table SI 5. Supporting Data for Scheme 4.6 **with 10% PCy_3**

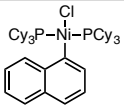
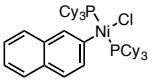
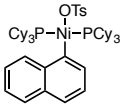
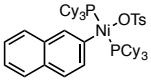


entry	catalyst	time (min)	convn/ yield (%)	time (min)	convn(%)	time (min)	convn(%)
1		38	99	40	98	40	99*
		48	100	50	100	50	99*
		-	-	60	100	60	100*
2		37	99	40	97	40	99*
		47	100	50	99	60	100*
		-	-	60	100	-	-
3		40	94	40	94	40	100*
		50	100	50	99	50	100*
		-	-	60	100	60	100*
4		42	97	40	96	40	100*
		53	100	50	99	50	100*
		-	-	60	100	60	100*
5		40	100/98 (**3k**)	40	97	40	100*
		50	100	50	98	50	100*
		-	-	60	99	60	100*
6		40	98	40	95	40	100*
		50	100	50	96	50	100*
		-	-	60	98	60	100*

[a]Conversion by GC, isolated yields, both as percentages. Reactions were duplicated by three different chemists.

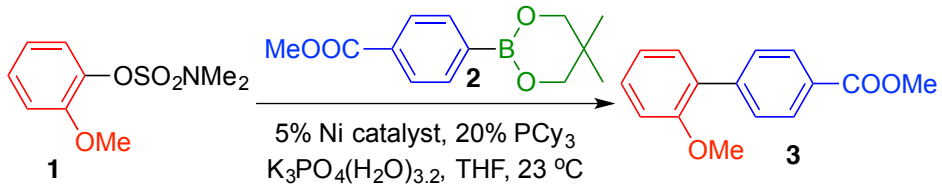
Table SI 6. Supporting Data for Scheme 4.6 **with 15% PCy_3**

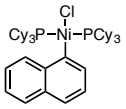
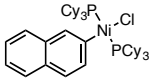
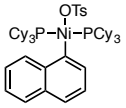
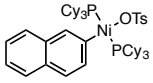
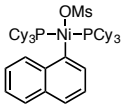
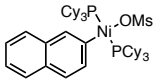


entry	catalyst	time(min)	convn(%)
1		30	99
		40	100
2		34	98
		44	100
3		57	100
		67	100
4		45	97
		55	100
		65	100

[a]Conversion by GC as percentages.

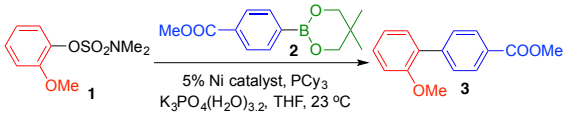
Table SI 7. Supporting Data for Scheme 4.6 **with 20% PCy_3**

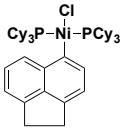
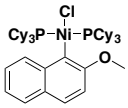
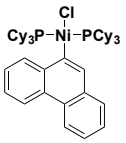
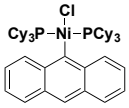


entry	catalyst	time(min)	convn(%)	time(min)	convn(%)
1		40	97/97 (**3l**)	40	97
		50	99	50	97
		-	-	60	97
2		50	99	40	98
		60	100	50	98
		-	-	60	99
3		40	100/99 (**3m**)		
		50	100		
4		40	100		
		50	100/96 (**3n**)		
5		40	100	30	100
		50	100/98 (**3o**)	40	100
6		30	100	30	100
		40	100	40	100

[a]Conversion by GC as percentages. Reactions were duplicated by two different chemists.

Table SI 8. Supporting Data for Scheme 4.7



entry	catalyst	PCy3	time (min)	convn (%)
1		0	40	97
			50	99
			70	99/95 (3p)
		10	50	97
			60	98
			70	99
		20	30	95
			40	99
			50	100
2		0	40	85
			60	95
			70	97
3		0	60	97
			70	99
		10	80	99
			50	98
			60	99
			70	100
		20	40	96
			50	98
			60	99
4		0	40	97
			50	99
			60	100
		10	50	99
			60	100
			70	100
		20	40	96
			50	97
			60	99

aConversion was determined by GC as percentages.

Table SI 9. Isolated Yields and Spectroscopy Data for Kinetics Experiments

entry	compound number	isolated yield (mg)	isolated yield (%)
1	**3a**	51.41	71
2	**3b**	64.45	89
3	**3c**	69.80	96
4	**3d**	68.97	95
5	**3e**	68.32	94
6	**3f**	36.56	50
7	**3g**	34.59	48
8	**3h**	69.19	95
9	**3i**	70.52	91
10	**3j**	68.79	95
11	**3k**	71.09	98
12	**3l**	70.52	97
13	**3m**	72.11	99
14	**3n**	69.42	96
15	**3o**	71.06	98
16	**3p**	69.28	95

4.2.3.8 Experiments to Study the Activation of Precatalyst 6

Procedure for Monitoring the Activation of Precatalyst 6 by ^{1}H NMR

In an oven dried screw cap vial (4 mL) charged with a stirring bar were added methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (78.15 mg, 0.315 mmol, 1.05 equiv), and $K_3PO_4(H_2O)_n$ (191.02 mg, ~ 9 mmol, ~ 3 equiv), in a separate oven dried screw cap vial (4 mL) was added $Ni^{II}Cl(1\text{-Naphthyl})(PCy_3)_2$ (11.72 mg, 0.015 mmol, 5% catalyst loading). The vials were brought into a nitrogen filled glove box (moisture level < 10 ppm) through three degassing cycles (5 min each). Distilled THF (1 mL) was added inside the glove box to the second vial to dissolve $Ni^{II}Cl(1\text{-naphthyl})(PCy_3)_2$ and the solution was transferred to the first vial. The vial was capped and left stirring for 5 min. A sample (100 μL) was taken and injected into an NMR tube. The tube was brought outside the glove box. C_6D_6 (0.5 mL) was added outside the glove box and ^{1}H NMR was carried out right away. The spectra are shown in Figure SI 1.

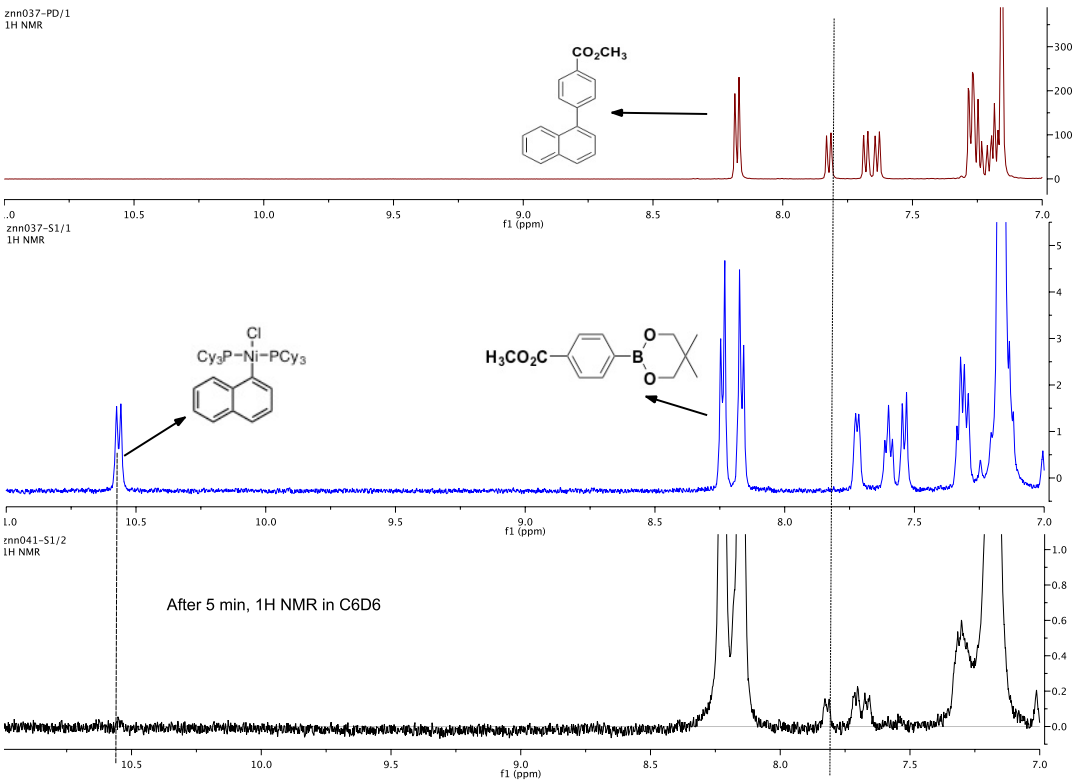


Figure SI 1. Activation of precatalyst **6** monitored by ^{1}H NMR in C_6D_6.

Procedure for Model Reaction of Activation of Precatalyst 6

In an oven dried screw cap vial (4 mL) charged with a stirring bar were added methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (49.60 mg, 0.2 mmol, 2 equiv), $Ni^{II}Cl(1\text{-naphthyl})(PCy_3)_2$ (78.31 mg, 0.1 mmol) and $K_3PO_4(H_2O)_n$ (63.62 mg, ~ 0.3 mmol, ~ 3 equiv). The vial was brought into a nitrogen filled glove box (moisture level < 10 ppm) through three degassing cycles. Distilled THF (1 mL) was added inside the glove box, the vial was capped, and then left stirring for 12 h. The reaction mixture was dissolved in DCM, filtered and concentrated. The crude product was purified by silica gel column chromatography with DCM/hexanes = 1:1 eluent twice. Methyl 4-(naphthalen-1-yl)benzoate (**16**) was isolated to yield: 21.4 mg, 88%. White solid, m.p. 70 ^{o}C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.17 (dd, *J* = 8.3, 2.4 Hz, 2H), 7.90 (dd, *J* = 13.8, 8.2 Hz, 2H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.63 - 7.48 (m, 4H), 7.44 (dd, *J* = 12.8, 7.2 Hz, 2H),

3.97 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 145.7, 139.3, 133.9, 131.38, 130.3, 129.7, 129.2, 128.5, 128.4, 127.1, 126.5, 126.1, 125.8, 125.5, 52.3. NMR spectra match with literature data.[7]

4.2.4 Characterization of the Reaction Products

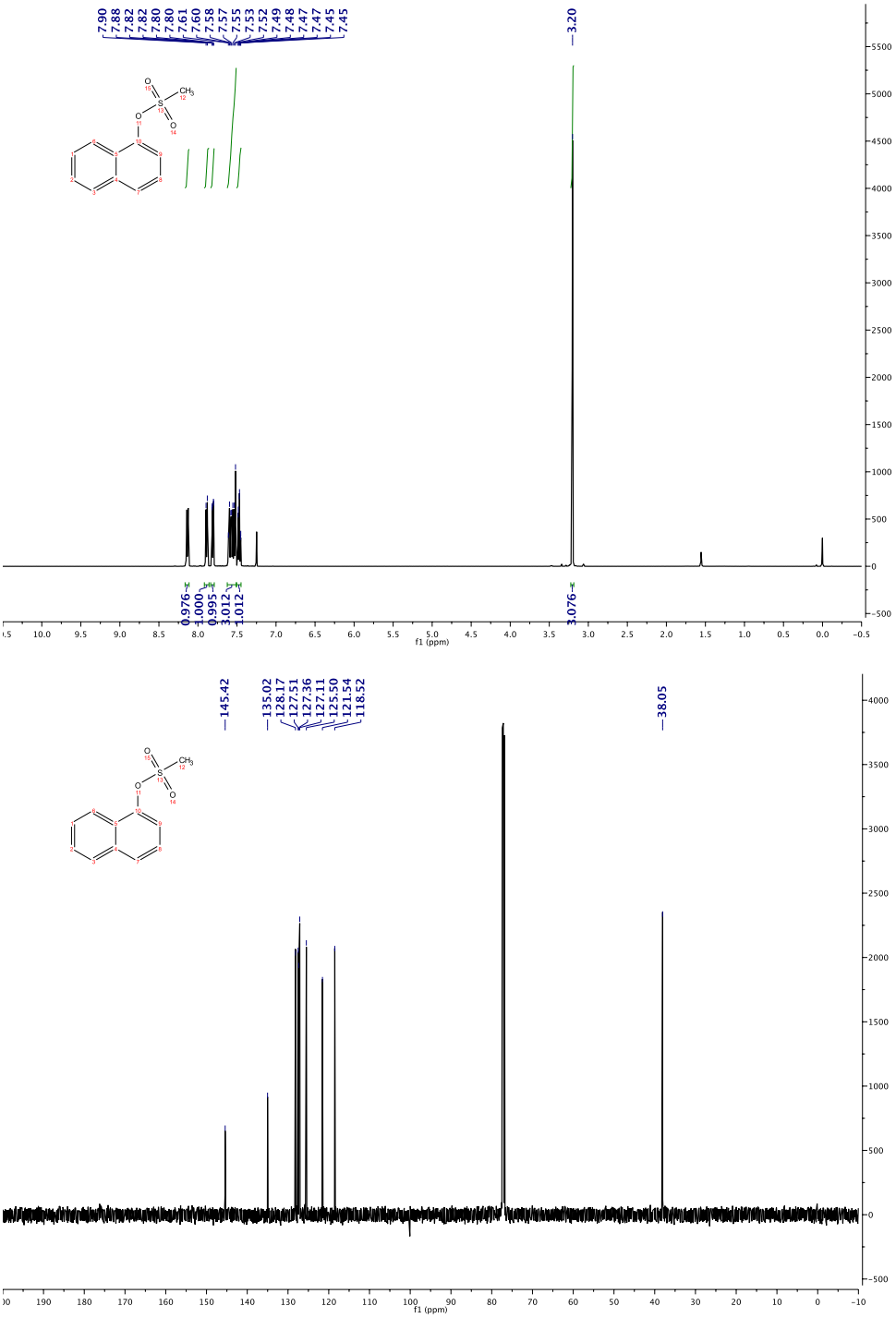


Figure SI 2. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of 1-naphthyl methanesulfonate in $CDCl_3$.

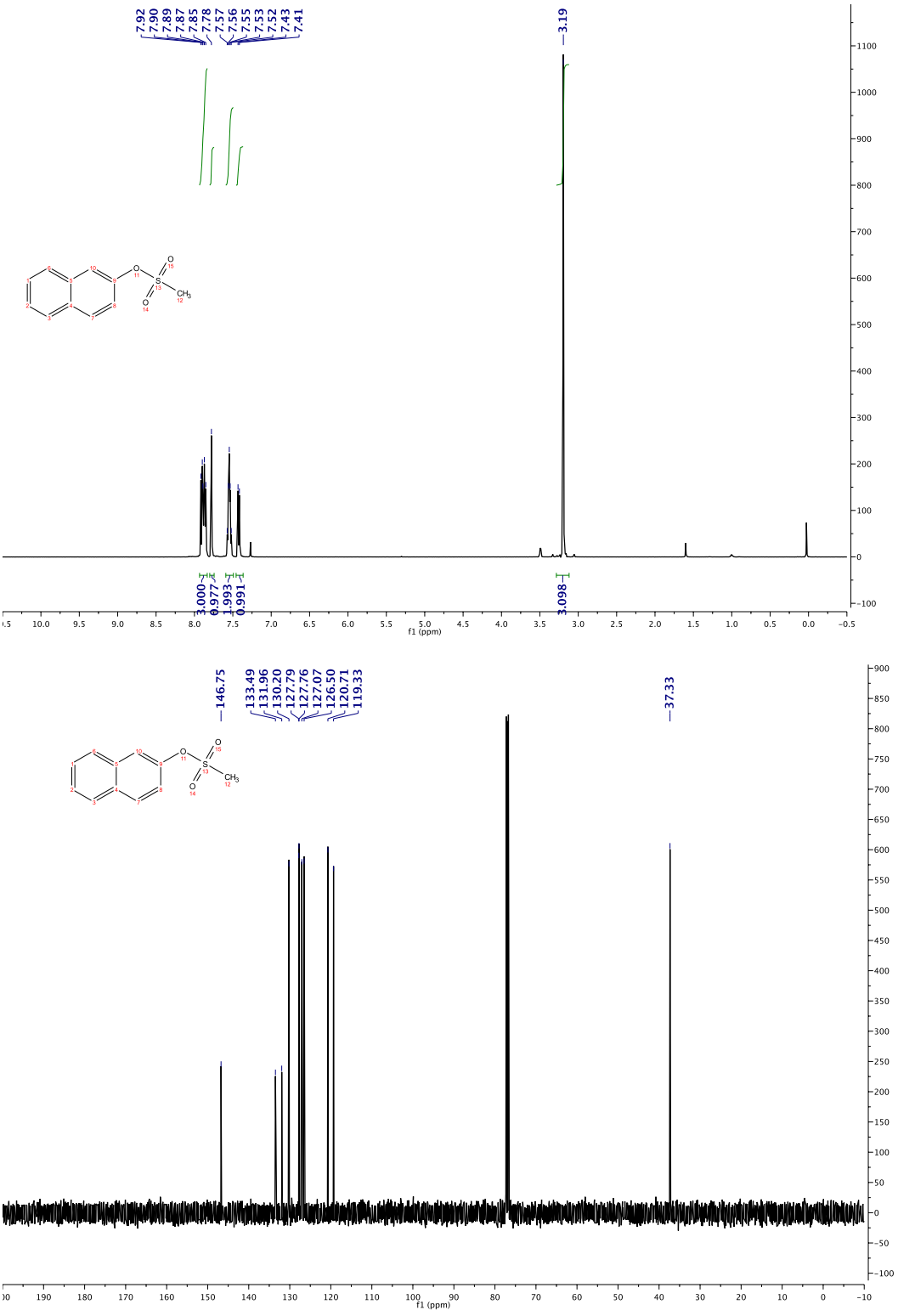


Figure SI 3. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of 2-naphthyl methanesulfonate in $CDCl_3$.

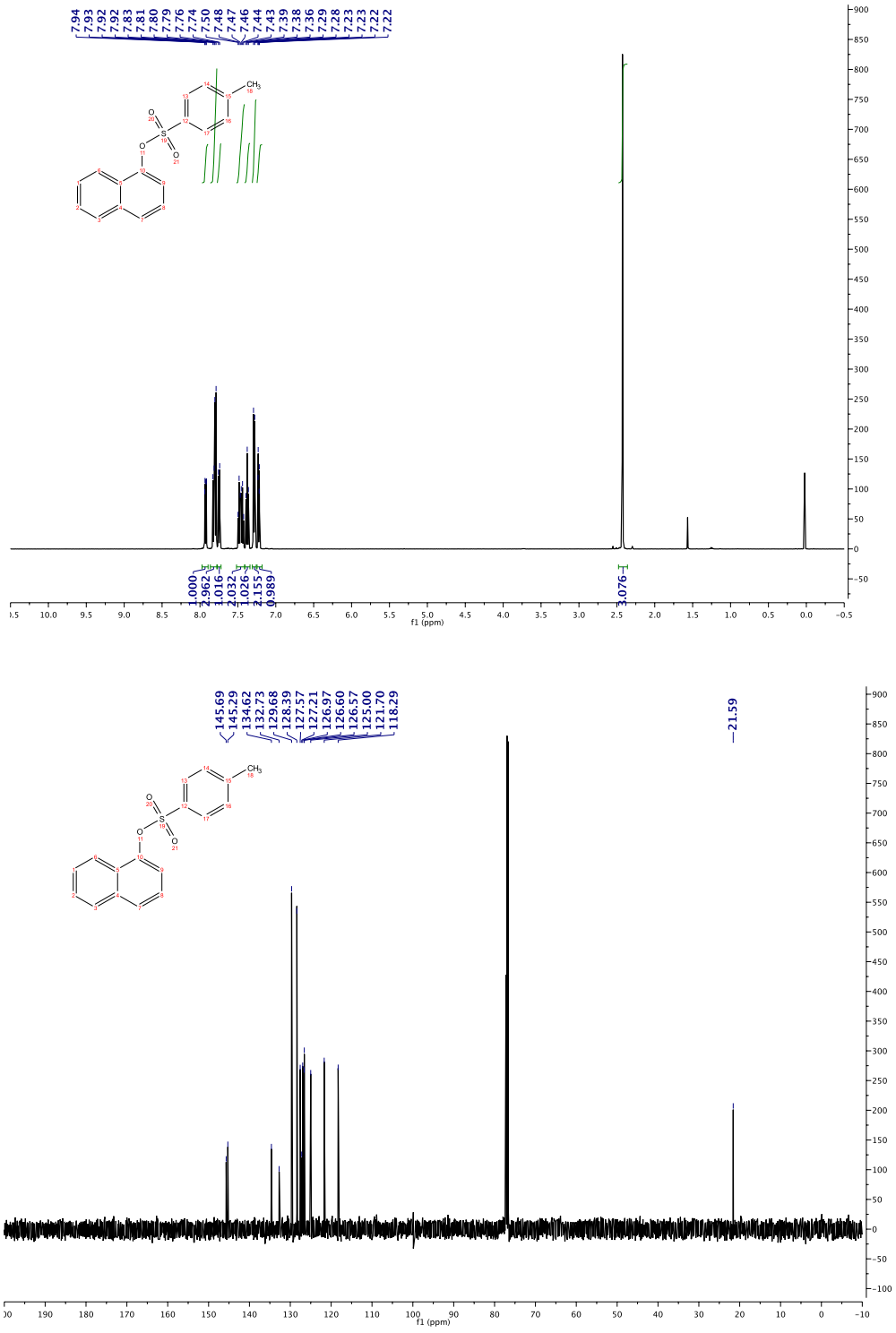


Figure SI 4. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of 1-naphthyl 4-methylbenzenesulfonate in $CDCl_3$.

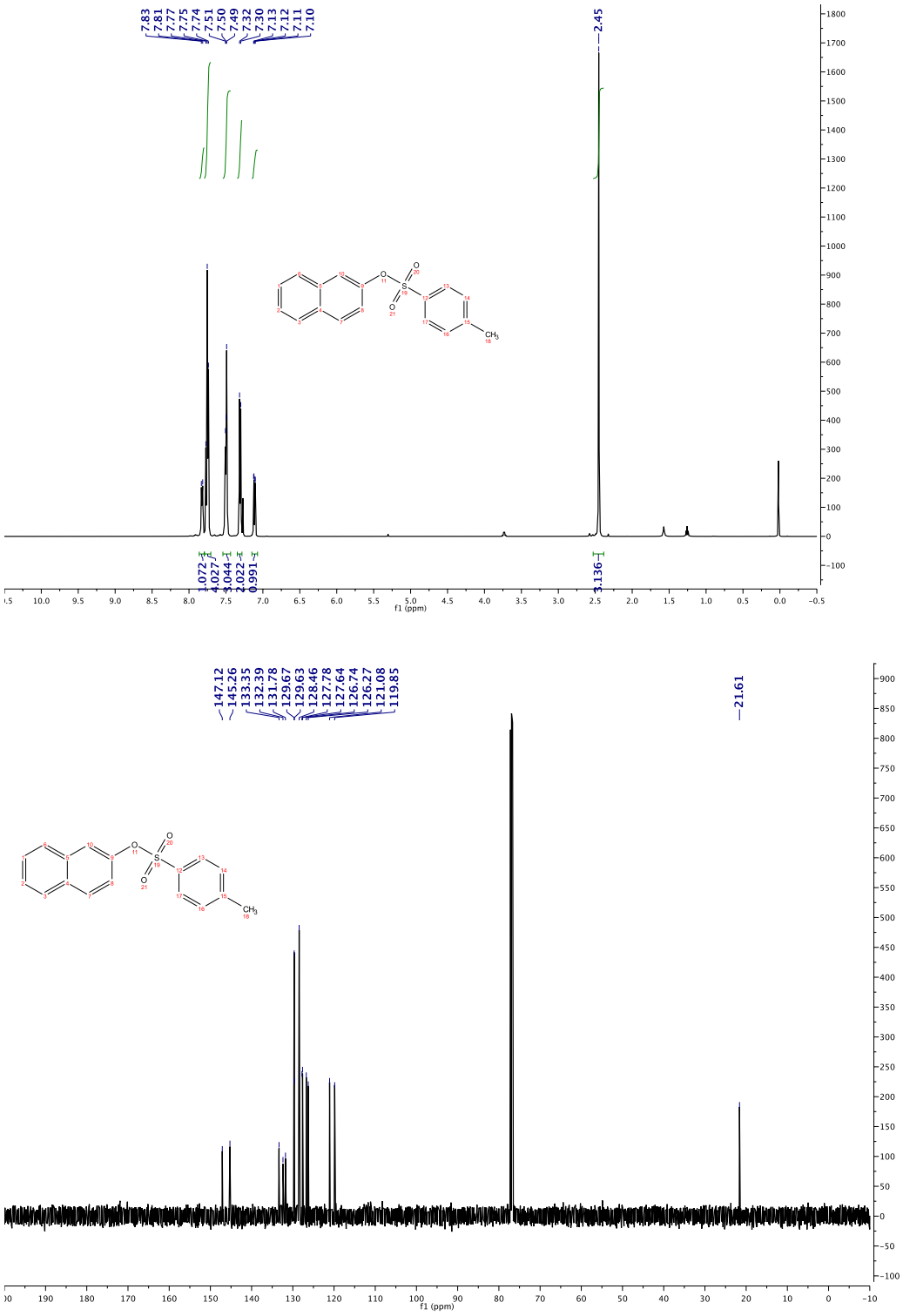


Figure SI 5. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of 2-naphthyl 4-methylbenzenesulfonate in $CDCl_3$.

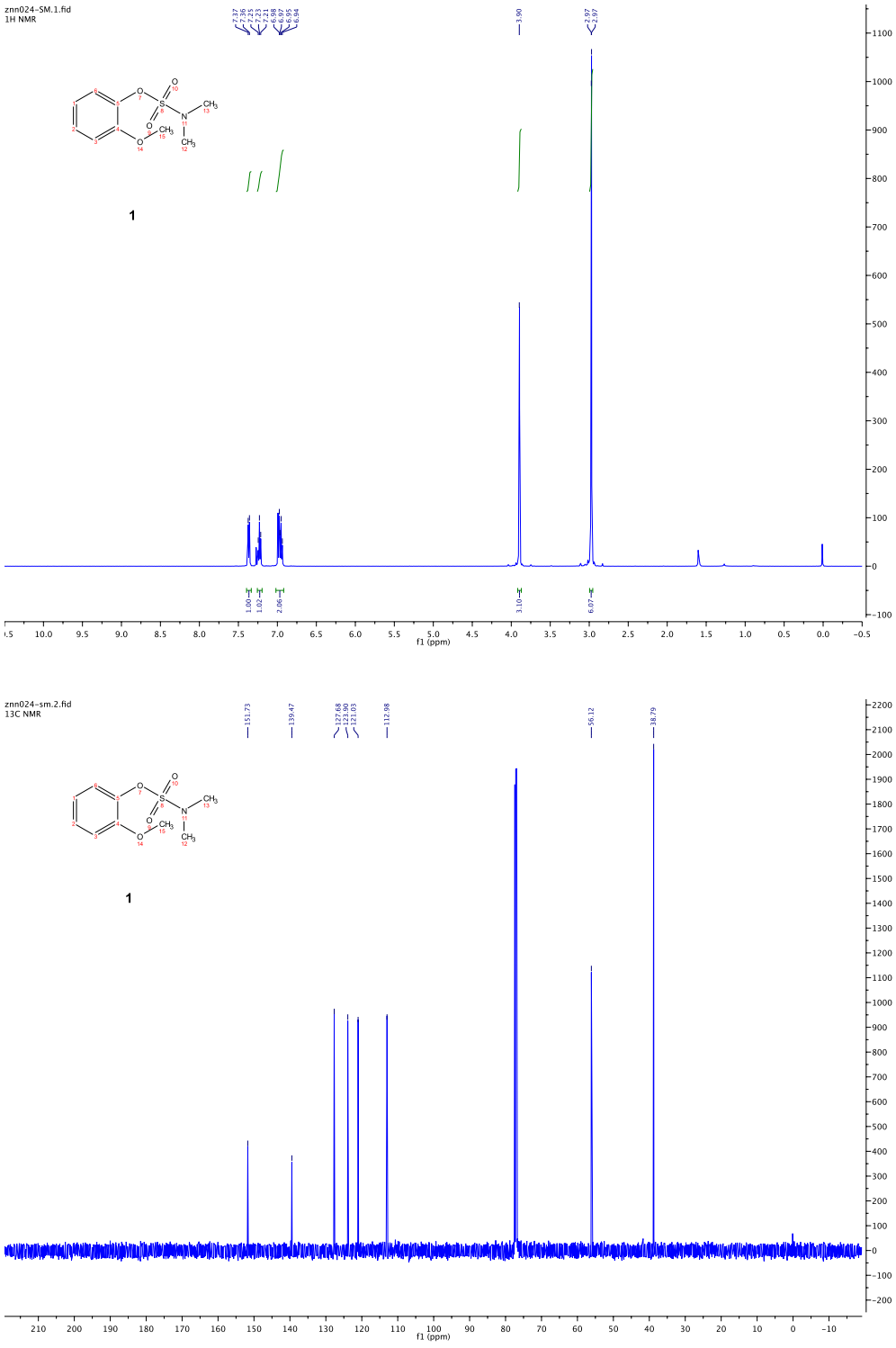


Figure SI 6. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of 2-methoxyphenyl dimethylsulfamate in $CDCl_3$.

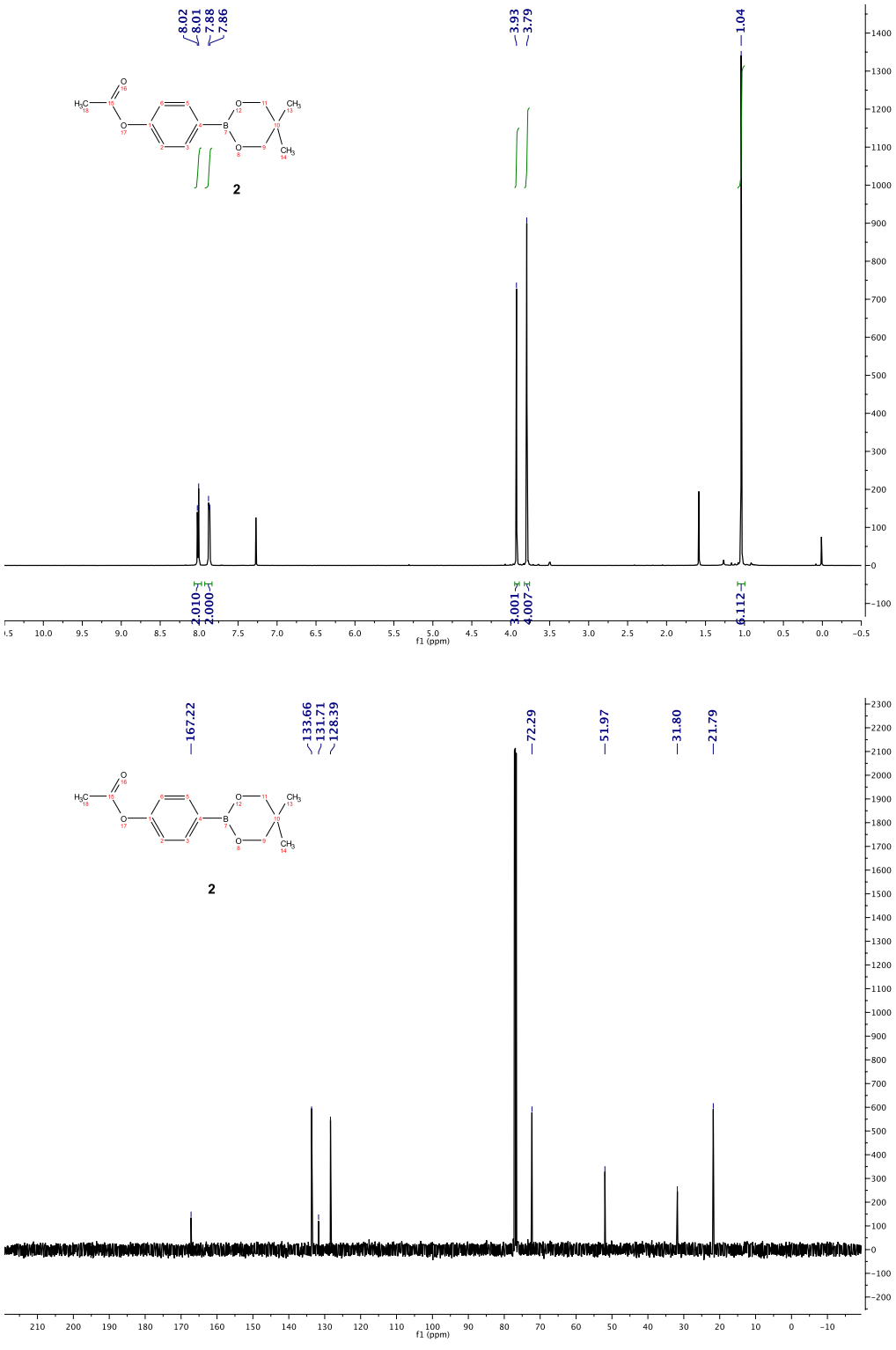


Figure SI 7. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenyl acetate in $CDCl_3$.

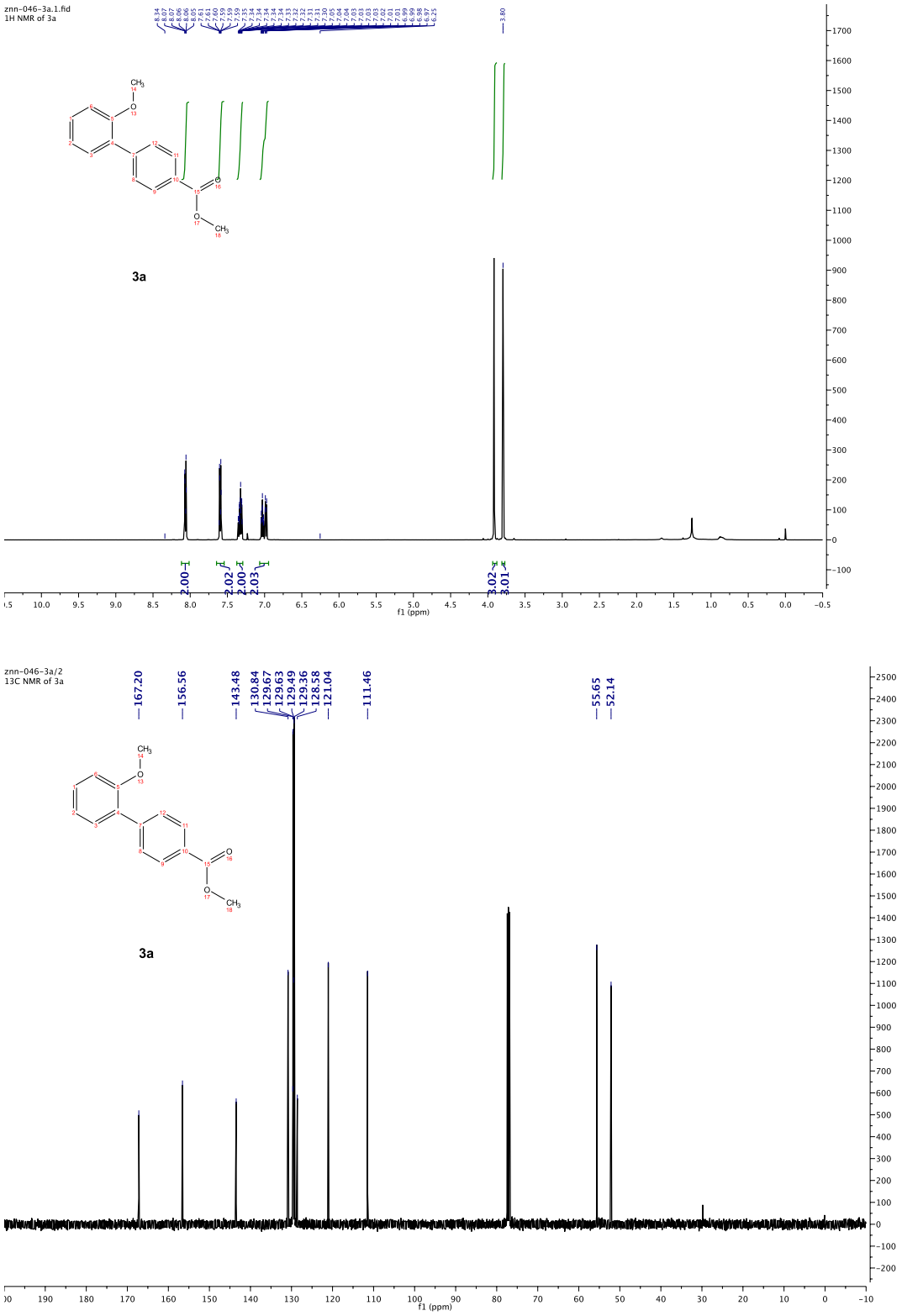


Figure SI 8. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of **3a** in $CDCl_3$.

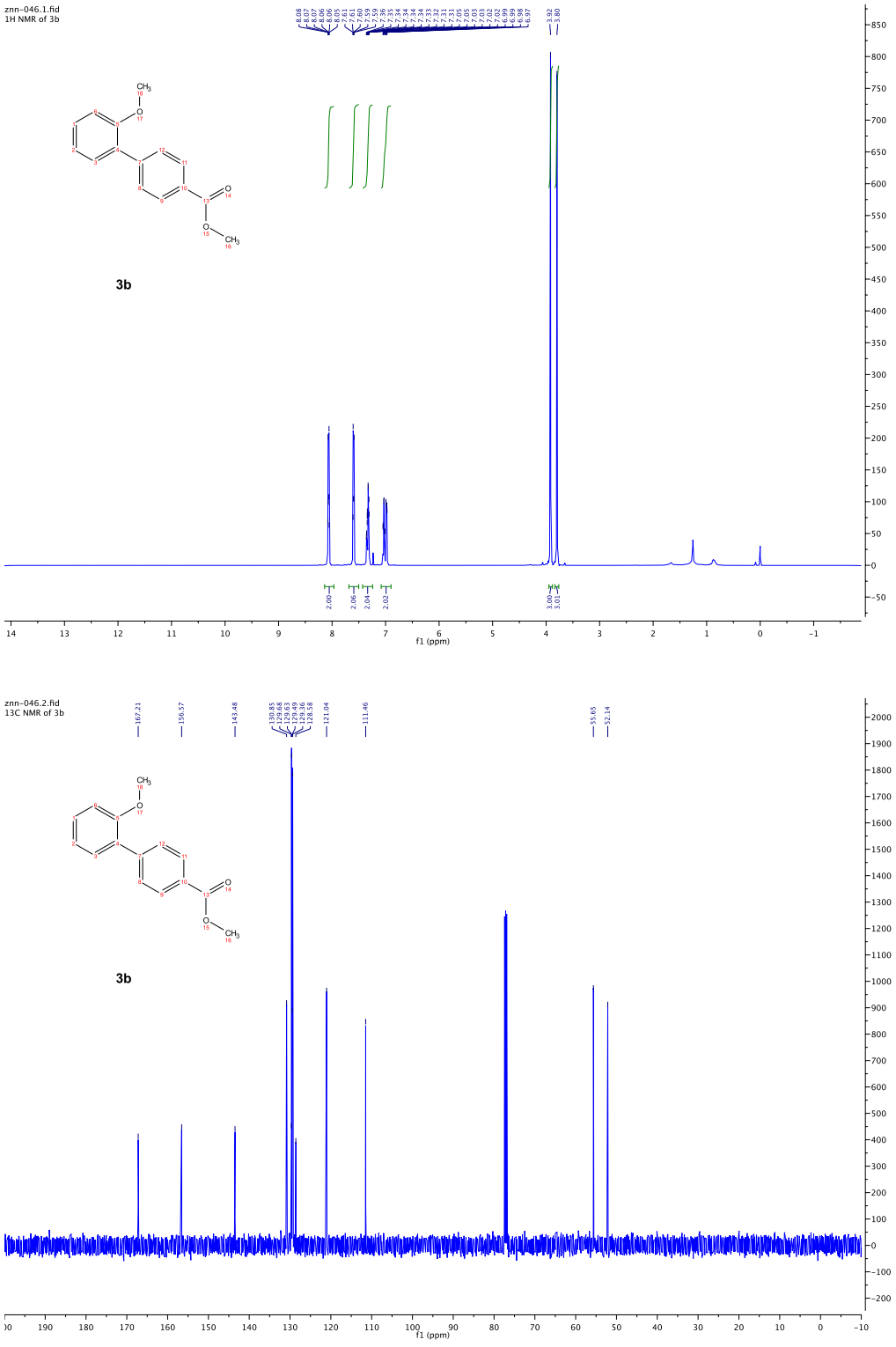


Figure SI 9. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of **3b** in $CDCl_3$.

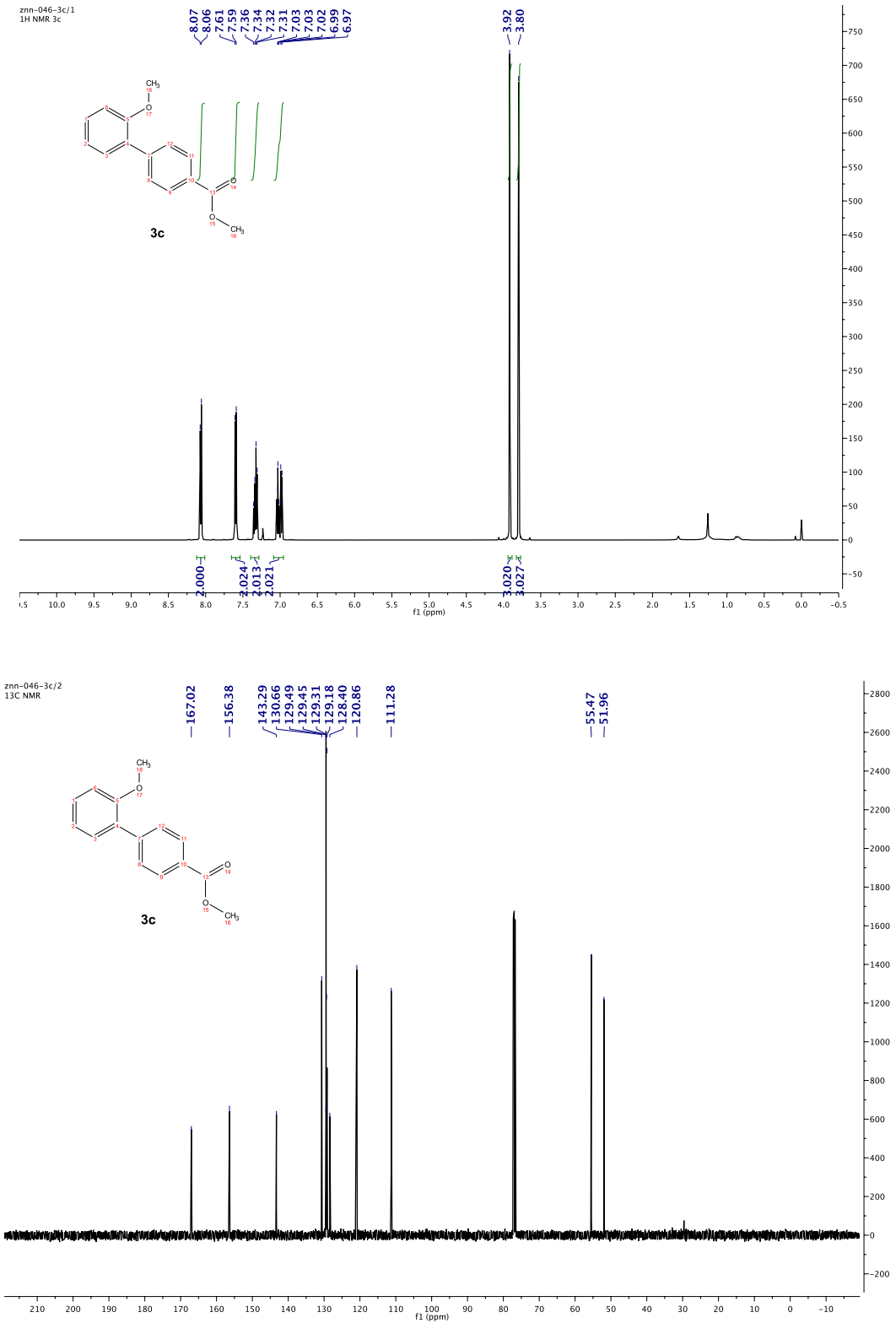


Figure SI 10. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of **3c** in $CDCl_3$.

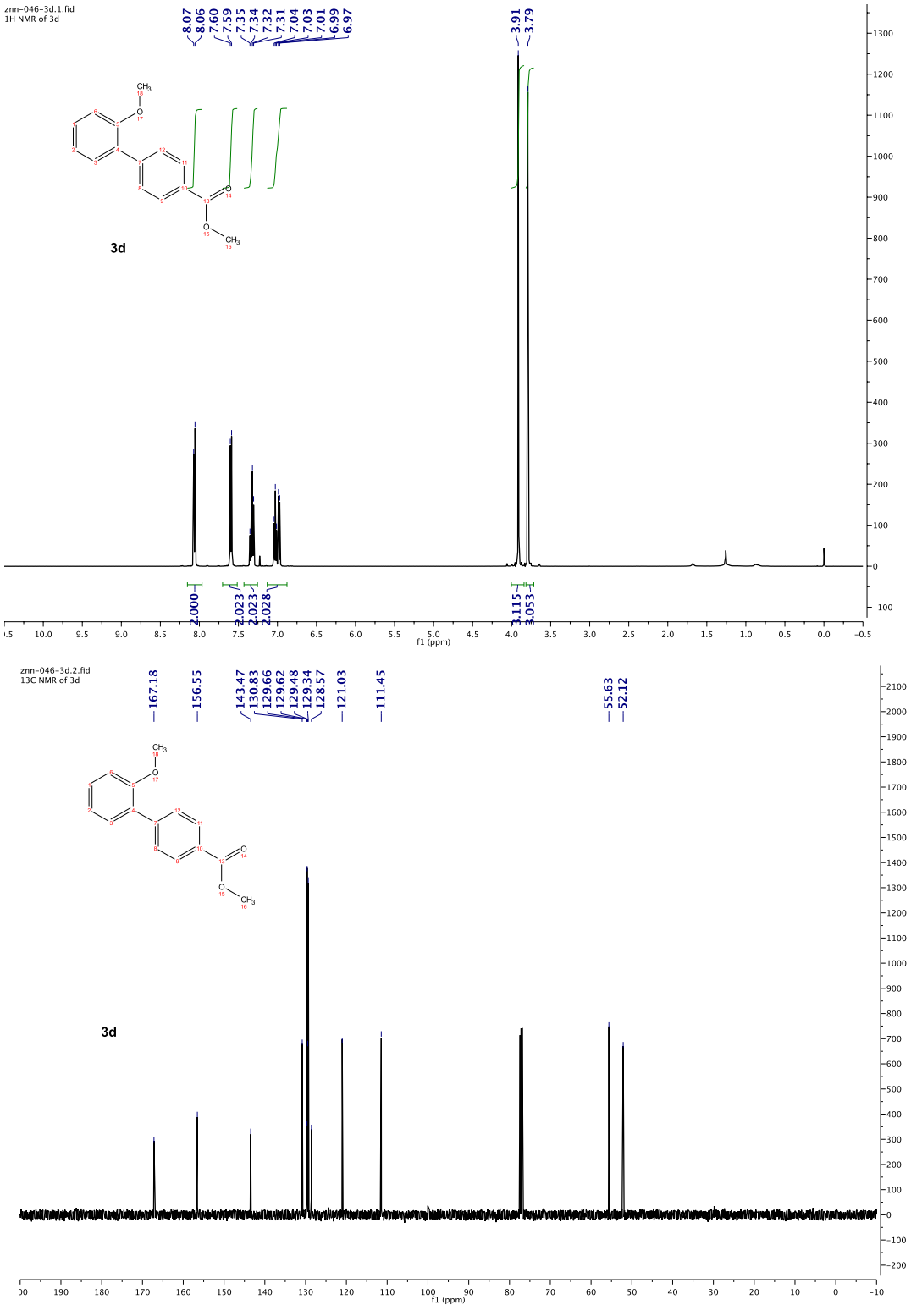


Figure SI 11. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of **3d** in $CDCl_3$.

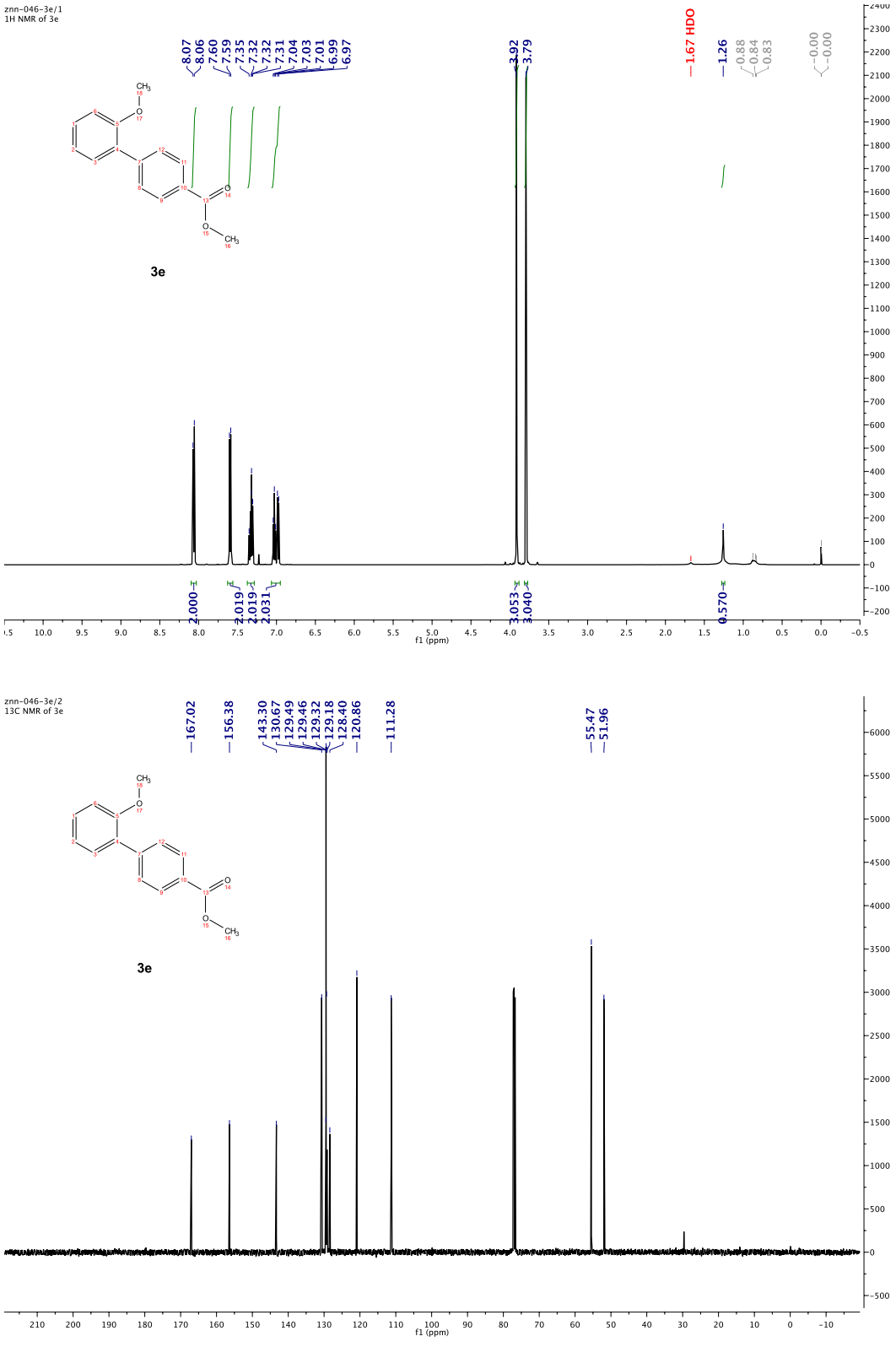


Figure SI 12. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of **3e** in $CDCl_3$.

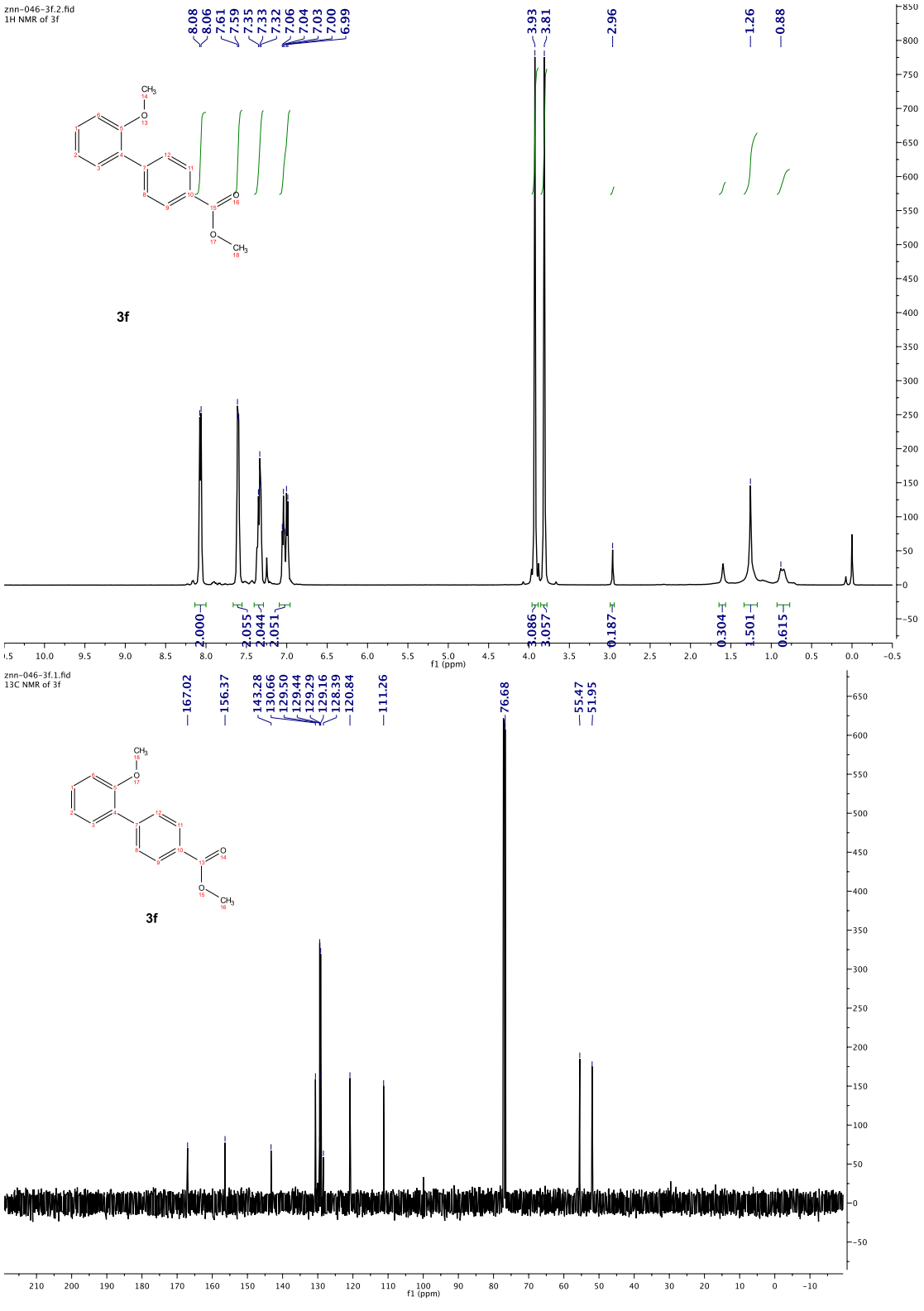


Figure SI 13. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of **3f** in $CDCl_3$.

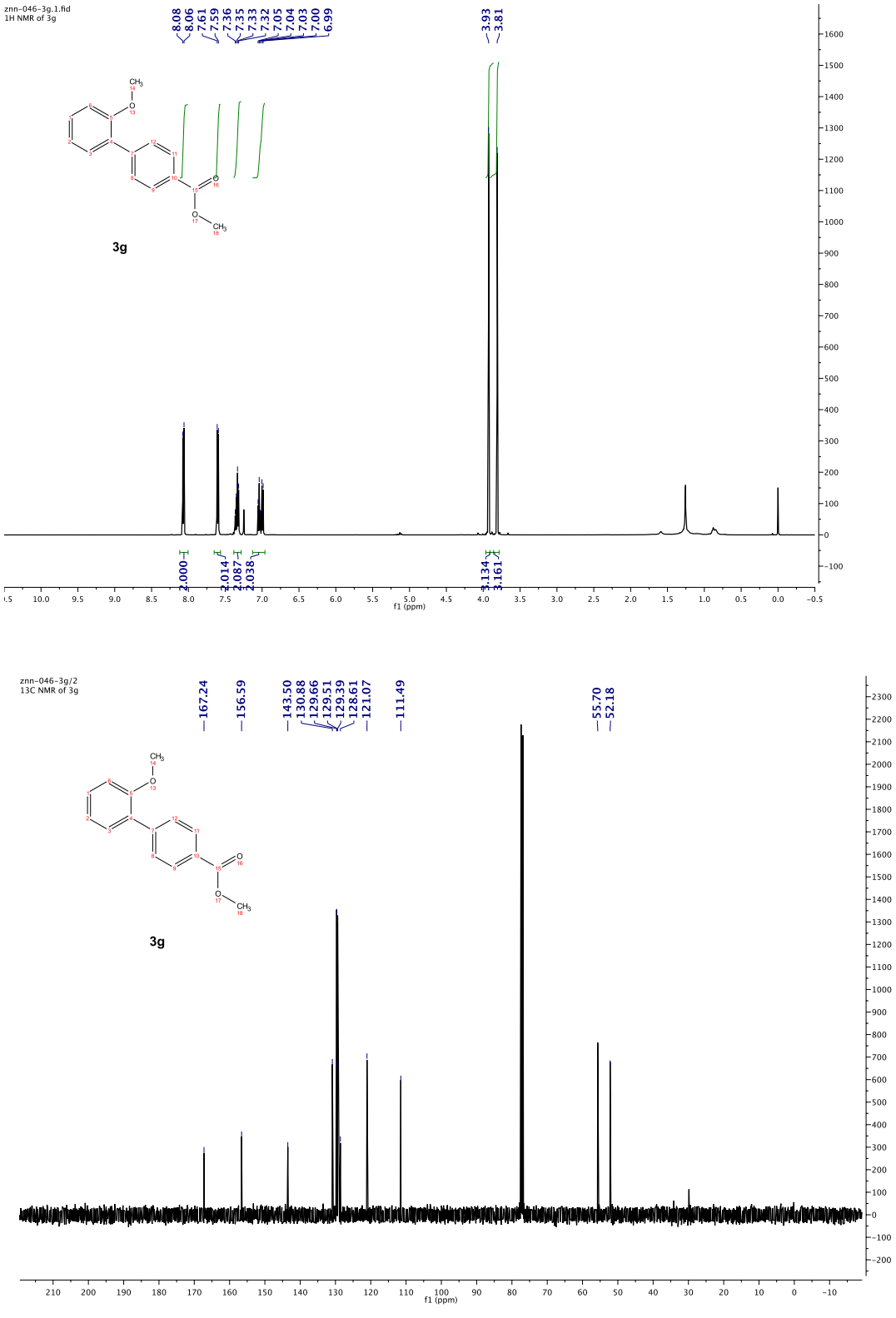


Figure SI 14. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of **3g** in $CDCl_3$.

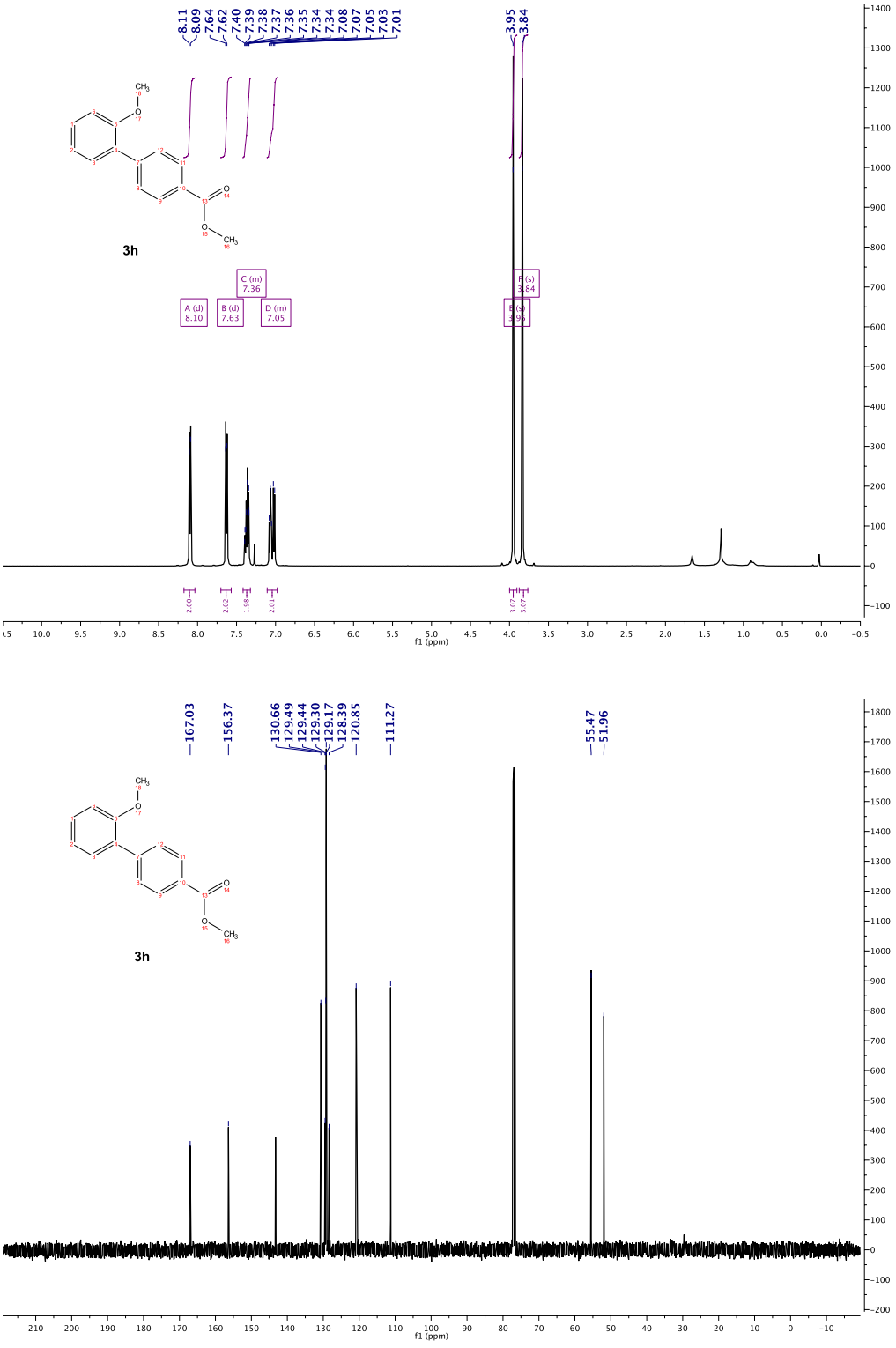


Figure SI 15. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of **3h** in $CDCl_3$.

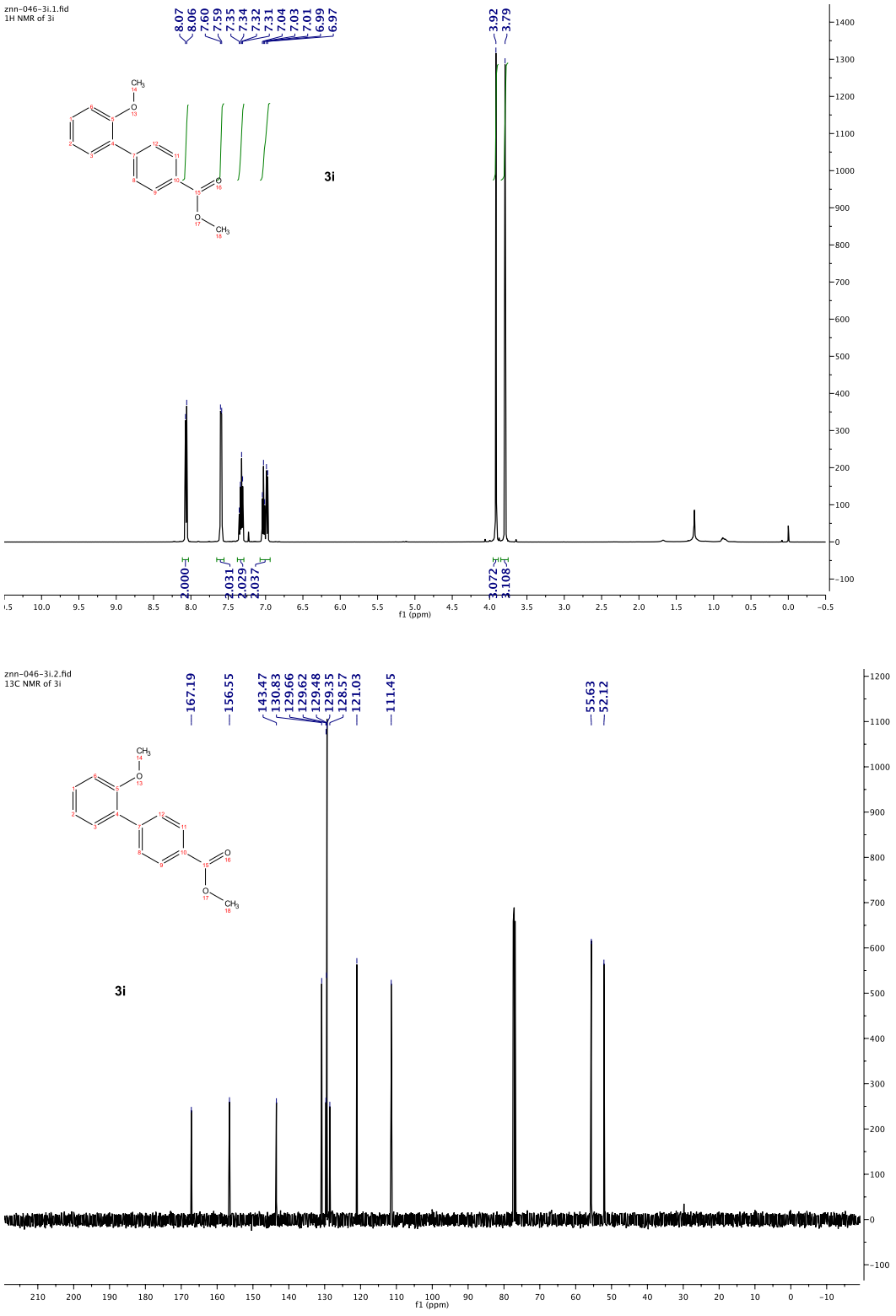


Figure SI 16. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of **3i** in $CDCl_3$.

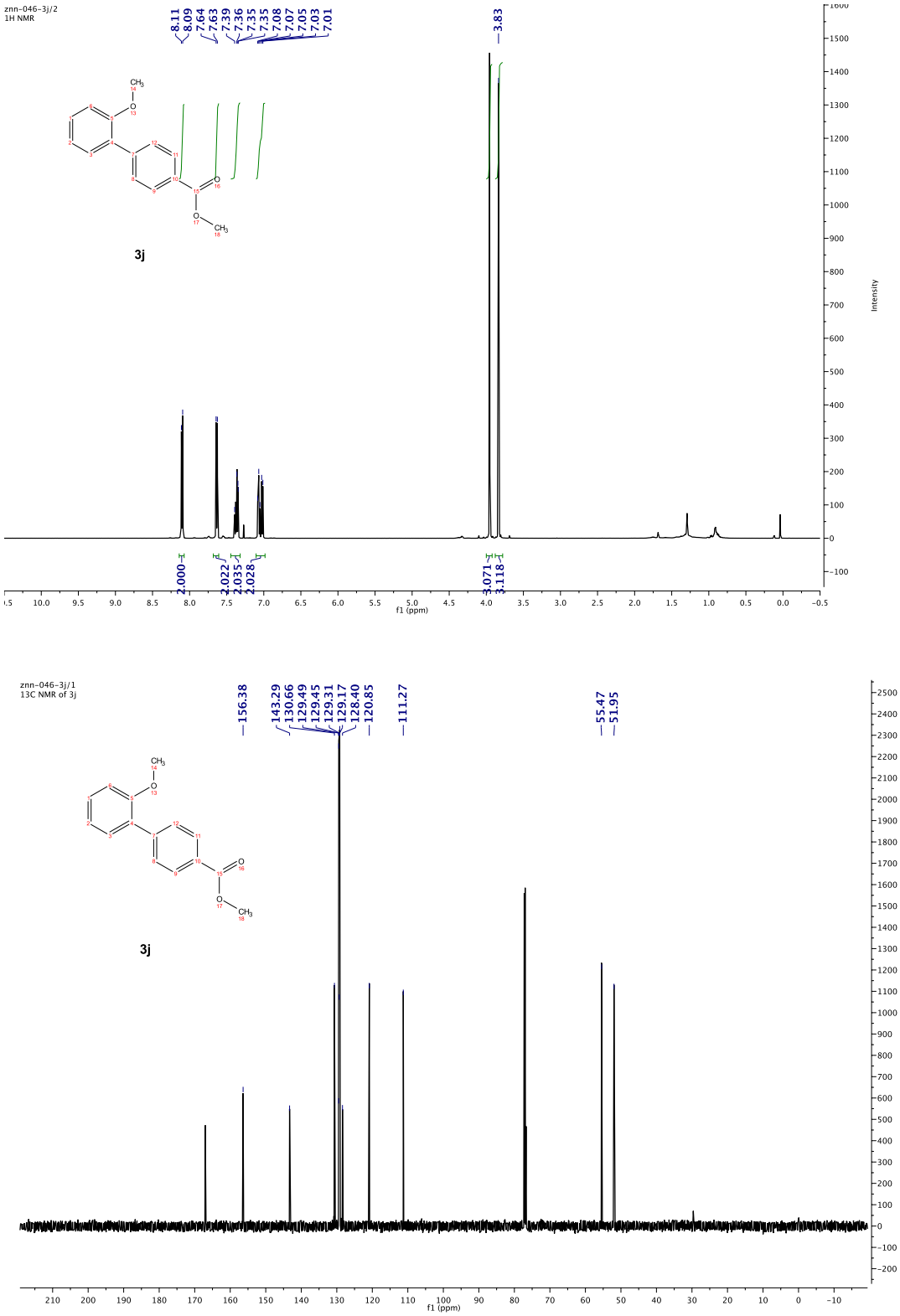


Figure SI 17. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of **3j** in $CDCl_3$.

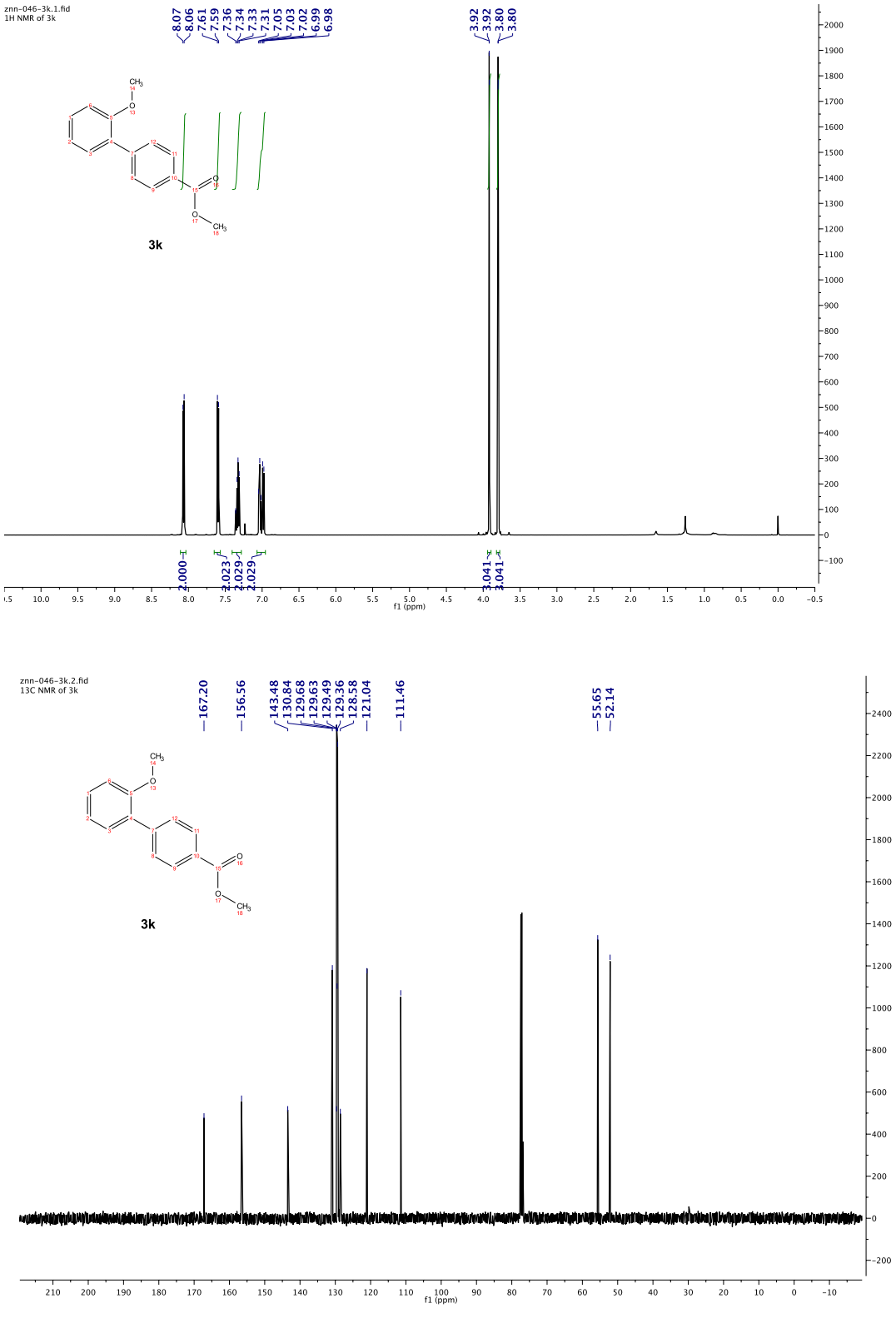


Figure SI 18. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of **3k** in $CDCl_3$.

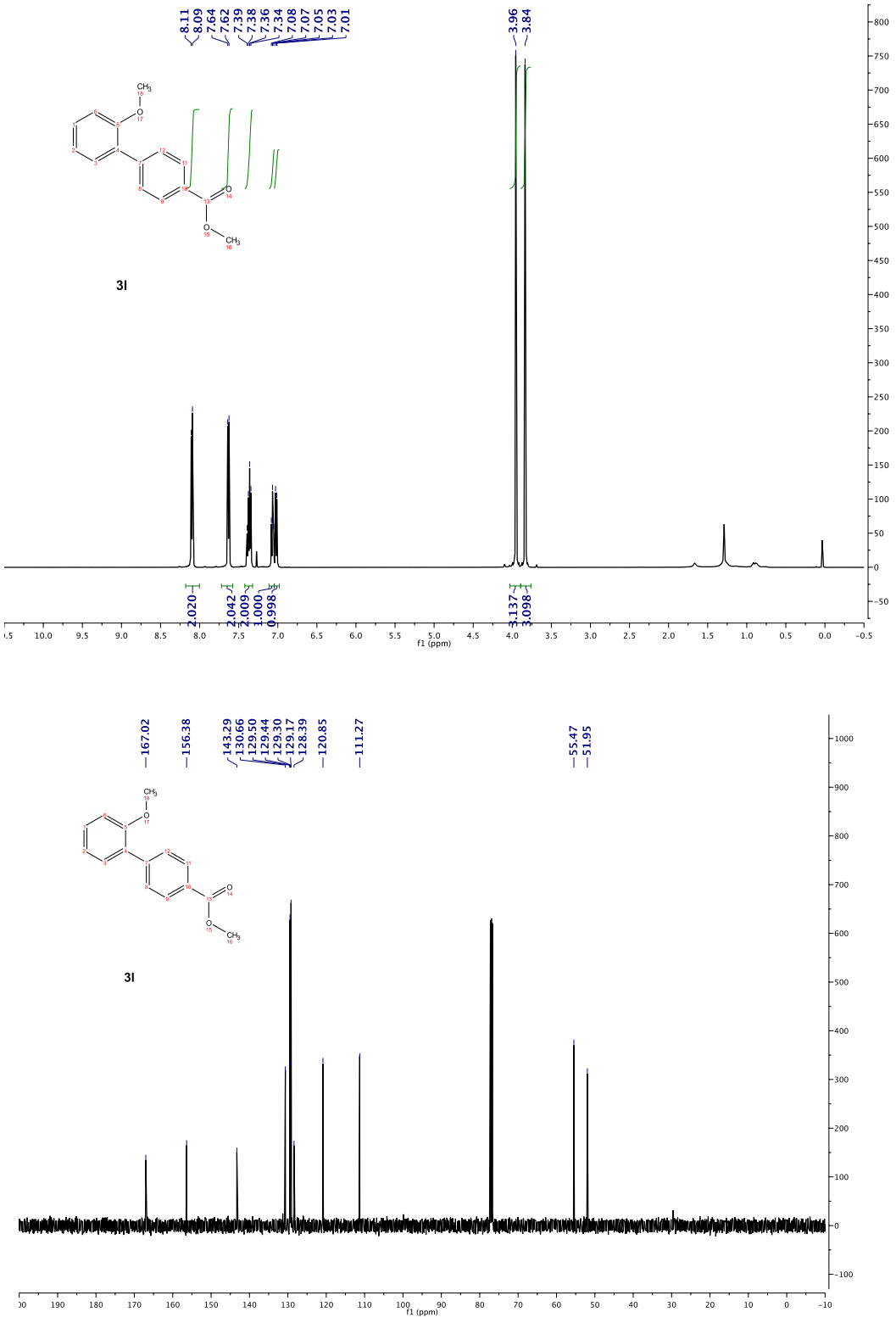


Figure SI 19. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of **3l** in $CDCl_3$.

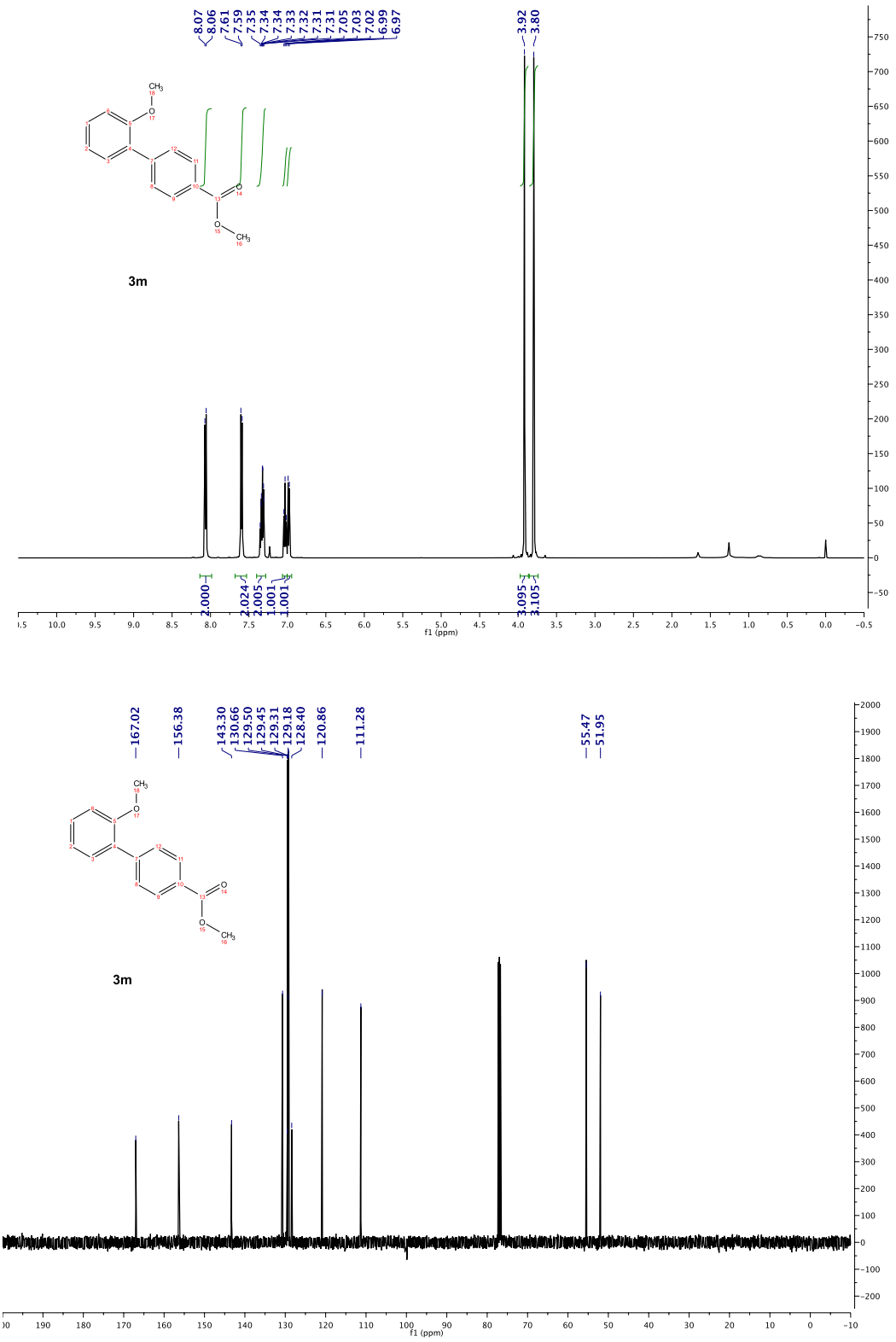


Figure SI 20. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of **3m** in $CDCl_3$.

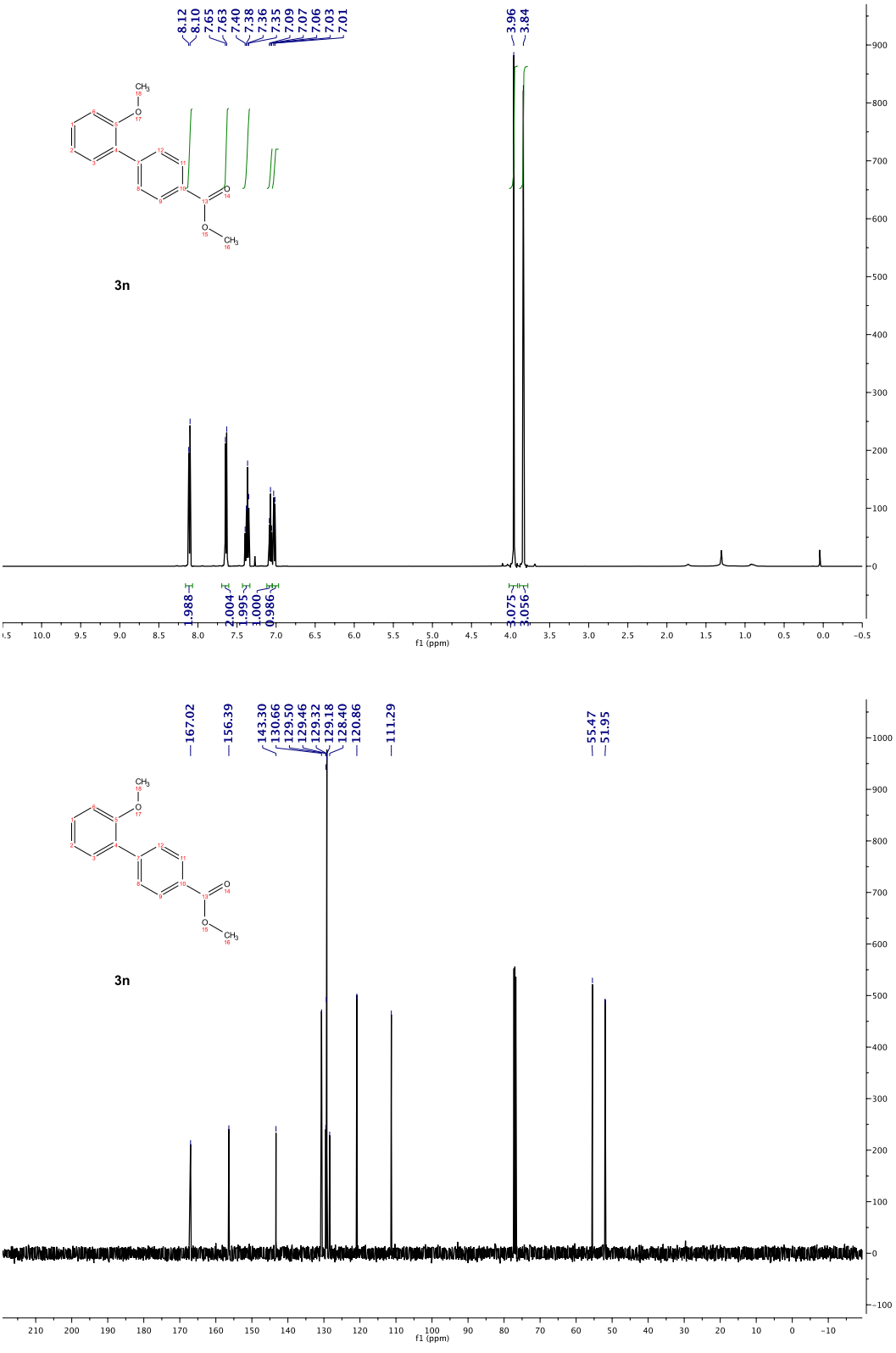
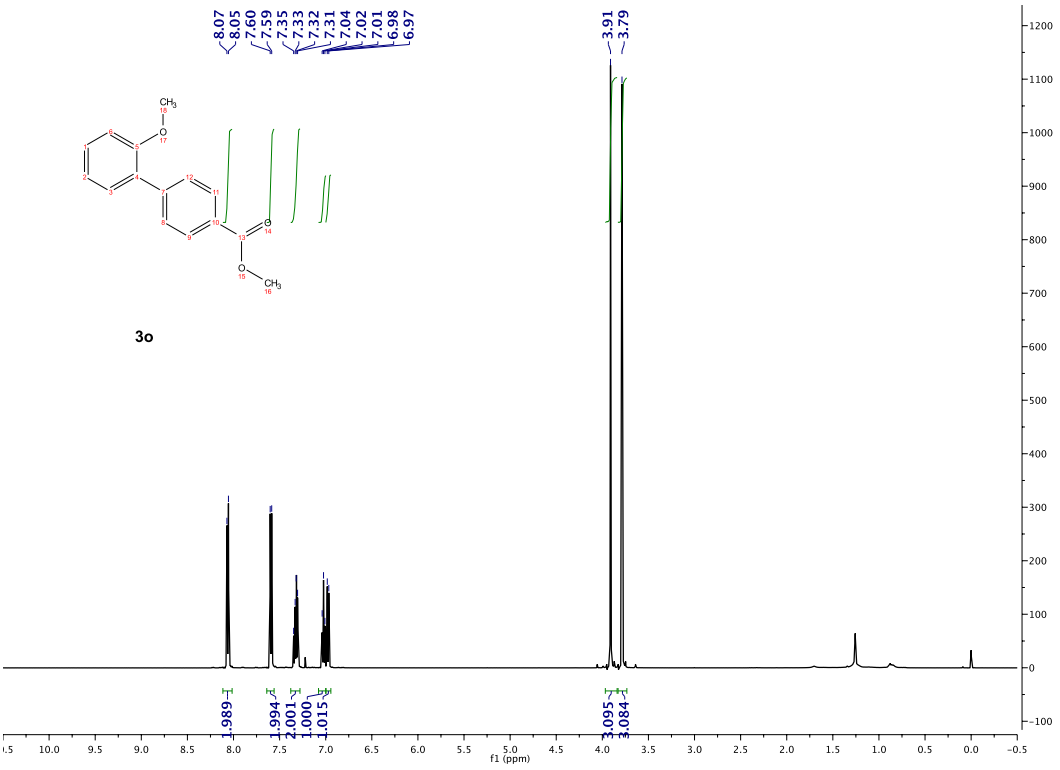


Figure SI 21. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of **3n** in $CDCl_3$.



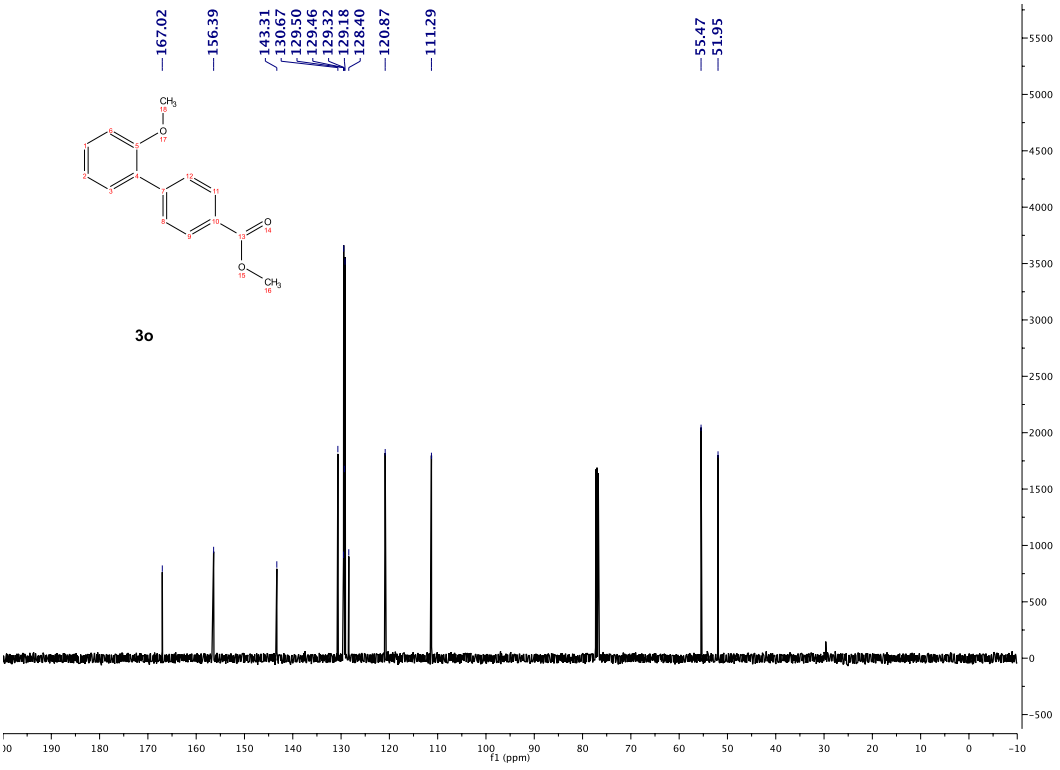


Figure SI 22. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of **3o** in $CDCl_3$.

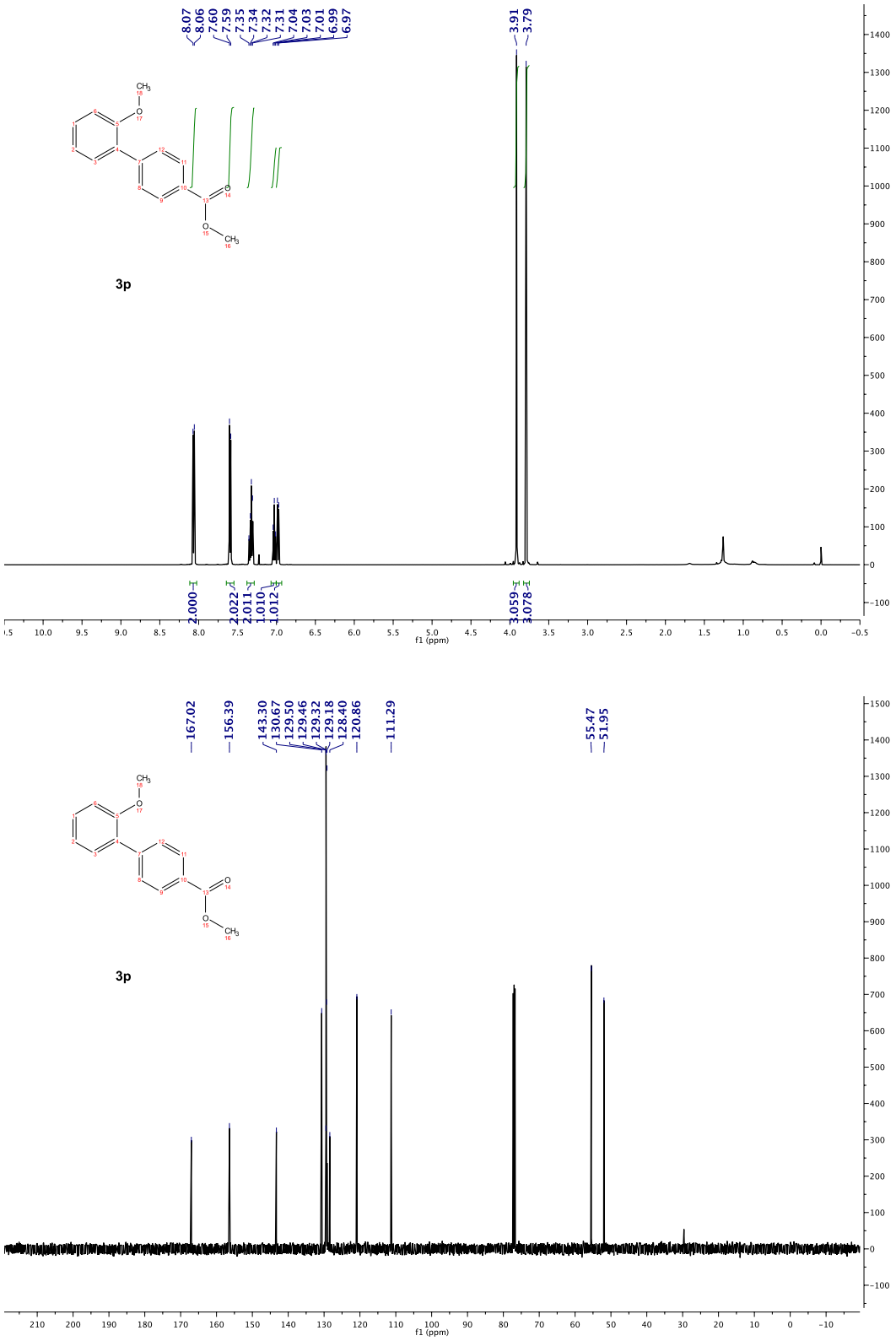
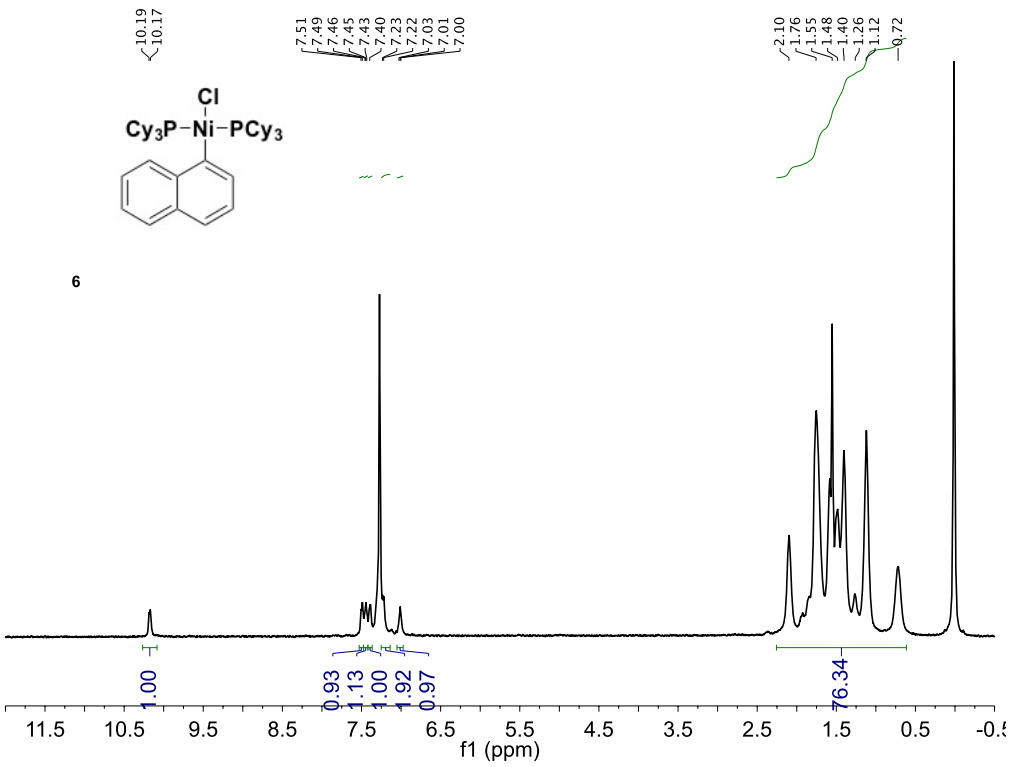
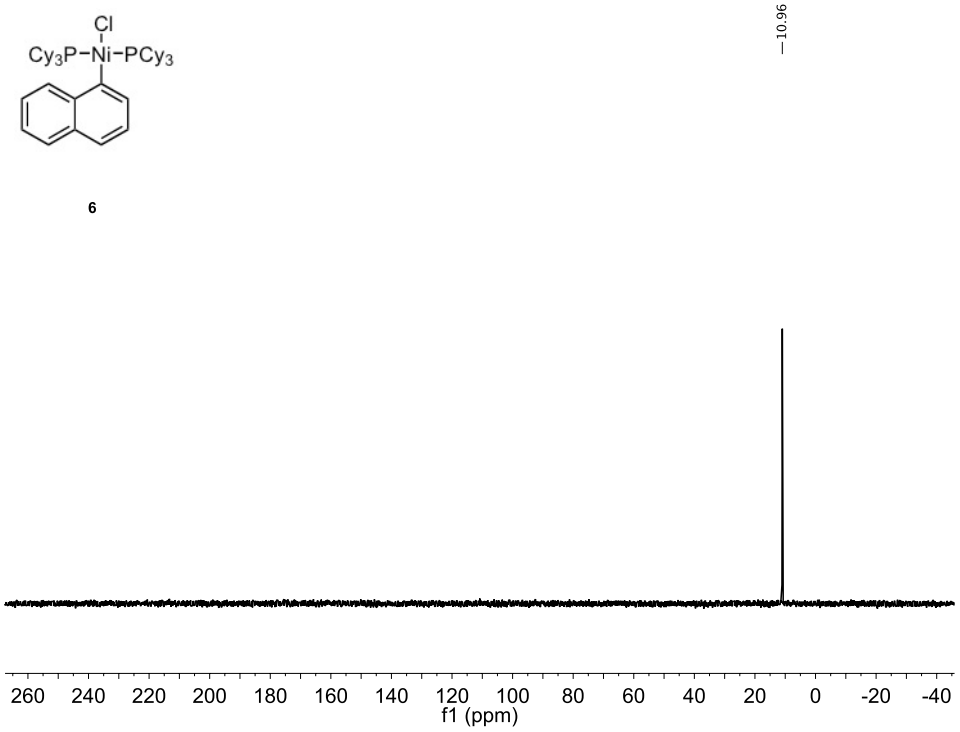


Figure SI 23. ^{1}H NMR (top, 500 MHz), and ^{13}C NMR (bottom, 125 MHz) spectra of **3p** in $CDCl_3$.


10.19
10.17
7.51
7.49
7.46
7.45
7.43
7.40
7.23
7.22
7.03
7.01
7.00
2.10
1.76
1.55
1.48
1.40
1.26
1.12
0.72
Cl
Cy3P–Ni–PCy3
6
1.00
0.93
1.13
1.00
1.92
0.97
76.34
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)


Cl
Cy3P–Ni–PCy3
6
10.96
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
f1 (ppm)

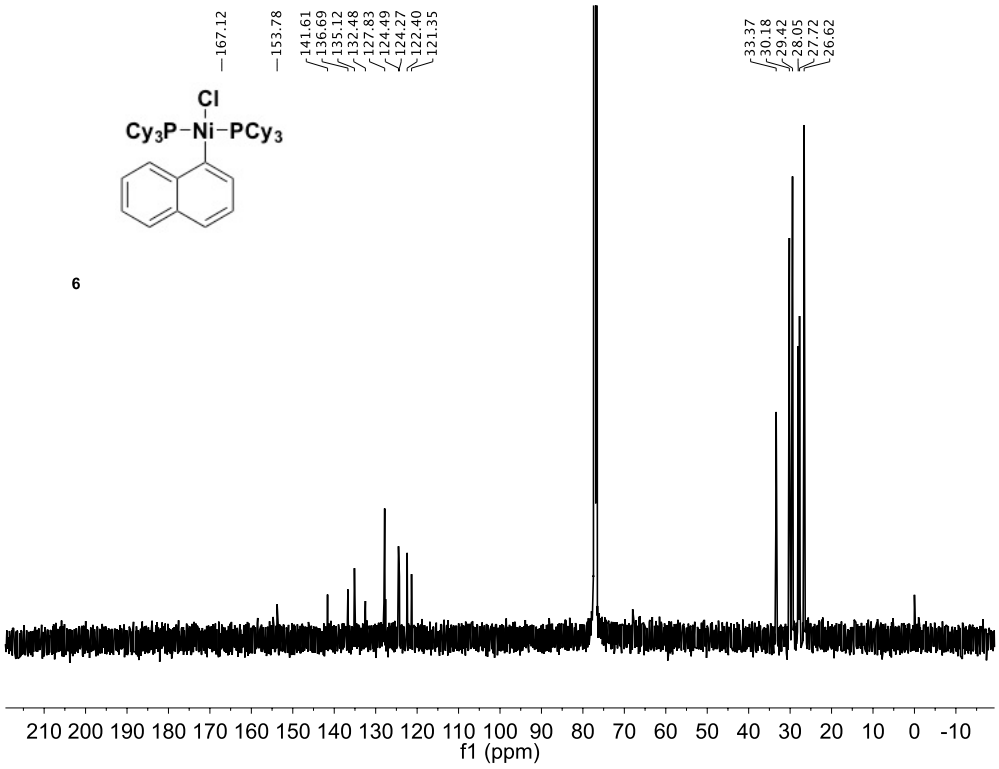
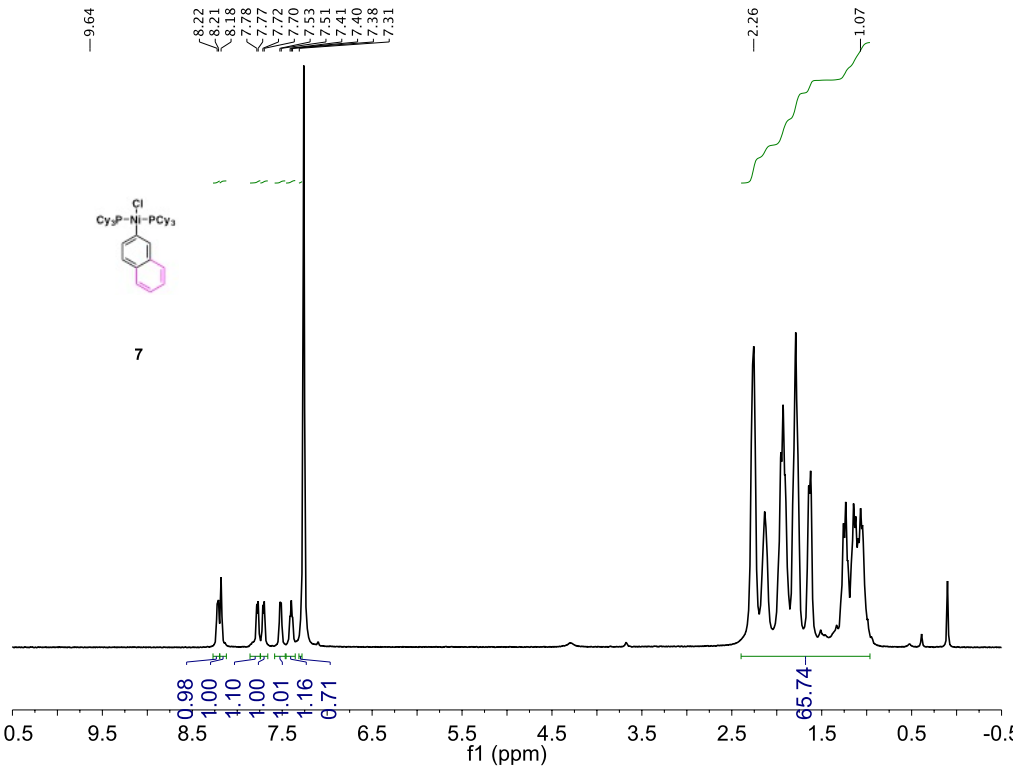
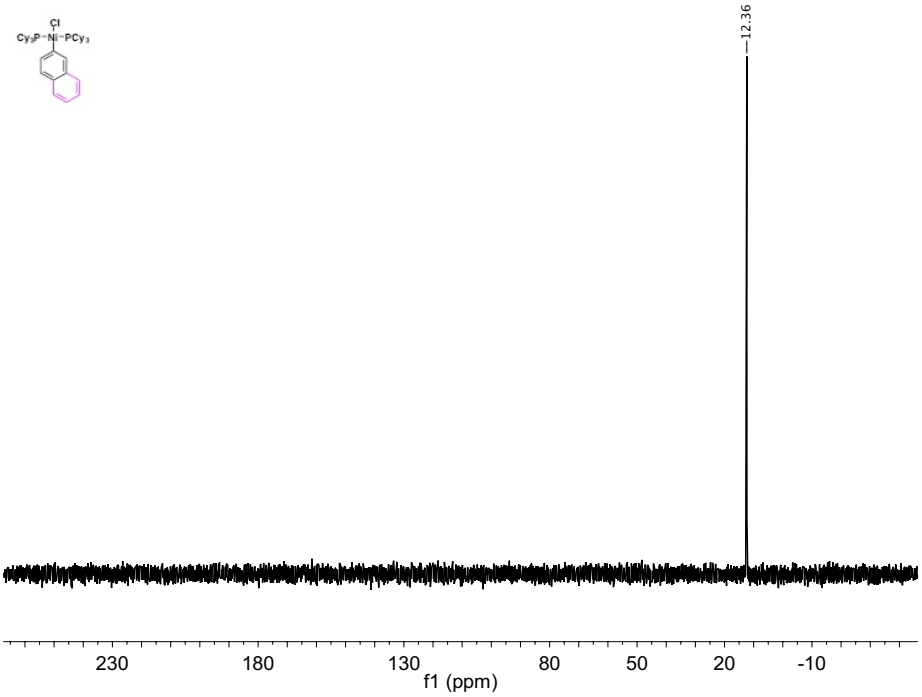


Figure SI 24. ^{1}H NMR (top, 500 MHz), ^{31}P NMR (middle, 203 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of $Ni^{II}Cl(1\text{-naphthyl})(PCy_3)_2$ in C_6D_6.


9.64
8.22
8.21
8.18
7.78
7.77
7.72
7.70
7.53
7.51
7.41
7.40
7.38
7.31
2.26
1.07
Cl
Cy3P–Ni–PCy3
7
0.98
1.00
1.10
1.00
1.01
1.16
6.71
65.74
0.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)


Cl
Cy3P–Ni–PCy3
12.36
230
180
130
80
50
20
-10
f1 (ppm)

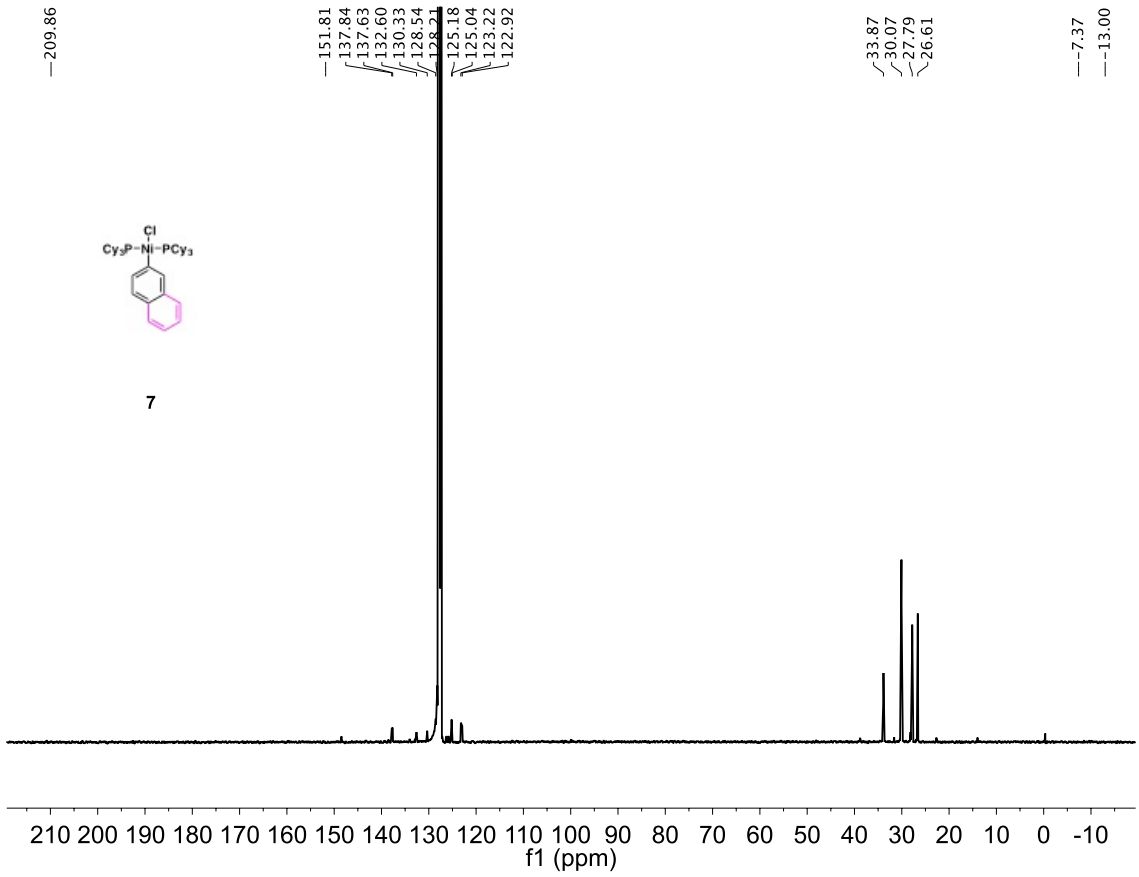
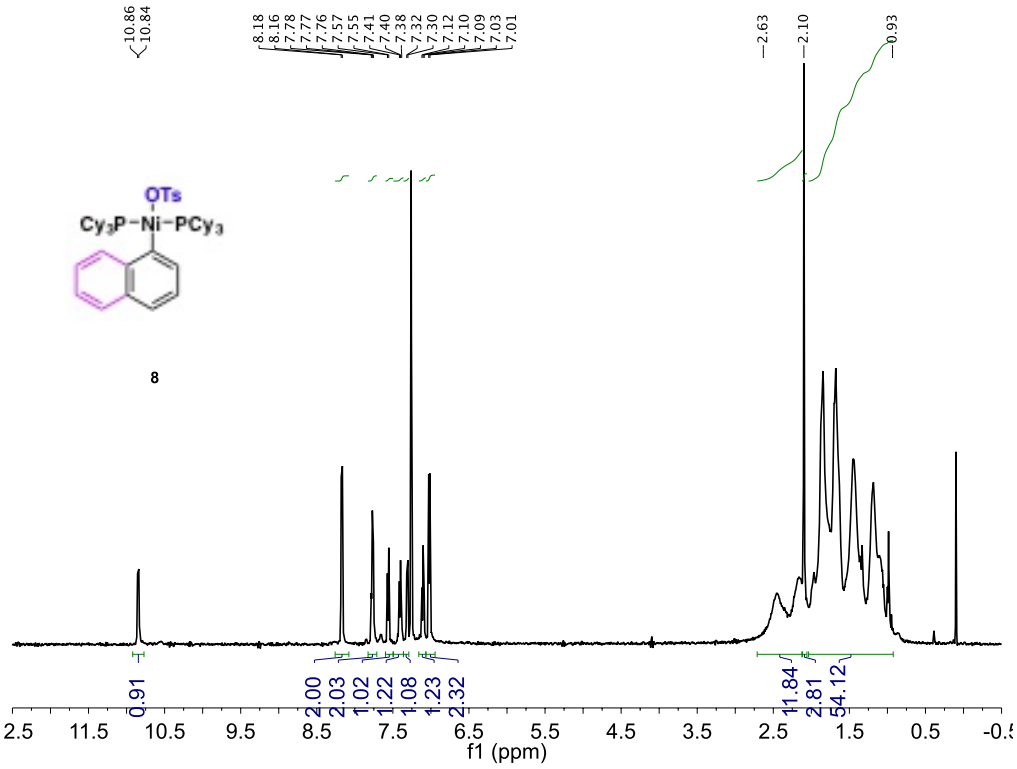
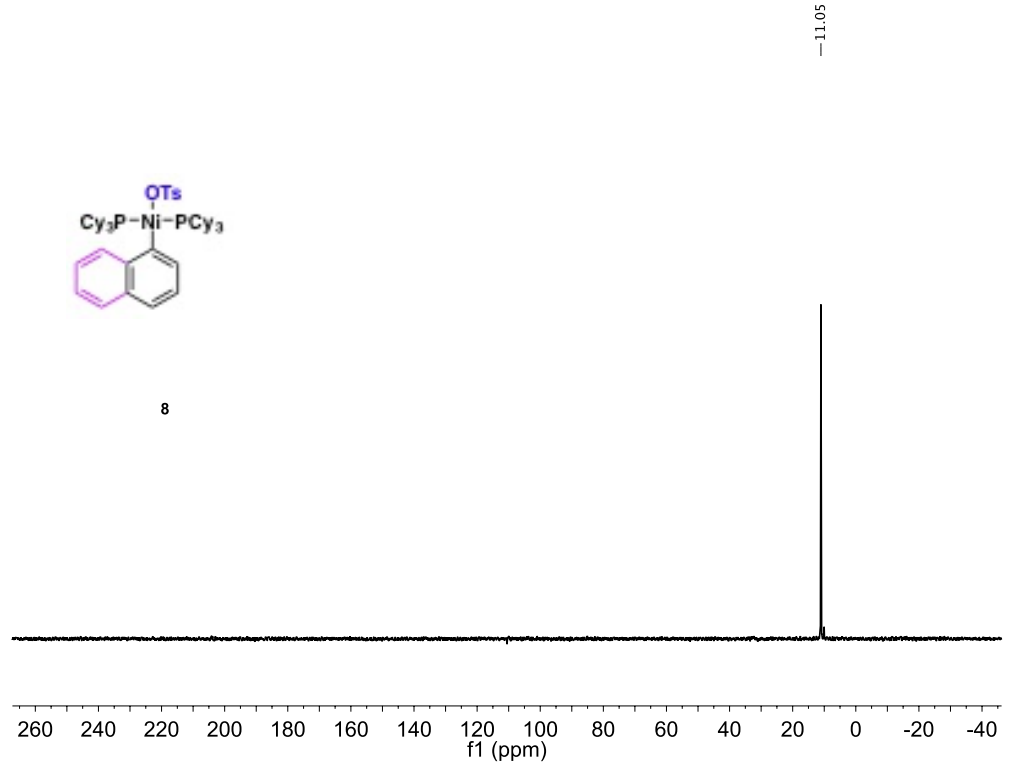


Figure SI 25. ^{1}H NMR (top, 500 MHz), ^{31}P NMR (middle, 203 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of $Ni^{II}Cl(2\text{-naphthyl})(PCy_3)_2$ in C_6D_6.


10.86
10.84
8.18
8.16
7.78
7.77
7.76
7.57
7.55
7.41
7.40
7.38
7.32
7.30
7.12
7.10
7.09
7.03
7.01
2.63
2.10
0.93
OTs
Cy3P–Ni–PCy3
8
0.91
2.00
2.03
1.02
1.22
1.08
1.23
2.32
11.84
2.81
54.12
2.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)


11.05
OTs
Cy3P–Ni–PCy3
8
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
f1 (ppm)

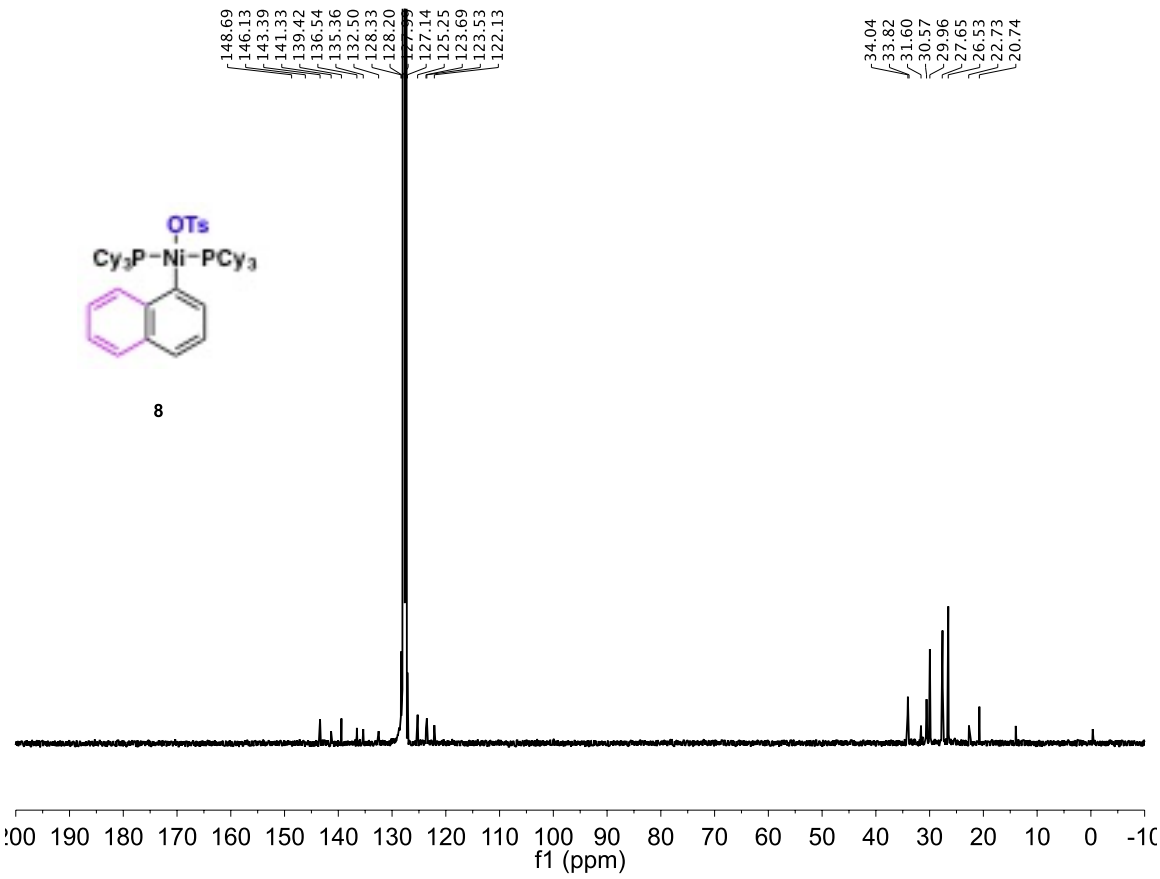
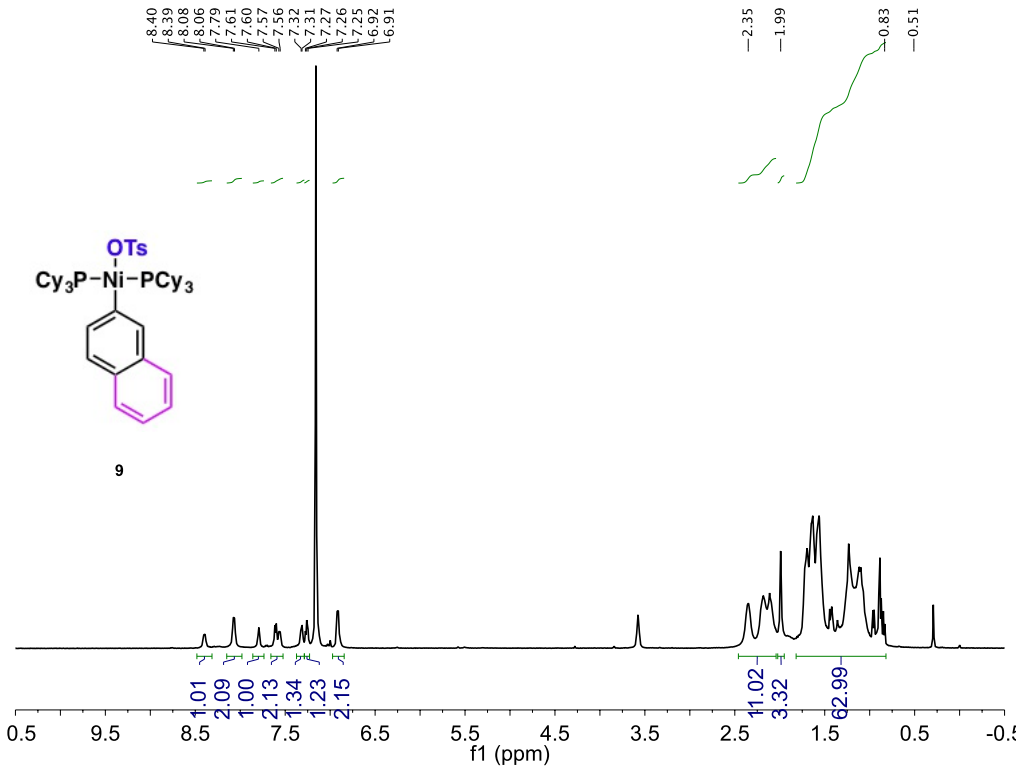
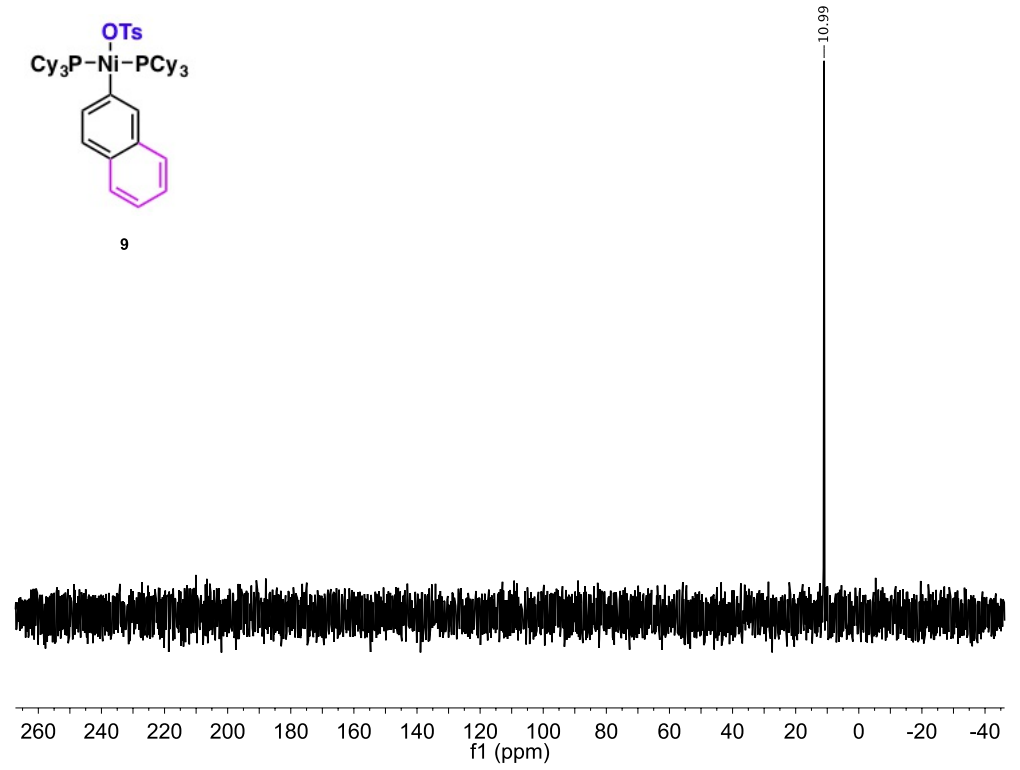


Figure SI 26. ^{1}H NMR (top, 500 MHz), ^{31}P NMR (middle, 203 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of $Ni^{II}OTs(1\text{-naphthyl})(PCy_3)_2$ in C_6D_6.


8.40
8.39
8.08
8.06
7.79
7.61
7.60
7.57
7.56
7.32
7.31
7.27
7.26
7.25
6.92
6.91
2.35
1.99
0.83
0.51
OTs
Cy3P–Ni–PCy3
9
1.01
2.09
1.00
2.13
1.34
1.23
2.15
11.02
3.32
62.99
0.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)


OTs
Cy3P–Ni–PCy3
9
10.99
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
f1 (ppm)

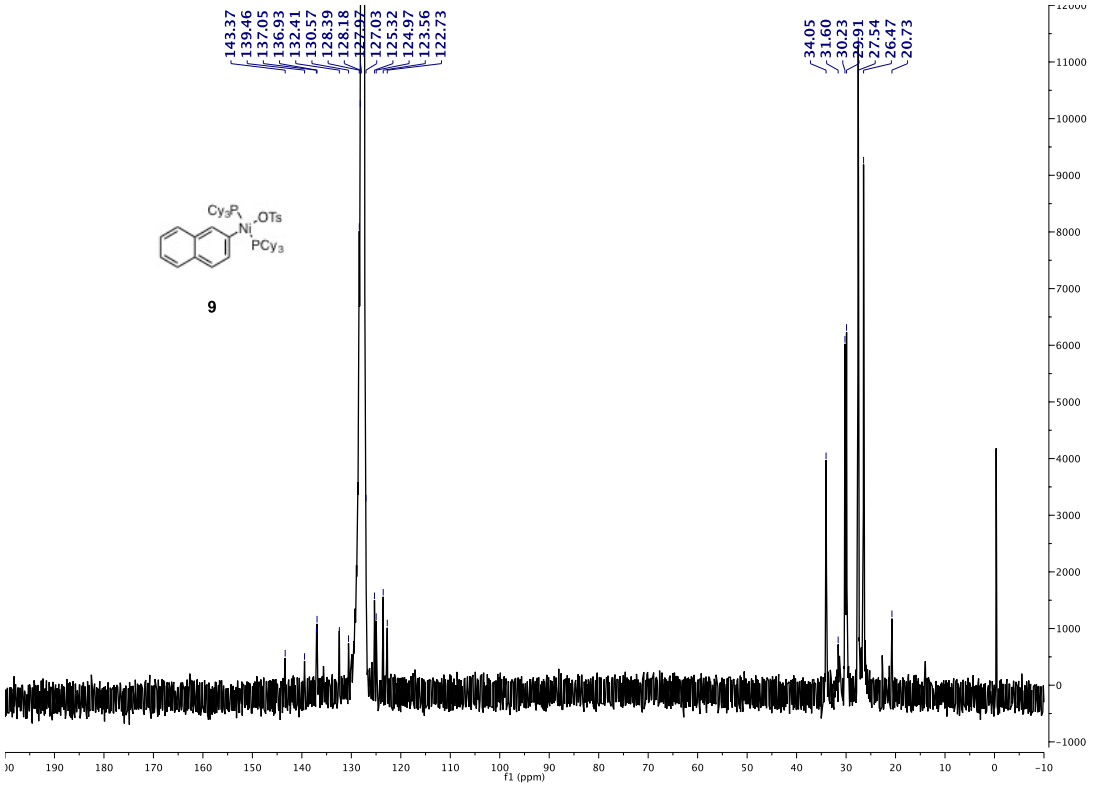
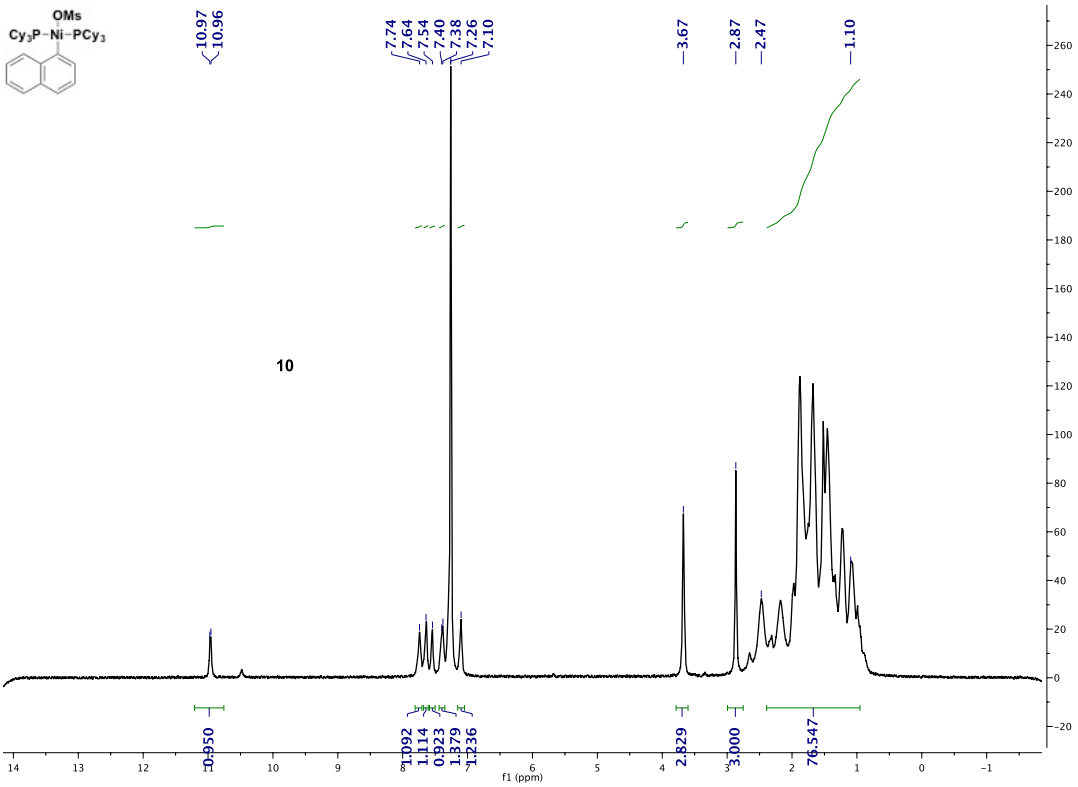
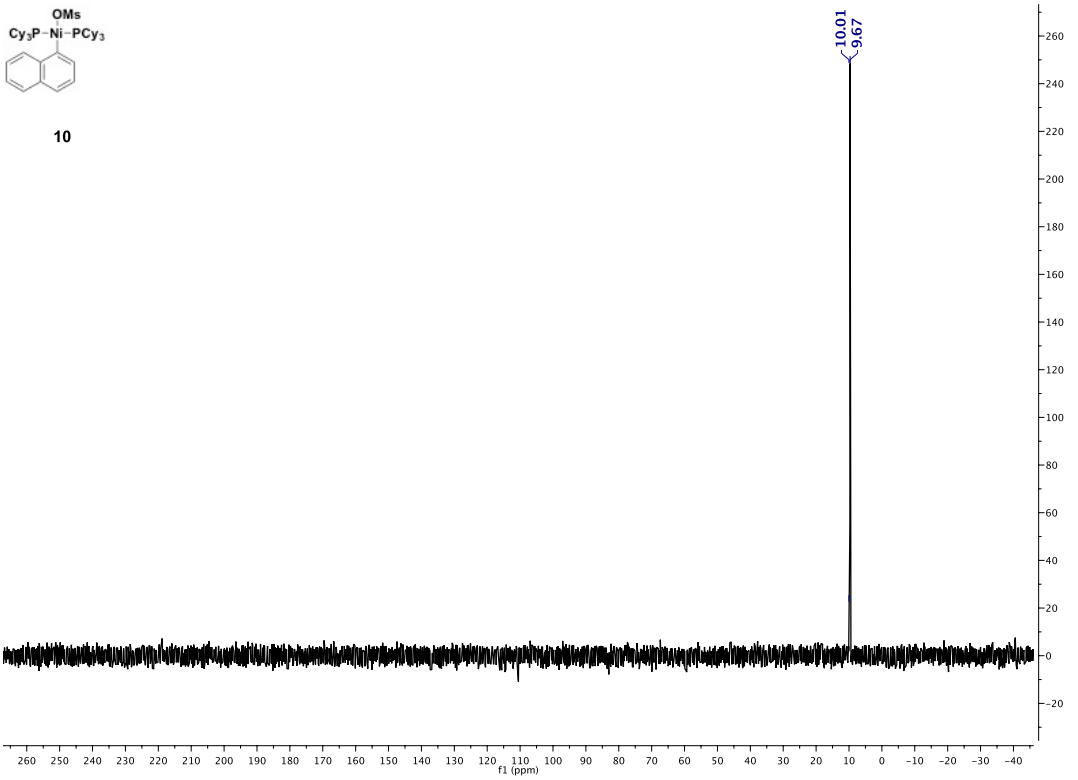


Figure SI 27. ^{1}H NMR (top, 500 MHz), ^{31}P NMR (middle, 203 MHz) and ^{13}C NMR (bottom, 126 MHz) spectra of $Ni^{II}OTs(2\text{-naphthyl})(PCy_3)_2$ in C_6D_6.


OMs
Cy3P–Ni–PCy3
10.97
10.96
7.74
7.64
7.54
7.40
7.38
7.26
7.10
3.67
2.87
2.47
1.10
10
0.950
1.092
1.114
0.923
1.379
1.236
2.829
3.000
76.547
f1 (ppm)


OMs
Cy3P–Ni–PCy3
10
10.01
9.67
f1 (ppm)

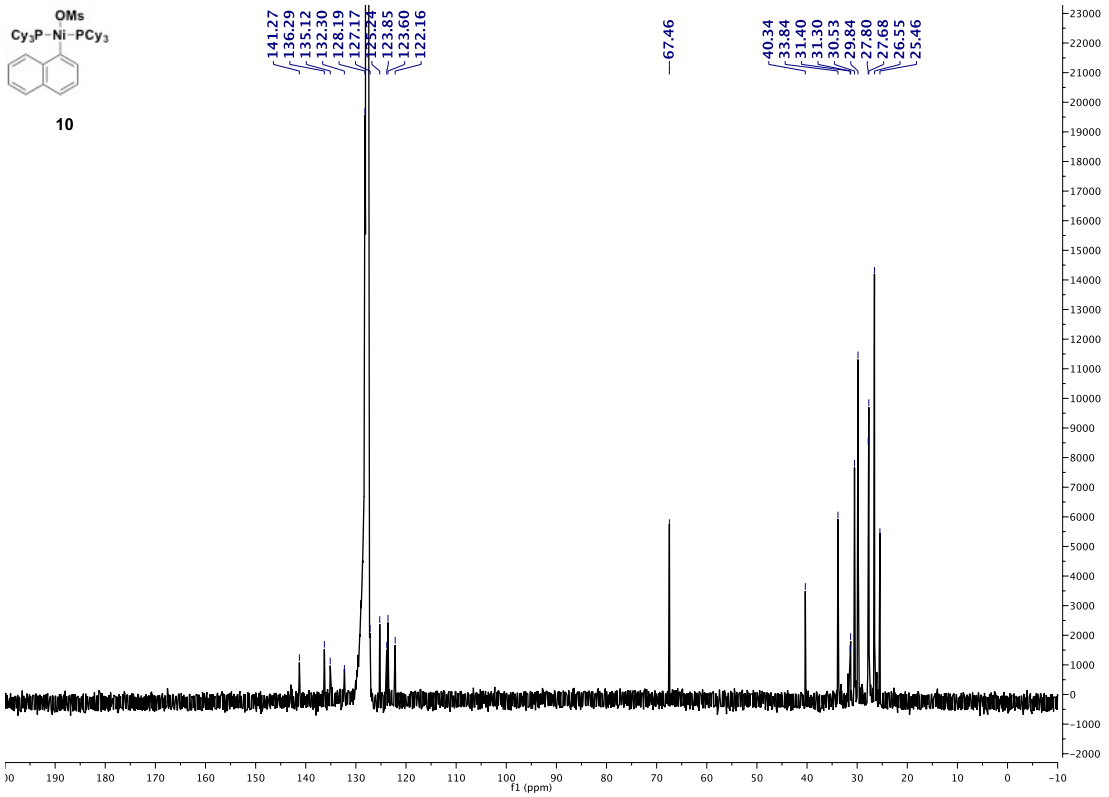
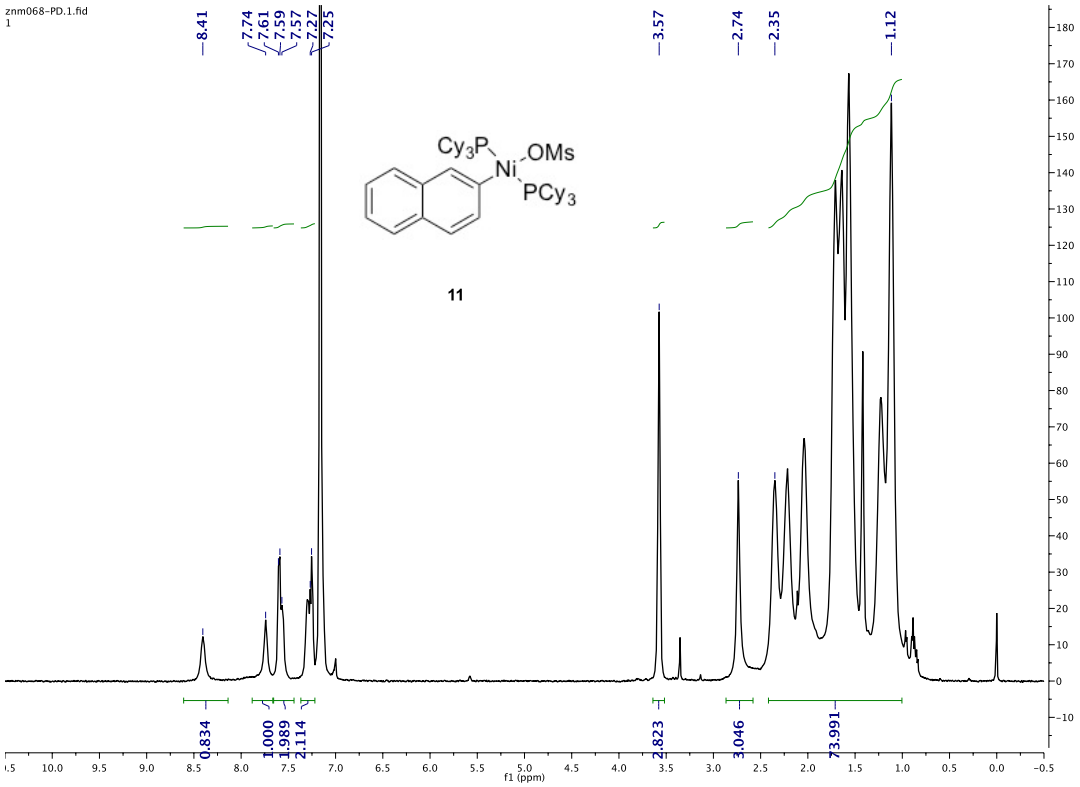
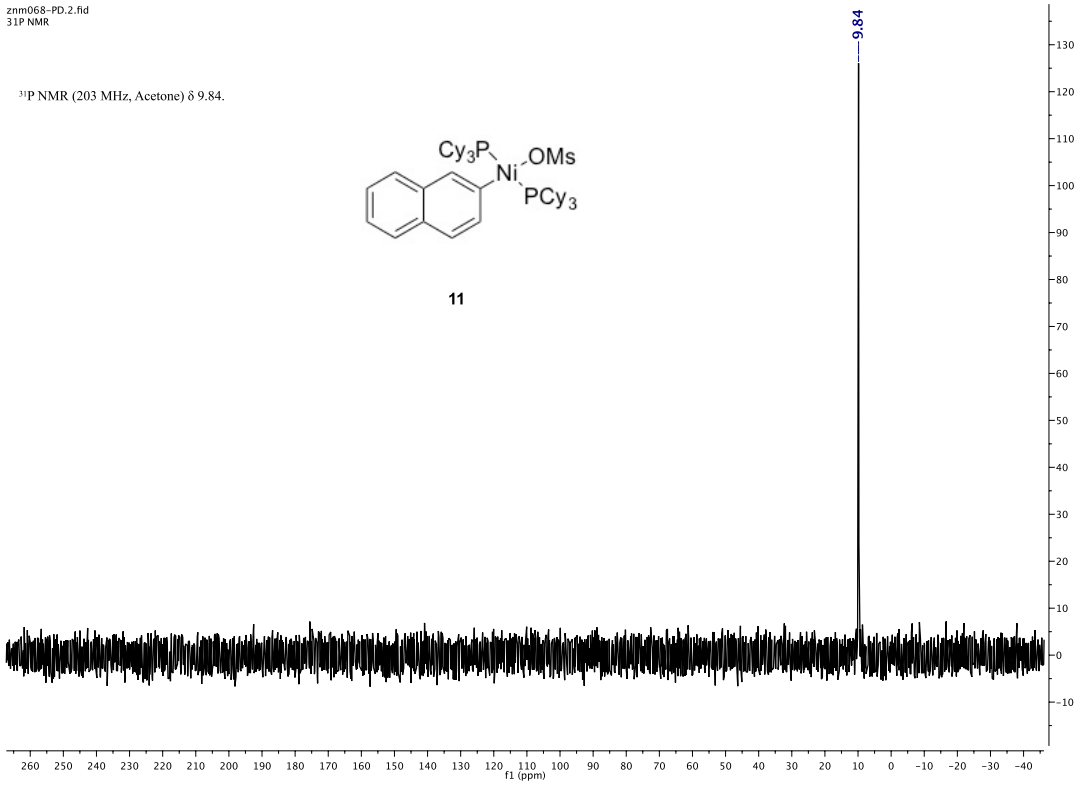


Figure SI 28. ^{1}H NMR (top, 500 MHz), and ^{31}P NMR (bottom, 203 MHz) spectra of $Ni^{II}OMs(1\text{-naphthyl})(PCy_3)_2$ in C_6D_6.





^{31}P NMR (203 MHz, Acetone) δ 9.84.

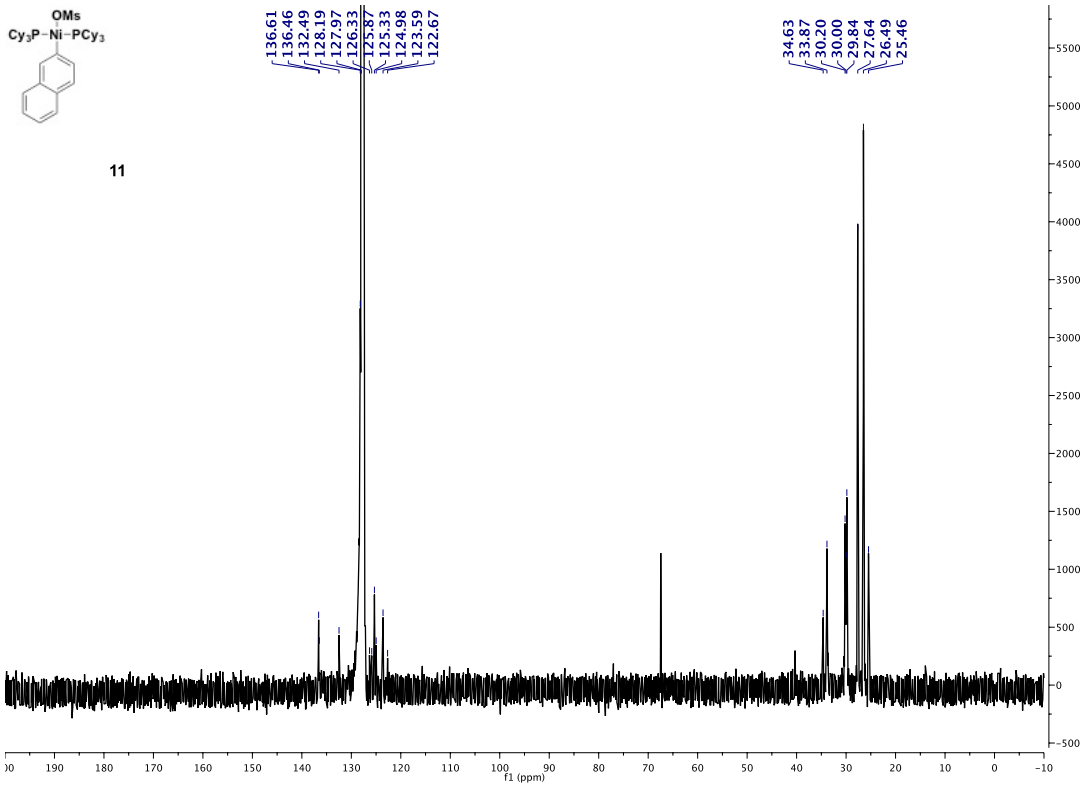
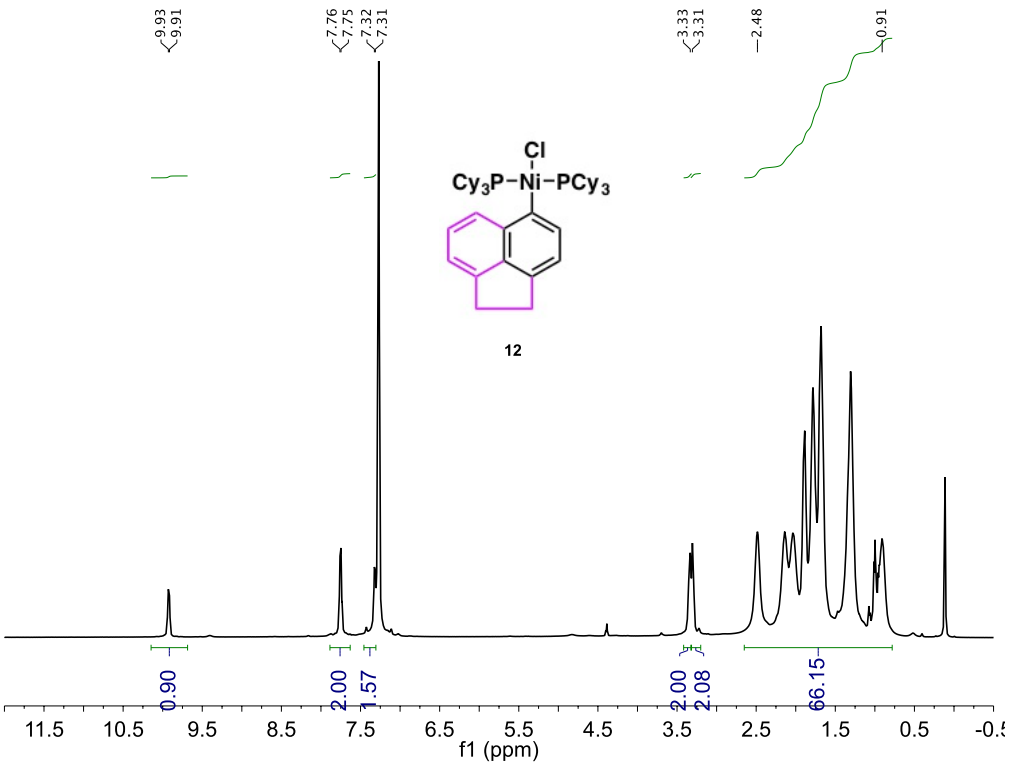
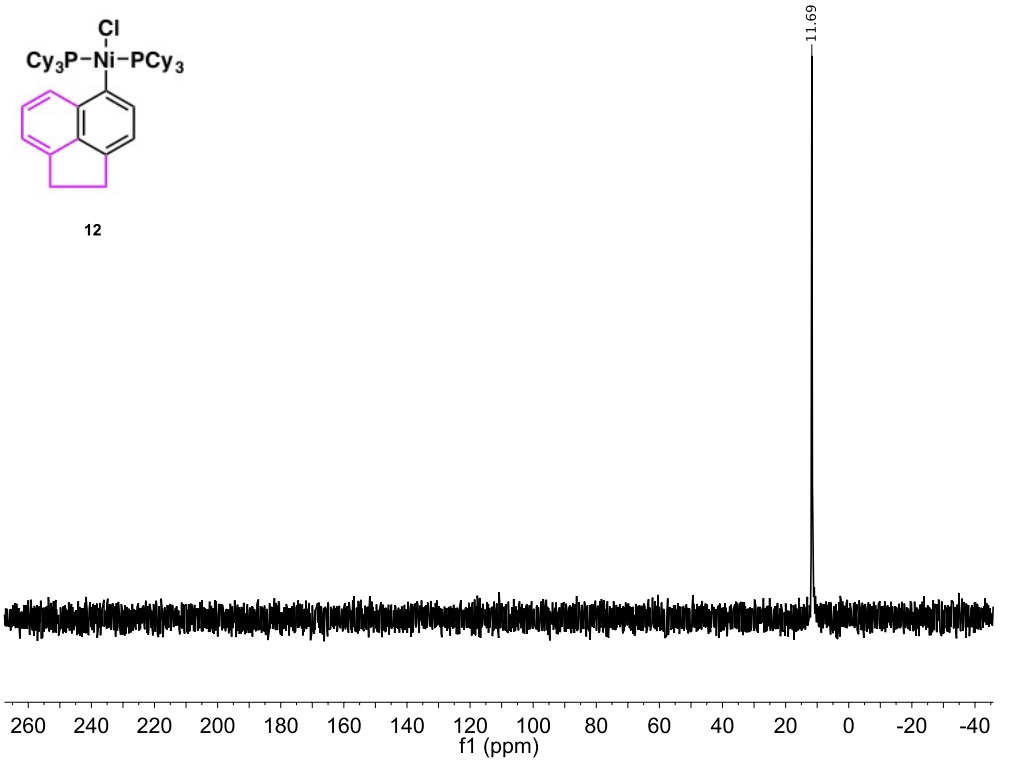


Figure SI 29. ^{1}H NMR (top, 500 MHz), and ^{31}P NMR (bottom, 203 MHz) spectra of $Ni^{II}OMs(2\text{-naphthyl})(PCy_3)_2$ in C_6D_6.


9.93
9.91
7.76
7.75
7.32
7.31
3.33
3.31
2.48
0.91
Cl
Cy3P–Ni–PCy3
12
0.90
2.00
1.57
2.00
2.08
66.15
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)


Cl
Cy3P–Ni–PCy3
12
11.69
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
f1 (ppm)

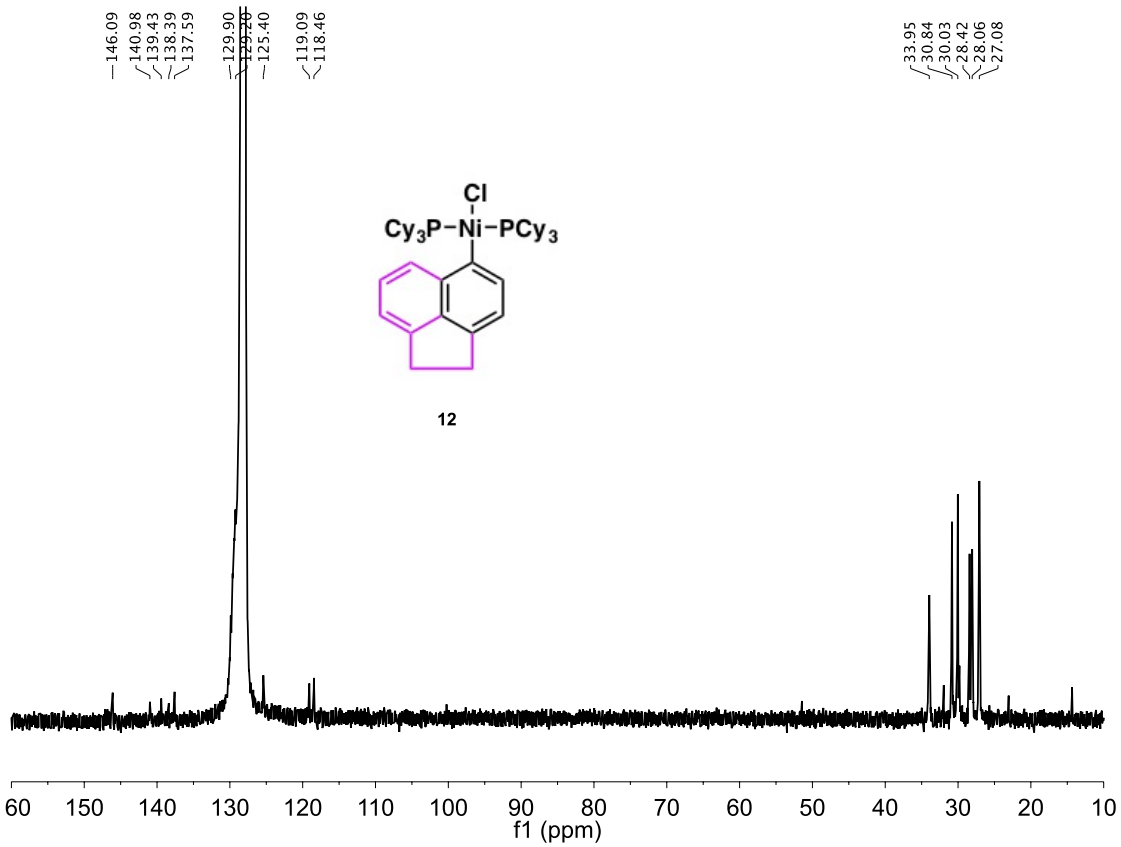
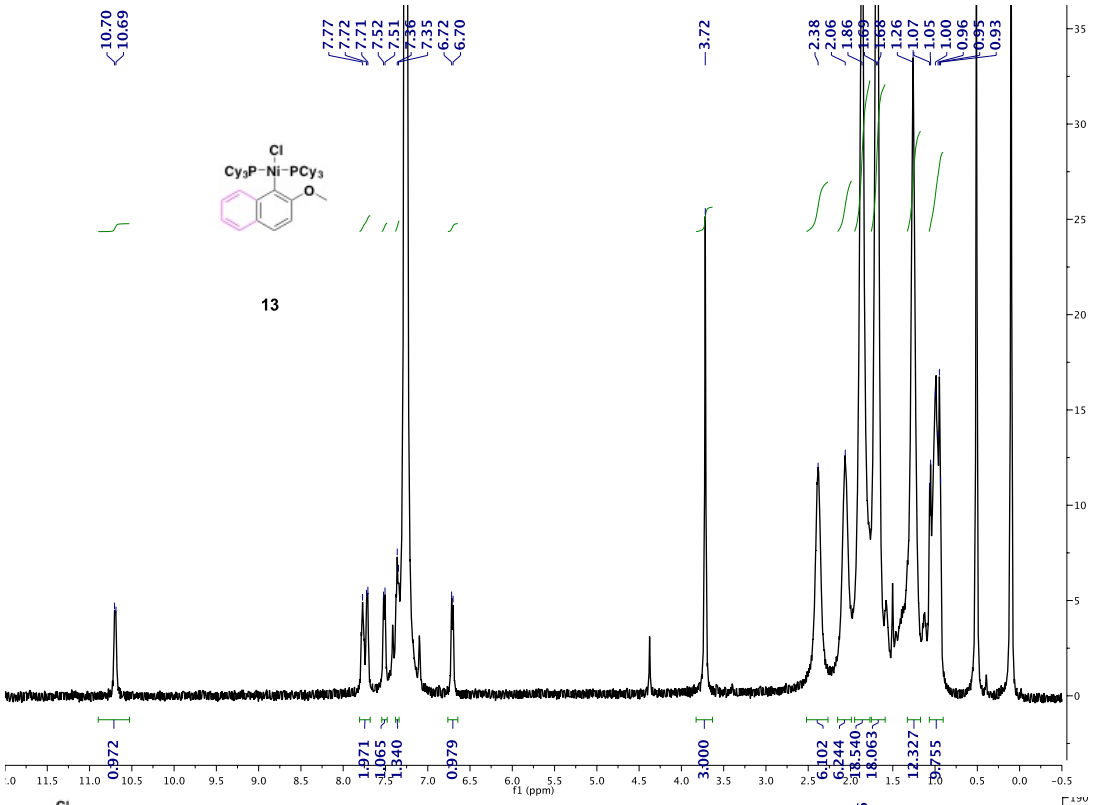
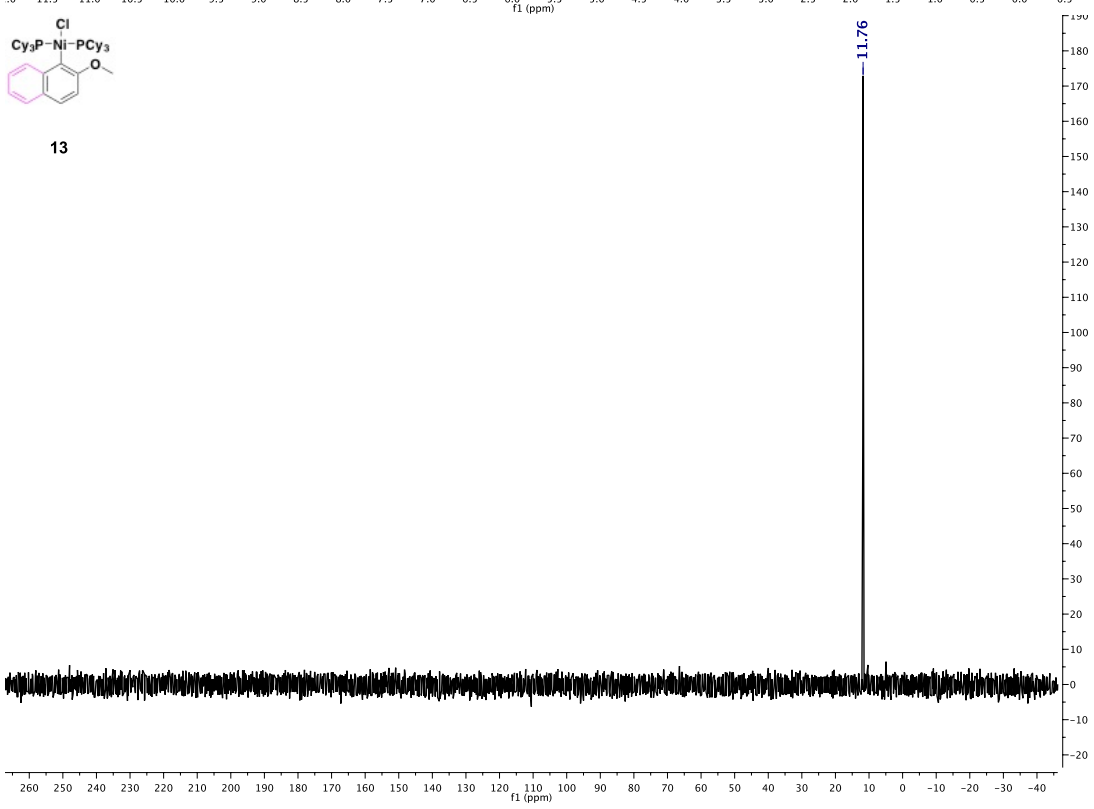


Figure SI 30. ^{1}H NMR (top, 500 MHz), ^{31}P NMR (middle, 203 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of $Ni^{II}Cl(5\text{-acenaphthyl})(PCy_3)_2$ in $CDCl_3$.


10.70
10.69
7.77
7.72
7.71
7.52
7.51
7.36
7.35
6.72
6.70
3.72
2.38
2.06
1.86
1.69
1.68
1.26
1.07
1.05
1.00
0.96
0.95
0.93
Cl
Cy3P–Ni–PCy3
O
13
0.972
1.971
1.065
1.340
0.979
3.000
6.102
6.244
18.540
18.063
12.327
9.755
f1 (ppm)


Cl
Cy3P–Ni–PCy3
O
13
11.76
f1 (ppm)

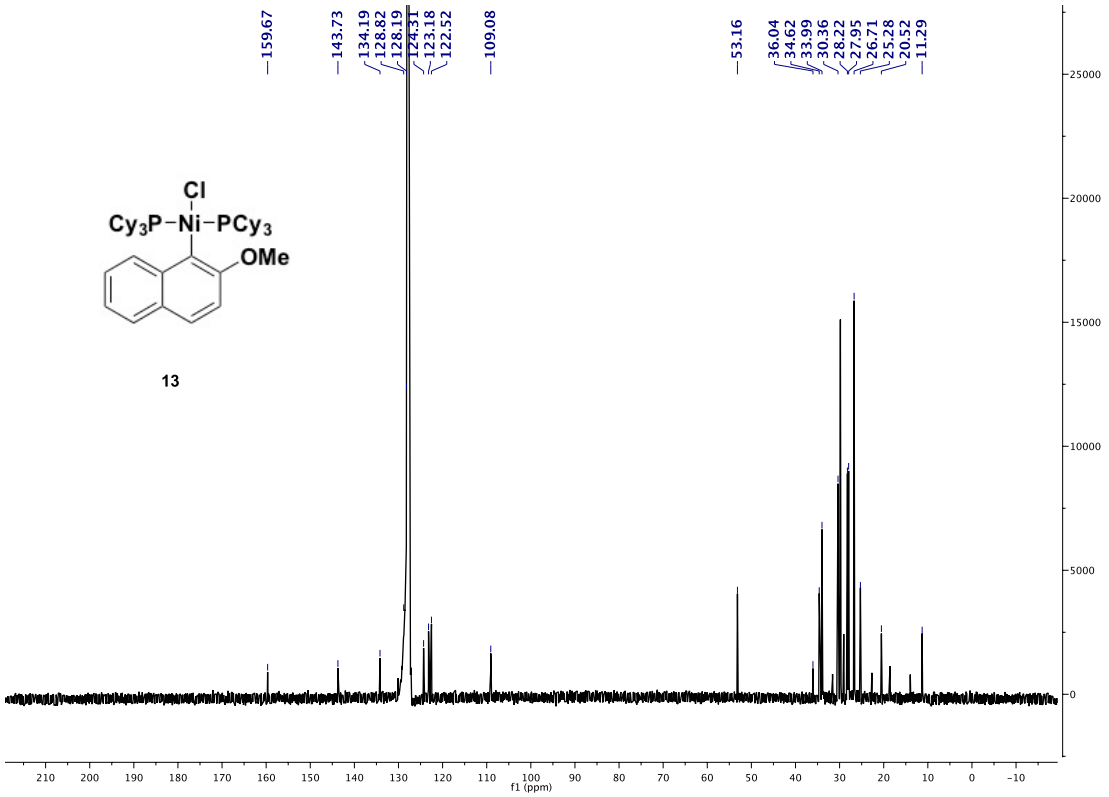
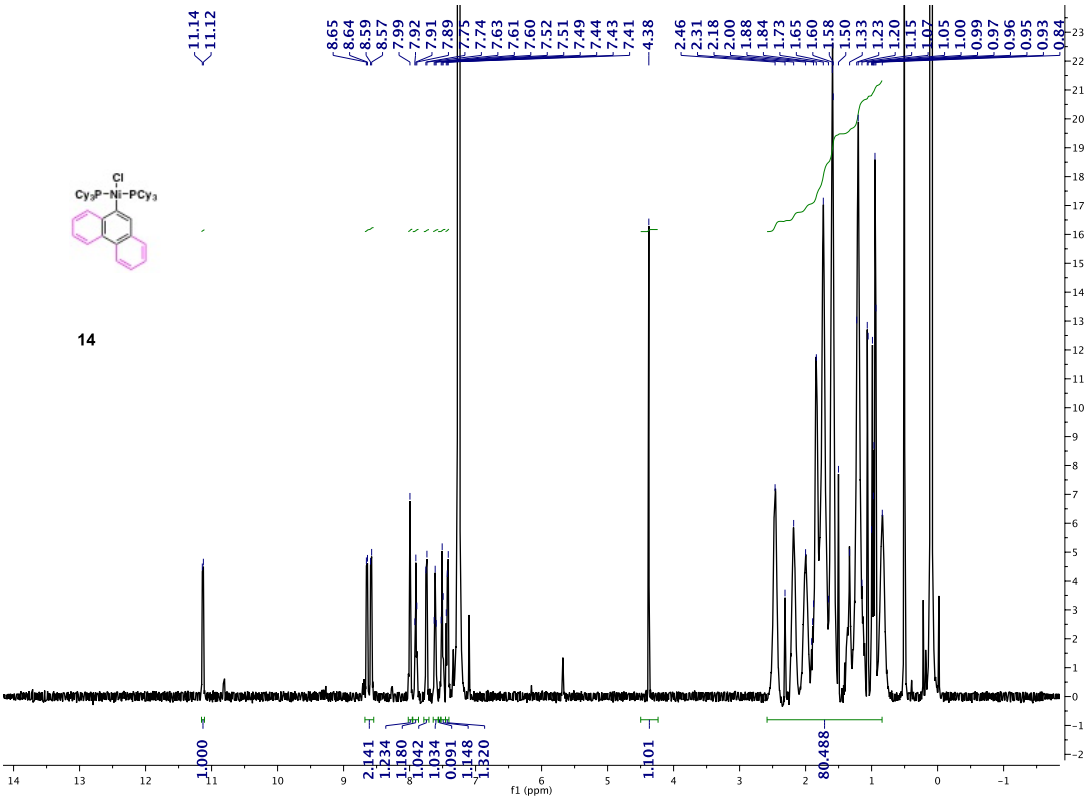
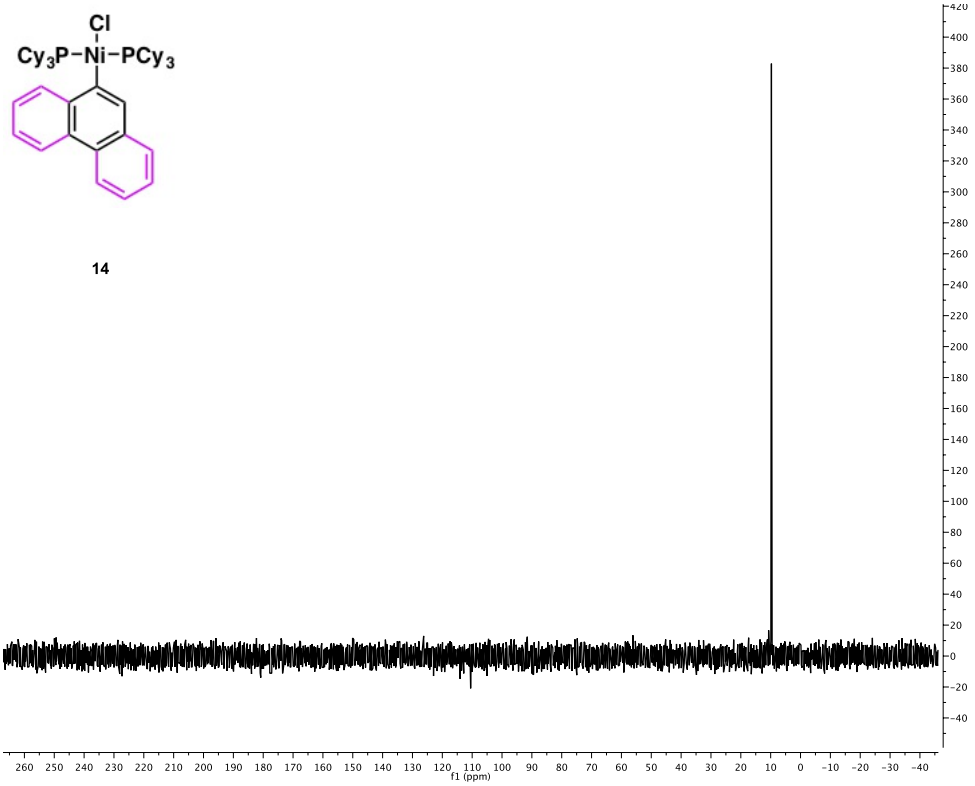


Figure SI 31. ^{1}H NMR (top, 360 MHz), ^{31}P NMR (middle, 203 MHz) and ^{13}C NMR (bottom, 91 MHz) spectra of $Ni^{II}Cl(2\text{-}OMeNaphthyl)(PCy_3)_2$ in C_6D_6.


11.14
11.12
8.65
8.64
8.59
8.57
7.99
7.92
7.91
7.89
7.75
7.74
7.63
7.61
7.60
7.52
7.51
7.49
7.44
7.43
7.41
4.38
2.46
2.31
2.18
2.00
1.88
1.84
1.73
1.65
1.60
1.58
1.50
1.33
1.23
1.20
1.15
1.02
1.05
1.00
0.99
0.97
0.96
0.95
0.93
0.84
Cl
Cy3P–Ni–PCy3
14
1.000
2.141
1.234
1.180
1.042
1.034
0.091
1.148
1.320
1.101
80.488
f1 (ppm)


Cl
Cy3P–Ni–PCy3
14
f1 (ppm)

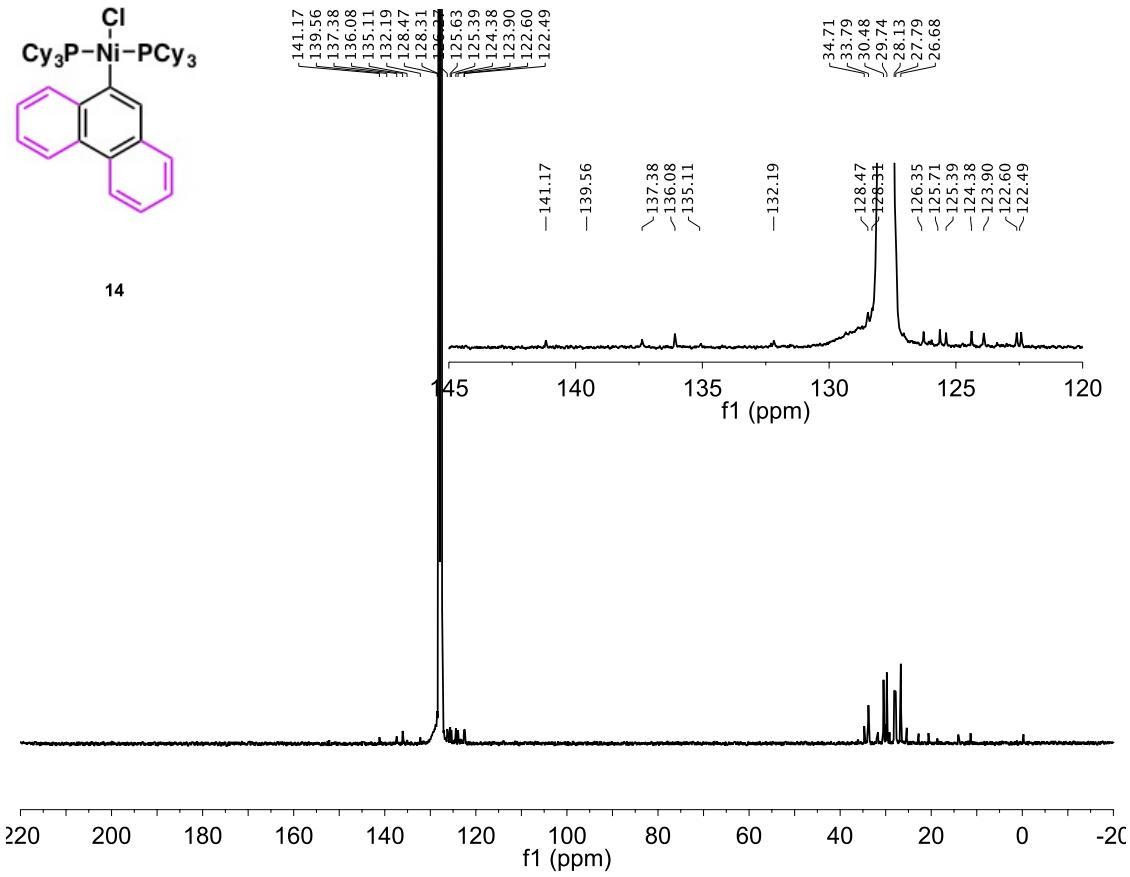
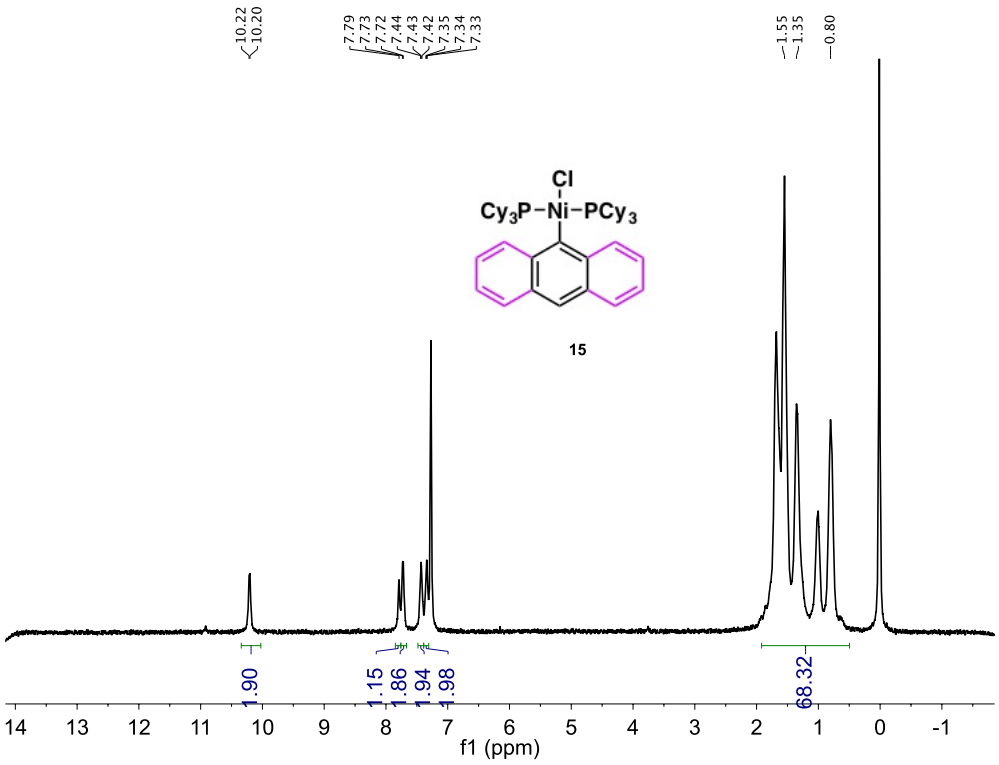
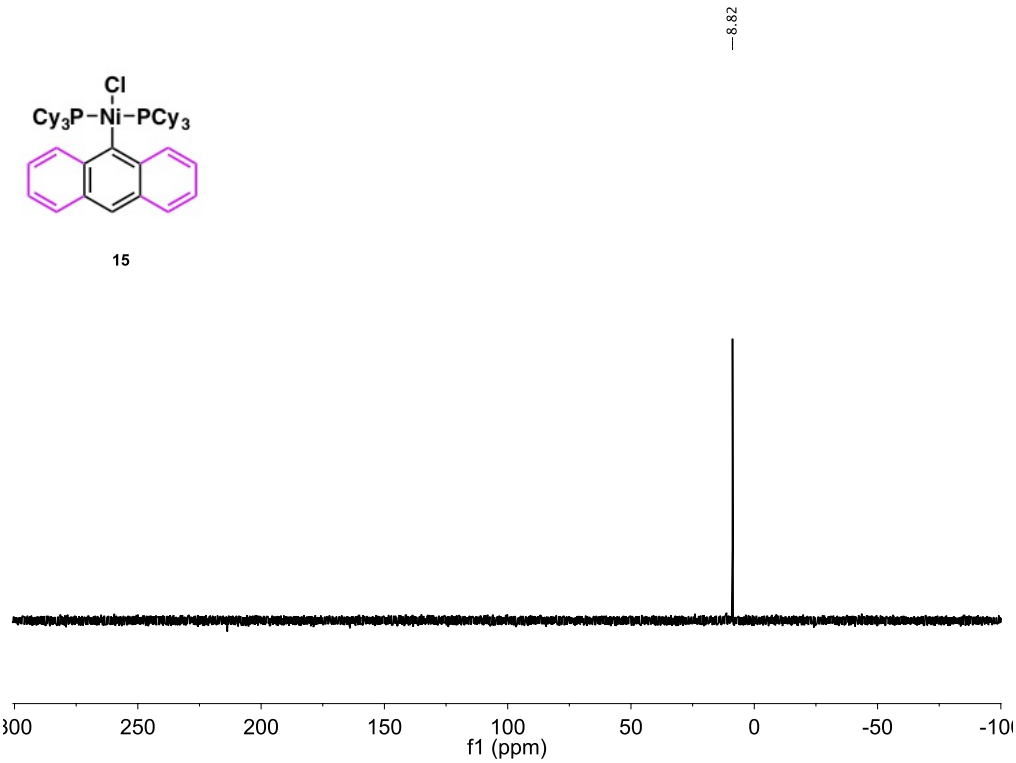


Figure SI 32. ^{1}H NMR (top, 360 MHz), ^{31}P NMR (middle, 203 MHz) and ^{13}C NMR (bottom, 91 MHz) spectra of $Ni^{II}Cl(9\text{-phenathrenyl})(PCy_3)_2$ in C_6D_6 and $CDCl_3$.


10.22
10.20
7.79
7.73
7.72
7.44
7.43
7.42
7.35
7.34
7.33
1.55
1.35
0.80
Cl
Cy3P–Ni–PCy3
15
1.90
1.15
1.86
1.94
1.98
68.32
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


8.82
Cl
Cy3P–Ni–PCy3
15
300 250 200 150 100 50 0 -50 -100
f1 (ppm)

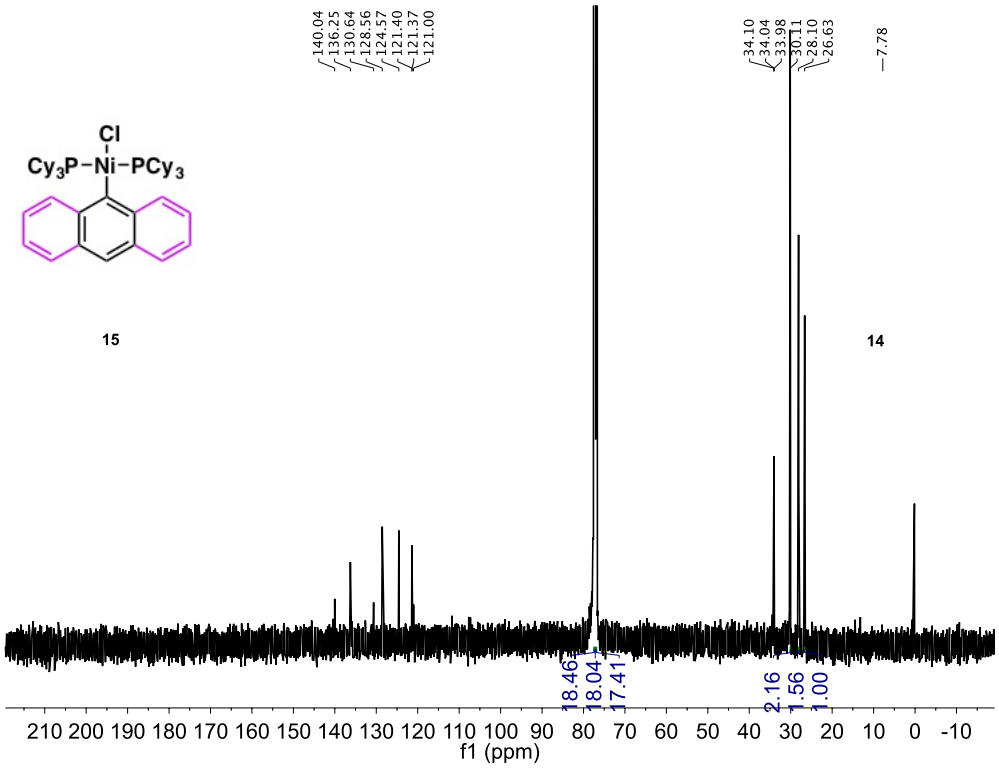


Figure SI 33. ^{1}H NMR (top, 500 MHz), ^{31}P NMR (middle, 203 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of $Ni^{II}Cl(9\text{-anthracyl})(PCy_3)_2$ in $CDCl_3$.

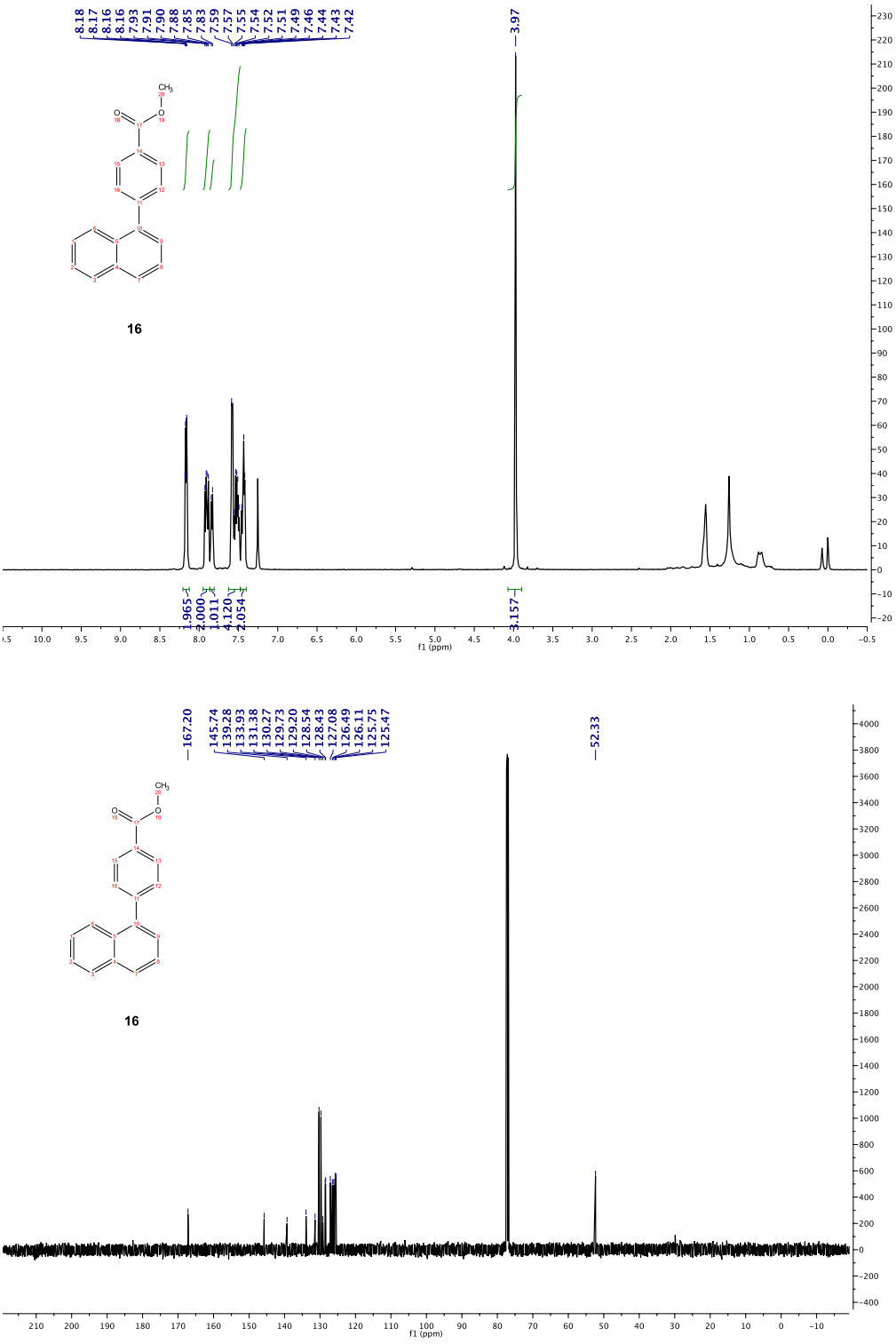


Figure SI 34. ^{1}H NMR (top, 500 MHz), ^{31}P NMR (middle, 203 MHz) and ^{13}C NMR (bottom, 125 MHz) spectra of methyl 4-(naphthalen-1-yl)benzoate in $CDCl_3$.

4.2.5 Account of Contribution

I contributed to the experimental work including preparation of precatalysts, part of data in Scheme 4.4, Scheme 4.5 and Scheme 4.6, which is marked with "*" in experimental part. I also contribute solely with the help of Professor Percec to data in Scheme 4.7, data organization, manuscript preparation and revising.

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