NANYANG TECHNOLOGICAL UNIVERSITY

Part I Catalytic Asymmetric Arylation of Esters for Profen Synthesis

Part II Fast Suzuki Coupling of Heteroaryl Chlorides

YANG JUNFENG

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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Part I Catalytic Asymmetric Arylation of Esters for Profen Synthesis

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YANG JUNFENG

School of Physical and Mathematical Sciences

A thesis submitted to the Nanyang Technological University
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I would start by thanking the person who is responsible for instilling me the desire to be a chemist. Some may say that is not a person you thank but you resent. Fortunately, I do not resent my surporvisor for helping me discover the potentials and perseverance I have. Steve has evolved through my time at NTU. It has been a transformative experience to be a member in his group, and it will mark (or scar) in the rest of my life.

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miles away.

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TABLE OF CONTENTS

Appendix

Abstract

Transition metal-catalyzed cross-coupling reaction has become a useful methodology for the formation of C-C bond. This thesis describes two new improved methods of the C-C bond formation catalyzed by palladium catalyst.

Chapter one reports a general method of palladium-catalyzed coupling of ester to produce tertiary carbon centers with high yield and exellent ee. It offers a general method for the synthesis of profen drugs. Aryl triflates carrying *para*-elctron-withdrawing and electron-donating groups are tolerated. Vinyl triflates can also be converted to the corresponding vinyl ester with excellent ee. The use of a new biarylphosphine improved stereoselectivity as compared to the previously reported catalyst. The two CF_3 groups on the benzyl side chain of the ligand may acidify the benylic CH bonds. This probably makes the C-H bond better hydrogen donors in the interaction with Pd-bound enolate, which is responsible for excellent stereoinduction and ligand design.

Chapter two describes a new catalytic system for Suzuki-Miyaura coupling of heteroaryl chlorides and heteroayl boronic acids. Most of the major families of heteroaryl chlorides can reached full conversion within minutes to hours at room temperature. The relative reactivity of coupling partners is also studied in this part. Firstly, for heteroaryl chloride, the more electron-rich ones reacted more slowly than electron-deficient ones because of the slower oxidative addition. Secondly, for the heteroarylboronic acids, the more electron-deficient ones reacted more slowly.

LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
Ad	adamantyl
Ar	aryl
BINAP	1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
calcd	calculated
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichoromethane
conv.	conversion
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
DME	1,2-dimethoxylethane
DMF	dimethylformamide
dt	doublet of trifplets
ee	enantiomeric excess
EI	electronic Ionization
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
Et2O	diethyl ether
EtOAc	ethyl acetate
g	gram
GC	gas chromotography
h	hour(s)
Hz	herts
IMes	1,3-bis(mesityl)imidazole-2-ylidene

*i*Pr	*iso*-propyl
IPr	1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene
m	multiplet
M^+	parent ion peak (mass spectrum)
Me	methyl
min	minute(s)
mL	milliliter(s)
mmol	millimole
mol%	mole percent
MS	mass spectrometry
Nap	naphthyl
*n*Bu	*n*-butyl
*n*hex	*n*-hexyl
NMR	nuclear magnetic resonance
°C	degree centigrade
OTf	trifluoromethanesulfonate
PCy_3	tricyclopentylphosphine
Ph	phenyl
$PhCF_3$	a,a,a-trifluorotoluene
PhMe	toluene
ppm	perts per million
q	quartet
rt	room temperature
TBME	methyl tert-butyl ether
*t*Bu	*tert*-butyl
THF	tetrahyDr.ofuran
TMEDA	N,N,N′,N′-Tetramethylethylenediamine
TMS	trimethylsilyl
Tol	toluene
δ	chemical shift

Chapter 1: Asymmetric Synthesis of Profen Drugs via Pd-Catalyzed Ester Coupling

1.1 Background

Profens belong to an important class of nonsteroidal antiinflammatory drugs and examples include Ibuprofen, Naproxen, Ketoprofen, etc (Figure 1.1). They are all α-arylpropionic acid carrying tertiary α-stereocenters.[1] For example, optically pure (*S*)-Naproxen was first introduced by Syntex in 1976.[1a] In 1991, (*S*)-Naproxen ranked the fourth in sales of all chiral pharmaceuticals. In 1995, the sales of (*S*)-Naproxen reached $1 billion. All of other members of profens, however, are marked as racemic drugs.

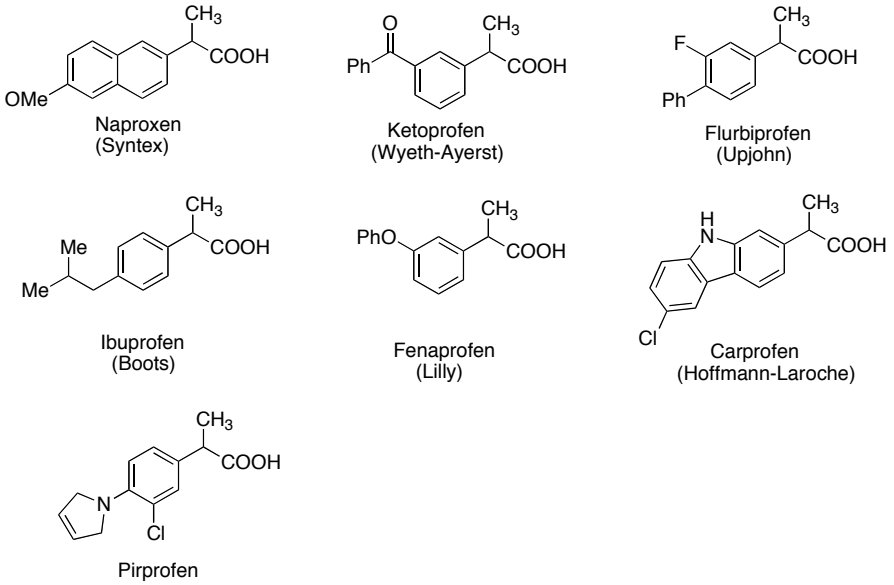


Figure 1.1 Examples of profen drugs.

The two enantiomers of profens act significantly different in both pharmacodynamics and pharmacokinetics. The (*S*)-profens are the biologically active

enantiomers that inhibit the cyclooxygenases COX-1 and COX-2 in the prostaglandine synthesis.[2] Some profens can undergo *in vivo* inversion from the (*R*)- to (*S*)-form. Coenzyme A causes the unidirectional inversion via the formation of thioesters of profens.[3] Thus, when racemic profens were administered, the (*S*)-forms accumulated after hours. However, this inversion could lead to uncertainty in the actual dosage of the active (*S*)-profens. Moreover, (*S*)-profens are absorbed faster *in vivo* than the racemic samples.[4] It has long been postulated that enantioenriched profens may be directly accessed via metal-catalyzed, asymmetric arylation of propionates.

Over the past two decades, metal-catalyzed asymmetric *α*-arylation has received significant attention in synthetic community. In 1997, Hartwig,[5] Buchwald[6] and Miura[7] independently reported that Pd-catalyzed coupling of ketones and aryl bromides can be conducted in the presence of bases, without using preformed silyl or tin enolates. This method greatly simplified the synthetic operation for enolate arylations.[8] Later, the asymmetric version was developed based on these conditions that directly used strong bases.

In 1998, Buchwald *et al.* reported the first asymmetric coupling in high ee, by using aryl bromides, 2-methyl-*α*-tetralone and NaO*t*Bu. The BINAP ligand gave >90% ee in some examples (Figure 1.2a).[9] Later, Hartwig *et al.*[10] and Chan *et al.*[11] showed that the ee can be improved by using bisphosphines possessing smaller natural dihedral angles such as Difluorphos and P-Phos (Figure 1.2b and 1.2c).

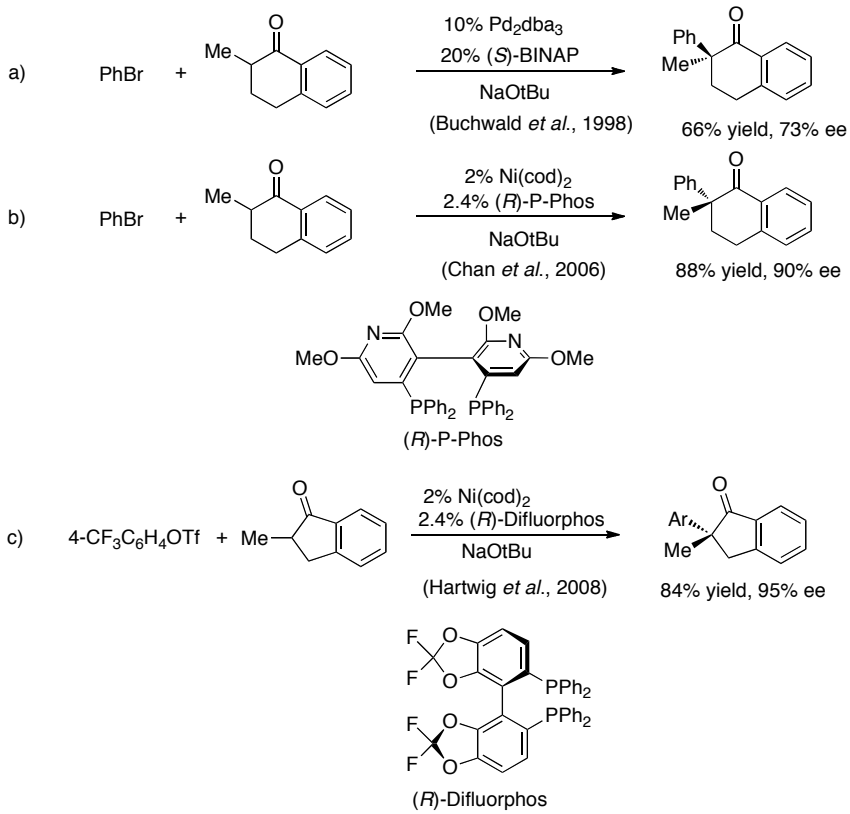


Figure 1.2 Asymmetric arylations of cyclic ketones

A typical catalytic cycle of the asymmetric arylation is shown in Figure 1.3, consisting of three key steps as shown below. The stereodetermining step can be C-C reductive elimination of one stereoisomer of *C*-bound Pd enolates and several *C*-bound and *O*-bound enolate species existed in equilibrium in solution.[8a] Alternatively, enolate transmetalation to Pd centers may selectively form one diastereomeric *C*-bound Pd enolates.

(1) Oxidative addition of the aryl halide to Pd(0) forms the ArPdX species.

(2) Substitution of the halide by the in situ generated enolate gives a palladium enolate complex.

(3) C-C reductive elimination affords the coupling product and regenerates the catalyst.

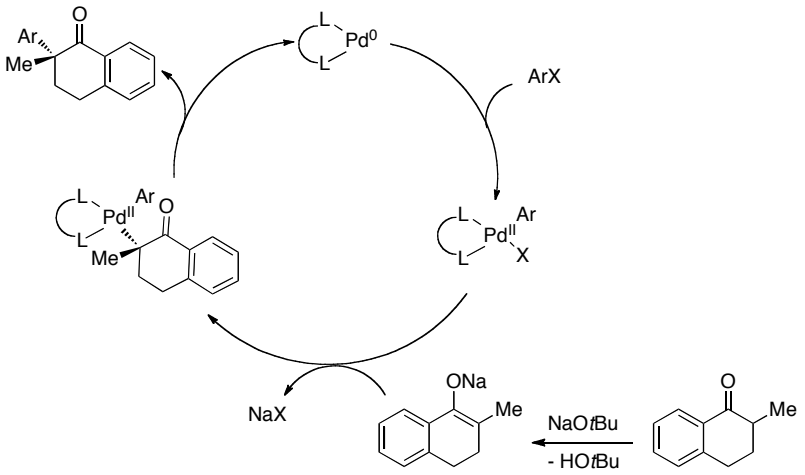


Figure 1.3 A catalytic cycle for Pd-catalyze α-arylation of ketones

Later, the *in situ* enolate generation was extended to asymmetric arylation and vinylation of other classes of carbonyl compounds such as aldehydes,[12] lactones[13] and oxindoles (Figure 1.4).[14]

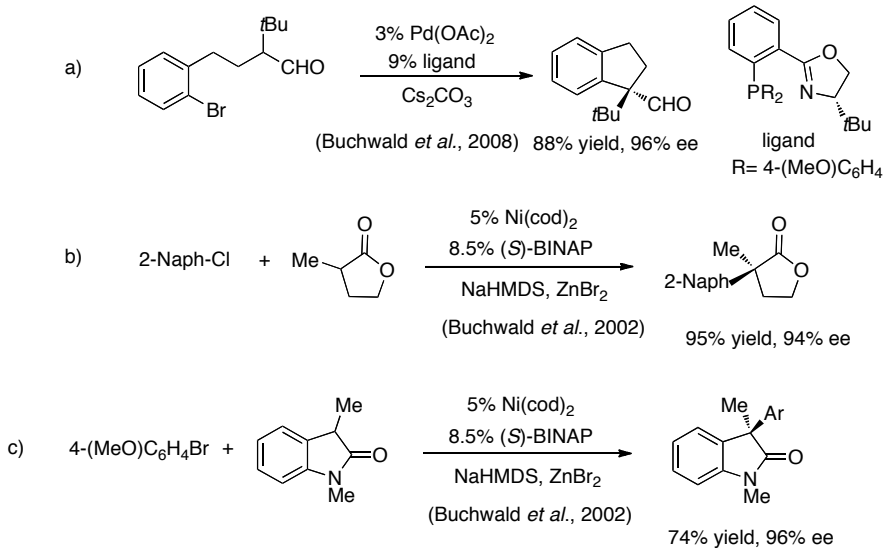


Figure 1.4 Asymmetric arylations of carbonyl compounds

However, for many years, the metal-catalyzed asymmetric arylation was limited to the formation of quaternary α-stereocenters. Arylation products carrying tertiary α-centers are readily deprotonated and racemized under strongly basic conditions. Previously, asymmetric arylation of esters was attempted to produce tertiary centers

by Santi *et al*, but only ~50% ee was obtained in the best scenario using BINAP ligand and silyl ketene acetals.[15]

In 2011, Dr. Zhiyan Huang in our group successfully realized highly enantioselective asymmetric arylation of esters (Figure 1.5).[16] In this reaction, a silyl ketene acetal derived from *tert*-butyl propionate and the aryl triflate were used as coupling partners.

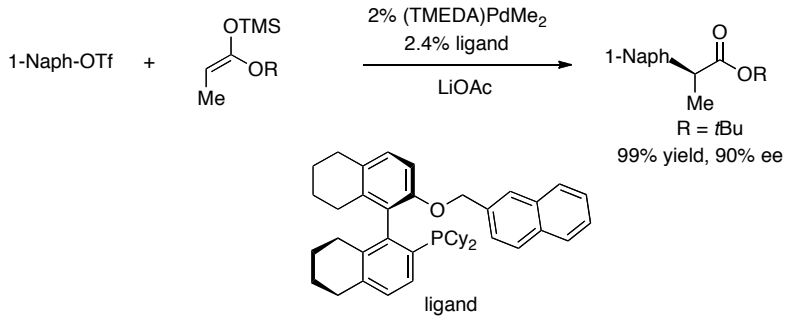


Figure 1.5 Asymmetric coupling of aryl triflate with ester enolates

This work revealed several critical factors that affected the enantioselectivity. First, the size of *R* groups in ketene acetals affected the ee significantly. The ee is highest when *R* is *tert*-butyl group.

Second, the (*E*)-geometry of the *O*-TMS ketene acetals was crucial for the obtained high enantioselectivity. The (*Z*)-isomer gave around 50% ee.

Third, LiOAc promoted efficient transmetalation of the enolate and it was not basic enough to cause product racemization.

Fourth, 2-naphthyl side chain on chiral biarylphosphine was important for high ee. Based on our results from related asymmetric arylation of ketones[17] and lactones,[18] the C-H bonds of ligand probably form weak hydrogen bonds with Pd enolates. The hydrogen bonds facilitated the stereoselection during the enolate transfer (Figure 1.6).

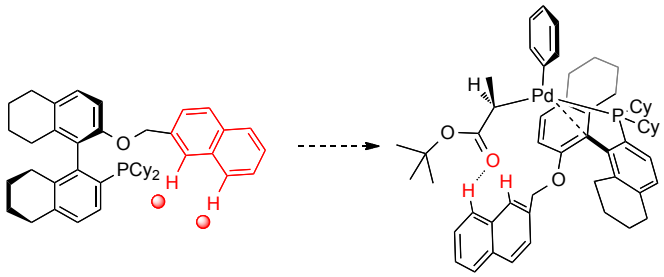


Figure 1.6 Proposed hydrogen bonds.

Besides aryl halides, diaryliodonium salts can also be used as carbon electrophiles, in the presence of chiral copper catalysts. Recently, MacMillan and Gaunt independently reported asymmetric arylation of enamines that were in situ from aldehydes and a chiral amine cocatalysts[19] and silyl enolates derived from acylimides.[20] One example of silyl enolates derived from a lactone was also reported (Figure 1.7).

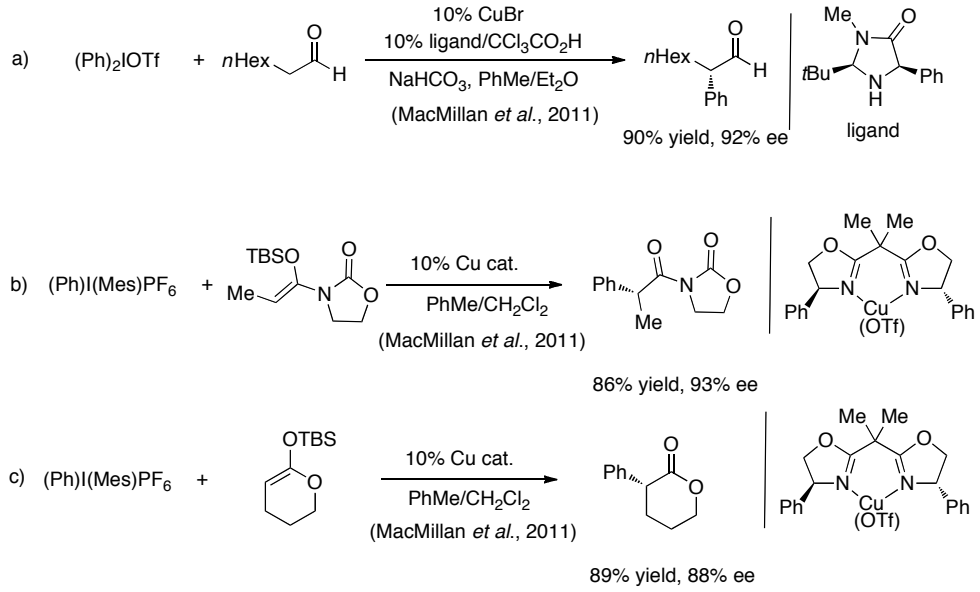


Figure 1.7 Asymmetric coupling of diaryliodonium salts

The catalytic cycle is supposed as shown below (Figure 1.8): (1) Oxidative insertion of Cu(I) complex to the diaryliodonium salt forms the highly electrophilic aryl-Cu(III) species. (2) transmetalation of a silyl enolate in the presence of bases gave the key Cu-bound enolate. (3) C-C reductive elimination gives the α-arylated carbonyl products and regenerates the Cu(I) catalyst.

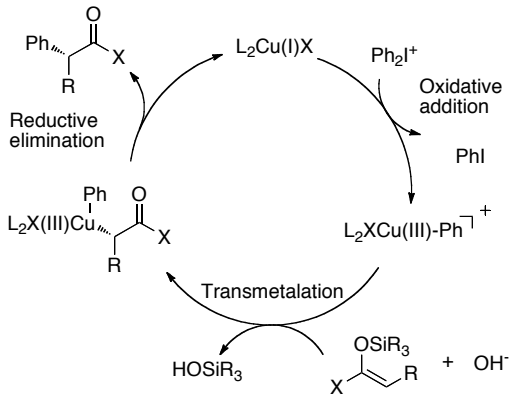


Figure 1.8 A catalytic cycle for Cu-catalyze asymmetric coupling of diaryliodonium salts

In an Umpulung approach, Fu *et al*. used arylsilanes and racemic α-bromoester electrophiles as reaction partners to obtained α-arylesters in 2008.[21] Chiral nickel catalysts based on diamines were used to generate tertiary stereocenters in high ee (Figure 1.9). The condition was mild enough so that no ee erosion was detected. Later, the nickel catalysis was successfully applied to asymmetric α-arylation of α–halogenated amides,[22] ketones[23] and nitriles.[24]

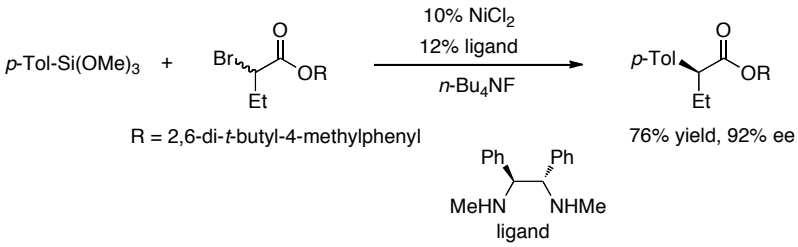
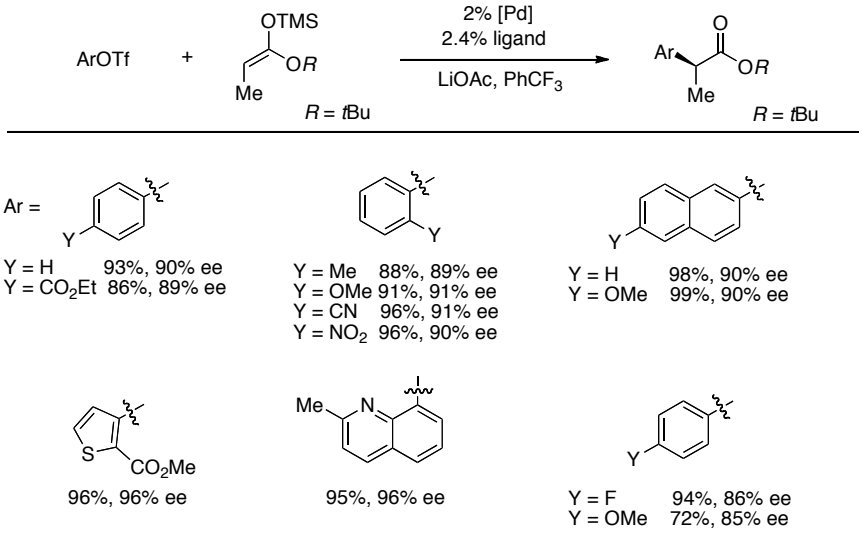


Figure 1.9 Asymmetric coupling of arylsilanes and α-bromoesters

Based on these developments, we believe that palladium-catalyzed asymmetric arylation of ester enolate represents one of most efficient method to obtain the α-arylester product. Although our reported catalyst gave good results for many examples, there are limitations in the aryl substrates. Aryl triflates carrying *para*-electron-withdrawing and electron-donating groups gave <90% ee and incomplete

conversion of the triflates. For example, *p*-fluorophenyl triflate afforded the coupling product in 86% ee. *p*-Methoxyphenyl triflate resulted in moderate yield and 85% ee.

Table 1.1. Substrate scope of palladium-catalyzed asymmetric arylation



1.2 Conditions Optimization

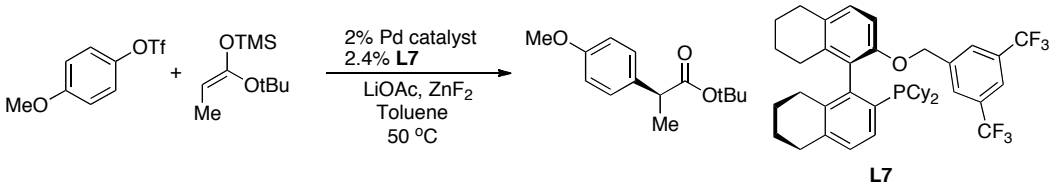
Herein, we developed a rather general method for the synthesis of profen drugs via asymmetric *α*-arylation of ester enolates. A new biarylphosphine ligand was developed, which gave excellent ee for various aromatic/vinyl triflates. Several profen drugs were successfully prepared using this method.

Initially, we examined a model coupling between the *para*-methoxyphenyl triflate and silyl ketene acetal of *tert*-butyl propionate. Among the common palladium complexes, (TMEDA)$PdMe_2$ proved to be the most efficient. When it was replaced by

$Pd(OAc)_2$, the coupling became slower and the ee decreased. $Pd(dba)_2$ showed very low reactivity, probably due to strong binding of dba to the active catalyst LPd(0).

In addition, inclusion of 0.2 equiv of ZnF_2 coactivitor can increase the activity and afford the product in 98% yield and 94% ee after 24 h at 50 ^oC. The use of LiOAc as activator was essential for the coupling.

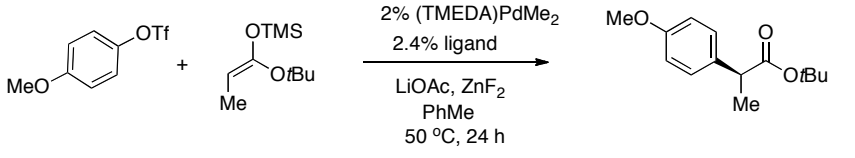
Table 1.2 Effect of Palladium Catalyst

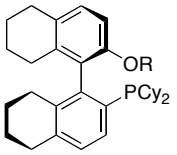


Entry	Catalyst	Reaction Time (h)	Conversion (%)	GC Yield (%)	ee (%)
1	$(TMEDA)PdMe_2$	6	94	92	94
		24	100	98	94
2	$Pd(OAc)_2$	6	71	67	91
		24	82	75	
3	$Pd(dba)_2$	6	19	2	
		24	23	5	
4	$PdCl_2$	6	0	0	
		24	0	0	
5	$Pd(acac)_2$	6	0	0	
		24	0	0	
6	$(TMEDA)PdMe_2$ No ZnF_2	6	85	78	94
		24	100	93	
7	$(TMEDA)PdMe_2$ No LiOAc	6	21	3	
		24	23	5	
8	$(TMEDA)PdMe_2$ 100% ZnF_2	6	87	86	94
		6	95	94	

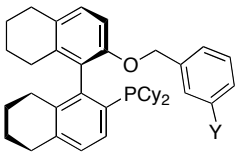
Previously, we learned that biarylphosphines built on a partially saturated binaphthyl backbone were more stereoselective than those carrying the parent binaphthyl skeleton in the arylation of esters.[16] Our old ligands **L3** and **L4** gave <90% ee. Thus, we synthesized a series of new ligands bearing different *O*-benzyl group. The results showed that **L7** carrying two CF_3 groups at *meta* positions of the benzyl ring was optimal in terms of both reactivity and ee. **L5** carrying only one *m*-CF_3 group was also same as **L7**. **L9** and **L10** carrying two bulky *t*-butyl and two phenyl groups at *meta* positions gave only about 70% ee.

Table 1.3 Effect of chiral phosphine ligands

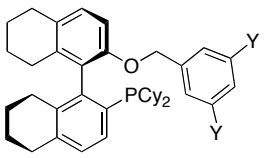




L1 R = H 72%, 60% ee
L2 R = Me 82%, 78% ee
L3 R = CH_2Ph 99%, 85% ee
L4 R = CH_2(2-Naph) 70%, 85% ee



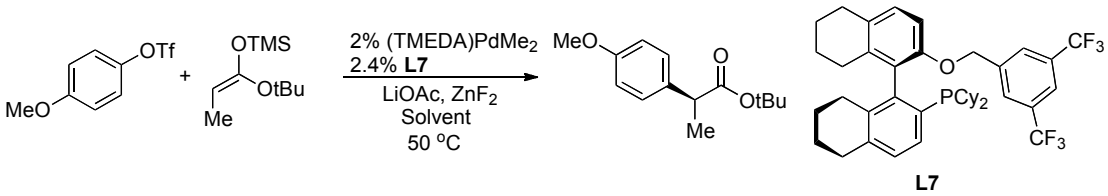
L5 Y = CF_3 96%, **93% ee**
L6 Y = NH_2 56%, 88% ee



L7 Y = CF_3 98%, **94% ee**
L8 Y = CH_3 99%, 83% ee
L9 Y = *t*Bu 72%, 87% ee
L10 Y = Ph 74%, 87% ee
L11 Y = OMe 95%, 88% ee

In the model reaction of *p*-anisyl trilfate, toluene was better than $PhCF_3$ in terms of the reactivity and stereoselectivity. When THF and dioxane were used, the ee was slightly lower. In Et_2O and TBME, the ee remained high but the reactivity was slightly reduced.

Table 1.4 Effect of solvent



L7

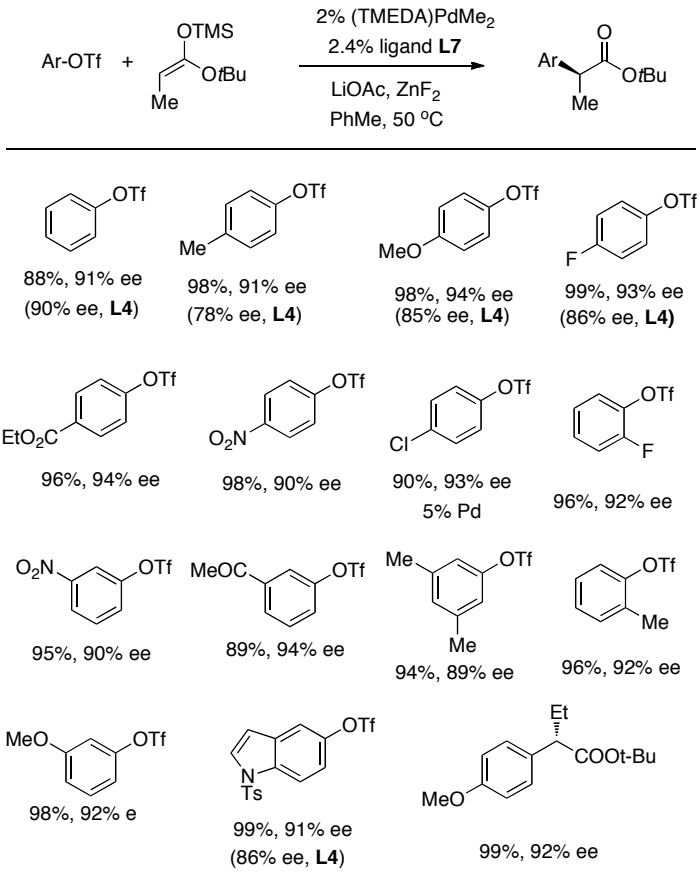
Entry	Solvent	Reaction Time (h)	Conversion (%)	GC Yield (%)	ee (%)
1	$PhCF_3$	6	40	25	92
		24	58	41	
2	Toluene	6	94	92	94
		24	100	98	
3	*o*-Xylene	6	89	84	93
		24	100	95	
4	Benzene	6	86	79	93
		24	100	93	
5	DME	6	27	4	28
		24	28	5	
6	THF	6	27	10	88
		24	48	28	
7	Dioxane	6	22	8	88
		24	45	31	
8	Ether	6	77	69	94
		6	92	84	
9	TBME	6	69	60	94
		24	82	77	

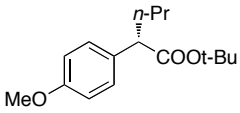
1.3 Substrate Scope

1.3.1 Scope of Aryl Triflate

We next explored the scope of this new catalyst (Table 1.5). Most of the reactions afford the α-arylesters in high yields and excellent ee. Aryl triflates can have substituents on various positions of the aryl rings. For example, *p*-nitrophenyl triflate coupled in 90% ee. For aryl triflates carrying Ar-Cl and Ar-F moieties, the coupling was selectively at the Ar-OTf site. Notably, electron-deficient aryl triflates reacted faster than electron-rich ones, probably due to faster oxidative addition of the former. Toluene was found to be the better solvent than $PhCF_3$ for electron-rich aryl triflates.

Table 1.5 Scope of aryl triflates



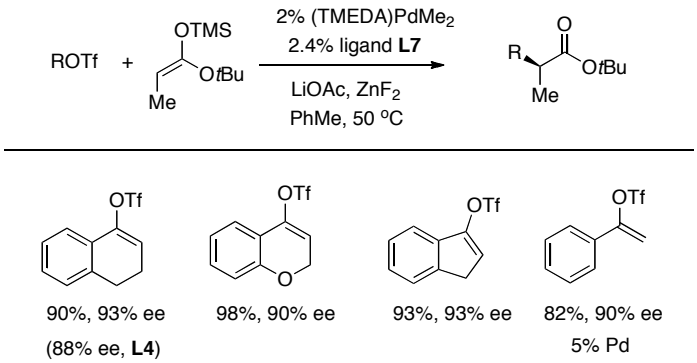


98%, 90% ee

1.3.2 Scope of Vinyl Triflate

Next, we turned our attention to vinyl triflates. As shown in Table 1.6, vinyl triflates derived from 1-tetralone, 4-chromone, 1-indanone and acetophenone can give desired α-arylated product in high yield and >90% ee. When 1-cylcohexenyl triflate was used, however, no product was detected probably due to slow oxidative addition.

Table 1.6 Scope of vinyl triflates

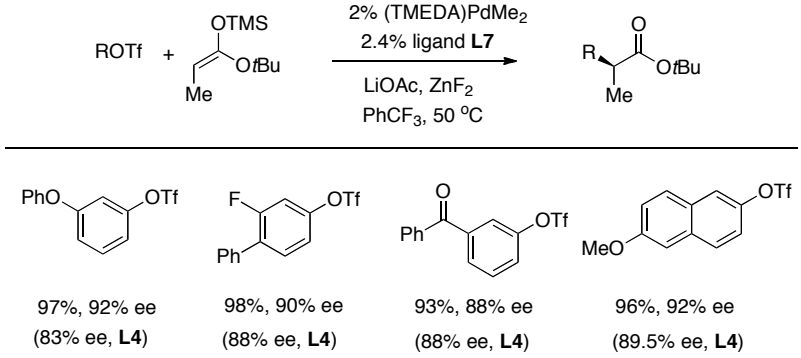


90%, 93% ee (88% ee, **L4**) | 98%, 90% ee | 93%, 93% ee | 82%, 90% ee 5% Pd

1.3.3 Application in the Synthesis of Profen drugs

To demonstrate the utility of the new catalyst, the synthesis of some profen drugs is shown in Table 1.7. Phenoprofen, Flurbiprofen, Ketoprofen and Naproxen were obtained in the esters of excellent ee.

Table 1.7 Synthesis of profen esters



In addition, the reaction can be scaled up to produce 1.19 g of (*S*)-Flurbiprofen ester without loss of ee. After acidic hydrolysis of the ester, (S)-Flurbiprofen was obtained in quantitative yield. The ee can be improved from 90% to 99% after a simple recrystallization (Figure 1.10).

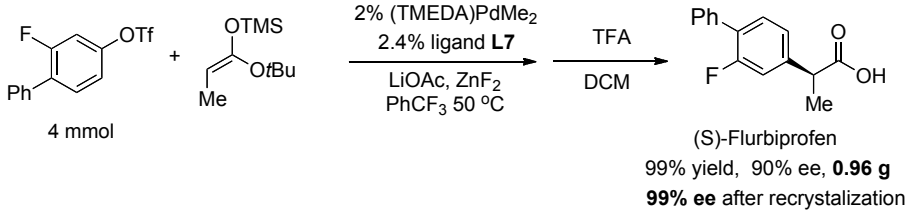


Figure 1.10 Gram-scale reaction

1.4 Challenging Substrates

We found that several heteroaryl triflates did not give the desired coupling products, probably due to competitive binding of aromatic nitrogens to cationic heteroaryl-Pd species. The reaction of 2-mesityl triflate occurred in low conversion due to steric hindrance (Entry 9).

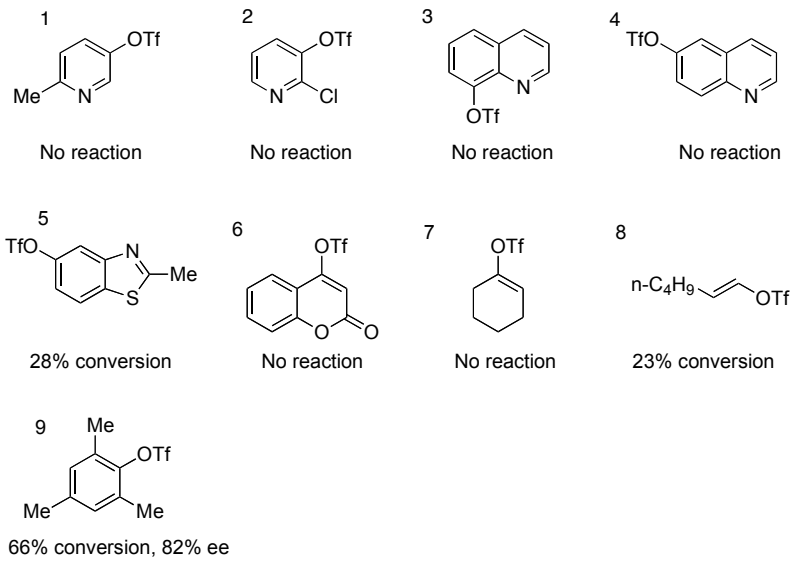


Figure 1.11 Challenging substrates

1.5 Summary

In summary, we have developed a general method of α-arylation of esters to form profen drugs in high yield and excellent ee. The use of a new biarylphosphine improved stereoselectivity as compared to our previous catalyst. The two CF_3 group on the benzyl side chain of the ligand may acidify the CH bonds. This probably makes the benzylic CH bond better hydrogen donors so that they can form stronger CH/O hydrogen bonding with the Pd-bound *C*-enolate. The enolate transfer step may be the stereodetermining step in our catalytic cycle, which is now under DFT studies by us.

1.6 Experimental Section

I. General

^{1}H NMR spectra were acquired at 400 MHz or 300 MHz and chemical shifts were recorded relative to $SiMe_4$ (δ 0.00) or residual protiated solvents ($CDCl_3$: δ 7.26; C_6D_6: δ 7.16; CD_2Cl_2: 5.30). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiple). The number of protons (n) for a given resonance was indicated by *n*H. Coupling constants were reported as a *J* value in Hz. ^{13}C NMR spectra were obtained at 100 MHz on 400 MHz or 75 MHz on 300 MHz instruments and chemical shifts were recorded relative to solvent resonance ($CDCl_3$: δ 77.23; CD_2Cl_2: δ 128.0). Proof of purity of new compounds was demonstrated with copies of ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR spectra.

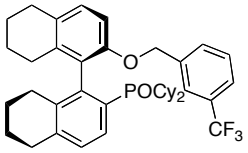
Anhydrous a,a,a-trifluorotoluene (Aldrich) was degassed by argon bubbling and then stored over activated 4 Å molecular sieve beads in the glove box before use. Dry diethyl ether, toluene, hexane and dichloromethane were collected from a solvent purification system containing a column of activated alumina (1 m x 2) under argon. Anhydrous $PhCF_3$ (Aldrich), *t*-butyl methyl ether (Aldrich) and cyclopentyl methyl ether were used without further purification and were stored in the glove box. Dry THF was freshly distilled from sodium/benzophenone under argon before use. Dry triethylamine and trimethylsilyl chloride were distilled from CaH_2 under argon before use. Diisopropylamine was distilled from anhydrous KOH under argon before use. *o*-Xylene was distilled from sodium under argon before use. All of anhydrous solvents were stored in Schlenk tubes in the glove box. The GC standard, *n*-dodecane was degassed and dried over activated 4 Å molecular sieve beads before use.

Unless noted otherwise, commercially available chemicals were used without further purification. $PdMe_2(TMEDA)$[25] and biarylphosphines L1-4[16] were prepared

according to reported procedures. Anhydrous lithium acetate (Aldrich) was dissolved in acetic acid, then concentrated and dried in a vacuum oven (29 inHg of partial vacuum at 120 ^{o}C) for 12 hours before use (important!). (*E*)-1-*t*-Butoxy-1-(trimethylsiloxy)-propene was prepared according to our reported procedure and the final aqueous workup was important![16]

Glassware was dried at 120 ^{o}C for at least 3 hours before use. Flash chromatography was preformed using Merck 40-63D 60 Å silica gel. GC and GC/MS analysis were conducted with Agilent J&W GC column DB-5MS-UI. Chiral HPLC analysis was performed on a Shimadzu LC-20AD instrument using Daicel Chiracel columns at 25°C. Optical rotation was measured using a JASCO P-1030 Polarimeter equipped with a sodium vapor lamp at 589 nm and the concentration of samples was denoted as *c*.

II. Synthesis of chiral phosphines



(*R*)-2-(Dicyclohexylphosphinyl)-2′-(*m*-trifluoromethylbenzyloxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl. Under argon, to a 25 mL two-necked RBF equipped with a condenser was added (*R*)-2-(dicyclohexylphosphinyl)-2′-hydroxy-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl (147 mg, 0.30 mmol) and anhydrous K_2CO_3 (207 mg, 1.5 mmol). Then analytical-grade acetone (6 mL) was added, followed by 3-(trifluoromethyl)benzyl bromide (358 mg, 1.5 mmol), . The resulting mixture was refluxed under argon for 1 day until all the starting material was consumed (monitored by ^{31}P NMR spectroscopy). After the mixture was cooled to 25 ^{o}C, it was filtered through a pad of Celite with ethyl acetate washings (10 mL × 2).

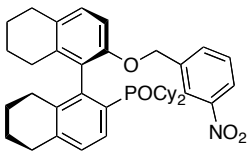
The filtrate was concentrated on a rotary evaporator and the resulting residue was purified by flash chromatography (ethyl acetate/hexane 3:2), which afforded the desired compound (165 mg, 85%) as yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.42 (m, 1H), 7.36-7.32 (m, 1H), 7.30-7.26 (m, 2H), 7.17-7.15 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 4.98 (ys, 2H), 2.88-2.71 (m, 4H), 2.54-2.48 (m, 1H), 2.27-2.21 (m, 1H), 2.17-2.09 (m, 1H), 2.05-1.98 (m, 1H), 1.88-1.06 (m, 27H), 0.95-0.70 (m, 3H).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 45.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.78.

ESI-MS: Calcd for $C_{40}H_{49}F_3O_2P$ $(M+H)^+$: 649.33. Found: 649.45.

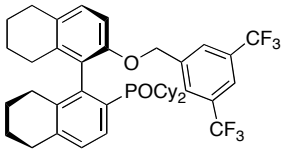


(*R*)-2-(Dicyclohexylphosphinyl)-2′-(*m*-nitrobenzyloxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl. Under argon, to a 25-mL two-necked RBF equipped with a condenser was added (*R*)-2-(dicyclohexylphosphinyl)-2′-hydroxy-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl (147 mg, 0.30 mmol) and anhydrous K_2CO_3 (207 mg, 1.5 mmol). Then analytical-grade acetone (6 mL) was added, followed by *m*-nitrobenzyl bromide (324 mg, 1.5 mmol). The resulting mixture was refluxed under argon for 1 day until all the starting material was consumed (monitored by ^{31}P NMR spectroscopy). After the mixture was cooled to 25 ^{o}C, it was filtered through a pad of Celite with ethyl acetate washings (10 mL × 2). The filtrate was concentrated on a rotary evaporator and the resulting residue was purified by flash chromatography (ethyl acetate/hexane 3:2), which afforded the desired compound (187 mg, quantitative) as yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06-8.03 (m, 1H), 7.83 (s, 1H), 7.45-7.39 (m, 2H), 7.30-7.25 (m, 1H), 7.20-7.18 (m, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 5.06-4.99 (m, 2H), 2.99-2.72 (m, 4H), 2.54-2.47 (m, 1H), 2.29-2.34 (m, 1H), 2.20-2.14 (m, 1H), 2.07-1.99 (m, 1H), 1.78-1.09 (m, 27H), 0.97-0.73 (m, 3H).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 44.9.

ESI-MS: Calcd for $C_{39}H_{49}NO_4P$ $(M+H)^+$: 626.33. Found: 626.44.



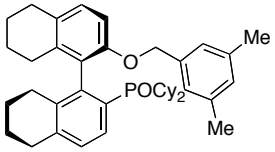
(*R*)-2-(Dicyclohexylphosphinyl)-2′-[*m,m*-bis(trifluoromethyl)benzyloxy]-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl. Under argon, to a 25-mL two-necked was added (*R*)-2-(dicyclohexylphosphinyl)-2′-hydroxy-5,5',6,6',7,7',8,8'-octahydro-binaphthyl (470 mg, 0.96 mmol) and *m,m*-bis(trifluoromethyl)benzyl bromide (460 mg, 1.5 mmol), then anhydrous DMF (5 mL) was added, followed by NaH (73 mg, 3.1 mmol). The resulting mixture was stirred at room temperature for 12 h until all the starting material was consumed (monitored by ^{31}P NMR spectroscopy). Then, the reaction mixture was diluted with EA (20 ml) and washed by saturated ammonium chloride solution (20 ml), water (20 ml) and brine (20 ml), then dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the resulting residue was purified by flash chromatography (ethyl acetate/hexane 2:1 to DCM/MeOH 20:1), which afforded the desired compound (620 mg, 90%) as yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.43 (s, 2H), 7.24-7.22 (m, 1H), 7.19-7.16 (m, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 5.03 (ys, 2H), 2.89-2.73 (m, 4H), 2.57-2.51 (m, 1H), 2.25-2.13 (m, 2H), 2.07-2.00 (m, 1H), 1.87-1.01 (m, 27H), 0.90-0.62 (m, 3H).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 45.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.0.

ESI-MS: Calcd for $C_{41}H_{48}F_6O_2P$ $(M+H)^+$: 717.32. Found: 717.46.

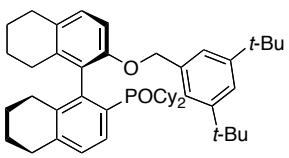


(*R*)-2-(Dicyclohexylphosphinyl)-2′-(*m,m*-dimethylbenzyloxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl. The same procedure as above was used. (*R*)-2-(Dicyclohexylphosphinyl)-2′-hydroxy-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl (200 mg, 0.41 mmol), *m,m*-dimethylbenzyl bromide (121 mg, 0.61 mmol), NaH (30 mg, 1.23 mmol) and DMF (3 mL) were used. The reaction was stirred at room temperature for 1 h. The crude product was purified by flash chromatography (ethyl acetate/hexane 2:1 to DCM/MeOH 20:1), which afforded the desired compound (240 mg, 97%) as white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (dd, J = 10.6, 8.0 Hz, 1H), 7.14 (dd, J = 8.0, 2.3 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.80 (s, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.64 (s, 2H), 4.90-4.83 (m, 2H), 2.89-2.80 (m, 3H), 2.77-2.71 (m, 1H), 2.52-2.44 (m, 1H), 2.32-2.13 (m, 10H), 2.05-1.95 (m, 1H), 1.84-0.87 (m, 28H).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 45.01.

ESI-MS: Calcd for $C_{41}H_{54}O_2P$ $(M+H)^+$: 609.38. Found: 609.63.

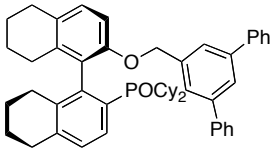


(*R*)-2-(Dicyclohexylphosphinyl)-2′-(*m,m*-di-*t*-butylbenzyloxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl. The same procedure as above was used. (*R*)-2-(Dicyclohexylphosphinyl)-2′-hydroxy-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl (100 mg, 0.20 mmol), *m,m*-di-*t*-butylbenzyl bromide (86 mg, 0.31 mmol), NaH (15 mg, 0.6 mmol) and DMF (2 mL) were used. The reaction was stirred at room temperature for 12 h. The crude product was purified by flash chromatography (ethyl acetate/hexane 2:1 to DCM/MeOH 20:1), which afforded the desired compound (140 mg, 99%) as white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.30 (m, 1H), 7.19 (s, 1H), 7.13-7.10 (m, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 1.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 1H), 4.98 (d, *J* = 12.0 Hz, 1H), 4.90 (d, *J* = 12.0 Hz, 1H), 2.87-2.72 (m, 4H), 2.49-2.42 (m, 1H), 2.37-2.29 (m, 1H), 2.19-2.13 (m, 1H), 2.00-1.94 (m, 1H), 1.75-0.85 (m, 46H), 0.65-0.59 (m, 2H).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 44.9.

ESI-MS: Calcd for $C_{47}H_{66}O_2P$ $(M+H)^+$: 693.47. Found: 693.66.



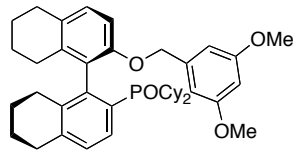
(*R*)-2-(Dicyclohexylphosphinyl)-2′-(*m,m*-diphenylbenzyloxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl. The same procedure as above was used. (*R*)-2-(Dicyclohexylphosphinyl)-2′-hydroxy-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl (200 mg, 0.41 mmol), *m,m*-diphenylbenzyl bromide (197 mg, 0.61 mmol), NaH (29 mg, 1.22 mmol) and DMF (4 mL) were used. The reaction was stirred at room temperature for 12 h. The crude product was purified by flash chromatography

(ethyl acetate/hexane 2:1 to DCM/MeOH 20:1), which afforded the desired compound (270 mg, 91%) as white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.47-7.34 (m, 11H), 7.26-7.24 (m, 2H), 7.18-7.15 (m, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 5.10-5.02 (m, 2H), 2.88-2.71 (m, 3H), 2.68-2.60 (m, 1H), 2.50-2.45 (m, 1H), 2.33-2.25 (m, 1H), 2.15-2.10 (m, 1H), 2.01-1.95 (m, 1H), 1.97-1.03 (m, 27H), 0.91-0.74 (m, 3H).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 45.2.

ESI-MS: Calcd for $C_{51}H_{58}O_2P$ $(M+H)^+$: 733.41. Found: 733.56.

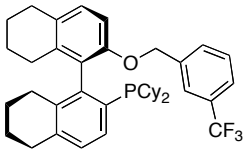


(*R*)-2-(Dicyclohexylphosphinyl)-2′-(*m,m*-dimethoxylbenzyloxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl. The same procedure as above was used. (*R*)-2-(Dicyclohexylphosphinyl)-2′-hydroxy-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl (100 mg, 0.20 mmol), *m,m*-dimethoxylbenzyl bromide (72 mg, 0.31 mmol), NaH (15 mg, 0.61 mmol) and DMF (2 mL) were used. The reaction was stirred at room temperature for 12 h. The crude product was purified by flash chromatography (ethyl acetate/hexane 2:1 to DCM/MeOH 20:1), which afforded the desired compound (66 mg, 51%) as white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.35 (m, 1H), 7.11-7.09 (m, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.27 (t, *J* = 2.3 Hz, 1H), 6.23-6.22 (m, 2H), 4.91 (ys, 2H), 3.61 (s, 6H), 2.87-2.74 (m, 4H), 2.48-2.43 (m, 1H), 2.30-2.26 (m, 1H), 2.15-2.11 (m, 1H), 2.01-1.94 (m, 1H), 1.89-1.07 (m, 27H), 0.97-0.81 (m, 3H).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 44.75.

ESI-MS: Calcd for $C_{41}H_{54}O_4P$ $(M+H)^+$: 641.37. Found: 641.57.



(*R*)-2-(Dicyclohexylphosphino)-2′-(*m*-trifluoromethylbenzyloxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl. Under argon, a 25-mL Schlenk tube was charged with the phosphine oxide (60 mg, 0.09 mmol), triethylamine (0.5 mL, 3.6 mmol) and dry toluene (2.0 mL). After the resulting solution was cooled to 0 ^{o}C, trichlorosilane (0.09 mL, 0.9 mmol) was added by syringe. The resulting mixture was heated with stirring in a 110 ^{o}C oil bath for 12 hours, until all the starting material was consumed (monitored by ^{31}P NMR spectroscopy). At the conclusion of the reaction, the mixture was cooled to 25 ^{o}C in the glove box and diluted with degassed diethyl ether (10 mL). After the resulting suspension was briefly chilled for 5 minutes in a -30 ^{o}C fridge of the glove box, a degassed, saturated Na_2CO_3 solution (1.0 mL) was added to quench the reaction. The desired ligand was obtained after the crude mixture was passed through a pad of silica gel and washed with diethyl ether in the glove box. The filtrate was concentrated under vacuum and afforded the desired compound (38 mg, 67%) as white foam.

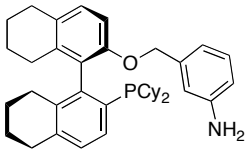
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.43 (m, 1H), 7.36-7.24 (m, 4H), 7.11-7.06 (m, 2H), 6.70 (d, J = 8.3 Hz, 1H), 5.01 (d, J = 12.8 Hz, 1H), 4.91 (d, J = 12.8 Hz, 1H), 2.85-2.72 (m, 4H), 2.42-2.27 (m, 2H), 2.15-1.94 (m, 3H), 1.79-0.80 (m, 28H), 0.62-0.60 (m, 1H).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ -10.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.8.

$[\alpha]^{21}_{D}$ = +24.6^{o} (c = 0.3, $CHCl_3$).

ESI-MS: Calcd for $C_{40}H_{49}F_3OP$ $(M+H)^+$: 633.34. Found: 633.48.



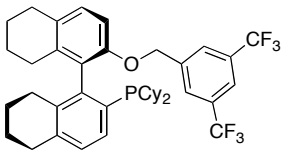
(*R*)-2-(Dicyclohexylphosphino)-2′-(*m*-aminobenzyloxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl. Under argon, a 25-mL Schlenk tube was charged with the phosphine oxide (100.0 mg, 0.16 mmol), triethylamine (0.89 mL, 6.4 mmol) and dry toluene (3.0 mL). After the resulting solution was cooled to 0 ^{o}C, trichlorosilane (0.16 mL, 1.6 mmol) was added by syringe. The resulting mixture was heated with stirring in a 110 ^{o}C oil bath for 12 hours, until all the starting material was consumed (monitored by ^{31}P NMR spectroscopy). At the conclusion of the reaction, the mixture was cooled to 25 ^{o}C in the glove box and diluted with degassed diethyl ether (10 mL). After the resulting suspension was briefly chilled for 5 minutes in a -30 ^{o}C fridge of the glove box, a degassed, saturated Na_2CO_3 solution (1.0 mL) was added to quench the reaction. The desired ligand was obtained after the crude mixture was passed through a pad of silica gel and washed with diethyl ether in the glove box. The filtrate was concentrated under vacuum and afforded the desired compound (47 mg, 50%) as white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.31 (m, 1H), 7.09-6.98 (m, 3H), 6.69 (d, J = 8.4 Hz, 1H), 6.52-6.48 (m, 2H), 6.33 (s, 1H), 4.87 (d, J = 12.8 Hz, 1H), 4.82 (d, J = 12.8 Hz, 1H), 3.48 (br s, 2H), 2.86-2.74 (m, 4H), 2.38-2.30 (m, 2H), 2.14-2.08 (m, 1H), 2.02-1.92 (m, 2H), 1.75-0.79 (m, 29H).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ -10.2.

$[\alpha]^{21}_{D}$ = +27.3^{o} (c = 0.3, $CHCl_3$).

ESI-MS: Calcd for $C_{39}H_{51}NOP$ $(M+H)^{+}$: 580.36. Found: 580.55.



(*R*)-2-(Dicyclohexylphosphino)-2′-[*m,m*-bis(trifluoromethyl)benzyloxy]-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl. The same procedure as described above was used. The corresponding phosphine oxide (147 mg, 0.20 mmol), triethylamine (1.13 mL, 8.2 mmol), trichlorosilane (0.20 mL, 2.0 mmol) and dry toluene (5 mL) were used. The reaction was finished after heating at 110 ^{o}C for 12 hours. After workup, the resulting residue was purified in the glove box by flash chromatography (degassed diethyl ether), which afforded the desired compound (107 mg, 75%) as white foam.

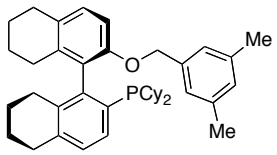
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.45 (s, 2H), 7.34-7.31 (m, 1H), 7.13-7.08 (m, 2H), 6.70 (d, J = 8.3 Hz, 1H), 5.05 (d, J = 13.2 Hz, 1H), 4.95 (d, J = 13.2 Hz, 1H), 2.84-2.74 (m, 4H), 2.44-2.39 (m, 1H), 2.29-2.23 (m, 1H), 2.16-2.03 (m, 2H), 1.95-1.91 (m, 1H), 1.80-1.01 (m, 23H), 0.92-0.74 (m, 4H), 0.53-0.49 (m, 1H).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ -10.3

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.0

$[\alpha]^{21}_{D}$ = +50.7^{o} (c = 0.3, $CHCl_3$).

ESI-MS: Calcd for $C_{41}H_{48}F_6OP$ $(M+H)^+$: 701.33. Found: 701.60.



(*R*)-2-(Dicyclohexylphosphino)-2′-(*m,m*-dimethylbenzyloxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl. The same procedure as described above was used. The corresponding phosphine oxide (240 mg, 0.39 mmol), triethylamine (2.17 mL, 15.6

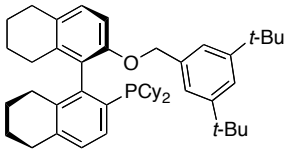
mmol), trichlorosilane (0.41 mL, 4.07 mmol) and dry toluene (5 mL) were used. The reaction was finished after heating at 110 ^{o}C for 12 hours. After workup, the resulting residue was purified in the glove box by flash chromatography (degassed diethyl ether), which afforded the desired compound (190 mg, 83%) as white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.30 (m, 1H), 7.08-7.02 (m, 2H), 6.80 (s, 1H), 6.70-6.68 (m, 3H), 4.87 (d, *J* = 12.5 Hz, 1H), 4.81 (d, *J* = 12.5 Hz, 1H), 2.85-2.73 (m, 4H), 2.38-2.31 (m, 2H), 2.19 (s, 6H), 2.13-2.08 (m, 1H), 2.04-1.93 (m, 2H), 1.78-0.88 (m, 28H), 0.78-0.74 (m, 1H).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ -10.2.

$[\alpha]^{21}_{D}$ = +35.2 (*c* = 0.3, $CHCl_3$).

ESI-MS: Calcd for $C_{41}H_{54}OP$ $(M+H)^{+}$: 593.38. Found: 593.56.



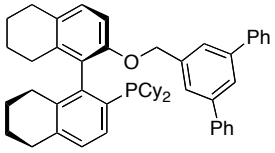
(*R*)-2-(Dicyclohexylphosphino)-2′-(*m*,*m*-di-*t*-butylbenzyloxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl. The same procedure as described above was used. The corresponding phosphine oxide (200 mg, 0.29 mmol), triethylamine (1.61 mL, 11.6 mmol), trichlorosilane (0.29 mL, 2.9 mmol) and dry toluene (5 mL) were used. The reaction was finished after heating at 110 ^{o}C for 12 hours. After workup, the resulting residue was purified in the glove box by flash chromatography (degassed diethyl ether), which afforded the desired compound (158 mg, 80%) as white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.30 (m, 1H), 7.22 (s, 1H), 7.12-7.07 (m, 2H), 6.92-6.91 (m, 2H), 6.79 (d, *J* = 8.4 Hz, 1H), 5.04 (d, *J* = 12.2 Hz, 1H), 4.85 (d, *J* = 12.2 Hz, 1H), 2.89-2.74 (m, 4H), 2.46-2.34 (m, 2H), 2.19-2.12 (m, 1H), 2.05-1.98 (m, 2H), 1.75-0.79 (m, 45H), 0.66-0.47 (m, 2H).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ -10.0.

$[\alpha]^{21}_{D} = +31.3^{o}$ (c = 0.3, $CHCl_3$).

ESI-MS: Calcd for $C_{47}H_{66}OP$ $(M+H)^{+}$: 677.48. Found: 677.63.



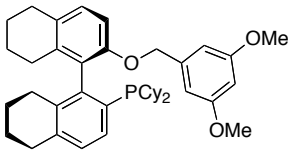
(*R*)-2-(Dicyclohexylphosphino)-2′-(*m,m*-diphenylbenzyloxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl. The same procedure as described above was used. The corresponding phosphine oxide (200 mg, 0.27 mmol), triethylamine (1.50 mL, 10.8 mmol), trichlorosilane (0.27 mL, 2.7 mmol) and dry toluene (5 mL) were used. The reaction was finished after heating at 110 ^{o}C for 12 hours. After workup, the resulting residue was purified in the glove box by flash chromatography using degassed diethyl ether, which afforded the desired compound (165 mg, 85%) as white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.49-7.41 (m, 8H), 7.38-7.34 (m, 3H), 7.27 (d, J = 1.1 Hz, 2H), 7.13-7.08 (m, 2H), 6.78 (d, J = 8.4 Hz, 1H), 5.10 (d, J = 12.6 Hz, 1H), 5.02 (d, J = 12.6 Hz, 1H), 2.86-2.74 (m, 3H), 2.68-2.63 (m, 1H), 2.42-2.33 (m, 2H), 2.15-2.07 (m, 1H), 2.04-1.97 (m, 2H), 1.79-1.16 (m, 23H), 1.06-0.73 (m, 5H), 0.61-0.56 (m, 1H).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ -10.0.

$[\alpha]^{21}_{D} = +48.5^{o}$ (c = 0.3, $CHCl_3$).

ESI-MS: Calcd for $C_{51}H_{58}OP$ $(M+H)^{+}$: 717.41. Found: 717.55.



(*R*)-2-(Dicyclohexylphosphino)-2′-(*m*,*m*-dimethoxylbenzyloxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl. The same procedure as described above was used. The corresponding phosphine oxide (100 mg, 0.16 mmol), triethylamine (0.87 mL, 6.2 mmol), trichlorosilane (0.16 mL, 1.6 mmol) and dry toluene (3 mL) were used. The reaction was finished after heating at 110 ^{o}C for 12 hours. After workup, the resulting residue was purified in the glove box by flash chromatography (degassed diethyl ether), which afforded the desired compound (67 mg, 69%) as white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.08-7.03 (m, 2H), 6.72 (d, *J* = 7.4 Hz, 1H), 6.29-6.26 (m, 3H), 4.94 (d, *J* = 12.8 Hz, 1H), 4.85 (d, *J* = 12.8 Hz, 1H), 3.62 (s, 6H), 2.88-2.73 (m, 4H), 2.40-2.33 (m, 2H), 2.15-2.11 (m, 1H), 2.01-1.97 (m, 2H), 1.76-0.83 (m, 28H), 0.72-0.69 (m, 1H).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ -10.2.

$[\alpha]^{21}_{D}$ = +54.6 (*c* = 0.3, $CHCl_3$).

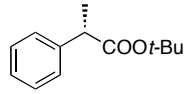
ESI-MS: Calcd for $C_{41}H_{54}O_3P$ $(M+H)^+$: 625.37. Found: 625.54

III. Condition optimization of asymmetric arylation

Typical procedure: In an argon-filled glove box, a dry 4-mL vial was charged with $PdMe_2$(TMEDA) (0.5 mg, 0.002 mmol), ligand **L7** (1.5 mg, 0.0024 mmol) and 0.3 mL of dry toluene. After stirring at 25 ^oC for 30 minutes, the mixture was treated successively with anhydrous LiOAc (13 mg, 0.20 mmol), ZnF_2 (2.1 mg, 0.02 mmol), 4-methoxylphenyl triflate (28 mg, 0.10 mmol), (*E*)-1-*tert*-butoxy-1-(trimethylsiloxy)-propene (30 mg, 0.15 mmol) and *n*-dodecane (10 *u*L). The vial was capped tightly and the mixture was heated with stirring in a 50 ^oC heating block for 24 h, until aryl triflate was fully consumed. At intervals, an aliquot of the reaction mixture was taken inside the glove box and passed through a silica gel plug with diethyl ether washing (1.5 mL). The filtrate was used to determine the GC conversion of ArOTf. The solvent of the filtrate was removed by argon blowing and the residue was dissolved in 10% *i*-PrOH in hexanes for chiral HPLC analysis (Daicel CHIRALCEL OJ-H; 1% *i*-PrOH in hexanes). To facilitate the determination of the ee, the racemic product was prepared by using SPhos.

IV. Isolation of arylation products

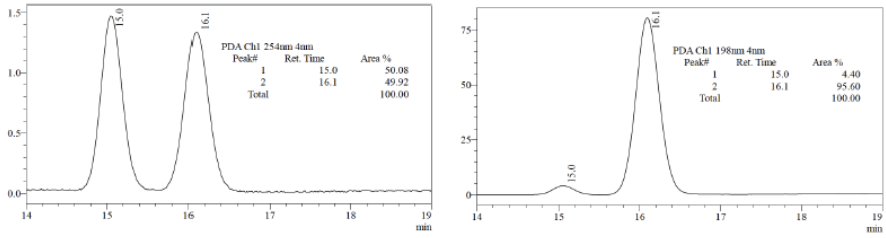
General procedure for asymmetric arylation: In an argon-filled glove box, a dry 4-mL vial was charged with $PdMe_2$(TMEDA) (2.5 mg, 0.010 mmol), ligand **L7** (8.5 mg, 0.012 mmol) and 1.5 mL of dry toluene or $PhCF_3$. After stirring at 25 ^oC for 30 minutes, the mixture was treated successively with anhydrous LiOAc (66 mg, 1.0 mmol, 2 equiv), ZnF_2 (10 mg, 0.1 mmol, 0.2 equiv), aryl triflate (0.50 mmol), (*E*)-1-*tert*-butoxy-1-(trimethylsiloxy)propene (150 mg, 0.75 mmol, 1.5 equiv) and GC standard *n*-dodecane (50 *u*L). The vial was capped tightly and the mixture was heated with stirring in a 50 ^oC heating block. After aryl triflate was fully consumed (monitored by GC), the reaction mixture was cooled to room temperature and filtered through a pad of silica gel with diethyl ether washing (20 mL). The filtrate was concentrated and the residue was purified by flash silica gel chromatography. The general procedure was used for all the isolation with 0.50 mmol of aryl triflate, unless stated otherwise. The racemic products were prepared using a similar procedure with SPhos as supporting ligand.



(*S*)-*tert*-Butyl 2-phenylpropionate [59415-37-1]. The reaction was finished within 18 hours at 50 ^oC in $PhCF_3$. The title compound was obtained as colorless oil (91 mg, 88% yield, 91% ee) by flash chromatography using EA/hexane (1:40) as eluent. The ee of the product was determined to be 87% when PhMe was used.

The ee of the purified products was determined to be 91% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 99:1; detection wave-

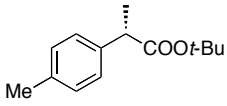
lengths = 254 nm and 198 nm; flow rate = 0.5 mL/min). T_R = 15.0 min (minor) and 16.1 min (major).



$[\alpha]^{21}_D = +28.5^o$ (c = 0.3, $CHCl_3$).

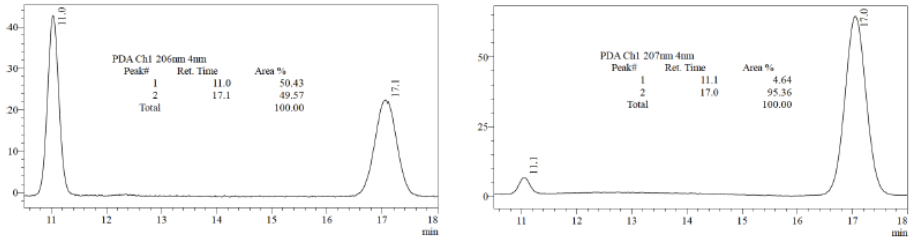
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.21 (m, 5H), 3.61 (q, J = 7.1, 1H), 1.45 (d, J = 7.1 Hz, 3H), 1.39 (s, 9H).

GCMS (EI): calcd for $C_{13}H_{18}O_2$ M: 206.1. Found: 206.0.



(*S*)-*tert*-Butyl 2-(*p*-tolyl)propionate [197659-36-2 for racemate]. The reaction was finished within 12 hours at 50 ^{o}C in toluene. The title compound was obtained as yellow oil (108 mg, 98% yield) by flash chromatography using EA/hexane (1:30) as eluent.

The ee of the purified products was determined to be 91% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 98:2; detection wave-lengths = 207 nm; flow rate = 0.5 mL/min). T_R = 11.1 min (minor) and 17.0 min (major).

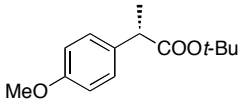


$[\alpha]^{21}_D = +26.9^o$ (c = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 3.56 (q, J = 7.2 Hz, 1H), 2.32 (s, 3H), 1.42 (d, J = 7.2 Hz, 3H), 1.39 (s, 9H).

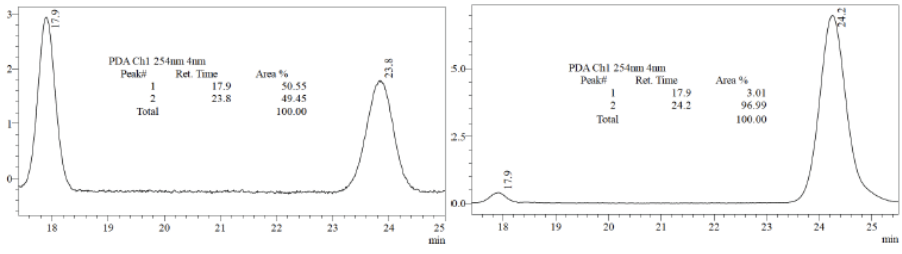
^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 138.2, 136.3, 129.1, 127.3, 80.3, 46.1, 28.0, 21.0, 18.6.

GCMS (EI): calcd for $C_{14}H_{22}O_2$ M^+: 220.2. Found: 220.1.



(*S*)-*tert*-Butyl 2-(*p*-anisyl)propionate [138623-00-4 for racemate]. The reaction was finished within 24 hours at 50 °C in toluene. The title compound was obtained as yellow oil (116 mg, 98% yield, 94% ee) by flash chromatography using EA/hexane (1:30) as eluent. The ee of the product was determined to be 92% when $PhCF_3$ was used.

The ee of the purified products was determined to be 94% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 99:1; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). T_R = 17.9 min (minor) and 24.2 min (major).

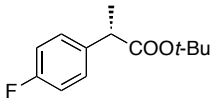


$[\alpha]^{21}_D$ = +24.5° (c = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.19 (m, 2H), 6.87-6.84 (m, 2H), 3.79 (s, 3H), 3.55 (q, J = 7.2 Hz, 1H), 1.42 (d, J = 7.2 Hz, 3H), 1.39 (s, 9H).

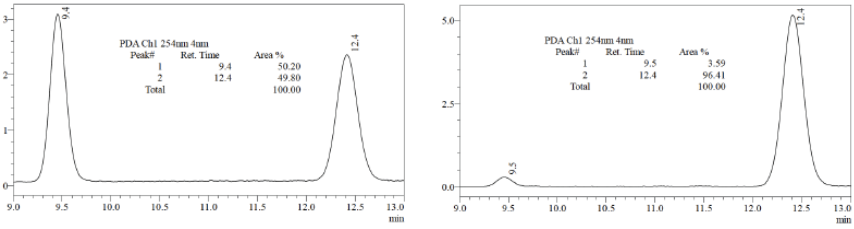
^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 158.5, 133.3, 128.4, 113.8, 80.3, 55.2, 45.6, 27.9, 18.6.

GCMS (EI): calcd for $C_{14}H_{19}O_3$ M^+: 236.1. Found: 236.1.



(*S*)-*tert*-Butyl 2-(*p*-fluorophenyl)propionate [1019322-29-2 for racemate]. The reaction was finished within 18 hours at 50 °C in $PhCF_3$. The title compound was obtained as yellow oil (111 mg, 99% yield, 93% ee) by flash chromatography using EA/hexane (1:30) as eluent. The ee of the product was determined to be 91% when PhMe was used.

Ee of the purified products was determined to be 93% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 98:2; detection wave-lengths = 254 nm; flow rate = 0.5 mL/min). T_R = 9.5 min (minor) and 12.4 min (major).



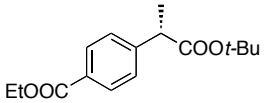
$[\alpha]^{21}_D$ = +34.1° (*c* = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.23 (m, 2H), 7.01-6.97 (m, 2H), 3.59 (q, *J* = 7.2 Hz, 1H), 1.43 (d, *J* = 7.2 Hz, 3H), 1.39 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 161,8 (J_{CF} = 244.7 Hz), 136.8 (J_{CF} = 3.1 Hz), 128.9 (J_{CF} = 7.8 Hz), 115.2 (J_{CF} = 21.4 Hz), 80.6, 45.8, 27.9, 18.5.

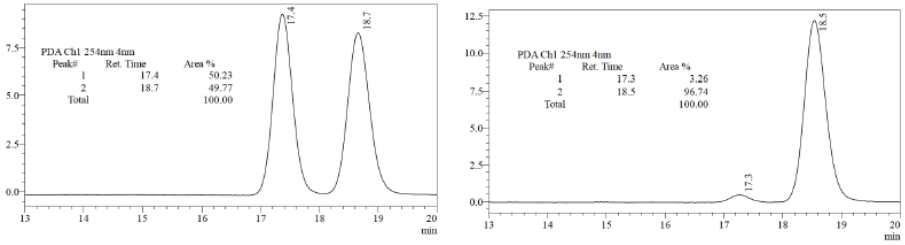
^{19}F NMR (376 MHz, $CDCl_3$): δ -116.3.

GCMS (EI): calcd for $C_{13}H_{17}FO_2$ M^+: 224.1. Found: 224.1.



(*S*)-*tert*-Butyl 2-(*p*-ethoxycarbonylphenyl)propionate [1334591-49-9]. The reaction was finished within 18 hours at 50 °C in $PhCF_3$. The title compound was obtained as colorless oil (133 mg, 96% yield, 94% ee) by flash chromatography using EA/hexane (1:30) as eluent. The ee of the product was determined to be 90% when PhMe was used.

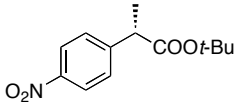
Ee of the purified products was determined to be 94% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 99.5:0.5; detection wave-lengths = 254 nm; flow rate = 0.5 mL/min). T_R = 17.3 min (minor) and 18.5 min (major).



$[\alpha]^{21}_D = +23.2^o$ (c = 0.3, $CHCl_3$).

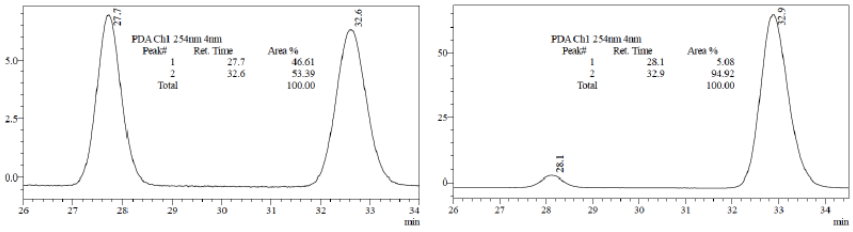
^{1}H NMR (400 MHz, CDCl3): δ 8.00-7.97 (m, 2H), 7.36-7.33 (m, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.65 (q, J = 7.1 Hz, 1H), 1.45 (d, J = 7.2 Hz, 3H), 1.44-1.35 (m, 12H).

GCMS (EI): calcd for $C_{16}H_{23}O_4$ $(M+H)^+$: 279.2. Found: 279.2.



(*S*)-*tert*-Butyl 2-(*p*-nitrophenyl)propionate [89278-22-8 for racemate]. The reaction was finished within 6 hours at 50 ^{o}C in $PhCF_3$. The title compound was obtained as yellow oil (123 mg, 98% yield, 90% ee) by flash chromatography using EA/hexane (1:30) as eluent. The ee of the product was determined to be 85% when PhMe was used.

Ee of the purified products was determined to be 90% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 99.5:0.5; detection wave-lengths = 254 nm; flow rate = 0.5 mL/min). T_R = 28.1 min (minor) and 32.9 min (major).

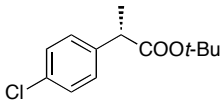


$[\alpha]^{21}_{D}$ = +21.7^{o} (*c* = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20-7.17 (m, 2H), 7.48-7.45 (m, 2H), 3.73 (q, *J* = 7.2 Hz, 1H), 1.49 (d, *J* = 7.2 Hz, 3H), 1.40 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 148.5, 147.0, 128.4, 123.7, 81.4, 46.5, 27.9, 18.3.

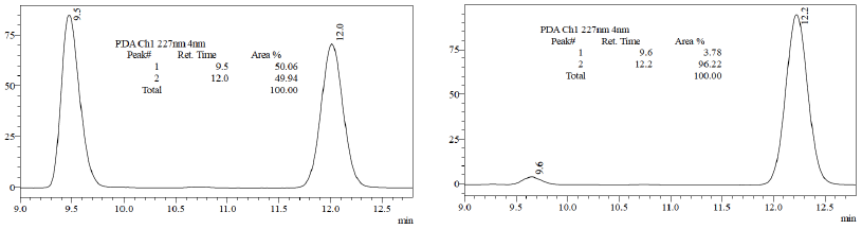
GCMS (EI): calcd for $C_{13}H_{17}NO_4$ $(M+H)^{+}$: 252.1. Found: 252.1.



(*S*)-*tert*-Butyl 2-(*p*-chlorophenyl)propionate [465529-75-3 for racemate]. The same procedure with $PdMe_2$(TMEDA) (6.5 mg, 0.025 mmol, 5 mol% Pd) and ligand **L7** (21 mg, 0.030 mmol) was used in $PhCF_3$. The reaction was finished within 40

hours at 50 °C. The title compound was obtained as colorless oil (108 mg, 90% yield, 93% ee) by flash chromatography using EA/hexane (1:30) as eluent. The ee of the product was determined to be 89% when PhMe was used.

Ee of the purified products was determined to be 93% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 99:1; detection wavelengths = 227 nm; flow rate = 0.5 mL/min). T_R = 9.6 min (minor) and 12.2 min (major).

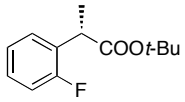


$[\alpha]^{21}_D = +25.4^o$ (c = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.26 (m, 2H), 7.23-7.21 (m, 2H), 3.58 (q, J = 7.2 Hz, 1H), 1.43 (d, J = 7.2 Hz, 3H), 1.39 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 139.6, 132.7, 128.8, 128.6, 80.7, 45.9, 27.9, 18.4.

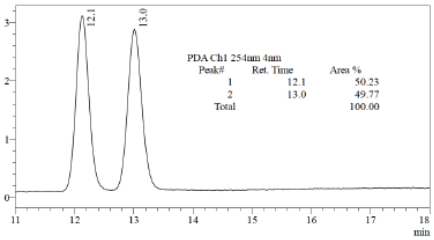
GCMS (EI): calcd for $C_{13}H_{17}ClO_2$ M^+: 240.1. Found: 240.1.

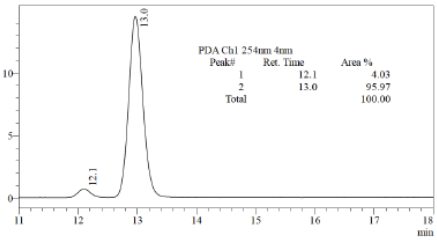


***(S)*-*tert*-Butyl 2-(*o*-fluorophenyl)propionate.** The reaction was finished within 18 hours at 50 °C in $PhCF_3$. The title compound was obtained as yellow oil (107 mg, 96% yield, 92% ee) by flash chromatography using EA/hexane (1:30) as eluent. The ee of the product was determined to be 90% when PhMe was used.

The ee of the purified products was determined to be 92% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 99:1; detection wave-

lengths = 254 nm; flow rate = 0.5 mL/min). T_R = 12.1 min (minor) and 13.0 min (major).





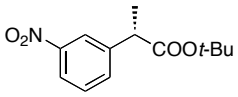
$[\alpha]^{21}_D = +32.9^{o}$ (c = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.26 (m, 1H), δ 7.23-7.19 (m, 1H), δ 7.12-7.08 (m, 1H), 7.05-7.00 (m, 1H), 3.92 (q, J = 7.2 Hz, 1H), 1.45 (d, J = 7.2 Hz, 3H), 1.40 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 160.4 (J_{CF} = 245.9 Hz), 128.56 (J_{CF} = 4.5 Hz), 128.5 (J_{CF} = 14.1 Hz), 128.3 (J_{CF} = 8.2 Hz), 124.1 (J_{CF} = 3.7 Hz), 115.3 (J_{CF}= 22.4 Hz), 80.7, 39.4 (J_{CF} = 2.4 Hz), 27.9, 17.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ -118.3.

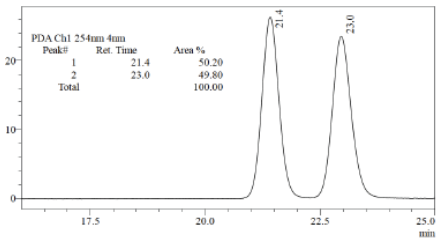
GCMS (EI): Calcd for $C_{13}H_{17}FO_2$ M^+: 224.1. Found: 224.1.

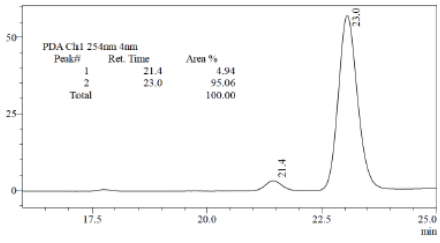


***(S)-tert*-Butyl 2-(*m*-nitrophenyl)propionate [183180-54-3 for racemate].** The reaction was finished within 20 hours at 50 ^{o}C in $PhCF_3$. The title compound was obtained as yellow oil (119 mg, 95% yield, 90% ee) by flash chromatography using EA/hexane (1:20) as eluent. The ee of the product was determined to be 83% when PhMe was used.

The ee of the purified products was determined to be 90% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 99.5:0.5; detection wave-

lengths = 254 nm; flow rate = 0.5 mL/min). T_R = 21.4 min (minor) and 23.0 min (major).



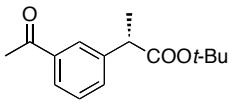


$[\alpha]^{21}_D = +22.3^o$ (c = 0.3, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ 8.19-8.18 (m, 1H), δ 8.14-8.11 (m, 1H), δ 7.65 (d, J = 7.8 Hz, 1H), 7.50 (yt, J = 7.9 Hz, 1H), 3.74 (q, J = 7.2 Hz, 1H), 1.52 (d, J = 7.2 Hz, 3H), 1.41 (s, 9H).

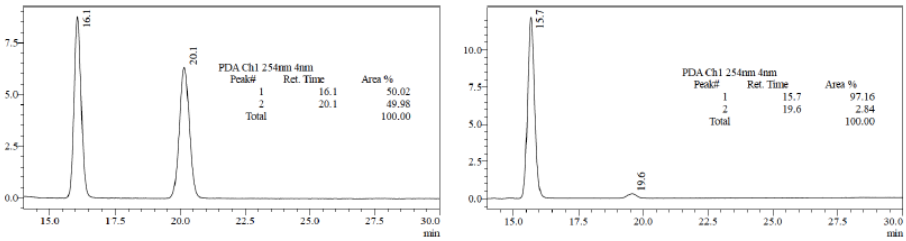
^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 148.4, 143.0, 133.7, 129.3, 122.7, 122.0, 81.4, 46.2, 27.9, 18.3.

GCMS (EI): calcd for $C_{13}H_{18}NO_4$ $(M+H)^+$: 252.1. Found: 252.1.



***(S)-tert*-Butyl 2-(*m*-acetophenyl)propionate.** The reaction was finished within 20 hours at 50 ^oC in $PhCF_3$. The title compound was obtained as yellow oil (110 mg, 89% yield, 94% ee) by flash chromatography using EA/hexane (1:20) as eluent. The ee of the product was determined to be 91% when PhMe was used.

The ee of the purified products was determined to be 94% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 98:2; detection wave-lengths = 254 nm; flow rate = 0.5 mL/min). T_R = 15.7 min (major) and 19.6 min (minor).

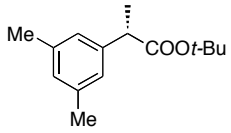


$[\alpha]^{21}_{D} = +31.6^{o}$ (c = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.88 (m, 1H), 7.86-7.83 (m, 1H), 7.53-7.51 (m, 1H), 7.42 (yt, J = 7.7 Hz, 1H), 3.69 (q, J = 7.2 Hz, 1H), 2.61 (s, 3H), 1.48 (d, J = 7.2 Hz, 3H), 1.40 (s, 9H).

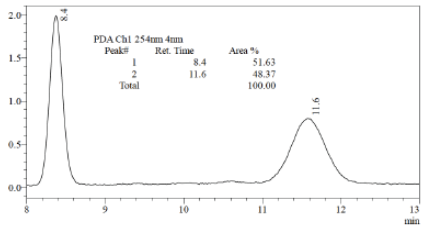
^{13}C NMR (75 MHz, $CDCl_3$): δ 198.0, 173.3, 141.7, 137.4, 132.2, 128.7, 127.5, 127.0, 80.8, 46.4, 27.9, 26.7, 18.5.

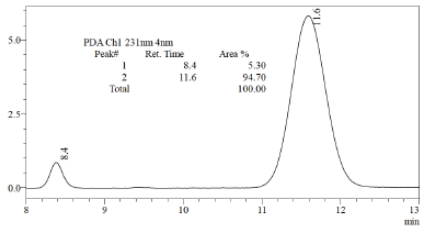
GCMS (EI): calcd for $C_{15}H_{20}O_3$ M: 248.1. Found: 248.2.



***(S)*-*tert*-Butyl 2-(*m*-xylyl)propionate [1226783-49-8 for racemate].** The reaction was finished within 24 hours at 50 ^{o}C in toluene. The title compound was obtained as colorless oil (110 mg, 94% yield) by flash chromatography using EA/hexane (1:30) as eluent.

The ee of the purified products was determined to be 89% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 99:1; detection wave-lengths = 254 nm and 231 nm; flow rate = 0.5 mL/min). T_R = 8.4 min (minor) and 11.6 min (major).



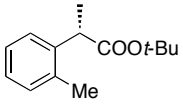


$[\alpha]^{21}_{D} = +23.9^{o}$ (c = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90 (s, 2H), 6.88 (s, 1H), 3.53 (q, J = 7.1 Hz, 1H), 2.30 (s, 6H), 1.43-1.41 (m, 12H).

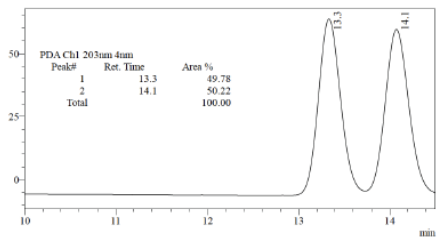
^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 141.1, 137.9, 128.5, 125.2, 80.3, 46.3, 28.0, 21.3, 18.7.

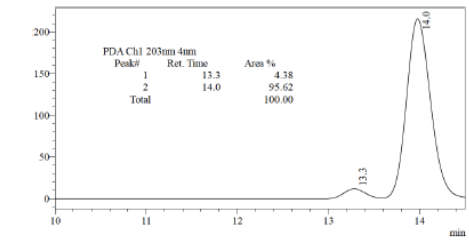
GCMS (EI): calcd for $C_{15}H_{22}O_2$ M^{+}: 234.2. Found: 234.1.



***(S)*-*tert*-Butyl 2-(*o*-tolyl)propionate [1334591-54-6].** The reaction was finished within 60 hours at 50 ^{o}C in $PhCF_3$. The title compound was obtained as yellow oil (106 mg, 96% yield) by flash chromatography using EA/hexane (1:30) as eluent.

The ee of the purified products was determined to be 91% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 99.5:0.5; detection wave-lengths = 203 nm; flow rate = 0.4 mL/min). T_R = 13.3 min (minor) and 14.0 min (major).

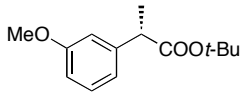




$[\alpha]^{21}_{D} = +40.9^{o}$ (c = 0.3, $CHCl_3$).

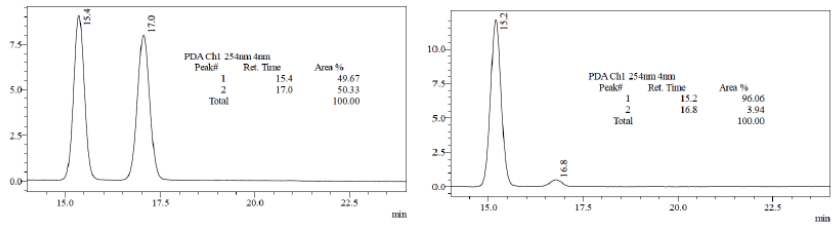
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.25 (m, 1H), 7.20-7.12 (m, 3H), 3.85 (q, *J* = 7.1 Hz, 1H), 2.36 (s, 3H), 1.42 (d, *J* = 7.1 Hz, 3H), 1.38 (s, 9H).

GCMS (EI): calcd for $C_{14}H_{20}O_2$ M: 220.2. Found: 220.1.



***(S)*-*tert*-Butyl 2-(*m*-anisyl)propionate [62381-22-0 for racemate].** The reaction was finished within 20 hours at 50 ^{o}C in $PhCF_3$. The title compound was obtained as yellow oil (116mg, 98% yield, 92% ee) by flash chromatography using EA/hexane (1:30) as eluent. The ee of the product was determined to be 90% when PhMe was used.

The ee of the purified products was determined to be 92% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 99:1; detection wave-lengths = 254 nm; flow rate = 0.5 mL/min). T_R = 15.2 min (major) and 16.8 min (minor).

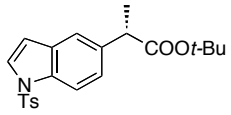


$[\alpha]^{21}_D$ = +37.6 (*c* = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.20 (m, 1H), 6.89-6.84 (m, 2H), 6.80-6.77 (m, 1H), 3.80 (s, 3H), 3.57 (q, *J* = 7.2 Hz, 1H), 1.44 (d, *J* = 7.2 Hz, 3H), 1.39 (s, 9H).

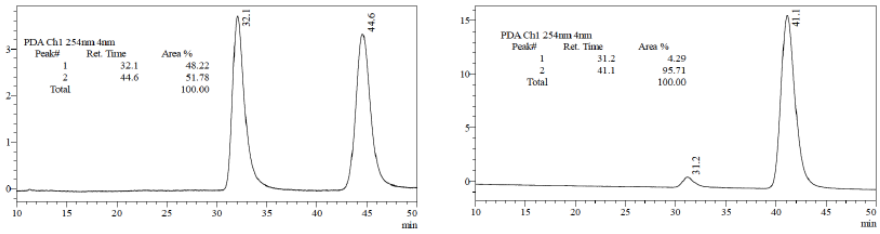
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 159.7, 142.8, 129.4, 119.8, 113.1, 112.3, 80.5, 55.2, 46.5, 27.9, 18.5.

GCMS (EI): calcd for $C_{14}H_{20}O_3$ M: 236.1. Found: 236.1.



(*S*)-*N*-Tosyl *tert*-butyl 2-(5-indolyl)propionate. The reaction was finished within 12 hours at 50 ^{o}C in toluene. The title compound was obtained as yellow oil (201 mg, 99% yield) by flash chromatography using EA/hexane (1:10) as eluent.

The ee of the purified products was determined to be 91% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 95:5; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). T_R = 31.2 min (minor) and 41.1 min (major).

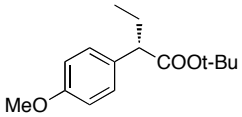


$[\alpha]^{21}_{D}$ = +7.9 (*c* = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.4 Hz, 2H), 7.54 (d, *J* = 3.7 Hz, 1H), 7.44 (d, *J* = 1.2 Hz, 1H), 7.26-7.20 (m, 3H), 6.61 (d, *J* = 3.6 Hz, 1H), 3.66 (q, *J* = 7.2 Hz, 1H), 1.45 (d, *J* = 7.2 Hz, 3H), 1.37 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 144.9, 136.3, 135.4, 133.9, 130.9, 129.9, 126.8, 126.6, 124.4, 120.9, 113.4, 109.0, 80.5, 46.3, 27.9, 21.5,18.9.

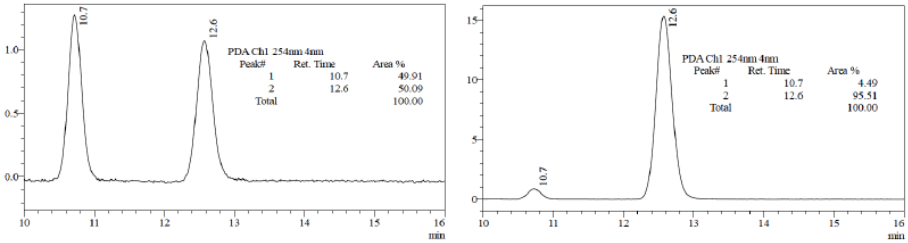
GCMS (EI): calcd for $C_{22}H_{25}NO_4S$ M 399.2. Found: 399.2.



(*S*)-*tert*-Butyl 2-(*p*-anisyl) butanoate. The same procedure with (*E*)-1-*tert*-butoxy-1-(trimethylsiloxy)butene (216 mg, 1.5 mmol) was used in toluene. The reaction was finished within 10 hours at 50 ^{o}C. The title compound was obtained as

colorless oil (124 mg, 99% yield) by flash chromatography using EA/hexane (1:30) as eluent.

Ee of the purified products was determined to be 92% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 99:1; detection wavelengths = 227 nm; flow rate = 0.5 mL/min). T_R = 10.7 min (minor) and 12.6 min (major).

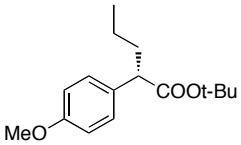


$[\alpha]^{20}_D = +18.0^o$ (c = 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.20 (m, 2H), 6.85-6.83 (m, 2H), 3.79 (s, 3H), 3.28 (t, J = 7.7 Hz, 1H), 2.06-1.96 (m, 1H), 1.73-1.66 (m, 1H), 1.40 (s, 9H), 0.88 (t, J = 7.4 Hz, 3H).

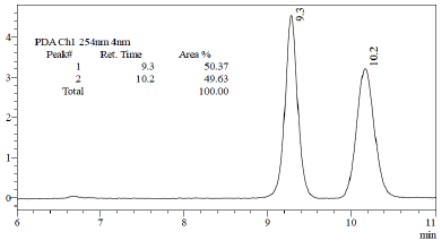
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 158.5, 131.9, 128.8, 113.8, 80.3, 55.2, 53.7, 28.0, 26.8, 12.2.

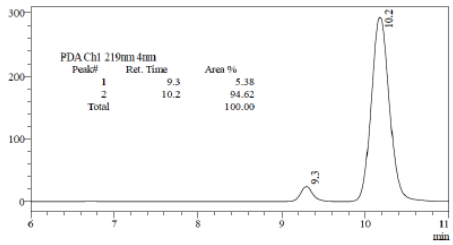
GCMS (EI): calcd for $C_{15}H_{22}O_3$ M^+: 250.2. Found: 250.1.



(*S*)-*tert*-Butyl 2-(*p*-anisyl) pentanoate. The same procedure with (*E*)-1-*tert*-butoxy-1-(trimethylsiloxy)pentene (230 mg, 1.5 mmol) was used in toluene. The reaction was finished within 10 hours at 50 ^{o}C. The title compound was obtained as colorless oil (129 mg, 98% yield) by flash chromatography using EA/hexane (1:30) as eluent.

Ee of the purified products was determined to be 90% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 99:1; detection wavelengths = 227 nm; flow rate = 0.5 mL/min). T_R = 9.3 min (minor) and 10.2 min (major).



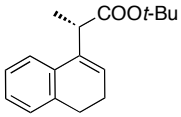


$[\alpha]^{20}_{D} = +12.3^{o}$ (c = 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.20 (m, 2H), 6.85-6.83 (m, 2H), 3.79 (s, 3H), 3.38 (t, J = 7.7 Hz, 1H), 2.01-1.92 (m, 1H), 1.70-1.61 (m, 1H), 1.39 (s, 9H), 1.32-1.22 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H).

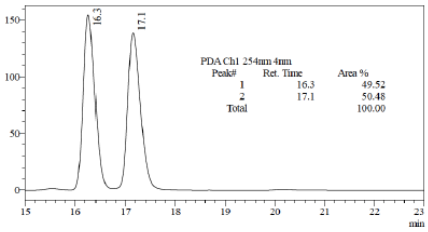
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 158.5, 132.1, 128.8, 113.8, 80.3, 55.2, 51.7, 35.8, 28.0, 20.8, 13.9.

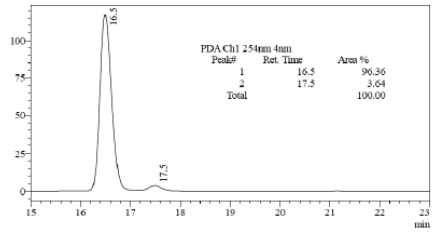
GCMS (EI): calcd for $C_{16}H_{24}O_3$ M^{+}: 264.2. Found: 264.1.



***(S)*-*tert*-Butyl 2-(3′,4′-dihydro-1-naphthyl)propionate [26732-57-0].** The reaction was finished within 18 hours at 50 ^{o}C in toluene. The title compound was obtained as colorless oil (116 mg, 90% yield, 93% ee) by flash chromatography using EA/hexane (1:30) as eluent. The ee of the product was determined to be 81% when $PhCF_3$ was used.

The ee of the purified products was determined to be 93% based on chiral HPLC analysis (Daicel CHIRALCEL IC; hexanes: *i*-PrOH = 99.8:0.2; detection wave-lengths = 254 nm; flow rate = 0.5 mL/min). T_R = 16.5 min (major) and 17.5 min (minor).



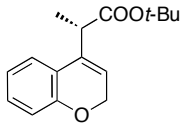


$[\alpha]^{21}_{D} = +29.1$ (c = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.28 (m, 1H), 7.20-7.12 (m, 3H), 6.01 (t, *J* = 4.1 Hz, 1H), 3.63 (q, *J* = 7.1 Hz, 1H), 2.75-2.71 (m, 2H), 2.30-2.24 (m, 2H), 1.40-1.38 (m, 12H).

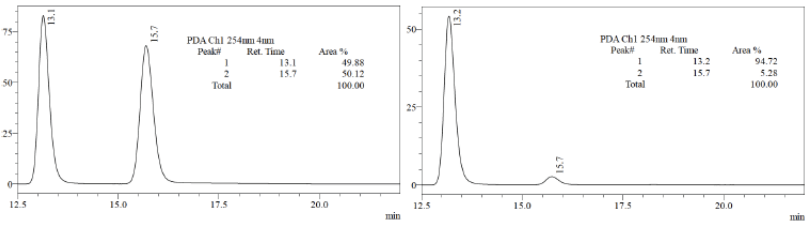
^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4, 136.8, 136.4, 134.5, 127.6, 126.7, 126.2, 125.4, 122.6, 80.3, 42.3, 28.3, 27.9, 23.1, 16.7.

GCMS (EI): calcd for $C_{17}H_{22}O_2$ M^+: 258.2. Found: 258.1.



***(S)-tert*-Butyl 2-(2*H*-4-chromenyl)propionate.** The reaction was finished within 6 hours at 50 ^{o}C in toluene. The title compound was obtained as colorless oil (127 mg, 98% yield) by flash chromatography using EA/hexane (1:30) as eluent.

The ee of the purified products was determined to be 90% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 99:1; detection wave-lengths = 254 nm; flow rate = 0.5 mL/min). T_R = 13.2 min (major) and 15.7 min (minor).

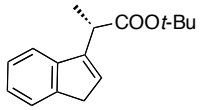


$[\alpha]^{21}_D$ = +21.7 (*c* = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.14-7.10 (m, 1H), 6.91-6.87 (m, 1H), 6.82 (dd, *J* = 8.0, 1.1 Hz, 1H), 5.73 (t, *J* = 3.8 Hz, 1H), 4.76 (d, *J* = 3.8 Hz, 2H), 3.56 (q, *J* = 7.1 Hz, 1H), 1.40-1.38 (m, 12H).

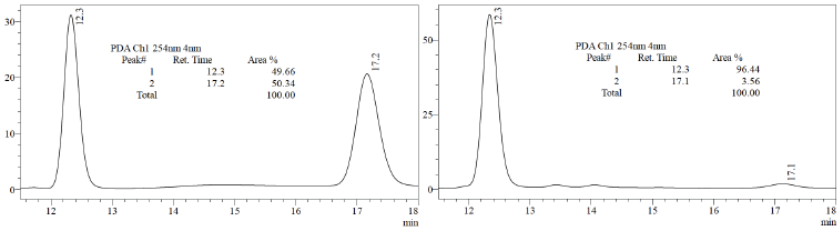
^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 154.5, 134.1, 129.0, 123.3, 122.9, 121.1, 118.4, 116.1, 80.7, 65.2, 41.5, 27.9, 16.3.

GCMS (EI): calcd for $C_{16}H_{20}O_3$ M: 260.1. Found: 260.1.



***(S)-tert*-Butyl 2-(1-indenyl)propionate.** The reaction was finished within 30 hours at 50 ^{o}C in toluene. The title compound was obtained as colorless oil (113 mg, 93% yield) by flash chromatography using EA/hexane (1:30) as eluent.

The ee of the purified products was determined to be 93% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 99:1; detection wave-lengths = 254 nm; flow rate = 0.5 mL/min). T_R = 12.3 min (major) and 17.1 min (minor).

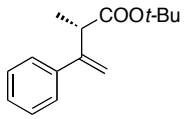


$[\alpha]^{21}_{D}$ = +25.1^{o} (*c* = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.43 (m, 2H), 7.30-7.27 (m, 1H), 7.22-7.17 (m, 1H), 6.37 (d, *J* = 1.1 Hz, 1H), 3.56 (q, *J* = 7.1 Hz, 1H), 3.36 (s, 2H), 1.49 (d, *J* = 7.1 Hz, 3H), 1.42 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 144.3, 144.2, 143.6, 128.9, 125.9, 124.7, 123.8, 119.5, 80.6, 39.9, 37.8, 28.0, 16.5.

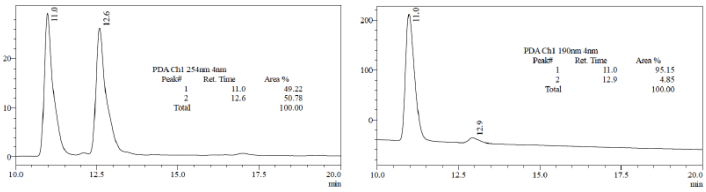
GCMS (EI): calcd for $C_{16}H_{22}O_2$ M+: 244.2. Found: 244.1.



***(S)-tert*-Butyl 2-(α-styryl)propionate.** The same procedure with $PdMe_2$(TMEDA) (6.3 mg, 0.025 mmol, 5 mol% Pd) and ligand **L7** (21 mg, 0.030

mmol) was used in toluene. The reaction was finished within 18 hours at 50 ^{o}C. The title compound was obtained as colorless oil (95 mg, 82% yield) by flash chromatography using EA/hexane (1:30) as eluent.

Ee of the purified products was determined to be 90% based on chiral HPLC analysis (Daicel CHIRALCEL OD-H; hexanes: *i*-PrOH = 99.8:0.2; detection wave-lengths = 254 nm and 190 nm; flow rate = 0.5 mL/min). T_R = 11.0 min (major) and 112.9 min (minor).

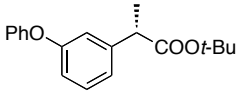


$[\alpha]^{21}_{D}$ = +9.8 (*c* = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.38 (m, 2H), 7.34-7.24 (m, 3H), 5.36 (s, 1H), 5.21 (s, 1H), 3.58 (q, *J* = 7.0 Hz, 1H), 1.37-1.33 (m, 12H).

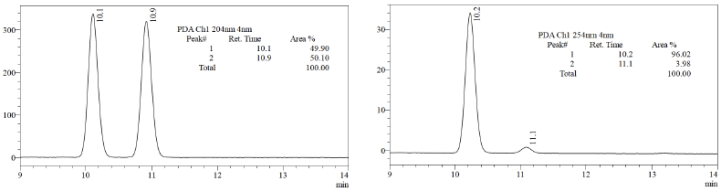
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 148.6, 141.5, 128.2, 127.4, 126.6, 113.5, 80.4, 45.4, 27.8, 16.8.

GCMS (EI): calcd for $C_{15}H_{20}O_2$ M^+: 232.2. Found: 232.1.



***(S)*-*tert*-Butyl 2-(*m*-phenoxyphenyl)propionate [1226783-55-6 for racemate].** The reaction was finished within 18 hours at 50 ^{o}C in $PhCF_3$. The title compound was obtained as colorless oil (144 mg, 97% yield, 92% ee) by flash chromatography using EA/hexane (1:30) as eluent. The ee of the product was determined to be 88% when PhMe was used.

The ee of the purified products was determined to be 92% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 98:2; detection wave-lengths = 254 nm and 204 nm; flow rate = 0.5 mL/min). T_R = 10.2 min (minor) and 11.1 min (major).

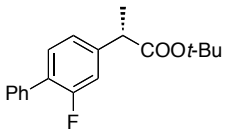


$[\alpha]^{21}_D$ = +24.2 (*c* = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.30 (m, 2H), 7.29-7.25 (m, 1H), 7.11-7.07 (m, 1H), 7.04-6.96 (m, 4H), 6.90-6.87 (m, 1H), 3.58 (q, *J* = 7.2 Hz, 1H), 1.42 (d, *J* = 7.2 Hz, 3H), 1.38 (s, 9H).

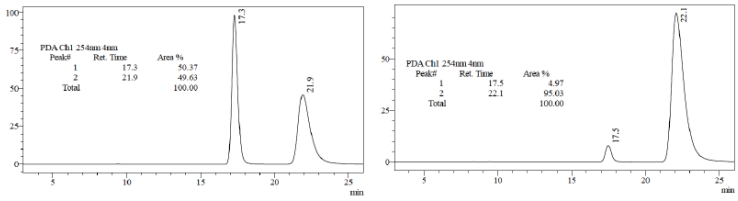
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 157.3, 143.2, 129.70, 129.67, 123.2, 122.3, 118.8 (2 overlapping signals), 118.1, 117.3, 80.6, 46.4, 27.9, 18.3

GCMS (EI): calcd for $C_{19}H_{22}O_3$ M: 298.2. Found: 298.1.



***(S)*-*tert*-Butyl 2-(*m*-fluoro-*p*-biphenyl)propionate [362523-47-5].** The reaction was finished within 6 hours at 50 ^oC in $PhCF_3$. The title compound was obtained as colorless oil (147 mg, 98% yield, 90% ee) by flash chromatography using EA/hexane (1:30) as eluent. The ee of the product was determined to be 83% when PhMe was used.

The ee of the purified products was determined to be 90% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*PrOH = 99:1; detection wave- lengths = 254 nm; flow rate = 0.5 mL/min). T_R = 17.5 min (minor) and 22.1 min (major).



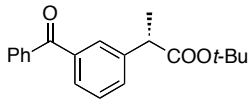
$[\alpha]^{21}_{D}$ = +16.6 (*c* = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.53 (m, 2H), 7.45-7.33 (m, 4H), 7.15-7.09 (m, 2H), 3.64 (q, *J* = 7.2 Hz, 1H), 1.48 (d, *J* = 7.2 Hz, 3H), 1.43 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 159.7 (J_{CF} = 247.9 Hz), 142.6 (J_{CF} = 7.7 Hz), 135.7, 130.6 (J_{CF} = 3.9 Hz), 128.9 (J_{CF} = 3.0 Hz), 128.4, 127.5, 127.4, 123.5 (J_{CF} = 3.4 Hz), 115.1 (J_{CF} = 23.5 Hz), 80.9, 46.0, 28.0, 18.4.

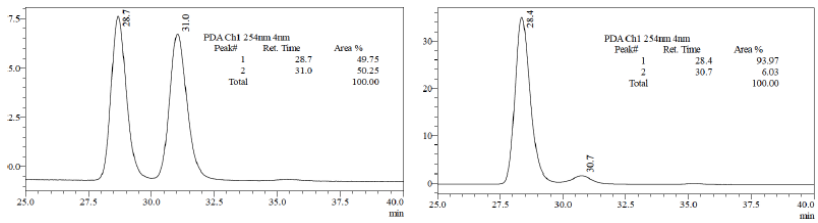
^{19}F NMR (376 MHz, $CDCl_3$): -118.0.

GCMS (EI): calcd for $C_{19}H_{21}FO_2$ M: 300.1. Found: 300.1



(*S*)-*tert*-Butyl 2-(*m*-benzoylphenyl)propionate [1334591-51-3]. The reaction was finished within 12 hours at 50 °C in $PhCF_3$. The title compound was obtained as colorless oil (144 mg, 97% yield) by flash chromatography using EA/hexane (1:10) as eluent.

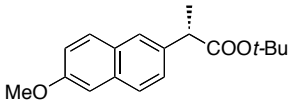
The ee of the purified products was determined to be 88% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 99.5:0.5; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). T_R = 28.4 min (major) and 30.7 min (minor).



$[\alpha]^{21}_{D}$ = +44.5 (*c* = 0.3, $CHCl_3$).

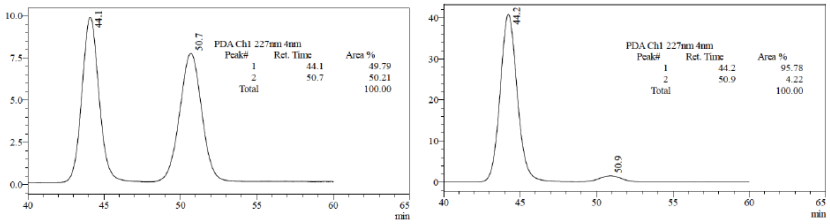
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.82 (m, 2H), 7.76-7.75 (m, 1H), 7.72-7.69 (m, 1H), 7.64-7.60 (m, 1H), 7.58-7.56 (m, 1H), 7.53-7.45 (m, 3H), 3.68 (q, *J* = 7.2 Hz, 1H), 1.48 (d, *J* = 7.2 Hz, 3H), 1.40 (s, 9H).

GCMS (EI): calcd for $C_{20}H_{22}O_3$ M: 310.2. Found: 310.2.



(*S*)-*tert*-Butyl 2-(6′-methoxy-2′-naphthyl)propionate [92455-03-3]. The reaction was finished within 36 hours at 50 °C in $PhCF_3$. The title compound was obtained as white solid (137 mg, 96% yield) by flash chromatography using EA/hexane (1:30) as eluent.

The ee of the purified products was determined to be 92% based on chiral HPLC analysis (Daicel CHIRALCEL OJ-H; hexanes: *i*-PrOH = 99:1; detection wavelengths = 227 nm; flow rate = 0.5 mL/min). T_R = 44.2 min (major) and 50.9 min (minor).



$[\alpha]^{21}_D$ = +18.9 (*c* = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.65 (m, 3H), 7.41 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.15-7.11 (m, 2H), 3.92 (s, 3H), 3.75 (q, *J* = 7.1 Hz, 1H), 1.53 (d, *J* = 7.1 Hz, 3H), 1.40 (s, 9H).

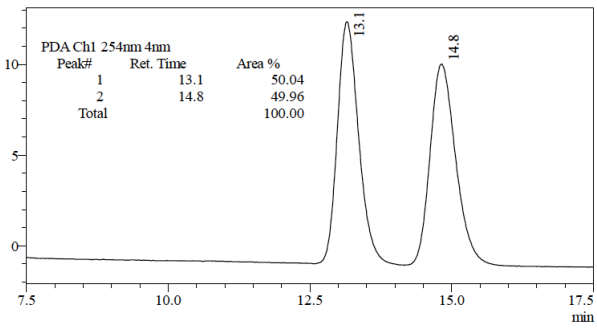
GCMS (EI): calcd for $C_{18}H_{22}O_3$ M: 286.2. Found: 286.1.

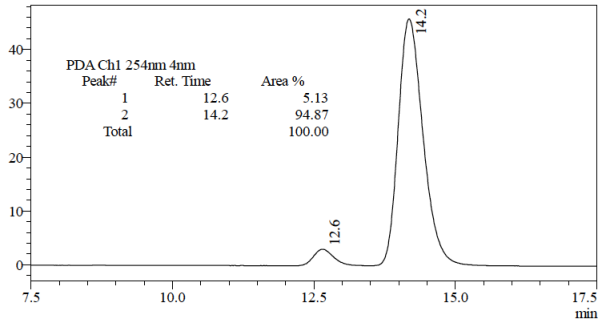
V. Gram-scale synthesis of (*S*)-Flurbiprofen ester

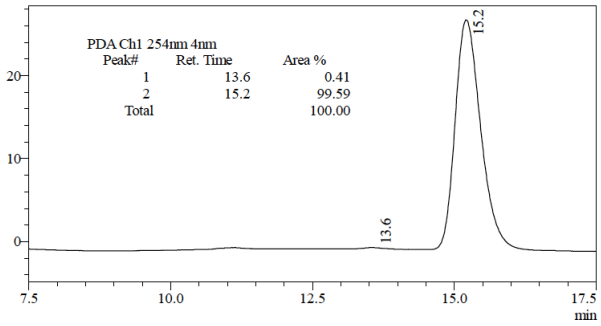
Procedure without using a glove box: Under argon, a 50-mL dry Schlenk tube was charged with $PdMe_2$(TMEDA) (20 mg, 0.08 mmol), ligand **L7** (67 mg, 0.10

mmol) and dry $PhCF_3$ (12 mL). After the resulting mixture was stirred at room temperature for 30 minutes, anhydrous LiOAc (528 mg, 8.0 mmol), ZnF_2 (82 mg, 0.8 mmol), *m*-fluoro-*p*-biphenyl triflate (1.28 g, 4.0 mmol) and (*E*)-1-*tert*-butoxy-1-(trimethylsiloxy)propene (1.21 g, 6.0 mmol) were added into the Schlenk tube against argon flow, followed by GC standard, dry *n*-dodecane (400 *u*L). The Schlenk tube was tightly capped and the reaction mixture was heated with vigorous stirring in a 50 ^{o}C oil bath. After stirring at 50 ^{o}C for 9 hours, the reaction reached completion (monitored by GC). At the end of the reaction, the mixture was cooled to 25 ^{o}C, and filtered through a pad of silica gel (~20 g) with diethyl ether washing (50 mL). The filtrate was concentrated on a rotary evaporator and the residue was purified by flash silica gel chromatography (1:30 ethyl acetate/hexane), which afforded (*S*)-Flurbiprofen ester (1.19 g, 98% yield, 90% ee) as yellow oil. The product was dissolved in analytical-grade DCM (10 mL) under argon, followed by the addition of trifluoroacetic acid (10 mL). The hydrolysis was carried out at room temperature with stirring for 4 hours. At the end of the reaction, the solvent and trifluoroacetic acid was concentrated on a rotary evaporator. The residue was directly purified by flash chromatography (1:3 ethyl acetate/hexane), which afforded (*S*)-Flurbiprofen (1.17 g, 99% yield, 90% ee) as off-white solid.

The ee of (*S*)-Flurbiprofen was improved to 99% after a recrystallization from a solvent of Et_2O/hexane (424mg, 44% yield, colorless needle).







For a sample with 99% ee, $[\alpha]^{20}_{D} = +40.6^{o}$ (c = 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.52 (m, 2H), 7.46-7.35 (m, 4H), 7.19-7.13 (m, 2H), 3.79 (q, J = 7.2 Hz, 1H), 1.56 (d, J = 7.2 Hz, 3H).

^{19}F NMR (376 MHz, $CDCl_3$): δ -117.4.

1.7 Reference:

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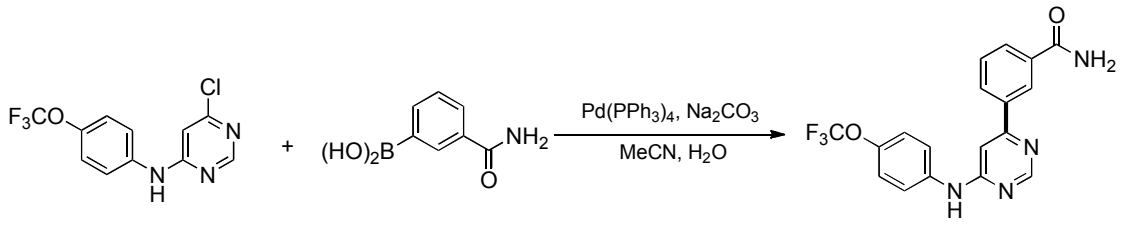
Chapter 2: Room-Temperature Suzuki-Miyaura Coupling of Heteroaryl Chlorides

2.1 Background

Biaryls are important motifs in medicines, agrochemicals and conjugated polymers. Among the numerous cross-coupling methods to construct the aryl-aryl bonds, Suzuki coupling represents one of the most commonly used methods.[1] Compared with other cross-couplings, Suzuki coupling tolerates many polar groups. The carbon nucleophiles, organoboronic acids and esters, are stable to water, oxygen and heat. The boron starting materials and byproducts are of low toxicity. In addition, most of these boron reagents are now commercially available. Many functionalized arylboronic acid or ester can be easily prepared by metal-catalyzed borylation of arene C-H bonds[2] and aryl halides.[3] These attributes make Suzuki coupling especially attractive in drug discovery and development.[4]

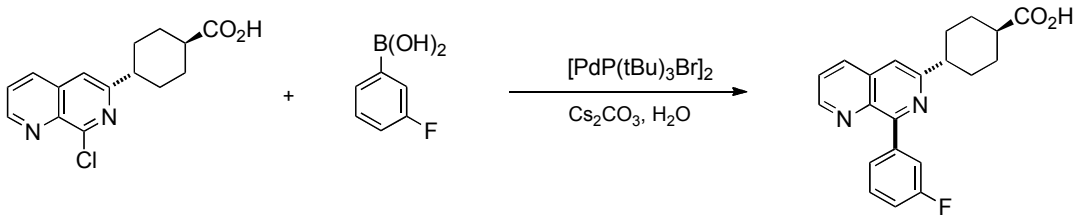
In the past two decades, extensive efforts have been devoted to finding highly active Pd catalysts, which led to discovery of bulky, electron–rich ligands, such as trialkylphophines,[5] dialkylbiaryl phosphines,[6] *N*–heterocyclic carbenes[7] and others.[8] These catalysts allowed coupling of challenging aryl electrophiles, such as electron–rich aryl chlorides,[9] tosylates and mesylates,[10] and sterically aryl electrophiles.[11] Recently, Ni/PCy_3 catalyst also enabled aryl esters,[12] carbamates and sulfamates[13] to be used efficiently in Suzuki coupling.

Aryl–heteroaryl and heteroaryl–heteroaryl bonds are commonly present in drugs and drug candidates (Figure 2.1). Suzuki coupling is often employed to prepare these compounds.[4] A typical example is GNF-2, an allosteric inhibitor,[14] and other examples include a PDE–4 inhibitor for treatment of asthma,[15] a subtype–selective $GABA_A$ receptor agonist for treatment of anxiety,[16] and AR–C123196 for treatment of asthma and rhinitis.[17] Suzuki coupling of heteroaryls have also been applied in total syntheses of bioactive natural products, such as dragmacidin D and F,[18] ratanhine,[19] and diazonamide A.[20]



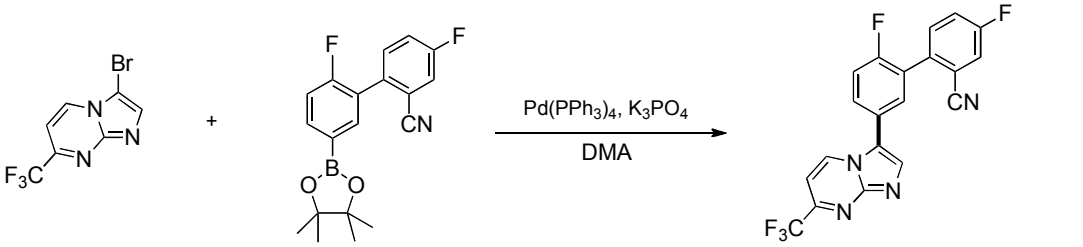
(1)

GNF-2



(2)

PDE-4 inhibitor (Novartis)



(3)

$GABA_A$ receptor agonist (Merck)

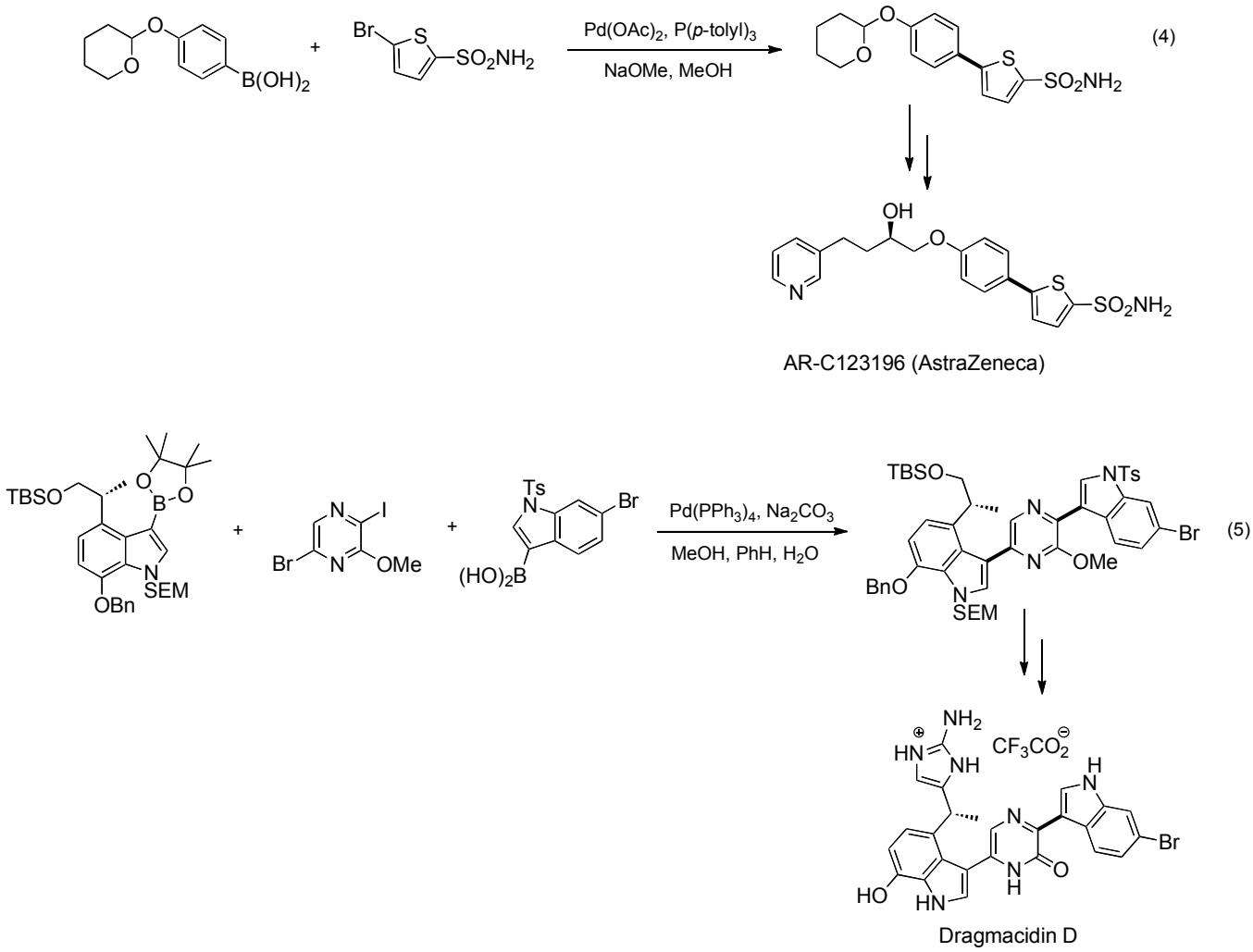
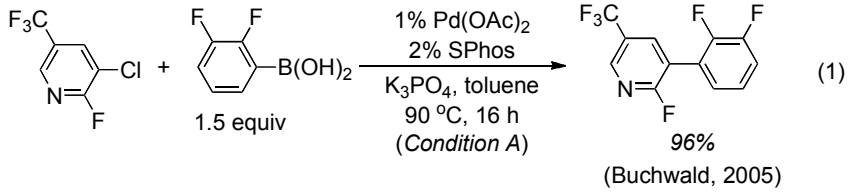
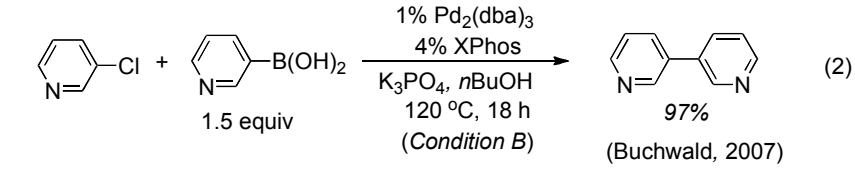


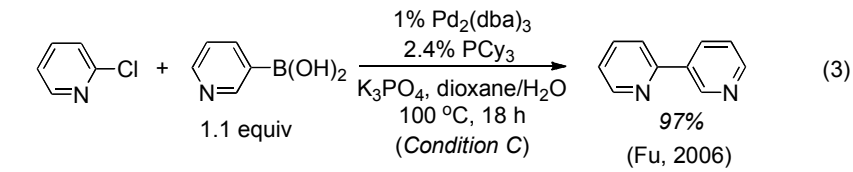
Figure2.1 Bioactive compounds containing heteroaryl groups

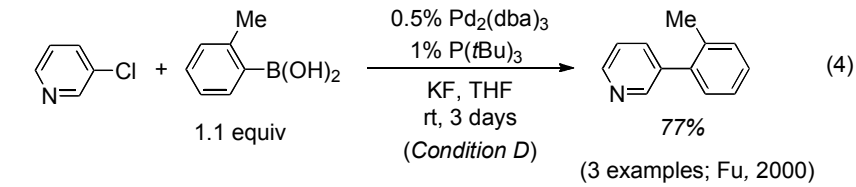
Coupling of heteroaryl halides is generally considered to be more challenging than aryl ones. In particular, nitrogen–containing heterocycles, such as pyridines and quinolines, can displace some phosphine ligands on Pd(II) complexes.[21] In the past decade, a dozen of Pd catalysts have been reported for Suzuki reactions of heteroaryl chlorides.[22] Some typical examples are shown in eq 1–3, using Buchwald phosphines,[23] bulky trialkylphosphines,[24] and other dialkylarylphosphines.[25] However, most of reported methods required high temperatures, usually 100–120 ^{o}C. The high temperature, together with basic conditions, is unsuitable for base–sensitive polar groups and thermally unstable molecular structures. Before our study, only a few isolated examples of heteroaryl chlorides were documented to undergo Suzuki

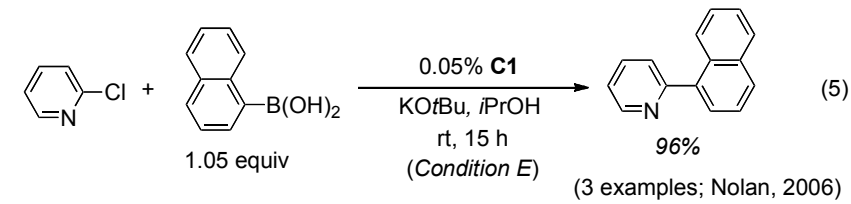
coupling at room temperature using P(*t*Bu)$_3$,[26] IPr[27] and XPhos[28] (eq 4–6). Recently, Buchwald *et al.* reported that **C2** was an exceptionally active precatalyst for Suzuki coupling, but only four examples of heteroaryl chlorides were shown to undergo coupling at room temperature (eq 6).[28]

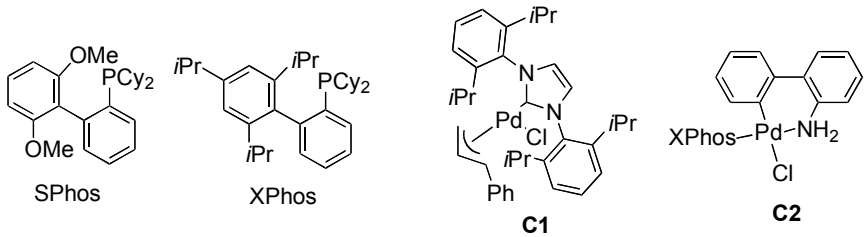












In addition, some heterocyclic boronic acids, especially the five membered 2-heterocyclic boronic acids, which are prone to undergo protondeboronation, cause the reaction problematic. Several types of surrogates have been developed,[23d,29] for example, MIDA ester (MIDA = *N*-methyliminodiacetic acid) and triisopropyl borate. However, these surrogates are typically prepared from the free boronic acids.

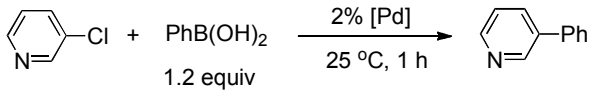
Thus, a general Suzuki coupling operating at room–temperature is desirable due to its wide application in medicine chemistry and materials science. Herein, we developed a general room–temperature Suzuki coupling for major families of heteroaryl chlorides.

2.2 Conditions Optimization

At the onset of our project, we aimed to develop a general fast Suzuki coupling of heteroaryl chlorides at room temperature. We chose 3–chloropyridine and phenyl boronic acid as model substrates to search for efficient Pd catalysts. The pyridine substrate was used because substituted pyridines are the most widely used heterocycles in pharmaceuticals.[4]

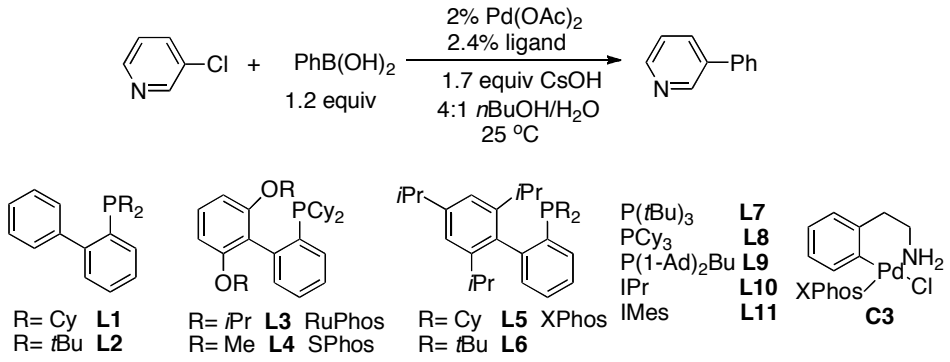
We have tested the model reaction using reported procedures A–F (Table 2.1) by using 2 mol% Pd loading (Table 2.1). Most of them gave very low conversion after 1 h at 25 ^{o}C. The best result was obtained from condition F using precatalyst **C2**, 72% conversion after 1 h. We have also attempted to optimize bases and solvents for the catalysts in A-F, but to no avail.

Table 2.1 Coupling of 3–chloropyridine and phenylboronic acid at 25 ^{o}C



Entry	Condition	Conversion (%)	Yield (%)
1	A	10	10
2	B	3	0
3	C	0	0
4	D	14	14
5	E	29	17
6	F	72	66

After extensive research of catalysts and conditions, we found that $Pd(OAc)_2$ and XPhos were exceptionally active when CsOH was used in 4:1 *n*–butanol/water. It gave almost quantitative yield of the product at 25 °C within 5 minutes (Figure 2.2). Other common ligands were also examined and the yields of the product after 5, 15 and 60 minutes are summarized in Figure 2.2. Some Buchwald ligands were highly active such as RuPhos, SPhos and XPhos. In comparison, $P(tBu)_3$, PCy_3 and $P(1–Ad)_2Bu$ were much less active. Bisphosphines such as dppf, BINAP, Xantphos and Josiphos, did not give >10% yield after 1 h.



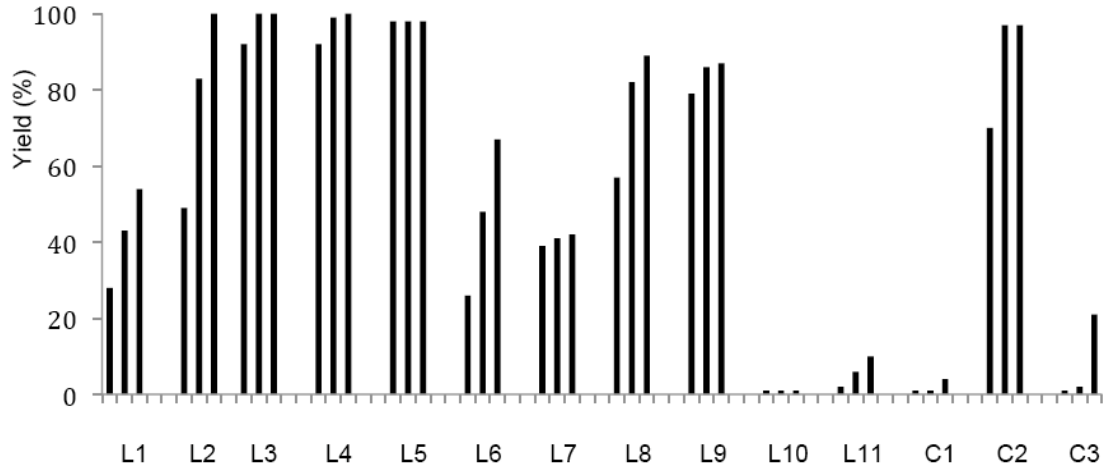


Figure 2.2 Effect of ligands and catalysts (yields after 5, 15 and 60 min)

The way that active catalyst (XPhos)Pd(0) was generated was crucial for fast coupling. When $Pd(dba)_2$ and $Pd_2(dba)_3$ were used together with XPhos, no coupling reaction was observed after 1 h. This is most probably due to strong binding of dba to (XPhos)Pd(0).[30] When $Pd(OAc)_2$ and XPhos were used as precatalyst, 84% and 96% of biphenyl (with respect to 2 mol% $Pd(OAc)_2$) was produced in 30 and 60 seconds, respectively (Figure 2.3). This result confirms that double transmetalation of $PhB(OH)_2$ to $LPd(OAc)_2$ and subsequent reductive elimination of biphenyl is the major pathway for fast generation of LPd(0).[31]

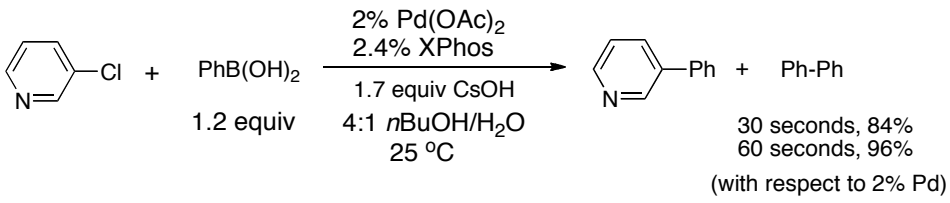
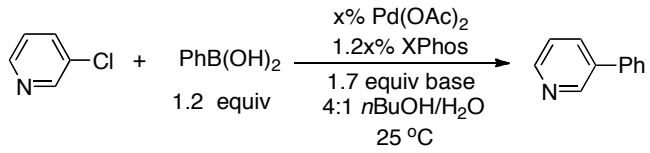


Figure 2.3 Reduction of $Pd(OAc)_2$ via double transmetalation

Some palladium complexes of XPhos were also tested as precatalysts. When complex **C3** was used, the model reaction gave only 20% of the product after 1 h, due to slow release of the active catalyst. Precatalyst **C2** was much more active than **C3** (70% yield after 5 min).

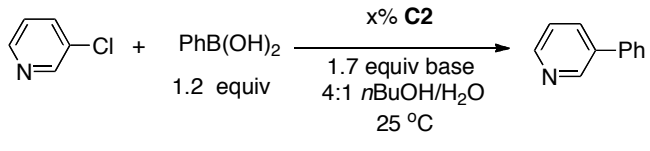
In comparison, at 0.5 mol% Pd loading, $Pd(OAc)_2$/XPhos gave 73% yield at 5 min (Table 2.2), while complex C2 gave 35% yield (Table 2.3). The loading of $Pd(OAc)_2$/XPhos can be even lowered to 0.1 mol% (87% yield after 1 h).

Table 2.2 Model reaction using low loading of $Pd(OAc)_2$ and XPhos



Entry	Catalyst Loading	5 min		15 min		1 h	
		Conv. (%)	Yield (%)	Conv. (%)	Yield (%)	Conv. (%)	Yield (%)
1	2%	100	98	100	98	100	98
2	1%	97	97	100	98	100	98
3	0.5%	73	73	96	96	100	99
4	0.2%	65	61	70	69	100	98
5	0.1%	70	63	73	70	87	87

Table 2.3 Model reaction using low loading of precatalyst **C2**

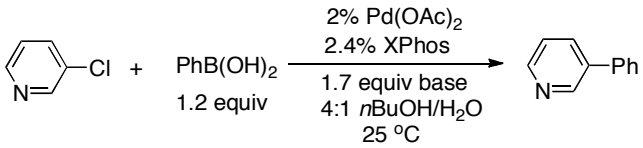


Entry	Catalyst Loading	5 min		15 min		1 h	
		Conv. (%)	Yield (%)	Conv. (%)	Yield (%)	Conv. (%)	Yield (%)
1	2%	77	76	100	98	100	98

2	1%	75	74	100	98	100	98
3	0.5%	35	35	73	73	100	99

We have examined catalytic activity of Pd complexes of NHC ligands. (a) A combination of $Pd(OAc)_2$ and NHC ligands (IPr and IMes) showed little coupling activity (Figure 2.2). (b) The use of NHC salts did not form active catalysts. (c) Nolan *et al*. previously reported that LPdCl(π–cinnamyl) complex **C1** (L = IPr) was moderately active for Suzuki coupling at room temperature (eq 5). Under our model reaction, LPdCl(π–cinnamyl) complexes (L = IPr, IMes) gave <5% of the product after 1 h at room temperature.

In Suzuki reaction, the choice of base and solvent can significantly influence the coupling efficiency, because the transmetalation step can be rate–limiting.[26,32] In our room–temperature coupling, it is important to use CsOH as base and 4:1 *n*–butanol/water for the fast coupling. Among common bases, CsOH proved to be most effective, while LiOH, NaOH and KOH gave slightly lower rates (Figure 2.4). Weaker bases such as Cs_2CO_3, K_2CO_3 and K_3PO_4 led to even slower coupling.



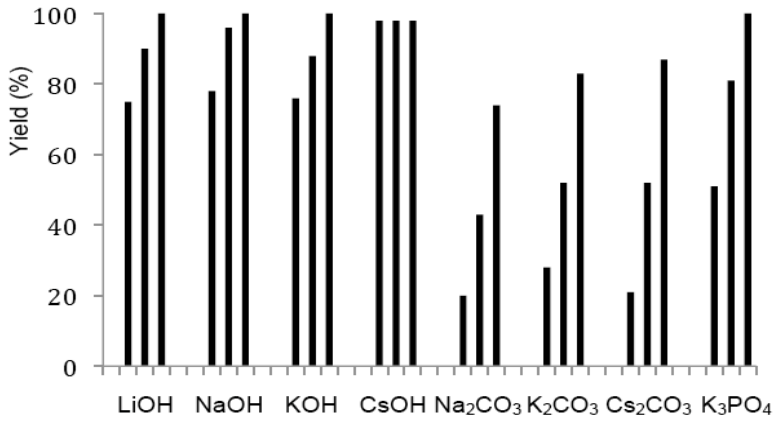


Figure 2.4 Effect of bases (yields after 5, 15 and 60 min)

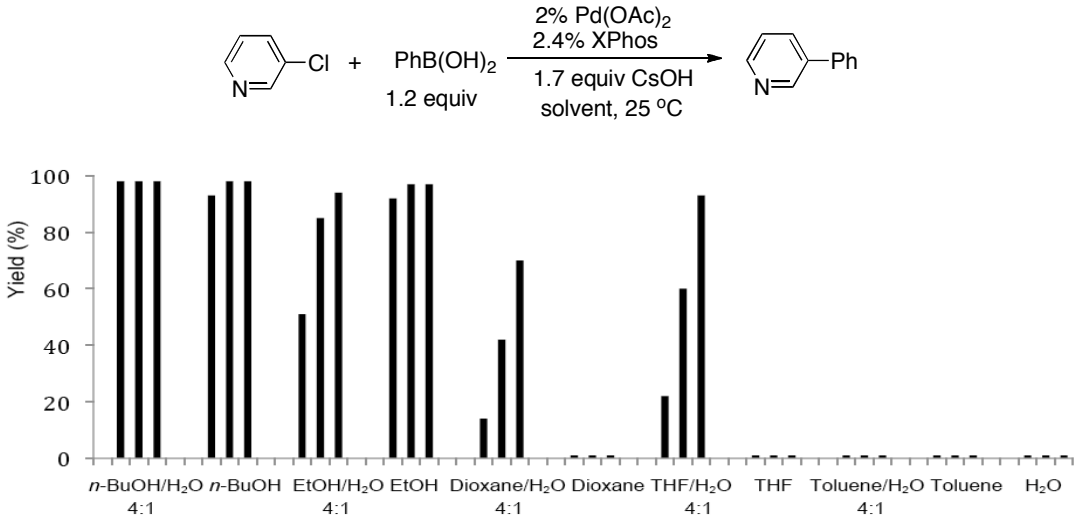


Figure 2.5 Effect of solvents (yields after 5, 15 and 60 min)

The solvents had direct influence on the coupling efficiency. When CsOH was used as base, 4:1 *n*–butanol/water was optimal for the fast coupling. In dry *n*–butanol or ethanol it was slightly slower (Figure 2.5). In other alcohols such as isopropyl and *t*–amyl alcohol, the coupling was slower. In aqueous solvents of dioxane and THF, the reaction was even slower. In pure ethereal solvents, little coupling occurred. In aqueous toluene, pure toluene or pure water, no coupling product was observed.

Notably, the model reaction can be set up in air using non-degassed *n*-butanol/water. The reaction vial was then capped. In the presence of 2% Pd loading and 1.2 equiv of $PhB(OH)_2$, the coupling product was obtained in 90% yield after 1 h at room temperature (Figure 2.6).

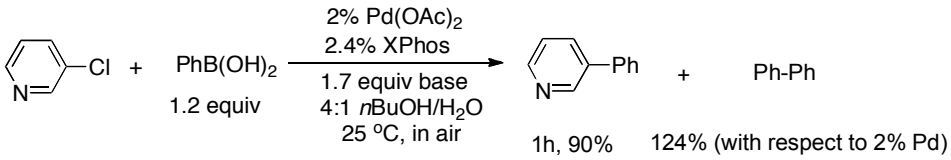
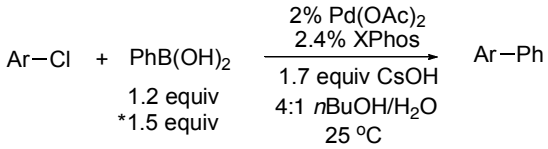


Figure 2.6 Bench-top Suzuki coupling.

2.3 Substrate Scope

2.3.1 Scope of Heteroaryl Chlorides

With the optimized condition in hand, $PhB(OH)_2$ was used to couple with major families of heteroaryl chlorides. Most of the reactions gave full conversion after a period of 5 min to 1 h (Figure 2.7). Overall, the more electron–rich heterocycles were less reactive due to slower oxidative addition. Their reactivity follows the order of pyrrole, indole < thiophene, furan < pyridine. Consistent with this trend, electron-withdrawing groups on the heterocyclic chlorides accelerated the overall couplings. Notably, for amino–substituted pyridine chlorides, no *N*–arylation was observed. Furthermore, no hydrolysis of the ester group was observed.



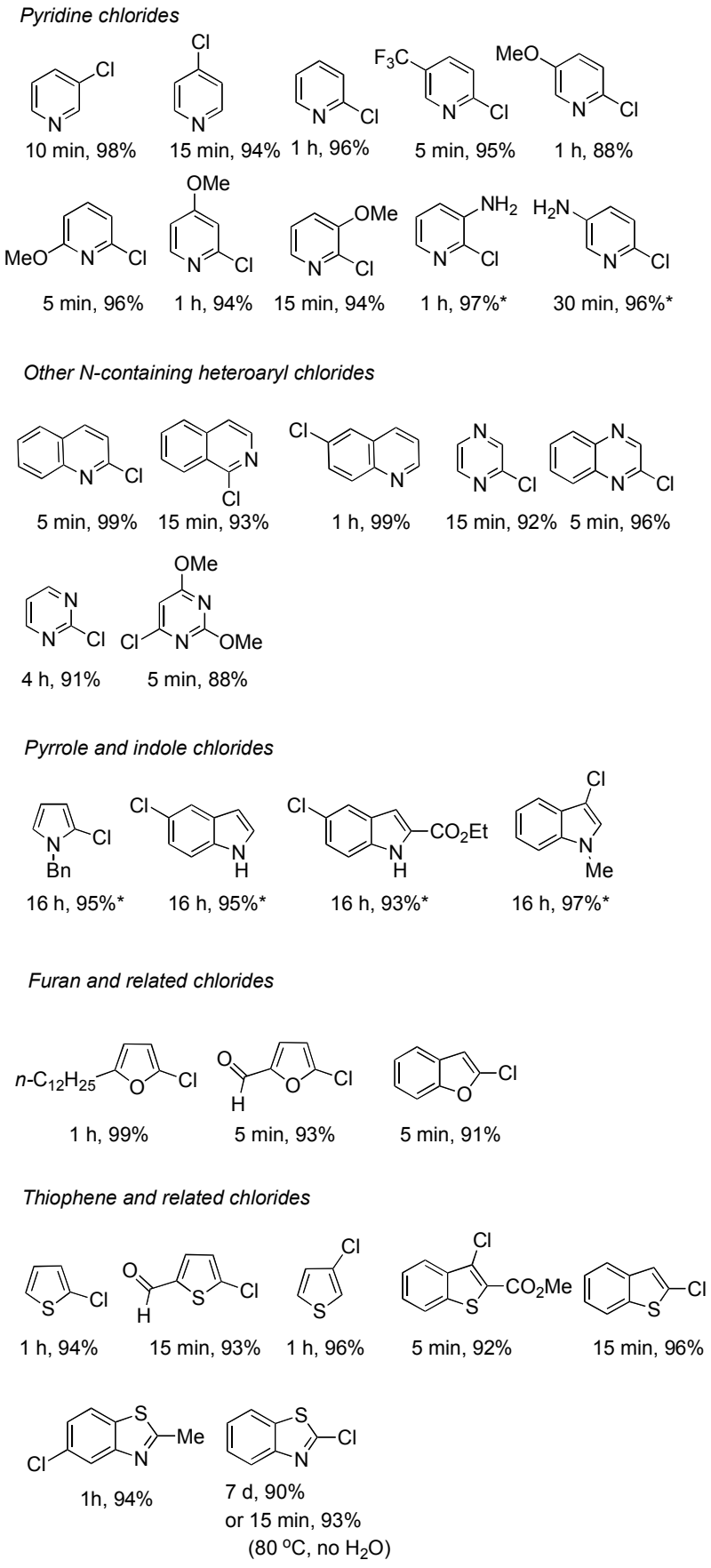
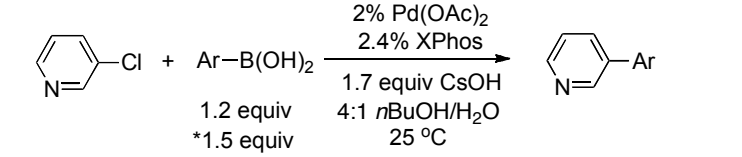


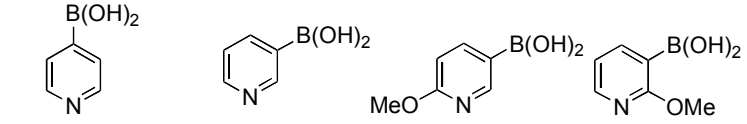
Figure 2.7 Scope of heteroaryl chlorides

2.3.2 Scope of Heteroarylboronic Acids

Pyridine is one of the most commonly used heterocycles in pharmaceuticals and pyridines carrying aryl or heteroaryl groups are frequently present in drugs and drug candidates.[15,33] We chose 3-chloropyridine as electron-deficient heteroaryl electrophile to couple with various heteroarylboronic acids (Figure 2.8). Under the optimized condition, almost all reactions gave full conversion within minutes to 1 hour at room temperature. As exceptions, 3– and 4–pyridylboronic acids required heating at 80 ^{o}C. Five–membered 2–heteroarylboronic acids of furan, thiophene, pyrrole and indole were known to undergo fast base– and/or catalyst–induced protodeborylation in aqueous solvents. However, these boronic acids gave good yield of the coupling product under our coupling condition.

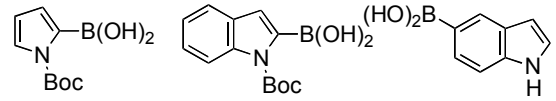


Pyridine boronic acids



1 h, 90% (80 ^{o}C) | 15 min, 88% (80 ^{o}C) | 1 h, 95% | 5 min, 96%

Pyrrole and indole boronic acids



5 min, 96% | 5 min, 97%, **1.14 g** | 15 min, 91%

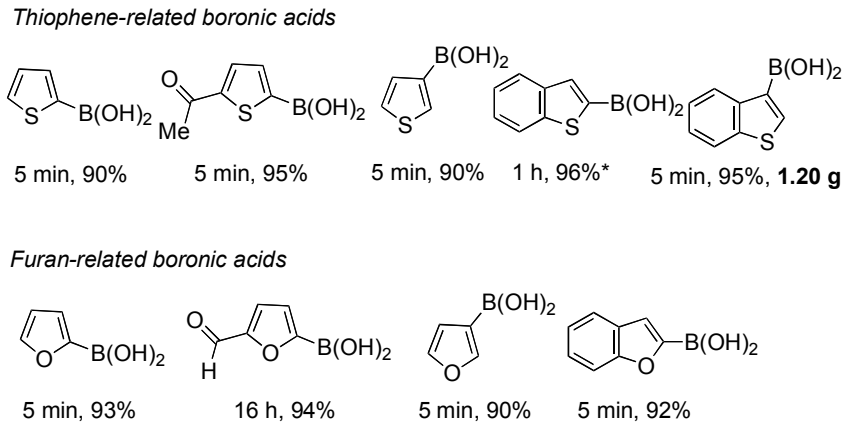


Figure 2.8 Scope of heteroarylboronic acids in coupling of 3-chloropyridine

In these reactions, a general trend emerged that the more electron–rich heteroarylboronic acids underwent faster coupling, probably due to faster transmetalation or reductive eliminaiton. For instance, 2-furanylboronic acid reacted much faster than (5-formyl-2-furyl)boronic acid.

(Hetero)aryl–substituted thiophenes are common in drug candidates[17,34] and oligo– and polythiophenes are widely used in electron–conducting materials and photosensitizers in solar cells.[35] Suzuki coupling was often used to synthesize these compounds. We have studied the coupling of 2–chlorothiophene with various heteroarylboronic acids (Figure 2.9). Almost all of heterocyclic boronic acids underwent coupling at room temperature. As exceptions, 3– and 4–pyridylboronic acids required heating at 80 ^{o}C. Compared with 3–chloropyridine, 2–chlorothiophene usually coupled slower and needed more organoboronic acids (1.5 equiv). Again, in couplings of 2–chlorothiophene, the more electron–rich heteroarylboronic acids coupled faster. For instance, 2-furanylboronic acid reacted much faster than (5-formyl-2-furyl)boronic acid.. Notably, the aldehyde and ketone groups survived well under the basic condition.

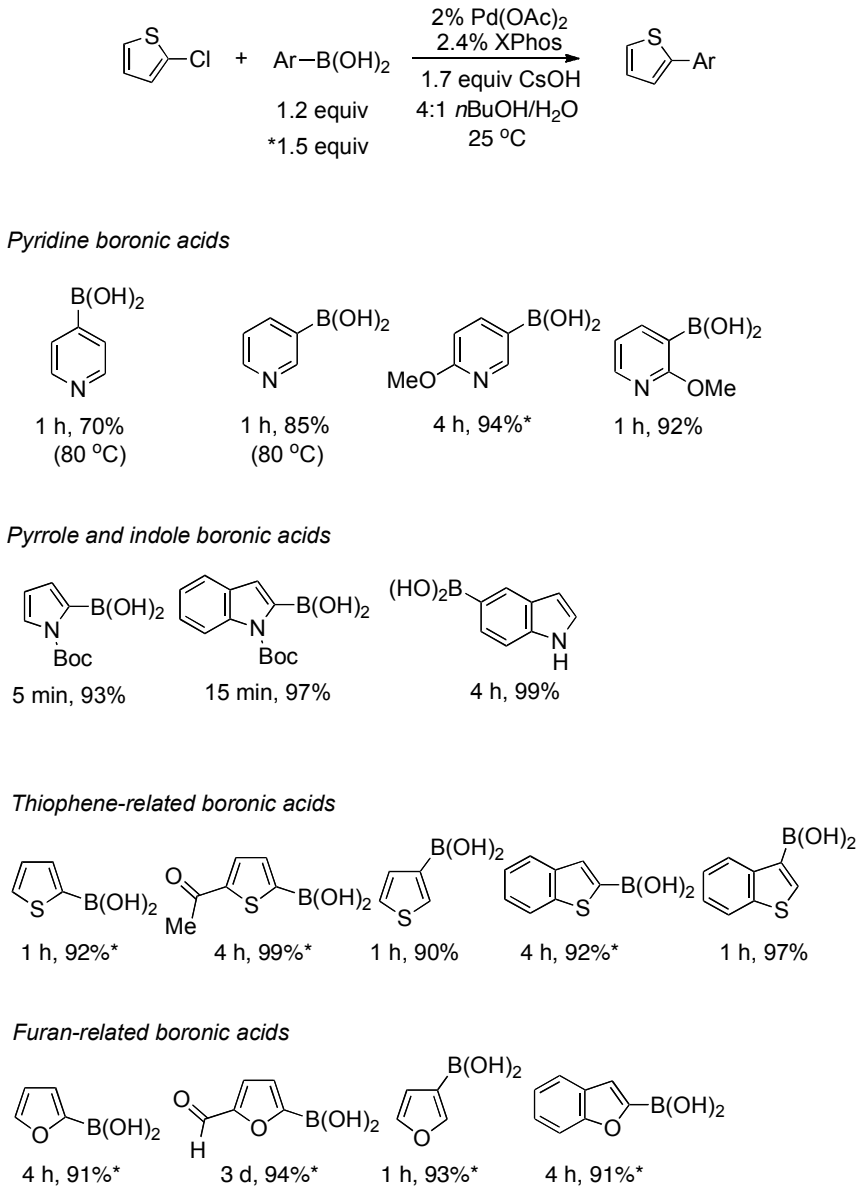


Figure 2.9 Scope of heteroarylboronic acids in coupling of 2–chlorothiophene

Overall, in coupling of 3–chloropyridine and 2–chlorothiophene, slow coupling reactions of parent pyridylboronic acids were attributed to rate–limiting transmetalation or reductive elimination.

2.3.3 Scope of Arylboronic Acids

Our fast coupling method can be extended to the couplings of arylboronic acids (Figure 2.10). In reactions of various arylboronic acids and 3–chloropyridine, almost

all proceeded efficiently and finished over minutes to 1 h. Notably, the reactions were compatible with ketone and aldehyde groups at *ortho* positions, which may have caused problem by chelating on the palladium(II) center.

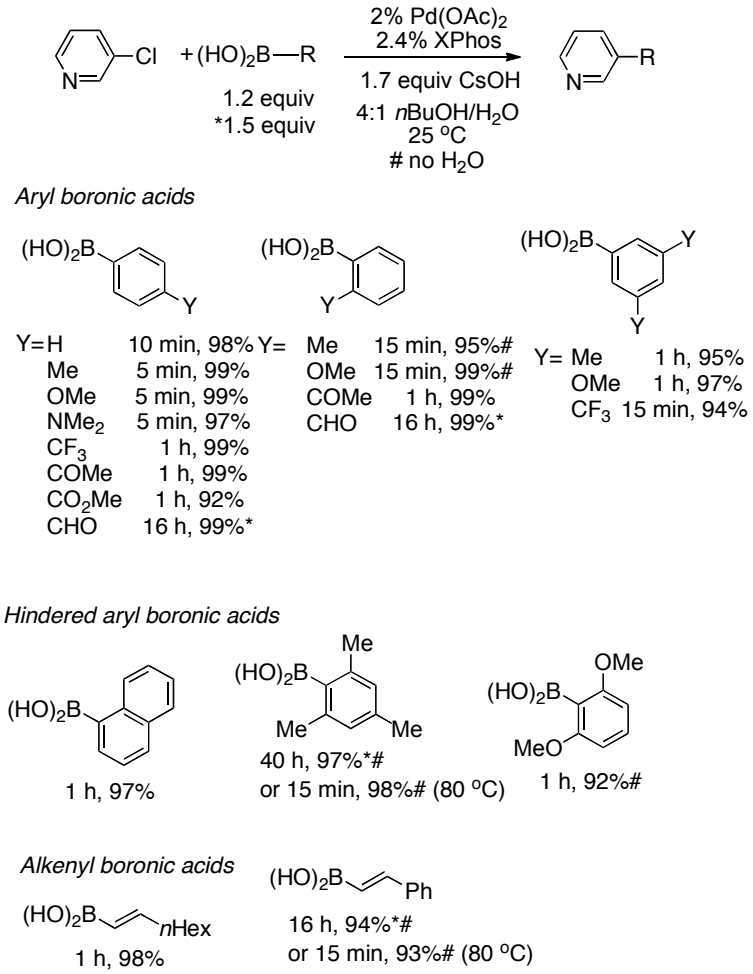


Figure 2.10 Scope of aryl and vinylboronic acids in coupling of 3-chloropyridine

In mono–substituted arylboronic acids, the electron–deficient ones coupled slower than the electron–neutral ones.[36] In particular, the arylboronic acids carrying aldehyde groups coupled very slowly. We noticed that electron–rich and electron–neutral ones showed similar coupling rates.

Steric effect also came into play. In particular, coupling of 2–mesityl boronic acid required 40 h at room temperature to complete. In comparison, the more electron–rich 2,6–dimethoxyphenylboronic acid reacted much faster at room temperature.

Next, 2–chlorothiophene was used to compare relative reactivity of arylboronic acids (Figure 2.11). In general, these reactions were slower than those of 3–chloropyridine. For instance, in the series of *ortho*–substituted phenylboronic acids, electron–poor ones coupled slower than the electron–rich and electron-neutral ones. Again, 2–mesityl boronic acid reacted very slowly.

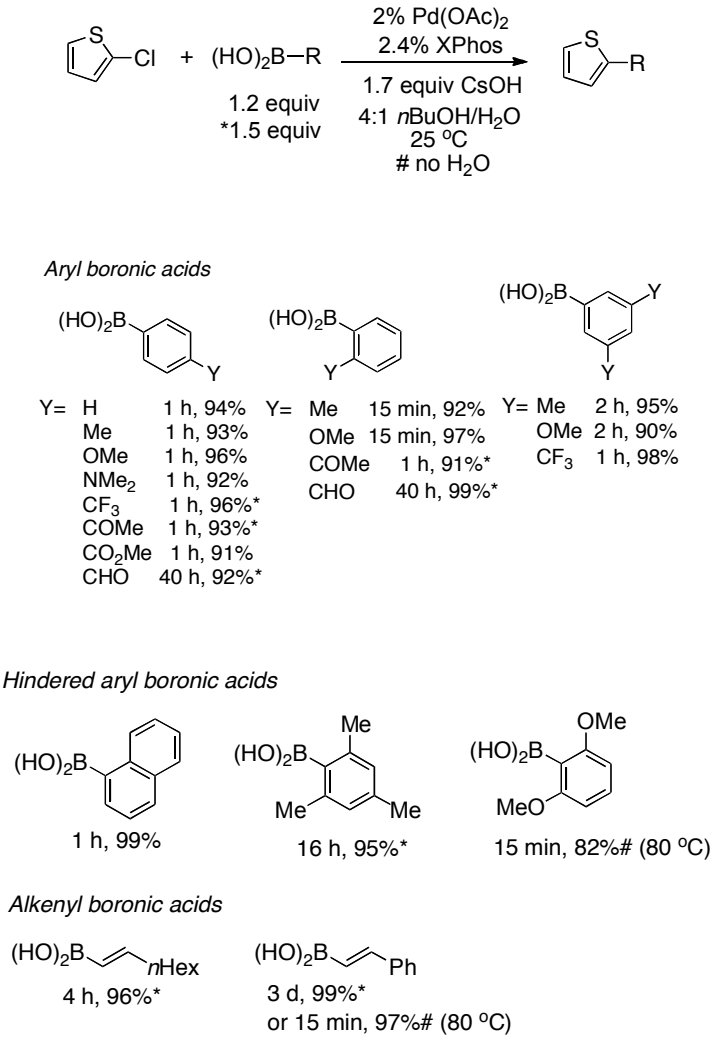


Figure 2.11 Scope of aryl and vinyl boronic acid in coupling of 2–chlorothiophene

2.4 Reaction Mechanism

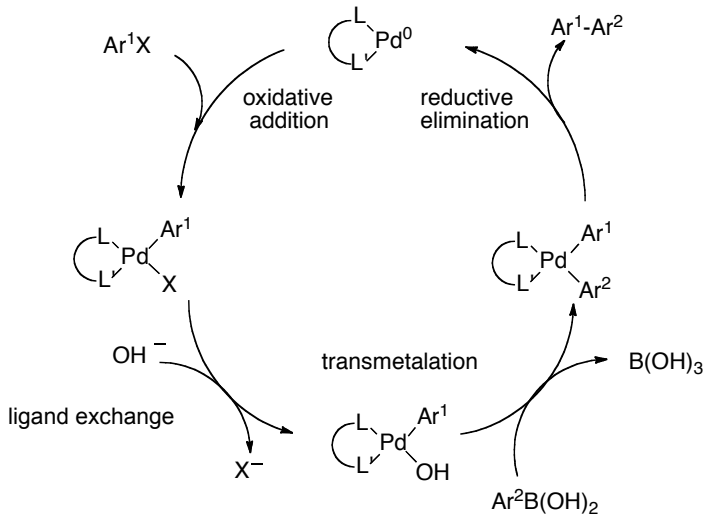


Figure 2.12 Proposed catalytic cycle

Suzuki reaction is believed to follow a sequence of the oxidative addition of aryl halide, transmetalation with arylboronic acid and reductive eliminaiton to afford the biaryl product (Figure 2.12).

The role of hydroxide bases in Suzuki coupling was clarified recently by Jutand, Murray and Hartwig *et al*.[37] The transmetalation of $ArB(OH)_2$ to ArLPd(OH) was revealed to be a preferred pathway than that of $ArB(OH)_3^-$ to ArLPdX. Three roles of the hydroxide anion were identified: (a) acceleration of transmetalation via formation of hydroxo complexes LPd(Ar)(OH), (b) inhibition of transmetalation via equilibrial formation of anionic $ArB(OH)_3^-$ and (c) acceleration of reductive elimination via formation of pentavalent palladium complexes. Overall, a higher ratio of $[OH^-]/[ArB(OH)_2]$ leads to faster coupling. When weak bases are used, hydroxide anion is formed via hydrolytic equilibrium with water and its concentration is low. Under our

condition, the use of hydroxide bases in an aqueous alcohol ensures high [OH^-], which can accelerate transmetalation and perhaps, also reductive elimination.

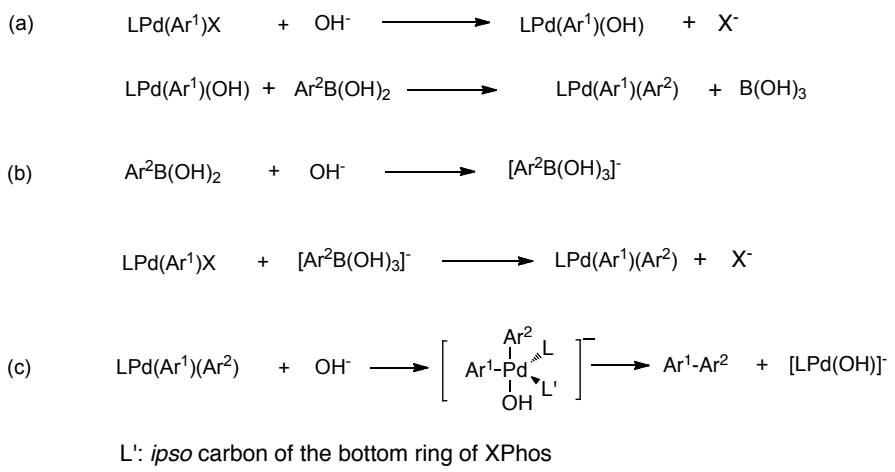


Figure 2.13 The role of hydroxide bases

2.5 DFT Calculations of Transmetalation and Reductive elimination

In Suzuki couplings, it is common to observe very slow couplings of pyridylboronic acids and other highly electron-poor arylboronic acids.[38] In order to understand its origin, we conducted DFT calculations (B3LYP) on the steps of transmetalation and C-C reductive elimination in collaboration with Prof. Hajime Hirao. (XPhos)Pd(Ph)(OH) and $ArB(OH)_2$ were used as model reactants for transmetalation. Three different organoboronic acids (Ar =Ph, 4-CHO-Ph, 4-pyridyl) were used to compare their relative reactivity. The B3LYP functional was used in conjunction with the Lanl2dz ECP basis set for Pd. The solvent effect of *n*-butyl alcohol was accounted for by using IEFPCM method.

The total electronic energy for each species during transmetalation is shown in Figure 2.14. The transmetalation starts from **RC1**, a binary complex whereby phenylboronic acid coordinates to the Pd-hydroxo oxygen of (XPhos)Pd(Ph)(OH).

After minor conformational changes (**TSrot** and **RC2**), transmetalation takes place whereby the *B*-phenyl group replaces hydroxo group on Pd via a four-membered transition state. In all stable species, Pd centers maintain the square-planar geometry and the bottom benzene ring of XPhos is too far away from Pd centers to have any π-coordination to Pd.

On the basis of the calculated energies, the overall barrier for transmetalation is very small, only around 10 kcal/mol for all three arylboronic acids. Furthermore, the transfer of 4-pyridyl group is only 1 kcal/mol higher in barrier than phenyl group. This is in contrast to common belief that electron-deficient pyridylboronic acids undergo slow Suzuki couplings because of their intrinsic poor transmetalating ability.

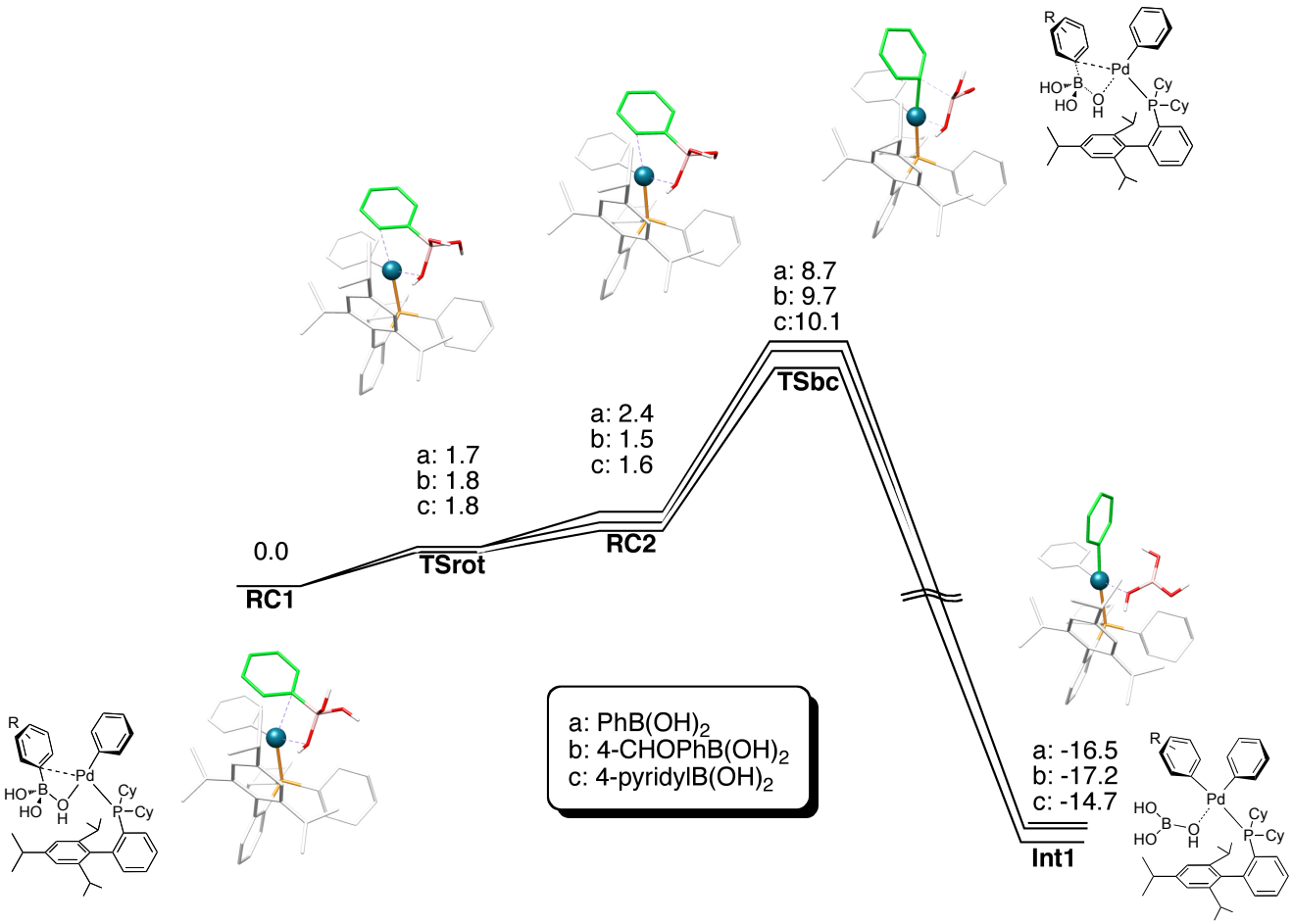


Figure 2.14 Total electronic energy profile for transmetalation (in kcal/mol)

We also conducted DFT calculations on the step of reductive elimination of the different organoboronic acids (Ar =Ph, 4-CHO-Ph, 4-pyridyl) (Figure 2.15). Again, the energy barrier is very small (around 5 kcal/mol) for all three aryl groups on Pd centers. Notably, π coordination of the bottom benzene ring to Pd is present in ground state, but not in the transition state and immediate product. The Pd(II) interaction with arenes of biarylphosphine ligands was reported by Kočovský, Buchwald, Pregosin, and others.[38]

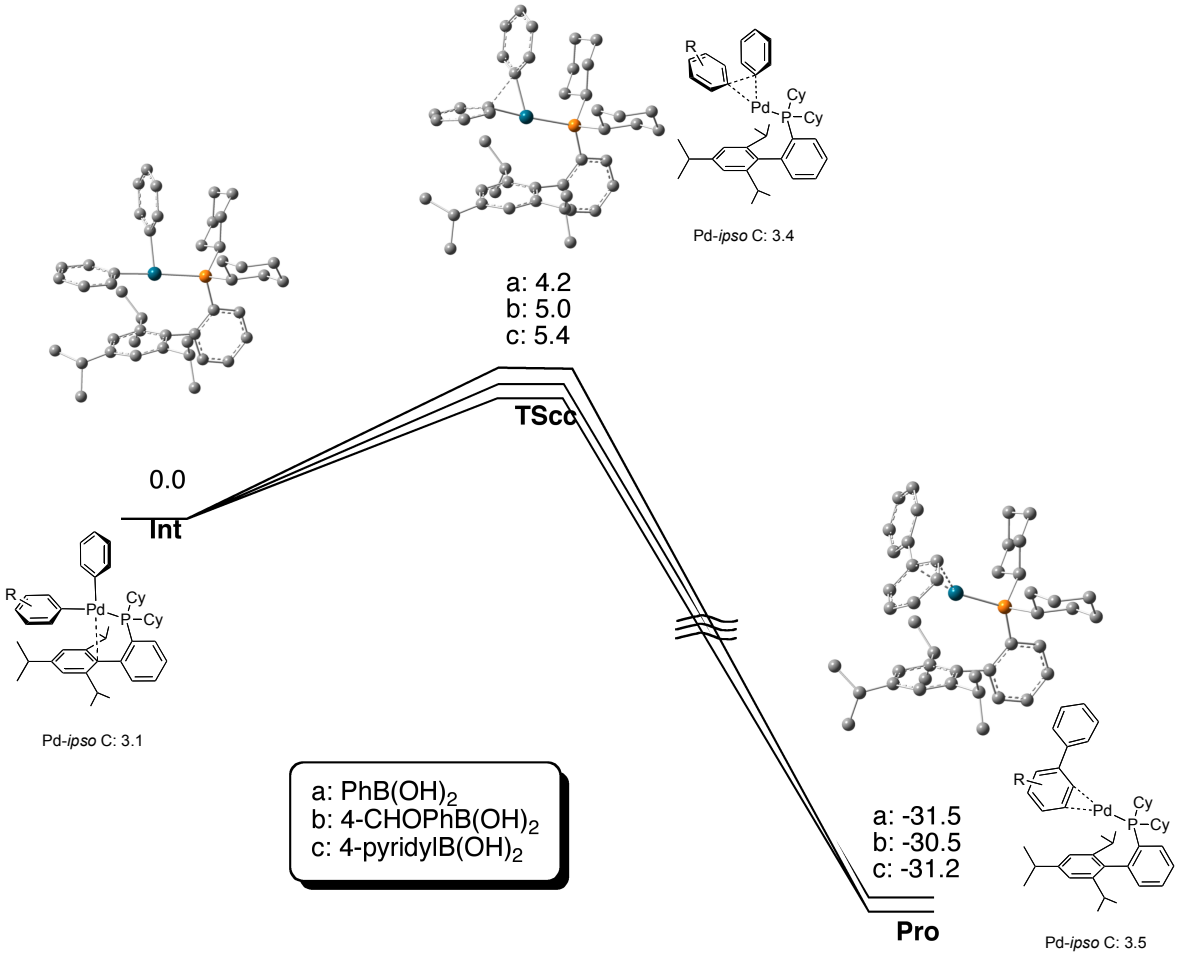


Figure 2.15 Total electronic energy profile for reductive elimination (in kcal/mol)

Under our catalytic condition which was very basic, electron-deficient pyridylboronic acid forms a stable anionic aryltrihydroxyborate, which is an inactive species for transmetalation.[36a] In conclusion, slow couplings of pyridylboronic acids in Suzuki couplings can be attributed to sequestration in the anionic $ArB(OH)_3^-$ form, instead of intrinsically slow transmetalation or slow reductive elimination.

2.6 Challenging Substrates

In the reaction of 3-chloropyridine, 3- and 4-pyridyboronic acids required heating at 80 ^oC for coupling to proceed. 2–Pyridylboronic acid was well known to be prone to hydrolysis, and several types of surrogates have been developed.[23d,39] 2–Pyridylboronic acid and its MIDA ester (MIDA = *N*-methyliminodiacetic acid)[23d] did not give the coupling products at 80 ^oC under our conditions. In the reaction of 3-chloropyridine, *p*-nitrophenyl and pentafluorophenyl boronic acids did not give the coupling products.

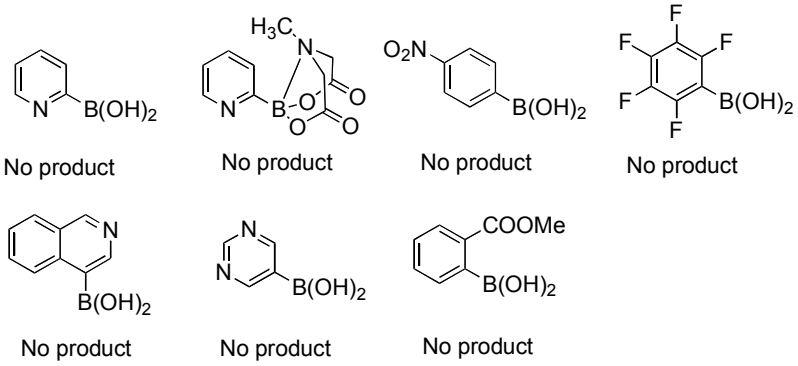


Figure 2.16 Challenging Substrate

2.7 Summary

We have developed a general method for fast coupling of heteroaryl chloride and heteroarylboronic acid. The method can be applied to major families of heterocyclic substrates, and most reaction finished within minutes to hours.

In this work, we revealed the relative reactivity of reaction partners. Firstly, for heteroaryl chloride, the more electron-rich ones reacted more slowly than electron-deficient ones because of the slower oxidative addition, in the order of indole, pyrrole < furan, thiophene < pyridine. Secondly, for the heteroarylboronic acids, the trends was reversed – the more electron-deficient ones coupled more slowly, in the order of indole, pyrrole > furan, thiophene > pyridine.

2.8 Experimental Section

I. General

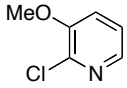
^{1}H NMR spectra were acquired at 400 MHz and chemical shifts were recorded relative to $SiMe_4$ (δ 0.00) or the residue protiated solvent ($CDCl_3$: d 7.26). Multiplicities were given as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance in a compound was indicated by nH. Coupling constants were reported as a *J* value in Hz. ^{13}C NMR spectra were obtained at 100 MHz on 400 MHz instruments and chemical shifts were recorded relative to a solvent resonance ($CDCl_3$: d 77.25). Proof of purity of new compounds was demonstrated with copies of ^{1}H and ^{13}C NMR spectra.

GC and GC/MS analysis was conducted with Agilent J&W GC column DB-5MS-UI. Flash chromatography was preformed using Merck 40-63D 60Å silica gel.

Unless noted otherwise, all manipulations were conducted inside an argon-filled glove box at room temperature. Glassware was dried at 120 ^{o}C for at least 3 hours before use. Anhydrous *n*-butanol and dioxane from Alfa Aesar were used as reaction solvent after degassing, although the use of the anhydrous solvent was not necessary to prepare the aqueous alcohol solvent for the coupling reactions. Ethanol were dried by refluxing with sodium chips and then distilled under argon. Toluene and diethyl ether for reactions were collected from a solvent purification system containing a 1 m column of activated alumina under argon. THF was freshly distilled from sodium/benzophenone under argon. Dry acetonitrile was purchased from Fischer Scientific. All of the anhydrous solvents were stored in Schlenk tubes in the glove box.

Unless noted otherwise, commercially available chemicals were used in the glove box after degassing. The GC internal standard, *n*-dodecane was dried over activated 4 Å molecular sieve for at least 2 days before use. LPdCl(p-cinnamyl) complexes (L = IPr and IMes) **C1** and **C4** were prepared according to reported procedure.[40] Pd complex of XPhos **C2** was prepared according to a reported procedure,[41] and Pd complex of XPhos **C3** was purchased from Aldrich.

I. Synthesis of Heteroaryl Chlorides



2-Chloro-3-methoxypyridine [52605-96-6]. Under argon, to a solution of 2-chloropyridin-3-ol (0.52 g, 4.0 mmol) in dry DMF (16 mL) at 25 ^{o}C was added sodium methoxide (0.22 g, 4.0 mmol) in one portion. After the resulting mixture was stirred at 25 ^{o}C for 4 h, methyl iodide (0.57 g, 4.0 mmol) was added and stirring was continued for 16 h. At the end of the reaction, the mixture was diluted with water (20 mL) and then extracted with ethyl acetate (16 mL x 3). The combined organic extracts were dried over Mg_2SO_4 and then concentrated under reduced pressure on a rotary evaporator. The resulting residue was purified by silica gel flash chromatography with ethyl acetate/hexane (1:5) as eluent to afford the target product as white solid (0.55 g, 96% yield).

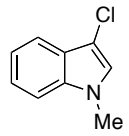
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (pseudotriplet m, J = 3.2 Hz, 1H), 7.18 (pseudodoublet, J = 3.2 Hz, 2H), 3.89 (s, 3H).

ESI-MS: Calcd for C_6H_6ClNO $(M+H)^+$: 144.01. Found: 144.22.

***N*-Benzyl-2-chloropyrrole [56454-01-4].** The compound was prepared according to a reported procedure.[42] Under argon, to a solution of *N*-benzylpyrrole (0.78 g, 5.0 mmol) in dry Et_2O (10 mL) at 0 °C was added dropwise a solution of SO_2Cl_2 (0.41 mL, 5.0 mmol) in dry Et_2O (5 mL). The mixture was allowed to warm up to 25 ^oC and then was stirred for additional 15 min. At the end of the reaction, the crude mixture was treated with dropwise addition of a saturated solution of $NaHCO_3$ until the pH reached 7 and then extracted with Et_2O (20 mL x 3). The combined organic extracts were washed with brine and then concentrated under reduced pressure. The resulting residue was purified by flash chromatography with pentane as eluent to afford the target product as colorless oil (0.51 g, 54% yield).

^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.28 (m, 3H), 7.10 (d, J = 6.8 Hz, 2H), 6.40 (m, 1H), 6.15 (pseudotriplet, J = 3.6 Hz, 1H), 6.10-6.09 (m, 1H), 5.10 (s, 2H).

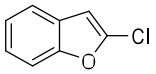
EI-MS: Calcd for $C_{11}H_{10}ClN$ M^+: 191.05. Found: 191.0.



3-Chloro-1-methylindole [124589-41-9]. The compound was prepared according to a reported procedure.[42] Under argon, to a solution of *N*-methylindole (0.25 g, 1.9 mmol) in dry MeCN (6 mL) at 25 ^oC was added *N*-chlorosuccinimide (0.25 g, 1.9 mmol) in one portion. The resulting mixture was stirred at 25 ^oC overnight. The crude product was quenched with water (20 mL) and then extracted with EtOAc (20 mL x 3). The combined organic extracts were dried over Mg_2SO_4 and then concentrated under reduced pressure. The resulting residue was purified by flash chromatography with ethyl acetate/hexanes (1:50) as eluent to afford the desired product as colorless oil (0.18 g, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.4 Hz, 1H), 7.33-7.28 (m, 2H), 7.22-7.18 (m, 1H), 7.03 (s, 1H), 3.76 (s, 3H).

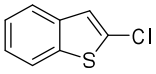
EI-MS: Calcd for C_9H_8ClN M^+: 165.0. Found: 165.0.



2-Chlorobenzofuran [63361-60-4]. The compound was prepared according to a reported procedure.[42] Under argon, to a solution of benzofuran (437 mg, 3.7 mmol) in dry THF (20 mL) in a -78 °C bath was added dropwise a 2.0 M solution of *n*-BuLi in hexanes (2.2 mL, 4.4 mmol). After stirring at -78 °C for 20 min, hexachloroethane (878 mg, 3.7 mmol) was added in 5 portions. The resulting mixture was warmed to 25 ^oC over 1 h and then quenched by slow addition of a saturated solution of NH_4Cl (20 mL). The crude product was extracted with EtOAc (20 mL x 3). The combined organic extracts were washed with water (10 mL), dried over Mg_2SO_4, and then concentrated under reduced pressure. The resulting residue was purified by flash chromatography (pentane) to afford the desired product as colorless oil (460 mg, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.47 (m, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.29-7.21 (m, 2H), 6.58 (s, 1H).

EI-MS: Calcd for C_8H_5ClO M^+: 152.0. Found: 152.2.

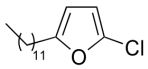


2-Chlorobenzothiophene [7342-85-0]. The compound was prepared according to a reported procedure.[42] Under argon, to a solution of benzothiophene (0.54 g, 4.0 mmol) in dry THF (16 mL) in a -78 °C bath was added dropwise a 2.0 M solution of

n-BuLi in hexanes (2.4 mL, 4.8 mmol). After stirring at -78 °C for 30 min, hexachloroethane (0.95 g, 4.0 mmol) was added in five portions. The resulting mixture was warmed up to 25 ^{o}C over 1 h and then quenched by slow addition of a saturated solution of NH_4Cl (20 mL). The crude product was extracted with ethyl acetate (20 mL x 3) and the combined organic extracts were washed with water, dried over Mg_2SO_4 and then concentrated under reduced pressure. The resulting residue was purified by flash chromatography (pentane) to afford the target product as white solid (0.55 g, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.63 (m, 2H), 7.35-7.28 (m, 2H), 7.15 (s, 1H).

EI-MS: Calcd for C_8H_5ClS M^+: 168.0. Found: 167.9.



2-Chloro-5-dodecylfuran. Under argon, to a solution of 5-dodecylfuran[43] (0.50 g, 2.1 mmol) in dry Et_2O (10 mL) at 0 °C was added dropwise a solution of SO_2Cl_2 (0.20 mL, 2.2 mmol) in dry Et_2O (5 mL). The mixture was allowed to warm up to 25 ^{o}C and then was stirred for 12 h. At the end of the reaction, the crude mixture was treated with dropwise addition of a saturated solution of $NaHCO_3$ until the pH reached 7 and then extracted with Et_2O (20 mL x 3). The combined organic extracts were washed with brine and then concentrated under reduced pressure. The resulting residue was purified by flash chromatography with pentane as eluent to afford the target product as colorless oil (0.35 g, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.01 (d, J = 3.2 Hz, 1H), 5.96-5.95 (doublet of triplet, J = 3.2, 0.8 Hz, 1H), 2.55 (t, J = 7.4 Hz, 2H), 1.61 (pseudoquintet, J = 7.4 Hz, 2H), 1.30-1.26 (m, 18H), 0.88 (t, J = 6.9 Hz, 3H).

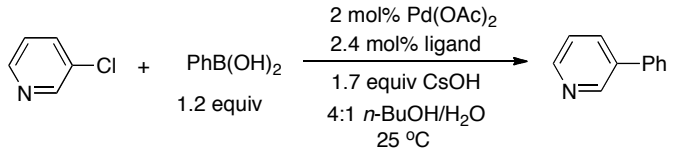
^{13}C NMR (100 MHz, $CDCl_3$): 156.4, 133.8, 107.0, 106.5, 32.0, 29.76, 29.74, 29.72, 29.6, 29.5, 29.4, 29.2, 28.2, 27.9, 22.8, 14.2.

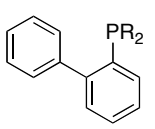
ESI-MS: Calcd for $C_{16}H_{27}ClO$ $(M+H)^+$: 270.99. Found: 270.84

II. Condition Optimization

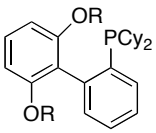
Typical Procedure: In an argon-filled glove box, to a 4 mL vial was charged sequentially $Pd(OAc)_2$ (0.6 mg, 0.0025 mmol), XPhos (1.4 mg, 0.003 mmol), 3-chloropyridine (14.1 mg, 0.125 mmol), and phenyl boronic acid (18.3 mg, 0.15 mmol), followed by 10 μl of *n*-dodecane (GC internal standard). Then 0.7 mL of *n*-butanol was added and the mixture was pre-stirred at 25 ^oC for 15 min. At last, a solution of $CsOH·H_2O$ (37 mg, 0.21 mmol) in 0.17 mL of degassed H_2O was added to initiate the Suzuki reaction. The vial was capped tightly and the reaction mixture was stirred vigorously with a magnetic stir bar at 25 ^oC until all the aryl chloride was consumed. At internals, an aliquot of the reaction mixture was taken and passed through a short plug of silica gel with Et_2O washings. GC analysis of the samples allows determination of conversion of the organic chloride and yields of the product, which are summarized in Tables below. The 15 min prestirring helped to improve reproducibility of the reaction kinetics by allowing $Pd(OAc)_2$ and XPhos to have time to ligate and allow some organiboronic acid to dissolve in the solvent. Without the prestirring, the coupling was still very fast, but data were less reproducible between runs. Other mixing and prestirring were also tried, but they gave worse results.

Table S1. Effect of Ligands and Catalysts

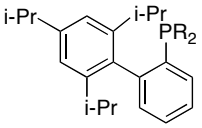




R= Cy **L1**
R= *t*-Bu **L2**



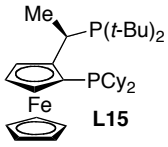
R= *i*-Pr **L3**
R= Me **L4**



R= Cy **L5**
R= *t*-Bu **L6**

P(t-Bu)$_3$ **L7**
PCy$_3$ **L8**
P(1-Ad)$_2$(*n*-Bu) **L9**
IPr **L10**
IMes **L11**

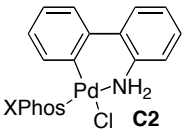
dppf **L12**
(*R*)-BINAP **L13**
Xantphos **L14**



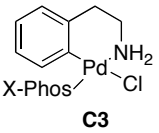
L15

(π-cinnamyl)Pd(IPr) **C1**

(π-cinnamyl)Pd(IMes) **C4**



C2



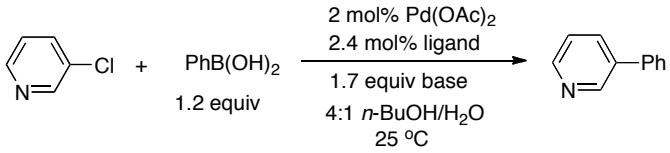
C3

Entry	Ligand	5 min		15 min		1 h	
		Conv. (%)	Yield (%)	Conv. (%)	Yield (%)	Conv. (%)	Yield (%)
1	**L1**	28	28	44	43	56	54
2	**L2**	54	49	83	83	100	100
3	**L3**	92	92	100	100	100	100
4	**L4**	92	92	99	99	100	100
5	**L5**	100	98	100	98	100	98
6	**L6**	27	26	48	48	67	67
7	**L7**	40	39	43	41	45	42
8	**L8**	57	57	82	82	89	89
9	**L9**	79	79	86	86	87	87
10	**L10**	0	0	0	0	0	0
11	**L11**	2	2	9	6	13	10
12	**L12**	0	0	0	0	0	0
13	**L13**	0	0	0	0	0	0
14	**L14**	0	0	0	0	0	0
15	**L15**	9	3	15	4	18	6
16	**C1**[a]	2	0	2	0	4	4
17	**C2**[a]	71	70	100	97	100	97
18	**C3**[a]	3	0	5	2	22	21

19	**C4**[a]	0	0	0	0	0	0

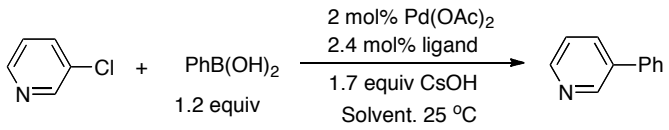
[a] No $Pd(OAc)_2$ was added.

Table S2. Effect of Bases



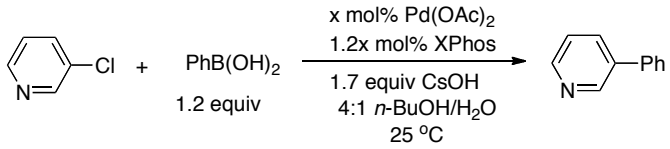
Entry	Base	5 min		15 min		1 h	
		Conv. (%)	Yield (%)	Conv. (%)	Yield (%)	Conv. (%)	Yield (%)
1	LiOH	75	75	90	90	100	100
2	NaOH	78	78	96	96	100	100
3	KOH	76	76	89	88	100	100
4	CsOH	100	98	100	98	100	98
5	Na_2CO_3	20	20	43	43	74	74
6	K_2CO_3	28	28	52	52	83	83
7	Cs_2CO_3	21	21	53	52	91	87
8	K_3PO_4	51	51	81	81	100	100

Table S3. Effect of Solvents



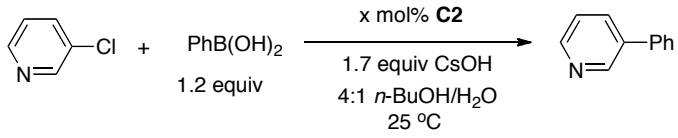
Entry	Solvent	5 min		15 min		1 h	
		Conv. (%)	Yield (%)	Conv. (%)	Yield (%)	Conv. (%)	Yield (%)
1	4:1 *n*-BuOH/ H_2O	100	98	100	98	100	98
2	dry *n*-BuOH	95	93	100	98	100	98
3	4:1 EtOH/ H_2O	60	51	95	85	100	94
4	dry EtOH	92	92	100	97	100	97
5	4:1 dioxane/ H_2O	16	14	45	42	70	70
6	dry dioxane	0	0	0	0	0	0
7	4:1 THF/ H_2O	26	22	63	60	93	93
8	dry THF	0	0	0	0	8	8
9	4:1 toluene/ H_2O	0	0	0	0	0	0
10	dry toluene	0	0	0	0	0	0
11	H_2O	0	0	0	0	0	0

Table S4. Suzuki coupling using low loading of $Pd(OAc)_2$ and XPhos



Entry	Catalyst Loading	5 min		15 min		1 h	
		Conv. (%)	Yield (%)	Conv. (%)	Yield (%)	Conv. (%)	Yield (%)
1	2%	100	98	100	98	100	98
2	1%	97	97	100	98	100	98
3	0.5%	73	73	96	96	100	99
4	0.2%	65	61	70	69	100	98
5	0.1%	70	63	73	70	87	87

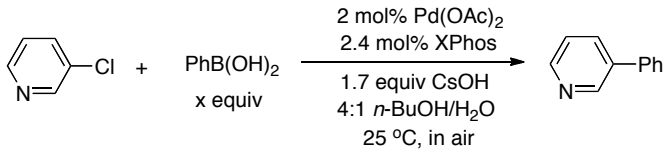
Table S5. Suzuki coupling using low loading of precatalyst **C2**



Entry	Catalyst Loading	5 min		15 min		1 h	
		Conv. (%)	Yield (%)	Conv. (%)	Yield (%)	Conv. (%)	Yield (%)
1	2%	77	76	100	98	100	98
2	1%	75	74	100	98	100	98
3	0.5%	35	35	73	73	100	99

Procedure for bench-top Suzuki coupling in air: In air, to a 4-ml vial containing a magnetic stir bar was charged sequentially $Pd(OAc)_2$ (2.4 mg, 0.010 mmol), XPhos (5.7 mg, 0.012 mmol), 3-chloropyridine (56 mg, 0.50 mmol), phenyl boronic acid (0.60 or 0.75 mmol), *n*-dodecane (40 μL as GC internal standard), and 2.80 mL of non-degassed *n*-butanol. The vial was capped and the mixture was stirred at 25 °C for 15 min. A solution of $CsOH \cdot H_2O$ (148 mg, 0.85 mmol) in 0.68 mL of non-degassed H_2O was added to initiate the Suzuki reaction. The vial was capped and the reaction mixture was stirred vigorously at 25 °C. At internals, the cap was removed and an aliquot of the reaction mixture was taken in air and passed through a short plug of silica gel with Et_2O washings. GC analysis of the samples allows determination of conversion of the 3-chloropyridine and yield of the product.

Table S6. Bench-top Suzuki coupling



Entry	Amount of $PhB(OH)_2$	5 min		15 min		1 h	
		Conv. (%)	Yield (%)	Conv. (%)	Yield (%)	Conv. (%)	Yield (%)
1	1.2 equiv	5	0	83	76	94	90
2	1.5 equiv	88	87	100	99	100	98

Condition A: A screw-cap test tube containing a magnetic stir bar was charged with $Pd(OAc)_2$ (1.1 mg, 1.0 mol%), SPhos (4.1 mg, 2 mol%), the phenylboronic acid (0.75 mmol, 1.5 equiv.) and K_3PO_4 (212 mg, 1.0 mmol, 2.0 equiv.). The tube was sealed with a teflon-coated screw cap and then evacuated and backfilled with argon through

an 18 gauge needle (this sequence was repeated three times). The 3- chloropyridine (0.5 mmol, 1.0 equiv.) and dry THF (1.0 mL) were added sequentially via syringe through the septum. The screwcap was quickly replaced with a non-punctured teflon-coated screwcap. The reaction mixture was stirred vigorous. After 1h, the yield of the product was judged by GC analysis.

Condition B:

An-oven dried Schlenk tube was charged with $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol), XPhos (0.02 mmol), phenyl boronic acid (0.75 mmol, 1.5 equiv) and powdered, anhydrous K_3PO_4 (212 mg, 1.00 mmol). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out two times). *n*-Butanol (1.0 mL) was added via syringe, through the septum, followed by the addition of 3- chloropyridine (0.5 mmol). The septum was then replaced with a Teflon screwcap and the Schlenk tube was sealed. The reaction mixture was stirred vigorous. After 1h, the yield of the product was judged by GC analysis.

Condition C:

In the air, an-oven dried Schlenk tube was charged with $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol), PCy_3 (3.3 mg, 0.012 mmol) and phenyl boronic acid (0.55 mmol, 1.1 equiv). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out five times). Dioxane (1.33 mL), 3-chloropyridine (0.5 mmol) and aqueous K_3PO_4 (1.27 M, 0.67 mL, 0.85 mmol) were added via syringe. The Schlenk tube was sealed. The reaction mixture was stirred vigorous. After 1h, the yield of the product was judged by GC analysis.

Condition D:

In the golvebox, an-oven dried Schlenk tube was charged with $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol), P(*t*-Bu)$_3$ (1.0 mg, 0.005 mmol), phenyl boronic acid (0.55 mmol, 1.1

equiv), KF (96 mg, 3.3 equiv), 3-chloropyridine (0.5 mmol) and THF (1.0 mL). The reaction mixture was stirred vigorous. After 1h, the yield of the product was judged by GC analysis.

Condition E:

Preparation of the catalyst solutions: In a glove-box, 6.5 mg (0.01 mmol) of **C1** was added to a vial equipped with a magnetic bar, and closed with a screw cup with a septum. Outside the glove-box, technical grade isopropanol (1.0 mL) was injected into the vial and the mixture stirred on a stirring plate at room temperature for 15 min prior to the injection of the required amount in the reaction vials.

General Procedure of Condition E: In a glove-box, potassium *tert*- butoxide (0.55 mmol, 62 mg) and boronic acid (0.525 mmol) were added in turn to a vial equipped with a magnetic bar, and closed with a screw cup with a septum. Outside the glove-box, the required amount of catalyst **C1** solution (catalyst loading 0.05 mol%, 100 μL) was injected through the septum, followed by technical grade isopropanol to a final volume of 0.5 mL. The mixture was stirred on a stirring plate at room temperature for 15 min. 3-Chloropyridine (0.5 mmol) was then injected. The reaction mixture was stirred vigorous. After 1h, the yield of the product was judged by GC analysis.

Condition F:

A vial was equipped with a magnetic stir bar and charged with precatalyst **C2** (2 mol%) and the boronic acid (0.75 mmol). The vessel was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of 3 times). Then, 3-chloropyridine (0.5 mmol) and degassed THF (1 mL) were added via syringe. Then, degassed 0.5 M aqueous K_3PO_4 solution (2 mL) was added

via syringe. The reaction mixture was stirred vigorous. After 1h, the yield of the product was judged by GC analysis.

III. Mechanistic Study

Reduction of $Pd(OAc)_2$ via double transmetalation: In an argon-filled glove box, a 20-mL vial was sequentially charged with $Pd(OAc)_2$ (4.5 mg, 0.020 mmol), XPhos (11.4 mg, 0.024 mmol), 3-chloropyridine (113 mg, 1.0 mmol), and phenyl boronic acid (146 mg, 1.2 mmol), followed by 20 μl of *n*-dodecane (GC internal standard). 5.6 mL of *n*-butanol was added and the mixture was pre-stirred at 25 ^{o}C for 15 min. Then, a solution of $CsOH{\cdot}H_2O$ (284 mg, 1.7 mmol) in 1.4 mL of degassed H_2O was added to initiate the Suzuki reaction. The vial was capped tightly and the reaction mixture was stirred vigorously with a magnetic stir bar at 25 ^{o}C. At internals, an aliquot of the reaction mixture was taken and quickly passed through a plug of silica gel with Et_2O washings. GC analysis of the filtrates allowed determination of yield of biphenyl: 0 min (right before addition of base): 7%; 0.5 min: 84%; 1 min: 96%.

^{31}P NMR analysis of the model Suzuki reaction: 8 mol% $Pd(OAc)_2$ and 9.6 mol% XPhos were used for better signal-to-noise ratio on ^{31}P NMR spectra. In an argon-filled glove box, a 4-mL vial was sequentially charged with $Pd(OAc)_2$ (8.9 mg, 0.040 mmol, 8 mol%), XPhos (22.8 mg, 0.048 mmol, 9.6 mol%), 3-chloropyridine (57 mg, 0.5 mmol), and phenyl boronic acid (73 mg, 0.6 mmol). 1.4 mL of *n*-butanol was added and the mixture was pre-stirred at 25 ^{o}C for 15 min. Then, a solution of $CsOH{\cdot}H_2O$ (142 mg, 0.85 mmol) in 0.35 mL of degassed H_2O was added to initiate the Suzuki reaction. The vial was capped tightly and the reaction mixture was stirred vigorously with a magnetic stir bar at 25 ^{o}C. After stirring for 5 min and 1 h, 0.5 mL

of the reaction mixture was transferred to an NMR tube and directly analyzed by ^{31}P NMR spectroscopy. In both cases, the NMR spectra were complex containing the signal of XPhos (-11.9 ppm), but no XPhos oxide was detected at 48.2 ppm.

Synthesis of XPhos oxide: Under argon, a 25-ml flask was charged with Xphos (100 mg, 0.21 mmol) and 5 ml of dichloromethane. The stirred solution was chilled to 0 ^{o}C and then treated with 0.5 ml of 30% aqueous H_2O_2. After stirring at 0 ^{o}C for 1 hour, 10 ml of H_2O was added to stop the reaction and the mixture was extracted with dichloromethane (10 ml x 2). The organic extracts were dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure to give viscous yellow oil. After crystallization from 5 ml of boiling hexane, pure XPhos oxide (92%, 95 mg) was collected as white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.68 (m, 1H), 7.46-7.38 (m, 2H), 7.18-7.16 (m, 1H), 6.98 (s, 2H), 2.93-2.86 (m, 1H), 2.43-2.37 (m, 2H), 1.91-1.63 (m, 10H), 1.44-1.35 (m, 4H), 1.29-1.24 (m, 12H), 1.18-1.10 (m, 6H), 0.94 (d, J = 6.7 Hz, 6H)

^{31}P NMR (121 MHz, $CDCl_3$): 44.1.

^{31}P NMR (121 MHz, 4:1 *n*-butanol/H_2O): 48.2.

^{13}C NMR (100 MHz, $CDCl_3$): 147.7, 145.7, 145.1 (d, J_{cp} = 6.3 Hz), 136.0 (d, J_{cp} = 2.1 Hz), 133.5 (d, J_{cp} = 9.8 Hz), 132.0, 131.6 (d, J_{cp} = 90.3 Hz), 129.8 (d, J_{cp} = 2.5 Hz), 126.0 (d, J_{cp} = 10.7 Hz), 120.2, 37.6 (d, J_{cp} = 65.0 Hz), 34.1, 30.8, 26.8 (d, J_{cp} = 3.3 Hz), 26.7 (d, J_{cp} = 4.0 Hz), 26.2 (d, J_{cp} = 3.4 Hz), 26.04 (d, J_{cp} = 2.4 Hz), 26.00, 25.9, 24.1, 22.8.

ESI-MS: Calcd for $C_{11}H_9N$ $(M+H)^+$: 493.72. Found: 493.63.

Formation of arytrihydroxyborate:

(a) Under argon, to a 4-ml vial was charged with phenylboronic acid (61 mg, 0.5 mmol), *n*-BuOH (0.5 mL) and H_2O (50 μL). After stirring for 10 min, the solution was subjected to ^{11}BNMR. A singlet of $PhB(OH)_2$ was detected at δ = 28.5.

(b) Under argon, to a 4-ml vial was charged with phenylboronic acid (61 mg, 0.5 mmol), CsOH (108 mg, 0.65mmol), *n*-BuOH (0.5 mL) and H_2O (50 μL). After stirring for 10 min, the solution was subjected to ^{11}BNMR. A singlet of $PhB(OH)_3^-$ was detected at δ = 3.4. The singlet of $PhB(OH)_2$ at δ = 28.5 disappeared.

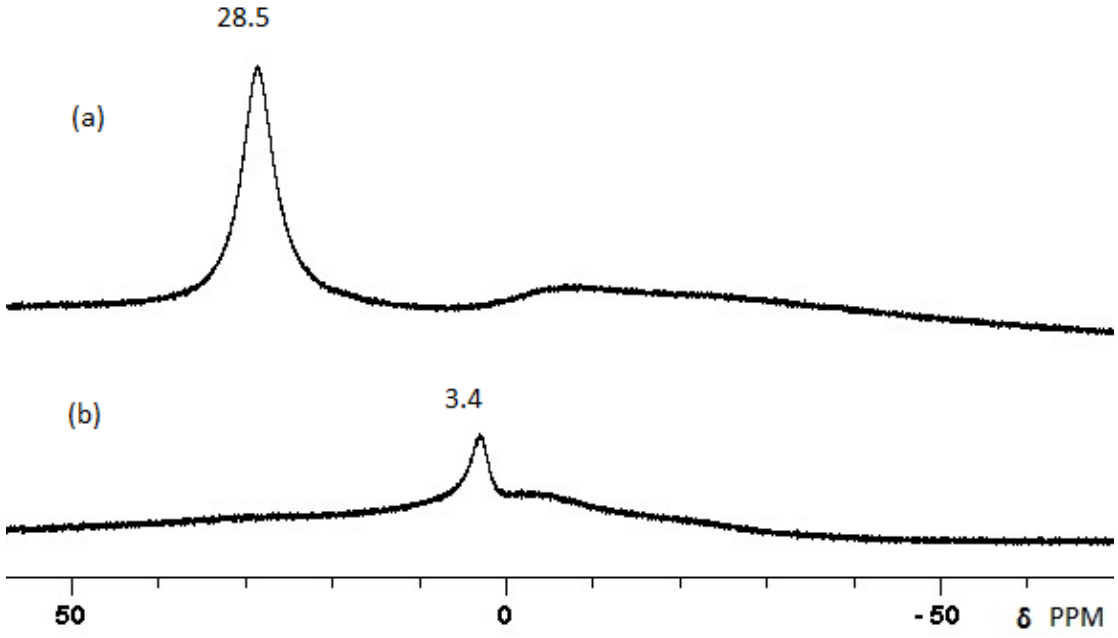
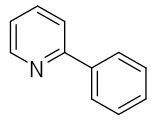


Figure S1. Formation of Arytrihydroxyborate

IV. Scope of Heteroaryl Chlorides

General procedure for product isolation. In an argon-filled glove box, to a 25 mL Schlenk tube was charged sequentially $Pd(OAc)_2$ (2.4 mg, 0.010 mmol), XPhos (5.7 mg, 0.012 mmol), heteroaryl chloride (0.50 mmol), organoboronic acid (0.60 mmol), *n*-dodecane (40 μL as GC internal standard), and 2.80 mL of *n*-butanol. The mixture was stirred at 25 ^{o}C for 15 min, and then a solution of $CsOH·H_2O$ (148 mg, 0.85 mmol) in 0.68 mL of degassed H_2O was added to initiate the Suzuki reaction.

The Schlenk tube was capped tightly and the reaction mixture was stirred vigorously at 25 ^{o}C until all the heteroaryl chloride was consumed (monitored by GC). At the end of the reaction, the organic phase was separated and the aqueous phase was further extracted with ethyl acetate (3 mL x 3). The organic extracts were combined and concentrated on a rotary evaporator. The resulting residue was purified by silica gel flash chromatography to provide the desired coupling product. All the Suzuki reactions were conducted according to the general procedure, unless specified otherwise. The 15 min prestirring helped to improve reproducibility of the reaction kinetics. Without the prestirring, the coupling was still very fast.

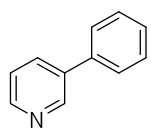


2-Phenylpyridine [1008-89-5]. Phenyl boronic acid (73 mg, 0.60 mmol) and 2-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 1 h until the reaction reached completion. Conversion of the heteroaryl chloride was monitored by GC: 5 min, 20%; 15 min, 74%; 1 h, 100%.

After flash chromatography with ethyl acetate/hexane (1:12) as eluent, the title compound was isolated as colorless oil (74 mg, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 4.8 Hz, 1H), 8.00-7.98 (m, 2H), 7.75-7.73 (m, 2H), 7.48-7.41 (m, 3H), 7.25-7.21 (m, 1H).

ESI-MS: Calcd for $C_{11}H_9N$ $(M+H)^+$: 156.1. Found: 156.3.



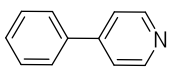
3-Phenylpyridine [1008-88-4]. Phenyl boronic acid (73 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 10 min until the reaction reached completion. Conversion of the heteroaryl chloride was monitored by GC: 5 min, 91%, 7 min, 98%, 10 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:8) as eluent, the title compound was isolated as colorless oil (76 mg, 98% yield).

Procedure using a Schlenk manifold: a 25 ml Schlenck tube containing a magnetic stir bar was charged with $Pd(OAc)_2$ (2.4 mg, 0.010 mmol), XPhos (5.7 mg, 0.012 mmol) and phenyl boronic acid (73 mg, 0.60 mmol). The reaction vessel was evacuated and then refilled with argon three times. Then, 3-chloropyridine (57 mg, 0.50 mmol), *n*-dodecane (40 μL; GC internal standard) and 2.80 mL of degassed *n*-butanol were added via syringe. After the mixture was vigorously stirred at 25 ^{o}C for 15 min, a solution of $CsOH{\cdot}H_2O$ (148 mg, 0.85 mmol) in 0.68 mL of degassed H_2O was added to initiate the coupling reaction. Conversion of the heteroaryl chloride was monitored by GC: 5 min, 83%; 10 min, 100%. Isolation yield: 91%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (d, J = 2.0 Hz, 1H), 8.60 (dd, J = 4.8, 2.0 Hz, 1H), 7.88 (doublet of pseudotriplet, J = 8.0, 2.0 Hz, 1H), 7.60-7.51 (m, 2H), 7.49-7.47 (m, 2H), 7.43-7.37 (m, 2H).

EI-MS: Calcd for $C_{11}H_9N$ M^+: 155.1. Found: 155.0



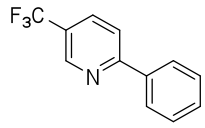
4-Phenylpyridine [939-23-1]. Phenyl boronic acid (73 mg, 0.60 mmol), 4-chloropyridine hydrochloride (75 mg, 0.50 mmol) and $CsOH{\cdot}H_2O$ (1.35 mmol, 227 mg) in 1.08 mL of degassed H_2O were used and the reaction was stirred at 25 ^{o}C for

15 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 88%; 15 min, 100%.

After flash chromatography with ethyl acetate/hexane (from 1:8 to 1:5) as eluent, the title compound was isolated as white solid (73 mg, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, J = 4.8 Hz, 2H), 7.66-7.62 (m, 2H), 7.52-7.49 (m, 5H).

ESI-MS: Calcd for $C_{11}H_9N$ $(M+H)^+$: 156.07. Found: 156.43.

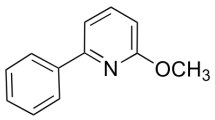


2-Phenyl-5-(trifluoromethyl)pyridine [188527-56-2]. Phenyl boronic acid (73 mg, 0.60 mmol) and 2-chloro-5-(trifluoromethyl)pyridine (91 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:50) as eluent, the title compound was isolated as white solid (106 mg, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (s, 1H), 8.05-8.03 (m, 2H), 7.99 (dd, J = 8.4, 2.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.54-7.48 (m, 3H).

ESI-MS: Calcd for $C_{12}H_9F_3N$ $(M+H)^+$: 224.1. Found: 224.4.



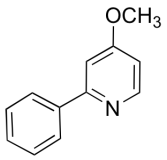
2-Methoxy-6-phenylpyridine [35070-08-7]. Phenyl boronic acid (73 mg, 0.60 mmol) and 2-chloro-6-methoxypyridine (72 mg, 0.50 mmol) were used and the

reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:8) as eluent, the title compound was isolated as colorless oil (89 mg, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06-8.03 (m, 2H), 7.62 (pseudotriplet, J = 8.0 Hz, 1H), 7.47-7.43 (m, 4H), 7.41-7.39 (m, 4H), 7.34 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 4.04 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{12}$ NO $(M+H)^{+}$: 186.1. Found: 186.3.

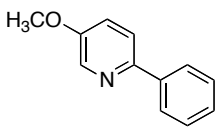


4-Methoxy-2-phenylpyridine [53698-56-9]. Phenyl boronic acid (73 mg, 0.60 mmol) and 2-chloro-4-methoxypyridine (72 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 66%; 1 h, 100%.

After flash chromatography with ethyl acetate/hexane (1:8) as eluent, the title compound was isolated as colorless oil (87 mg, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, J = 5.6 Hz, 1H), 7.97-7.94 (m, 2H), 7.48-7.40 (m, 3H), 7.22 (d, J = 2.4 Hz, 1H), 6.77 (dd, J = 5.6, 2.4 Hz, 1H), 3.89 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{12}NO$ $(M+H)^{+}$: 186.08. Found: 186.35.

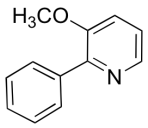


5-Methoxy-2-phenylpyridine [53698-54-7]. Phenyl boronic acid (73 mg, 0.60 mmol) and 2-chloro-5-methoxypyridine (72 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 1 h until the reaction reached completion.

After flash chromatography with ethyl acetate/hexane (1:5) as eluent, the title compound was isolated as white solid (81 mg, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, J = 2.8 Hz, 1H), 7.94-7.91 (m, 2H), 7.69 (d, J = 8.8 Hz, 1H), 7.47-7.43 (m, 2H), 7.38-7.34 (m, 1H), 7.27 (dd, J = 8.8, 2.8 Hz, 1H), 3.90 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{12}NO$ $(M+H)^{+}$: 186.08. Found: 186.35.

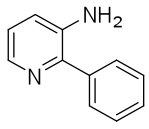


3-Methoxy-2-phenylpyridine [53698-56-9]. Phenyl boronic acid (73 mg, 0.60 mmol) and 2-chloro-3-methoxypyridine (72 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 15 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 15%; 15 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:8) as eluent, the title compound was isolated as colorless oil (87 mg, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (dd, J = 4.4, 1.2 Hz, 1H), 7.90-7.87 (m, 2H), 7.45-7.41 (m, 2H), 7.39-7.37 (m, 1H), 7.29-7.27 (dd, J = 8.4, 1.2 Hz, 1H), 7.23 (dd, J = 8.4, 4.4 Hz, 1H), 3.85 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{12}$ NO $(M+H)^{+}$: 186.08. Found: 186.23.

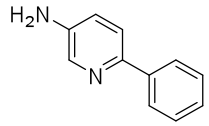


3-Amino-2-phenylpyridine [101601-80-3]. Phenyl boronic acid (92 mg, 0.75 mmol) and 3-amino-2-chloropyridine (64 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 64%; 1 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:5) as eluent, the title compound was isolated as yellow oil (82 mg, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (m, 1H), 7.67-7.65 (m, 2H), 7.49-7.45 (m, 2H), 7.45-7.39 (m, 1H), 7.08-7.02 (m, 2H), 3.85 (br s, 2H).

ESI-MS: Calcd for $C_{11}H_{11}N_2$ $(M+H)^+$: 171.08. Found: 171.41.

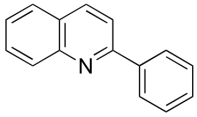


5-Amino-2-phenylpyridine [126370-67-0]. Phenyl boronic acid (92 mg, 0.75 mmol) and 5-amino-2-chloropyridine (64 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 30 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 76%; 15 min, 95%; 30 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:4) as eluent, the title compound was isolated as yellow solid (81 mg, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = 2.8 Hz, 1H), 7.91-7.88 (m, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.45-7.41 (m, 2H), 7.35-7.31 (m, 1H), 7.03(dd, J = 8.4, 2.8 Hz, 1H), 3.75 (br s, 2H).

ESI-MS: Calcd for $C_{11}H_{11}N_2$ $(M+H)^+$: 171.08. Found: 171.39.

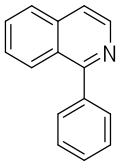


2-Phenylquinoline [612-96-4]. Phenyl boronic acid (73 mg, 0.60 mmol) and 2-chloroquinoline (82 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:15) as eluent, the title compound was isolated as white solid (101 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23-8.17 (m, 4H), 7.90-7.87 (d, J = 8.4 Hz, 1H), 7.83 (dd, J = 8.4, 1.2 Hz, 1H), 7.76-7.72 (m, 1H), 7.57-7.52 (m, 3H), 7.50-7.46 (m, 1H).

ESI-MS: Calcd for $C_{15}H_{12}$ N $(M+H)^{+}$: 206.09. Found: 206.39.

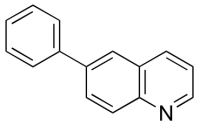


1-Phenylisoquinoline [3297-72-1]. Phenyl boronic acid (73 mg, 0.60 mmol) and 1-chloroisoquinoline (82 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 15 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 84%; 15 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:10) as eluent, the title compound was isolated as white solid (95 mg, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J = 7.0 Hz, 1H), 8.11 (dd, J = 8.4, 0.8 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.70-7.63 (m, 4H), 7.55-7.49 (m, 4H).

ESI-MS: Calcd for $C_{15}H_{12}$ N $(M+H)^{+}$: 206.09. Found: 206.39.

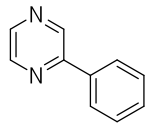


6-Phenylquinoline [612-95-3]. Phenyl boronic acid (73 mg, 0.60 mmol) and 6-chloroquinoline (82 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 53%; 1 h, 100%.

After flash chromatography with ethyl acetate/hexane (1:8) as eluent, the title compound was isolated as white solid (101 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (d, *J* = 3.2 Hz, 1H), 8.23-8.17 (m, 2H), 8.01-7.98 (m, 2H), 7.73 (d, *J* = 7.8 Hz, 2H), 7.50 (pseudotriplet, *J* = 7.5 Hz, 2H), 7.42-7.38 (m, 2H).

ESI-MS: Calcd for $C_{15}H_{12}N$ $(M+H)^{+}$: 206.09. Found: 206.52.

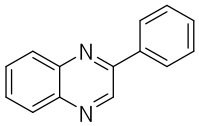


2-Phenylpyrazine [29460-97-7] Phenyl boronic acid (73 mg, 0.60 mmol) and 2-chloropyrazine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 15 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 84%; 15 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:10) as eluent, the title compound was isolated as white solid (72 mg, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (s, 1H), 8.65-8.64 (m, 1H), 8.52 (d, *J* = 2.0 Hz, 1H), 8.04-8.01 (m, 2H), 7.55-7.49 (m, 3H).

ESI-MS: Calcd for $C_{10}H_9N_2$ $(M+H)^{+}$: 157.07. Found: 157.36.

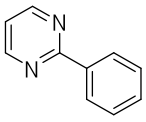


2-Phenylquinoxaline [5021-43-2]. Phenyl boronic acid (73 mg, 0.60 mmol) and 2-chloroquinoxaline (82 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:10) as eluent, the title compound was isolated as white solid (99 mg, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (s, 1H), 8.21-8.11 (m, 4H), 7.81-7.73 (m, 2H), 7.60-7.50 (m, 3H).

ESI-MS: Calcd for $C_{14}H_{11}N_2$ $(M+H)^+$: 207.08. Found: 207.36.

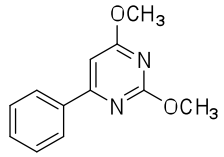


2-Phenylpyrimidine [7431-45-0]. Phenyl boronic acid (73 mg, 0.60 mmol) and 2-chloropyrimidine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 4 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 28%; 15 min, 49%; 1 h, 93%; 4 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:8) as eluent, the title compound was isolated as colorless oil (71 mg, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (d, J = 5.2 Hz, 2H), 8.47-8.42 (m, 2H), 7.51-7.48 (m, 3H), 7.18 (t, J = 5.2, 1H).

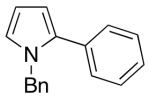
ESI-MS: Calcd for $C_{10}H_9N_2$ $(M+H)^+$: 157.07. Found: 157.36.



2,4-Dimethoxy-6-phenylpyrimidine [1137536-95-8]. Phenyl boronic acid (73 mg, 0.60 mmol) and 4-chloro-2,6-dimethoxypyrimidine (87 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:15) as eluent, the title compound was isolated as white solid (95 mg, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07-8.04 (m, 2H), 7.48-7.44 (m, 3H), 6.78 (s, 1H), 4.08 (s, 3H), 4.01 (s, 3H). ESI-MS: Calcd for $C_{12}H_{13}N_2O_2$ $(M+H)^+$: 217.09. Found: 217.22.

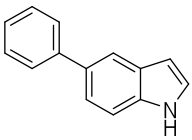


***N*-Benzyl-2-phenylpyrrole [78979-71-2].** Phenyl boronic acid (92 mg, 0.75 mmol) and *N*-benzyl-2-chloropyrrole (96 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 16 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 1 h, 33%; 4 h, 83%; 16 h, 100%.

After flash chromatography with hexane as eluent, the title compound was isolated as yellow solid (111 mg, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.25 (m, 8H), 7.01 (d, J = 7.0 Hz, 2H), 6.75 (pseudotriplet, J = 2.3 Hz, 1H), 6.28 (d, J = 2.3 Hz, 2H), 5.16 (s, 2H).

ESI-MS: Calcd for $C_{11}H_{12}$ N $(M+H)^+$: 234.12. Found: 234.17.

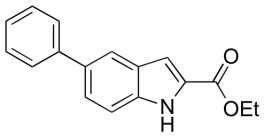


5-Phenylindole [66616-72-6]. Phenyl boronic acid (92 mg, 0.75 mmol) and 5-chloroindole (76 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 16 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 1 h, 14%; 4 h, 64%; 16 h, 100%.

After flash chromatography with ethyl acetate/hexane (1:10) as eluent, the title compound was isolated as green solid (91 mg, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (br s, 1H), 7.86 (s, 1H), 7.67-7.64 (m, 2H), 7.45-7.41 (m, 4H), 7.32-7.29 (m, 1H), 7.24-7.23 (m, 1H), 6.60 (pseudotriplet, J = 2.7 Hz, 1H).

EI-MS: Calcd for $C_{14}H_{12}N$ M^{+}: 193.1. Found: 193.2.

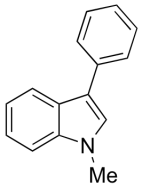


2-Ethoxycarbonyl-5-phenylindole [66616-69-1]. Phenyl boronic acid (92 mg, 0.75 mmol) and 5-chloro-2-ethoxycarbonylindole (76 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 16 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 4 h, 37%; 16 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:5) as eluent, the title compound was isolated as white solid (123 mg, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (br s, 1H), 7.89 (s, 1H), 7.65-7.63 (m, 2H), 7.59 (dd, J = 8.6, 1.6 Hz, 1H), 7.50-7.43 (m, 3H), 7.35-7.26 (m, 2H), 7.27 (d, J = 1.6 Hz, 1H), 4.43 (q, J = 8.0 Hz, 2H), 1.43 (t, J = 8.0 Hz, 3H).

ESI-MS: Calcd for $C_{17}H_{16}NO_2$ $(M+H)^{+}$: 266.11. Found: 266.08.

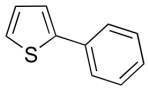


***N*-Methyl-3-phenylindole [30020-98-5].** Phenyl boronic acid (92 mg, 0.75 mmol) and *N*-methyl-3-chloroindole (83 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 16 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 22%; 1 h, 54%; 4 h, 87%; 16 h, 100%.

After flash chromatography with hexane as eluent, the title compound was isolated as yellow oil (100 mg, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.45-7.41 (m, 2H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.30-7.26 (m, 2H), 7.23 (s, 1H), 7.20-7.17 (m, 1H), 3.84 (s, 3H).

ESI-MS: Calcd for $C_{15}H_{14}N$ $(M+H)^{+}$: 208.10. Found: 208.27.

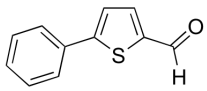


2-Phenylthiophene [825-55-8]. Phenyl boronic acid (73 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 38%; 1 h, 100%.

After flash chromatography with ethyl acetate/hexane (1:200) as eluent, the title compound was isolate as white solid (77 mg, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.62 (m, 2H), 7.40-7.37 (m, 2H), 7.33-7.26 (m, 3H), 7.10-7.08 (m, 1H).

EI-MS: Calcd for $C_{10}H_8S$ M^+: 160.03. Found: 159.8.

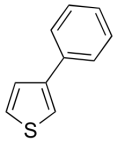


2-Formyl-5-phenylthiophene [19163-21-4]. Phenyl boronic acid (73 mg, 0.60 mmol) and 2-chloro-5-formylthiophene (83 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^oC for 15 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 71%; 15 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:15) as eluent, the title compound was isolate as white solid (87 mg, 93% yield).

^1H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 7.74 (d, J = 4.0 Hz, 1H), 7.68-7.66 (m, 2H), 7.46-7.39 (m, 4H).

ESI-MS: Calcd for $C_{10}H_9OS$ $(M+H)^+$: 189.03. Found: 189.16.

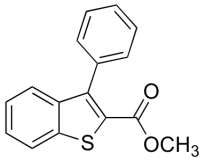


3-Phenylthiophene [2404-87-7]. Phenyl boronic acid (73 mg, 0.60 mmol) and 3-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^oC for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 23%; 1 h, 100%.

After flash chromatography with ethyl acetate/hexane (1:200) as eluent, the title compound was isolate as white solid (61 mg, 96% yield).

^1H NMR (400 MHz, $CDCl_3$): δ 7.61-7.58 (m, 2H), 7.45-7.44 (m, 1H), 7.41-7.37 (m, 4H), 7.31-7.24 (m, 1H).

EI-MS: Calcd for $C_{10}H_8S$ M^+: 160.0. Found: 159.8.

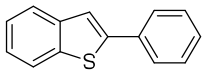


2-Methoxycarbonyl-3-phenylbenzothiophene [445476-88-0]. Phenyl boronic acid (73 mg, 0.60 mmol) and 2-methoxycarbonyl-3-chlorobenzothiophene (113 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After flash chromatography with hexane as eluent, the title compound was isolate as white solid (123 mg, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.52-7.46 (m, 4H), 7.42-7.40 (m, 2H), 7.40-7.35 (m, 1H), 3.79 (s, 3H).

ESI-MS: Calcd for $C_{16}H_{13}O_2S$ $(M+H)^+$: 269.06. Found: 268.94.

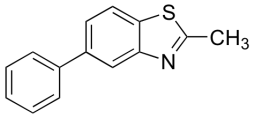


2-Phenylbenzothiophene [1207-95-0]. Phenyl boronic acid (73 mg, 0.60 mmol) and 2-chlorobenzothiophene (83 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 15 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 22%; 15 min, 100%.

After purification by flash chromatography using hexane as eluent, the title compound was isolated as white solid (101 mg, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.55 (s, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.36-7.31 (m, 3H).

EI-MS: Calcd for $C_{14}H_{11}S$ M^+: 210.0. Found: 209.9.

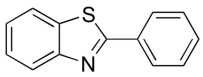


2-Methyl-5-phenylbenzothiazole [71215-89-9]. Phenyl boronic acid (73 mg, 0.60 mmol) and 5-chloro-2-methylbenzothiazole (92 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^oC for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 39%; 15 min, 86%; 1 h, 100%.

After flash chromatography with ethyl acetate/hexane (1:10) as eluent, the title compound was isolated as white solid (106 mg, 94% yield).

^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 1.7 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.67-7.64 (m, 2H), 7.59 (dd, J = 8.2, 1.6 Hz, 1H), 7.48-7.45 (m, 2H), 7.39-7.35 (m, 1H), 2.85 (s, 3H).

ESI-MS: Calcd for $C_{14}H_{12}$ NS $(M+H)^+$: 226.06. Found: 226.34.



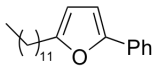
2-phenylbenzothiazole [213329-51-2]. Phenyl boronic acid (110 mg, 0.90 mmol) and 5-chloro-2-methylbenzothiazole (92 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^oC for 7 d until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 40 h, 78%; 3 d, 85%; 5 d, 93%, 7 d, 100%.

After flash chromatography with hexane as eluent, the title compound was isolated as white solid (95 mg, 90% yield).

When the reaction was conducted in *n*-butanol at 80 ^{o}C with 1.2 equiv of (*E*)-styryl boronic acid, it reached completion in 15 min. After flash chromatography, the title compound was isolated as white solid (98 mg, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11-8.07 (m, 3H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.52-7.48 (m, 4H), 7.39 (pseudotriplet, *J* = 7.6 Hz, 1H).

ESI-MS: Calcd for $C_{13}H_9NS$ $(M+H)^+$: 212.05. Found: 212.35.



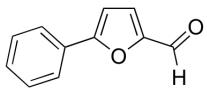
2-Dodecyl-5-phenylfuran. Phenyl boronic acid (110 mg, 0.90 mmol) and 2-chloro-5-dodecylfuran (92 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 64%; 15 min, 94%; 1 h, 100%.

After flash chromatography with hexane as eluent, the title compound was isolated as colorless liquid (154 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.65 (m, 2H), 7.38-7.34 (m, 2H), 7.26-7.22 (m, 1H), 6.55 (d, *J* = 3.2 Hz, 1H), 6.06 (d, *J* = 3.2 Hz, 1H), 2.69 (t, *J* = 7.6 Hz, 2H), 1.70 (pseudoquintet, *J* = 7.5 Hz, 2H), 1.39-1.28 (m, 18H), 0.90 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 152.2, 131.4, 128.7, 126.8, 123.4, 106.9, 105.7, 32.0, 29.78, 29.76 (two overlapping peaks), 29.67, 29.49, 29.46, 29.3, 28.3, 28.2, 22.8, 14.2.

EI-MS: Calcd for $C_{22}H_{32}O$ M^+: 312.2. Found: 312.2

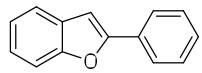


2-Formyl-5-phenylfuran [13803-39-9]. Phenyl boronic acid (73 mg, 0.60 mmol) and 2-chloro-5-formylfuran (66 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 97%.

After flash chromatography with ethyl acetate/hexane (1:15) as eluent, the title compound was isolate as colorless oil (80 mg, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (s, 1H), 7.84-7.81 (m, 2H), 7.47-7.37 (m, 3H), 7.32 (d, J = 3.7 Hz, 1H), 6.85 (d, J = 3.7 Hz, 1H).

ESI-MS: Calcd for $C_{11}H_9O_2$ $(M+H)^+$: 173.05. Found: 173.25.



2-Phenylbenzofuran [1839-72-1]. Phenyl boronic acid (73 mg, 0.60 mmol) and 2-chlorobenzofuran (76 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After flash chromatography with hexane as eluent, the title compound was isolate as white solid (88 mg, 91% yield).

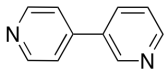
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 7.3 Hz, 2H), 7.58 (d, J = 7.3 Hz, 1H), 7.53-7.51 (d, J = 8.0 Hz, 1H), 7.46-7.42 (m, 2H), 7.36-7.33 (m, 1H), 7.30-7.20 (m, 2H), 7.02 (s, 1H).

EI-MS: Calcd for $C_{14}H_{10}O$ M^+: 194.1. Found: 193.9.

VI. Scope of Heteroaryl Boronic Acids

The procedure for product isolation was the same as in part IV.

(a) Couplings of 3-chloropyridine

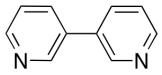


3, 4'-Bipyridine [4394-11-0]. 4-Pyridinyl boronic acid (74 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 80 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 58%; 1 h, 100%. When the reaction was conducted at 25 ^{o}C, no conversion of 3-chloropyridine was observed after 16 h.

After flash chromatography with MeOH/DCM (1:20) as eluent, the title compound was isolated as yellow solid (70 mg, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (d, *J* = 2.0 Hz, 1H), 8.72 (d, *J* = 2.0 Hz, 2H), 8.69 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.92 (doublet of pseudotriplet, *J* = 8.0, 1.6 Hz, 1H), 7.54-7.50 (m, 2H), 7.43 (dd, *J* = 8.0, 4.8 Hz, 1H).

ESI-MS: Calcd for $C_{10}H_8N_2$ $(M+H)^+$: 157.07. Found: 157.33.

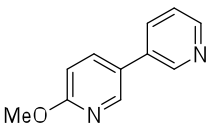


3, 3'-Bipyridine [581-46-4]. 3-Pyridinyl boronic acid (74 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 80 ^{o}C for 15 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 100%. When the reaction was conducted at 25 ^{o}C, no conversion of 3-chloropyridine was observed after 16 h.

After flash chromatography with MeOH/DCM (1:20) as eluent, the title compound was isolated as yellow solid (69 mg, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (d, *J* = 1.6 Hz, 2H), 8.66 (dd, *J* = 4.8, 1.6 Hz, 2H), 7.88 (doublet of pseudotriplet, *J* = 7.6, 1.6 Hz, 2H), 7.41 (dd, *J* = 7.6, 4.8 Hz, 2H).

ESI-MS: Calcd for $C_{10}H_8N_2$ $(M+H)^+$: 157.07. Found: 157.27.

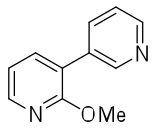


6-Methoxy-3,3'-bipyridine [475275-77-5]. 6-Methoxy-3-pyridyl boronic acid (92 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^oC for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 2%; 15 min, 19%; 1 h, 100%.

After flash chromatography with ethyl acetate/hexane (1:1) as eluent, the title compound was isolated as white solid (88 mg, 95% yield).

^1H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, J = 1.6 Hz, 1H), 8.60 (dd, J = 4.8, 1.6 Hz, 1H), 8.40 (d, J = 1.6 Hz, 1H), 7.84-7.78 (m, 2H), 7.38 (dd, J = 8.0, 4.8 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 3.99 (s, 3H).

ESI-MS: Calcd for $C_{11}H_{11}N_2O$ $(M+H)^+$: 187.08. Found: 187.32.

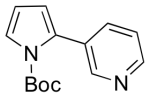


2-Methoxy-3,3'-bipyridine [929284-27-5]. 2-Methoxy-3-pyridyl boronic acid (92 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^oC for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:1) as eluent, the title compound was isolated as colorless oil (89 mg, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, *J* = 1.6 Hz, 1H), 8.59 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.21 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.90 (7.2, 2.2 Hz, 1H), 7.63 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.35 (dd, *J* = 7.7, 5.0 Hz, 1H), 7.00 (dd, *J* = 7.5, 5.2 Hz, 1H), 3.98 (s, 3H).

ESI-MS: Calcd for $C_{11}H_{11}N_2O$ $(M+H)^+$: 187.08. Found: 187.31.

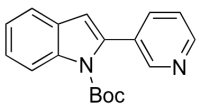


***N*-(*tert*-Butoxycarbonyl)-2-(3-pyridyl)pyrrole [215187-35-2].** *N*-(*tert*-Butoxycarbonyl)-2-pyrrolyl boronic acid (127 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 °C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After purification by flash chromatography using diethyl ether/pentane (1:1) as eluent, the title compound was isolated as yellow oil (117 mg, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 2.1 Hz, 1H), 8.53 (dd, *J* = 4.8, 1.0 Hz, 1H), 7.66 (doublet of pseudotriplet, *J* = 7.8, 1.7 Hz, 1H), 7.42-7.41 (m, 1H), 7.28 (dd, *J* = 7.8, 4.8), 6.27-6.24 (m, 2H), 1.38 (s, 9H).

ESI-MS: Calcd for $C_{14}H_{17}N_2O_2$ $(M+H)^+$: 245.21, Found: 244.95.



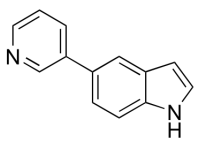
***N*-(*tert*-Butoxycarbonyl)-2-(3-pyridyl)indole [157427-58-2].** *N*-(*tert*-Butoxy-carbonyl)-2-indolyl boronic acid (157 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 °C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by

GC: 5 min, 100%. After purification by flash chromatography using ethyl acetate/hexane (1:50) as eluent, the title compound was isolate as white solid (141 mg, 96% yield).

Gram-scale procedure using Schlenk manifold: Under argon, a 100-mL Schlenk flask containing a magnetic stir bar was sequentially charged with $Pd(OAc)_2$ (17.8 mg, 0.080 mmol), XPhos (45.6 mg, 0.096 mmol), 3-chloropyridine (452 mg, 4.0 mmol), *N*-(*tert*-butoxy-carbonyl)-2-indolyl boronic acid (1.252 g, 4.8 mmol), *n*-dodecane (320 μL as GC internal standard), and 22.4 mL of degassed *n*-butanol. The mixture was prestirred at 25 ^{o}C for 15 min, and then a solution of $CsOH \cdot H_2O$ (1.135 g, 6.8 mmol) in 5.6 mL of degassed H_2O was added in one portion to initiate the Suzuki reaction. The Schlenk flask was capped tightly and the reaction mixture was stirred vigorously at 25 ^{o}C for 5 min until all the 3-chloropyridine was consumed (monitored by GC). After routine workup and purification by flash chromatography (1:50 ethyl acetate/hexane as eluent), the titled compound was obtained as white solid (1.140 g, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, J = 1.8 Hz, 1H), 8.60 (dd, J = 4.8, 1.6 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 7.73 (doublet of pseudotriplet, J = 7.8, 1.9 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.39-7.33 (m, 2H), 7.29 (d, J = 7.7 Hz, 1H), 6.62 (s, 1H), 1.35 (s, 9H).

ESI-MS: Calcd for $C_{18}H_{19}N_2O_2$ $(M+H)^+$: 295.14, Found: 294.98.



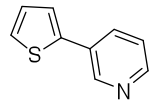
5-(3-Pyridinyl)indole [144104-49-4]. 5-Indolyl boronic acid (97 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was

stirred at 25 ^{o}C for 15 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 80%; 15 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:1) as eluent, the title compound was isolate as white solid (88 mg, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (d, *J* = 2.1 Hz, 1H), 8.57-8.55 (m, 2H), 7.95-7.92 (m, 1H), 7.87 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.42 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.36 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.30-7.28 (m, 1H), 6.64 (s, 1H).

ESI-MS: Calcd for $C_{13}H_{11}N_2$ $(M+H)^+$: 195.08, Found: 195.34.

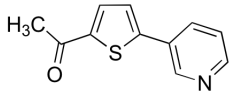


3-(2-Thienyl)pyridine [21298-53-3]. 2-Thienyl boronic acid (77 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:3) as eluent, the title compound was isolate as yellow oil (73 mg, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (d, *J* = 1.9 Hz, 1H), 7.51 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.86(doublet of pseudotriplet, *J* = 7.9, 1.7 Hz, 1H), 7.37-7.36 (m, 2H), 7.30 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.13 (dd, *J* = 4.8, 3.9 Hz, 1H).

ESI-MS: Calcd for C_9H_8NS $(M+H)^+$: 162.03. Found: 162.24.



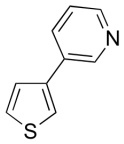
2-Acetyl-5-(3-pyridyl)thiophene [187540-78-9]. 5-Acetyl-2-thienyl boronic acid (102 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and

the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:4) as eluent, the title compound was isolate as yellow oil (96 mg, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (d, *J* = 2.0 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.91 (doublet of pseudotriplet, *J* = 8.0, 2.0 Hz, 1H), 7.69 (d, *J* = 4.0 Hz, 1H), 7.38-7.34 (m, 2H), 2.59 (s, 3H).

ESI-MS: Calcd for $C_{11}H_{10}NOS$ $(M+H)^{+}$: 204.04. Found: 204.29.

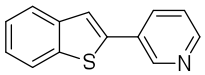


3-(3-Thienyl)pyridine [21308-81-6]. 3-Thienyl boronic acid (77 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:3) as eluent, the title compound was isolate as yellow oil (73 mg, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (d, *J* = 1.6 Hz, 1H), 8.53 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.86 (doublet of pseudotriplet, *J* = 7.9, 1.7 Hz, 1H), 7.52 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.44 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.39 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.32 (dd, *J* = 7.9, 4.8 Hz, 1H).

ESI-MS: Calcd for C_9H_8NS $(M+H)^{+}$: 162.03. Found: 162.24.

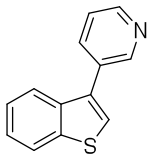


3-(2-Benzothienyl)pyridine [936734-97-3]. 2-Benzothienyl boronic acid (134 mg, 0.75 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 62%; 15 min, 76%; 1 h, 100%.

After flash chromatography with hexane as eluent, the title compound was isolate as a yellow solid (101 mg, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 (d, J = 2.0 Hz, 1H), 8.58 (dd, J = 4.8, 1.6 Hz, 1H), 7.8 (doublet of pseudotriplet, J = 8.0, 2.4 Hz, 1H), 7.87-7.80 (m, 2H), 7.61 (s, 1H), 7.41-7.34 (m, 3H).

EI-MS: Calcd for $C_{13}H_{10}NS$ M^{+}: 211.0. Found: 211.0.



3-(3-Pyridinyl)benzothiophene. 3-Benzothienyl boronic acid (107 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%. After flash chromatography with ethyl acetate/hexane (1:3) as eluent, the title compound was isolate as yellow oil (97 mg, 92% yield).

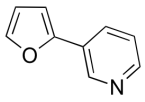
Gram-scale procedure using Schlenk manifold: Under argon, a 100-mL Schlenk flask containing a magnetic stir bar was sequentially charged with $Pd(OAc)_2$ (26.7 mg, 0.120 mmol), XPhos (68.5 mg, 0.144 mmol), 3-chloropyridine (678 mg, 6.0 mmol), 3-benzothienyl boronic acid (1.280 g, 7.2 mmol), *n*-dodecane (480 μL as GC internal standard), and 33.6 mL of degassed *n*-butanol. The mixture was prestirred at 25 ^{o}C for 15 min, and then a solution of $CsOH{\cdot}H_2O$ (1.703 g, 10.2 mmol) in 8.4 mL

of degassed H_2O was added in one portion to initiate the Suzuki reaction. The Schlenk flask was capped tightly and the reaction mixture was stirred vigorously at 25 ^oC for 5 min until all the 3-chloropyridine was consumed (monitored by GC). After routine workup and purification by flash chromatography (1:3 ethyl acetate/hexane as eluent), the titled compound was obtained as white solid (1.200 g, 95% yield).

^1H NMR (400 MHz, $CDCl_3$): δ 8.86 (s, 1H), 8.66 (d, *J* = 3.8 Hz, 1H), 7.96-7.85 (m, 3H), 7.48 (s, 1H), 7.40-7.45 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.5, 148.69, 140.72, 137.5, 135.9, 134.3, 131.9, 124.8, 124.7 (two overlapping peaks), 123.6, 123.1, 122.4.

ESI-MS: Calcd for $C_{13}H_{10}NS$ $(M+H)^+$: 212.05. Found: 212.44.

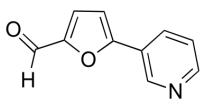


3-(2-Furyl)pyridine [31557-62-7]. 2-Furyl boronic acid (67 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^oC for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:3) as eluent, the title compound was isolate as yellow oil (67 mg, 93% yield).

^1H NMR (400 MHz, $CDCl_3$): δ 8.93 (d, *J* = 2.0 Hz, 1H), 8.49 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.93 (ddd, *J* = 8.0, 2.0, 1.5 Hz, 1H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.31 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.75 (d, *J* = 3.4 Hz, 1H), 6.51 (dd, *J* = 3.4, 1.8 Hz, 1H).

ESI-MS: Calcd for C_9H_8NO $(M+H)^+$: 146.05, Found: 146.30.

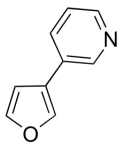


2-Formyl-5-(3-pyridyl)furan [38588-49-7]. 5-Formyl-2-furyl boronic acid (84 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 16 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 1 h, 42%; 3 h, 76%; 16 h, 100%.

After flash chromatography with ethyl acetate/hexane (1:1) as eluent, the title compound was isolate as yellow oil (81 mg, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (s, 1H), 9.06 (d, *J* = 1.7 Hz, 1H), 8.64 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.13 (doublet of pseudotriplet, *J* = 8.0, 1.8 Hz, 1H), 7.41 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.35 (d, *J* = 3.7 Hz, 1H), 6.95 (d, *J* = 3.7 Hz, 1H)

ESI-MS: Calcd for C_9H_8NO $(M+H)^+$: 174.05, Found: 174.30.

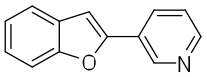


3-(2-Furyl)pyridine [55484-06-5]. 3-Furyl boronic acid (67 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:2) as eluent, the title compound was isolated as yellow oil (65 mg, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, *J* = 1.8 Hz, 1H), 8.50 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.78-7.75 (m, 2H), 7.52-7.51 (m, 1H), 7.31 (dd, *J* = 7.5, 4.9 Hz, 1H), 6.71 (d, *J* = 0.9 Hz, 1H).

ESI-MS: Calcd for C_9H_8NO $(M+H)^+$: 146.05, Found: 146.25.



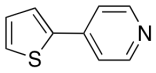
3-(2-Benzofuryl)pyridine [7035-06-5]. 2-Benzofuryl boronic acid (97 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:3) as eluent, the title compound was isolate as white solid (90 mg, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12 (dd, J = 2.0, 1.2 Hz, 1H), 8.58 (dd, J = 4.8, 1.6 Hz, 1H), 8.12 (doublet of pseudotriplet, J = 7.6, 1.6 Hz, 1H), 7.62-7.53 (m, 2H), 7.33-7.26 (m, 3H), 7.12 (d, J = 0.8 Hz, 1H).

ESI-MS: Calcd for $C_{13}H_{10}NO$ $(M+H)^{+}$: 196.07, Found: 196.43.

(b) Couplings of 2-chlorothiophene



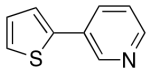
4-(Thiophen-2-yl)pyridine [21298-54-4]. 4-Pyridinyl boronic acid (74 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) and CsOH (149 mg, 0.85 mmol) were used and the reaction was stirred at 80 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 35%; 1 h, 100%.

After flash chromatography with MeOH/DCM (1:20) as eluent, the title compound was isolated as yellow solid (56 mg, 70% yield).

When K_3PO_4 (180 mg, 0.85 mmol) was used as base instead, the reaction reached completion within 1 h at 80 ^{o}C. Isolation yield: 75 mg, 93% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60-8.58 (m, 2H), 7.52-7.47 (m, 3H), 7.41 (dd, *J* = 5.2, 1.0 Hz, 1H), 7.13 (dd, *J* = 5.0, 3.7 Hz, 1H).

ESI-MS: Calcd for C_9H_7NS $(M+H)^+$: 162.03, Found: 162.29.

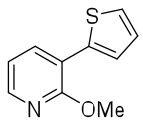


3-(2-Thienyl)pyridine [21298-53-3]. 3-Pyridinyl boronic acid (74 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction was stirred at 80 ^{o}C for 2 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 44%; 1 h, 92%; 2h, 100%

After flash chromatography with MeOH/DCM (1:20) as eluent, the title compound was isolated as yellow solid (68 mg, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (d, *J* = 1.9 Hz, 1H), 8.51 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.86 (ddd, *J* = 7.9, 1.9, 1.5 Hz, 1H), 7.37-7.36 (m, 2H), 7.30 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.13 (dd, *J* = 4.8, 3.9 Hz, 1H).

ESI-MS: Calcd for C_9H_7NS $(M+H)^+$: 162.03, Found: 162.29.



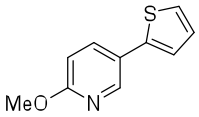
2-Methoxy-3-(2-thienyl)pyridine. 2-Methoxy-3-pyridyl boronic acid (92 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 57%; 15 min, 77%; 1 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:50) as eluent, the title compound was isolated as yellow oil (88 mg, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.89 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.58 (dd, *J* = 3.7, 1.0 Hz, 1H), 7.36 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.10 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.95 (dd, *J* = 7.5, 4.9 Hz, 1H), 4.08 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 145.4, 138.0, 136.1, 127.4, 126.2, 126.1, 118.1, 117.2, 53.7.

ESI-MS: Calcd for $C_{10}H_{10}NOS$ $(M+H)^+$: 192.04. Found: 192.12.

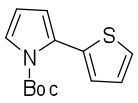


2-Methoxy-5-(2-thienyl)pyridine [475275-84-4]. 2-Methoxy-5-pyridyl boronic acid (115 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 4 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5min, 5%; 15 min, 15%; 1 h, 52%; 4 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:10) as eluent, the title compound was isolated as yellow oil (90 mg, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, *J* = 2.4 Hz, 1H), 7.77 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.27 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.21 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.08 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 3.97 (s, 3H).

ESI-MS: Calcd for $C_{10}H_{10}NOS$ $(M+H)^+$: 192.04. Found: 192.15.



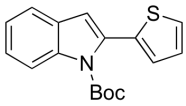
***N*-(*tert*-Butoxycarbonyl)-2-(2-thienyl)pyrrole [215187-33-0].** *N*-(*tert*-Butoxycarbonyl)-2-pyrrolyl boronic acid (127 mg, 0.60 mmol) and 2-chlorothiophene

(59 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:50) as eluent, the title compound was isolated as yellow oil (116 mg, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 3.3, 1.8 Hz, 1H), 7.31 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.06-7.05 (m, 1H), 7.01 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.31 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.21 (pseudotriplet, *J* = 3.3 Hz 1H), 1.43 (s, 9H).

ESI-MS: Calcd for $C_{13}H_{16}NO_2S$ $(M+H)^+$: 250.08. Found: 249.87.

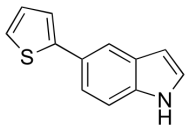


***N*-(*tert*-Butoxycarbonyl)-2-(2-thienyl)indole [929284-23-1].** *N*-(*tert*-Butoxy-carbonyl)-2-indolyl boronic acid (157 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 15 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 81%; 15 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:50) as eluent, the title compound was isolated as yellow oil (145 mg, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.38-7.31 (m, 2H), 7.27-7.24 (m, 1H), 7.10 (dd, *J* = 3.5, 1.2 Hz, 1H), 7.06 (dd, *J* = 5.1, 3.5 Hz 1H), 6.67 (s, 1H), 1.41 (s, 9H),

ESI-MS: Calcd for $C_{17}H_{18}NO_2S$ $(M+H)^+$: 300.10. Found: 299.83.

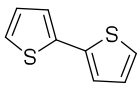


5-(2-Thienyl)indole [144104-54-1]. 5-Indolyl boronic acid (97 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 4 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5min, 26%; 15 min, 35%; 1 h, 90%; 4 h, 99%.

After purification by flash chromatography using ethyl acetate/hexane (1:50) as eluent, the title compound was isolated as yellow oil (98 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (br s, 1H), 7.93-7.92 (m, 1H), 7.52 (d, J = 8.4, 1.7 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.31 (dd, J = 3.6, 1.1 Hz, 1H), 7.26-7.24 (m, 2H), 7.10 (dd, J = 5.1, 3.6 Hz, 1H), 6.62-6.60 (m, 1H).

EI-MS: Calcd for $C_{12}H_8NS$ M^+: 199.1. Found: 199.0.

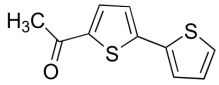


2, 2'-Bithiophene [492-97-7]. 2-Thienyl boronic acid (96 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used. Since the organoboronic acid underwent fast hydrolysis, it was added at last together with the aqueous CsOH solution after pre-stirring. The reaction was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 40%; 15 min, 72%; 1 h, 98%.

After flash chromatography with pentane as eluent, the title compound was isolated as yellow solid (76 mg, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.20 (m, 4H), 7.05-7.02 (m, 2H).

EI-MS: Calcd for $C_8H_6S_2$ M^+: 166.0. Found: 165.7.

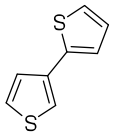


5-Acetyl-2, 2'-bithiophene [3515-18-2]. 5-Acetyl-2-thienyl boronic acid (128 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 16 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 27%; 15 min, 41%; 1 h, 74%; 4 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:10) as eluent, the title compound was isolated as yellow oil (103 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 4.0 Hz, 1H), 7.33-7.31 (m, 2H), 7.18 (d, J = 4.0 Hz, 1H), 7.06 (dd, J = 5.0, 3.8 Hz, 1H), 2.55 (s, 3H).

EI-MS: Calcd for $C_{10}H_9OS_2$ M^+: 208.0. Found: 207.9.

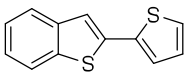


2, 3'-Bithiophene [2404-89-9]. 3-Thienyl boronic acid (96 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 64%; 15 min, 78%; 1 h, 95%.

After purification by flash chromatography using pentane as eluent, the title compound was isolated as yellow solid (75 mg, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.32 (m, 3H), 7.23-7.21 (m, 2H), 7.05 (dd, J = 4.8, 3.6 Hz, 1H).

EI-MS: Calcd for $C_8H_6S_2$ M^+: 166.0. Found: 165.9.

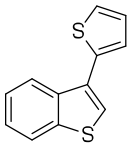


2-(2-Thienyl)benzothiophene [55164-48-2]. 2-Benzothienyl boronic acid (134 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 4 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 11%; 15 min, 31%; 1 h, 84%; 4 h, 100%.

After purification by flash chromatography using hexane as eluent, the title compound was isolated as yellow solid (99 mg, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.73 (m, 2H), 7.41 (s, 1H), 7.36-7.31 (m, 4H), 7.09-7.07 (m, 1H).

EI-MS: Calcd for $C_{12}H_9S_2$ M^+: 216.0. Found: 216.2.

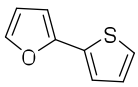


3-(2-Thienyl)benzothiophene [105789-79-5]. 3-Benzothienyl boronic acid (107 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used. Since the organoboronic acid underwent fast hydrolysis, it was added at last together with the aqueous CsOH solution after pre-stirring. The reaction was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC (modified procedure): 5 min, 77%; 15 min, 94%; 1 h, 100%.

After purification by flash chromatography using hexane as eluent, the title compound was isolated as yellow oil (105 mg, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.7 Hz, 1H), 7.91 (d, J = 7.3 Hz, 1H), 7.51(s, 1H), 7.47-7.34 (m, 4H), 7.17(dd, J = 4.8, 3.6 Hz, 1H)

EI-MS: Calcd for $C_{12}H_9S_2$ M^+: 216.0. Found: 215.9.

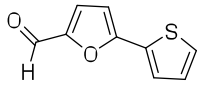


2-(2-Thienyl)furan [27521-80-8]. 2-Furyl boronic acid (84 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used. Since the organoboronic acid underwent fast hydrolysis, it was added at last together with the aqueous CsOH solution after pre-stirring. The reaction was stirred at 25 ^{o}C for 4 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 43%; 15 min, 86%; 1 h, 97%; 4 h, 100%.

After flash chromatography with ethyl ether/pentane (1:5) as eluent, the title compound was isolated as yellow oil (68 mg, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 1.8 Hz, 1H), 7.25-7.21 (m, 2H), 7.04 (dd, J = 5.0, 3.6 Hz, 1H), 6.50 (d, J = 3.3 Hz, 1H), 6.44 (dd, J = 3.3, 1.8 Hz, 1H).

EI-MS: Calcd for C_8H_6OS M^+: 150.0. Found: 149.9.

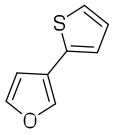


2-Formyl-5-thienylfuran [32364-30-0]. 5-Formyl-2-furyl boronic acid (105 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 3 d until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 1 h, 20%; 4 h, 30%; 16 h, 77%; 40 h, 85%; 3 d, 100%.

After purification by flash chromatography using ethyl ether/pentane (1:5) as eluent, the title compound was isolated as brown oil (84 mg, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.62 (s, 1H), 7.53 (dd, *J* = 3.7, 1.0 Hz, 1H), 7.41 (dd, *J* = 5.2, 1.0 Hz, 1H), 7.29 (d, *J* = 3.7 Hz, 1H), 7.11 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.68 (d, *J* = 3.7 Hz, 1H).

ESI-MS: Calcd for $C_9H_7O_2S$ $(M+H)^+$: 179.01. Found: 179.16.

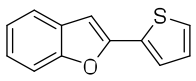


3-(2-Thienyl)furan [27521-81-9]. 3-Furyl boronic acid (84 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 33%; 15 min, 64%; 1 h, 100%.

After purification by flash chromatography using ethyl ether/pentane (1:5) as eluent, the title compound was isolated as yellow oil (70 mg, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (br s, 1H), 7.44 (pseudotriplet, *J* = 1.7 Hz, 1H), 7.20 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.10 (dd, *J* = 3.5, 1.1 Hz, 1H), 7.03 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.62 (dd, *J* = 1.7, 0.8 Hz, 1H).

EI-MS: Calcd for C_8H_6OS M^+: 150.0. Found: 149.7.



2-(2-Thienyl)benzofuran [65246-50-6]. 2-Benzofuryl boronic acid (122 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 4 h until the reaction reached completion. The conversion of

heteroaryl chloride was monitored by GC: 5min, 15%; 15 min, 32%; 1 h, 75%; 4 h, 99%.

After purification by flash chromatography using hexane as eluent, the title compound was isolated as white solid (91 mg, 91% yield).

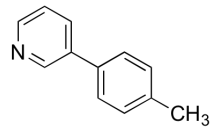
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.54 (m, 1H), δ 7.51-7.49 (m, 2H), 7.35 (dd, J = 5.0, 1.2 Hz, 1H), 7.30-7.22 (m, 2H), 7.11 (dd, J = 5.0, 3.6 Hz, 1H), 6.87 (s, 1H).

EI-MS: Calcd for $C_{12}H_9OS$ M^+: 200.0. Found: 200.0.

V. Scope of Aryl and Alkenyl Boronic Acids

The procedure in part IV was used for product isolation.

(a) Couplings of 3-chloropyridine

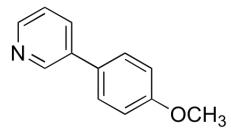


3-(*p*-Tolyl)pyridine [4423-09-0]. *p*-Tolyl boronic acid (82 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. Conversion of heteroaryl chloride was monitored by GC: 5 min, 100 %.

After flash chromatography with ethyl acetate/hexane (1:10) as eluent, the title compound was isolate as white solid (84 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (d, *J* = 1.7 Hz, 1H), 8.56 (d, *J* = 3.8 Hz, 1H), 7.86 (doublet of pseudotriplet, *J* = 7.8, 1.7 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.35 (dd, *J* = 7.8, 3.8 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 2.41 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{12}N$ $(M+H)^{+}$: 170.09. Found: 170.35.

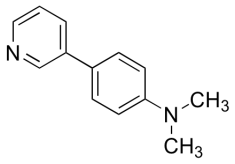


3-(*p*-Anisyl)pyridine [5958-02-1]. *p*-Anisyl boronic acid (91 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 100%.

After flash chromatography with ethyl ether/pentane (1:1) as eluent, the title compound was isolate as white solid (92 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (d, *J* = 1.8 Hz, 1H), 8.55 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.83 (doublet of pseudotriplet, *J* = 7.6, 1.7 Hz, 1H), 7.53-7.51 (m, 2H), 7.33 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.02-7.00 (m, 2H), 3.86 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{12}NO$ $(M+H)^+$: 186.08. Found: 186.30.

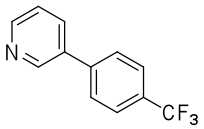


***N*,*N*-Dimethyl-4-(3-pyridyl)aniline [908145-70-0].** 4-(*N,N*-Dimethylamino)-phenyl boronic acid (99 mg, 0.60 mmol) and 3-chloropyridine (457 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 5 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 97%.

After flash chromatography with ethyl acetate/hexane (1:5) as eluent, the title compound was isolate as white solid (96 mg, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (d, *J* = 1.9 Hz, 1H), 8.49 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.84 (doublet of pseudotriplet, *J* = 7.9, 2.0 Hz, 1H), 7.50-7.48 (m, 2H), 7.31 (dd, *J* = 7.9, 4.7 Hz, 1H), 6.83-6.81 (m, 2H), 3.01 (s, 6H).

ESI-MS: Calcd for $C_{13}H_{15}N_2$ $(M+H)^+$: 199.12. Found: 199.33.



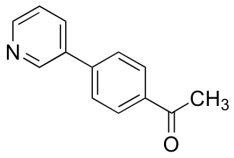
1-(3-Pyridinyl)-4-(trifluoromethyl)benzene [426823-25-8]. 4-Trifluoro-methylphenyl boronic acid (114 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 1 h until the reaction

reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 26%; 15 min, 72%; 1 h, 100%.

After flash chromatography with ethyl acetate/hexane (1:5) as eluent, the title compound was isolated as yellow oil (110 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (s, 1H), 8.65 (d, J = 4.8 Hz, 1H), 7.89 (doublet of pseudotriplet, J = 7.9, 1.8 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H), 7.41 (dd, J = 7.9, 4.8 Hz, 1H).

ESI-MS: Calcd for $C_{12}H_9F_3N$ $(M+H)^+$: 224.06. Found: 224.37.

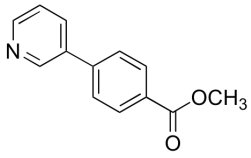


4-(3-Pyridinyl)acetophenone [90395-45-2]. 4-Acetylphenyl boronic acid (98 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 1 h until the reaction reached completion. Conversion of heteroaryl chloride was monitored by GC: 5 min, 22%; 15 min, 61%; 1 h, 100%.

After flash chromatography with ethyl ether/pentane (1:2) as eluent, the title compound was isolated as white solid (97 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (br s, 1H), 8.65 (d, J = 4.0 Hz, 1H), 8.08 (d, J = 6.6 Hz, 2H), 7.92 (doublet of pseudotriplet, J = 7.9, 1.7 Hz, 1H), 7.69 (d, J = 6.6 Hz, 2H), 7.41 (dd, J = 7.9, 4.0 Hz, 1H), 2.66 (s, 3H).

ESI-MS: Calcd for $C_{13}H_{12}NO$ $(M+H)^+$: 198.08. Found: 198.35.

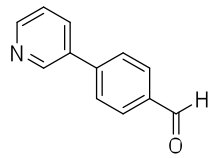


Methyl 4-(3-pyridyl)benzoate [90395-47-4]. 4-(Methoxycarbonyl)phenyl boronic acid (108 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 61%; 15 min, 79%; 1 h, 96%;

After flash chromatography with ethyl ether/pentane (1:2) as eluent, the title compound was isolated as white solid (98 mg, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (d, J = 2.0 Hz, 1H), 8.64 (dd, J = 4.8, 1.4 Hz, 1H), 8.15 (d, J = 8.3 Hz, 2H), 7.91 (doublet of pseudotriplet, J = 7.9, 1.9 Hz, 1H), 7.65 (d, J = 8.3 Hz, 2H), 7.39 (dd, J = 7.9, 4.8 Hz, 1H), 3.95 (s, 3H).

ESI-MS: Calcd for $C_{13}H_{12}NO_2$ $(M+H)^+$: 214.08. Found: 214.36.

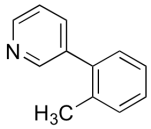


4-(3-Pyridinyl)benzaldehyde [127406-55-7]. 4-Formylphenyl boronic acid (113 mg, 0.75 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction was stirred at 25 ^{o}C for 16 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5min, 14%; 15 min, 31%; 1 h, 70%; 4 h, 85%; 16 h, 100%.

After purification by flash chromatography using ethyl ether/pentane (1:2) as eluent, the title compound was isolated as white solid (90 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.09 (s, 1H), 8.91 (d, J = 2.1 Hz, 1H), 8.67 (dd, J = 4.8, 1.1 Hz, 1H), 8.00 (d, J = 8.2 Hz, 2H), 7.93 (doublet of pseudotriplet, J = 7.9, 2.0 Hz, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.42 (dd, J = 7.9, 4.8 Hz, 1H).

ESI-MS: Calcd for $C_{12}H_{10}NO$ $(M+H)^+$: 184.07. Found: 184.35.

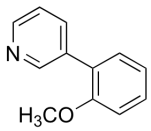


3-(*o*-Tolyl)pyridine [90395-49-6]. *o*-Tolyl boronic acid (82 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used. Since the organoboronic acid underwent fast hydrolysis in the aqueous mixed solvent, it was added after the rest of reaction components were prestirred in pure *n*-butanol at 25 ^{o}C for 15 min. Then the whole reaction mixture was stirred in *n*-butanol at 25 ^{o}C for 15 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 87 %; 15 min, 100%.

After flash chromatography with ethyl ether/pentane (1:1) as eluent, the title compound was isolated as brown oil (80 mg, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60-8.59 (m, 2H), 7.65 (doublet of pseudotriplet, J = 7.8, 1.8 Hz, 1H), 7.35 (dd, J = 7.8, 4.8 Hz, 1H), 7.32-7.27 (m, 3H), 7.21 (d, J = 6.9 Hz, 1H), 2.28 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{12}N$ $(M+H)^{+}$: 170.09. Found: 170.36.



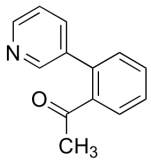
3-(*o*-Anisyl)pyridine [5958-01-0]. *o*-Anisyl boronic acid (91 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used. The organoboronic acid underwent fast hydrolysis in the aqueous solvent, so it was added after the rest of reaction components were prestirred in pure *n*-butanol at 25 ^{o}C for 15 min. The whole reaction mixture was stirred at 25 ^{o}C for 15 min until the reaction reached

completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 78%; 15 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:1) as eluent, the title compound was isolated as brown oil (92 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, J = 1.6 Hz, 1H), 8.55 (dd, J = 4.8, 1.6 Hz, 1H), 7.86 (doublet of pseudotriplet, J = 8.0, 1.6 Hz, 1H), 6.38-6.31 (m, 3H), 7.08-7.00 (m, 2H), 3.83 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{12}NO$ $(M+H)^+$: 186.08. Found: 186.30.

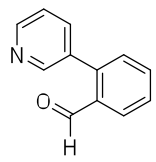


2-(3-Pyridinyl)acetophenone [90395-44-1]. 2-Acetylphenyl boronic acid (98 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 37 %; 1 h, 100%.

After purification by flash chromatography using ethyl ether/pentane (1:2) as eluent, the title compound was isolated as yellow oil (97 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (dd, J = 4.8, 1.6 Hz, 1H), 8.59 (d, J = 2.4 Hz, 1H), 7.67-7.63 (m, 2H), 7.58-7.55 (m, 1H), 7.51-7.49 (m, 1H), 7.38-7.34 (m, 2H), 2.20 (s, 3H).

ESI-MS: Calcd for $C_{13}H_{12}NO$ $(M+H)^+$: 198.08. Found: 198.30.

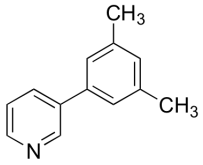


2-(3-Pyridinyl)benzaldehyde [176690-44-1]. 2-Formylphenyl boronic acid (113 mg, 0.75 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 16 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 33%; 1 h, 74%; 4 h, 88%; 16 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:10) as eluent, the title compound was isolated as white solid (90 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.70 (dd, J = 4.8, 1.6 Hz, 1H), 8.67 (d, J = 2.0 Hz, 1H), 8.07 (dd, J = 7.6, 1.2 Hz, 1H), 7.73-7.69 (m, 2H), 7.58 (pseudotriplet, J = 7.6 Hz, 1H), 7.44-7.41 (m, 2H).

ESI-MS: Calcd for $C_{12}H_{10}NO$ $(M+H)^{+}$: 184.07. Found: 184.31.

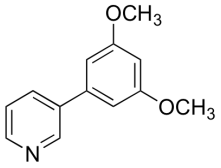


3,5-Dimethyl-1-(3-pyridyl)benzene [743406-91-9]. 3,5-Dimethylphenyl boronic acid (90 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 79%; 15 min, 84%; 1 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:1) as eluent, the title compound was isolated as yellow oil (87 mg, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 2.1 Hz, 1H), 8.57 (dd, J = 4.8, 1.5 Hz, 1H), 7.85 (doublet of pseudotriplet, J = 7.9, 2.1 Hz, 1H), 7.33 (dd, J = 7.9, 4.8 Hz, 1H), 7.19 (s, 2H), 7.05 (s, 1H), 2,39 (s, 6H).

ESI-MS: Calcd for $C_{13}H_{13}N$ $(M+H)^{+}$: 184.10. Found: 184.33.

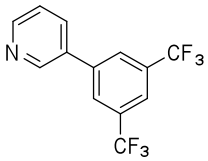


3,5-Dimethoxyl-1-(3-pyridyl)benzene [732276-79-8]. 3,5-Dimethoxylphenyl boronic acid (108 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 66%; 15 min, 90%; 1 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:20) as eluent, the title compound was isolated as yellow oil (104 mg, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, J = 2.3 Hz, 1H), 8.59 (dd, J = 4.8, 1.3 Hz, 1H), 7.86 (doublet of pseudotriplet, J = 7.9, 1.6 Hz, 1H), 7.35 (dd, J = 7.9, 4.8 Hz, 1H), 6.70 (d, J = 2.2 Hz, 2H), 6.51-6.50 (t, J = 2.2 Hz, 1H), 3.85 (s, 6H).

ESI-MS: Calcd for $C_{13}H_{13}NO_2$ $(M+H)^+$: 216.09. Found: 216.21.

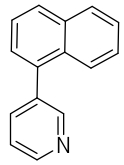


1-(3-Pyridinyl)-3,5-Bis(trifluoromethyl)benzene [1214337-69-5]. 3,5-Bis(trifluoromethyl)phenyl boronic acid (155 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 15 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 36%; 15 min, 97 %.

After purification by flash chromatography using ethyl acetate/hexane (1:10) as eluent, the title compound was isolated as white solid (137 mg, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (s, 1H), 8.72 (d, J = 4.4 Hz, 1H), 8.01 (s, 2H), 7.93-7.91 (m, 2H), 7.46 (dd, J = 7.6, 4.8 Hz, 1H).

ESI-MS: Calcd for $C_{13}H_8F_6N$ $(M+H)^+$: 292.05. Found: 292.41.

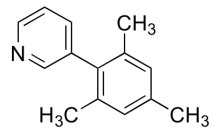


3-(1-Naphthyl)pyridine [189193-21-3]. 1-Naphthyl boronic acid (104 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 87%; 15 min, 92%; 1 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:2) as eluent, the title compound was isolated as yellow oil (99 mg, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, J = 1.6 Hz, 1H), 8.69 (dd, J = 4.8, 1.6 Hz, 1H), 7.95-7.91 (m, 2H), 7.84-7.80 (m, 2H), 7.58-7.42 (m, 5H).

ESI-MS: Calcd for $C_{15}H_{11}N$ $(M+H)^+$: 206.09. Found: 206.43.



3-(2-Mesityl)pyridine [75601-34-2]. 2-Mesityl boronic acid (123 mg, 0.75 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used. The organoboronic acid underwent slow cross-coupling, so pure *n*-butanol was used as reaction solvent to minimize hydrolysis of the organoboronic acid. The reaction mixture was stirred at 25 ^{o}C for 40 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 1 h, 10%; 2 h, 21%; 16 h, 88%; 40 h, 100%.

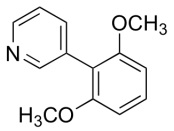
After purification by flash chromatography using diethyl ether/pentane (1:1) as eluent, the title compound was isolated as white solid (95 mg, 97% yield).

When the reaction was conducted in *n*-butanol at 80 ^{o}C with 1.5 equiv of 2-mesityl boronic acid, it reached completion in 15 min. After purification by flash chromatography, the title compound was isolated as white solid (97 mg, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (dd, J = 4.8, 1.5 Hz 1H), 8.42 (d, J = 1.5 Hz 1H), 7.50 (doublet of pseudotriplet, J = 7.7, 1.9 Hz, 1H), 7.35 (dd, J = 7.7, 4.8 Hz 1H), 6.97 (s, 2H), 2.34 (s, 3H), 2.00 (3, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 147.9, 137.6, 137.1, 136.7, 136.2, 135.0, 128.3, 123.4, 21.1, 20.8.

EI-MS: Calcd for $C_{14}H_{15}N$ M^{+}: 197.1. Found: 197.1.

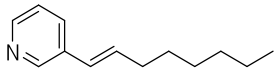


1,3-Dimethoxy-2-(3-pyridyl)benzene [334977-38-7]. 2,6-Dimethoxyphenyl boronic acid (109 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used. The organoboronic acid underwent fast hydrolysis in the aqueous solvent, so it was added after the rest of reaction components were prestirred in *n*-butanol at 25 ^{o}C for 15 min. Then the reaction mixture was stirred in *n*-butanol at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 36 %; 15 min, 63 %; 1 h, 95%.

After flash chromatography with ethyl acetate/hexane (1:1) as eluent, the title compound was isolated as white solid (99 mg, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, J = 1.6 Hz, 1H), 8.52 (dd, J = 4.8, 1.6 Hz, 1H), 7.68 (doublet of pseudotriplet, J = 8.0, 1.6 Hz, 1H), 7.34-7.30 (m, 2H), 6.66 (d, J = 8.4 Hz, 2H), 3.75 (s, 6H).

ESI-MS: Calcd for $C_{13}H_{14}NO_2$ $(M+H)^+$: 216.09. Found: 216.23.

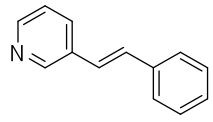


(*E*)-3-(1-Octenyl)pyridine [502699-04-9]. (*E*)-1-Octenyl boronic acid (94 mg, 0.60 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 50%; 15 min, 72%; 1 h, 100%.

After flash chromatography with ethyl acetate/hexane (1:10) as eluent, the title compound was isolated as white solid (93 mg, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (br s, 1H), 8.42 (d, J = 3.6 Hz, 1H), 7.65 (doublet of pseudotriplet, J = 8.0, 2.0 Hz, 1H), 7.21 (dd, J = 8.0, 3.6 Hz, 1H), 6.38-6.28 (m, 2H), 2.23 (pseudoquartet, J = 7.0 Hz, 2H), 1.43 (pseudoquintet, J = 7.3 Hz, 2H), 1.38-1.28 (m, 6H), 0.89 (t, J = 6.8 Hz, 3H).

ESI-MS: Calcd for $C_{13}H_{20}N$ $(M+H)^+$: 190.15. Found: 190.25.



(*E*)-3-Styrylpyridine [2633-06-9]. (*E*)-Styryl boronic acid (111 mg, 0.75 mmol) and 3-chloropyridine (57 mg, 0.50 mmol) were used. The organoboronic acid underwent slow coupling, so pure *n*-butanol was used as reaction solvent to minimize hydrolysis of the organoboronic acid. The reaction mixture was stirred at 25 ^{o}C for 16

h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 1 h, 37%; 2 h, 50%; 16 h, 94%.

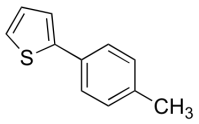
After purification by flash chromatography using ethyl acetate/hexane (1:5) as eluent, the title compound was isolated as white solid (85 mg, 94% yield).

When the reaction was conducted in *n*-butanol at 80 ^{o}C with 1.2 equiv of (*E*)-styryl boronic acid, it reached completion in 15 min. After purification by flash chromatography using ethyl acetate/hexane (1:5) as eluent, the title compound was isolated as white solid (84 mg, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, *J* = 2.0 Hz, 1H), 8.49 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.84 (ddd, *J* = 8.0, 2.0, 1.4 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.38 (pseudotriplet, *J* = 7.6 Hz, 2H), 7.37-7.27 (m, 2H), 7.17 (d, *J* = 16.4 Hz, 1H), 7.07 (d, *J* = 16.4 Hz, 1H).

ESI-MS: Calcd for $C_{13}H_{12}N$ $(M+H)^{+}$: 182.09. Found: 182.35.

(b) Couplings of 2-chlorothiophene

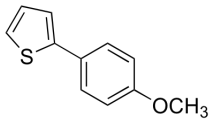


2-(*p*-Tolyl)thiophene [16939-04-1]. *p*-Tolyl boronic acid (82 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 40%; 15 min, 73 %; 1 h, 100%.

After flash chromatography with hexane as eluent, the title compound was isolated as white solid (81 mg, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 8.1 Hz, 2H), 7.27-7.24 (m, 2H), 7.19 (d, J = 8.1, 2H), 7.07 (dd, J = 5.1, 3.6 Hz, 1H), 2.36 (s, 3H).

EI-MS: Calcd for $C_{11}H_{10}S$ M^+: 174.1. Found: 174.0.

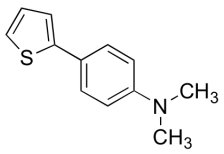


2-(*p*-Anisyl)thiophene [42545-43-7]. *p*-Anisyl boronic acid (91 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 33%; 15 min, 70%; 1 h, 100%.

After flash chromatography with ethyl acetate/hexane (1:200) as eluent, the title compound was isolated as white solid (91 mg, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.53 (m, 2H), 7.22-7.19 (m, 2H), 7.06 (dd, J = 5.1, 3.6 Hz, 1H), 6.93-6.91 (m, 2H), 3.84 (s, 3H).

EI-MS: Calcd for $C_{11}H_{10}OS$ $(M+H)^+$: 190.05. Found: 190.20.

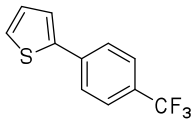


***N*,*N*-Dimethyl-4-(2-thienyl)aniline [88613-62-1].** 4-(*N,N*-Dimethylamino)-phenyl boronic acid (99 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 55%; 15 min, 75%; 1 h, 100%.

After flash chromatography with ethyl acetate/hexane (1:20) as eluent, the title compound was isolated as white solid (93 mg, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.48 (m, 2H), 7.16-7.15 (m, 2H), 7.04-7.02 (m, 1H), 6.74-6.72 (m, 2H), 2.98 (s, 6H).

ESI-MS: Calcd for $C_{12}H_{14}NS$ $(M+H)^+$: 204.08. Found: 204.13.

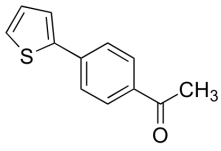


1-(2-Thienyl)-4-(trifluoromethyl)benzene [115933-15-8]. 4-(Trifluoromethyl)-phenyl boronic acid (143 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 41%; 15 min, 74%; 1 h, 100%.

After flash chromatography with hexane as eluent, the title compound was isolated as white solid (109 mg, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 7.40 (dd, J = 3.6, 1.2 Hz, 1H), 7.36 (dd, J = 5.2, 1.2 Hz, 1H), 7.12 (dd, J = 5.2, 3.6 Hz, 1H).

EI-MS: Calcd for $C_{11}H_9F_3S$ M^+: 228.0. Found: 227.9.

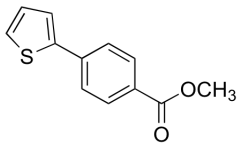


4-(2-Thienyl)acetophenone [35294-37-2]. 4-Acetylphenyl boronic acid (123 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5min, 38%; 15 min, 65 %; 1 h, 100%.

After flash chromatography with ethyl acetate/hexane (1:20) as eluent, the title compound was isolated as white solid (94 mg, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98-7.96 (m, 2H), 7.71-7.69 (m, 2H), 7.43 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.37 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.12 (dd, *J* = 5.1, 3.6 Hz, 1H), 2.62 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{11}OS$ $(M+H)^+$: 203.05. Found: 203.11.

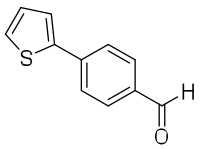


Methyl 4-(2-thienyl)benzoate [17595-86-7]. 4-(Methoxycarbonyl)phenyl boronic acid (108 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 22%; 15 min, 67%, 1 h, 100%.

After flash chromatography with ethyl acetate/hexane (1:25) as eluent, the title compound was isolated as white solid (99 mg, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05-8.03 (m, 2H), 7.69-7.67 (m, 2H), 7.42 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.37 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.12 (dd, *J* = 5.1, 3.6 Hz, 1H), 3.93 (s, 3H).

EI-MS: Calcd for $C_{12}H_{10}O_2S$ M^+: 218.0. Found: 217.9.

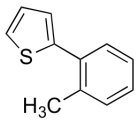


4-(2-Thienyl)benzaldehyde [107834-03-7]. 4-Formylphenyl boronic acid (113 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 40 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 1 h, 36%; 3 h, 65%; 16 h, 86%; 20 h, 88%; 40 h, 100%.

After flash chromatography with ethyl acetate/hexane (1:10) as eluent, the title compound was isolated as colorless oil (86 mg, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.01 (s, 1H), 7.90-7.88 (m, 2H), 7.78-7.76 (m, 2H), 7.47 (dd, J = 4.0, 1.2 Hz, 1H), 7.40 (dd, J = 5.2, 1.2 Hz, 1H), 7.14 (dd, J = 5.2, 4.0 Hz, 1H).

EI-MS: Calcd for $C_{11}H_9OS$ M^+: 188.0. Found: 188.0.

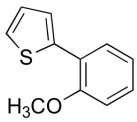


2-(*o*-Tolyl)thiophene [99846-56-7]. *o*-Tolyl boronic acid (82 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 15 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 78%; 15 min, 100%.

After flash chromatography with hexane as eluent, the title compound was isolated as yellow oil (80 mg, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.39 (m, 1H), 7.33-7.32 (m, 1H), 7.25-7.21 (m, 3H), 7.09-7.05 (m, 2H), 2.42 (s, 3H).

EI-MS: Calcd for $C_{11}H_{10}S$ M^+: 174.1. Found: 174.0.

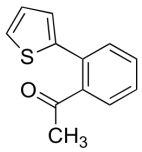


2-(*o*-anisyl)thiophene [17595-92-5] o-Anisyl boronic acid (91 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 °C for 15 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 80 %; 15 min, 100%.

After flash chromatography with ethyl acetate/hexane (1:200) as eluent, the title compound was isolated as green oil (92 mg, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, J = 7.5, 1.5 Hz, 1H), 7.50 (d, J = 3.7 Hz, 1H), 7.33 (d, J = 5.1 Hz, 1H), 7.27 (doublet of pseudotriplet, J = 7.5, 1.6 Hz, 1H), 7.09 (dd, J = 5.1, 3.7 Hz, 1H), 7.02-6.98 (m, 2H), 3.94 (s, 3H).

ESI-MS: Calcd for $C_{11}H_{11}OS$ $(M+H)^+$: 191.05. Found: 191.20.

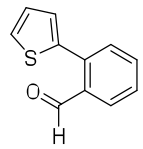


2-(2-Thienyl)acetophenone [893739-40-7]. 2-Acetylphenyl boronic acid (123 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 °C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 47 %; 1 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:3) as eluent, the title compound was isolated as yellow oil (92 mg, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.46 (m, 3H), 7.42-7.39 (m, 2H), 7.08 (dd, J = 4.8, 3.2 Hz, 1H), 7.00 (dd, J = 3.6, 0.8 Hz, 1H), 2.14 (s, 3H).

EI-MS: Calcd for $C_{12}H_{11}OS$ M^+: 202.0. Found: 201.4.

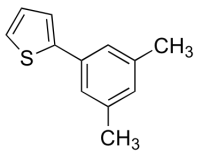


2-(2-Thienyl)benzaldehyde [99902-07-5]. 2-Formylphenyl boronic acid (113 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 40 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 18%; 1h, 41%; 4 h, 64%; 16 h, 92 %; 40 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:10) as eluent, the title compound was isolated as yellow oil (93 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.19 (s, 1H), 8.02 (dd, J = 7.8, 1.2 Hz, 1H), 7.62 (doublet of pseudotriplet, J = 7.7, 1.3 Hz, 1H), 7.55 (dd, J = 7.7, 1.0 Hz, 1H), 7.50(d, J = 7.7 Hz, 1H), 7.47 (dd, J = 5.1, 1.1 Hz, 1H) 7.16 (dd, J = 5.1, 3.6 Hz, 1H), 7.08 (dd, J = 3.6, 1.1 Hz, 1H).

ESI-MS: Calcd for $C_{11}H_8OS$ $(M+H)^+$: 189.03. Found: 189.10.

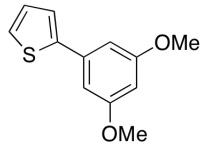


2-(3,5-Dimethylphenyl)thiophene [1070403-62-1]. 3,5-Dimethylphenyl boronic acid (90 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 2 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 25%, 15 min, 70%; 2 h, 100%.

After purification by flash chromatography using hexane as eluent, the title compound was isolated as colorless oil (89 mg, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.24 (m, 4H), 7.07-7.05 (m, 1H), 6.93 (s, 1H), 2.35 (s, 6H).

EI-MS: Calcd for $C_{12}H_{12}S$ M^+: 188.1. Found: 188.0.



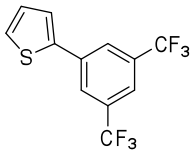
2-(3,5-Dimethoxyphenyl)thiophene. 3,5-Dimethoxyphenyl boronic acid (108 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 2 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 20%; 15 min, 54%; 2 h, 100%.

After purification by flash chromatography using hexane as eluent, the title compound was isolated as colorless oil (99 mg, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, J = 3.6, 1.1 Hz, 1H), 7.28 (dd, J = 5.1, 1.1 Hz, 1H), 7.07 (dd, J = 5.1, 3.6 Hz, 1H), 6.77 (d, J = 2.2 Hz, 2H), 6.42 (t, J = 2.2 Hz, 1H), 3.84 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 144.3, 136.3, 127.9, 124.9, 123.5, 104.4, 99.6, 55.4.

ESI-MS: Calcd for $C_{12}H_{12}SO_2$ $(M+H)^+$: 221.06. Found: 221.17.

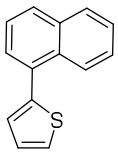


1-(2-Thienyl)-3,5-bis(trifluoromethyl)benzene [460743-68-4]. 3,5-Bis(trifluoromethyl)phenyl boronic acid (155 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 49 %; 1 h, 100%.

After flash chromatography with hexane as eluent, the title compound was isolated as yellow solid (145 mg, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 2H), 7.76 (s, 1H), 7.44 (dd, J = 3.6, 1.1 Hz, 1H), 7.42 (dd, J = 5.1, 1.1 Hz, 1H), 7.15 (dd, J = 5.1, 3.6 Hz, 1H).

EI-MS: Calcd for $C_{12}H_7F_6S$ M^+: 296.0. Found: 296.0.

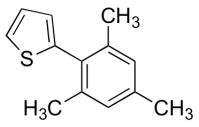


2-(1-Naphthyl)thiophene [4632-51-3]. 1-Naphthyl boronic acid (104 mg, 0.60 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 1 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 93%; 1 h, 100%.

After purification by flash chromatography using hexane as eluent, the title compound was isolated as colorless oil (104 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24-8.22 (m, 1H), 7.92-7.86 (m, 2H), 7.59-7.43 (m, 5H), 7.27-7.25 (m, 1H), 7.19 (dd, J = 5.2, 3.6 Hz, 1H).

EI-MS: Calcd for $C_{14}H_{10}S$ M^+: 210.0. Found: 210.2.

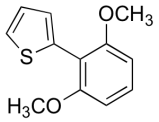


2-Mesitylthiophene [920449-57-6]. 2-Mesityl boronic acid (123 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 ^{o}C for 16 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 22%; 1 h, 65%; 4 h, 84%; 16 h, 97%.

After purification by flash chromatography using hexane as eluent, the title compound was isolated as colorless crystal (96 mg, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (dd, J = 5.2, 1.2 Hz, 1H), 7.09 (dd, J = 5.2, 3.6 Hz, 1H), 6.93 (s, 2H), 6.80 (dd, J = 3.6, 1.2 Hz, 1H), 2.32 (s, 3H), 2.11 (s, 6 H).

EI-MS: Calcd for $C_{13}H_{14}S$ M^{+}: 202.1, Found: 202.0.

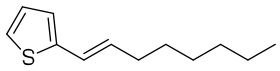


2-(2,6-Dimethoxyphenyl)thiophene [30143-75-0]. 2,6-Dimethoxyphenyl boronic acid (137 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 80 ^{o}C for 15 min until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 15 min, 100%.

After flash chromatography with hexane as eluent, the title compound was isolated as yellow oil (90 mg, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.36 (m, 2H), 7.25 (t, J = 8.3 Hz, 1H), 7.10 (dd, J = 5.1, 3.6 Hz, 1H), 6.65 (d, J = 8.3 Hz, 2H), 3.83 (s, 6H).

ESI-MS: Calcd for $C_{12}H_{13}O_2S$ $(M+H)^+$: 221.06. Found: 221.15.

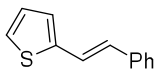


(*E*)-2-(1-Octenyl)thiophene [109786-59-6]. (*E*)-1-Octenyl boronic acid (117 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 °C for 4 h until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 5 min, 19%; 15 min, 32%; 1 h, 70%; 4 h, 100%.

After purification by flash chromatography using hexane as eluent, the title compound was isolated as yellow oil (93 mg, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, J = 4.8 Hz, 1H), 6.93 (dd, J = 5.2, 3.6 Hz, 1H), 6.86 (d, J = 3.2 Hz, 1H), 6.49 (d, J = 15.6 Hz, 1H), 6.07 (dt, J = 15.6, 7.1 Hz, 1H), 2.17 (pseudoquartet, J = 7.1 Hz, 2H), 1.43 (pseudoquintet, J = 7.6 Hz, 2H), 1.35-1.30 (m, 6H), 0.90 (t, J = 6.7 Hz, 3H).

EI-MS: Calcd for $C_{12}H_{18}S$ M^+: 194.1. Found: 194.0.



(*E*)-2-Styrylthiophene [26708-50-9]. (*E*)-Styryl boronic acid (111 mg, 0.75 mmol) and 2-chlorothiophene (59 mg, 0.50 mmol) were used and the reaction mixture was stirred at 25 °C for 3 days until the reaction reached completion. The conversion of heteroaryl chloride was monitored by GC: 1 h, 23%; 4 h, 43%; 16 h, 77%; 40 h, 89%; 3 d, 100%.

After purification by flash chromatography using hexane as eluent, the title compound was isolated as yellow solid (92 mg, 99% yield).

When the reaction was conducted in *n*-butanol at 80 ^{o}C with 1.2 equiv of (*E*)-styryl boronic acid, it reached completion in 15 min. After flash chromatography with hexane as eluent, the title compound was isolated as white solid (90 mg, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 7.6 Hz, 2H), 7.35 (pseudotriplet, J = 7.6 Hz, 2H), 7.27-7.19 (m, 3H), 7.08 (d, J = 4.8 Hz, 1H), 7.02-7.00 (m, 1H), 6.94 (d, J = 16.0 Hz, 1H).

EI-MS: Calcd for $C_{12}H_{10}S$ M^{+}: 186.0. Found: 186.3.

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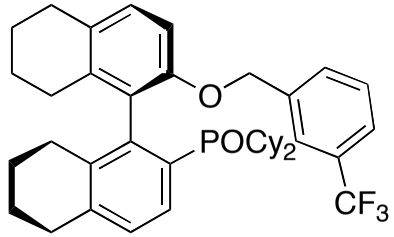

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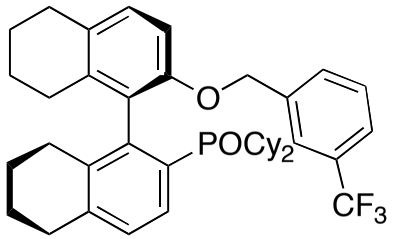

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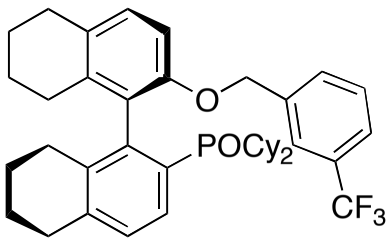

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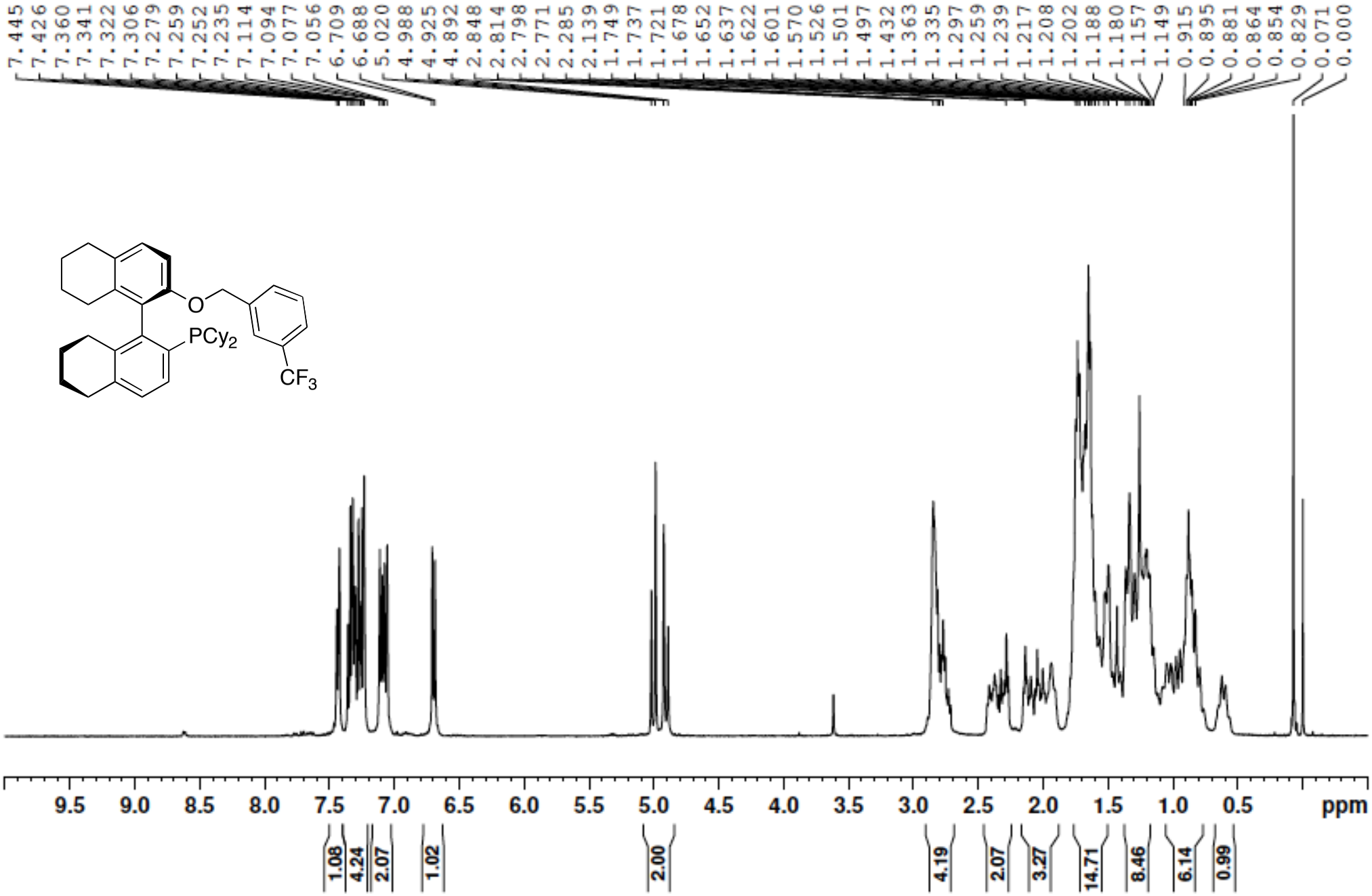

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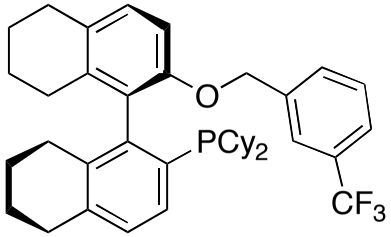

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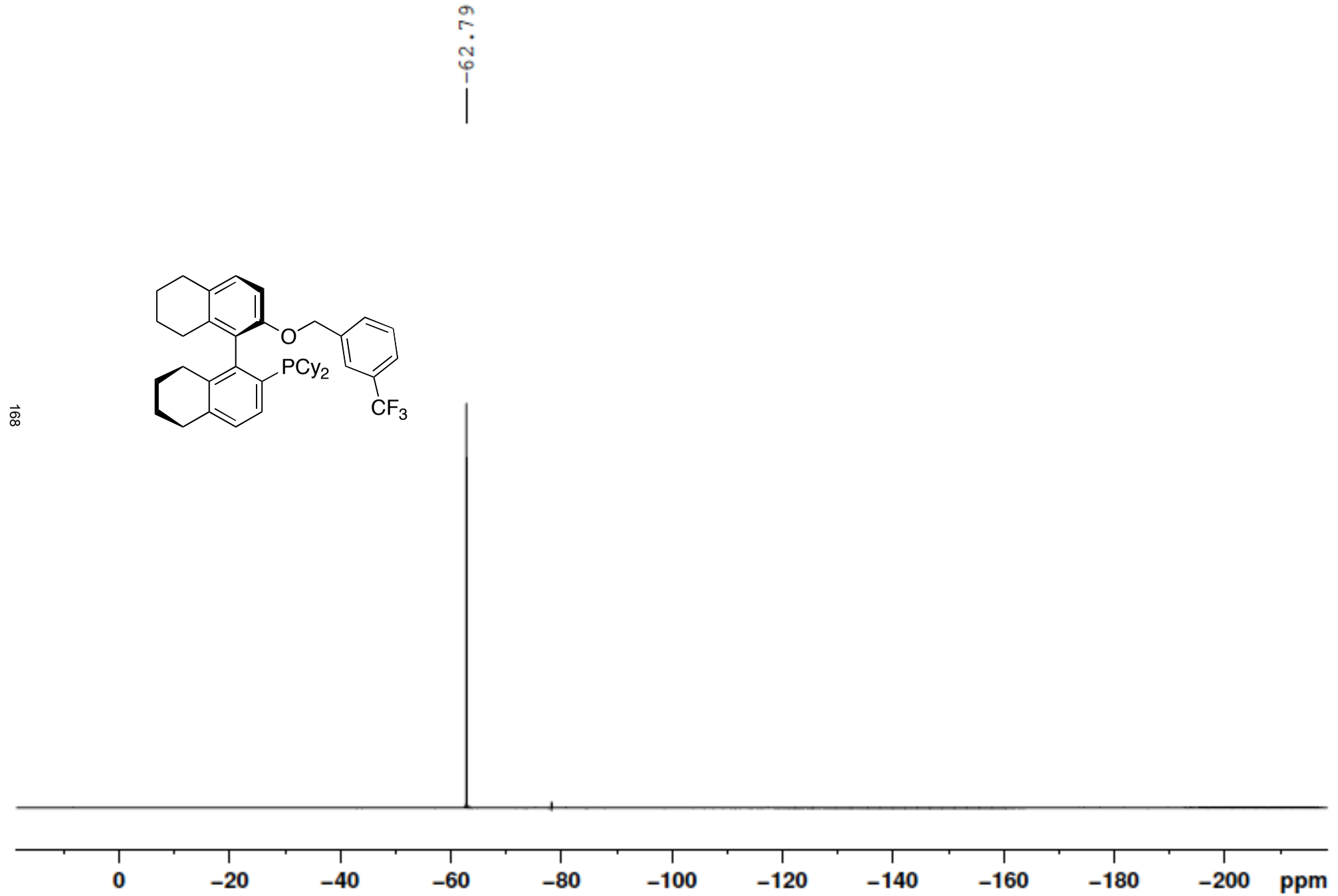
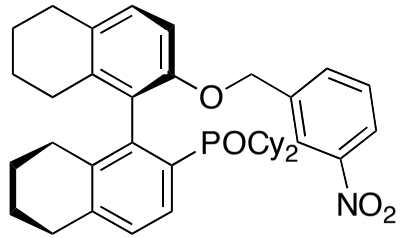
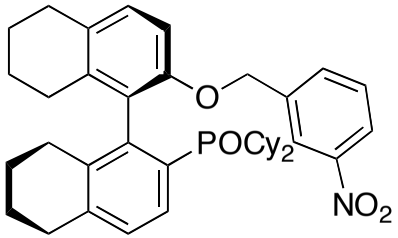


JF11-52-3-oxide CDCl3 1HNMR BBFO2
2013-08-02

8.058 8.053 8.044 8.039 8.034 7.828 7.448 7.429 7.424 7.405 7.386 7.300 7.280 7.274 7.264 7.254 7.203 7.197 7.183 7.177 7.043 7.023 6.713 6.692 5.031 2.952 2.894 2.876 2.853 2.835 2.816 2.759 2.251 2.180 2.051 1.780 1.768 1.753 1.727 1.714 1.698 1.686 1.671 1.660 1.626 1.453 1.429 1.191 1.171 1.151 1.122 1.107 1.095 1.086 0.909 0.902 0.874 0.871 0.000

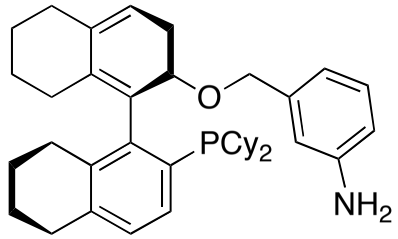


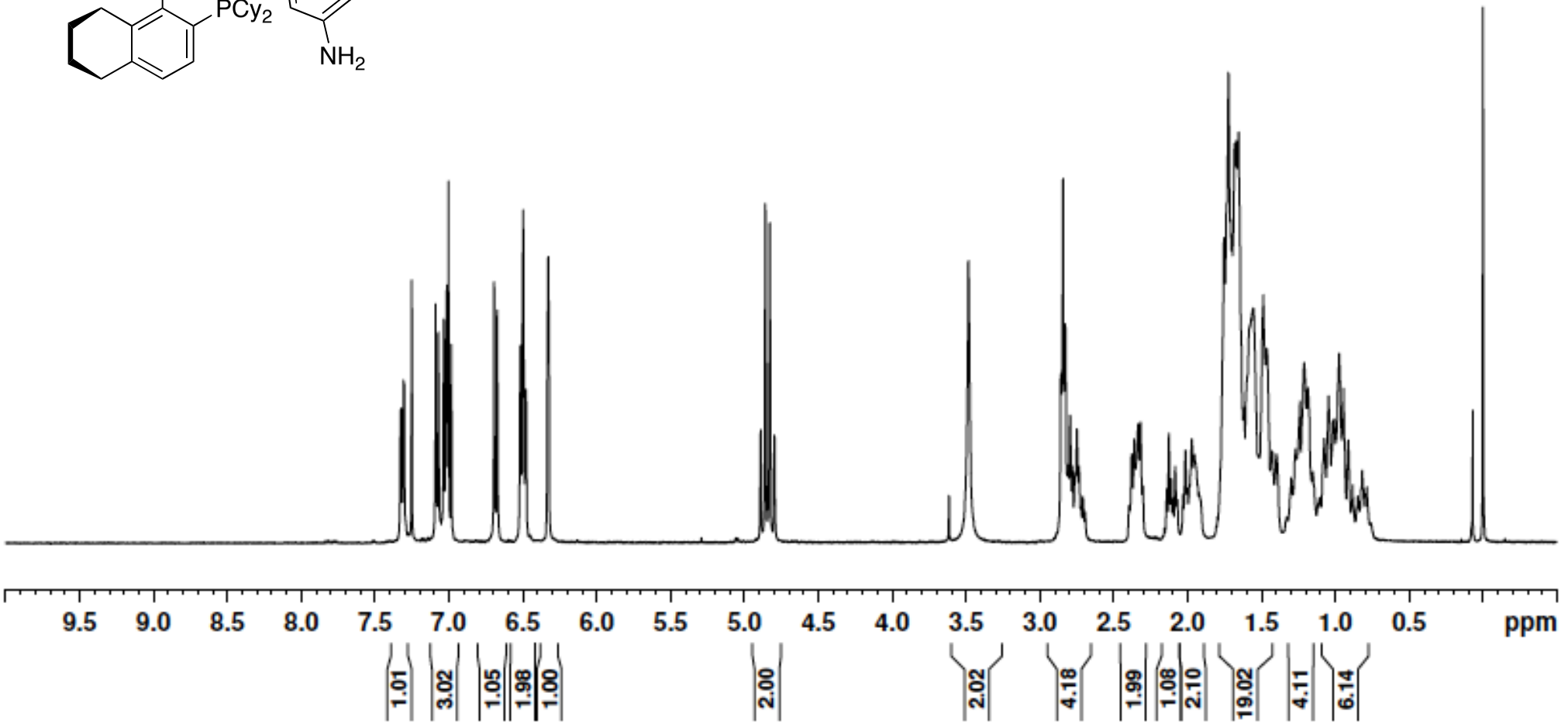
JF11-52-3-oxide CDCl3 31PNMR BBFO2
2013-08-02



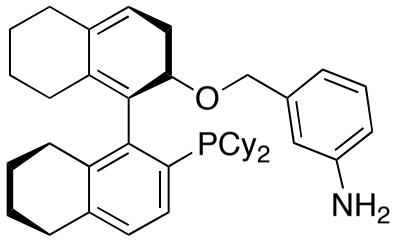
JF11-52-3-redo 1HNMR BBFO1 CDC13
2013-8-4

7.325 7.309 7.253 7.092 7.072 7.037 7.024 7.016 7.005 6.985 6.696 6.675 6.518 6.500 6.486 6.480 6.330 4.891 4.859 4.830 4.798 3.484 2.858 2.844 2.828 2.795 2.750 2.361 2.335 2.318 2.126 2.016 1.973 1.753 1.724 1.710 1.700 1.683 1.670 1.662 1.655 1.619 1.556 1.488 1.464 1.430 1.268 1.239 1.211 1.186 1.076 1.045 1.013 1.006 0.974 0.944 0.912 0.070 0.000





JF11-52-3-redo 31PNMR BBFO1 CDCl3
2013-8-4

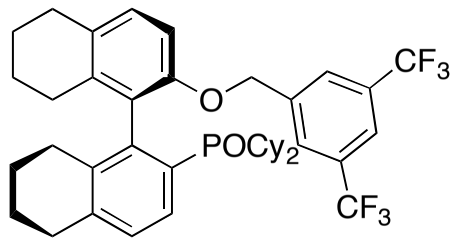


-10.18

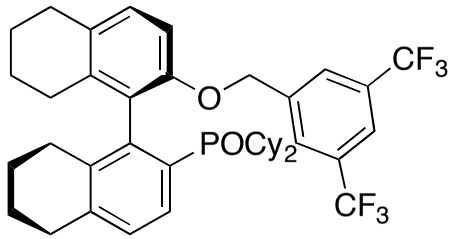
200 150 100 50 0 −50 −100 −150 −200 ppm

JF11-46-redo CDC13 1HNMR BBFO2
2013-08-05

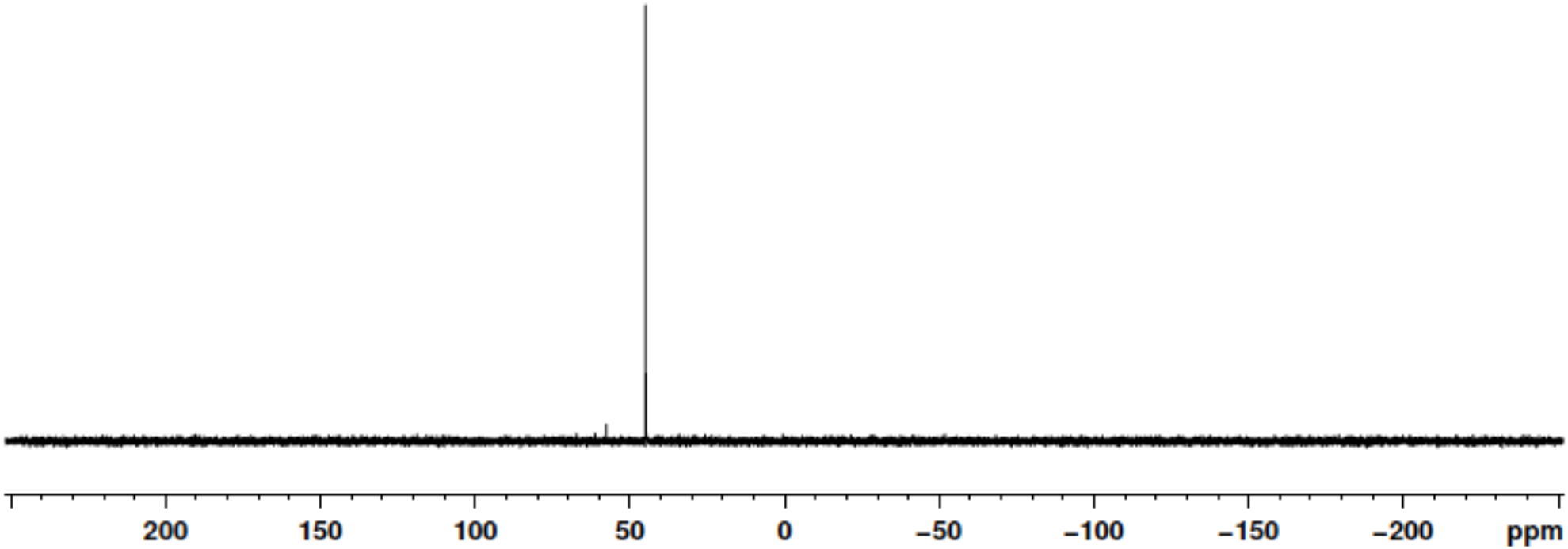
7.692 7.430 7.261 7.243 7.218 7.185 7.178 7.165 7.158 7.065 7.045 6.722 6.701 5.032 2.886 2.874 2.847 2.829 2.767 2.525 2.215 2.196 2.178 2.172 2.058 1.906 1.826 1.802 1.789 1.763 1.746 1.730 1.714 1.707 1.700 1.676 1.668 1.644 1.554 1.380 1.255 1.230 1.209 1.190 1.161 1.125 1.093 1.082 1.061 1.054 1.045 1.033 1.023 0.900 0.880 0.872 0.650 0.071 0.000



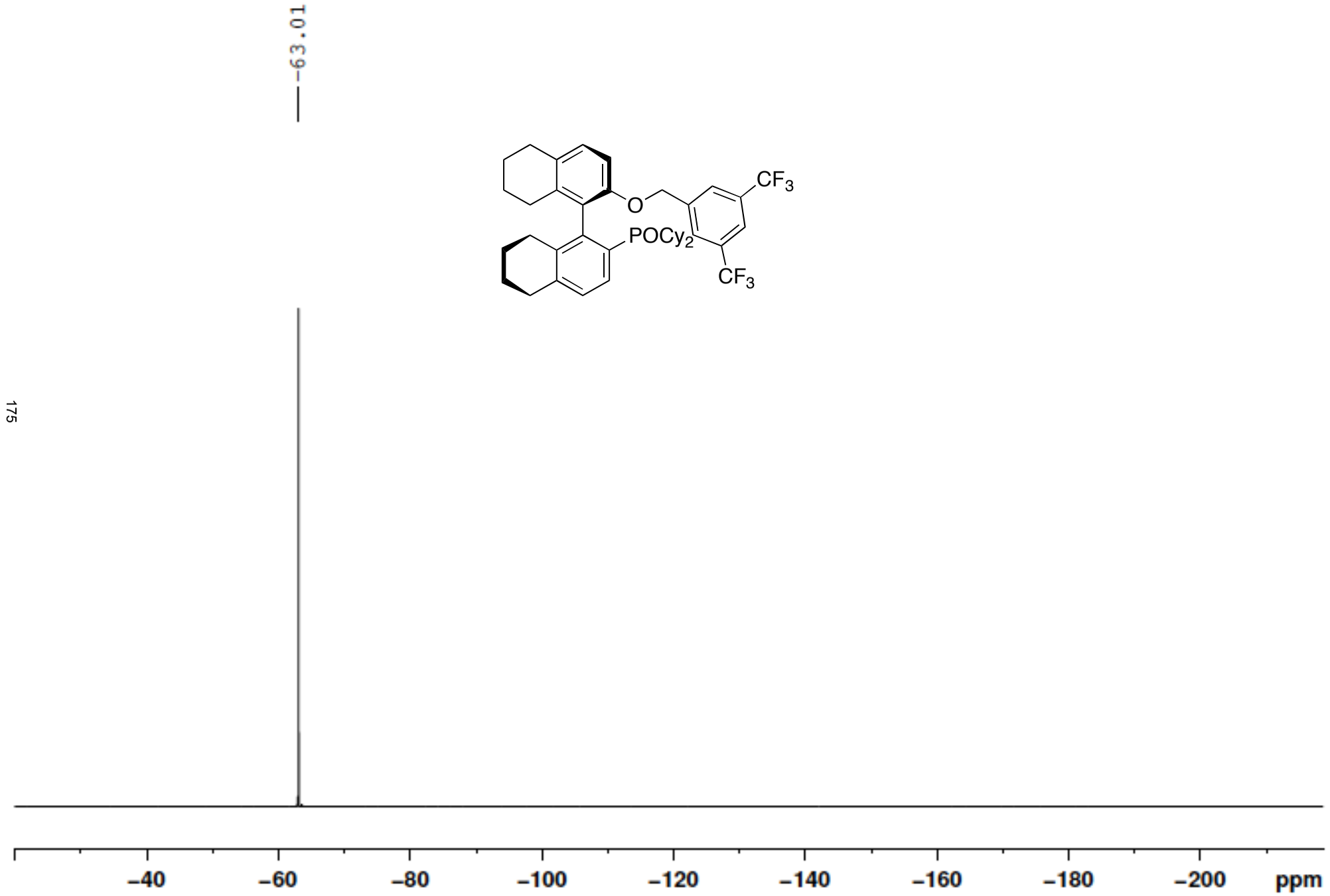
JF11-46-redo 31PNMR BBFO1 CDC13
2013-8-2



45.03

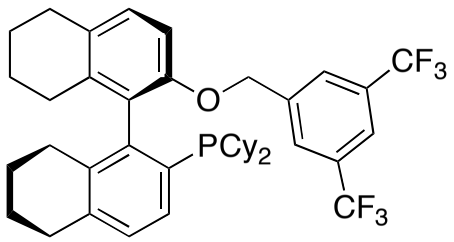


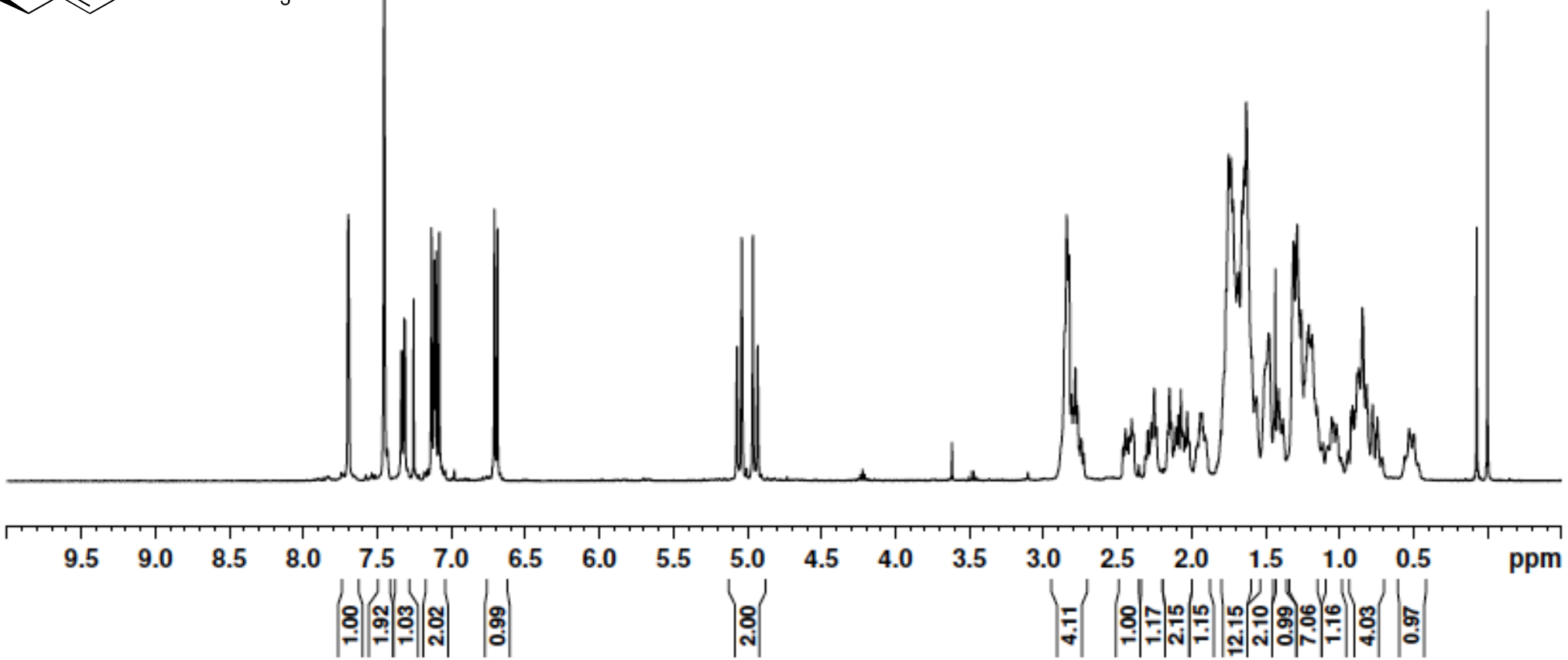
JF11-46 19FNMR BBFO1 CDC13
2013-8-2



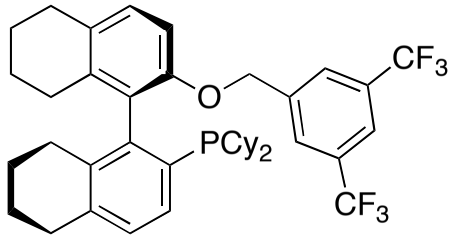
JF10-131 1HNMR, CDC13, BBFO1
2013-07-22

7.696 7.453 7.337 7.332 7.317 7.313 7.254 7.133 7.113 7.103 7.082 6.709 6.688 5.070 5.037 4.963 4.930 2.842 2.826 2.809 2.784 2.769 2.251 2.148 2.071 1.765 1.748 1.740 1.732 1.720 1.682 1.657 1.644 1.638 1.629 1.614 1.591 1.563 1.477 1.433 1.410 1.310 1.286 1.257 1.237 1.225 1.214 1.208 1.191 1.185 1.153 0.913 0.879 0.869 0.846 0.816 0.775 0.072 0.000

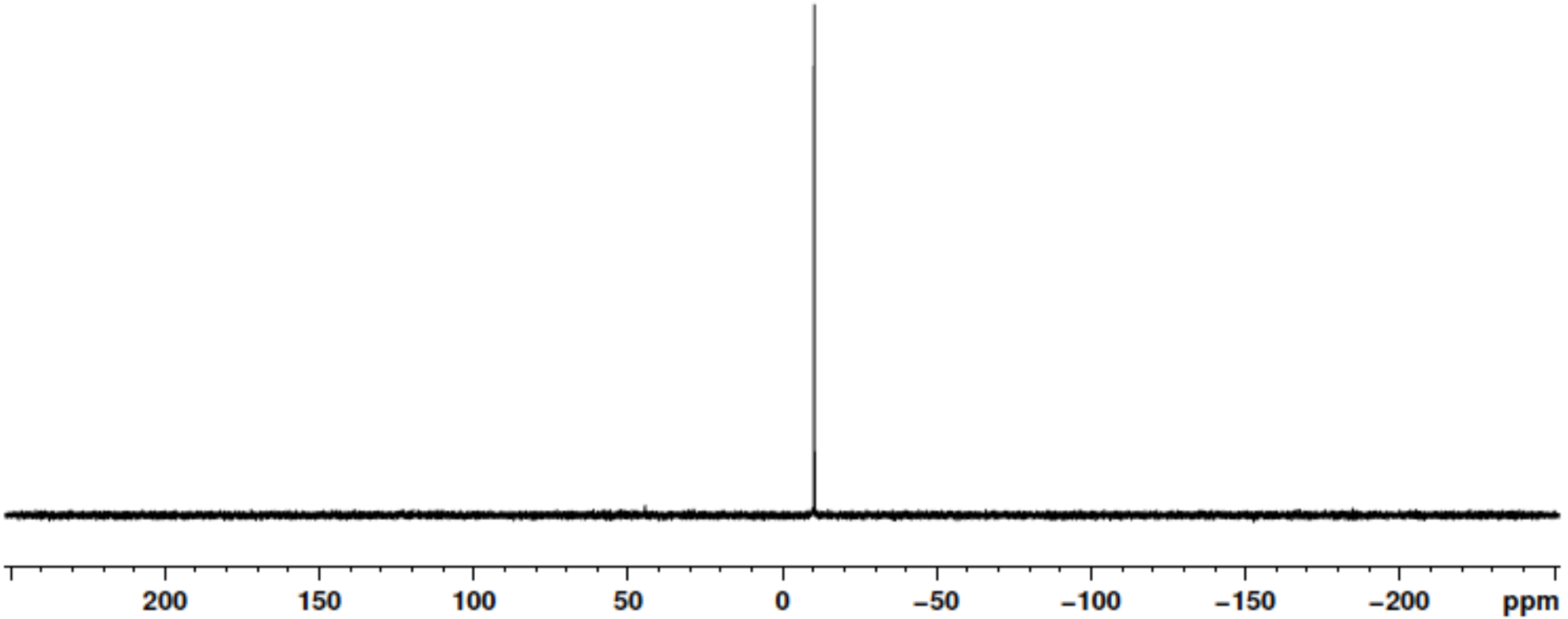




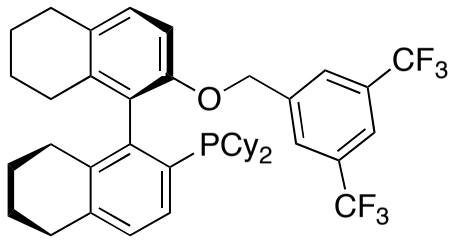
JF11-49 31PNMR, CDCl3, BBFO1
2013-07-22



-10.25

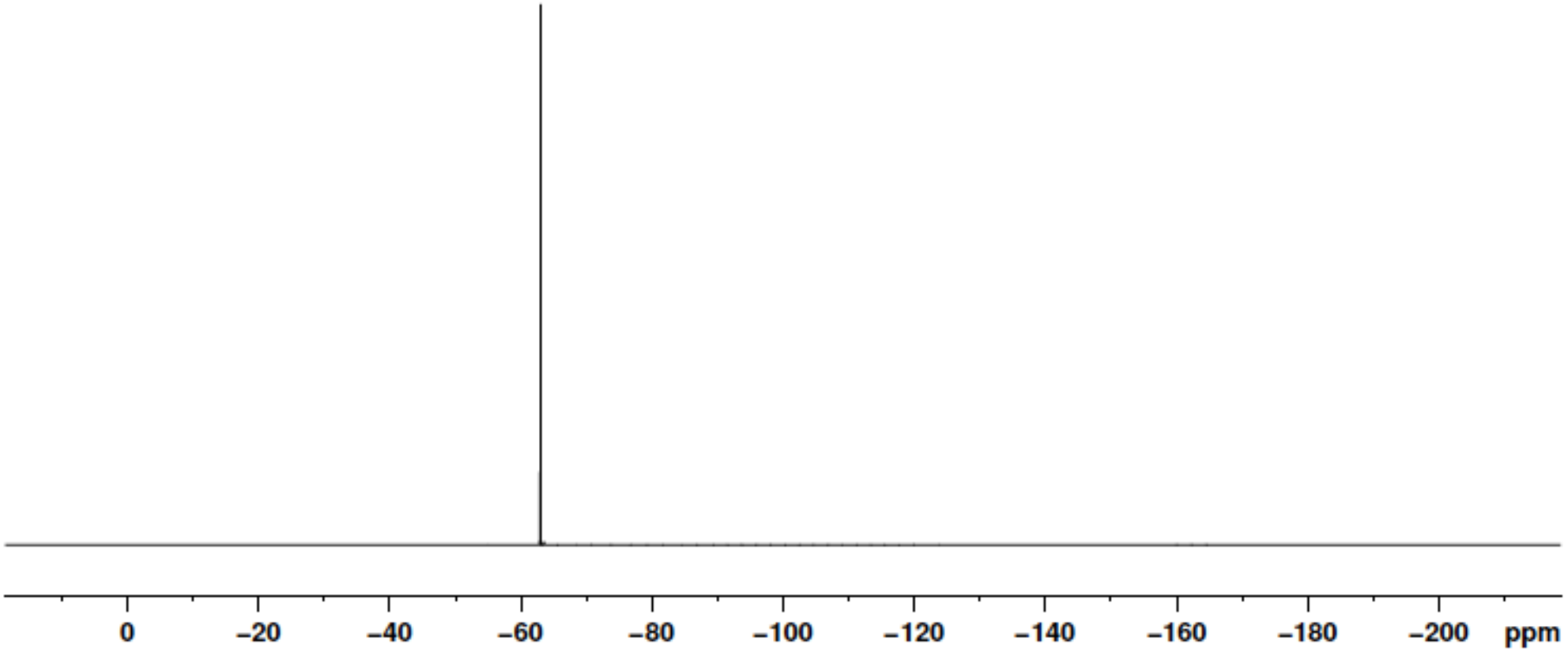


JF11-49 19FNMR, CDCl3, BBFO1
2013-07-22

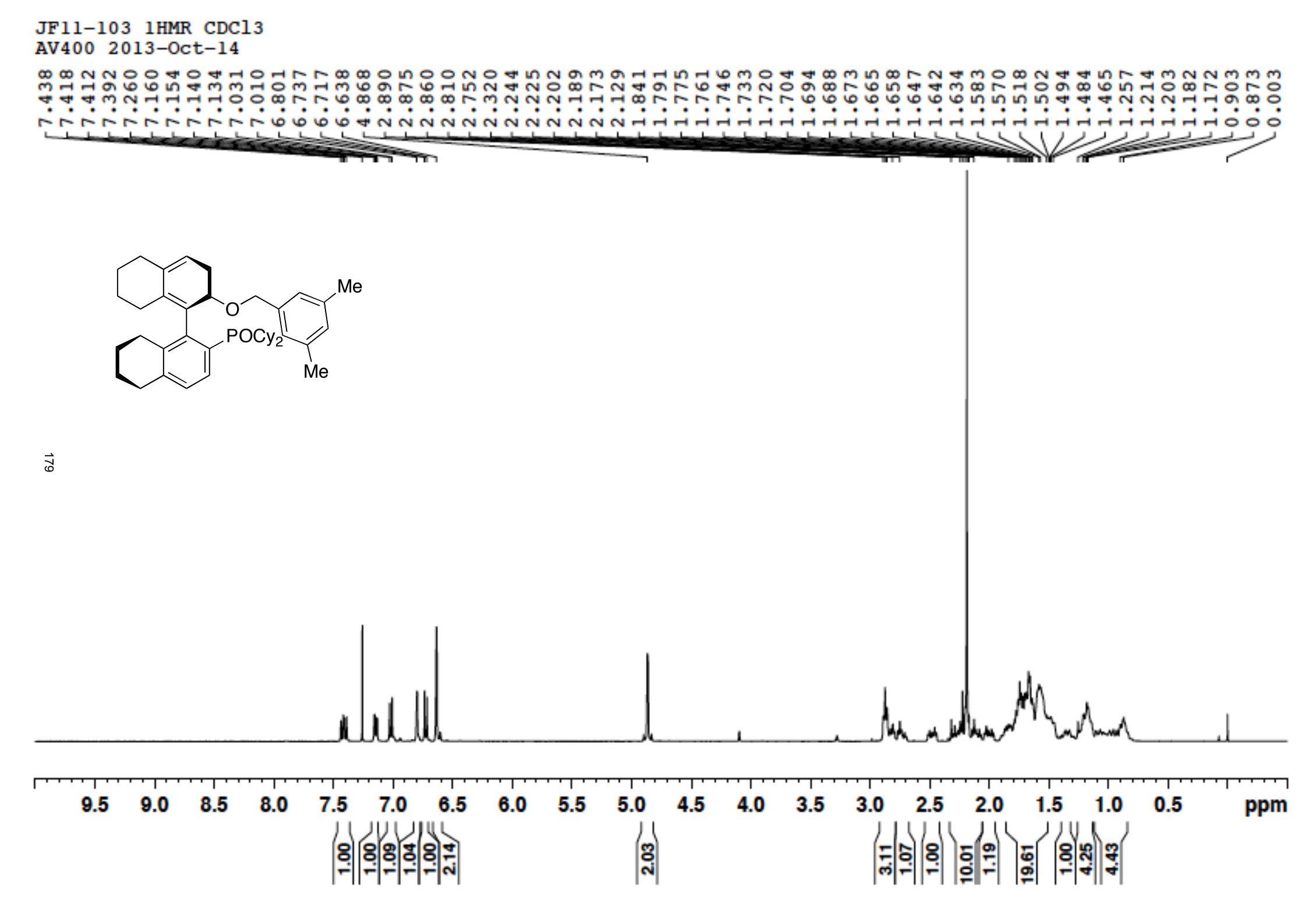


-63.03

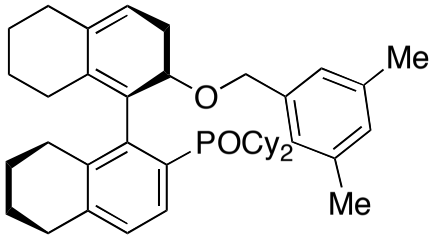
178



JF11-103 1HMR CDCl3
AV400 2013-Oct-14



JF11-103 31PNMR CDCl3
AV400 2013-Oct-14



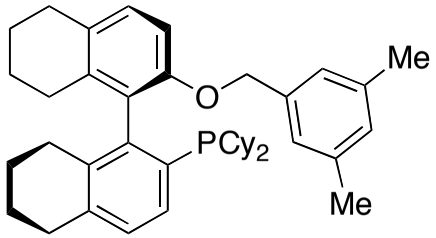
45.01

180

200 150 100 50 0 −50 −100 −150 −200 ppm

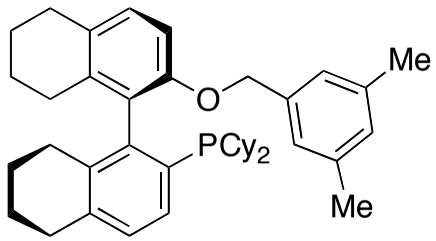
JF11-106 1HNMR CDCl3
AV400 2013-Oct-16

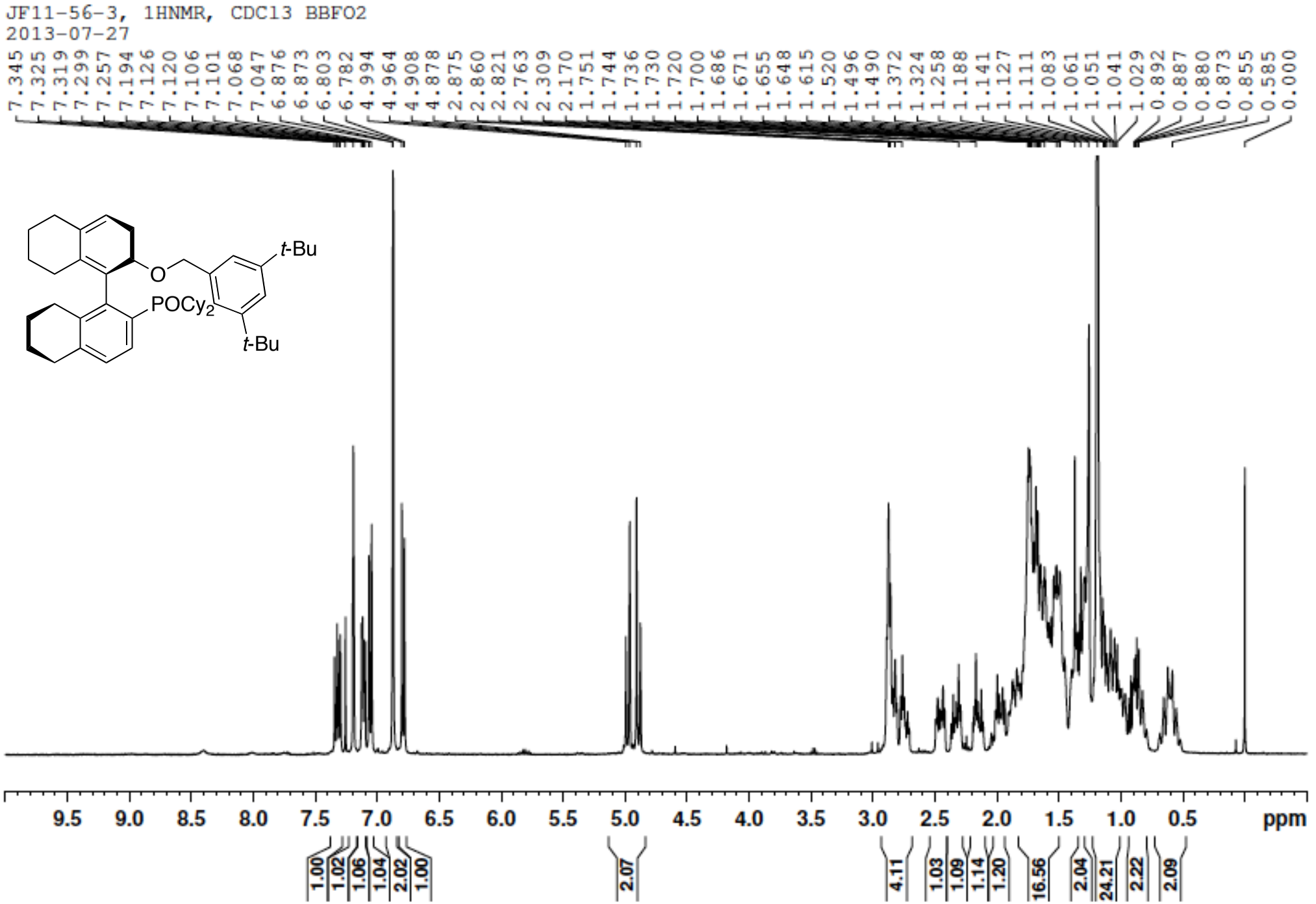
7.318 7.314 7.299 7.295 7.243 7.084 7.064 7.041 7.020 6.799 6.700 6.678 4.889 4.858 4.824 4.793 2.852 2.837 2.822 2.798 2.751 2.367 2.352 2.342 2.324 2.195 2.118 1.977 1.748 1.723 1.711 1.698 1.691 1.683 1.672 1.666 1.656 1.619 1.598 1.582 1.558 1.470 1.442 1.409 1.268 1.255 1.241 1.213 1.188 1.112 1.058 1.037 1.027 0.981 0.951 0.927 0.922 0.916 0.884



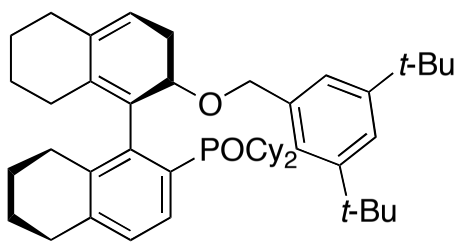
181

JF11-106 31PNMR CDCl3
AV400 2013-Oct-16

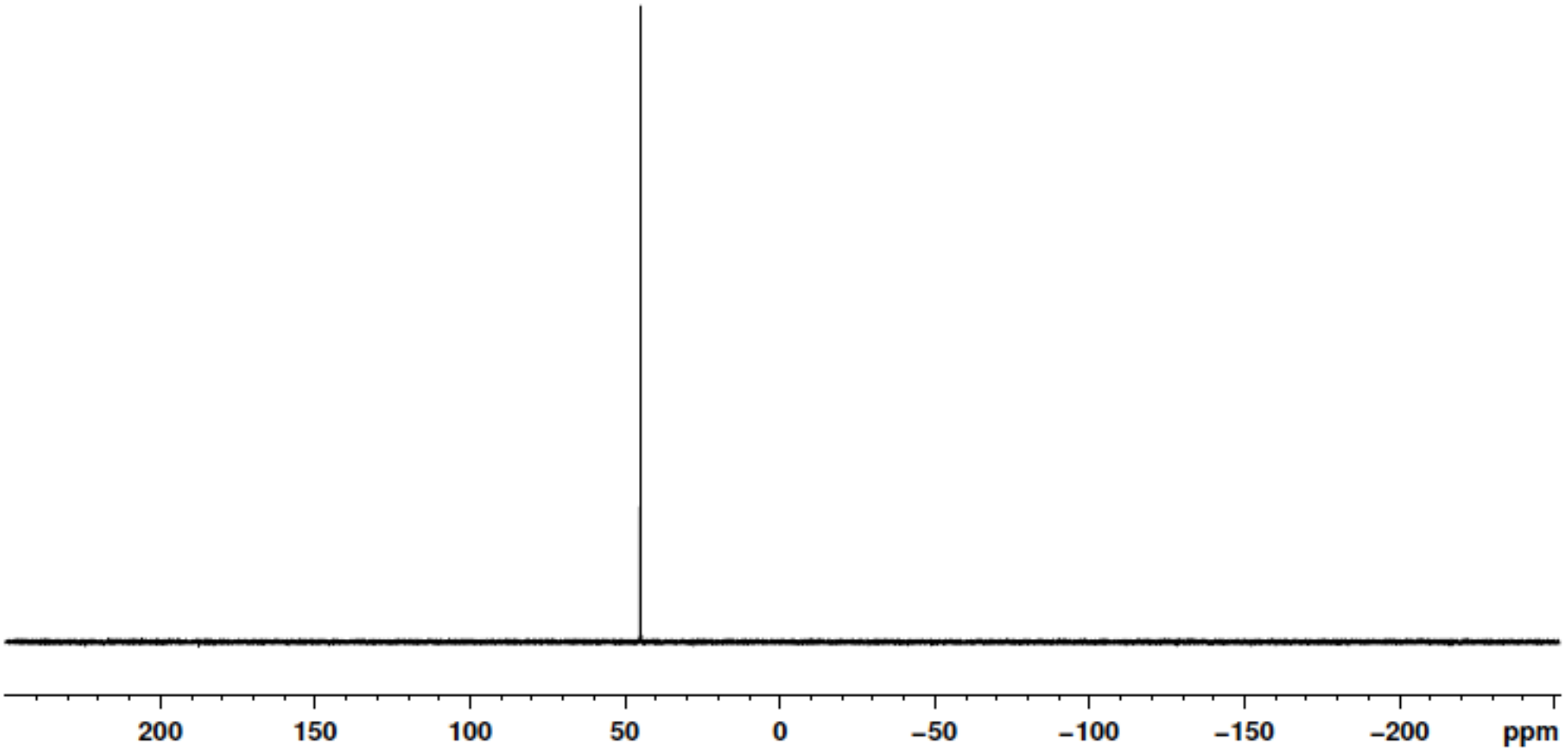


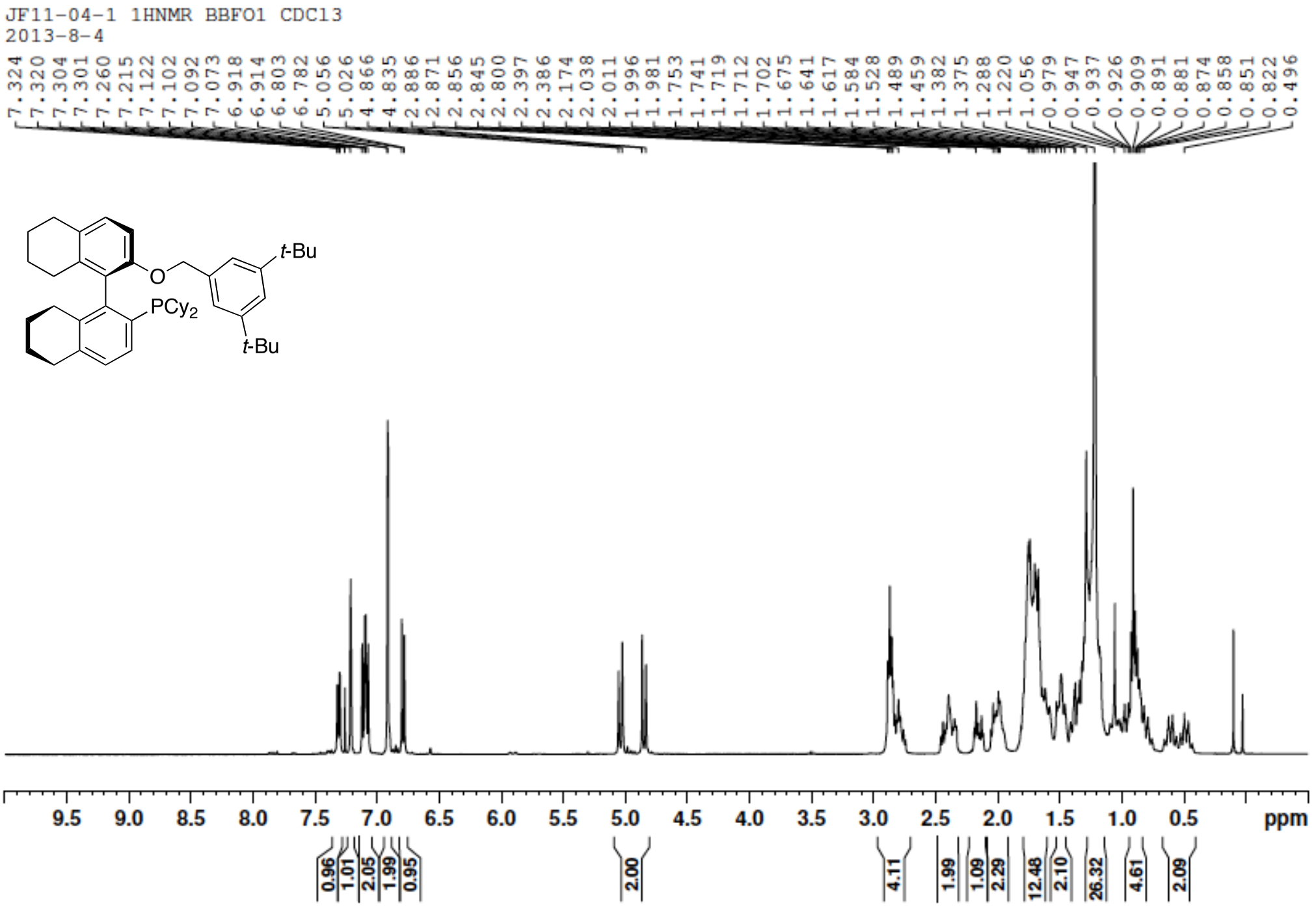

JF11-56-3, 1HNMR, CDC13 BBFO2
2013-07-27
7.345 7.325 7.319 7.299 7.257 7.194 7.126 7.120 7.106 7.101 7.068 7.047 6.876 6.873 6.803 6.782 4.994 4.964 4.908 4.878 2.875 2.860 2.821 2.763 2.309 2.170 1.751 1.744 1.736 1.730 1.720 1.700 1.686 1.671 1.655 1.648 1.615 1.520 1.496 1.490 1.372 1.324 1.258 1.188 1.141 1.127 1.111 1.083 1.061 1.051 1.041 1.029 0.892 0.887 0.880 0.873 0.855 0.585 0.000
O
POCy2
t-Bu
t-Bu
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 ppm
1.00 1.02 1.06 1.04 2.02 1.00
2.07
4.11 1.03 1.09 1.14 1.20 16.56 2.04 24.21 2.22 2.09

JF11-56-3, 31PNMR, CDC13 BBFO2
2013-07-27

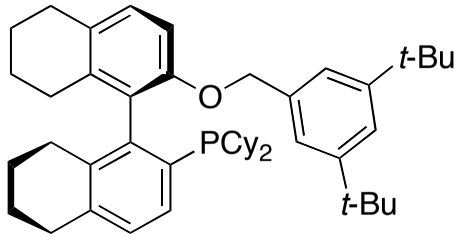


44.89

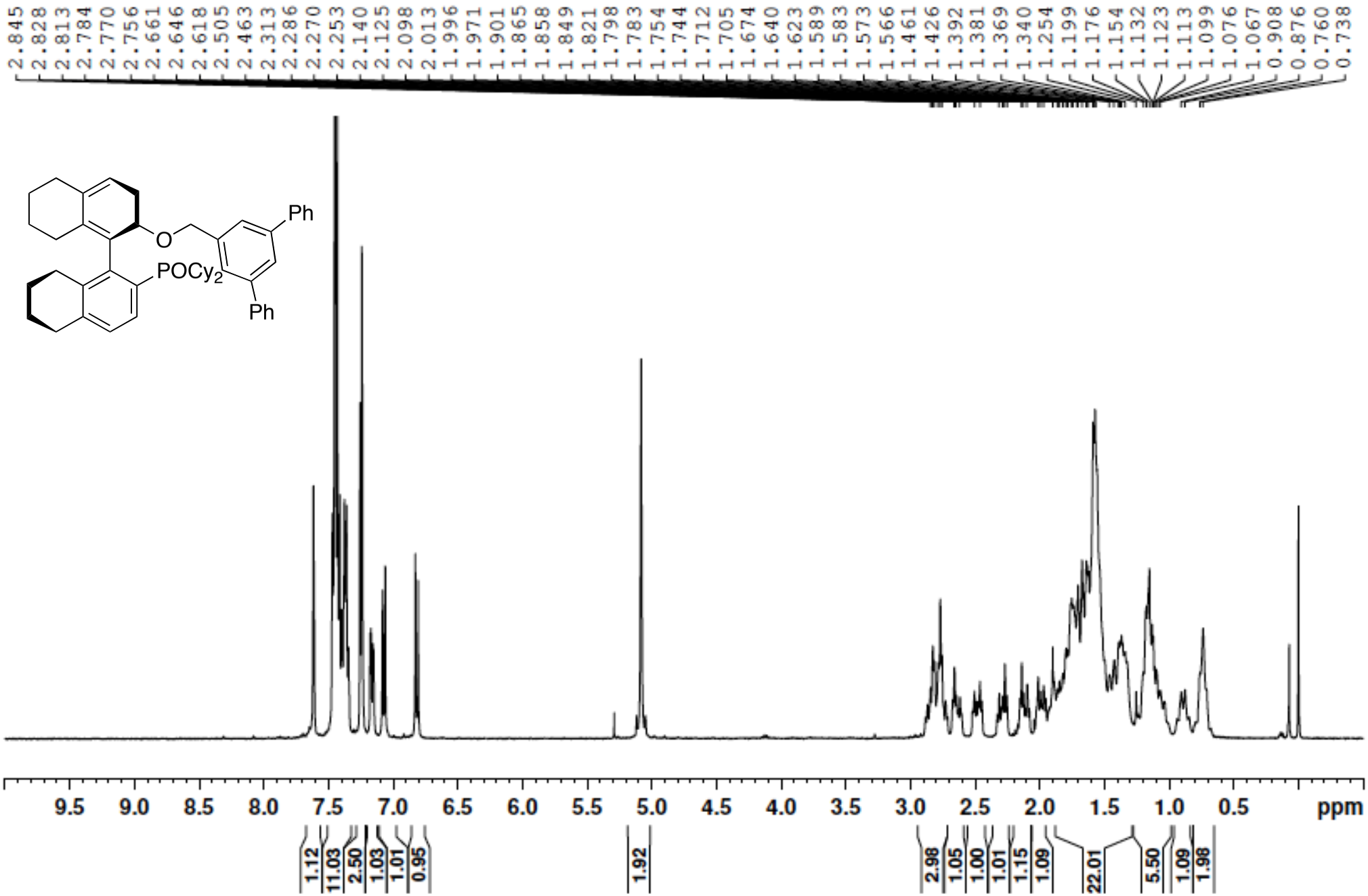



JF11-04-1 1HNMR BBFO1 CDC13
2013-8-4
7.324
7.320
7.304
7.301
7.260
7.215
7.122
7.102
7.092
7.073
6.918
6.914
6.803
6.782
5.056
5.026
4.866
4.835
2.886
2.871
2.856
2.845
2.800
2.397
2.386
2.174
2.038
2.011
1.996
1.981
1.753
1.741
1.719
1.712
1.702
1.675
1.641
1.617
1.584
1.528
1.489
1.459
1.382
1.375
1.288
1.220
1.056
0.979
0.947
0.937
0.926
0.909
0.891
0.881
0.874
0.858
0.851
0.822
0.496
O
PCy2
t-Bu
t-Bu
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
ppm
0.96
1.01
2.05
1.99
0.95
2.00
4.11
1.99
1.09
2.29
12.48
2.10
26.32
4.61
2.09

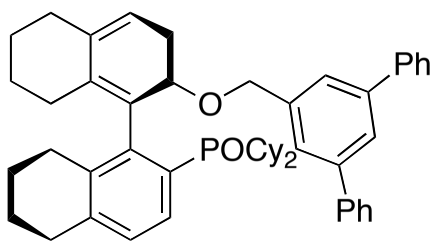
JF11-04-1 31PNMR BBFO1 CDCl3
2013-8-4

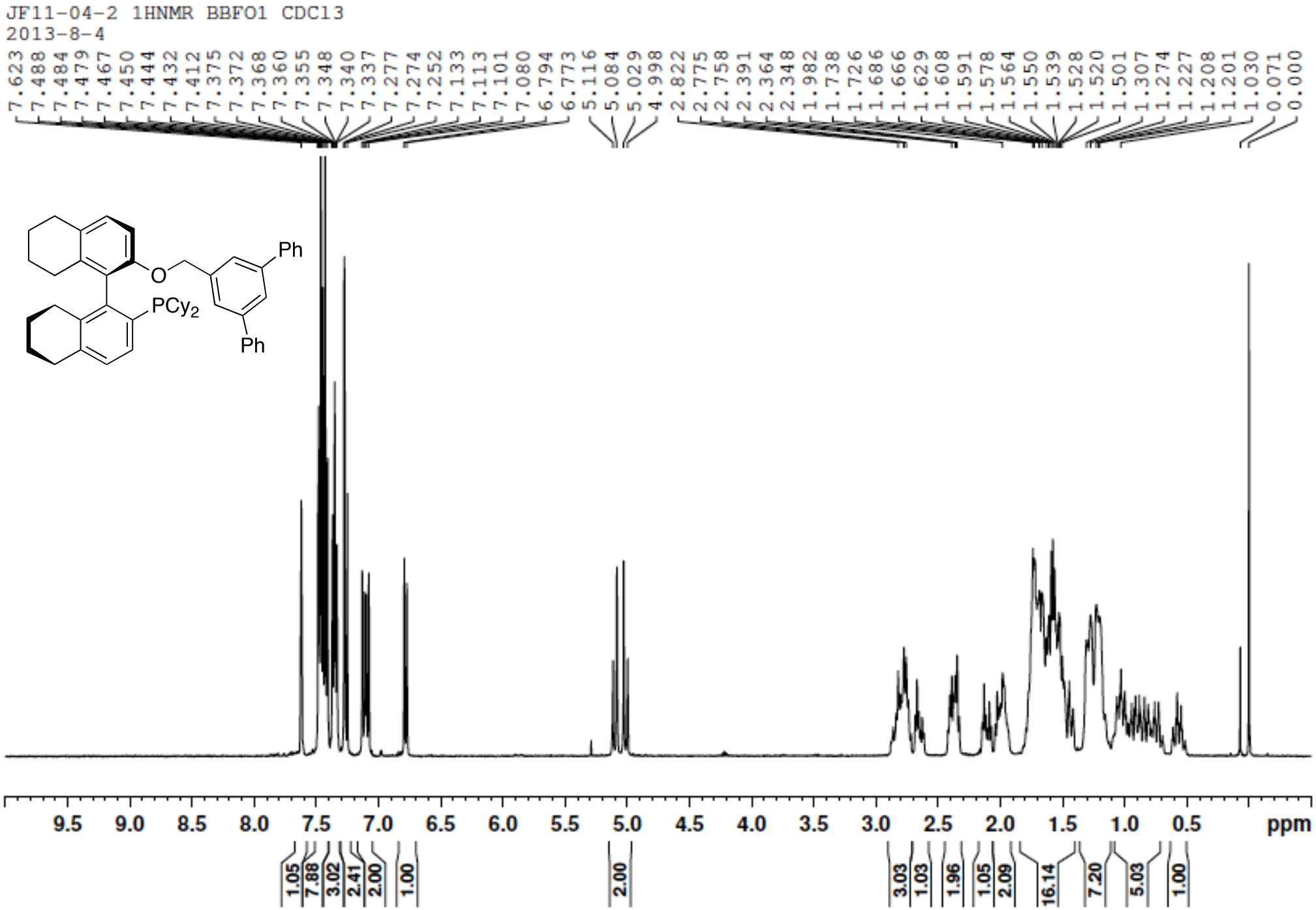


JF11-03-2 CDC13 1HNMR BBFO2
2013-08-02

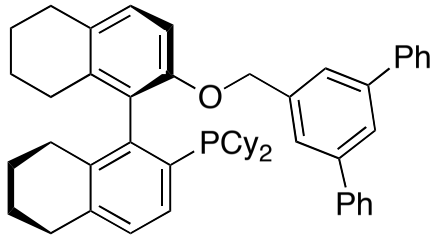


JF11-03-2 CDCl3 31PNMR BBFO2
2013-08-02



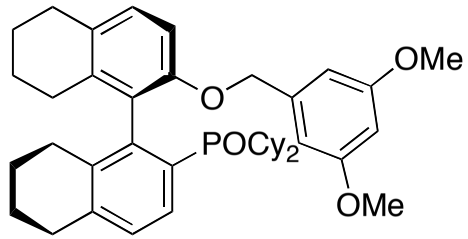

JF11-04-2 1HNMR BBFO1 CDC13
2013-8-4
7.623
7.488
7.484
7.479
7.467
7.450
7.444
7.432
7.412
7.375
7.372
7.368
7.360
7.355
7.348
7.340
7.337
7.277
7.274
7.252
7.133
7.113
7.101
7.080
6.794
6.773
5.116
5.084
5.029
4.998
2.822
2.775
2.758
2.391
2.364
2.348
1.982
1.738
1.726
1.686
1.666
1.629
1.608
1.591
1.578
1.564
1.550
1.539
1.528
1.520
1.501
1.307
1.274
1.227
1.208
1.201
1.030
0.071
0.000
O
PCy2
Ph
Ph
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
ppm
1.05
7.88
3.02
2.41
2.00
1.00
2.00
3.03
1.03
1.96
1.05
2.09
16.14
7.20
5.03
1.00

JF11-04-2 31PNMR BBFO1 CDC13
2013-8-4



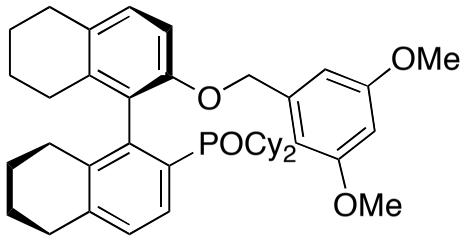
BBFO1 2013-09-25

7.398 7.378 7.372 7.352 7.261 7.112 7.106 7.092 7.087 7.042 7.021 6.742 6.722 6.276 6.270 6.265 6.229 6.223 4.905 3.614 2.870 2.855 2.839 2.829 2.811 2.796 2.767 2.752 2.260 2.150 1.836 1.809 1.786 1.771 1.755 1.741 1.725 1.707 1.700 1.665 1.651 1.639 1.607 1.587 1.564 1.526 1.479 1.454 1.254 1.189 1.168 1.159 1.147 1.140 1.109 0.865 0.841 0.071 0.000



191

JF11-81-2 31PNMR CDCl3
BBFO1 2013-09-22

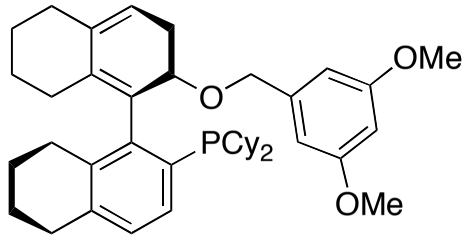


44.75

200 150 100 50 0 −50 −100 −150 −200 ppm

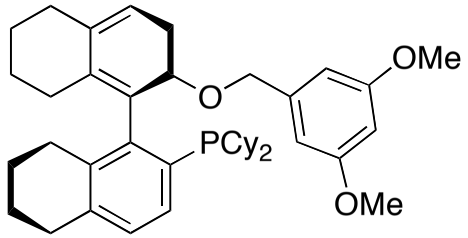
JF11-82 1HNMR CDCl3
AV400 2013-09-26

7.333 7.329 7.314 7.309 7.260 7.082 7.061 7.053 7.034 6.730 6.709 6.287 6.282 6.276 6.263 6.258 4.955 4.923 4.867 4.835 3.618 2.836 2.819 2.804 2.789 2.775 2.365 2.345 1.972 1.760 1.740 1.695 1.689 1.667 1.653 1.635 1.614 1.598 1.563 1.458 1.444 1.426 1.379 1.268 1.256 1.231 1.219 1.210 1.201 1.063 1.055 1.032 1.023 0.958 0.953 0.934 0.926 0.894 0.084



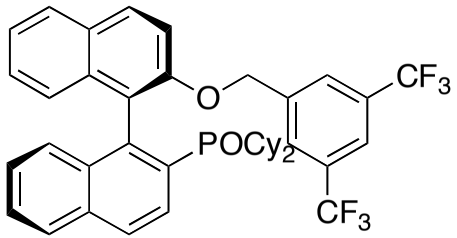
193

JF11-83 31PNMR CDCl3
AV400 2013-09-26



BBFO1 400MHz,
2013, 06, Dec

8.040 8.035 8.017 7.994 7.980 7.960 7.889 7.869 7.791 7.768 7.746 7.604 7.542 7.533 7.527 7.521 7.513 7.507 7.399 7.377 7.347 7.330 7.312 7.310 7.264 7.258 7.251 7.221 7.218 7.200 7.197 7.180 7.048 7.027 5.239 5.207 5.095 5.063 1.606 1.510 1.485 1.417 1.306 1.294 1.261 1.254 1.226 1.217 1.208 1.195 1.186 1.175 1.066 1.042 1.015 0.886 0.865 0.853 0.000

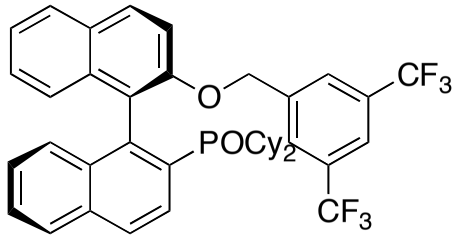


195

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 ppm

2.90 1.00 1.00 0.95 1.00 0.96 0.99 2.56 3.02 0.98 0.98 0.99 5.16 5.91 5.39 2.09 4.07

JF12-017,31P, CDCl3
BBFO1 400MHz,
2013, 06, Dec

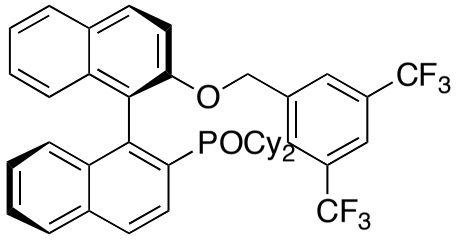


45.63

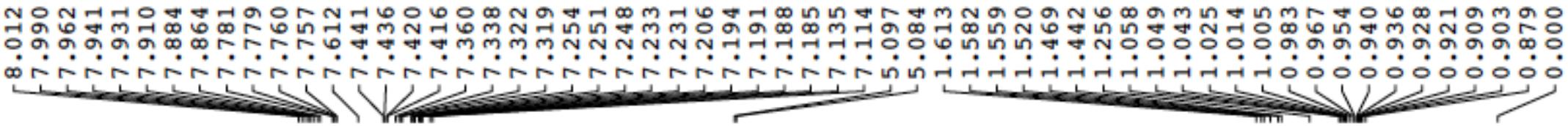
196

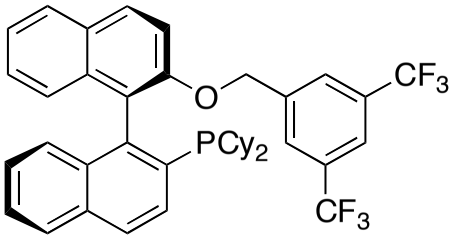
150 100 50 0 −50 −100 −150 ppm

BBF01 400MHz,
2013, 010, Dec



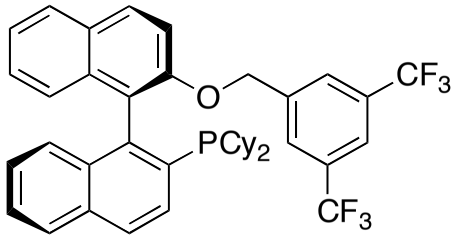
JF12-019,1H, CDCl3
BBFO1 400MHz,
2013, 08, Dec





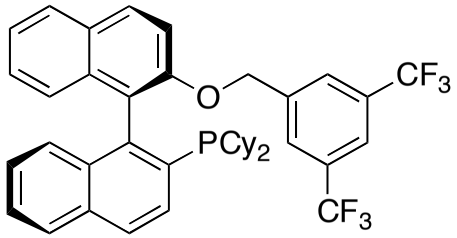
198

JF12-019,31P, CDCl3
BBFO1 400MHz,
2013, 09, Dec

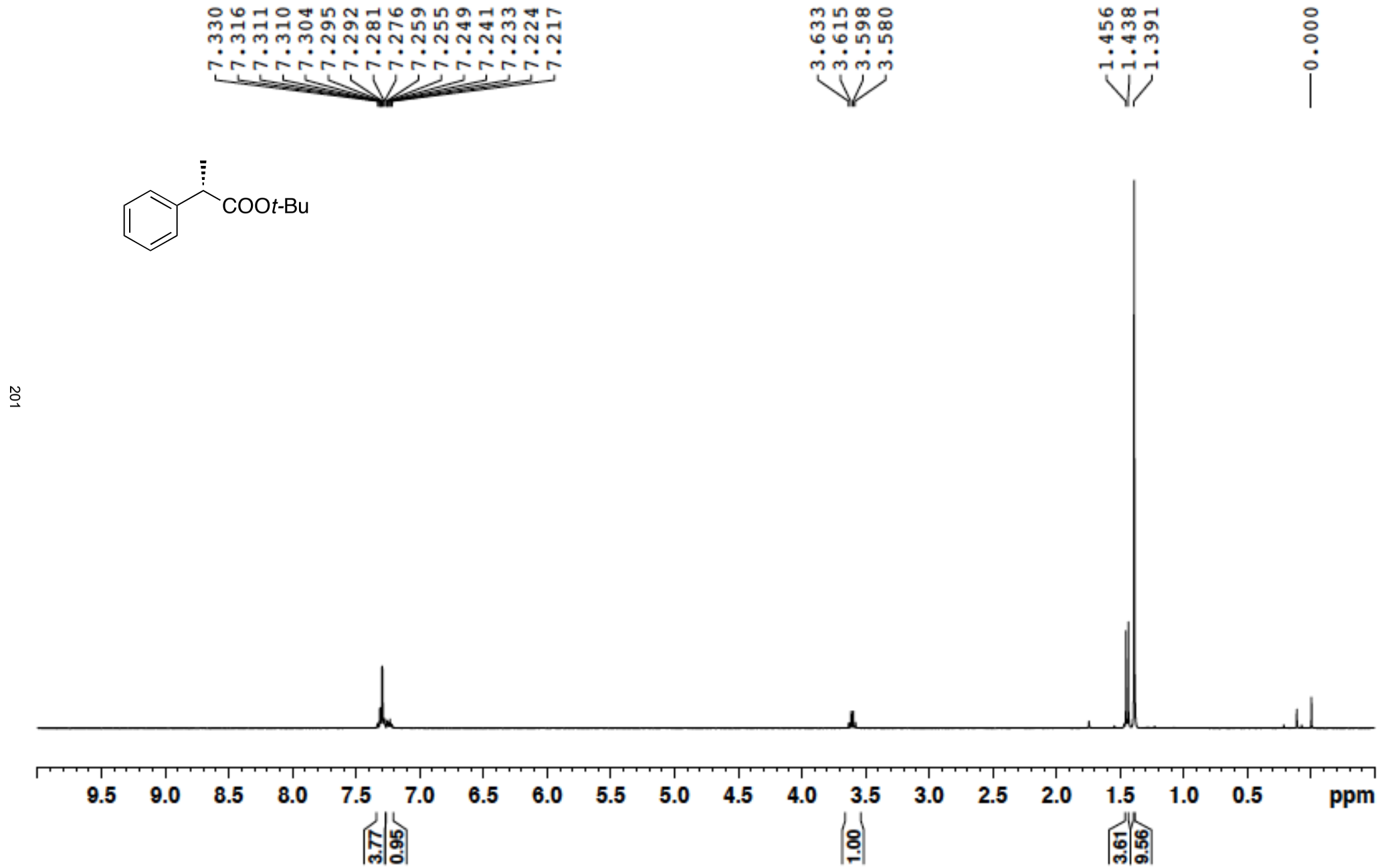


199

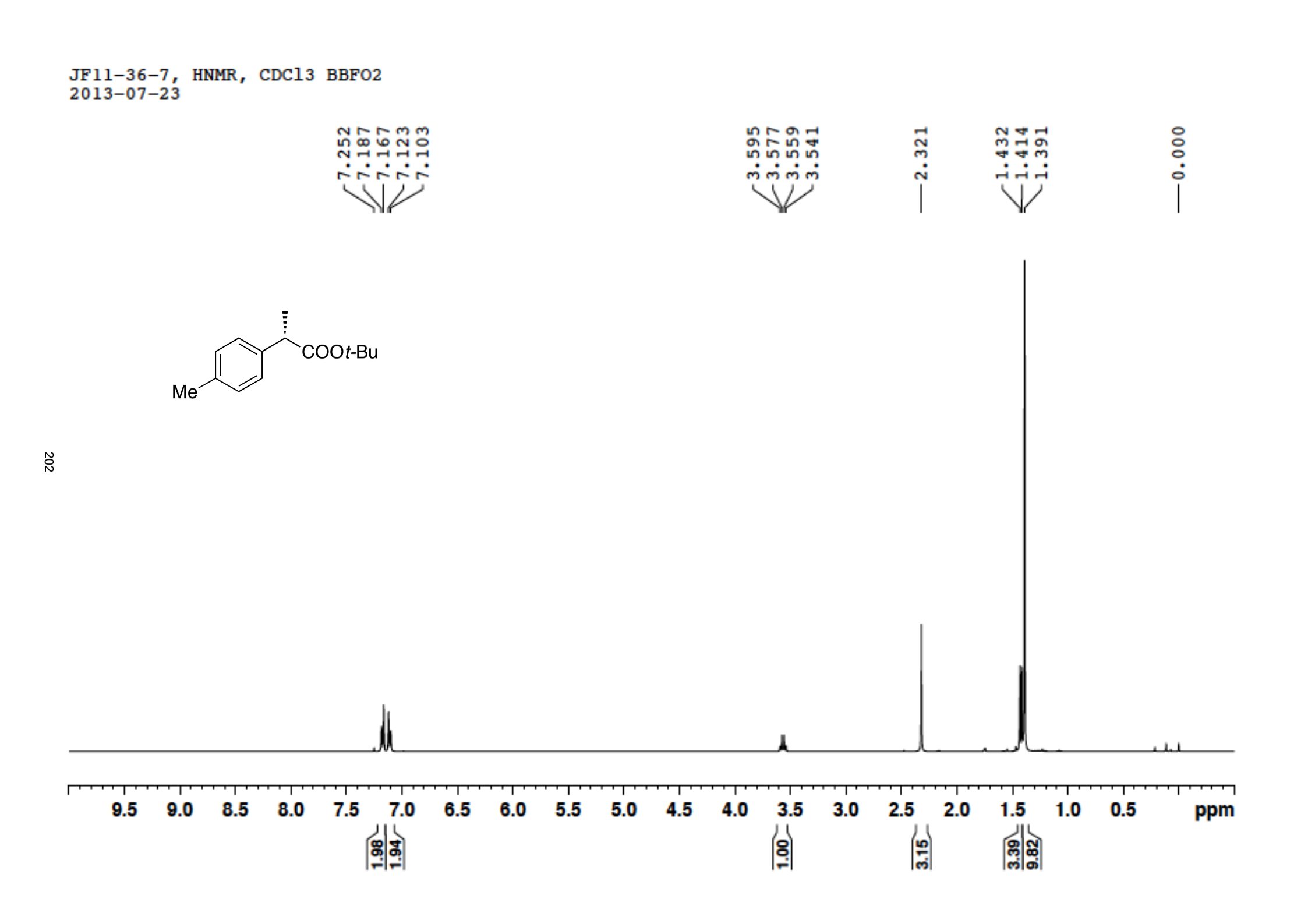
JF12-019,19F, CDCl3
BBFO1 400MHz,
2013, 09, Dec



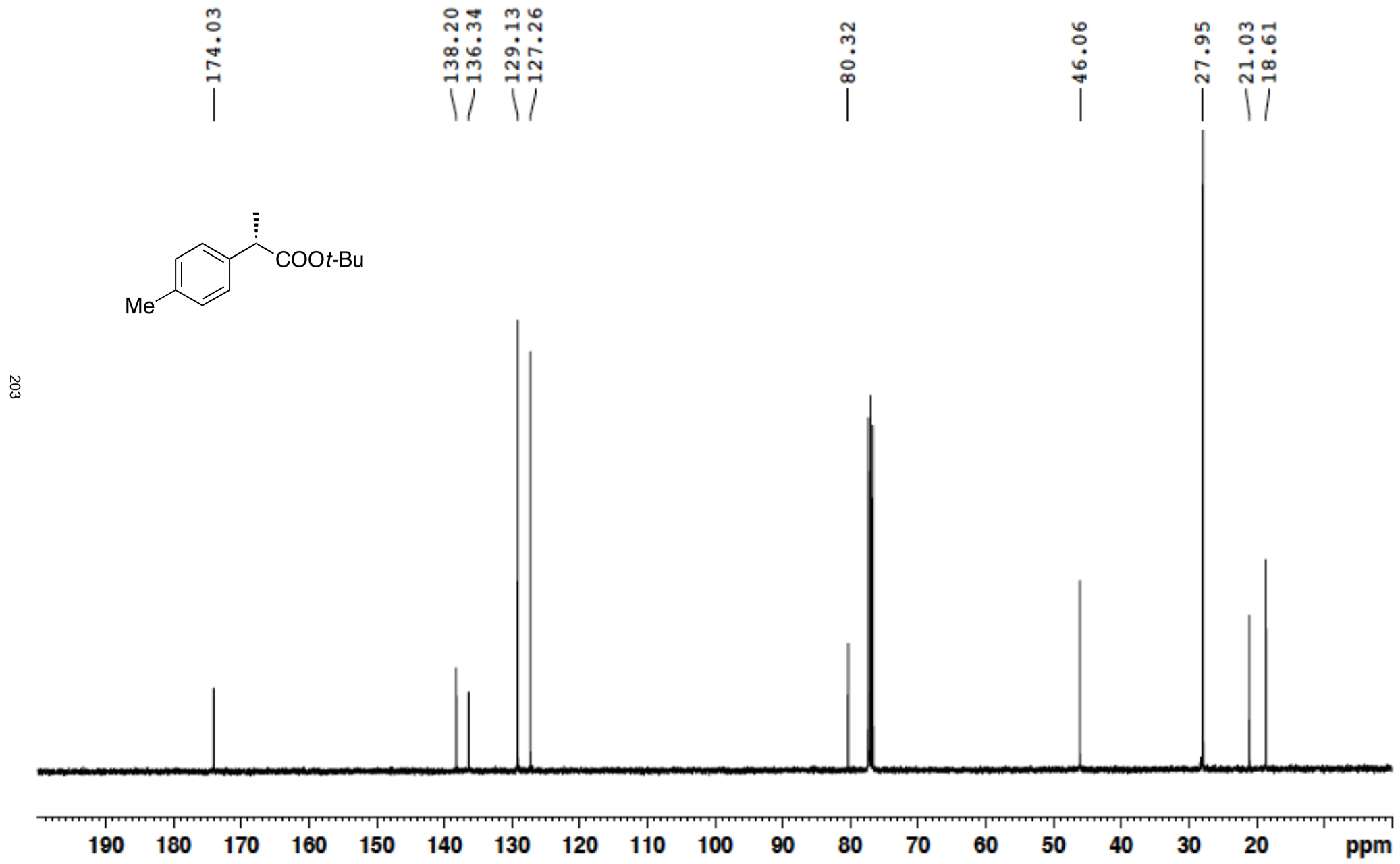
JF11-53-6 CDCl3 1HNMR BBFO2
2013-08-02



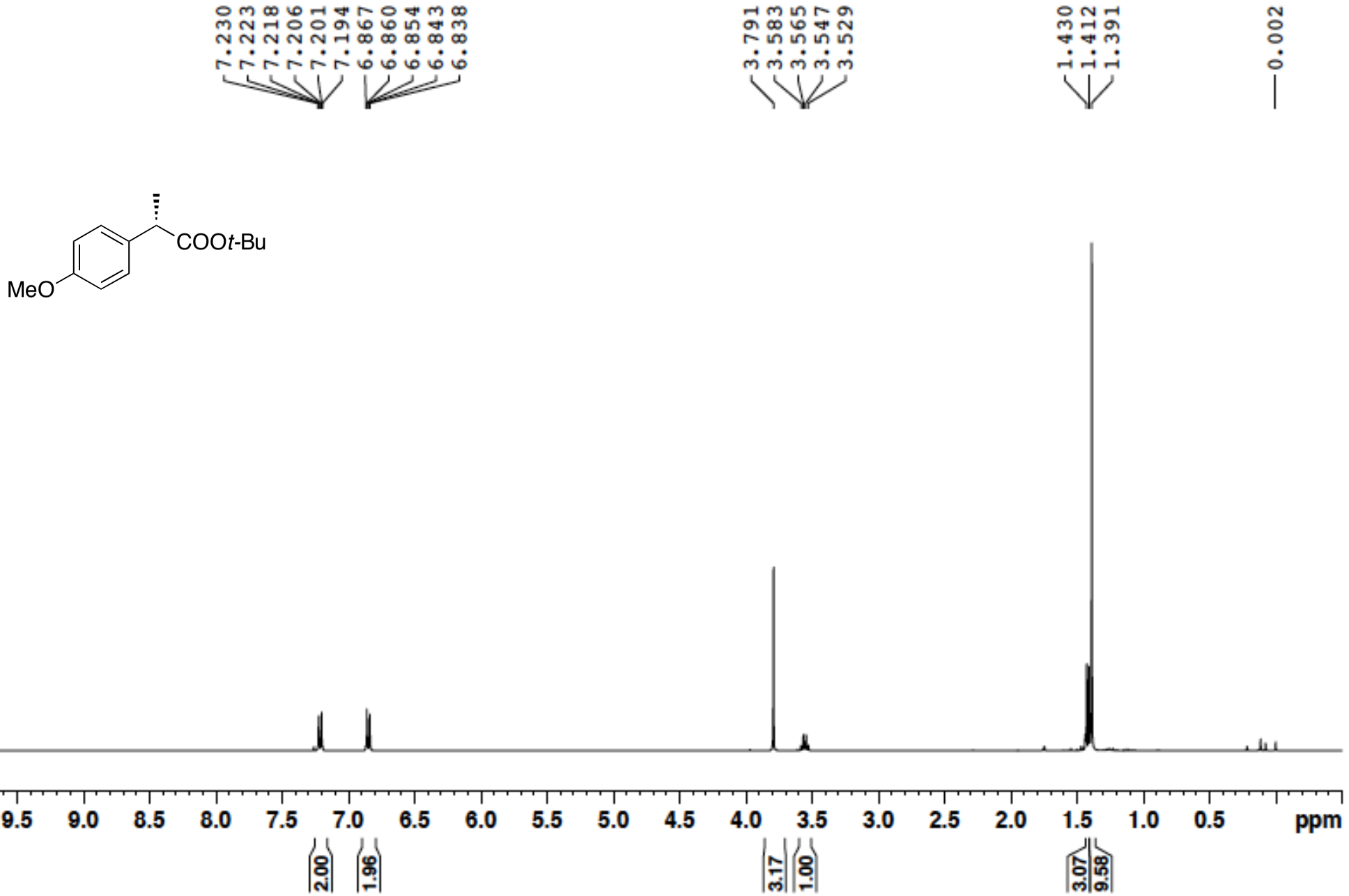
JF11-36-7, HNMR, CDCl3 BBFO2
2013-07-23



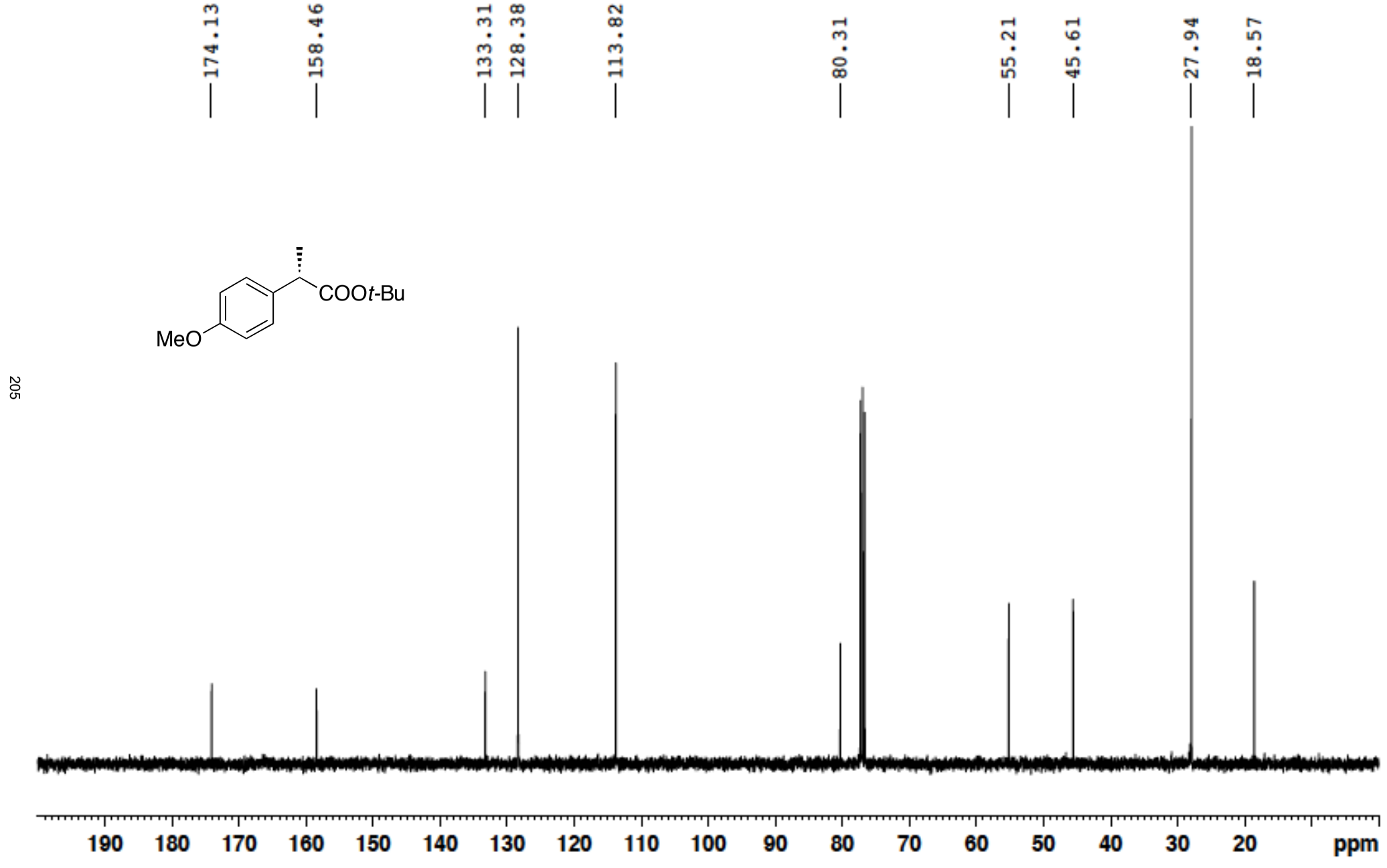
JF11-36-7 13CNMR, CDCl3, BBFO1
2013-07-23



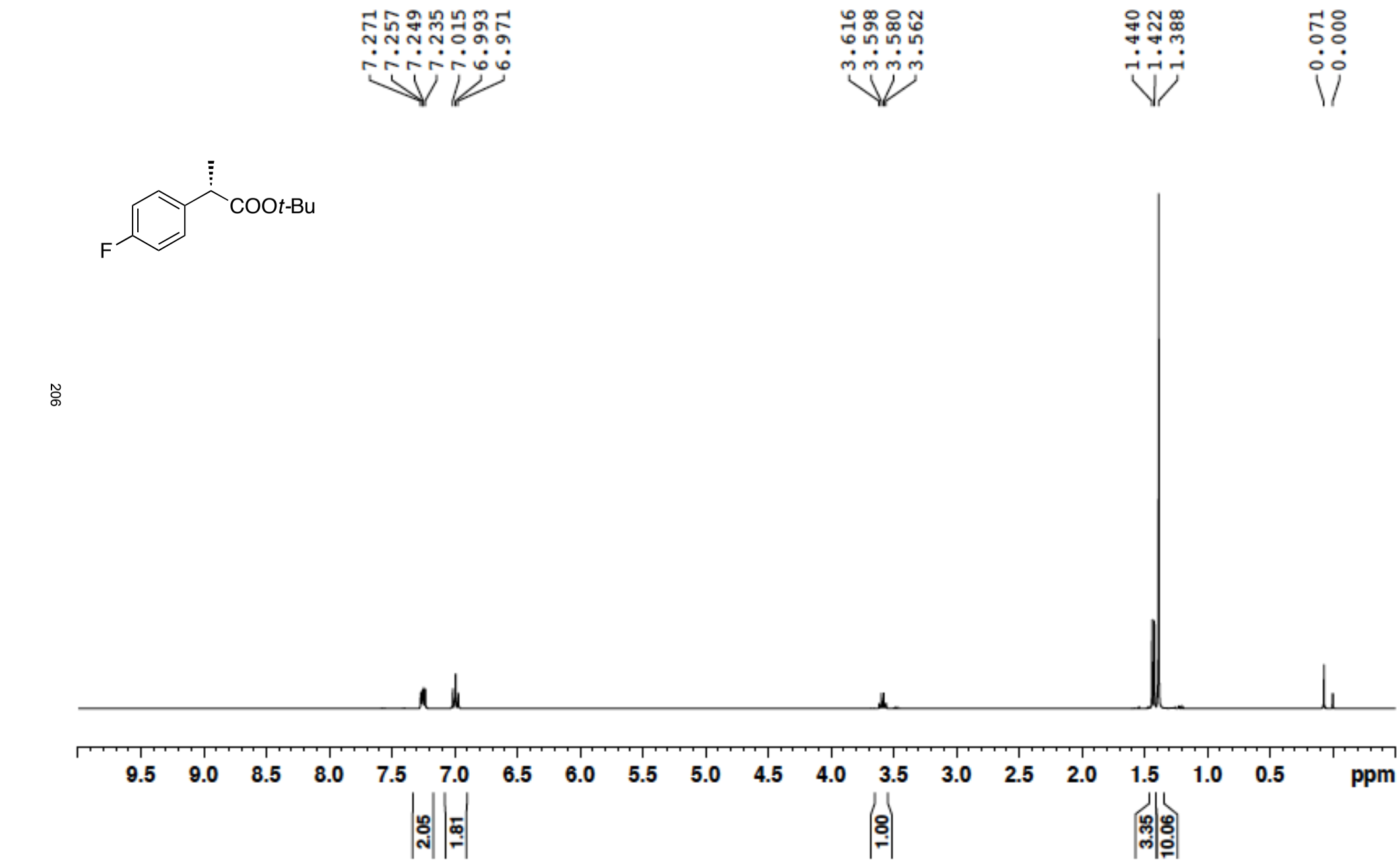
JF11-36-5, HNMR, CDCl3 BBFO2
2013-07-21



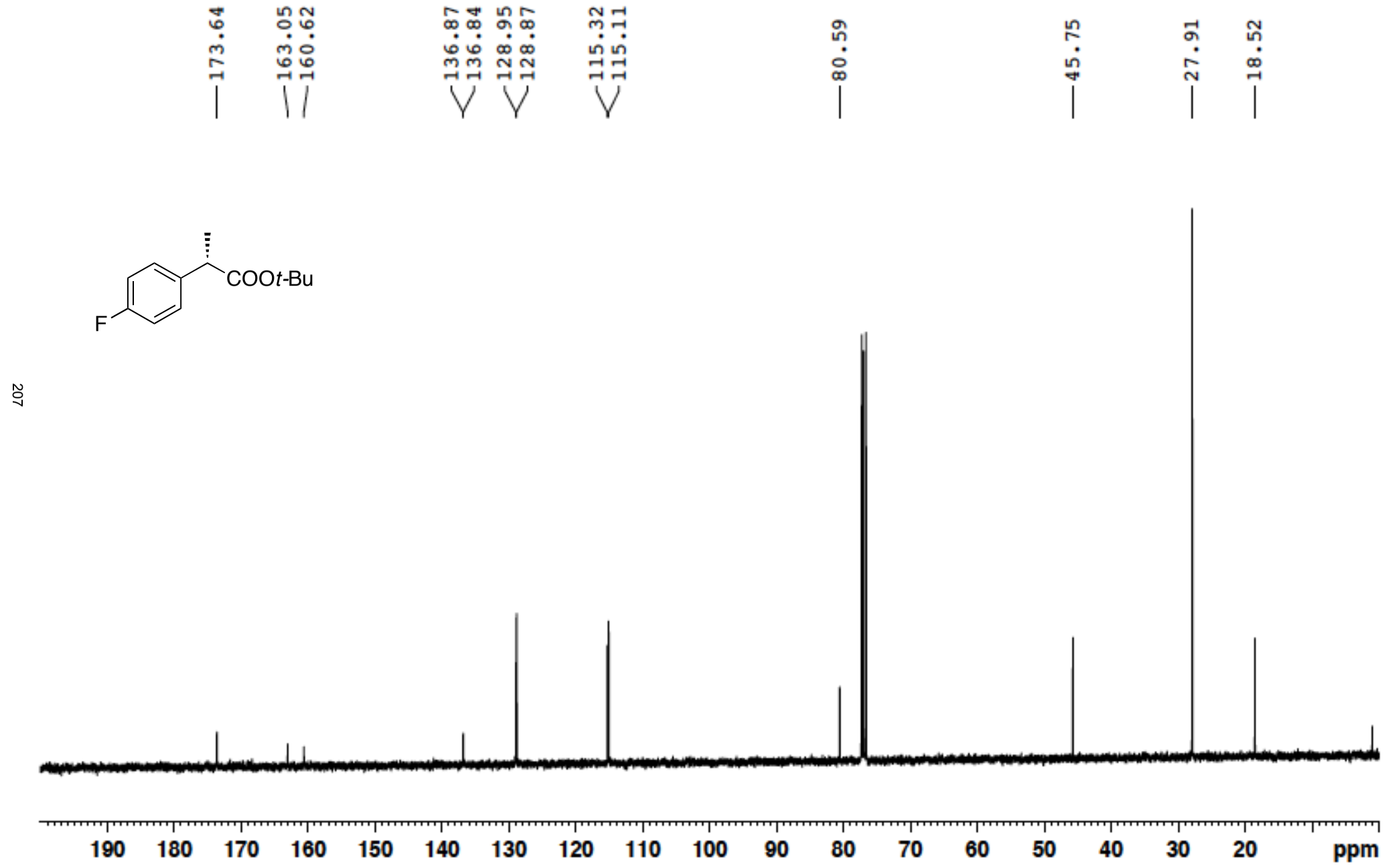
JF11-36-5 13CNMR, CDCl3, BBFO1
2013-07-22



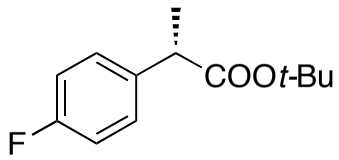
JF11-23-3, HNMR, CDCl3 BBFO2
2013-07-05



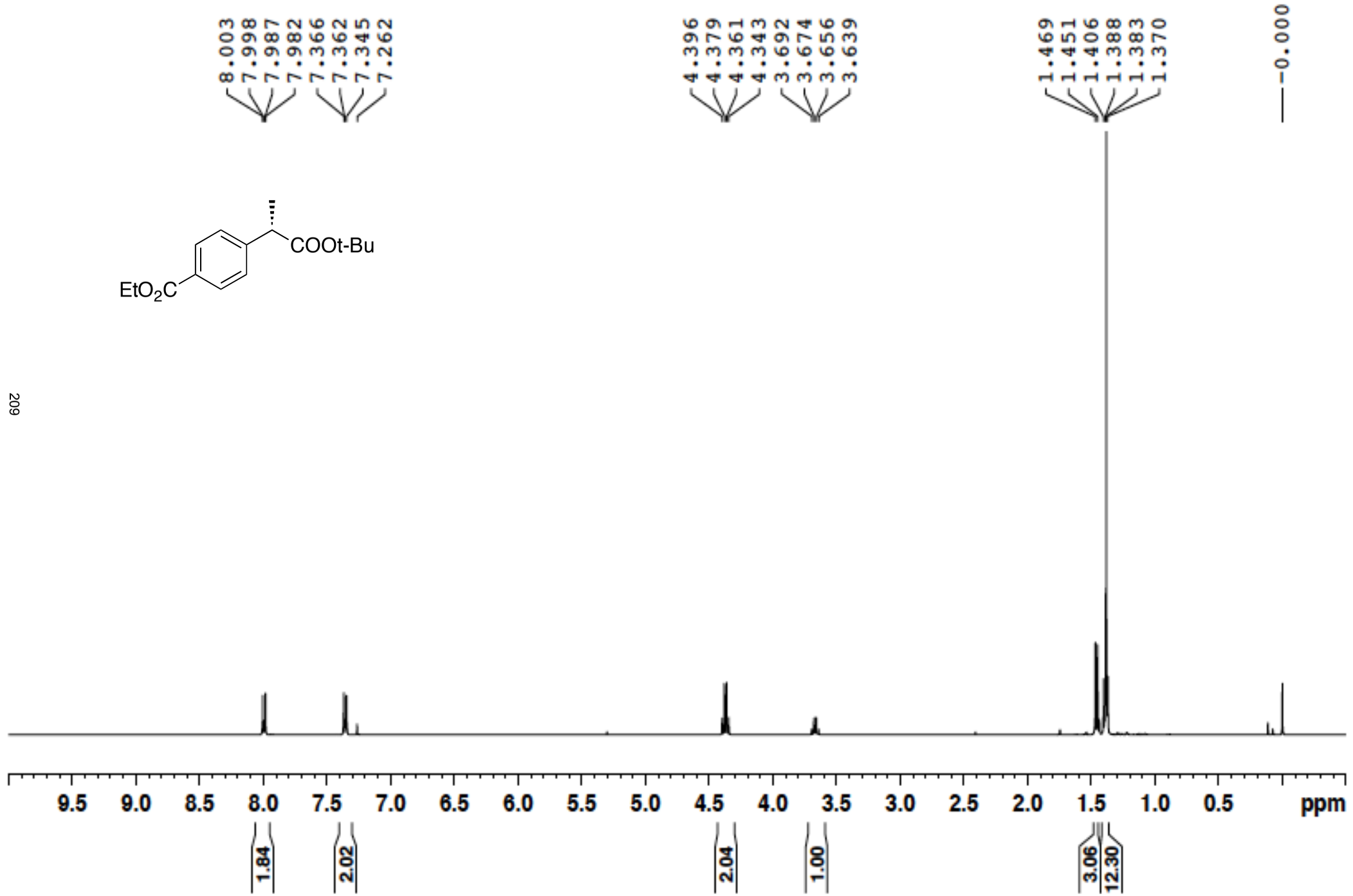
JF11-23-3, 13CNMR, CDCl3 BBFO2
2013-07-05



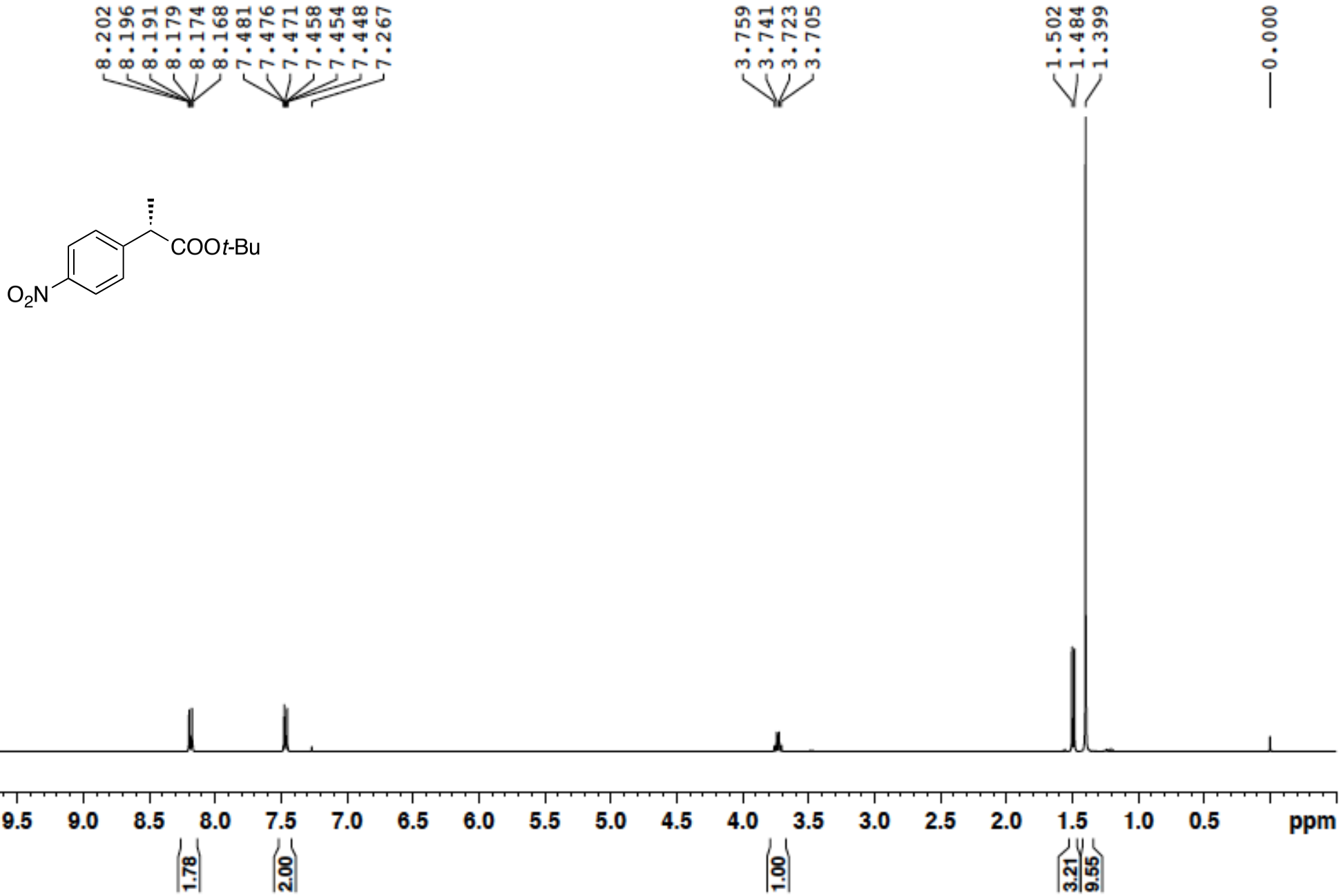
JF11-23-3-F 1HNMR BBFO1 CDCl3
2013-8-2



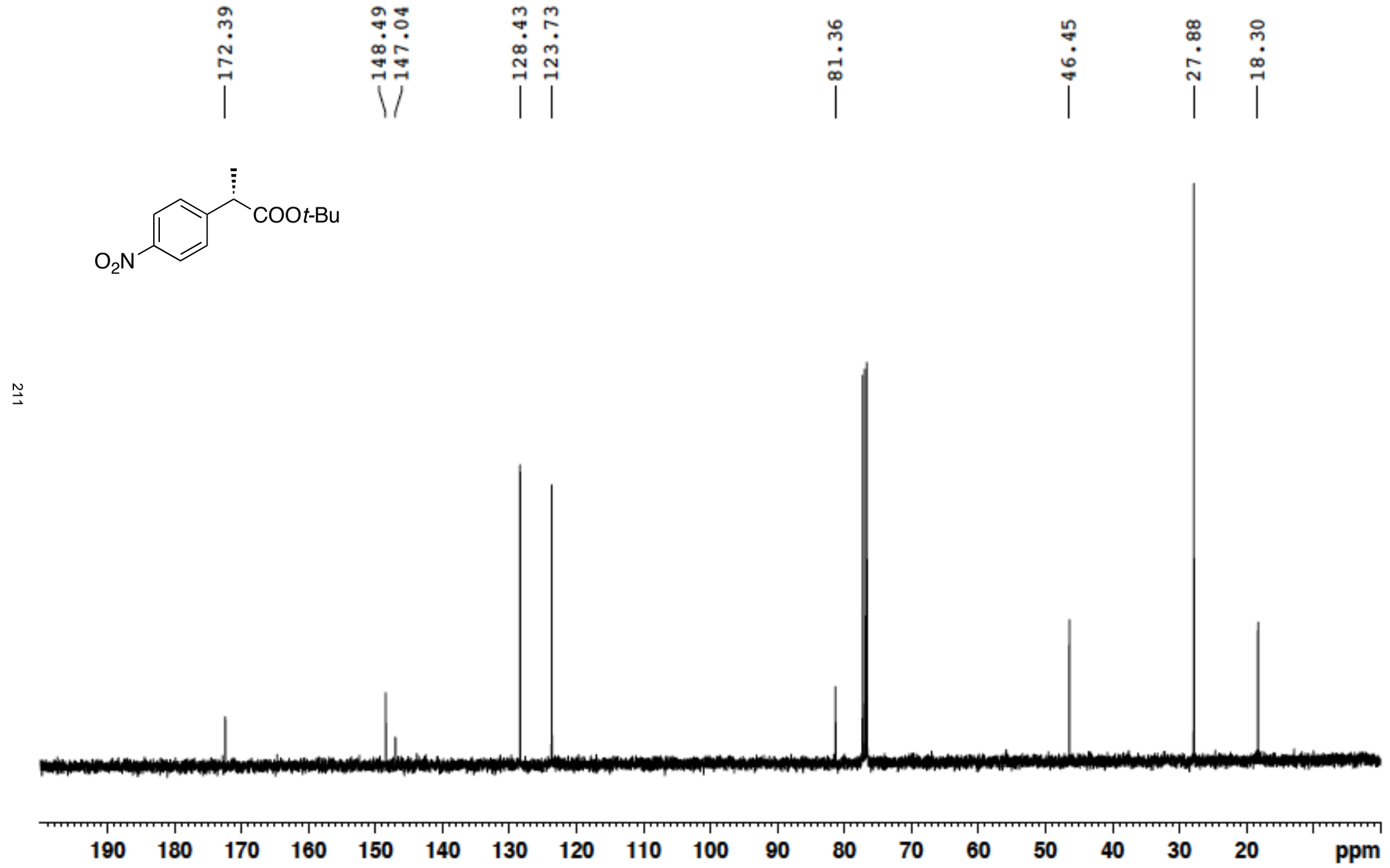
JF11-30-2 CDCl3 1HNMR BBFO2
2013-08-02



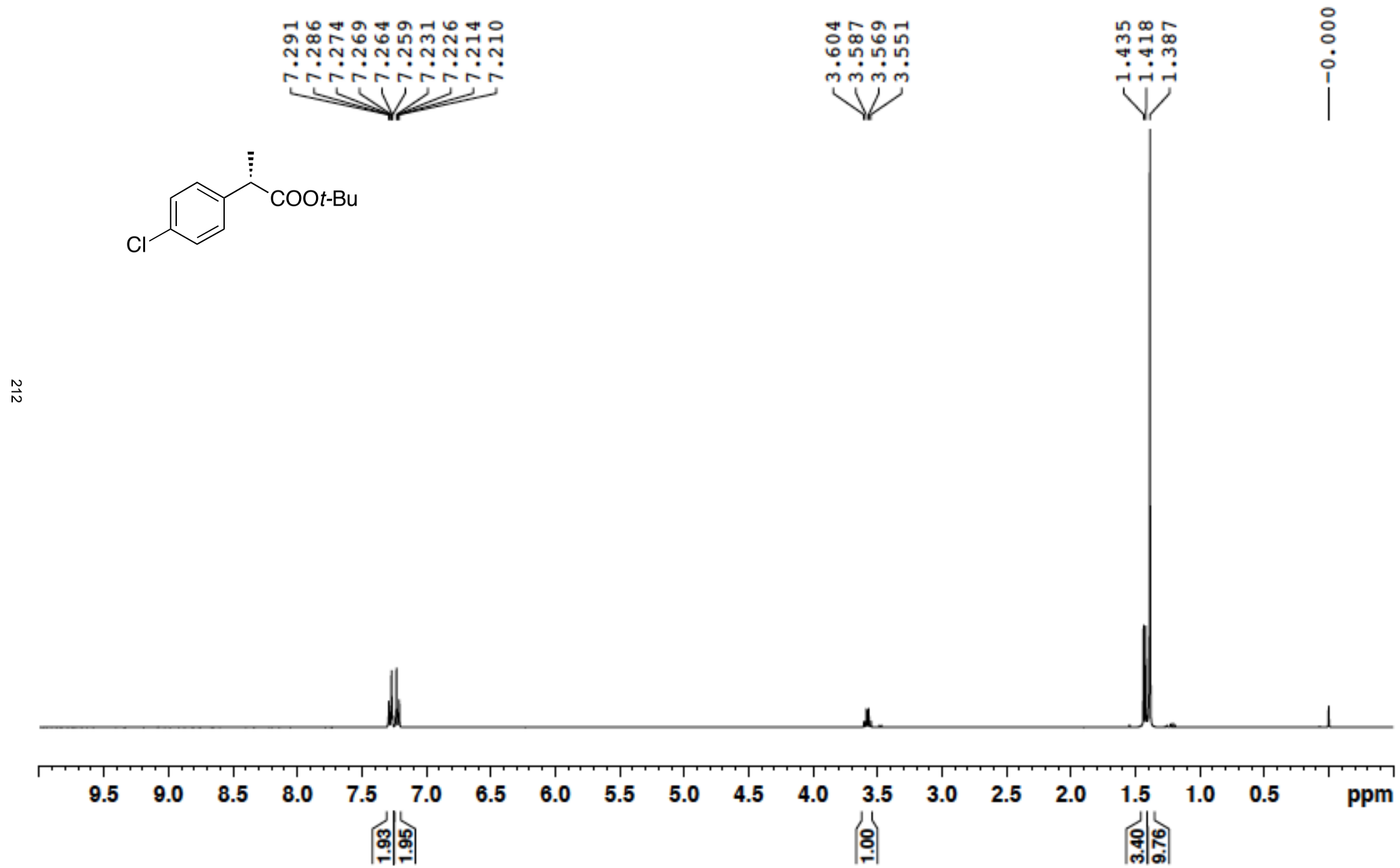
JF11-23-11, HNMR, CDCl3 BBFO2
2013-07-05



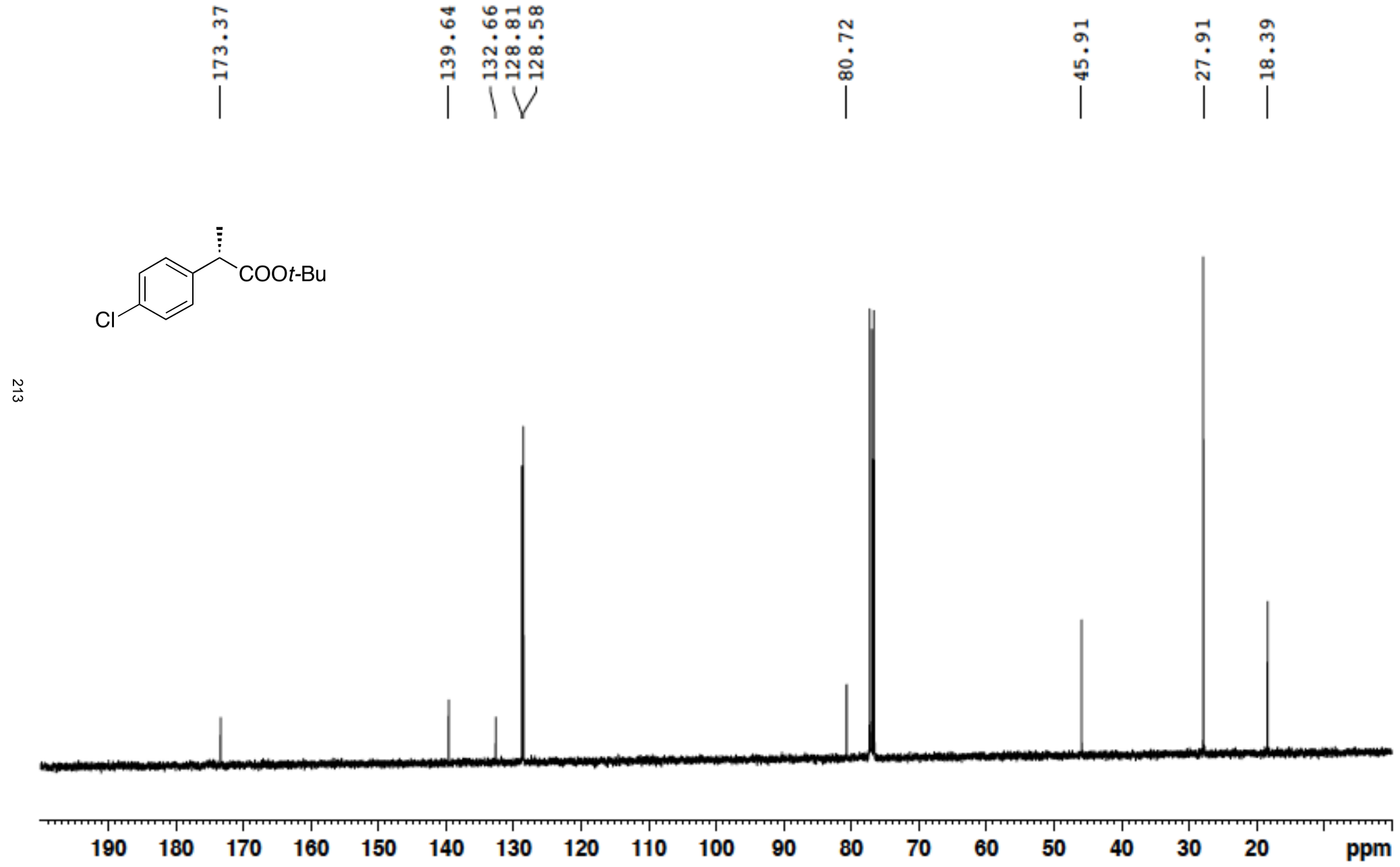
JF11-23-11, 13CNMR, CDCl3 BBFO2
2013-07-05



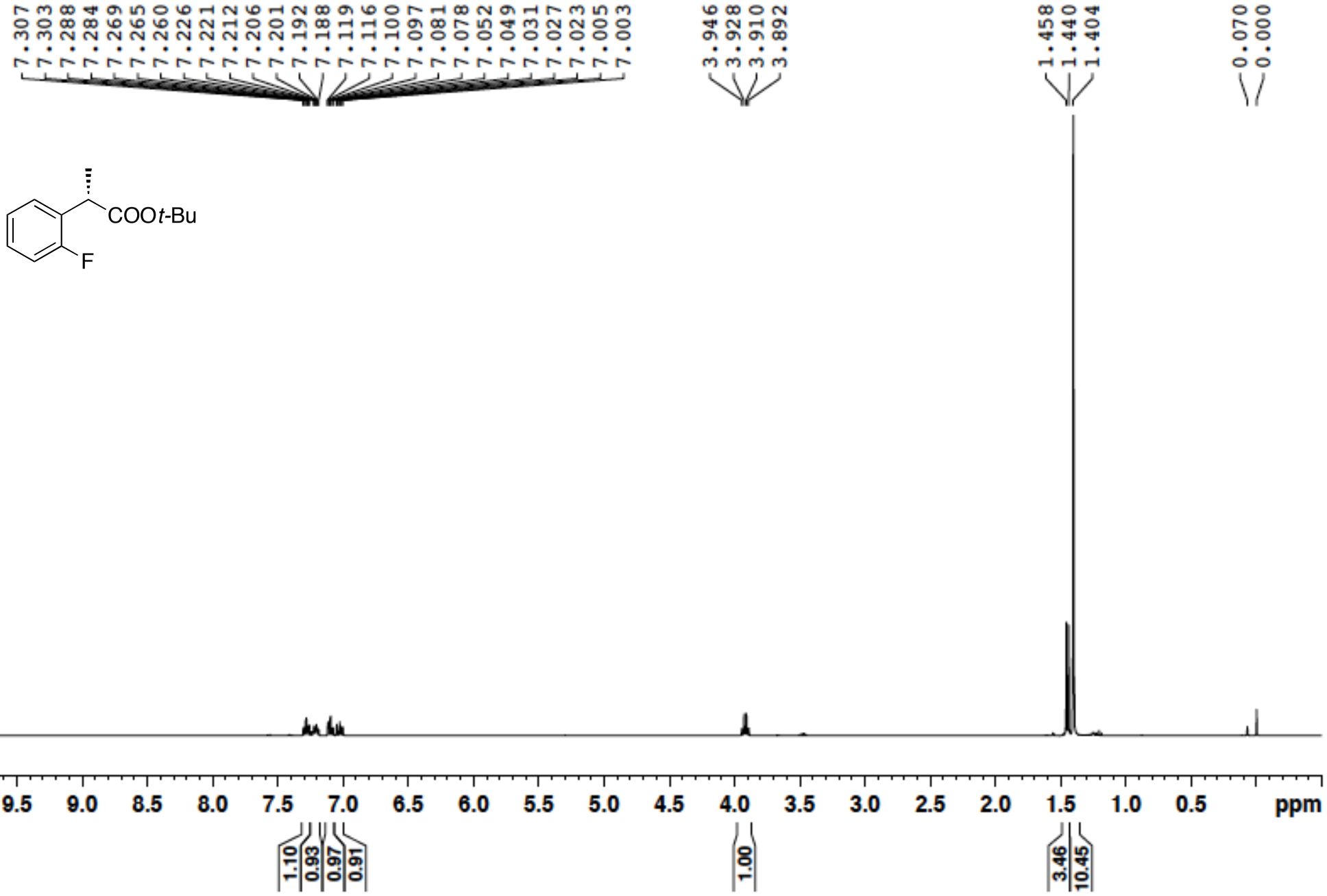
JF11-23-1, HNMR, CDCl3 BBFO2
2013-07-05



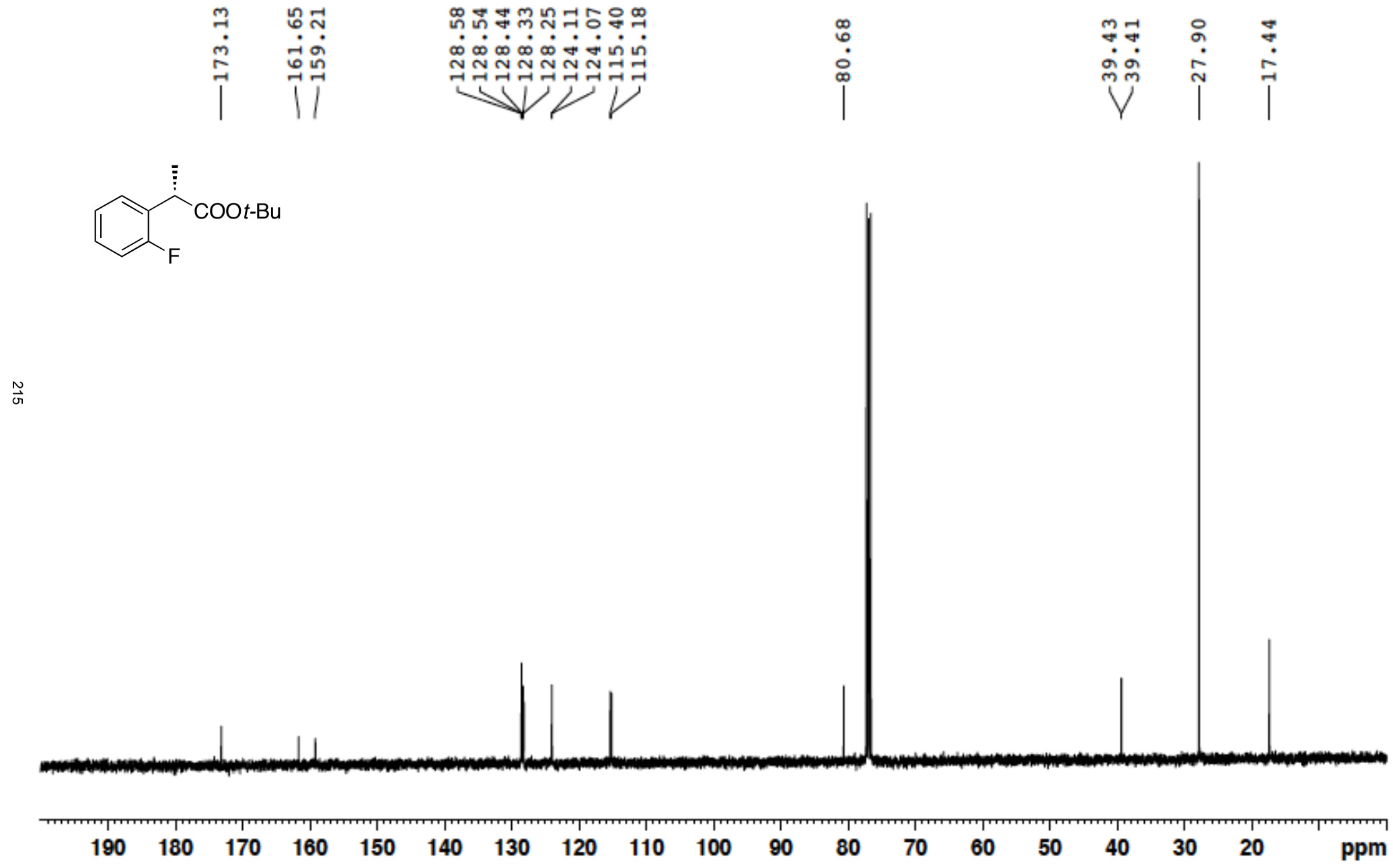
JF11-23-1, 13CNMR, CDCl3 BBFO2
2013-07-05



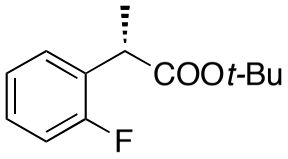
JF11-23-7, HNMR, CDCl3 BBFO2
2013-07-05



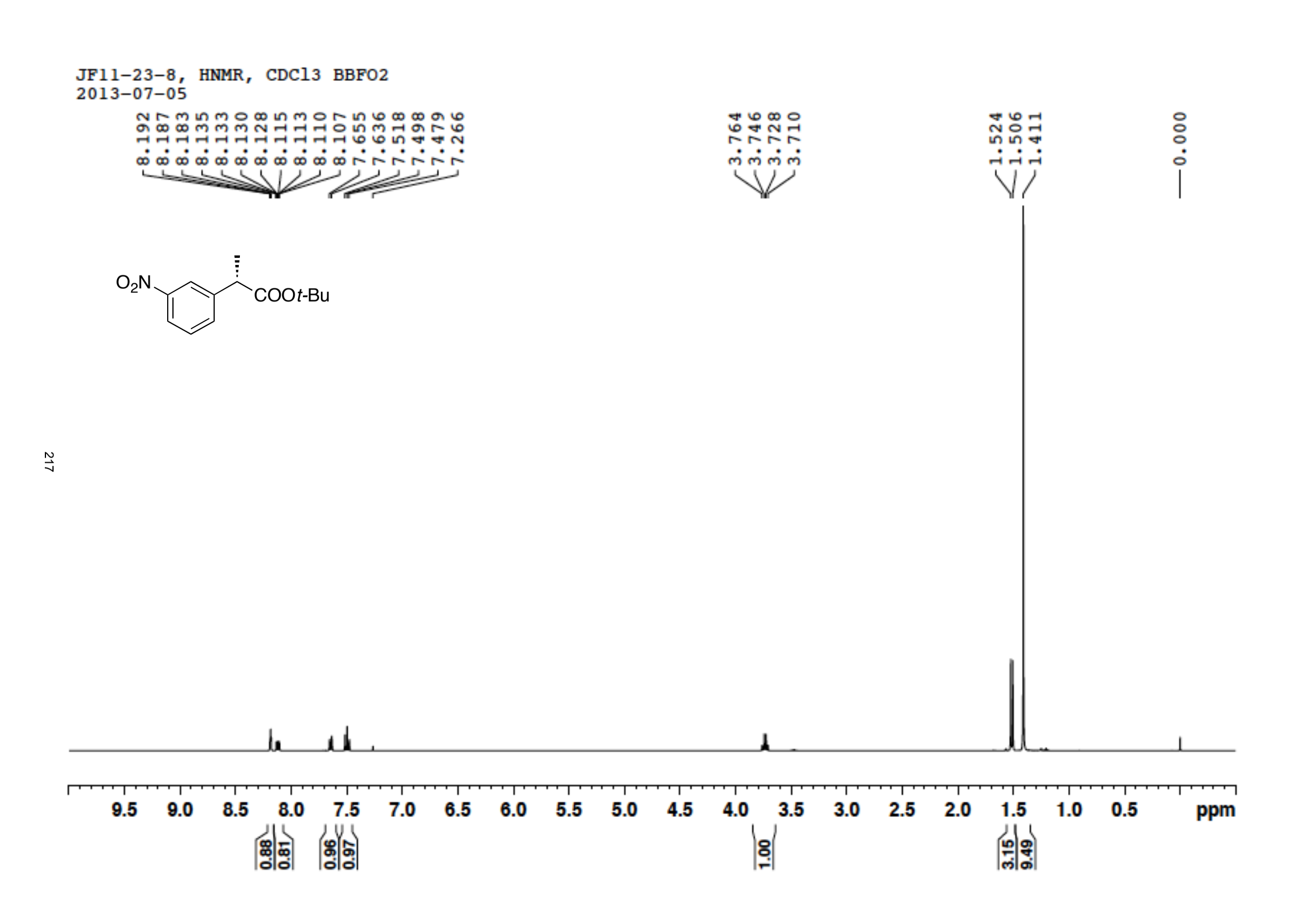
JF11-23-7, 13CNMR, CDCl3 BBFO2
2013-07-05



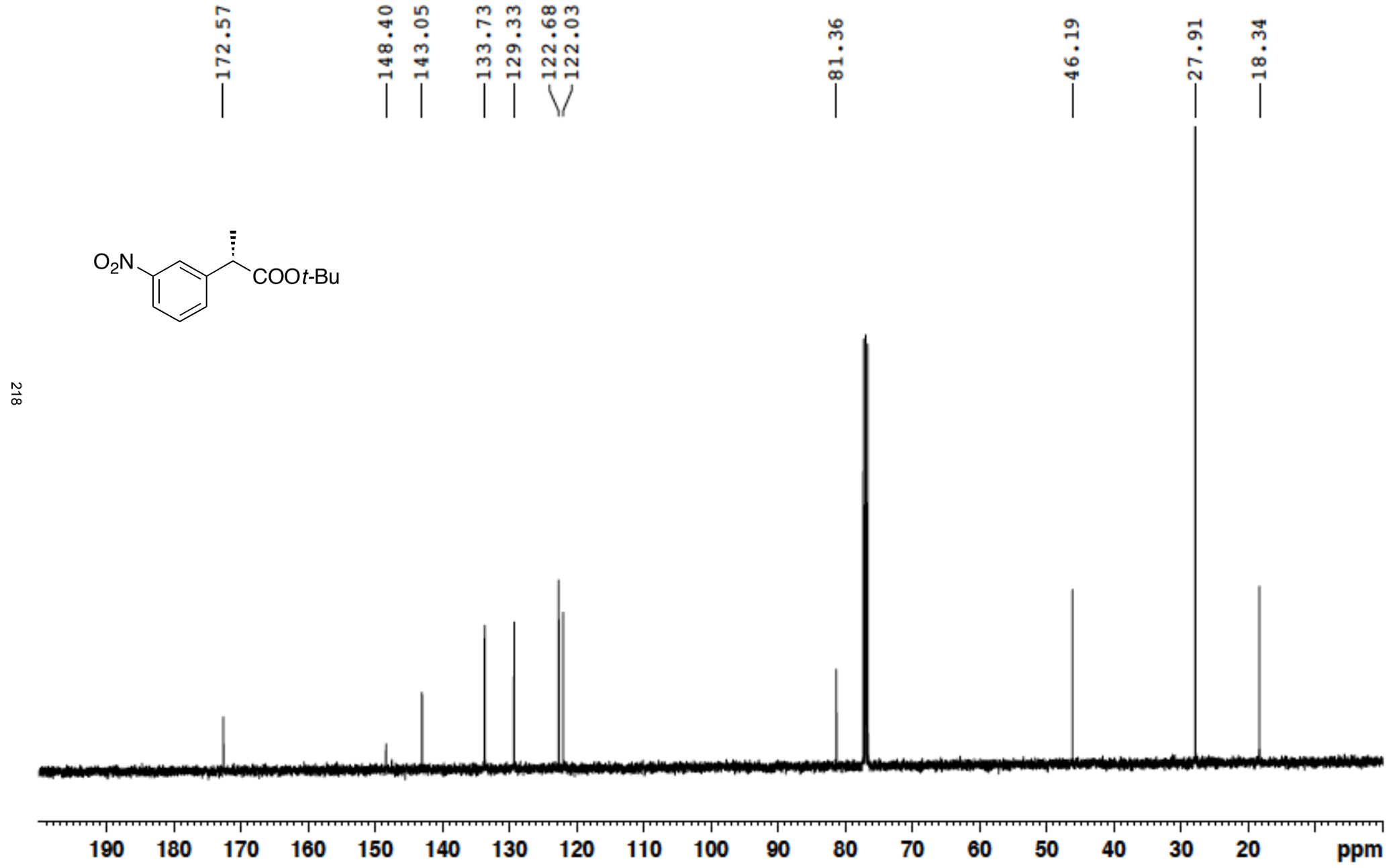
JF11-23-7-F 1HNMR BBFO1 CDC13
2013-8-2



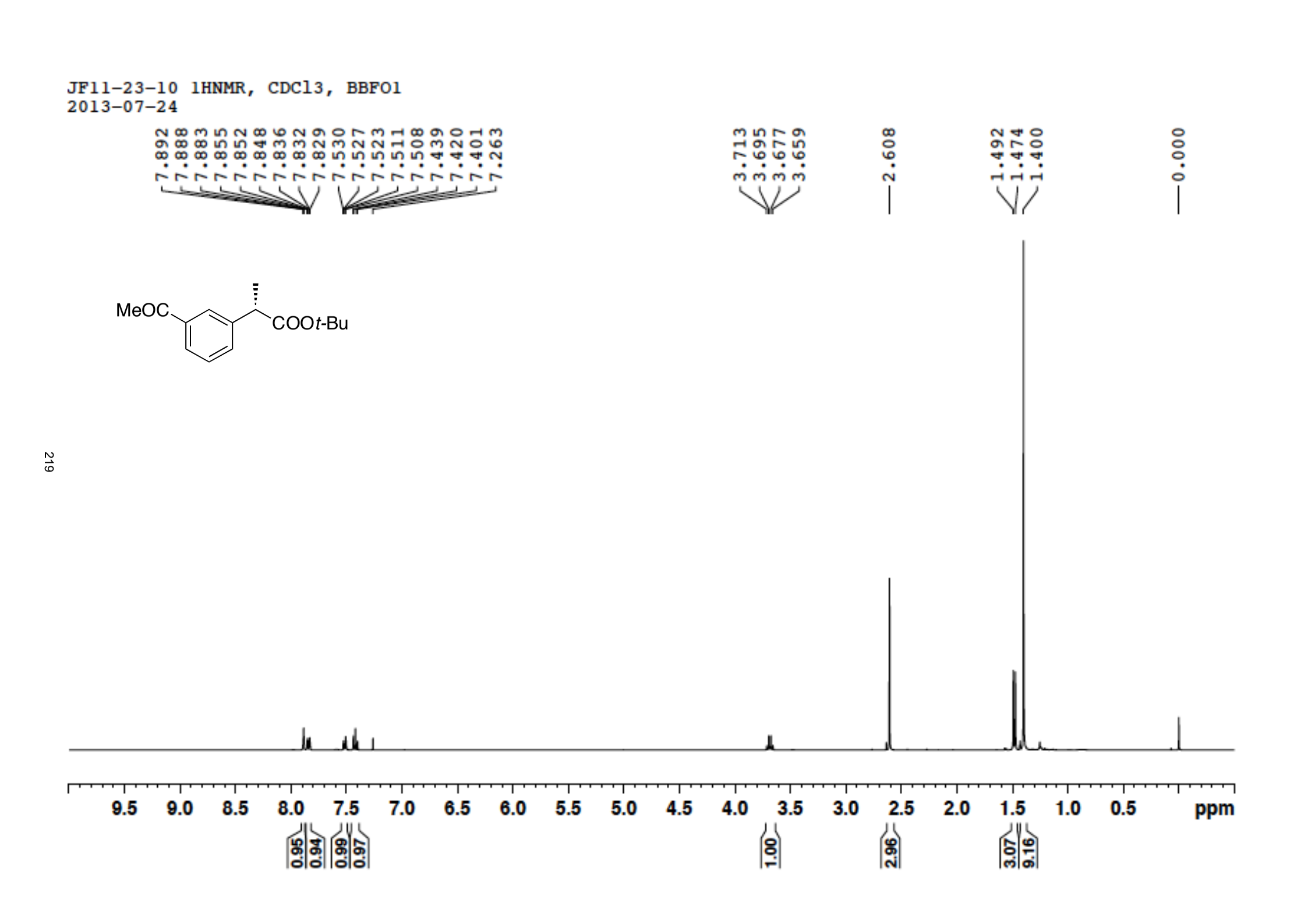
JF11-23-8, HNMR, CDCl3 BBFO2
2013-07-05



JF11-23-8, 13CNMR, CDCl3 BBFO2
2013-07-05

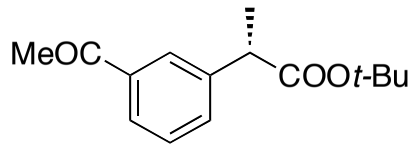


JF11-23-10 1HNMR, CDCl3, BBFO1
2013-07-24



JF11-23-10 13CNMR, CDCl3, BBFO1
2013-07-24

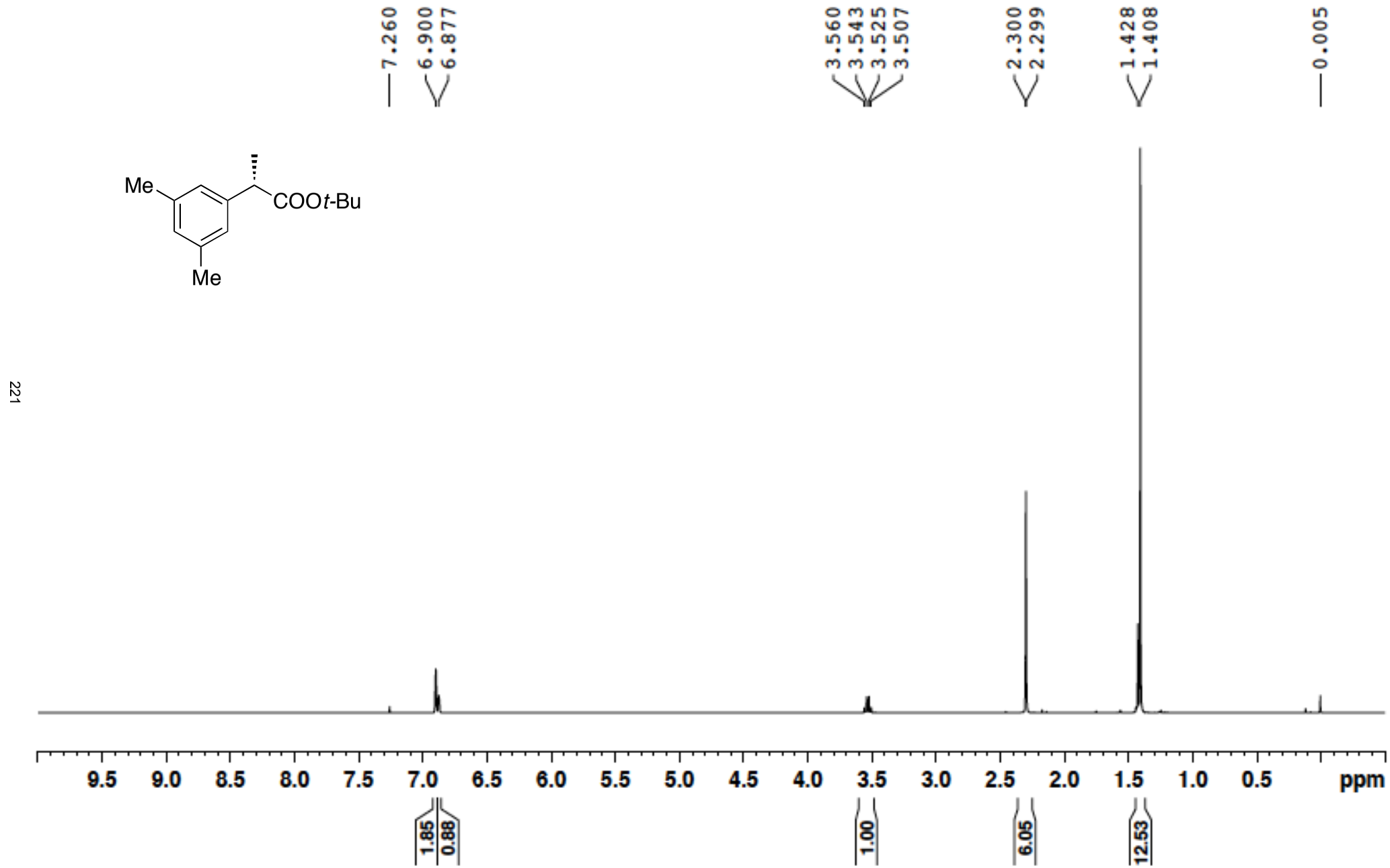
198.03
173.34
141.73
137.37
132.16
128.73
127.46
126.98
80.84
46.37
27.93
26.67
18.49



220

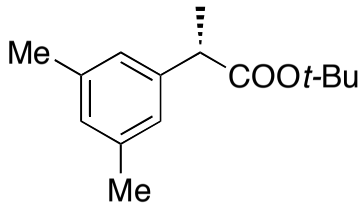
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

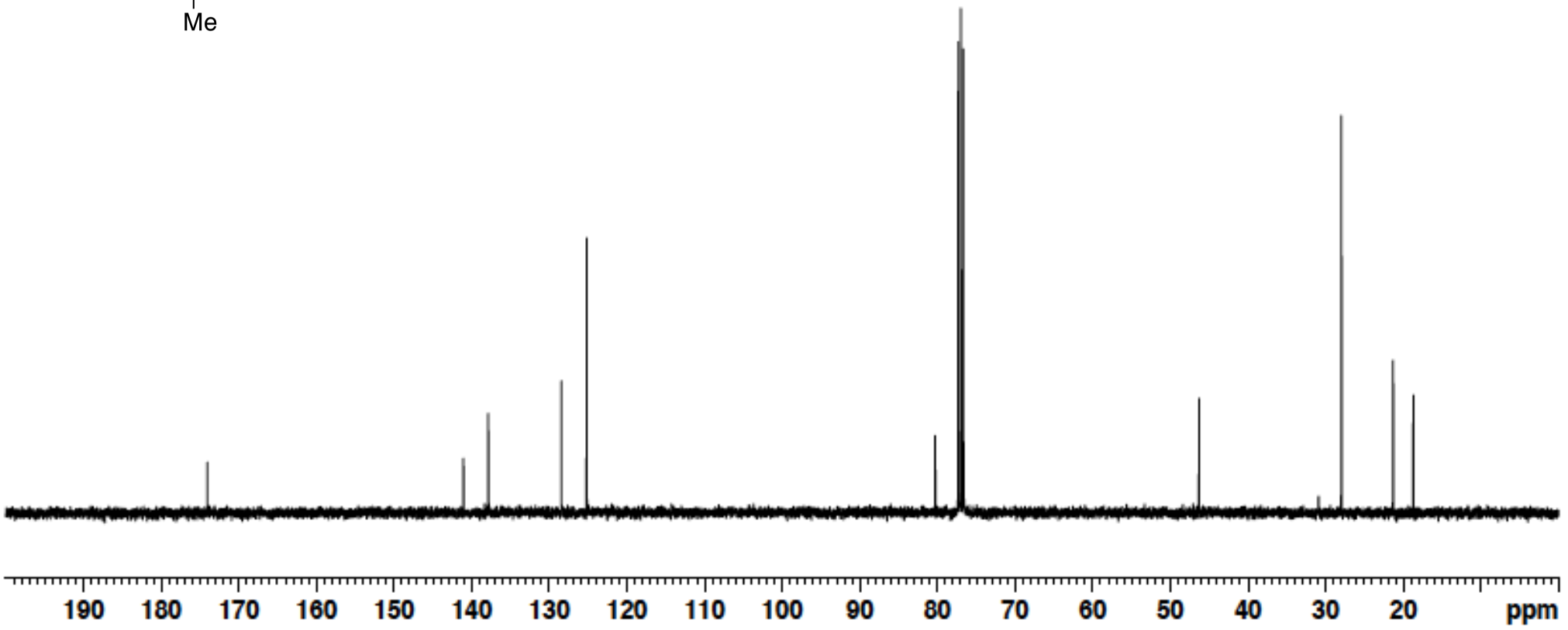
JF11-29-9, HNMR, CDCl3 BBFO2
2013-07-21



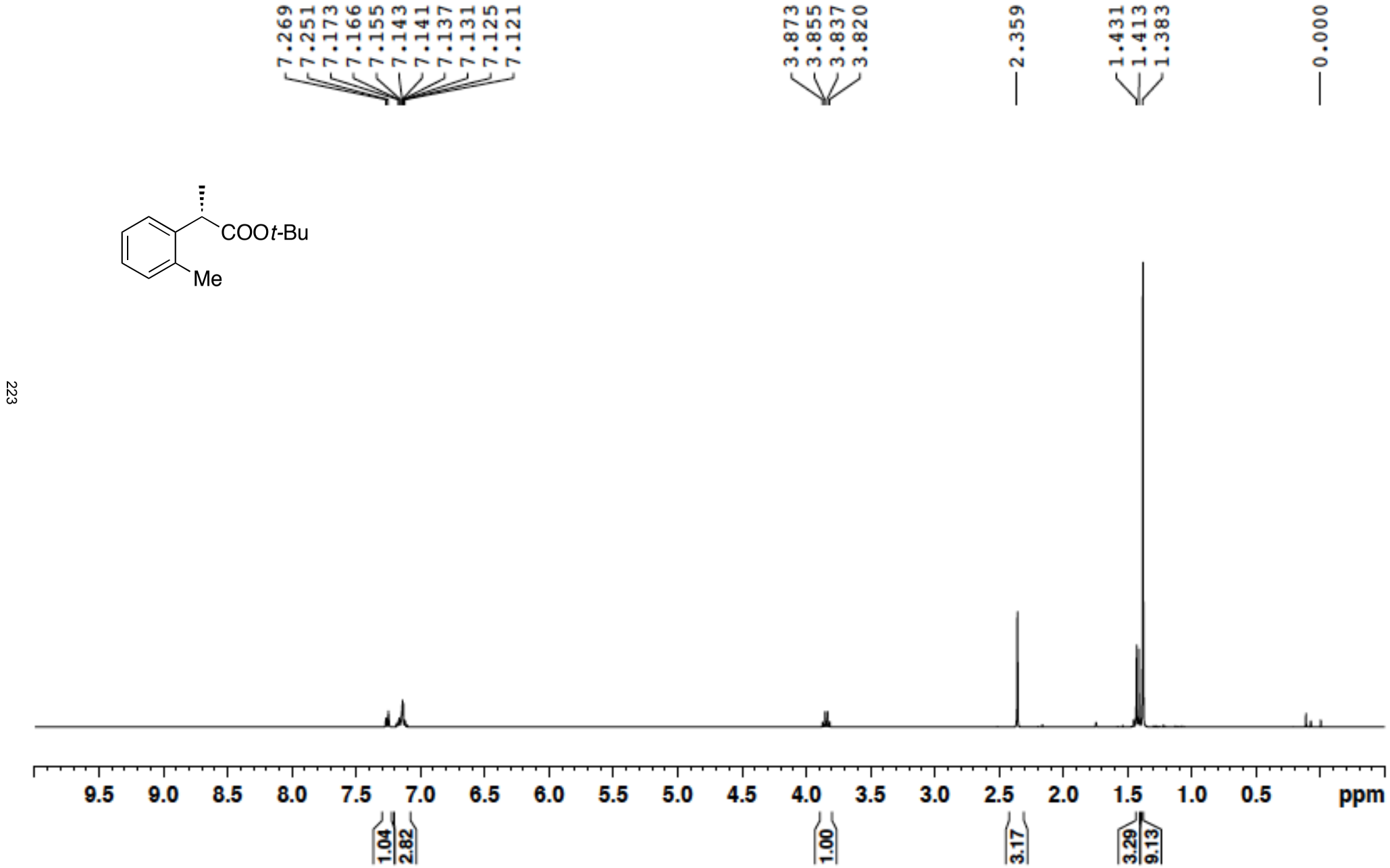
JF11-29-9 13CNMR, CDCl3, BBFO1
2013-07-22

174.07
141.07
137.86
128.46
125.20
80.31
46.30
27.97
21.30
18.71

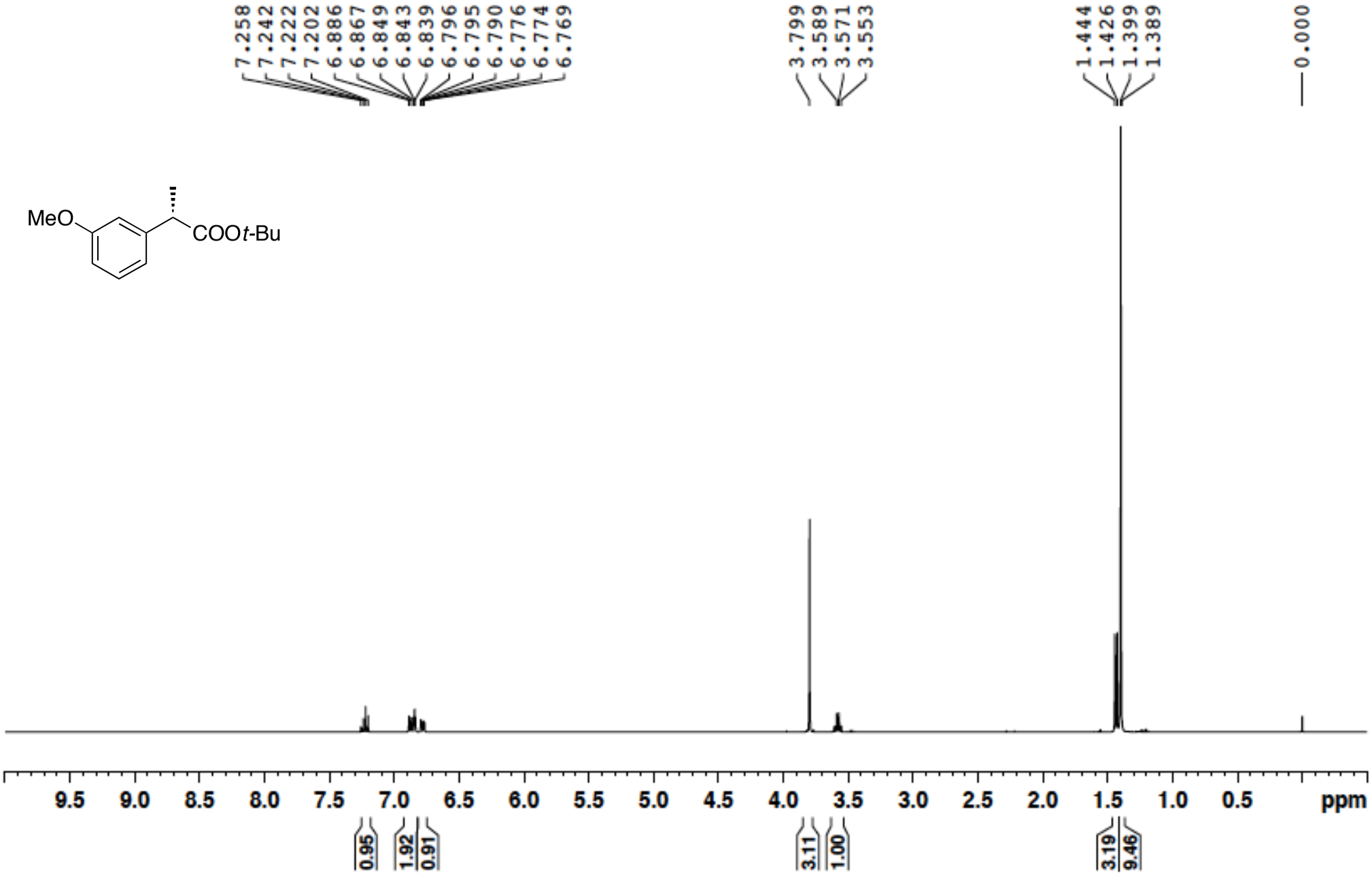




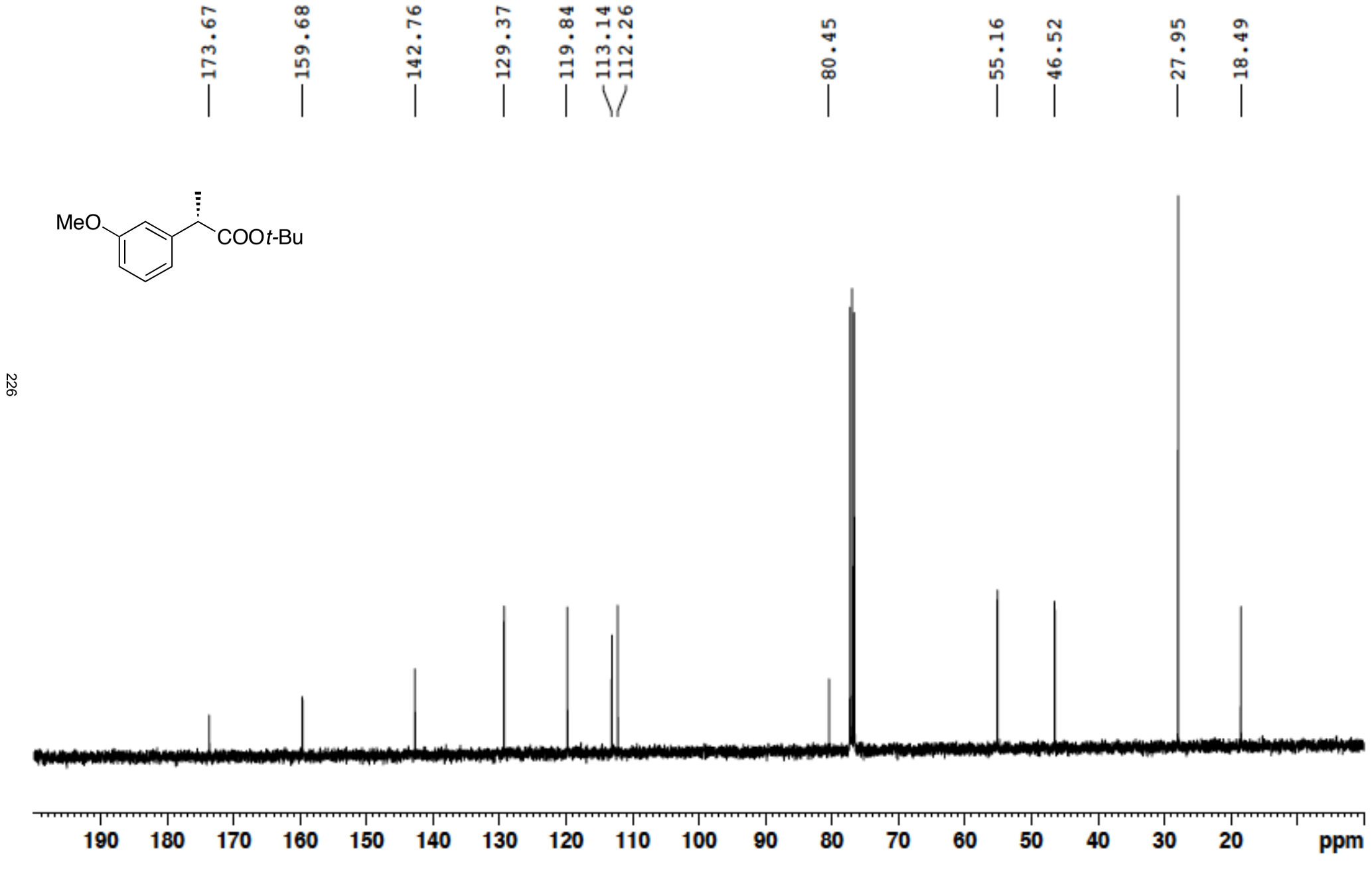
JF11-36-8, HNMR, CDCl3 BBFO2
2013-07-21



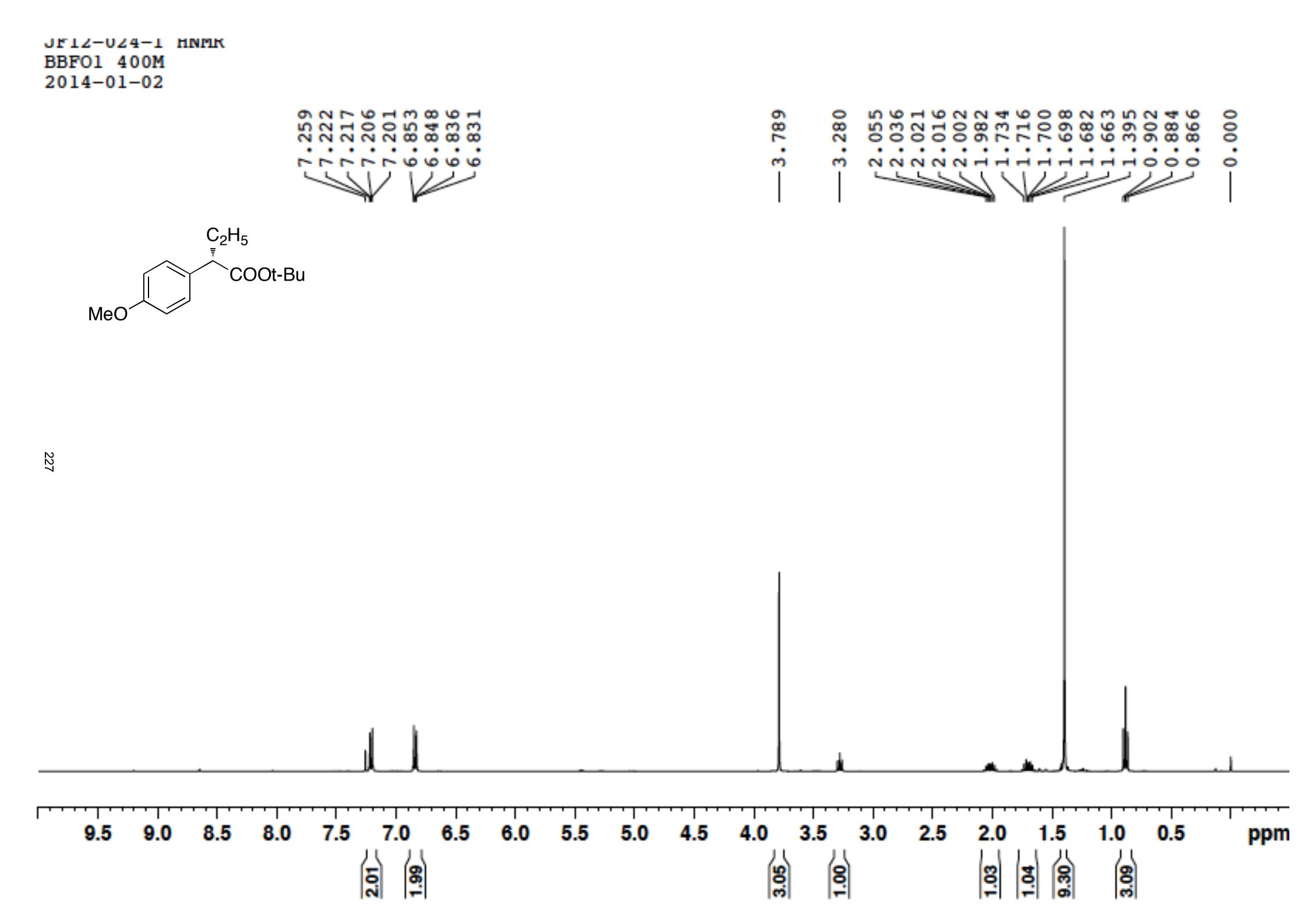
JF11-23-9, HNMR, CDCl3 BBFO2
2013-07-05



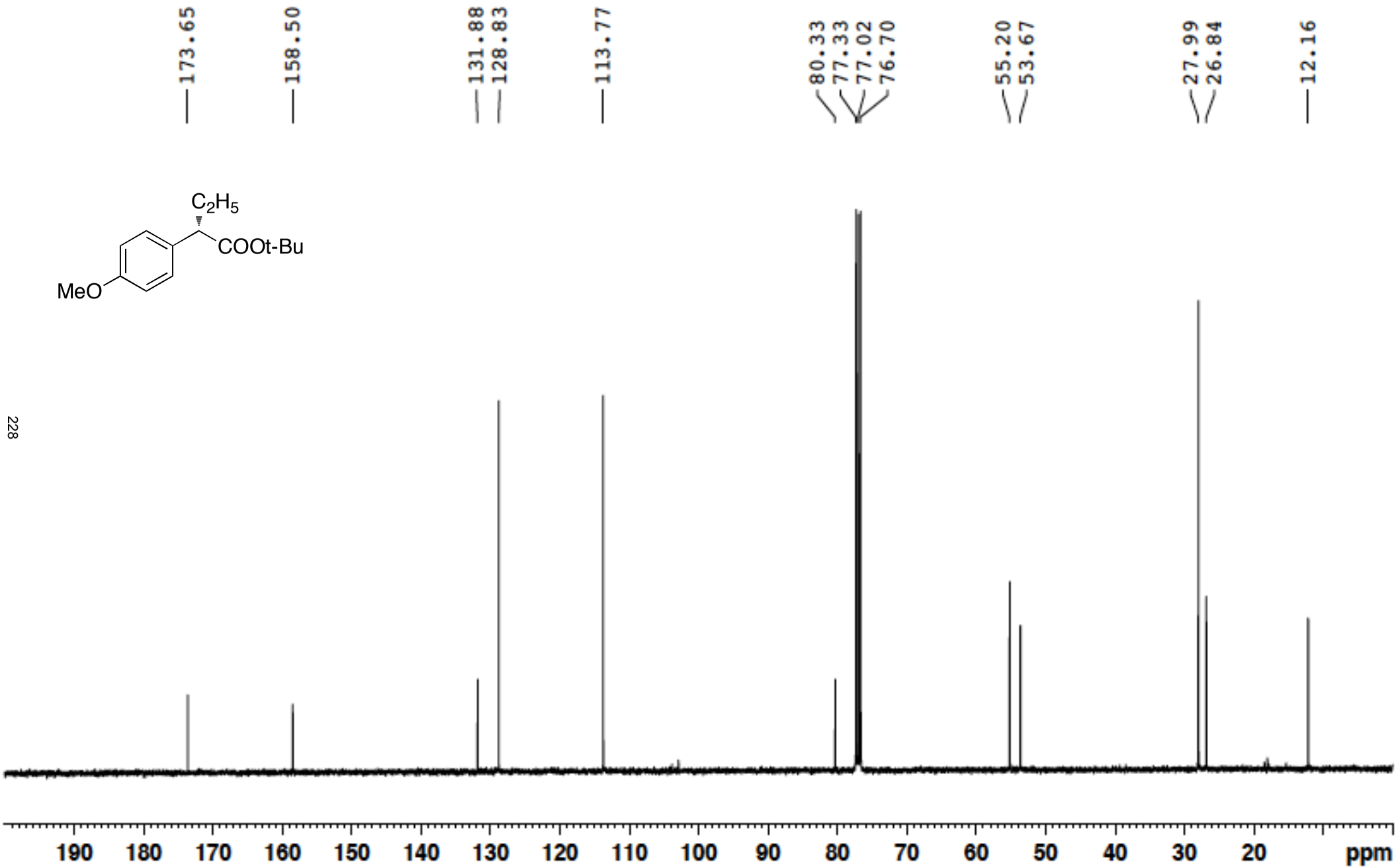
JF11-23-9, 13CNMR, CDCl3 BBFO2
2013-07-05



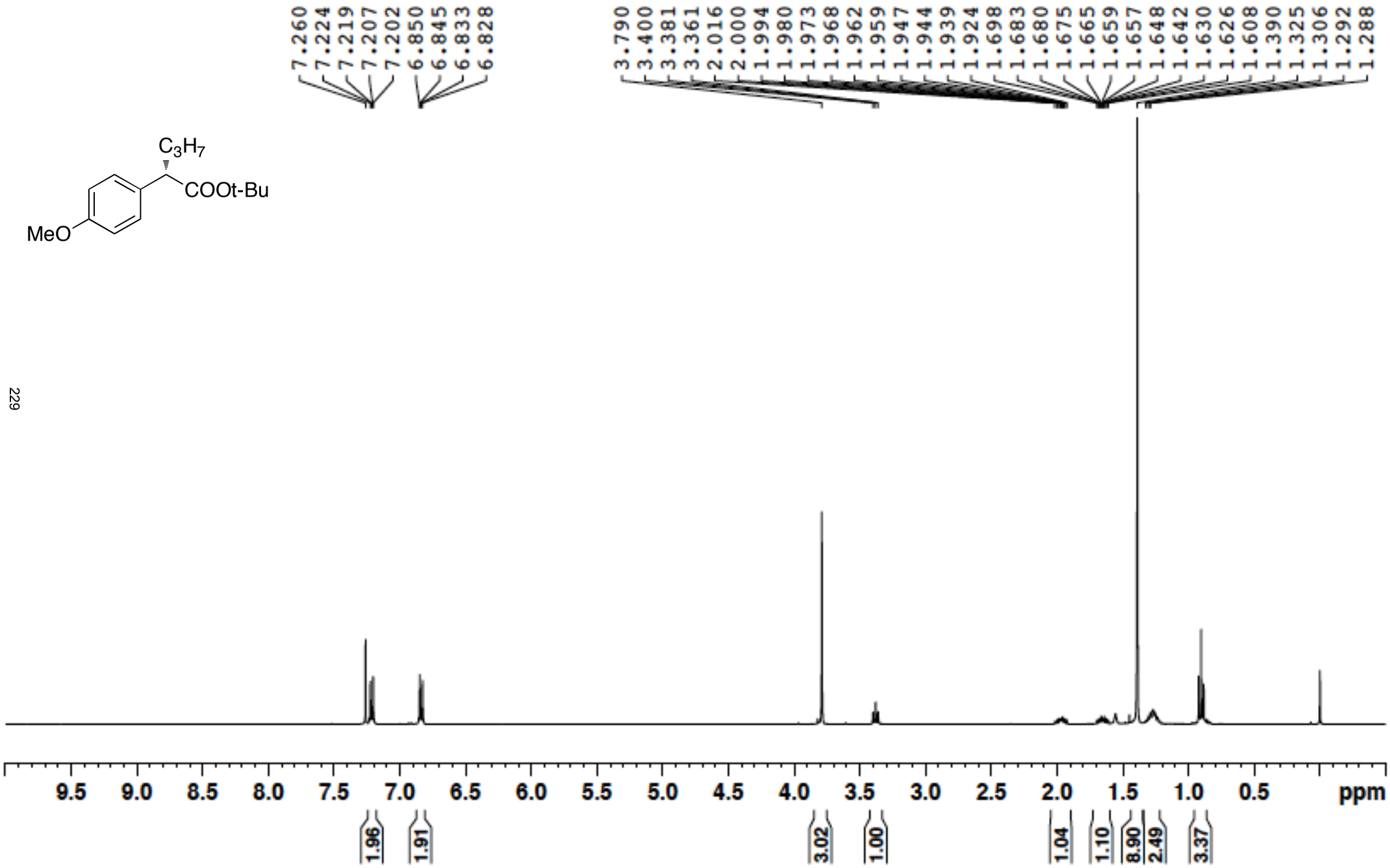
JF12-024-1 HNMR
BBFO1 400M
2014-01-02



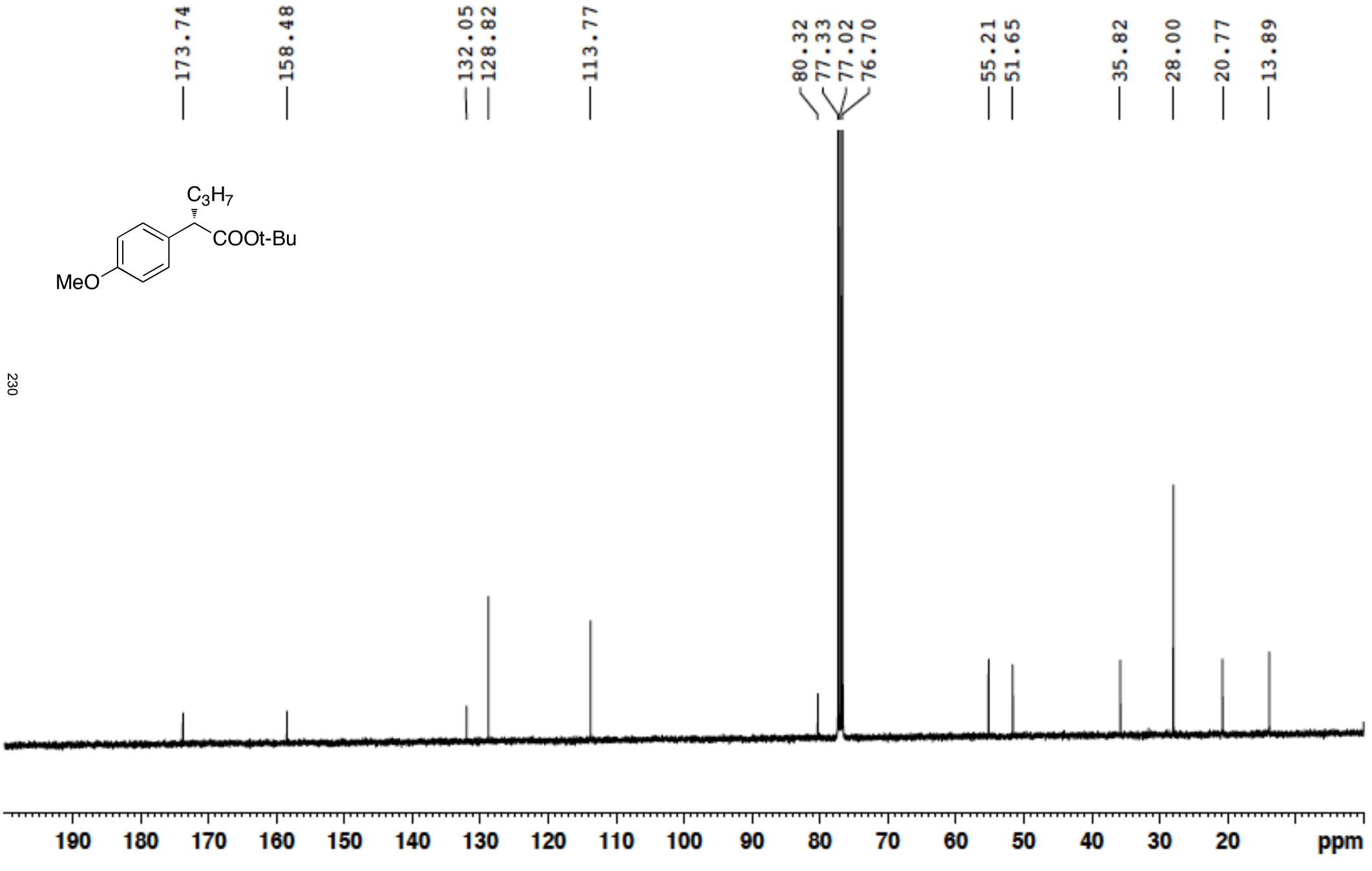
BBFO1 400M
2014-01-02

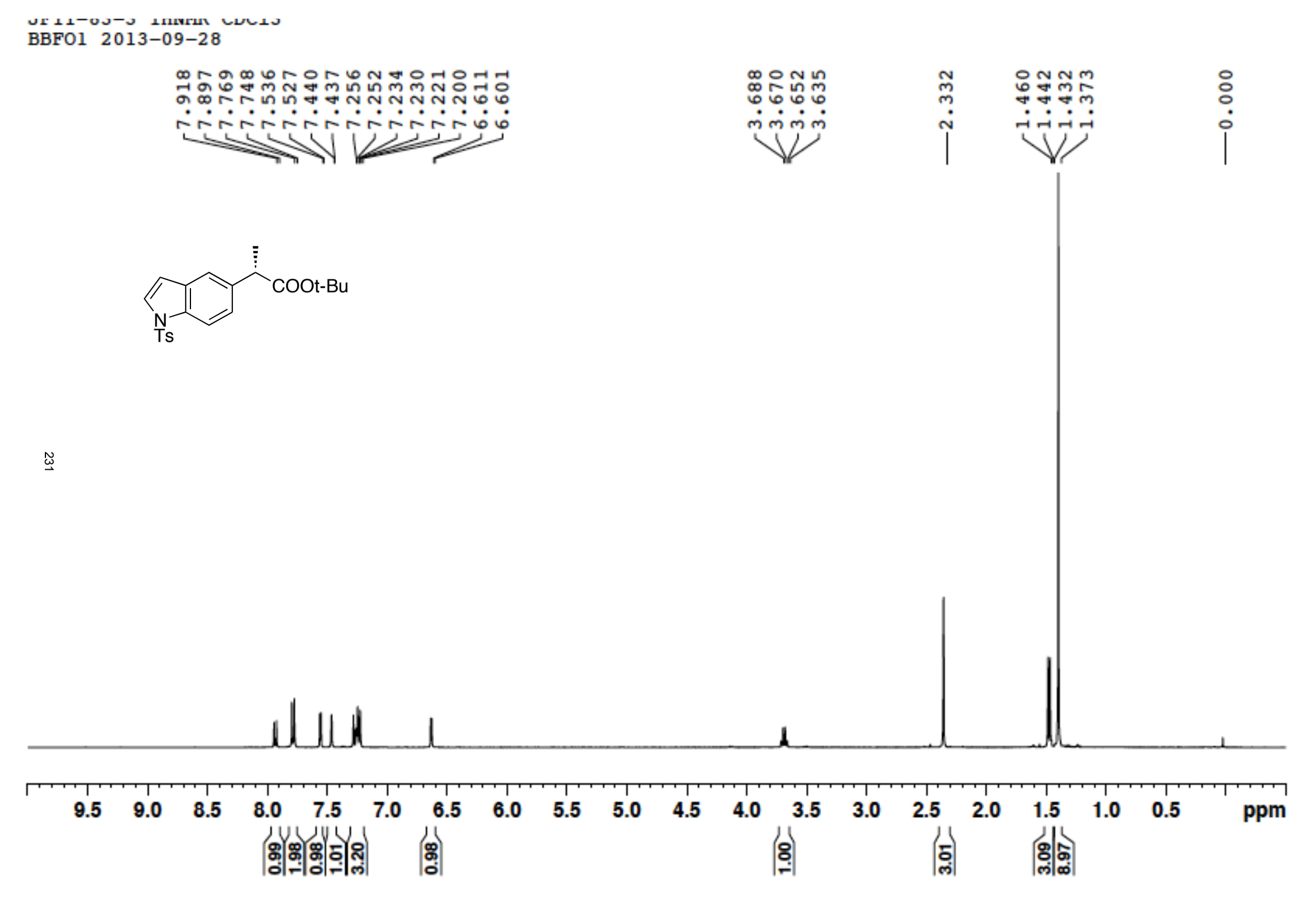


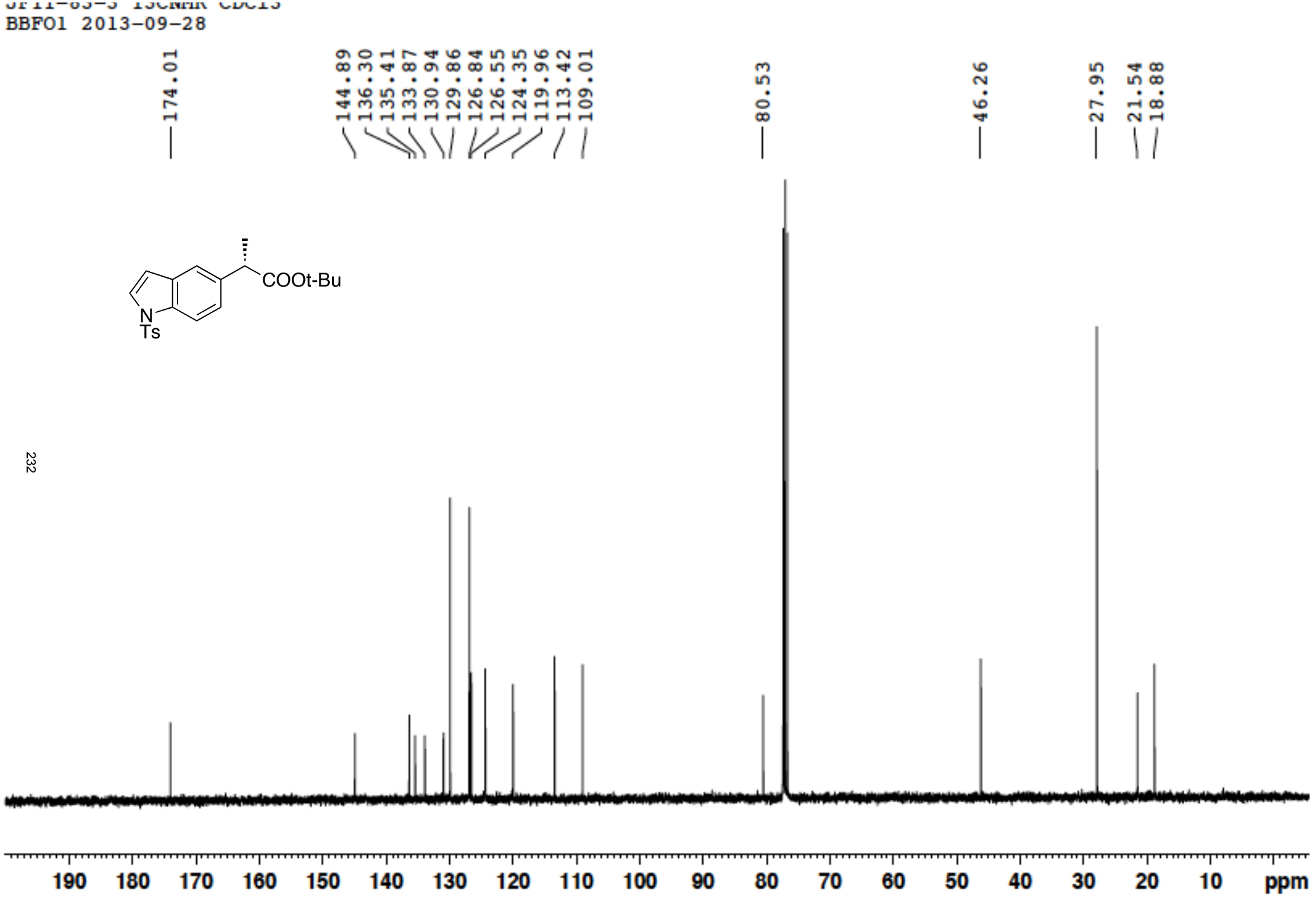
JF12-023 HNMR
BBFO1 CDCl3
2014-01-02



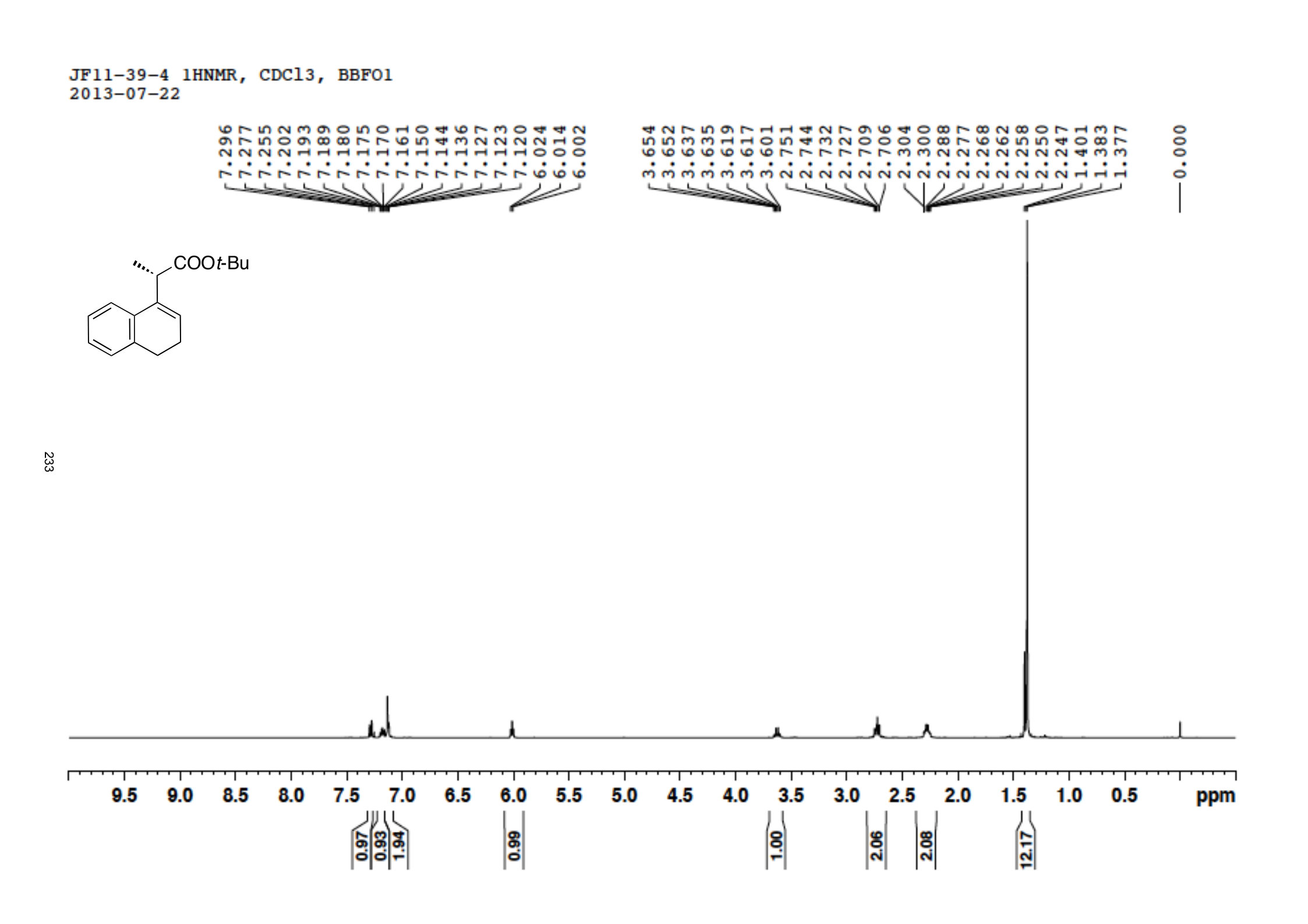
JF12-023 CNMR
BBFO1 CDCl3
2014-01-02



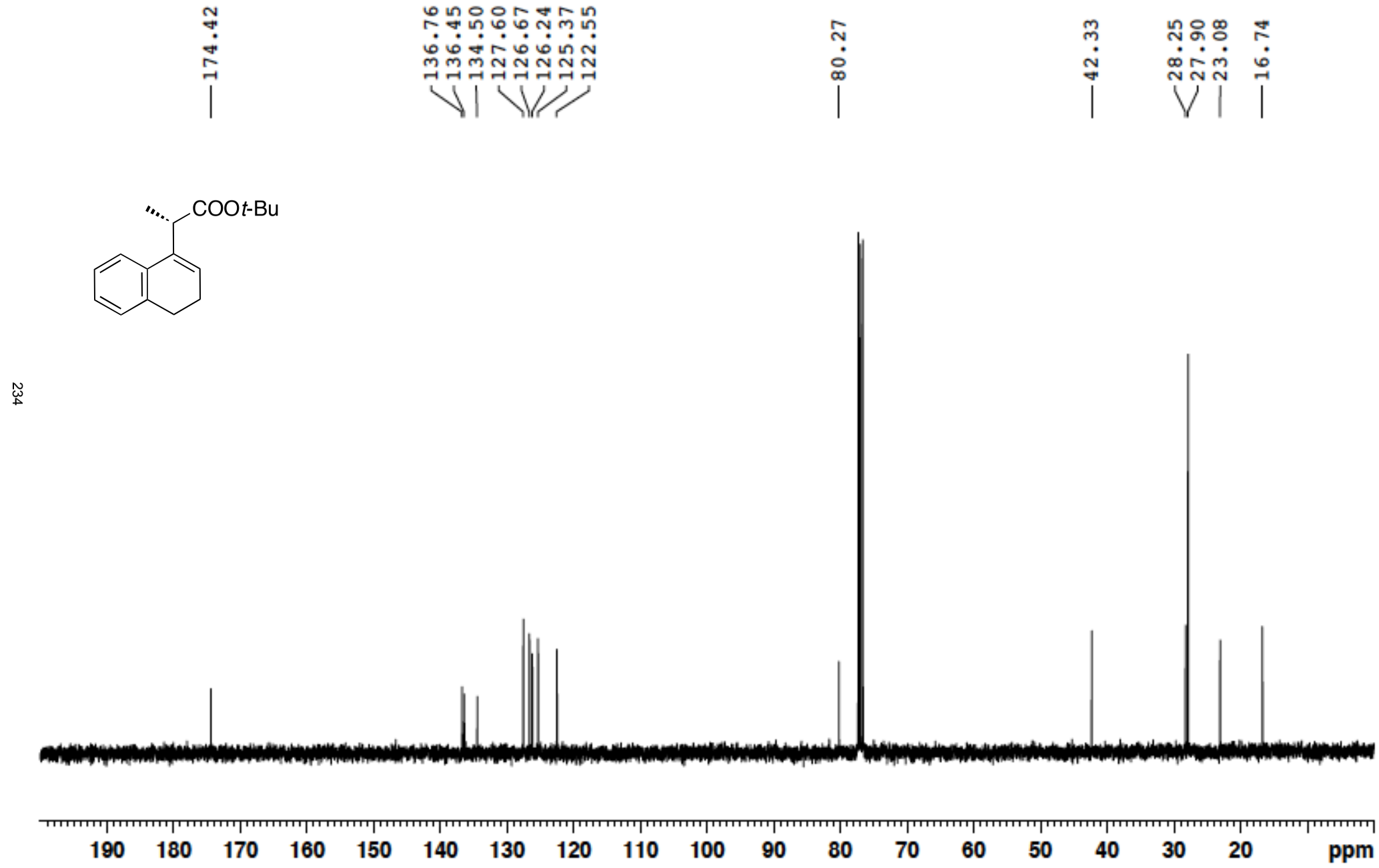

BBFO1 2013-09-28
7.918
7.897
7.769
7.748
7.536
7.527
7.440
7.437
7.256
7.252
7.234
7.230
7.221
7.200
6.611
6.601
3.688
3.670
3.652
3.635
2.332
1.460
1.442
1.432
1.373
0.000
COOt-Bu
N
Ts
231
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.99
1.98
0.98
1.01
3.20
0.98
1.00
3.01
3.09
8.97


BBFO1 2013-09-28
174.01
144.89
136.30
135.41
133.87
130.94
129.86
126.84
126.55
124.35
119.96
113.42
109.01
80.53
46.26
27.95
21.54
18.88
COOt-Bu
N
Ts
232
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

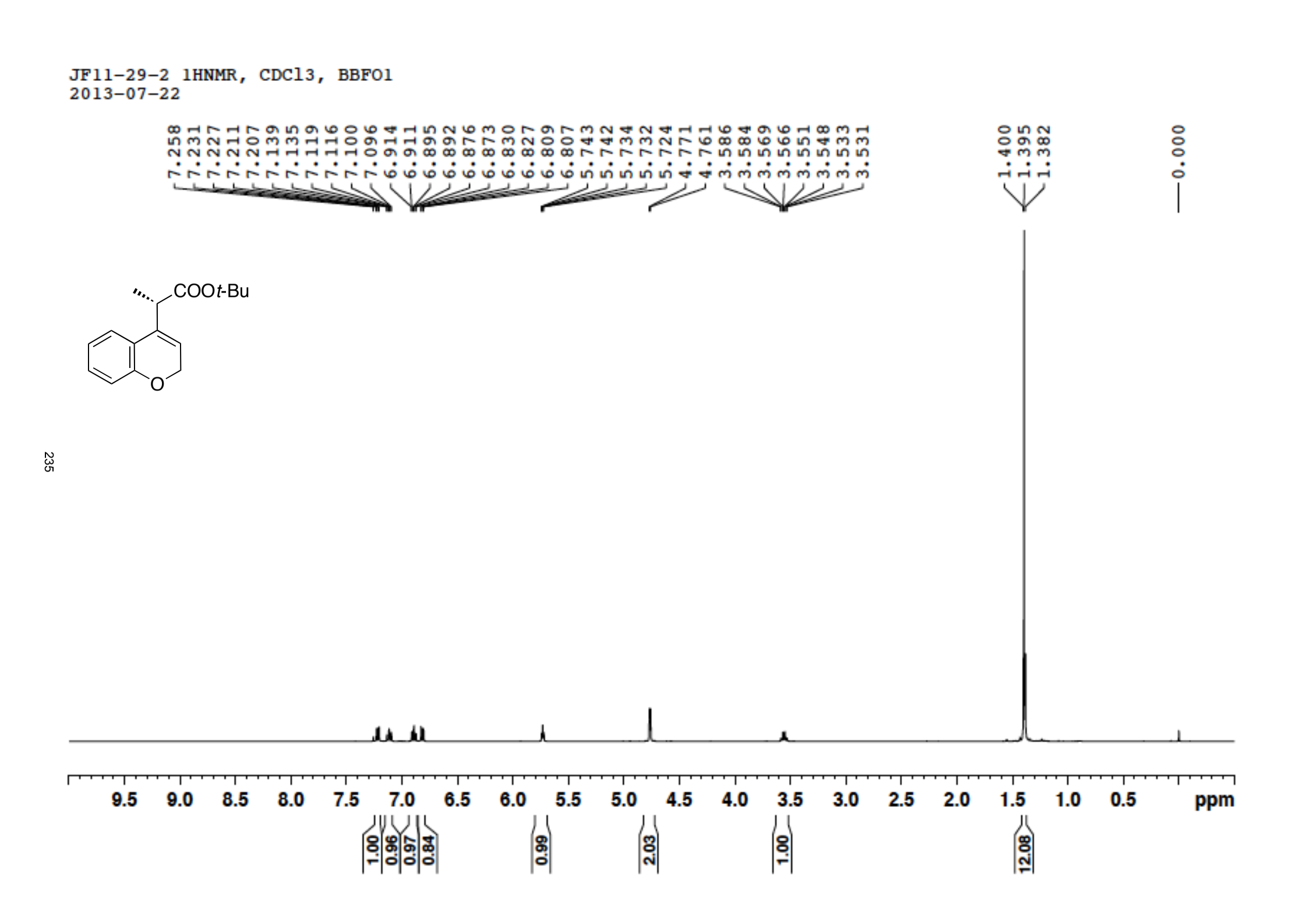
JF11-39-4 1HNMR, CDCl3, BBFO1
2013-07-22



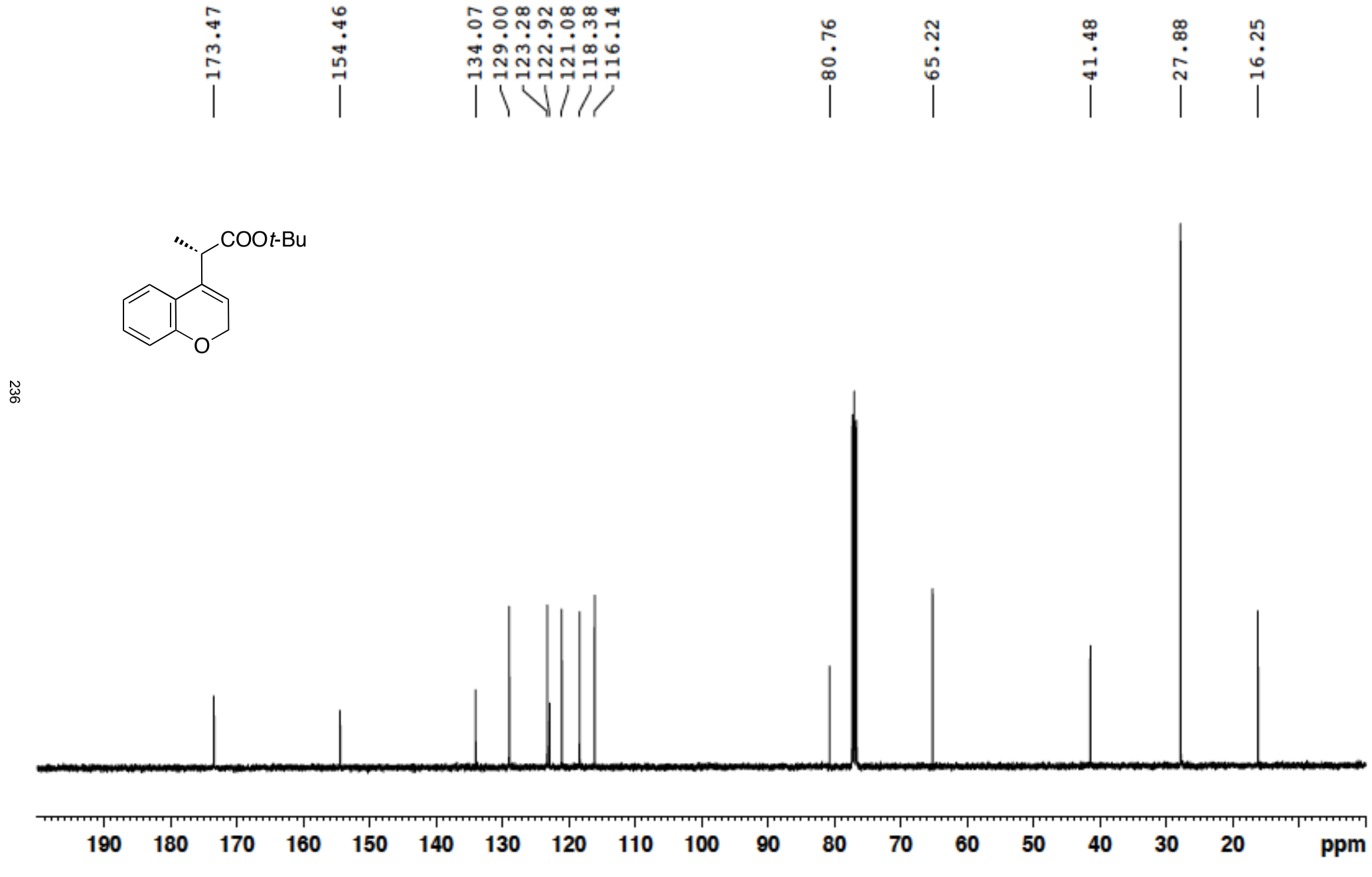
JF11-39-4 13CNMR, CDCl3, BBFO1
2013-07-22



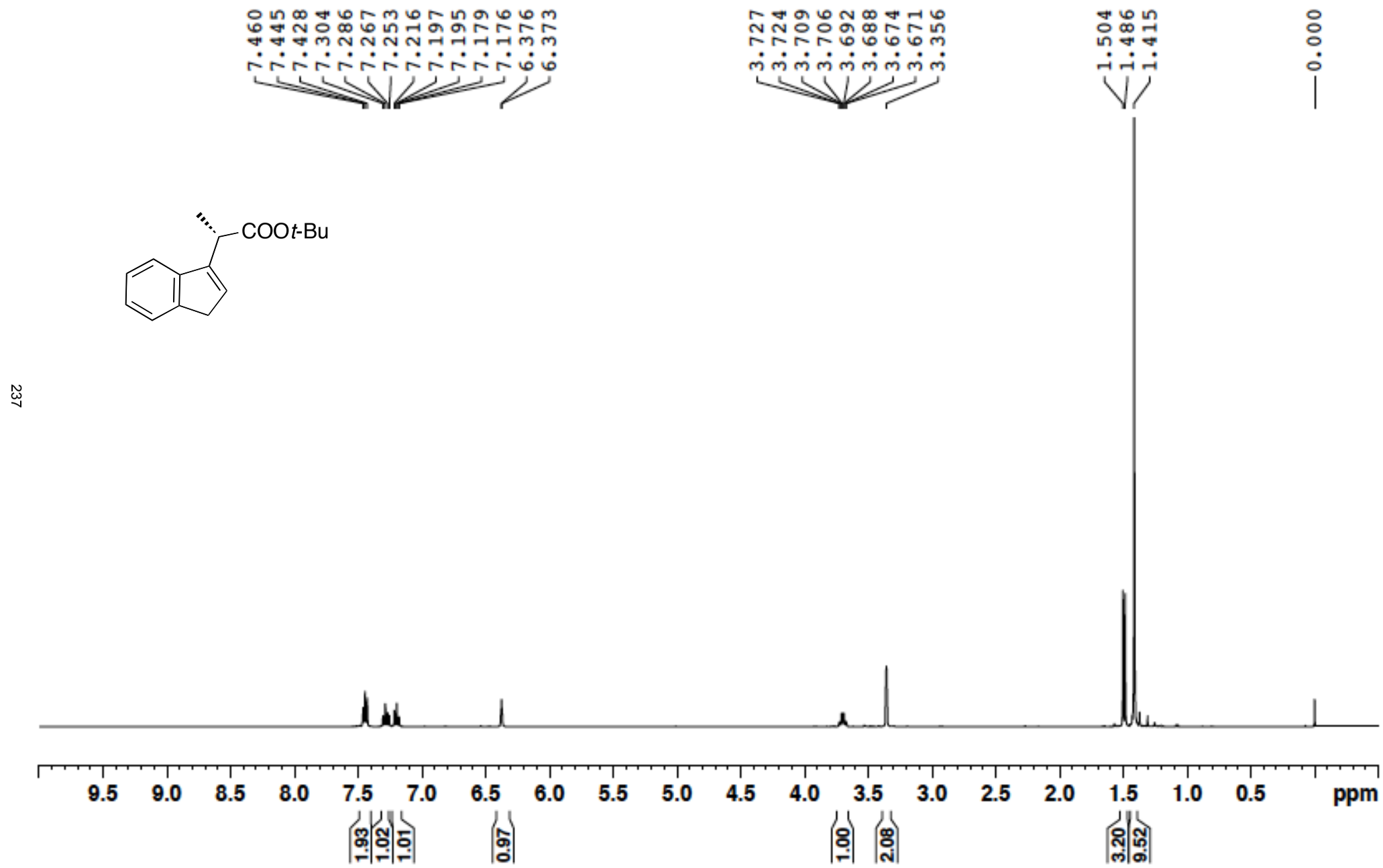
JF11-29-2 1HNMR, CDCl3, BBFO1
2013-07-22



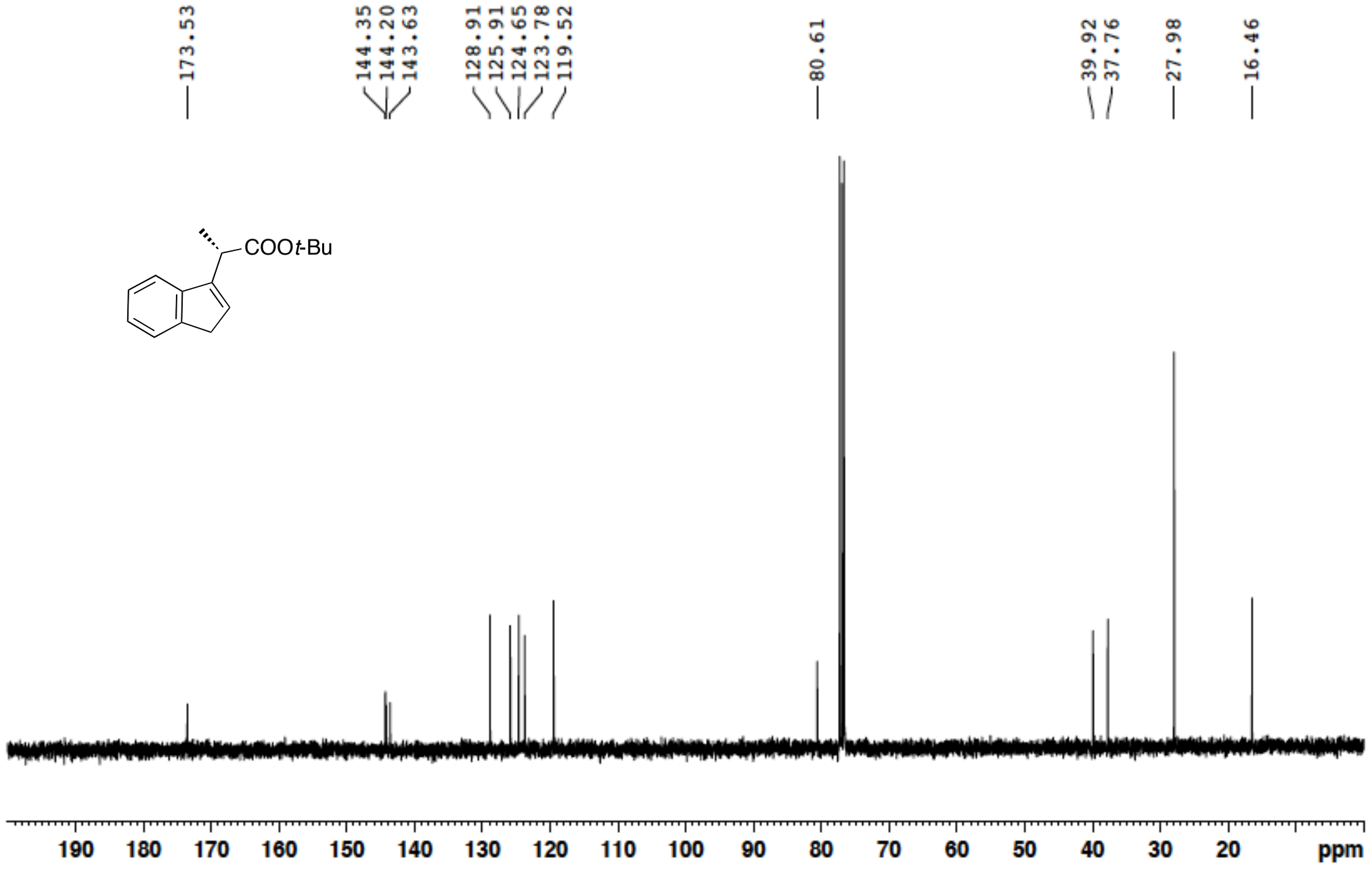
JF11-29-2 13CNMR, CDCl3, BBFO1
2013-07-22



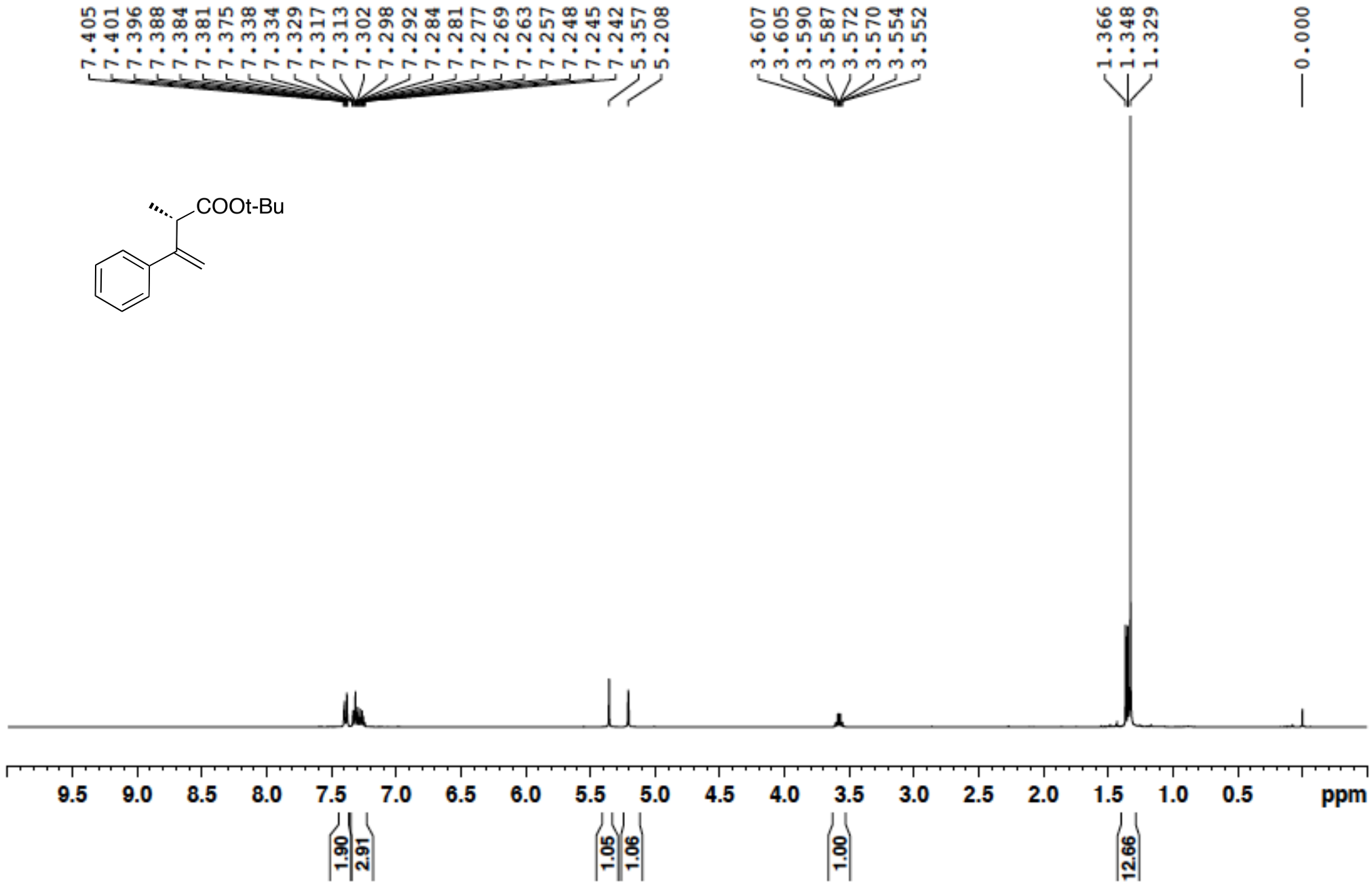
JF11-29-3 1HNMR, CDCl3, BBFO1
2013-07-22



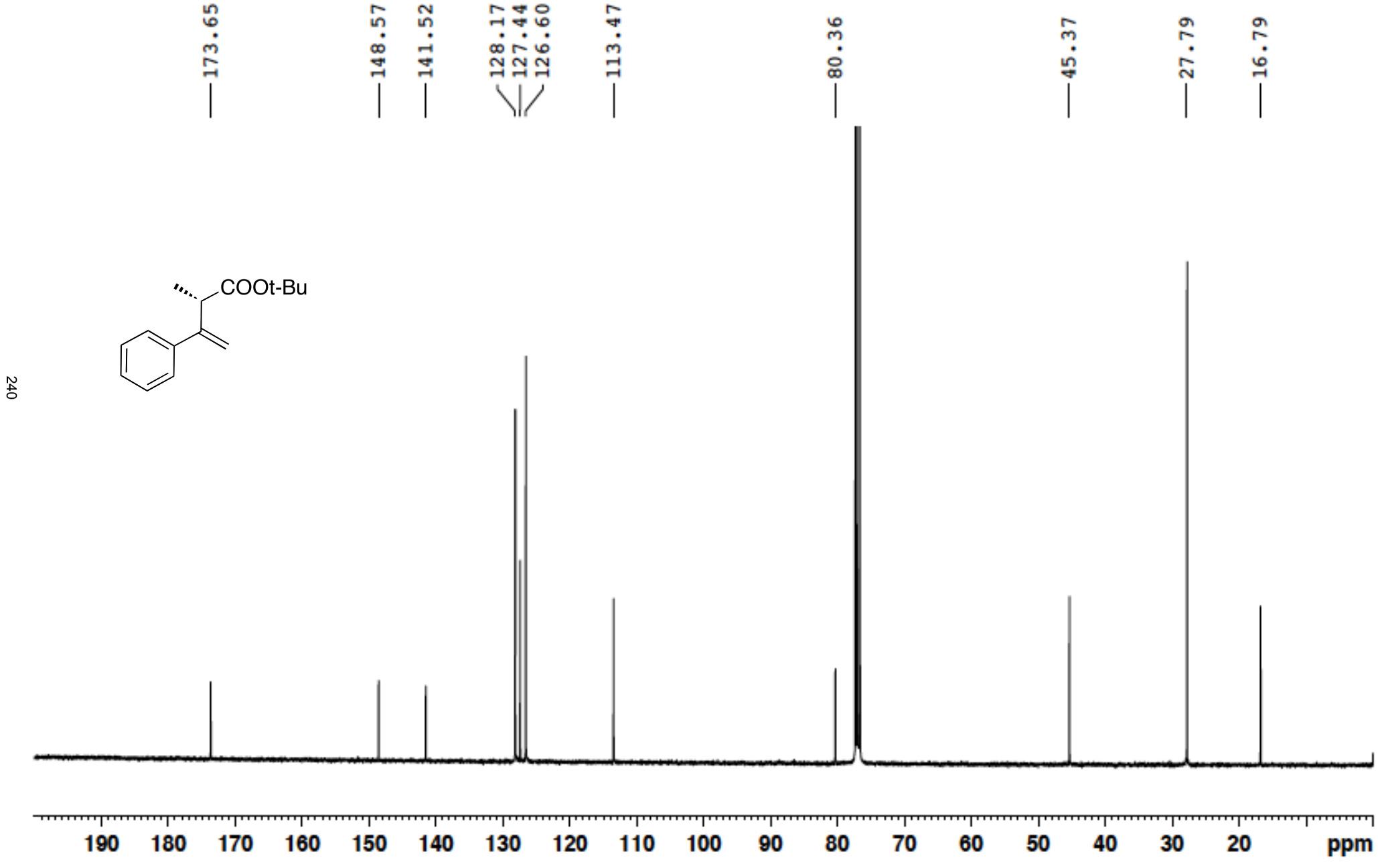
JF11-29-3 13CNMR, CDCl3, BBFO1
2013-07-22



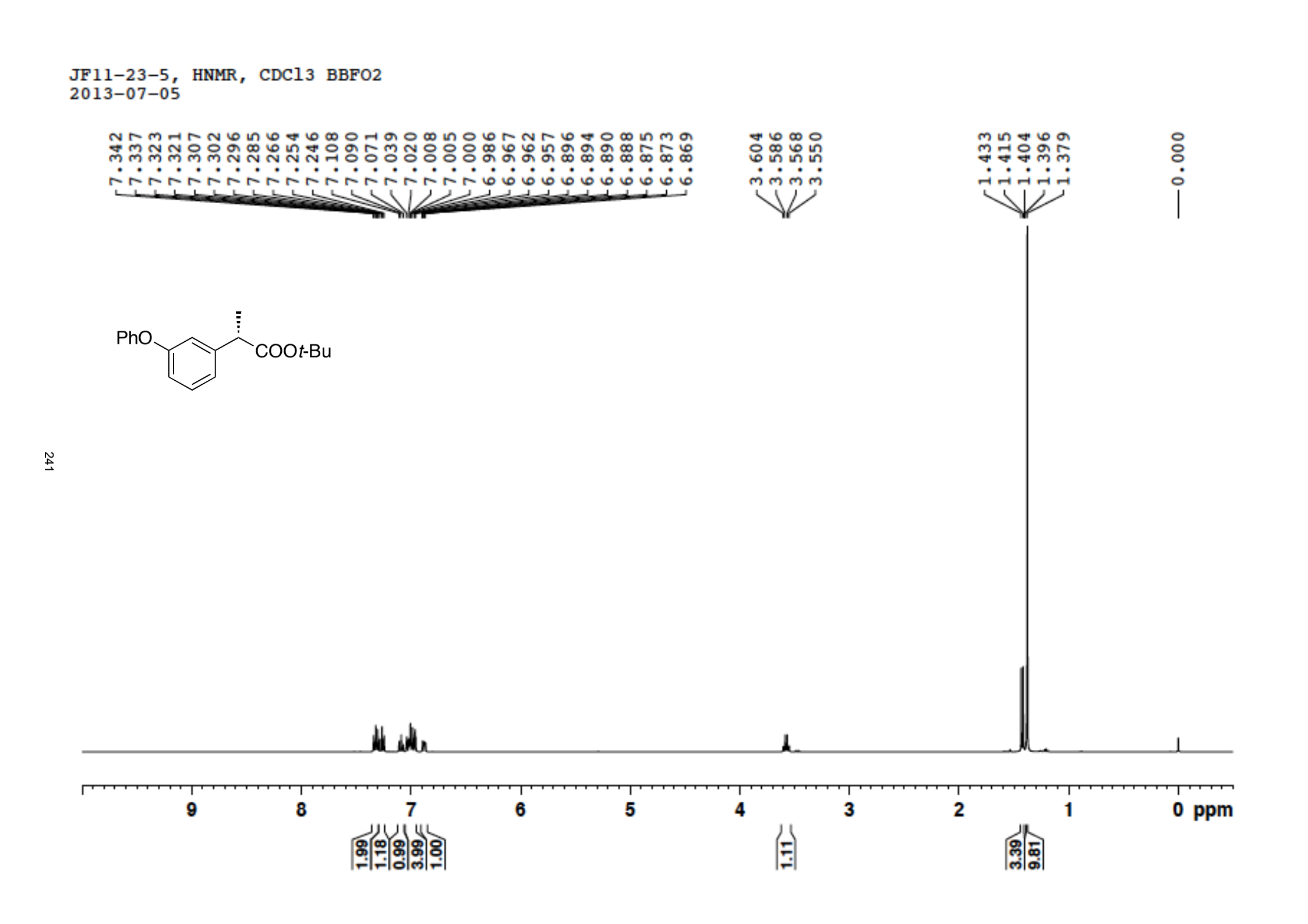
JF11-29-1 1HNMR BBFO1 CDCl3
2013-8-9



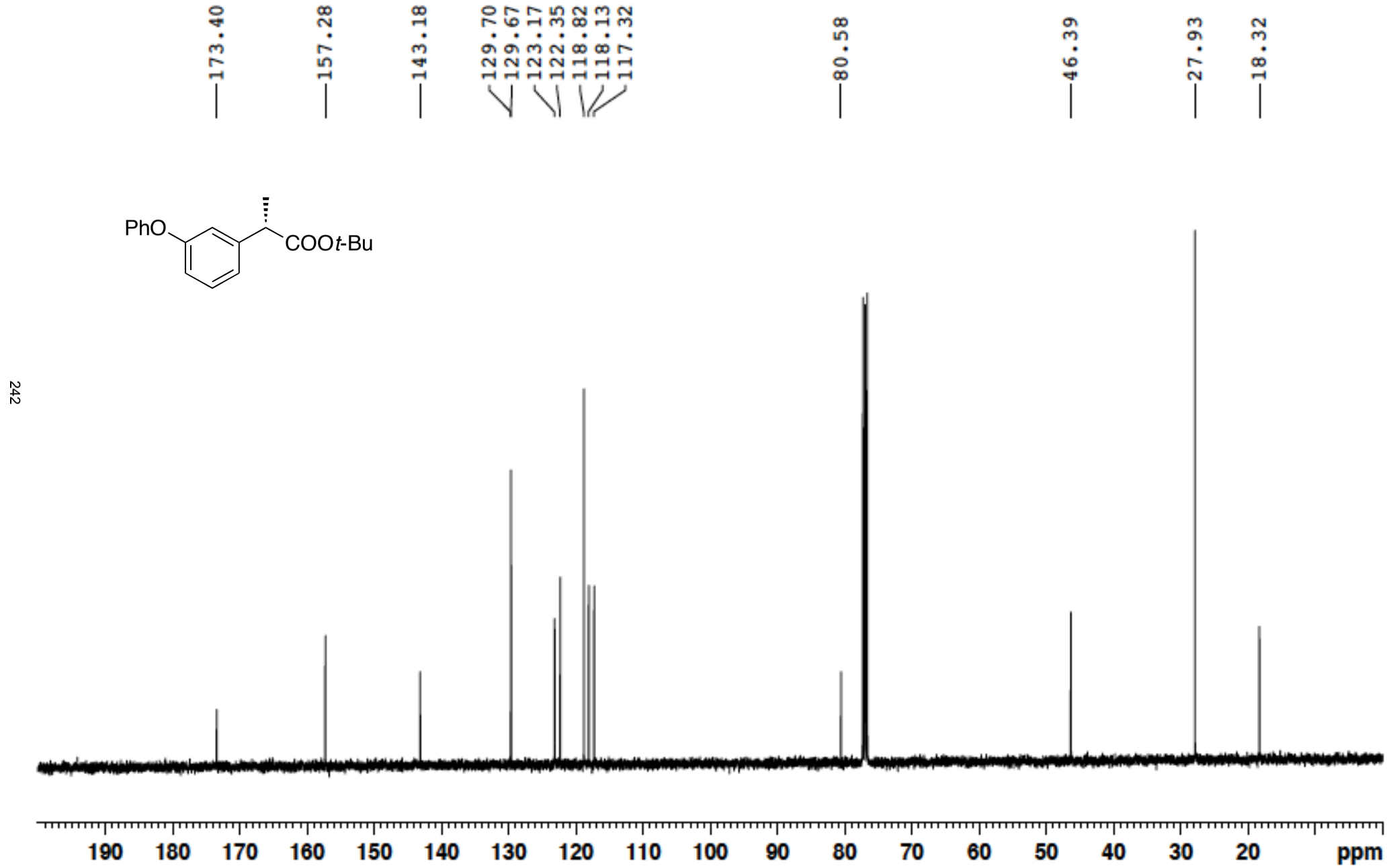
JF11-29-1 CDCl3 13CNMR BBFO2
2013-08-09



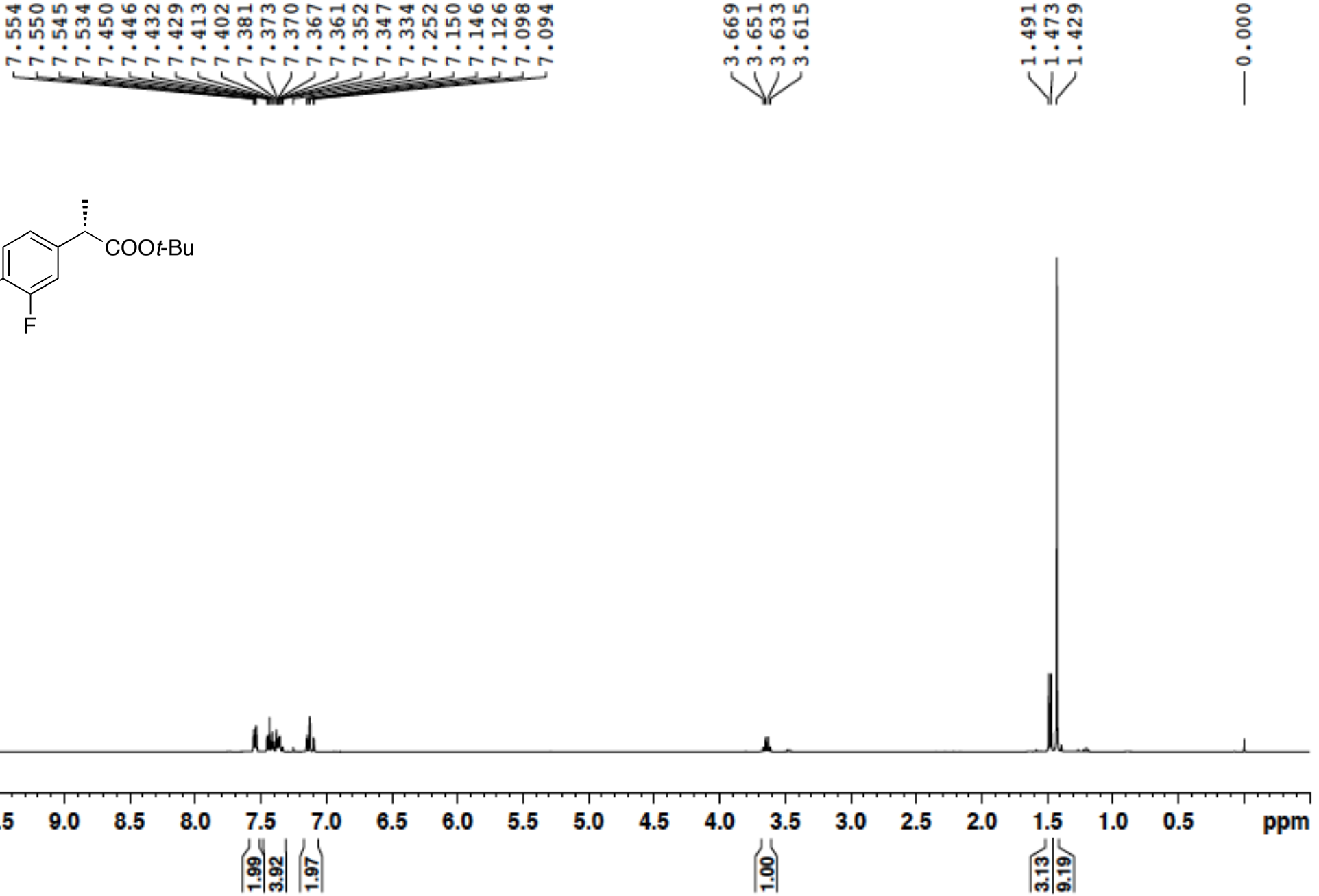
JF11-23-5, HNMR, CDCl3 BBFO2
2013-07-05



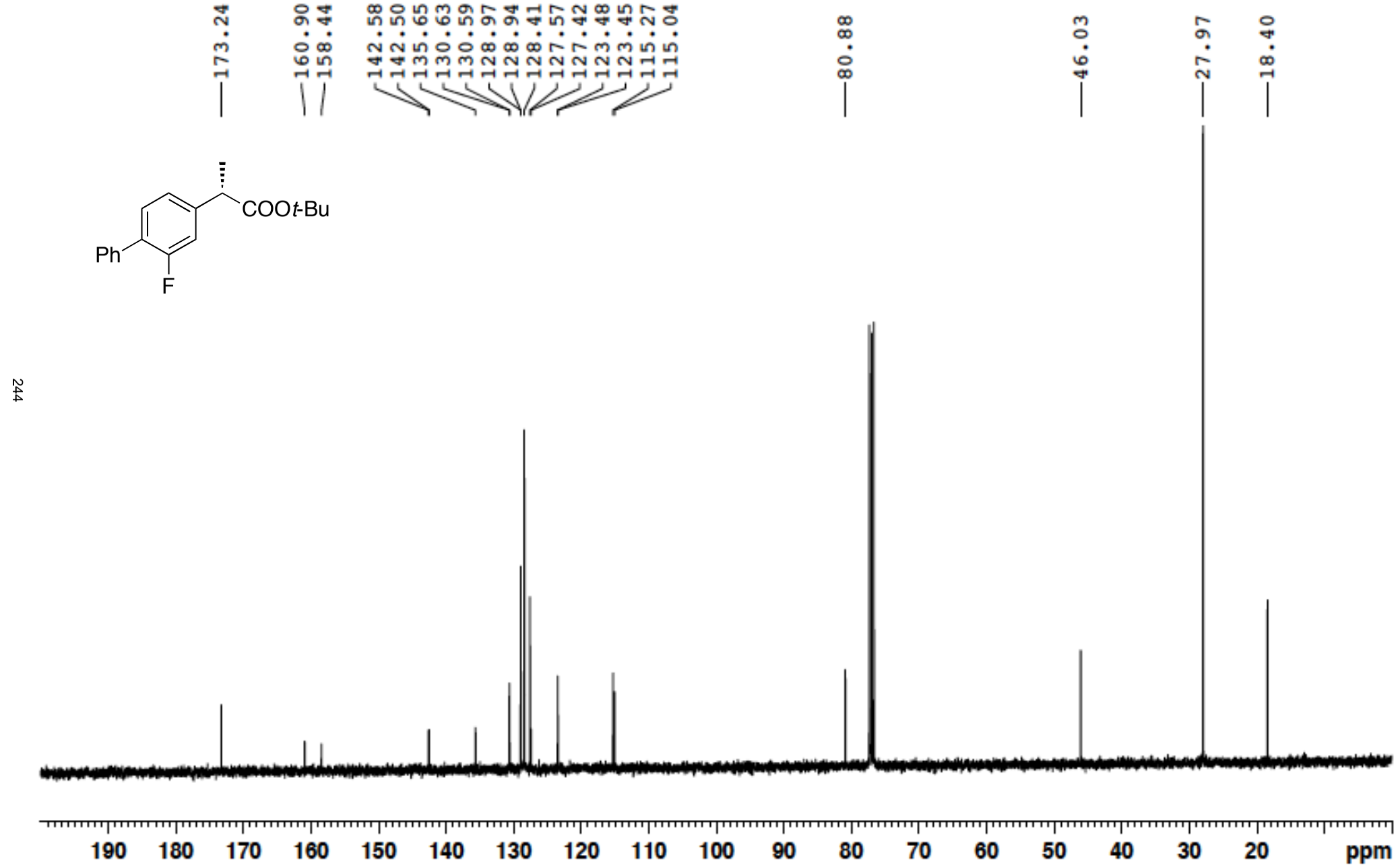
JF11-23-5, 13CNMR, CDCl3 BBFO2
2013-07-05



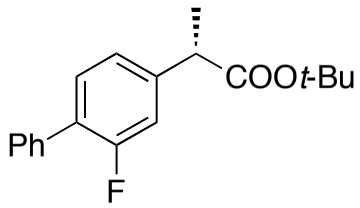
JF11-23-6, HNMR, CDCl3 BBFO2
2013-07-05



JF11-23-6, 13CNMR, CDCl3 BBFO2
2013-07-05



JF11-23-6 1HNMR BBFO1 CDCl3
2013-8-2



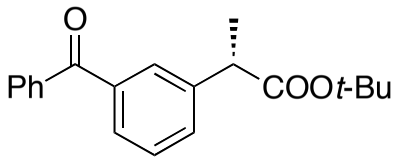
JF11-53-4 CDCl3 1HNMR BBFO2
2013-08-02

7.797 7.792 7.788 7.732 7.728 7.691 7.688 7.684 7.672 7.669 7.665 7.612 7.598 7.593 7.589 7.578 7.575 7.572 7.549 7.530 7.501 7.482 7.467 7.463 7.455 7.436 7.417 7.261

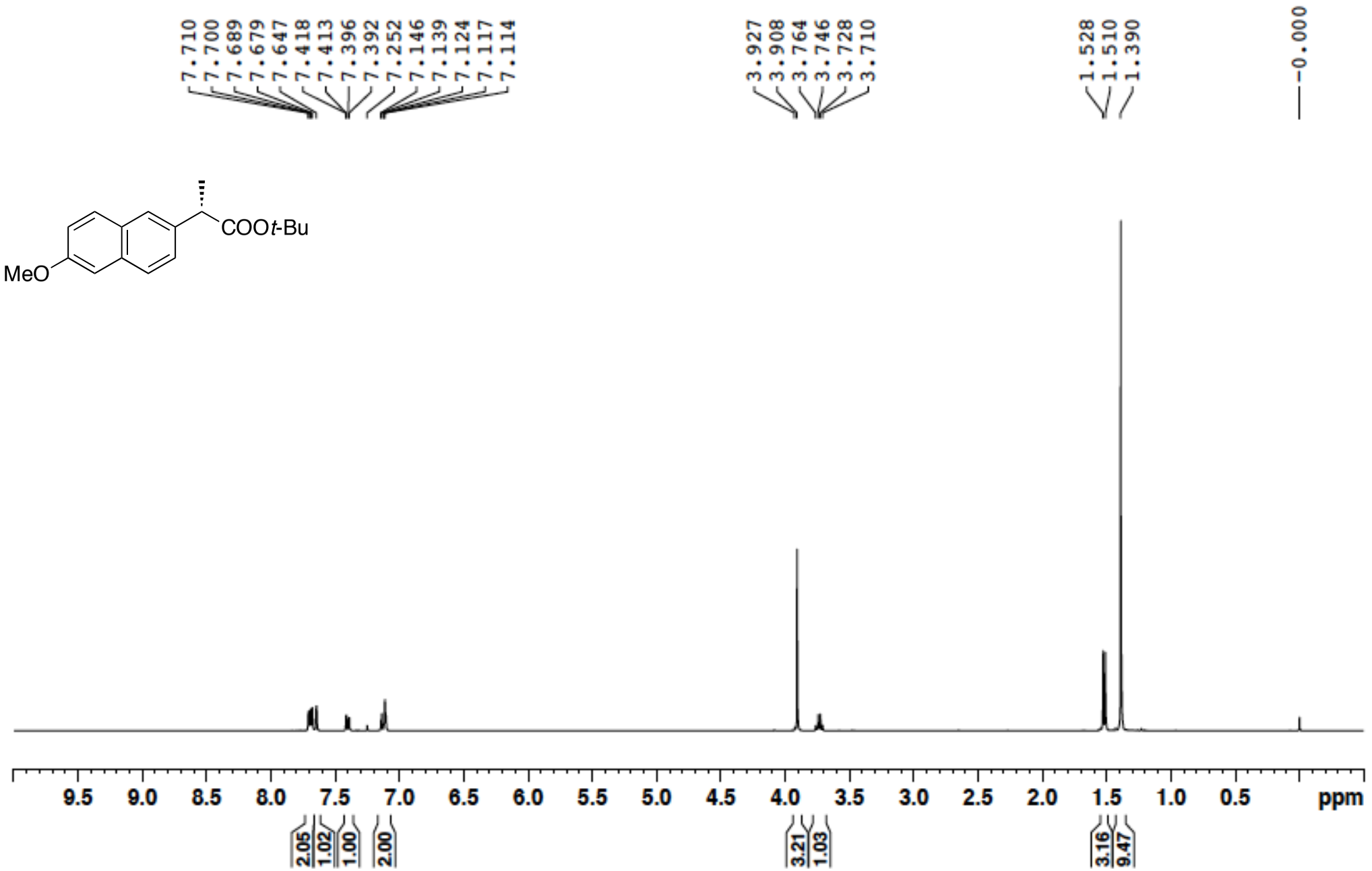
3.714 3.696 3.678 3.660

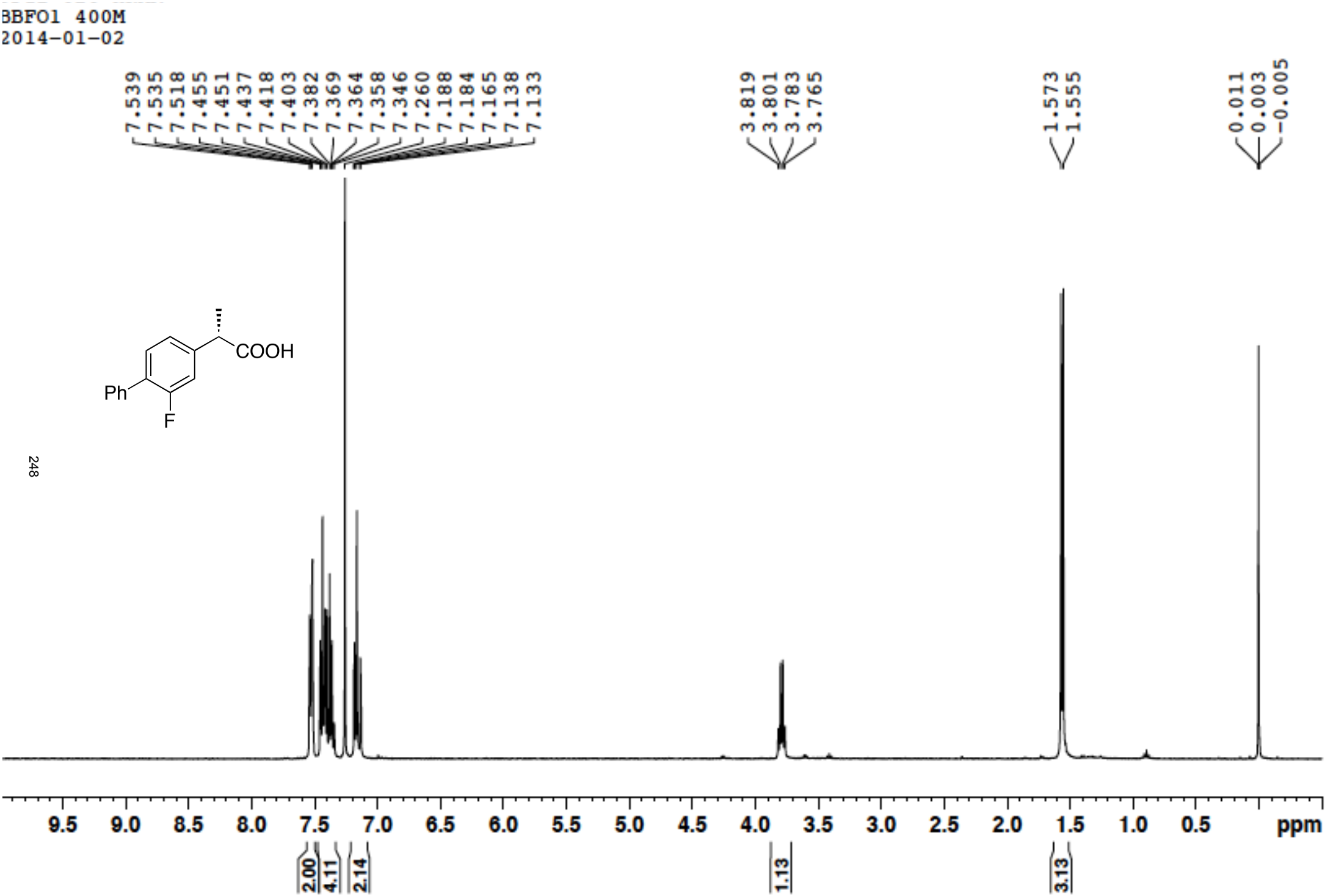
1.488 1.470 1.402

0.000

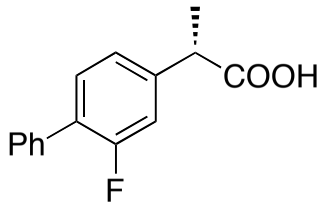


JF11-23-15 CDCl3 1HNMR BBFO2
2013-08-02




BBFO1 400M
2014-01-02
7.539
7.535
7.518
7.455
7.451
7.437
7.418
7.403
7.382
7.369
7.364
7.358
7.346
7.260
7.188
7.184
7.165
7.138
7.133
3.819
3.801
3.783
3.765
1.573
1.555
0.011
0.003
-0.005
COOH
Ph
F
248
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
ppm
2.00
4.11
2.14
1.13
3.13

BBFO1 400M
2014-01-02



249