

Ligand-Accelerated Non-Directed C–H Cyanation of Arenes

Luoyan Liu, Kap-Sun Yeung, jin-quan yu

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We herein report the first example of a 2-pyridone accelerated non-directed C–H cyanation with an arene as the limiting reagent. This protocol is compatible with a broad scope of arenes, including advanced intermediates, drug molecules, and natural products. A kinetic isotope experiment ($k_H/k_D = 4.40$) indicates that the C–H bond cleavage is the rate-limiting step. Also, the reaction is readily scalable, further showcasing the synthetic utility of this method.

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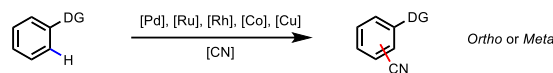
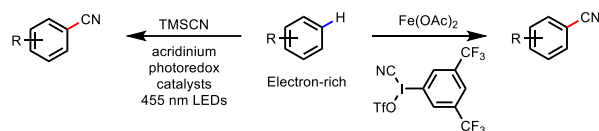
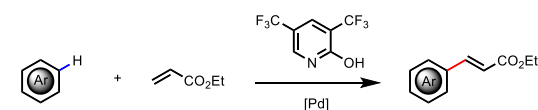
Luo-Yan Liu, Kap-Sun Yeung and Jin-Quan Yu*

Abstract: We herein report the first example of a 2-pyridone accelerated non-directed C–H cyanation with an arene as the limiting reagent. This protocol is compatible with a broad scope of arenes, including advanced intermediates, drug molecules, and natural products. A kinetic isotope experiment ($k_H/k_D = 4.40$) indicates that the C–H bond cleavage is the rate-limiting step. Also, the reaction is readily scalable, further showcasing the synthetic utility of this method.

Cyanoarenes are abundant in natural products, drug molecules, and advanced synthetic intermediates.¹ The cyano functional group is highly versatile in organic synthesis and can be readily converted to carboxyl, carbonyl, amino, and other heterocyclic groups.² Thus, installation of cyano groups in a direct and facile manner is of high interest. However, introduction of cyano groups onto arenes have traditionally relied heavily on the Sandmeyer reaction³ and other transition-metal-mediated cross-coupling reactions with aryl halides.⁴ The use of highly reactive diazonium intermediate and the requirement to prefunctionalize arenes render these traditional methods undesirable and inefficient, often with limited scope and functional group tolerance.

On the other hand, direct C–H cyanation of arenes offers a potentially superior alternative. In the past decade, tremendous efforts have been devoted to the development of directed C–H cyanation of arenes. Pyridines, pyrimidines, and oximes have been employed as directing groups for *ortho* C–H cyanation with Pd, Ru, Rh, and Co catalysts (**Fig. 1a**).⁵ A *meta*-selective C–H cyanation has been realized using a U-shaped template.⁶ More recently, two examples of non-directed C–H cyanation of arenes through radical pathways have also been achieved (**Fig. 1b**).⁷ However, these reactions are largely limited to only electron-rich and simple arenes. In a continuing effort to improve the reactivity and selectivity of non-directed C–H functionalizations of arenes, we have successively discovered 2,6-dialkyl pyridine ligands⁸ that can accelerate non-directed C–H olefination of electron-deficient arenes and electron-deficient 2-pyridone ligands⁹ that can enable C–H olefination with arenes as the limiting reagent (**Fig. 1c**).

Guided by these ligand developments, we wondered whether these ligands could be used to enable C–H cyanation. We began our study by treating the model substrate mesitylene (1.0 equiv.) with Pd(OAc)₂ (10 mol%), AgCN (1.1 equiv.), and AgOAc (3.0 equiv.) in HFIP at 100 °C. Encouragingly, the desired C(sp²)-H cyanation product was detected in 18% yield. We first evaluated several mono-dentate pyridine-based ligands (**L1–L3**), which have been

(a) Transition-Metal-Catalyzed Directed C(sp²)-H Cyanation(b) Non-Directed C(sp²)-H Cyanation(c) Ligand-Accelerated Non-Directed C(sp²)-H Olefination of Arenes

(d) This Work

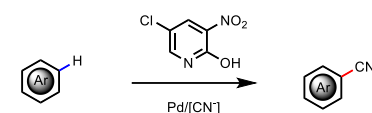


Figure 1. (a) Previous work about transition-metal-catalyzed directed C(sp²)-H cyanation. (b) Non-directed cyanation of arenes via radical mechanism (c) Ligand-accelerated non-directed C(sp²)-H olefination of arenes. (d) Ligand-accelerated non-directed C(sp²)-H cyanation of arenes.

Table 1. Ligand Evaluation^{a,b}

without ligand			
18%	L1 trace	L2 trace	L3 trace
L4 < 10%	L5 25%	L6 21%	L7 < 10%
L8 < 10%	L9 77%	L10 87%	L11 < 10%
L12 16%	L13 trace	L14 trace	L15 trace

[a] Conditions: mesitylene (0.2 mmol, 1.0 equiv), Pd(OAc)₂ (10 mol%), ligand (20 mol%), AgOAc (3.0 equiv), AgCN (1.1 equiv.), HFIP (0.5 mL), 100 °C, under air, 24 h. See SI for work up procedures. [b] The yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as the internal standard.

[*] L.-Y. Liu, Prof. Dr. J.-Q. Yu
Department of Chemistry, The Scripps Research Institute (TSRI)
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
E-mail: yu200@scripps.edu
Dr. Kap-Sun Yeung
Discovery Chemistry, Bristol-Myers Squibb Research and Development,
5 Research Parkway, Wallingford, CT 06492 (USA)
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shown to promote C–H activation.¹⁰ However, only trace amounts of product were observed. Based on our previous studies on non-directed C(sp²)–H olefination promoted by electron-deficient 2-pyridone ligands, we set out to extensively screen 2-pyridone ligands for this non-directed C(sp²)–H cyanation reaction. The addition of a simple 2-pyridone ligand suppressed the reactivity (**L4**). To our delight, the use of 5-nitro-2-pyridone, which has previously demonstrated efficiency for γ -C(sp³)–H arylation,¹¹ slightly increased the yield to 25% (**L5**). Incorporation of a trifluoromethyl or a nitro group at the 3 position of **L5** led to lower yields (**L6**, **L7**). A significant drop in reactivity was observed with 3-nitro-2-pyridone (**L8**). Intriguingly, the yield increased to 77% when a trifluoromethyl group was installed at the 5-position of **L8** (**L9**). The replacement of 5-CF₃ in **L9** with 5-Cl further improved the yield to 87% (**L10**). However, the use of 3,5-dichloro-2-pyridone resulted in loss of reactivity (**L11**). These results suggest that this cyanation reaction is exceptionally sensitive to the steric and electronic environments of the 2-pyridone ligands. Other structural variations of 2-pyridone ligands resulted in low reactivity (**L12–L15**) (Table 1).

With the optimal ligand **L10** identified, we next examined different cyanide sources and their loadings (Table 2). We first tested several commercially available cyanide salts and found that increasing the loading of AgCN to 2.0 equivalents from 1.1 equivalents decreased yield to 50% from 84%, presumably due to palladium catalyst deactivation by excess cyanide coordination. Screening of two other cyanide sources showed that CuCN and Zn(CN)₂ gave lower yields. Other reaction parameters have also

Table 2. Optimization of Reaction Conditions^{a,b,c}

Entry	Variations from the 'Standard Conditions'	Total Yield (%)
1	none	84
2	2.0 equiv. AgCN	50
3	1.1 equiv. CuCN	67
4	2.0 equiv. CuCN	39
5	0.6 equiv. Zn(CN) ₂	37
6	1.0 equiv. Zn(CN) ₂	32
7	1.1 equiv. KCN	trace
8	0.2 equiv. K ₃ Fe(CN) ₆	18
9	0.5 equiv. K ₃ Fe(CN) ₆	6
10	1.1 equiv. TMSCN	trace
11	no AgOAc	trace
12	1.0 equiv. AgOAc	45
13	2.0 equiv. AgOAc	50
14	2.0 equiv. Cu(OAc) ₂	trace
15	2.0 equiv. CuBr ₂	trace
16	CHCl ₃ as solvent instead of HFIP	trace
17	CHCl ₃ /HFIP = 1/1	30
18	45 mol% ligand	68
19	80 °C	60
20	120 °C	72

[a] Conditions: *o*-xylene (0.2 mmol, 1.0 equiv), Pd(OAc)₂ (10 mol%), ligand (20 mol%), AgOAc (3.0 equiv), AgCN (1.1 equiv.), HFIP (0.5 mL), 100 °C, under air, 24 h. See SI for work up procedures. [b] The yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as the internal standard. [c] The product was isolated as a mixture of two isomers: 3-cyano and 4-cyano *o*-xylene.

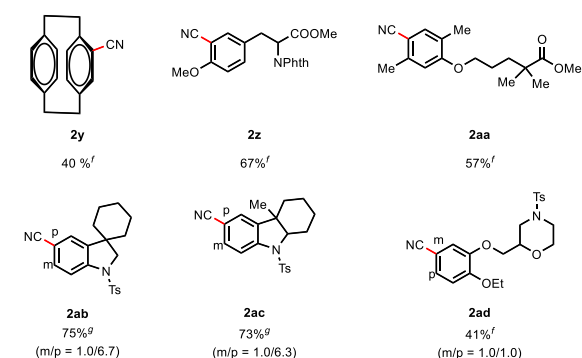
been examined, such as oxidants, solvents, and temperature. Further, minimal products were afforded with KCN, K₃Fe(CN)₆, and TMSCN as the cyanation reagents. Oxidants other than AgOAc only provided trace products, while other variations of the reaction parameters resulted in inferior reactivity.

With the optimal reaction conditions established, we next explored the scope of arenes for this non-directed cyanation reaction. Electron neutral to rich arenes such as simple benzene, alkyl substituted benzenes, and alkoxy benzenes consistently afforded the mono-cyanated products in good yields (**2a–2q**, **2t–2u**). The mono selectivity could be explained by the electron-deficient nature of cyanated arenes. Mono-alkylated arenes were cyanated at the less sterically hindered *meta* and *para* positions, providing *meta*- and *para*-isomers as the main products (**2b–2d**). Arenes with bulkier substituents such as *tert*-butyl group (**2d**) afforded considerably

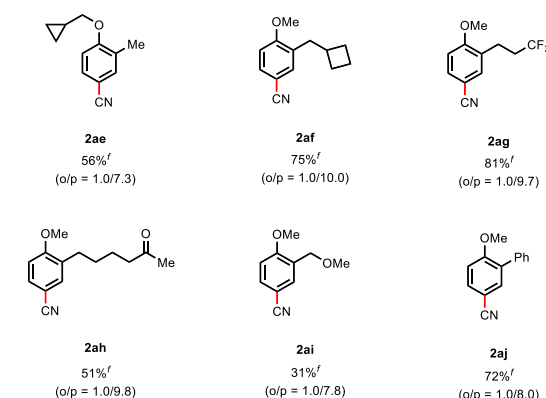
Table 3. Substrate Scope^{a,b}

Ar-H	Ar-CN	Yield (%)	Isomer Ratio (m/p)
1	2		
Simple arenes and heterocycles			
2a	2b	2c	2d
66% ^c	56% ^h (o/m/p = 1.0/1.7/2.3)	50% ^h (m/p = 1.0/1.3)	74% ^h (m/p = 1.0/6.1)
2e	2f	2g	2h
84% ^h (m/p = 1.0/7.5)	90% ^h	77% ^h (α/α'/β = 12.5/1.0/3.8)	87% ^h
2i	2j	2k	2l
65% (o/p = 1.0/1.9)	58% (α/β = 1.0/7.1)	82%	73% (α/β = 2.0/1.0)
2m	2n	2o	2p
55% ^f	64% ^{g,f} (α/α'/γ = 2.5/1.4/1.0)	50% ^{g,f} (p/others = 10.0/1.0)	81% (o/p = 1.0/5.5)
2q	2r	2s	2t
70% (o/p = 1.0/7.5)	63% ^f (p/others = 2.4/1.0)	50% ^d (o/m/p = 1.0/6.4/1.7)	55% ^d (o/m/p = 5.0/1.0/1.2)
2u	2v	2w	2x
83% (α/β = 1.0/1.5)	74% (o/p = 1.0/1.2)	81% ^f (1/2/4 = 1.0/1.3/3.1)	93% ^f (4/others = 2.4/1.0)

Late-stage functionalization



2-Alkyl/aryl-1-alkoxy substrates



[a] Conditions: **1** (0.2 mmol, 1.0 equiv), Pd(OAc)₂ (10 mol%), **L9** (20 mol%), AgOAc (3.0 equiv), AgCN (1.1 equiv.), HFIP (0.5 mL), 100 °C, under air, 24 h. See SI for work up procedures. [b] The product was isolated as mixture of regio-isomers. [c] 3.0 equiv. of benzene were used. [d] 8.0 equiv. of substrates were used. [e] The reaction was conducted at 120 °C. [f] 15 mol% Pd(OAc)₂ were used instead of 10 mol%. [g] 20 mol% Pd(OAc)₂ were used instead of 10 mol%. [h] **L10** was used instead of **L9**. [i] The reaction was conducted at 90 °C for 12 h.

better *para* site selectivity. Di-alkylated and tri-alkylated arenes all provided the mono-cyanated products in good yields with various selectivities depending on the substitution patterns of the alkylated arenes (**2e–2h**). Strong electron-donating substituents such as alkoxy groups, only provide *ortho*- and *para*-cyanated isomers, owing to its electronic effect. The bulkier silyl-protected phenol gave *para*-cyanated product as the main isomer because of steric effect (**2p** and **2q**). Naphthalene also provided the cyanated products in 73% yield, with a 2.0/1.0 selectivity ratio (α/β) (**2l**). This non-directed cyanation occurred selectively on the relative electron-rich arene for diaryl substrates (**2m**). For 2-chloroanisole and 3-chloroanisole (**2n** and **2o**), the yields dropped to only 20% under the same conditions due to the electron-withdrawing effect of the chloride on the benzene ring. However, heating up the reaction to 120 °C improved yields to 64% and 50% respectively. Electron-deficient arenes such as chlorobenzene and methyl benzoate, are unreactive to this reaction condition, thus 8.0 equiv. of arenes and 1.0 equiv. of cyanide were used to secure 45% and 50% yields respectively (**2s** and **2t**).

To further examine the practicality of this reaction, we also examined cyanation on advanced intermediates and biologically relevant substrates (**2v–2x**, **2ab–2ac**). Gladly, O, S, N- heterocycles could be cyanated in good yields. Interestingly, for both

dibenzofuran and dibenzothiophene, cyanation proceeded selectively at the 4 position, while olefination occurred at the 2 position in our previous studies for non-directed olefination.^{ref} This suggests that electronic effect is more important to selectivity compared to steric effect in this cyanation reaction. Some natural products and drug molecules can also be cyanated under the optimal conditions in moderate to good yields (**2y–2aa**, **2ad**). 2-Alkyl/aryl anisoles were observed to give better selectivity (**2ae–2aj**), which could be rationalized by a combination of electronic effect and steric effect (**Table 3**).

To further showcase the synthetic utility of this method, non-directed cyanation of mesitylene (**1h**) was carried out on 2.0 mmol scale, yielding the desired product in 75% yield (**Fig. 2a**).

To gain insight into the reaction mechanism, we carried out kinetic isotope effect (KIE) experiments. Inter-molecular one-pot

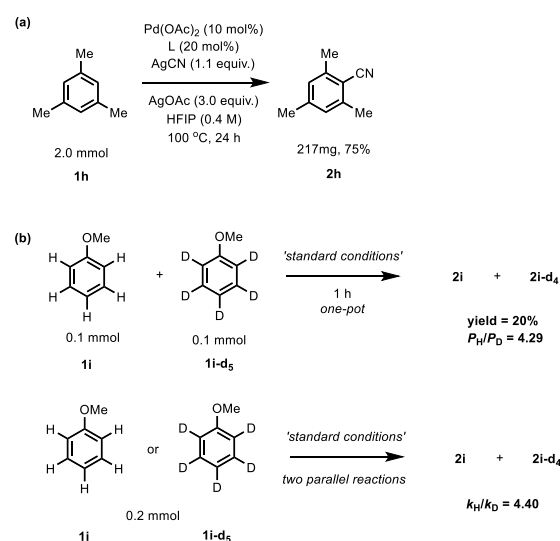


Figure 2. (a) Scale-up reaction. (b) Primary kinetic isotope effect.

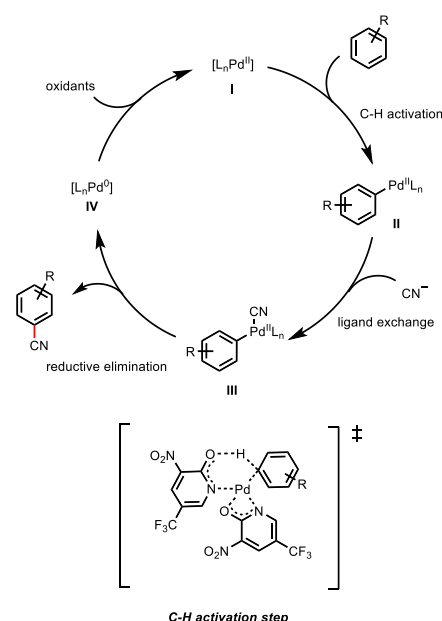


Figure 3. Proposed mechanism

and parallel experiments provided a P_H/P_D value of 4.29 and a k_H/k_D value of 4.40, respectively, which suggest that the C–H activation step is rate-limiting step (**Fig. 2b**).

A plausible catalytic cycle is outlined in Figure 4. 2-pyridone ligand functions as an analogue of OAc and accelerates C–H cleavage to form intermediate **II**. Ligand Exchange of CN[−] between AgCN and Pd complex intermediate **II** forms **III**. Then reductive elimination from **III** provides the desired product (**Fig. 3**).

In summary, we have developed the first example of a Pd-catalyzed non-directed cyanation of arenes, enabled by an electron-deficient 2-pyridone ligands. The reaction features broad substrate scope and high functional group compatibility, exemplified by successful C–H cyanation of a range of complex molecules. Currently, we are attempting to achieve better site selectivity for non-directed C–H activation through ligand design.

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Keywords: cyanation • C–H activation • palladium • 2-pyridone

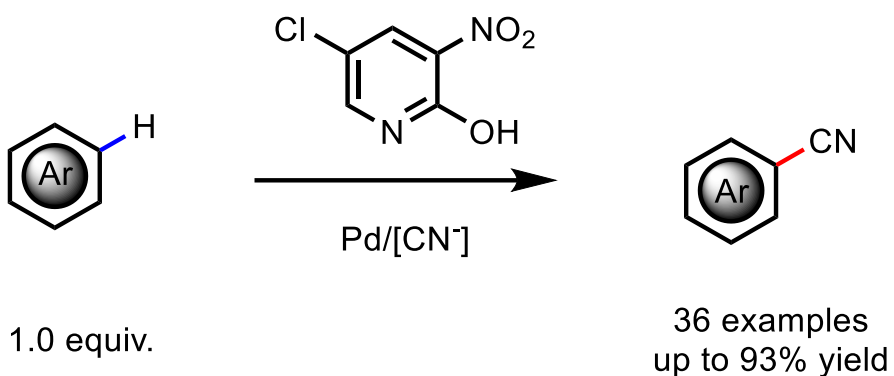
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C–H Activation

L.-Y. Liu, K.-S. Yeung, J.-Q. Yu*

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[*] L.-Y. Liu, Prof. Dr. J.-Q. Yu
Department of Chemistry, The Scripps Research Institute (TSRI)
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
E-mail: yu200@scripps.edu
Dr. Kap-Sun Yeung
Discovery Chemistry, Bristol-Myers Squibb Research and Development,
5 Research Parkway, Wallingford, CT 06492 (USA)
Supporting information for this article is available on the WWW under
<http://dx.doi.org/>.

[a] Conditions: mesitylene (0.2 mmol, 1.0 equiv), Pd(OAc)₂ (10 mol%), ligand (20 mol %), AgOAc (3.0 equiv), AgCN (1.1 equiv.), HFIP (0.5 mL), 100 °C, under air, 24 h. See SI for work up procedures. [b] The yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as the internal standard.

shown to promote C–H activation.¹⁰ However, only trace amounts of product were observed. Based on our previous studies on non-directed C(sp³)–H olefination promoted by electron-deficient 2-pyridone ligands, we set out to extensively screen 2-pyridone ligands for this non-directed C(sp³)–H cyanation reaction. The addition of a simple 2-pyridone ligand suppressed the reactivity (**L4**). To our delight, the use of 5-nitro-2-pyridone, which has previously demonstrated efficiency for γ -C(sp³)–H arylation,¹¹ slightly increased the yield to 25% (**L5**). Incorporation of a trifluoromethyl or a nitro group at the 3 position of **L5** led to lower yields (**L6**, **L7**). A significant drop in reactivity was observed with 3-nitro-2-pyridone (**L8**). Intriguingly, the yield increased to 77% when a trifluoromethyl group was installed at the 5-position of **L8** (**L9**). The replacement of 5-CF₃ in **L9** with 5-Cl further improved the yield to 87% (**L10**). However, the use of 3,5-dichloro-2-pyridone resulted in loss of reactivity (**L11**). These results suggest that this cyanation reaction is exceptionally sensitive to the steric and electronic environments of the 2-pyridone ligands. Other structural variations of 2-pyridone ligands resulted in low reactivity (**L12–L15**) (**Table 1**).

With the optimal ligand **L10** identified, we next examined different cyanide sources and their loadings (**Table 2**). We first tested several commercially available cyanide salts and found that increasing the loading of AgCN to 2.0 equivalents from 1.1 equivalents decreased yield to 50% from 84%, presumably due to palladium catalyst deactivation by excess cyanide coordination. Screening of two other cyanide sources showed that CuCN and Zn(CN)₂ gave lower yields. Other reaction parameters have also

Table 2. Optimization of Reaction Conditions^{a,b,c}

been examined, such as oxidants, solvents, and temperature. Further, minimal products were afforded with KCN, K₃Fe(CN)₆, and TMSCN as the cyanation reagents. Oxidants other than AgOAc only provided trace products, while other variations of the reaction parameters resulted in inferior reactivity.

With the optimal reaction conditions established, we next explored the scope of arenes for this non-directed cyanation reaction. Electron neutral to rich arenes such as simple benzene, alkyl substituted benzenes, and alkoxy benzenes consistently afforded the mono-cyanated products in good yields (**2a–2q**, **2t–2u**). The mono selectivity could be explained by the electron-deficient nature of cyanated arenes. Mono-alkylated arenes were cyanated at the less sterically hindered *meta* and *para* positions, providing *meta*- and *para*-isomers as the main products (**2b–2d**). Arenes with bulkier substituents such as *tert*-butyl group (**2d**) afforded considerably

Table 3. Substrate Scope^{a,b}

[a] Conditions: *o*-xylene (0.2 mmol, 1.0 equiv), Pd(OAc)₂ (10 mol%), ligand (20 mol %), AgOAc (3.0 equiv), AgCN (1.1 equiv.), HFIP (0.5 mL), 100 °C, under air, 24 h. See SI for work up procedures. [b] The yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as the internal standard. [c] The product was isolated as a mixture of two isomers: 3-cyano and 4-cyano *o*-xylene.

dibenzofuran and dibenzothiophene, cyanation proceeded selectively at the 4 position, while olefination occurred at the 2 position in our previous studies for non-directed olefination.^{ref} This suggests that electronic effect is more important to selectivity compared to steric effect in this cyanation reaction. Some natural products and drug molecules can also be cyanated under the optimal conditions in moderate to good yields (**2y–2aa**, **2ad**). 2-Alkyl/aryl anisoles were observed to give better selectivity (**2ae–2aj**), which could be rationalized by a combination of electronic effect and steric effect (**Table 3**).

To further showcase the synthetic utility of this method, non-directed cyanation of mesitylene (**1h**) was carried out on 2.0 mmol scale, yielding the desired product in 75% yield (**Fig. 2a**).

To gain insight into the reaction mechanism, we carried out kinetic isotope effect (KIE) experiments. Intermolecular one-pot

[a] Conditions: **1** (0.2 mmol, 1.0 equiv), Pd(OAc)₂ (10 mol%), **L9** (20 mol%), AgOAc (3.0 equiv), AgCN (1.1 equiv.), HFIP (0.5 mL), 100 °C, under air, 24 h. See SI for work up procedures. [b] The product was isolated as mixture of regio-isomers. [c] 3.0 equiv. of benzene were used. [d] 8.0 equiv. of substrates were used. [e] The reaction was conducted at 120 °C. [f] 15 mol% Pd(OAc)₂ were used instead of 10 mol%. [g] 20 mol % Pd(OAc)₂ were used instead of 10 mol%. [h] **L10** was used instead of **L9**. [i] The reaction was conducted at 90 °C for 12 h.

better *para* site selectivity. Di-alkylated and tri-alkylated arenes all provided the mono-cyanated products in good yields with various selectivities depending on the substitution patterns of the alkylated arenes (**2e–2h**). Strong electron-donating substituents such as alkoxy groups, only provide *ortho*- and *para*-cyanated isomers, owing to its electronic effect. The bulkier silyl-protected phenol gave *para*-cyanated product as the main isomer because of steric effect (**2p** and **2q**). Naphthalene also provided the cyanated products in 73% yield, with a 2.0/1.0 selectivity ratio (α/β) (**2l**). This non-directed cyanation occurred selectively on the relative electron-rich arene for diaryl substrates (**2m**). For 2-chloroanisole and 3-chloroanisole (**2n** and **2o**), the yields dropped to only 20% under the same conditions due to the electron-withdrawing effect of the chloride on the benzene ring. However, heating up the reaction to 120 °C improved yields to 64% and 50% respectively. Electron-deficient arenes such as chlorobenzene and methyl benzoate, are unreactive to this reaction condition, thus 8.0 equiv. of arenes and 1.0 equiv. of cyanide were used to secure 45% and 50% yields respectively (**2s** and **2t**).

To further examine the practicality of this reaction, we also examined cyanation on advanced intermediates and biologically relevant substrates (**2v–2x**, **2ab–2ac**). Gladly, O, S, N- heterocycles could be cyanated in good yields. Interestingly, for both

(a)

Figure 2. (a) Scale-up reaction. (b) Primary kinetic isotope effect.

Figure 3. Proposed mechanism

and parallel experiments provided a P_H/P_D value of 4.29 and a k_H/k_D value of 4.40, respectively, which suggest that the C–H activation step is rate-limiting step (**Fig. 2b**).

A plausible catalytic cycle is outlined in Figure 4. 2-pyridone ligand functions as an analogue of OAc and accelerates C–H cleavage to form intermediate **II**. Ligand Exchange of CN^- between AgCN and Pd complex intermediate **II** forms **III**. Then reductive elimination from **III** provides the desired product (**Fig. 3**).

In summary, we have developed the first example of a Pd-catalyzed non-directed cyanation of arenes, enabled by an electron-deficient 2-pyridone ligands. The reaction features broad substrate scope and high functional group compatibility, exemplified by successful C–H cyanation of a range of complex molecules. Currently, we are attempting to achieve better site selectivity for non-directed C–H activation through ligand design.

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Keywords: cyanation • C–H activation • palladium • 2-pyridone

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Ligand-Accelerated Non-Directed C–
H Cyanation of Arenes

We herein report the first example of a 2-pyridone accelerated non-directed C–H cyanation with an arene as the limiting reagent. This protocol is compatible with a broad scope of arenes, including advanced intermediates, drug molecules, and natural products. A kinetic isotope experiment ($k_H/k_D = 4.40$) indicates that the C–H bond cleavage is the rate-limiting step. Also, the reaction is readily scalable, further showcasing the synthetic utility of this method.

Nondirected CyanationYu.docx (689.81 KiB)

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Ligand-Accelerated Non-Directed C–H Cyanation of Arenes

Luo-Yan Liu[†], Kap-Sun Yeung[‡] and Jin-Quan Yu^{*,†}

[†]Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road,
La Jolla, California 92037, United States

[‡]Discovery Chemistry, Bristol-Myers Squibb Research and Development, 5 Research
Parkway, Wallingford, CT 06492, United States

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General Information

Substrates were obtained from the commercial sources or synthesized following literature procedures. AgOAc and HFIP (Hexafluoro-2-propanol) were obtained from Oakwood. Solvents were obtained from Sigma-Aldrich, Alfa-Aesar and Acros and used directly without further purification. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F254. Visualization was carried out with UV light and Vogel's permanganate. ¹H NMR was recorded on Bruker AMX-400 instrument (400 MHz) or Bruker DRX-600 instrument (600 MHz). Chemical shifts were quoted in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants, *J*, were reported in Hertz unit (Hz). ¹³C NMR spectra were recorded on Bruker AMX-400 instrument (100 MHz) or Bruker DRX-600 instrument (150 MHz), and were fully decoupled by broad band proton decoupling. ¹⁹F NMR spectra were recorded on Bruker AMX-400 instrument (100 MHz), and were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.0 ppm of chloroform-*d*. High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight) or APCI (atmospheric chemical ionization).

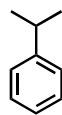
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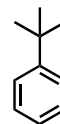
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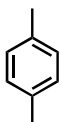
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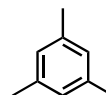
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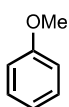
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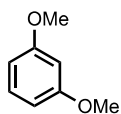
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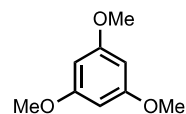
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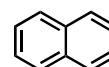
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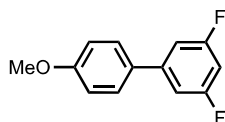
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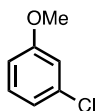
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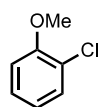
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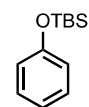
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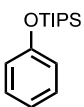
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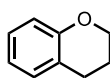
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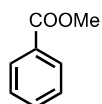
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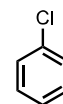
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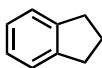
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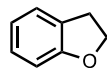
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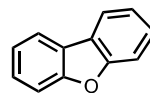
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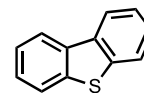
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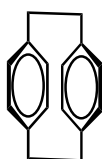
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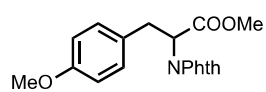
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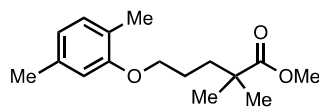
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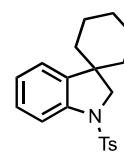
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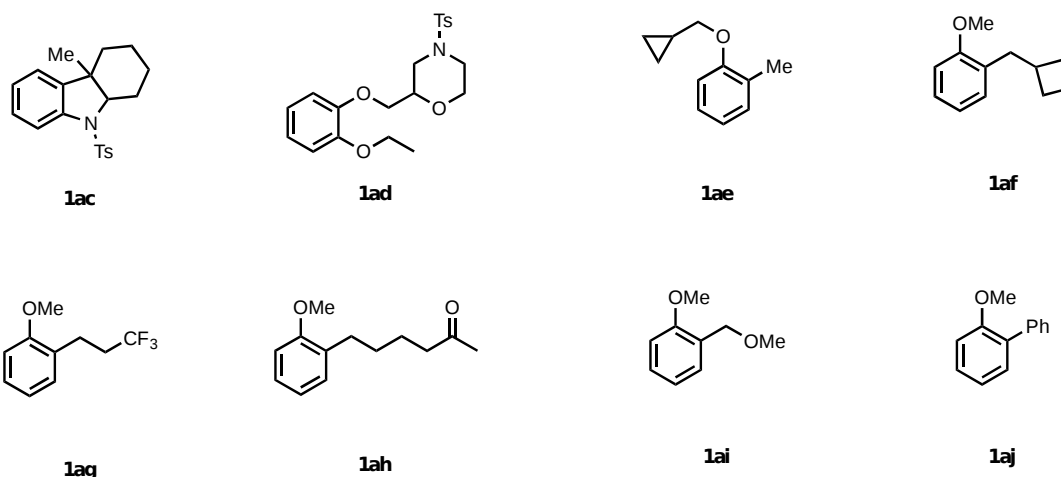
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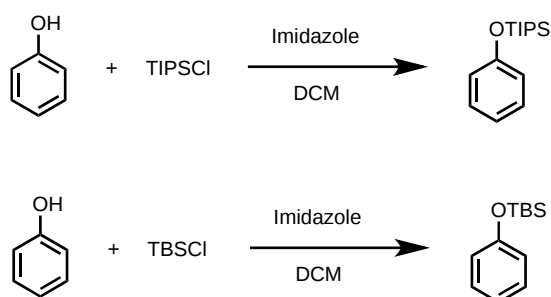
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Experimental Section

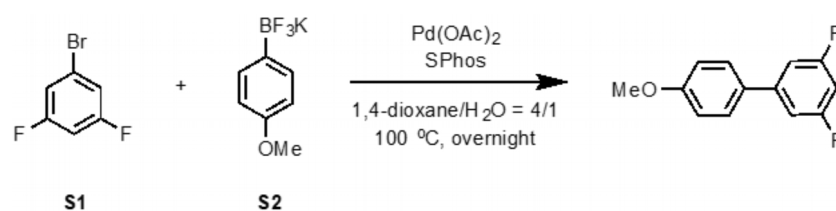
Substrate Preparation

Substrates **1a-1l**, **1n**, **1r-1y**, **1aj** are commercially available. Substrates **1z-1ad** were synthesized based on literatures¹.

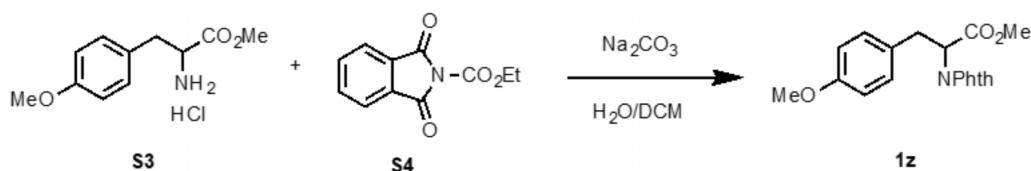


Tert-butyldimethyl(phenoxy)silane (1p)¹: Phenol (0.47 mg, 5.0 mmol) and imidazole (0.85 g, 12.5 mmol) were dissolved in 20 mL of DCM. TBSCl (0.9 g, 6.0 mmol) was added to the mixture and the mixture stirred at room temperature until no starting material remained by TLC. The reaction mixture was extracted with distilled water (1 x 20 ml) and the organic layer was washed with 1 N NaOH (1 x 20 ml) and brine (1 x 20 ml), dried using anhydrous Na₂SO₄ and concentrated under vacuum to afford pure product as a pale yellow oil (1.0 g, 85 %). Analytical data matched that reported in the literature¹.

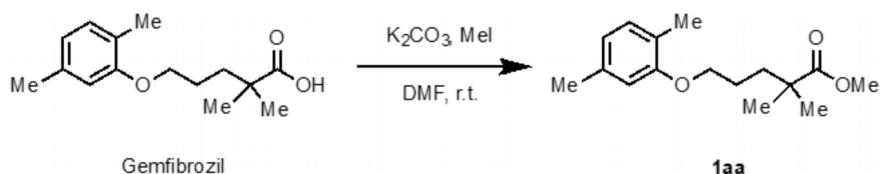
Triisopropyl(phenoxy)silane (1q)¹: Phenol (0.47 mg, 5.0 mmol) and imidazole (0.85 g, 12.5 mmol) were dissolved in 20 mL of DCM. TIPSCl (1.29 mL, 6.0 mmol) was added to the mixture and the mixture stirred at room temperature until no starting material remained by TLC. The reaction mixture was extracted with distilled water (1 x 20 ml) and the organic layer was washed with 1 N NaOH (1 x 20 ml) and brine (1 x 20 ml), dried using anhydrous Na₂SO₄ and concentrated under vacuum to afford pure product as a colorless oil (1.0 g, 80 %). Analytical data matched that reported in the literature¹.



3',5'-Difluoro-4-methoxy-[1,1'-biphenyl]-3-carbonitrile (1m)²: To a solution of palladium acetate (5 mol%), Sphos ligand (10 mol%), **S1** (1.1 equiv.), **S2** (1.0 equiv.) and potassium carbonate (2.0 equiv.) in 1,4-dioxane/H₂O (4:1), was stirred under nitrogen atmosphere at 100 °C overnight. The reaction mixture was then cooled to r.t., filtered through celite and diluted with diethyl ether (20 mL). The organic layer was successively washed with water and brine and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired products.

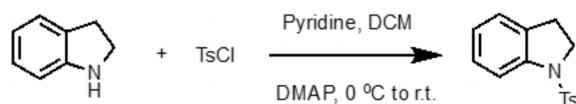


Methyl (S)-2-(1,3-dioxoisindolin-2-yl)-3-(3-methoxyphenyl)propanoate (1z)¹: To a suspension of **S4** (737,1 mg, 3.0 mmol) and Na₂CO₃ (635.9 mg, 6.0 mmol) in water (7.0 ml) and DCM (2.0 ml) was added **S3** (658.4 mg, 3.0 mmol). The mixture was stirred at room temperature overnight. Then the mixture was extracted with DCM (3 x 30 ml). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The resulting mixture was purified by silica gel chromatography to afford **1z** as a white solid (702.4 mg, 69%). Analytical data matched that reported in the literature¹.

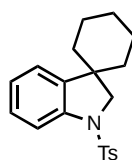


Methyl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (1aa)¹: To a suspension of Gemfibrozil (500.6 mg, 2.0 mmol) and K₂CO₃ (552 mg, 2.6 mmol) in DMF (5.0 mL) was added MeI (0.2 mL, 3.9 mmol) at room temperature. After the reaction completed, the reaction was dilute with ethyl acetate (40 mL), and then washed with water, brine. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum.

The resulting mixture was purified by silica gel chromatography to afford **1z** as a colorless liquid (450.1 mg, 85% yield). Analytical data matched that reported in the literature¹.

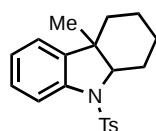


General procedure to protect the indoline substrates¹: To a solution of indoline (238.3 mg, 2.0 mmol), DMAP (10 mg) and pyridine (0.5 mL) under 0 °C was added TsCl (457.4 mg, 2.4 mmol). The mixture was allowed to warm up to room temperature overnight. After the reaction completed, the solvent was removed under vacuum, and the resulting mixture was purified by silica gel chromatography to afford desired Ts-protected indolines **1ab** and **1ac**.



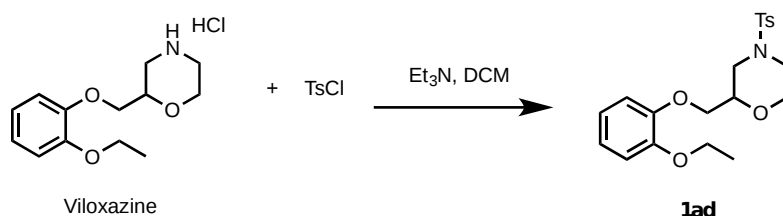
1ab

1'-Tosylspiro[cyclohexane-1,3'-indoline]¹



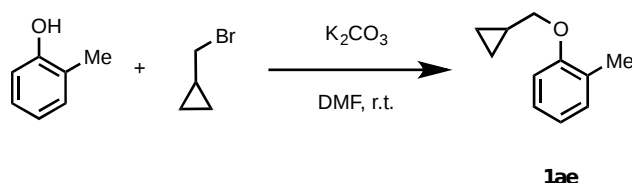
1ac

4a-Methyl-9-tosyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-6-carbonitrile¹



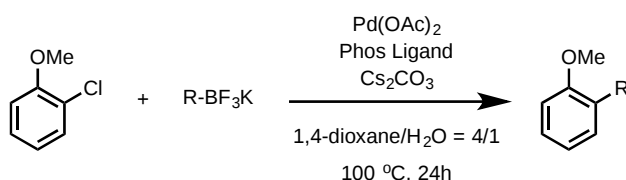
2-((2-Ethoxyphenoxy)methyl)-4-tosylmorpholine (1ad)¹: To a solution of Viloxazine[⊗] HCl (82.14 mg, 0.3 mmol) and Et₃N (0.12 mL, 0.9 mmol) in DCM (5.0 ml) was added TsCl (62.9 mg, 0.33 mmol) at room temperature. After the reaction completed, the solvent was removed

under vacuum, and the resulting mixture was purified by silica gel chromatography to afford **2ad** as a white solid (108.1 mg, 92% yield). Analytical data matched that reported in the literature¹.

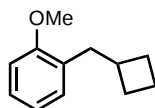


1-(Cyclopropylmethoxy)-2-methylbenzene (1ae): *Ortho*-cresol (0.22 g, 2.0 mmol) and potassium carbonate (0.83 g, 6.0 mmol) were suspended in N, N-dimethylformamide (10 mL). Cyclopropyl methyl chloride (0.23 mL, 2.4 mmol) was added to this suspension, and stirred overnight at room temperature. This mixture was partitioned into ethyl acetate and water. The organic layer was separated, washed with water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to obtain **1ae** as a colorless oil (288.0 mg, 89% yield).

¹H NMR (600 MHz, CDCl₃) δ 7.12 (m, 2H), 6.84 (td, *J* = 7.4, 1.2 Hz, 1H), 6.79 (dd, *J* = 8.2, 1.0 Hz, 1H), 3.82 (d, *J* = 6.7 Hz, 2H), 2.25 (s, 3H), 1.31-1.24 (m, 1H), 0.65-0.57 (m, 2H), 0.39-0.31 (m, 2H), ¹³C NMR (150 MHz, CDCl₃) δ 157.19, 130.60, 127.08, 126.65, 120.26, 111.49, 72.56, 16.26, 10.42, 2.99. HRMS (ESI-TOF) Calcd for C₁₁H₁₅O⁺ [M+H]⁺: 163.1123, found: 163.1119.



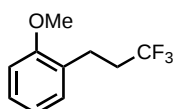
General procedure for Suzuki-Coupling: To a solution of palladium acetate (5 mol%), Sphos ligand (10 mol%), 2-chloroanisole (1.1 equiv.), RBF₃K (1.0 equiv.) and cesium carbonate (2.0 equiv.) in 1,4-dioxane/H₂O (4:1), was stirred under nitrogen atmosphere at 100 °C overnight. The reaction mixture was then cooled to r.t., filtered through celite and diluted with diethyl ether (20 mL). The organic layer was successively washed with water and brine and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired products.



1af

1-(Cyclobutylmethyl)-2-methoxybenzene (1af)

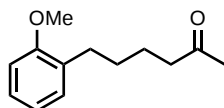
^1H NMR (600 MHz, CDCl_3) δ 7.60 (d, J = 8.4 Hz, 2.6H), 7.53 (d, J = 1.8 Hz, 1H), 7.49 (m, 2H), 7.42 (m, 1H), 7.34 (d, J = 8.4 Hz, 2.6H), 2.99 (m, 2.3H), 1.29 (d, 13.8H), ^{13}C NMR (150 MHz, CDCl_3) δ 154.33, 132.21, 131.17, 130.13, 129.58, 129.07, 127.27, 34.38, 33.38, 23.64, 23.52 17.63. HRMS (ESI-TOF) Calcd for $\text{C}_{12}\text{H}_{17}\text{O}^+$ $[\text{M}+\text{H}]^+$: 177.1279, found: 177.1277.



1ag

1-Methoxy-2-(3,3,3-trifluoropropyl)benzene (1ag)

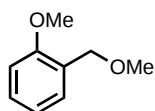
^1H NMR (600 MHz, CDCl_3) δ 7.23 (td, J = 7.8, 1.6 Hz, 1H), 7.13 (dt, J = 7.5, 1.3 Hz, 1H), 7.49 (m, 1H), 6.91-6.88 (m, 1H), 6.86 (d, J = 8.2, 1.2 Hz, 1H), 3.84 (d, J = 1.0 Hz, 3H), 2.88-2.84 (m, 2H), 2.42-2.32 (m, 2H), ^{13}C NMR (150 MHz, CDCl_3) δ 157.40, 129.87, 127.99, 127.95, 127.40, 126.12, 120.53, 110.26, 55.18, 34.01, 33.82, 33.64, 33.45, 23.54. ^{19}F NMR (376 MHz, CDCl_3) δ -66.91 (s, 3F). HRMS (ESI-TOF) Calcd for $\text{C}_{10}\text{H}_{12}\text{F}_3\text{O}^+$ $[\text{M}+\text{H}]^+$: 205.0840, found: 205.0842.



1ah

6-(2-Methoxyphenyl)hexan-2-one (1ah)

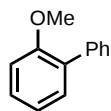
^1H NMR (600 MHz, CDCl_3) δ 7.17 (ddd, J = 8.2, 7.4, 1.8 Hz, 1H), 7.11 (dd, J = 7.4, 1.8 Hz, 1H), 6.87 (td, J = 7.4, 1.1 Hz, 1H), 6.83 (dd, J = 8.1, 1.1 Hz, 1H), 3.81 (s, 3H), 2.61 (t, J = 7.4 Hz, 2H), 2.45 (t, J = 7.2 Hz, 2H), 2.12 (s, 3H), 1.66-1.56 (m, 4H), ^{13}C NMR (150 MHz, CDCl_3) δ 157.37, 130.56, 129.75, 126.95, 120.33, 110.20, 55.21, 43.66, 29.88, 29.85, 29.33, 23.75. HRMS (ESI-TOF) Calcd for $\text{C}_{13}\text{H}_{19}\text{O}_2^+$ $[\text{M}+\text{H}]^+$: 207.1385, found: 207.1387.



1ai

1-Methoxy-2-(methoxymethyl)benzene (1ai)

^1H NMR (600 MHz, CDCl_3) δ 7.35 (dd, J = 7.6, 1.8 Hz, 1H), 7.29-7.25 (m, 1H), 6.96 (td, J = 7.4, 1.2 Hz, 1H), 6.88 (dd, J = 8.2, 1.0 Hz, 1H), 4.51 (s, 2H), 3.84 (s, 3H), 3.42 (s, 3H), ^{13}C NMR (150 MHz, CDCl_3) δ 157.20, 129.11, 128.74, 126.47, 120.38, 110.23, 69.56, 58.32, 55.38. HRMS (ESI-TOF) Calcd for $\text{C}_9\text{H}_{13}\text{O}_2^+$ $[\text{M}+\text{H}]^+$: 153.0916, found: 153.0913.

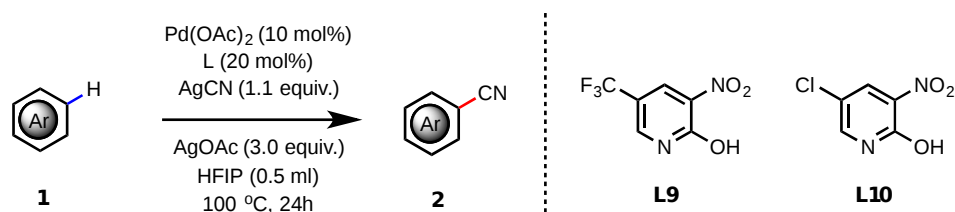


1aj

2-Methoxy-1,1'-biphenyl (**1aj**)

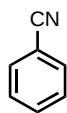
^1H NMR (600 MHz, CDCl_3) δ 7.56-7.52 (m, 2H), 7.42 (dd, J = 8.1, 7.2 Hz, 2H), 7.35-7.31 (m, 3H), 7.04 (tt, J = 7.3, 0.9 Hz, 1H), 7.00 (dd, J = 8.6, 1.0 Hz, 1H), 3.82 (s, 3H), ^{13}C NMR (150 MHz, CDCl_3) δ 156.43, 138.51, 130.87, 130.70, 129.52, 128.58, 127.95, 126.89, 120.80, 111.20, 55.53. HRMS (ESI-TOF) Calcd for $\text{C}_{13}\text{H}_{13}\text{O}^+$ $[\text{M}+\text{H}]^+$: 185.0961, found: 185.0964.

Cyanation of Simple Arenes



General procedure for cyanation of simple arenes: Arenes (0.2 mmol), AgCN (1.1 equiv.), $\text{Pd}(\text{OAc})_2$ (10 mol%), **L9** or **L10** (20 mol%), AgOAc (3.0 equiv.), and HFIP (0.5 ml) were added to a reaction vial (10 ml). The vial was capped and closed tightly. Then the reaction mixture was stirred at 100 °C for 24 hours. After cooling to room temperature, the mixture was passed through a pad of celite with ethyl acetate as the eluent to remove the insoluble precipitate. The resulting solution was concentrated and purified by preparative thin-layer chromatography to afford the desired product **2**. The ratio of the isomers were determined by the crude ^1H NMR.

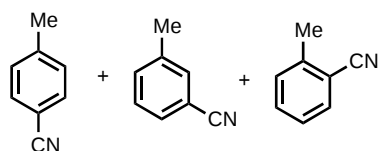
Scope of Arenes



2a

Benzonitrile (**2a**)³

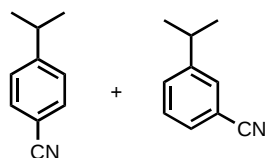
Benzene **1a** was cyanated following the general procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2a** was obtained as a colorless oil (13.6 mg, 66%).



2b-a, 2b-b, 2b-c

Tolunitrile (2b)³

Toluene **1b** was cyanated following the general procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2b** was obtained as a colorless oil (13.1 mg, 56%). The ratio of **2b-a**, **2b-b** and **2b-c** isomers is 2.3/1.7/1.0, determined by the crude ¹H NMR.

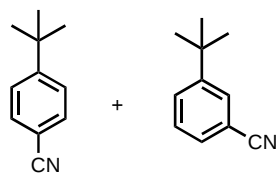


2c-a, 2c-b

***p*-Cyanocumen and *m*-Cyanocumen (2c)⁴**

Isopropylbenzene **1c** was cyanated following the general procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2c** was obtained as a colorless oil (14.5 mg, 50%). The ratio of **2c-a** and **2c-b** isomers is 1.3/1.0, determined by the crude ¹H NMR.

¹H NMR (600 MHz, CDCl₃) δ 7.60 (d, *J* = 8.4 Hz, 2.6H), 7.53 (d, *J* = 1.8 Hz, 1H), 7.49 (m, 2H), 7.42 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 2.6H), 2.99 (m, 2.3H), 1.29 (d, 13.8H), ¹³C NMR (150 MHz, CDCl₃) δ 154.33, 132.21, 131.17, 130.13, 129.58, 129.07, 127.27, 34.38, 33.38, 23.64, 23.52 17.63.

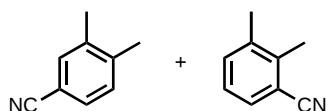


2d-a, 2d-b

3-Tert-butyl-1-cyanobenzene (2d)⁵

Tert-butylbenzene **1d** was cyanated following the general procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2d** was obtained as a colorless oil (23.6 mg, 74%). The ratio of **2d-a** and **2d-b** isomers is 6.1/1.0, determined by the crude ¹H NMR.

¹H NMR (600 MHz, CDCl₃) δ 7.66 (m, 0.8H), 7.63 (m, 0.8H), 7.59 (m, 2H), 7.47 (m, 2.8H), 7.40 (m, 0.8H), 1.33 (s, 16.2H), ¹³C NMR (150 MHz, CDCl₃) δ 156.60, 152.43, 131.93, 129.99, 129.19, 129.13, 128.84, 126.13, 119.33, 119.12, 112.05, 109.27, 35.23, 34.85, 30.99, 30.91.

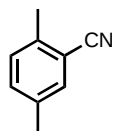


2e-a, 2e-b

3,4-Dimethylbenzonitrile (2e)⁶

o-Xylene **1e** was cyanated following the general procedure, 15 mol% Pd(OAc)₂ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2e** was obtained as a colorless oil (22.0 mg, 84%). The ratio of **2e-a** and **2e-b** isomers is 7.5/1.0, determined by the crude ¹H NMR.

¹H NMR (600 MHz, CDCl₃) δ 7.40 (d, *J* = 1.6 Hz, 1H), 7.38 (dd, *J* = 7.7, 1.8 Hz 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 2.32 (s, 3H), 2.29 (s, 3H), ¹³C NMR (150 MHz, CDCl₃) δ 142.41, 137.83, 132.79, 130.23, 129.59, 119.25, 109.47, 20.09, 19.51.

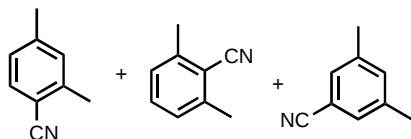


2f

2,5-Dimethylbenzonitrile (2f)⁶

p-Xylene **1f** was cyanated following the general procedure, 15 mol% Pd(OAc)₂ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2f** was obtained as a pale yellow oil (23.6 mg, 90%).

¹H NMR (600 MHz, CDCl₃) δ 7.39 (d, *J* = 1.8 Hz, 1H), 7.29-7.26 (m, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 2.49 (s, 3H), 2.34 (s, 3H), ¹³C NMR (150 MHz, CDCl₃) δ 138.81, 136.01, 133.52, 132.67, 130.06, 118.31, 112.49, 20.59, 19.91.

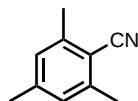


2g-a, 2g-b, 2g-c

2,4-Dimethylbenzonitrile and 2,6-dimethylbenzonitrile and 3,5-dimethylbenzonitrile (2g)⁶

m-Xylene **1g** was cyanated following the general procedure, 15 mol% Pd(OAc)₂ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2g** was obtained as a pale yellow oil (20.2 mg, 77%). The ratio of **2g-a**, **2g-b** and **2g-c** is 12.5/1.0/3.8, determined by the crude ¹H NMR.

¹H NMR (600 MHz, CDCl₃) δ 7.47 (d, *J* = 7.8 Hz, 1H), 7.26 (m, 0.6H), 7.21 (m, 0.3H), 7.12(m, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 2.50 (s, 3H), 2.37 (s, 3H), 2.34 (s, 1.8H), ¹³C NMR (150 MHz, CDCl₃) δ 143.42, 142.09, 141.72, 138.98, 134.56, 132.35, 132.02, 130.96, 129.62, 127.25, 126.99, 119.18, 118.43, 112.00, 109.65, 21.67, 21.00, 20.73, 20.31.

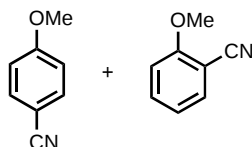


2h

2,4,6-Trimethylbenzonitrile (2h)⁶

Mesitylene **1h** was cyanated following the general procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 20:1 as eluent), **2h** was obtained as a white solid (25.3 mg, 87%).

¹H NMR (600 MHz, CDCl₃) δ 6.93 (s, 2H), 2.48 (s, 6H), 2.32 (s, 3H), ¹³C NMR (150 MHz, CDCl₃) δ 142.75, 141.92, 128.15, 117.59, 110.28, 21.53, 20.59.

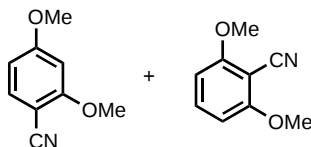


2i-a, 2i-b

4-Methoxybenzonitrile and 2-methoxybenzonitrile (2i)³

Anisole **1i** was cyanated following the general procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2i** was obtained as a white solid (17.3 mg, 65%). The ratio of **2i-a** and **2i-b** is 1.9/1.0, determined by the crude ¹H NMR.

¹H NMR (600 MHz, CDCl₃) δ 7.59 (d, *J* = 9.0 Hz, 2H), 7.57-7.52 (m, 1H), 7.02-6.97 (m, 1H), 6.95 (d, *J* = 8.9 Hz, 2H), 3.93 (s, 1.5H), 3.86 (s, 3H), ¹³C NMR (150 MHz, CDCl₃) δ 162.79, 161.18, 134.33, 133.93, 133.71, 120.71, 119.18, 116.44, 114.70, 111.24, 103.91, 101.77, 55.94, 55.50.

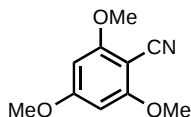


2j-a 2j-b

2,4-Dimethoxybenzonitrile and 2,6-dimethoxybenzonitrile (2j)³

1,3-Dimethoxybenzene **1j** was cyanated following the general procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2j** was obtained as a white solid (18.9 mg, 58%). The ratio of **2j-a** and **2j-b** is 7.1/1.0, determined by the crude ¹H NMR.

¹H NMR (600 MHz, CDCl₃) δ 7.46 (d, *J* = 8.6 Hz, 1H), 7.43 (t, *J* = 8.5 Hz, 1.4H), 6.54 (d, *J* = 8.5 Hz, 0.28H), 6.51 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.45 (d, *J* = 2.3 Hz, 1H), 3.90 (s, 0.64H), 3.89 (s, 3H), 3.85 (s, 3H), ¹³C NMR (150 MHz, CDCl₃) δ 164.58, 162.79, 134.84, 116.89, 105.73, 98.42, 93.91, 55.91, 55.66.

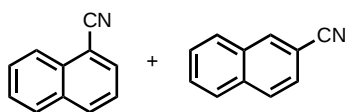


2k

2,4,6-Trimethoxynemzonitrile (2k)⁷

1,3,5-Trimethoxybenzene **1k** was cyanated following the general procedure at 90 °C for 12 h. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 2:1 as eluent), **2k** was obtained as a white solid (31.7 mg, 82%).

¹H NMR (600 MHz, CDCl₃) δ 6.07 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), ¹³C NMR (150 MHz, CDCl₃) δ 165.29, 163.75, 114.55, 90.33, 84.08, 56.06, 55.66.

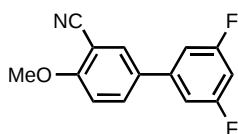


2l-a, 2l-b

1-Naphthonitrile and 2-naphthonitrile (2l)⁴

Naphthalene **1l** was cyanated following the general procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 20:1 as eluent), **2l** was obtained as a pale yellow oil (22.4 mg, 74%). The ratio of **2l-a** and **2l-b** is 2.0/1.0, determined by the crude ¹H NMR.

¹H NMR (600 MHz, CDCl₃) δ 8.25-8.21 (m, 1.5H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.93-7.90 (m, 2H), 7.90-7.86 (m, 1.5H), 7.69 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.66-7.58 (m, 2.5H), 7.52 (dd, *J* = 8.3, 7.1 Hz, 1H), ¹³C NMR (150 MHz, CDCl₃) δ 134.59, 134.10, 133.23, 132.88, 132.58, 132.31, 132.19, 129.14, 128.99, 128.61, 128.35, 128.00, 127.60, 127.50, 126.28, 125.10, 124.88, 119.20, 117.77, 110.15, 109.32.

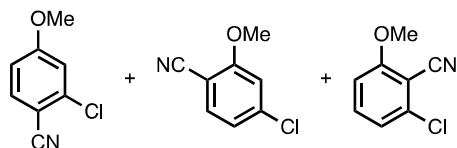


2m

3',5'-Difluoro-4-methoxy-[1,1'-biphenyl]-3-carbonitrile (2m)

3,5-Difluoro-4'-methoxy-1,1'-biphenyl **1m** was cyanated following the general procedure, 15 mol% Pd(OAc)₂ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2m** was obtained as a white solid (27.0 mg, 55%).

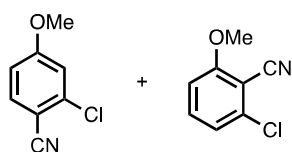
¹H NMR (600 MHz, CDCl₃) δ 7.74 (d, *J* = 2.4 Hz, 1H), 7.72 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 7.02 (dt, *J* = 6.8, 2.1 Hz, 2H), 6.80 (tt, *J* = 8.8, 2.3 Hz, 1H), ¹³C NMR (150 MHz, CDCl₃) δ 164.22 (d, *J* = 13.2 Hz), 162.57 (d, *J* = 13.1 Hz), 161.23, 141.84 (t, *J* = 9.6 Hz), 132.81, 132.03, 131.81 (t, *J* = 2.6 Hz), 128.34, 115.95, 114.76, 111.90, 109.54 (dd, *J* = 20.4, 5.4 Hz), 102.94 (t, *J* = 25.3 Hz), 102.56, 56.30. ¹⁹F NMR (376 MHz, CDCl₃) δ -109.10 (s, 2F). HRMS (APCI) Calcd for C₁₄H₁₀F₂NO [M+H]: 246.0730, found: 246.0738.



2n-a, 2n-b, 2n-c

2-Chloro-4-methoxybenzonitrile, 4-chloro-2-methoxybenzonitrile and 3-chloro-2-methoxybenzonitrile (2n)⁷

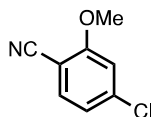
3-Chloroanisole **1n** was cyanated following the general procedure under 120 °C, 15 mol% Pd(OAc)₂ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2n** was obtained as a pale yellow oil (21.7 mg, 64%). The ratio of **2n-a**, **2n-b** and **2n-c** is 1.4/2.5/1.0, determined by the crude ¹H NMR.



2n-a, 2n-c

2-Chloro-4-methoxybenzonitrile and 3-chloro-2-methoxybenzonitrile (2n-a, 2n-c)

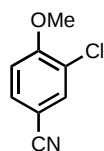
¹H NMR (600 MHz, CDCl₃) δ 7.57 (d, *J* = 8.7 Hz, 1H), 7.45 (t, *J* = 8.3 Hz, 0.12H), 7.07 (d, *J* = 8.1, 0.8 Hz, 0.11H), 7.01 (d, *J* = 2.5 Hz, 1H), 6.89-6.85 (m, *J* = 8.7, 2.5 Hz, 1.12H), 3.95 (s, 0.35H), 3.87 (s, 3H), ¹³C NMR (150 MHz, CDCl₃) δ 163.32, 138.30, 134.22, 121.68, 116.35, 115.53, 113.51, 109.33, 105.03, 56.47, 55.93.



2n-b

4-Chloro-2-methoxybenzonitrile (2n-b)

¹H NMR (600 MHz, CDCl₃) δ 7.49 (d, *J* = 8.2 Hz, 1H), 7.01 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.98 (d, *J* = 1.8 Hz, 1H), 3.94 (s, 3H), ¹³C NMR (150 MHz, CDCl₃) δ 161.71, 140.63, 121.29, 115.64, 112.33, 100.48, 56.36.



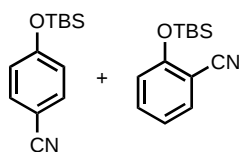
2o-a

3-Chloro-4-methoxybenzonitrile and 3-chloro-2-methoxybenzonitrile (2o)⁸

2-Chloroanisole **1o** was cyanated following the general procedure under 120 °C, 15 mol% Pd(OAc)₂ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2o** was obtained as a pale yellow oil (16.8 mg, 50%). **2o-a** was isolated as the main isomer (>10:1).

¹H NMR (600 MHz, CDCl₃) δ 7.66 (d, *J* = 2.1 Hz, 1H), 7.56 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.98

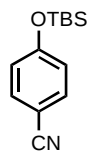
(d, J = 8.6 Hz, 1H), 3.97 (s, 3H), ^{13}C NMR (150 MHz, CDCl_3) δ 158.56, 133.57, 132.30, 123.56, 117.75, 112.13, 104.73, 56.44.



2p-a 2p-b

Tert-butyl(4-cyanophenoxy)dimethylsilane and tert-butyl(2-cyanophenoxy)dimethylsilane (2p)

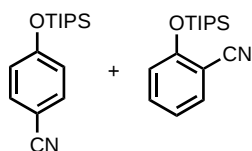
Tert-butyldimethyl(phenoxy)silane **1p** was cyanated following the general procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2p** was obtained as a white solid (37.8 mg, 81%). The ratio of **2p-a** and **2p-b** is 5.5/1.0, determined by the crude ^1H NMR.



2p-a

Tert-butyl(4-cyanophenoxy)dimethylsilane (2p-a)

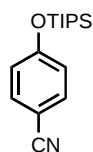
^1H NMR (600 MHz, CDCl_3) δ 7.54 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 0.98 (s, 9H), 0.23 (s, 6H), ^{13}C NMR (150 MHz, CDCl_3) δ 159.22, 133.53, 120.39, 118.75, 25.06, 17.76. HRMS (ESI-TOF) Calcd for $\text{C}_{13}\text{H}_{20}\text{NOSi}^+$ $[\text{M}+\text{H}]^+$: 234.1309, found: 234.1319.



2q-a 2q-b

4-((Triisopropylsilyl)oxy)benzonitrile and 2-((triisopropylsilyl)oxy)benzonitrile (2q)

Tert-butyldimethyl(phenoxy)silane **1q** was cyanated following the general procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2q** was obtained as a white solid (38.6 mg, 70%). The ratio of **2q-a** and **2q-b** is 7.5/1.0, determined by the crude ^1H NMR.

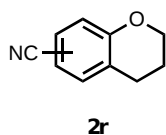


2q-a

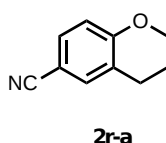
4-((Triisopropylsilyl)oxy)benzonitrile (2q-a)

^1H NMR (600 MHz, CDCl_3) δ 7.53 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 1.27 (m,

2H), 1.10 (d, $J = 7.5$ Hz, 18H), ^{13}C NMR (150 MHz, CDCl_3) δ 160.05, 133.97, 120.65, 119.24, 104.26, 17.78, 12.62. HRMS (ESI-TOF) Calcd for $\text{C}_{16}\text{H}_{26}\text{NOSi}^+$ $[\text{M}+\text{H}]^+$: 276.1779, found: 276.1790.

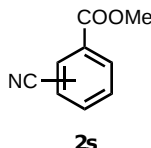


Chromane **1r** was cyanated following the general procedure, 15 mol% $\text{Pd}(\text{OAc})_2$ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 20:1 as eluent), **2r** was obtained as a colorless oil (23.8 mg, 83%). The ratio of **2r-a** and **other isomers** is 2.4/1.0, determined by the crude ^1H NMR.

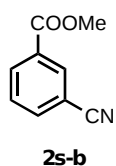


Chromane-6-carbonitrile (**2r-a**)⁸

^1H NMR (600 MHz, CDCl_3) δ 7.37-7.33 (m, 2H), 6.82 (d, $J = 8.3$ Hz, 1H), 4.26-4.23 (m, 2H), 2.79 (t, $J = 6.4$ Hz, 2H), 2.05-2.00 (m, 2H), ^{13}C NMR (150 MHz, CDCl_3) δ 158.58, 134.34, 131.36, 123.44, 119.42, 117.70, 103.13, 66.93, 24.52, 21.55.

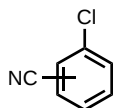


Methyl benzoate **1s** was cyanated following the general procedure, 8.0 equiv. of arene substrate was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 20:1 as eluent), **2s** was obtained as a colorless oil (16.2 mg, 50%). The ratio of *ortho* (**2s-a**), *meta* (**2s-b**) and *para* (**2s-c**) is 1.0/6.4/1.7, determined by the crude ^1H NMR.



Methyl 3-cyanobenzoate (**2s-b**)⁹

^1H NMR (600 MHz, CDCl_3) δ 8.33 (td, $J = 1.7, 0.6$ Hz, 1H), 8.27 (ddd, $J = 7.9, 1.7, 1.3$ Hz, 1H), 7.84 (ddd, $J = 7.7, 1.7, 1.2$ Hz, 2H), 7.59 (td, $J = 7.8, 0.6$ Hz, 1H), 3.97 (s, 3H), ^{13}C NMR (150 MHz, CDCl_3) δ 165.07, 135.95, 133.63, 133.26, 131.41, 129.42, 117.85, 112.97, 52.70.

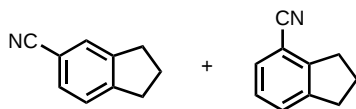


2t

2-Chlorobenzonitrile, 3-chlorobenzonitrile and 4-chlorobenzonitrile (2t)¹⁰

Chlorobenzene **1t** was cyanated following the general procedure, 8.0 equiv. of arene substrate was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 20:1 as eluent), **2t** was obtained as a colorless oil (15.1 mg, 55%). The ratio of *ortho*, *meta* and *para*-isomer is 5.0/1.0/1.2, determined by the crude ¹H NMR.

¹H NMR (600 MHz, CDCl₃) δ 7.68 (ddd, *J* = 7.8, 1.6, 0.6 Hz, 1H), 7.65 (ddd, *J* = 2.1, 1.5, 0.5 Hz, 0.2H), 7.61-7.59 (m, 0.5H), 7.59-7.58 (m, 0.2H), 7.57-7.55 (m, 0.4H), 7.54 (dd, *J* = 7.1, 1.6 Hz, 1H), 7.52 (ddd, *J* = 8.2, 1.6, 0.5 Hz, 1H), 7.47 (m, 0.5H), 7.43 (ddd, *J* = 8.2, 7.7, 0.5 Hz, 0.2H), 7.38 (ddd, *J* = 7.8, 7.1, 1.6 Hz, 1H).

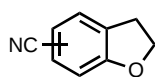


2u-a, 2u-b

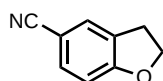
5-Cyanoindane and 4-cyanoindane (2u)¹¹

Indane **1u** was cyanated following the general procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 20:1 as eluent), **2u** was obtained as a colorless oil (23.8 mg, 83%). The ratio of **2u-a** and **2u-b** is 1.5/1.0, determined by the crude ¹H NMR.

¹H NMR (600 MHz, CDCl₃) δ 7.48 (d, *J* = 1.5 Hz, 1H), 7.44-7.39 (m, 1.6H), 7.31-7.28 (m, 1H), 7.23-7.19 (m, 0.3H), 3.12-3.08 (t, *J* = 7.5 Hz, 0.6H), 3.00-2.92 (m, 4.6H), 2.18-2.09 (m, 2.6H), ¹³C NMR (150 MHz, CDCl₃) δ 150.02, 148.38, 145.58, 130.31, 129.58, 128.76, 127.87, 127.85, 126.77, 125.05, 119.62, 118.10, 109.67, 108.61, 33.28, 33.16, 32.51, 32.47, 25.09, 24.67.



2v



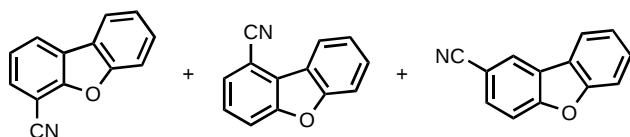
2v-a

5-Cyano-2,3-dihydrobenzofuran (2v-a)¹²

2,3-Dihydrobenzofuran **1v** was cyanated following the general procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2v** was obtained as a colorless oil (21.5 mg, 74%). The ratio of **2v-a** and **other isomers** is 1.2/1.0, determined by the crude ¹H NMR.

¹H NMR (600 MHz, CDCl₃) δ 7.46 (d, *J* = 1.4 Hz, 0.8H), 7.45-7.42 (m, 0.8H), 7.38 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.31 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.88 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 0.8H), 4.73 (t, *J* = 8.8 Hz, 2H), 4.67 (t, *J* = 8.8 Hz, 2H), 3.30-3.23 (m, 3.9H), ¹³C NMR (150 MHz, CDCl₃) δ 163.73, 162.41, 135.50, 130.67, 129.44, 128.82, 128.69, 128.52, 120.75,

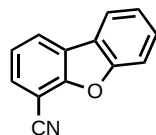
119.57, 115.85, 110.21, 103.49, 93.92, 72.61, 72.06, 29.20, 28.95.



2w-a, 2w-b, 2w-c

Dibenzo[*b,d*]furan-4-carbonitrile and dibenzo[*b,d*]furan-1-carbonitrile and dibenzo[*b,d*]furan-2-carbonitrile (2w-a, 2w-b, 2w-c)

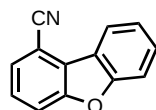
Dibenzo[*b,d*]furan **1w** was cyanated following the general procedure, 15 mol% Pd(OAc)₂ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2w** was obtained as a white solid (31.3 mg, 81%). The ratio of **2w-a**, **2w-b** and **2w-c** is 3.1/1.0/1.3, determined by the crude ¹H NMR.



2w-a

Dibenzo[*b,d*]furan-4-carbonitrile (2w-a)¹³

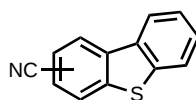
¹H NMR (600 MHz, CDCl₃) δ 8.16 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.97 (ddd, *J* = 7.8, 1.3, 0.7 Hz, 1H), 7.72 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.67 (dt, *J* = 8.3, 0.8 Hz, 1H), 7.56 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H), 7.44-7.40 (m, 2H), ¹³C NMR (150 MHz, CDCl₃) δ 156.33, 156.13, 130.37, 128.61, 125.61, 125.40, 123.79, 122.97, 122.83, 121.00, 115.02, 112.24, 96.66.



2w-b

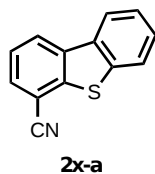
Dibenzo[*b,d*]furan-1-carbonitrile (2w-b)¹⁴

¹H NMR (600 MHz, CDCl₃) δ 8.41 (ddd, *J* = 7.8, 1.3, 0.7 Hz, 1H), 7.81 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.67-7.62 (m, 1H), 7.59 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.53 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.48-7.45 (m, 1H), ¹³C NMR (150 MHz, CDCl₃) δ 156.65, 155.69, 129.18, 127.26, 126.98, 125.87, 123.68, 122.00, 121.78, 117.42, 116.34, 111.91, 104.47.



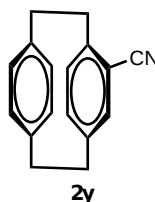
2x

Dibenzo[*b,d*]thiophen **1x** was cyanated following the general procedure, 15 mol% Pd(OAc)₂ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2x** was obtained as a white solid (38.9 mg, 93%). The ratio of **2x-a** and **othe isomers** is 2.4/1.0, determined by the crude ¹H NMR.



Dibenzo[*b,d*]thiophene-4-carbonitrile (2x-a)

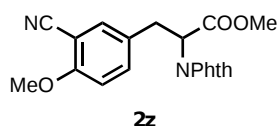
^1H NMR (600 MHz, CDCl_3) δ 8.33 (dd, J = 8.0, 1.1 Hz, 1H), 7.17 (m, 1H), 7.92 (m, 1H), 7.78 (dd, J = 7.5, 1.1 Hz, 1H), 7.54 (m, 1H), ^{13}C NMR (150 MHz, CDCl_3) δ 142.90, 138.99, 136.55, 134.53, 130.99, 127.98, 125.52, 125.15, 124.53, 123.03, 121.98, 117.14, 106.91. HRMS (ESI-TOF) Calcd for $\text{C}_{17}\text{H}_{16}\text{N}^+$ $[\text{M}+\text{H}]^+$: 210.0377, found: 210.0383.



1,4(1,4)-Dibenzenacyclohexaphane-1²-carbonitrile (2y)

1,4(1,4)-Dibenzenacyclohexaphane **1y** was cyanated following the general procedure, 15 mol % $\text{Pd}(\text{OAc})_2$ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 20:1 as eluent), **2y** was obtained as a white solid (18.7 mg, 40%).

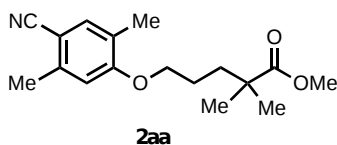
^1H NMR (600 MHz, CDCl_3) δ 6.92-6.89 (m, 1H), 6.76 (d, J = 1.9 Hz, 1H), 6.72 (dd, J = 7.9, 1.9 Hz, 1H), 6.59 (d, J = 7.9 Hz, 1H), 6.53 (d, J = 1.2 Hz, 2H), 6.49 (m, 1H), ^{13}C NMR (150 MHz, CDCl_3) δ 144.22, 140.90, 139.50, 139.09, 137.09, 136.75, 134.49, 133.49, 132.86, 132.67, 130.93, 118.91, 114.87, 35.30, 35.06, 34.44, 34.21. HRMS (ESI-TOF) Calcd for $\text{C}_{17}\text{H}_{16}\text{N}^+$ $[\text{M}+\text{H}]^+$: 234.1278, found: 234.1282.



Methyl 3-(3-cyano-4-methoxyphenyl)-2-(1,3-dioxoisindolin-2-yl)propanoate (2z)

Methyl 2-(1,3-dioxoisindolin-2-yl)-3-(4-methoxyphenyl)propanoate **1z** was cyanated following the general procedure, 15 mol% $\text{Pd}(\text{OAc})_2$ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 2:1 as eluent), **2z** was obtained as a colorless oil (48.8 mg, 67%).

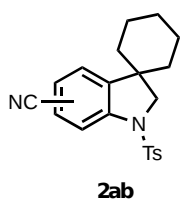
^1H NMR (600 MHz, CDCl_3) δ 7.79 (dd, J = 5.5, 3.0 Hz, 2H), 7.71 (dd, J = 5.5, 3.0 Hz, 2H), 7.36 (dd, J = 8.7, 2.3 Hz, 1H), 7.32 (d, J = 2.3 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 5.06 (dd, J = 11.1, 5.3 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.55-3.43 (m, 2H), ^{13}C NMR (150 MHz, CDCl_3) δ 168.79, 167.31, 160.10, 134.77, 134.31, 133.82, 131.30, 129.30, 123.58, 116.05, 111.52, 101.69, 55.91, 52.94, 52.81, 33.40. HRMS (ESI-TOF) Calcd for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_5^+$ $[\text{M}+\text{H}]^+$: 365.1132, found: 365.1140.



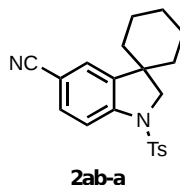
Methyl 5-(4-cyano-2,5-dimethylphenoxy)-2,2-dimethylpentanoate (2aa)⁸

Gemfibrozil methyl ester **1aa** was cyanated following the general procedure, 15 mol% Pd(OAc)₂ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2aa** was obtained as a colorless oil (33.0 mg, 57%).

¹H NMR (600 MHz, CDCl₃) δ 7.32 (s, 1H), 6.65 (s, 1H), 3.96 (t, *J* = 6.1 Hz, 2H), 3.67 (s, 3H), 2.48 (s, 3H), 2.17 (s, 3H), 1.79-1.73 (m, 2H), 1.72-1.68 (m, 2H), 1.22 (s, 6H), ¹³C NMR (150 MHz, CDCl₃) δ 178.10, 160.22, 141.75, 133.92, 125.26, 118.86, 112.04, 103.43, 68.15, 51.75, 42.02, 36.87, 25.15, 24.88, 20.54, 15.15.

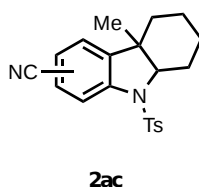


1'-Tosylspiro[cyclohexane-1,3'-indoline] **1ab** was cyanated following the general procedure, 20 mol% Pd(OAc)₂ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2ab** was obtained as a white solid (36.6 mg, 50%). The ratio of **2ab-a** and **other isomers** is 6.7/1.0, determined by the crude ¹H NMR.

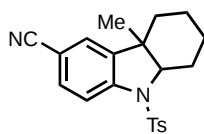


1'-Tosylspiro[cyclohexane-1,3'-indoline]-5'-carbonitrile (2ab-a)

¹H NMR (600 MHz, CDCl₃) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.28 (dd, *J* = 8.3, 6.4 Hz, 3H), 3.80 (s, 2H), 2.40 (s, 3H), 1.72-1.65 (m, 2H), 1.45-1.21 (m, 8H), ¹³C NMR (150 MHz, CDCl₃) δ 144.82, 144.77, 141.62, 133.80, 132.90, 129.90, 127.01, 126.86, 119.09, 114.43, 106.48, 59.57, 44.39, 36.74, 35.01, 22.58, 21.57. HRMS (ESI-TOF) Calcd for C₂₁H₂₃N₂O₂S⁺ [M+H]⁺: 367.1475, found: 367.1476.



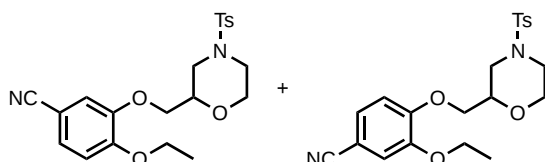
4a-Methyl-9-tosyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole **1ac** was cyanated following the general procedure, 20 mol% Pd(OAc)₂ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 2:1 as eluent), **2ac** was obtained as a white solid (53.5 mg, 73%). The ratio of **2ac-a** and **other isomers** is 6.3/1.0, determined by the crude ¹H NMR.



2ac-a

4a-Methyl-9-tosyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole-6-carbonitrile (2ac-a)

^1H NMR (600 MHz, CDCl_3) δ 7.72 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 1H), 7.51 (dd, J = 8.4, 1.7 Hz, 1H), 7.29-7.25 (m, 2H), 7.24 (d, J = 1.7 Hz, 1H), 3.89 (dd, J = 8.7, 5.8 Hz, 1H), 2.39 (s, 3H), 2.18-2.10 (m, 1H), 2.01-1.96 (m, 1H), 1.58-1.48 (m, 4H), 1.32-1.24 (m, 1H), 1.18-1.09 (m, 1H), 0.67 (s, 3H), ^{13}C NMR (150 MHz, CDCl_3) δ 144.46, 144.30, 140.30, 135.69, 132.88, 129.82, 126.75, 126.03, 119.17, 115.30, 106.58, 70.37, 43.83, 32.33, 30.23, 29.58, 21.55, 20.87, 20.75. HRMS (ESI-TOF) Calcd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_2\text{S}^+$ $[\text{M}+\text{H}]^+$: 367.1475, found: 367.1475.

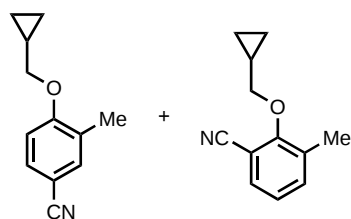


2ad-a, 2ad-b

4-Ethoxy-3-((4-tosylmorpholin-2-yl)methoxy)benzonitrile and 3-ethoxy-4-((4-tosylmorpholin-2-yl)methoxy)benzonitrile (2ad-a, 2ad-b)

2-((2-Ethoxyphenoxy)methyl)-4-tosylmorpholine **1ad** was cyanated following the general procedure, 15 mol% $\text{Pd}(\text{OAc})_2$ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 2:1 as eluent), **2ad** was obtained as a white solid (34.2 mg, 41%). The ratio of **2ad-a** and **2ad-b** is 1.0/1.0, determined by the crude ^1H NMR.

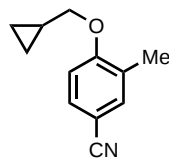
^1H NMR (600 MHz, CDCl_3) δ 7.67-7.64 (m, 2H), 7.35 (ddd, J = 6.5, 2.8, 1.4 Hz, 2H), 7.28 (dd, J = 8.4, 1.9 Hz, 0.6H), 7.21 (dd, J = 8.3, 1.9 Hz, 0.4H), 7.09 (d, J = 2.0 Hz, 0.6H), 7.07 (d, J = 2.0 Hz, 0.4H), 6.88 (dd, J = 8.4, 3.1 Hz, 1H), 4.12-3.92 (m, 6H), 3.80-3.71 (m, 2H), 3.57 (ddd, J = 11.6, 2.8, 1.5 Hz, 1H), 2.50-2.45 (m, 1H), 2.45 (s, 3H), 2.37 (ddd, J = 11.4, 9.8, 7.5, 1H), 1.45 (t, J = 7.0 Hz, 1.8H), 1.42 (t, J = 7.0 Hz, 1.2H), ^{13}C NMR (150 MHz, CDCl_3) δ 153.23, 151.98, 149.16, 148.15, 144.02, 132.07, 129.78, 127.85, 127.54, 126.01, 119.01, 117.78, 115.91, 113.93, 112.78, 104.91, 103.51, 73.43, 73.32, 70.27, 69.61, 65.99, 64.75, 64.55, 47.60, 45.47, 21.52, 14.53. HRMS (ESI-TOF) Calcd for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_5\text{S}^+$ $[\text{M}+\text{H}]^+$: 417.1479, found: 417.1484.



2ae-a, 2ae-b

4-(Cyclopropylmethoxy)-3-methylbenzonitrile and 2-(cyclopropylmethoxy)-3-methylbenzonitrile (2ae-a, 2ae-b)

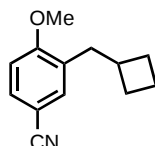
1-(Cyclopropylmethoxy)-2-methylbenzene **1ae** was cyanated following the general procedure, 15 mol% Pd(OAc)₂ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2ae** was obtained as a white solid (21.0 mg, 56%). The ratio of **2ae-a** and **2ae-b** is 7.3/1.0, determined by the crude ¹H NMR.



2ae-a

4-(Cyclopropylmethoxy)-3-methylbenzonitrile (2ae-a)

¹H NMR (600 MHz, CDCl₃) δ 7.45 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.40 (dd, *J* = 2.1, 1.0 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 3.87 (d, *J* = 6.7 Hz, 2H), 2.24 (s, 3H), 1.28 (ttt, *J* = 8.1, 6.8, 4.9 Hz, 1H), 0.65 (m, 2H), 0.37 (m, 2H), ¹³C NMR (150 MHz, CDCl₃) δ 160.56, 133.90, 131.78, 128.55, 119.55, 111.03, 103.12, 16.08, 10.02. HRMS (ESI-TOF) Calcd for C₁₂H₁₄NO⁺ [M+H]⁺: 188.1070, found: 188.1078.

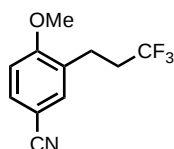


2af-a

3-(Cyclobutylmethyl)-4-methoxybenzonitrile (2af-a)

3-(Cyclobutylmethyl)-4-methoxybenzene **1af** was cyanated following the general procedure, 15 mol% Pd(OAc)₂ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2af** was obtained as a white solid (26.3 mg, 75%). **2af-a** was isolated as the main isomer (10.0/1.0).

¹H NMR (600 MHz, CDCl₃) δ 7.16 (td, *J* = 7.8, 1.8 Hz, 1H), 7.08 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.86 (td, *J* = 7.4, 1.1 Hz, 1H), 6.83 (dd, *J* = 8.2, 1.0 Hz, 1H), 3.81 (s, 3H), 2.70 (d, *J* = 7.4 Hz, 2H), 2.65-2.56 (m, 1H), 2.05-1.99 (m, 2H), 1.86-1.80 (m, 2H), 1.75-1.67 (m, 2H), ¹³C NMR (150 MHz, CDCl₃) δ 157.43, 129.73, 129.64, 126.74, 120.16, 110.08, 55.19, 36.83, 35.75, 28.27, 18.36. HRMS (ESI-TOF) Calcd for C₁₃H₁₆NO⁺ [M+H]⁺: 202.1227, found: 202.1233.

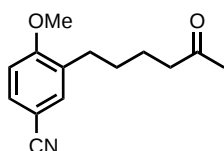


2ag-a

4-Methoxy-3-(3,3,3-trifluoropropyl)benzonitrile (2ag-a)

1-Methoxy-2-(3,3,3-trifluoropropyl)benzene **1ag** was cyanated following the general procedure, 15 mol% Pd(OAc)₂ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2ag** was obtained as a white solid (37.1 mg, 81%). **2ag-a** was isolated as the main isomer (9.7/1.0).

¹H NMR (600 MHz, CDCl₃) δ 7.56 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.42 (d, *J* = 2.2 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 3.91 (s, 3H), 2.89-2.84 (d, *J* = 7.5 Hz, 2H), 2.41-2.32 (d, *J* = 7.5 Hz, 2H), ¹³C NMR (150 MHz, CDCl₃) δ 160.70, 133.39, 133.01, 129.40, 128.84, 127.57, 123.90, 119.00, 110.78, 103.92, 55.70, 33.41, 33.22, 33.04, 32.85, 23.24, 23.22, 23.20. ¹⁹F NMR (376 MHz, CDCl₃) δ -66.78 (s, 3F). HRMS (ESI-TOF) Calcd for C₁₁H₁₁F₃NO⁺ [M+H]⁺: 230.0787, found: 230.0782.

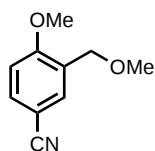


2ah-a

4-Methoxy-3-(5-oxohexyl)benzonitrile (2ah-a)

6-(2-Methoxyphenyl)hexan-2-one **2ah** was cyanated following the general procedure, 15 mol % Pd(OAc)₂ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2ah** was obtained as a pale yellow oil (21.0 mg, 51%). **2ah-a** was isolated as the main isomer (9.8/1.0).

¹H NMR (600 MHz, CDCl₃) δ 7.49 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.38 (d, *J* = 2.1 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 3.87 (s, 3H), 2.62-2.58 (m, 2H), 2.46 (t, *J* = 7.1 Hz, 2H), 2.13 (s, 3H), 1.64-1.52 (m, 4H), ¹³C NMR (150 MHz, CDCl₃) δ 208.78, 160.73, 133.07, 132.01, 131.97, 119.43, 110.46, 103.49, 55.52, 43.36, 29.86, 29.51, 28.69, 23.43. HRMS (ESI-TOF) Calcd for C₁₄H₁₈NO₂⁺ [M+H]⁺: 232.1332, found: 232.1340.



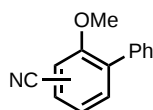
2ai-a

4-Methoxy-3-(methoxymethyl)benzonitrile (2ai-a)

1-Methoxy-2-(methoxymethyl)benzene **1ai** was cyanated following the general procedure, 15 mol% Pd(OAc)₂ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2ai** was obtained as a colorless oil (11.0 mg, 31%). **2ai-a** was isolated as the main isomer (7.8/1.0).

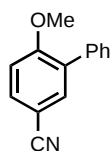
¹H NMR (600 MHz, CDCl₃) δ 7.67 (dd, *J* = 2.1, 1.0 Hz, 1H), 7.59-7.56 (m, 1H), 6.91 (d, *J* =

8.5 Hz, 1H), 4.47 (s, 2H), 3.89 (s, 3H), 3.45 (s, 3H), ^{13}C NMR (150 MHz, CDCl_3) δ 159.94, 133.23, 131.85, 128.39, 119.29, 110.44, 103.84, 68.54, 58.72, 55.69. HRMS (ESI-TOF) Calcd for $\text{C}_{10}\text{H}_{12}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$: 178.0863, found: 178.0868.



2aj

2-Methoxy-1,1'-biphenyl **1aj** was cyanated following the general procedure, 15 mol% $\text{Pd}(\text{OAc})_2$ was used. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 20:1 as eluent), **2aj** was obtained as a white solid (11.0 mg, 31%). **2aj-a** was isolated as the main isomer (8.0/1.0).

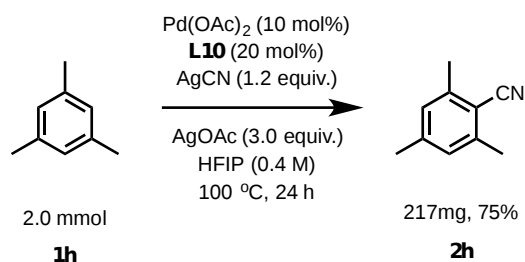


2aj-a

6-Methoxy-[1,1'-biphenyl]-3-carbonitrile (**2aj-a**)

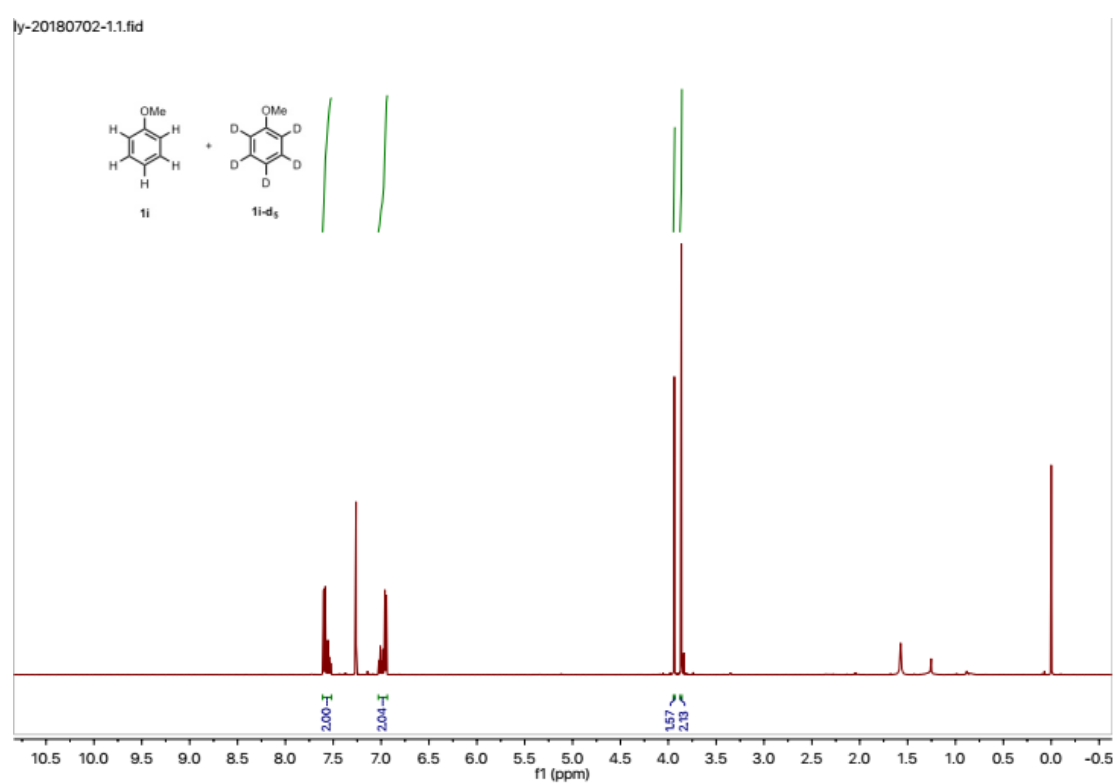
^1H NMR (600 MHz, CDCl_3) δ 7.63 (dd, J = 8.5, 2.2 Hz, 1H), 7.58 (d, J = 2.2 Hz, 1H), 7.46 (m, 2H), 7.43 (m, 2H), 7.38 (m, 1H), 7.02 (d, J = 8.6 Hz, 1H), 3.87 (s, 3H), ^{13}C NMR (150 MHz, CDCl_3) δ 159.76, 136.20, 134.38, 133.12, 131.91, 129.31, 128.23, 127.85, 119.13, 111.53, 104.18, 55.83. HRMS (ESI-TOF) Calcd for $\text{C}_{14}\text{H}_{12}\text{NO}^+$ $[\text{M}+\text{H}]^+$: 210.0913, found: 210.0915.

Scale-Up Reaction



General Procedure for Scale-Up Reaction: Substrate **1h** (2.0 mmol, 240 mg), $\text{Pd}(\text{OAc})_2$ (0.2 mmol, 45 mg), **L10** (0.4 mmol, 140 mg), AgCN (1.1 equiv., 295 mg) and AgOAc (6.0 mmol, 1.0 g) were weighed into a sealed tube (100 mL) with a magnetic stir bar under air. HFIP (5 mL) was added, and the tube was sealed with a cap. The reaction mixture was stirred at 100 °C for 24 hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with ethyl acetate. Then the reaction mixture was filtered through a short celite plug and transferred to a reaction round bottom flask (50 mL). The solvent was evaporated under vacuum and the resulting mixture was purified by flash chromatography by using Hexane/EtOAc (20:1) as the eluent to give 217 mg of **2h** (75% yield).

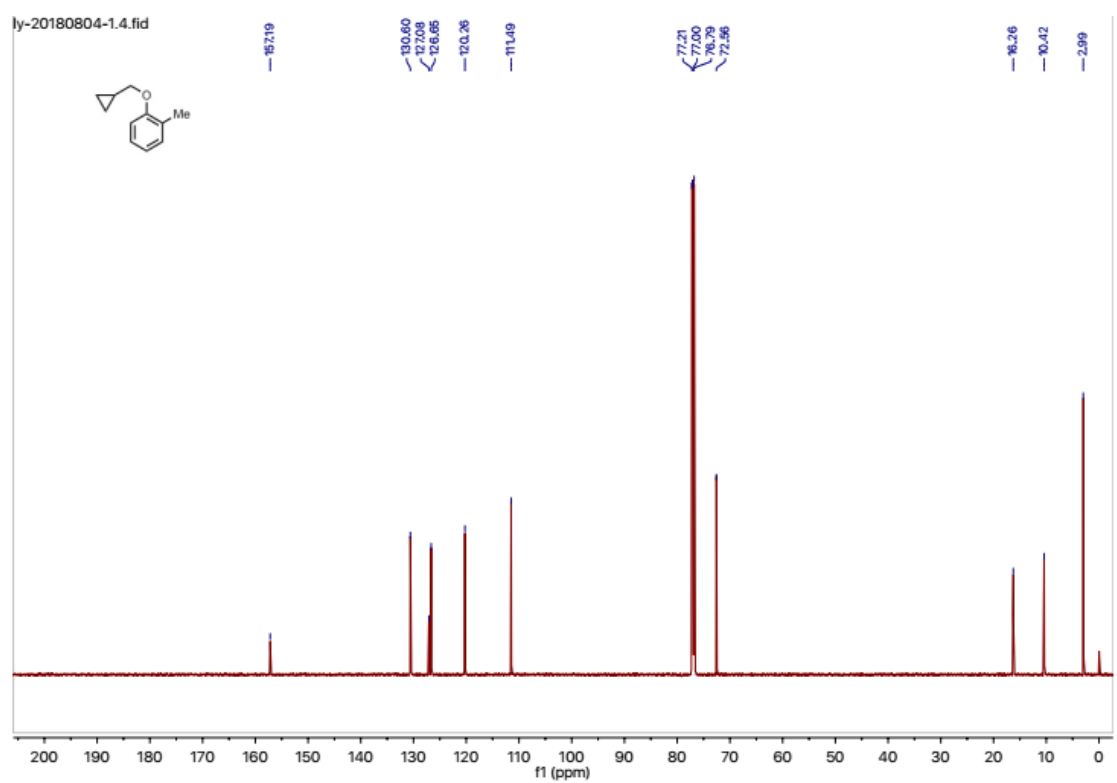
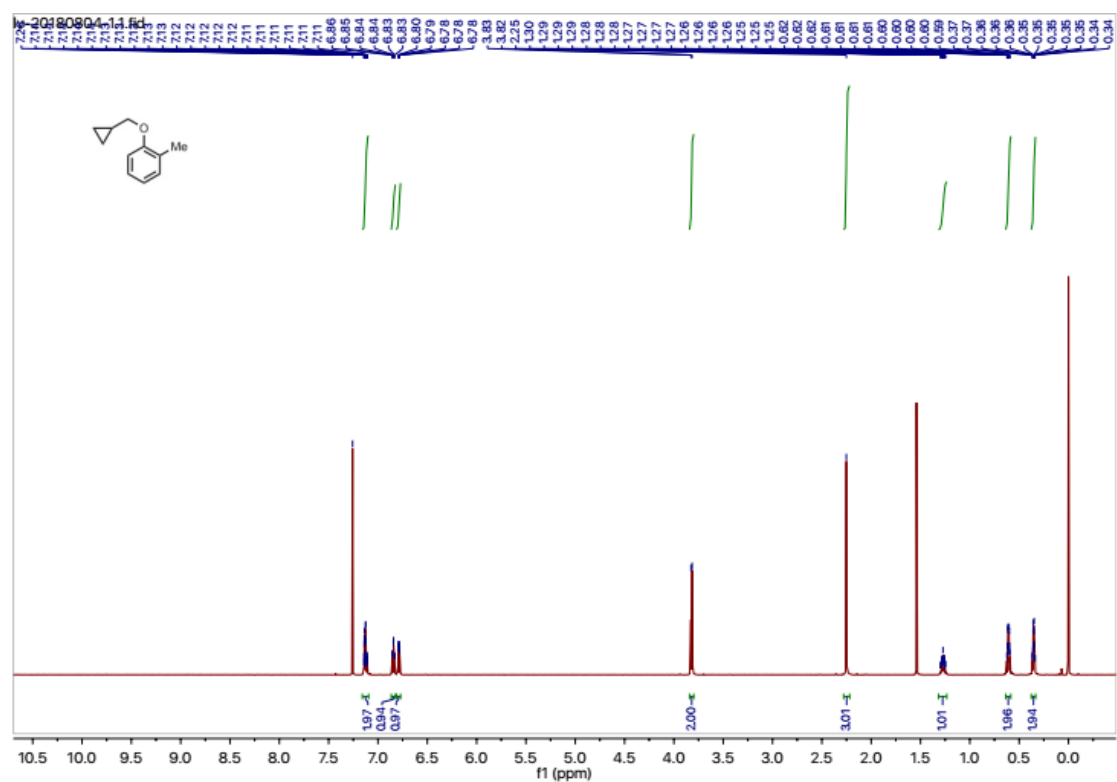
Measurement of the Kinetic isotope Effect

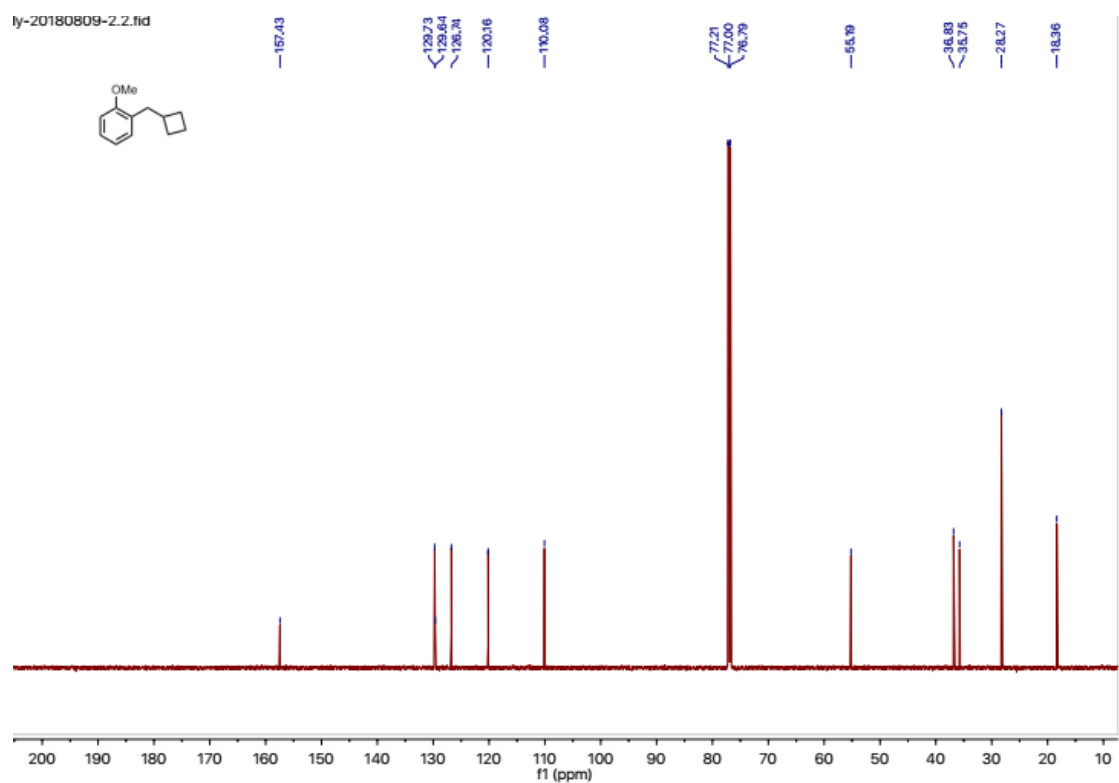
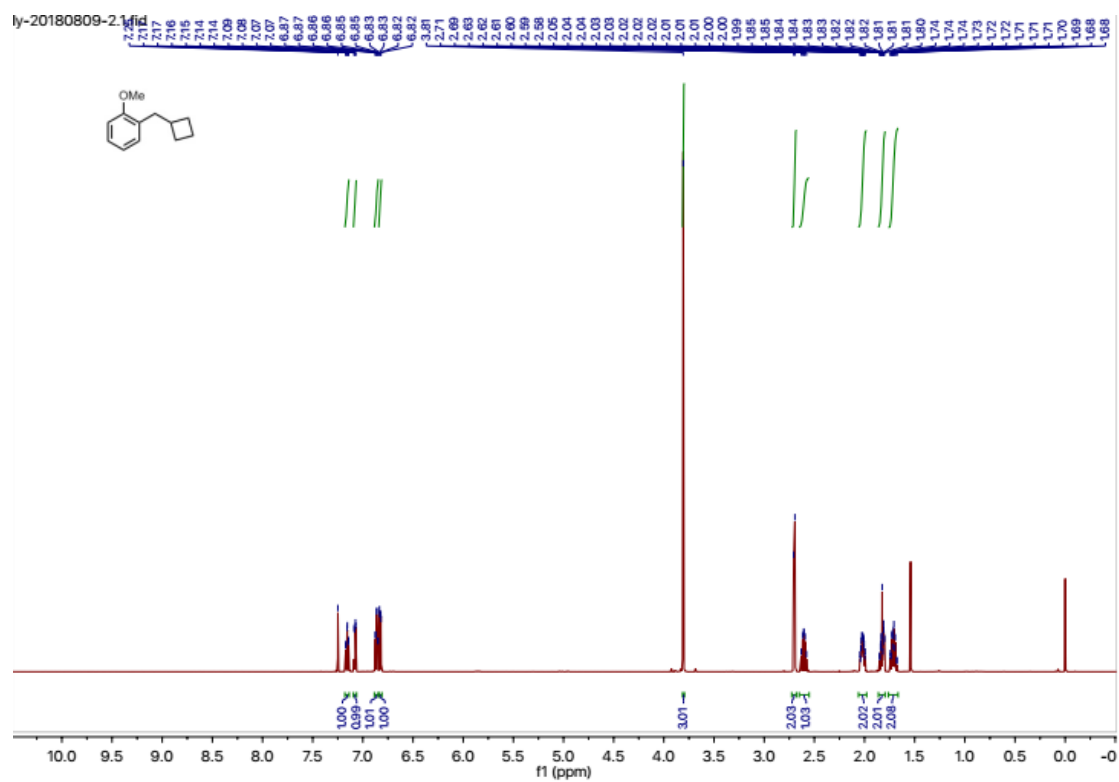


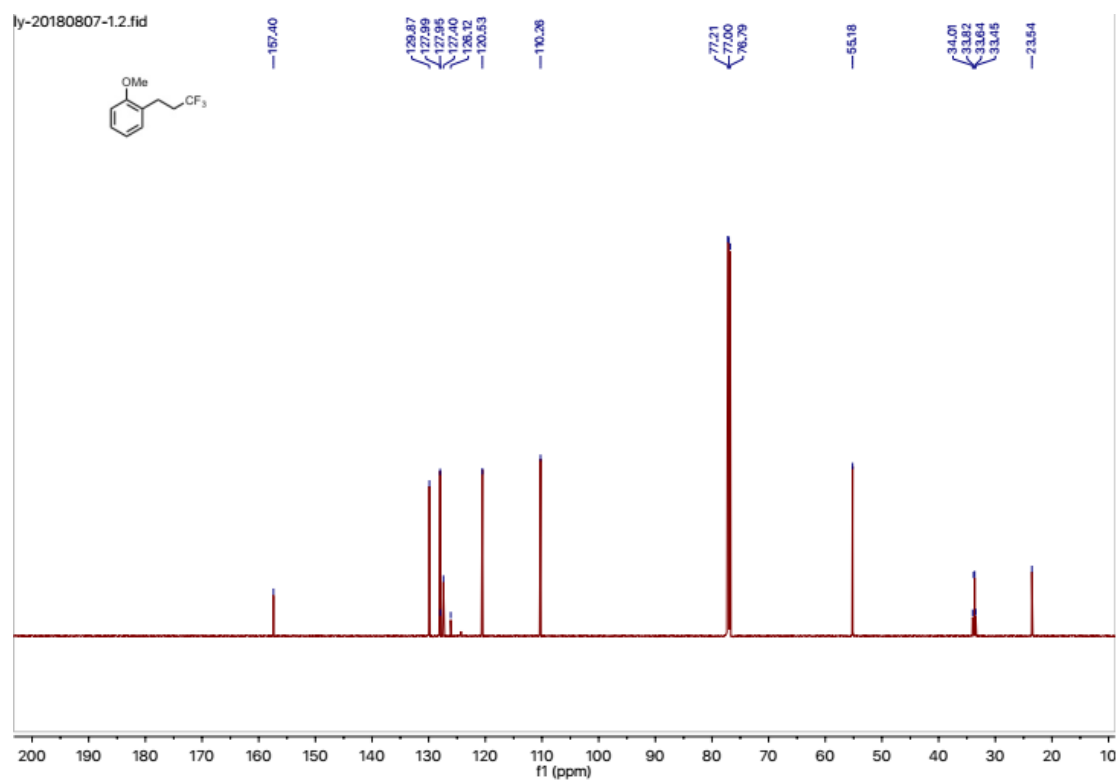
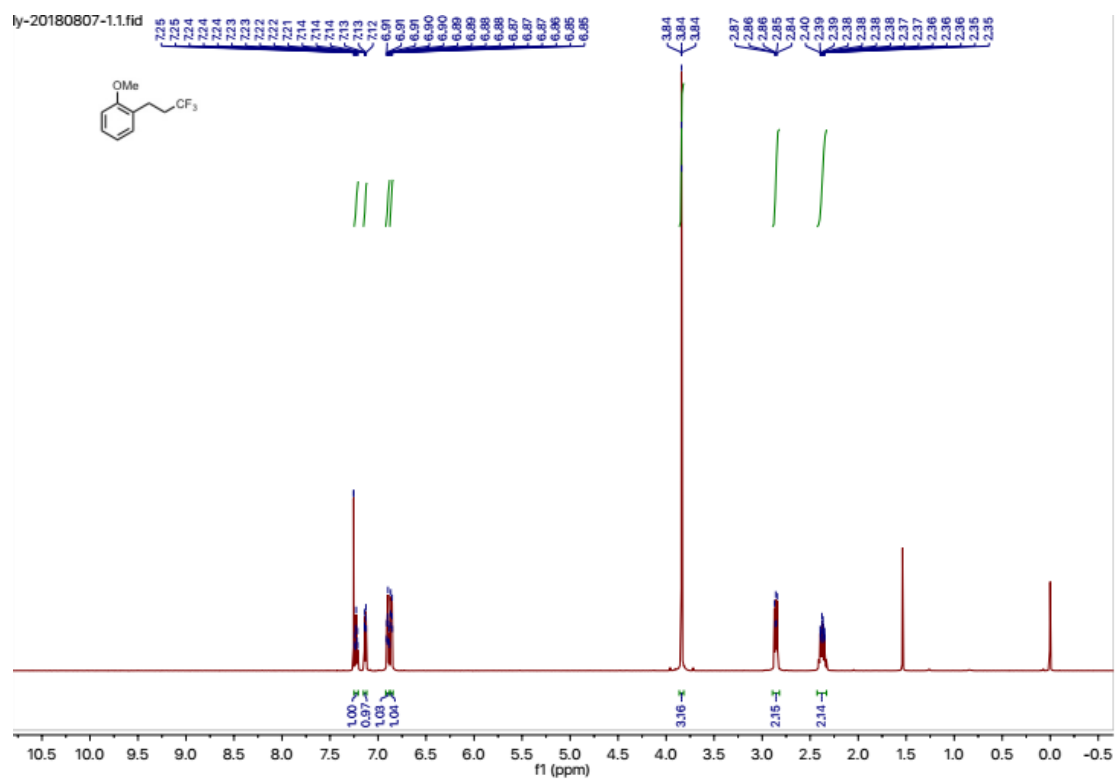
References

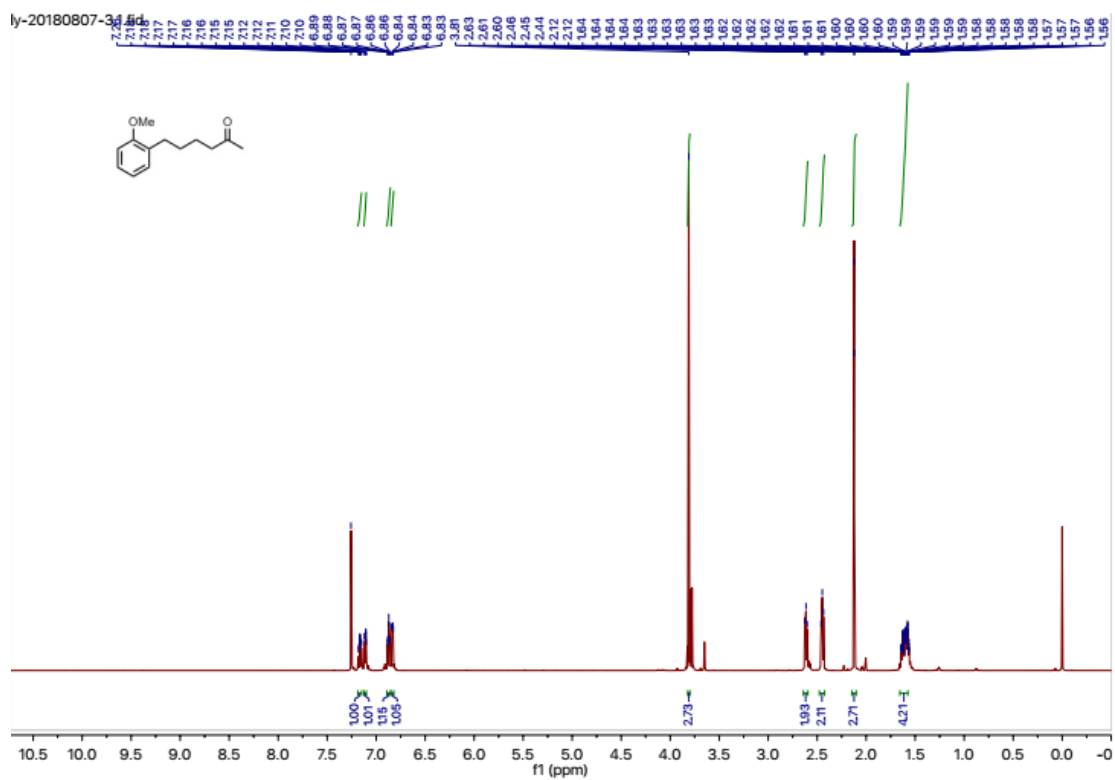
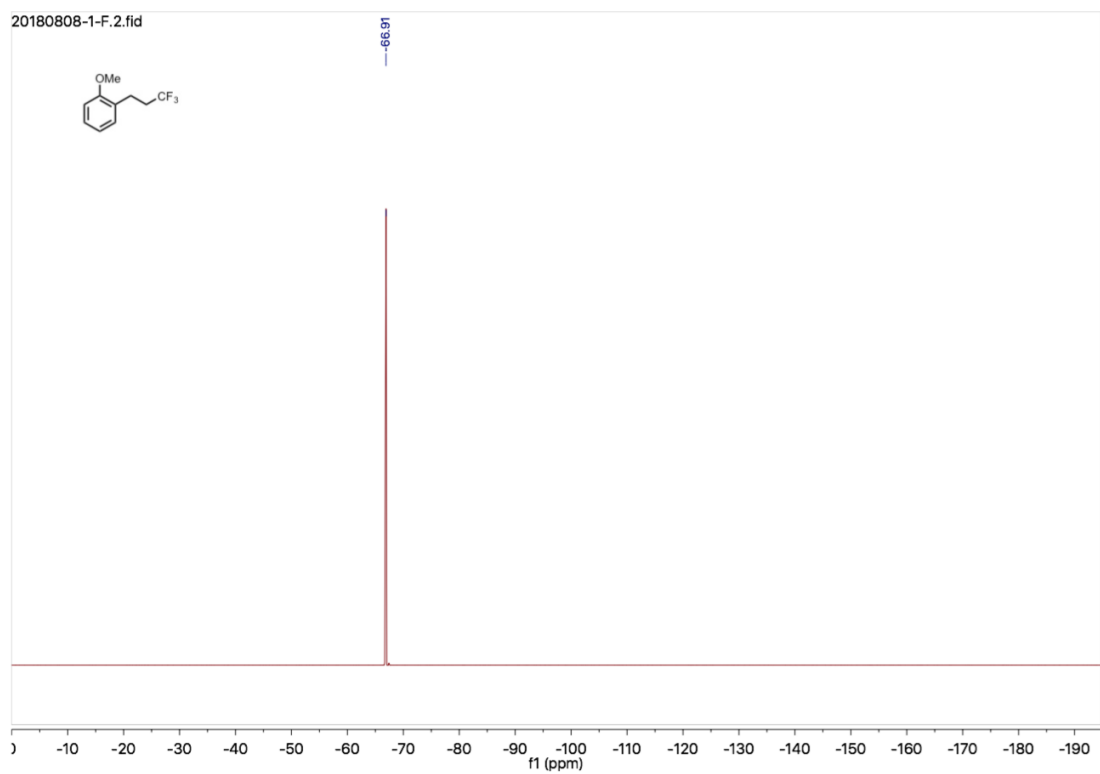
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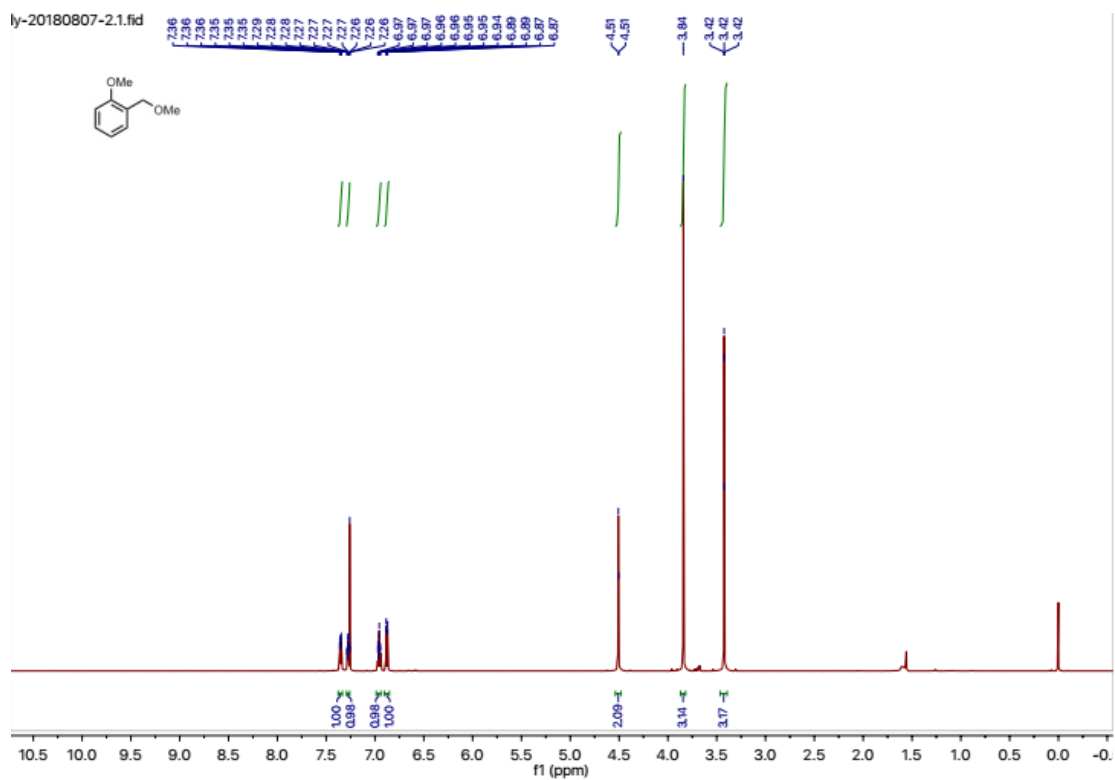
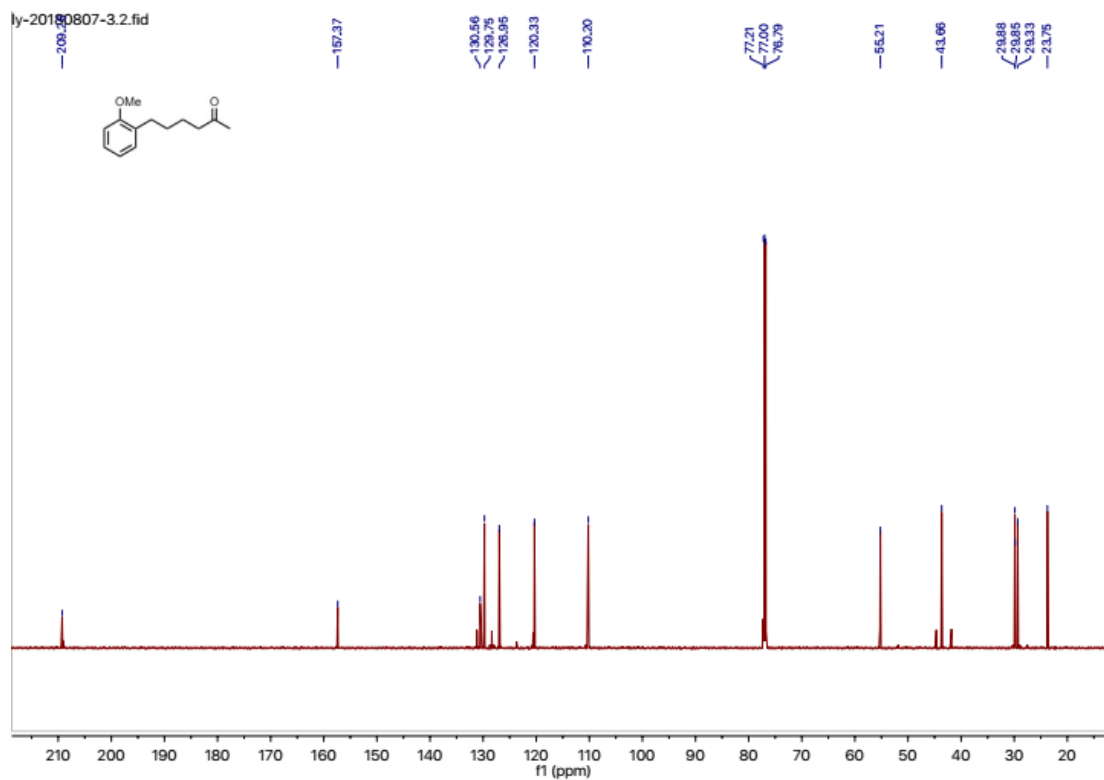
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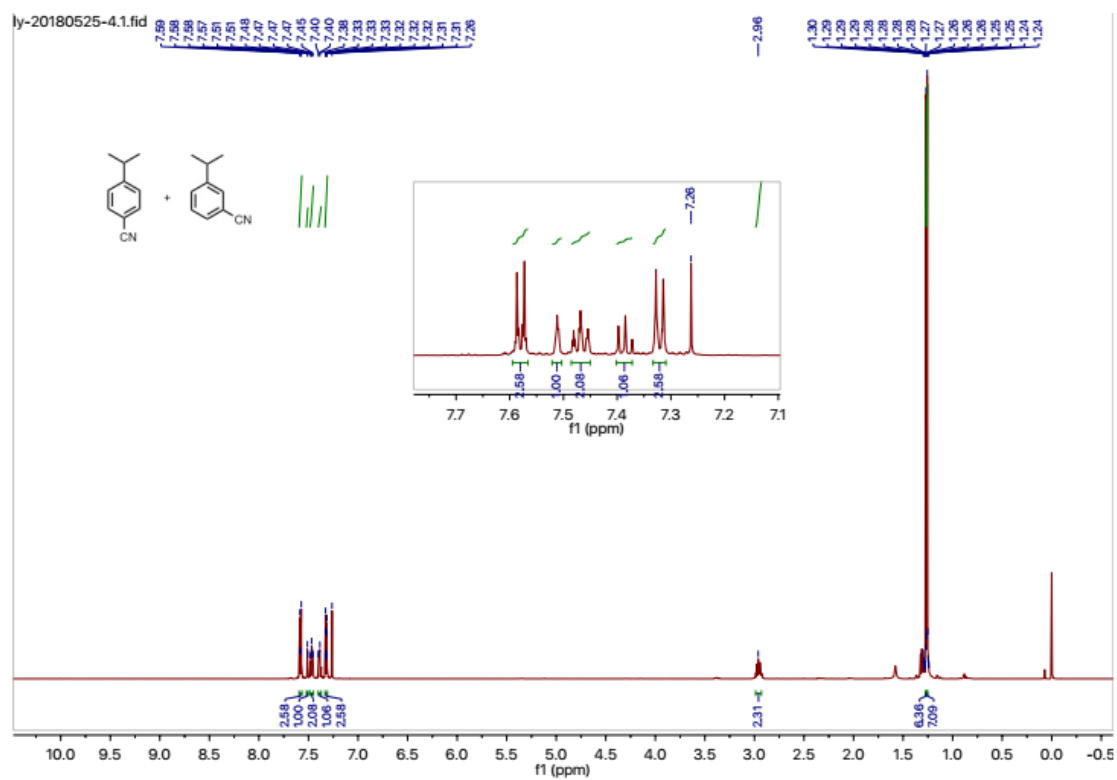


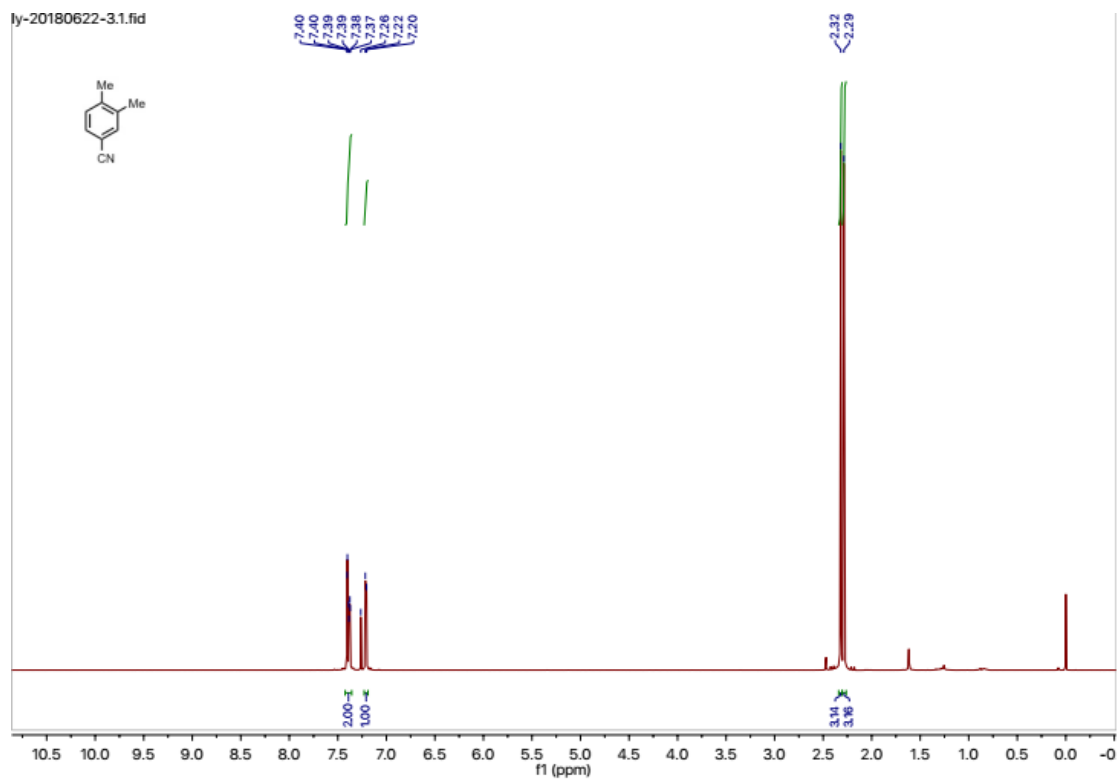
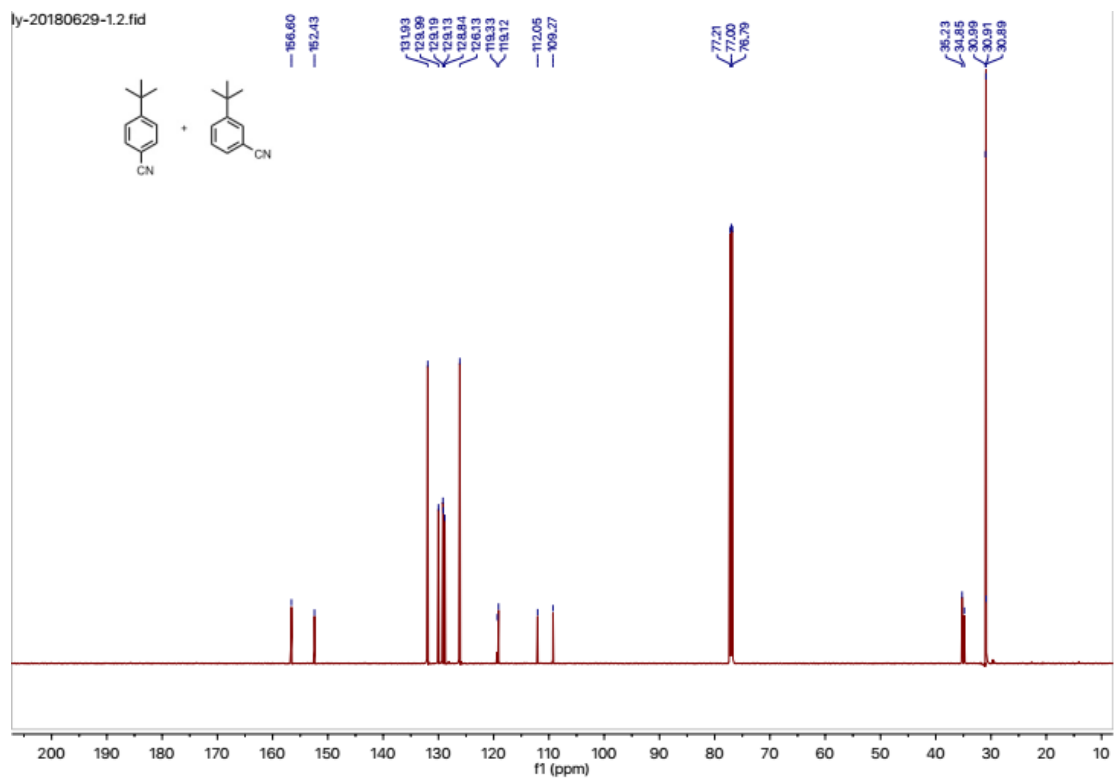


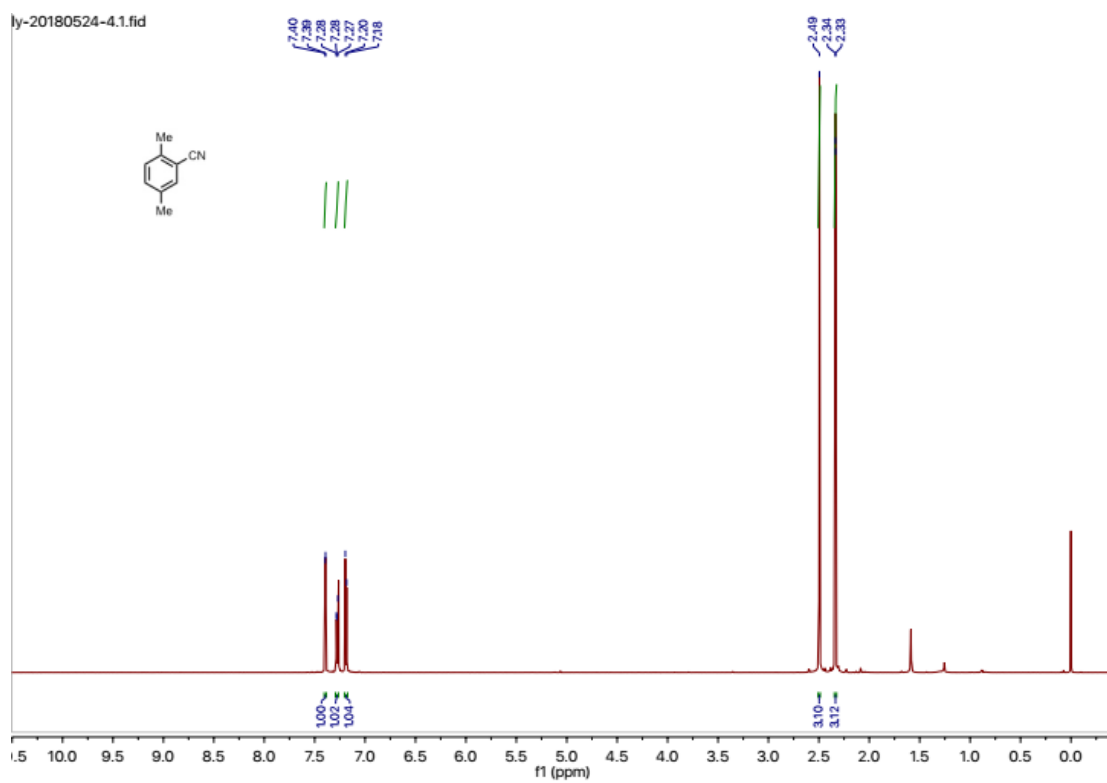
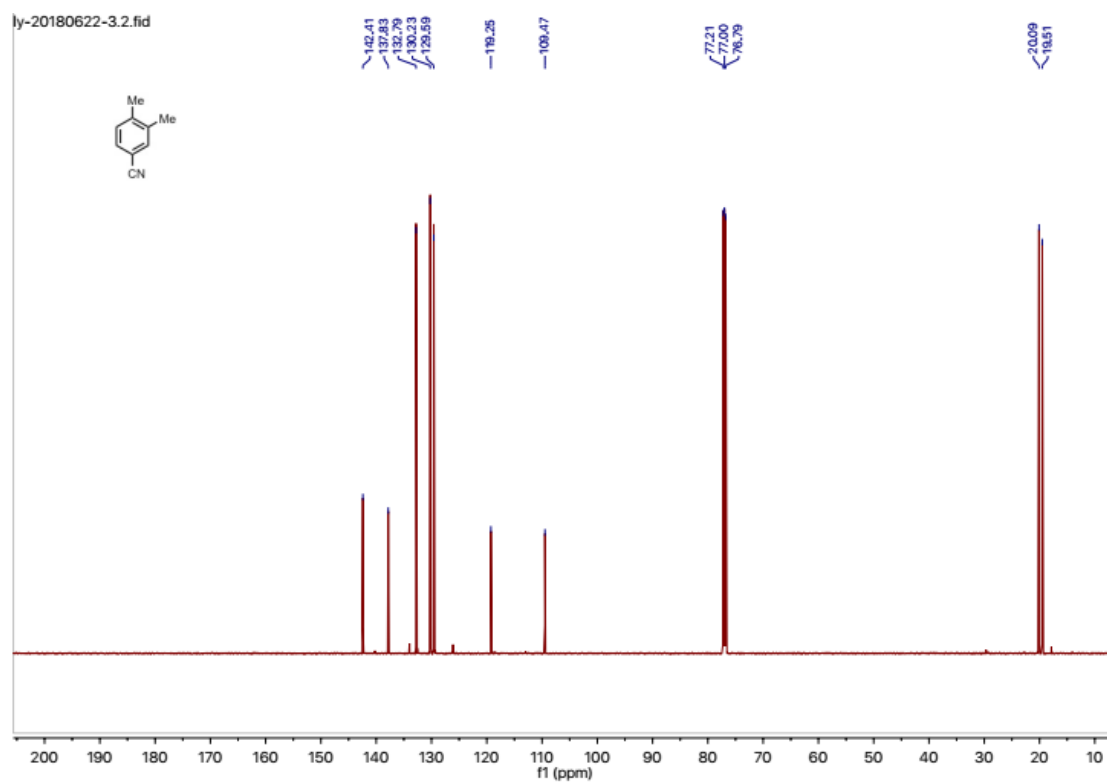




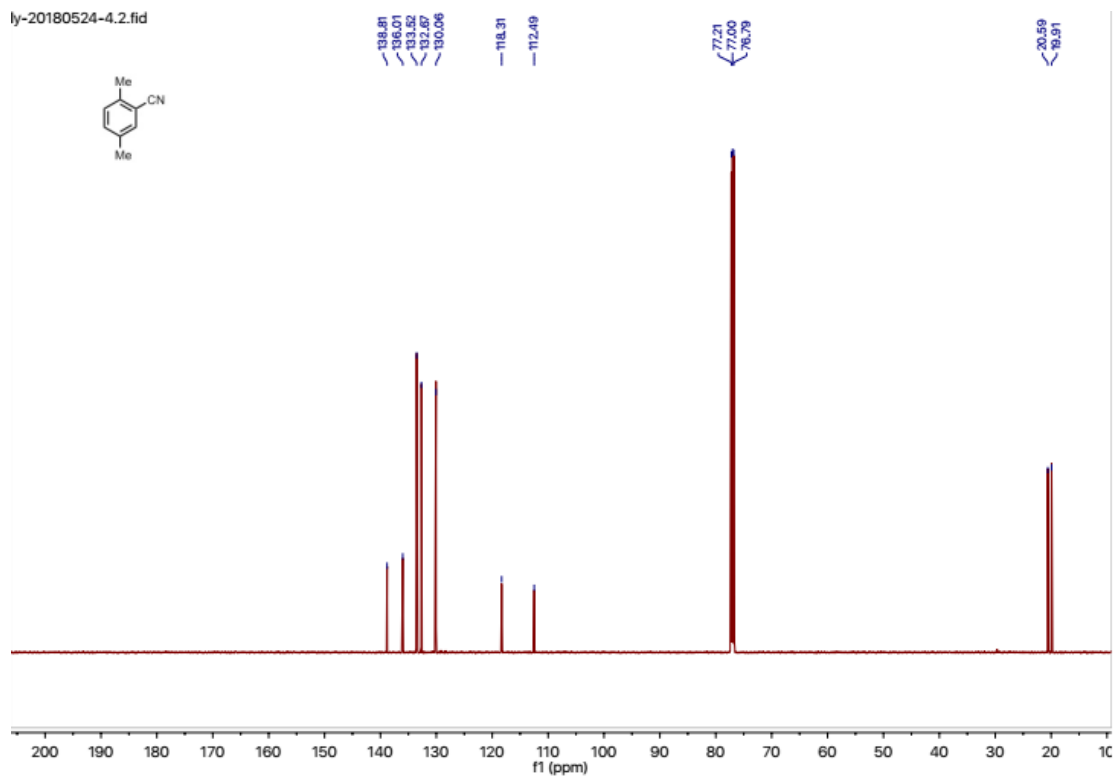




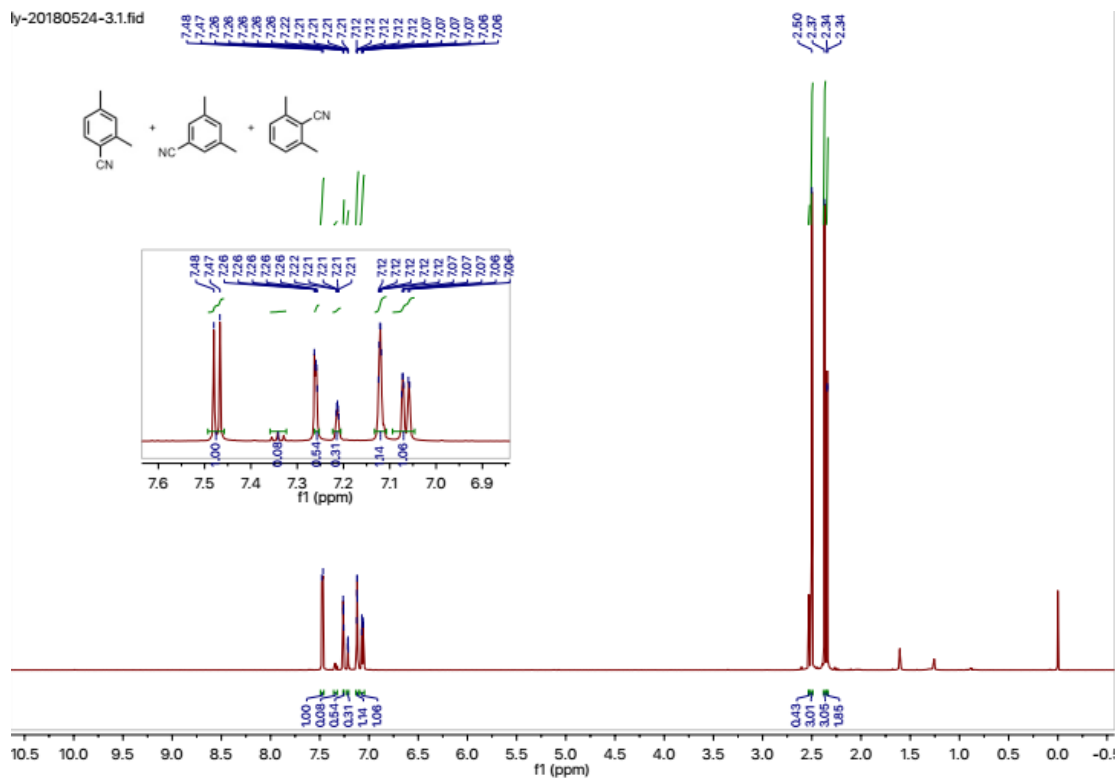




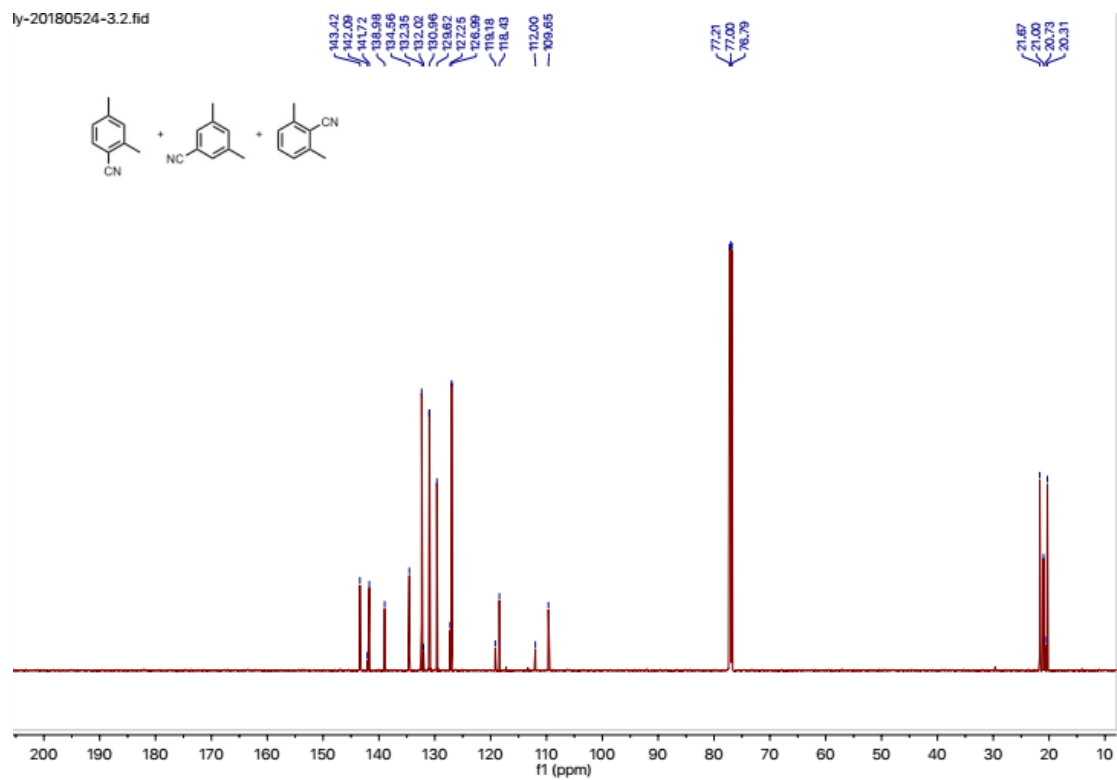
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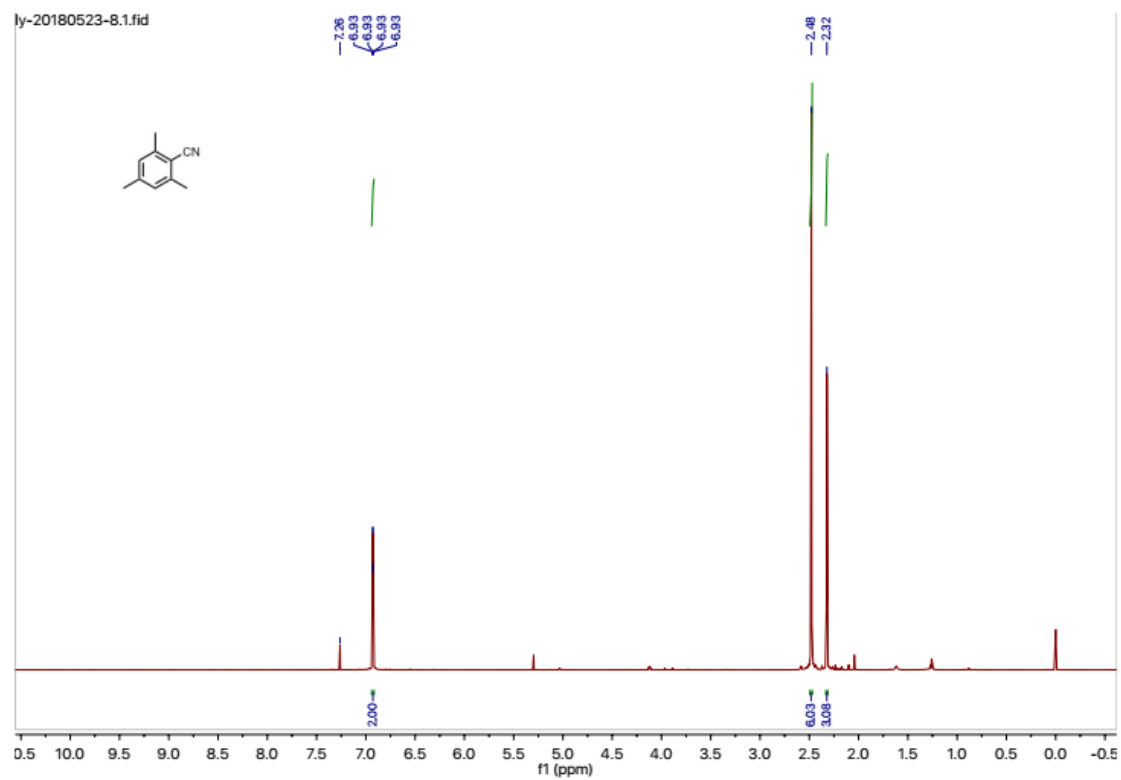
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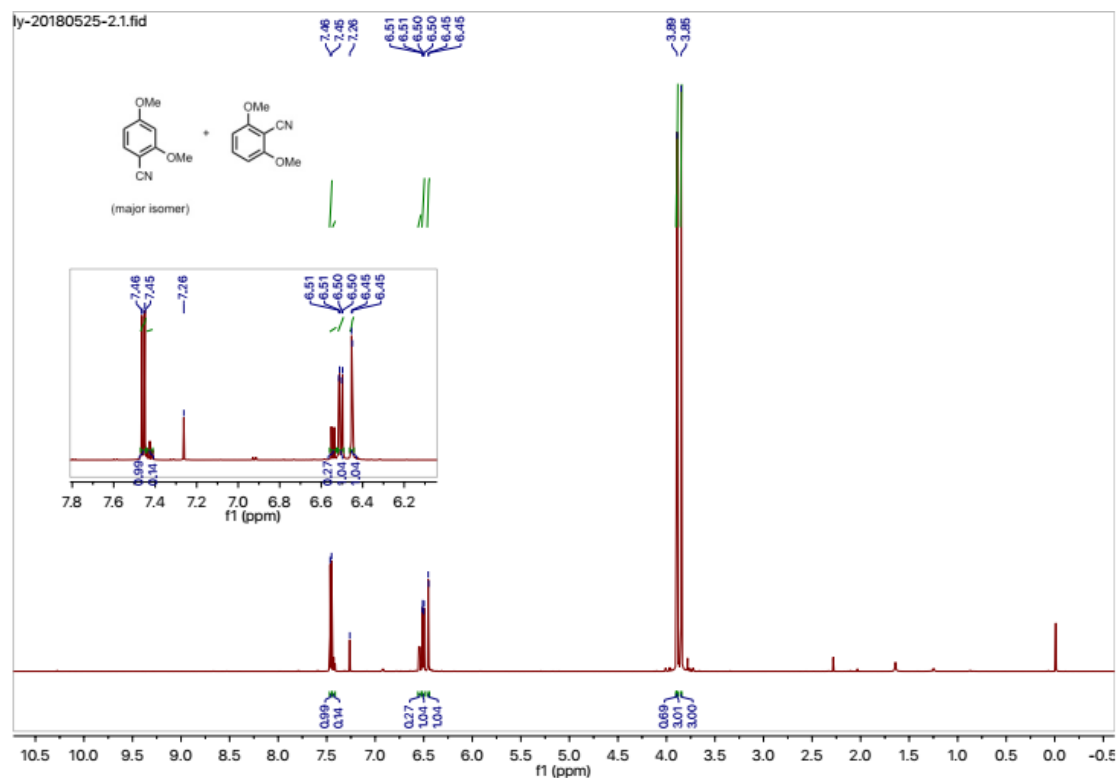
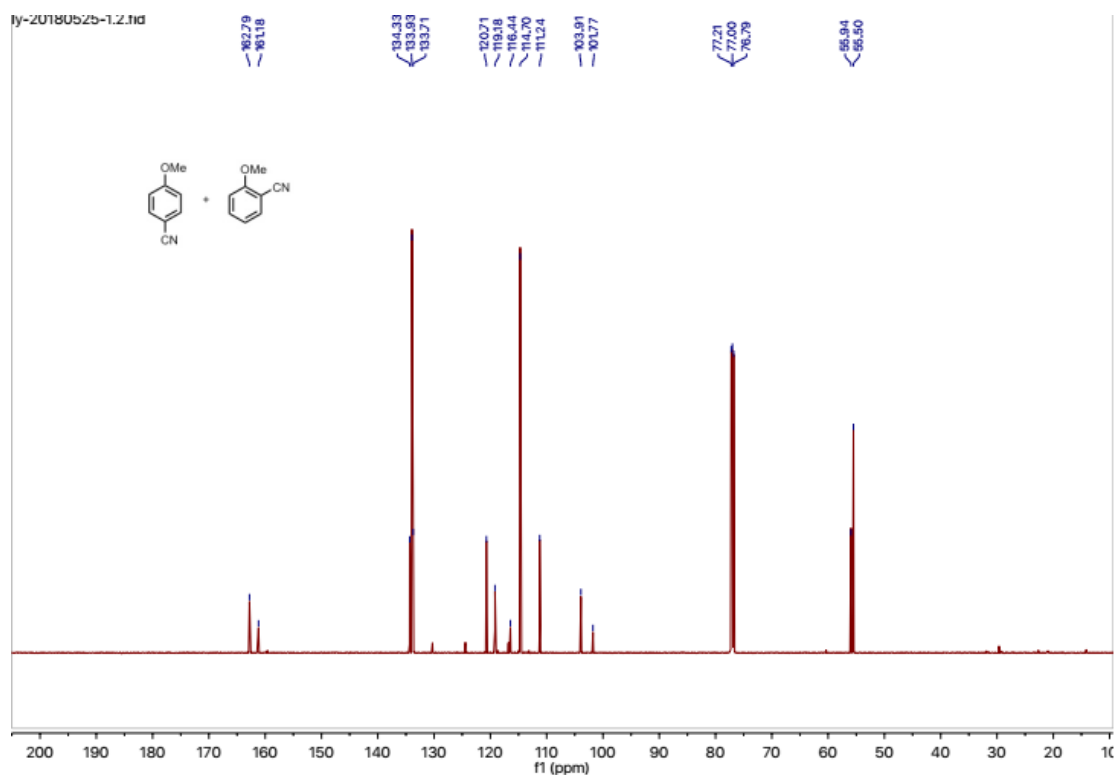


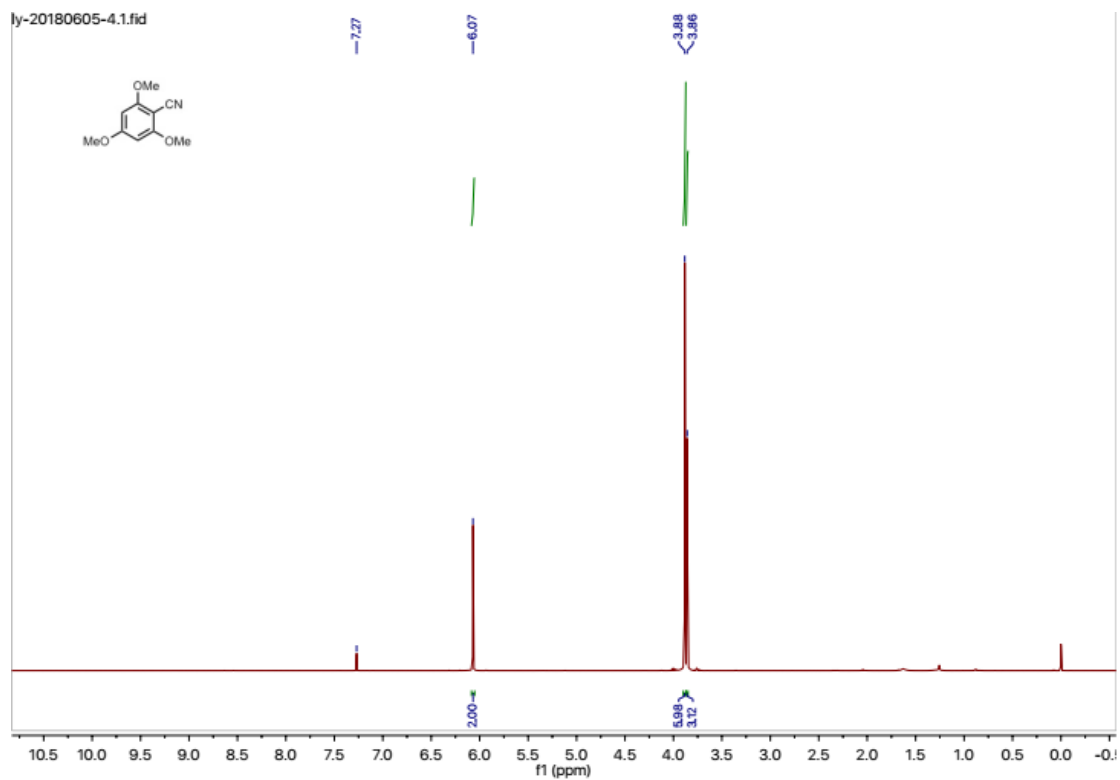
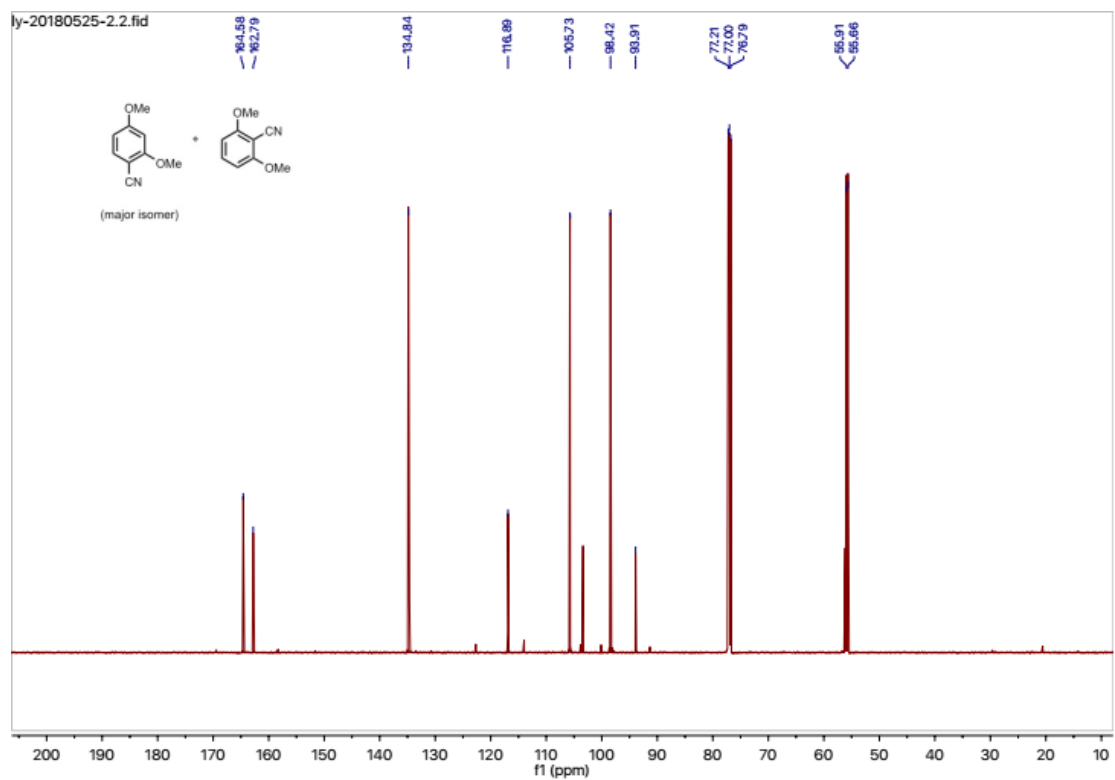
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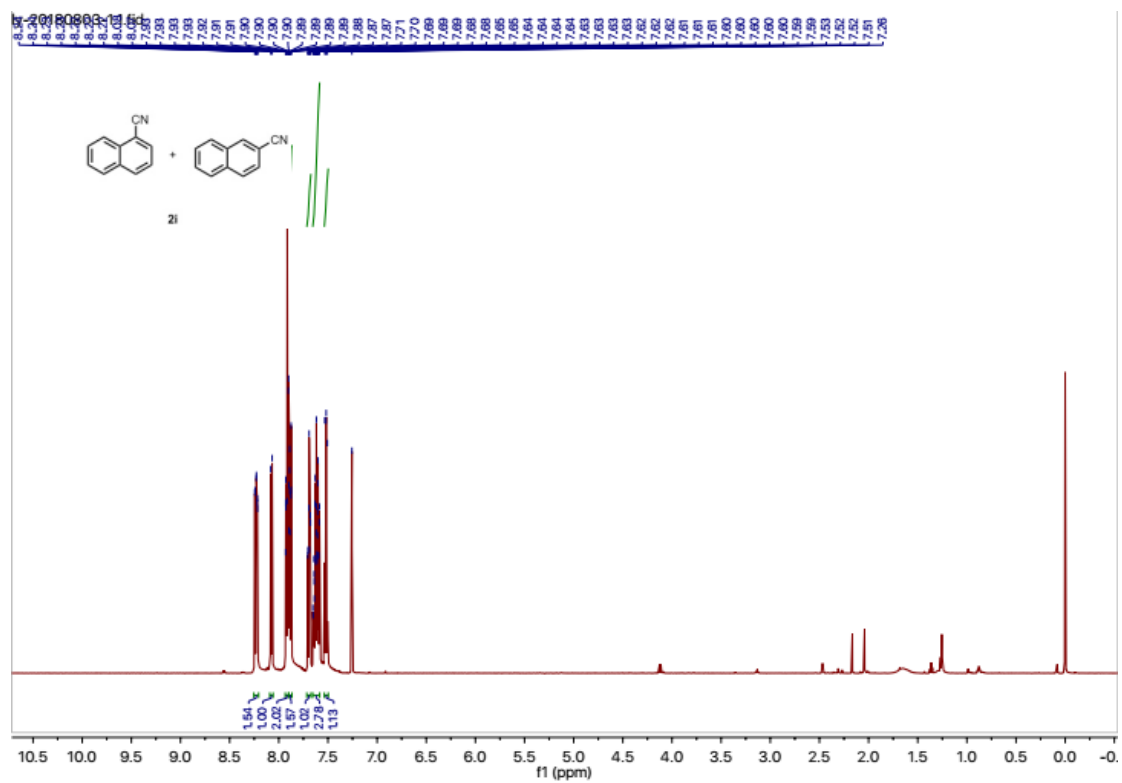
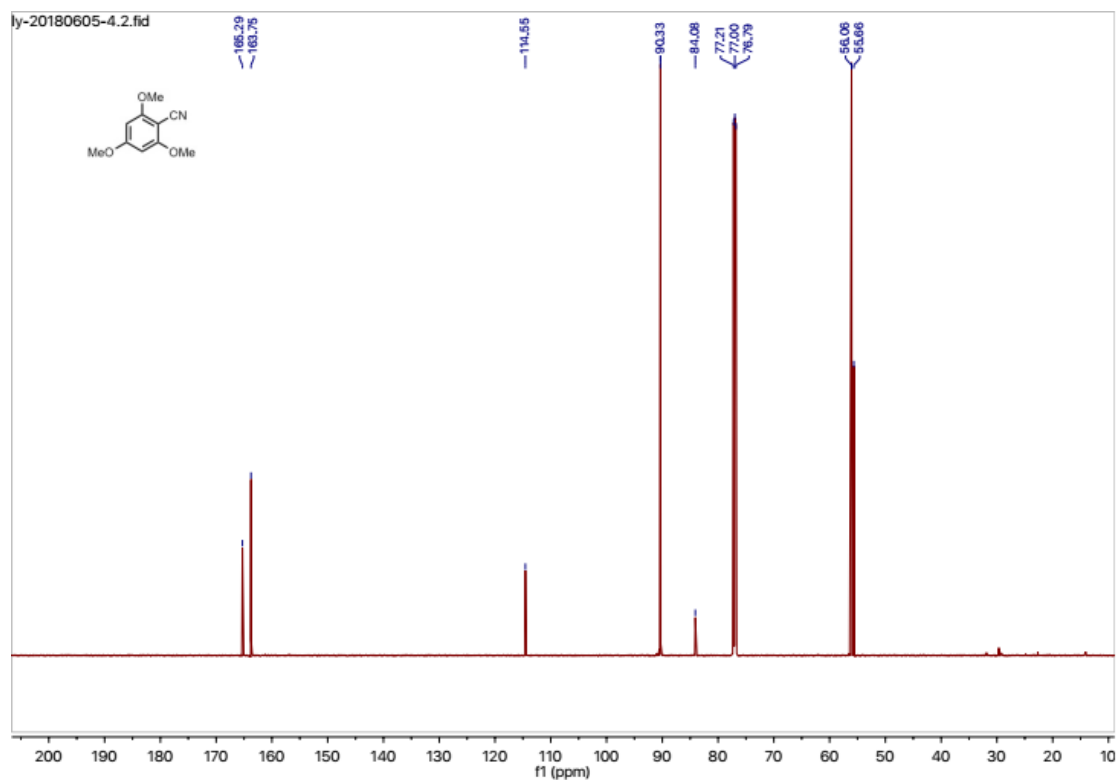


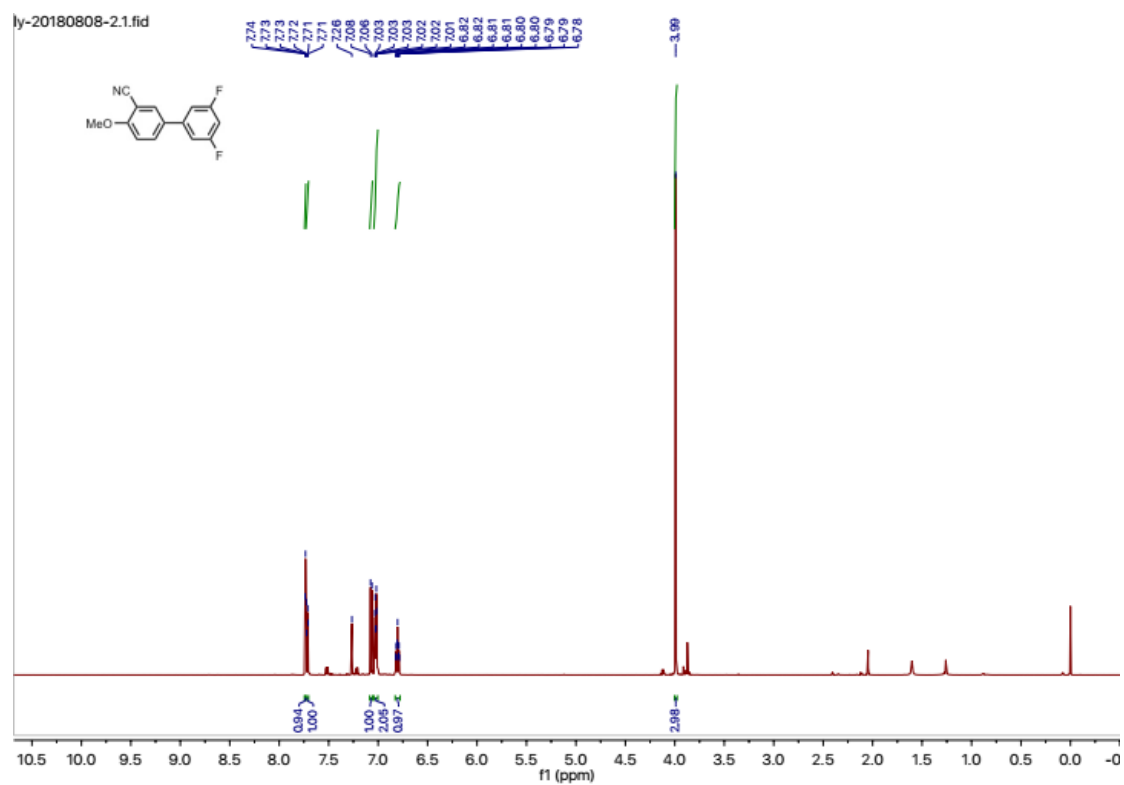
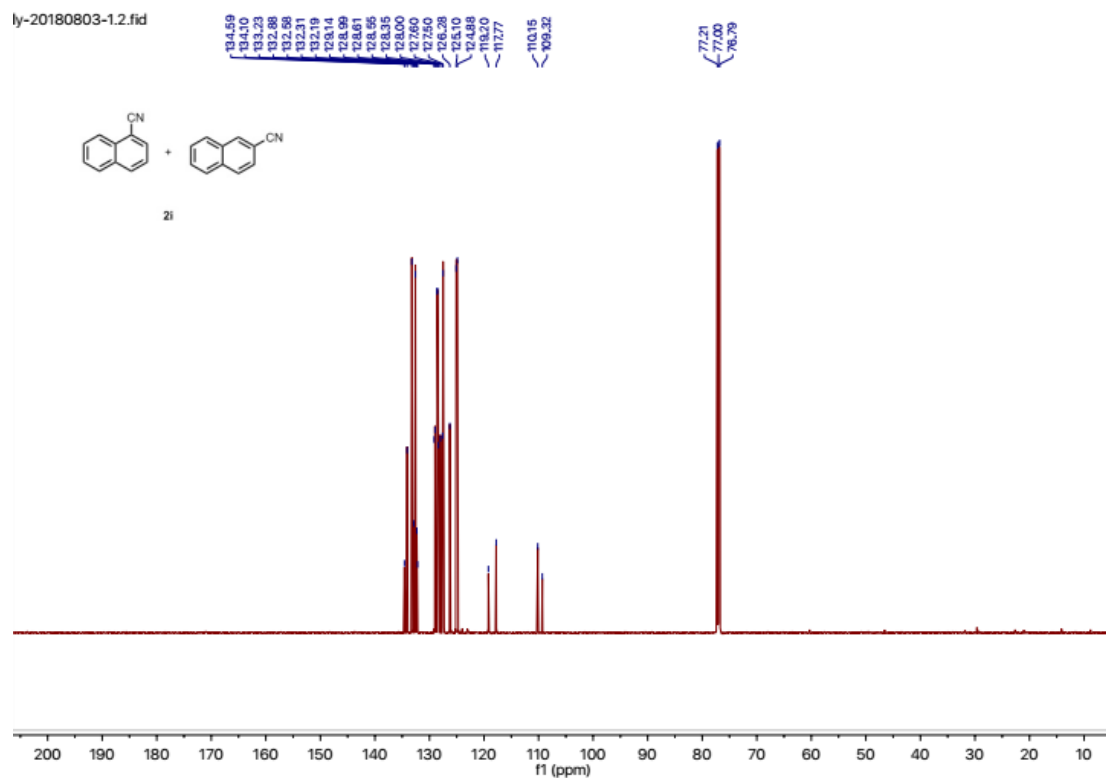
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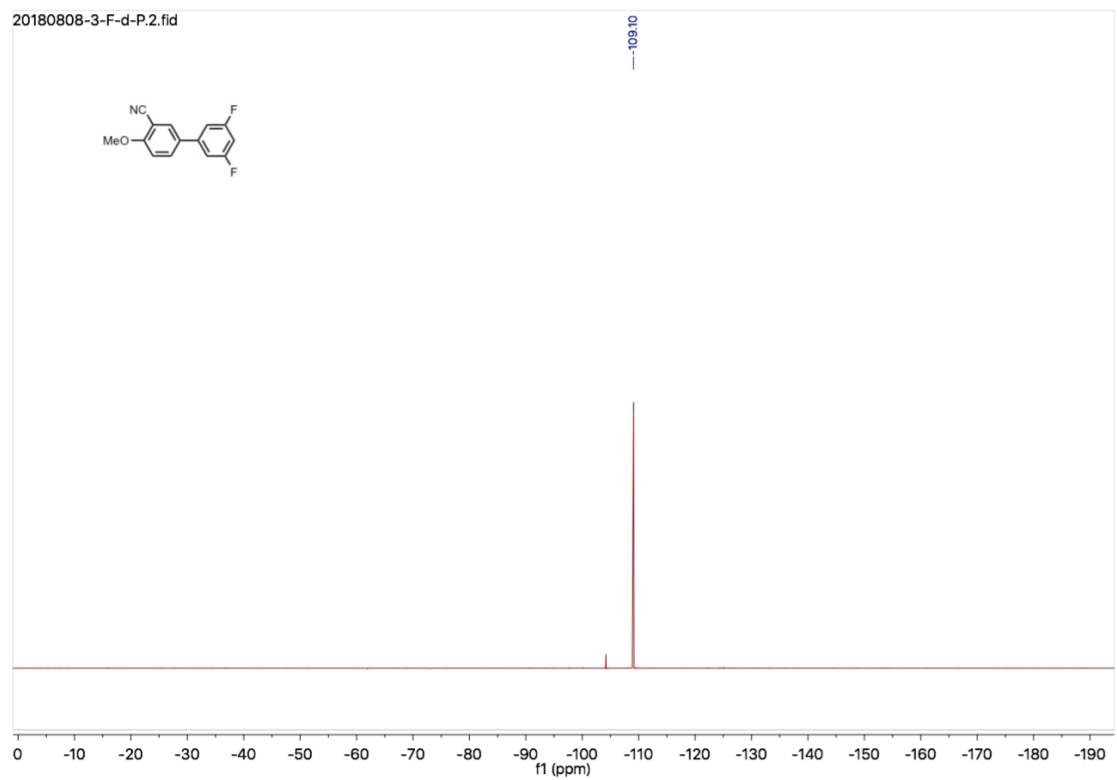
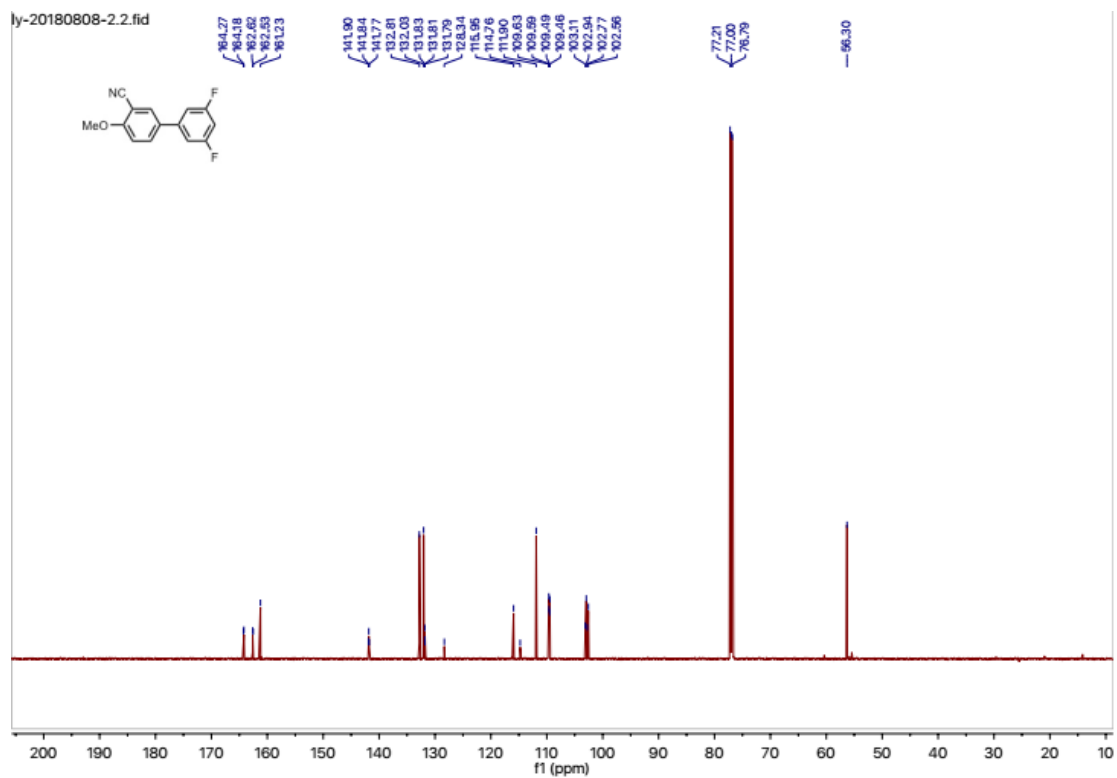


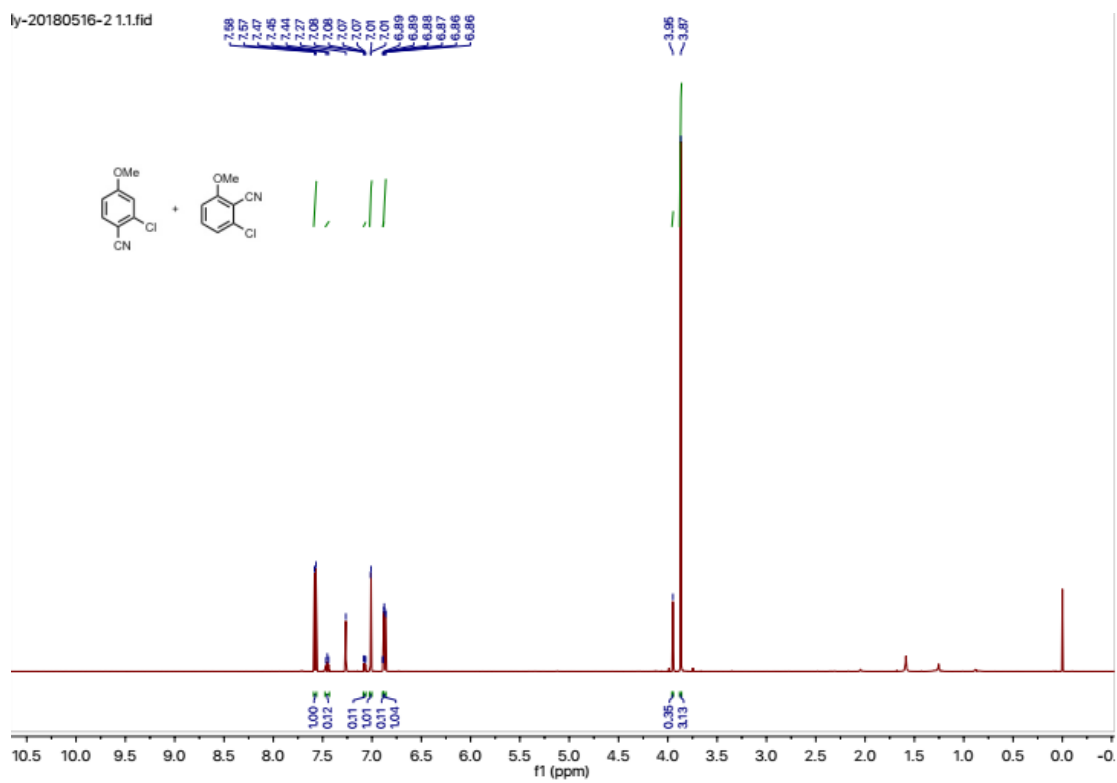
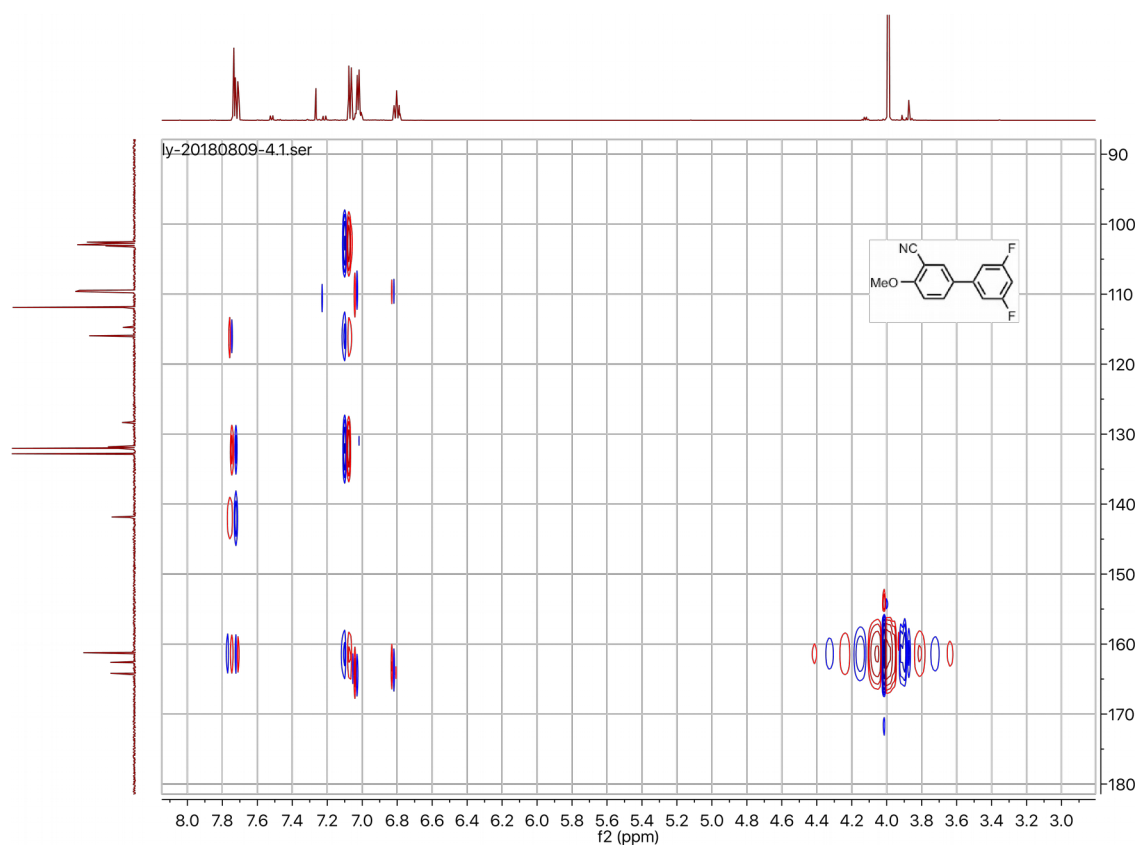


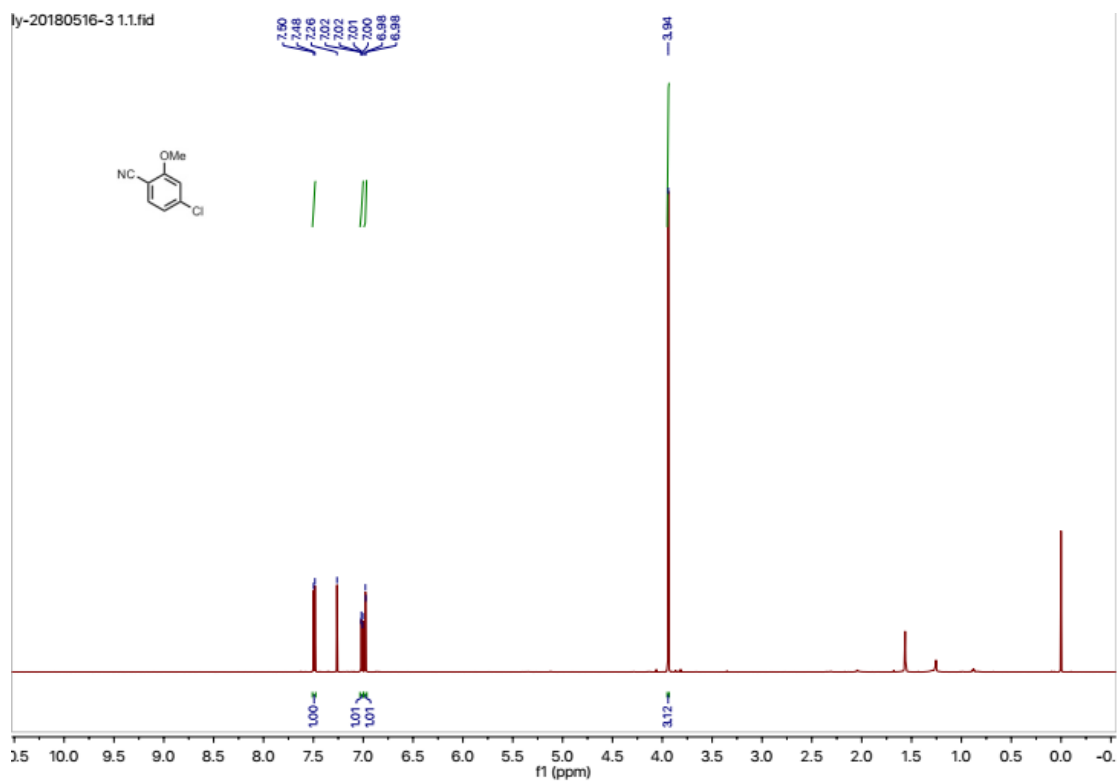
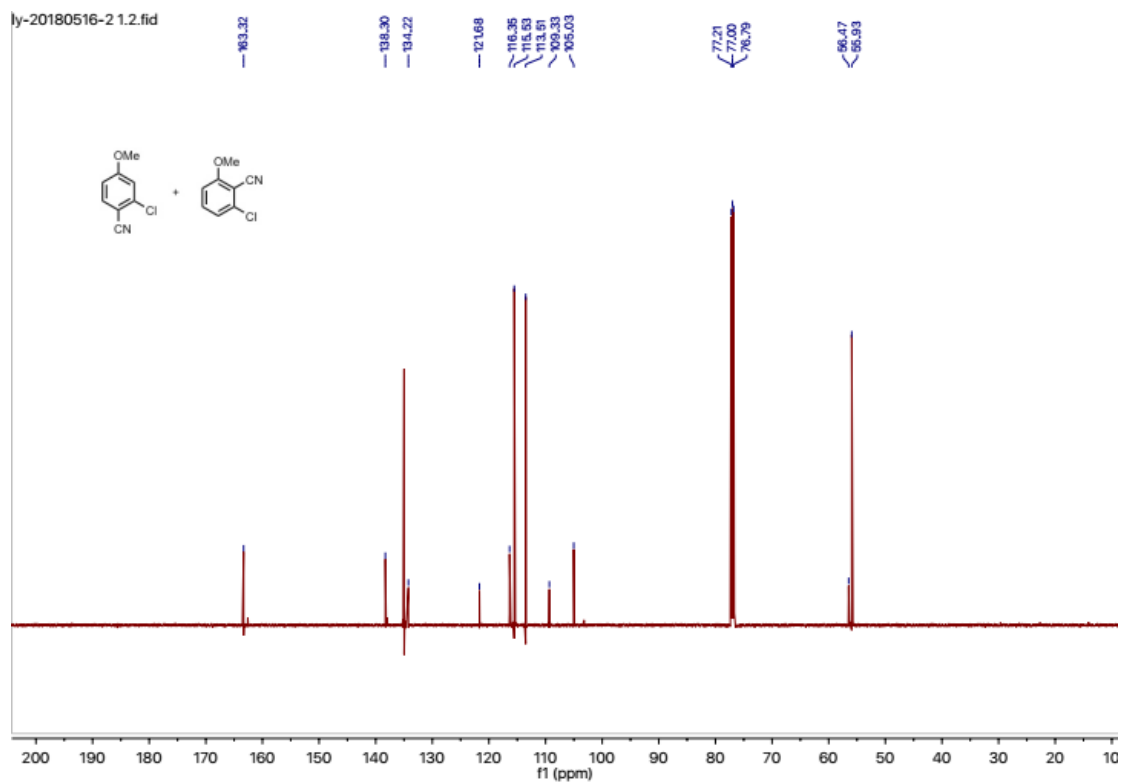


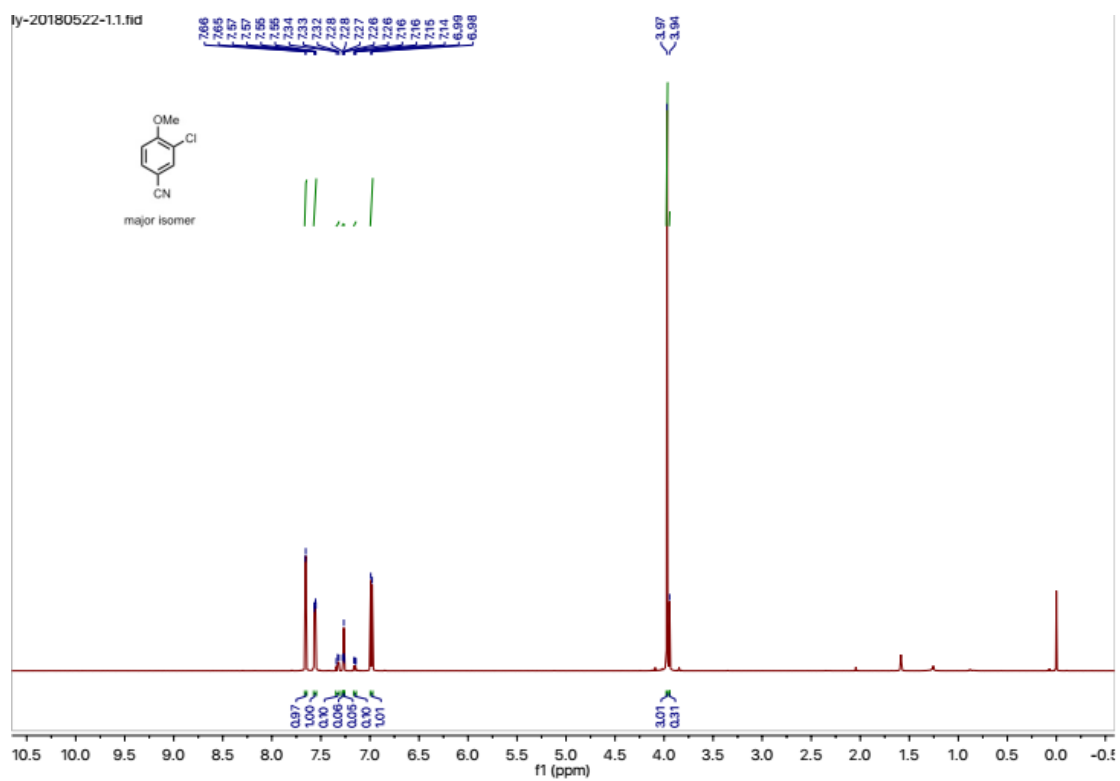
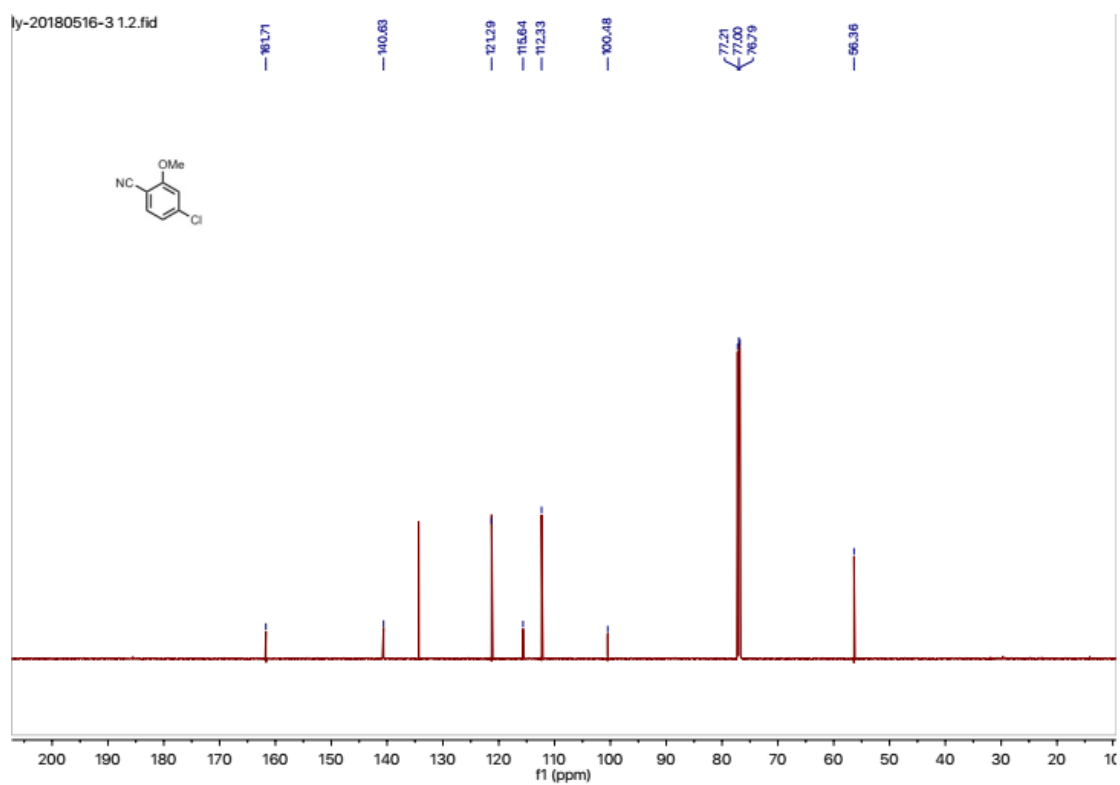


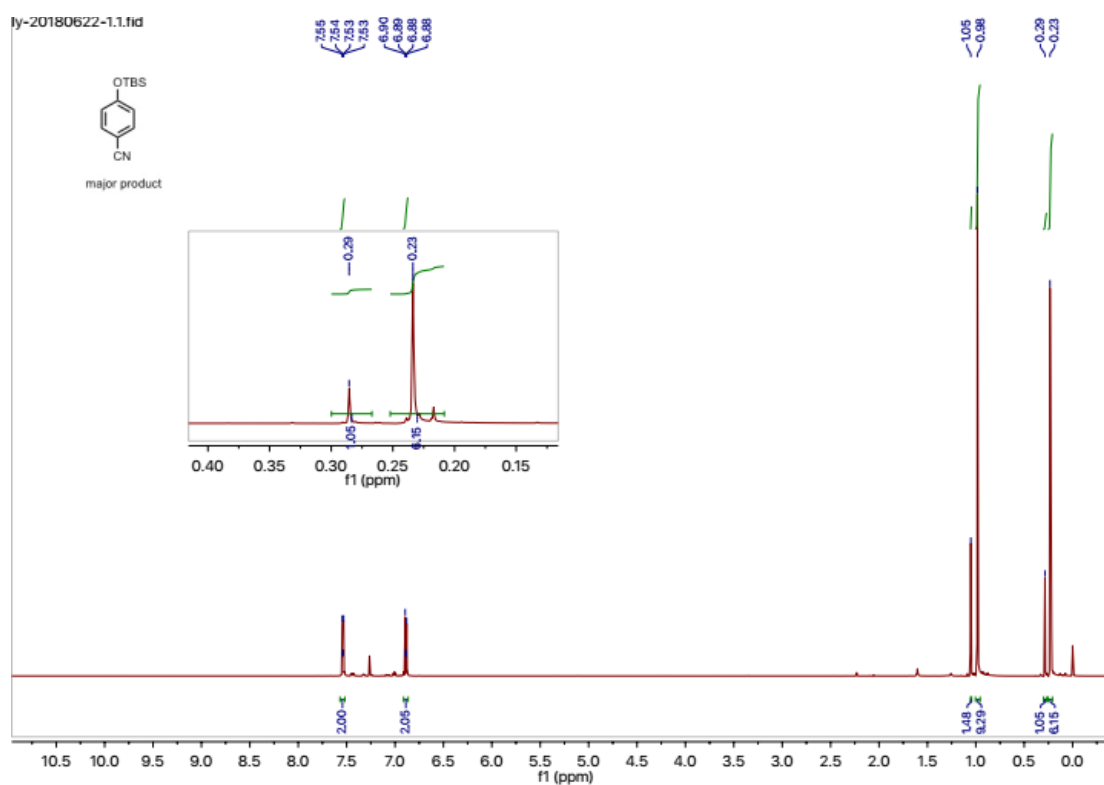
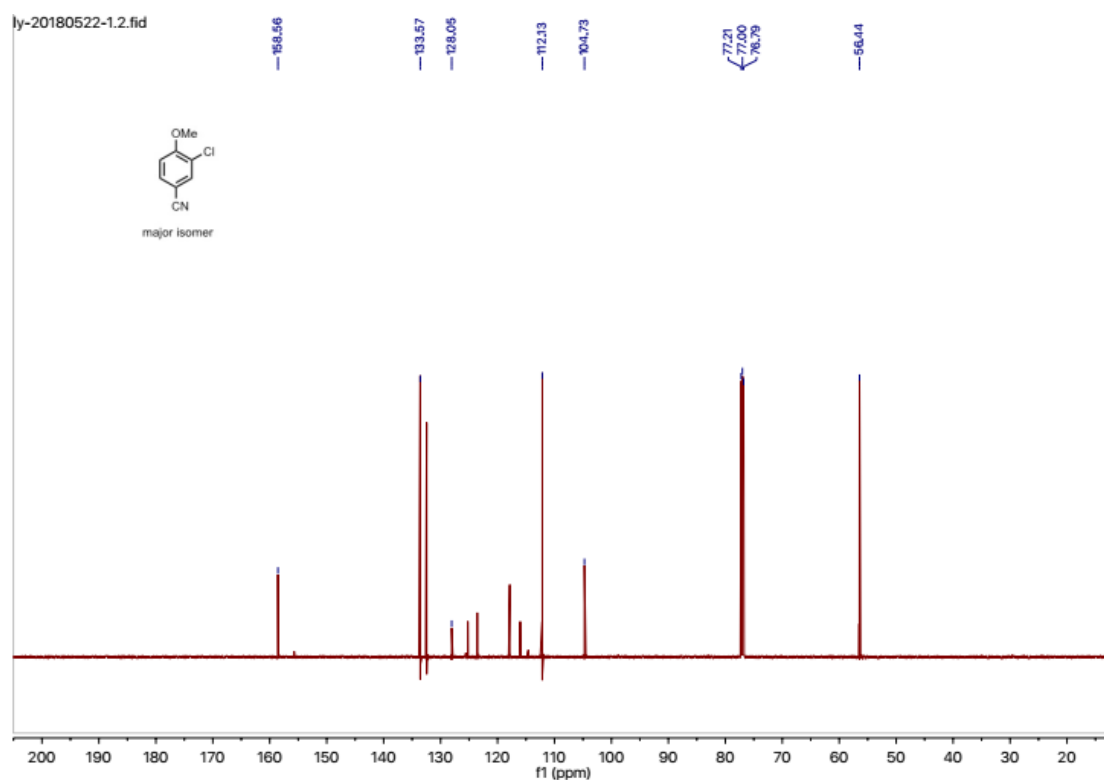




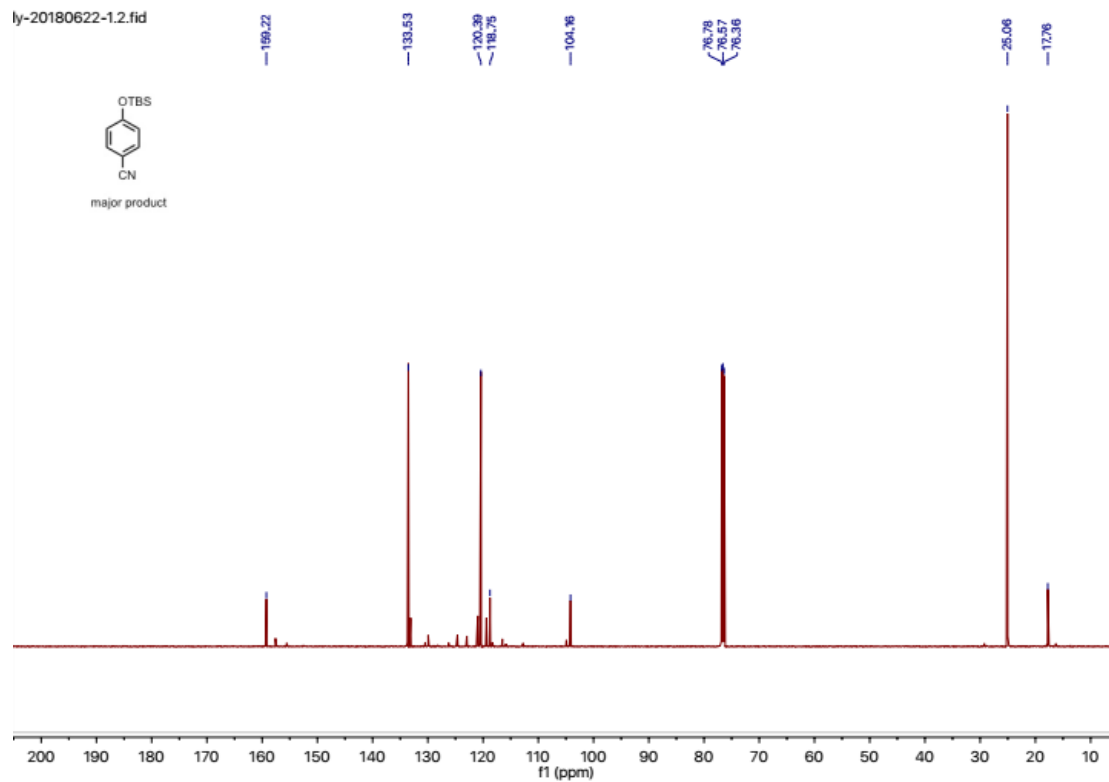




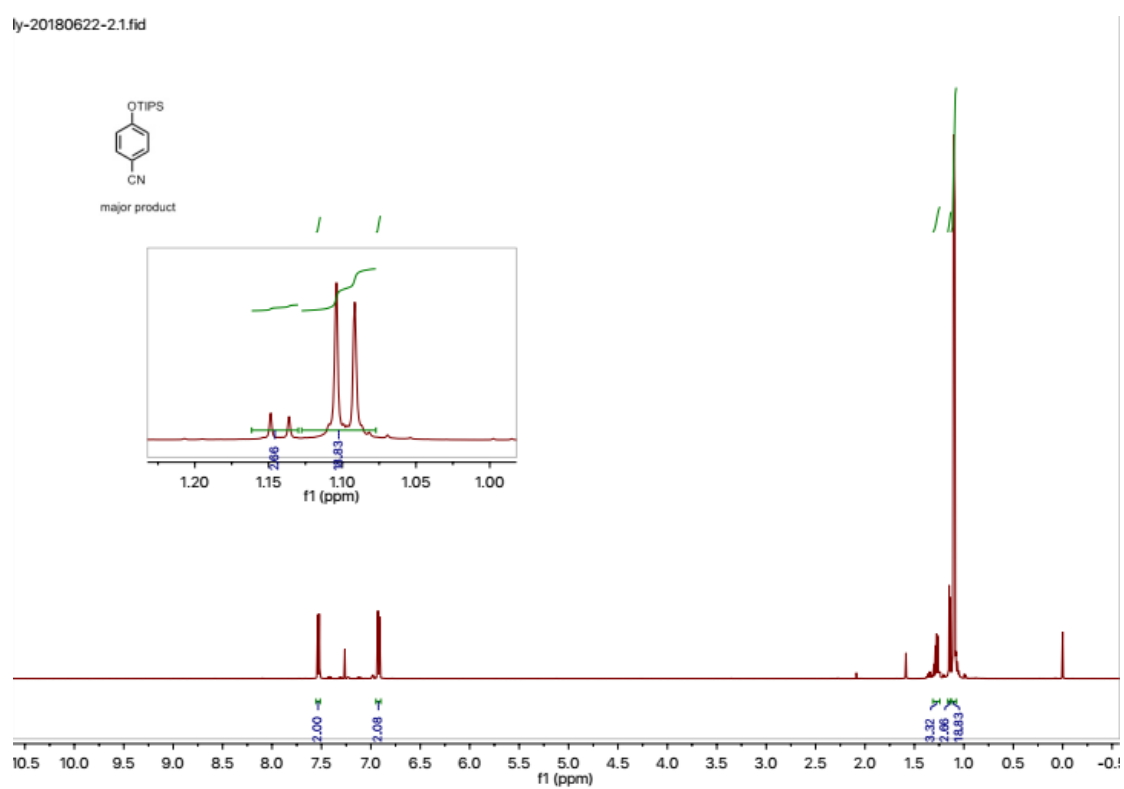


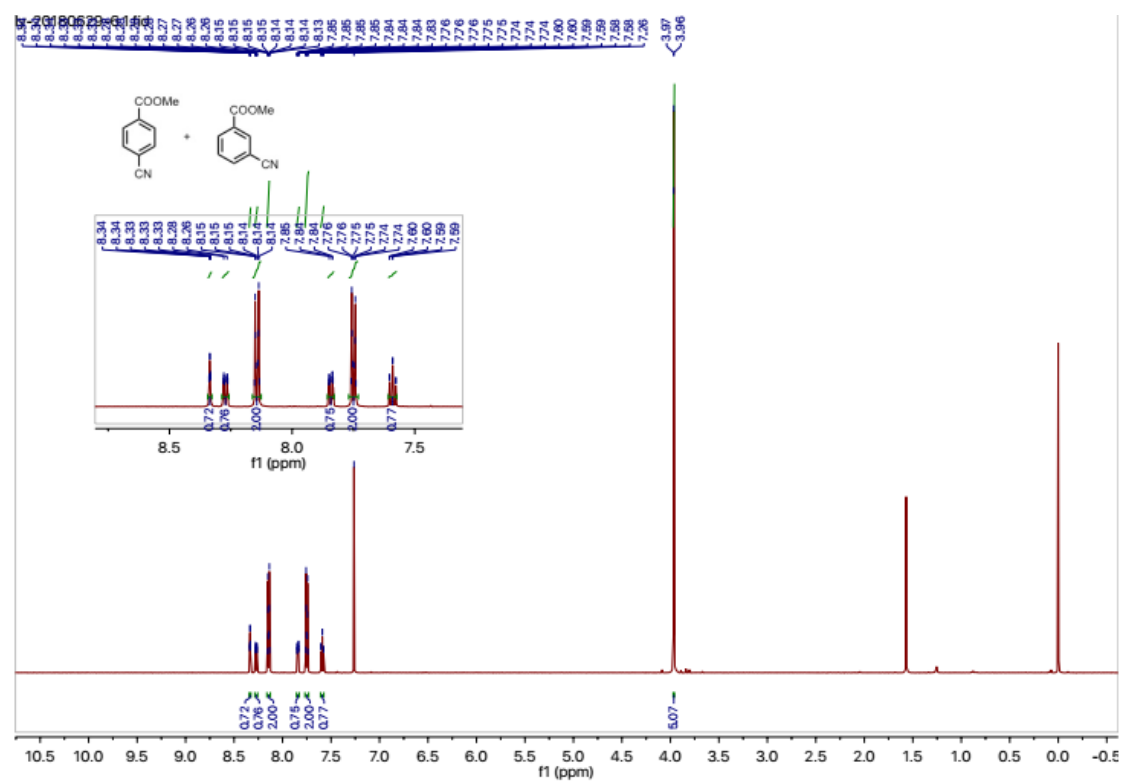
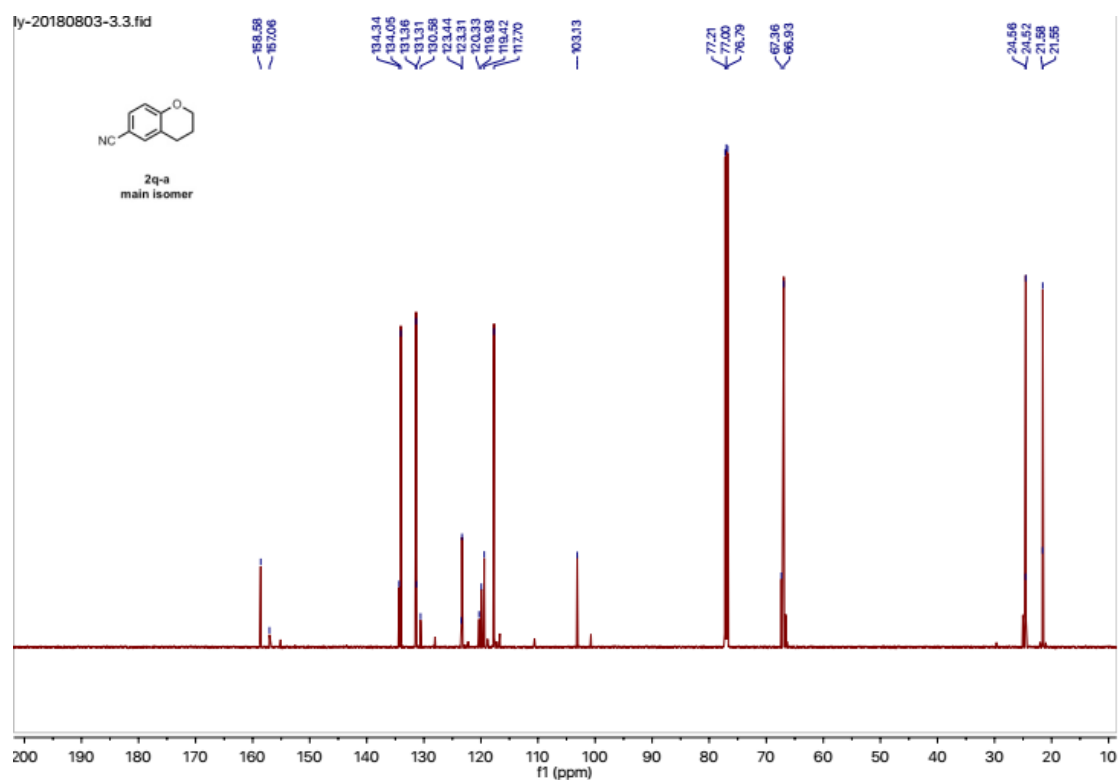


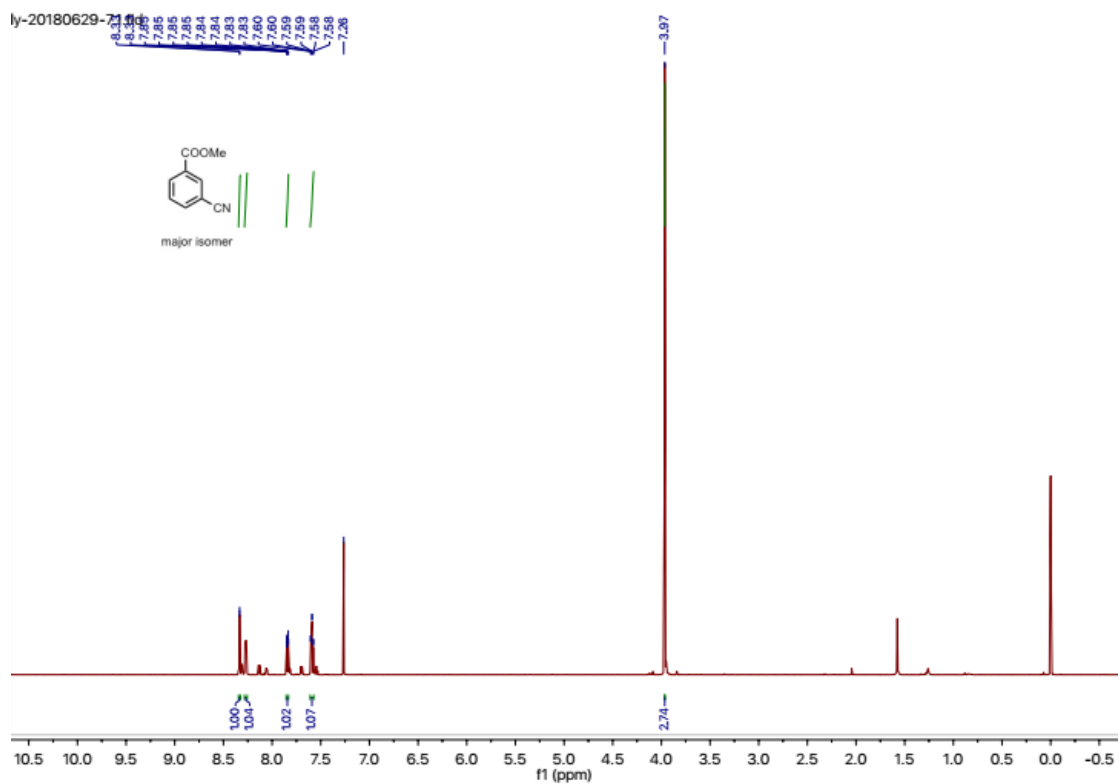
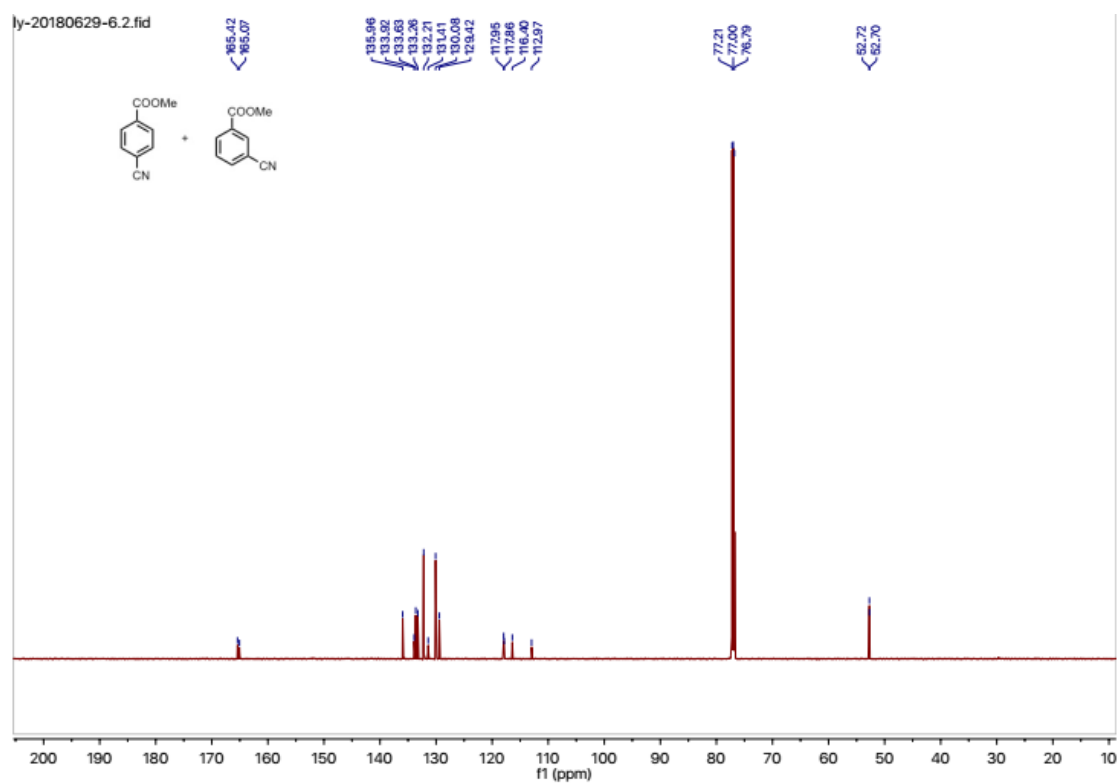
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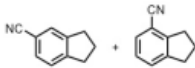


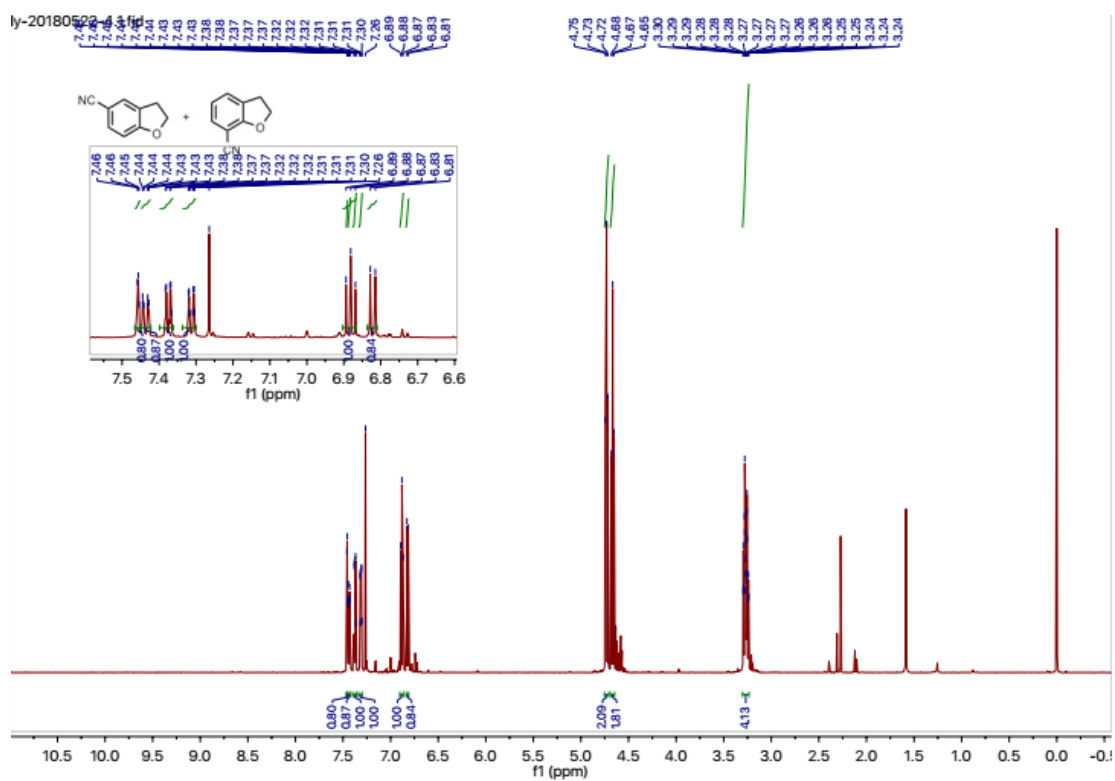
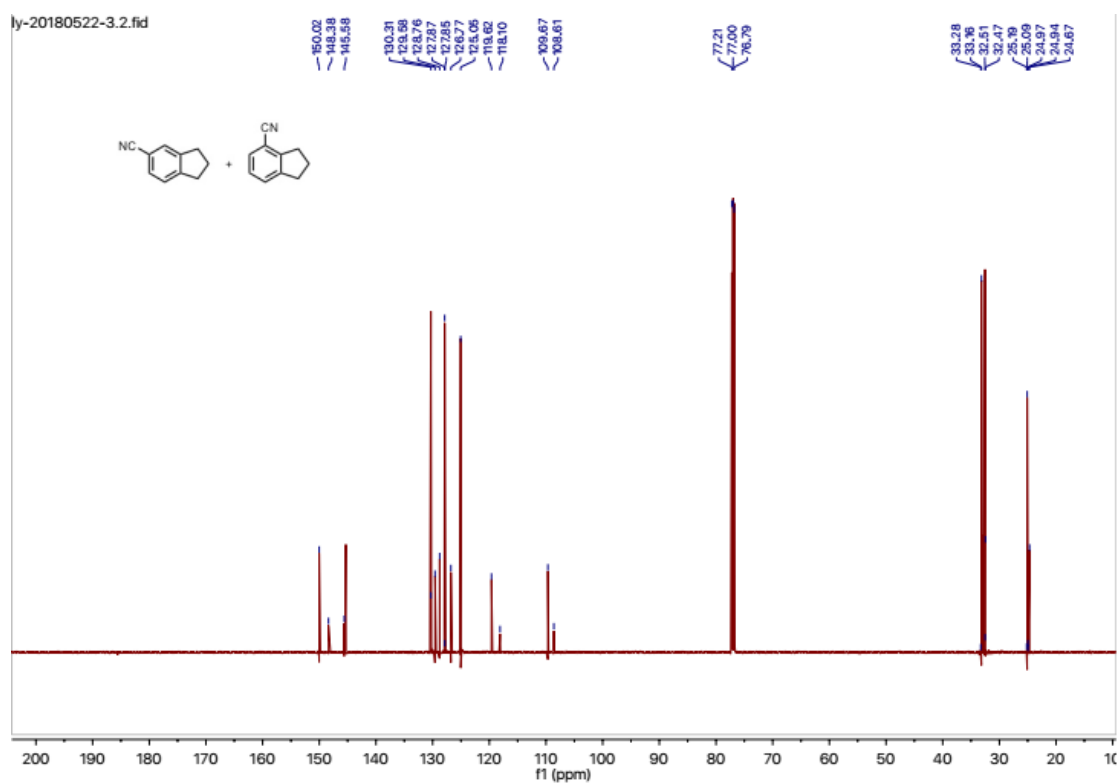
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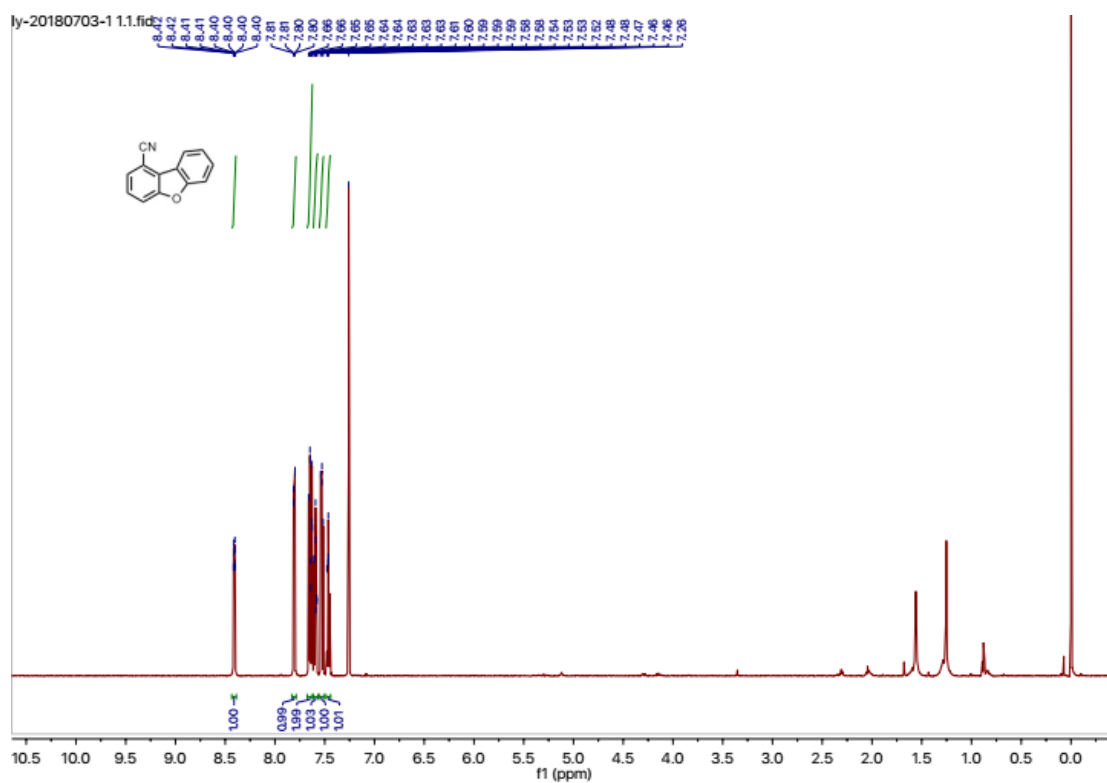
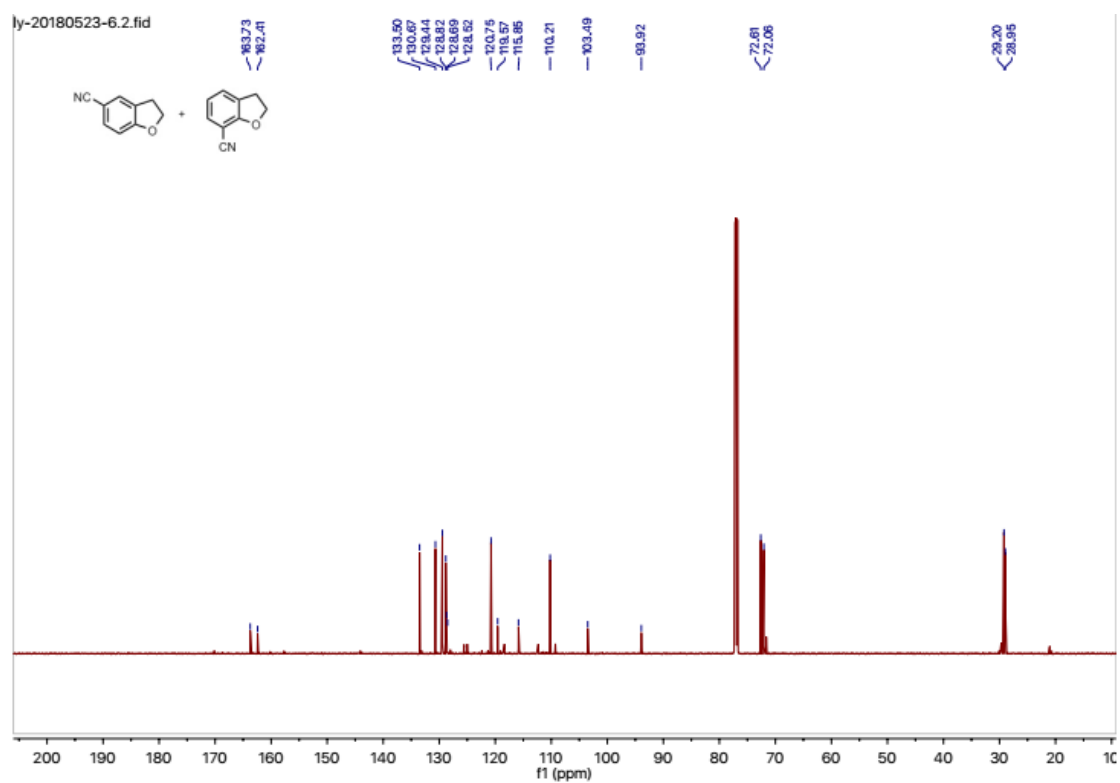




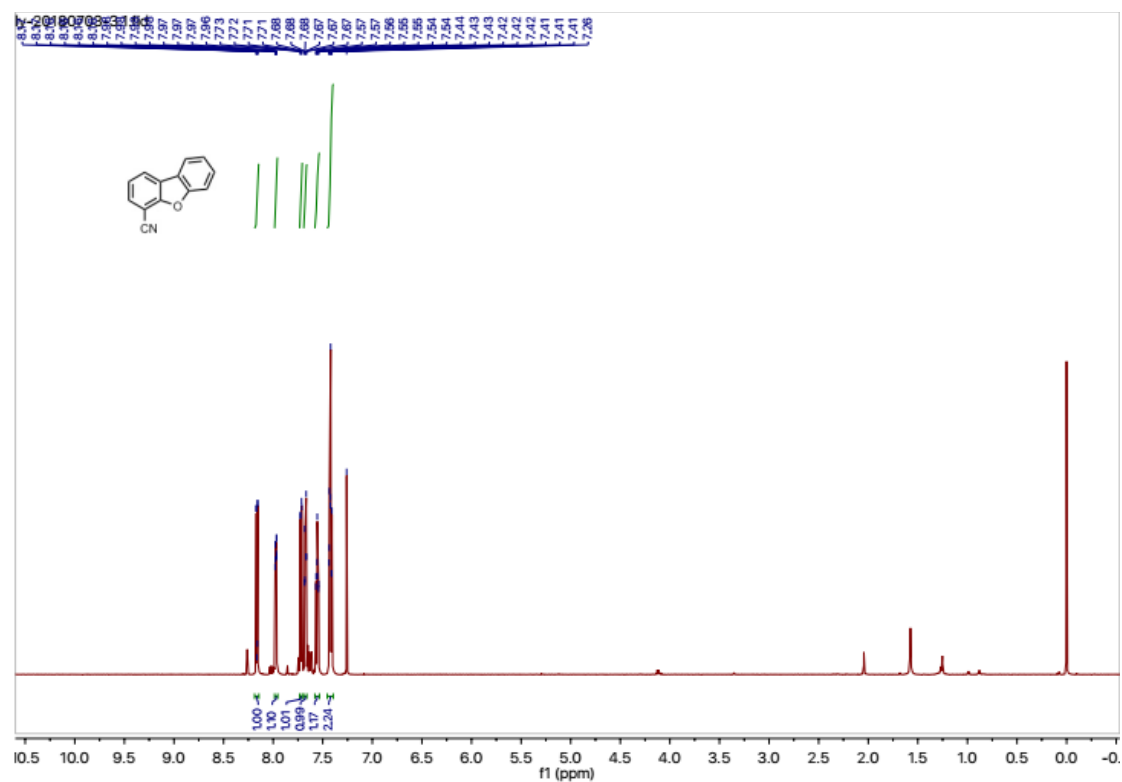
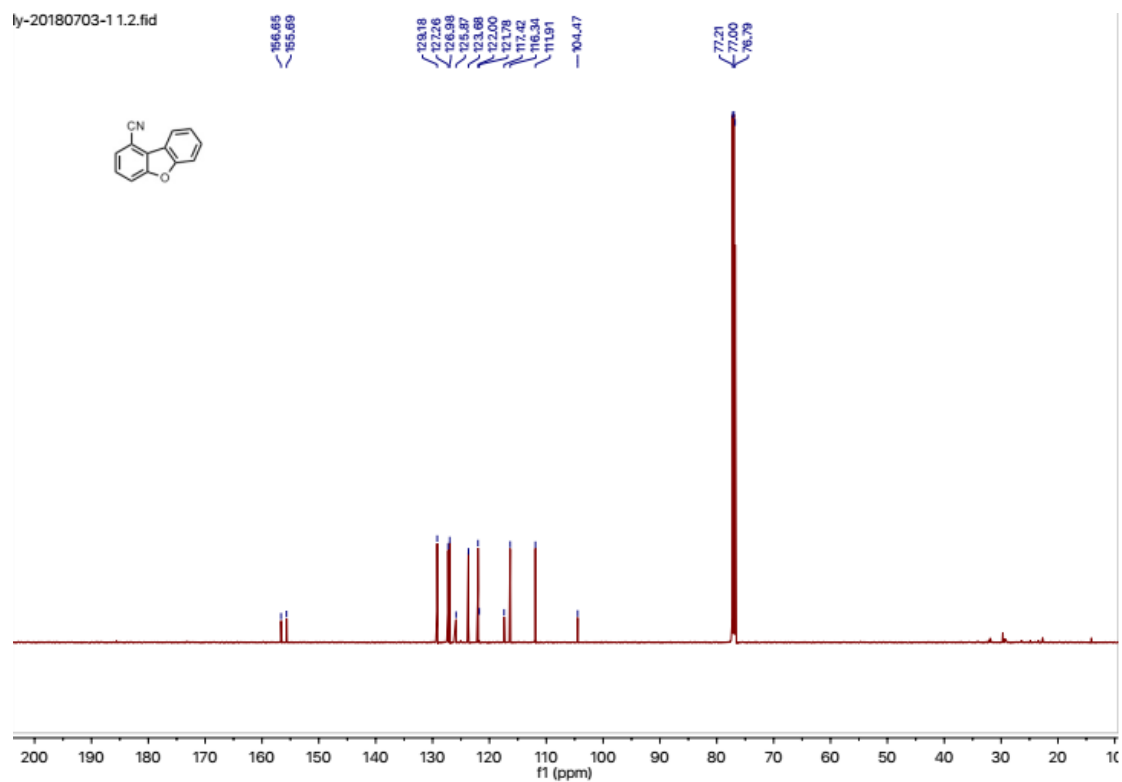




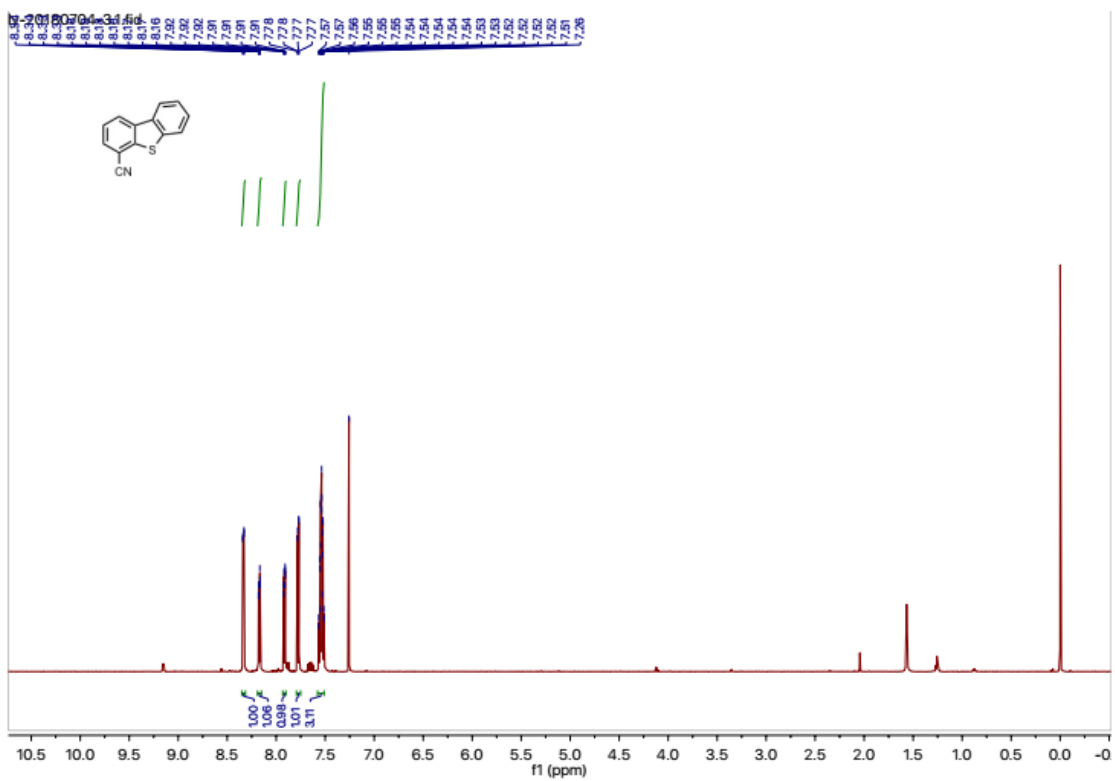
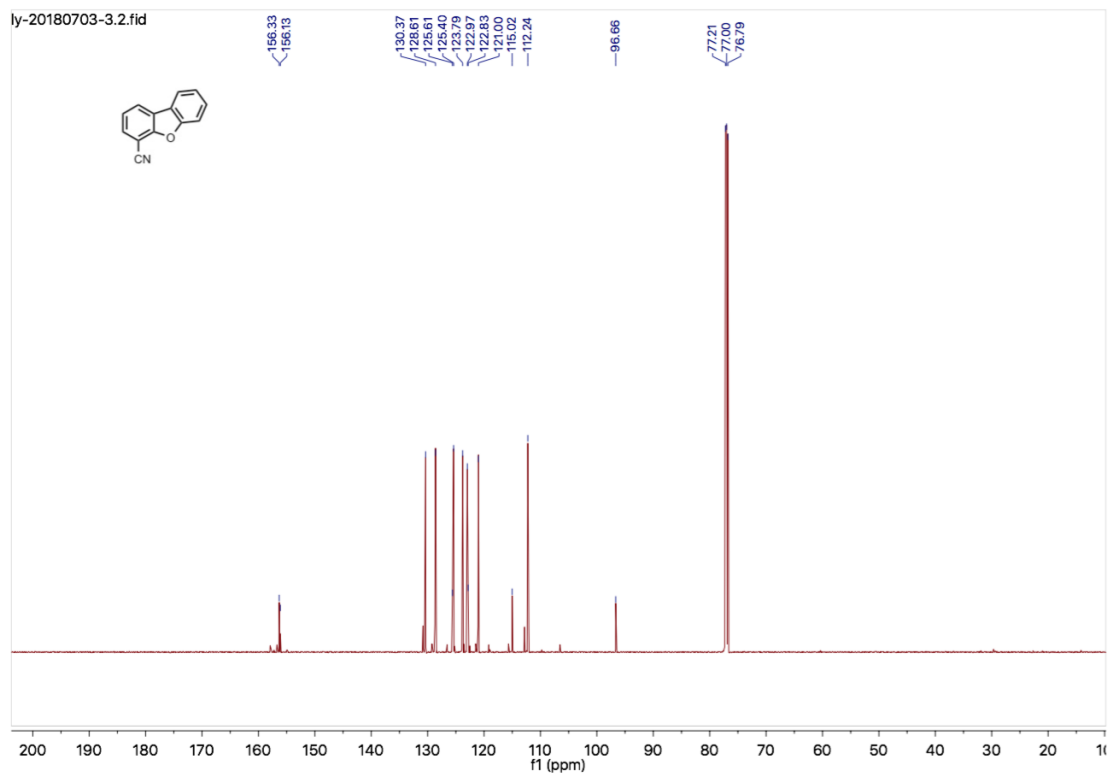


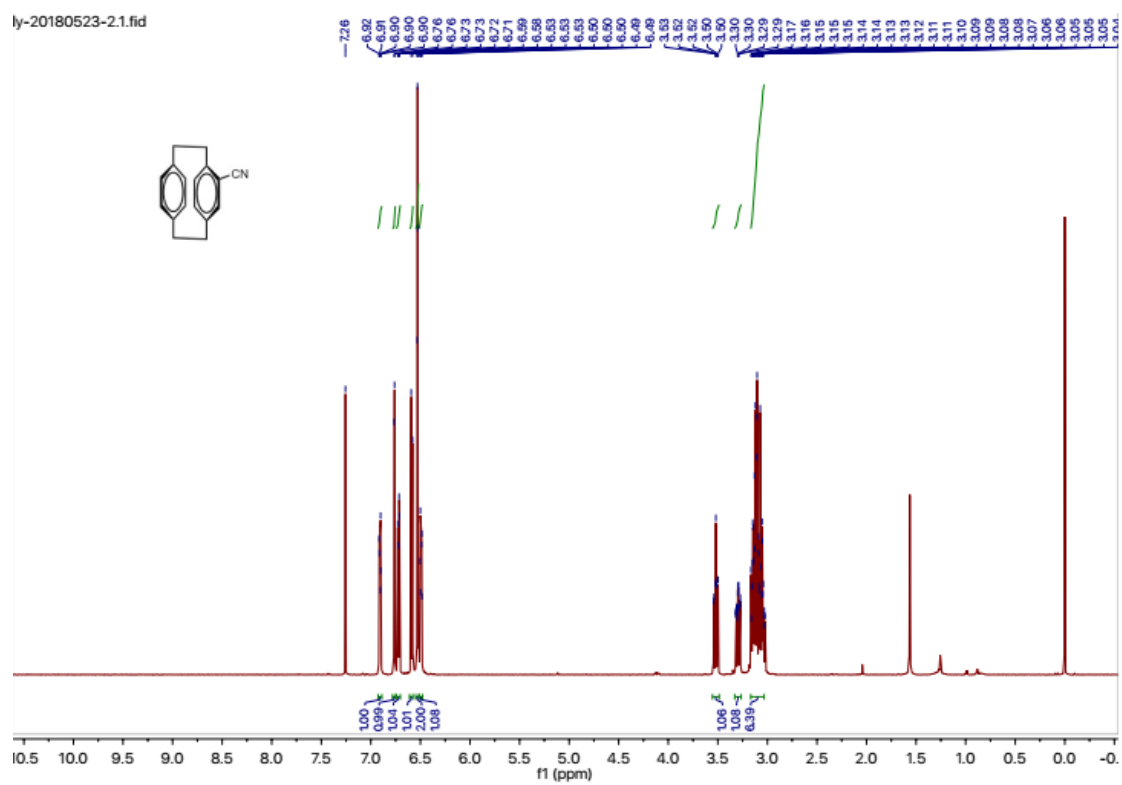
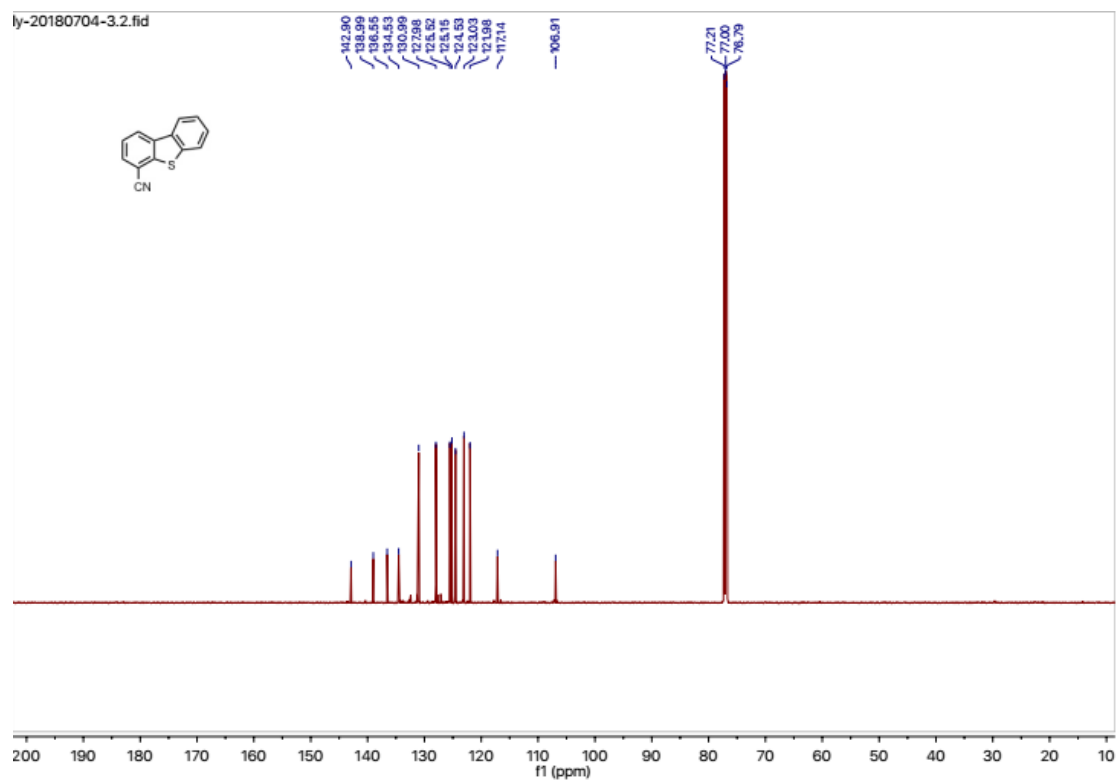


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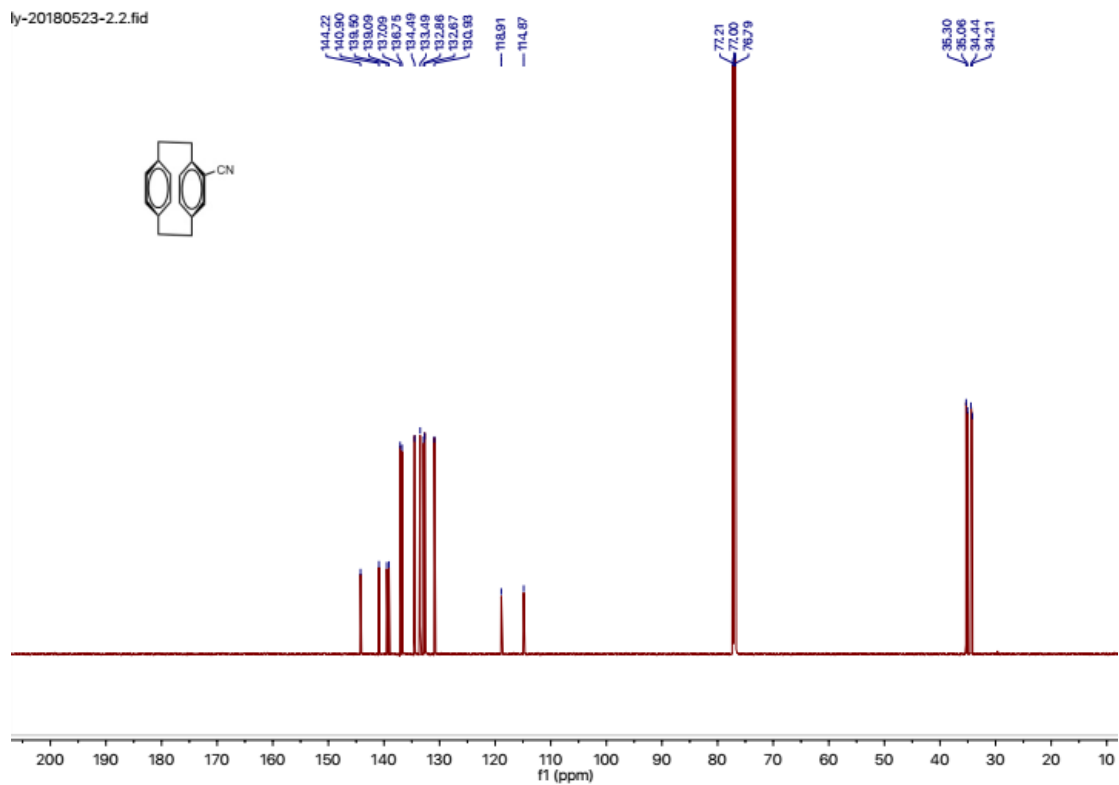


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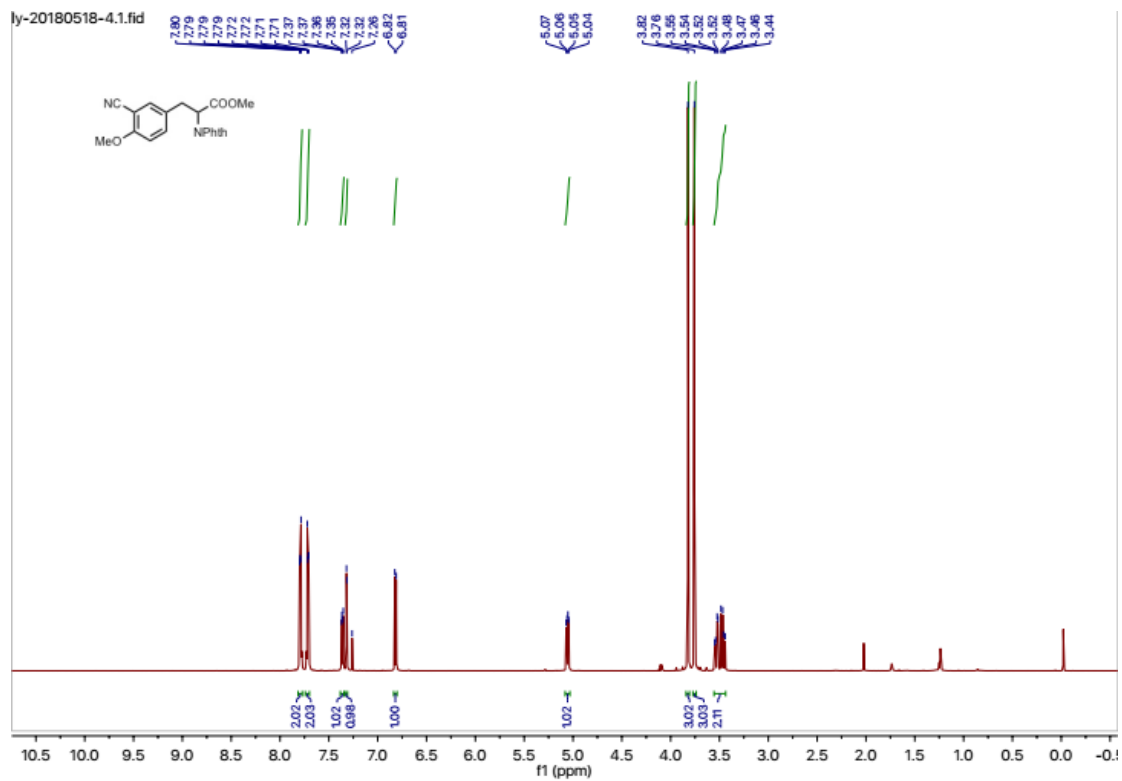


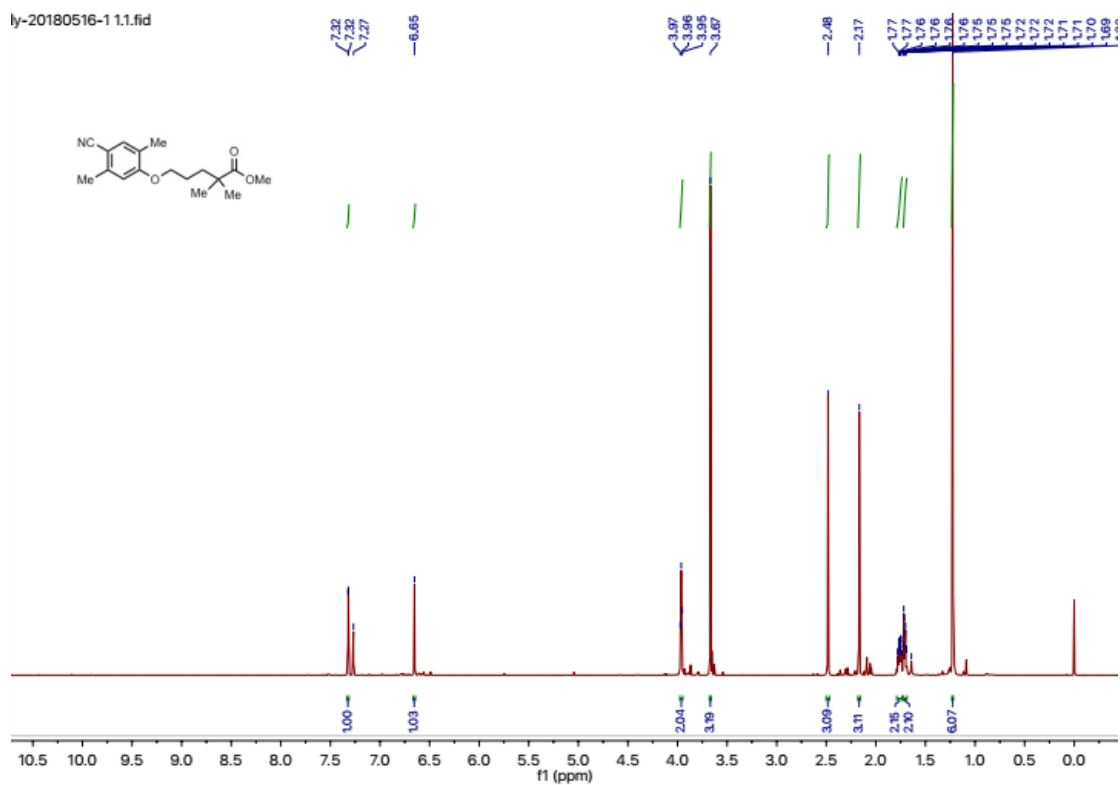
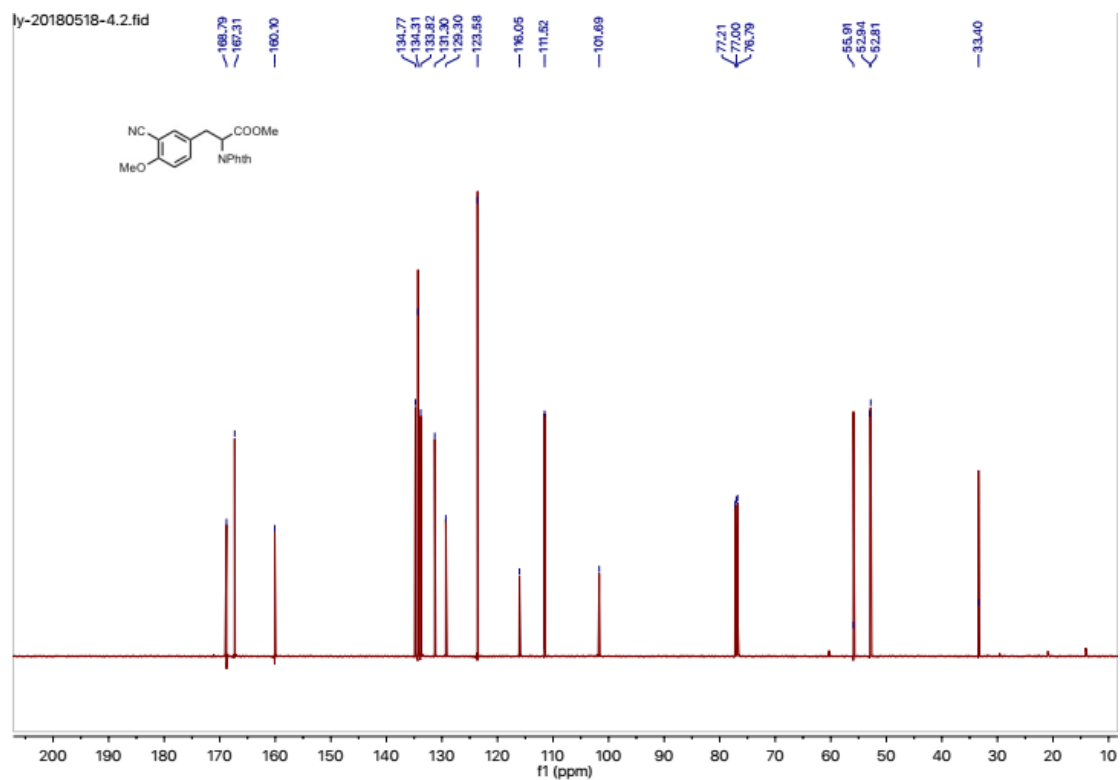


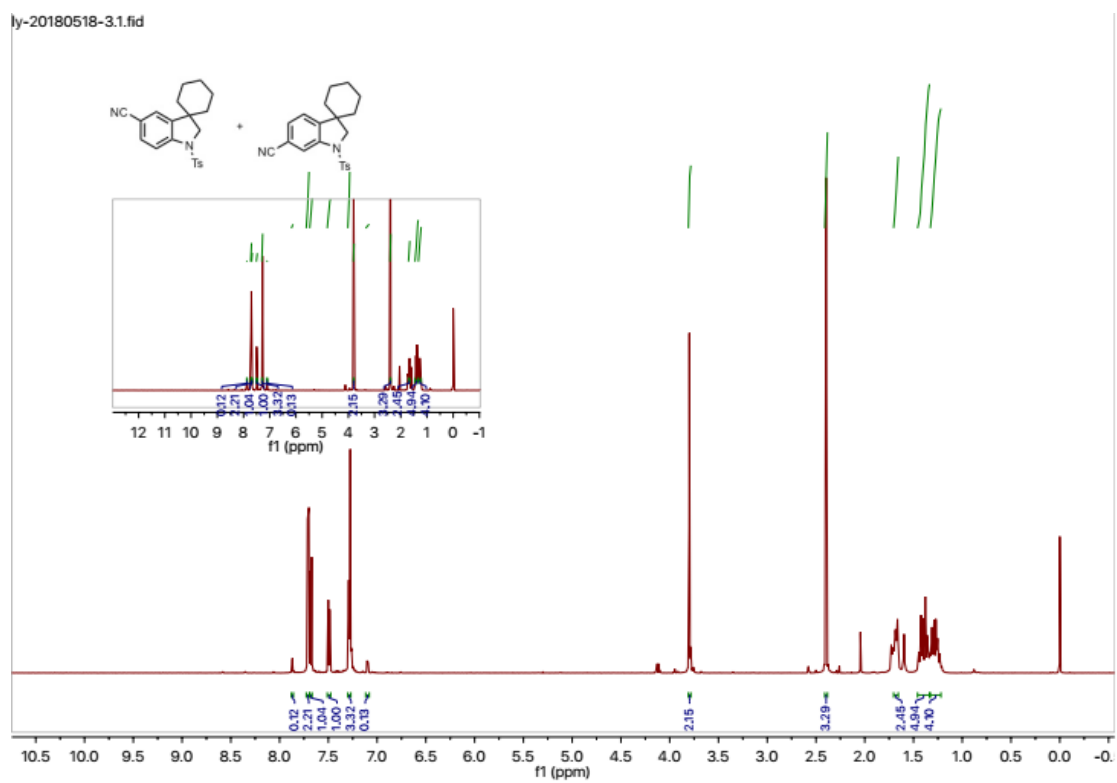
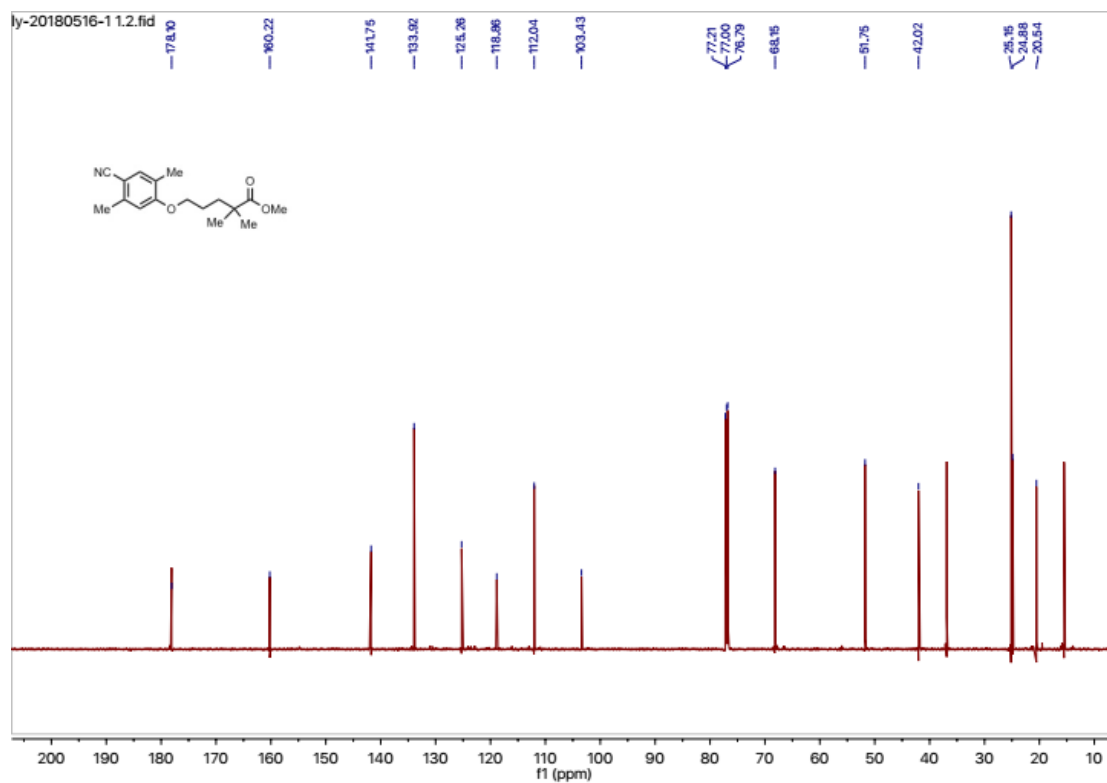
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ly-20180518-4.1.fid







ly-20180518-3.2.fid

Chemical structures of the reactants are shown above the spectrum:

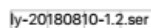
Structure 1: 1-(4-cyanophenyl)-2-(4-(tritylsilyl)phenyl)pyrrolidine

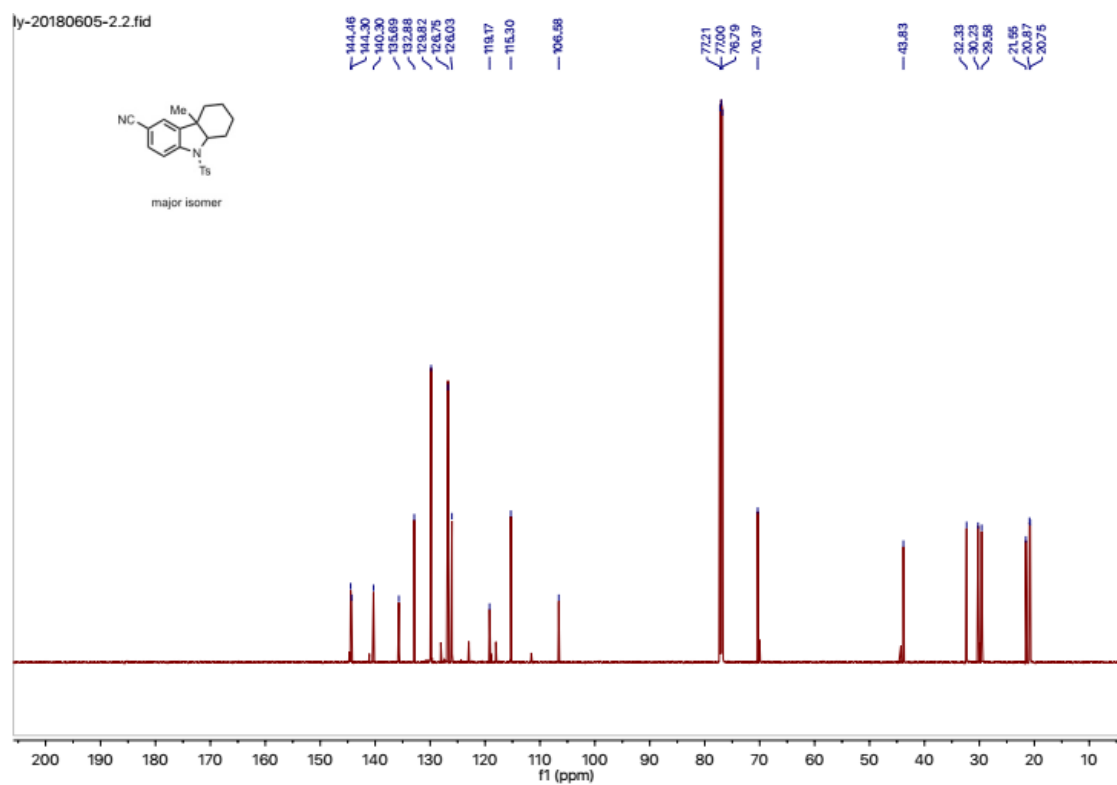
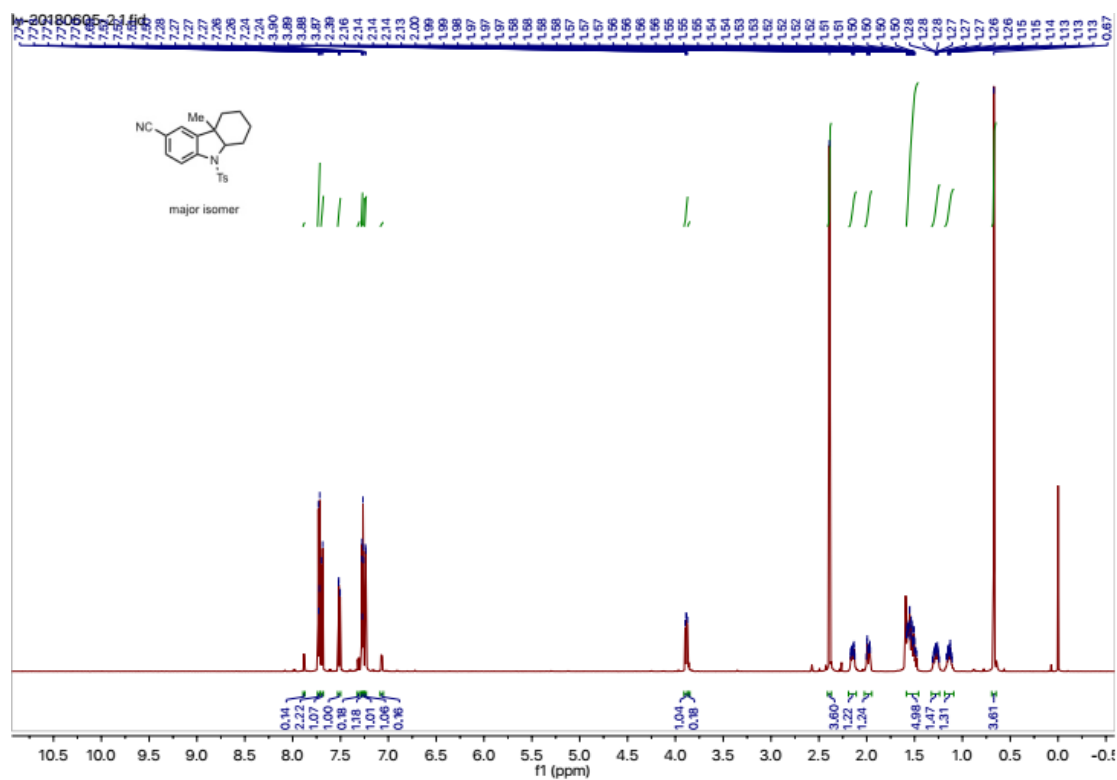
Structure 2: 1-(4-cyanophenyl)-2-(4-(tritylsilyl)phenyl)pyrrolidine

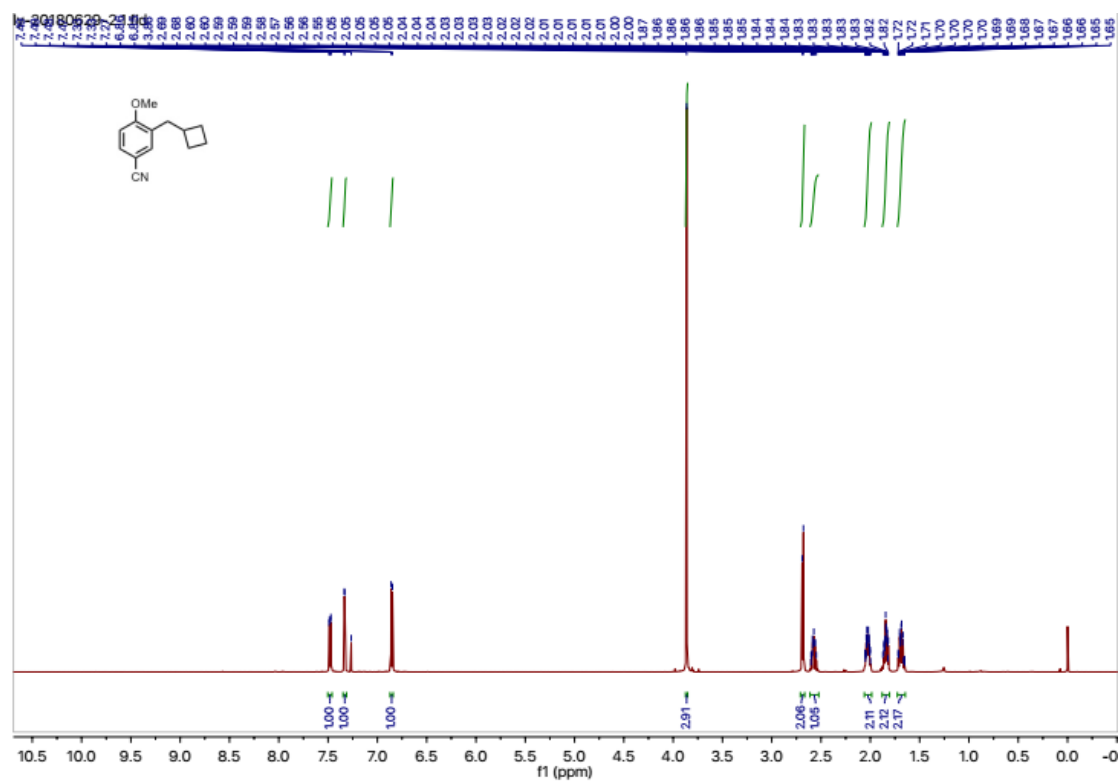
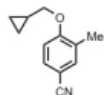
The spectrum displays chemical shifts (f1) in ppm, ranging from 200 to 10. Key peaks are labeled with their corresponding chemical shift values:

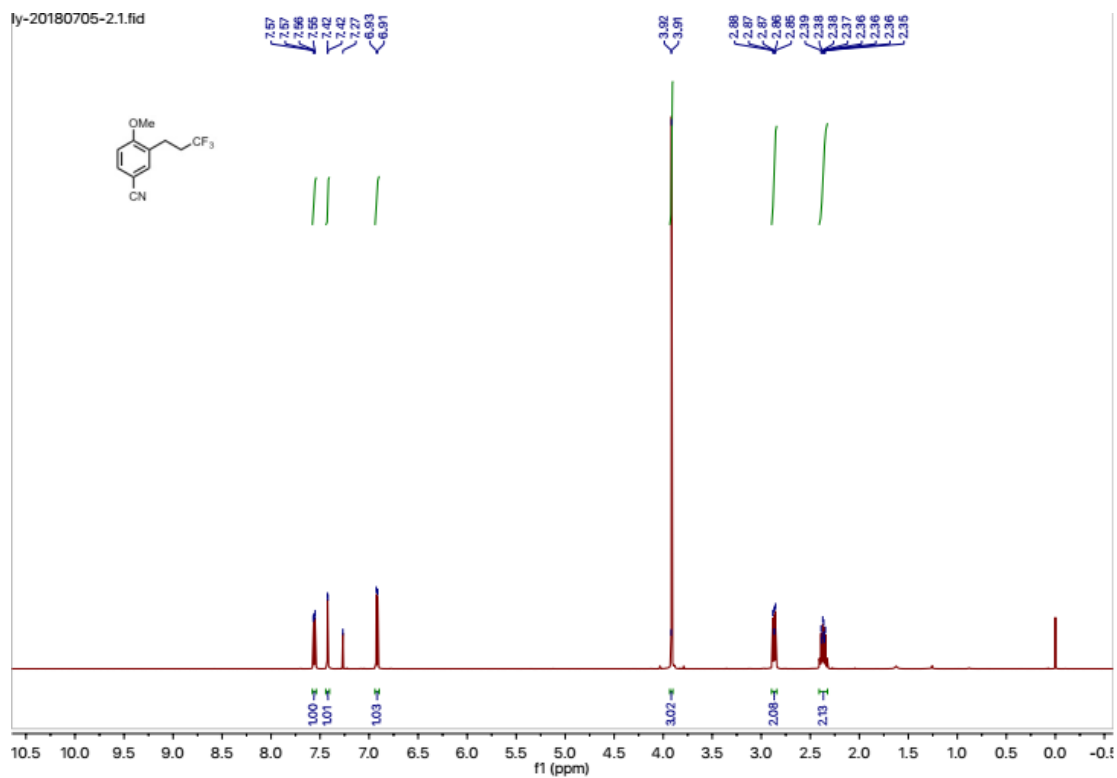
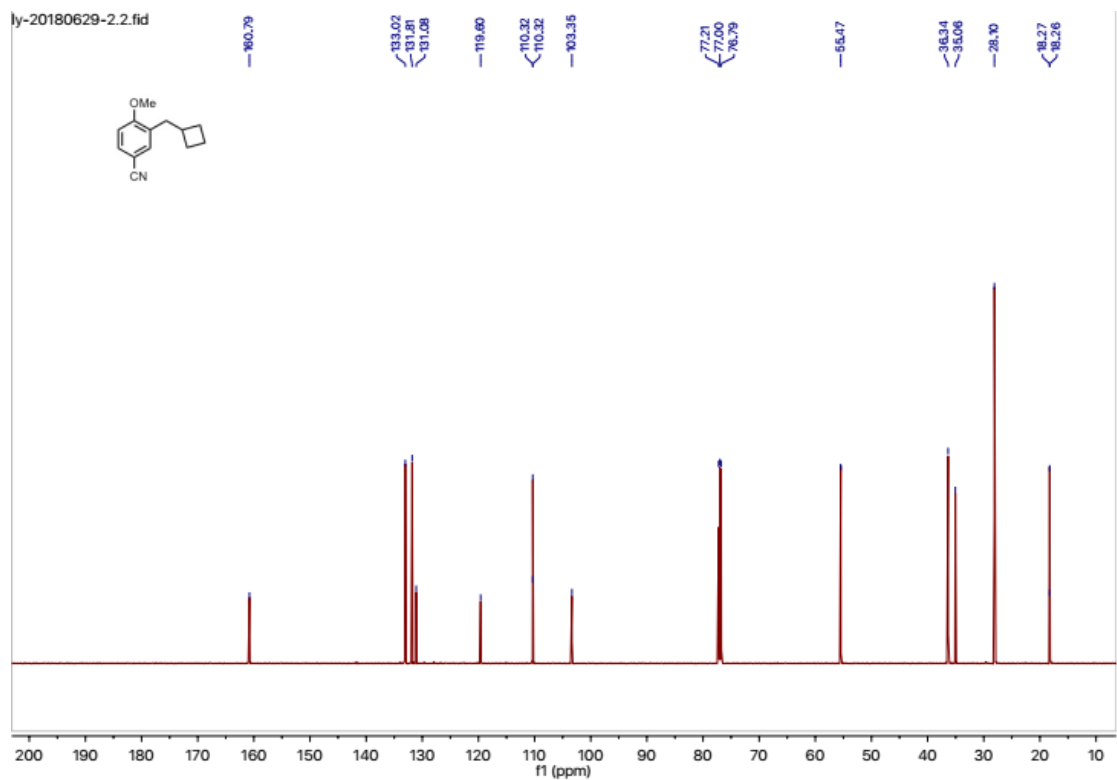
- 144.82, 144.77, 141.62
- 133.80, 132.90, 132.60, 128.66
- 119.09, 114.43, 106.48
- 77.21, 77.00, 76.79
- 59.57
- 44.39
- 36.74
- 25.01, 22.69, 21.57

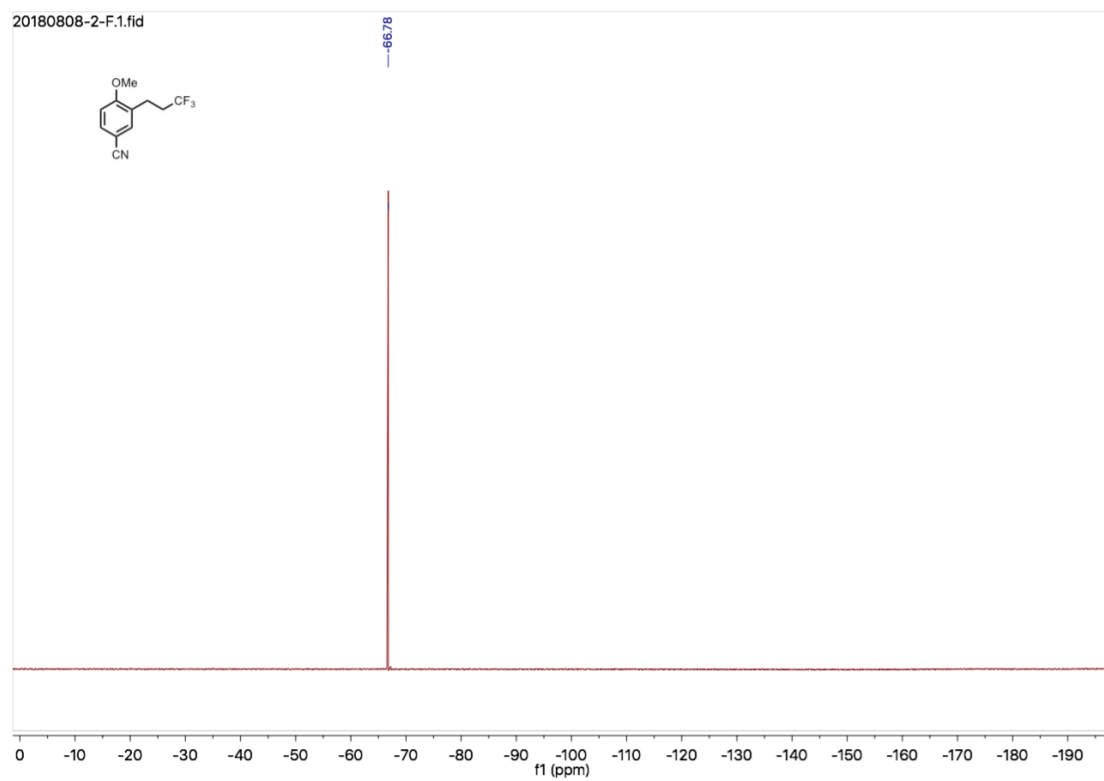
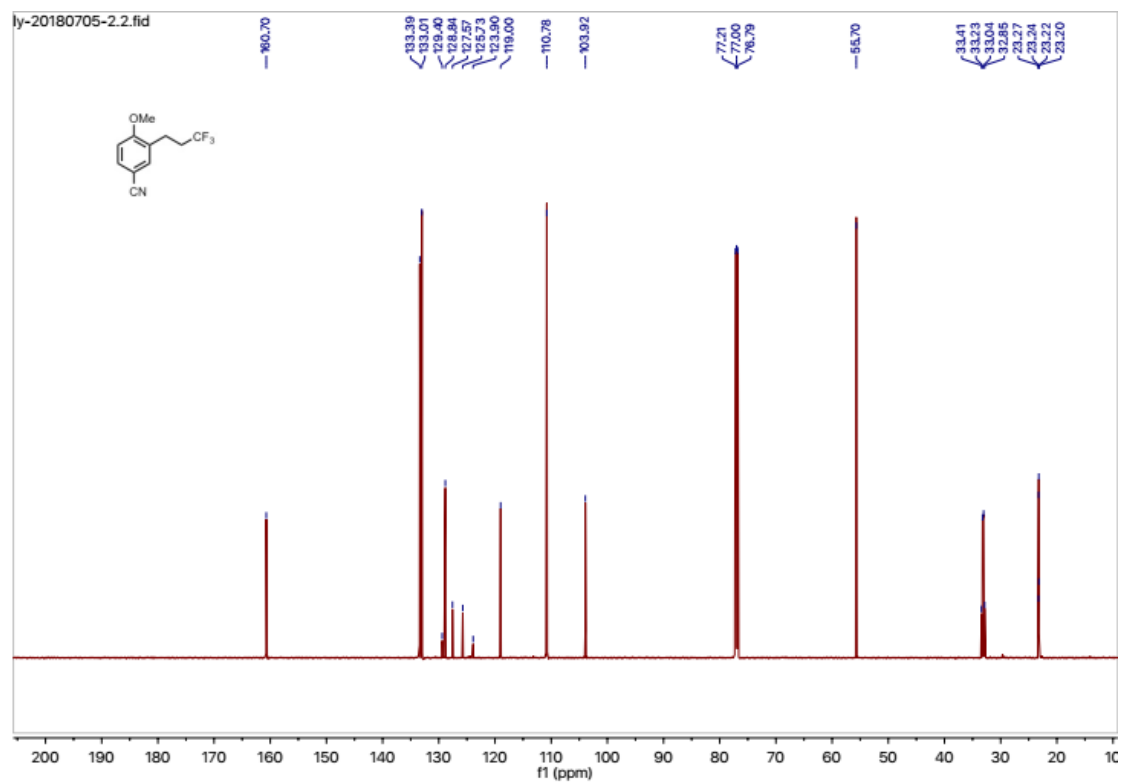
The spectrum shows a complex pattern of peaks, indicating the presence of multiple compounds. The aromatic region (10-15 ppm) contains several sharp peaks. The aliphatic region (1-5 ppm) shows a cluster of peaks, likely corresponding to the pyrrolidine and silyl groups. The solvent peak (77 ppm) is prominent.

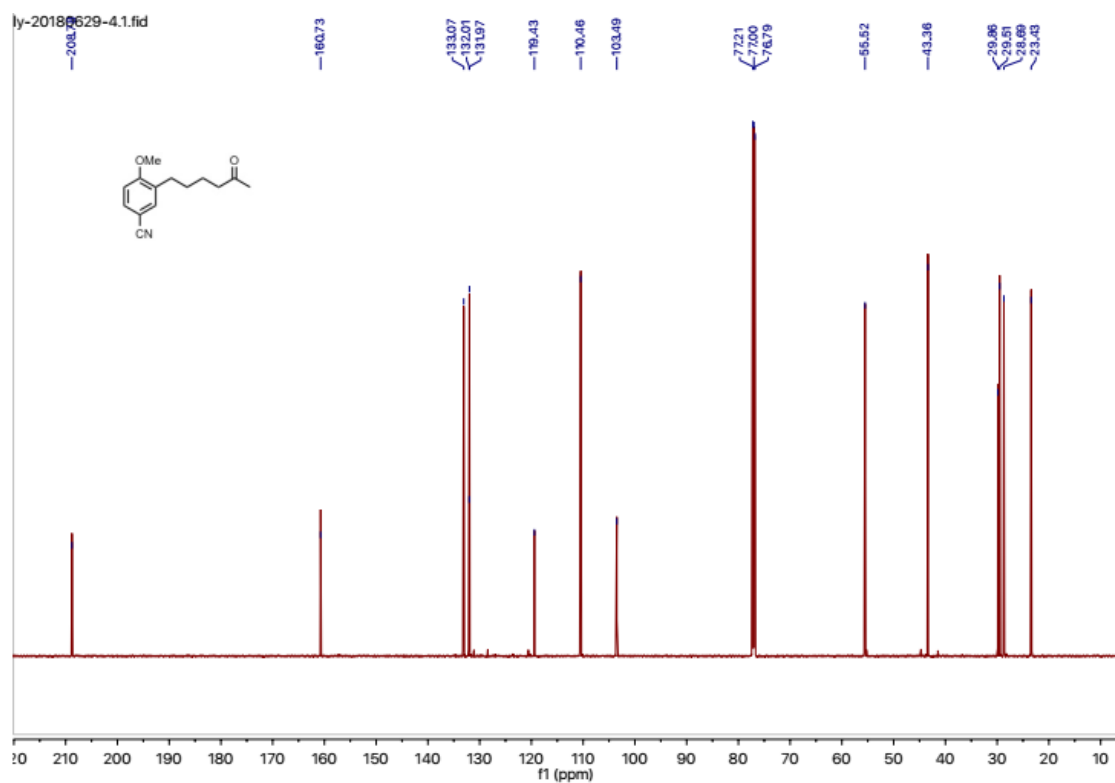
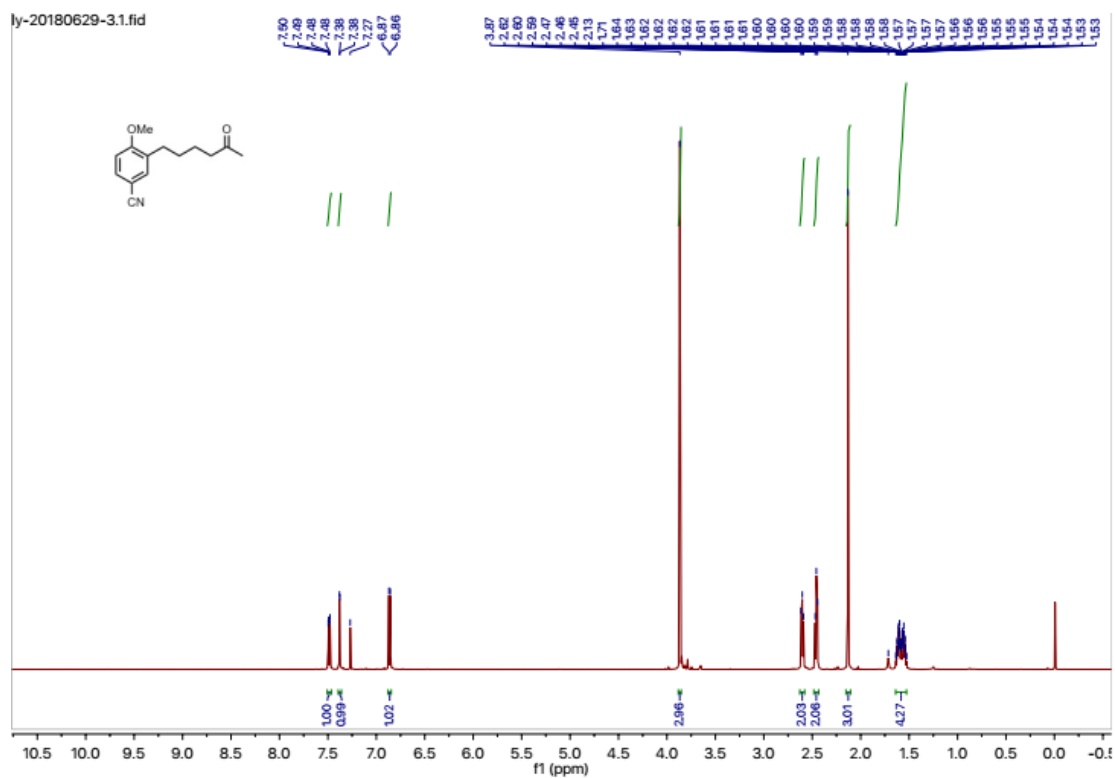


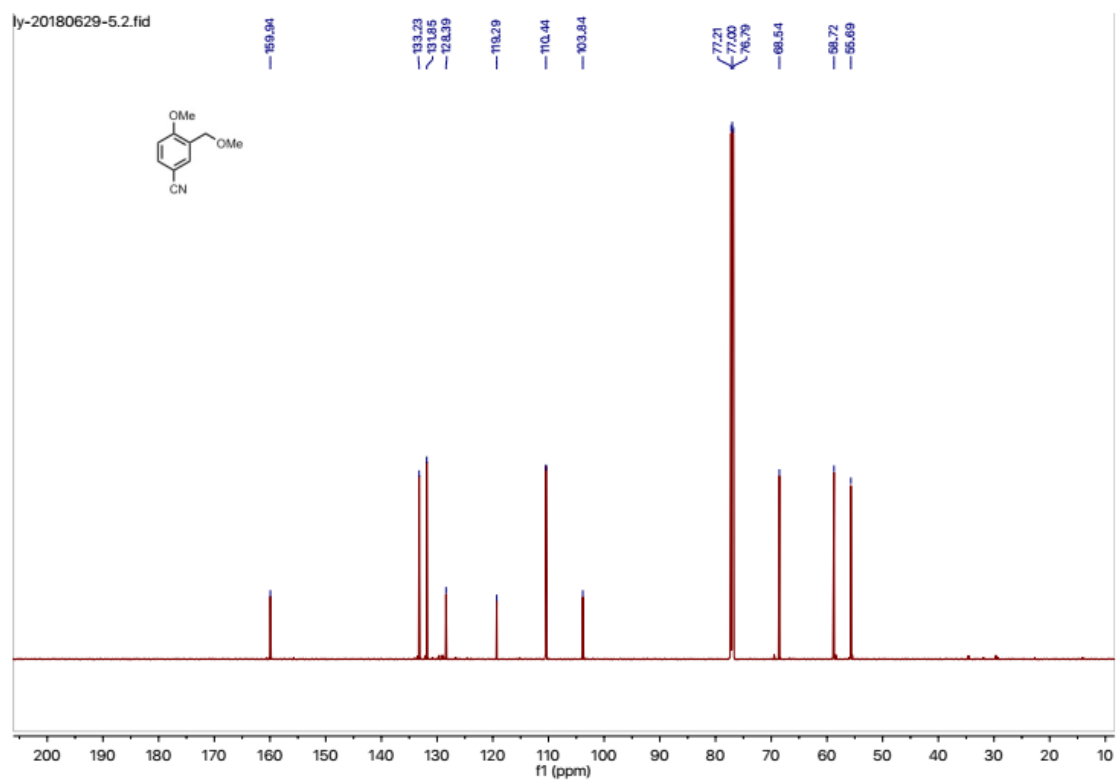
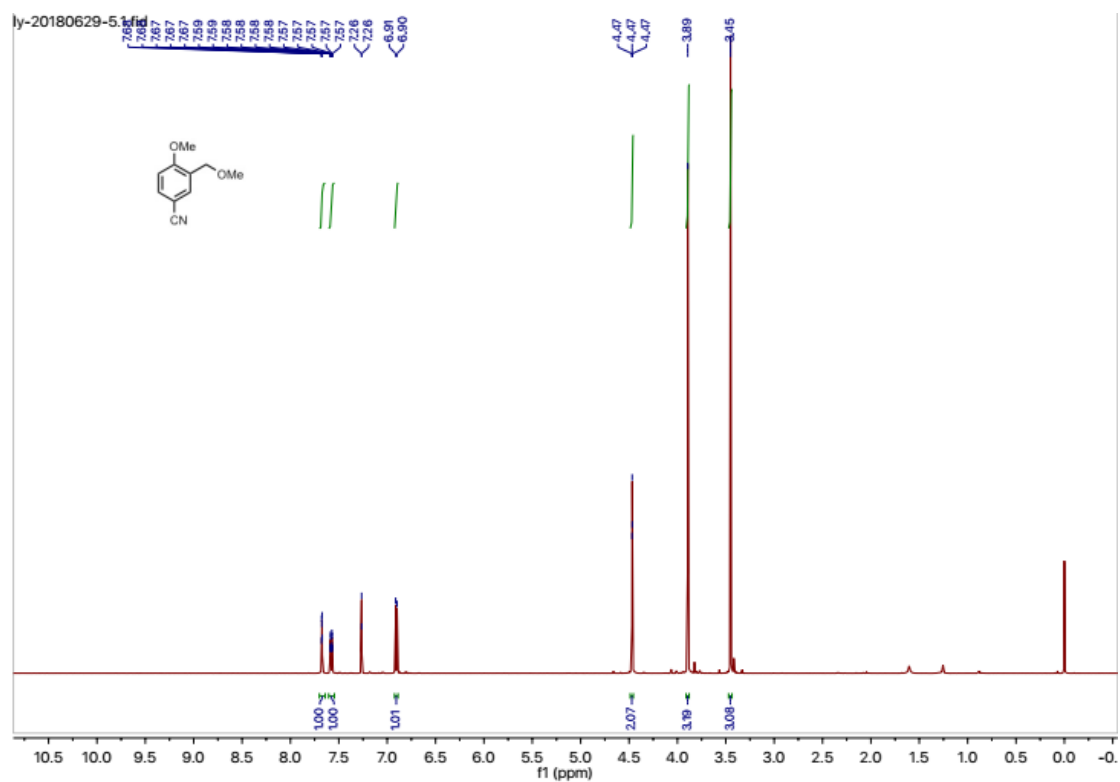












Non-directed Cyanation SI.docx (5.44 MiB)

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