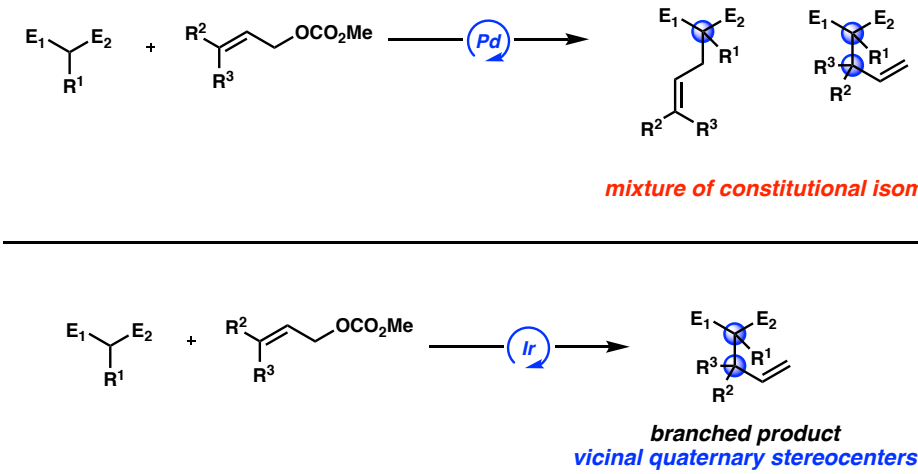
APPENDIX 2

Doubly Stereoselective Construction of Vicinal Quaternary Stereocenters via Ir-Catalyzed Asymmetric Allylic Alkylation

A2.1 INTRODUCTION

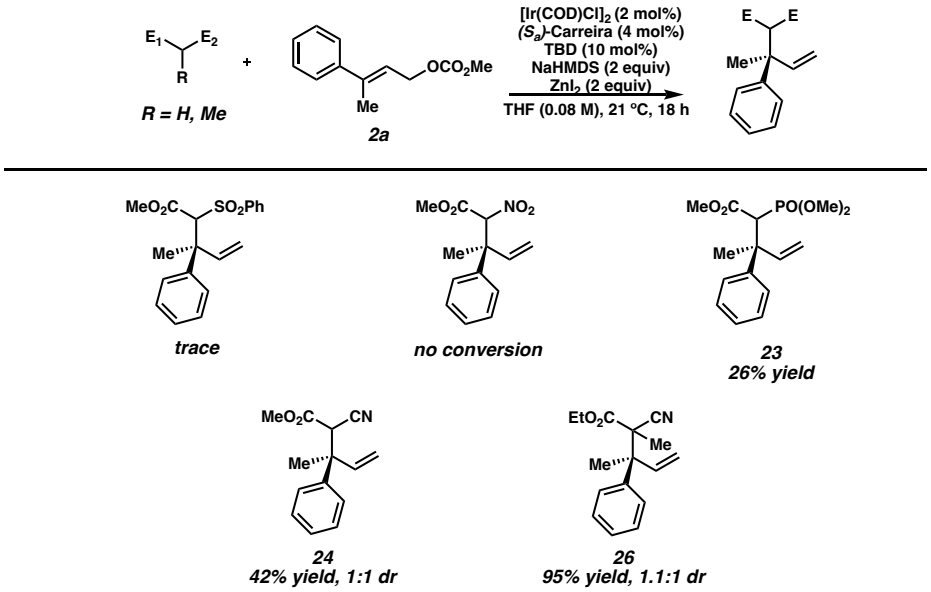
Gratified by the success of our efforts with the malonate nucleophile class, we looked to pursue the more challenging enantio- and diastereoselective formation of vicinal quaternary centers by virtue of this methodology. In the more typical Pd-catalyzed regime, reaction of a prochiral nucleophile with the same class of linear, trisubstituted electrophile utilized in our previous studies would likely exhibit poor regioselectivity, affording a mixture of constitutional isomers with little synthetic utility.[1] Otherwise, specialized ligand systems are necessary to override the intrinsic selectivity of this catalyst for the linear product.[2] Leveraging the exquisite selectivity of iridium for the branched alkylation product, one can imagine that these coupling partners would, in the case of this catalyst, result in the formation of vicinal quaternary stereogenic centers, a property that has thus far not been leveraged successfully (Scheme A2.1). Indeed, only a limited number of catalytic methods involving the construction of vicinal quaternary centers have been developed, with cyclopropanation, cycloaddition, and allylic alkylation prominent among these reports.[3,4] Many of the reactions, however, are either intramolecular in nature, involve highly tailored coupling partners, or proceed with poor diastereoselectivity, limiting their synthetic utility.

Scheme A2.1. *Prochiral Nucleophiles in Asymmetric Allylic Alkylation*



In previous reports detailing the generation of vicinal quaternary centers in Ir-catalyzed allylic alkylation, the issue of diastereoselectivity has been avoided through the use of nucleophiles containing symmetrical substitution patterns. During our investigations with the diethyl malonate system, we were pleased to find that while most stabilized carbon nucleophiles were not compatible with our chemistry (Scheme A2.2), the unsubstituted α-cyano ester afforded the desired product in 42% yield and 1:1 dr (**24**). More excitingly, a substituted derivative of this substrate class led to the formation of the vicinal quaternary product in a 95% NMR yield, albeit as a 1.1:1 mixture of diastereomers (**26**). Additional nucleophiles probed under similar conditions are included in the Experimental Section. Considering the remarkable reactivity of the cyanoester nucleophile under our reaction conditions, we imagined that this nucleophile would serve as a suitable template for the development of an allylic alkylation reaction with stereocontrol at two generated quaternary stereocenters.

Scheme A2.2. *Miscellaneous Stabilized Carbon Nucleophiles*[a]

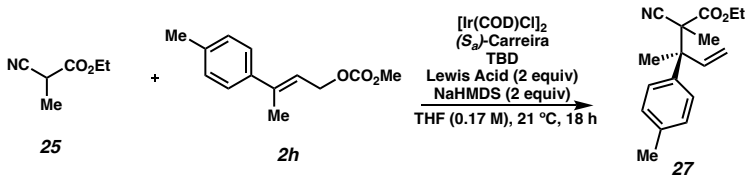


[a] Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

A2.2 RESULTS

Using the *p*-Me substituted allylic methyl carbonate **2h** as the model electrophile, an isolated yield of 85% and 1.1:1 dr of **27** was obtained with nucleophile **25** under the previously optimized conditions (Scheme A2.3). We were pleased to find that reduction of the catalyst loading to 1 mol% $[Ir(COD)Cl]_2$ did not lead to any deterioration in the yield, so this new stoichiometry would be employed therein. Later optimization would reveal that decreasing the catalyst loading by another factor of 2 — to just 0.5 mol% of the dimer — facilitated quantitative conversion to product as observed by NMR analysis of the crude mixture. Further, the ZnI_2 stoichiometry could be reduced to 1.2 equivalents without any detriment to the reaction.

Scheme A2.3. *Initial Optimization of Substituted α-Cyanoester Coupling*[a]



Entry	$[Ir(COD)Cl]_2$	(S_a)-Carreira	TBD	Lewis Acid	Yield	dr[a]
1	2 mol%	4 mol%	10 mol%	ZnI_2	85%	1.1:1
2	2 mol%	4 mol%	10 mol%	CuI	51%	1.1:1
3	1 mol%	2 mol%	5 mol%	ZnI_2	87%	1.1:1

[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

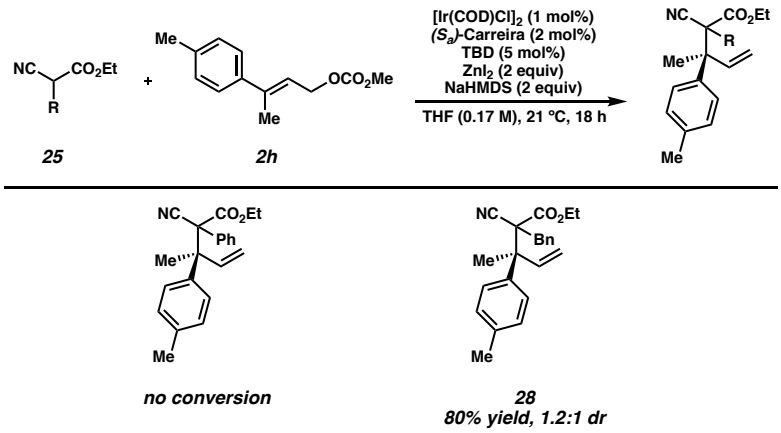
In an effort to improve the stereoselectivity, we predicted that perhaps a more π-philic metal could bind to both functional groups of the nucleophile. CuI was thus probed as a replacement for ZnI_2. However, much like in the case of the malonate nucleophiles, this caused a significant decrease in yield to 51%, albeit with no change in the dr. While the ee of each diastereomer of **27** could not be determined explicitly, SFC analysis indicated an average ee of 93% through combined integration of the two major peaks and two minor peaks.

A2.2.1 INITIAL SUBSTRATE SCOPE

An elementary substrate investigation was conducted to gauge the breadth of this transformation with respect to nucleophile substitution patterns (Scheme A2.4). While the phenyl-substituted cyanoester did not prove suitable in the reaction, we were delighted that a benzyl substituent was accommodated, leading to the formation of vicinal quaternary scaffold **28** in 80% yield and 1.2:1 dr. Like the model product, **28**

was produced in enantioenriched form, with an estimated 93% average ee for the two diastereomers.

Scheme A2.4. *Initial Survey of Nucleophile Substitution*

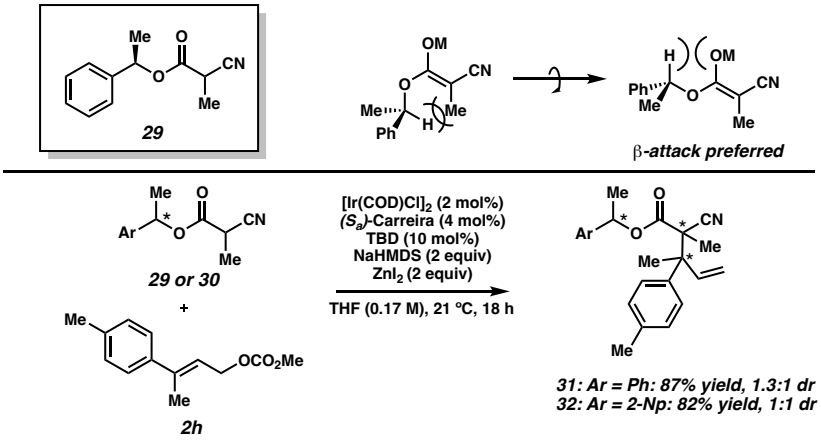


A2.2.2 CHIRAL ESTER APPROACH

Understanding that perhaps the lack of diastereoselectivity in this reaction could be attributed to poor facial selectivity for attack of the electrophile from a given isomer of the enolate, we imagined that a chiral auxiliary could be appended to the ester, resulting in an $A_{1,3}$ minimized enolate conformation (Scheme A2.5) preferring alkylation over the less sterically encumbered face.

With *(R)*-1-phenylethanol as the model auxiliary, we found that the corresponding nucleophile (**29**) could undergo the desired reaction to form **31** in 87% NMR yield but only a moderately improved 1.3:1 dr. Surprisingly, replacement of the phenyl group with a more sterically demanding 2-napthyl substituent in nucleophile **30** resulted in a decrease of the dr to 1:1 (**32**), implying that either the hypothesized enolate projection

Scheme A2.5. *Chiral Ester Approach to Facial Selectivity of Enolate Addition*[a]



[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

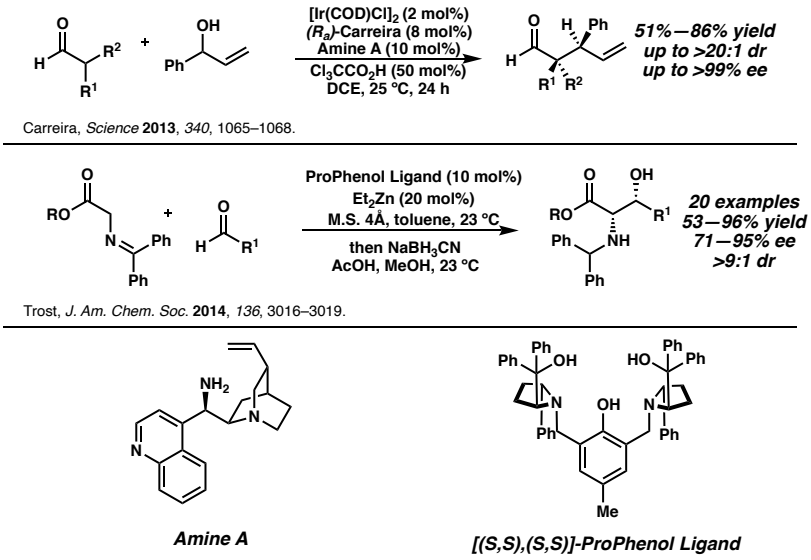
was incorrect or that poor control over the enolate geometry is at least partially responsible for the low dr.

A2.2.3 CHIRAL LEWIS ACID

We were then inspired by other strategies employed in diastereoselective couplings of enolate nucleophiles, such as those employed by Carreira and Trost (Scheme A2.6).[5] In the former case, the Carreira group was able to subject an aldehyde nucleophile to typical allylic alkylation conditions in the presence of a cinchona alkaloid-derived amine to form the corresponding coupling product in high levels of diastereoselectivity. Trost, on the other hand, found that stabilized carbon nucleophiles could be treated with a chiral zinc complex bearing a ProPhenol ligand to facilitate a stereoselective carbonyl addition process.

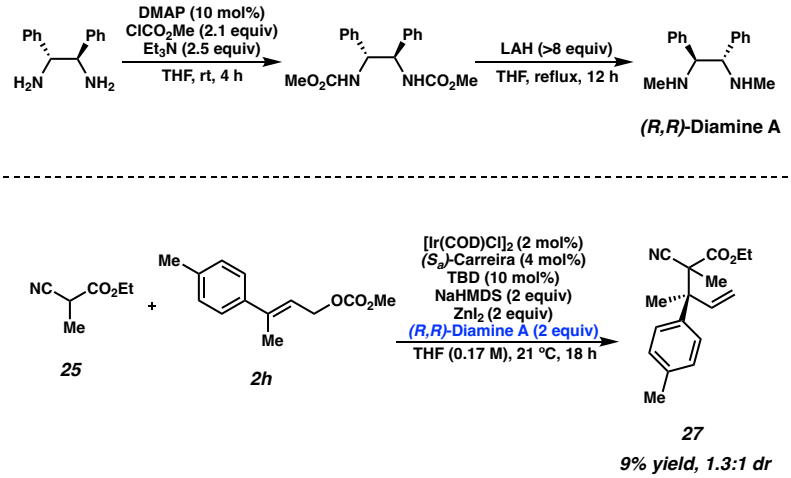
Combining these concepts, we looked to investigate the effect of a chiral Zn lewis

Scheme A2.6. *Strategies for Diastereoselective Enolate Alkylation*



acid on the Ir-catalyzed allylic alkylation we have developed. Starting from commercially available *(1R,2R)*-diphenylethylenediamine, a simple acylation-reduction sequence resulted in the demethylated analog (Scheme A2.7). Reasoning that a C_2-symmetric zinc complex could impart facial selectivity upon the enolate, we added the potential diamine ligand to the reaction mixture. Unfortunately, inclusion of 2 equivalents of this compound resulted in a precipitous decrease in the yield to 9% by NMR, as well as a relatively similar 1.3:1 dr. Together with the failure of the chiral esters to effect diastereoselectivity, this suggested that either our understanding of the mechanism as involving outer sphere nucleophilic substitution is erroneous or that the enolate geometry is the factor that must be controlled.

Scheme A2.7. *C_2-Symmetric Zn System in Ir-catalyzed Allylic Alkylation*[a]



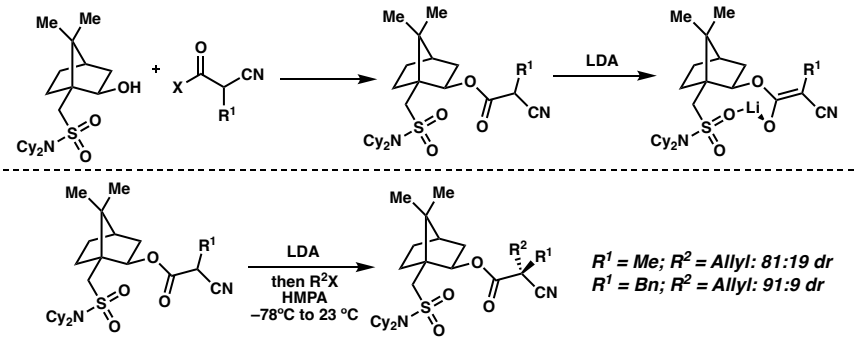
[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

A2.2.4 ISOBORNEOL-DERIVED CYANOESTER

We were also intrigued by a report from Cativiela and coworkers[6] where an isoborneol-derived chiral auxiliary was utilized for similar alkyl-substituted cyanoester systems, forming a Li-chelate upon treatment with LDA. This species could then be trapped by an electrophile to form the corresponding alkylated product in high levels of diastereoselectivity (Scheme A2.8). This is of particular note, as some of the substrates employed in the study greatly resemble those that have already proven competent under our Ir-catalyzed conditions, including methyl and benzyl substitution patterns.

Following the known synthesis for the *N*-dicyclohexylsulfamoyl auxiliary, the α-methyl cyanoester bearing this unique group (**33**) was obtained via coupling with the parent carboxylic acid. We were delighted to find that when subjected to our reaction,

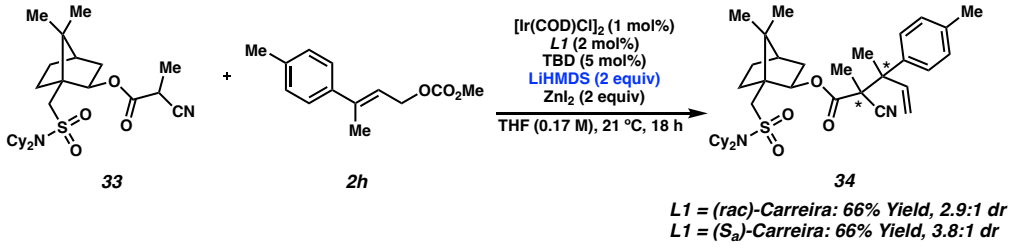
Scheme A2.8. *Isoborneol-derived Chiral Auxiliary in Asymmetric Alkylation*



with LiHMDS used instead of NaHMDS to ensure the formation of a Li chelate, the reaction proceeded in a 66% yield and improved 2.9:1 dr with **(*rac*)-L1**. When **(S_a)-L1** was employed instead, the dr increased to 3.8:1, suggestive of a match between substrate and catalyst stereochemistry (Scheme A2.9).

While not exquisitely stereoselective, this result provided encouraging evidence that a fully stereocontrolled process is attainable. Nevertheless, due to the laborious

Scheme A2.9. *Application of Nucleophile **33** to Ir-catalyzed Asymmetric Allylic Alkylation*[a]



[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

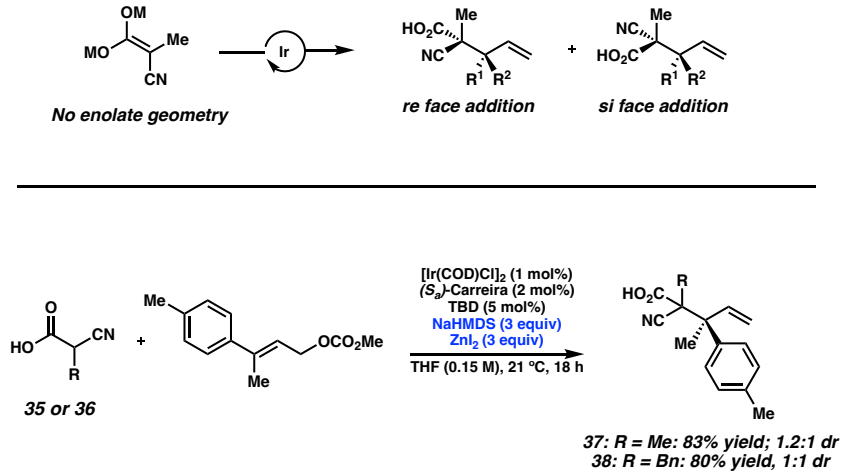
synthesis of the chiral auxiliary and the moderate levels of diastereoselectivity from our initial results, this approach was abandoned in favor of changes to the substrate design that would control factors pertinent to the stereochemical outcome.

A2.2.5 CYANOACID NUCLEOPHILES

Controlling for the assumption that enolate geometry may be entirely responsible for the observed diastereomeric mixture of products, we envisioned that use of a α-cyanoacid nucleophile rather than the α-cyanoester scaffold may be effective. Following two deprotonation events of the cyanoacid, the resulting enolate would not exhibit geometric isomerism, delivering diastereomeric products entirely on the basis of facial bias. Under modified reaction conditions, with larger stoichiometries of Lewis acid and base, we were delighted to observe the competency of these nucleophiles, as we obtained the corresponding allylic alkylation products in good yields (Scheme A2.10). Unfortunately, this was not accompanied by an improvement to the diastereoselectivity, providing further evidence that both facial selectivity and enolate geometry must be controlled in order to induce a stereochemical preference at the nucleophile-derived quaternary stereocenter.

Intrigued by the prospect of substrate design to eliminate enolate isomerism, we posited that a nucleophile with a larger steric profile retaining this feature would provide sufficient differentiation of the diastereomeric transition states of nucleophilic attack. The most obvious way that we imagined this could be done was to constrain the

Scheme A2.10. *Cyanoacid Nucleophile*[a]



[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

enolate in the form of a cyclic scaffold. As such, we targeted α-cyano γ-lactones as our next nucleophile of choice.

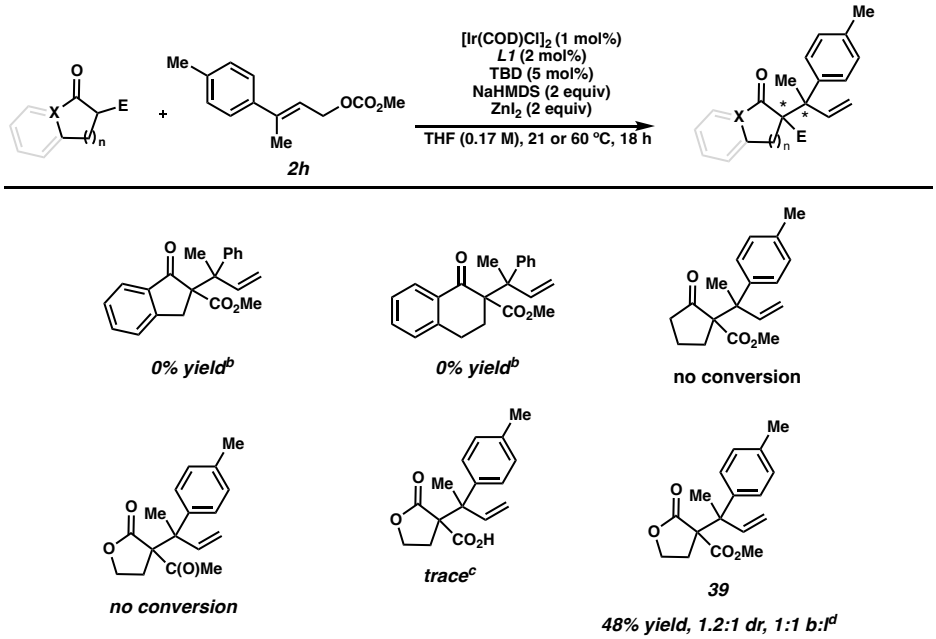
A2.2.6 CYCLIC MANIFOLDS

Indeed, our group has found in the past that cyclic and acyclic manifolds often behave much differently under Ir-catalyzed regimes,[14] with the former in some cases offering superior stereocontrol. Considering the notable differences in reactivity between the two classes of nucleophiles, we first decided to investigate a library of cyclic stabilized carbon nucleophiles resembling the acyclic nucleophiles that we had probed in our earlier investigations, with the hope that they may offer sufficient reactivity and an opportunity for improved diastereoselectivity.

Empirically, we found that motifs posing challenges in the acyclic systems were also not suitable in a cyclic manifold, even at elevated temperatures (Scheme A2.11).

Though the yield was below synthetically useful levels, we were intrigued by the reactivity of the α-carboxy lactone system to form **39**, comparing favorably to the results observed for its acyclic relatives. Nevertheless, the product was formed as a mixture both of diastereomers and constitutional isomers, limiting its utility.

Scheme A2.11. *Cyclic Nucleophiles Under Typical Reaction Conditions*[a,b,c,d]



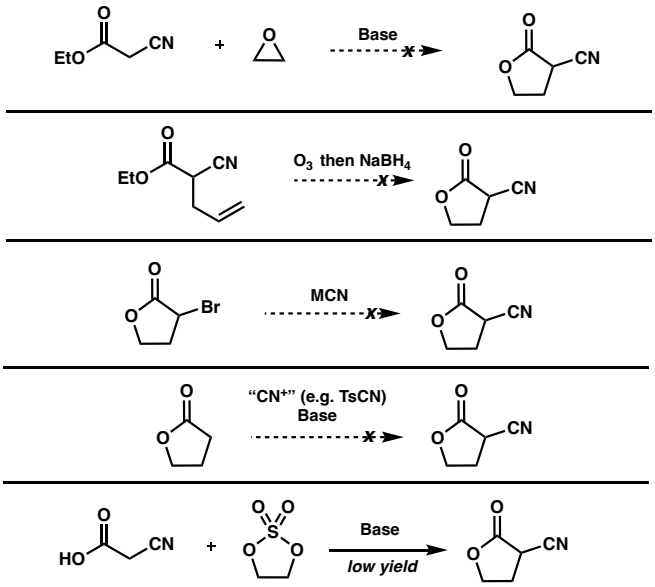
[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard. [b]Reaction performed using 2a instead of 2h. Conducted at 60 °C with 1.2 equiv ZnI_2. [c]Conducted with 3 equiv each of NaHMDS and ZnI_2. [d] 2 mol% $[Ir(COD)Cl]_2$ employed and reaction conducted at 60 °C.

A2.2.7 CYANOLACTONE SYNTHESIS AND APPLICATION

Convinced by the specter that control of enolate geometry could still govern the dr of the reaction with cyanoester nucleophiles, we embarked in earnest on a campaign to synthesize the cyanolactone scaffold. Despite our best efforts, several methods to

access the unsubstituted model substrate (α-cyano γ-butyrolactone) proved unsuccessful (Figure A2.1). Base-promoted opening of ethylene oxide with ethyl cyanoacetate and subsequent ring-closing did not lead to detectable amounts of the desired product. Similarly, reductive ozonolysis of the allylated cyanoester did not afford the cyanolactone. Both nucleophilic and electrophilic cyanation were investigated to no avail, and only a trace amount of the cyclic compound was observed upon treatment of cyanoacetic acid with ethylene sulfate in the presence of base.

Figure A2.1. *Failed Routes to Access α-Cyano γ-Lactones*

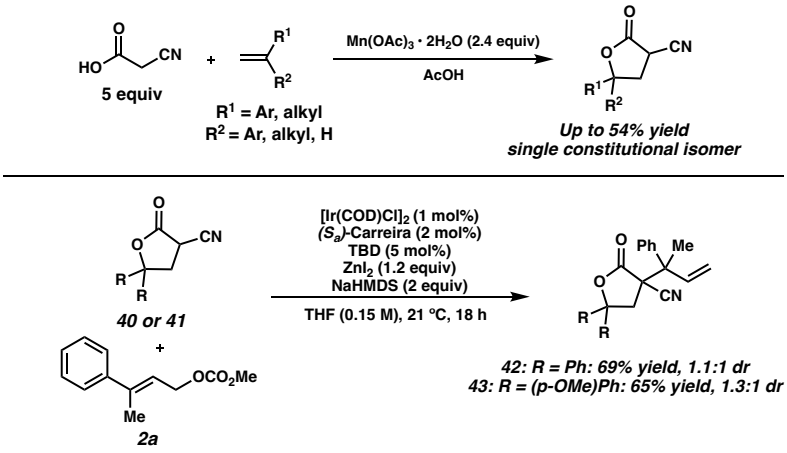


After exhaustive literature investigation, we uncovered a Mn(III)-mediated oxidative cyclization uniting cyanoacetic acid and olefins regioselectively. First discovered by Heiba and Finkbauer in 1968[7] and expanded by Fristad and Corey in 1985,[8] this reaction is predicated on the formation of an enolate radical intermediate, which undergoes regioselective addition into an olefin to form the more stable alkyl

radical.[9] This radical is then oxidized and trapped by the acid moiety to furnish substituted lactone products. Applying this technology, we were able to access a range of substituted cyanolactone substrates, including γ-disubstituted variants we were hopeful would be compatible to our reaction (Scheme A2.12).

However, as had been the case with many of our explored nucleophile classes, we found that the cyanolactones could indeed undergo the allylic alkylation in moderate yield, but no improvement in the diastereoselectivity was evident. This confirmed that, in addition to control of enolate geometry, an explicit facial bias would need to be installed into the nucleophile for stereocontrol at the nucleophile-derived center.

Scheme A2.12. *Synthesis and Application of Cyanolactone Substrates*



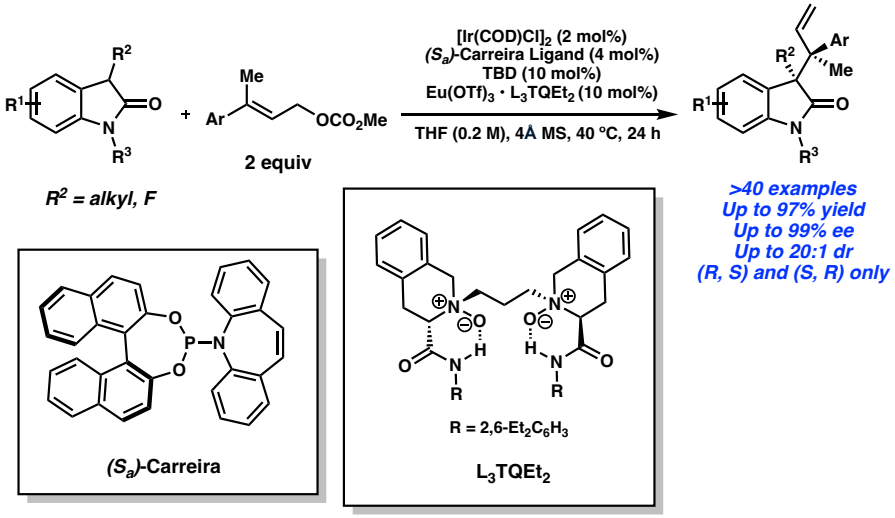
[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

A2.2.8 FENG REPORT CONSTRUCTING VICINAL QUATERNARY CENTERS

During our studies, Feng and coworkers reported the first and only example of an enantio- and diastereoselective Ir-catalyzed allylic alkylation forging the vicinal

quaternary motif, employing the linear electrophiles and catalytic system pursued by our research group in the construction of electrophile-derived quaternary stereocenters (Scheme A2.13).[10] In their transformation, a europium co-catalyst bound to a chiral bis(*N*-oxide) ligand serves to generate the operative enolate. While the enantioenriched ligand does indeed provide high levels of both enantio- and diastereoselectivity, only 2 of 4 possible stereoisomers could be accessed through the protocol.

Scheme A2.13. *First Reported Example of Doubly Stereoselective Construction of Vicinal Quaternary Centers via Ir-catalyzed Allylic Alkylation by Feng*



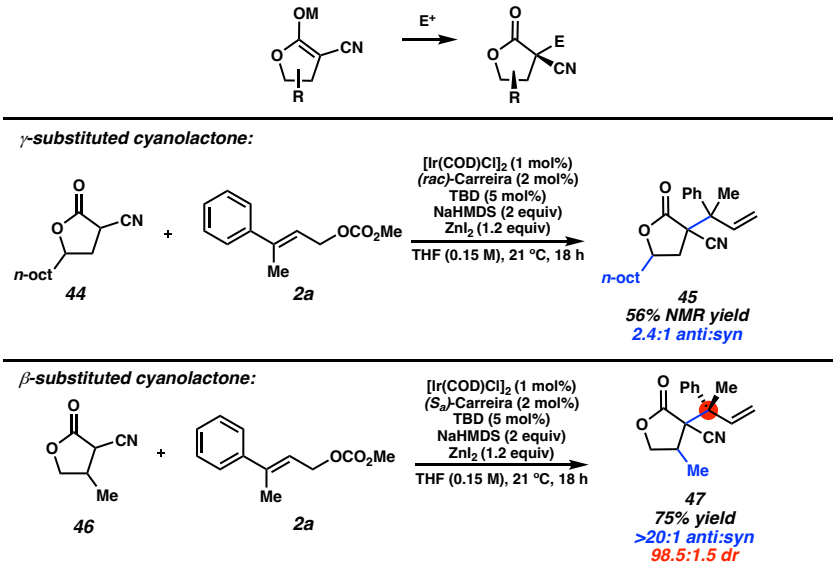
Despite this report, we remained interested in taking advantage of the incredible reactivity of cyanoesters under our developed reaction conditions, and we believed the cyanolactone scaffold remained a good candidate for substrate design enforcing the necessary facial bias to confer diastereoselectivity. We hypothesized that a cyanolactone nucleophile containing a substituent at either the γ- or β-position could

promote nucleophilic attack over the less sterically encumbered face of the lactone, finally effecting stereocontrol at the nucleophile-derived center.

A2.2.9 MONO-SUBSTITUTED CYANOLACTONES

Gratifyingly, we found that a γ-monosubstituted cyanolactone, synthesized by the Mn(III)-promoted oxidative coupling reaction, generated a 2.4:1 mixture of products corresponding to *anti*- or *syn*-addition relative to the γ-substituent (Scheme A2.14). Naturally, we wondered if shifting this group one methylene closer to the site of nucleophilic attack would further improve the stereoselectivity. To our delight, β-methyl cyanolactone **46** could be subjected successfully to our optimized reaction conditions, resulting in exquisite selectivity for *anti*-addition. The configuration at the electrophile-borne center was governed by the chiral catalyst, and **47** was obtained with

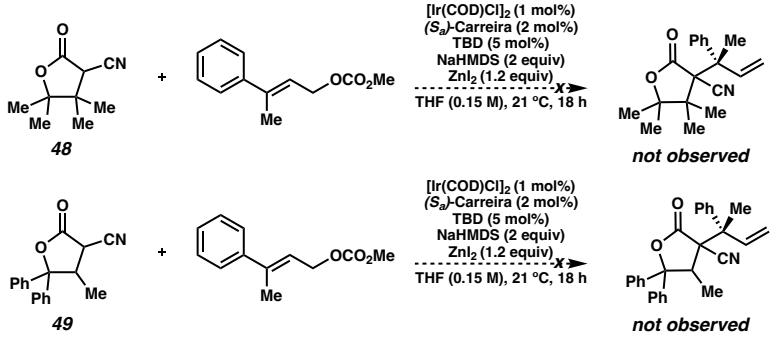
Scheme A2.14. *Application of Mono-substituted Cyanolactone Nucleophiles*



excellent levels of stereocontrol at both quaternary centers.

Attempts to utilize higher order substitution patterns on the lactone, including incorporation of a quaternary center at the γ-position along with tertiary or quaternary substitution at the β-position, did not result in product formation (Scheme A2.15).

Scheme A2.15. *Highly-substituted Cyanolactones*

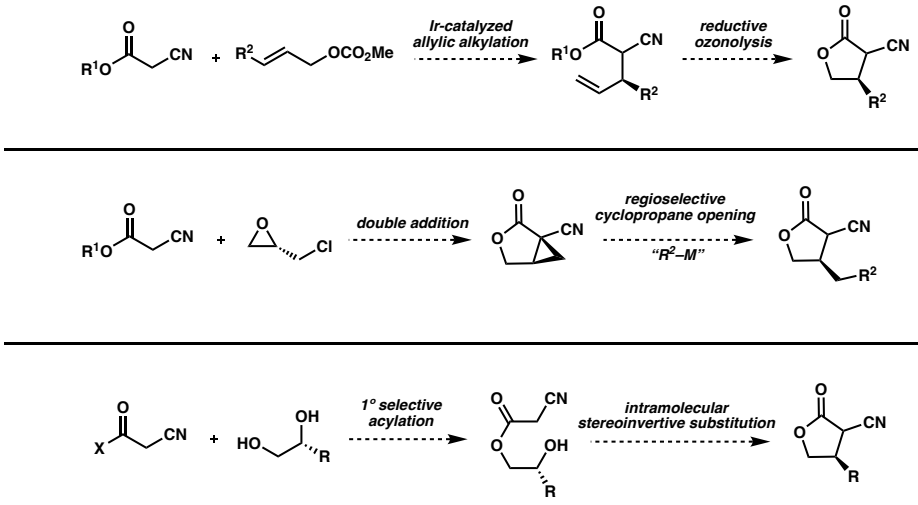


A2.2.10 SYNTHESIS AND APPLICATION OF STEREOENRICHED SUBSTRATE

Given that a third stereocenter was introduced to the substrate, we were aware that to obtain only one stereoisomer of product as the major reaction outcome, a nucleophile stereoenriched at the β-position would need to be employed. The pursuit of such lactones served as another synthetic challenge (Figure A2.2). An initial approach involved a precedented Ir-catalyzed allylic alkylation of a cyanoester nucleophile with disubstituted allylic electrophiles,[11] after which a reductive ozonolysis of the terminal olefin would furnish the stereoenriched material. Unfortunately, this plan was plagued with irreproducible enantioselectivity of the allylic alkylation and competitive reduction of the cyanoester observed upon attempted reduction of the aldehyde.

Another attempt, inspired by a literature protocol,[12] involved the reaction of cyanoesters with abundant chiral epichlorohydrin, resulting in the formation of a fused cyclopropane. This intermediate could then undergo regioselective opening at the secondary carbon of the cyclopropane with an organometallic reagent, delivering stereoenriched β-susbstituted α-cyano lactones. While the cyclopropane was possibly constructed in trace amounts, the subsequent ring-opening reaction did not prove fruitful under a range of conditions.

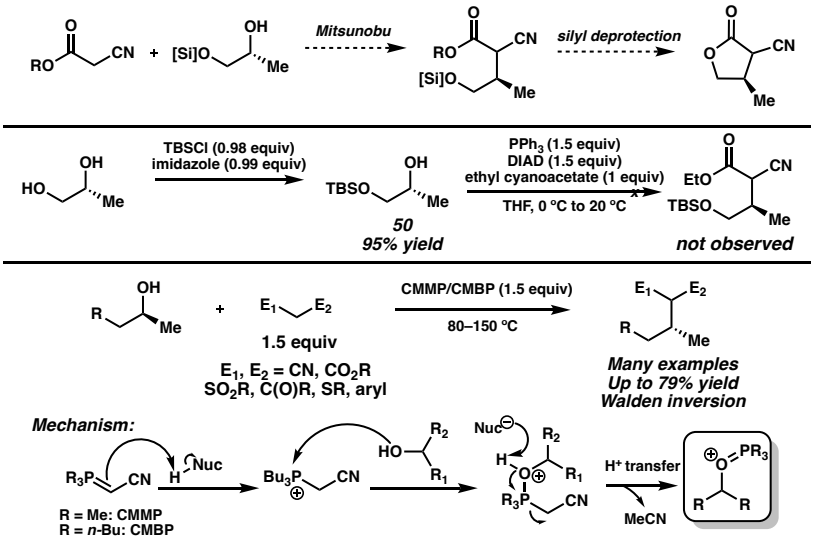
Figure A2.2. *Early Approaches to the Construction of Stereoenriched Cyanolactones.*



Without much literature precedent for asymmetric conjugate addition into α-cyanobutenolides or of their asymmetric hydrogenation, we resigned ourselves to a stepwise approach, with an envisioned acylation of the primary alcohol of a commercial, enantiopure 1,2-diol with cyanoacetic acid or a derivative thereof, followed by stereoinvertive, intramolecular substitution.

Despite a range of explored conditions, the acylation of these alcohols at exclusively the primary alcohol could not be achieved. As such, a "substitution first" strategy was employed, wherein the diol could be TBS-protected at the primary alcohol with well-precedented regiocontrol, and the secondary alcohol would be functionalized either in-situ or prior to introduction of the cyanoester nucleophile. The former, which would reduce the complexity of substrate synthesis, was examined first.

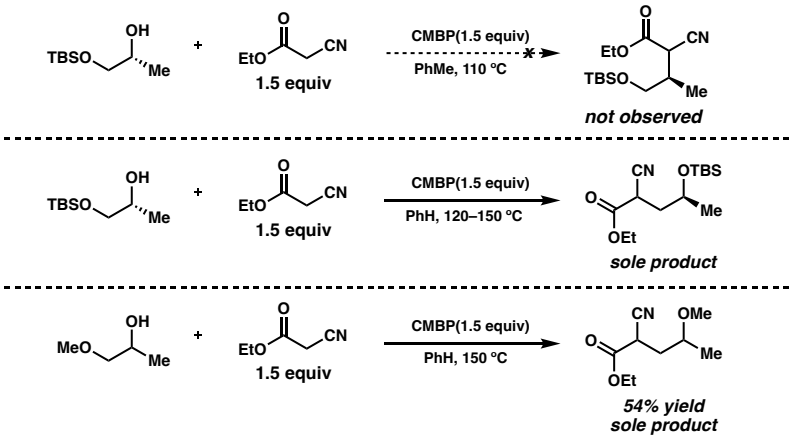
Scheme A2.16. *Attempted Intermolecular Mitsunobu Reaction*



Appel conditions did not furnish any of the desired product, but we were hopeful that treatment with a Mitsunobu reagent would allow for the desired reaction (Scheme A2.16). When DIAD did not prove compatible with the desired substitution, we turned to a series of reagents developed by Tsunoda and coworkers.[13] Unlike the traditional Mitsunobu conditions, these functionalized ylides have been utilized for the coupling of secondary alcohols with numerous stabilized carbon nucleophiles, enabled by the

temperature stability of CMMP/CMBP and the basicity of the coupling reagent. Nevertheless, in our hands, use of these conditions with ethyl cyanoacetate as the nucleophile did not lead to any observed product (Scheme A2.17). When the temperature was increased, the sole compound observed corresponded to TBS migration to the secondary alcohol and substitution at the primary position. The same phenomenon was observed even when a methyl group was used to protect the primary alcohol, dissuading us from further investigation of the Mitsunobu reaction.

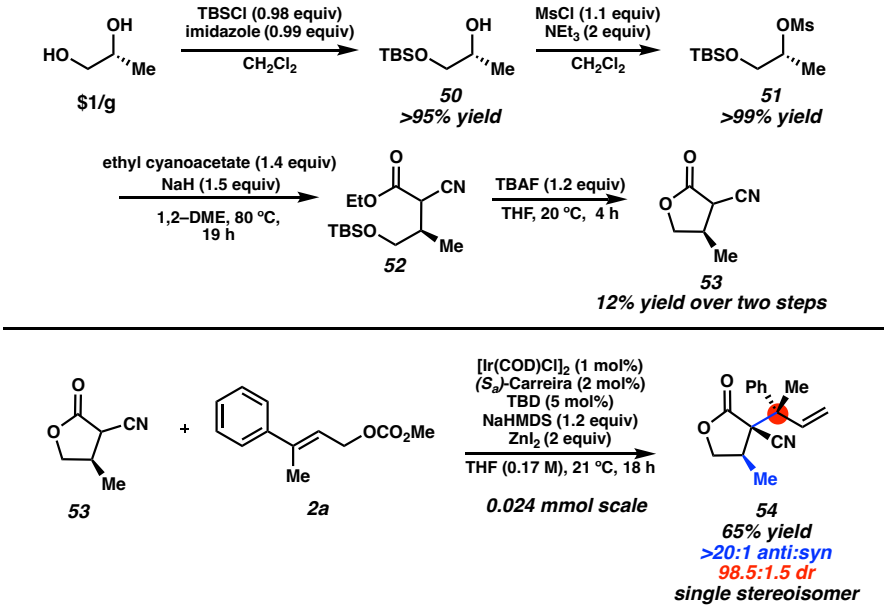
Scheme A2.17. *Tsunoda Reagents as Applied to Desired System*



With all other options exhausted, we settled upon the most elementary strategy we could imagine – activation of the secondary alcohol as a pseudo-halide and nucleophilic substitution in a separate step under forcing conditions. We ultimately arrived at the conditions presented in Scheme A2.18, allowing for the isolation of stereoenriched cyanolactone **54**. A slightly improved set of conditions for the substitution reaction is described in the Experimental Section. As anticipated, **54** could undergo the reaction

under optimal conditions to form the corresponding product containing three contiguous stereocenters as one major stereoisomer.

Scheme A2.18. *Synthesis and Coupling of Stereoenriched Cyanolactone Substrate*

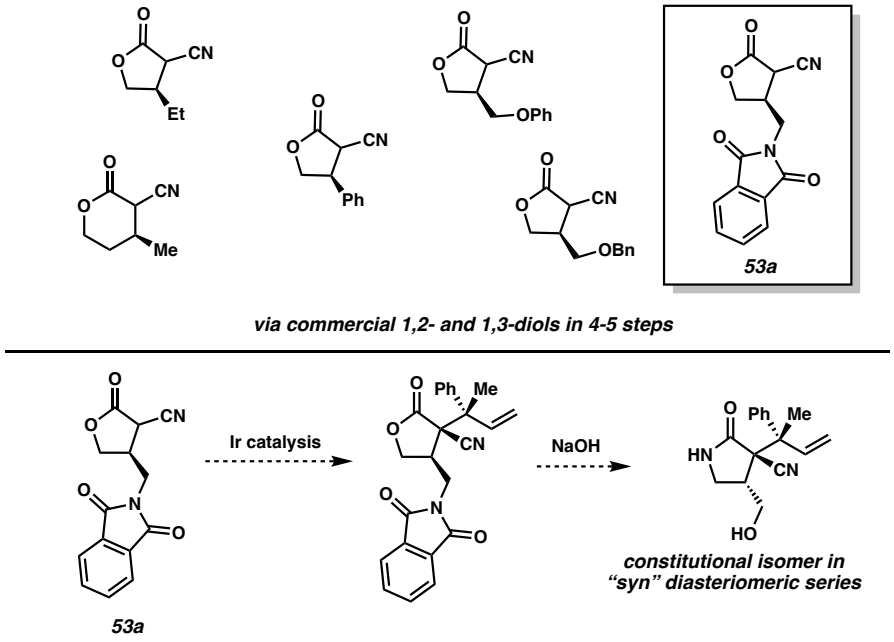


A2.3 CONCLUSION

Utilizing this synthetic sequence and a related protocol involving an intramolecular substitution, we were able to access several nucleophiles we imagine could be suitable to the desired reaction, with varying substitution at the β-position and varying ring sizes represented in the library of substrates (Scheme A2.3). Efforts are ongoing to determine the applicability of the reaction to these nucleophiles and electrophiles with differential substitution on the arene. We are particularly excited by products containing peripheral functionality, such as **53a**, which we imagine could undergo the allylic alkylation, followed by deprotection to the primary amine and lactamization to deliver a lactam

with the opposite relative stereochemistry between the α- and β-positions, thereby giving some access to the "*syn*" diastereomeric series of materials.

Figure A2.3. *Prospective Nucleophile Scope and Inversion of Relative Stereochemistry.*



In conclusion, we are enthusiastic about the pursuit of an efficient cross-coupling of two highly substituted reaction partners to form vicinal quaternary stereocenters in a doubly stereoselective fashion. Though the diastereoselectivity of the reaction we have developed has thus far only been substantially improved by the introduction of a stereocenter on the nucleophile, we are hopeful that these promising results, invoking atypically low catalyst loadings and mild reaction conditions, lay the groundwork for future research in our group's Ir-catalysis program.

A2.4 EXPERIMENTAL SECTION

A2.4.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[14] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for flash chromatography. ^{1}H NMR spectra were recorded on Varian Inova 500 MHz and Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak (IH) or Chiralcel (OD-H) columns (4.6 mm x 25 cm) both obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H

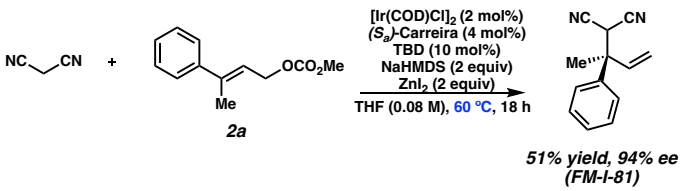
High Resolution Mass Spectrometer in field ionization (FI+) or field desorption (FD+) mode, or an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI), or mixed ionization mode (MM: ESI-APCI+). Absolute configuration of **3a** was determined by vibrational circular dichroism, and all other products are assigned by analogy. Reagents were purchased from commercial sources and used as received unless otherwise stated.

List of Abbreviations:

ee – enantiomeric excess, SFC – supercritical fluid chromatography, HPLC – high-performance liquid chromatography, TLC – thin-layer chromatography, TBD – 1,5,7-triazabicyclo[4.4.0]dec-5-ene, COD – *cis,cis*-1,5-cyclooctadiene, COE – *cis*-cyclooctene, DIBAL – diisobutylaluminum hydride, LAH – lithium aluminum hydride, NaHMDS – sodium bis(trimethylsilyl)amide, IPA – isopropanol, EtOAc – ethyl acetate, Dr – dram

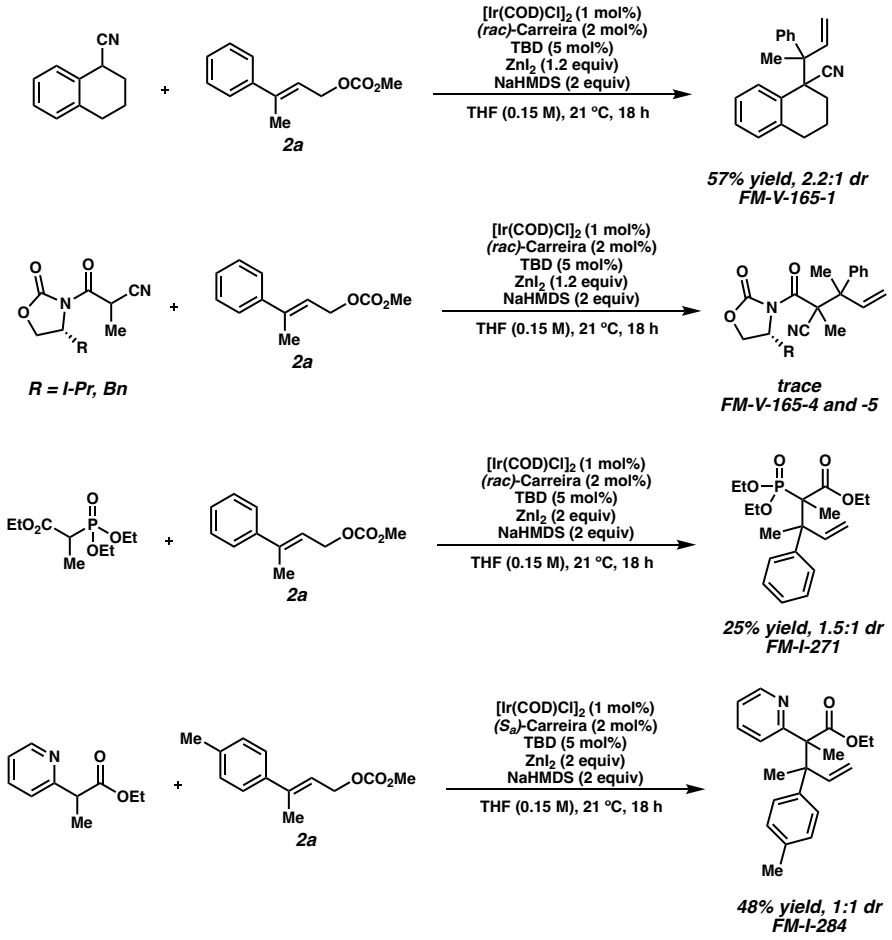
A2.4.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

Scheme A2.19. *Performance of Malononitrile*[a]



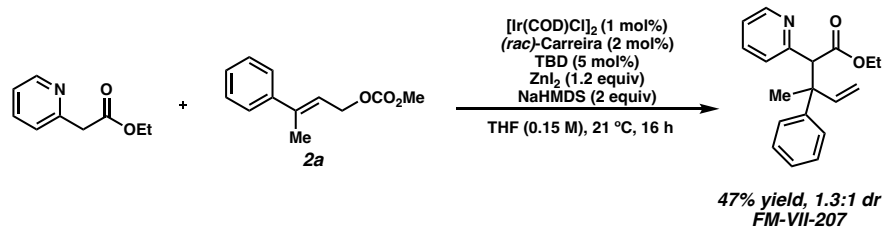
[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

Scheme A2.20. *Performance of Other Trisubstituted Nucleophiles*[a]



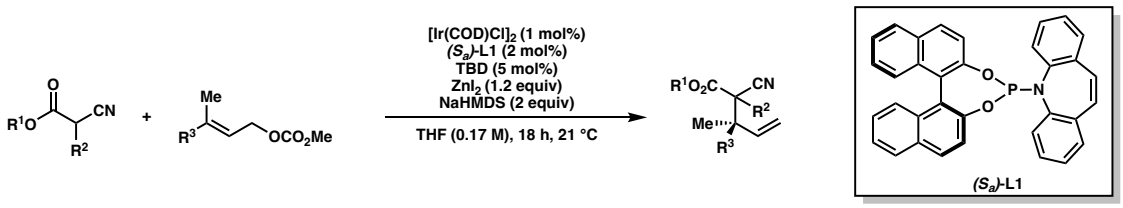
[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

Scheme A2.21. *Performance of Ethyl 2-Pyridyl Acetate*

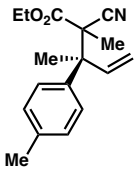


crude NMR: possible 2.5:1 mixture of branched and linear product isomers

Iridium-Catalyzed Allylic Alkylation Reactions: General Procedure A (0.1mmol scale)



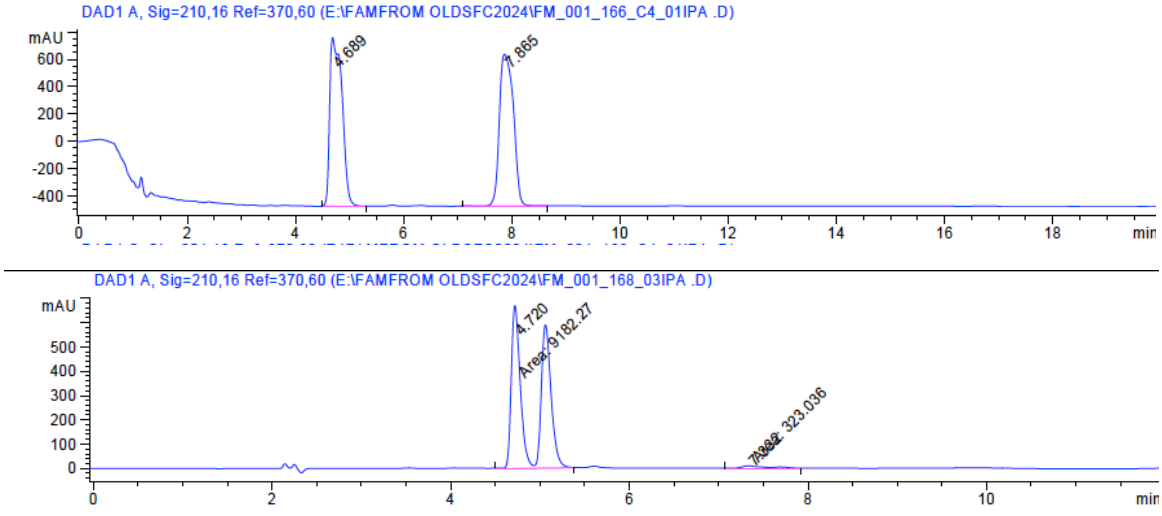
In a nitrogen-filled glovebox, a catalyst (2 mol% [Ir]) solution of $[Ir(COD)Cl]_2$ (3.3 mg/mL), ***(S$_a$)-L1*** (5 mg/mL), and TBD (3.5 mg/mL) in THF was stirred for 20 min at 25 °C. In separate vials, solutions of *(E)*-allylic carbonate (0.5 mmol/mL) and of nucleophile (0.5 mmol/mL) were prepared in THF. During that time, the reaction vial was charged with ZnI_2 (64 mg, 0.12 mmol, 1.2 equiv) and NaHMDS (36.7 mg, 0.2 mmol, 2.0 equiv). 0.23 mL of the nucleophile solution (0.1 mmol, 1.0 equiv) was added to the reaction vial and stirred for 5 min, followed by 0.20 mL of catalyst solution, and finally 0.22 mL of allylic carbonate solution (0.1 mmol, 1.0 equiv). The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 21 °C for 18 h unless noted otherwise. After 18 h, 3 mL 0.5 M HCl was added to the crude reaction mixture, which was then extracted three times with ethyl acetate, dried over Na_2SO_4, concentrated, and purified by preparatory TLC to provide the desired alkylation product.



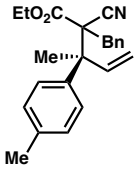
ethyl (3*S*)-2-cyano-2,3-dimethyl-3-(*p*-tolyl)pent-4-enoate (27)

Purified by preparatory TLC (10% EtOAc/Hexanes) to deliver **27** as a clear oil (23.5 mg, 0.087 mmol, 87% yield, 93% avg. ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 2H), 7.17 – 7.09 (m, 2H), 6.84 – 6.61 (m, 1H), 5.40 – 5.32 (m, 1H), 5.26 – 5.16 (m, 1H), 4.11 – 3.93 (m, 2H), 2.36 – 2.30 (m, 3H), 1.75 – 1.64 (m, 3H), 1.55 – 1.49 (m, 3H), 1.13 – 1.03

(m, 3H). SFC Conditions: 7% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): minor = 7.87, major = 4.72.

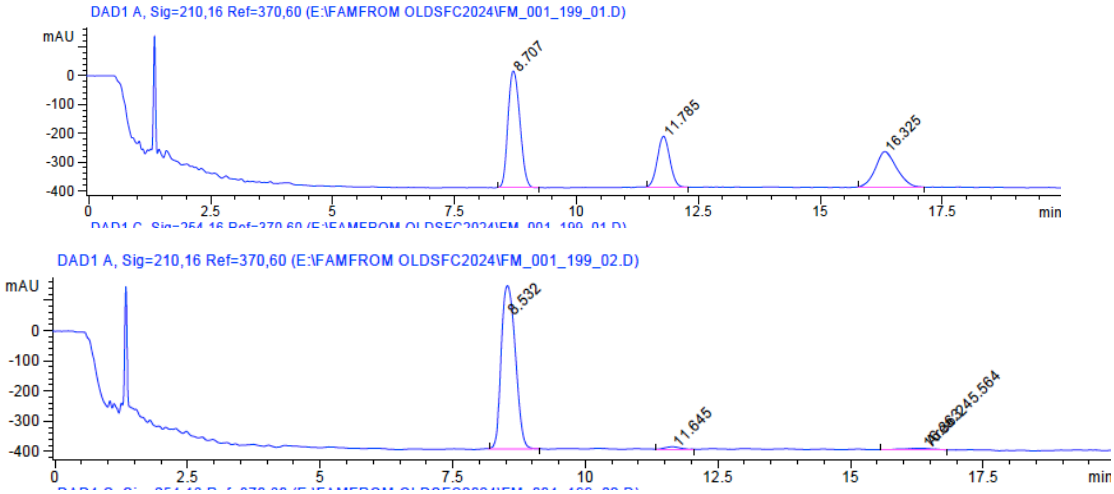


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.720	MM	0.2272	9182.27051	673.68793	96.6015
2	7.332	MM	0.4251	323.03613	12.66609	3.3985

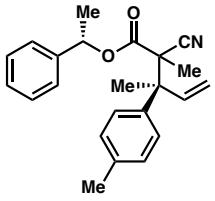


ethyl (3*S*)-2-benzyl-2-cyano-3-methyl-3-(*p*-tolyl)pent-4-enoate (28)

Purified by preparatory TLC (10% EtOAc/Hexanes) to deliver **28** as a clear oil (27.9 mg, 0.080 mmol, 80% yield, 93% avg. ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.38 (m, 2H), 7.32 – 7.20 (m, 5H), 7.19 – 7.10 (m, 2H), 7.06 – 6.86 (m, 1H), 5.50 – 5.40 (m, 1H), 5.36 – 5.26 (m, 1H) 3.95 – 3.73 (m, 2H), 3.56 – 2.78 (m, 2H), 2.36 – 2.31 (m, 3H), 1.88 – 1.81 (m, 3H), 0.86 (q, J = 7.3 Hz, 3H). SFC Conditions: 1% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): minor = 11.79 and 16.33, major = 8.53.

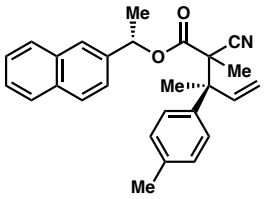


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.532	BB	0.3008	1.00230e4	539.46515	96.3114
2	11.645	BB	0.2457	138.30000	7.84340	1.3289
3	16.363	MM	0.7200	245.56386	5.68445	2.3596



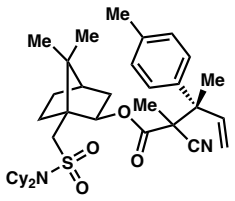
(*S*)-1-phenylethyl (3*S*)-2-cyano-2,3-dimethyl-3-(*p*-tolyl)pent-4-enoate (31)

Crude yield determined by ^{1}H NMR relative to CH_2Br_2 internal standard (30.0 mg) assuming peaks at 6.59 ppm and 6.81 ppm belong to diastereomers of product and integrate to 1H (87% yield, 1.3:1 dr).



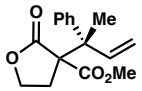
(*S*)-1-(naphthalen-2-yl)ethyl (3*S*)-2-cyano-2,3-dimethyl-3-(*p*-tolyl)pent-4-enoate (32)

Crude yield determined by ^{1}H NMR relative to CH_2Br_2 internal standard (26.2 mg) assuming peaks at 6.68 ppm and 6.76 ppm belong to diastereomers of product and integrate to 1H (82% yield, 1:1 dr).



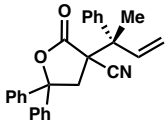
(1*R*,2*R*,4*R*)-1-((*N*,*N*-dicyclohexylsulfamoyl)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl (3*S*)-2-cyano-2,3-dimethyl-3-(*p*-tolyl)pent-4-enoate (34)

Crude yield determined by ^{1}H NMR relative to CH_2Br_2 internal standard (25.1 mg) assuming peaks at 6.67 ppm and 7.00 ppm belong to diastereomers of product and integrate to 1H (66% yield, 3.8:1 dr).



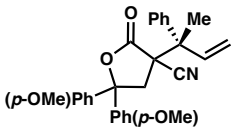
methyl 2-oxo-3-((*S*)-2-phenylbut-3-en-2-yl)tetrahydrofuran-3-carboxylate (39)

Crude yield determined by ^{1}H NMR relative to CH_2Br_2 internal standard assuming peaks at 5.17 ppm and 5.08 ppm belong to diastereomers of product and integrate to 1H (48% yield, 1.2:1 dr).



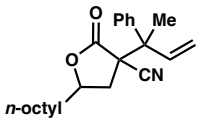
2-oxo-5,5-diphenyl-3-((*S*)-2-phenylbut-3-en-2-yl)tetrahydrofuran-3-carbonitrile (42)

Crude yield determined by ^{1}H NMR relative to CH_2Br_2 internal standard (25.4 mg) assuming combined peaks at 5.27 ppm and 5.45 ppm belong to diastereomers of product and integrate to 2H (69% yield, 1.1:1 dr).



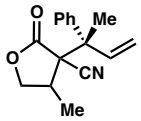
5,5-bis(4-methoxyphenyl)-2-oxo-3-((*S*)-2-phenylbut-3-en-2-yl)tetrahydrofuran-3-carbonitrile (43)

Crude yield determined by ^{1}H NMR relative to CH_2Br_2 internal standard (24.5 mg) assuming peaks at 6.20 ppm and 6.28 ppm belong to diastereomers of product and integrate to 1H (65% yield, 1.3:1 dr).



5-octyl-2-oxo-3-(2-phenylbut-3-en-2-yl)tetrahydrofuran-3-carbonitrile (45)

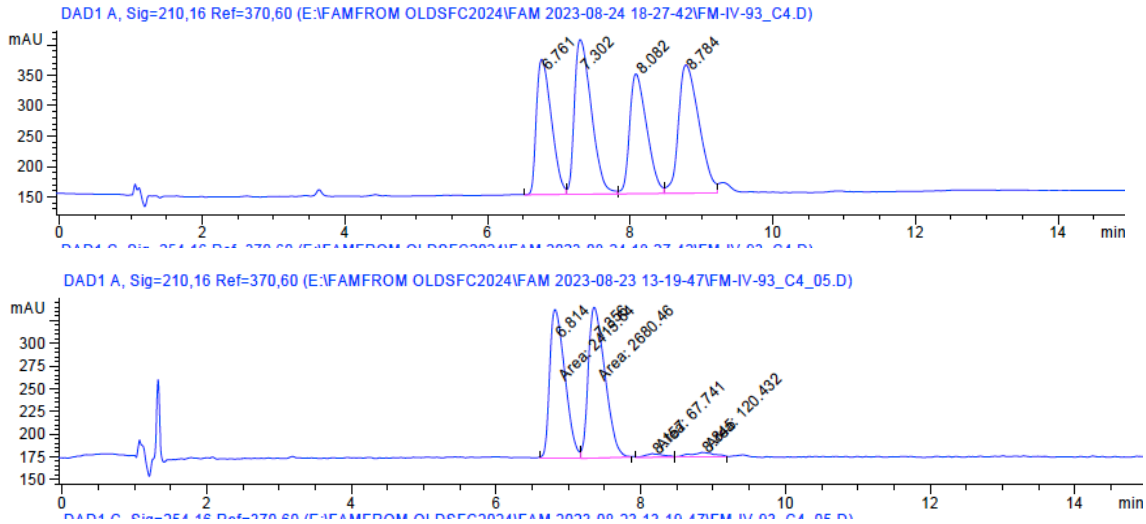
Reaction performed with racemic ligand using 1.2 equiv of **44**. Crude yield determined by by ^{1}H NMR relative to CH_2Br_2 internal standard (30.7 mg) assuming peaks at 6.35 ppm, 6.50 ppm, 6.59 ppm, and 6.69 ppm belong to diastereomers of product and integrate to 1H (56% yield, 2.4:1 dr).



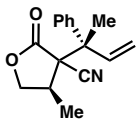
4-methyl-2-oxo-3-((*S*)-2-phenylbut-3-en-2-yl)tetrahydrofuran-3-carbonitrile (47)

Reaction performed using 1.5 equiv of **48**. Purified by silica gel chromatography (20–60% EtOAc/Hexanes) to afford **47** as a waxy solid (19.4 mg, 0.076mmol, 76% yield). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.54 – 7.43 (m, 2H), 7.42 – 7.30 (m, 3H), 6.71 – 6.52 (m, 1H), 5.55 – 5.37 (m, 1H), 5.31 – 5.19 (m, 1H), 3.71 – 3.59 (m, 1H), 3.53 – 3.36 (m, 1H), 2.77 – 2.57 (m, 1H), 1.93 – 1.76 (m, 3H), 1.12 – 0.92 (m, 3H). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): minor = 8.08 and 8.78, major = 6.81 and 7.36.



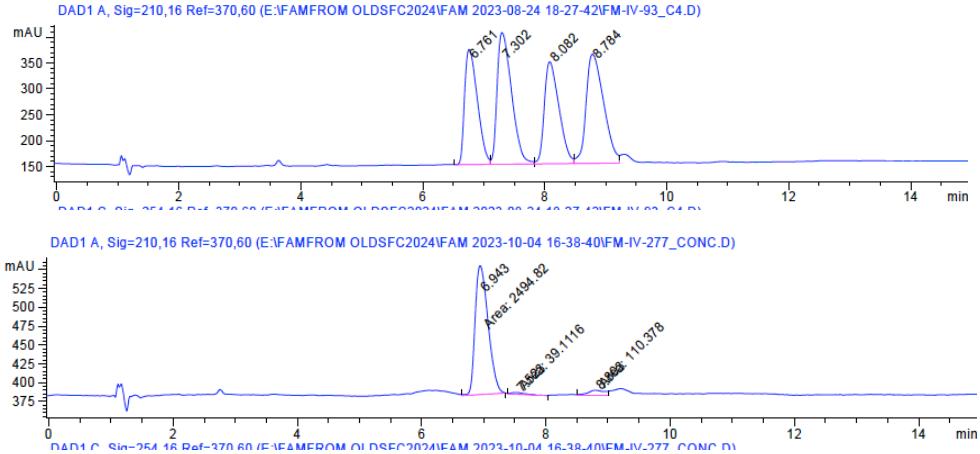
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.814	MM	0.2449	2415.64038	164.38982	159.9982
2	7.356	MM	0.2686	2680.45825	166.32680	177.5383
3	8.157	MM	0.2775	67.74096	4.06903	4.4868
4	8.845	MM	0.3913	120.43221	5.12974	7.9767
Totals :				5284.27180	339.91538	



(4*R*)-4-methyl-2-oxo-3-((*S*)-2-phenylbut-3-en-2-yl)tetrahydrofuran-3-carbonitrile (54)

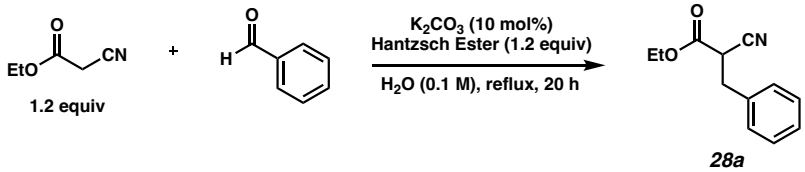
Reaction performed at 0.024 mmol scale. Purified by silica gel chromatography to afford **54** as an oil (3.5 mg, 0.016 mmol, 65% yield, >20:1 dr, 98.5:1.5 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.44 (m, 2H), 7.43 – 7.28 (m, 3H), 6.58 (dd, J = 17.5, 11.1 Hz, 1H), 5.49 (d, J = 11.1 Hz, 1H), 5.26 (d, J = 17.5 Hz, 1H), 3.63 (dd, J = 9.1, 5.5 Hz, 1H), 3.41 (dd, J

= 9.2, 7.5 Hz, 1H), 2.71 (pd, J = 7.2, 5.5 Hz, 3H), 1.82 (s, 1H), 1.01 (d, J = 7.1 Hz, 3H). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): minor = 7.52 and 8.80, major = 6.94.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.943	MM	0.2427	2494.81714	171.31042	330.2136
2	7.523	MM	0.2654	39.11162	2.45623	5.1768
3	8.803	MM	0.2976	110.37820	6.18095	14.6096
Totals :				2644.30695	179.94760	

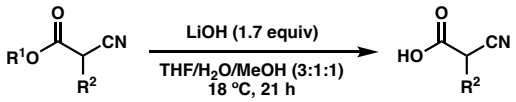
Synthesis of Benzyl-Substituted Cyanoester 28a[15]



Ethyl cyanoacetate (542.9 mg, 4.8 mmol, 1.2 equiv), benzaldehyde (424.5 mg, 4 mmol), K_2CO_3 (55.3 mg, 0.4 mmol, 0.1 equiv), and Hantzsch ester (1.216 g, 4.8 mmol, 1.2 equiv) were combined in a roundbottom flask equipped with a stir bar and dissolved in H2O (40 mL, 0.1 M). The reaction was then heated to reflux and stirred for 20 h, at which point the temperature was lowered to ambient conditions. The solution was extracted three times with ethyl acetate, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (10%

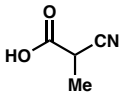
EtOAc/Hexanes), resulting in a mixture of the product and the pyridine biproduct. This was dissolved in EtOAc and washed three times with 5 M aq. H_2SO_4, and the organic layer was dried, filtered, and concentrated to deliver ethyl 2-cyano-3-phenylpropanoate (**28a**) as a clear oil (142 mg, 0.7 mmol, 18% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 4.30 – 4.18 (m, 2H), 3.72 (dd, J = 8.4, 5.8 Hz, 1H), 3.33 – 3.14 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H). Characterization data was in agreement with the literature.

Saponification of Cyanoester Substrates[16]



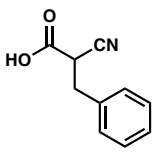
35 or 36

The appropriate cyanoester (10 mmol) was dissolved in a mixture of THF, H_2O and MeOH (THF:H_2O:MeOH = 30 mL: 10 mL: 10 mL), and LiOH (0.713 g, 17 mmol, 1.7 equiv) was added. The reaction was stirred at 18 ºC for 21 h, at which point it was quenched with 20 mL 1.0 M aq. HCl. The mixture was extracted with ethyl acetate, dried with Na_2SO_4, filtered, and concentrated to deliver the cyanoacid without the need for further purification.



2-cyanopropanoic acid (35)

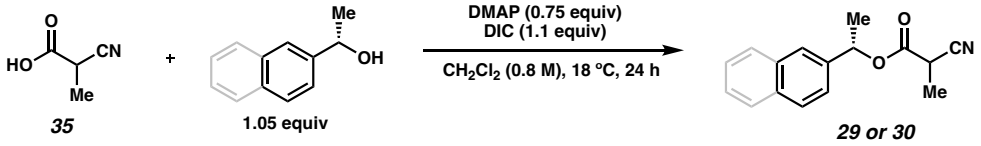
Product was obtained as a yellow oil (980 mg, 9.9 mmol, 99% yield) from ethyl 2-cyanopropanoate. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (q, J = 7.4 Hz, 1H), 1.67 (d, J = 7.4 Hz, 3H). Characterization data was in agreement with the literature.[17]



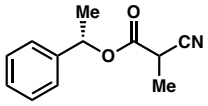
2-cyano-3-phenylpropanoic acid (36)

Reaction performed at 7.2 mmol scale using **28a**. Additional purification involved extraction from CH_2Cl_2 with 1 M NaOH, followed by acidification of the aqueous layer with 2 M HCl and extraction from the aqueous phase with ethyl acetate. Product was obtained as a clear oil (145 mg, 0.83 mmol, 12% yield). ^{1}H NMR (400 MHz, MeOD) δ 7.50 – 7.14 (m, 5H), 3.63 (dd, J = 9.2, 5.5 Hz, 1H), 3.28 – 3.04 (m, 2H).

Esterification of Cyanoacids[18]

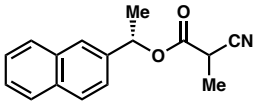


A mixture of cyanoacid **35** (396.4 mg, 4 mmol), chiral alcohol (4.2 mmol, 1.05 equiv), and DMAP (366.5 mg, 3 mmol, 0.75 equiv) was prepared under inert atmosphere and dissolved in CH_2Cl_2 (5 mL, 0.8 M). Diisopropylcarbodiimide (555.3 mg, 0.69 mL, 1.1 equiv) was then added via syringe, and the solution was stirred at 18 ºC for 24 h. The reaction mixture was then filtered and washed thoroughly with ethyl acetate. The filtrant was concentrated and purified by silica gel chromatography (20% EtOAc/Hexanes) to furnish the corresponding chiral ester.



(*S*)-1-phenylethyl 2-cyanopropanoate (29)

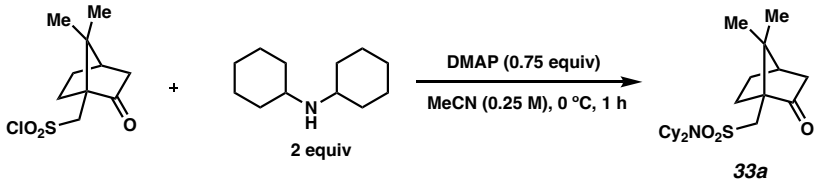
Isolated as a white solid (652 mg, 3.2 mmol, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 5.94 (q, J = 6.6 Hz, 1H), 3.55 (dq, J = 14.8, 7.4 Hz, 1H), 1.65 – 1.54 (m, 6H).



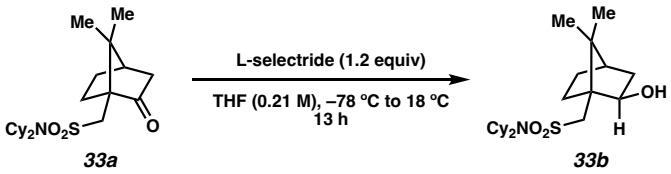
(*S*)-1-(naphthalen-2-yl)ethyl 2-cyanopropanoate (30)

Isolated as a white solid (680 mg, 2.68 mmol, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.80 (m, 4H), 7.55 – 7.45 (m, 3H), 6.11 (q, J = 6.6 Hz, 1H), 3.65 – 3.50 (m, 1H), 1.70 (dd, J = 6.7, 4.5 Hz, 3H), 1.58 (dd, J = 7.4, 3.5 Hz, 3H).

Synthesis of Isoborneol-Derived Chiral Cyanoester 33

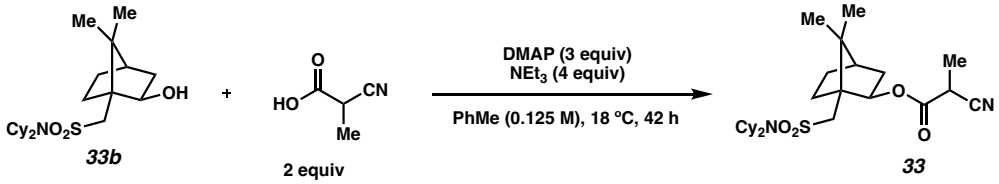


Amidation[19]**:** Inspired by a literature protocol, (+)-camphor-10-sulfonyl chloride (1.25 g, 5 mmol) was dissolved in acetonitrile (20 mL, 0.25 M) under N_2. To this solution at 0 ºC were added dicyclohexylamine (1.82 mL, 10 mmol, 2 equiv) and DMAP (160 mg, 1.32 mmol, 0.26 equiv). The reaction proceeded for 1 h at this temperature, at which point it was quenched with H_2O (13 mL), 1 M aq. HCl (4 mL), and 2 M aq. HCl (2 mL). The mixture was extracted three times with ethyl acetate, and the organic layers were combined, dried with Na_2SO_4, filtered, and concentrated. Crude sulfonamide **33a** was advanced to the next step without additional purification.



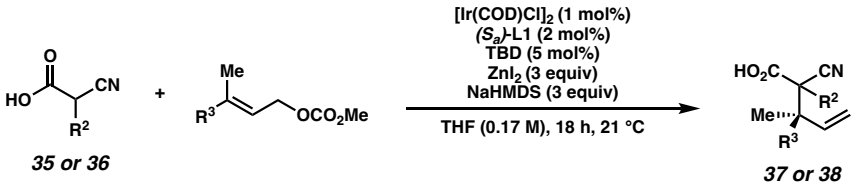
Reduction[20]**:** Sulfonamide **33a** was then dissolved in THF (9 mL, 0.21 M) under inert atmosphere and cooled to –78 ºC. A solution of L-selectride (2.27 mL, 1.0 M in THF, 1.19

equiv) was added, and the resulting mixture was allowed to warm slowly to ambient temperature overnight. After 13 h, the reaction was deemed complete by TLC and quenched by the addition of 8 mL H_2O and 2 mL sat. aq. Na_2CO_3. Three extractions were performed with ethyl acetate, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography (0–20% EtOAc/Hexanes) to deliver N,N-dicyclohexyl-1-(*(1R,2R,4R)*-2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)methanesulfonamide [**33b**] (894.3 mg, 2.25 mmol, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (dt, J = 7.9, 4.0 Hz, 1H), 3.50 (d, J = 3.7 Hz, 1H), 3.34 – 3.19 (m, 3H), 2.66 (d, J = 13.3 Hz, 1H), 1.90 – 1.56 (m, 20H), 1.39 – 1.08 (m, 6H), 1.06 (s, 3H), 0.81 (s, 3H). Characterization data was in agreement with the literature.

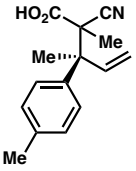


Esterification[21]: To a solution of DMAP (367 mg, 3 mmol, 3 equiv), NEt_3, (404.8mg, 0.558 mL, 4 mmol, 4 equiv), cyanoacid **35** (200 mg, 2 mmol, 2 equiv) and isoborneol **33** (397.6 mg, 1 mmol) in PhMe (8 mL, 0.125 M) and under N_2 was added 2,4,6-trichlorobenzoylchloride (731.7 mg, 0.469 mL, 3 mmol, 3 equiv). The reaction was stirred for 42 h at this temperature and quenched by the addition of 3 mL sat. aq. NH_4Cl. The mixture was extracted three times with ethyl acetate. The organic extracts were dried with Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography (20% EtOAc/Hexanes) to deliver *(1R,2R,4R)*-1-((N,N-dicyclohexylsulfamoyl)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl 2-cyanopropanoate [**33**] (148.5 mg, 0.62 mmol, 62% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (ddd, J = 7.6, 4.8, 2.8 Hz, 1H), 3.53 (dq, J = 15.1, 7.5 Hz, 1H), 3.37 (dd, J = 20.9, 13.3 Hz, 1H), 3.33 – 3.22 (m, 2H), 2.66 (dd, J = 14.9, 13.3 Hz, 1H), 2.06 – 1.58 (m, 23H), 1.48 – 1.09 (m, 7H), 1.08 (s, 3H), 0.90 (s, 3H). Characterization data was in agreement with the literature.

Iridium-Catalyzed Allylic Alkylation of Cyanoacid Nucleophiles

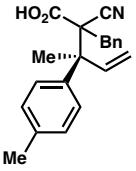


The allylic alkylation of cyanoacid nucleophiles was conducted via General Procedure A, with the exception of the stoichiometries of ZnI_2 and NaHMDS. Both were used in greater excess (3 equiv), equating to 95.8 mg ZnI_2 and 55.0 mg NaHMDS.



(3*S*)-2-cyano-2,3-dimethyl-3-(*p*-tolyl)pent-4-enoic acid (37)

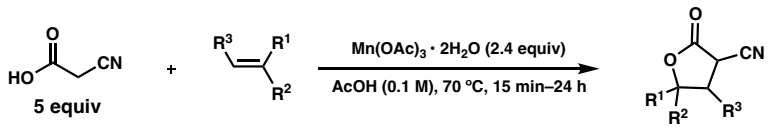
Crude yield determined by ^{1}H NMR relative to CH_2Br_2 internal standard (21.6 mg) assuming peaks at 6.62 ppm and 6.76 ppm belong to diastereomers of product and integrate to 1H (83% yield, 1.2:1 dr).



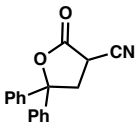
(3*S*)-2-benzyl-2-cyano-3-methyl-3-(*p*-tolyl)pent-4-enoic acid (38)

Crude yield determined by ^{1}H NMR relative to CH_2Br_2 internal standard (27.9 mg) assuming peaks at 6.83 ppm and 6.95 ppm belong to diastereomers of product and integrate to 1H (80% yield, 1:1 dr).

Mn-mediated Oxidative Cyclization

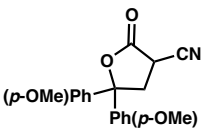


Cyanoacetic acid (1.7 g, 20 mmol, 8 equiv), $Mn(OAc)_2$•H2O (1.6 g, 6 mmol, 2.4 equiv), and the olefin (2.5 mmol) were dissolved in AcOH (25 mL, 0.1 M). The mixture was heated to 70 ºC, and the reaction proceeded at this temperature until a color change from deep red to clear was observed or after 21 h. At this point, the reaction was cooled to ambient temperature and carefully neutralized with sat. aq. $NaHCO_3$. Three extractions were performed with either Et_2O, EtOAc, or CH_2Cl_2, then the organics were dried with Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (10% EtOAc/Hexanes) to deliver the corresponding cyanolactone.



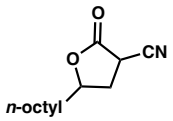
2-oxo-5,5-diphenyltetrahydrofuran-3-carbonitrile (40)

Isolated as a waxy solid (303.6 mg, 1.15 mmol, 46% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.28 (m, 10H), 3.68 (dd, J = 12.2, 8.0 Hz, 1H), 3.47 (dd, J = 12.7, 8.0 Hz,1H), 3.14 (dd, J = 12.8, 12.2 Hz, 1H). Characterization data was in agreement with the literature.[22]



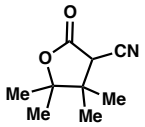
5,5-bis(4-methoxyphenyl)-2-oxotetrahydrofuran-3-carbonitrile (41)

Isolated as a waxy solid (135 mg, 0.42 mmol, 14% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.12 (m, 2H), 7.12 – 7.06 (m, 2H), 6.96 – 6.92 (m, 2H), 6.86 – 6.79 (m, 2H), 5.89 (t, J = 7.4 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.15 (d, J = 7.4 Hz, 2H).



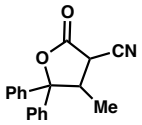
5-octyl-2-oxotetrahydrofuran-3-carbonitrile (44)

Isolated as a crusty solid (285 mg, 1.28 mmol, 51% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (ddt, J = 10.5, 7.6, 5.5 Hz, 1H), 3.71 (dd, J = 11.9, 8.9 Hz, 1H), 2.79 (ddd, J = 12.8, 9.0, 5.5 Hz, 1H), 2.29 – 2.19 (m, 1H), 1.98 – 0.75 (m, 17H). Characterization data was in agreement with the literature.[8]



4,4,5,5-tetramethyl-2-oxotetrahydrofuran-3-carbonitrile (48)

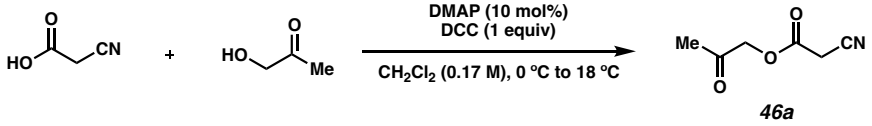
Reaction performed at 5 mmol scale. Isolated as a clear oil (84 mg, 0.50 mmol, 10% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 1H), 1.42 (s, 3H), 1.37 (s, 3H), 1.28 (s, 3H), 1.23 (s, 3H). Characterization data was in agreement with the literature.[8]



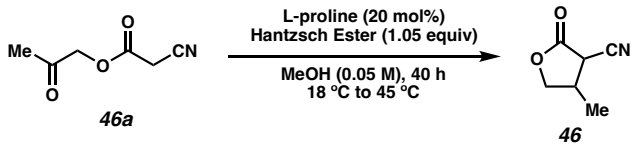
4-methyl-2-oxo-5,5-diphenyltetrahydrofuran-3-carbonitrile (49)

Reaction performed at 2 mmol scale (362 mg, 1.31 mmol, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 1H), 7.44 – 7.27 (m, 8H), 7.08 – 7.02 (m, 1H), 3.91 – 3.41 (m, 2H), 1.32 – 1.01 (m, 3H).

Synthesis of Racemic β-substituted Cyanolactone 46



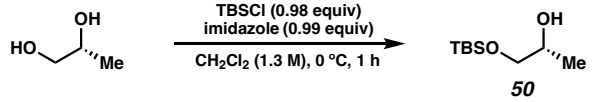
Steglich Esterification: Cyanoacetic acid (850.6 mg, 10 mmol), acetol (740 mg, 0.7 mL, 10 mmol, 1 equiv), and DMAP (122 mg, 1 mmol, 0.1 equiv) were combined in a flask under N_2 and CH_2Cl_2 (40 mL, 0.25 M) was added. The mixture was cooled to 0 ºC. To another flask under N2 were added DCC (2.063 g, 10 mmol, 1 equiv) and CH_2Cl_2 (20 mL, 0.5 M). The DCC solution was added to the first mixture at 0 ºC, and the reaction was allowed to warm slowly to ambient temperature. After 4 h, the reaction mixture was filtered and washed with CH_2Cl_2. The filtrant was concentrated and purified by silica gel chromatography (50% EtOAc/Hexanes) to afford 2-oxopropyl 2-cyanoacetate [**46a**] (0.919 g, 6.52 mmol, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (s, 2H), 3.61 (s, 2H), 2.20 (s, 3H). Characterization data was in agreement with the literature.[23]



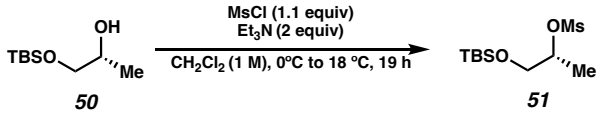
Reductive Knoevenagel[24]: The ketoester **46a** (0.919 g, 6.52 mmol), L-proline (150 mg, 1.30 mmol, 0.2 equiv), and Hantzsch ester (1.672 g, 6.6 mmol, 1.05 equiv) were combined in MeOH (130 mL, 0.05 M). The reaction was stirred at 18 ºC for 20 h, and then the temperature was raised to 45 ºC. After another 20 h, the reaction was cooled back to ambient temperature and concentrated by rotatory evaporation to remove methanol. To the residue were added ethyl acetate and water, and three extractions were performed with ethyl acetate before the organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (50% EtOAc/Hexanes) to deliver a mixture of the desired product and the unsaturated cyanobutenolide. This mixture of white solids and a viscous oil was forced through a small plug of cotton to remove the

solids. The remaining oil was found to contain solely 4-methyl-2-oxotetrahydrofuran-3-carbonitrile (**46**), which was then used in the allylic alkylation without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 – 4.42 (m, 1H), 4.17 – 3.23 (m, 2H), 3.06 – 2.90 (m, 1H), 1.41 – 1.31 (m, 3H).

Synthesis of Stereoenriched β-substituted Cyanolactone 53

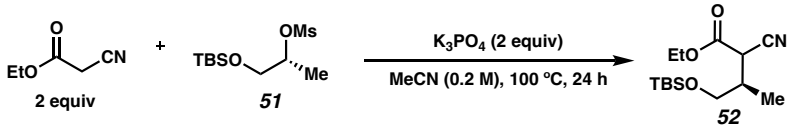


Regioselective TBS-protection[25]: To a solution of (*R*)-propane 1,2-diol (761 mg, 0.732 mL, 15 mmol) and imidazole (1.011 g, 14.85 mmol, 0.99 equiv) in CH_2Cl_2 (11.4 mL, 1.3 M) at 0 ºC was added TBSCl (2.204 g, 14.63 mmol, 0.975 equiv).The mixture was stirred at this temperature for 1 h, at which point it was filtered and rinsed with CH_2Cl2. Concentration afforded crude *(R)*-1-((tert-butyldimethylsilyl)oxy)propan-2-ol **50** as a clear oil (2.96 g, 15 mmol, quant.), which was pure enough to advance without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (td, J = 9.3, 4.7 Hz, 1H), 3.60 (dd, J = 9.9, 3.4 Hz, 1H), 3.35 (dd, J = 9.9, 7.8 Hz, 1H), 1.13 (d, J = 6.3 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 6H). Characterization data was in agreement with the literature.

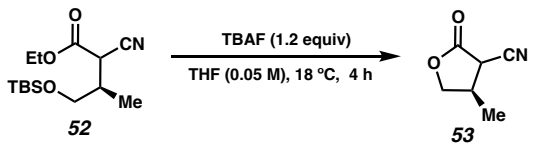


Mesylation[26]: To a roundbottom flask equipped with a stir bar and under N_2 were added **50** (190.4 mg, 1 mmol), Et_3N (202.4 mg, 0.279 mL, 2 mmol, 3 equiv), and CH_2Cl_2 (1 mL, 1 M). The solution was cooled to 0 ºC and MsCl (126.1 mg, 85.2 uL, 1.1 mmol, 1.1 equiv) was added slowly in a single portion. The reaction was allowed to warm to ambient temperature and reacted for 19 h until it was quenched by the addition of 1 mL sat. aq. NH_4Cl. Following three extractions with CH_2Cl_2, the organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel

chromatography (10% Et_2O/Pentanes) to afford *(R)*-1-((tert-butyldimethylsilyl)oxy)propan-2-yl methanesulfonate (**51**) as a clear oil (275 mg, 1 mmol, quant.). Use of crude material without silica gel chromatography was also successful. 1H NMR (400 MHz, $CDCl_3$) δ 4.75 (pd, J = 6.5, 3.9 Hz, 1H), 3.76 – 3.61 (m, 2H), 3.03 (s, 3H), 1.38 (d, J = 6.4 Hz, 3H), 0.90 (s, 9H), 0.08 (d, J = 2.4 Hz, 6H). Characterization data was in agreement with the literature.



Intermolecular Substitution: To a mixture of ethylcyanoacetate (43 uL, 0.4 mmol, 2 equiv) and K_3PO_4 (85 mg, 0.4 mmol, 2 equiv) and MeCN (1 mL, 0.2 M) in a microwave vial under N_2 was added mesylate **51** (54 mg, 0.2 mmol). The reaction was heated to 100 ºC and stirred at this temperature for 24 h. The vessel was cooled to ambient temperature, and 50 mL sat. aq. NH4Cl was added. Three extractions were performed with ethyl acetate, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography (10% EtOAc/Hexanes) to deliver ethyl (3*R*)-4-((*tert*-butyldimethylsilyl)oxy)-2-cyano-3-methylbutanoate [**52**] (16.2 mg, 0.057 mmol, 28% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 – 4.20 (m, 2H), 4.05 – 3.39 (m, 3H), 2.52 – 2.42 (m, 1H), 1.43 – 1.22 (m, 3H), 1.14 – 0.97 (m, 3H), 0.94 – 0.88 (m, 9H), 0.15 – 0.02 (m, 6H).



TBAF Deprotection/Lactonization: To a solution of **52** (10.8 mg, 0.04 mmol) in THF (0.8 mL, 0.05 M) was added a solution of TBAF (0.06 mL, 1.0 M in THF, 0.06 mmol). The reaction was stirred for 4 h at 18 ºC and quenched with 1 mL sat. aq. NH_4Cl. Three

extractions were performed with ethyl acetate, and the combined organic extracts were dried with Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (50% EtOAc/Hexanes) to afford the stereoenriched cyanolactone **53** as a light yellow, maple-scented oil (3 mg, 0.026 mmol, 64% yield). ^{1}H NMR data consistent with **46**.

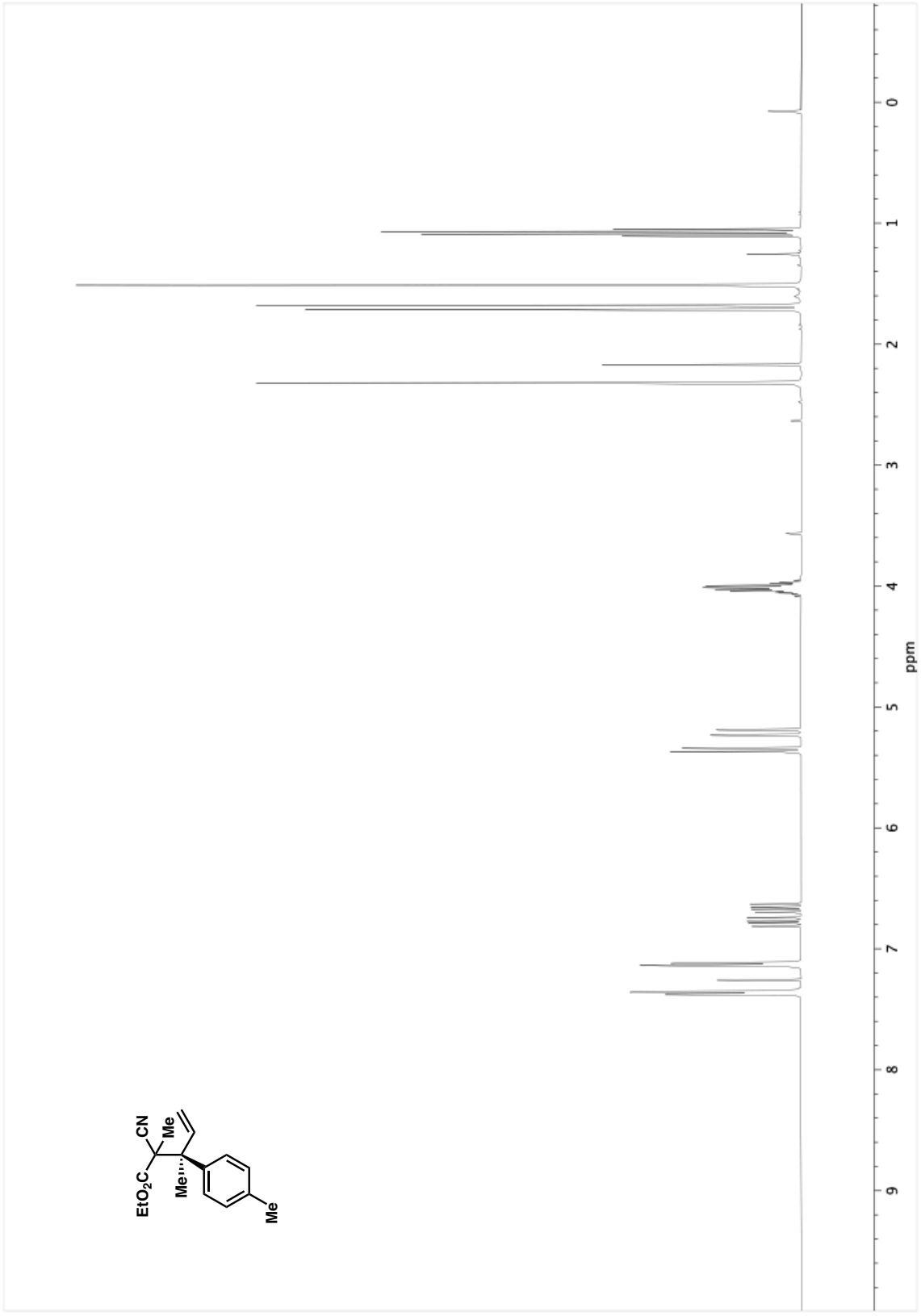


Figure A2.4. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***27****.*

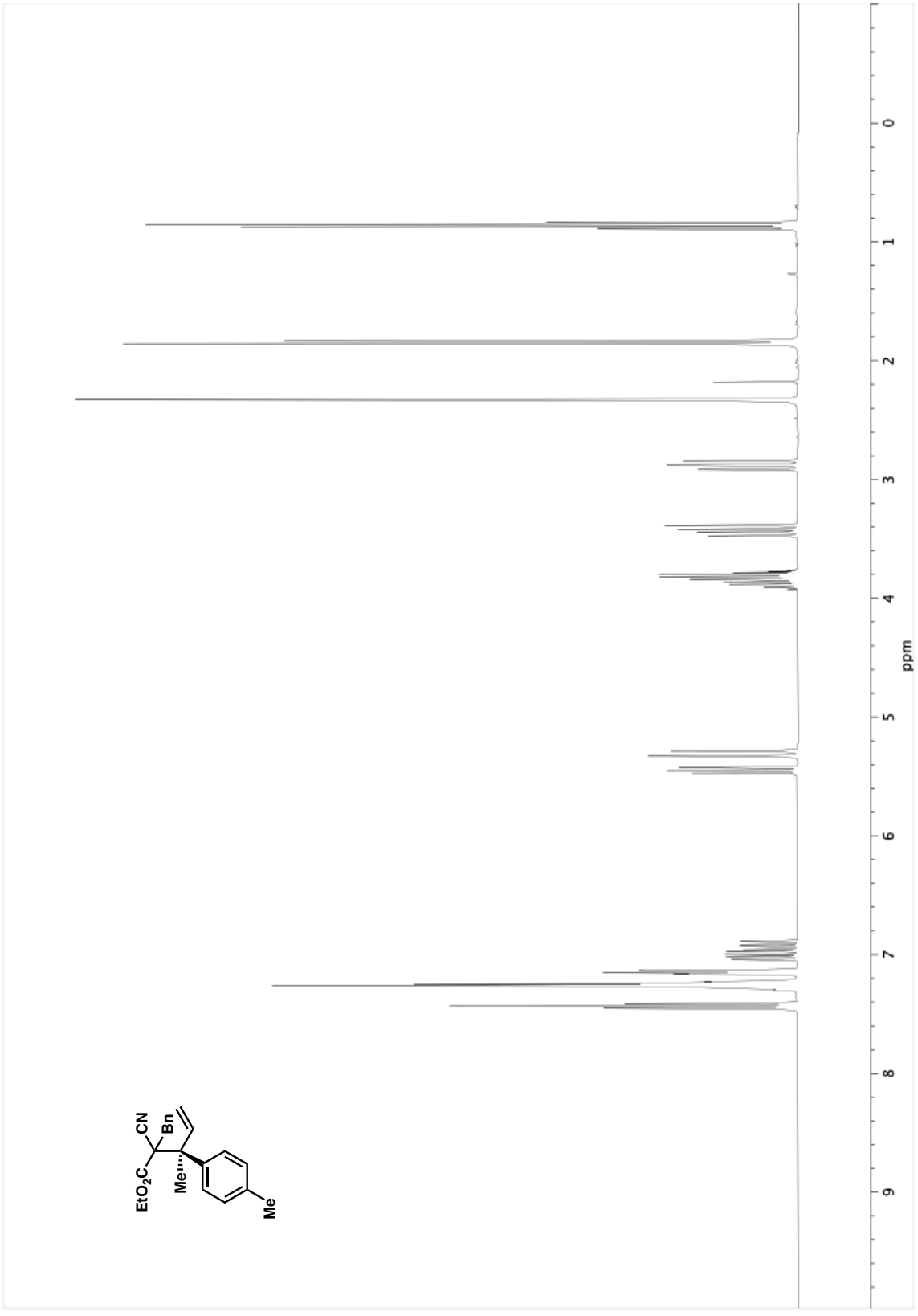


Figure A2.5. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***28****.*

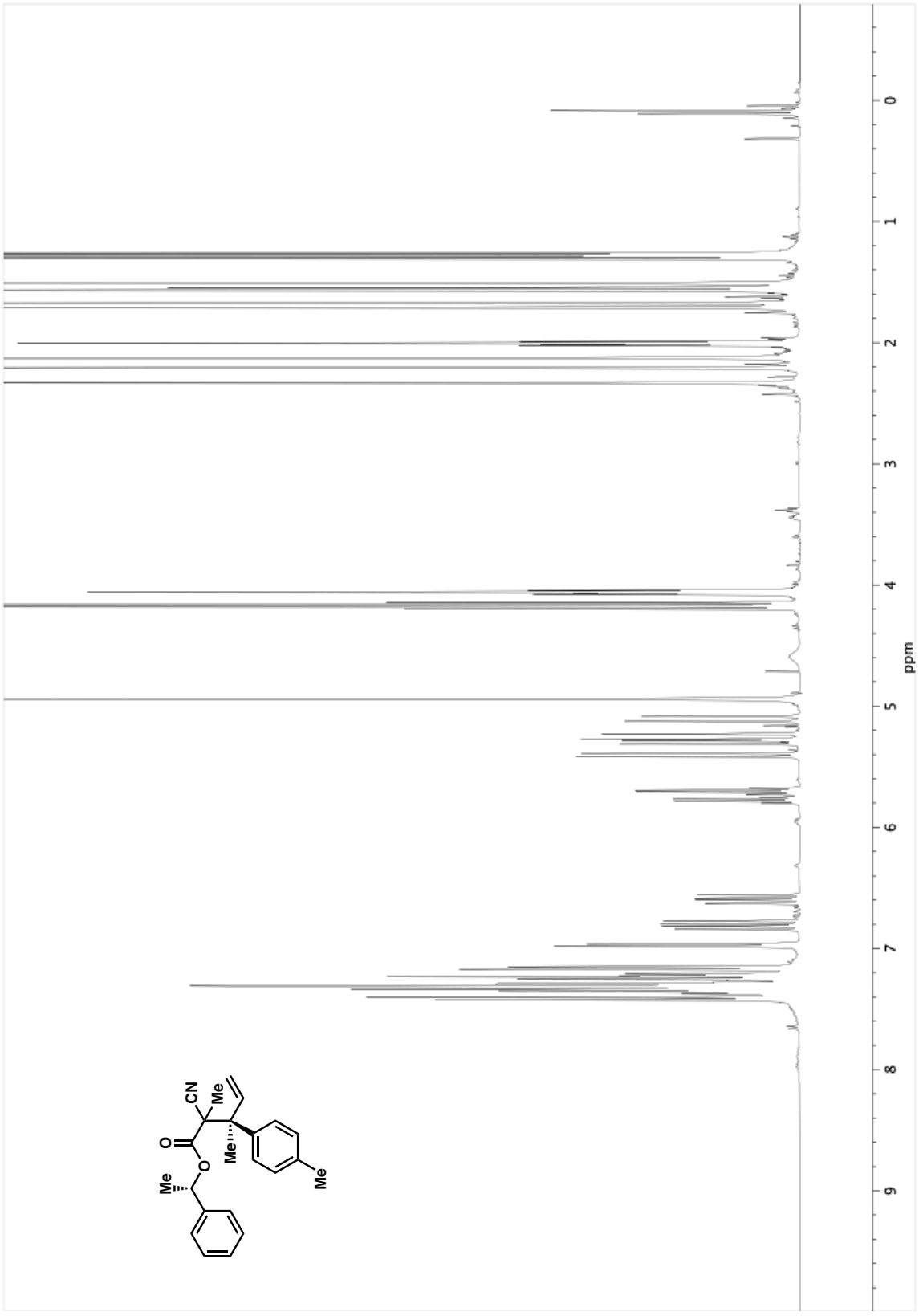


Figure A2.6. *Crude ^{1}H NMR (400 MHz, $CDCl_3$) of compound **31**.*

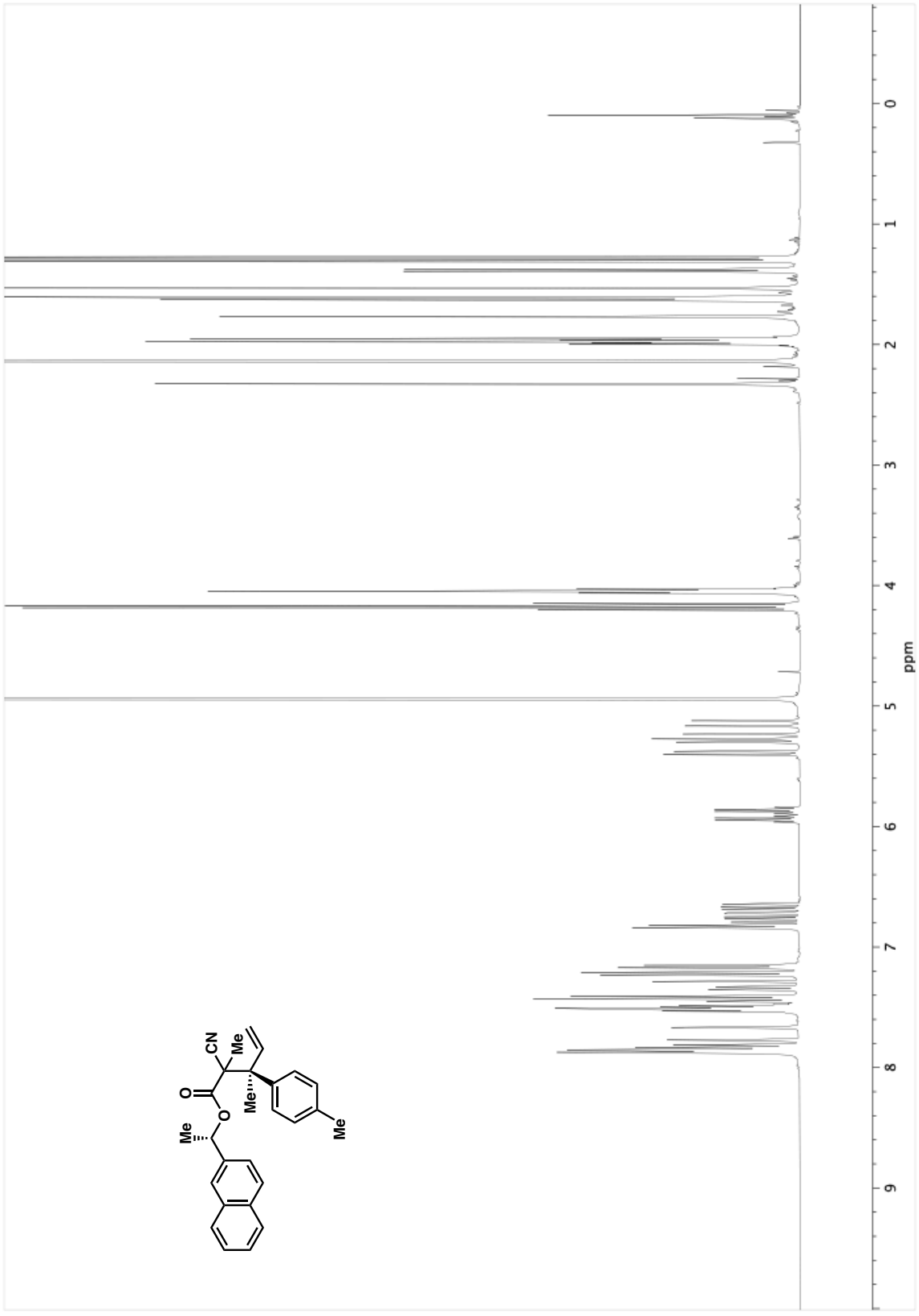


Figure A2.7. *Crude ^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***32***.

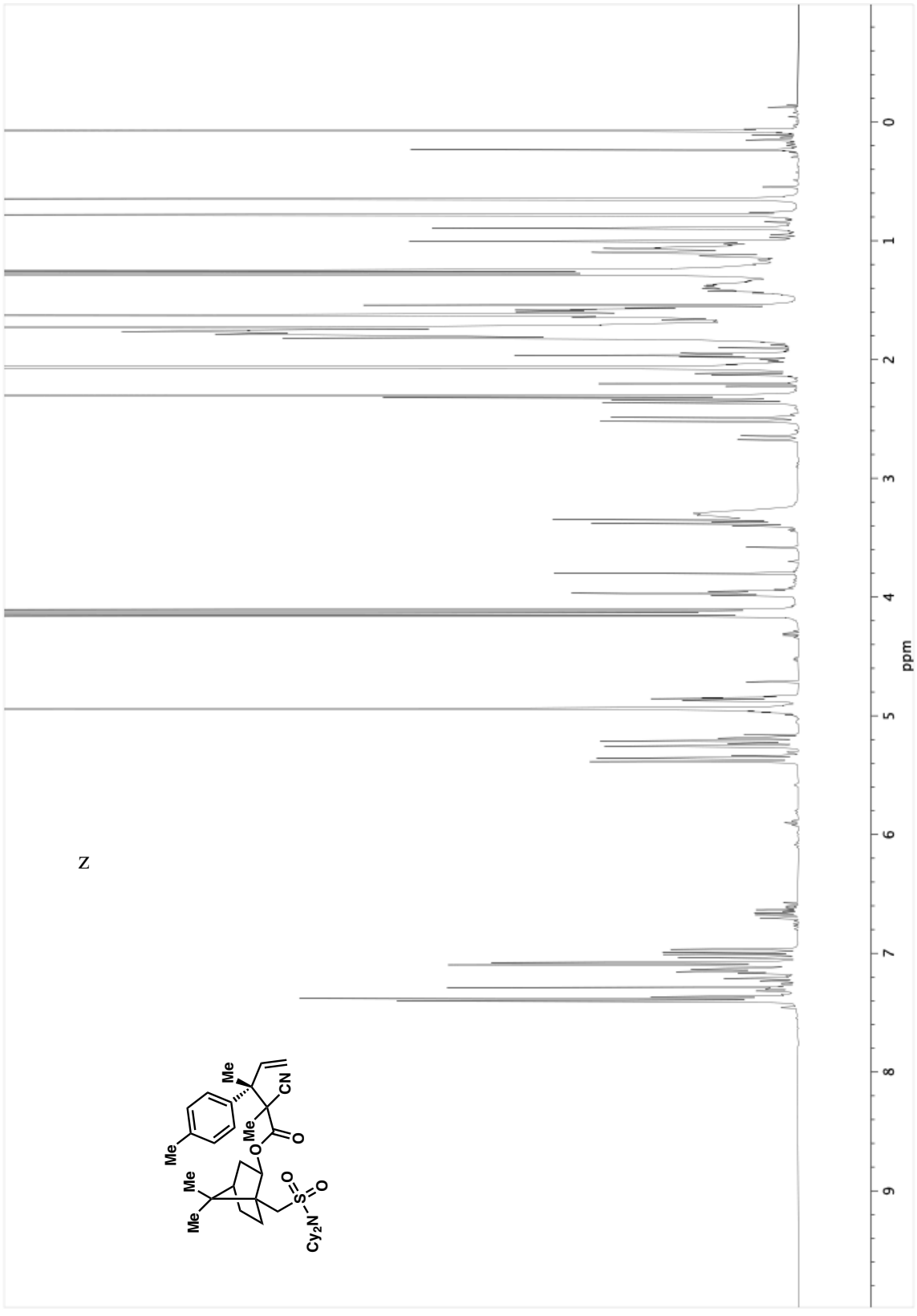


Figure A2.8. *Crude ^1H NMR (400 MHz, $CDCl_3$) of compound **34**.*

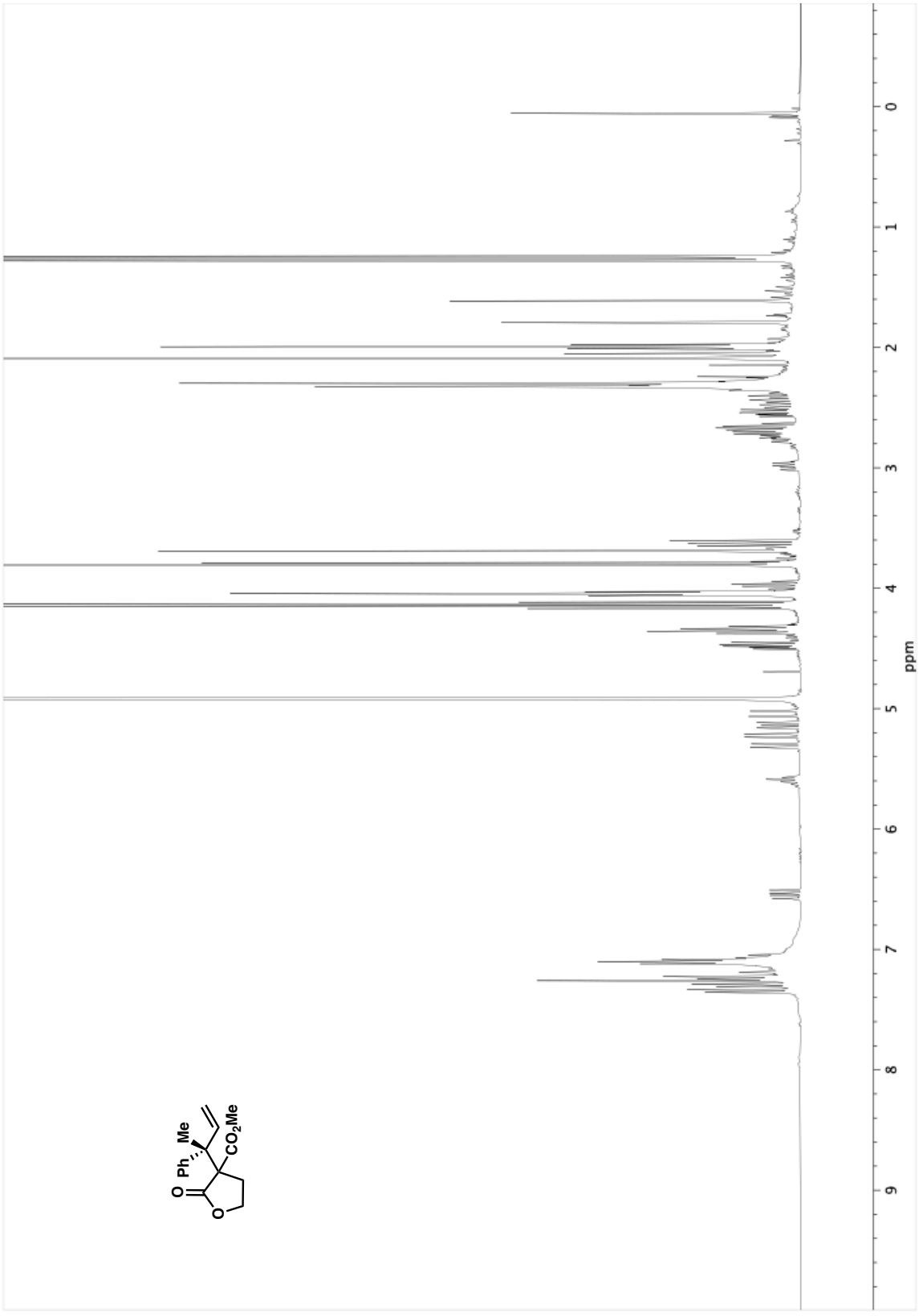


Figure A2.9. *Crude ^{1}H NMR (400 MHz, $CDCl_3$) of compound **39**.*

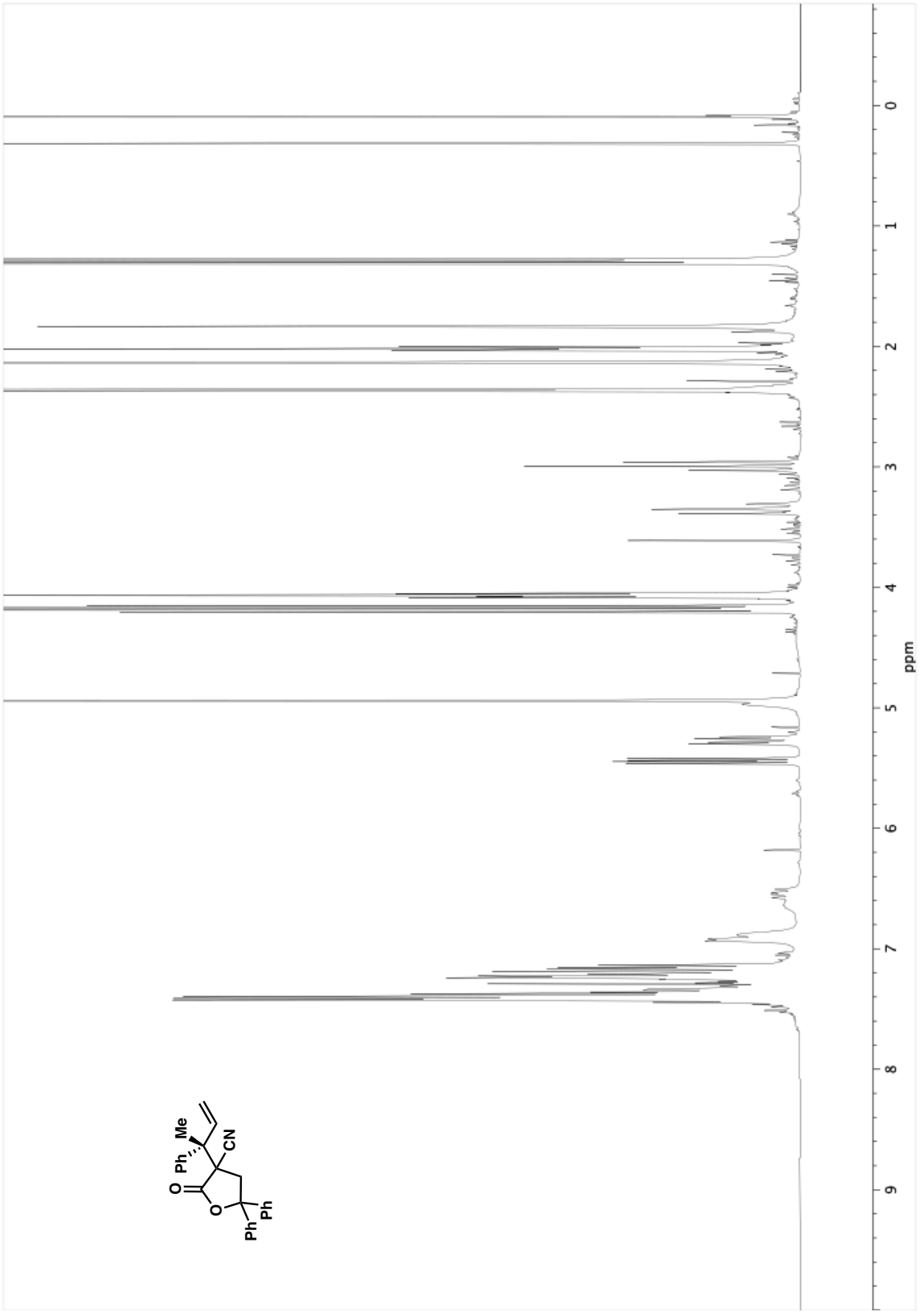


Figure A2.10. *Crude ^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***42****.*

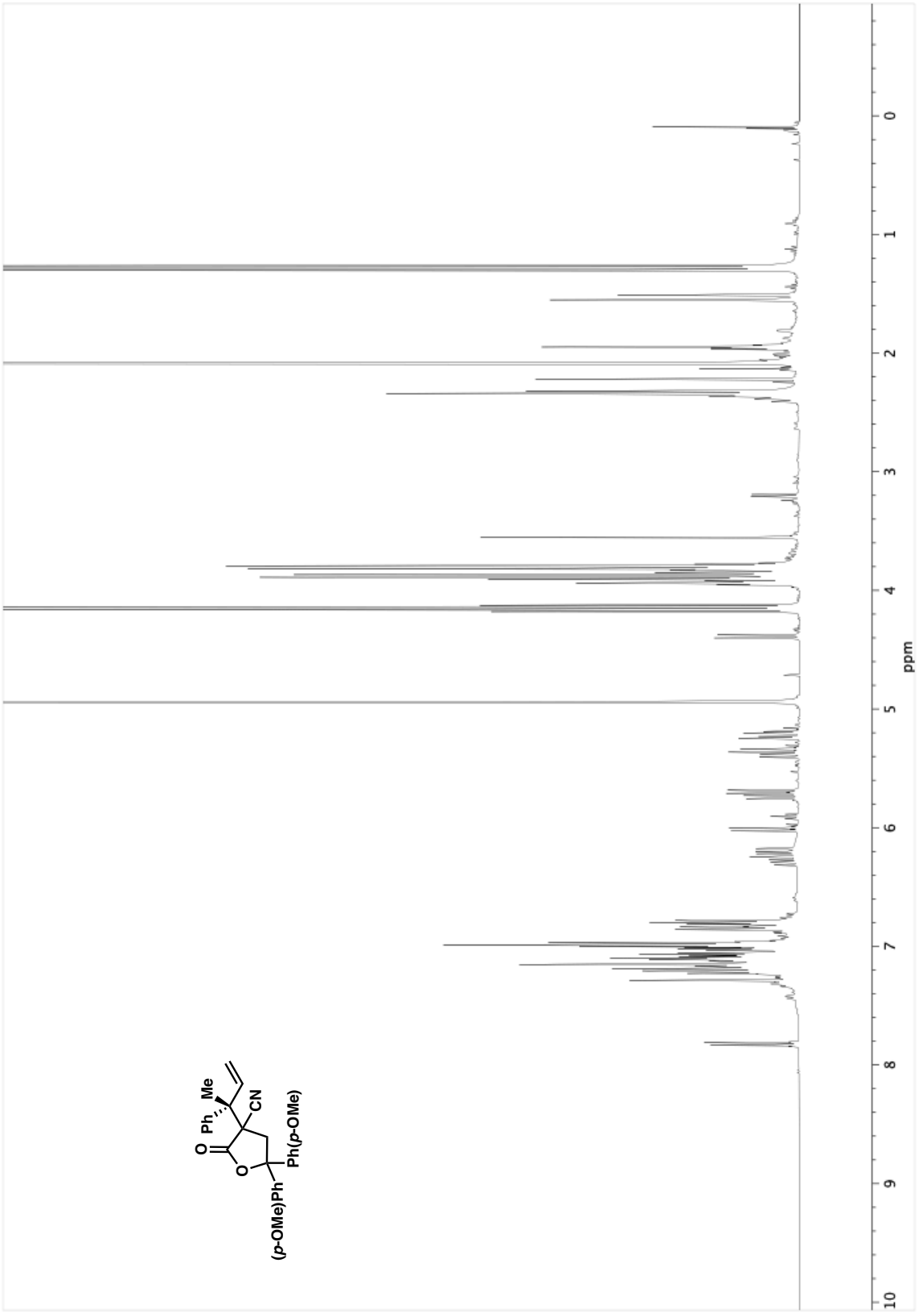


Figure A2.11. *Crude ^1H NMR (400 MHz, $CDCl_3$) of compound* ***43***.

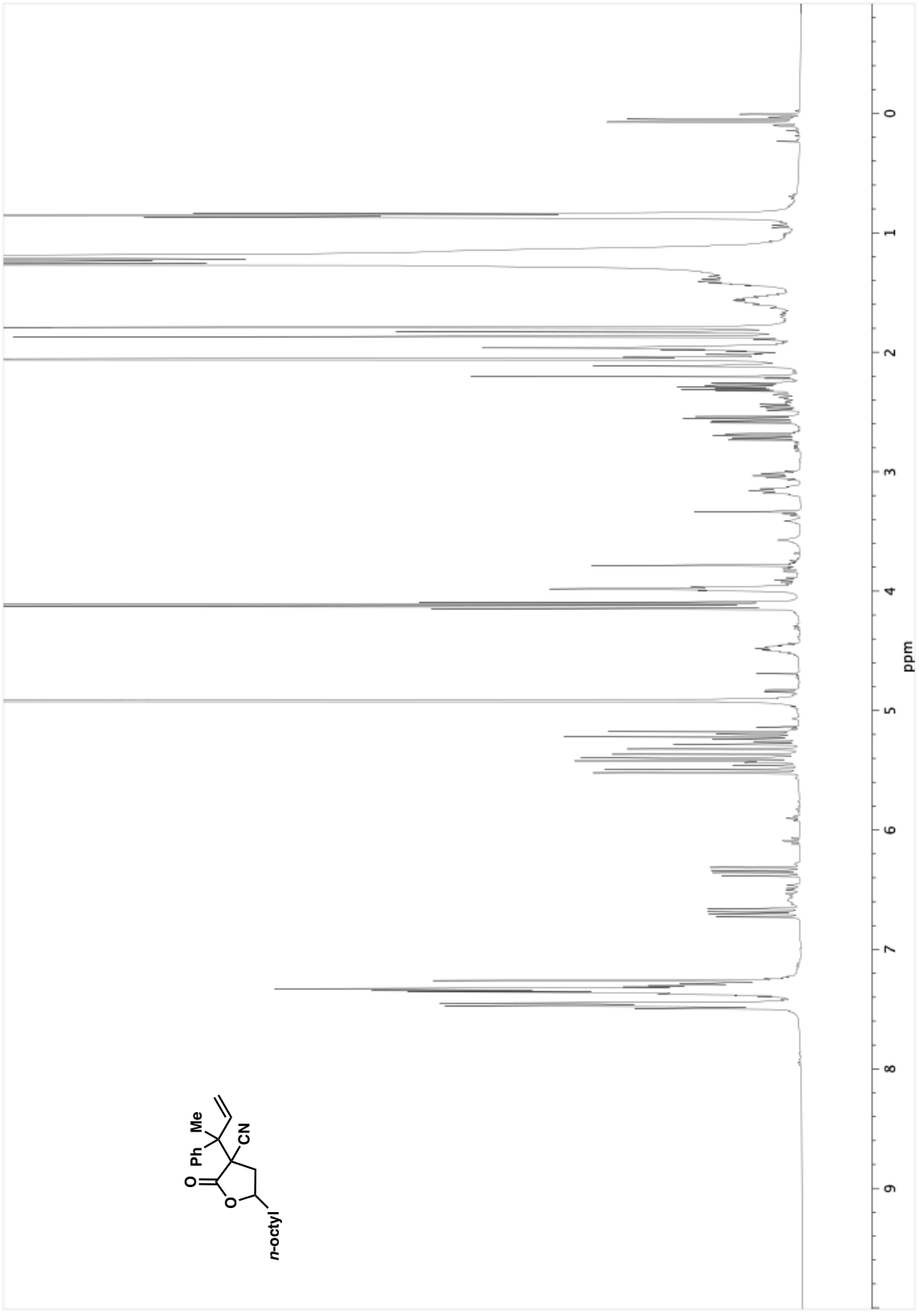


Figure A2.12. *Crude ^{1}H NMR (400 MHz, $CDCl_3$) of compound **45**.*

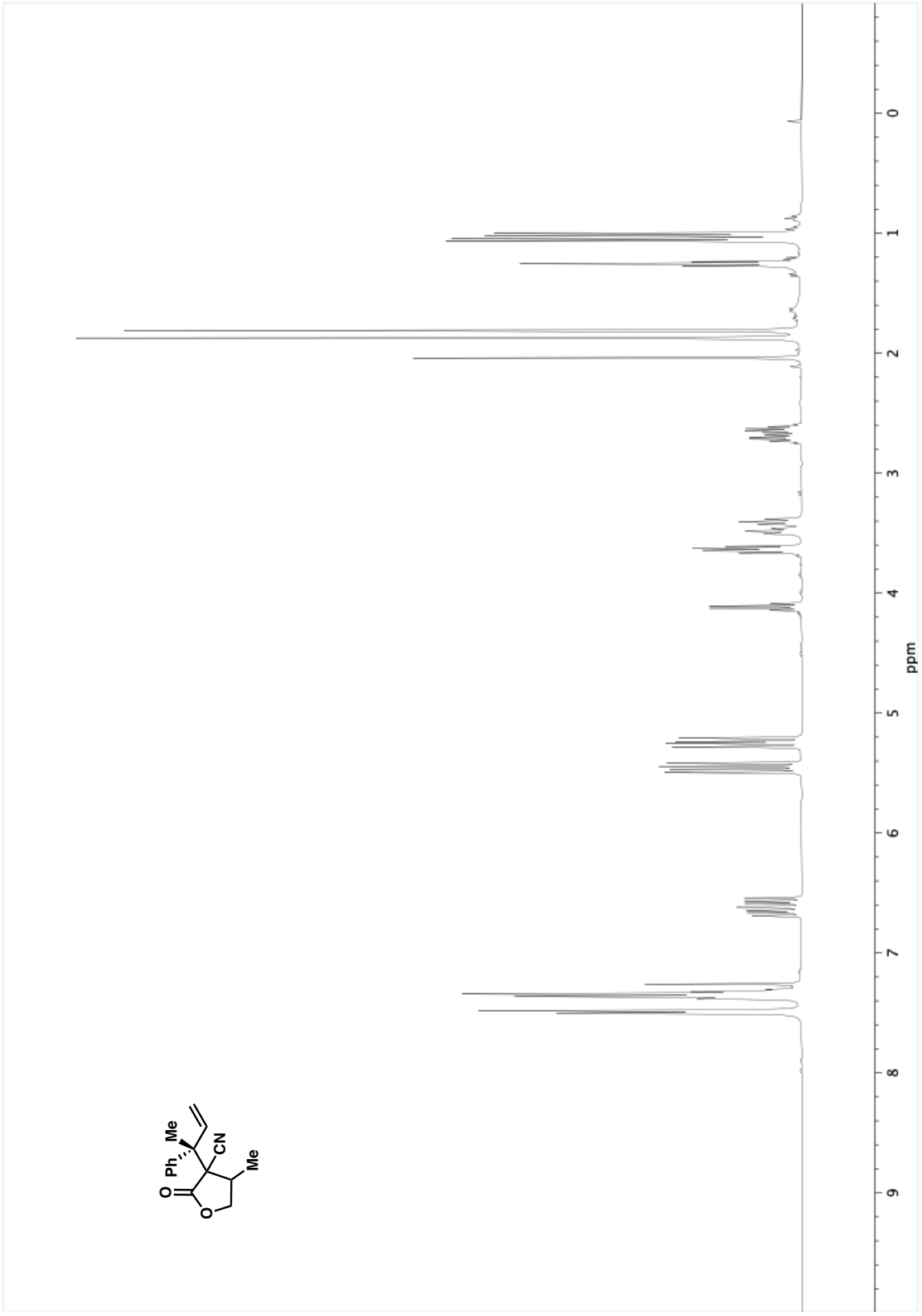


Figure A2.13. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **47**.*

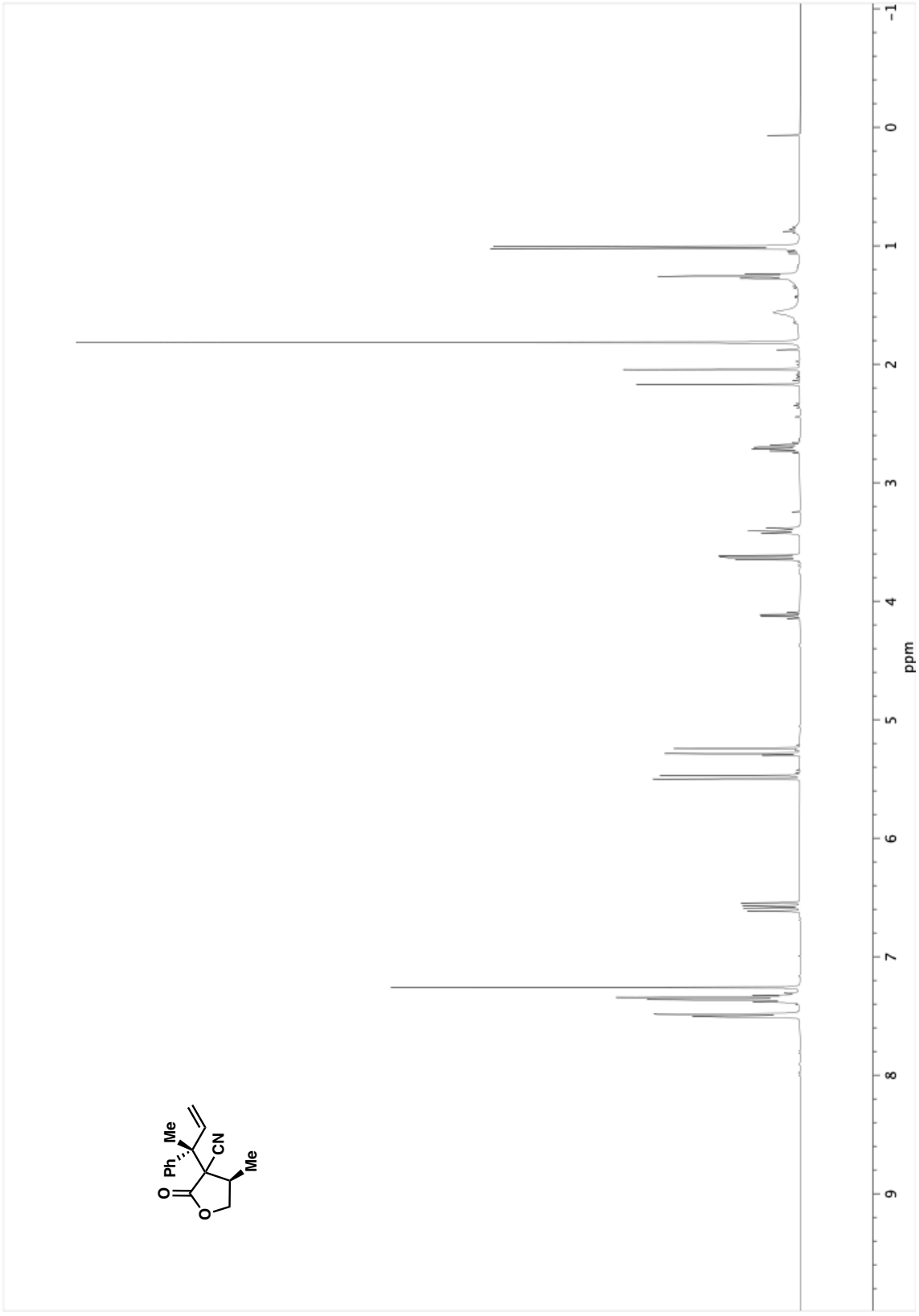


Figure A2.14. *^1H NMR (400 MHz, $CDCl_3$) of compound **54**.*

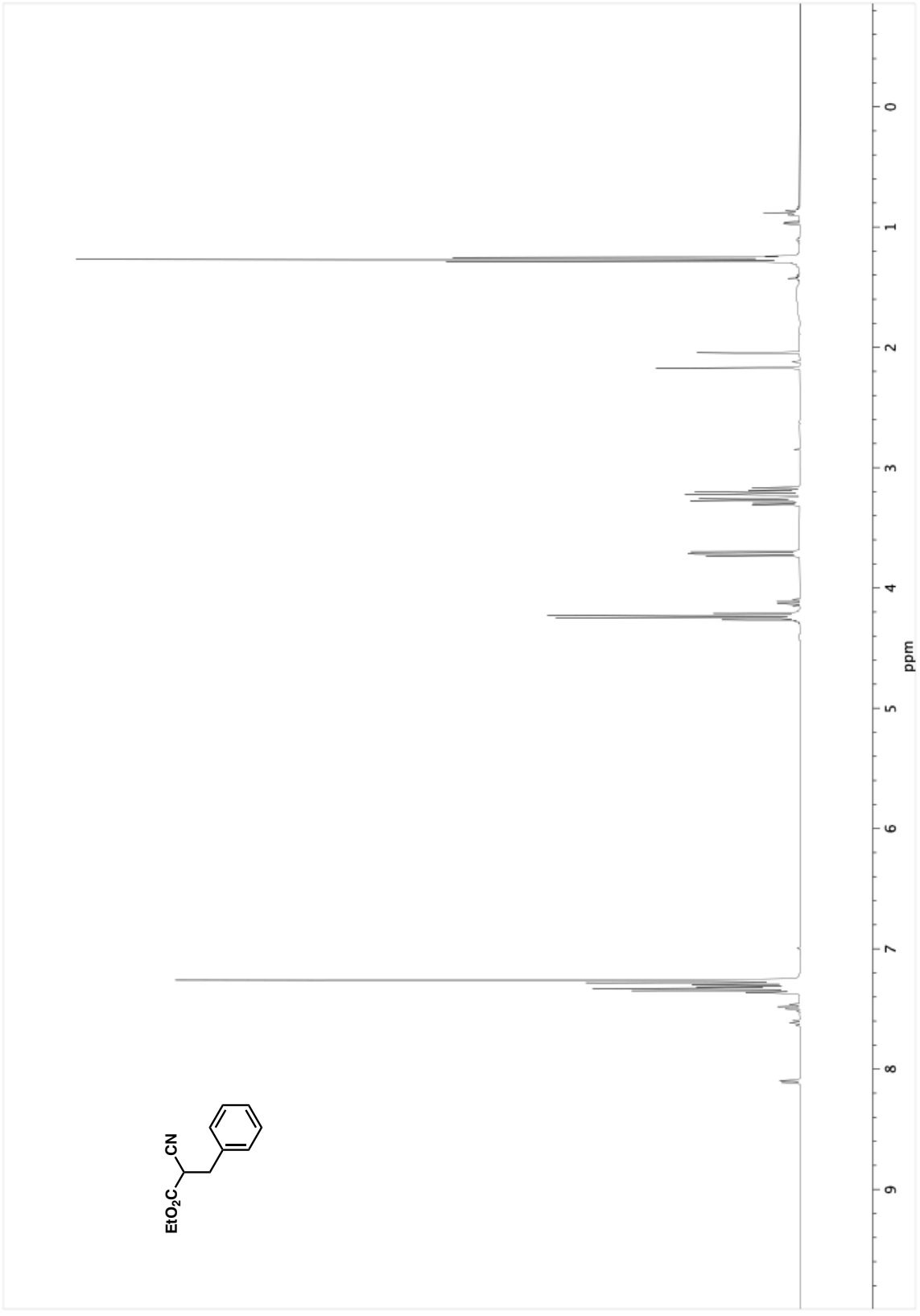


Figure A2.15. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***28a****.*

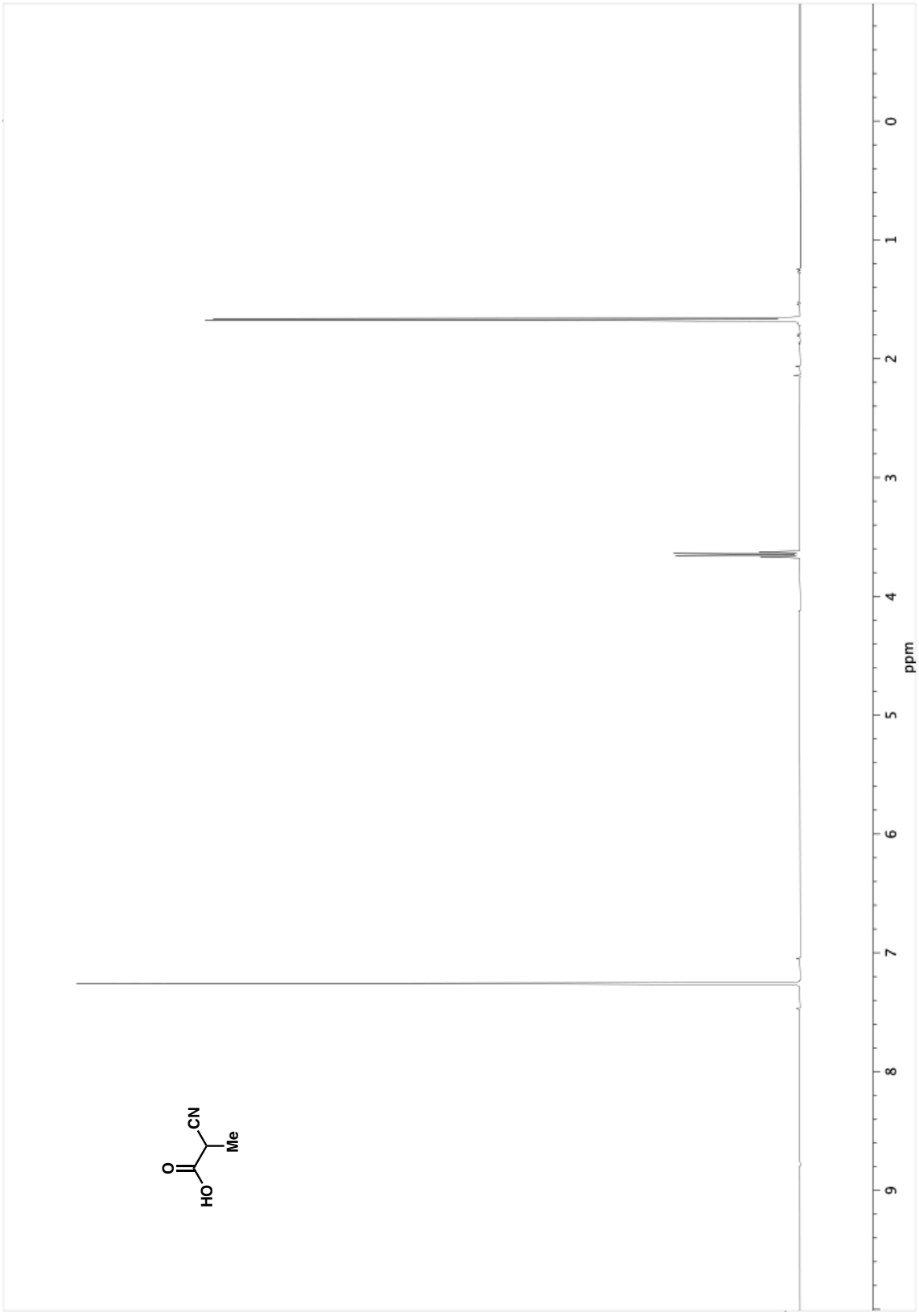


Figure A2.16. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***35****.*

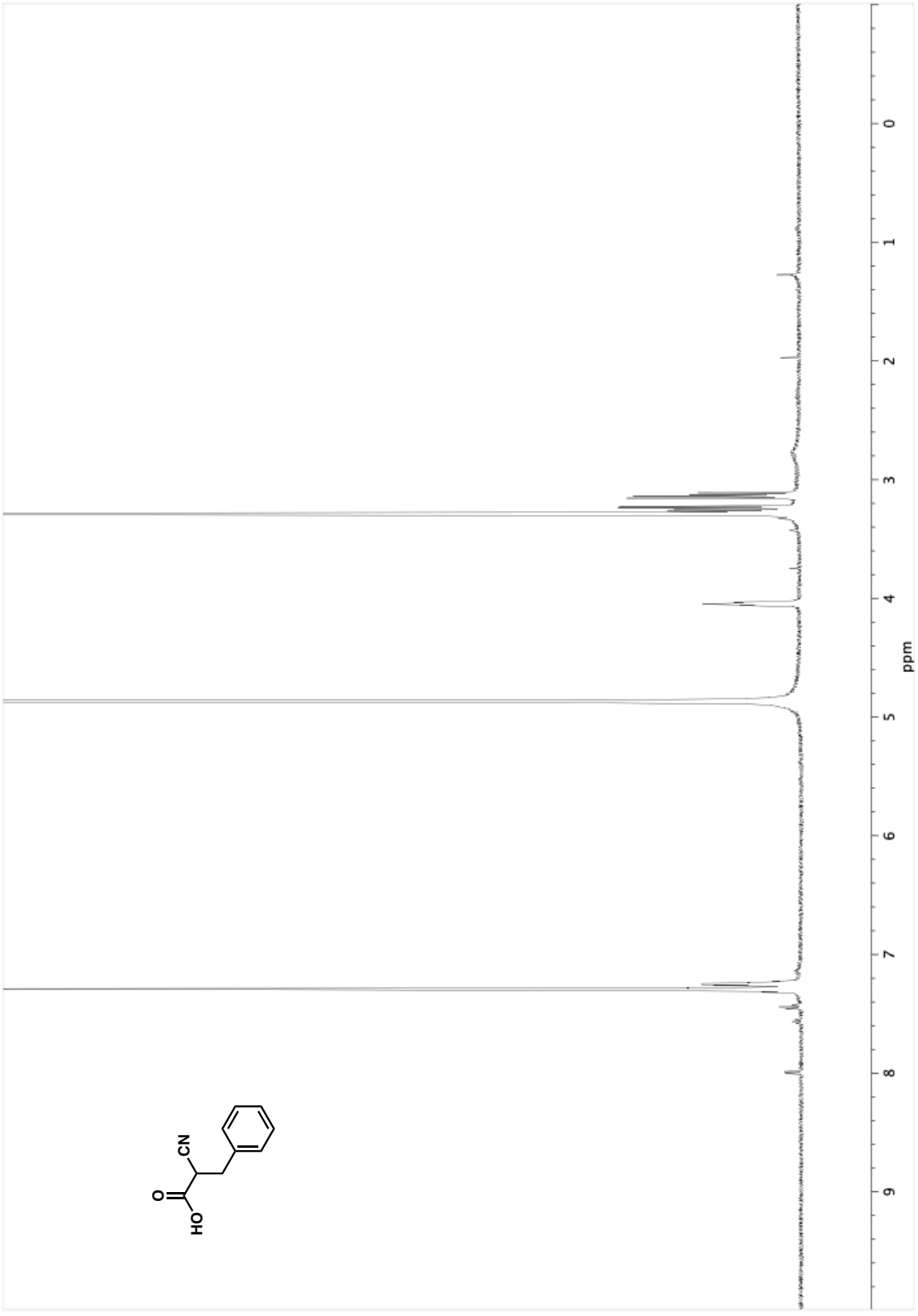


Figure A2.17. *^1H NMR (400 MHz, $CDCl_3$) of compound **36**.*

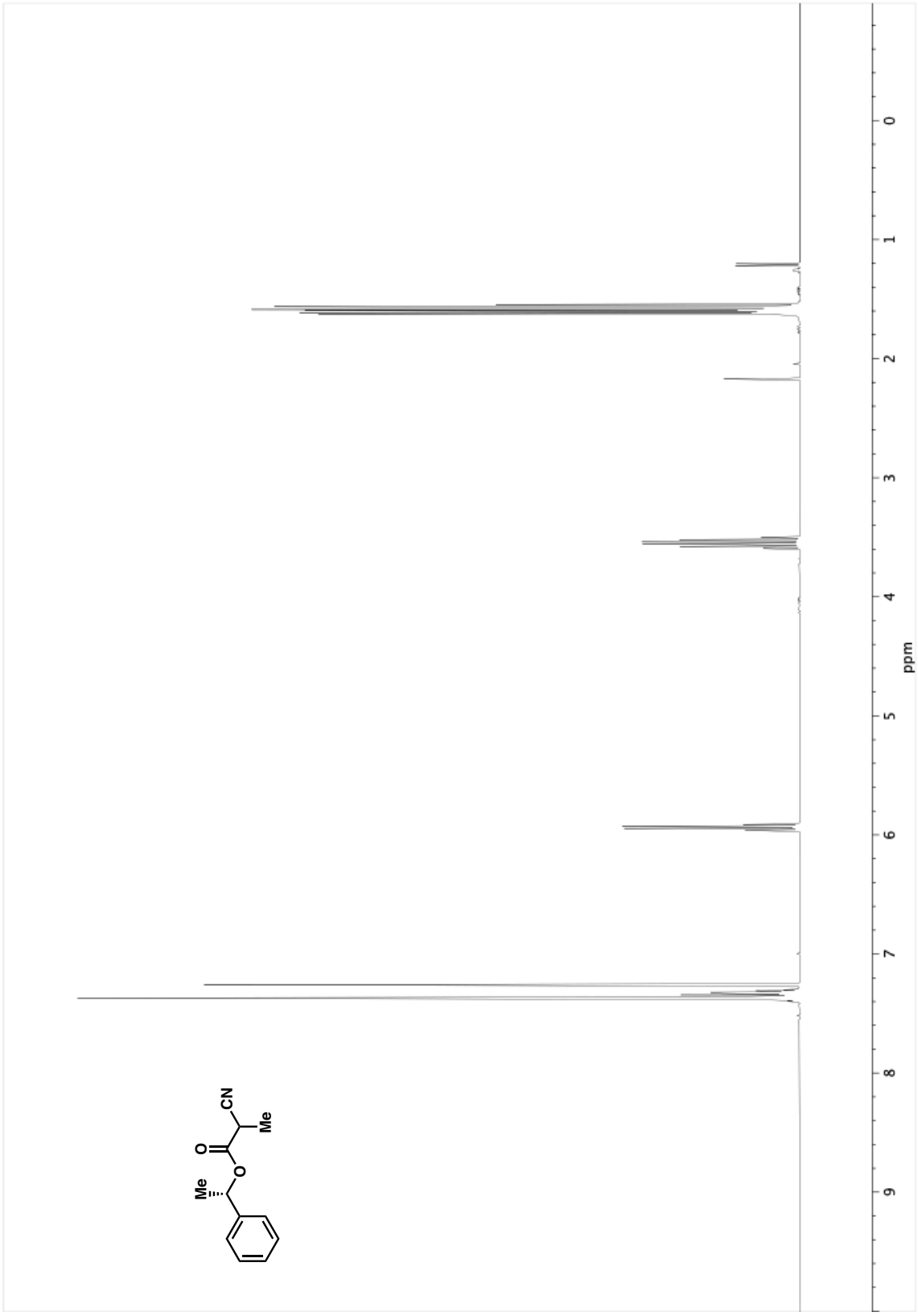


Figure A2.18. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***29****.*

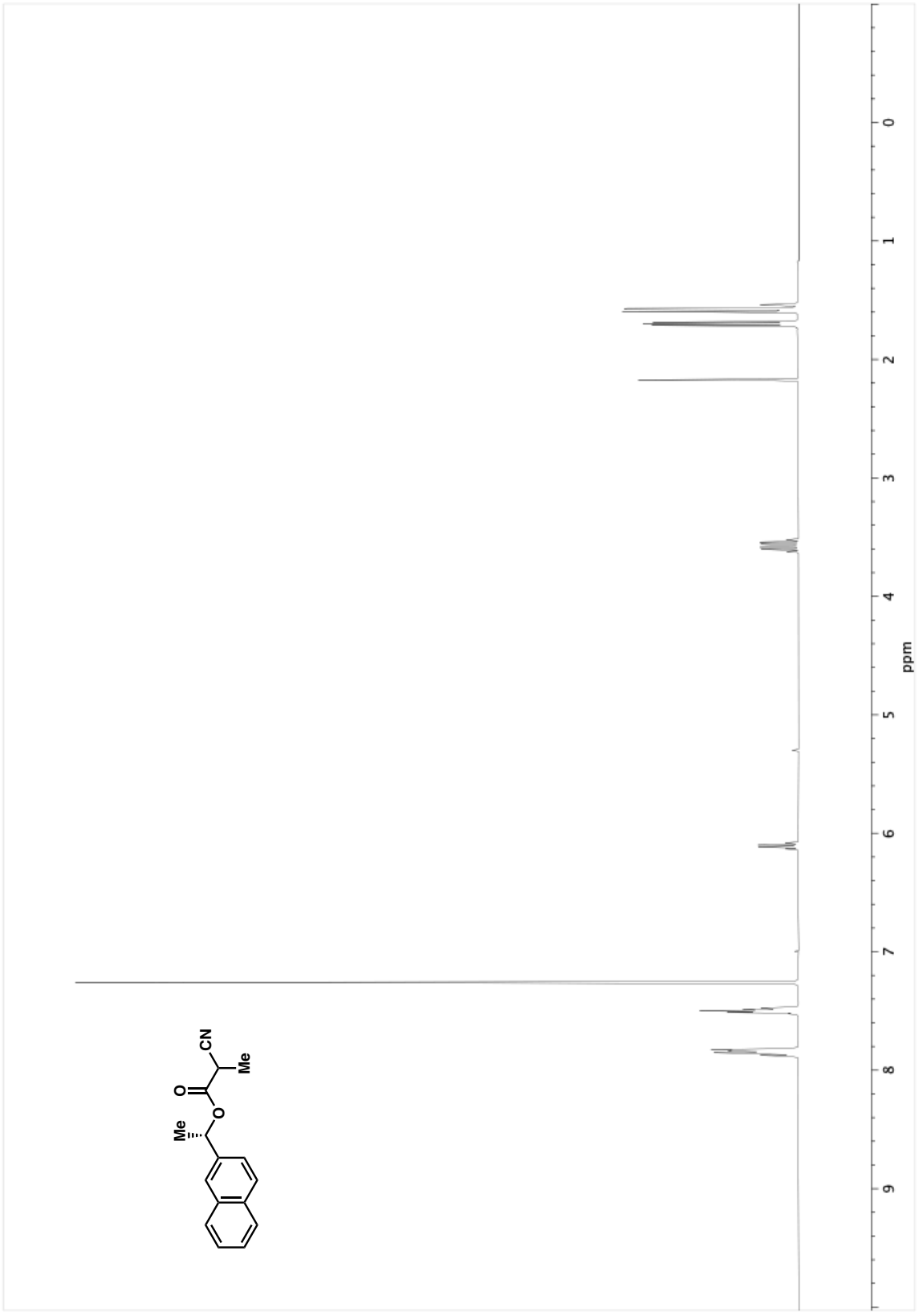


Figure A2.19. *^1H NMR (400 MHz, $CDCl_3$) of compound **30**.*

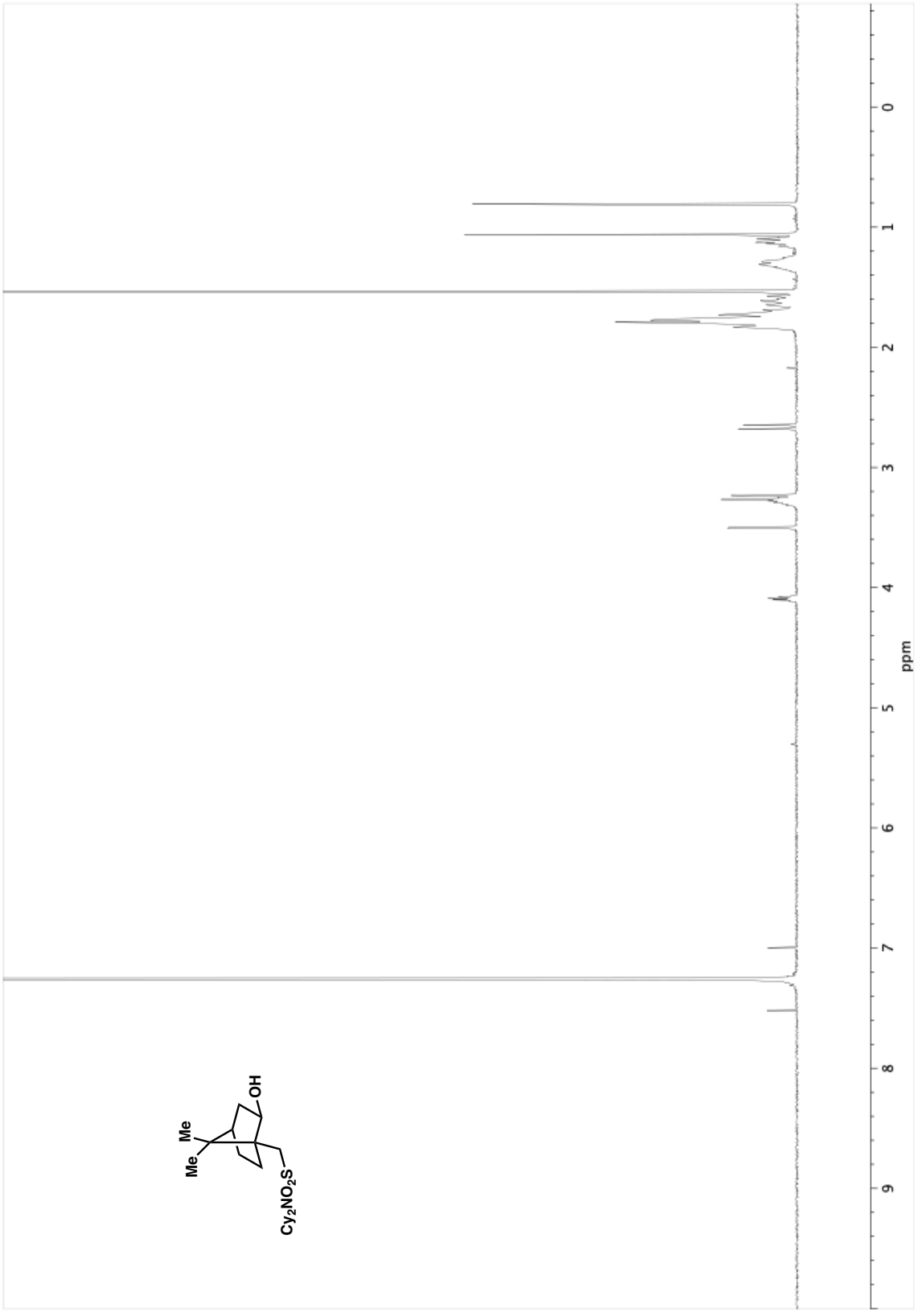


Figure A2.20. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***33b****.*

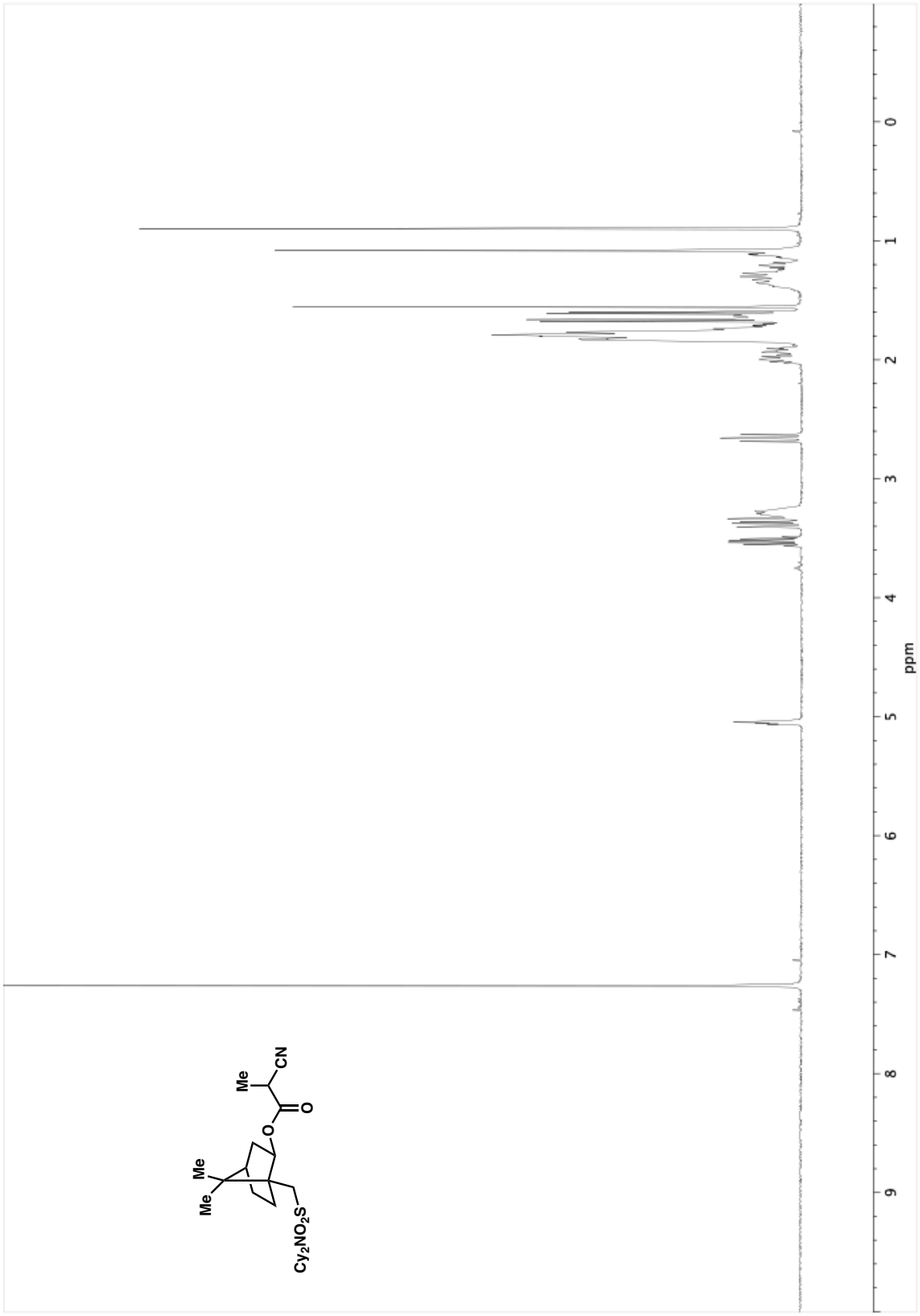


Figure A2.21. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***33****.*

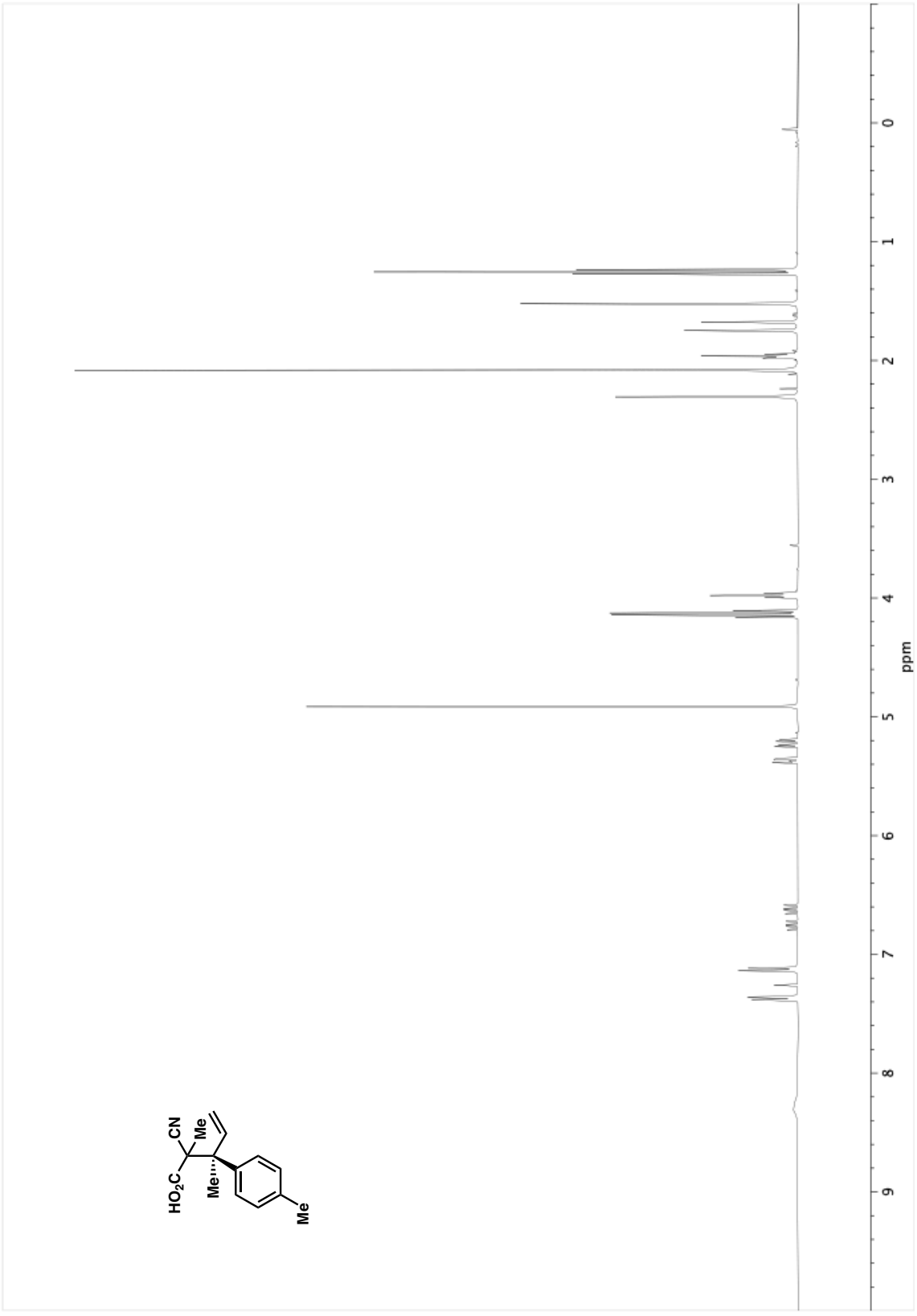


Figure A2.22. *Crude ^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***37****.*

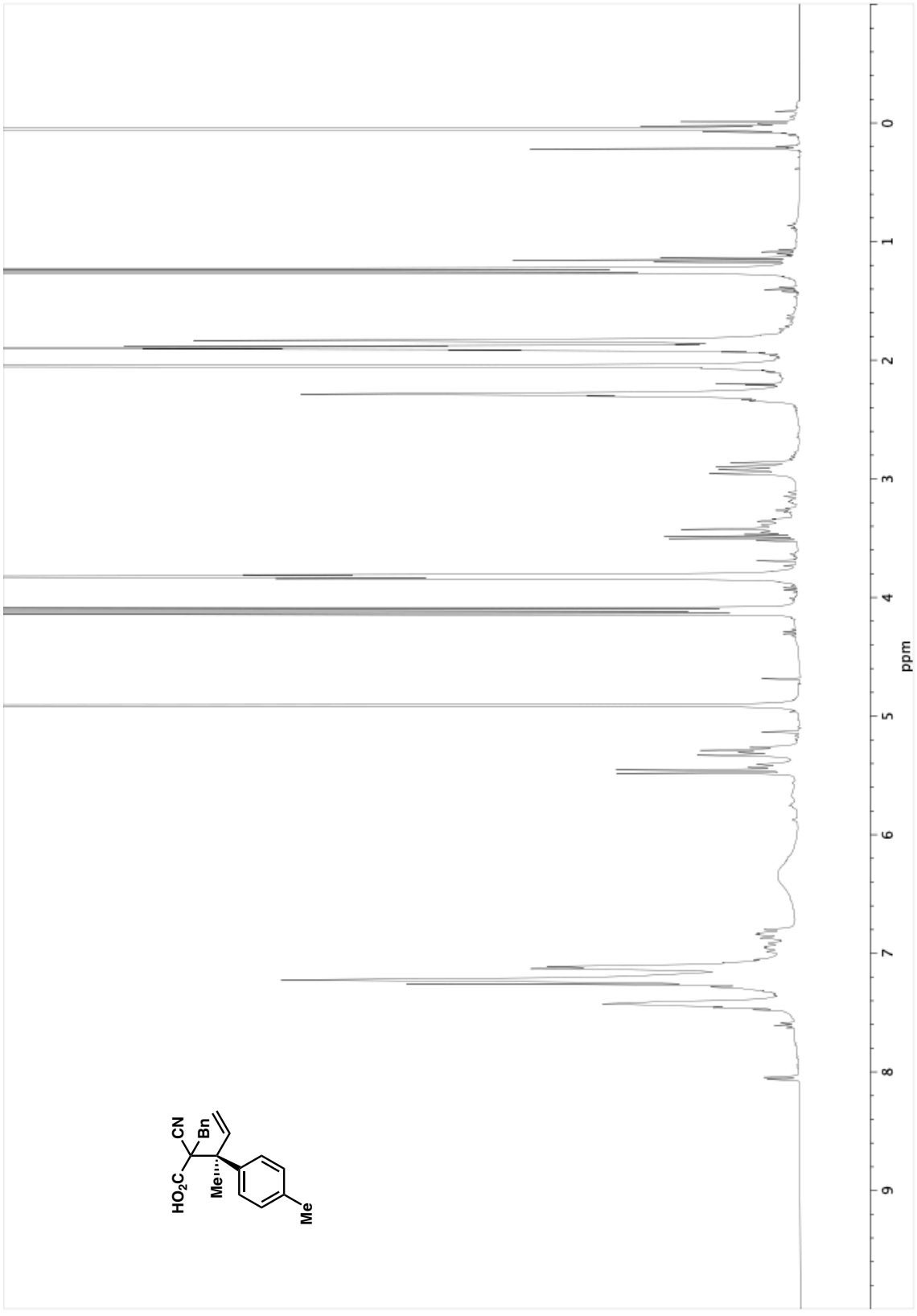


Figure A2.23. *Crude ^1H NMR (400 MHz, $CDCl_3$) of compound **38**.*

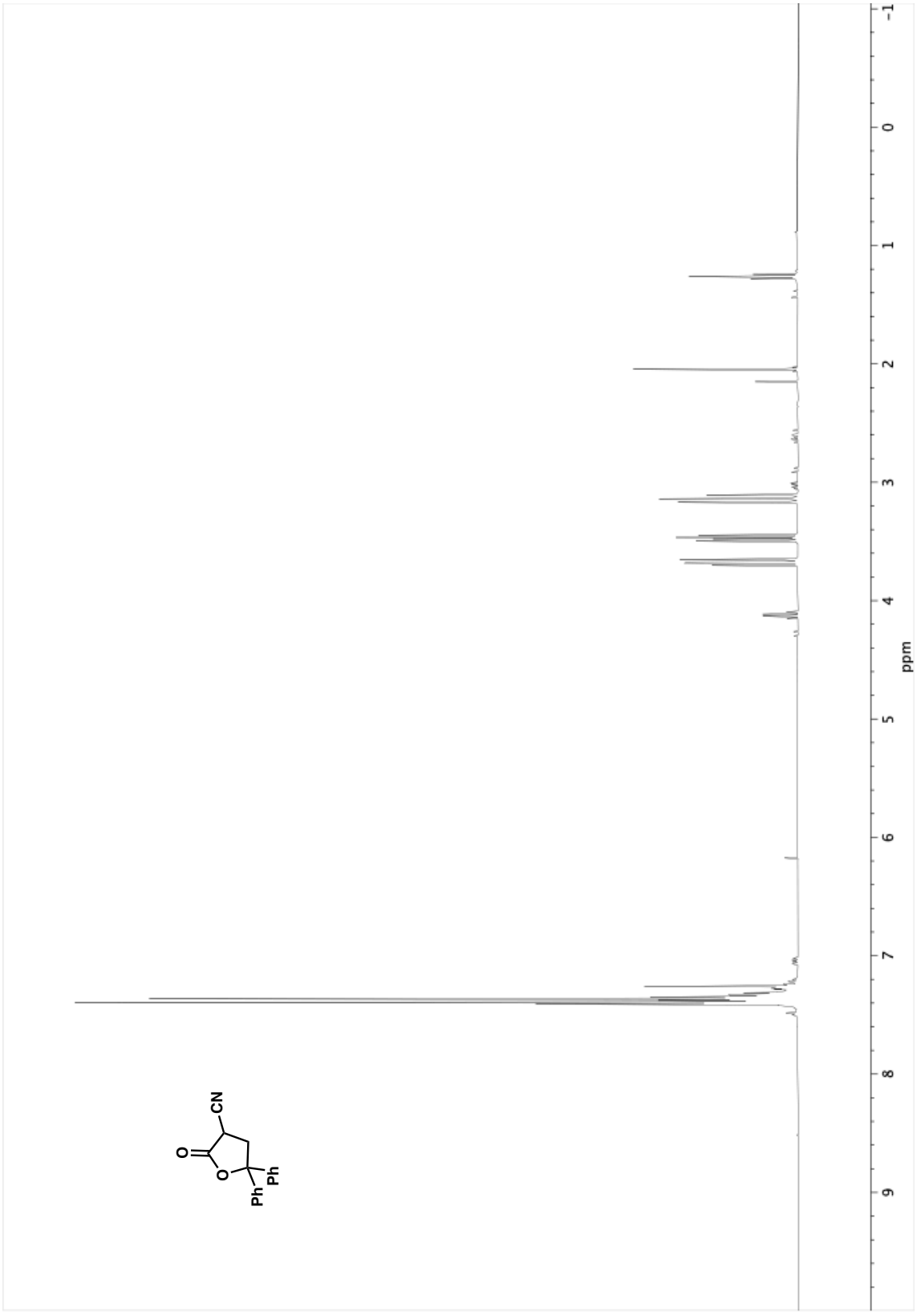


Figure A2.24. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***40****.*

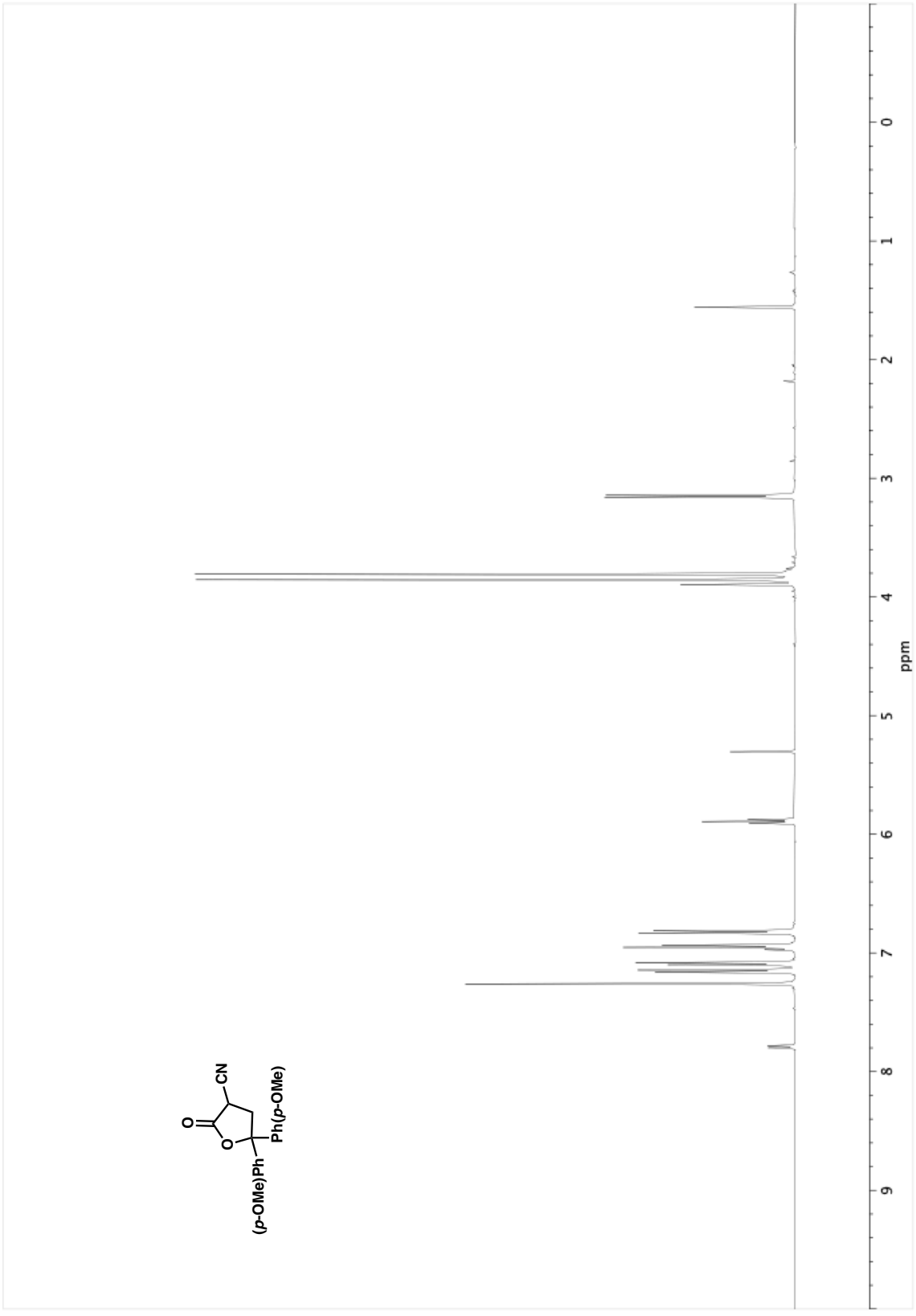


Figure A2.25. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***41****.*

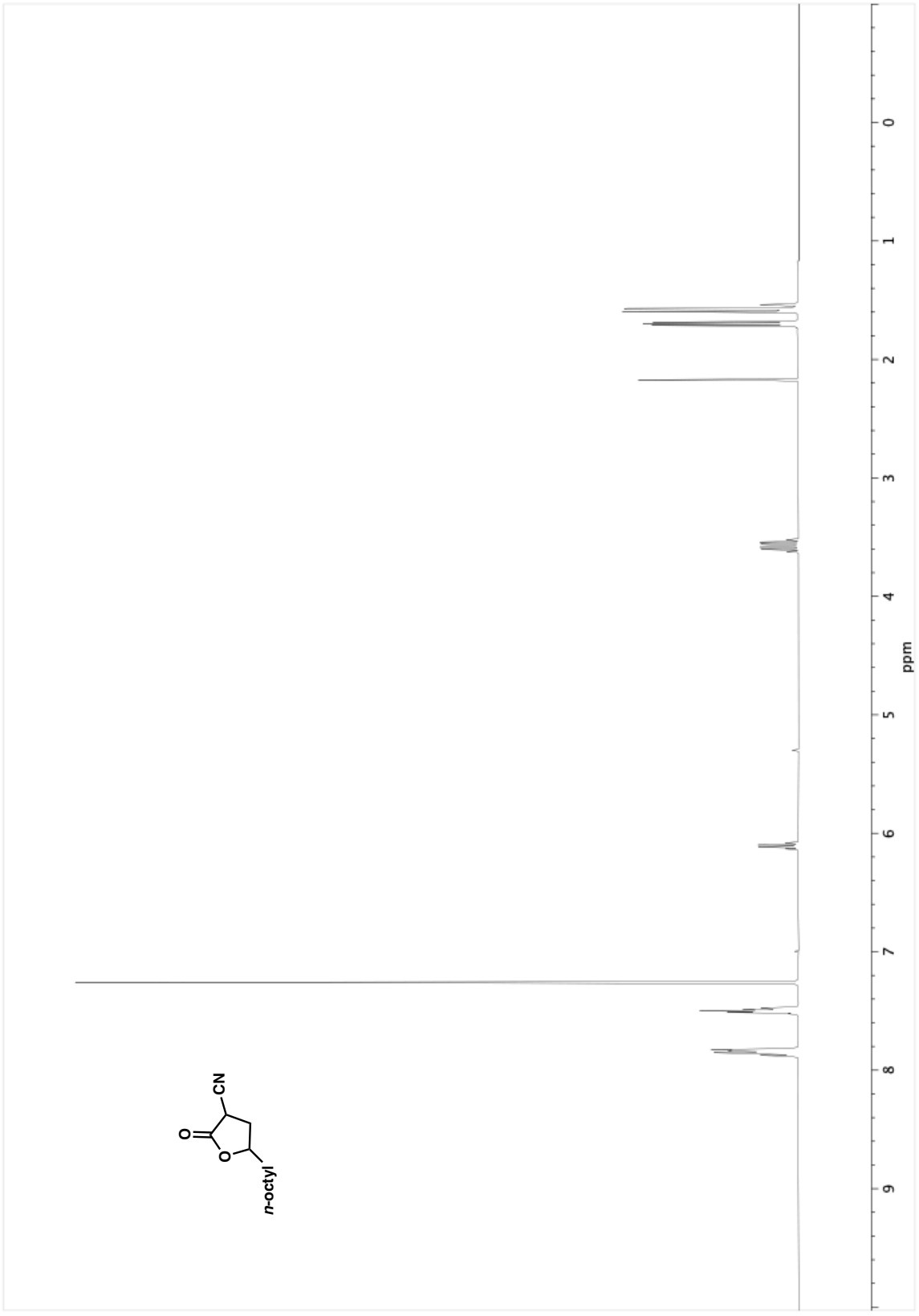


Figure A2.26. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***44****.*

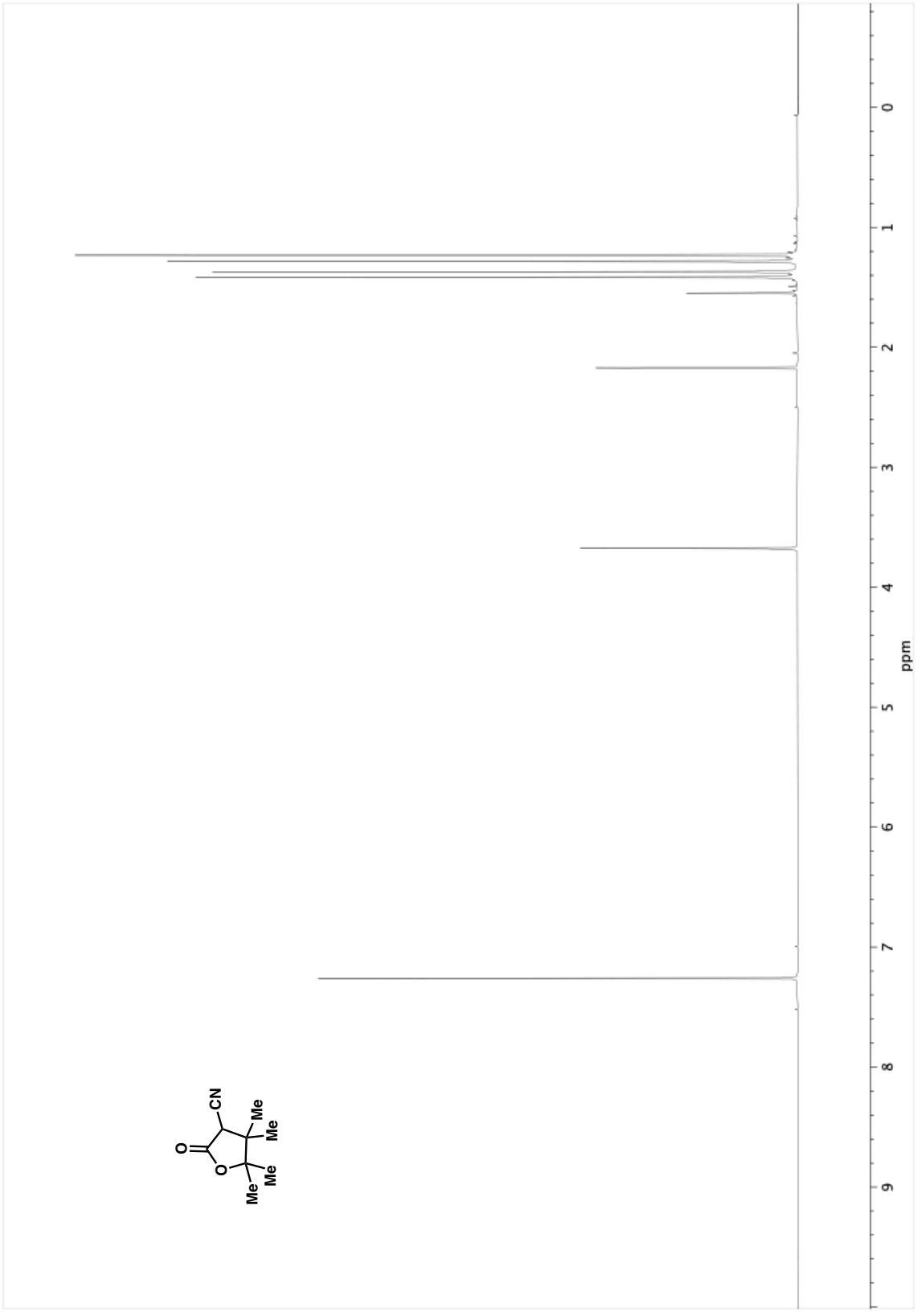


Figure A2.27. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***48****.*

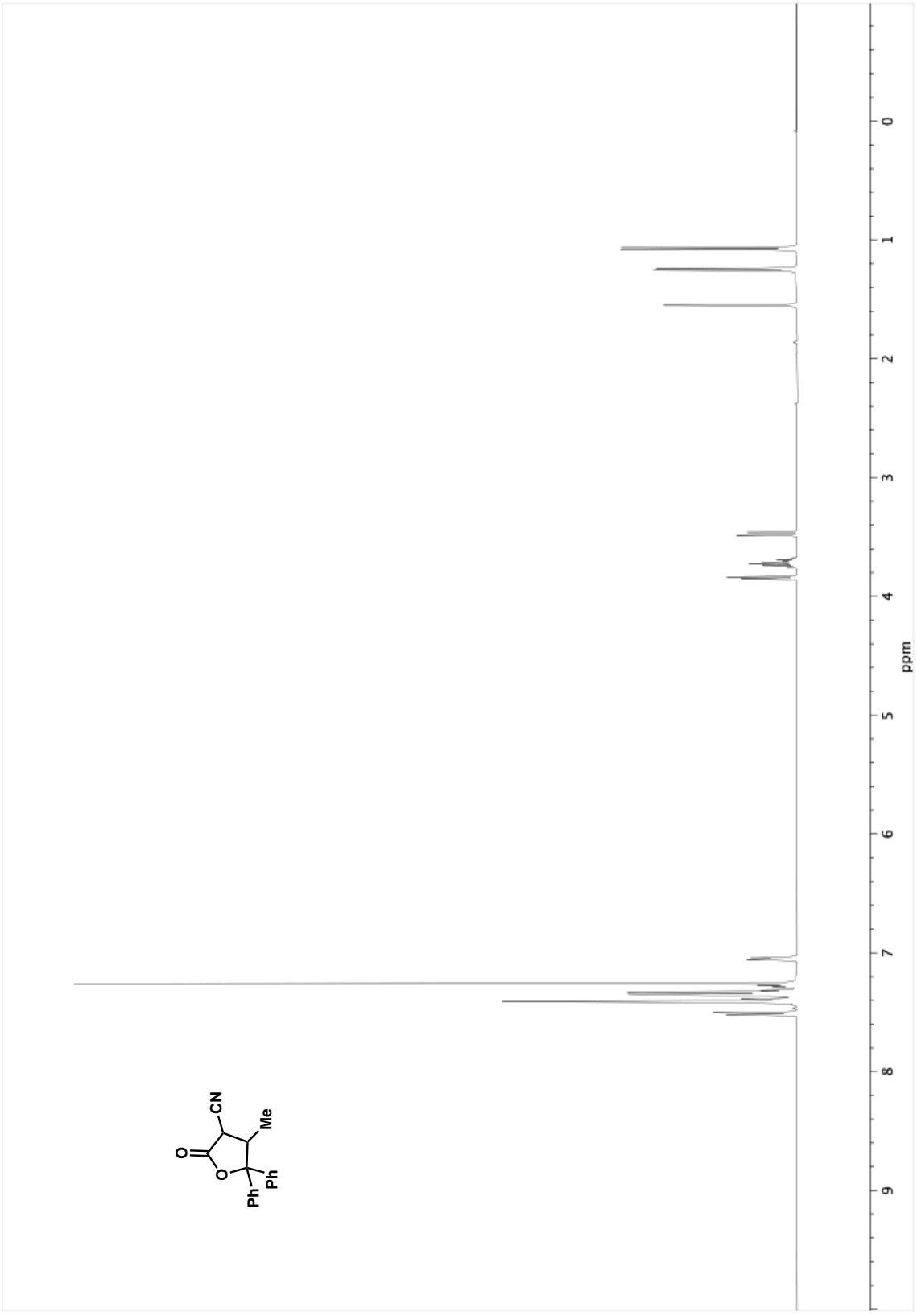


Figure A2.28. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***49***.

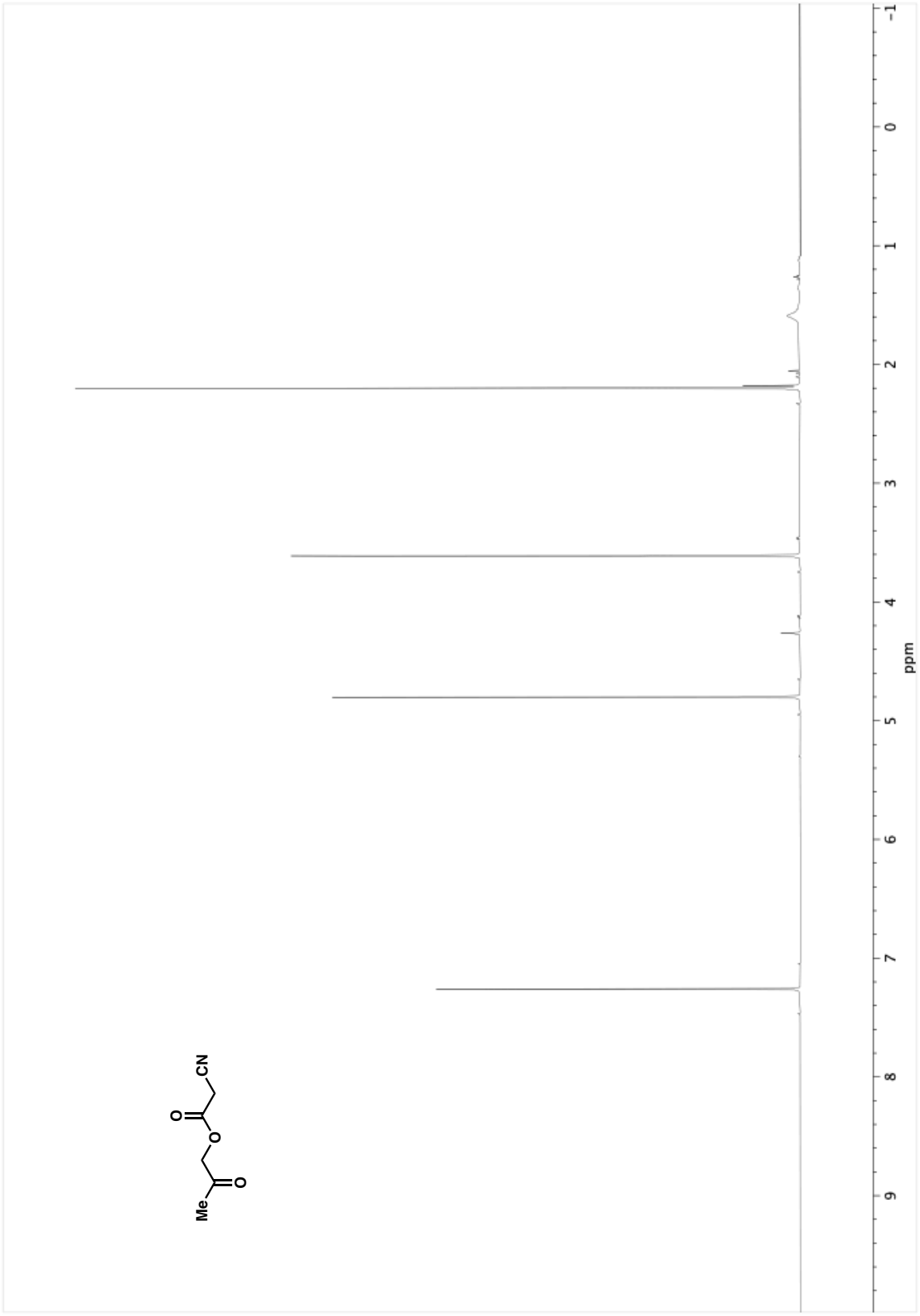


Figure A2.29. *^{1}H NMR (500 MHz, $CDCl_3$) of compound* ***46a****.*

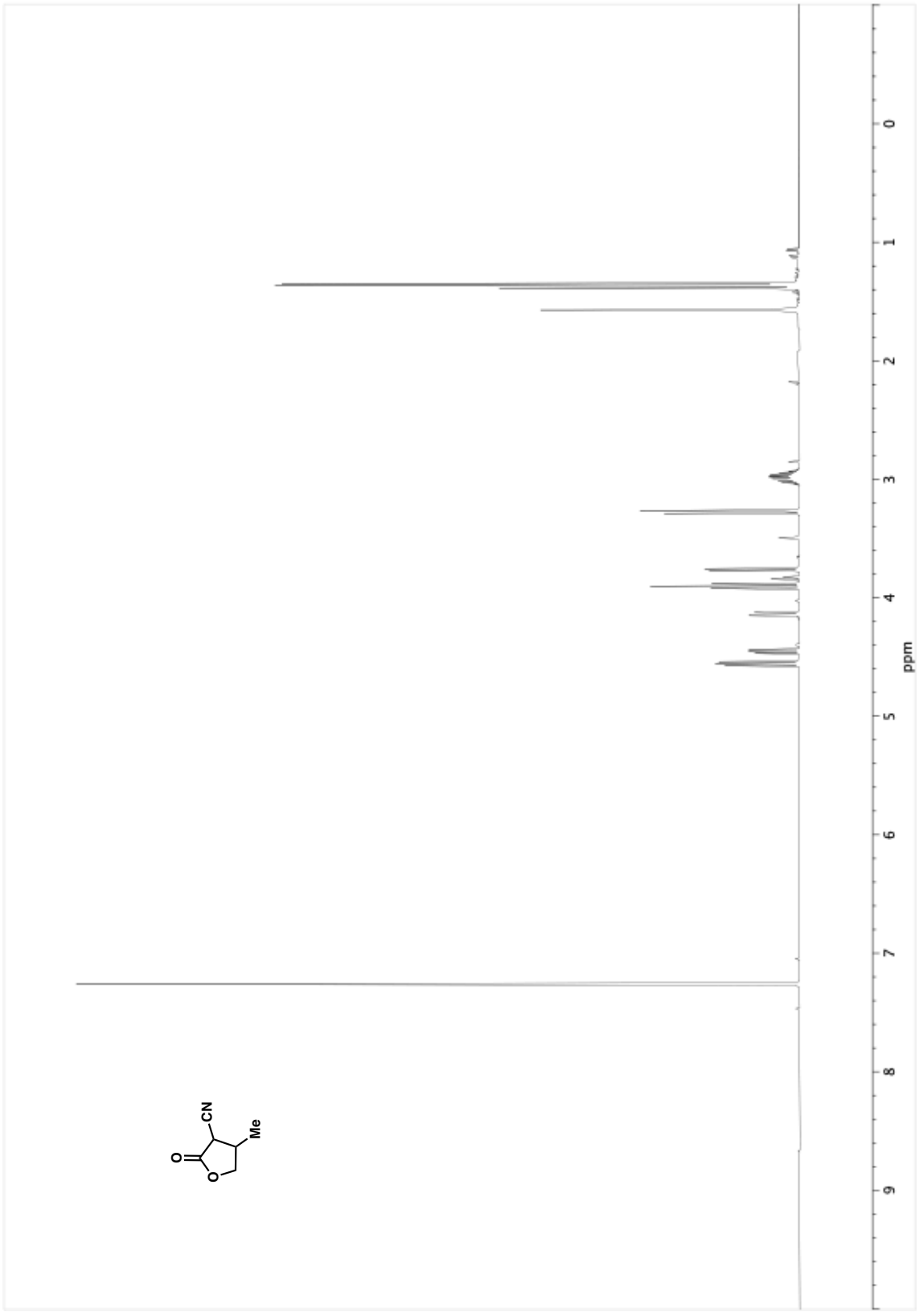


Figure A2.30. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***46****.*

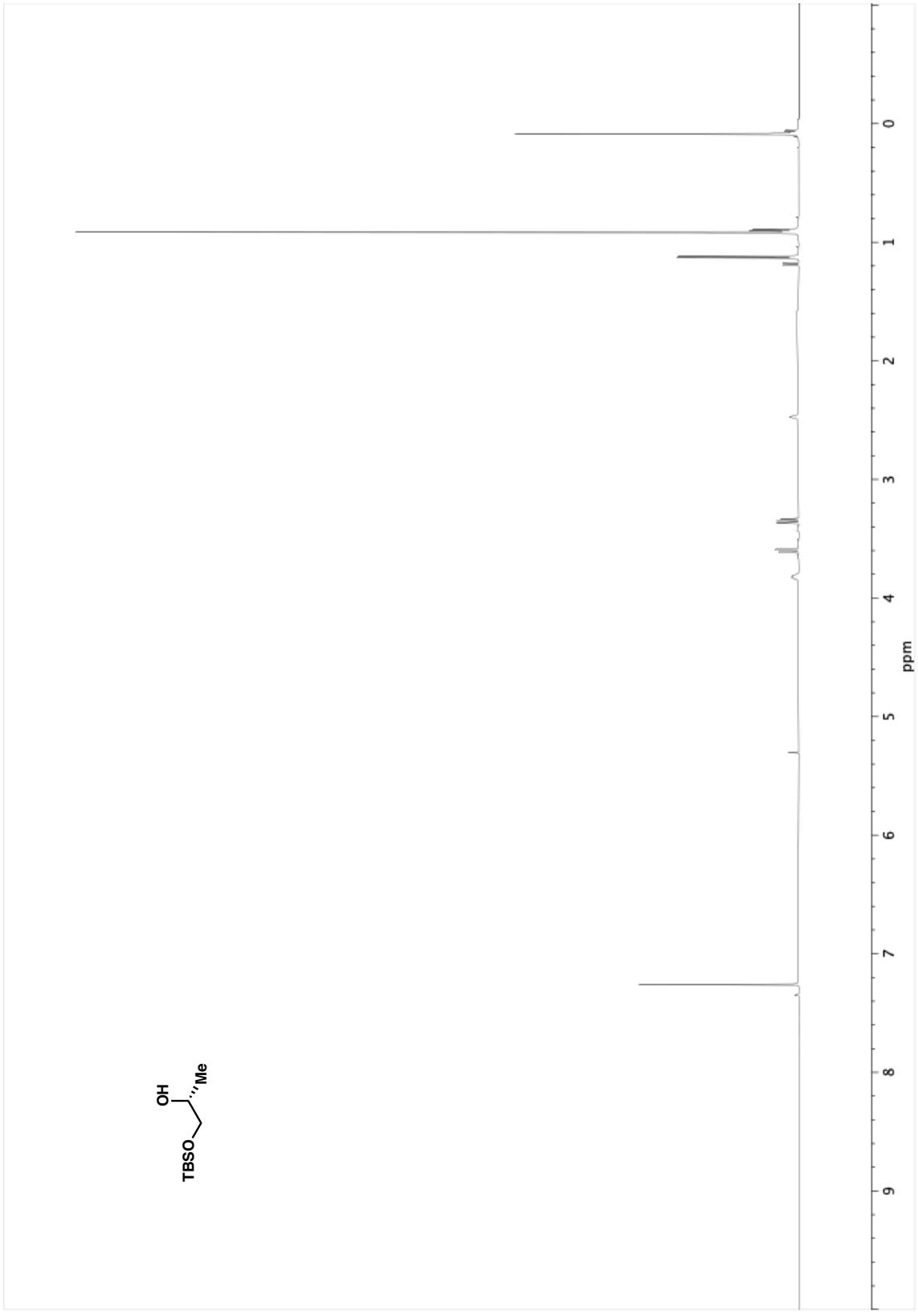


Figure A2.31. *^1H NMR (500 MHz, $CDCl_3$) of compound **50**.*

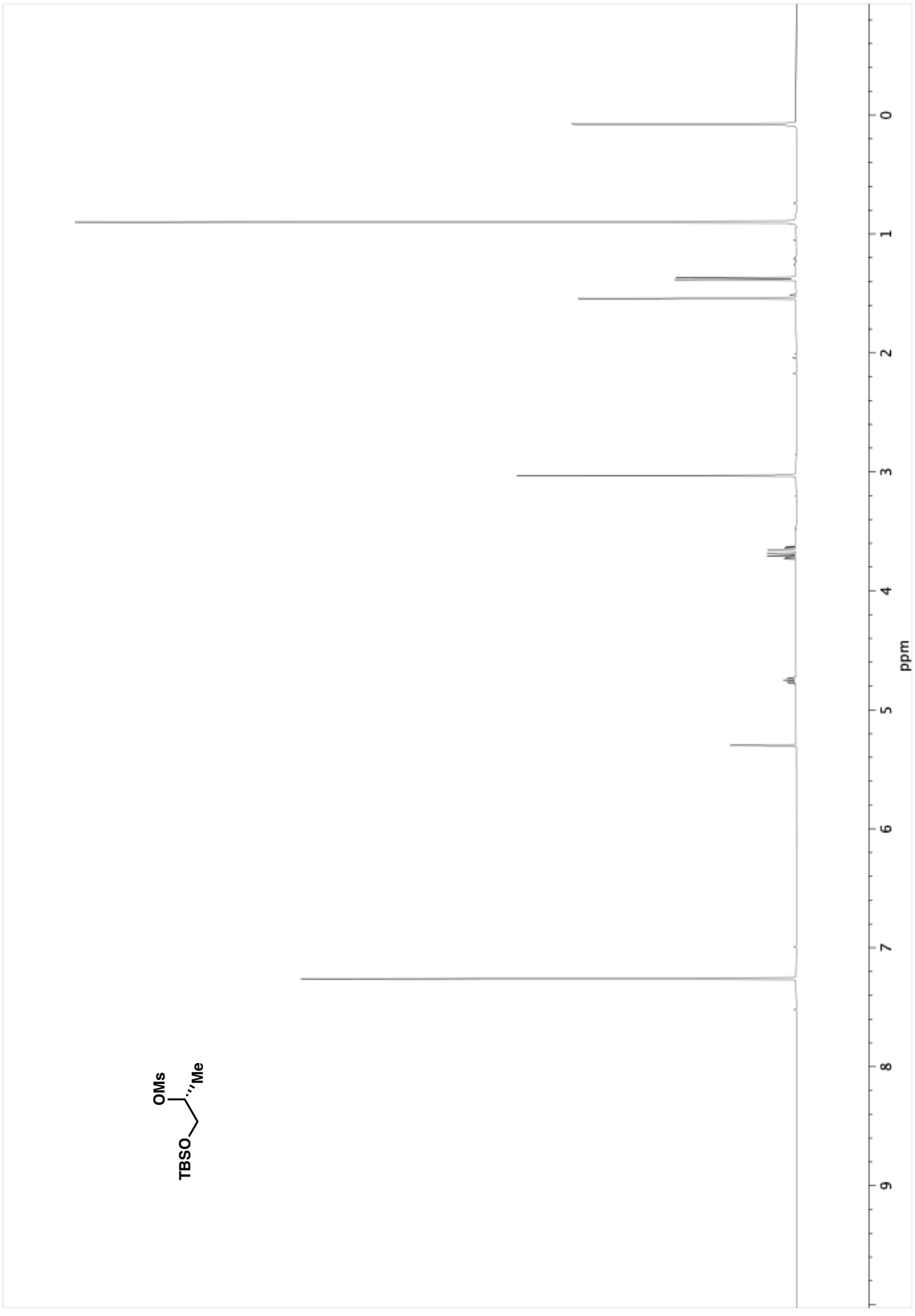


Figure A2.32. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **51**.*

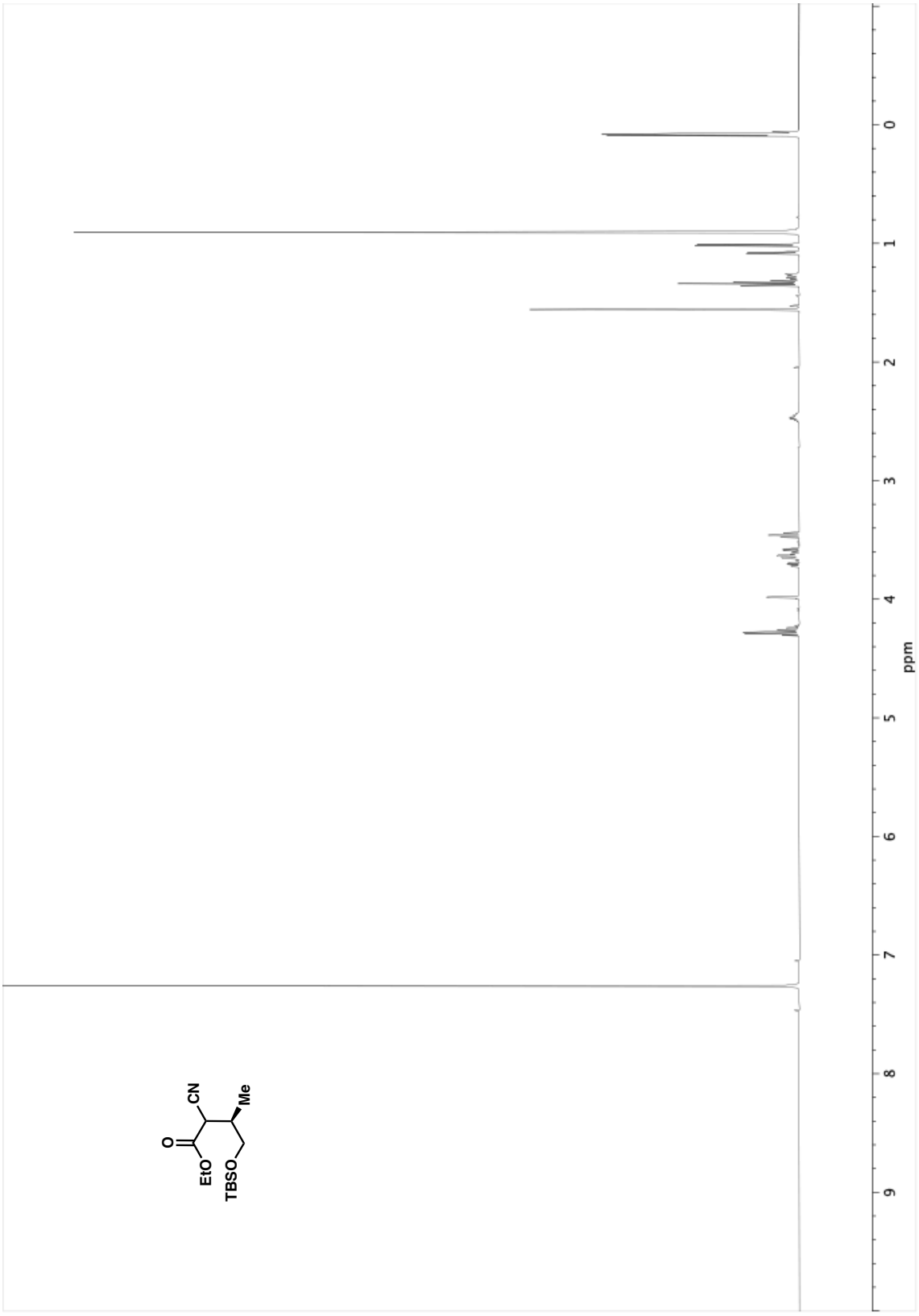


Figure A2.33. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***52****.*

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