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Synthetic Study Of Karlotoxins And Investigation Of Alpha-Diaminoboryl Carbanion Chemistry

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SYNTHETIC STUDY OF KARLOTOXINS AND INVESTIGATION OF α-DIAMINOBORYL CARBANION CHEMISTRY

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ABSTRACT

Karlotoxins (KmTxs), produced by a toxic marine/estuarine phytoplankton, the dinoflagellate *Karlodinium veneficum*, are known to be ichthyotoxic, thus being associated with numerous fish deaths events worldwide. They have also been reported to show a variety of biological activities such as hemolytic, cytotoxic, and anti-fungal activities. Recently, the Hamann group successfully assigned the absolute configurations of KmTx2, the first complete structure elucidation among the congeners. In a structural sense, karlotoxins are a family of linear polyketides with three distinctive regions; a bis-tetrahydropyran core fragment, a long, highly oxygenated carbon chain, and a lipophilic chlorodiene unit. Such potent biological activities as well as novel molecular complexity engaged our interest in the synthesis of KmTx molecules in the purpose of supplying more samples for further biological evaluations. We have successfully established a synthetic route to access the C(40-61) B-ring fragment of the KmTx5, a congener of KmTx2, in a twelve-step reaction sequence starting from a reported tetrahydropyranyl intermediate which can be readily prepared from D-mannose in four steps following the literature precedent.

α-Boryl carbanion species are known to exhibit excellent olefinating abilities *via* boron-Wittig reaction. This type of reaction was first reported in the 1960's, and actively studied mainly by Rathke, Pelter, and Matteson during the last third of the 20th century.

We, however, had an impression that this area of chemistry has still been underrepresented in the literature, thus has more room to explore into. Utilizing the α-diaminobory carbanion-mediated one-pot olefination protocols we have developed, we successfully prepared a variety of substituted acrylonitriles, including tetrasubstituted alkenes, by olefinating aldehydes and ketones. We have also demonstrated a useful application of the α-boryl carbanion species for the synthesis of 2-aminoquinoline-based alkaloids.

DEDICATION

I dedicate this dissertation to my parents, Hiroshi and Sachiko Takahashi,

and all the friends I have met during my entire college carrer,

who have been always there to encourage me, share their times with me, and support my life in the United States of America to make me go forward to accomplish this great work.

LIST OF ABBREVIATIONS AND SYMBOLS

α	optical rotation
Ac	Acetyl
AD	asymmetric dihydroxylation
AIBN	2,2'-azo*bis*isobutyronitrile
aq.	aqueous
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonyl
Bn	benzyl
Bu	butyl
°C	degree Celcius
calcd	calculated
cat.	Catalytic
cm^{-1}	wavenumber(s)
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
DCM	dichloromethane

Δ	heat
DIAD	diisopropyl azodicarboxylate
DIBAL(H)	diisobutylaluminum hydride
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
ee	enantiomeric excess
ES	electrospray
eq. (equiv.)	equivalent
Et	ethyl
EtOAc	ethyl acetate
EWG	electron-withdrawing group
g	gram(s)
gem	geminal
h or hr(s)	hour(s)
HCl	hydrochloric acid
Hex	hexanes/hexyl
HPLC	high performance liquid chromatography
HR	high resolution
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
i-Pr	isopropyl

IR	infrared spectroscopy
KHMDS	potassium hexamethyldisilazane
LDBB	lithium 4,4’-*tert*-butylbiphenylide
LHMDS	lithium hexamethyldisilazane
lit.	literature value
m	meta
M	molarity
Me	methyl
MeOH	methanol
Mes	mesityl
min	minute
mL	milliliter
mp	melting point
Ms	mesyl (methanesulfonyl)
MS	mass spectrometry
n	normal (*e.g.*, unbranched alkyl chain)
NaHMDS	sodium hexamethyldisilazane
NMR	nuclear magnetic resonance
NR	no reaction
Nu	nucleophile
o	ortho
p	para

Pd	palladium
%	percent
Ph	phenyl
Pr	*n*-propyl
PT	1-phenyl-1*H*-tetrazol-yl
Py	pyridine
quant.	quantitative
↑↓	reflux condition
r.t.	room temperature
R_f	retention factor
sat.	saturated
sec	secondary
SiO_2	silica gel
t or *tert*	tertiary
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TEA	triethylamine
temp	temperature
Tf	trifluoromethanesulfonyl (triflyl)
THF	tetrahydrofuran
THP	tetrahydropyranyl

TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N*’,*N*’-tetramethyl-1,2-ethylenediamine
TOF	time of flight
Tol	toluene
UV	ultraviolet
vic	vicinal
vol	volume

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Needless to say, I am extremely grateful to have worked alongside the former/current members of the Tomioka/Mattern groups; Rambabu Sankranti, Trey G.

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A special thank you to Dr. Naohito Abe, Joonseok Oh, and Mike Cunningham from our neighbors, the Pharmacy school and the National Center for Natural Product Research, for valuable discussions on their research expertise as well as fun, casual conversations every once in a while, which always served me as incentive towards my research life.

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Finally, big, special thanks to my Mom, Dad, my sister and all of my friends in Japan for always believing in me and for providing endless encouragement from the other side of the Earth as I pursued my goal in the United States of America. This dissertation would have simply been impossible to complete without the support of all the aforementioned people. Thank you!

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

CHAPTER 1: SYNTHETIC STUDY OF KARLOTOXINS: THE C(40-61) B-RING FRAGMENT SYNTHESIS OF KMTX5

1.1. Introduction

1.1.1. Karlotoxins and *karlodinium veneficum*

Karlodinium veneficum, a mixotrophic dinoflagellate with a size of 10-15 µm, is a common member of the phytoplankton in marine/estuarine ecosystems.[1-2] This microorganism is frequently present at relatively low cell abundance (10^2-10^3/mL), but capable of forming blooms of 10^4-10^5 cells/mL[3] that have been associated with numerous fish-kill events all over the world including Europe, south Africa, the eastern United States seaboard, south Asia and western Australia.[4-6]

Even though *K. veneficum* is easily identified live, its small size, poor fixation, a lack of distinguishing features and nomenclature confusion has made it difficult to relate the blooms of this organism with the fish-kill events in the past.[7] For instance, *K. veneficum* was first described as *Gymnodinium galatheanum* when its first collection was made in Walvis Bay (Namibia) in 1950.[8-10] Since then, the taxonomic identity of this species has been changed multiple times upon re-examinations of samples from the mortality events.[11] Synonyms now include *Gymnodinium*/*Gyrodinium galatheanum*, *Gymnodinium micrum*, *Gymnodinium veneficum*, and *Karlodinium micrum*.[12-13]

After decades of fish mortality events associated with *K. veneficum*, responsible toxic substances were discovered and named karlotoxins (KmTxs) in 2002.[14-15] Karlotoxins, both isolated from water samples at the mortality sites and from laboratory-

harvested cultures from field samples, are thus ichthyotoxic[16-17] and have shown hemolytic, cytotoxic, and anti-fungal activities.[18-19] In addition, there is a set of growing evidence that the karlotoxins play a number of important biological roles for *K. veneficum*, including deterring predation and assisting prey capture by immobilization of prey organisms[20] as allelopathic agents to outcompete the co-occurring phytoplanktons in the surrounding eco-system.[21-22] Karlotoxins appear to function by non-specifically increasing the ionic permeability of biological membranes resulting in osmotic cell lysis.[23] This cytotoxic activity has been reported to be modulated by membrane sterol composition[24-25], which also appears to be responsible for the biological mechanism of *K. veneficum* avoiding autotoxicity.[26-27] A recent study demonstrated that the toxins possess a unique, strong binding affinity to cholesterol,[28] which is one of the major components of lipid rafts. Since the lipid rafts, a cholesterol-rich membrane domain, have important clinical implications in major human diseases such as cancer, HIV (human immunodeficiency virus), TB (tubercle bacillus), and neurological disorders, the study of KmTx-cholesterol interactions may help to reveal further mechanistic aspects for the chemopreventive and drug design.[29] In a current report, toxicity of karlotoxins was investigated *in vivo* in mice through both intraperitoneal injection and oral administration.[30]

1.1.2. Karlotoxins from a structural perspective

Karlotoxins are a class of linear polyketides, just like amphidinols that have been isolated from the dinoflagellate *Amphidinium* with various structural/biological

similarities in common.[31] Originally two families of karlotoxins were described as belonging to the KmTx1 & 3 and KmTx2 groups, which differ from one another in potency, geographic distribution, and UV absorbance maxima.[32-33] The structures of karlotoxins are characterized by their hairpin-like molecular silhouette with three distinct sections: a highly oxidized and methylated polyol domain, a middle region including two tetrahydropyran (THP) rings, and a lipophilic side chain with a conjugated diene at the end, which gives these compounds their distinctive UV spectra.[34] Although several decades have already passed since the earliest appearance of *K. veneficum*-derived toxins in the literature,[35-36] only a handful of reports on structural determination has been published until now.[37-38] Recently, Hamann's group revealed the absolute configurations of KmTx2, obtained from a clonal culture of *K. veneficum* collected from a fish-kill event in Georgia. It was the first complete structural elucidation of the karlotoxin family (Figure 1.1).[39]

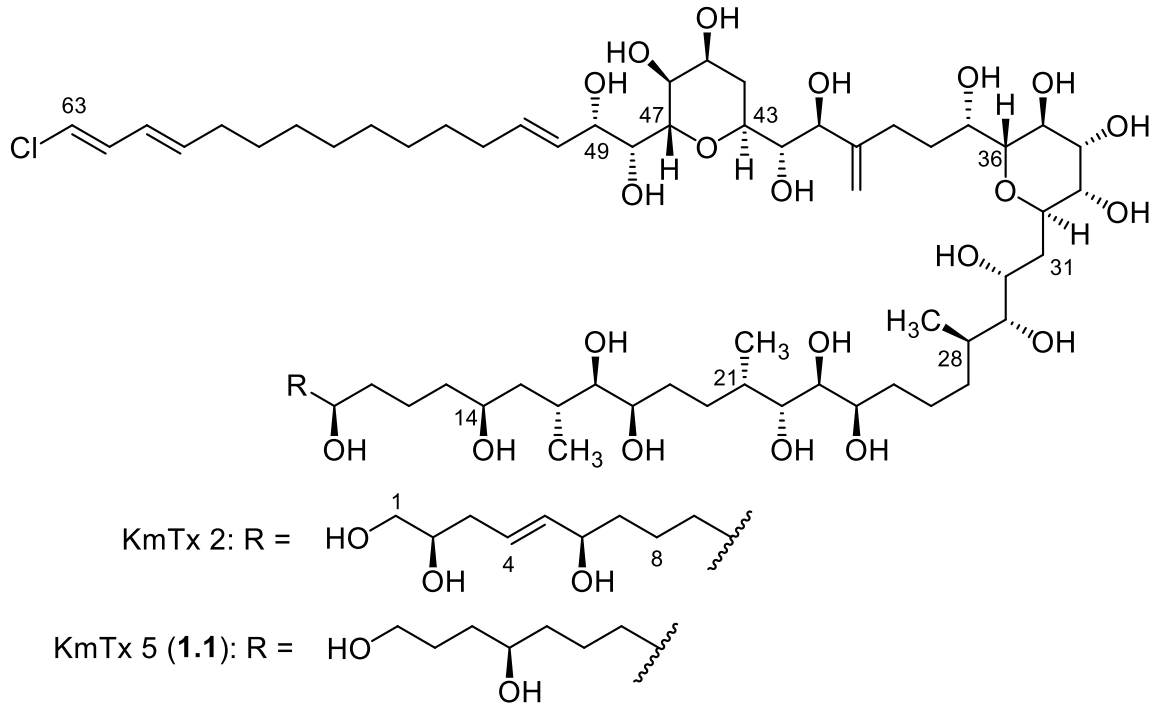
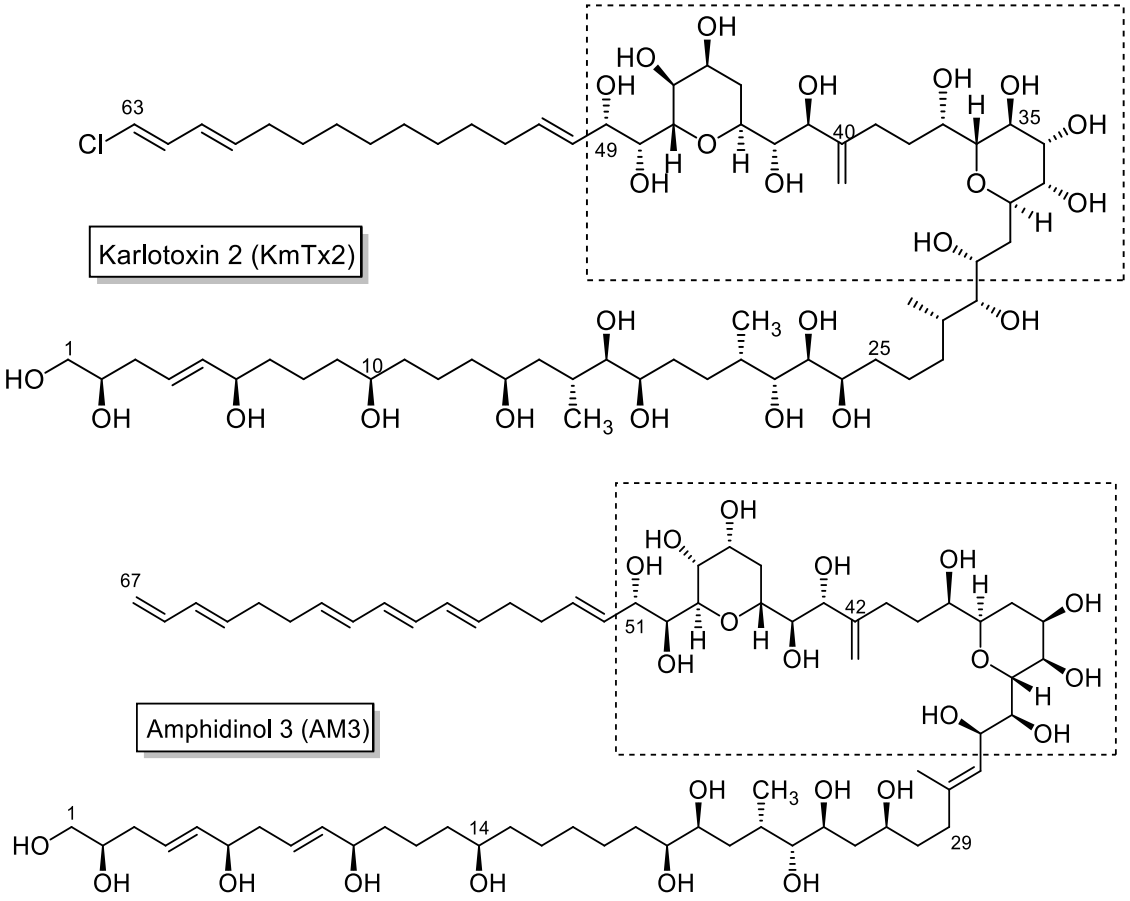


Figure 1.1 Structures of two karlotoxin molecules

Owing to their novel structural features as well as such potent biological activities, karlotoxins are attractive synthetic targets for us. Besides, there has been an increasing demand toward a total synthesis of KmTx-related congeners mainly due to their low availabilities: indeed, only several 1-10 mg batches of the samples have been provided to date to be utilized for *in vitro* bio-assays and structure-elucidation studies. Therefore, we embarked on the synthesis of karlotoxins; among all the karlotoxin analogues known so far, we have set our first aim on karlotoxin 5 based on our perspective that polyol chain synthesis would be a little more concise for KmTx5 (**1.1**) than for KmTx2 due to the absence of any unsaturated bond in the polyol chain of KmTx5. (Figure 1.1).

1.1.3. Karlotoxins and amphidinols

As briefly described in the introduction, karlotoxins and amphidinols are closely related both biologically and structurally.[40] In a structural aspect, both families are characterized with a linear polyhydroxy moiety, a bis-tetrahydropyran core fragment, and a hydrophobic polyene unit. Among their homologues, karlotoxin 2 and amphidinol 3 (AM3), whose structure and absolute configuration were disclosed by Murata *et al*. in 1999,[41] are particularly comparable to each other due to their similar structures (Figure 1.2).



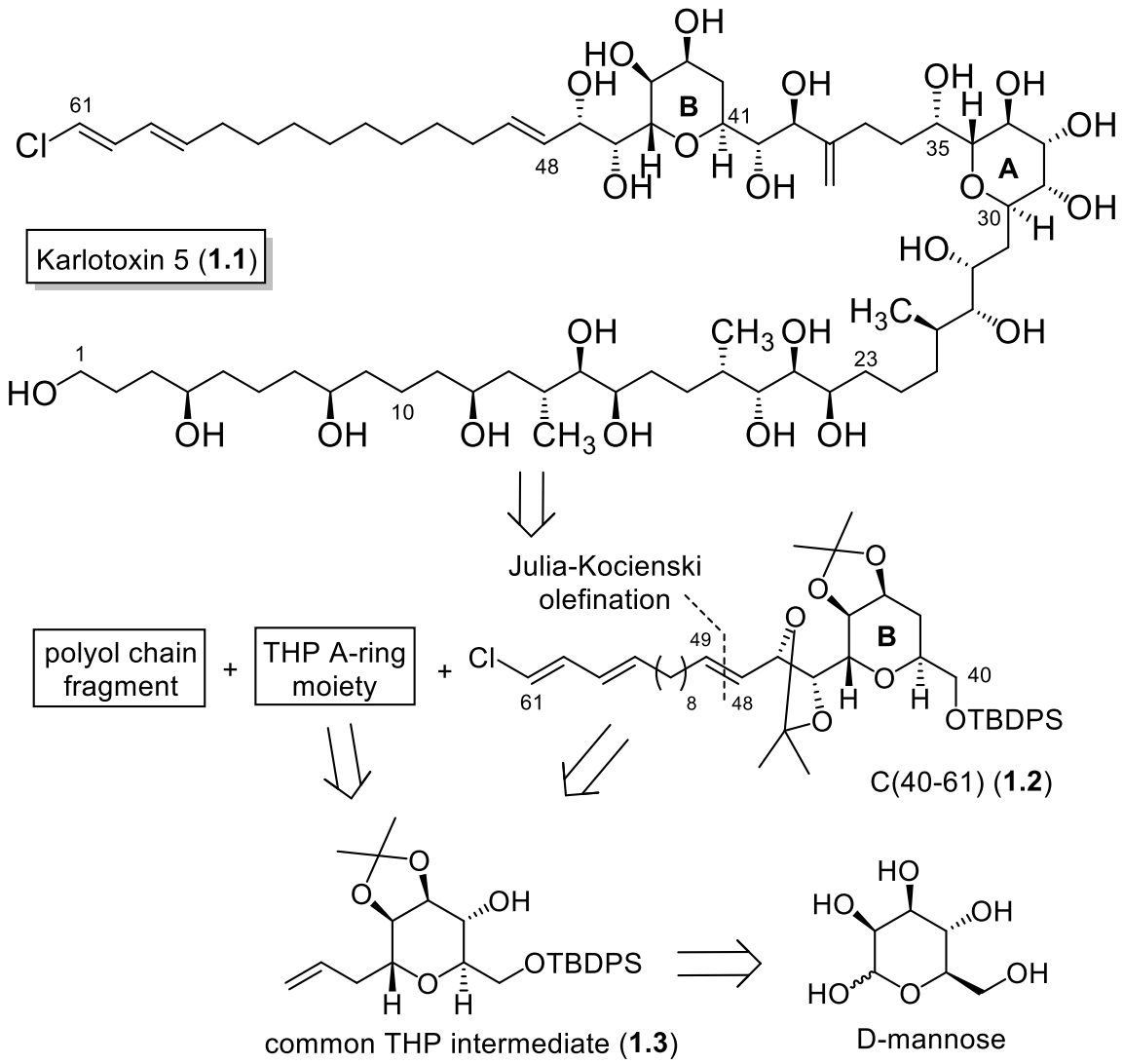
Fugure 1.2 KmTx2 and AM3

Ever since the complete structure and the absolute stereochemistry of karlotoxin 2 were successfully assigned by Hamann's group in 2010, its bis-THP region and the corresponding region of AM3, differing constitutionally only in the position of a few hydroxyl groups, have been under discussion in terms of their stereochemical relationship: their relative stereoconfigurations are identical except for C49, yet their absolute configurations are mirror-image to each other (Figure 1.2) [Note: The bis-THP regions of KmTx2 and KmTx5 are identical, as shown in Figure 1.1]. Although several synthetic groups worldwide have been actively engaged in the total/partial synthesis of AM3,[42-45,55] nobody has yet accomplished its total synthesis, primarily due to the recent structural revisions/re-evaluations of AM3 by Murata's group;[46-49] thus the stereochemistry of KmTx2 and AM3, especially in the bis-THP regions, still remains debatable. In order to resolve this stereochemical dispute, the demand for the synthesis of karlotoxin molecules has been increasing.

1.2. Retrosynthetic Analysis

In our retrosynthetic approach highlighted in Scheme 1.1, we disassembled KmTx5 into three major parts: two THP ring moieties (A and B) and a polyol chain module. Both THP fragments were further disconnected into a known common THP intermediate that can be readily prepared from natural D-mannose. While the Hamann group mainly worked on the THP A-ring fragment and the polyol chain, our group focused on the C(40-61) B-ring moiety with the lipophilic chain on it. Julia-Kocienski

olefination was proposed as a key reaction to furnish the C48-C49 bond and connect the B-ring fragment and the chlorodiene unit together.

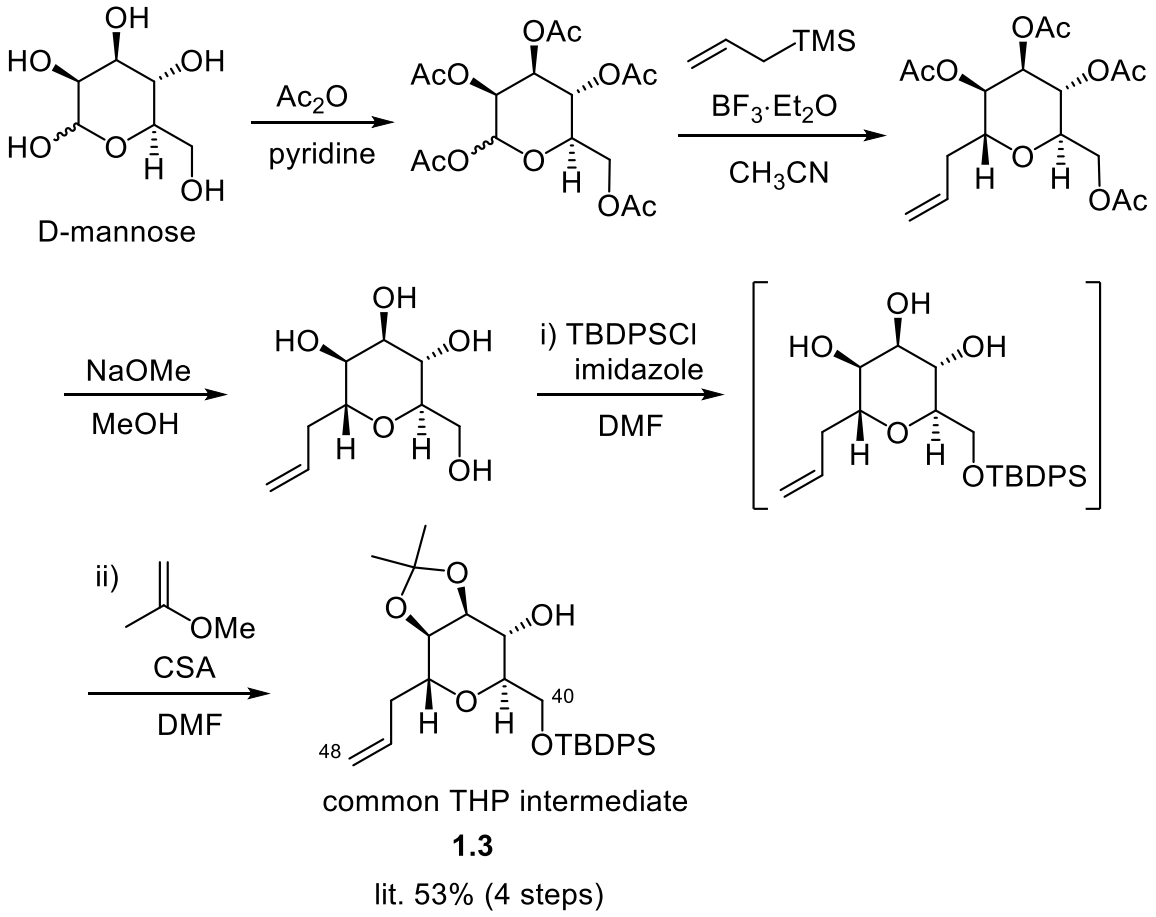


Scheme 1.1 Retrosynthetic analysis of KmTx5

1.3. Synthesis of the C(40-61) B-ring Fragment of KmTx5

1.3.1. Preparation of 1.10 from D-mannose

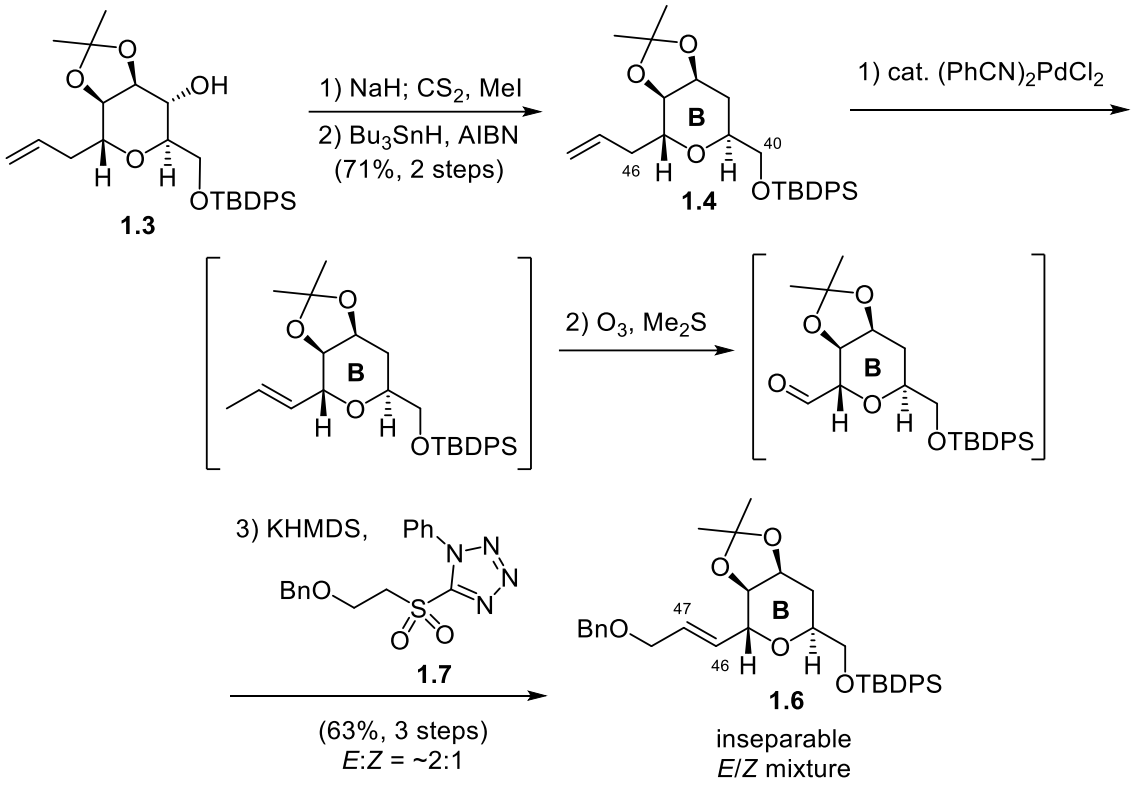
Our starting common THP intermediate **1.3** was readily synthesized with a known four-step reaction sequence from an inexpensive, commercially available starting material, D-mannose (43% over 4 steps) (Scheme 1.2).[50-52]



Scheme 1.2 Synthesis of **1.3** from D-mannose

The free hydroxyl group in **1.3** was removed by the standard Burton-McCombie deoxygenation condition[53], which yielded alkene **1.4** in 71% yield over two steps. An

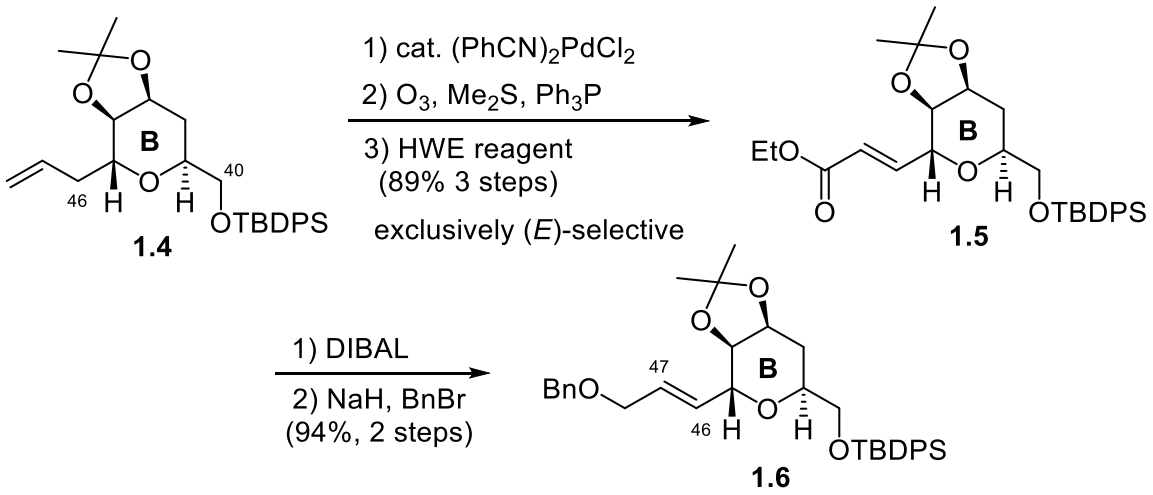
internal alkene formation *via* palladium (II) catalyzed isomerization of **1.4** followed by ozonolysis gave the corresponding aldehyde. Subjection of sulfone **1.7** to the aldehyde provided benzyl ether **1.6** in 63% over 3 steps. (*E*)-Stereoselectivity, however, was mediocre (*E*:*Z* = ~2:1) and those isomers were inseparable by silica gel column chromatography (Scheme 1.3).



Scheme 1.3 First attempt for the synthesis of **1.6**

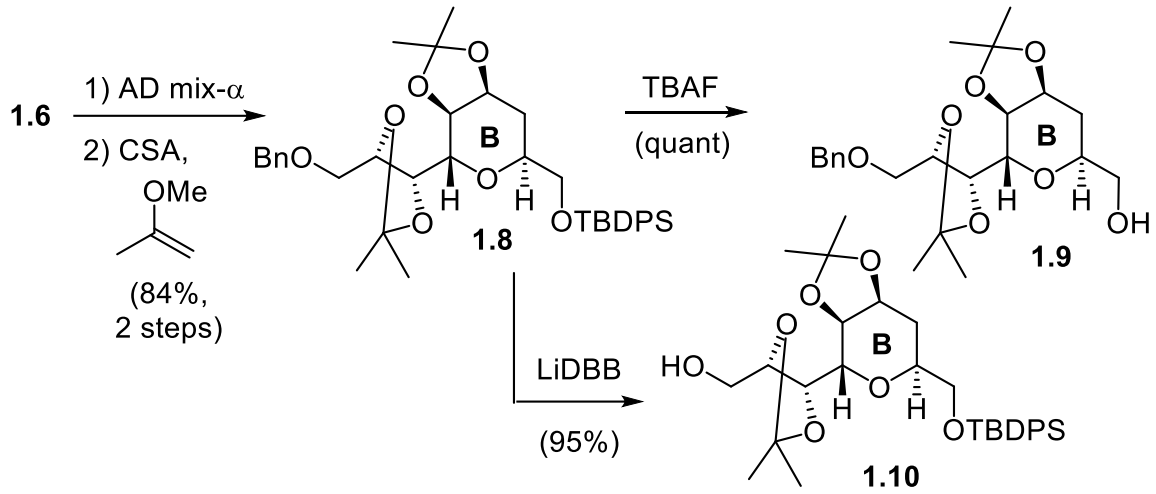
As an alternative method to avoid this dead end, a Horner-Wadsworth-Emmons reagent was treated with the aldehyde from ozonolysis (Scheme 1.4). Fortunately, the desired (*E*)-α,β-unsaturated ester **1.5** was obtained almost exclusively over the (*Z*)-isomer with an excellent yield (89% over three steps). As another alternative method, a Wittig reagent was also tested in place of the HWE reagent for the same reaction sequence.

However, the overall yield was inferior (60 % over three steps). Reduction of ester **1.5** with DIBALH gave an allyl alcohol, which was then protected with a benzyl group to produce benzyl ether **1.6** in 94% yield over two steps (Scheme 1.4).



Scheme 1.4 Successful synthesis of **1.6**

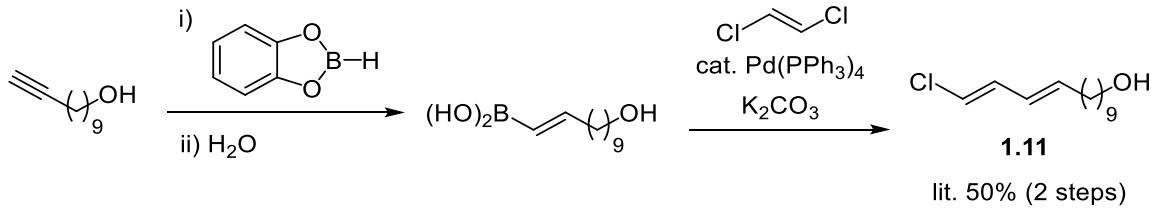
Two vicinal stereocenters on C46-C47 of benzyl ether **1.6** were established *via* the Sharpless asymmetric dihydroxylation reaction (Scheme 1.5).[54] The product diol was accordingly protected as an acetonide to give diacetonide **1.8** (84% over two steps). In order to confirm the stereoconfiguration of **1.8**, it was converted to primary alcohol **1.9** by simply removing the silyl protection; an enantiomer of **1.9** was reported as a synthetic intermediate by Crimmins *et al*. in the synthesis of Amphidinol 3 in 2010.[55] Gratifyingly, **1.9** totally matched with the Crimmins' enantiomer spectroscopically with only the sign of the optical rotation inverted {**1.9**: $[\alpha]_D^{20}$ -3.75° (*c* 0.40, CH_2Cl_2), lit.: $[\alpha]_D^{23.5}$ +3.76° (*c* 3.3, CH_2Cl_2)}. A radical-mediated debenzylation of **1.8** with lithium di-*tert*-butylbiphenylide (LiDBB)[56] provided primary alcohol **1.10** in 95% yield (Scheme 1.5).



Scheme 1.5 Synthesis of **1.10**

1.3.2. Chlorodiene unit synthesis

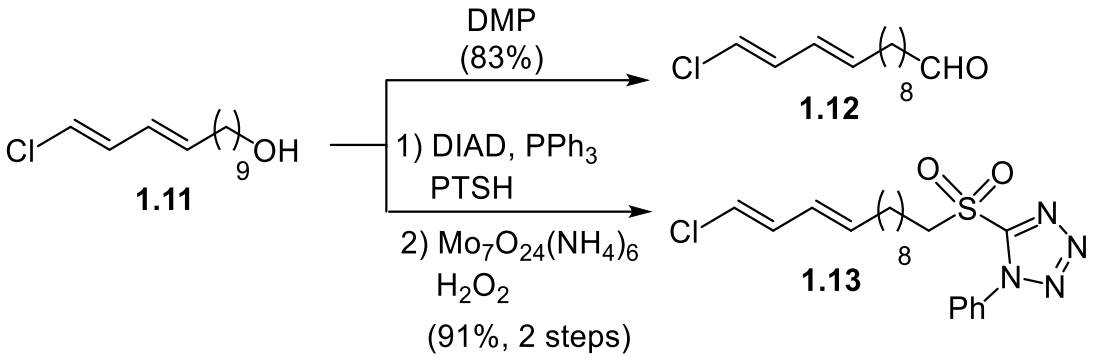
The chlorodiene fragment synthesis was readily accomplished. A two-step literature procedure furnished primary alcohol **1.11** from commercially available undec-10-yn-1-ol (23% over 2 steps) (Scheme 1.6).[57]



Scheme 1.6 Reported synthesis of **1.11**

Although (*E*)-selectivity is normally expected from the Julia-Kocienski olefination, its stereochemical outcome is often substrate-dependent and thus hard to predict; for this reason, both aldehyde **1.12** and sulfone **1.13** were prepared so that the olefination could be attempted in both possible directions. A simple DMP oxidation of **1.11** gave aldehyde **1.12** in 83 % yield. One-pot Mitsunobu reaction of **1.11** provided a

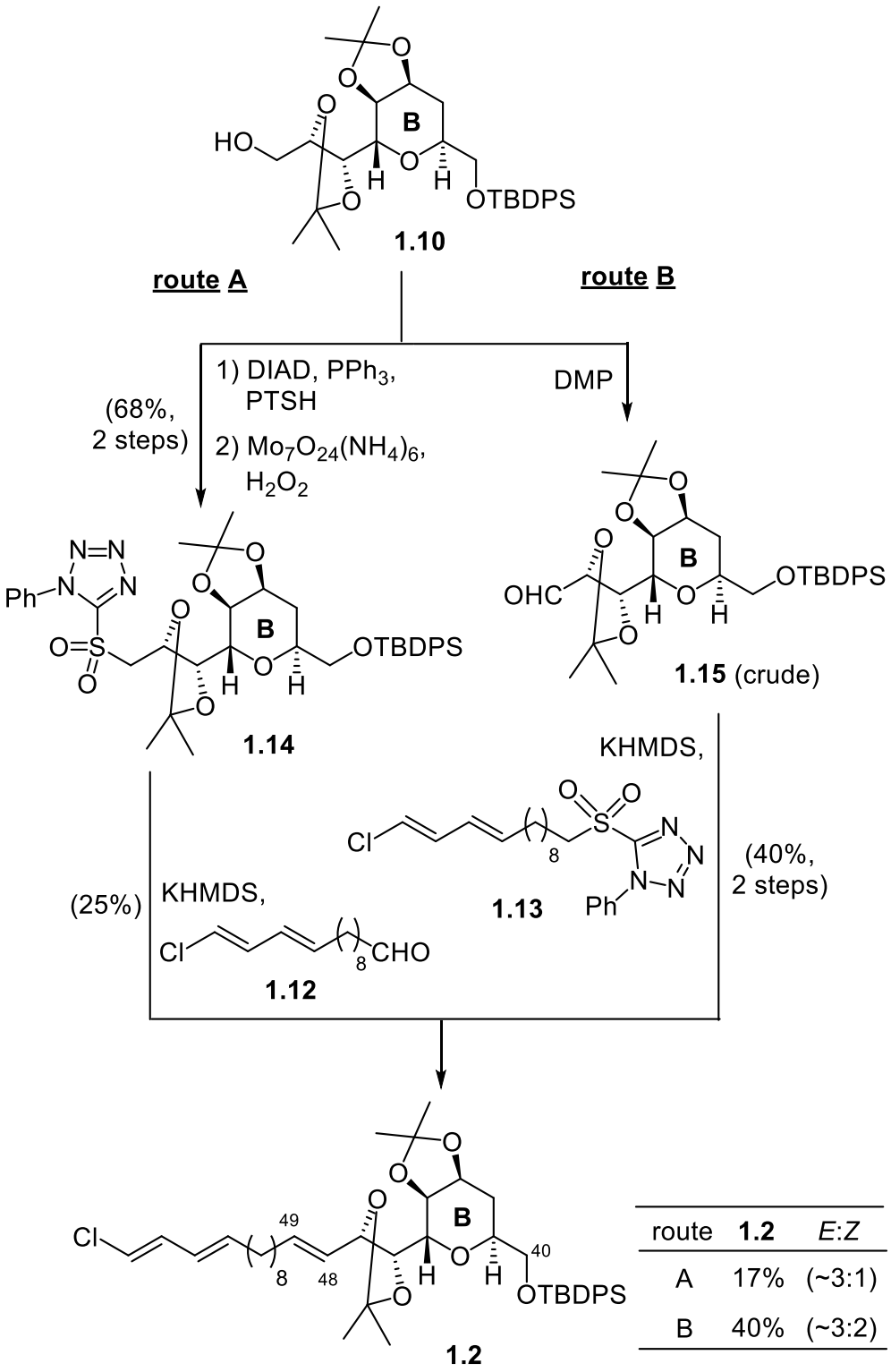
thioether intermediate, which was oxidized with ammonium molybdate tetrahydrate in hydrogen peroxide to afford sulfone **1.13** (91% over two steps) (Scheme 1.7).



Scheme 1.7 Syntheses of **1.12** and **1.13**

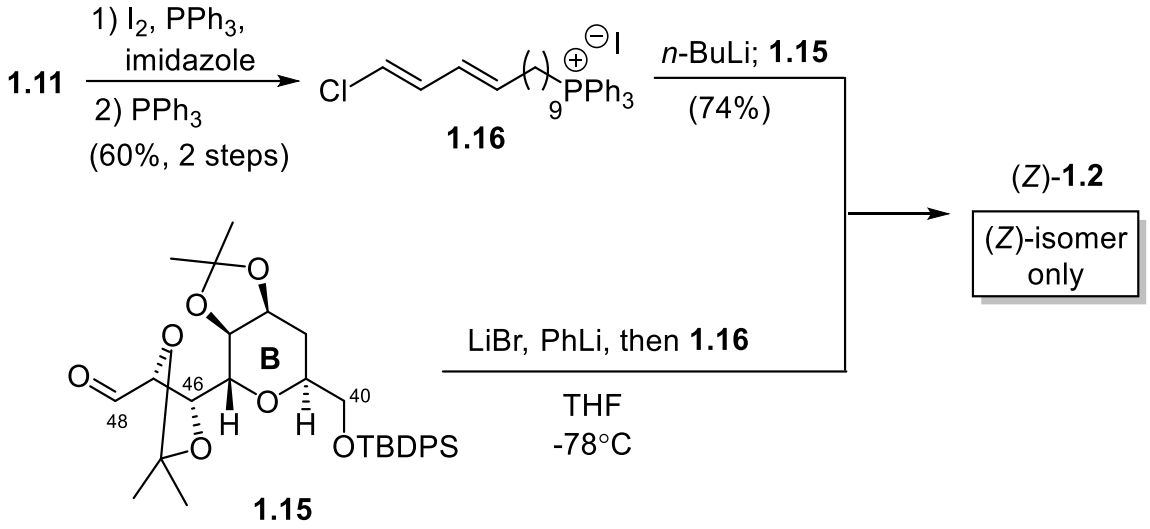
1.3.3. Attachment of the chlorodiene unit to the B-ring moiety

In the same manner, primary alcohol **1.10** was transformed into sulfone **1.14** and aldehyde **1.15**, respectively (Scheme 1.8). These fragments (namely **1.12** & **1.14**, and **1.13** & **1.15**) were finally assembled together to build the C48-C49 connection *via* the Julia-Kocienski olefination. Although both route A and route B successfully produced the desired adduct **1.2**, the former resulted in a better (*E*)-stereoselectivity (*E*:*Z* = ~3:1) whereas the latter gave a better overall yield (40% over two steps). (*E*)-**1.2** and (*Z*)-**1.2** were only separable by HPLC.

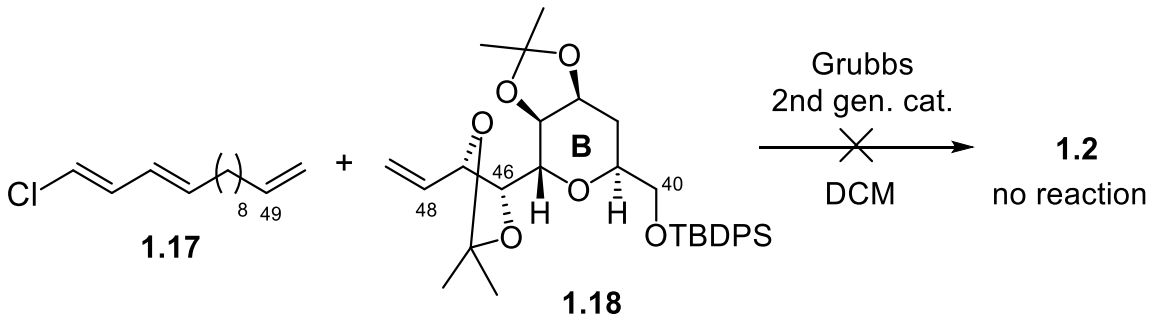


Scheme 1.8 Julia-Kocienski reaction

As back-up approach for the C48-C49 double bond construction, Wittig reactions were also examined by converting primary alcohol **1.11** to triphenylphosphine iodide salt **1.16** (Scheme 1.9). Unfortunately, just as we suspected, Wittig olefination *via* non-stabilized phosphorus ylide exclusively afforded the (*Z*)-isomer of **1.2**. Schlosser's modified Wittig condition often gives (*E*)-alkene from non-stabilized ylide as a major isomer;[58-59] however, it failed to provide us any of the olefin products this time. In addition, an attempt of olefin cross metathesis using second-generation Grubb's catalyst only came to naught (Scheme 1.10).



Scheme 1.9 Wittig reactions



Scheme 1.10 Olefin cross metathesis

1.4. Summary

In summary, we have accomplished concise synthesis of the C(40-61) B-ring THP fragment starting from readily-available common THP intermediate **1.3** in a 12-step reaction sequence (11% overall yield from **1.3**, 83% average per step). The Julia-Kocienski olefination was efficiently utilized to construct the C48-C49 connection by coupling the core B-ring THP moiety and the chlorodiene unit at the end of the synthesis. This work was published in *Tetrahedron Letters* in September 2013 with the help of Dr. Toshihide Maejima, Dr. Yuki Yabe, and Hiroki Iwata in pioneering and working on the reaction steps.[60]

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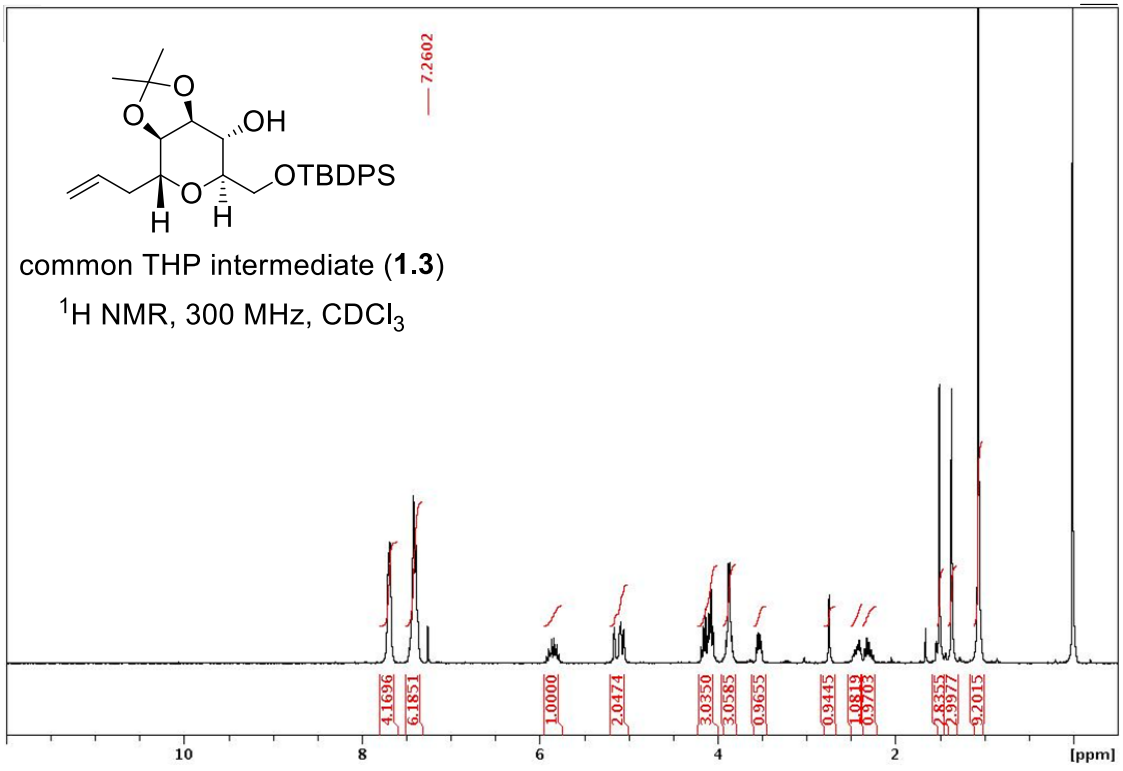
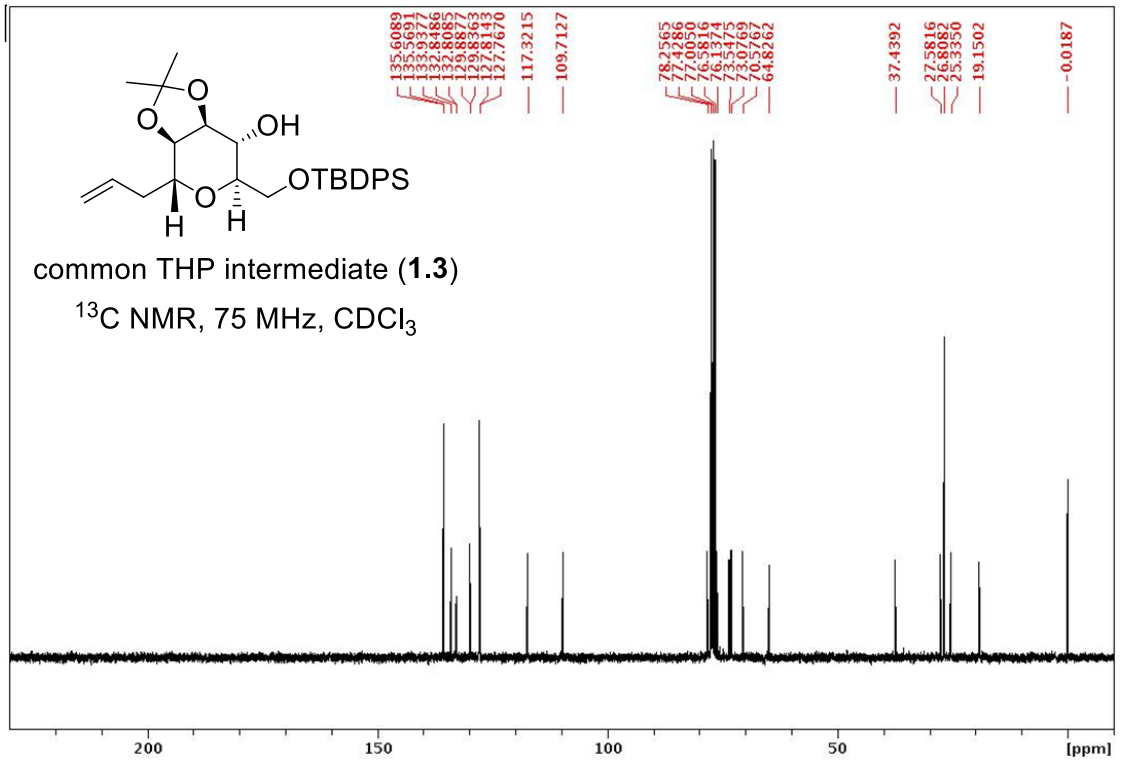
APPENDIX: SPECTRAL DATA



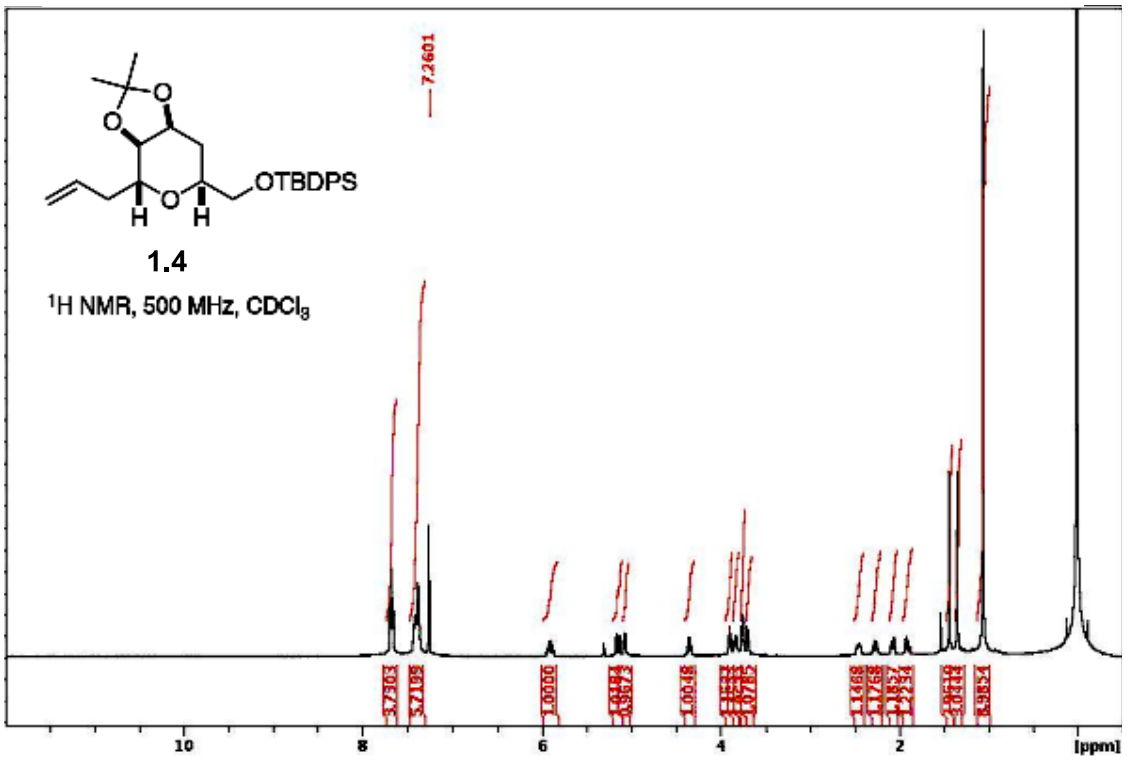
common THP intermediate (**1.3**)

^{1}H NMR, 300 MHz, $CDCl_3$



common THP intermediate (**1.3**)

^{13}C NMR, 75 MHz, $CDCl_3$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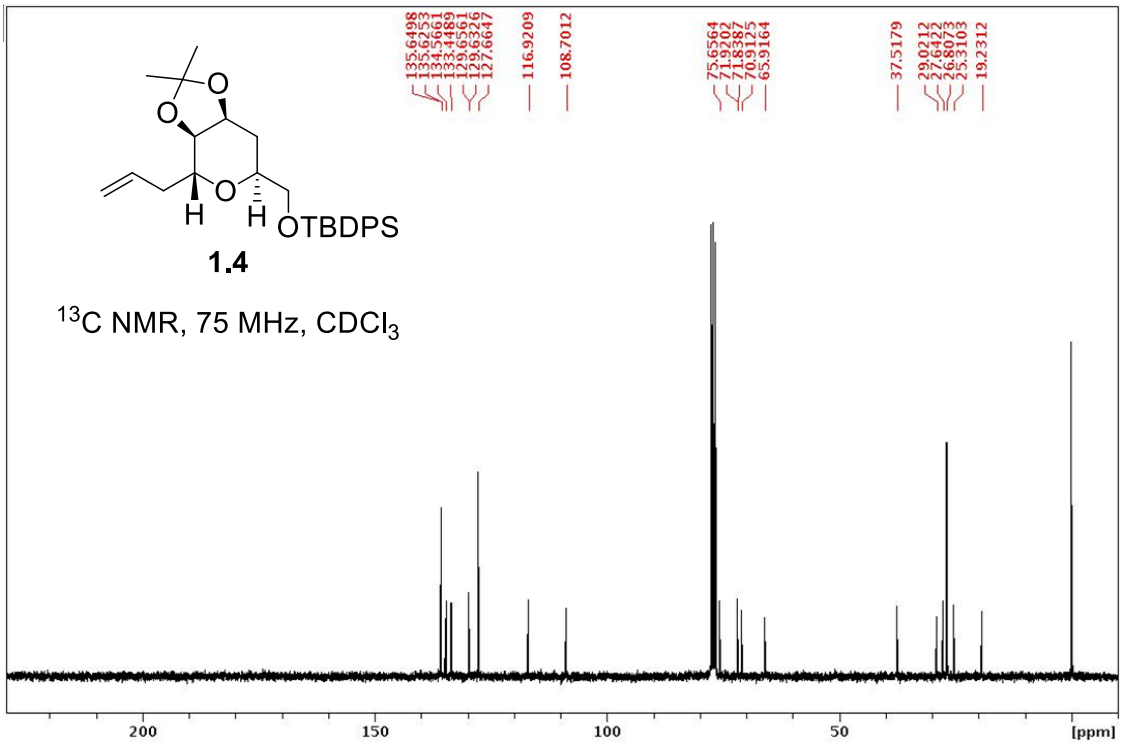
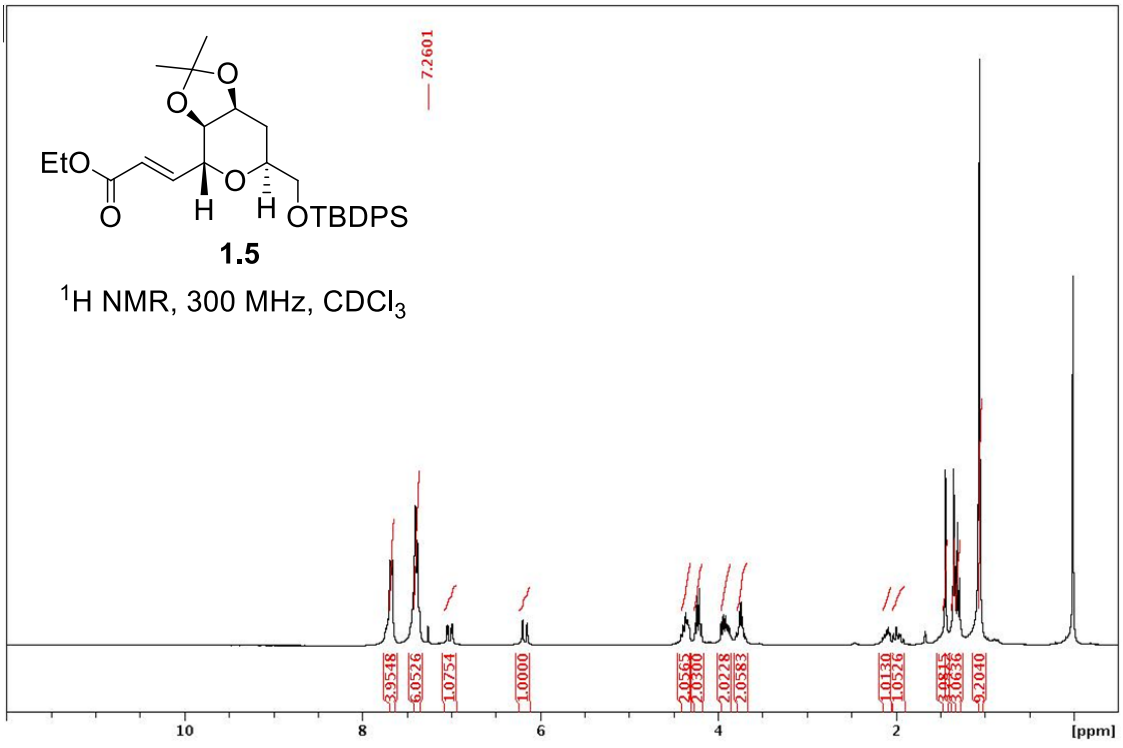
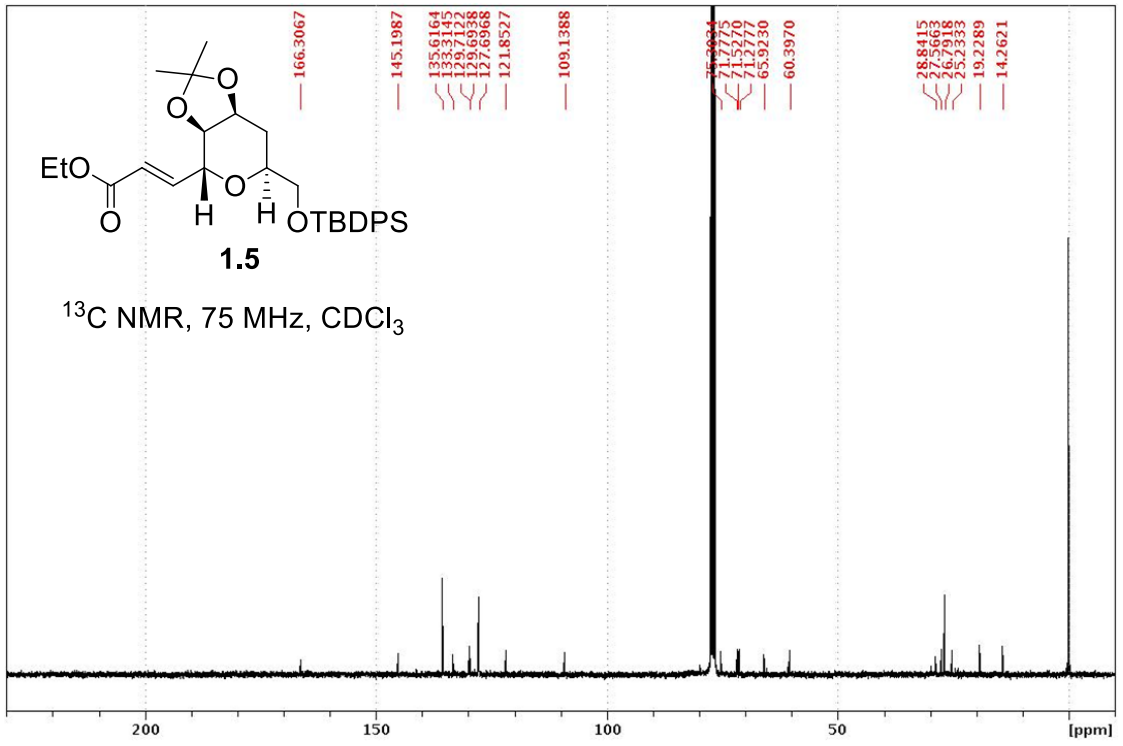
7.2601
10
8
6
4
2
[ppm]


OTBDPS
1.4
^{13}C NMR, 75 MHz, $CDCl_3$
135.6498
135.6253
134.5661
133.4489
129.6561
129.6326
127.6647
116.9209
108.7012
75.6564
71.9202
71.8387
70.9125
65.9164
37.5179
29.0212
27.6422
26.8073
25.3103
19.2312
200
150
100
50
[ppm]


EtO
O
O
O
H
H
OTBDPS
1.5
^{1}H NMR, 300 MHz, $CDCl_3$
7.2601
3.9548
6.0526
1.0754
1.0000
2.0565
2.0300
2.0228
2.0583
1.0130
1.0526
3.0815
3.0636
9.2040
10
8
6
4
2
[ppm]


EtO
O
O
O
H
H
OTBDPS
1.5
^{13}C NMR, 75 MHz, $CDCl_3$
166.3067
145.1987
135.6164
133.3145
129.7122
129.6938
127.6968
121.8527
109.1388
71.7775
71.7277
71.1277
65.9230
60.3970
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27.5663
26.7338
25.2333
19.2289
14.2621
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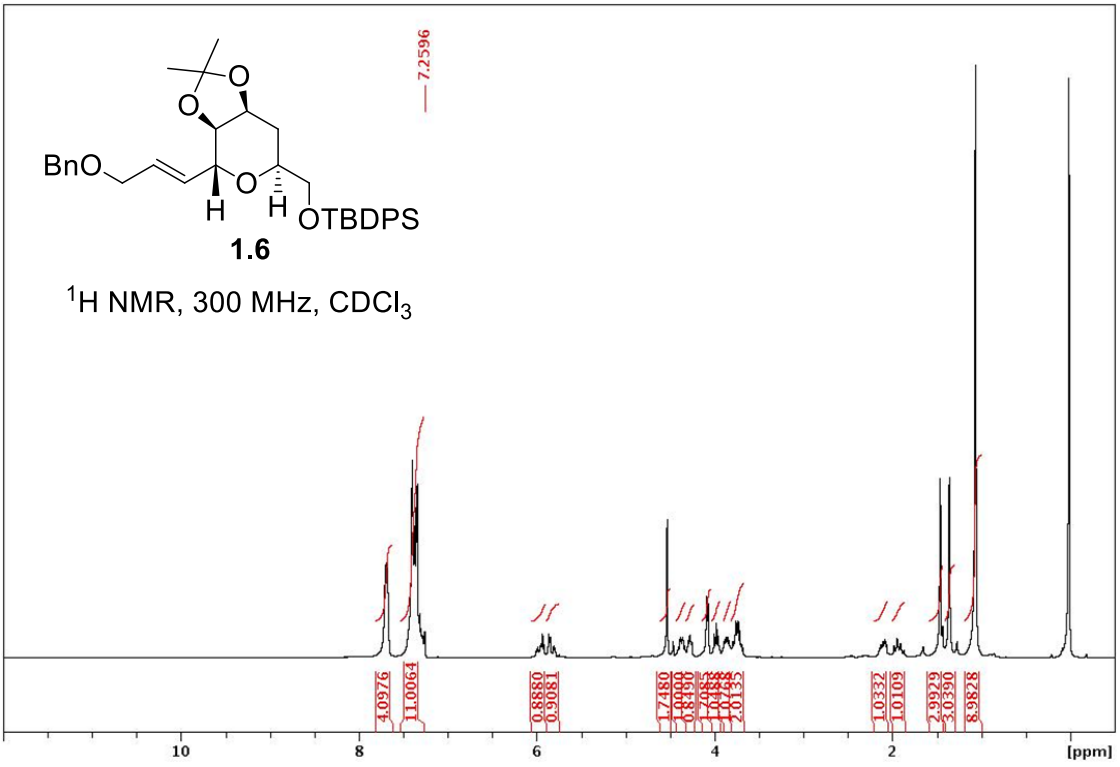
150
100
50
[ppm]


BnO
O
O
O
H
H
OTBDPS
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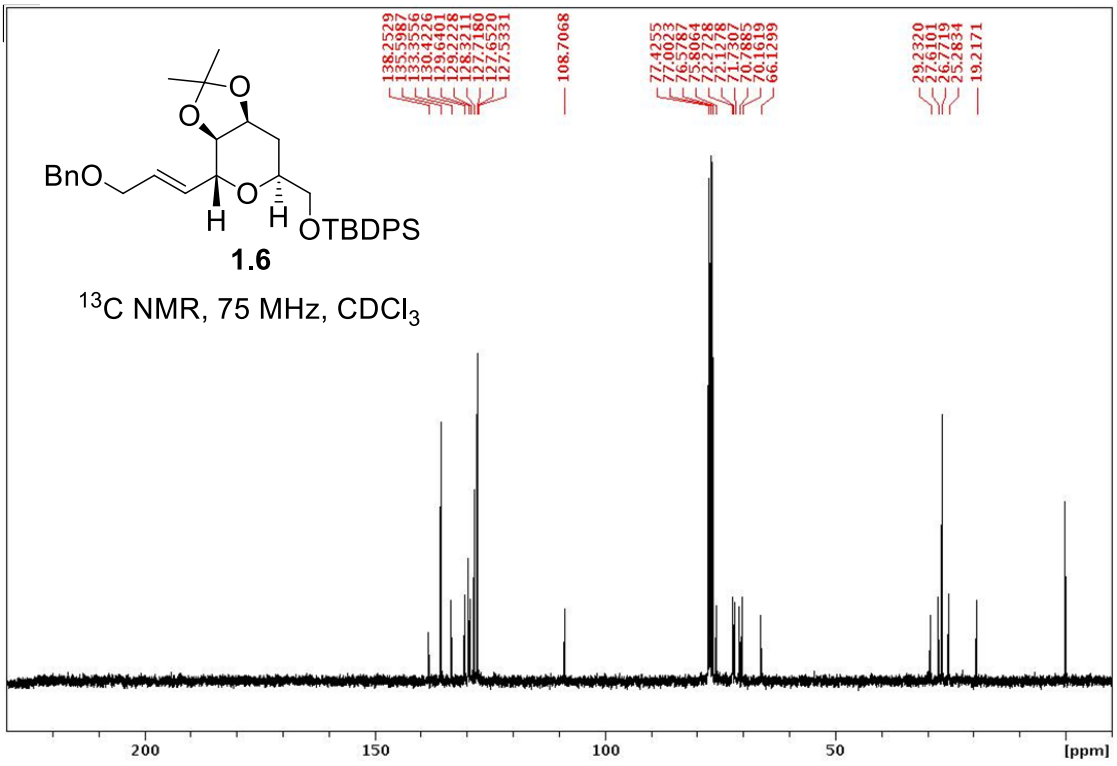
1.0332
1.0109
2.9929
3.0390
8.9828
10
8
6
4
2
[ppm]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O
O
H
H
OTBDPS
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130.4226
129.6401
129.2228
128.3711
127.6520
127.5331
108.7068
77.4255
77.0023
76.5787
75.8064
72.2728
72.1278
71.7307
70.7885
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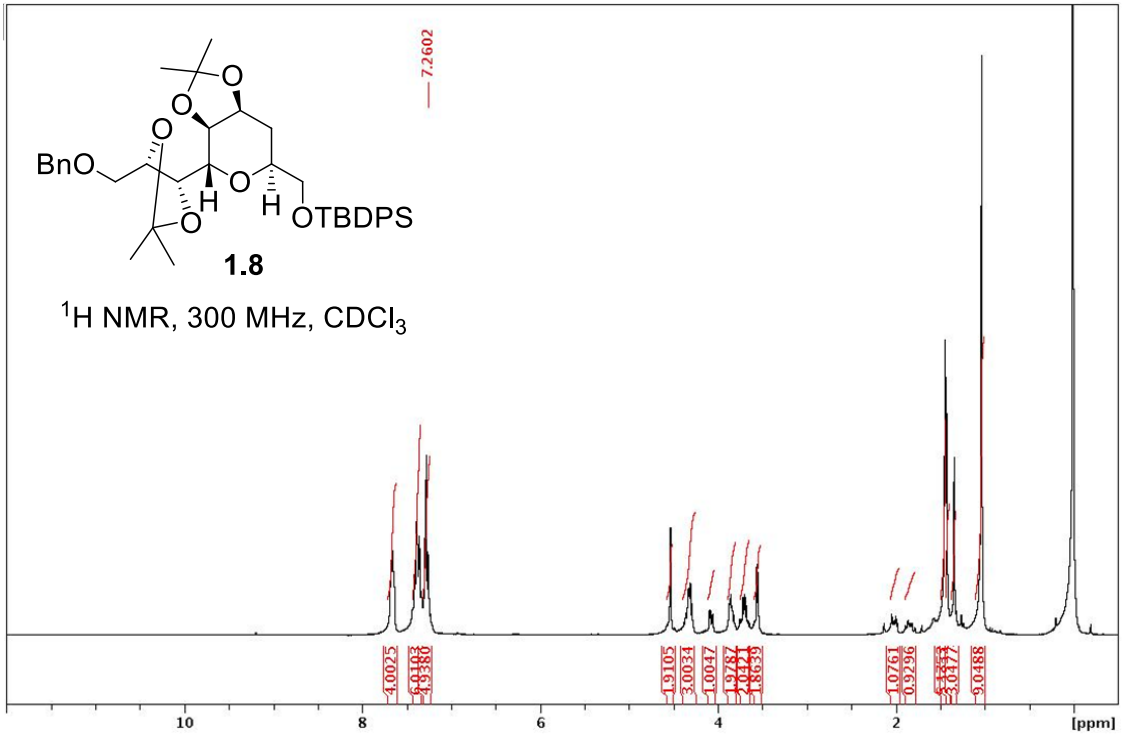
29.2320
27.6101
26.7719
25.2834
19.2171
200
150
100
50
[ppm]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H
H
OTBDPS
1.8
^{1}H NMR, 300 MHz, $CDCl_3$
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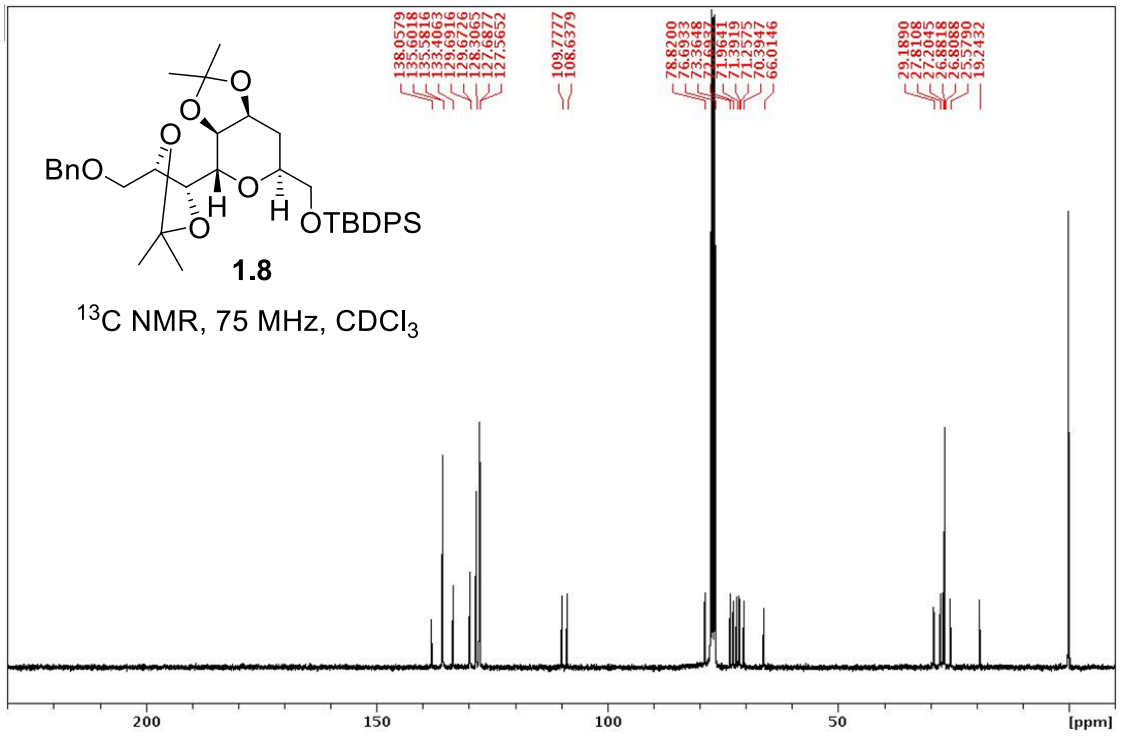
4.0025
6.0103
4.9380
1.9105
3.0034
1.0047
1.9787
2.0421
1.8639
1.0761
0.9296
6.1353
3.0477
9.0488
10
8
6
4
2
[ppm]


BnO
H
H
OTBDPS
1.8
^{13}C NMR, 75 MHz, $CDCl_3$
138.0579
135.6018
135.5816
133.4063
129.6916
129.6726
128.3065
127.6877
127.3652
109.7777
108.6379
78.8200
76.6933
73.3648
72.0647
71.3919
71.2575
70.3947
66.0146
29.1890
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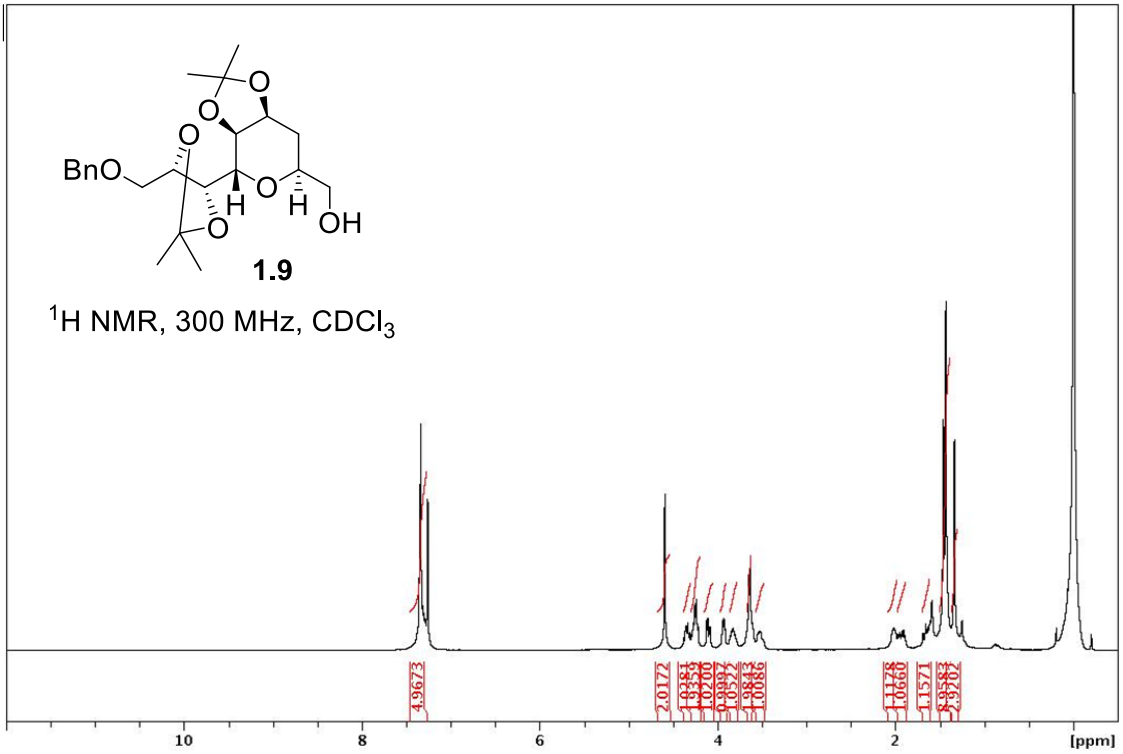
27.2045
26.8818
26.8088
25.5790
19.2432
200
150
100
50
[ppm]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O
O
O
H
H
O
OH
1.9
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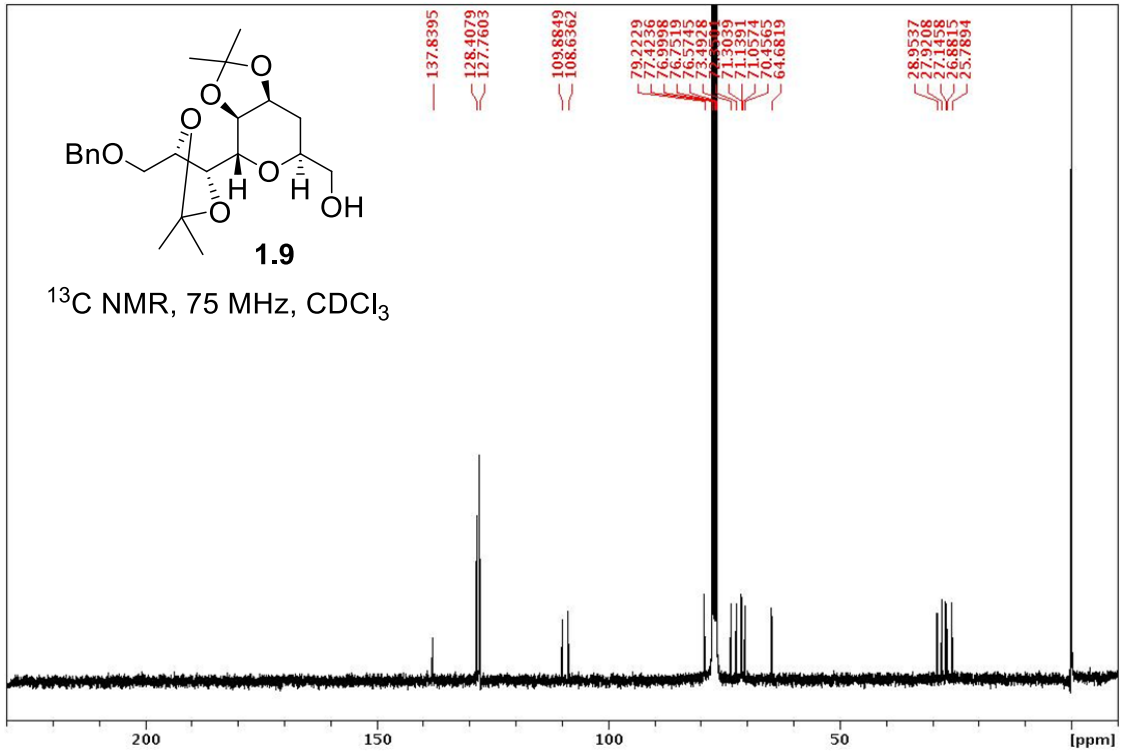
1.0000
1.1571
10
8
6
4
2
[ppm]


BnO
O
O
O
O
H
H
O
OH
1.9
^{13}C NMR, 75 MHz, $CDCl_3$
137.8395
128.4079
127.7603
109.8849
108.6362
79.2229
77.4236
76.9998
76.7519
76.5745
73.4928
71.3039
71.1391
71.0574
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28.9537
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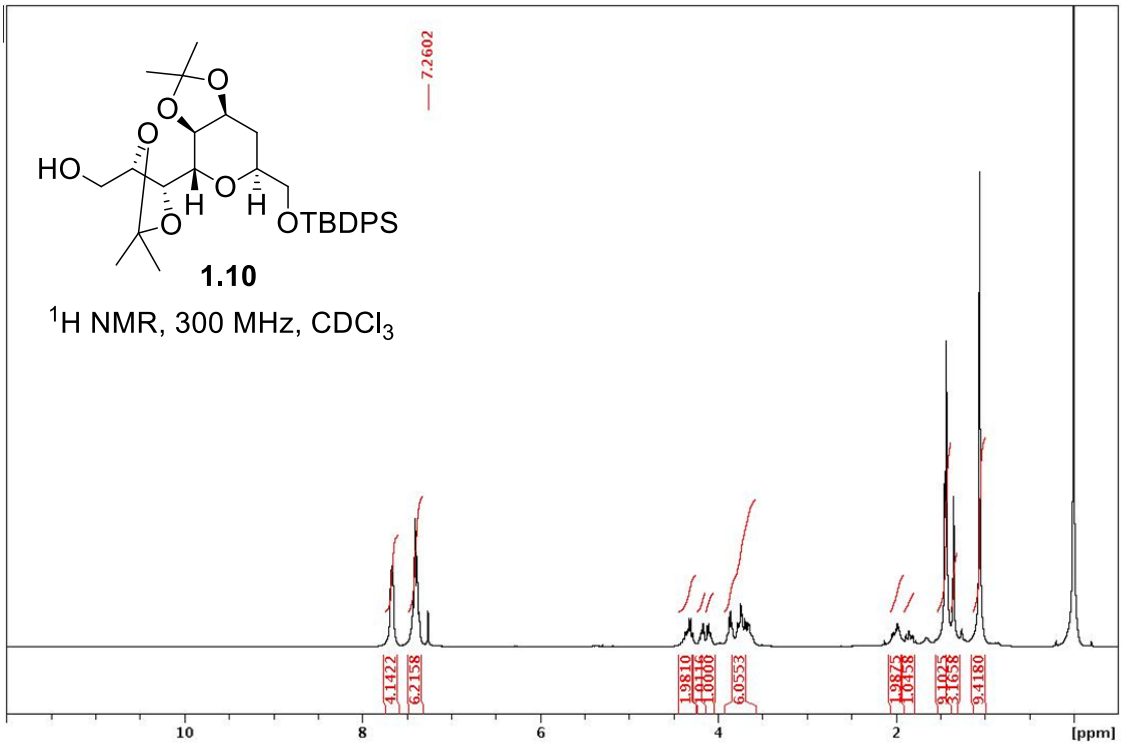
26.8815
25.7894
200
150
100
50
[ppm]



1.10

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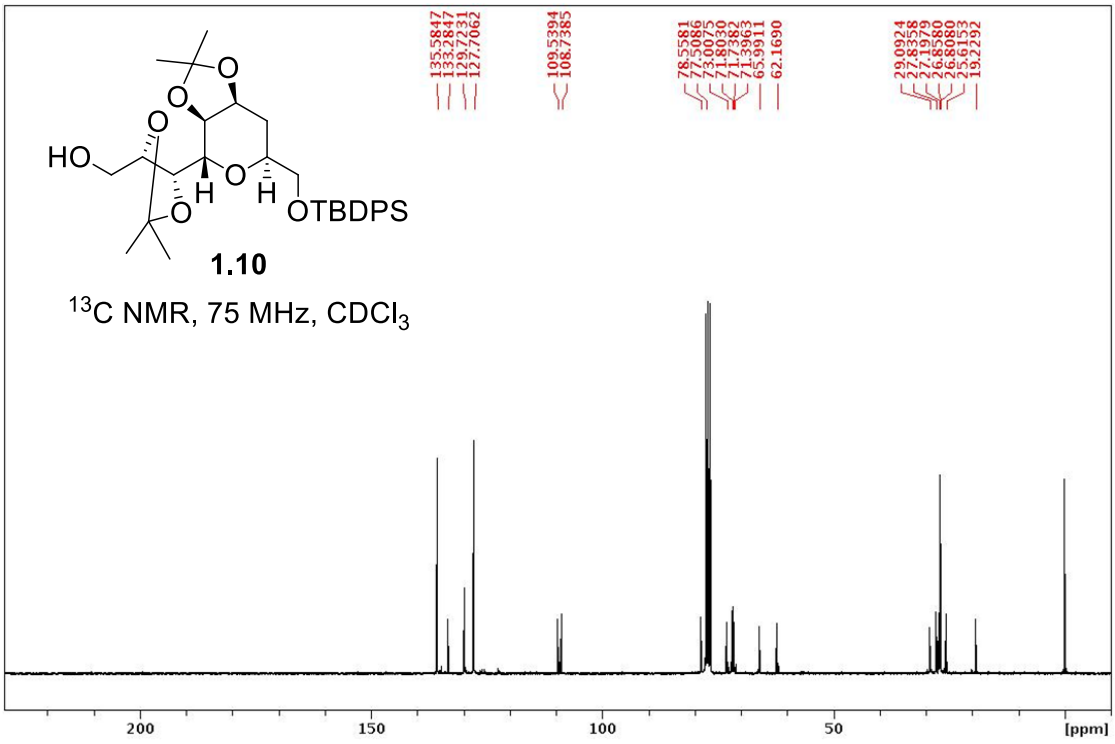
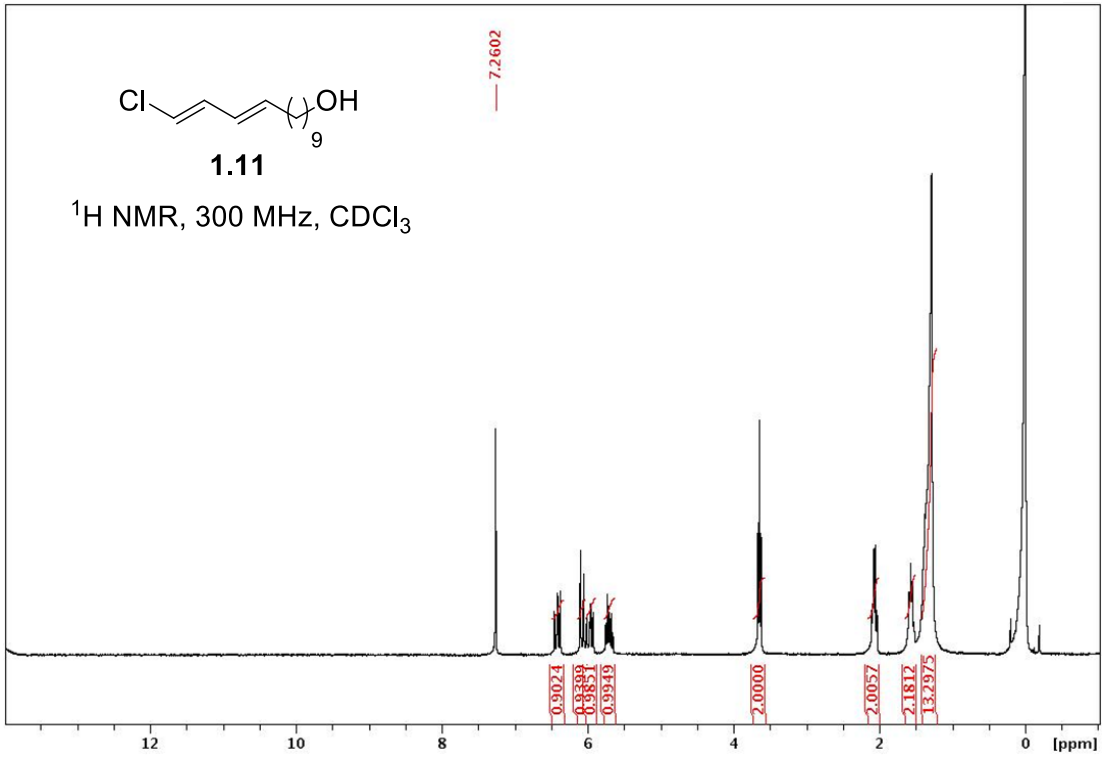


1.10

^{13}C NMR, 75 MHz, $CDCl_3$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OH
9
1.11
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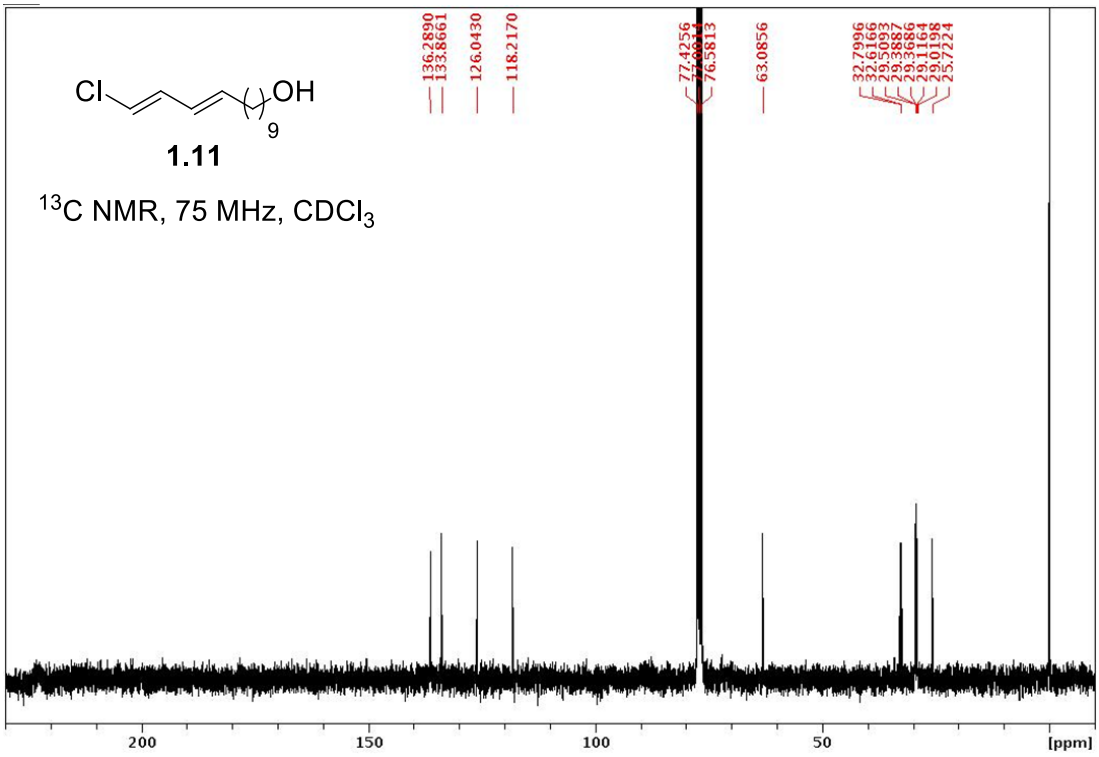
2.0000
2.0057
2.1812
13.2975
12
10
8
6
4
2
0
[ppm]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OH
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126.0430
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77.4256
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76.5813
63.0856
32.7996
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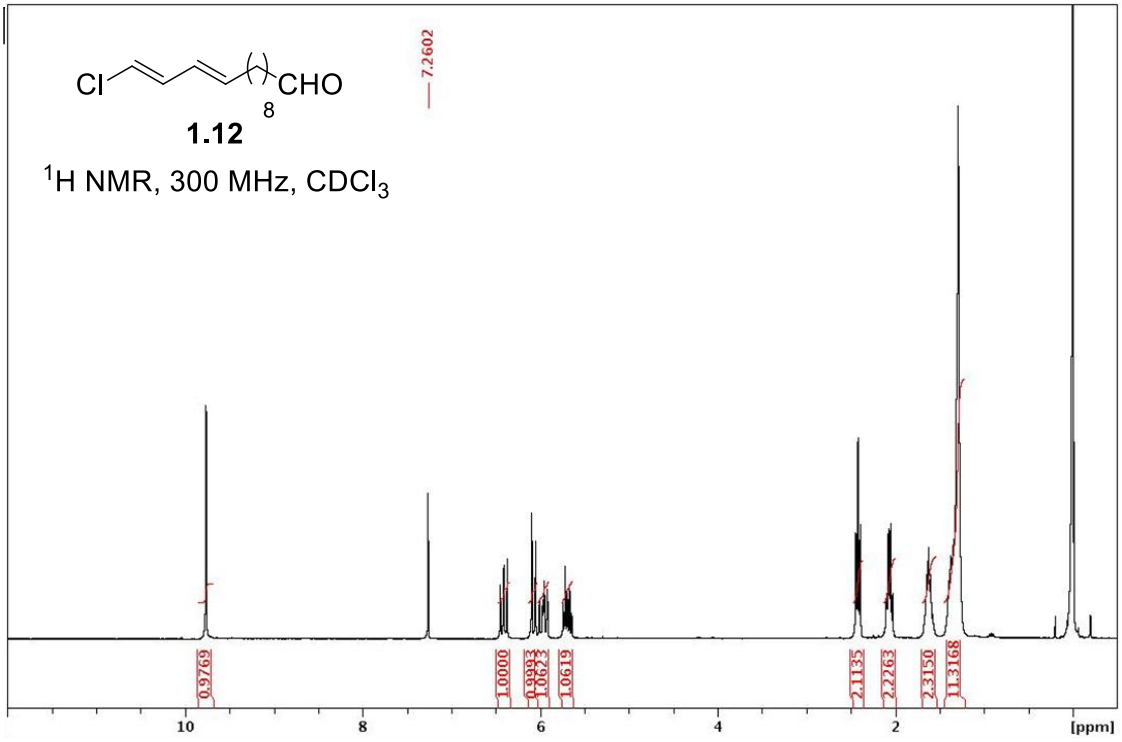
29.0198
25.7224
200
150
100
50
[ppm]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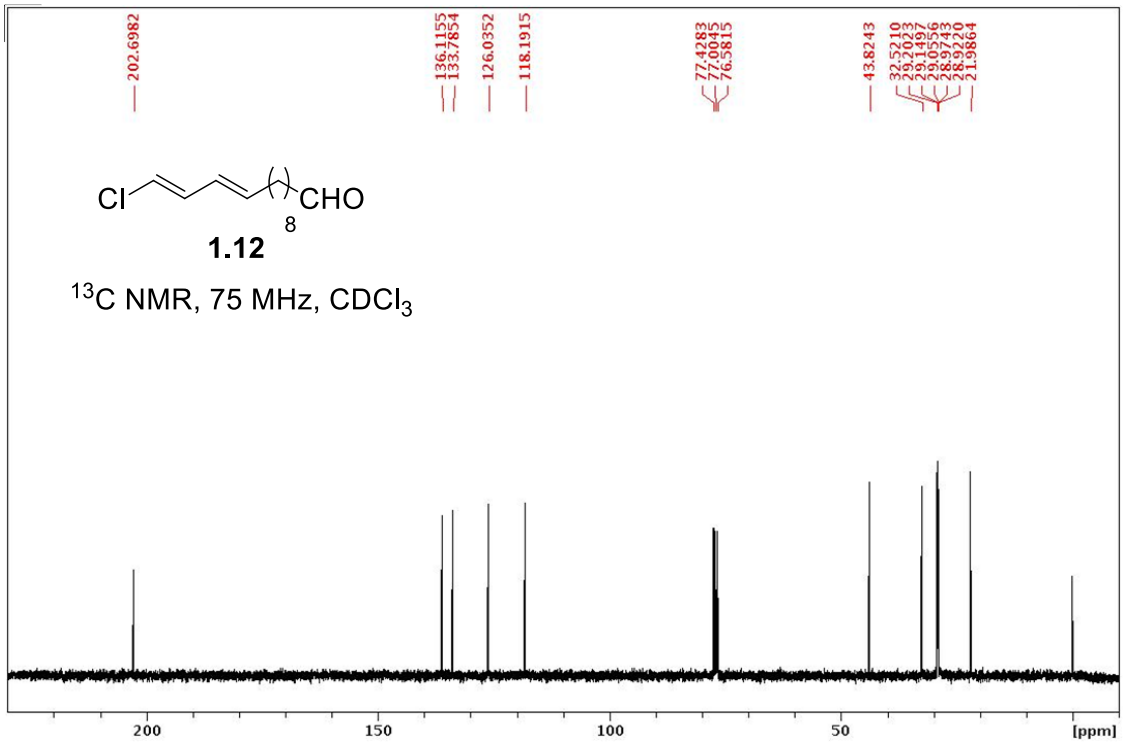
1.0619
2.1135
2.2263
2.3150
11.3168
10
8
6
4
2
[ppm]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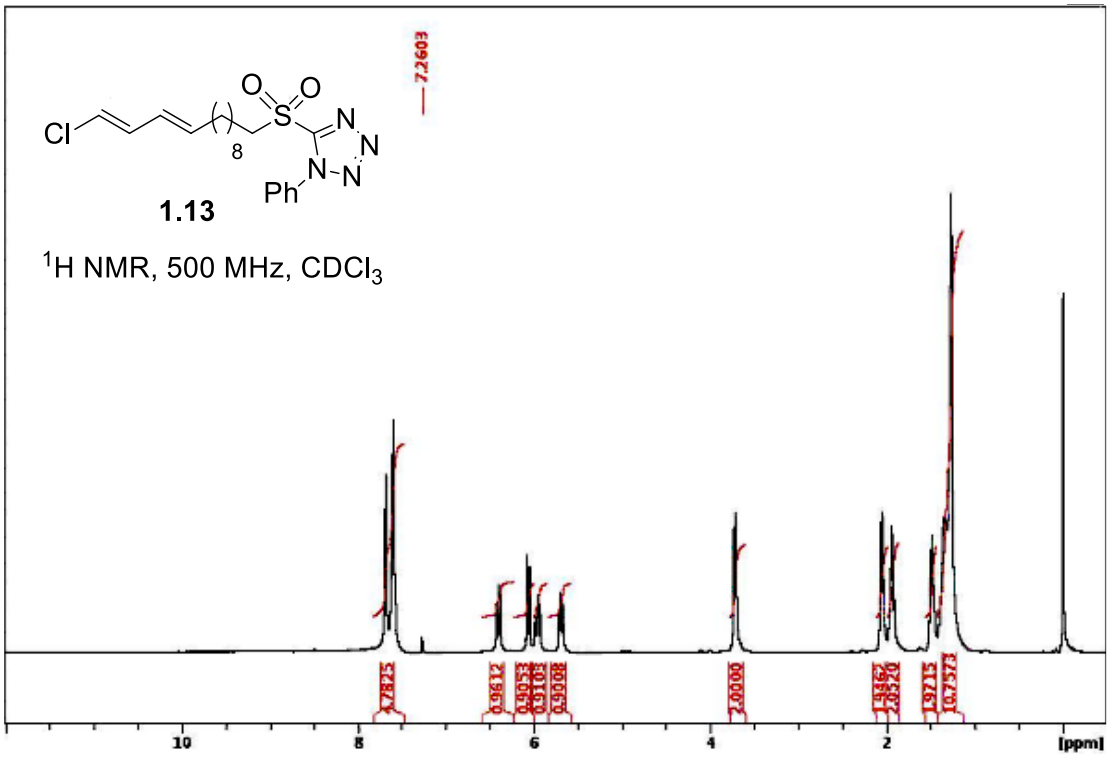
32.5210
29.2023
29.1497
29.0576
28.9723
28.9220
21.9864
Cl
CHO
8
1.12
^{13}C NMR, 75 MHz, $CDCl_3$
200
150
100
50
[ppm]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O
S
N
N
N
N
Ph
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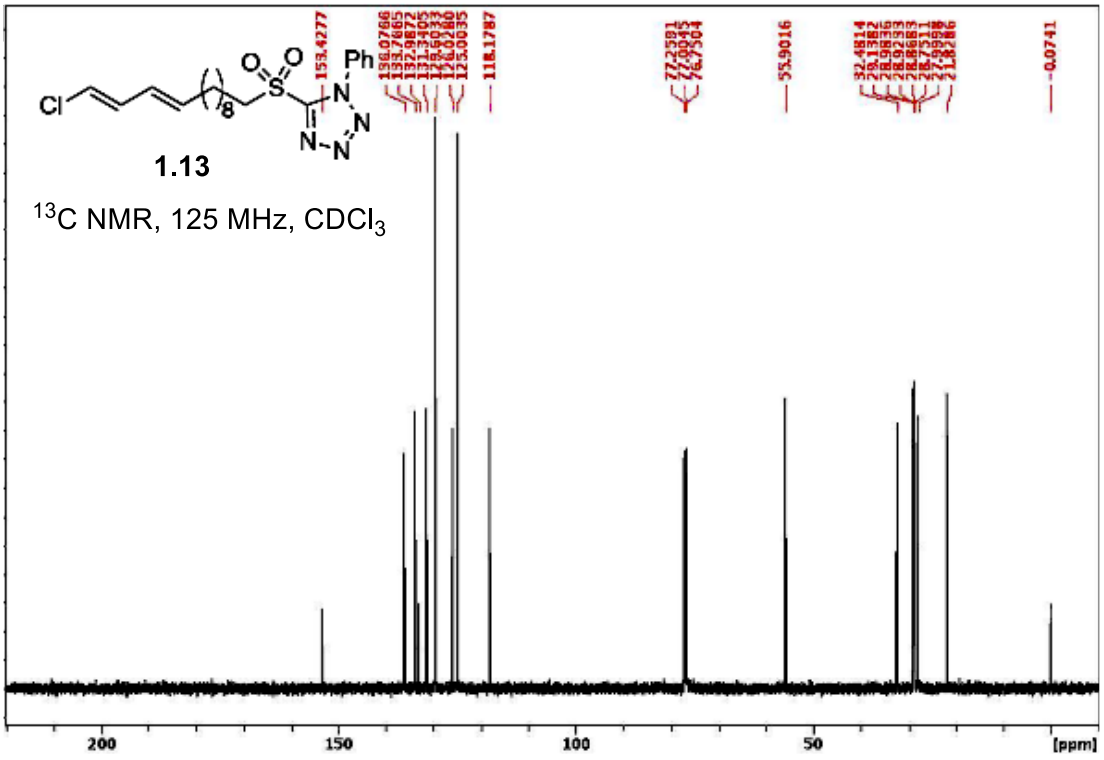
10
8
6
4
2
[ppm]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O
O
S
N
N
N
N
Ph
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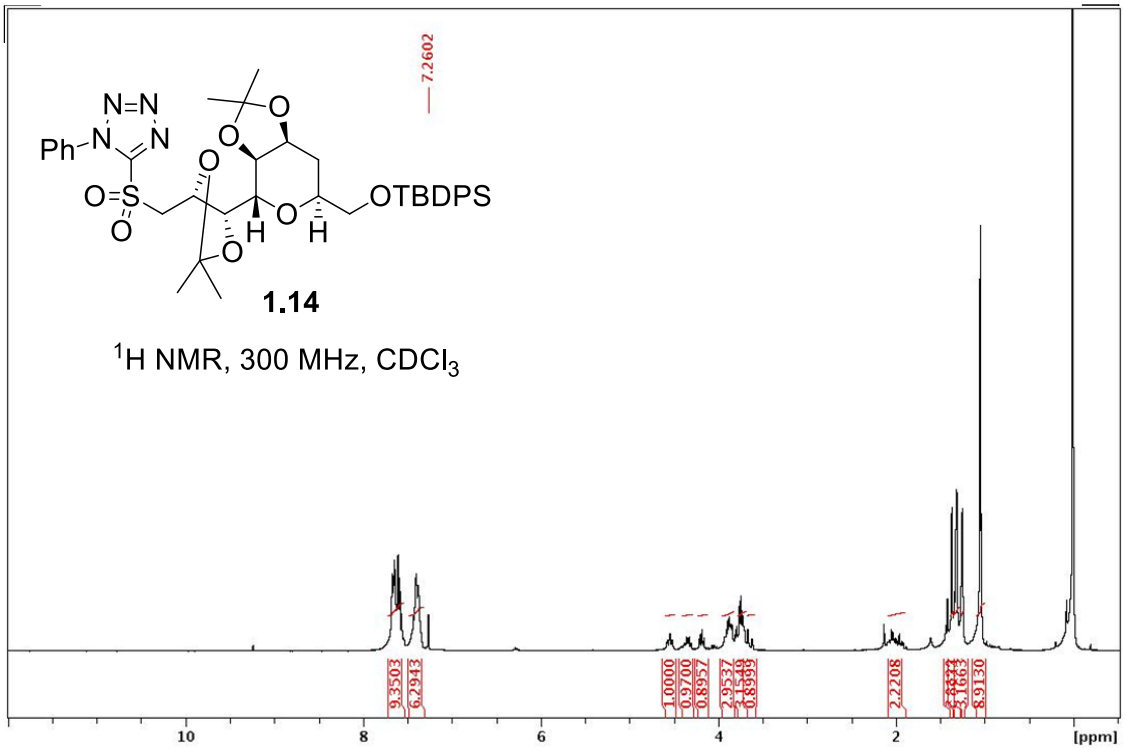
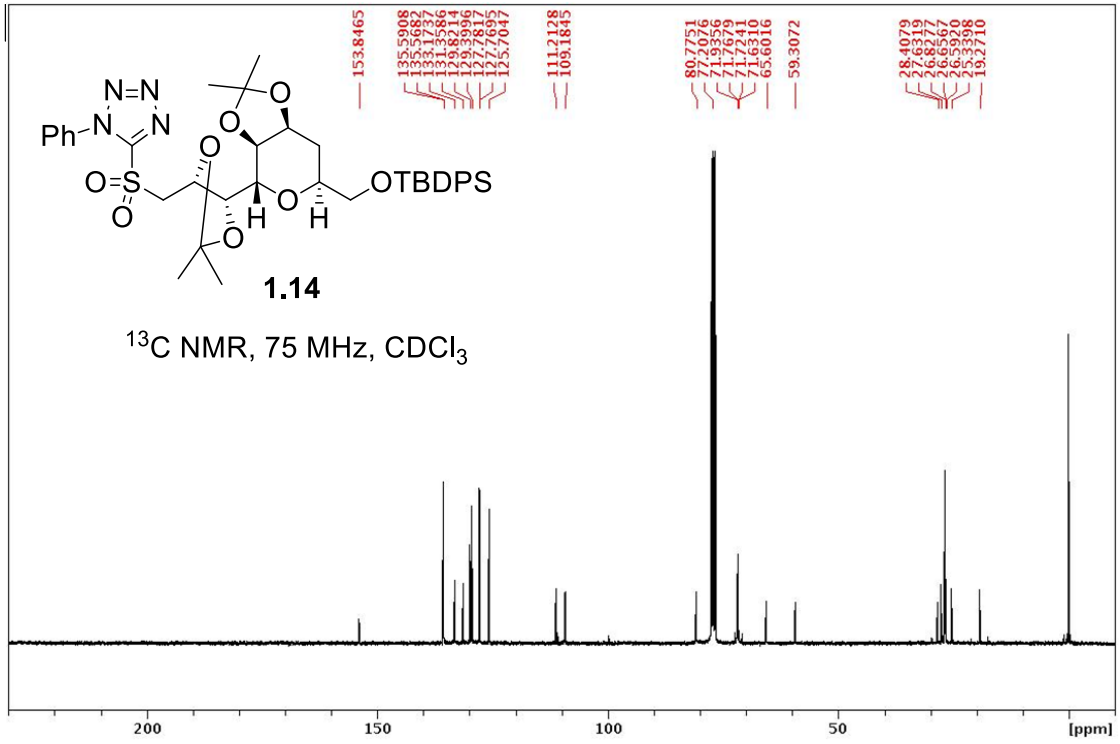
118.1787
77.2581
77.0045
76.7504
55.9016
32.4814
-0.0741
1.13
^{13}C NMR, 125 MHz, $CDCl_3$
200
150
100
50
[ppm]



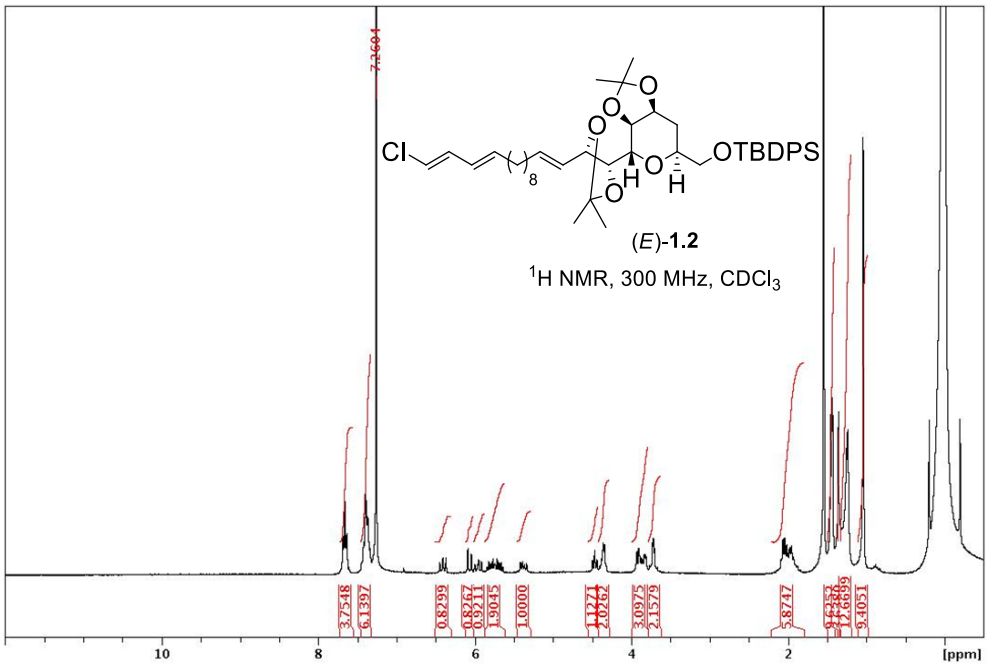
1.14

^{1}H NMR, 300 MHz, $CDCl_3$



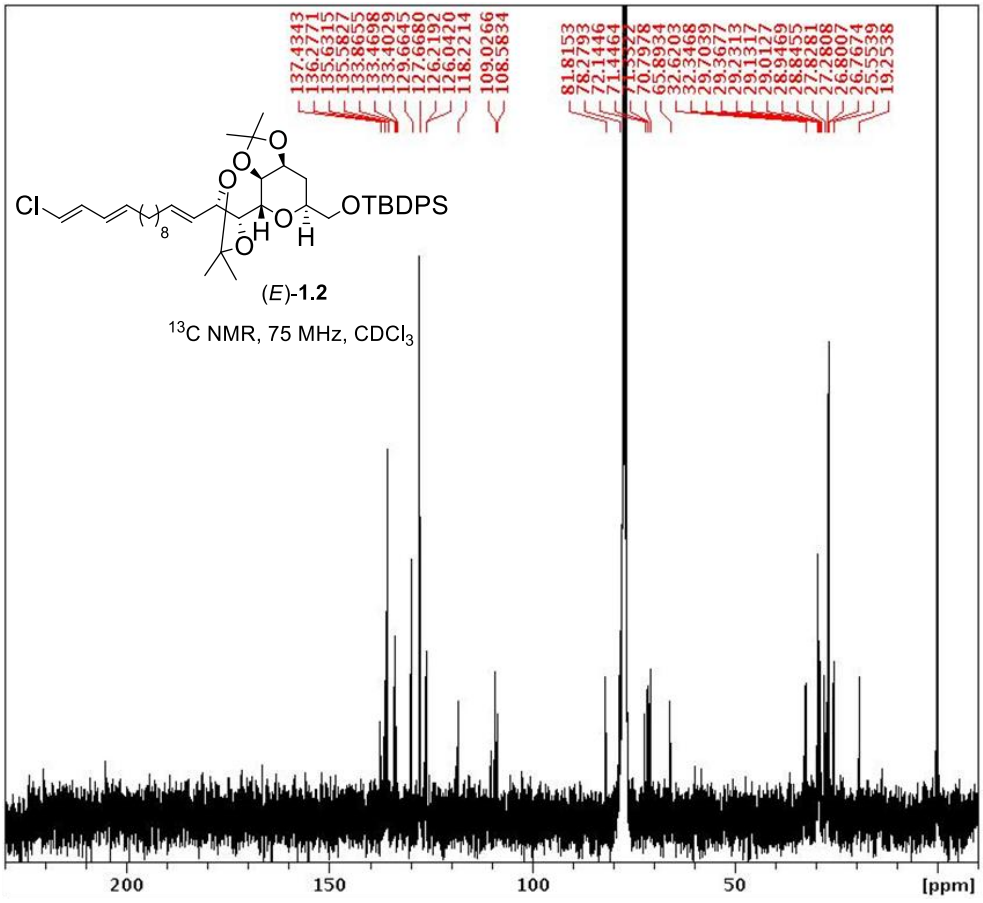
1.14

^{13}C NMR, 75 MHz, $CDCl_3$



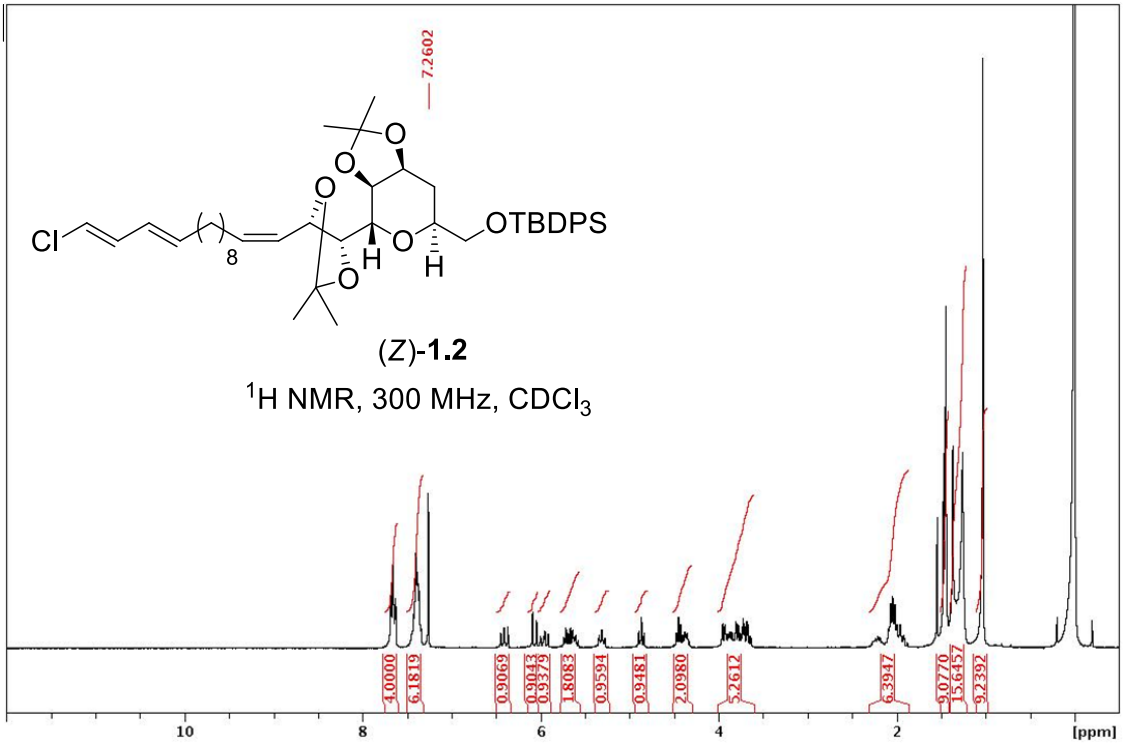
(*E*)-**1.2**

^{1}H NMR, 300 MHz, $CDCl_3$



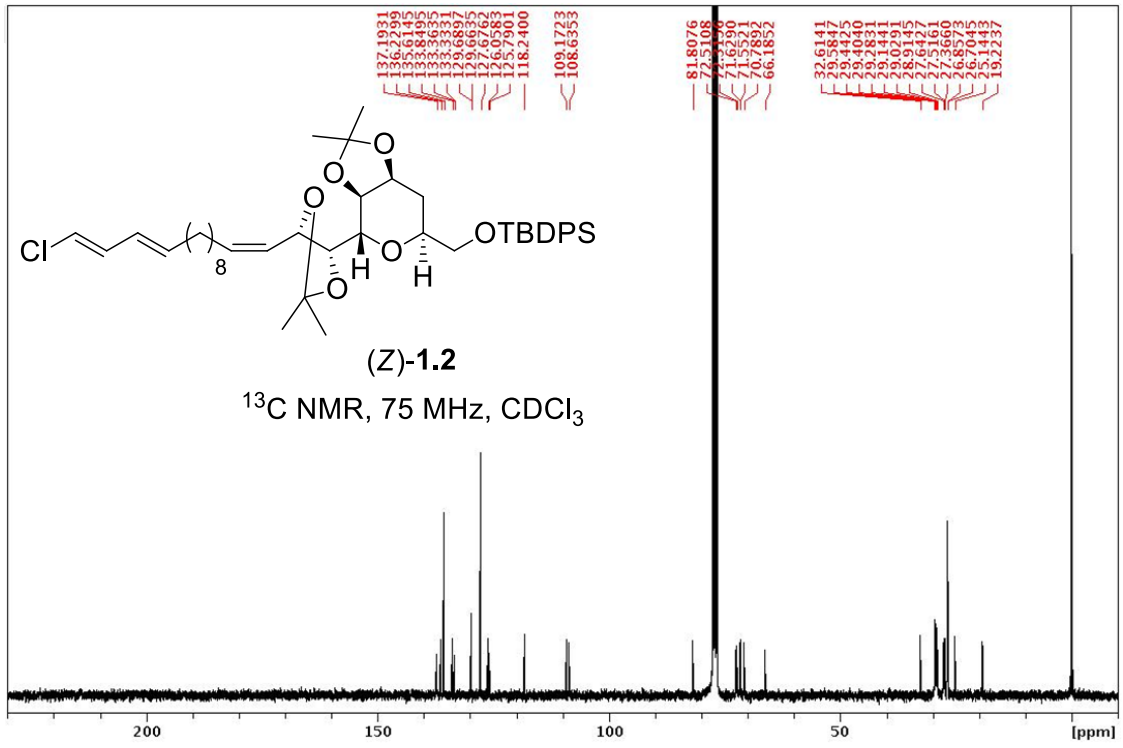
(*E*)-**1.2**

^{13}C NMR, 75 MHz, $CDCl_3$



(*Z*)-**1.2**

^{1}H NMR, 300 MHz, $CDCl_3$



(*Z*)-**1.2**

^{13}C NMR, 75 MHz, $CDCl_3$

CHAPTER 2: UTILIZATION OF NOVEL ALPHA-DIAMINOBORYL CARBANION SPECIES FOR ORGANIC SYNTHESIS

2.1. Introduction

2.1.1. One-pot reaction protocol as green chemistry

Ever since Paul T. Anastas and John C. Warner proposed "The 12 Principles of Green Chemistry" in 1998,[61] the concept of environmentally benign science has occupied an important place in the organic chemistry community.[62-65] Indeed, the 2005 Nobel Prize in chemistry was awarded jointly to Chauvin, Grubbs, and Schrock for the development of the metathesis method in organic synthesis that is more efficient, simpler to use, and environmentally friendlier than alternative reactions. The press release by the Committee stated that "This represents a great step forward for `green chemistry', reducing potentially hazardous waste through smarter production. Metathesis is an example of how important basic science has been applied for the benefit of man, society and the environment".[66]

As one of many green chemical approaches, a one-pot reaction strategy has been employed as a powerful synthetic tool since it can construct complex chemical structures quite efficiently. In a one-pot reaction, multiple reaction steps are operated in a single reaction vessel without changing solvent and without isolating intermediate compounds throughout the whole process. Some of its advantages over other reaction strategies include utilization of lower amount of solvents, generally higher yields, and shorter reaction times. In this manner, the energy/resource consumption is expected to be lower

since less energy/heat is used for shorter reaction processes; likewise, the materials that would have been required for isolation of each reaction intermediate will be saved as well. This one-pot protocol especially demonstrates its true value when a reaction intermediate is unstable and thus hard to isolate. Furthermore, because multiple reactions (*i.e.* functional group inter-conversions, or FGI) are consecutively achieved in a single flask, it is well-applied for the synthesis of "multi-functionalized reagents" that are chemical species bearing more than one functional group within their own molecules. They are often recognized as synthetic precursors or building blocks of complex molecules and utilized for the construction of various types of natural/unnatural products. Preparation of these reagents, however, can be troublesome at times due to several reasons (*e.g.*, stability issues, solubility issues, and reagent compatibility issues with the functional groups within the same molecule). These problematic issues have emerged as an obstacle to be overcome in the field of synthetic chemistry. As a group, our interest is to design, synthesize, and develop a variety of novel multi-functionalized reagents that are useful and stable enough to be utilized for further transformations to access a broad range of desired target molecules of synthetic importance. As part of our research interest, within myriad functionalities in the field of organic synthesis, we particularly focus on organoboron chemistry.

2.1.2. History of boron in organic synthesis

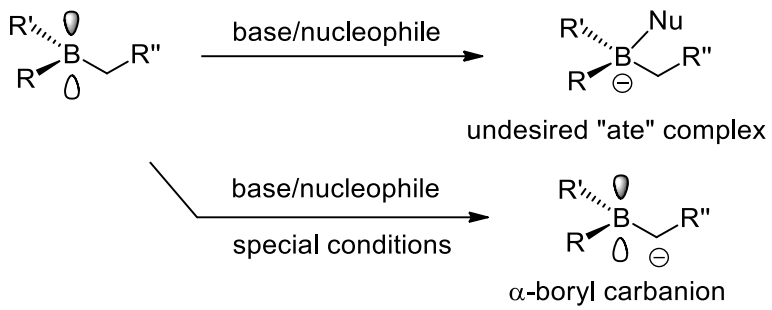
Compared to the long history of organic chemistry, boron is a relatively new element to be incorporated in organic chemical reactions: in fact, it was only after H. C.

Brown found its application for the hydroboration reaction in 1956 that boron became one of the essential elements in the field of organic synthesis.[67] Since then, a great amount of effort worldwide has been dedicated to preparing and utilizing boron-containing compounds. Many of them exhibit chemically and structurally unique properties, which makes them valuable reagents as well as attractive synthetic targets. As organoboron chemistry gains recognition as a powerful tool for organic synthesis, the demand for boron-based reactions and methodologies has been dramatically increased, especially over the past few decades. Those boron-containing compounds have been widely utilized in symmetric/asymmetric reductions (*e.g.*, $NaBH_4$, Corey-Bakshi-Shibata reduction),[68-69] hydroboration-oxidation reactions,[70] and cross-coupling reactions (*e.g.*, Suzuki-Miyaura cross-coupling reaction),[71] and many other useful organic transformations.[72-74] Within a large scope of applications of organoboron compounds, α-boryl carbanion species[75] are known to show excellent olefinating abilities just like α-silyl[76-77] and α-phosphoryl[78-79] species do. Those α-boryl carbanion-based olefinations are often considered as a boron-analog of Wittig reaction, therefore called "boron-Wittig" reactions. Preliminary studies for this particular area of chemistry were first conducted by Cainelli[80] and co-workers in the mid 1960's; then Rathke,[81] Pelter,[82] and Matteson[83] developed/expanded its scope and applications mainly during the 1970's, 80's, and early 90's. Each group successfully developed their own methods to efficiently generate α-boryl carbanion species. Nevertheless, we still find enormous potential out of those species for further improvement and progress on various aspects, such as reactivity, molecular design, and stereoselectivity. Moreover, we strongly believe that we can

contribute our unique idea to provide an extra depth to this chemistry; hence we have decided to explore the chemistry of highly functionalized organoboron species (*i.e*., α-boryl carbanions), utilizing a one-pot protocol to gain access to a variety of target molecules of synthetic interest.

2.1.3. Background chemistry

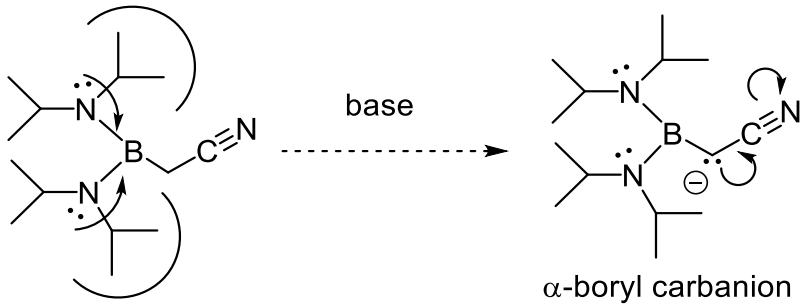
A boron atom in a molecule in its neutral ground state is sp^2-hybridized, thus making such organoboron molecules trivalent and possessing a trigonal planar geometry with only six valence electrons and with an empty p orbital. Owing to this make-up of the boron atom, organoboron compounds are normally electron deficient and thereupon are more or less Lewis acidic. Largely attributed to this Lewis acidity, these compounds are typically very reactive toward a Lewis base and/or nucleophile to accordingly form a tetracoordinate "ate" (*i.e*., borate) complexes. Those borate complexes are of no interest to us since synthetic application of those species has been exhaustively demonstrated in the literature (*e.g*., reductive hydride delivery, Suzuki-Miyaura cross-coupling reaction, *etc*.). In special conditions, however, it is observed that the carbon atom in the α-position to a boron atom is deprotonated by a base/nucleophile, thus forming an α-boryl carbanion species (Scheme 2.1) that can be utilized for various types of synthetic applications, including olefination reaction.



Scheme 2.1 Generation of α-boryl carbanion

The groups of Rathke, Pelter, and Matteson in the last third of 20th century attempted smoother generation of those species, and they successfully devised effective solutions of their own: (i) the use of non-nucleophilic base with sufficient steric bulkiness,[84] (ii) attachment of sterically hindered ligands on boron,[85-86] and (iii) geminal allocation of electron-rich heteroatoms on boron.[87-88] Based on these preliminary studies, we can clearly conclude that there are two factors playing crucial roles in the process of efficient generation of the anionic α-boryl species: steric and electronic environments around the boron atom. Taking these into consideration, we have designed and proposed a novel diaminoboryl acetonitrile reagent "$(R_2N)_2BCH_2CN$" with effectively suppressed Lewis acidity and sterically tunable dialkylamino ligands on it (Scheme 2.2). The key diaminoboryl moiety consists of two dialkyl amino groups that provide spatial protection to the boron site from the attack of a base and/or nucleophile. In addition, there is strong donation of the electron density from the lone pair electrons on the two nitrogen atoms to the boron's vacant p-orbital.[89-90] Due to these steric and electronic effects, this particular diaminoboryl species possesses an unusually mild Lewis acidic property, which makes it highly base-compatible. The electron-withdrawing cyano group in the α-position to the boron helps increase the acidity of the α-hydrogens, thus making the deprotonation

process easier. The cyano group also stabilizes the newly-generated α-boryl carbanion through both an inductive and a resonance effect. Such a diaminoboryl acetonitrile molecule, both sterically and electronically well-controlled, therefore seems to be an ideal tool for us to study α-boryl carbanion chemistry. To the best of our knowledge, there is no general synthetic path known in the literature to access such boryl acetonitriles, though the potassium salt form of the trifluoroborate (KBF_3CH_2CN) was recently reported by the Molander group.[91]



2.1 **2.2**

Scheme 2.2 α-Diaminoboryl carbanion

2.2. Preparation of β–Monosubstituted (*Z*)-Acrylonitriles

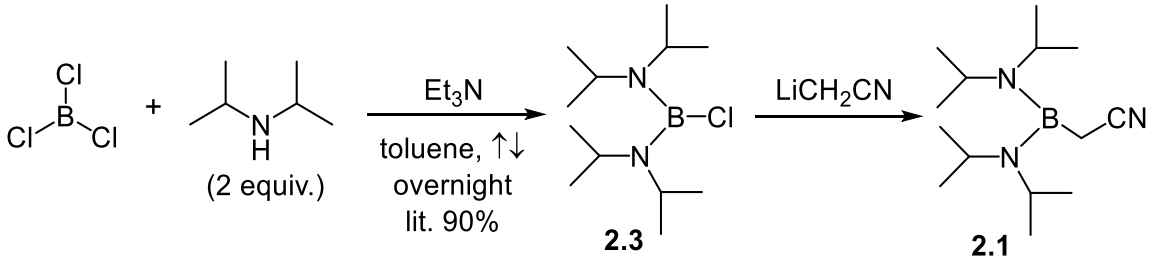
2.2.1. Acrylonitriles and olefination reactions

Acrylonitriles (*i.e.*, variously-substituted vinyl cyanides) are frequently seen in the field of organic synthesis as useful reaction intermediates. Due in large part to their electron deficiency as alkene, they are commonly utilized as electrophiles in a variety of organic transformations, such as the Diels-Alder reaction,[92] the Heck-Mizoroki cross-coupling reaction,[93] the Morita-Baylis-Hillmann reaction,[94] the Michael addition

reaction,[95] and many others.[96] Typical methods to prepare those acrylonitriles are phosphorus-based (*e.g.*, Wittig-type[97]/Horner-Wadsworth-Emmons[98]) or silicon-based (Peterson-type[99-100]) olefination reactions, often in a stereoselective fashion. However, (*Z*)-stereoselective conditions[101] in the literature are still limited and less accomplished in terms of the overall reaction efficiency and operational simplicity.

2.2.2. First one-pot olefination attempt

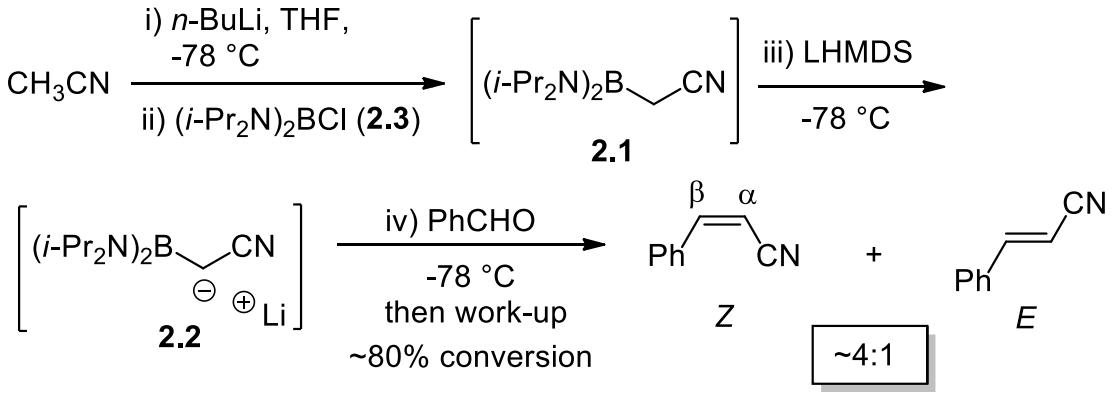
Upon start of the project, bis(diisopropylamino)chloroborane **2.3** was readily prepared according to the literature procedure from commercially available boron trichloride and diisopropylamine in an excellent yield.[102] Treatment of $LiCH_2CN$, generated in the reaction between *n*-BuLi and CH_3CN *in situ*, with **2.3** leads to the formation of diaminoboryl acetonitrile **2.1** (Scheme 2.3).



Scheme 2.3 Formation of diaminoboryl acetonitrile

In order to test its olefinating ability, **2.1** was immediately exposed to a sterically hindered, non-nucleophilic base (*e.g.*, LHMDS) to generate α-boryl carbanion **2.2**. Subsequent addition of a seemingly suitable electrophile, benzaldehyde, to the reaction mixture successfully afforded the desired olefination products (*i.e.*, β-phenyl acrylonitriles), based on ^{1}H NMR analysis (Scheme 2.4). All four reaction steps were

performed in a single flask: (i) deprotonation of acetonitrile, (ii) formation of boryl acetonitrile, (iii) generation of α-boryl carbanion, and (iv) olefination of aldehyde. Interestingly, not only did the reaction give relatively high conversion (~80%), it also produced an unusual stereochemical outcome: the major form of the alkene was the (*Z*)-isomer, rather than the more thermodynamically stable (*E*)-isomer (*Z*:*E* = ~4:1).



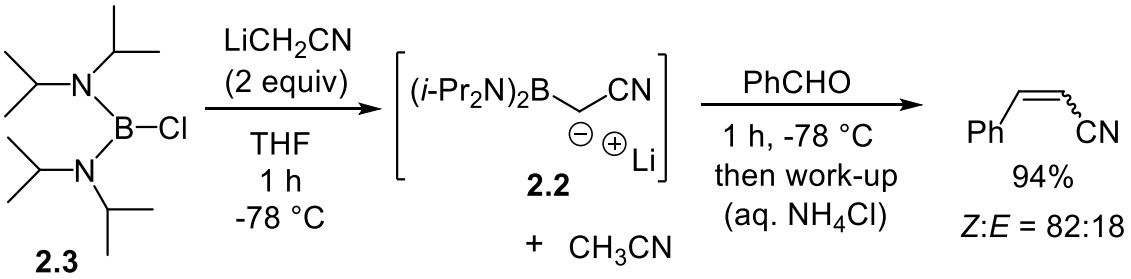
Scheme 2.4 First olefination attempt

2.2.4. Optimization of reaction conditions

As part of optimization attempts, a series of reaction conditions were investigated in terms of a few reaction parameters: solvent (Et_2O), reaction temperature (-20, -40, and -100 °C), additive (TMEDA), and base (MeMgBr, LiTMP, KHMDS, and LDA). Unfortunately, they gave inferior reaction conversions and/or stereoselectivities.

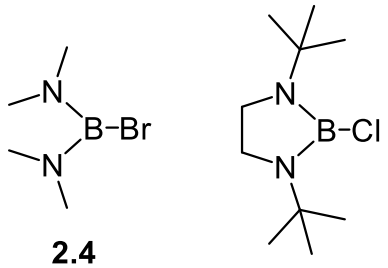
After further optimizing effort, we finally figured out that using two equivalents of highly nucleophilic $LiCH_2CN$ followed by the addition of an aldehyde provided the same, desired β-phenylacrylonitriles in a better reaction yield (94%) and with the original stereoselectivity (*Z*:*E* = 82:18) (Scheme 2.5). This implies the dual-role of $LiCH_2CN$ in

the reaction: the first equivalent acts as a nucleophile to substitute for the chloride on the boron center while the second equivalent now acts as a base to deprotonate the α-carbon to generate the corresponding carbanion species **2.2**. Not only did discovery of this method give extra operational simplicity for this one-pot reaction protocol, it also practically demonstrated the superior anion-compatibility of our diaminoboryl acetonitrile species, since this shows it to be a stronger acid than acetonitrile itself.



Scheme 2.5 Optimized one-pot olefination

In addition to bis(diisopropylamino)chloroborane **2.3**, a sterically less demanding diaminoboryl reagent, $(Me_2N)_2BBr$ (**2.4**), and a sterically more challenging diaminoboryl reagent, the cyclic *t*-butyl substituted **2.5**[103], were also tested (Figure 2.1). However, both gave lower product conversions (~60 % for **2.4** and ~30 % for **2.5**) along with alcohol side adducts (*e.g.*, $PhCH(OH)CH_2CN$) under the same reaction conditions. The alcohol adducts presumably forms because the formation of the boryl carbanion **2.2** is incomplete, leaving excess $LiCH_2CN$ to react with benzaldehyde. The major isomer was an (*E*)-olefin (*Z*:*E* = ~1:2) for **2.4**, while **2.5** exhibited comparable (*Z*)-selectivity to **2.3** (*Z*:*E* = 79:21).

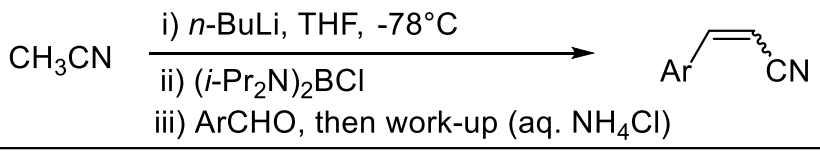


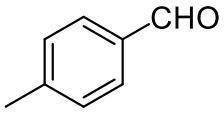
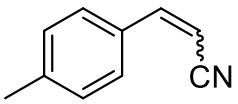
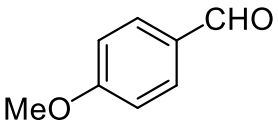
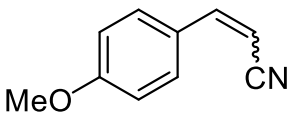
2.4 **2.5**

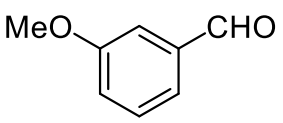
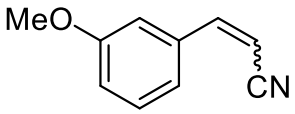
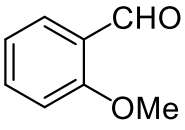
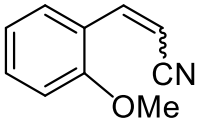
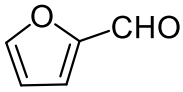
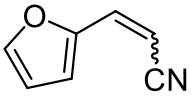
Figure 2.1 Diaminochloroboranes **2.4** and **2.5**

2.2.5. Synthesis of acrylonitrile derivatives

A series of aldehydes were smoothly converted into the corresponding acrylonitriles, according to the optimized recipe, in a highly (*Z*)-stereoselective manner. First, we examined assorted aromatic aldehydes (Table 2.1). Regardless of the substitution patterns (entries 1-4) on the aromatic rings, including the heteroaromatic furfural (entry 5), they consistently showed good to excellent reaction conversions and (*Z*)-stereoselectivities.



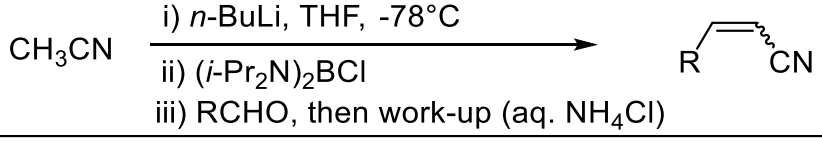
entry	aldehyde	products	*E*:*Z*[a]	yield[b]
1			19:81	97
2			17:83	86

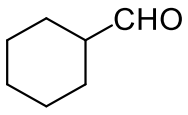
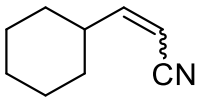
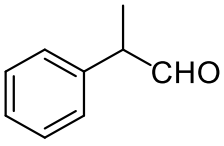
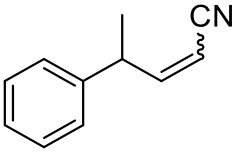
3			22:78	80
4			27:73	94
5			20:80	82

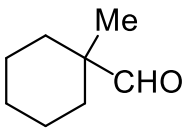
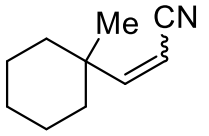
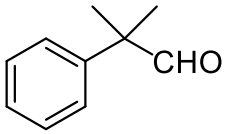
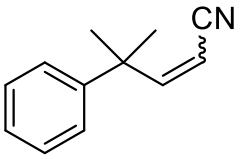
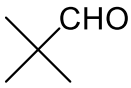
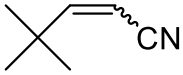
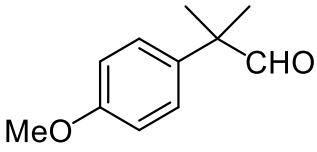
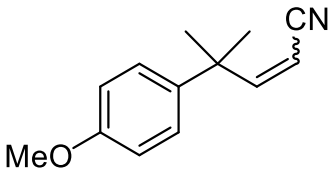
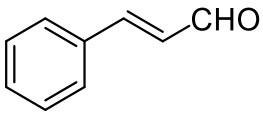
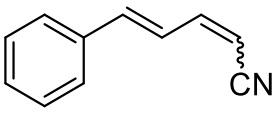
[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] Combined isolated yield of *Z* and *E* isomers.

Table 2.1 One-pot synthesis of β–substituted acrylonitriles from aromatic aldehydes

Next, non-aromatic aldehydes were screened accordingly (Table 2.2). To our delighted surprise, aliphatic aldehydes with acidic α-protons almost exclusively underwent olefination rather than potentially competing enolization (entries 6 and 7). The highest stereoselectivities (*Z*:*E* = 96:4) were achieved when highly sterically congested aldehydes were used (entries 8-11). When the sterically much less hindered aldehyde, *trans*-cinnamaldehyde (entry 12) was used, however, the *Z*/*E* stereoselectivity dropped significantly.



entry	aldehyde	products	*E*:*Z*[a]	yield[b]
6			12:88	92
7			17:83	94

8			4:96	98
9			4:96	91
10			5:95	98
11			6:94	86
12			35:65	88

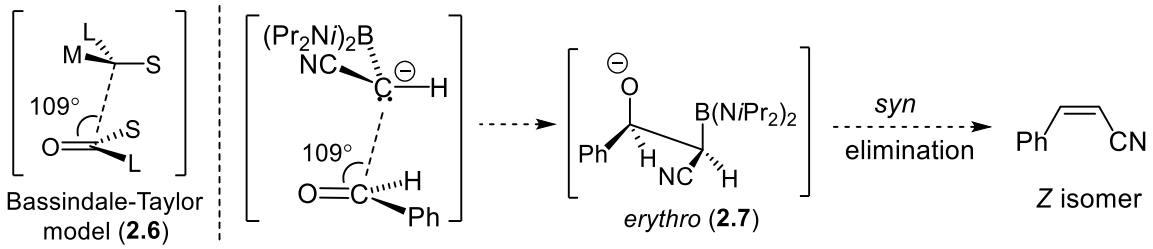
[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] Combined isolated yield of *Z* and *E* isomers.

Table 2.2 One-pot synthesis of β–substituted acrylonitriles from aliphatic aldehydes

2.2.6. Result and discussion

Based on these experimental observations, it would be reasonable to say that the steric factor of both the aldehyde and the diaminoboryl reagent plays an importantt role here in determining the stereochemical outcome of the reactions. In contrast, the electronic factor of the reagents seems much less significant on the basis of comparisons of stereoselectivities among benzaldehyde, *p*-tolualdehyde, and *p*-anisaldehyde. Although the exact mechanism is not clear at this point, the Bassindale-Taylor steric-approach model may be applicable in explaining our olefination mechanism.[104] Our (*Z*)-

stereoselective outcome is reasonably explained as in the Peterson-type olefination. Thus, the use of a bulky diaminoboryl reagent as well as aldehyde would preferentially lead to an *erythro* oxyanion intermediate **2.7** (or anionic oxaboratane species) through the carbanion approach model **2.6** (Scheme 2.6). Subsequently, a possible *syn* elimination of **2.7** should afford the (*Z*)-olefin product as the major isomer.



Scheme 2.6 Plausible (*Z*)-stereoselective olefination mechanism

2.2.7. Summary

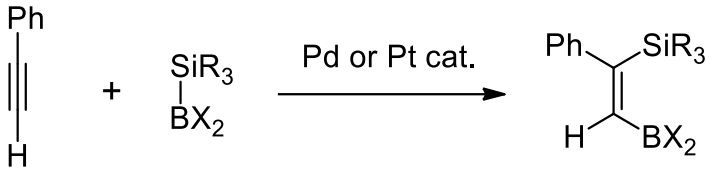
In summary, a simple three-step one-pot procedure for the synthesis of a β-monosubstituted (*Z*)-acrylonitrile, employing a novel α-diaminoboryl carbanion mediated olefination, has been established. A variety of aromatic and aliphatic aldehydes were efficiently converted into the corresponding (*Z*)-olefin products. In addition, our approach utilizing a mildly Lewis acidic diaminoboryl group successfully overcame a common technical difficulty to access an α-boryl carbanion, which is a potentially versatile species in organic synthesis. This work was published in *Organic Letters* in March, 2010 with the help of Dr. Takayoshi Yanase and Trey G. Vaughn.[105]

2.3. Pursuit of Multi-Functionalized Reagent Synthesis

2.3.1. Multi-functionalized molecules

There has been a growing demand for the development of new strategies in organic synthesis with shorter reaction sequences. One of the leading methods is the use of multi-functionalized molecules: they serve as useful synthetic intermediates, enabling more facile, efficient assembly of complex molecular structures. Recently, much attention has been focused on organoboron and organosilicon compounds in their application to organic synthesis and functional materials due to their elemental nature in that they form highly stable, covalent bonds with carbon. Development of a variety of transformation reactions using organoboron and organosilicon compounds greatly enhances their utility in synthetic organic chemistry.

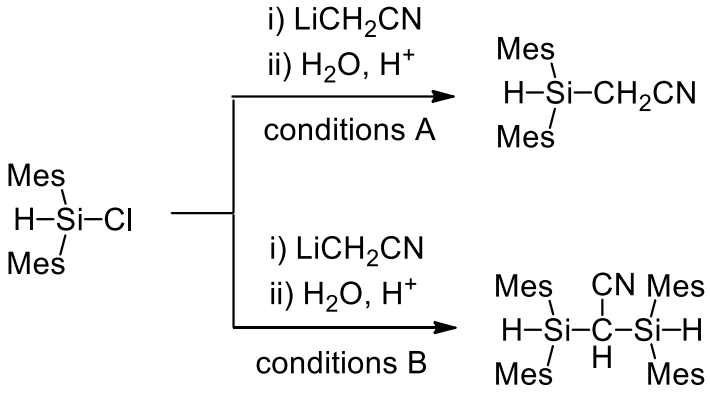
One of the conspicuous applications of these compounds has been established by Suginome and co-workers. They successfully developed a highly efficient "silaboration" method to simultaneously add both silyl and boryl groups onto unsaturated carbon bonds with an assist of group 10 transition metal catalysts (Scheme 2.7).[106]



Scheme 2.7 Suginome's silaboration method

Another noteworthy chemistry has been demonstrated by Krempner and co-workers. They disclosed a facile method for the synthesis of sterically demanding silyl

acetonitriles, including bis-silyl acetonitrile species *via* salt metathesis between silicon halide and lithiated acetonitrile (Scheme 2.8).[107]

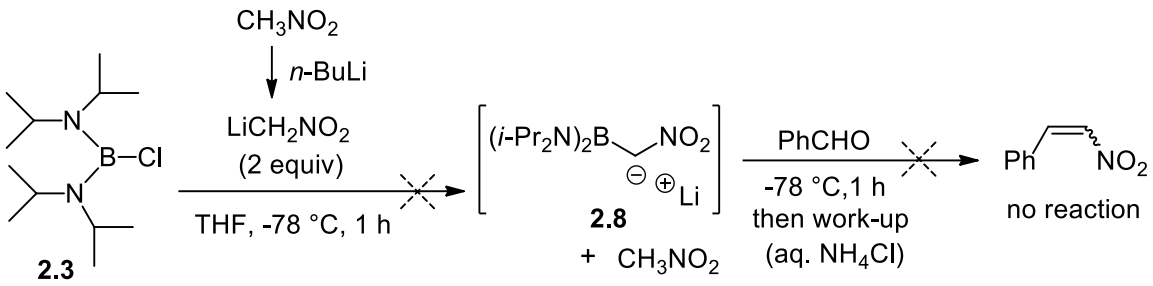


Scheme 2.8 Krempner's work

2.3.2. Attempt of β–substituted nitroolefin synthesis

Nitroolefins are versatile synthetic intermediates in organic synthesis.[108] They are frequently considered as synthetic equivalent of acrylonitriles, and utilized as an olefin activator in reactions such as the Michael, Diels-Alder cycloaddition, and Morita-Baylis-Hillman reaction. In addition, the nitro group can be easily converted into other useful functional groups.[109] Observing our successful synthesis of β-substituted acrylonitriles previously (section 2.2), our aim was pointed at the synthesis of nitroolefins.

Using two equivalents of lithiated nitromethane, in place of acetonitrile, did not produce the expected nitroolefin, unfortunately (Scheme 2.9). Attempts to examine the effects of different reaction temperatures (0 °C, r.t.) and reaction time (20 min) ended up in vain.

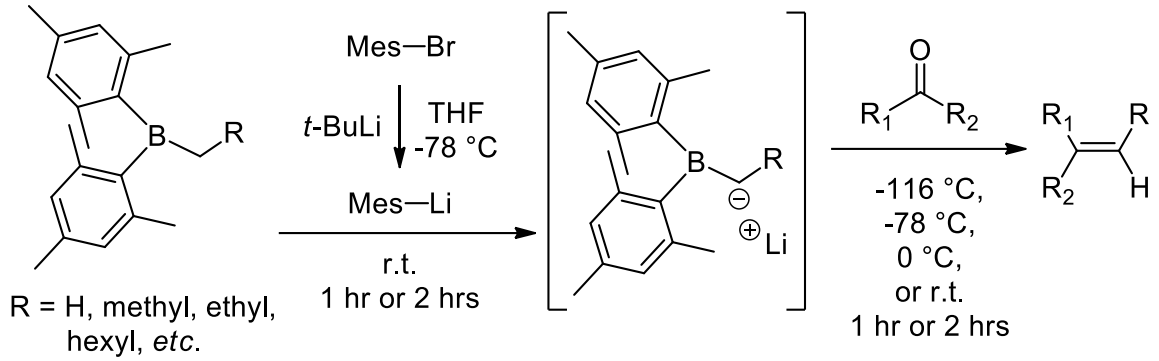


Scheme 2.9 Attempt of nitroolefin formation

Even though we could not figure out what was exactly blocking the olefination from happening, our postulation was that the presumed anionic species **2.8** was not formed properly considering the fact that the crude product contained an alcohol side adduct (*i.e.*, $PhCH(OH)CH_2NO_2$), which suggests the successful generation of $LiCH_2NO_2$ at the first step by deprotonation. Since no sign of olefin formation was confirmed after multiple attempts, this project was suspended.

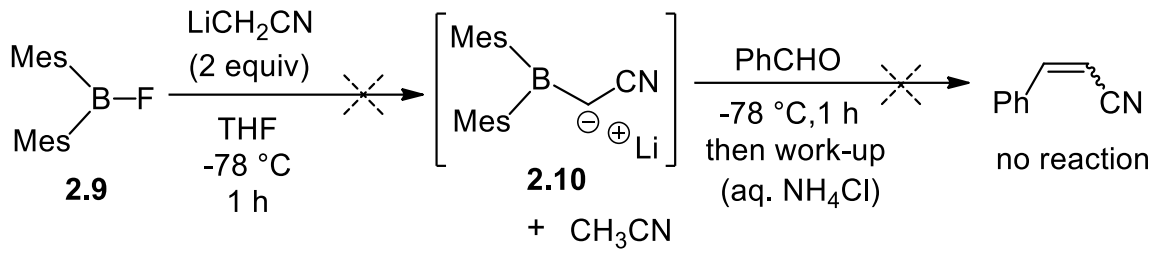
2.3.3. Olefination attempt using dimesitylboron species

Dimesityl groups as efficient ligands for α-boryl carbanion generation have been actively researched by Pelter *et al*. since the 1980's.[110] They have demonstrated its excellent olefinating ability using various types of electrophiles, such as aldehydes and ketones (Scheme 2.10). We thus embraced our vision that having a cyano group at the α-position of a mesityl-substituted borane might lead to a new kind of α-boryl carbanion species with an even better olefinating ability.



Scheme 2.10 Pelter's method

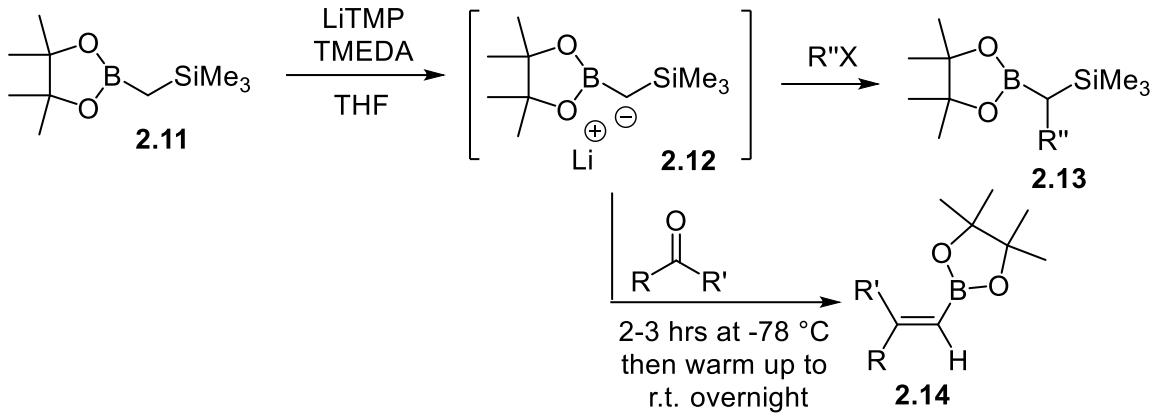
Our idea was carried out by treating dimesitylfluoroborane with two equivalents of lithiated acetonitrile at -78 °C followed by an addition of benzaldehyde (Scheme 2.11). This first attempt, however, failed to yield any desired olefins: what was observed in the crude product was the starting materials **2.9** and benzaldehyde along with a side alcohol adduct (*i.e.*, $PhCH(OH)CH_2CN$). This observation made us conclude that the postulated anion intermediate **2.10** did not form. Therefore, we tested a few different conditions for the first step. Higher temperatures (-40 °C, 0 °C, and r.t.) were applied only to give the same result. Silver additives ($AgC_2H_3O_2$, AgI, Ag_2O, and $AgNO_3$) were accordingly utilized with the purpose of a better substitution of fluoride by taking advantage of silver-halogen affinity. Unfortunately, this modification failed to give the alkene products as well. Having attempted numerous times with no sign of alkene formation, we suspended this project.



Scheme 2.11 Olefination attempt using dimesitylfluoroborane

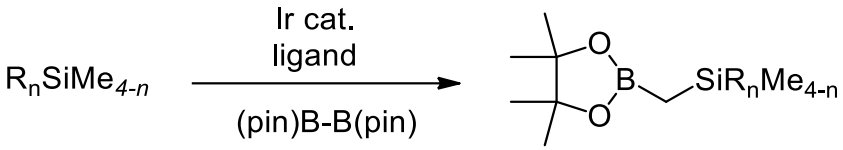
2.3.4. Olefination attempt using a novel α-boryl-α-silyl carbanion species

Among the numerous examples of geminated organodimetallics reported in the literature,[111] α-boryl silane species have shown their own significance in the field of synthetic organic chemistry. An extensive study was conducted mainly in the 1970's and the 80's by Matteson *et al*. for the synthesis method and its application in organic synthesis.[112] Their study utilized pinacol lithio(trimethylsilyl)-methaneboronate **2.12** that was generated *in situ* by treating α-silyl boronate **2.11** with LiTMP and TMEDA to synthesize pinacol 1-alkene-1-boronates **2.14** from aldehydes and ketones (Scheme 2.12). Generation of the α-boryl-α-silyl carbanion species **2.12** *in situ* was confirmed by the formation/isolation of the alkylated species **2.13** by treating **2.12** with an alkyl halide (Scheme 2.12). The silyl group was exclusively eliminated upon olefination, leaving the boryl group intact in the product. Furthermore, the stereochemical outcome of the olefination with aldehydes was (*Z*)-selective.



Scheme 2.12 Matteson's utilization of α-boryl-α-silyl-carbanion species

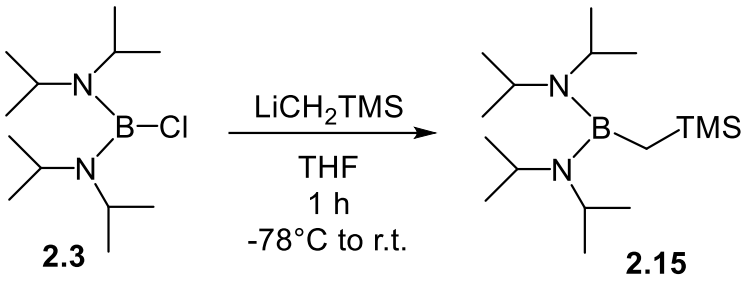
Additional notable research on α-boryl silane species was demonstrated by Suginome *et al*. very recently.[113] In their report, a pinacol borate moiety was inserted at the α-position of a silyl group *via* a C-H activation protocol they developed using an iridium catalyst and an appropriate ligand (Scheme 2.13).



Scheme 2.13 Suginome's synthesis of (borylmethyl)silanes *via* iridium-catalyzed C-H activation

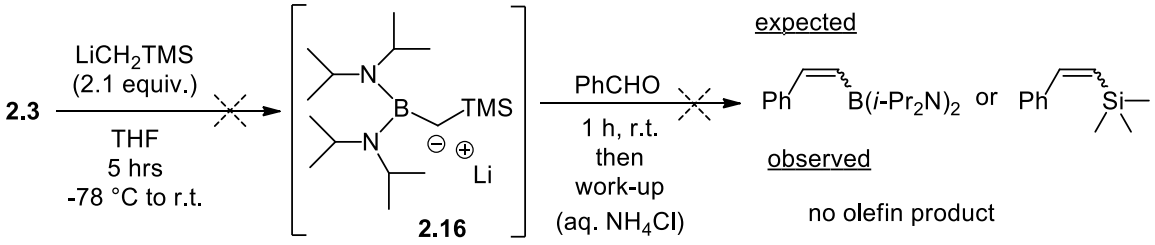
Considering the reasonable Lewis acidity and the base-compatibility of diaminochloroborane **2.3** as well as the feasible nucleophilicity of carbanion **2.2**, we envisioned that we would be able to design, synthesize, and characterize a new form of geminated bimetallic compounds using our α–boryl carbanion chemistry.

Our first attempt was the formation of α-boryl silane species **2.15** *via* stoichiometric reaction of trimethylsilylmethylithium ($LiCH_2TMS$) and diaminochloroborane **2.3** (Scheme 2.14).



Scheme 2.14 Formation of **2.15**

Stirring the reaction for 1 hr at -78 °C gave a small set of different peaks [^{1}H NMR (300 MHz, $CDCl_3$) δ 3.54 (sep, *J* = 6.9 Hz, 4H), 1.18 (d, *J* = 6.9 Hz, 24H), 0.36 (s, 2H)], possibly indicating the formation of the desired adduct based on the ^{1}H NMR evidence of the crude product. Longer reaction times (~15 hrs) improved the product conversion up to 70 %. Finally, the use of a little excess of $LiCH_2TMS$ (1.2~1.4 equiv.) maximized the formation of the presumed desired adduct **2.15** almost quantitatively. Employing these optimized conditions, olefination was attempted in a one-pot manner using a little more than two equivalents of $LiCH_2TMS$ in the hope of getting some olefin product(s) (Scheme 2.15).

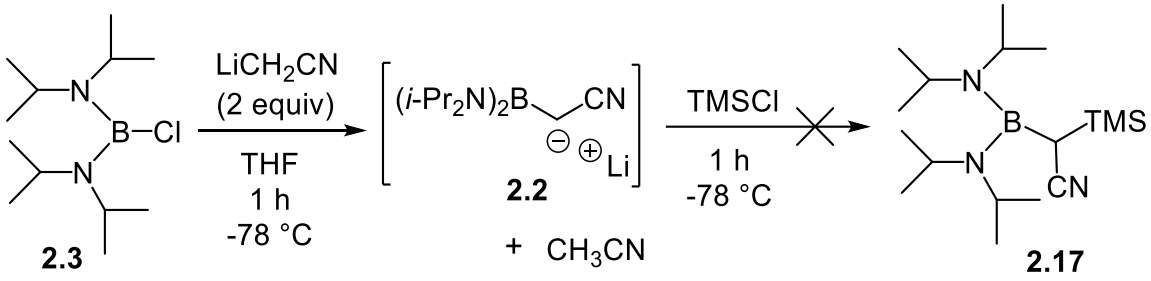


Scheme 2.15 Olefination attempt

Unfortunately, no sign of olefin product was observed in the ^{1}H NMR spectrum of the raw product. Instead, unreacted benzaldehyde and supposed silyl fragments were spotted. Our postulation for this observation is that after the formation of the adduct

2.15, presumed anionic species **2.16** did not form, or if it did, it was not reactive enough to perform the olefination with benzaldehyde. Since no olefin product was obtained, we suspended this project.

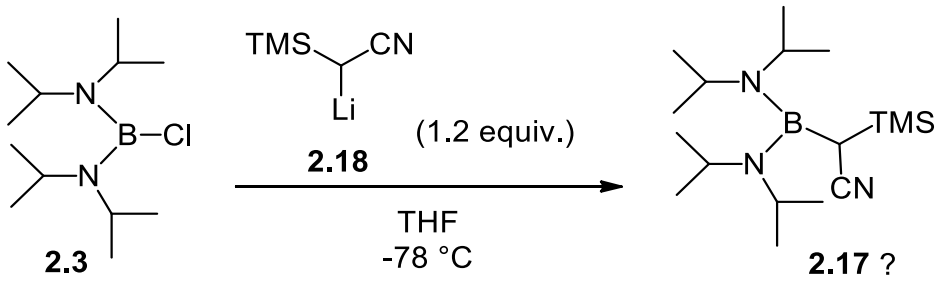
Considering the reactivity of our α-boryl carbanion species so far, we decided to combine some of our ideas already carried out to attempt the synthesis of α-silyl-α-boryl acetonitrile species **2.17**. We first put this idea into practice by treating α-boryl carbanion **2.2** with TMSCl (Scheme 2.16). However, none of **2.17** was detected in the crude product; instead, boryl acetonitrile **2.1** was obtained, which means that TMS substitution did not occur at the 2nd step.



Scheme 2.16 Attempted formation of **2.17**

In order to synthesize **2.17** in a different way, lithiated (trimethylsilyl)acetonitrile **2.18** was used to introduce both silyl and cyano functionalities simultaneously (Scheme 2.17). After multiple attempts examining the best reaction conditions, using 1.5 equivalents of **2.18** was found to maximize the production of a new set of peaks (~70%), indicating a possible formation of **2.17**, with ~30% of intact starting material **2.3** left in the crude product. Longer reaction times (~3 hrs) and higher temperatures (0 °C, r.t.) did not improve the reaction conversion. A potential reason why the reaction did not shift all the way to the presumed product would be that formation of **2.17** and deprotonation of

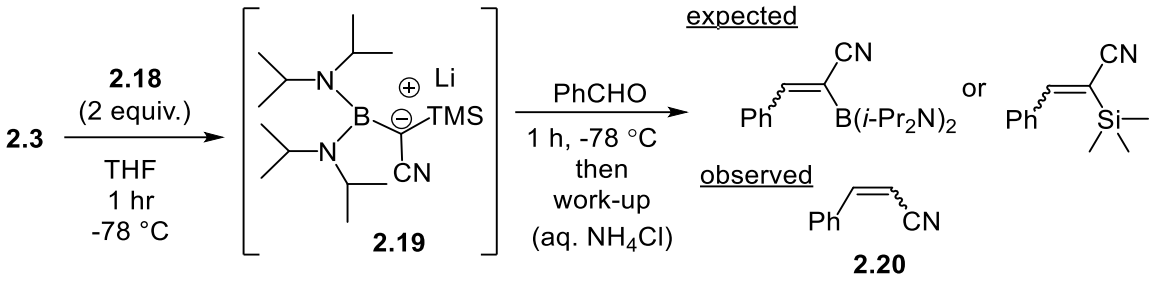
2.17 were competing; thus there was certain amount of **2.3** left unreacted. The potentially deprotonated species of **2.17** might have picked up a proton upon exposure to air and transformed back into **2.17** again to be observed in the crude product.



Scheme 2.17 Possible formation of **2.17**

Even though we were not completely certain about the generation of **2.17**, we proceeded to the next olefination step (Scheme 2.18). Unfortunately, neither of the expected products was observed; instead, β-phenyl acrylonitrile **2.20** was obtained. A possibly reasonable explanation for this result would be that the C-B bond or the C-Si bond of the expected product might have been cleaved upon acidic aqueous work up. Another possible reasoning would be that one equivalent of lithium anion **2.18** may have worked as nucleophile to substitute the chloride on boron, but the second equivalent of **2.18** may have not worked as base, thus failing to deprotonate the α-carbon of the α-boryl cyanide adduct to form anion **2.19**. Therefore, the second batch of **2.18** may have remained intact until the benzaldehyde addition, olefinating the aldehyde to possibly give silyl olefins whose C-Si bond may have cleaved upon acidic work up. These reasonings, however, seem to be contradicting to Matteson's work in Scheme 2.12 considering the fact that they quenched their reaction with diluted aqueous HCl solution, a stronger acid than the NH_4Cl that we used, to obtain **2.14**. This might suggest a stability difference

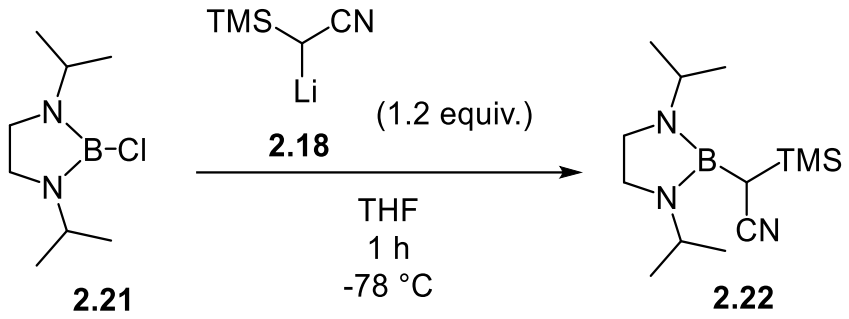
between the vinyl diaminoboryl and the pinacol borate moieties: otherwise, failure in furnishing the vinyl diaminoboryl or vinyl silyl group in our reaction system might be attributed to the cyano functionality, a strongly electron-withdrawing group, which sucks the electron density away from the alkene system, thus making the possible C-B bond or C-Si bond a little unstable. Since no expected functionalized acrylonitrile was obtained, this project was suspended.



Scheme 2.18 Olefination attempt

The unsatisfactory installation of silyl and cyano functional groups simultaneously to diaminochloroborane **2.3** gave us a motivation to synthesize another type of diaminoborylchloroborane, **2.21**, that was readily prepared in the same manner as the cyclic *t*-buyl substituted **2.5** was synthesized. Cyclic diaminochloroborane **2.21** was subjected to a reaction with **2.18** in the hope of forming the desired adduct **2.22** (Scheme 2.19). Based on the ^{1}H NMR analysis of the raw product, small peaks that are supposedly from the desired adduct were confirmed along with a significant amount of (trimethylsilyl)acetonitrile and decomposed diaminochloroborane **2.21** [*e.g.*, $(CH_3)_2CHNHCH_2CH_2NHCH(CH_3)_2$]. Our insight into this observed phenomenon would be that either **2.21** was too electrophilic toward **2.18**, thus eventually decomposing, or that **2.22** did form in the course of reaction but decomposed upon rotary evaporation or

exposure to air. No more study was conducted because of the extremely low yield of this reaction.



Scheme 2.19 Formation of **2.22**

2.4. Preparation of α,β-Disubstituted Acrylonitriles

{*This work was accomplished at the hands of current and former members of our group: Rambabu Sankranti, Trey G. Vaughan, Dr. Toshihide Maejima, and Dr. Takayoshi Yanase under the direction of Dr. Takashi Tomioka. Although I was not directly involved, its concept, chemistry, and methodology are closely related to my following projects (sections 2.6 and 2.8.7). Therefore, I believe a brief description of this project is highly necessary herein.*}

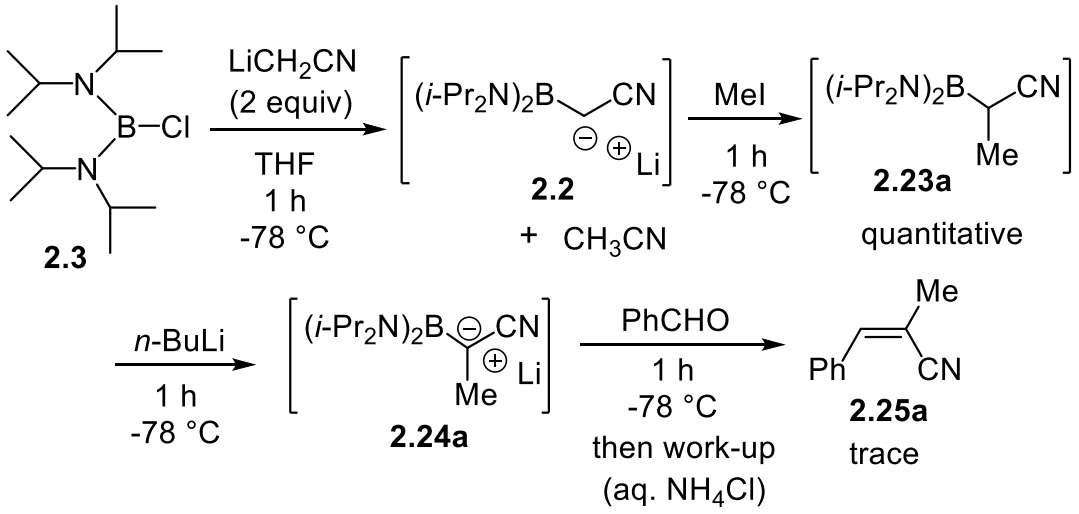
2.4.1. α,β-Disubstituted acrylonitriles

In response to the success of our prior project in section 2.2, we set as our next goal the synthesis of more functionalized acrylonitriles using the same one-pot protocol with a little modification. Highly substituted acrylonitriles are synthetically precious and

useful; when it comes to their preparation, however, especially to the preparation of α,β-disubstituted ones, it can often be troublesome due to the limited availability of proper olefination methods. Thus, we wanted to utilize an α-boryl carbanion species to further extend the scope of acrylonitrile syntheses.

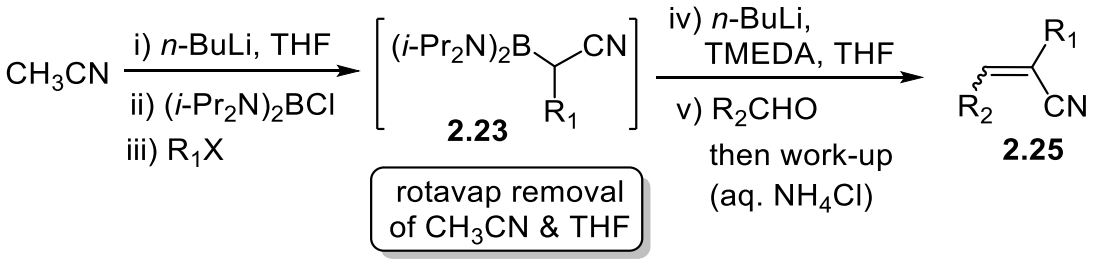
2.4.2. Modification of the one-pot protocol

To begin, upon the generation of carbanion **2.2** after treating diaminochloroborane **2.3** with two equivalents of $LiCH_2CN$, methyl iodide was introduced into the reaction mixture to test the nucleophilicity of **2.2**. The desired methyl-substituted diaminoboryl acetonitrile **2.23a** (where "a" indicates a methyl substituent) was formed nearly quantitatively, which was confirmed by the ^1H NMR of the crude product (Scheme 2.20). However, subsequent exposure of this crude material to *n*-BuLi to generate the corresponding α-boryl carbanion **2.24a** *in situ*, followed by the addition of benzaldehyde, only gave the desired olefin **2.25a** in a trace amount (Scheme 2.20).



Scheme 2.20 Initial one-pot approach

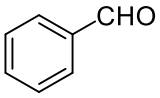
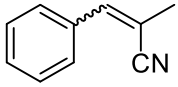
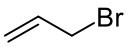
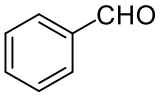
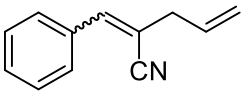
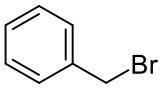
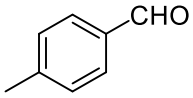
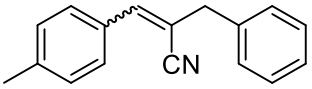
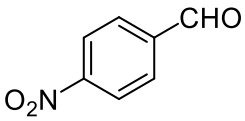
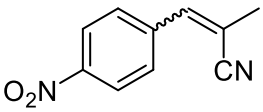
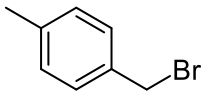
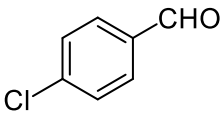
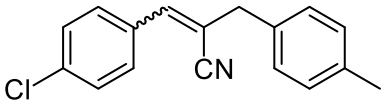
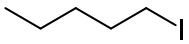
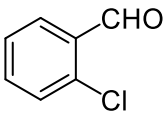
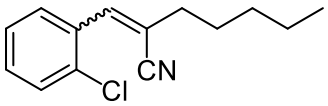
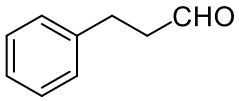
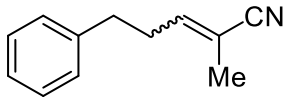
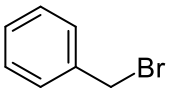
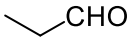
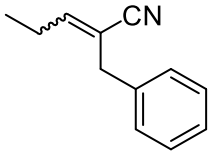
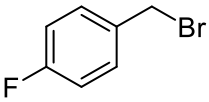
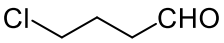
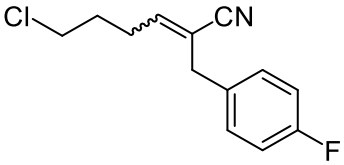
A reasonable explanation for this result would be that there was one equivalent of acetonitrile left over as a by-product of the formation of boryl carbanion **2.2** when methylated borylacetonitrile **2.23a** was formed (Scheme 2.18). Because of this, *n*-BuLi preferentially deprotonated acetonitrile rather than the sterically congested α-carbon of **2.23a**, thereby failing to generate **2.24a** and **2.25a**. In order to remove acetonitrile from the system, the reaction mixture was simply concentrated *in vacuo* after the generation of **2.23a**. This easy modification helped afford **2.25a** in 30% yield. After further trial and error, it was revealed that the use of TMEDA as an additive with *n*-BuLi was essential for a smooth deprotonation of the α-carbon of methyl-substituted boryl acetonitrile **2.23a**, which greatly improved the yield of **2.25a** up to 83%. Using this modified procedure (Scheme 2.21), a variety of α,β-disubstituted acrylonitriles were prepared in decent to excellent yields.

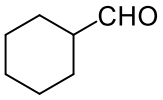
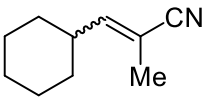
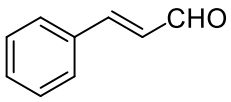
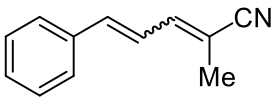


Scheme 2.21 One-pot synthesis of **2.25** *via* the modified approach

2.4.3. Synthesis of 2.23 using the modified protocol

Interestingly, the stereoselectivity came out with a very unique tendency: while aromatic aldehydes gave (*Z*)-isomer as a major product, aliphatic aldehydes reacted in an (*E*)-stereoselective manner (Table 2.3).

entry	RX	aldehyde	products		E:Z[a]	yield[b]
1	MeI			**2.25a**	30:70	83
2				**2.25b**	30:70	83
3				**2.25c**	12:88	96
4	MeI			**2.25d**	19:81	80
5				**2.25e**	14:86	90
6				**2.25f**	15:85	72
7	MeI			**2.25g**	89:11	87
8				**2.25h**	84:16	99
9				**2.25i**	88:12	76

10	MeI			**2.25j**	76:24	84
11	MeI			**2.25k**	31:69	82

[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] Combined isolated yield of *Z* and *E* isomers.

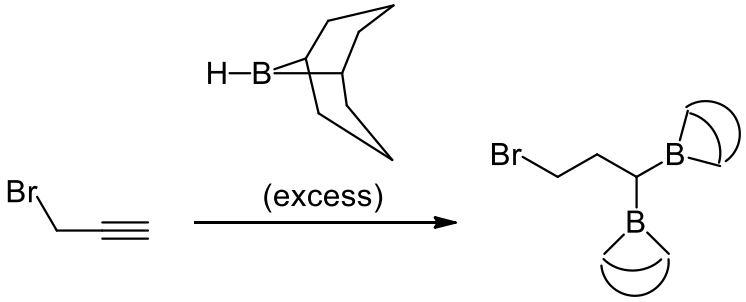
Table 2.3 Preparation of α,β-disubstituted acrylonitriles

This work was published in *Journal of Organic Chemistry* in August, 2011.[114]

2.5. Investigation into *gem*-Organodiboron Chemistry

2.5.1. Geminated organodiboron species

Geminated organodiboron compounds, among an array of organodimetallic species known today, were reported more than half a century ago;[115] yet they seem to have been somewhat unexplored. In a practical sense, double-hydroboration[116] was first reported to get access to such diboron structures (Scheme 2.22), and still has been a predominant method except for a few variations of the same reaction.[117] Therefore, there should be much more room left to be investigated into this field of organic synthesis.

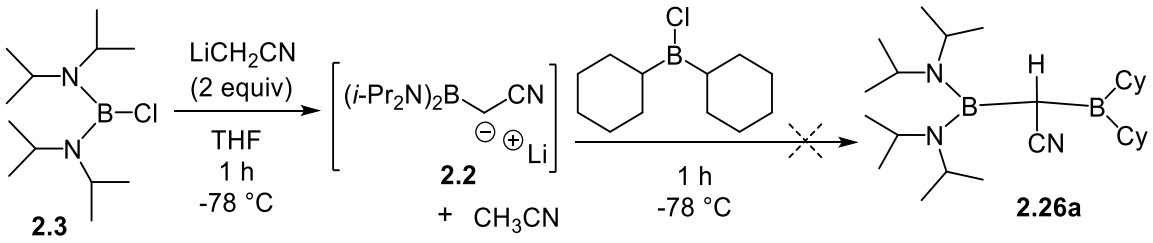


Scheme 2.22 Formation of *gem*-diboron species *via* dihydroboration

2.5.2. Synthetic attempt for diboron compounds

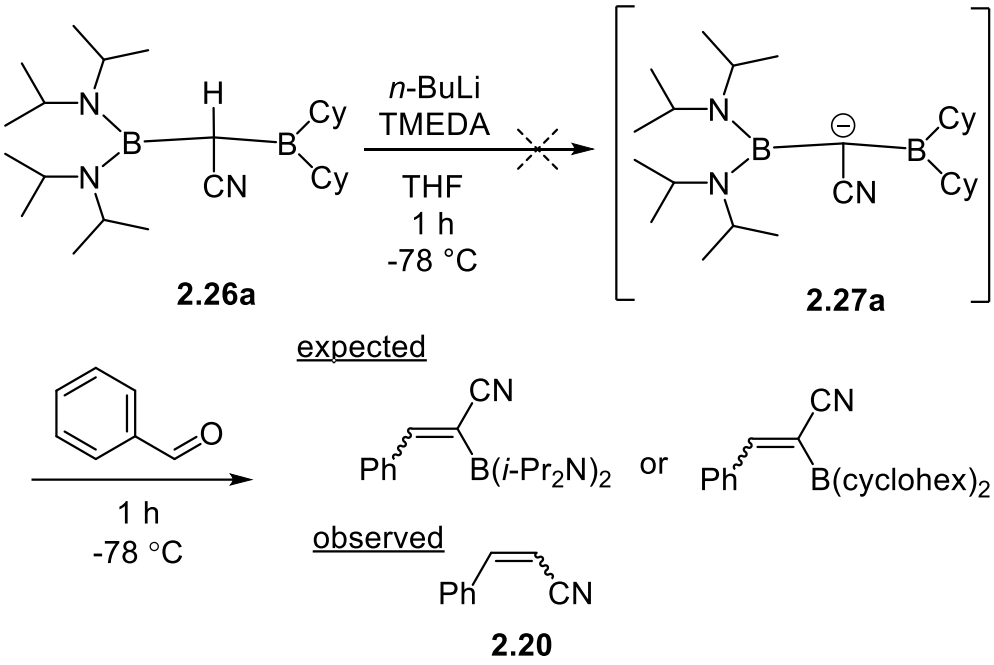
After observing sufficient nucleophilicity of our novel α-boryl carbanion species **2.2** and **2.24** toward aldehydes and alkyl halides so far, we conceived of an idea that diboron species would form by treating an appropriate organoborane reagent with our α-boryl carbanion species *via* a substitution manner, and that the resulting diboron species would olefinate a carbonyl compound. To carry out this idea, a series of organoboron compounds was tested in reactions with **2.2** to further understand the nucleophilicity of **2.2**.

To begin, chlorodicyclohexylborane was reacted with α-boryl carbanion **2.2** to see whether the desired boron dimer compound **2.26a** formed or not (Scheme 2.23).



Scheme 2.23 Formation of **2.26a**

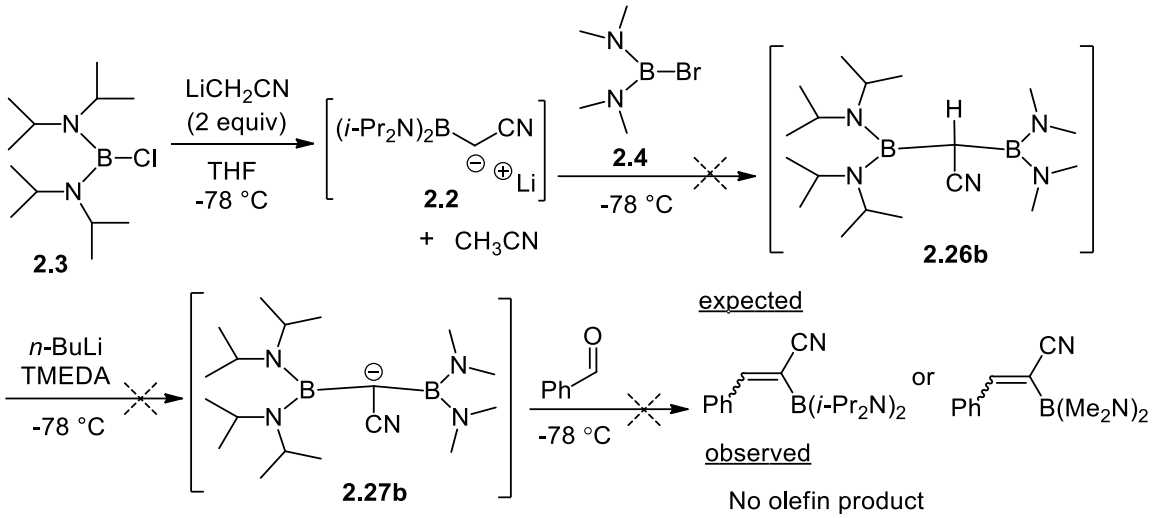
Unfortunately, we were doubtful about the formation **2.26a** based on the ^{1}H NMR analysis of the crude product because the peaks from the expected dimer species **2.26a** were not confirmed. Rather, we confirmed large peaks from **2.3**, which clearly indicated no reaction between **2.2** and chlorodicyclohexylborane. Despite this unpromising result from the 1st substitution step, we proceeded to the next olefination step without further purification of **2.26a**. The crude **2.26a** was treated with *n*-BuLi with TMEDA as an additive, then reacted with benzaldehyde to see if olefination took place (Scheme 2.24).



Scheme 2.24 Olefination attempt using **2.26a**

Within the crude product was confirmed **2.20** (*E*:*Z* = 21:79), along with none of the boryl olefin product. Based on this observation, what happened would be that **2.2** was simply re-generated from **2.26a** upon the treatment of *n*-BuLi/TMEDA and olefinated benzaldehyde to give **2.20**; that is, either **2.26a** was never formed, or its reactivity was not competitive with that of **2.2**.

The next organoboron substrate we chose for the second boronation was bromobis(dimethylamino)borane **2.4**. In the same manners as illustrated in Scheme 2.23 and Scheme 2.24, diboron compound synthesis with **2.4** was attempted, followed by olefination (Scheme 2.25).

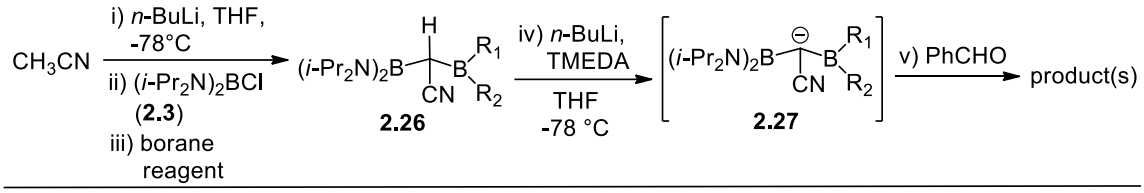


Scheme 2.25 Olefination attempt using **2.4**

After the 1st substitution reaction with **2.4**, the crude product showed highly-possible formation of the desired adduct **2.26b** based on the ^{1}H NMR evidence: peaks that were different from starting diaminoboranes were observed, and their proton ratio by integration seems to be matched with the desired diboron species peaks [^{1}H NMR (300 MHz, $CDCl_3$) δ 3.50 (sep, J = 6.9 Hz, 4H), 2.52 (s, 12H), 2.05 (s, 1H), 1.19 (d, J = 6.9 Hz, 24H]. Subsequent treatment with *n*-BuLi/TMEDA followed by benzaldehyde gave, however, no olefin product, but recovered benzaldehyde instead. Even though the exact mechanism is inconclusive at this point, our rationale for this result is that **2.26b** was not appropriately deprotonated due to the extremely high steric hindrance by the alkyl groups from both boron moieties. Consequently, **2.27b** did not form, and **2.26b** was destroyed upon the acidic aqueous work up at the end of the reaction. Indeed, a few small broad singlet peaks were identified in the ^{1}H NMR spectrum of the crude residue, possibly indicating the presence of boric acid by-products generated upon the decomposition of

2.26b. Another possible reasoning would be that **2.27b** could have formed but been sterically blocked from adding to benzaldehyde.

Employing the same reaction conditions, a variety of organoboranes in place of **2.4** were investigated (Table 2.4).



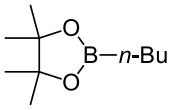
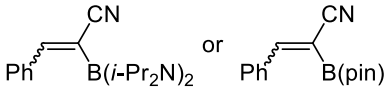
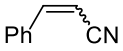
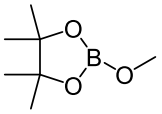
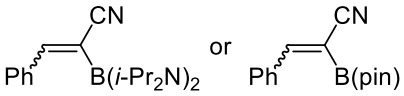
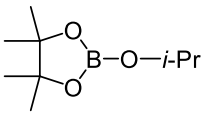
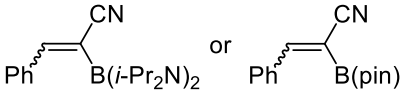
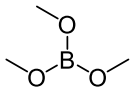
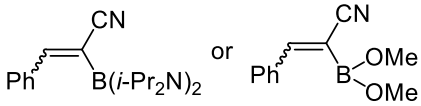
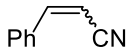
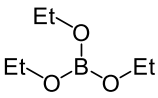
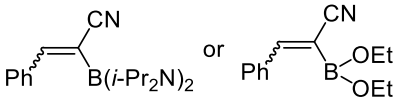
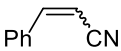
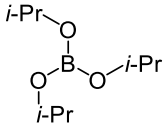
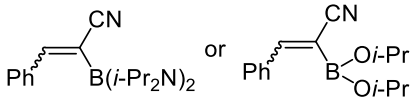
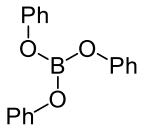
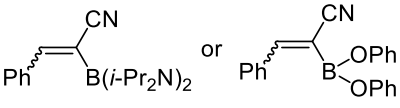
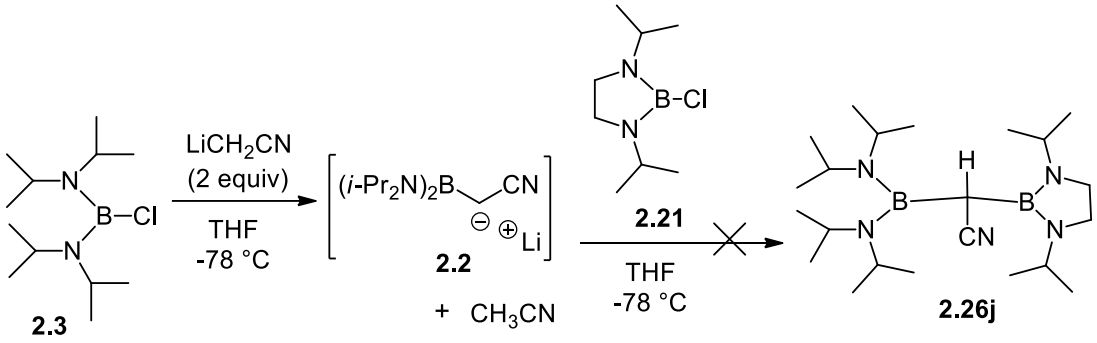
entry	borane reagent	diboron	product(s) desired	product(s) observed	*E*:*Z*
1		**2.26c**		 **2.20**	17:83
2		**2.26d**		no olefin	n/a
3		**2.26e**		no olefin	n/a
4		**2.26f**		 **2.20**	20:80
5		**2.26g**		 **2.20**	24:76
6		**2.26h**		no olefin	n/a
7		**2.26i**		no olefin	n/a

Table 2.4 Screening of a variety of organoboranes

Among all the organoboranes tested, only entry 3 gave the suspected peaks from the desired diboron species (*i.e.*, **2.26e**) even though their signals were fairly weak by the ^{1}H NMR analysis of the crude product. Entry 3, however, failed to produce any olefin product but gave the intact benzaldehyde and a few small broad singlets, most probably from boric acid(s). Even though this observation could be explained by the same steric argument given in the discussion for Scheme 2.25, another possible interpretation would be that *n*-BuLi, with its basicity/nucleophilicity increased by co-presence of TMEDA, acted as a nucleophile and thus attacked either/both of the boron nuclei of **2.26e**: This might have collapsed the whole molecule, preventing olefination from taking place. Remainder of the aldehyde as well as the alcohol peaks could be well-explained by this hypothesis, too.

Formation of the desired diboron species **2.26** from entries 1-2 and 4-7 were not confirmed by ^{1}H NMR analyses, implying ineffective nucleophilicity of **2.2** towards organoborane electrophiles. For entries 2, 6, and 7 which did not even produce β-phenylacrylonitriles **2.20**, the reason for not producing any olefin product is unclear; however, one could conclude that α–boryl carbanion species **2.27** or even **2.2** was not appropriately generated based on the ^{1}H NMR spectra of the crude products, showing large peaks from residual benzaldehyde. On the other hand, β-phenylacrylonitriles **2.20** were obtained from entries 1, 4, and 5. These results would have been brought about in the way that unreacted **2.2** from the 1st substitution step was regenerated upon the treatment of *n*-BuLi/TMEDA, and then olefinated benzaldehyde.

As another type of organoboron electrophile, cyclic diaminochloroborane **2.21** was utilized (Scheme 2.26).



Scheme 2.26 Attempted formation of **2.26j**

Unfortunately, the presence of the expected diboron species **2.26j** was not confirmed in the crude product based on the ^{1}H NMR analysis. Instead, boryl acetonitrile **2.1** and **2.21** were observed, which clearly indicates that the reaction between **2.2** and **2.21** did not occur.

2.5.3. Summary

Overall, we could not observe practical nucleophilicity of α-boryl carbanion **2.2** on organoboron-based electrophiles, while it had exhibited excellent nucleophilicity on carbonyl compounds and alkyl halides previously. As a potential explanation, we would point out the relatively robust B-O and B-X bonds where the boron nucleus is electronically extra-stabilized by the back-donation of electron density from oxygen's or halogen's lone pair electrons to boron's vacant p orbital. Because of this, boron's electrophilicity was somewhat decreased as well. Our α-boryl carbanion species **2.2** might not have been nucleophilic enough to attack on such less-electrophilic boron

nuclei, and accordingly replace this strong bond of the organoboranes we tested. Since no sign of desired boryl acrylonitrile formation was recognized, this project has been suspended.

2.6. One-pot Synthesis of 2-Aminoquinoline-based Alkaloids

2.6.1. 2-Aminoquinolines

2-Aminoquinoline (Figure 2.2) and its derivatives are found in a large number of natural products[118-120] and drug-like compounds.[121] Those pharmaceutically important alkaloids thus have attracted a remarkable attention due to their unique biological activities, such as anthelmintic,[122] antiprotozoal,[123] antidepressant,[124] antihypertensive,[125] *etc*.[126] According to a recent study, 2-aminoquinolines possess subnanomolar potency for BACE1 (beta-site amyloid precursor protein cleaving enzyme 1) and may serve as a small BACE inhibitor for Alzheimer's disease therapeutics.[127] Another recent report revealed weak to moderate binding affinity of 2-aminoquinolines to Tec SH3 (the Src homology 3) domain that is known to have strong biological implications with human diseases including cancer and osteoporosis.[128-129] Therefore, these compounds continue to be an attractive study target and are anticipated as potent leads in the medicinal chemistry community.

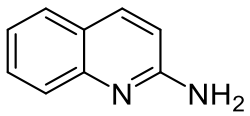
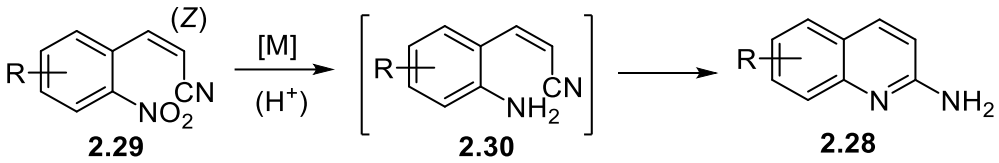


Figure 2.2 2-Aminoquinoline

2.6.2. 2-Aminoquinolines as synthetic target

Among numerous synthetic approaches that have been developed for 2-aminoquinoline-based alkaloids synthesis, one of the most common methods is reductive cyclization (Scheme 2.22).[130] The common 2-aminoquinoline framework, **2.28**, is often synthesized from a nitrophenyl acrylonitrile, **2.29**, that is accordingly reductively cyclized through a presumed aminocyano olefin **2.30** in the presence of some reducing metal,[131-134] typically in acidic conditions (Scheme 2.27). Since (*E*)-nitrophenyl acrylonitriles would not participate in cyclization, the presence of (*Z*)-acrylonitrile is essential unless photochemical isomerization (*E* → *Z*) is performed.[135]



2.29 **2.30** **2.28**

[M] = Fe, Zn, Sn, Sm, In and *etc*.

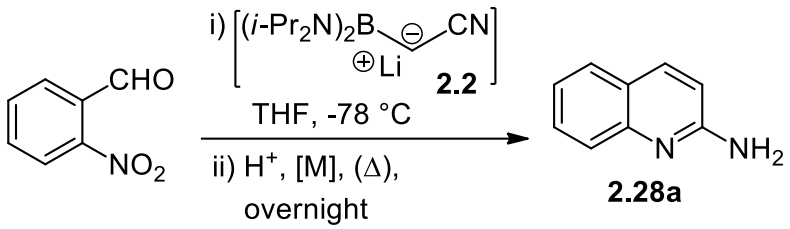
Scheme 2.27 Reductive cyclization of **2.29** into **2.28**

In sections 2.2 and 2.4, we reported the one-pot synthesis of β-monosubstituted acrylonitriles as well as α,β-disubstituted acrylonitriles using our novel diaminoboryl acetonirile reagent. In this reaction protocol, the product acrylonitriles were consistently (*Z*)-stereoselective when aryl aldehydes were used. As promising preliminary data, an excellent compatibility of a nitro-group with the α-boryl carbanion species **2.2** was demonstrated in our prior investigation (entry 4 in Table 2.3). Plus, the reaction was quenched with aqueous NH_4Cl solution, leaving us with an acidic reaction mixture. Such an acidic medium seems to be already in an appropriate condition for the reductive cyclization of nitrophenyl acrylonitriles **2.29** for the synthesis of 2-aminoquinolines **2.28**,

just by adding an appropriate reducing metal to it. Based on these assumptions, we attempted the syntheses of various 2-aminoquinoline-based alkaloids to broaden the applicability of our novel α-diaminoboryl carbanion species. The reaction sequence started with acetonitrile, and no isolation/purification of reaction intermediates was required over the course of the whole process.

2.6.3. Initial attempt and condition optimization

As our initial attempt, *ortho*-nitrobenzaldehyde was olefinated with α-boryl carbanion **2.2**. The desired 2-nitrophenyl acrylonitrile **2.29a** (R = H) was obtained, in favor of (*Z*)-stereoisomer (*E*:*Z* = 19:81) based on the ^{1}H NMR evidence of the crude product. Fortunately, subsequent treatment of the crude reaction mixture with zinc metal (5 equiv.) with overnight stirring at room temperature afforded the desired 2-aminoquinoline product **2.28a** in 68% isolated yield. Observing this pleasing preliminary result, we tackled the next task: finding the best reaction conditions (*i.e*., sources of acid, reducing metals, reaction temperatures, *etc*.) for the reductive cyclization step (Table 2.5).



entry	H^+ source (mL)	[M] (equiv.)	temp	**2.28a** (%)
1	sat. NH_4Cl (5)	Zn (5)	r.t.	68
2	sat. NH_4Cl (5)	Zn (5)	reflux	65
3	sat. NH_4Cl (5)	Fe (5)	r.t.	38
4	AcOH (1)	Zn (5)	r.t.	76
5	AcOH (1)	Zn (5)	reflux	76
6	AcOH (1)	Zn (3)	r.t.	37
7	AcOH (1)	Fe (5)	r.t.	16
8	MeOH (10)	Zn (5)	reflux	28

Reaction conditions: 2'-nitrobenzaldehyde (1.0 mmol), **2.2** (1.1 mmol), THF (6.0 mL)

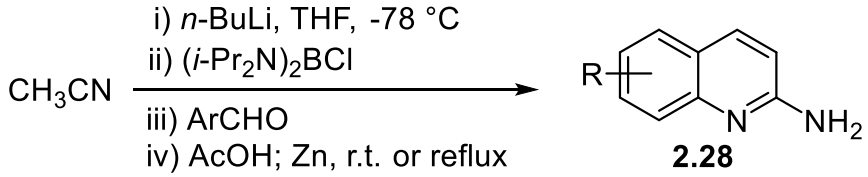
Table 2.5 Condition optimization for one-pot reductive cyclization

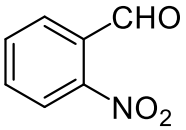
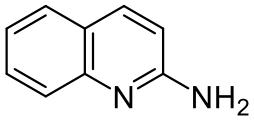
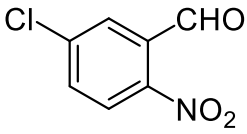
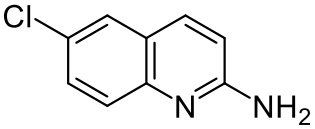
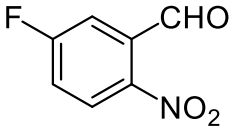
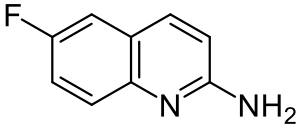
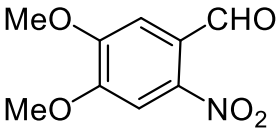
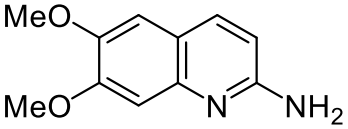
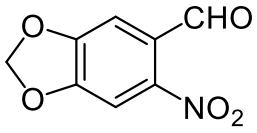
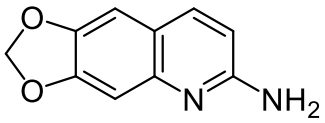
Acetic acid seemed slightly better as a proton donor than ammonium chloride (aq.), since THF and saturated aqueous NH_4Cl solution are immiscible and thus biphasic, which clearly loses efficiency as an acidic reaction system (entries 1-2, and 4-5). Despite its high miscibility with THF, methanol gave a much lower yield than acetic acid or NH_4Cl, even with the assistance of heat (entry 8). With regard to the metal equivalency, obviously three equivalents were not enough to shift the reaction all the way to completion (entry 6). Lastly, iron was tested as an alternative reducing metal, yet it failed to give a satisfactory result (entries 3 and 7). After all the screening trials, five equivalents of zinc were revealed to be acceptable and acetic acid fit best in this acid-driven reductive cyclization protocol, yet reaction temperature apparently did not have

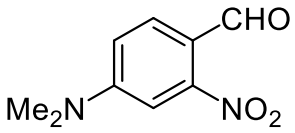
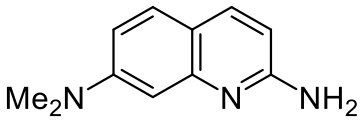
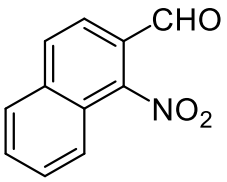
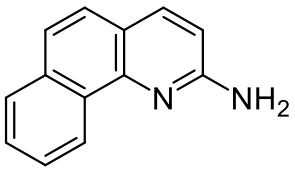
much of an effect (entries 4 and 5, both 76%). In addition, this figure (*i.e.*, 76%) should be quite close to the theoretical yield, considering the ratio of cyclizable (*Z*)-acrylonitrile formed after olefination (*Z*:*E* = ~4:1).

2.6.4. Preparation of 2-aminoquinoline derivatives

Illustrated in Table 2.6 are a series of *ortho*-nitrobenzaldehydes investigated under the optimized one-pot reaction conditions. The desired 2-aminoquinoline analogues **2.28** were successfully obtained in 41-77% yield.



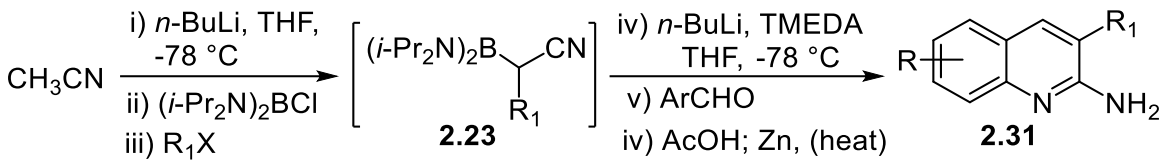
entry	aldehyde	product		yield (%)
1			**2.28a**	76
2			**2.28b**	67
3[b]			**2.28c**	67
4			**2.28d**	55
5[b]			**2.28e**	77

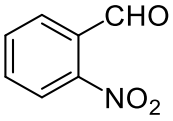
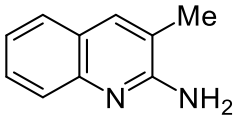
6[b]			**2.28f**	71
7[b]			**2.28g**	41

[a] 1.0 mmol reaction scale [b] Reflux conditions

Table 2.6 One-pot synthesis of 2-aminoquinolines **2.28**

Since our α-boryl carbanion protocol can be applied to the synthesis of α,β-disubstituted (*Z*)-acrylonitriles as well (see Schemes 2.20 and 2.21 in section 2.4.2), we subsequently prepared 3-substituted-2-aminoquinoline derivatives **2.31** *via* carbanion **2.23**, again in a one-pot manner (Table 2.7).



entry	RX	aldehyde	product	yield
1	MeI			**2.31a** 66

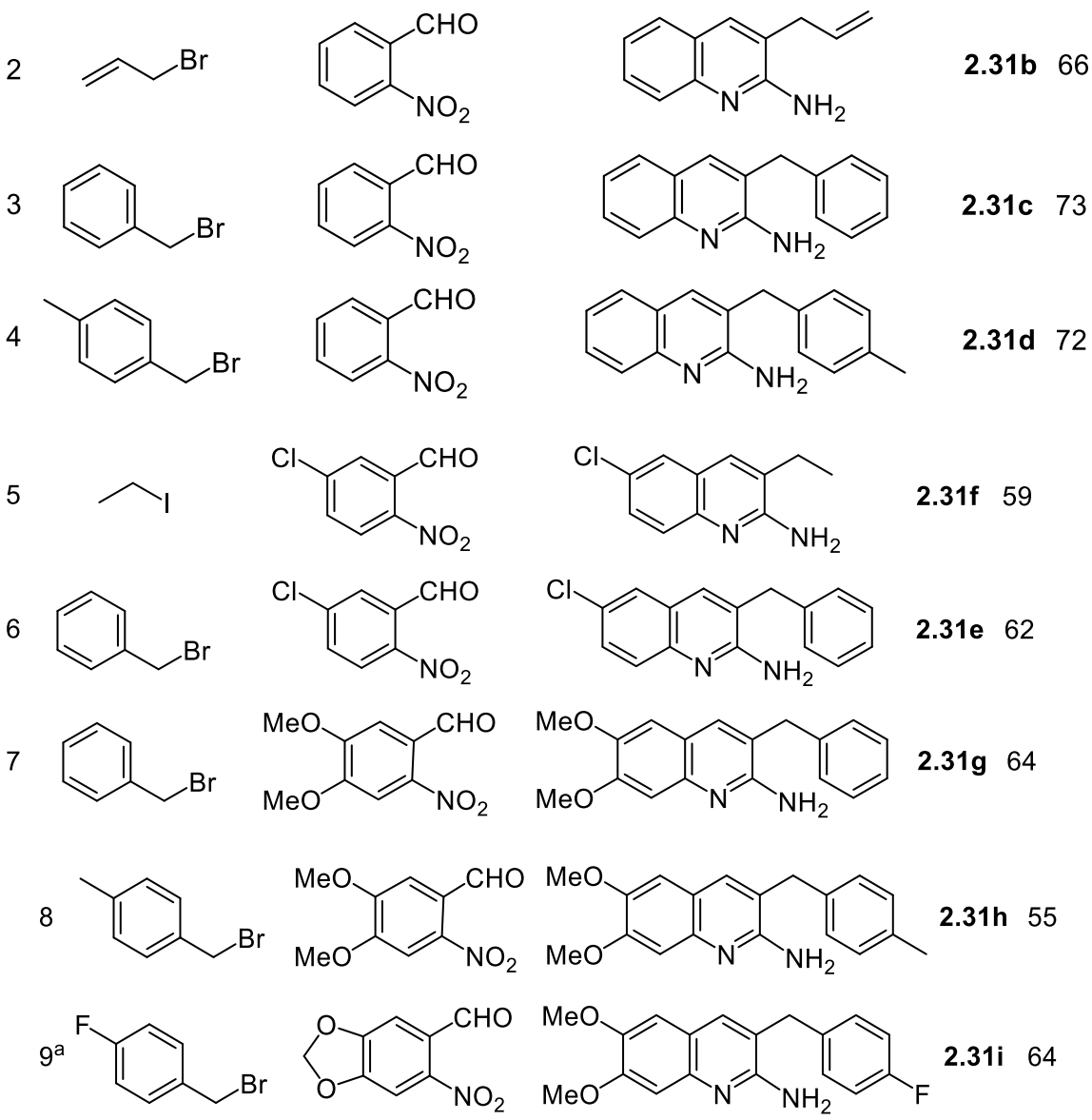
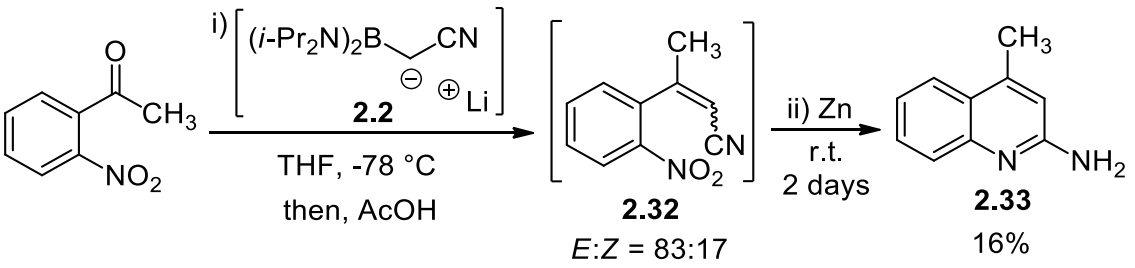


Table 2.7 One-pot synthesis of 3-substituted-2-aminoquinolines **2.31**

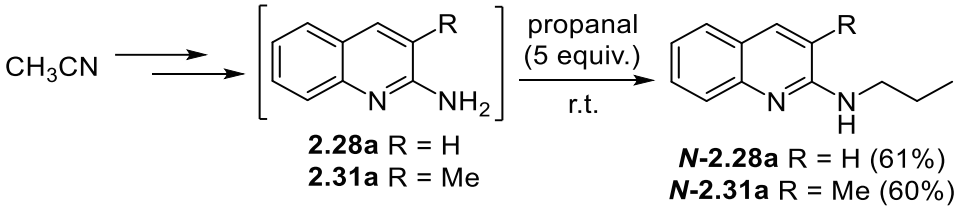
To further evaluate the versatility of this one-pot protocol, 4-subsituted-2-aminoquinoline synthesis was also attempted by utilizing a ketone instead of an aldehyde (Scheme 2.28).



Scheme 2.28 One-pot synthesis of 4-substituted-2-aminoquinoline

After treating 2'-nitroacetophenone with α-boryl carbanion **2.2**, acetic acid was added to the reaction mixture to give the expected β,β-disubstituted acrylonitrile **2.32** even though the olefination underwent (*E*)-stereoselectively [Note: we reported *E*/*Z* ratio and yield incorrectly in our publication[136]; the correct ratio is *E*:*Z* = 83:17 and the yield is 16%]. Subsequent cyclic reduction with zinc under the optimized conditions furnished the desired 4-methyl-2-aminoquinoline **2.33**, albeit in low yield.

Following the successful preparation of a 4-substituted-2-aminoquinoline, we realized a further potential of this one-pot reaction: reductive *N*-alkylation of the 2-aminoquinoline products. Among ample examples of reductive *N*-alkylation of aminoarenes as well as nitroarenes reported in the literature thus far, some of them[137-138] were conducted in conditions highly analogous to ours (*i.e.*, Zn-AcOH system); hence our one-pot protocol seemed well-applicable to the preparation of *N*-alkylated 2-aminoquinolines directly from acetonitrile (Scheme 2.29).



Scheme 2.29 One-pot synthesis of *N*-alkylated-2-aminoquinolines

Upon the generation of **2.28a** or **2.31a**, propanal was directly introduced to the reaction mixture without isolating the 2-aminoquinolines. The expected *N*-alkylated products ***N*-2.28a** and ***N*-2.31a** were successfully obtained.

2.6.5. Summary

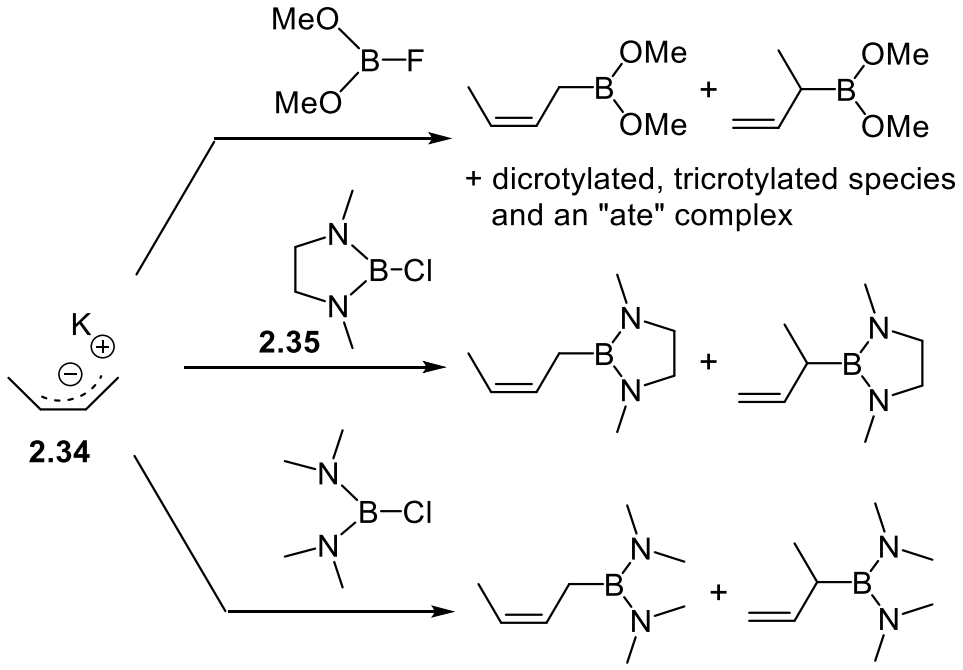
The use of a readily-accessible α-diaminoboryl carbnion species generated from acetonitrile enabled facile one-pot synthesis of a variety of substituted 2-aminoquinoline derivatives. This protocol was well applicable to prepare 3-substituted-2-aminoquinolines (**2.31**) using the method we recently developed (section 2.4.2). 4-Substituted-2-aminoquinoline (**2.33**) was also accessible by employing a ketone in place of an aldehyde. In addition, it was demonstrated that this one-pot protocol was suitable not only for reductive cyclization of nitrophenyl acrylonitriles but also for *N*-alkylation of the 2-aminoquinolines (***N*-2.28a** and ***N*-2.31a**). This work was published in *Organic & Biomolecular Chemistry* in May, 2012 with the help of Dr. Toshihide Maejima.[136]

2.7. Investigation of Cyclic Diaminochloroboranes for Their Olefinating Abilities

2.7.1. Cyclic diaminochloroboranes

Diaminochloroboranes have been widely utilized in both synthetic organic and inorganic/coordination chemistry fields.[139-141] Due mainly to their mildly suppressed Lewis acidity, they exhibit unique reactivities towards Lewis bases to form a variety of

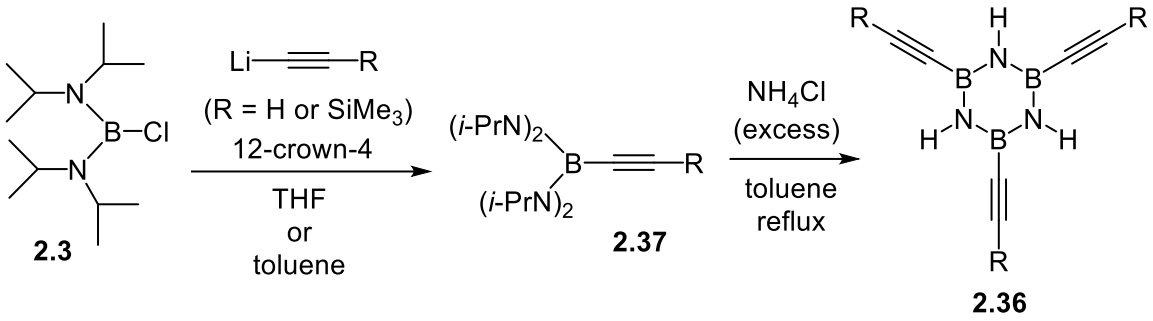
both cyclic and acylic boron-incorporated species. For example, Hoffmann *et al.* successfully synthesized their desired crotylboron reagents by taking advantage of the milder Lewis acidity of diaminoborane species over dialkoxyboranes (Scheme 2.30).[142] According to their observation, the reaction of dialkoxyboranes with (*Z*)-butenyl potassium **2.34** yielded mono-crotylated products along with over-crotylated products with the formation of an "ate" complex while the reaction of diaminoboranes with **2.34** gave the desired mono-crotylated products. They ascribe the over-crotylation and the borate formation to the higher Lewis acidity of dialkoxyboranes.



Scheme 2.30 Hoffmann's method

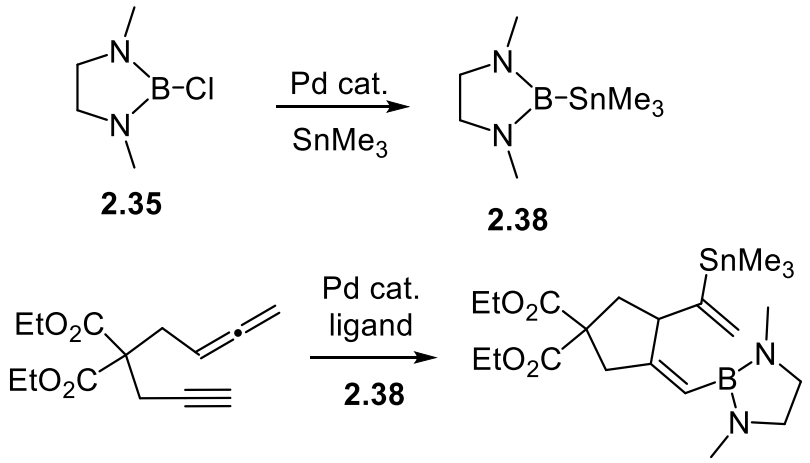
Another remarkable literature precedent that employs the chemistry of diaminochloroborane species has been reported by Grùtzmacher and co-workers.[102] In their work, trialkynylborazines **2.36** were prepared by reacting powdered ammonium chloride with alkynyl-bis(diisopropylamino)borane **2.37** that was one step away from

chloro-bis(diisopropylamino)borane **2.3** (Scheme 2.31). They used borazines **2.36** as catalysts in hydrosilylation reactions.



Scheme 2.31 Grützmacher's method

In sharp contrast to the frequent appearance of acyclic diaminochloroborane species in the literature, cyclic diaminochloroboranes [*e.g.*, diazaborolidines (five-membered rings), and diazaborinane (six-membered rings), *etc*.] have been rarely utilized in organic synthesis. One of the few practical examples, other than Hoffmann's work in Scheme 2.30, was demonstrated by RajanBabu and co-workers.[143] They utilized cyclic diaminochloroborane **2.35** for the synthesis of a borostannane compound which was then employed for their novel allenyne cyclization reactions (Scheme 2.32).



Scheme 2.32 RajanBabu's method

Suginome *et al*. have also proved the cyclic diaminoborane species to be a useful functionality in organic synthesis.[144] They prepared several derivatives of cyclic diaminochloroboranes (Figure 2.3) to be used in the palladium-catalyzed three-component carboboration reactions they have developed (Scheme 2.33). Not only did these reactions proceed in highly regio- and stereoselective manners, Suginome also implies in the paper that triorganoboranes or trihaloboranes, more Lewis acidic borane-derivatives, would have shown far different reactivities.

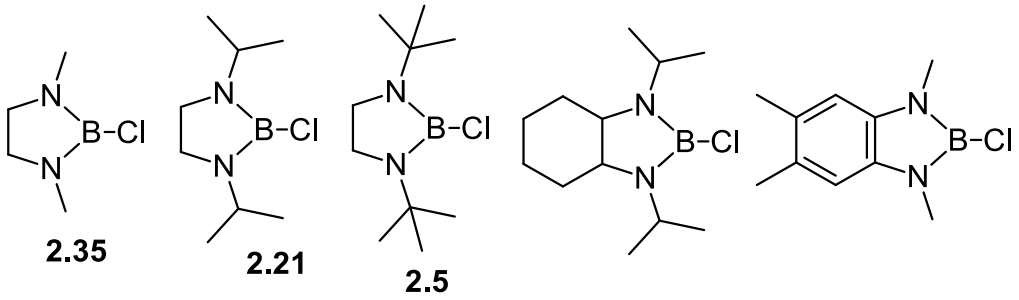
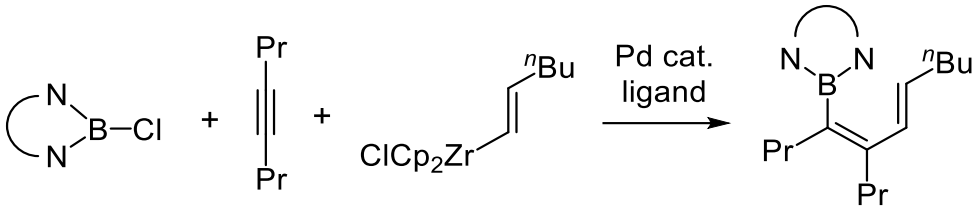


Figure 2.3 Diaminohloroboranes prepared by the Suginome group



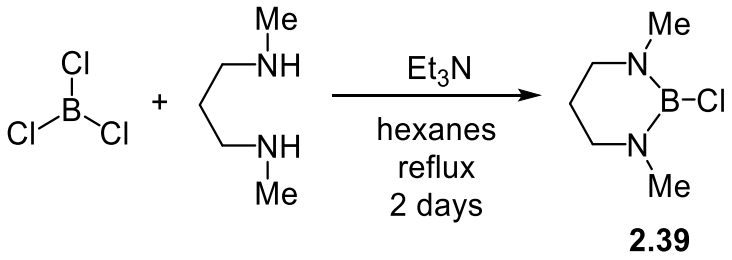
Scheme 2.33 Suginome's carboboration protocol

As seen from the above, the use of cyclic diaminochloroboranes in transition-metal-catalyzed reactions has been demonstrated; however, we have an impression that the synthetic utilities of those species have not been explored thoroughly, especially when it comes to their fundamental reactivities (*e.g*., stability issues, base/nucleophile compatibility, *etc.*). In fact, unfortunately, the Suginome group has not disclosed the

characterization data of those cyclic diaminochloroborane species, which makes it difficult for other organic chemists to study them. Despite this challenging situation, we decided to investigate more into this area of chemistry, especially in terms of α-boryl carbanion species of cyclic diaminochloroboranes.

2.7.2. Six-membered diaminochloroboranes

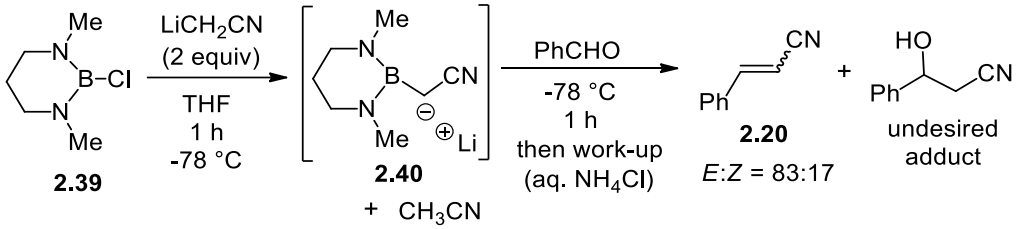
To begin, we prepared *N*,*N*'-dimethylchlorodiazaborinane **2.39** by modifying the literature procedure (*i.e.*, a longer reaction time) by which diazaborolidines **2.5** and **2.21** were prepared (Scheme 2.34).



Scheme 2.34 Formation of **2.39**

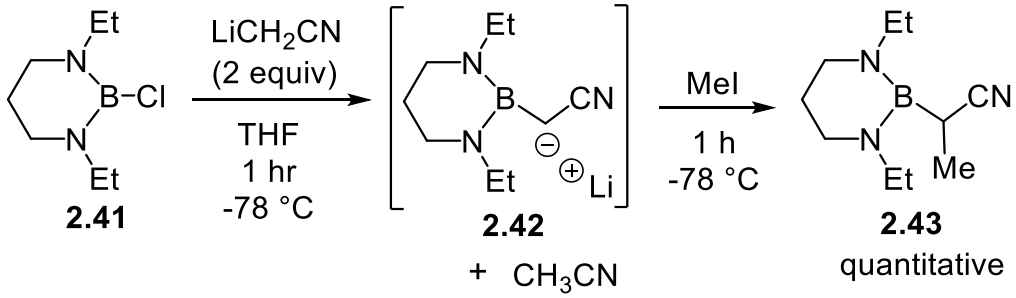
In order to test the olefinating ability of **2.39**-derived α-boryl carbanion species, **2.39** was subjected to our optimized one-pot conditions with benzaldehyde (Scheme 2.35). Based on the ^{1}H NMR analysis of the crude product, the expected β-phenyl acrylonitriles **2.20** were obtained along with an alcohol side adduct and unreacted benzaldehyde, showing a relatively low conversion to the olefinated products **2.20**. Surprisingly, the reaction proceeded (*E)*-stereoselectively contrary to our empirical observation for aromatic aldehydes so far. Diazaborinane **2.39**, however, was unstable

even in a refrigerator: salt precipitation was observed in a few days. This result motivated us to examine other diaminochloroborinanes for their reactivities.



Scheme 2.35 Olefination using **2.39**

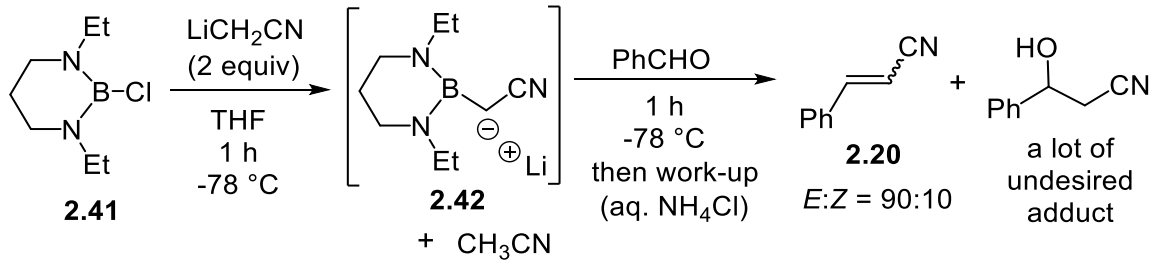
Following the same recipe as shown in Scheme 2.34, *N*,*N*'-diethylchlorodiazaborinane **2.41** and *N*,*N*'-diisopropylchlorodiazaborinane **2.44** were prepared in good yields using the corresponding *N*,*N*'-dialkyl-1,3-propanediamine for each reaction. In order to confirm the generation of α-boryl carbanion species **2.42** *in situ*, methyl iodide was introduced to the reaction mixture after treating **2.41** with two equivalents of $LiCH_2CN$ (Scheme 2.36).



Scheme 2.36 Formation of **2.43**

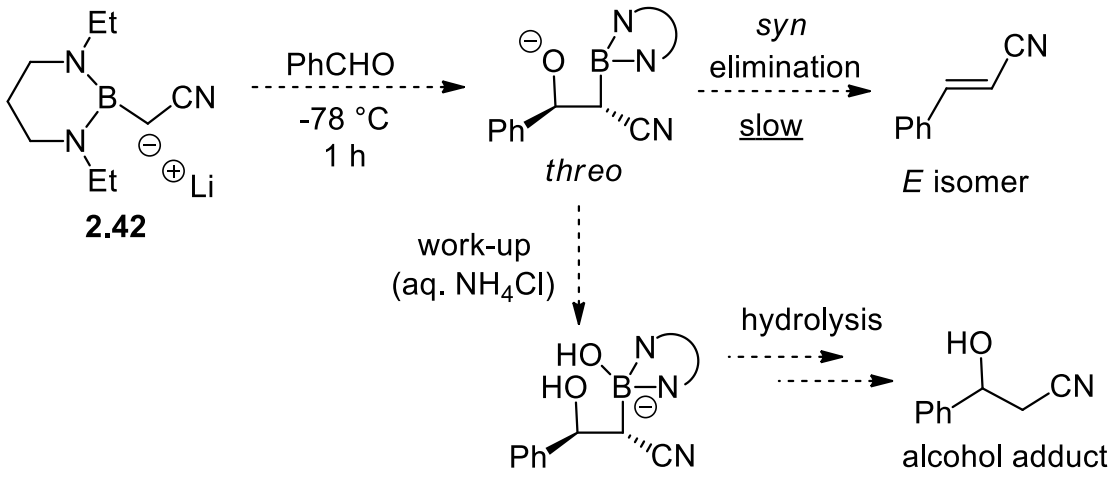
The expected methyl-substituted cyclic diaminoboryl acetonitrile **2.43** was most presumably formed roughly quantitatively, as indicated by the ^{1}H NMR analysis of the crude product for the newly-formed characteristic doublet and the quartet peaks from a methyne proton and neighboring methyl protons [^{1}H NMR (300 MHz, $CDCl_3$) δ 2.97 (q,

J = 6.9 Hz, 4H), 2.87 (t, *J* = 5.7 Hz, 4H), 2.37 (q, *J* = 7.5 Hz, 1H), 1.81 (p, *J* = 5.7 Hz, 2H), 1.32 (d, *J* = 7.5 Hz, 3H), 1.07 (t, *J* = 6.9 Hz, 6H)]. Formation of **2.43** indirectly, but practically, suggests the formation of **2.42** *in situ*. Observing this pleasing preliminary result, an olefination reaction was attempted using diethylchloroborinane **2.41** (Scheme 2.37).



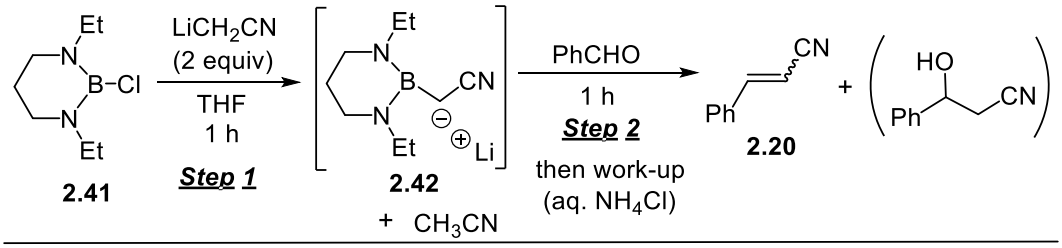
Scheme 2.37 Olefination using **2.41**

To our delighted surprise, the expected olefination products **2.20** were obtained in an even higher (*E)*-selective manner than the reaction with dimethylchlorodiazaborinane **2.39**. The formation of alcohol side adduct, however, was significant: in addition, almost entire consumption of aldehyde was confirmed. Taking these observations into account, our conclusion for this result would be that after a nucleophilic attack of α-boryl carbanion species **2.42** on the carbonyl carbon of benzaldehyde, the *syn*-elimination process was extremely sluggish, thus the boron moiety survived and was cleaved by hydrolysis upon acidic aqueous work-up (Scheme 2.38).



Scheme 2.38 Mechanism for an (*E*)-isomer and an alcohol adduct formation

In an effort to increase the olefin products conversion, a variety of conditions were investigated in terms of the reaction temperatures for both steps and the temperatures upon quenching (Table 2.8).



entry	***step 1*** temp (°C)	***step 2*** temp (°C)	quench temp (°C)	alcohol side adduct formation	PhCHO left-over	*E:Z*[a] of **2.20**
1	-78	-78	-78	significant	negligible	90:10
2	0	0	-78	none	negligible	40:60
3	-78	0	-78	none	negligible	41:59
4	-78	0	0	none	none	41:59
5	-78	-40	-40	significant	a little	88:12
6	-40	-40	-40	significant	negligible	61:39
7	-40	-40	-78	significant	negligible	65:35

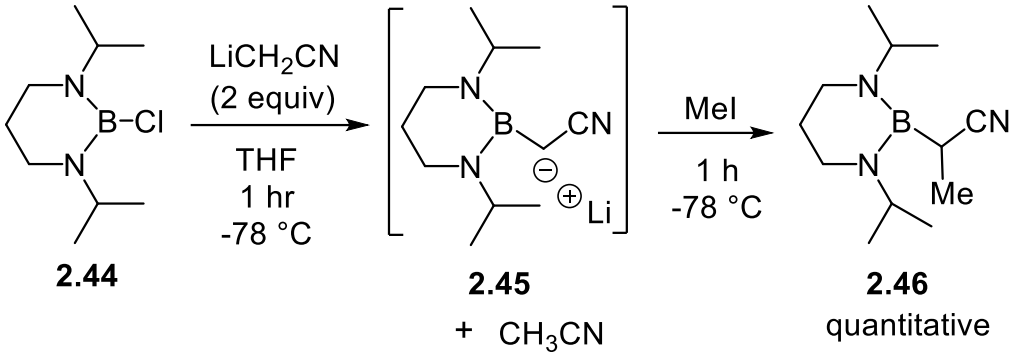
[a] Determined by ^{1}H NMR of the crude reaction mixture.

Table 2.8 Attempted condition optimization for the reaction of **2.41**

Reactions took place very smoothly for entries 2-4 with almost full conversion of aldehyde to olefin products **2.20** without the alcohol side adduct formation. This would be attributed to a higher temperature (*i.e.*, 0 °C) at the second step regardless of the quenching temperature even though *E*:*Z* stereoselectivity was compromised for each case, down to *E*:*Z* = ~40:60. This would also mean that the elimination process is expeditious at higher temperature. The reaction outcomes from entries 6 and 7 at intermediate temperatures were akin to each other with lots of alcohol side adduct formation and a similar *E*/*Z* selectivity, suggesting that whether the quenching temperature was -40 °C or -78 °C did not affect the product outcomes. Likewise, entry 5 turned out to be almost the same result as entry 1 including the stereoselectivity, which indicates the indifference of the results of the step 2 reaction temperature and the quenching temperature between -40 °C and -78 °C.

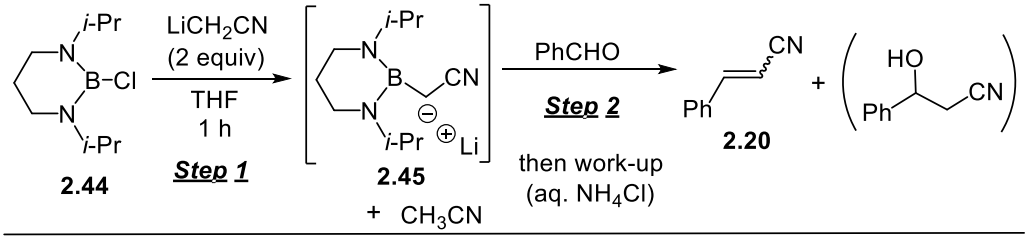
To sum up, lower reaction temperatures at the second step induced excellent (*E*)-selectivities but with lower yields of the desired olefin products **2.20**. On the other hand, as temperatures went up at step 2, (*E*)-selectivity started to drop significantly with the increased formation of **2.20**. Temperatures at the first step do not seem to have much of an effect on the overall reaction outcomes. Since none of the tested conditions exhibited a satisfactory result, we moved on to examine the next diaminochloroborinane substrate, **2.44**.

In the same method as shown in Scheme 2.36 above, we verified the formation of an α-boryl carbanion **2.45** by trapping it with methyl iodide (Scheme 2.39).



Scheme 2.39 Formation of **2.46**

The crude product of **2.46** showed the wanted doublet and the quartet peaks from a methyne proton and methyl protons almost quantitatively [^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (sep, *J* = 6.6 Hz, 2H), 2.79 (t, *J* = 5.7 Hz, 4H), 2.47 (q, *J* = 7.5 Hz, 1H), 1.74 (p, *J* = 5.7 Hz, 2H), 1.30 (d, *J* = 7.5 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 12H)]. After confirming the successful formation of **2.45** *in situ*, we attempted various reaction conditions to olefinate benzaldehyde (Table 2.9).



entry	step 1 temp (°C)	step 2 time	step 2 temp (°C)	alcohol side adduct formation	PhCHO left-over	*E:Z*[a] of **2.20**
1	-78	1 h	-78	significant	negligible	62:38
2	-78	2.5 h	-78	significant	none	78:22
3	-78	1 h	0	none	negligible	41:59
4	-40	1 h	-40	significant	none	78:22
5	-78	1 h	-40	significant	negligible	81:19

All the reactions were quenched at the same temperature as step 2.

[a] Determined by ^{1}H NMR of the crude reaction mixture.

Table 2.9 Condition optimization for the reaction of **2.44**

For all the reaction conditions tested, aldehyde consumption was sufficient; however, a significant amount of side alcohol adduct was formed for all the entries except for entry 3 where reaction temperature at the second step was 0 °C. Even with a high conversion of aldehyde into the desired alkenes **2.20** for entry 3, (*E*)-selectivity was considerably compromised. On the contrary, higher *E*/*Z* selectivities were achieved from entries 2, 4, and 5 where colder temperatures *(i.e.*, -40 °C and -78 °C) were applied, albeit with remarkable formations of an alcohol side adduct. From entry 1 to entry 2, we observed a longer reaction time at the second step enhanced *E*/*Z* selectivity for an unknown reason.

Overall, colder temperatures and formation of olefin products **2.20** were observed to be inversely proportional to each other. Correlation between bulkiness of the alkylamino ligand and *E*/*Z* stereoselectivity was not observed. Since none of the reaction results were pleasing to us, we proceeded to the next project.

2.7.3. Five-membered diaminochloroboranes

To further investigate the cyclic diaminochloroborane species, we now set our aim to diazaborolidines, the five-membered cyclic diaminoboranes. In accordance with the recipe shown in Scheme 2.34, three diazaborolidines with straight alkyl chains on them (*i.e.*, **2.47**, **2.49**, and **2.51**), in addition to **2.5**[103] and **2.21**[144] with branched alkyl chains on them (Figure 2.4), were synthesized using the corresponding *N*,*N*'-dialkyl-1,2-ethanediamine in place of a propanediamine in moderate to good yields (Scheme 2.40).

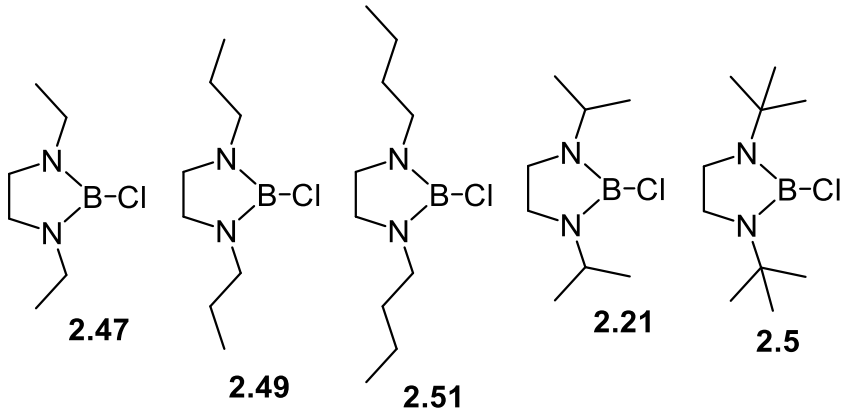
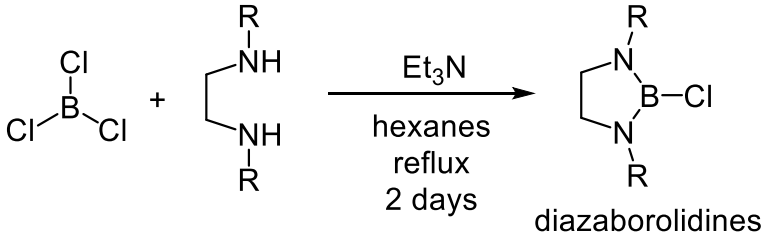
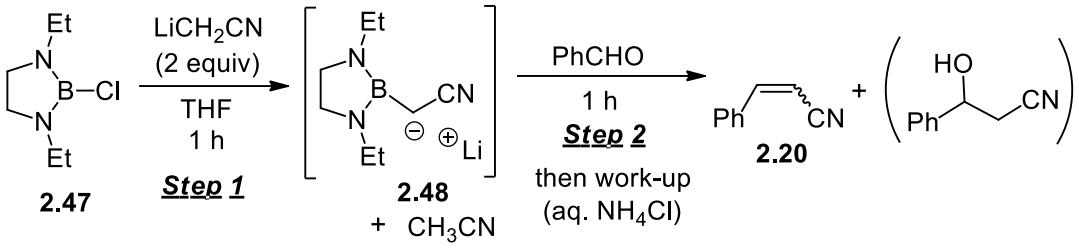


Figure 2.4 Synthesized diazaborolidines



Scheme 2.40 Synthesis of diazaborolidines

As our initial attempt, diethylchlorodiazaborolidine **2.47** was exposed to our standardized one-pot olefination conditions with benzaldehyde with a wide variety of reaction temperatures (Table 2.10).



entry	***step 1*** temp (°C)	***step 2*** temp (°C)	alcohol side adduct formation	PhCHO left-over	unknown impurity(s)	*E:Z*[a] of **2.20**
1	-78	-78	some	some	some	41:59
2	-40	-40	a little	a little	a little	33:67
3	-40	-29	significant	none	significant	60:40
4	-40	r.t.	somewhat	none	significant	83:17
5	-29	-29	significant	none	significant	60:40
6	-10.5	-10.5	negligible	none	significant	65:35
7	0	0	negligible	none	significant	71:29

All the reactions were quenched at the same temperature as step 2.

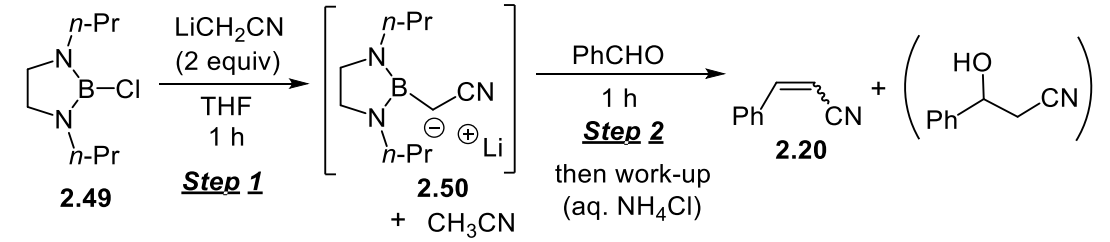
[a] Determined by ^{1}H NMR of the crude reaction mixture.

Table 2.10 Condition optimization for the reaction of **2.47**

First, what was remarkable about the reactions with this diazaborolidine substrate was a formation of unknown/uncharacterized by-product(s) alongside the alcohol adduct we have obtained so far. Their appearance became significant as the reaction temperature went up, especially -29 °C and above (entries 3-7). The reaction temperature of the 1st step did not have much of an effect on the reactivity when that of the 2nd step was held the same (entries 3 and 5). Entries 1 and 2 were the only cases that yielded the (*Z*)-isomer as a major product: moreover, it would be worth mentioning that only entry 2 (-40 °C for both reaction steps) proceeded in a relatively clean fashion without producing a lot of by-products. As a general trend, we could say that as the temperature of the 2nd step increases, the *E*/*Z* selectivity also increases (entries 1-6). Even though we observed

a solid correlation of reaction temperature and the stereochemical outcome, the formation of by-products hindered the olefination process excessively; therefore, we moved on to investigate the next diazaborolidine.

The next diazaborolidine we tested was di-*n*-propylchloroborolidine **2.49**, having one-carbon homologated alkyl chains on both nitrogen atoms compared to **2.47** (Table 2.11).



entry	***step 1*** temp (°C)	***step 2*** temp (°C)	alcohol side adduct formation	PhCHO left-over	unknown impurity(s)	*E*:*Z*[a] of **2.20**
1	-78	-78	significant	none	a little	46:54
2	-40	-40	none	none	a little	29:71
3	-78	-40	significant	none	somewhat	43:57
4	-78	0	none	none	significant	61:39

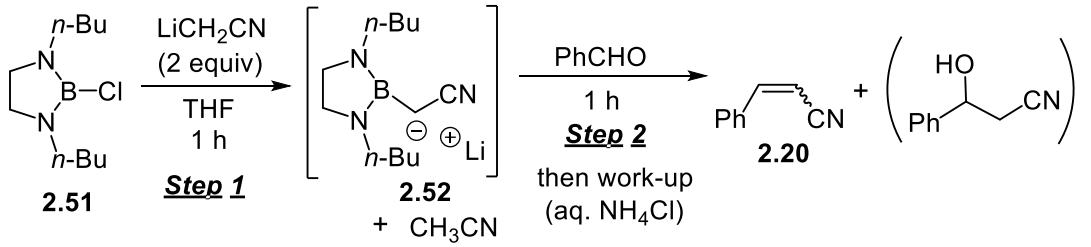
All the reactions were quenched at the same temperature as step 2.
[a] Determined by ^{1}H NMR of the crude reaction mixture.

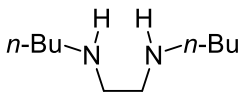
Table 2.11 Condition screening for the reaction of **2.49**

Among the four different conditions we examined, entry 2 yielded the cleanest reaction outcome when both steps were operated at -40 °C, exhibiting the highest (*Z*)-selectivity. In contrast, entry 4 was the only case giving the (*E*)-isomer of **2.20** as a major product while producing significant amount of unknown impurities that were presumably derived from the decomposed diazaborolidine moiety due to a higher temperature (*i.e.*, 0 °C). A considerable amount of the alcohol side adduct was observed from entries 1 and

3, suggesting that the generation of α-boryl carbanion species **2.50** was incomplete at -78 °C at the step 1. Therefore, the unreacted portion of $LiCH_2CN$ ended up attacking benzaldehyde, which led to the formation of the alcohol adduct.

Di-*n*-butylchloroborolidine **2.51**, with even longer alkyl chains on both nitrogen atoms, was examined next.



entry	***step 1*** temp (°C)	***step 2*** temp (°C)	alcohol side adduct formation	PhCHO left-over		*E*:*Z*[a] of **2.20**
1	-78	-78	significant	none	significant	50:50
2	-78	-40	a little	none	significant	31:69
3	-40	-40	negligible	none	a little	40:60
4[b]	-40	0	none	none	significant	85:15
5[b]	0	0	none	none	significant	85:15
6	-40	-78	somewhat	none	significant	40:60

All the reactions were quenched at the same temperature as step 2.
[a] Determined by ^1H NMR of the crude reaction mixture.
[b] A lot of unknown/uncharacterized impurity(s) were obtained.

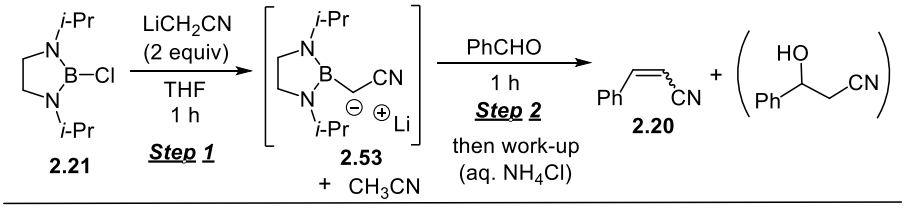
Table 2.12 Condition optimization for the reaction of **2.51**

The crude products from all the entries except for entry 3 contained a notable amount of *N*,*N*'-di-*n*-butylethylenediamine that must have been either generated upon the decomposition of **2.51** or **2.52** *in situ*, or extracted into an organic layer upon the extraction operation after the aqueous work up of each reaction. Even though entries 4 and 5 at higher temperatures resulted in the highest *E*/*Z* stereoselectivity (*i.e.*, *E*:*Z* =

85:15), olefin products **2.20** were barely obtained: in fact, their crude products consisted mostly of the ethylenediamine and unknown/uncharacterized impurities. Entries 2, 3, and 6 demonstrated practically the same (*Z*)-selectivity (*i.e.*, *E*:*Z* = ~40:60); yet entry 3 (both step 1 and 2 were carried out at -40 °C) gave the cleanest crude product with almost sole formation of the olefins **2.20**.

So far, we have employed diamino ligands with straight alkyl chains on them (*i.e.*, ethyl, *n*-propyl, and *n*-butyl) for diazaborolidines, and they have consistently given relatively clean reactions with superior (*Z*)-stereoselectivities when both 1st and 2nd steps were operated at -40 °C. Now we steer our research direction to the diazaborolidines with branched alkyl chains on them, which would greatly change the steric environment around the boron nucleus as well as the behavior of α-boryl carbanion species in reactions.

Diazaborolidine **2.21**, with two isopropyl groups on it, was subjected to a series of olefination reactions at different temperatures (Table 2.13).



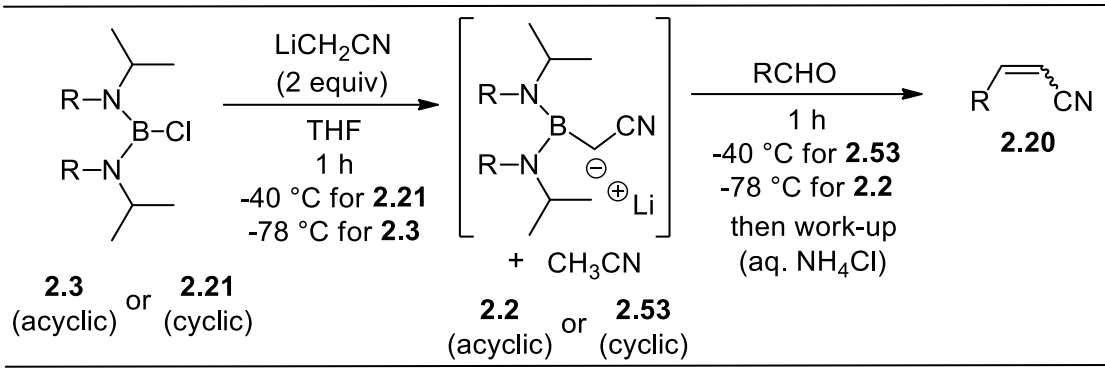
entry	***step 1*** temp (°C)	***step 2*** temp (°C)	alcohol side adduct formation	PhCHO left-over	unknown impurity(s)	*E*:*Z*[a] of **2.20**
1	-78	-78	significant	none	none	71:29
2	-40	-40	none	none	none	19:81
3	-29	-29	none	none	significant	29:71
4	-10.5	-10.5	none	none	significant	76:24

All the reactions were quenched at the same temperature as step 2.
[a] Determined by ^{1}H NMR of the crude reaction mixture.

Table 2.13 Condition optimization for the reaction of **2.21**

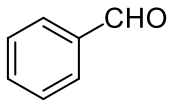
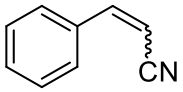
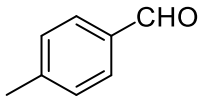
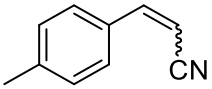
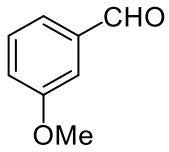
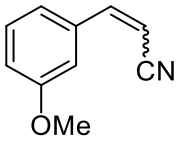
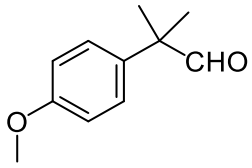
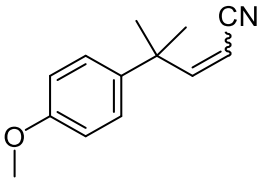
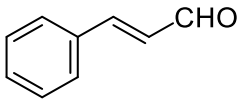
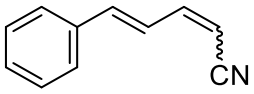
Finally, the reaction of entry 2 proceeded in an extremely clean manner, exclusively producing the desired β-phenyl acrylonitriles **2.20** without any by-products or impurities. Not only that, the reaction was highly (*Z*)-stereoselective. When a slightly higher temperature was applied (-29 °C), the reaction became less (*Z*)-selective and also started to give unknown/uncharacterized impurity(s) (entry 3). Application of an even higher temperature (-10.5 °C) produced a remarkable amount of the same unknown by-product(s), yet olefin products **2.20** were obtained in a (*E*)-selective manner this time (entry 4). The reaction of entry 1 also demonstrated a good (*E*)-stereoselectivity at -78 °C, albeit with a considerable amount of alcohol side adduct.

Observing this promising result from entry 2, we employed this modified one-pot protocol for a variety of aldehydes that we utilized in Table 2.1 (section 2.2.5) to compare the olefinating ability of cyclic boryl carbanion **2.53** and acyclic boryl carbanion **2.2** (Table 2.14) [Note: The *E*:*Z* selectivities and yields of the reactions with α-diaminoboryl carbanion **2.2** are directly from Table 2.1, meaning those reactions were conducted at -78 °C during their entire course].



2.3 (acyclic) or **2.21** (cyclic)

2.2 (acyclic) or **2.53** (cyclic)

entry	aldehyde	products	**2.2** (acyclic) *E:Z*[a]	**2.2** (acyclic) yield (%)[b]	**2.53** (cyclic) *E:Z*[a]	**2.53** (cyclic) yield (%)[b]
1			20:80	94	19:81	90
2			19:81	97	17:83	90
3			22:78	80	17:83	84
4			6:94	86	7:93	98
5			35:65	88	36:64	98

[a] Determined by ^{1}H NMR of the crude reaction mixture.
[b] isolated yield

Table 2.14 Olefination of aldehydes using the modified one-pot protocol

Both carbanions **2.53** and **2.2** converted aldehydes into the corresponding acrylonitriles in a highly similar fashion: both *E*:*Z* ratios and % yields turned out to be

almost identical to each other. For entry 4, both carbanion species exhibited an outstanding (*Z*)-stereoselectivity from the highly sterically challenging aldehyde. Meanwhile, when the sterically much less demanding aldehyde, *trans*-cinnamaldehyde, (entry 5) was used, the *Z*/*E* ratio of the olefin products dropped significantly, just as we observed previously in section 2.2.5. Except for a slight boost in (*Z*)-selectivity for *m*-methoxybenzaldehyde (entry 3), cyclic α-boryl carbanion **2.53** showed a highly similar olefinating ability as **2.2** on benzaldehyde and its derivatives (entries 1-3).

So far, we have investigated four different five-membered cyclic diaminochloroboranes **2.47** (diethyl), **2.49** (di-*n*-propyl), **2.51** (di-*n*-butyl), and **2.21** (di-*i*-propyl), all of which have demonstrated moderate to excellent *Z*/*E* stereoselectivities. Below is a brief summary of empirical reactivity tendency of these species we have observed (Figure 2.5).

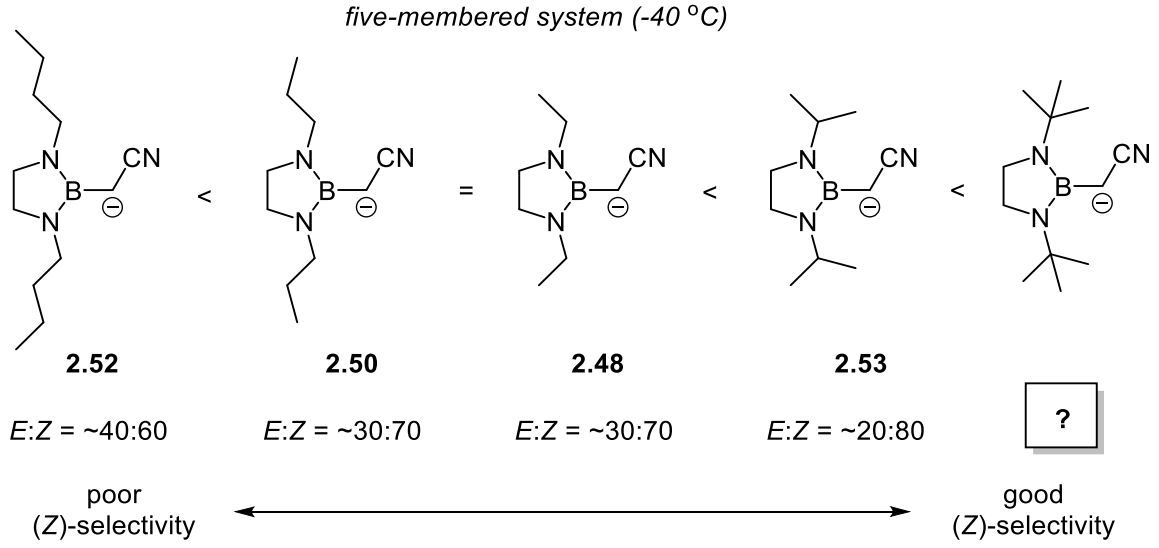
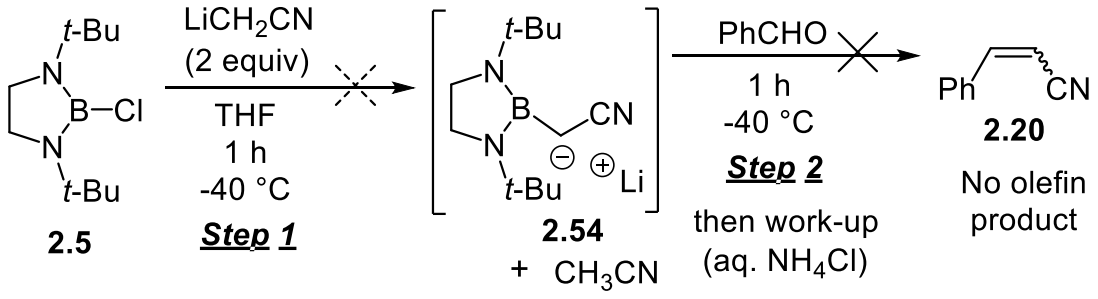


Figure 2.5 Reactivity of five-membered system

Clearly, having a longer straight alkyl chain did not cause much of an effect; rather, a decrease in (*Z*)-selectivity was observed from **2.50** to **2.52**. From **2.50** or **2.48** to **2.53**, however, we saw a boost in *Z*/*E* ratio by switching to a sterically bulkier isopropyl group. This observation motivated us to investigate the olefinating ability of an even bulkier *tert*-butyl substituted diazaborolidine, **2.5**.

Di-*tert*-butylchlorodiazaborolidine **2.5** was subjected to our modified one-pot conditions with benzaldehyde. However, to our disappointment, absolutely none of olefination products was detected in the raw product by ^{1}H NMR analysis (Scheme 2.41). What was obtained instead was an almost pure alcohol side adduct (*i.e.*, PhCH(OH)CH_2CN). Employing a higher temperature (0 °C) for both 1st and 2nd steps did not produce any olefin product, either. Based on these observations, our postulation for this case would be that two equivalents of LiCH_2CN did not convert chloroborane **2.5** into a boryl carbanion **2.54** at all, perhaps due to the two extremely bulky tertiary butyl groups; thus intact LiCH_2CN directly attacked benzaldehyde upon addition, leading to the formation of the side alcohol adduct.



Scheme 2.41 Olefination attempt using **2.5**

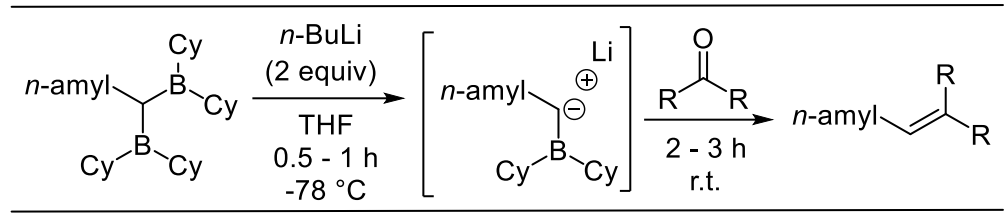
2.7.4. Summary

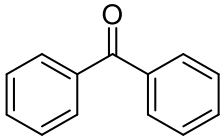
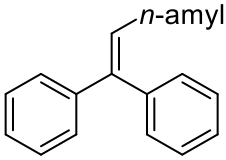
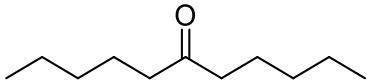
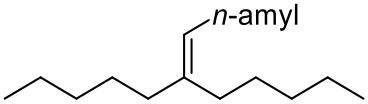
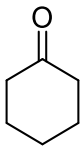
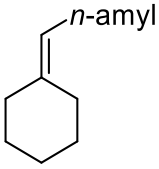
Six-membered cyclic diaminoboranes either produced disappointing yields with the (*E*)-isomer as a major alkene product or low stereoselectivities. In the meantime, five-membered cyclic substrates exhibited moderate to excellent (*Z*)-selectivities. The use of straight alkyl chains was not as effective as that of a branched alkyl chain (*i.e.*, isopropyl group) in terms of *Z*/*E* stereoselectivity. Diisopropylchlorodiazaborolidine **2.21** demonstrated an outstanding reactivity, and converted a series of both aromatic and aliphatic aldehydes into the corresponding olefin products in good yield and stereoselectivity.

2.8. Olefination of Ketones

2.8.1. Olefination of ketones with α-boryl carbanion species in the literature

After observing the exceptional olefinating ability of the five-membered cyclic diaminochloroborane **2.53** towards aldehydes (Table 2.14), we now embrace our curiosity on the reactivity of **2.53** towards ketones. In fact, reactions of α-boryl carbanions with ketones have been reported from time to time in the literature by the pioneers of this field of organic synthesis. Cainelli *et al*., for instance, reported a few olefination reactions of their α-boryl carbanion species with symmetric ketones in the earliest stages of the α-boryl carbanion chemistry (Table 2.15).[80] Olefin conversion of the reactions were low to mediocre. The stereochemical issue did not arise here because they used symmetric ketones.

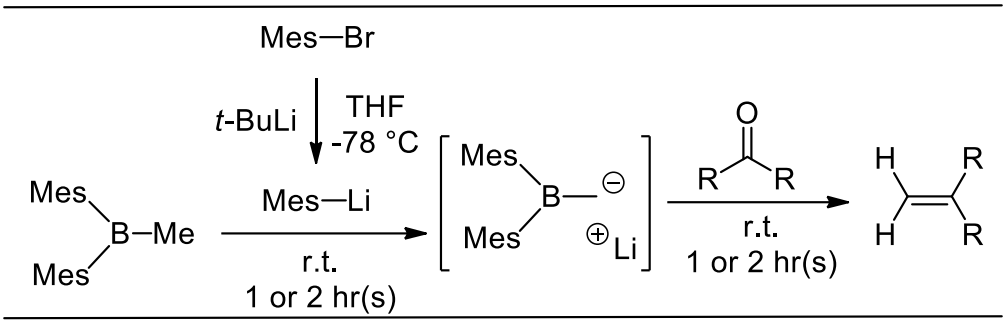


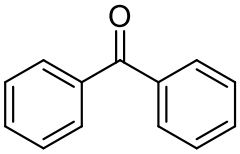
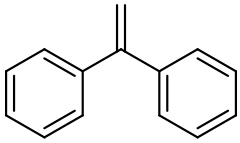
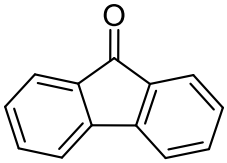
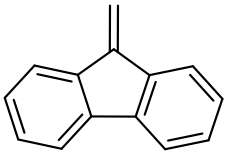
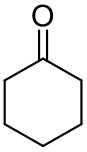
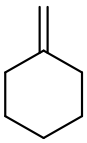
entry	ketone	product	yield (%)[a]
1			45-50
2			30-35
3			20-25

[a] isolated yield

Table 2.15 Cainelli's olefination of ketones

Pelter and co-workers also screened a few ketones to test their novel dimesityl boryl carbanion.[145] They utilized symmetric ketones as well in order to avoid stereochemical issues of the alkene products (Table 2.16). Benzophenone (entry 1) and fluorenone (entry 2) were selected as they do not have a possibility of enolization by lithium-proton exchange at the carbonyl α-carbons. Indeed, they obtained the olefin products in good yields. When it comes to entry 3, however, cyclohexanone gave a much inferior product conversion, implying that enolization competed with olefination.



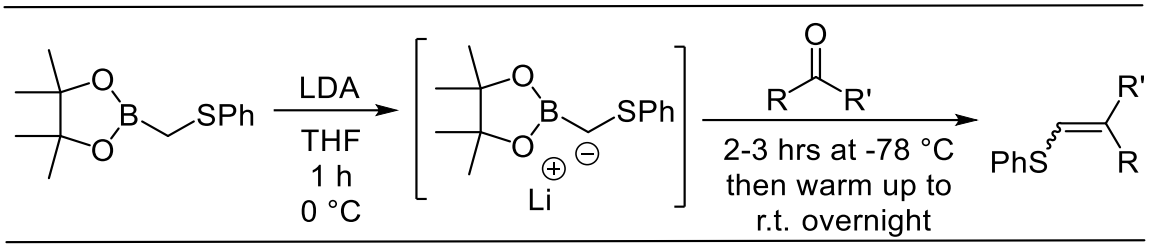
entry	ketone	product	yield (%)[a]
1			75
2			80
3			30

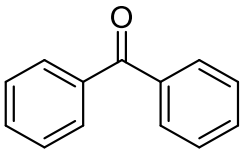
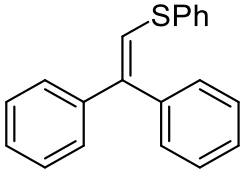
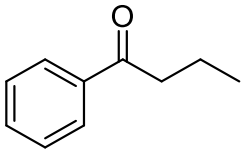
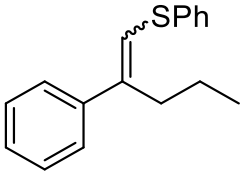
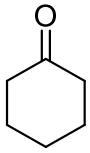
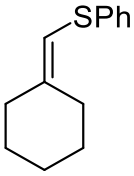
[a] isolated yield

Table 2.16 Pelter's olefination of ketones

Matteson *et al*., on the other hand, evaluated both symmetric and asymmetric ketones even though *E*:*Z* ratios where applicable were hardly ever reported for the asymmetric ketones (Table 2.17 and Scheme 2.42).[146-147] In Table 2.17, they examined benzophenone (entry 1) and cyclohexanone (entry 3) just as the Cainelli group and the Pelter group did for their investigations. For entry 3, the Matteson group obtained a lot more olefin product than the other groups did, perhaps because enolate formation was far less significant from their α-boryl carbanion. Entry 2 is a reaction of an asymmetric

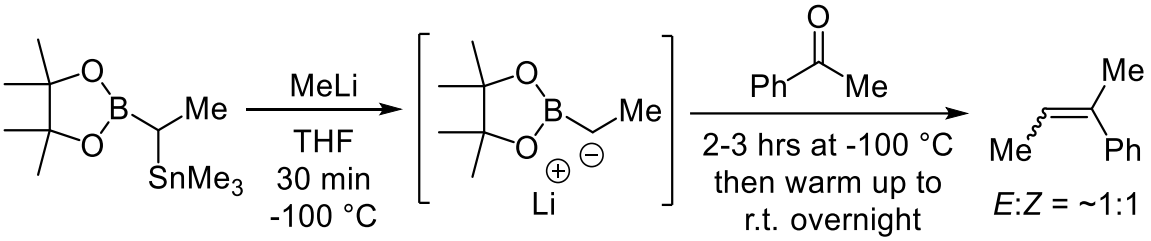
ketone; however, they did not specify the *E*:*Z* selectivity of the olefin products for this particular reaction.



entry	ketone	product	*E:Z*	yield (%)[a]
1			n/a	71
2			not reported	82
3			n/a	71

[a] isolated yield

Table 2.17 Matteson's olefination of ketones



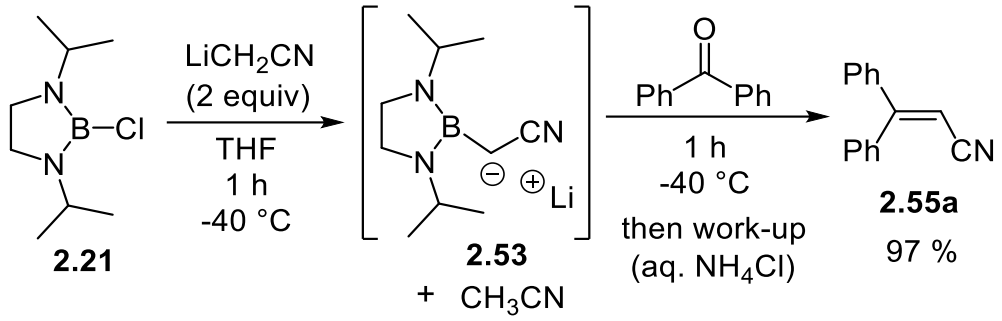
Scheme 2.42 Matteson's olefination of acetophenone

Illustrated in Scheme 2.42 is an extremely rare case of a reaction with an asymmetric ketone where an *E*:*Z* stereochemical outcome is reported. This olefination of acetophenone, however, did not exhibit any stereoselectivity: plus, they did not mention the yield of the products.

Previously, our novel acyclic α-boryl carbanion **2.2** also proved its olefinating ability towards a ketone in Scheme 2.28 in section 2.6.4. However, after observing the phenomenal olefinating ability of diazaborolidine-based carbanion **2.53** on aldehydes (section 2.7.3), we now have a strong urge to find out the reactivity of cyclic α-boryl carbanion **2.53** towards ketones. As aforementioned above, only little has been reported on the olefination reactions of ketones with α-boryl carbanions in the literature, especially with *E*:*Z* stereochemical outcome of the reactions particularized. Therefore, we decided to investigate the olefination of ketones using **2.53**, with a focus on the *E*:*Z* stereoselecvity of the products.

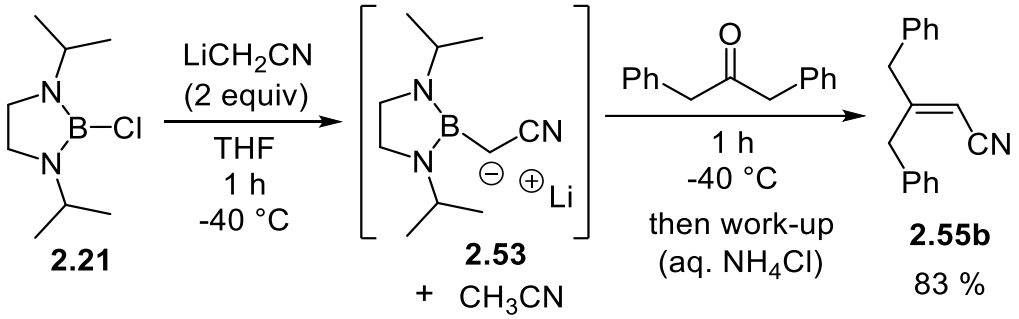
2.8.2. Olefination of symmetric ketones

As the first test substrate, as aforementioned research groups have done (section 2.8.1), a diaryl symmetric ketone, benzophenone, was selected for the purpose of avoiding potential enolization as well as a stereochemical issue of the product. Benzophenone was subjected to our modified one-pot olefination conditions using cyclic diaminochloroborane **2.21** to see whether an olefination takes place or not. Fortunately, the expected β,β-diphenylacrylonitrile **2.55a** was obtained almost quantitatively (Scheme 2.43).



Scheme 2.43 Olefination of benzophenone

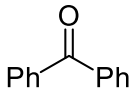
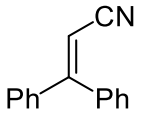
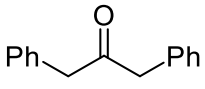
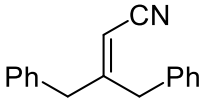
Pleased with this promising result, we employed another symmetric ketone, dibenzyl ketone, using the same reaction conditions (Scheme 2.44).



Scheme 2.44 Olefination of dibenzyl ketone

Due to the relatively high acidity of the carbonyl α-protons, enolization could have competed with olefination, slightly compromising the reaction yield. However, the reaction proceeded in a very clean fashion, giving a fairly high product conversion overall.

Based off of our curiosity, we let the acyclic boryl carbanion **2.2** react with those symmetric ketones in the modified one-pot olefination conditions (-40 °C for the entire course of the reaction) for comparison with the reactions of cyclic boryl carbanion **2.53** (Table 2.18).

entry	ketone	product		**2.2** (acyclic) yield (%)[a]	**2.53** (cyclic) yield (%)[a]
1			**2.55a**	9	97
2			**2.55b**	0	83

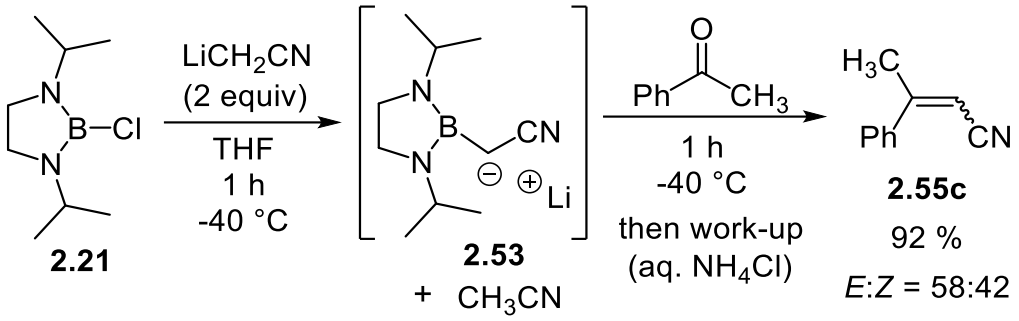
[a] isolated yield

Table 2.18 Reactivity of **2.2** and **2.53** with symmetric ketones

Acyclic α-boryl carbanion **2.2** turned out to be rather inert towards the ketones. In particular, the reaction with dibenzyl ketone (entry 2) did not afford any of the expected acrylonitrile. In both reactions of **2.2**, the crude products consisted almost entirely of the starting ketones, as confirmed by the ^{1}H NMR analysis. Overall, cyclic boryl carbanion **2.53** showed a highly superior olefination capability towards the symmetric ketones over the acyclic carbanion **2.2**.

2.8.3. Olefination of acetophenone and its steric-equivalents

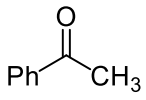
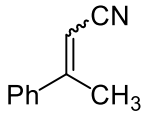
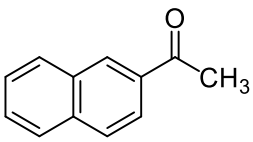
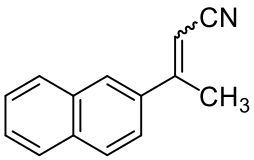
As seen in the above section, symmetric ketones have been smoothly converted to their corresponding acrylonitriles with cyclic α-boryl carbanion **2.53**. Now we switch our focus to asymmetric ketones in order to examine their *E*:*Z* stereochemical outcomes. We first utilized acetophenone as an example of an asymmetric, aromatic ketone of reasonable bulk. The reaction of acetophenone with α-boryl carbanion **2.53** is shown in Scheme 2.45 below.

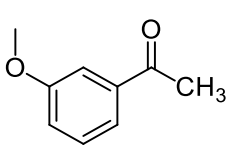
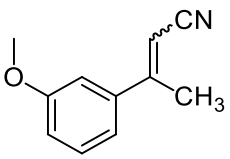
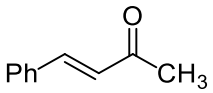
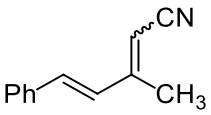


Scheme 2.45 Olefination of acetophenone

Again, α-boryl carbanion **2.53** very smoothly converted acetophenone into the corresponding β,β-disubstituted acrylonitrile products **2.55c** in an excellent yield. The reaction took place in a somewhat (*E*)-stereoselective manner.

A few more ketones with similar steric profiles to that of acetophenone were accordingly investigated by utilizing both boryl carbnions **2.2** and **2.53** to compare their reactivities on the ketones (Table 2.19).

				2.2 (acyclic)		**2.53** (cyclic)	
entry	ketone	products		*E:Z*[a]	yield (%)[b]	*E:Z*[a]	yield (%)[b]
1			**2.55c**	77:23	71	58:42	92
2			**2.55d**	72:28	21	60:40	94

3			**2.55e**	73:27	64	60:40	96
4			**2.55f**	n/d[c]	n/d[c]	63:37	71

[a] Determined by ^{1}H NMR of the crude reaction mixture.
[b] isolated yield [c] not determined

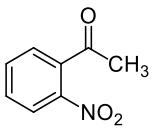
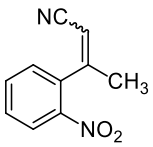
Table 2.19 Reactivity of **2.2** and **2.53** with asymmetric ketones similar to acetophenone

Reactions of cyclic boryl carbanion **2.53** afforded the corresponding olefinated products in nearly quantitative yields for entries 1-3, which are remarkably higher than the reactions of **2.2**. In a stereochemical sense, all the attempted reactions turned out to be (*E*)-stereoselective, with consistently higher *E*/*Z* ratios for the reactions of acyclic boryl carbanion **2.2** where applicable (entries 1-3). Entry 4, a reaction with a vinyl methyl ketone, also showed a similar reactivity albeit in a somewhat lower yield. The (*E*)- and (*Z*)-isomers of the acrylonitrile products **2.55c**-**2.55e** (entries 1-3) were separable by conventional silica-gel column chromatography whereas **2.55f** (entry 4) was isolated as a mixture.

2.8.4. Olefination of *ortho*-monosubstituted acetophenone-derivatives

In the preceding section, we observed (*E*)-stereoselective reactions of asymmetric ketones that are relatively sterically less congested. Our interest is now directed to sterically more demanding ketones based on the reactions we observed previously in Table 2.2 in section 2.2.5 where acyclic α-boryl carbanion **2.2** olefinated aldehydes that had significant steric hindrance in highly (*Z*)-stereoselective fashions. Moreover, we

have observed another intriguing precedent reaction in Scheme 2.28 in section 2.6.4, where *ortho*-nitroacetophenone was olefinated highly (*E*)-stereoselectively by acyclic boryl carbanion **2.2**. Based on these appealing reaction data so far, we envisaged that asymmetric ketones with sufficient steric bulkiness on one side of the carbonyl group would give even better *E*:*Z* stereoselectivities by using cyclic α-boryl carbanion **2.53**. In order to confirm this hypothesis, we started with olefination of the familiar *ortho*-nitroacetophenone by both boryl carbanions **2.2** and **2.53** using the modified one-pot conditions (Table 2.20).

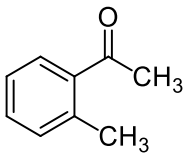
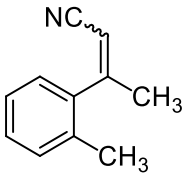
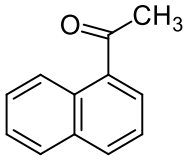
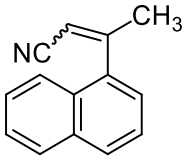
				2.2 (acyclic)		**2.53** (cyclic)	
entry	ketone	products		*E*:*Z*[a]	yield (%)[b]	*E*:*Z*[a]	yield (%)[b]
1			**2.55g**	90:10	43	4:96	89

[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] isolated yield

Table 2.20 Reactivity of **2.2** and **2.53** with *ortho*-nitroacetophenone

Surprisingly, α-boryl carbanions **2.2** and **2.53** exhibited two extreme results in terms of *E*:*Z* stereoselectivity. Acyclic carbanion **2.2** olefinated *ortho*-nitroacetophenone in a highly (*E*)-selective manner, whereas **2.53** almost exclusively gave the (*Z*)-isomer in an excellent yield. Fortunately, those observed high stereoselectivities were in accordance with our hypothesis, even though the unusual stereo-preference from each carbanion was somewhat unexpected.

Being curious of getting a similar result again, we chose another *ortho*-substituted acetophenone, 2'-methylacetophenone, and the sterically similar 1-acetonaphthone, to explore their reactions with α-boryl carbanions **2.2** and **2.53** (Table 2.21).

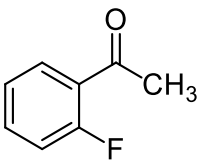
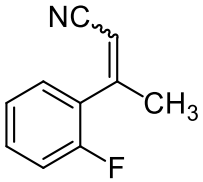
entry	ketone	products		**2.2** (acyclic) *E:Z*[a]	yield (%)[b]	**2.53** (cyclic) *E:Z*[a]	yield (%)[b]
1			**2.55h**	n/a	0	14:86	89
2			**2.55i**	n/a	0	24:76	86

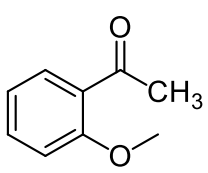
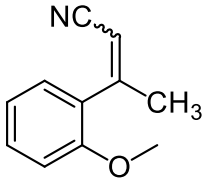
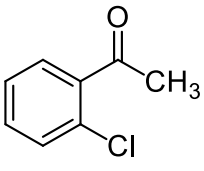
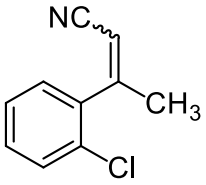
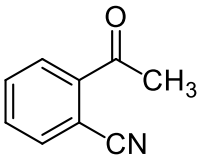
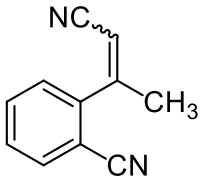
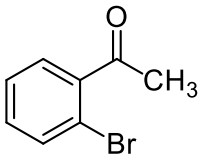
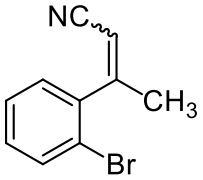
[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] isolated yield

Table 2.21 Reactivity of **2.2** and **2.53** towards *ortho*-substituted aryl methyl ketones

Cyclic boryl carbanion **2.53** converted both ketones into the corresponding β,β-disubstituted acrylonitriles very smoothly in favor of (*Z*)-isomers. In the meantime, acyclic boryl carbanion **2.2** failed to give any olefin product, leaving the unreacted ketone behind in the crude product in both cases. These results would imply that enolization dominated rather than olefination, or **2.2**, which is presumably bulkier than **2.53**, may have been too sterically hindered to react with the ketones.

In order to see more of the reactivity of **2.53** towards *ortho*-substituted aryl ketones, a series of acetophenone derivatives were investigated (Table 2.22).

entry	ketone	products		**2.53** (cyclic) *E:Z*[a]	yield (%)[b]
1			**2.55j**	39:61	87

2			**2.55k**	19:81	78
3			**2.55l**	11:89	93
4			**2.55m**	10:90	47
5			**2.55n**	4:96	94

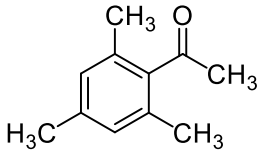
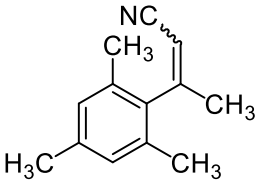
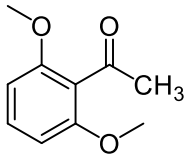
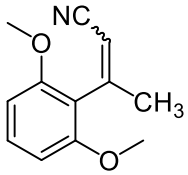
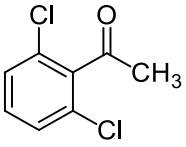
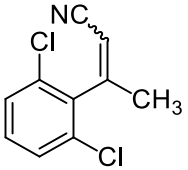
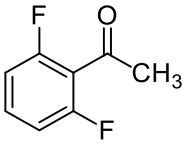
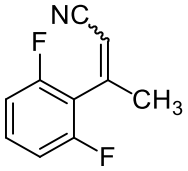
[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] isolated yield

Table 2.22 Reactivity of **2.53** towards *ortho*-substituted acetophenones

Just as we observed for **2.55g-2.55i**, all of ketones in Table 2.2 consistently reacted (*Z*)-stereoselectively, giving moderate to excellent products conversions. Based on these experimental results, a stereo-determining factor seems to heavily lie on the bulkiness of the substituent at the *ortho* position. For instance, *ortho*-fluoroacetophenone (entry 1), having a fluoride as the smallest *ortho*-substituent in the table, gave a relatively mediocre *E/Z* ratio. As the size of the *ortho*-substituent increased, the reactions proceeded more (*Z*)-stereoselectively. When it comes to the reaction of 2'-bromoacetophenone, having the largest *ortho*-substituent, a bromide group, the (*Z*)-isomer was formed almost entirely (entry 5).

2.8.5. Olefination of *ortho*-disubstituted acetophenone-derivatives

In order to verify this stereochemical propensity of the reactions, we employed even more sterically challenging *ortho*-disubstituted acetophenones for the reactions with α-boryl carbanions **2.2** and **2.53** (Table 2.23).

				2.2 (acyclic)		**2.53** (cyclic)	
entry	ketone	products		*E:Z*[a]	yield (%)[b]	*E:Z*[a]	yield (%)[b]
1			**2.55o**	n/a	0	n/a	0
2			**2.55p**	n/a	n/a	0:100	72
3			**2.55q**	n/a	n/a	n/a	0
4			**2.55r**	n/a	n/a	10:90	81

[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] isolated yield

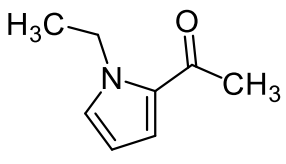
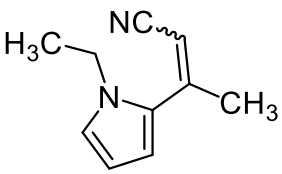
Table 2.23 Reactivity of **2.2** and **2.53** with *ortho*-disubstituted aryl methyl ketones

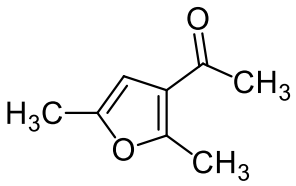
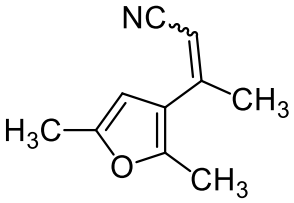
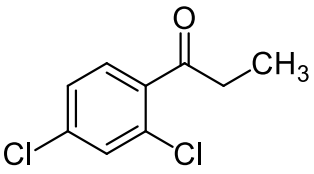
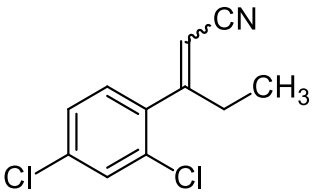
Neither α-boryl carbanion **2.2** nor **2.53** was able to olefinate mesityl methyl ketone (entry 1), presumably due to the excessive steric hindrance from two *ortho*-methyl groups that are blocking **2.2** and **2.53** from accessing the carbonyl carbon. In fact, almost

pure mesityl methyl ketone was confirmed in the crude product for both cases. Presubably for the same reason, *ortho*-dichloroacetophenone (entry 3) failed to produce any desired acrylonitrile product. When a sterically somewhat milder *ortho*-dihaloacetophenone, *ortho*-difluoroacetophenone, was utilized, cyclic boryl carbanion **2.53** very smoothly converted it into the desired olefin products in a highly (*Z*)-stereoselective manner (entry 4). For entry 2, *ortho*-dimethoxyacetophenone finally achieved a 100% stereoselective olefination in favor of the (*Z*)-isomer in a good yield. Based on these observations, we would conclusively say that the stereoselectivity of the reactions of **2.53** correlates well with the steric degree of the ketones: more specifically, the more steric difference there is between the two sides of the carbonyl group, the more (*Z*)-stereoselective the olefin formation is.

2.8.6. Olefination of other types of ketones

To further test the generality of this one-pot olefination protocol of ketones, hetero-aromatic ketones as well as an aryl-ethyl ketone were accordingly examined (Table 2.24).

entry	ketone	products	**2.53** (cyclic) *E:Z*[a]	yield (%)[b]
1			**2.55s** 22:78	50

2			**2.55t**	27:73	74
3			**2.55u**	61:39	81

[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] isolated yield

Table 2.24 Reactivity of **2.53** towards other asymmetric ketones

Both pyrrole-based- and furan-based methyl ketones were olefinated in a relatively similar manner (entries 1-2): they both exhibited good (*Z*)-stereoselectivities while the product conversion for entry 1 was a little less efficient. Despite an *ortho*-substitution (*i.e.*, a chloride) on the aryl ring for entry 3, the reaction turned out to be (*E*)-selective as opposed to what we have observed in Tables 2.20-2.23. This would be presumably due to the ethyl group, which is on the other side of the aryl moiety relative to the carbonyl, decreasing the steric difference between the two sides of the carbonyl group as we postulated previously in section 2.8.5.

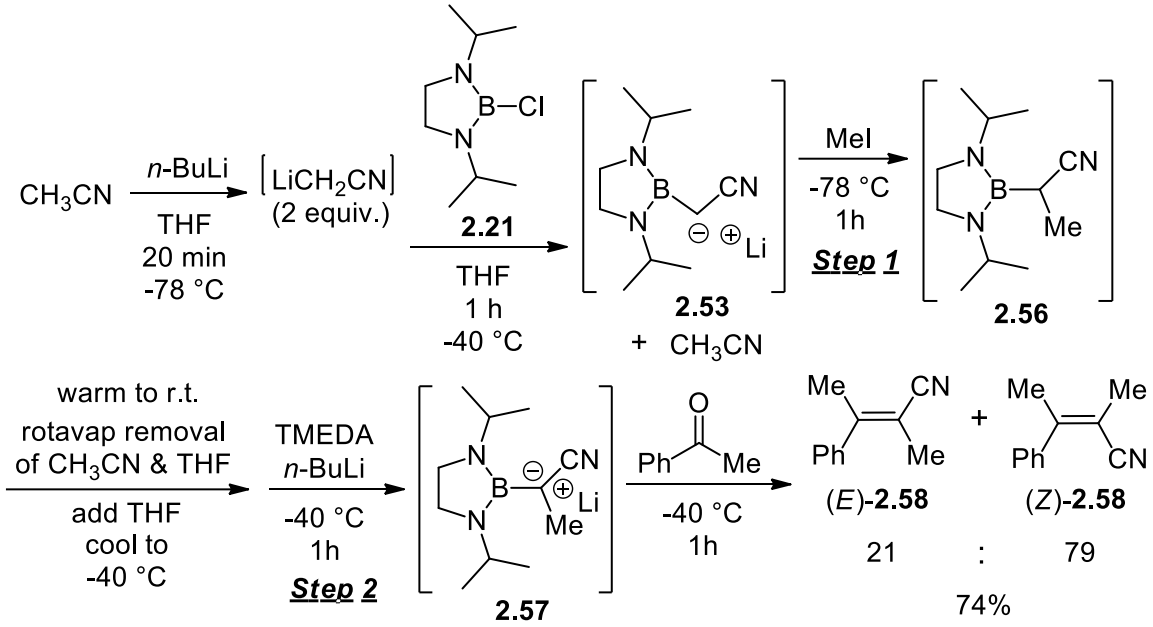
2.8.7. Stereoselective synthesis of tetrasubstituted olefins

Previously in section 2.4.2, we reported a method for synthesizing α,β-disubstituted acrylonitriles (*i.e.*, trisubstituted olefins) *via* the α-alkyl substituted boryl carbanion **2.24**. This substituted carbanion **2.24** was generated *in situ* by deprotonation of α-alkyl diaminoboryl acetonitrile **2.23**, which was formed by alkylation of α-boryl carbanion **2.2** with an alkyl halide (Schemes 2.20 and 2.21 in section 2.4.2). An efficient

application of this one-pot protocol was demonstrated in Table 2.7 in section 2.6.4 where we prepared a variety of 3-substituted-2-aminoquinoline derivatives.

In order to further expand the research scope of our α-boryl carbanion chemistry, we attempted a synthesis of tetrasubstituted alkenes (*i.e.*, α,β,β-trisubstituted acrylonitriles) by combining this chemistry and the modified one-pot reaction protocol that we developed using cyclic α-boryl carbanion **2.53** as shown in section 2.8.2.

After screening a multiple different reaction conditions changing the reaction time and the reaction temperature, we found the best reaction conditions that maximized the formation of the desired tetrasubsituted alkenes **2.58** (Scheme 2.46), where -78 °C was applied in Step 1 while Step 2 was run at -40 °C. The reaction proceeded in a (*Z*)-stereoselective manner (*E*:*Z* = 21:79), and both (*E*)- and (*Z*)-isomers were isolated independently by conventional silica gel column chromatography to give a combined yield of 74%.



Scheme 2.46 Successful attempt of a one-pot tetrasubstituted alkene synthesis

2.8.8. Summary

In summary, diazaborolidine-based α-boryl carbanion **2.53** smoothly converted a variety of ketones into the corresponding acrylonitriles in highly stereoselective fashions. Olefination of acetophenone and its steric equivalents proceeded in moderately (*E*)-selective manners, while most acetophenone derivatives with *ortho* substituent(s) exhibited excellent (*Z*)-stereoselectivities. For those *ortho*-substituted acetophenones, (*Z*)-selectivity seemed to be almost directly proportional to the steric bulkiness of the ketones. Hetero-aromatic ketones were also olefinated in favor of (*Z*)-isomers. In the meantime, α-boryl carbanion **2.53** was demonstrated to be well compatible with various functionalities, such as ether, nitro group, cyano group, and halogens. In addition, this

one-pot olefination protocol was efficiently applied for a synthesis of tetrasubstituted alkenes.

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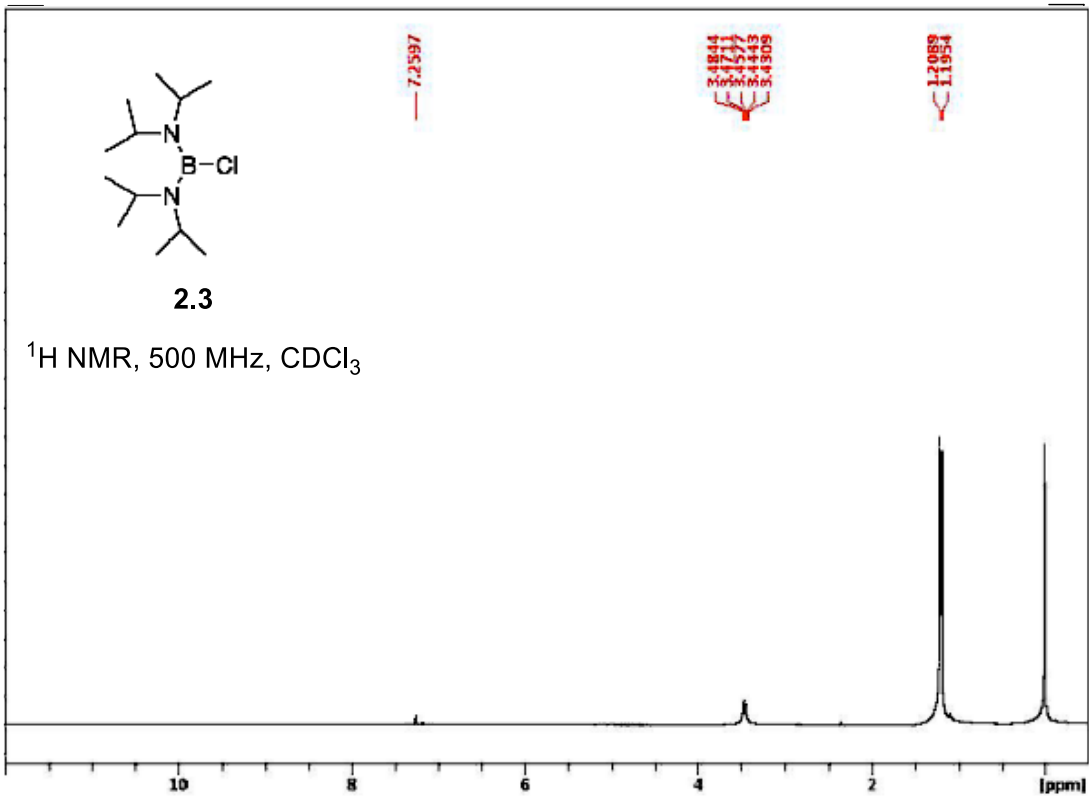
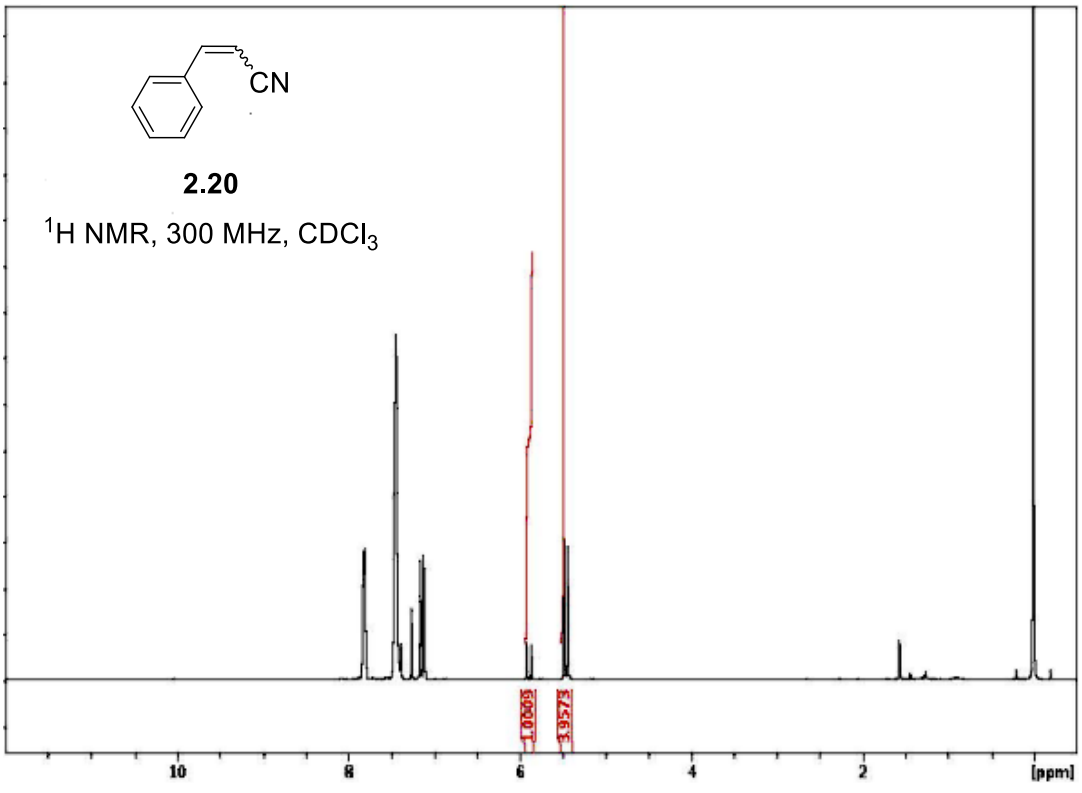
APPENDIX: SPECTRAL DATA



2.3

^{1}H NMR, 500 MHz, $CDCl_3$



2.20

^{1}H NMR, 300 MHz, $CDCl_3$

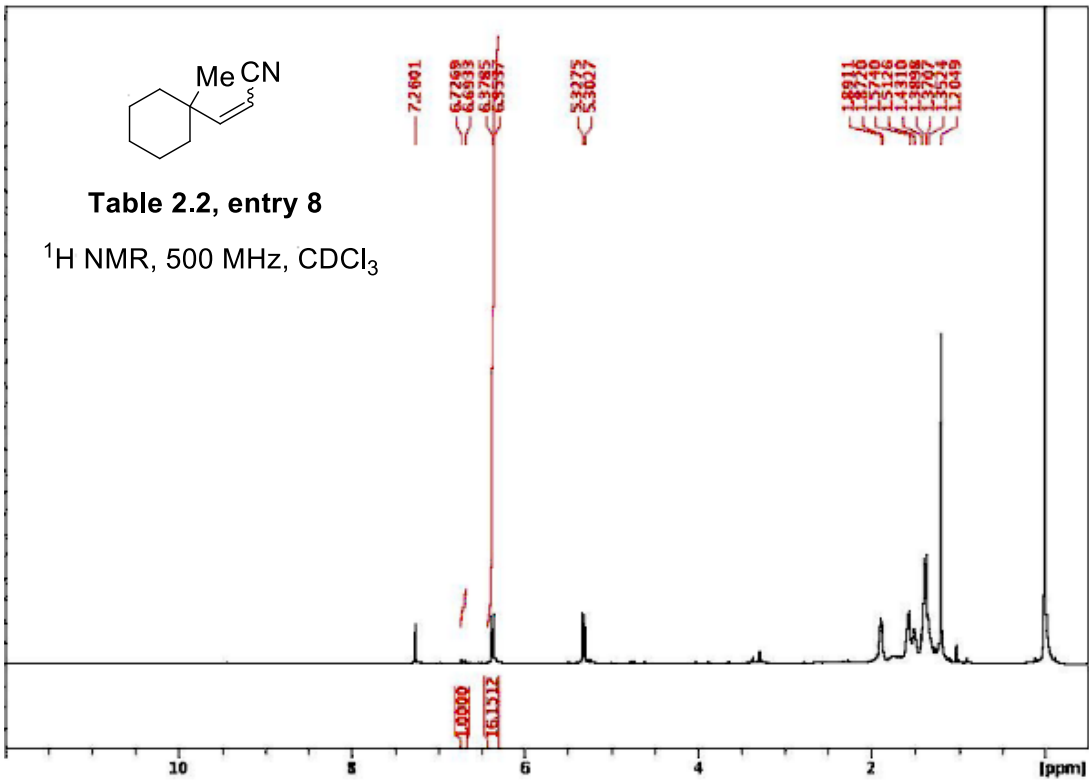


Table 2.2, entry 8

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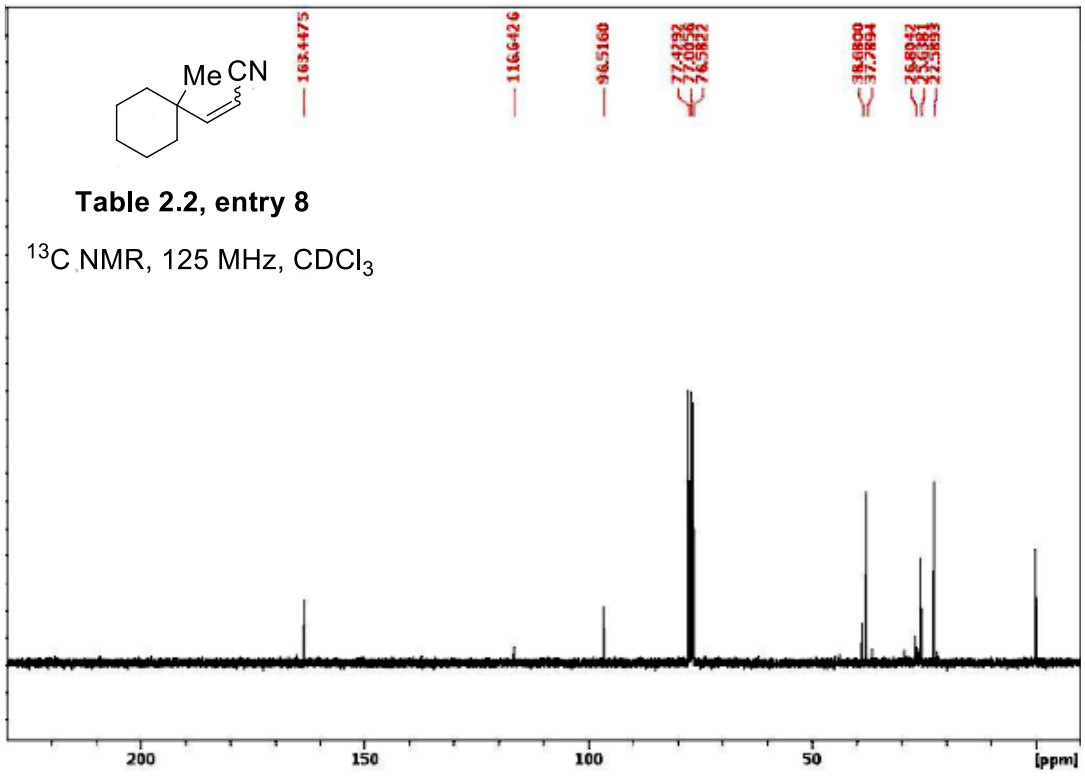

Table 2.2, entry 8

^{13}C NMR, 125 MHz, $CDCl_3$

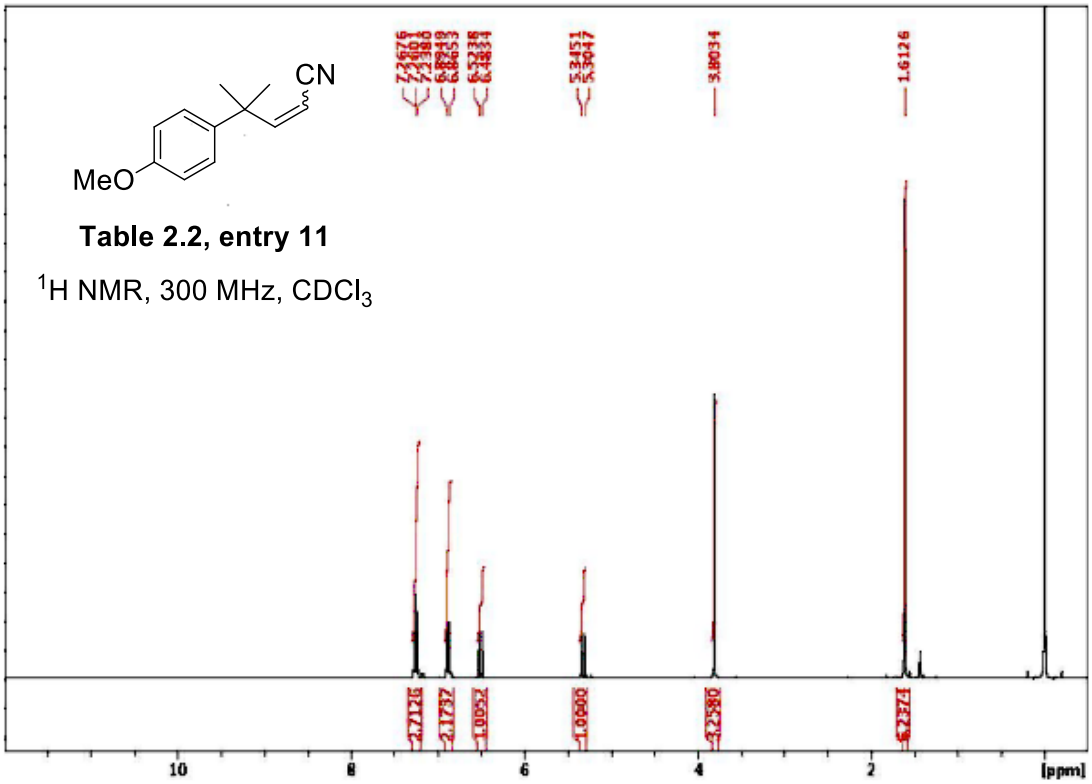

Table 2.2, entry 11

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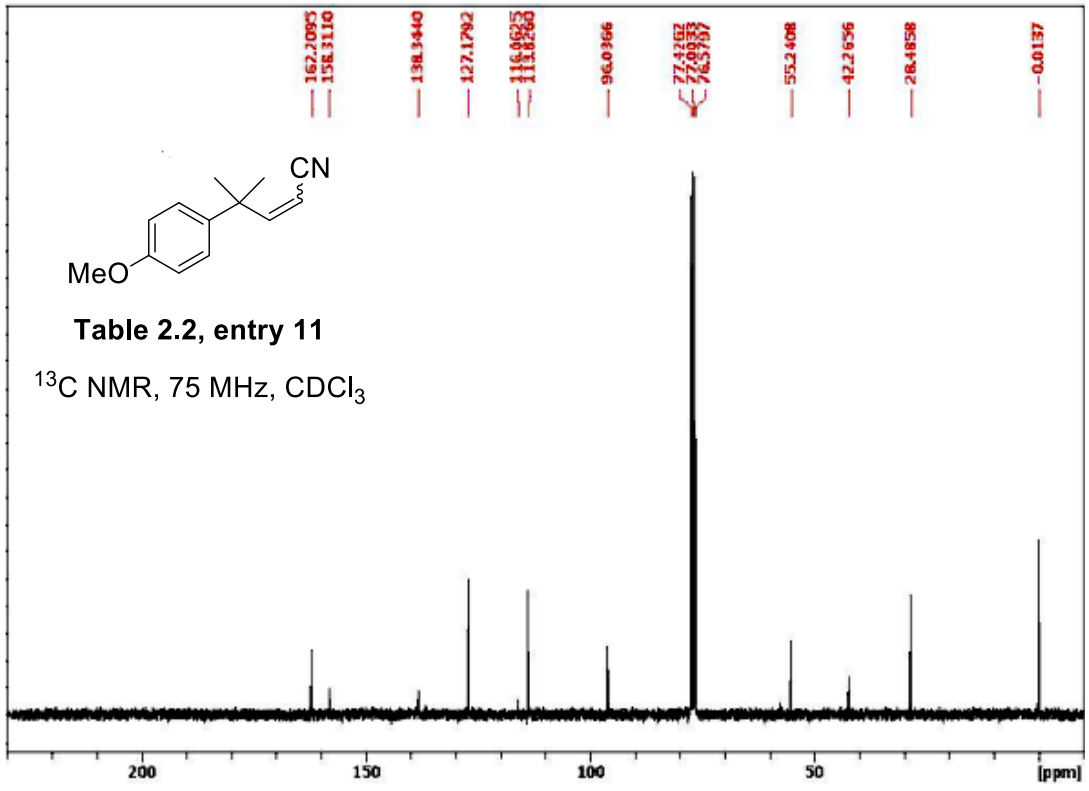
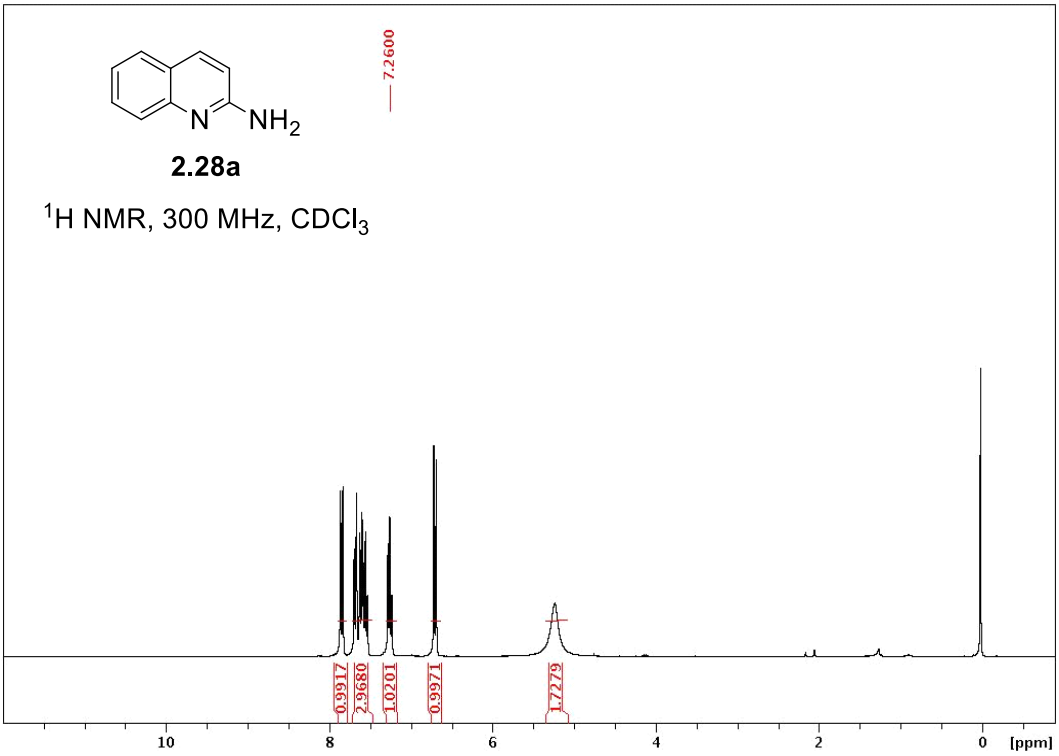


Table 2.2, entry 11

^{13}C NMR, 75 MHz, $CDCl_3$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2.28a
1H NMR, 300 MHz, CDCl3
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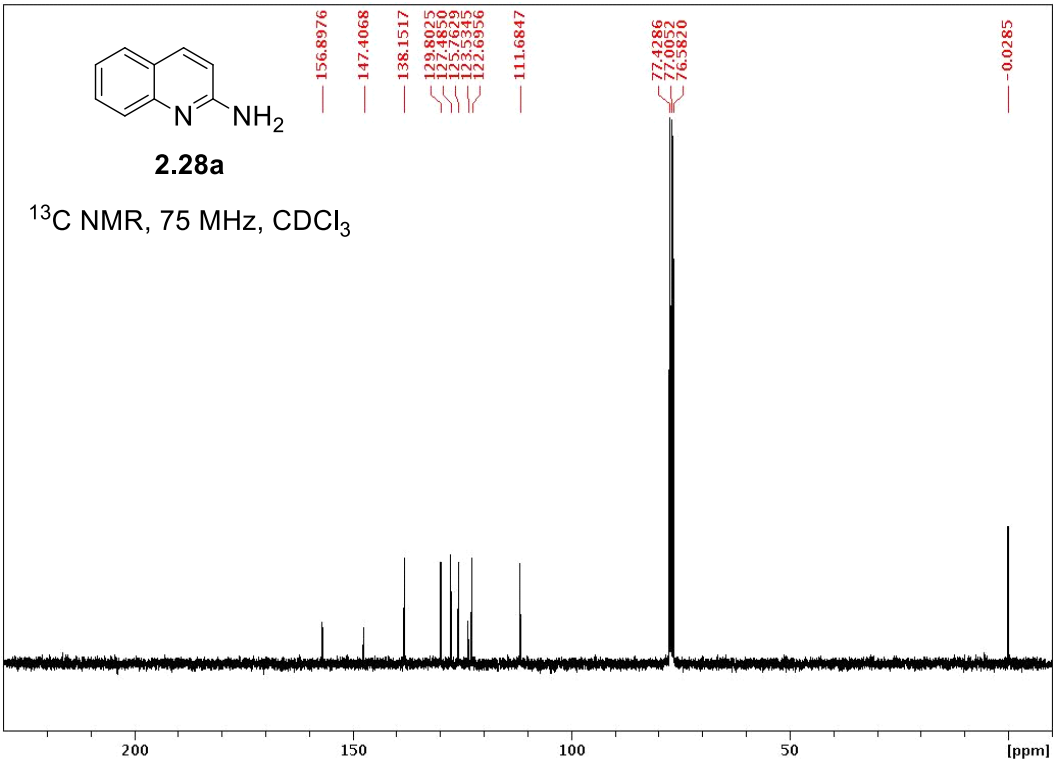
2.9680
1.0201
0.9971
1.7279
10
8
6
4
2
0
[ppm]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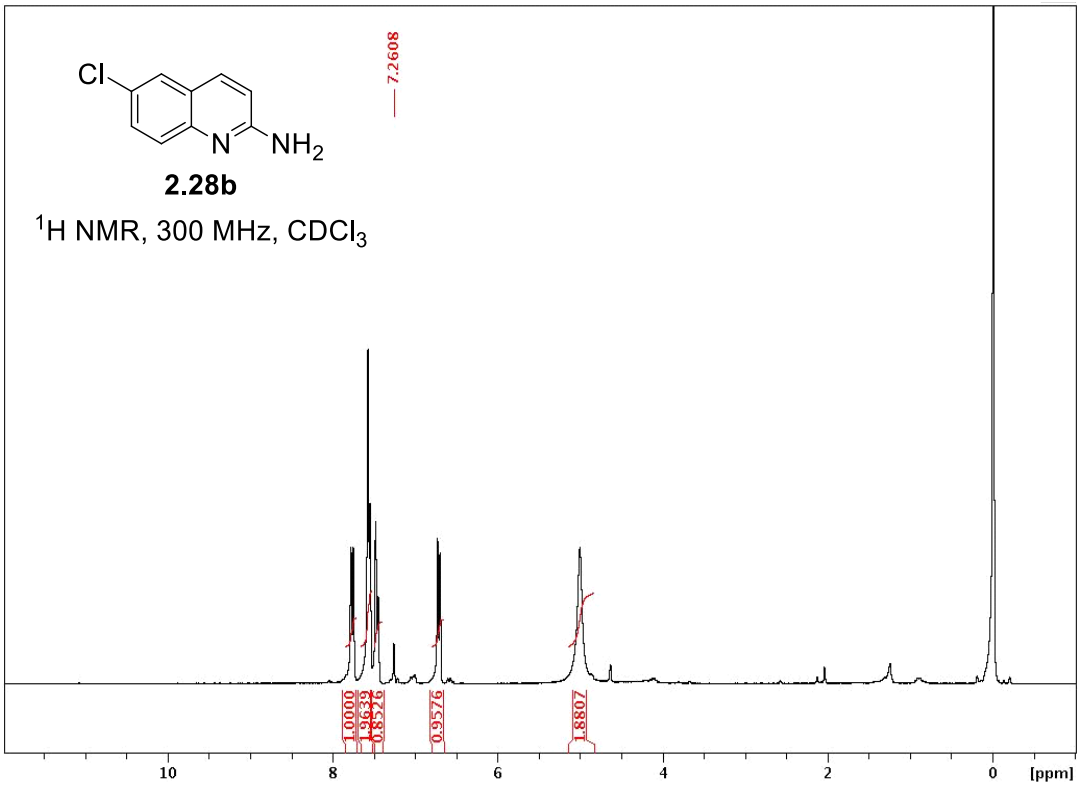
147.4068
138.1517
129.8025
127.4850
125.7629
123.5345
122.6956
111.6847
77.4286
77.0052
76.5820
-0.0285
2.28a
13C NMR, 75 MHz, CDCl3
200
150
100
50
[ppm]


Cl
N
NH2
7.2608
2.28b
1H NMR, 300 MHz, CDCl3
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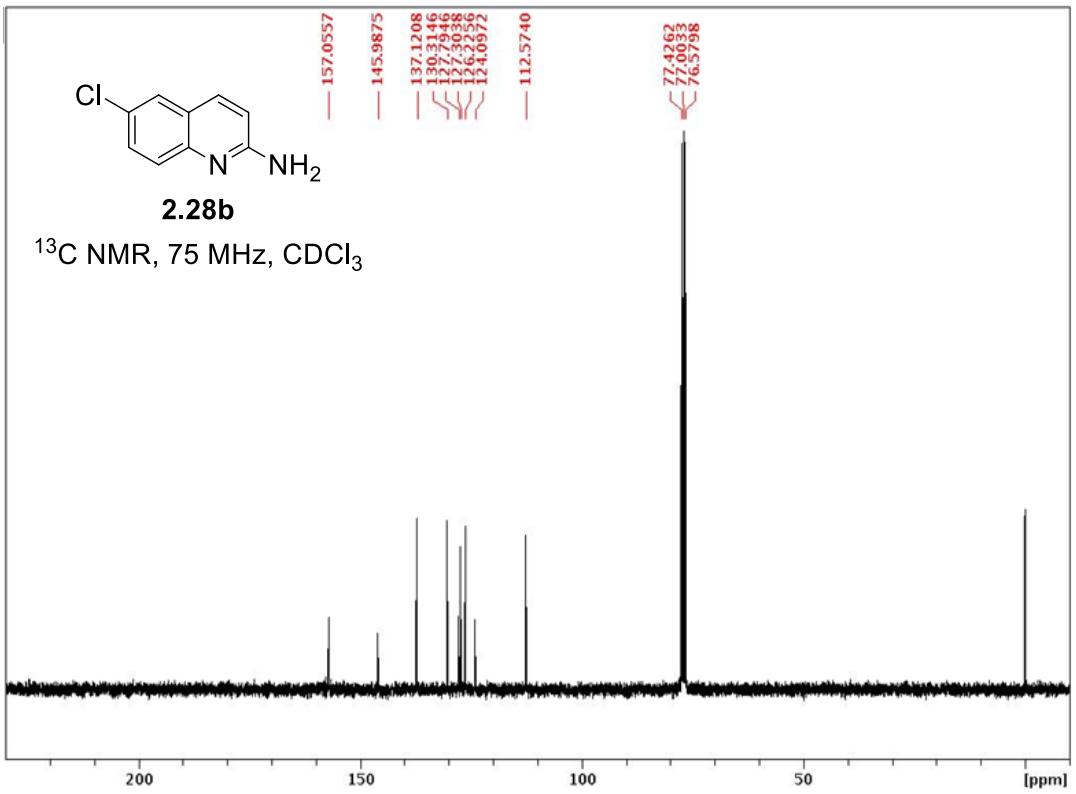
0.8826
0.9576
1.8807
10
8
6
4
2
0
[ppm]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NH2
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124.0972
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77.0033
76.5798
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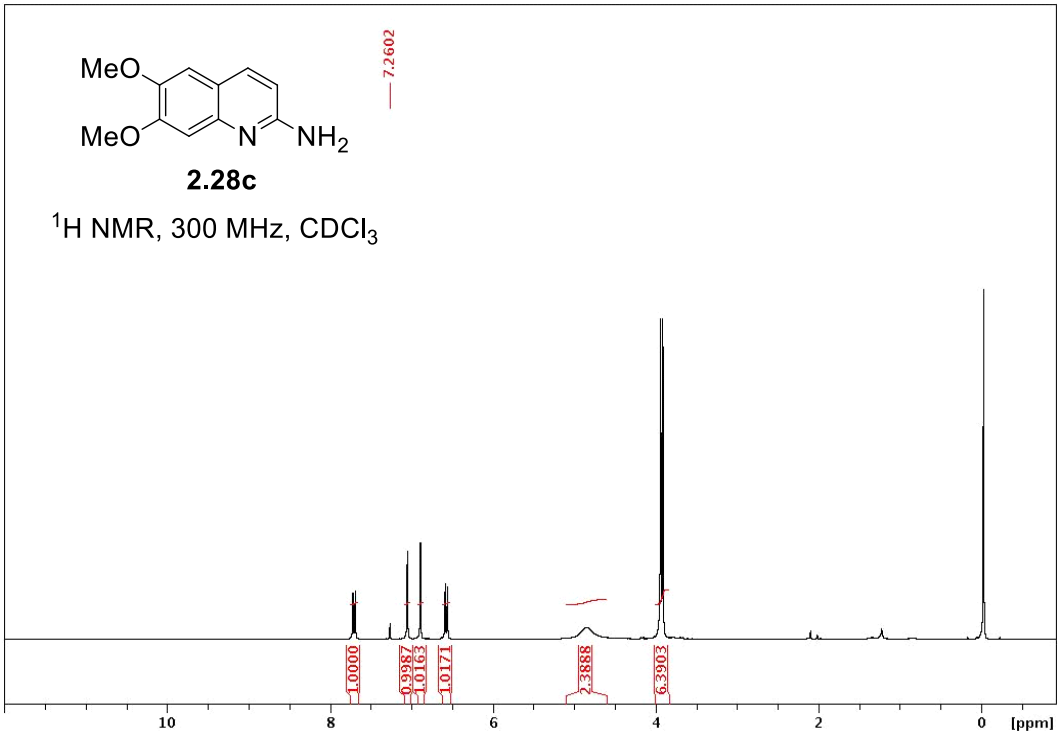
13C NMR, 75 MHz, CDCl3
200
150
100
50
[ppm]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MeO
N
NH2
7.2602
2.28c
1H NMR, 300 MHz, CDCl3
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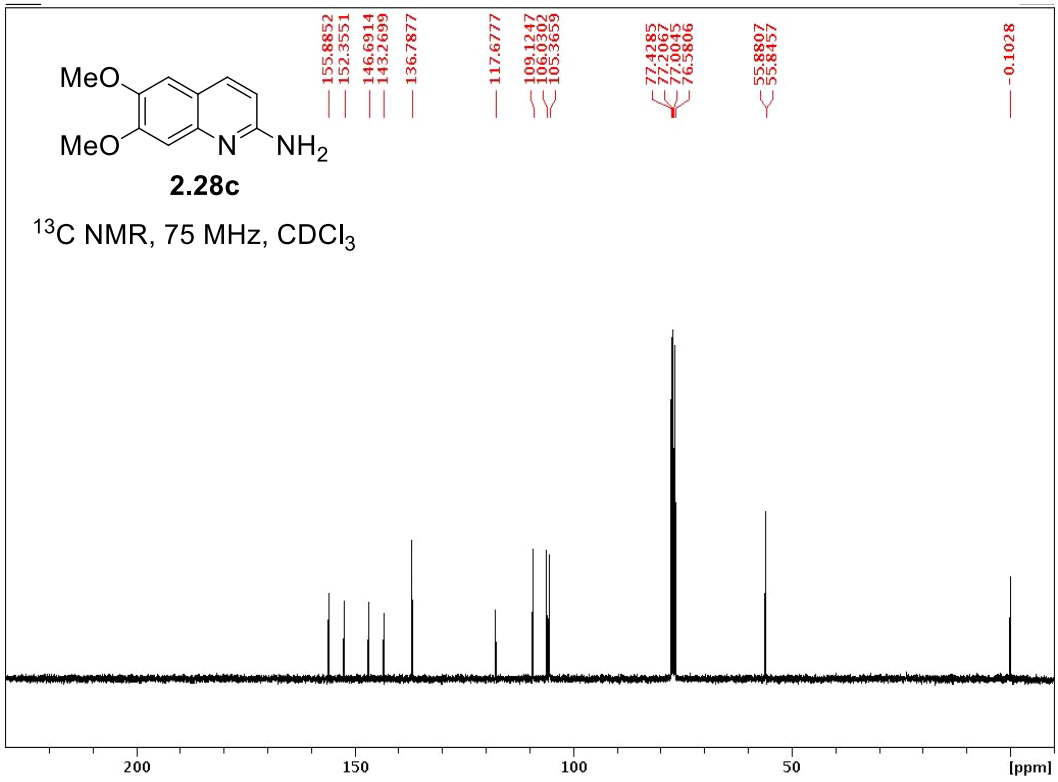
1.0163
1.0171
2.3888
6.3903
10
8
6
4
2
0
[ppm]


MeO
MeO
N
NH2
2.28c
13C NMR, 75 MHz, CDCl3
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146.6914
143.2699
136.7877
117.6777
109.1247
106.0302
105.3659
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77.0045
76.5806
55.8807
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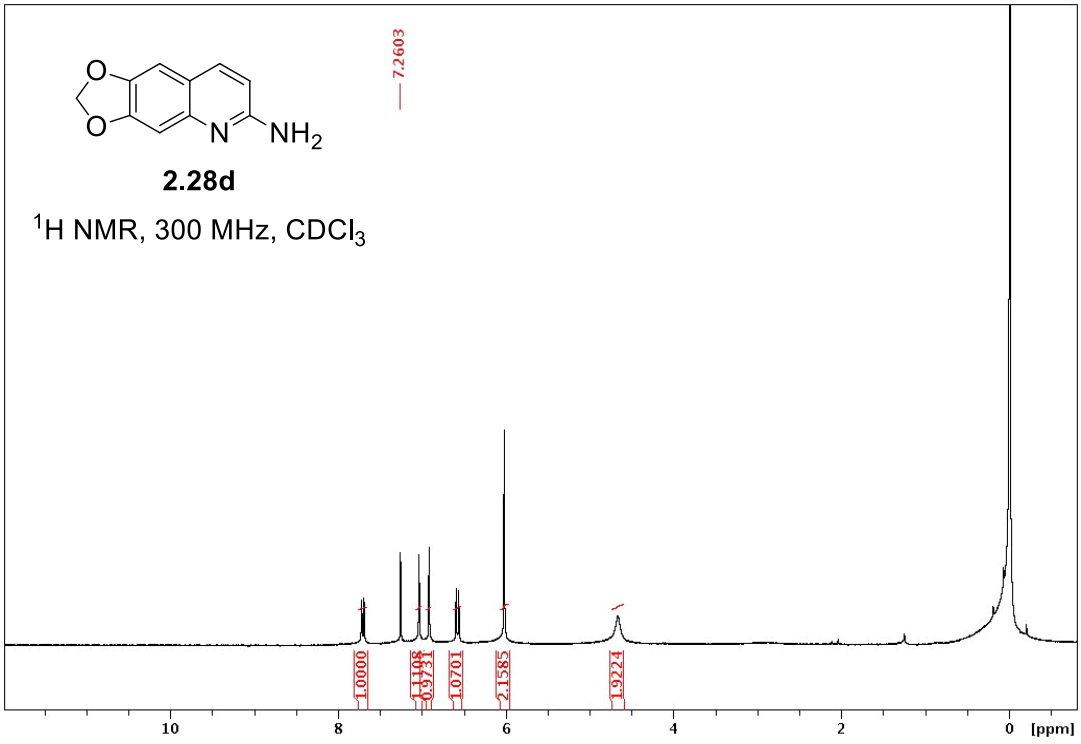
-0.1028
200
150
100
50
[ppm]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2.28d
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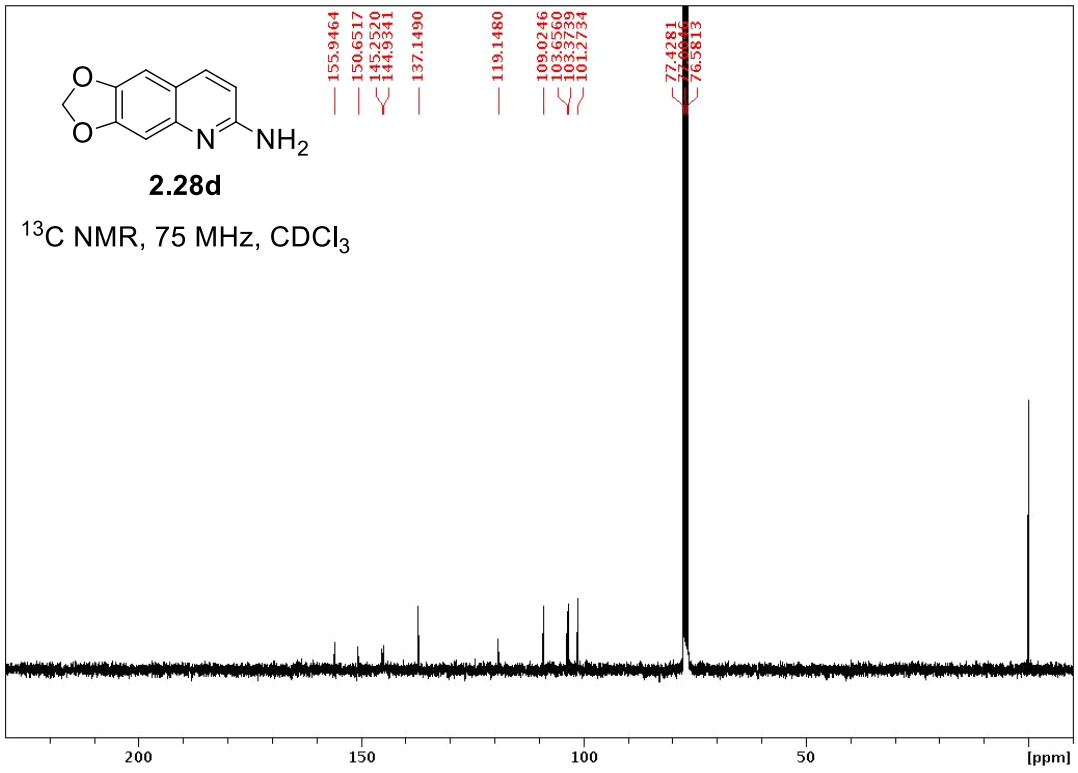
2.1585
1.9224
10
8
6
4
2
0
[ppm]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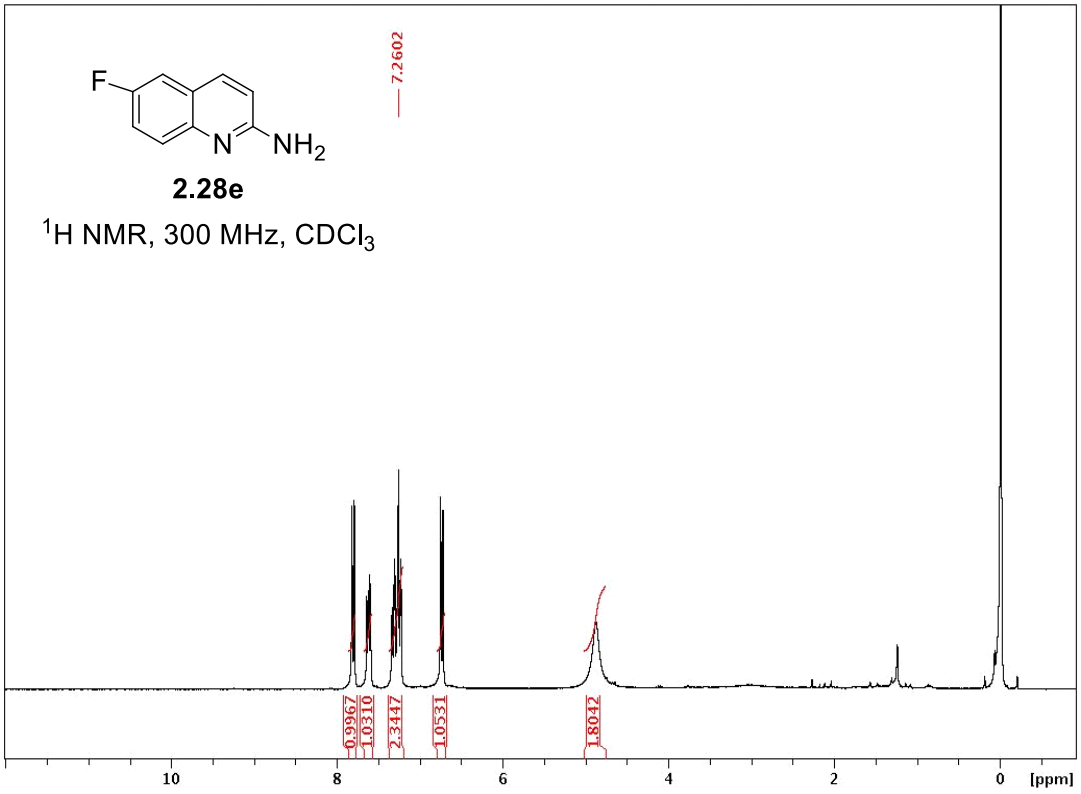
150.6517
145.2520
144.9341
137.1490
119.1480
109.0246
103.6560
103.3739
101.2734
77.4281
76.5813
2.28d
13C NMR, 75 MHz, CDCl3
200
150
100
50
[ppm]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N
NH2
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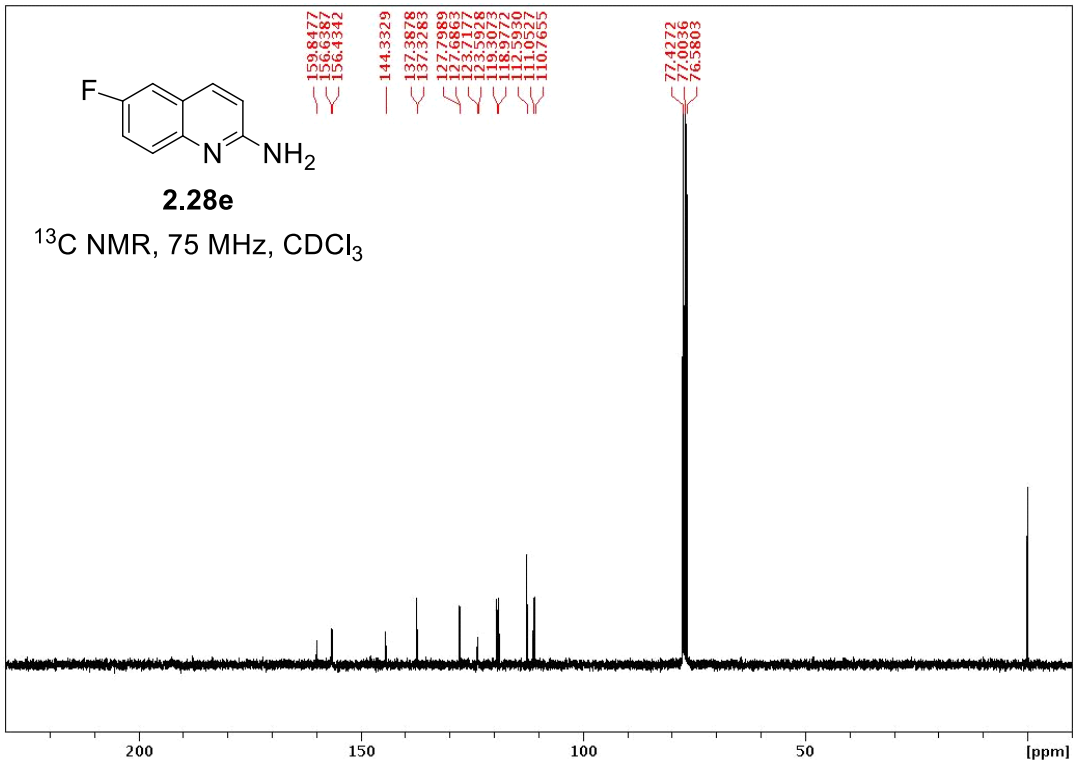
1.8042
10
8
6
4
2
0
[ppm]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N
NH2
2.28e
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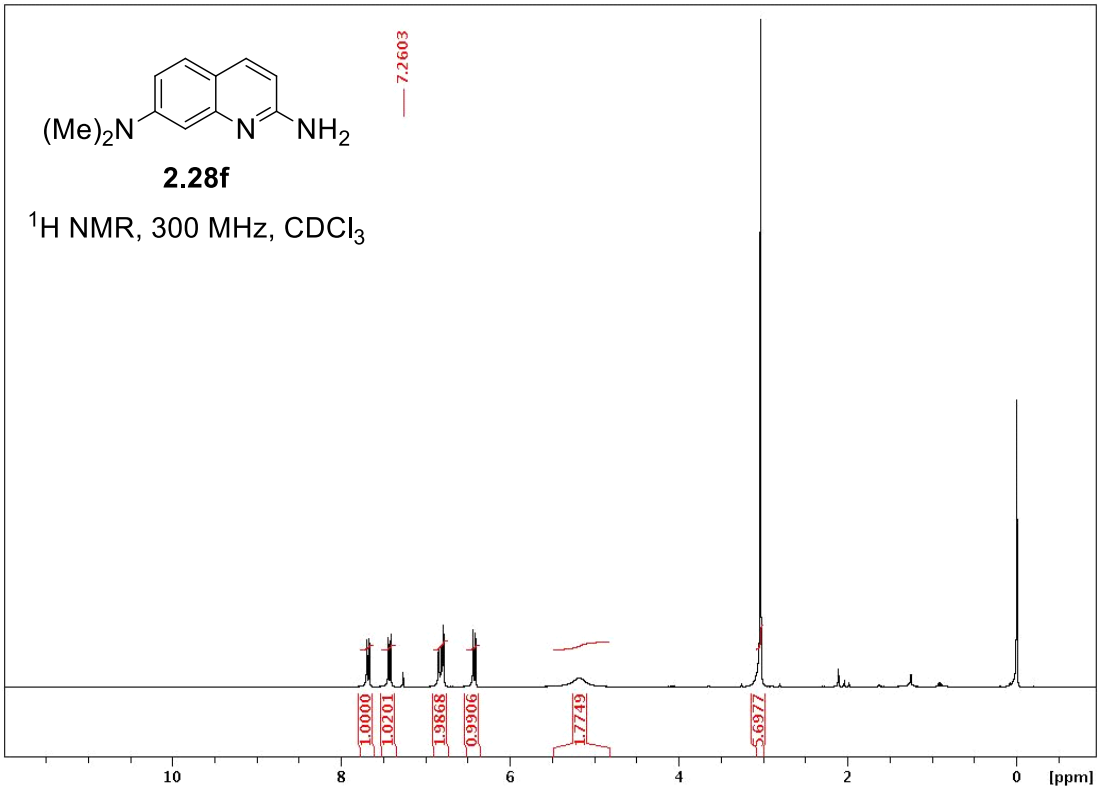
156.4342
144.3329
137.3878
137.3283
127.7989
127.6863
123.7177
123.5928
118.3773
118.3573
112.5530
111.0527
110.7655
77.4272
77.0036
76.5803
200
150
100
50
[ppm]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NH2
2.28f
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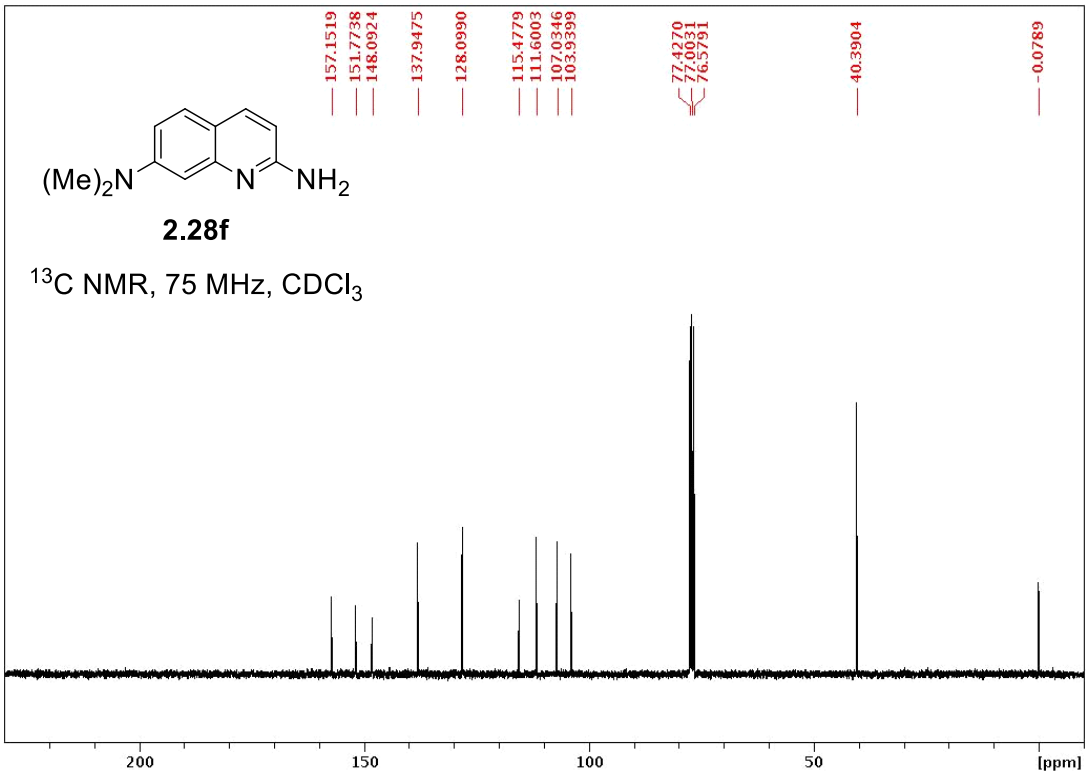
1.9868
0.9906
1.7749
5.6977
10
8
6
4
2
0
[ppm]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NH2
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151.7738
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137.9475
128.0990
115.4779
111.6003
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77.0031
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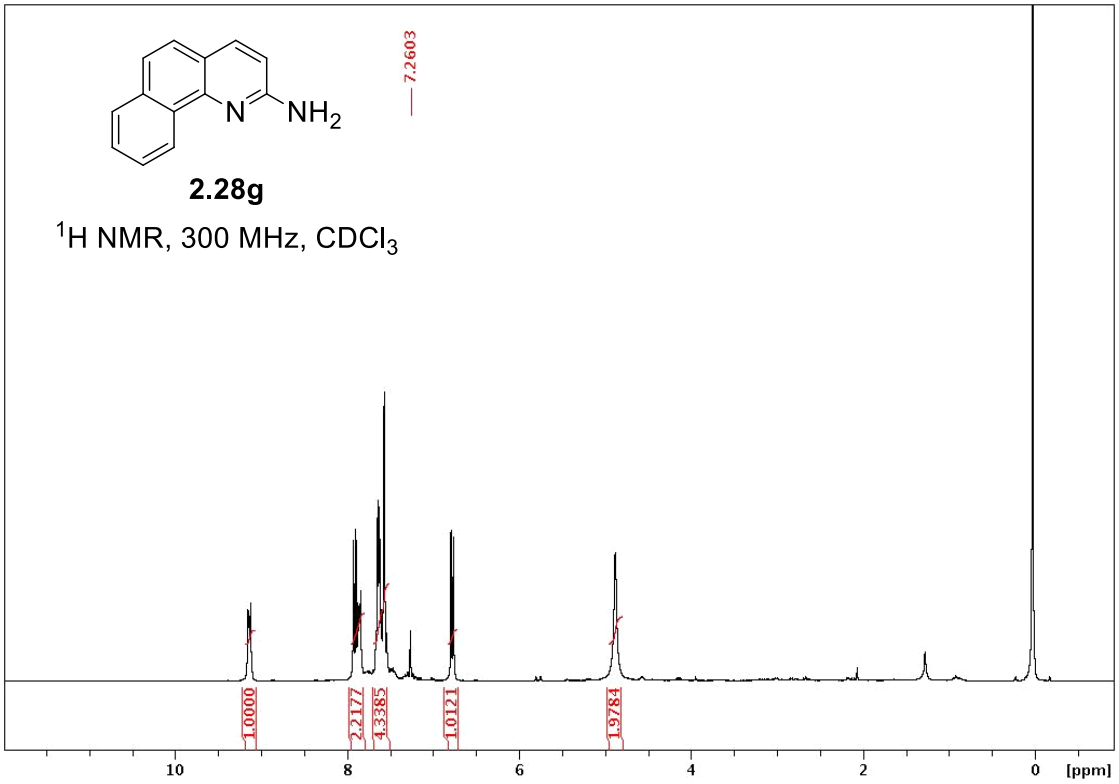
-0.0789
200
150
100
50
[ppm]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NH2
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10
8
6
4
2
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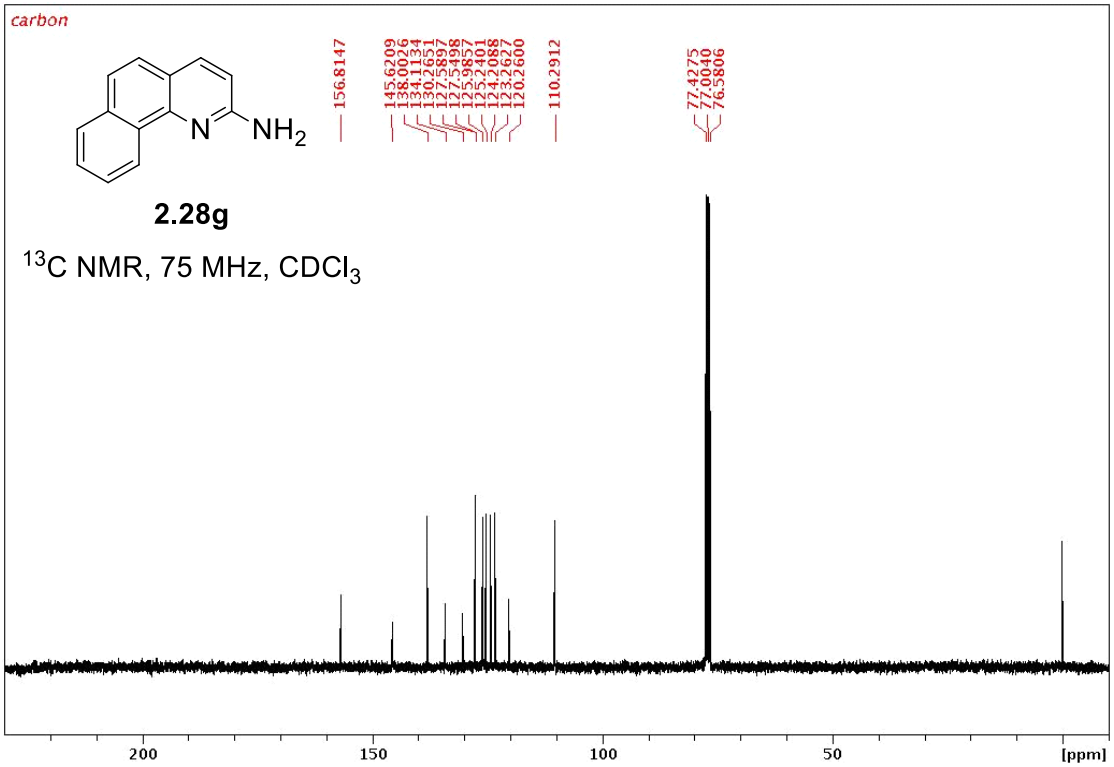
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130.2651
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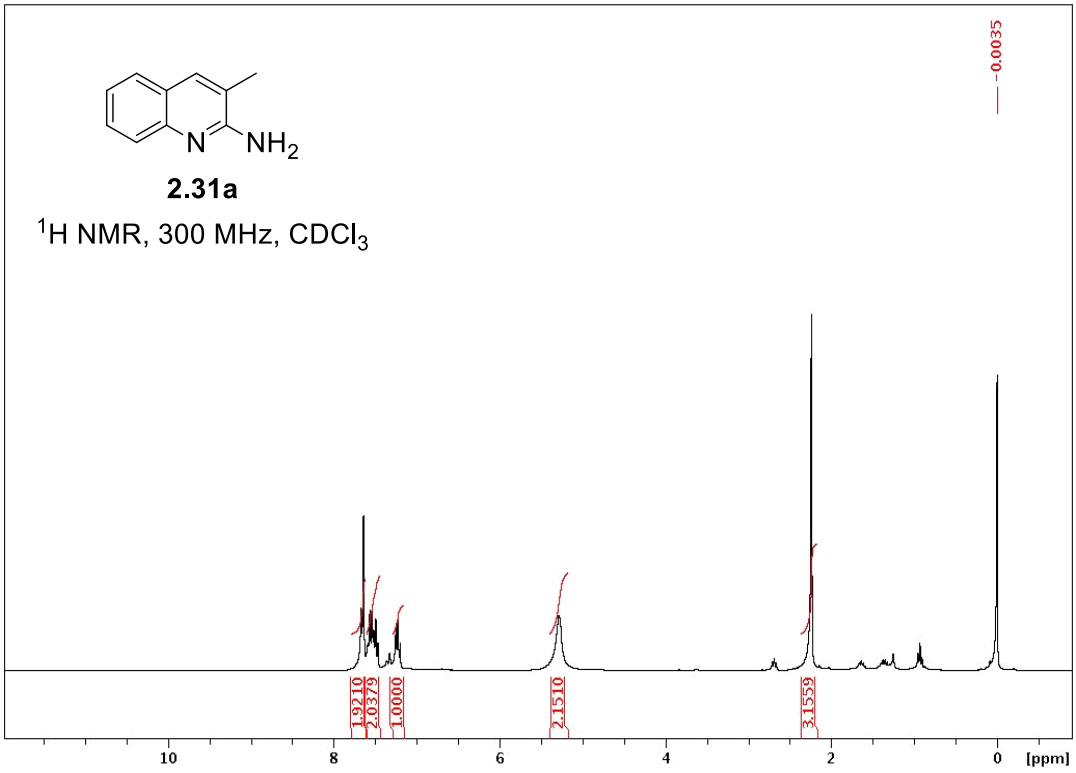
125.9857
125.2401
124.2088
123.2627
120.2600
110.2912
77.4275
77.0040
76.5806
N
NH2
2.28g
13C NMR, 75 MHz, CDCl3
200
150
100
50
[ppm]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10
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4
2
0
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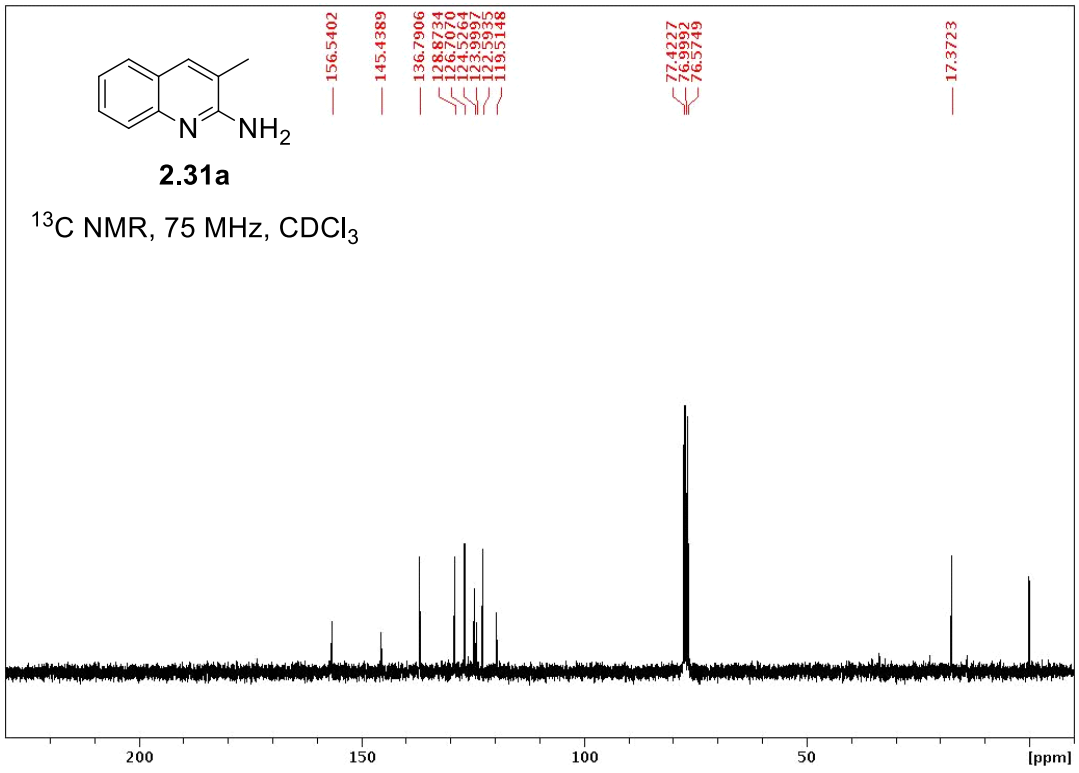
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128.8734
126.7070
124.7674
123.9997
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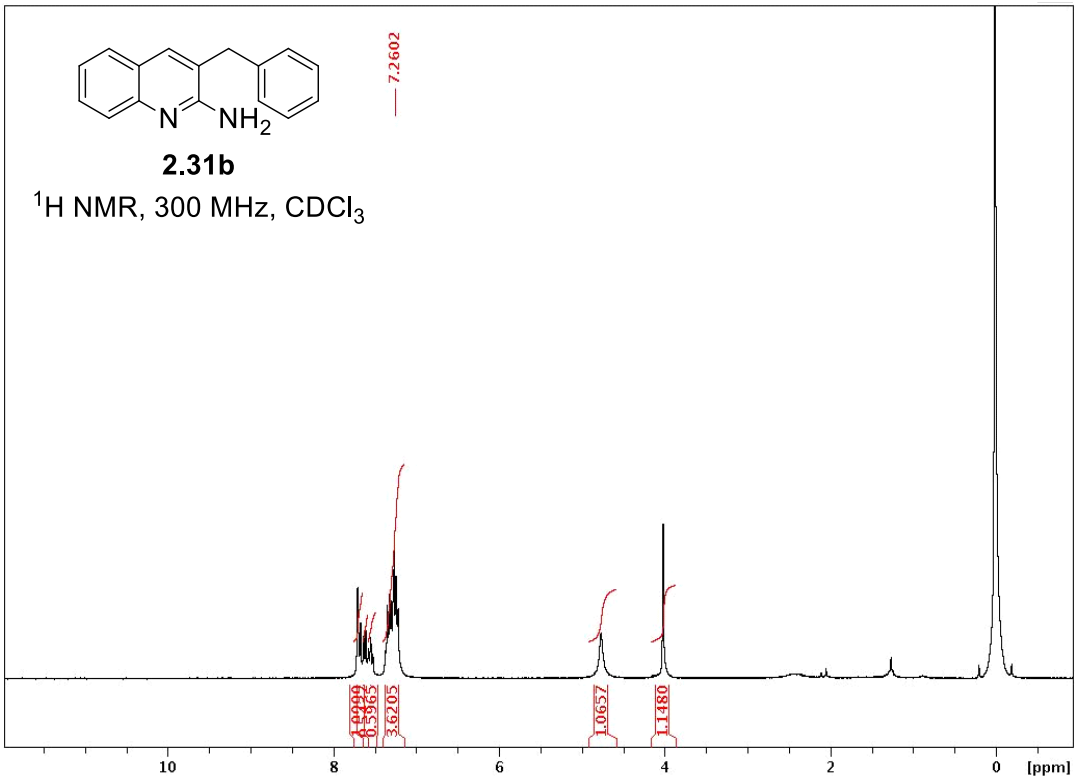
119.5148
77.4227
76.9992
76.5749
17.3723
200
150
100
50
[ppm]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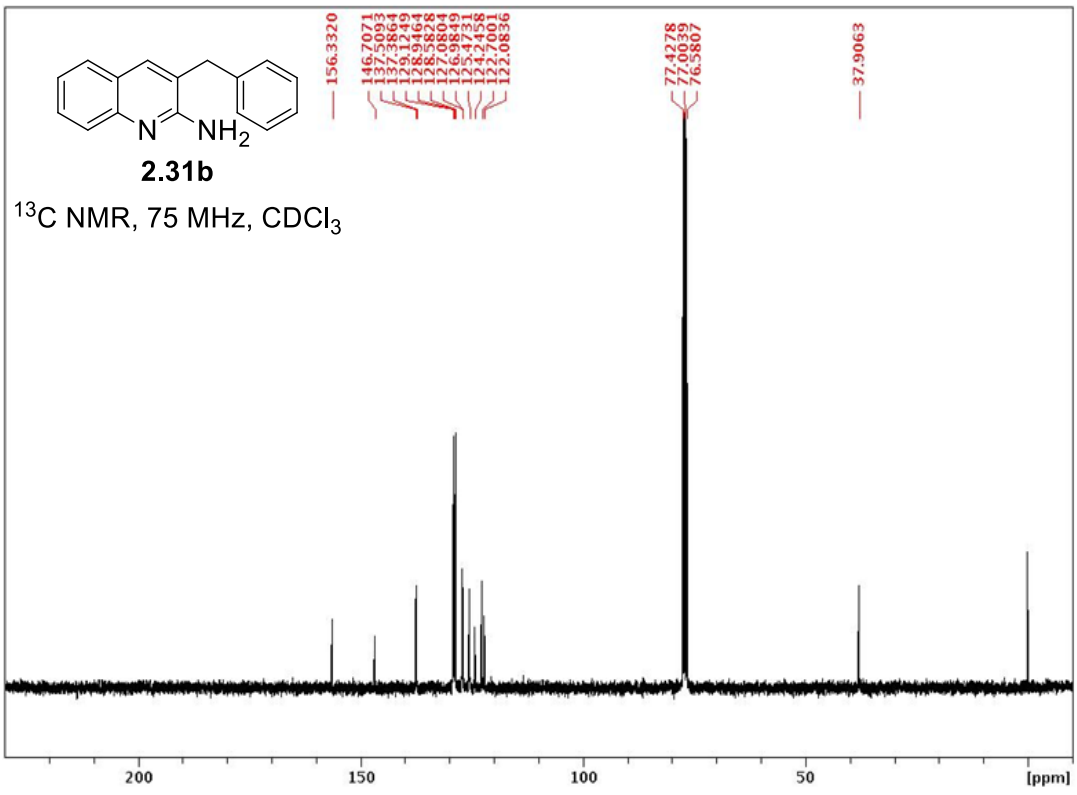
10
8
6
4
2
0
[ppm]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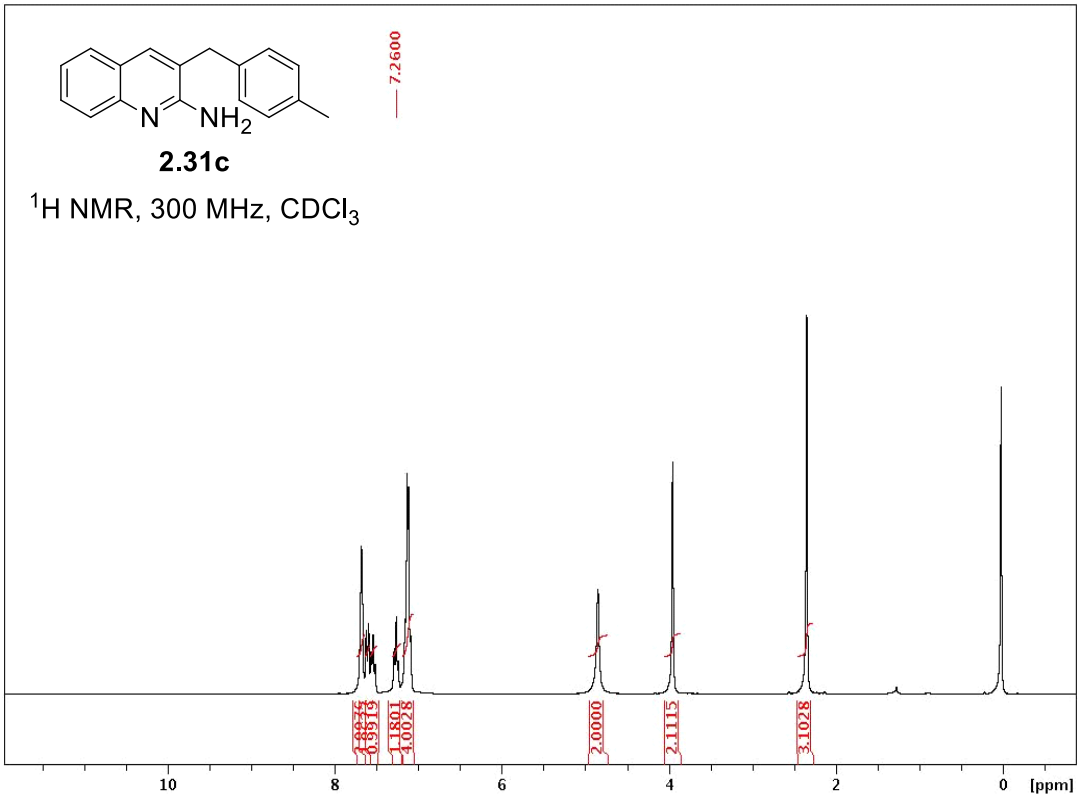
126.9849
125.4731
124.2458
122.7091
122.0836
77.4278
77.0039
76.5807
37.9063
2.31b
13C NMR, 75 MHz, CDCl3
200
150
100
50
[ppm]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N
NH2
2.31c
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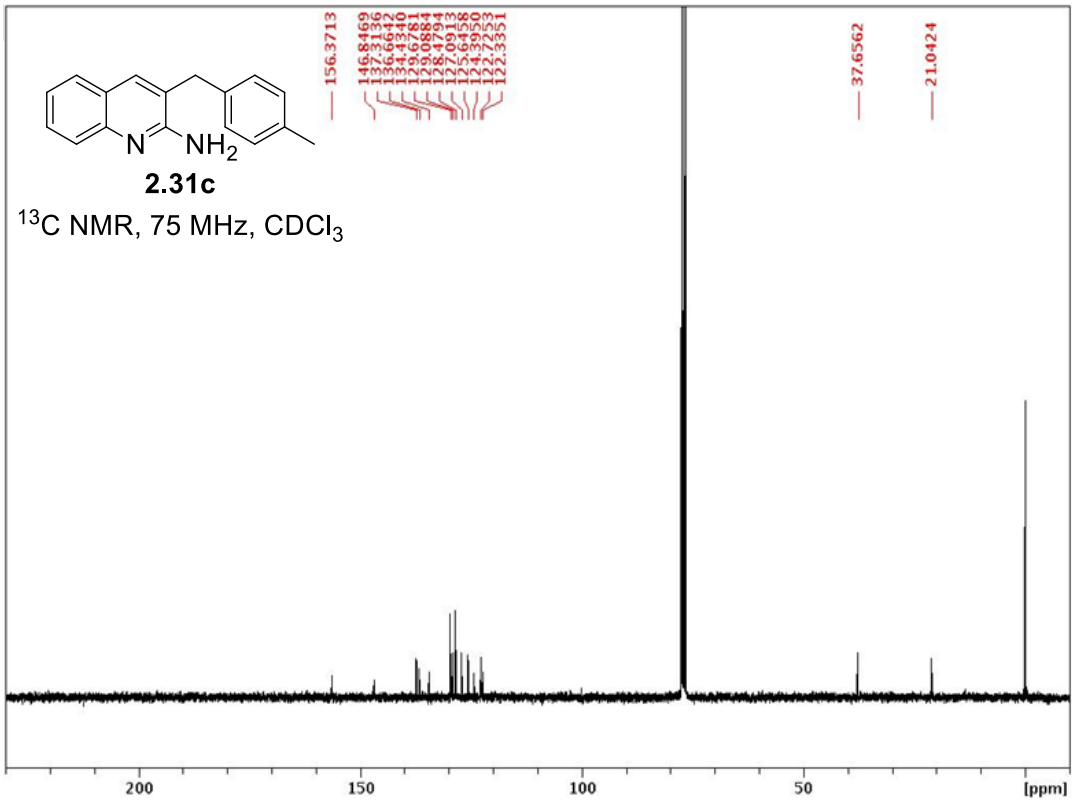
4.0028
2.0000
2.1115
3.1028
10
8
6
4
2
0
[ppm]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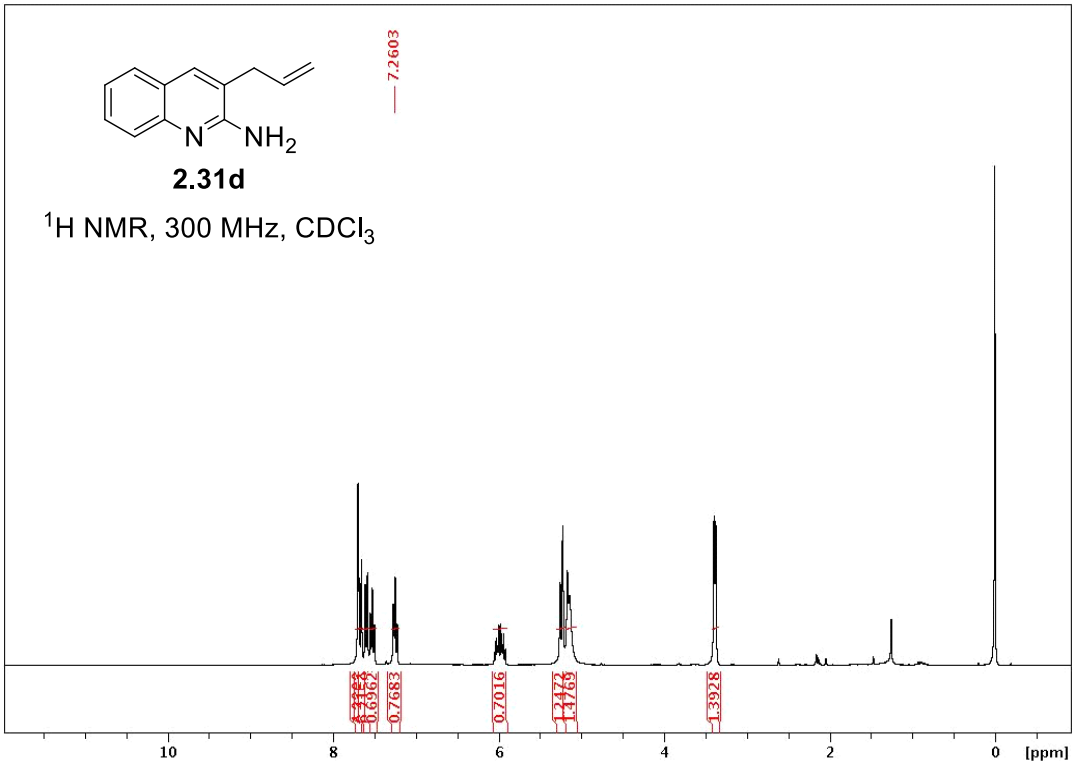
128.4794
127.0913
125.9458
124.9950
122.7253
122.3351
37.6562
21.0424
N
NH2
2.31c
13C NMR, 75 MHz, CDCl3
200
150
100
50
[ppm]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N
NH2
2.31d
1H NMR, 300 MHz, CDCl3
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0.7016
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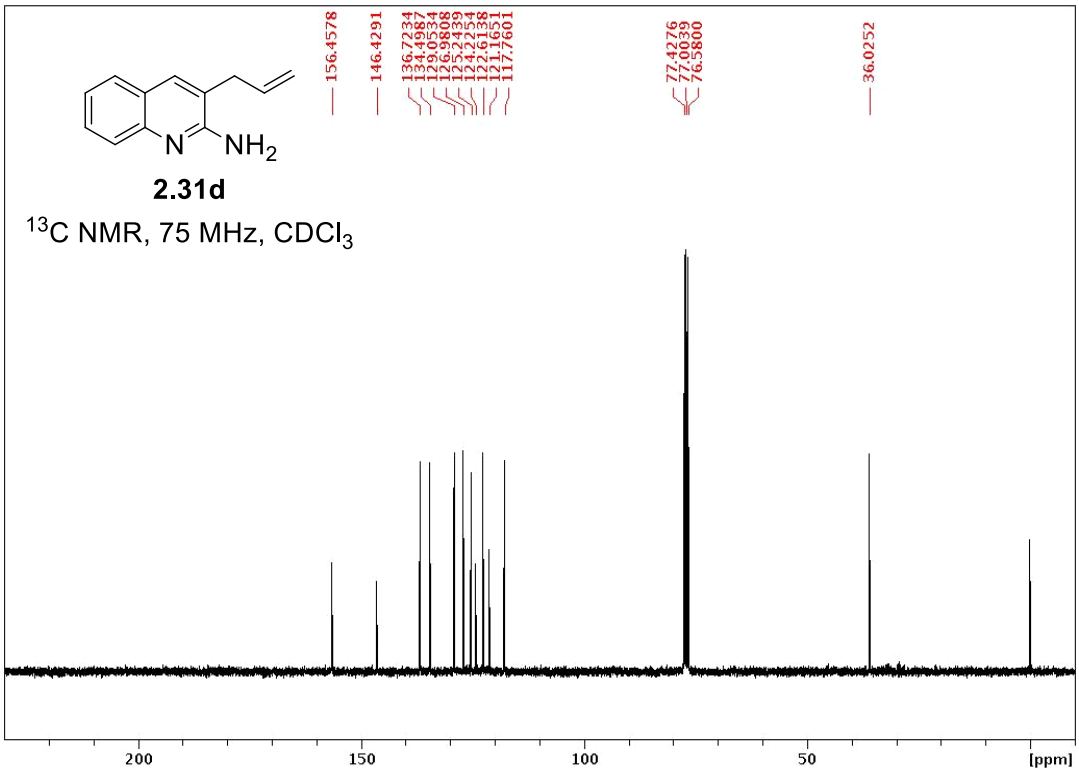
1.4769
1.3928
10
8
6
4
2
0
[ppm]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122.6138
121.1651
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77.4276
77.0639
76.5800
36.0252
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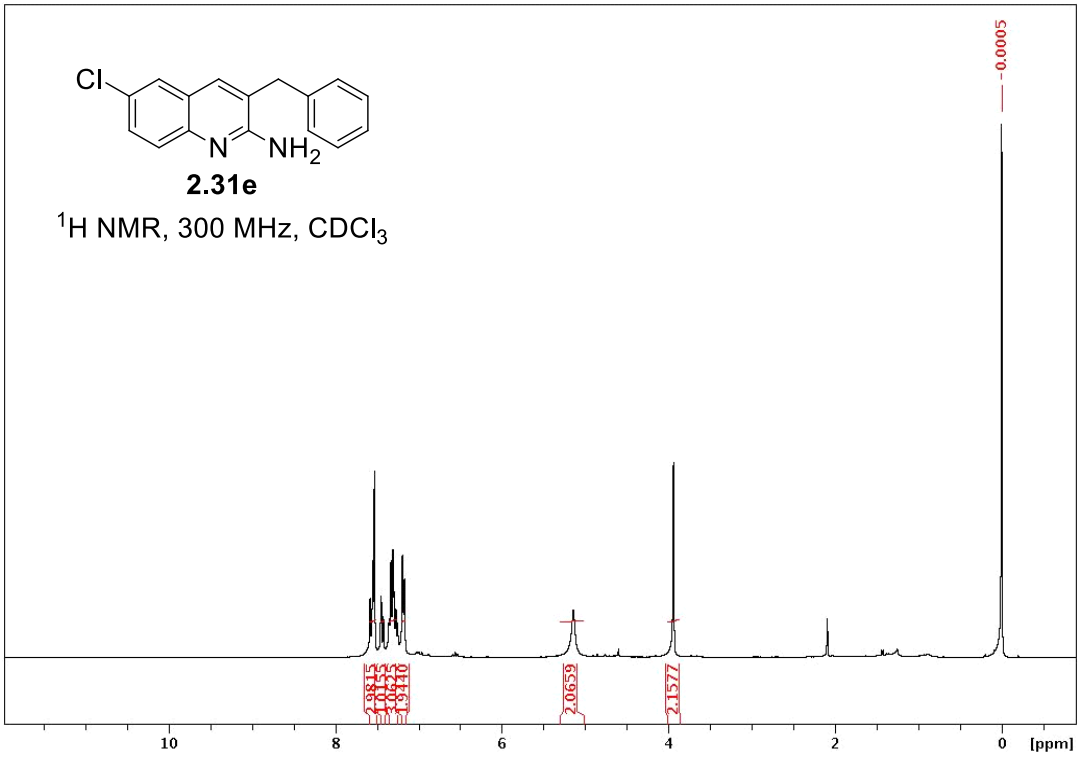
2.31d
13C NMR, 75 MHz, CDCl3
200
150
100
50
[ppm]


Cl
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NH2
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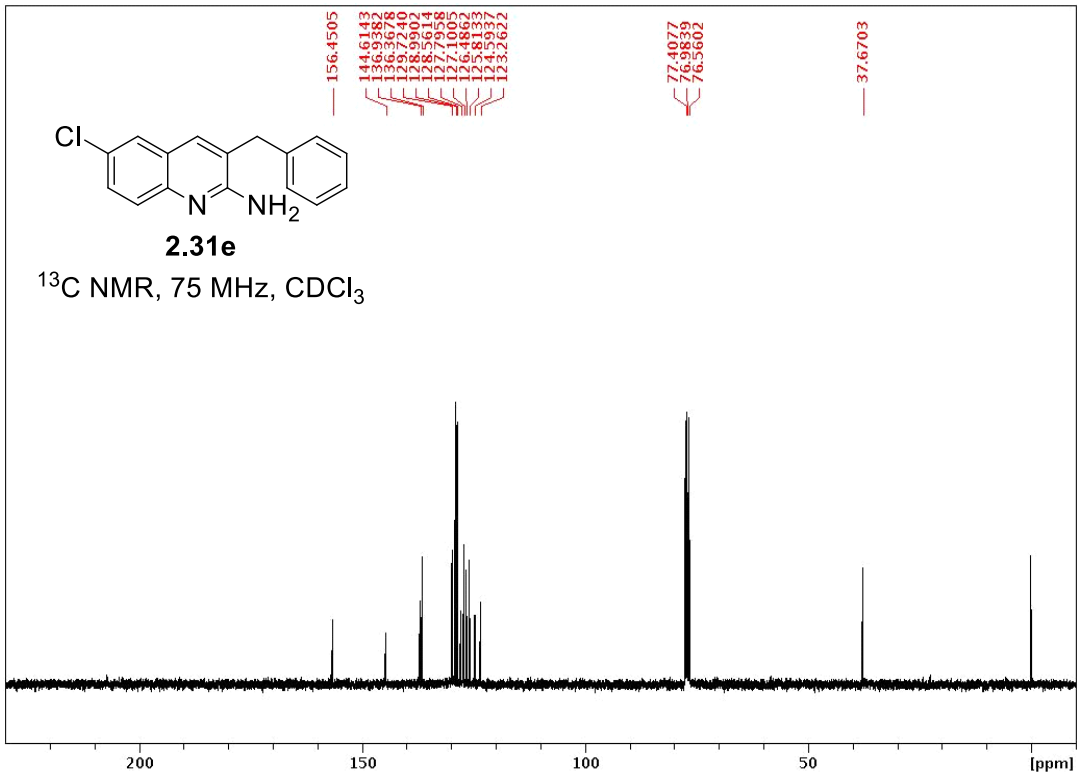
2.1577
10
8
6
4
2
0
[ppm]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136.9382
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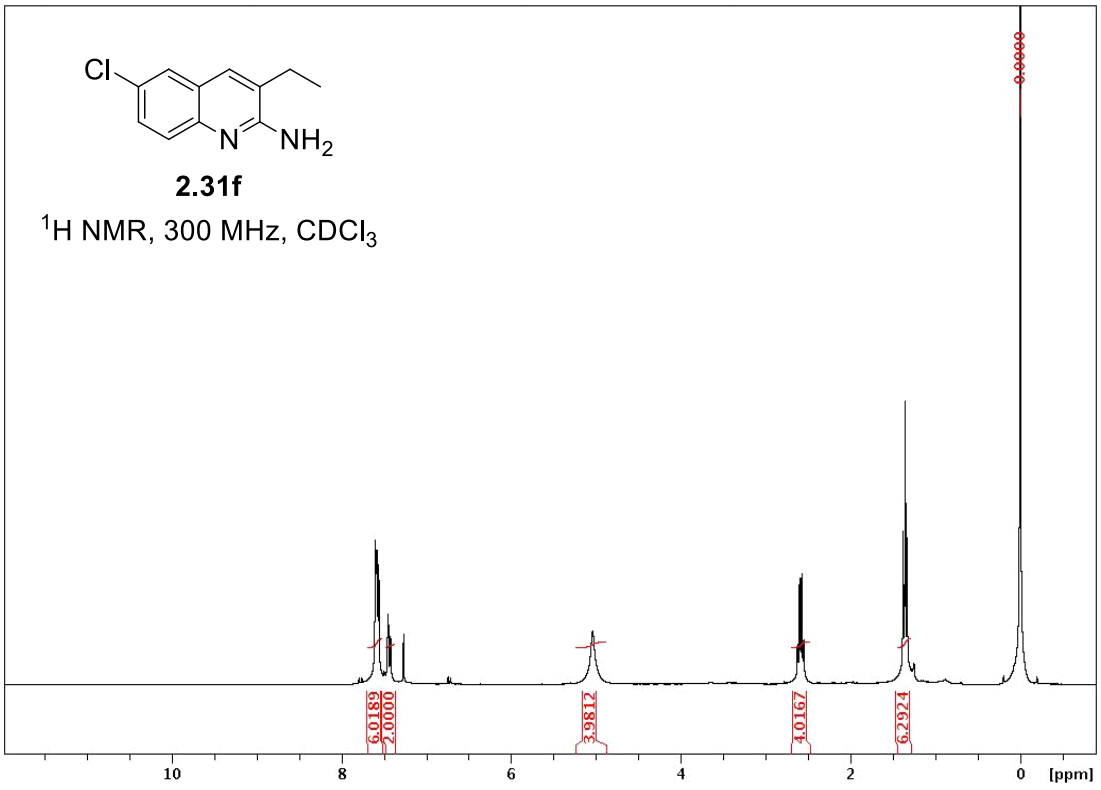
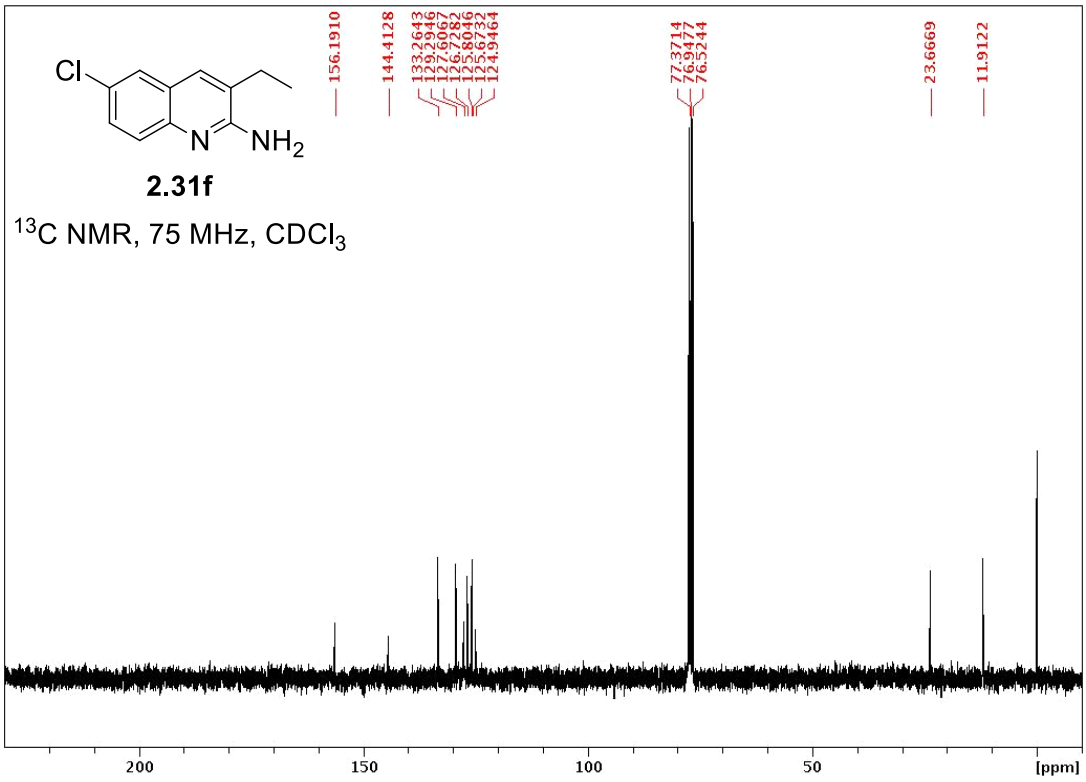
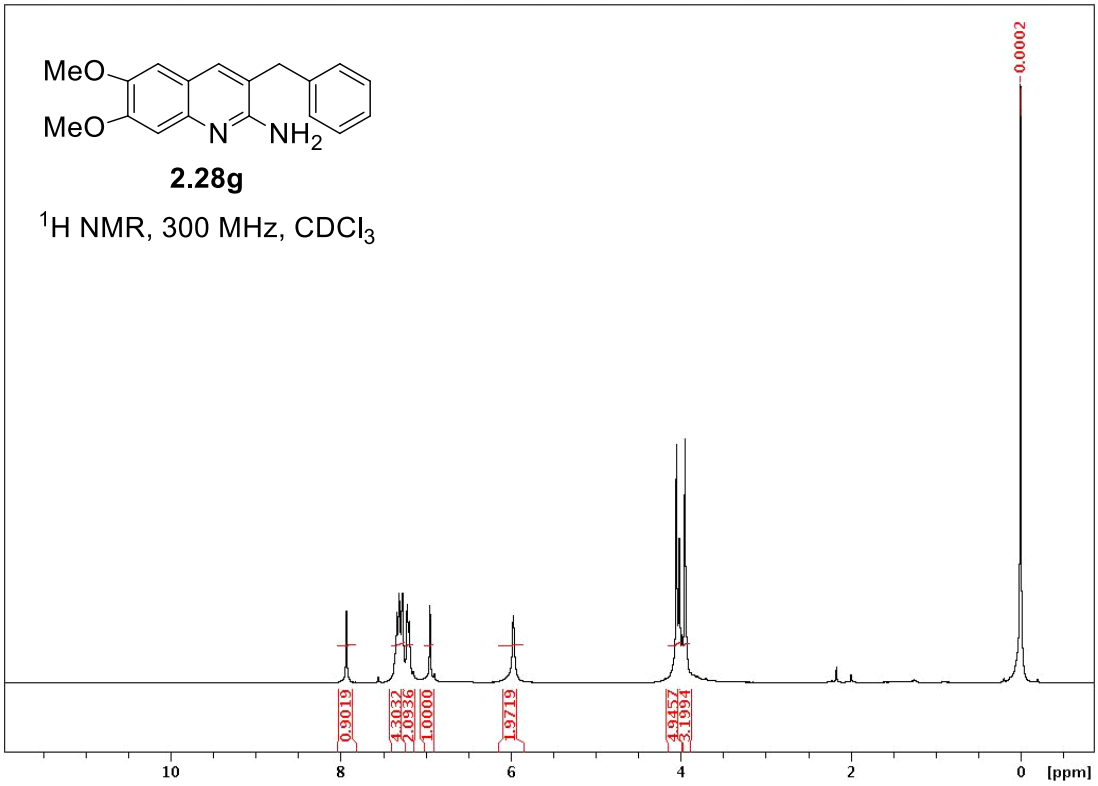
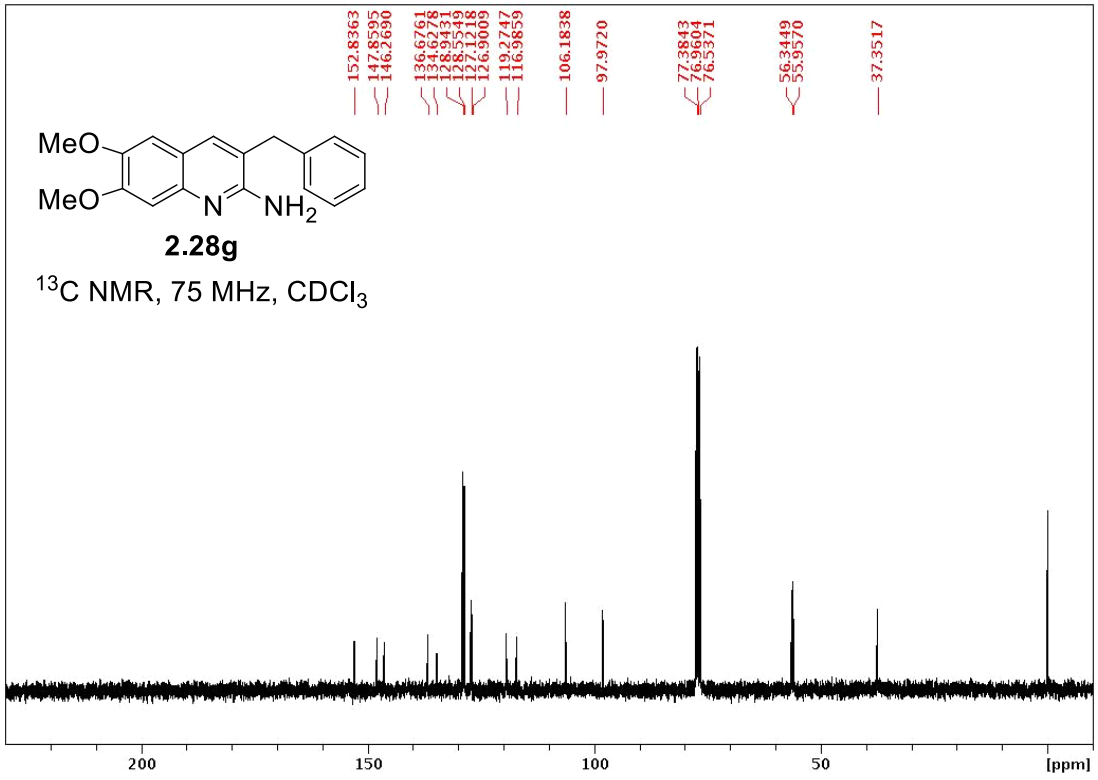
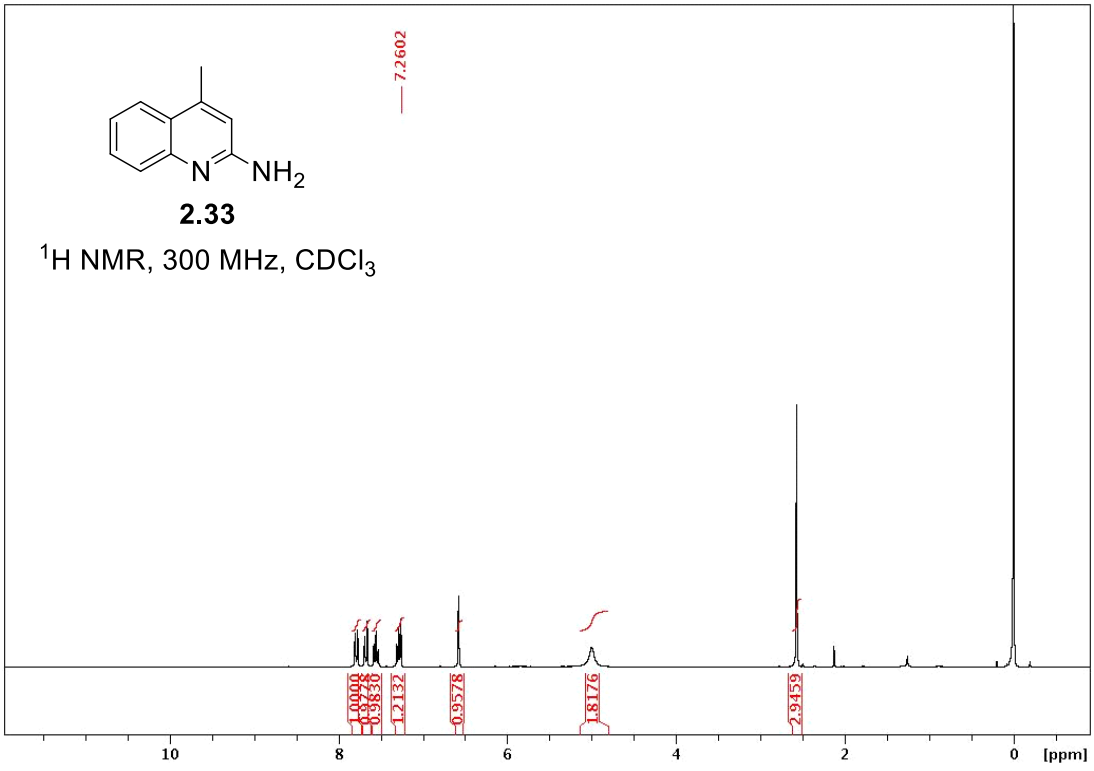
124.5937
123.2622
77.4077
76.9839
76.5602
37.6703
Cl
N
NH2
2.31e
13C NMR, 75 MHz, CDCl3
200
150
100
50
[ppm]

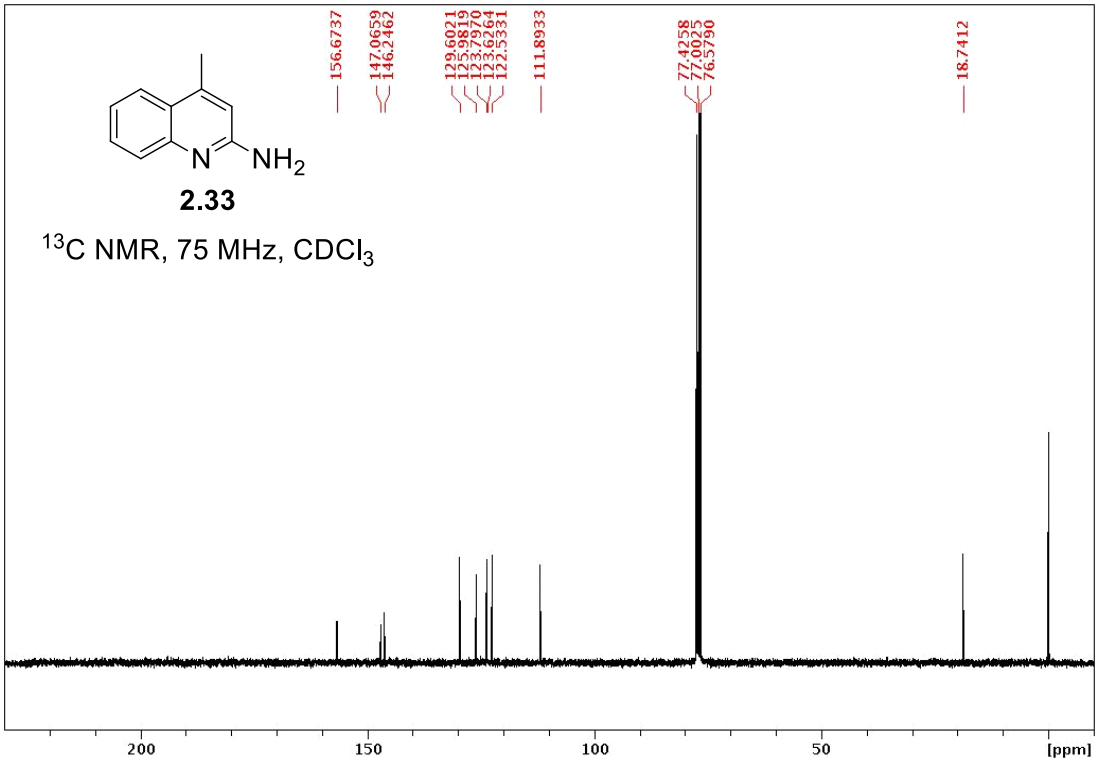

Cl
N
NH2
2.31f
1H NMR, 300 MHz, CDCl3
0.0000
6.0189
2.0000
3.9812
4.0167
6.2924
10
8
6
4
2
0
[ppm]

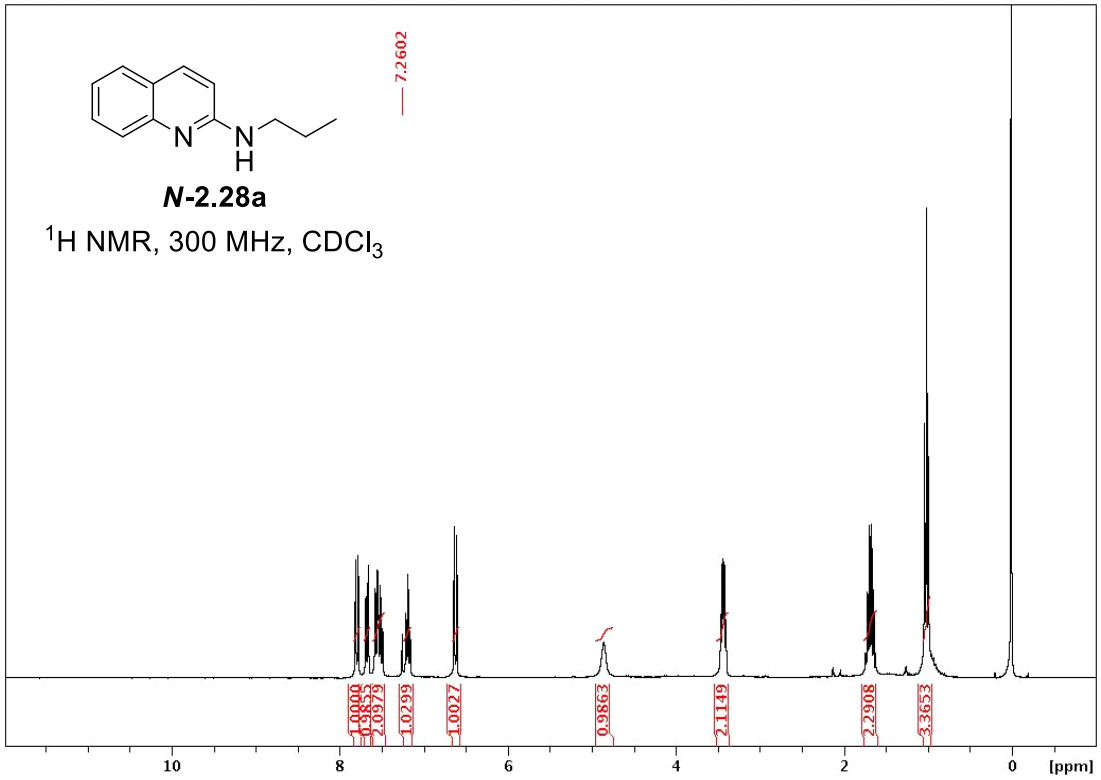

Cl
N
NH2
2.31f
13C NMR, 75 MHz, CDCl3
156.1910
144.4128
133.2643
129.2946
127.6067
126.7282
125.8046
125.6732
124.9464
77.3714
76.9477
76.5244
23.6669
11.9122
200
150
100
50
[ppm]


MeO
MeO
N
NH2
2.28g
1H NMR, 300 MHz, CDCl3
0.0002
0.9019
4.3032
2.0936
1.0000
1.9719
4.9457
3.1994
10
8
6
4
2
0
[ppm]


152.8363
147.8595
146.2690
136.6761
134.4278
128.9431
128.5549
127.1218
126.9009
119.2747
116.9859
106.1838
97.9720
77.3843
76.9604
76.5371
56.3449
55.9570
37.3517
MeO
MeO
N
NH2
2.28g
13C NMR, 75 MHz, CDCl3
200
150
100
50
[ppm]

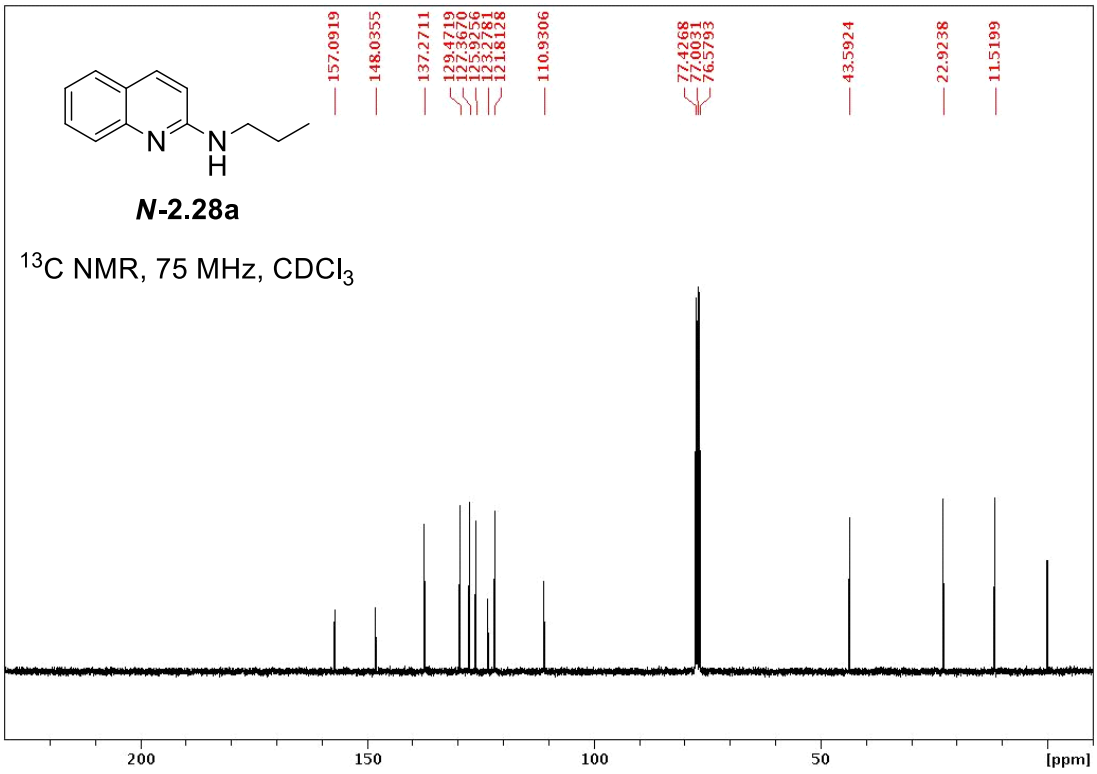

7.2602
N
NH2
2.33
1H NMR, 300 MHz, CDCl3
1.0000
0.9748
0.9830
1.2132
0.9578
1.8176
2.9459
10
8
6
4
2
0
[ppm]


156.6737
147.0659
146.2462
129.6021
123.9870
123.7710
123.6264
122.5331
111.8933
77.4258
77.0025
76.5790
18.7412
N
NH2
2.33
13C NMR, 75 MHz, CDCl3
200
150
100
50
[ppm]



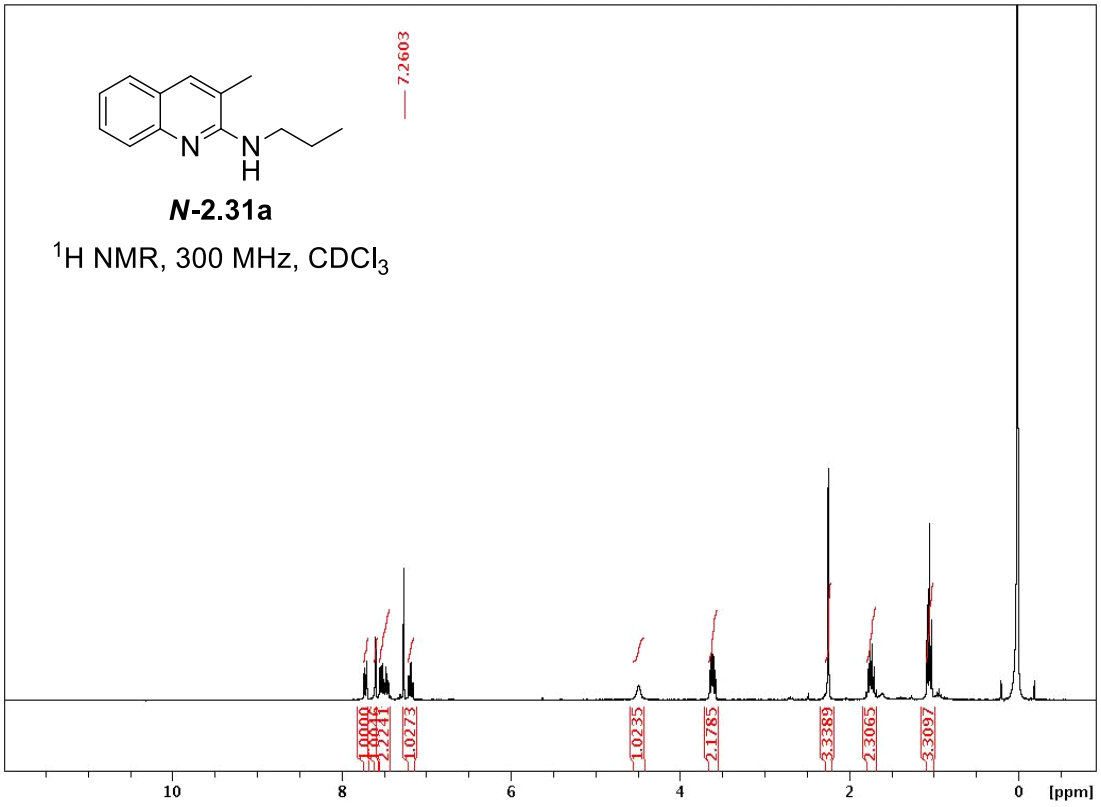
***N*-2.28a**

^{1}H NMR, 300 MHz, $CDCl_3$



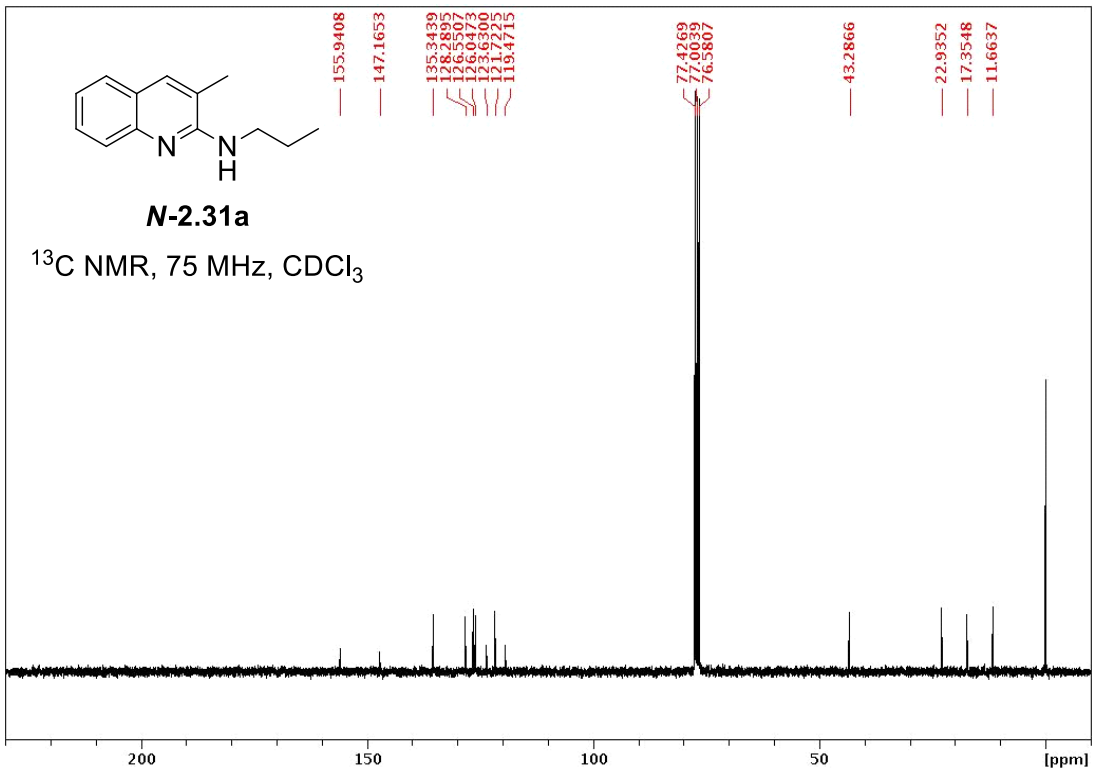
***N*-2.28a**

^{13}C NMR, 75 MHz, $CDCl_3$



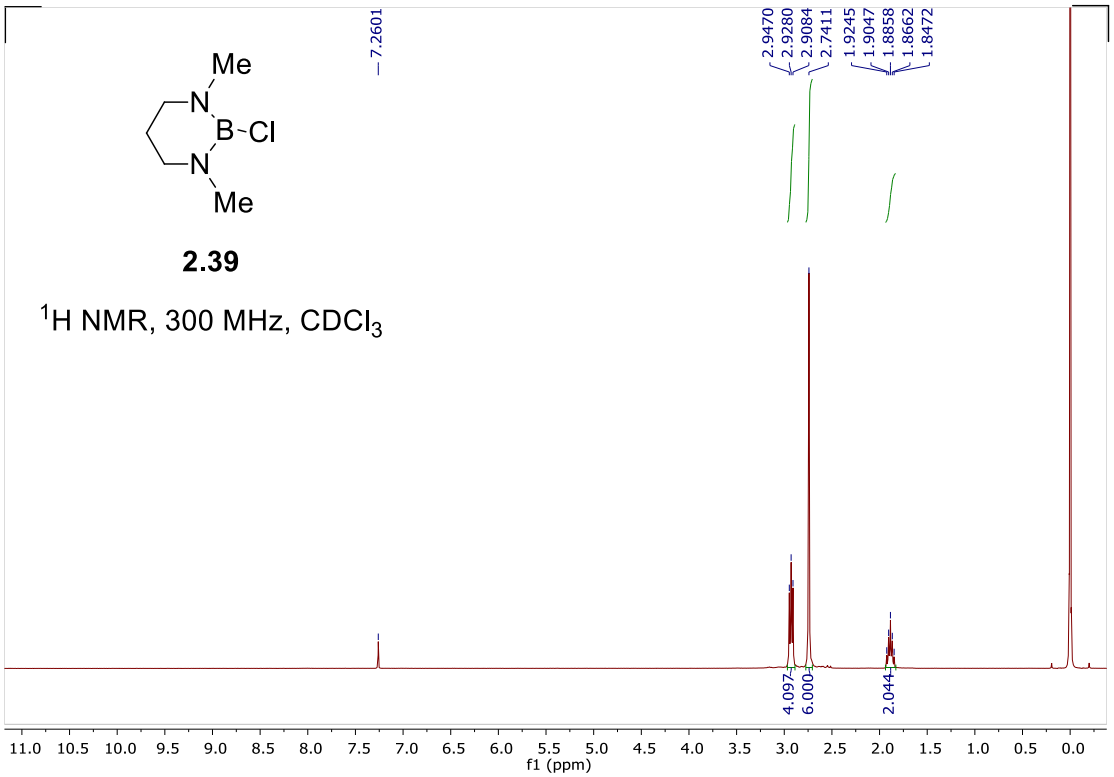
***N*-2.31a**

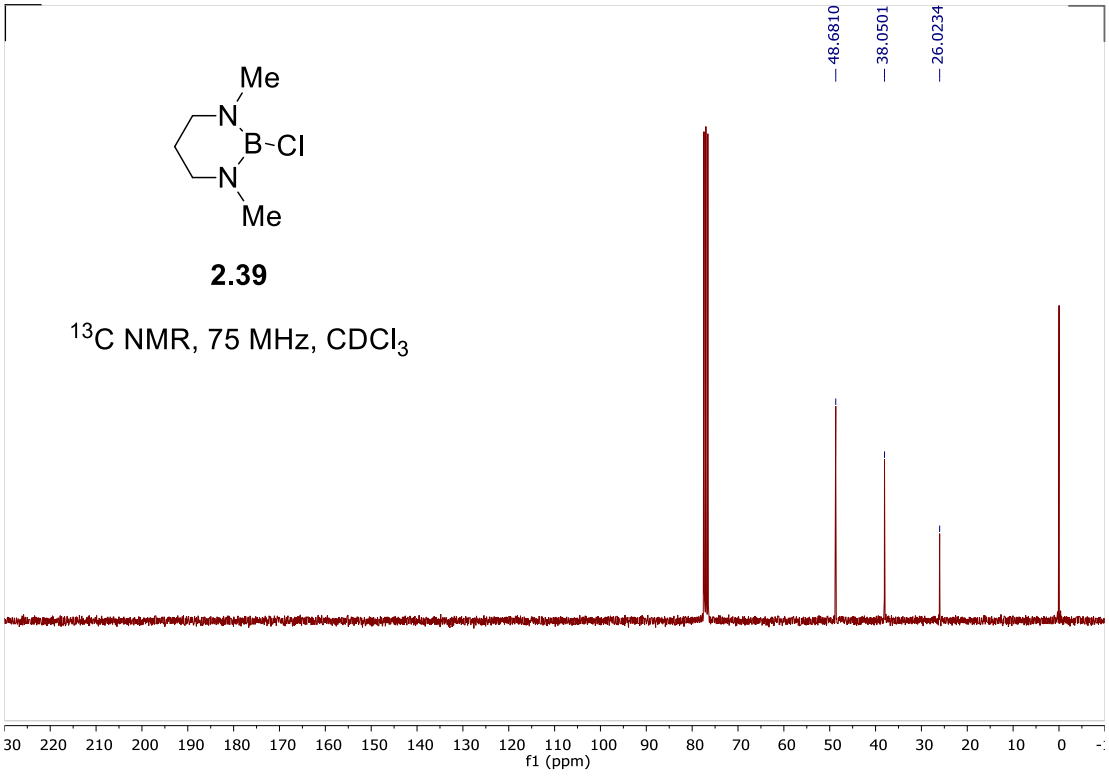
^{1}H NMR, 300 MHz, $CDCl_3$

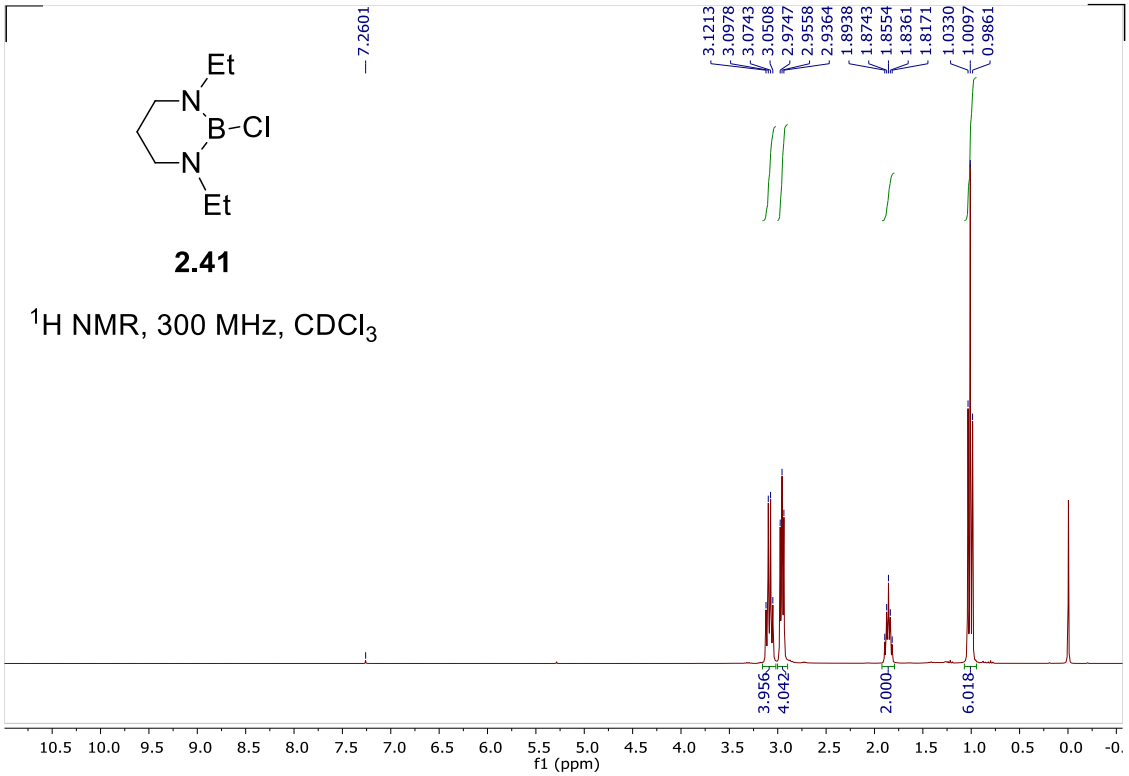


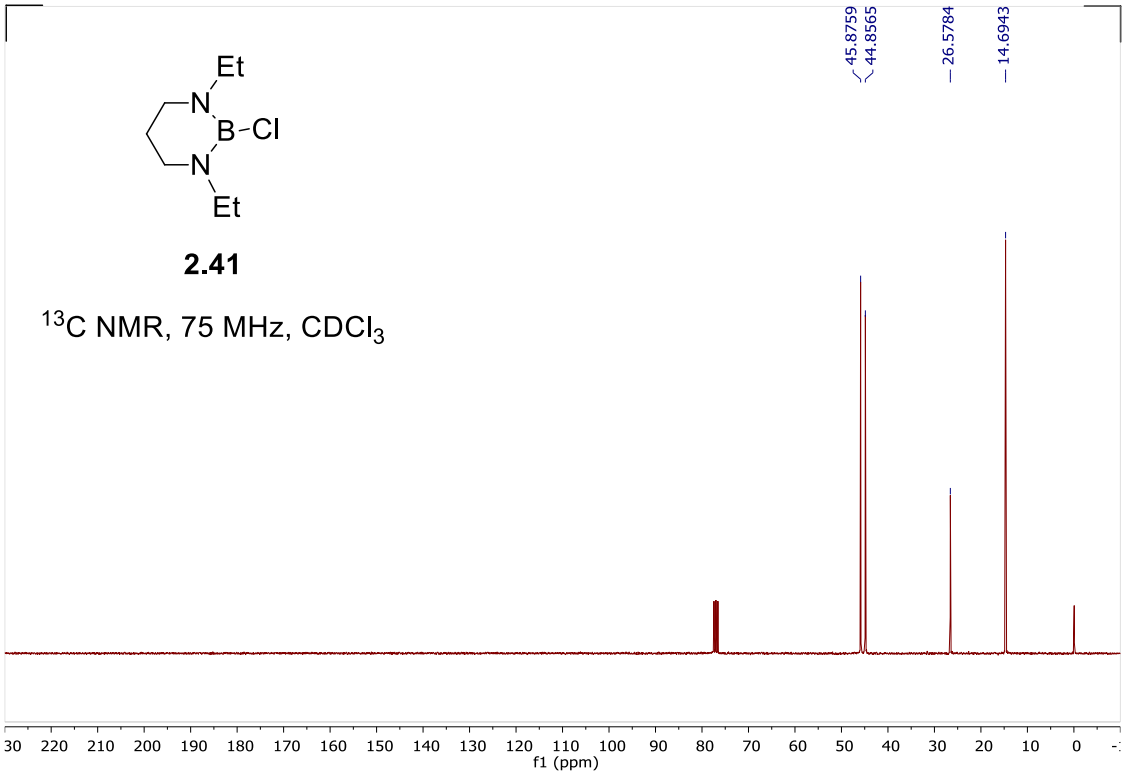
***N*-2.31a**

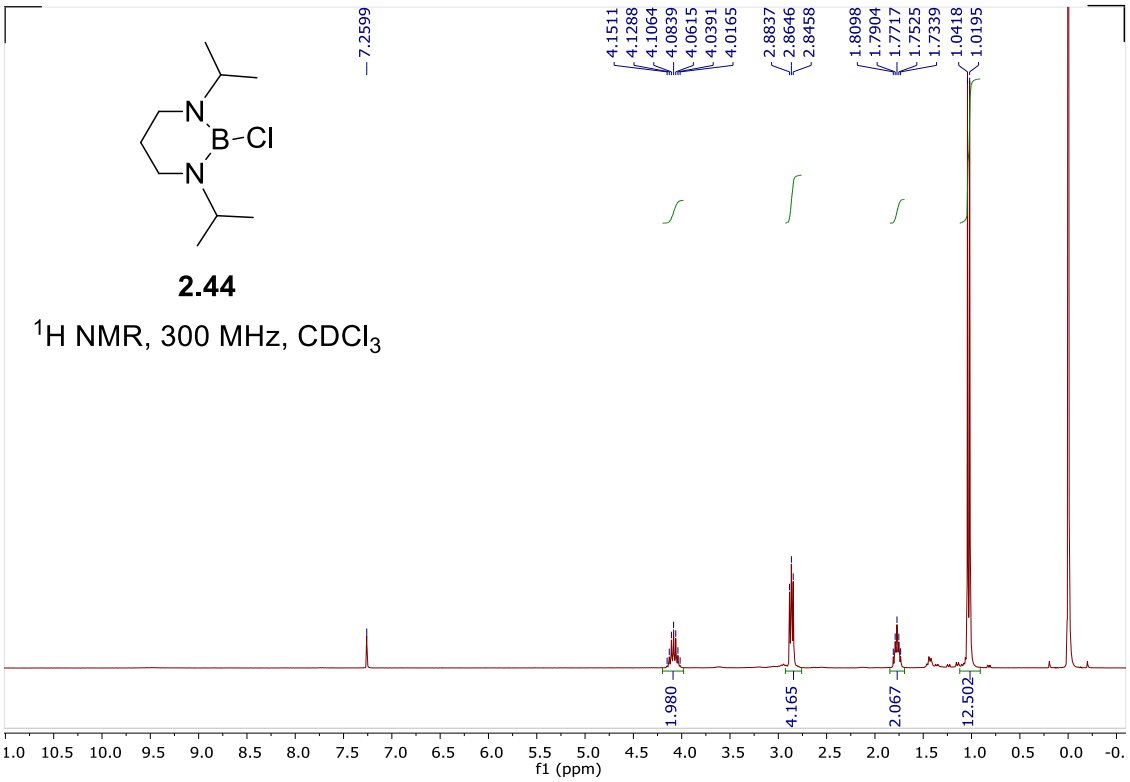
^{13}C NMR, 75 MHz, $CDCl_3$


Me
N
B-Cl
N
Me
2.39
1H NMR, 300 MHz, CDCl3
7.2601
2.9470
2.9280
2.9084
2.7411
1.9245
1.9047
1.8858
1.8662
1.8472
4.097
6.000
2.044
f1 (ppm)


Me
N
B-Cl
N
Me
2.39
13C NMR, 75 MHz, CDCl3
48.6810
38.0501
26.0234
f1 (ppm)

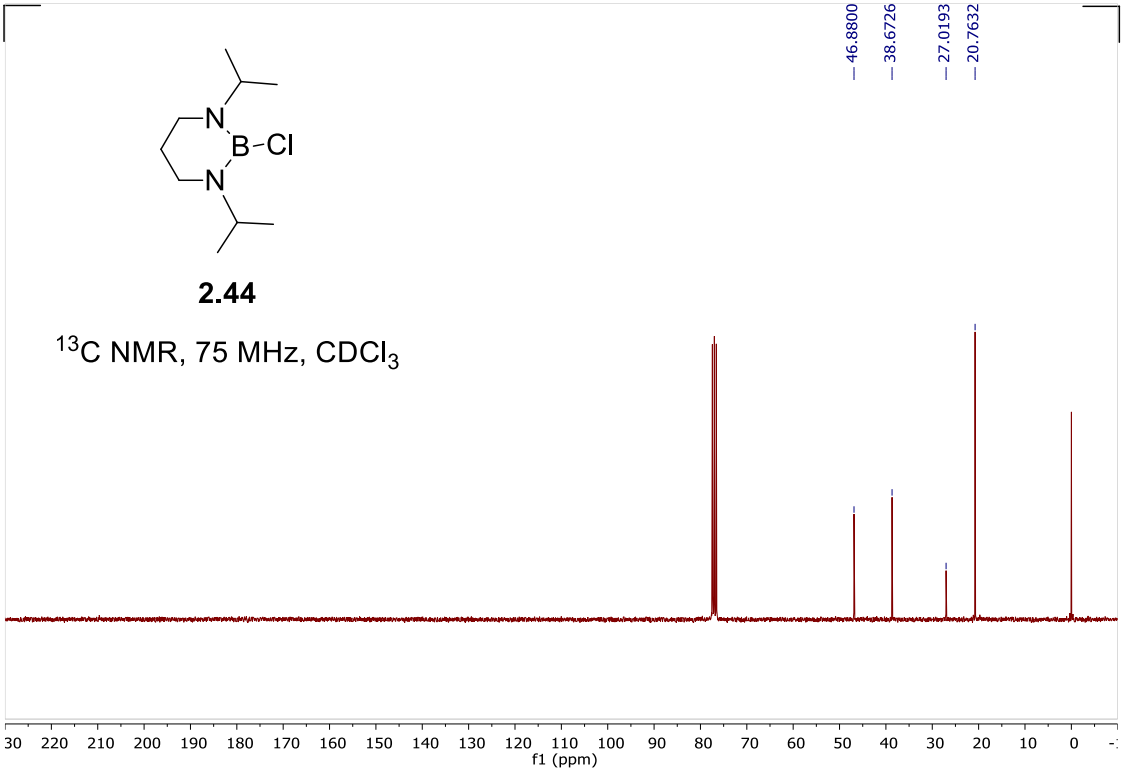

Et
N
B–Cl
N
Et
2.41
1H NMR, 300 MHz, CDCl3
7.2601
3.1213
3.0978
3.0743
3.0508
2.9747
2.9558
2.9364
1.8938
1.8743
1.8554
1.8361
1.8171
1.0330
1.0097
0.9861
3.956
4.042
2.000
6.018
f1 (ppm)


Et
N
B–Cl
N
Et
2.41
13C NMR, 75 MHz, CDCl3
45.8759
44.8565
26.5784
14.6943
f1 (ppm)



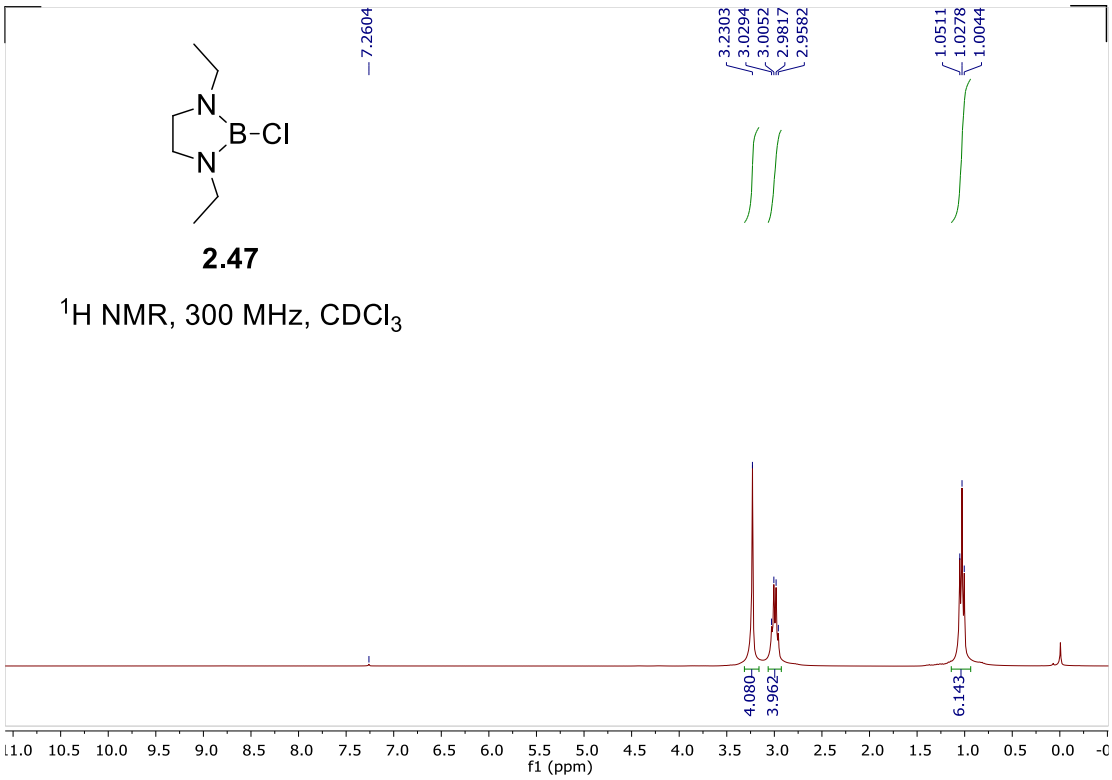
2.44

^{1}H NMR, 300 MHz, $CDCl_3$



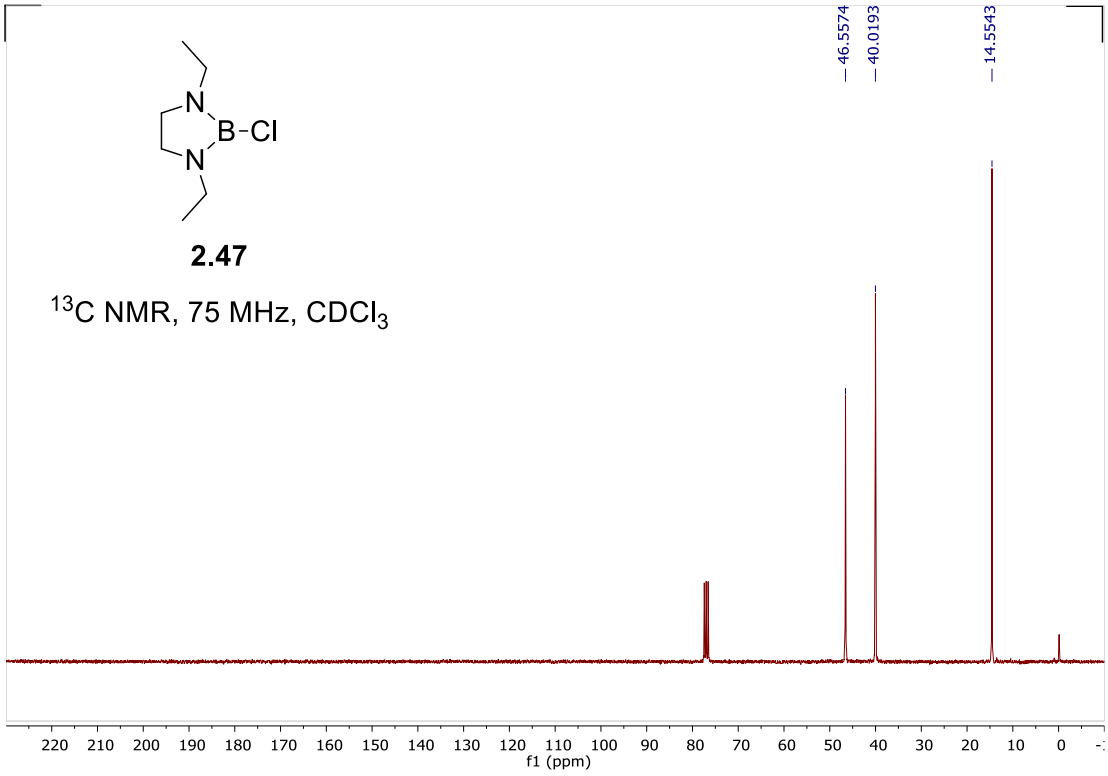
2.44

^{13}C NMR, 75 MHz, $CDCl_3$



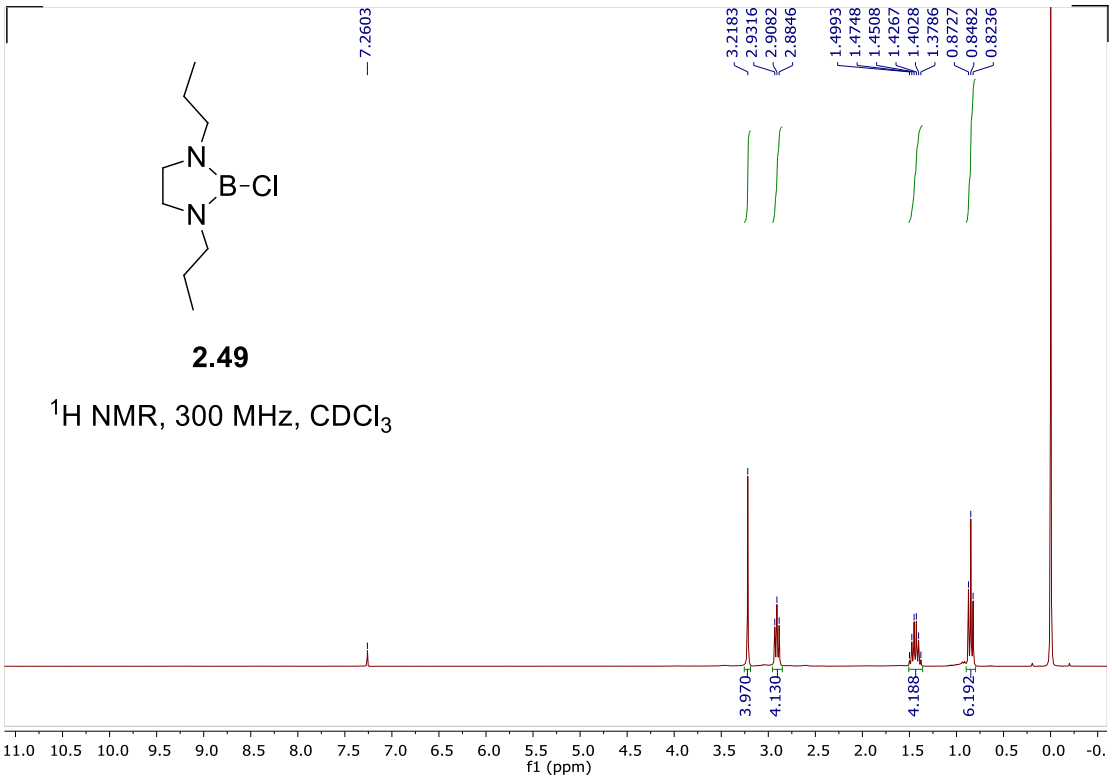
2.47

^{1}H NMR, 300 MHz, $CDCl_3$



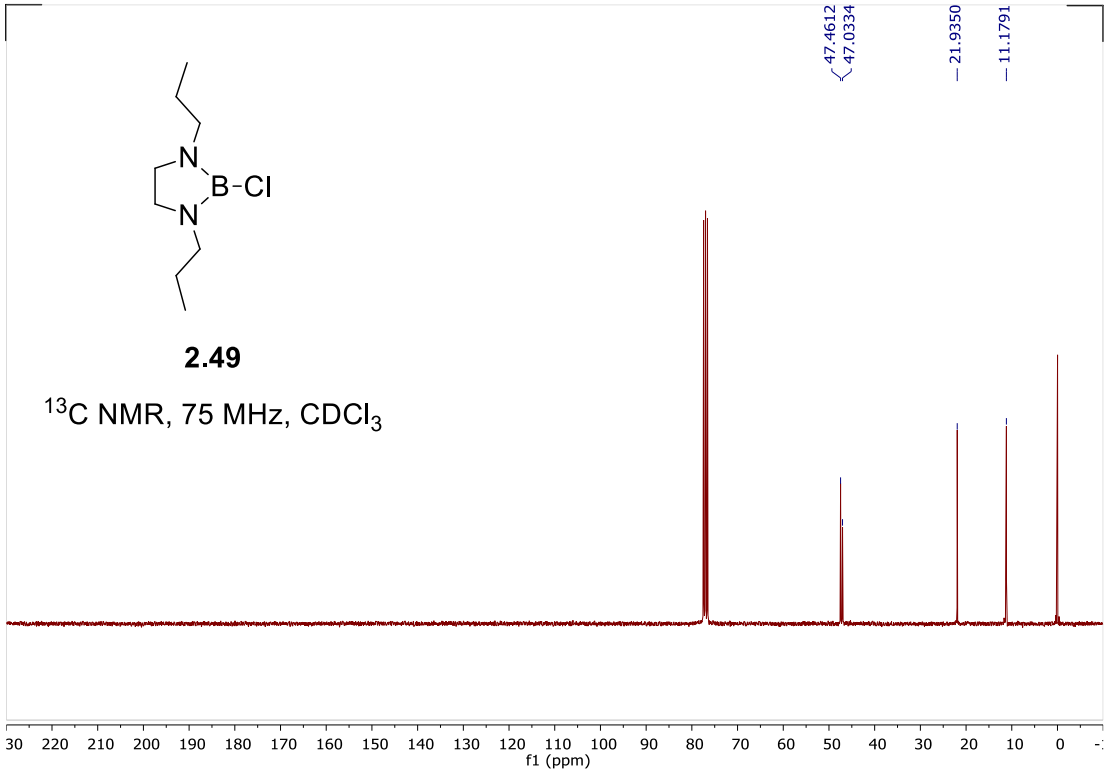
2.47

^{13}C NMR, 75 MHz, $CDCl_3$



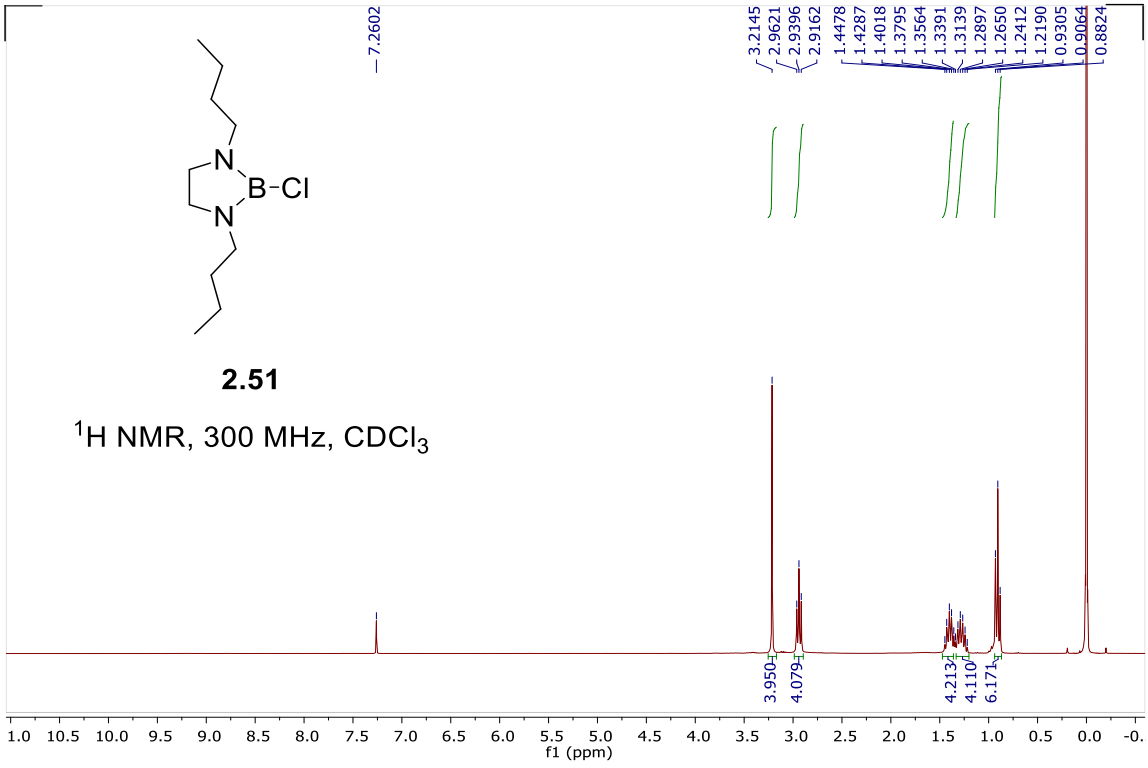
2.49

^{1}H NMR, 300 MHz, $CDCl_3$



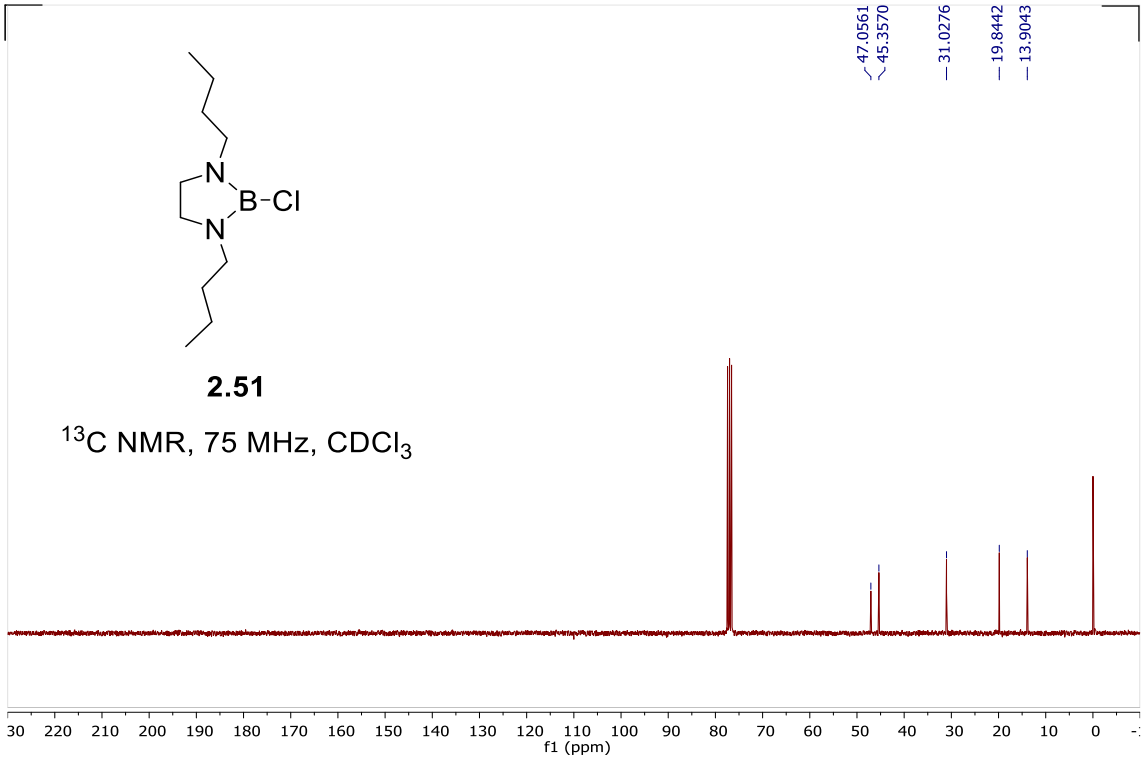
2.49

^{13}C NMR, 75 MHz, $CDCl_3$



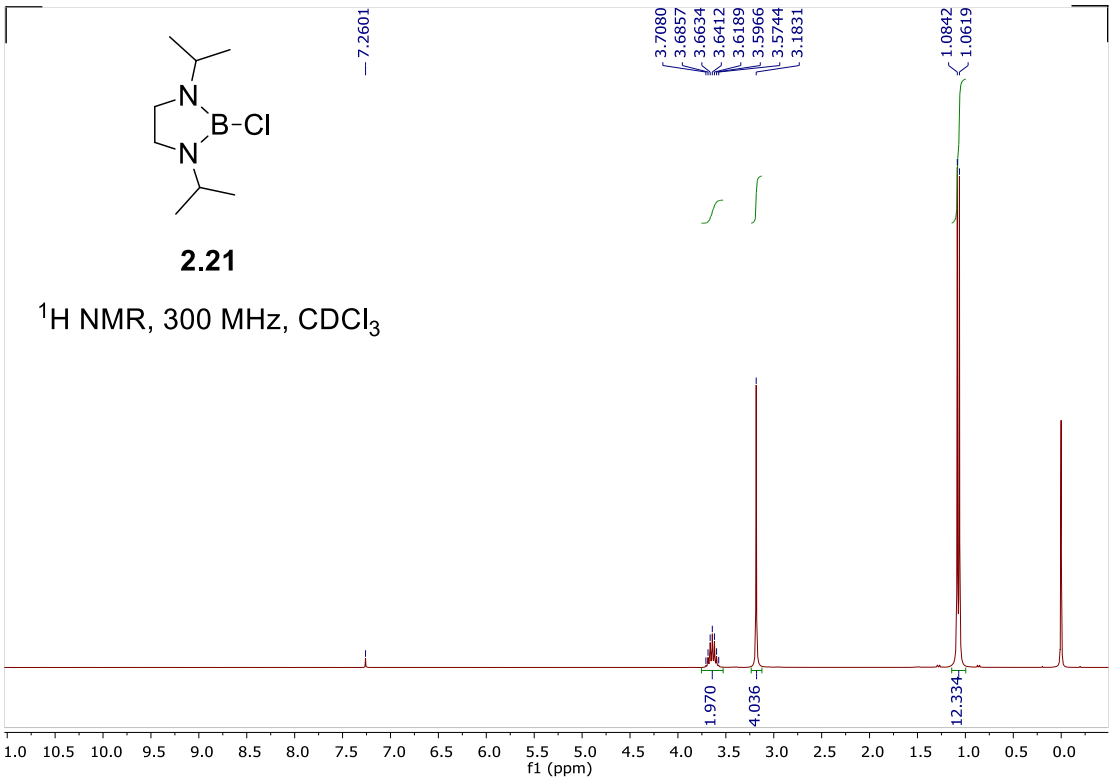
2.51

^{1}H NMR, 300 MHz, $CDCl_3$



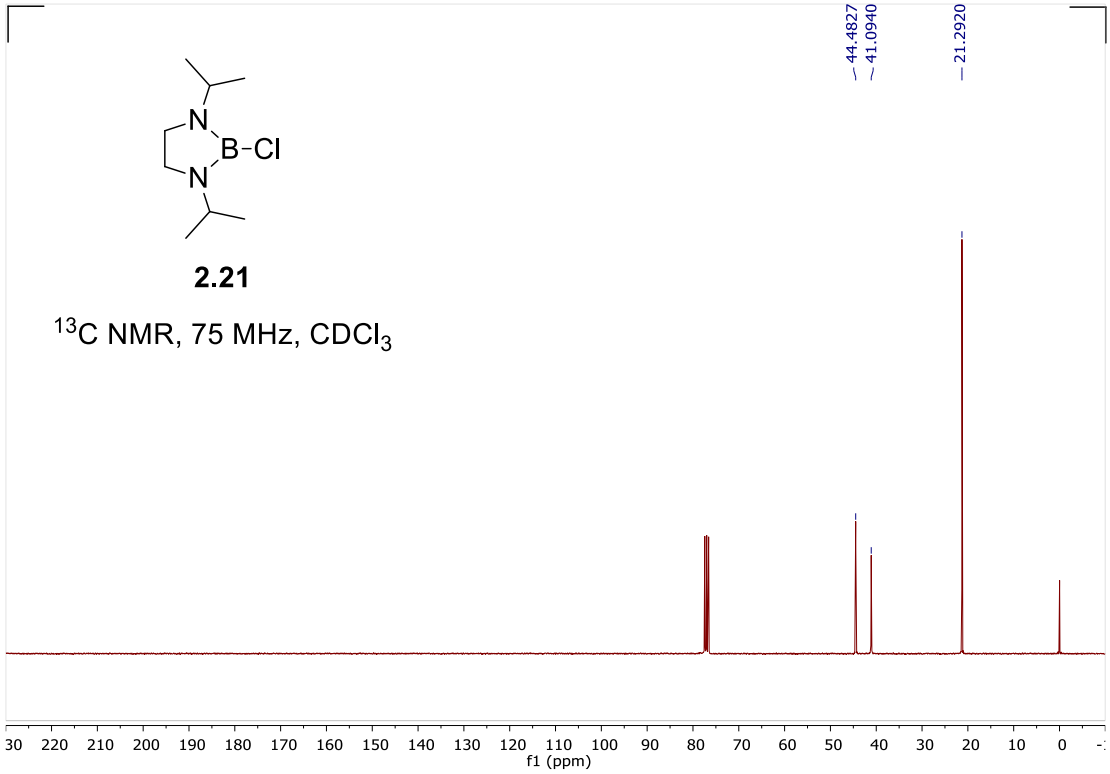
2.51

^{13}C NMR, 75 MHz, $CDCl_3$



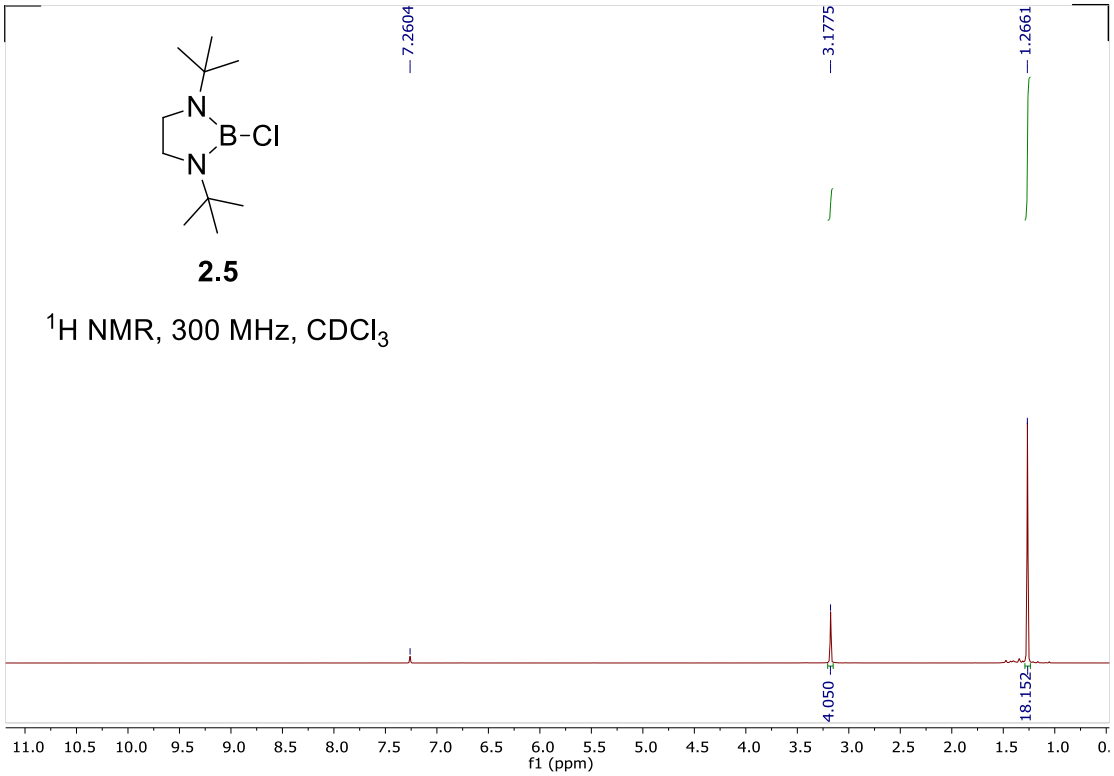
2.21

^{1}H NMR, 300 MHz, $CDCl_3$



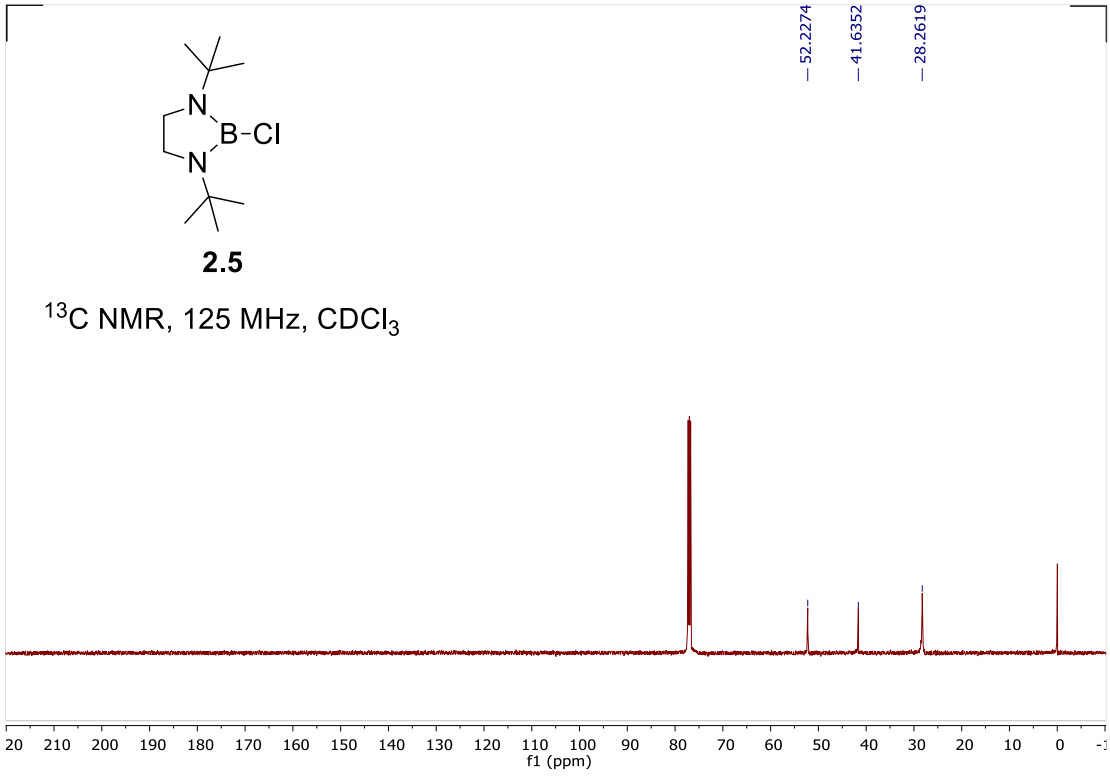
2.21

^{13}C NMR, 75 MHz, $CDCl_3$



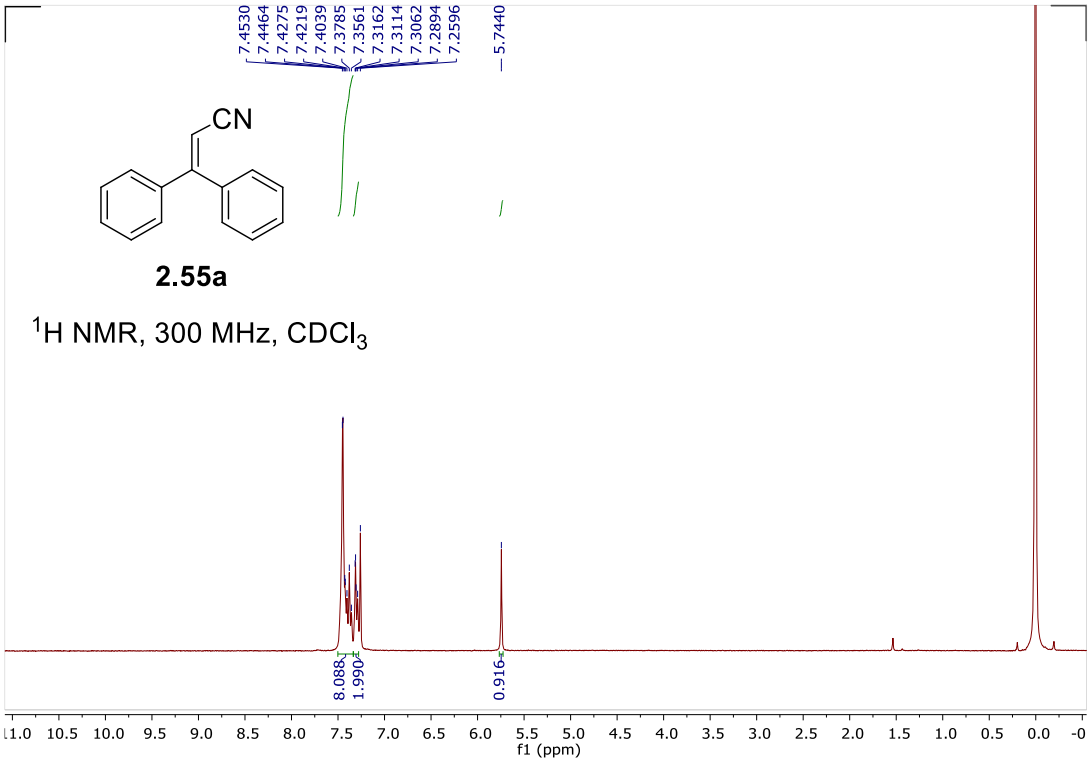
2.5

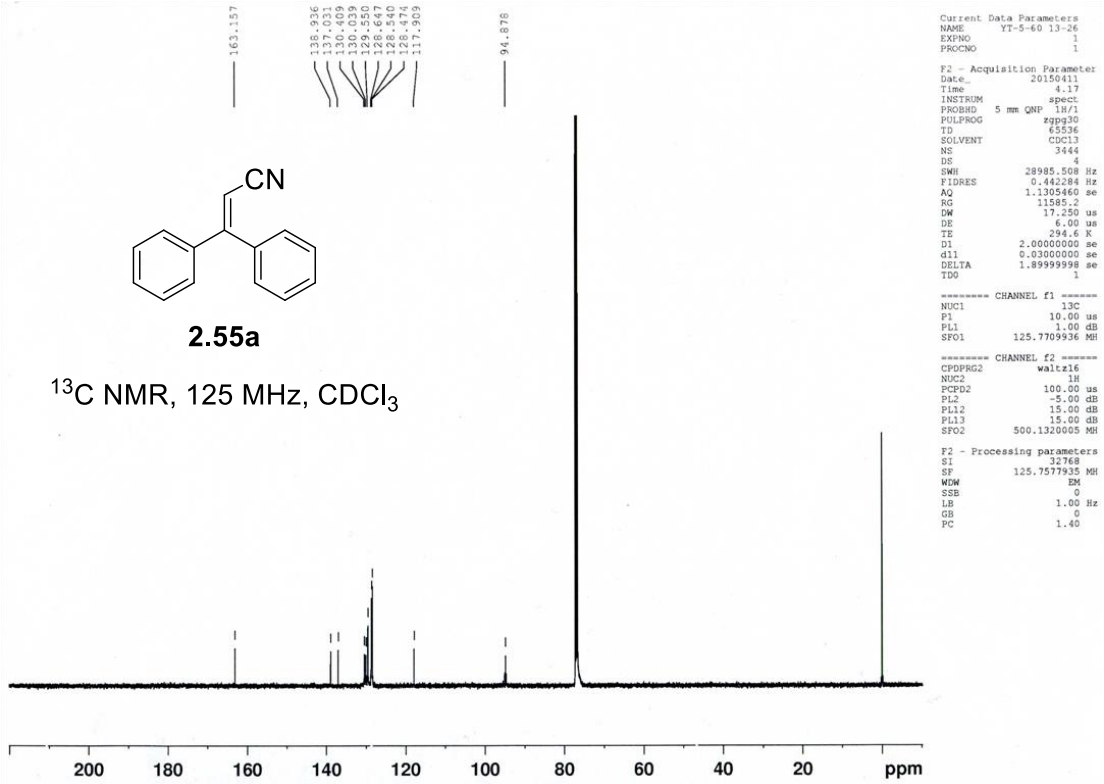
^{1}H NMR, 300 MHz, $CDCl_3$

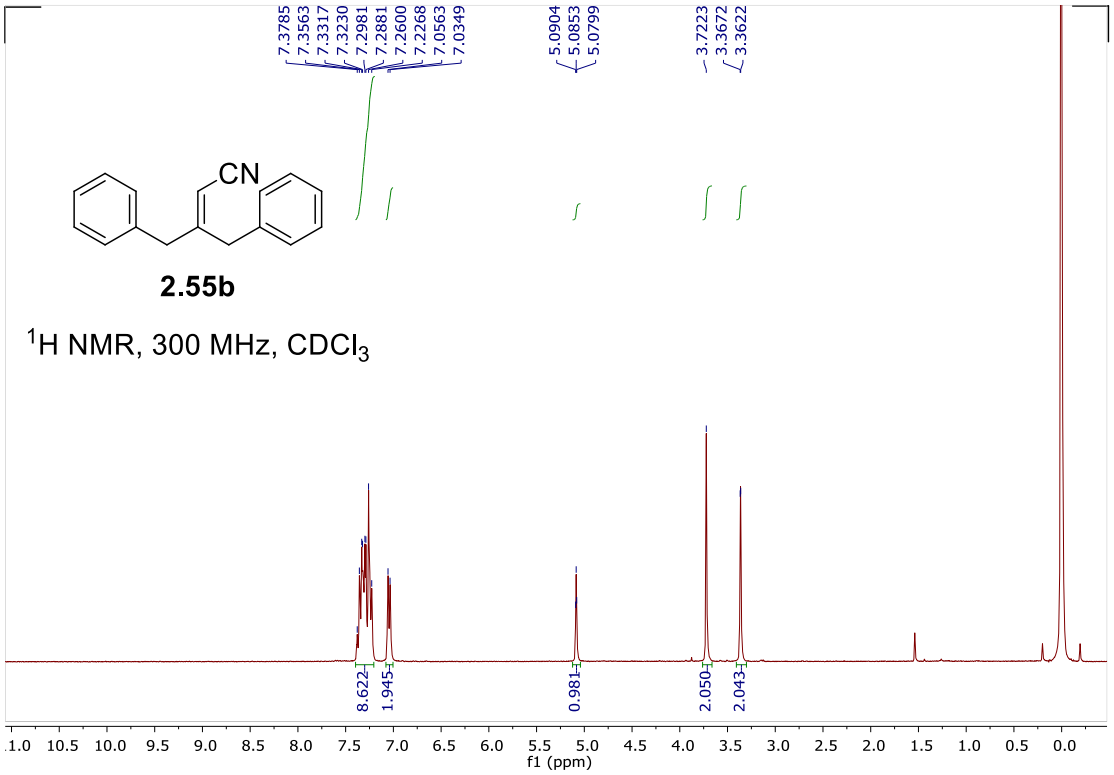


2.5

^{13}C NMR, 125 MHz, $CDCl_3$

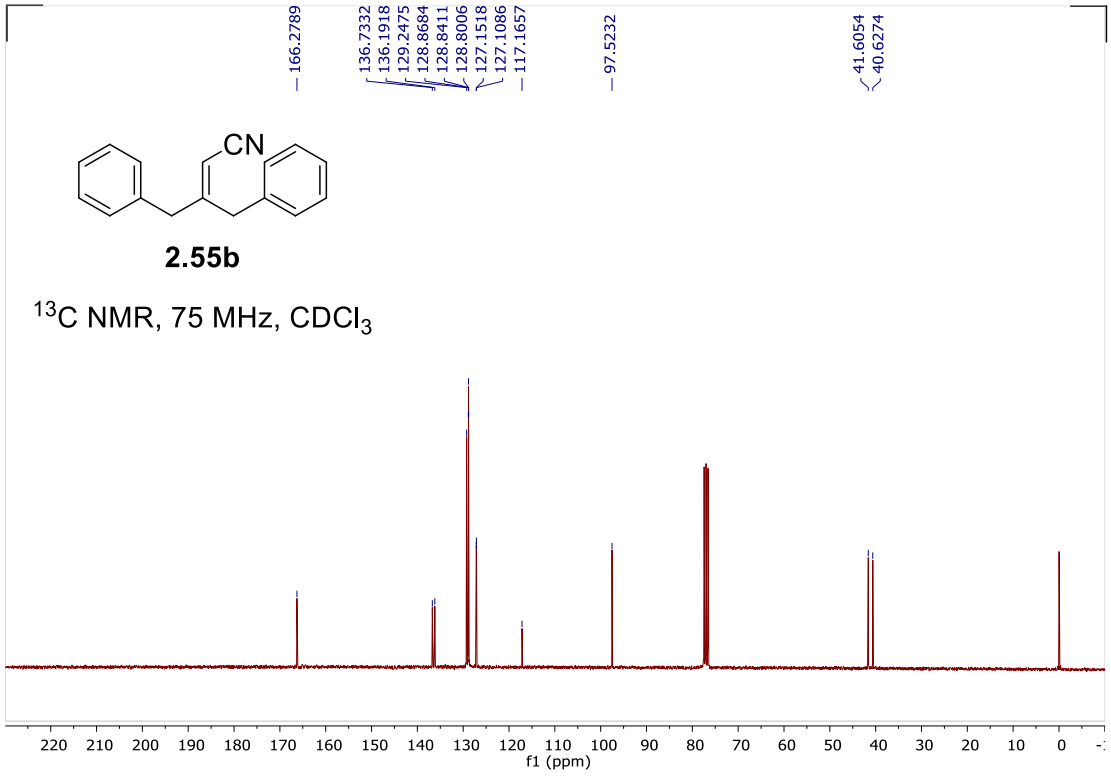

7.4530
7.4464
7.4275
7.4219
7.4039
7.3785
7.3561
7.3162
7.3114
7.3062
7.2894
7.2596
5.7440
CN
2.55a
1H NMR, 300 MHz, CDCl3
8.088
1.990
0.916
f1 (ppm)


163.157
136.936
131.031
130.409
130.039
129.550
128.647
128.540
128.474
117.909
94.878
CN
2.55a
13C NMR, 125 MHz, CDCl3
ppm



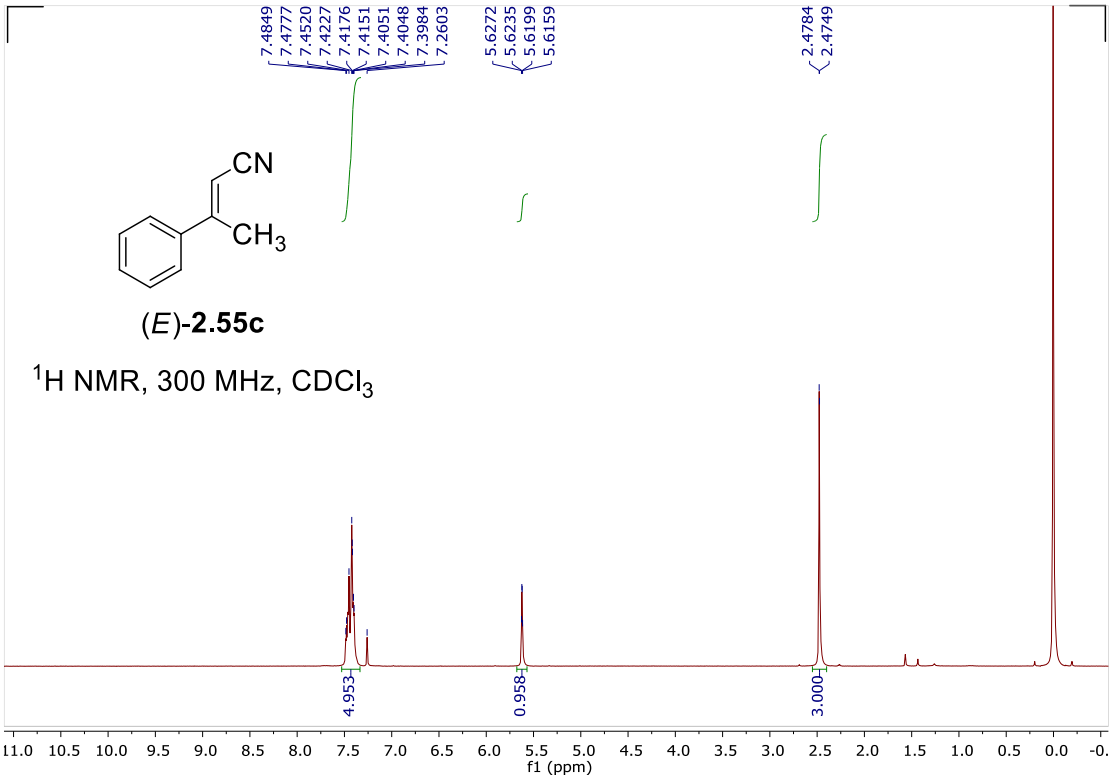
2.55b

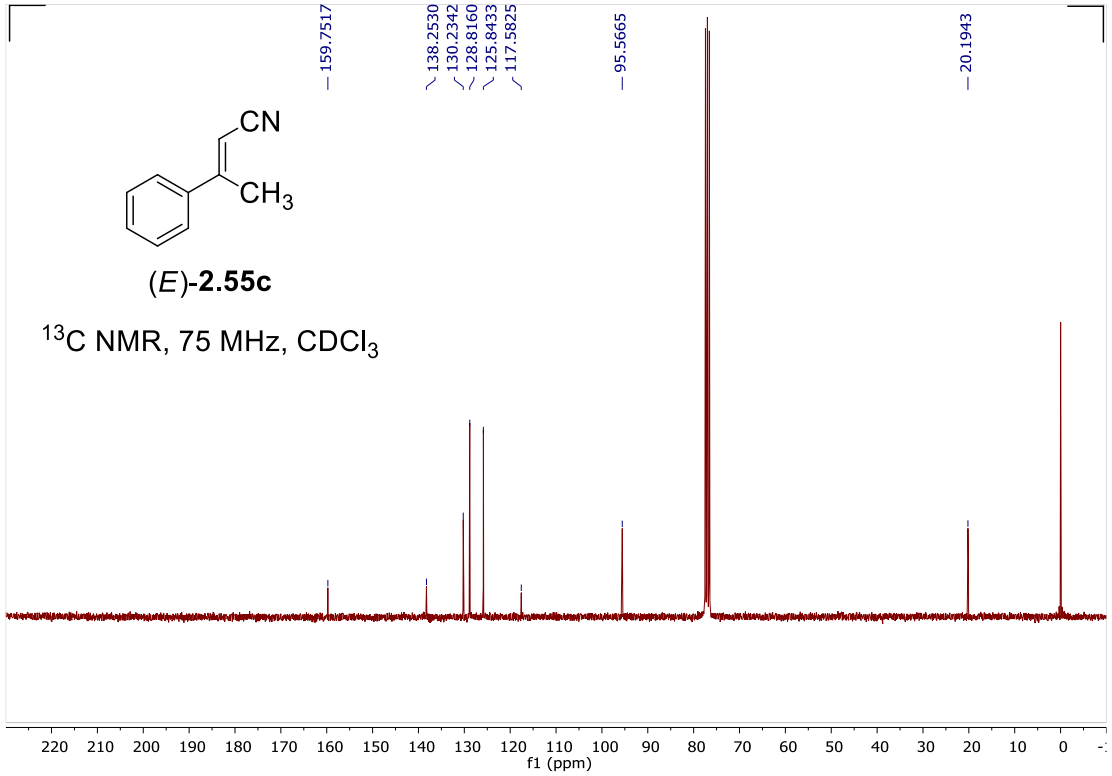
^{1}H NMR, 300 MHz, $CDCl_3$

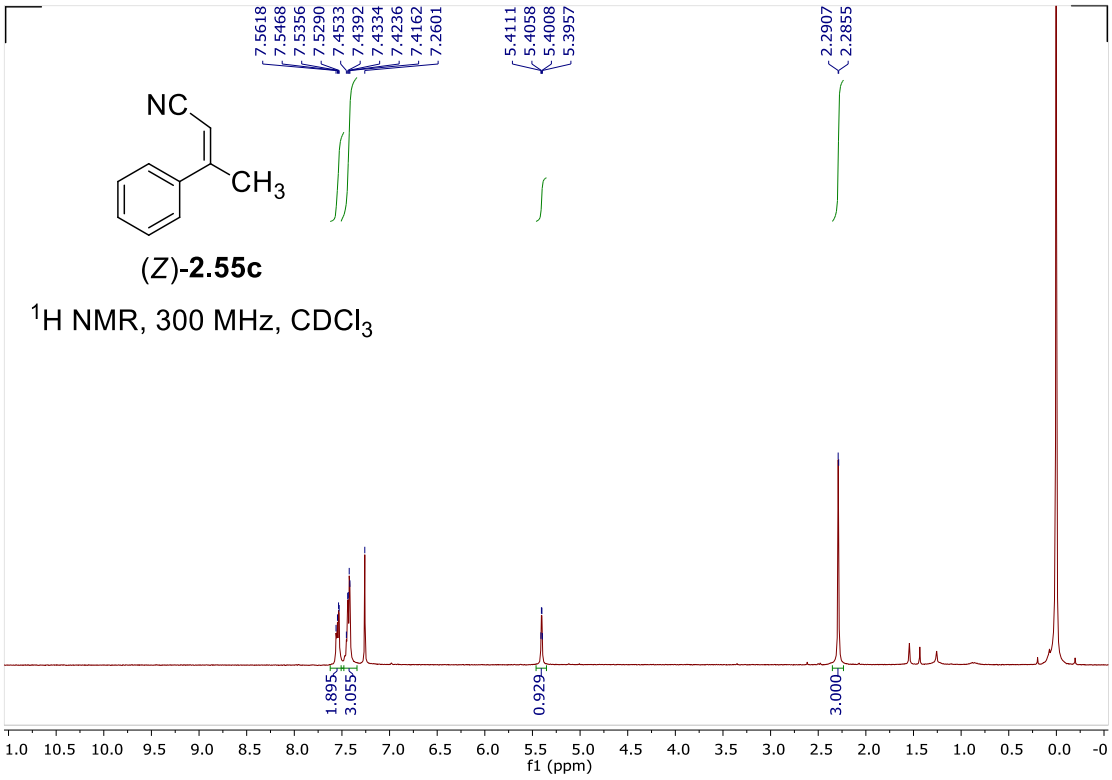


2.55b

^{13}C NMR, 75 MHz, $CDCl_3$

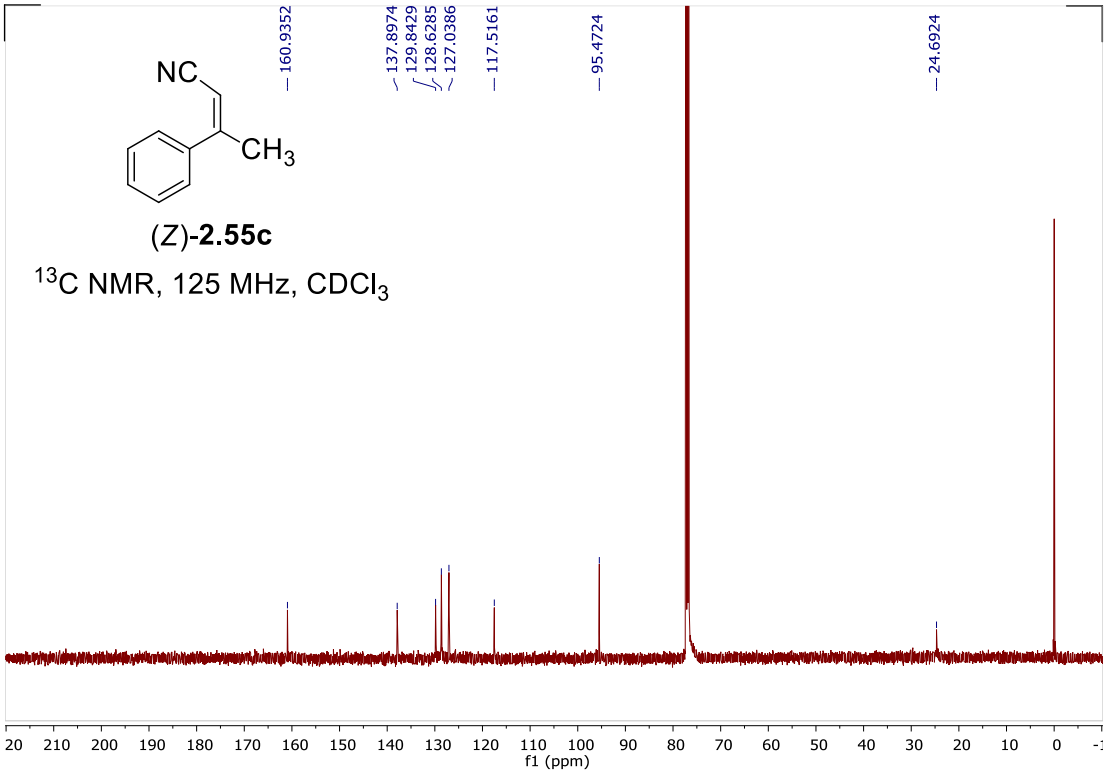

7.4849
7.4777
7.4520
7.4227
7.4176
7.4151
7.4051
7.4048
7.3984
7.2603
5.6272
5.6235
5.6199
5.6159
2.4784
2.4749
CN
CH3
(E)-2.55c
1H NMR, 300 MHz, CDCl3
4.953
0.958
3.000
f1 (ppm)


159.7517
138.2530
130.2342
128.8160
125.8433
117.5825
95.5665
20.1943
CN
CH3
(E)-2.55c
13C NMR, 75 MHz, CDCl3
f1 (ppm)



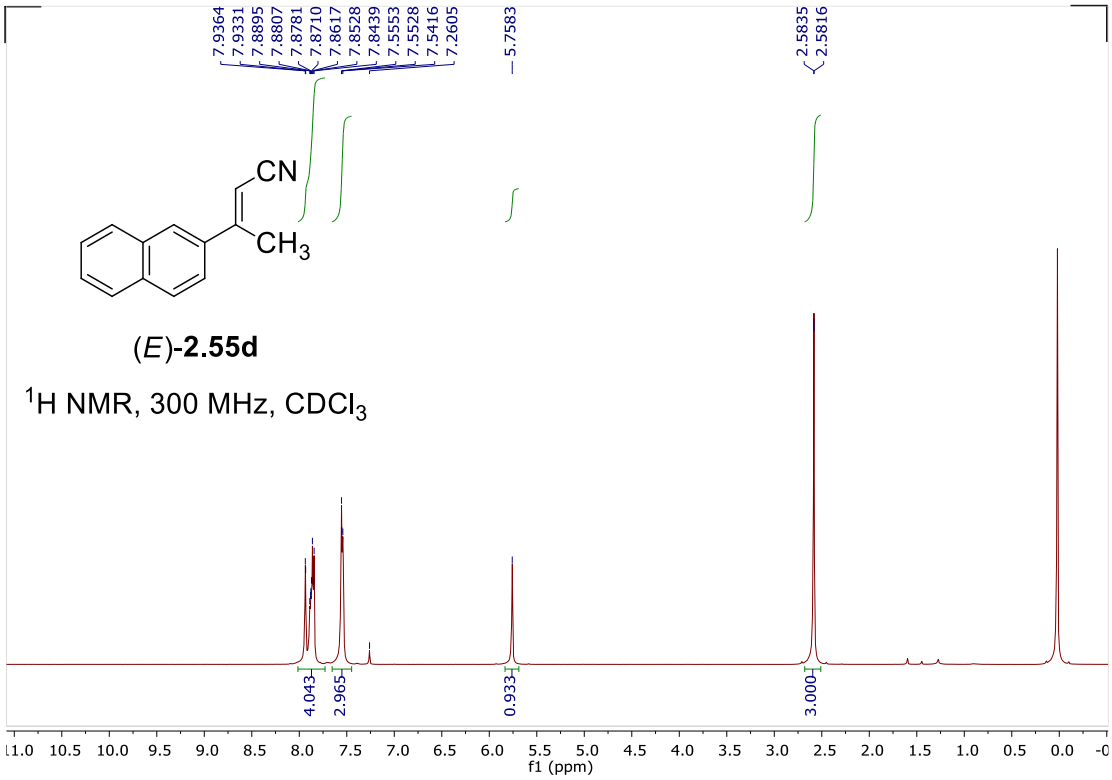
(*Z*)-**2.55c**

^{1}H NMR, 300 MHz, $CDCl_3$



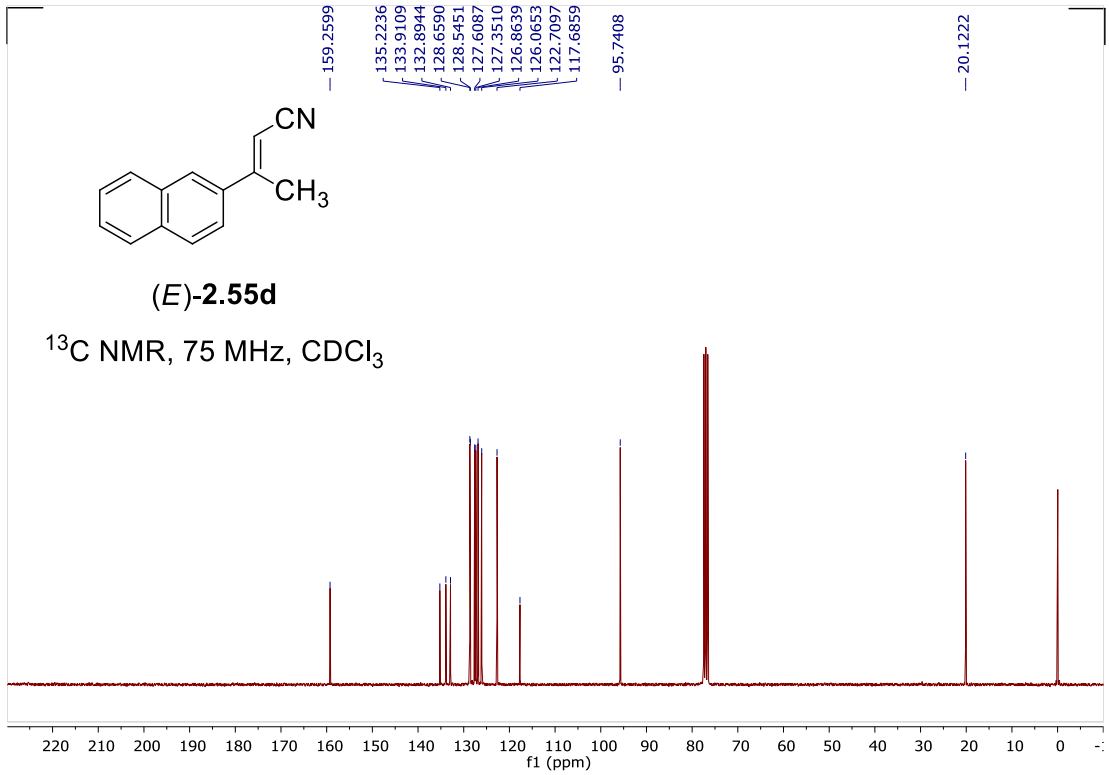
(*Z*)-**2.55c**

^{13}C NMR, 125 MHz, $CDCl_3$



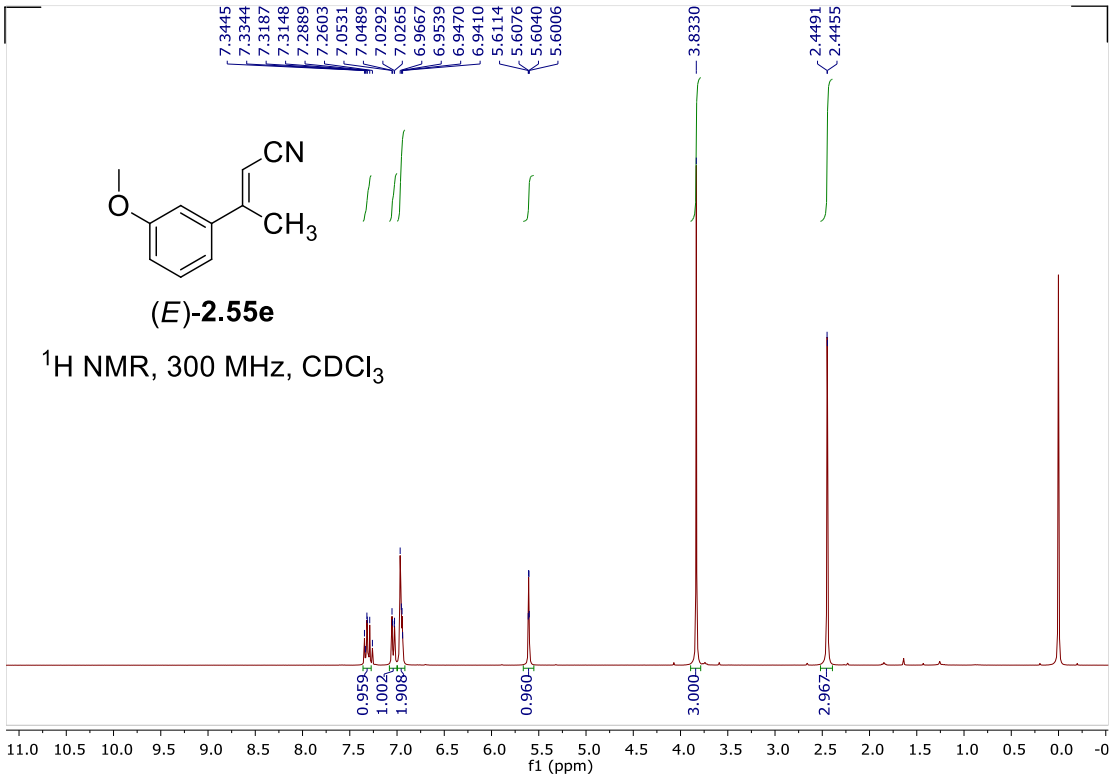
(*E*)-**2.55d**

^{1}H NMR, 300 MHz, $CDCl_3$



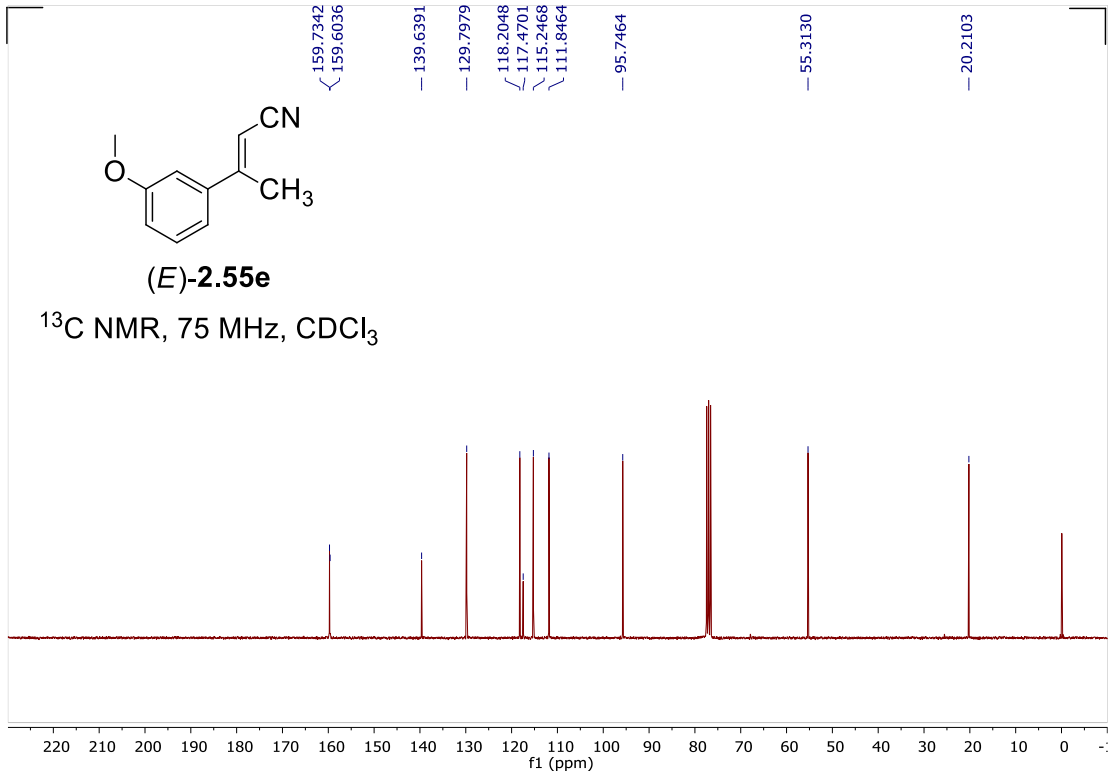
(*E*)-**2.55d**

^{13}C NMR, 75 MHz, $CDCl_3$



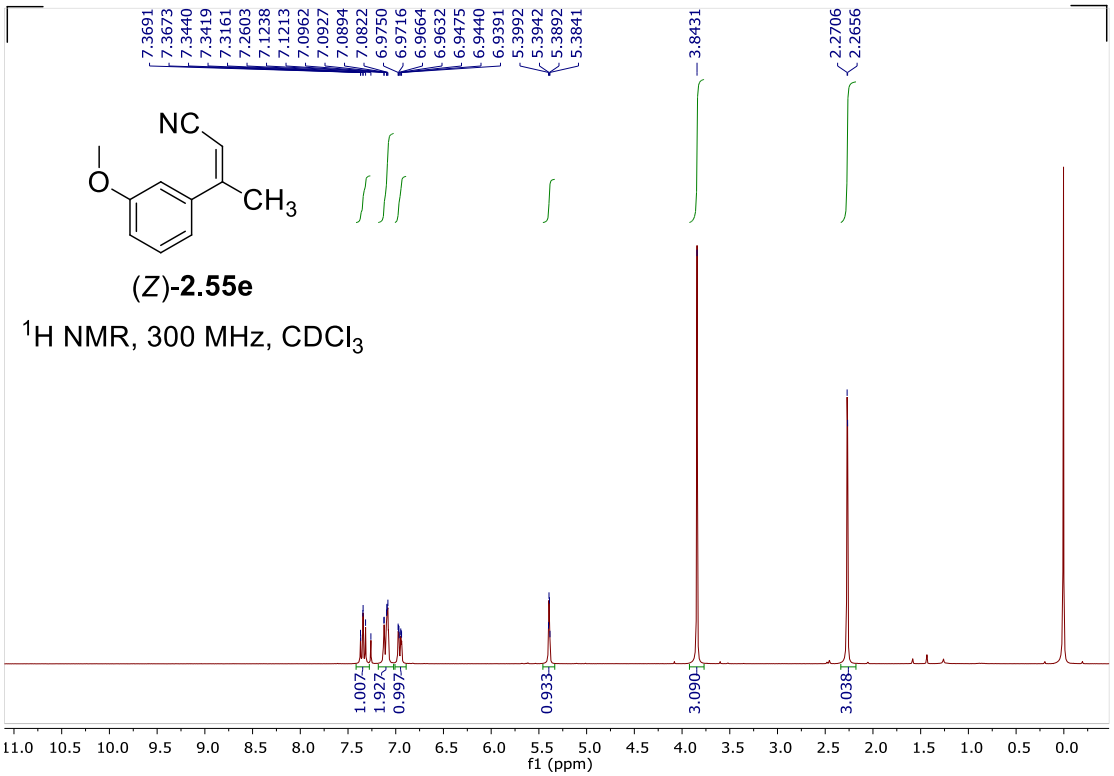
(*E*)-**2.55e**

^{1}H NMR, 300 MHz, $CDCl_3$



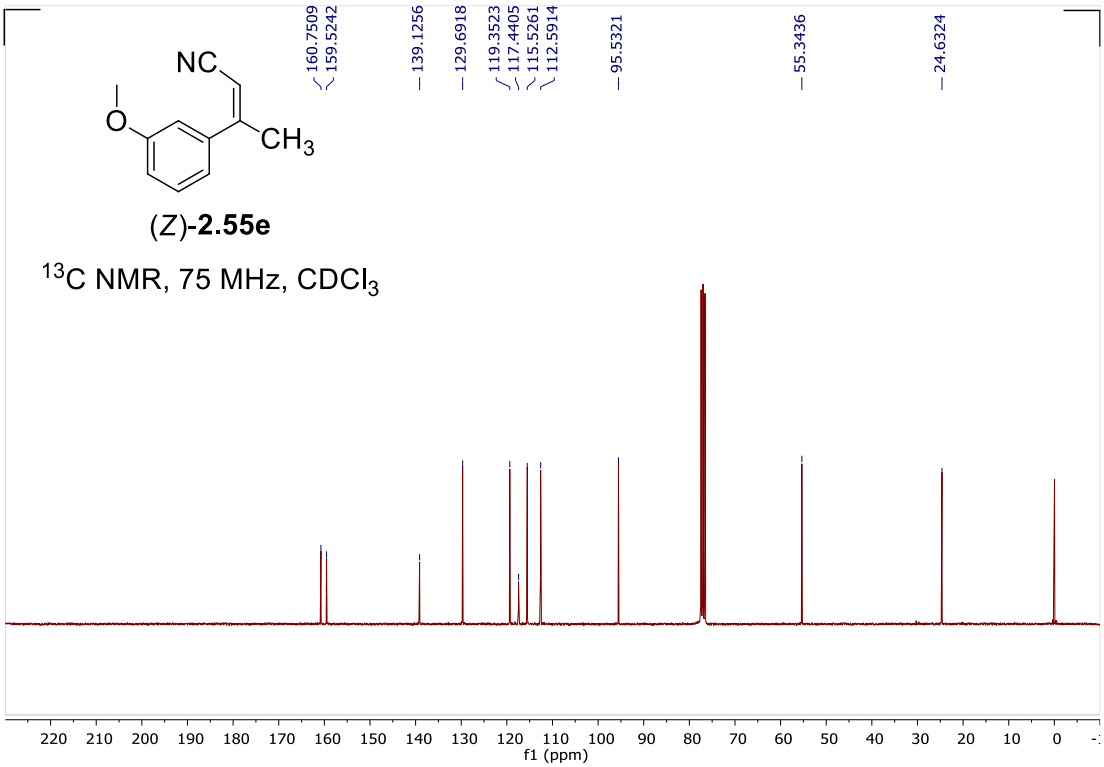
(*E*)-**2.55e**

^{13}C NMR, 75 MHz, $CDCl_3$



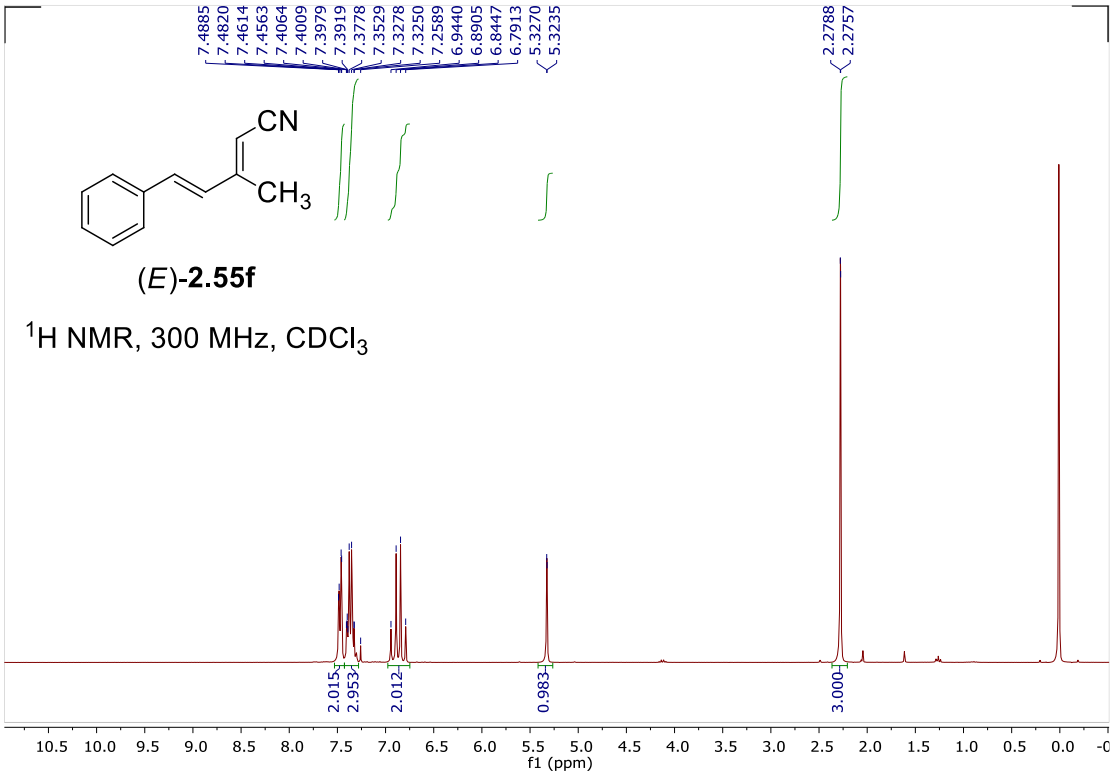
(*Z*)-**2.55e**

^{1}H NMR, 300 MHz, $CDCl_3$



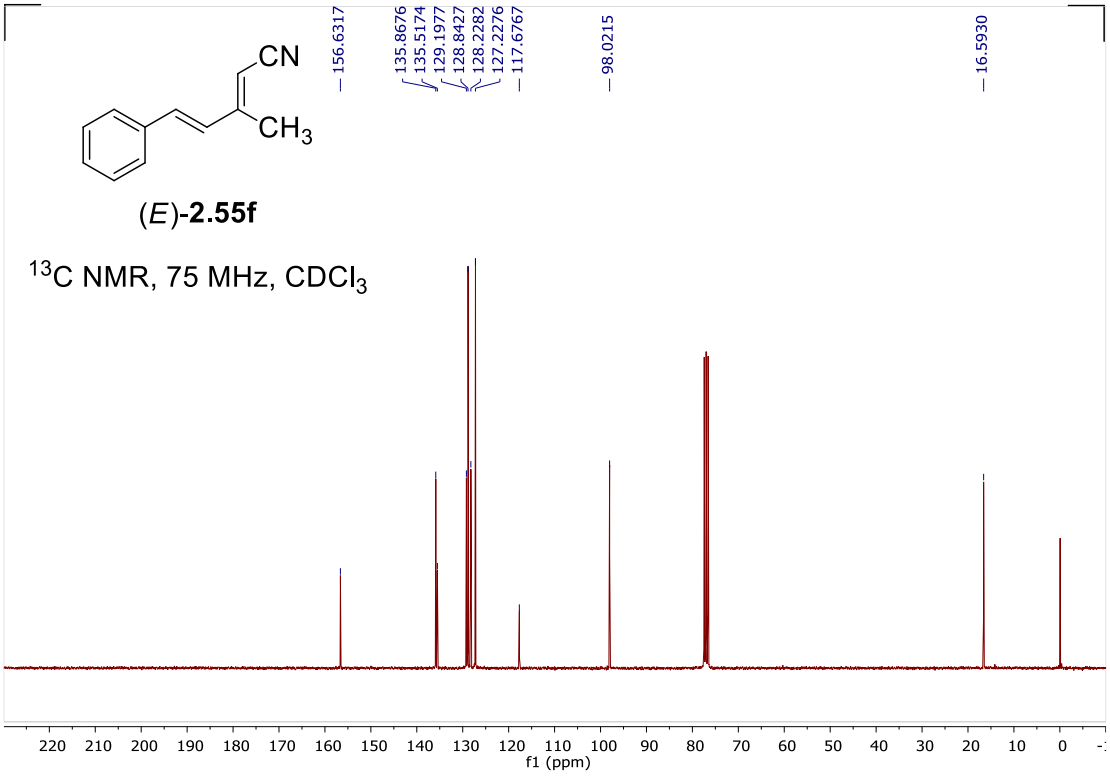
(*Z*)-**2.55e**

^{13}C NMR, 75 MHz, $CDCl_3$



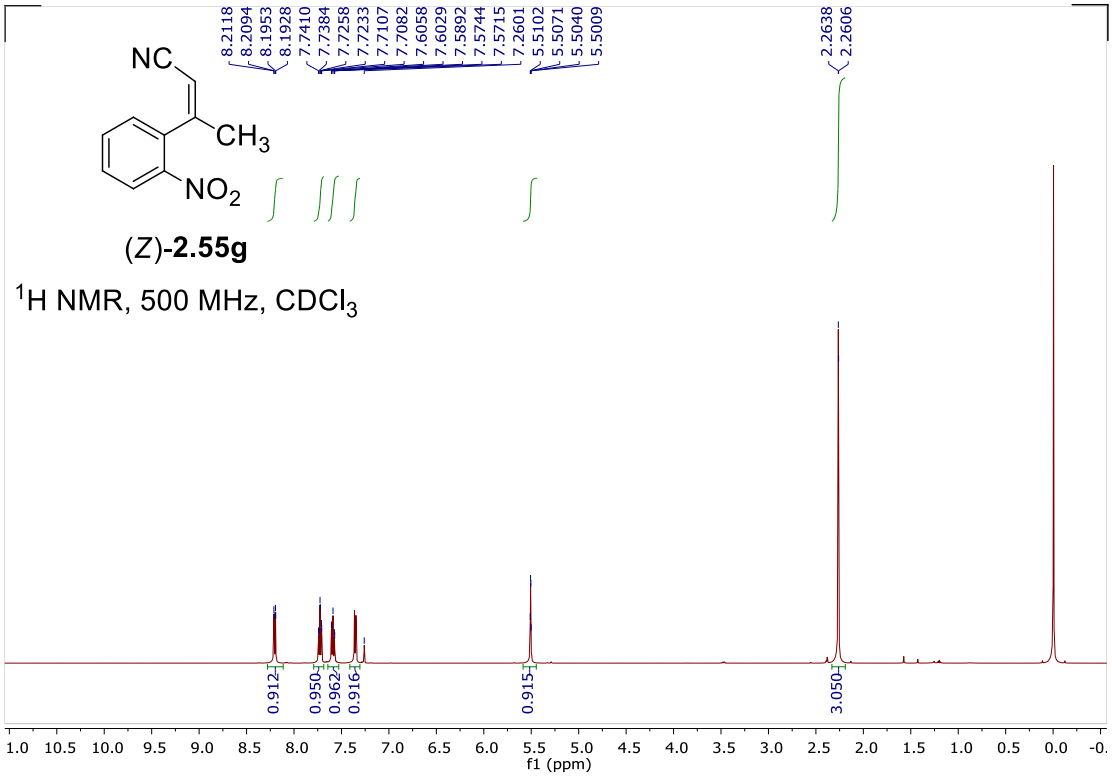
(*E*)-**2.55f**

^{1}H NMR, 300 MHz, $CDCl_3$



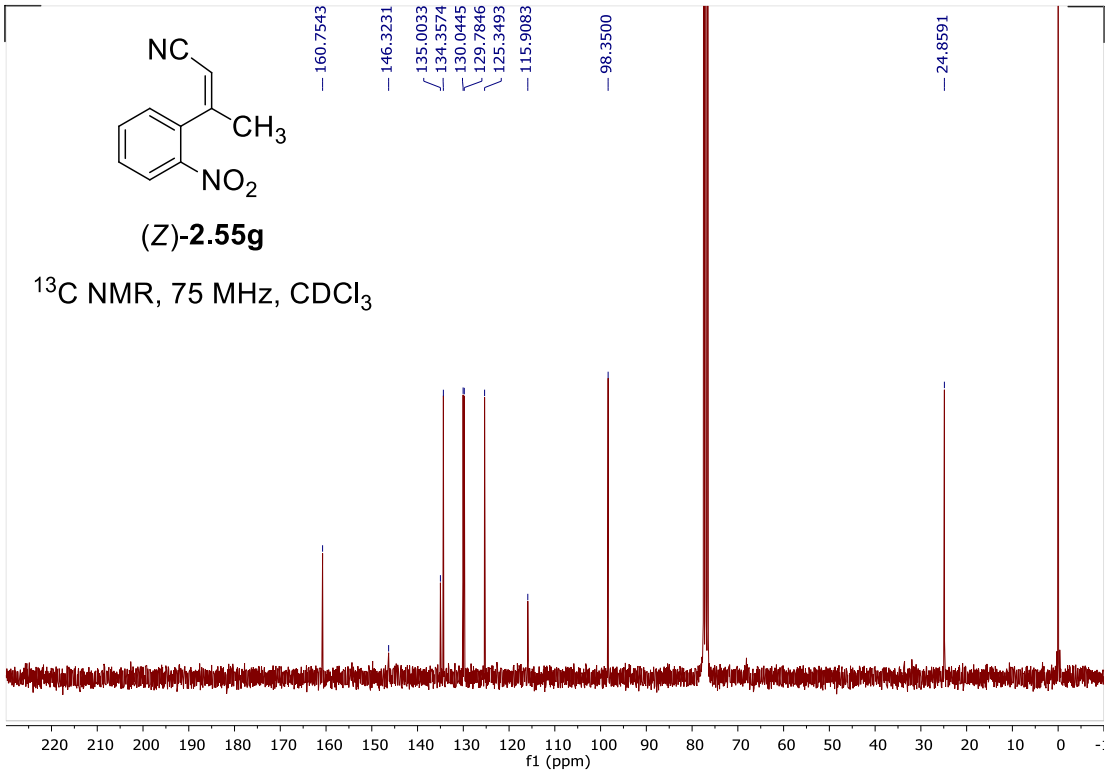
(*E*)-**2.55f**

^{13}C NMR, 75 MHz, $CDCl_3$



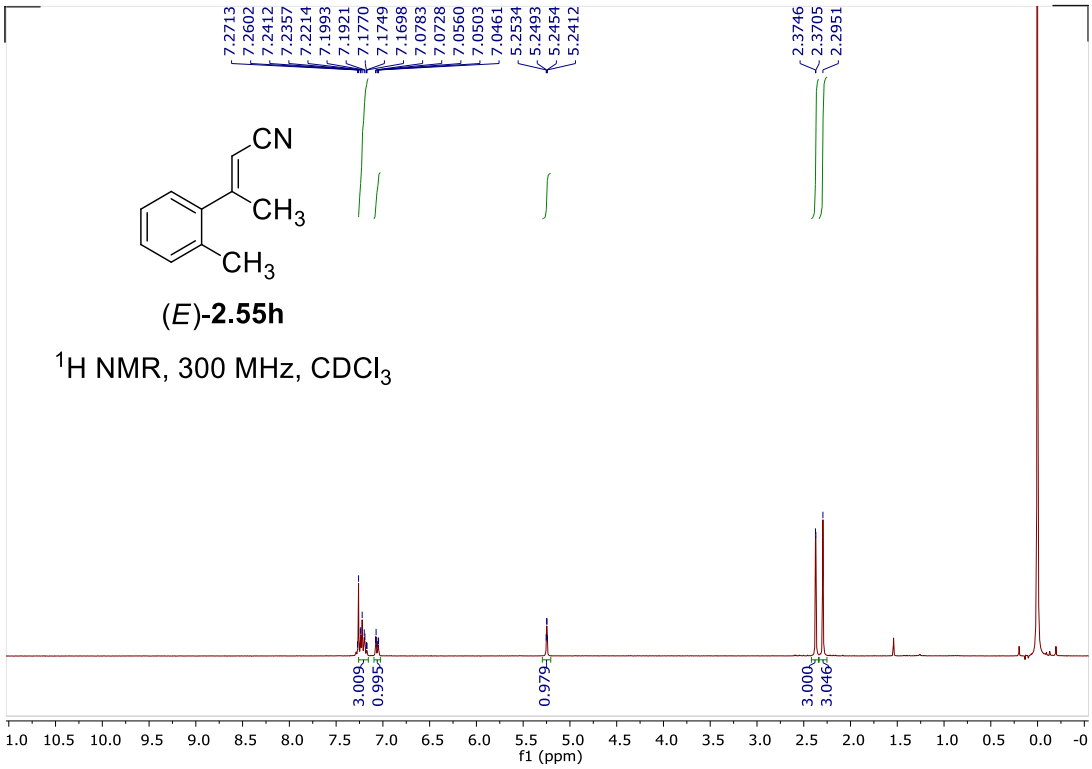
(*Z*)-**2.55g**

^{1}H NMR, 500 MHz, $CDCl_3$



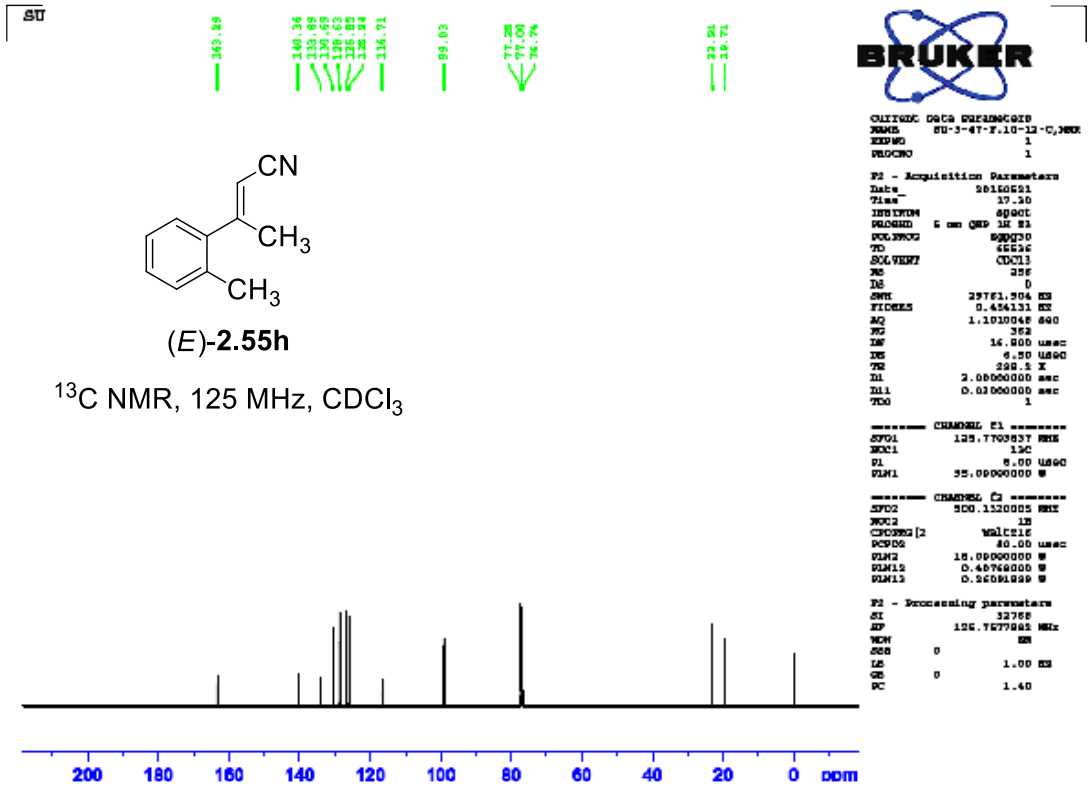
(*Z*)-**2.55g**

^{13}C NMR, 75 MHz, $CDCl_3$



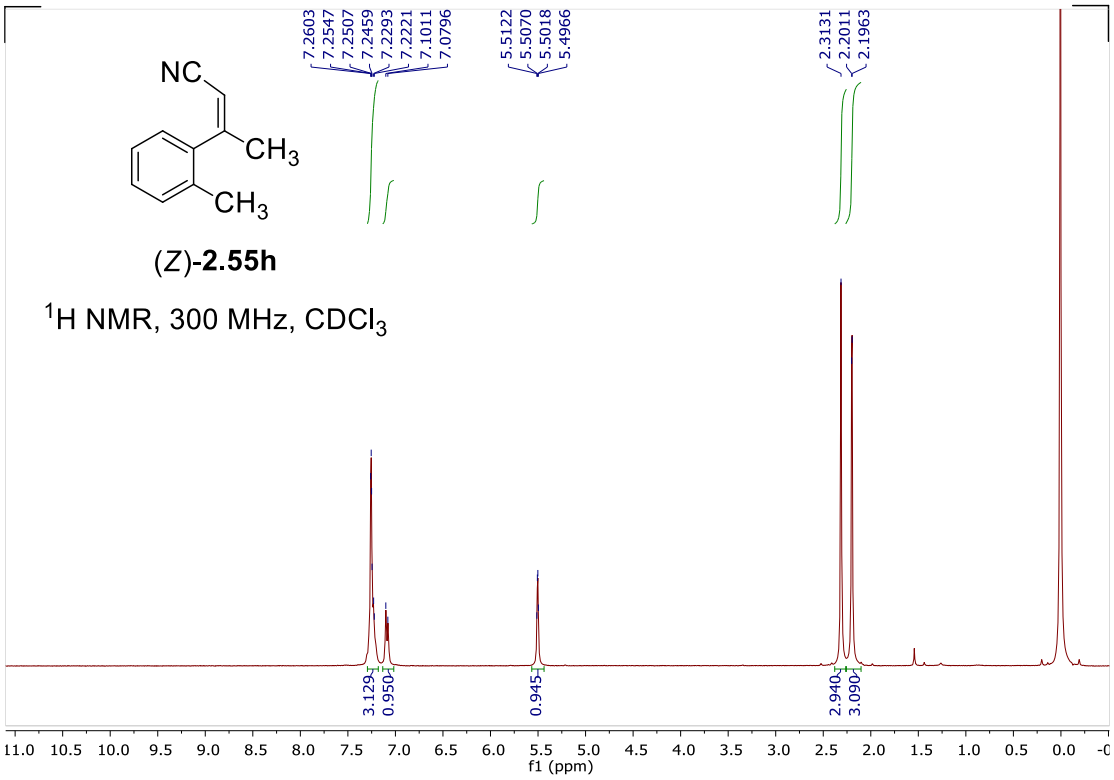
(*E*)-**2.55h**

^{1}H NMR, 300 MHz, $CDCl_3$



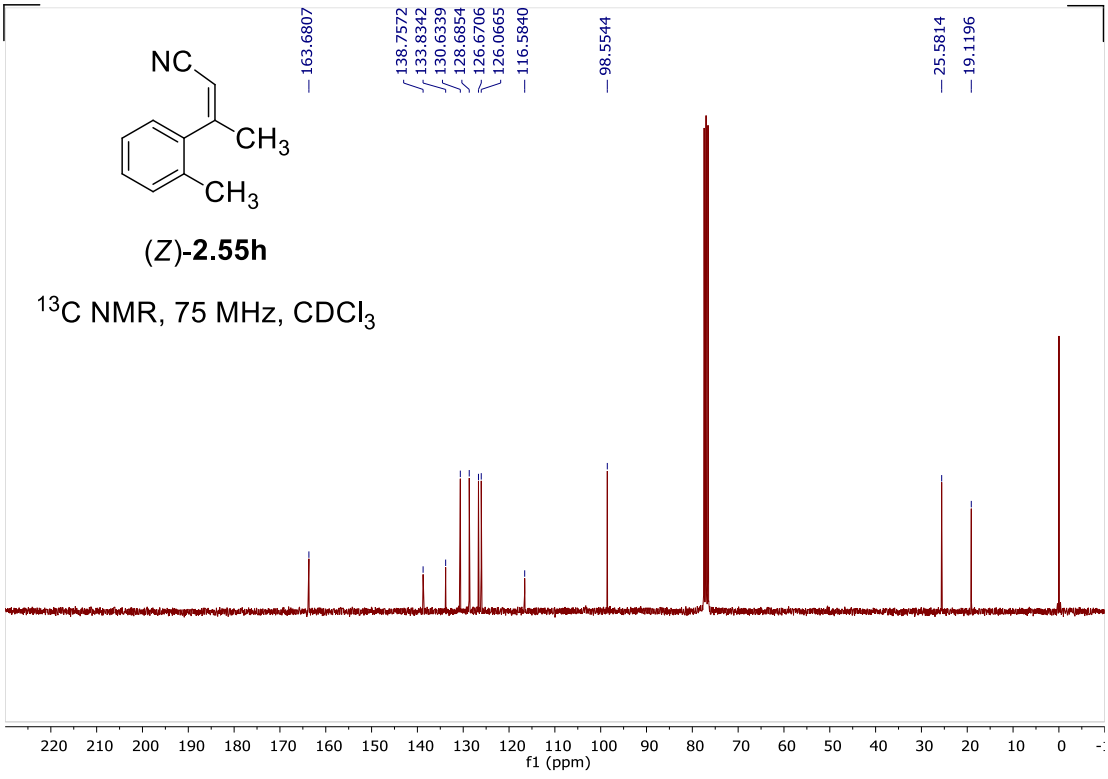
(*E*)-**2.55h**

^{13}C NMR, 125 MHz, $CDCl_3$



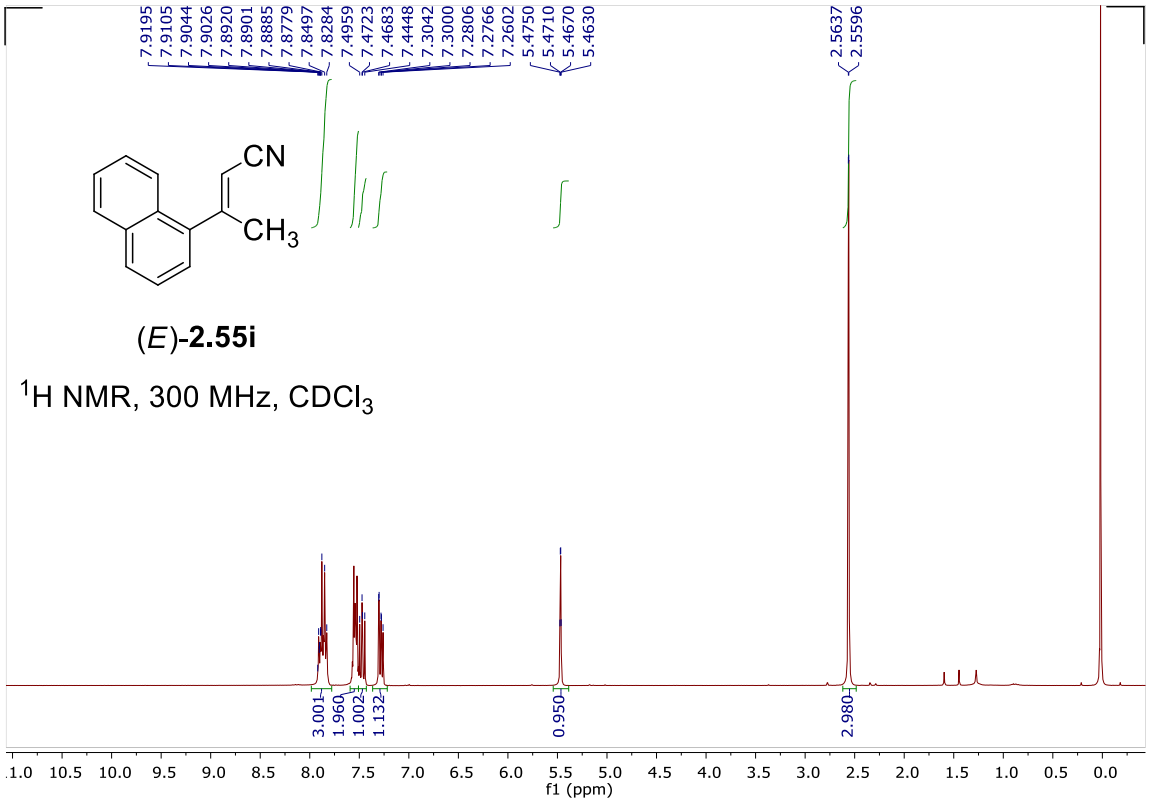
(*Z*)-**2.55h**

^{1}H NMR, 300 MHz, $CDCl_3$



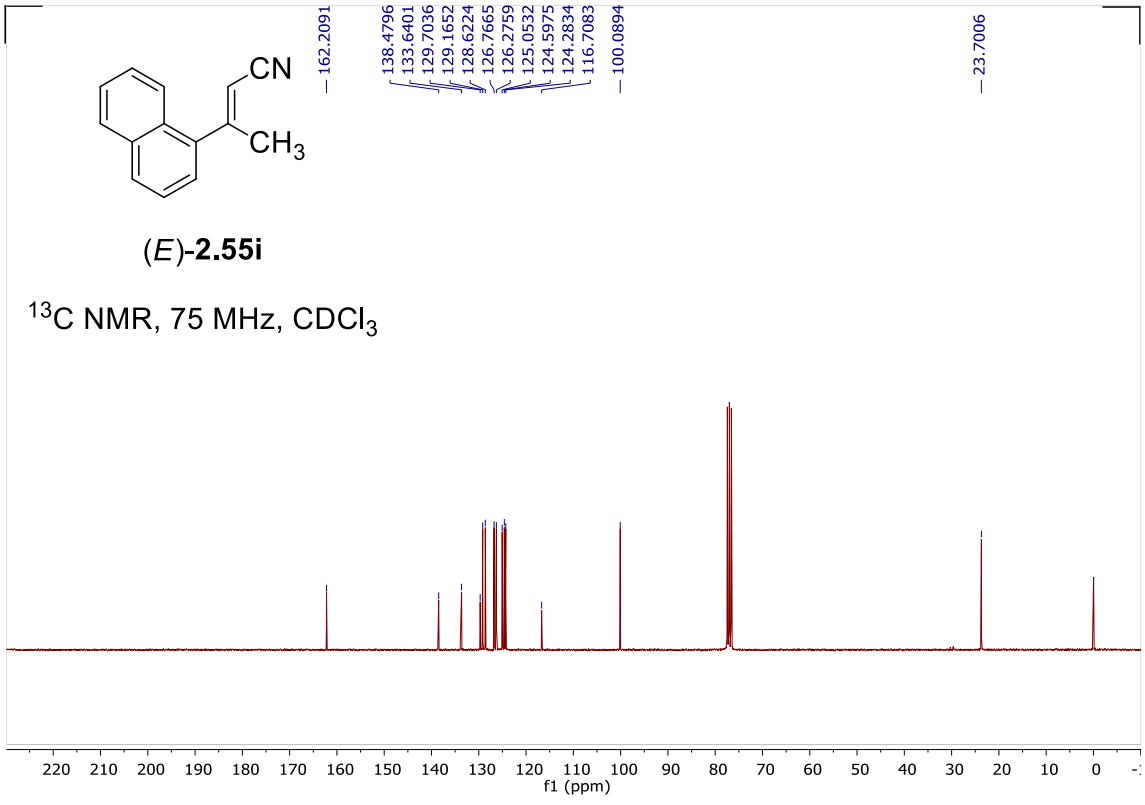
(*Z*)-**2.55h**

^{13}C NMR, 75 MHz, $CDCl_3$



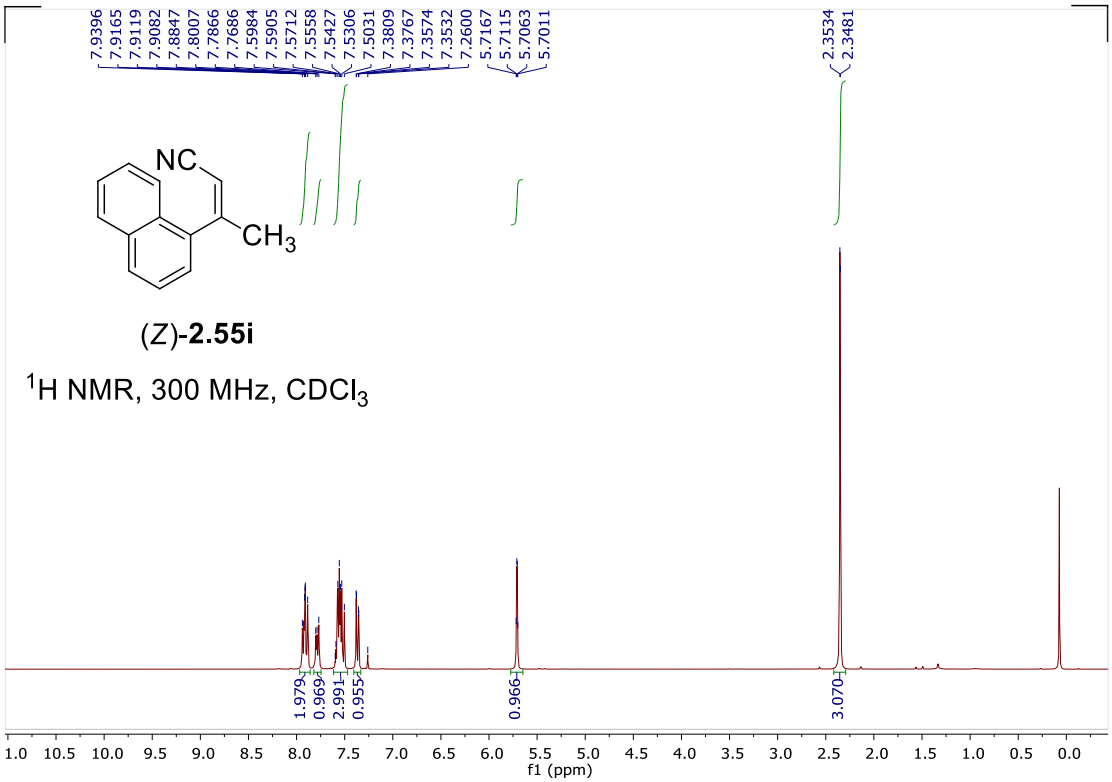
(*E*)-**2.55i**

^{1}H NMR, 300 MHz, $CDCl_3$



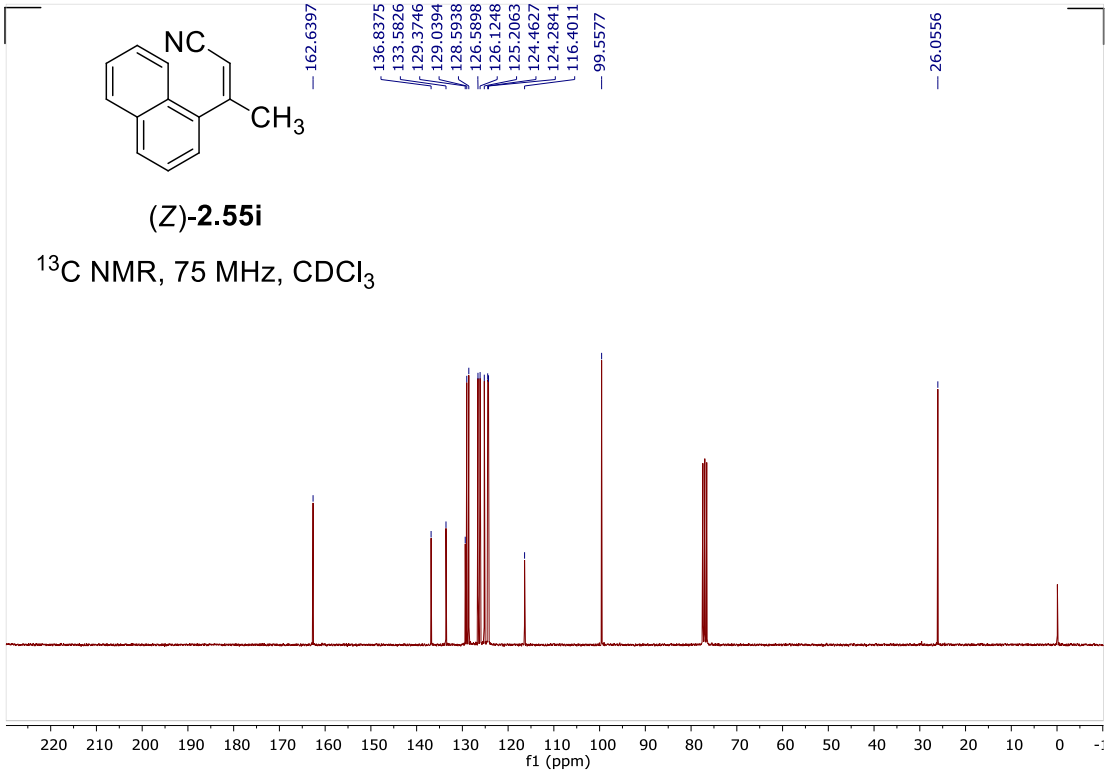
(*E*)-**2.55i**

^{13}C NMR, 75 MHz, $CDCl_3$



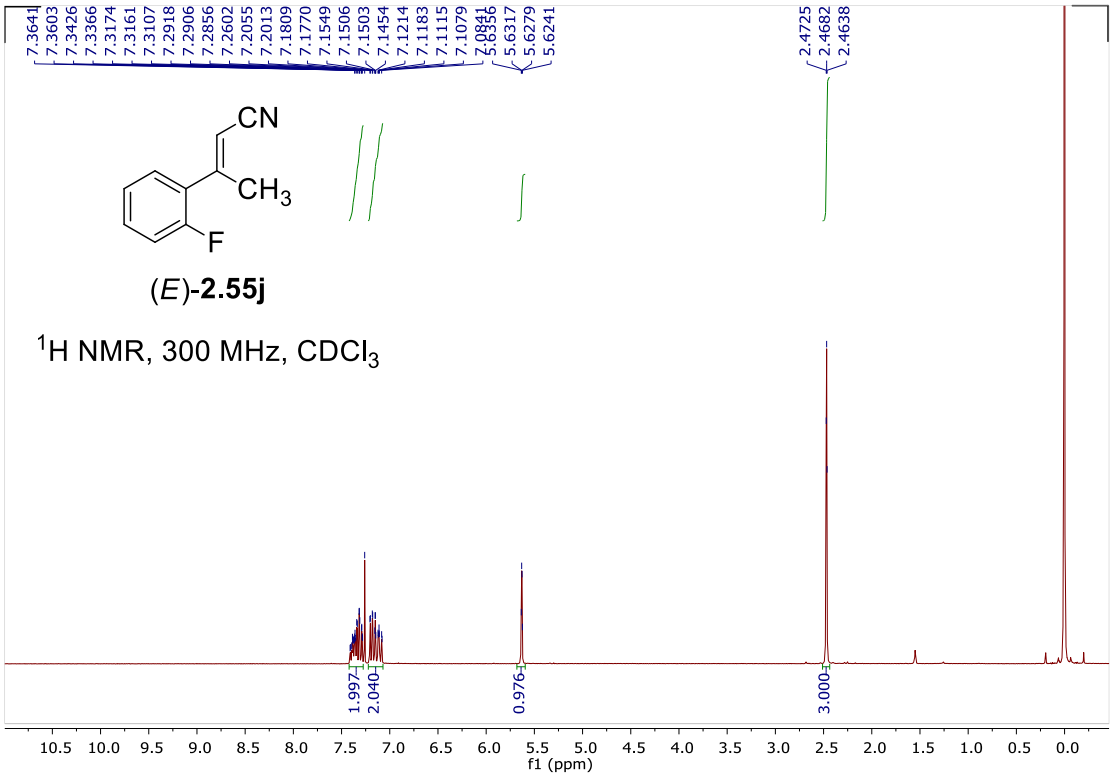
(*Z*)-**2.55i**

^{1}H NMR, 300 MHz, $CDCl_3$



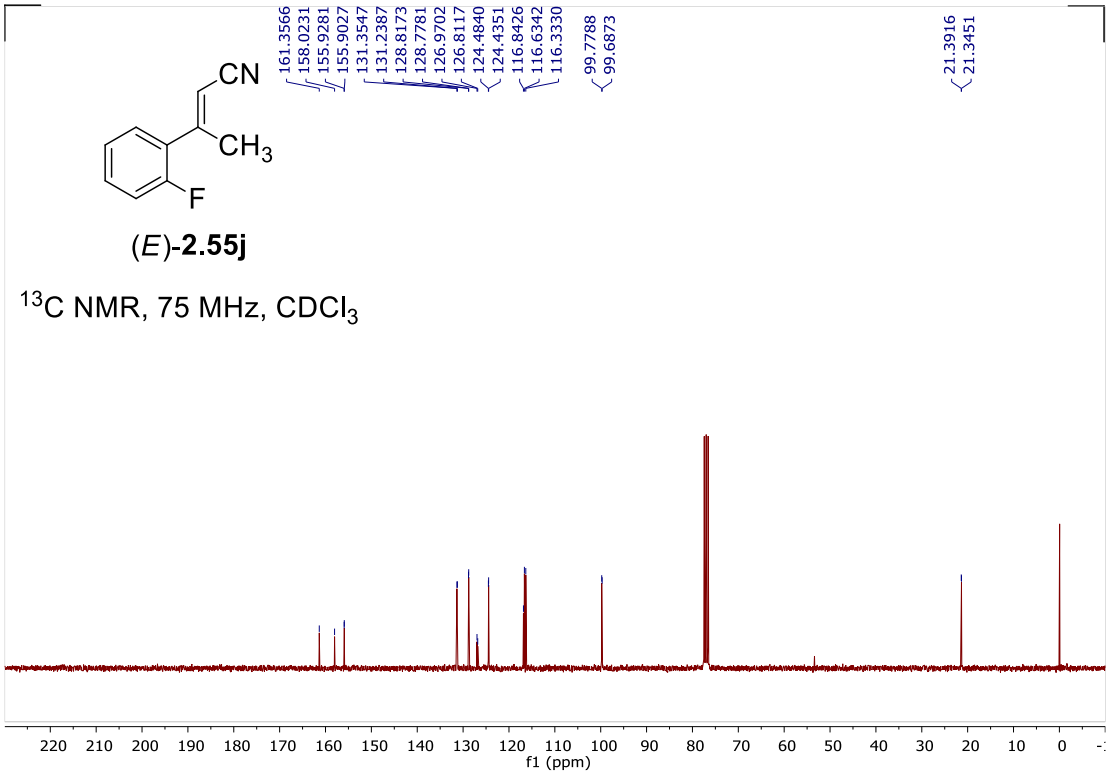
(*Z*)-**2.55i**

^{13}C NMR, 75 MHz, $CDCl_3$



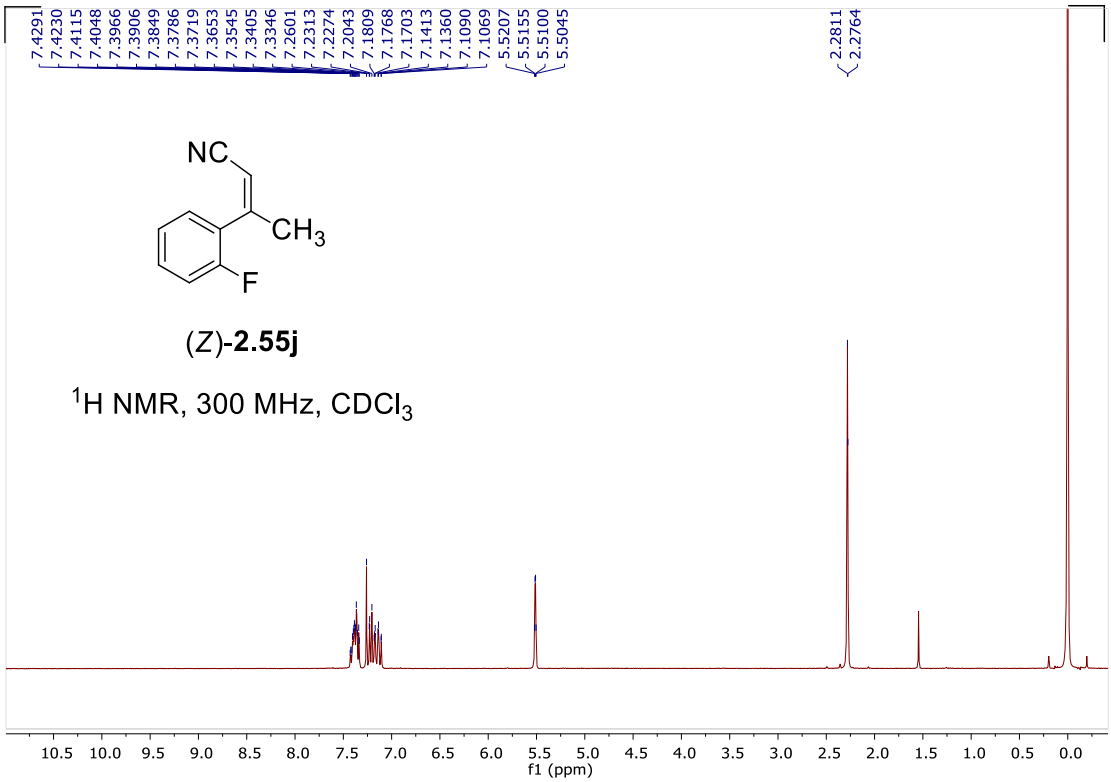
(*E*)-**2.55j**

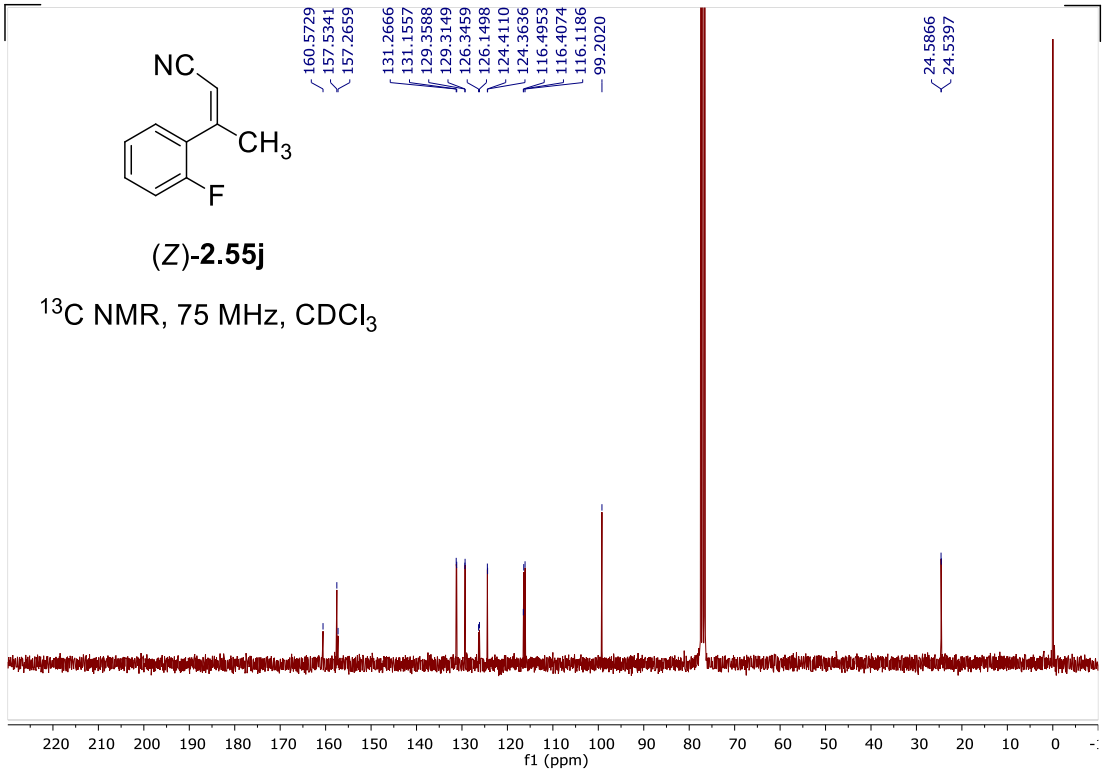
^{1}H NMR, 300 MHz, $CDCl_3$

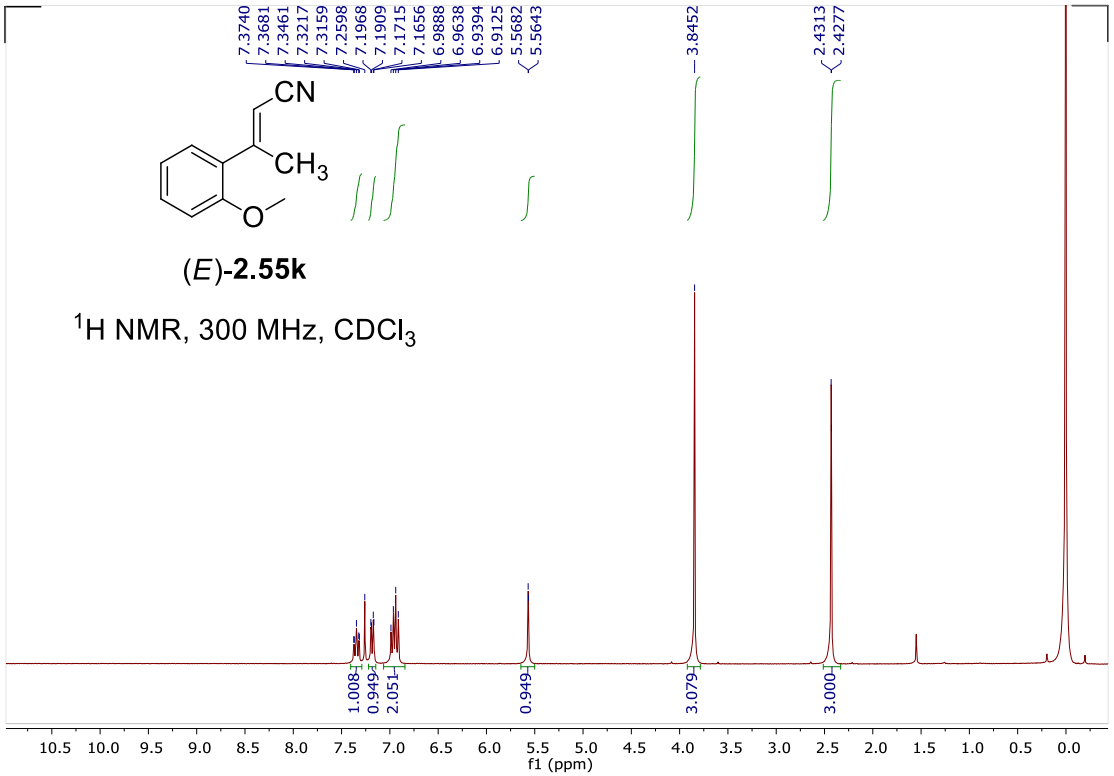


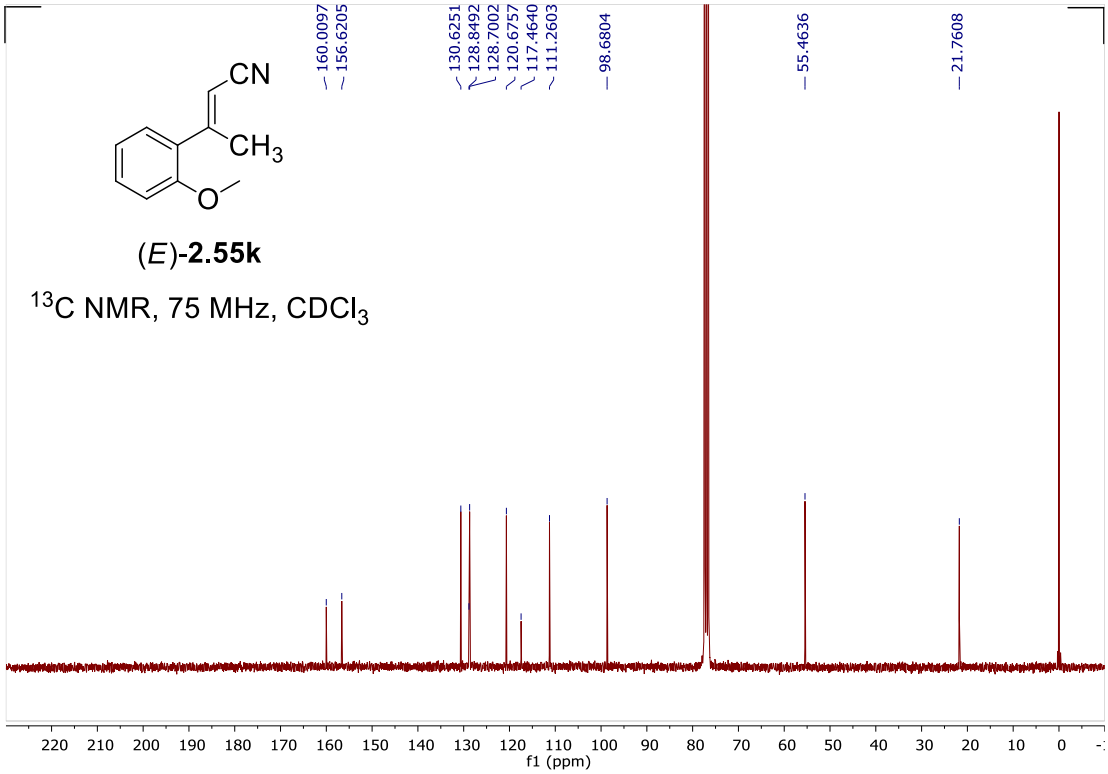
(*E*)-**2.55j**

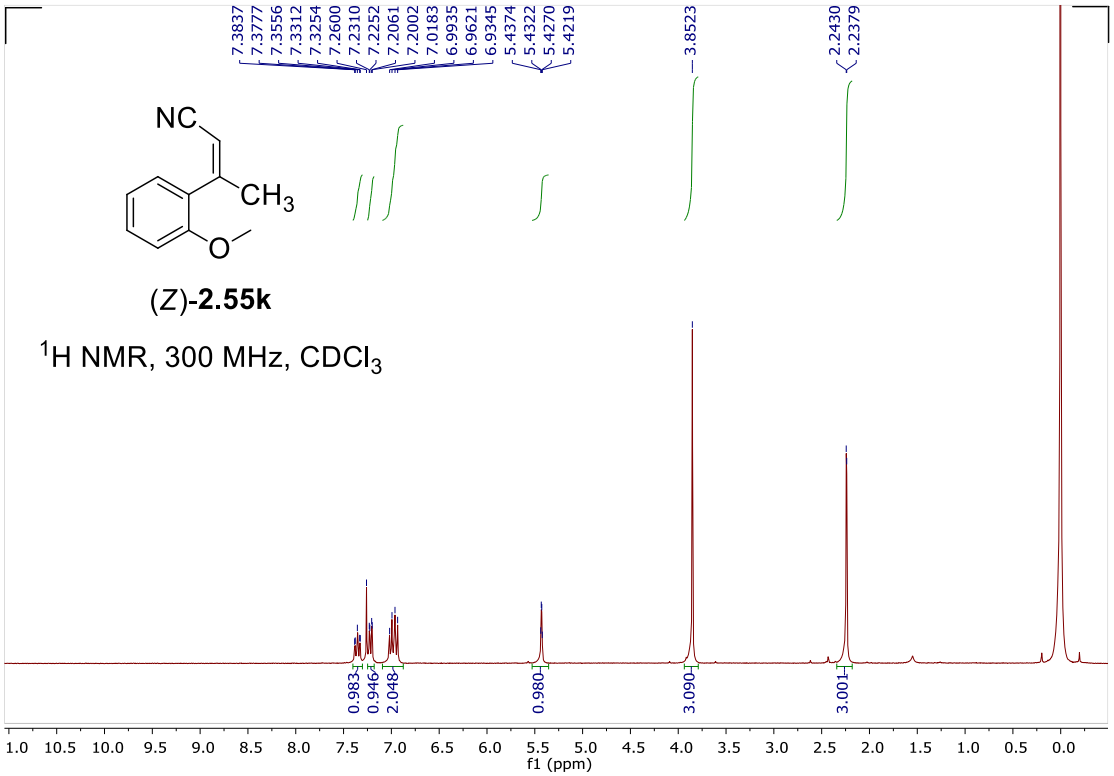
^{13}C NMR, 75 MHz, $CDCl_3$

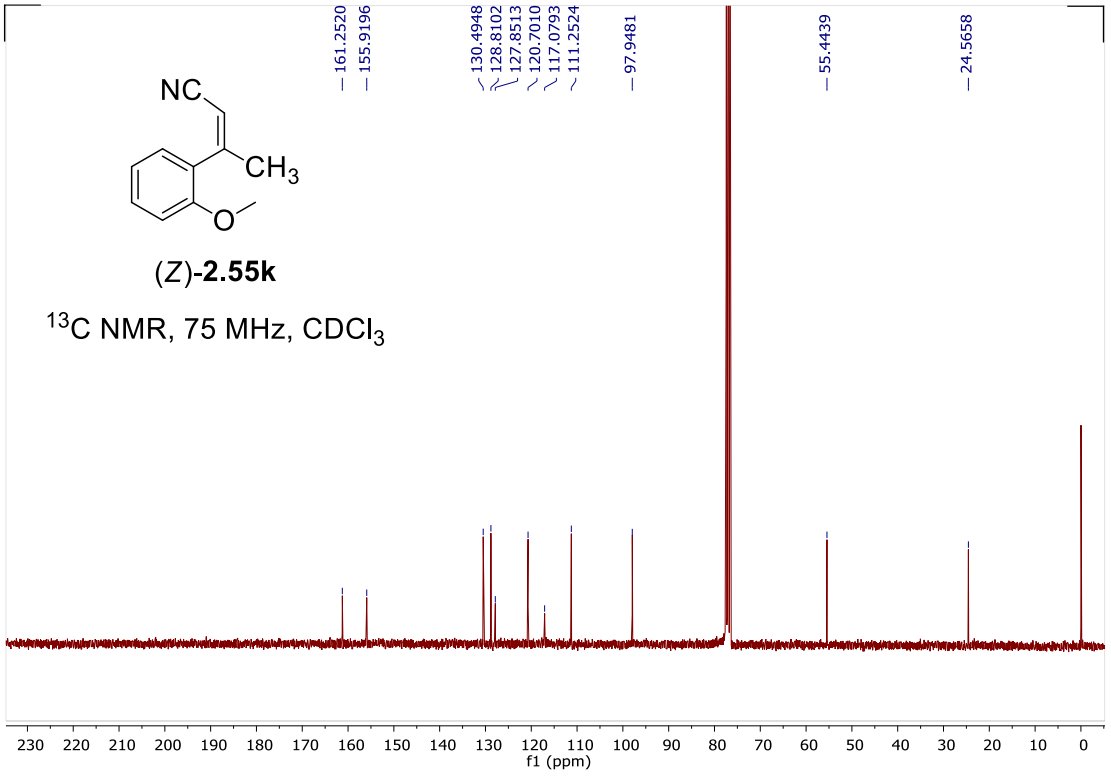

7.4291
7.4230
7.4115
7.4048
7.3966
7.3906
7.3849
7.3786
7.3719
7.3653
7.3545
7.3405
7.3346
7.2601
7.2313
7.2274
7.2043
7.1809
7.1768
7.1703
7.1413
7.1360
7.1090
7.1069
5.5207
5.5155
5.5100
5.5045
2.2811
2.2764
NC
CH3
F
(Z)-2.55j
1H NMR, 300 MHz, CDCl3
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

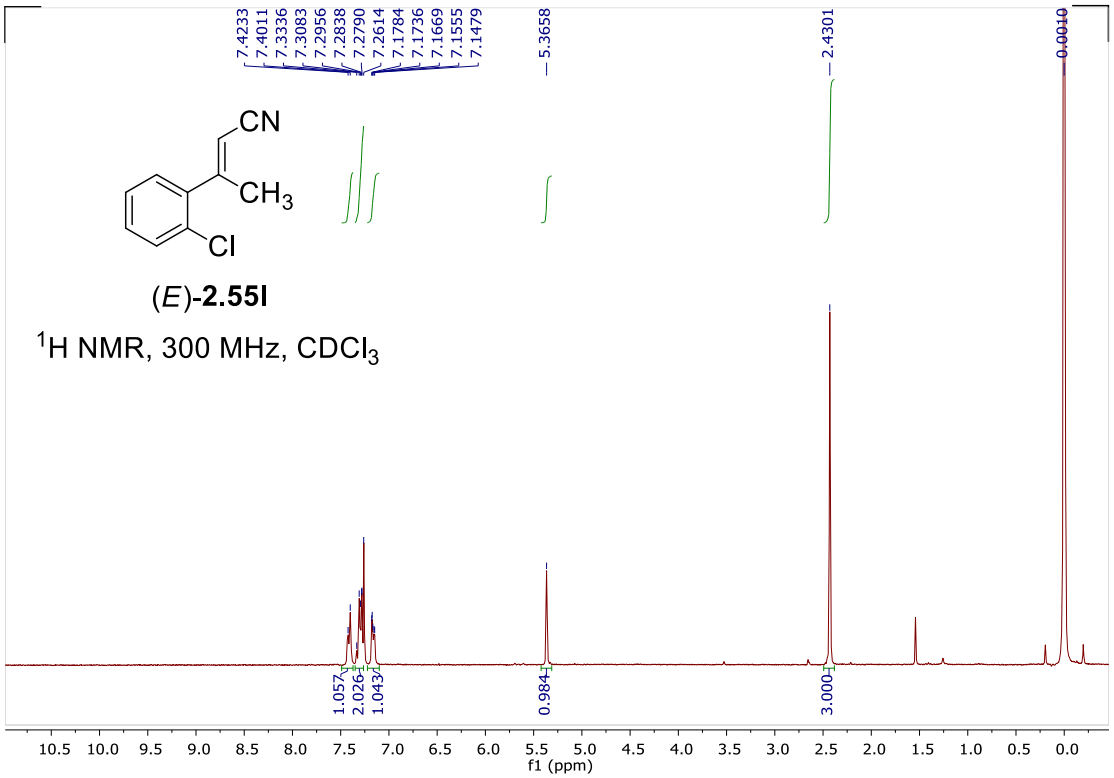

160.5729
157.5341
157.2659
131.2666
131.1557
129.3588
129.3149
126.3459
126.1498
124.4110
124.3636
116.4953
116.4074
116.1186
99.2020
24.5866
24.5397
NC
CH3
F
(Z)-2.55j
13C NMR, 75 MHz, CDCl3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.3740
7.3681
7.3461
7.3217
7.3159
7.2598
7.1968
7.1909
7.1715
7.1656
6.9888
6.9638
6.9394
6.9125
5.5682
5.5643
3.8452
2.4313
2.4277
CN
CH3
O
(E)-2.55k
1H NMR, 300 MHz, CDCl3
1.008
0.949
2.051
0.949
3.079
3.000
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


160.0097
156.6205
130.6251
128.8492
128.7002
120.6757
117.4640
111.2603
98.6804
55.4636
21.7608
CN
CH3
O
(E)-2.55k
13C NMR, 75 MHz, CDCl3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

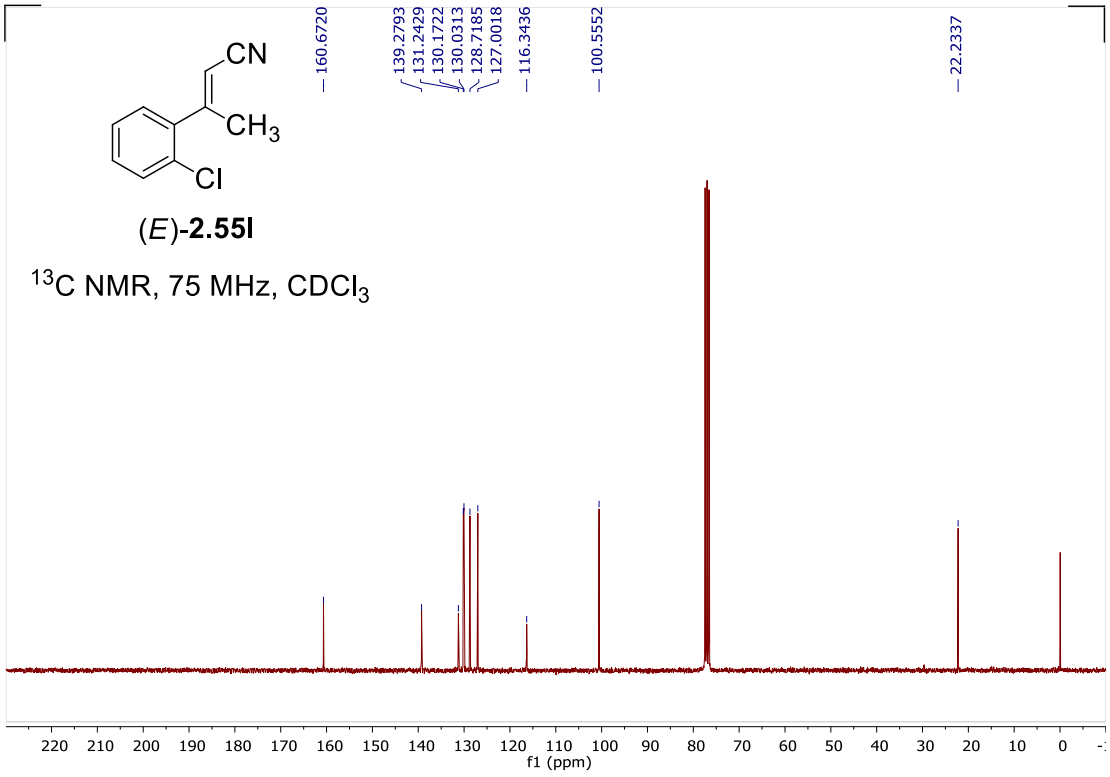

7.3837
7.3777
7.3556
7.3312
7.3254
7.2600
7.2310
7.2252
7.2061
7.2002
7.0183
6.9935
6.9621
6.9345
5.4374
5.4322
5.4270
5.4219
3.8523
2.2430
2.2379
NC
CH3
O
(Z)-2.55k
1H NMR, 300 MHz, CDCl3
0.983
0.946
2.048
0.980
3.090
3.001
f1 (ppm)


161.2520
155.9196
130.4948
128.8102
127.8513
120.7010
117.0793
111.2524
97.9481
55.4439
24.5658
NC
CH3
O
(Z)-2.55k
13C NMR, 75 MHz, CDCl3
f1 (ppm)



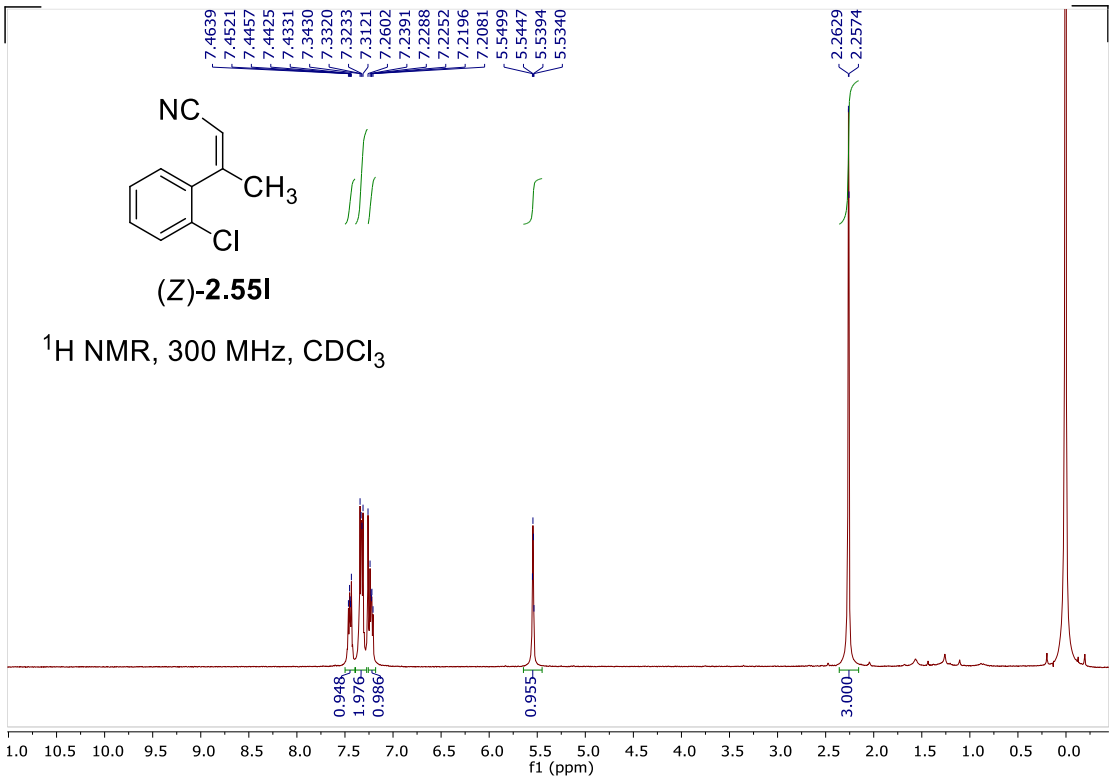
(*E*)-**2.55l**

^{1}H NMR, 300 MHz, $CDCl_3$



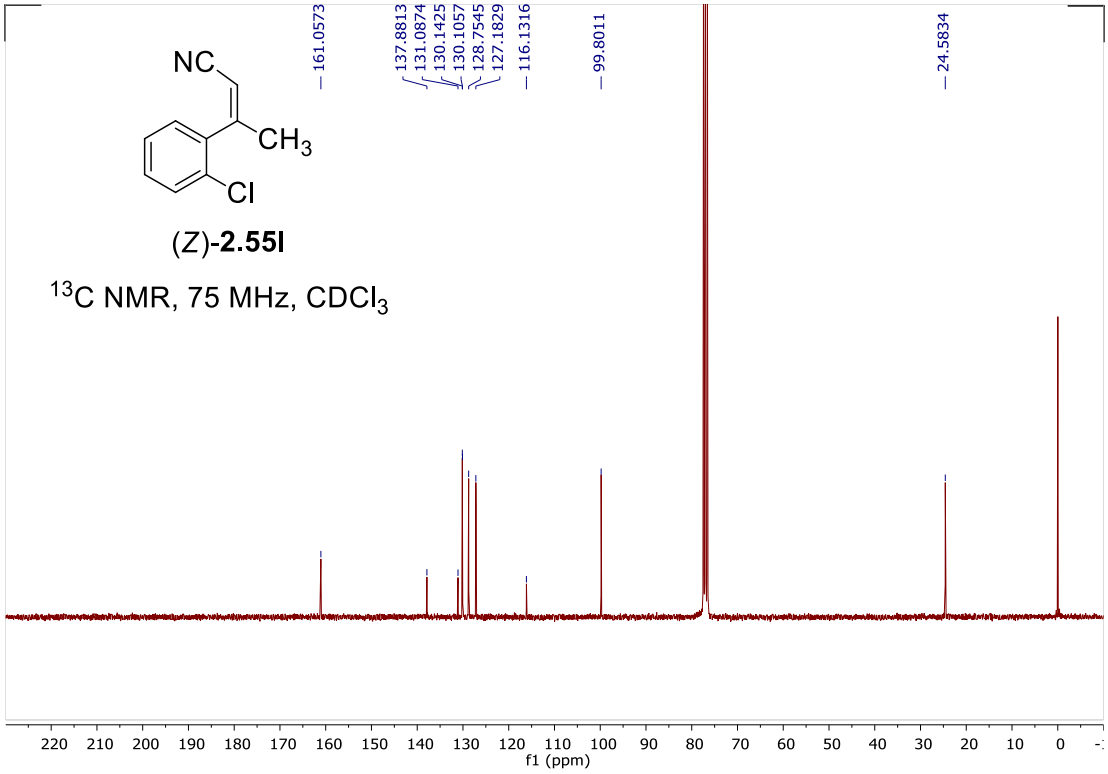
(*E*)-**2.55l**

^{13}C NMR, 75 MHz, $CDCl_3$



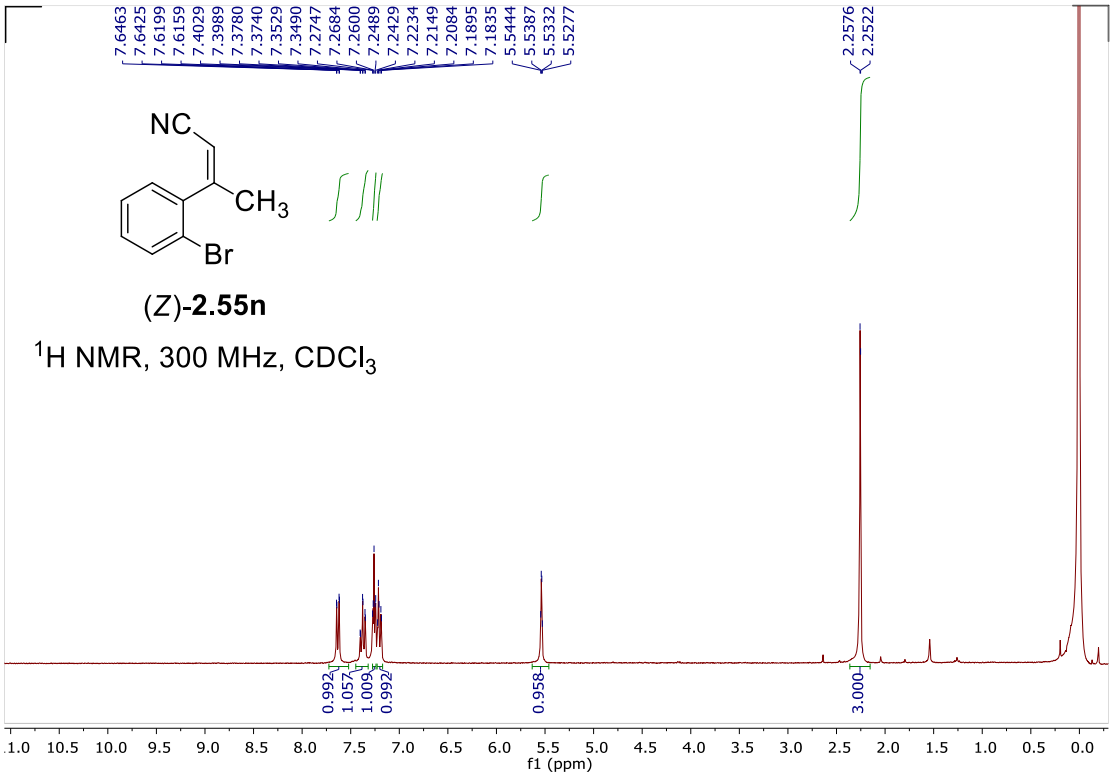
(*Z*)-**2.55l**

^{1}H NMR, 300 MHz, $CDCl_3$



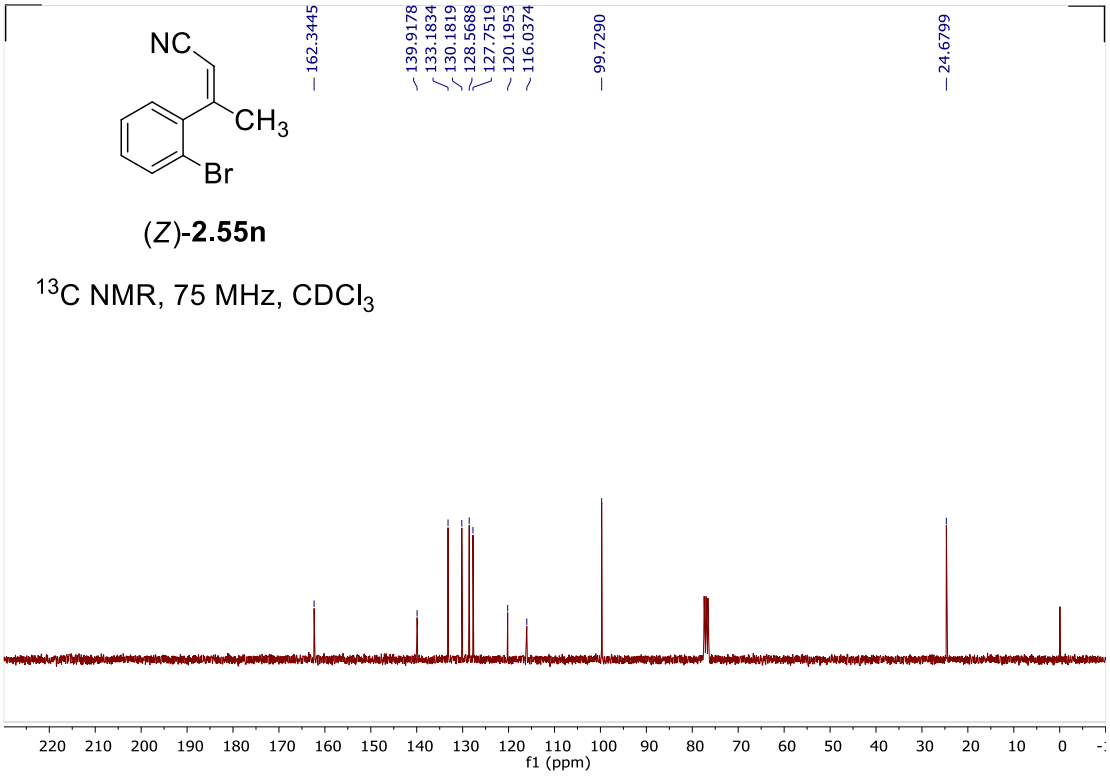
(*Z*)-**2.55l**

^{13}C NMR, 75 MHz, $CDCl_3$



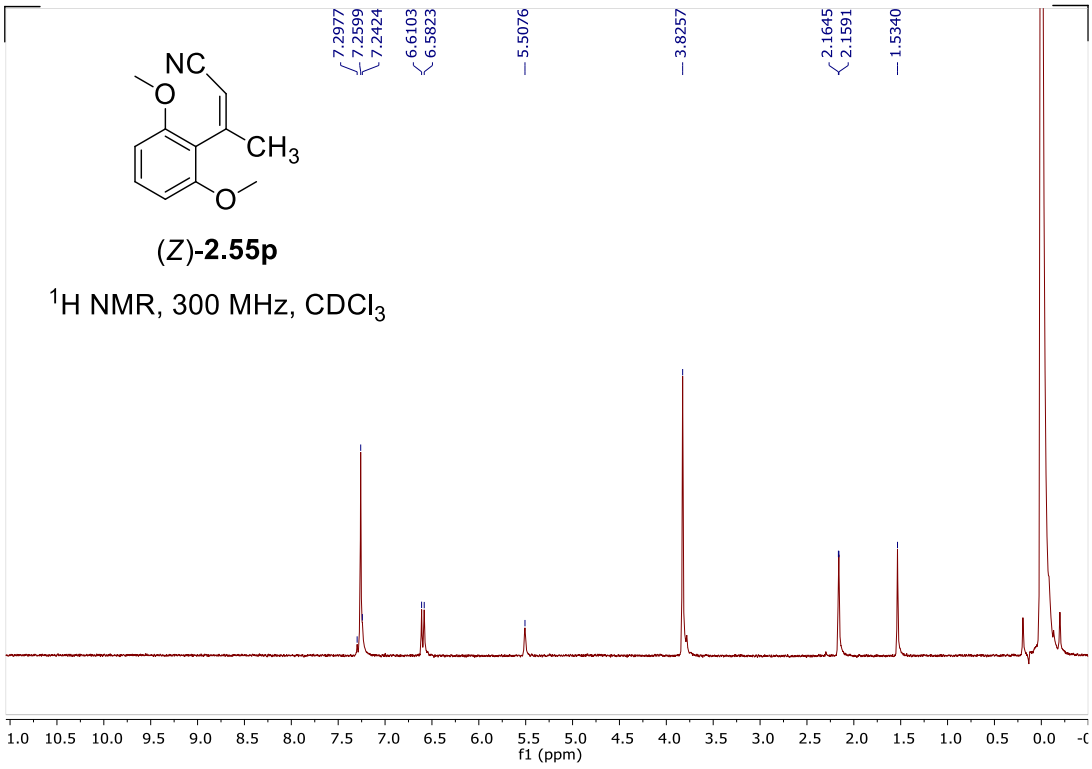
(*Z*)-**2.55n**

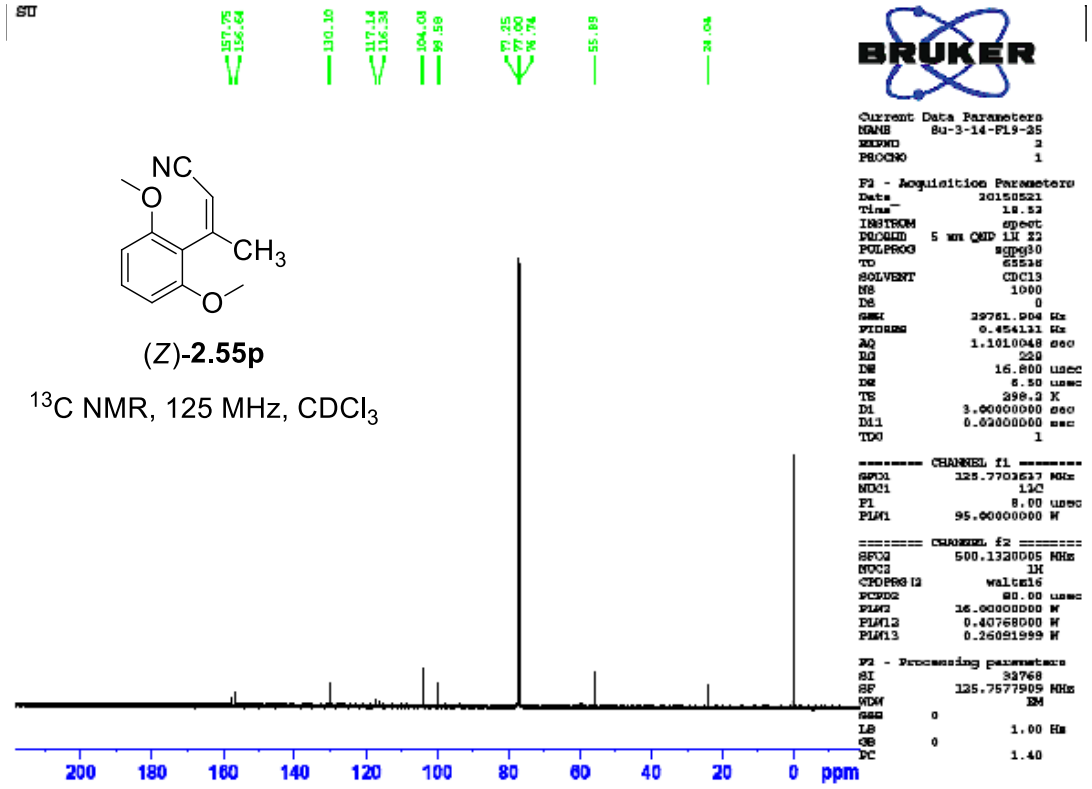
^{1}H NMR, 300 MHz, $CDCl_3$

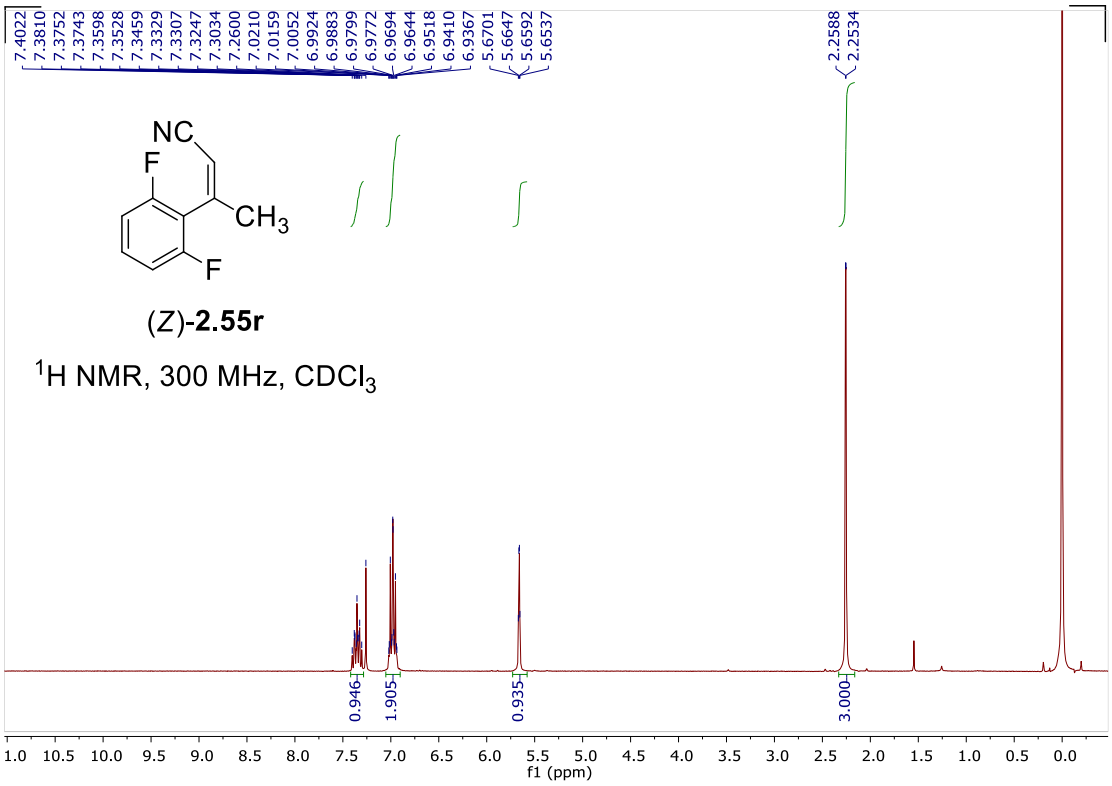


(*Z*)-**2.55n**

^{13}C NMR, 75 MHz, $CDCl_3$

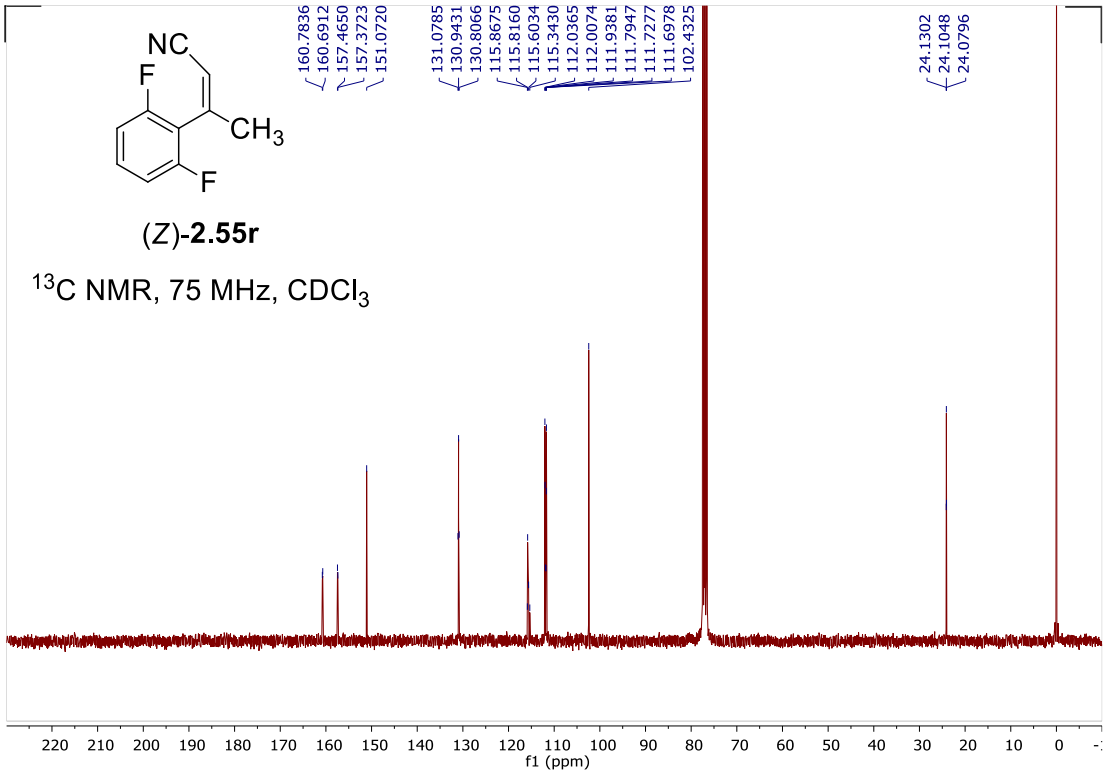

NC
O
CH3
O
(Z)-2.55p
1H NMR, 300 MHz, CDCl3
7.2977
7.2599
7.2424
6.6103
6.5823
5.5076
3.8257
2.1645
2.1591
1.5340
f1 (ppm)


NC
O
CH3
O
(Z)-2.55p
13C NMR, 125 MHz, CDCl3
157.75
156.84
130.10
117.14
116.34
104.08
99.59
77.25
77.00
76.74
55.89
24.04
BRUKER
ppm



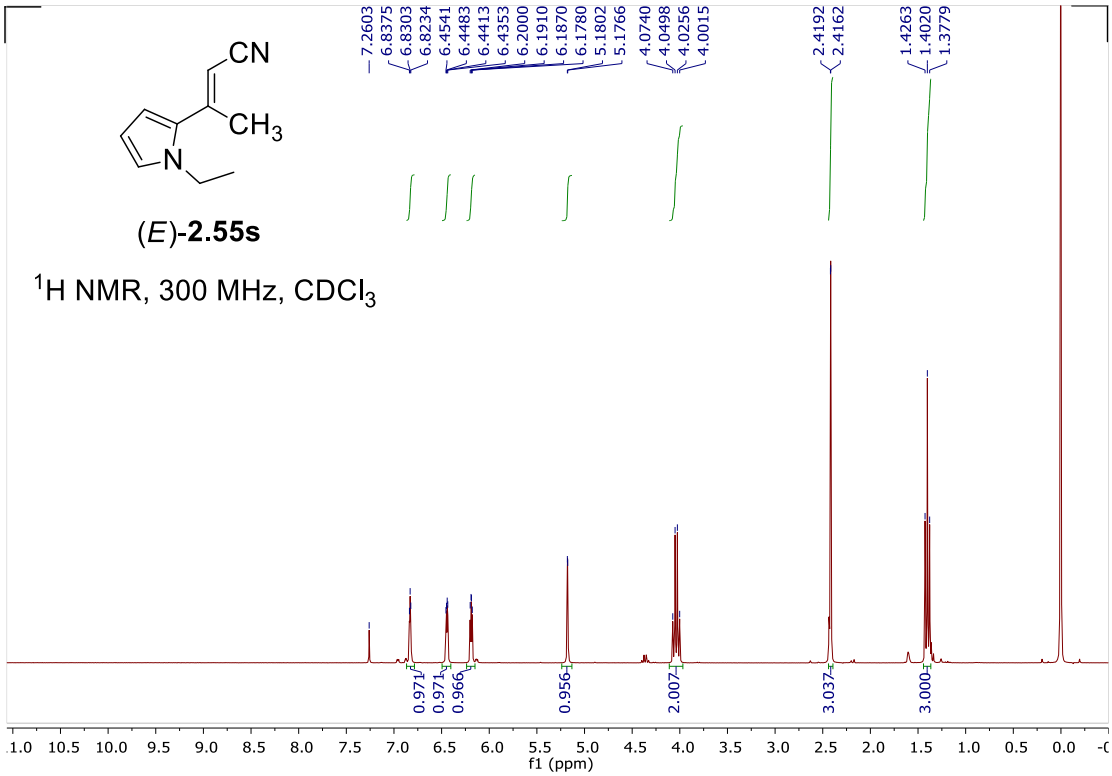
(*Z*)-**2.55r**

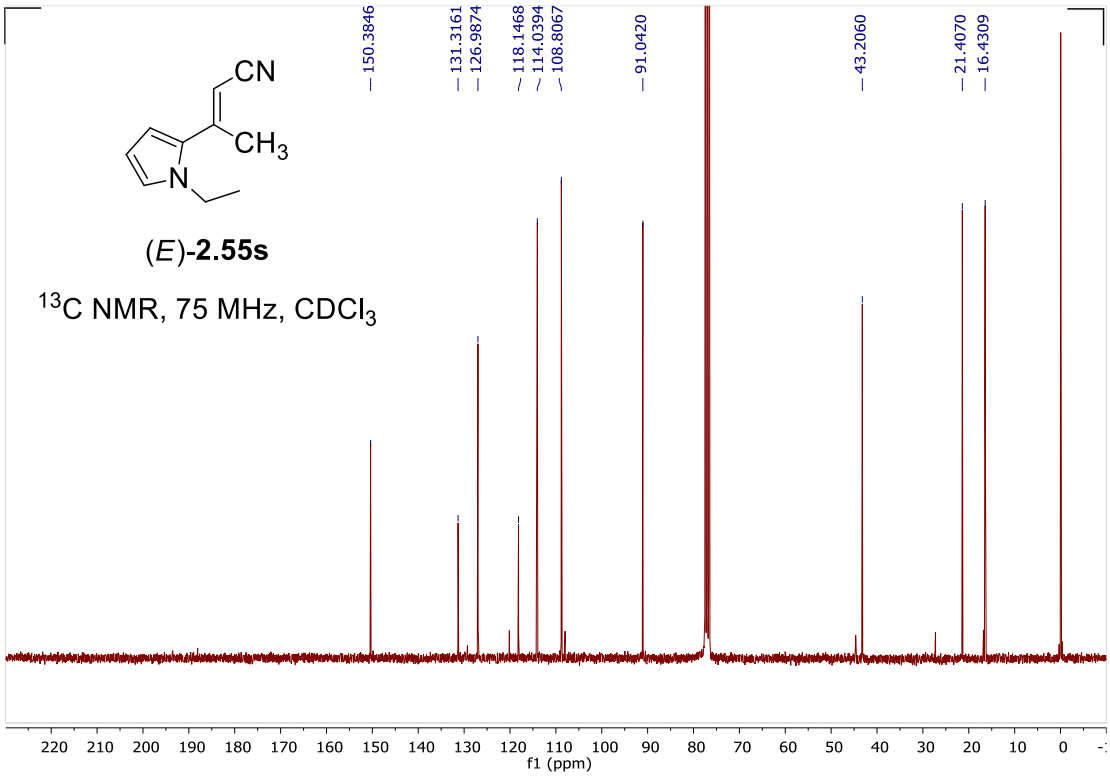
^{1}H NMR, 300 MHz, $CDCl_3$

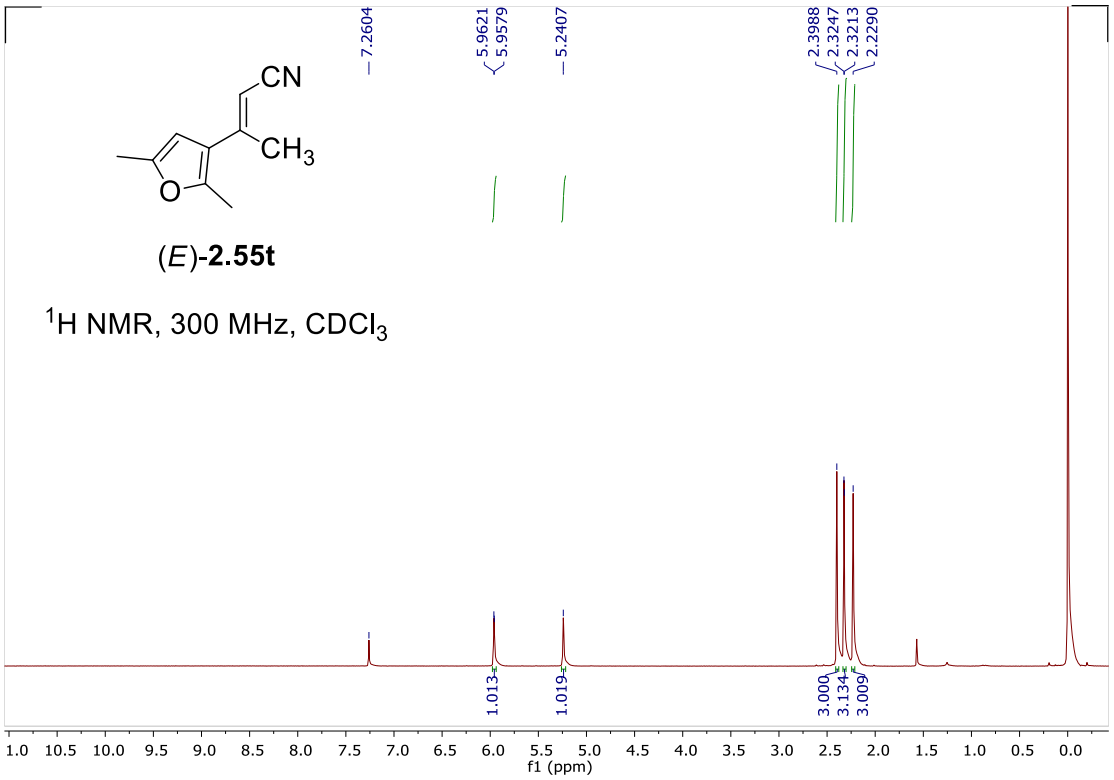


(*Z*)-**2.55r**

^{13}C NMR, 75 MHz, $CDCl_3$

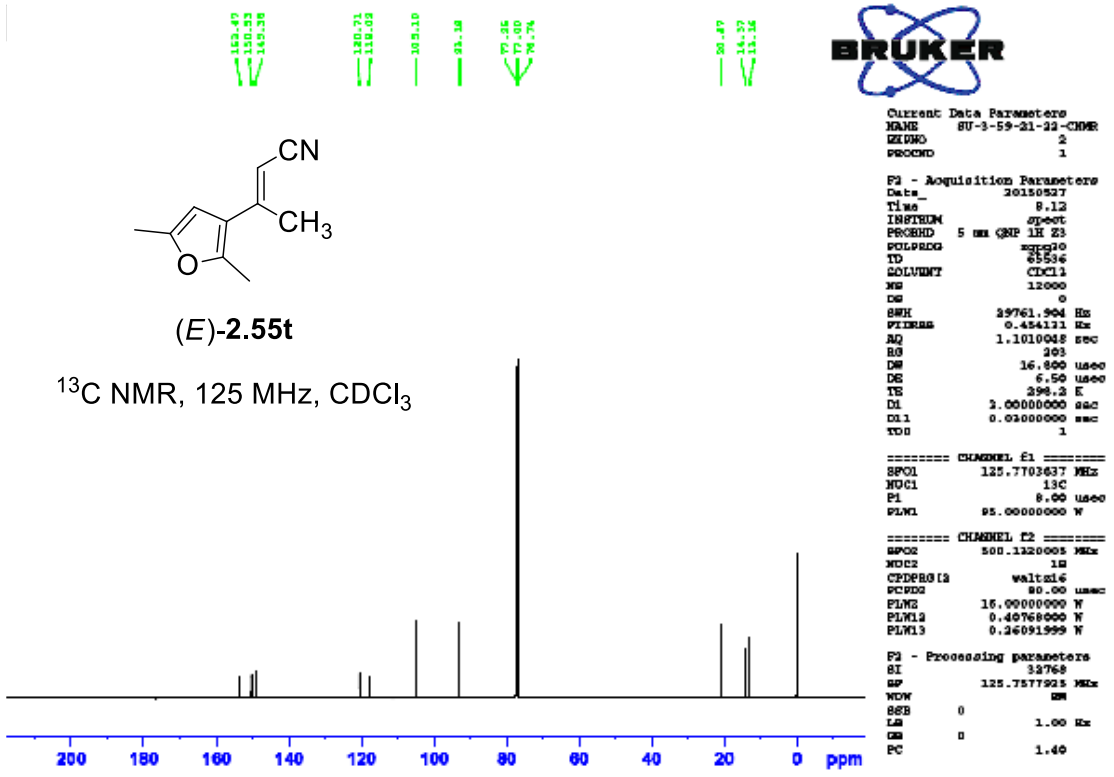

CN
CH3
N
(E)-2.55s
1H NMR, 300 MHz, CDCl3
7.2603
6.8375
6.8303
6.8234
6.4541
6.4483
6.4413
6.4353
6.2000
6.1910
6.1870
6.1780
5.1802
5.1766
4.0740
4.0498
4.0256
4.0015
2.4192
2.4162
1.4263
1.4020
1.3779
0.971
0.971
0.966
0.956
2.007
3.037
3.000
f1 (ppm)


CN
CH3
N
(E)-2.55s
13C NMR, 75 MHz, CDCl3
150.3846
131.3161
126.9874
118.1468
114.0394
108.8067
91.0420
43.2060
21.4070
16.4309
f1 (ppm)



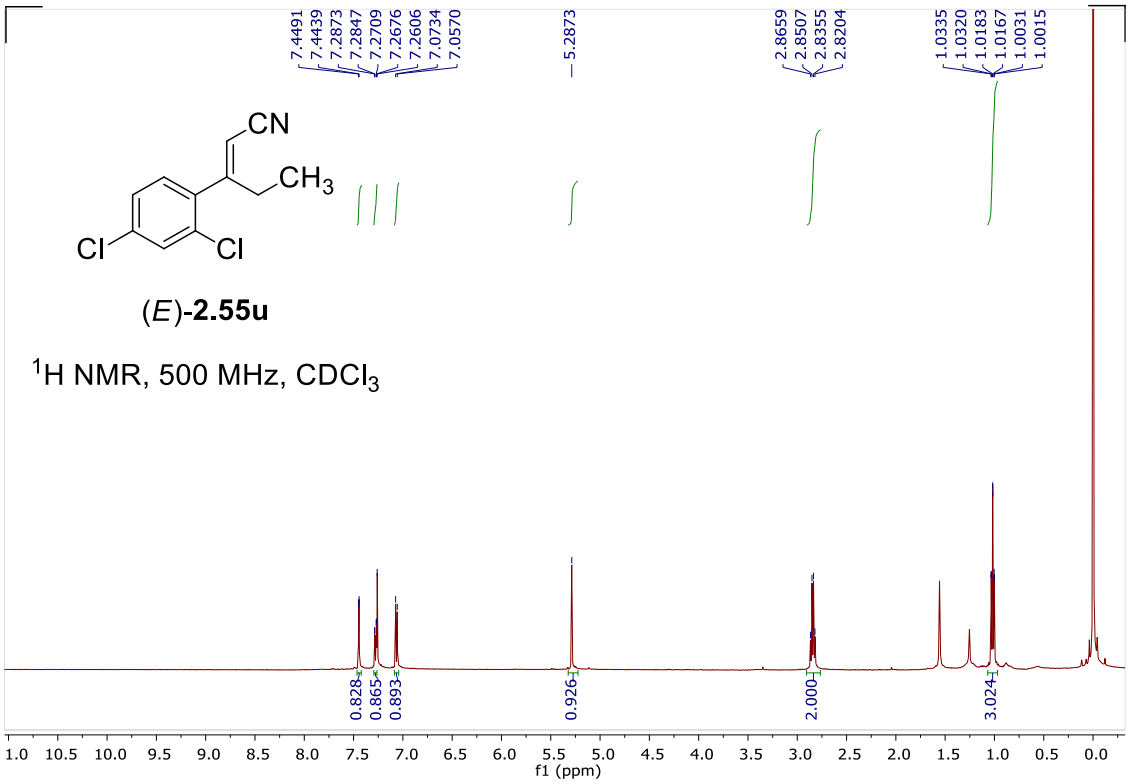
(*E*)-**2.55t**

^{1}H NMR, 300 MHz, $CDCl_3$



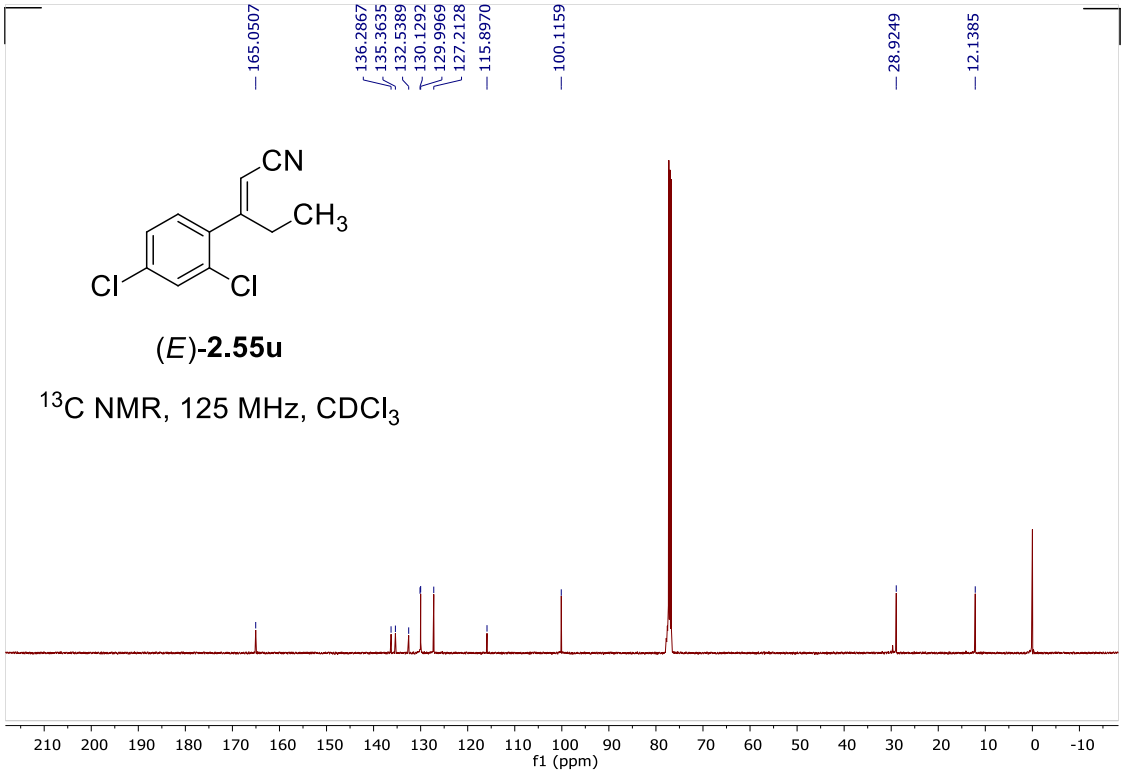
(*E*)-**2.55t**

^{13}C NMR, 125 MHz, $CDCl_3$



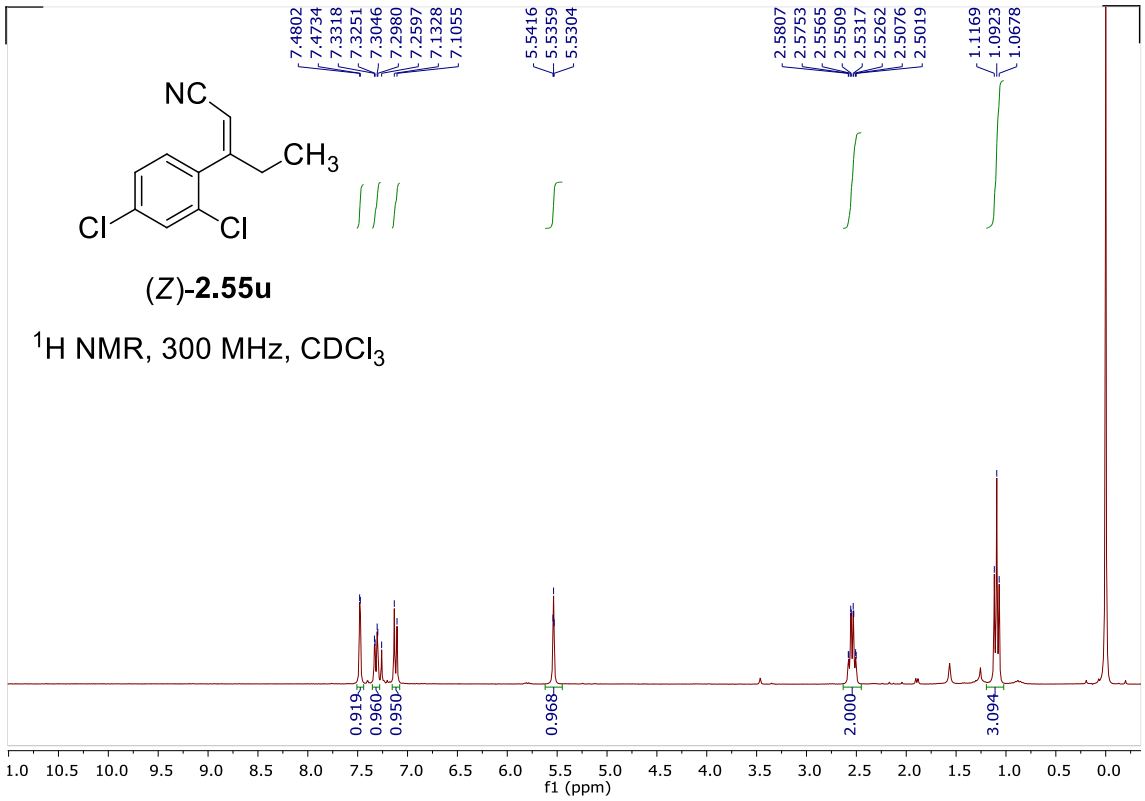
(*E*)-**2.55u**

^{1}H NMR, 500 MHz, $CDCl_3$



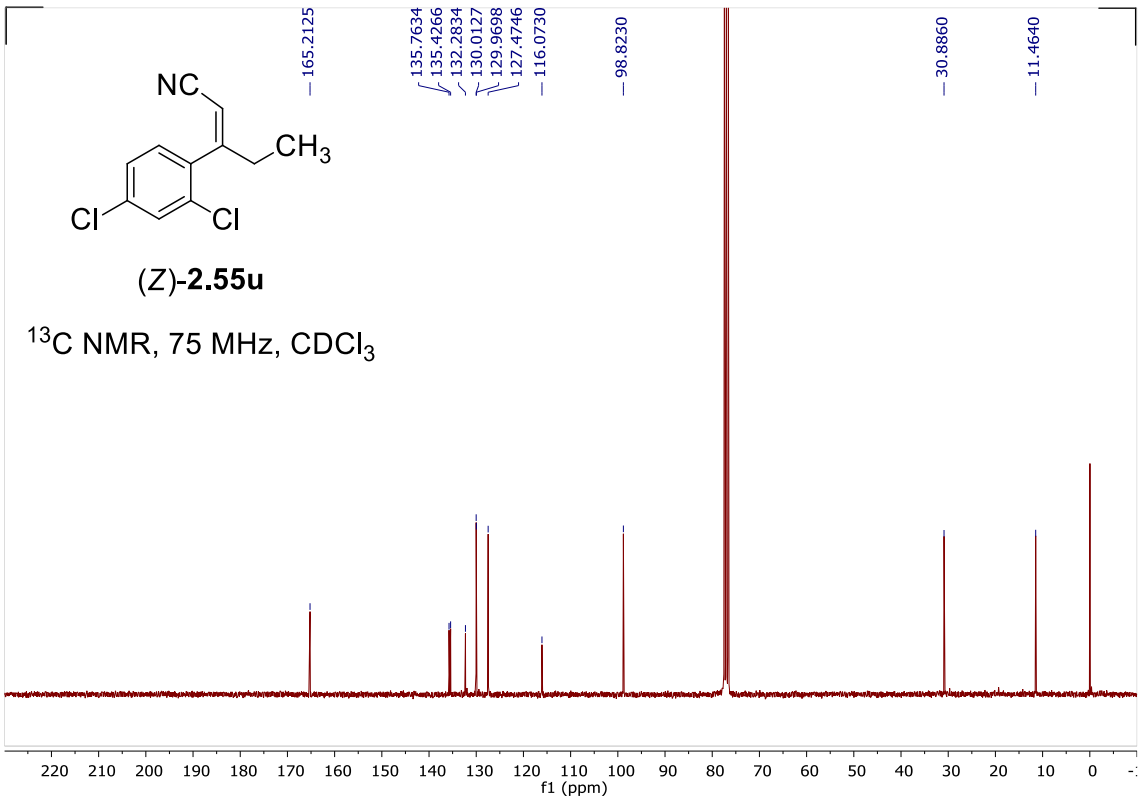
(*E*)-**2.55u**

^{13}C NMR, 125 MHz, $CDCl_3$



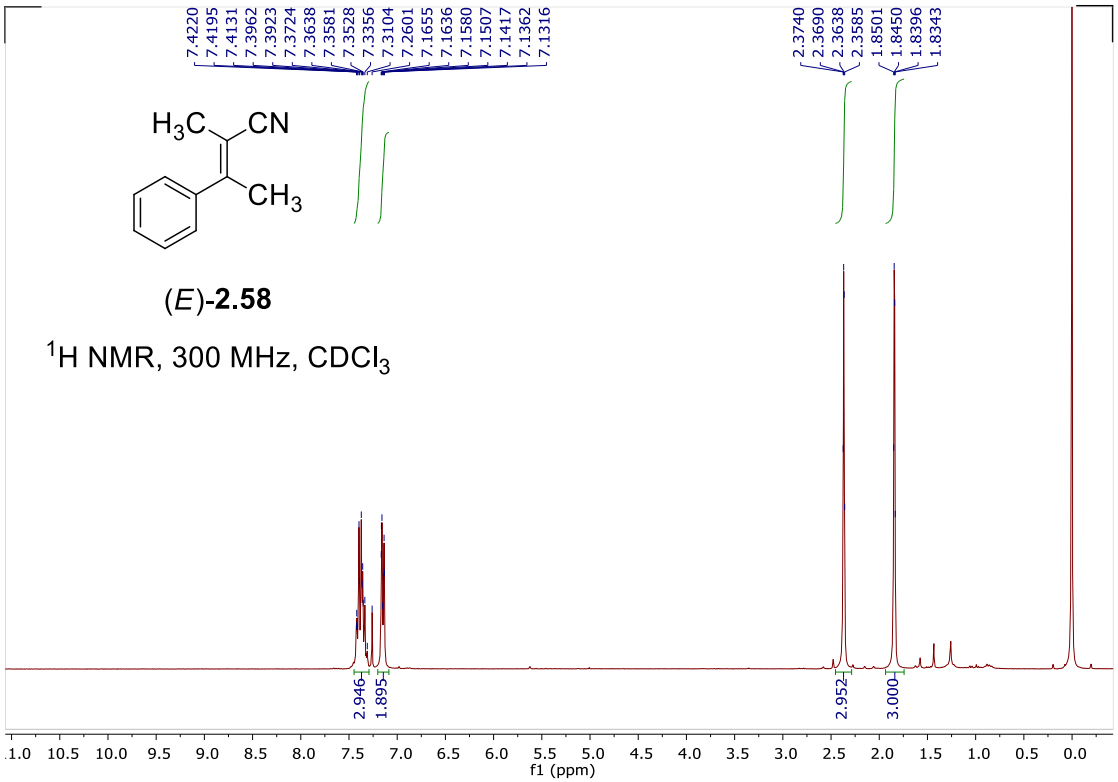
(*Z*)-**2.55u**

^{1}H NMR, 300 MHz, $CDCl_3$



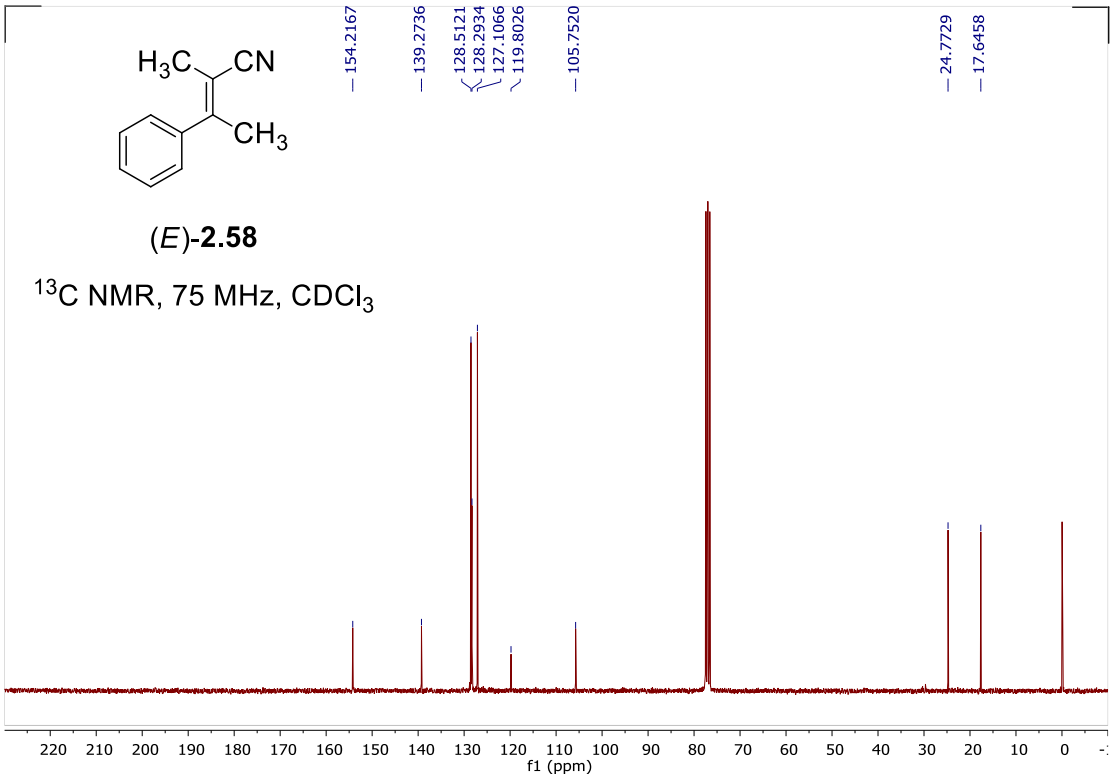
(*Z*)-**2.55u**

^{13}C NMR, 75 MHz, $CDCl_3$



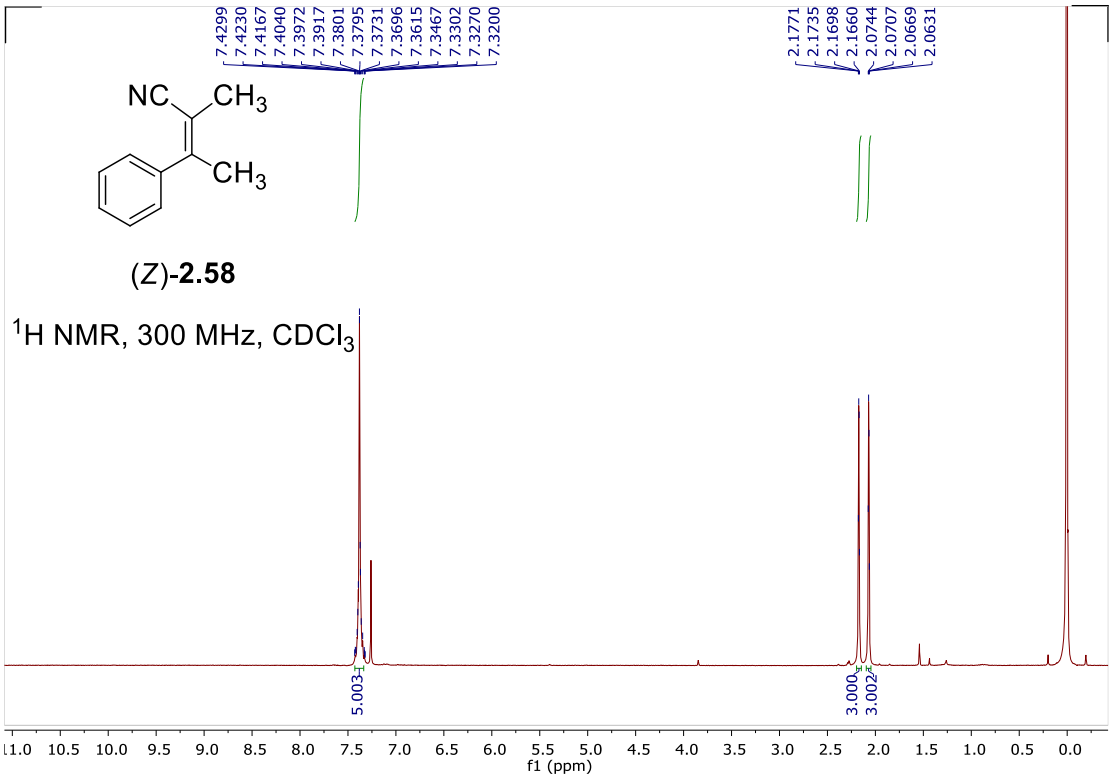
(*E*)-**2.58**

^{1}H NMR, 300 MHz, $CDCl_3$



(*E*)-**2.58**

^{13}C NMR, 75 MHz, $CDCl_3$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7.4167
7.4040
7.3972
7.3917
7.3801
7.3795
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7.3696
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7.3467
7.3302
7.3270
7.3200
2.1771
2.1735
2.1698
2.1660
2.0744
2.0707
2.0669
2.0631
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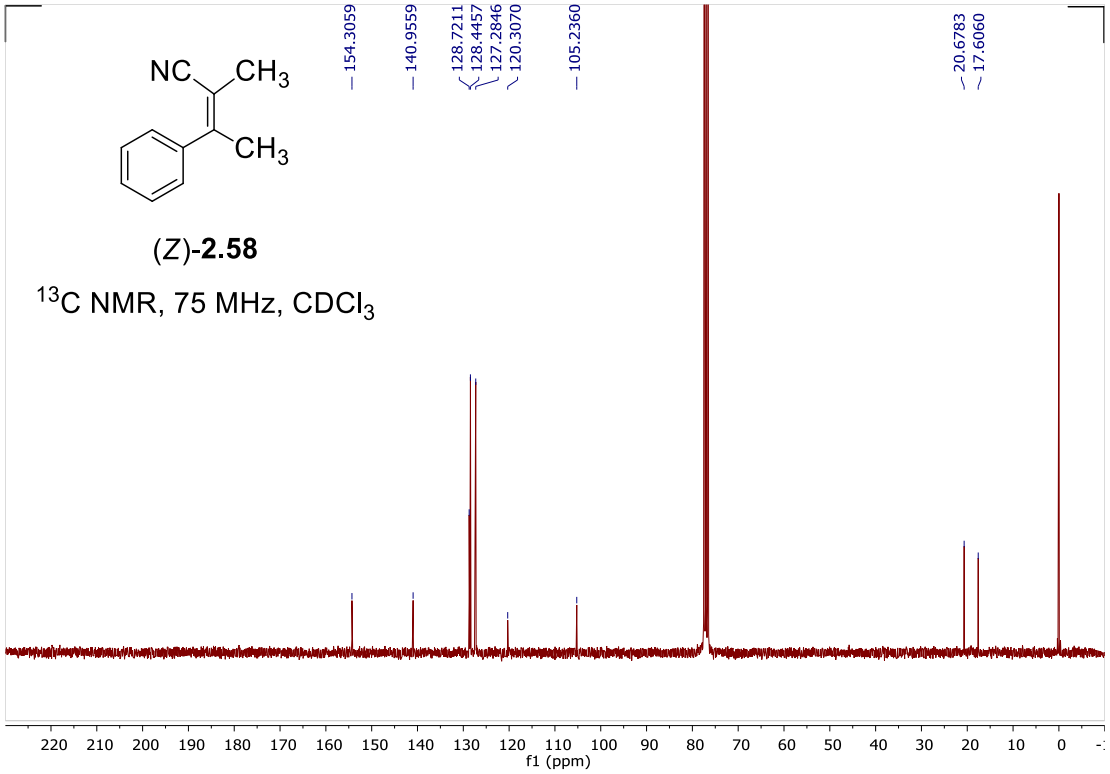
CH3
CH3
(Z)-2.58
1H NMR, 300 MHz, CDCl3
5.003
3.000
3.002
f1 (ppm)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CH3
CH3
(Z)-2.58
13C NMR, 75 MHz, CDCl3
f1 (ppm)

CHAPTER 3: EXPERIMENTAL

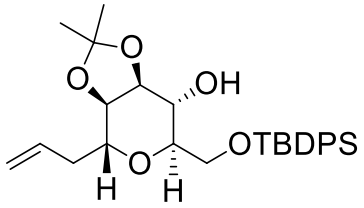
General Methods:

Moisture and oxygen sensitive reactions were carried out in flame-dried glassware fitted with rubber septa under an inert gas (*e.g.*, argon) atmosphere. Anhydrous tetrahydrofuran (THF) was distilled over sodium metal in the presence of benzophenone indicator. Anhydrous dichloromethane (DCM or CH_2Cl_2), toluene, hexanes, acetonitrile, tetramethylethylenediamine (TMEDA), and any types of liquid amine reagents were distilled over calcium hydride (CaH_2) upon necessity. All commercially available reagents and starting materials were used without further purification unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on glass-backed TLC plates coated with silica gel. TLCs were visualized under UV light (254 nm) and by staining either with vanillin, iodine, *p*-anisaldehyde, or potassium permanganate solution. Flash column chromatography was performed on silica gel 60A (32-63D). ^{1}H Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker Avance DRX 300 (300 MHz) or DRX 500 (500 MHz) spectrometers. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δH 7.26 for the residual protons in $CDCl_3$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, br = broad), coupling constant (*J*/Hz), and integration. Coupling constants were taken directly from the spectra and are uncorrected. ^{13}C NMR spectra were recorded at 75 or 125 MHz using the spectrometers above. All the chemical

shift values are reported in ppm on the δ scale, with an internal reference of δC 77.0 for $CDCl_3$. Infrared (IR) spectra were recorded on either a Bruker TENSOR 27 or an ALPHA-P FT-IR spectrometer and are reported in units of cm^{-1}. High-resolution mass spectra (HR-MS) were recorded using a Waters SYNAPT HDMS quadrupole time of flight (Q-TOF) mass spectrometer. All the HR-MS experiments were conducted at the hands of the graduate students either in the Dass research group or in the Hamann research group at the University of Mississippi.

Chapter 1

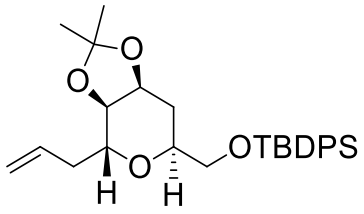
(3aR,4R,6S,7R,7aS)-4-Allyl-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-7-ol (1.3, "the common THP intermediate"):



1.3

Compound **1.3** was prepared from D-mannose in accordance with literature procedures.[50,51,52] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.64 (m, 4H), 7.48-7.32 (m, 6H), 5.86 (ddt, *J* = 17.5, 10.2, 6.2 Hz, 1H), 5.18-5.03 (m, 2H), 4.19-4.03 (m, 3H), 3.93-3.81 (m, 3H), 3.57-3.50 (m, 1H), 2.75 (d, *J* = 3.0 Hz, 1H), 2.49-2.25 (m, 2H), 1.51 (s, 3H), 1.37 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.61, 135.57, 133.9, 132.84, 132.81, 129.9, 129.8, 127.81, 127.77, 117.3, 109.7, 78.3, 76.1, 73.5, 73.0, 70.6, 64.8, 37.4, 27.6, 26.8, 25.3, 19.2; HRMS (TOF MS ES$^+$) calcd = 505.2381 $[M + Na]^+$, obsd = 505.2377.

(((3aR,4R,6R,7aS)-4-Allyl-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)methoxy)(*tert*-butyl)diphenylsilane (1.4)

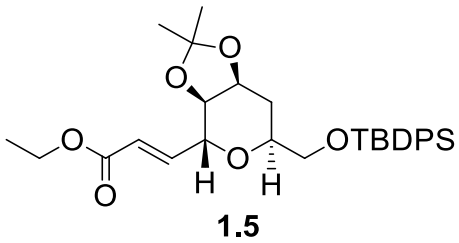


1.4

Formation of methyl xanthate (step 1): Into a solution of alcohol **1.3** (1.71 g, 3.53 mmol) in dry THF (24 mL) were added imidazole (14 mg, 0.21 mmol) and NaH (205 mg, 60% dispersion in mineral oil, 5.12 mmol), at room temperature. After stirring for 15 min, carbon disulfide (1.25 mL, 20.8 mmol) was slowly added over 15 min. After stirring for another 15 min, MeI (1.40 mL, 22.4 mmol) was then added into the reaction mixture. After stirring for 40 min, the reaction was quenched by sequentially adding EtOAc (10 mL), H_2O (8 mL), and brine (10 mL). After phase separation, the aqueous layer was extracted with EtOAc (x3). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude yellow solid was subjected to the next step without further purification. *Removal of xanthate (step 2):* Into a stirred solution of the crude methyl xanthate in dry toluene (12 mL) under an argon atmosphere were added AIBN (1.06 mL, 0.2 M in toluene, 0.212 mmol) and Bu_3SnH (5.30 mL, 1.0 M in cyclohexane, 5.30 mmol). The reaction mixture was refluxed for another 1.5 hrs and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (Hex:EtOAc = 5:1) to afford **1.4** (1.17 g, 2.51 mmol, 71% over 2 steps) as a colorless oil: $[\alpha]_D^{20}$ +14.8 (*c* 4.3, DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.65 (m, 4H), 7.45-7.35 (m, 6H), 5.89 (ddt, *J* = 17.5, 10.5, 6.7 Hz, 1H), 5.14 (dd, *J* = 17.5, 1.3 Hz, 1H), 5.06 (dd, *J* = 10.5, 1.3 Hz, 1H), 4.34 (apparent dt, *J* = 9.5, 6.0 Hz, 1H),

3.89 (apparent t, *J* = 7.0 Hz, 1H), 3.82 (apparent dt, *J* = 10.0, 5.0 Hz, 1H), 3.77-3.71 (m, 2H), 3.68 (dd, *J* = 10.5, 5.0 Hz, 1H), 2.49-2.42 (m, 1H), 2.30-2.22 (m, 1H), 2.07 (apparent dt, *J* = 14.0, 5.3 Hz, 1H), 1.90 (apparent dt, *J* = 14.0, 9.8 Hz, 1H), 1.43 (s, 3H), 1.34 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 135.6, 134.6, 133.4, 129.7, 129.6, 127.7, 116.9, 108.7, 75.7, 71.9, 71.8, 70.9, 65.9, 37.5, 29.0, 27.6, 26.8, 25.3, 19.2; HRMS (TOF MS ES$^+$) calcd = 489.2432 $[M + Na]^+$, obsd = 489.2404.

(*E*)-Ethyl 3-((3aS,4R,6R,7aS)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)acrylate (1.5)



1.5

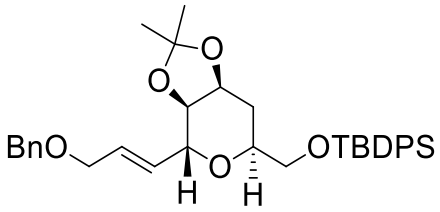
<u>*Isomerization (step 1):*</u> Alkene **1.4** (26 mg, 0.056 mmol), $PdCl_2(PhCN)_2$ (6.4 mg, 0.016 mmol), and dry benzene (2 mL) were added into a flame-dried flask under argon. The resulting mixture was stirred at 80 °C for 15 hrs. The mixture was then filtered through a silica gel pad (Hex:EtOAc = 3:1) and concentrated under reduced pressure. The crude product was subjected to the next step without further purification. <u>*Ozonolysis (step 2):*</u> To a stirred solution of the crude alkene in DCM (5 mL) and MeOH (1 mL) at -78 °C ozone was bubbled until a blue color persisted. Argon was then bubbled into the solution until the solution became colorless and dimethyl sulfide (5 mL) was added. The solution was then gradually warmed up to room temperature and stirred overnight. After concentration *in vacuo*, the crude aldehyde was subjected to the next step without further

purification. *HWE olefination (step 3):* Into a solution of the HWE reagent that was prepared from diethyl phosphono acetic acid ethyl ester (19 μL, 0.095 mmol) and NaH (4 mg, 60% dispersion in mineral oil, 0.10 mmol) in dry toluene (0.5 mL) was added a solution of the crude aldehyde in dry toluene (0.5 mL) at 0 °C. The reaction mixture was stirred overnight (0 °C → r.t.) and quenched with aqueous NH_4Cl solution. After phase separation, the aqueous layer was extracted with EtOAc (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (Hex:EtOAc = 10:1) to afford α,β-unsaturated ester **1.5** (26 mg, 0.050 mmol, 89% over 3 steps) as a pale yellow oil: $[\alpha]_D^{20}$ +24.7 (*c* 0.68, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.61 (m, 4H), 7.45-7.32 (m, 6H), 7.00 (dd, *J* = 15.9, 3.9 Hz, 1H), 6.15 (dd, *J* = 15.9, 1.8 Hz, 1H), 4.37 (apparent dt, *J* = 9.0, 6.3 Hz, 1H), 4.35-4.30 (m, 1H), 4.21 (q, *J* = 6.9 Hz, 2H), 3.97-3.84 (m, 2H), 3.78 (dd, *J* = 10.7, 4.9 Hz, 1H), 3.70 (dd, *J* = 10.8, 4.8 Hz, 1H), 2.10 (ddd, J = 13.5, 6.0, 4.5, 1H), 2.02-1.90 (m, 1H), 1.44 (s, 3H), 1.35 (s, 3H), 1.30 (t, *J* = 7.5 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 145.2, 135.6, 133.3, 129.71, 129.69, 127.7, 121.9, 109.1, 75.3, 71.8, 71.5, 71.3, 65.9, 60.4, 28.8, 27.6, 26.8, 25.2, 19.2, 14.3. This product spectroscopically matched that of the known compound.[40]

A*lternative method for the synthesis of **1.5***: <u>*Isomerization (step 1):*</u> Alkene **1.4** (373 mg, 0.80 mmol), $PdCl_2(PhCN)_2$ (92 mg, 0.24 mmol), and dry benzene (12 mL) were added into a flame-dried flask under argon. The resulting mixture was stirred at 80 °C for 15 hrs. The mixture was then filtered through a silica gel pad (Hex:EtOAc = 3:1) and concentrated under reduced pressure. The crude product was subjected to the next step

without further purification. *Ozonolysis (step 2):* To a stirred solution of the crude alkene in DCM (21 mL) and MeOH (6 mL) at -78 °C ozone was bubbled until a blue color persisted. Argon was then bubbled into the solution until the solution became colorless. Dimethyl sulfide (353 μL) was then added to the reaction mixture, followed by PPh_3 (210 mg, 0.80 mmol). The solution was gradually warmed up to room temperature in 30 min. After concentration *in vacuo*, the crude aldehyde was subjected to the next step without further purification. *Wittig olefination (step 3):* Into a solution of the crude aldehyde in dry benzene (10 mL) was added the Wittig reagent (344 mg, 0.99 mmol) at room temperature. After stirring overnight, the reaction mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (Hex:EtOAc = 9:1) to afford α,β-unsaturated ester **1.5** (218 mg, 0.48 mmol, 60% over 3 steps) as a pale yellow oil

(((3aS,4R,6R,7aS)-4-((*E*)-3-(Benzyloxy)prop-1-en-1-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)methoxy)(*tert*-butyl)diphenylsilane (1.6)

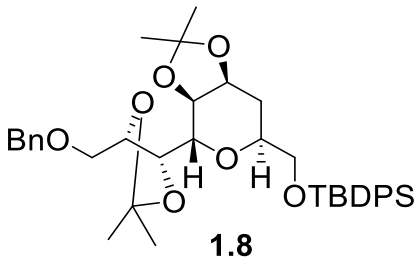


1.6

DIBAL reduction (step 1): Into a -78 °C solution of α,β-unsaturated ester **1.5** (220 mg, 0.419 mmol) in DCM (5 mL) was added DIBAL solution (1.05 mL, 1.0 M solution in toluene, 1.05 mmol) dropwise. After stirring for 30 min, the cooling bath was removed.

The reaction mixture was stirred for an additional 30 min at room temperature and quenched with saturated Rochelle's salt solution. After phase separation, the aqueous layer was extracted with EtOAc (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude allyl alcohol was subjected to the next step without further purification. *Benzylation (step 2):* Into a stirred solution of the allyl alcohol in THF (3 mL) at 0 °C were added TBAI (19 mg, 0.051 mmol) and NaH (50 mg, 60% dispersion in mineral oil, 1.25 mmol). After stirring for 10 min, BnBr (89 μL, 0.75 mmol) and DMF (1.0 mL) were added to the mixture and the ice bath was then removed. After stirring for 2 hrs at room temperature, the reaction mixture was quenched with aqueous NH_4Cl solution at 0 °C and diluted with Et_2O. After phase separation, the aqueous layer was extracted with Et_2O (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (Hex:EtOAc = 5:1) to afford benzyl ether **1.6** (226 mg, 0.395 mmol, 94 % over 2 steps) as a colorless oil: $[\alpha]_D^{20}$ +12.4 (*c* 0.68, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.67 (m, 4H), 7.40-7.25 (m, 11H), 5.95 (dt, *J* = 15.7, 5.2 Hz, 1H), 5.81 (dd, *J* = 15.7, 4.7 Hz, 1H), 4.52 (s, 2H), 4.35 (apparent dt, *J* = 9.1, 6.7 Hz, 1H), 4.26 (apparent t, *J* = 6.0 Hz, 1H), 4.06 (d, *J* = 5.2 Hz, 2H), 3.96 (apparent t, *J* = 6.9Hz, 1H), 3.88-3.82 (m, 1H), 3.79-3.67 (m, 2H), 2.13-2.02 (m, 1H), 1.96-1.85 (m, 1H), 1.44 (s, 3H), 1.34 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 135.6, 133.4, 130.4, 129.6, 128.3, 127.7, 127.6, 127.5, 108.7, 75.8, 72.3, 72.1, 71.7, 70.8, 70.2, 66.1, 29.2, 27.6, 26.8, 25.3, 19.2; HRMS (TOF MS ES$^+$) calcd = 595.2850 $[M + Na]^+$, obsd = 595.2882.

(((3aS,4S,6S,7aS)-4-((4S)-5-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)methoxy)(*tert*-butyl)diphenylsilane (1.8)

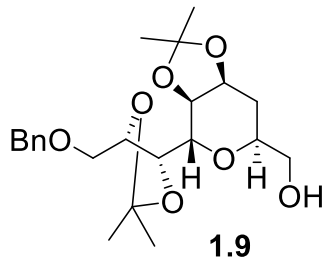


1.8

<u>*Sharpless AD (step 1):*</u> Into a solution of benzyl ether **1.6** (88 mg, 0.15 mmol) in *tert*-butyl alcohol (0.5 mL) and water (0.5 mL) were added AD-mix-α (226 mg) and methanesulfonamide (17 mg, 0.18 mmol). The reaction mixture was stirred at room temperature for 2 days, quenched with sodium thiosulfate ($Na_2S_2O_3$), stirred for 30 min, and diluted with EtOAc. After phase separation, the aqueous layer was extracted with EtOAc (x3). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude diol product was subjected to the next step without further purification. <u>*Acetonide formation (step 2):*</u> Into a stirred solution of the crude diol in DCM (1.5 mL) at room temperature were added 2-methoxypropene (29 μL, 0.30 mmol) and camphor sulfonic acid (0.7 mg, 0.003 mmol). After stirring for 1 hr at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. After phase separation, the aqueous layer was extracted with DCM (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography

(Hex:EtOAc = 10:1 to 5:1) to afford diacetonide **1.8** (83 mg, 0.13 mmol, 84 % over 2 steps) as a colorless oil: $[\alpha]_D^{20}$ -1.3 (*c* 0.68, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.75-7.60 (m, 4H), 7.50-7.20 (m, 11H), 4.53 (s, 2H), 4.39-4.26 (m, 3H), 4.07 (dd, *J* = 8.4, 3.0 Hz, 1H), 3.90-3.80 (m, 2H), 3.76-3.64 (m, 2H), 3.60-3.53 (m, 2H), 2.08-1.96 (m, 1H), 1.90-1.77 (m, 1H), 1.44 (s, 6H), 1.43 (s, 3H), 1.34 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 135.60, 135.58, 133.4, 129.69, 129.67, 128.3, 127.7, 109.8, 108.6, 78.8, 76.7, 73.4, 72.7, 72.0, 71.4, 71.3, 70.4, 66.0, 29.2, 27.8, 27.2, 26.9, 26.8, 25.6, 19.2; HRMS (TOF MS ES^+) calcd = 669.3223 $[M + Na]^+$, obsd = 669.3237.

((3aS,4S,6S,7aS)-4-((4S)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)methanol (1.9)

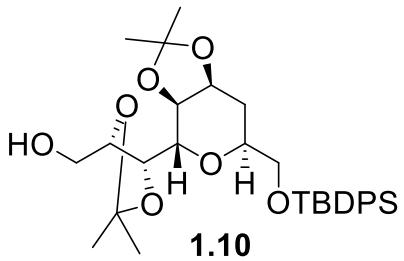


1.9

Into a solution of diacetonide **1.8** (10 mg, 0.015 mmol) in THF (1 mL) was added TBAF in THF (1.0 M solution, 23 µL, 0.023 mmol). After stirring for 3 hrs at room temperature, the reaction mixture was quenched with half saturated aqueous NH_4Cl solution. After phase separation, the aqueous layer was extracted with Et_2O (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (Hex:EtOAc = 3:1 to 1:1) to afford primary alcohol **1.9** (6 mg, 0.015 mmol, quantitative)

as a colorless oil: $[\alpha]_D^{20}$ -3.75 (*c* 0.40, DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.29 (m, 5H), 4.60 (s, 2H), 4.36-4.29 (m, 1H), 4.28-4.22 (m, 2H), 4.10 (dd, *J* = 8.3, 3.6 Hz, 1H), 3.93 (dd, *J* = 5.4, 3.6 Hz, 1H), 3.89-3.79 (m, 1H), 3.64 (m, 3H), 3.57-3.47 (m, 1H), 2.01 (br, 1H), 1.97-1.88 (m, 1H), 1.69-1.61 (m, 1H), 1.46 (s, 3H), 1.44 (s, 6H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 128.4, 127.8, 109.9, 108.6, 79.2, 76.8, 73.5, 72.4, 71.3, 71.14, 71.06, 70.5, 64.7, 28.9, 27.9, 27.1, 26.9, 25.8. This product spectroscopically matched that of the known compound.[55]

((5S)-5-((3aS,4S,6S,7aS)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (1.10)

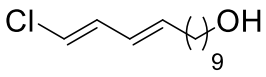


1.10

A solution of 4,4'-di-*tert*-butylbiphenyl (2.48 g, 9.31 mmol) in THF (9.3 mL) was treated with lithium (76 mg, 11 mmol) under sonication at 0 °C until deep green color persisted (~1 hr). In a separate flask, a solution of benzyl ether **1.8** (223 mg, 0.345 mmol) in THF (1.4 mL) was cooled to -78 °C (acetone/dry ice bath). The deep green solution was then added portion wise (0.5 mL) until starting material **1.8** was not detected by TLC (~1.5 hrs). The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution at -78 °C and gradually warmed up to room temperature. After phase separation, the

aqueous layer was extracted with EtOAc (x3). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (Hex:EtOAc = 10:1 to 1:1) to afford primary alcohol **1.10** (180 mg, 0.323 mmol, 94%) as a colorless oil: $[\alpha]_D^{20}$ +2.2 (*c* 0.68, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.70-7.64 (m, 4H), 7.46-7.34 (m, 6H), 4.42-4.27 (m, 2H), 4.22-4.05 (m, 2H), 3.91-3.59 (m, 6H), 2.05-1.77 (m, 3H), 1.45 (s, 3H), 1.43 (s, 6H), 1.35 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 133.3, 129.7, 127.7, 109.5, 108.7, 78.6, 77.5, 73.0, 71.8, 71.7, 71.4, 66.0, 62.2, 29.1, 27.8, 27.2, 26.9, 26.8, 25.6, 19.2; HRMS (TOF MS ES^+) calcd = 579.2749 $[M + Na]^+$, obsd = 579.2726.

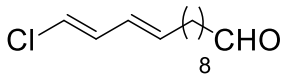
(10*E*,12*E*)-13-Chlorotrideca-10,12-dien-1-ol (1.11)



1.11

Alcohol **1.11** was prepared from undec-10-yn-1-ol in accordance with literature procedures.[57] ^1H NMR (300 MHz, $CDCl_3$) δ 6.41 (dd, *J* = 13.2, 10.8 Hz, 1H), 6.07 (d, *J* = 12.9 Hz, 1H), 5.96 (dd, *J* = 15.0, 10.8 Hz, 1H), 5.70 (dt, *J* = 15.0, 7.2 Hz, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.06 (apparent q, *J* = 6.9 Hz, 2H), 1.41-1.25 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 133.9, 126.0, 118.2, 63.1, 32.8, 32.6, 29.5, 29.39, 29.37, 29.1, 29.0, 25.7. This product spectroscopically matched that of the known compound.[57]

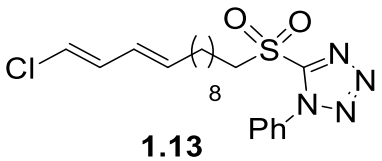
(10*E*,12*E*)-13-Chlorotrideca-10,12-dienal (1.12)



1.12

Into a solution of alcohol **1.12** (46 mg, 0.20 mmol) in DCM (2 mL) was added Dess-Martin periodinane (102 mg, 0.24 mmol) at room temperature. After stirring for 3 hrs, the reaction mixture was quenched with $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solution. The mixture was stirred until both layers became clear. After phase separation, the aqueous layer was extracted with DCM (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (Hex:EtOAc = 3:1) to afford aldehyde **1.12** (38 mg, 0.17 mmol, 83%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.8 Hz, 1H), 6.41 (dd, *J* = 13.2, 10.8 Hz, 1H), 6.07 (d, *J* = 13.2 Hz, 1H), 5.96 (dd, *J* = 15.3, 10.8 Hz, 1H), 5.69 (dt, *J* = 15.3, 6.9 Hz, 1H), 2.41 (td, *J* = 7.2, 1.8 Hz, 2H), 2.06 (apparent q, *J* = 6.9 Hz, 2H), 1.94 (apparent p, *J* = 7.2 Hz, 2H), 1.40-1.20 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 136.1, 133.8, 126.0, 118.2, 43.8, 32.5, 29.20, 29.15, 29.06, 28.97, 28.92, 22.0; HRMS (TOF MS ES$^+$) calcd = 227.1203 [M - H]$^-$, obsd = 227.1236.

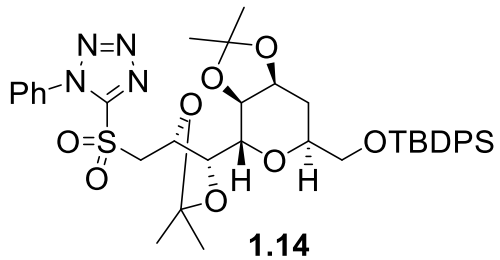
5-(((10*E*,12*E*)-13-Chlorotrideca-10,12-dien-1-yl)sulfonyl)-1-phenyl-1H-tetrazole (1.13)



1.13

Mitsunobu reaction (step1): Alcohol **1.11** (139 mg, 0.60 mmol), Ph_3P (221 mg, 0.84 mmol), 1-phenyltetrazole-1-thiol (153 mg, 0.84 mmol), and DIAD (177 µl, 0.84 mmol) were dissolved in THF (6 mL) and then stirred for 3 hrs at room temperature. After diluting with CH_2Cl_2 and H_2O, the separated aqueous layer was extracted with CH_2Cl_2 (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude sulfide product was subjected to the next step without further purification. *Oxidation (step 2)*: The crude sulfide was dissolved in EtOH (12 mL) and then cooled to 0 °C. In a separate flask, $(NH_4)_6Mo_7O_{24}•4H_2O$ (148 mg, 0.120 mmol) was dissolved in 30% aqueous H_2O_2 (1.23 mL, 12.0 mmol) at 0 °C. The H_2O_2 solution was added to the sulfide solution dropwise. The resulting mixture was stirred for 24 hrs and then quenched with water and diluted with CH_2Cl_2. After phase separation, the aqueous layer was extracted with CH_2Cl_2 (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (Hex:EtOAc = 3:1) to afford sulfone **1.13** (211 mg, 0.50 mmol, 83% over 2 steps) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75-.55 (m, 5H), 6.40 (dd, *J* = 13.0, 11.0 Hz, 1H), 6.06 (d, *J* = 13.0 Hz, 1H), 5.96 (dd, *J* = 15.0, 11.0 Hz, 1H), 5.69 (dt, *J* = 15.0, 7.0 Hz, 1H), 3.72 (t, *J* = 7.5 Hz, 2H), 2.05 (apparent q, *J* = 7.0 Hz, 2H), 1.94 (apparent p, *J* = 7.7 Hz, 2H), 1.48 (apparent p, *J* = 7.2 Hz, 2H), 1.40-1.20 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 136.1, 133.8, 133.0, 131.3, 129.6, 126.0, 125.0, 118.2, 55.9, 32.5, 29.1, 29.0, 28.92, 28.87, 28.75, 28.0, 21.8; HRMS (TOF MS ES$^+$) calcd = 423.1616 $[M + H]^+$, obsd = 423.1613.

5-((((5R)-5-((3aS,4S,6S,7aS)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)sulfonyl)-1-phenyl-1H-tetrazole (1.14)

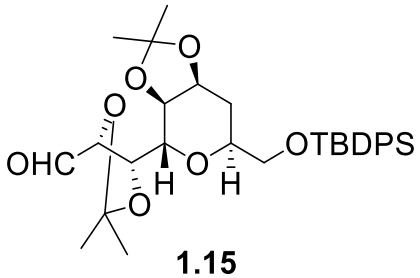


1.14

Mitsunobu reaction (step 1): Primary alcohol **1.10** (24 mg, 0.043 mmol), Ph_3P, (17 mg, 0.065 mmol) and 1-phenyltetrazole-1-thiol (12 mg, 0.067 mmol) were dissolved in THF (0.5 mL) at room temperature. Into the solution was added DIAD (13 µL, 0.066 mmol) dropwise. The reaction mixture was then stirred for 3 hrs and diluted with CH_2Cl_2 and H_2O. After the phase separation, the aqueous layer was extracted with CH_2Cl_2 (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude sulfide was subjected to the next reaction without further purification. *Oxidation (step 2)*: The crude sulfide was dissolved in EtOH (0.5 mL) and cooled to 0 °C. In a separate flask, $(NH_4)_6Mo_7O_{24}•4H_2O$ (11 mg, 0.0089 mmol) was dissolved in 30% aqueous H_2O_2 (88 µL, 0.86 mmol) at 0 °C. The H_2O_2 solution was added to the substrate solution dropwise. The resulting mixture was stirred for 24 hrs and then diluted with water and CH_2Cl_2. After phase separation, the aqueous layer was extracted with CH_2Cl_2 (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by

SiO_2 column chromatography (Hex:EtOAc = 10:1 to 3:1) to afford sulfone **1.14** (14 mg) as a colorless oil and also the sulfoxide, which was re-subjected to oxidation with $(NH_4)_6Mo_7O_{24}•H_2O$ (5 mg, 0.004 mmol) and 30% aqueous H_2O_2 (42 μL, 0.41 mmol) at 0 °C to afford additional sulfone **1.14** (8 mg) for a total of 22 mg (68% over 2 steps): $[\alpha]_D^{20}$ -4.8 (*c* 0.68, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66-7.56 (m, 9H), 7.42-7.37 (m, 6H), 4.54 (apparent td, *J* = 8.7, 2.1 Hz, 1H), 4.34 (apparent dt, *J* = 8.7, 6.0 Hz, 1H), 4.18 (apparent t, *J* = 7.0 Hz, 1H), 3.92-3.84 (m, 2H), 3.80-3.69 (m, 4H), 3.63 (dd, *J* = 14.7, 2.1 Hz, 1H), 2.08-1.90 (m, 2H), 1.36 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 135.6, 135.6, 133.2, 131.4, 129.8, 129.4, 127.8, 127.8, 125.7, 111.2, 109.2, 80.8, 77.2, 71.9, 71.8, 71.7, 71.6, 65.6, 59.3, 28.4, 27.6, 26.8, 26.7, 26.6, 25.3, 19.3; HRMS (TOF MS ES$^+$) calcd = 771.2854 $[M + Na]^+$, obsd = 771.2889.

(5R)-5-((3aS,4S,6S,7aS)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-4-yl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (1.15)

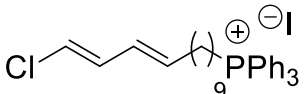


1.15

Into a solution of alcohol **1.10** (83 mg, 0.150 mmol) and DMSO (74 μL, 1.0 mmol) in DCM (1.5 mL) at 0 °C were added Hünig base (78 μL, 0.45 mmol) and SO_3/pyridine

complex (190 mg, 0.60 mmol). After stirring for 20 min at 0 °C, triethylamine (62 μL, 0.45 mmol) was added and the ice bath was removed. The reaction mixture was stirred overnight (0 °C to r.t.). It was quenched with saturated aq. $NaHCO_3$ solution, extracted with DCM (x2), dried over $MgSO_4$, and concentrated in *vacuo* to give a crude yellow oil (33 mg, 0.059 mmol, 38%). It was used for next reaction steps without further purification.

((10*E*,12*E*)-13-Chlorotrideca-10,12-dien-1-yl)triphenylphosphonium iodide (1.16)

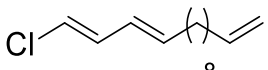


1.16

Iodation (1st step): A solution of PPh_3 (610 mg, 2.14 mmol) and imidazole (242 mg, 3.56 mmol) in DCM (9 mL) was protected from light by wrapping the whole glassware with aluminum foil. Iodine (543 mg, 2.14 mmol) was introduced to the reaction mixture at 0 °C and stirred for 15 min. Then alcohol **1.11** was added and the mixture was stirred overnight (0 °C to r.t.). The reaction mixture was quenched with $Na_2O_3S_2$ and water. After phase separation, the aqueous layer was extracted with CH_2Cl_2 (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was subjected to the next step without further purification.
Wittig salt formation: Into a solution of iodide (106 mg, 0.31 mmol) in acetonitrile (2 mL) under argon atmosphere was added PPh_3 (105 mg, 0.373 mmol) and the mixture was refluxed for 2 days. The solvent was removed under reduced pressure to give a crude yellow pasty gel. The crude product was triturated with Et_2O and toluene first; however,

it was found out that THF works better, presumably because THF dissolves impurity (phosphine oxide) well. Insoluble were 131 mg (0.217 mmol, 70% over 2 steps) of **1.16**. It was used for next reactions without further purification.

(1*E*,3*E*)-1-Chlorotetradeca-1,3,13-triene (1.17)

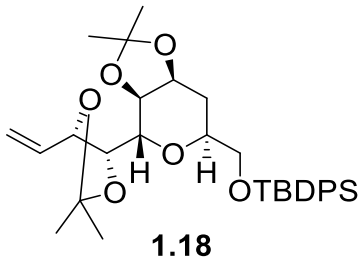


1.17

A mixture of triphenyl methyl phosphonium bromide (174 mg, 0.476 mmol) in THF (2.4 mL) was cooled to -78 °C [Note: at this point, the bromide salt was undissolved in THF]. *n*-BuLi (2.5 M in hexanes, 173 μL, 0.433 mmol) was added dropwise and stirred for 30 min. All the bromide salt dissolved and the mixture turned yellowish orange. In a separate flask, aldehyde **1.12** (99 mg, 0.433 mmol) was dissolved in THF (2 mL) and added to the reaction mixture dropwise at -78 °C. The acetone/dry ice bath was removed, and the reaction was stirred overnight (from -78 °C to r.t.). The reaction was quenched with saturated aq. NH_4Cl solution. After phase separation, the aqueous layer was extracted with Et_2O (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (100 % Hexanes) to afford triene **1.17** (51 mg, 0.225 mmol, 52%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44-6.39 (dd, *J* = 12.0, 2.0 Hz, 1H), 6.07 (d, *J* = 13.5 Hz, 1H), 5.96 (dd, *J* = 13.0, 4.5 Hz, 1H), 5.81 (m, 1H), 5. 71 (apparent septet, *J* = 7.5 Hz, 1H), 5.02-4.92 (m, 2H), 2.10-2.00 (m, 4H), 1.38-1.28 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 136.3, 133.9, 126.0, 118.2, 114.1, 33.8,

32.6, 29.4, 29.12, 29.11, 29.0, 28.9 [Note: A carbon signal from upfield is missing most probably due to two carbons in the long alkyl chain having the same chemical shift].

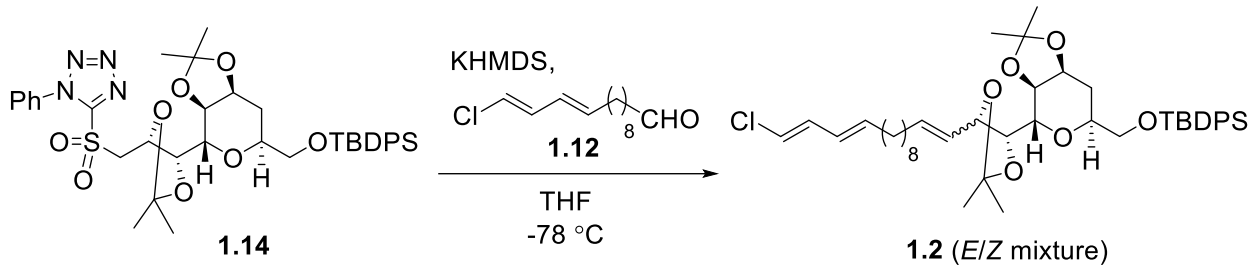
***tert*-Butyl(((3aS,4S,6S,7aS)-4-((4S)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-6-yl)methoxy)diphenylsilane (1.18)**



1.18

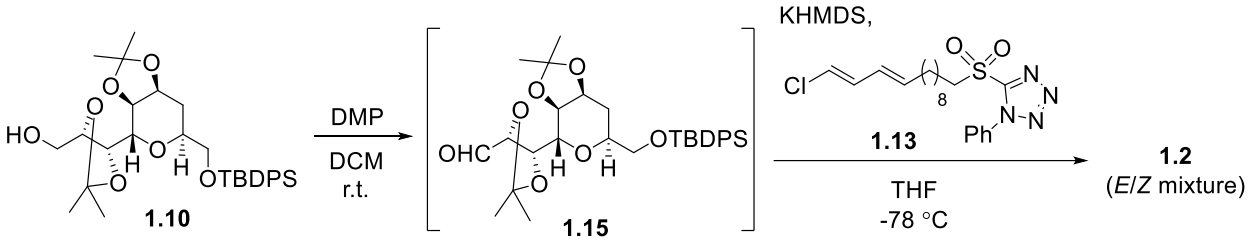
A mixture of triphenyl methyl phosphonium bromide (27 mg, 0.073 mmol) in THF (1 mL) was cooled to -78 °C [Note: at this point, the bromide salt was undissolved in THF]. *n*-BuLi (2.5 M in hexanes, 27 μL, 0.066 mmol) was added dropwise and stirred for 30 min. All the bromide salt dissolved and the mixture turned yellowish orange. In a separate flask, aldehyde **1.15** (36 mg, 0.066 mmol) was dissolved in THF (1 mL) and added to the reaction mixture dropwise at -78 °C. The acetone/dry ice bath was removed, and the reaction was stirred overnight (from -78 °C to r.t.). The reaction was quenched with saturated aq. NH_4Cl solution. After the phase separation, the aqueous layer was extracted with Et_2O (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. This crude product was subjected to the next step without further purification.

Julia-Kocienski olefination (route A):



The sulfone **1.14** (28 mg, 0.037 mmol) in THF (0.40 mL) was dissolved and cooled to -78 °C. To the solution was added KHMDS in toluene (0.5 M solution, 90 µL, 0.045 mmol) and the mixture was maintained at -78 °C for 1 hr. The aldehyde **1.12** (17 mg, 0.074 mmol) in THF (0.40 mL) was added dropwise. After the mixture was stirred for 1 hr, the cooling bath was removed and stirring continued for an additional 2 hrs from -78 °C to room temperature. The reaction was then quenched with aq. NH_4Cl solution. After phase separation, the aqueous layer was extracted with EtOAc (x2). The combined organics were then washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (Hex:EtOAc = 12:1) to afford a mixture of *E*/*Z* isomers of **1.2** (7 mg, 0.0093 mmol, 25%, *E*:*Z* = 3:1) as a colorless oil.

Julia-Kocienski olefination (route B):

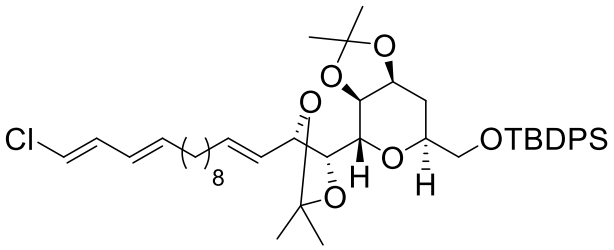


Into a solution of Dess-Martin periodinane (34 mg, 0.079 mmol) in CH_2Cl_2 (0.5 mL) was added alcohol **1.10** (22 mg, 0.040 mmol) and the mixture was stirred at room temperature. After 3 h, the reaction mixture was quenched with $Na_2S_2O_3$ and aq. saturated $NaHCO_3$ solution. The mixture was stirred until both layers were clear. After phase separation, the aqueous layer was extracted with CH_2Cl_2 twice. The combined organics were then washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude aldehyde product was then subjected to the next step without purification. Into another flask was added sulfone **1.13** (12 mg, 0.028 mmol) in THF (0.4 mL) and the solution was cooled to -78 °C. To the solution was added KHMDS in THF (1.0 M solution, 35 µL, 0.035 mmol) and the mixture was maintained at -78 °C for 1 hr. The crude aldehyde in THF (0.1 mL) was added dropwise. After the mixture stirred for 1 hr, the cooling bath was removed and the reaction was stirred for an additional 2 hrs from -78 °C to room temperature. It was then quenched with aq. saturated NH_4Cl. After phase separation, the aqueous layer was extracted with EtOAc twice. The combined organics were then washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (toluene, then Hex:EtOAc = 3:1) to afford a mixture of *E*/*Z* isomers of **1.2** (12 mg, 0.016 mmol, 40% over 2 steps, *E*:*Z* = 3:2) as a colorless oil.

HPLC separation of *E*/*Z* isomers of 1.2:

The *E*/*Z* isomers of **1.2** were separated by HPLC (Waters LC Module 1 equipped by Millenium software). HPLC conditions are as follows. Column: Luna 00A-4162-B0, 30 × 2 mm; eluant: Hex:EtOAc = 95:5; flow rate: 5 ml/min; t_R[(*E*)-**1.2**] = 23.0 min, t_R[(*Z*)-**1.2**] = 27.5 min. The detection was performed at 254 nm. The final amount of (*E*)-**1.2** after HPLC separation was 1 mg.

***tert*-Butyl(((3aS,4S,6S,7aS)-4-((4S)-5-((1*E*,11*E*,13*E*)-14-chlorotetradeca-1,11,13-trien-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)methoxy)diphenylsilane (*E*-1.2):**

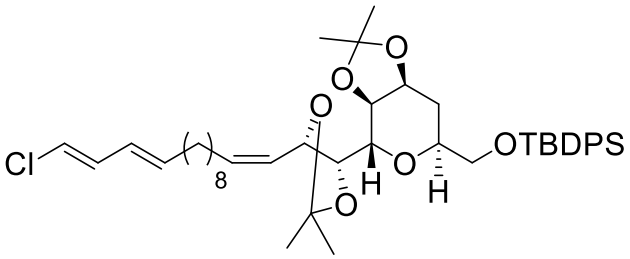


(*E*)-**1.2**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.61 (m, 4H), 7.44-7.31 (m, 6H), 6.41 (dd, *J* = 13.1, 10.7 Hz, 1H), 6.06 (d, *J* = 13.2 Hz, 1H), 5.96 (dd, *J* = 15.2, 10.9 Hz, 1H), 5.79 (dt, *J* = 15.4, 6.6 Hz, 1H), 5.69 (dt, *J* = 15.2, 7.1 Hz), 5.38 (dd, *J* = 15.4, 8.0 Hz, 1H), 4.47 (apparent t, *J* = 8.3 Hz, 1H), 4.41-4.31 (m, 2H), 3.95-3.80 (m, 3H), 3.74 (dd, *J* = 10.7, 4.2 Hz, 1H), 3.69 (dd, *J* = 10.9, 5.2 Hz, 1H), 2.10-1.84 (m, 6H), 1.46 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.32-1.20 (m, 12H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 136.3, 135.63, 135.58, 133.9, 133.5, 133.4, 129.7, 127.7, 126.2, 126.0, 118.2,

109.0, 108.6, 81.8, 78.3, 72.1, 71.4, 71.3, 70.8, 65.9, 32.6, 32.3, 29.4, 29.2, 29.1, 29.0, 28.9, 28.8, 27.8, 27.3, 26.8, 26.8, 25.6; HRMS (TOF MS ES$^+$) calcd = 773.3980 [M + Na]$^+$, obsd = 773.3960.

***tert*-Butyl(((3aS,4S,6S,7aS)-4-((4S)-5-((1*Z*,11*E*,13*E*)-14-chlorotetradeca-1,11,13-trien-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)methoxy)diphenylsilane (*Z*-1.2):**

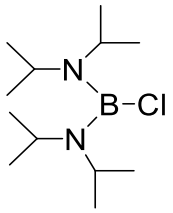


(*Z*)-**1.2**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.62 (m, 4H), 7.45-7.30 (m, 6H), 6.41 (dd, *J* = 12.9, 10.8 Hz, 1H), 6.07 (d, *J* = 13.2 Hz, 1H), 5.96 (dd, *J* = 15.3, 10.8Hz, 1H), 5.69 (dt, *J* = 15.0, 7.2 Hz, 1H), 5.62 (apparent dt, *J* = 10.8, 7.2 Hz, 1H), 5.31 (apparent dd, *J* = 10.5, 9.3 Hz, 1H), 4.87 (apparent t, *J* = 9.3 Hz, 1H), 4.45 (apparent t, *J* = 7.2 Hz, 1H), 4.41-4.32 (m, 1H), 3.94 (dd, *J* = 9.0, 2.1 Hz, 1H), 3.87 (m, 1H), 3.79 (dd, *J* = 7.5, 2.1 Hz, 1H), 3.73 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.65 (dd, *J* = 10.5, 4.3 Hz, 1H), 2.25-1.90 (m, 6H), 1.47 (s, 3H), 1.45 (s, 6H), 1.37 (s, 3H), 1.34-1.23 (m, 12H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 136.2, 135.6, 133.9, 133.4, 133.3, 129.69, 129.66, 127.7, 126.1, 125.8, 118.2, 109.2, 108.6, 81.8, 72.5, 72.3, 71.62, 71.55, 70.8, 66.2, 32.6, 29.6, 29.44, 29.40, 29.3, 29.1, 29.0, 28.9, 27.6, 27.5, 27.4, 26.9, 26.7, 25.1, 19.2; HRMS (TOF MS ES$^+$) calcd = 773.3980 [M + Na]$^+$, obsd = 773.3975.

Chapter 2

1-Chloro-*N*,*N*,*N*',*N*'-tetraisopropylboranediamine (2.3):

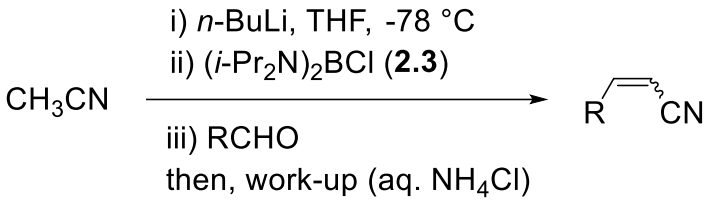


2.3

A 1000 mL, three necked, round-bottomed flask equipped with a magnetic stir bar, rubber septum, and a reflux condenser connected to an argon inlet adapter was assembled. The system was flame-dried, flushed with argon, and dry toluene (100 mL) followed by diisopropylamine (57.5 mL, 410 mmol) were added to the flask *via* a syringe. The flask was cooled in an ice-water bath and solution of trichloroboron (100 mL, 1 M in DCM, 100 mmol) was added dropwise. The stirring was continued for 30 min at 0 °C. The cooling bath was removed and the mixture was stirred at room temperature for an additional 30 min. The rubber septum was replaced with a glass stopper under argon flow, and all glass joints were secured with Keck clips. The mixture was brought to reflux, and reacted for two days. After cooling to room temperature, the resulting mixture was filtered. The product was highly sensitive to moisture, thus any contact with air/moisture was minimized. The salt was washed with dry hexanes, and the combined filtrates were concentrated *in vacuo*. The residue was distilled under reduced pressure (65~80 °C, 0.1 mmHg) to get 21.4 g (86.8 mmol, 87%) of a clear oil. This

product released fumes upon exposure to atmosphere. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.6 Hz, 24H), 3.46 (sep, *J* = 6.6 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.0, 23.4; this product spectroscopically matched that of the known compound.[102]

General procedure for one-pot synthesis of β–monosubstituted (*Z*)-acrylonitriles:



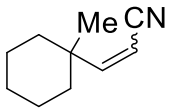
(*Z*)-3-Phenylacrylonitrile (Scheme 2.5): Into a flame-dried 25 mL round-bottomed flask was added dry THF (8 mL) under an argon atmosphere. After cooling to -78 °C (acetone/dry-ice bath), *n*-BuLi (880 µL, 2.5 M in hexanes, 2.2 mmol) and dry CH_3CN (172 µL, 3.3 mmol) were added dropwise, respectively. After stirring for 20 min, (*i*-$Pr_2N)_2BCl$ (**2.3**) (271 mg, 1.1 mmol) was then slowly added. After stirring for 1 h, benzaldehyde (102 µL, 1.0 mmol) was added. The reaction mixture was stirred for an additional hour at -78 °C and then quenched with 50% saturated aqueous NH_4Cl solution (5 mL) at -78 °C, then warmed up to room temperature over 30 min. After phase separation, the aqueous layer was extracted with Et_2O (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product (*E*:*Z* = 18:82) [Note: *E*:*Z* ratio was determined by the olefin signals in the ^{1}H NMR spectrum of the crude reaction mixture] was purified by SiO_2 column chromatography (Hex:EtOAc = 9.5:0.5) to afford 121 mg of a colorless oil in 94% yield

as a *E*/*Z* mixture. These products spectroscopically matched those of the known compounds.[148]

Spectral data of the new compounds:

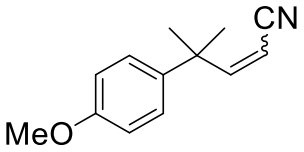
The products (**Table 2.1**, entries **1**-**5**, and **Table 2.2**, entries **6**, **7**, **9**, **10**, and **12**) are known compounds and their spectral data matched those reported.[149]

(*Z*)-3-(1-Methylcyclohexyl)acrylonitrile (Table 2.2, entry 8):



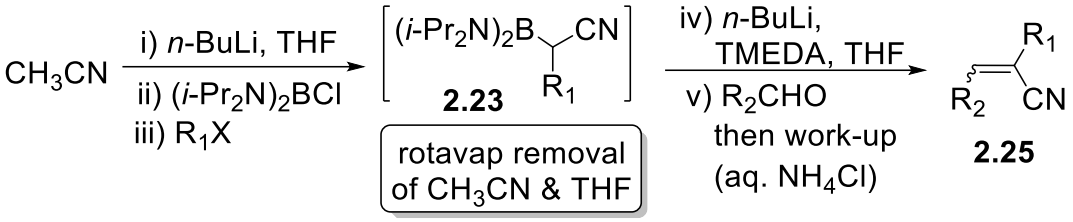
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (d, *J* = 12.4 Hz, 1H), 5.32 (d, *J* = 12.4 Hz, 1H), 1.92-1.86 (m, 2H), 1.62-1.29 (m, 8H), 1.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 116.6, 96.5, 38.7, 37.8, 26.8, 25.6, 22.6; IR spectra (neat): 2218; HRMS m/z $[M+H]^+$ calcd = 150.1283, obsd = 150.1199.

(*Z*)-4-(4-Methoxyphenyl)-4-methylpent-2-enenitrile (Table 2.2, entry 11):



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (apparent d, *J* = 8.9 Hz, 2H), 6.88 (apparent d, *J* = 8.9 Hz, 2H), 6.50 (d, *J* = 12.1 Hz, 1H), 5.32 (d, *J* = 12.1 Hz, 1H), 3.80 (s, 3H), 1.61 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 158.3, 138.3, 127.2, 116.1, 113.8, 96.0, 55.2, 42.3, 28.5; IR spectra (neat): 2219; HRMS m/z $[M + H]^+$ calcd = 201.1154, obsd = 201.1151.

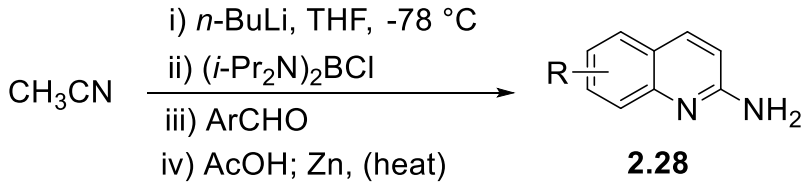
General procedure for one-pot synthesis of α,β-disubstituted acrylonitriles:



α,β-Disubstituted acrylonitriles 2.25: Into a flame-dried round-bottomed flask was added dry THF (8 mL) under an argon atmosphere. After the mixture was cooled to -78 °C (acetone/dry ice bath), *n*-BuLi (1.0 mL, 2.5 M in hexanes, 2.5 mmol) and dry CH_3CN (195 μL, 3.75 mmol) were added dropwise, respectively. After the mixture was stirred for 20 min, $(i\text{-}Pr_2N)_2BCl$ (**2.3**) (342 μL, 1.25 mmol) was then slowly added. After another 1 h of stirring, alkyl halide (1.25 mmol) was added. The reaction mixture was sttired for an additional 1 h at 0 °C. and then concentrated under reduced pressure. Subsequently, dry THF (6 mL) was added into the crude mixture under an argon atmosphere. After the mixture as cooled to -78 °C, *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (188 μL, 1.25 mmol) and *n*-BuLi (500 μL, 2.5 M in hexanes, 1.25 mmol) were added dropwise. After the mixture was stirred for 1 h, an aldehyde (1.0 mmol) was slowly added, and the resulting mixture was stirred for 1.5 h at the same temperature. The reaction mixture was then quenched with 50% aqueous NH_4Cl (6 mL) and warmed up to room temperature (-78 °C to r.t. over 30 min). After phase separation, the aqueous layer was extracted with Et_2O (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding

acrylonitrile as a mixture of *E*/*Z* isomers. [Note: *E*/*Z* ratio was determined by ^{1}H NMR of the crude reaction mixture.] The *E*/*Z* mixture was subsequently separated for characterization purpose. The use of toluene as an eluent for silica gel column chromatography allowed for isolation of each isomer. The *E*/*Z* configurations were determined based on the fact that, in ^{13}C NMR spectrum, the allylic carbon (on the α-carbon) of an α,β-disubstituted (*E*)-acrylonitrile appears upper field than the same carbon of the (*Z*)-isomer, and ^{1}H NMR spectrum, the vinylic proton on the β-carbon of (*Z*)-isomer appears upper field than the same proton of the (*E*)-isomer.

Synthesis of 2-aminoquinolines 2.28 (2.28a-2.28g):

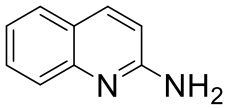


2.28

Into a flame-dried 25 mL round-bottomed flask was added dry THF (6 mL) under an argon atmosphere. After cooling to -78 °C (acetone/dry-ice bath), *n*-BuLi (880 µL, 2.5 M in hexanes, 2.2 mmol) and dry CH_3CN (172 µL, 3.3 mmol) were added dropwise, respectively. After stirring for 20 min, (*i*-$Pr_2N)_2BCl$ (**2.3**) (301 µL, 1.1 mmol) was then slowly added. After stirring for 1 h, an aldehyde (1.0 mmol) was added slowly with stirring. The reaction mixture was stirred for an additional hour at -78 °C and quenched with acetic acid (1.0 mL, 17.5 mmol) at -78 °C, then warmed up to room temperature over 30 min. The reaction mixture was treated with zinc powder (0.33 g, 5.0 mmol) and stirred overnight at room temperature (for entries 1 and 2) or refluxed overnight (for

entries 3-6). The mixture was basified with excess ammonium hydroxide (~15 mL) to pH 9-10. After stirring 30 min, the aqueous layer was extracted with EtOAc (x3). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography ($CHCl_3$-MeOH eluent system) to give a 2-aminoquinoline derivative **2.28**.

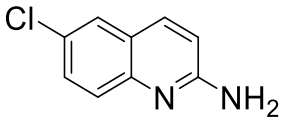
2-Aminoquinoline (2.28a):



2.28a

SiO_2 column chromatography ($CHCl_3$-MeOH = 9:1) yielded **2.28a** (110 mg, 76%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.7 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.60-7.54 (m, 1H), 7.30-7.24 (m, 1H), 6.72 (d, *J* = 8.7 Hz, 1H), 4.73 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 147.4, 138.2, 129.8, 127.5, 125.8, 123.5, 122.7, 111.7; HRMS (TOF MS ES^+) calcd = 145.0766 $[M + H]^+$, obsd = 145.0740. This product spectroscopically matched that of the known compound.[135]

6-Chloroquinolin-2-amine (2.28b):

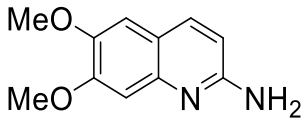


2.28b

SiO_2 column chromatography ($CHCl_3$-MeOH = 9:1) yielded **2.28b** (120 mg, 67%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.7 Hz, 1H), 7.68-7.42 (m, 3H), 6.72 (d, *J* = 8.7

Hz, 1H), 5.01 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 146.0, 137.1, 130.3, 127.8, 127.3, 126.2, 124.1, 112.6; HRMS (TOF MS ES$^+$) calcd = 179.0376 $[M + H]^+$, obsd = 179.0383.

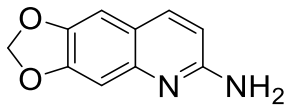
6,7-Dimethoxyquinolin-2-amine (2.28c):



2.28c

SiO_2 column chromatography ($CHCl_3$-MeOH = 9:1) yielded **2.28c** (112 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.7 Hz, 1H), 7.05 (s, 1H), 6.89 (s, 1H), 6.57 (d, *J* = 8.7 Hz, 1H), 4.85 (brs, 2H), 3.94 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 152.4, 146.7, 143.3, 136.8, 117.7, 109.1, 106.0, 105.4, 55.9, 55.8; HRMS (TOF MS ES$^+$) calcd = 205.0977 $[M + H]^+$, obsd = 205.0976.

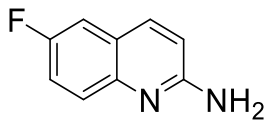
[1,3]Dioxolo[4,5-g]quinolin-6-amine (2.28d):



2.28d

SiO_2 column chromatography ($CHCl_3$-MeOH = 9:1) yielded **2.28d** (145 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.7 Hz, 1H), 7.04 (s, 1H), 6.92 (s, 1H), 6.58 (d, *J* = 8.7 Hz, 1H), 6.02 (s, 2H), 4.67 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 150.7, 145.3, 144.9, 137.1, 119.1, 109.0, 103.7, 103.4, 101.3; HRMS (TOF MS ES$^+$) calcd = 189.0664 $[M + H]^+$, obsd = 189.0643.

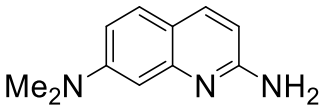
6-Fluoroquinolin-2-amine (2.28e):



2.28e

SiO_2 column chromatography ($CHCl_3$-MeOH = 9:1) yielded **2.28e** (108 mg, 67%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.7 Hz, 1H), 7.67-7.57 (m, 1H), 7.36-7.20 (m, 2H), 6.73 (d, *J* = 8.7 Hz, 1H), 4.87 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2 (d, $^1J_{CF}$ = 240.9 Hz), 156.4, 144.3, 137.4 (d, $^4J_{CF}$ = 4.5 Hz), 127.7 (d, $^3J_{CF}$ = 8.5 Hz), 123.7 (d, $^3J_{CF}$ = 9.4 Hz), 119.1 (d, $^2J_{CF}$ = 24.8 Hz), 112.6, 110.9 (d, $^2J_{CF}$ = 21.5 Hz); HRMS (TOF MS ES$^+$) calcd = 163.0672 $[M + H]^+$, obsd = 163.0659.

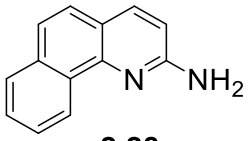
***N*^{7},*N*^{7}-Dimethylquinolin-2,7-diamine (2.28f):**



2.28f

SiO_2 column chromatography ($CHCl_3$-MeOH = 9:1) yielded **2.28f** (133 mg, 71%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 6.87-6.75 (m, 2H), 6.42 (d, *J* = 8.4 Hz, 1H), 5.17 (brs, 2H), 3.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 151.8, 148.1, 137.9, 128.1, 115.5, 111.6, 107.0, 103.9, 40.4; HRMS (TOF MS ES$^+$) calcd = 188.1159 $[M + H]^+$, obsd = 188.1188.

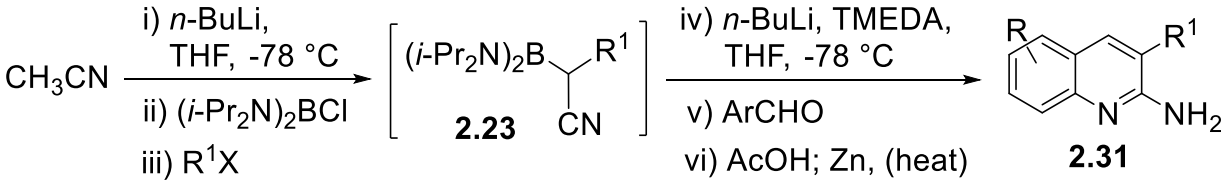
Benzo[*h*]quinolin-2-amine (2.28g):



2.28g

SiO_2 column chromatography ($CHCl_3$-MeOH = 9.8:0.2) yielded **2.28g** (80 mg, 41%). ^1H NMR (300 MHz, $CDCl_3$) δ 9.18.-9.10 (m, 1H), 7.95-7.81 (m, 2H), 7.69-7.51 (m, 4H), 6.77 (d, *J* = 8.4 Hz, 1H), 4.88 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 145.6, 138.0, 134.1, 130.3, 127.59, 127.55, 126.0, 125.2, 124.2, 123.3, 120.3, 110.3; HRMS (TOF MS ES^+) calcd = 195.0922 $[M + H]^+$, obsd = 195.0917.

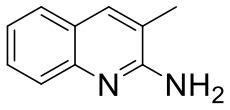
Synthesis of 3-substituted-2-aminoquinolines 2.31 (2.31a-2.31i):



Into a flame-dried 25 mL round-bottomed flask was added dry THF (6 mL) under an argon atmosphere. After cooling to -78 °C (acetone/dry-ice bath), *n*-BuLi (880 µL, 2.5 M in hexanes, 2.2 mmol) and dry CH_3CN (172 µL, 3.3 mmol) were added dropwise, respectively. After stirring for 20 min, $(i\text{-}Pr_2N)_2BCl$ (**2.3**) (301 µL, 1.1 mmol) was then slowly added. After stirring for 1 h, an alkylhalide (1.1 mmol) was added slowly with stirring at -78 °C and the mixture was stirred for another hour. After the reaction mixture was allowed to warm up to room temperature, THF and acetonitrile were rotary evaporated. Another portion of THF (6 mL) was added to the reaction vessel and it was cooled to -78 °C. TMEDA (165 µL, 1.1 mmol) and *n*-BuLi in hexanes (2.5 M; 0.44 mL,

1.1 mmol) were then added dropwise with stirring in this order at -78°C. After 1 hour, an aldehyde (1.0 mmol) was added slowly with stirring. The reaction mixture was stirred for an additional hour at -78 °C and quenched with acetic acid (1.0 mL, 17.5 mmol) at -78 °C, then warmed up to room temperature over 30 min. The reaction mixture was treated with zinc powder (0.33 g, 5.0 mmol) and stirred overnight at room temperature (for entries 1-8) or refluxed overnight (for entry 9). The mixture was basified with excess ammonium hydroxide (~15 mL) to pH 9-10. After stirring 30 min, the aqueous layer was extracted with EtOAc (x3). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography to give a 3-substituted-2-aminoquinoline derivative **2.31**.

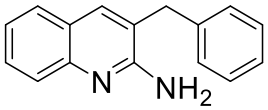
3-Methylquinolin-2-amine (2.31a):



2.31a

SiO_2 column chromatography ($CHCl_3$-MeOH = 5:1) yielded **2.31a** (105 mg, 66%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.69-7.45 (m, 4H), 7.22 (apparent t, *J* = 7.5 Hz, 1H), 5.28 (brs, 2H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 145.5, 136.9, 129.0, 126.8, 124.6, 124.1, 122.7, 119.6, 17.5; HRMS (TOF MS ES^+) calcd = 159.0922 $[M + H]^+$, obsd = 159.0901. This product spectroscopically matched that of the known compound.[5]

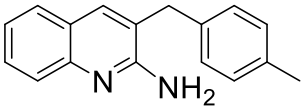
3-Benzylquinolin-2-amine (2.31b):



2.31b

SiO_2 column chromatography ($CHCl_3$-MeOH = 5:1) yielded **2.31b** (172 mg, 73%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.79-7.50 (m, 4H), 7.50-7.15 (m, 6H), 4.84 (brs, 2H), 4.00 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 146.7, 137.5, 137.4, 129.1, 128.9, 128.6, 127.1, 127.0, 125.5, 124.2, 122.7, 122.1, 37.9; HRMS (TOF MS ES^+) calcd = 235.1235 $[M + H]^+$, obsd = 235.1227.

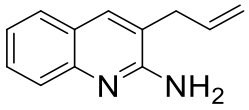
3-(4-Methylbenzyl)quinolin-2-amine (2.31c):



2.31c

SiO_2 column chromatography (Benzene-Acetone = 1:1) yielded **2.31c** (178 mg, 72%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.72-7.64 (m, 2H), 7.64-7.49 (m, 2H), 7.26 (apparent t, *J* = 7.5 Hz, 1H), 7.18-7.06 (m, 4H), 4.85 (brs, 2H), 3.95 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 146.8, 137.3, 136.7, 134.4, 129.7, 129.1, 128.5, 127.1, 125.6, 124.4, 122.7, 122.3, 37.7, 21.0; HRMS (TOF MS ES^+) calcd = 249.1392 $[M + H]^+$, obsd = 249.1383.

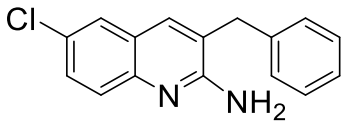
3-Allylquinolin-2-amine (2.31d):



2.31d

SiO_2 column chromatography (Benzene-Acetone = 1:1) yielded **2.31d** (122 mg, 66%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.72-7.63 (m, 2H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.52 (apparent t, *J* = 7.5 Hz, 1H), 7.25 (apparent t, *J* = 7.5 Hz, 1H), 6.03-5.91 (m, 1H), 5.28-5.06 (m, 4H), 3.38 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 146.4, 136.7, 134.5, 129.1, 127.0, 125.2, 124.2, 122.6, 121.2, 117.8, 36.0; HRMS (TOF MS ES^+) calcd = 185.1058 $[M + H]^+$, obsd = 185.1079.

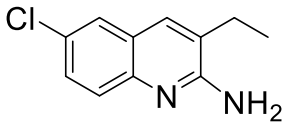
3-Benzyl-6-chloroquinolin-2-amine (2.31e):



2.31e

SiO_2 column chromatography ($CHCl_3$-MeOH = 5:1) yielded **2.31e** (166 mg, 62%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.60-7.51 (m, 3H), 7.43 (dd, *J* = 2.1 Hz, 9.0 Hz, 1H), 7.36-7.24 (m, 3H), 7.21-7.15 (m 2H), 5.14 (brs, 2H), 3.94 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 144.6, 136.9, 136.4, 129.7, 129.0, 128.6, 127.8, 127.1, 126.5, 125.8, 124.6, 123.3, 37.7; HRMS (TOF MS ES^+) calcd = 269.0846 $[M + H]^+$, obsd = 269.0832.

6-Chloro-3-ethylquinolin-2-amine (2.31f):

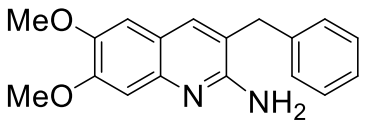


2.31f

SiO_2 column chromatography ($CHCl_3$-MeOH = 10:1) yielded **2.31e** (121 mg, 59%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.63-7.53 (m, 3H), 7.43 (dd, *J* = 2.4 Hz, 8.7 Hz, 1H), 5.04

(brs, 2H), 2.59 (q, *J* = 7.5 Hz, 2H), 1.36 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 144.4, 133.3, 129.3, 127.6, 126.7, 125.8, 125.7, 124.9, 23.7, 11.9; HRMS (TOF MS ES$^+$) calcd = 207.0689 $[M + H]^+$, obsd = 207.0687.

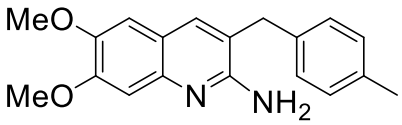
3-Benzyl-6,7-dimethoxyquinolin-2-amine (2.31g):



2.31g

SiO_2 column chromatography ($CHCl_3$-MeOH = 5:1) yielded **2.31g** (188 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.39-7.15 (m, 6H), 6.95 (s, 1H), 5.97 (brs, 2H), 4.05 (s, 3H), 4.01 (s, 2H), 3.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 147.9, 146.3, 136.7, 134.6, 128.9, 128.6, 127.1, 126.9, 119.3, 117.0, 106.2, 98.0, 56.3, 56.0, 37.4; HRMS (TOF MS ES$^+$) calcd = 295.1447 $[M + H]^+$, obsd = 295.1467.

6,7-Dimethoxy-3-(4-methylbenzyl)quinolin-2-amine (2.31h):

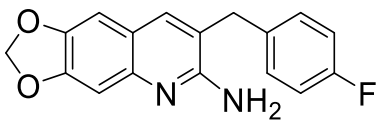


2.31h

SiO_2 column chromatography ($CHCl_3$-MeOH = 5:1) yielded **2.31h** (170 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.28 (s, 1H), 7.14 (d, *J* = 7.5, 2H), 7.09 (d, *J* = 7.5 Hz, 2H), 7.00 (s, 1H), 5.89 (brs, 2H), 4.06 (s, 3H), 3.98 (s, 2H), 3.95 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 147.9, 146.3, 136.8, 134.7, 133.5, 129.7,

128.4, 126.7, 119.5, 117.1, 106.2, 98.1, 56.4, 56.0, 37.1, 21.0; HRMS (TOF MS ES$^+$) calcd = 309.1603 $[M + H]^+$, obsd = 309.1612.

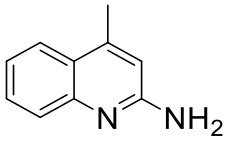
7-(4-Fluorobenzyl)-[1,3]dioxolo[4,5-*g*]quinolin-6-amine (2.31i):



2.31i

SiO_2 column chromatography (Hex-EtOAc-MeOH = 5:5:1) yielded **2.31i** (190 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.20-7.12 (m, 2H), 7.05-6.90 (m, 3H), 6.90 (s, 1H), 6.02 (s, 2H), 4.53 (brs, 2H), 3.91 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8 (d, $^1J_{CF}$ = 243.9 Hz), 155.0, 150.2, 145.0, 144.5, 136.6, 133.5, (d, $^4J_{CF}$ = 3.2 Hz), 130.0 (d, $^3J_{CF}$ = 7.9 Hz), 119.9, 119.3, 115.8, (d, $^2J_{CF}$ = 3.2 Hz), 103.5, 102.9, 101.2, 36.9; HRMS (TOF MS ES$^+$) calcd = 297.1039 $[M + H]^+$, obsd = 297.1038.

Synthesis of 4-methylquinolin-2-amine (2.33):

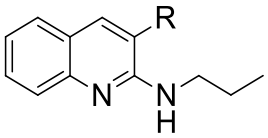


2.33

Into a flame-dried 25 mL round-bottomed flask was added dry THF (6 mL) under an argon atmosphere. After cooling to -78 °C (acetone/dry-ice bath), *n*-BuLi (880 µL, 2.5 M in hexanes, 2.2 mmol) and dry CH_3CN (172 µL, 3.3 mmol) were added dropwise, respectively. After stirring for 20 min, (*i*-$Pr_2N)_2BCl$ (**2.3**) (301 µL, 1.1 mmol) was then slowly added. After stirring for 1 hr, 2'-nitroacetophenone (107 µL, 1.0 mmol) was

added slowly with stirring. The reaction mixture was stirred for an additional hour at -78 °C and quenched with acetic acid (1.0 mL, 17.5 mmol) at -78°C, then warmed up to room temperature over 30 min. The reaction mixture was treated with zinc powder (0.33 g, 5.0 mmol) and stirred for 2 days at room temperature. The mixture was basified with excess ammonium hydroxide (~15 mL) to pH 9-10. After stirring 30 min, the aqueous layer was extracted with EtOAc (x3). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography (EtOAc:MeOH = 1:1) to give **2.33**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.55 (td, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.33-7.24 (m, 1H), 6.57 (s, 1H), 5.00 (brs, 2H), 2.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 147.1, 146.2, 129.6, 126.0, 123.8, 123.6, 122.5, 111.9, 18.7; HRMS (TOF MS ES$^+$) calcd = 159.0922 $[M + H]^+$, obsd = 159.0915.

Synthesis of *N*-propyl-2-aminoquinolines (*N*-2.28a and *N*-2.31a):

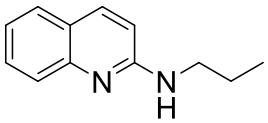


R = H or Me

The reaction mixture of **2.28a**/**2.31a** prepared as described in the general procedure above was quenched with acetic acid (1 mL, 17.5 mmol) and allowed to warm up to room temperature. The resulting mixture was then treated with zinc powder (0.523 g, 8.0 mmol) and stirred overnight at room temperature. Subsequently, propanal (364 µL, 5.0 mmol) was added and the mixture was stirred for 4 days at room temperature. The

mixture was basified with excess ammonium hydroxide (~15 mL) to pH 9-10. After stirring for 30 min, the aqueous layer was extracted with EtOAc (x3). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography to give the final products, ***N*-2.28a**/***N*-2.31a**.

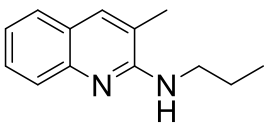
_N_-Propylquinolin-2-amine (*N*-2.28a):



***N*-2.28a**

SiO_2 column chromatography (Hex-EtOAc-MeOH = 5:5:1) yielded ***N*-2.28a** (114 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.7 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.60-7.47 (m, 2H), 7.19 (m, 1H), 6.63 (d, *J* = 9.0 Hz, 1H), 4.86 (brs, 1H), 3.48-3.40 (m, 2H), 1.68 (dq, *J* = 7.2 Hz, 7.2 Hz, 2H), 1.02 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 148.0, 137.3, 129.5, 127.4, 125.9, 123.3, 121.8, 110.9, 43.6, 22.9, 11.5; HRMS (TOF MS ES$^+$) calcd = 187.1235 $[M + H]^+$, obsd = 187.1245.

3-Methyl-*N*-Propylquinolin-2-amine (*N*-2.31a):

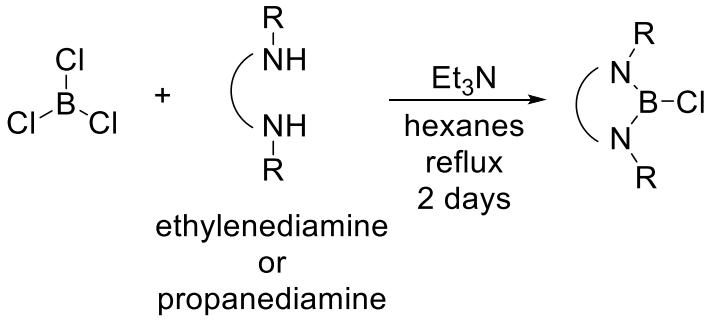


***N*-2.31a**

SiO_2 column chromatography (EtOAc-MeOH = 95:5) yielded ***N*-2.31a** (120 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 1H), 7.60 (s, 1H), 7.56-7.43 (m, 2H),

7.18 (td, *J* = 7.4 Hz, 0.9 Hz, 1H), 4.49 (brs, 1H), 3.60 (dt, *J* = 5.4 Hz, 7.2 Hz, 2H), 2.24 (s, 3H), 1.74 (tq, *J* = 7.2 Hz, 7.2 Hz, 2H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 147.2, 135.3, 128.3, 126.6, 126.0, 123.6, 121.7, 119.5, 43.3, 22.9, 17.4, 11.7; HRMS (TOF MS ES$^+$) calcd = 201.1392 $[M + H]^+$, obsd = 201.1390.

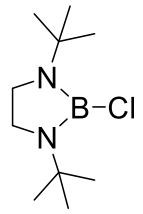
Synthesis of cyclic diaminochloroboranes (2.5, 2.21, 2.39, 2.41, 2.44, 2.47, 2.49, 2.51):



A 1000 mL, three necked, round-bottomed flask equipped with a magnetic stir bar, rubber septum, and a reflux condenser connected to an argon inlet adapter was assembled. The system was flame-dried, flushed with argon, and hexanes (150 mL) followed by triethylamine (25.8 mL, 185 mmol) were added to the flask *via* a syringe. The flask was cooled in an ice-water bath and a solution of trichloroboron (100 mL, 1 M in DCM, 100 mmol) was added dropwise. The stirring was continued for 30 min at 0 °C. The cooling bath was removed and the mixture was stirred at room temperature for an additional 30 min. *N*,*N*'-Diisopropylethylenediamine or *N*,*N*'-dialkylpropanediamine (90 mmol) was added slowly to the reaction mixture via a syringe over 15 min at room temperature. After the addition was complete, the rubber septum was replaced with a glass stopper under argon flow, and all glass joints were secured with Keck clips. The mixture was brought to reflux, and reacted for two days. After cooling to room

temperature, the resulting mixture was filtered. The product was highly sensitive to moisture, thus any contact with air/moisture was minimized. The salt by-product was washed with dry hexanes, and the combined filtrates were concentrated *in vacuo*. The residue was distilled under reduced pressure to give a clear liquid.

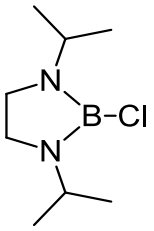
1,3-Di-*tert*-butyl-2-chloro-1,3,2-diazaborolidine (2.5):



2.5

Short-path distillation (Kugelrohr) under reduced pressure (0.1 mm Hg, 102 °C) gave 1.8 g (8.3 mmol, 9%) of **2.5** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.18 (s, 4H), 1.27 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.2, 41.6, 28.3.

2-Chloro-1,3-diisopropyl-1,3,2-diazaborolidine (2.21):

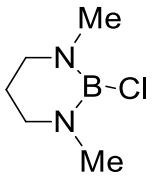


2.21

Distillation under reduced pressure (0.1 mm Hg, 90-100 °C) gave 14.2 g (75.1 mmol, 83%) of **2.21** as a clear liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (sep, J = 6.6 Hz, 2H),

3.18 (s, 4H), 1.07 (d, J = 6.6 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.5, 41.1, 21.3; HRMS (TOF MS ES$^+$) calcd = 189.1331 $[M + H]^+$, obsd = 189.1361.

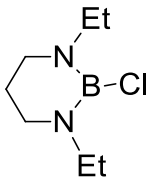
2-Chloro-1,3-dimethyl-1,3,2-diazaborinane (2.39):



2.39

This reaction was performed at a 40.8 mmol scale. Distillation under reduced pressure (0.1 mm Hg, 66-75 °C) gave 3.4 g (25.7 mmol, 63%) of **2.39** as a clear liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 (t, J = 6.0 Hz, 4H), 2.74 (s, 6H), 1.89 (p, J = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.7, 38.0, 26.0; HRMS (TOF MS ES$^+$) calcd = 147.0861 $[M + H]^+$, obsd = 147.0823.

2-Chloro-1,3-diethyl-1,3,2-diazaborinane (2.41):

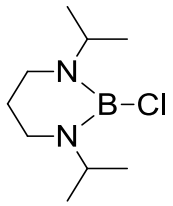


2.41

This reaction was performed at a 70.4 mmol scale. Distillation under reduced pressure (0.1 mm Hg, 140-160 °C) gave 8.2 g (47.2 mmol, 67%) of **2.41** as a clear liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09 (q, J = 7.2 Hz, 4H), 2.96 (t, J = 5.7 Hz, 4H), 1.86 (p, J =

5.7 Hz, 2H), 1.01 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.9, 44.9, 26.6, 14.7.

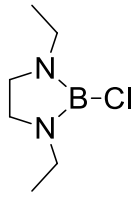
2-Chloro-1,3-diisopropyl-1,3,2-diazaborinane (2.44):



2.44

This reaction was performed at a 60.7 mmol scale. Distillation under reduced pressure (0.1 mm Hg, 110-125 °C) gave 9.3 g (45.7 mmol, 75%) of **2.44** as a clear liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (sep, J = 6.6 Hz, 2H), 2.87 (t, J = 5.7 Hz, 4H), 1.77 (p, J = 5.7 Hz, 2H), 1.03 (d, J = 6.6 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.9, 38.7, 27.0, 20.8; HRMS (TOF MS ES$^+$) calcd = 203.1488 $[M + H]^+$, obsd = 203.1438.

2-Chloro-1,3-diethyl-1,3,2-diazaborolidine (2.47):

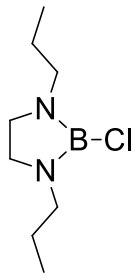


2.47

This reaction was performed in an 80.3 mmol scale. Distillation under reduced pressure (0.1 mm Hg, 118-140 °C) gave 8.3 g (51.6 mmol, 64%) of **2.47** as a clear liquid. ^{1}H

NMR (500 MHz, $CDCl_3$) δ 3.24 (s, 4H), 3.00 (q, *J* = 7.0 Hz, 4H), 1.04 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.6, 40.0, 14.6.

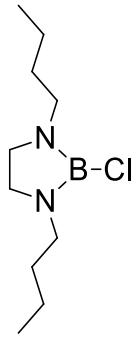
2-Chloro-1,3-dipropyl-1,3,2-diazaborolidine (2.49):



2.49

This reaction was performed at a 34.8 mmol scale. Distillation under reduced pressure (0.1 mm Hg, 110-125 °C) gave 5.5 g (29.2 mmol, 84%) of **2.49** as a clear liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 3.22 (s, 4H), 2.91 (t, *J* = 7.2 Hz, 4H), 1.44 (q, *J* = 7.2 Hz, 4H), 0.85 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.5, 47.0, 21.9, 11.2.

1,3-Dibutyl-2-chloro-1,3,2-diazaborolidine (2.51):

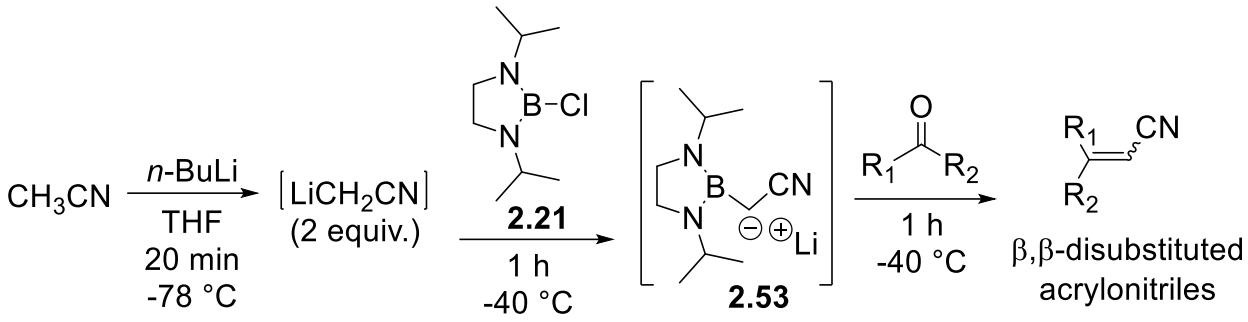


2.51

This reaction was performed in an 88 mmol scale. Distillation under reduced pressure (0.1 mm Hg, 130-170 °C) gave 13.7 g (63.4 mmol, 72%) of **2.51** as a clear liquid. ^1H

NMR (300 MHz, $CDCl_3$) δ 3.22 (s, 4H), 2.94 (t, *J* = 7.2 Hz, 4H), 1.40 (m, 4H), 1.29 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.1, 45.4, 31.0, 19.8, 13.9.

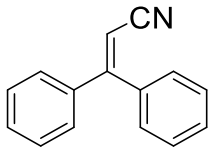
General procedure for one-pot olefination of ketones:



β,β-Disubstituted acrylonitriles (Scheme 2.43-2.45, Table 2.18-2.24): Into a flame-dried 25 mL round-bottomed flask was added dry THF (6 mL) under an argon atmosphere. After cooling to -78 °C (acetone/dry-ice bath), *n*-BuLi (880 µL, 2.5 M in hexanes, 2.2 mmol) and dry CH_3CN (172 µL, 3.3 mmol) were added dropwise, respectively. After stirring for 20 min, the acetone/dry-ice bath was replaced by an acetonitrile/dry-ice bath (-40 °C). Cyclic diaminochloroborane **2.3** (218 µL, 1.1 mmol) was then slowly added to the reaction mixture. After stirring for 1 h, a ketone (1.0 mmol) was added. The reaction mixture was stirred for an additional hour at -40 °C and then quenched with 50% saturated aqueous NH_4Cl solution (10 mL) at -40 °C, then warmed up to room temperature over 30 min. After phase separation, the aqueous layer was extracted with Et_2O (x2). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography. In the case where the crude product was a mixture of

(*E*)- and (*Z*)-isomers, it was usually possible to isolate some pure fractions of those stereoisomers during SiO_2 column chromatography.

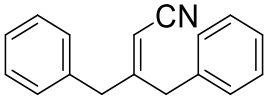
3,3-Diphenylacrylonitrile (2.55a):



2.55a

SiO_2 column chromatography (Hexanes:EtOAc = 95:5; R_f = 0.24) yielded **2.55a** (200 mg, 97%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.36 (m, 8H), 7.31-7.29 (m, 2H), 5.74 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 138.9, 137.0, 130.4, 130.0, 129.6, 128.6, 128.54, 128.47, 117.9, 94.9. This product spectroscopically matched that of the known compound.[150]

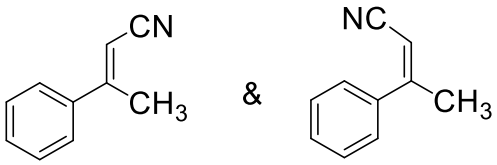
3-Benzyl-4-phenylbut-2-enenitrile (2.55b):



2.55b

SiO_2 column chromatography (Hexanes:EtOAc = 14:1; R_f = 0.33) yielded **2.55b** (193 mg, 83%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.23 (m, 8H), 7.06-7.03 (m, 2H), 5.09 (t, ^4J = 1.2 Hz, 1H), 3.72 (s, 2H), 3.36 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 136.7, 136.2, 129.3, 128.88, 128.85, 128.81, 127.16, 127.12, 117.2, 97.5, 41.6, 40.6; HRMS (TOF MS ES$^+$) calcd = 366.0259 [M + Cs]$^+$, obsd = 366.0211.

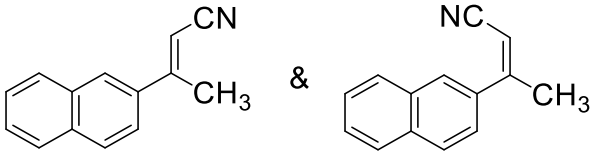
3-Phenylbut-2-enenitriles (2.55c):



(*E*)-**2.55c** (*Z*)-**2.55c**

SiO_2 column chromatography (Hexanes:EtOAc = 20:1) yielded **2.55c** (132 mg, 92%, *E*:*Z* = 58:42) as a clear liquid. **(*E*)-isomer**: R_f = 0.24; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.40 (m, 5H), 5.62 (q, ^4J = 0.9 Hz, 1H), 2.48 (d, ^4J = 0.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 138.3, 130.3, 128.8, 125.9, 117.6, 95.6, 20.2. **(*Z*)-isomer**: R_f = 0.17; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.53 (m, 2H), 7.45-7.42 (m, 3H), 5.40 (q, ^4J = 1.5 Hz, 1H), 2.29 (d, ^4J = 1.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 137.9, 129.9, 128.6, 127.1, 117.5, 95.5, 24.7. These products spectroscopically matched those of the known compounds.[151]

3-(Naphthalen-2-yl)but-2-enenitriles (2.55d):

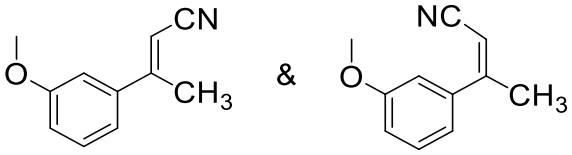


(*E*)-**2.55d** (*Z*)-**2.55d**

SiO_2 column chromatography (Hexanes:EtOAc = 14:1) yielded **2.55d** (182 mg, 94%, *E*:*Z* = 60:40) as a yellow oil. **(*E*)-isomer**: R_f = 0.29; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.89-7.84 (m, 3H), 7.56-7.54 (m, 3H), 5.76 (brs, 1H), 2.58 (d, ^4J = 1.0 Hz, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 159.3, 135.2, 133.9, 132.9, 128.7, 128.6, 127.6, 127.4, 126.9, 126.1, 122.7, 117.7, 95.7, 20.1. This product spectroscopically matched that of the known compound.[151] **(*Z*)-isomer**: R_f = 0.21; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.92-7.85 (m, 3H), 7.67-7.64 (m, 1H), 7.55-7.52 (m, 2H), 5.49 (q, ^4J = 1.5 Hz, 1H), 2.38 (d, ^4J = 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 135.2, 133.7, 132.9, 128.6, 128.4, 127.7, 127.2, 127.0, 126.7, 124.2, 117.6, 95.7, 24.7.

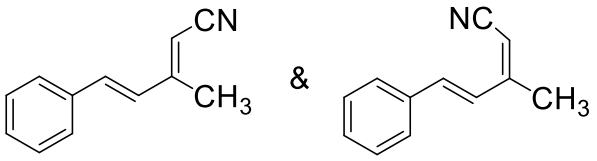
3-(3-Methoxyphenyl)but-2-enenitriles (2.55e):



(*E*)-**2.55e** (*Z*)-**2.55e**

SiO_2 column chromatography (Hexanes:EtOAc = 11:1) yielded **2.55e** (166 mg, 96%, *E*:*Z* = 60:40) as a yellow oil. **(*E*)-isomer**: R_f = 0.26; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.29 (m, 1H), 7.05-7.03 (m, 1H), 6.97-6.94f (m, 2H), 5.60 (q, ^4J = 0.9 Hz, 1H), 3.83 (s, 3H), 2.45 (d, ^4J = 0.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 159.6, 139.6, 129.8, 118.2, 117.5, 115.3, 111.9, 95.8, 55.3, 20.2; HRMS (TOF MS ES$^+$) calcd = 305.9790 [M + Cs]$^+$, obsd = 305.9759. This product spectroscopically matched that of the known compound.[151] **(*Z*)-isomer**: R_f = 0.18; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.32 (m, 1H), 7.13-7.08 (m, 2H), 6.98-6.94 (m, 1H), 5.39 (q, ^4J = 1.5 Hz, 1H), 3.84 (s, 3H), 2.27 (d, ^4J = 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 159.5, 139.1, 129.7, 119.4, 117.4, 115.5, 112.6, 95.5, 55.3, 24.6; HRMS (TOF MS ES$^+$) calcd = 305.9790 [M + Cs]$^+$, obsd = 305.9759.

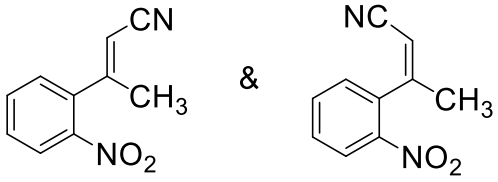
(4*E*)-3-Methyl-5-phenylpenta-2,4-dienenitriles (2.55f):



(*E*)-**2.55f** (*Z*)-**2.55f**

SiO_2 column chromatography (Hexanes:EtOAc = 5:1) yielded **2.55f** (104 mg, 71%, *E*:*Z* = 63:37) as a white solid. **(*E*)-isomer**: R_f = 0.45; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.46 (m, 2H), 7.41-7.33 (m, 3H), 6.94-6.79 (m, 2H), 5.33 (brd, ^4J = 1.0 Hz, 1H), 2.28 (d, ^4J = 0.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 136.6, 135.5, 129.4, 128.9, 127.5, 125.5, 117.0, 96.7, 19.4. This product spectroscopically matched that of the known compound.[152] The **(*Z*)-isomer** could not be isolated.

3-(2-Nitrophenyl)but-2-enenitriles (2.55g):

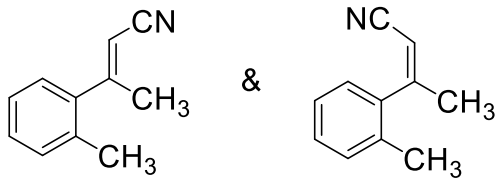


(*E*)-**2.55g** (*Z*)-**2.55g**

SiO_2 column chromatography (Hexanes:EtOAc = 6:1) yielded **2.55g** (168 mg, 89%, *E*:*Z* = 4:96) as a yellow oil. The **(*E*)-isomer**: R_f = 0.15; Almost entirely pure (*E*)-isomer with a little contamination of (*Z*)-isomer was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.1 Hz, 1.4 Hz, 1H), 7.67 (dt, *J* = 7.5 Hz, 1.4 Hz, 1H), 7.57 (apparent dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.28 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 5.29 (q, ^4J = 1.2 Hz, 1H), 2.39 (d, ^4J =

1.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 146.6, 136.0, 133.8, 129.9, 129.6, 124.9, 115.9, 98.9, 22.4. This product spectroscopically matched that of the known compound.[153] **(*Z*)-isomer**: R_f = 0.13; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 8.4 Hz, 0.9 Hz, 1H), 7.73 (dt, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.60 (apparent dt, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.36 (dd, *J* = 7.5 Hz, 1.2 Hz, 1H), 5.51 (q, ^4J = 1.5 Hz, 1H), 2.69 (d, ^4J = 1.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 146.3, 135.0, 134.3, 130.0, 129.7, 125.3, 115.9, 98.3, 24.8; HRMS (TOF MS ES$^+$) calcd = 320.9640 $[M + Cs]^+$, obsd = 320.9615.

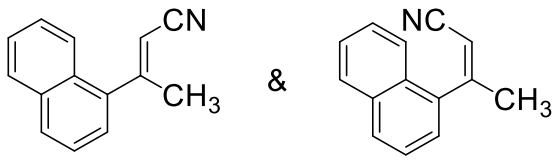
3-(*o*-Tolyl)but-2-enenitriles (2.55h):



(*E*)-**2.55h** (*Z*)-**2.55h**

This reaction was performed in a 2 mmol scale. SiO_2 column chromatography (Hexanes:Benzene:EtOAc = 17:3:1) yielded **2.55h** (230 mg, 89%, *E*:*Z* = 14:86) as a yellow oil. **(*E*)-isomer**: R_f = 0.35; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.17 (m, 3H), 7.10-7.05 (m, 1H), 5.25 (q, ^4J = 0.9 Hz, 1H), 2.37 (d, ^4J = 0.9 Hz, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 140.4, 133.9, 130.7, 128.6, 126.9, 125.9, 116.7, 99.0, 22.9, 19.7. This product spectroscopically matched that of the known compound.[151] **(*Z*)-isomer**: R_f = 0.25; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.22 (m, 3H), 7.10-7.08 (m, 1H), 5.50 (q, ^4J = 1.5 Hz, 1H), 2.31 (s, 3H), 2.20 (d, ^4J = 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 138.8, 133.8, 130.6, 128.7, 126.7, 126.1, 116.6, 98.6, 25.6, 19.1; HRMS (TOF MS ES$^+$) calcd = 158.1075 $[M + H]^+$, obsd = 158.1107.

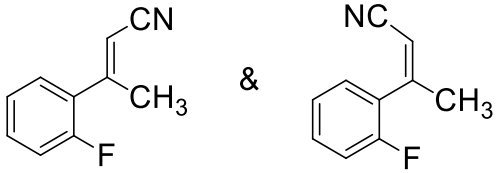
3-(Naphthalen-1-yl)but-2-enenitriles (2.55i):



(*E*)-**2.55i** (*Z*)-**2.55i**

SiO_2 column chromatography (Hexanes:DCM:EtOAc = 17:1:1) yielded **2.55i** (166 mg, 86%, *E*:*Z* = 24:76) as a yellow solid. **(*E*)-isomer**: R_f = 0.33; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.83 (m, 3H), 7.58-7.45 (m, 3H), 7.30-7.28 (m, 1H), 5.47 (q, ^4J = 1.1 Hz, 1H), 2.56 (d, ^4J = 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 138.5, 133.6, 129.7, 129.2, 128.6, 126.8, 126.3, 125.1, 124.6, 124.3, 116.7, 100.1, 23.7. This product spectroscopically matched that of the known compound.[154] **(*Z*)-isomer**: R_f = 0.18; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.89 (m, 2H), 7.80-7.77 (m, 1H), 7.60-7.50 (m, 3H), 7.37 (dd, *J* = 7.2, 1.2 Hz, 1H), 5.71 (q, ^4J = 1.5 Hz, 1H), 2.35 (d, ^4J = 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 136.8, 133.6, 129.4, 129.0, 128.6, 126.6, 126.1, 125.2, 124.5, 124.3, 116.4, 99.6, 26.1; HRMS (TOF MS ES$^+$) calcd = 325.9841 $[M + Cs]^+$, obsd = 305.9868.

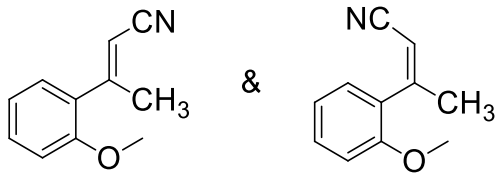
3-(2-Fluorophenyl)but-2-enenitriles (2.55j):



(*E*)-**2.55j** (*Z*)-**2.55j**

SiO_2 column chromatography (Hexanes:EtOAc = 8:1) yielded **2.55j** (120 mg, 87%, *E*:*Z* = 39:61) as a light yellow oil. **(*E*)-isomer**: R_f = 0.42; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 2H), 7.21-7.11 (m, 2H), 5.63 (q, ^4J = 1.2 Hz, 1H), 2.47 (d, ^4J = 1.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7 (d, ^1J = 251.6 Hz), 155.9 (d, ^3J = 1.8 Hz), 131.3 (d, ^3J = 8.8 Hz), 128.8 (d, ^2J = 2.9 Hz), 126.9 (d, ^3J = 12.1 Hz), 124.5 (d, ^4J = 3.6 Hz), 116.9, 116.5 (d, ^2J = 22.7 Hz), 99.7 (d, ^4J = 6.9 Hz), 21.4 (d, ^4J = 3.4 Hz). This product spectroscopically matched that of the known compound.[155] **(*Z*)-isomer**: R_f = 0.32; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.36 (m, 2H), 7.23-7.17 (m, 2H), 5.51 (q, ^4J = 1.5 Hz, 1H), 2.28 (d, ^4J = 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9 (d, ^1J = 249.6 Hz), 157.5, 131.2 (d, ^3J = 8.3 Hz), 129.3 (d, ^2J = 3.3 Hz), 126.2 (d, ^3J = 14.6 Hz), 124.4 (d, ^4J = 3.7 Hz), 116.5, 116.3 (d, ^2J = 21.8 Hz), 99.2, 24.5 (d, ^4J = 3.5 Hz).

3-(2-Methoxyphenyl)but-2-enenitriles (2.55k):

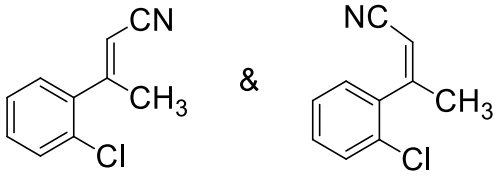


(*E*)-**2.55k** (*Z*)-**2.55k**

This reaction was performed in a 2 mmol scale. SiO_2 column chromatography (Toluene:EtOAc = 50:1) yielded **2.55k** (260 mg, 78%, *E*:*Z* = 19:81) as a clear oil. **(*E*)-isomer**: R_f = 0.49; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.32 (m, 1H), 7.20-7.17 (m, 1H), 6.99-6.91 (m, 2H), 5.57 (brd, ^4J = 1.2 Hz, 1H), 3.85 (s, 3H), 2.43 (d, ^4J = 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 156.6, 130.6, 128.9, 128.7, 120.7, 117.5, 111.3, 98.7, 55.5, 21.8. **(*Z*)-isomer**: R_f = 0.33; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.33 (m,

1H), 7.23-7.20 (m, 1H), 7.02-6.94 (m, 2H), 5.43 (q, ^4J = 1.5 Hz, 1H), 3.85 (s, 3H), 2.24 (d, ^4J = 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 155.9, 130.5, 128.8, 127.9, 120.7, 117.1, 111.3, 98.0, 55.4, 24.6.

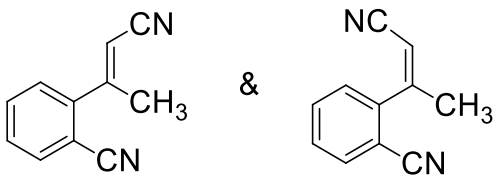
3-(2-Chlorophenyl)but-2-enenitriles (2.55l):



(*E*)-**2.55l** (*Z*)-**2.55l**

This reaction was performed in a 2.0 mmol scale. SiO_2 column chromatography (Hexanes:Benzene:EtOAc = 17:3:1) yielded **2.55l** (330 mg, 93%, *E*:*Z* = 11:89) as an orange oil. **(*E*)-isomer**: R_f = 0.40; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.40 (m, 1H), 7.33-7.28 (m, 2H), 7.18-7.15 (m, 1H), 5.37 (brs, 1H), 2.43 brs, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 139.3, 131.3, 130.2, 130.0, 128.7, 127.0, 116.4, 100.6, 22.2. **(*Z*)-isomer**: R_f = 0.29; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.42 (m, 1H), 7.36-7.30 (m, 2H), 7.24-7.21 (m, 1H), 5.41 (q, ^4J = 1.5 Hz, 1H), 2.26 (d, ^4J = 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 137.9, 131.1, 130.2, 130.1, 128.8, 127.2, 116.1, 99.8, 24.6.

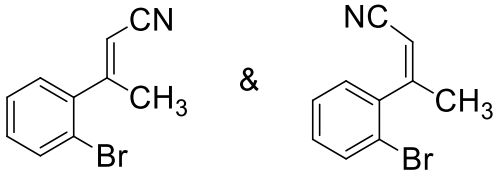
2-(1-Cyanoprop-1-en-2-yl)benzonitriles (2.55m):



(*E*)-**2.55m** (*Z*)-**2.55m**

SiO_2 column chromatography (Toluene:EtOAc = 8:1) yielded **2.55m** (132 mg, 47%, *E*:*Z* = 10:90) as a blackish oil. The **(*E*)-isomer** could not be isolated. **(*Z*)-isomer**: R_f = 0.45; Almost entirely pure (*Z*)-isomer with a little contamination of (*E*)-isomer was obtained; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.75 (m, 1H), 7.68 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.52 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.41 (dd, *J* = 7.8, 0.6 Hz, 1H), 5.65 (q, ^4J = 1.5 Hz, 1H), 2.36 (d, ^4J = 1.5 Hz, 3H).

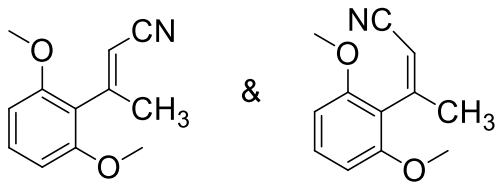
3-(2-Bromophenyl)but-2-enenitriles (2.55n):



(*E*)-**2.55n** (*Z*)-**2.55n**

SiO_2 column chromatography (Hexanes:EtOAc = 12:1) yielded **2.55n** (210 mg, 94%, *E*:*Z* = 4:96) as a light yellow oil. The **(*E*)-isomer** could not be isolated. **(*Z*)-isomer**: R_f = 0.22; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.38 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.27-7.19 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.22-7.18 (m, 1H), 5.54 (q, ^4J = 1.5 Hz, 1H), 2.26 (d, ^4J = 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 139.9, 133.2, 130.2, 128.6, 127.8, 120.2, 116.1, 99.7, 24.7.

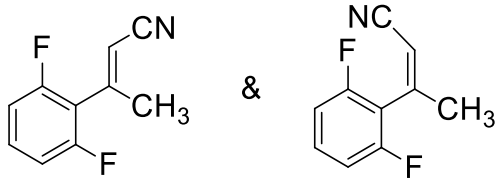
(*Z*)-3-(2,6-Dimethoxyphenyl)but-2-enenitrile (2.55p):



(*E*)-**2.55p** (*Z*)-**2.55p**

SiO_2 column chromatography (Hexanes:EtOAc = 4:1) yielded **2.55p** (130 mg, 72%, *E*:*Z* = 0:100) as a white solid. The **(*E*)-isomer** was not obtained. **(*Z*)-isomer**: R_f = 0.39; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (t, *J* = 8.4 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 2H), 5.51 (brs, 1H), 3.83 (s, 6H), 2.16 (d, ^4J = 1.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 156.6, 130.1, 117.1, 116.4, 104.1, 99.6, 55.9, 24.0; HRMS (TOF MS ES$^+$) calcd = 204.1129 [M + H]$^+$, obsd = 204.1193.

3-(2,6-Difluorophenyl)but-2-enenitriles (2.55r):

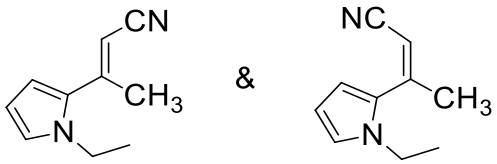


(*E*)-**2.55r** (*Z*)-**2.55r**

SiO_2 column chromatography (Hexanes:DCM:EtOAc = 17:1:1) yielded **2.55r** (145 mg, 81%, *E*:*Z* = 10:90) as a clear oil. **(*E*)-isomer**: R_f = 0.31; Almost entirely pure (*E*)-isomer with a little contamination of (*Z*)-isomer was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.27 (m, 1H), 6.99-6.91 (m, 2H), 5.49 (brs, 1H), 2.42 (apparent q, ^4J = 1.2 Hz, 3H). **(*Z*)-isomer**: R_f = 0.24; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.30 (m, 1H), 7.02-6.94 (m, 2H), 5.66 (q, ^4J = 1.6 Hz, 1H), 2.26 (d, ^4J = 1.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

159.1 (dd, ^{1}J = 250.5, 22.7 Hz), 151.1, 130.9 (t, ^{3}J = 10.3 Hz), 115.8, 115.6 (t, ^{2}J = 19.6 Hz), 111.9 (m), 102.4, 24.1 (t, ^{4}J = 1.9 Hz).

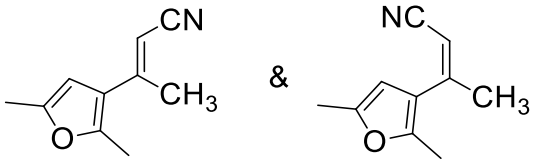
3-(1-Ethyl-1H-pyrrol-2-yl)but-2-enenitriles (2.55s):



(*E*)-**2.55s** (*Z*)-**2.55s**

SiO_2 column chromatography (Hexanes:EtOAc = 10:1) yielded **2.55s** (80 mg, 50%, *E*:*Z* = 22:78) as a clear oil. **(*E*)-isomer**: R_f = 0.22; Almost entirely pure (*E*)-isomer with a little contamination of the starting ketone was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (apparent t, *J* = 2.1 Hz, 1H), 6.45 (dd, *J* = 3.8, 1.7 Hz, 1H), 6.19 (apparent dt, *J* = 3.3, 1.2 Hz, 1H), 5.18 (brd, ^{4}J = 1.1 Hz, 1H), 4.04 (q, *J* = 0.72 Hz, 2H), 2.42 (d, ^{4}J = 0.9 Hz, 3H), 1.40 (t, *J* = 0.72 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 131.3, 127.0, 118.2, 114.0, 108.8, 91.1, 43.2, 21.4, 16.4. The R_f value of the **(*Z*)-isomer** was extremely close to that of the **(*E*)-isomer**; thus the pure **(*Z*)-isomer** could not be isolated.

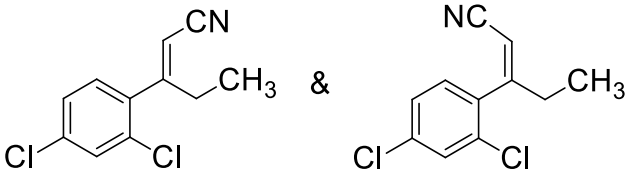
3-(2,5-Dimethylfuran-3-yl)but-2-enenitriles (2.55t):



(*E*)-**2.55t** (*Z*)-**2.55t**

SiO_2 column chromatography (Hexanes:Toluene:EtOAc = 12:1:1) yielded **2.55t** (119 mg, 74%, *E*:*Z* = 27:73) as a light yellow solid. **(*E*)-isomer**: R_f = 0.35; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (brd, ^4J = 1.3 Hz, 1H), 5.24 (brs, 1H), 2.40 (s, 3H), 2.32 (d, ^4J = 1.0 Hz, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 150.5, 149.4, 120.7, 118.0, 105.1, 93.2, 20.9, 14.4, 13.2. The R_f value of the **(*Z*)-isomer** was extremely close to that of the **(*E*)-isomer**; thus the pure **(*Z*)-isomer** could not be isolated.

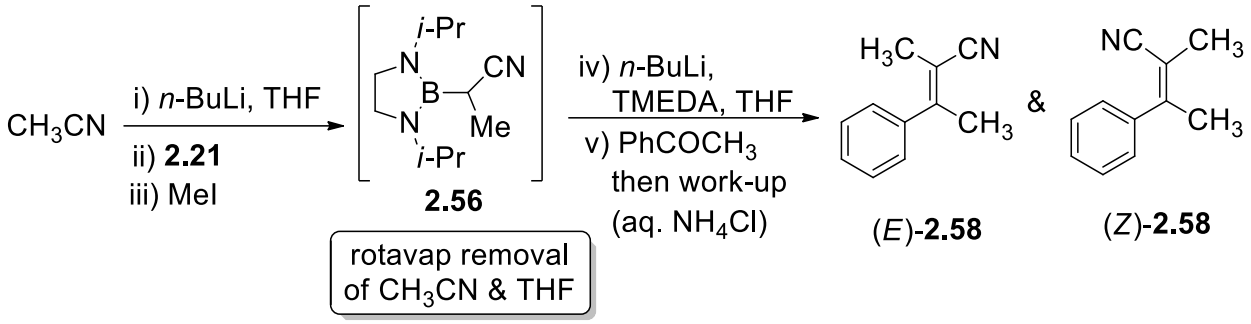
3-(2,4-Dichlorophenyl)but-2-enenitriles (2.55u):



(*E*)-**2.55u** (*Z*)-**2.55u**

SiO_2 column chromatography (Hexanes:DCM:EtOAc = 20:1:1) yielded **2.55u** (183 mg, 81%, *E*:*Z* = 61:39) as an yellow oil. **(*E*)-isomer**: R_f = 0.37; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 2.6 Hz, 1H), 7.29 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 5.29 (brs, 1H), 2.85 (q, *J* = 2.6 Hz, 2H), 1.02 (dt, ^3J = 7.6, ^5J = 0.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 136.3, 135.4, 132.5, 130.1, 130.0, 127.2, 115.9, 100.1, 28.9, 12.1. **(*Z*)-isomer**: R_f = 0.26; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 2.0 Hz, 1H), 7.31 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 5.54 (t, ^4J = 1.6 Hz, 1H), 4.12 (dq, ^2J = 7.3, ^4J = 1.4 Hz, 2H), 1.09 (t, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 135.8, 135.4, 132.3, 130.02, 129.98, 127.5, 116.1, 98.8, 30.9, 11.5.

Synthesis of 2-methyl-3-phenylbut-2-enenitriles (2.58):



Into a flame-dried round-bottomed flask was added dry THF (6 mL) under an argon atmosphere. After the mixture was cooled to -78 °C (acetone/dry ice bath), *n*-BuLi (880 μL, 2.5 M in hexanes, 2.2 mmol) and dry CH_3CN (172 μL, 3.3 mmol) were added dropwise, respectively. After the mixture was stirred for 20 min, cyclic diaminochloroborane **2.21** (218 μL, 1.1 mmol) was then slowly added. The acetone/dry ice bath replaced by an acetonitirle/dry ice bath (-40 °C). After 1 h of stirring, methyl iodide (1.1 mmol) was added. The acetonitrile/dry ice bath was replaced by an acetone/dry ice bath (-78 °C). The reaction mixture was stirred for an additional 1 h at -78 °C, and then concentrated under reduced pressure at room temperature. Subsequently, dry THF (6 mL) was added into the crude mixture under an argon atmosphere. After the mixture was cooled to -40 °C, *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (165 μL, 1.1 mmol) and *n*-BuLi (440 μL, 2.5 M in hexanes, 1.1 mmol) were added dropwise. After the mixture was stirred for 1 h, acetophenone (1.0 mmol) was slowly added, and the resulting mixture was stirred for 1 h at the same temperature. The reaction mixture was then quenched with 50% aqueous NH_4Cl (6 mL) at -40 °C and warmed up to room temperature (-40 °C to r.t. over 30 min). After phase separation, the aqueous layer was extracted with Et_2O (x2). The combined organics were washed with brine, dried over

$MgSO_4$, and concentrated under reduced pressure. The crude product was obtained as a mixture of *E*/*Z* isomers. [Note: *E*/*Z* ratio was determined by ^{1}H NMR of the crude reaction mixture.] The *E*/*Z* mixture was purified/separated by silica gel column chromatography (Toluene:Benzene = 4:1) yielding **2.58** (116 mg, 74%, *E*:*Z* = 21:79) as a light yellow liquid. **(*E*)-isomer**: R_f = 0.49; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.31 (m, 3H), 7.17-7.13 (m, 2H), 2.37 (q, ^5J = 1.6 Hz, 3H), 1.84 (q, ^5J = 1.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 139.3, 128.5, 128.3, 127.1, 119.8, 105.8, 24.8, 17.6. **(*Z*)-isomer**: R_f = 0.28; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.32 (m, 5H), 2.17 (q, ^5J = 1.1 Hz, 3H), 2.07 (q, ^5J = 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 141.0, 128.7, 128.4, 127.3, 120.3, 105.3, 20.7, 17.6. These products spectroscopically matched those of the known compounds.[156]

VITA

Yusuke Takahashi was born in Koshigaya city, Saitama, Japan on December 4th, 1985. Upon graduation from the Urawa High School, Saitama city, Japan, in March 2004, he pursued his higher education oversea, and initiated his college study at the Sam Houston State University, Huntsville, TX in the Fall of 2004. After the five, fulfilling semesters at SHSU, he transferred to the University of Mississippi, where his chemistry research career started. He received his Bachelor of Science degree in Chemistry from the University of Mississippi in December 2009, and joined the doctoral program in the Department of Chemistry and Biochemistry at Ole Miss in the spring of 2010, with a research focus on synthetic organic chemistry. He successfully completed all the requirements for the Ph.D. degree in the summer of 2015, and finished his long, productive years of college life in the United States of America. He will begin employment at Eli Liily Japan K.K. in September 2015.

Yusuke Takahashi

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EDUCATION

Ph.D., Chemistry, University of Mississippi, Fall 2015

Concentration: Synthetic Organic Chemistry

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TEACHING EXPERIENCE

Teaching Assistant, Spring 2010 – Spring 2013

University of Mississippi

Courses: Chem 225 Elementary Organic Chemistry Laboratory I, Chem 226 Elementary Organic Chemistry Laboratory II

Teaching Assistant, Summer 2006 – Fall 2006

Sam Houston State University

Courses: CHM 115 Inorganic and Environmental Chemistry Laboratory, CHM 116 Organic and Biochemistry Laboratory

HONORS AND FELLOWSHIPS

American Chemical Society Graduate Research Scholar Award, 2014 - 2015
Department of Chemistry and Biochemistry, University Mississippi

International Undergraduate Student Scholarship, Fall 2008 – Fall 2009
University of Mississippi

Dean's List, Spring 2008 – Fall 2008
University of Mississippi

PUBLICATIONS AND PRESENTATIONS

Tomioka, T.; Takahashi, Y.; Maejima, T.; Yabe, Y.; Iwata, H.; Hamann, M. T., Karlotoxin synthetic studies: concise synthesis of a C(42-63) B-ring tetrahydropyran fragment. *Tetrahedron Lett*ers **2013**, 54, 6584 – 6586

Tomioka, T.; Takahashi, Y.; Maejima, T., One-Pot Synthesis of 2-aminoquinoline-based Alkaloids from Acetonitrile. *Organic & Biomolecular Chemistry* **2012**, 10, 5113-5118

Research Poster Presentation at the American Chemical Society Ole Miss Local Section 17th Annual Research Poster Session (November, 2012)

Poster Title: Synthetic Studies of Karlotoxin 2

National Center for Natural Products Research Center, University, MS

Tsuda, T.; Kondo, K.; Tomioka, T.; Takahashi, Y.; Matsumoto, H.;Kuwabata, S.; Hussey, C. L., Design, Synthesis, and Electrochemistry of Room-Temperature Ionic Liquids Functionalized with Propylene Carbonate. *Angewandte Chemie International Edition* **2011**, 50, 1310-1313

Oral Research Presentation at the American Chemical Society South Eastern Regional Meeting (October, 2011)

Presentation Title: Development of One-Pot Synthesis of 2-Aminoquinoline Derivatives Utilizing α–Diaminoboryl Carbnion

Omni Hotel, Richmond, VA

Tomioka, T.; Takahashi, Y.; Vaughan, H. G.; Yanase, T., A Facile, One-Pot Synthesis of β-substituted (*Z*)-Acrylonitriles Utilizing an α-Diaminoboryl Carbanion. *Organic Letters* **2010**, 12, 2171-2173

Oral Research Presentation at the 29th Annual Undergraduate Research Conference hosted by the Department of Chemistry at the University of Memphis (February, 2009)

Presentation Title: Design and synthesis of a uniquely functionalized ionic liquid: Towards electrochemical applications

University of Memphis, Memphis, TN