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Exhaustive Reduction of Esters Enabled by Nickel Catalysis

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We report a one-step procedure to directly reduce unactivated aryl esters into their corresponding tolyl-derivatives. This is achieved by the action of a Ni/NHC catalyst and an organosilane reducing agent that is activated in situ by stoichiometric KOtBu. The resulting conditions provide a direct and efficient alternative to multi-step procedures for this transformation that often require use of hazardous metal hydrides. Applications in the synthesis of –CD3 containing products, derivatization of bioactive molecules, and chemoselective reduction in the presence of other C–O bonds is demonstrated.

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Exhaustive Reduction of Esters Enabled by Nickel Catalysis

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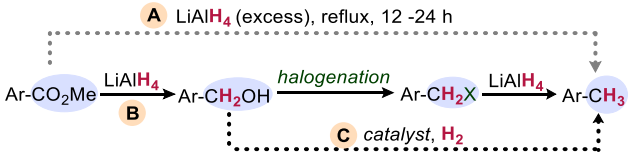
ABSTRACT: We report a one-step procedure to directly reduce unactivated aryl esters into their corresponding tolyl-derivatives. This is achieved by the action of a Ni/NHC catalyst and an organosilane reducing agent that is activated in situ by stoichiometric KO^{t}Bu. The resulting conditions provide a direct and efficient alternative to multi-step procedures for this transformation that often require use of hazardous metal hydrides. Applications in the synthesis of –CD_3 containing products, derivatization of bioactive molecules, and chemoselective reduction in the presence of other C–O bonds is demonstrated.

Introduction

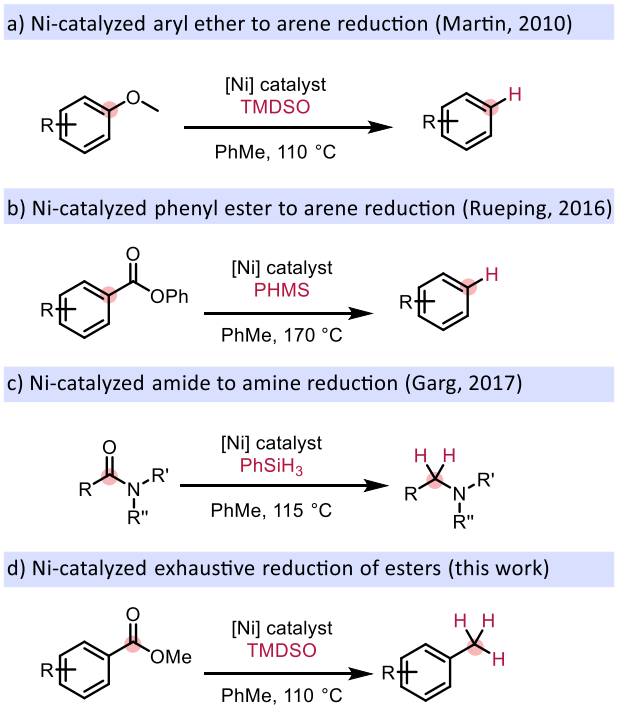
The reduction of carboxylic acids, as well as their derivatives such as esters and amides, is of fundamental importance in organic synthesis.[1] This is most commonly achieved by the action of aggressive metal hydride reducing agents, enabling the formation of the corresponding alcohol product.[2] Exhaustive reduction – that is, reduction all the way to the methyl oxidation state – is less readily achieved. Reasons why one may seek to perform this reaction include the profound effects of methyl groups on bioactivity, [3a-b] the ability to exploit the electronic effects of an ester group prior to reduction,[3c] or its ability to create deuterium-labelled tolyl derivatives.[3d-e] In rare cases, single step transformation of an ester into a methyl group can be realized,[4] for example by the use of excess lithium aluminum hydride in refluxing ethereal solvent (Scheme 1a).[5] More often, this transformation is carried out by a three-step sequence via initial reduction to the alcohol, functional group interconversion to an alkyl halide, and further reduction to the methyl product (Scheme 1b).[6] Alternatively, catalytic hydrogenolysis can be used to reduce an alcohol to the methyl oxidation state (Scheme 1c).[7]

Scheme 1. Contemporary methods to achieve the ester-to-methyl transformation



Our group and others have recently demonstrated that Ni catalysts are capable of catalytic activation of methyl esters, presumably initiated by oxidative addition into the C(acyl)–O bond.[8] In the course of these studies, we hypothesized that useful catalytic reductions of these esters may be achievable using a similar strategy. Related work from the Martin lab for reducing anisoles to arenes (Scheme 2a),[9] the Rueping lab on the reduction of phenyl esters to arenes (Scheme 2b),[10] and the Garg lab on transforming amides to amines (Scheme 2c),[11] among others,[12] served as inspiration that silane reagents could act as mild hydride donors in Ni-catalyzed reactions. With this precedent in mind, we initiated a study on the reaction of silanes with methyl esters in the presence of Ni. To our surprise, when using 1,1,3,3-tetramethyldisiloxane (TMDSO)[13] as a reducing agent in the presence of Ni(cod)$_2$, 1,3-dicyclohexylimidazolium tetrafluoroborate salt (ICy·HBF$_4$), and potassium tert-butoxide,

Scheme 2. Ni-catalyzed reductions mediated by organosilane reducing agents.

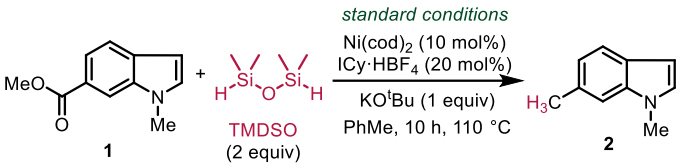


the major product was the corresponding tolyl derivative (Scheme 2d). Given the absence of general, functional group tolerant methods to achieve this transformation in a single step, we further explored this reaction and report the results herein.

The Ni-catalyzed exhaustive reduction of methyl esters to the corresponding tolyl derivative was optimized using N-Me indole **1**. Heating the substrate at 110 °C in toluene in the presence of $Ni(cod)_2$ (10 mol%), $ICy{\cdot}HBF_4$ (20 mol%), TMDSO (2 equiv), and KO^{t}Bu (1 equiv) afforded methyl-bearing indole **2** in 84% yield (Table 1, entry 1). Running the reaction in the absence of either KO^{t}Bu or siloxane resulted in no conversion (entry 2). However, removing just the $Ni(cod)_2$ led to complete consumption of **1**, with the corresponding benzyl alcohol as the only major identifiable product after working the reaction up with TBAF (entry 3). Using this alcohol as a starting material in the presence of the Ni catalyst resulted in efficient formation of **2**, suggesting that the reaction proceeds through a non-catalyzed reduction to a silylated alcohol[14] followed by catalytic reduction of this species to form the alkane (entry 4). Alternative ligands (entry 5, 6), bases (entry 7, 8) and organosilane reducing agents (entry 9, 10) were all less efficient. Despite being highly reducing conditions, Ni(II) precatalysts such as $NiCl_2$ (entry 11) or $NiBr_2{\cdot}$glyme (entry 12) gave poor yields. The addition of 0.2 equiv Mn gave a moderate improvement to 35% (entry 13), while 1 equivalent of Mn gave 78% yield (entry 14), providing a viable alternative set of conditions that can be performed without the use of a glovebox. Applying these conditions in the absence of TMDSO resulted in no formation of **2** (entry 15), indicating that TMDSO is ultimately responsible for the substrate reduction. Notably, the reaction was found to be similarly efficient when starting from the corresponding ^{t}Bu, Bn or Ph ester (entry 16).

With optimized conditions, we turned our attention towards the reaction scope (Scheme 3). Electron-neutral and rich methyl arenes **3-7** were formed from their corresponding esters in 73–86% yield. Subjecting a styrene-bearing methyl ester to the conditions led to partial reduction of the olefin; however, slightly milder conditions enabled **8** to be selectivity formed in 74% yield. Slightly milder conditions also allowed recovery of stilbene **9** in similar yields. In contrast with prior work on Ni-catalyzed hydrogenolysis of anisoles and related compounds,[9a,12c-f] no C(aryl)–O cleavage was observed when using ethereal or phenol-containing substrates (**10**–**15**). In many classical heterocycle-forming reactions, ester-containing starting materials like malonates or propiolates are used to facilitate cyclizations, thus making the ester-containing products more accessible than the corresponding methyl analogs. With this in mind, we were excited to see that many heterocycles were tolerated, including pyridines (**16**–**20**), morpholines (**21, 22**), piperidines (**23, 24**), indoles (**25-29**), carbazoles (**30**–**32**), an indazole (**33**), quinoline (**34**), benzofuran (**35**), and dibenzofuran (**36**). Derivatization of commercial pharmaceuticals bifendatatum and probenecid successfully formed reduction products **37** and **38**, respectively. Lastly, reduction of a lactone proceeded smoothly to form alcohol-bearing tolyl-derivative **39** upon quenching with TBAF.

Table 1. Optimization of ester reduction reaction[a]



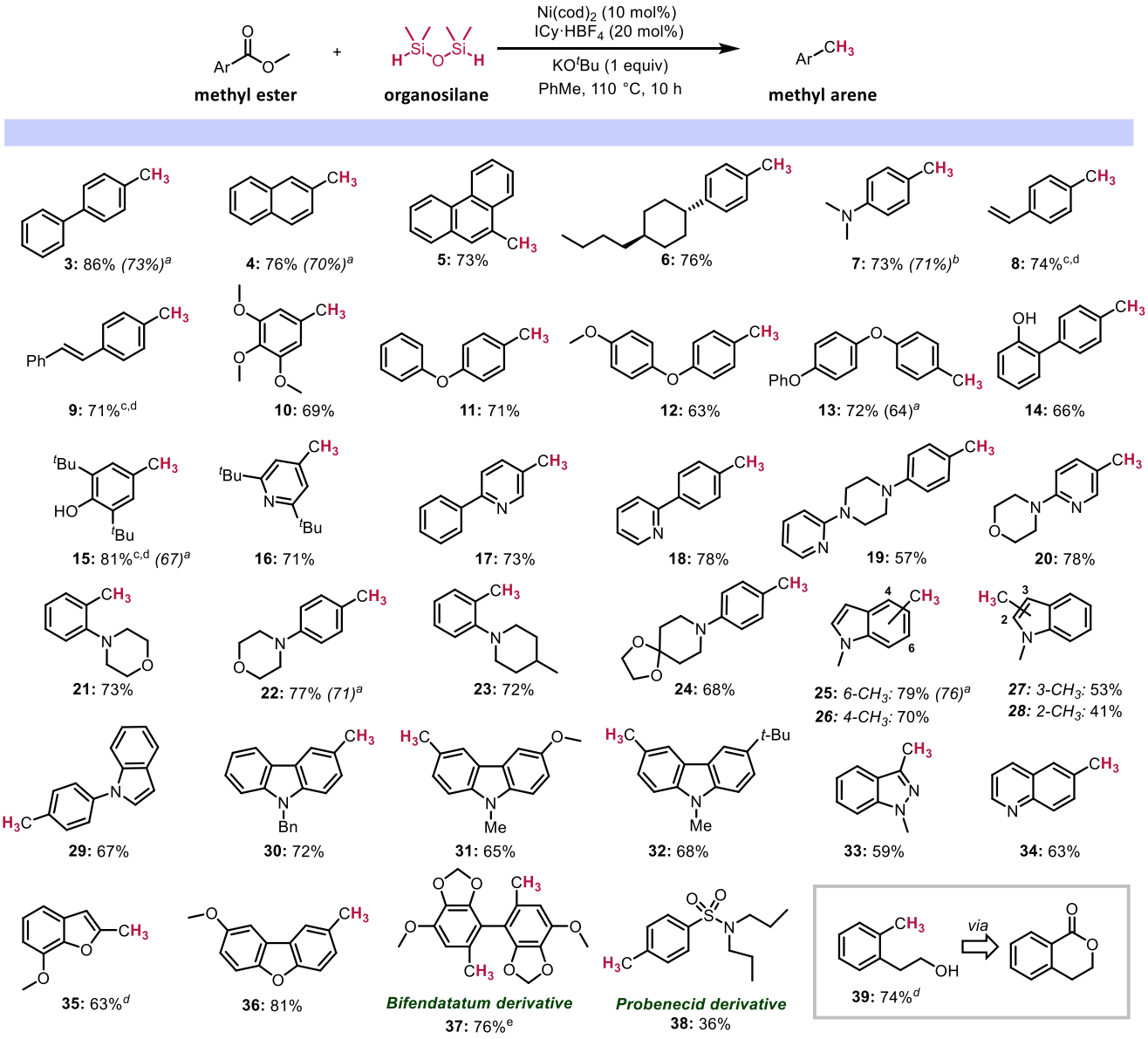
Entry	Deviation from standard reaction conditions	% Yield
1	None	84
2	No base or no siloxane	0
3	No nickel	0[b]
4	Alcohol as starting material *instead of ester*	73
5	IPr·HCl *instead of* $ICy{\cdot}HBF_4$	70
6	Xantphos *instead of* $ICy{\cdot}HBF_4$	35
7	KOH *instead of* KO^{t}Bu	12
8	KOEt *instead of* KO^{t}Bu	51
9	Et_3SiH (4.0 equiv)	42
10	$(EtO)_3SiH$ (4.0 equiv)	20
11	$NiCl_2$ *instead of* $Ni(cod)_2$	4
12	$NiBr_2{\cdot}$glyme *instead of* $Ni(cod)_2$	7
13	$NiBr_2{\cdot}$glyme + Mn (0.2 equiv)	35
14	$NiBr_2{\cdot}$glyme + Mn (1.0 equiv)	78
15	$NiBr_2{\cdot}$glyme + Mn (1.0 equiv), *no TMDSO*	0
16	-^{t}Bu, -Bn, or -Ph ester *instead of -Me ester*	73-77

[a]Reactions ran on a 0.20 mmol scale. Yields determined by NMR using 1,3,5-trimethoxybenzene as internal standard. [b] Alcohol (1-methyl-1*H*-indol-6-yl)methanol observed as major product after work-up with TBAF.

Alkyl-substituted esters, carbon–halogen containing substrates, free N–H bonds, and several other functional groups were unfortunately not tolerated (Scheme S3, Supporting Information). Glovebox-free conditions using $NiBr_2{\cdot}$glyme were also studied with a range of substrates – these conditions were observed to give synthetically viable yields, albeit with slightly lower efficiency than when using $Ni(cod)_2$. Lastly, a gram scale reaction was performed in a round-bottom flask, providing **7** in 71% yield.

Given the importance of deuterated molecules in the study of reaction mechanisms, pharmaceuticals, and as tools for understanding metabolic pathways,[15] we next explored the potential of our exhaustive reduction to synthetically introduce $-CD_3$ groups. While the development of methods to perform this transformation is of contemporary interest,[16] this is commonly achieved by using $LiAlD_4$ or $LiEt_3BD$ as a reducing agent in the three-step procedure described in Scheme 1.[6f-k] For instance, Salvadori and co-workers used a three-step, three-day procedure to synthesize CD_3-containing 2,5-dimethoxy-d_3-toluene (**40**) towards the preparation of d_3-δ-tocopherol.[17] Reduction of the corresponding ester to alcohol with $LiAlD_4$, halogenation with PBr_3, and a second $LiAlD_4$ reduction afforded product in an overall yield of 69%. Using d_2-TMDSO[18] alongside $Ni(cod)_2$ gave incomplete deuterium incorporation. In contrast, the

Scheme 3. Scope of substrates tolerated in the methyl ester reduction



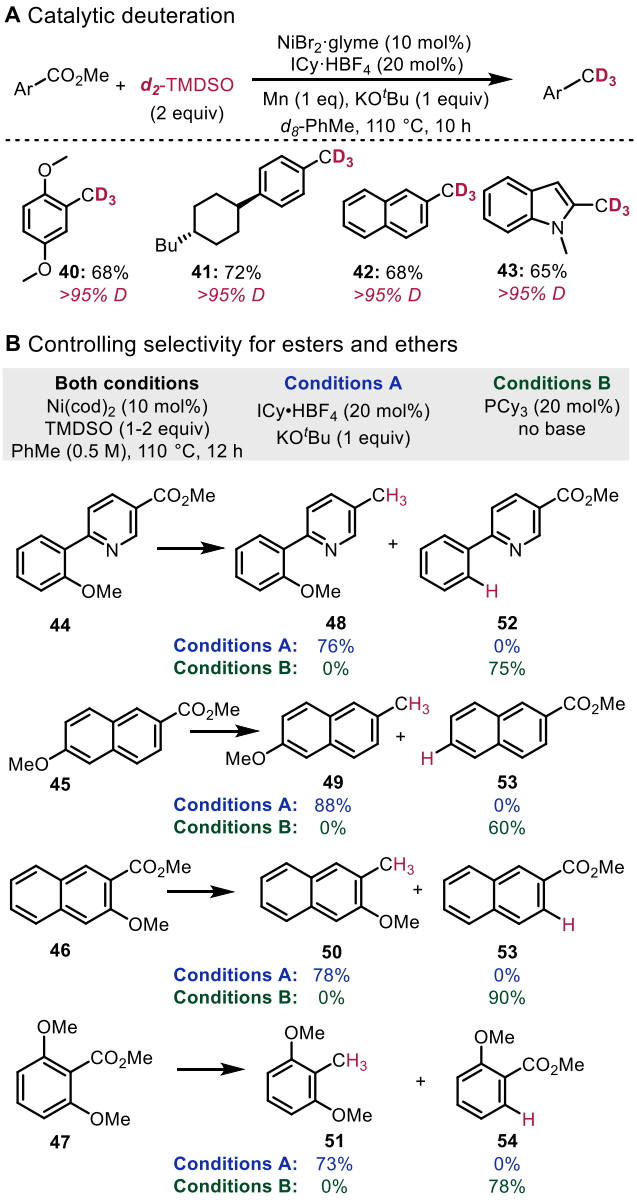
General reaction conditions: ester (0.20 mmol), TMDSO (0.40 mmol), KO^{t}Bu (0.20 mmol), ICy·HBF_4 (20 mol%), $Ni(cod)_2$ (0.02 mmol) in toluene (0.8 mL), 110 °C for 10 h. [*a*] $NiBr_2$·glyme (0.02 mmol) and Mn (0.20 mmol) used instead of $Ni(cod)_2$; reactions setup without use of a glovebox. [*b*] Reaction performed on 5.58 mmol (1 g) of starting material. [*c*] TMDSO (0.30 mmol). [*d*] 90 °C for 6 h. [*e*] TMDSO (0.80 mmol), KO^{t}Bu (0.40 mmol).

use of $NiBr_2$·glyme/TMDSO/Mn in toluene-d_8 resulted in an efficient 73% yield with >95%D incorporation(Scheme 4a). This procedure was found to be general, enabling the synthesis of several –CD_3-containing molecules in good yield and high deuterium incorporation (**41-43**). Experiments in non-deuterated toluene gave ~5-10% reduced deuterium incorporation.

We were intrigued by the similarity between our conditions to reduce methyl esters and those which Martin and coworkers used to reduce anisole derivatives.[9a] Notably, these methods differ primarily in the choice of ligand and the presence of base. To directly probe the selectivity, esters **44-47** were subjected to both sets of reaction conditions (Scheme 4b). Using a Ni/ICy catalyst in the presence of KO^{t}Bu resulted in chemoselective formation of the ester reduction products **48-51** in 54–82% yield Using base-free conditions with a Ni/PCy_3 catalyst resulted in a complete switch, cleaving of the ethereal bond while leaving the methyl ester untouched in products **52**–**54**. The Ni/PCy_3 system has been proposed to act via a Ni(I)– SiR_3 active cata-

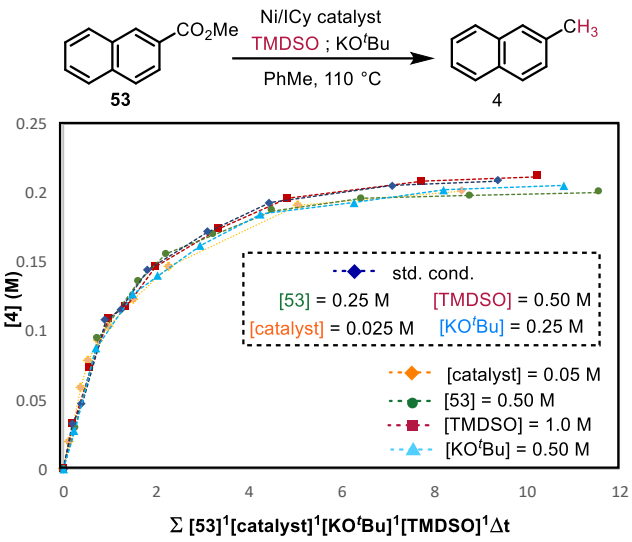
lyst;[9b] the contrasting chemoselectivity in our system suggests that both a different active catalyst and different mechanistic pathway are operative.

Scheme 4. Applications of exhaustive reduction of esters



To gain further mechanistic information, the method of variable time normalization analysis was applied to the reduction of methyl naphthoate **53** (Scheme 5).[19] Positive apparent first order kinetics were observed for all studied species – the Ni catalyst, substrate, siloxane, and base. While the exact nature of reducing agent is not clear, the rate dependency on the base and literature precedent both support a hypervalent O^{t}Bu-siloxane species being involved in the key hydrogen transfer.[20] We tentatively propose that this hypervalent siloxane reduces the ester into a silylated alcohol, which reacts with a Ni(0) catalyst by oxidative addition to form a benzylic Ni(II) intermediate that is reduced in a rate-determining hydride transfer.

Scheme 5. Apparent rate law determination by variable time normalization kinetic analysis



In summary, we have developed a new method to convert methyl esters into the corresponding tolyl derivative. In contrast to established multi-step sequences for this transformation, the reaction takes place under a single set of conditions, comprised of a rapid, non-catalyzed siloxane-mediated reduction to a silylated alcohol followed by subsequent Ni-catalyzed reduction to the corresponding $-CH_3$ group. We believe this reaction will be particularly useful in the synthesis of methyl-bearing heterocycles, where the corresponding esters are more readily abundant, as well as in reductive deuteration as a method to install $-CD_3$ groups. This transformation sharply contrasts previous reports of Ni-catalyzed reductions with siloxanes of, e.g., amides, ethers, and phenyl esters. The inclusion of a KO^{t}Bu is proposed to be a key feature, which generates a more aggressive siloxane reducing agent in situ.

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Author Contributions

The manuscript was written through contributions of all authors.

Supporting Information

Information regarding experimental procedures, optimization tables, troubleshooting, characterization of organic molecules, mechanistic studies is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) (a) Pritchard, J.; Filonenko, G. A.; van Putten, R.; Hensen, E. J.; Pidko, E. A. Heterogeneous and Homogeneous Catalysis for the Hydrogenation of Carboxylic Acid Derivatives: History, Advances and Future Directions. *Chem. Soc. Rev*. **2015**, *44*, 3808–3833. (b) Magano, J.; Dunetz, J. R. Large-Scale Carbonyl Reductions in the Pharmaceutical Industry. *Org. Process Res. Dev*. **2012**, *16*, 1156–1184. (c) Addis, D.; Das, S.; Junge, K.; Beller, M. Selective Reduction of Carboxylic Acid Derivatives by Catalytic Hydrosilylation. *Angew. Chem. Int. Ed.* **2011**, *50*, 6004–6011.

(2) (a) Berk, S. C.; Kreutzer, K. A.; Buchwald, S. L. A Catalytic Method for the Reduction of Esters to Alcohols. *J. Am. Chem. Soc.* **1991**, *113*, 5093–5095. (b) Turek, D.; Trimm, D.; Cant, N.W. The Catalytic Hydrogenolysis of Esters to Alcohols. *Catal. Rev. - Sci. Eng.* **1994**, *36*, 645–683. (c) Krishnamurthy, S.; Brown, H. C. Forty Years of Hydride Reductions. *Tetrahedron*. **1979**, *35*, 567–607. (d) Zheng, J., Darcel, C., Sortais, J.P. A Convenient Nickel-catalyzed Hydrosilylation of Carbonyl Derivatives. *Catal. Sci. Technol.* **2012**, *3*, 81–84.

(3) (a) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M. The Methylation Effect in Medicinal Chemistry. *Chem. Rev*. **2011**, *111*, 5215–5246. (b) Schönherr, H.; Cernak, T. Profound Methyl Effects in Drug Discovery and a Call for New C–H Methylation Reactions. *Angew. Chem. Int. Ed*. **2013**, *52*, 12256–12267. (c) Shnurch, M. et al. A Comprehensive Overview of Directing Groups Applied in Metal-catalyzed C-H Functionalization Chemistry. *Chem. Soc. Rev.* **2018**, *47,* 6603–6743. (d) Pirali, T.; Serafini, M.; Cargnin, S.; Genazzani, A.A. Applications of Deuterium in Medicinal Chemistry. *J. Med. Chem.* **2019**, *62,* 5276–5297 (e) Liu, J.F. et al. Chapter Fourteen – A Decade of Deuteration in Medicinal Chemistry. *Annu. Rep. Med. Chem.* **2017**, *50,* 519–542.

(4) (a) Yamamoto, Y.; Bajracharya, G. B.; Nogami, T.; Jin, T.; Matsuda, K.; Gevorgyan, V. Reduction of Carbonyl Function to a Methyl Group. *Synthesis.* **2004**, *2*, 308–311 (b) Yamamoto, Y.; Liu, J.; Rubin, M.; Gevorgyan, V. A Direct Reduction of Aliphatic Aldehyde, Acyl choride and Carboxylic Functions into a Methyl Group. *J. Org. Chem.* **2001**, *66*, 1672–1675. (c) Okita, T.; Muto, K.; Yamaguchi, J. Decarbonylative Methylation of Aromatic Esters by a Nickel Catalyst. *Org. Lett*. **2018**, *20*, 3132–3135.

(5) (a) Zhang, J.; Kohlbouni, S. T.; Borhan, B. Cu-Catalyzed Oxidation of C_2 and C_3 Alkyl-Substituted Indole via Acyl Nitroso Reagents. *Org. Lett.* **2019**, *21*, 14–17. (b) Zhang, Z.; Ji, C. L.; Yang, C.; Chen, J.; Hong, X.; Xia, J. B. Nickel Catalyzed Kumada Coupling of boc-Activated Aromatic Amines via Nondirected Selective Aryl C-N bond Cleavage. *Org. Lett.* **2019**, *21*, 1226–1231. (c) Borger, C.; Knolker, H. J. A General Approach to 1,6-Dioxygenated Carbazole Alkaloids – First Total Synthesis of Clausine G, Clausine I and Clausine Z. *Synlett*. **2008**, *11*, 1698–1702. (d) Conover, L.H.; Tarbell, D.S. Hydrogenolysis of Certain Substituted Aromatic Acids and Carbonyl Compounds by Lithium Aluminum Hydride. *J. Am. Chem. Soc.* **1950**, *72*, 3586-3588.

(6) (a) Fuchs, B.; Zizuashvili, J.; Abramson, S. Geometrically Biased Homoconjugated Ketones. Synthetic Avenues to 1-acyl-2,4-cyclohexadienes. *J. Org. Chem.* **1982,** *47*, 3474–3477. (b) Beckwith, A.; Gerba, S. The Stereochemistry of Ring Closure of Some Monosubstituted o-(but-3-enyl)phenyl Radicals. *J. Aus. Chem.* **1992**, *45*, 289–308. (c) Kanomata, N.; Sakaguchi, R.; Sekine, K.; Yamashita, S.; Tanaka, H. Enantioselective Cyclopropanation Reactions with Planar-Chiral Pyridinium Ylides: a Substituent Effect and a Remote Steric Effect. *Adv. Synth. & Cat.* **2010,** *352*, 2966–2978. (d) Robaa, D.; Enzensperger, C.; Abulazm, S. E.; M. Hefnawy, M.; I. El-Subbagh, H.; A. Wani, T.; Lehmann, J. Chiral Indole [3,2-f][3]benzecine-type Dopamine Receptor Antagonists: Synthesis and Activity of Racemic and Enantiopure Derivatives. *J. Med. Chem.* **2011,** *54*, 7422–7426. (e) Crockett, Marc, et al. Preparation of Phenolics from Biomass. Nederlandse Organisatie voor Toegepast-Natuurwetenschappeljik Onderzoek TNO, Neth. *WO 2016114668*. 21 July **2016**. (f) Pollack, S.K.; Raine, B.C.; Hehre, W.J. Determination of the Heats of Formation of the Isomeric Xylylenes by Ion Cyclotron Double-Resonance Spectroscopy. *J. Am. Chem. Soc.* **1981,** *103,* 6308–6313. (g) Holland, H.L.; Brown, F.M.; Conn, M. Side Chain Hydroxylation of Aromatic Compounds by Fungi. Influence of the para Substituent on Kinetic Isotope Effects During Benzylic Hydroxylation by Mortierella isabelline. *J. Chem. Soc. Perkin Trans. 2* **1990**, *10*, 1651–1655. (h) Hanzlik, R. P.; Schaefer, A. R.; Moon, J. B.; Judson, C. M. Primary and Secondary Kinetic Deuterium Isotope Effects and Transition-state Structures for Benzylic Chlorination and Bromination of Toluene. *J. Am. Chem. Soc.* **1987**, *109*, 4926–4930. (i) Koshiyama, T.; Hirai, K.; Tomioka, H. Generation, Reactions, and Kinetics of Di(naphthyl)carbenes: Effects of the Methyl Group. *The Journal of Physical Chemistry A.* **2002**, *106*, 10261–10274. (j) Hayama, T.; Baldridge, K. K.; Wu, Y.-T.; Linden, A.; Siegel, J. S. Steric Isotope Effects Gauged by the Bowl-Inversion Barrier in Selectively Deuterated Pentaarylcorannulenes. *J. Am. Chem. Soc*. **2008**, *130*, 1583–1591. (k) Courchay, F. C.; Sworen, J. C.; Ghiviriga, I.; Abboud, K. A.; Wagener, K. B. Understanding Structural Isomerization During Ruthenium-Catalyzed Olefin Metathesis: A Deuterium Labelling Study. *Organometallics*. **2006**, *25*, 6074–6086.

(7) (a) Barfield, M.; Collins, M. J.; Gready, J. E.; Sternhell, S.; Tansey, C. W. Bond-order Dependence o Orthobenzylic Coupling Constants Involving a Methyl Group. *J. Am. Chem. Soc.* **1989**, *111,* 4285–4290. (b) Maj, A. M.; Suisse, I.; Hardouin, C.; Agbossou-Niedercorn, F. Synthesis of New Chiral 2-functionalized-1,2,3,4-tetrahydroquinoline Derivatives via Asymmetric Hydrogenation of Substituted Quinolines. *Tetrahedron* **2013**, *69,* 9322–9328. (c) Sorella, G. L.; Sperni, L.; Canton, P.; Coletti, L.; Fabris, F.; Strukul, G.; Scarso, A. Selective Hydrogenations and Dechlorinations in Water Mediated by Anionic Surfactant-Stabilized Pd Nanoparticles. *J. Org. Chem.* **2018,** *83*, 7438–7446. (d) Shiraishi, Y.; Fujiwara, K.; Sugano, Y.; Ichikawa, S.; Hirai, T. N-Monoalkylation of Amines with Alcohols by Tandem Photocatalytic and Catalytic Reactions on TiO_2 Loaded with Pd Nanoparticles. *ACS Catal.* **2013,** *3,* 312–320. (e) He, J.; Zhao, C.; Lercher, J. A. Ni-Catalyzed Cleavage of Aryl Ethers in the Aqueous Phase. *J. Am. Chem. Soc.* **2012,** *134,* 20768–20775. (f) Covert, L. W.; Connor, R.; Adkins, H. Use of Nickel as a Catalyst for Hydrogenation. *J. Am. Chem. Soc.* **1932,** *54,* 1651–1663. (g) Baltzly, R.; Buck, J. S. Catalytic Debenzylation. The Effect of Substitution on the Strength of the O-Benzyl and N-Benzyl Linkages. *J. Am. Chem. Soc.* **1943,** *65,* 1984–1992.

(8) (a) Ben Halima, T.; Masson-Makdissi, J.; Newman, S. G. Nickel Catalyzed Amide Bond Formation from Methyl Esters. *Angew. Chemie. Int. Ed.* **2018**, *57,* 12925–12929. (b) Zheng, Y.-L.; Newman, S. G. Methyl esters as cross-coupling electrophiles: Direct Synthesis of Amide Bonds. *ACS Catal.* **2019**, *9*, 4426–4433. (c) Hie, L.; Fine Nathel, N. F.; Hong, X.; Yang, Y.-F.; Houk, K. N.; Garg, N. K. Nickel-Catalyzed Activation of Acyl C–O Bonds of Methyl Esters. *Angew. Chemie. Int. Ed*. **2016**, *55*, 2810–2814. (d) Yue, H.; Zhu, C.; Rueping, M. Catalytic Ester to Stannane Functional Group Interconversion via Decarbonylative Cross-Coupling of Methyl Esters. *Org. Lett.*

2018, *20*, 385–388. (e) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A. M.; Garg, N. K.; Percec, V. Nickel-Catalyzed Cross-Couplings Involving Carbon–Oxygen Bonds. *Chem. Rev.* **2011**, *111*, 1346–1416. (f) Walker, J. A., Jr; Vickerman, K. L.; Humke, J. N.; Stanley, L. M. Ni-Catalyzed Alkene Carboacylation via Amide C–N Bond Activation. *J. Am. Chem. Soc.* **2017**, *139*, 10228–10231.

(9) (a) Alvarez-Bercedo, P.; Martin, R. Ni-Catalyzed Reduction of Inert-C–O Bonds: A New Strategy for Using Aryl Ethers as Easily Removable Directing Groups. *J. Am. Chem. Soc.* **2010**, *132*, 17352–17353. (b) Cornella, J.; Gómez-Bengoa, E.; Martin, R. Combined Experimental and Theoretical Study on the Reductive Cleavage of Inert C–O Bonds with Silanes: Ruling out a Classical Ni(0)/Ni(II) Catalytic Couple and Evidence for Ni(I) Intermediates. *J. Am. Chem. Soc.* **2013**, *135,* 1997–2009.

(10) Yue, H.; Guo, L.; Lee, S.-C.; Liu, X.; Rueping, M. Selective Reductive Removal of Ester and Amide Groups from Arenes and Heteroarenes through Nickel-Catalyzed C–O and C–N Bond Activation. *Angew. Chem. Int. Ed.* **2017**, *129*, 4030–4034.

(11) Simmons, B. J.; Hoffmann, M.; Hwang, J.; Jackl, M. K.; Garg, N. K. Nickel-Catalyzed Reduction of Secondary and Tertiary Amides. *Org. Lett.* **2017**, *19*, 1910–1913.

(12) (a) Ritleng, V.; Henrion, M.; Chetcuti, M. J. Nickel N-Heterocyclic Carbene-Catalyzed C–Heteroatom Bond Formation, Reduction, and Oxidation: Reactions and Mechanistic Aspects. *ACS Catal*. **2016**, *6*, 890–906. (b) Dey, A.; Sasmal, S.; Seth, K.; Lahiri, G. K.; Maiti, D. Nickel-Catalyzed Deamidative Step-Down Reduction of Amides to Aromatic Hydrocarbons. *ACS Catal*. **2016**, *7*, 433–437. (c) Tobisu, M.; Morioka, T.; Ohtsuki, A.; Chatani, N. Nickel-Catalyzed Reductive Cleavage of Aryl Alkyl Ethers to Arenes in Absence of External Reductant. *Chem. Sci.* **2015**, *6*, 3410–3414. (d) Sergeev, A.; Webb, J.; Hartwig, J. F. A Heterogenous Nickel Catalyst for the Hydrogenation of Ethers without Arene Hydrogenation. *J. Am. Chem. Soc*. **2012**, *134*, 20226–20229. (e) Sergeev, A.; Hartwig, J. F. Selective Nickel-Catalyzed Hydrogenolysis of Ethers. *Science*. **2011**, *332*, 439–443. (f) Tobisu, M.; Yamakawa, K.; Shimasaki, T.; Chatani, N. Nickel-Catalyzed Reductive Cleavage of Aryl-Oxygen Bonds in Alkoxy and Pivaloxyarenes using Hydrosilanes as a Mild Reducing Agent. *Chem. Comm.* **2011**, *47*, 2946–2948. (g) Iosub, A.V.; Moravcik, S.; Wallentin, C.-J.; Bergman, J. Nickel-Catalyzed Selective Reduction of Carboxylic Acids to Aldehydes. *Org. Lett.* **2019**, 10.1021/acs.orglett.9b02779 .

(13) Pesti, J.; Larson, G. L. Tetramethyldisiloxane: A Practical Organosilane Reducing Agent. *Org. Process Res. Dev*. **2016**, *20*, 1164–1181.

(14) The combination of base and organosilanes are known to form species capable of reducing carbonyl groups. For examples, see: (a) Kobayashi, Y.; Takahisa, E.; Nakano, M.; Watatani, K. Reduction of Carbonyl Compounds by using Polymethylhydro-Siloxane: Reactivity and Selectivity. *Tetrahedron*. **1997**, *53*, 1627–1634 (b) Fernández-Salas, J. A.; Manzini, S.; Nolan, S. P. Facile and Efficient KOH-Catalysed Reduction of Esters and Tertiary Amides. *Chem. Comm*. **2013**, *49*, 9758–9760. (c) Hojo, M.; Murakami, C.; Fujii, A.; Hosomi, A. New Reactivity of Methoxyhydridosilane in the Catalytic Activation System. *Tetrahedron Lett.* **1999**, *40*, 911–914. (d) Beller, M. et al. Hydrosilylation of Ketones: From Metal-Organic Frameworks to Simple Base Catalysts. *Chem. Asian J.* **2010**, *5*, 2341–2345. (e) Hosomi, A.; Hayashida, H.; Kohra, S; Tominaga, Y. Pentacoordinate Silicon Compounds in Synthesis: Chemo- and Stereo-selective Reduction of Carbonyl Compounds using Trialkoxy-substituted Silanes and Alkali Metal Alkoxides. *J. Chem. Soc. Chem. Commun.* **1986**, *18*, 1411–1412.

(15) (a) Mullard, A. Deuterated Drugs Draw Heavier Backing. *Nat. Rev. Drug Discov*, **2016**, *15*, 219–221. (b) Pirali, T.; Serafini, M.; Cargnin, S.; Genazzani, A. A. Applications of Deuterium in Medicinal Chemistry. *J. Med. Chem.* **2019,** *62,* 5276–5297. (c) Tung, R. D. Deuterium Medicinal Chemistry Comes of Age. *Future Med. Chem.* **2016**, *8*, 491–494.

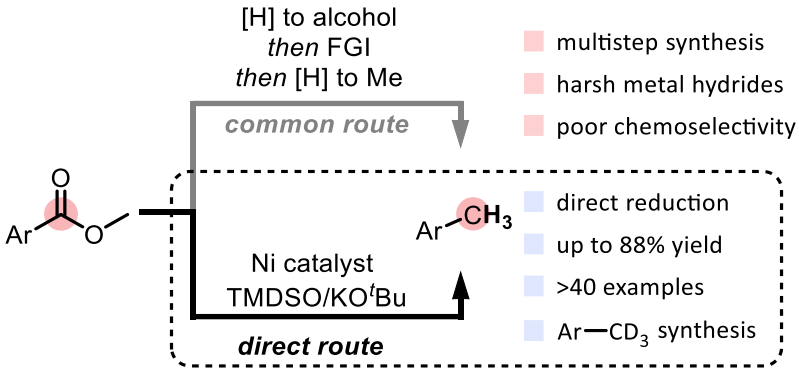
(16) (a) Shen, Z.; Shang, S.; Geng, H.; Wang, J.; Zhang, X.; Zhou, A.; Yao, C.; Chen, X.; Want, W. Trideuteromethylation Enabled by a Sulfoxonium Metathesis Reaction. *Org. Lett*. **2019**, *21*, 448–452. (b) He, Z.-T.; Li, H.; Haydl, A.; Whiteker, G.; Hartwig, J. F. Trimethylphosphate as a Methylating Agent for Cross Coupling: A Slow-Release Mechanism for the Methylation of Arylboronic Esters. *J. Am. Chem. Soc.* **2018**, *140*, 17197–17202. (c) Han, X.; Yuan, Y.; Shi, Z. Rhodium-Catalyzed Selective C–H Trideuteromethylation of Indole at C7 Position Using Acetic-d_6 Anhydride. *J. Org. Chem.* **2019**. 10.1021/acs.joc.9b01114 (d) Hu, L.; Liu, X.; Liao, X. Nickel-Catalyzed Methylation of Aryl Halides with Deuterated Methyl Iodide. *Angew. Chem. Int. Ed*. **2016**, *55*, 9743–9747.

(17) Mazzini, F.; Alpi, E.; Salvadori, P.; Netscher, T. First Synthesis of (8-$^2H_3$)-(all-*rac*)-δ-Tocopherol. *Eur. J. Org. Chem*. **2003**, *15*, 2840–2844.

(18) (a) Smart, K. A.; Mothes-Martin, E.; Annaka, T.; Grellier, M.; Sabo-Etienne, S. Silane Deuteration Catalyzed by Ruthenium Bis(dihydrogen) Complexes or Simple Metal Salts. *Adv. Synth. Catal*. **2014**, *356*, 759–764. (b) Zhou, R.; Li, J.; Cheo, H. W.; Chua, R.; Zhan, G.; Hou, Z.; Wu, J. Visible-Light Mediated Deuteration of Silanes with Deuterium Oxide. *Chem. Sci*. **2019**, *10*, 7340–7344.

(19) (a) Burés, J. Variable Time Normalization Analysis: General Graphical Elucidation of Reaction Orders from Concentration Profiles. *Angew. Chem. Int. Ed.* **2016**, *55*, 16084–16087. (b) Neilsen, D.-T. C.; Burés, J. Visual Kinetic Analysis. *Chem. Sci.* **2019**, *10*, 348–353.

(20) (a) L. Larson, G.; L. Fry, J. Ionic and Organometallic-Catalyzed Organosilane Reductions. In Organic Reactions, (Ed.). doi:10.1002/0471264180.or071.01 (b) Rendler, S.; Oestreich, M. Hypervalent Silicon as a Reactive Site in Selective Bond-Forming Processes. *Synthesis*. **2005**, *11*, 1727–1747. (c) Dieters, J. A.; Holmes, R. R. Enhanced Reactivity of Pentacoordinated Silicon Species. An ab Initio Approach. *J. Am. Chem. Soc.* **1990**, *112*, 7197–7202. (d) Revunova, K.; Nikonov, G. I. Base-Catalyzed Hydrosilylation of Ketones and Esters and Insight into the Mechanism. *Chem. Eur. J*. **2013**, *20*, 839–845. (e) Drew, M. D.; Lawrence, N. J.; Fontaine, D.; Sehkri, D.; Bowles, S. A.; Watson, W. A Convenient Procedure for the Reduction of Esters, Carboxylic Acids, Ketones and Aldehydes using Tetrabutylammonium Fluoride and Polymethylhydrosiloxane. *Synlett.* **1997**, *8*, 989–911. (f) Brook, M. A. Silicon in Organic, Organometallic, and Polymer Chemistry; Interscience Publisher, Inc.: New York, **2000**, Chap. 4, 97.


[H] to alcohol
then FGI
then [H] to Me
common route
multistep synthesis
harsh metal hydrides
poor chemoselectivity
Ar
O
O
Ar—CH3
Ni catalyst
TMDSO/KO^tBu
direct route
direct reduction
up to 88% yield
>40 examples
Ar—CD3 synthesis

Exhaustive Reduction of Esters Enabled by Nickel Catalysis

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Supplementary information

Table of Contents

1. General considerations

1.1 General experimental details

Unless otherwise indicated, reactions were conducted under an atmosphere of nitrogen in 8 mL screw capped vials that were oven dried (120 °C). Column chromatography was either performed manually using Silicycle F60 40−63 μm silica gel or by using a Combiflash Rf+ automated chromatography system with commercially available Biotage normal-phase Silica Flash columns (35−70 μm). Analytical thin layer chromatography (TLC) was conducted with aluminum-backed EMD Millipore Silica Gel 60 F254 pre-coated plates. Unless otherwise noted, visualization of developed plates was performed under UV light (254 nm) and/or using $KMnO_4$ stain.

1.2 Instrumentation

^1H NMR and ^{13}C NMR were recorded on a Bruker AVANCE 400 MHz spectrometer. ^1H NMR spectra were internally referenced to the residual solvent signal (e.g., $CDCl_3$ = 7.27 ppm). ^{13}C NMR spectra were internally referenced to the residual solvent signal (e.g., $CDCl_3$ = 77.00 ppm). Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), coupling constant (Hz), integration. NMR yields for optimization studies were obtained by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. GC data was obtained via a 5-point calibration curve using FID analysis on an Agilent Technologies 7890B GC with 30 m x 0.25 mm HP-5 column. Accurate mass data (EI) was obtained from an Agilent 5977A GC/MSD using MassWorks 4.0 from CERNO Bioscience.

1.3 Materials

Organic solvents were purified by rigorous degassing with nitrogen before passing through a PureSolv solvent purification system. Low water content was confirmed by Karl Fischer titration (<20 ppm for all solvents). Unless otherwise noted, starting materials were obtained commercially from Sigma Aldrich, Alfa Aesar or Combi-Blocks and used as received. d_8-Toluene was purchased from Sigma Aldrich (99 %D). $Ni(cod)_2$ was purchased from Sigma Aldrich. $Ni(OTf)_2$ (96% purity) was purchased from Alfa Aesar. $NiBr_2$·glyme (97% purity) was purchased from Sigma Aldrich. Granulated Mn was purchased from Alfa Aesar (99.6% purity, < 10 micron). D_2 (g) was purchased as a 458 mL cylinder from Sigma Aldrich (99.8% D). ICy·HBF_4 was made according to the literature.[1]

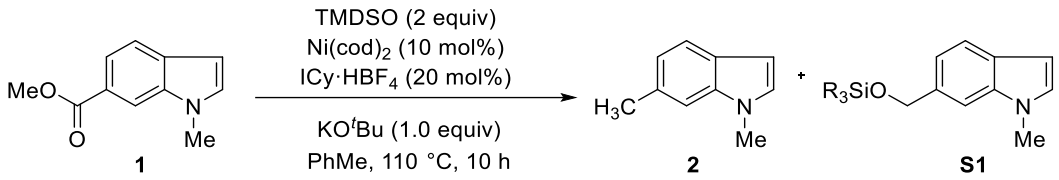
2. Synthesis of starting materials

The following ester starting materials were prepared from the corresponding carboxylic acid through acid catalyzed esterification reactions: methyl [1,1'-biphenyl]-4-carboxylate (**3**), methyl 2-naphthoate (**4**), methyl phenanthrene-9-carboxylate (**5**), methyl 4-((1s,4r)-4-butylcyclohexyl)benzoate (**6**), methyl 4-(dimethylamino)benzoate (**7**), methyl 4-vinylbenzoate (**8**), methyl 3,4,5-trimethoxybenzoate (**10**), methyl 3,5-di-*tert*-butyl-4-hydroxybenzoate (**15**), methyl 2,6-di-*tert*-butylisonicotinate (**16**), methyl 4-morpholinobenzoate (**20**), methyl 1-methyl-1*H*-indazole-3-carboxylate (**33**), methyl quinoline-6-carboxylate (**34**) and methyl 4-(*N*,*N*-dipropylsulfamoyl)benzoate (**39**).

Esters including methyl 1-methyl-1*H*-indole-6-carboxylate (**25**), methyl 7-methoxybenzofuran-2-carboxylate (**35**), isochroman-1-one (**37**) and Bifendatatum (**38**) were purchased commercially and used as such for the reduction reaction.

The following ester starting materials were synthesized according to the noted citations: methyl 4-(phenoxy)benzoate (**11**),[2] methyl 4-(4-methoxyphenoxy)benzoate (**12**),[3] methyl 4-(4-phenoxyphenoxy)benzoate (**13**),[4] methyl 2'-hydroxy-[1,1'-biphenyl]-4-carboxylate (**14**),[5] methyl 6-phenylnicotinate (**17**),[6] methyl 6-(2-methoxyphenyl)nicotinate (**45**),[6] methyl 4-(pyridin-2-yl)benzoate (**18**),[6] methyl 6-morpholinonicotinate (**20**),[7] methyl 4-(4-(pyridin-2-yl)piperazin-1-yl)benzoate (**19**),[7] methyl 2-morpholinobenzoate (**21**),[8] methyl 4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)benzoate (**24**),[8] methyl 2-(4-methylpiperidin-1-yl)benzoate (**23**),[8] methyl 4-(1*H*-indol-1-yl)benzoate (**26**),[9] methyl 9-benzyl-9*H*-carbazole-3-carboxylate (**30**),[10] methyl 6-(*tert*-butyl)-9-methyl-9*H*-carbazole-3-carboxylate (**32**),[10] methyl 6-methoxy-9-methyl-9*H*-carbazole-3-carboxylate (**31**),[11] methyl 8-methoxydibenzo[*b,d*]furan-2-carboxylate (**36**)[12].

3. Reaction optimization



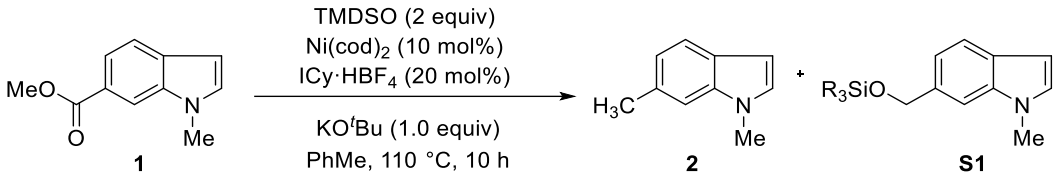
Scheme S1. General method for the reduction of esters

To an oven dried 8mL screw-top test-tube, 0.20 mmol of methyl ester starting material is added alongside an oven dried micro-stir bar. The screw-top test-tube is subsequently brought into a nitrogen-filled glovebox. Once under the inert atmosphere, 0.04 mmol ICy·HBF_4, 0.02 mmol $Ni(cod)_2$ and 0.20 mmol of KO^tBu are added. 0.8 mL of toluene is added to the test-tube, followed by 0.4 mmol of 1,1,3,3-tetramethyldisiloxane. The reaction vessel is quickly sealed with a Teflon-septa equipped cap and brought outside of the glovebox, where it is stirred inside of a mineral-oil bath at 600 rpm for 10 hours at 110 °C. After 10 hours, the reaction vessel is allowed to come to room temperature before being opened to the atmosphere. 0.80 mmol of tetra-n-butylammonium fluoride is added slowly as a 1.0 M solution in tetrahydrofuran and the resulting solution is heated to 65 °C and stirred for 2 hours.* The reaction solution is filtered through a short plug of silica before 100 µL of 1,3,5-trimethoxybenzene in toluene is added to act as an internal standard. Solvent is removed via rotary evaporation, yielding crude product which is subsequently dissolved in 0.75 mL of $CDCl_3$ before being submitted for NMR analysis. All yields are obtained via ^{1}H-NMR, setting the integral value of the peak corresponding to the three methyl protons at 2.54 ppm to 3.00 and referencing it with respect to the peak at 6.08 ppm for 1,3,5-trimethoxybenzene.

* **S1** is initially formed as a mixture of silylated species – TBAF is added to the reaction solution in order to deprotect these species so that the alcohol can be quantified.

3.1 Control Experiments

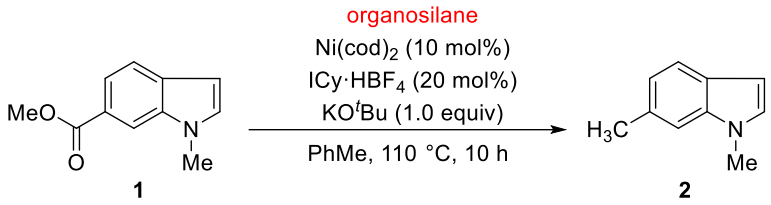
Table S1. Control experiments for the ester to methyl reduction



entry	deviation from standard conditions	yield 2 (%)	yield S1 (%)
1	No deviation	84	0
2	*remove* KO^tBu	0	0
3	*remove* TMDSO	0	0
4	*remove* $Ni(cod)_2$	trace	52
5	*remove* $ICy{\cdot}HBF_4$	14	0
6	*remove all except* TMDSO and KO^tBu	trace	66
7	*remove all except* $Ni(cod)_2$	0	0
8	room temperature	14	61
9	1 h	13	67

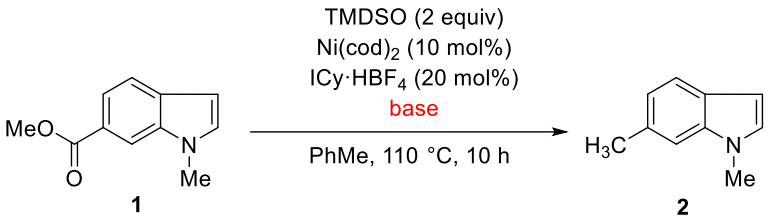
3.2 Optimization of reaction conditions

Table S2. Organosilane optimization for the ester to methyl reduction



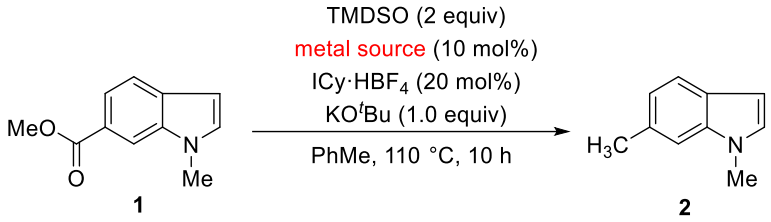
entry	organosilane	yield 2 (%)
1	Et_3SiH (4.0 equiv)	42
2	$^{i}Pr_3SiH$ (4.0 equiv)	5
3	$(EtO)_3SiH$ (4.0 equiv)	20
4	PMHS (10.0 equiv)	trace
5	$PhSiH_3$ (2.0 equiv)	trace
6	$[(Me_3SiO)_2SiHMe]$ (4.0 equiv)	48
7	$[(CH_3)_2SiHO)_2Si(CH_3)_2]$ (4.0 equiv)	65
8	TMDSO (1.0 equiv)	52
9	TMDSO (1.5 equiv)	76
10	TMDSO (2.0 equiv)	84
11	TMDSO (2.5 equiv)	74

Table S3. Base optimization for the ester to methyl reduction



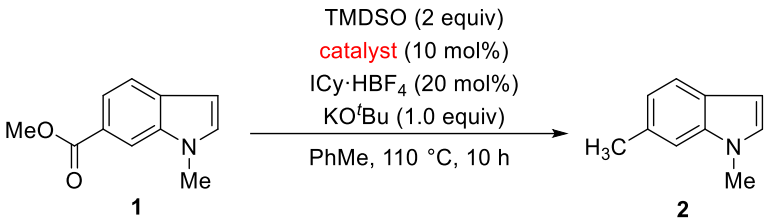
entry	base	yield, 2 [%]
1	NaOH (1.0 eq)	4
2	LiOH (1.0 eq)	0
3	KOH (1.0 eq)	12
4	Et_3N (1.0 eq)	0
5	Cs_2CO_3 (1.0 eq)	0
6	K_2CO_3 (1.0 eq)	3
7	$NMe_4OH{\cdot}5H_2O$ (1.0 eq)	37
8	KHF_2 (1.0 eq)	0
9	NaOMe (1.0 eq)	56
10	KOEt (1.0 eq)	51
11	LiO^tBu (1.0 eq)	trace
12	NaO^tBu (1.0 eq)	75
13	KO^tBu (1 eq)	78
14	KO^tBu (0.5 eq)	69
15	KO^tBu (1.5 eq)	74
16	KO^tBu (2.0 eq)	68

Table S4. Optimization of metal source for the ester to methyl reduction



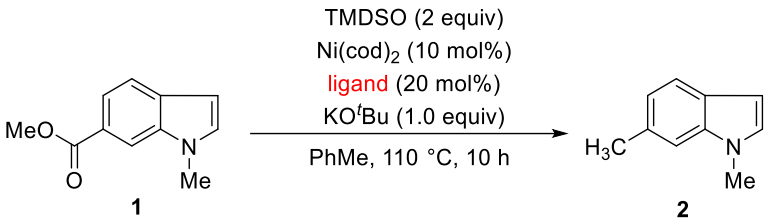
entry	Metal source	yield, 2 [%]
1	$Ni(cod)_2$	84
2	$NiCl_2$	4
3	$Ni(P(OPh)_3)_4$	0
4	$NiCl_2(PCy_3)_2$	67
5	$Ni(OAc)_2$	trace
6	$Ni(OTf)_2$	5
7	$NiBr_2$·glyme	7
8	$PdCl_2$	29
9	$Pd(OAc)_2$	28
10	Pd_2dba_3	34
11	$RhCl(PPh_3)_3$	trace
12	Pt/C	11
13	$Ir(cod)_2Cl_2$	13
14	$[Ru(p\text{-cymene})Cl_2]_2$	7
15	CuI	0
16	$FeCl_3$	0
17	$Ni(cod)_2$ (5 mol%)	62
18	$Ni(cod)_2$ (20 mol%)	86
19	$Ni(cod)_2$ (30 mol%)	82

Table S5. Optimization of reaction with air stable Ni(II) salts

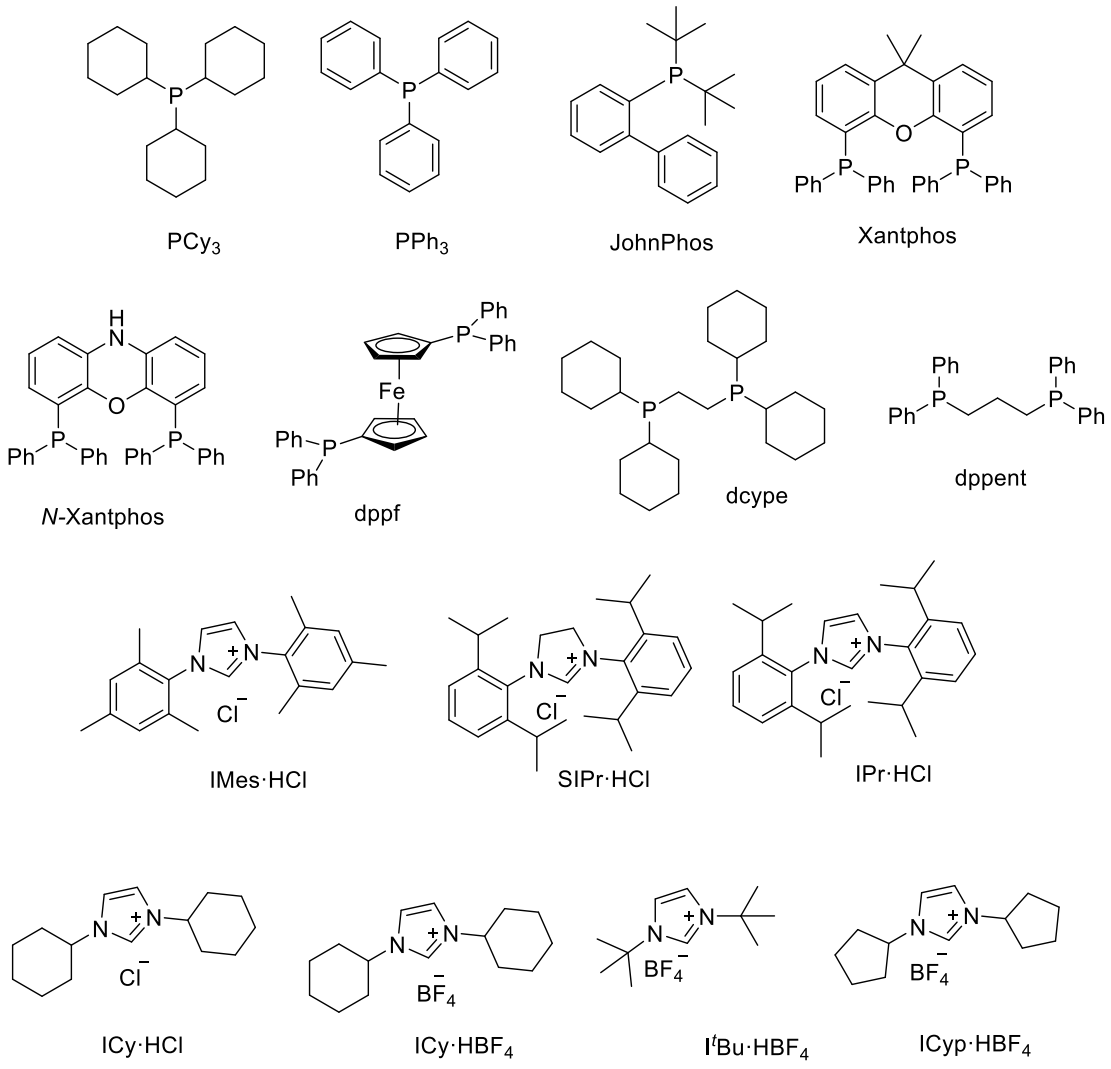


entry	**catalyst**	**deviation from standard procedure**	**yield, 2 [%]**
1	$Ni(OAc)_2$	none	trace
2	$Ni(OAc)_2$	added Mn (1 eq)	56
3	$Ni(OAc)_2$	added Mn (20 mol%)	13
5	$Ni(OAc)_2$	added Mn (1 eq)/*no TMDSO*	0
6	$Ni(OAc)_2$	added Mn (1 eq)/*no TMDSO/no base*	0xx
7	$Ni(OAc)_2$	added Mn (1 eq)/0.2 eq base	27
8	$Ni(OAc)_2$	added Mn (1 eq)/*no base*	trace
9	$Ni(OAc)_2$	added Mn (1 eq)/*no ICy*	33
10	$NiBr_2$·glyme	none	7
11	$NiBr_2$·glyme	added Mn (1 eq)	78
12	$NiBr_2$·glyme	added Mn (20 mol%)	35

Table S6. Ligand optimization for the ester to methyl reduction

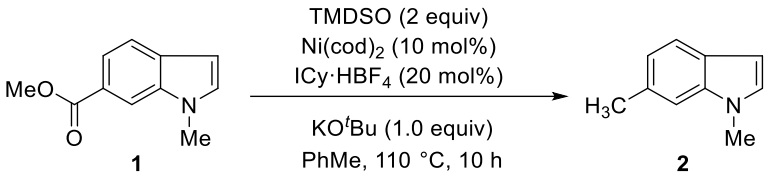


entry	ligand	yield, 2 [%]
1	PCy_3	53
2	PPh_3	15
3	JohnPhos	16
4	Xantphos	35
5	*N*-Xantphos	29
6	dppf	27
7	dcype	44
8	dppent	35
9	IMes·HCl	3
10	SIPr·HCl	53
11	IPr·HCl	70
12	ICy·HCl	77
13	ICy·HBF_4	84
14	I^{t}Bu·HBF_4	73
15	ICyp·HBF_4	60



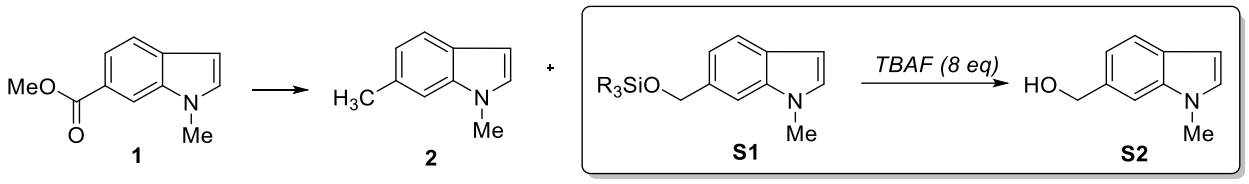
Scheme S2. Structures of ligands

Table S7. Miscellaneous optimization for the ester to methyl reduction



entry	deviation from standard conditions	yield, 2 [%]
1	temperature = 80 °C	51
2	temperature = 100 °C	71
3	temperature = 120 °C	81
4	temperature = 150 °C	67
5	reaction time = 3 h	25
6	reaction time = 6 h	54
7	reaction time = 9 h	79
8	reaction time = 10 h	84
9	reaction time = 16 h	81
10	solvent = xylene	71
11	solvent = DMF	0
12	solvent = benzene	78

3.3 Work-up



The major side products in the reduction of esters to tolyl derivatives are the corresponding silylated alcohol (e.g. **S1**) and various siloxane derivatives arising from the TMDSO. While the quantity of silylated alcohol is minimized by running the reaction to completion, purification can still be hindered by the siloxane byproducts. This is particularly true when purifying non-polar products by silica gel chromatography. We found that quenching the reaction with 8 equivalents of 1.0 M TBAF in THF and stirring for 2 h at 65 °C (or alternatively, 6 h at room temperature) prior to isolation was beneficial. While not mandatory, this work-up procedure was followed throughout to ensure the products obtained were spectroscopically pure.

4. Reaction scope

4.1. General procedures

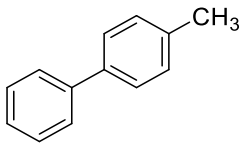
General procedure A

To an oven dried 8 mL screw-top test-tube, 0.20 mmol of methyl ester starting material is added alongside an oven dried micro-stir bar. The screw-top test-tube is subsequently brought into a nitrogen-filled glovebox. Once under the inert atmosphere, 0.04 mmol ICy·HBF_4, 0.02 mmol $Ni(cod)_2$ and 0.20 mmol of KO^tBu are added. 0.8 mL of toluene is added to the test-tube, followed by 0.40 mmol of 1,1,3,3-tetramethyldisiloxane. The reaction vessel is quickly sealed with a Teflon-septa equipped cap and brought outside of the glovebox, where it is stirred inside of a mineral-oil bath at 600 rpm for 10 hours at 110 °C. After 10 hours, the reaction vessel is allowed to come to room temperature before being opened to the atmosphere. 0.80 mmol of tetra-n-butylammonium fluoride is added slowly as a 1.0 M solution in tetrahydrofuran and the resulting solution is heated to 65 °C and stirred for 2 hours. The crude reaction solution is subsequently added directly to a 10 g Biotage SNAP silica-packed column where it is purified on a CombiFlash Rf+ automated chromatography instrument using a mixture of ethyl acetate in hexanes.

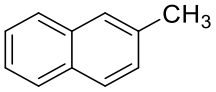
General procedure B – glovebox free conditions

To an 8 mL screw-top test-tube, 0.20 mmol of methyl ester starting material is added alongside a micro-stir bar. 0.20 mmol Mn, 0.02 mmol $NiBr_2$·glyme, 0.04 mmol ICy·HBF_4 and 0.20 mmol of KO^tBu are subsequently added. 0.8 mL of toluene is introduced to the test-tube, followed by 0.40 mmol of 1,1,3,3-tetramethyldisiloxane. The reaction vessel is quickly sealed with a Teflon-septa equipped cap and stirred inside of a mineral-oil bath at 600 rpm for 10 hours at 110 °C. After 10 hours, the reaction vessel is allowed to come to room temperature before being opened to the atmosphere. 0.80 mmol of tetra-n-butylammonium fluoride is added slowly as a 1.0 M solution in tetrahydrofuran and the resulting solution is heated to 65 °C and stirred for 2 hours. The crude reaction solution is subsequently added directly to a 10 g Biotage SNAP silica-packed column where it is purified on a CombiFlash Rf+ automated chromatography instrument using a mixture of ethyl acetate in hexanes.

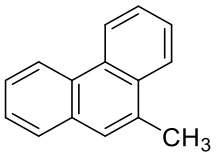
4.2 Reaction products and characterization data



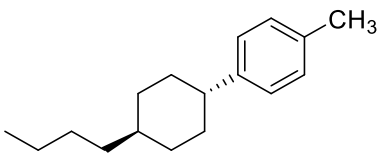
4-Methyl-1,1'-biphenyl (3) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% ethyl acetate in hexanes to afford (**3**) as a yellow liquid (30 mg, 86% yield). The reaction was repeated according to general procedure B (24 mg, 73% yield). Characterization data matched those previously reported.[13] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62-7.60 (d*, J* = 7.8 Hz, 2H), 7.54-7.42 (t, *J* = 8.4 Hz, 2H), 7.37-7.33 (d*, J* = 7.8 Hz, 2H), 7.29-7.27 (d, *J* = 7.8 Hz, 2H), 7.25 (m, 1H) 2.47 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): 141.1, 138.3, 136.9, 129.4, 127.6, 126.9, 126.8, 126.9, 21.0.



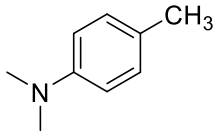
2-Methylnaphthalene (4) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% ethyl acetate in hexanes to afford (**4**) as an off-white solid (26 mg, 76% yield). The reaction was repeated according to general procedure B (22 mg, 70% yield). Characterization data matched those previously reported.[14] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.80-7.78 (d, *J* = 8.0 Hz, 3H), 7.79 (m, 1H), 7.45-7.41 (m, 2H), 7.37-7.34 (d, *J* = 8.4 Hz, 1H), 2.51 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 135.4, 133.6, 131.7, 128.0, 127.6, 127.5, 127.1, 126.0, 125.7, 124.9, 21.6.



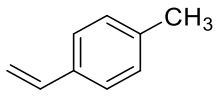
9-Methylphenanthrene (5) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% ethyl acetate in hexanes to afford (**5**) as a faint yellow solid (32 mg, 73% yield). Characterization data matched those previously reported.[15] **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 8.77-8.67 (m, 3H), 8.11-8.09 (m, 1H), 7.94-7.57 (m, 5H), 2.77 (s, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$): 141.2, 138.4, 137.0, 129.5, 128.7, 127.0, 127.0, 21.1.



1-(*trans*-4-Butylcyclohexyl)-4-methylbenzene (6) was prepared according to general procedure A. Purification was done using a gradient of 1→5% EtOAc in hexane to afford (**6**) as colourless liquid (35 mg, 76% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.11-7.10 (m, 4H), 2.46-2.39 (m, 1H), 2.32 (s, 3H), 1.90-1.85 (m, 4 H), 1.49-1.38 (m, 2H), 1.34-1.21 (m, 7H), 1.10-1.00 (m, 2H), 0.93-0.89 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 144.9, 135.1, 128.9, 126.7, 44.2, 37.3, 37.1, 34.4, 33.7, 29.2, 23.0, 20.9, 14.1; **Accurate mass (EI)**: Theoretical: 230.2035. Found: 230.2029. Spectral Accuracy: 98.5%. **Melting Point:** 164-167 °C.

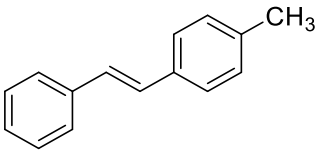


***N*,*N*,4-Trimethylaniline (7)** was prepared according to general procedure A. Purification was performed using a gradient of 1→15% ethyl acetate in hexanes to afford (**7**) as a yellow liquid (28 mg, 73% yield). The reaction was repeated in a 50 mL heavy-walled pressure tube using 5.58 mmol (1.0 g) methyl 4-(dimethylamino)benzoate, 11.2 mmol (1.97 mL) TMDSO, 5.58 mmol (626 mg) KO^{t}Bu, 0.558 mmol (153 mg) $Ni(cod)_2$ and 1.12 mmol (357 mg) ICy·HBF_4 in 22 mL toluene – purification was performed using column chromatography with a gradient of 1→15% ethyl acetate in hexanes to afford (**7**) as a white solid (708 mg, 71% yield). Characterization data matched those previously reported.[16] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.07-7.05 (d, J = 8.8 Hz, 2H), 6.79-6.68 (d, J = 8.8 Hz, 2H), 2.92 (s, 6H), 2.26 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 129.5, 129.2, 113.3, 41.1, 21.2, 21.1.

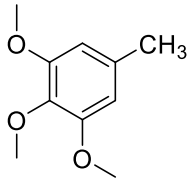


1-Methyl-4-vinylbenzene (8) was prepared according to a modified general procedure A using 1.5 equivalents of TMDSO, a reaction temperature of 90 °C and a reaction time of 6 h. Purification was

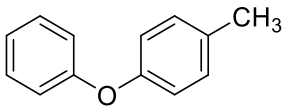
performed using a gradient of 1→5% ethyl acetate in hexanes to afford (**8**) as a colourless liquid (26 mg, 74% yield). Characterization data matched those previously reported.[17] **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 7.38-7.36 (d, *J* = 8.2 Hz, 2H), 7.24-7.21 (d, *J* = 8.0 Hz, 2H), 6.79-6.72 (dd, *J* = 18.0, 11.4 Hz, 1H), 5.78-5.74 (dd, *J* = 18.0, 1.4 Hz, 1H), 5.26-5.23 (dd, *J* = 10.8, 1.4 Hz, 1H), 2.40 (s, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$): 137.6, 136.7, 134.9, 129.2, 126.1, 112.7, 21.2.



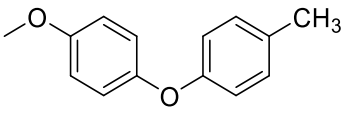
1-Methyl-4-(2-phenylethenyl)benzene (9) was prepared according to a modified general procedure A using 1.5 equivalents of TMDSO, a reaction temperature of 90 °C and a reaction time of 6 h. Purification was performed using a gradient of 1→5% ethyl acetate in hexanes to afford (**9**) as a white solid (22 mg, 71% yield). Characterization data matched those previously reported.[18] **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 7.53-7.51 (m, 1H), 7.51-7.50 (m, 1H), 7.36-7.28 (m, 4H), 7.26-7.24 (m, 3H), 7.18-7.11 (m, 2H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 131.1, 130.0, 129.0, 128.9, 128.7, 128.3, 127.5, 126.7, 126.3, 125.3, 21.4.



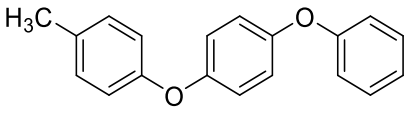
1,2,3-Trimethoxy-5-methylbenzene (10) was prepared according to general procedure A. Purification was done using a gradient of 1→5% EtOAc in hexane to afford (**10**) as colourless liquid (25 mg, 69% yield). Characterization data matched those previously reported.[19] **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 6.40 (s, 2H), 3.82-3.79 (m, 9H), 2.29 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 152.9, 135.7, 133.5, 105.9, 60.8, 55.9, 21.8.



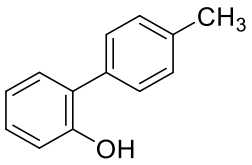
1-Methyl-4-phenoxybenzene (11) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% EtOAc in hexane to afford (**11**) as colorless solid (28 mg, 71% yield). Characterization data matched those previously reported.[20] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 (t*, J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.13-7.10 (m, 3H), 6.91-6.88 (d, *J* = 8.0 Hz, 2H), 2.33 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 158.8, 155.3, 132.4, 130.1, 129.8, 123.2, 120.4, 118.6, 20.7.



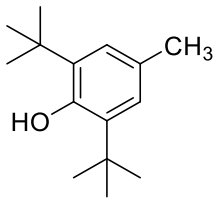
1-Methoxy-4-(*p*-tolyloxy)benzene (12) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% EtOAc in hexane to afford (**12**) as colourless liquid (26 mg, 63% yield). Characterization data matched those previously reported.[20] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.10-7.07 (d, *J* = 8.2 Hz*,* 2H), 6.96-6.92 (d, *J* = 8.8 Hz*,* 2H), 6.87-6.82 (m, 4H), 3.78 (s, 3H), 2.30 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 156.0, 155.6, 150.7, 132.0, 130.0, 120.3, 117.8, 114.7, 55.6, 20.6.



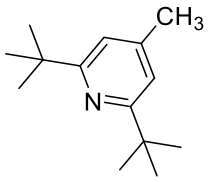
1-Methyl-4-(4-phenoxyphenoxy)benzene (13) was prepared according to general procedure A. Purification was performed using a gradient of 1→ 5% EtOAc in hexane to afford (**13**) as a colourless liquid (23 mg, 72% yield). The reaction was repeated according to general procedure B (17 mg, 64% yield). Characterization data matched those previously reported.[20] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34-7.29 (m, 2H), 7.14-7.05 (m, 2H), 7.05 (t, *J* = 1.2 Hz, 1H), 7.01-6.95 (m, 6H), 6.93-6.89 (m, 2H), 2.33 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 157.9, 155.2, 153.3, 152.3, 132.6, 130.2, 129.7, 122.9, 120.4, 119.9, 118.5, 118.1, 20.7.



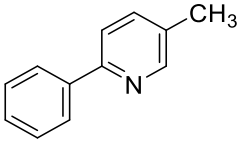
4'-Methyl-[1,1'-biphenyl]-2-ol (14) was prepared according to general procedure A. After the TBAF workup, the reaction solution was quenched with 1.0 M HCl. A liquid-liquid extraction was performed with 2 x 5 mL of ethyl acetate – the resulting organic fractions were collected and solvent was evaporated via rotary evaporation. The subsequent crude mixture was redissolved in 0.8 mL of dichloromethane and purified on a Combiflash Rf automated chromatography instrument using a gradient of 1→5% EtOAc in hexane to afford (**14**) as yellow liquid (19 mg, 66% yield). Characterization data matched those previously reported.[21] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.32 (m, 2H), 7.29-7.27 (m, 2H), 7.25-7.19 (m, 2H), 6.98-6.94 (m, 2H), 5.18 (s, 1H), 2.39 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 152.4, 137.7, 133.9, 130.1, 130.0, 129.0, 128.9, 128.0, 120.7, 115.6, 21.2.



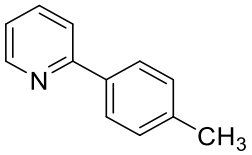
2,6-Bis(1,1-dimethylethyl)-4-methylphenol (15) was prepared according to the general procedure A, modified to use a reaction temperature of 90 °C and a reaction time of 6 h. After the TBAF workup, the reaction solution was quenched with 1.0 M HCl. A liquid-liquid extraction was performed with 2 x 5 mL of ethyl acetate – the resulting organic fractions were collected and solvent was evaporated via rotary evaporation. The subsequent crude mixture was dissolved in 0.8 mL of dichloromethane and purified on a Combiflash Rf automated chromatography instrument using a gradient of 1→5% EtOAc in hexanes to afford (**15**) as an off-white solid (23 mg, 81% yield). The reaction was repeated according to general procedure B (15 mg, 67% yield). Characterization data matched those previously reported.[22] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.06 (s, 2H), 5.08 (s, 1H), 2.36 (s, 3H), 1.52 (t, J = 7.8 Hz; 0.8 Hz, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$): 151.6, 135.8, 128.3, 125.6, 34.3, 30.4. 21.3.



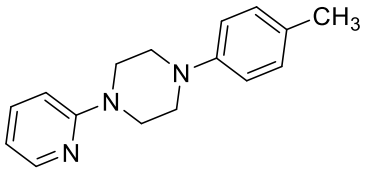
2,6-Bis(1,1-dimethylethyl)-4-methylpyridine (16) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% EtOAc in hexane to afford (**16**) as a brown solid (23 mg, 71% yield). Characterization data matched those previously reported.[23] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.94 (s, 2H), 2.33 (s, 3H), 1.37 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$): 167.4, 146.4, 116.2, 37.4, 30.2, 21.4.



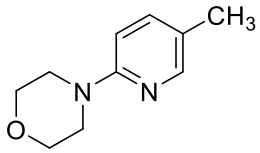
5-Methyl-2-phenylpyridine (17) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% EtOAc in hexane to afford (**17**) as colorless solid (29 mg, 73% yield). Characterization data matched those previously reported.[24] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.50 (d, J = 2.0 Hz, 1H), 7.95-7.92 (m, 2H), 7.62-7.60 (m, 1H), 7.55-7.53 (m, 1H), 7.46-7.41 (m, 2H), 7.39-7.34 (m, 1H), 2.35 (s, 3H); **13C NMR** (100 MHz, $CDCl_3$): 154.7, 150.0, 139.3, 137.4, 131.7, 128.7, 128.6, 126.7, 120.1, 18.2.



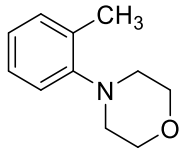
2-(p-Tolyl)pyridine (18) was prepared according to the general procedure A. Purification was performed using a gradient of 1→5% EtOAc in hexane to afford (**18**) as colorless liquid (26 mg, 78% yield). Characterization data matched those previously reported.[25] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.67-8.65 (d, J = 8.4 Hz, 1H), 7.89-7.86 (m, 2H), 7.77-7.67 (m, 2H), 7.27-7.24 (d, J = 8.0 Hz, 2H), 7.19-7.16 (m, 1H), 2.39 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 157.4, 149.5, 138.9, 136.7, 136.6, 129.4, 126.7, 121.7, 120.2, 21.2.



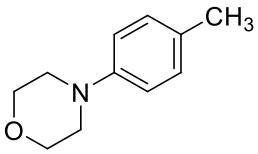
1-(4-Methylphenyl)-4-phenylpiperazine (19) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% ethyl acetate in hexanes to afford (**19**) as a white solid (28 mg, 67% yield). Characterization data matched those previously reported.[26] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.20 (m, 1H), 7.51-7.47 (m, 1H), 7.10-7.07 (m, 1H), 6.90-6.88 (m, 2H), 6.70-6.62 (m, 3H), 3.70-3.68 (m, 4H), 3.25-3.21 (m, 4H), 2.27 (s, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$): 159.4, 149.2, 147.9, 137.5, 129.7, 116.7, 113.5, 107.2, 49.8, 45.3, 30.9, 20.4.



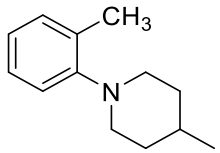
4-(5-Methyl-2-pyridinyl)-morpholine (20) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% ethyl acetate in hexanes to afford (**20**) as a white solid (28 mg, 78% yield). Characterization data matched those previously reported.[26] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.02 (m, 1H), 7.35-7.32 (m, 1H), 6.68-6.56 (m, 1H), 3.81 (m, 4H), 3.43 (m, 4H), 2.20 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 158.1, 147.5, 138.4, 122.8, 106.8, 68.7, 46.1, 17.1.



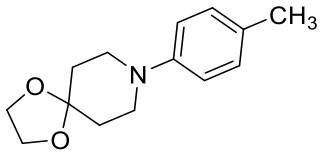
4-(2-methylphenyl)-morpholine (21) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% ethyl acetate in hexanes to afford (**21**) as a white solid (25 mg, 73% yield). Characterization data matched those previously reported.[27] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.21-7.18 (m, 2H), 7.05-6.98 (m, 2H), 3.87-3.85 (m, 4H), 2.93-2.91 (m, 4H), 2.33 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 167.0, 153.9, 138.4, 137.6, 131.2, 120.1, 113.6, 107.1, 51.6, 47.2, 44.8.



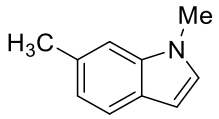
4-(p-Tolyl)morpholine (22) was prepared according to general procedure A. Purification was done using a gradient of 1→5% EtOAc in hexanes to afford (**22**) as off-white solid (27 mg, 77% yield). The reaction was repeated according to general procedure B (21 mg, 71% yield). Characterization data matched those previously reported.[27] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.08 (d, *J* = 6.8 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 3.85 (m, 4H), 3.10 (t, *J* = 4.8 Hz, 4H), 2.27 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 149.1, 129.6, 129.5, 115.9, 66.9, 49.8, 20.3.



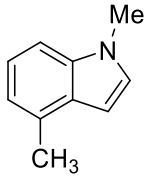
4-Methyl-1-(o-tolyl)piperidine (23) was prepared according to general procedure A. Purification was done a gradient of 1→5% EtOAc in hexane to afford (**23**) as colorless liquid (24 mg, 72% yield). Characterization data matched those previously reported.[28] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.16-7.11 (m, 2H), 7.00-6.91 (m, 2H), 3.09-3.06 (t, *J* = 8.4 Hz, 2H), 2.64-2.57 (dt, *J* = 8.6, 3.4 Hz, 2H), 2.28 (s, 3H), 1.72-1.69 (m, 2H), 1.63-1.58 (m, 1H) 1.41-1.33 (m, 2H), 0.99-0.96 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 168.8, 152.9, 131.4, 123.8, 120.5, 118.7, 53.1, 51.9, 34.5, 30.7, 21.9.



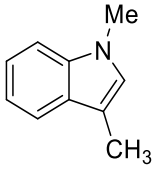
8-(4-Methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane (24) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% ethyl acetate in hexanes to afford **(24**) as a white solid (31 mg, 68% yield). Characterization data matched those previously reported.[29] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.07-7.06 (m, 2H), 6.89-6.87 (m, 2H), 3.99 (s, 4H), 3.29-3.26 (m, 4H), 2.28 (s, 3H), 1.87-1.84 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): 148.4, 129.5, 128.7, 116.3, 106.9, 65.3, 48.2, 24.5, 20.1.



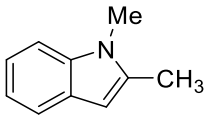
1,6-Dimethylindole (25) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% EtOAc in hexanes to afford (**25**) as colorless liquid (26 mg, 79% yield). The reaction was repeated according to general procedure B (24 mg, 76% yield).Characterization data matched those previously reported.[30] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.15 (s, 1H), 7.00-6.98 (m, 2H), 6.48-6.46 (m, 1H), 3.77 (s, 3H) 2.54 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 137.0, 131.1, 128.1, 126.2, 121.0, 120.4, 109.1, 100.6, 32.6, 21.8.



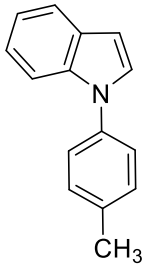
1,4-Dimethylindole (26) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% EtOAc in hexanes to afford (**26**) as colorless liquid (22 mg, 70% yield). Characterization data matched those previously reported.[31] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.18-7.16 (m, 2H), 7.11-7.03 (d, *J* = 3.2 Hz, 1H), 6.92-6.89 (m, 1H), 6.50-6.49 (d, *J* = 3.2 Hz, 1H), 3.80 (s, 3H), 2.56 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 136.4, 130.3, 128.36, 128.12, 121.6, 119.5, 106.8, 99.4, 33.0, 18.7.



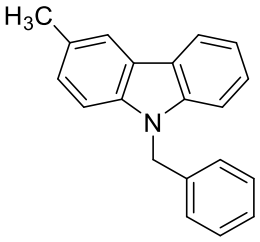
1,3-Dimethylindole (27) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% EtOAc in hexanes to afford (**27**) as colorless liquid (16 mg, 53% yield). Characterization data matched those previously reported.[31] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.65-7.62 (d, *J* = 7.5 Hz, 1H), 7.34 (m, 1H), 7.34-7.29 (m, 1H), 7.21-7.18 (t, *J* = 6.4 Hz, 1H), 6.87 (m, 1H), 3.79 (s, 3H), 2.41 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 137.1, 128.9, 126.7, 121.5, 119.2, 118.4, 110.1, 109.4, 32.4, 9.5.



1,2-Dimethylindole (28) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% EtOAc in hexanes to afford (**28**) as colorless liquid (12 mg, 41% yield). Characterization data matched those previously reported.[31] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 5.4 Hz, 1H), 7.21-7.16 (m, 2H), 6.34-6.31 (s, 1H), 3.71 (s, 3H), 2.43 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 137.4, 136.8, 127.8, 120.4, 119.7, 119.4, 108.7, 99.7, 29.5, 12.7.

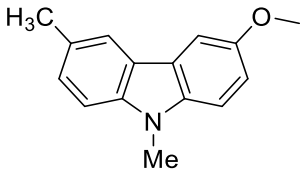


1-(p-Tolyl)-indole (29) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% EtOAc in hexane to afford (**29**) as yellow liquid (28 mg, 67% yield). Characterization data matched those previously reported.[32] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.40-7.38 (m, 2H), 7.32-7.30 (m, 3H), 7.23-7.14 (m, 2H), 6.67 (d, *J* = 3.2 Hz, 1H), 2.43 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 137.2, 136.2, 135.9, 130.1, 129.1, 128.0, 124.3, 122.1, 121.0, 120.1, 110.4, 103.1, 21.0.

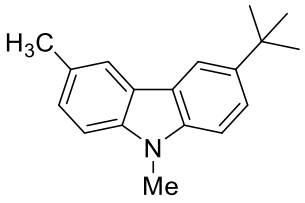


9-Benzyl-3-methylcarbazole (30) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% EtOAc in hexanes to afford (**30**) as white solid (39 mg, 72% yield). Characterization data matched those previously reported.[33] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.6 Hz, 1H), 7.91 (s, 1H), 7.41-7.36 (m, 1H), 7.33-7.30 (m, 1 H), 7.25-7.18 (m, 6H), 7.12-7.10 (m, 2H), 5.48 (s,

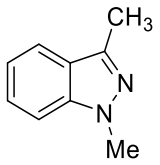
2H), 2.52 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 140.8, 138.9, 137.3, 128.7, 128.5, 127.3, 127.1, 126.3, 125.6, 123.1, 122.8, 120.3, 120.2, 118.9, 108.8, 108.5, 46.5, 21.3.



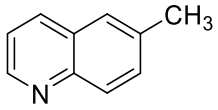
3-Methoxy-6,9-dimethyl-9H-carbazole (31) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% EtOAc in hexanes to afford (**31**) as off-white solid (29 mg, 65% yield). Characterization data matched those previously reported.[34] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.55 (d, *J* = 2.4 Hz, 1H), 7.28-7.23 (m, 3H), 7.09 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.92 (s, 2H), 3.77 (s, 3H), 2.53 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 153.4, 139.9, 136.4, 127.5, 127.0, 122.8, 122.6, 120.1, 114.6, 109.0, 108.2, 103.3, 56.1, 29.2, 21.3.



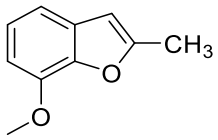
3-(*tert*-Butyl)-6,9-dimethyl-carbazole (32) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% EtOAc in hexanes to afford (**32**) as brown solid (35 mg, 68% yield). Characterization data matched those previously reported.[34] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 2.0 Hz, 1H), 7.89 (s, 1H), 7.52 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.25 (s, 2H), 3.79 (s, 3H), 2.53 (s, 3H), 1.43 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): 141.5, 139.7, 139.4, 127.7, 126.7, 123.3, 123.0, 122.2, 120.1, 116.3, 108.0, 107.8, 34.6, 32.0, 29.1, 21.4.



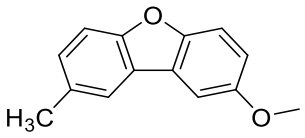
1,3-Dimethylindazole (33) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% EtOAc in hexanes to afford (**33**) as yellow liquid (17 mg, 59% yield). Characterization data matched those previously reported.[35] **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 7.63 (dt, *J* = 8.4, 0.8 Hz, 1H), 7.37-7.28 (m, 2H), 7.11-7.07 (m, 1H), 3.98 (s, 3H) 2.56 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 141.2, 140.8, 126.1, 123.2, 120.3, 119.5, 108.7, 35.0, 11.8.



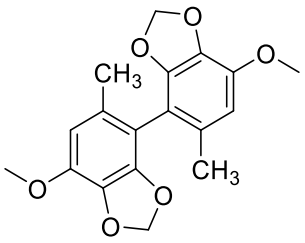
6-Methylquinoline (34) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% ethyl acetate in hexanes to afford (**34**) as a yellow-green oil (23 mg, 63% yield). Characterization data matched those previously reported.[23] **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 8.86 (m, 1H), 8.08-8.01 (m, 2H), 7.58-7.55 (m, 2H), 7.38-7.35 (m, 1H), 2.59 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 149.1, 146.7, 136.3, 135.1, 130.2, 128.1, 127.5, 125.9, 120.8, 21.6.



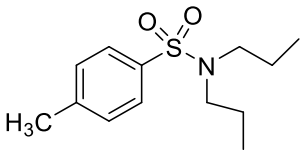
7-methoxy-2-methylbenzofuran (35) was prepared according to a modified general procedure A using a reaction temperature of 90 °C and a reaction time of 6 h Purification was done by CombiFlash column chromatography followed by preparatory TLC using a gradient of 1→5% EtOAc in hexanes to afford (**35**) as colourless liquid (21 mg, 63% yield). Characterization data matched those previously reported.[36] **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 7.10-7.04 (m, 2H), 6.71 (dd, *J* = 7.2, J = 1.6 Hz, 1H), 6.34 (s, 1H), 3.98 (s, 3H), 2.45 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 155.5, 144.8, 143.7, 130.7, 123.0, 112.6, 105.3, 102.9, 55.9, 14.0.



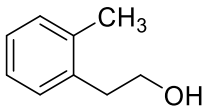
2-Methoxy-8-methyl-dibenzofuran (36) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% ethyl acetate in hexanes to afford (**36**) as a white solid (26 mg, 81% yield). Characterization data matched those previously reported.[37] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.71-7.69 (s, 2H), 7.46-7.38 (m, 3H), 7.06-7.01 (m, 1H), 3.91 (s, 3H), 2.51 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 155.7, 155.2, 151.1, 131.8, 128.2, 124.6, 124.4, 120.5, 114.9, 112.0, 111.2, 103.6, 56.0, 21.3.



7,7'-Dimethoxy-5,5'-dimethyl-4,4'-bibenzo[d][1,3]dioxole (37) was prepared according to a modified general procedure A using 4.0 equivalents of TMDSO and 2.0 equivalents of KO^{t}Bu. Purification was performed using a gradient of 1→10% ethyl acetate in hexanes to afford (**37**) as a white solid (38 mg, 76% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.43-7.31 (m, 2H), 6.08-6.07 (m, 4H), 3.82 (s, 6H), 2.51 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): 147.1, 142.3, 138.1, 137.7, 110.9, 102.2, 56.3, 51.7, 21.3. **Accurate mass (EI)**: Theoretical: 212.0832. Found: 212.0837. Spectral Accuracy: 96.3%. **FT-IR**: ν (cm^{-1}) 1718, 1626, 1489, 1422, 1389, 1220, 1085, 1010. **mp:** 148-151 °C.



4-Methyl-*N*,*N*-dipropylbenzenesulfonamide (38) was prepared according to general procedure A. Purification was done using a gradient of 5→10% EtOAc in hexane to afford (**38**) as yellow liquid (19 mg, 36% yield). Characterization data matched those previously reported.[39] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.0 Hz, 2H), 7.26 (dd, J = 8.4, 0.2 Hz, 2H), 3.05-3.01 (m, 4H), 1.57-1.47 (m, 4H), 0.84 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): 142.8, 137.2, 129.5, 127.0, 50.0, 22.0, 21.4, 11.1.

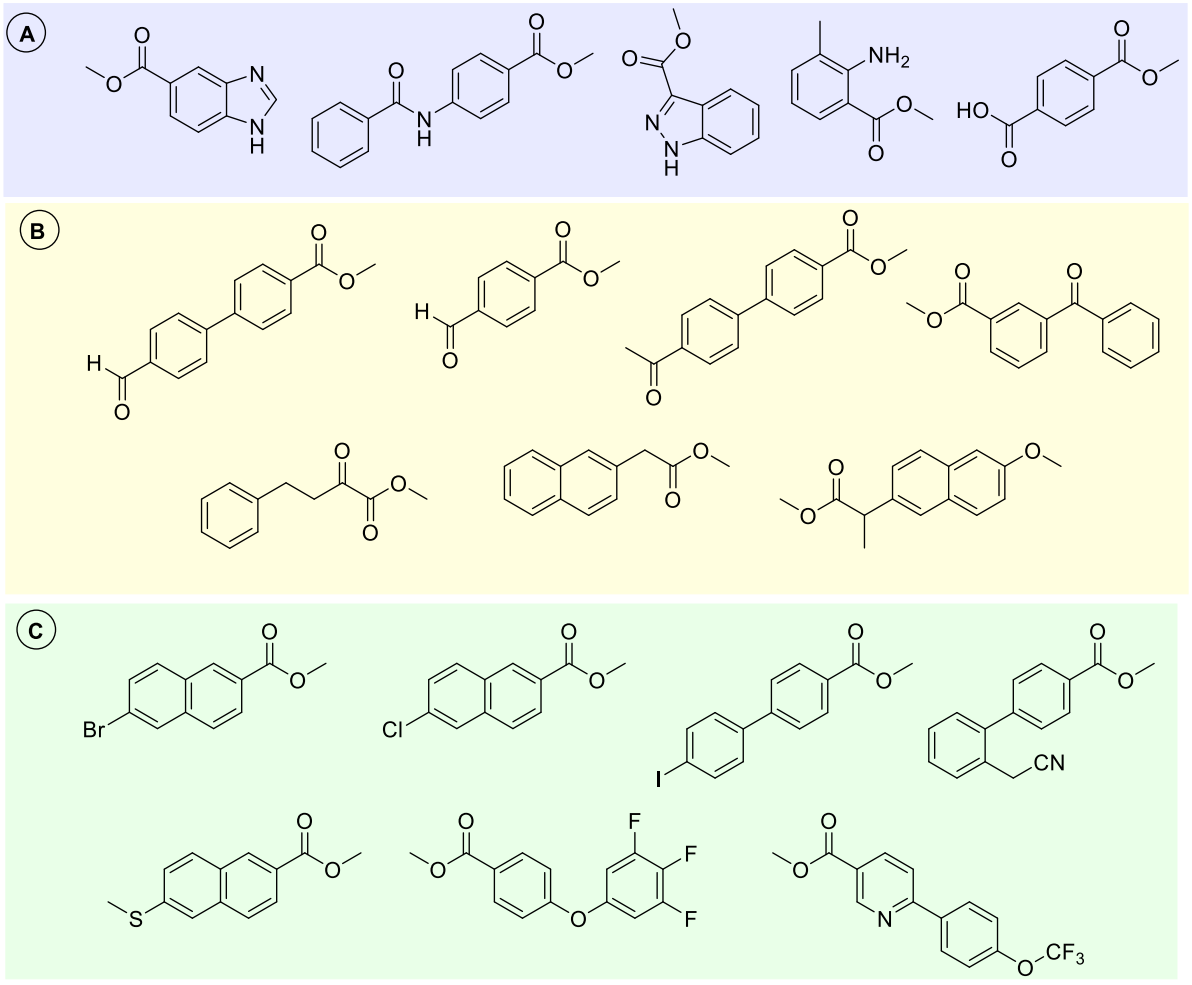


2-(Methylbenzene)ethanol (39) was prepared according to a modified general procedure A using 0.2 mmol of iso-chromanone as the starting material, a reaction temperature of 90 °C and a reaction time of 6 h. After the TBAF workup, the reaction solution was quenched with 1.0 M HCl. A liquid-liquid extraction was performed with 2 x 5 mL of ethyl acetate – the resulting organic fractions were collected and solvent was evaporated via rotary evaporation. The subsequent crude mixture was redissolved in 0.8 mL of dichloromethane and purified on a Combiflash Rf automated chromatography instrument using a gradient of 1→5% EtOAc in hexanes to afford (**39**) as an off-white solid (21 mg, 74% yield). Characterization data matched those previously reported.[38] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29-7.17 (m, 4H), 3.71-3.66 (m, 2H), 3.22 (m, 2H), 2.37(s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 137.7, 128.9, 128.8, 128.1, 125.9, 125.1, 57.7, 21.2, 18.0.

5. Troubleshooting

5.1. Scope Limitations

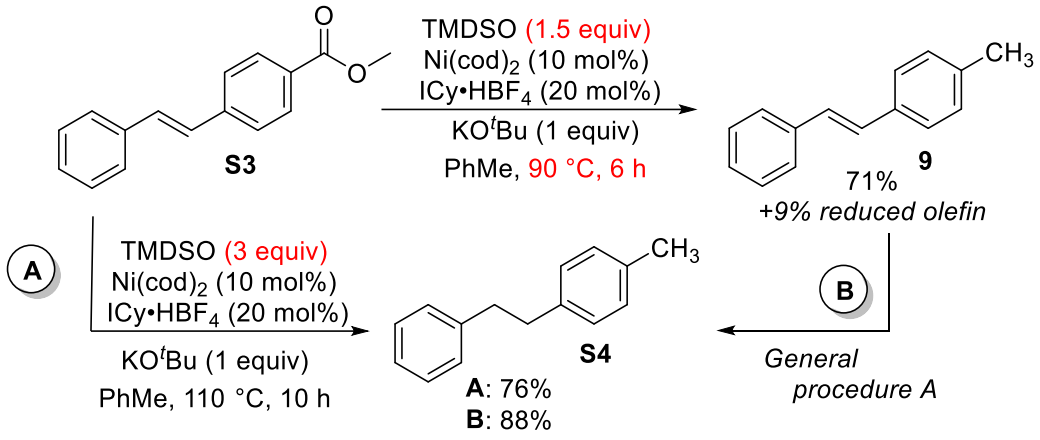
Several substrates, particularly those with free OH or NH bonds, were found to be inert to the reaction conditions, instead giving recovery of starting material (Scheme S3A). Substrates with other reducible carbonyl functionalities such as aldehydes, ketones and aliphatic esters were found to over-react (Scheme S3B). Lastly, esters bearing carbon-halogen bonds, carbon-sulfur bonds and select other functional groups were found to give intractable mixtures of products (Scheme S3C).



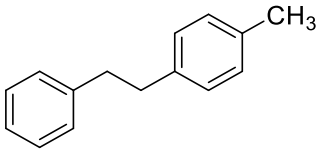
Scheme S3. Unsuccessful scope examples

5.2. Improving moderate yields

Several substrates afforded relatively low yields when subjected to the 'optimal' conditions. In general, yields could be improved by increasing the catalyst loading. In many cases, substrate-specific optimization resulted in improved yields without necessitating more catalyst. For instance, Substrate **S3**, bearing a stilbene backbone, was found to give desired product **9** upon reaction with 1.5 equivalents TMDSO at 90 °C for 6 h. Upon treatment with the general reaction conditions, product **S4** could be recovered. Further, **S4** could be recovered from substrate **S3** upon reaction with 3 equivalents of TMDSO.

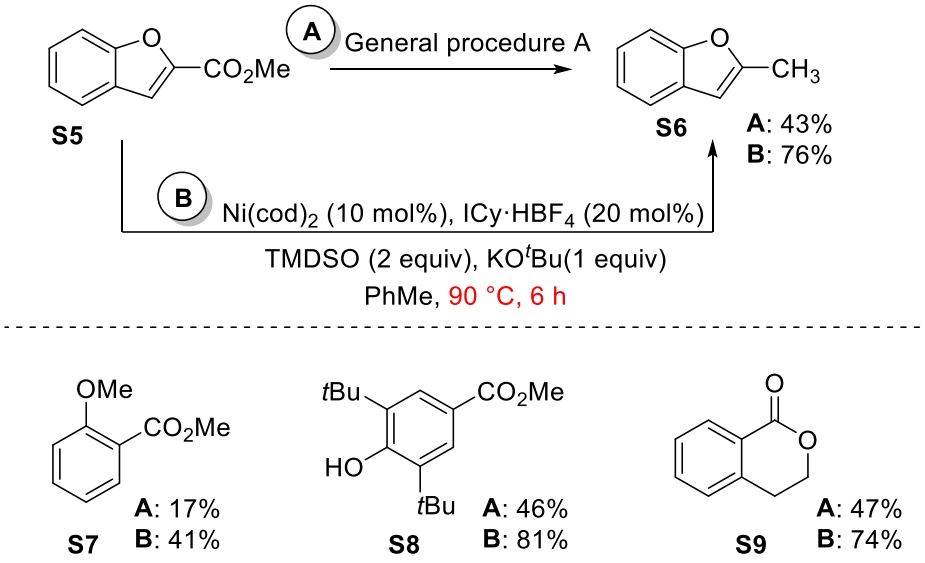


Scheme S4. Depicting control over olefin-containing ester substrates



1-Methyl-4-(2-phenethyl)benzene (**S4**) was prepared according to general procedure A. Purification was performed using a gradient of 1→5% ethyl acetate in hexanes to afford (**S4**) as a white solid (22 mg, 61% yield). Characterization data matched those previously reported.[40] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46-7.44 (d, J = 8.2 Hz, 2H), 7.34-7.32 (d, J = 8.0 Hz, 2H), 7.14-7.11 (m, 3H), 7.01-6.93 (m, 2H), 2.92-2.89 (m, 4H), 2.31 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 143.4, 137.6, 134.3, 128.3, 128.1, 127.3, 125.7, 39.4, 36.1, 20.5.

Substrate-specific optimization was performed on esters **S5**, **S7**, **S8** and **S9** after noting their modest yields upon exposure to the general procedure A. Higher yields could be obtained upon lowering the reaction temperature to 90 °C and shortening the reaction time to 6 h.



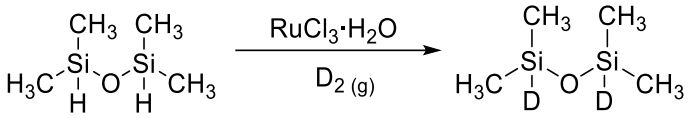
Scheme S5. Improved yields at reduced temperature and time

5.3. General comments

The quality of reagents was observed to be particularly important for reproducibly obtaining the yields reported. In the conditions using $Ni(cod)_2$, any exposure to oxygen was highly detrimental. The age of the $Ni(cod)_2$ was also found to be important – in one instance, replacing an old (>6 month) bottle of $Ni(cod)_2$ with a new source resulted in substantially improved yields. While somewhat lower yielding, reactions performed using general procedure B ($NiBr_2$·glyme/Mn) were found to be more robust.

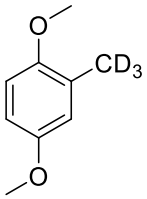
6. Additional experimental information

6.1. Catalytic deuteration

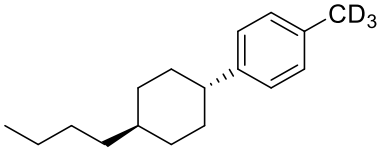


***d*$_2$-TMDSO**

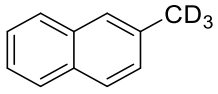
In order to transform TMDSO into its deuterated analog, a modified literature procedure was used.[41] Inside of a nitrogen-filled glovebox, 10 mg $RuCl_3 \cdot H_2O$ is crushed into a fine powder and added alongside 3.0 mL of TMDSO to a 25 mL heavy-walled vacuum Schlenk tube. The tube is connected to a Buchi "tinyclave" pressure reactor and sealed. The reaction vessel is subsequently brought outside of the glovebox. D_2 (g) is introduced to the pressure tube through a deuterium gas regulator via a T-shaped vacuum stopcock to a gauge pressure of 10-12 psi. The reactor is sealed and stirred rapidly for 1 h at room temperature. After 1 h, the reaction vessel is placed in a liquid nitrogen bath until the TMDSO solution freezes, at which point the vessel was placed under vacuum for 10 seconds. After evacuating, the pressure tube is brought out of the liquid nitrogen bath and allowed to return to room temperature. Once at room temperature, D_2 was reapplied at the same pressure. This cycle (pressurize vessel, stir, freeze-pump-thaw) was repeated 6 times until analysis of an aliquot by ^{1}H NMR showed >95% deuterium incorporation. The spectroscopically pure *d*$_2$-TMDSO (61% yield) can be purified by distillation to remove remaining $RuCl_3$;[41] however, this was not found to be necessary. The crude material was thus used in subsequent reduction reactions without further purification as a black, translucent liquid.



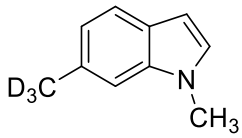
(*d*$_3$)-2,5-Dimethoxy-2-methylbenzene (41) was prepared according to general procedure B using *d*$_2$-TMDSO in *d*$_8$-toluene (use of non-deuterated toluene provides slightly reduced deuterium incorporation). Purification was performed using a gradient of 1→5% ethyl acetate in hexanes to afford (**41**) as a white solid (23 mg, 68% yield, >95% D). Characterization data matches the literature for the analogous non-deuterated compound.[42] **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 6.69-6.59 (m, 3H), 3.71 (s, 3H), 3.67 (s, 3H), 2.26 (s, <0.08 H); **^{13}C NMR** (100 MHz, $CDCl_3$): 153.1, 152.8, 152.7, 129.2, 114.5, 110.7, 58.3, 58.2, 18.6 (m, CD_3).



(*d*$_3$)-1-(*trans*-4-Butylcyclohexyl)-4-methylbenzene (**42**) was prepared according to general procedure B using *d*$_2$-TMDSO in *d*$_8$-toluene. Purification was performed using a gradient of 1→5% ethyl acetate in hexanes to afford (**42**) as a white solid (31 mg, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 7.11-7.10 (m, 4H), 2.46-2.39 (m, 1H), 2.32 (s, <0.08 H) 1.90-1.85 (m, 4 H), 1.49-1.38 (m, 2H), 1.34-1.21 (m, 7H), 1.10-1.00 (m, 2H), 0.93-0.89 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 144.9, 135.1, 128.9, 126.7, 44.2, 37.3, 37.1, 34.4, 33.7, 29.2, 23.0, 20.9, 14.1 (m, CD_3).



(*d*$_3$)-2 methylnapthalene (**43**) was prepared according to general procedure B using *d*$_2$-TMDSO in *d*$_8$-toluene. Purification was performed using a gradient of 1→5% ethyl acetate in hexanes to afford (**43**) as a white solid (23 mg, 68% yield). Characterization data matches the literature for the analogous non-deuterated compound.[14] **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 7.80-7.78 (d, *J* = 8.0 Hz, 3H), 7.79 (m, 1H), 7.45-7.41 (m, 2H), 7.37-7.34 (d, J = 8.4 Hz, 1H), 2.51 (s, <0.07 M); **^{13}C NMR** (100 MHz, $CDCl_3$): 135.4, 133.6, 131.7, 128.0, 127.6, 127.5, 127.1, 126.0, 125.7, 124.9, 21.6 (m, CD_3).



(*d*$_3$)-N-methyl-6-methylindole (**44**) was prepared according to general procedure B using *d*$_2$-TMDSO in *d*$_8$-toluene. Purification was performed using a gradient of 1→5% ethyl acetate in hexanes to afford (**44**) as a white solid (23 mg, 65% yield). Characterization data matches the literature for the analogous non-deuterated compound.[30] **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 7.55 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.15 (s, 1H), 7.00-6.98 (m, 1H), 6.48-6.46 (m, 1H), 3.77 (s, 3H), 2.53 (s, <0.07 H); **^{13}C NMR** (100 MHz, $CDCl_3$): 137.0, 131.1, 128.1, 126.2, 121.0, 120.4, 109.1, 100.6, 32.6, 21.8 (m, CD_3).

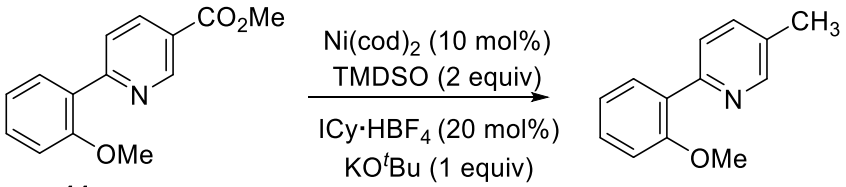
6.2. Chemoselectivity between ester reduction and ethereal cleavage

Both conditions	**Conditions A**	**Conditions B**
$Ni(cod)_2$ (10 mol%) TMDSO (1 equiv or 2 equiv) PhMe (0.5 M), 110 °C, 12 h	ICy·HBF_4 (20 mol%) KO^{t}Bu (1 equiv)	PCy_3 (20 mol%) no base

Ester reduction using the Ni/TMDSO/ICy/KO^{t}Bu system was done according to a modified general procedure A using 0.20 mmol of starting material, 0.4 mL of toluene and a reaction time of 12 h, affording products **48-51**.

Ether cleavage procedure (adopted from the method used by Martin and coworkers[43])

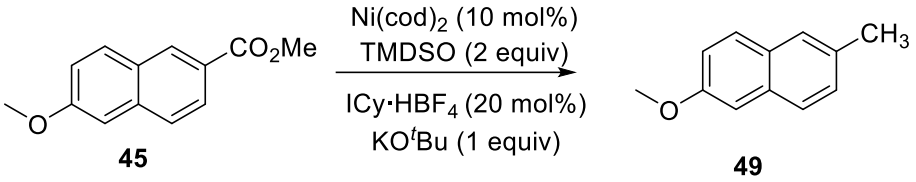
To an oven dried 8 mL screw-top test-tube, 0.20 mmol of starting material is added alongside an oven dried micro-stir bar. The screw-top test-tube is subsequently brought into a nitrogen-filled glovebox. Once under the inert atmosphere, 0.04 mmol PCy_3 and 0.02 mmol $Ni(cod)_2$ are added. 0.4 mL of toluene is added to the test-tube, followed by 0.20 mmol of 1,1,3,3-tetramethyldisiloxane. The reaction vessel is quickly sealed with a Teflon-septa equipped cap and brought outside of the glovebox, where it is stirred inside of a mineral-oil bath at 600 rpm for 12 hours at 110 °C. After 12 hours, the reaction vessel is allowed to come to room temperature before being opened to the atmosphere. 0.80 mmol of tetra-n-butylammonium fluoride is added slowly as a 1.0 M solution in tetrahydrofuran and the resulting solution is heated to 65 °C and stirred for 2 hours. The crude reaction solution is subsequently added directly to a 10 g Biotage SNAP silica-packed column where it is purified on a CombiFlash Rf+ automated chromatography instrument using a mixture of ethyl acetate in hexanes, affording products **52-55**.



44 **48**

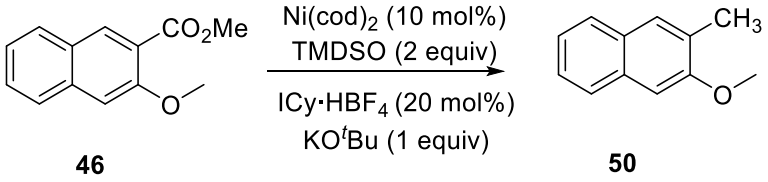
2-(2-Methoxyphenyl)-5-methylpyridine (48) was prepared according to a modified general procedure A using 0.2 mmol of starting material, 0.4 mL of toluene and a reaction time of 12 h. Purification was performed using a gradient of 1%→5% EtOAc in hexane to afford (**48**) as colorless solid (23 mg, 69% yield [76% yield via ^{1}H-NMR]). Characterization data matched those previously reported.[44] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.50 (d, J = 2.4 Hz, 1H), 7.72-7.66 (m, 2H), 7.49 (dd, J = 8.4, 2.4 Hz, 1H), 7.35-7.31 (m, 1H), 7.04

(t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 3.83 (s, 3H), 2.34 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 156.9, 153.4, 149.8, 136.3, 131.1, 131.0, 129.6, 129.2, 124.5, 121.0, 111.3, 55.6, 18.2.



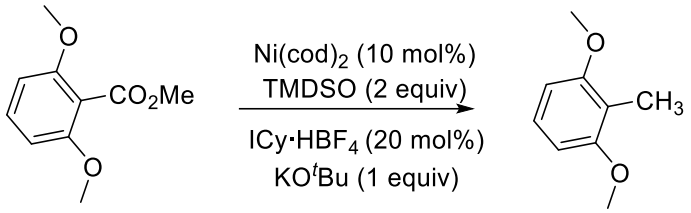
45 **49**

2-Methoxy-6-methylnaphthalene (49) was prepared according to a modified general procedure A using 0.2 mmol of starting material, 0.4 mL of toluene and a reaction time of 12 h. Purification was done a gradient of 1→5% EtOAc in hexanes to afford (**49**) as off-white solid (27 mg, 73% yield [88% yield via ^{1}H-NMR]). Characterization data matched those previously reported.[45] **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 7.64 (dd, *J* = 8.4, 3.2 Hz, 2H), 7.54 (s, 1H), 7.28 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.13-7.10 (m, 2 H), 3.90 (s, 3H), 2.48 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 157.0, 133.0, 132.6, 129.1, 128.7, 128.5, 126.7, 126.5, 118.6, 105.6, 55.2, 21.4.



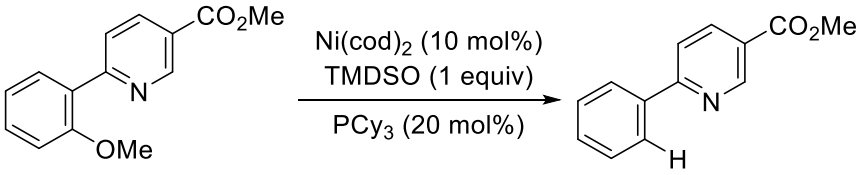
46 **50**

2-Methoxy-3-methylnapthalene (50) was prepared according to a modified general procedure A using 0.2 mmol of starting material, 0.4 mL of toluene and a reaction time of 12 h. Purification was performed using a gradient of 1→5% ethyl acetate in hexanes to afford (**50**) as an off-white solid (19 mg, 63% yield [78% yield via ^{1}H-NMR]). Characterization data matched those previously reported.[46] **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 7.73-7.69 (dd, *J* = 8.2, 3.4 Hz, 2H), 7.58 (m, 1H), 7.41-7.33 (m, 2H), 7.10-7.08 (m, 1H) 3.95 (s, 3H), 2.39 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 155.8, 131.1, 128.7, 126.8, 126.1, 125.3, 123.4. 104.3, 55.2, 16.8.



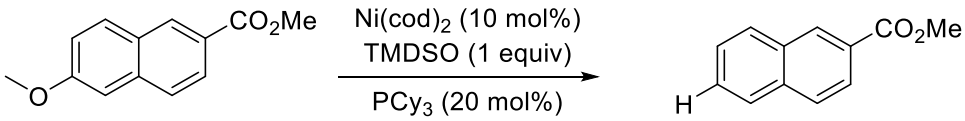
47 **51**

1,3-Dimethoxy-2-methylbenzene (51) was prepared according to a modified general procedure A using 0.2 mmol of starting material, 0.4 mL of toluene and a reaction time of 12 h. Purification was performed using a gradient of 1→5% EtOAc in hexanes to afford (**51**) as colourless solid (19 mg, 62% yield [73% yield via ^{1}H-NMR]). Characterization data matched those previously reported.[47] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.12-7.08 (m, 1H), 6.52 (d, J = 8.4 Hz, 2H), 3.81 (s, 6H), 2.09 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 158.3, 126.1, 114.5, 103.5, 55.7, 8.1.



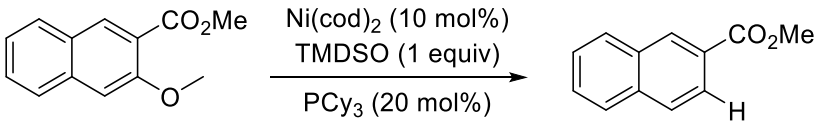
44 **52**

Methyl 5-phenylpyridine-3-carboxylate (52) was prepared according to the aforementioned ether cleavage procedure to afford (**52**) (25 mg, 68% yield [76% yield via ^{1}H-NMR]). Characterization data matched those previously reported.[48] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.30 (s, 1H), 8.38-8.32 (dd, J = 8.4, 2.0 Hz, 1H), 8.08-8.02 (dd, J = 9.0, 1.6 Hz, 2H), 7.83-7.80 (d, J = 8.4 Hz, 1H), 7.53-7.48 (m, 3H), 3.97 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 166.0, 160.8, 150.9, 138.1, 137.7, 129.8, 127.9, 124.1, 119.7, 52.3.



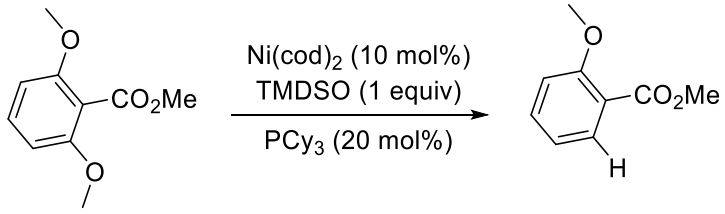
45 **53**

Methyl-2-napthoate (53) was prepared according to the aforementioned ether cleavage procedure to afford (**53**) (15 mg, 57% yield [60% yield via ^{1}H-NMR]). Characterization data matched those previously reported.[43] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.08-8.04 (dd, J = 8.6, 1.6 Hz, 1H), 7.58-7.53 (m, 2H), 3.98 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 167.1, 135.3, 132.4, 129.2, 128.0, 127.7, 126.3, 124.8, 51.7.



46 **53**

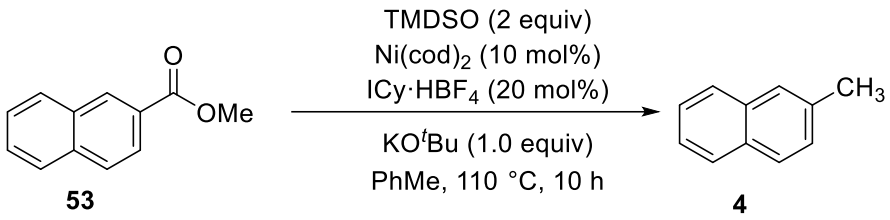
Methyl-2-napthoate (53) was prepared according to the aforementioned ether cleavage procedure to afford (**53**) (28 mg, 79% yield [90% yield via ^{1}H-NMR]). Characterization data matched those previously reported.[43] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.08-8.04 (dd, J = 8.6, 1.6 Hz, 1H), 7.58-7.53 (m, 2H), 3.98 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 167.1, 135.3, 132.4, 129.2, 128.0, 127.7, 126.3, 124.8, 51.7.



47 **54**

Methyl-2-methoxybenzoate (54) was prepared according to the aforementioned ether cleavage procedure to afford (**55**) (21 mg, 68% yield [78% yield via ^{1}H-NMR]). Characterization data matched those previously reported.[49] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.74-7.69 (dd, J = 7.5, 1.5 Hz, 1H), 7.44-7.38 (m, 1H), 6.97-6.93 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 164.7, 158.6, 133.1, 130.8, 118.9, 117.6, 111.3, 54.7, 51.4.

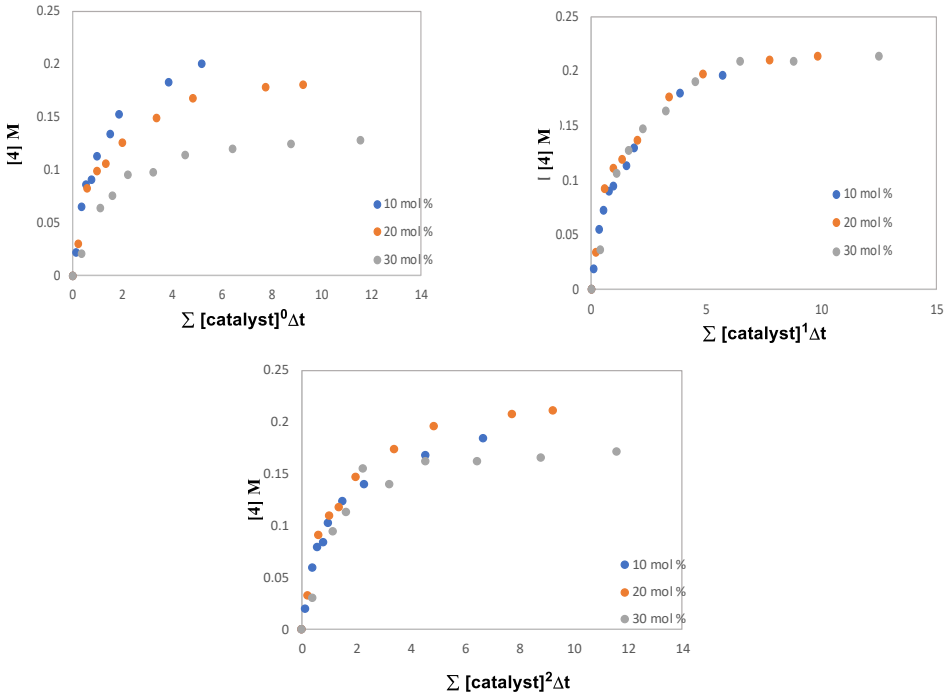
6.3. Kinetic experiments



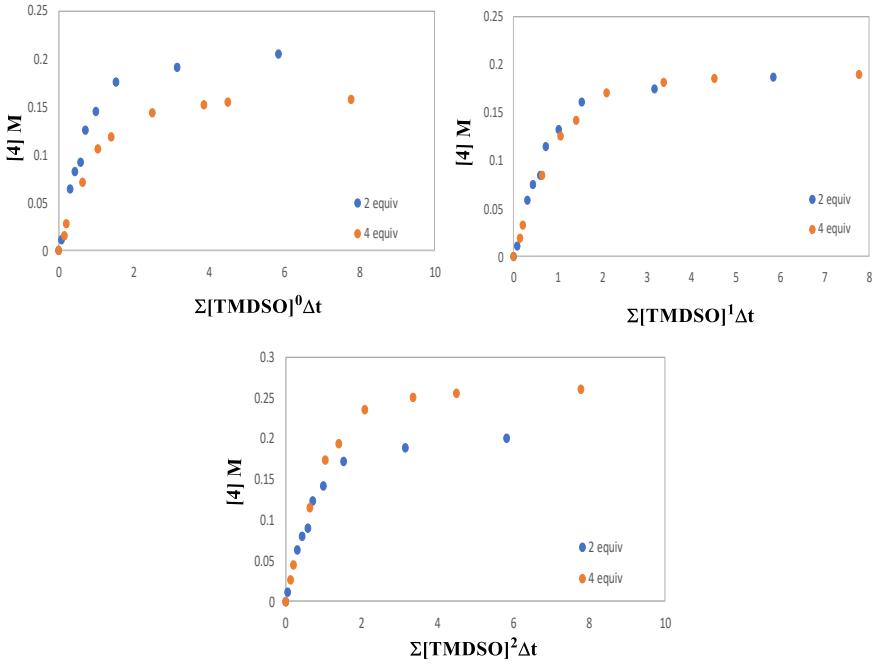
53 **4**

All individual kinetics experiments were performed according to general procedure A. Ten reactions were set up in parallel and stopped after 10 min, 20 min, 30 min, 1 h, 2 h, 3 h, 5 h, 7 h, 9 h and 10 h. Yields were obtained via ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. Variable time normalization analysis was conducted on the obtained time vs. yield data based on the method described by Bures and co-workers[50] in order to determine the observed rate equation.

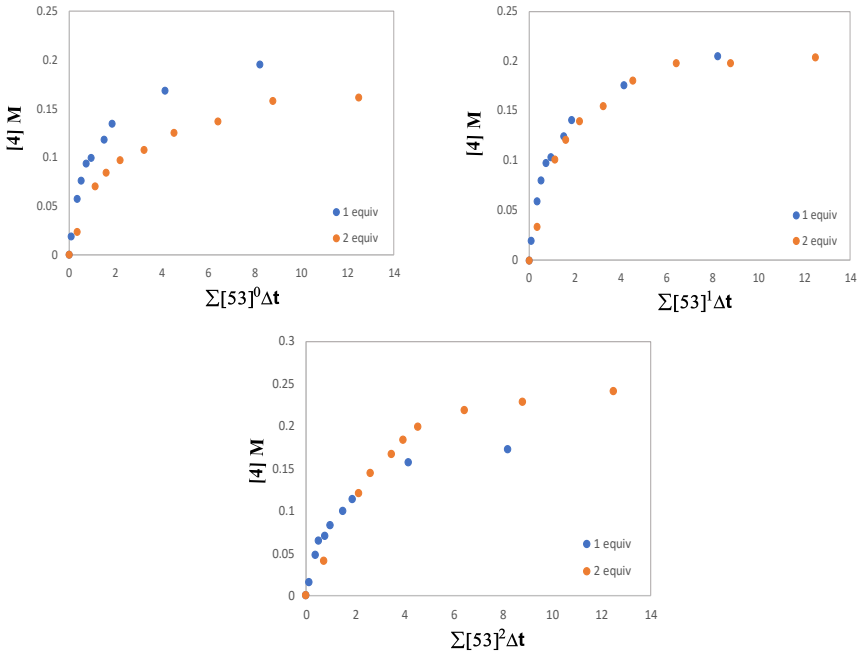
Standard reaction conditions were 0.25 M 2-methyl naphthoate (**53**), 0.25 M KO^{t}Bu, 0.50 M TMDSO, 0.025 M Ni(cod)$_2$ and 0.05 M ICy·HBF$_4$. Scheme **S9** was generated by setting [catalyst] (Ni(cod)$_2$ + ICy·HBF$_4$, 1:2 ratio) to 0.025 M (standard conditions), 0.050 M and 0.075 M. Scheme **S10** was generated by varying [TMDSO], setting it to 0.50 M (standard conditions) and 1.0 M. Scheme **S11** was generated by varying [**53**], setting it to 0.25 M (standard conditions) and 0.5 M. Scheme **S12** was generated by varying [KO^{t}Bu], setting it to 0.025 M (standard conditions) and 0.050 M.



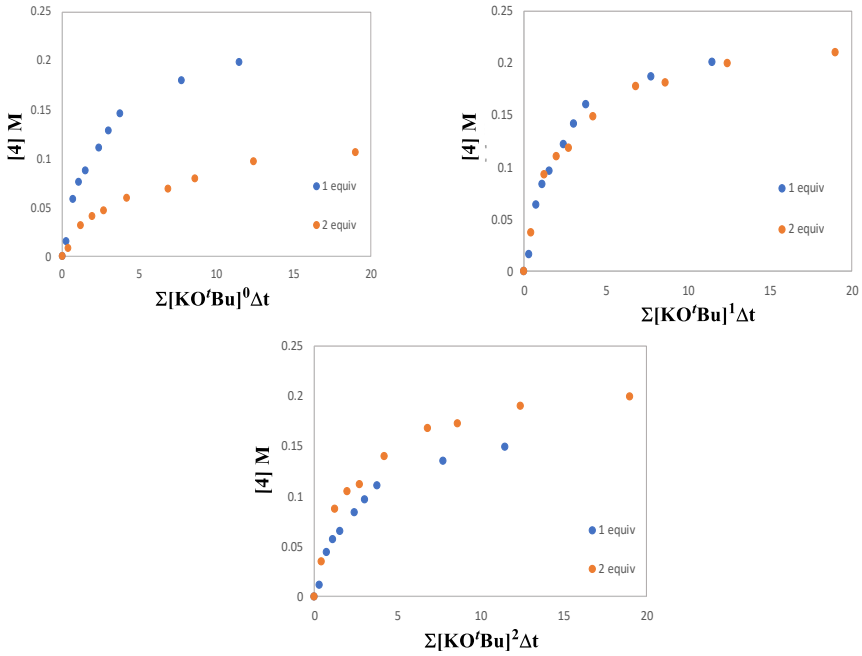
Scheme S9. Variation in catalyst: Variable time normalization plots suggest first order dependency.



Scheme S10. Variation in TMDSO: Variable time normalization plots suggest first order dependency.



Scheme S11. Variation in [53]: Variable time normalization plots suggest first order dependency.

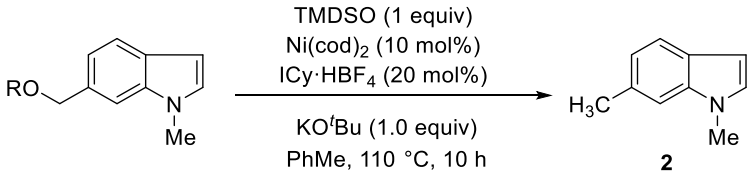


Scheme S12. Variation in KO^{t}Bu: Variable time normalization plots suggest first order dependency. Poor overlay was observed at higher concentrations of KO^{t}Bu further, possibly due to sparing solubility of KO^{t}Bu in toluene.

6.4. Reduction of proposed intermediates

To probe the catalytic reaction of benzyl alcohols, various indole-bearing alcohol derivatives were subjected to the reducing conditions to determine if this step of the reaction behaved differently in isolation (Table S9). Using 1.0 equivalents of TMDSO provided indole **2** in 58% yield (entry 1). Use of 0.6 equivalents TMDSO (formally 1.2 equivalents of hydride) gave a slightly lower yield (entry 2). As was the case in the direct reduction starting from the ester, both Ni and KO^{t}Bu were required for conversion (entry 3). In contrast to when using ester as a starting material, the base was only required in catalytic quantity (entry 4). Reactions performed using TBS, TMS, and Me protected alcohols led to a higher yield than that which was obtained when using the unprotected analog (Table S9, entries 5-7). These species are more analogous to the mixture of silyl-alcohol species that are believed to form in situ via ester hydrosilylation.

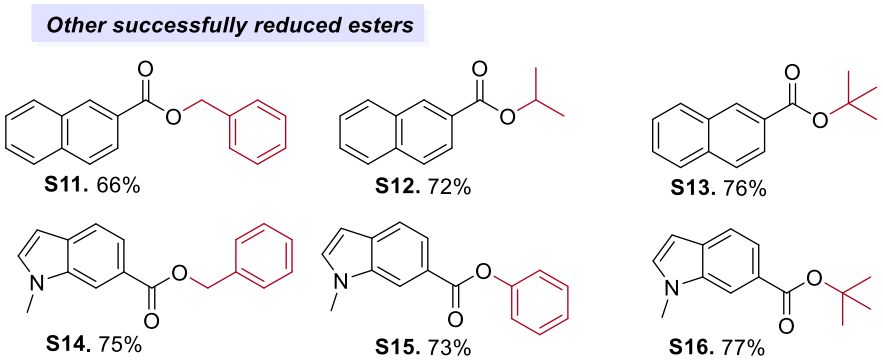
Table S9. Reduction of a benzyl alcohol intermediate



entry	R	deviation from standard conditions	yield, 2 [%]
1	R = H	1.0 equiv TMDSO	58
2	R = H	0.6 equiv TMDSO	46
3	R = H	No Ni(cod)$_2$ *or* no KO^{t}Bu	0
4	R = H	20 mol% KO^{t}Bu	48
5	R = TBS	1.0 equiv TMDSO	74
6	R = TMS	1.0 equiv TMDSO	71
7	R = Me	1.0 equiv TMDSO	77

6.5. Reduction of other alkyl and aryl esters

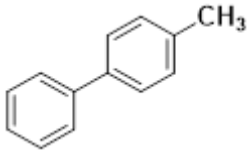
The following esters were reduced according to general procedure A, confirming that the reaction is not limited to just the reduction of methyl esters (Scheme S14). Both ester-bearing naphthalene species (**S11-S13**) and ester-bearing indole species (**S14-S16**) were tested.

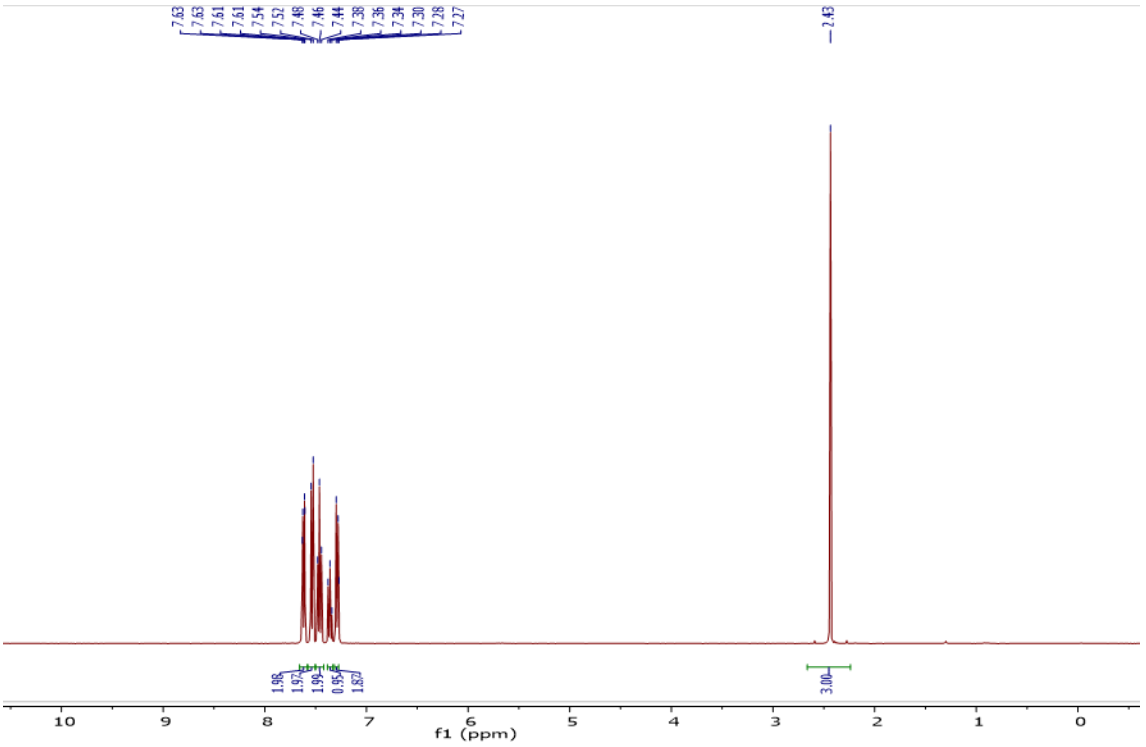


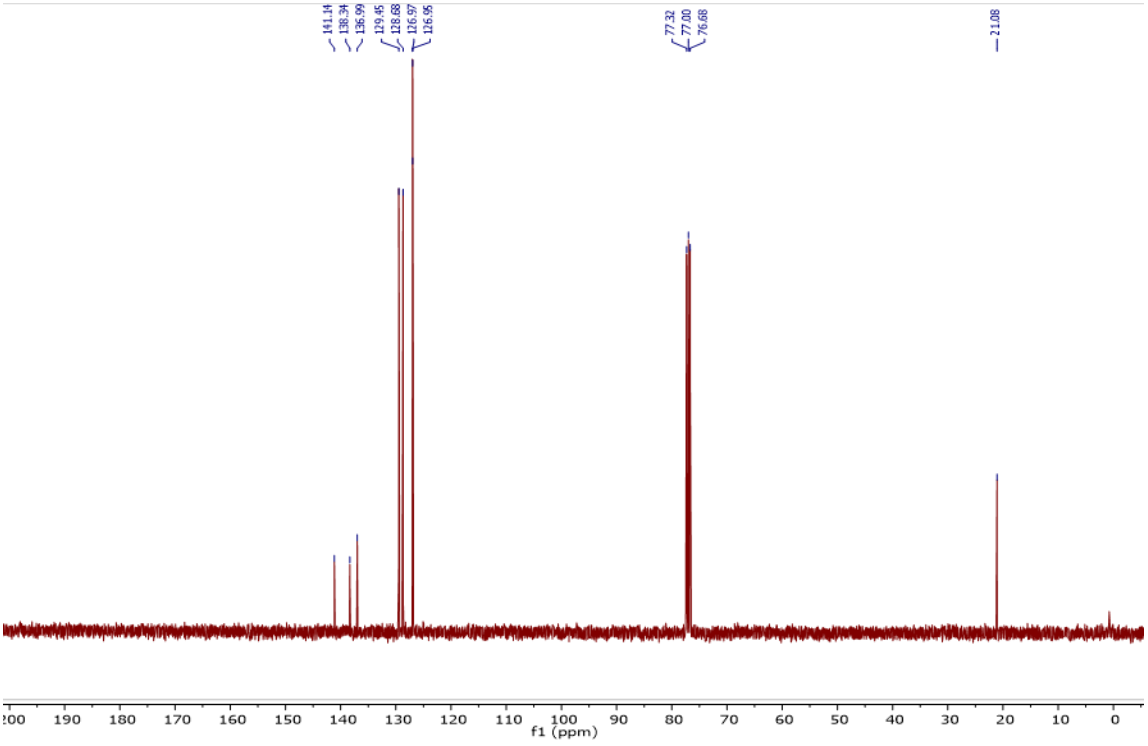
Scheme S14. Depicting the types of esters that could be reduced according to general procedure A

8. NMR Spectra

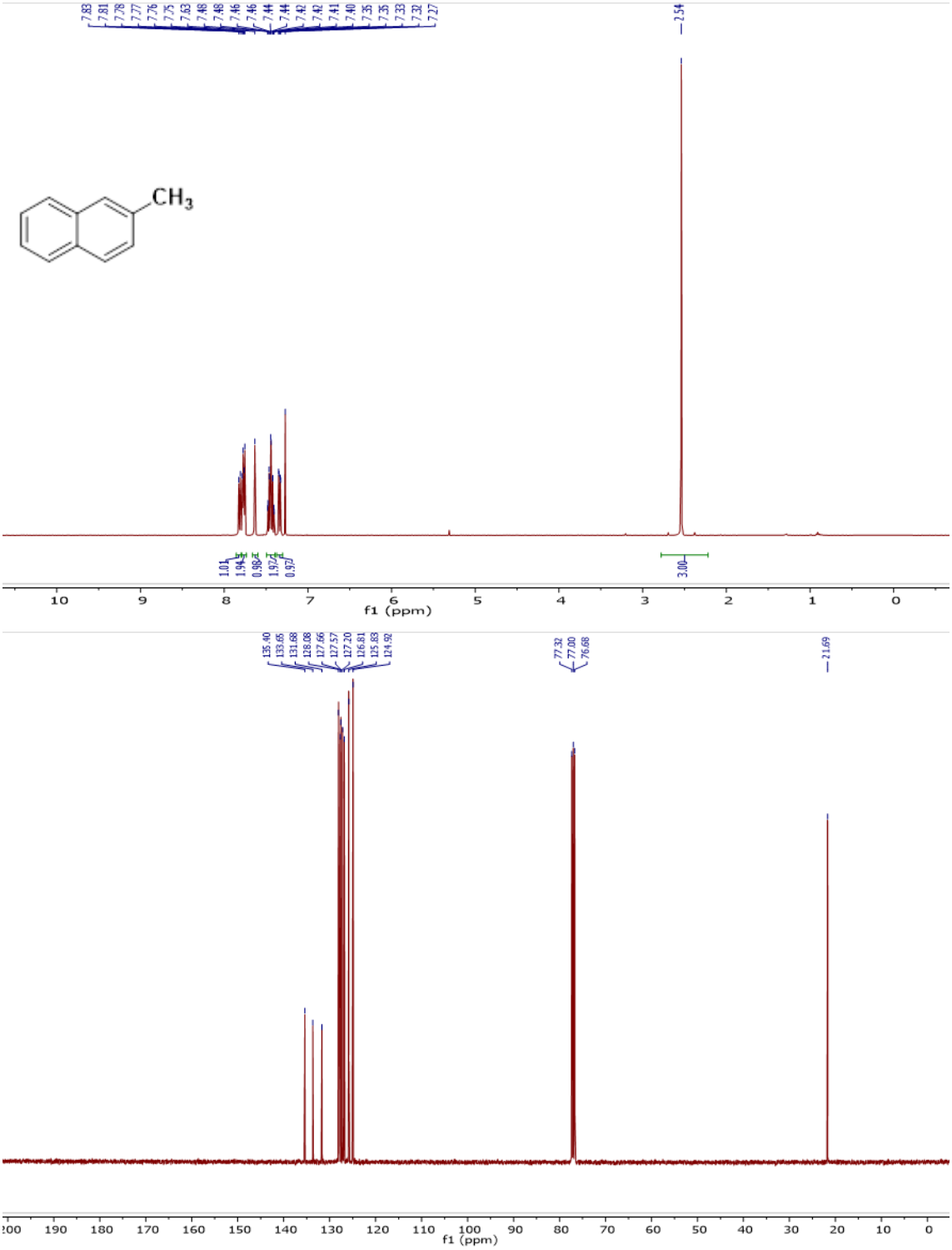
1-Methyl-4-phenylbenzene **3** ($CDCl_3$, 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR)



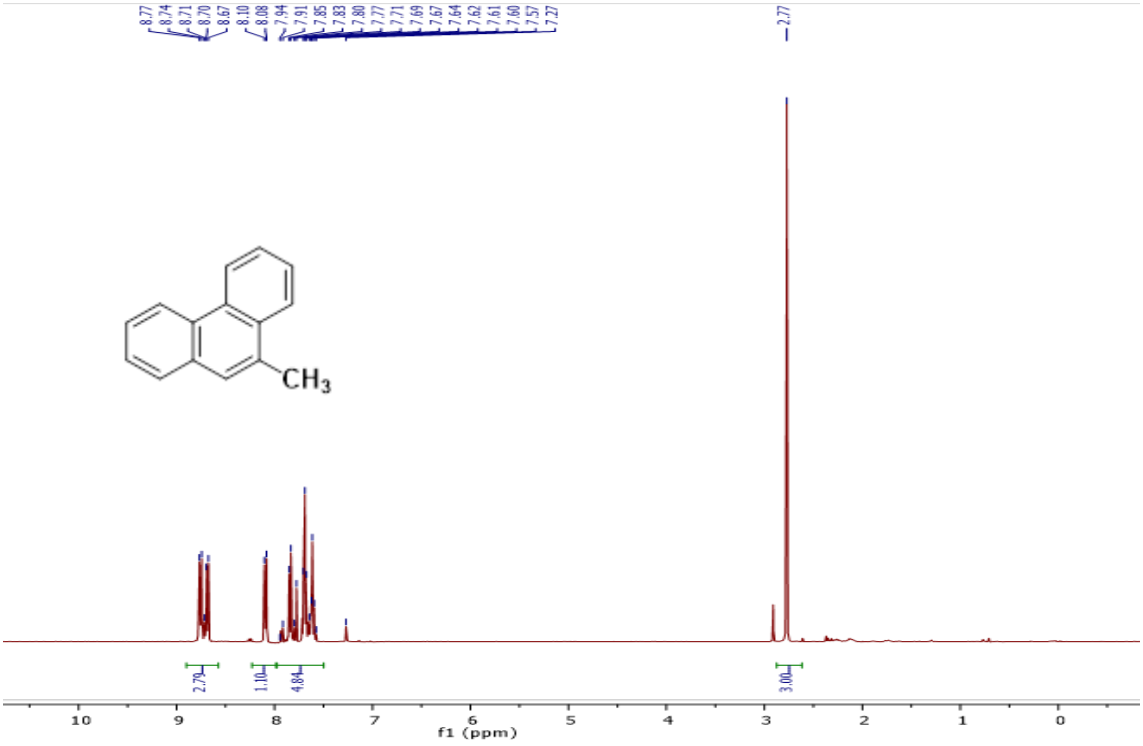

7.63
7.63
7.61
7.61
7.54
7.52
7.48
7.46
7.44
7.38
7.36
7.34
7.30
7.28
7.27
2.43
1.98
1.97
1.99
0.95
1.87
3.00
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

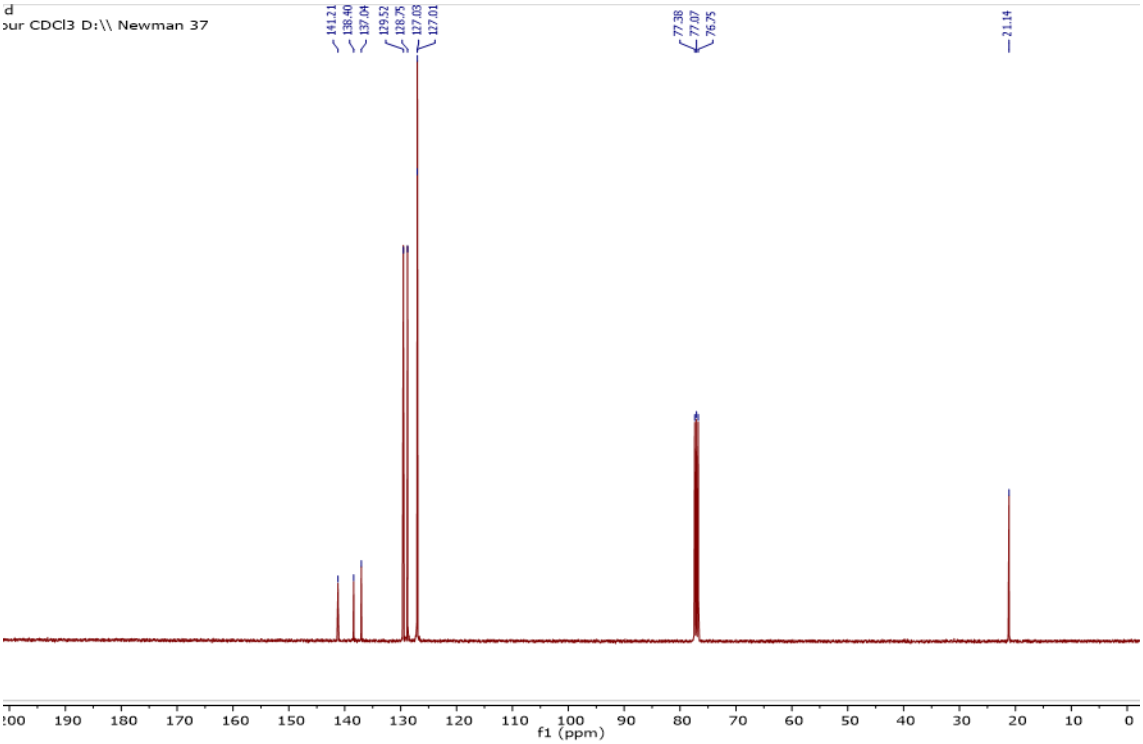

141.14
138.34
136.99
129.45
128.68
126.97
126.95
77.32
77.00
76.68
21.08
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

2-Methylnaphthalene **4** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)

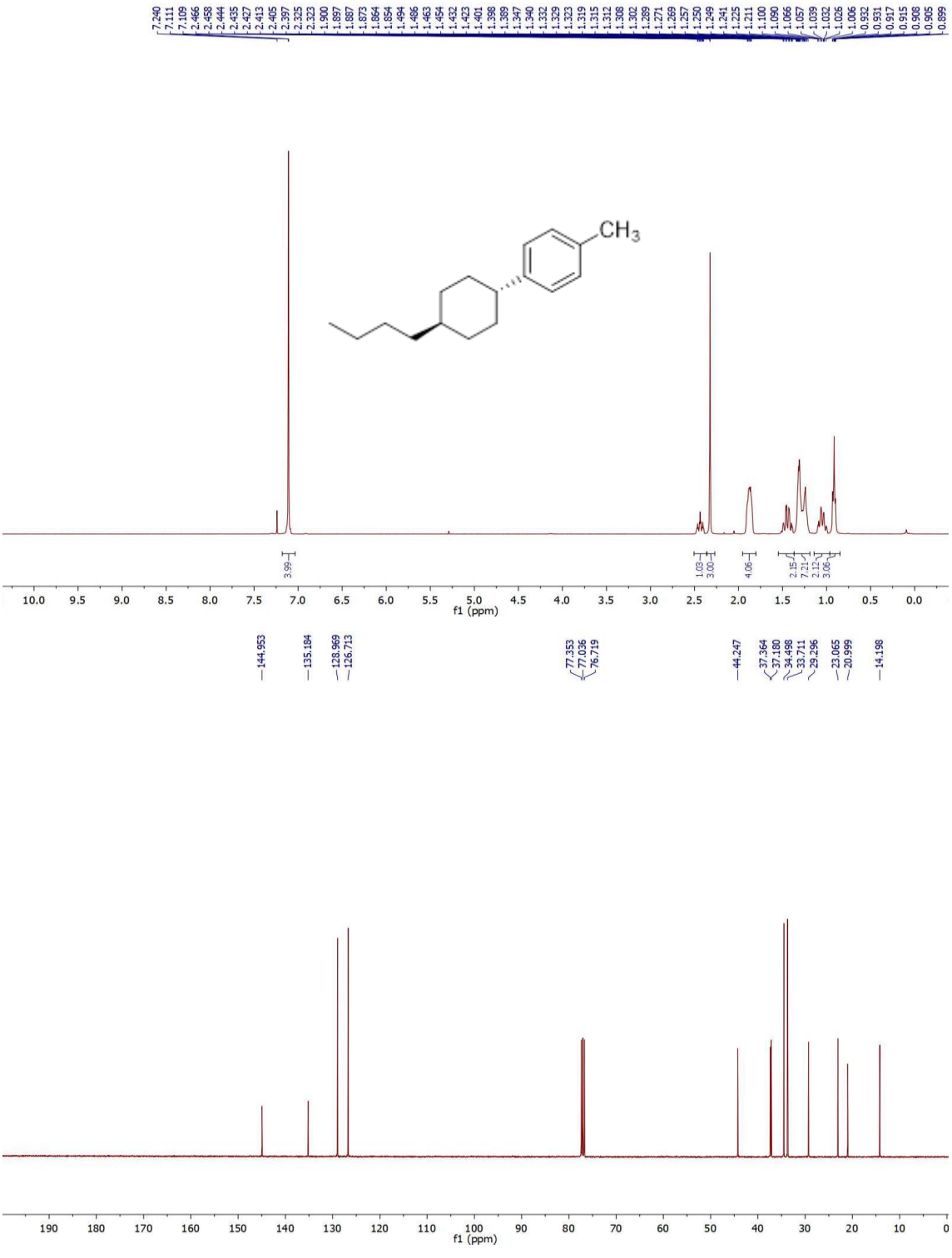


9-Methylphenanthrene **5** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)

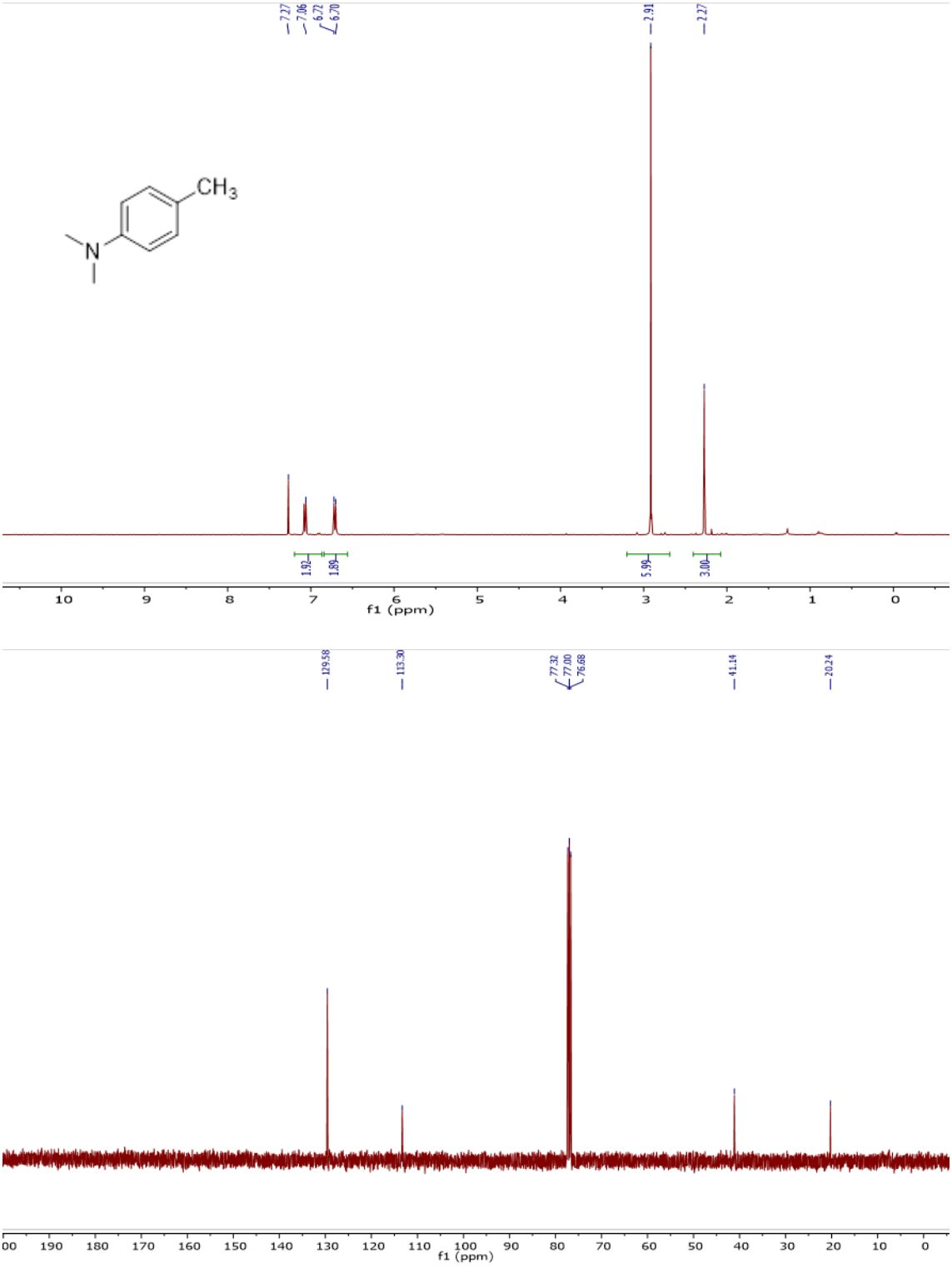




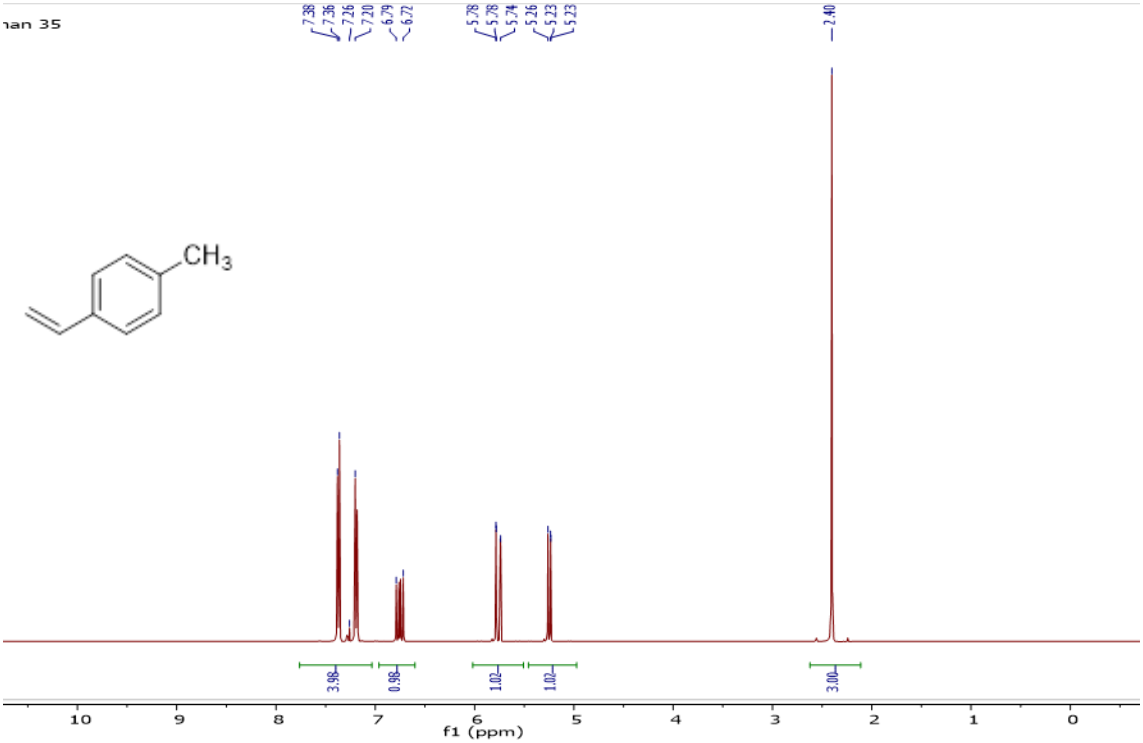
1-(*trans*-4-butylcyclohexyl)-4-methylbenzene **6** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)

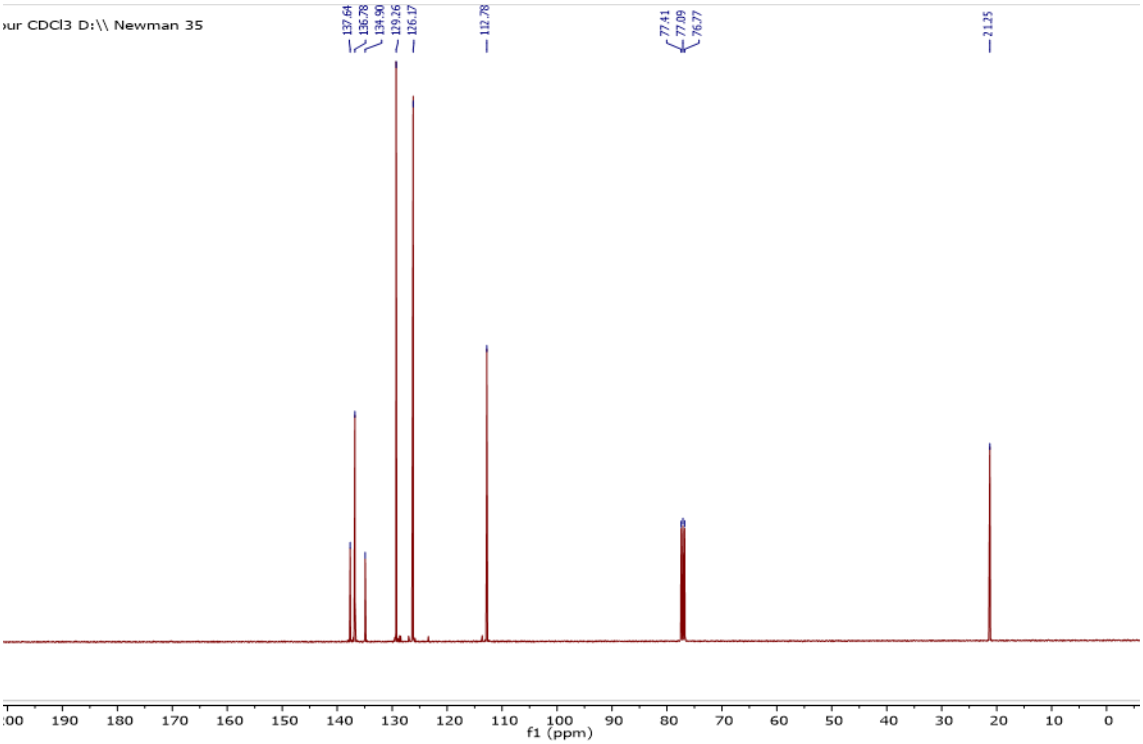


1-Methyl 4-dimethylamino benzene **7** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)

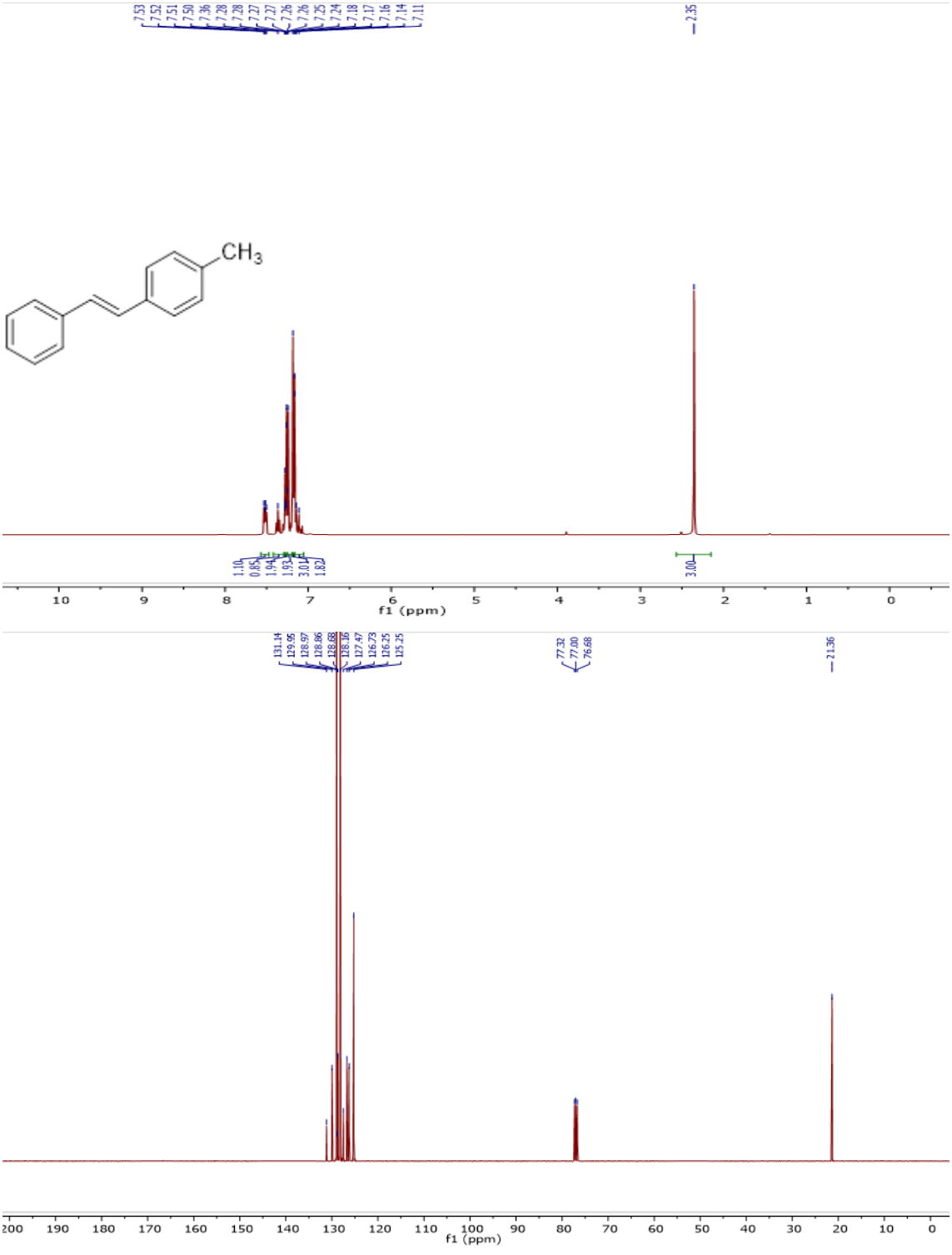


1-Methyl-4-vinylbenzene **8** ($CDCl_3$, 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR)

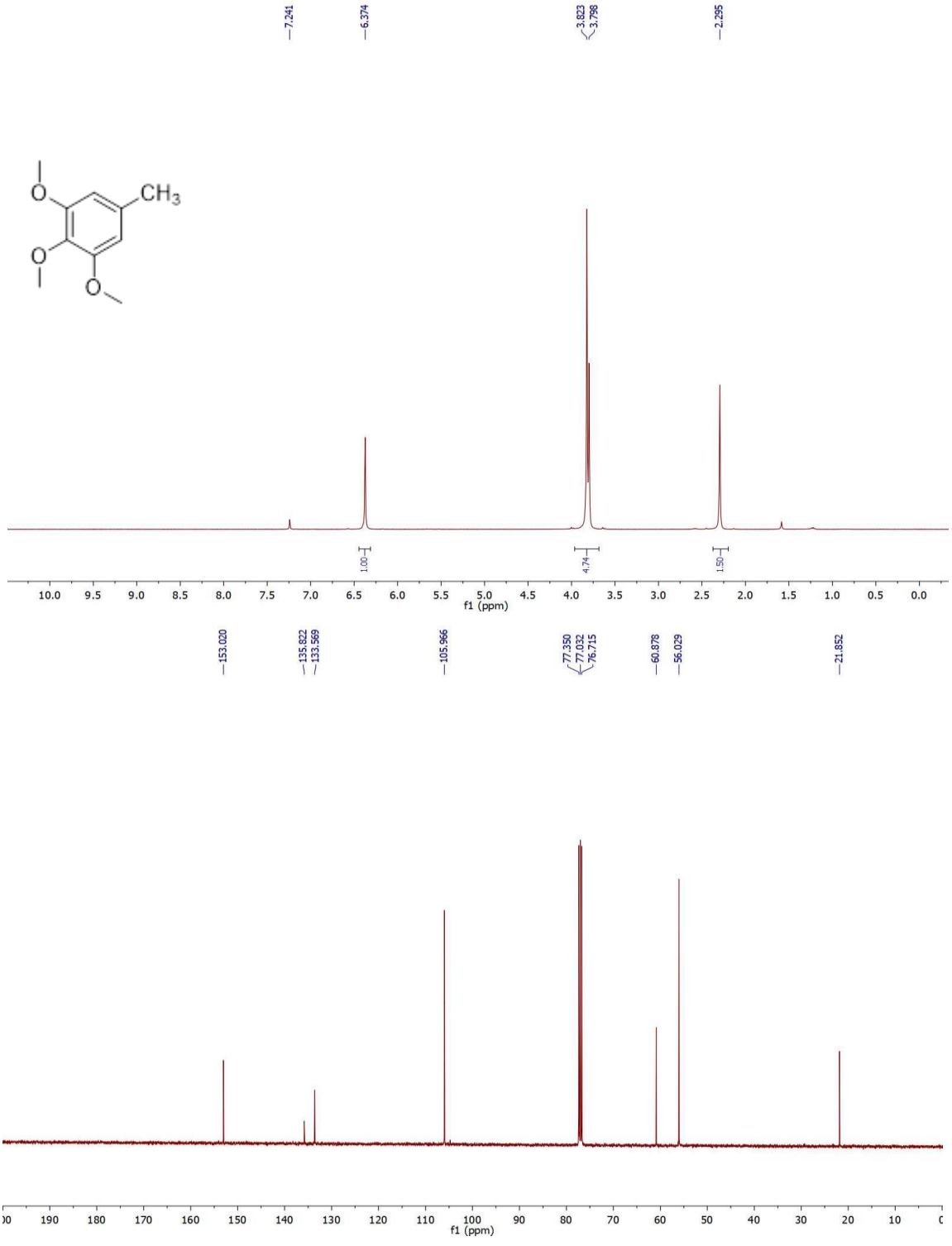




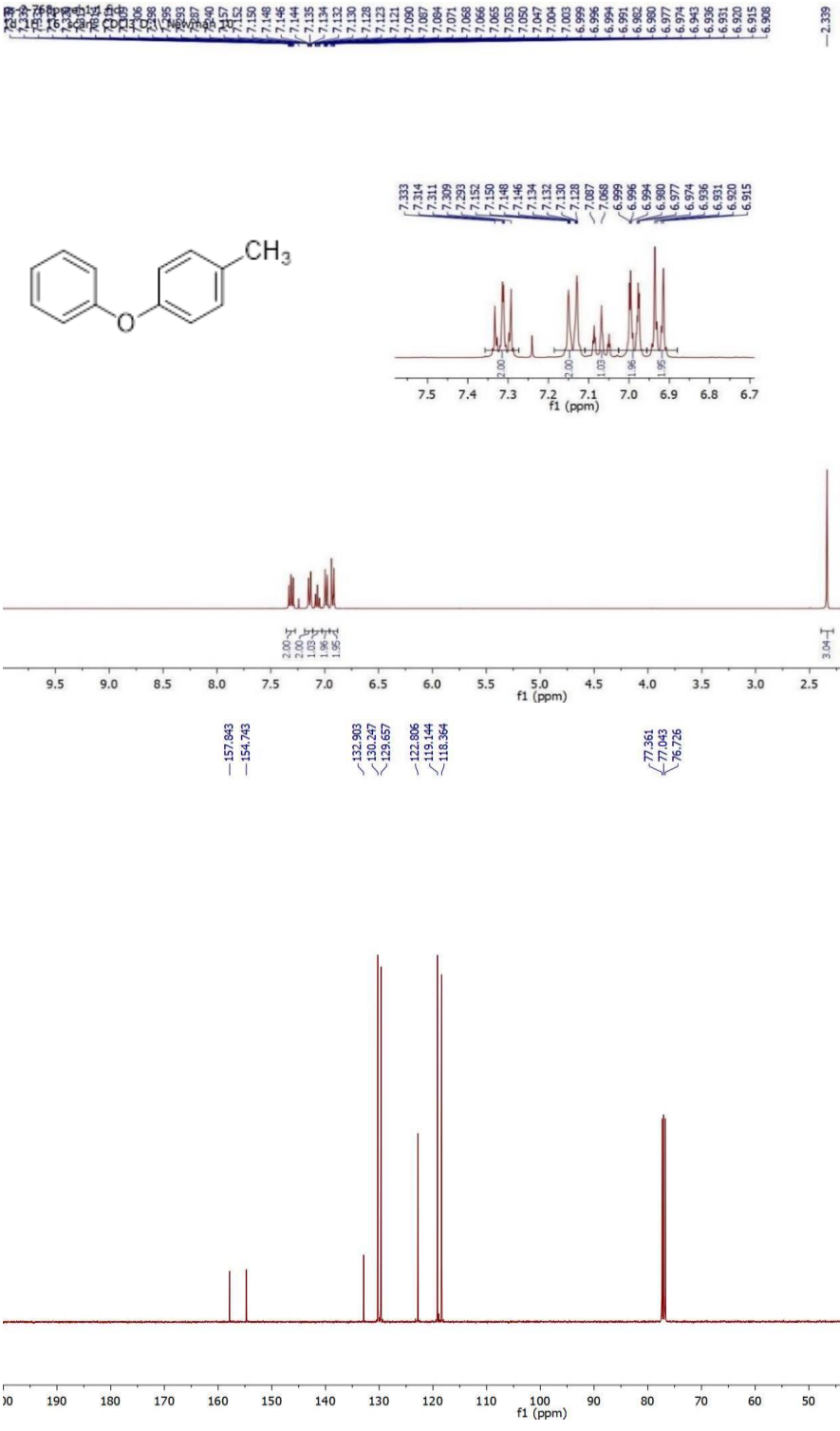
1-Methyl-4-(2-phenylethenyl)benzene **9** ($CDCl_3$, 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR)



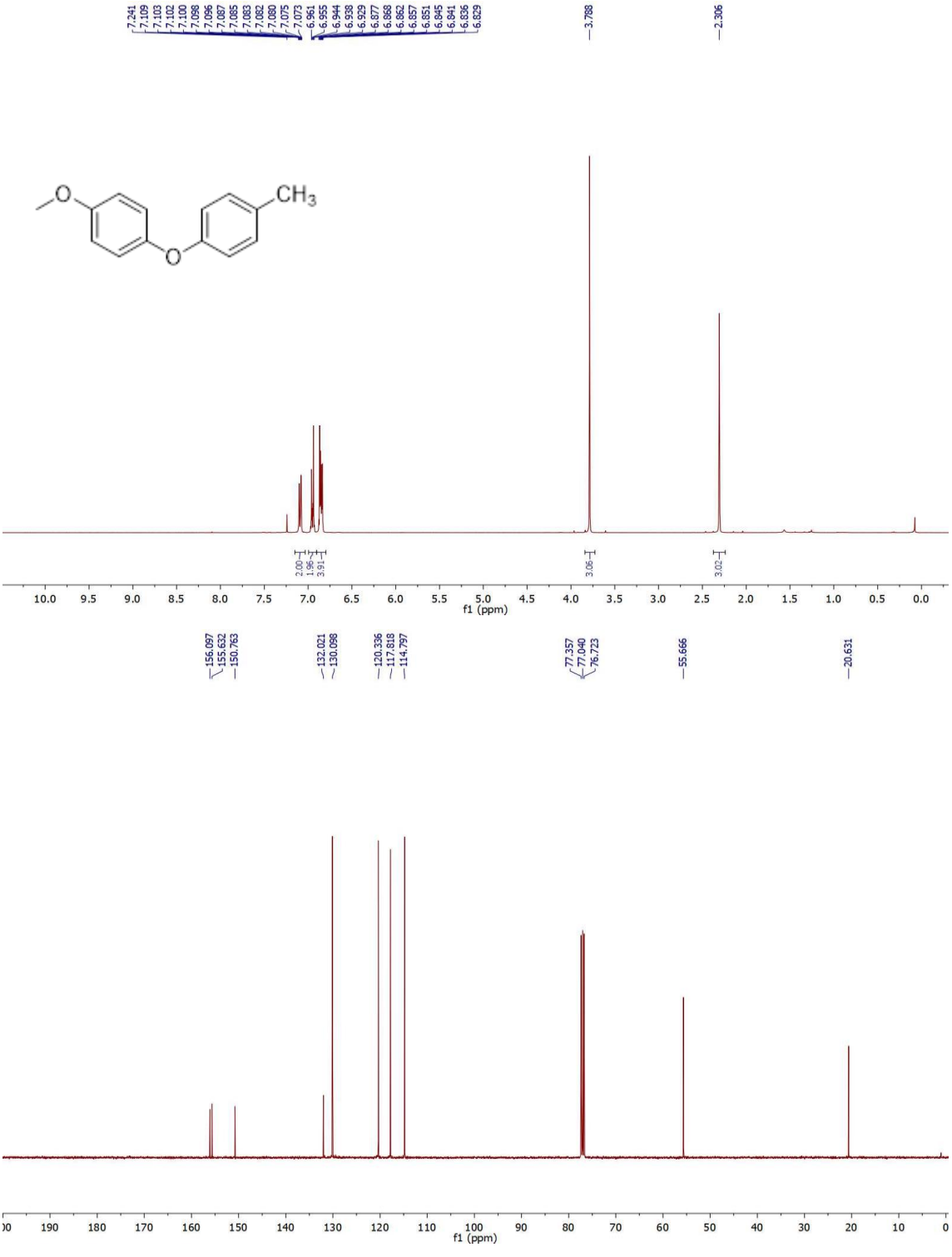
1,2,3-Trimethoxy-5-methylbenzene **1** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



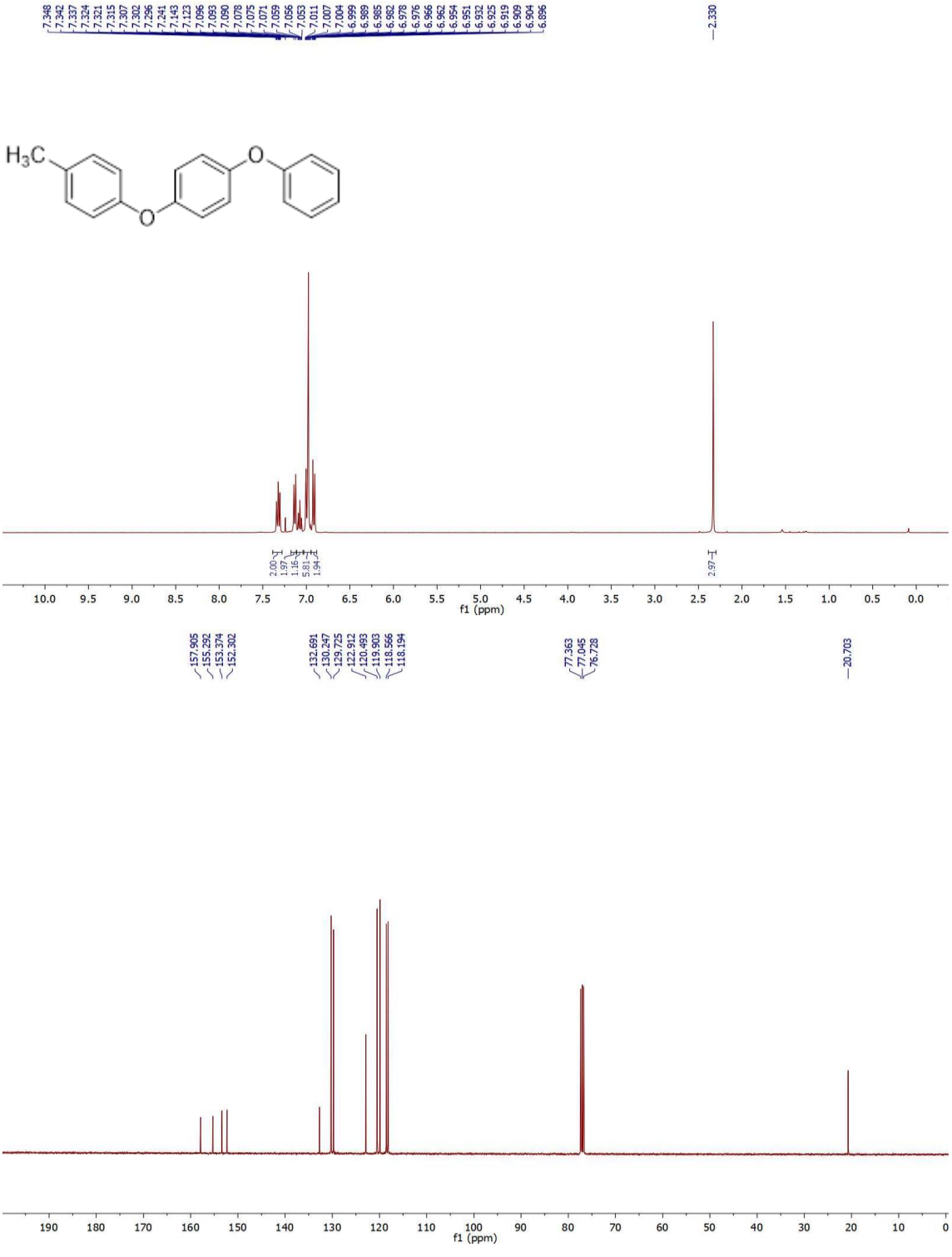
1-Methyl-4-phenoxybenzene **11** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



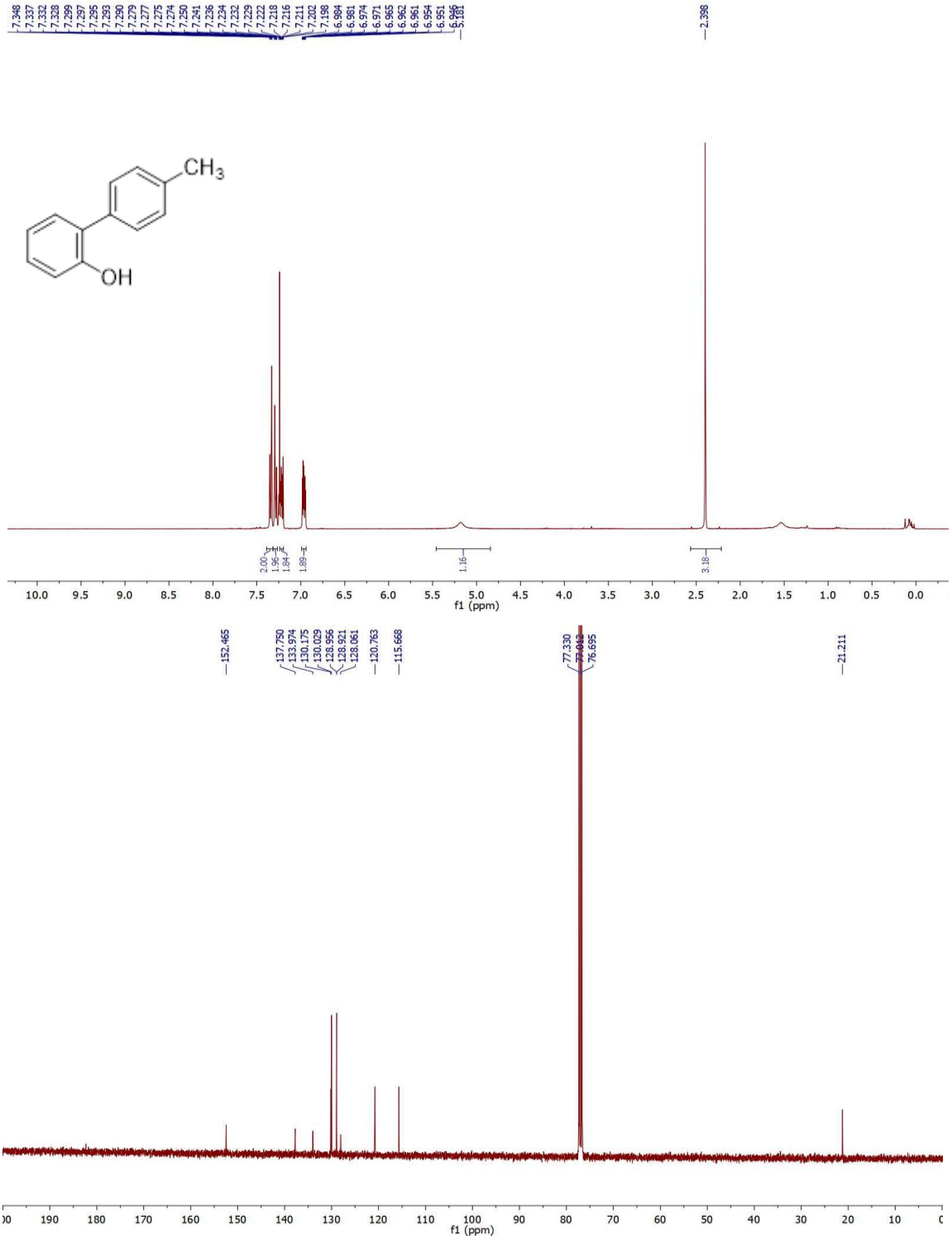
1-Methoxy-4-(4-methylphenoxy)benzene **12** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



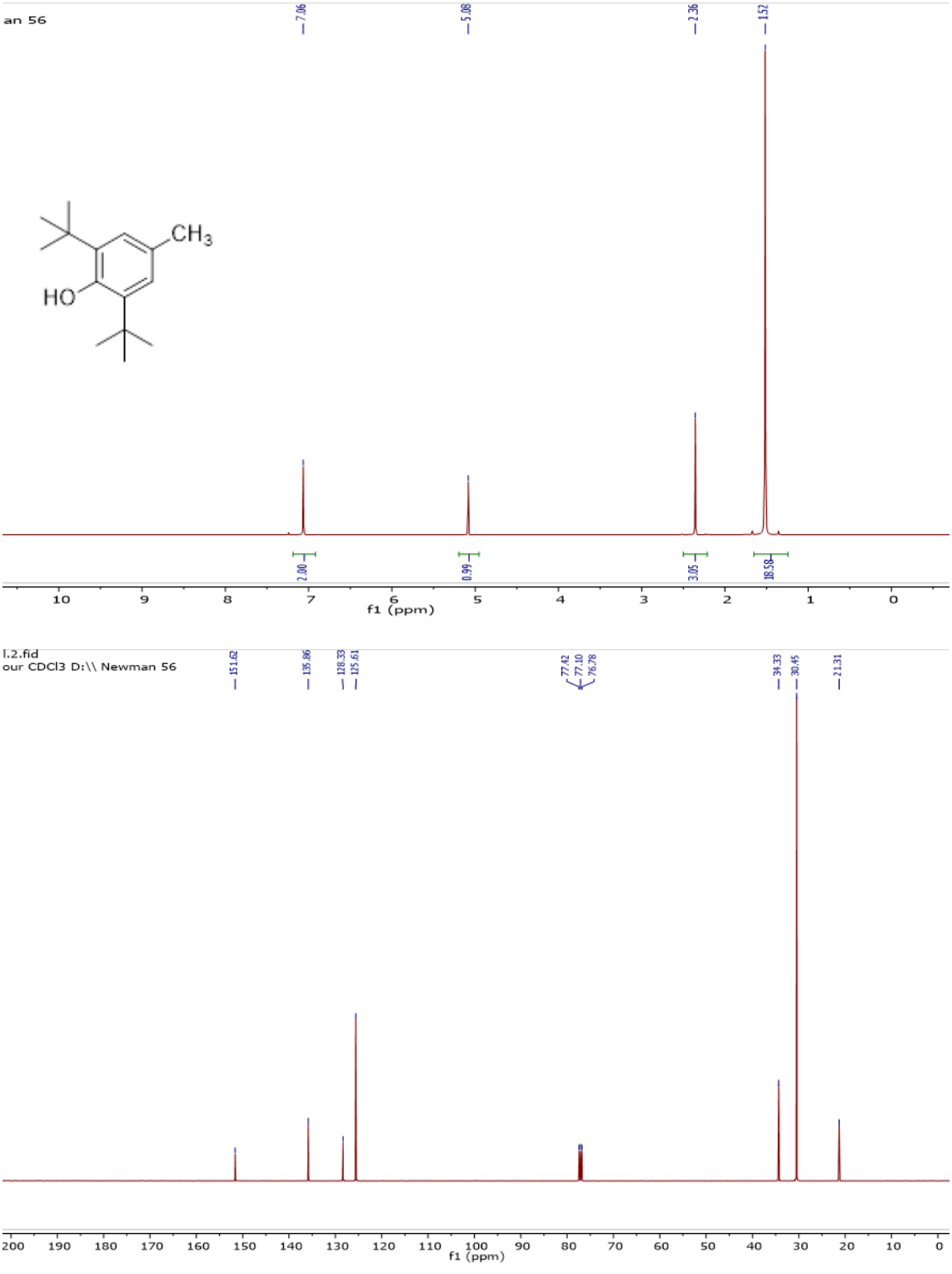
1-(4-Methylphenoxy)-4-phenoxybenzene **13** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



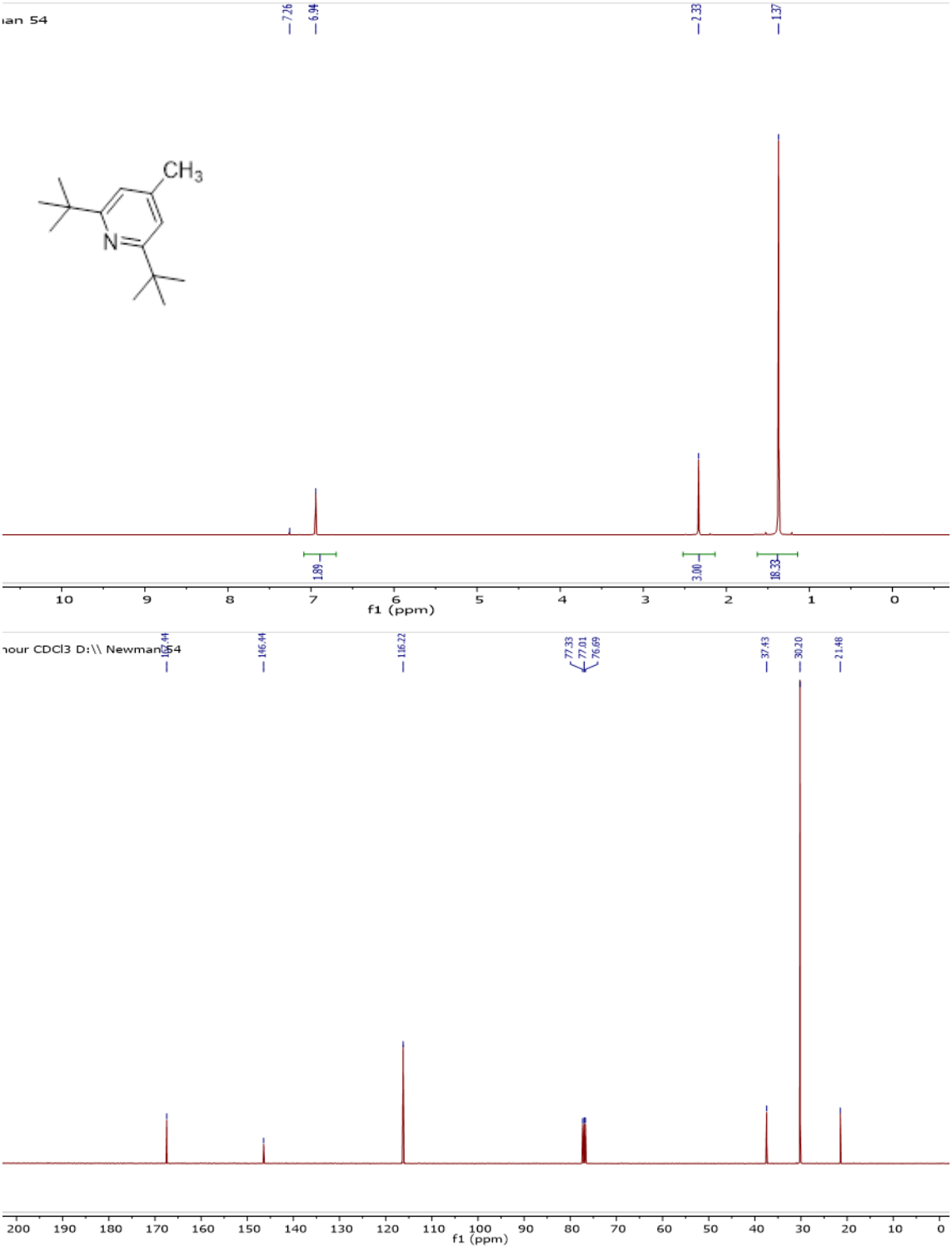
4'-Methyl-[1,1'-biphenyl]-2-ol **14** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



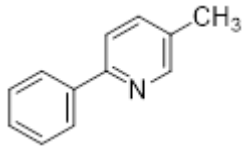
2,6-Bis(1,1-dimethylethyl)-4-methylphenol **15** ($CDCl_3$, 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR)

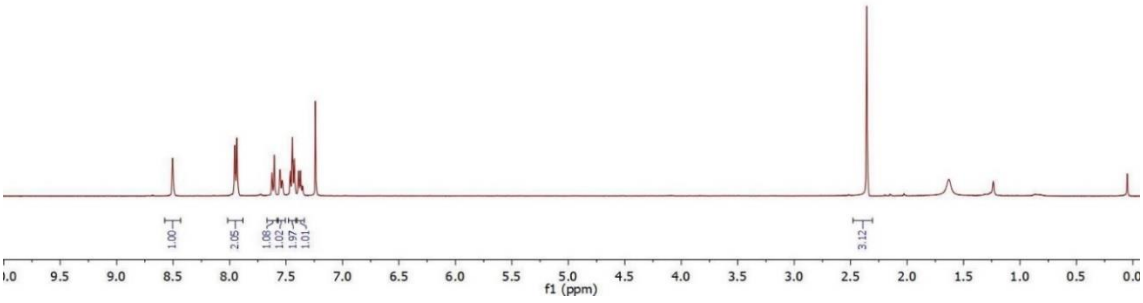


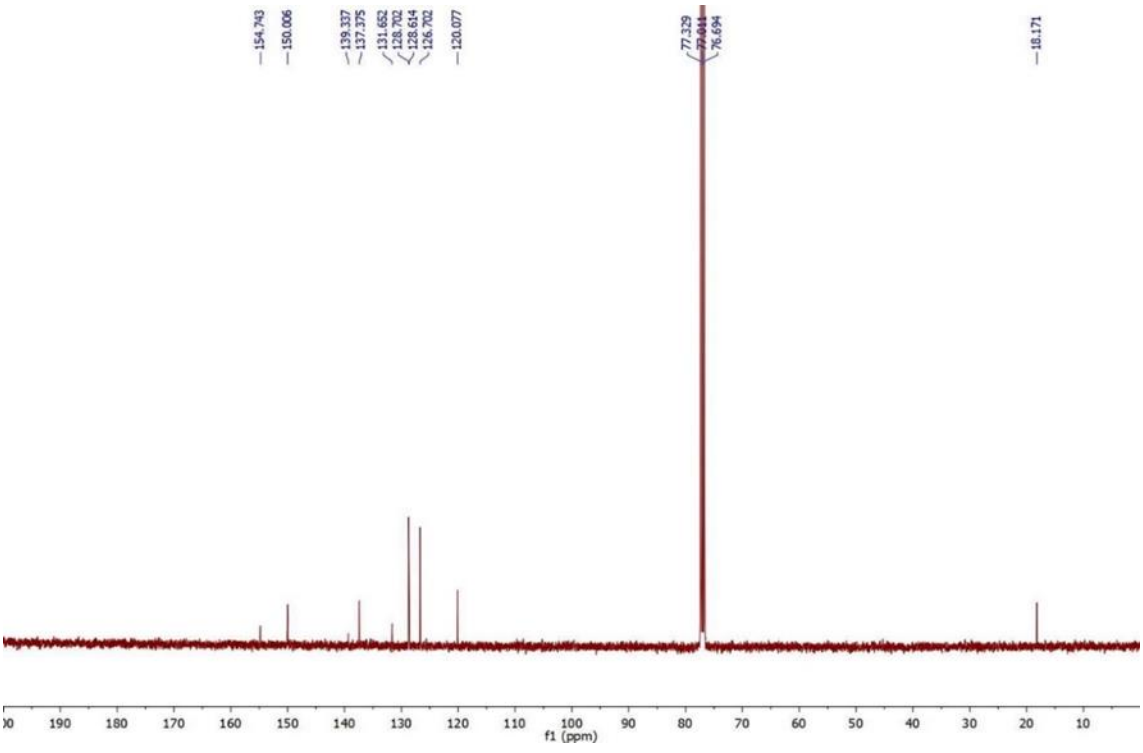
2,6-Bis(1,1-dimethylethyl)-4-methylpyridine **16** ($CDCl_3$, 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR)



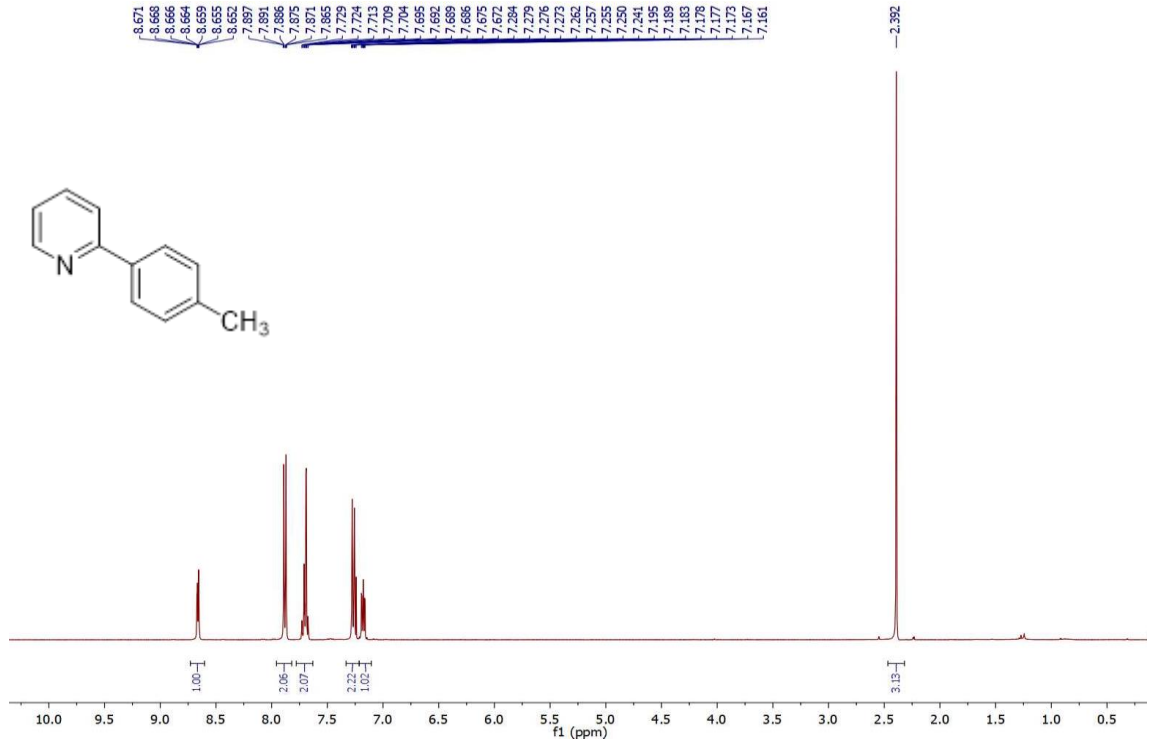
5-Methyl-2-phenylpyridine **17** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)

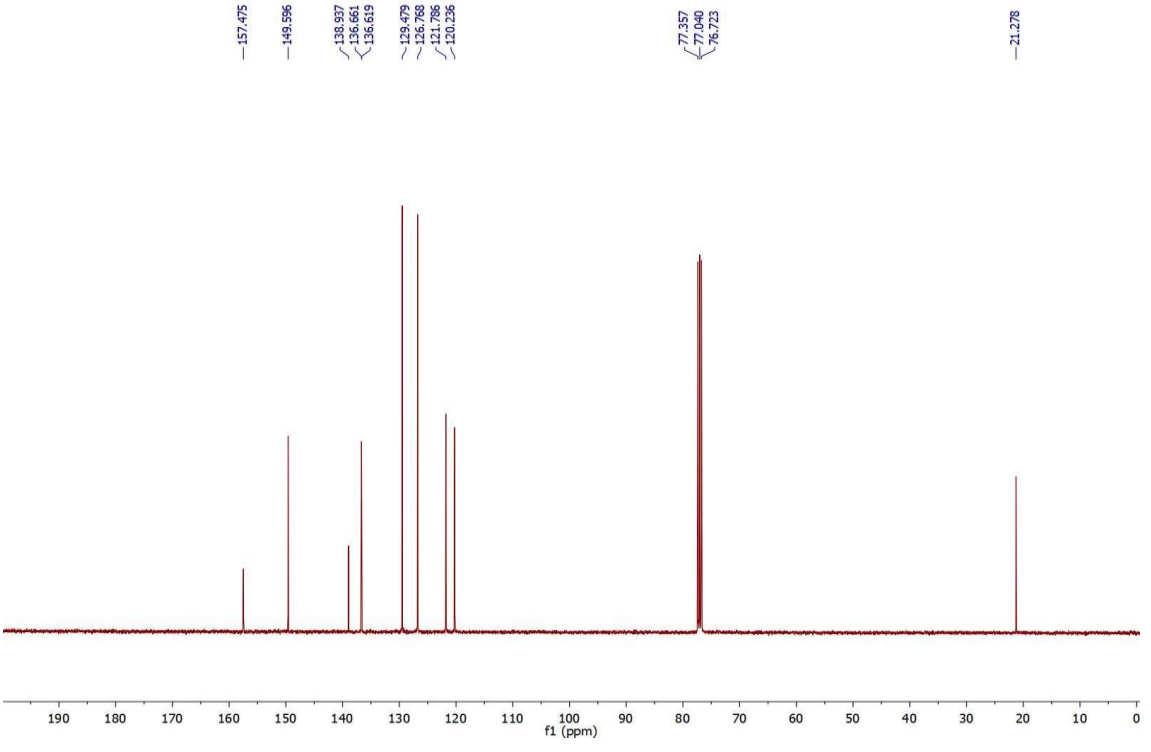




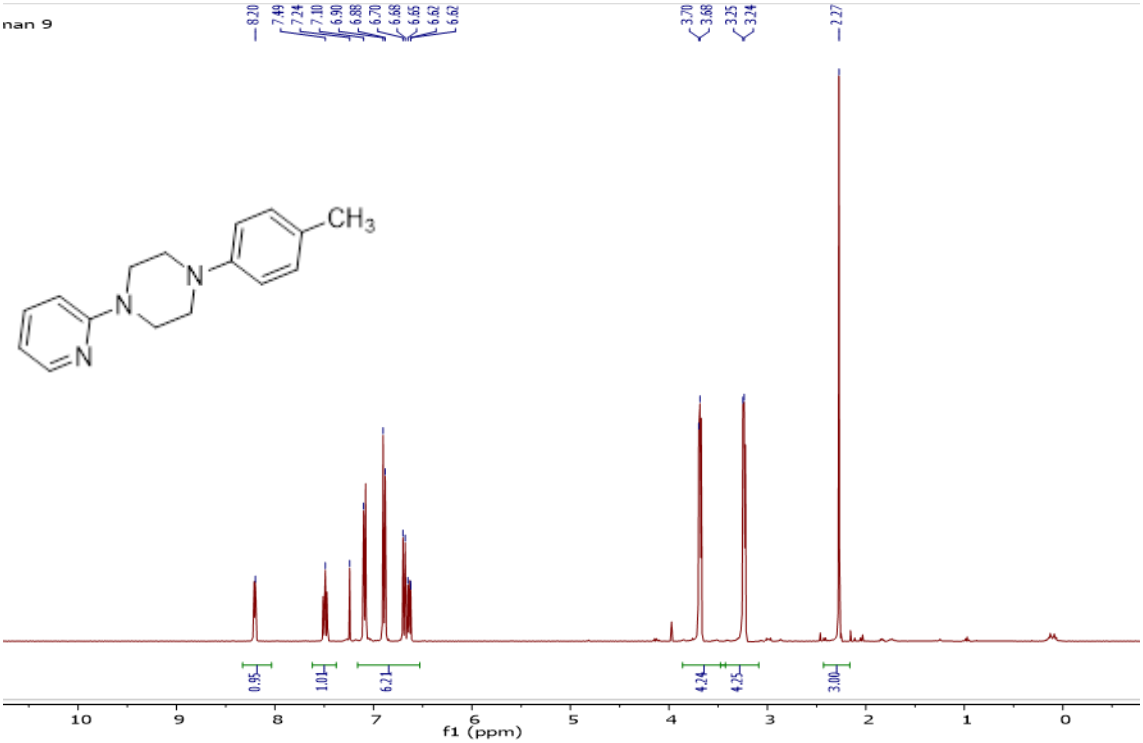


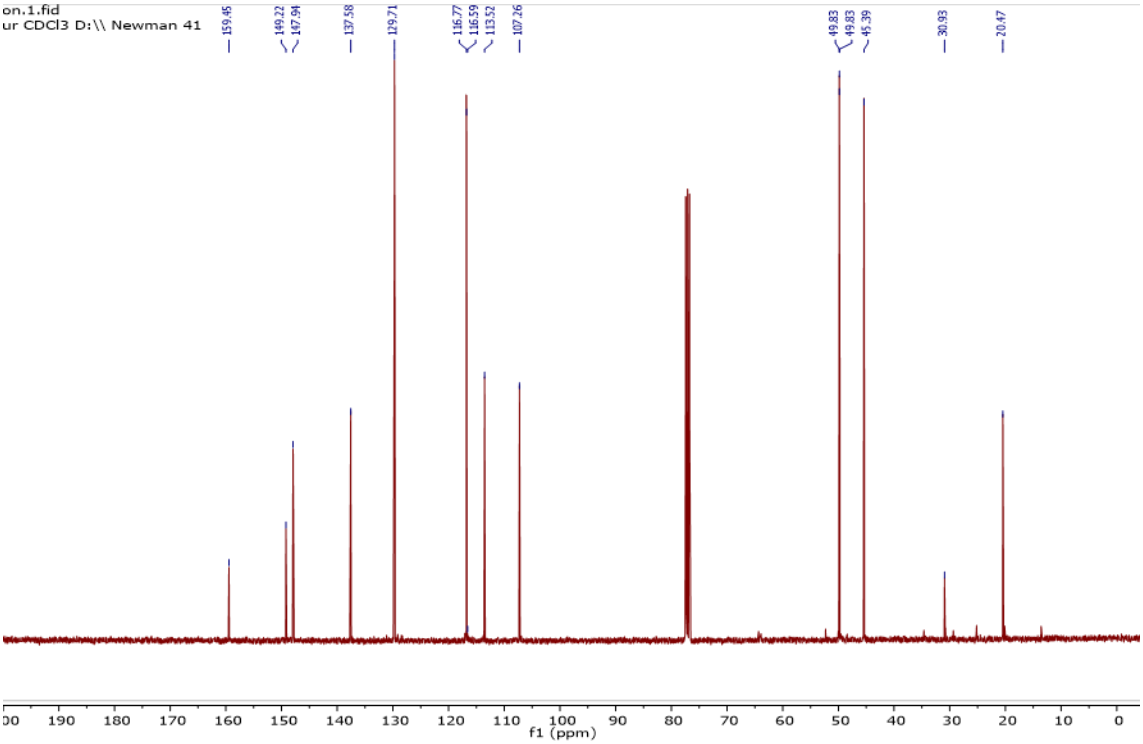
2-(p-Tolyl)pyridine **18** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



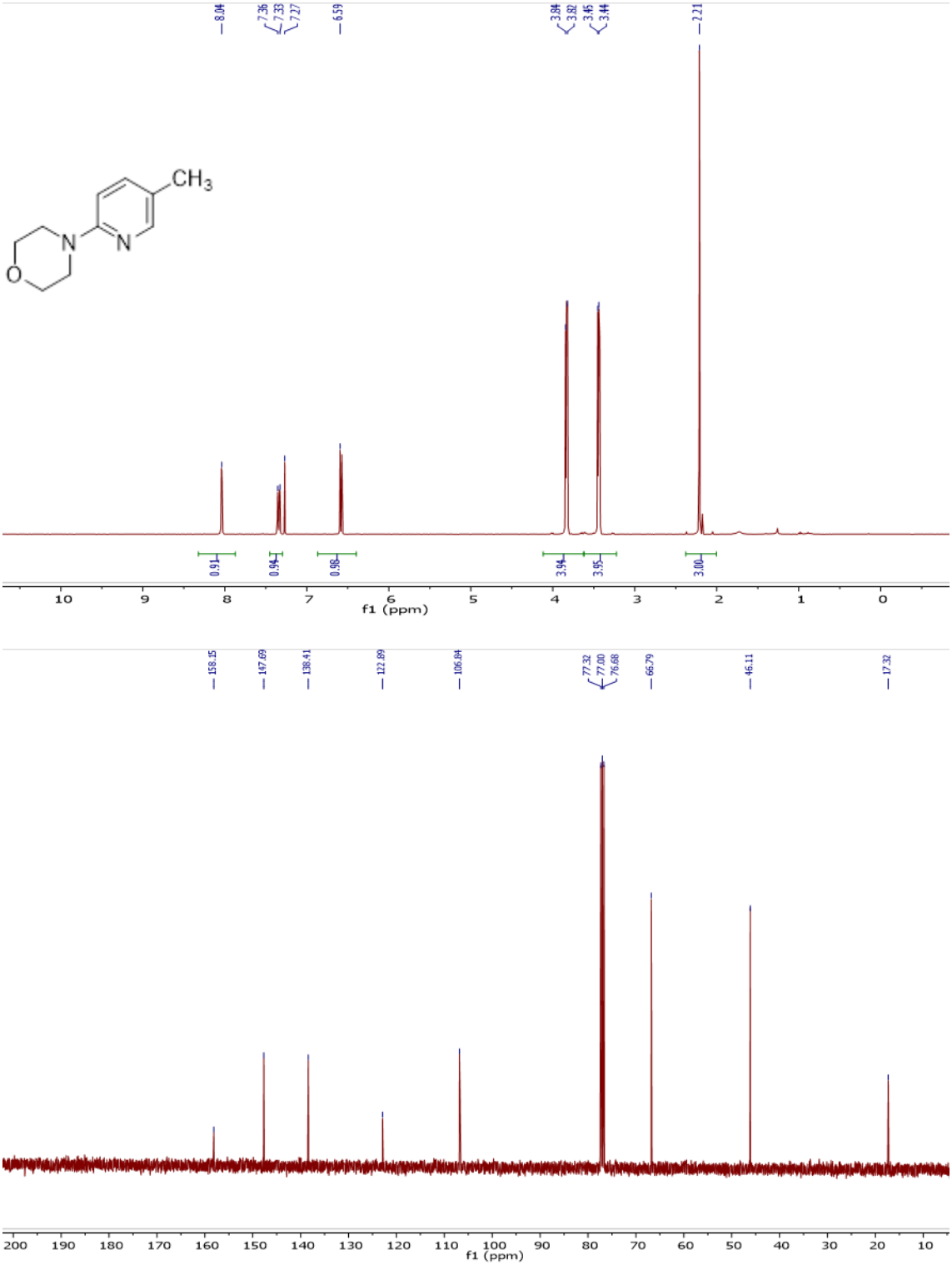


1-(4-Methylphenyl)-4-phenylpiperazine **19** ($CDCl_3$, 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR)

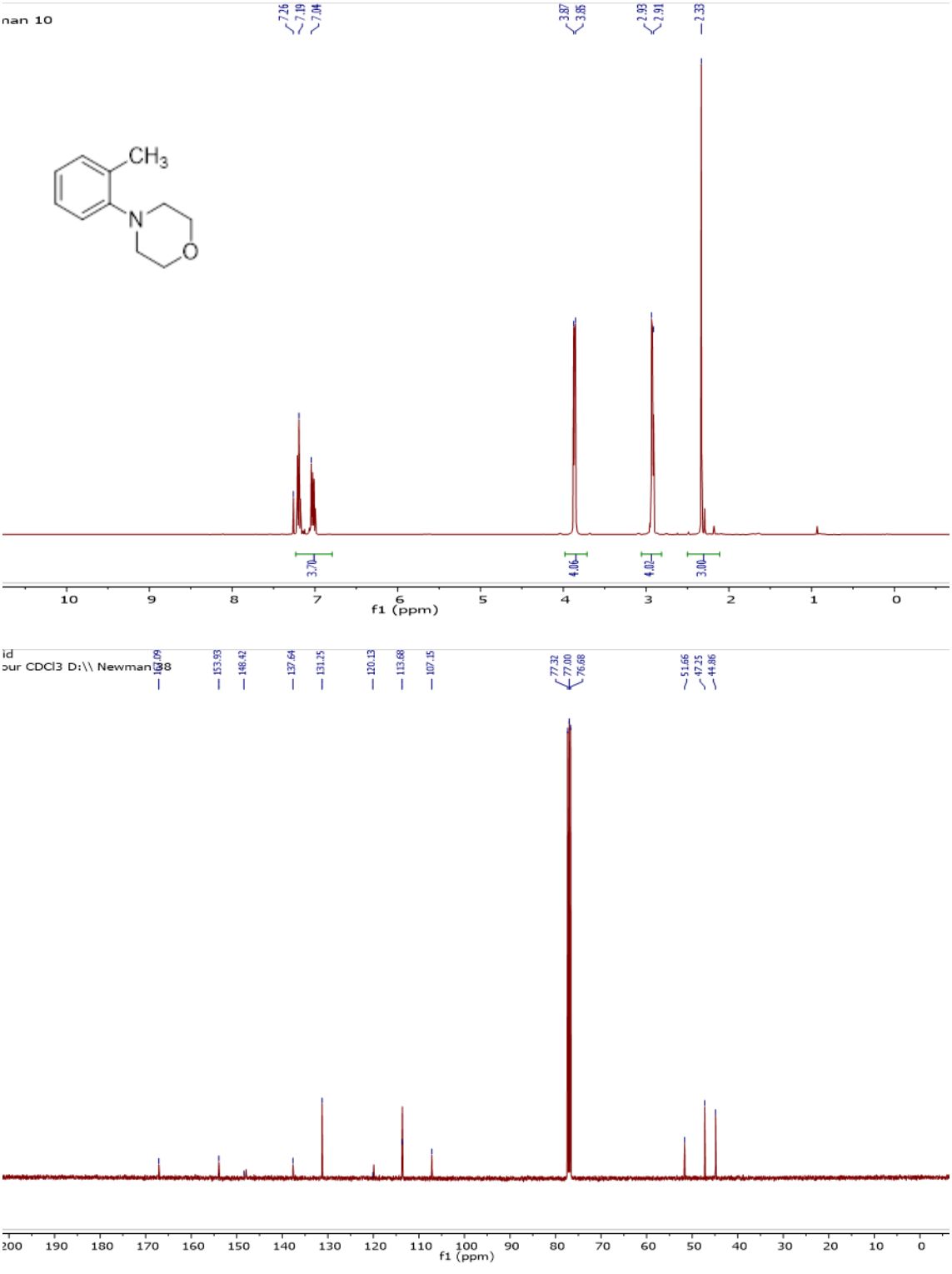




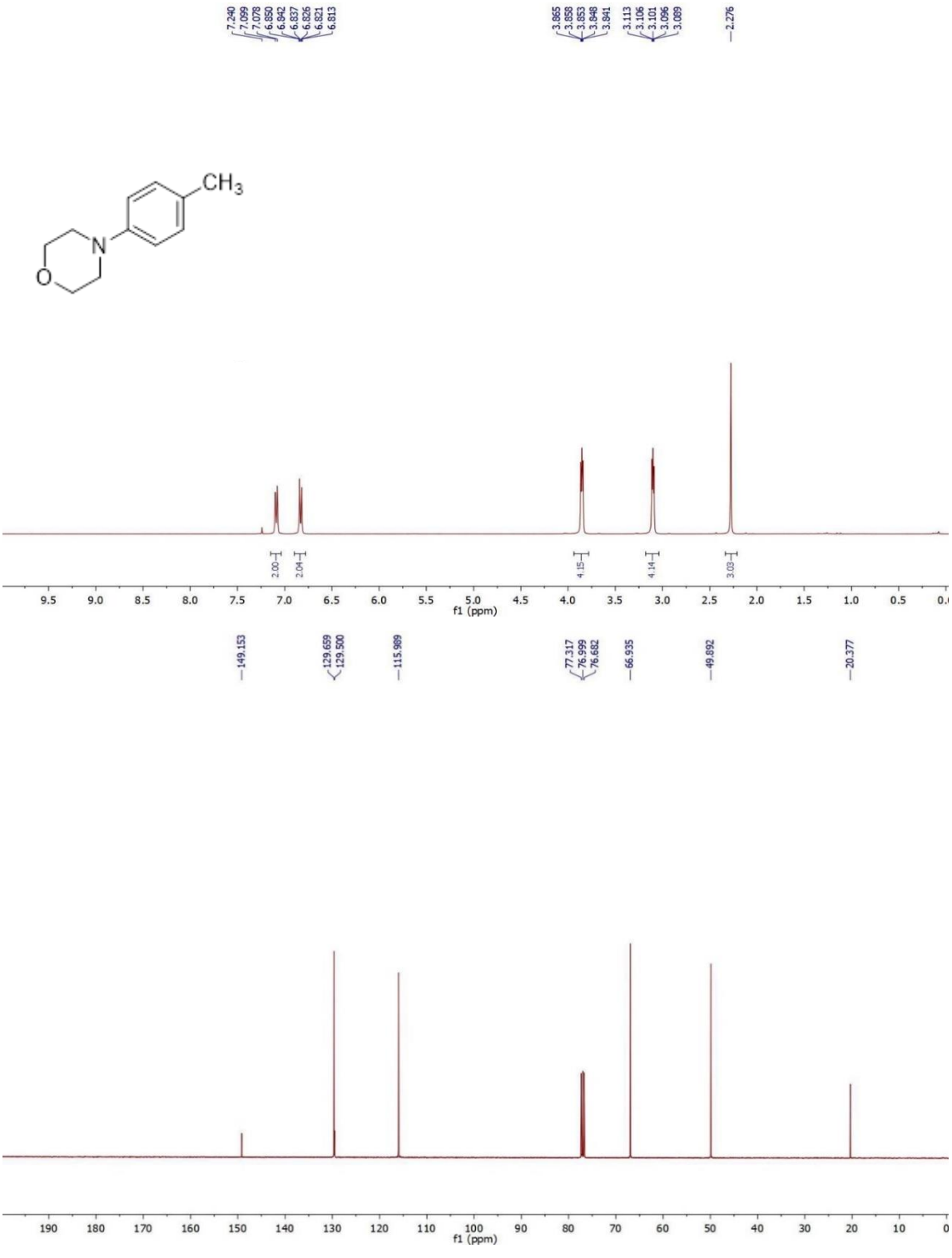
4-(5-Methyl-2-pyridinyl)-morpholine **20** ($CDCl_3$, 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR)



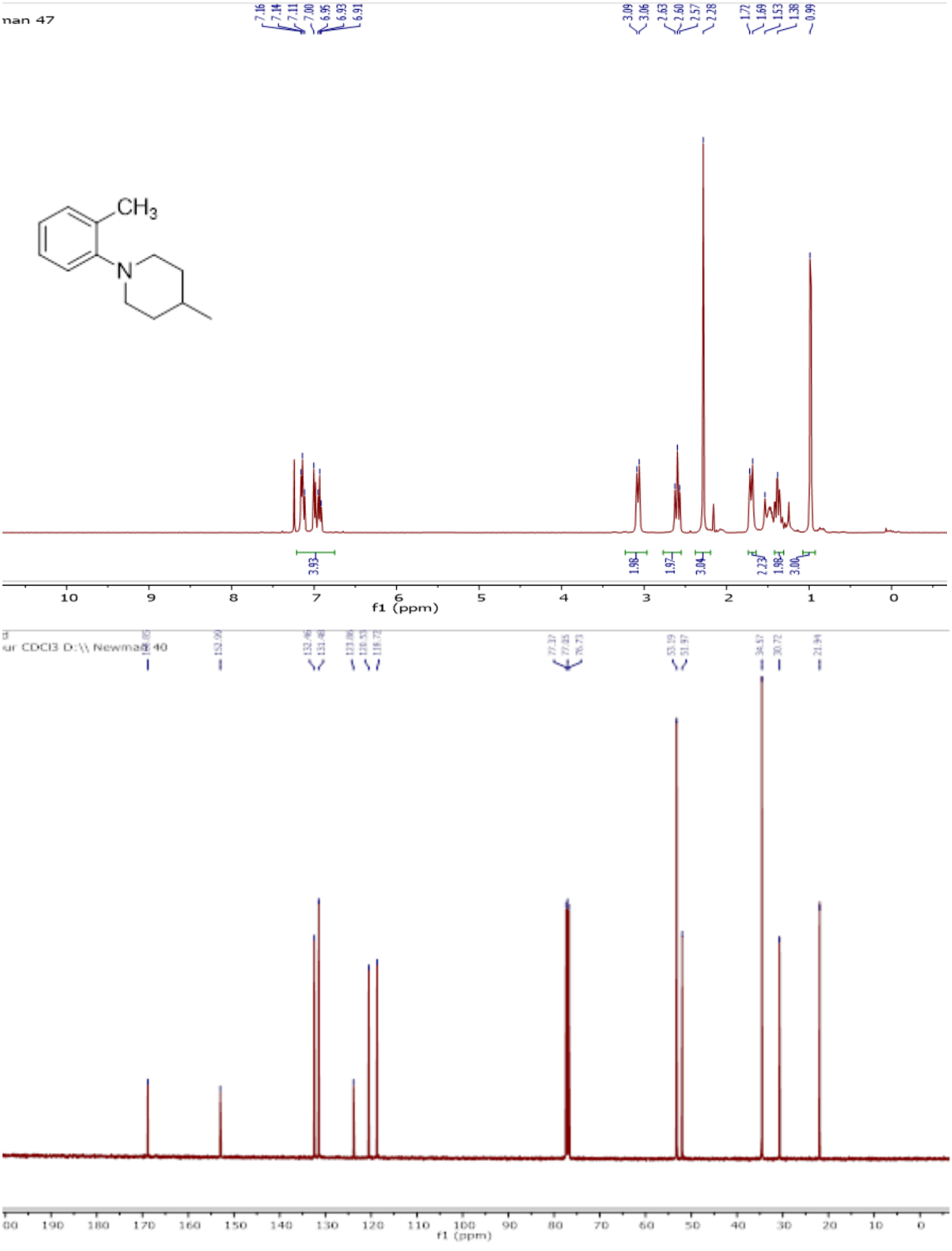
4-(2-Methylphenyl)-morpholine **21** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



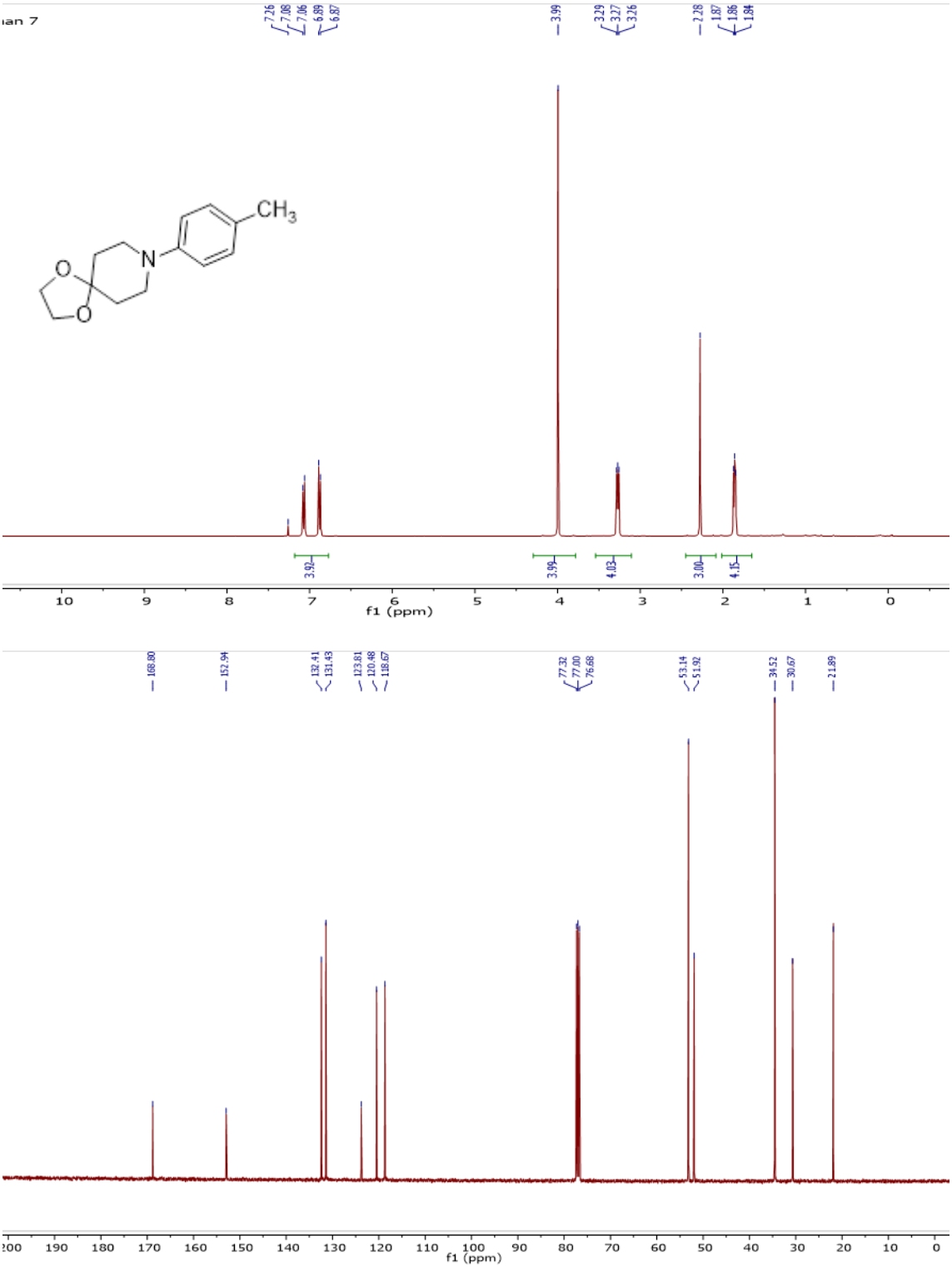
4-(p-Tolyl)morpholine **22** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



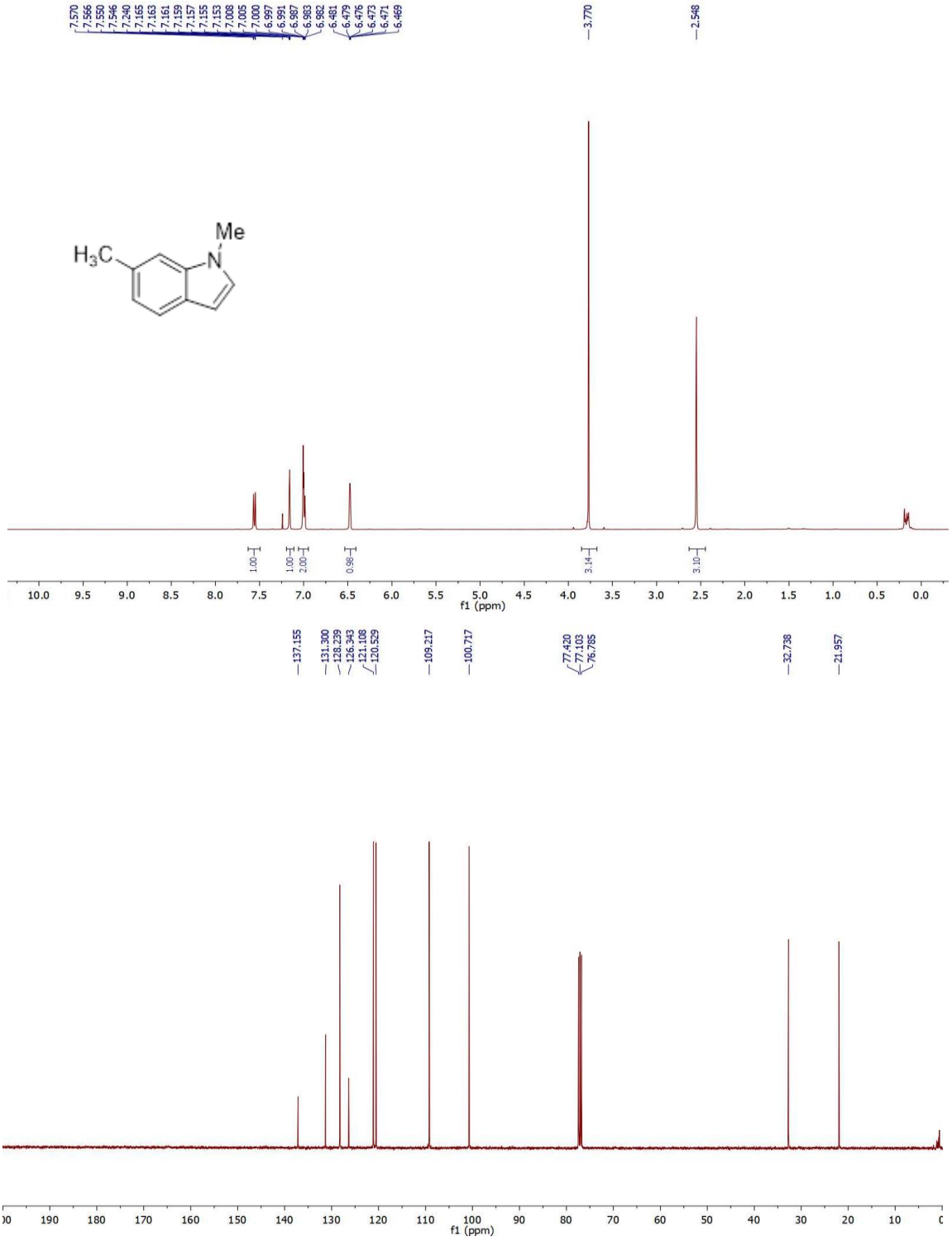
4-Methyl-1-(o-tolyl)piperidine **23** ($CDCl_3$, 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR)



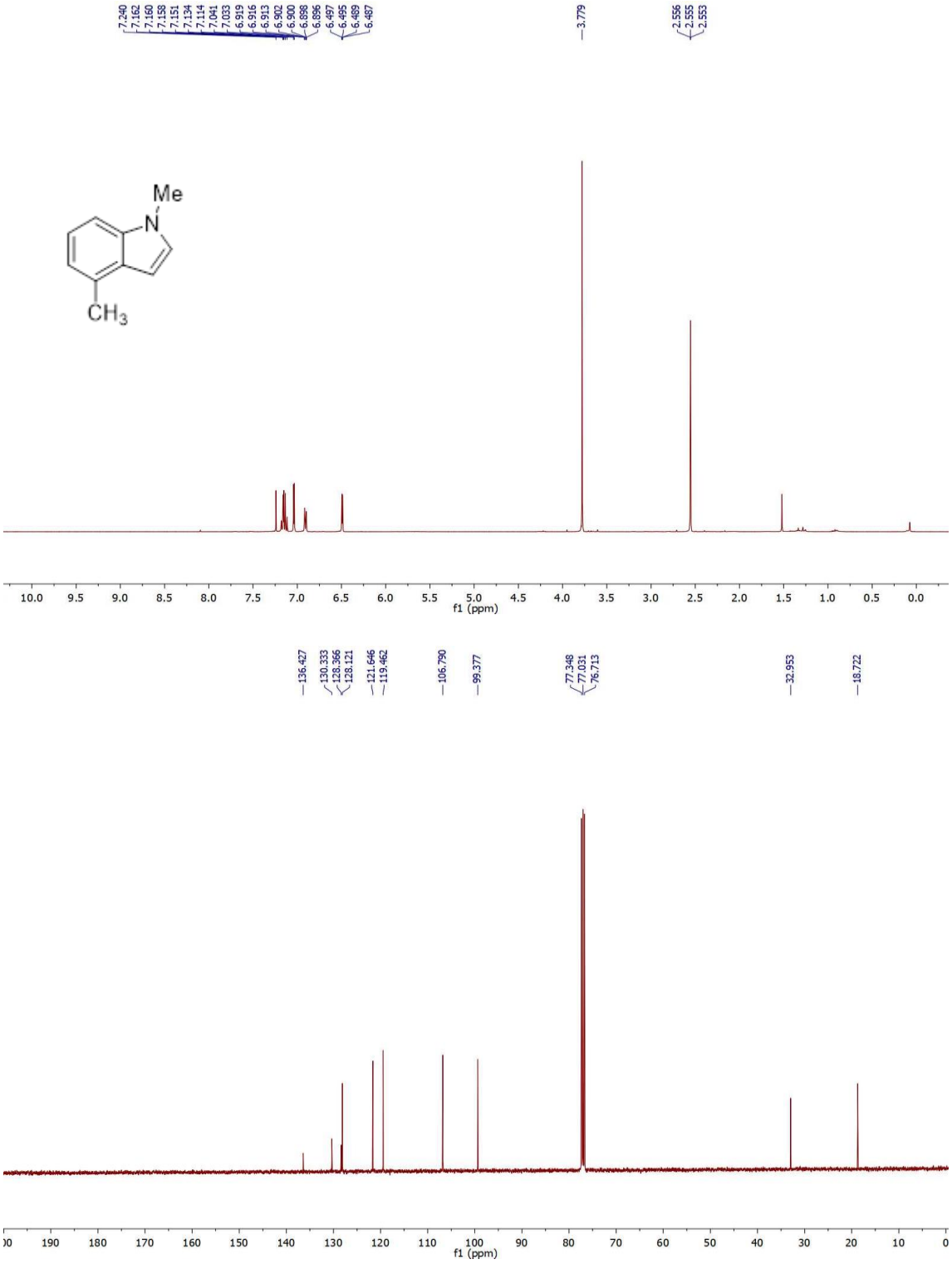
8-(4-Methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane **24** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



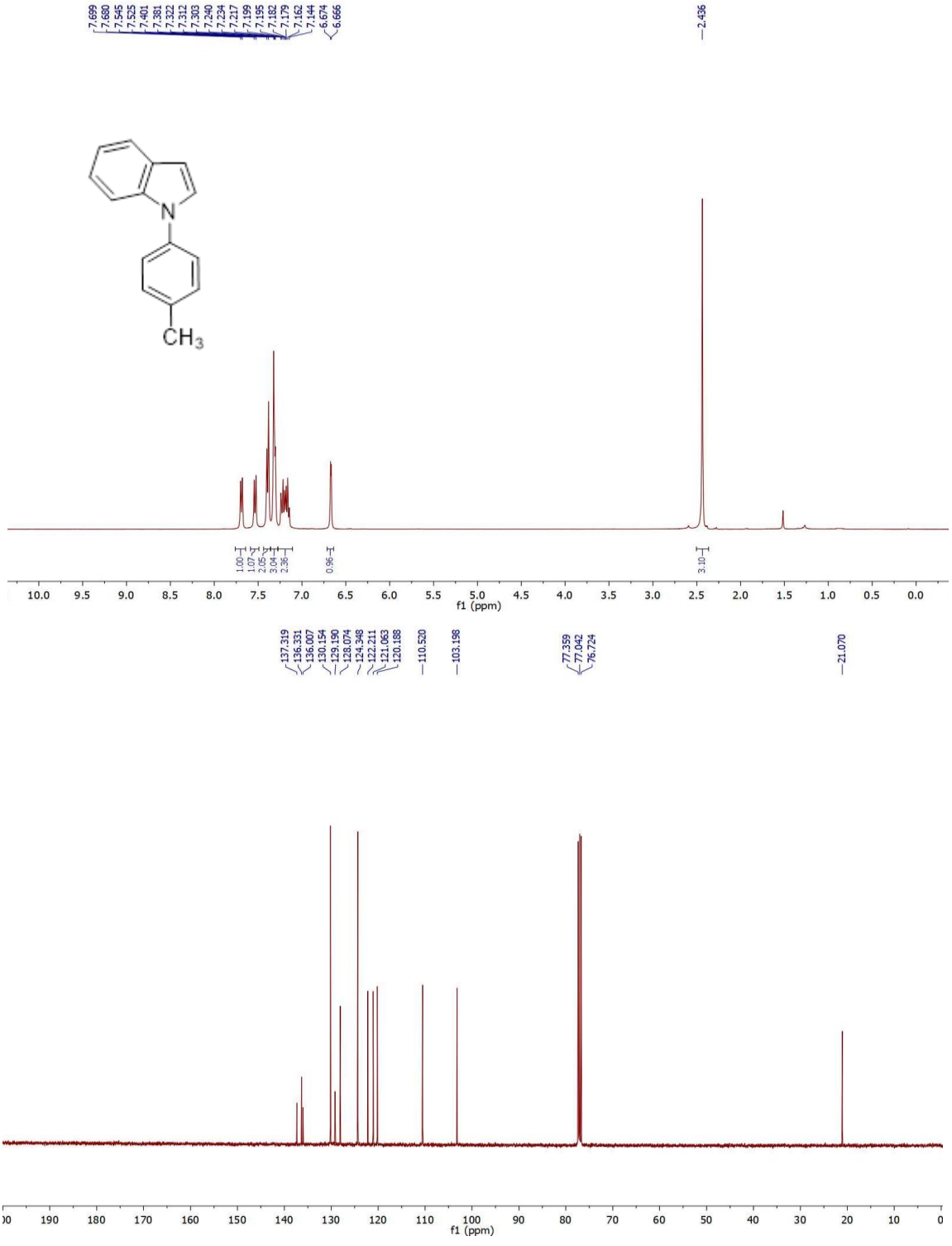
1,6-Dimethylindole **25** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



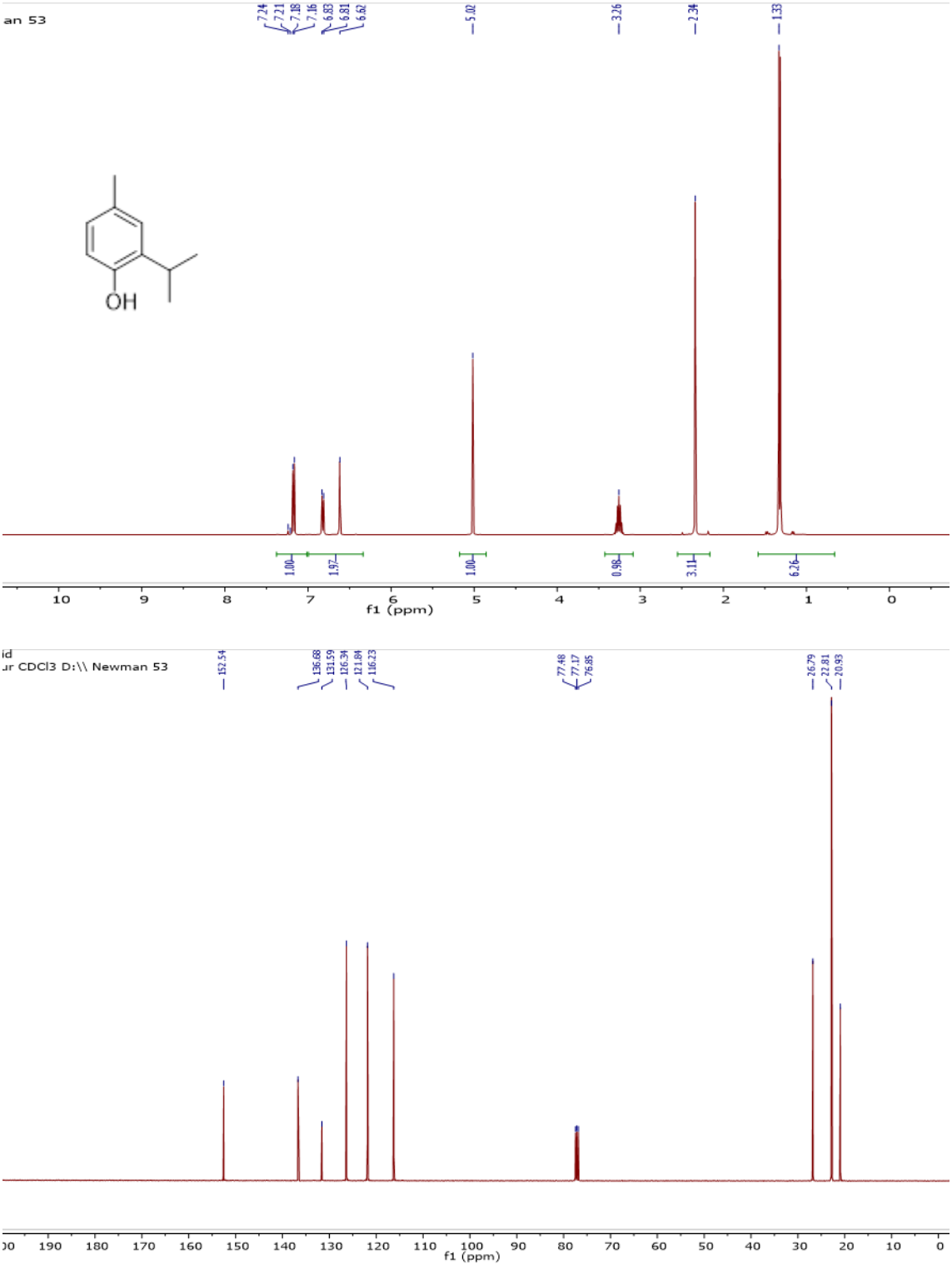
1,4-Dimethylindole **26** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



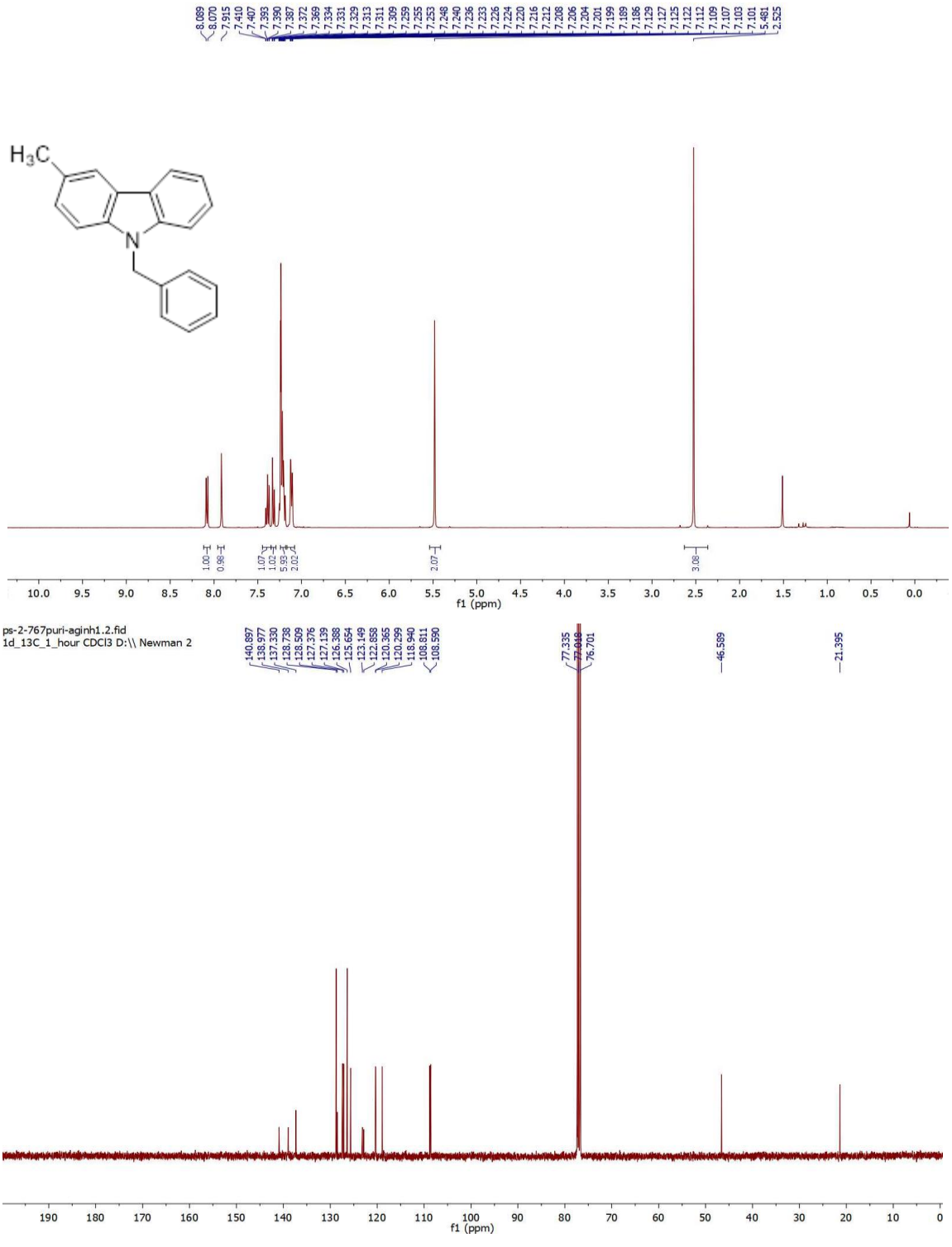
1-(p-Tolyl)-indole **27** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



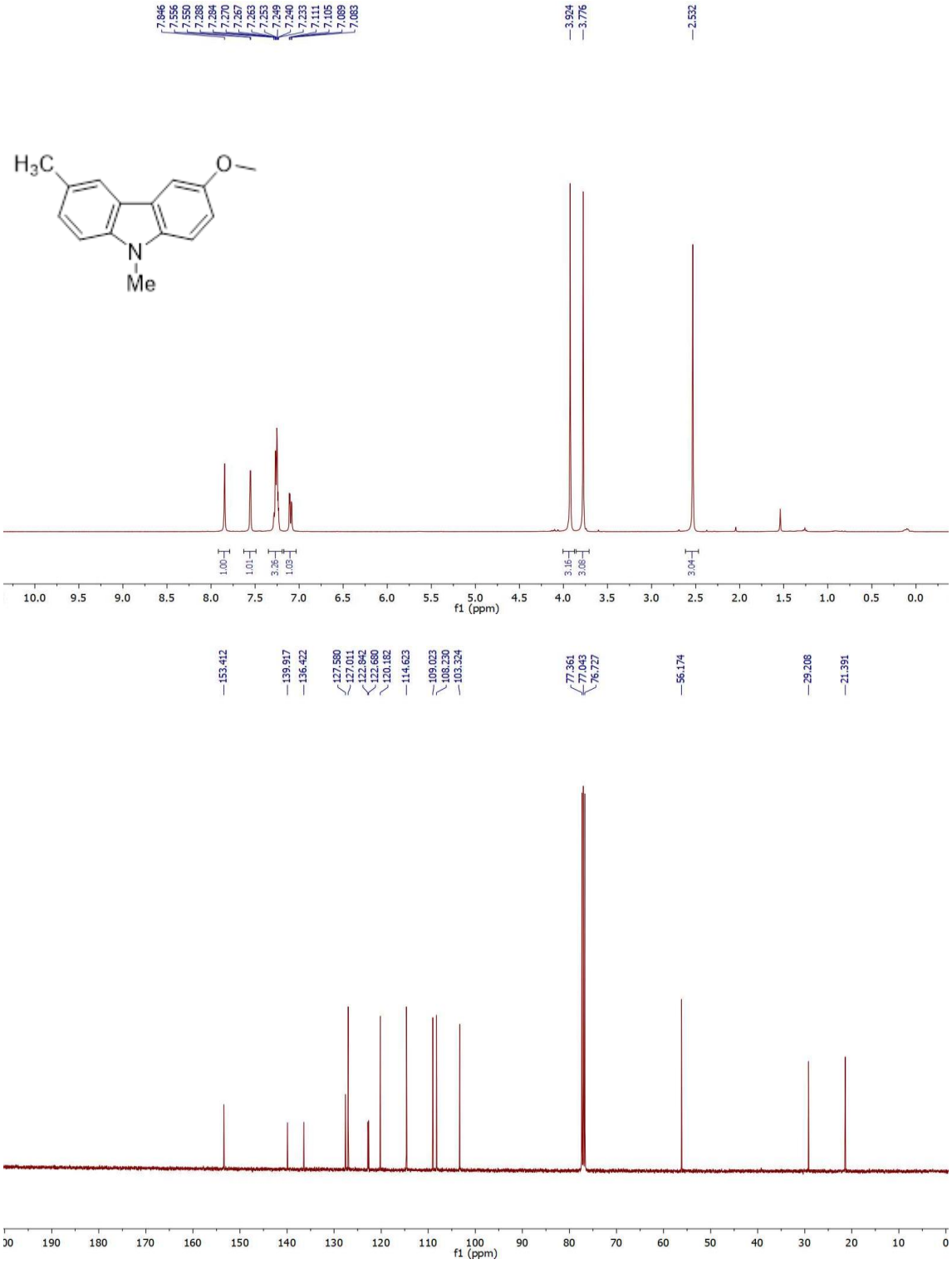
1-Methyl-3-hydroxy-4-isopropylbenzene **29** ($CDCl_3$, 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR)



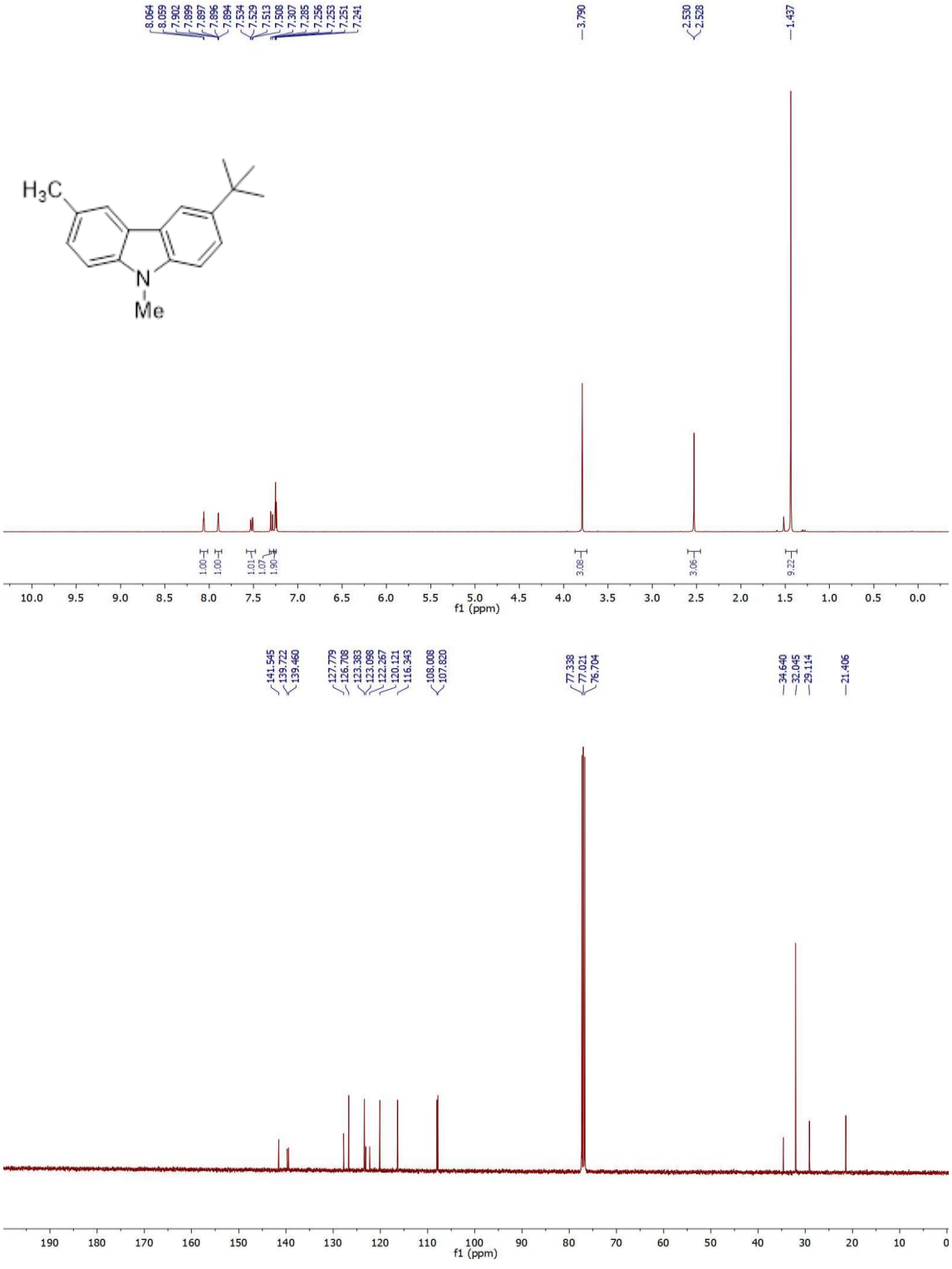
9-Benzyl-3-methylcarbazole **30** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



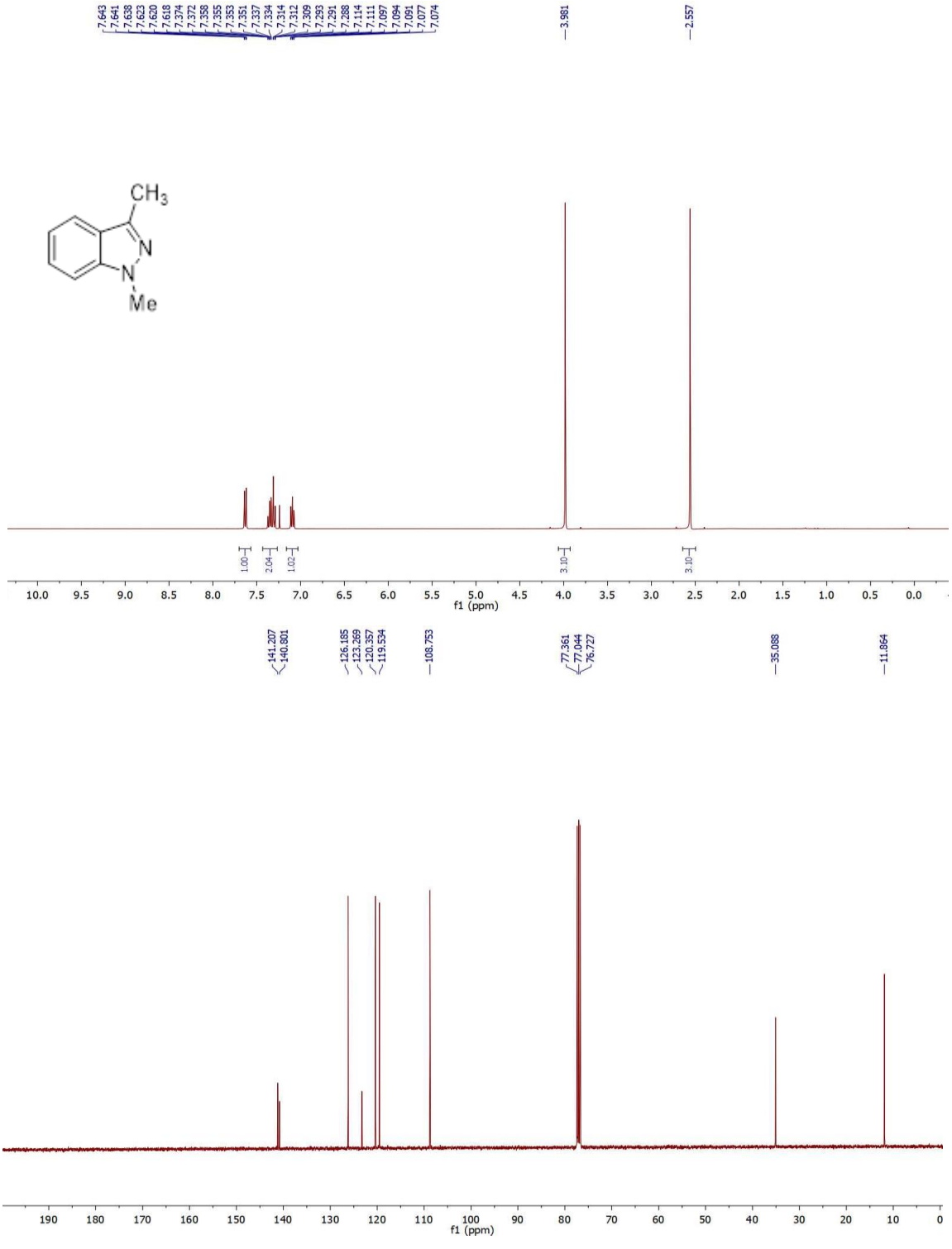
3-Methoxy-6,9-dimethyl-9-carbazole **31** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



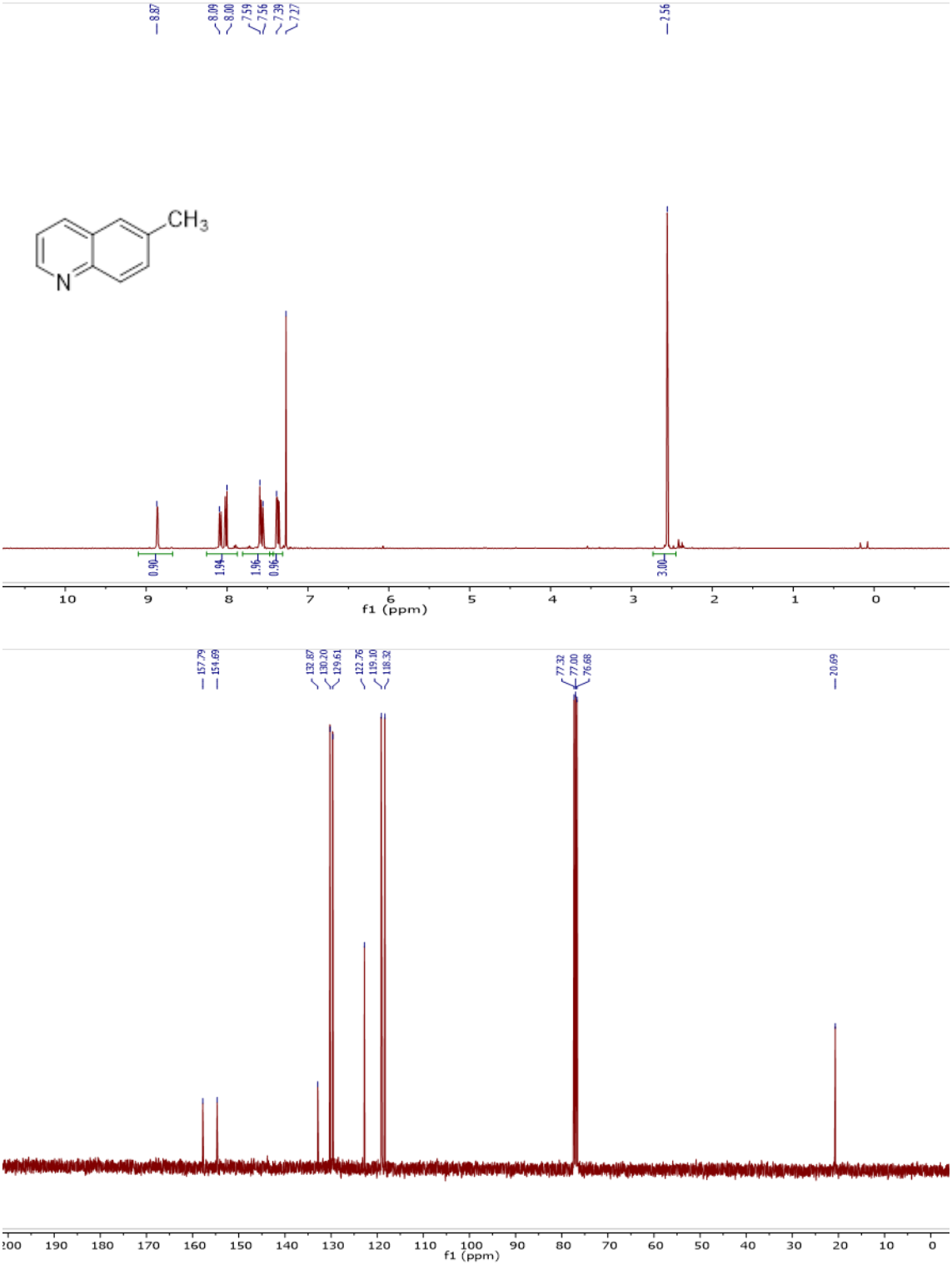
3-(*t*-Butyl)-6,9-dimethyl-carbazole **32** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



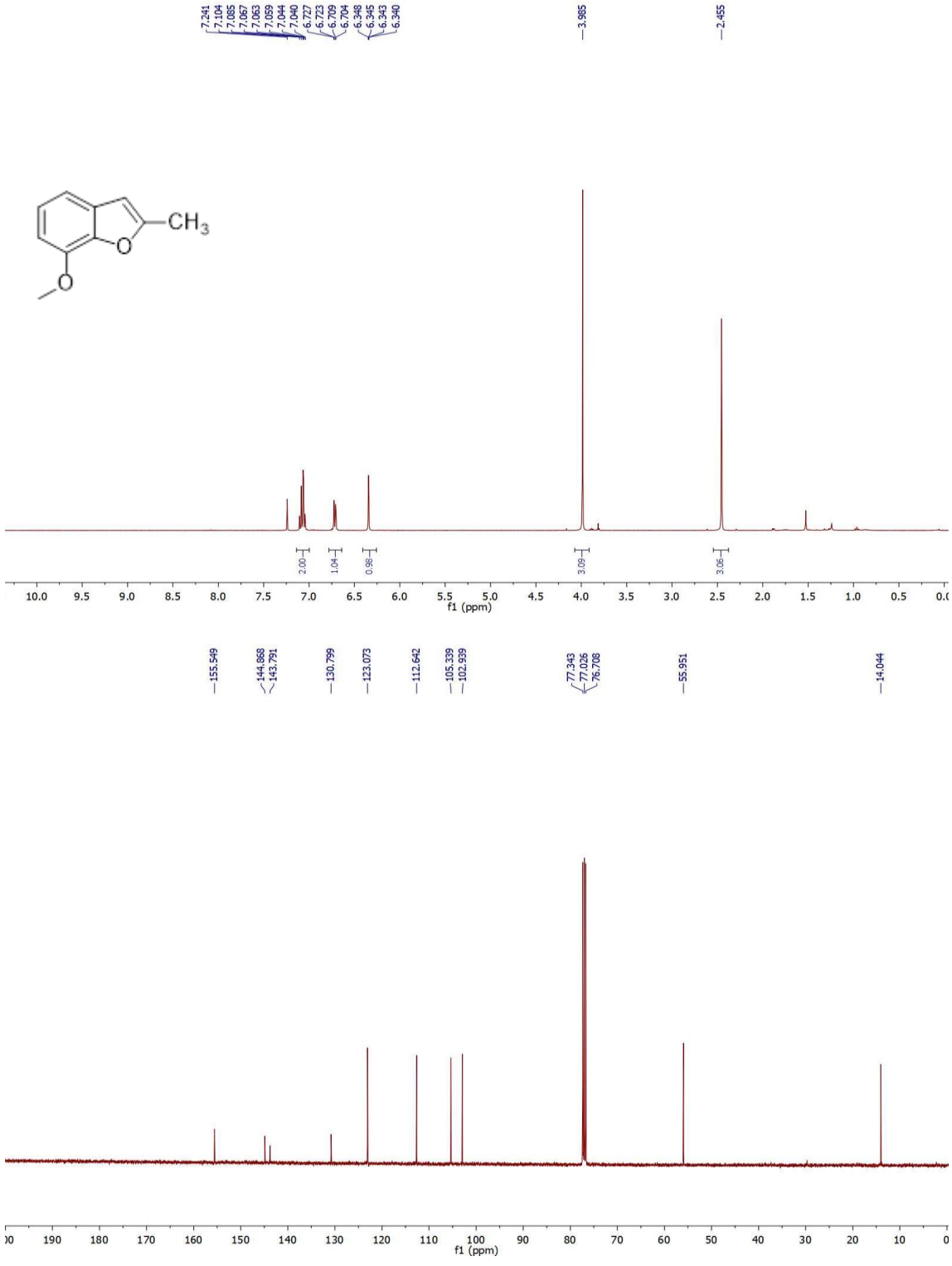
1,3-Dimethylindazole **33** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



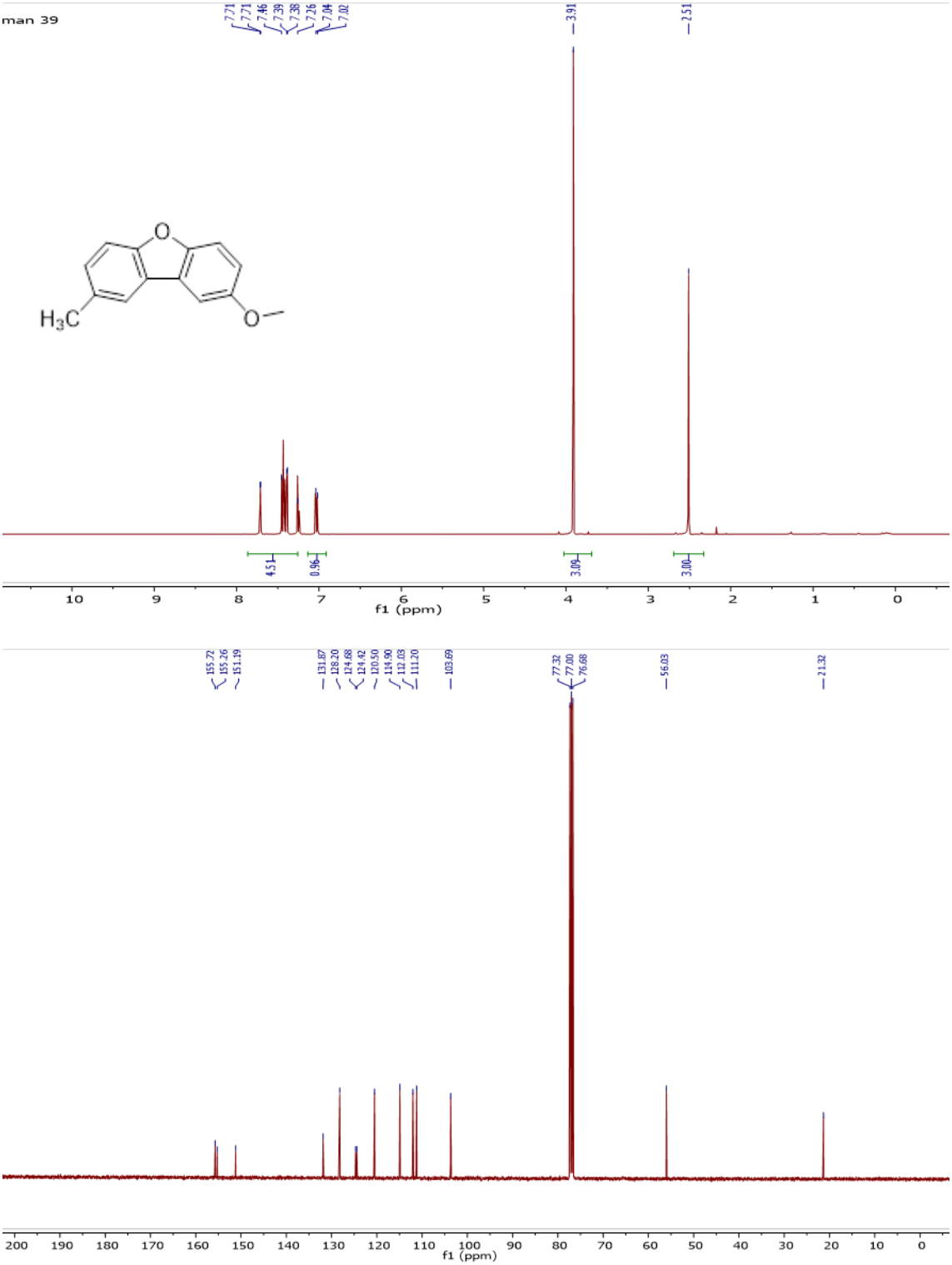
6-Methylquinoline **34** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



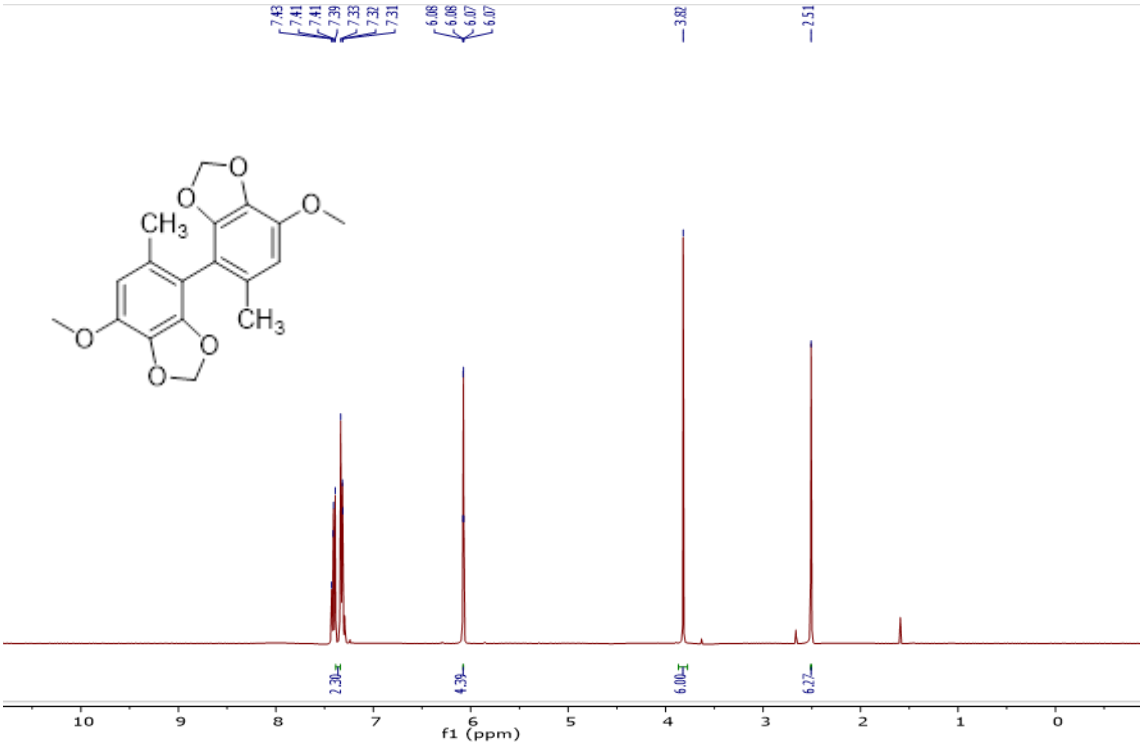
7-Methoxy-2-methylbenzofuran **35** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)

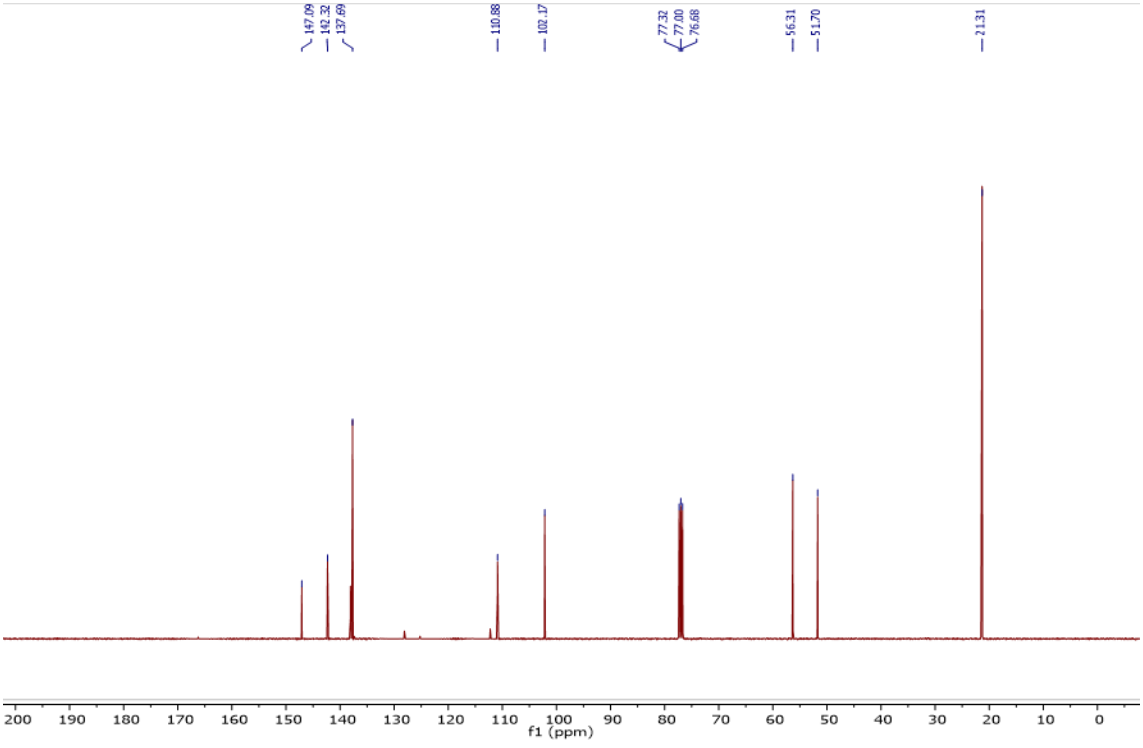


2-Methoxy-8-methyl-dibenzofuran **36** ($CDCl_3$, 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR)

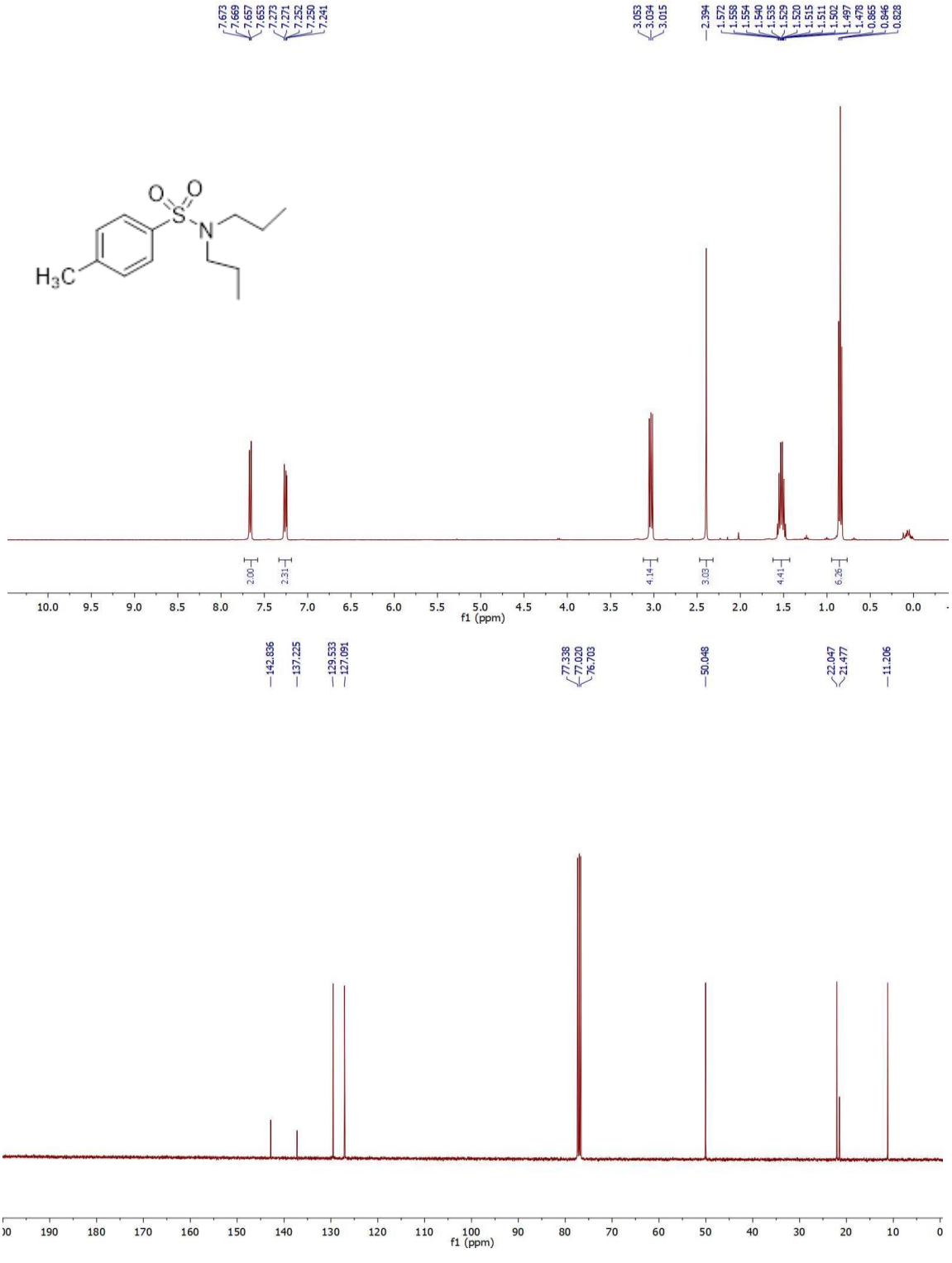


7,7'-Dimethoxy-5,5'-dimethyl-4,4'-bibenzo[d][1,3]dioxole **37** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)

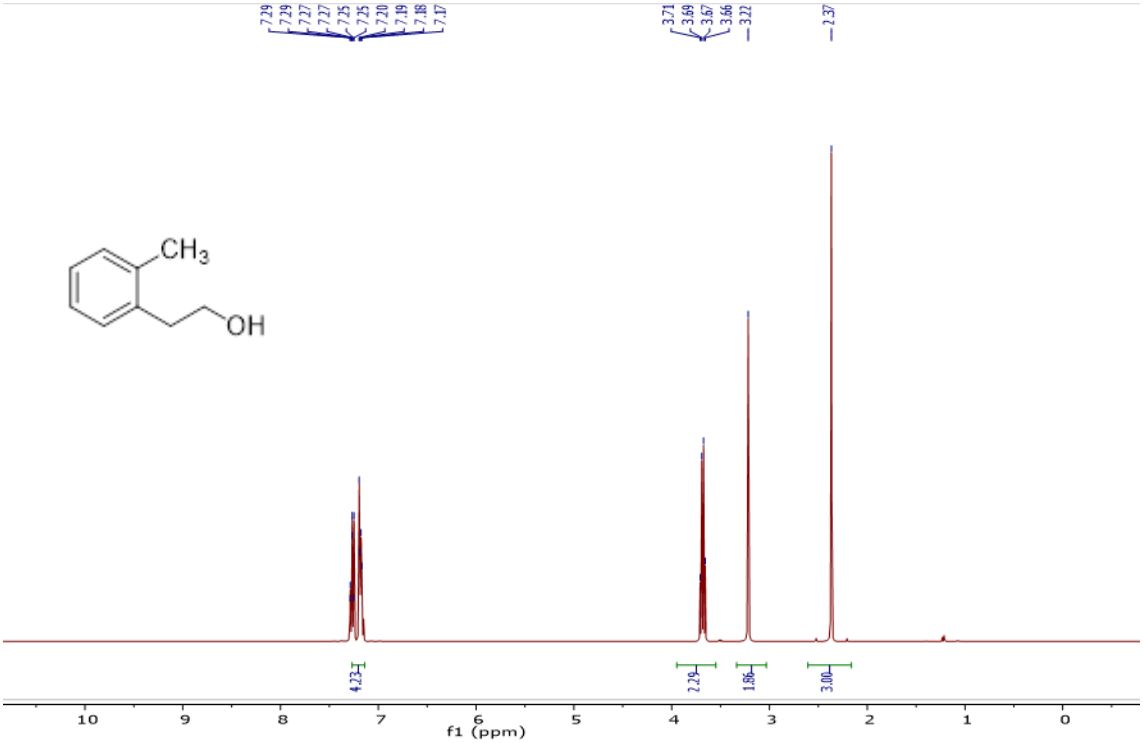


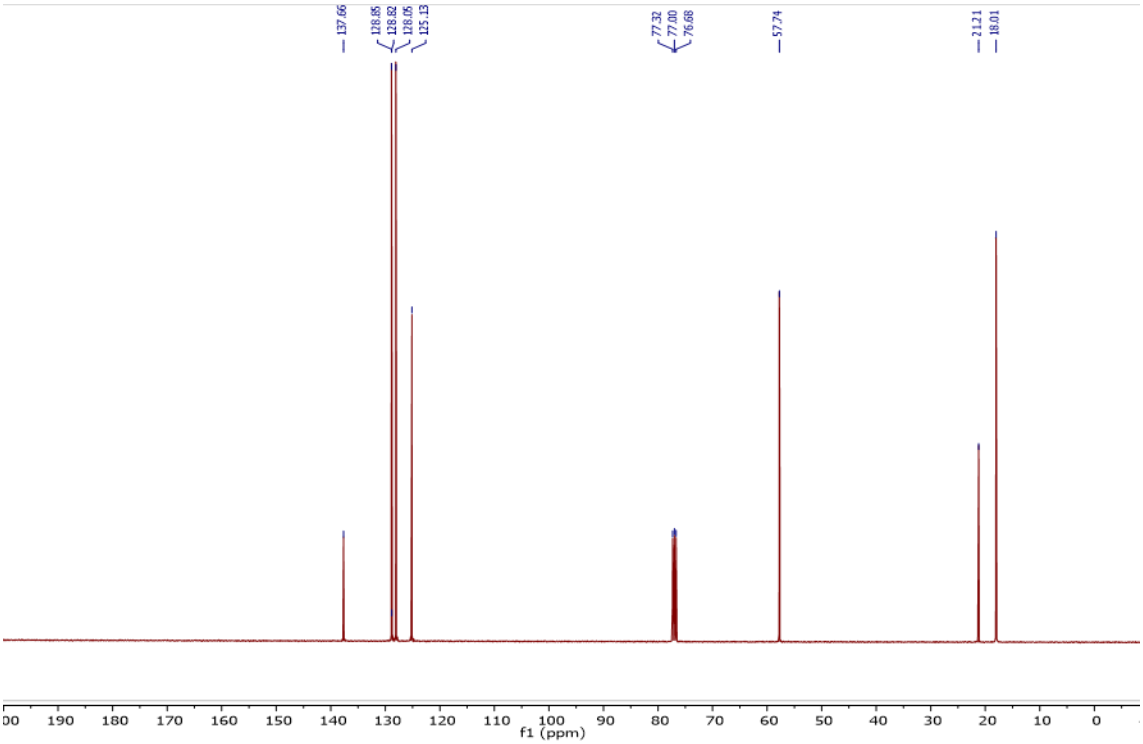


4-Methyl-*N,N*-dipropylbenzenesulfonamide **38** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)

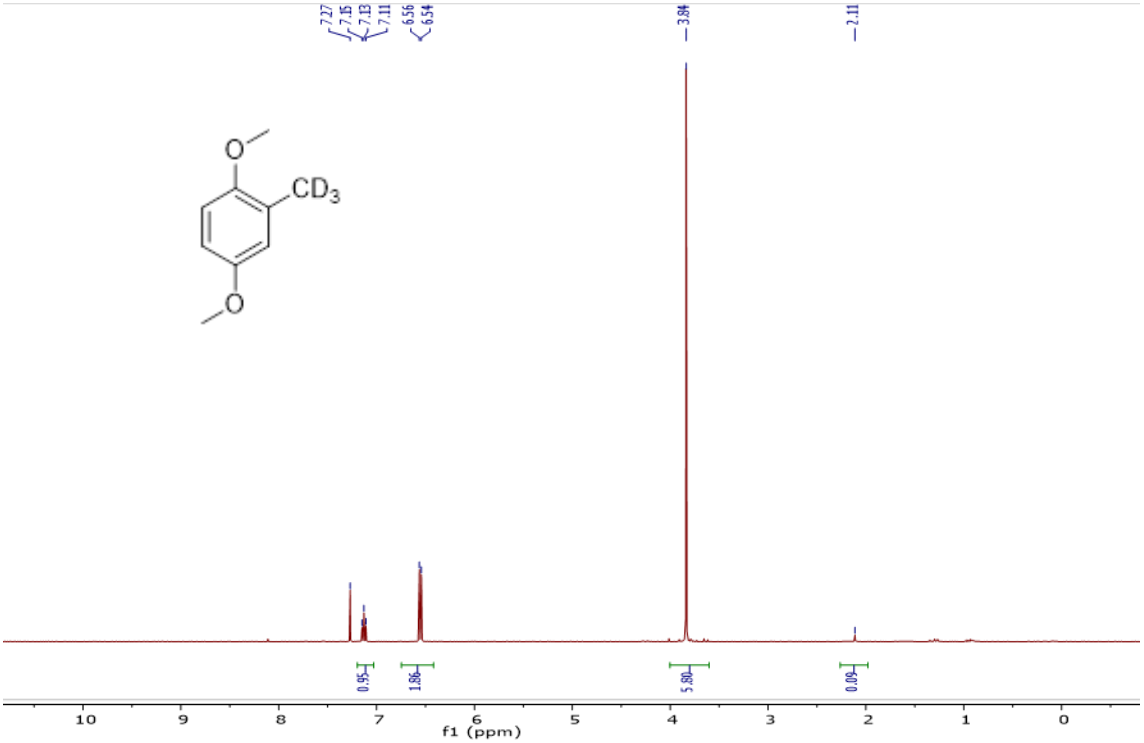


2-(Methylbenzene)ethanol **39** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)

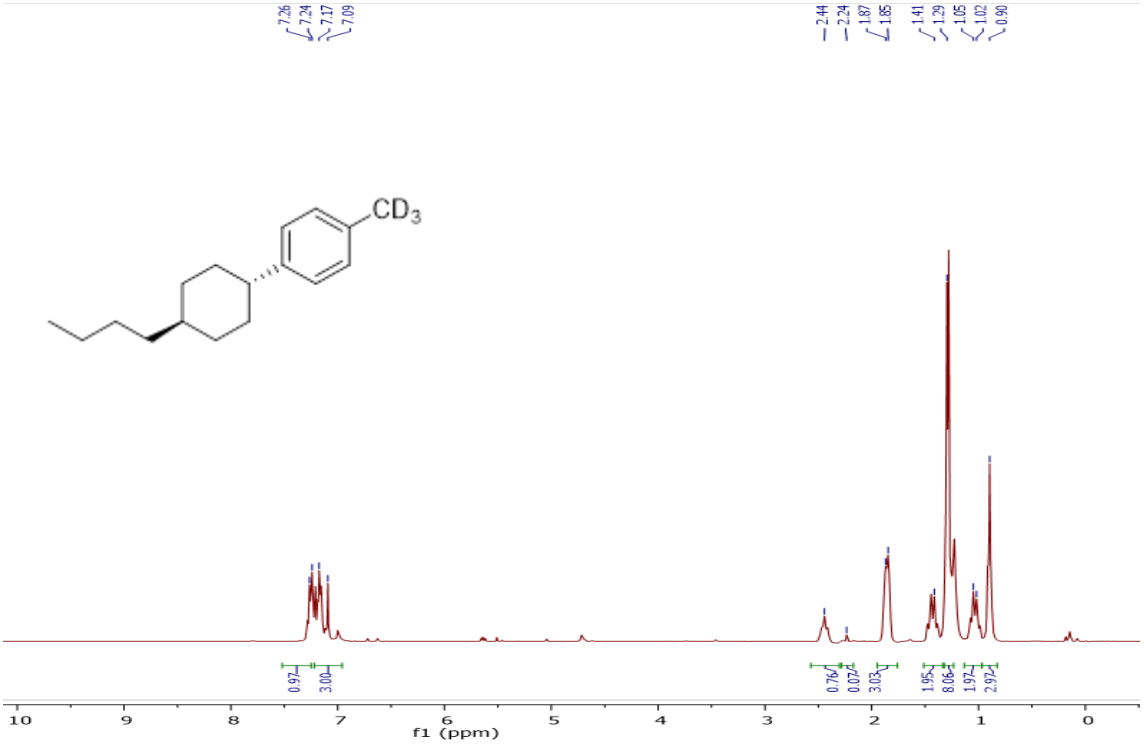




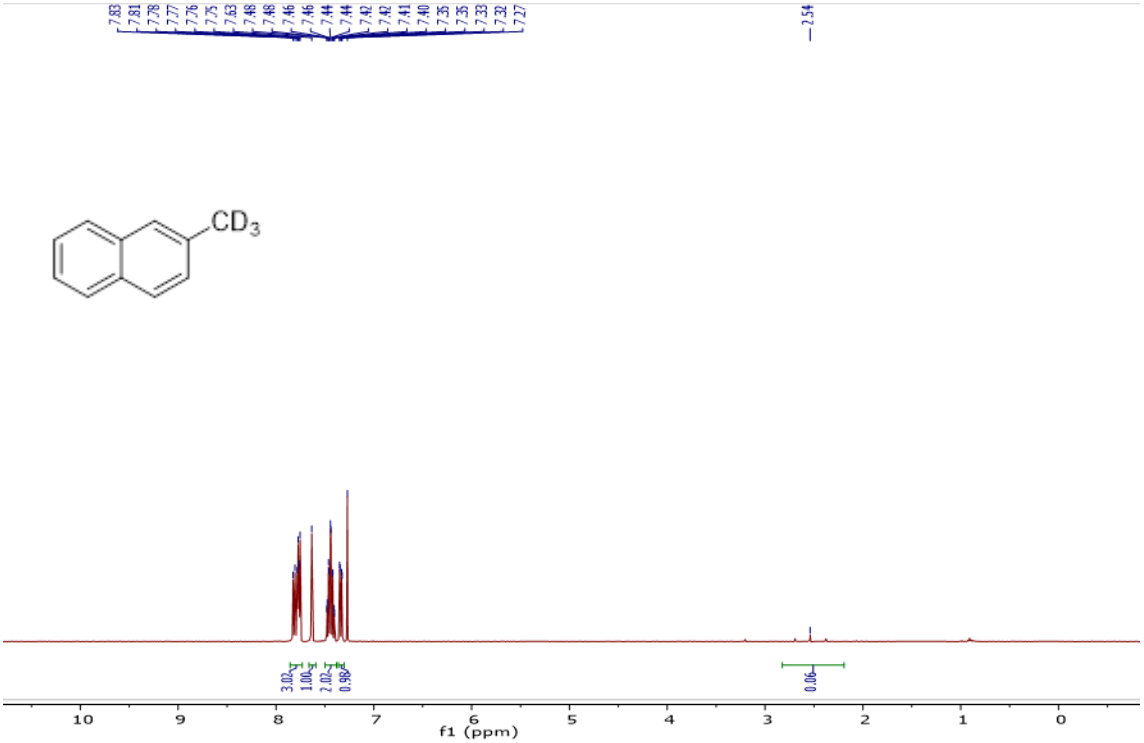
d^3-2,5-Dimethoxy-2-methylbenzene **40** ($CDCl_3$, 400 MHz for ^{1}H NMR)



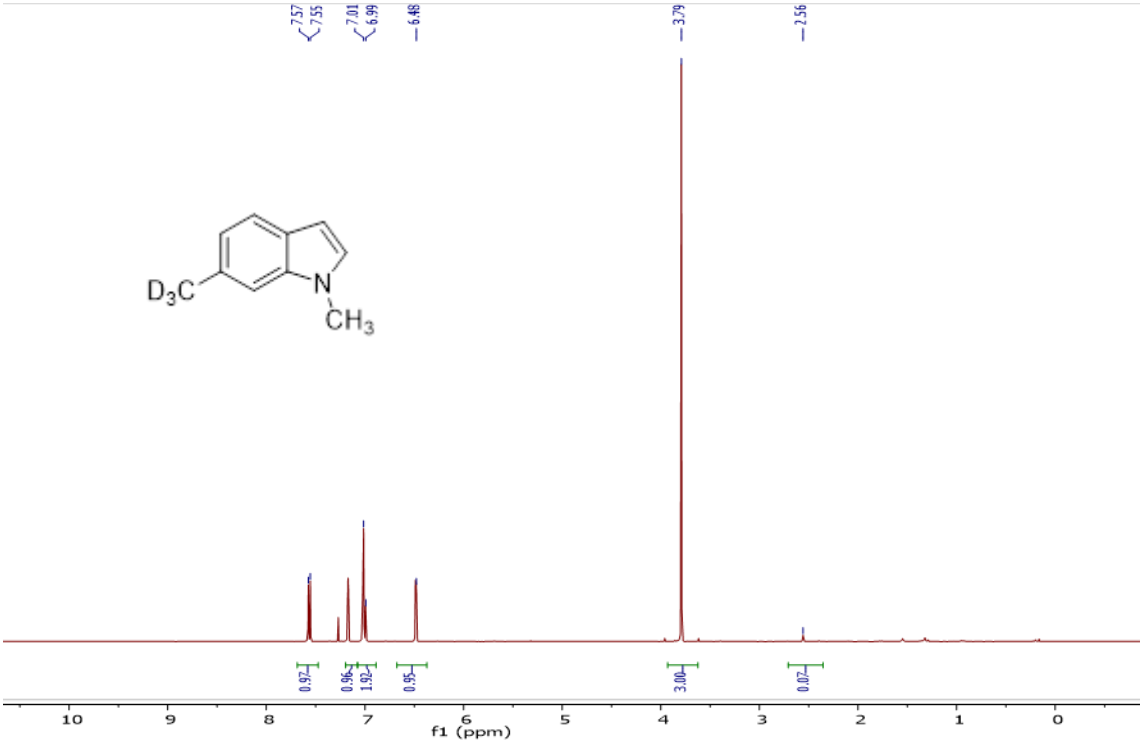
d^3-1-(*trans*-4-butylcyclohexyl)-4-methylbenzene **41** ($CDCl_3$, 400 MHz for ^{1}H NMR)



d^3-2-Methylnapthalene **42** ($CDCl_3$, 400 MHz for ^{1}H NMR)

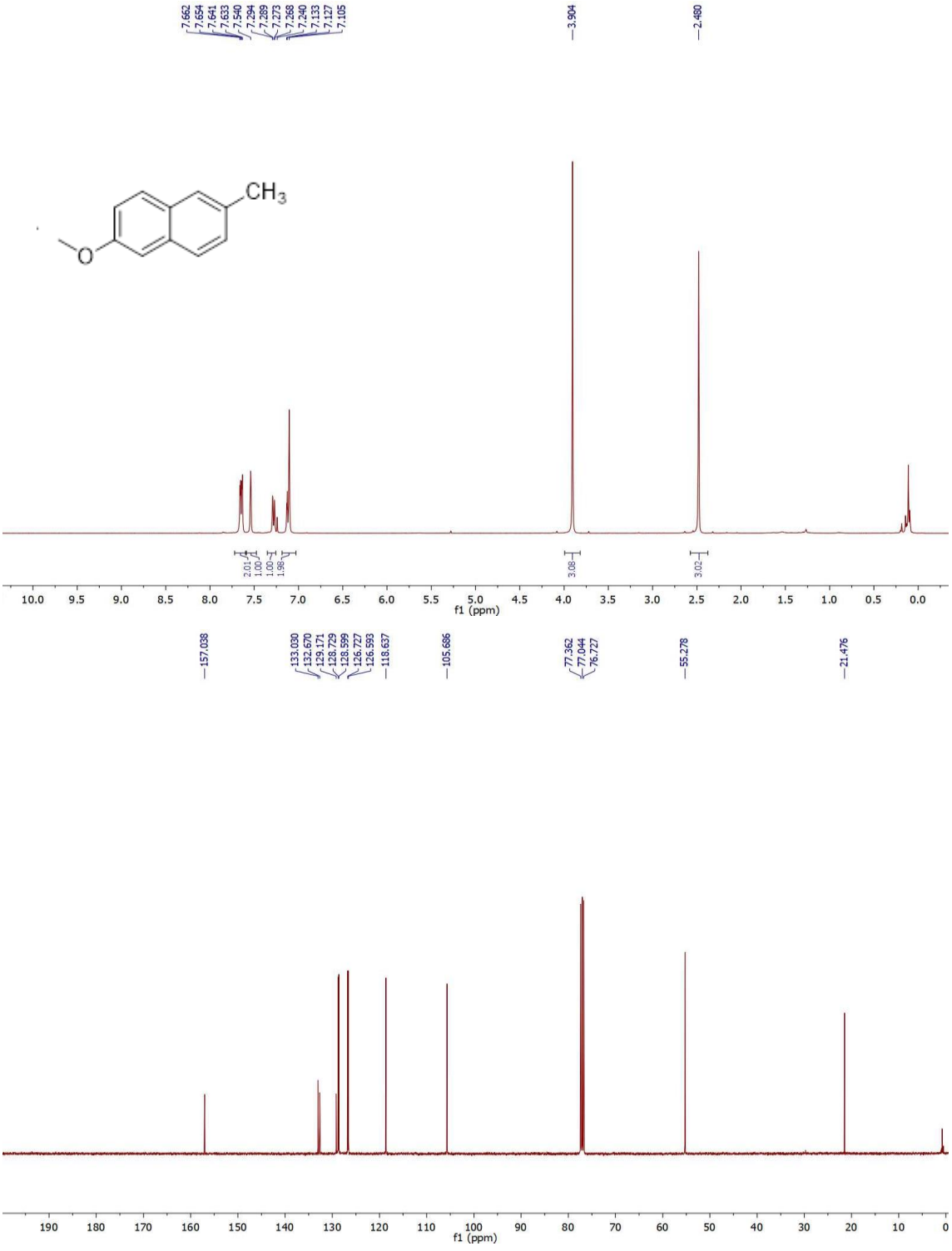


d^3-1,6-Dimethylindole **43** ($CDCl_3$, 400 MHz for ^{1}H NMR)

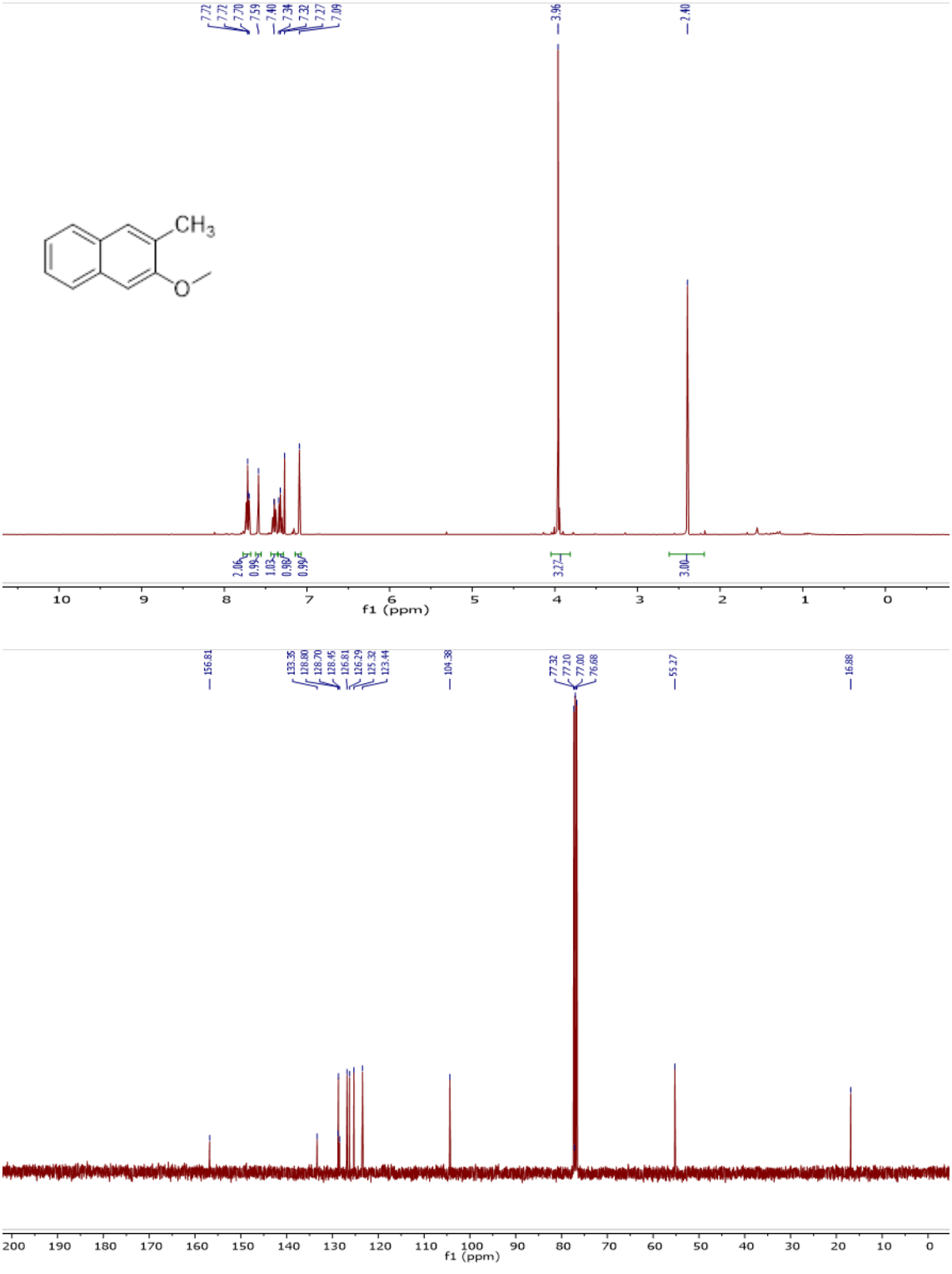


2-(2-Methoxyphenyl)-5-methylpyridine **48** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)

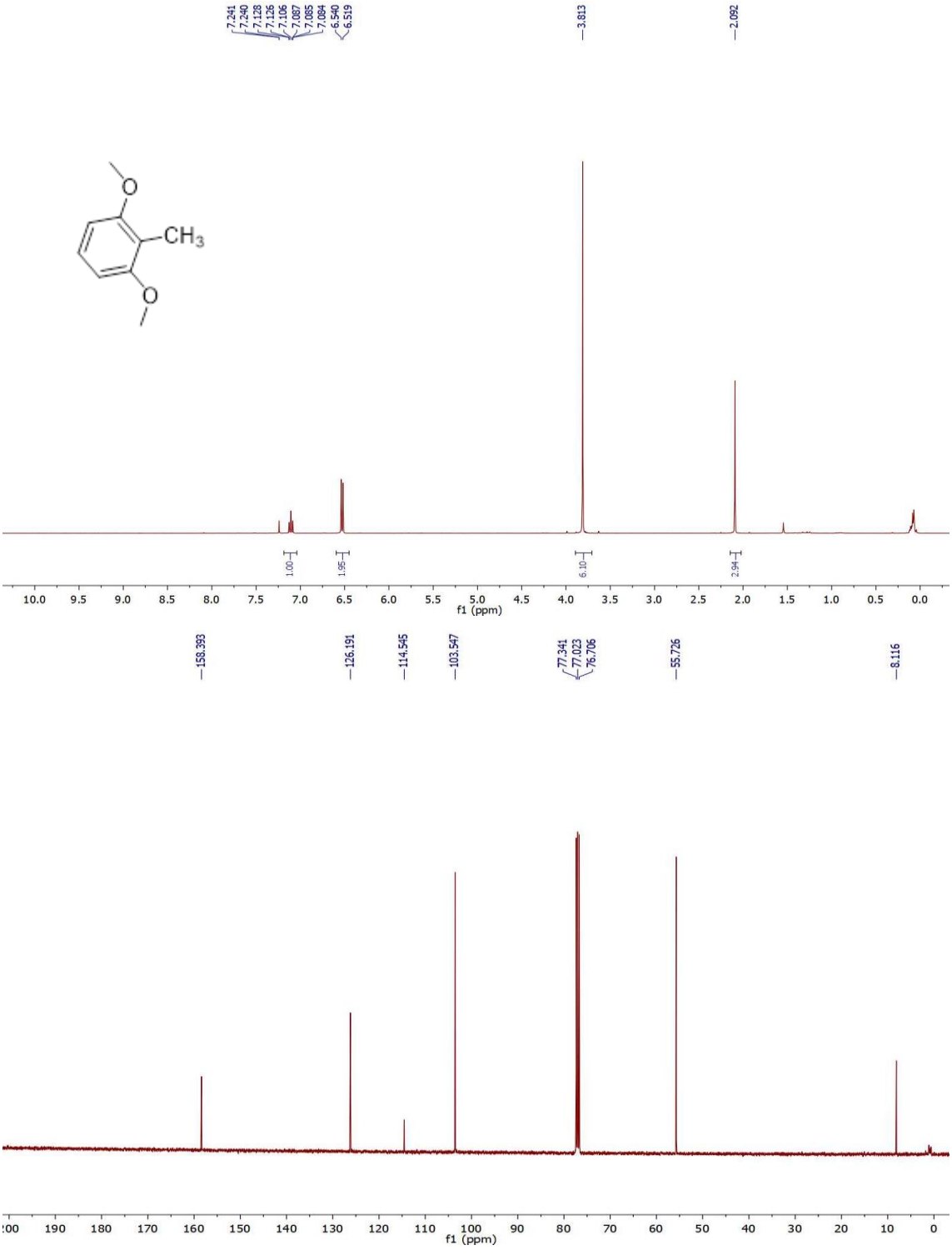
2-Methoxy-6-methylnaphthalene **49** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



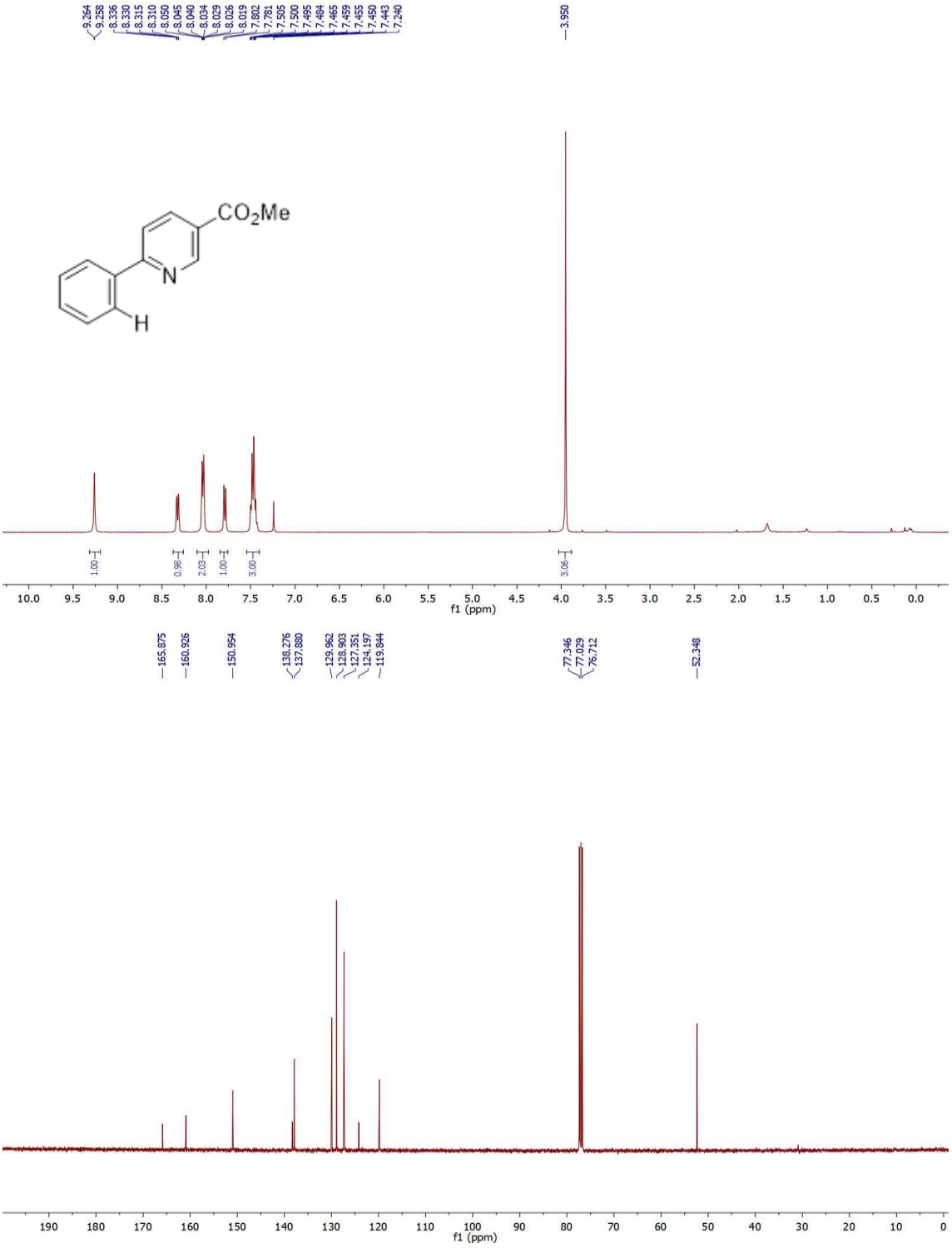
2-Methoxy-3-methylnapthalene **50** ($CDCl_3$, 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR)



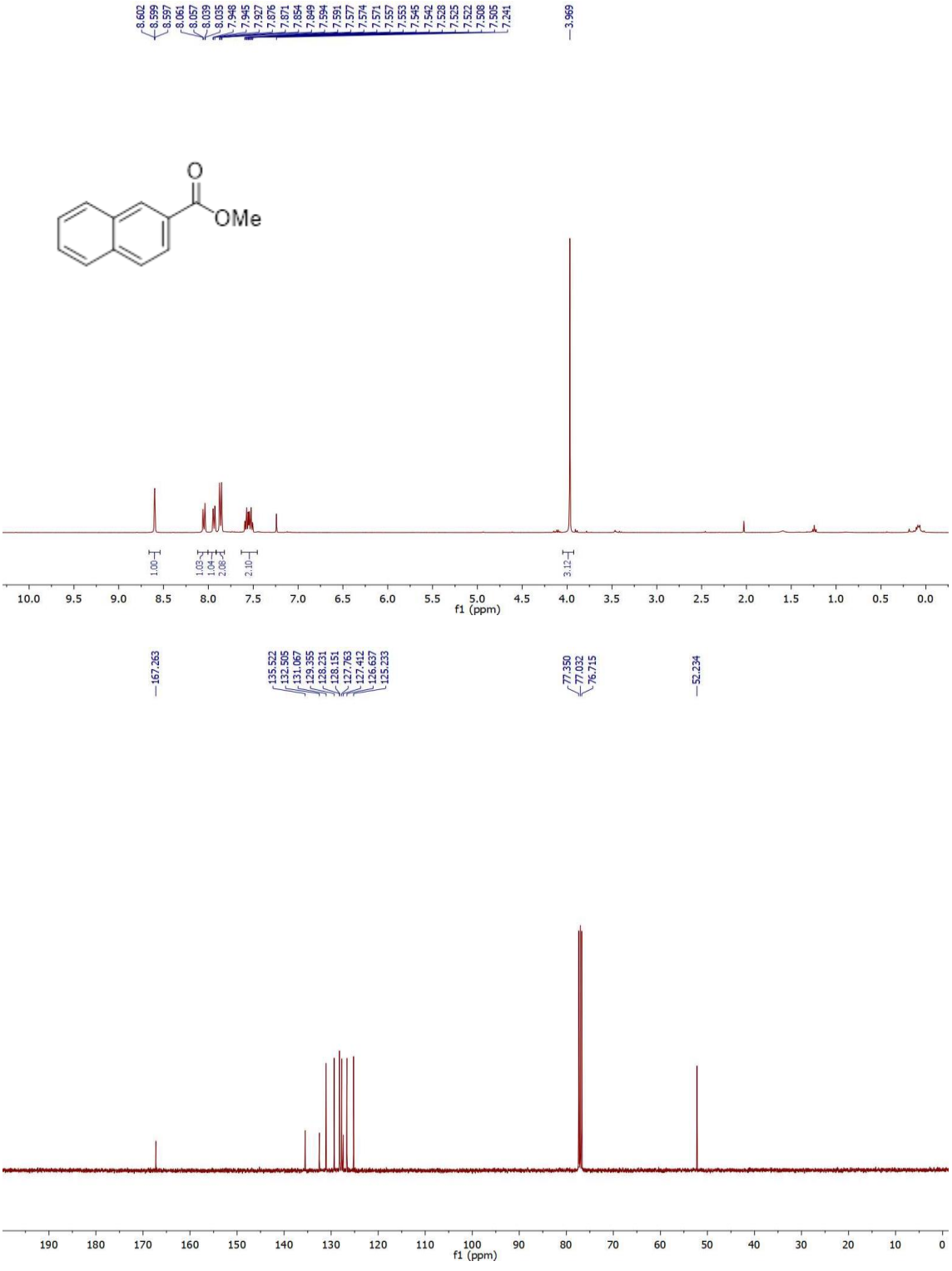
1,3-Dimethoxy-2-methylbenzene **51** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



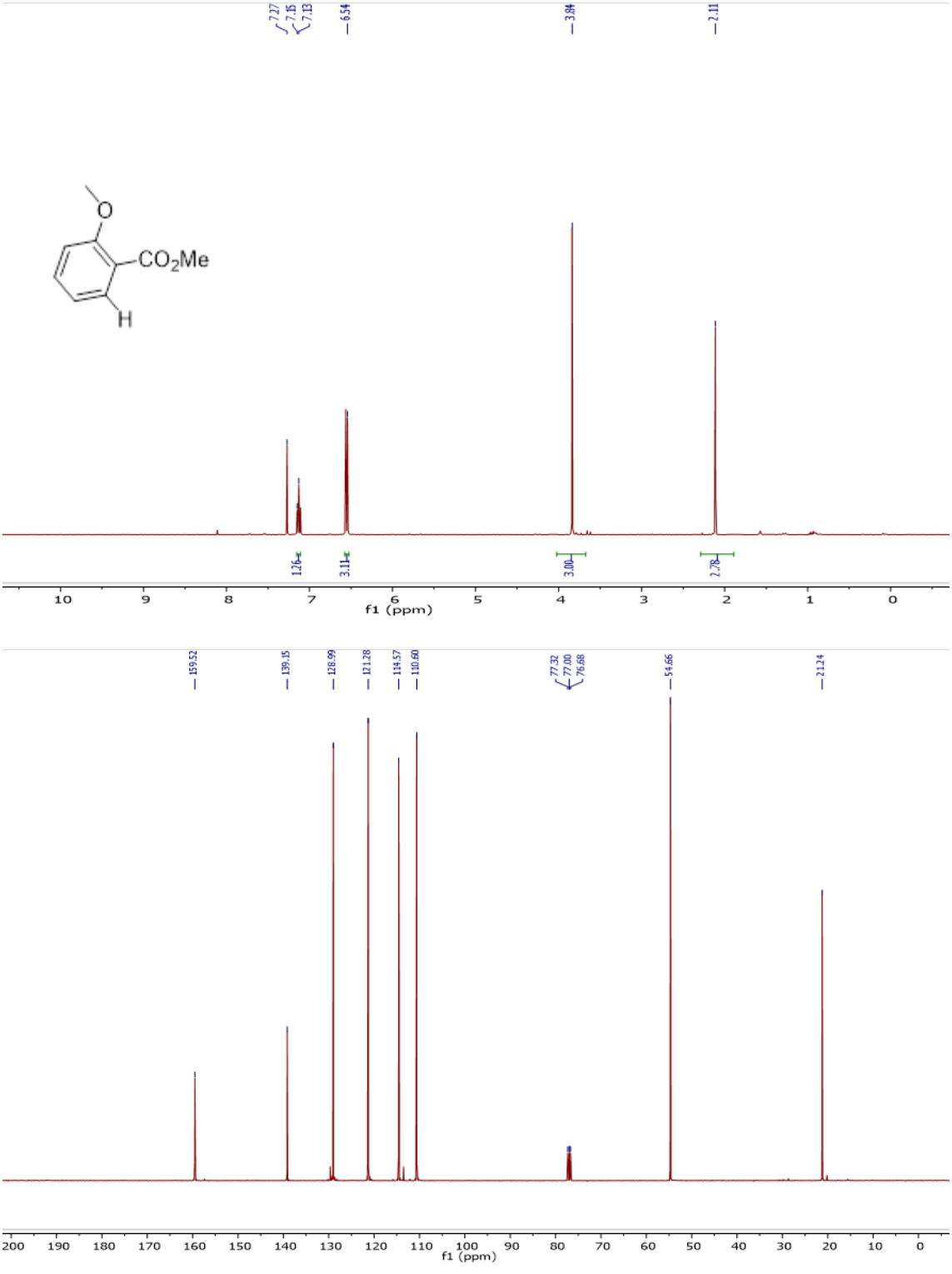
Methyl 5-phenylpyridine-3-carboxylate **52** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



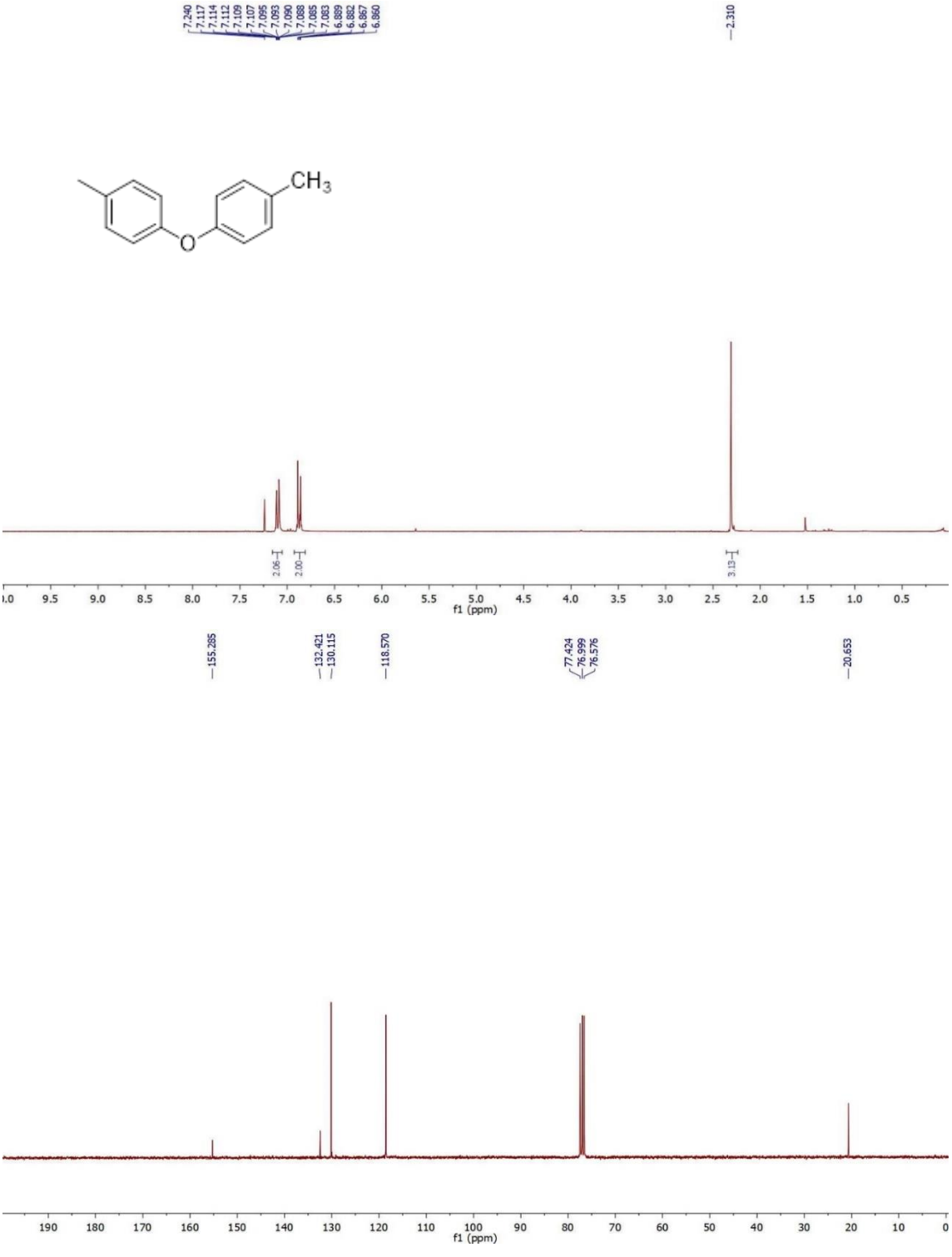
2-Methyl naphthoate **53** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



Methyl-2-methoxybenzoate **54** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



4,4'-Oxybis(methylbenzene) **55** ($CDCl_3$, 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR)



8. References

1) Hans, M.; Lorkowski, J.; Demonceau, A.; Delaude, L. *Beilstein. J. Org. Chem.* **2015,** *11,* 2318–2325.

2) Nishizawa, R.; Nishiyama, T.; Hisaichi, K.; Hirai, K.; Habashita, H.; Takaoka, Y.; Tada, H.; Sagawa, K.; Shibayama, S.; Maeda, K.; Mitsuya, H.; Nakai, H.; Fukushima, D.; Toda, M. *Bioorg. Med. Chem*. **2010**, *18*, 5208–5223.

3) Nimmagadda, S. K.; Liu, M.; Karunananda, M. K.; Gao, D.-W.; Apolinar, O.; Chen, J. S.; Liu, P.; Engle, K. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 3923–3927.

4) In, I.-K.; Lee, M. S.; Yang, J. E.; Kwak, J. H.; Lee, H.; Boovanahalli, S. K.; Lee, K.; Kim, S. J.; Moon, S. K.; Lee, S.; Choi, N. S.; Ahn, S. K.; Jung, J. K. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1799–1802.

5) Wei, Y.; Yoshikai, N. *Org. Lett.* **2011**, *13*, 5504–5507.

6) Yu, M.; Lizarzaburu, M.; Beckmann, H.; Connors, R.; Dai, K.; Haller, K.; Li, C.; Liang, L.; Lindstrom, M.; Ma, J.; Motani, A.; Wanska, M.; Zhang, A.; Li, L.; Medina, J. C. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1758–1762.

7) Nuss, J. M.; Harrison, S. D.; Ring, D. B.; Boyce, R. S.; Johnson, K.; Pfister, K. B.; Ramurthy, S.; Seely, L.; Wagman, A. S.; Desai, M.; Levine, B. H.; US 2002/0156087 A1, Oct. 24, 2002.

8) Delorme, D.; Zhou, Z. US 2004/0142953 A1, Jul. 22, 2004.

9) Alvarez-Bercedo, P.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132,* 17352–17353.

10) Wen, L.; Tang, L.; Yang, Y.; Zha, Z.; Wang, Z. *Org. Lett.* **2016,** *18*, 1278–1281.

11) Schuster, C.; Börger, C.; Julich-Gruner, K. K.; Hesse, R.; Jäger, A.; Kaufmann, G.; Schmidt, A. W.; Knölker, H. *Eur. J. Org. Chem.*, **2014**, 4741–4752.

12) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008,** *73*, 5022–5028.

13) Yamada, M.; Shio, Y.; Akiyama, T.; Honma, T.; Ohki, Y.; Takahashi, N.; Murai, K.; Arisawa, M. *Green. Chem.* **2019**, *21*, 4541–4549.

14) Hokamp, T.; Dewanji, A.; Lübbesmeyer, M.; Mück-Lichtenfeld, C.; Würthwein, E.-U.; Studer, A. *Angew. Chem. Int. Ed.* **2017**, *56*, 13275–13278.

15) Catti, L.; Tiefenbacher, K. *Angew. Chem. Int. Ed.* **2018**, *57*, 14589–14592.

16) Liu, X.-F.; Li, X.-Y.; Qiao, C.; Fu, H.-C.; He, L.-N. *Angew. Chem. Int. Ed.* **2017**, *56*, 7425–7429.

17) Yao, C. Z.; Li, Q. Q.; Wang, M. M.; Ning, X. S.; Kang, Y. B. *Chem. Commun*. **2015**, *51*, 7729–7732.

18) Cella, R.; Stefani, H. A. *Tetrahedron* **2006**, *62,* 5656-5662.

19) Wang, H.; Li, L.; Bai, X.-F.; Shang, J.-Y.; Yang, K.-F.; Xu, L.-W.; *Adv. Synth. Catal*. **2013**, *355*, 341–347.

20) Zhao, Y.; Wang, X.; Kodama, K.; Hirose, T. *ChemistrySelect*, **2018**, *3*, 12620–12624.

21) Huang, C.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Adv. Synth. Catal.* **2011**, *353*, 1285–1305.

22) Frost, J. R.; Cheong, C. B.; Donohoe, T. J. *Synthesis* **2017**, *49*, 910–916.

23) Haydl, A. M.; Hartwig, J. F. *Org. Lett.* **2019**, *21*, 1337–1341.

24) Zhang, E.; Tang, J.; Li, S.; Wu, P.; Moses, J. E.; Sharpless, K. B. *Chem. Eur. J.* **2016**, *22*, 5692–5697.

25) Abid, O. R.; Nawaz, M.; Ibad, M. F.; Khera, R. A.; Iaroshenko, V.; Langer, P. *Org. Biomol. Chem.* **2011**, *9*, 2185–2191.

26) Lerma, I. S.; Cawley, M. J.; Cloke, F. G. N.; Arentsen, K.; Scott, J. S.; Pearson, S. E.; Hayler, J.; Caddick, S., *J. Organomet. Chem.* **2005**, *690*, 5841–5848.

27) Pirkl, N.; Grosso, A. D.; Mallick, B.; Doppiuc, A.; Gooßen, L. J. *Chem. Commun*. **2019**, *55*, 5275–5278.

28) Zhang, J.; Park, S.; Chang, S. *J. Am. Chem. Soc.* **2018**, *140,* 13209-13213.

29) Manolikakes, G.; Gavryushin, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 1429–1434.

30) Benjamin, S.; Brown, L. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057.

31) Klare, H.; Oestreich, M.; Ito, J.; Nishiyama, H.; Ohki, Y.; Tatsumi, K. *J. Am. Chem. Soc.* **2011**, *133,* 3312-3315.

32) Patil, P. H.; Nallasivam, J. L.; Fernandes, R. A. *Asian. J. Org. Chem.* **2015**, *4*, 552–559.

33) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184–16186.

34) Hu, Z.-Y.; Zhang, Y.; Li, X.-C.; Zi, J.; Guo, X.-X; *Org. Lett*. **2019**, *21*, 989–992.

35) Counceller, C. M.; Eichman, C. C.; Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2008**, *105*, 1021–1023.

36) Fu, R.; Li, Z. *Org. Lett*. **2018**, *20*, 2342−2345.

37) Zhao, H. et al. *Org. Lett.* **2015**, *17*, 5744–5747.

38) Kennedy, N.; Lu, G.; Liu, P.; Cohen, T. *J. Org. Chem.* **2015**, *80*, 8571−8582

39) Lai, J.; Chang, L.; Yuan, G. *Org. Lett.* **2016**, *18*, 3194–3197.

40) Ruzicka, R.; Barakova, L.; Klan, P. *J. Phys Chem.* **2005**, *109,* 9346-9353.

41) Smart, K. A., Mothes-Martin, E., Annaka, T., Grellier, M., & Sabo-Etienne, S. *Adv. Synth. Catal.* **2014**, *356,* 759–764

42) Zhai, L.; Shukla, R.; Rathore, R. *Org. Lett.* **2009**, *11*, 3474–3477.

43) Alvarez-Bercedo, P., Martin, R. J. *Am. Chem. Soc.* **2010**, *132,* 17352-17353.

44) Abid, O.; Nawaz, M.; Ibad, F.N.; Khera, R.A.; Iaroshenko, V.; Langer, P. *Org. Biomol. Chem.* **2011**, 2185–2191.

45) Jolliffe, J. D.; Armstrong, R. J.; Smith, M. D. *Nature Chem.* **2017***, 9*, 558–562.

46) Barbero, N.; Martin, R. *Org. Lett*. **2012**, *14*, 796–799.

47) El-Deeb, I. Y.; Tian, M.; Funakoshi, T.; Matsubara, R.; Hayashi, M. *Eur. J. Org. Chem*. **2017**, *2*, 409–413.

48) Anderson, E.D.; Boger, D.L. *J. Am. Chem. Soc*. **2011**, *133*, 12285-12292.

49) Bodnar, B.S.; Vogt, P. F. *J. Org. Chem.* **2009**, 74, 2598-2600.

50) Neilsen, D.-T. C.; Burés, J. *Chem. Sci.* **2019**, 10, 348-353.