DEVELOPMENT OF CU- AND NI-CATALYZED C–C AND C–N BOND FORMING REACTIONS

Thesis by

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To the memory of Gregory P. Harlow

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ABSTRACT

Chapters 1 and 2 describe the development of photoinduced, Cu-catalyzed coupling reactions of unactivated secondary alkyl halides with amide and cyanide nucleophiles. These reactions may be conducted at room temperature under operationally simple conditions. Mechanistic studies are consistent with the intermediacy of alkyl radicals in these processes.

Chapter 3 describes progress toward the development of the first enantioselective Ni-catalyzed cross coupling of racemic alkyl halides and heteroatom nucleophiles. Borylation of secondary benzylic chlorides with $B_2(pin)_2$ may be achieved in good yield and promising levels of enantioselectivity.

Chapter 4 describes enantioselective Ni-catalyzed couplings of α-substituted lactam enolates with benzonitrile derivatives resulting in formal intermolecular C-acylation via in situ hydrolysis of an imine intermediate.

PUBLISHED CONTENT AND CONTRIBUTIONS

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S.B. participated in experiments, data analysis, and manuscript preparation.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
Ac	acetyl
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
atm	atmosphere(s)
BINAP	Bis(diphenylphosphino)-1,1′-binaphthyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
s-Bu	*sec*-butyl
t-Bu	*tert*-butyl

Bn	benzyl
Bz	benzoyl
B(pin)	pinacol boronic ester group
$B_2(pin)_2$	bis(pinacolato)diboron
c	concentration of sample for measurement of optical rotation
^{13}C	carbon-13 isotope
/C	supported on activated carbon charcoal
°C	degrees Celsius
calc'd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
cf.	consult or compare to (Latin: *confer*)
CFL	compact fluorescent light
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
conc.	concentrated
Cy	cyclohexyl group
d	doublet
D	dextrorotatory
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martine periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
E	trans (entgegen) olefin geometry
e.g.	for example (Latin: *exempli gratia*)
EI	electron impact
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
equiv	equivalent
EWG	electron withdrawing group
FAB	fast atom bombardment
g	gram(s)
GC	gas chromatography
h	hour(s)
^{1}H	proton
^{2}H	deuterium
^{3}H	tritium
[H]	reduction
n-Hex	hexyl or *norm* hexyl group

HMDS	hexamethyldisilamide or hexamethyldisilazide
$h\nu$	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i.e.	that is (Latin: *id est*)
IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
L	liter or neutral ligand
L	levorotatory
LA	Lewis acid
LDA	lithium diisopropylamide
m	multiplet or meter(s)
M	molar or molecular ion
m	meta
μ	micro
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz

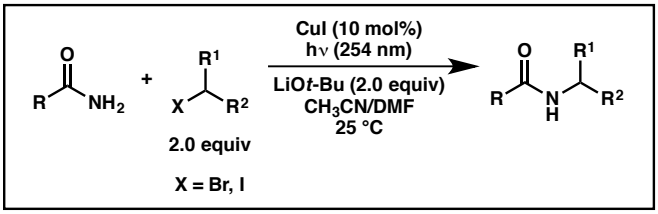
min	minute(s)
mL	milliliter(s)
mol	mole(s)
mp	melting point
m/*z*	mass-to-charge ratio
N	normal or molar
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu	nucleophile
o	ortho
[O]	oxidation
OMP	*ortho*-methoxyphenyl
p	para
PET	photosensitized electron transfer
n-pent	pentyl or *norm*-pentyl
Ph	phenyl
PG	protecting group
pH	hydrogen ion concentration in aqueous solution
pin	pinacol
pK_a	acid dissociation constant
PMP	*para*-methoxyphenyl

ppm	parts per million
Pr	propyl
i-Pr	isopropyl
i-Pr_2O	diisopropyl ether
n-Pr	propyl or *norm*-propyl
py	pyridine
pybox	pyridine bis(oxazoline)
q	quartet
R	alkyl group
R	rectus
r	selectivity = [major stereoisomer – minor stereoisomer]/[major stereoisomer + minor stereoisomer]
ref	reference
R_f	retention factor
rt	room temperature
s	singlet or seconds
s	selectivity factor = $k_{rel(fast/slow)} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C = conversion
S	sinister
sat.	saturated
SET	single electron transfer
S_N2	bimolecular nucleophilic substitution
t	triplet
TB_{amp}	TB with 100 μg/mL amp

TBACN	tetra-*n*-butylammonium cyanide
TBAI	tetra-*n*-butylammonium iodide
TBME	*tert*-butylmethyl ether
TBS	*tert*-butyldimethylsilyl
temp	temperature
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl
t_r	retention time
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
W	watt
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry

CHAPTER 1

Photoinduced, Copper-Catalyzed Alkylation of Amides with Unactivated Secondary Alkyl Halides at Room Temperature[†]



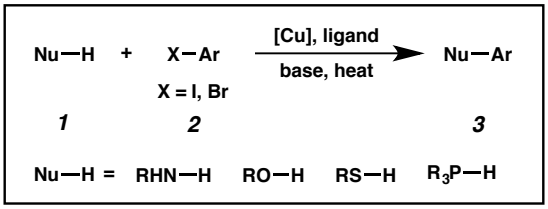
[†] This work was performed in collaboration with Dr. Hien-Quang Do and Dr. Alex C. Bissember, and was partially adapted from the publication: Do, H.-Q.; Bachman, S.; Bissember, A. C.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 2162–2167. Copyright 2014 American Chemical Society.

1.1 Introduction

The copper-mediated formation of C−C and C−heteroatom bonds, or the Ullman-type reaction, is a well-established process in organic chemistry.[1] The "classic" Ullman reaction, developed in 1901, used a stoichiometric amount of copper to couple two aryl halides, generating symmetrical biaryl products.[2] By 1929, the reaction scope was expanded to the cross coupling of aryl halides with anilines,[3] phenols,[4] amides,[5] and β-dicarbonyls.[6] Limitations of these pioneering studies include the requirement for high temperatures (170–210 °C)[2–6] and often stoichiometric amounts of copper.[2,3,6]

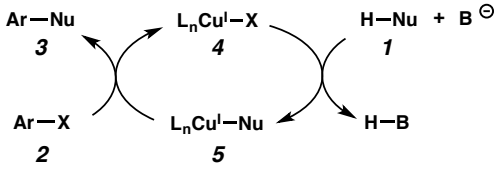
Milder conditions (80–100 °C) and catalytic amounts of copper are sufficient for a variety of Ullman-type reactions in which an organic additive is used (Scheme 1.1).[1] Proposed rationalizations for the rate-accelerating effect of an added ligand include improved solubility of copper–nucleophile intermediates,[7] prevention of copper aggregation in solution or disproportionation of the presumed copper(I) catalyst,[7b] increasing the copper species' propensity to undergo oxidative addition and/or reductive elimination,[8] and preventing multiple ligations of nucleophile to generate an inactive copper–nucleophile species.[7b,9]

Scheme 1.1 Scope of the Ullman-type reaction



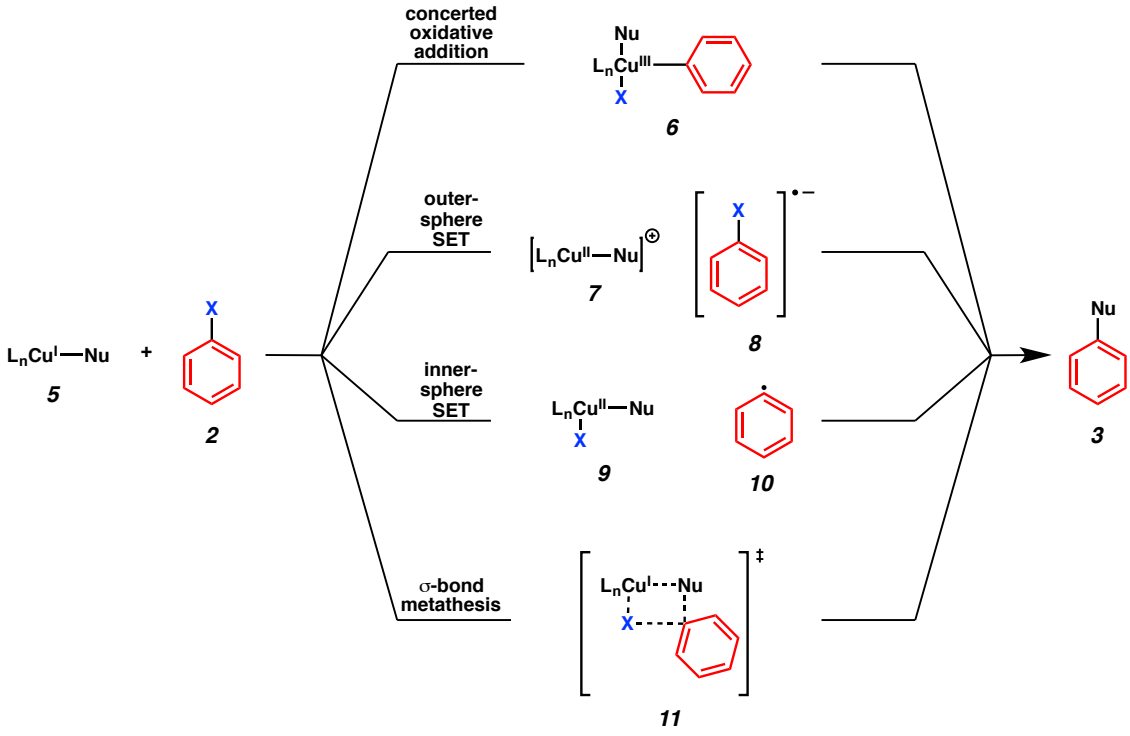
In efforts toward understanding the role of ancillary ligands in Ullman-type reactions, well-defined, ligated copper(I)–nucleophile complexes have been synthesized and shown to be kinetically and chemically competent intermediates.[9, 10] These experiments, as well as computational studies,[11] support the generally accepted proposal that Ullman-type reactions proceed by coordination of the deprotonated nucleophile (**1**) to a copper(I) species (**4**), followed by rate-determining activation of the aryl halide (Figure 1.1).[1] The mechanism of the aryl halide activation step remains under investigation.

Figure 1.1 Proposed intermediacy of a copper–nucleophile species in Ullman-type reactions



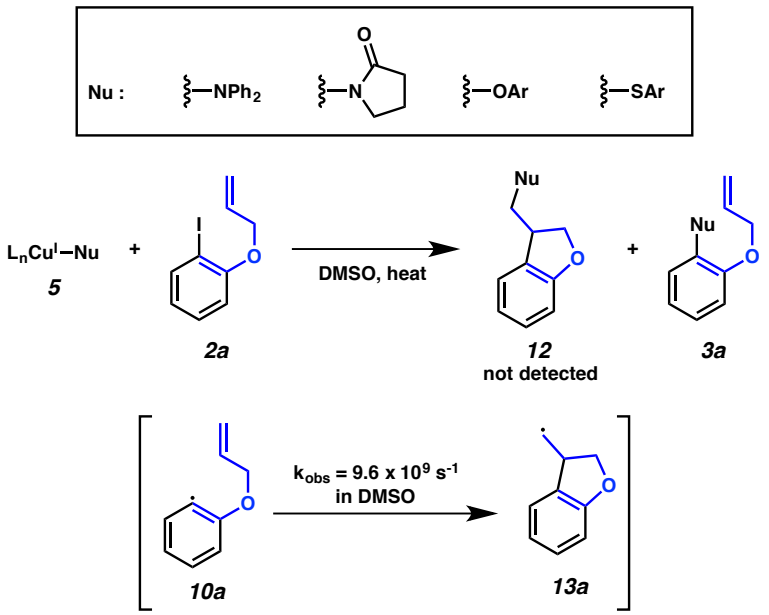
Proposed mechanisms for aryl halide activation include concerted oxidative addition, inner sphere or outer sphere single electron transfer (SET), and σ-bond metathesis (Figure 1.2).[1] SET pathways have been supported by computational studies,[11c,d,12] but little experimental evidence for such pathways existed until recently.[13]

Figure 1.2 Proposed mechanisms for aryl halide activation



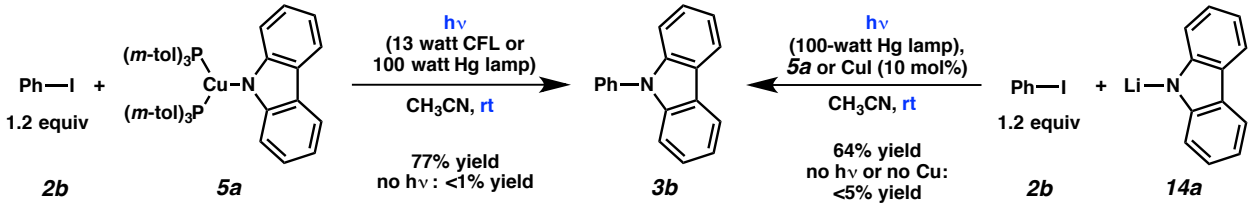
In several systems, experimental evidence has been considered inconsistent with the formation of aryl radical intermediates.[10a–d] For example, various copper–nucleophile complexes (**5**) were reported to couple with aryl iodide **2a** to generate exclusively the uncyclized products (**3a**, Scheme 1.2).[10a–d] Because aryl radical **10a** rearranges with a unimolecular rate constant of ~10^{10} s^{-1} in DMSO,[14] the absence of cyclized products (**12**) has been cited as evidence against SET to the aryl iodide.[10a–d]

Scheme 1.2 Coupling of various copper–nucleophile complexes with an aryl radical probe



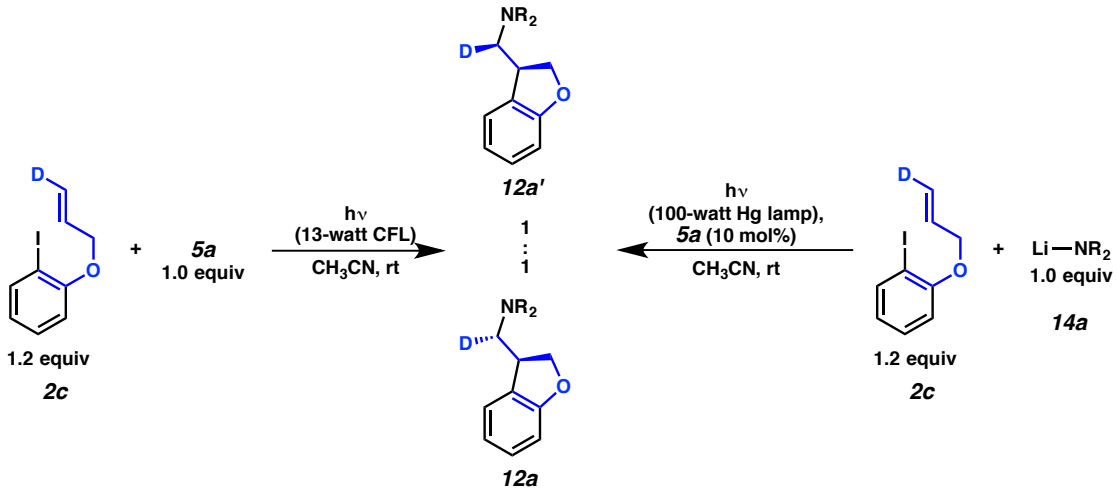
In 2012, Fu and Peters reported the light-mediated, room temperature C–N coupling of copper–carbazolide complex **5a** with aryl halides (Scheme 1.3).[15] *N*-arylation of lithium carbazolide (**14a**) with iodobenzene (**2b**) can also be achieved using a catalytic amount of either complex **5a** or CuI. For both stoichiometric and catalytic C–N bond forming processes, little to no reaction is observed in the dark.

Scheme 1.3 Light- and copper-mediated C–N bond formation at room temperature



A variety of data are consistent with an SET pathway for this photoinduced, copper-mediated C–N coupling. For example, in contrast to previous mechanistic studies of thermal copper-mediated *N*-arylation,[10a,b] radical probe **2a** generates exclusively the cyclized coupling product (**12**). Under both stoichiometric and catalytic conditions, deuterium-labeled aryl iodide **2c** yields a 1:1 mixture of diastereomeric cyclized C–N coupled products **12a** and **12a'** (Scheme 1.4). This is inconsistent with aryl halide cyclization via concerted oxidative addition/syn-insertion/reductive-elimination, which would be expected to give a single diastereomer.

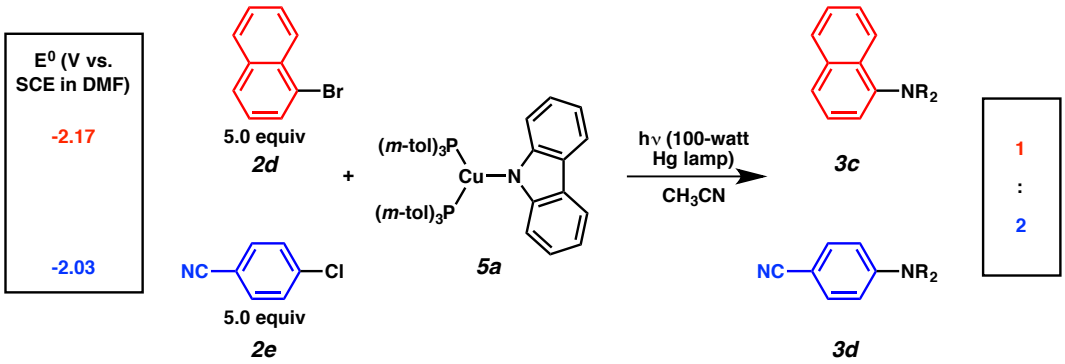
Scheme 1.4 Cyclization and coupling of a deuterium-labeled radical probe



Again contrasting previous studies of thermal copper-mediated C–N coupling,[10a,b] a competition experiment between 1-bromonapthalene (**2d**) and 4-chlorobenzonitrile (**2e**) results in predominant cross-coupling of the aryl chloride (Scheme 1.5). Because aryl chloride **2e** is easier to reduce than aryl bromide **2d**, and both substrates have similar

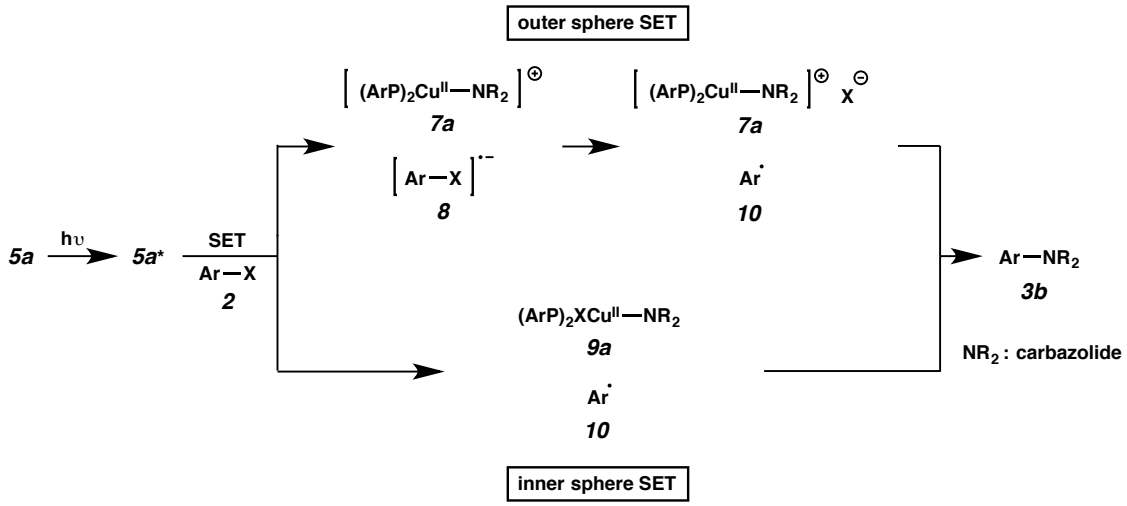
rates of dissociation of the halide from the radical anion, this result is consistent with an SET pathway.[10a]

Scheme 1.5 Competition experiment between aryl halides with different standard reduction potentials



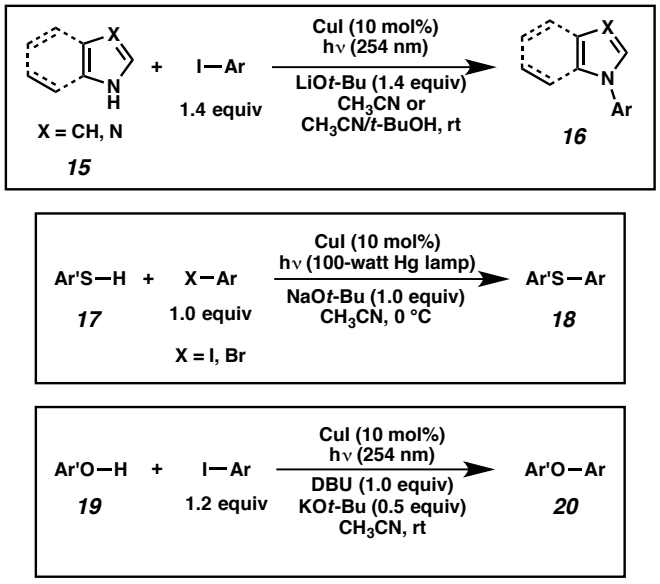
Additional evidence for an SET pathway includes EPR data consistent with the formation of a copper-containing radical when copper−carbazolide complex **5a** is irradiated in the presence of iodobenzene (**2b**). Thus, one possible mechanism for the aryl halide activation step could be SET from photoexcited species **5a*** to the aryl halide (**2**), thereby generating a copper(II) species and ultimately an aryl radical (**10**, Figure 1.3).

Figure 1.3 One possible mechanism for photoinduced aryl halide activation by a copper–carbazolide complex



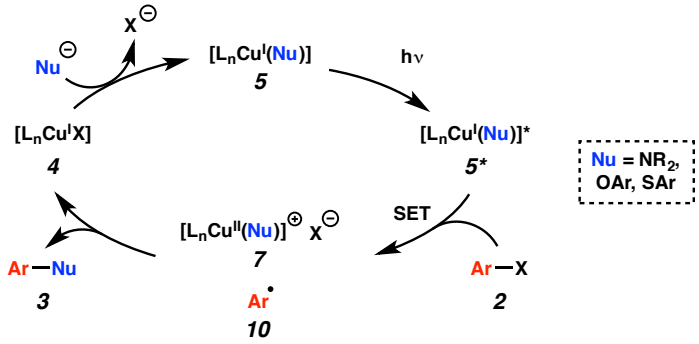
This initial discovery prompted the development of several general methods for copper-catalyzed arylation of heteroatom nucleophiles under mild conditions (Scheme 1.6).[16]

Scheme 1.6 Photoinduced, copper-catalyzed arylation of nitrogen heterocycles, thiols, and phenols



These copper-catalyzed, photoinduced C(aryl)−heteroatom bond formations do not necessarily proceed by a common mechanism; however, we hypothesize that in each case, photoexcitation of a copper−nucleophile complex (**5**) and single electron transfer to the aryl halide are involved in the catalytic cycle (Figure 1.4).

Figure 1.4 One possible catalytic cycle for photoinduced, copper-catalyzed arylation

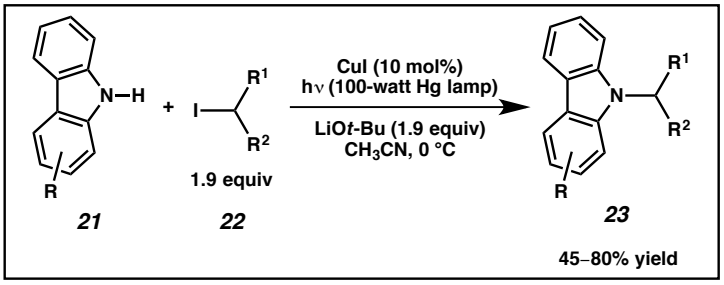


The cross-coupling of radical probe **2a** to generate *N*-alkylated carbazole (**12a** and **12a'**, Scheme 1.4) suggested that photoinduced, copper-catalyzed C(sp^3)−N bond forming reactions are also possible.[15] Traditional Ullman-type,[1] Buchwald-Hartwig,[17] and Chan-Lam reactions [18] are well-established strategies for C(sp^2)−N coupling, and reductive amination[19] and olefin hydroamination[20] are effective for the formation of C(sp^3)−N bonds, but there are few examples of transition metal-catalyzed functionalization of amines with alkyl halides.[21]

Fu and Peters reported that catalytic copper and light indeed effect *N*-alkylation of carbazoles (**21**) with unactivated secondary alkyl halides (**22**, Scheme 1.7).[22] This photoinduced, copper-catalyzed C(sp^3)−N coupling contrasts direct nucleophilic substitution of alkyl halides by amines, as it occurs under very mild conditions (0 °C) and is compatible with sterically hindered substrates. In addition, this represents one of the

few examples of transition metal-catalyzed couplings of amines with alkyl halides.[20] This work provided a proof-of-principle for C(sp^3)−N bond formations; however we were interested in expanding this strategy to a more general and ubiquitous class of nitrogen nucleophiles, such as amides.

Scheme 1.7 Photoinduced, copper-catalyzed N-alkylation of carbazole



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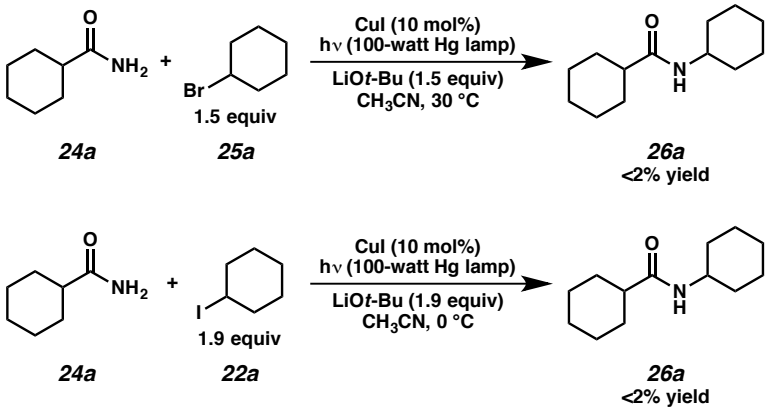
N-alkylated amides are an important motif in pharmaceuticals,[23] natural products,[24] and polymers.[25] Existing strategies for alkylation of primary amides include direct nucleophilic substitution of alkyl halides, transamidation of amides with alkyl amines,[26] hydroamidation of alkenes,[27] and amidation of unactivated alkanes.[28] Despite the efficacy of these reactions, there is a lack of a general and mild strategy for *N*-alkylation to generate α-branched *N*-alkyl amides.

1.2 Results and Discussion

The optimal conditions for coupling carbazoles with unactivated secondary alkyl bromides and iodides were ineffective when carbazole was replaced by cyclohexanecarboxamide (**24a**) (Scheme 1.8);[22] however the use of 254 nm light instead of a Hg lamp provided efficient coupling with bromocyclohexane at room temperature. The finalized conditions resulting from optimization of various reaction parameters are shown in Table 1, Entry 1.

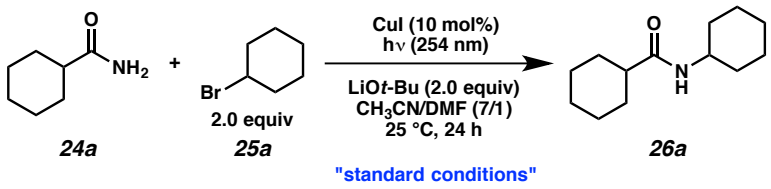
Scheme 1.8 Attempted amide alkylation under conditions previously described for carbazole alkylation



Control reactions in the absence of copper(I) iodide, light, or lithium *tert*-butoxide resulted in little to no C−N bond formation (Table 1.1, entries 2−3). Using copper(I) bromide or copper(I) chloride instead of copper(I) iodide as the precatalyst was only slightly detrimental to yield (entries 5, 6), whereas use of bases other than lithium *tert*-butoxide caused a significant decrease in yield (entries 7−10). While only a minor decrease in yield was observed in the absence of *N,N*-dimethylformamide (entry 11), the co-solvent was particularly helpful when aryl amides were used as coupling partners.[29]

Using a smaller excess of base and electrophile was significantly detrimental to yield (entry 12), whereas decreasing the catalyst loading to as low as 2.5 mol% had little effect on yield (entries 13−16). Irradiation of the reaction mixture with longer-wavelength light resulted in little to no cross-coupling (entries 17, 18), but a household Honeywell 36 W UVC air-treatment lamp was a highly effective light source (entry 19). Irradiation of the reaction mixture with the Honeywell UVC lamp at 0 °C instead of room temperature resulted in a decrease in yield (entry 20). Addition of 1.0 equivalent of water to the reaction mixture did not significantly affect the reaction efficiency (entry 21).

Table 1.1 Effect of reaction parameters on photoinduced, copper-catalyzed N-alkylation



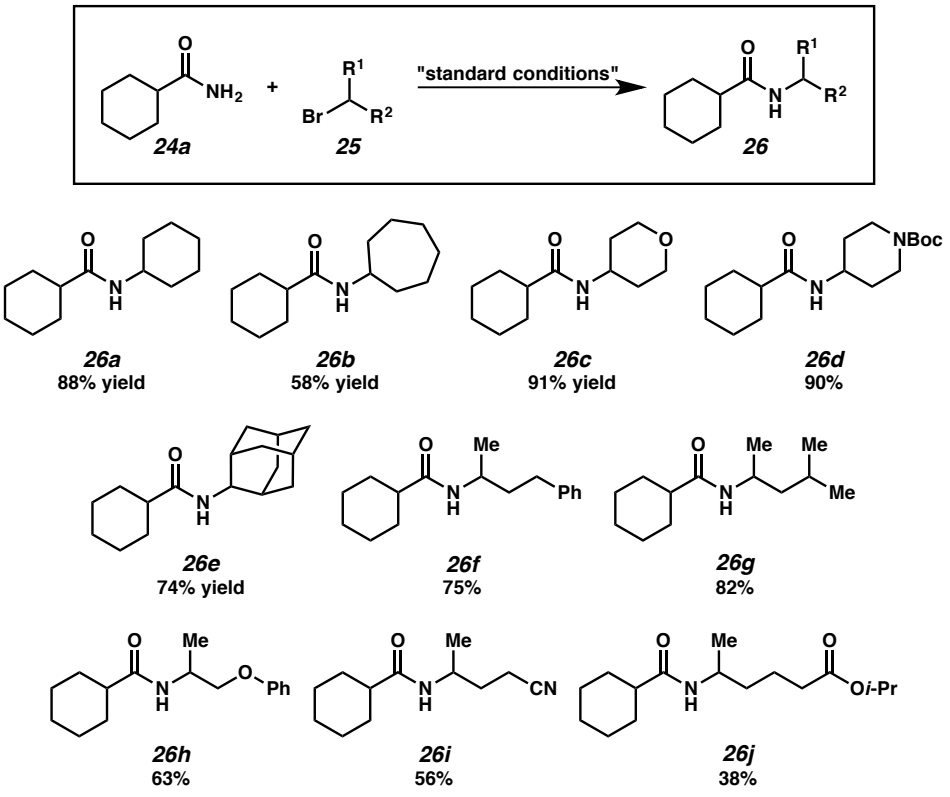
24a ***25a*** **"standard conditions"** ***26a***

entry	change from the "standard conditions"	yield (%)[a]
1	none	90
2	no CuI	<2
3	no hν	<2
4	no LiO*t*-Bu	<2
5	CuBr, instead of CuI	82
6	CuCl, instead of CuI	78
7	NaO*t*-Bu instead of LiO*t*-Bu	38
8	KO*t*-Bu instead of LiO*t*-Bu	10
9	Cs_2CO_3 instead of LiO*t*-Bu	9
10	K_3PO_4 instead of LiO*t*-Bu	4
11	no DMF	83
12	1.2 equiv CyBr and 1.2 equiv LiO*t*-Bu	40
13	CuI (5.0 mol%)	87
14	CuI (2.5 mol%)	83
15	CuI (1.0 mol%)	69
16	CuI (0.5 mol%)	30
17	hν (300 nm)	10
18	hν (100 W Hg lamp)	<2
19	Honeywell 36 W UVC air-treatment lamp	90
20	Honeywell 36 W UVC air-treatment lamp, 0 °C	33
21	1.0 equiv H_2O	85

[a]Determined through GC analysis (average of two experiments).

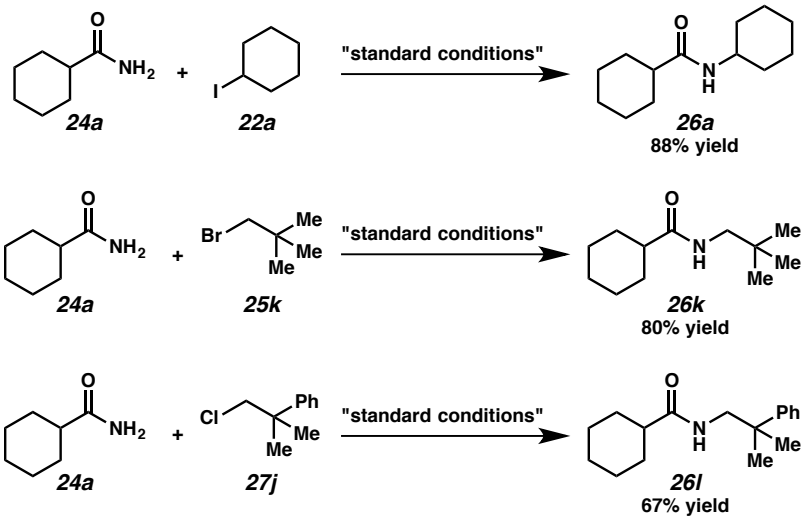
This photoinduced, copper-catalyzed C–N coupling reaction is compatible with a variety of both cyclic and acyclic alkyl bromides (Scheme 1.9). Functional groups including a cyclic ether (**26c**), an acyclic ether (**26h**), a carbamate (**26d**), and a nitrile (**26i**) are tolerated. A moderate yield was obtained for an alkyl bromide containing a pendant ester (**26j**), possibly due to transesterification with the *tert*-butoxide base.

Scheme 1.9 Scope with respect to unactivated secondary alkyl bromides



In addition to unactivated secondary alkyl bromides, an unactivated secondary alkyl iodide (**22a**), neopentyl bromide (**25k**) and neophyl chloride (**27j**) are suitable coupling partners (Scheme 1.10). The coupling of particularly poor S_N2 substrates **25k** and **27j** demonstrates this strategy's complementarity to direct nucleophilic substitution.

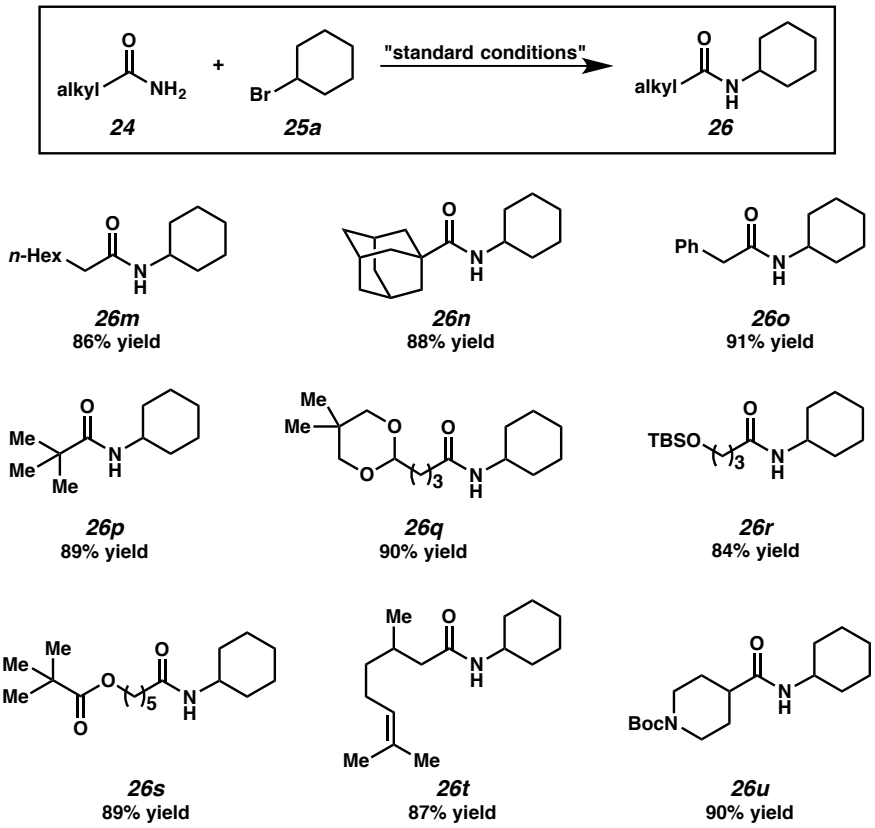
Scheme 1.10 Coupling of an unactivated secondary alkyl iodide and neopentyl halides



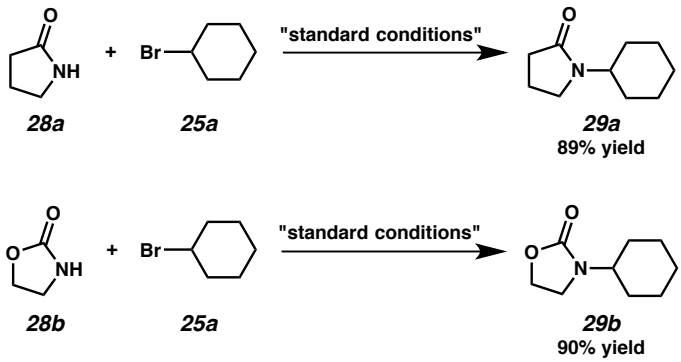
The scope of this *N*-alkylation reaction is broad with respect to the amide; an array of aliphatic primary amides can be coupled with unactivated secondary alkyl bromides in good yield (Scheme 1.11). The standard reaction conditions are effective for amides functionalized with a pendant acetal (**26q**), a TBS-protected alcohol (**26r**), an ester (**26s**), a trisubstituted olefin (**26t**), and a carbamate (**26u**).

Although we have not developed general conditions for the coupling of secondary amides, a lactam (**28a**) and an oxazolidinone (**28b**) furnish the corresponding tertiary amides **29a** and **29b**, respectively, in good yield (Scheme 1.12).

Scheme 1.11 Scope with respect to aliphatic amides



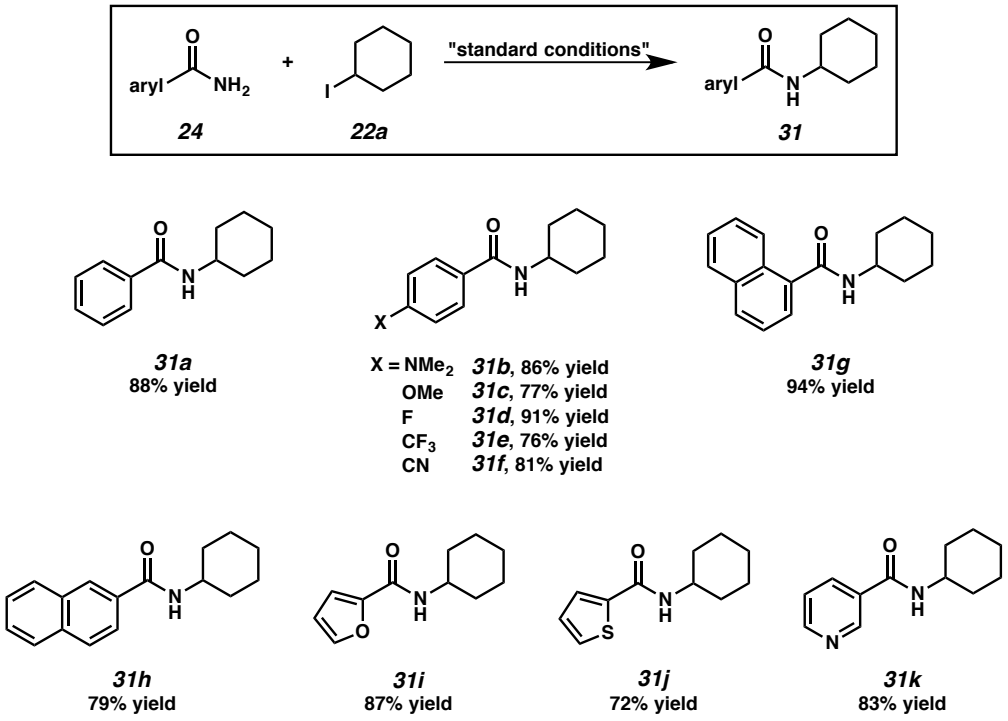
Scheme 1.12 C–N coupling of cyclic secondary amides



Primary aryl amides are also good substrates in this photoinduced, Cu-catalyzed C–N coupling; in this case unactivated secondary alkyl bromides are inferior to the corresponding alkyl iodides (Scheme 1.13). Aryl amides with substitution at the *para*

position are well-tolerated, including dimethylamino, methoxy, fluoro, trifluoromethyl, and cyano functional groups (**31b**–**f**). The aryl substituent can be a naphthyl-, furyl- , thiophenyl-, or pyridyl-derivative (**31g**–**k)**.

Scheme 1.13 Scope with respect to aryl amides



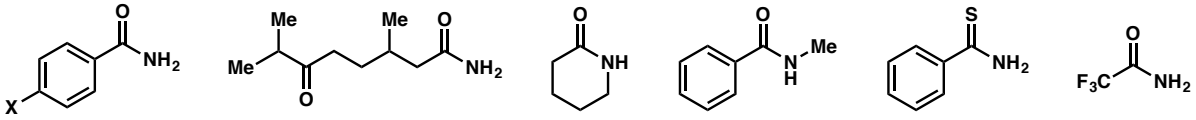
Despite the broad scope of this reaction with respect to both the amide and alkyl halide coupling partners, we are aware of several limitations. Under the standard conditions (Table 1.1, entry 1), an unactivated secondary alkyl chloride (**27m**), a tertiary alkyl bromide (**32a**), and an aryl bromide (**2f**) result in low yields (<50%) of C–N coupling (Figure 1.5), while an aryl iodide (**2g**) effects *N*-arylation in moderate yield (~50%).

Figure 1.5 Examples of electrophiles resulting in low to moderate yields

27m ***32a*** ***2f*** ***2g***

With respect to the nucleophile, aryl amides with a *para*-chloro or -bromo substituent (**30h** and **30i**) undergo transhalogenation and hydrodehalogenation, thus low yields of the desired alkylation are observed (Figure 1.6). An aliphatic amide containing a pendant ketone (**24v**), a δ-lactam (**28c**), *N*-methyl benzamide (**33**), and a thioamide (**34**) are poor substrates (<50% yield), while trifluoroacetamide (**35**) can be coupled with a secondary alkyl iodide in moderate (~50%) yield.

Figure 1.6 Examples of nucleophiles resulting in low to moderate yields



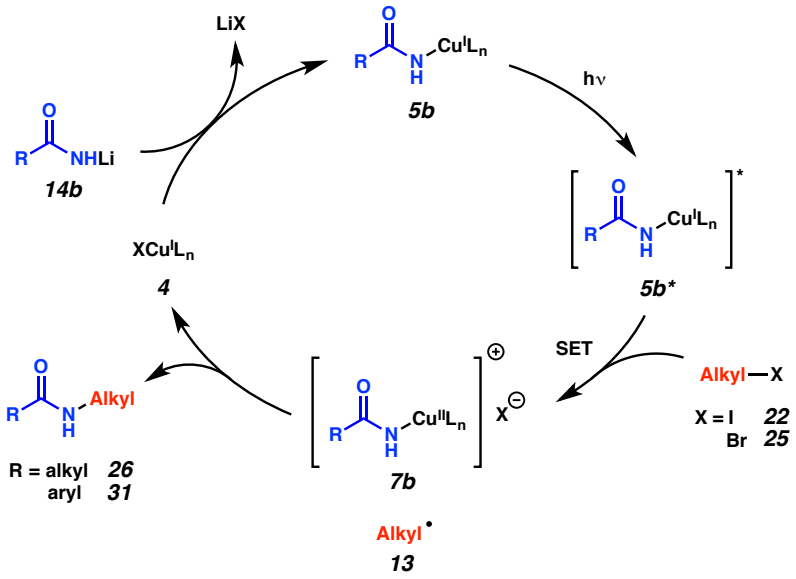
X = Cl ***30h***
Br ***30i***

24v ***28c*** ***33*** ***34*** ***35***

1.3 Mechanistic studies

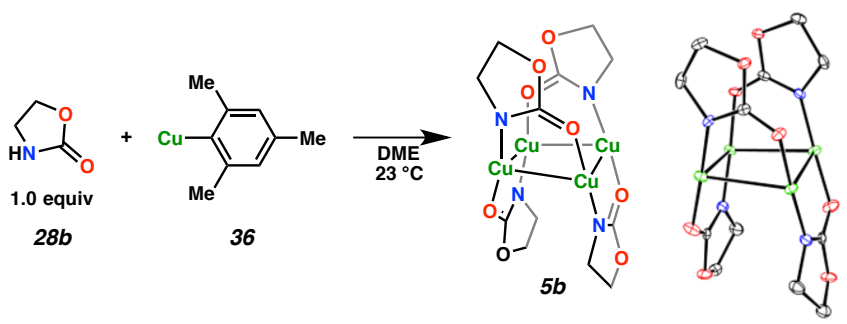
A possible mechanism for this photoinduced, copper-catalyzed *N*-alkylation reaction is shown in Figure 1.7. We hypothesize that irradiation of a copper(I)−amidate complex (**5b**) generates photoexcited species **5b***, which then reduces the alkyl halide by one electron, resulting in an alkyl radical intermediate (**13**).

Figure 1.7 One possible mechanism for photoinduced, Cu-catalyzed amide alkylation



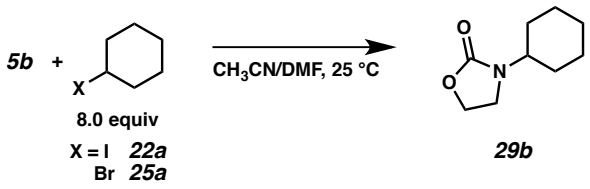
In order to test our hypothesis that a copper(I)−amidate complex (e.g., **5b**) is an intermediate in this photoinduced, copper-catalyzed C−N coupling, we hoped to obtain X-ray quality crystals of a copper complex containing a primary amide. Although these attempts were unsuccessful, we synthesized and crystallographically characterized copper−oxazolidinyl complex **5c** (Scheme 1.14).

Scheme 1.14 Synthesis of X-ray quality crystals of a copper–oxazolidinyl complex



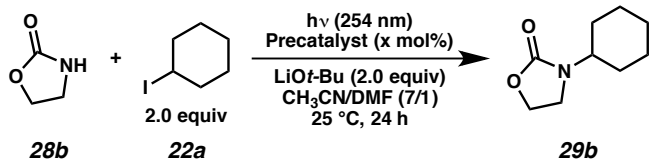
Complex **5b** reacts with an alkyl iodide (**22a**) and an alkyl bromide (**25a**) to furnish the corresponding *N*-alkylated oxazolidinone **29b** in good yield (Table 1.2). Either complex **5b** or CuI can be used as a precatalyst for C–N coupling between oxazolidinone **28b** and alkyl iodide **22a** (Table 1.3).

Table 1.2 Chemical competence of a copper–oxazolidinyl complex



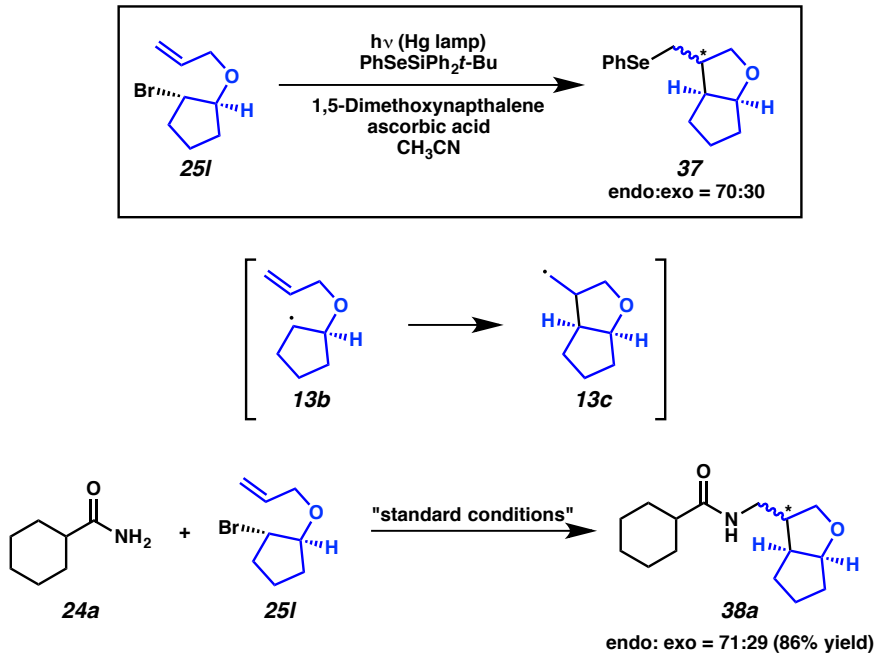
Conditions	Yield (%)
no hν, *22a* or *25a*	<2
hν (254 nm), *22a*	73
hν (254 nm), *25a*	80

Table 1.3 Use of a copper–oxazolidinyl complex or CuI as a precatalyst



Precatalyst	Yield (%)
CuI (10 mol%)	85
5b (2.5 mol%)	83

Scheme 1.15 Cyclization of an alkyl bromide under previously reported conditions and under N-alkylation conditions

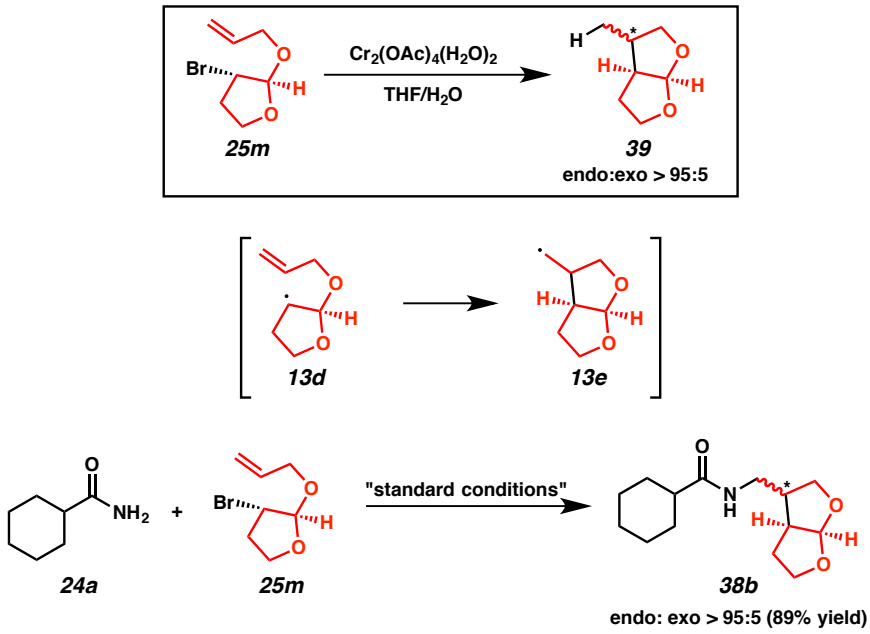


To explore the possibility of alkyl radical formation throughout the course of the reaction, alkyl bromides **25l** (Scheme 1.15) and **25m** (Scheme 1.16) were subjected to the standard conditions. **25l** has been reported in the literature to undergo photosensitized electron transfer (PET) cyclization and termination with *in situ*-generated PhSeSePh to generate **37** as a 70:30 mixture of diastereomers (Figure 1.24).[30] When **25l** is subjected

to our photoinduced, copper-catalyzed *N*-alkylation conditions, the C−N coupled/cyclized product **38a** is obtained in good yield, with similar diastereoselectivity. The analogous product distributions observed in these two reactions suggest the possibility of a common intermediate, such as alkyl radical **13b**.

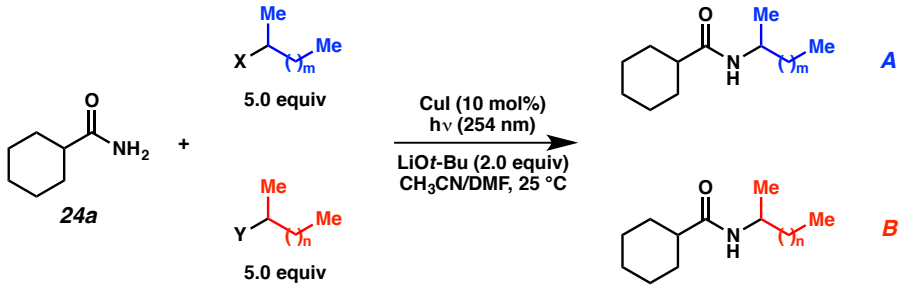
Similarly, the free-radical cyclization of alkyl bromide **25m** induced by chromium(II)-acetate has been reported to generate a >95:5 mixture of diastereomers (**39**),[31] and the same ratio of *N*-alkylated products (**38b**) is observed when **25m** is coupled under our standard conditions (Scheme 1.18). Overall, these data are consistent with the intermediacy of alkyl radicals in this photoinduced, copper-catalyzed C−N bond forming reaction.

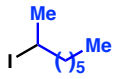
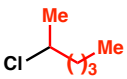
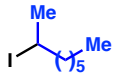
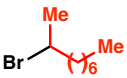
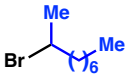
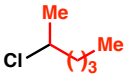
Scheme 1.16 Cyclization of an alkyl bromide under previously reported conditions and under N-alkylation conditions



An electrophile competition experiment demonstrates that a secondary alkyl iodide (**22b**) can be selectively coupled in the presence of a secondary alkyl chloride or bromide (**27o** and **25n**, respectively, Table 1.4). Secondary alkyl bromide **25n** also reacts preferentially in a competition experiment with alkyl chloride **27o**. This trend in reactivity is consistent with the alkyl halides' relative propensity to undergo one-electron reduction;[32] however these observations could also be accommodated by the alkyl halides' relative reactivity toward two-electron oxidative addition.

Table 1.4 Electrophile competition experiments



Substrates		A:B
		>50:1
22b	**27o**	
		10:1
22b	**25n**	
		>50:1
25n	**27o**	

1.4 Conclusion

We have developed, to the best of our knowledge, the first general method for transition metal-catalyzed *N*-alkylation of amides with unactivated secondary alkyl halides. Within our current program of study of photoinduced, copper-catalyzed cross-coupling reactions, this is the first reported class of nucleophiles that does not contain an aromatic ring on the heteroatom. This coupling reaction is effective for the synthesis of a variety of both aliphatic and aromatic *N*-alkyl amides under a single set of reaction conditions. The standard reaction conditions are operationally simple; no ligand is required, the reaction is run at room temperature, an inexpensive precatalyst (CuI) is used, and a commercial and readily available UVC lamp is an effective source of irradiation.

Under the standard reaction conditions, the stereochemical outcome of cyclization and cross-coupling of secondary alkyl bromides bearing pendant olefins are consistent with a possible SET/radical pathway. We have shown that a crystallographically characterized copper(I)−amidate undergoes C−N coupling when subjected to the reaction conditions and is a competent precatalyst for the cross-coupling of an amide with an alkyl iodide. These data are consistent with the photoexcitation of a copper−nucleophile complex and generation of an alkyl radical under the reaction conditions.

1.5 Experimental Procedures

1.5.1 General Information

The following reagents were purchased and used as received:

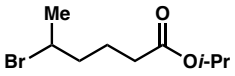
Aldrich: CuI (99.999%; 98% and 99.5% provide comparable results), 1-adamantanecarboxamide, cyclohexanecarboxamide, 2-oxazolidinone, pivalamide, 2-bromoadamantane, bromocyclohexane, bromocycloheptane, 1-bromo-2,2-dimethylpropane, *t*- butyl 4-bromopiperidine-1-carboxylate, 4-bromotetrahydro-2*H*-pyran, and iodocyclohexane; Alfa: LiO*t*-Bu, benzamide, 4-cyanobenzamide, 4-fluorobenzamide, 4-methoxybenzamide, 1-naphthamide, 2-naphthamide, thiophene-2-carboxamide, and 4-bromoheptane; Eastman: furan-2-carboxamide; Oakwood: 2-phenylacetamide; Matrix: 4-(trifluoromethyl)benzamide; Maybridge: *t*-butyl 4-carbamoylpiperidine-1-carboxylate; TCI: nicotinamide, *n*-octanamide.

DMF and CH_3CN were dried in a solvent-purification system with the aid of activated alumina. All reactions were carried out in oven-dried quartz tubes or quartz flasks under an inert atmosphere using a Luzchem LZC–4V photoreactor at 254 nm. ^{1}H and ^{13}C NMR data were collected on a VARIAN 500 MHz spectrometer at ambient temperature. GC analyses were carried out on an Agilent 6890 series system with a DB-1 column (length 30 m, i.d. 0.25 mm) and an Agilent 6850 series system with a G-TA column (length 30 m, i.d. 0.25 mm). GC-MS analyses were performed on an Agilent 6980 series system equipped with an Agilent 5973 Network Mass Selective Detector.

1.5.2 Preparation of Materials

These procedures have not been optimized.

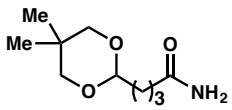
General procedure for the preparation of alkyl bromides. A 300-mL round-bottom flask was charged with PPh_3 (17.0 g, 65.0 mmol, 1.30 equiv), imidazole (4.42 g, 65.0 mmol, 1.30 equiv), and dichloromethane (150 mL). The resulting solution was stirred at 0 °C in an ice bath under a nitrogen atmosphere. Bromine (3.40 mL, 65.0 mmol, 1.30 equiv) was added dropwise over 2 min, yielding a colorless or light-yellow solution. After 5 min, the alcohol (50.0 mmol, 1.00 equiv) was added dropwise over 3 min. The ice bath was then removed, and the reaction mixture was stirred at 23 °C for 20 h. Next, the reaction mixture was concentrated under reduced pressure on a rotary evaporator to a volume of 40 mL, and then it was diluted with a mixture of pentane and ether (4/1, 100 mL). The resulting suspension was filtered and concentrated, and then the residue was purified by column chromatography.



Isopropyl 5-bromohexanoate (25j). The title compound was prepared according to the general procedure, using isopropyl 5-hydroxyhexanoate.[33] The product was obtained as a colorless oil (8.53 g, 72% yield).

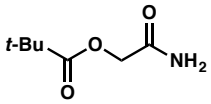
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (hept, J = 6.3 Hz, 1H), 4.17 – 4.07 (m, 1H), 2.34 – 2.24 (m, 2H), 1.91 – 1.67 (m, 7H), 1.23 (d, J = 6.3 Hz, 6H); ^{13}C NMR (126 MHz, CDCl3) δ 172.7, 67.6, 50.8, 40.3, 33.8, 26.4, 23.2, 21.8; FT-IR (neat) 2980, 2935, 1728, 1454, 1373, 1253, 1182, 1107 cm^{-1}; MS (EI) *m/z* ([M – C_3H_7O]$^+$) calcd for $C_6H_{10}BrO$: 177.0, found: 177.1.

Preparation of amides.



4-(5,5-Dimethyl-1,3-dioxan-2-yl)butanamide (24q). The title compound was prepared according to a reported procedure [34] from methyl 4-(5,5-dimethyl-1,3-dioxan-2-yl)butanoate.[35] The product was obtained as a white solid (65% yield).

^{1}H NMR δ (500 MHz, $CDCl_3$) 5.81 (brs, 1H), 5.67 (brs, 1H), 4.43 (t, *J* = 4.8 Hz, 1H), 3.58 (dt, *J* = 11.2, 1.4 Hz, 2H), 3.46 – 3.36 (m, 2H), 2.26 (t, *J* = 7.4 Hz, 2H), 1.84 – 1.62 (m, 4H), 1.16 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 101.8, 77.2, 35.6, 33.8, 30.1, 23.0, 21.8, 20.0; FT-IR (neat) 3387, 3304, 3195, 2966, 2955, 2903, 2872, 2843, 1657, 1631, 1466, 1410, 1346, 1318, 1240, 1216, 1176, 1127, 1097, 1075, 1020, 965, 925, 915, 818, 791 cm^{-1}; MS (EI) m/z (M^+) calcd for $C_{10}H_{19}NO_3$: 201.1, found: 201.2.

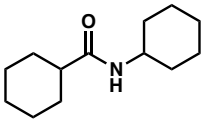


6-Amino-6-oxohexyl pivalate (24s). The title compound was prepared according to a reported procedure[36] from 6-hydroxyhexanamide.[37] The product was obtained as a white solid (61% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (brs, 1H), 5.59 (brs, 1H), 4.04 (t, *J* = 6.6 Hz, 2H), 2.22 (t, *J* = 7.5 Hz, 2H), 1.73 – 1.57 (m, 4H), 1.44 – 1.34 (m, 2H), 1.17 (s, 9H); ^{13}C NMR (126 MHz, CDCl3) δ 178.6, 175.4, 64.1, 38.7, 35.7, 28.4, 27.2, 25.5, 25.0; FT-IR (neat) 3346, 3172, 2970, 2947, 2869, 2812, 1718, 1667, 1629, 1476, 1413, 1395, 1352, 1284, 1176, 1156, 1062, 1032, 953 cm^{-1}; MS (EI) m/z ($[M - C_4H_9]^+$) calcd for $C_7H_{12}NO_3$: 158.1, found: 158.0.

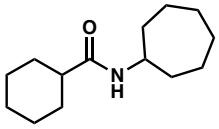
1.5.3 Photoinduced, Copper-Catalyzed Alkylations of Amides

General procedure for the alkylation of amides. CuI (19.5 mg, 0.10 mmol), the amide (1.00 mmol), and LiO*t*-Bu (160 mg, 2.00 mmol) were added to an oven-dried 10-mL quartz test tube that contained a stir bar (3 mm x 13 mm). The test tube was fitted with a rubber septum, the joint was wrapped with electrical tape, and the test tube was evacuated and backfilled with nitrogen (3 cycles). A solution of the alkyl bromide (2.00 mmol) in CH_3CN (5.4 mL) and DMF (0.80 mL) was added in turn by syringe. The test tube was detached from the nitrogen line, and the puncture holes of the septum were covered with vacuum grease. The resulting mixture was stirred vigorously for 5 min, and then the quartz test tube was placed in a Luzchem photoreactor. The stirring mixture was irradiated with a UVC lamp centered at 254 nm for 24 h. During the first 12 h, the reaction tube was occasionally shaken vertically (every 2-3 h) to ensure good mixing of the entire reaction mixture. After 24 h, the reaction mixture was purified by column chromatography.



***N*-Cyclohexylcyclohexanecarboxamide (26a, Figure 1.13) [7474-36-4].** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 180 mg (86%). Second run: 189 mg (90%).

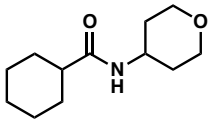
^{1}H NMR (500 MHz, CDCl3) δ 5.31 (brs, 1H), 3.80 – 3.71 (m, 1H), 2.02 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.98 – 1.56 (m, 9H), 1.46 – 1.04 (m, 11H).



***N*-Cycloheptylcyclohexanecarboxamide (26b, Figure 1.13) [550306-49-5].** The title compound was prepared according to the general procedure from

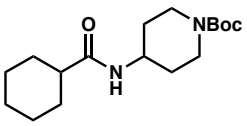
cyclohexanecarboxamide (1.0 mmol) and bromocycloheptane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 131 mg (59%). Second run: 128 mg (57%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 (d, *J* = 8.3 Hz, 1H), 3.99 – 3.87 (m, 1H), 2.02 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.94 – 1.14 (m, 22H).



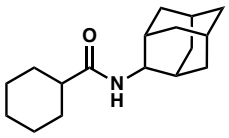
***N*-(Tetrahydro-*2H*-pyran-4-yl)cyclohexanecarboxamide (26c, Figure 1.13).** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and 4-bromotetrahydro-*2H*-pyran (2.0 mmol). The product was purified by column chromatography (hexanes → 50% EtOAc/hexanes). White solid. First run: 191 mg (90%). Second run: 194 mg (92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (d, *J* = 8.0 Hz, 1H), 4.04 – 3.90 (m, 3H), 3.47 (td, *J* = 11.7, 2.2 Hz, 2H), 2.03 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.92 – 1.62 (m, 7H), 1.49 – 1.15 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 66.8, 45.6, 45.3, 33.3, 29.7, 25.7; FT-IR (neat) 3250, 3072, 2969, 2928, 2851, 2832, 1627, 1549, 1446, 1389, 1364, 1335, 1236, 1216, 1142, 1133, 1012, 978, 953, 896, 847, 826, 691 cm^{-1}; MS (EI) m/z (M^+) calcd for $C_{12}H_{21}NO_2$: 211.2, found: 211.2.



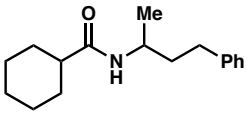
***t*-Butyl 4-(cyclohexanecarboxamido)piperidine-1-carboxylate (26d, Figure 1.13) [1233955- 27-5].** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and *t*-butyl 4-bromopiperidine-1-carboxylate (2.0 mmol). The product was purified by column chromatography (5% → 50% EtOAc/hexanes). Off-white solid. First run: 275 mg (89%). Second run: 284 mg (92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 (d, *J* = 8.0 Hz, 1H), 4.03 (brs, 2H), 3.97 – 3.87 (m, 1H), 2.91 – 2.79 (m, 2H), 2.03 (tt, *J* = 11.8, 3.4 Hz, 1H), 1.93 – 1.63 (m, 7H), 1.46 (s, 9H), 1.44 – 1.38 (m, 2H), 1.32 – 1.21 (m, 5H).



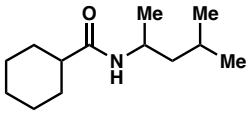
***N*-(Adamantan-2-yl)cyclohexanecarboxamide (26e, Figure 1.13).** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and 2- bromoadamantane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 196 mg (75%). Second run: 189 mg (72%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (d, *J* = 8.0 Hz, 1H), 4.03 (dd, *J* = 7.6, 3.6 Hz, 1H), 2.08 (tt, *J* = 11.7, 3.5 Hz, 1H), 1.92 – 1.61 (m, 19H), 1.49 – 1.37 (m, 2H), 1.36 – 1.16 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 52.7, 45.8, 37.5, 37.1, 32.0, 31.9, 29.9, 27.2, 27.1, 25.8; FT-IR (neat) 3324, 2906, 2850, 1733, 1640, 1538, 1471, 1444, 1387, 1310, 1252, 1211, 1179, 1141, 1110, 952, 894, 819, 668, 635 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_{17}H_{27}NO$: 261.2, found: 261.3.



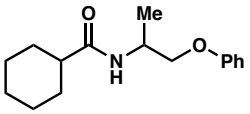
***N*-(4-Phenylbutan-2-yl)cyclohexanecarboxamide (26f, Figure 1.13) [545360-34-7].** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and (3-bromobutyl)benzene (2.0 mmol). The product was purified by column chromatograpy (hexanes → 30% EtOAc/hexanes). Beige solid. First run: 192 mg (74%). Second run: 197 mg (76%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.21 – 7.15 (m, 3H), 5.19 (d, *J* = 8.5, 1H), 4.11 – 4.02 (m, 1H), 2.64 (dd, *J* = 9.4, 6.7 Hz, 2H), 2.00 (tt, *J* = 11.8, 3.4 Hz, 1H), 1.87 – 1.58 (m, 7H), 1.47 – 1.35 (m, 2H), 1.31 – 1.18 (m, 3H), 1.16 (d, *J* = 6.6 Hz, 3H).



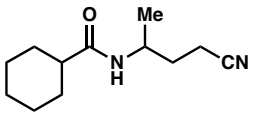
***N*-(4-Methylpentan-2-yl)cyclohexanecarboxamide (26g, Figure 1.13).** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and 2-bromo-4-methylpentane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 171 mg (81%). Second run: 176 mg (83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15 (d, *J* = 8.6 Hz, 1H), 4.10 – 4.00 (m, 1H), 2.01 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.88 – 1.52 (m, 6H), 1.48 – 1.13 (m, 7H), 1.09 (d, *J* = 6.5 Hz, 3H), 0.90 (dd, *J* = 6.6, 2.4 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 46.5, 45.8, 43.0, 29.9, 29.6, 25.79, 25.76, 25.74, 25.1, 22.8, 22.5, 21.6; FT-IR (neat) 3289, 3071, 2964, 2928, 2852, 1632, 1541, 1442, 1383, 1259, 1213, 1165, 1127, 953, 896, 697 cm^{-1}; MS (EI) *m/z* (M+) calcd for $C_{13}H_{25}NO$: 211.2, found: 211.3.



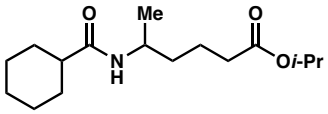
***N*-(1-Phenoxypropan-2-yl)cyclohexanecarboxamide (26h, Figure 1.13).** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and (2-bromopropoxy)benzene (2.0 mmol). The product was purified by column chromatography (20% EtOAc/hexanes → 50% EtOAc/hexanes). Off-white solid. First run: 163 mg (62%). Second run: 166 mg (64%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 6.96 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.93 – 6.90 (m, 2H), 5.70 (d, *J* = 8.3 Hz, 1H), 4.42 – 4.34 (m, 1H), 3.99 – 3.90 (m, 2H), 2.06 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.89 – 1.74 (m, 4H), 1.69 – 1.63 (m, 1H), 1.48 – 1.38 (m, 2H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.28 – 1.20 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 158.7, 129.5, 121.0, 114.5, 70.5, 45.6, 44.1, 29.6, 27.2, 25.7, 17.7; FT-IR (neat) 3307, 2930, 2919, 2852, 1636, 1533 cm^{-1}; LRMS (LCMS ESI) *m/z* (M^+ + H) calcd for $C_{16}H_{24}NO_2$: 262.2, found: 262.2.



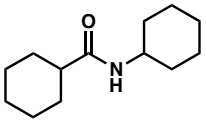
***N*-(4-Cyanobutan-2-yl)cyclohexanecarboxamide (26i, Figure 1.13).** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol), 4- bromopentanenitrile (2.0 mmol). The product was purified by column chromatography (20% EtOAc/hexanes → 50% EtOAc/hexanes). Beige solid. First run: 115 mg (55%). Second run: 116 mg (56%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (d, *J* = 8.5 Hz, 1H), 4.13 – 4.08 (m, 1H), 2.43 – 2.31 (m, 2H), 2.06 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.93 – 1.55 (m, 7H), 1.49 – 1.37 (m, 2H), 1.31 – 1.21 (m, 3H), 1.19 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 119.8, 45.5, 44.2, 32.7, 29.7, 29.6, 25.7, 20.8, 14.2; FT-IR (neat) 3295, 2974, 2931, 2852, 1637, 1541, 1443, 1428, 1390, 1376, 1261, 1217 cm^{-1}. LRMS (LCMS ESI) *m/z* (M^+ + H) calcd for $C_{12}H_{21}N_2O$: 209.2, found: 209.2.



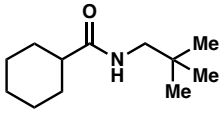
Isopropyl 5-(cyclohexanecarboxamido)hexanoate (26j, Figure 1.13). The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and isopropyl 5-bromohexanoate (2.0 mmol). The product was purified by column chromatography (hexanes → 50% EtOAc/hexanes). Light-tan solid. First run: 110 mg (39%). Second run: 104 mg (37%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 (d, *J* = 8.5 Hz, 1H), 4.99 (hept, *J* = 6.3 Hz, 1H), 4.04 – 3.92 (m, 1H), 2.36 – 2.19 (m, 2H), 2.02 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.92 – 1.69 (m, 4H), 1.70 – 1.53 (m, 3H), 1.51 – 1.35 (m, 4H), 1.34 – 1.13 (m, 3H), 1.22 (d, *J* = 6.1 Hz, 6H), 1.11 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 173.1, 67.5, 45.7, 44.5, 36.2, 34.2, 29.8, 29.6, 25.76, 25.74, 25.73, 21.8, 21.4, 21.1; FT-IR (neat) 3277, 3087, 2960, 2928, 2853, 1725, 1634, 1553, 1450, 1417, 1379, 1340, 1259, 1249, 1218, 1191, 1114, 957, 934, 895, 710 cm^{-1}; MS (EI) *m/z* (M+) calcd for $C_{16}H_{29}NO_3$: 283.2, found: 283.3.



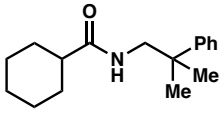
***N*-Cyclohexylcyclohexanecarboxamide (26a, Figure 1.14) [7474-36-4].** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 184 mg (88%). Second run: 189 mg (87%).

The ^{1}H NMR spectrum was identical to that obtained for 26a, Figure 1.13.



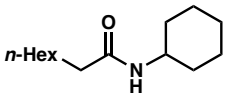
***N*-Neopentylcyclohexanecarboxamide (26k, Figure 1.14).** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and 1-bromo-2,2-dimethylpropane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). Off-white solid. First run: 154 mg (78%). Second run: 160 mg (81%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (brs, 1H), 3.05 (d, J = 6.3 Hz, 2H), 2.09 (tt, J = 11.8, 3.5 Hz, 1H), 1.91 – 1.83 (m, 2H), 1.83 – 1.76 (m, 2H), 1.71 – 1.63 (m, 1H), 1.50 – 1.40 (m, 2H), 1.33 – 1.17 (m, 3H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, CDCl3) δ 176.1, 110.0, 50.1, 45.9, 31.9, 29.9, 27.2, 25.8; FT-IR (neat) 3280, 3090, 2852, 1644, 1558, 1208 cm^{-1}; LRMS (LCMS EI) *m/z* (M^+ + H) calcd for $C_{12}H_{24}NO$: 198.2, found: 198.2.



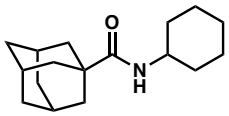
***N*-(2-Methyl-2-phenylpropyl)cyclohexanecarboxamide (26l, Figure 1.14) [1085543-93-6].** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and (1-chloro-2-methylpropan-2-yl)benzene (2.0 mmol) (reaction time: 48 h). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 172 mg (66%). Second run: 177 mg (68%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 4H), 7.30 – 7.19 (m, 1H), 5.09 (s, 1H), 3.46 (d, *J* = 6.0 Hz, 2H), 1.94 (tt, *J* = 11.8, 3.3 Hz, 1H), 1.85 – 1.58 (m, 5H), 1.33 (s, 6H), 1.39 – 1.13 (m, 5H).



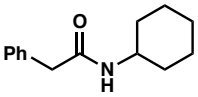
***N*-Cyclohexyloctanamide (26m, Figure 1.15) [42577-04-8].** The title compound was prepared according to the general procedure from *n*-octanamide (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 30% EtOAc/hexanes). White solid. First run: 194 mg (86%). Second run: 191 mg (85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (brs, 1H), 3.83 – 3.70 (m, 1H), 2.18 – 2.11 (m, 2H), 1.95 – 1.86 (m, 2H), 1.75 – 1.57 (m, 6H), 1.43 – 1.05 (m, 12H), 0.91 – 0.83 (m, 3H).



***N*-Cyclohexyl-1-adamantanecarboxamide (26n, Figure 1.15) [81311-58-2].** The title compound was prepared according to the general procedure from 1-adamantanecarboxamide (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes). Beige solid. First run: 220 mg (84%). Second run: 237 mg (91%).

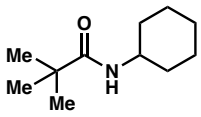
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (brs, 1H), 3.81 – 3.71 (m, 1H), 2.04 (s, 3H), 1.91 – 1.85 (m, 2H), 1.83 (d, *J* = 2.8 Hz, 6H), 1.77 – 1.65 (m, 9H), 1.43 – 1.32 (m, 2H), 1.22 – 1.05 (m, 3H).



***N*-Cyclohexyl-2-phenylacetamide (24o, Figure 1.15) [10264-08-1].** The title compound was prepared according to the general procedure from 2-phenylacetamide (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography

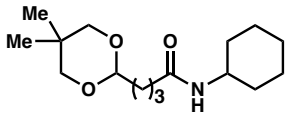
(hexanes → 20% EtOAc/hexanes). White solid. First run: 192 mg (88%). Second run: 201 mg (93%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.20 (m, 5H), 5.23 (brs, 1H), 3.80 – 3.71 (m, 1H), 3.55 (s, 2H), 1.90 – 1.49 (m, 5H), 1.39 – 1.26 (m, 2H), 1.18 – 0.95 (m, 3H).



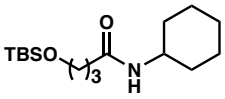
***N*-Cyclohexylpivalamide (26p, Figure 1.15) [4916-82-9].** The title compound was prepared according to the general procedure from pivalamide (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). Beige solid. First run: 165 mg (90%). Second run: 161 mg (88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (brs, 1H), 3.79 – 3.69 (m, 1H), 1.93 – 1.85 (m, 2H), 1.73 – 1.65 (m, 2H), 1.64 – 1.60 (m, 1H), 1.44 – 1.31 (m, 2H), 1.18 (s, 9H), 1.16 – 1.04 (m, 3H).



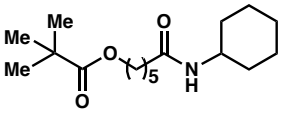
***N*-Cyclohexyl-4-(5,5-dimethyl-1,3-dioxan-2-yl)butanamide (26q, Figure 1.15).** The title compound was prepared according to the general procedure from 4-(5,5-dimethyl-1,3-dioxan-2-yl)butanamide (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 60% EtOAc/hexanes). Light-tan solid. First run: 251 mg (89%). Second run: 255 mg (90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 (d, J = 9.1 Hz, 1H), 4.42 (t, J = 4.8 Hz, 1H), 3.79 – 3.70 (m, 1H), 3.60 – 3.55 (m, 2H), 3.46 – 3.37 (m, 2H), 2.17 (t, J = 7.4 Hz, 2H), 1.93 – 1.54 (m, 9H), 1.40 – 1.28 (m, 2H), 1.22 – 1.03 (m, 3H), 1.17 (s, 3H), 0.71 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 102.0, 77.2, 47.9, 36.6, 33.8, 33.2, 30.1, 25.6, 24.8, 23.0, 21.8, 20.4; FT-IR (neat) 3254, 3074, 2932, 2855, 1630, 1550, 1473, 1448, 1396, 1363, 1176, 1133, 1112, 1090, 1026, 1012, 923, 870, 679 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_{16}H_{29}NO_3$: 283.2, found: 283.3.



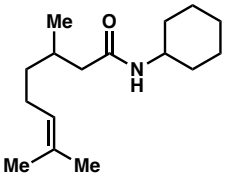
4-((*t*-Butyldimethylsilyl)oxy)-*N*-cyclohexylbutanamide (26r, Figure 1.15). The title compound was prepared according to the general procedure from 4-((*t*-butyldimethylsilyl)oxy)butanamide (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). Light-tan solid. First run: 245 mg (82%). Second run: 255 mg (85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (d, *J* = 8.1 Hz, 1H), 3.80 – 3.72 (m, 1H), 3.64 (t, *J* = 6.0 Hz, 2H), 2.23 (t, *J* = 7.4 Hz, 2H), 1.95 – 1.78 (m, 4H), 1.74 – 1.65 (m, 2H), 1.64 – 1.57 (m, 1H), 1.42 – 1.31 (m, 2H), 1.21 – 1.04 (m, 3H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 62.1, 48.0, 33.27, 33.25, 28.6, 26.0, 25.6, 24.9, 18.3, 5.3; FT-IR (neat) 3298, 3081, 2927, 2898, 2854, 1635, 1554, 1472, 1461, 1440, 1385, 1254, 1091, 1066, 991, 963, 879, 772, 723, 613 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_{16}H_{33}NO_2Si$: 299.2, found: 299.3.



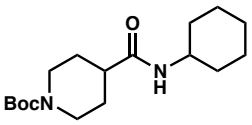
6-(Cyclohexylamino)-6-oxohexyl pivalate (26s, Figure 1.15). The title compound was prepared according to the general procedure from 6-amino-6-oxohexyl pivalate (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 50% EtOAc/hexanes). White solid. First run: 262 mg (88%). Second run: 263 mg (89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (brs, 1H), 4.03 (td, *J* = 6.6, 0.8 Hz, 2H), 3.79 – 3.70 (m, 1H), 2.19 – 2.10 (m, 2H), 1.94 – 1.78 (m, 4H), 1.74 – 1.56 (m, 5H), 1.44 – 1.26 (m, 4H), 1.22 – 1.01 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6, 171.7, 64.2, 48.1, 38.7, 36.9, 33.3, 28.4, 27.2, 25.6, 25.52, 25.47, 24.9; FT-IR (neat) 3291, 3075, 2930, 2898, 2854, 1728, 1638, 1541, 1480, 1451, 1398, 1363, 1284, 1151, 1039, 891 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_{17}H_{31}NO_3$: 297.2, found: 297.3.

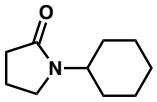


***N*-Cyclohexyl-3,7-dimethyloct-6-enamide (26t, Figure 1.15).** The title compound was prepared according to the general procedure from 3,7-dimethyloct-6-enamide (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). Light-tan solid. First run: 216 mg (86%). Second run: 222 mg (88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28 (d, J = 8.4 Hz, 1H), 5.11 – 5.06 (m, 1H), 3.83 – 3.73 (m, 1H), 2.16 (dd, J = 13.3, 5.7 Hz, 1H), 2.06 – 1.82 (m, 4H), 1.74 – 1.56 (m, 11H), 1.44 – 1.27 (m, 3H), 1.30 – 1.04 (m, 4H), 0.93 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 131.5, 124.4, 48.0, 44.8, 36.9, 33.3, 30.5, 25.7, 25.5, 25.4, 24.9, 19.5, 17.7; FT-IR (neat) 3292, 3079, 2929, 2853, 1634, 1546, 1446, 1376, 1359, 1308, 1250, 1153, 1101, 989, 891, 723, 626 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_{16}H_{29}NO$: 251.2, found: 251.3.

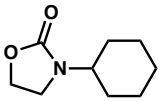


***t*-Butyl 4-(cyclohexylcarbamoyl)piperidine-1-carboxylate (26u, Figure 1.15).** The title compound was prepared according to the general procedure from *t*-butyl 4-carbamoylpiperidine-1-carboxylate (1.0 mmol) and 2-bromobutane (2.0 mmol). The product was purified by column chromatography (hexanes → 70% EtOAc/hexanes). Light-tan solid. First run: 243 mg (85%). Second run: 245 mg (85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (brs, 1H), 4.12 (brs, 2H), 3.79 – 3.70 (m, 1H), 2.72 (br s, 2H), 2.16 (tt, J = 11.6, 3.7 Hz, 1H), 1.92 – 1.84 (m, 2H), 1.81 – 1.74 (m, 3H), 1.74 – 1.53 (m, 4H), 1.48 – 1.42 (m, 9H), 1.42 – 1.29 (m, 2H), 1.21 – 1.03 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 154.7, 79.6, 48.0, 43.5, 33.2, 28.7, 28.4, 25.5, 24.8; FT-IR (neat) 3281, 3072, 2972, 2928, 2877, 2858, 1683, 1634, 1544, 1432, 1365, 1282, 1216, 1177, 1126, 1078, 956, 942, 875, 761, 692 cm^{-1}; MS (ESI) *m/z* ($[M - C_4H_8 + H]^+$) calcd for $C_{11}H_{21}N_2O_3$: 229.2, found: 229.1.



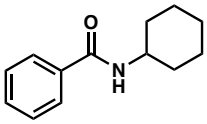
1-Cyclohexylpyrrolidin-2-one (29a, Figure 1.16) [6837-24-7]. The title compound was prepared according to the general procedure (except that no DMF was used; only CH_3CN (6.2 mL)) from 2-pyrrolidone (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 70% EtOAc/hexanes). Light-brown oil. First run: 149 mg (89%). Second run: 147 mg (88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99 – 3.86 (m, 1H), 3.36 – 3.28 (m, 2H), 2.41 – 2.34 (m, 2H), 2.02 – 1.92 (m, 2H), 1.84 – 1.61 (m, 5H), 1.45 – 1.28 (m, 4H), 1.16 – 1.00 (m, 1H).



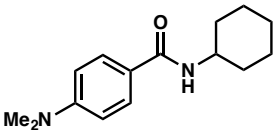
3-Cyclohexyloxazolidin-2-one (29b, Figure 1.16) [55390-61-9]. The title compound was prepared according to the general procedure (except that no DMF was used; only CH_3CN (6.2 mL)) from oxazolidin-2-one (1.0 mmol) and bromocyclohexane. The product was purified by column chromatography (hexanes → 70% EtOAc/hexanes). Light-brown oil. First run: 153 mg (91%). Second run: 150 mg (89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.36 – 4.25 (m, 2H), 3.72 – 3.63 (m, 1H), 3.57 – 3.46 (m, 2H), 1.87 – 1.74 (m, 4H), 1.72 – 1.62 (m, 1H), 1.45 – 1.28 (m, 4H), 1.17 – 1.01 (m, 1H).



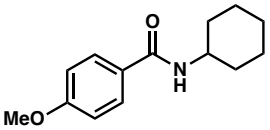
***N*-Cyclohexylbenzamide (31a, Figure 1.17) [1759-68-8].** The title compound was prepared according to the general procedure from benzamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (10% EtOAc/hexanes → 30% EtOAc/hexanes). Beige solid. First run: 178 mg (88%). Second run: 177 mg (87%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.73 (m, 2H), 7.51 – 7.46 (m, 1H), 7.45 – 7.40 (m, 2H), 5.95 (br s, 1H), 4.01 – 3.94 (m, 1H), 2.08 – 1.99 (m, 2H), 1.81 – 1.71 (m, 2H), 1.69 – 1.62 (m, 1H), 1.49 – 1.38 (m, 2H), 1.29 – 1.19 (m, 3H).



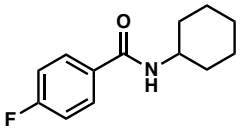
***N*-Cyclohexyl-4-(dimethylamino)benzamide (31b, Figure 1.17) [141557-50-8].** The title compound was prepared according to the general procedure from 4-(dimethylamino)benzamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 209 mg (85%). Second run: 213 mg (86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.60 (m, 2H), 6.69 – 6.61 (m, 2H), 5.83 (d, *J* = 8.1 Hz, 1H), 4.01 – 3.91 (m, 1H), 3.01 (s, 6H), 2.01 (dq, *J* = 12.1, 3.8 Hz, 2H), 1.79 – 1.59 (m, 3H), 1.48 – 1.36 (m, 2H), 1.27 – 1.14 (m, 3H).



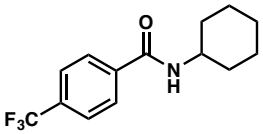
***N*-Cyclohexyl-4-methoxybenzamide (31c, Figure 1.17) [33739-91-2].** The title compound was prepared according to the general procedure from 4-methoxybenzamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 40% EtOAc/hexanes). White solid. First run: 184 mg (79%). Second run: 175 mg (75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.67 (m, 2H), 6.96 – 6.86 (m, 2H), 5.91 (d, *J* = 8.1 Hz, 1H), 4.01 – 3.91 (m, 1H), 3.84 (s, 3H), 2.07 – 1.98 (m, 2H), 1.80 – 1.60 (m, 3H), 1.48 – 1.36 (m, 2H), 1.29 – 1.14 (m, 3H).



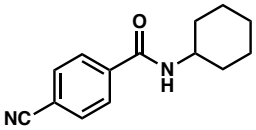
***N*-Cyclohexyl-4-fluorobenzamide (31d, Table 1.17) [2342-50-9].** The title compound was prepared according to the general procedure from 4-fluorobenzamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 200 mg (91%). Second run: 200 mg (91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.71 (m, 2H), 7.15 – 7.05 (m, 2H), 5.93 (d, *J* = 7.9 Hz, 1H), 4.01 – 3.91 (m, 1H), 2.07 – 1.98 (m, 2H), 1.81 – 1.61 (m, 3H), 1.48 – 1.36 (m, 2H), 1.29 – 1.14 (m, 3H).



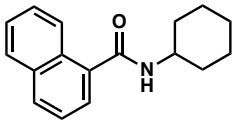
***N*-Cyclohexyl-4-(trifluoromethyl)benzamide (31e, Figure 1.17) [339094-67-6].** The title compound was prepared according to the general procedure from 4-(trifluoromethyl)benzamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 197 mg (73%). Second run: 211 mg (78%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.83 (m, 2H), 7.72 – 7.65 (m, 2H), 6.00 (d, *J* = 8.0 Hz, 1H), 4.03 – 3.93 (m, 1H), 2.09 – 2.00 (m, 2H), 1.82 – 1.72 (m, 2H), 1.72 – 1.62 (m, 1H), 1.50 – 1.37 (m, 2H), 1.32 – 1.11 (m, 3H).



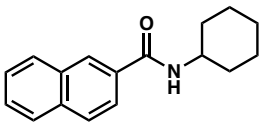
4-Cyano-*N*-cyclohexylbenzamide (31f, Figure 1.17) [167762-78-9]. The title compound was prepared according to the general procedure from 4-cyanobenzamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 40% EtOAc/hexanes). White solid. First run: 190 mg (83%). Second run: 179 mg (79%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.81 (m, 2H), 7.76 – 7.69 (m, 2H), 6.01 (d, *J* = 8.1 Hz, 1H), 4.02 – 3.92 (m, 1H), 2.08 – 1.99 (m, 2H), 1.82 – 1.62 (m, 3H), 1.49 – 1.36 (m, 2H), 1.30 – 1.14 (m, 3H).



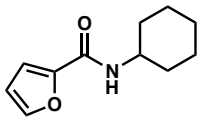
***N*-Cyclohexyl-1-naphthamide (31g, Table 1.17) [32255-83-7].** The title compound was prepared according to the general procedure from 1-naphthamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 239 mg (94%). Second run: 237 mg (94%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 – 8.24 (m, 1H), 7.93 – 7.82 (m, 2H), 7.62 – 7.40 (m, 4H), 5.87 (d, *J* = 8.3 Hz, 1H), 4.15 – 4.06 (m, 1H), 2.17 – 2.08 (m, 2H), 1.83 – 1.63 (m, 3H), 1.54 – 1.41 (m, 2H), 1.33 – 1.15 (m, 3H).



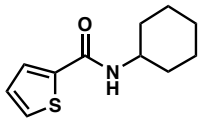
***N*-Cyclohexyl-2-naphthamide (31h, Figure 1.17) [82740-60-1].** The title compound was prepared according to the general procedure from 2-naphthamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 203 mg (80%). Second run: 197 mg (78%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 – 8.23 (m, 1H), 7.96 – 7.79 (m, 4H), 7.61 – 7.50 (m, 2H), 6.13 (d, *J* = 8.1 Hz, 1H), 4.10 – 4.00 (m, 1H), 2.13 – 2.04 (m, 2H), 1.84 – 1.64 (m, 3H), 1.52 – 1.40 (m, 2H), 1.35 – 1.17 (m, 3H).



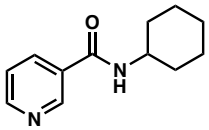
***N*-Cyclohexylfuran-2-carboxamide (31i, Figure 1.17) [10354-47-9].** The title compound was prepared according to the general procedure from furan-2-carboxamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 30% EtOAc/hexanes). Light-tan solid. First run: 165 mg (85%). Second run: 169 mg (88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.09 (dd, *J* = 3.5, 0.9 Hz, 1H), 6.49 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.22 (br s, 1H), 3.99 – 3.89 (m, 1H), 2.07 – 1.95 (m, 2H), 1.80 – 1.60 (m, 3H), 1.48 – 1.35 (m, 2H), 1.30 – 1.14 (m, 3H).



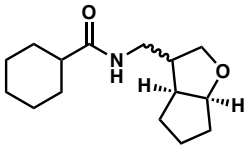
***N*-Cyclohexylthiophene-2-carboxamide (31j, Figure 1.17) [10354-42-4].** The title compound was prepared according to the general procedure from thiophene-2-carboxamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 30% EtOAc/hexanes). Light-tan solid. First run: 145 mg (69%). Second run: 154 mg (74%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.40 (m, 2H), 7.06 (dd, *J* = 5.0, 3.7 Hz, 1H), 5.83 (br s, 1H), 4.01 – 3.88 (m, 1H), 2.07 – 1.98 (m, 2H), 1.81 – 1.59 (m, 3H), 1.48 – 1.35 (m, 2H), 1.29 – 1.13 (m, 3H).



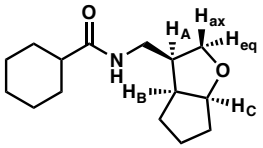
***N*-Cyclohexylnicotinamide (31k, Figure 1.17) [10354-56-0].** The title compound was prepared according to the general procedure from nicotinamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 100% EtOAc). White solid. First run: 167 mg (82%). Second run: 171 mg (84%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.71 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.12 – 8.08 (m, 1H), 7.37 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 6.06 (d, *J* = 7.7 Hz, 1H), 4.04 –3.94 (m, 1H), 2.09 – 2.00 (m, 2H), 1.82 – 1.62 (m, 3H), 1.50 – 1.37 (m, 2H), 1.32 – 1.15 (m, 3H).

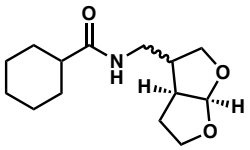


***N*-((Hexahydro-2*H*-cyclopenta[b]furan-3-yl)methyl)cyclohexanecarboxamide (38a, Figure 1.24).** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and *trans*-1-(allyloxy)-2-bromocyclopentane (2.0 mmol). The ratio of diastereomers was determined by GC analysis of the unpurified reaction mixture. The product was isolated as a mixture of diastereomers by column chromatography (30% EtOAc/hexanes → 75% EtOAc/hexanes). Yellow solid. First run: 214 mg (85%, 71:29). Second run: 219 mg (87%, 72:28).

Major diastereomer. The major diastereomer could be purified by preparative HPLC (IA column, 5% IPA/hexanes).

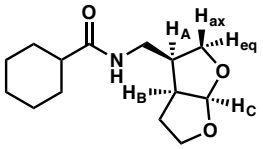


^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (brs, 1H), 4.50 (td, J = 5.8, 2.2 Hz, 1H), 3.84 (dd, J = 8.4, 7.1 Hz, 1H), 3.45 (t, J = 8.8 Hz, 1H), 3.38 – 3.25 (m, 2H), 2.59 – 2.46 (m, 2H), 2.05 (tt, J = 11.8, 3.5 Hz, 1H), 1.88 – 1.13 (m, 16H); 2D NOESY (500 MHz, $CDCl_3$) δ [2.51 (H_A), 3.84 (H_{eq})], [2.51 (H_A), 4.51 (H_C)], [2.56 (H_B), 4.51 (H_C)], [3.85 (H_{eq}), 2.51 (H_A)], [3.84 (H_{eq}), 4.51 (H_C)], [4.51 (H_C), 2.56 (H_B)], [4.51 (H_C), 3.85 (H_{eq})]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 86.3, 70.7, 45.54, 45.48, 43.1, 38.3, 34.2, 29.7, 26.1, 25.7, 25.4. FT-IR (neat) 3280, 3089, 2853, 1638, 1549, 1462, 1448, 1435, 1258, 1217, 1040 cm^{-1}; LRMS (LCMS ESI) *m/z* (M^+ + H) calcd for $C_{15}H_{26}NO_2$: 252.2, found: 252.2.

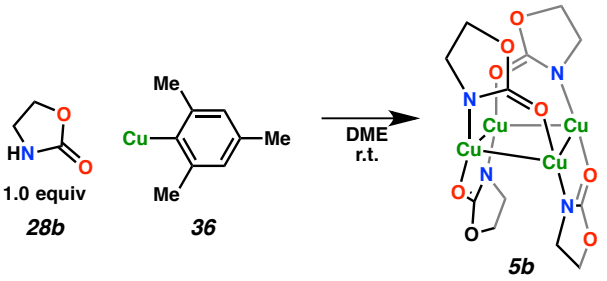


***N*-((Hexahydrofuro[2,3-*b*]furan-3-yl)methyl)cyclohexanecarboxamide (38b, Figure 1.25).** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and *trans*-2-(allyloxy)-3-bromotetrahydrofuran (2.0

mmol). The ratio of diastereomers was determined by ^{1}H NMR analysis of the unpurified reaction mixture. The product was isolated by column chromatography (75% EtOAc/hexanes → EtOAc). Yellow solid. First run: 234 mg (92%, 96:4). Second run: 217 mg (86%, 96:4).



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (d, J = 5.0 Hz, 1H), 5.49 (s, 1H), 3.95 (dd, J = 8.7, 7.3 Hz, 1H), 3.92 – 3.86 (m, 2H), 3.55 (dd, J = 11.2, 8.6 Hz, 1H), 3.47 – 3.39 (m, 1H), 3.36 – 3.29 (m, 1H), 2.87 – 2.80 (m, 1H), 2.58 – 2.48 (m, 1H), 2.06 (tt, J = 11.8, 3.4 Hz, 1H), 1.97 – 1.59 (m, 7H), 1.47 – 1.37 (m, 2H), 1.30 – 1.19 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 109.8, 70.9, 69.2, 45.5, 44.5, 42.5, 37.7, 29.72, 29.68, 25.7, 25.1; FT-IR (neat) 3323, 2977, 2883, 2852, 1644, 1541, 1448, 1442, 1021, 1004, 955 cm^{-1}; LRMS (LCMS ESI) *m/z* (M^+ + H) calcd for $C_{14}H_{24}NO_3$: 254.2, found: 254.2.



Complex 5b. In a nitrogen-filled glovebox, a 20-mL vial was charged with mesitylcopper(I) (183 mg, 1.00 mmol) and 2-oxazolidone (87.0 mg, 1.00 mmol, 1.00 equiv). 1,2-Dimethoxyethane (18.0 mL) was added, and the reaction mixture was stirred at room temperature for 4 h, resulting in a pale-yellow precipitate. The suspension was allowed to settle overnight, and then the solvent was decanted. The solid was washed with pentane (2x3 mL) and dried under vacuum, affording complex **4** as a pale-yellow solid (124 mg, 83% yield).

Anal. calcd for $C_{12}H_{16}Cu_4N_4O_8$: C, 24.08; H, 2.69; N, 9.36. Found: C, 24.23; H, 2.69; N, 9.33.

Preparation of X-ray quality crystals. In a nitrogen-filled glovebox, a 4-mL vial was charged with mesitylcopper(I) (37 mg, 0.20 mmol, 1.0 equiv) and 2-oxazolidone (17 mg, 0.20 mmol, 1.0 equiv). 1,2-Dimethoxyethane (4.0 mL) was added, and the reaction mixture was stirred at room temperature for 30 min. The resulting suspension was filtered through an acrodisc, and the filtrate was kept at room temperature for 24 h, furnishing pale-yellow crystals that were suitable for X-ray diffraction.

A crystal of $C_{12}H_{16}Cu_4N_4O_8$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Bruker APEX-II with filtered Mo-K" radiation at a temperature of 100 K. Using Olex2,[38] the structure was solved with the ShelXS[39] structure solution program using Direct Methods and refined with the ShelXL refinement package using Least Squares minimization.

1.6 Notes and Citations

(1) For recent reviews, see (a) Ribas, X.; Güell, I. *Pure Appl. Chem.* **2014**, *86*, 345–360. (b) Sambiagio, C.; Marsden, S.P.; Blacker, A.J.; McGowan, P.C. *Chem. Soc. Rev.* **2014**, *43*, 3225–3550.

(2) Ullman, F.; Bielecki, J. *Chem. Ber.* **1901**, *34*, 2174–2185.

(3) Ullman, F. *Chem. Ber.* **1903**, *34*, 2174–2185.

(4) Ullman, F.; Sponagel, P. *Chem. Ber.* **1905**, *38*, 2211–2212.

(5) Goldberg, I. *Chem. Ber.* **1906**, *39*, 1691–1692.

(6) Hurtley, W.R.H. *J. Chem. Soc.* **1929**, 1870–1873.

(7) (a) Marcoux, J.-F.; Doye, S.; Buchwald, S.L. *J. Am. Chem. Soc.* **1997**, *119*, 10539–10540. (b) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S.L. *Tetrahedron Lett.* **1999**, *40*, 2657–2660.

(8) (a) Kelkar, A.A.; Patil, N.M.; Chaudhari, R.V. *Tetrahedron Lett.* **2002**, *43*, 7143–7146. (b) Ouali, A.; Spindler, J.-F.; Jutand, A.; Taillefer *Adv. Synth. Catal.* **2007**, *349*, 1906–1916.

(9) (a) Strieter, E.R.; Blackmond, D.G.; Buchwald, S.L. *J. Am. Chem. Soc.* **2005**, *127*, 4120–4121. (b) Strieter, E.R.; Bhayana, B.; Buchwald, S.L. *J. Am. Chem. Soc.* **2009**, *131*, 78–88.

(10) (a) Tye, J.W.; Weng, Z.; Johns, A.M.; Incarvito, C.D.; Hartwig, J.F. *J. Am. Chem. Soc.* **2008**, *130*, 9971–9983. (b) Giri, R.; Hartwig, J.F. *J. Am. Chem. Soc.* **2010**, *132*, 15860–15863. (c) Tye, J. W.; Weng, Z.; Giri, R.; Hartwig, J.F. *Angew. Chem. Int. Ed.* **2010**, *49*, 2185–2189. (d) Chen, C.; Weng, Z.; Hartwig, J.F.

Organometallics **2012**, *31*, 8031–8037. (e) Liu, X.; Zhang, S.-L.; Ding, Y. *Dalton Trans.* **2012**, *41*, 5897–5902.

(11) (a) Zhang, S.-L. Liu, L.; Fu, Y.; Guo, Q.-X. *Organometallics* **2007**, *26*, 4546–4554. (b) Zhang, S.-L.; Ding, Y. *Organometallics* **2011**, *30*, 633–641. (c) Zhang, S.-L. *Dalton Trans.* **2012**, *41*, 1382–13840. (d) Zhang, S.-L.; Fan, H.-J. *Organometallics* **2013**, *32*, 4944–4951.

(12) Jones, G.O.; Liu, P.; Houk, K.N.; Buchwald, S.L. *J. Am. Chem. Soc.* **2010**, *132*, 6205–6213.

(13) There is some experimental evidence for radical intermediates in systems using highly specialized aryl halides: (a) Arai, S.; Yamagishi, T.; Ototake, S.; Hida, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 547–548. (b) Arai, S.; Hida, M.; Yamagishi, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 277–282.

(14) Annunziata, A.; Galli, C.; Marinelli, M.; Tullia, P. *Eur. J. Org. Chem.* **2001**, 1323−1329.

(15) Creutz, S.E.; Lotito, K.J.; Fu, G.C.; Peters, J.C. *Science* **2012**, *338*, 647–651.

(16) (a) Ziegler, D.T.; Choi, J.; Muñoz-Molina, J.M.; Bissember, A.C.; Peters, J.C.; Fu, G.C. *J. Am. Chem. Soc.* **2013**, *135*, 13107–13112. (b) Uyeda, C.; Tan, Y.; Fu, G.C.; Peters, J.C. *J. Am. Chem. Soc.* **2013**, *135*, 9548–9552. (c) Tan, Y.; Muñoz-Molina, J.M.; Fu, G.C.; Peters, J.C. *Chem. Sci.* **2014**, 2831–2835.

(17) Paradies, J. Palladium-Catalyzed Aromatic Carbon-Nitrogen Bond Formation. In *Metal-Catalyzed Cross-Coupling Reactions and More;* De Meijere, A.; Brase, S.; Oestreich, M., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2014, pp 995-1065.

(18) (a) Rao, K.S.; Wu, T.-S. *Tetrahedron* **2012**, *68*, 7735–7754. (b) Fischer, C.; Koenig, B. *Beilstein J. Org. Chem.* **2011**, *7*, 59–74.

(19) Wang, C.; Xiao, J. Asymmetric Reductive Amination. In *Topics in Current Chemistry*; Li, W.; Zhang, X.; Springer Berlin Heidelberg, 2014; Vol. 343; pp 261–282.

(20) Hultzsch, K.C.; *Adv. Synth. Catal.* **2005**, *347*, 367–391.

(21) (a) Aydın, A.; Kaya, I.; *Electrochim. Acta.* **2012**, *65*, 104–114. (b) Tu, X.; Fu, X.; Jiang, Q.; Liu, Z.; Chen, G. *Dyes Pigm.* **2011**, *88*, 39–43. (c) Kozuka, M.; Tsuchida, T.; Mitani, M.; *Tetrahedron Lett.* **2005**, *46*, 4527–4530.

(22) Bissember, A.C.; Lundgren, R.J.; Creutz, S.E.; Peters, J.C. Fu, G.C. *Angew. Chem. Int. Ed.* **2013**, *52*, 5129–5133.

(23) Carey, J.S.; Laffan, D.; Thomson, C.; Williams, M.T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.

(24) Blunt, J.W.; Copp, B.R.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. *Nat. Prod. Rep.* **2004**, *21*, 15–61.

(25) Knight, A.S.; Zhou, E.Y.; Francis, M.B.; Zuckermann, R.N. *Adv. Mater.* **2015**, doi:10.1002/adma.201500275.

(26) For reviews, see (a) Lanigan, R.M.; Sheppard, T.D. *Eur. J. Org. Chem.* **2013**, 7453–7465. (b) González-Rosende, M.E.; Castillo, E.; Lasri, J.; *Sepúlveda*-Arques, J. *Prog. React. Kinet. Mech.* **2004**, *29*, 311–332.

(27) For a review, see Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L.J. *Chem. Rev.* **2015**, *115*, 2596–2697.

(28) Tran, B.L.; Li, B.; Driess, M.; Hartwig, J.F. *J. Am. Chem. Soc.* **2014**, *136*, 2555–2563.

(29) Aryl amides were observed to be particularly insoluble in CH_3CN.

(30) Pandey, G.; Rao, K.S.S.P.; Palit, D.K.; Mittal, J.P. *J. Org. Chem.* **1998**, *63*, 3968–3978.

(31) Hackmann, C.; Schäfer, H.J. *Tetrahedron* **1993**, *49*, 4559–4574.

(32) Isse, A.A.; Lin, C.Y.; Coote, M.L.; Gennaro, A. *J. Phys. Chem. B* **2011**, *115*, 678–684.

(33) Nemoto, H.; Zhong, W.; Kawamura, T.; Kamiya, M.; Nakano, Y.; Sakamoto, K. *Synlett* **2007**, 2343–2346.

(34) Bundesmann, M.W.; Coffey, S.B.; Wright, S.W. *Tetrahedron Lett.* **2010**, *51*, 3879–3882.

(35) The ester was synthesized from 4-(5,5-dimethyl-1,3-dioxan-2-yl)butanal (Alfa) using a literature method: Maki, B.E.; Scheidt, K.A. *Org. Lett.* **2008**, *10*, 4331–4334.

(36) Miranda, M.O.; Pietrangelo, A.; Hillmyer, M.A.; Tolman, W.B. *Green Chem.* **2012**, *14*, 490–494.

(37) Zhou, J.; Fu, G.C. *J. Am. Chem. Soc.* **2003**, *125*, 12527–12530.

(38) Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339–341.

(39) Sheldrick, G.M. *Acta Cyrst. A* **2008**, *64*, 112–122.

APPENDIX 1

Spectra Relevant to Chapter 1:

Photoinduced, Copper-Catalyzed Alkylation of Amides with Unactivated Secondary Alkyl Halides at Room Temperature

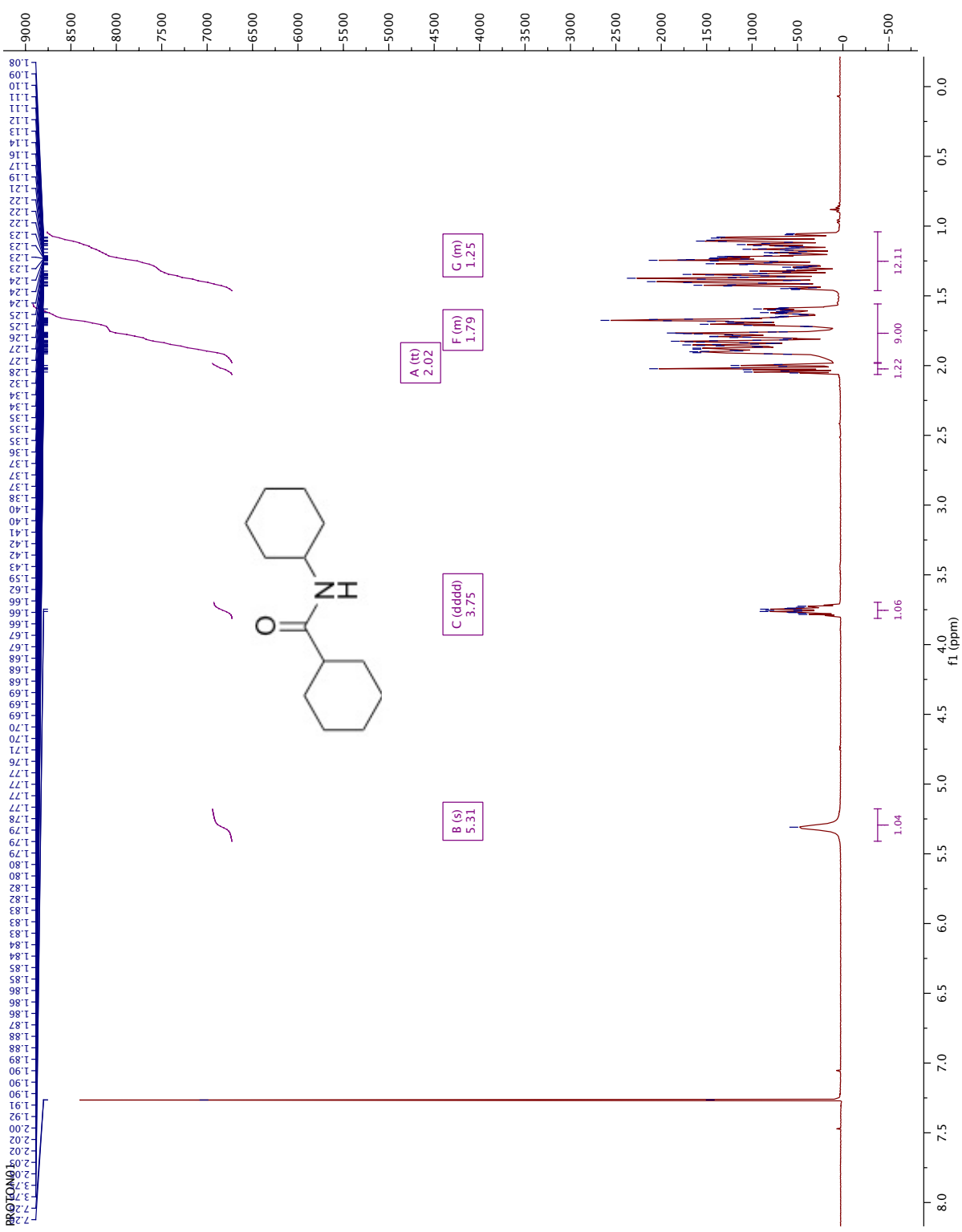


Figure A1.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26a**.

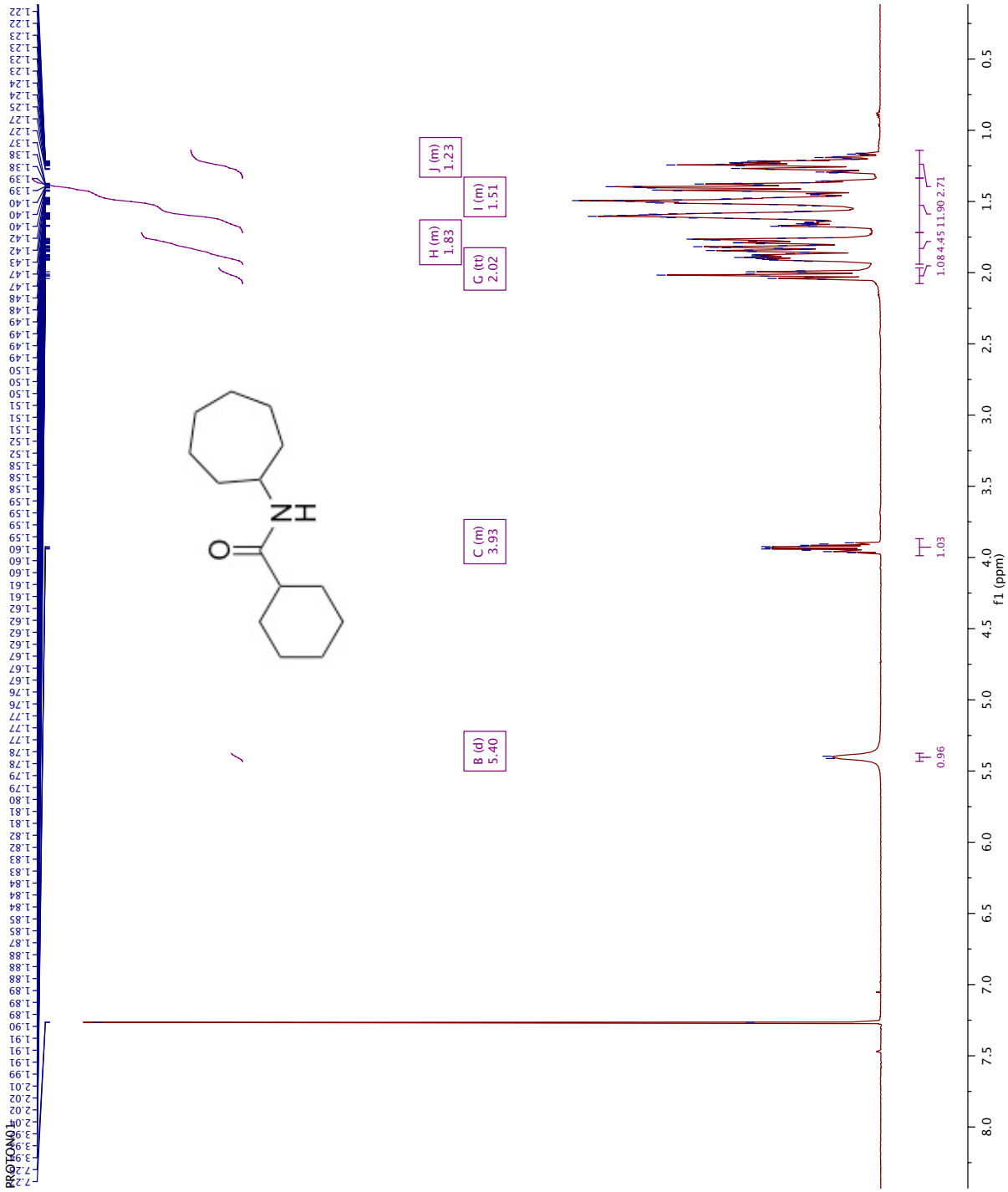


Figure A1.2. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26b**.

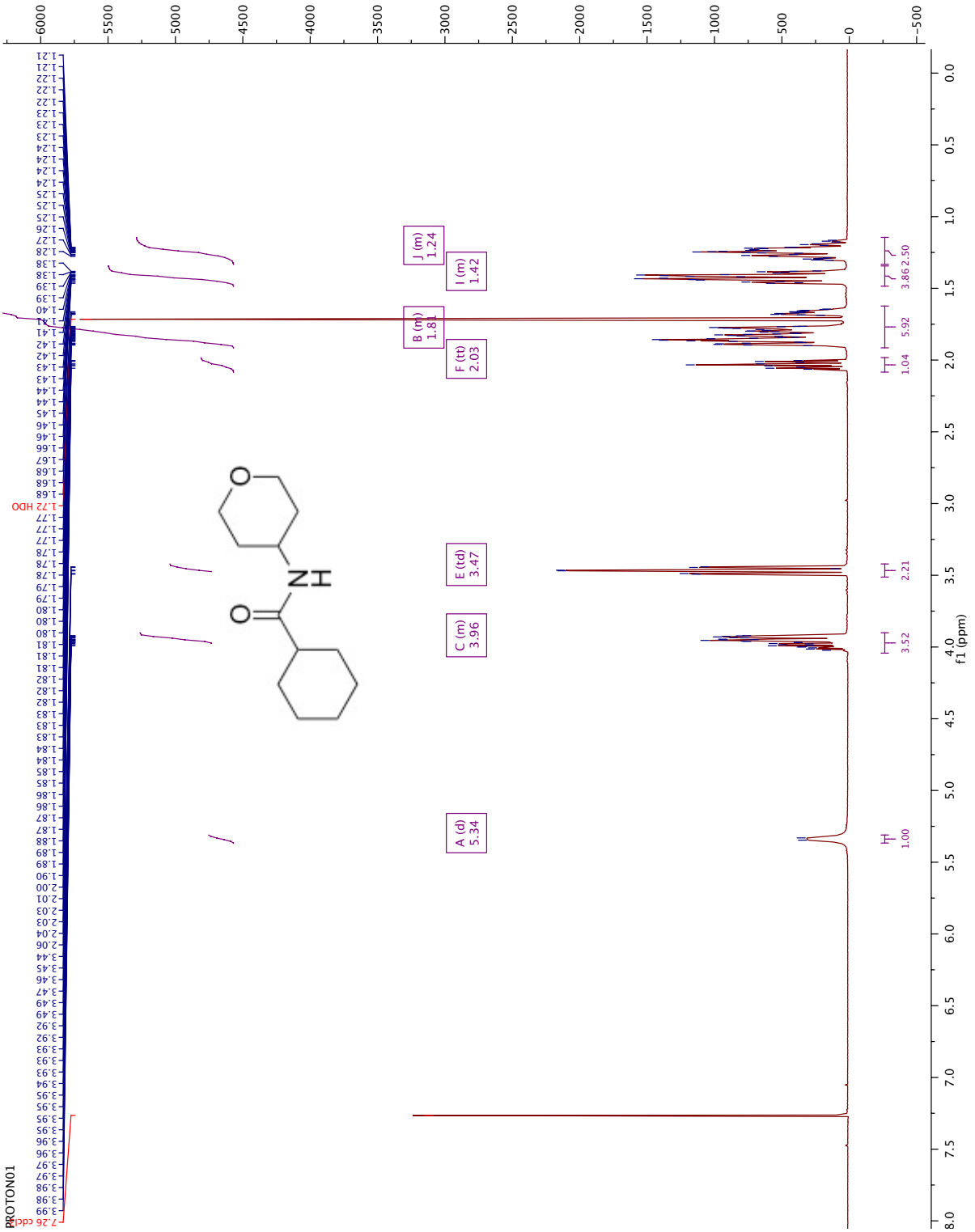


Figure A1.3. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26c**.

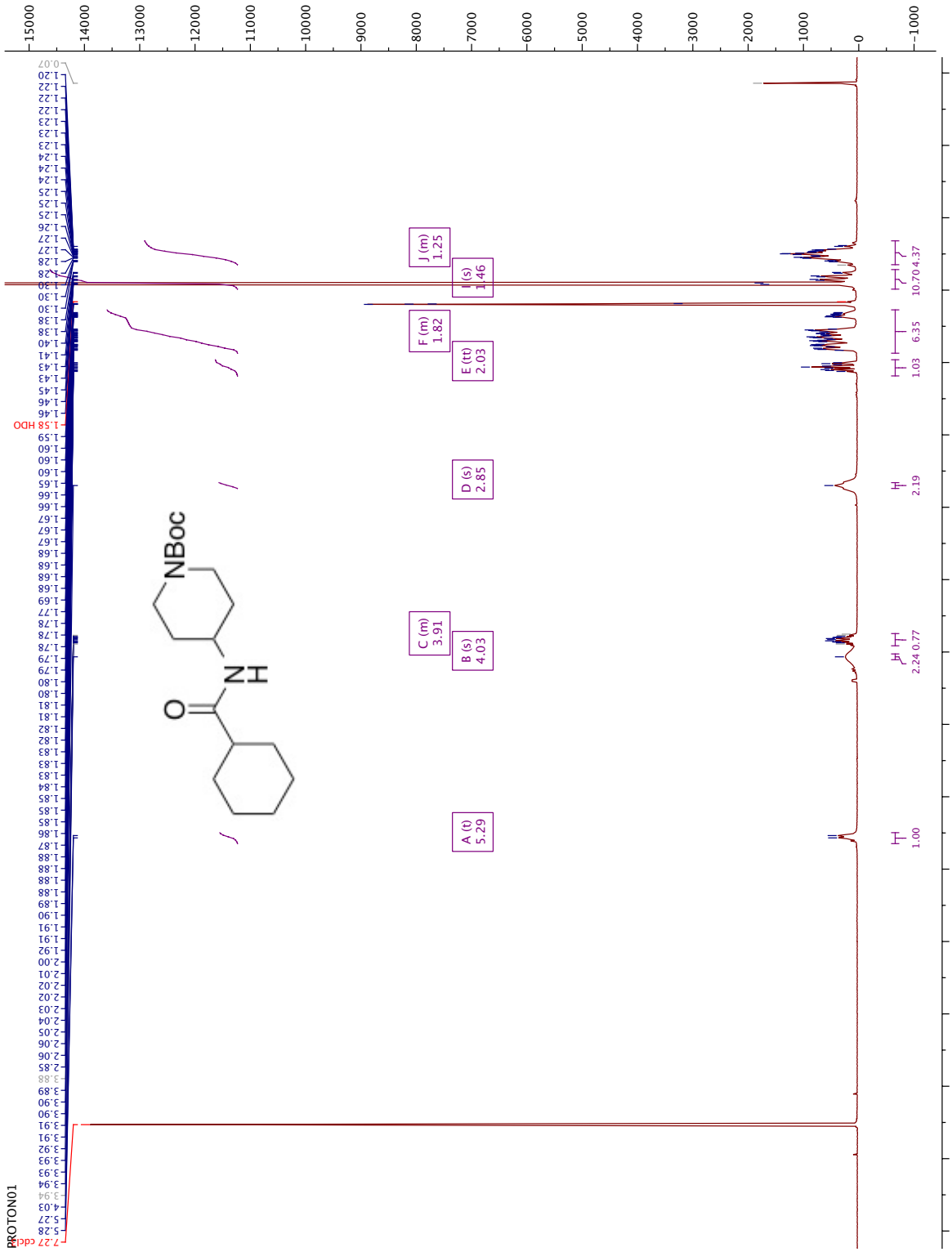


Figure A1.4. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26d**.

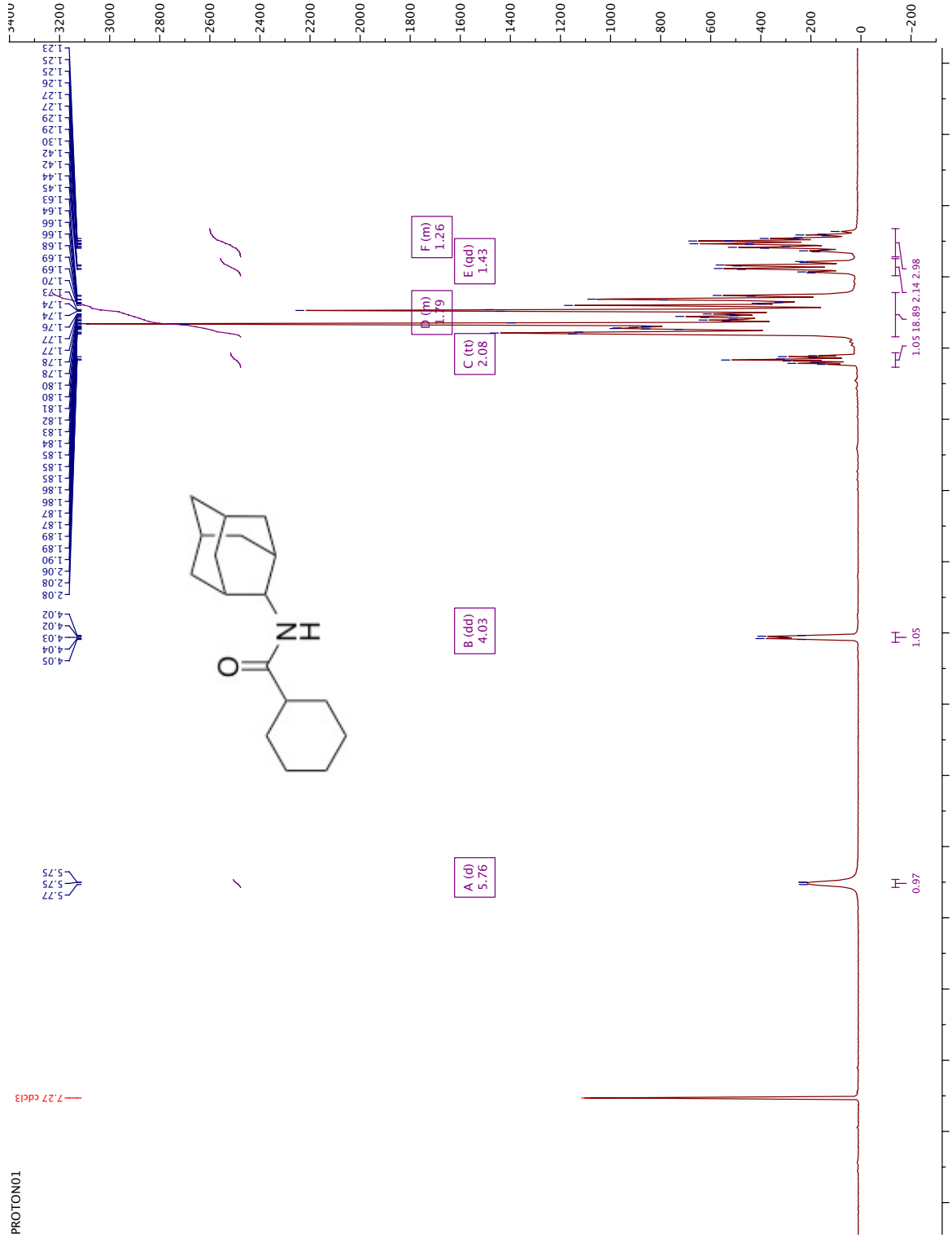


Figure A1.5. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26e**.

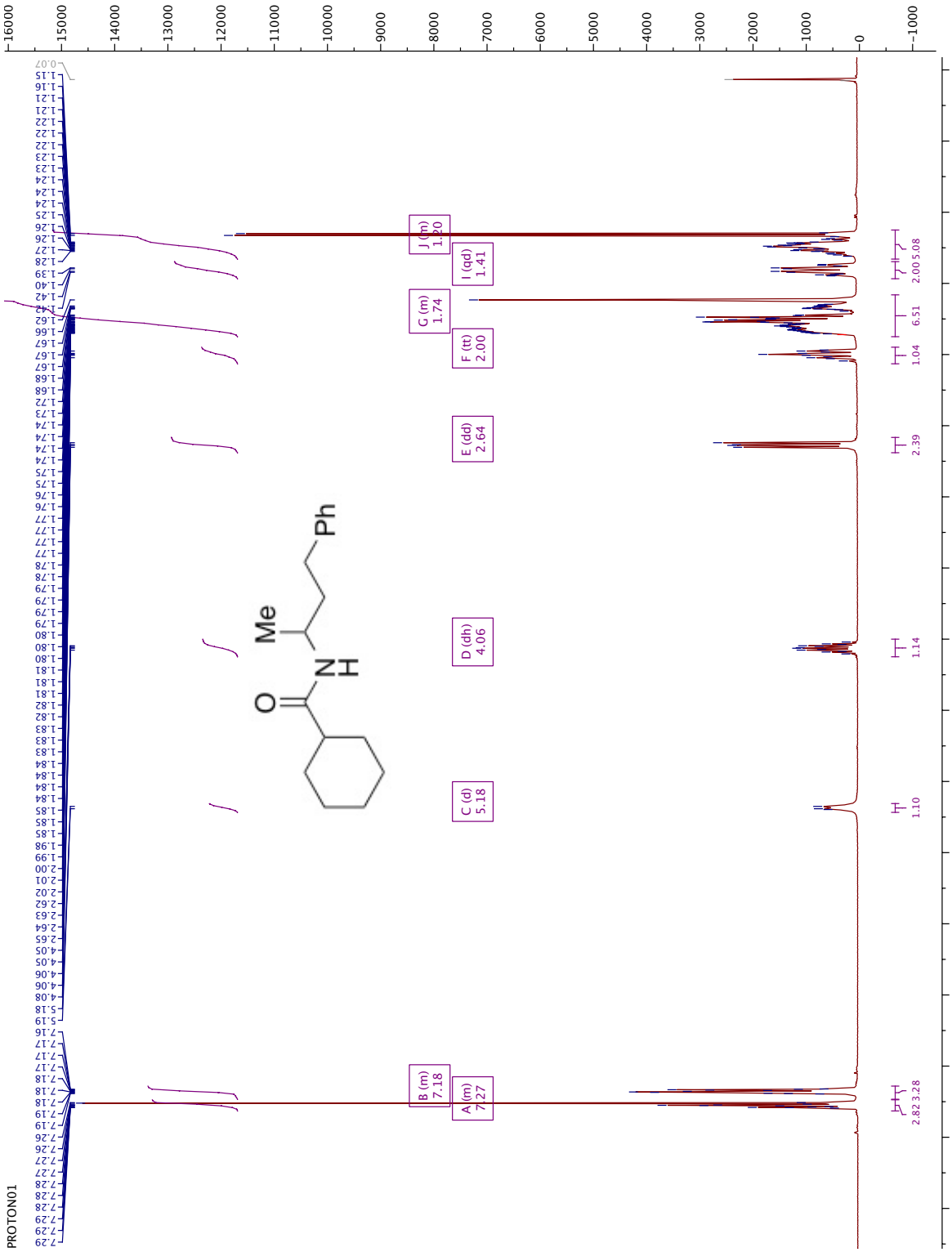


Figure A1.6. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26f**.

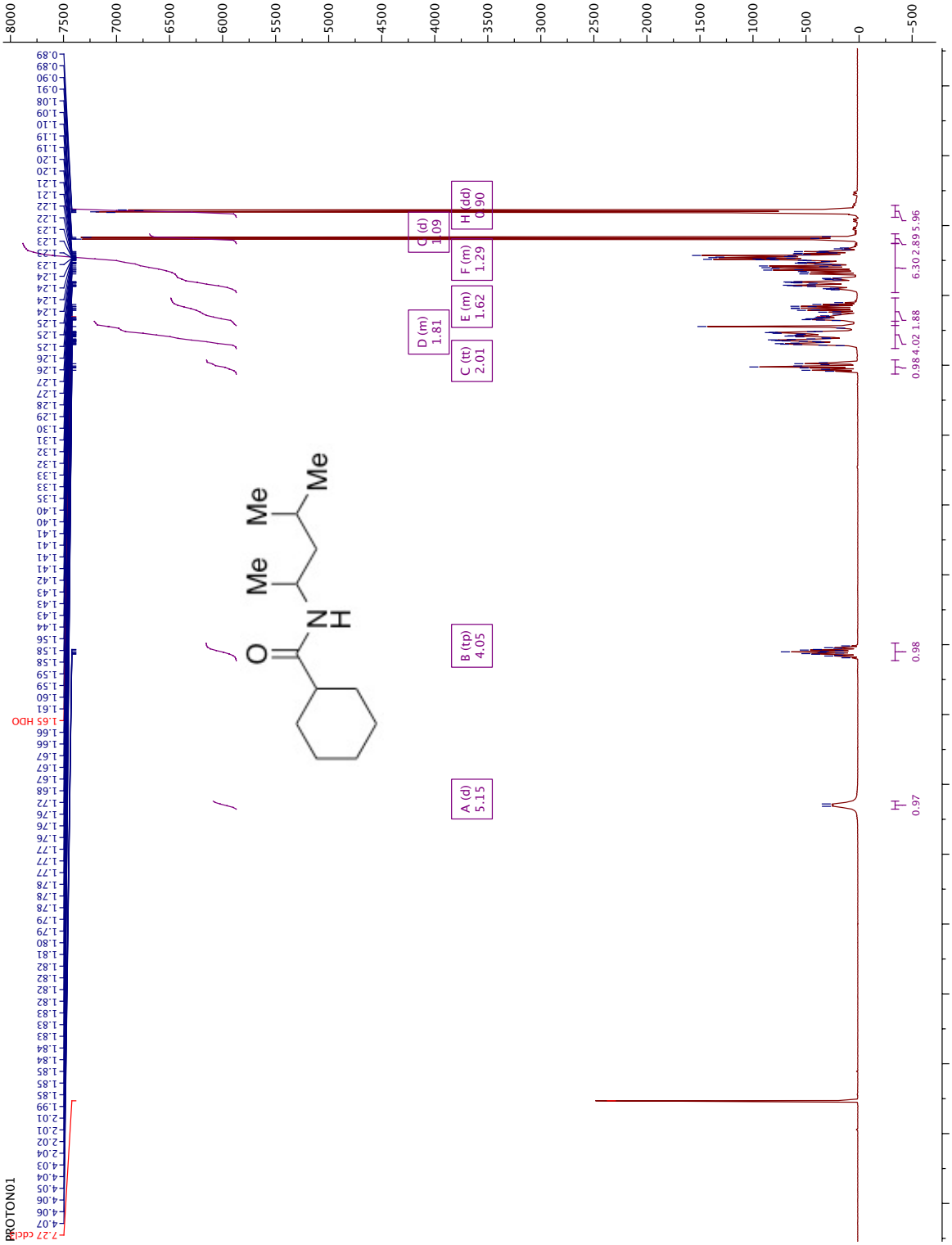


Figure A1.7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26g**.

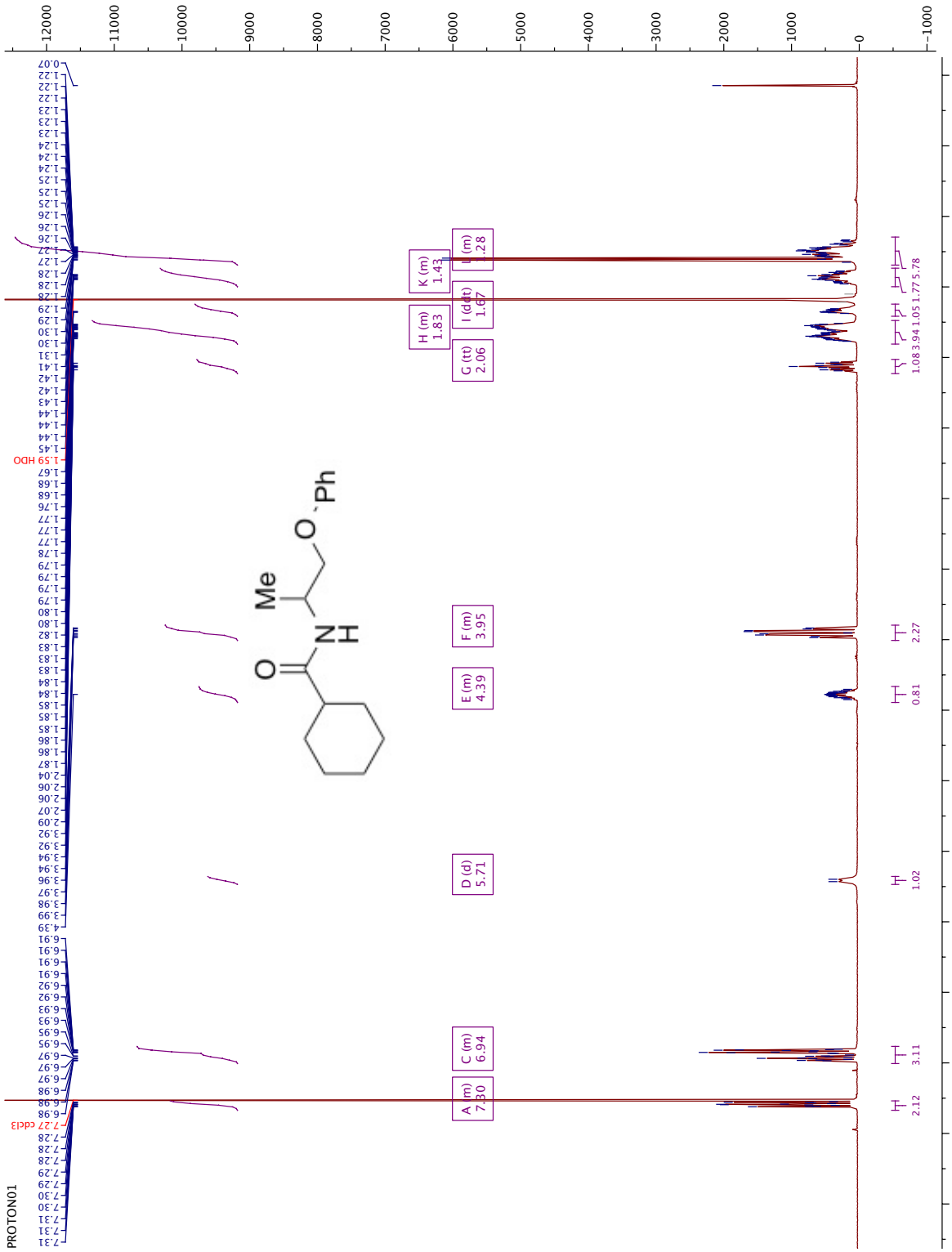


Figure A1.8. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26h**.

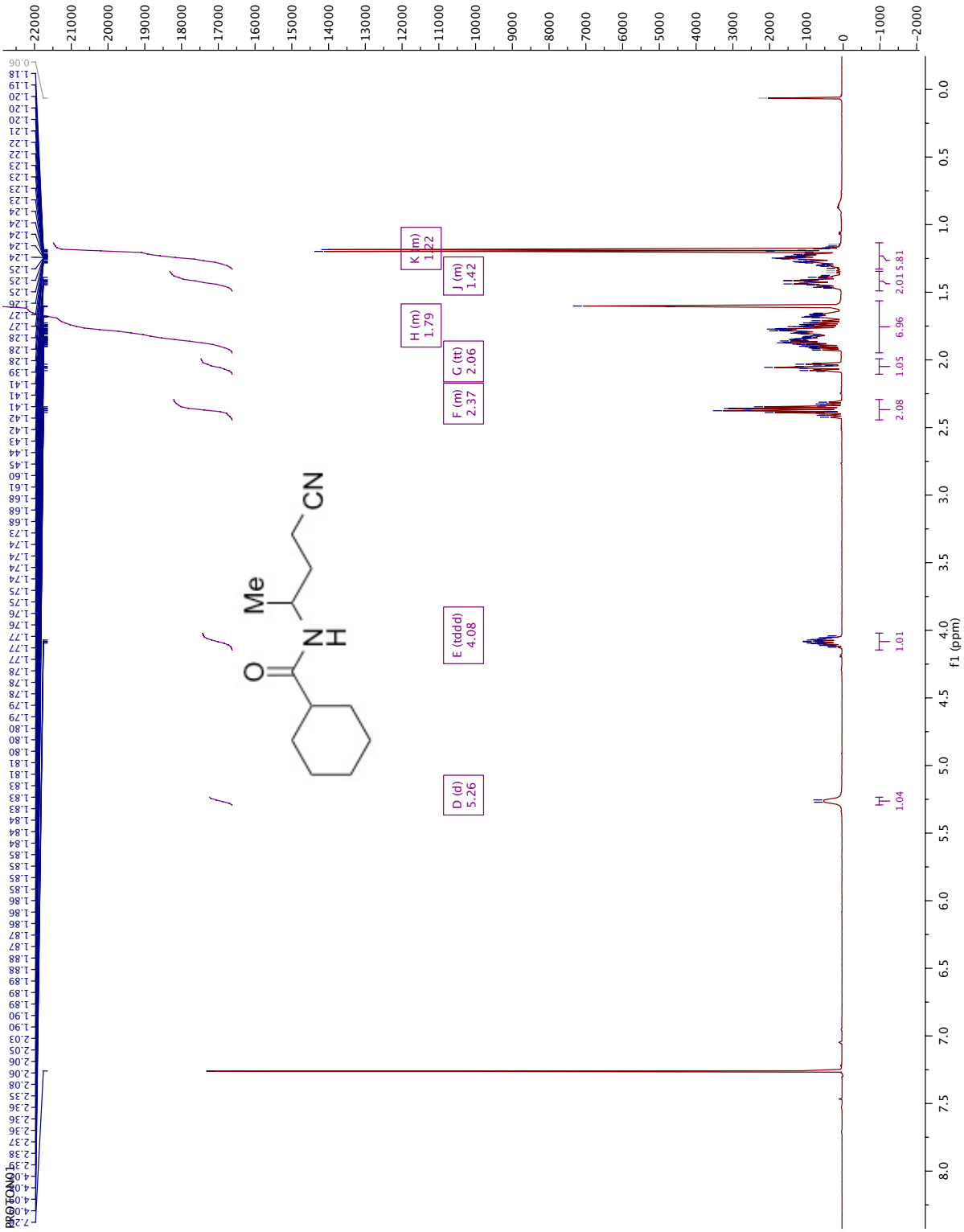


Figure A1.9. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26i**.

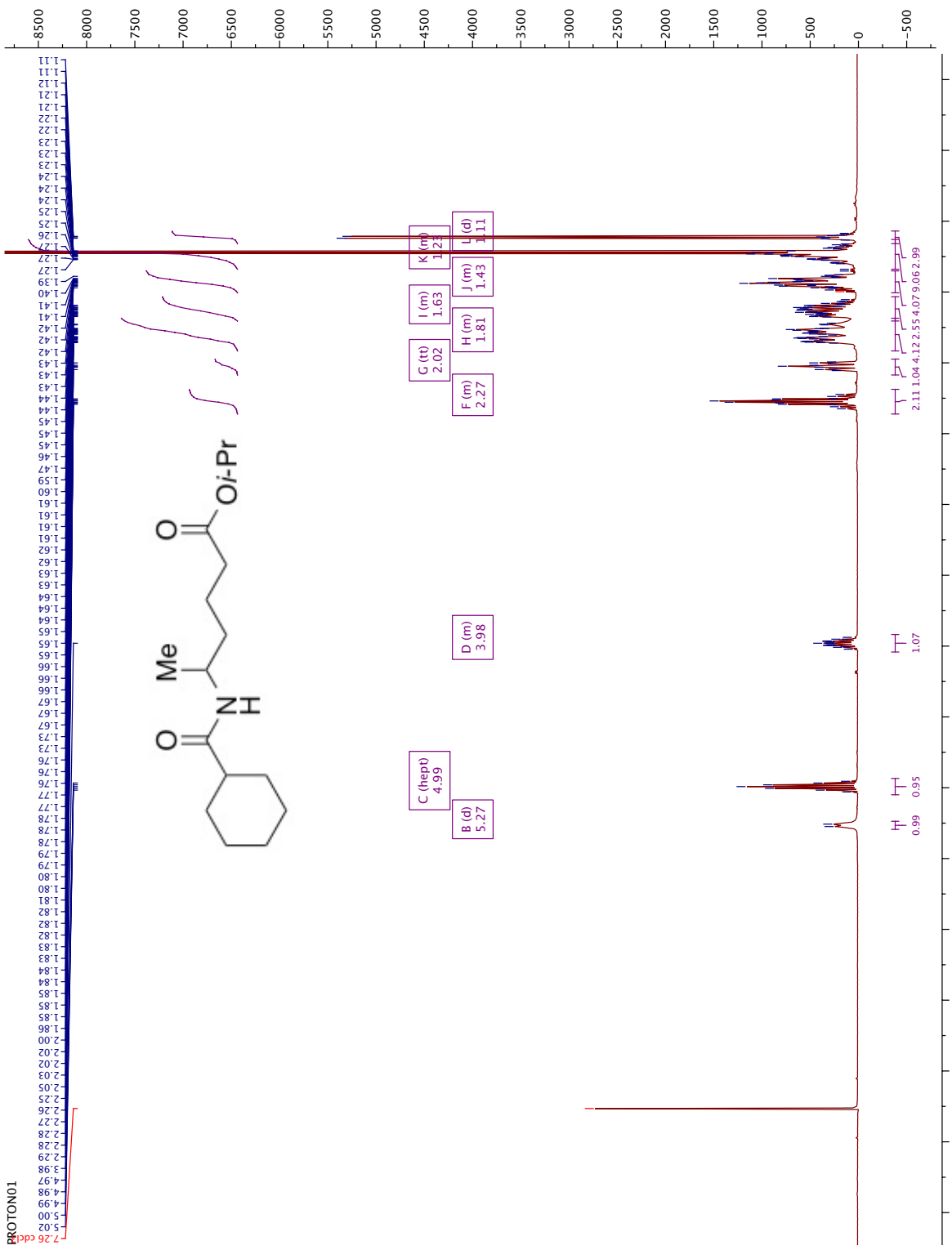


Figure A1.10. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26j**.

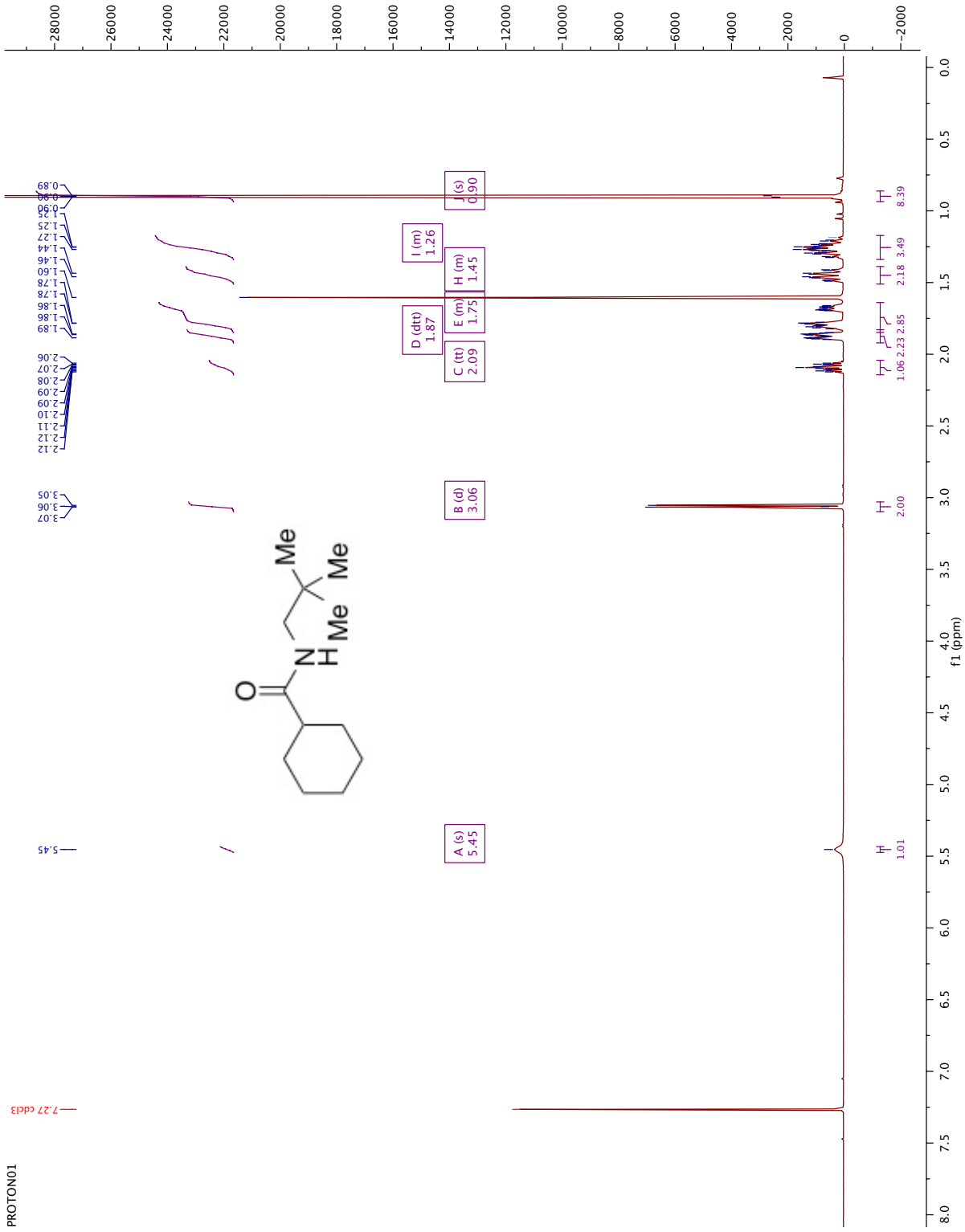


Figure A1.11. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26k**.

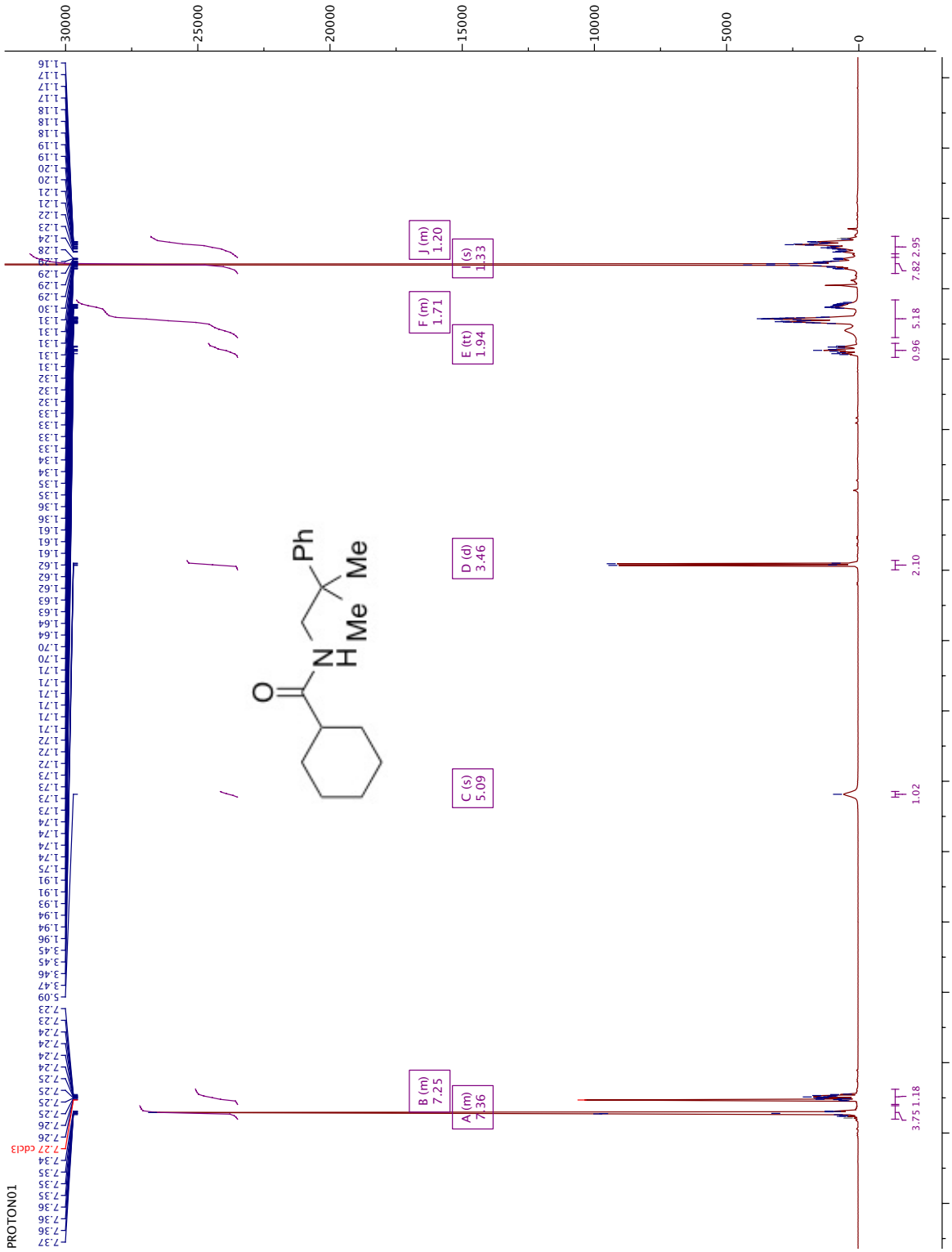


Figure A1.12. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26l**.

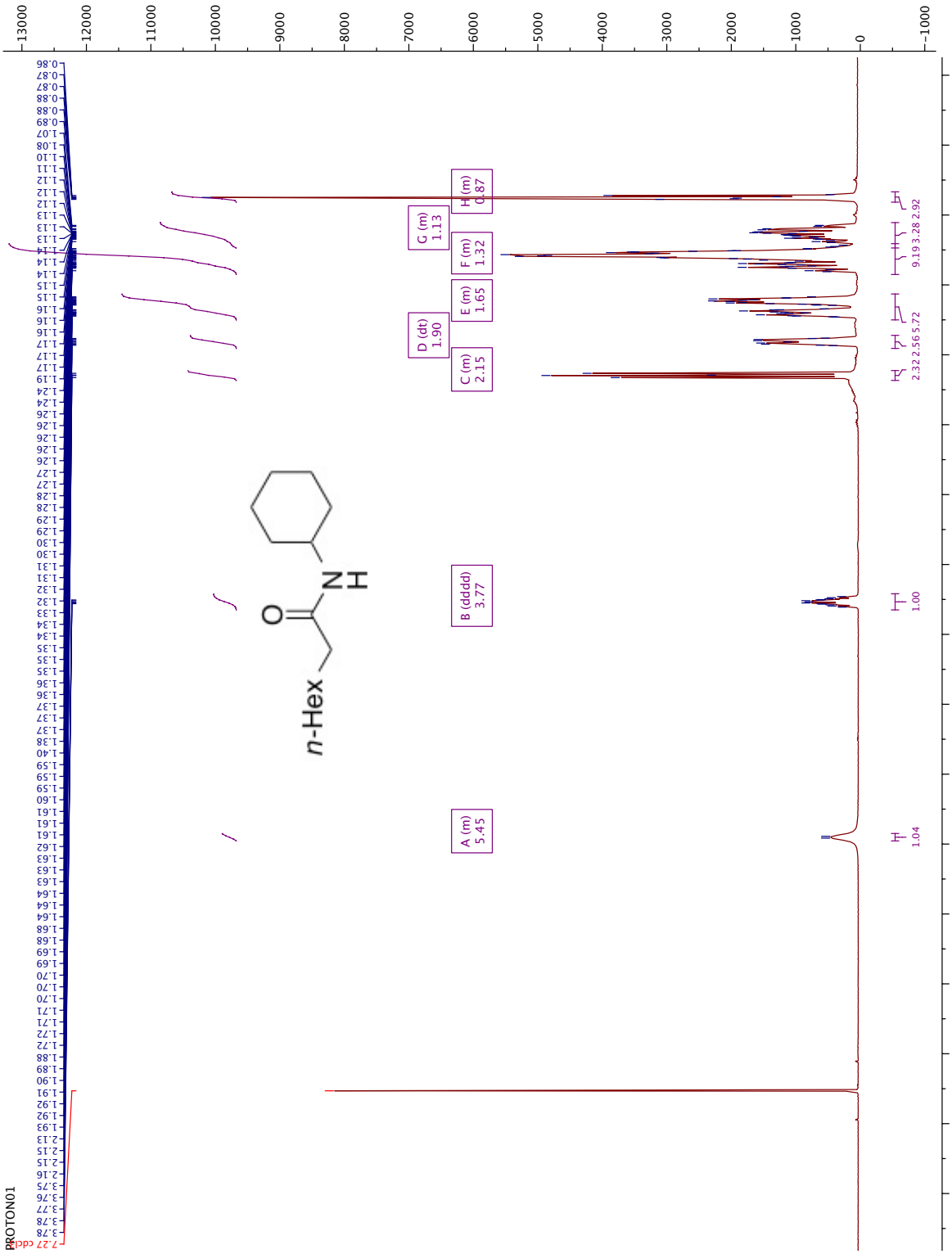


Figure A1.13. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26m**.

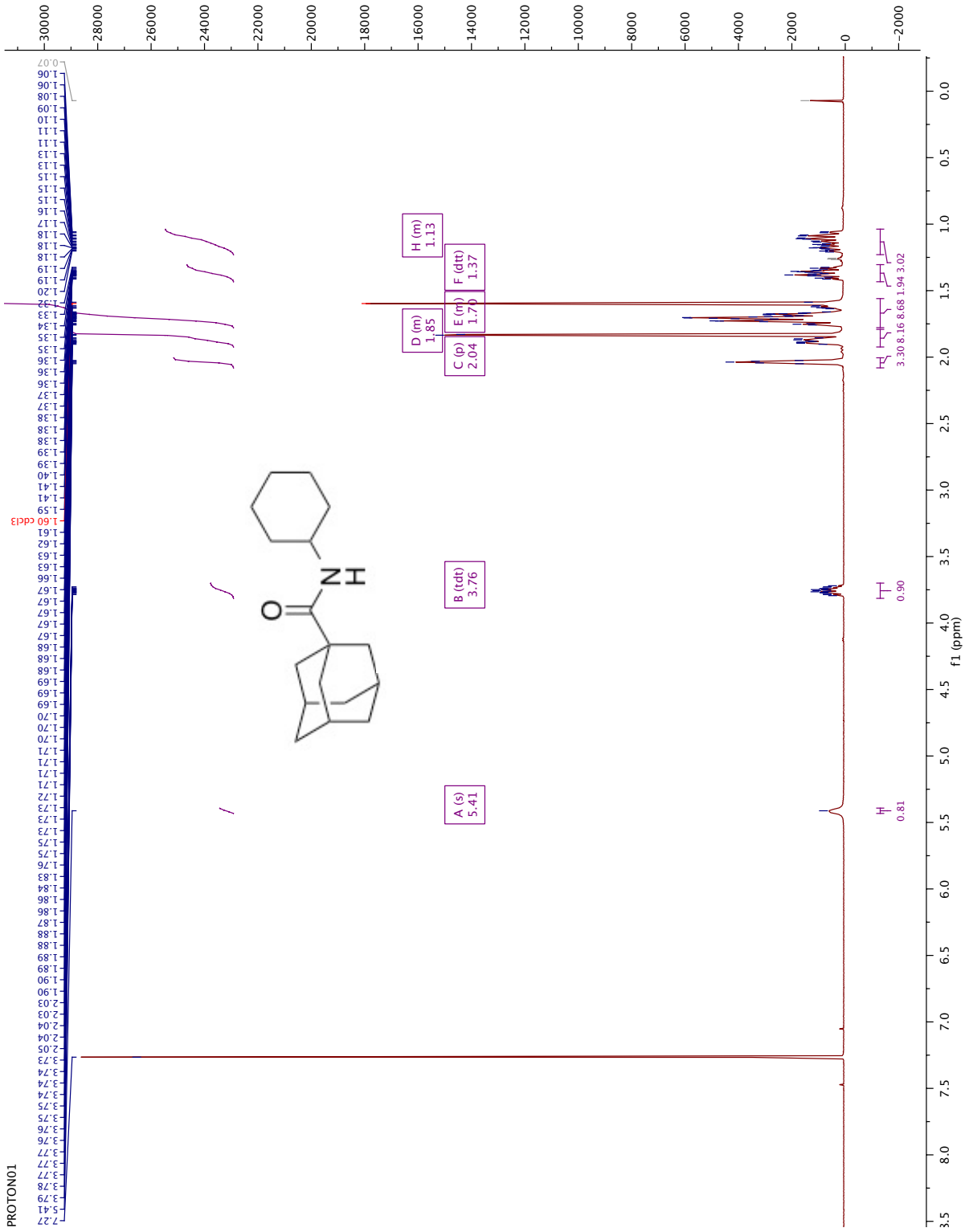


Figure A1.14. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26n**.

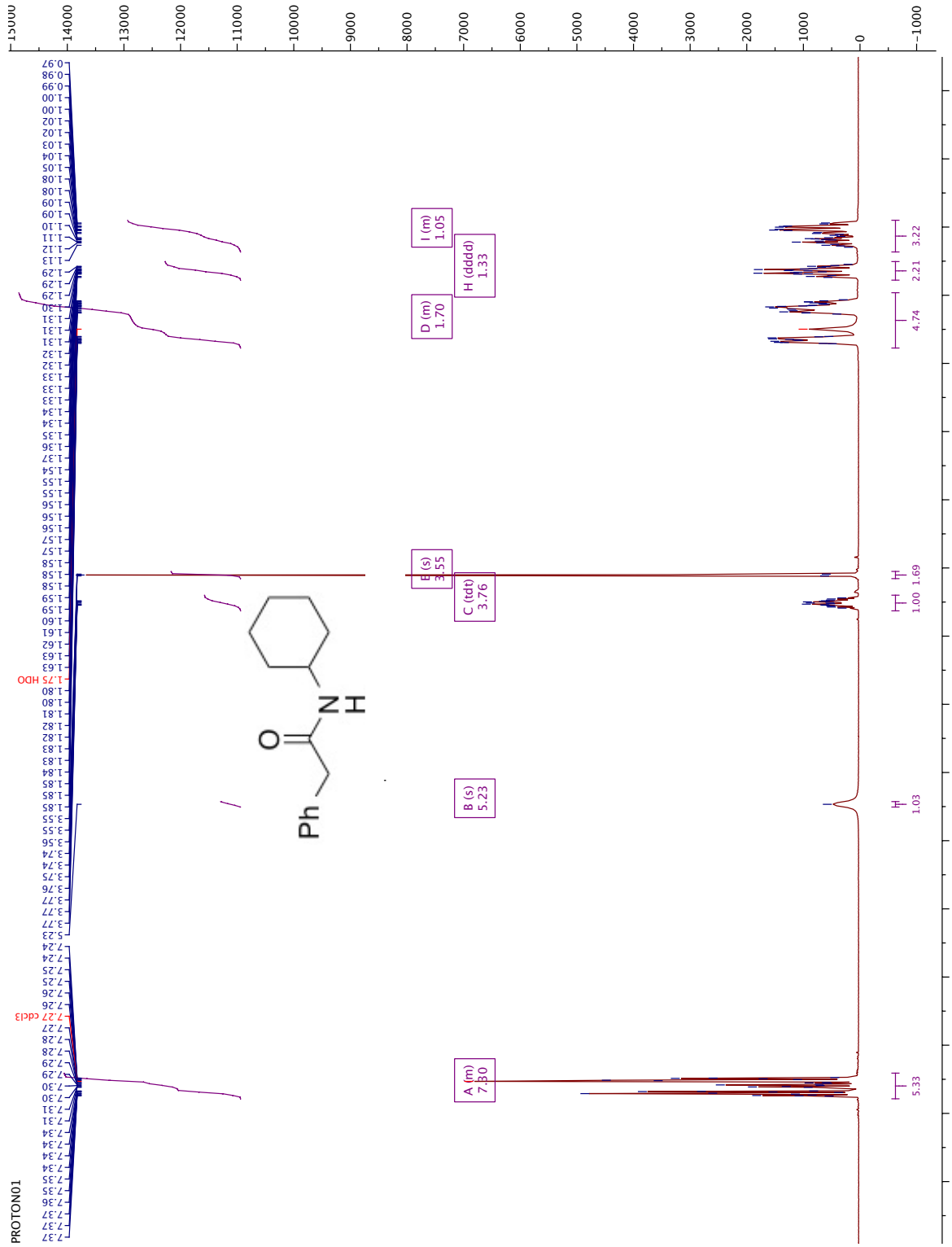


Figure A1.15. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26o**.

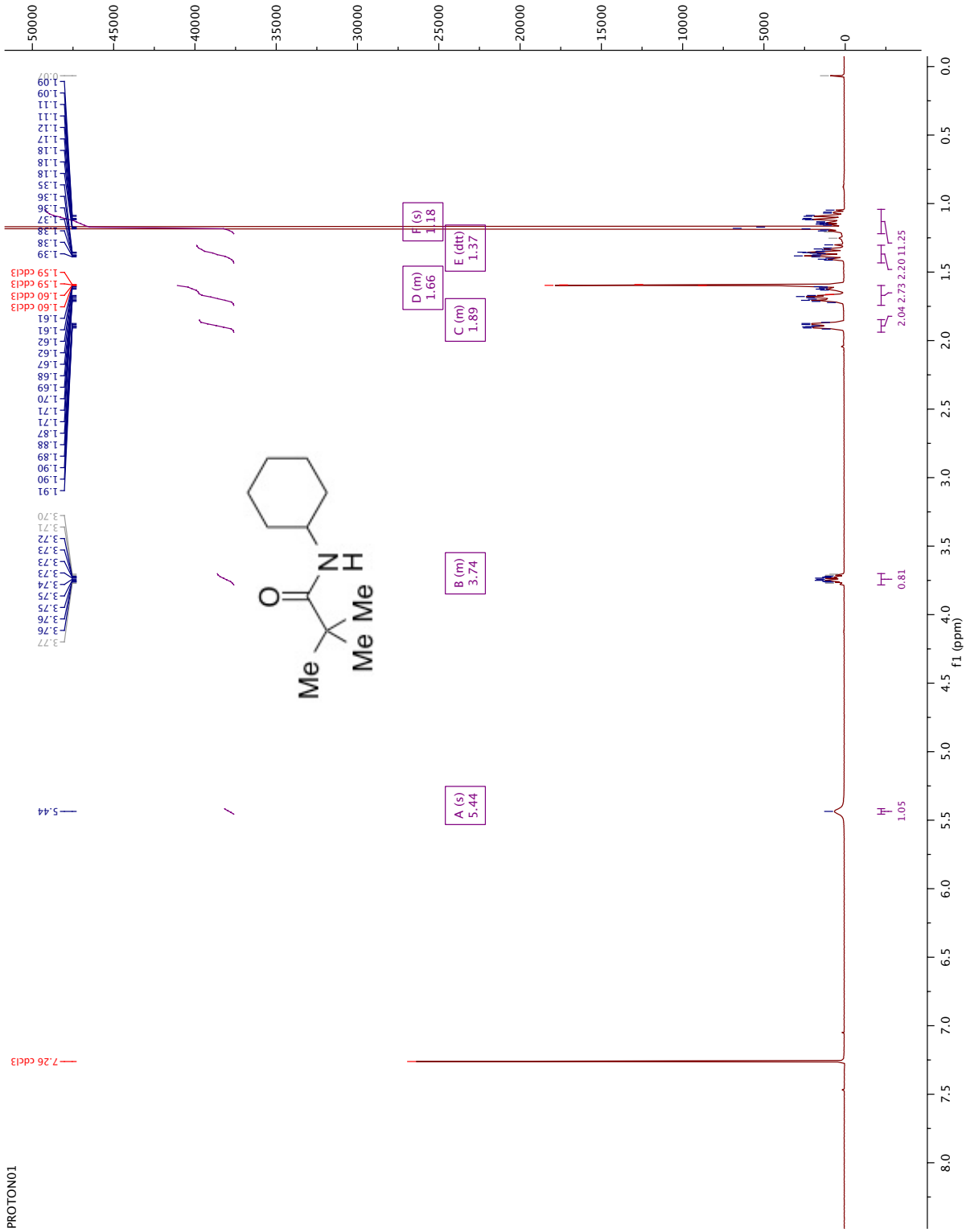


Figure A1.16. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26p**.

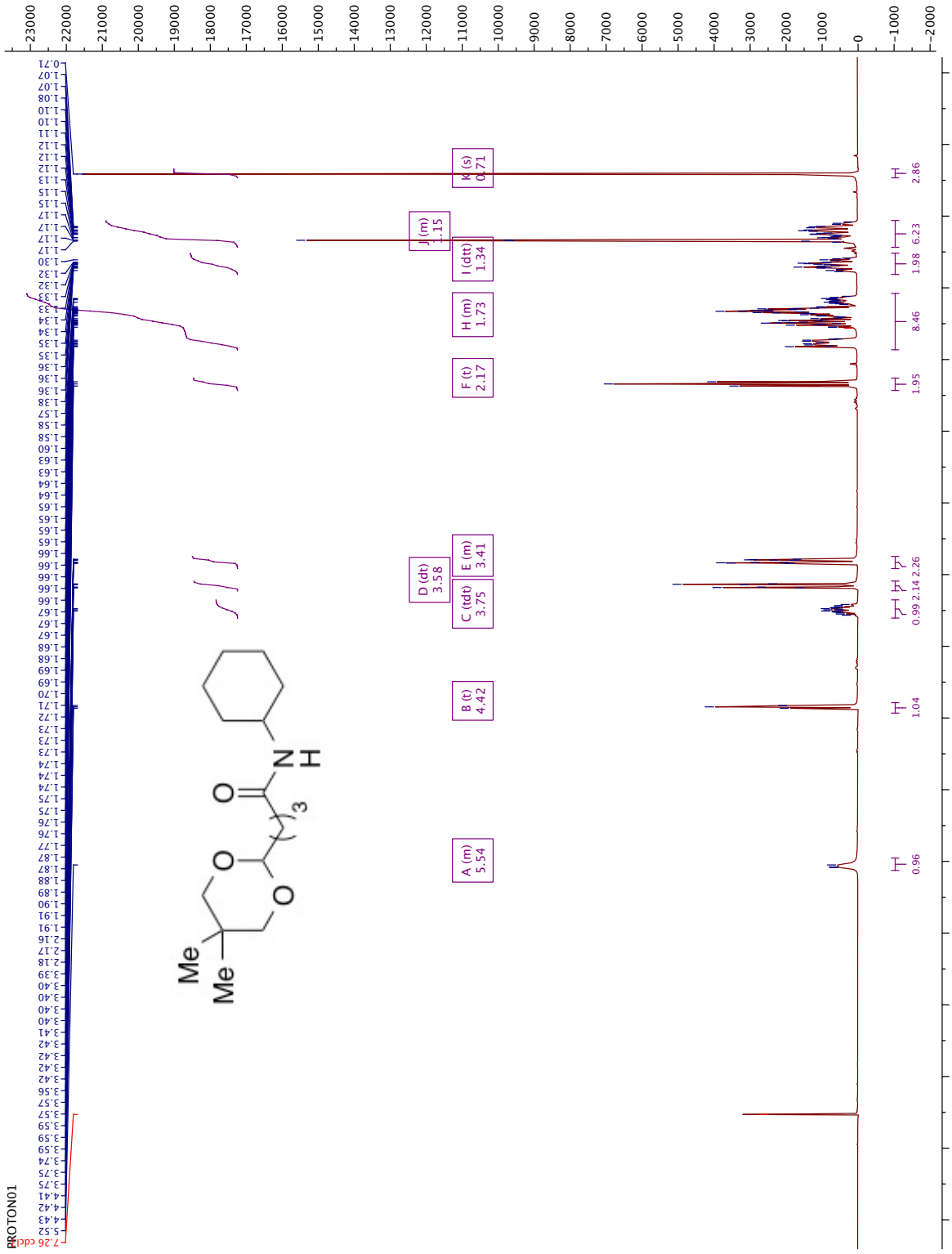


Figure A1.17. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26q**.

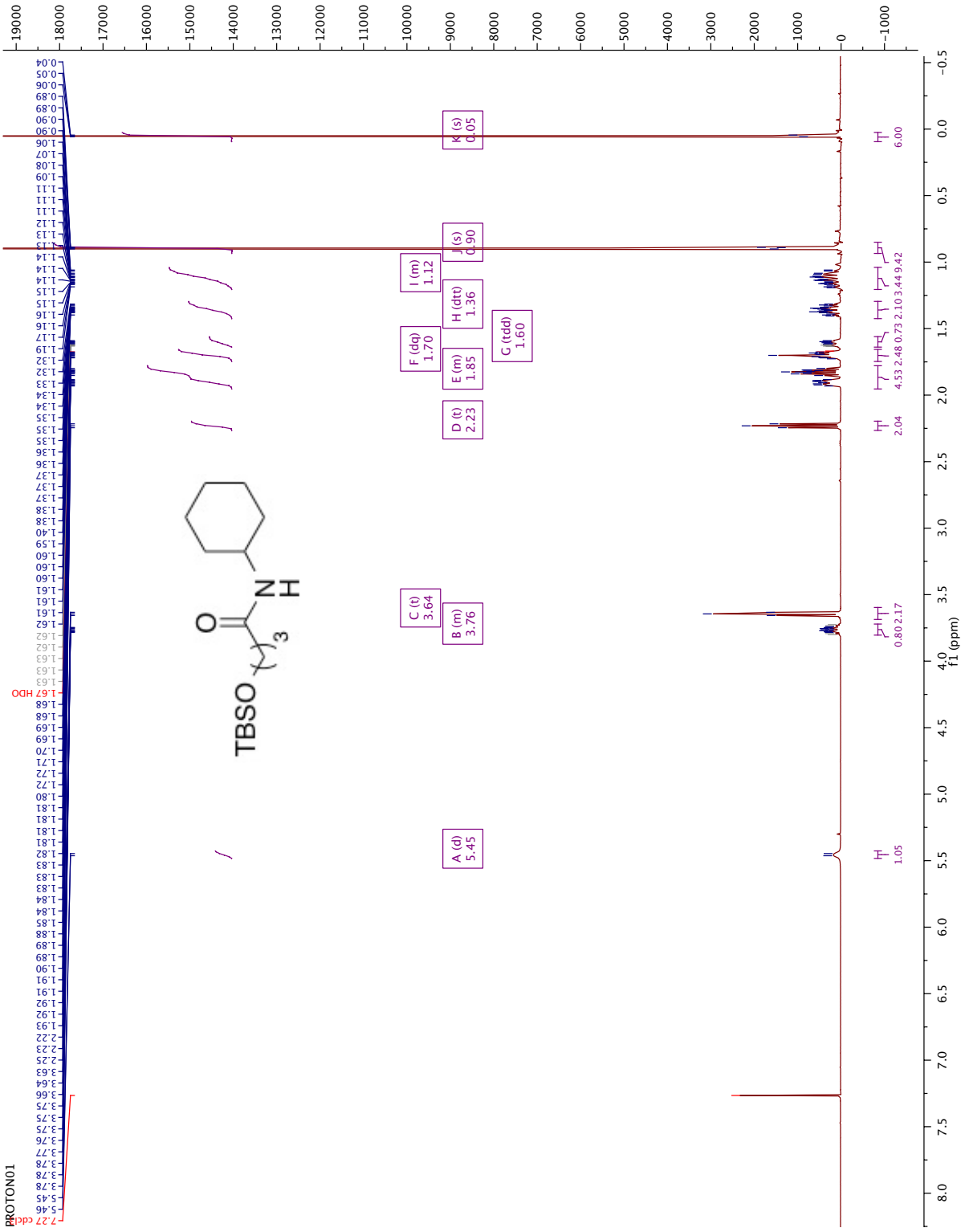


Figure A1.18. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26r**.

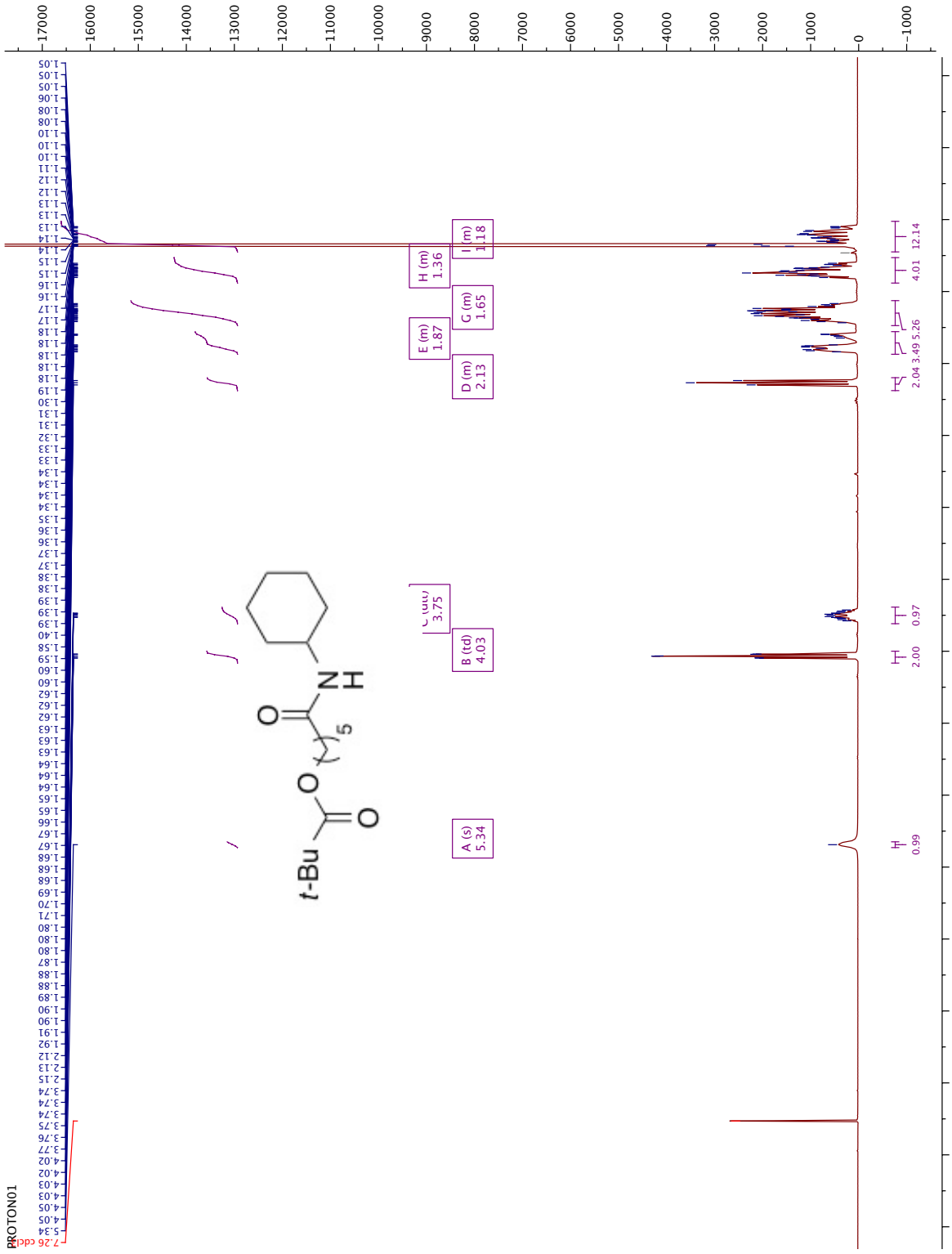


Figure A1.19. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26s**.

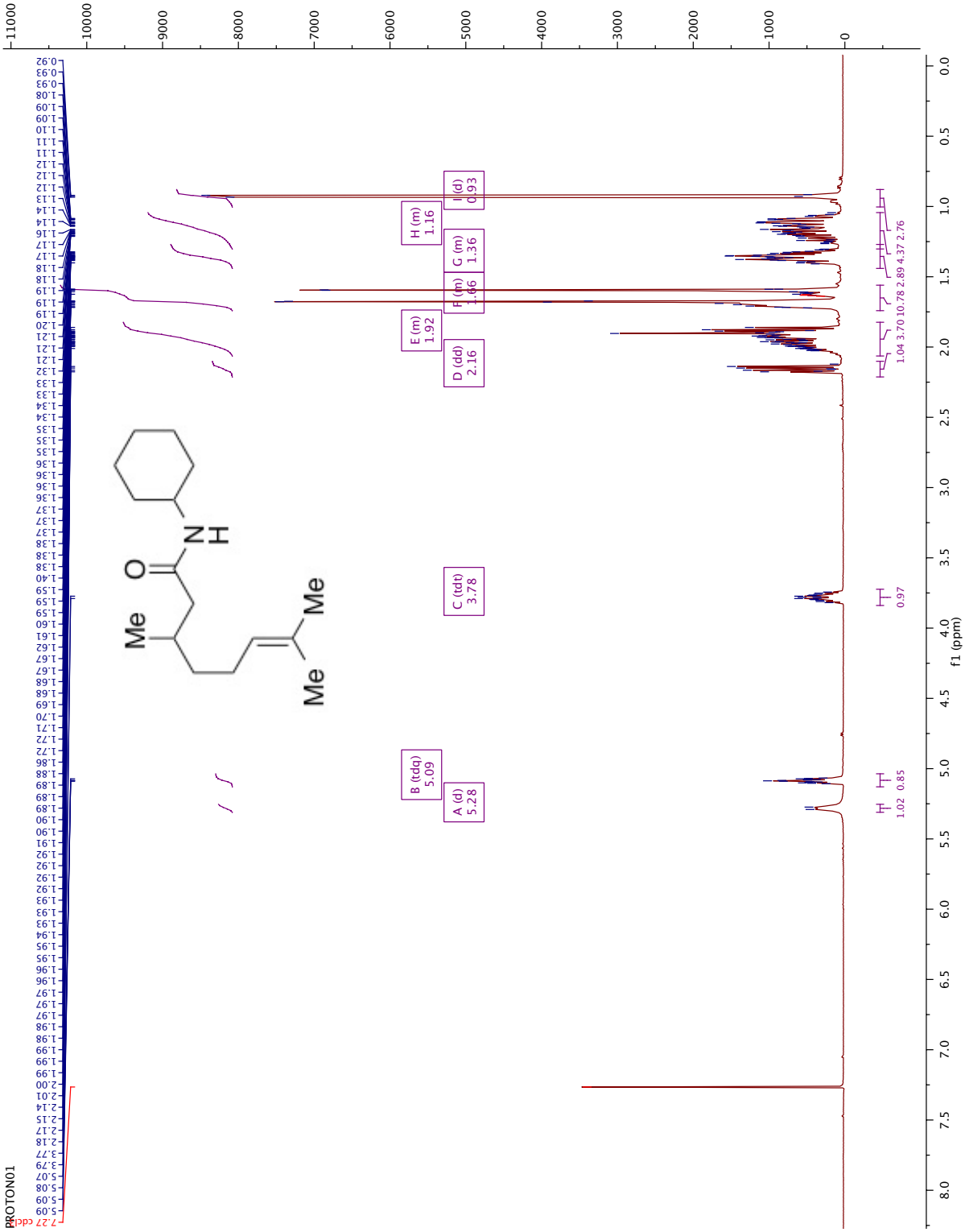


Figure A1.20. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26t**.

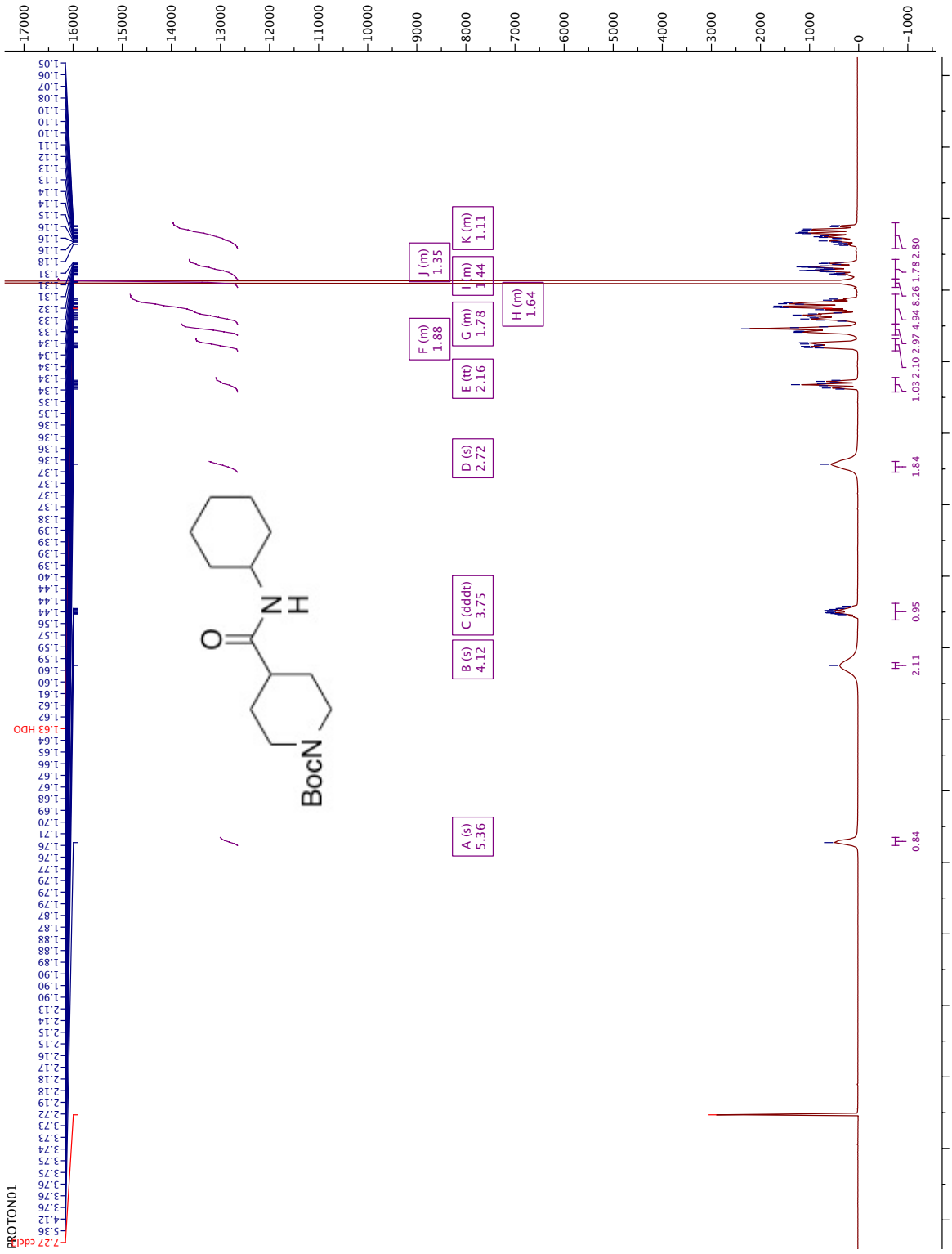


Figure A1.21. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **26u**.

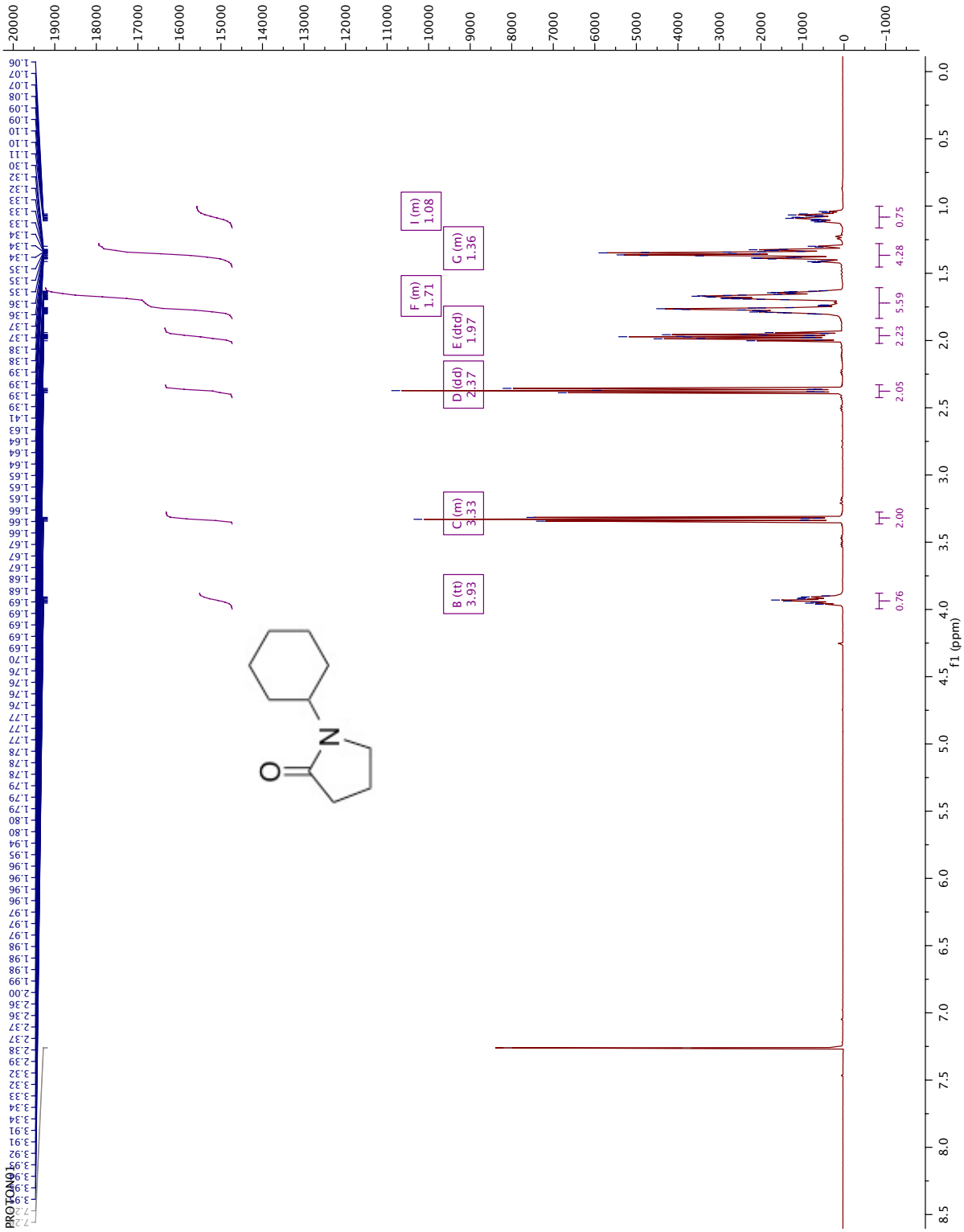


Figure A1.22. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **29a**.

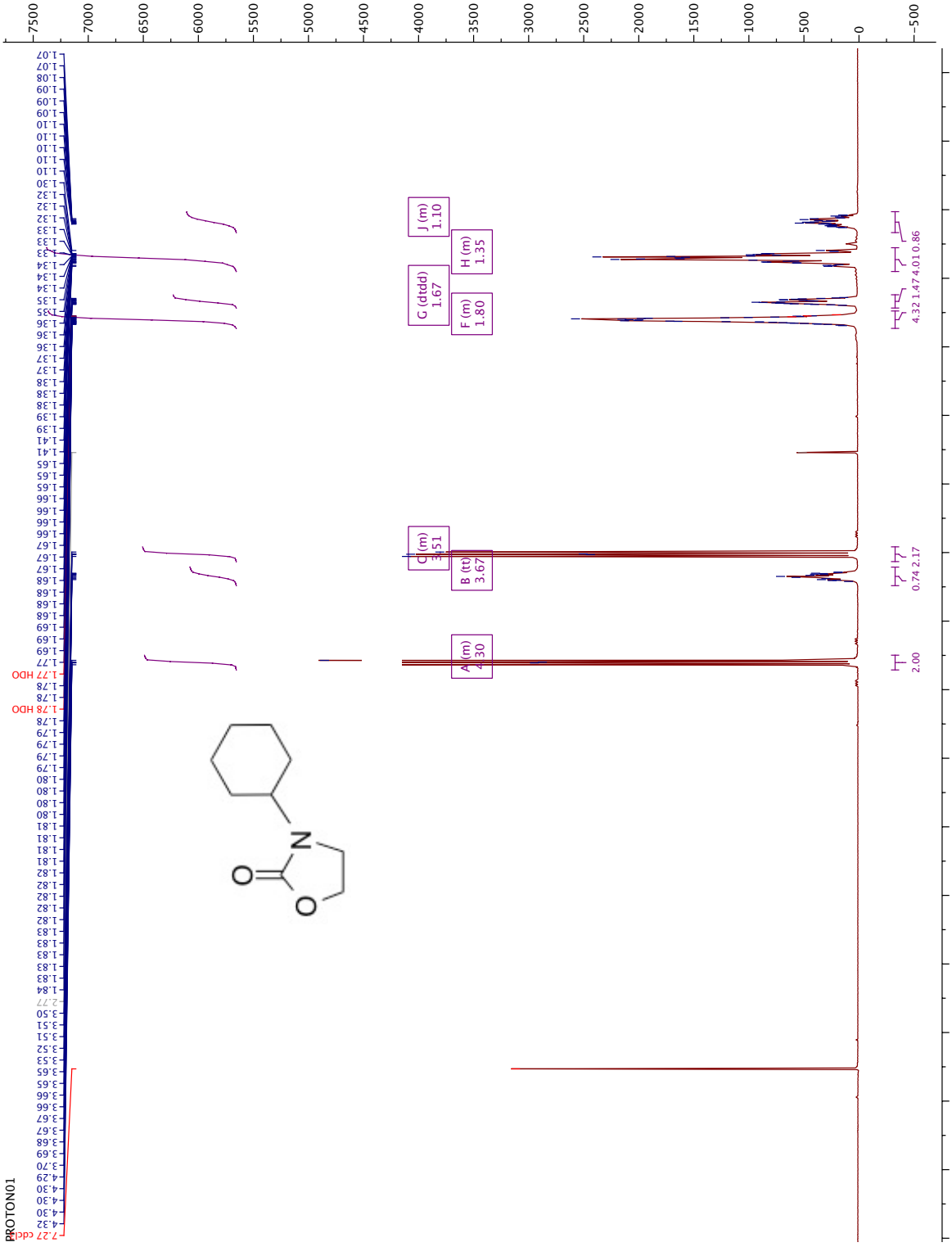


Figure A1.23. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **29b**.

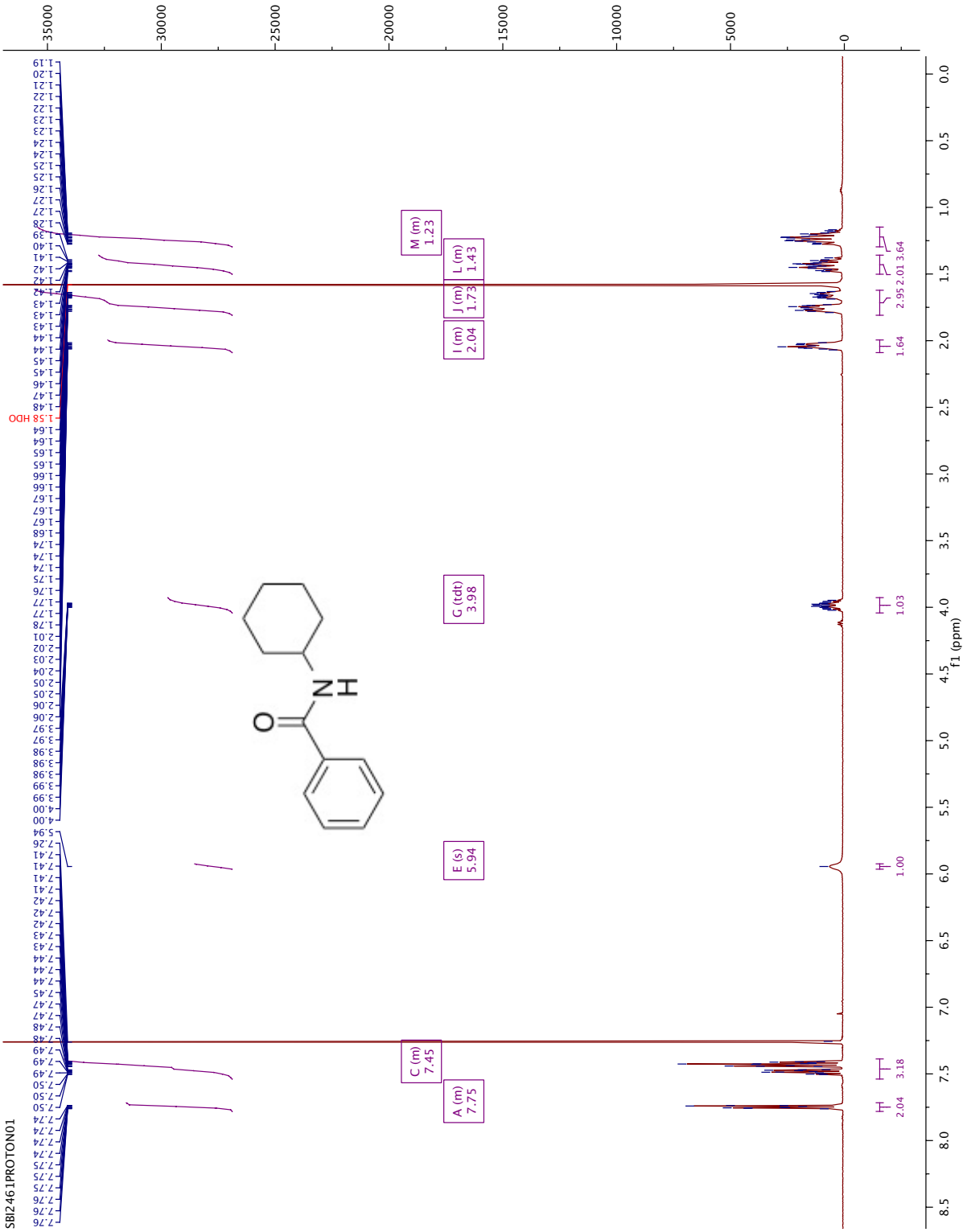


Figure A1.24. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **31a**.

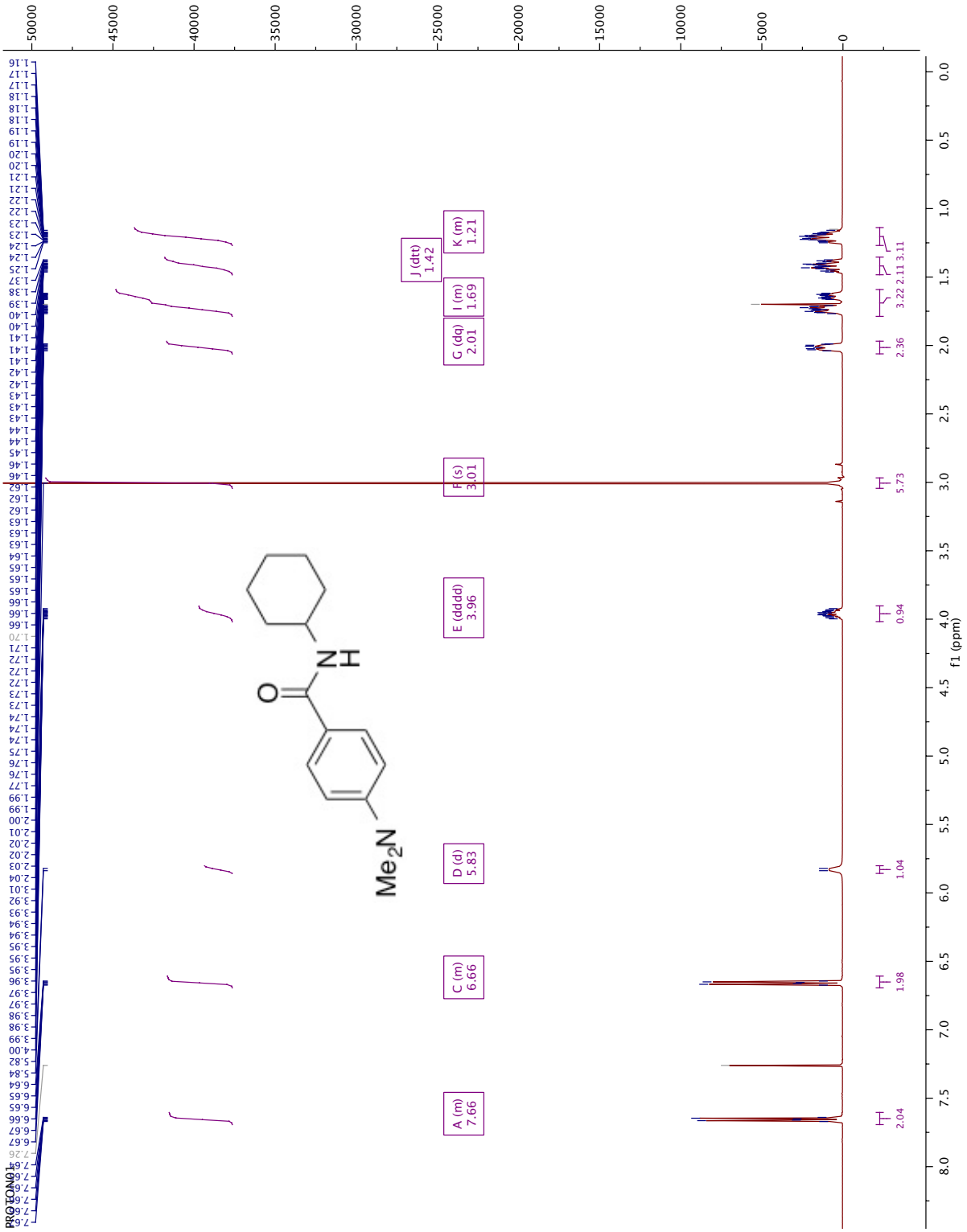


Figure A1.25. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **31b**.

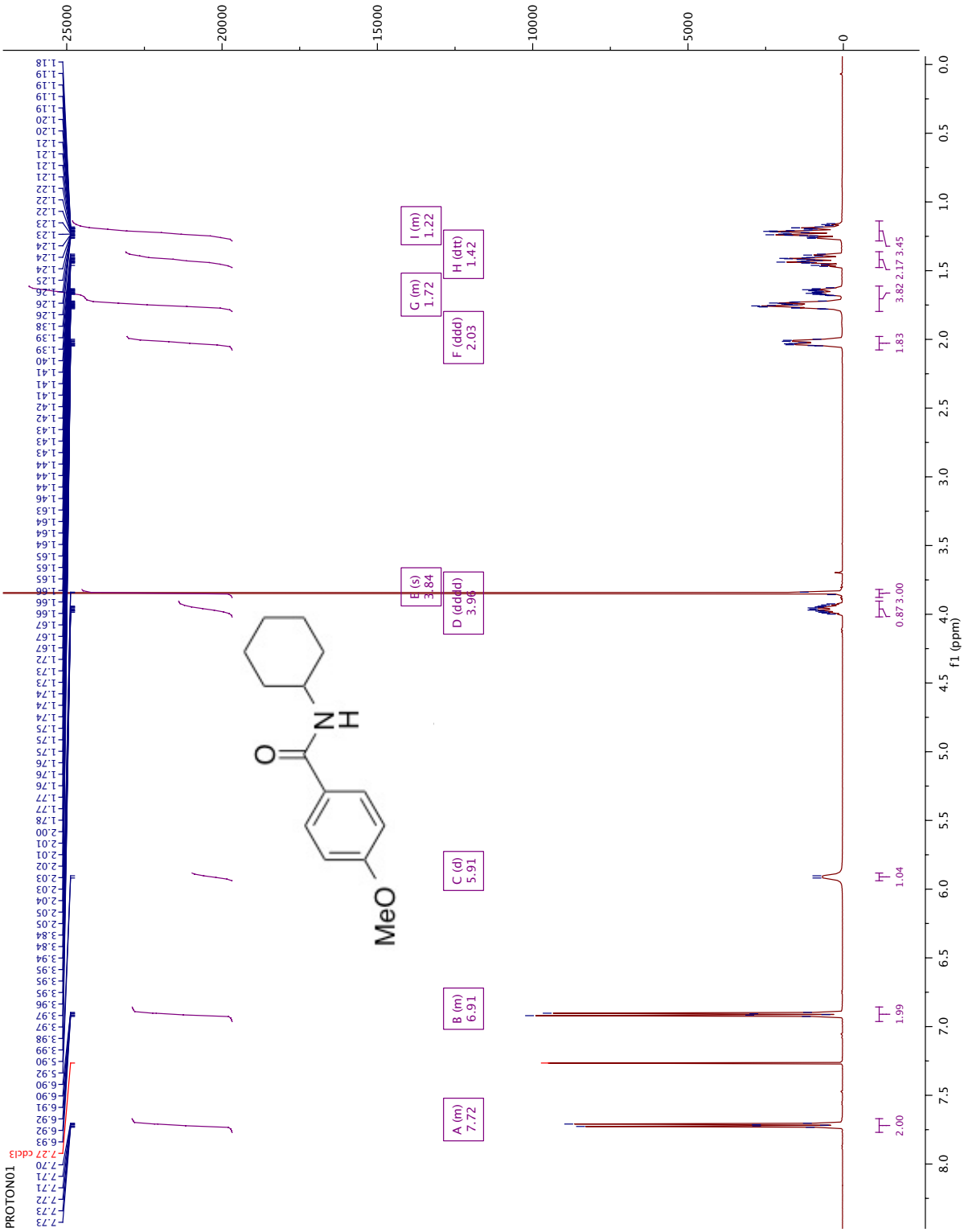


Figure A1.26. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **31c**.

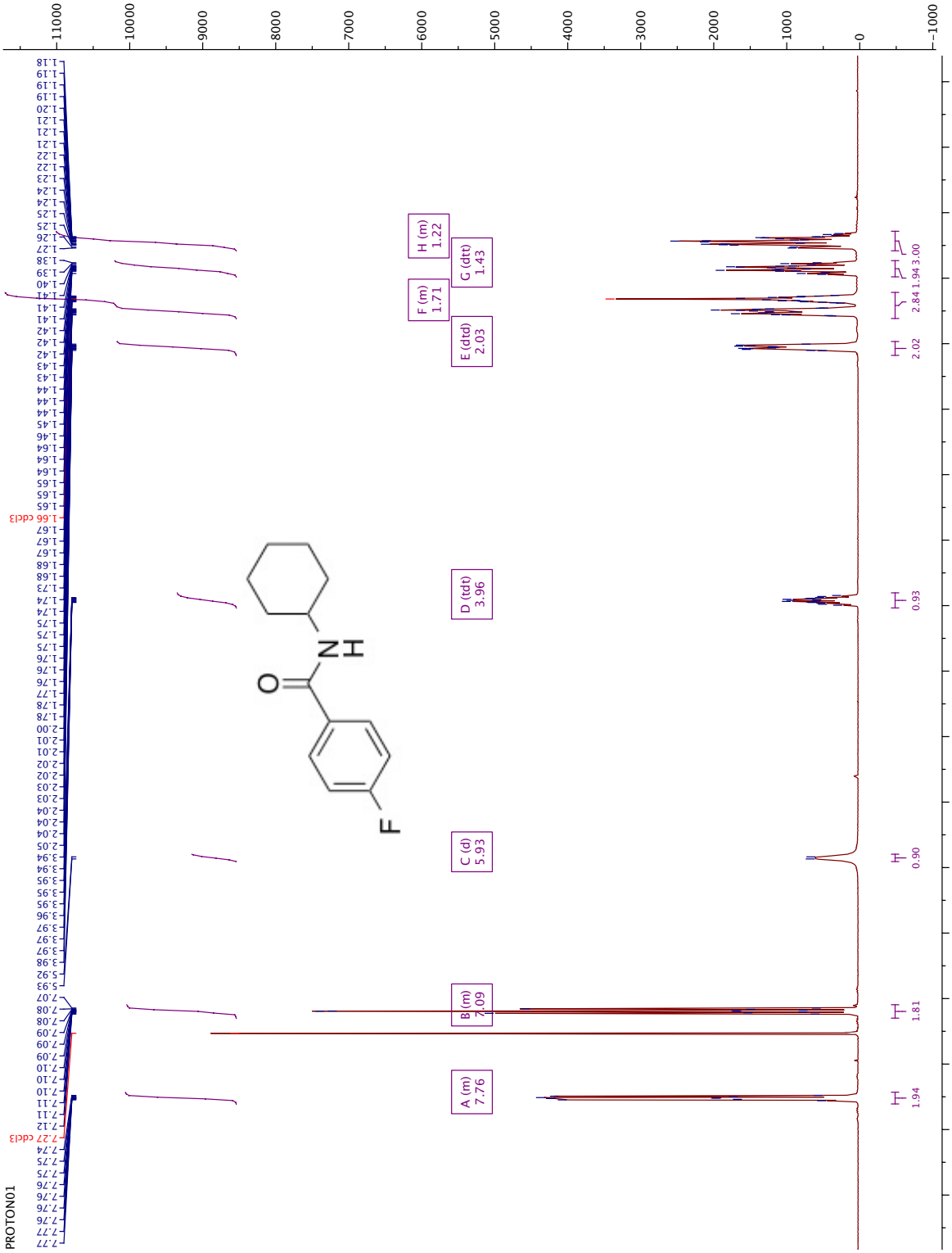


Figure A1.27. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **31d**.

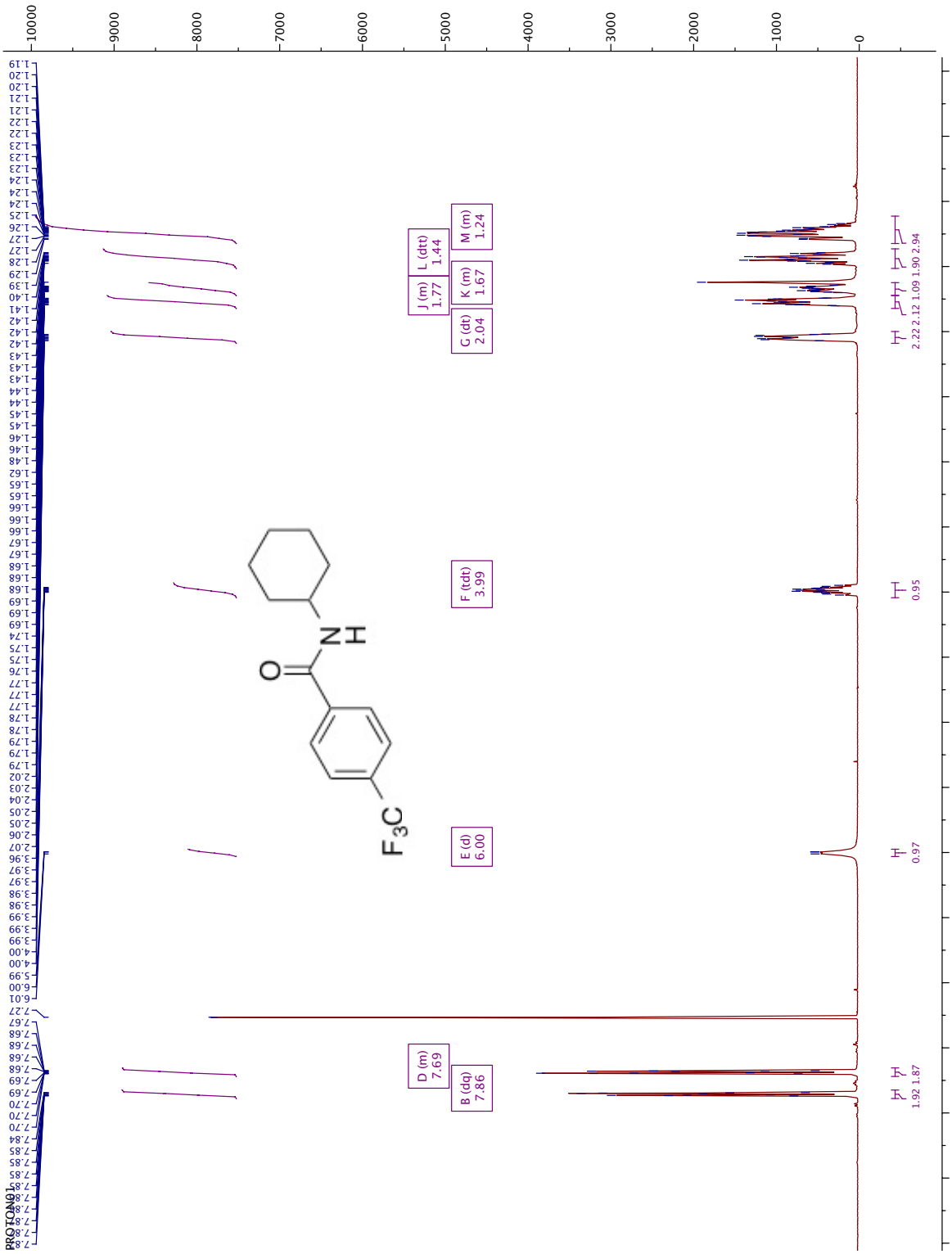


Figure A1.28. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **31e**.

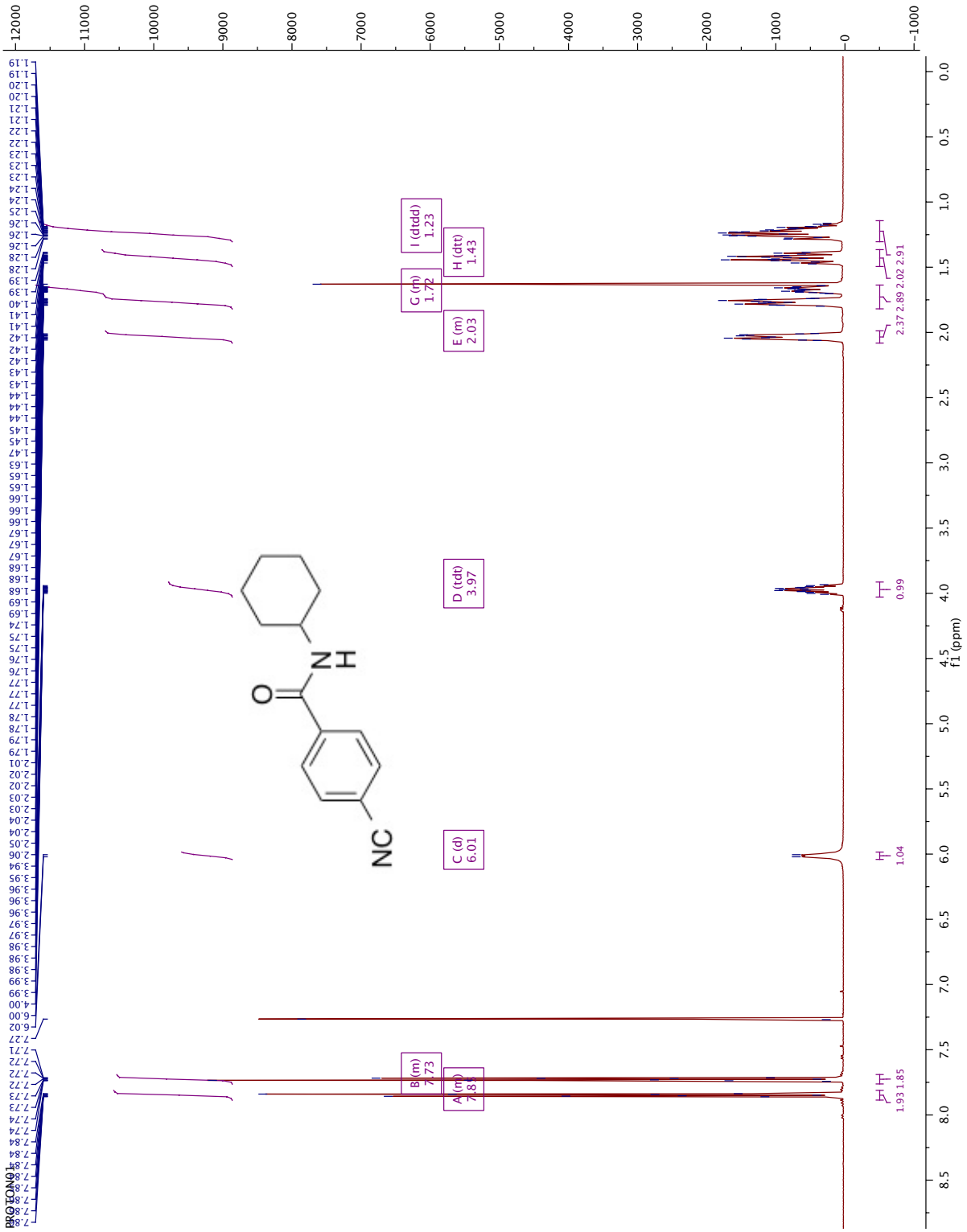


Figure A1.29. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **31f**.

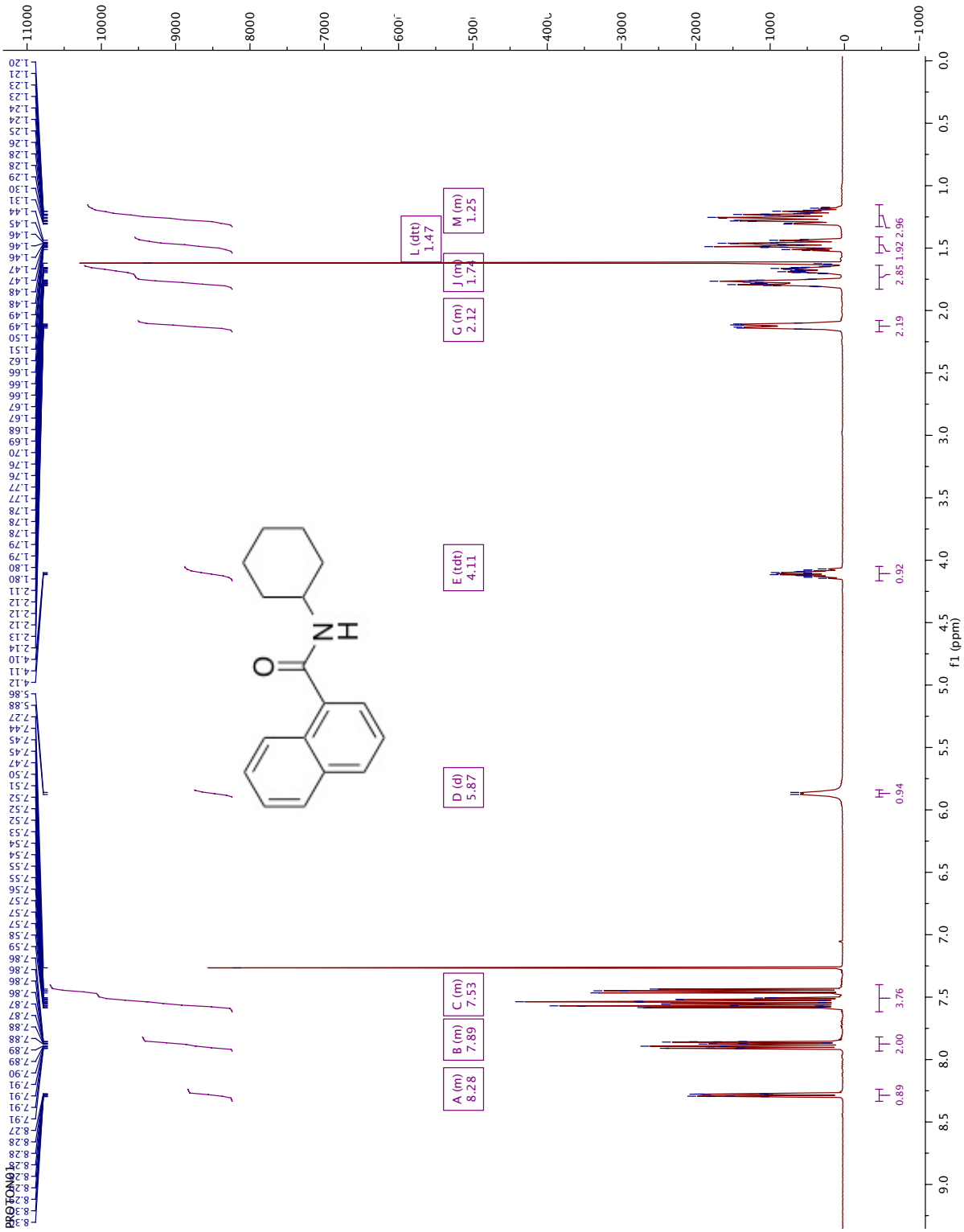


Figure A1.30. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **31g**.

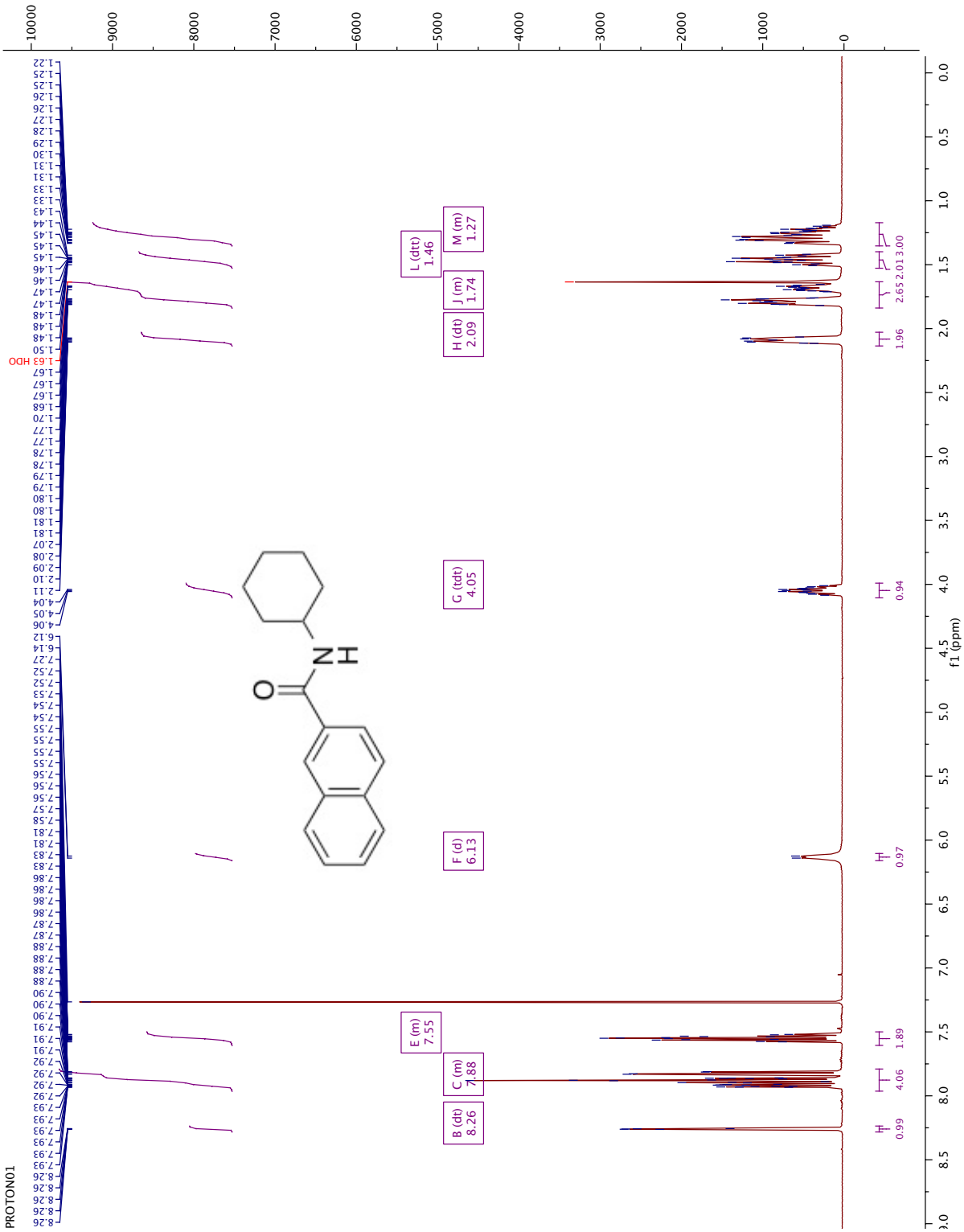


Figure A1.31. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **31h**.

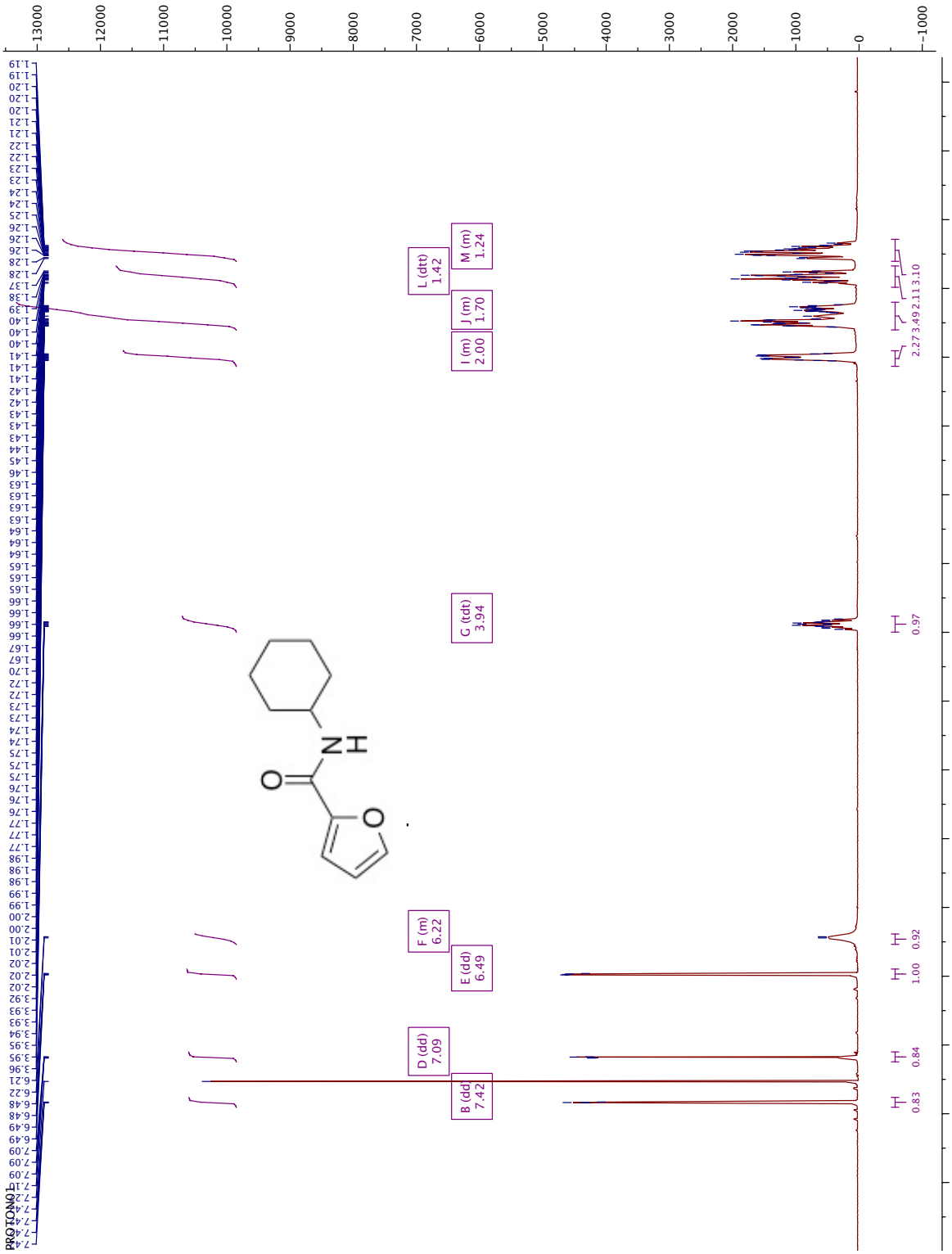


Figure A1.32. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **31i**.

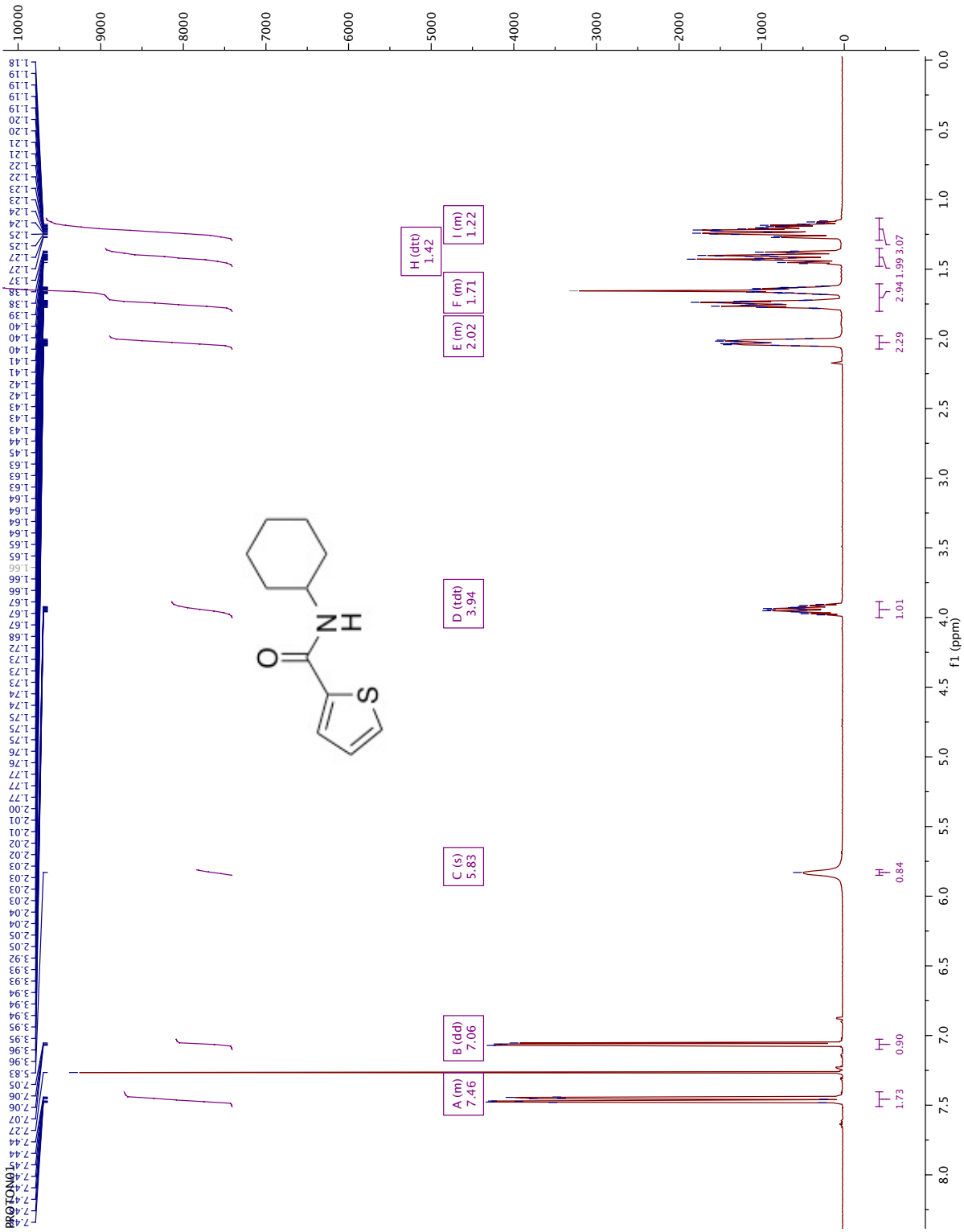


Figure A1.33. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **31j**.

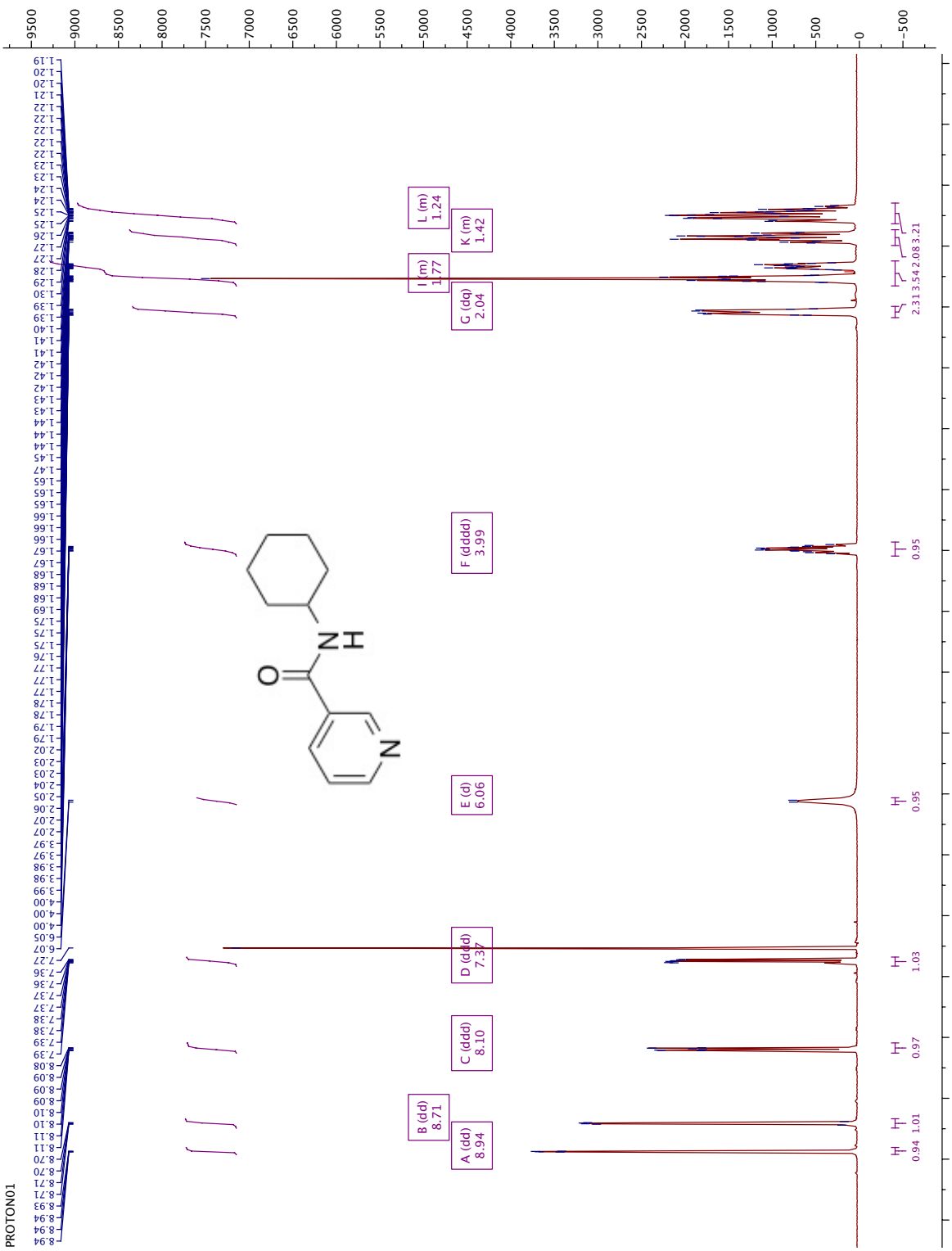


Figure A1.34. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **31k**.

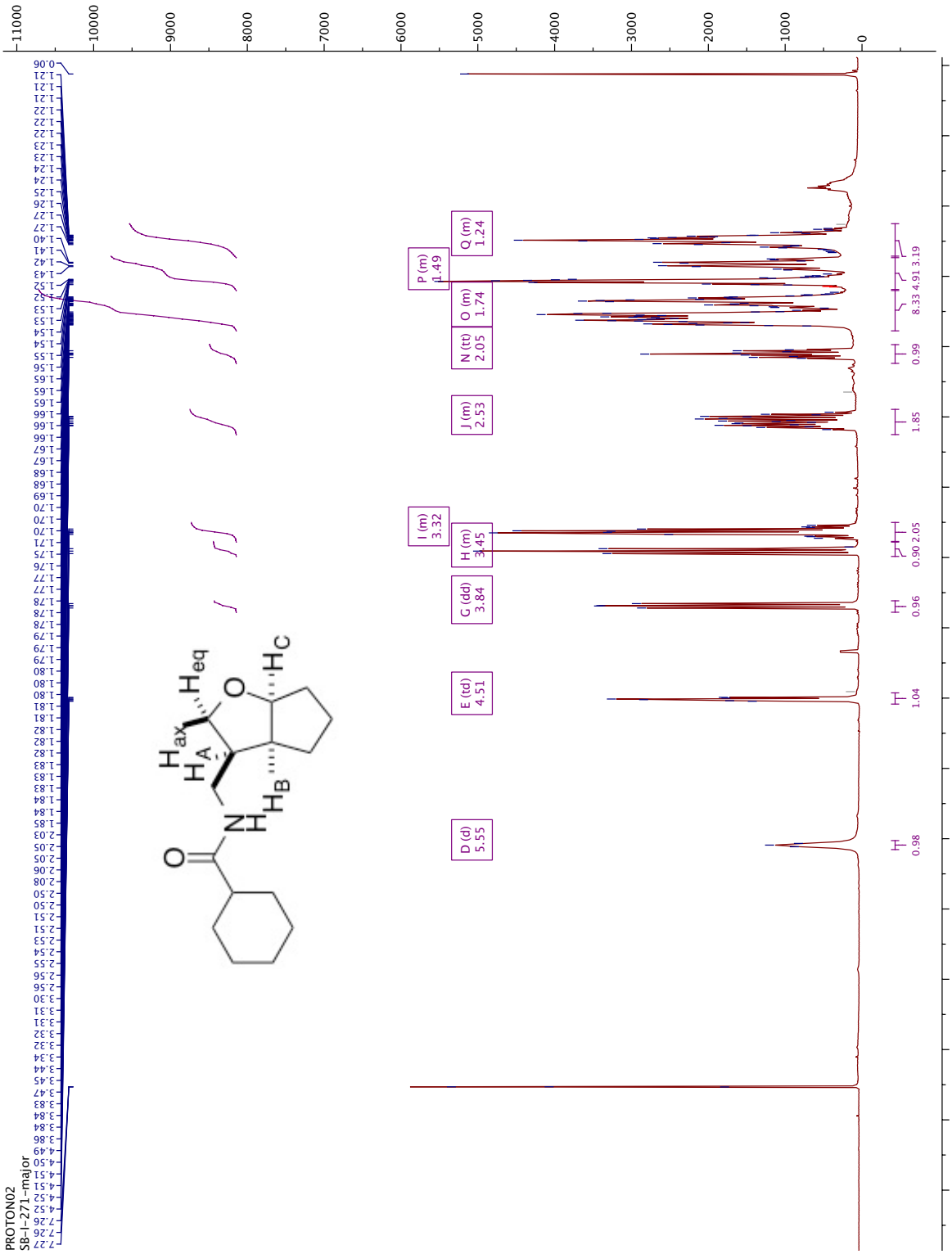


Figure A1.35. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **38a**.

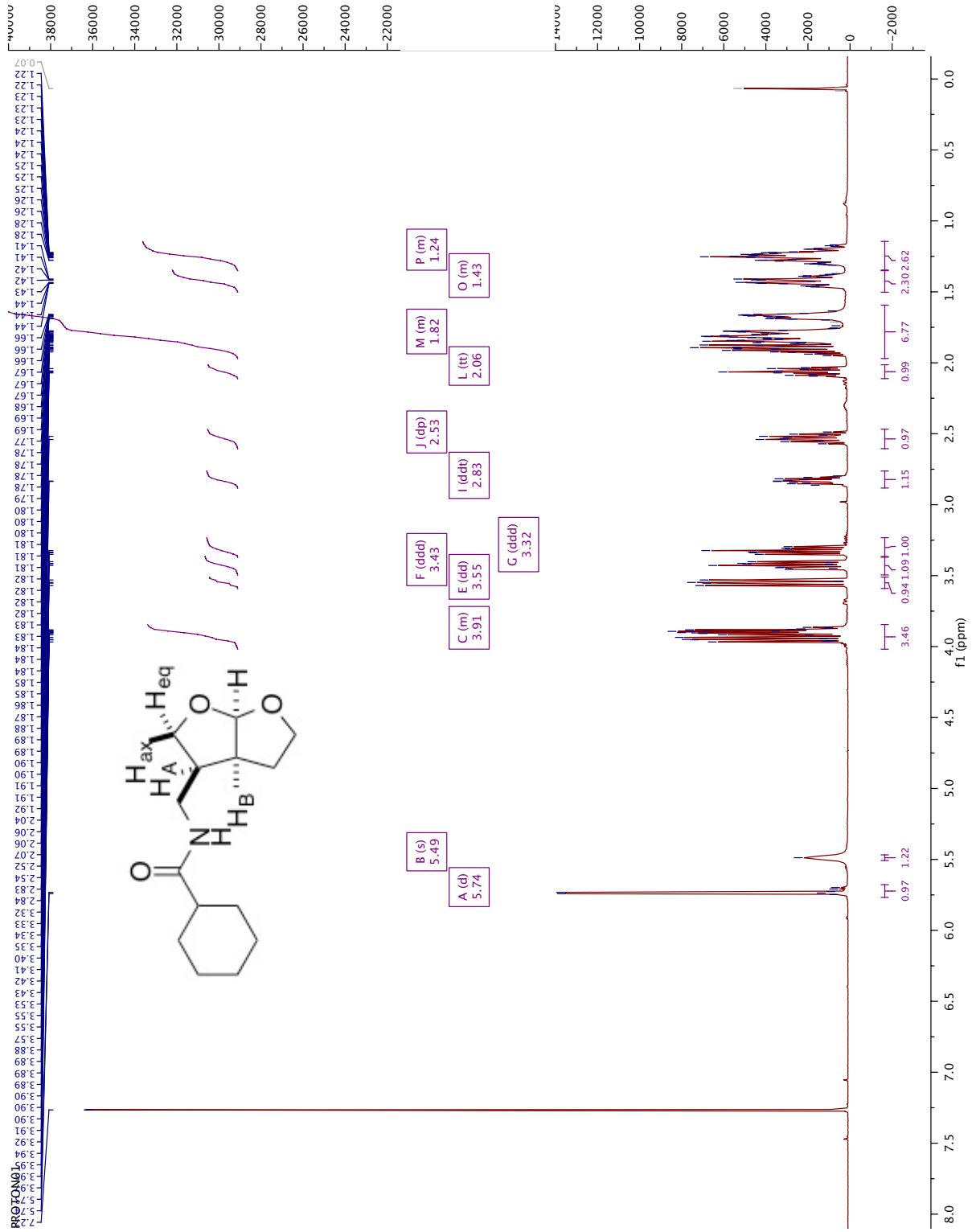
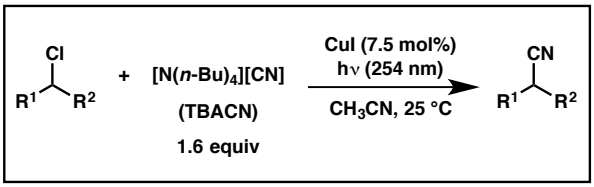


Figure A1.36. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **38b**.

CHAPTER 2

Photoinduced, Copper-Catalyzed Carbon–Carbon Bond Formation: Cyanation of Unactivated Secondary Alkyl Chlorides at Room Temperature[†]



[†]This work was performed in collaboration with Tanvi Ratani and was partially adapted from the publication: Ratani, T.S.[‡]; Bachman, S.[‡]; Fu, G.C.; Peters, J.C. *J. Am. Chem. Soc.* **2015**, *137*, 13902–13907. [‡]Contributed equally

2.1 Introduction

Nitriles are a prevalent class of molecules in pharmaceuticals,[1] natural products,[2] and industrial processes.[3] The unique properties of the nitrile group include minimal steric demand, high polarization, and ability to act as a hydrogen bond acceptor and a hydroxyl or carboxyl isostere.[4] In addition, nitriles provide a versatile synthetic handle for transformations such as α-alkylation, [5] α-arylation, [6] conjugate addition, [7] cycloaddition,[8] hydration,[9] hydrolysis,[10] hydrogenation,[11] and cyclopropanation.[12]

With respect to the conversion of alkyl halides to the corresponding nitriles, S_N2-type conditions are generally employed for primary and secondary halides.[13] Radical cyanation of alkyl halides has been described but is limited to alkyl iodides.[14] While some transition metal-mediated cyanation reactions of benzylic alkyl chlorides have been developed,[15] there have been no similar advancements for unactivated alkyl halides.

Nucleophilic substitution of unactivated primary and secondary alkyl halides by cyanide typically requires the use of phase transfer reagents,[13a−f] cyanide-impregnated inorganic solid support systems,[13g−i] or the combination of elevated temperature and polar solvent.[13k−m] These conditions often result in competitive or even exclusive elimination of unactivated secondary alkyl halides.[13e, 13f, 13n] There are only limited examples of room temperature S_N2 reactions of unactivated secondary alkyl bromides and iodides,[13n] and there are virtually no examples of unactivated secondary alkyl chlorides undergoing the transformation at temperatures less than 75 °C.[13o]

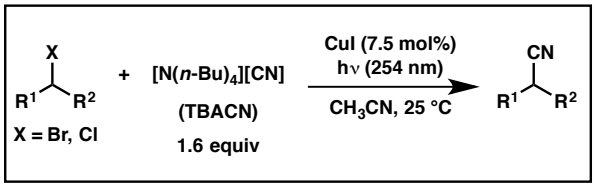
A potential alternative to direct nucleophilic substitution of unactivated secondary alkyl halides is the transition metal-catalyzed cross coupling of cyanide with alkyl

halides. Thus, we were interested in developing such a method for the cyanation of challenging S_N2 substrates, for example unactivated secondary alkyl chlorides.

We have recently reported photoinduced, copper-catalyzed cross-couplings of unactivated alkyl iodides and bromides with nitrogen nucleophiles.[16] We postulate that these and related processes involve one electron reduction of the electrophile by a photoexcited copper–nucleophile species.[16, 17] Achieving the desired cyanation reaction could therefore be dependent on the ability of a relevant copper−cyanide complex to undergo photoexcitation and subsequently reduce a secondary unactivated alkyl chloride.[18]

Prior to this study, we were uncertain as to whether either carbon nucleophiles or unactivated secondary alkyl chlorides would be appropriate coupling partners in these photoinduced, copper-catalyzed bond-forming processes; herein we report that the room temperature C−C coupling of cyanide and a variety of unactivated secondary alkyl halides can indeed be achieved (Scheme 2.1).

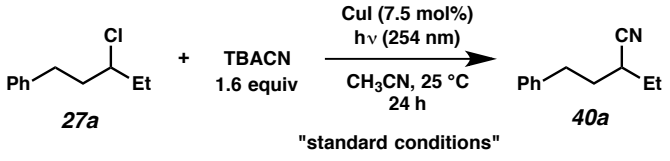
Scheme 2.1 Photoinduced, Cu-catalyzed cyanation of unactivated secondary alkyl halides



2.2 Results and Discussion

After optimization of various reaction parameters, cyanation of an unactivated secondary alkyl chloride (**27a**) proceeded in good yield using tetrabutylammonium cyanide (TBACN) as the cyanide source, CuI as the precatalyst, and 15-watt UVC compact fluorescent light bulbs[19] as the irradiation source (Table 2.1, entry 1).[20] This C−C coupling was efficient even at 0 °C (entry 2). By contrast, in the absence of CuI and light, efficient cyanation required heating to 92 °C (82% yield after 24 h).

Table 2.1 Effect of reaction parameters on photoinduced, Cu-catalyzed cyanation



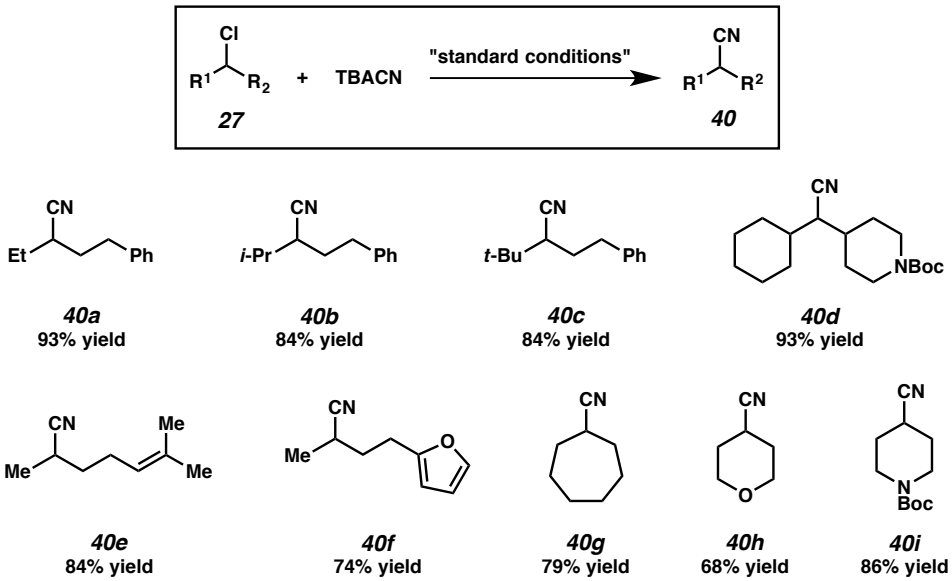
entry	change from the "standard conditions"	yield (%)[a]
1	none	88
2	0 °C (60 h)	85
3	no CuI	<1
4	no hν	<1
5	no CuI and no hν	<1
6	hν (photoreactor at 254 nm)	86
7	hν (photoreactor at 300 nm)	15
8	hν (photoreactor at 350 nm)	12
9	CuBr, instead of CuI	42
10	CuCl, instead of CuI	48
11	15 mol% CuCl, instead of CuI	66
12	Cu_2O, instead of CuI	32
13	$CuCl_2$, instead of CuI	44
14	$Cu(OTf)_2$, instead of CuI	42
15	Cu nanopowder (60-80 nm), instead of CuI	23
16	NaCN, instead of TBACN	25
17	KCN, instead of TBACN	27
18	$K_4[Fe(CN)_6]$, instead of TBACN	<1
19	CuI (5.0 mol%)	83
20	CuI (2.5 mol%)	78
21	CuI (1.0 mol%)	47
22	12 h	82
23	1.2, instead of 1.6, equiv TBACN	75
24	under an atmosphere of air, instead of nitrogen	32
25	0.1 equiv H_2O added	87

[a]All data are the average of two or more experiments. The yield was determined through GC analysis with the aid of a calibrated internal standard.

In the absence of light, copper, or both light and copper, formation of the nitrile (**40a**) was not observed (Table 1, entries 3−5), and longer wavelengths of light resulted in dramatically reduced reaction efficiency (entries 7 and 8). Substituting CuI by other copper(I) halides furnished the product in significantly lower yield (entries 9 and 10), but a moderate yield could be obtained when the amount of CuCl was increased to 15 mol% (entry 11). Copper(I) oxide, copper(II) sources, and copper nanopowder provide inferior results compared to CuI (entries 12−15). Metal cyanides were significantly less effective cyanide sources than TBACN (entries 16–18). The amount of CuI precatalyst could be reduced to as low as 2.5 mol% and still effect cross-coupling in good yield (entries 19, 20), and even 1 mol% CuI afforded a moderate yield of the nitrile (entry 21). Using a smaller excess of TBACN or shorter reaction time decreased the amount of product formation slightly (entries 22 and 23). The reaction is sensitive to air (entry 24) but not highly sensitive to water (entry 25).

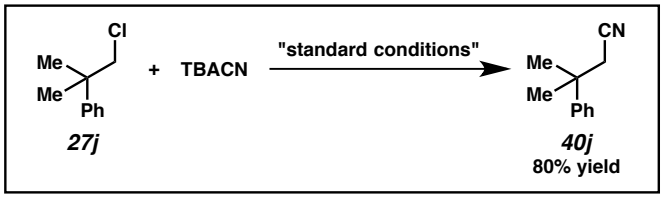
A variety of unactivated secondary alkyl chlorides can be converted to the corresponding nitriles at room temperature (Scheme 2.2). Both acyclic (**40a–f**) and cyclic (**40g–i**) alkyl chlorides are good coupling partners in this cyanation reaction. The reaction is tolerant of sterically demanding alkyl side chains, including isopropyl and *tert*-butyl groups at the α-position (**40b** and **40c**). Even when both alkyl substituents are α-branched, C−C bond formation occurs in good yield (**40d**). The reaction is compatible with various functional groups, including a Boc-protected amine (**40d** and **40i**), a trisubstituted olefin (**40e**), a furan (**40f**), and an ether (**40h**). This method is also effective for a gram-scale (1.3 g of product) synthesis of **40a** in 94% yield.

Scheme 2.2 Scope with respect to unactivated secondary alkyl chlorides

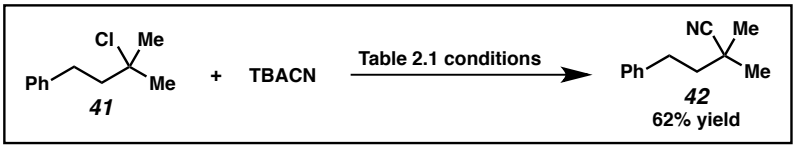


Under our standard reaction conditions, a particularly poor S_N2-substrate, neophyl chloride (**27j**), can be cross-coupled in good yield (Scheme 2.3), whereas under thermal conditions (DMF, 80 °C), <1% of the product was observed after 24 h. In addition, an unactivated tertiary alkyl chloride (**41**) can be converted to the nitrile in moderate yield, generating a quaternary center (Scheme 2.4). In a competition experiment, a tertiary alkyl chloride undergoes cyanation more rapidly than a secondary alkyl chloride (Scheme 2.5), which could be because the tertiary alkyl chloride has a greater propensity to undergo one electron reduction.[18]

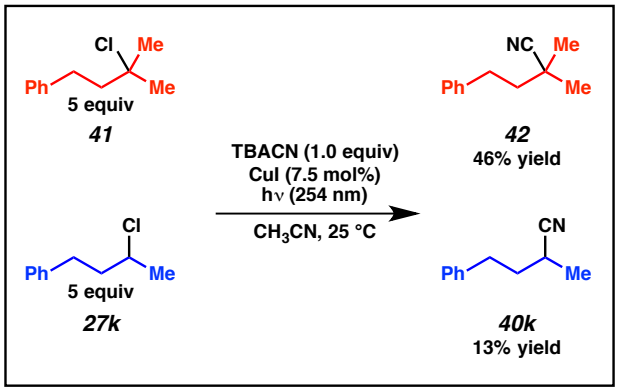
Scheme 2.3 Cyanation of neophyl chloride



Scheme 2.4 Cyanation of a tertiary chloride

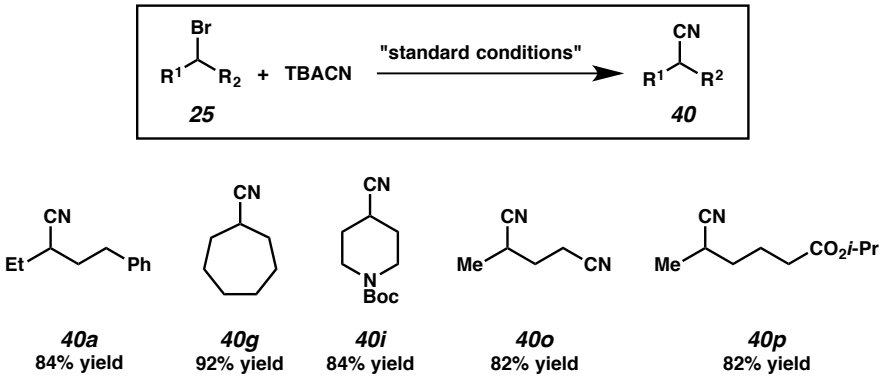


Scheme 2.5 Relative reactivity of a tertiary and secondary alkyl chloride

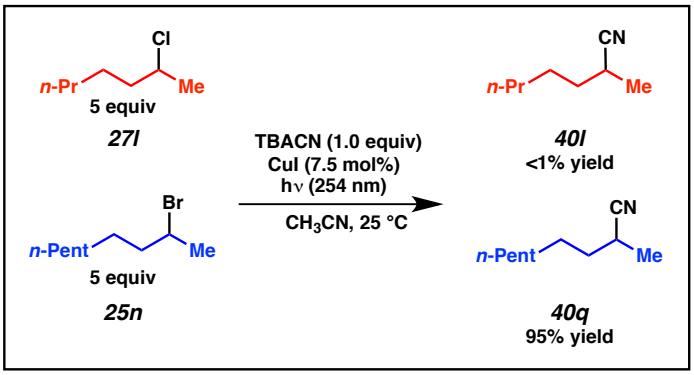


Without modification of the reaction conditions, a variety of unactivated secondary alkyl bromides are also effective in this photoinduced, copper-catalyzed cyanation reaction (Scheme 2.6). Although a background cyanation of alkyl bromides is observed in the absence of copper and light, the catalyzed process is at least five times faster. The reaction is compatible with both cyclic and acyclic alkyl bromides and tolerates a Boc-protected amine (**40i**), a nitrile (**40o**), and an ester (**40p**). An unactivated secondary alkyl bromide (**25n**) can be selectively coupled in the presence of a secondary alkyl chloride (**27l**, Scheme 2.7).

Scheme 2.6 Scope with respect to unactivated secondary alkyl bromides

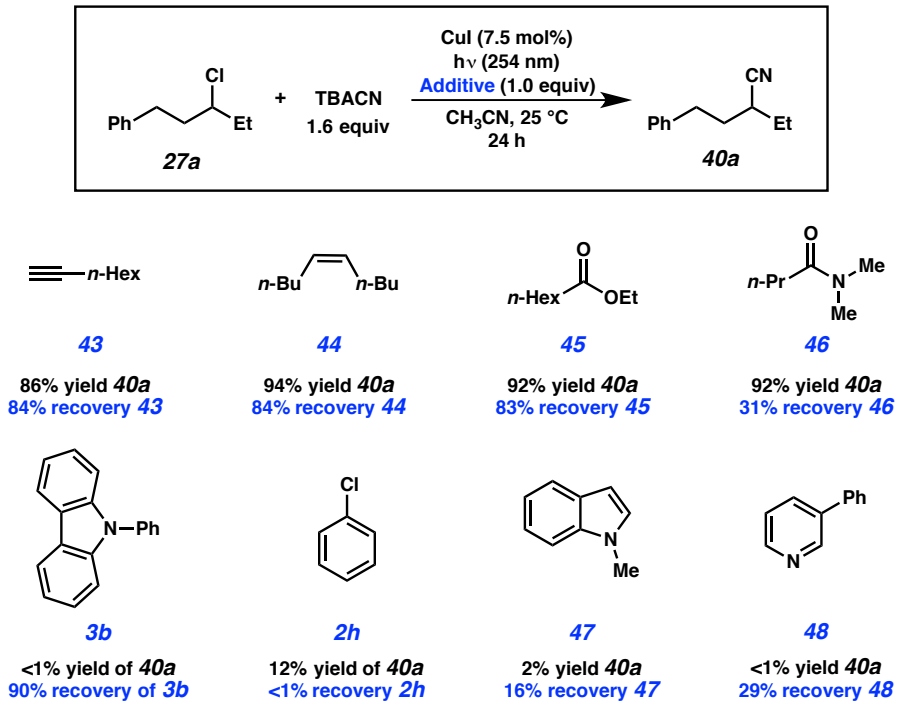


Scheme 2.7 Relative reactivity of a secondary alkyl chloride and bromide



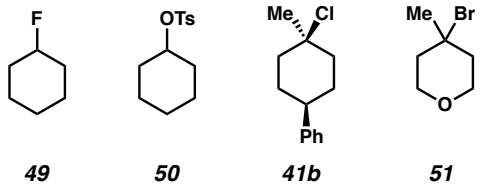
We further explored the functional group compatibility of this reaction with a robustness screen (Scheme 2.8).[21] This photoinduced, Cu-catalyzed cyanation is compatible with a terminal alkyne (**43**), an internal olefin (**44**), and an ester (**45**). A tertiary amide (**46**) was recovered in poor yield but did not inhibit product formation, whereas *N*-phenyl carbazole (**3b**) could be recovered in good yield but resulted in no observable C−C coupling. An aryl chloride (**2h**) and nitrogen-containing heterocycles **47** and **48** were not tolerated.

Scheme 2.8 Additional exploration of functional group tolerance



With respect to the limitations of this methodology, in preliminary studies, we were not able to couple a secondary alkyl fluoride (**49**) or tosylate (**50**) using these conditions (Figure 2.1). Although we have established the first example of a tertiary alkyl halide as a coupling partner in these photoinduced, Cu-catalyzed processes, this is not yet a general method. Attempts to couple other tertiary halides (e.g. **41b** and **51**) resulted in low conversion of the electrophile even at increased reaction times.

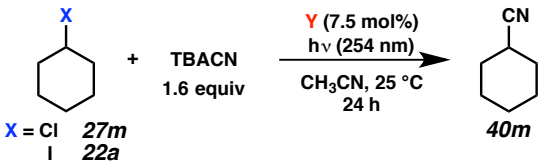
Figure 2.1 Examples of unsuccessful substrates



2.3 Mechanistic studies

During reaction optimization, it was observed that the use of CuI as a precatalyst resulted in significantly better yield than CuCl or CuBr (Table 2.1, entries 9−11). This effect is also pronounced when chlorocyclohexane (**27m**) is used as the electrophile (Table 2.2, entries 1 and 2). In addition, the combination of both catalytic CuCl and TBAI provides dramatically better results than iodide-free conditions (Table 2.2, entry 3).

Table 2.2 Increased reaction efficiency in the presence of an iodide source



entry	X	Y	yield (%)[a]
1	Cl	CuCl	34
2	Cl	CuI	82
3	Cl	CuCl + TBAI	78
4	I	CuI	57
5	Cl	TBAI	5
6	I	none	26
7	I	none (no light)	<1
8	Cl	$[Cu(CN)_2]TBA$	26
9	Cl	$[Cu(CN)_2]TBA$ + TBAI	76

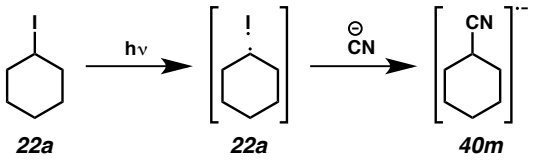
[a]The yield was determined through GC analysis with the aid of a calibrated internal standard (average of two runs).

One possible rationalization for this effect could be the *in situ* conversion of the alkyl chloride to a catalytic amount of the alkyl iodide, which undergoes cyanation more rapidly. When the analogous alkyl iodide (**22a**) is used as the substrate, a modest yield of the corresponding nitrile (**40m**) is observed (Table 2.2, entry 4), which could be due to unproductive consumption of the alkyl iodide in the presence of UV light.[22] Thus, generation of only a catalytic amount of the alkyl iodide, followed by rapid conversion to the nitrile, could be advantageous compared to cyanation of an alkyl iodide substrate. A

catalytic amount of tetrabutylammonium iodide, instead of CuI, does not result in significant product formation (entry 5), indicating that copper is still essential to the overall transformation.

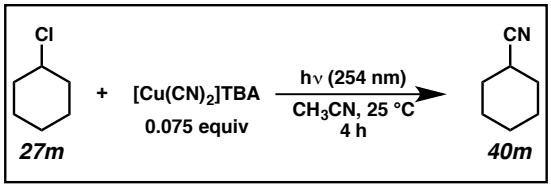
When iodocyclohexane (**22a**) is used as a substrate in the absence of copper, a small amount of the nitrile is generated, whereas no product formation is observed in the absence of both light and copper (Table 2.2, entries 6 and 7). This suggests that, if the alkyl iodide is generated *in situ*, conversion to the nitrile by S_N2 substitution is not a major pathway. However, direct photolysis of the alkyl iodide and recombination with cyanide could still be a minor contributor (Scheme 2.9).

Scheme 2.9 Possible contribution of a photoinduced, Cu-free pathway for cyanation of an in situ-generated alkyl iodide



In light of our working hypothesis that the photoexcitation of a relevant Cu−Nu complex is critical in these photoinduced, Cu-catalyzed coupling reactions, we also attempted the cyanation of chlorocyclohexane (**27m**) using catalytic $[Cu(CN)_2]TBA$[23] instead of CuI. Consistent with our previous observations, these iodide-free conditions result in a low yield of C−C coupling (Table 2.2, entry 8), but the combination of catalytic $[Cu(CN)_2]TBA$ and TBAI results in restored reaction efficiency (entry 9). Similarly, in the absence of additional TBACN, this copper−cyanide complex reacts stoichiometrically with chlorocyclohexane to generate the nitrile in low yield, whereas a 1:1 ratio of $[Cu(CN)_2]TBA$ and TBAI results in efficient cyanation (Scheme 2.10).

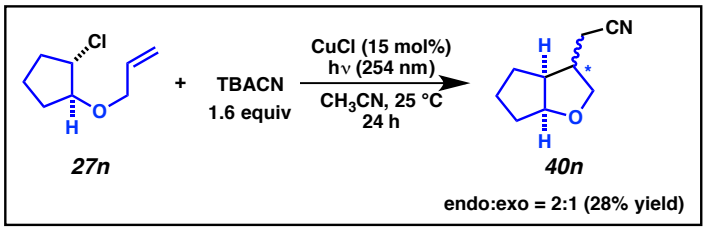
Scheme 2.10 Chemical competence of a copper–cyanide complex



Above conditions: 14% yield
0.075 equiv. TBAI added: 98% yield
(yields based on copper)

In order to gain insight into the possible intermediacy of alkyl radicals in this C−C coupling, we subjected alkyl chloride **27n** to our iodide-free reaction conditions (Scheme 2.11). While we are aware that iodide-free conditions are not optimal for generating high yields of product (Table 2.1, entry 1 vs. 11) this ensures that alkyl radical formation does not occur by halogen exchange followed by direct photolysis.[24] The alkyl chloride reacts to form exclusively the cyclized/coupled product with a diastereoselectivity consistent with that observed for radical cyclization of the corresponding alkyl bromide.[25]

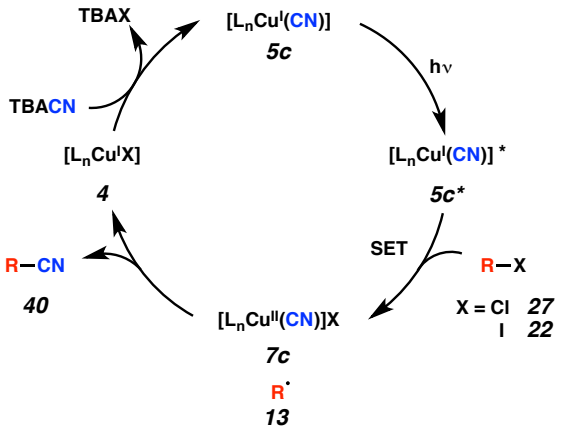
Scheme 2.11 Cyclization and coupling of an alkyl chloride bearing a pendant olefin



Our preliminary mechanistic observations are thus consistent with the intermediacy of alkyl radical intermediates and suggest the intermediacy of $[Cu(CN)_2]TBA$ and alkyl iodides. A possible mechanism for this photoinduced, copper-catalyzed cyanation is shown in Figure 2.2. The copper(I)−halide complex (**4**) reacts

with TBACN to yield a copper−cyanide complex (**5c**). Irradiation of **5c** and SET to the alkyl halide result in the formation of a copper(II) species (**7c**) and an alkyl radical. Reaction of the alkyl radical with the copper(II)−cyanide complex then generates the nitrile (**40**) and regenerates a copper(I)−halide complex (**4**).

Figure 2.2 Cyclization and coupling of an alkyl chloride bearing a pendant olefin



2.4 Conclusion

We have developed, to the best of our knowledge, the first method for the transition metal-catalyzed cyanation of unactivated secondary alkyl halides. This photoinduced, copper-catalyzed cyanation reaction uses a commercially available and inexpensive light source and proceeds efficiently at room temperature. Under a single set of conditions, unactivated secondary alkyl chlorides and bromides, including sterically hindered substrates, undergo C−C bond formation in generally good yield. For the first time, we have established that both carbon nucleophiles, as well as unactivated secondary alkyl chlorides, are appropriate coupling partners in photoinduced, copper-catalyzed bond forming processes. Initial mechanistic observations are consistent with the formation of an alkyl radical intermediate during the course of the reaction.

2.5 Experimental Procedures

2.5.1 General Information

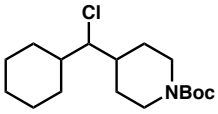
The following reagents were purchased and used as received: Copper(I) iodide (Aldrich; 99.999%), tetrabutylammonium cyanide (Aldrich; 95%), 4-chlorotetrahydro-*2H*-pyran (Acros), *tert*-butyl 4-bromopiperidine-1-carboxylate (Aldrich), (1-chloro-2-methylpropan-2-yl)benzene (Aldrich). CH_3CN was deoxygenated and dried by sparging with nitrogen followed by passage through an activated alumina column (S. G. Water) prior to use.

^{1}H and ^{13}C spectroscopic data were collected on a Varian 500 MHz spectrometer or a Varian 400 MHz spectrometer at ambient temperature. GC analyses were carried out on an Agilent 6890 series system with an HP-5 column (length 30 m, I.D. 0.25 mm). All photoreactions were carried out in oven-dried quartz test tubes or a quartz flask, under an inert atmosphere, with the use of 15W, 120V, UV Germicidal Compact Lamps (Norman Lamps, Inc.) and a Fantec 172 x 150 x 51 mm Dual Ball Bearing AC high speed fan (240 CFM).

2.5.2 Preparation of Materials

These procedures have not been optimized.

General Procedure for the Chlorination of Secondary Alcohols. To an oven-dried 500-mL round-bottom flask containing a stir bar was added dry CH_2Cl_2 (0.2 M) and the alcohol (1.00 equiv). The mixture was cooled to 0 °C in an ice bath, and PPh_3 (1.00 equiv) and NCS (1.00 equiv) were slowly added in turn. The round-bottom flask was then capped with a rubber septum and placed under a nitrogen atmosphere with the use of a needle attached to a vacuum manifold. The reaction was allowed to warm to room temperature as it remained in the water bath. After 5−8 hours, the reaction was quenched by the addition of saturated aqueous NH_4Cl. The organic phase was separated, dried over anhydrous Na_2SO_4, and then concentrated carefully by rotary evaporator (careful concentration was important for volatile products). The product was purified by column chromatography (hexanes or Et_2O/hexanes).

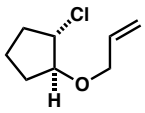


***tert*-Butyl 4-(chloro(cyclohexyl)methyl)piperidine-1-carboxylate (27d, Figure 2.2)**.

Cyclohexylmagnesium chloride (2.0 M in Et_2O; 23.5 mL, 46.9 mmol) was added dropwise to a solution of *tert*-butyl 4-formylpiperidine-1-carboxylate (10.0 g, 46.9 mmol) in THF (230 mL) at −78 °C (dry ice/acetone bath). The resulting solution was allowed to warm to room temperature while remaining in the acetone bath and stirring for 6 h. Next, the reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL), and the resulting mixture was extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated by rotary evaporator. The residue was passed through a plug of silica gel (60% Et_2O/hexanes), and the resulting filtrate was concentrated by rotary evaporator and used in the next step without further purification.

The title compound was prepared according to the general procedure for chlorination of secondary alcohols, using the unpurified *tert*-butyl 4-

(cyclohexyl(hydroxy)methyl)piperidine-1-carboxylate. The product was purified by flash chromatography (5%→30% Et_2O/hexanes). Off-white solid (1.05 g, 7% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 – 4.12 (m, 2H), 3.58 (dd, 1H, *J* = 6.8, 5.5 Hz), 2.73 – 2.62 (m, 2H), 1.96 – 1.75 (m, 5H), 1.73 – 1.65 (m, 2H), 1.65 – 1.57 (m, 2H), 1.47 (s, 9H), 1.45 – 1.17 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 79.8, 74.7, 40.8, 39.9, 31.5, 28.8, 26.61, 26.60, 26.2; ATR-IR (neat) 2928, 2848, 1682, 1445, 1417, 1368, 1284, 1265, 1246, 1163, 1121, 773 cm^{-1}; HRMS (ESI) *m/z* $[M–(isobutylene)–(CO_2)+H]^+$ calcd for $C_{13}H_{23}ClNO_2$: 216.1519, found: 216.1504.

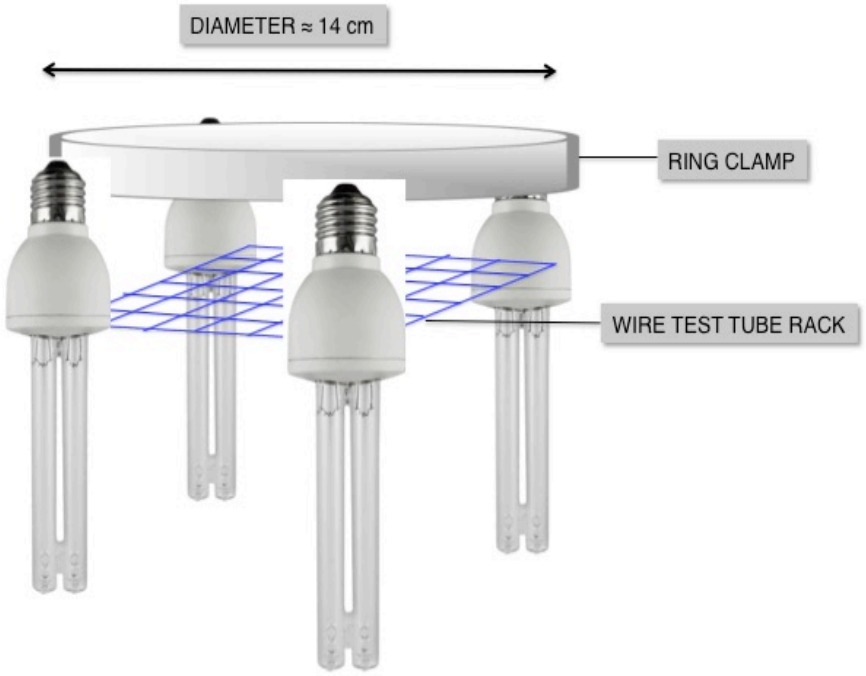


(1*S*,2*S*)-1-(allyloxy)-2-chlorocyclopentane (27n, Figure 2.12). This procedure was adapted from a literature procedure.[26] Cyclopentene (5.00 mL, 56.6 mmol) was added dropwise over 30 minutes to a suspension of *N*-chlorosuccinimide (7.60 g, 56.6 mmol) in dry CH_2Cl_2 (100 mL). The resulting suspension was stirred at room temperature for 2 h, and then allyl alcohol (7.70 mL, 113.2 mmol) was added dropwise by syringe pump over 2 h. The reaction mixture was stirred at room temperature for 6 h. The solvent was then removed by rotary evaporator, and the crude residue was poured into a separatory funnel containing H_2O (100 mL). The mixture was extracted with Et_2O (3 x 50 mL), and the combined organic phases were washed with water (50 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporator. The product was purified by column chromatography (100% hexanes). Clear oil (695 mg, 4% yield).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddt, 1H, *J* = 17.2, 10.4, 5.6 Hz), 5.28 (dq, 1H, *J* = 17.2, 1.7 Hz), 5.21 – 5.16 (m, 1H), 4.22 – 4.17 (m, 1H), 4.08 – 4.01 (m, 2H), 4.00 – 3.95 (m, 1H), 2.27 – 2.06 (m, 2H), 1.93 – 1.72 (m, 3H), 1.70 – 1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 117.0, 87.2, 70.5, 63.1, 34.2, 29.9, 21.4; ATR-IR (neat) 3100, 2960, 2861, 1651, 1463, 1433, 1341, 1256, 1082, 1013, 922, 793, 702, 655, 560 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_8H_{13}ClO$: 160.1, found: 160.1.

2.5.3 Photoinduced, Copper-Catalyzed Cyanation Reactions

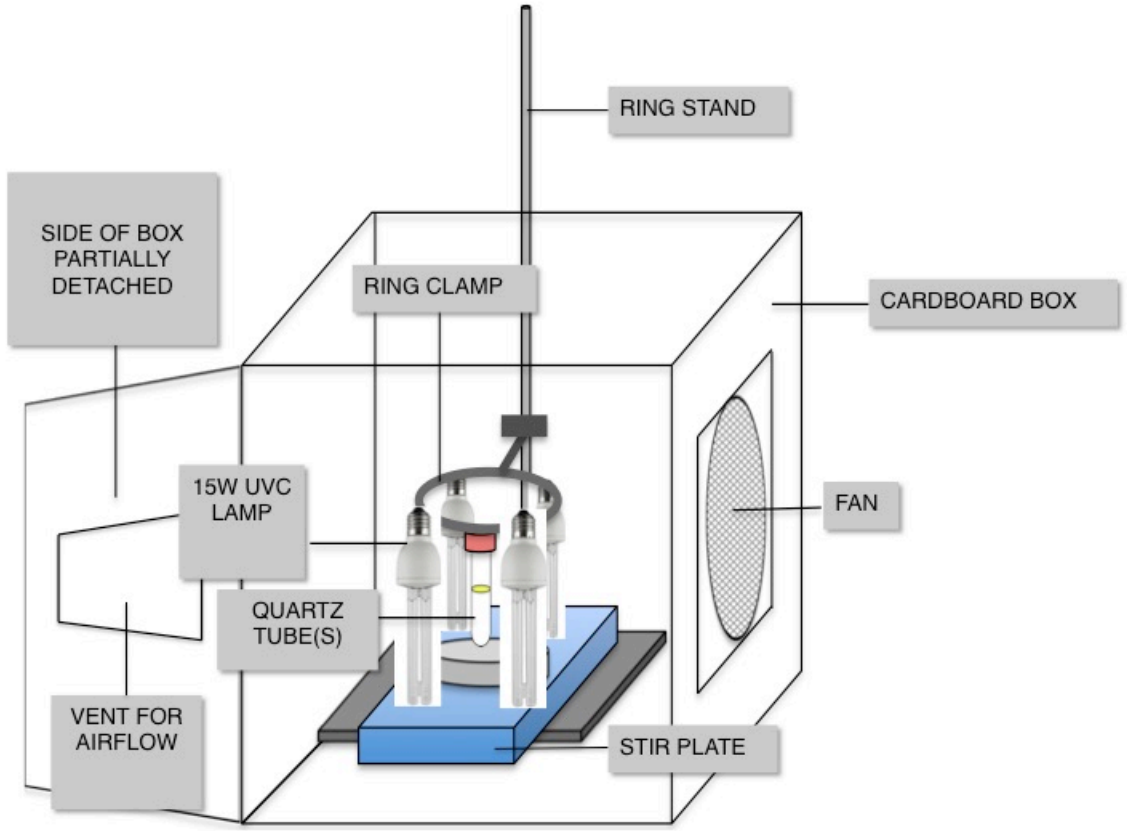
Four 15W, 120V UV germicidal CFL lamps were suspended from a ring clamp on a ring stand (Figure 2.13). The lamps were spaced approximately evenly around the circumference of the ring clamp with a diameter of ≈14 cm. In a second clamp below the ring clamp, the top of a wire test tube rack was placed interior to the lamps.

Figure 2.13 Placement of CFL lamps around a ring clamp



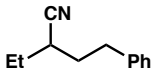
A stir plate covered in aluminum foil was placed underneath the lamps (Figure 2.14). A cardboard box lined with aluminum foil was placed over the ring stand, lamps, and stir plate. In one side of the cardboard box, a space was cut out, and a 172 x 150 x 51 mm high-speed (240 CFM) fan was fitted into this side of the box. In the side of the box directly opposite the fan, a vent was cut out. Photoreactions were carried out in quartz tubes or a quartz flask placed approximately in the center of the wire test tube rack, ensuring that the reaction vessels were within the line of airflow from the fan and did not directly touch the lamps.

Figure 2.14 Placement of cardboard box and fan relative to the CFL lamps



General Procedure. Inside a glovebox, an oven-dried 20-mL vial equipped with a stir bar was charged with TBACN (***Caution: Highly toxic!*** 601 mg, 2.24 mmol, 1.60 equiv) and capped with a PTFE-lined pierceable cap sealed with electrical tape. The vial was then removed from the glovebox, and MeCN (18.0 mL) was added via syringe. The mixture was vigorously stirred for 5 minutes, resulting in a colorless suspension. An oven-dried 20-mL quartz tube containing a stir bar was then charged with CuI (20.0 mg, 0.105 mmol, 0.0750 equiv), capped with a rubber septum, and sealed with electrical tape. The tube was evacuated and backfilled with nitrogen three times (through a needle attached to a vacuum manifold), and the TBACN suspension was added via syringe, followed by the electrophile (1.40 mmol, 1.00 equiv) via microsyringe (if the electrophile is a solid, then it was added immediately after the addition of CuI). The reaction mixture was stirred vigorously for one minute. The quartz tube was then removed from the manifold, and the resulting mixture was then stirred vigorously and irradiated in the

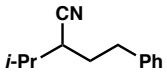
center of four, 15W UVC compact fluorescent light bulbs at room temperature for 24 h. Then, the reaction mixture was transferred to a 100-mL round-bottom flask and concentrated using a rotary evaporator in a well-ventilated fume hood. The residue was purified by column chromatography.



2-Ethyl-4-phenylbutanenitrile (40a, Figure 2.2) [1126479-77-3]. The title compound was prepared according to the General Procedure from (3-chloropentyl)benzene (258 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (5→10% EtOAc/hexanes). Tan oil. First run: 223 mg (92% yield). Second run: 227 mg (94% yield).

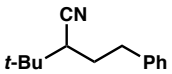
Gram-scale reaction. In a glove box, a 200-mL quartz flask was charged with TBACN (3.44 g, 12.8 mmol, 1.60 equiv), and a stir bar was added. The flask was capped with a rubber septum and sealed with electrical tape and then removed from the glove box. A separate 250-mL flask (borosilicate glass) was then charged with CuI (114 mg, 0.600 mmol, 0.0750 equiv), and acetonitrile (110 mL) and a stir bar were added. The CuI/acetonitrile solution was vigorously stirred for 1 minute under a nitrogen atmosphere, after which the homogeneous solution was cannula transferred to the quartz flask containing TBACN. Then, the alkyl chloride (1.50 mL, 8.00 mmol, 1.00 equiv) was added via syringe. The reaction mixture was irradiated for 24 h using the same irradiation set-up as described above. Then, the stir bar was removed, and the reaction mixture was concentrated using a rotary evaporator in a well-ventilated fume hood. The product was purified by column chromatography on silica gel (10→20% Et_2O/hexanes). Tan oil. 1.30 g, 94% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 2H), 7.26 – 7.19 (m, 3H), 2.91 (ddd, 1H, *J* = 14.2, 9.1, 5.2 Hz), 2.75 (ddd, 1H, *J* = 13.8, 8.9, 7.6 Hz), 2.49 – 2.43 (m, 1H), 2.01 – 1.92 (m, 1H), 1.90 – 1.82 (m, 1H), 1.70 – 1.63 (m, 2H), 1.09 (t, 3H, *J* = 7.4 Hz).

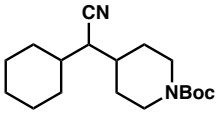


2-Isopropyl-4-phenylbutanenitrile (40b, Figure 2.2). The title compound was prepared according to the General Procedure from (3-chloro-4-methylpentyl)benzene (280 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (5→10% EtOAc/hexanes). Tan oil. First run: 220 mg (84% yield). Second run: 222 mg (85% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 2H), 7.25 – 7.19 (m, 3H), 2.92 (ddd, 1H, *J* = 14.1, 9.2, 5.0 Hz), 2.71 (ddd, 1H, *J* = 13.8, 9.0, 7.6 Hz), 2.40 (dt, 1H, *J* = 10.4, 5.0 Hz), 1.96 (dddd, 1H, *J* = 13.9, 10.7, 9.0, 5.0 Hz), 1.89 – 1.78 (m, 2H), 1.08 – 1.02 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.6, 129.0, 128.8, 126.7, 121.3, 38.8, 33.9, 32.2, 30.4, 21.3, 19.0; ATR-IR (neat) 3028, 2964, 2932, 2900, 2874, 2236, 1603, 1497, 1455, 1391, 1373, 751, 701 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_{13}H_{17}N$: 187.1, found 187.2.

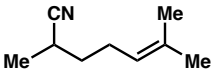


3,3-Dimethyl-2-phenethylbutanenitrile (40c, Figure 2.2). The title compound was prepared according to the General Procedure from (3-chloro-4,4-dimethylpentyl)benzene (95.0 μL, 0.440 mmol) as the electrophile. The product was purified by column chromatography on silica gel (hexanes→10% Et_2O/hexanes). Yellow oil. First run: 75.0 mg (85% yield). Second run: 74.1 mg (84% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.29 (m, 2H), 7.25 – 7.20 (m, 3H), 3.01 (ddd, 1H, *J* = 13.8, 8.9, 4.9 Hz), 2.67 (dt, 1H, *J* = 13.8, 8.5 Hz), 2.25 (dd, 1H, *J* = 11.6, 4.3 Hz), 1.92 – 1.79 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7, 129.0, 128.8, 126.7, 121.6, 43.8, 34.5, 33.3, 29.5, 27.8; ATR-IR (neat) 3028, 2963, 2938, 2875, 2233, 1602, 1498, 1488, 1472, 1463, 1456, 1399, 1375, 1368, 1317, 1233, 1030, 770, 757, 701 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_{14}H_{19}N$: 201.2, found 201.2.



***t*-Butyl 4-(cyano(cyclohexyl)methyl)piperidine-1-carboxylate (40d, Figure 2.2)**. The title compound was prepared according to the General Procedure from tert-butyl 4-(chloro(cyclohexyl)methyl)piperidine-1-carboxylate (442 mg, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (20→60% Et_2O/hexanes). Off-white solid. First run: 392 mg (91% yield). Second run: 406 mg (95% yield).

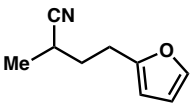
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 – 4.06 (m, 2H), 2.74 – 2.61 (m, 2H), 2.22 (t, 1H, J = 7.0 Hz), 1.91 – 1.84 (m, 2H), 1.83 – 1.72 (m, 3H), 1.72 – 1.56 (m, 4H), 1.45 (s, 9H), 1.36 – 1.10 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 120.3, 80.0, 44.9, 36.0, 35.0, 32.0, 30.7, 29.8, 26.4, 26.3, 26.1; ATR-IR (neat) 2930, 2923, 2855, 2236, 1692, 1452, 1431, 1365, 1285, 1235, 1179, 1135 cm^{-1}; HRMS (ESI) *m/z* $[M–(isobutylene)–(CO_2)+H]^+$ calcd for $C_{13}H_{23}N_2$: 207.1861, found: 207.1848.



2,6-Dimethylhept-5-enenitrile (40e, Figure 2.2) [54088-65-2].

The title compound was prepared according to the General Procedure from 6-chloro-2-methylhept-2-ene (205 mg, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (4% Et_2O/hexanes). Clear oil. First run: 161 mg (84% yield). Second run: 164 mg (85% yield).

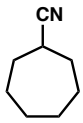
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 – 5.02 (m, 1H), 2.67 – 2.55 (m, 1H), 2.23 – 2.11 (m, 2H), 1.72 – 1.62 (m, 7H), 1.59 – 1.49 (m, 1H), 1.33 – 1.29 (m, 3H).



4-(Furan-2-yl)-2-methylbutanenitrile (40f, Figure 2.2) [71649-14-4]. The title compound was prepared according to the General Procedure from 2-(3-chlorobutyl)furan (221 mg, 1.40 mmol) as the electrophile. The product was purified by column

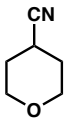
chromatography on silica gel (10% Et_2O/hexanes). Yellow oil. First run: 160 mg (77% yield). Second run: 148 mg (71% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.30 (m, 1H), 6.31 – 6.27 (m, 1H), 6.08 – 6.04 (m, 1H), 2.92 – 2.75 (m, 2H), 2.67 – 2.56 (m, 1H), 2.01 – 1.85 (m, 2H), 1.36 – 1.31 (m, 3H).



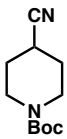
Cycloheptanecarbonitrile (40g, Figure 2.2) [32730-85-1]. The title compound was prepared according to the General Procedure from chlorocycloheptane (193 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (10→20% EtOAc/hexanes). Clear oil. First run: 138 mg (80% yield). Second run: 135 mg (78% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.79 (tt, 1H, J = 7.9, 4.6 Hz), 1.96 – 1.82 (m, 4H), 1.80 – 1.70 (m, 2H), 1.67 – 1.53 (m, 6H).



Tetrahydro-2*H*-pyran-4-carbonitrile (40h, Figure 2.2) [4295-99-2]. The title compound was prepared according to the General Procedure from 4-chlorotetrahydro-2*H*-pyran (152 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (10→50% EtOAc/hexanes). Tan oil. First run: 103 mg (66% yield). Second run: 111 mg (71% yield).

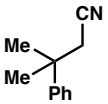
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 – 3.85 (m, 2H), 3.62 – 3.56 (m, 2H), 2.86 (tt, 1H, J = 8.2, 4.3 Hz), 1.96 – 1.90 (m, 2H), 1.89 – 1.82 (m, 2H).



***t*-Butyl 4-cyanopiperidine-1-carboxylate (40i, Figure 2.2) [91419-52-2]**. The title compound was prepared according to the General Procedure from *tert*-butyl 4-

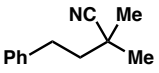
chloropiperidine-1-carboxylate (277 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (40→70% Et_2O/hexanes). Off-white solid. First run: 262 mg (89% yield). Second run: 248 mg (84% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 – 3.60 (m, 2H), 3.37 – 3.29 (m, 2H), 2.83 – 2.76 (m, 1H), 1.91 – 1.83 (m, 2H), 1.82 – 1.74 (m, 2H), 1.47 – 1.43 (m, 9H).



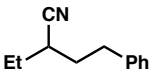
3-Methyl-3-phenylbutanenitrile (40j, Figure 2.3) [17684-33-2]. The title compound was prepared according to the General Procedure from (1-chloro-2-methylpropan-2-yl)benzene (226 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (10→20% EtOAc/hexanes). Tan oil. First run: 184 mg (83% yield). Second run: 174 mg (78% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 4H), 7.28 – 7.24 (m, 1H), 2.62 (s, 2H), 1.52 (s, 6H).



2,2-Dimethyl-4-phenylbutanenitrile (42, Figure 2.4) [75490-38-9]. The title compound was prepared according to the General Procedure from (3-chloro-3-methylbutyl)benzene (256 mg, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (hexanes→10% Et_2O/hexanes). Clear oil. First run: 149 mg (61% yield). Second run: 153 mg (63% yield).

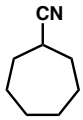
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.25 – 7.18 (m, 3H), 2.85 – 2.76 (m, 2H), 1.88 – 1.78 (m, 2H), 1.42 (s, 6H).



2-Ethyl-4-phenylbutanenitrile (40a, Figure 2.6) [1126479-77-3]. The title compound was prepared according to the General Procedure from (3-bromopentyl)benzene (259 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on

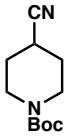
silica gel (10→20% Et_2O/hexanes). Tan oil. First run: 202 mg (83% yield). Second run: 205 mg (84% yield).

The ^{1}HNMR spectrum of the product was identical to that of **40a**, Figure 2.2.



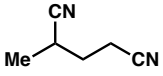
Cycloheptanecarbonitrile (40g, Figure 2.6) [32730-85-1]. The title compound was prepared according to the General Procedure from bromocycloheptane (208 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (20→40% Et_2O/hexanes). Yellow oil. First run: 157 mg (91% yield). Second run: 160 mg (93% yield).

The ^{1}HNMR spectrum of the product was identical to that of **40g**, Figure 2.2.



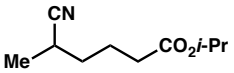
***t*-Butyl 4-cyanopiperidine-1-carboxylate (40i, Figure 2.6) [91419-52-2]**. The title compound was prepared according to the General Procedure from *tert*-butyl 4-bromopiperidine-1-carboxylate (276 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (40→80% Et_2O/hexanes). Off-white solid. First run: 242 mg (82% yield). Second run: 250 mg (85% yield).

The ^{1}HNMR spectrum of the product was identical to that of **40i**, Figure 2.2.



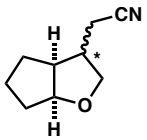
2-Methylpentanedinitrile (40o, Figure 2.6) [4553-62-2]. The title compound was prepared according to the General Procedure from 4-bromopentanenitrile (162 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (40→80% Et_2O/hexanes). Yellow oil. First run: 124 mg (82% yield). Second run: 122 mg (81% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.87 – 2.79 (m, 1H), 2.65 – 2.51 (m, 2H), 2.02 – 1.91 (m, 2H), 1.42 – 1.39 (m, 3H).



Isopropyl 5-cyanohexanoate (40p, Figure 2.6). The title compound was prepared according to the General Procedure from isopropyl 5-bromohexanoate (237 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (20→60% Et_2O/hexanes). Yellow oil. First run: 211 mg (82% yield). Second run: 208 mg (81% yield).

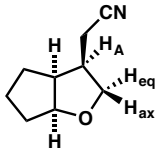
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 – 4.96 (m, 1H), 2.66 – 2.58 (m, 1H), 2.32 (t, 2H, J = 7.2 Hz), 1.89 – 1.70 (m, 2H), 1.69 – 1.55 (m, 2H), 1.34 – 1.31 (m, 3H), 1.23 (d, 6H, J = 6.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 122.8, 68.0, 34.0, 33.4, 25.5, 22.5, 22.0, 18.0; ATR-IR (neat) 2982, 2940, 2878, 2239, 1729, 1457, 1420, 1375, 1340, 1294, 1274, 1253, 1181, 1146, 1110 cm^{-1}; MS (EI) *m/z* $[M - (C_3H_7O)]^+$ calcd for $C_7H_{10}NO$: 124.1, found: 124.1.



2-((3a*S*,6a*S*)-Hexahydro-2*H*-cyclopenta[*b*]furan-3-yl)acetonitrile (40n, Figure 2.12). In an N_2-atmosphere glovebox, a 20-mL vial was charged with TBACN (266 mg, 0.991 mmol) and a stir bar. To this vial was added 8.3 mL of MeCN, and the solution was stirred vigorously for 5 minutes. Next, CuCl (9.33 mg) was weighed into an oven-dried 20-mL quartz test tube, and the TBACN solution was added to the tube. To this suspension was added trans-1-(allyloxy)-2-chlorocyclopentane (100 mg, 0.622 mmol), and the tube was capped with a rubber septum and sealed with electrical tape. The solution was stirred for another 3 minutes, and was then brought out of the glovebox and irradiated in the center of four, 15 watt UVC compact fluorescent light bulbs at room temperature` for 24 h. The ratio of diastereomers was determined by GC analysis of the unpurified reaction mixture. The product was isolated as a mixture of diastereomers by

column chromatography (5% Et_2O/hexanes→Et_2O). Clear liquid. First run: 25 mg (27%, 2.3:1). Second run: 28 mg (30%, 2.1:1).

Major diastereomer. The major diastereomer could be purified by preparative HPLC (ZORBAX RX-SIL column, 9.4 x 250 mm, 20% EtOAc/hexanes).



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (td, 1H, J = 5.8, 2.5 Hz), 3.97 – 3.89 (m, 1H), 3.48 (t, 1H, J = 8.3 Hz), 2.75 – 2.62 (m, 2H), 2.46 – 2.33 (m, 2H), 1.87 – 1.58 (m, 5H), 1.53 – 1.41 (m, 1H); 2D NOESY (400 MHz, $CDCl_3$) δ [4.55 (H_C), 3.91 (H_{eq})], [4.55 (H_C), 2.68 (H_A/H_B)], [3.91 (H_{eq}), 4.55 (H_C)], [3.91 (H_{eq}), 2.68 (H_A/H_B)], [2.68 (H_A/H_B), 3.91 (H_{eq})], [2.68 (H_A/H_B), 4.55 (H_C)]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.9, 86.5, 71.5, 46.1, 39.6, 34.2, 26.2, 25.7, 16.7; ATR-IR (neat) 2955, 2869, 2246, 1483, 1468, 1451, 1426, 1339, 1307, 1261, 1205, 1154, 1080, 1043, 960, 950, 922, 901, 806, 649 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_9H_{13}NO$: 151.1, found: 151.1.

1.6 Notes and Citations

(1) (a) Fleming, F.F.; Yao, L.; Ravikumar, P.C.; Funk, L.; Shook, B.C. *J. Med. Chem.* **2010**, *53*, 7902–7917. (b) Jones, L.H.; Summerhill, N.W.; Swain, N.A.; Mills, J.E. *Med. Chem. Comm.* **2010**, *1*, 309–318.

(2) Fleming, F.; *Nat. Prod. Rep.* **1999**, *16*, 597–606.

(3) Velankar, H.; Clarke, K. G.; Preez, R. d.; Cowan, D. A.; Burton, S. G. *Trends Biotechnol.* **2010,** *28*, 561–569.

(4) Fleming, F. F.; Zhang, Z. *Tetrahedron* **2005,** *61*, 747–789.

(5) (a) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002,** *58*, 1–23; (b) Fleming, F. F.; Gudipati, S. *Eur. J. Org. Chem.* **2008,** 5365–5374.

(6) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003,** *36*, 234–245.

(7) Fleming, F. F.; Wang, Q. Z. *Chem. Rev.* **2003,** *103*, 2035–2077.

(8) Varela, J. A.; Saá, C. *Chem. Rev.* **2003,** *103*, 3787–3802.

(9) a) Garcia-Alvarez, R.; Crochet, P.; Cadierno, V. *Green Chem.* **2013,** *15*, 46–66. (b) Ahmed, T. J.; Knapp, S. M. M.; Tyler, D. R. *Coord. Chem. Rev.* **2011,** *255*, 949–974.

(10) Kukushkin, V. Y.; Pombeiro, A. J. L. *Inorg. Chim. Acta* **2005,** *358*, 1–21.

(11) Gomez, S.; Peters, J. A.; Maschmeyer, T. *Adv. Synth. Catal.* **2002,** *344*, 1037–1057.

(12) Wolan, A.; Six, Y. *Tetrahedron* **2010,** *66*, 15–61.

(13) a) Tamami, B.; Ghasemi, S. *J. Iran. Chem. Soc.* **2008,** *5*, S26–S32. (b) Shimizu, S.; Kito, K.; Sasaki, Y.; Hirai, C., *Chem. Comm.* **1997**, 1629–1630. (c) Chiappe, C.; Pieraccini, D.; Saullo, P. *J. Org. Chem.* **2003,** *68*, 6710–6715. (d) Tomoi, M.;

Ford, W. T., *J. Am. Chem. Soc.* **1980,** *102*, 7140–7141. (e) Cook, F. L.; Bowers, C. W.; Liotta, C. L. *J. Org. Chem.* **1974,** *39*, 3416–3418. (f) Thoman, C. J.; Habeeb, T. D.; Huhn, M.; Korpusik, M.; Slish, D. F., *J. Org. Chem.* **1989,** *54*, 4476–4478. (g) Regen, S. L.; Quici, S.; Liaw, S.-J. *J. Org. Chem.* **1979,** *44*, 2029–2030. (h) Sukata, K. *J. Org. Chem.* **1985,** *50*, 4388–4390. (i) Saito, K.; Harada, K. *Bull. Chem. Soc. Jpn.* **1989,** *62*, 2562–2566. (j) Clark, J. H.; Duke, C. V. A. *J. Org. Chem.* **1985,** *50*, 1330–1332. (k) Harusawa, S.; Yoneda, R.; Omori, Y.; Kurihara, T., *Tet. Lett.* **1987,** *28*, 4189–4190. (l) Soli, E. D.; Manoso, A. S.; Patterson, M. C.; DeShong, P.; Favor, D. A.; Hirschmann, R.; Smith, A. B. *J. Org. Chem.* **1999,** *64*, 3171–3177. (m) Friedman, L.; Shechter, H. *J. Org. Chem.* **1960,** *25*, 877–879. (n) Shaw, J. E.; Hsia, D. Y.; Parries, G. S.; Sawyer, T. K. *J. Org. Chem.* **1978,** *43*, 1017–1018. (o) Reddy, M. S.; Rajan, S. T.; Eswaraiah, S.; Satyanarayana, R. Improved Process for Manufacture of Pregabalin. Patent WO 2009/001372 A2, Dec 31, 2008.

(14) a) Kim, S.; Song, H.-J. *Synlett* **2002,** 2110–2112. (b) Cho, C. H.; Lee, J. Y.; Kim, S. *Synlett* **2009**, 81–84.

(15) a) Ren, Y.; Dong, C.; Zhao, S.; Sun, Y.; Wang, J.; Ma, J.; Hou, C. *Tet. Lett.* **2012,** *53*, 2825–2827. (b) Zieger, H. E.; Wo, S. *J. Org. Chem.* **1994,** *59*, 3838–3840. (c) Ren, Y.; Yan, M.; Zhao, S.; Sun, Y.; Wang, J.; Yin, W.; Liu, Z. *Tet. Lett.* **2011,** *52*, 5107–5109. (d) Satoh, Y.; Obora, Y. *RSC Adv.* **2014,** *4*, 15736–15739.

(16) a) Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2013,** *52*, 5129–5133. (b) Do, H.-Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2014,** *136*, 2162–2167.

(17) a) Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. *Science* **2012,** *338*, 647–651. (b) Tan, Y.; Munoz-Molina, J. M.; Fu, G. C.; Peters, J. C. *Chem. Sci.* **2014,** *5*, 2831–2835. (c) Uyeda, C.; Tan, Y.; Fu, G. C.; Peters, J. C. *J. Am. Chem. Soc.* **2013,** *135*, 9548–9552. (d) Ziegler, D. T.; Choi, J.; Muñoz-Molina, J. M.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2013,** *135*, 13107–13112.

(18) Isse, A. A.; Lin, C. Y.; Coote, M. L.; Gennaro, A. *J. Phys. Chem. B* **2010,** *115*, 678–684.

(19) The UVC bulbs can be purchased from a retailer such as Amazon.com ($15).

(20) The solution temperature of a reaction run under the standard conditions has been observed not to exceed 25 °C.

(21) Collins, K.D.; Glorius, F. *Nat. Chem.* **2013**, *5*, 597−601.

(22) We have observed that, in the absence of cyanide or copper, iodocyclohexane is consumed over 24 h under the standard irradiation conditions. By contrast, chlorocylohexane is stable to irradiation under the same conditions.

(23) Nilsson, M. *Acta Chem. Scand. B* **1982**, *36*, 125–126.

(24) Notes: (a) This alkyl chloride is stable to irradiation at 254 nm. (b) If CuI is employed as the catalyst, at partial conversion we observe a trace of the two diastereomers of the [3.3.0] bicyclic primary alkyl iodide, which could be formed through Cl→I transhalogenation of the starting electrophile, homolysis of the C–I bond, radical cyclization, and then radical–radical recombination to generate a C–I bond.

(25) Pandey, G.; Rao, K. S. S. P.; Palit, D. K.; Mittal, J. P. *J. Org. Chem.* **1998**, *63*, 3968–3978.

(26) Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510–511.

APPENDIX 2

Spectra Relevant to Chapter 2:

Photoinduced, Copper-Catalyzed Carbon–Carbon Bond Formation: Cyanation of Unactivated Secondary Alkyl Chlorides at Room Temperature

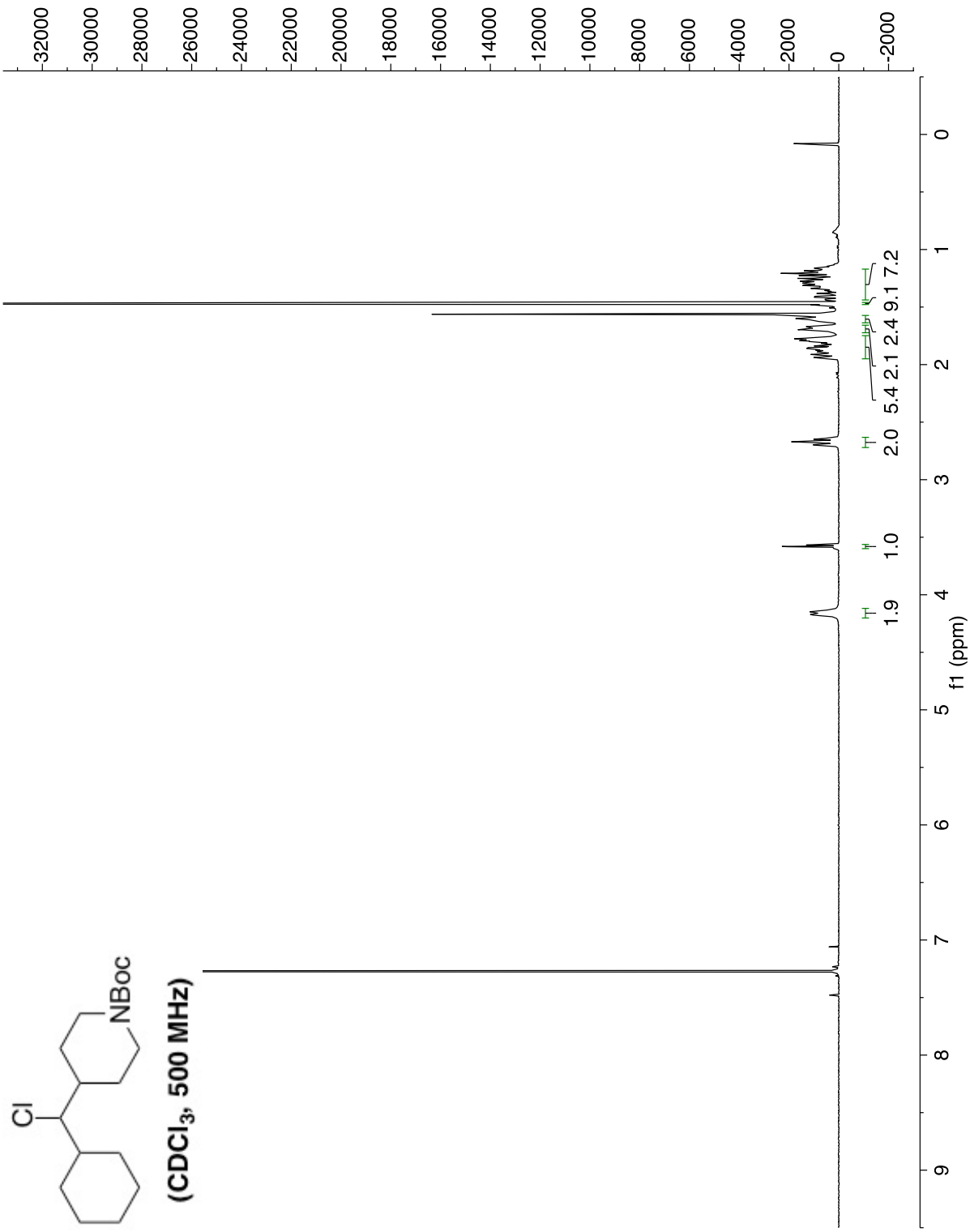


Figure A2.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **27d**.

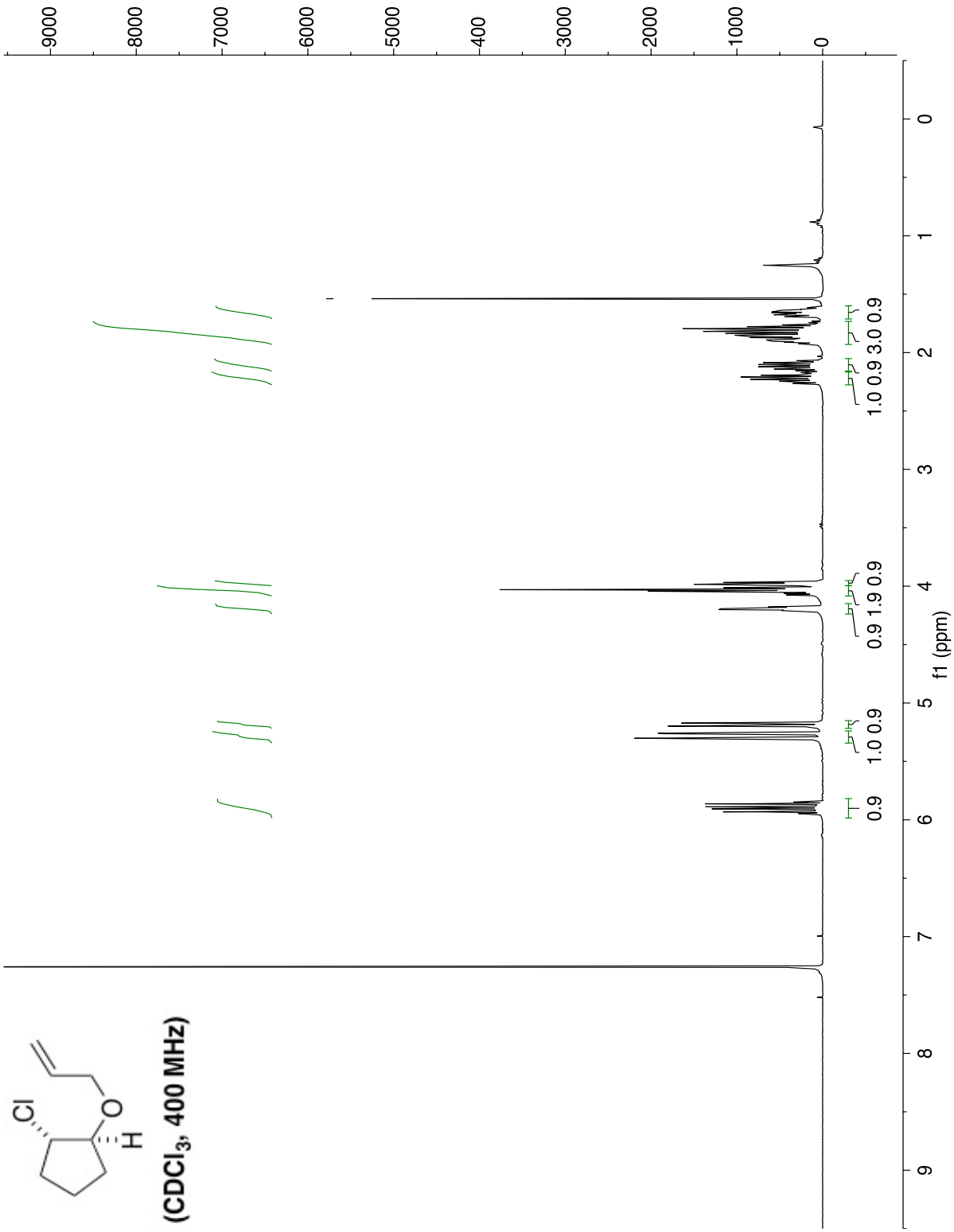


Figure A2.2. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **27n**.

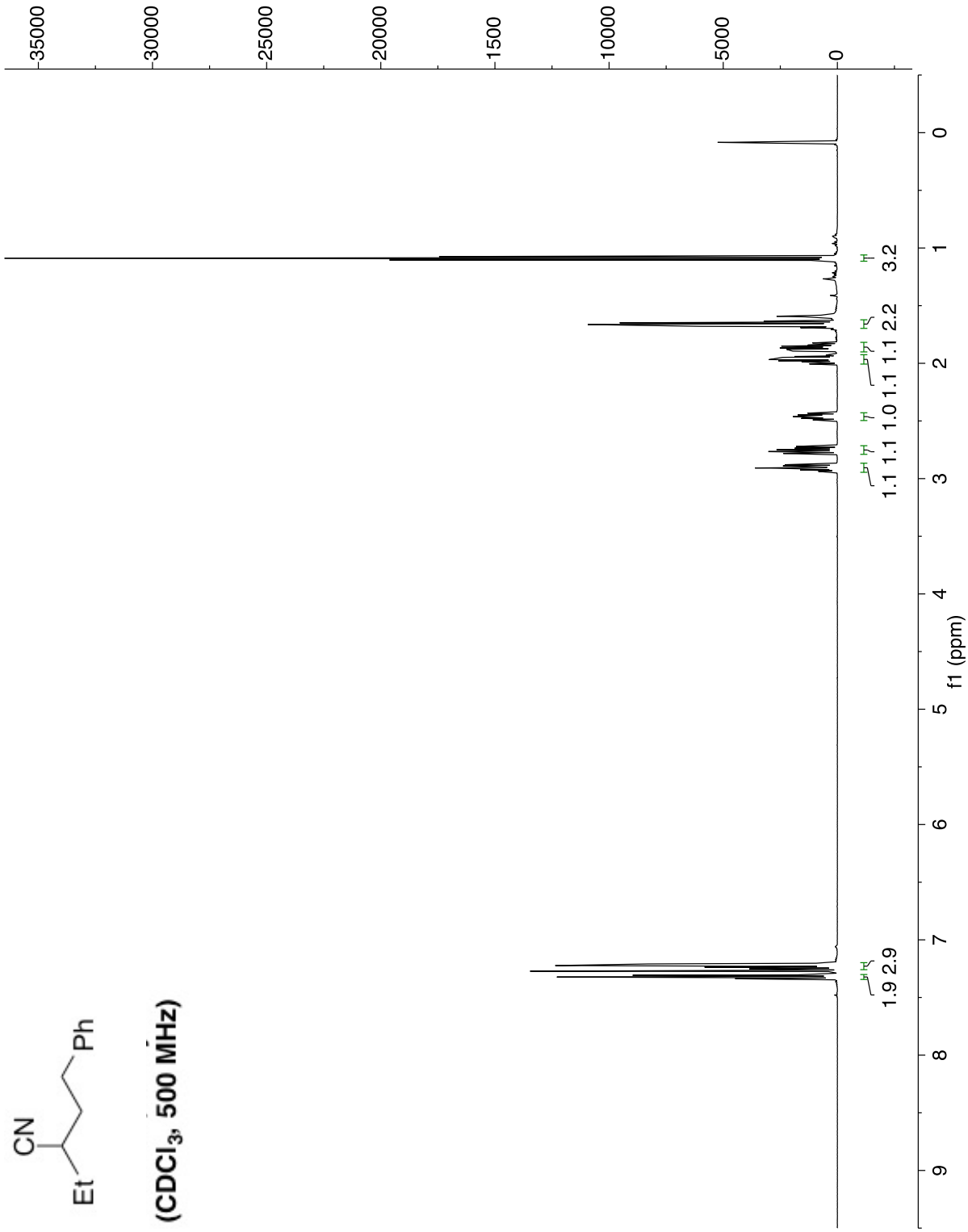


Figure A2.3. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **40a**.

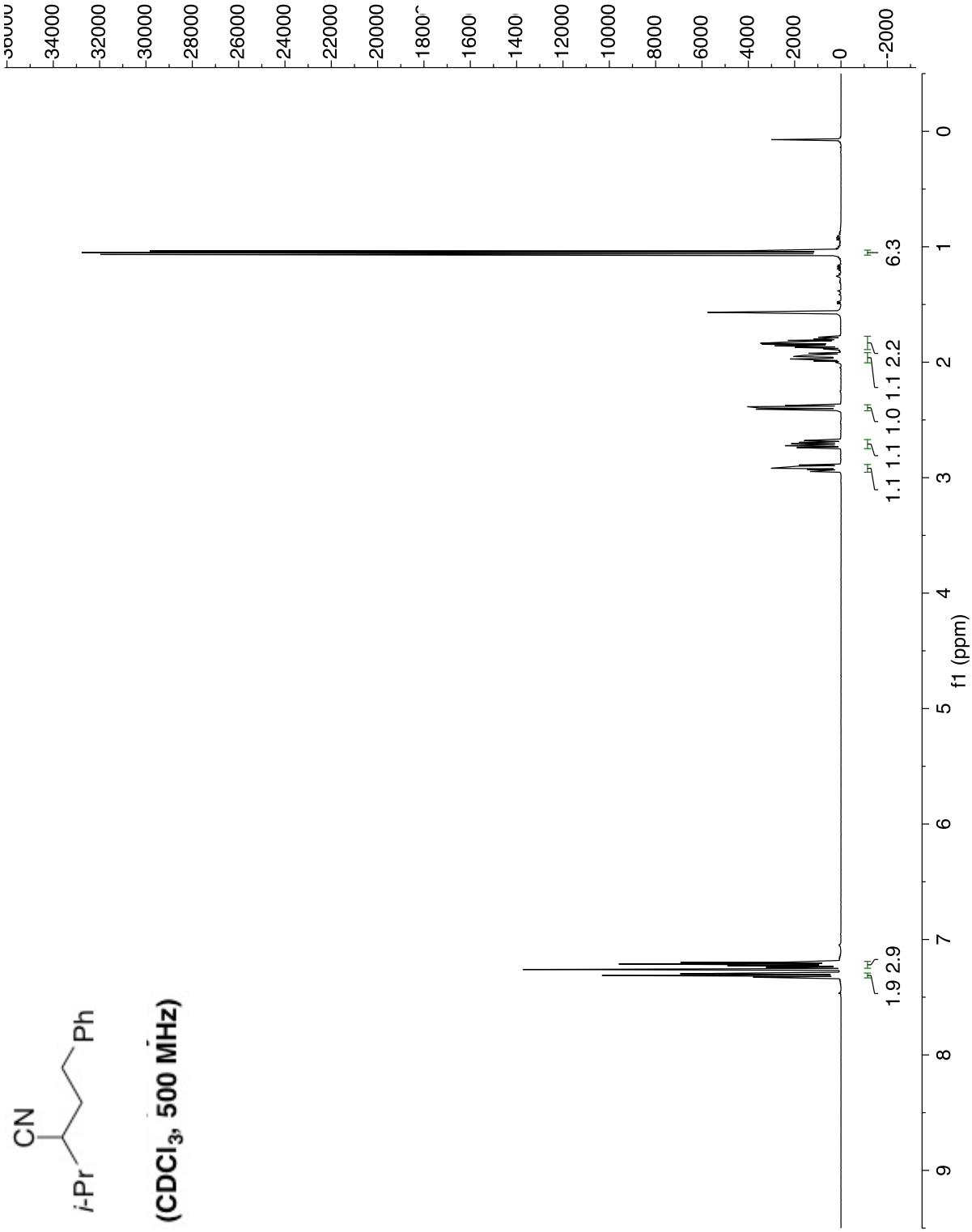


Figure A2.4. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **40b**.

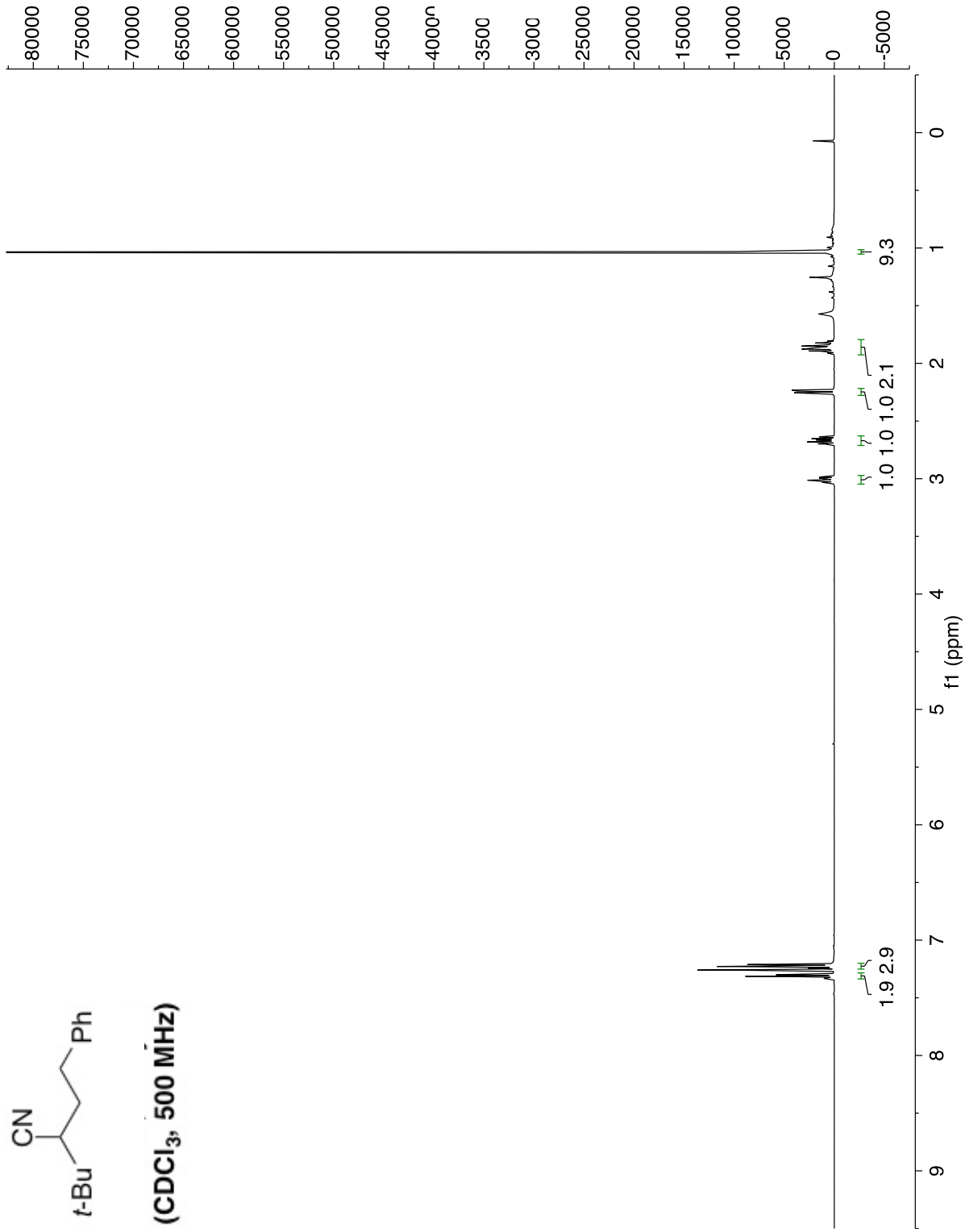


Figure A2.5. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **40c**.

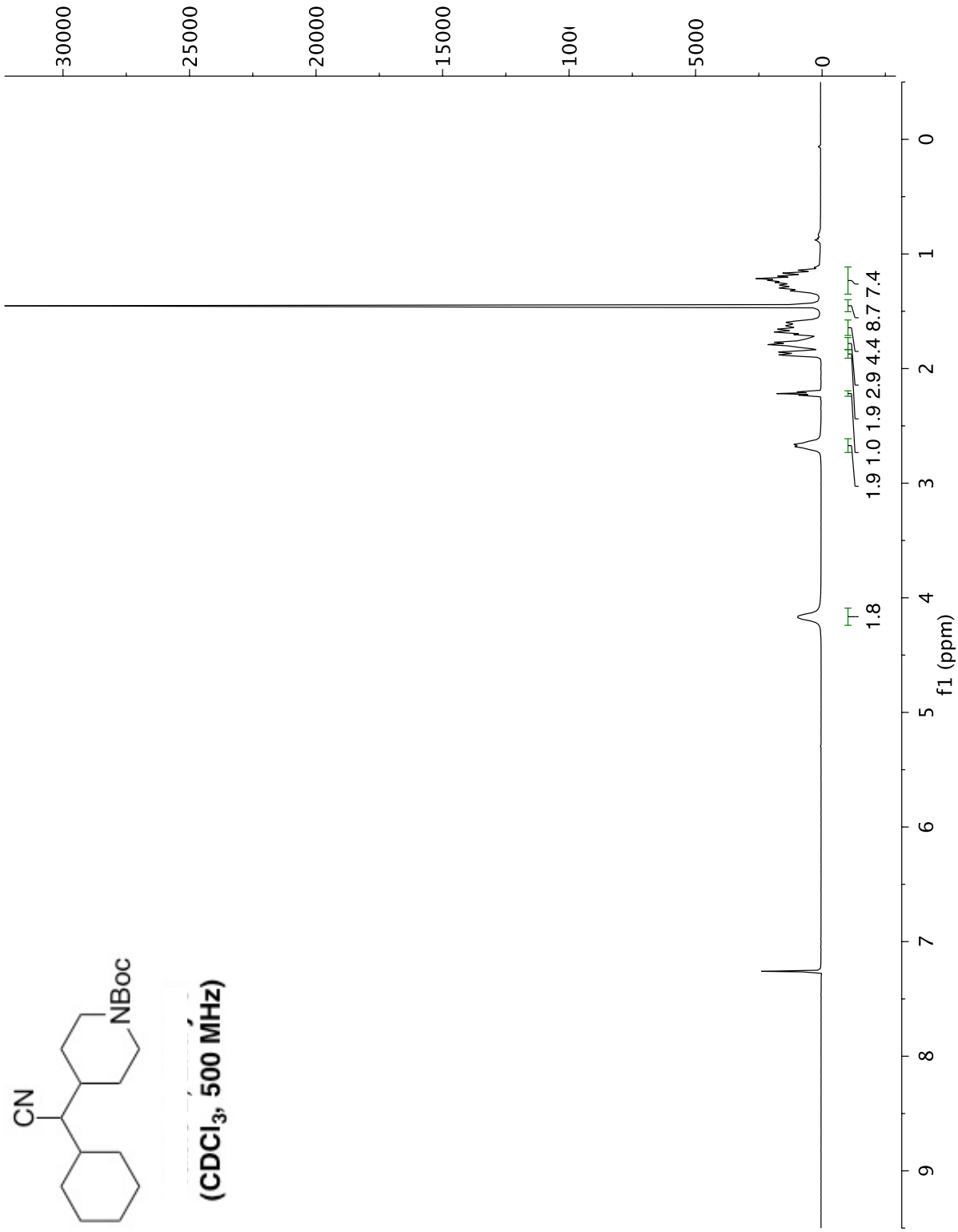


Figure A2.6. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **40d**.

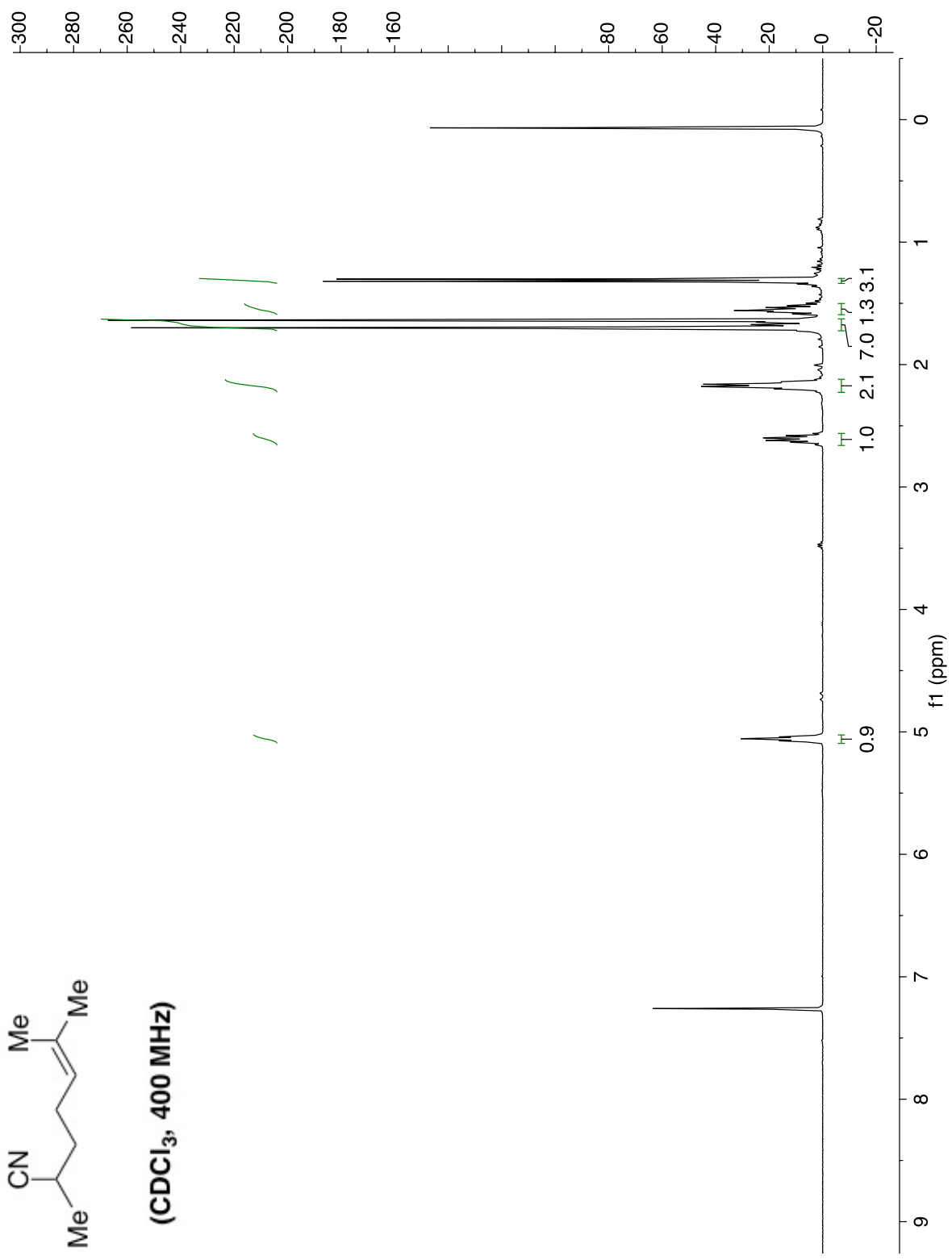


Figure A2.7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **40e**.

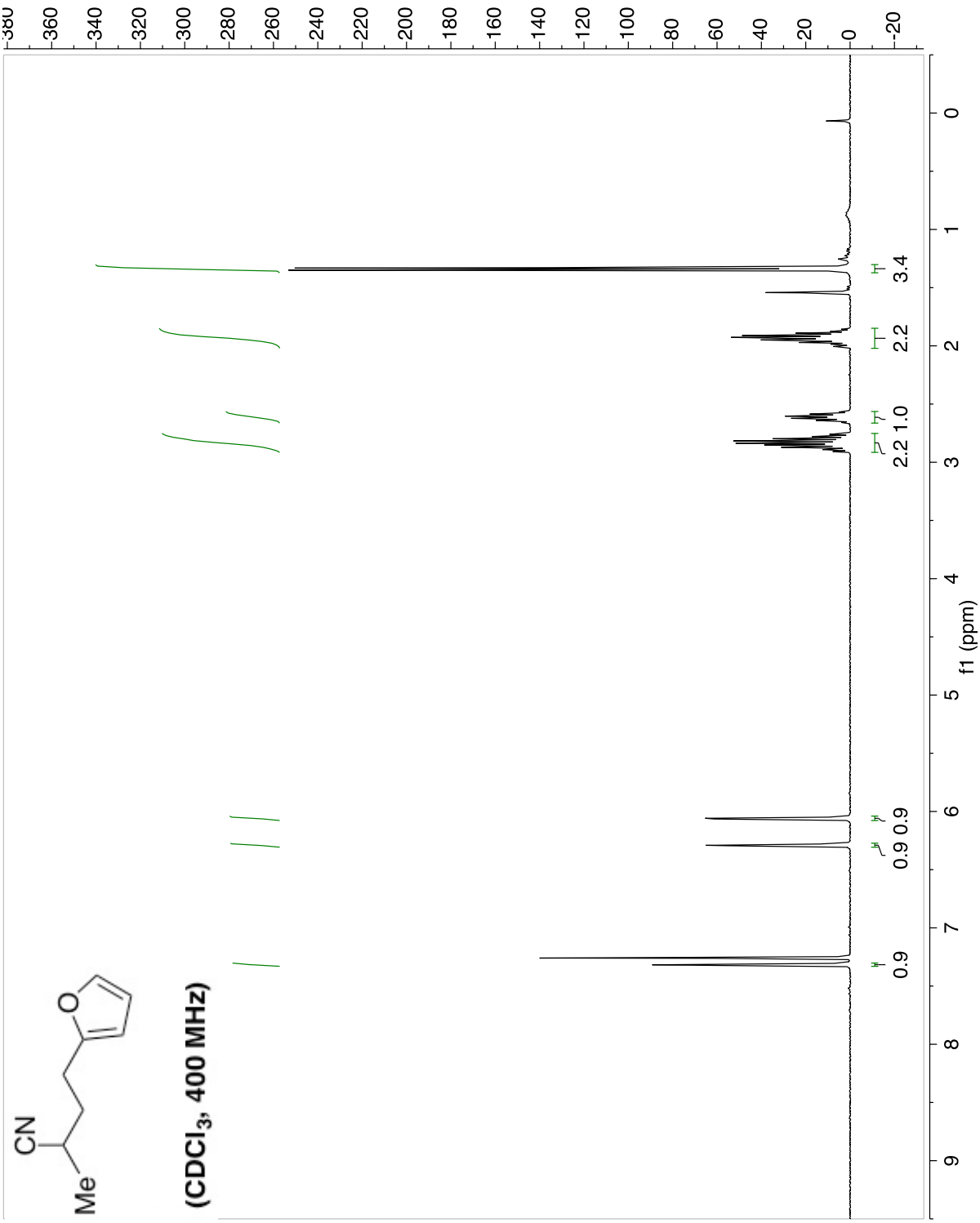


Figure A2.8. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **40f**.

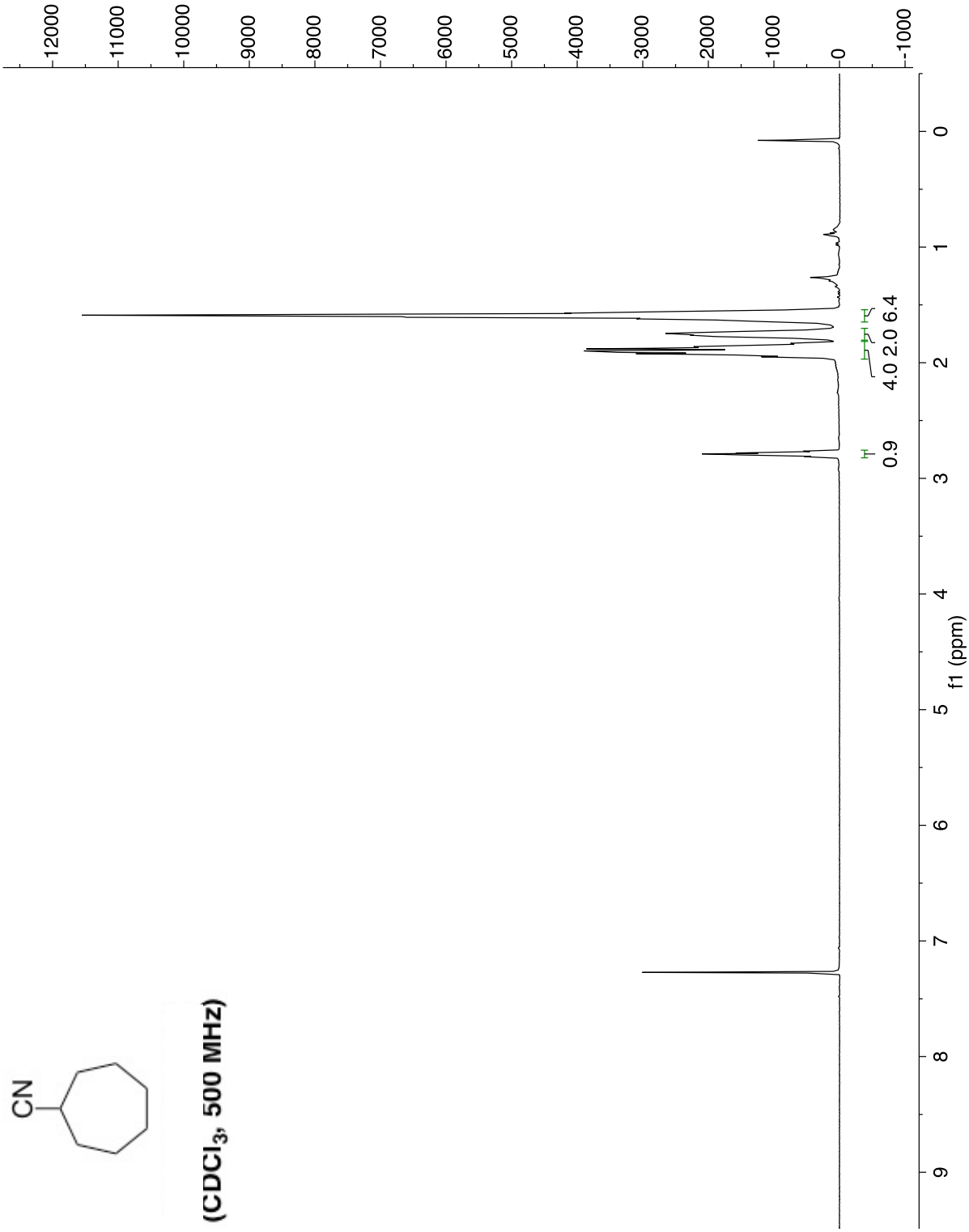


Figure A2.9. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **40g**.

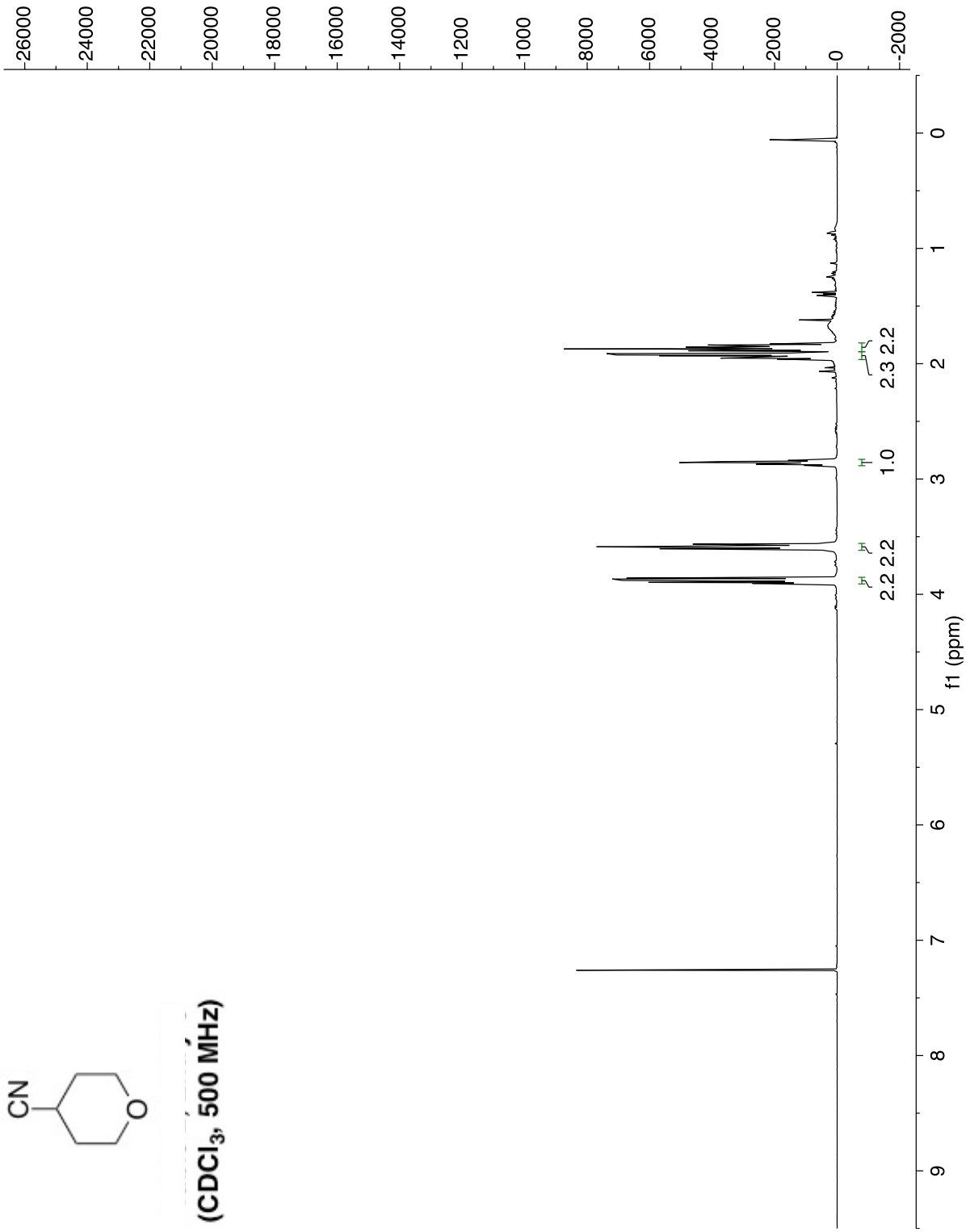


Figure A2.10. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **40h**.

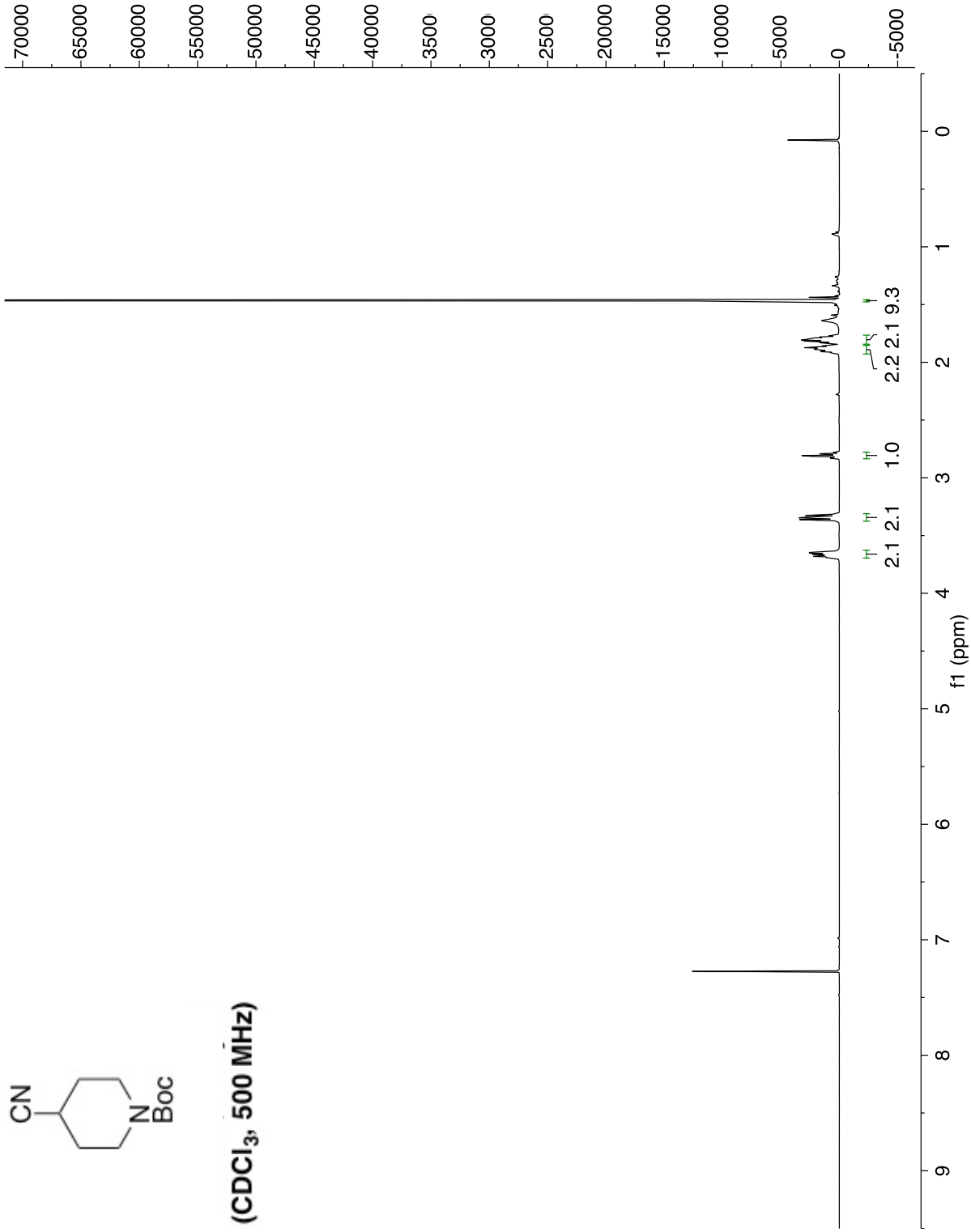


Figure A2.11. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **40i**.

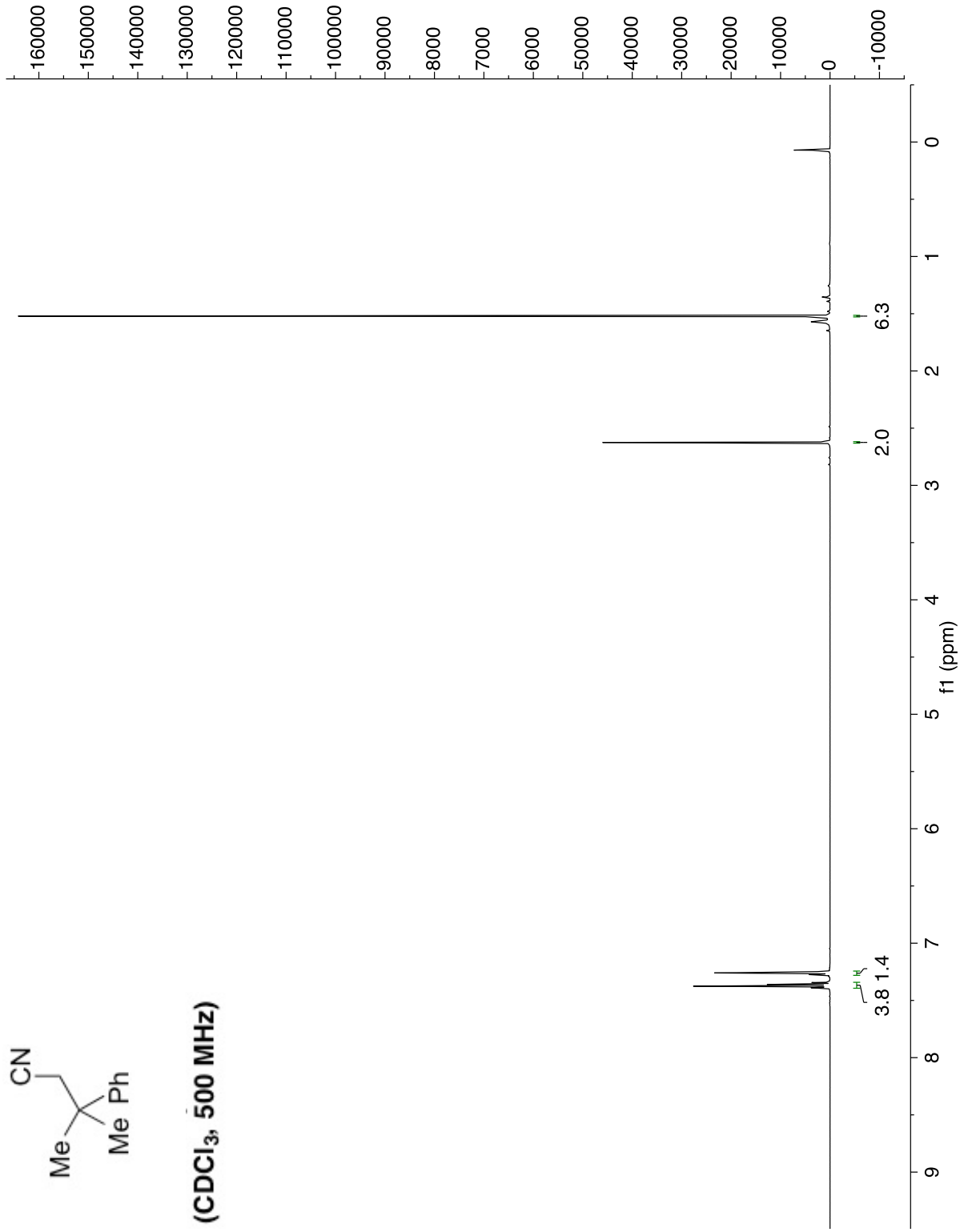


Figure A2.12. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **40j**.

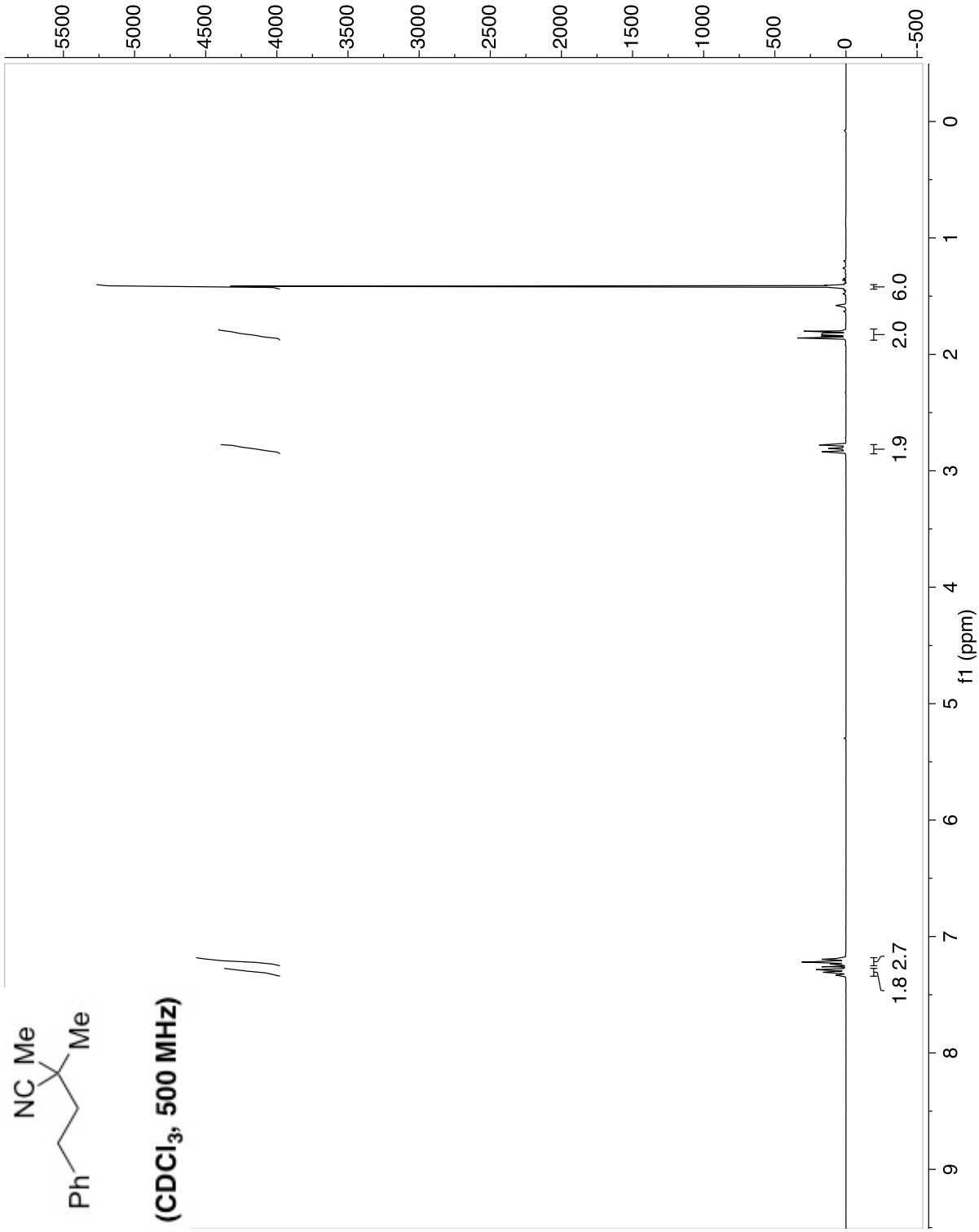


Figure A2.13. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **42**.

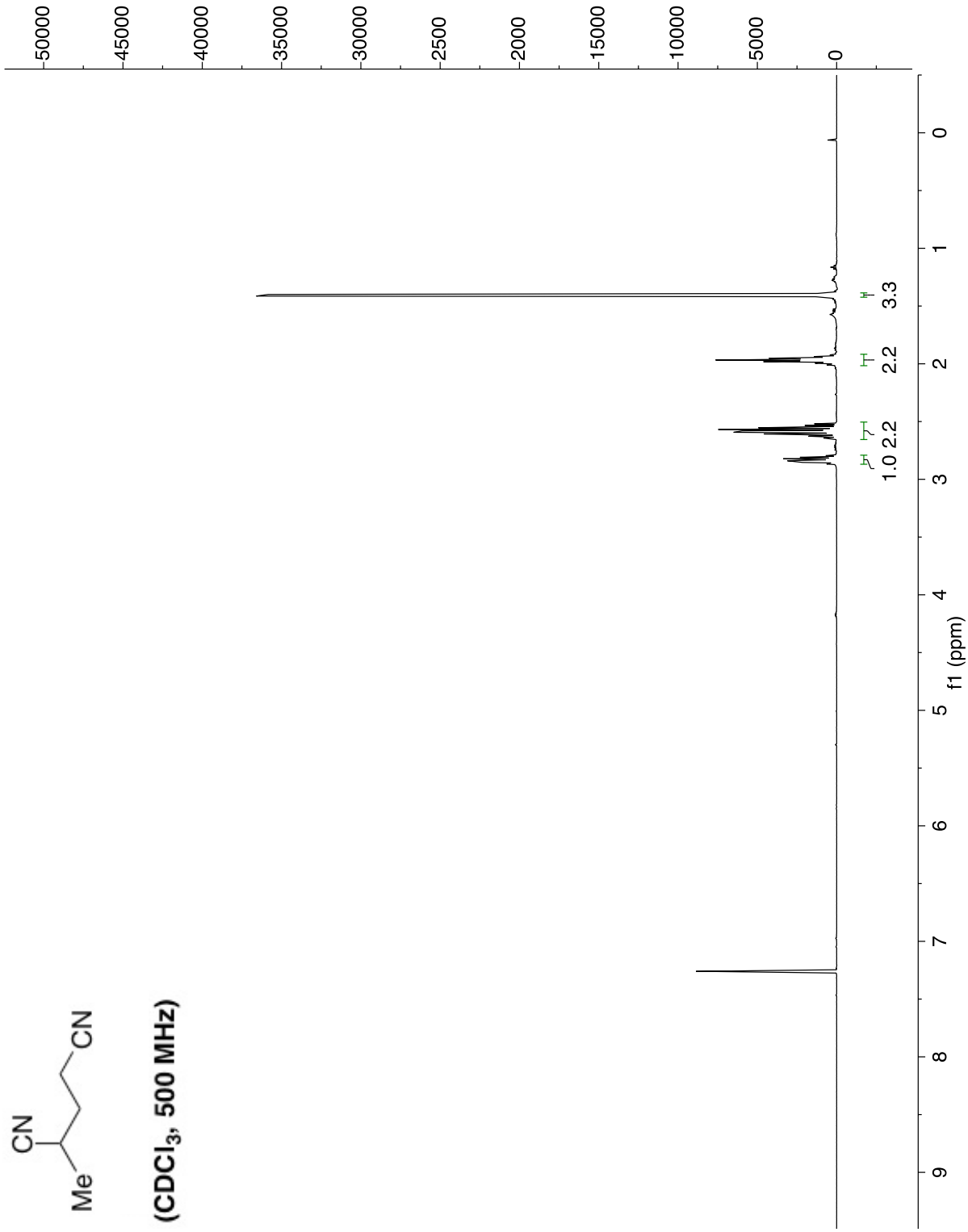


Figure A2.14. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **40o**.

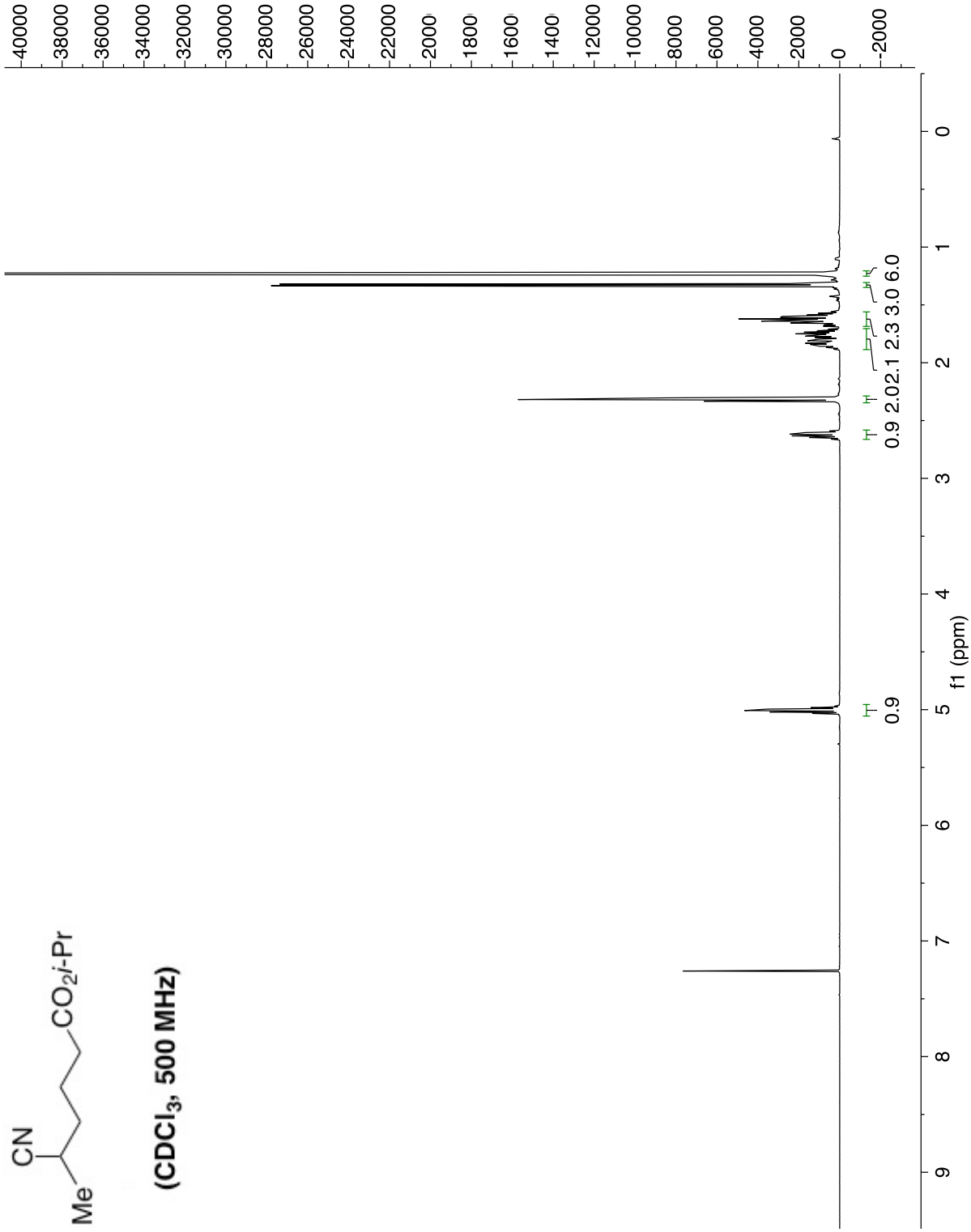


Figure A2.15. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **40p**.

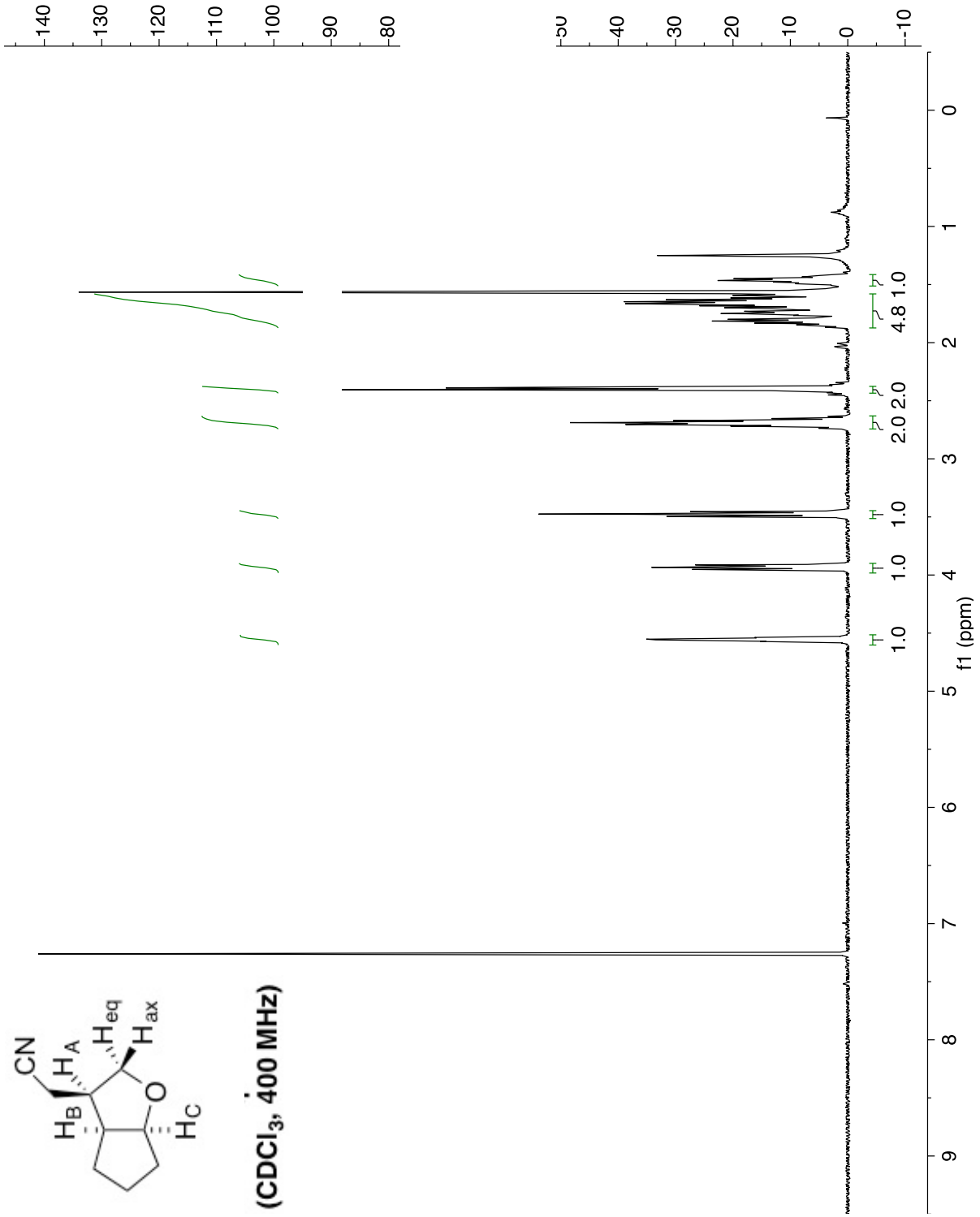
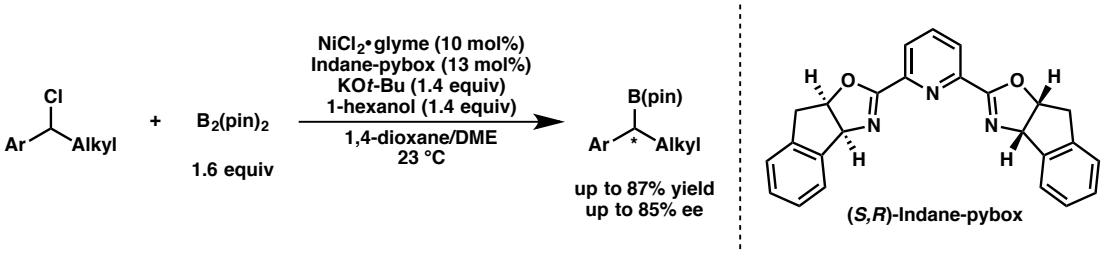


Figure A2.16. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **40n**.

CHAPTER 3

Enantioselective Ni-Catalyzed Borylation of Secondary Benzylic Chlorides[†]

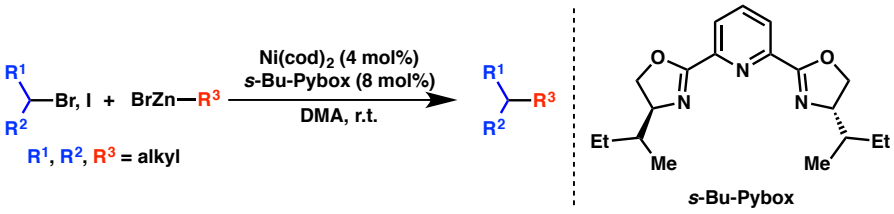


[†]This work was performed in collaboration with Dr. Alex Dudnik

3.1 Introduction

While palladium catalysis has been at the forefront of multiple advancements in cross coupling, nickel catalysis has recently proved to furnish complementary and equally powerful reactivity.[1] The broad expansion of nickel-catalyzed coupling reactions can be attributed to the utility imparted by the unique properties of nickel. For example, the accessibility of Ni(0), Ni(I), Ni(II), and Ni(III) oxidation states facilitates versatile modes of reactivity, including radical mechanisms.[1] In addition, β-hydride elimination is considered to be slower for nickel than for palladium.[2] These features have rendered Ni catalysts particularly efficient for cross coupling historically challenging substrates such as secondary alkyl halides.[3] In 2003, the Fu group reported the first example of a Ni- or Pd- catalyzed cross coupling of β-hydrogen-containing, unactivated, secondary alkyl halides.[4] The use of a $Ni(COD)_2$/*s*-Bu-Pybox catalyst system opened the door to the possibility of developing asymmetric variants (Scheme 3.1).

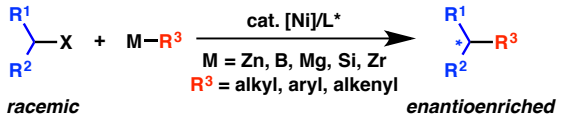
Scheme 3.1 Ni-catalyzed cross coupling of unactivated secondary alkyl halides



The Fu group has subsequently reported a variety of stereoconvergent, enantioselective Ni-catalyzed cross coupling reactions of both activated and unactivated racemic secondary alkyl halides with alkyl, aryl, and alkenyl

organometallic reagents (Scheme 3.2).[3] These reactions and related systems are postulated to proceed through a single electron transfer pathway for cleavage of the alkyl halide C–X bond resulting in an alkyl radical intermediate.[5,6,7,8,9]

Scheme 3.2 Stereoconvergent Ni-catalyzed cross coupling of secondary alkyl halides



In terms of an overall catalytic cycle, the enantioselective Negishi arylation of propargylic bromides is proposed to proceed via a bimetallic oxidative addition, radical chain pathway in which the catalyst resting state is an arylnickel(II) species (Figure 3.1).[6a] In the case of unactivated alkyl halides, it has been postulated that the mechanism involves transmetallation followed by an inner-sphere electron transfer pathway for oxidative addition (Figure 3.2).[10] It is likely that the reaction mechanism varies depending on the specific ligand, coupling partners, and reaction conditions.

Figure 3.1 Postulated radical chain mechanism for Ni-catalyzed Negishi arylation of propargylic bromides

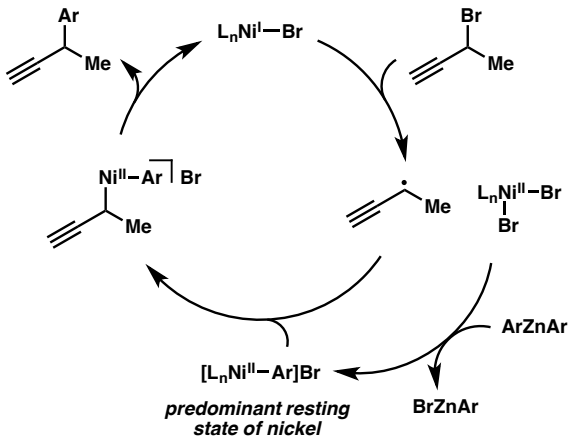
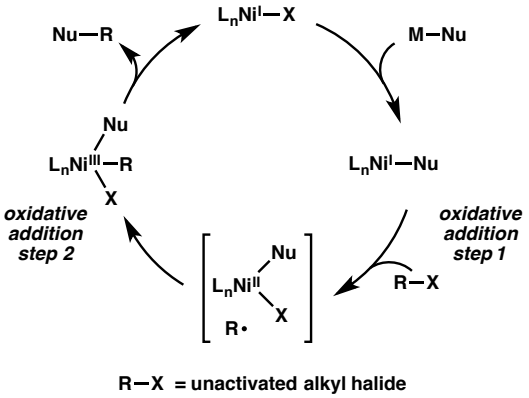


Figure 3.2 Outline of a possible mechanism for nickel-catalyzed coupling of unactivated alkyl halides

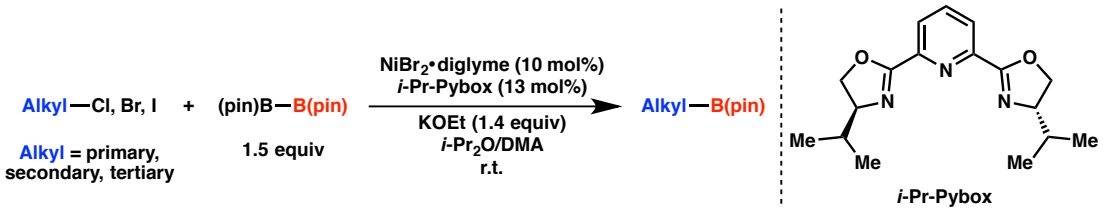


Several recent developments have focused on expanding the scope of these stereoconvergent cross coupling reactions to include new classes of electrophiles, including α-haloboronates,[11] α-halo-α-trifluoromethyl electrophiles,[12] and α-halo-sulfonamides and -sulfones.[7] These enantioselective Ni-catalyzed coupling reactions of racemic secondary alkyl halides have been demonstrated with a variety of organometallic nucleophiles, including organozinc, -boron, -magnesium, -silicon, and

-zirconium reagents.[3] Despite these advancements, an enantioselective coupling reaction of a secondary alkyl halide has yet to be established with a heteroatom nucleophile.

It has been reported that unactivated primary, secondary, and tertiary alkyl halides are effective coupling partners in Miyaura-type borylation reactions using a $NiBr_2$•diglyme/*i*-Pr-Pybox catalyst system (Scheme 3.3).[9a] A $NiBr_2$•diglyme/achiral terpyridine catalyst system has also been shown to effect borylation of unactivated secondary alkyl bromides.[13] Several other transition metals have been used to achieve Miyaura-type borylation of secondary alkyl halides, including copper,[14] zinc,[15] iron,[16] manganese,[17] and iridium;[18] however, no catalytic asymmetric variant has been established.[19]

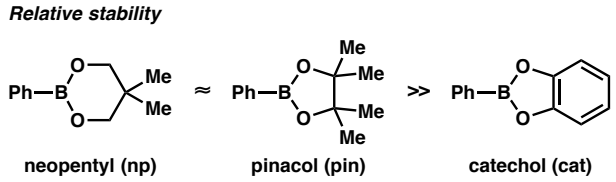
Scheme 3.3 Ni-catalyzed borylation of unactivated alkyl halides



Organoboron compounds are versatile intermediates in organic synthesis, serving as reaction partners in Suzuki couplings and as precursors to esters, alcohols, carboxylic acids, and amino acids.[20] The stability of alkylboronic esters to air, moisture, and retention of configuration renders them particularly valuable.[21] Most boronic esters exhibit lower reactivity as compared to boronic acids and may be purified by column chromatography and dissolved in nonpolar organic solvents.

Pinacol, neopentyl-, and catechol boronic esters are commonly used due to their relative stability, reactivity, and ease of preparation (Figure 3.3).[22] Enantioenriched secondary and tertiary boronic esters have garnered recent interest as substrates for stereospecific coupling reactions.[23]

Figure 3.3 Relative stability of commonly used boronic esters

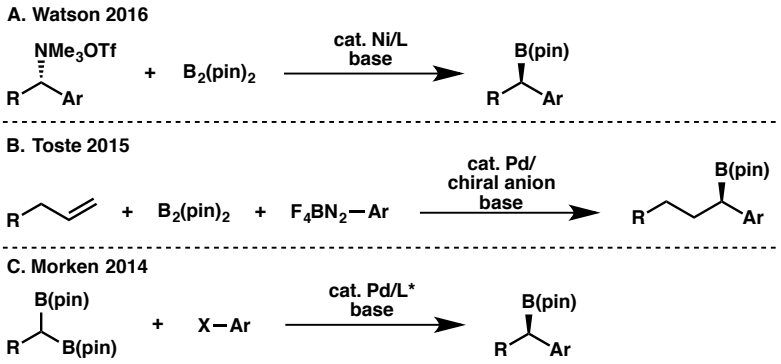


Among well-established strategies for synthesis of enantioenriched organoboronates are methods using stoichiometric chiral auxiliaries such as Brown's hydroboration [24] and Matteson's asymmetric homologation. [25] More recently developed catalytic enantioselective methods are focused on two approaches, borylation of organic functional groups (late-stage borylation), and the modification of boron-containing substrates (early-stage borylation). Catalytic enantioselective borylation reactions include hydroboration,[26] diboration,[27] allylic borylation,[28] and conjugate borylation.[29] Sate-of-the-art strategies include stereospecific Miyaura-borylations of enantioenriched electrophiles (Scheme 3.4A) [30] and the three-component coupling of olefins, aryldiazonium salts, and bis(pinacolato)diboron (B_2pin_2) via cooperative chiral anion phase transfer and Pd-catalysis (Scheme 3.4B).[31]

With respect to early-stage borylation, effective methods include the enantioselective conjugate addition of an organometallic or diboron reagent to a β-borylated substrates,[32] enantioselective hydrogenation of vinyl boronates,[33] and

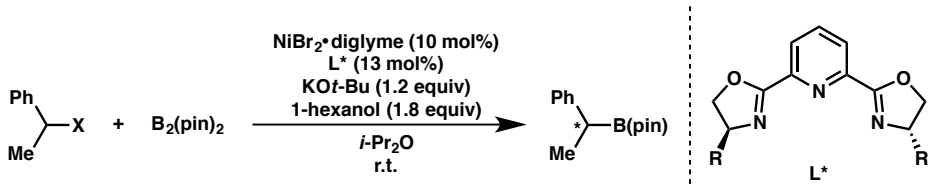
enantiotopic-group-selective Suzuki coupling of achiral germinal bis(pinacolboronates) (Scheme 3.4C).[34] Recent advances include the Fu group's stereoconvergent Ni-catalyzed cross coupling reactions of α-haloboronates.[10]

Scheme 3.4 Recent examples of stereoselective synthesis of benzylic boronic esters



A catalytic enantioselective method for borylation of racemic alkyl halides would add to the breadth of work focused on synthesis of enantioenriched organoboronates. We hoped that the $NiBr_2$•diglyme/*i*-Pr-Pybox catalyst system established by Dr. Alex Dudnik would provide a feasible starting point for the development of a Ni-catalyzed enantioselective borylation of secondary alkyl halides. Preliminary investigations by Dr. Alex Dudnik resulted in moderate ee (61%) and modest yield in the enantioselective borylation of a racemic benzylic halide (Scheme 3.5). The goal of this project is to improve upon these initial results and therein demonstrate the first example of an enantioselective Ni-catalyzed coupling of a racemic secondary alkyl halide with a heteroatom nucleophile.

Scheme 3.5 Enantioselective borylation of benzylic halides: preliminary studies



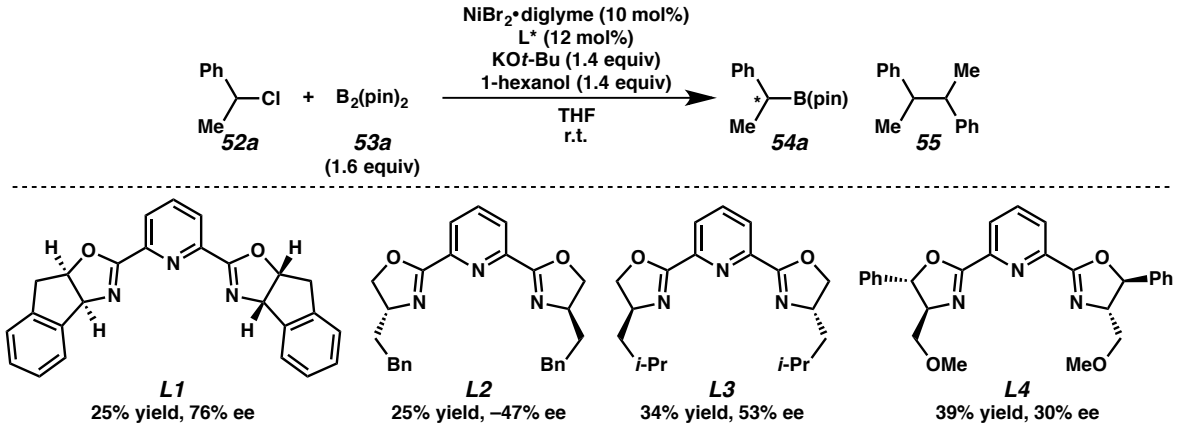
X	R	Yield (%)	ee (%)
Br	CH_2Bn	27	59
Cl	*i*-Bu	17	62

3.2 Results and Discussion

With Dr. Alex Dudnik's best conditions as a general starting point (Scheme 3.5), a variety of reaction parameters were explored in greater detail. Pyridine bis(oxazoline) (pybox) ligands resulted in superior ee values compared to other classes of ligands including bis(oxazoline), diamine, and quinoline oxazoline. It was found that other ethereal solvents than *i*-Pr_2O, such as THF or DME, resulted in greater ee values. Yields of the desired product were generally higher with an alkyl chloride than with an alkyl bromide.

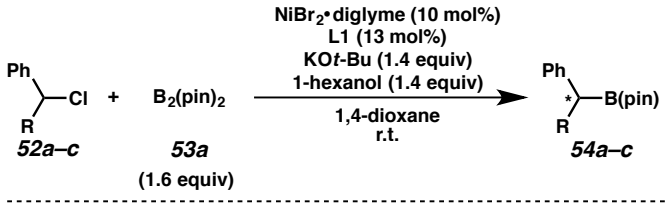
Evaluation of a variety of pybox ligands for the coupling of benzylic chloride **52a** in THF revealed that indane-pybox **L1** resulted in a significant increase in enantioselectivity, although the desired product was formed in low yield due to electrophile homocoupling (**55**) (Scheme 3.6).

Scheme 3.6 Effect of pybox ligands on the borylation of a benzylic chloride



After a more detailed exploration of solvent effects, 1,4-dioxane was determined to provide a small increase in enantioselectivity. Increasing the steric demand of the benzylic chloride alkyl substituent from Me (**52a**) to Et (**52b**) improved yield but did not significantly affect enantioselectivity (Table 3.1).

Table 3.1 Effect of various benzylic chloride alkyl substituents

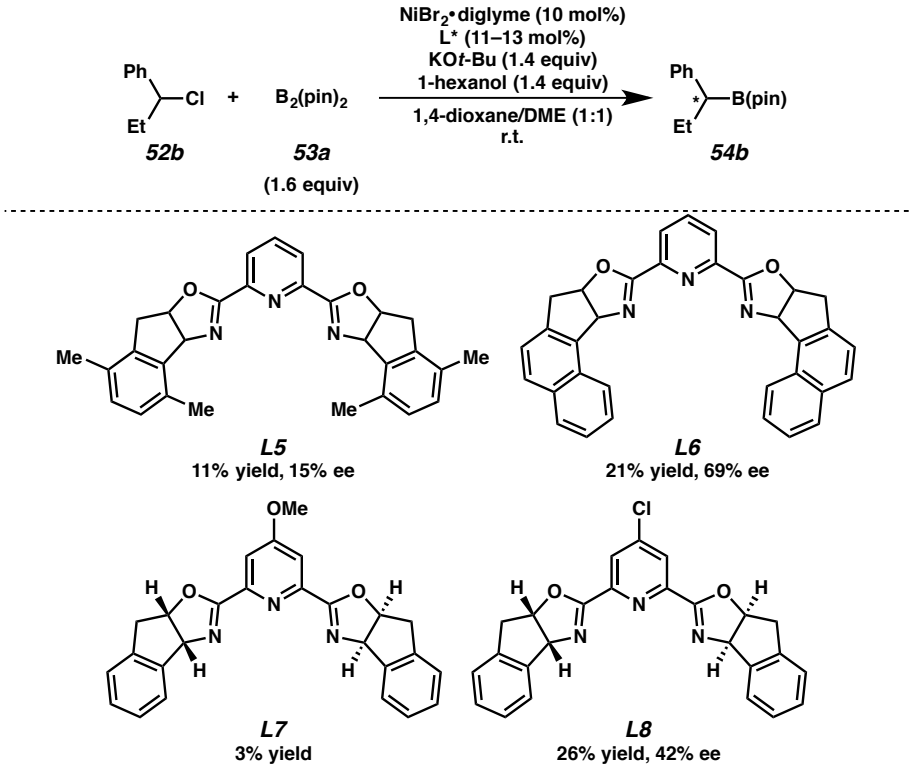


	R	Yield (%)	ee (%)
52a*→*54a	Me	38	82
52b*→*54b	Et	75	83
52c*→*54c	*n*-Bu	64 (uncalibrated)	80

Other variations to the reaction conditions, such as using $NiCl_2$•glyme instead of $NiBr_2$•diglyme, and using a mixture of 1,4-dioxane and DME, resulted in improved yields but unaffected enantioselectivity. Various indane-pybox derivatives were investigated (Scheme 3.7). Increasing the steric bulk or extending the π-system of the ligand (**L5** and **L6**, respectively) resulted in substantially decreased yields and

low to moderate enantioselectivity. Ligands with either an electron-donating or an electron-withdrawing substituent on the pyridine ring (**L7** and **L8**, respectively) were also detrimental to yield and/or enantioselectivity.

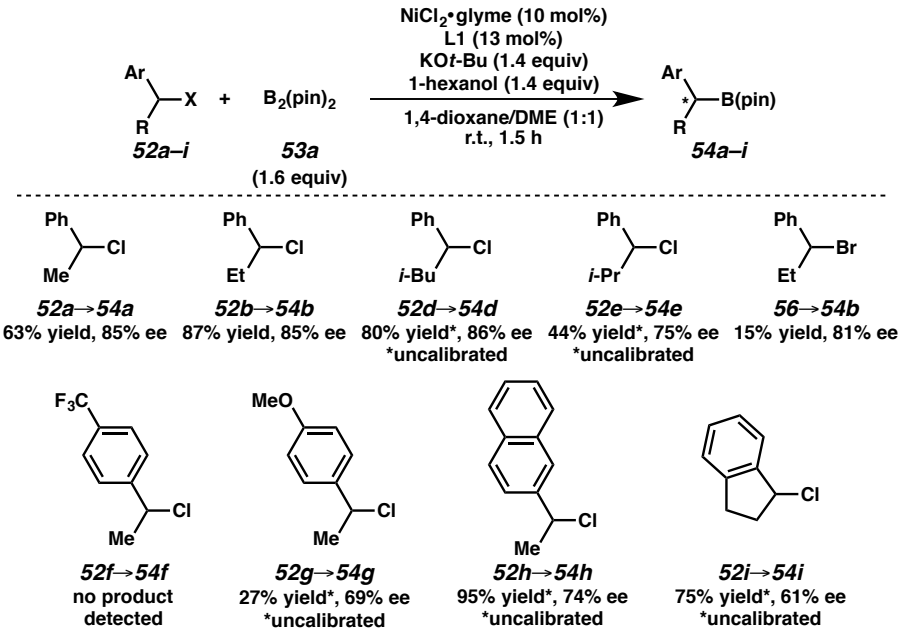
Scheme 3.7 Effect of indane-pybox derivatives on Ni-catalyzed borylation of a benzylic chloride



Under the optimized conditions, the scope of the reaction was explored with respect to the alkyl halide coupling partner (Scheme 3.8). Benzylic chlorides with a methyl (**52a**), ethyl (**52b**), isobutyl (**52d**), or isopropyl (**52e**) α-substituent undergo Ni-catalyzed borylation in moderate to good enantioselectivity. Benzylic bromide **56** results in high enantioselectivity but low yield of the desired boronic ester **54b**. The yield and enantioselectivity of the reaction are sensitive to the electronics of the aryl substituent; an electron-poor benzylic chloride (**52f**) results in no detectable

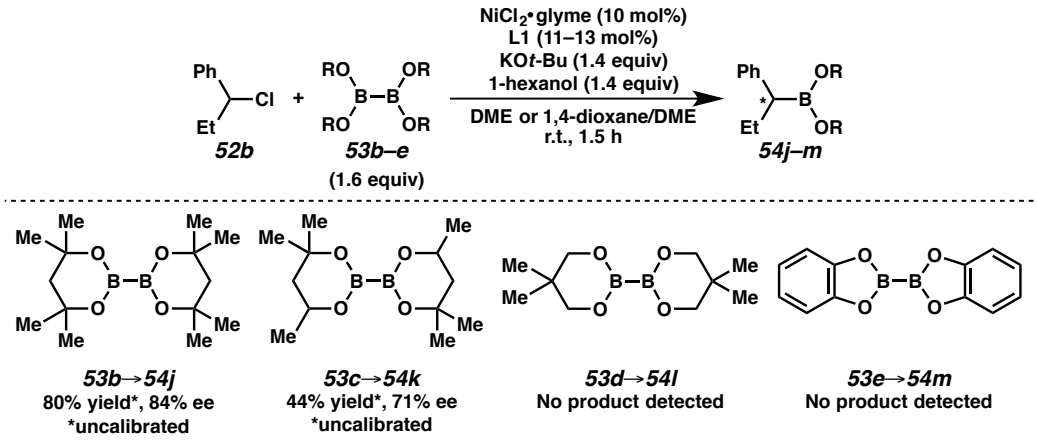
borylation, while an electron-rich benzylic chloride (**52g**) furnishes the boronic ester in low yield and moderate enantioselectivity. Decreased enantioselectivity is also observed in the case of a benzylic chloride with a naphthyl substituent (**52h**) and 1-chloroindane (**52i**).

Scheme 3.8 Effect of electrophile structure on yield and enantioselectivity under optimized conditions



The reaction is also sensitive to the structure of the boron-containing reagent. For example, bis(hexylene glycolato) diboron (**53b**) results in lower enantioselectivity, while bis(neopentylglycolato)diboron (**53d**) and bis(catecholato)diboron (**53e**) do not result in any product formation (Scheme 3.9). In addition, pinacolborane and tetrahydroxydiboron do not yield the desired product under similar conditions.

Scheme 3.9 Effect of diboron structure on yield and enantioselectivity under optimized conditions



3.3 Conclusion

We have developed, to the best of our knowledge, progress toward the first example of enantioselective Ni-catalyzed cross coupling of racemic alkyl halides and *heteroatom* nucleophiles. Specifically, the borylation of secondary benzylic chlorides with $B_2(pin)_2$ can be achieved in up to 87% yield and 85% ee using a $NiCl_2$•glyme/indane-pybox catalyst system. This is the first method for catalytic enantioselective Miyaura-type borylation of alkyl halides. This C(sp^3)–B coupling reaction occurs under mild conditions (room temperature) with commercially available, air-stable reagents: $NiCl_2$•glyme, indane-pybox, and $B_2(pin)_2$. Although the substrate scope with respect to both the benzylic chloride and diboron coupling partners remains modest, we have established a valuable proof-of-concept that enantioselective Ni-catalyzed cross coupling of racemic alkyl halides can be extended beyond C–C bond formation.

3.4 Experimental Procedures

3.4.1 General Information

The following reagents were purchased and used as received: $NiCl_2$•glyme (Aldrich), ligand **L1** (Aldrich), 1,4-dioxane (anhydrous, 99.8%; Aldrich), DME (anhydrous, 99.5%, inhibitor-free; Aldrich), KO*t*-Bu (Strem), 1-hexanol (anhydrous, ≥99%; Aldrich). Diboron reagents were purchased from Frontier Scientific or Combi-Blocks. Benzylic chlorides[35] and bromides[6b] were prepared from the corresponding alcohols according to literature procedures. All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen.

^{1}HNMR spectroscopic data were collected on a Varian 500 MHz spectrometer at ambient temperature. GC analyses were obtained on an Agilent 6890 Series GC system with a DB-1 column (length 30 m, internal diameter 0.25 mm). HPLC analyses were carried out on an Agilent 1100 Series system with Daicel CHIRALPAK columns (internal diameter 4.6 mm, column length 25.0 cm, particle size 5 μm).

3.4.2 Ni-Catalyzed Borylation of Benzylic Chlorides

General procedure for evaluating benzylic chloride scope on a small-scale: To a 4-mL vial **A** open to air was added $NiCl_2$•glyme (2.2 mg, 0.010 mmol, 0.10 equiv) and **L1** (5.2 mg, 0.013 mmol, 0.13 equiv). Vial **A** was then brought into a nitrogen-filled glovebox and 0.5 mL dioxane were added. (Note: Due to the poor solubility of **L1** in ethereal solvent, a stock solution of Ni/**L1** cannot be made. The procedure for **A** was repeated *n* times for the number of reactions in the screen.) The Ni/**L1** solution was then stirred for 45 min. A stock solution of diboron reagent and base was then prepared in a separate 4-mL vial **B**. To vial **B** was added KO*t*-Bu (15.7*n* mg, 0.140*n* mmol, 1.40*n* equiv), 1-hexanol (17.5*n* μL, 0.140*n* mmol, 1.40*n* equiv), and 0.2*n* mL DME. The contents of **B** were stirred for 1 minute, then a solution of B_2pin_2 (40.6*n* mg, 0.160*n* mmol, 1.60*n* equiv) in 0.2*n* mL DME was added. The contents of **B** were then stirred for 45 min, after which the solution was diluted to a total volume of 0.5*n* mL with DME. To vial **A** was then added the benzylic chloride (0.100 mmol, 1.00 equiv) followed by 0.5 mL of the stock solution in vial **B**. Vial **A** was then sealed with a PTFE-lined cap and removed from the glovebox. After 1.5 h, the vial was opened to air and dodecane (17.0 mg, 0.100 mmol, 1.00 equiv) was added. The mixture was then filtered through a small silica plug, eluting with diethyl ether. An aliquot of the eluate was then removed for GC determination of the yield with respect to dodecane as an internal standard. The remaining eluate was then concentrated by rotary evaporator and oxidized with $NaBO_3$•$4H_2O$ (~20 mg) in 1:1 H_2O/THF (2 mL) at room temperature for 30 min. The mixture was extracted with Et_2O, the combined organic phases were dried over Na_2SO_4 and concentrated by

rotary evaporator, and the residue was purified by preparative TLC (Et_2O/hexanes). The purified alcohol was then dissolved in hexanes for HPLC analysis on a CHIRALPAK OD column (2–3% IPA/hexanes, 1.0 mL/min).

3.5 Notes and Citations

(1) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299–309.

(2) Lin, B. -L.; Liu, L.; Fu, Y.; Luo, S. -W.; Chen, Q.; Guo, Q. -X. *Organometallics* **2004**, *23*, 2114–2123.

(3) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587–9652.

(4) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726–14727.

(5) Non-asymmetric Ni-catalyzed cross coupling of alkyl halides with organometallic reagents: (a) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340–1341. (b) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788–7789. (c) González-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360–5361. (f) Liang, Y.; Fu, G. C. *Angew. Chem. Int. Ed.* **2015**, *54*, 9047–9051. (h) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 624–627. (i) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175–13183. (j) Breitenfeld, J.; Ruiz, J.; Wodrich, W. D.; Hu, X. *J. Am. Chem. Soc.* **2013**, *135*, 12004–12012. (k) Hu, X. *Chem. Sci.* **2011**, *2*, 1867–1886. (l) An, L.; Xiao, Y.-L.; Min, Q.-Q.; Zhang, X. *Angew. Chem. Int. Ed.* **2015**, *54*, 9079–9083.

(6) Enantioselective Ni-catalyzed cross coupling of activated alkyl halides with organometallic reagents: (a) Schley, N. D.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 16588–16593. (b) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483. (c) Choi, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 9102–9105.

(7) Enantioselective Ni-catalyzed cross coupling of unactivated alkyl halides with organometallic reagents: Choi, J.; Martín-Gago, P.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 12161–12165.

(8) Ni-catalyzed reductive coupling of alkyl halides and aryl halides: (a) Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 10480–10483. (b) Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192–16197. (c) Weix, D. J. *Acc. Chem. Res.* **2015**, *48*, 1767–1775. (d) Wang, X.; Wang, S.; Xue, W.; Gong, H. *Angew. Chem. Int. Ed.* **2015**, *137*, 11562–11565.

(9) Ni-catalyzed borylation and silylation of alkyl halides: (a) Dudnik, A. S.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 10693–10697. (b) Chu, C. K.; Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.*, **2016**, *138*, 6404–6407.

(10) (a) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794–5797. (b) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154–8157.

(11) Schmidt, J.; Choi, J.; Liu, A. T.; Slusarczyk, M.; Fu, G. C. *Science* **2016**, *354*, 1265–1269.

(12) Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 9523–9526.

(13) Yi, J.; Liu, J.-H.; Liang, J.; Dai, J.-J.; Yang, C.-T.; Fu, Y.; Liu, L. *Adv. Synth. Catal.* **2012**, *354*, 1685–1691.

(14) (a) Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 528–532. (b) Ito, H.; Kubota, K. *Org. Lett.* **2012**, *14*, 890–893.

(15) Bose, S. K.; Fucke, K.; Liu, L.; Steel, P. G.; Marder, T. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 1799–1803.

(16) Atack, T. C.; Lecker, R. M.; Cook, S. P. *J. Am. Chem. Soc.* **2014**, *136*, 9521–9523.

(17) Atack, T. C.; Cook, S. P. *J. Am. Chem. Soc.* **2016**, *138*, 6139–6142.

(18) Jiang, M.; Yang, H.; Fu, H. *Org. Lett.* **2016**, *18*, 5248–5251.

(19) Kubota, K.; Iwamoto, H.; Ito, H. *Org. Biomol. Chem.* **2017**, *15*, 285–300.

(20) (a) Hall, D. G.; Lee, J. C. H.; Ding, J. *Pure Appl. Chem.*, **2012**, *84*, 2263–2277. (b) Bull, J. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 8930–8932.

(21) Lloyd-Jones, G. C.; Lennox, A. J. J. *Chem. Soc. Rev.* **2014**, *43*, 412–443.

(22) Roy, C. D.; Brown, H. C. *J. Organomet. Chem.* **2007**, *692*, 784–790.

(23) Leonori, D.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2015**, *54*, 1082–1096.

(24) Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988**, *21*, 287–293.

(25) (a) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555–10607. (b) Burns, M.; Essafi, S.; Bame, J. R.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.; Butts, C. P.; Harvey, J. N.; Aggarwal, V. K. *Nature* **2015**, *513*, 183–188.

(26) (a) Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2013**, 4695–4712. (b) Carroll, A.-M.; O'Sullivan, T. P.; Guiry, P. J. *Adv. Synth. Catal.* **2005**, *347*, 609–631.

(27) (a) Burks, H. E.; Morken, J. P. *Chem. Commun.* **2007**, 4717–4725. (b) Takaya, J.; Iwasawa, N. *ACS Catal.* **2012**, *2*, 1993–2006. (c) Coombs, J. R.; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 16140–16143.

(28) (a) Han, J. T.; Jang, W. J.; Kim, N.; Yun, J. *J. Am. Chem. Soc.* **2016**, *138*, 15146–15149. (b) Yamamoto, E.; Takenouchi, Y.; Ozaki, T.; Miya, T.; Ito, H. *J. Am.*

Chem. Soc. **2014**, *136*, 16515–16521. (c) Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; McQuade, D. T. *J. Am. Chem. Soc.* **2011**, *133*, 2410–2413. (d) Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634–10637. (e) Ito, H.; Ito, S.; Sasaki, Y.; Matsura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856–14857.

(29) Schiffner, J. A.; Müther, K.; Oestreich, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1194–1196.

(30) (a) Zhou, Q.; Srinivas, H. D.; Zhang, S.; Watson, M. P. *J. Am. Chem. Soc.* **2016**, *138*, 11989–11995. (b) Basch, C. H.; Cobb, K. M.; Watson, M. P. *Org. Lett.* **2016**, *18*, 136–139.

(31) Nelson, H. M.; Williams, B. D.; Miró, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213–3216.

(32) (a) Lee, J. C. H.; Hall, D. G. *J. Am. Chem. Soc.* **2010**, *132*, 5544–5545. (b) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894–899.

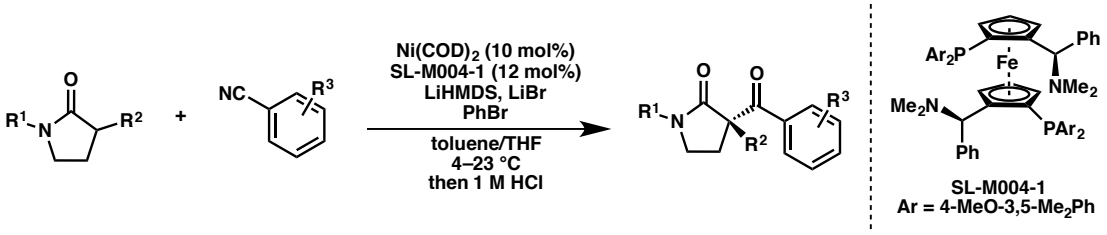
(33) (a) Smilović, I. G.; Casas-Arcé, E.; Roseblade, S. J.; Nettekoven, U.; Zanotti-Gerosa, A.; Kovačevič, M.; Časar, Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 1014–1018. (c) Paptchikhine, A.; Cheruku, P.; Engman, M.; Andersson, P. G. *Chem. Commun.* **2009**, 5996–5998. (d) Moran, W. J.; Morken, J. P. *Org. Lett.* **2006**, *8*, 2413–2415.

(34) (a) Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534–6537. (b) Potter, B.; Edelstein, E. K.; Morken, J. P. *Org. Lett.* **2016**, *18*, 3286–3289.

(35) Cherney, A. H.; Reisman, S. E. *J. Am. Chem. Soc.* **2014**, *136*, 14365–14368.

CHAPTER 4

Ni-Catalyzed Enantioselective C-Acylation of α-Substituted Lactams[†]

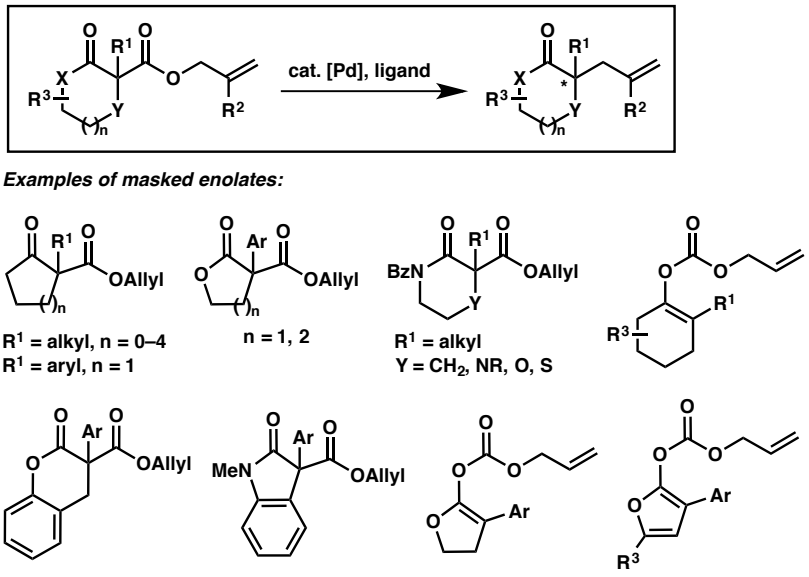


[†]This work was performed in collaboration with Masaki Hayashi, Satoshi Hashimoto, and Chad Eichman and was partially adapted from the publication: Hayashi, M.; Bachman, S.; Hashimoto, S.; Eichman, C. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2016**, *138*, 8997–9000. Copyright 2016 American Chemical Society.

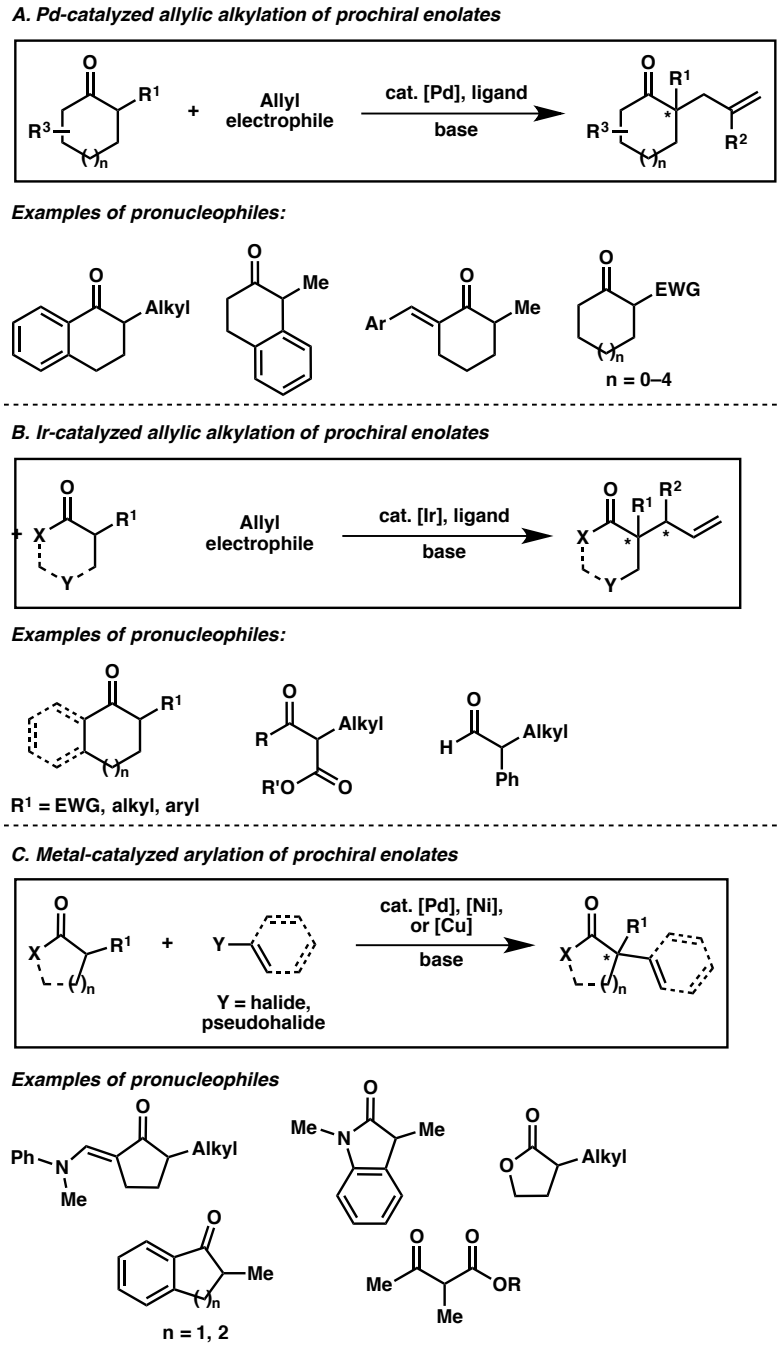
4.1 Introduction

Catalytic enantioselective construction of all-carbon quaternary stereocenters is a particular challenge in organic synthesis.[1] One successful approach has been stereoselective metal-catalyzed coupling of prochiral tetrasubstituted enolate nucleophiles with alkyl, aryl and alkenyl electrophiles. The nucleophile may be generated via either activation of a masked enolate or enolization of a pronucleophile. For example, Pd-catalyzed decarboxylative asymmetric allylic alkylation reactions provide access to a variety of α-quaternary products (Scheme 4.1).[2] Both Pd[3] and Ir[4] catalysts are effective for asymmetric allylic alkylation of α,α-disubstituted pronucleophiles (Scheme 4.2A, B); Ir catalysis provides access to vicinal quaternary and tertiary stereocenters. Enantioselective α-functionalization of prochiral enolates with aryl and alkenyl (pseudo)halides may be achieved under Pd[5] and Ni,[6] or Cu catalysis[7] (Scheme 4.2C).[8]

Scheme 4.1 Formation of α-quaternary stereocenters via Pd-catalyzed decarboxylative allylic alkylation



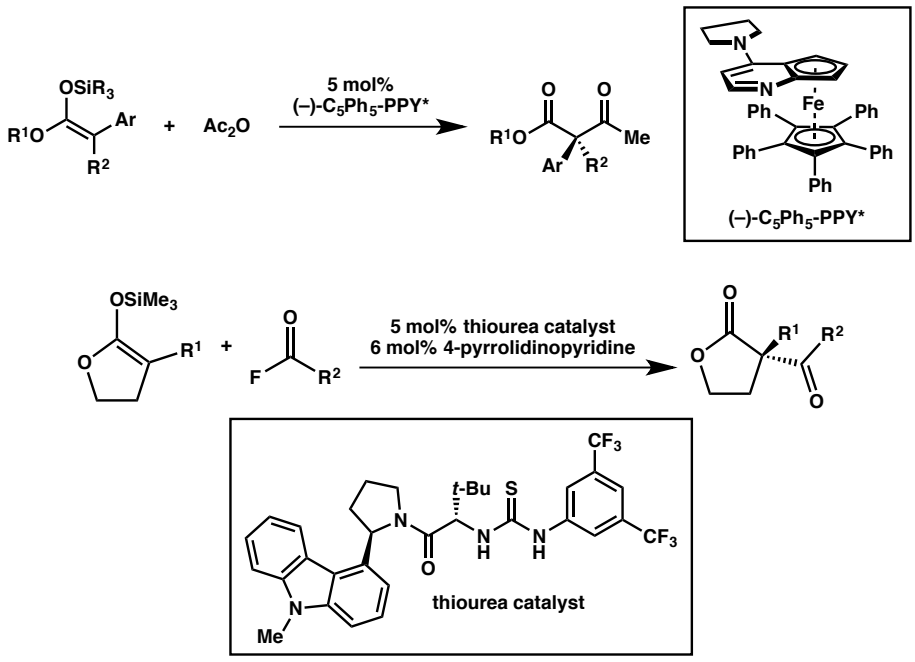
Scheme 4.2 Synthesis of α-quaternary stereocenters via functionalization of in situ-generated prochiral enolates



Despite the success of these processes, there are no general methods for stereoselective metal-catalyzed coupling of in situ-generated tetrasubstituted enolates

with *acyl* electrophiles. While intramolecular acyl transfer strategies have been developed,[9] intermolecular *C*-acylation reactions of enolates or enol ethers are more limited. Acylation conditions may result in competitive *O*-acylation of enolates.[10] However, α-acyl quaternary stereocenters have been accessed through organocatalyzed couplings of silyl ketene acetals with acyl derivatives (Scheme 4.3). [11] To our knowledge, there have been no reports of intermolecular enantioselective *C*-acylation reactions of carbonyl derivatives other than silyl ketene acetals. Herein, we report a new strategy for catalytic enantioselective formal *C*-acylation that enables the preparation of lactams bearing α-quaternary stereocenters.

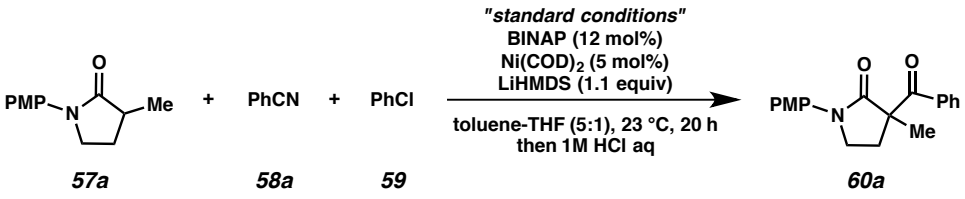
Scheme 4.3 Enantioselective organocatalyzed coupling of silyl ketene acetals with acyl derivatives



4.2 Results and Discussion

During the course of our investigations into enolate functionalization reactions, we observed the formation of α-acylated product **60a** under the conditions shown in Table 4.1, entry 1. In the absence of Ni, ligand, or chlorobenzene (**59**), <5% product was observed (entries 2–4), indicating that direct nucleophilic addition of the lithium enolate derived from lactam **57a** to the nitrile **58a** is not the predominant reaction pathway. Both Pd(0) and Ni(II) sources were ineffective (entries 5–6). Either chlorobenzene or chlorotoluene resulted in the formation of product **60a**, consistent with the phenyl group in the product arising from benzonitrile incorporation (entry 7).

Table 4.1 Effect of various reaction parameters on enantioselective Ni-catalyzed C-acylation



57a ***58a*** ***59*** ***60a***

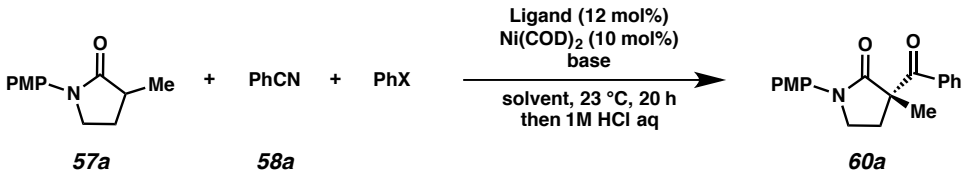
entry	deviation from standard conditions	yield (%)[a]
1	none	31
2	no $Ni(COD)_2$ or (*R*)-BINAP	0
3	no (*R*)-BINAP	3[b]
4	no PhCl	0
5	$Pd(dba)_2$ instead of $Ni(COD)_2$	0
6	$NiCl_2$ instead of $Ni(COD)_2$	0
7	*p*-tolylCl instead of PhCl	41

[a]Conditions: lactam (1 equiv), PhCN (2 equiv), aryl chloride (2 equiv), LiHMDS (1.1 equiv), $Ni(COD)_2$ (10 mol%), ligand (12 mol%), in 5:1 toluene/THF (0.2 M) at 23 °C for 20 h, then 1 M HCl aq at 23 °C for 0.5 h.
[b]HPLC conversion

After confirming the involvement of Ni and ligand in this formal lactam α-acylation reaction, we turned our attention to optimization of the reaction parameters. Ferrocene-based ligands were found to be optimal, with both Josiphos and Mandyphos ligand classes providing promising results. In TBME, LiHMDS (Table 4.2, entry 3) provided higher levels of conversion and enantioselectivity than NaHMDS and KHMDS (entries 1 and 2). Using phenyl triflate in place of chlorobenzene resulted in similar conversion but lower levels of enantioselectivity (entry 4), while iodobenzene provided slightly lower conversion and similar enantioselectivity (entry 5). The highest conversion and enantioselectivity were obtained with bromobenzene (entry 6). Switching from **L9** to **L10** and using a 10:1 mixture of toluene/THF resulted in decreased conversion but a small increase in enantioselectivity (entry 7). The addition of excess LiBr was found to substantially increase both conversion and enantioselectivity (entry 8). The synthesis of 1.1 g of product (69% yield, 90% ee) was achieved under conditions using reduced (1.3) equivalents of lactam **57a** (Scheme 4.4).

With optimized conditions in hand, we explored the scope of the reaction with respect to the *N*-aryl moiety. Electron-rich aryl rings resulted in generally good yields and high levels of enantioselectivity (Scheme 4.5). Switching from a *p*-OMe-phenyl substrate (**57a**) to an *o*-OMe-phenyl substrate (**57b**) resulted in improved enantioselectivity but lower yield. The yield was improved upon lowering the temperature from 23 °C to 4 °C and increasing the reaction time. Under these lower temperature conditions, both **57c** and **57d** resulted in moderate to good yield and high ee.

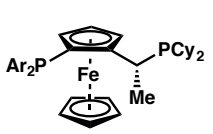
Table 4.2 Effect of base, halide, solvent, and LiBr on Ni-catalyzed C-acylation



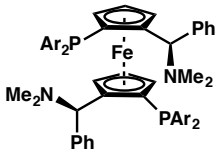
57a ***58a*** ***60a***

entry	ligand	base	PhX	solvent	additive	conversion (%)	ee (%)[a]
1[a]	*L9*	NaHMDS	PhCl	TBME	-	42	0
2[a]	*L9*	KHMDS	PhCl	TBME	-	51	0
3[a]	*L9*	LiHMDS	PhCl	TBME	-	74	–54
4[a]	*L9*	LiHMDS	PhOTf	TBME	-	73	–28
5[a]	*L9*	LiHMDS	PhI	TBME	-	65	–55
6[a]	*L9*	LiHMDS	PhBr	TBME	-	83	–61
7[b]	*L10*	LiHMDS	PhBr	toluene-THF (10:1)	-	55	68
8[b]	*L10*	LiHMDS	PhBr	toluene-THF (10:1)	LiBr (5 equiv)	98	89

[a]Conditions: lactam (1 equiv), PhCN (2 equiv), PhX (2 equiv), base (1.1 equiv), $Ni(COD)_2$ (10 mol%), ligand (12 mol%), in solvent (0.2 M) at 23 °C for 20 h, then 1 M HCl aq at 23 °C for 0.5 h. [b]Conditions: lactam (2 equiv), PhCN (1 equiv), PhX (1 equiv), base (1.2 equiv), $Ni(COD)_2$ (10 mol%), ligand (12 mol%), in solvent (0.2 M) at 23 °C for 20 h, then 1 M HCl aq at 23 °C for 0.5 h.

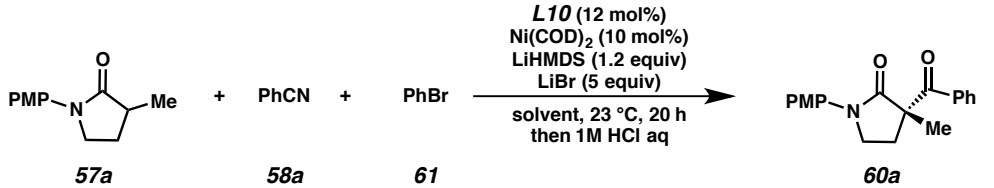


L9: SL-J006-1
Ar = 3,5-$(CF_3)_2$Ph



L10: SL-M004-1
Ar = 4-MeO-3,5-Me_2Ph

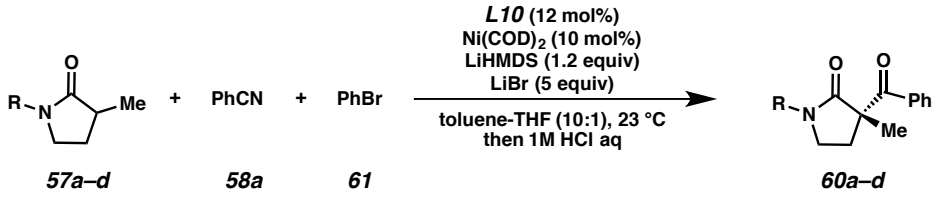
Scheme 4.4 Gram-scale Ni-catalyzed C-acylation



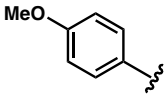
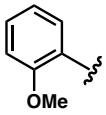
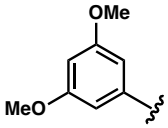
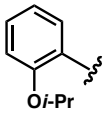
57a ***58a*** ***61*** ***60a***

1.3 equiv 1.0 equiv 1.5 equiv 1.1 g, 69% yield, 90% ee

Scheme 4.5 Effect of N-aryl substituent on Ni-catalyzed C-acylation



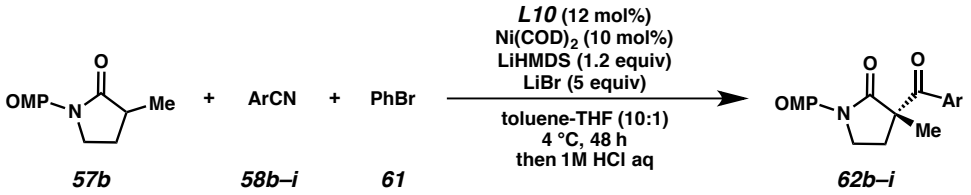
57a–d *58a* *61* *60a–d*

R				
	60a	***60b***	***60c***	***60d***
yield,[a] ee	86%, 88% ee[b]	61%, 92% ee[b] 81%, 92% ee[c]	80%, 85% ee[c]	69%, 86% ee[c]

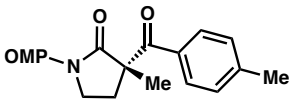
[a]Conditions: lactam (2 equiv), PhCN (1 equiv), PhBr (1.5 equiv), LiHMDS (1.2 equiv), LiBr (5 equiv), $Ni(COD)_2$ (10 mol%), ligand (12 mol%), in toluene/THF (10:1, 0.09 M), then 1 M HCl aq. [b]Reactions were conducted at 23 °C for 24 h. [c]Reactions were conducted at 4 °C for 48 h.

The scope of the reaction is broad with respect to the benzonitrile (Scheme 4.6). Me-substitution at the para, meta, and ortho positions is well-tolerated (**58b–e→62b–e**). High levels of enantioselectivity are observed for both electron-poor and electron-rich benzonitriles (**58f–h**), but electron-poor benzonitriles result in low yields (**58g**, **h**). Alkyl nitriles did not result in significant product formation.

Scheme 4.6 Scope with respect to the benzonitrile coupling partner

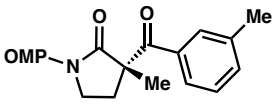


57b *58b–i* *61* *62b–i*



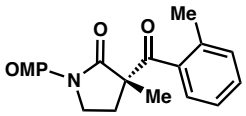
62b

92% yield, 91% ee



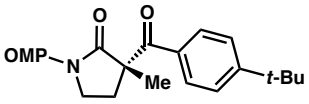
62c

91% yield, 93% ee



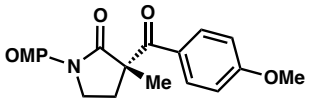
62d

69% yield, 94% ee



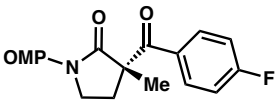
62e

89% yield, 92% ee



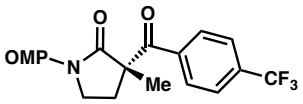
62f

85% yield, 89% ee



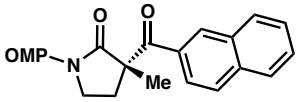
62g

36% yield, 93% ee



62h

23% yield,[b] 87% ee



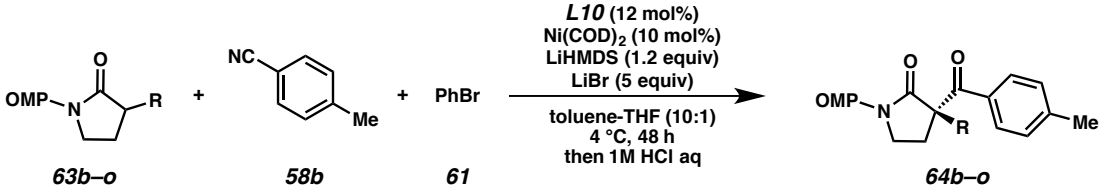
62i

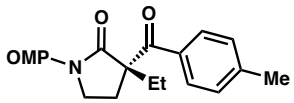
66% yield, 91% ee

[a]Conditions: lactam (2 equiv), ArCN (0.2 mmol, 1 equiv), PhBr (1.5 equiv), Ni(COD)2 (10 mol%), ligand (12 mol%), in toluene/THF (10:1, 0.09 M) at 4 °C for 48 h, then 1 M HCl aq. [b]The reaction was carried out at 23 °C for 24 h.

The reaction is significantly affected by the nature of the lactam α-substituent. Increasing the steric demand from methyl to ethyl (Scheme 4.7, **63b→64b**) results in both reduced yield and enantioselectivity. Benzyl substituents provide moderate to good yields and levels of enantioselectivity (**63c–e→64c–e**). Moderate to high levels of enantioselectivity are also observed for crotyl- and cinnamyl-substituted lactams (**63h–n→64h–n**).

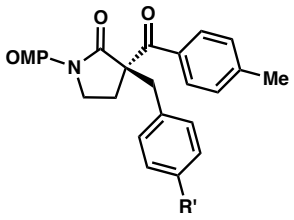
Scheme 4.7 Scope with respect to the lactam α-substituent



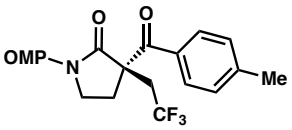


64b

50% yield, 78% ee

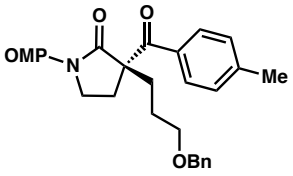


64c (R' = H): 61% yield, 81% ee
64d (R' = OMe): 77% yield, 81% ee
64e (R' = F): 76% yield, 74% ee



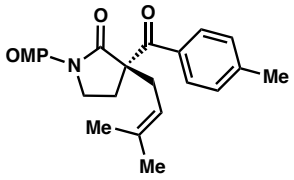
64f

58% yield, 71% ee



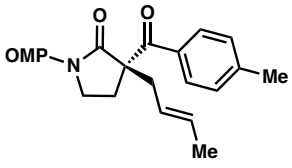
64g

67% yield, 60% ee



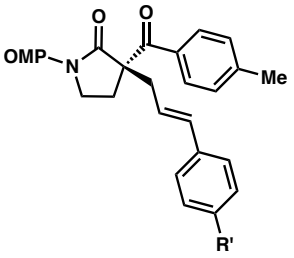
64h

71% yield, 76% ee

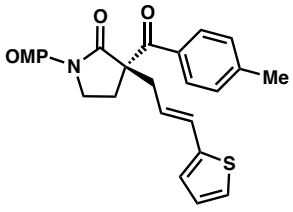


64i

70% yield, 86% ee

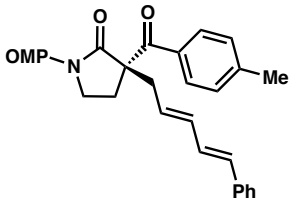


64j (R' = H): 50% yield, 86% ee
64k (R' = Me): 85% yield, 88% ee
64l (R' = OMe): 68% yield, 88% ee
64m (R' = F): 62% yield, 83% ee



64n

76% yield, 83% ee



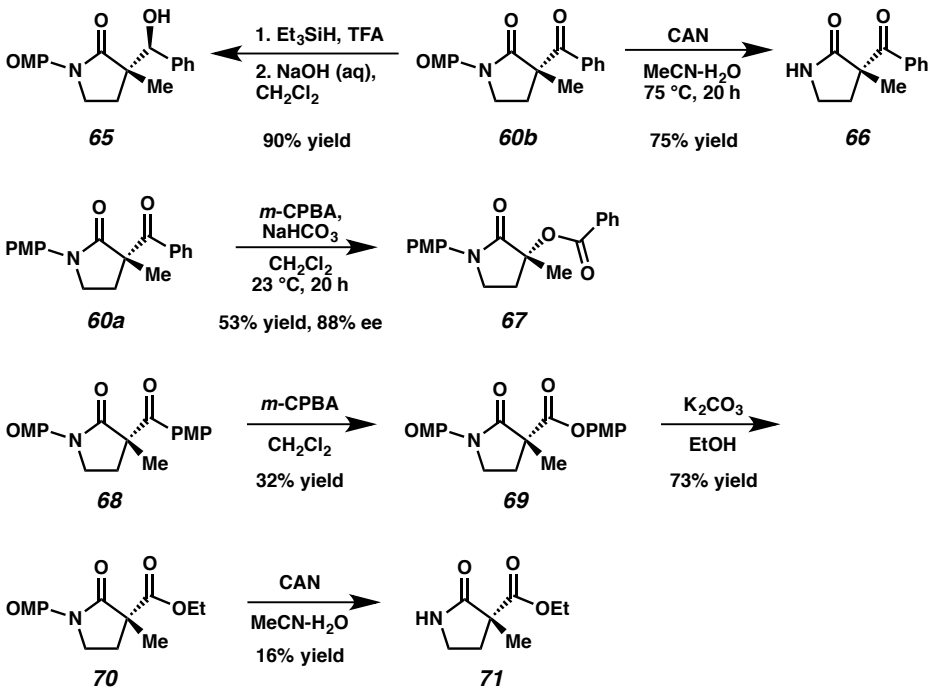
64o

35% yield, 84% ee

[a]Conditions: lactam (2 equiv), p-tolunitrile (0.2 mmol, 1 equiv), PhBr (1.5 equiv), Ni(COD)2 (10 mol%), ligand (12 mol%), in toluene/THF (10:1, 0.09 M) at 4 °C for 48 h, then 1 M HCl aq.

The enantioenriched α-acylated lactam products were subjected to a variety of further transformations. Lactam **60b** was reduced with Et_3SiH to a single isomer of alcohol **65** in good yield (Scheme 4.8). Deprotection by CAN oxidation furnished lactam **66**. Lactams **60a** and **68** were subjected to Baeyer-Villiger oxidation, giving an α-benzoyloxy lactam (**67**) or an α-aryloxycarbonyl lactam (**69**), respectively. To determine absolute stereochemistry, lactam **69** was converted to known compound **71** through ester exchange followed by deprotection of the *o*-methoxyphenyl group.

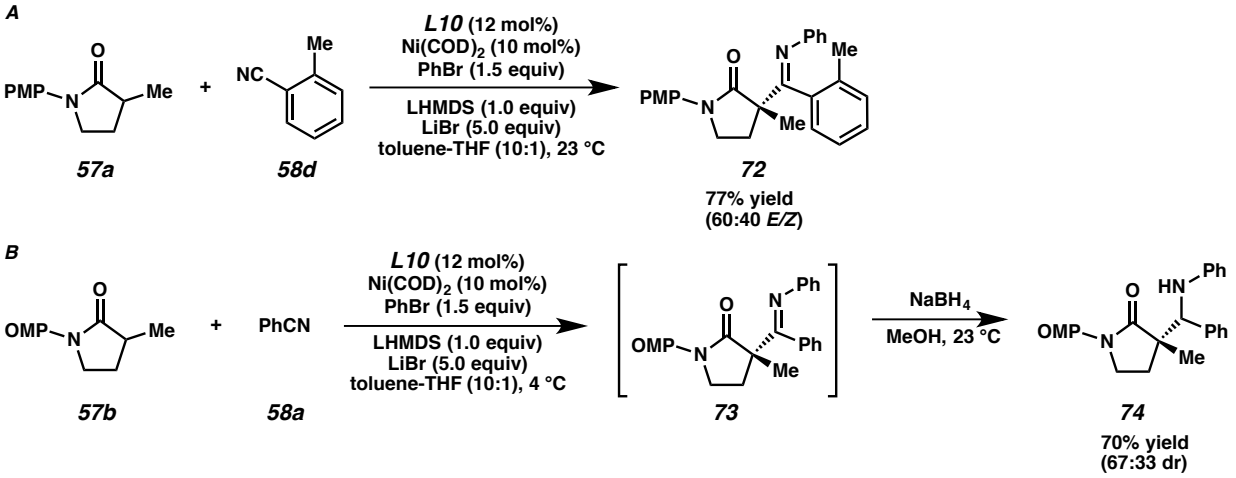
Scheme 4.8 Derivatization of α-acylated lactam products



When the standard reaction conditions were carried out in the absence of an acidic workup, imine **72** was isolated from the reaction of lactam **57a** with *o*-tolunitrile (**58d**, Scheme 4.9A). In addition, the in situ reduction of a reaction mixture

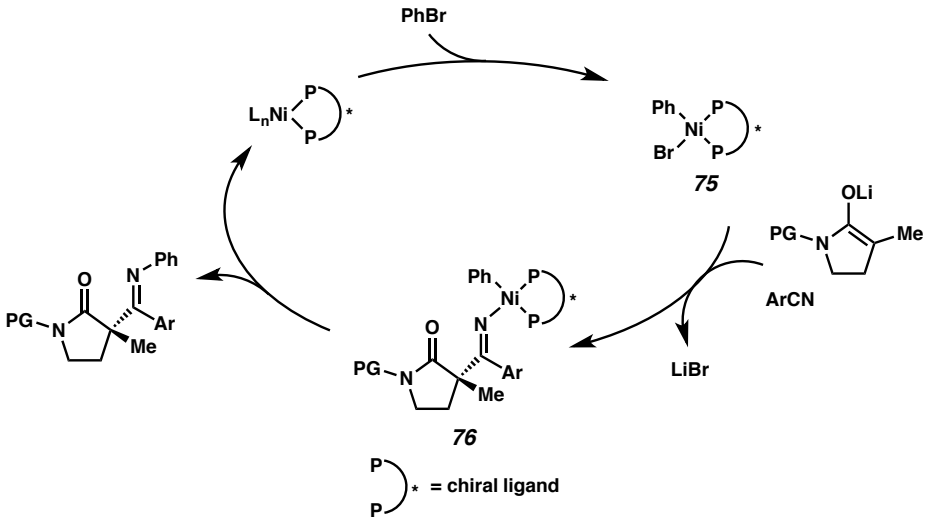
containing lactam **57b** and benzonitrile (**58a**) resulted in the formation of amine **74**. These results are consistent with a reaction pathway involving initial imine formation followed by hydrolysis to reveal the corresponding α-acylated products.

Scheme 4.9A. Isolation of an imine intermediate B. In situ generation and reduction of an imine intermediate



Although we do not have a complete understanding of the mechanism of this process, a possible catalytic cycle is shown in Figure 4.1. Oxidative addition of the aryl bromide to a Ni^0 species generates $Ni^{II}ArBr$ complex **75**. Subsequent insertion of the benzonitrile and lactam enolate produce Ni^{II}-imino complex **76**. Reductive elimination furnishes the imine product, which is then hydrolyzed upon workup.

Figure 4.1 Possible catalytic cycle for enantioselective Ni-catalyzed C-acylation



4.3 Conclusion

We have developed the first intermolecular enantioselective *C*-acylation of lactams via Ni-catalyzed coupling of a lithium enolate, a benzonitrile, and an aryl bromide. The reaction is hypothesized to proceed through initial generation of an imine intermediate followed by hydrolysis to furnish the formal *C*-acylation product. The use of a Mandyphos-type ligand and LiBr as an additive are essential to achieving high yields and levels of enantioselectivity.

4.4 Experimental Procedures

4.4.1 General Information

Unless otherwise stated, reactions were performed in flame-dried or oven-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. Reaction temperatures were controlled by an IKAmag temperature modulator unless otherwise indicated. Glove box manipulations were performed under a N_2 atmosphere. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, $KMnO_4$ or PMA (phosphomolybdic acid) staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.064 mm) was used for flash column chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralcel OD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralcel (OJ-H) column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) and are reported in terms of chemical shift relative to $CHCl_3$ (δ 7.26 and δ 77.16, respectively). Data for ^{1}H NMR 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, app = apparent. Data for ^{13}C are reported in terms of chemical shifts (d ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000

spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or 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+). 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 and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent). Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number.

THF, Et_2O, CH_2Cl_2, toluene, CH_3CN, TBME and dioxane were dried by passage through an activated alumina column under argon. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. Commercially available reagents were purchased from Sigma-Aldrich, Acros Organics, TCI, Oakwood chemicals, Strem, or Alfa Aesar and used as received unless otherwise stated. LiBr was purchased from Aldrich and dried for 3 h at 140 ◦C in vacuo.

(3-Bromopropoxy)methyl)benzene,[12] 1-bromo-2-butene,[13] (*E*)-1-(3-chloroprop-1-en-1-yl)-4-methylbenzene,[14] (*E*)-1-(3-chloroprop-1-en-1-yl)-4-methoxybenzene,[15] (*E*)-1-(3-chloroprop-1-en-1-yl)-4-fluoro--benzene,[16] (E)-3-(thiophen-3-yl)prop-2-en-1-ol,[17] and ((1*E*,3*E*)-5-bromopenta-1,3-dien-1-yl)benzene [18] were prepared by known

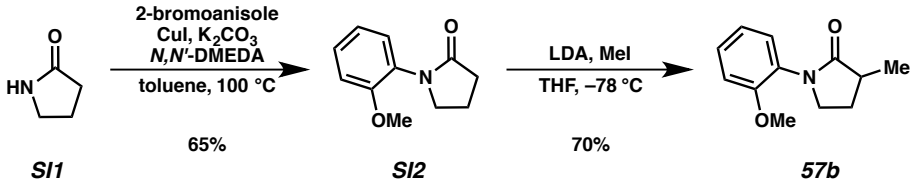
methods and used without purification. (*E*)-3-(3-Chloroprop-1-en-1-yl)thiophene was prepared from (E)-3-(thiophen-3-yl)prop-2-en-1-ol and $SOCl_2$ in CH_2Cl_2 and used without purification.

List of Abbreviations:

ee – enantiomeric excess, dr – diastereomeric ratio, HPLC – high-performance liquid, chromatography, SFC – supercritical fluid chromatography, TLC – thin-layer chromatography, AcOEt – ethyl acetate, THF – tetrahydrofuran, MeOH – methanol, MeCN – acetonitrile, IPA – isopropanol, BINAP – (2,2'–bis(diphenylphosphino)–1,1'–binaphthyl), LHMDS – lithium hexamethyldisilazide, NaHMDS – sodium hexamethyldisilazide, KHMDS – potasium hexamethyldisilazide, PMP – *p*-methoxyphenyl, CAN – ceric ammonium nitrate, TFA – trifluoroacetic acid, *m*-CPBA – *m*-chloroperoxybenzoic acid

4.4.2 Preparation of Materials

General Procedure for a-Substituted Lactam Substrates



General procedure 1: 1-(2-methoxyphenyl)pyrrolidin-2-one (SI2)

To a suspension of lactam **SI1** (8.17 g, 96.0 mmol, 1.20 equiv), K_2CO_3 (22.1 g, 160 mmol, 2.00 equiv) and CuI (1.52 g, 8.00 mmol, 0.10 equiv) in toluene (80 mL) were added 2-bromoanisole (9.84 mL, 80.0 mmol, 1.00 equiv) and N,N'-dimethylethylendiamine (1.68 mL, 16.0 mmol, 0.20 equiv). The reaction mixture was stirred at 100 °C for 18 h then allowed to cool to ambient temperature and filtered through a pad of silica gel eluting with AcOEt (250 mL). The eluate was concentrated under reduced pressure and the residue was purified by flash column chromatography (1:1 EtOAc:hexanes) on silica gel to give lactam **SI2** as a pale yellow oil (9.88 g, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 2H), 7.06 – 6.97 (m, 2H), 3.88 (s, 3H), 3.80 (t, *J* = 7.0 Hz, 2H), 2.60 (t, *J* = 8.1 Hz, 2H), 2.23 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 154.8, 128.7, 128.6, 127.2, 120.9, 112.0, 55.6, 49.9, 31.2, 19.0; IR (Neat Film NaCl) 2968, 2889, 2838, 1694, 1504, 1461, 1408, 1304, 1281, 1253, 1023, 755 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{14}NO_2$ $[M+H]^+$: 192.1019, found 192.1019.

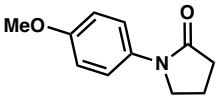
General procedure 2: 1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (57b)

To a solution of diisopropylamine (3.07 mL, 22.0 mmol, 1.10 equiv) in THF (17 mL) was added a solution of *n*-BuLi (8.80 mL, 22.0 mmol, 2.5 M in hexanes, 1.10 equiv) dropwise at -78 °C. After 20 min at -78 °C, a solution of lactam **SI2** (3.82 g, 20.0 mmol, 1.00 equiv) in THF (50 mL) was added dropwise. After an additional 20 min, a solution of methyl iodide (15.0 mL, 30.0 mmol, 2.0 M in TBME, 1.50 equiv) was added and the reaction mixture was stirred at -78 °C for 3 h. Saturated NH_4Cl

aqueous solution (50 mL) was added and the mixture was allowed to ambient temperature. The mixture was extracted with AcOEt (100 mL), washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:4 to 1:2 EtOAc:hexanes) on silica gel to give lactam **57b** as a yellow oil (2.86 g, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 3H), 7.06 – 6.96 (m, 2H), 3.87 (s, 3H), 3.79 – 3.66 (m, 2H), 2.69 (tq, *J* = 8.7, 7.1 Hz, 1H), 2.41 (dddd, *J* = 12.2, 8.5, 7.3, 3.5 Hz, 1H), 1.86 (dq, *J* = 12.4, 8.5 Hz, 1H), 1.36 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.5, 154.8, 128.6, 128.5, 127.6, 120.8, 112.0, 55.6, 47.9, 36.9, 28.1, 16.3; IR (Neat Film NaCl) 2965, 2932, 2874, 1695, 1504, 1463, 1456, 1403, 1311, 1296, 1277, 1251, 1024, 754 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1176, found 206.1176.

Spectroscopic Data for *N*-Protected Lactams

1-(4-Methoxyphenyl)pyrrolidin-2-one (SI3)

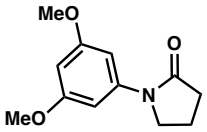


SI3

Lactam **SI3** was prepared according to the general procedure 1, using 4-iodoanisole and K_3PO_4 in place of 2-bromoanisole and K_2CO_3 respectively, and isolated by recrystallization in hexanes/AcOEt (4/1) as a white crystal. 89% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.45 (m, 2H), 7.01 – 6.90 (m, 2H), 3.87 (t, *J* = 7.0 Hz, 2H), 3.84 (s, 3H), 2.64 (t, *J* = 8.1 Hz, 2H), 2.20 (tt, *J* = 15.1, 7.5 Hz, 1H); ^{13}C NMR

(126 MHz, $CDCl_3$) δ 173.9, 156.5, 132.6, 121.8, 114.0, 55.5, 49.2, 32.5, 18.1; IR (Neat Film NaCl) 2952, 2907, 1683, 1517, 1255, 1226, 1182, 1126, 1032, 829 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{14}NO_2$ $[M+H]^+$: 192.1019, found 192.1021.

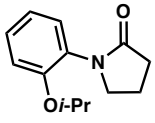
1-(3,5-Dimethoxyphenyl)pyrrolidin-2-one (SI4)



SI4

Lactam **SI4** was prepared according to the general procedure 1, using 1-bromo-3,5-dimethoxybenzene in place of 2-bromoanisole, and isolated by recrystallization in hexanes/AcOEt (5/1) as a white crystal. 89% yield. ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (d, *J* = 2.2 Hz, 2H), 6.31 (t, *J* = 2.2 Hz, 1H), 3.87 (t, *J* = 7.0 Hz, 2H), 3.84 (s, 6H), 2.65 (t, *J* = 8.1 Hz, 2H), 2.19 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 160.8, 141.2, 98.4, 96.5, 77.3, 77.0, 76.8, 55.4, 49.0, 33.1, 17.9; IR (Neat Film NaCl) 2959, 1694, 1593, 1474, 1455, 1424, 1397, 1276, 1245, 1198, 1152, 1071, 1056, 922, 840, 825, 683 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{16}NO_3$ $[M+H]^+$: 222.1125, found 222.1129.

1-(2-Isopropoxyphenyl)-pyrrolidin-2-one (SI5)

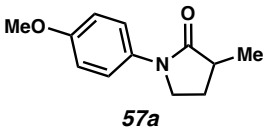


SI5

Lactam **SI5** was prepared according to the general procedure 1, using 1-bromo-2-isopropoxybenzene in place of 2-bromoanisole, and isolated by flash column chromatography (1:2 to 1:1 EtOAc:hexanes) on silica gel as a pale yellow oil. 57% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2H), 7.03 – 6.96 (m, 2H), 4.58 (hept, *J* = 6.0 Hz, 1H), 3.82 (t, *J* = 6.7 Hz, 2H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.28 – 2.16 (m, 2H), 1.38 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 153.1, 128.9, 128.4, 128.4, 120.8, 114.7, 70.8, 49.9, 31.4, 22.2, 19.2; IR (Neat Film NaCl) 2976, 2933, 1697, 1595, 1500, 1456, 1405, 1385, 1304, 1282, 1251, 1125, 1111, 957, 753 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{13}H_{18}NO_2$ $[M+H]^+$: 220.1332, found 220.1328.

Spectroscopic Data for α-Substituted Lactams

1-(4-Methoxyphenyl)-3-methylpyrrolidin-2-one (57a)

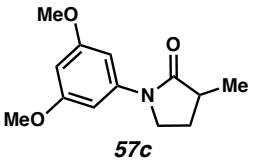


57a

Lactam **57a** was prepared according to the general procedure 2 from **SI3** in place of **SI2**, and isolated by flash column chromatography (1:3 EtOAc:hexanes) on silica gel as a white solid. 82% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.45 (m, 2H), 7.01 – 6.90 (m, 2H), 3.87 (t, J = 7.0 Hz, 2H), 3.84 (s, 3H), 2.64 (t, J = 8.1 Hz, 2H), 2.20 (tt, J = 15.1, 7.5 Hz, 1H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 176.3, 156.4, 133.0, 121.4, 114.0, 55.5, 46.9, 38.1, 27.1, 16.3; IR (Neat Film NaCl) 2952, 2882, 2835, 1682,

1516, 1251, 1225, 1122, 1099, 1030, 829 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1176, found 206.1177.

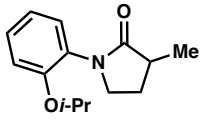
1-(3,5-Dimethoxyphenyl)-3-methylpyrrolidin-2-one (57c)



57c

Lactam **57c** was prepared according to the general procedure 2 from **SI4** in place of **SI2**, and isolated by flash column chromatography (1:4 EtOAc:hexanes) on silica gel as a white solid. 87% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, *J* = 2.2 Hz, 2H), 6.31 (t, *J* = 2.2 Hz, 1H), 3.84 (s, 6H), 3.79 (dd, *J* = 8.8, 5.0 Hz, 2H), 2.78 – 2.66 (m, 1H), 2.45 – 2.35 (m, 1H), 1.86 – 1.74 (m, 1H), 1.35 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 160.8, 141.5, 97.9, 96.5, 77.3, 77.0, 76.8, 55.4, 46.8, 38.6, 26.9, 16.1; IR (Neat Film NaCl) 2964, 1698, 1597, 1474, 1392, 1273, 1246, 1208, 1154, 1071, 927, 834, 682 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{13}H_{18}NO_3$ $[M+H]^+$: 236.1281, found 236.1284.

1-(2-Isoproxyphenyl)-3-methylpyrrolidin-2-one (57d)

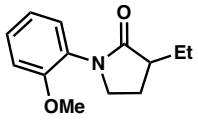


57d

Lactam **57d** was prepared according to the general procedure 2 from **SI5** in place of **SI2**, and isolated by flash column chromatography (1:3 to 1:2 EtOAc:hexanes) on silica gel as a pale yellow oil. 83% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.22

(m, 2H), 7.03 – 6.96 (m, 2H), 4.57 (hept, J = 6.1 Hz, 1H), 3.80 – 3.67 (m, 2H), 2.67 (tq, J = 8.4, 7.1 Hz, 1H), 2.46 – 2.35 (m, 1H), 1.84 (dq, J = 12.3, 8.2 Hz, 1H), 1.37 (d, J = 6.1 Hz, 6H), 1.35 (d, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.5, 153.2, 129.0, 128.7, 128.3, 120.8, 114.8, 70.8, 47.9, 36.9, 28.2, 22.2, 22.2, 16.4; IR (Neat Film NaCl) 2974, 2930, 1701, 1595, 1499, 1457, 1405, 1277, 1249, 1124, 1111, 955, 750 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{20}NO_2$ $[M+H]^+$: 234.1489, found 234.1482.

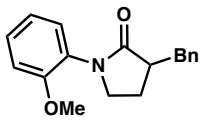
1-(2-Methoxyphenyl)-3-ethypyrrolidin-2-one (63b)



63b

Lactam **63b** was prepared according to the general procedure 2 using ethyl iodide in place of methyl iodide, and isolated by flash column chromatography (1:3 EtOAc:hexanes) on silica gel as a pale yellow oil. 81% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.19 (m, 2H), 7.01 – 6.92 (m, 2H), 3.82 (s, 3H), 3.76 – 3.69 (m, 1H), 3.69 – 3.60 (m, 1H), 2.53 (qd, J = 8.7, 4.3 Hz, 1H), 2.38 – 2.27 (m, 1H), 2.04 – 1.92 (m, 1H), 1.92 – 1.81 (m, 1H), 1.63 – 1.49 (m, 1H), 1.04 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 154.8, 128.7, 128.5, 127.5, 120.8, 112.0, 55.6, 48.2, 43.4, 25.1, 24.2, 11.5; IR (Neat Film NaCl) 2961, 1695, 1596, 1505, 1462, 1404, 1280, 1249, 1024, 752 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{13}H_{18}NO_2$ $[M+H]^+$: 220.1332, found 220.1334.

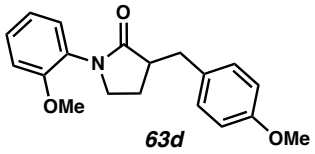
3-Benzyl-1-(2-methoxyphenyl)pyrrolidin-2-one (63c)



63c

Lactam **63c** was prepared according to the general procedure 2 using benzyl bromide in place of methyl iodide, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a pale yellow oil. 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.08 (m, 7H), 6.99 – 6.90 (m, 2H), 3.80 (s, 3H), 3.63 (dt, *J* = 9.5, 7.7 Hz, 1H), 3.49 (ddd, *J* = 9.5, 8.6, 3.7 Hz, 1H), 3.30 (dd, *J* = 13.7, 4.0 Hz, 1H), 2.93 – 2.83 (m, 1H), 2.77 (dd, *J* = 13.6, 9.7 Hz, 1H), 2.20 – 2.10 (m, 1H), 1.94 – 1.83 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 154.8, 139.7, 129.1, 128.6, 128.5, 128.5, 128.4, 127.4, 126.3, 120.9, 112.0, 55.6, 48.0, 43.8, 37.0, 25.1; IR (Neat Film NaCl) 2942, 1694, 1596, 1504, 1454, 1407, 1279, 1252, 1025, 753, 701 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{20}NO_2$ $[M+H]^+$: 282.1489, found 282.1491.

3-(4-Methoxybenzyl)-1-(2-methoxyphenyl)pyrrolidin-2-one (63d)

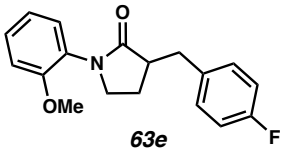


63d

Lactam **63d** was prepared according to the general procedure 2 using 4-methoxybenzyl chloride in place of methyl iodide, and isolated by flash column chromatography (1:3 EtOAc:hexanes) on silica gel as a pale yellow oil. 59% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 1H), 7.24 – 7.14 (m, 3H), 7.00 – 6.90 (m, 2H), 6.88 – 6.80 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.62 (dt, *J* = 9.5, 7.6 Hz, 1H),

3.47 (ddd, *J* = 9.5, 8.6, 3.8 Hz, 1H), 3.21 (dd, *J* = 13.7, 4.0 Hz, 1H), 2.90 – 2.80 (m, 1H), 2.74 (dd, *J* = 13.8, 9.4 Hz, 1H), 2.20 – 2.09 (m, 1H), 1.93 – 1.81 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 158.1, 154.8, 131.6, 130.1, 128.6, 128.5, 127.4, 120.8, 113.8, 112.1, 55.6, 55.3, 48.1, 43.9, 36.0, 25.0; IR (Neat Film NaCl) 2936, 1696, 1596, 1512, 11506, 1462, 1406, 1300, 1279, 1249, 1179, 1028, 753 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{22}NO_3$ $[M+H]^+$: 312.1594, found 312.1589.

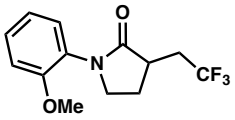
3-(4-Fluorobenzyl)-1-(2-methoxyphenyl)pyrrolidin-2-one (63e)



63e

Lactam **63e** was prepared according to the general procedure 2 using 4-fluorobenzyl bromide in place of methyl iodide, and isolated by flash column chromatography (1:3 to 1:2 EtOAc:hexanes) on silica gel as a pale yellow oil. 77% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.18 (m, 4H), 7.04 – 6.92 (m, 4H), 3.81 (s, 3H), 3.65 (dt, *J* = 9.6, 7.7 Hz, 1H), 3.50 (ddd, *J* = 9.5, 8.6, 3.6 Hz, 1H), 3.24 (dd, *J* = 13.5, 3.8 Hz, 1H), 2.93 – 2.76 (m, 2H), 2.22 – 2.12 (m, 1H), 1.94 – 1.82 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 162.6, 160.6, 154.8, 135.2, 135.1, 130.6, 130.6, 128.6, 128.5, 127.3, 120.9, 115.3, 115.1, 112.0, 55.6, 48.0, 43.7, 36.1, 24.9; IR (Neat Film NaCl) 2942, 1696, 1597, 1507, 1459, 1406, 1252, 1221, 1158, 1025, 752 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{19}FNO_2$ $[M+H]^+$: 300.1394, found 300.1390.

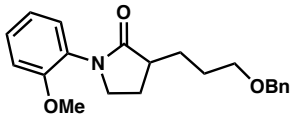
1-(2-Methoxyphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidin-2-one (63f)



63f

Lactam **63f** was prepared according to the general procedure 2 using 2-trifluoroethyl iodide in place of methyl iodide, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a yellow oil. 36% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (ddd, *J* = 8.2, 7.5, 1.7 Hz, 1H), 7.23 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.03 – 6.93 (m, 2H), 3.83 (s, 3H), 3.80 – 3.72 (m, 1H), 3.65 (ddd, *J* = 9.7, 8.8, 1.6 Hz, 1H), 3.04 – 2.93 (m, 1H), 2.93 – 2.84 (m, 1H), 2.56 – 2.46 (m, 1H), 2.14 (s, 1H), 2.07 – 1.95 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 154.7, 128.9, 128.5, 128.1, 126.8, 125.9, 120.9, 112.0, 55.6, 48.0, 37.0, 36.9, 35.9, 35.7, 35.4, 35.2, 26.8; IR (Neat Film NaCl) 2946, 1703, 1597, 1505, 1462, 1414, 1282, 1252, 1135, 1039, 753, 615 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{13}H_{15}F_3NO_2$ $[M+H]^+$: 274.1049, found 274.1049.

3-(3-(Benzyloxy)propyl)-1-(2-methoxyphenyl)pyrrolidin-2-one (63g)

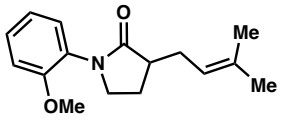


63g

Lactam **63g** was prepared according to the general procedure 2 using ((3-bromopropoxy)methyl)benzene[1] in place of methyl iodide, and isolated by flash column chromatography (1:3 to 1:2 EtOAc:hexanes) on silica gel as a pale yellow oil. 76% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.18 (m, 7H), 6.99 – 6.90 (m, 2H),

4.50 (s, 2H), 3.80 (s, 3H), 3.73 – 3.64 (m, 1H), 3.64 – 3.58 (m, 1H), 3.58 – 3.46 (m, 2H), 2.63 – 2.53 (m, 1H), 2.36 – 2.25 (m, 1H), 2.05 – 1.94 (m, 1H), 1.90 – 1.80 (m, 1H), 1.80 – 1.68 (m, 2H), 1.64 – 1.52 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.7, 154.8, 138.6, 128.6, 128.5, 128.4, 127.7, 127.5, 127.4, 120.8, 112.0, 73.0, 70.4, 55.6, 48.2, 41.8, 28.0, 27.5, 25.8; IR (Neat Film NaCl) 2939, 2860, 1697, 1596, 1504, 1454, 1405, 1279, 1252, 1102, 1026, 749, 699 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{26}NO_3$ $[M+H]^+$: 340.1907, found 340.1915.

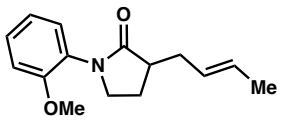
1-(2-Methoxyphenyl)-3-(3-methylbut-2-en-1-yl)pyrrolidin-2-one (63h)



63h

Lactam **63h** was prepared according to the general procedure 2 using 1-bromo-3-methyl-2-butene in place of methyl iodide, and isolated by flash column chromatography (1:3 EtOAc:hexanes) on silica gel as a pale yellow oil. 75% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.20 (m, 2H), 7.01 – 6.92 (m, 2H), 5.24 – 5.16 (m, 1H), 3.83 (s, 3H), 3.73 – 3.59 (m, 2H), 2.69 – 2.53 (m, 2H), 2.33 – 2.22 (m, 2H), 1.91 – 1.80 (m, 1H), 1.74 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6, 154.8, 133.6, 128.6, 128.5, 127.6, 121.3, 120.8, 112.0, 55.6, 55.6, 48.2, 42.3, 29.5, 25.9, 25.9, 25.1, 18.0; IR (Neat Film NaCl) 2913, 1698, 1596, 1505, 1459, 1405, 1279, 1252, 1025, 751 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{22}NO_2$ $[M+H]^+$: 260.1645, found 260.1644.

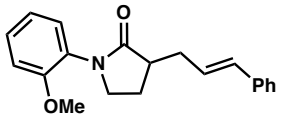
(*E*)-3-(But-2-en-1-yl)-1-(2-methoxyphenyl)pyrrolidin-2-one (63i)



63i

Lactam **63i** was prepared according to the general procedure 2 using 1-bromo-2-butene[2] in place of methyl iodide, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a pale yellow oil. 24% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 2H), 7.01 – 6.92 (m, 2H), 5.62 – 5.43 (m, 2H), 3.83 (s, 3H), 3.73 – 3.58 (m, 2H), 2.68 – 2.53 (m, 2H), 2.32 – 2.19 (m, 2H), 1.95 – 1.82 (m, 1H), 1.72 – 1.66 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 154.8, 128.6, 128.6, 128.6, 128.1, 127.4, 120.9, 112.1, 55.6, 48.2, 42.0, 34.3, 24.8, 18.1; IR (Neat Film NaCl) 2937, 1699, 1596, 1505, 1456, 1436, 1404, 1298, 1279, 1252, 1107, 1046, 1025, 968, 751 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.1489, found 246.1487.

(*E*)-3-Cinnamyl-1-(2-methoxyphenyl)pyrrolidin-2-one (63j)

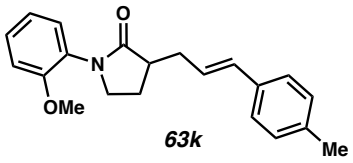


63j

Lactam **63j** was prepared according to the general procedure 2 using cinnamyl bromide in place of methyl iodide, and isolated by flash column chromatography (1:5 to 1:2 EtOAc:hexanes) on silica gel as a pale yellow oil. 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 2H), 7.36 – 7.17 (m, 5H), 7.02 – 6.93 (m, 2H), 6.51 (d, J = 15.7 Hz, 1H), 6.29 (dt, J = 15.7, 7.1 Hz, 1H), 3.81 (s, 3H), 3.75 – 3.61 (m,

2H), 2.84 – 2.73 (m, 2H), 2.57 – 2.46 (m, 1H), 2.38 – 2.27 (m, 1H), 2.03 – 1.92 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 154.8, 137.5, 132.2, 128.6, 128.6, 128.5, 127.5, 127.4, 127.1, 126.1, 120.9, 112.0, 55.6, 48.2, 41.9, 34.7, 24.8; IR (Neat Film NaCl) 2941, 1694, 1596, 1504, 1463, 1407, 1253, 1025, 967, 749, 694 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{22}NO_2$ $[M+H]^+$: 308.1645, found 308.1645.

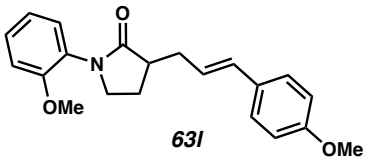
(*E*)-1-(2-Methoxyphenyl)-3-(3-(p-tolyl)allyl)pyrrolidin-2-one (63k)



63k

Lactam **63k** was prepared according to the general procedure 2 using (*E*)-1-(3-chloroprop-1-en-1-yl)-4-methylbenzene[3] in place of methyl iodide, and isolated by flash column chromatography (1:3 EtOAc:hexanes) on silica gel as a pale yellow oil. 90% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.21 (m, 4H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.03 – 6.94 (m, 2H), 6.49 (d, *J* = 15.7 Hz, 1H), 6.24 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.83 (s, 3H), 3.77 – 3.62 (m, 2H), 2.84 – 2.73 (m, 2H), 2.58 – 2.44 (m, 1H), 2.40 – 2.27 (m, 4H), 2.04 – 1.92 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 154.8, 136.9, 134.7, 132.0, 129.2, 128.6, 128.6, 127.4, 126.4, 126.0, 120.9, 112.0, 55.6, 48.2, 41.9, 34.7, 24.8, 21.2; IR (Neat Film NaCl) 2939, 1695, 1596, 1504, 1462, 1405, 1279, 1252, 1181, 1122, 1107, 1045, 1025, 968, 891, 752 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{24}NO_2$ $[M+H]^+$: 322.1802, found 322.1803.

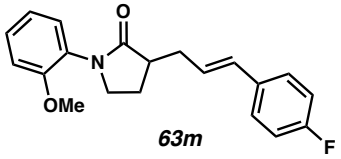
(*E*)-1-(2-Methoxyphenyl)-3-(3-(4-methoxyphenyl)allyl)pyrrolidin-2-one (63l)



63l

Lactam **63l** was prepared according to the general procedure 2 using (*E*)-1-(3-chloroprop-1-en-1-yl)-4-methoxybenzene[4] in place of methyl iodide, and isolated by flash column chromatography (1:3 EtOAc:hexanes) on silica gel as a pale yellow oil. 100% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.18 (m, 4H), 7.02 – 6.94 (m, 2H), 6.94 – 6.82 (m, 2H), 6.45 (dt, *J* = 15.8, 1.4 Hz, 1H), 6.14 (dt, *J* = 15.7, 7.1 Hz, 1H), 3.81 (s, 3H), 3.81 (s, 3H), 3.76 – 3.60 (m, 2H), 2.81 – 2.69 (m, 2H), 2.54 – 2.43 (m, 1H), 2.37 – 2.26 (m, 1H), 2.02 – 1.91 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 158.9, 154.8, 131.5, 130.3, 128.6, 128.6, 127.4, 127.2, 125.2, 120.9, 113.9, 112.0, 55.6, 55.3, 48.2, 42.0, 34.7, 24.8; IR (Neat Film NaCl) 2934, 1694, 1606, 1510,1505, 1463, 1406, 1249, 1175, 1027, 753 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{24}NO_3$ $[M+H]^+$: 338.1751, found 338.1748.

(*E*)-3-(3-(4-Fluorophenyl)allyl)-1-(2-methoxyphenyl)pyrrolidin-2-one (63m)

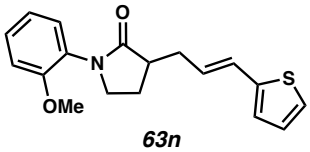


63m

Lactam **63m** was prepared according to the general procedure 2 using (*E*)-1-(3-chloroprop-1-en-1-yl)-4-fluorobenzene[5] in place of methyl iodide, and isolated by flash column chromatography (1:3 EtOAc:hexanes) on silica gel as a white solid. 52% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H), 7.30 – 7.21 (m, 2H), 7.05 – 6.93 (m, 4H), 6.51 – 6.43 (m, 1H), 6.20 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.81 (s, 3H),

3.75 – 3.61 (m, 2H), 2.83 – 2.73 (m, 2H), 2.56 – 2.45 (m, 1H), 2.38 – 2.27 (m, 1H), 1.96 (ddt, *J* = 12.8, 8.6, 7.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 163.0, 161.1, 154.8, 133.7, 133.6, 131.0, 128.7, 128.6, 127.6, 127.5, 127.3, 127.8, 127.2, 120.9, 115.5, 115.3, 112.0, 55.6, 48.2, 41.9, 34.7, 24.9; IR (Neat Film NaCl) 2942, 1696, 1597, 1507, 1458, 1405, 1279, 1253, 1225, 1158, 1046, 1025, 968, 839, 753 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{21}FNO_2$ $[M+H]^+$: 326.1551, found 326.1544.

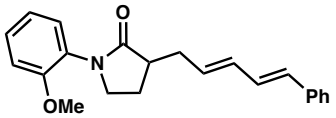
(*E*)-1-(2-Methoxyphenyl)-3-(3-(thiophen-3-yl)allyl)pyrrolidin-2-one (63n)



63n

Lactam **63n** was prepared according to the general procedure 2 using (*E*)-3-(3-chloroprop-1-en-1-yl)thiophene in place of methyl iodide, and isolated by flash column chromatography (1:2 EtOAc:hexanes) on silica gel as a pale yellow oil. 62% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.19 (m, 4H), 7.10 (dd, *J* = 3.1, 1.2 Hz, 1H), 7.01 – 6.92 (m, 2H), 6.52 (d, *J* = 15.7 Hz, 1H), 6.13 (dt, *J* = 15.7, 7.1 Hz, 1H), 3.81 (s, 3H), 3.75 – 3.59 (m, 2H), 2.81 – 2.71 (m, 2H), 2.53 – 2.42 (m, 1H), 2.37 – 2.26 (m, 1H), 2.02 – 1.90 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 154.8, 140.1, 128.6, 128.6, 127.3, 127.3, 126.4, 125.9, 125.0, 121.0, 120.9, 112.1, 55.6, 48.2, 41.9, 34.6, 24.9; IR (Neat Film NaCl) 2936, 1694, 1596, 1504, 1463, 1408, 1279, 1252, 1181, 1122, 1046, 1025, 966, 890, 862, 753 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{20}NO_2S$ $[M+H]^+$: 314.1209, found 314.1206.

1-(2-Methoxyphenyl)-3-((2*E*,4*E*)-5-phenylpenta-2,4-dien-1-yl)pyrrolidin-2-one (63o)

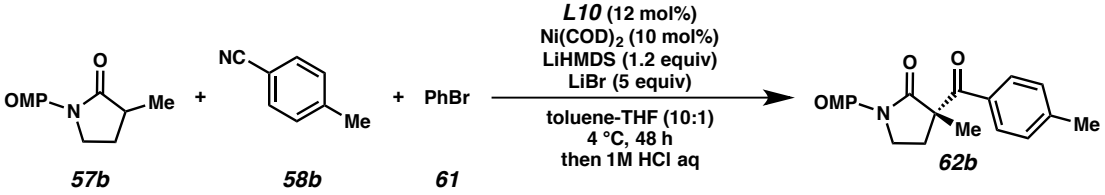


63o

Lactam **63o** was prepared according to the general procedure 2 using ((1*E*,3*E*)-5-bromopenta-1,3-dien-1-yl)benzene[7] in place of methyl iodide, and isolated by flash column chromatography (1:2 EtOAc:hexanes) on silica gel as a colorless oil. 73% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 2H), 7.36 – 7.17 (m, 4H), 7.02 – 6.92 (m, 2H), 6.79 (ddd, *J* = 15.7, 10.4, 0.8 Hz, 1H), 6.49 (d, *J* = 15.7 Hz, 1H), 6.33 (ddd, *J* = 15.1, 10.4, 0.8 Hz, 1H), 5.93 – 5.83 (m, 1H), 3.83 (s, 3H), 3.76 – 3.61 (m, 2H), 2.80 – 2.68 (m, 2H), 2.47 – 2.37 (m, 1H), 2.36 – 2.26 (m, 1H), 1.99 – 1.87 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 154.8, 137.4, 132.8, 132.0, 130.9, 129.0, 128.6, 128.6, 128.6, 127.4, 127.3, 126.2, 120.9, 112.0, 55.6, 48.1, 41.9, 34.6, 25.0; IR (Neat Film NaCl) 2941, 1694, 1596, 1505, 1463, 1407, 1300, 1279, 1252, 1181, 1123, 1107, 1046, 1026, 992, 911, 891, 750, 693 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{24}NO_2$ $[M+H]^+$: 334.1802, found 334.1801.

General Procedure for Ni-Catalyzed C-Acylation

*Please note that the absolute configuration was determined only for compound **10** by transforming to a known compound. The absolute configuration for all other products has been inferred by analogy. For respective HPLC and SFC conditions, please refer to Table S1.*



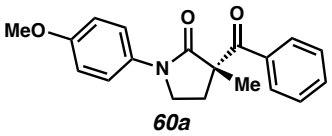
General procedure 3: (*S*)-1-(2-methoxyphenyl)-3-methyl-3-(4-methylbenzoyl) pyrrolidin-2-one (62b)

In a nitrogen-filled glovebox, to an oven-dried 4 mL vial equipped with a stir bar was added LHMDS (40.2 mg, 0.240 mmol, 1.20 equiv), LiBr (86.9 mg, 1.00 mmol, 5.00 equiv), a solution of lactam **57b** (82.1 mg, 0.400 mmol, 2.00 equiv) in toluene (1.0 mL) and THF (0.2 mL), bromobenzene (**61**, 31.5 μL, 0.300 mmol, 1.50 equiv), and *p*-tolunitrile **58b** (23.4 mg, 0.200 mmol, 1.00 equiv). To a separate oven-dried 4 mL vial equipped with a stir bar was added $Ni(COD)_2$ (5.50 mg, 0.0200 mmol, 0.100 equiv), SL-M004-1 (Solvias, 25.3 mg, 0.0240 mmol, 0.120 equiv), and toluene (1.0 mL). Both the lactam suspension and the Ni/ligand solution were stirred at ambient temperature for several minutes and then cooled to 4 °C. The Ni/ligand solution was added to the lactam suspension at 4 °C, and the vial was closed with a PTFE-lined

septum cap. *Note*: *Although this effect has not yet been studied in detail, we have observed lower yields when the vial containing the lactam suspension was first closed with a PTFE-lined septum cap, and then the catalyst solution was added through the septum cap.* The reaction mixture was stirred at 4 °C for 48 h and then removed from the glovebox. AcOEt (6 mL) and 1 M HCl aqueous solution (5 mL) were added and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was extracted with AcOEt (24 mL), washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) on silica gel to give lactam **62** as a white solid (59.4 mg, 92% yield, 91% ee). $[a]_D^{25}$ +2.1° (c 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 – 8.02 (m, 2H), 7.33 – 7.20 (m, 4H), 7.03 – 6.95 (m, 2H), 3.94 – 3.87 (m, 1H), 3.85 (s, 3H), 3.84 – 3.78 (m, 1H), 2.94 (ddd, *J* = 12.9, 8.4, 6.4 Hz, 1H), 2.40 (s, 3H), 2.07 (ddd, *J* = 12.8, 8.0, 4.8 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.4, 174.9, 155.0, 143.2, 133.0, 129.6, 129.0, 129.0, 128.4, 126.9, 120.9, 112.1, 56.6, 55.7, 47.1, 32.5, 21.6; IR (Neat Film NaCl) 2973, 2929, 1701, 1696, 1606, 1503, 1459, 1408, 1272, 1255, 1185, 1121, 1023, 1009, 970, 753 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{22}NO_3$ $[M+H]^+$: 324.1594, found 324.1599.

Spectroscopic Data for Ni-Catalyzed C-Acylation Products

(*S*)-3-Benzoyl-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one (60a)



60a

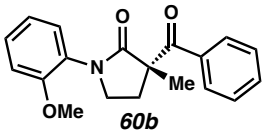
Lactam **60a** was prepared according to the general procedure 3 from **57a** using benzonitrile in place of *p*-tolunitrile, reacting at ambient temperature for 24 h in place of 0 °C for 48 h, and isolated by flash column chromatography (1:10 EtOAc:hexanes) on silica gel as a white solid. 79.9 mg, 86% yield, 88% ee.

Gram-scale reaction

In a nitrogen-filled glovebox, to a solution of LHMDS (1.00 g, 6.00 mmol, 1.20 equiv) in toluene (10 mL) at 23 °C, was slowly added a solution of **57a** (1.33 g, 6.50 mmol, 1.30 equiv) in toluene (13 mL). The flask containing the solution of **57a** was then rinsed with toluene (2 mL), and the rinse was added to the LHMDS/**57a** solution. LiBr (2.17 g, 25.0 mmol, 5.00 equiv) was dissolved in THF (5 mL) and then added to the reaction mixture, followed by benzonitrile (515 μL, 5.00 mmol, 1.00 equiv) and bromobenzene (785 μL, 7.50 mmol, 1.50 equiv). Then, a solution of $Ni(COD)_2$ (138 mg, 0.500 mmol, 0.100 equiv) and SL-M004-1 (632 mg, 0.600 mmol, 1.20 equiv) in toluene (23 mL) was added slowly, followed by a 2 mL toluene rinse. The reaction mixture was stirred at 23 °C for 45 h. The reaction mixture was then removed from the glovebox, AcOEt (150 mL) and 1 M HCl aqueous solution (125 mL) were added, and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was extracted with AcOEt (200 mL), washed with brine (100 mL), dried over Na_2SO_4,

and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) on silica gel to give lactam **60a** as an off-white solid. 1.06 g, 69% yield, 90% ee. $[a]_D^{25}$ –27.1° (c 1.45, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 – 8.00 (m, 2H), 7.58 – 7.47 (m, 3H), 7.46 – 7.38 (m, 2H), 6.96 – 6.87 (m, 2H), 3.95 (ddd, *J* = 9.5, 7.9, 6.1 Hz, 1H), 3.86 (ddd, *J* = 9.6, 8.2, 5.1 Hz, 1H), 3.82 (s, 3H), 2.93 (ddd, *J* = 13.0, 8.0, 5.1 Hz, 1H), 2.08 (ddd, *J* = 12.9, 8.3, 6.1 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 2930, 199.0, 173.2, 156.9, 135.9, 132.5, 132.4, 129.2, 128.4, 121.8, 114.1, 58.3, 55.5, 46.5, 31.7, 22.0; IR (Neat Film NaCl) 1685, 1512, 1399, 1268, 1249, 1182, 1090, 1032, 970, 830, 702 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{20}NO_3$ $[M+H]^+$: 310.1438, found 310.1442.

(*S*)-3-Benzoyl-1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (60b)

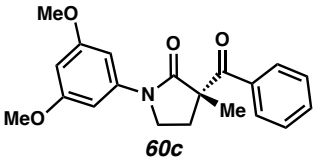


60b

Lactam **60b** was prepared according to the general procedure 3 from **57b** using benzonitrile in place of *p*-tolunitrile, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a white solid. 50.3 mg, 81% yield, 92% ee. $[a]_D^{25}$ +4.0° (c 1.21, $CHCl_3$, 92% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 – 8.11 (m, 2H), 7.56 – 7.48 (m, 1H), 7.47 – 7.40 (m, 2H), 7.34 – 7.25 (m, 2H), 7.04 – 6.95 (m, 2H), 3.90 (ddd, *J* = 9.6, 8.4, 4.8 Hz, 1H), 3.86 – 3.78 (m, 1H), 3.85 (s, 3H), 2.95 (ddd, *J* = 12.9, 8.4, 6.3 Hz, 1H), 2.08 (ddd, *J* = 12.8, 8.0, 4.8 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 1989.0, 174.7, 155.0, 135.8, 132.4, 129.4, 129.0, 128.3,

128.3, 126.8, 121.0, 112.1, 56.8, 55.7, 47.1, 32.4, 21.6; IR (Neat Film NaCl) 2974, 2930, 1701, 1697, 1596, 1503, 1459, 1410, 1305, 1270, 1256, 1121, 1023, 1010, 970, 750, 702 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{20}NO_3$ $[M+H]^+$: 310.1438, found 310.1441.

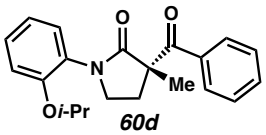
(*S*)-3-Benzoyl-1-(3,5-dimethoxyphenyl)-3-methylpyrrolidin-2-one (60c)



60c

Lactam **60c** was prepared according to the general procedure 3 from **57c** using benzonitrile in place of *p*-tolunitrile, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a white solid. 54.5 mg, 80% yield, 85% ee. $[a]_D^{25}$ –30.0° (c 1.04, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 2H), 7.55 – 7.48 (m, 1H), 7.47 – 7.38 (m, 2H), 6.92 (d, *J* = 2.2 Hz, 2H), 6.31 (t, *J* = 2.2 Hz, 1H), 3.97 (ddd, *J* = 9.6, 8.0, 6.0 Hz, 1H), 3.87 (ddd, *J* = 9.6, 8.3, 5.1 Hz, 1H), 3.81 (s, 6H), 2.92 (ddd, *J* = 13.1, 8.0, 5.2 Hz, 1H), 2.07 (ddd, *J* = 12.9, 8.3, 6.0 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.6, 173.8, 160.9, 141.0, 135.7, 132.6, 129.2, 128.4, 98.3, 97.1, 58.7, 55.5, 46.4, 31.4, 22.0; IR (Neat Film NaCl) 2937, 2840, 1696, 1598, 1480, 1393, 1277, 1249, 1206, 1156, 1067, 972, 834, 722, 699, 682, 661 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{22}NO_4$ $[M+H]^+$: 340.1543, found 340.1552.

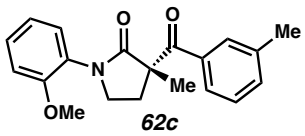
(*S*)-3-Benzoyl-1-(2-isopropoxyphenyl)-3-methylpyrrolidin-2-one (60d)



60d

Lactam **60d** was prepared according to the general procedure 3 from **57d** using benzonitrile in place of *p*-tolunitrile, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a white solid. 46.7 mg, 69% yield, 86% ee. $[a]_D^{25}$ +9.4° (c 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 – 8.14 (m, 2H), 7.59 – 7.51 (m, 1H), 7.51 – 7.43 (m, 2H), 7.35 – 7.26 (m, 2H), 7.06 – 6.97 (m, 2H), 4.63 (hept, *J* = 6.1 Hz, 1H), 3.98 (ddd, *J* = 9.5, 8.2, 4.9 Hz, 1H), 3.85 (ddd, *J* = 9.6, 8.0, 6.3 Hz, 1H), 3.00 (ddd, *J* = 12.8, 8.2, 6.3 Hz, 1H), 2.10 (ddd, *J* = 12.8, 8.0, 4.9 Hz, 1H), 1.73 (s, 3H), 1.36 (d, *J* = 6.0 Hz, 3H), 1.35 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.0, 174.5, 153.2, 135.9, 132.4, 129.4, 128.8, 128.8, 128.3, 127.7, 120.6, 114.1, 70.4, 56.9, 47.2, 32.6, 22.1, 22.1, 21.6; IR (Neat Film NaCl) 2977, 2930, 1697, 1596, 1500, 1455, 1407, 1281, 1270, 1255, 1124, 954, 750, 701cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{24}NO_3$ $[M+H]^+$: 338.1751, found 338.1744.

(*S*)-1-(2-Methoxyphenyl)-3-methyl-3-(3-methylbenzoyl)pyrrolidin-2-one (62c)

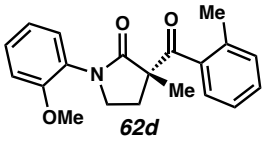


62c

Lactam **62c** was prepared according to the general procedure 3 from **57b** using *m*-tolunitrile in place of *p*-tolunitrile, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 59.1 mg, 91% yield, 93% ee. $[a]_D^{25}$ +5.5° (c 0.52, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 – 7.90 (m, 1H), 7.89 –

7.88 (m, 1H), 7.33 – 7.26 (m, 4H), 7.04 – 6.95 (m, 2H), 3.90 (ddd, *J* = 9.6, 8.4, 4.7 Hz, 1H), 3.86 – 3.78 (m, 1H), 3.84 (s, 3H), 2.93 (ddd, *J* = 12.9, 8.4, 6.5 Hz, 1H), 2.40 (s, 3H), 2.11 – 2.02 (m, 1H), 1.67 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.3, 174.8, 155.06, 138.0, 135.8, 133.1, 129.8, 129.0, 128.3, 128.1, 126.9, 126.5, 121.0, 112.1, 56.8, 55.7, 47.1, 32.4, 21.6, 21.5; IR (Neat Film NaCl) 2973, 2931, 1694, 1598, 1504, 1455, 1409, 1276, 1255, 1182, 1121, 1092, 1044, 1024, 976, 905, 789, 754, cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{22}NO_3$ $[M+H]^+$: 324.1594, found 324.1602.

(*S*)-1-(2-Methoxyphenyl)-3-methyl-3-(2-methylbenzoyl)pyrrolidin-2-one (62d)

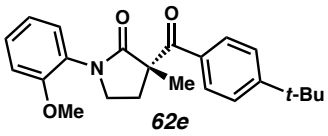


62d

Lactam **62d** was prepared according to the general procedure 3 from **57b** using *o*-tolunitrile in place of *p*-tolunitrile, reacting with aqueous HCl at 70 °C in place of ambient temperature, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 44.9 mg, 69% yield, 94% ee. $[a]_D^{25}$ – 29.6° (c 0.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.34 – 7.25 (m, 2H), 7.25 – 7.16 (m, 3H), 7.01 – 6.93 (m, 2H), 3.82 (s, 3H), 3.73 (dd, *J* = 7.6, 6.3 Hz, 2H), 2.82 – 2.73 (m, 1H), 2.33 (s, 3H), 2.14 – 2.05 (m, 1H), 1.59 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.5, 173.8, 154.9, 139.1, 135.6, 130.9, 129.7, 128.9, 128.4, 126.9, 126.0, 125.2, 120.9, 112.1, 58.4, 55.6, 47.2, 31.9, 21.3, 20.1; IR (Neat Film NaCl) 2971, 2932, 1694, 1597, 1505, 1456, 1409, 1305, 1281, 1256,

1122, 1045, 1025, 969, 755 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{22}NO_3$ $[M+H]^+$: 324.1594, found 324.1601.

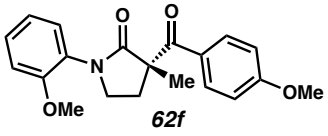
(*S*)-3-(4-(*tert*-Butyl)benzoyl)-1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (62e)



62e

Lactam **62e** was prepared according to the general procedure 3 from **57b** using 4-(*tert*-butyl)benzonitrile in place of *p*-tolunitrile, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a white solid. 64.7 mg, 89% yield, 92% ee. $[a]_D^{25}$ +6.9° (c 1.04, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.07 (m, 2H), 7.47 – 7.41 (m, 2H), 7.33 – 7.25 (m, 2H), 7.04 – 6.95 (m, 2H), 3.93 – 3.80 (m, 2H), 3.85 (s, 3H), 2.96 (ddd, *J* = 12.9, 8.4, 6.5 Hz, 1H), 2.08 (ddd, *J* = 12.8, 7.9, 4.8 Hz, 1H), 1.69 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.2, 175.0, 156.0, 155.0, 132.7, 129.5, 128.9, 128.4, 126.9, 125.2, 120.9, 112.1, 56.6, 55.7, 47.1, 35.0, 32.5, 31.1, 21.6; IR (Neat Film NaCl) 2963, 1701, 1676, 1603, 1504, 1459, 1406, 1272, 1255, 1121, 1109, 1023, 971, 752 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{28}NO_3$ $[M+H]^+$: 366.2064, found 366.2072.

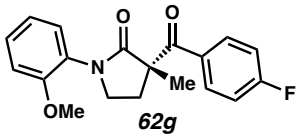
(*S*)-3-(4-Methoxybenzoyl)-1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (62f)



62f

Lactam **62f** was prepared according to the general procedure 3 from **57b** using 4-methoxybenzonitrile in place of *p*-tolunitrile, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 57.8 mg, 85% yield, 89% ee. $[a]_D^{25}$ –3.7° (c 0.73, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 – 8.17 (m, 2H), 7.32 – 7.27 (m, 2H), 7.03 – 6.88 (m, 4H), 3.93 – 3.87 (m, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.83 – 3.77 (m, 1H), 2.97 (ddd, *J* = 12.8, 8.2, 6.2 Hz, 1H), 2.07 (ddd, *J* = 12.9, 8.0, 5.0 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.8, 175.0, 162.9, 155.0, 132.1, 128.9, 128.3, 128.2, 127.0, 120.9, 113.4, 112.1, 56.6, 55.7, 55.4, 47.2, 32.7, 21.8; IR (Neat Film NaCl) 2971, 2933, 1695, 1600, 1504, 1464, 1456, 1410, 1307, 1259, 1174, 1027, 971, 845, 754, 699, 610 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{22}NO_4$ $[M+H]^+$: 340.1543, found 340.1547.

(*S*)-3-(4-Fluorobenzoyl)-1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (62g)

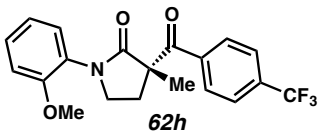


62g

Lactam **62g** was prepared according to the general procedure 3 from **57b** using 4-fluorobenzonitrile in place of *p*-tolunitrile, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a white solid. 23.3 mg, 36% yield, 93% ee. $[a]_D^{25}$ –1.8° (c 0.77, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 – 8.20 (m, 2H), 7.34 – 7.27 (m, 1H), 7.27 – 7.20 (m, 1H), 7.14 – 7.06 (m, 2H), 7.04 – 6.95 (m, 2H), 3.91 (ddd, *J* = 9.6, 8.3, 5.0 Hz, 1H), 3.85 – 3.76 (m, 4H), 3.83 (s, 3H), 2.95 (ddd, *J* = 12.8, 8.3, 6.1 Hz, 1H), 2.12 – 2.03 (m, 1H), 1.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.1, 174.5, 165.2, 154.9, 132.4, 131.9, 129.1, 128.3, 126.7,

121.0, 115.3, 112.1, 56.9, 55.7, 47.2, 32.5, 21.7; IR (Neat Film NaCl) 2974, 1697, 1684, 1597, 1506, 1457, 1410, 1271, 1256, 1235, 1160, 1024, 972, 848, 754, 609 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{19}FNO_3$ $[M+H]^+$: 328.1343, found 328.1353.

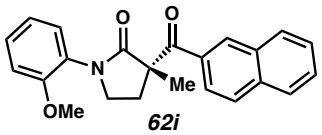
(*S*)-1-(2-Methoxyphenyl)-3-methyl-3-(4-(trifluoromethyl)benzoyl)pyrrolidin-2-one (62h)



62h

Lactam **62h** was prepared according to the general procedure 3 from **57b** using 4-trifluoromethylbenzonitrile in place of *p*-tolunitrile, reacting at ambient temperature for 24 h in place of 0 °C for 48 h, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 21.5 mg, 23% yield, 87% ee. $[a]_D^{25}$ +2.7° (c 0.71, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 – 8.22 (m, 2H), 7.78 – 7.61 (m, 2H), 7.35 – 7.29 (m, 1H), 7.24 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.05 – 6.95 (m, 2H), 3.91 (ddd, *J* = 9.7, 8.3, 5.0 Hz, 1H), 3.84 (s, 3H), 3.83 – 3.77 (m, 1H), 2.93 (ddd, *J* = 12.9, 8.3, 6.2 Hz, 1H), 2.09 (ddd, *J* = 13.0, 8.0, 5.0 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.4, 174.1, 154.9, 139.0, 133.7, 133.6, 129.7, 129.2, 128.3, 125.3, 123.6, 121.0, 112.1, 57.2, 55.7, 47.2, 32.1, 21.5; IR (Neat Film NaCl) 2975, 2934, 1697, 1505, 1409, 1328, 1316, 1257, 1169, 1127, 1068, 1020, 1009, 973, 858, 753; cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{19}F_3NO_3$ $[M+H]^+$: 378.1312, found 378.1325.

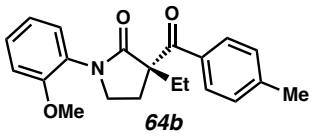
(*S*)-3-(2-Naphthoyl)-1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (62i)



62i

Lactam **62i** was prepared according to the general procedure 3 from **57b** using 2-naphthonitrile in place of *p*-tolunitrile, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 47.5 mg, 66% yield, 91% ee. $[a]_D^{25}$ +15.8° (c 0.52, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, *J* = 1.3 Hz, 1H), 8.14 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.98 – 7.92 (m, 1H), 7.87 (t, *J* = 8.4 Hz, 2H), 7.62 – 7.56 (m, 1H), 7.56 – 7.49 (m, 1H), 7.35 – 7.27 (m, 2H), 7.06 – 6.97 (m, 2H), 3.96 (ddd, *J* = 9.6, 8.3, 4.9 Hz, 1H), 3.90 – 3.81 (m, 1H), 3.84 (s, 3H), 3.04 (ddd, *J* = 12.9, 8.3, 6.2 Hz, 1H), 2.17 – 2.08 (m, 1H), 1.75 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.9, 174.7, 155.0, 135.1, 133.0, 132.4, 131.1, 129.8, 129.0, 128.3, 128.3, 128.0, 127.6, 127.0, 126.5, 125.4, 121.0, 112.2, 57.1, 55.7, 47.2, 32.6, 21.8; IR (Neat Film NaCl) 2930, 1694, 1505, 1463, 1409, 1281, 1255, 1120, 1024, 750 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{22}NO_3$ $[M+H]^+$: 360.1594, found 360.1589.

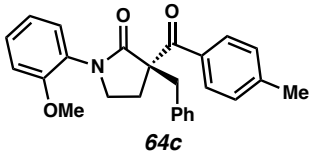
(*S*)-3-Ethyl-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64b)



64b

Lactam **64b** was prepared according to the general procedure 3 from **63b**, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 33.9 mg, 50% yield, 78% ee. $[a]_D^{25}$ +14.6° (c 0.81, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.3 Hz, 2H), 7.31 – 7.18 (m, 4H), 7.01 – 6.92 (m, 2H), 3.90 (ddd, *J* = 9.5, 8.1, 6.7 Hz, 1H), 3.79 (s, 3H), 3.71 (ddd, *J* = 9.5, 8.7, 4.3 Hz, 1H), 2.95 (ddd, *J* = 13.0, 8.0, 4.2 Hz, 1H), 2.41 – 2.30 (m, 4H), 2.17 – 2.05 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.3, 173.5, 154.9, 143.0, 134.0, 129.5, 128.9, 128.9, 128.4, 127.1, 120.9, 112.1, 61.8, 55.6, 47.5, 29.5, 29.1, 21.6, 8.8; IR (Neat Film NaCl) 2962, 1700, 1606, 1504, 1461, 1253, 1159, 1024, 752 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{24}NO_3$ $[M+H]^+$: 338.1751, found 338.1753.

(*S*)-3-Benzyl-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64c)

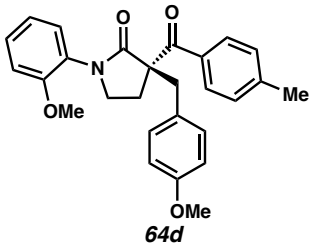


64c

Lactam **64c** was prepared according to the general procedure 3 from **63c**, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 48.8 mg, 61% yield, 81% ee. $[a]_D^{25}$ +62.3° (c 0.90, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.06 (m, 2H), 7.31 – 7.16 (m, 8H), 6.93 – 6.83 (m, 3H), 3.77 (s, 3H),

3.62 (td, *J* = 9.1, 4.1 Hz, 1H), 3.53 (d, *J* = 13.7 Hz, 1H), 3.34 (d, *J* = 13.7 Hz, 1H), 2.90 – 2.72 (m, 2H), 2.37 (s, 3H), 2.26 (ddd, *J* = 13.0, 8.4, 4.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.7, 173.1, 154.9, 143.2, 136.7, 133.3, 130.6, 129.7, 129.0, 128.9, 128.4, 127.9, 126.9, 126.7, 120.8, 112.0, 61.4, 55.6, 47.0, 40.9, 28.7, 21.7; IR (Neat Film NaCl) 2928, 1696, 1604, 1502, 1457, 1405, 1240, 1185, 1025, 741, 702 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{26}H_{26}NO_3$ $[M+H]^+$: 400.1907, found 400.1919.

(*S*)-3-(4-Methoxybenzyl)-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64d)

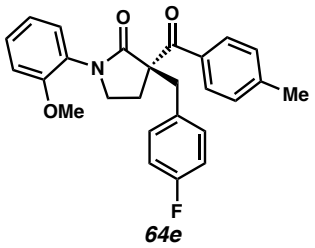


64d

Lactam **64d** was prepared according to the general procedure 3 from **63d**, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 65.8 mg, 77% yield, 81% ee. $[a]_D^{25}$ +50.4° (c 1.21, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 – 8.09 (m, 2H), 7.30 – 7.18 (m, 5H), 6.99 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.98 – 6.88 (m, 2H), 6.88 – 6.80 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.67 (td, *J* = 9.2, 4.2 Hz, 1H), 3.51 (d, *J* = 13.9 Hz, 1H), 3.32 (d, *J* = 13.9 Hz, 1H), 2.95 (ddd, *J* = 9.4, 8.6, 6.5 Hz, 1H), 2.80 (ddd, *J* = 13.3, 9.0, 6.4 Hz, 1H), 2.40 (s, 3H), 2.27 (ddd, *J* = 13.0, 8.6, 4.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.9, 173.2, 158.7, 154.9, 143.1, 133.4, 131.5, 129.7, 129.0, 128.8, 128.6, 127.9, 126.7, 120.8, 113.7, 112.0, 61.5, 55.6, 55.3, 47.0, 40.1, 28.7, 21.6; IR (Neat Film NaCl) 2930, 1694, 1606, 1505,

1463, 1409, 1301, 1248, 1180, 1028, 832, 753 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{27}H_{28}NO_4$ $[M+H]^+$: 430.2013, found 430.2006.

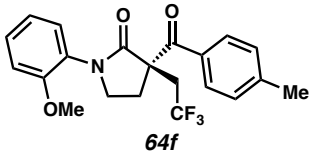
(*S*)-3-(4-Fluorobenzyl)-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64e)



64e

Lactam **64e** was prepared according to the general procedure 3 from **63e**, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a white foam. 63.5 mg, 76% yield, 74% ee. $[a]_D^{25}$ +38.9° (c 3.08, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 – 8.08 (m, 2H), 7.31 – 7.21 (m, 5H), 7.04 – 6.91 (m, 5H), 3.79 (s, 3H), 3.67 (td, *J* = 9.3, 4.4 Hz, 1H), 3.54 (d, *J* = 13.9 Hz, 1H), 3.34 (d, *J* = 13.9 Hz, 1H), 3.00 (ddd, *J* = 9.5, 8.7, 6.3 Hz, 1H), 2.81 (ddd, *J* = 13.4, 9.1, 6.3 Hz, 1H), 2.41 (s, 3H), 2.26 (ddd, *J* = 13.3, 8.7, 4.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.6, 172.9, 163.1, 161.1, 154.8, 143.3, 133.2, 132.4, 132.0, 132.0, 129.6, 129.1, 128.9, 127.8, 126.5, 120.9, 115.3, 115.1, 112.0, 61.4, 55.6, 47.0, 40.1, 28.6, 21.7; IR (Neat Film NaCl) 2931, 1697, 1604, 1504, 1465, 1410, 1222, 1185, 1026, 909, 833, 752, 731 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{26}H_{25}FNO_3$ $[M+H]^+$: 418.1813, found 418.1806.

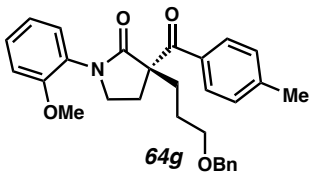
(*R*)-1-(2-Methoxyphenyl)-3-(4-methylbenzoyl)-3-(2,2,2-trifluoroethyl)pyrrolidin-2-one (64f)



64f

Lactam **64f** was prepared according to the general procedure 3 from **63f**, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil. 45.5 mg, 58% yield, 71% ee. $[a]_D^{25}$ +10.3° (c 2.16, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 – 8.09 (m, 2H), 7.34 – 7.28 (m, 1H), 7.28 – 7.17 (m, 3H), 7.03 – 6.92 (m, 2H), 4.00 (ddd, *J* = 9.6, 7.7, 6.8 Hz, 1H), 3.78 (s, 3H), 3.72 (ddd, *J* = 9.6, 8.7, 3.9 Hz, 1H), 3.34 (dq, *J* = 15.8, 11.1 Hz, 1H), 3.10 – 3.01 (m, 1H), 2.87 (dq, *J* = 15.7, 11.1 Hz, 1H), 2.40 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.1, 171.4, 154.8, 143.5, 133.0, 129.6, 129.3, 129.1, 128.1, 127.5, 126.4, 125.3, 121.0, 112.0, 57.7, 55.6, 47.6, 39.3, 39.1, 38.9, 38.7, 29.1, 29.0, 21.6; IR (Neat Film NaCl) 2952, 1703, 1673, 1505, 1464, 1373, 1299, 1260, 1143, 1021, 753 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{21}F_3NO_3$ $[M+H]^+$: 392.1468, found 392.1459.

(*S*)-3-(3-(Benzyloxy)propyl)-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64g)

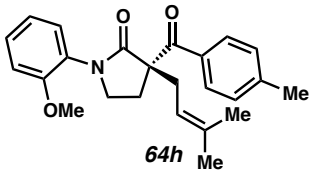


64g

Lactam **64g** was prepared according to the general procedure 3 from **63g**, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a colorless oil.

61.6 mg, 67% yield, 60% ee. $[a]_D^{25}$ +9.3° (c 2.90, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 – 8.10 (m, 1H), 7.37 – 7.18 (m, 6H), 7.01 – 6.92 (m, 1H), 4.45 (d, *J* = 2.3 Hz, 1H), 3.88 (ddd, *J* = 9.5, 8.0, 6.6 Hz, 1H), 3.77 (s, 1H), 3.76 – 3.66 (m, 1H), 3.46 (td, *J* = 6.4, 1.1 Hz, 1H), 2.38 (s, 2H), 2.19 – 2.07 (m, 1H), 1.77 – 1.58 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.0, 173.4, 154.9, 143.0, 138.5, 133.8, 129.5, 128.9, 128.9, 128.4, 128.3, 127.6, 127.5, 127.0, 120.9, 112.0, 72.8, 70.3, 61.1, 55.6, 47.5, 32.8, 30.0, 24.8, 21.6; IR (Neat Film NaCl) 2935, 1698, 1606, 1504, 1455, 1408, 1302, 1279, 1252, 1185, 1101, 1027, 750, 699 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{29}H_{32}NO_4$ $[M+H]^+$: 458.2326, found 458.2315.

(*S*)-1-(2-Methoxyphenyl)-3-(4-methylbenzoyl)-3-(3-methylbut-2-en-1-yl) pyrrolidin-2-one (64h)

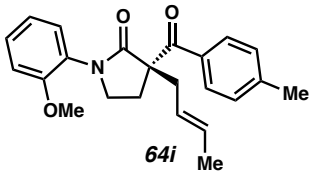


64h

Lactam **64h** was prepared according to the general procedure 3 from **63h**, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a pale yellow oil. 53.2 mg, 71% yield, 76% ee. $[a]_D^{25}$ +29.6° (c 2.15, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 – 8.07 (m, 2H), 7.32 – 7.25 (m, 2H), 7.25 – 7.18 (m, 2H), 7.02 – 6.92 (m, 2H), 5.23 – 5.15 (m, 1H), 3.88 (ddd, *J* = 9.5, 8.5, 5.7 Hz, 1H), 3.83 (s, 3H), 3.68 (ddd, *J* = 9.4, 8.7, 5.1 Hz, 1H), 3.02 – 2.93 (m, 1H), 2.89 – 2.73 (m, 2H), 2.39 (s, 3H), 2.14 (ddd, *J* = 13.0, 8.7, 5.7 Hz, 1H), 1.72 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.2, 173.5, 155.0, 142.9, 135.5, 133.8, 129.5, 128.9, 128.9, 128.3, 127.1, 120.9, 118.6, 112.1, 61.1, 55.6, 47.5, 34.5, 29.2, 26.1, 21.6, 18.0;

IR (Neat Film NaCl) 2917, 1698, 1606, 1504, 1463, 1408, 1248, 1184, 1123, 1024, 753 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{24}H_{28}NO_3$ $[M+H]^+$: 378.2064, found 378.2060.

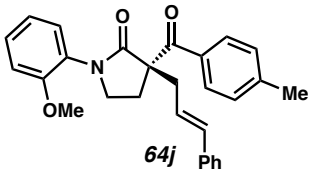
(*S*,*E*)-3-(But-2-en-1-yl)-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64i)



64i

Lactam **64i** was prepared according to the general procedure 3 from **63i**, and isolated by flash column chromatography (1:8 EtOAc:hexanes) on silica gel as a pale yellow oil. 51.0 mg, 70% yield, 86% ee. $[a]_D^{25}$ +45.5° (c 2.10, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.19 (m, 4H), 7.03 – 6.94 (m, 2H), 5.63 – 5.43 (m, 2H), 3.92 – 3.86 (m, 1H), 3.84 (s, 3H), 3.73 – 3.62 (m, 1H), 2.94 – 2.72 (m, 3H), 2.39 (s, 3H), 2.20 (ddd, *J* = 13.2, 8.7, 5.3 Hz, 1H), 1.68 (dq, *J* = 6.3, 1.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.0, 173.5, 155.0, 143.0, 133.7, 129.8, 129.5, 129.5, 128.9, 128.3, 127.0, 125.4, 120.9, 112.1, 60.7, 55.6, 47.4, 39.1, 28.9, 21.6, 18.2; IR (Neat Film NaCl) 2917, 1698, 1606, 1504, 1463, 1408, 1254, 1185, 1122, 1045, 1024, 973, 837, 750 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{26}NO_3$ $[M+H]^+$: 364.1907, found 364.1909.

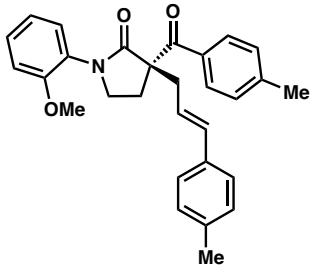
(*S*)-3-Cinnamyl-1-(2-methoxyphenyl)-3-(4-methylbenzoyl)pyrrolidin-2-one (64j)



64j

Lactam **64j** was prepared according to the general procedure 3 from **63j**, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a white foam. 51.1 mg, 60% yield, 86% ee. $[a]_D^{25}$ +55.5° (c 0.93, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 – 8.05 (m, 2H), 7.41 – 7.33 (m, 2H), 7.33 – 7.18 (m, 10H), 7.00 – 6.93 (m, 2H), 6.52 (d, *J* = 15.8 Hz, 1H), 6.29 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.92 – 3.82 (m, 1H), 3.80 (s, 3H), 3.75 (ddd, *J* = 9.6, 8.7, 5.7 Hz, 1H), 3.05 (dt, *J* = 7.4, 1.4 Hz, 2H), 2.85 (ddd, *J* = 13.3, 8.9, 5.8 Hz, 1H), 2.41 (s, 2H), 2.30 (ddd, *J* = 13.5, 8.7, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.9, 173.3, 155.0, 143.1, 137.3, 134.2, 133.5, 129.4, 129.0, 129.0, 128.5, 128.3, 127.4, 126.8, 126.2, 124.8, 121.0, 112.1, 60.7, 55.6, 47.3, 39.4, 28.8, 21.6; IR (Neat Film NaCl) 2961, 1698, 1606, 1504, 1463, 1409, 1279, 1255, 1185, 1025, 971, 911, 742, 694 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{28}H_{28}NO_3$ $[M+H]^+$: 426.2064, found 426.2067.

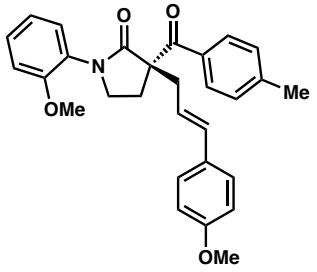
(*S*,*E*)-1-(2-Methoxyphenyl)-3-(4-methylbenzoyl)-3-(3-(p-tolyl)allyl)pyrrolidin-2-one (64k)



64k

Lactam **64k** was prepared according to the general procedure 3 from **63k**, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a pale yellow oil. 74.2 mg, 85% yield, 88% ee. $[a]_D^{25}$ +56.0° (c 2.93, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.25 (m, 2H), 7.25 – 7.19 (m, 4H), 7.14 – 7.08 (m, 2H), 7.00 – 6.93 (m, 2H), 6.49 (d, *J* = 15.7 Hz, 1H), 6.23 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.92 – 3.83 (m, 1H), 3.81 (s, 3H), 3.78 – 3.69 (m, 1H), 3.04 (d, *J* = 7.6 Hz, 2H), 2.85 (ddd, *J* = 13.2, 8.9, 5.8 Hz, 1H), 2.40 (s, 3H), 2.39 – 2.25 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.9, 173.4, 155.0, 143.1, 137.1, 134.5, 134.0, 133.5, 129.4, 129.2, 129.0, 129.0, 128.3, 126.8, 126.1, 123.6, 121.0, 112.0, 60.7, 55.6, 47.4, 39.4, 28.8, 21.6, 21.2; IR (Neat Film NaCl) 2920, 1694, 1606, 1505, 1463, 1409, 1279, 1254, 1184, 1121, 1045, 1025, 974, 911, 838, 752 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{29}H_{30}NO_3$ $[M+H]^+$: 440.2220, found 440.2220.

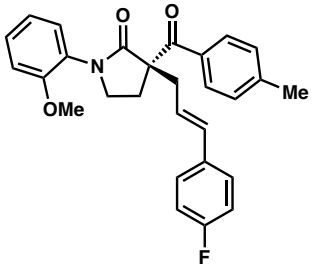
(*S*,*E*)-1-(2-Methoxyphenyl)-3-(3-(4-methoxyphenyl)allyl)-3-(4-methylbenzoyl) pyrrolidin-2-one (64l)



64l

Lactam **64l** was prepared according to the general procedure 3 from **63l**, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a white foam. 62.0 mg, 68% yield, 88% ee. $[a]_D^{25}$ +57.6° (c 1.09, $CHCl_3$, 88% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 – 8.05 (m, 2H), 7.34 – 7.26 (m, 3H), 7.26 – 7.17 (m, 3H), 7.00 – 6.93 (m, 2H), 6.87 – 6.81 (m, 2H), 6.46 (d, *J* = 15.7 Hz, 1H), 6.13 (dt, *J* = 15.5, 7.5 Hz, 1H), 3.88 (td, *J* = 9.2, 4.9 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.80 – 3.67 (m, 1H), 3.03 (dt, *J* = 7.6, 1.4 Hz, 2H), 2.85 (ddd, *J* = 13.2, 8.9, 5.8 Hz, 1H), 2.40 (s, 3H), 2.35 – 2.23 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.9, 173.4, 159.0, 155.0, 143.1, 133.5, 130.1, 129.4, 129.0, 128.9, 128.3, 127.4, 126.8, 122.4, 121.0, 113.9, 112.1, 60.8, 55.6, 55.3, 47.4, 39.4, 28.8, 21.6; IR (Neat Film NaCl) 2957, 1699, 1607, 1505, 1464, 1249, 1175, 1027, 838, 752 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{29}H_{30}NO_4$ $[M+H]^+$: 456.2169, found 456.2164.

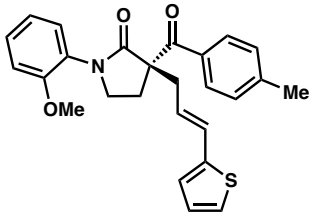
(*S*,*E*)-3-(3-(4-Fluorophenyl)allyl)-1-(2-methoxyphenyl)-3-(4-methylbenzoyl) pyrrolidin-2-one (64m)



64m

Lactam **64m** was prepared according to the general procedure 3 from **63m**, and isolated by flash column chromatography (1:10 EtOAc:hexanes) on silica gel as a white foam. 55.3 mg, 62% yield, 83% ee. $[a]_D^{25}$ +40.7° (c 0.55, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.26 (m, 3H), 7.26 – 7.22 (m, 2H), 7.22 – 7.18 (m, 1H), 7.06 – 6.93 (m, 4H), 6.51 – 6.44 (m, 1H), 6.20 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.88 (ddd, *J* = 9.6, 8.9, 5.0 Hz, 1H), 3.79 (s, 3H), 3.78 – 3.69 (m, 1H), 3.04 (ddd, *J* = 7.2, 3.6, 1.3 Hz, 2H), 2.86 (ddd, *J* = 13.2, 8.9, 5.7 Hz, 1H), 2.41 (s, 3H), 2.38 – 2.23 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 173.2, 163.1, 161.2, 154.9, 143.2, 133.5, 132.9, 129.4, 129.1, 129.0, 128.2, 127.7, 126.8, 124.6, 121.0, 115.5, 115.3, 112.1, 60.7, 55.6, 47.3, 39.3, 28.9, 21.6; IR (Neat Film NaCl) 2944, 1693, 1604, 1505, 1460, 1412, 1254, 1228, 1184, 1158, 1045, 1024, 910, 838, 753, 731 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{28}H_{27}FNO_3$ $[M+H]^+$: 444.1969, found 444.1969.

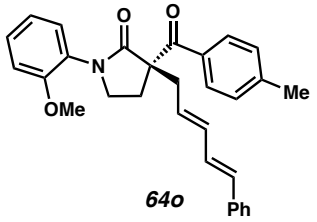
(*S*,*E*)-1-(2-Methoxyphenyl)-3-(4-methylbenzoyl)-3-(3-(thiophen-3-yl)allyl) pyrrolidin-2-one (64n)



64n

Lactam **64n** was prepared according to the general procedure 3 from **63n**, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a pale yellow oil. 65.2 mg, 76% yield, 83% ee. $[a]_D^{25}$ +46.7° (c 1.17, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.12 – 8.01 (m, 2H), 7.33 – 7.14 (m, 6H), 7.10 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.00 – 6.93 (m, 2H), 6.53 (d, *J* = 15.7 Hz, 1H), 6.13 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.88 (td, *J* = 9.1, 4.9 Hz, 1H), 3.81 (s, 3H), 3.79 – 3.68 (m, 1H), 3.01 (dd, *J* = 7.7, 1.3 Hz, 2H), 2.85 (ddd, *J* = 13.3, 8.9, 5.8 Hz, 1H), 2.40 (s, 3H), 2.28 (ddd, *J* = 13.5, 8.8, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 173.3, 155.0, 143.2, 139.9, 133.4, 129.4, 129.0, 129.0, 128.4, 128.2, 126.8, 126.0, 125.0, 124.6, 121.5, 121.0, 112.1, 60.7, 55.6, 47.3, 39.3, 28.8, 21.6; IR (Neat Film NaCl) 2958, 1698, 1606, 1504, 1463, 1409, 1302,1279, 1254, 1184, 1122, 1024, 967, 836, 753 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{26}H_{25}NO_3S$ $[M+H]^+$: 432.1628, found 432.1622.

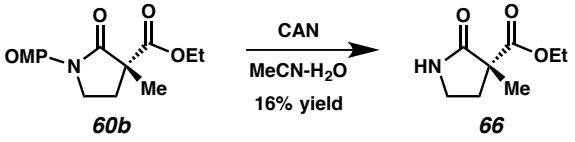
(*S*)-1-(2-Methoxyphenyl)-3-(4-methylbenzoyl)-3-((2*E*,4*E*)-5-phenylpenta-2,4-dien-1-yl)pyrrolidin-2-one (64o)



64o

Lactam **64o** was prepared according to the general procedure 3 from **63o**, and isolated by flash column chromatography (1:5 EtOAc:hexanes) on silica gel as a pale yellow oil. 31.7 mg, 35% yield, 84% ee. $[a]_D^{25}$ +40.6° (c 1.45, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.3 Hz, 2H), 7.42 – 7.36 (m, 2H), 7.36 – 7.16 (m, 6H), 6.98 (d, *J* = 7.8 Hz, 2H), 6.76 (ddd, *J* = 15.7, 10.5, 0.9 Hz, 1H), 6.49 (d, *J* = 15.7 Hz, 1H), 6.38 – 6.29 (m, 1H), 5.87 (dt, *J* = 15.2, 7.7 Hz, 1H), 3.90 (ddd, *J* = 9.5, 8.8, 5.1 Hz, 1H), 3.85 (s, 3H), 3.77 – 3.69 (m, 1H), 3.08 – 2.92 (m, 2H), 2.86 (ddd, *J* = 13.2, 8.8, 5.6 Hz, 1H), 2.41 (s, 3H), 2.25 (ddd, *J* = 13.7, 8.8, 5.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 173.2, 155.0, 143.1, 137.3, 134.8, 133.5, 131.6, 129.5, 129.1, 129.0, 129.0, 128.7, 128.6, 128.4, 127.4, 126.8, 126.3, 121.0, 112.1, 60.8, 55.7, 47.3, 39.3, 29.0, 21.6; IR (Neat Film NaCl) 3024, 1694, 1606, 1505, 1463, 1409, 1304, 1253, 1185, 1122, 1045, 1026, 992, 910, 747, 693 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{30}H_{30}NO_3$ $[M+H]^+$: 452.2220, found 452.2220.

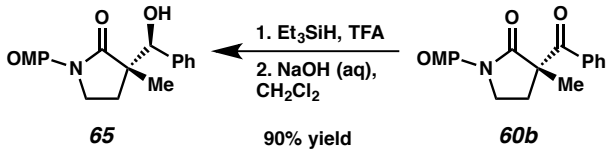
Procedures/Spectroscopic Data for Derivatization of C-Acylation Products



60b ***66***

(*S*)-3-Benzoyl-3-methylpyrrolidin-2-one (66)

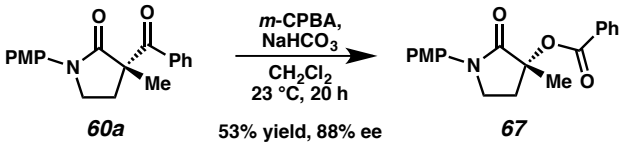
To a solution of lactam **60b** (93% ee, 40.0 mg, 0.129 mmol, 1.00 equiv) in MeCN (0.6 mL) and water (0.6 mL) was added CAN (424 mg, 0.774 mmol, 6.00 equiv) and the reaction mixture was stirred at 70 °C for 24 h. The reaction mixture was allowed to cool to ambient temperature and brine (5 mL) was added. The reaction mixture was extracted with AcOEt (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:2 to 2:1 EtOAc:hexanes) on silica gel to give lactam **66** as a white solid (19.6 mg, 75% yield). $[a]_D^{25}$ +25.7° (c 0.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 2H), 7.56 – 7.48 (m, 1H), 7.47 – 7.39 (m, 2H), 5.83 (s, 1H), 3.59 – 3.50 (m, 1H), 3.50 – 3.42 (m, 1H), 2.92 (ddd, *J* = 13.4, 8.1, 5.5 Hz, 1H), 2.08 (ddd, *J* = 13.3, 8.1, 5.5 Hz, 1H), 1.60 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.1, 178.3, 135.7, 132.5, 129.1, 128.4, 55.9, 39.6, 34.5, 21.5; IR (Neat Film NaCl) 3246, 2978, 1667, 1595, 1444, 1307, 1265, 1207, 1008, 973, 782, 701, 651 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{14}NO_2$ $[M+H]^+$: 204.1019, found 204.1015.



65 **90% yield** ***60b***

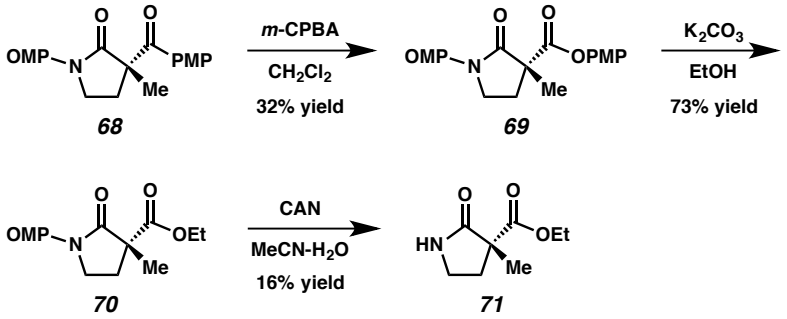
(*S*)-3-((*S*)-Hydroxy(phenyl)methyl)-1-(2-methoxyphenyl)-3-methylpyrrolidin-2-one (65)

To a solution of lactam **60b** (92% ee, 99.5 mg, 0.322 mmol, 1.00 equiv) in TFA (1.6 mL) was added Et_3SiH (0.102 mL, 643 mmol, 2.00 equiv) and the reaction mixture was stirred at ambient temperature for 24 h. CH_2Cl_2 (4 mL) and 2 M NaOH aqueous solution (8 mL) was added and the reaction mixture was stirred at ambient temperature for 3 h. The mixture was extracted with CH_2Cl_2 (30 mL, twice), washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) on silica gel to give lactam **65** as a white solid (90.2 mg, 90% yield). $[a]_D^{25}$ -12.5° (c 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 2H), 7.43 – 7.27 (m, 4H), 7.22 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.03 – 6.94 (m, 2H), 5.18 (br s, 1H), 4.99 (s, 1H), 3.84 (s, 3H), 3.69 (td, *J* = 9.4, 6.9 Hz, 1H), 3.54 (ddd, *J* = 9.6, 8.8, 2.2 Hz, 1H), 2.31 (dt, *J* = 12.6, 9.0 Hz, 1H), 1.54 (ddd, *J* = 12.6, 6.9, 2.2 Hz, 1H), 1.27 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.3, 154.8, 139.4, 129.1, 128.5, 127.9, 127.7, 127.3, 126.5, 120.9, 112.1, 77.8, 55.7, 47.3, 46.9, 30.8, 15.6; IR (Neat Film NaCl) 3400, 2966, 1672, 1596, 1504, 1459, 1413, 1305, 1281, 1256, 1180, 1161, 1121, 1082, 1046, 1026, 917, 885, 753, 725, 703, cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{22}NO_3$ $[M+H]^+$: 312.1594, found 312.1595.



(*R*)-1-(4-Methoxyphenyl)-3-methyl-2-oxopyrrolidin-3-yl benzoate (67)

To a solution of lactam **60a** (88% ee, 30.9 mg, 0.100 mmol, 1.00 equiv) in CH_2Cl_2 (1 mL) and were added $NaHCO_3$ (42.0 mg, 0.500 mmol, 5.00 equiv) and *m*-CPBA (75%, 115.0 mg, 0.500 mmol, 5.00 equiv) and the reaction mixture was stirred at ambient temperature for 20 h. 10% $NaHCO_3$ aqueous solution (3 mL) and brine (3 mL) were added and the mixture was extracted with CH_2Cl_2 (30 mL, twice), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) on silica gel to give lactam **67** as a white solid (17.1 mg, 53% yield, 88% ee). $[a]_D^{25}$ –3.3° (c 0.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 – 8.00 (m, 2H), 7.63 – 7.51 (m, 3H), 7.47 – 7.40 (m, 2H), 6.96 – 6.89 (m, 2H), 3.96 (td, *J* = 9.6, 3.2 Hz, 1H), 3.82 (s, 3H), 2.84 – 2.74 (m, 1H), 2.40 (ddd, *J* = 13.3, 8.1, 3.2 Hz, 1H), 1.75 (d, *J* = 0.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 165.5, 156.9, 133.2, 132.5, 129.9, 129.9, 128.3, 121.9, 114.1, 81.2, 55.5, 44.9, 30.6, 23.3; IR (Neat Film NaCl) 2963, 1705, 1512, 1451, 1403, 1317, 1292, 1251, 1136, 1116, 1091, 1072, 1032, 828, 715 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{20}NO_4$ $[M+H]^+$: 326.1387, found 326.1381.



(*R*)-4-Methoxyphenyl-1-(2-methoxyphenyl)-3-methyl-2-oxopyrrolidine-3-carboxylate (69)

To a solution of lactam **68** (160 mg, 0.471 mmol, 1.00 equiv) in CH_2Cl_2 (9.4 mL) was added *m*-CPBA (75%, 1.08 g, 4.71 mmol, 10.0 equiv) and the reaction mixture was stirred at ambient temperature for 24 h and then refluxed for 48 h. The reaction mixture was allowed to cool to ambient temperature and 10% Na_2SO_3 aqueous solution (30 mL) and saturated $NaHCO_3$ aqueous solution (10 mL) were added. The mixture was extracted with CH_2Cl_2 (130 mL), washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) on silica gel to give lactam **69** as a pale yellow oil (54.2 mg, 32% yield). $[a]_D^{25}$ -11.7° (c 0.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.09 – 7.02 (m, 2H), 7.02 – 6.93 (m, 2H), 6.93 – 6.85 (m, 2H), 3.92 – 3.75 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 2.84 (ddd, *J* = 12.9, 7.8, 4.5 Hz, 1H), 2.21 (ddd, *J* = 12.9, 8.3, 6.8 Hz, 1H), 1.67 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 171.6, 157.3, 154.9, 144.3, 129.0, 128.6, 126.9, 122.2, 120.9, 114.4, 112.1, 55.7, 55.6, 51.8, 47.1, 32.1, 20.2; IR (Neat Film NaCl) 2936, 1760, 1699, 1597, 1505, 1463, 1410, 1305, 1251, 1193, 1112, 1088, 1027, 754 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{22}NO_5$ $[M+H]^+$: 356.1492, found 356.1489.

(*R*)-Ethyl-1-(2-methoxyphenyl)-3-methyl-2-oxopyrrolidine-3-carboxylate (70)

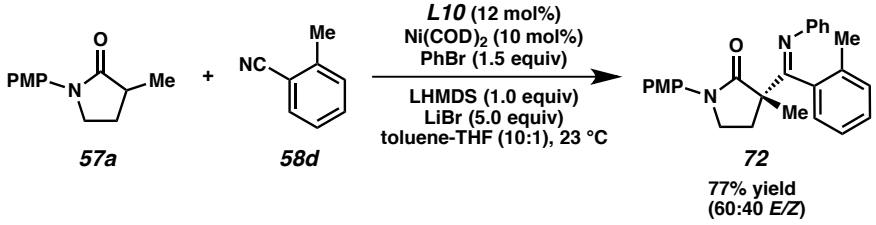
To a solution of lactam **69** (36.0 mg, 0.101 mmol, 1.00 equiv) in EtOH (2.0 mL) was added K_2CO_3 (70.0 mg, 0.506 mmol, 5.00 equiv) and the reaction mixture was stirred at ambient temperature for 30 h. The reaction mixture was concentrated under reduced pressure and brine was added to the residue. The mixture was extracted with AcOEt (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) on silica gel to give lactam **70** as a pale yellow oil (20.5 mg, 73% yield). $[a]_D^{25}$ -14.6° (c 0.98, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.03 – 6.88 (m, 2H), 4.31 – 4.17 (m, 2H), 3.83 (s, 3H), 3.82 – 3.70 (m, 2H), 2.64 (ddd, *J* = 12.8, 7.0, 4.7 Hz, 1H), 2.14 – 2.04 (m, 1H), 1.55 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 172.6, 154.9, 128.8, 128.5, 127.1, 120.9, 112.1, 61.5, 55.7, 51.6, 47.1, 32.2, 20.3, 14.2; IR (Neat Film NaCl) 2979, 1738, 1699, 1597, 1505, 1456, 1409, 1257, 1195, 1137, 1090, 1024, 754 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{20}NO_4$ $[M+H]^+$: 278.1387, found 278.1384.

(*R*)-Ethyl-3-methyl-2-oxopyrrolidine-3-carboxylate (71)

To a solution of lactam **70** (20.0 mg, 0.0721 mmol, 1.00 equiv) in MeCN (1.5 mL) and water (1.5 mL) was added CAN (237 mg, 0.433 mmol, 6.00 equiv) and the reaction mixture was stirred at 40 °C for 24 h. The reaction mixture was allowed to cool to ambient temperature and 10% Na_2SO_3 aqueous solution (3 mL) and brine (3 mL) were added. The reaction mixture was extracted with AcOEt (20 mL, twice),

dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (2:1 EtOAc:hexanes) on silica gel to give lactam **7** as a white solid (2.0 mg, 16% yield). $[a]_D^{25}$ +19.5° (c 0.09, MeOH) (reported data $[a]_D^{25}$ +19.0° (c 2, MeOH))[19]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (br s, 1H), 4.21 (m, 2H), 3.53 – 3.44 (m, 1H), 3.40 – 3.31 (m, 1H), 2.65 (ddd, *J* = 12.8, 7.8, 4.0 Hz, 1H), 2.05 (ddd, *J* = 13.0, 8.4, 7.0 Hz, 1H), 1.46 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 2981, 176.6, 172.2, 61.6, 50.5, 39.4, 34.0, 20.1, 14.1; IR (Neat Film NaCl) 3245, 2981, 1703, 1454, 1266, 1196, 1138, 1028 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_8H_{14}NO_3$ $[M+H]^+$: 171.0968, found 171.0965.

Procedures/Spectroscopic Data for Isolation/Reduction of Imine Intermediates

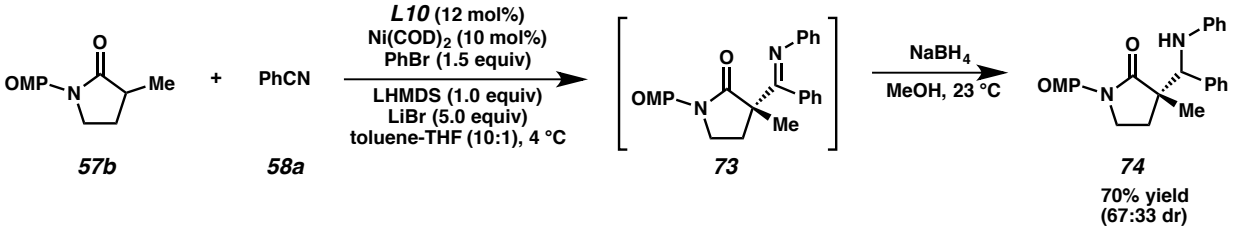


(*S*)-1-(4-Methoxyphenyl)-3-methyl-3-((phenylimino)(*o*-tolyl)methyl)pyrrolidin-2-one (72)

To a suspension of lactam **57a** (82.1 mg, 0.400 mmol, 2.00 equiv), *o*-tolunitrile **58d** (23.4 mg, 0.200 mmol, 1.00 equiv), bromobenzene (31.5 mL, 0.300 mmol, 1.5 equiv), LHMDS (40.2 mg, 0.240 mmol, 1.20 equiv) and LiBr (86.9 mg, 1.00 mmol, 5.00 equiv) in toluene (1.0 mL) and THF (0.20 mL) were added a solution of $Ni(COD)_2$

(5.50 mg, 0.0200 mmol, 0.100 equiv) and SL-M004-1 (Solvias, 25.3 mg, 0.0240 mmol, 0.120 equiv) at 25 °C and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was filtered through a pad of silica gel eluting with AcOEt (60 mL). The eluate was concentrated under reduced pressure and the residue was purified by flash column chromatography (1:10 EtOAc:hexanes) on silica gel to give imine **72** as a white foam (62 mg, 77% yield, 60/40 mixture of E/Z isomers). ^{1}H NMR (500 MHz, $CDCl_3$) for major isomer: δ 7.65 – 6.62 (m, 8H), 3.86 (s, 3H), 3.76 (ddd, *J* = 9.3, 8.2, 4.6 Hz, 1H), 3.62 (ddd, *J* = 9.3, 7.9, 6.6 Hz, 1H), 2.68 (ddd, *J* = 12.6, 7.9, 4.6 Hz, 1H), 2.17 (ddd, *J* = 12.8, 8.2, 6.6 Hz, 1H), 2.06 (s, 3H), 1.66 (s, 3H); for minor isomer: δ 7.61 – 6.62 (m, 8H), 4.09 (dt, *J* = 9.1, 7.7 Hz, 1H), 3.85 (s, 3H), 3.82 (td, *J* = 8.8, 3.6 Hz, 1H), 3.15 (ddd, *J* = 12.5, 7.8, 3.6 Hz, 1H), 2.27 – 2.20 (m, 1H), 2.07 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) for major and minor isomer: δ 175.1, 174.8, 174.7, 172.2, 156.7, 149.9, 136.1, 135.8, 134.2, 133.3, 132.9, 132.7, 130.1, 129.8, 128.4, 128.3, 128.1, 128.0, 124.8, 124.7, 123.56, 123.4, 122.98, 122.0, 120.59, 120.3, 114.0, 55.8, 55.5, 54.7, 47.0, 46.3, 33.4, 31.2, 22.5, 22.0, 20.5, 20.3; IR (Neat Film NaCl) 2931, 1688, 1512, 1485, 1398, 1289, 1249, 1181, 1090, 1033, 993, 829, 766, 731, 697 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{26}H_{27}N_2O_2$ $[M+H]^+$: 399.2067, found 399.2072.

(S)-1-(2-Methoxyphenyl)-3-methyl-3-(phenyl(phenylamino)methyl)pyrrolidin-2-one (74)



To a suspension of lactam **57b** (82.1 mg, 0.400 mmol, 2.00 equiv), benzonitrile (20.6 mg, 0.200 mmol, 1.00 equiv), bromobenzene (31.5 mL, 0.300 mmol, 1.5 equiv), LHMDS (40.2 mg, 0.240 mmol, 1.20 equiv) and LiBr (86.9 mg, 1.00 mmol, 5.00 equiv) in toluene (1.0 mL) and THF (0.20 mL) were added a solution of $Ni(COD)_2$ (5.50 mg, 0.0200 mmol, 0.100 equiv) and SL-M004-1(Solvias, 25.3 mg, 0.0240 mmol, 0.120 equiv) at 0 °C and the reaction mixture was stirred at 0 °C for 48 h. $NaBH_4$ (45.4 mg, 1.20 mmol, 6 equiv), THF (2 mL) and MeOH (2 mL) were added and the reaction mixture was stirred at 25 °C for 2 days. Water was added and the mixture was extracted with AcOEt (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) on silica gel to give amine **74** as a colorless oil (54.3 mg, 70% yield).

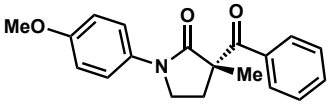
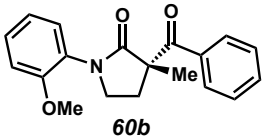
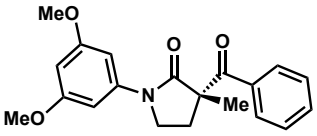
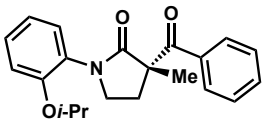
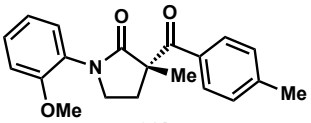
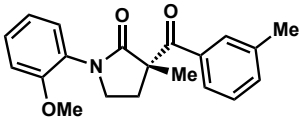
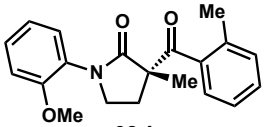
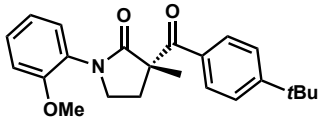
Spectroscopic data for amine **74** was taken after separation of the diastereomers by flash column chromatography on silica gel.

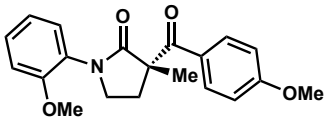
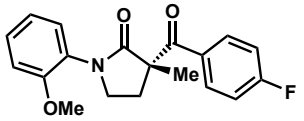
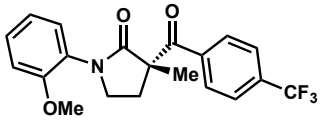
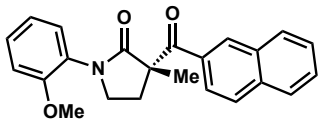
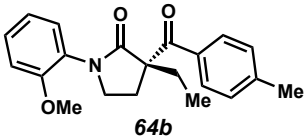
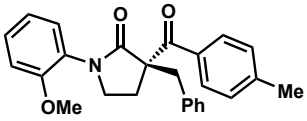
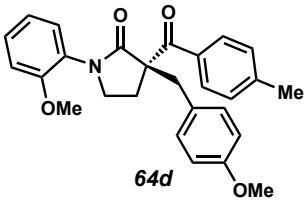
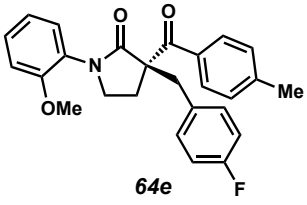
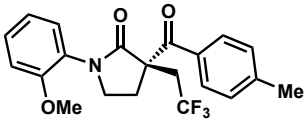
Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 2H), 7.38 – 7.31 (m, 2H), 7.31 – 7.23 (m, 5H), 7.12 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.06 – 6.99 (m, 2H), 6.99 – 6.88 (m, 2H), 6.62 (t, *J* = 7.3 Hz, 1H), 6.50 (d, *J* = 7.9 Hz, 2H), 5.51 (s, 1H), 4.50 (s,

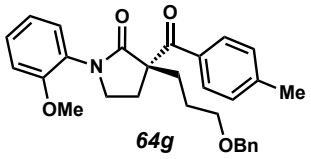
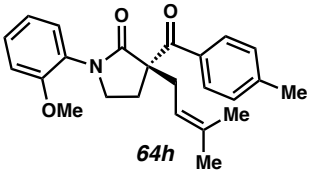
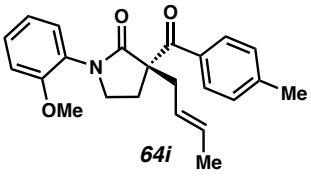
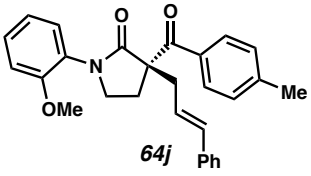
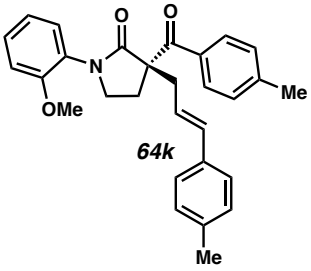
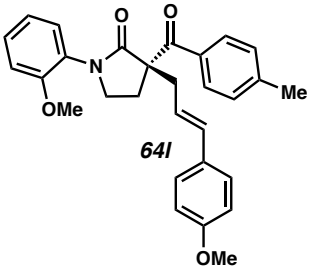
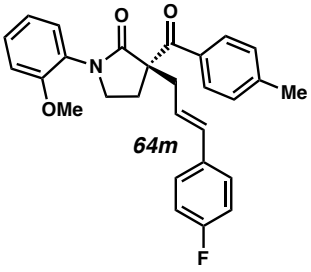
1H), 3.63 – 3.51 (m, 2H), 3.60 (s, 3H), 2.42 (ddd, *J* = 12.7, 7.6, 4.7 Hz, 1H), 1.81 (ddd, *J* = 13.0, 8.3, 6.8 Hz, 1H), 1.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9, 154.9, 148.3, 139.8, 129.0, 128.9, 128.6, 128.6, 128.2, 127.5, 127.0, 120.8, 117.4, 114.1, 112.9, 62.9, 55.4, 47.6, 46.7, 31.0, 19.7; IR (Neat Film NaCl) 3375, 2968, 1678, 1601, 1505, 1455, 1310, 1279, 1260, 1025, 749, 702 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{27}N_2O_2$ $[M+H]^+$: 387.2067, found 387.2070.

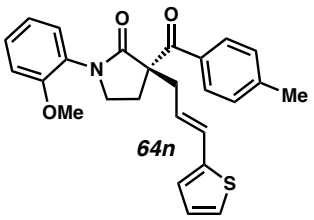
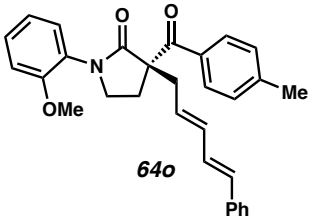
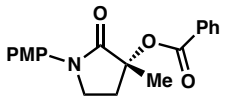
Minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 2H), 7.35 – 7.20 (m, 4H), 7.09 – 6.98 (m, 3H), 6.98 – 6.90 (m, 2H), 6.58 – 6.47 (m, 3H), 6.19 (br s, 1H), 4.37 (s, 1H), 3.78 (s, 3H), 3.41 (td, *J* = 9.1, 4.7 Hz, 1H), 2.62 (ddd, *J* = 9.4, 8.4, 6.4 Hz, 1H), 2.27 (ddd, *J* = 13.1, 8.4, 4.7 Hz, 1H), 1.98 (ddd, *J* = 13.0, 8.9, 6.4 Hz, 1H), 1.61 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.3, 154.6, 147.2, 140.6, 129.0, 128.8, 128.3, 128.3, 127.7, 127.5, 126.8, 120.7, 116.4, 112.9, 112.0, 64.5, 55.6, 47.2, 46.75, 30.8, 24.8; IR (Neat Film NaCl) 3375, 2929, 1674, 1600, 1505, 1455, 1418, 1308, 1256, 1026, 748, 704 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{27}N_2O_2$ $[M+H]^+$: 387.2067, found 387.2071.

Determination of Enantiomeric Excess (Table S1)

entry	compound	analytic conditions	ee (%)
1	 ***60a***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min, t_R(min): major 10.56, minor 8.06**	**88**
2	 ***60b***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 8.55, minor 7.66**	**92**
3	 ***60c***	**HPLC CHIRALCELL OD, λ = 254 nm 10% IPA/hexanes, 1.0 mL/min t_R(min): major 23.56, minor 16.84**	**85**
4	 ***60d***	**HPLC CHIRALCELL OD, λ = 254 nm 20% IPA/hexanes, 1.0 mL/min t_R(min): major 7.03, minor 6.39**	**86**
5	 ***62b***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 10.51, minor 7.66**	**91**
6	 ***62c***	**SFC Chiralpak OJ-H, λ = 254 nm 15% IPA/CO_2, 2.5 mL/min, t_R(min): major 4.20, minor 5.72**	**93**
7	 ***62d***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 8.14, minor 6.64**	**94**
8	 ***62e***	**HPLC CHIRALCELL OD, λ = 254 nm 15% IPA/hexanes, 1.0 mL/min t_R(min): major 11.57, minor 9.83**	**92**

entry	compound	analytic conditions	ee (%)
9	 ***62f***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **15% IPA/hexanes, 1.0 mL/min** **t_R(min): major 11.57, minor 9.83**	**89**
10	 ***62g***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **20% IPA/hexanes, 1.0 mL/min** **t_R(min): major 11.36, minor 9.98**	**93**
11	 ***62h***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **30% IPA/hexanes, 1.0 mL/min** **t_R(min): major 7.41, minor 6.76**	**87**
12	 ***62i***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **10% IPA/hexanes, 1.0 mL/min** **t_R(min): major 26.83, minor 23.63**	**91**
13	 ***64b***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **30% IPA/hexanes, 1.0 mL/min** **t_R(min): major 8.24, minor 6.39**	**78**
14	 ***64c***	**SFC** **Chiralpak OJ-H, λ = 254 nm** **2% IPA/CO_2, 2.5 mL/min,** **t_R(min): major 7.25, minor 6.34**	**81**
15	 ***64d***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **30% IPA/hexanes, 1.0 mL/min** **t_R(min): major 11.24, minor 8.72**	**81**
16	 ***64e***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **30% IPA/hexanes, 1.0 mL/min** **t_R(min): major 9.40, minor 7.41**	**74**
17	 ***64f***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **20% IPA/hexanes, 1.0 mL/min** **t_R(min): major 8.40, minor 7.49**	**71**

entry	compound	analytic conditions	ee (%)
18	 ***64g***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 11.38, minor 8.47**	**60**
19	 ***64h***	**HPLC CHIRALCELL OD, λ = 254 nm 20% IPA/hexanes, 1.0 mL/min t_R(min): major 9.61, minor 7.13**	**76**
20	 ***64i***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 7.31, minor 5.33**	**86**
21	 ***64j***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 12.63, minor 8.67**	**86**
22	 ***64k***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 11.30, minor 7.58**	**86**
23	 ***64l***	**HPLC CHIRALCELL OD, λ = 254 nm 40% IPA/hexanes, 1.0 mL/min t_R(min): major 11.68, minor 7.70**	**88**
24	 ***64m***	**HPLC CHIRALCELL OD, λ = 254 nm 30% IPA/hexanes, 1.0 mL/min t_R(min): major 12.54, minor 8.47**	**83**

entry	compound	analytic conditions	ee (%)
25	 ***64n***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **30% IPA/hexanes, 1.0 mL/min** **t_R(min): major 14.39, minor 8.96**	**83**
26	 ***64o***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **30% IPA/hexanes, 1.0 mL/min** **t_R(min): major 11.30, minor 7.58**	**84**
27	 ***67***	**HPLC** **CHIRALCELL OD, λ = 254 nm** **30% IPA/hexanes, 1.0 mL/min** **t_R(min): major 10.42, minor 7.88**	**88**

(1) For reviews, see: (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 0369–0396. (b) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597. (c) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5363–5367. (d) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, 181–191. (e) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740–751.

(2) (a) Nascimento de Oliveira, M.; Fournier, J.; Areseniyadis, S.; Cossy, J. *Org. Lett.* **2017**, *19*, 14–17. (b) James, J.; Guiry, P. J. *ACS Catal.* **2017**, *7*, 1397–1402. (b) Akula, R.; Guiry, P. J. *Org. Lett.* **2016**, *18*, 5472–5475. (c) Akula, R.; Doran, R.; Guiry, P. J. *Chem. Eur. J.* **2016**, *22*, 9938–9942. (d) Marziale, A. N.; Duquette, D. C.; Craig, R. A.; Kim, K. E.; Liniger, M.; Numajiri, Y.; Stoltz, B. M. *Adv. Synth. Catal.* **2015**, *357*, 2238–2245. (e) Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2015**, *54*, 179–183. (f) Craig, R. A.; Loskot, S. A.; Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 5160–5163. (g) Alberch, E.; Brook, C.; Asad, S. A.; Shevyrev, M.; Ulicki, J. S.; Hossain, M. M. *Synlett* **2015**, *26*, 388–392. (h) Liu, W.-B.; Reeves, C. M.; Virgil, S. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 10626–10629. (i) Kaiser, T. M.; Yang, J. *Eur. J. Org. Chem.* **2013**, 3983–3987. (j) Fournier, J.; Lozano, O.; Menozzi, C.; Arseniyadis, S.; Cossy, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 1257–1261. (k) Reeves, C. M.; Eidamshaus, C.; Kim, J.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 6718–6721. (l) Gartshore, C. J.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 4113–4116. (m) Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem. Int. Ed.* **2013**, *52*, 4117–4121. (n)

Shibuya, G. M.; Enquist, J. A.; Stoltz, B. M. *Org. Lett.* **2013**, *15*, 3480–3483. (o) Bennett, N. B.; Duquette, D. C.; Kim, J.; Liu, W.-B.; Marziale, A. N.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2013**, *19*, 4414–4418. (p) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2012**, *4*, 130–133. (q) Keither, J. A.; Behenna, D. C.; Sherden, N.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Nielsen, R. J.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A. *J. Am. Chem. Soc.* **2012**, *134*, 19050–19060. (r) Franckevičius, V.; Cuthbertson, J. D.; Pickworth, M.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2011**, *13*, 4264–4267. (s) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novak, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2011**, *17*, 14199–14223. (t) Streuff, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2010**, 192–196. (u) Chattopadhyay, K.; Jana, R.; Day, V. W.; Douglas, J. T.; Tunge, J. A. *Org. Lett.* **2010**, *12*, 3042–3045. (v) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343–18357. (w) Sherden, N. H.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6840–6843. (x) Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 3109–3112. (y) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927. (z) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847. (aa) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045.

(3) (a) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759–6760. (b) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, X.-Z. *Org. Lett.* **2001**, *3*, 149–151. (c) Trost,

B. M.; Schroeder, G. M.; Kristensen, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 3492–3495. (d) Trost, B. M.; Schroeder, G. M. *J. Org. Chem.* **2000**, *65*, 1569–1573. (e) Zhou, H.; Yang, H.; Liu, M.; Xia, C.; Jiang, G. *Org. Lett.* **2014**, *16*, 5350–5353. (f) Fukuda, Y.; Kondo, K.; Aoyama, T. *Tetrahedron Lett.* **2007**, *48*, 3389–3391. (g) Nemoto, T.; Fukuda, T.; Matsumoto, T.; Hitomi, T.; Hamada, Y. *Adv. Synth. Catal.* **2005**, *347*, 1504–1506. (h) Nemoto, T.; Masuda, T.; Matsumoto, T.; Hamada, Y. *J. Org. Chem.* **2005**, *70*, 7172–7178.

(4) (a) Hethcox, J. C.; Shockley, S. E. *Angew. Chem. Int. Ed.* **2016**, *55*, 16092–16095. (b) Liu, W.-B.; Reeves, C. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 17298–17301. (c) Liu, W.-B.; Reeves, C. M.; Virgil, S. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 10626–10629. (d) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013**, *340*, 1065–1068. (e) Chen, W.; Chen, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 15826–15828.

(5) (a) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402–3415. (b) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261–1268. (c) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900–9901. (d) Arao, T.; Kondo, K.; Aoyama, T. *Chem. Pharm. Bull.* **2006**, *12*, 1743–1744. (e) Liu, Lantao; Ishida, N.; Ashida, S.; Murakami, M. *Org. Lett.* **2011**, *13*, 1666–1669. (f) Luan, X.; Wu, L.; Drinkel, E.; Mariz, R.; Gatti, M.; Dorta, R. *Org. Lett.* **2010**, *12*, 1912–1915. (g) Ackermann, L.; Vicente, R.; Hofmann, N. *Org. Lett.* **2009**, *11*, 4274–4276. (h) Jiang, L.; Weist, S.; Jansat, S. *Org. Lett.* **2009**, *11*, 1543–1546. (i) García-Fortanet, J.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 8108–8111. (j) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195–200. (k)

Kündig, P.; Seidel, T. M.; Jia, Y.-X.; Bernardinelli, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 8484–8487.

(6) (a) Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500–3501. (b) Chen, G.; Kwong, F. Y.; Chan, H. O.; Yu, W.-Y.; Chan, A. S. C. *Chem. Commun.* **2006**, 1413–1415. (c) Ge, S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 16330–16333.

(7) Xie, X.; Chen, Y.; Ma, D. *J. Am. Chem. Soc.* **2006**, *128*, 16050–16051.

(8) For a review, see: Burtoloso, A. C. B. *Synlett*, **2009**, 320–327.

(9) (a) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532. (b) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368. (c) Seitzberg, J. G.; Dissing, C.; Søtofte, I.; Norrby, P.-O.; Johannsen, M. *J. Org. Chem.* **2005**, *70*, 8332. (d) Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925. (e) Nguyen, H. V.; Butler, D. C. D.; Richards, C. J. *Org. Lett.* **2006**, *8*, 769. (f) Busto, E.; Gotor-Fernández, V.; Gotor, V. *Adv. Synth. Catal.* **2006**, *348*, 2626. (g) Dietz, F. R.; Gröger, H. *Synlett* **2009**, 4208. (h) Dietz, F. R.; Gröger, H. *Synthesis*, **2009**, 4208. (i) Uraguchi, D.; Koshimoto, K.; Miyake, S.; Ooi, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 5567. (j) Zhang, Z.; Xie, F.; Jia, J.; Zhang, W. *J. Am. Chem. Soc.* **2010**, *132*, 15939. (k) Campbell, C. D.; Concellón, C.; Smith, A. D. *Tetrahedron: Asymmetry* **2011**, *22*, 797. (l) De, C. K.; Mittal, N.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 16802. (m) Viswambharan, B.; Okimura, T.; Suzuki, S.; Okamoto, S. *J. Org. Chem.* **2011**, *76*, 6678. (n) Joannesse, C.; Johnston, C. P.; Morrill, L. C.; Woods, P. A.; Kieffer, M.; Nigst, T. A.; Mayr, H.; Lebl, T.; Philp, D.; Bragg, R. A.; Smith, A. D. *Chem. Eur. J.* **2012**, *18*, 2398. (o) Mandai, H.; Fujiwara,

T.; Noda, K.; Fujii, K.; Mitsudo, K.; Korenaga, T.; Suga, S. *Org. Lett.* **2015**, *17*, 4436. (p) Hills, I. D.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 3921. (q) Ismail, M.; Nguyen, H. V.; Ilyashenko, G.; Motevalli, M.; Richards, C. J. *Tetrahedron Lett.* **2009**, *50*, 6332. (r) Duffey, T. A.; Shaw, S. A.; Vedejs, E. *J. Am. Chem. Soc.* **2009**, *131*, 14. (s) Wang, M.; Zhang, Z.; Liu, S.; Xie, F.; Zhang, W. *Chem. Commun.* **2014**, *50*, 1227.

(10) (a) Fleming, I.; Iqbal, J.; Krebs, E.-P. *Tetrahedron* **1983**, *39*, 841–846. (b) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425–5428. (c) Crabtree, S. R.; Chu, W. L. A.; Mander, L. N. *Synlett* **1990**, *3*, 169–70. (d) Le Roux, C.; Mandrou, S.; Dubac, J. *J. Org. Chem.* **1996**, *61*, 3885–3887. (e) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Tetrahedron Lett.* **2002**, *43*, 2945–2948.

(11) (a) Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 4050–4051. (b) Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 5604–5607. (c) Birrell, J. A.; Desrosiers, J.-N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 13872–13875. (d) Woods, P.A.; Morrill, L. C.; Bragg, R. A.; Smith, A. D. *Chem. Eur. J.* **2011**, *17*, 11060–11067. (e) Woods, P.A.; Morrill, L. C.; Lebl, T.; Slawin, A. M. Z.; Bragg, R. A.; Smith, A. D. *Org. Lett.* **2010**, *12*, 2660–2663.

(12) Hasserodt, J.; Janda, K. D.; Lerner, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 5993–5998.

(13) Wang, K.-B.; Ran, R.-Q.; Xiu, S.-D.; Li, C.-Y. *Org. Lett*. **2013** *15*, 2374–2377.

(14) Lölsberg, W.; Ye, S.; Schmalz, H. G. *Adv. Synth. Catal.* **2010**, *352*, 2023–2031.

(15) Meiß, R.; Kumar, K.; Waldmann, H. *Chem. Eur. J*. **2015**, *21*, 13526–13530.

(16) Tian, Y.; Wang, Y.; Shang, H.; Xua, X.; Tang Y. *Org. Biomol. Chem.* **2015**, *13*, 612–619

(17) Kurauchi, D.; Hirano, K.; Kato, H.; Saito, T.; Miyamoto K.; Uchiyama, M. *Tetrahedron* **2015**, *71*, 5849–5857.

(18) Kim, D. D.; Lee, S. J.; Beak, P. *J. Org. Chem*. **2005**, *70*, 5376-5386.

(19) Banerjee, S.; Smith, J.; Smith, J.; Faulkner, F.; Masterson, D. S. *J. Org. Chem*. **2012**, *77*, 10925− 10930.

APPENDIX 3

Spectra Relevant to Chapter 4:

Ni-Catalyzed Enantioselective C-Acylation of α-Substituted Lactams

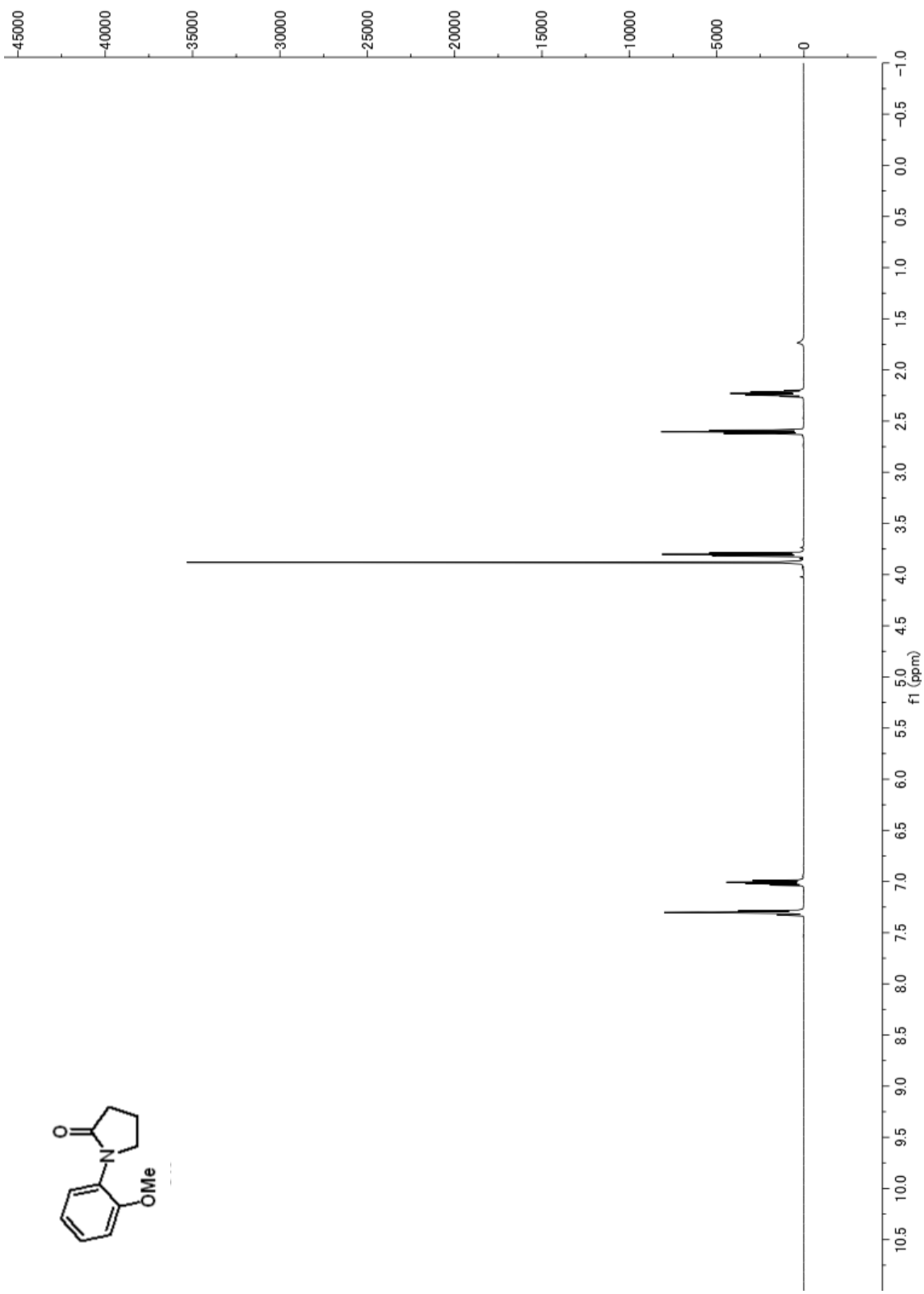


Figure A3.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI2**.

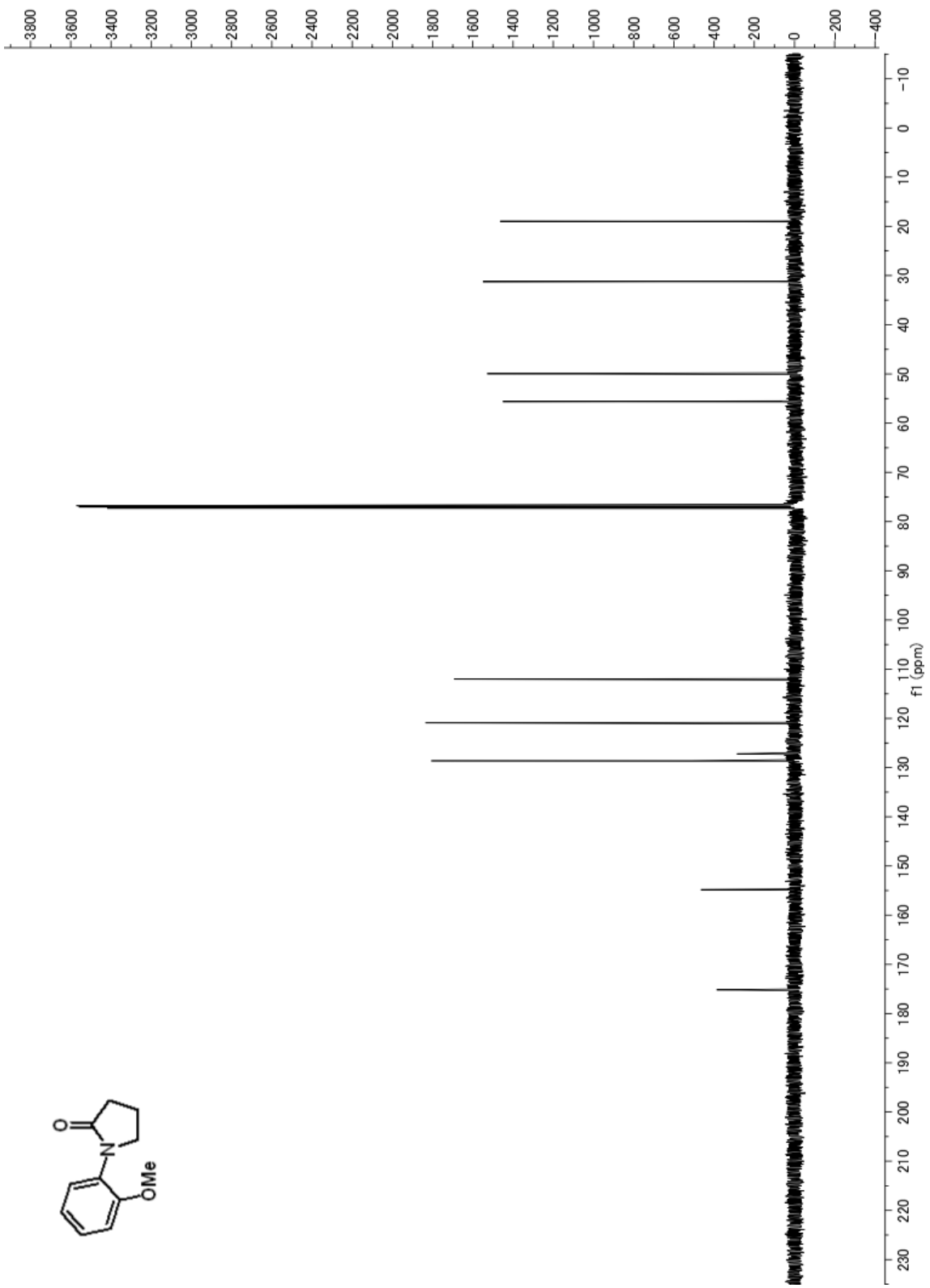


Figure A3.2. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **SI2**.

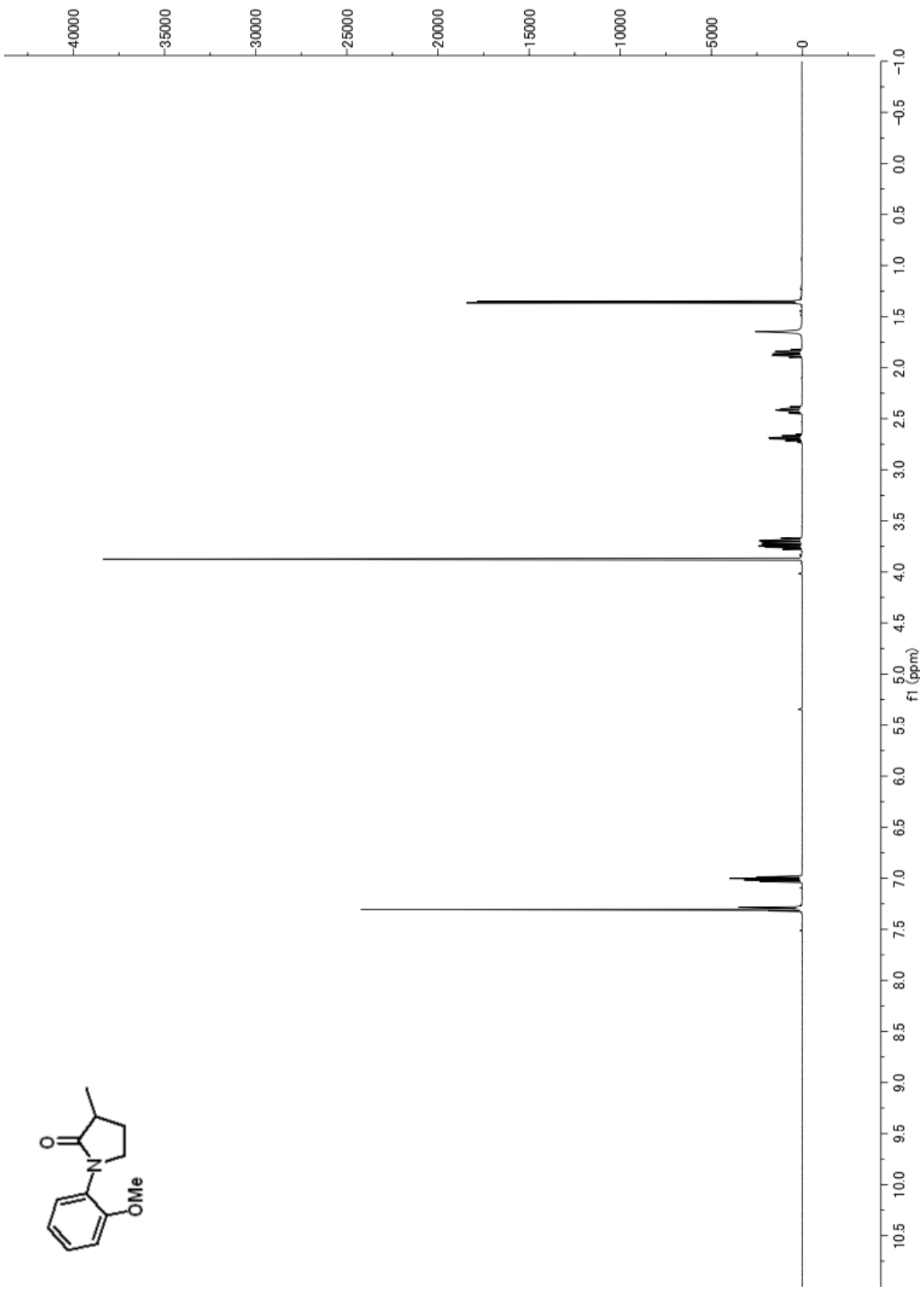


Figure A3.3. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **57b**.

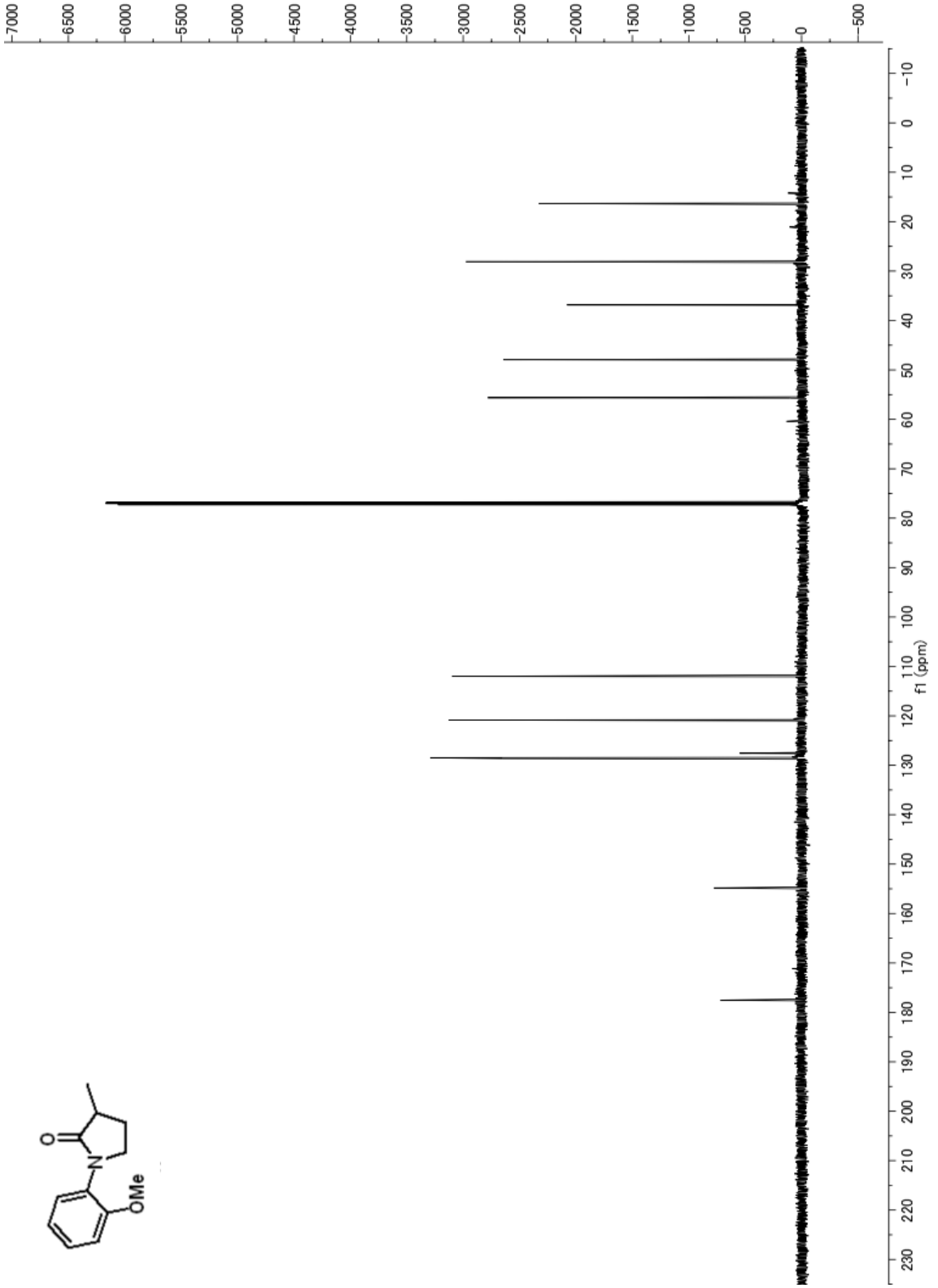


Figure A3.4. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **57b**.

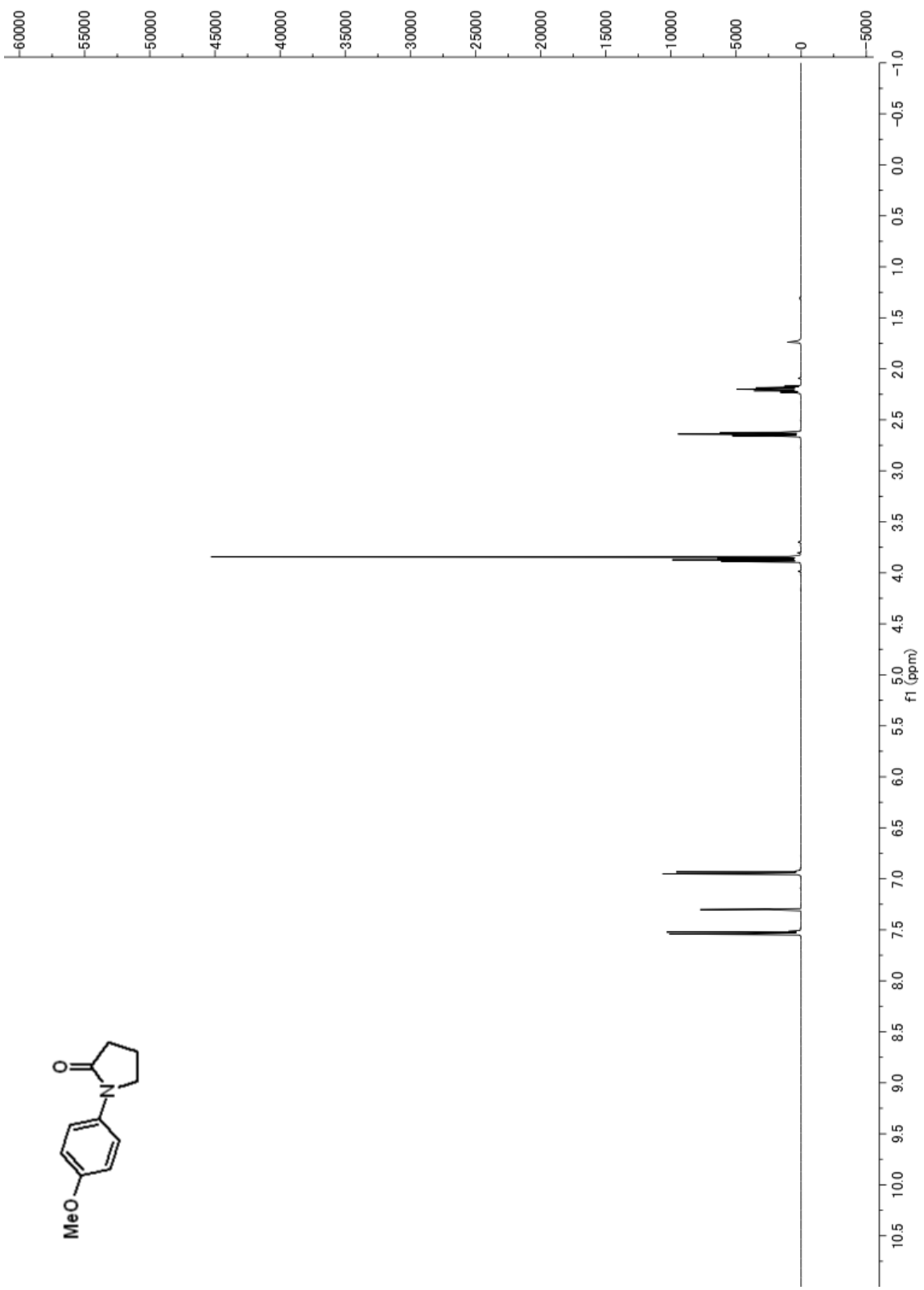


Figure A3.5. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI3**.

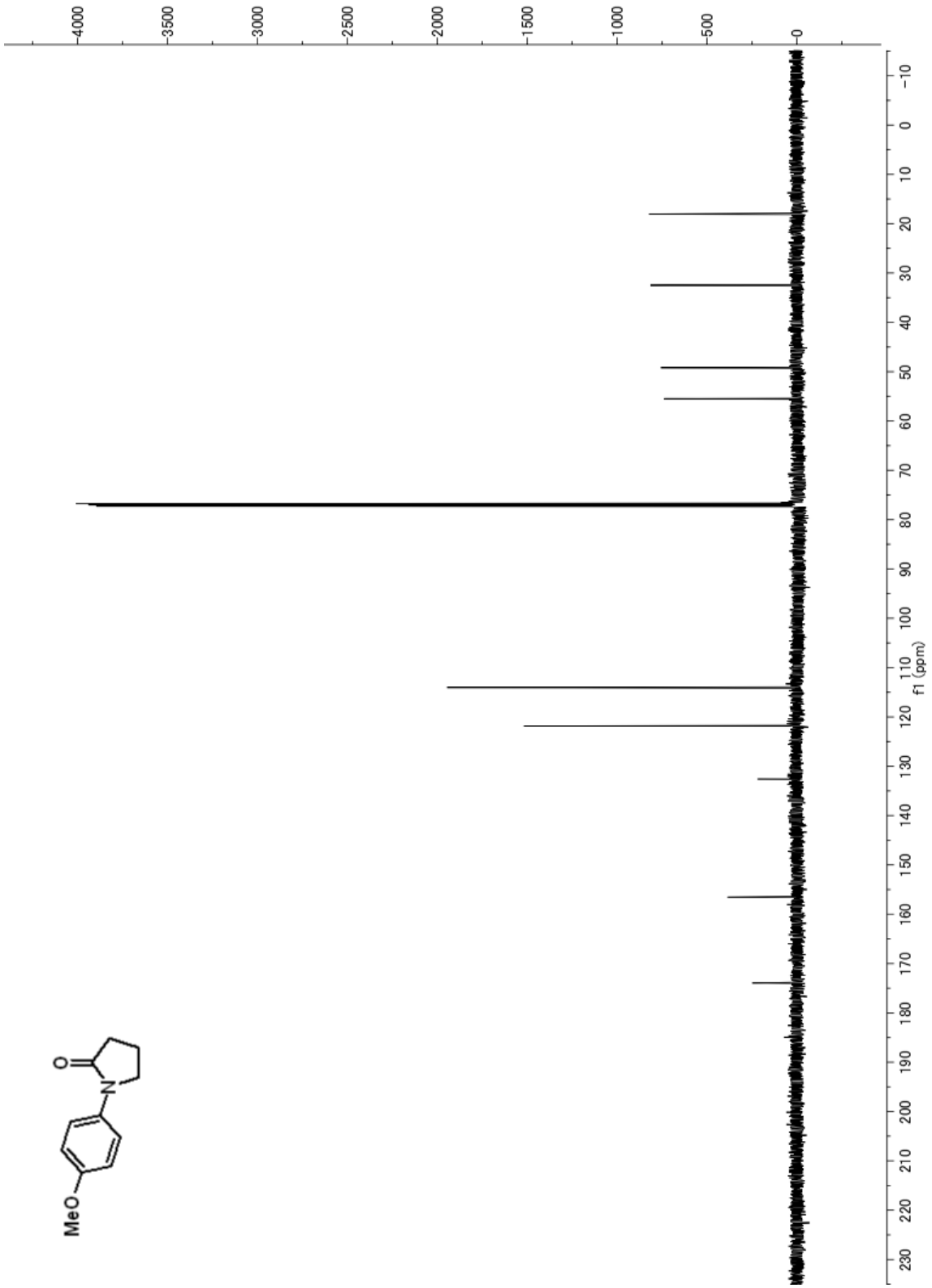


Figure A3.6. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **SI3**.

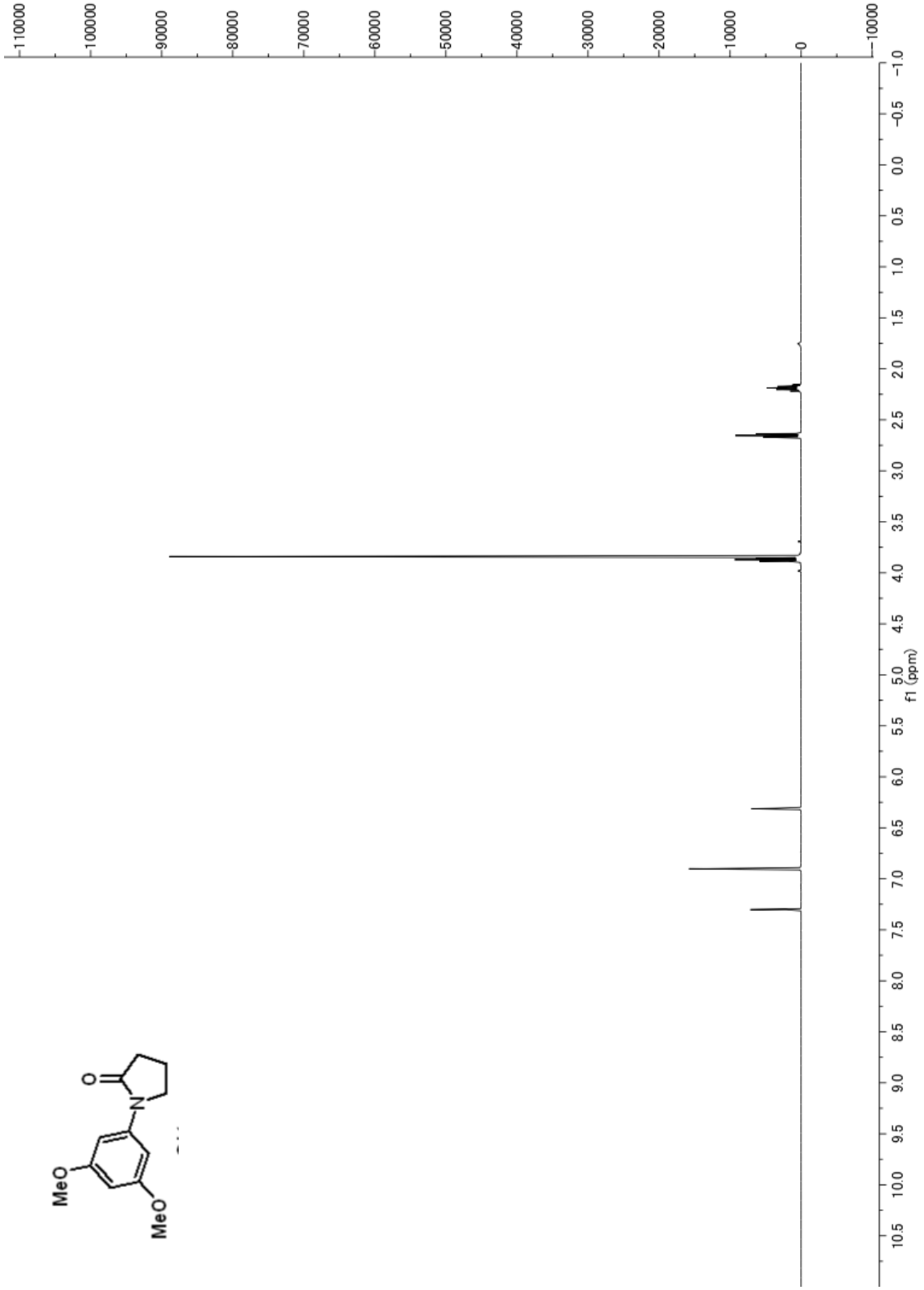


Figure A3.7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI4**.

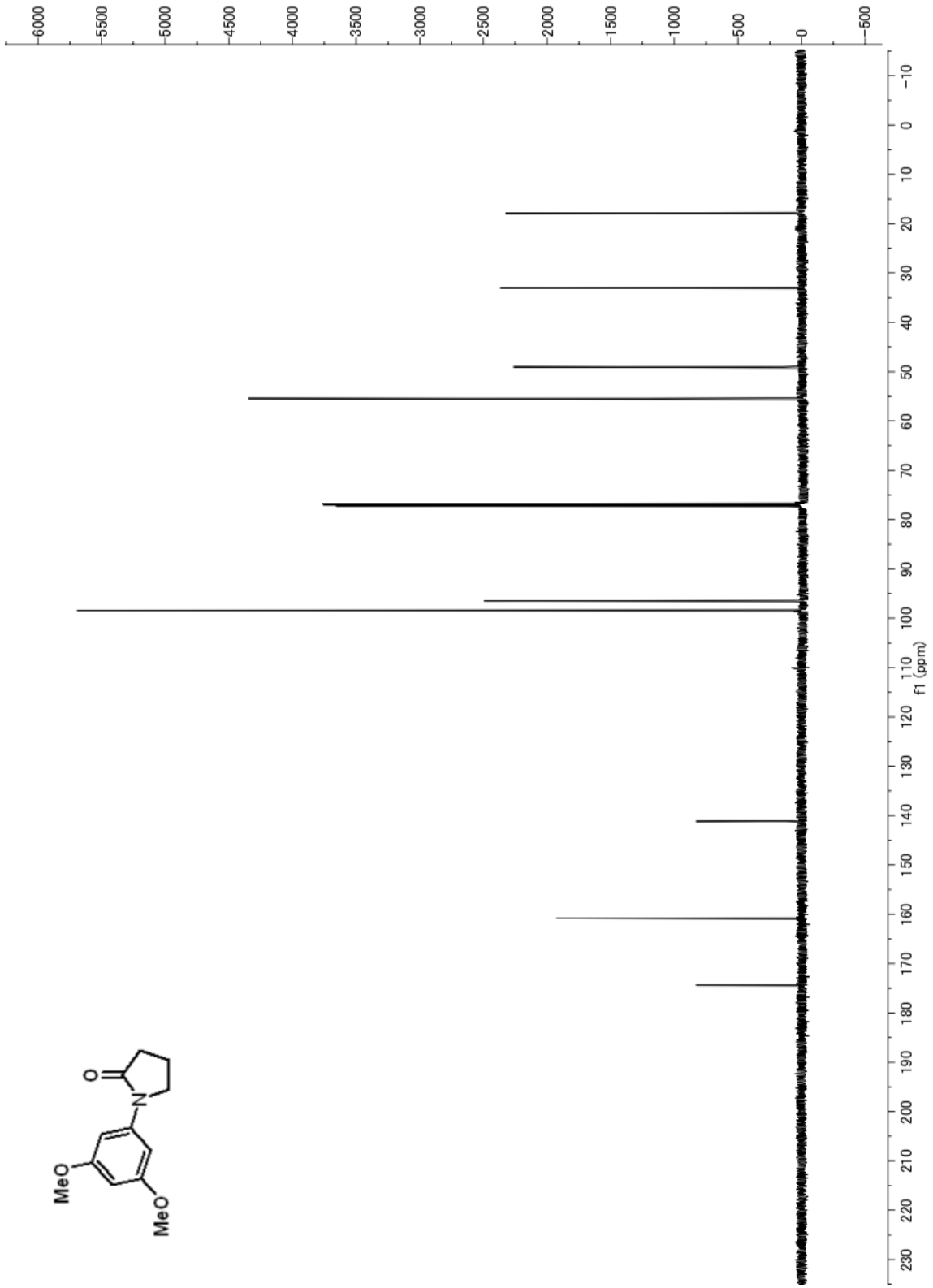


Figure A3.8. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **SI4**.

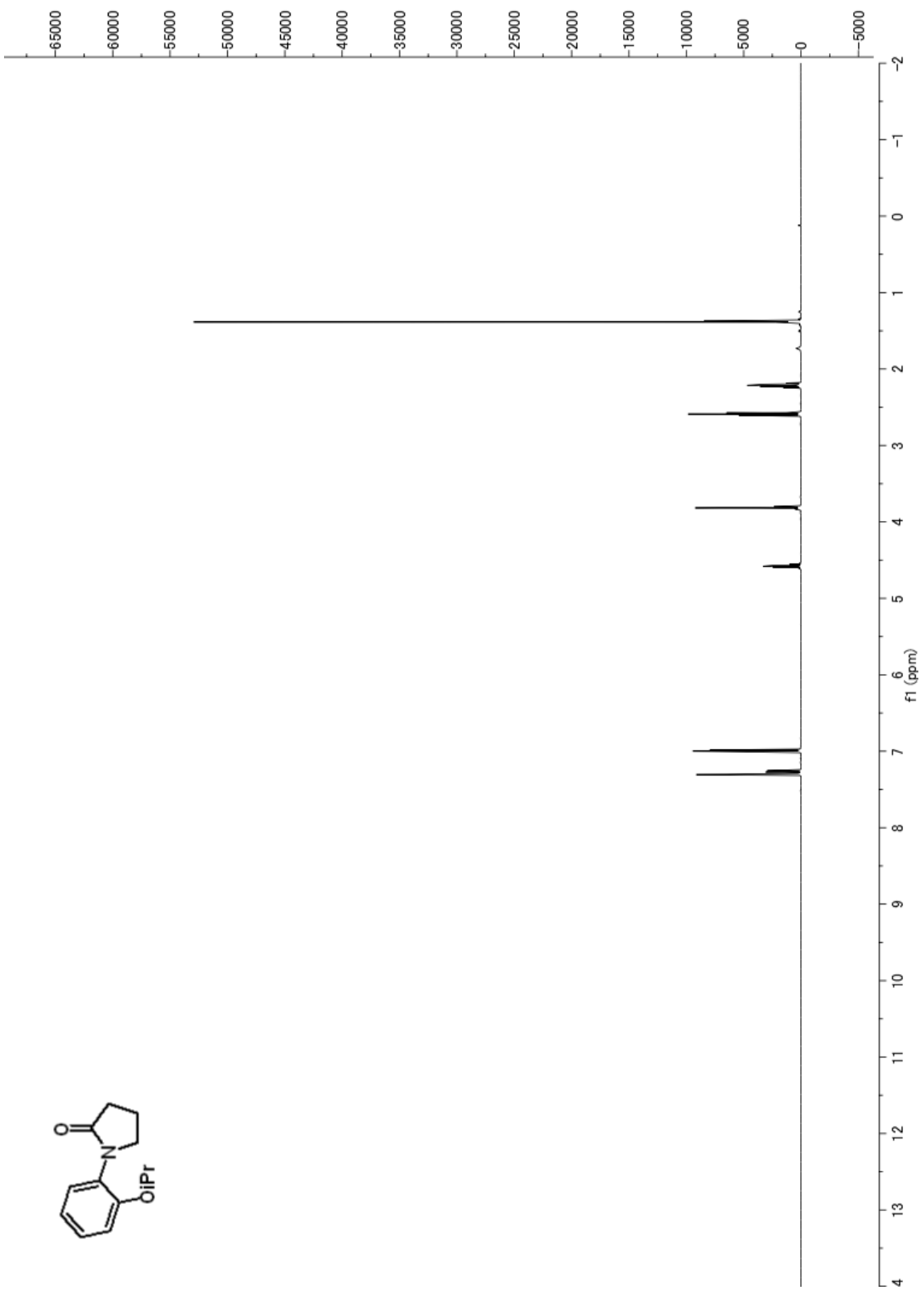


Figure A3.9. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **SI5**.

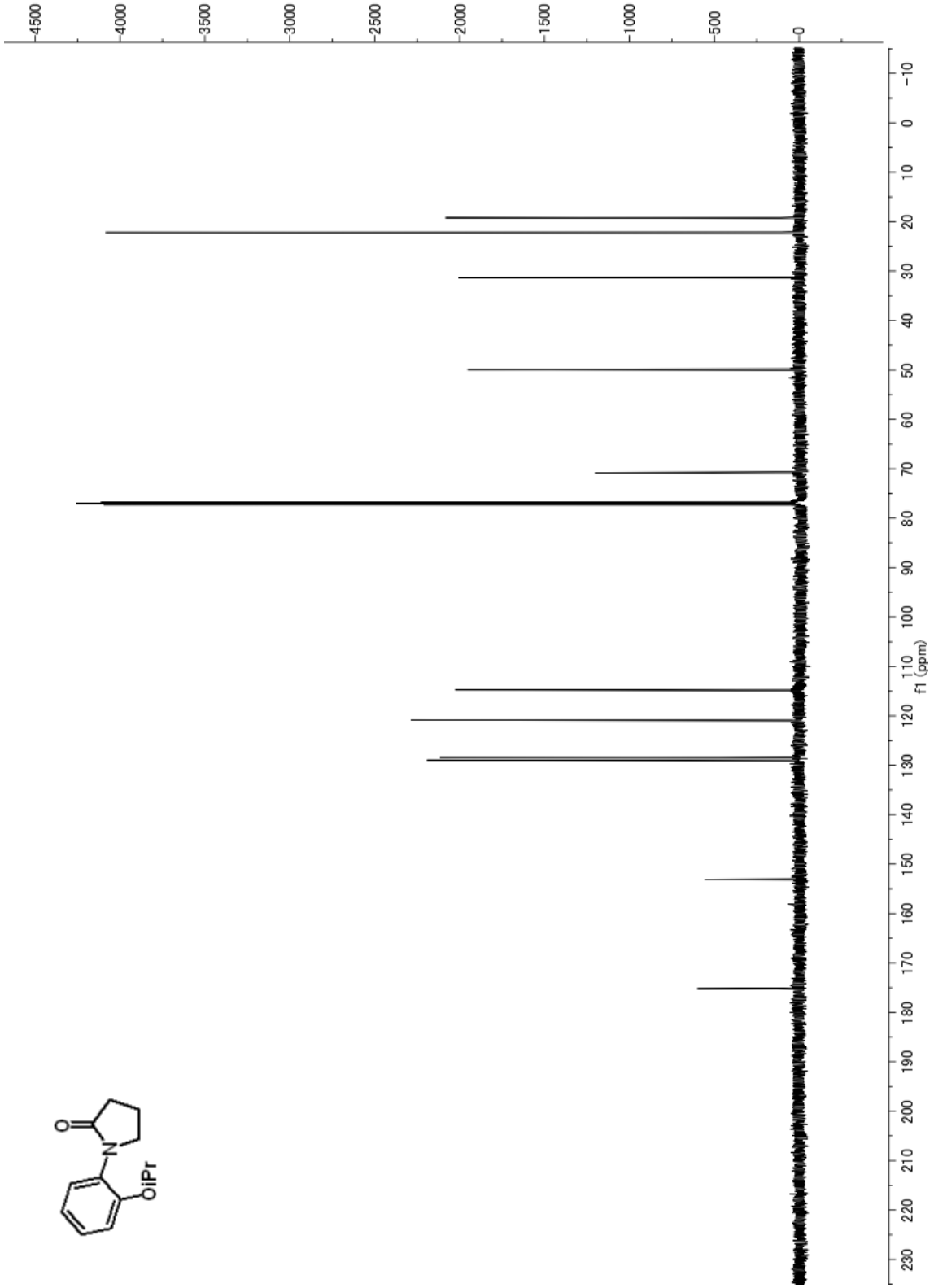


Figure A3.10. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **SI5**.

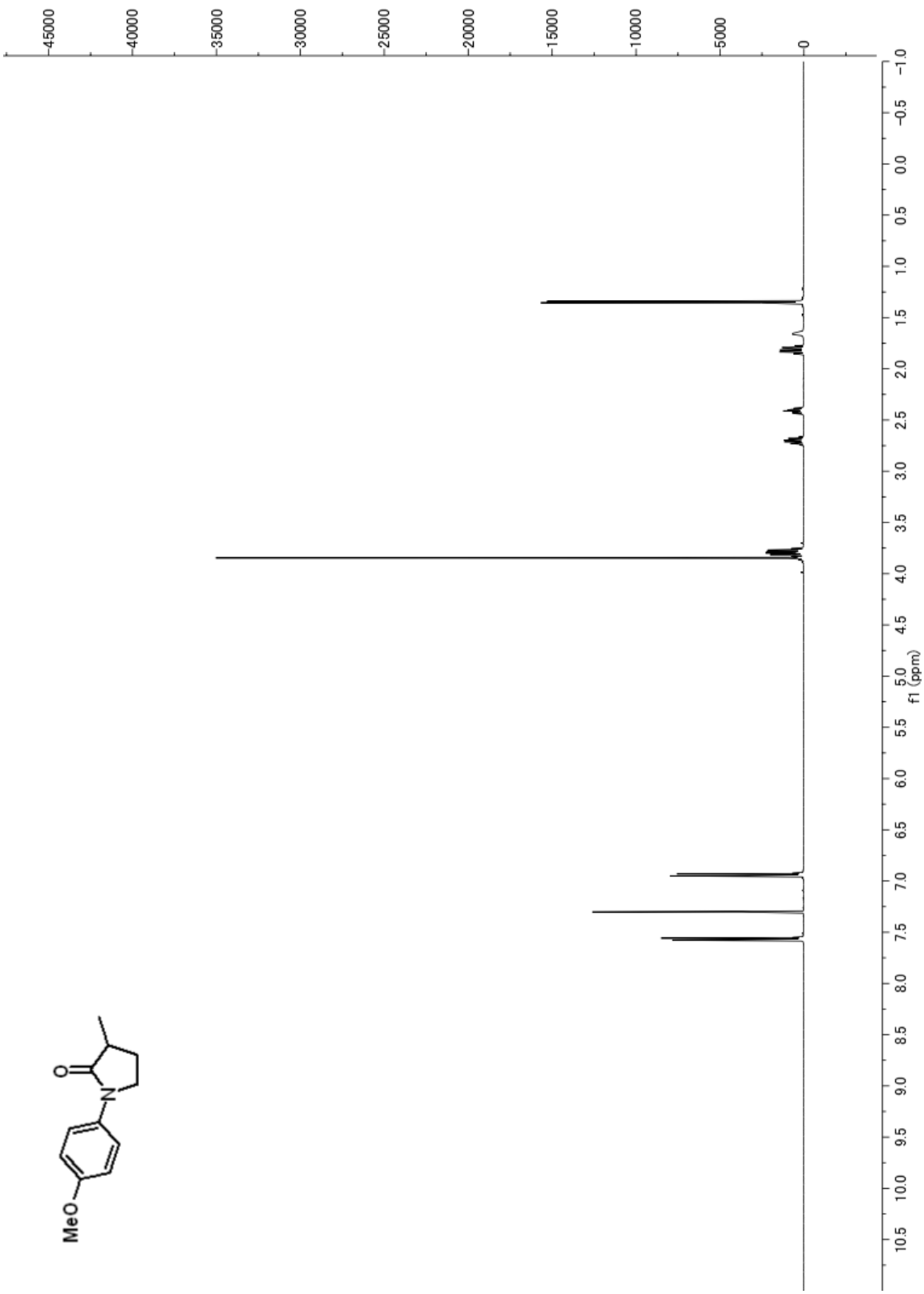


Figure A3.11. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **57a**.

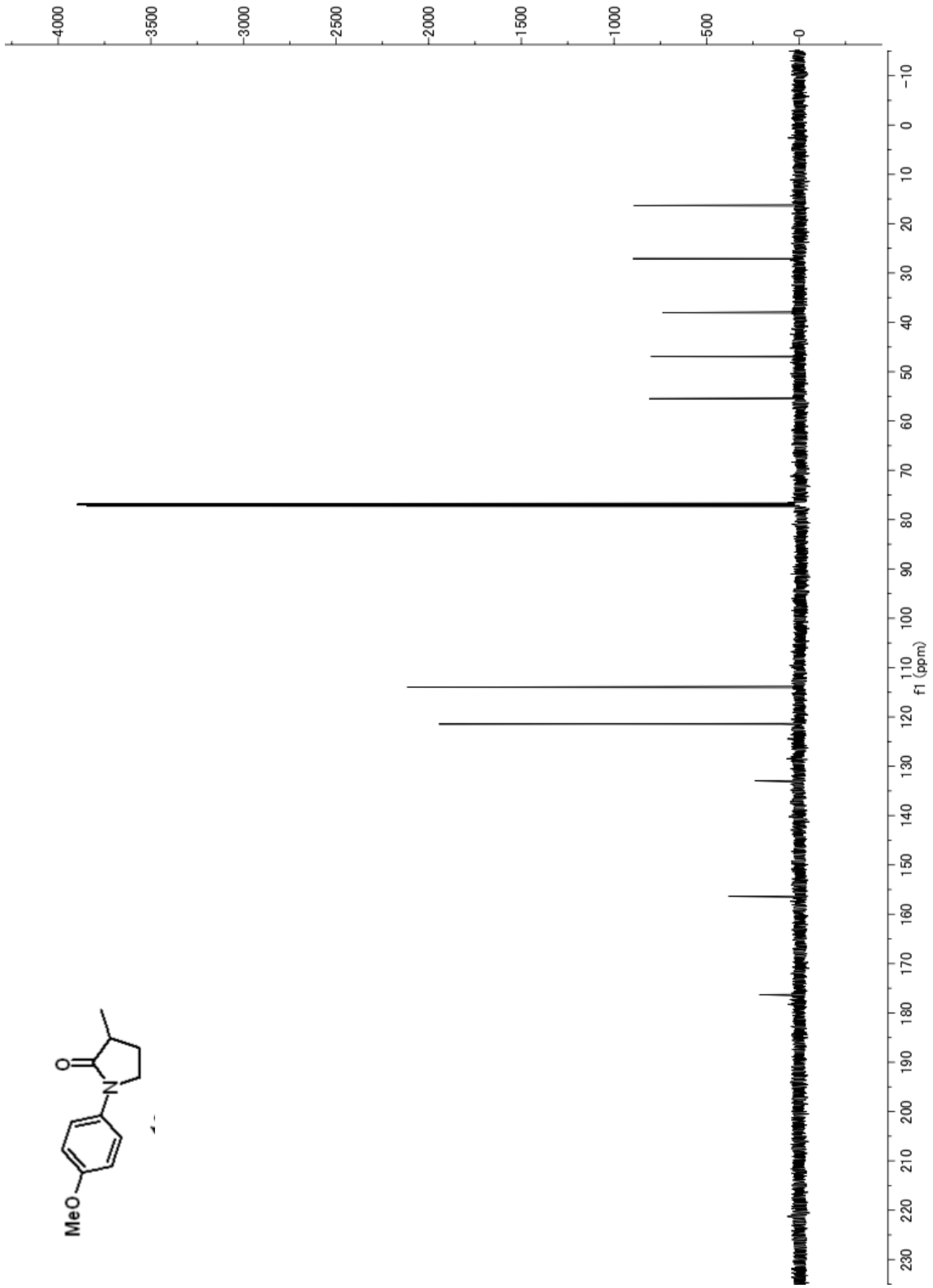


Figure A3.12. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **57a**.

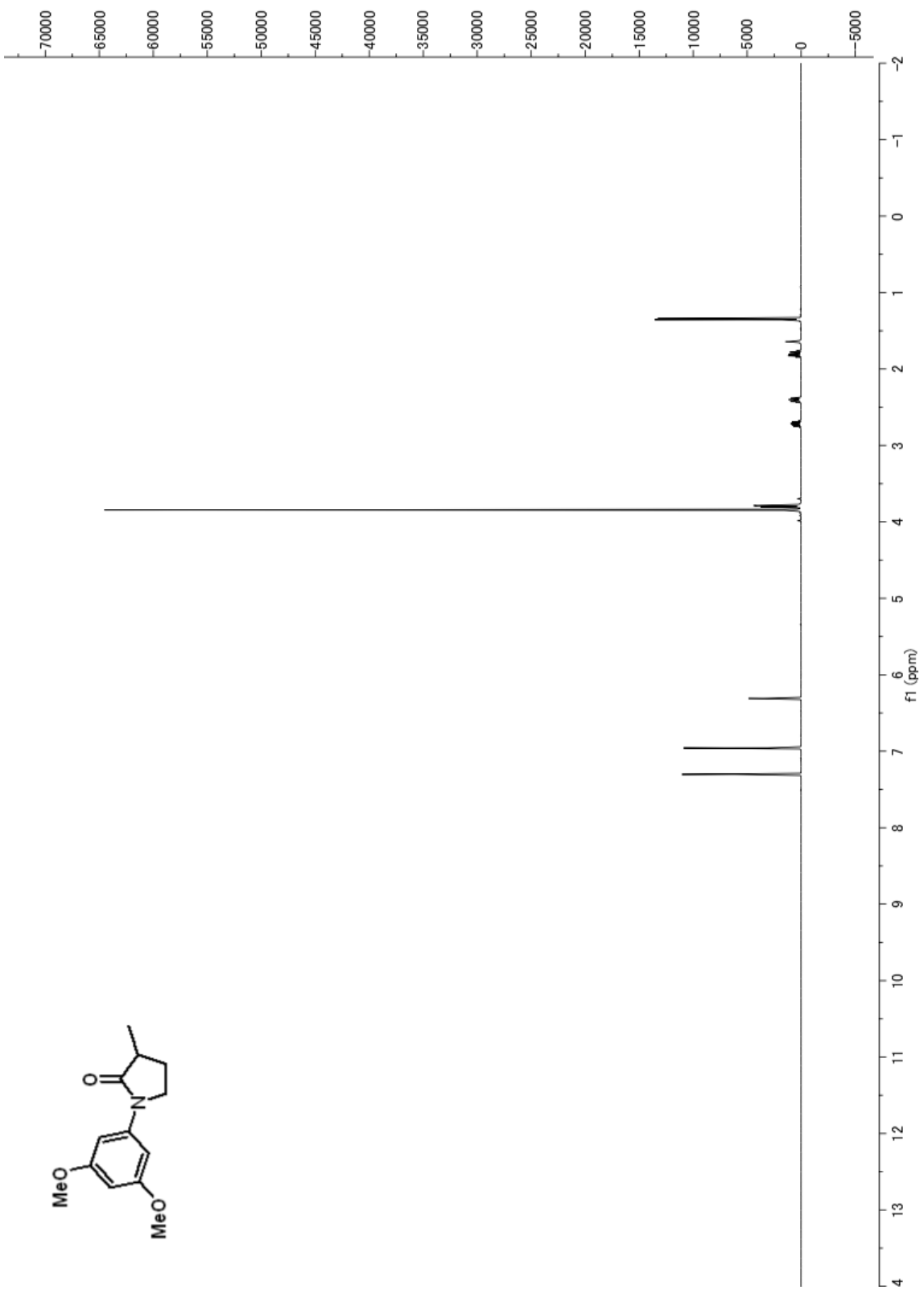


Figure A3.13. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **57c**.

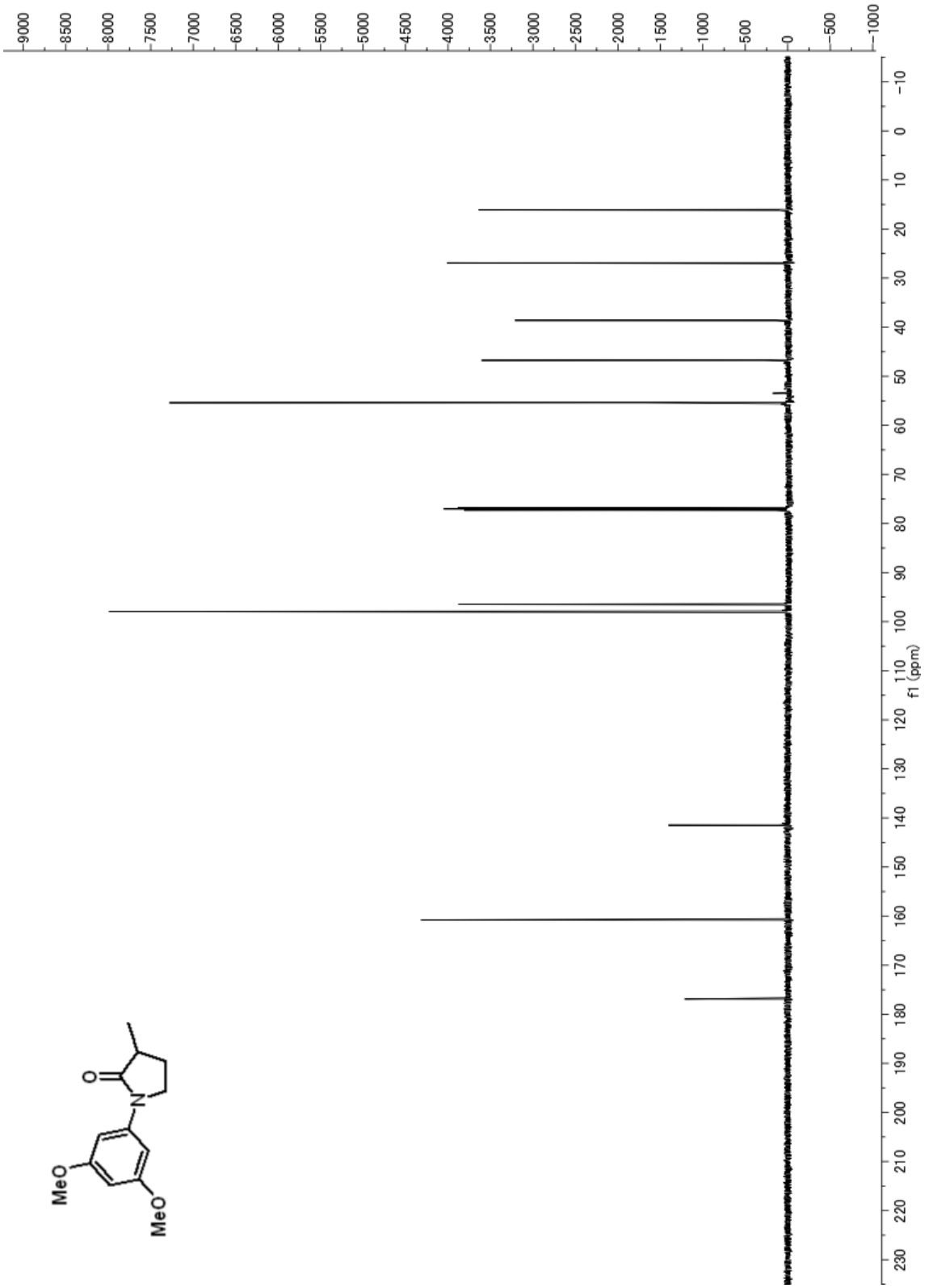


Figure A3.14. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **57c**.

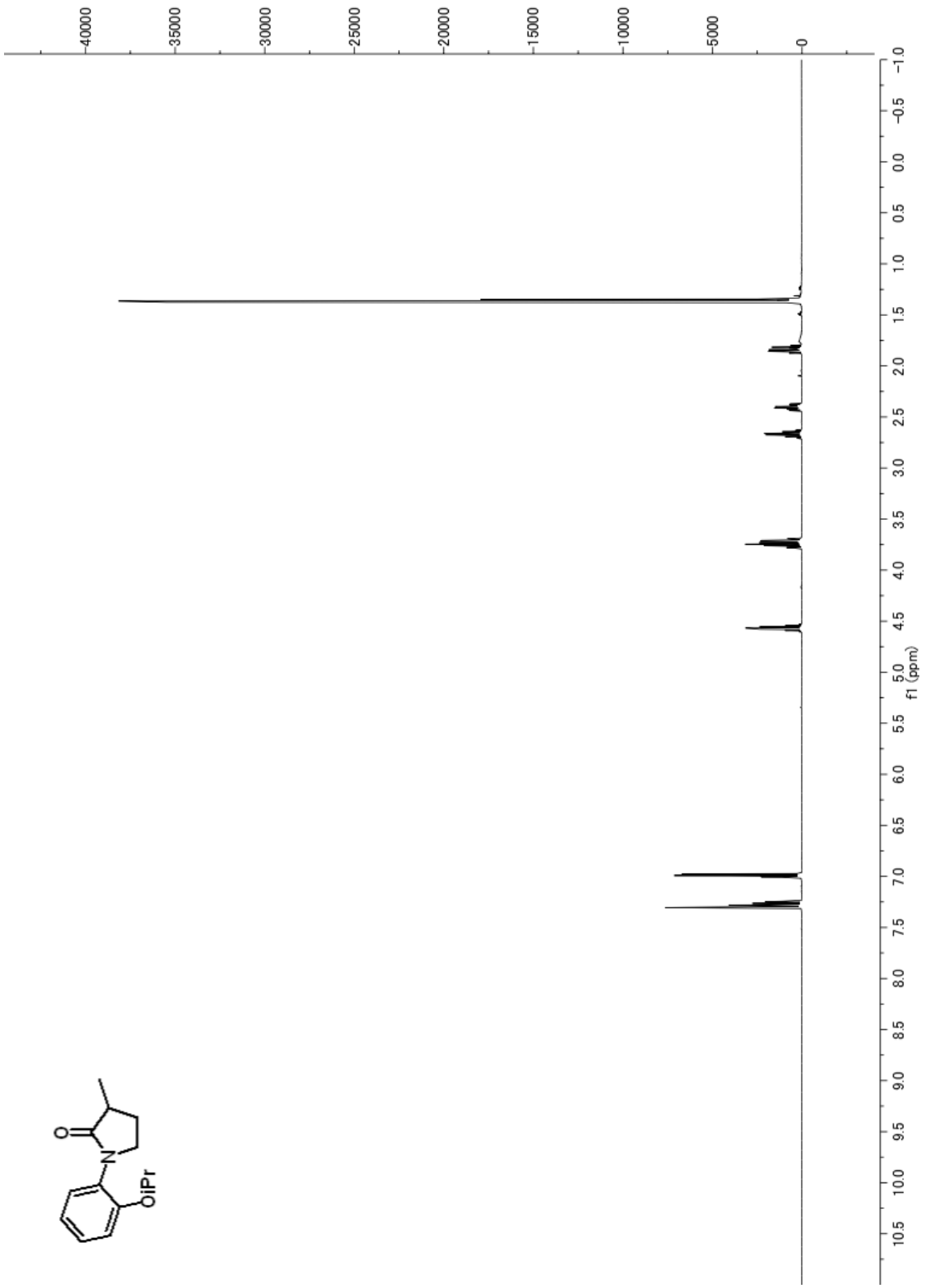


Figure A3.15. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **57d**.

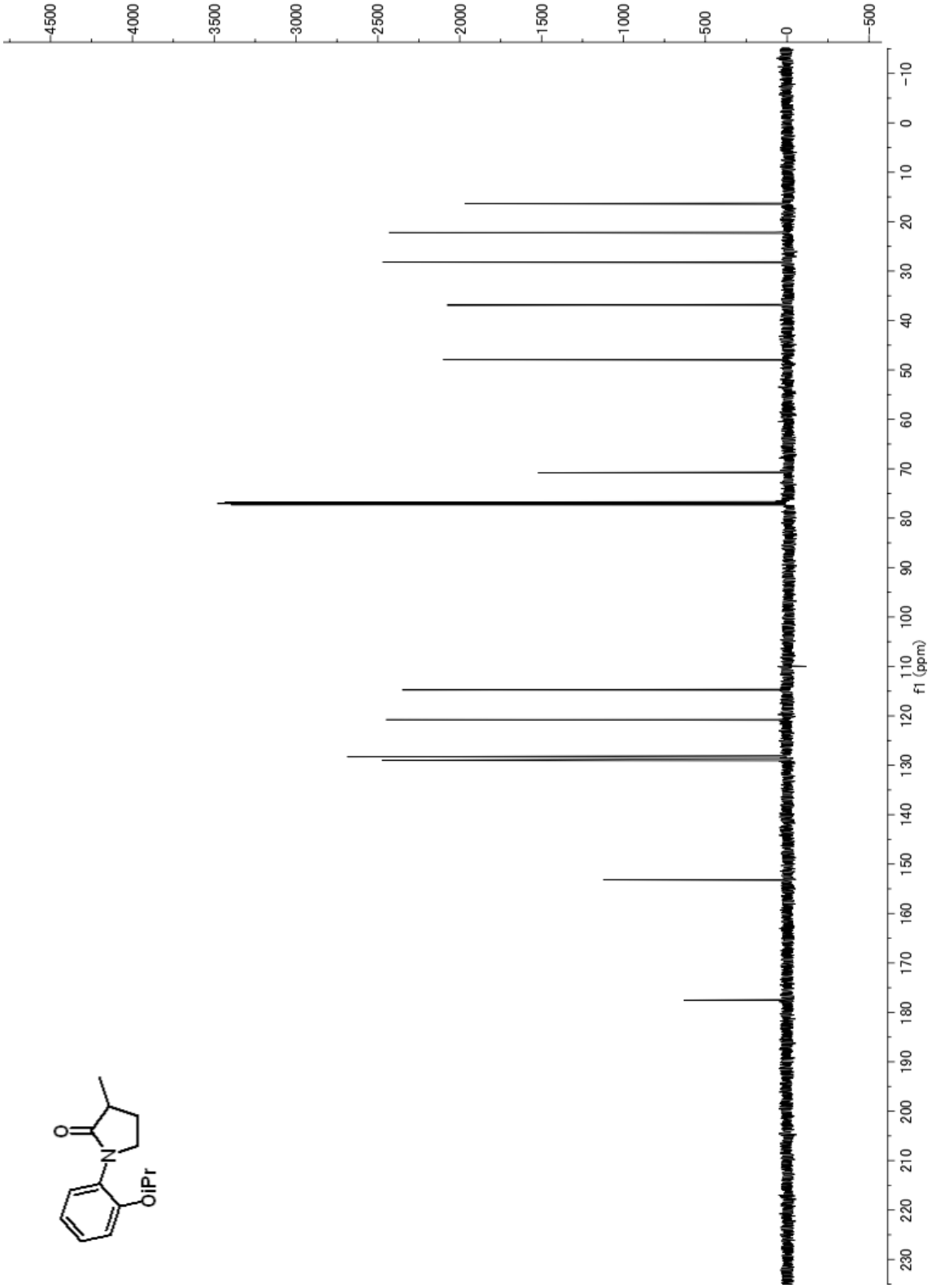


Figure A3.16. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **57d**.

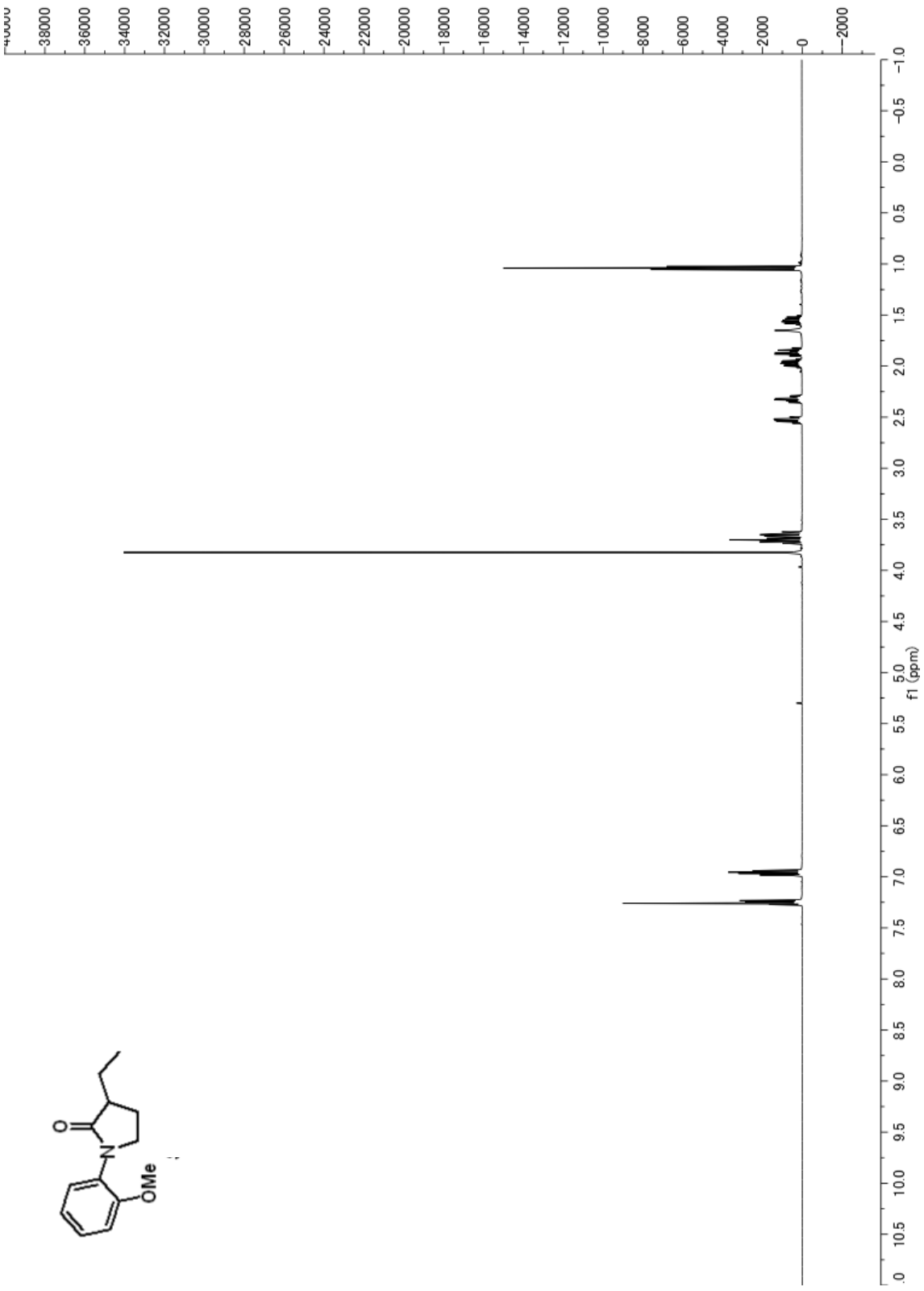


Figure A3.17. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **63b**.

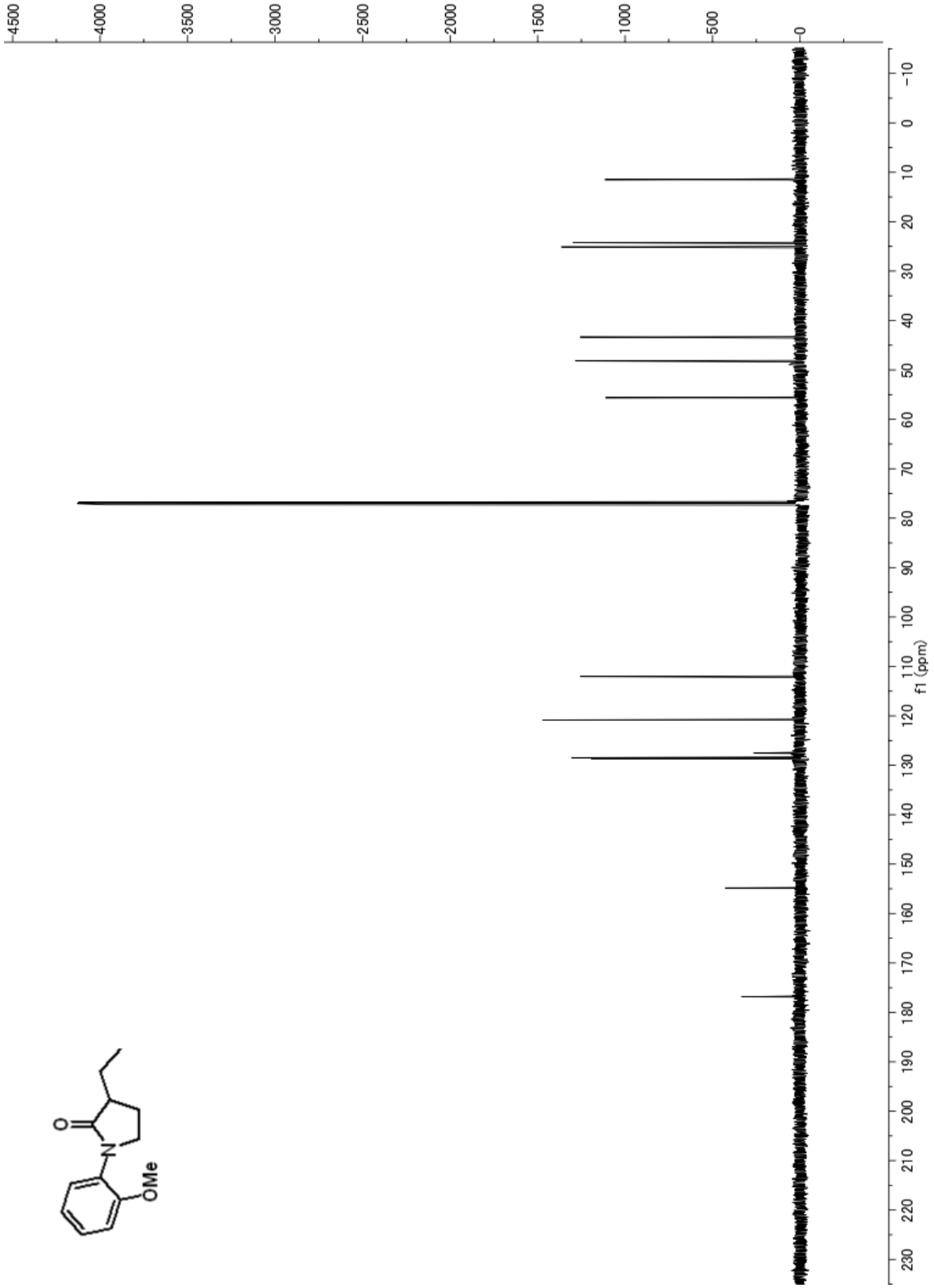


Figure A3.18. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **63b**.

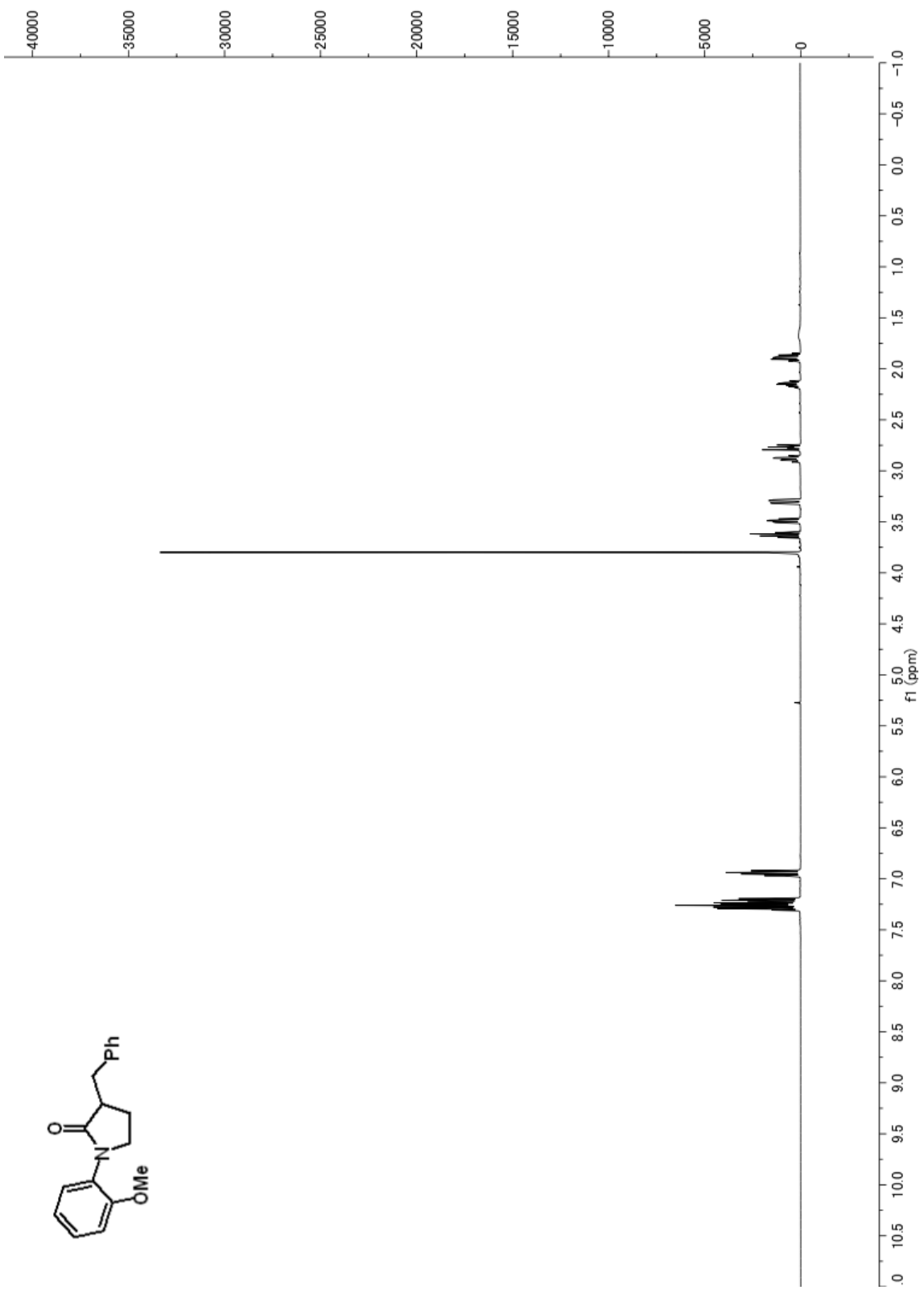


Figure A3.19. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **63c**.

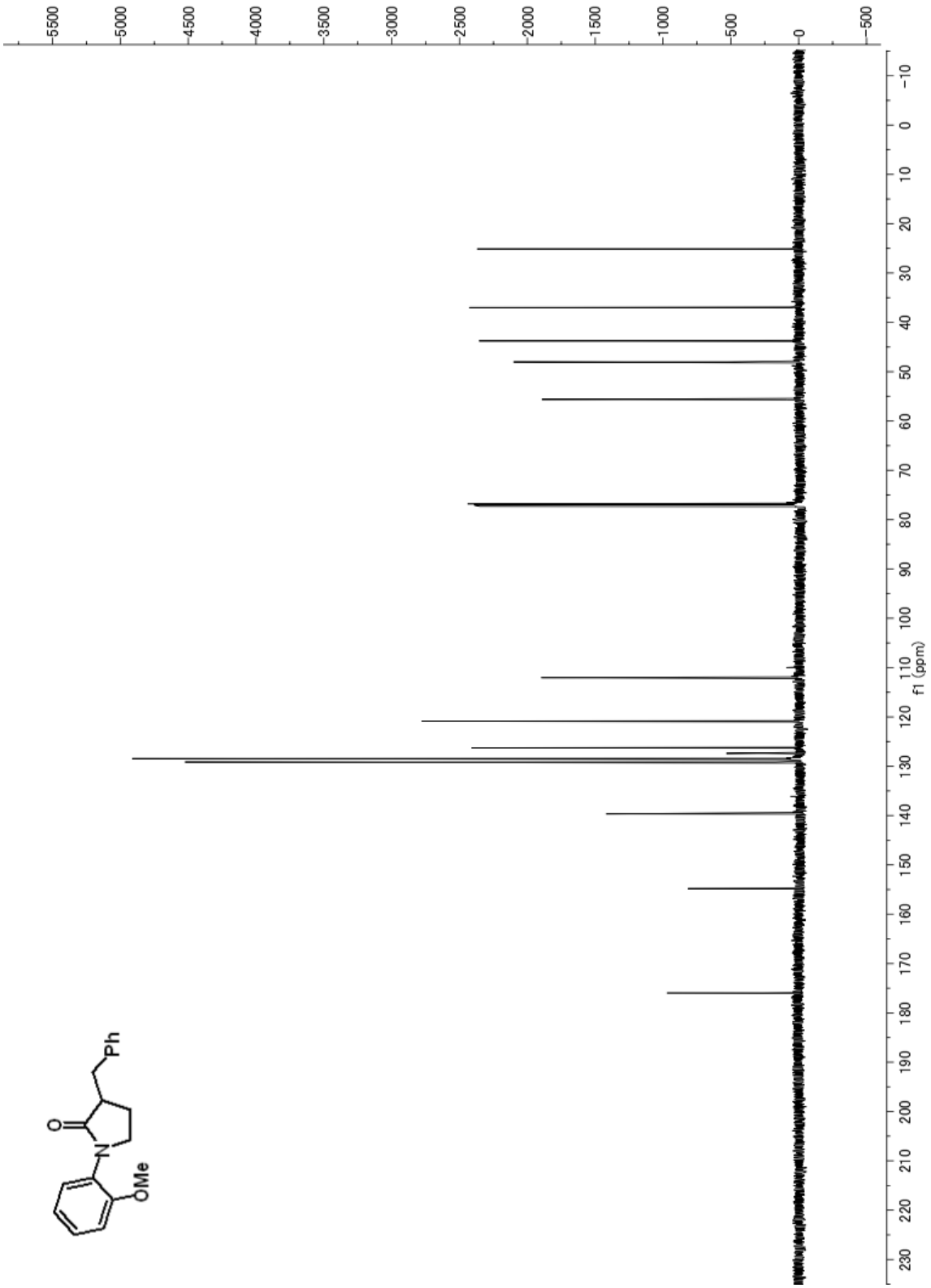


Figure A3.20. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **63c**.

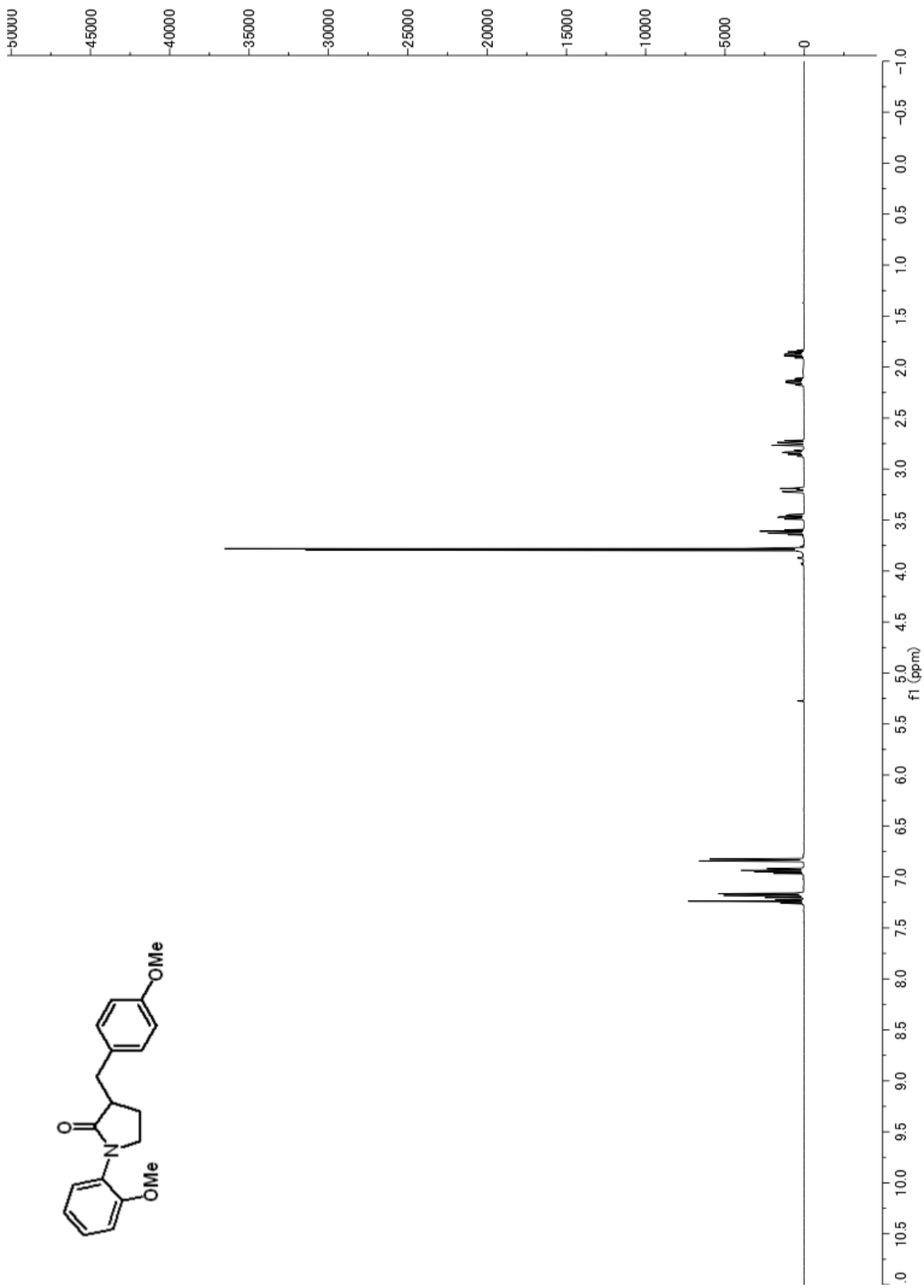


Figure A3.21. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **63d**.

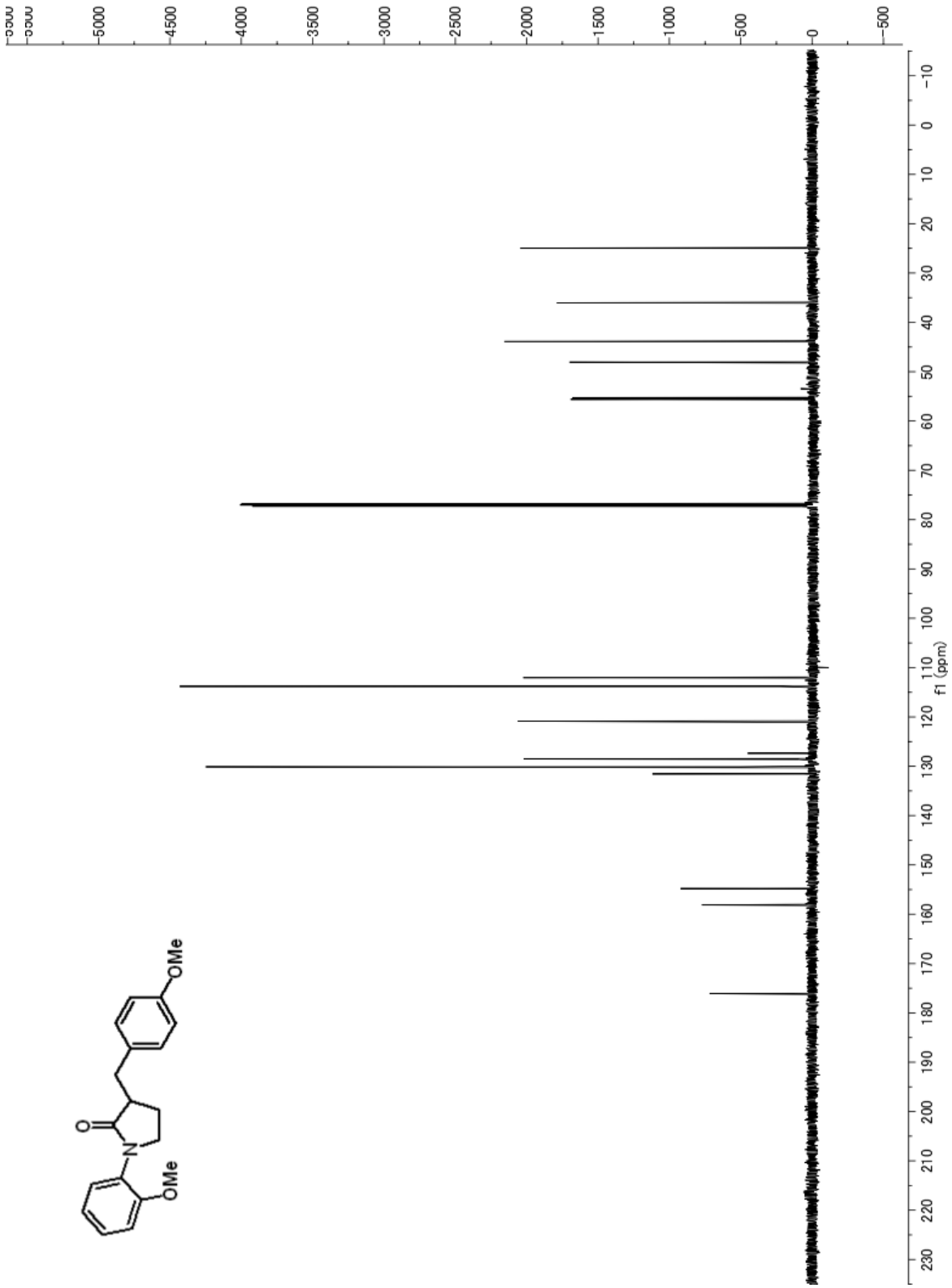


Figure A3.22. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **63d**.

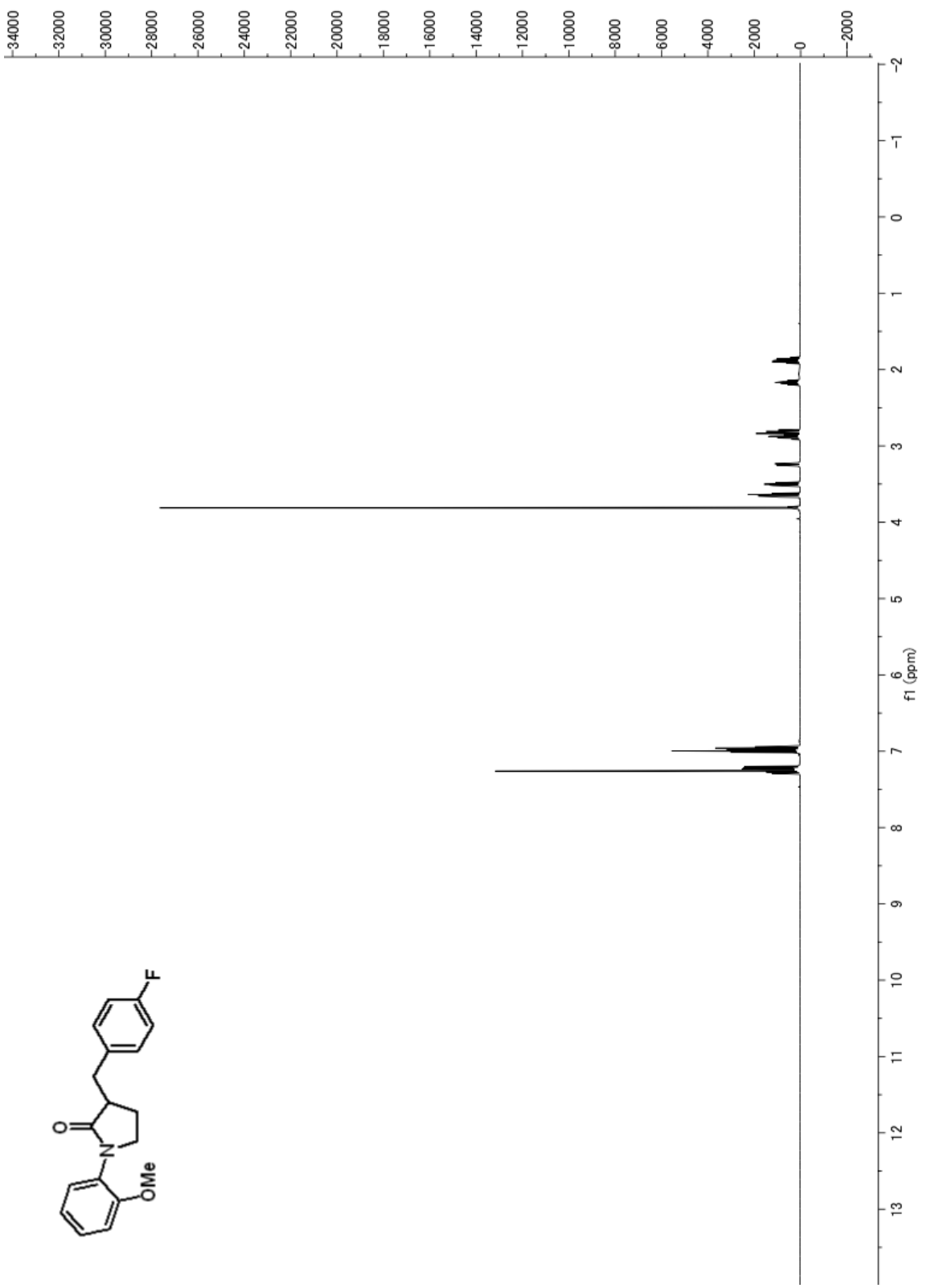


Figure A3.23. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **63e**.

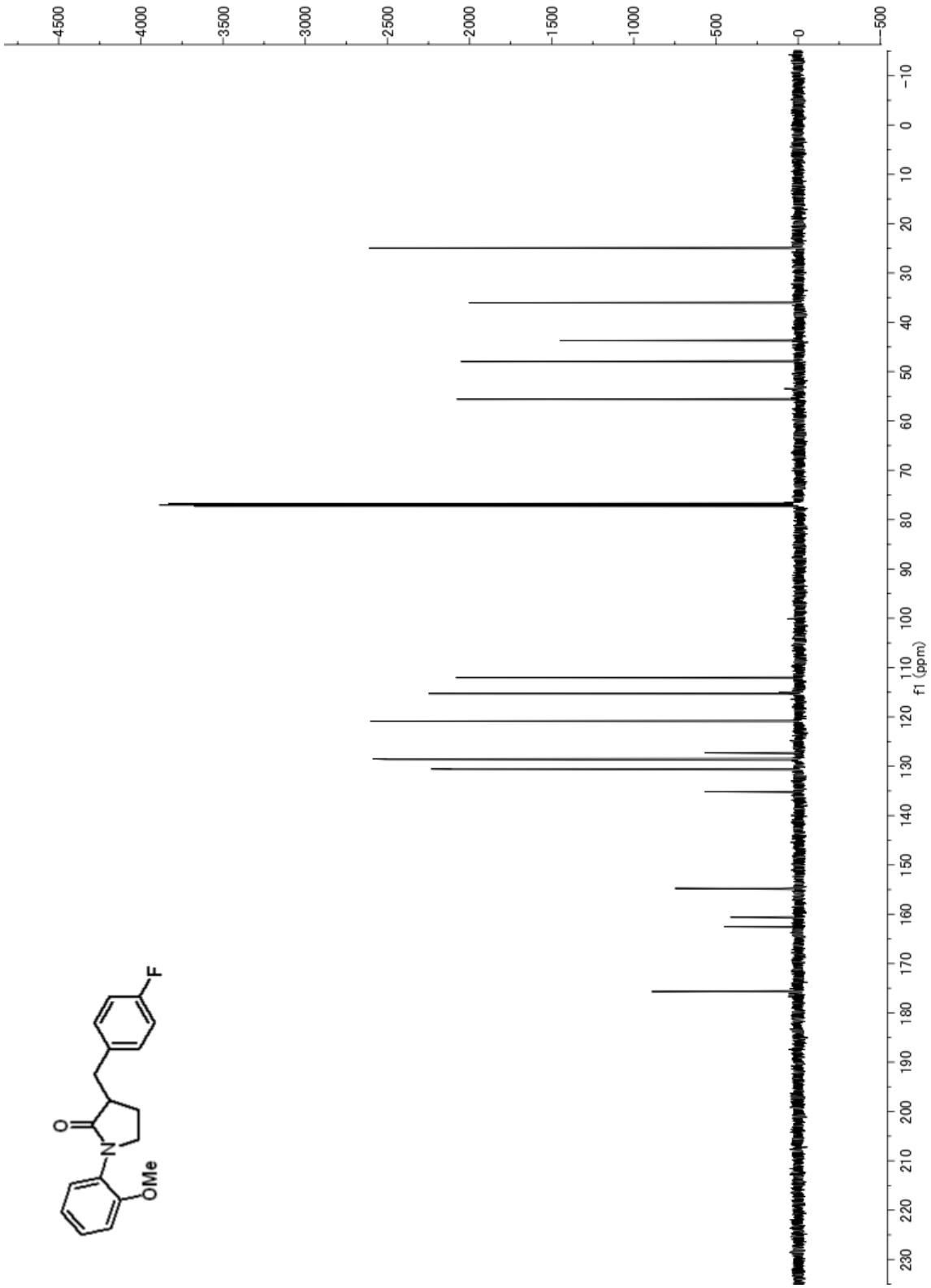


Figure A3.24. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **63e**.

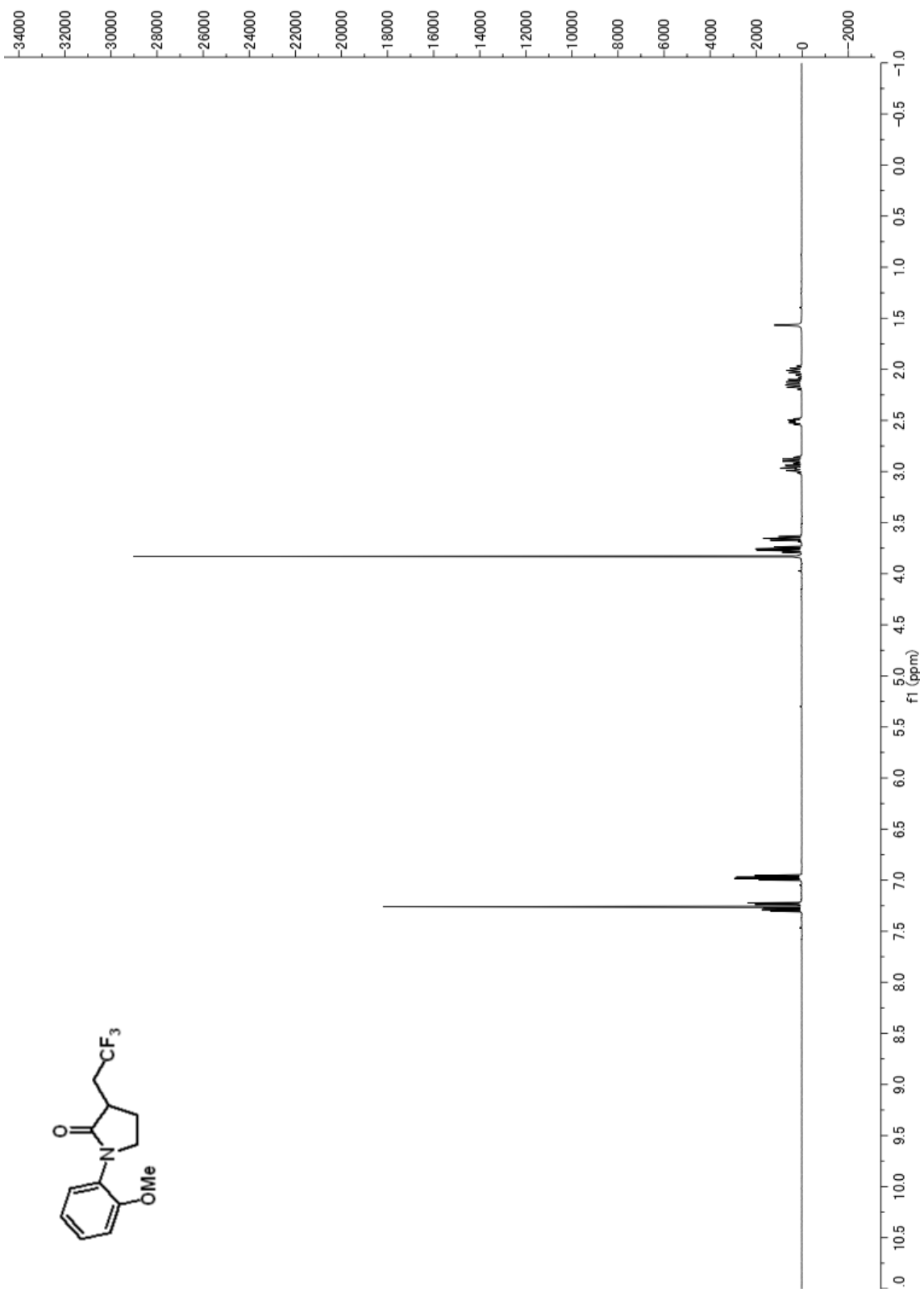


Figure A3.25. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **63f**.

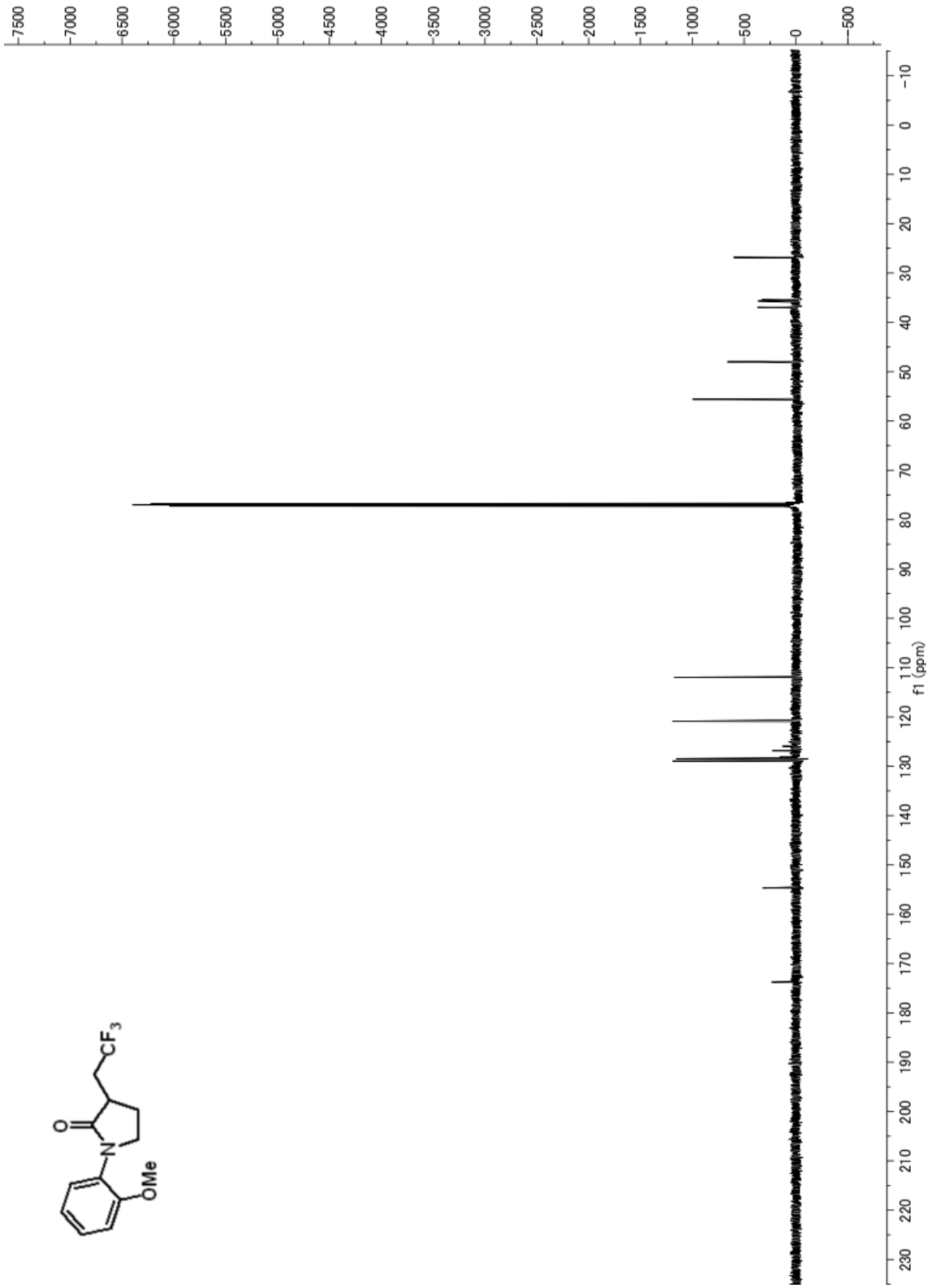


Figure A3.26. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **63f**.

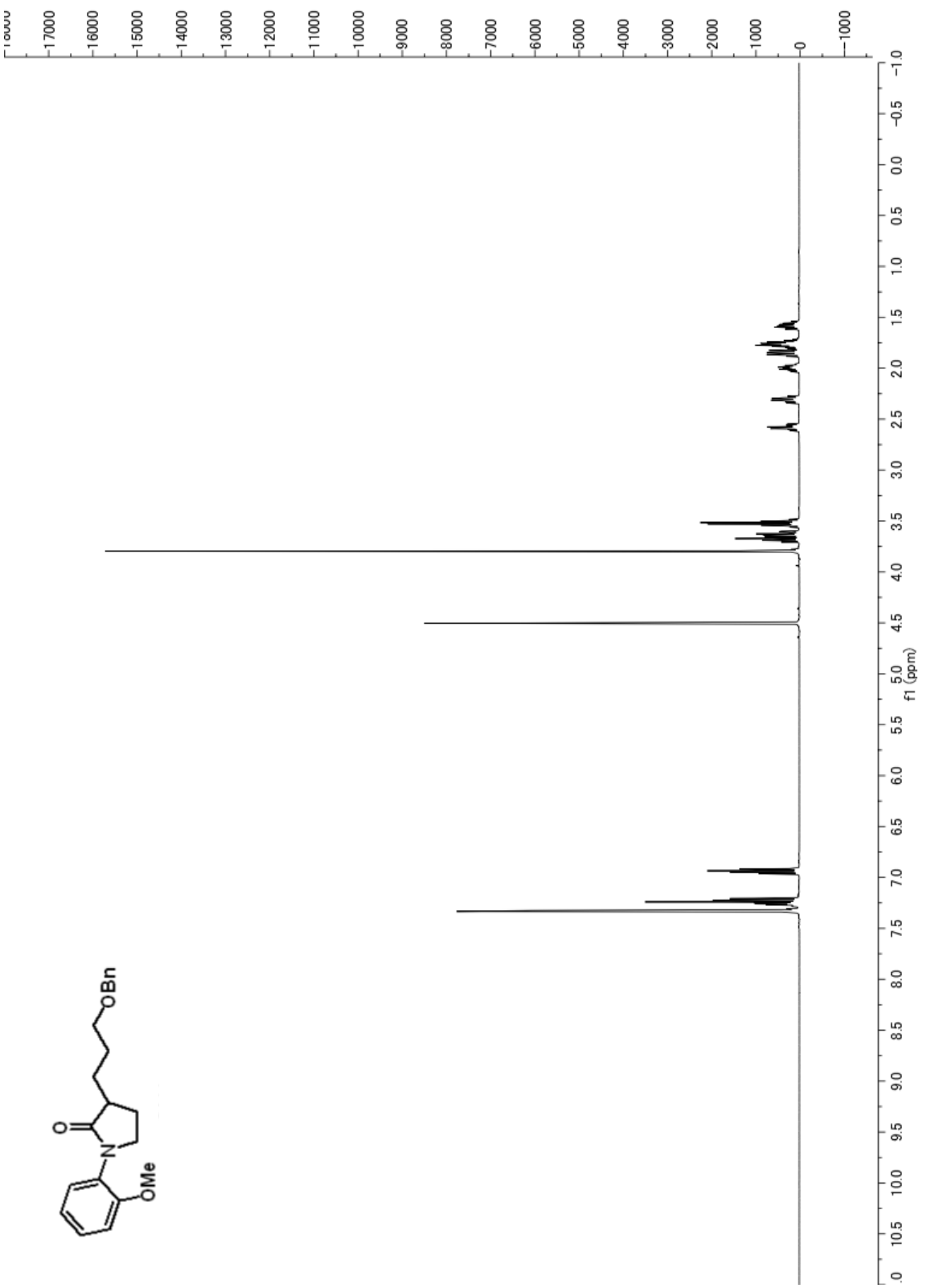


Figure A3.27. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **63g**.

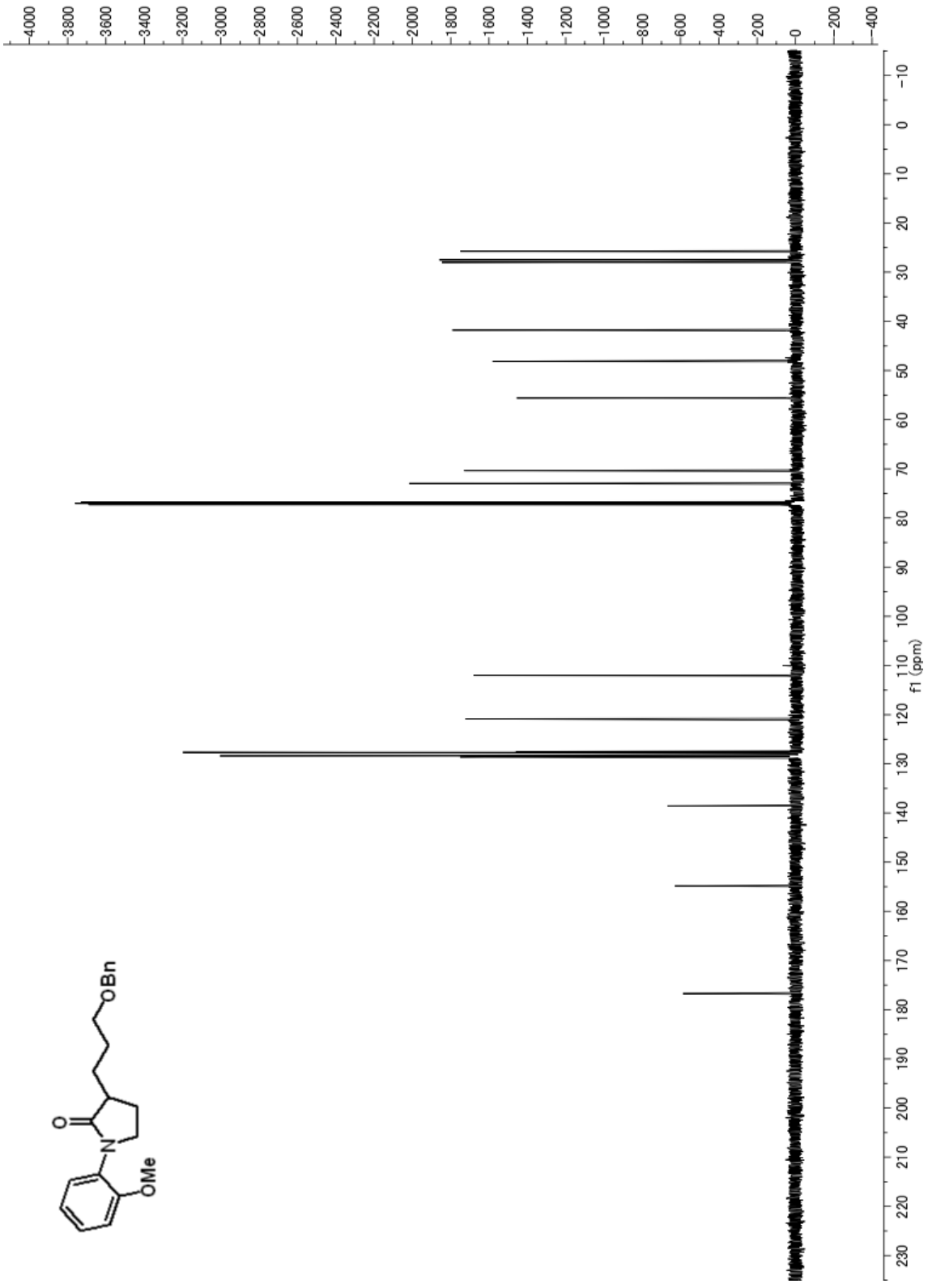


Figure A3.28. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **63g**.

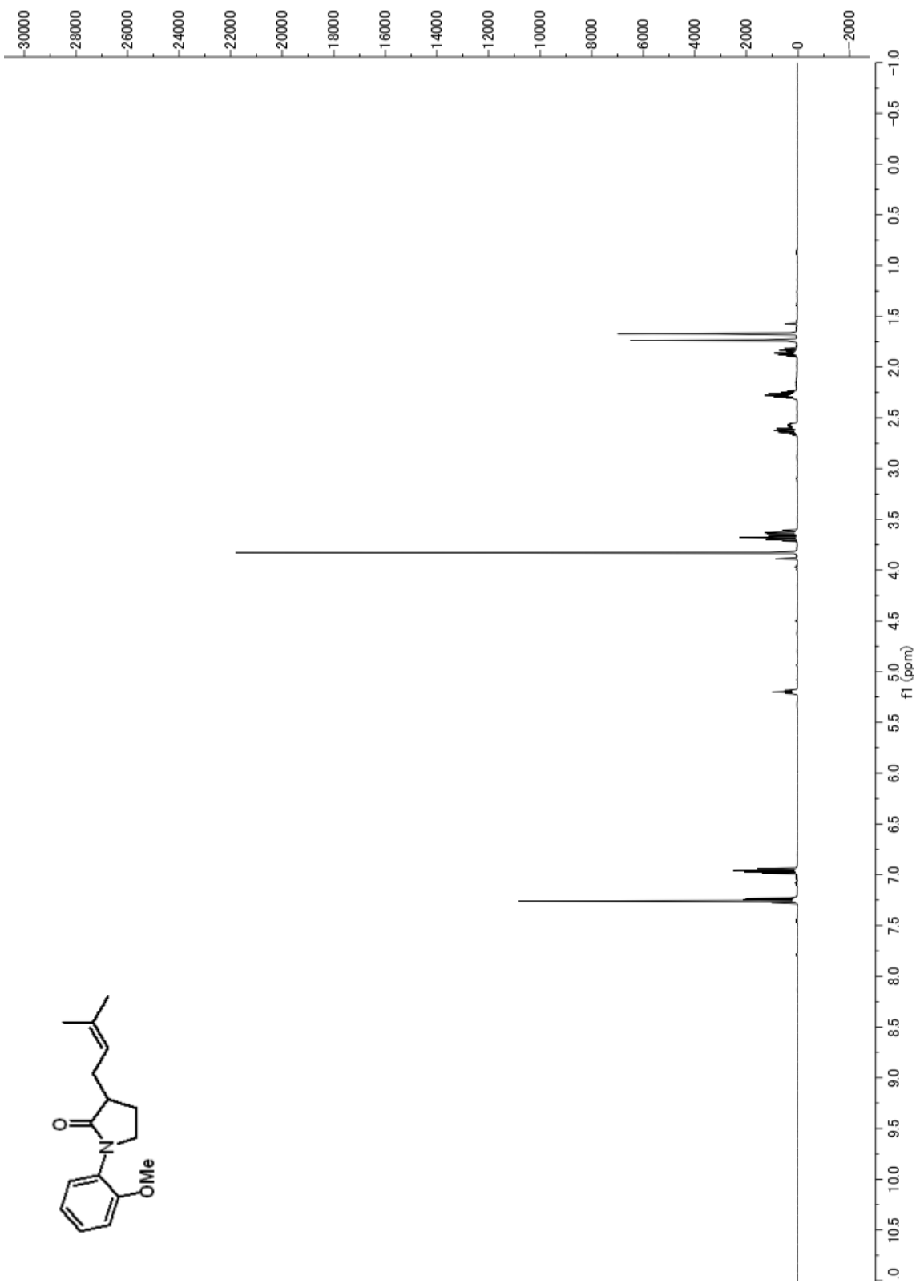


Figure A3.29. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **63h**.

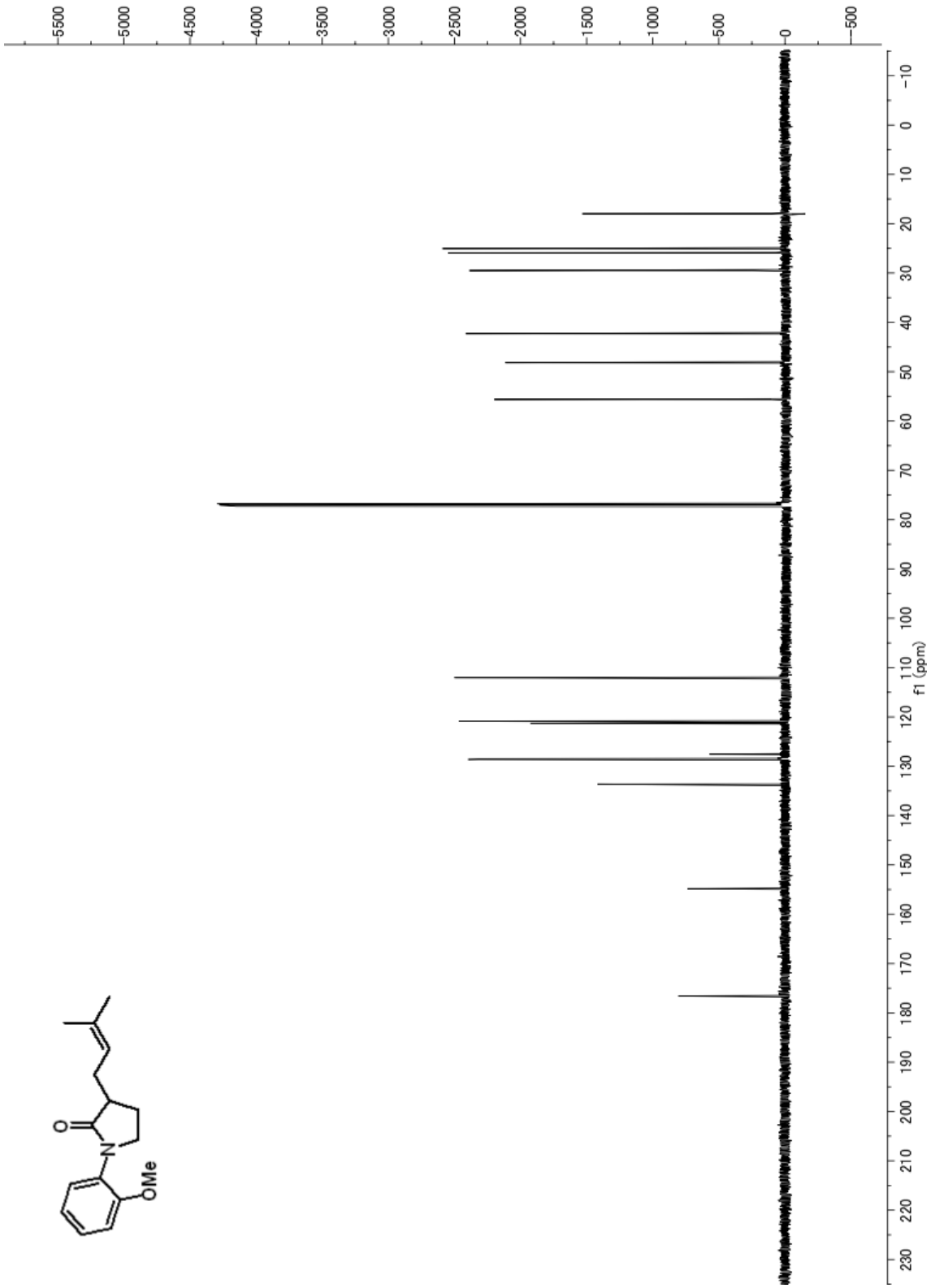


Figure A3.30. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **63h**.

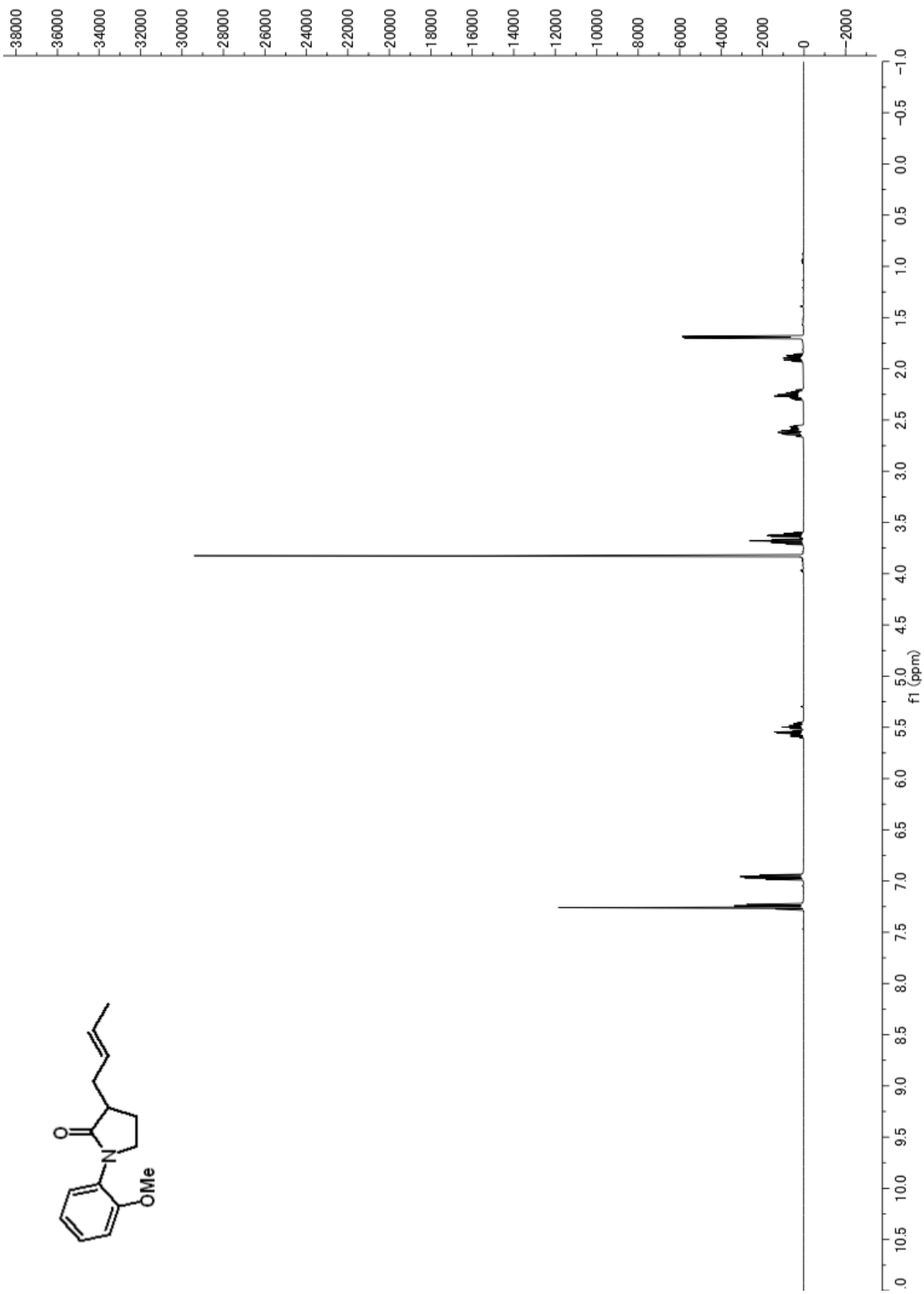


Figure A3.31. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **63i**.

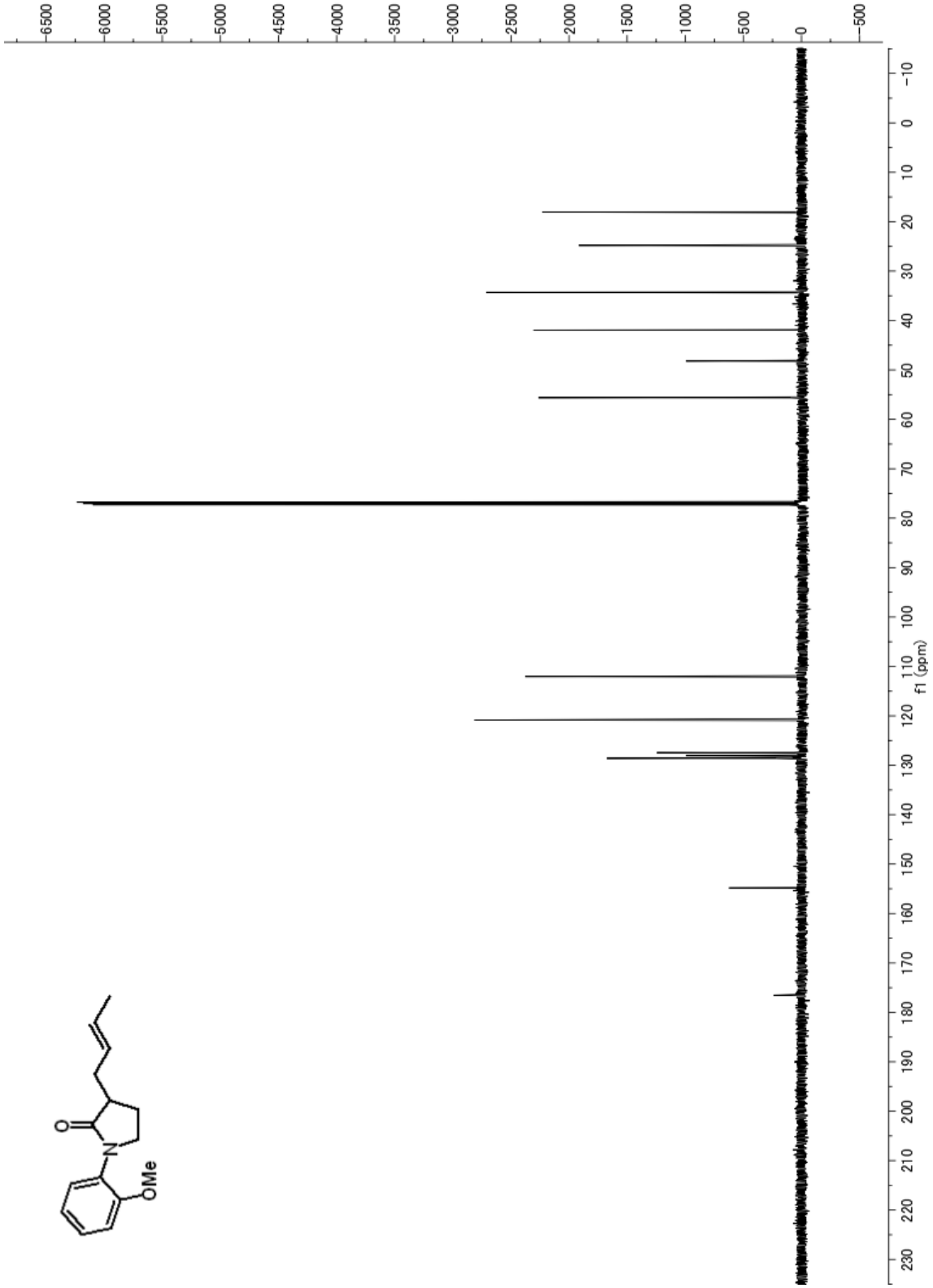


Figure A3.32. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **63i**.

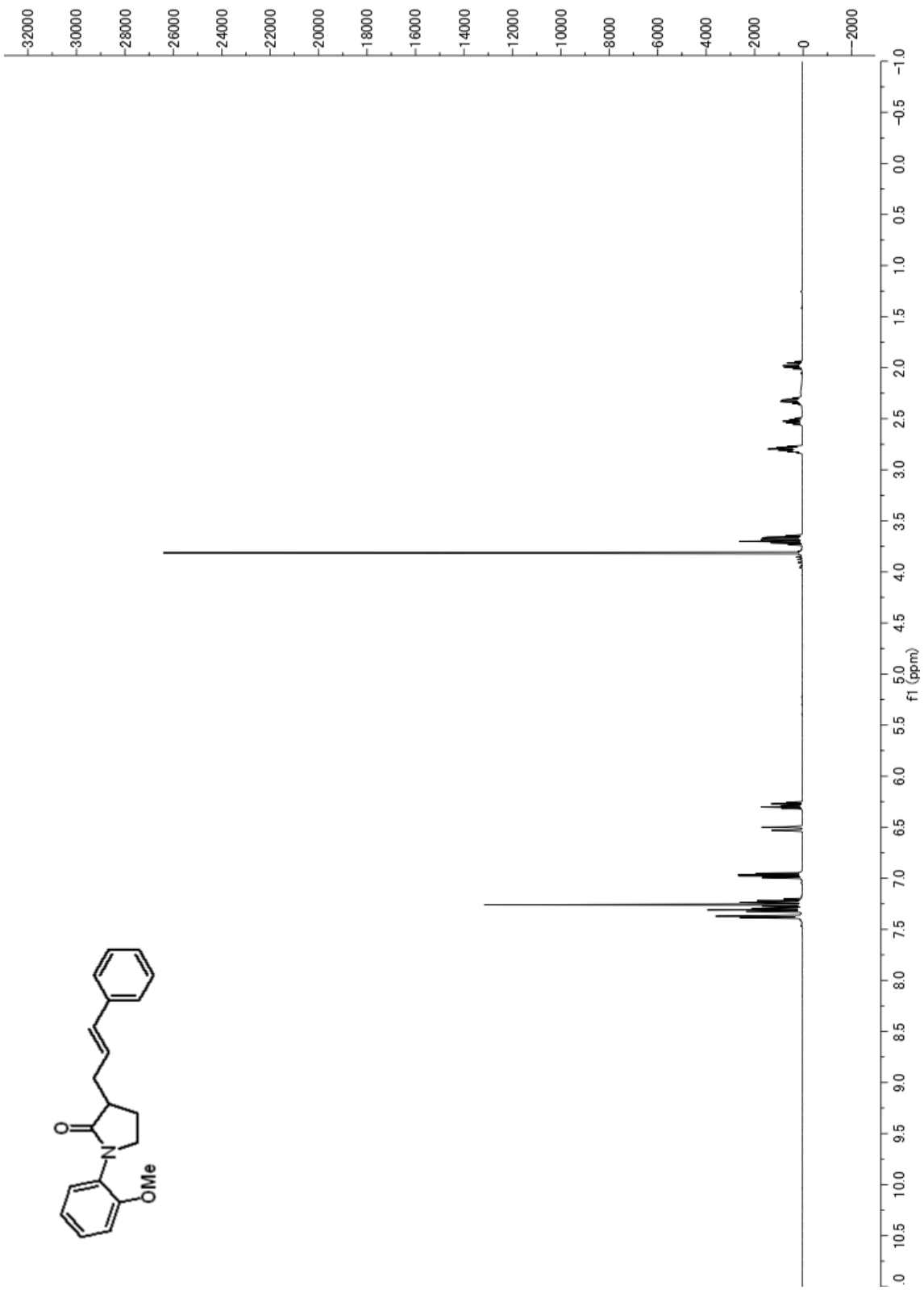


Figure A3.33. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **63j**.

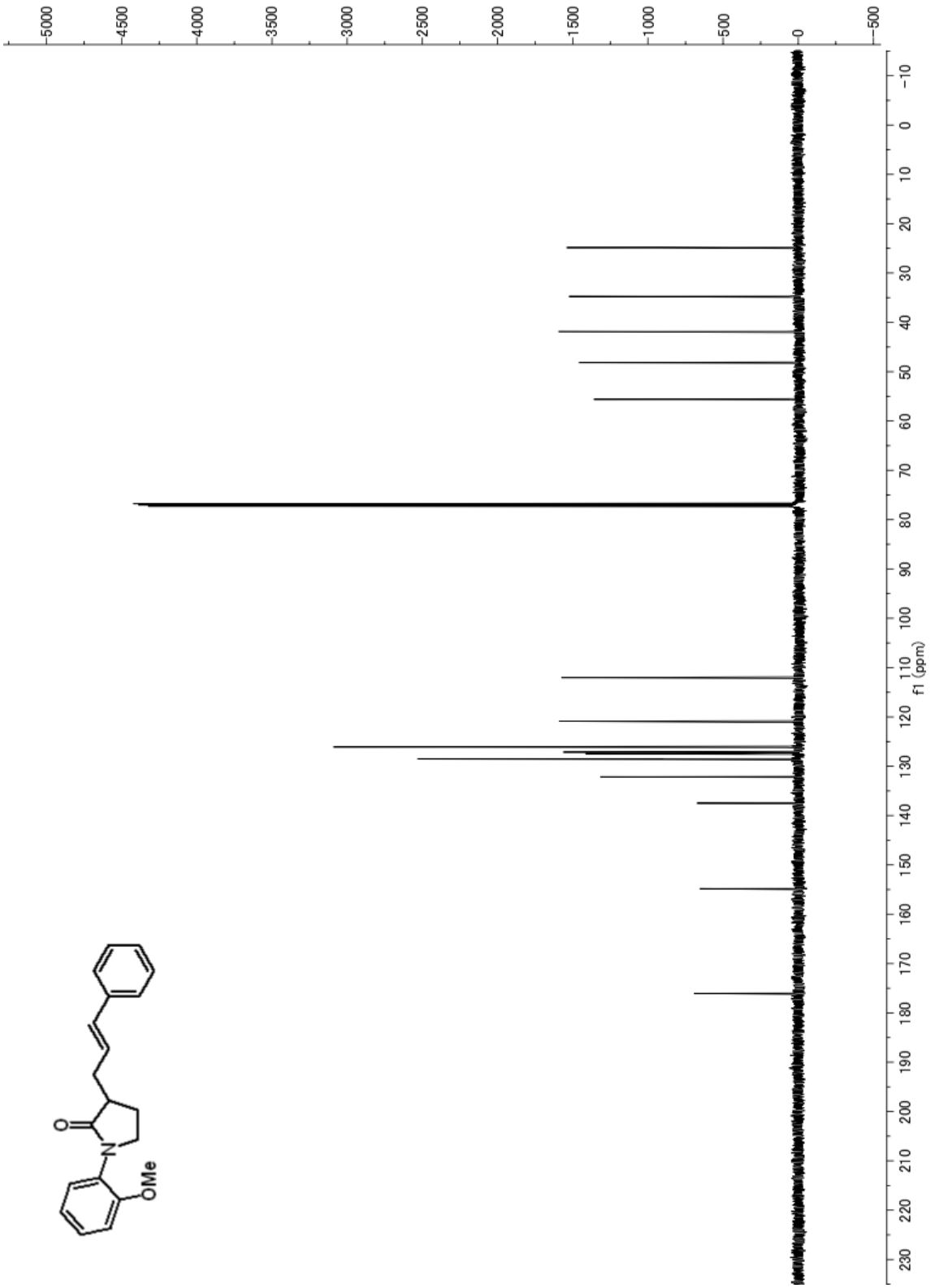


Figure A3.34. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **63j**.

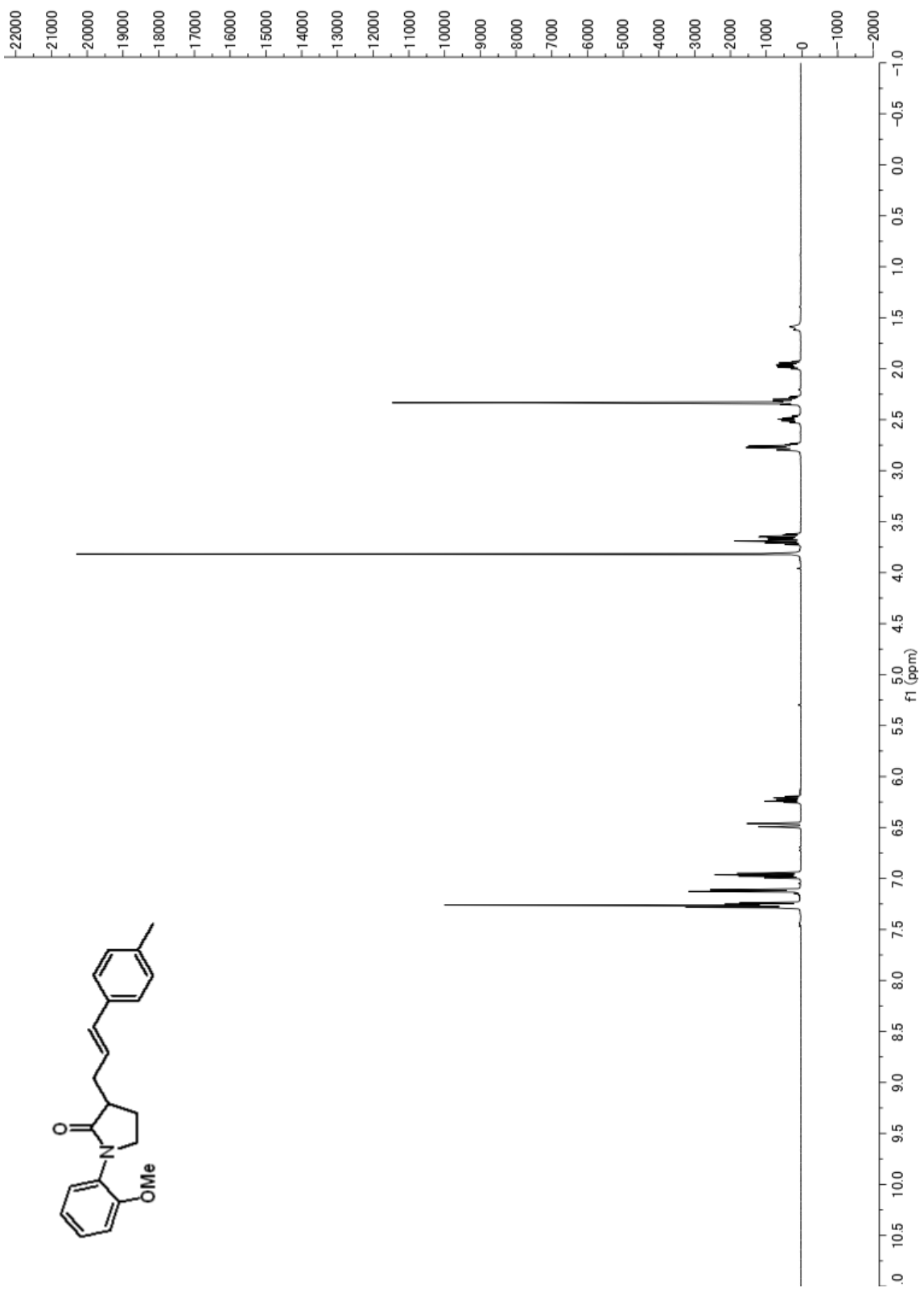


Figure A3.35. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **63k**.

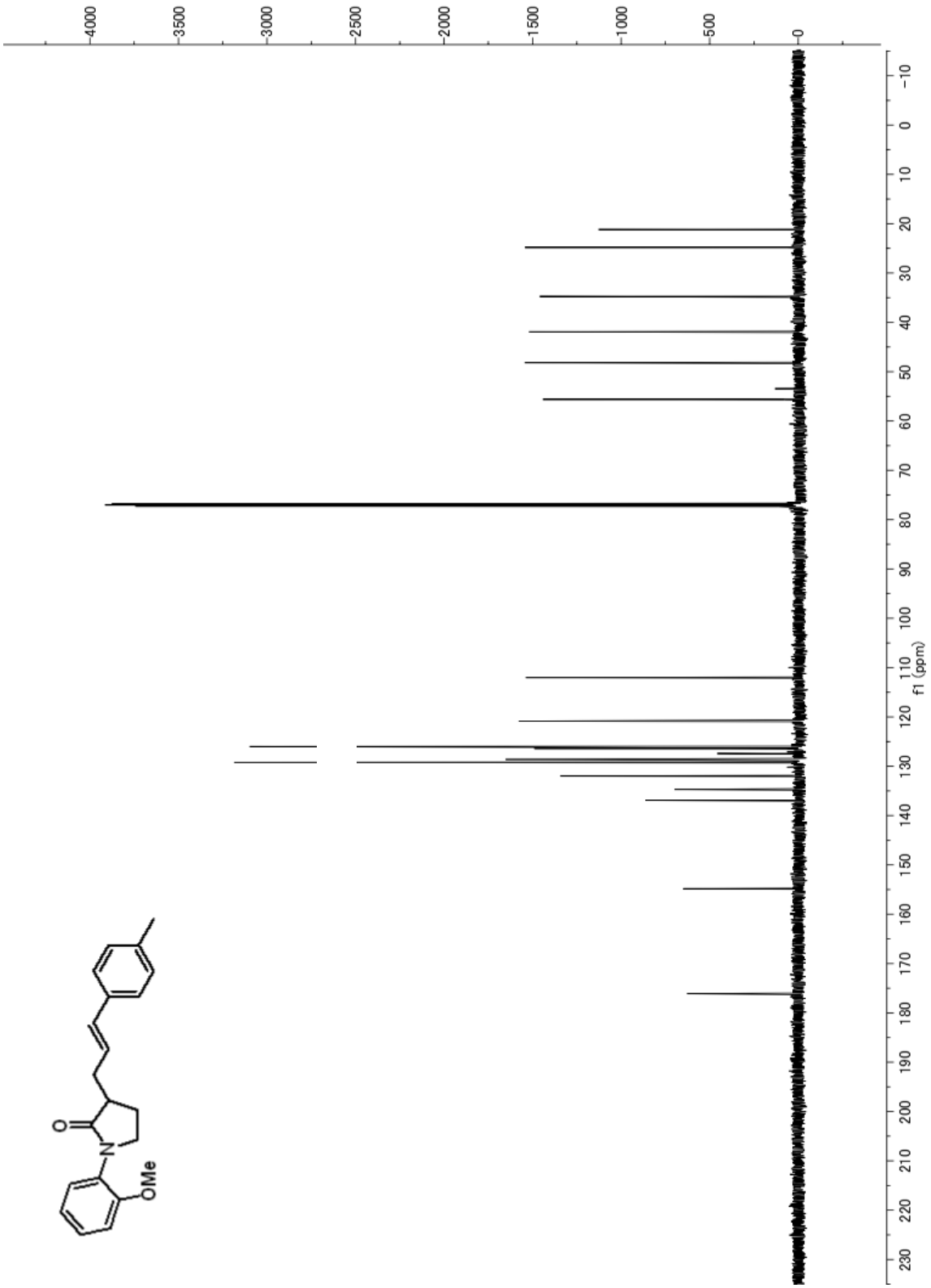


Figure A3.36. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **63k**.

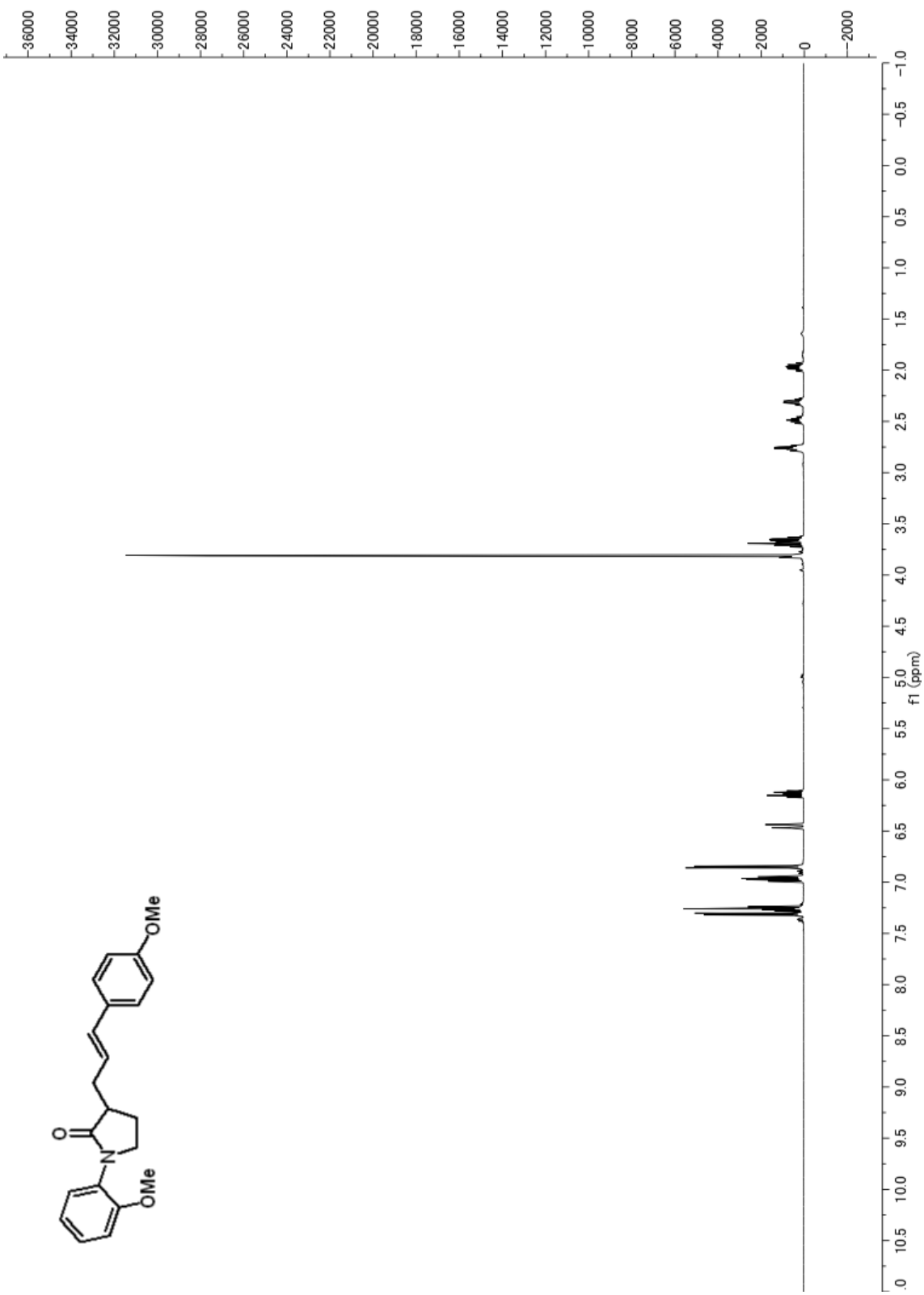


Figure A3.37. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **63l**.

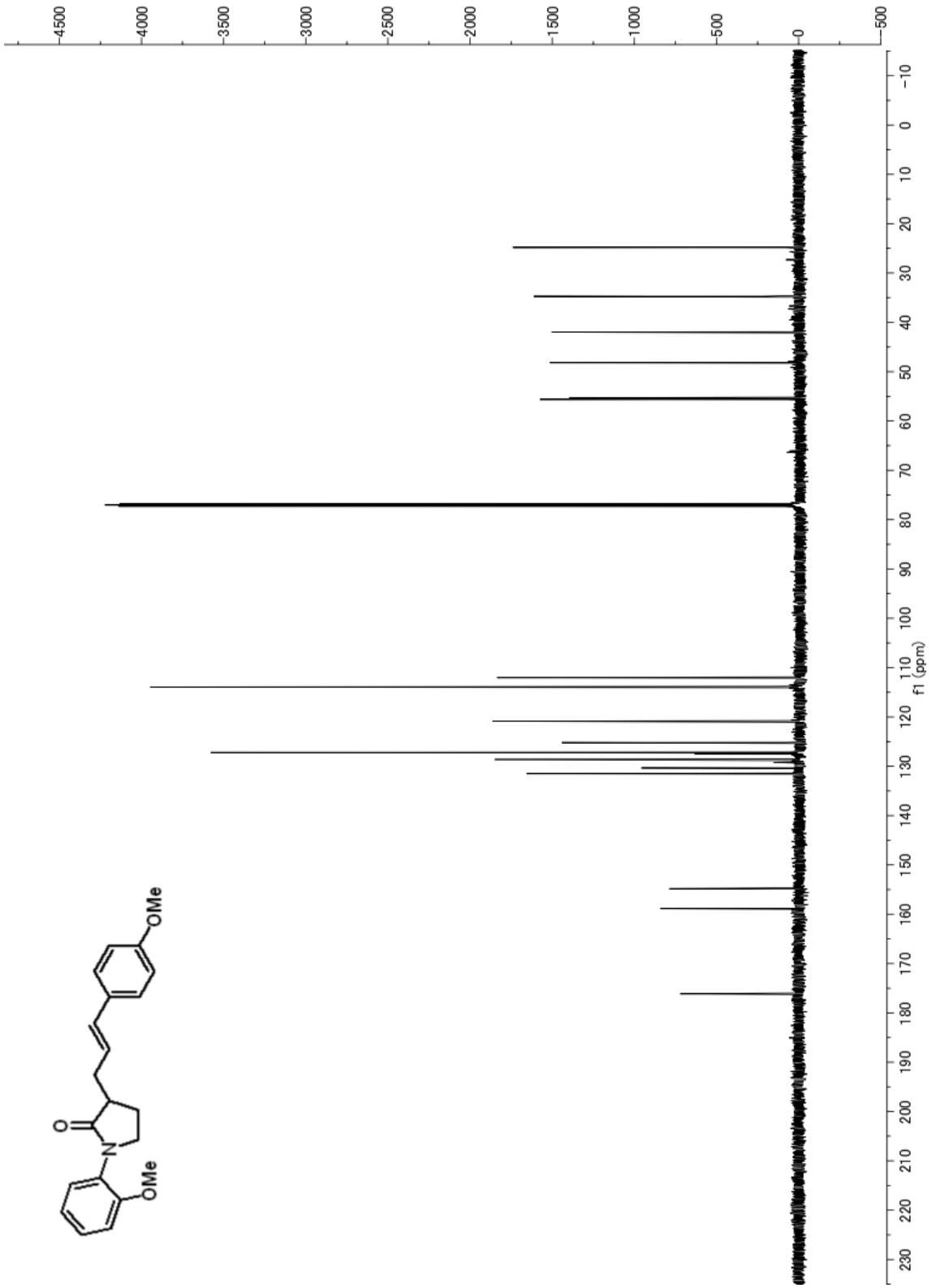


Figure A3.38. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **63l**.

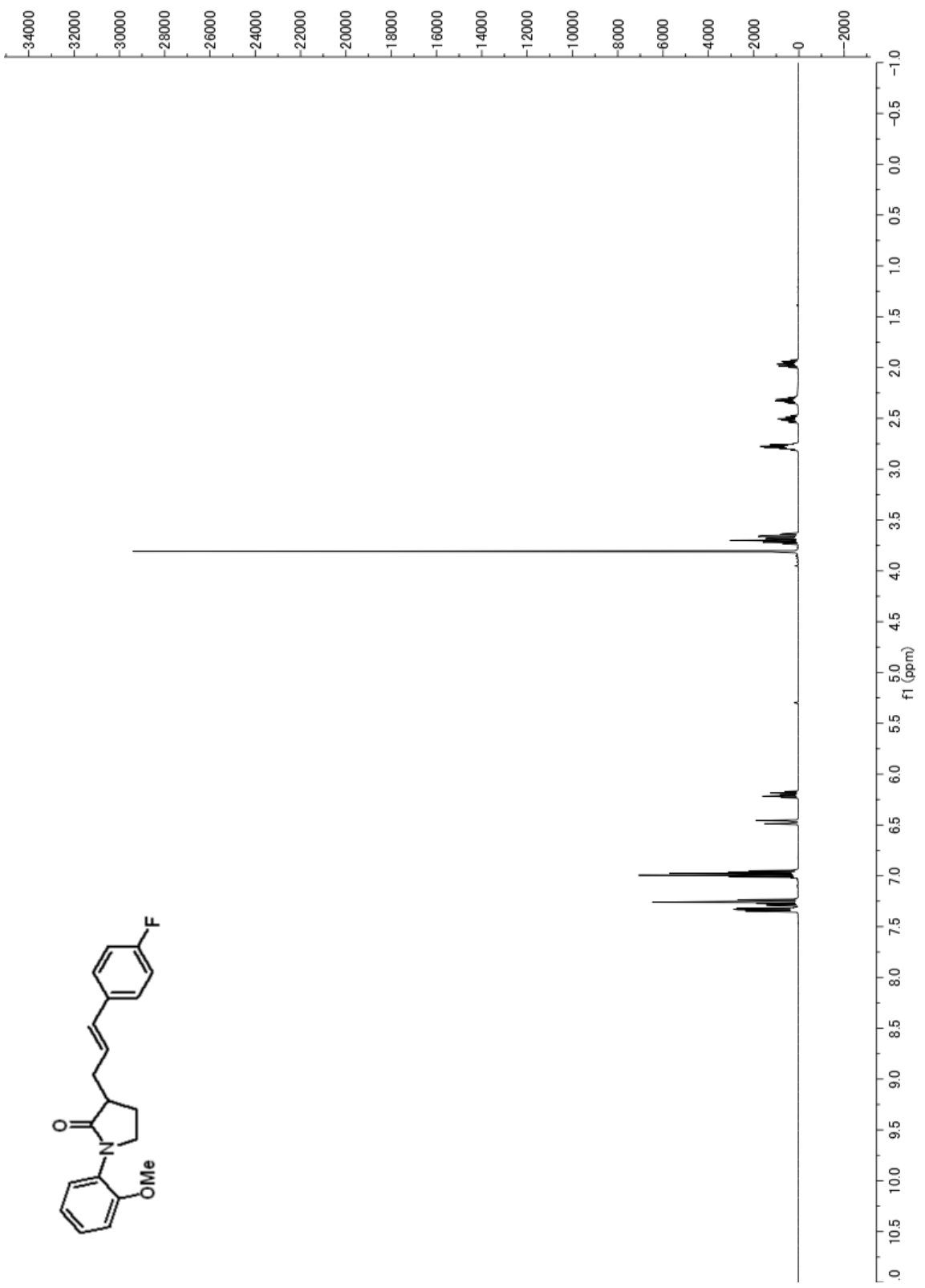


Figure A3.39. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **63m**.

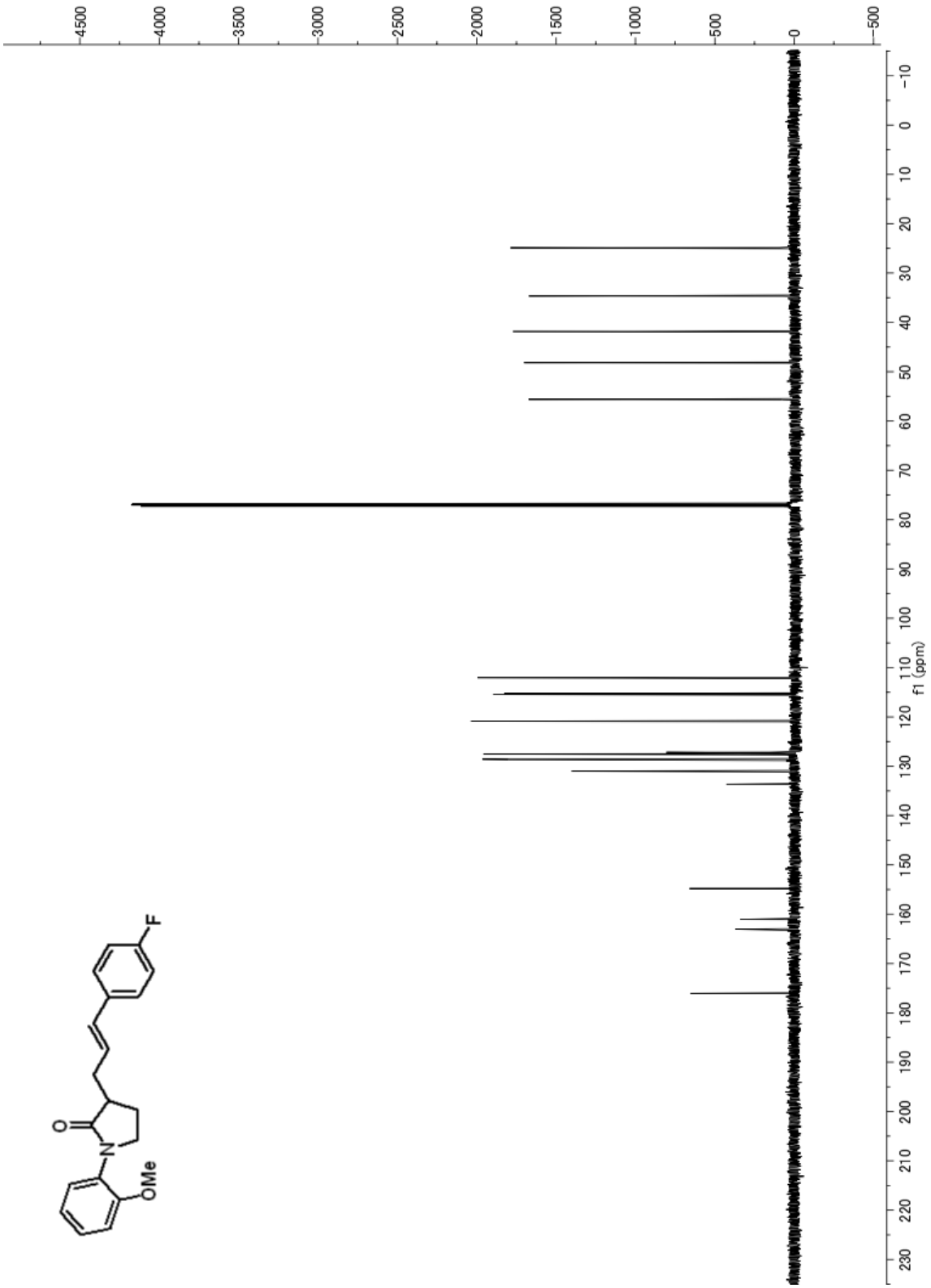


Figure A3.40. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **63m**.

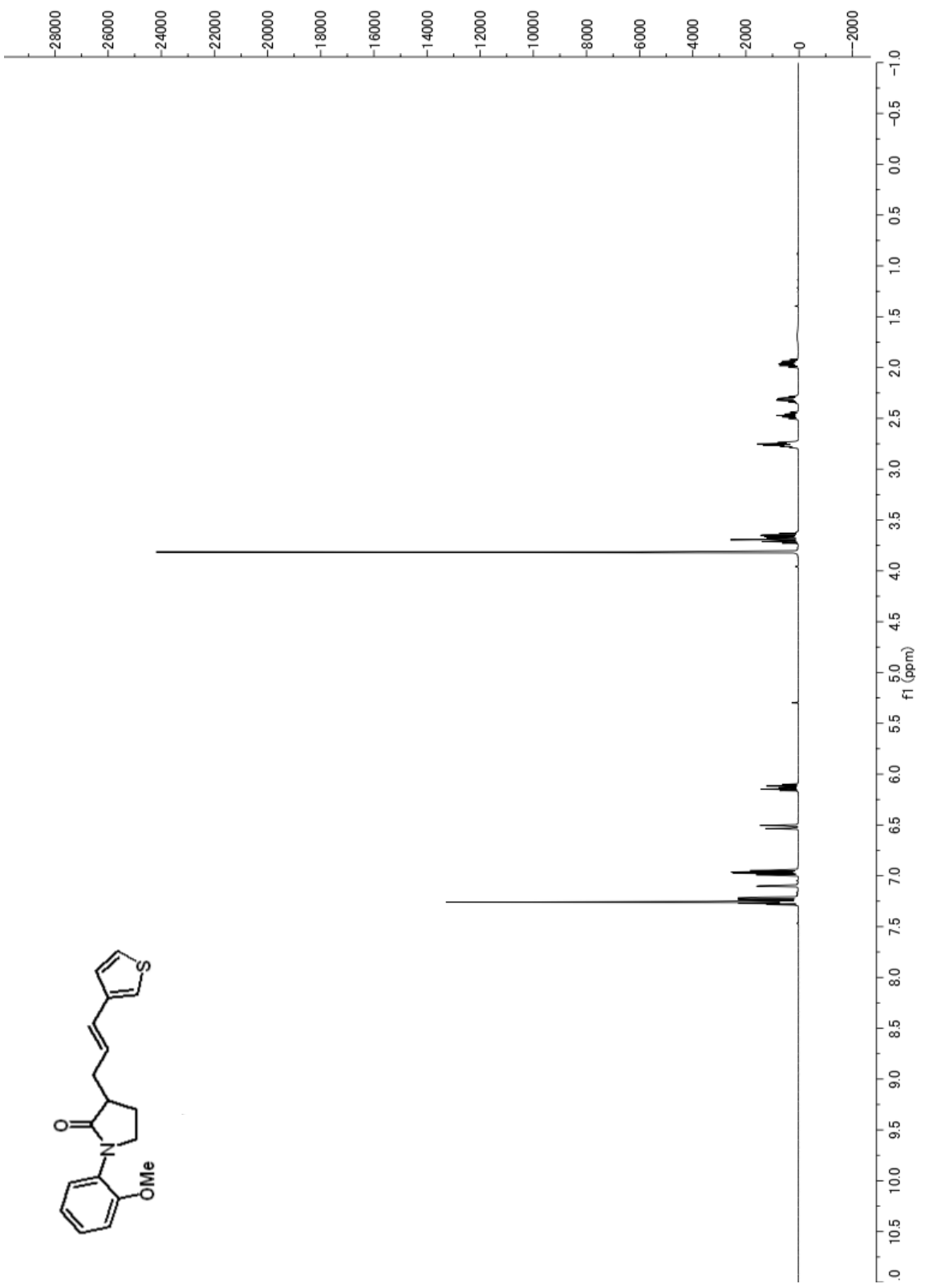


Figure A3.41. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **63n**.

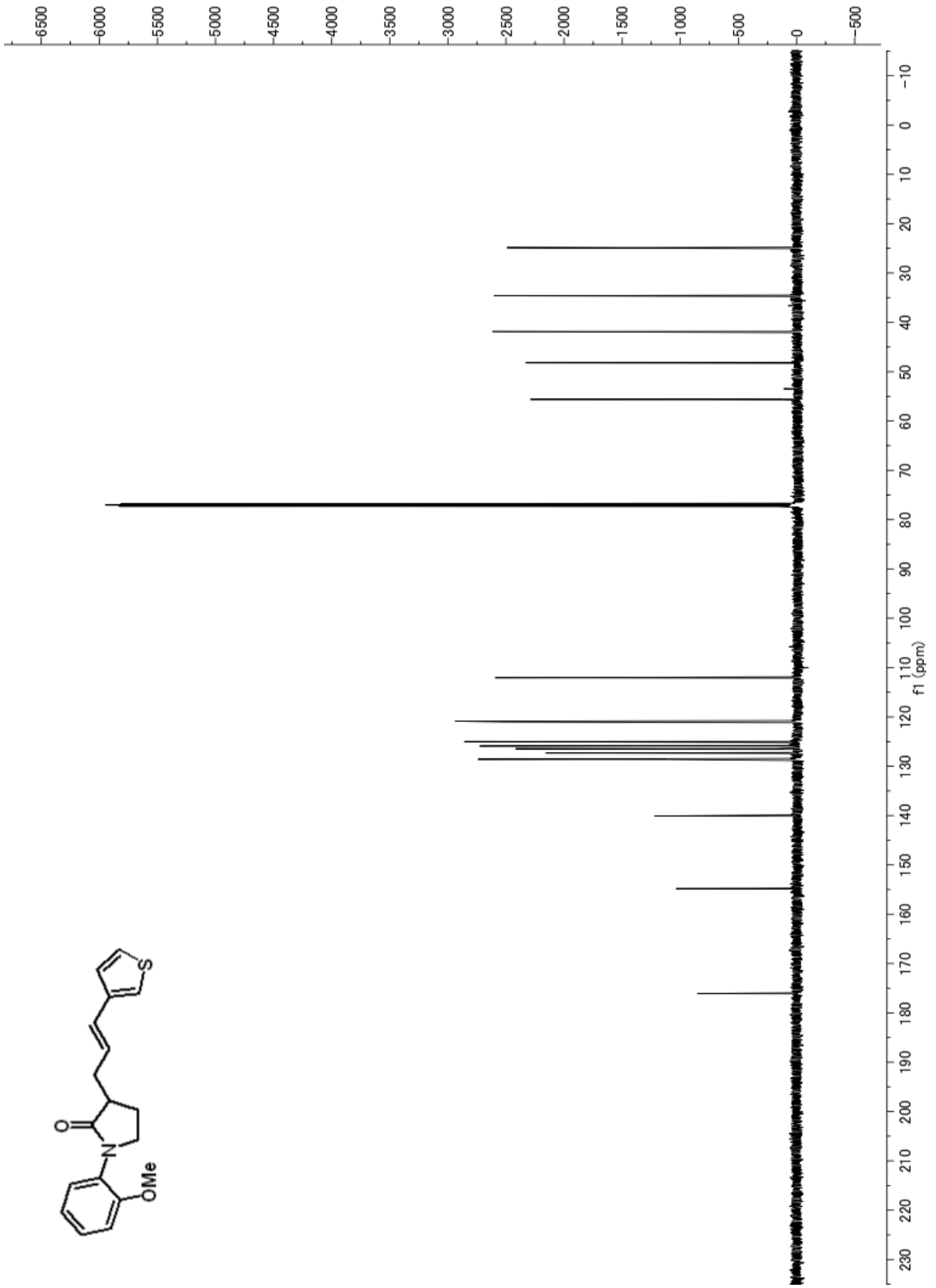
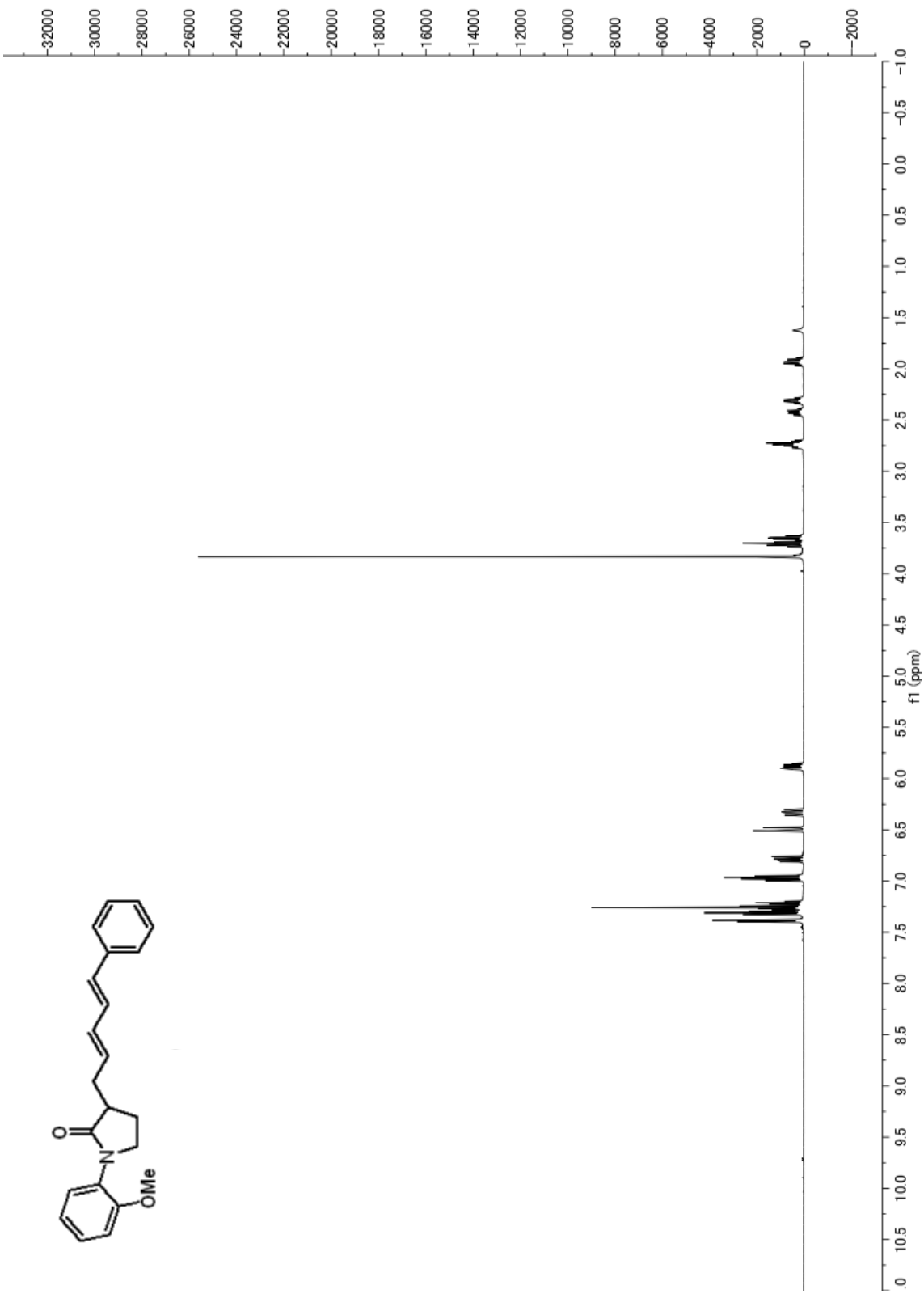


Figure A3.42. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **63n**.



d *Figure A3.43.* ^{1}H NMR (500 MHz, $CDCl_3$) of compound **63o**.

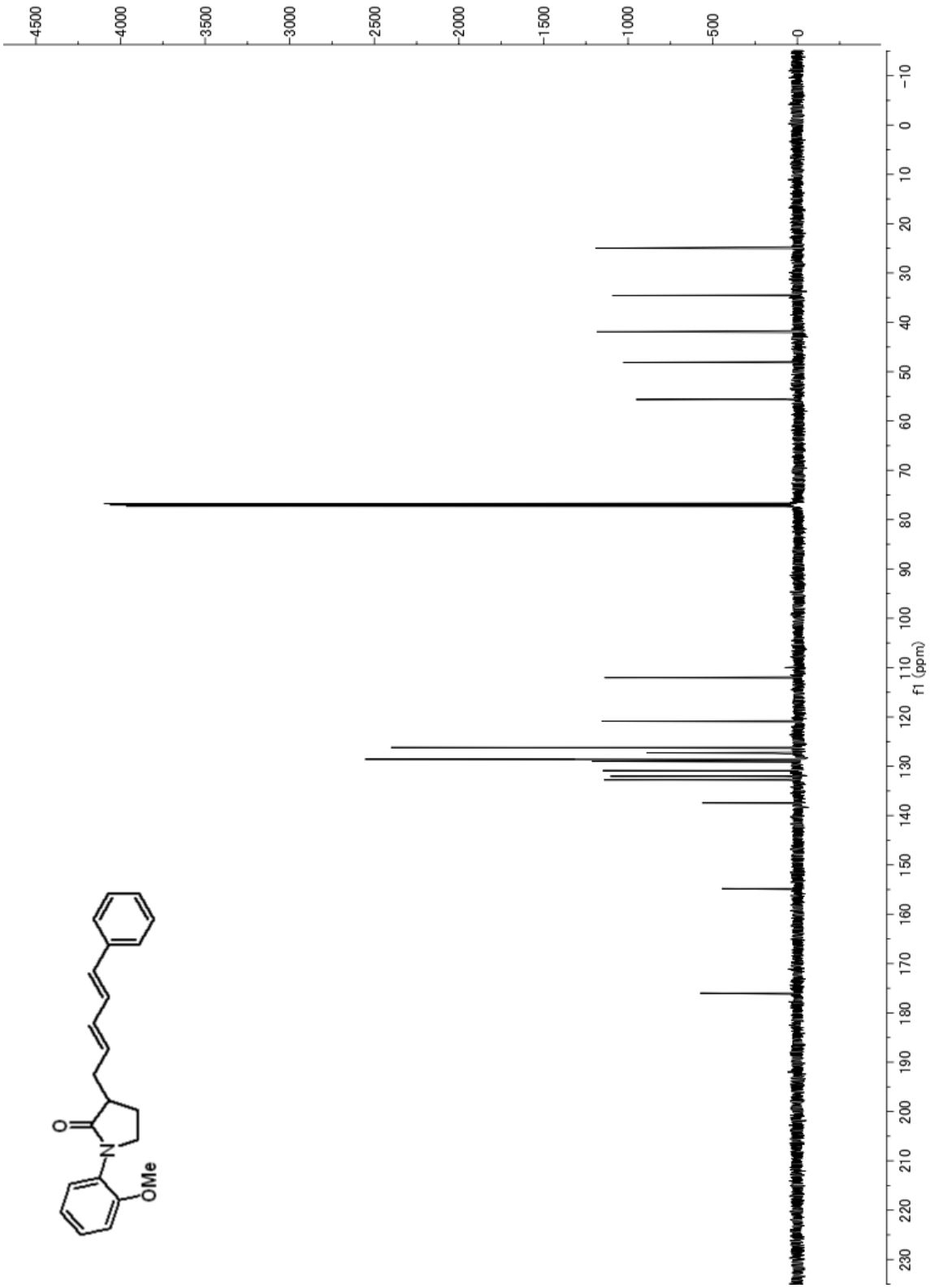


Figure A3.44. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **63o**.

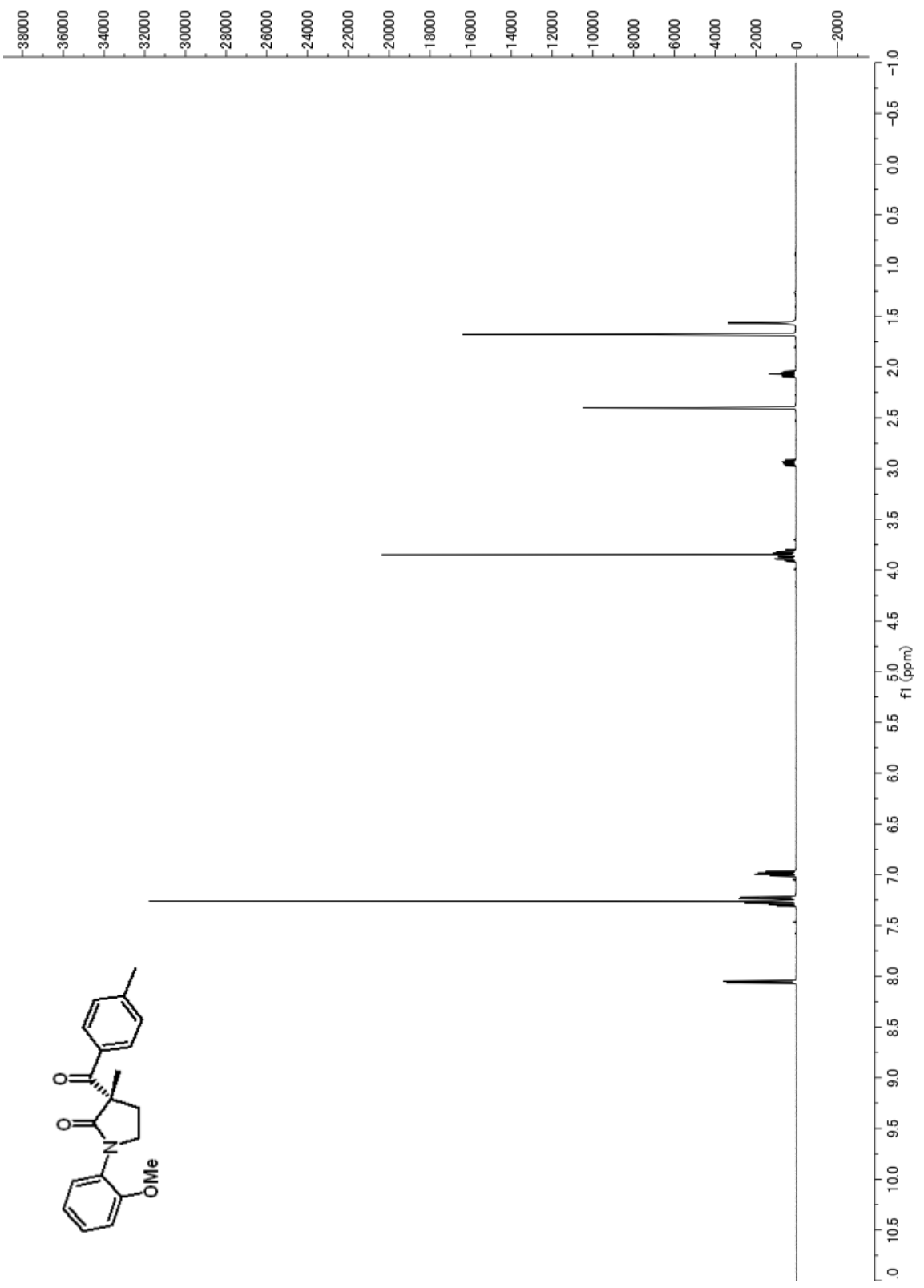


Figure A3.45. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **62b**.

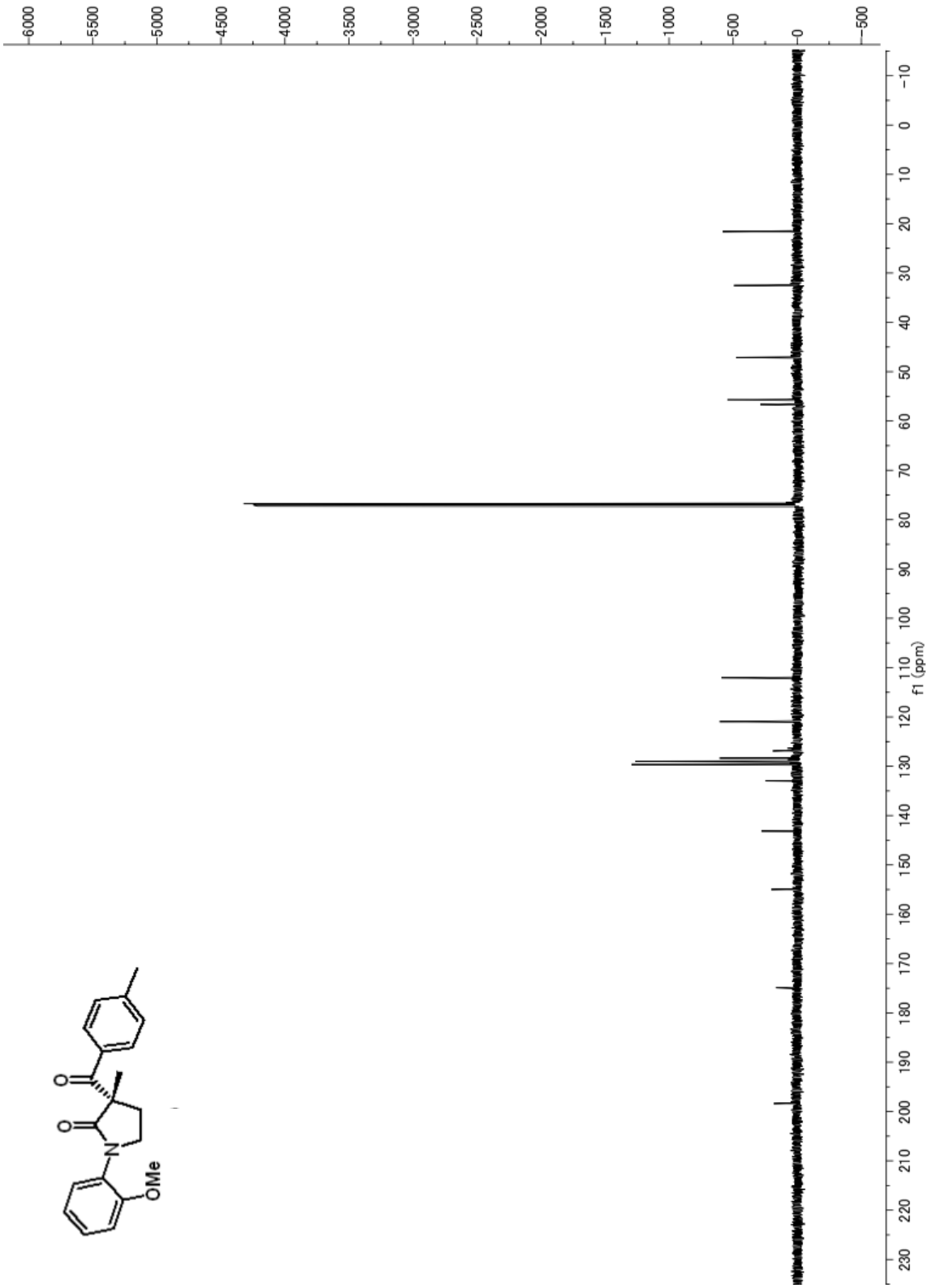


Figure A3.46. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **62b**.

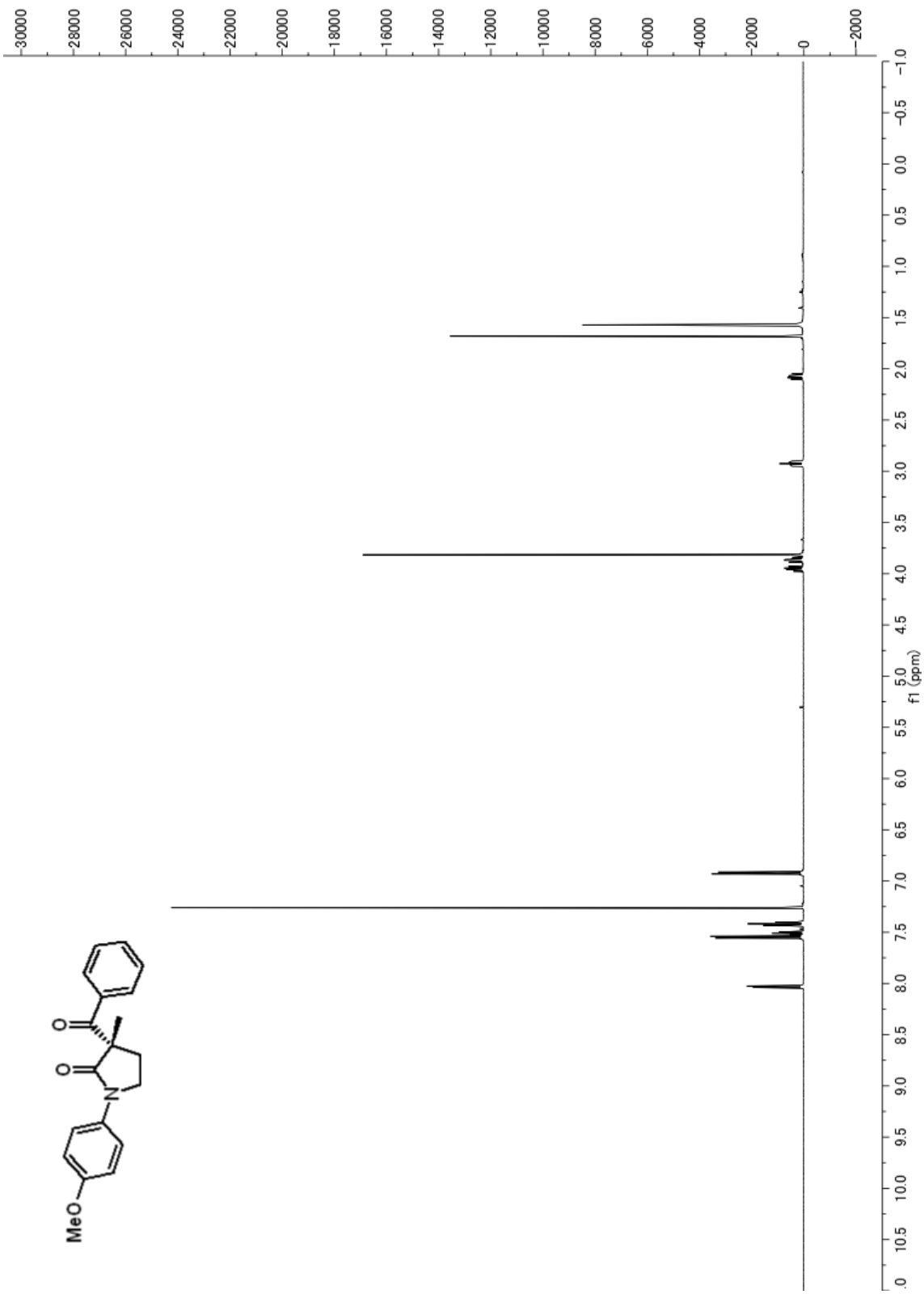


Figure A3.47. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **60a**.

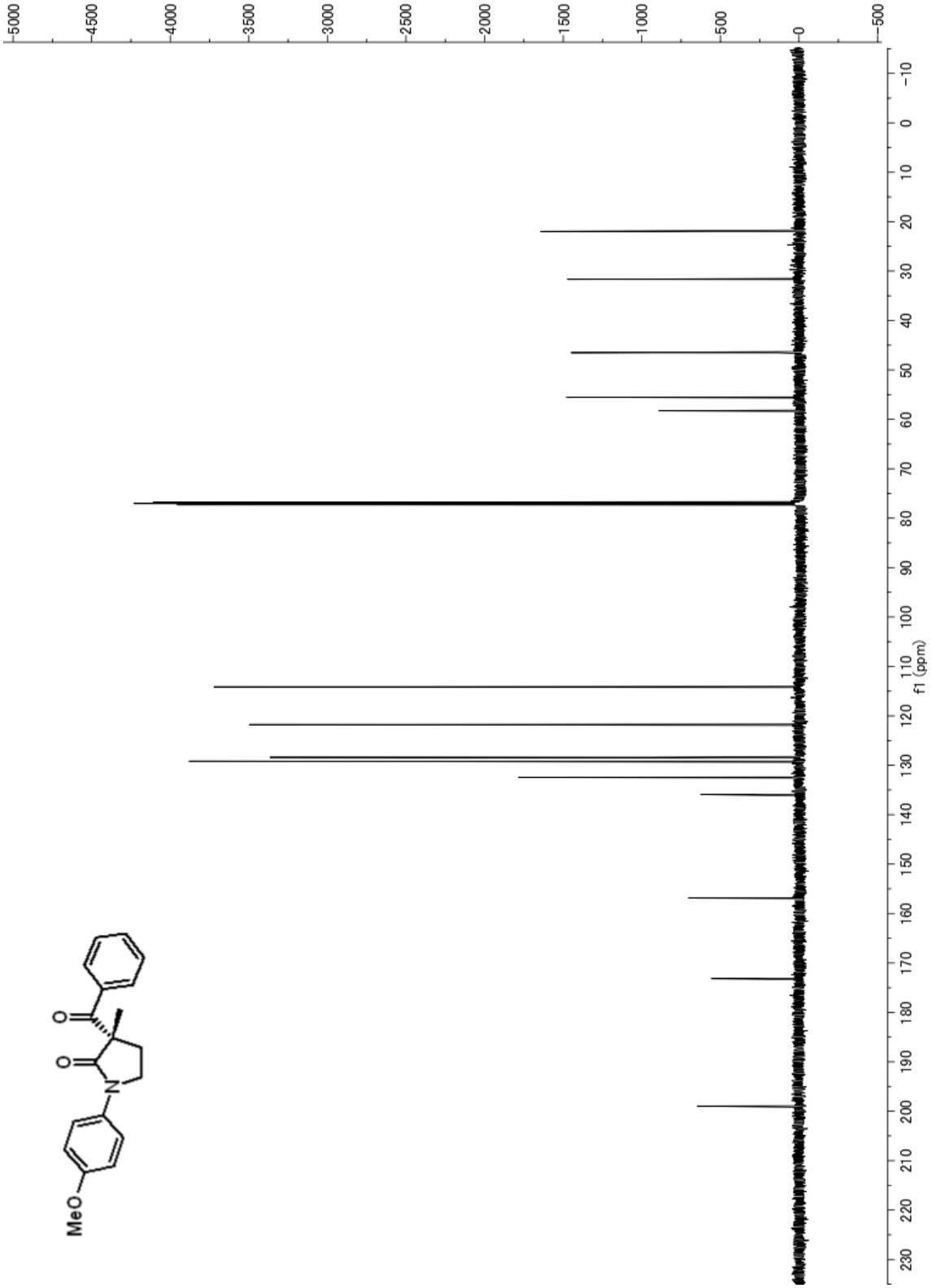


Figure A3.48. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **60a**.

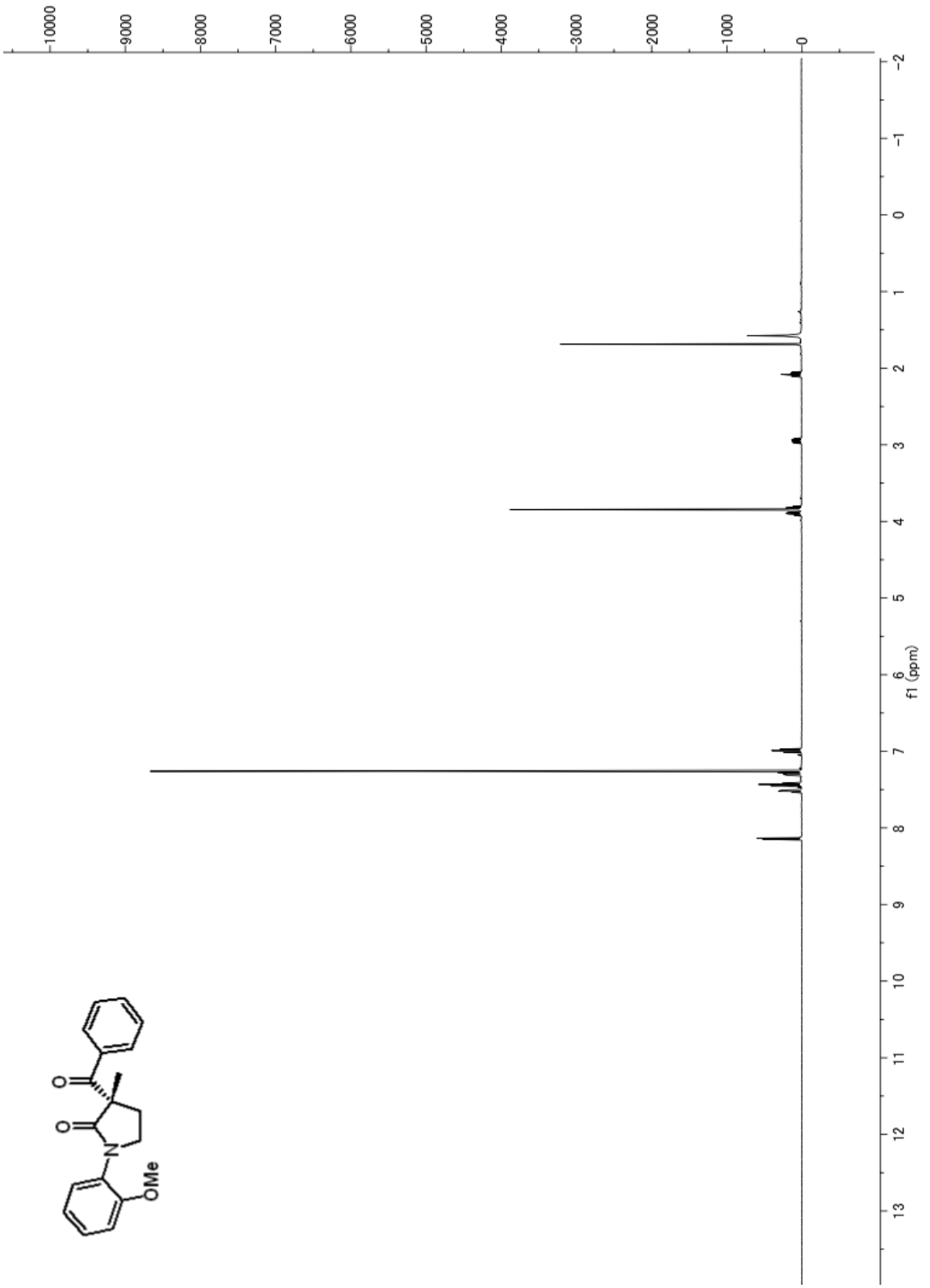


Figure A3.49. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **60b**.

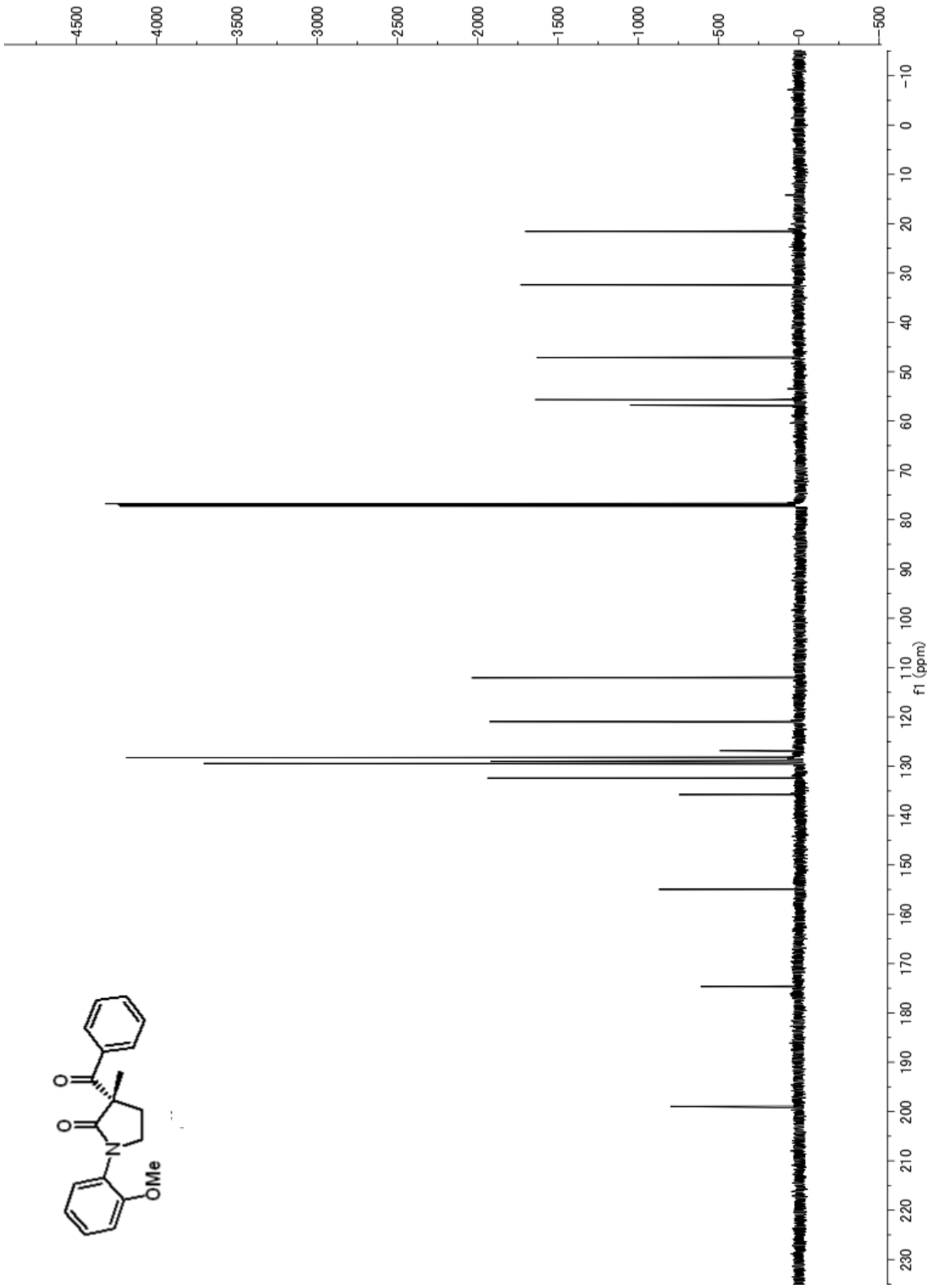


Figure A3.50. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **60b**.

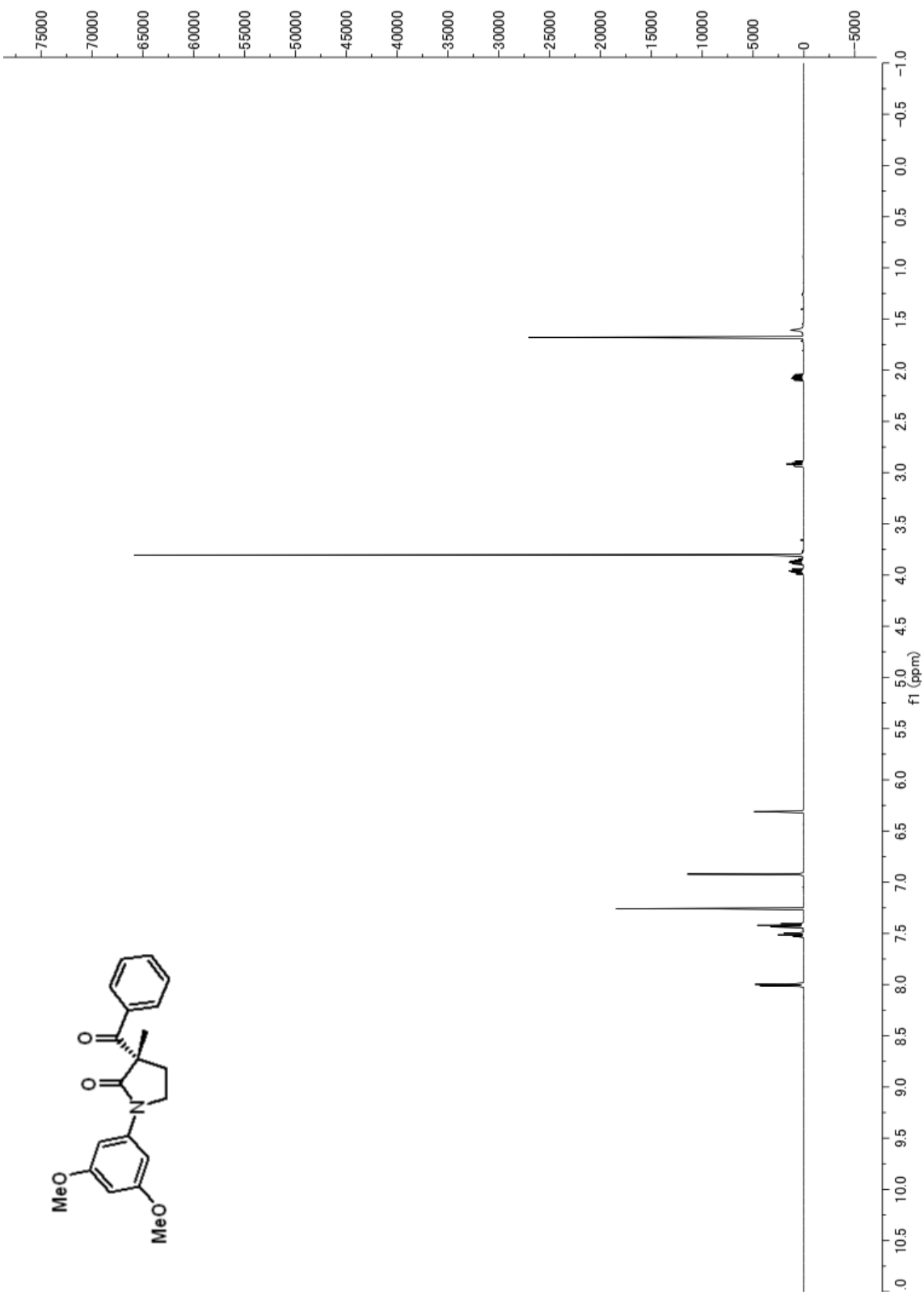


Figure A3.51. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **60c**.

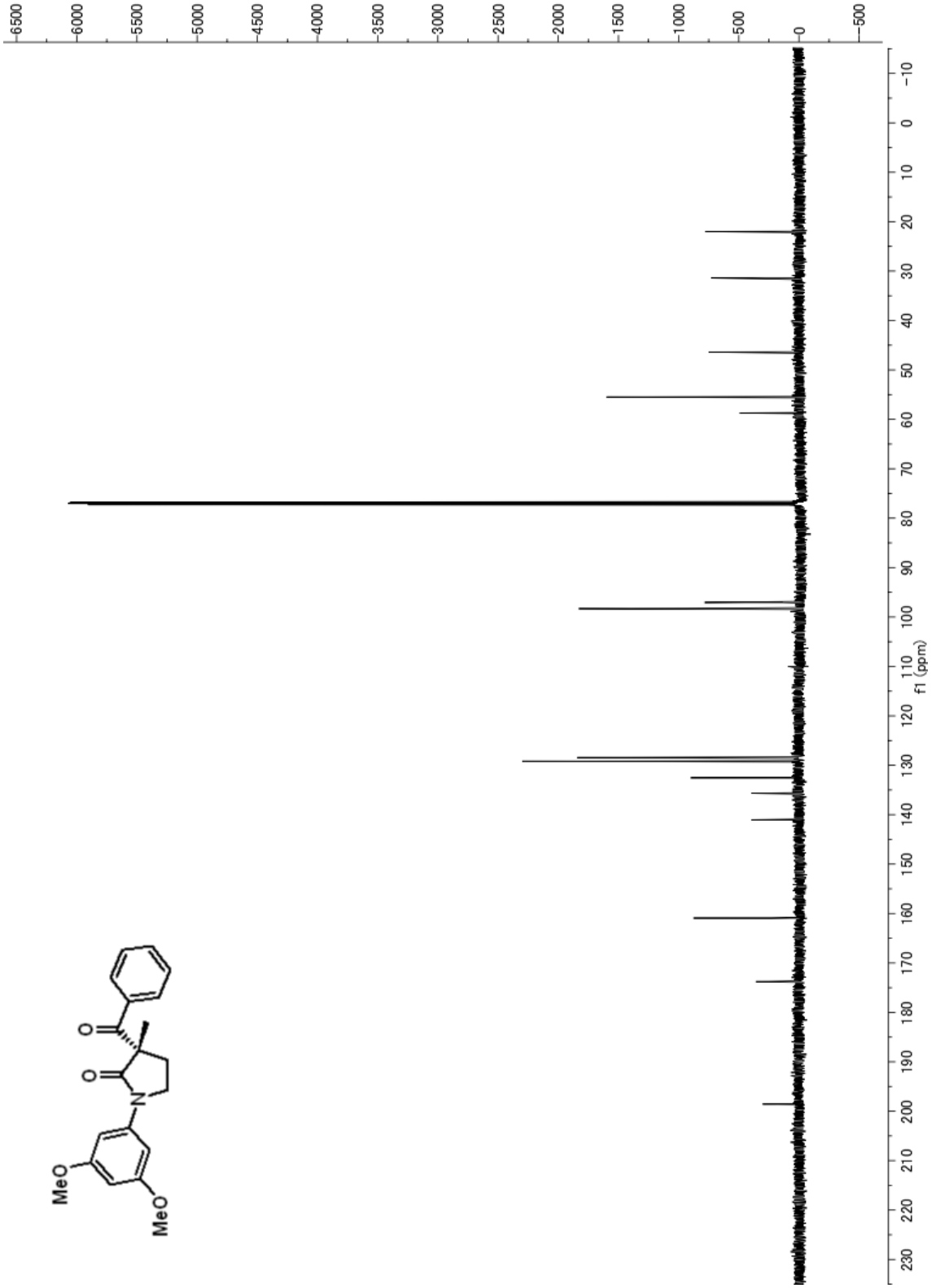


Figure A3.52. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **60c**.

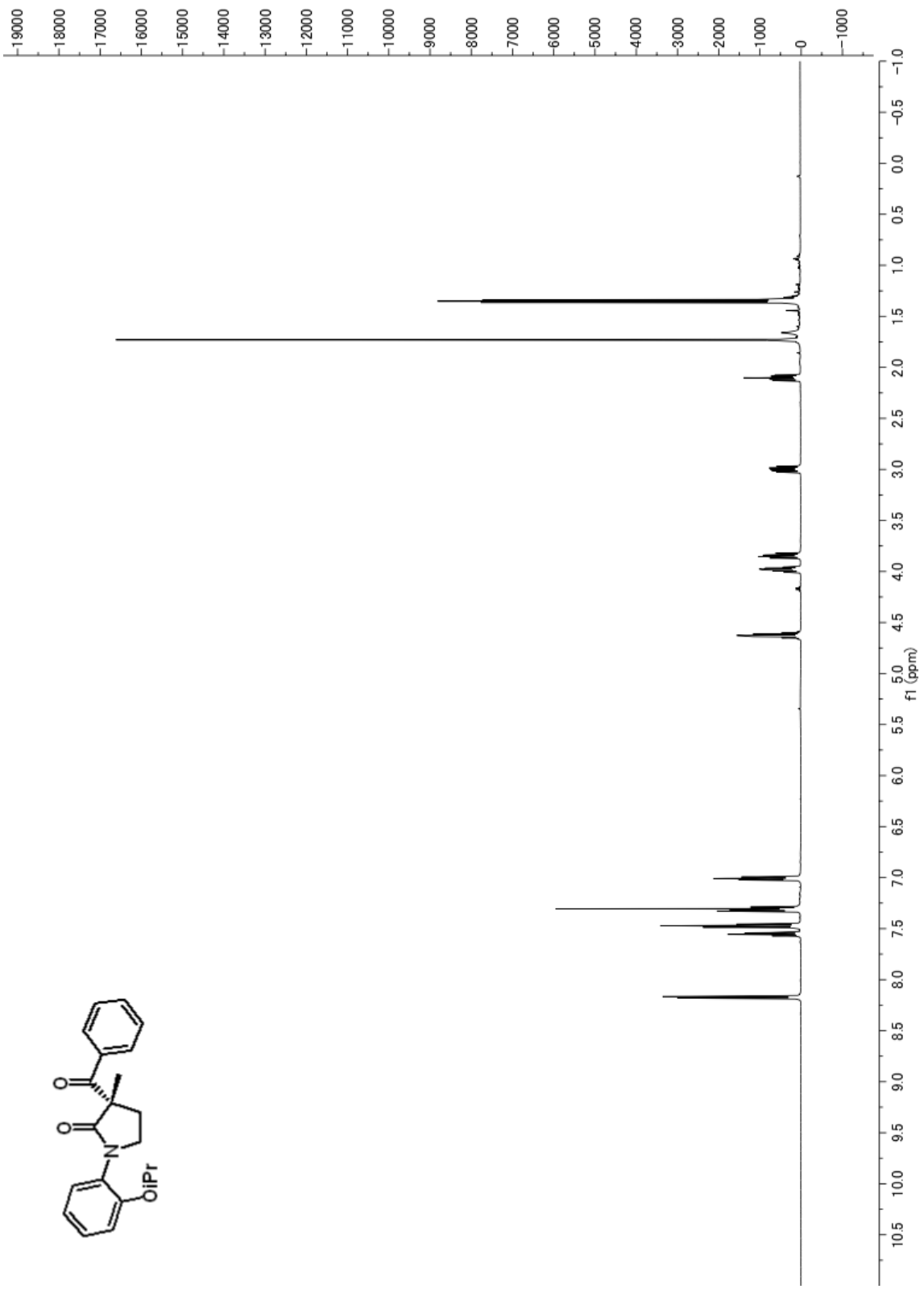


Figure A3.53. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **60d**.

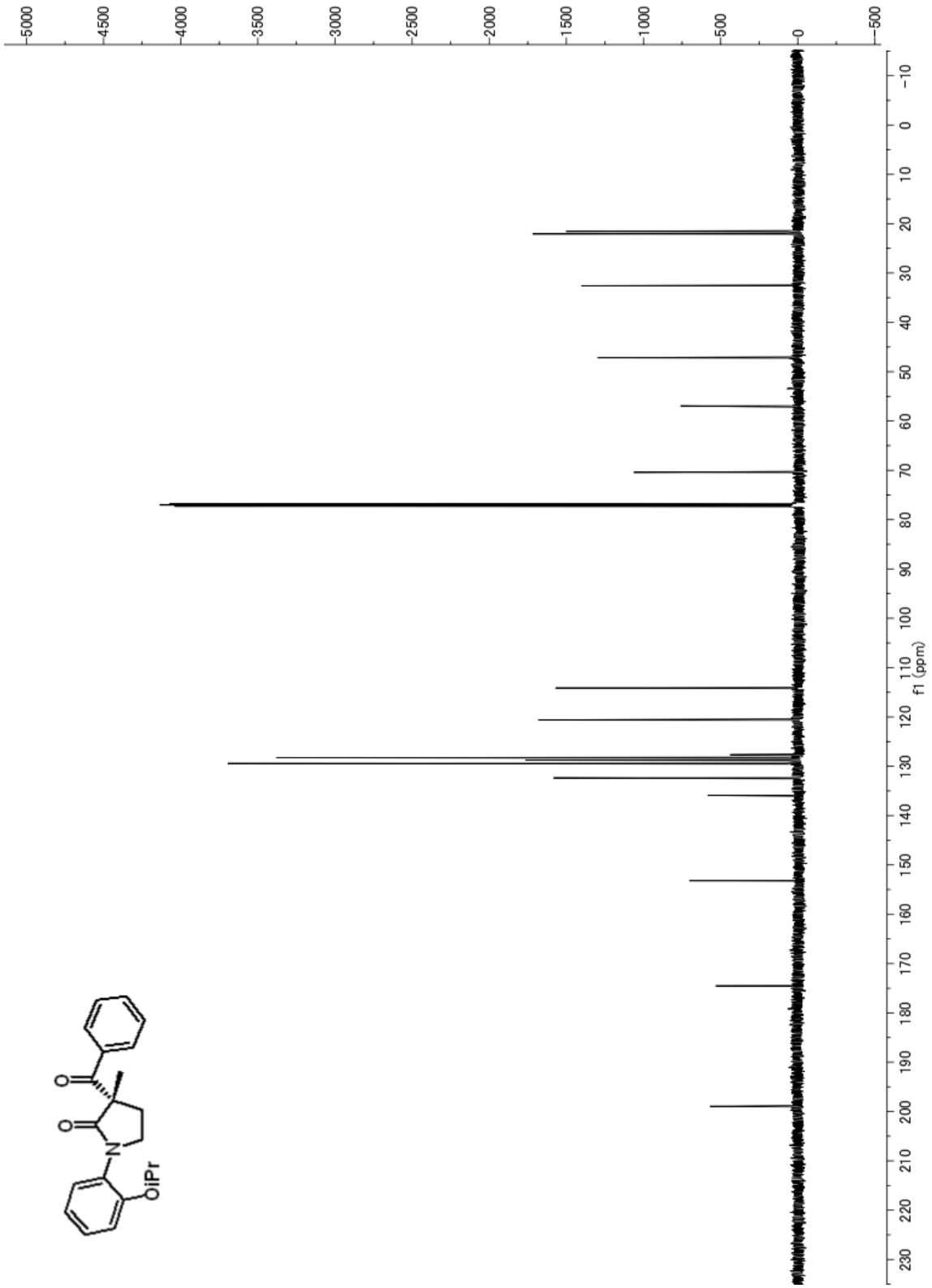


Figure A3.54. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **60d**.

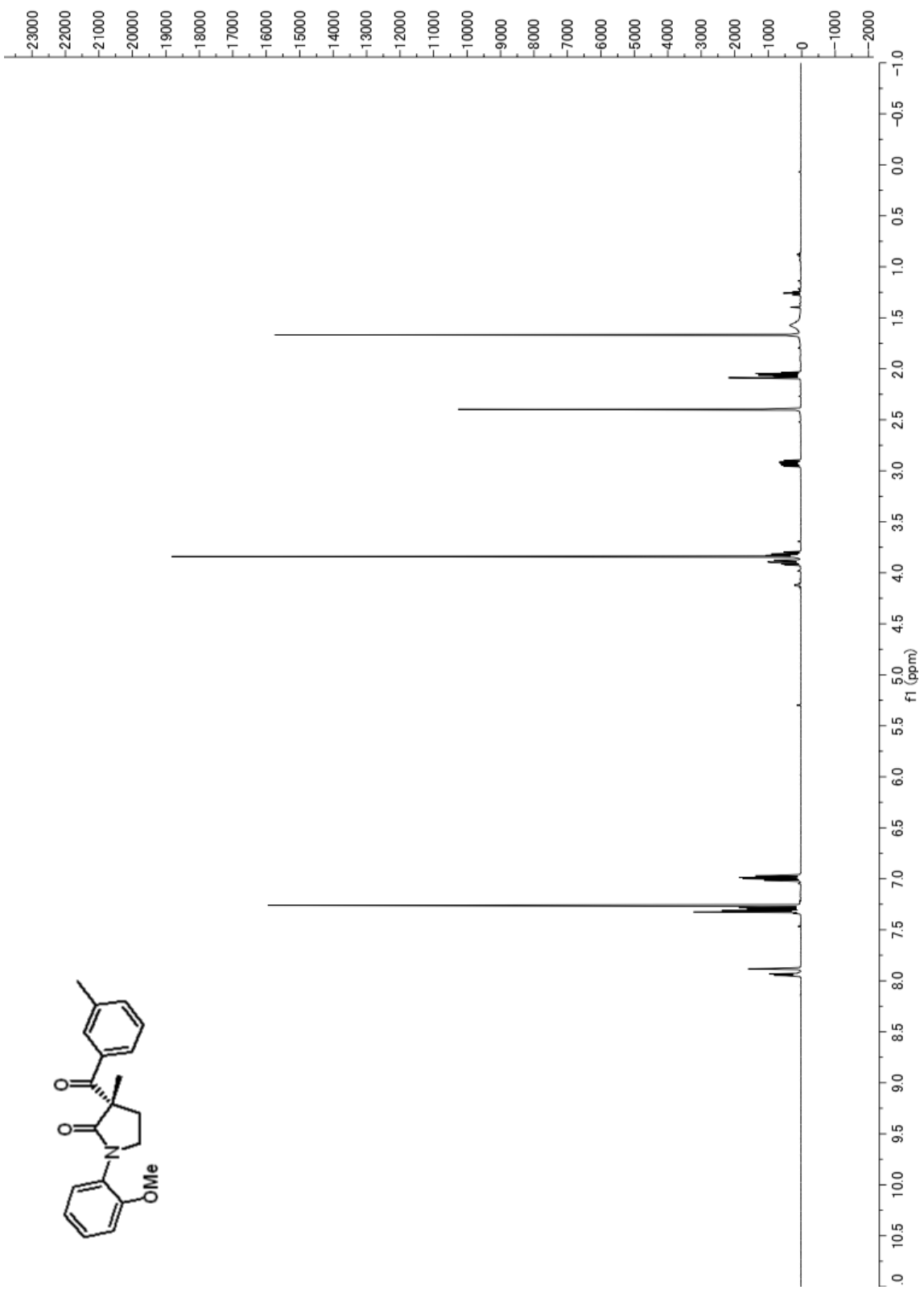


Figure A3.55. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **62c**.

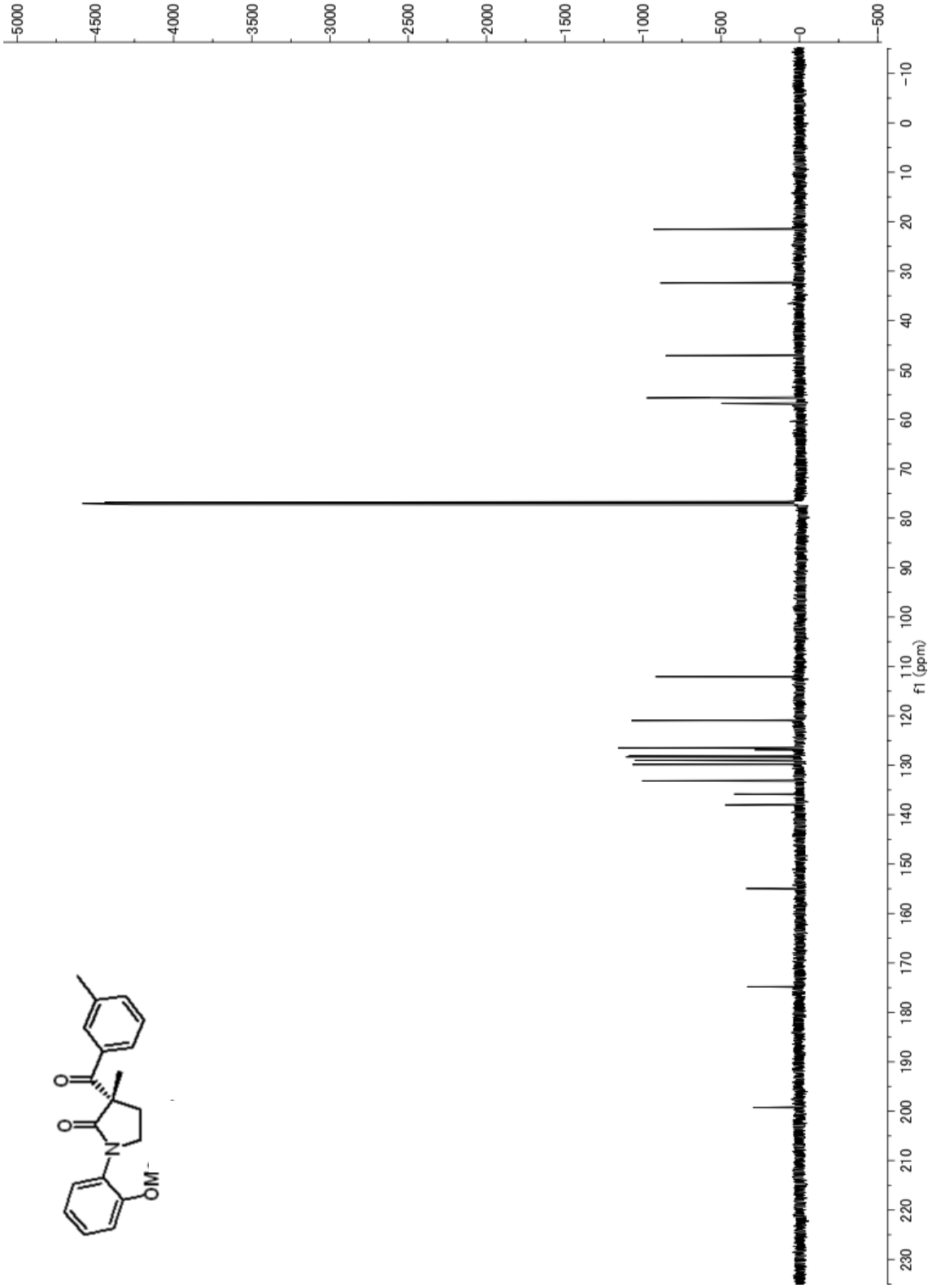


Figure A3.56. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **62c**.

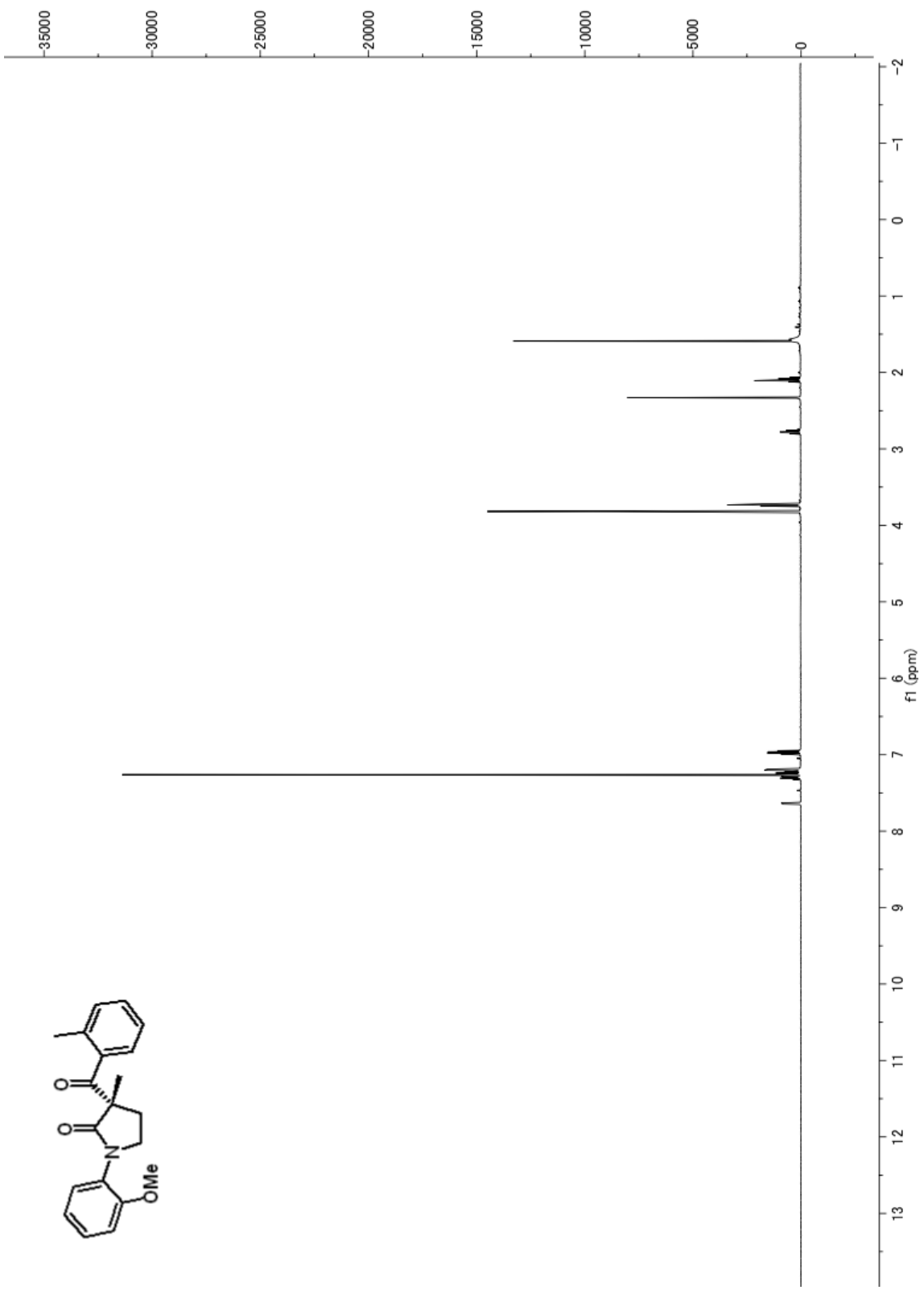


Figure A3.57. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **62d**.

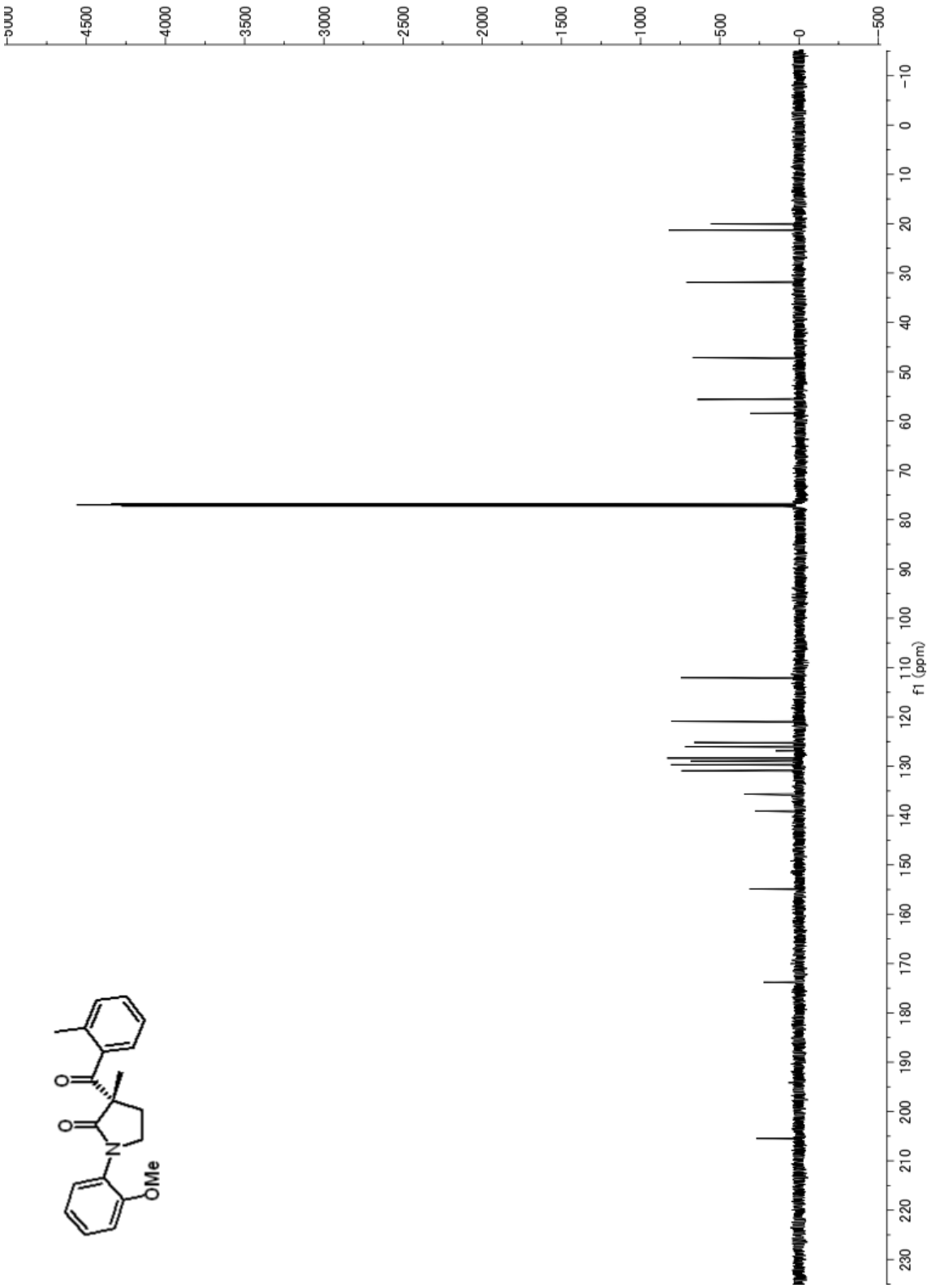


Figure A3.58. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **62d**.

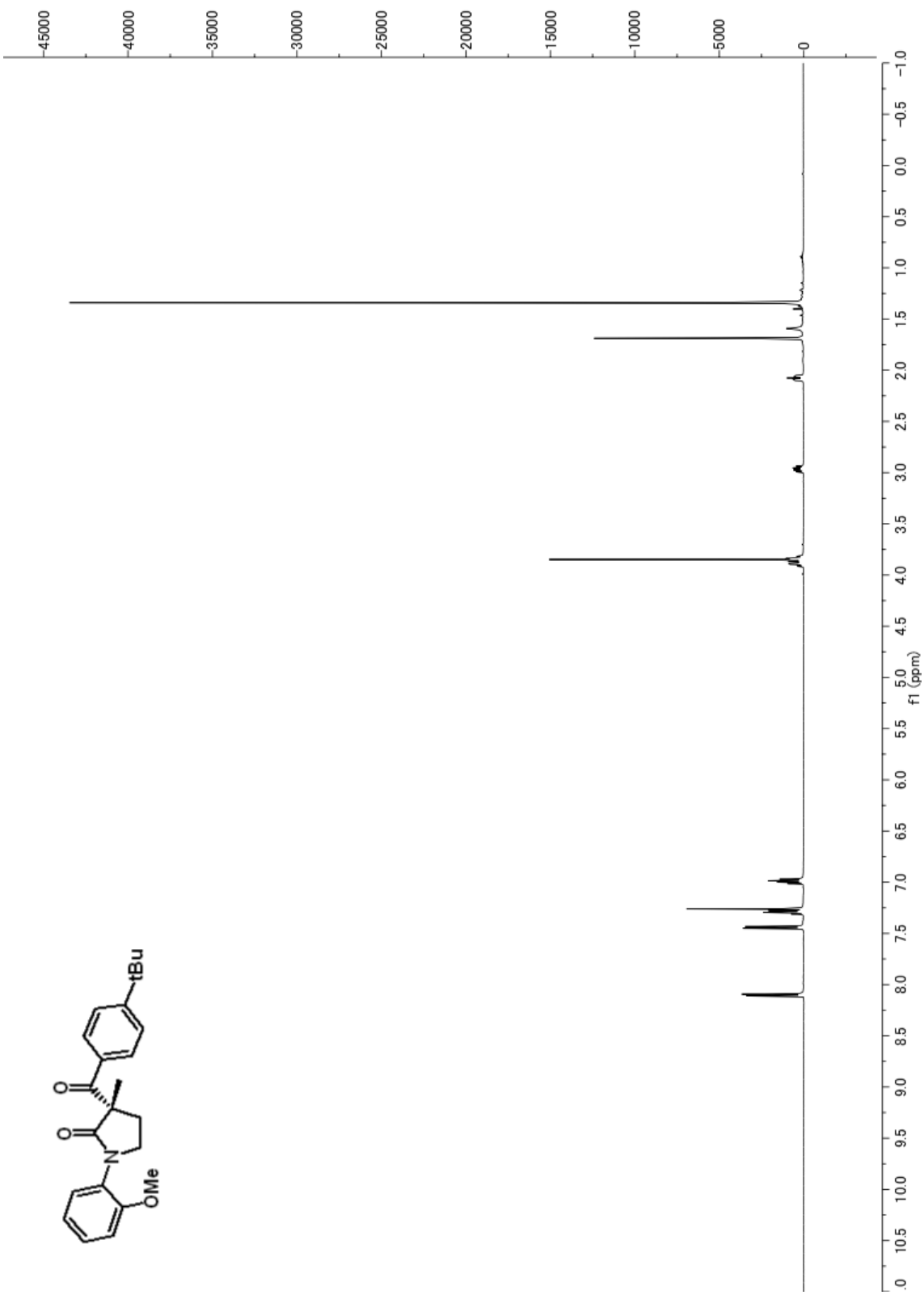


Figure A3.59. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **62e**.

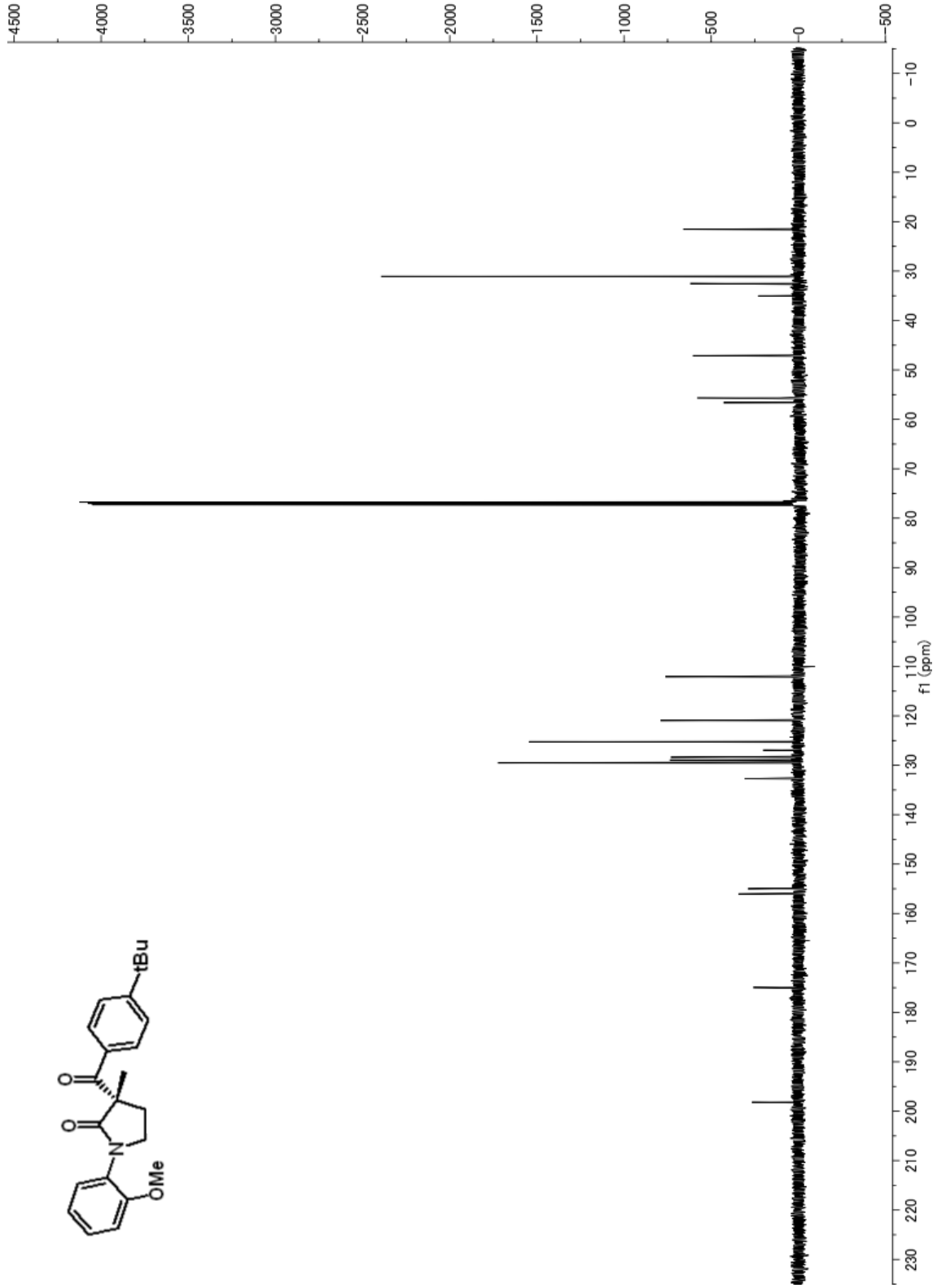


Figure A3.60. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **62f**.

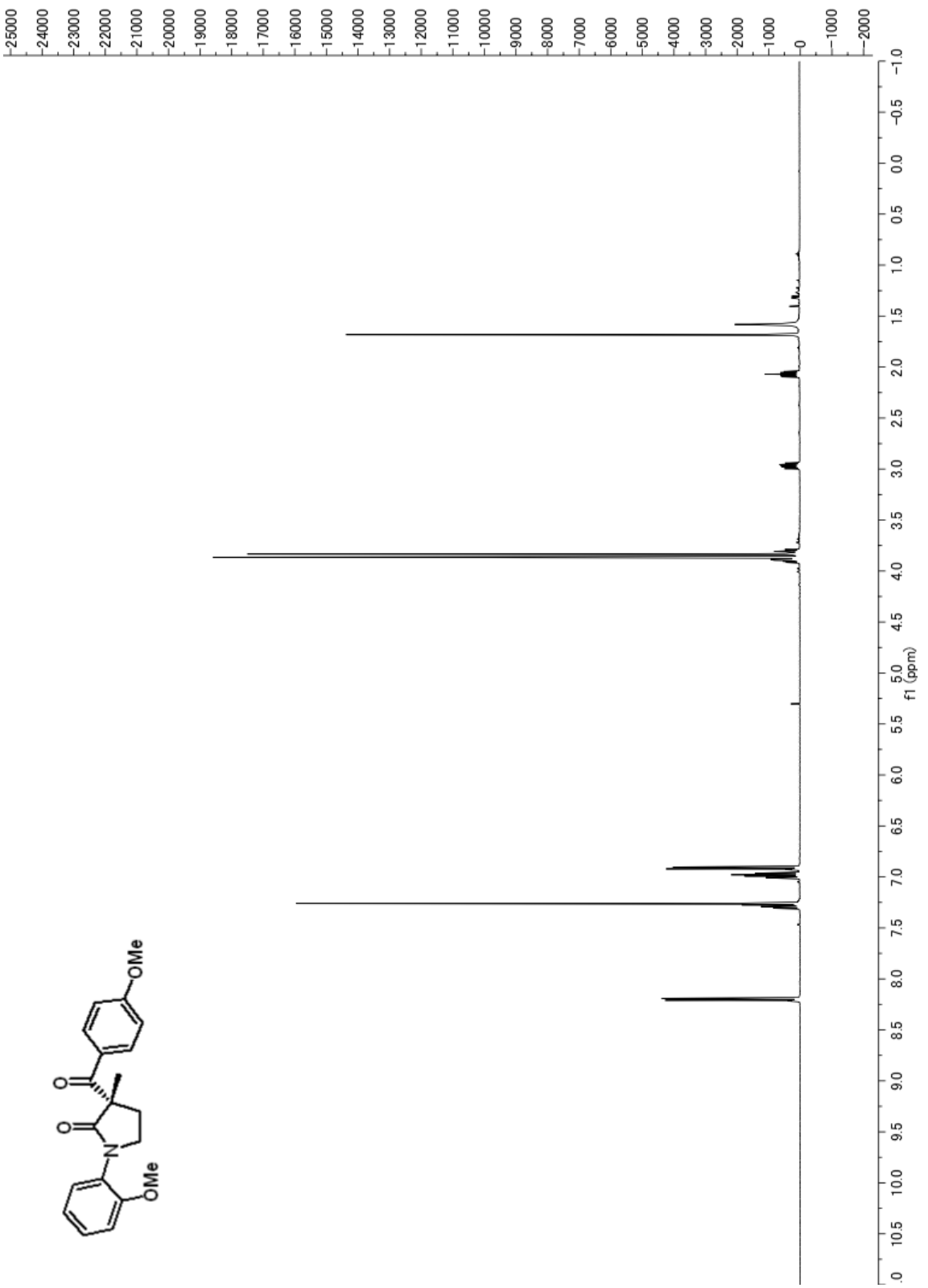


Figure A3.61. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **62f**.

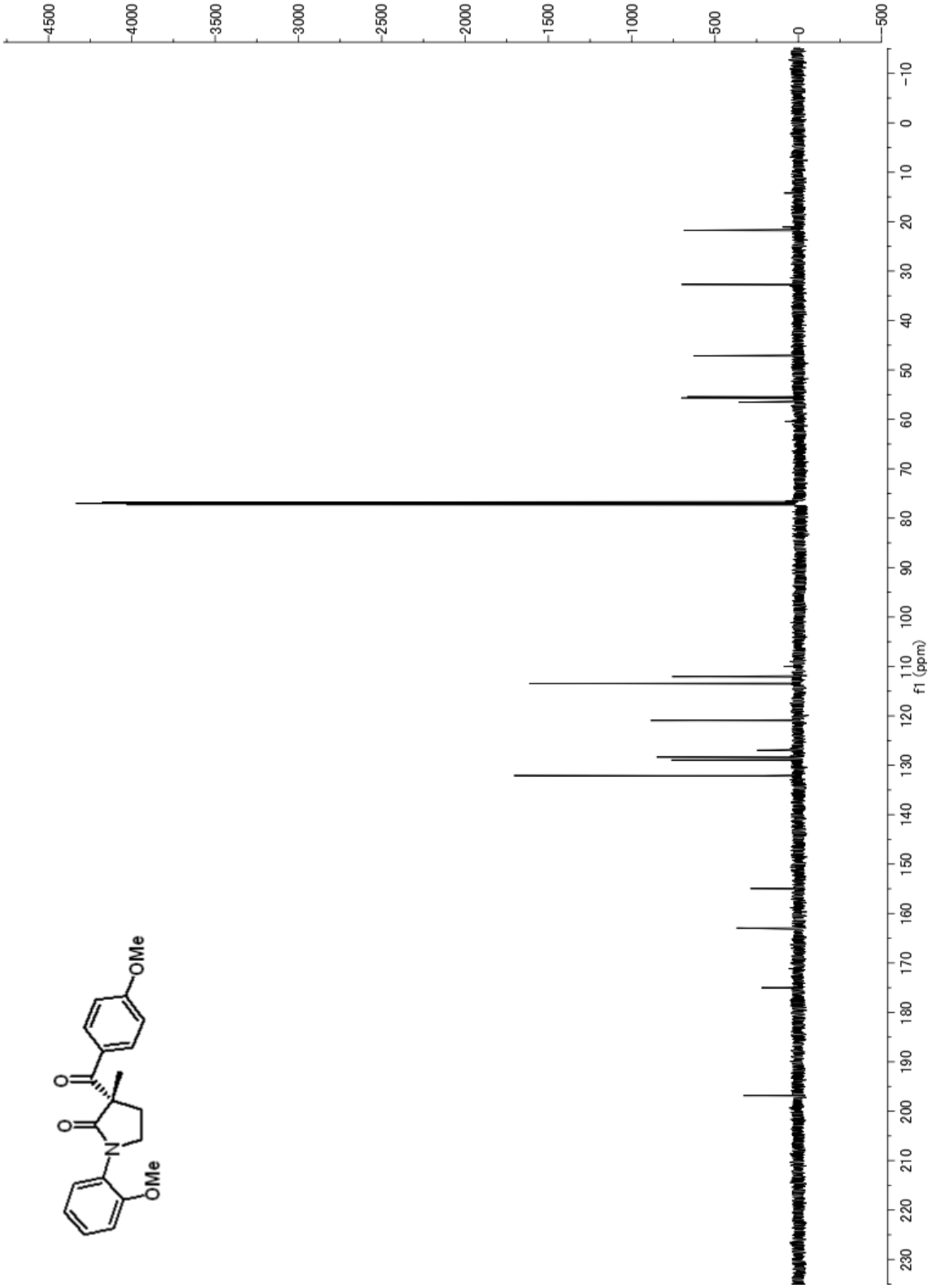


Figure A3.62. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **62f**.

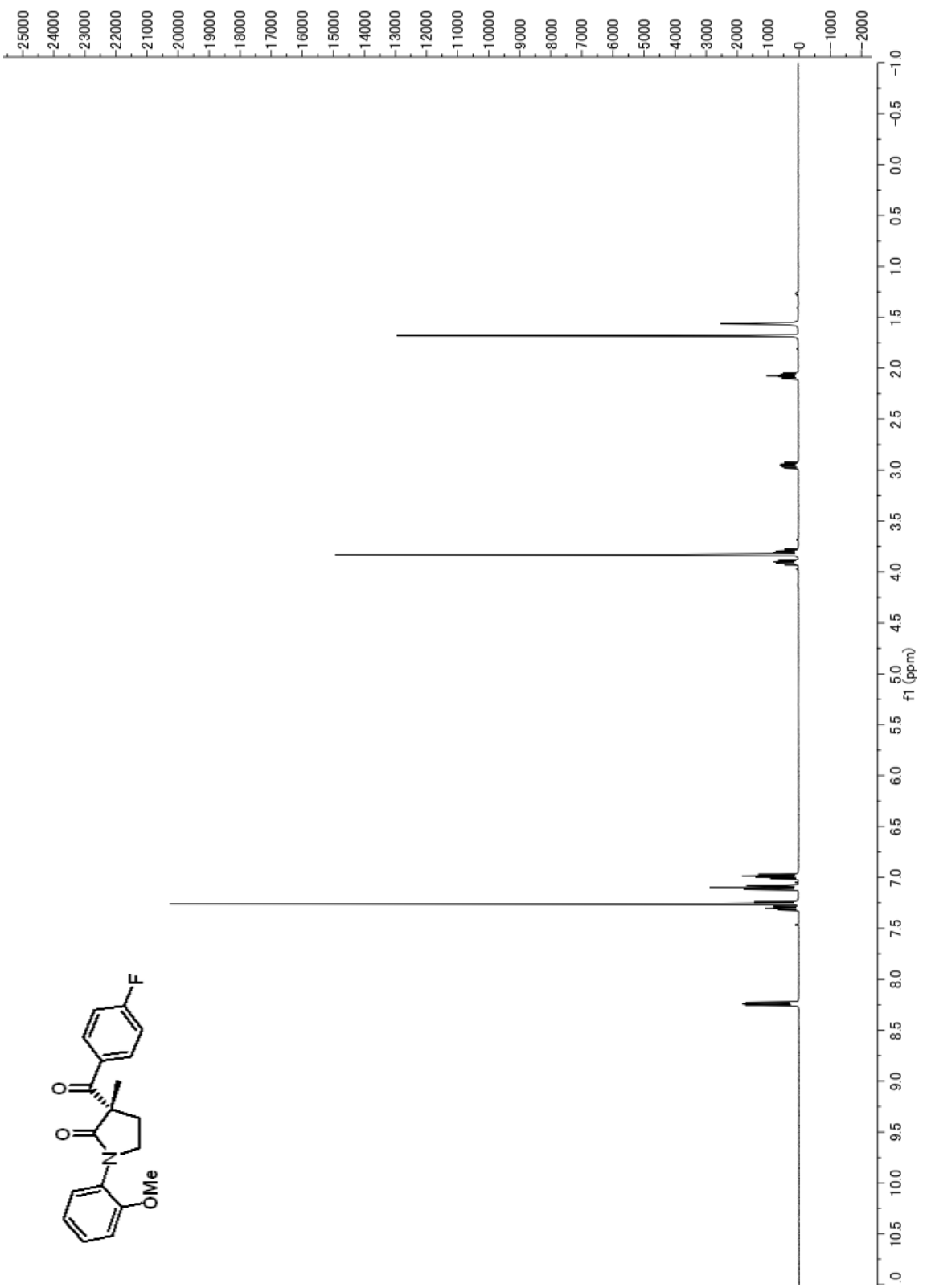


Figure A3.63. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **62g**.

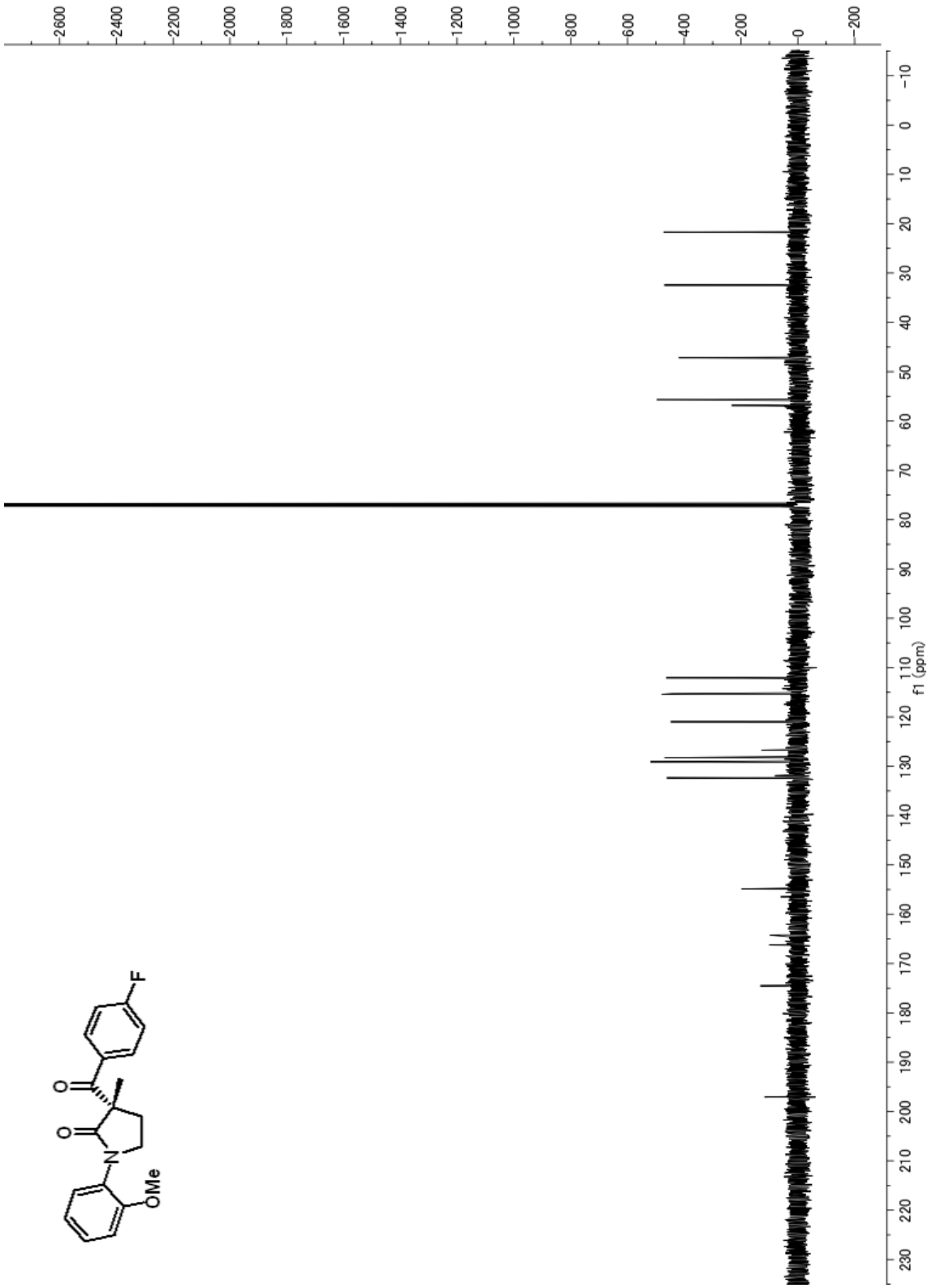


Figure A3.64. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **62g**.

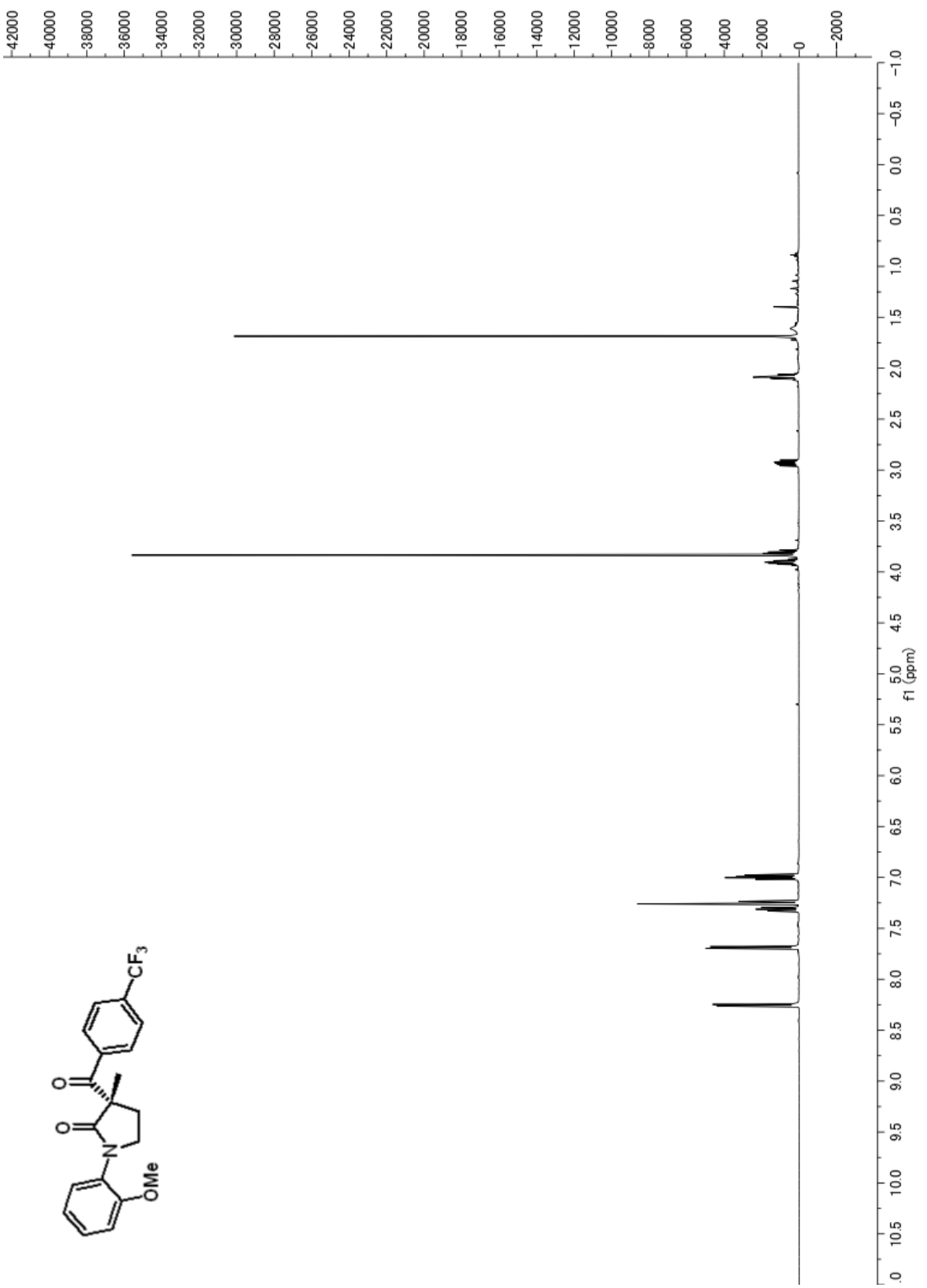


Figure A3.65. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **62h**.

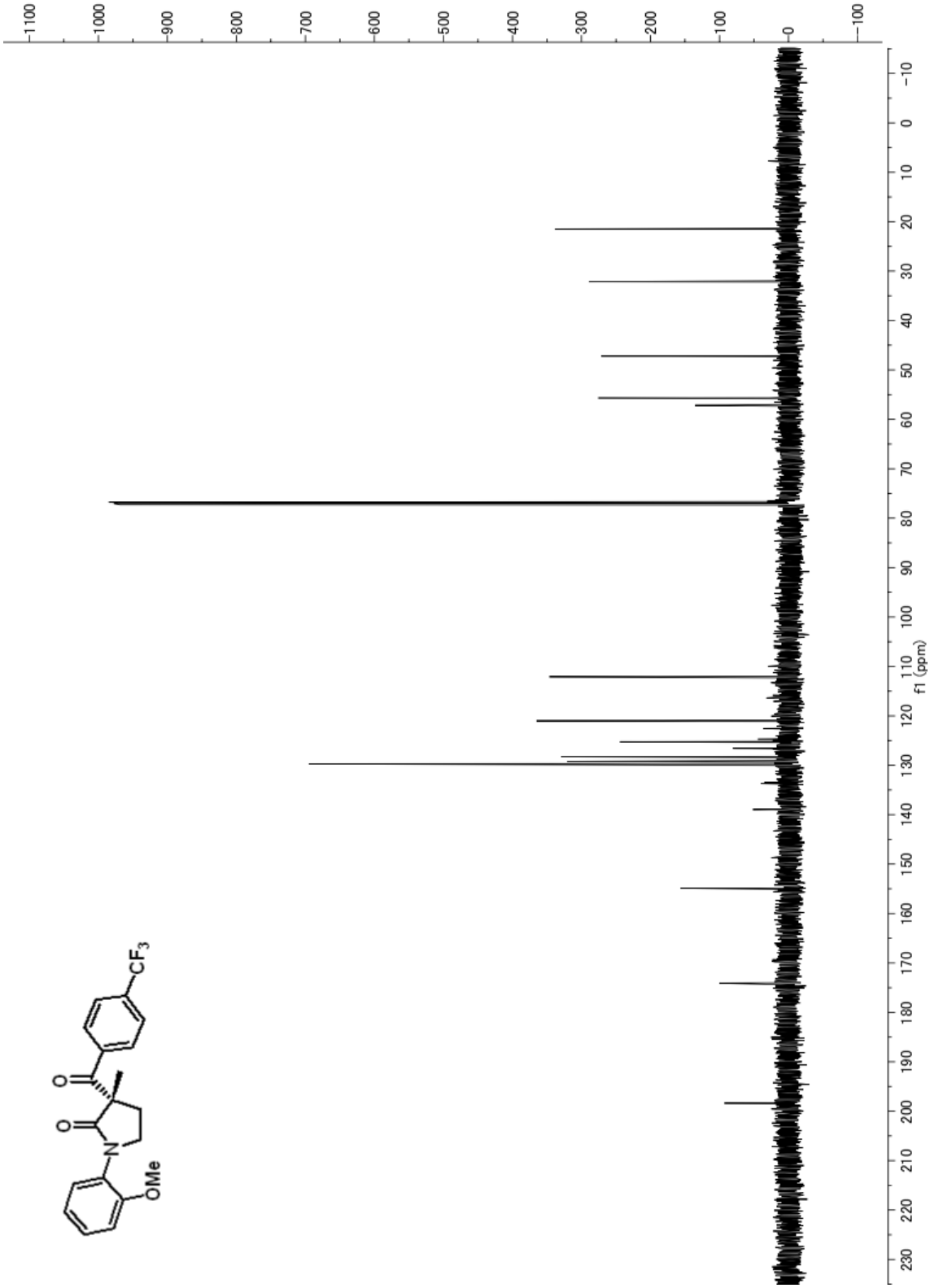


Figure A3.66. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **62h**.

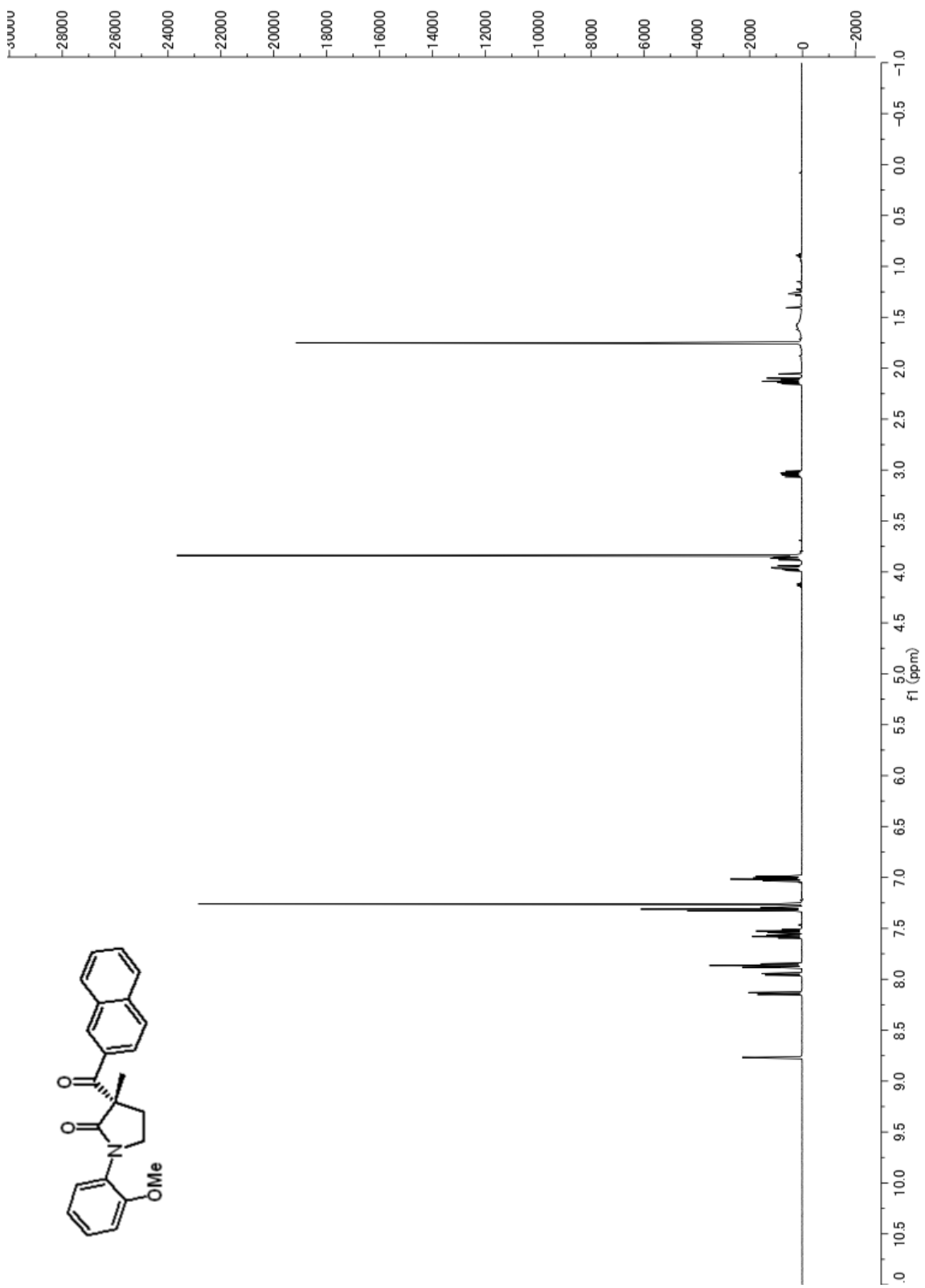


Figure A3.67. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **62i**.

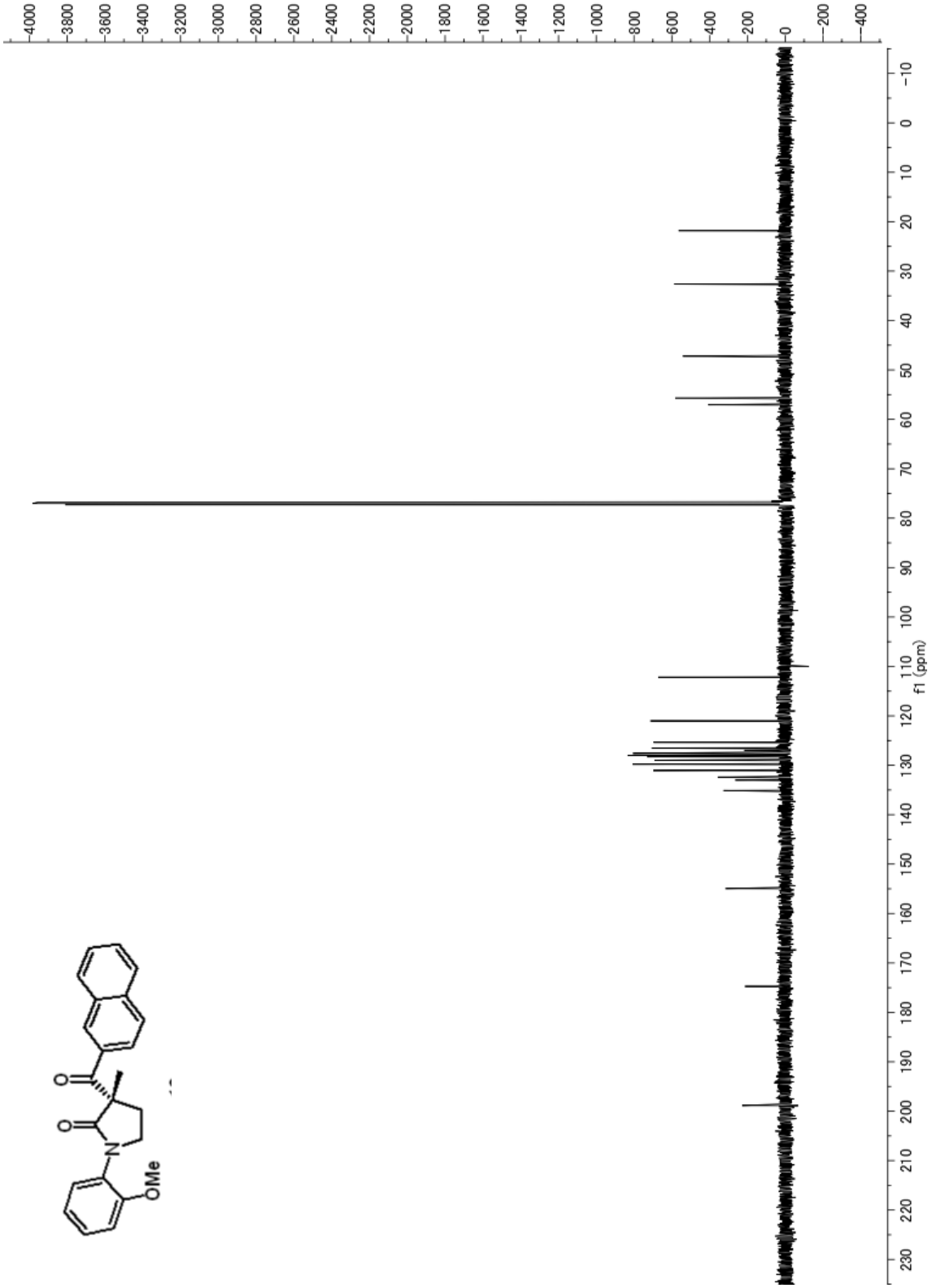


Figure A3.68. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **62i**.

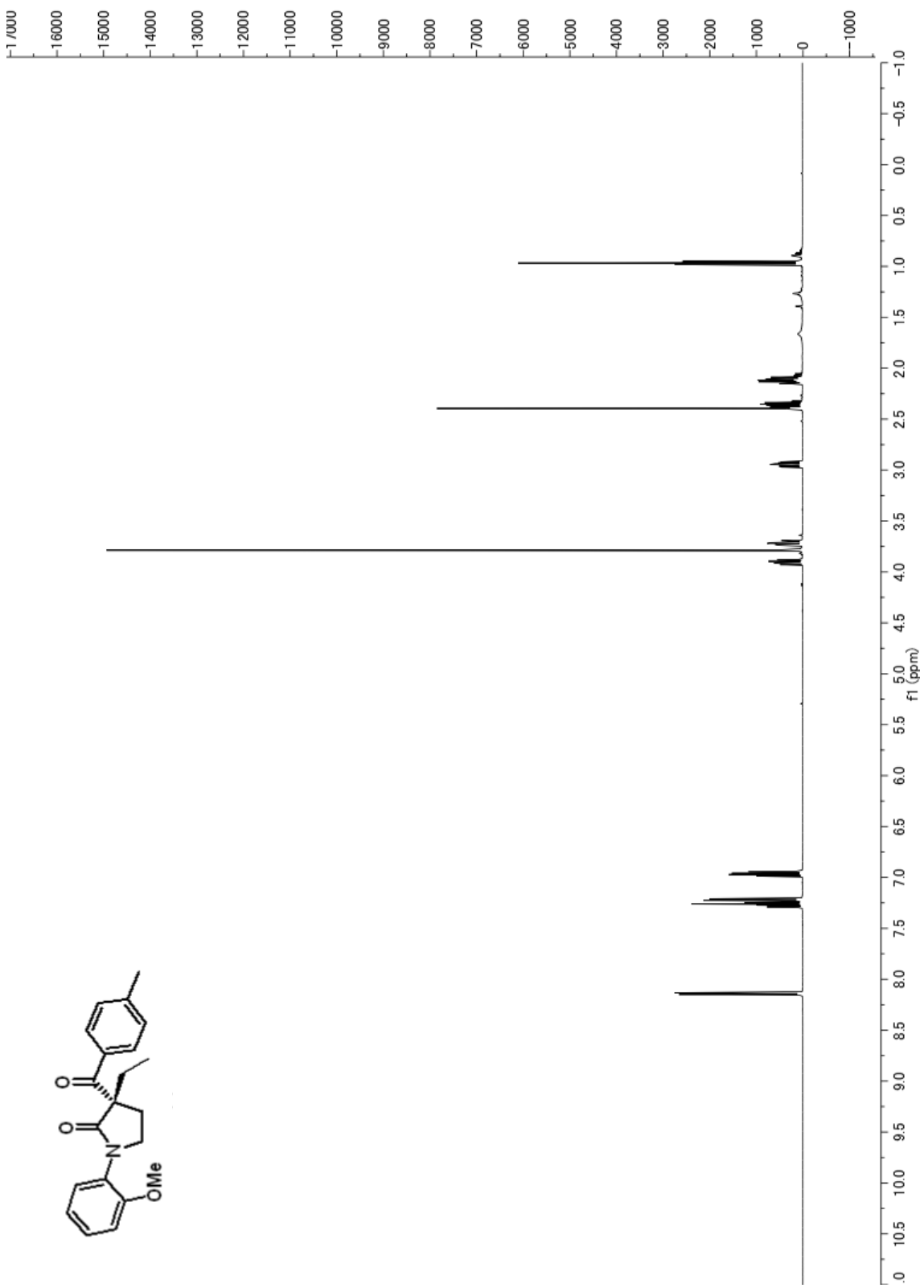


Figure A3.69. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **64b**.

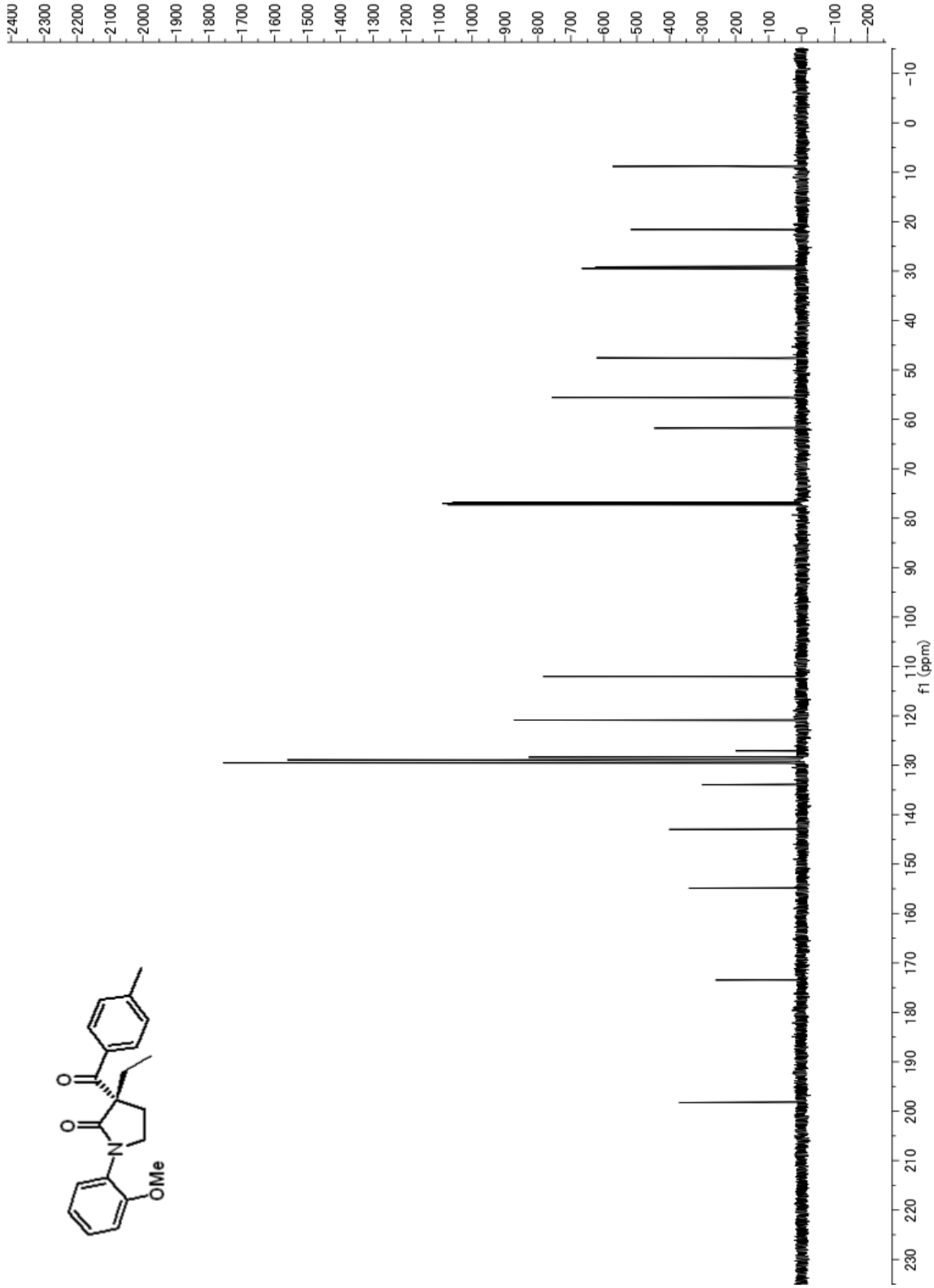


Figure A3.70. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **64b**.

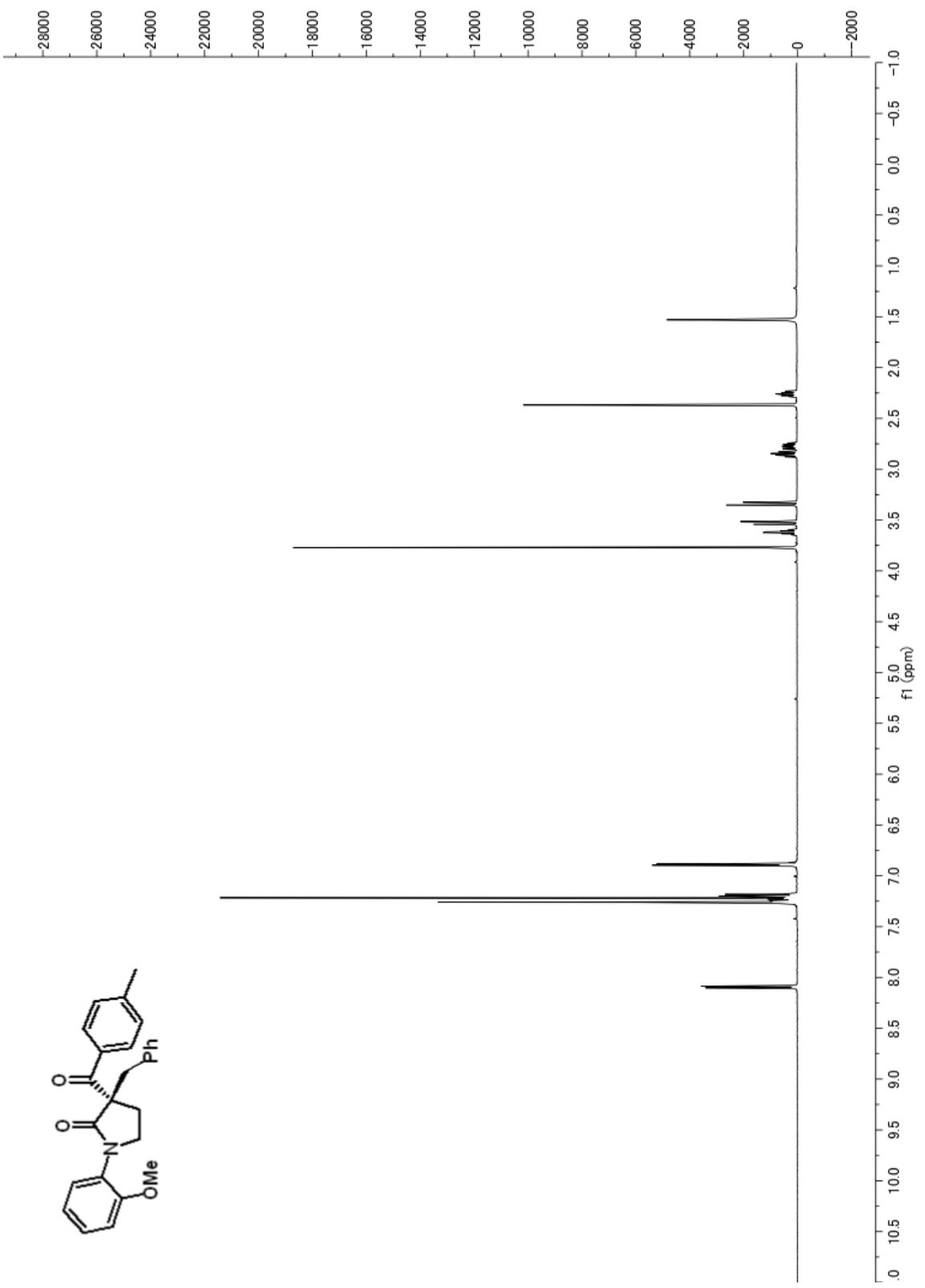


Figure A3.71. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **64c**.

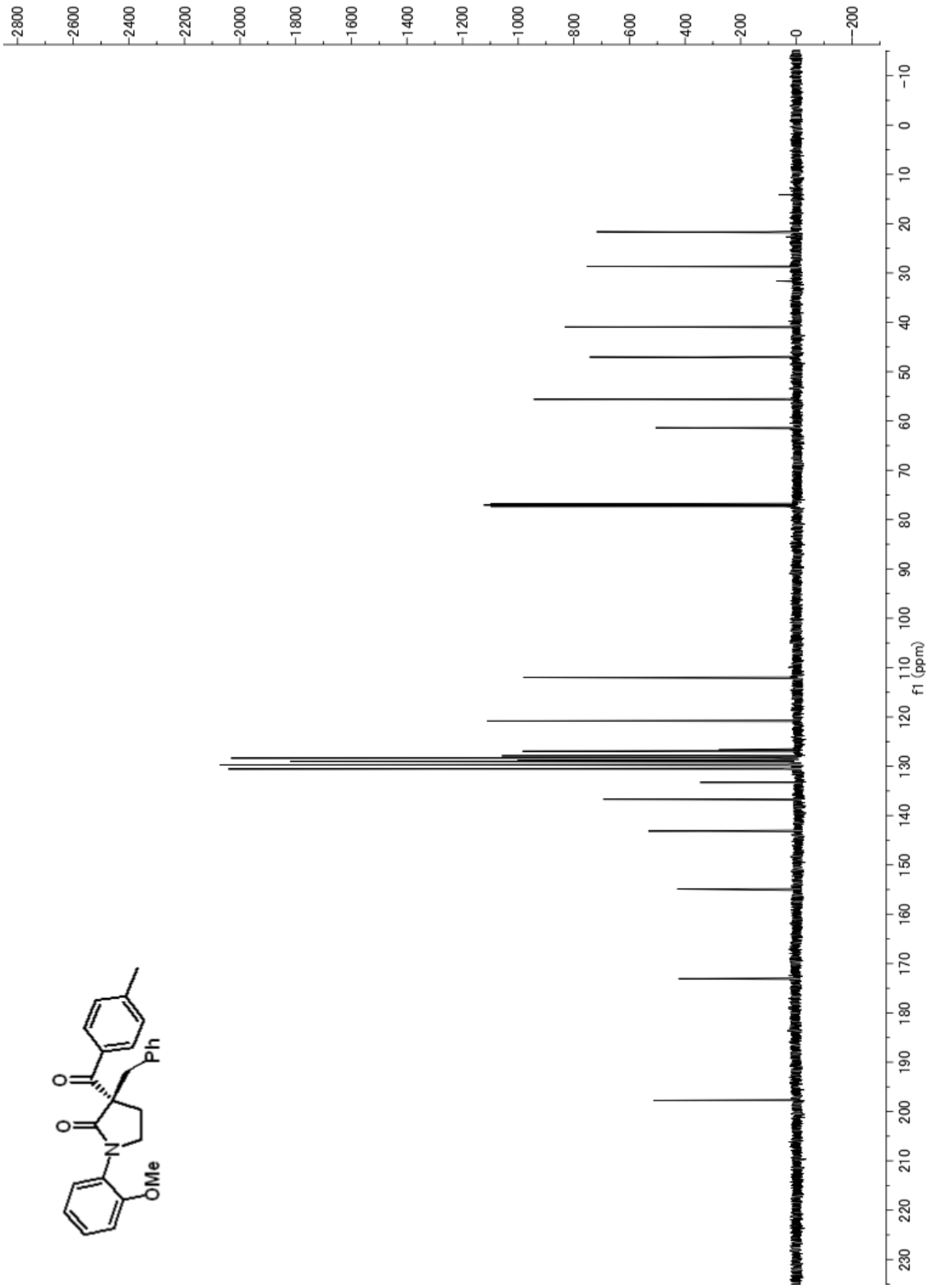


Figure A3.72. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **64c**.

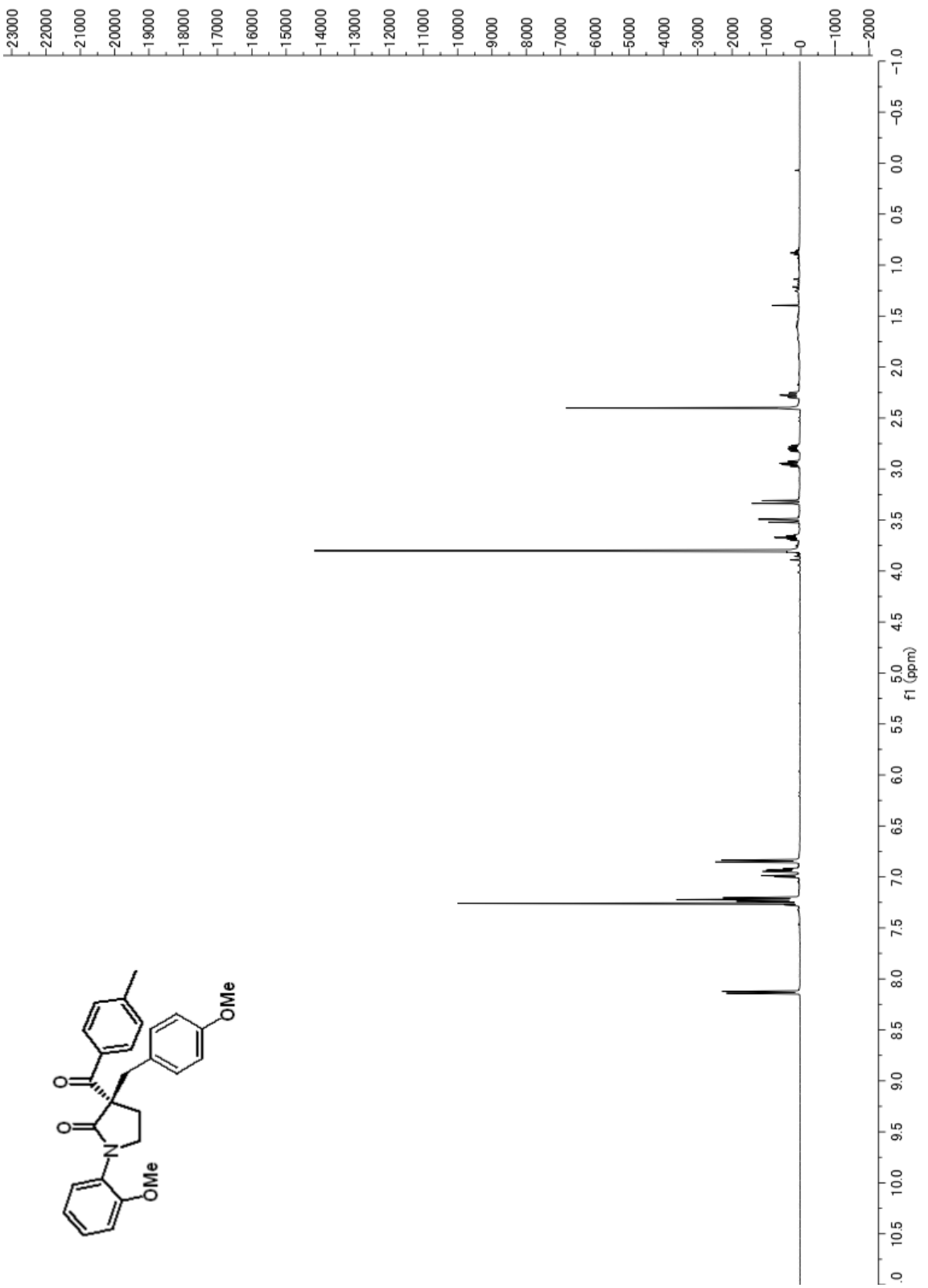


Figure A3.73. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **64d**.

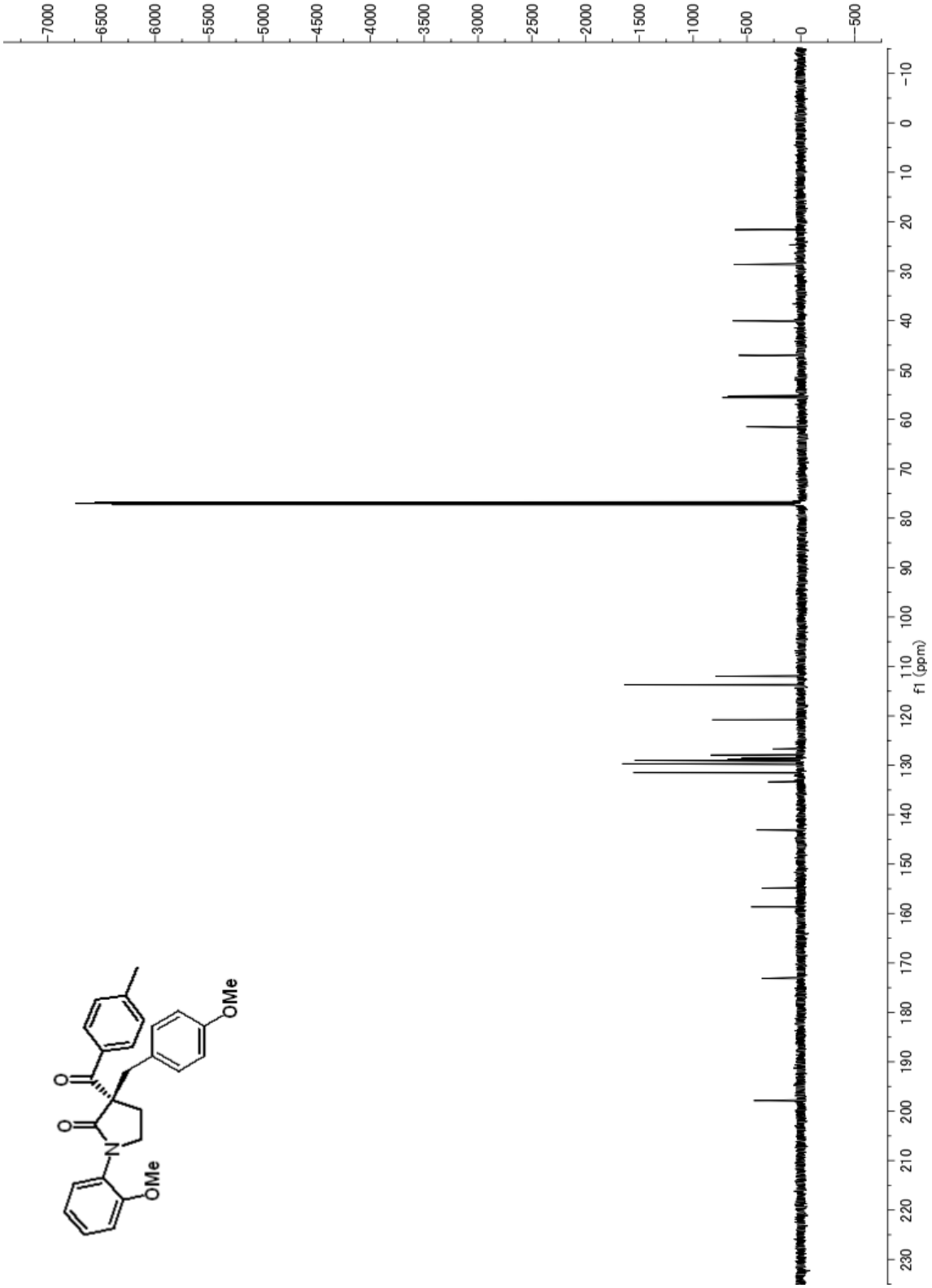


Figure A3.74. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **64d**.

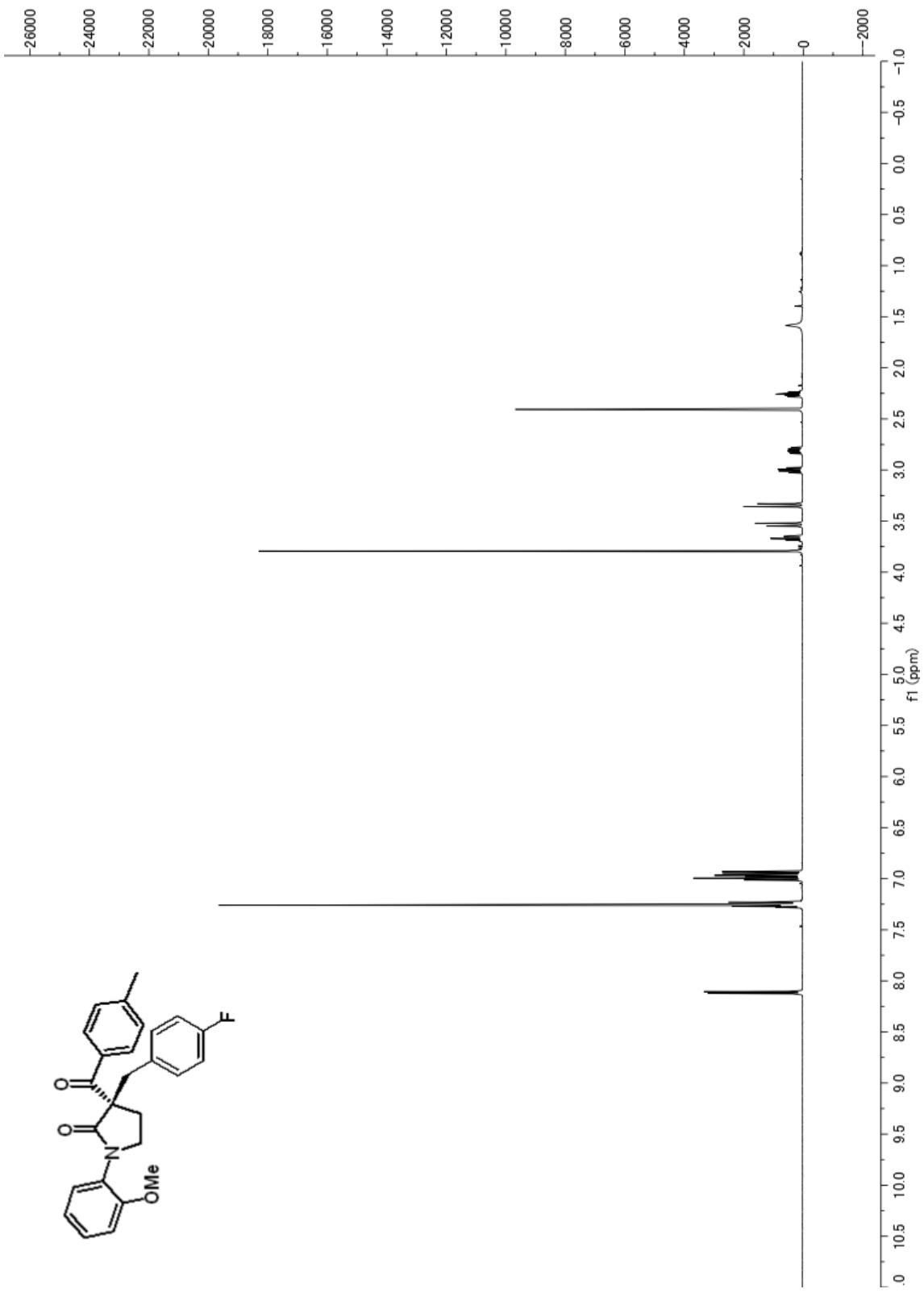


Figure A3.75. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **64e**.

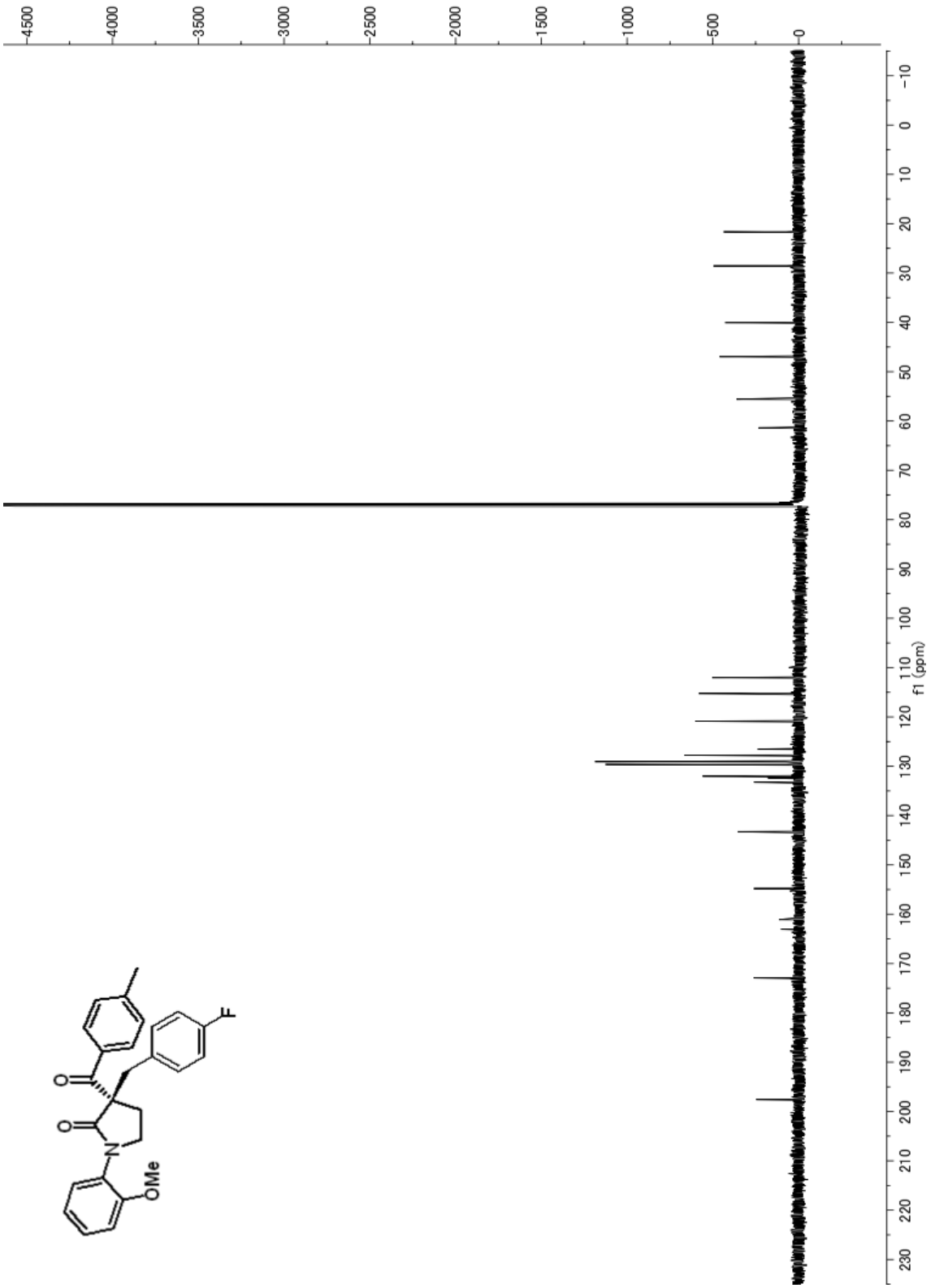


Figure A3.76. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **64e**.

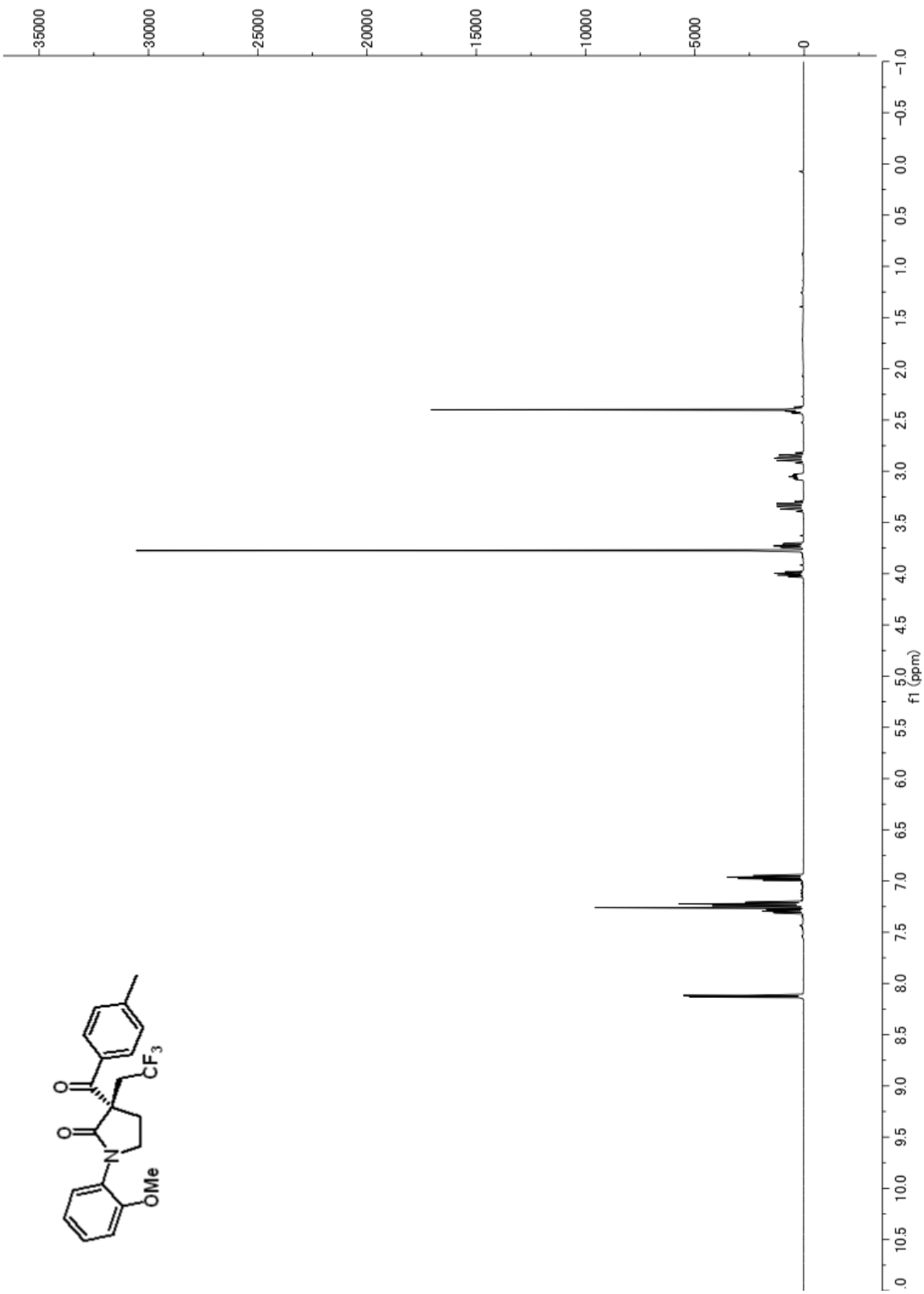


Figure A3.77. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **64f**.

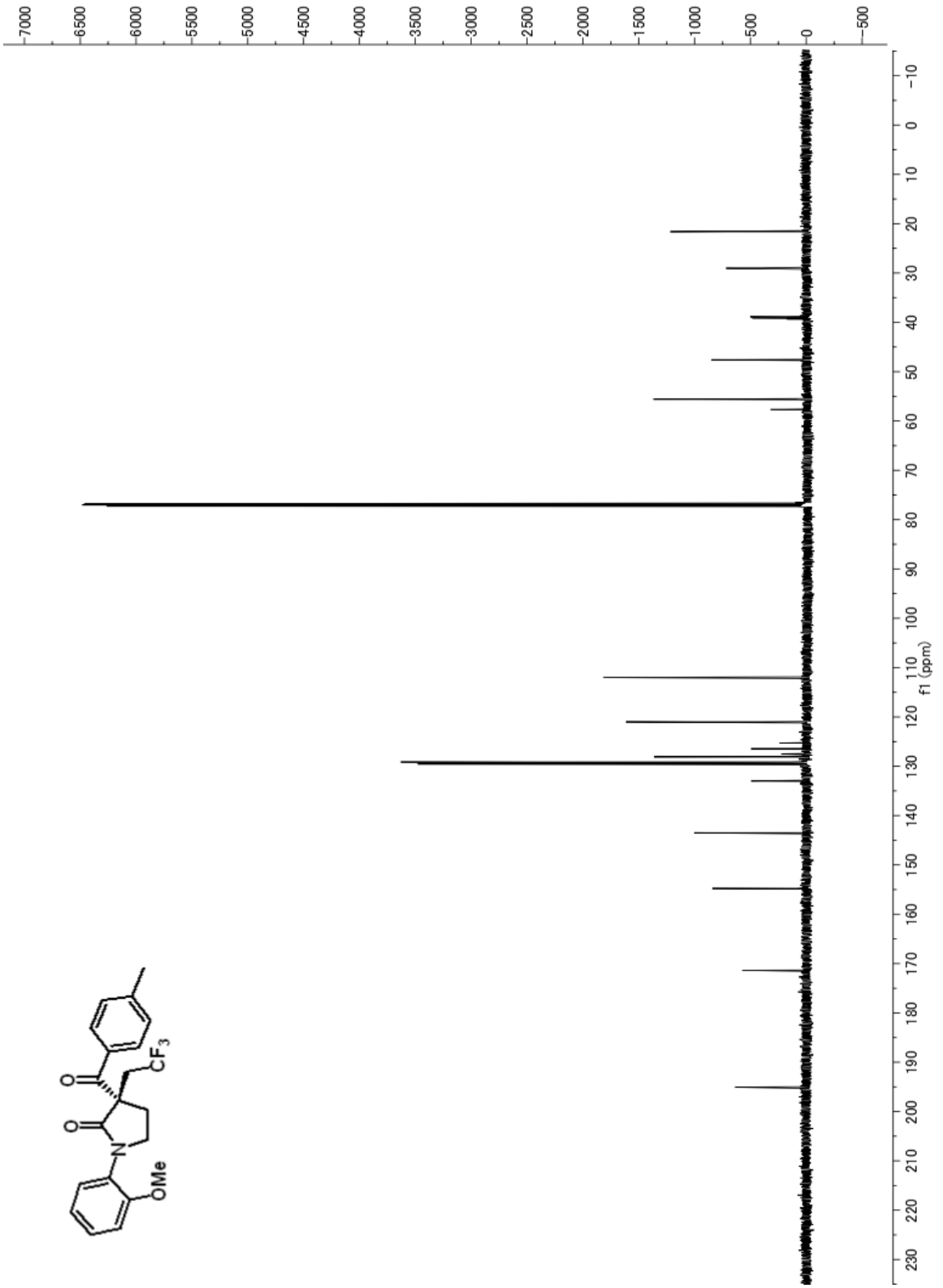


Figure A3.78. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **64f**.

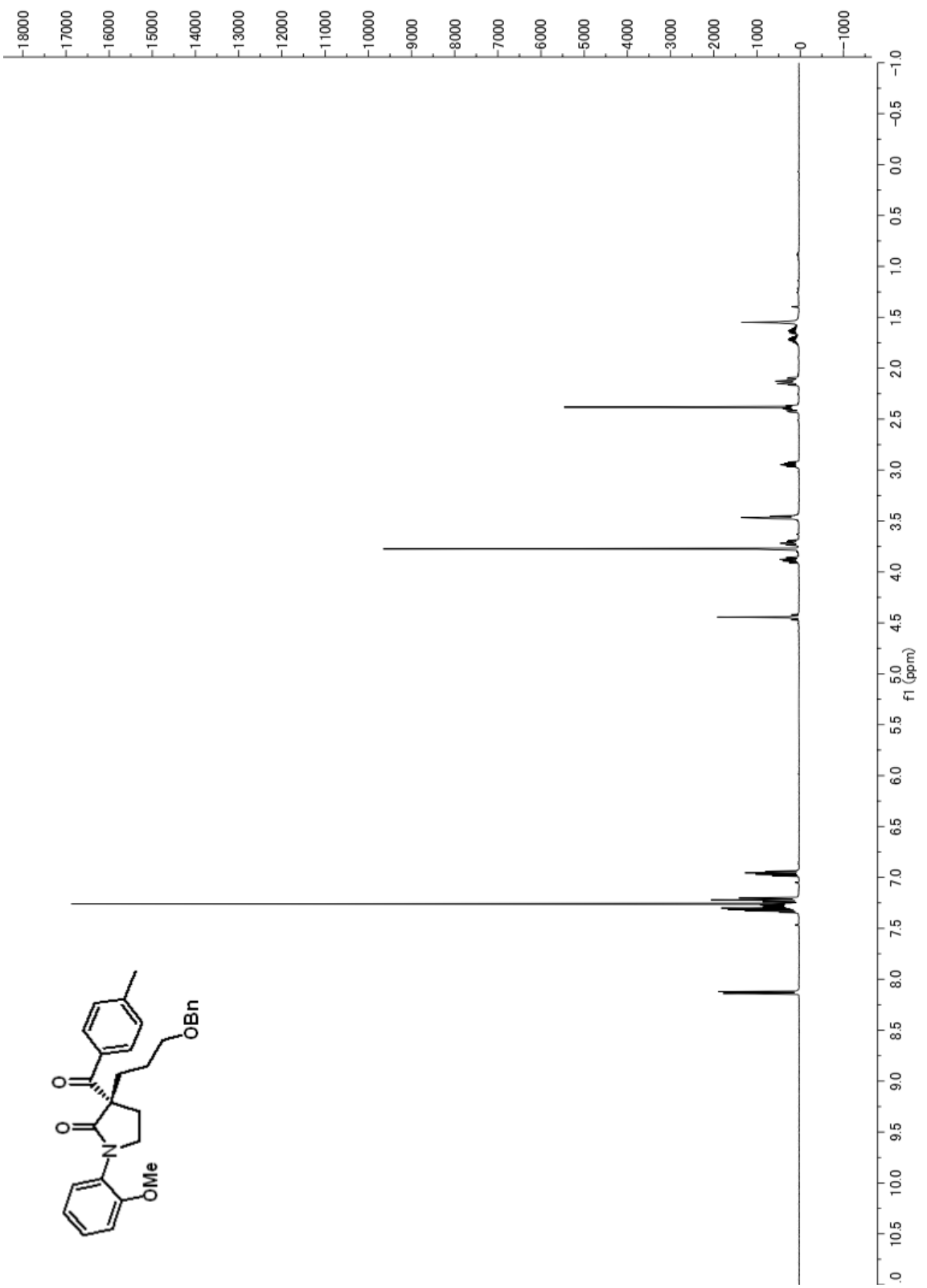


Figure A3.78. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **64g**.

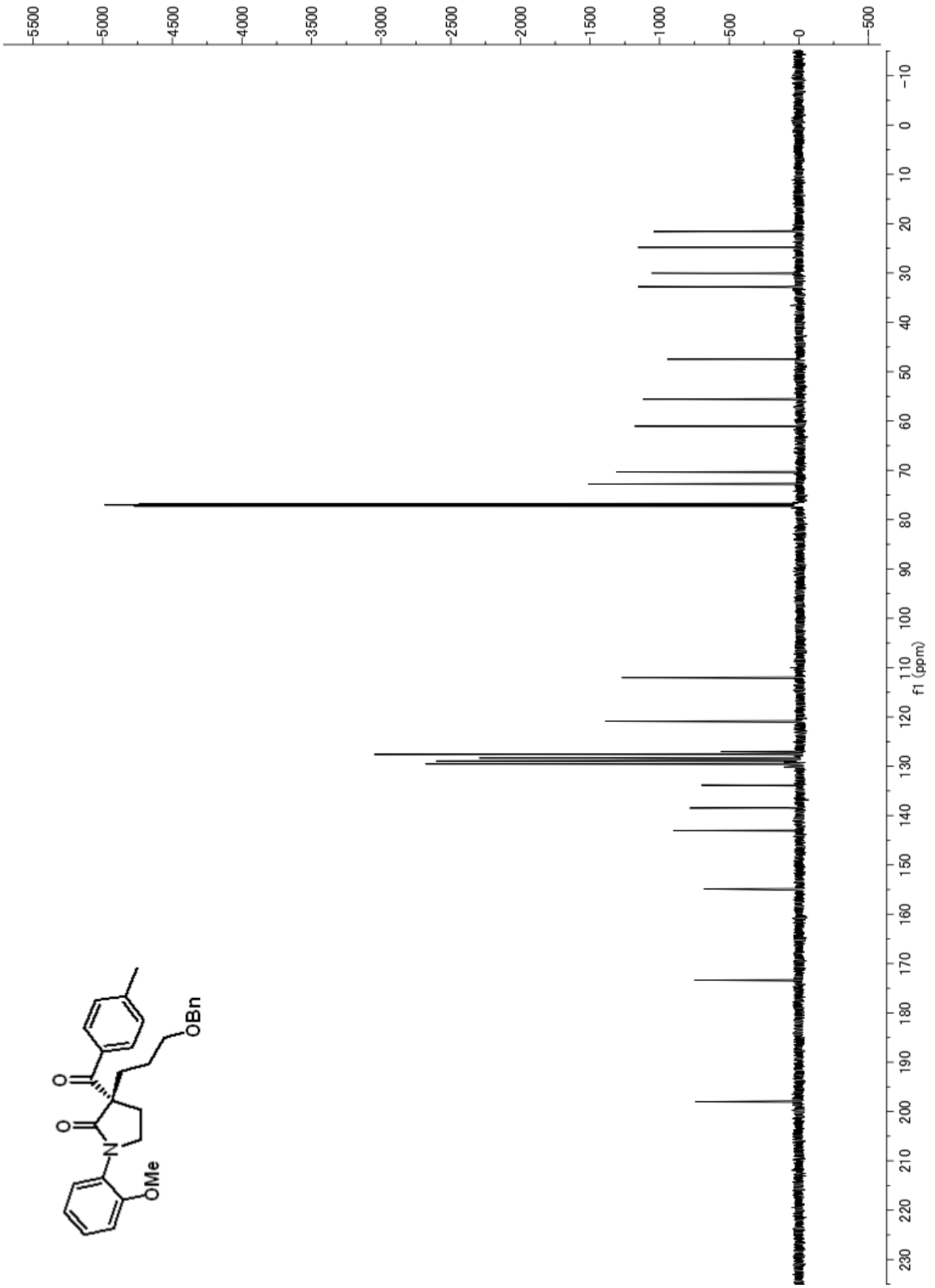


Figure A3.79. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **64g**.

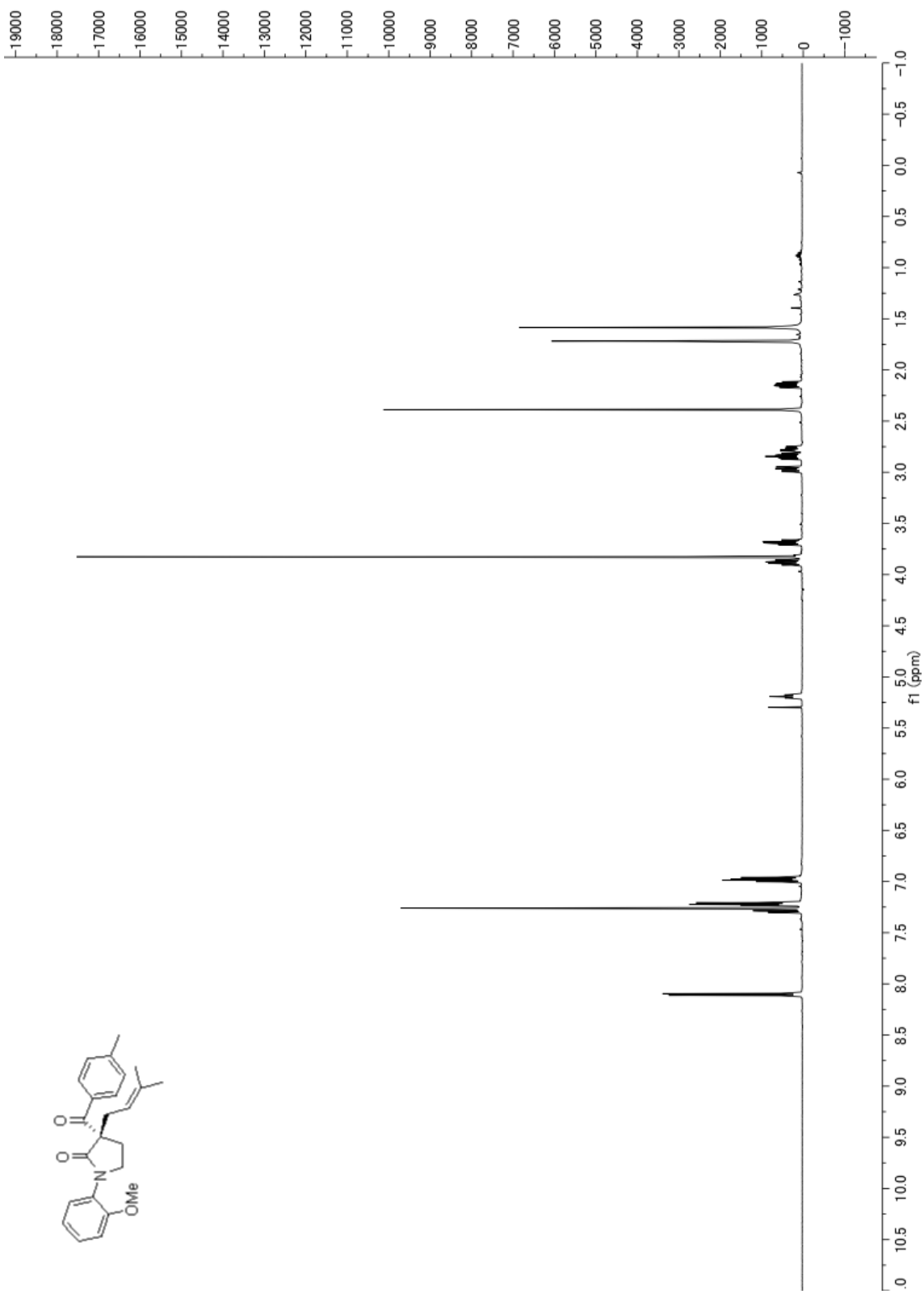


Figure A3.80. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **64h**.

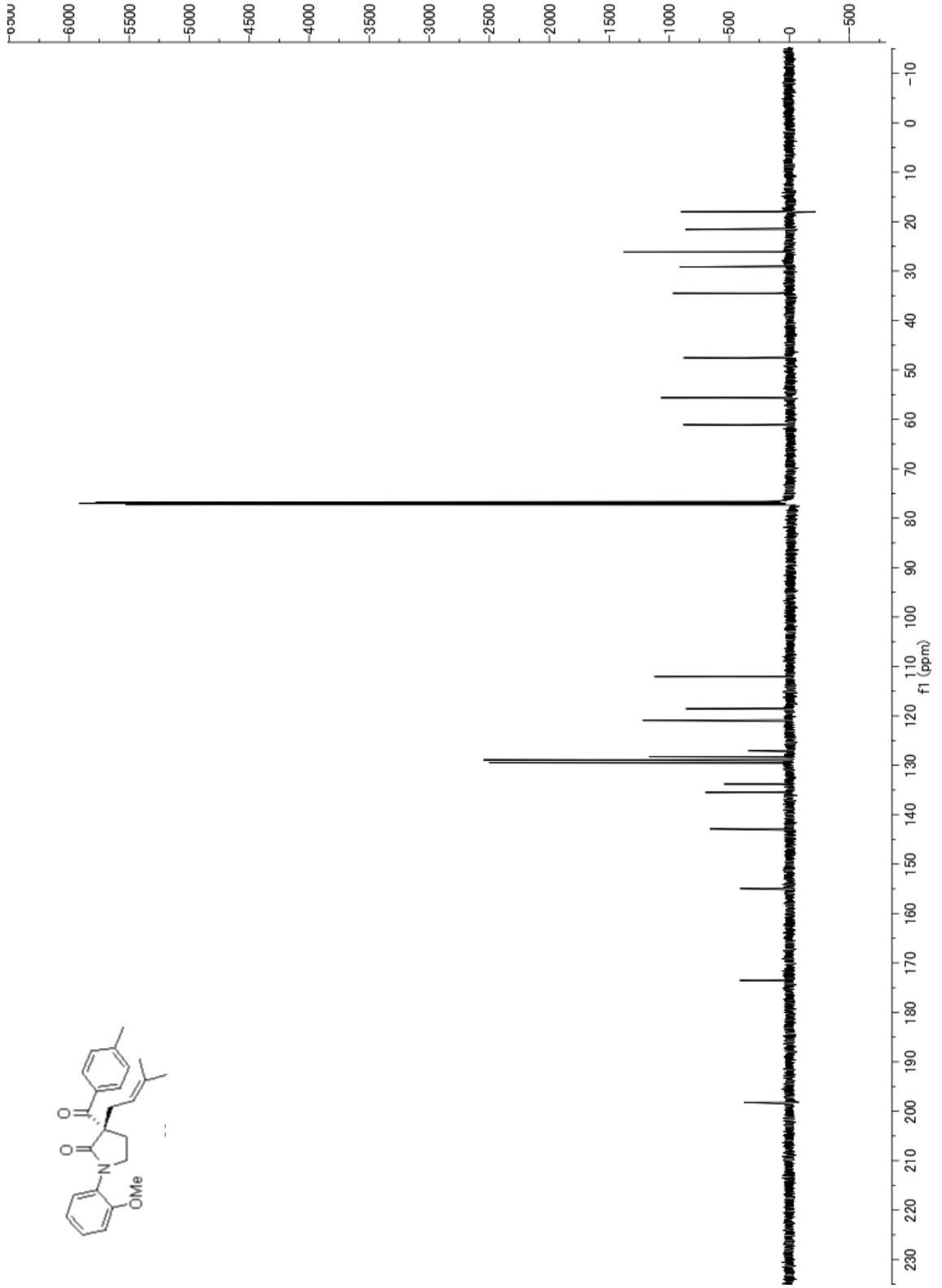


Figure A3.81. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **64h**.

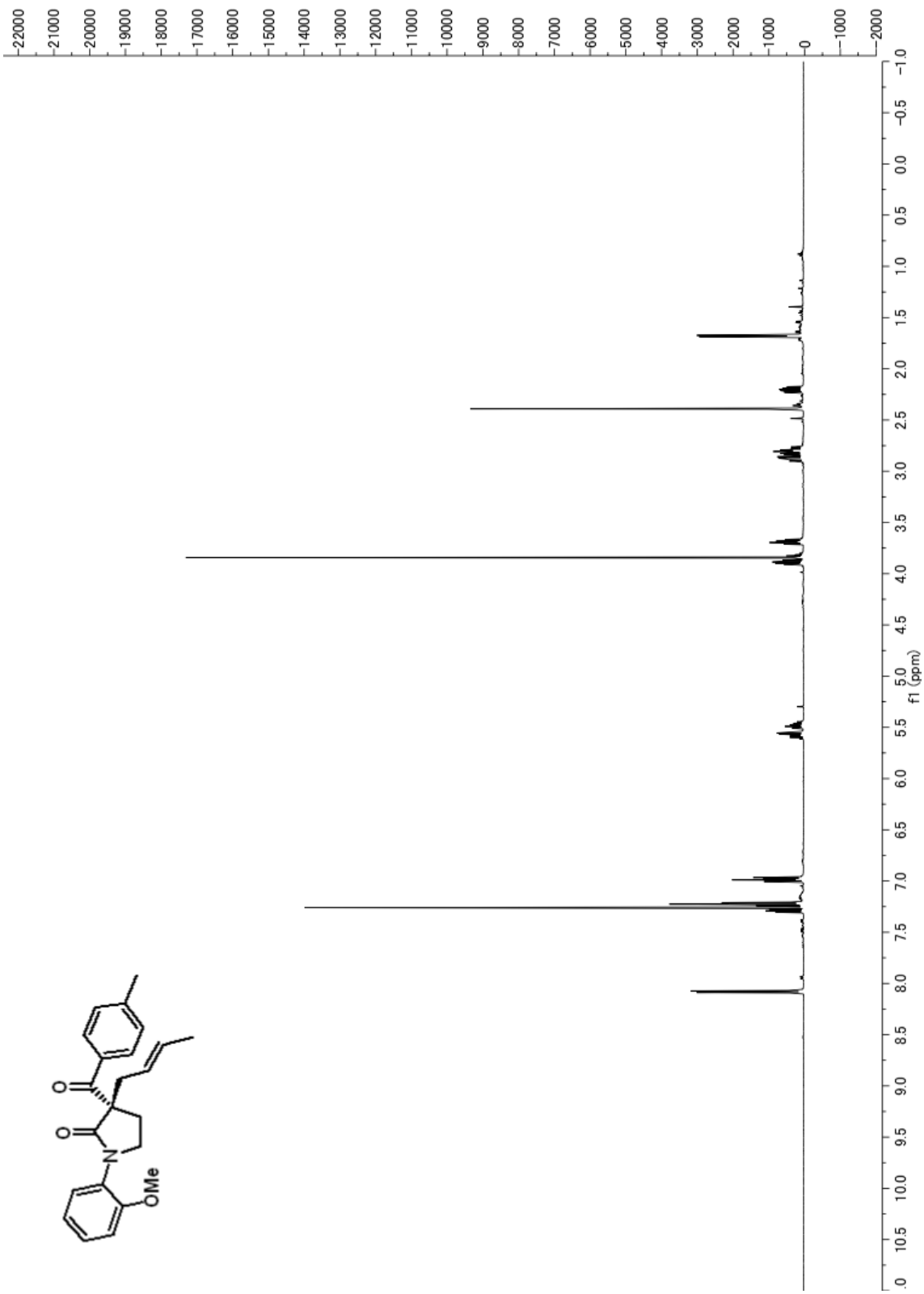


Figure A3.82. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **64i**.

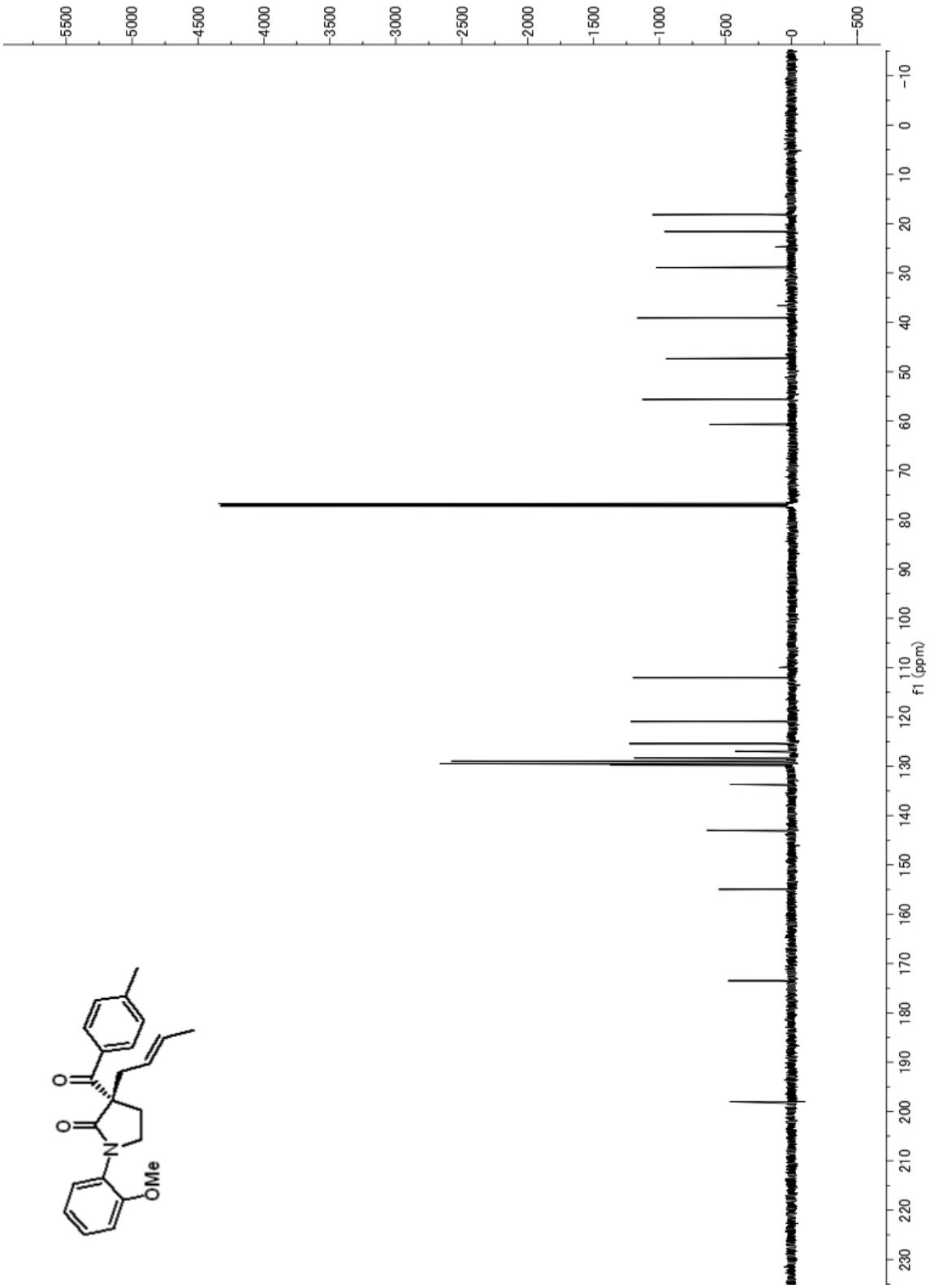


Figure A3.83. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **64i**.

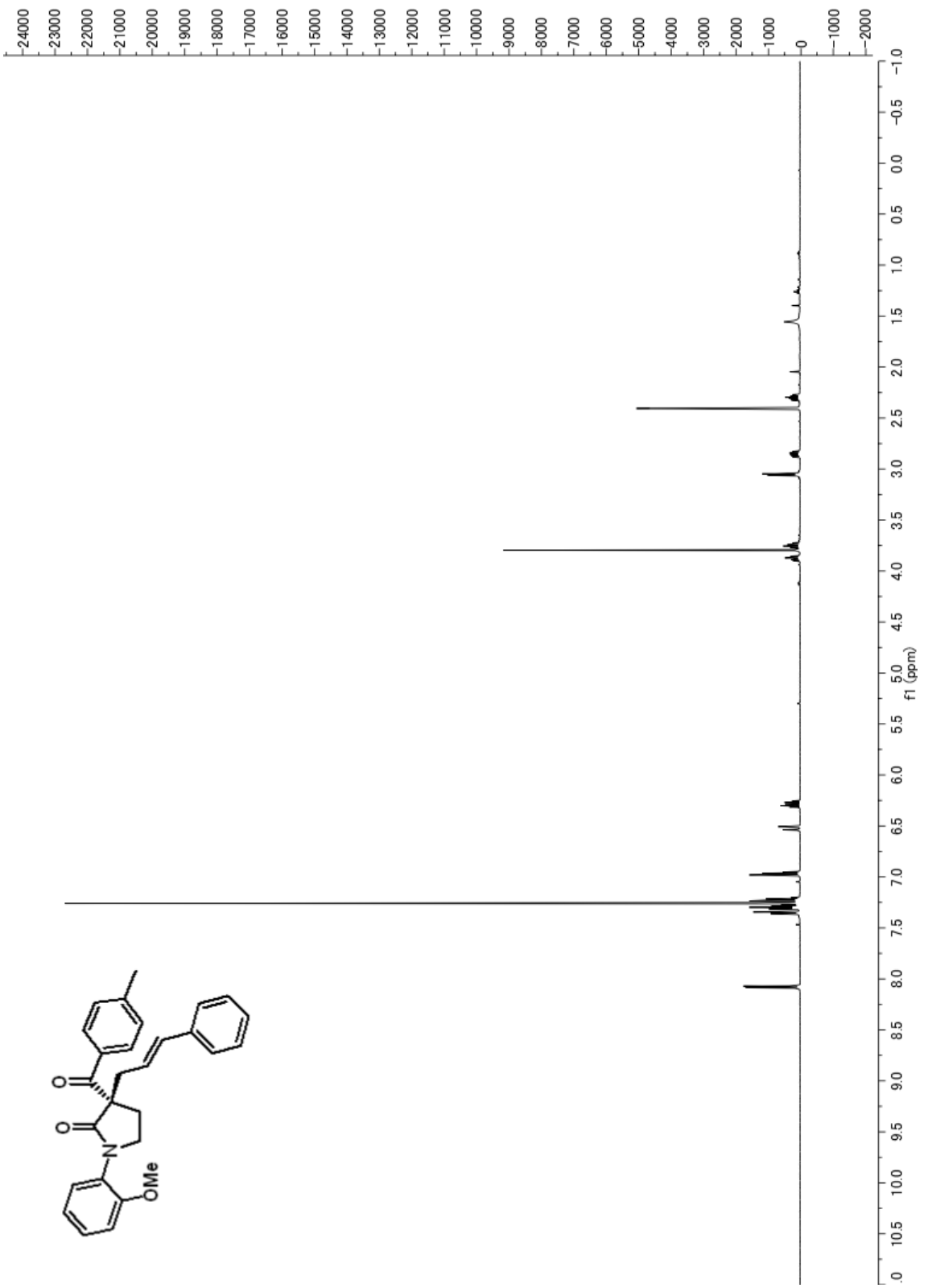


Figure A3.84. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **64j**.

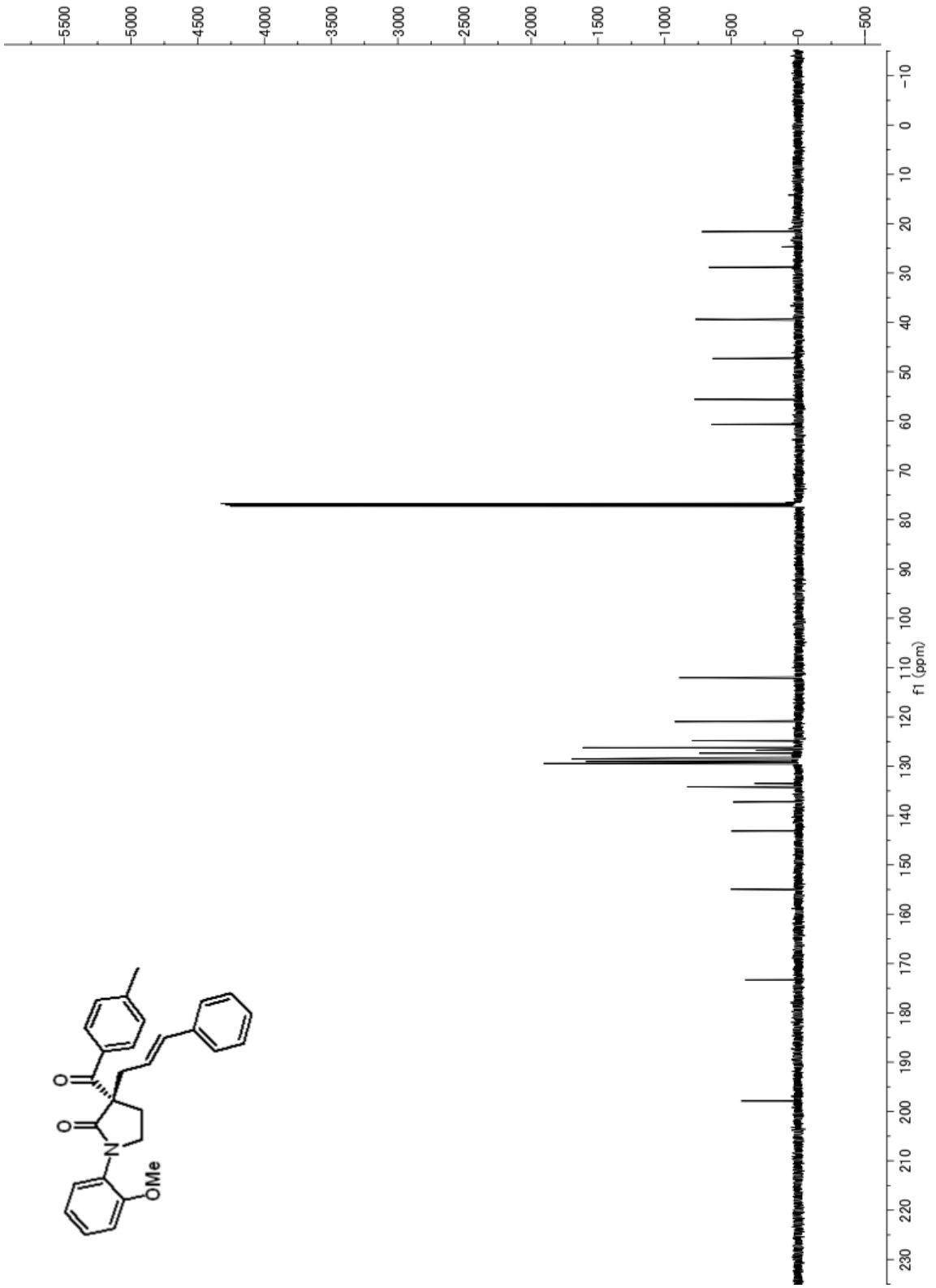


Figure A3.85. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **64j**.

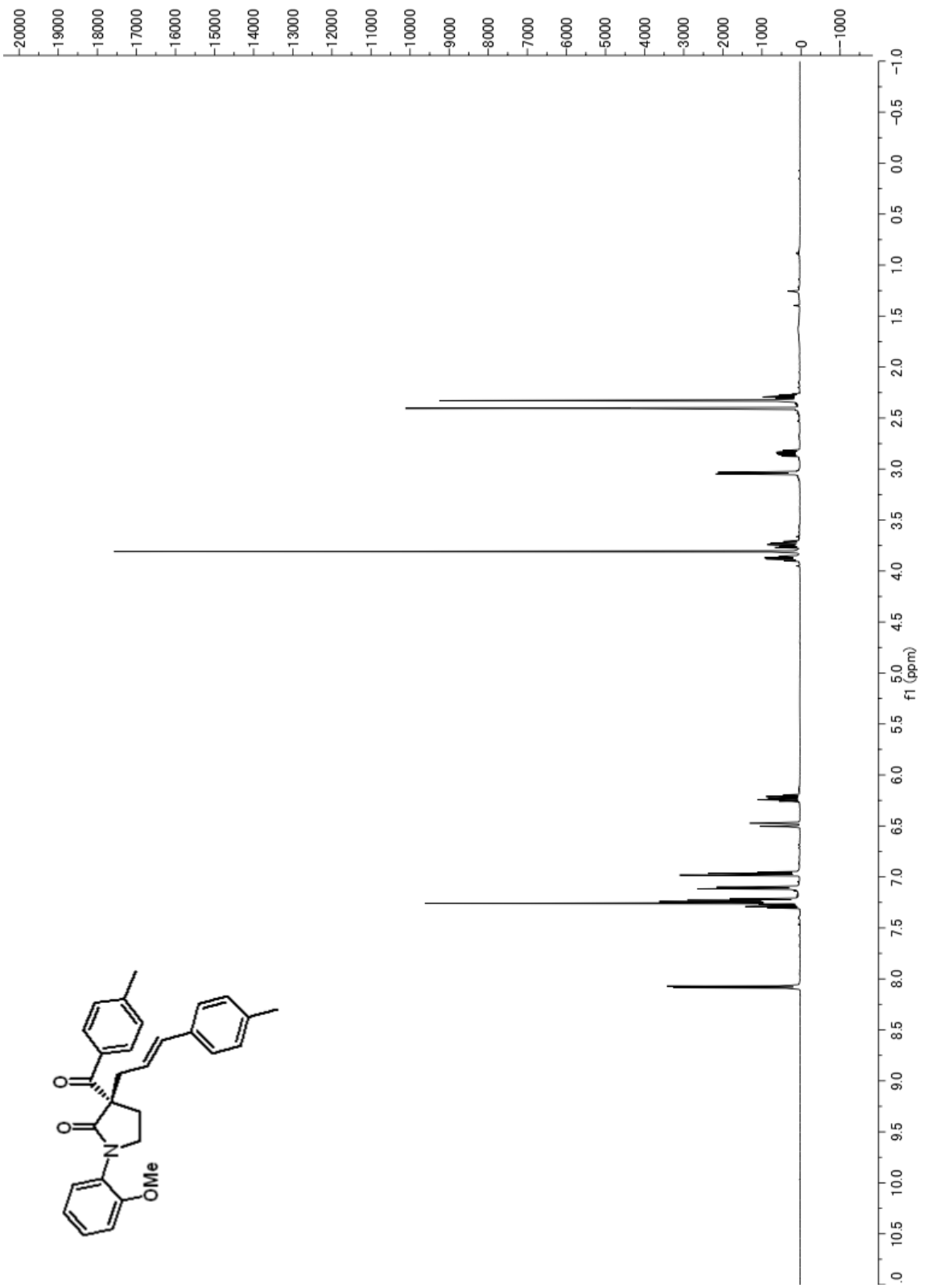


Figure A3.86. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **64k**.

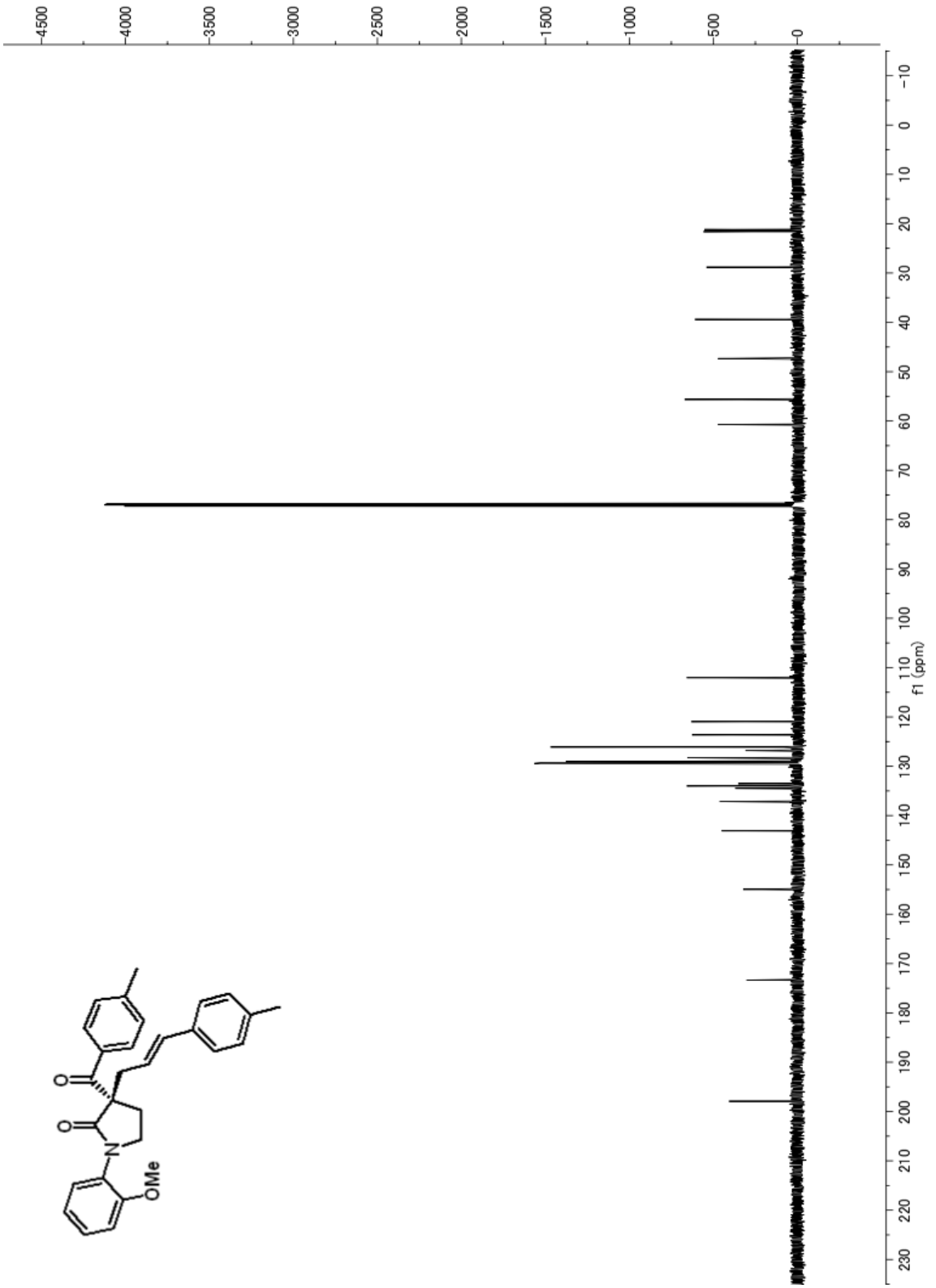


Figure A3.87. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **64k**.

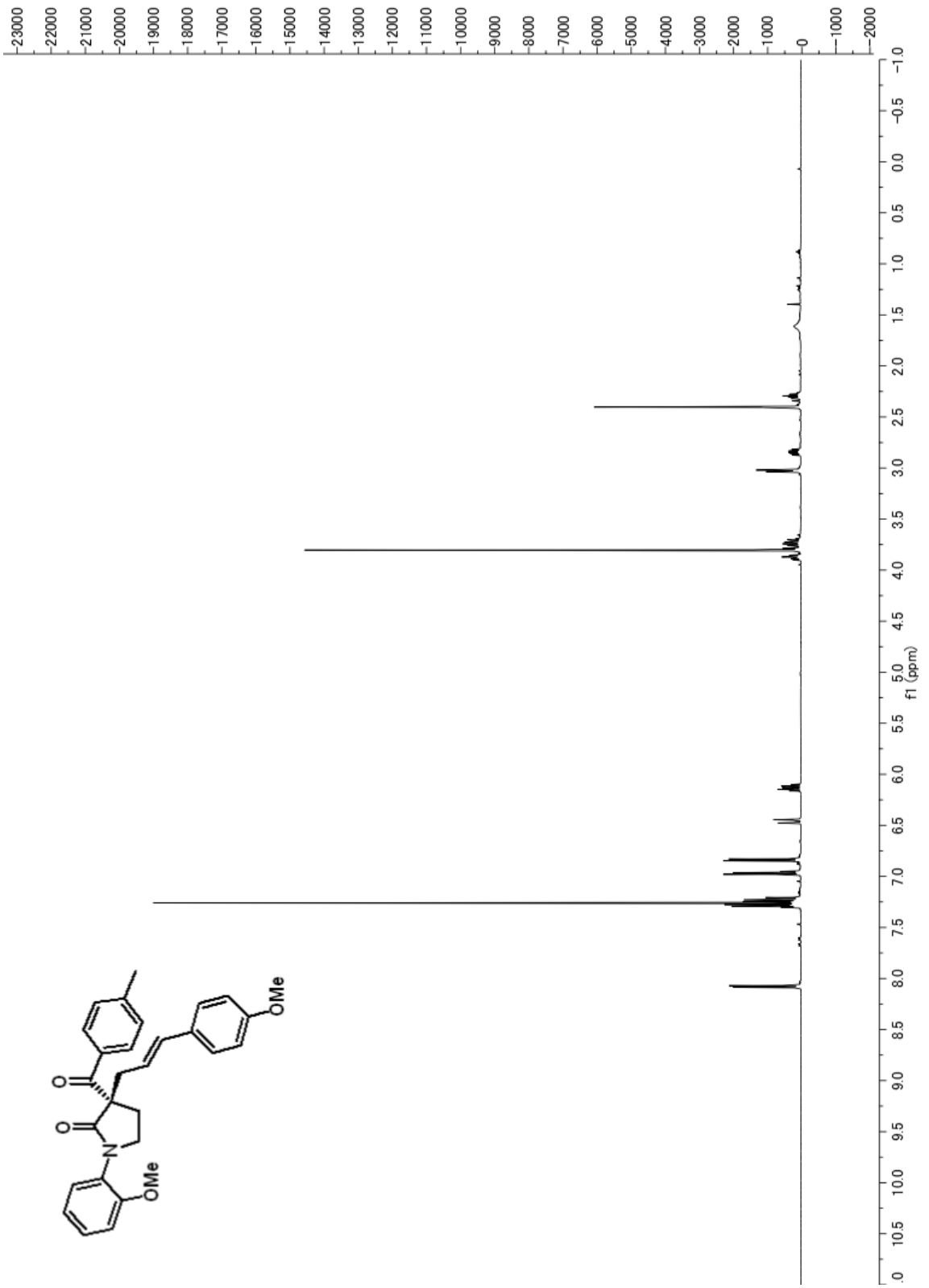


Figure A3.88. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **64l**.

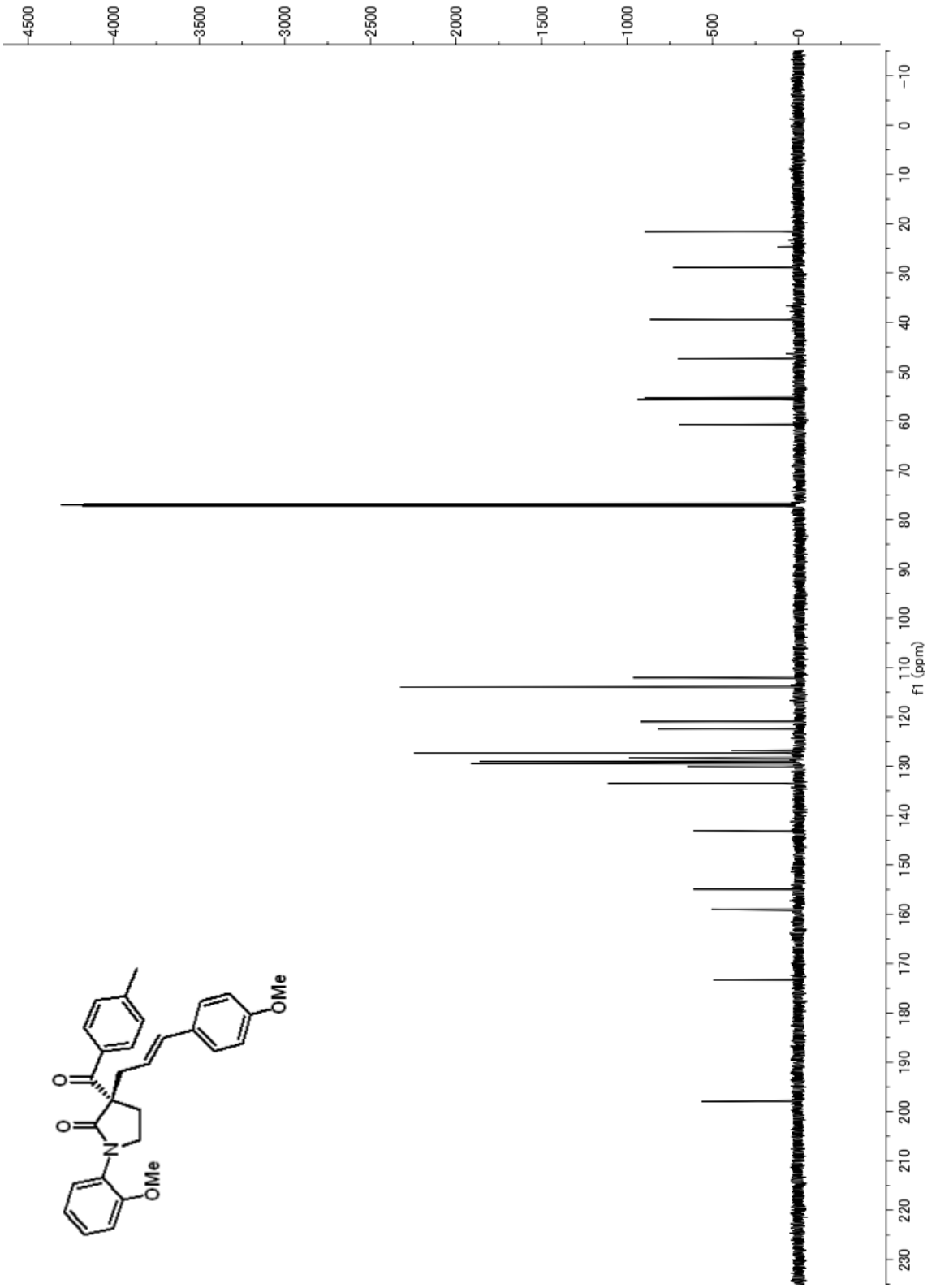


Figure A3.89. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **64l**.

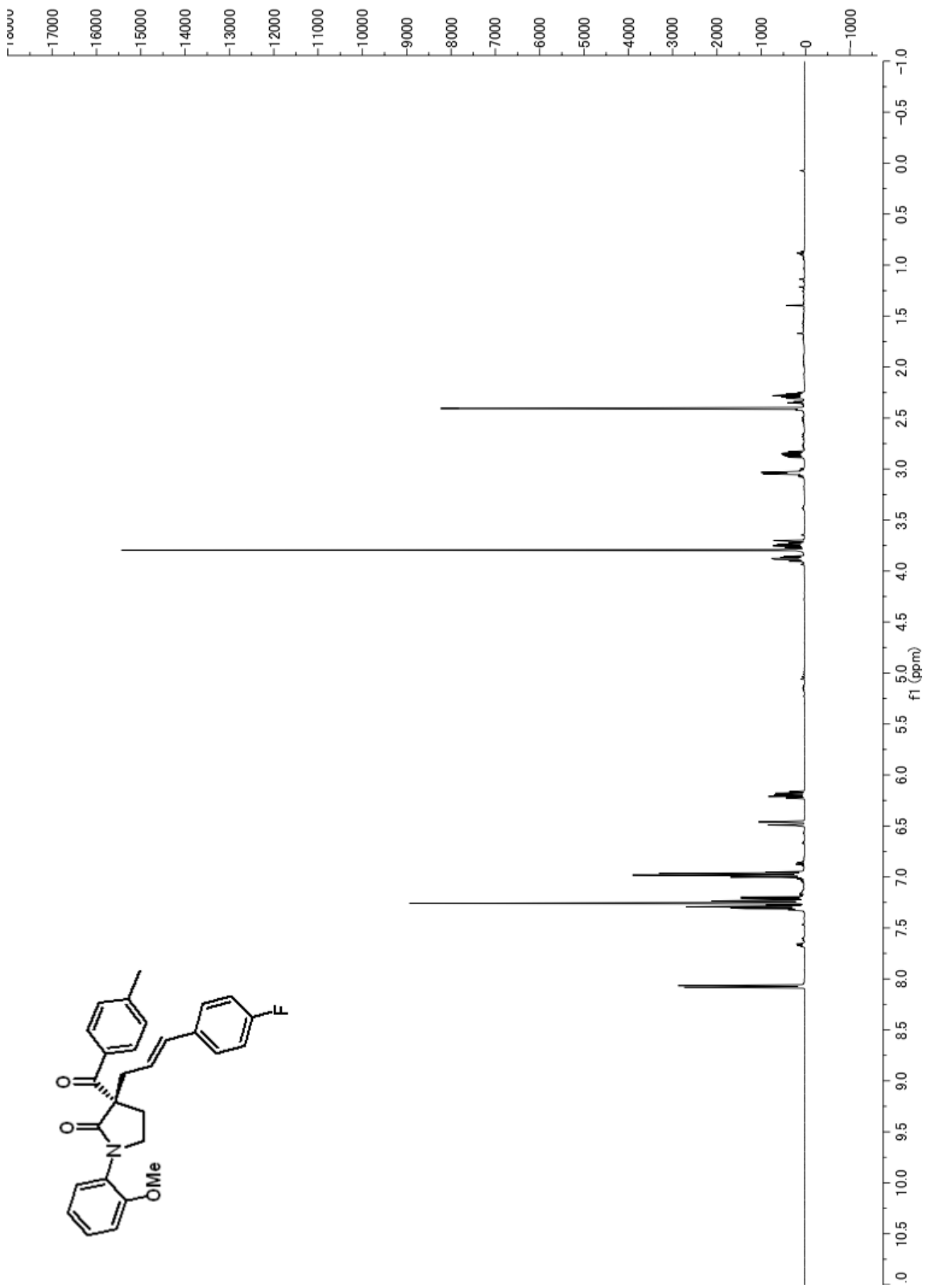


Figure A3.90. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **64m**.

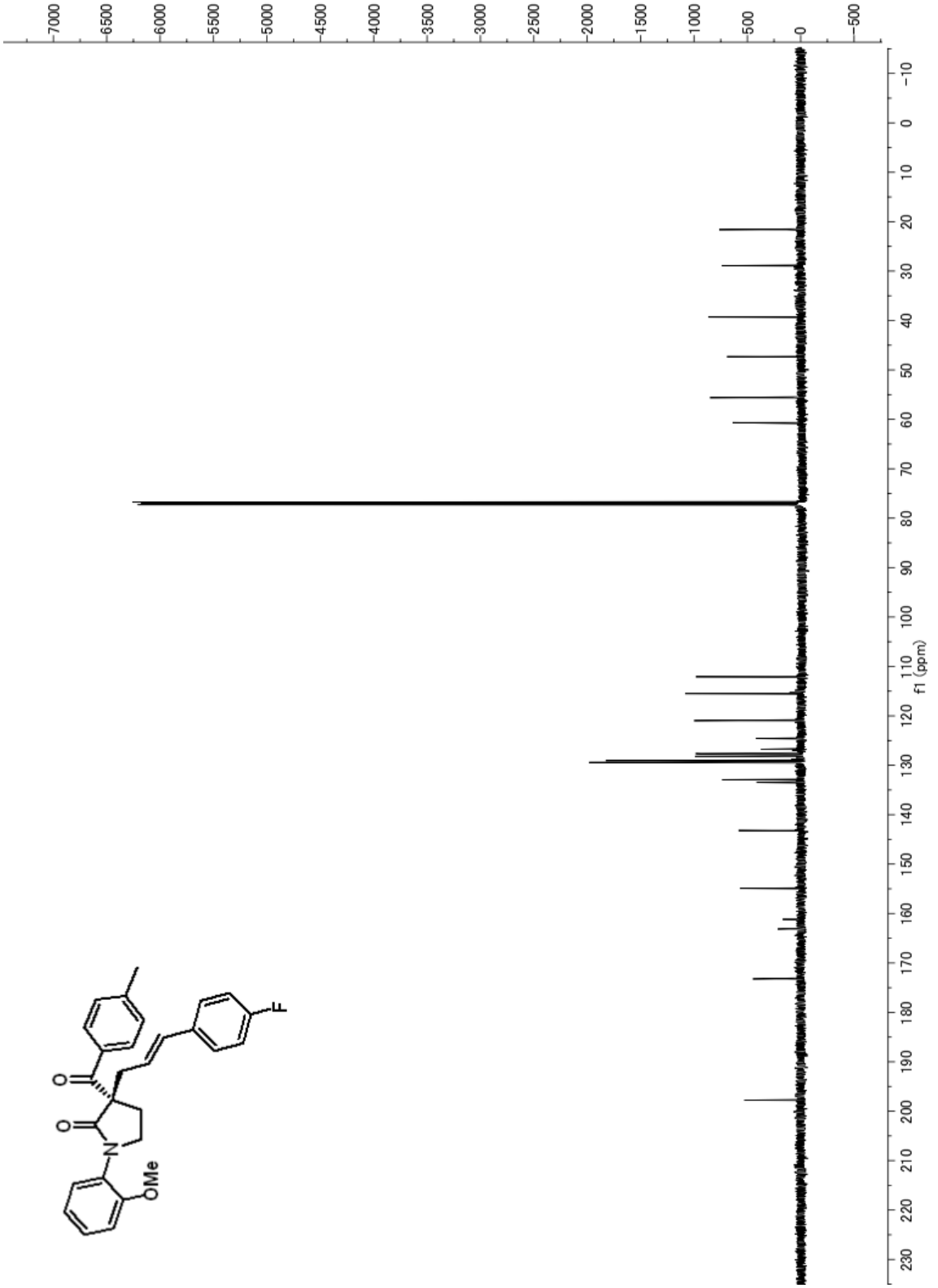


Figure A3.91. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **64m**.

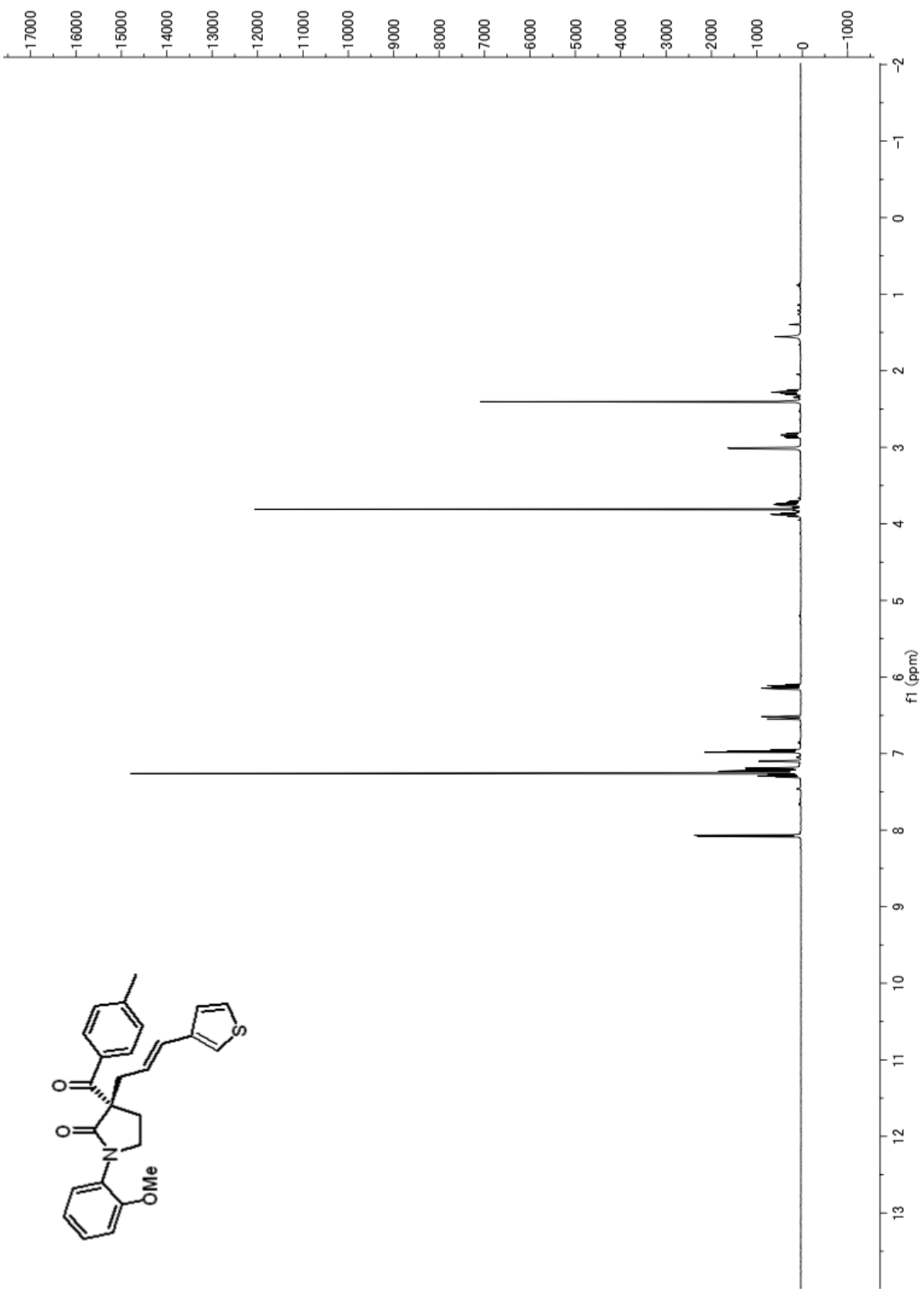


Figure A3.92. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **64n**.

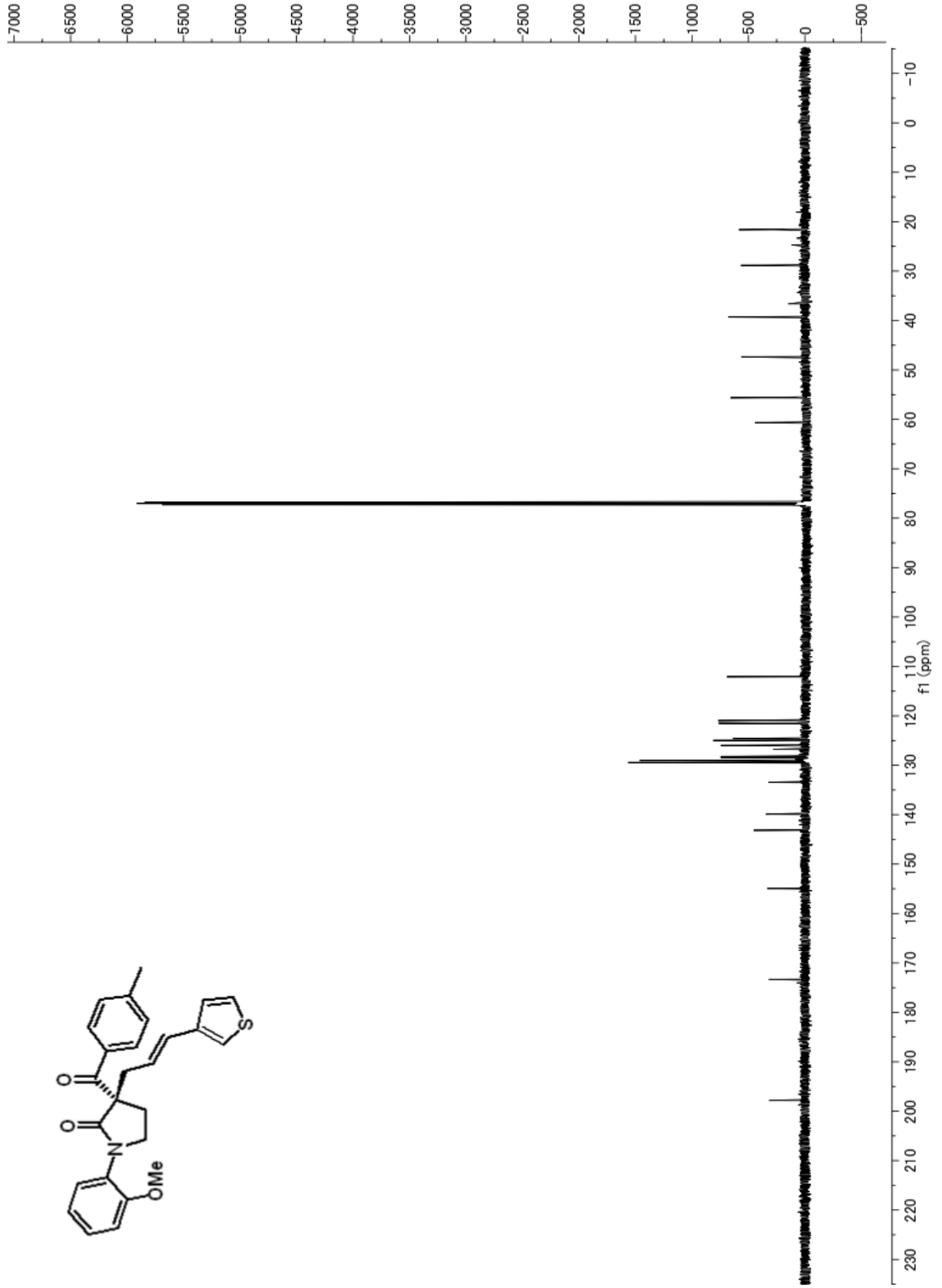


Figure A3.93. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **64n**.

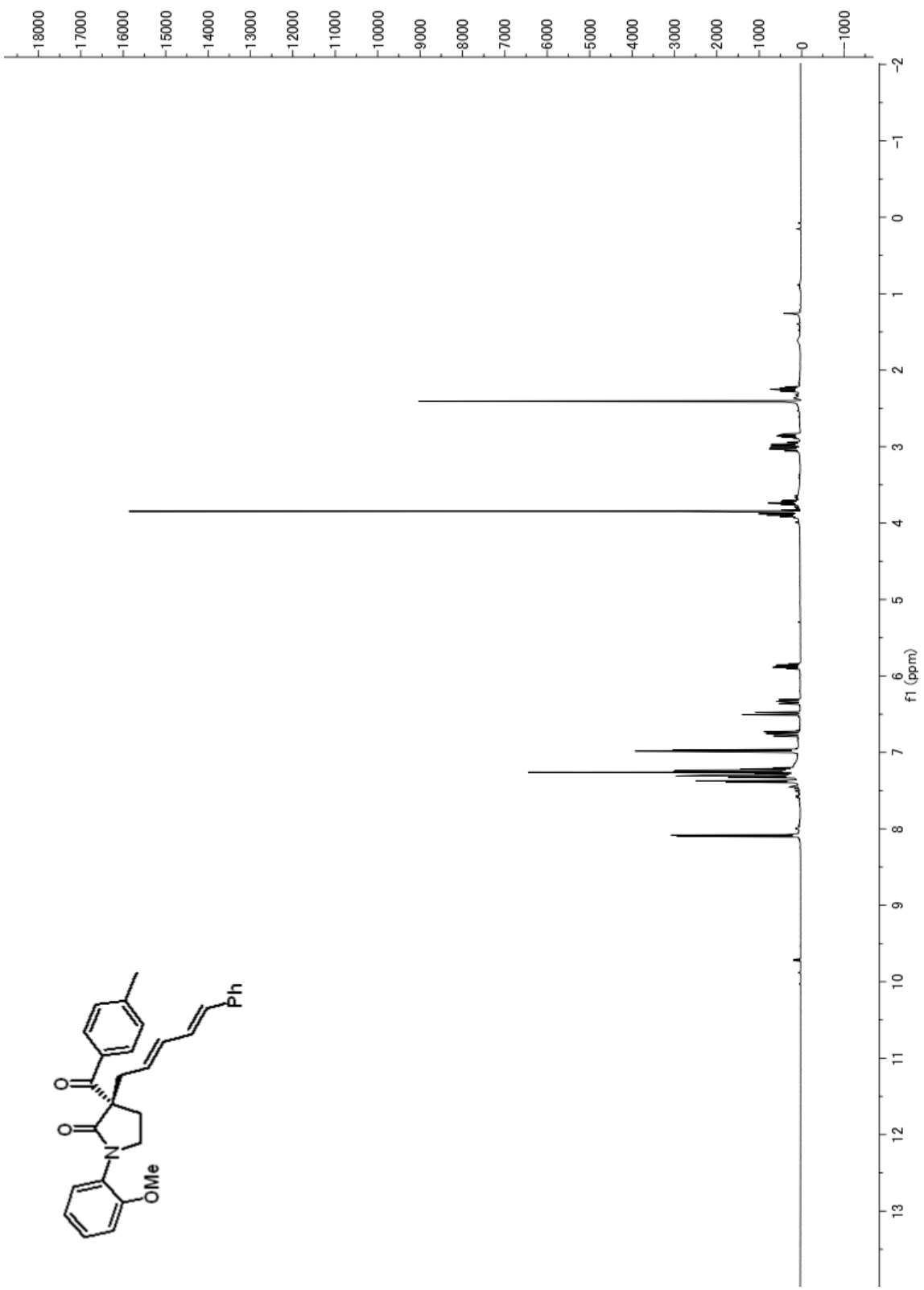


Figure A3.94. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **64o**.

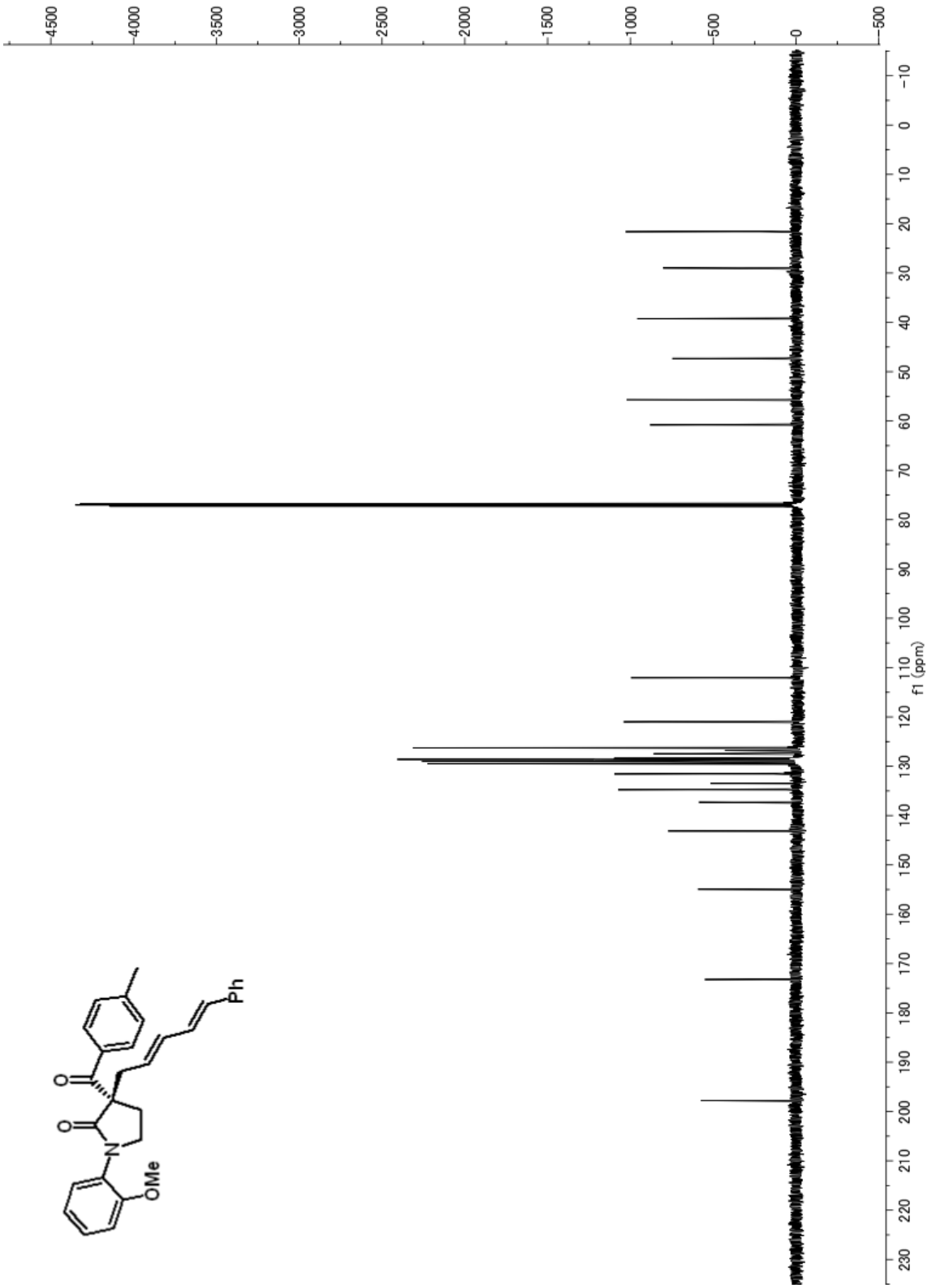


Figure A3.95. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **64o**.

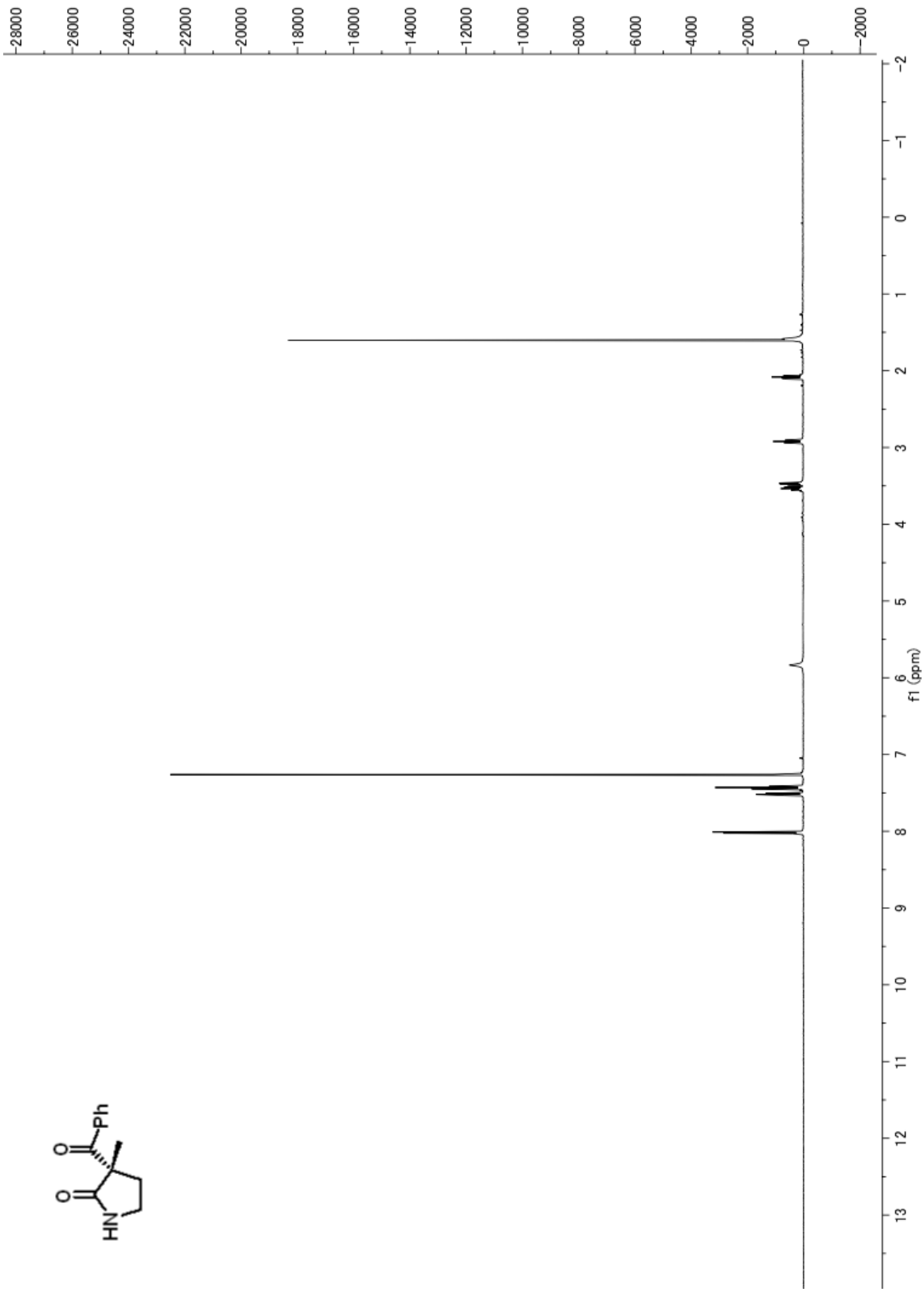


Figure A3.95. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **66**.

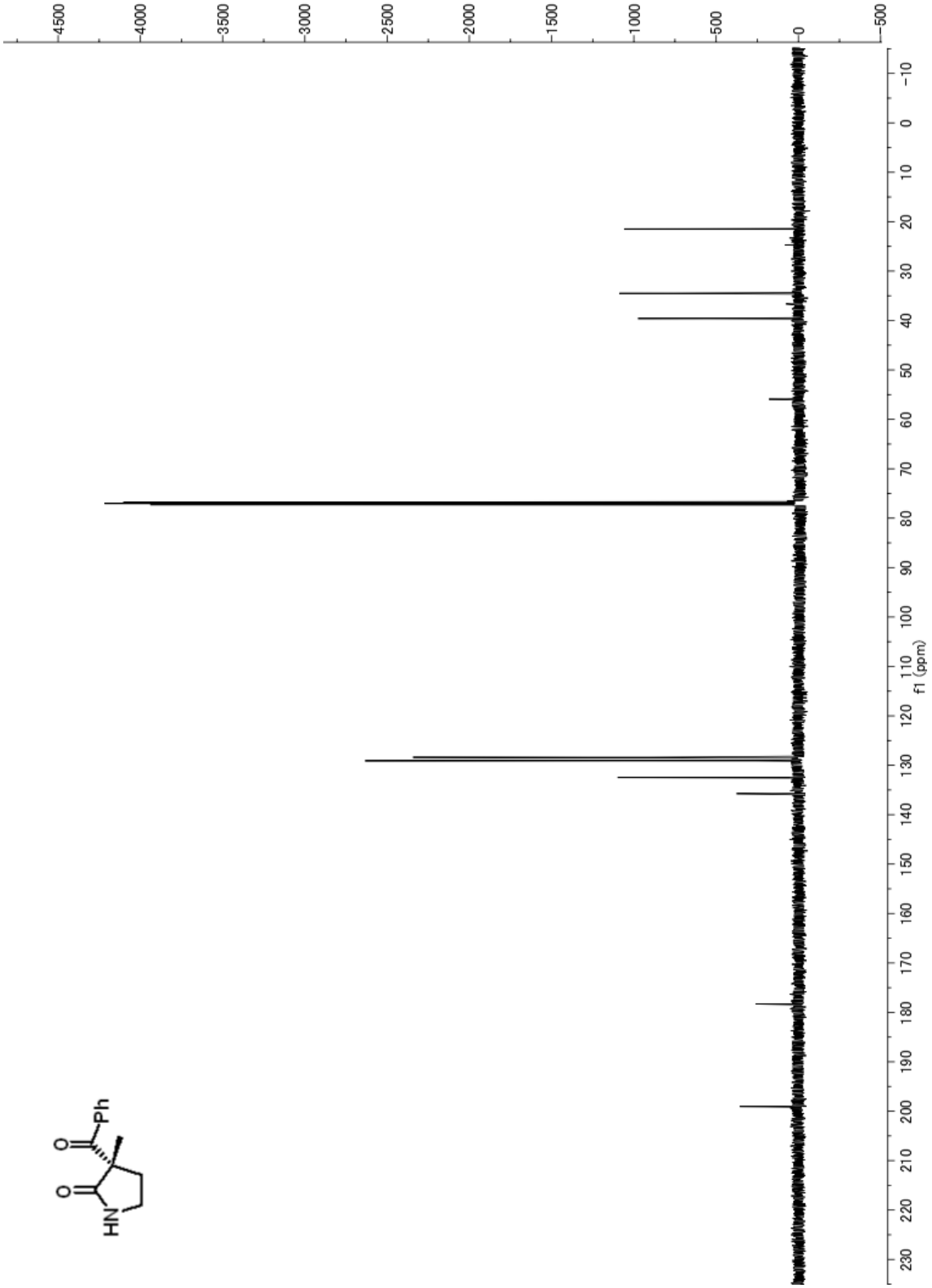


Figure A3.96. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **66**.

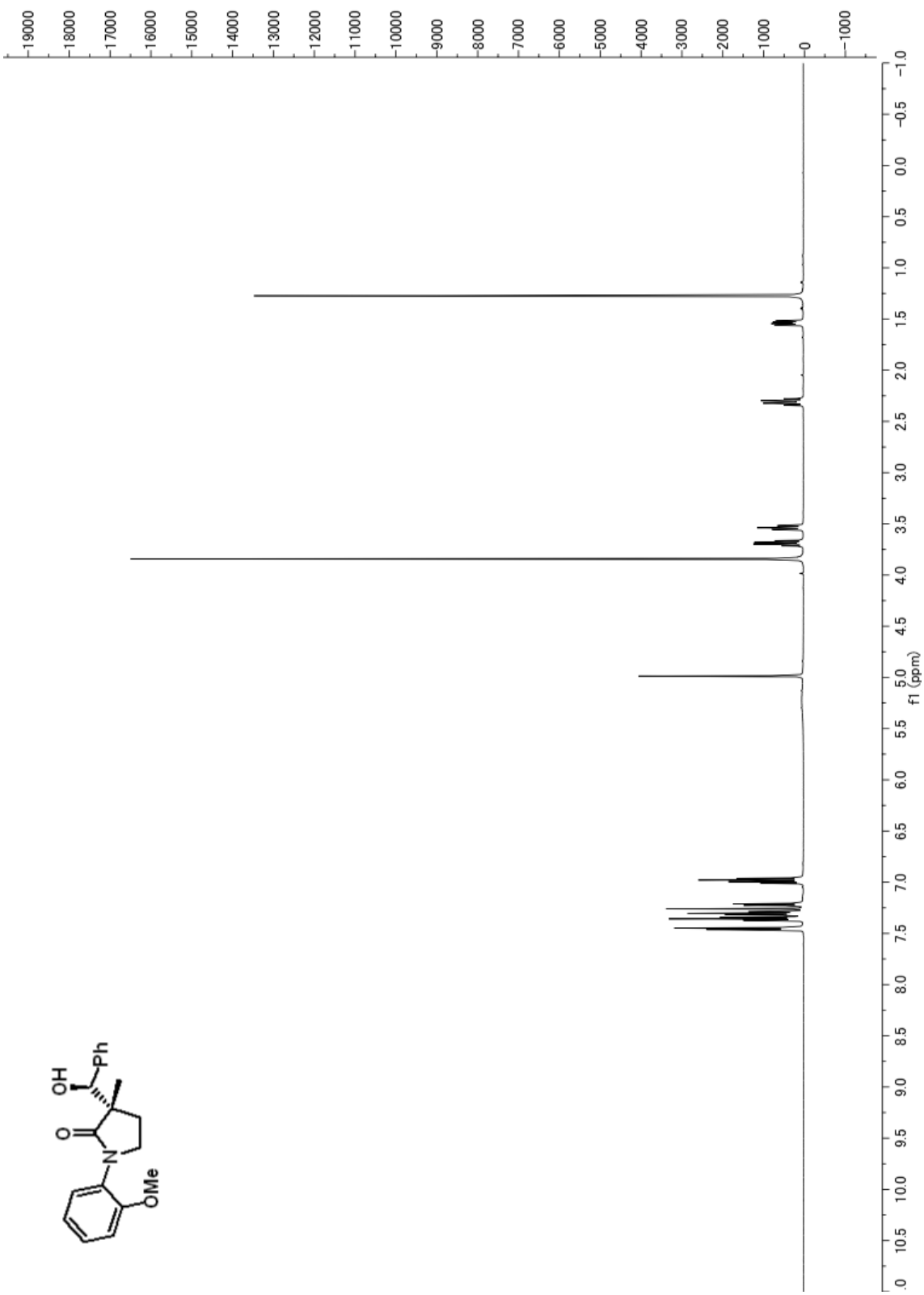


Figure A3.97. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **65**.

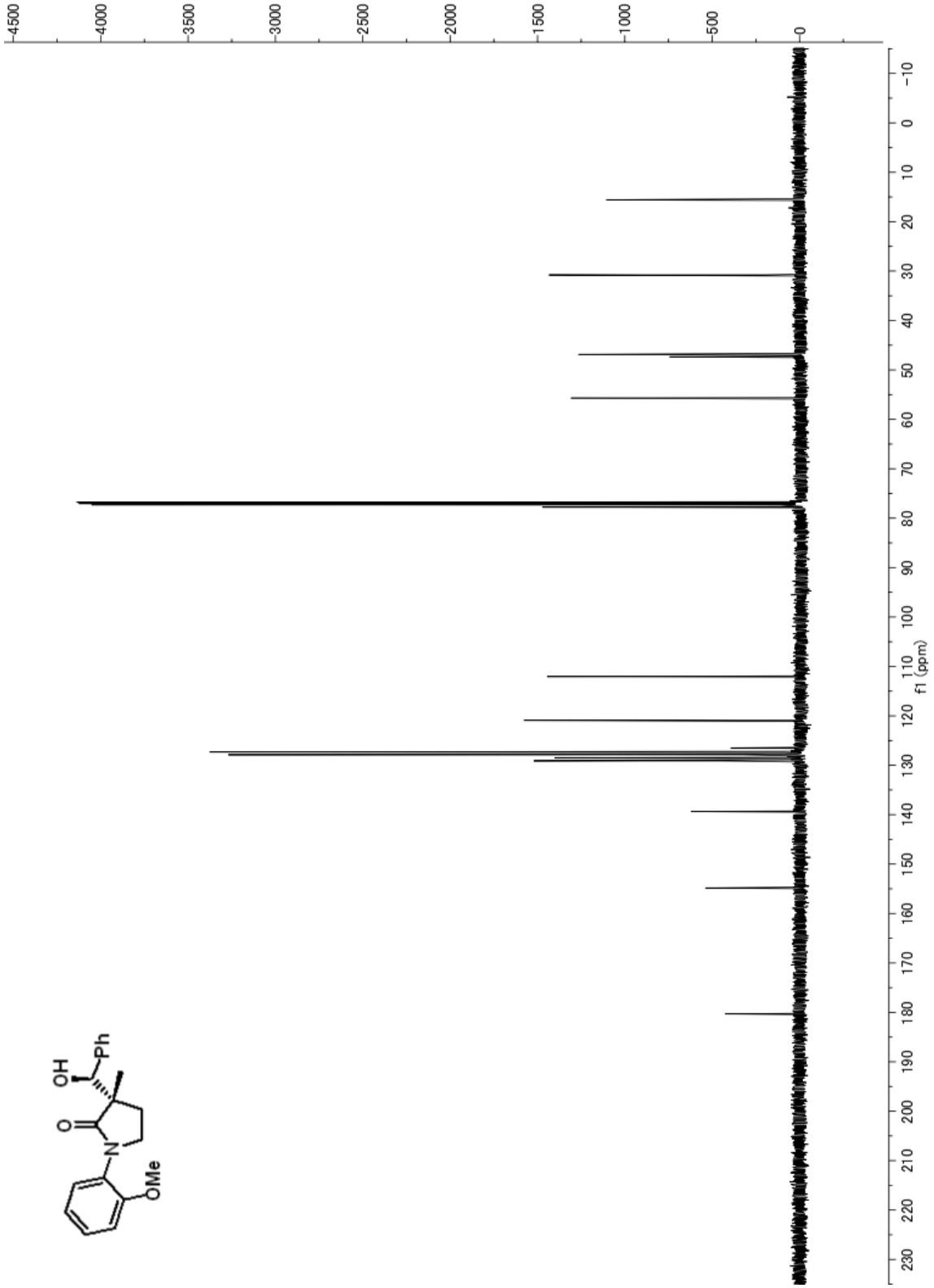


Figure A3.98. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **65**.

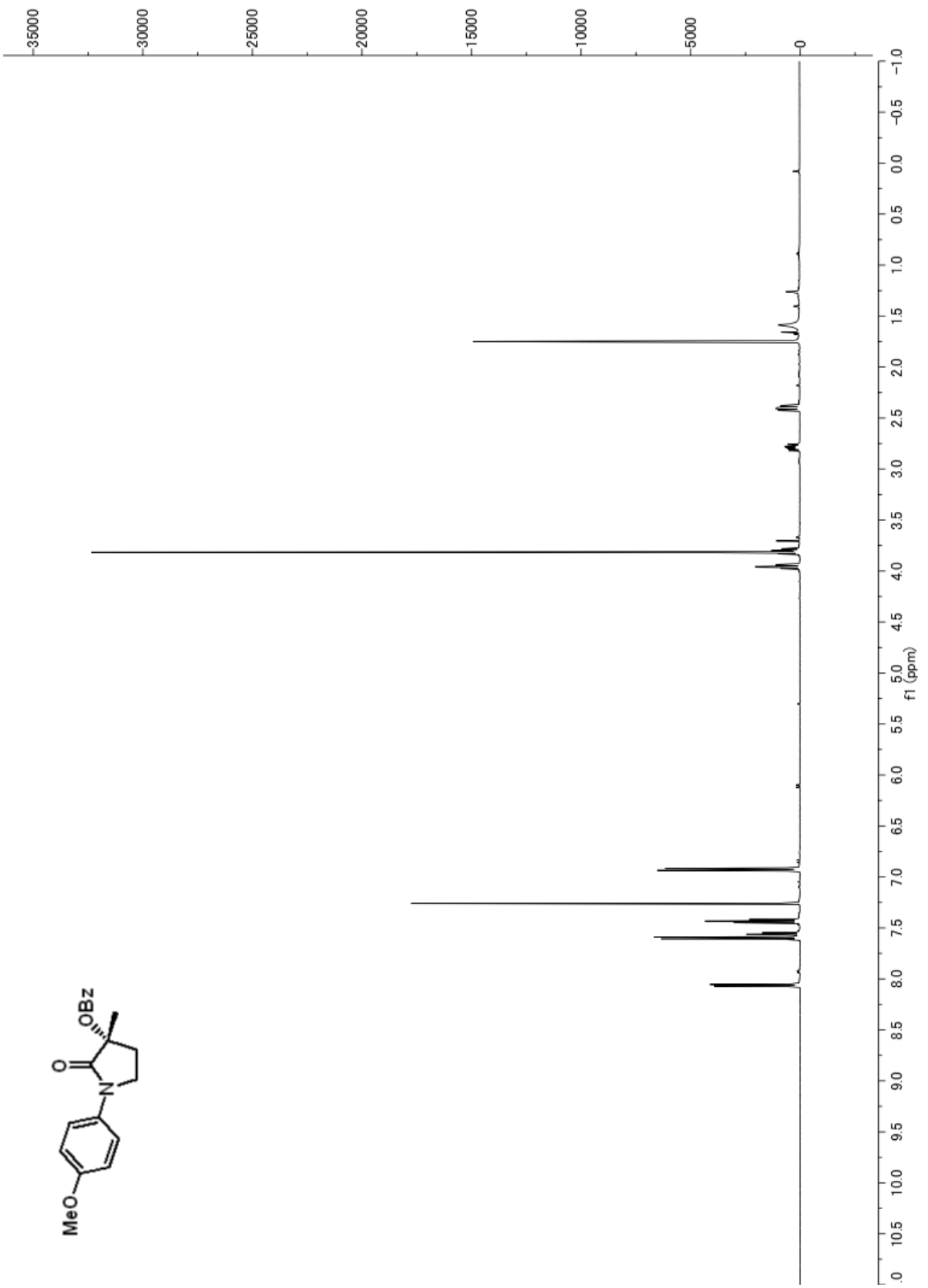


Figure A3.101. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **67**.

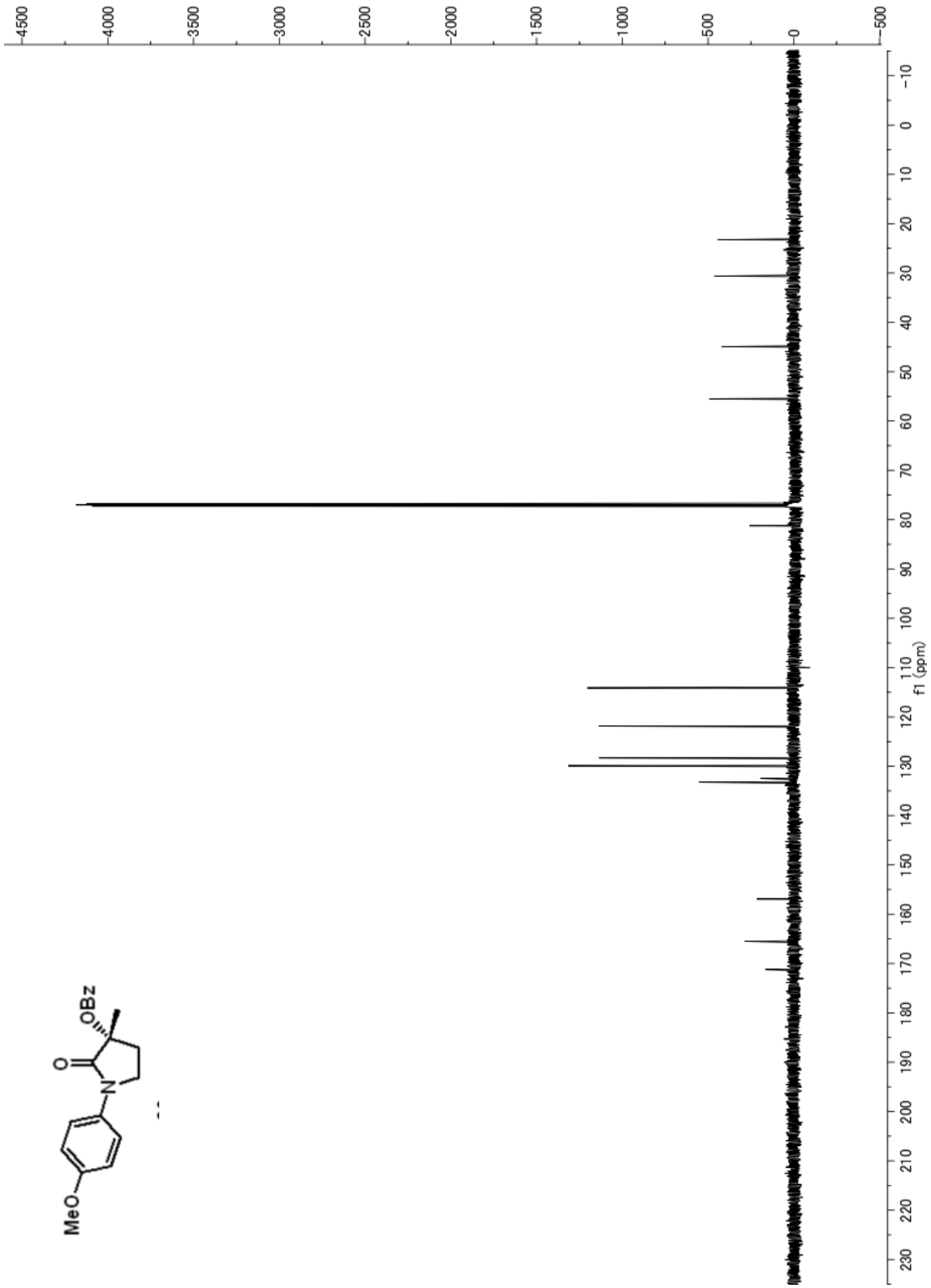


Figure A3.102. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **67**.

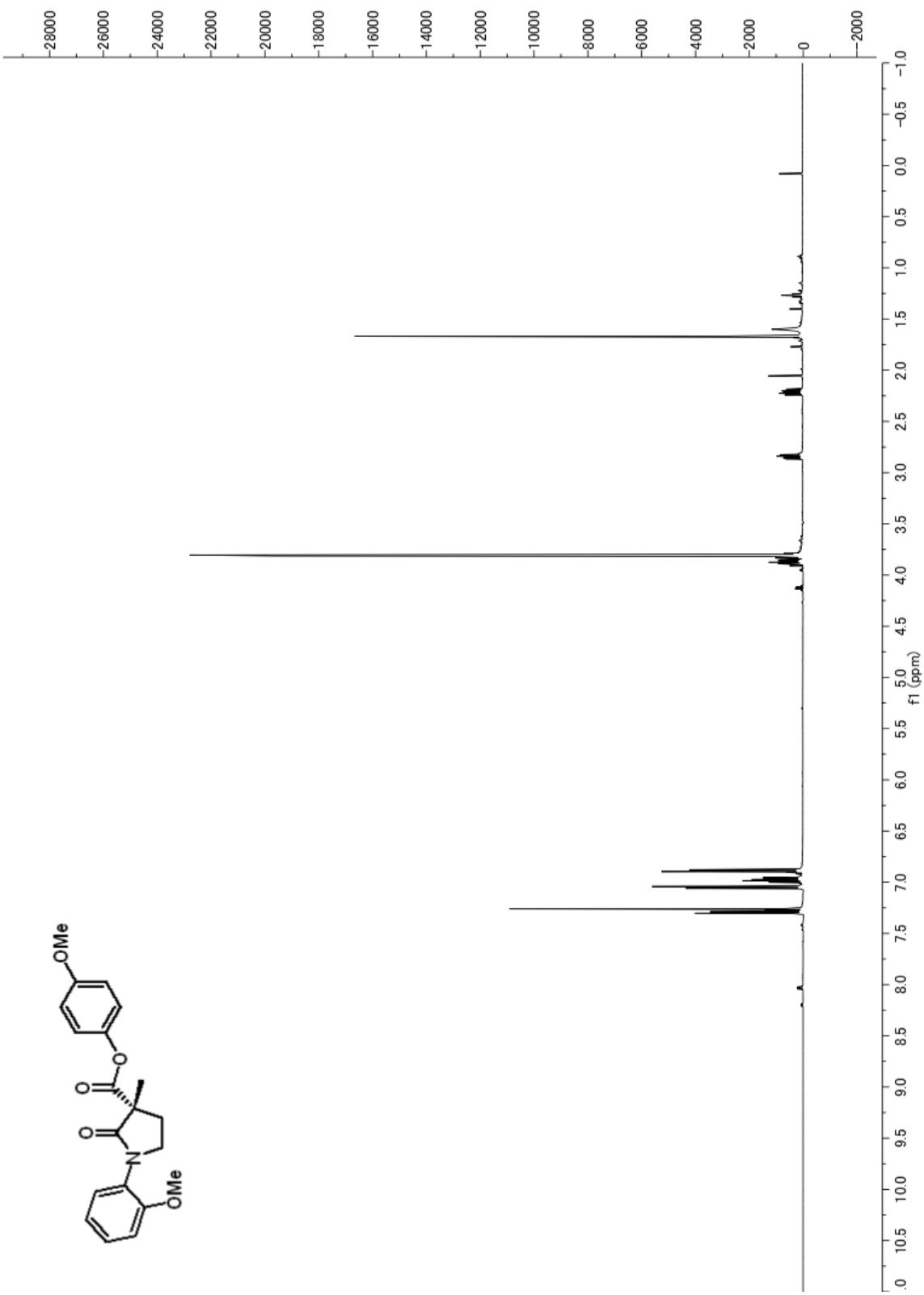


Figure A3.103. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **69**.

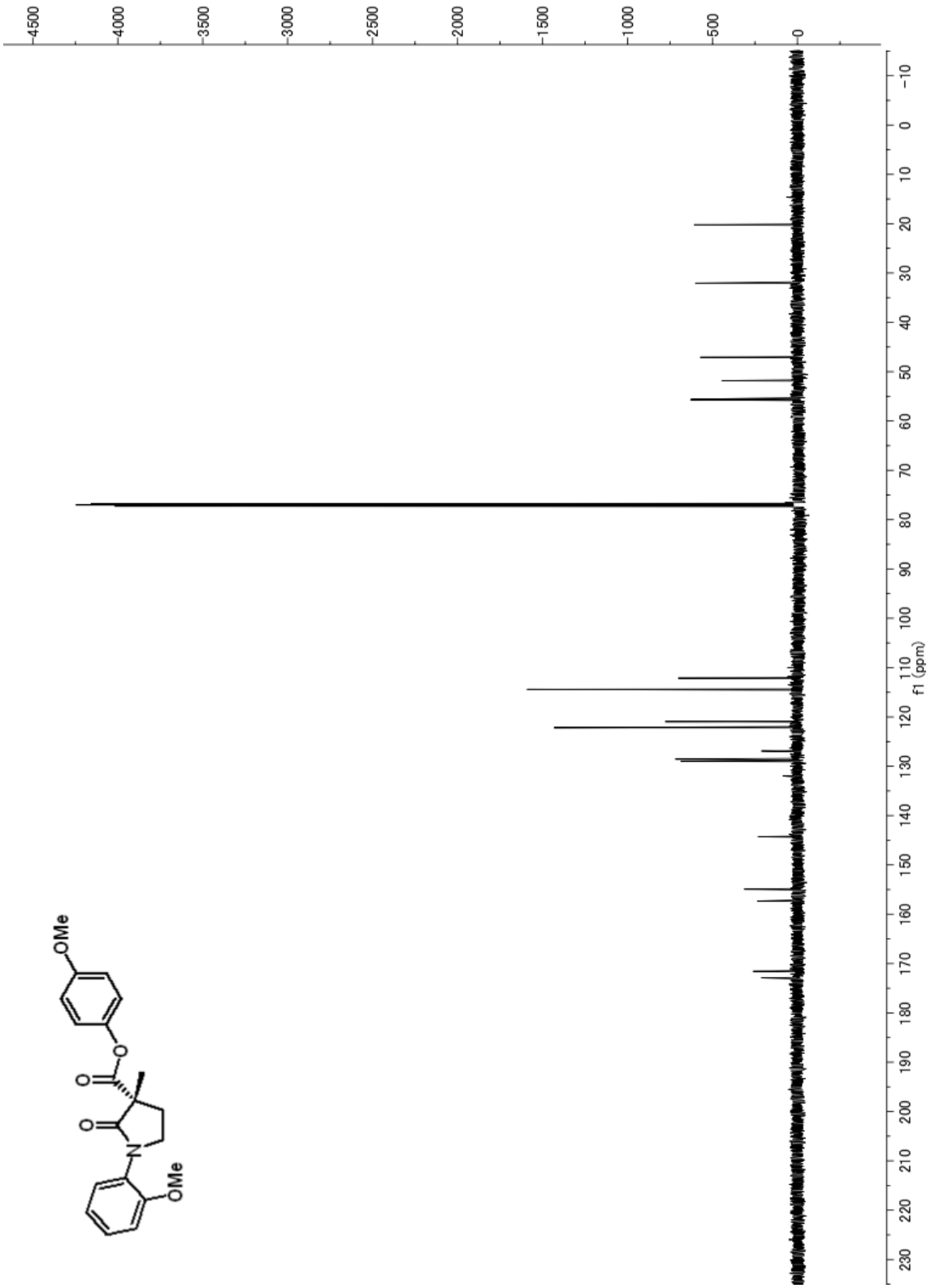


Figure A3.104. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **69**.

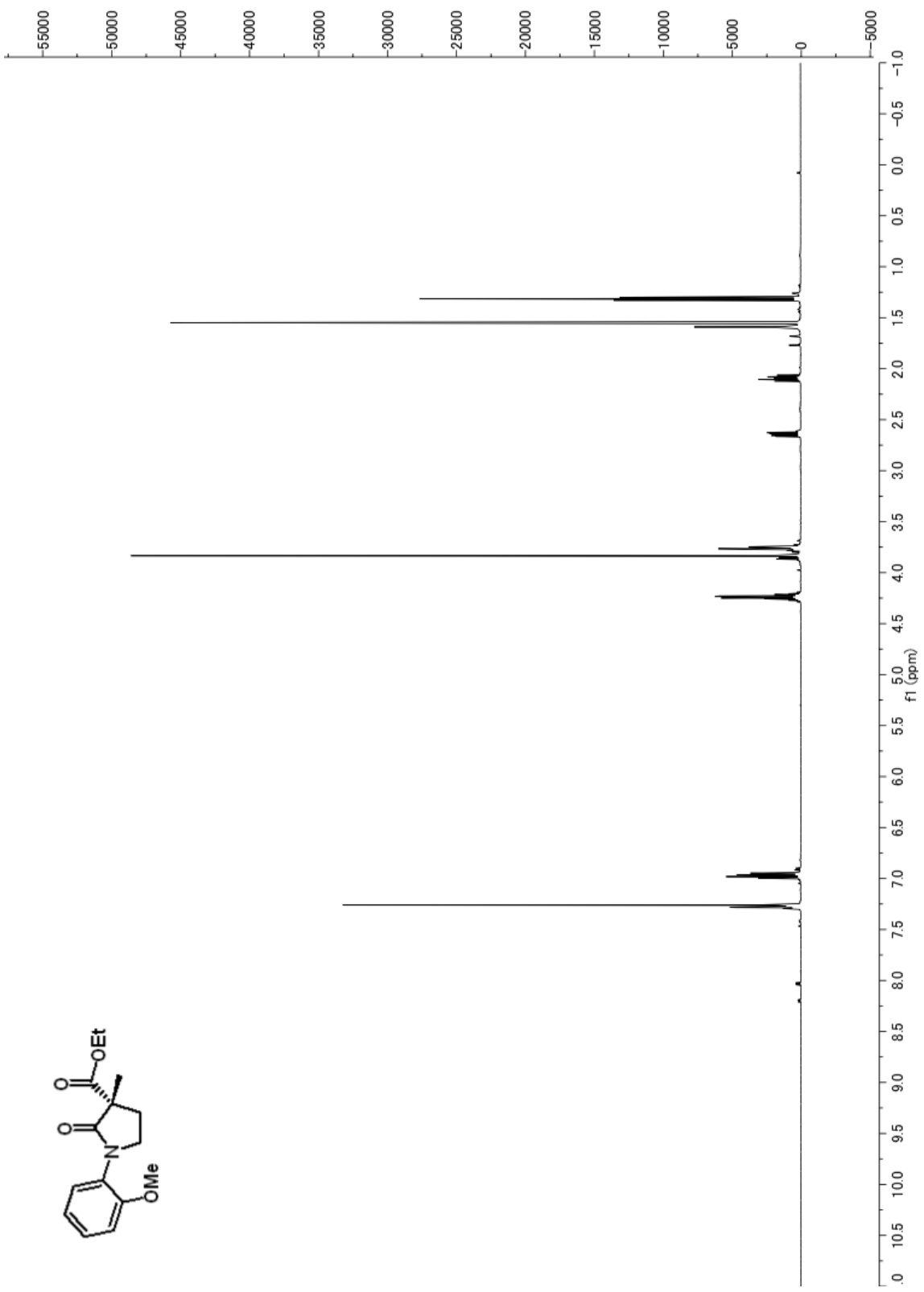


Figure A3.105. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **70**.

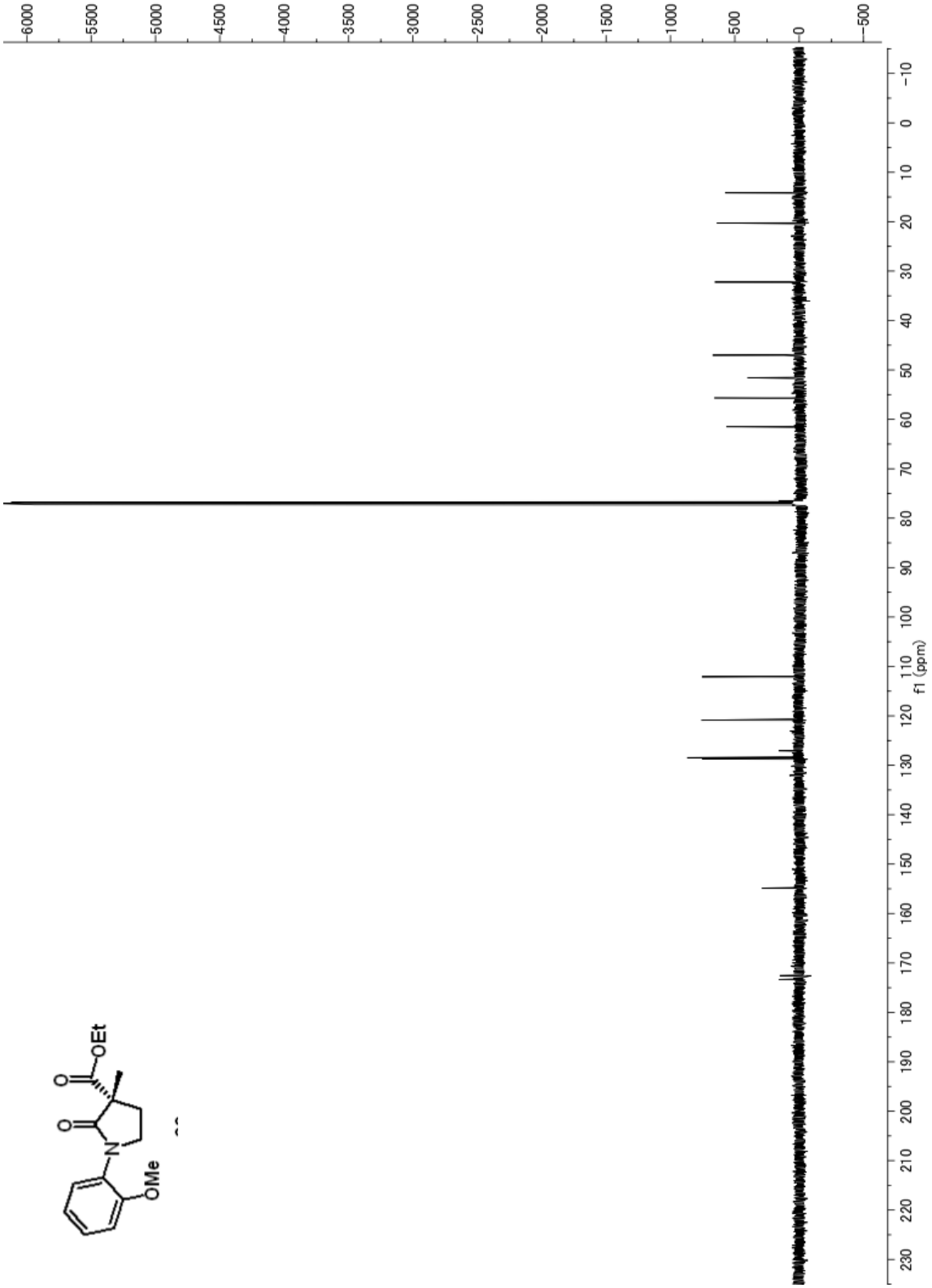


Figure A3.106. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **70**.

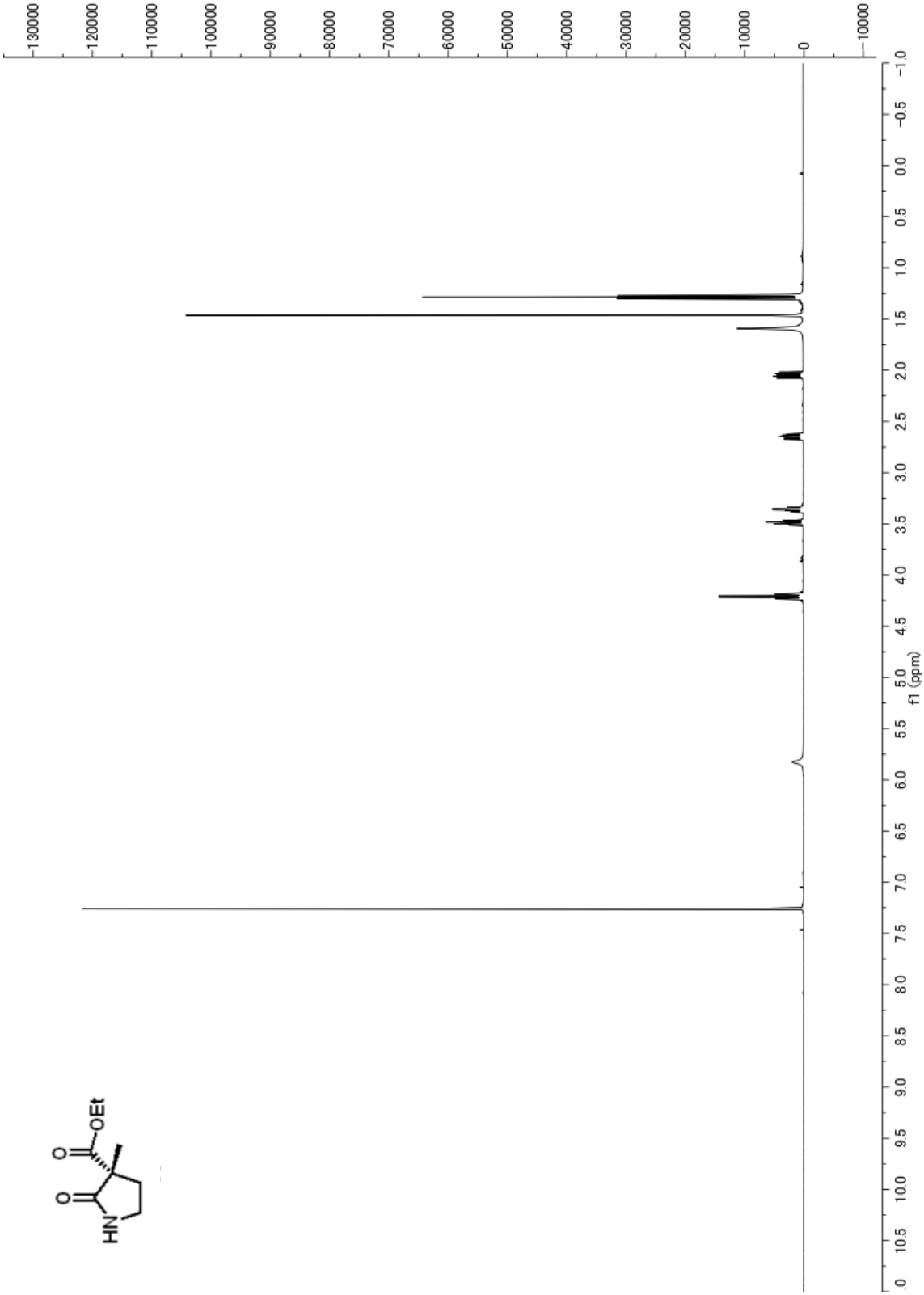


Figure A3.107. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **71**.

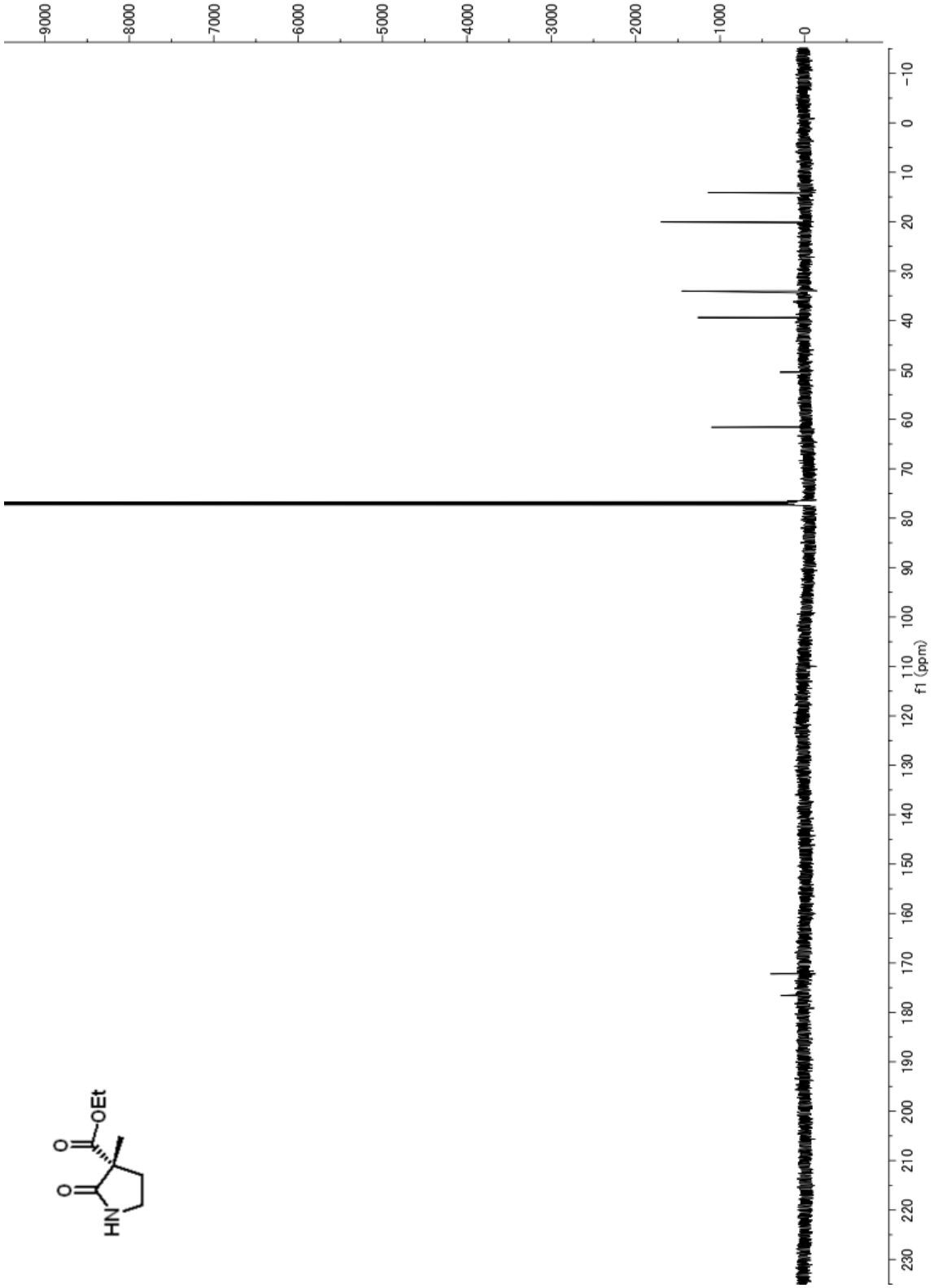


Figure A3.108. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **71**.

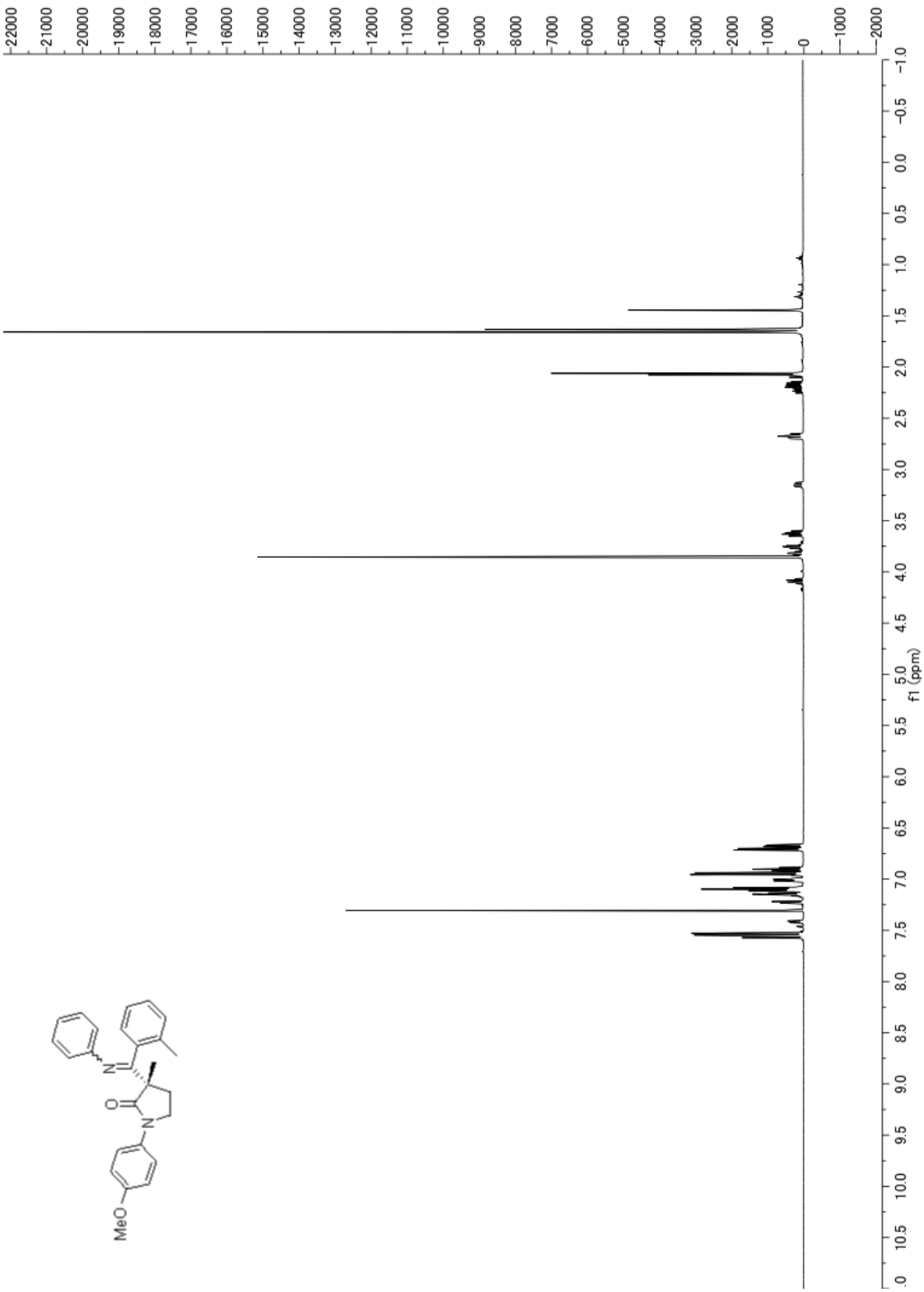


Figure A3.109. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **72**.

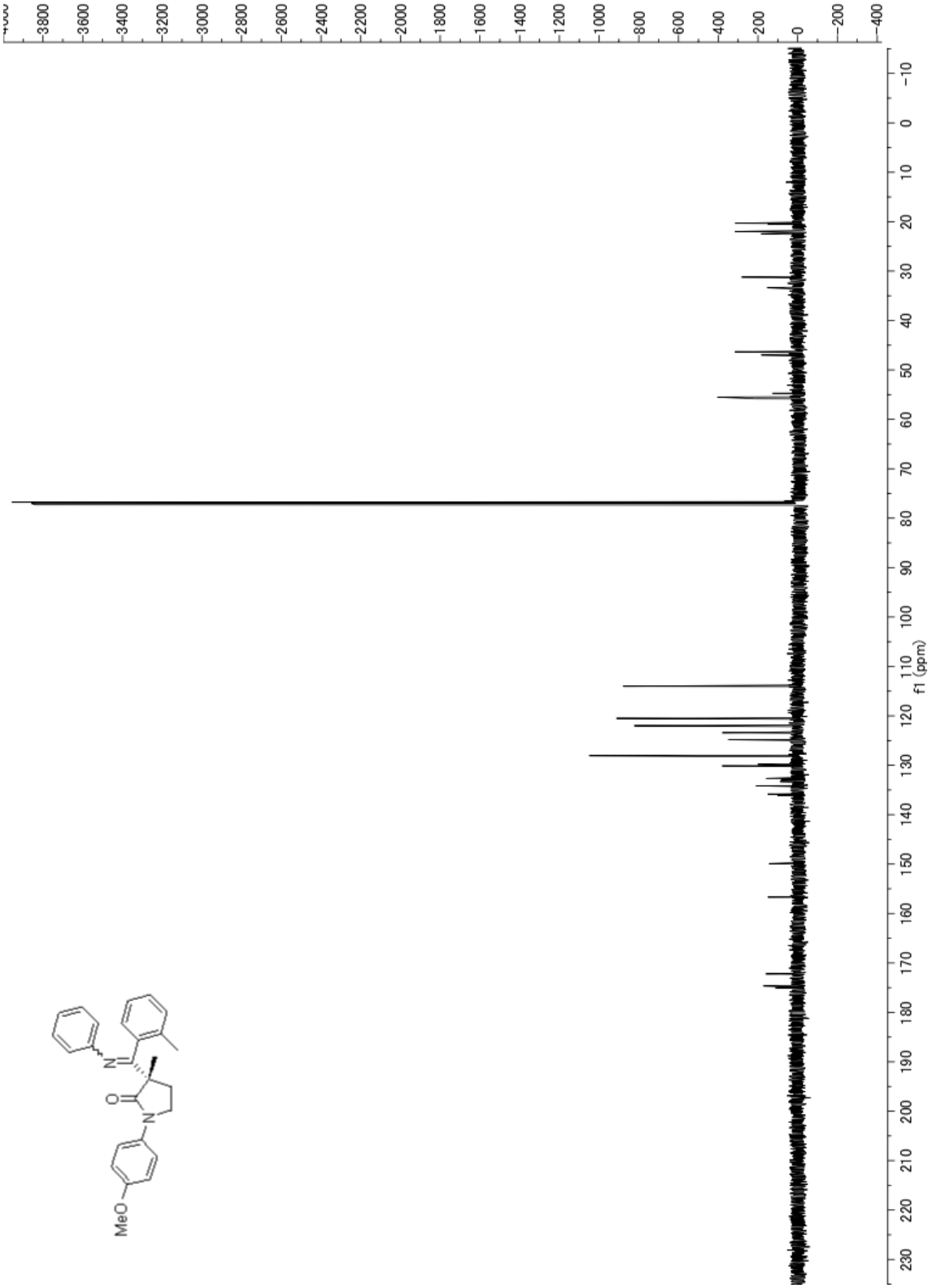


Figure A3.110. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **72**.

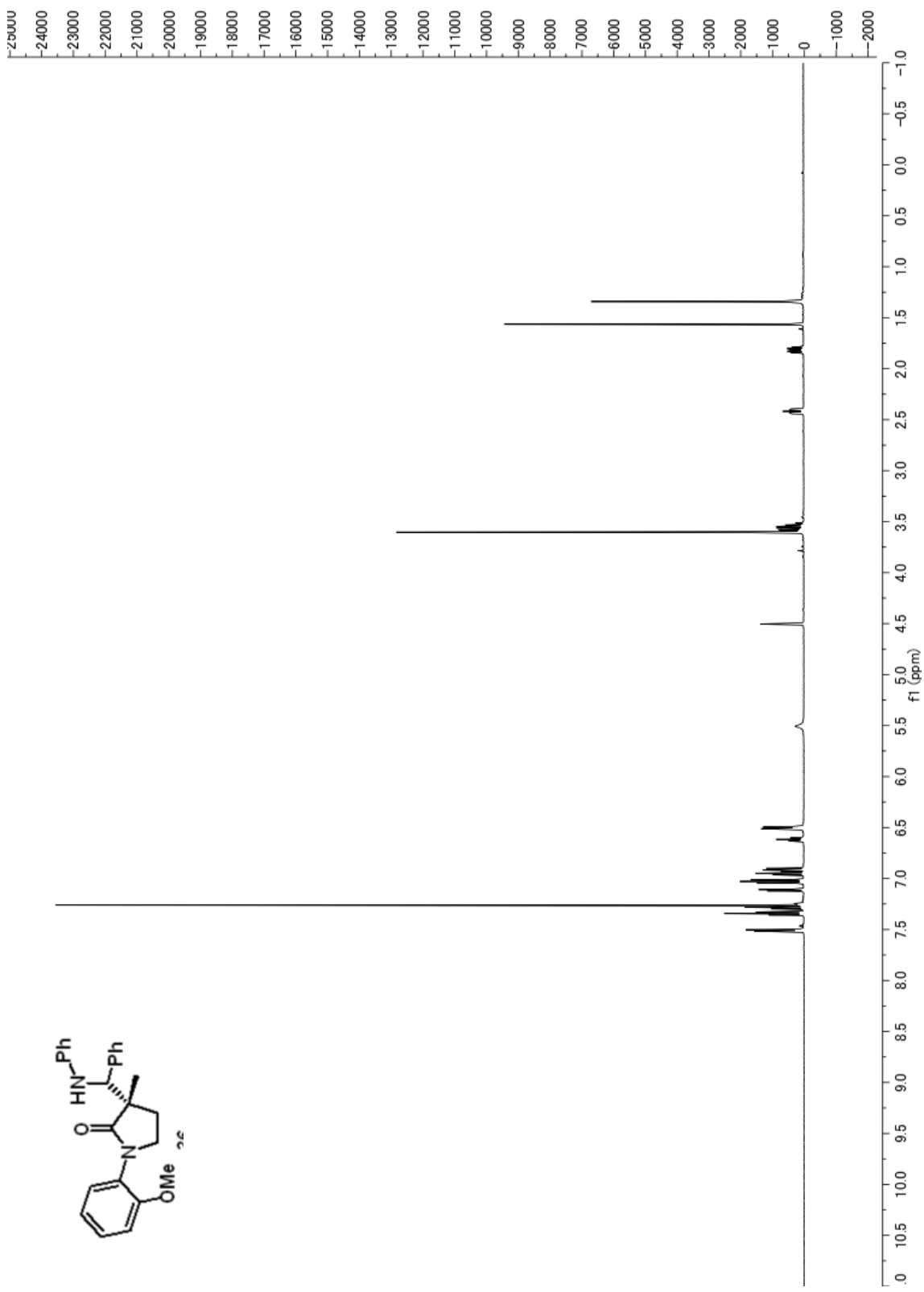


Figure A3.111. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **74**.

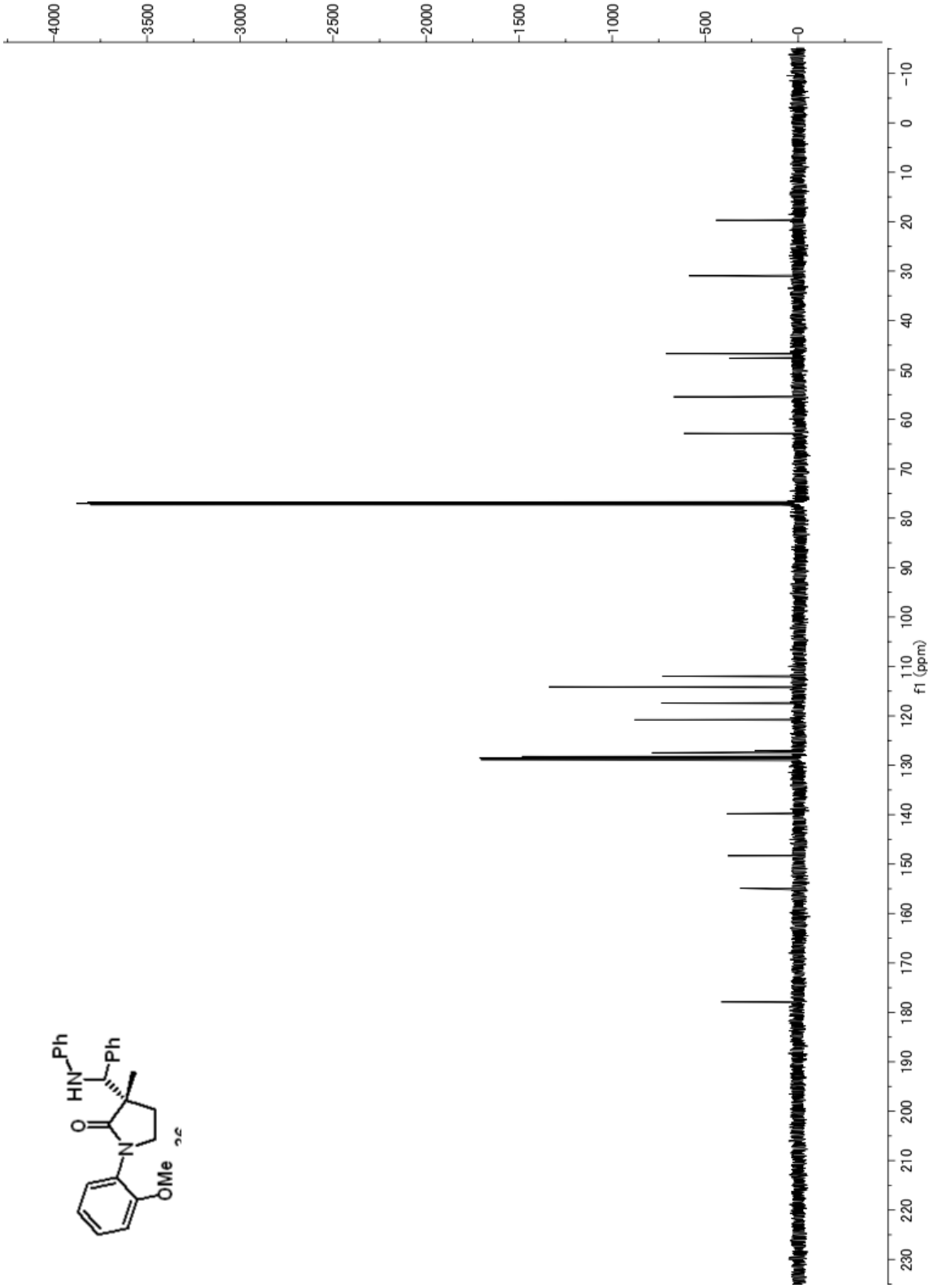


Figure A3.112. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **74**.

COMPREHENSIVE BIBLIOGRAPHY

Ackermann, L.; Vicente, R.; Hofmann, N. *Org. Lett.* **2009**, *11*, 4274–4276.

Ahmed, T. J.; Knapp, S. M. M.; Tyler, D. R. *Coord. Chem. Rev.* **2011,** *255*, 949–974.

Akula, R.; Doran, R.; Guiry, P. J. *Chem. Eur. J.* **2016**, *22*, 9938–9942.

Akula, R.; Guiry, P. J. *Org. Lett.* **2016**, *18*, 5472–5475.

Alberch, E.; Brook, C.; Asad, S. A.; Shevyrev, M.; Ulicki, J. S.; Hossain, M. M. *Synlett* **2015**, *26*, 388–392.

An, L.; Xiao, Y.-L.; Min, Q.-Q.; Zhang, X. *Angew. Chem. Int. Ed.* **2015**, *54*, 9079–9083.

Annunziata, A.; Galli, C.; Marinelli, M.; Tullia, P. *Eur. J. Org. Chem.* **2001**, 1323–1329.

Arai, S.; Hida, M.; Yamagishi, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 277–282.

Arai, S.; Yamagishi, T.; Ototake, S.; Hida, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 547–548.

Arao, T.; Kondo, K.; Aoyama, T. *Chem. Pharm. Bull.* **2006**, *12*, 1743–1744.

Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483.

Atack, T. C.; Cook, S. P. *J. Am. Chem. Soc.* **2016**, *138*, 6139–6142.

Atack, T. C.; Lecker, R. M.; Cook, S. P. *J. Am. Chem. Soc.* **2014**, *136*, 9521–9523.

Aydın, A.; Kaya, I.; *Electrochim. Acta*. **2012**, *65*, 104–114.

Banerjee, S.; Smith, J.; Smith, J.; Faulkner, F.; Masterson, D. S. *J. Org. Chem*. **2012**, *77*, 10925− 10930.

Basch, C. H.; Cobb, K. M.; Watson, M. P. *Org. Lett.* **2016**, *18*, 136–139.

Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2012**, *4*, 130–133.

Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novak, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2011**, *17*, 14199–14223.

Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045.

Bennett, N. B.; Duquette, D. C.; Kim, J.; Liu, W.-B.; Marziale, A. N.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2013**, *19*, 4414–4418.

Birrell, J. A.; Desrosiers, J.-N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 13872–13875.

Bissember, A.C.; Lundgren, R.J.; Creutz, S.E.; Peters, J.C. Fu, G.C. *Angew. Chem. Int. Ed.* **2013**, *52*, 5129–5133.

Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192–16197.

Blunt, J.W.; Copp, B.R.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. *Nat. Prod. Rep.* **2004**, *21*, 15–61.

Bose, S. K.; Fucke, K.; Liu, L.; Steel, P. G.; Marder, T. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 1799–1803.

Breitenfeld, J.; Ruiz, J.; Wodrich, W. D.; Hu, X. *J. Am. Chem. Soc.* **2013**, *135*, 12004–12012.

Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988**, *21*, 287–293.

Bull, J. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 8930–8932.

Bundesmann, M.W.; Coffey, S.B.; Wright, S.W. *Tetrahedron Lett*. **2010**, *51*, 3879–3882.

Burks, H. E.; Morken, J. P. *Chem. Commun.* **2007**, 4717–4725.

Burns, M.; Essafi, S.; Bame, J. R.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.;

Butts, C. P.; Harvey, J. N.; Aggarwal, V. K. *Nature* **2015**, *513*, 183–188.

Burtoloso, A. C. B. *Synlett*, **2009**, 320–327.

Busto, E.; Gotor-Fernández, V.; Gotor, V. *Adv. Synth. Catal.* **2006**, *348*, 2626.

Campbell, C. D.; Concellón, C.; Smith, A. D. *Tetrahedron: Asymmetry* **2011**, *22*, 797.

Carey, J.S.; Laffan, D.; Thomson, C.; Williams, M.T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.

Carroll, A.-M.; O'Sullivan, T. P.; Guiry, P. J. *Adv. Synth. Catal.* **2005**, *347*, 609–631.

Chattopadhyay, K.; Jana, R.; Day, V. W.; Douglas, J. T.; Tunge, J. A. *Org. Lett.* **2010**, *12*, 3042–3045.

Chen, C.; Weng, Z.; Hartwig, J.F. *Organometallics* **2012**, *31*, 8031–8037.

Chen, G.; Kwong, F. Y.; Chan, H. O.; Yu, W.-Y.; Chan, A. S. C. *Chem. Commun.* **2006**, 1413–1415.

Chen, W.; Chen, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 15826–15828.

Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587–9652.

Cherney, A. H.; Reisman, S. E. *J. Am. Chem. Soc.* **2014**, *136*, 14365–14368.

Chiappe, C.; Pieraccini, D.; Saullo, P. *J. Org. Chem.* **2003,** *68*, 6710–6715.

Choi, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 9102–9105.

Choi, J.; Martín-Gago, P.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 12161–12165.

Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597.

Chu, C. K.; Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.*, **2016**, *138*, 6404–6407.

Clark, J. H.; Duke, C. V. A. *J. Org. Chem.* **1985,** *50*, 1330–1332.

Collins, K.D.; Glorius, F. *Nat. Chem.* **2013**, *5*, 597–601.

Cook, F. L.; Bowers, C. W.; Liotta, C. L. *J. Org. Chem.* **1974,** *39*, 3416–3418.

Coombs, J. R.; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 16140–16143.

Crabtree, S. R.; Chu, W. L. A.; Mander, L. N. *Synlett* **1990**, *3*, 169–70.

Craig, R. A.; Loskot, S. A.; Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 5160–5163.

Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. *Science* **2012,** *338*, 647–651.

Creutz, S.E.; Lotito, K.J.; Fu, G.C.; Peters, J.C. *Science* **2012**, *338*, 647–651.

Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2013**, 4695–4712.

Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003,** *36*, 234–245.

De, C. K.; Mittal, N.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 16802.

Dietz, F. R.; Gröger, H. *Synlett* **2009**, 4208.

Dietz, F. R.; Gröger, H. *Synthesis*, **2009**, 4208.

Do, H.-Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2014,** *136*, 2162–2167.

Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339–341.

Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5363–5367.

Dudnik, A. S.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 10693–10697.

Duffey, T. A.; Shaw, S. A.; Vedejs, E. *J. Am. Chem. Soc.* **2009**, *131*, 14.

Fischer, C.; Koenig, B. *Beilstein J. Org. Chem.* **2011**, *7*, 59–74.

Fleming, F. F.; Gudipati, S. *Eur. J. Org. Chem.* **2008,** 5365–5374.

Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002,** *58*, 1–23.

Fleming, F. F.; Wang, Q. Z. *Chem. Rev.* **2003,** *103*, 2035–2077.

Fleming, F. F.; Zhang, Z. *Tetrahedron* **2005,** *61*, 747–789.

Fleming, F.; *Nat. Prod. Rep.* **1999**, *16*, 597–606.

Fleming, F.F.; Yao, L.; Ravikumar, P.C.; Funk, L.; Shook, B.C. *J. Med. Chem.* **2010**, *53*, 7902–7917.

Fleming, I.; Iqbal, J.; Krebs, E.-P. *Tetrahedron* **1983**, *39*, 841–846.

Fournier, J.; Lozano, O.; Menozzi, C.; Arseniyadis, S.; Cossy, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 1257–1261.

Franckevičius, V.; Cuthbertson, J. D.; Pickworth, M.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2011**, *13*, 4264–4267.

Friedman, L.; Shechter, H. *J. Org. Chem.* **1960,** *25*, 877–879.

Fukuda, Y.; Kondo, K.; Aoyama, T. *Tetrahedron Lett.* **2007**, *48*, 3389–3391.

Garcia-Alvarez, R.; Crochet, P.; Cadierno, V. *Green Chem.* **2013,** *15*, 46–66.

García-Fortanet, J.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 8108–8111.

Gartshore, C. J.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 4113–4116.

Ge, S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 16330–16333.

Giri, R.; Hartwig, J.F. *J. Am. Chem. Soc.* **2010**, *132*, 15860–15863.

Goldberg, I. *Chem. Ber.* **1906**, *39*, 1691–1692.

Gomez, S.; Peters, J. A.; Maschmeyer, T. *Adv. Synth. Catal.* **2002,** *344*, 1037–1057.

González-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360–5361.

González-Rosende, M.E.; Castillo, E.; Lasri, J.; *Sepúlveda*-Arques, J. *Prog. React. Kinet. Mech.* **2004**, *29*, 311–332.

Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634–10637.

Hackmann, C.; Schäfer, H.J. *Tetrahedron* **1993**, *49*, 4559–4574.

Hall, D. G.; Lee, J. C. H.; Ding, J. *Pure Appl. Chem.*, **2012**, *84*, 2263–2277.

Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261–1268.

Han, J. T.; Jang, W. J.; Kim, N.; Yun, J. *J. Am. Chem. Soc.* **2016**, *138*, 15146–15149.

Harusawa, S.; Yoneda, R.; Omori, Y.; Kurihara, T., *Tet. Lett.* **1987,** *28*, 4189–4190.

Hasserodt, J.; Janda, K. D.; Lerner, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 5993–5998.

Hethcox, J. C.; Shockley, S. E. *Angew. Chem. Int. Ed.* **2016**, *55*, 16092–16095.

Hills, I. D.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 3921.

Hu, X. *Chem. Sci.* **2011**, *2*, 1867–1886.

Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L.J. *Chem. Rev.* **2015**, *115*, 2596–2697.

Hultzsch, K.C.; *Adv. Synth. Catal.* **2005**, *347*, 367–391.

Hurtley, W.R.H. *J. Chem. Soc.* **1929**, 1870–1873.

Ismail, M.; Nguyen, H. V.; Ilyashenko, G.; Motevalli, M.; Richards, C. J. *Tetrahedron Lett.* **2009**, *50*, 6332.

Isse, A. A.; Lin, C. Y.; Coote, M. L.; Gennaro, A. *J. Phys. Chem. B* **2010,** *115*, 678–684.

Isse, A.A.; Lin, C.Y.; Coote, M.L.; Gennaro, A. *J. Phys. Chem. B* **2011**, *115*, 678–684.

Ito, H.; Ito, S.; Sasaki, Y.; Matsura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856–14857.

Ito, H.; Kubota, K. *Org. Lett.* **2012**, *14*, 890–893.

James, J.; Guiry, P. J. *ACS Catal.* **2017**, *7*, 1397–1402.

Jiang, L.; Weist, S.; Jansat, S. *Org. Lett.* **2009**, *11*, 1543–1546.

Jiang, M.; Yang, H.; Fu, H. *Org. Lett.* **2016**, *18*, 5248–5251.

Joannesse, C.; Johnston, C. P.; Morrill, L. C.; Woods, P. A.; Kieffer, M.; Nigst, T. A.; Mayr, H.; Lebl, T.; Philp, D.; Bragg, R. A.; Smith, A. D. *Chem. Eur. J.* **2012**, *18*, 2398.

Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175–13183.

Jones, G.O.; Liu, P.; Houk, K.N.; Buchwald, S.L. *J. Am. Chem. Soc.* **2010**, *132*, 6205–6213.

Jones, L.H.; Summerhill, N.W.; Swain, N.A.; Mills, J.E. *Med. Chem. Comm.* **2010**, *1*, 309–318.

Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 10480–10483.

Kaiser, T. M.; Yang, J. *Eur. J. Org. Chem.* **2013**, 3983–3987.

Keither, J. A.; Behenna, D. C.; Sherden, N.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Nielsen, R. J.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A. *J. Am. Chem. Soc.* **2012**, *134*, 19050–19060.

Kelkar, A.A.; Patil, N.M.; Chaudhari, R.V. *Tetrahedron Lett.* **2002**, *43*, 7143–7146.

Kim, D. D.; Lee, S. J.; Beak, P. *J. Org. Chem.* **2005**, *70*, 5376-5386.

Kim, S.; Song, H.-J. *Synlett* **2002,** 2110–2112.

Cho, C. H.; Lee, J. Y.; Kim, S. *Synlett* **2009**, 81–84.

Kiyomori, A.; Marcoux, J.-F.; Buchwald, S.L. *Tetrahedron Lett.* **1999**, *40*, 2657–2660.

Knight, A.S.; Zhou, E.Y.; Francis, M.B.; Zuckermann, R.N. *Adv. Mater.* **2015**, doi:10.1002/adma.201500275.

Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2015**, *54*, 179–183.

Kozuka, M.; Tsuchida, T.; Mitani, M.; *Tetrahedron Lett.* **2005**, *46*, 4527–4530.

Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013**, *340*, 1065–1068.

Kubota, K.; Iwamoto, H.; Ito, H. *Org. Biomol. Chem.* **2017**, *15*, 285–300.

Kukushkin, V. Y.; Pombeiro, A. J. L. *Inorg. Chim. Acta* **2005,** *358*, 1–21.

Kündig, P.; Seidel, T. M.; Jia, Y.-X.; Bernardinelli, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 8484–8487.

Kurauchi, D.; Hirano, K.; Kato, H.; Saito, T.; Miyamoto K.; Uchiyama, M. *Tetrahedron* **2015**, *71*, 5849–5857.

Lanigan, R.M.; Sheppard, T.D. *Eur. J. Org. Chem.* **2013**, 7453–7465.

Le Roux, C.; Mandrou, S.; Dubac, J. *J. Org. Chem.* **1996**, *61*, 3885–3887.

Lee, J. C. H.; Hall, D. G. *J. Am. Chem. Soc.* **2010**, *132*, 5544–5545.

Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894–899.

Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402–3415.

Leonori, D.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2015**, *54*, 1082–1096.

Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem. Int. Ed.* **2013**, *52*, 4117–4121.

Liang, Y.; Fu, G. C. *Angew. Chem. Int. Ed.* **2015**, *54*, 9047–9051.

Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 9523–9526.

Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195–200.

Lin, B. -L.; Liu, L.; Fu, Y.; Luo, S. -W.; Chen, Q.; Guo, Q. -X. *Organometallics* **2004**, *23*, 2114–2123.

Liu, Lantao; Ishida, N.; Ashida, S.; Murakami, M. *Org. Lett.* **2011**, *13*, 1666–1669.

Liu, W.-B.; Reeves, C. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 17298–17301.

Liu, W.-B.; Reeves, C. M.; Virgil, S. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 10626–10629.

Liu, X.; Zhang, S.-L.; Ding, Y. *Dalton Trans*. **2012**, *41*, 5897–5902.

Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740–751.

Lloyd-Jones, G. C.; Lennox, A. J. J. *Chem. Soc. Rev.* **2014**, *43*, 412–443.

Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154–8157.

Luan, X.; Wu, L.; Drinkel, E.; Mariz, R.; Gatti, M.; Dorta, R. *Org. Lett.* **2010**, *12*, 1912–1915.

Lölsberg, W.; Ye, S.; Schmalz, H. G. *Adv. Synth. Catal.* **2010**, *352*, 2023–2031.

Maki, B.E.; Scheidt, K.A. *Org. Lett*. **2008**, *10*, 4331–4334.

Mandai, H.; Fujiwara, T.; Noda, K.; Fujii, K.; Mitsudo, K.; Korenaga, T.; Suga, S. *Org. Lett.* **2015**, *17*, 4436.

Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425–5428.

Marcoux, J.-F.; Doye, S.; Buchwald, S.L. *J. Am. Chem. Soc*. **1997**, *119*, 10539–10540.

Marziale, A. N.; Duquette, D. C.; Craig, R. A.; Kim, K. E.; Liniger, M.; Numajiri, Y.; Stoltz, B. M. *Adv. Synth. Catal.* **2015**, *357*, 2238–2245.

Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555–10607.

Meiß, R.; Kumar, K.; Waldmann, H. *Chem. Eur. J.* **2015**, *21*, 13526–13530.

Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 4050–4051.

Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 5604–5607.

Miranda, M.O.; Pietrangelo, A.; Hillmyer, M.A.; Tolman, W.B. *Green Chem*. **2012**, *14*, 490–494.

Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927.

Moran, W. J.; Morken, J. P. *Org. Lett.* **2006**, *8*, 2413–2415.

Nascimento de Oliveira, M.; Fournier, J.; Areseniyadis, S.; Cossy, J. *Org. Lett.* **2017**, *19*, 14–17.

Nelson, H. M.; Williams, B. D.; Miró, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213–3216.

Nemoto, H.; Zhong, W.; Kawamura, T.; Kamiya, M.; Nakano, Y.; Sakamoto, K. *Synlett* **2007**, 2343–2346.

Nemoto, T.; Fukuda, T.; Matsumoto, T.; Hitomi, T.; Hamada, Y. *Adv. Synth. Catal.* **2005**, *347*, 1504–1506.

Nemoto, T.; Masuda, T.; Matsumoto, T.; Hamada, Y. *J. Org. Chem.* **2005**, *70*, 7172–7178.

Nguyen, H. V.; Butler, D. C. D.; Richards, C. J. *Org. Lett.* **2006**, *8*, 769.

Nilsson, M. *Acta Chem. Scand. B* **1982**, *36*, 125–126.

Ouali, A.; Spindler, J.-F.; Jutand, A.; Taillefer *Adv. Synth. Catal.* **2007**, *349*, 1906–1916.

Pandey, G.; Rao, K.S.S.P.; Palit, D.K.; Mittal, J.P. *J. Org. Chem.* **1998**, *63*, 3968–3978.

Paptchikhine, A.; Cheruku, P.; Engman, M.; Andersson, P. G. *Chem. Commun.* **2009**, 5996–5998.

Paradies, J. Palladium-Catalyzed Aromatic Carbon-Nitrogen Bond Formation. In *Metal-Catalyzed Cross-Coupling Reactions and More;* De Meijere, A.; Brase, S.; Oestreich, M., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2014, pp 995-1065.

Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; McQuade, D. T. *J. Am. Chem. Soc.* **2011**, *133*, 2410–2413.

Potter, B.; Edelstein, E. K.; Morken, J. P. *Org. Lett.* **2016**, *18*, 3286–3289.

Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788–7789.

Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510–511.

Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, 181–191.

Rao, K.S.; Wu, T.-S. *Tetrahedron* **2012**, *68*, 7735–7754.

Reddy, M. S.; Rajan, S. T.; Eswaraiah, S.; Satyanarayana, R. Improved Process for Manufacture of Pregabalin. Patent WO 2009/001372 A2, Dec 31, 2008.

Reeves, C. M.; Eidamshaus, C.; Kim, J.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 6718–6721.

Regen, S. L.; Quici, S.; Liaw, S.-J. *J. Org. Chem.* **1979,** *44*, 2029–2030.

Ren, Y.; Dong, C.; Zhao, S.; Sun, Y.; Wang, J.; Ma, J.; Hou, C. *Tet. Lett.* **2012,** *53*, 2825–2827.

Ren, Y.; Yan, M.; Zhao, S.; Sun, Y.; Wang, J.; Yin, W.; Liu, Z. *Tet. Lett.* **2011,** *52*, 5107–5109.

Ribas, X.; Güell, I. *Pure Appl. Chem.* **2014**, *86*, 345–360.

Roy, C. D.; Brown, H. C. *J. Organomet. Chem.* **2007**, *692*, 784–790.

Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532.

Saito, K.; Harada, K. *Bull. Chem. Soc. Jpn.* **1989,** *62*, 2562–2566.

Sambiagio, C.; Marsden, S.P.; Blacker, A.J.; McGowan, P.C. *Chem. Soc. Rev.* **2014**, *43*, 3225–3550.

Satoh, Y.; Obora, Y. *RSC Adv.* **2014,** *4*, 15736–15739.

Schiffner, J. A.; Müther, K.; Oestreich, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1194–1196.

Schley, N. D.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 16588–16593.

Schmidt, J.; Choi, J.; Liu, A. T.; Slusarczyk, M.; Fu, G. C. *Science* **2016**, *354*, 1265–1269.

Seitzberg, J. G.; Dissing, C.; Søtofte, I.; Norrby, P.-O.; Johannsen, M. *J. Org. Chem.* **2005**, *70*, 8332.

Shaw, J. E.; Hsia, D. Y.; Parries, G. S.; Sawyer, T. K. *J. Org. Chem.* **1978,** *43*, 1017–1018.

Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925.

Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368.

Sheldrick, G.M. *Acta Cyrst. A* **2008**, *64*, 112–122.

Sherden, N. H.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6840–6843.

Shibuya, G. M.; Enquist, J. A.; Stoltz, B. M. *Org. Lett.* **2013**, *15*, 3480–3483.

Shimizu, S.; Kito, K.; Sasaki, Y.; Hirai, C., *Chem. Comm.* **1997**, 1629–1630.

Smilović, I. G.; Casas-Arcé, E.; Roseblade, S. J.; Nettekoven, U.; Zanotti-Gerosa, A.;

Kovačevič, M.; Časar, Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 1014–1018.

Soli, E. D.; Manoso, A. S.; Patterson, M. C.; DeShong, P.; Favor, D. A.; Hirschmann, R.; Smith, A. B. *J. Org. Chem.* **1999,** *64*, 3171–3177.

Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500–3501.

Streuff, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2010**, 192–196.

Strieter, E.R.; Bhayana, B.; Buchwald, S.L. *J. Am. Chem. Soc.* **2009**, *131*, 78–88.

Strieter, E.R.; Blackmond, D.G.; Buchwald, S.L. *J. Am. Chem. Soc.* **2005**, *127*, 4120–4121.

Sukata, K. *J. Org. Chem.* **1985,** *50*, 4388–4390.

Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534–6537.

Takaya, J.; Iwasawa, N. *ACS Catal.* **2012**, *2*, 1993–2006.

Tamami, B.; Ghasemi, S. *J. Iran. Chem. Soc.* **2008,** *5*, S26–S32.

Tan, Y.; Munoz-Molina, J. M.; Fu, G. C.; Peters, J. C. *Chem. Sci.* **2014,** *5*, 2831–2835.

Tan, Y.; Muñoz-Molina, J.M.; Fu, G.C.; Peters, J.C. *Chem. Sci.* **2014**, 2831–2835.

Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299–309.

Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900–9901.

Thoman, C. J.; Habeeb, T. D.; Huhn, M.; Korpusik, M.; Slish, D. F., *J. Org. Chem.* **1989,** *54*, 4476–4478.

Tian, Y.; Wang, Y.; Shang, H.; Xua, X.; Tang Y. *Org. Biomol. Chem.* **2015**, *13*, 612–619

Tomoi, M.; Ford, W. T., *J. Am. Chem. Soc.* **1980,** *102*, 7140–7141.

Tran, B.L.; Li, B.; Driess, M.; Hartwig, J.F. *J. Am. Chem. Soc.* **2014**, *136*, 2555–2563.

Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 3109–3112.

Trost, B. M.; Jiang, C. *Synthesis* **2006**, 0369–0396.

Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759–6760.

Trost, B. M.; Schroeder, G. M. *J. Org. Chem.* **2000**, *65*, 1569–1573.

Trost, B. M.; Schroeder, G. M.; Kristensen, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 3492–3495.

Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847.

Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343–18357.

Tu, X.; Fu, X.; Jiang, Q.; Liu, Z.; Chen, G. *Dyes Pigm*. **2011**, *88*, 39–43.

Tye, J. W.; Weng, Z.; Giri, R.; Hartwig, J.F. *Angew*. *Chem*. *Int*. *Ed*. **2010**, *49*, 2185–2189.

Tye, J.W.; Weng, Z.; Johns, A.M.; Incarvito, C.D.; Hartwig, J.F. *J*. *Am*. *Chem*. *Soc*. **2008**, *130*, 9971–9983.

Ullman, F. *Chem*. *Ber*. **1903**, *34*, 2174–2185.

Ullman, F.; Bielecki, J. *Chem*. *Ber*. **1901**, *34*, 2174–2185.

Ullman, F.; Sponagel, P. *Chem*. *Ber*. **1905**, *38*, 2211–2212.

Uraguchi, D.; Koshimoto, K.; Miyake, S.; Ooi, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 5567.

Uyeda, C.; Tan, Y.; Fu, G. C.; Peters, J. C. *J*. *Am*. *Chem*. *Soc*. **2013,** *135*, 9548–9552.

Varela, J. A.; Saá, C. *Chem. Rev*. **2003,** *103*, 3787–3802.

Velankar, H.; Clarke, K. G.; Preez, R. d.; Cowan, D. A.; Burton, S. G. *Trends Biotechnol*. **2010,** *28*, 561–569.

Viswambharan, B.; Okimura, T.; Suzuki, S.; Okamoto, S. *J. Org. Chem.* **2011**, *76*, 6678.

Wang, C.; Xiao, J. Asymmetric Reductive Amination. In *Topics in Current Chemistry*; Li, W.; Zhang, X.; Springer Berlin Heidelberg, 2014; Vol. 343; pp 261–282.

Wang, K.-B.; Ran, R.-Q.; Xiu, S.-D.; Li, C.-Y. *Org. Lett*. **2013** *15*, 2374–2377.

Wang, M.; Zhang, Z.; Liu, S.; Xie, F.; Zhang, W. *Chem. Commun.* **2014**, *50*, 1227.

Wang, X.; Wang, S.; Xue, W.; Gong, H. *Angew. Chem. Int. Ed.* **2015**, *137*, 11562–11565.

Weix, D. J. *Acc. Chem. Res.* **2015**, *48*, 1767–1775.

Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Tetrahedron Lett.* **2002**, *43*, 2945–2948.

Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794–5797.

Wolan, A.; Six, Y. *Tetrahedron* **2010,** *66*, 15–61.

Woods, P.A.; Morrill, L. C.; Bragg, R. A.; Smith, A. D. *Chem. Eur. J.* **2011**, *17*, 11060–11067.

Woods, P.A.; Morrill, L. C.; Lebl, T.; Slawin, A. M. Z.; Bragg, R. A.; Smith, A. D. *Org. Lett.* **2010**, *12*, 2660–2663.

Xie, X.; Chen, Y.; Ma, D. *J. Am. Chem. Soc.* **2006**, *128*, 16050–16051.

Yamamoto, E.; Takenouchi, Y.; Ozaki, T.; Miya, T.; Ito, H. *J. Am. Chem. Soc.* **2014**, *136*, 16515–16521.

Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 528–532.

Yi, J.; Liu, J.-H.; Liang, J.; Dai, J.-J.; Yang, C.-T.; Fu, Y.; Liu, L. *Adv. Synth. Catal.* **2012**, *354*, 1685–1691.

You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, X.-Z. *Org. Lett.* **2001**, *3*, 149–151.

Zhang, S.-L. *Dalton Trans*. **2012**, *41*, 1382–13840.

Zhang, S.-L. Liu, L.; Fu, Y.; Guo, Q.-X. *Organometallics* **2007**, *26*, 4546–4554.

Zhang, S.-L.; Ding, Y. *Organometallics* **2011**, *30*, 633–641.

Zhang, S.-L.; Fan, H.-J. *Organometallics* **2013**, *32*, 4944–4951.

Zhang, Z.; Xie, F.; Jia, J.; Zhang, W. *J. Am. Chem. Soc.* **2010**, *132*, 15939.

Zheng, L.; Xiang, J.; Bai, X. *J. Heterocycl. Chem*. **2006**, *43*, 321–324.

Zhou, H.; Yang, H.; Liu, M.; Xia, C.; Jiang, G. *Org. Lett.* **2014**, *16*, 5350–5353.

Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726–14727.

Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340–1341.

Zhou, J.; Fu, G.C. *J. Am. Chem. Soc.* **2003**, *125*, 12527–12530.

Zhou, Q.; Srinivas, H. D.; Zhang, S.; Watson, M. P. *J. Am. Chem. Soc.* **2016**, *138*, 11989–11995.

Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746–15749.

Zieger, H. E.; Wo, S. *J. Org. Chem.* **1994,** *59*, 3838–3840.

Ziegler, D. T.; Choi, J.; Muñoz-Molina, J. M.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2013,** *135*, 13107–13112.

Ziegler, D.T.; Choi, J.; Muñoz-Molina, J.M.; Bissember, A.C.; Peters, J.C.; Fu, G.C. *J. Am. Chem. Soc.* **2013**, *135*, 13107–13112.

Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 624–627.

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