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CYCLOADDITIONS AND YLIDE CHEMISTRY OF DONOR/ACCEPTOR-SUBSTITUTED CARBENES FROM THERMAL DECOMPOSITION OF ARYLDIAZOCARBONYL COMPOUNDS

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By

Stephanie Ramona Ovalles

M.A., University at Buffalo, The State University of New York, 2008

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Abstract

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By Stephanie Ramona Ovalles

It has been demonstrated that free carbenes derived from aryldiazocarbonyl compounds can be generated thermally in refluxing trifluorotoluene. In the presence of alkenes, the carbenes undergo diastereoselective cyclopropanations. Very high diastereoselectivity can be observed in moderate to excellent yields if the aryl group is electron rich. Aryldiazoketones generate ketocarbenes that undergo the Wolff rearrangement to form ketenes under the thermal conditions. The ketene undergoes thermal [2+2]-cycloaddition with alkene substrates present. Through kinetic studies, it has been shown that electron-withdrawing aryl groups stabilize the diazo compound. A ~100-fold reactivity difference was observed between nitro and methoxy-substituted aryldiazoacetates.

The thermally generated carbenes from aryldiazoacetates undergo ylide formation in the presence of oxygen or nitrogen-containing substrates. This was utilized to achieve N–H insertions with a variety of primary and secondary amines to afford unusual α-amino acid precursors. Tertiary allylic and propargylic amines can undergo a [2,3]-sigmatropic rearrangement from the ylide to produce exotic amino esters with α-quaternary centers.

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decides to do next with his life as a college student. I am sure that whatever he chooses, he will be great at it.

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Para mi Mama

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List of Abbreviations

$Rh_2(OAc)_4$	Dirhodium tetrakisacetate
DOSP	4-dodecyl phenylsulfonylprolinate
EWG	Electron withdrawing group
ρ	Hammett reaction constant
σ	Substituent parameter
EDG	Electron donating group
LUMO	Lowest unoccupied molecular orbital
dr	Diastereomeric ratio
Nu	Nucleophile
THF	Tetrahydrofuran
M	Metal
h	Planck's constant
ν	Frequency

GC	Gas chromatography
DFT	Density Functional Theory
G	Gibbs free energy
OAc	Acetate
RT	Room temperature
acac	Acetylacetonate
N/A	Not applicable
$\mathbf{k_{rel}}$	Relative rate constant
A	Absorbance
k	Rate constant
T	Temperature
TPN	tris(2-pyridyl)amine
NMR	Nuclear Magnetic Resonance
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
FTIR	Fourier-transform Infrared
HRMS	High-resolution mass spectrometry
APCI	Atmospheric pressure chemical ionization
TFT	Trifluorotoluene

Chapter 1

Cycloaddition Chemistry of Free Donor/Acceptor Carbenes

1.1 Introduction

1.1.1 Properties and Reactivity of Carbenes

Carbenes are neutral divalent derivatives of carbon.[1] They can exist as a triplet or singlet species, which depends on whether the nonbonding electrons are of the same or opposite spin (Figure 1).[1-4] The two electronic configurations have different geometry and reactivity. The triplet state carbene has its two electrons spread over two of the p-orbitals of the carbon atom. This carbene electronic state has reactivity similar to that of radicals. The bond angle for the H–C–H for the triplet carbene is predicted by MO calculations to be 136 °C and 105 °C for the singlet carbene (Figure 1). [1-5]

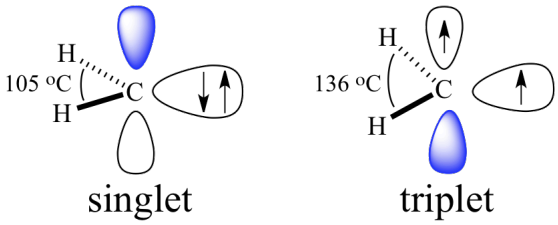


Figure 1 Singlet and triplet carbene.[1,2]

All simple dialkyl carbenes have a triplet ground state,[1] but by changing the substituents α to the carbene (i.e. N, O, halogen) can reverse this preference and make the singlet ground state more favorable.[4-9] Computational analysis of these carbenes states have shown that there is a linear correlation between the singlet-triplet gap and the electron

pair donating ability of the α-substituents of the carbene.[3] Substituents that act as electron-pair donors stabilize the singlet state more than the triplet state by delocalization of an electron pair into the empty *p* orbital (Figure 2).[3]

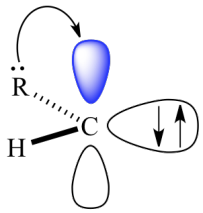


Figure 2: Electron donating group α to the carbene stabilize the singlet ground state.[3]

Thermodynamic stabilization corresponds to a lowering of the radical energy ground state[10] - an intrinsic property that is principally influenced by the ability of the substituents to delocalize the unpaired electron. This can reduce the reactivity by reducing the spin density on the radical center.[10] Polar substituents can also provide certain chemical inertia. Free radicals can be thermodynamically stabilized both by electron donors and electron acceptors.[10] This stabilization is commonly termed ***captodative effect*** in the literature;[10] which is simply the combined action of an electron-withdrawing (captor) and and electron-releasing (donor) substituent on a radical center, leading to an enhanced stabilization.[10]

1.1.2 Carbene Reactivity

The electronic states state of carbenes dictate their reactivity profiles.[1,6,11-14] The singlet state, with its unfilled *p* orbital, should be electrophilic and exhibit reactivity similar to that of other electrophiles.[14] Singlet carbenes have been experimentally and computationally been shown to react in a concerted fashion. Thus, it was predicted that additions of singlet carbenes would be stereospecific whereas those of triplet carbenes

would not be.[12] A singlet carbene gives 100% stereospecific reactions (Figure 3).[12] The singlet carbene when reacted with a *cis*-alkene produces a *cis*-cyclopropane, and a *trans*-alkene produces a *trans*-cyclopropane.[12] This prediction has been confirmed, and the stereoselectivity of addition reactions with alkenes has come to be used as a test for the involvement of the singlet vs triplet carbene in specific reactions.[12] Carbenes are very electron deficient species, and because of this they tend to have high reactivity. A theoretical study on the addition of singlet methylene to ethylene suggests that there is no activation barrier.[15]

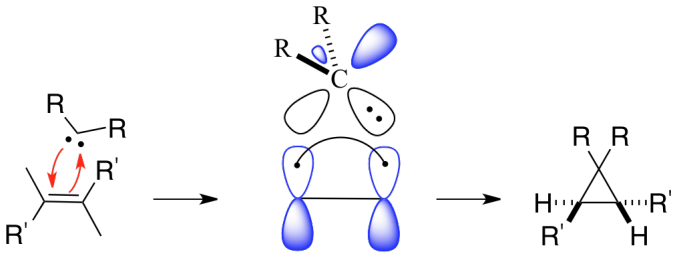


Figure 3: Singlet carbene addition to an alkene.[15]

Unlike the singlet carbene that reacts in a concerted fashion, a triplet carbene has been observed as proceeding through a stepwise mechanism.[13,14] It reacts like a diradical and should exhibit selectivity similar to that of free radicals.[13,14] Also, a triplet carbene must go through an intermediate that has two unpaired electrons of the same spin.[13,14] Thus, the addition of a triplet carbene should not be stereospecific, producing a mixture of diastereomers (Figure 4).[13,14]

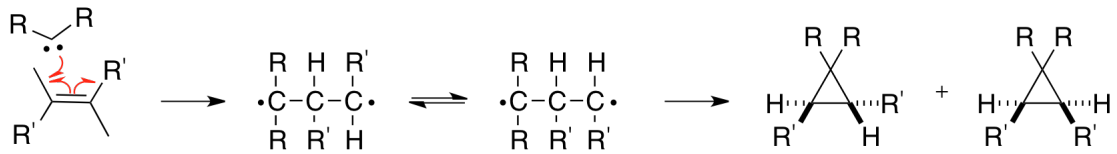


Figure 4: Triplet carbene addition to an alkene.[13,14]

Another type of carbene reactivity is that of a carbene inserting into a C–H bond.[1,10] If the carbene is in the triplet state it will insert itself into the C–H bond via a radical abstraction followed by a recombination (Figure 5).[1,10] Due to the high reactivity of the intermediates that are involved, intermolecular carbene insertion reactions are not very selective.[1,10] There is some increase in selectivity with functionally substituted carbenes, but the selectivity is still not high enough to prevent formation of mixtures.[1,10] The low selectivity of free carbene in intermolecular insertion reactions has traditionally prevented them from being useful in synthesis. It is difficult to distinguish clearly between a singlet or triplet carbene insertion, but determination of reaction stereochemistry provides one approach.[1,10] In the case of the triplet carbene; the two-step process will depend on the rate of recombination in competition with stereorandomization of the radical intermediate.[1,10]

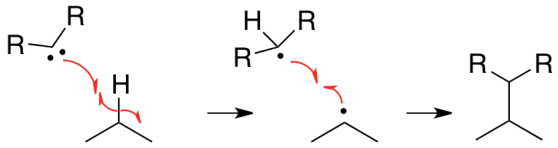


Figure 5: Triplet carbene insertions into a C–H bond.[1,10]

Unlike a triplet carbene, a singlet carbene will insert itself into the C–H bond in a concerted fashion (Figure 6).[1,10] Intramolecular insertion reactions usually occur at the C–H bond that is closest to the carbene, and good yields can frequently be obtained.[1,10]

[16,17]Intramolecular insertion reactions can provide routes to highly strained structures that would be difficult to obtain in other ways.[1,10]

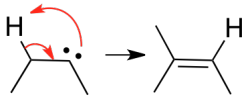
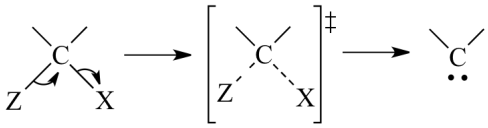


Figure 6: Singlet carbene insertion into a C–H bond.[1,10]

1.1.3 Carbene Generation

A variety of methods have been used to generate carbene intermediates.[1,10] The decomposition of carbenes is a quite general reaction. One way to generate a carbene is through α-elimination reactions (scheme 1). [1,10]

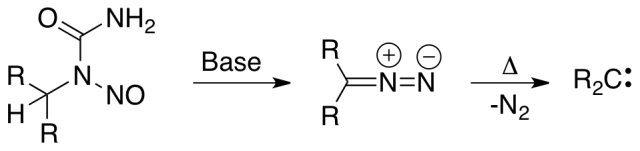
Scheme 1: Carbene α-elimination reactions.[1,10]



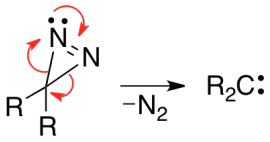
Next, the decomposition of diazomethane and other diazoalkane, diazoalkene, and diazo compounds with aryl and acyl substituents is commonly used for the generation of carbenes.[1,10] The main restriction with this method is the limitations with the synthesis of the diazo compounds and their instability.[17] Diazomethane and diazoalkene are toxic and potentially explosive.[17] They are usually prepared immediately before use. A general protocol for the generation of diazoalkane involves the base induced elimination of *N*-nitrosoureas.[17] Diazoalkanes can then be used for the generation of carbenes through thermal or photochemical decomposition (Scheme 2).[1,17] Diazo compounds can also be synthesized by oxidation of the corresponding hydrazone.[17] This method is used most frequently when one of the substituents is an aromatic ring. Another method for

generating free carbenes is through the decomposition of diazirine compounds (Scheme 3).[17]

Scheme 2: Thermal decomposition of diazoalkane to generate a free carbene.[17]

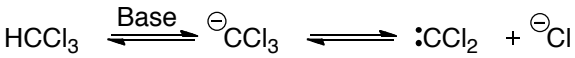


Scheme 3: Diazirine decomposition to generate a free carbene.[17]



The classical way of generating a free carbene is through the base catalyzed α–elimination of chloroform to generate dichlorocarbene (Scheme 4).[1,11] This method is not restricted to chloroform, other haloforms may be used as well.[1,11] The α–elimination is restricted to reactants that do not have β-hydrogens, because dehydrohalogenation by β-elimination dominates when this can occur.[1,11] This reaction displays second-order kinetics, first order in both base and haloform.[1,11] This supports a mechanism involving an equilibrium deprotonation prior to rate-determining α–halogen elimination.[1,11]

Scheme 4: Base-catalyzed generation of a free carbene from chloroform.[1,11]

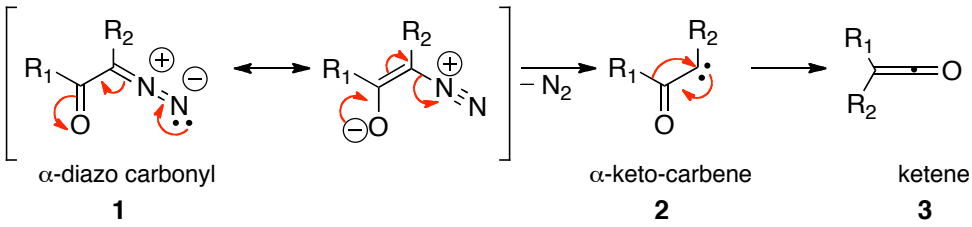


1.1.4 Free Carbenes in Synthesis

α-Diazo ketone compounds can decompose to form free ketocarbenes through photolysis, thermolysis or catalytically.[17] This carbene can rearrange to form a ketene through what

is known as a Wolff rearrangement.[18] The photochemical method of the Wolff rearrangement (discovered by Horner) is frequently used and is often considered superior to the alternatives.[18] The rearrangement is believed to proceed via a ketocarbene **1**, generated by the extrusion of N_2, followed by the α-keto-carbene **2** rearrangement to the more stable ketene **3** via a nucleophilic 1,2-shift of substituent R (Scheme 5).[18] The Wolff rearrangement is commonly used in synthesis as a part of the Arndt-Eistert homologation or as a method for ring contraction to generate strained cyclic systems.[18] The Arndt Eistert homologation has been successfully applied to syntheses of alkaloids, terpenes and other complex natural products.[18]

Scheme 5: Wolff Rearrangement.[18]



1.1.5 Metal-Stabilized Donor/Acceptor-Substituted Carbenes

Generation of carbenes in the presence of metals can lead to carbenoid complexes in which the carbene is stabilized by coordination to the metal.[17] This can dramatically influence the reactivity and selectivity of the carbene.[16,17] However, the selectivity of many transient metal carbenes has been experimentally shown to be greatly influenced by the α-substituents on the carbene.[19,20] The transient metal carbenes often fall under three distinct classifications which are; acceptor, acceptor/acceptor, and donor/acceptor-substituted carbenoids (Figure 7).[21] The term "donor" and "acceptor" refer to the electron donation or withdrawal through resonance effects. An acceptor group affects the

carbenoid's electrophilicity thus making it more reactive; while a donor group stabilizes the carbenoid center making it more chemoselective.[21] The donor/acceptor carbenoids have been found to be very selective in intermolecular reactions.[22-25] The combination of the aryl or vinyl donor and the acceptor group is believed to give the carbenoid the right balance between electrophilicity and stability, which allows for selective reactions to occur.[21] The acceptor carbenoids are typically the least selective and rapidly form carbene homodimerization products in competition with productive reactions.[17,26] Although acceptor/acceptor carbenoids have two electron withdrawing groups, the selectivity is often in between that of acceptor and donor/acceptor-carbenoids. This may be related to a larger degree of steric effects influencing these carbenoids in reactions. A major conclusion from these observations is that, although metals can be used to tune the electronic nature and reactivity of carbenes, the carbene α-substitutents play a central role in determining the reactivity and selectivity of reactions.[21]

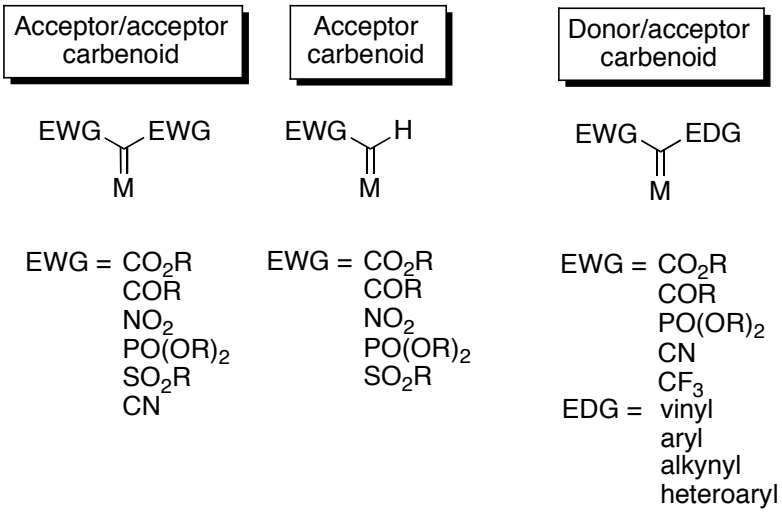
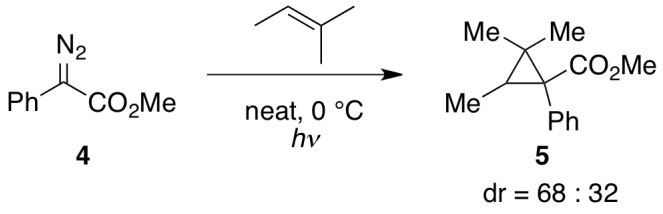


Figure 7: Carbenoid classification based on α-substituents.[21]

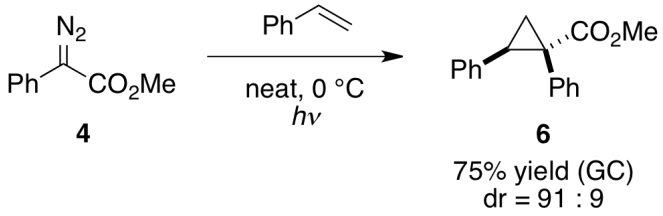
1.1.6 Cyclopropanation chemistry of Free Donor/Acceptor Aryl-Carbenes

In metal carbene chemistry, the donor/acceptor substituted carbenes, i.e. those derived from aryl- or vinyldiazoacetates, have been shown to be particularly selective.[24] The exploration of free donor/acceptor carbenes has not been described to great extent in the literature, but a few reports of reactions involving such intermediates exist. Tomioka and co-workers described specific examples where methyl phenyldiazoacetate was used in photochemical carbene reactions; however, no systematic study of the use of carbenes derived from aryldiazoacetates was conducted.[27-29] In an investigation of solvent effects on phenylcarbene reactivities, **4** was photolytically decomposed in the presence of 2-methylbut-2-en and the corresponding cyclopropane was formed in 68 : 32 dr in 68% combined yield with methanol O–H insertion product (scheme 6). When studying matrix effects of cyclopropanations with arylcarbenes, Tomioka also reported one entry with photolysis of diazo compound **4** in the presence of styrene, which resulted in the formation of the cyclopropane **6** in 75% yield and 91 : 9 dr (scheme 7). These studies demonstrate that the carbene derived from **4** can be generated through photolysis and participate in cyclopropanation chemistry with alkenes.

Scheme 6: Cyclopropanation of 2-methylbut-2-en via photolysis of **4**.[28]



Scheme 7: Cyclopropanation of styrene via photolysis of **4**.[27]



1.1.7 Electronic structure

Hadad, Toscano and co-workers conducted computational and experimental studies of the effects of substituents on the singlet–triplet energy gap in phenyl(carbomethoxy)carbenes (donor/acceptor carbenes) using IR spectroscopy and gas-phase computations.[30] They found in DFT calculations that the ground state of the p-substituted carbenes changes from triplet state in the case of p-nitro substitution (ΔG_{ST} = 6.1 kcal/mol) to singlet state in the case of p-amino substituted carbenes (ΔG_{ST} = -2.8 kcal/mol)(Scheme 8, Table 1).[30] These results were supported by IR studies. Good correlation was found between the singlet-triplet energy gaps and σ_p^+, which implies that the interaction between the aromatic system and the empty p-orbital on the singlet carbene is the most important factor in the substituent effect.[30] This study suggests that the preferred electronic state of such carbenes can be tuned by appropriate choice of substituents on the aryl group. This could potentially influence the reactivity and selectivity of these carbenes in reactions with other substrates.

Scheme 8: Singlet-triplet free energy differences.[30]

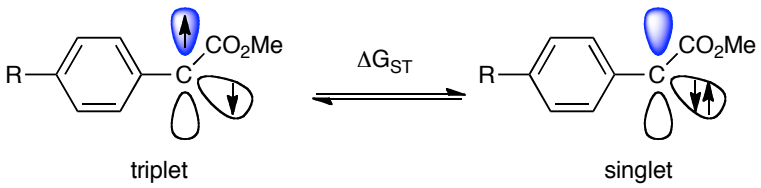


Table 1: Substituent effects on singlet-triplet gap.[30]

Entry	R =	ΔG_{ST}
1	4-NO_2	+6.1
2	H	+2.5
3	4-Me	+1.6
4	4-OMe	-0.8
5	4-NH_2	-2.8

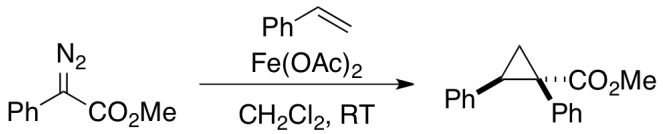
This chapter will explore how donor/acceptor carbenes from aryldiazo compounds can be generated thermally and undergo selective cycloaddition reactions. Although the photochemical decomposition of aryldiazoacetates is known, no reports exist that explores in detail how aryldiazoacetates form carbenes thermally and how such conditions systematically affect the chemistry of these species. Diazo compounds have traditionally been considered to be thermally unstable and prone to explosive behavior upon heating. The discussion herein will show that these compounds are relatively well-behaved and more stable than what is commonly thought. It will also be demonstrated that, contrary to common wisdom, free carbenes can undergo highly selective reactions and therefore be of potential synthetic utility.[31]

1.2 Results and Discussion

1.2.1 Discovery

Iron is a very interesting metal in the field of catalysis due to its low cost and abundance in nature.[32] While investigating the potential for using iron(II) acetate as a catalyst for the decomposition of diazo compounds, Mr. Evan Davies observed that methyl phenyldiazoacetate (**4**) was slowly consumed in a reaction mixture consisting of the diazo compound, excess styrene and the iron catalyst in dichloromethane at room temperature.[33] (Scheme 9). The reaction was studied by reactIR, which showed that it proceeded at a very slow rate (figure 8). This was an interesting discovery, because it implied that iron could be a potential new metal catalyst for reactions that have traditionally been rhodium-catalyzed.

Scheme 9: Iron(II)-catalyzed decomposition of **4**.



4 **6**

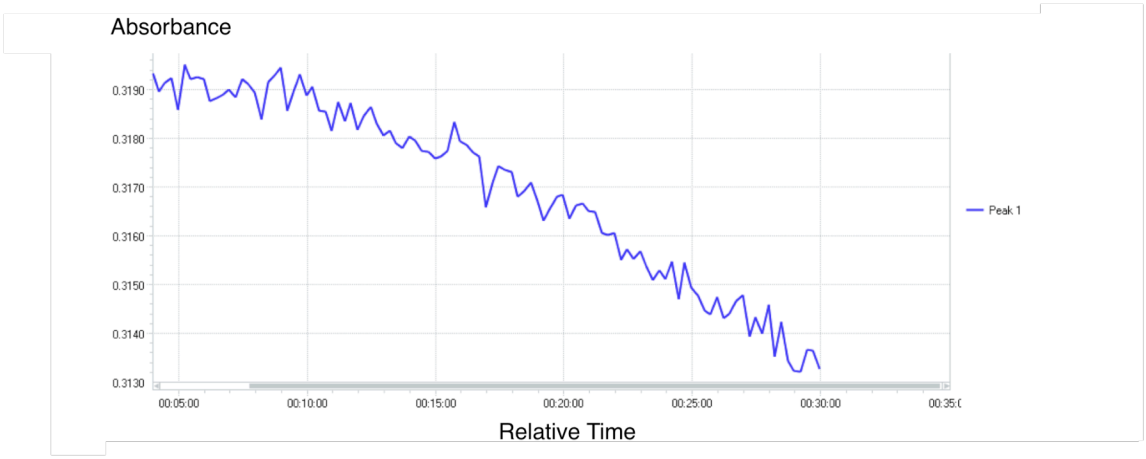
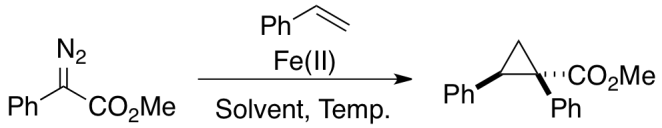


Figure 8: Consumption of diazo compound as function of time.[33]

The iron-catalyzed reaction was studied further. It was shown that the reaction led to small amounts of cyclopropane products (**6**), but at an extremely slow rate. The reaction was left at room temperature for 48 hours and still only partial conversion of the limiting diazo compound had been observed. In an attempt to increase the reaction rate, a series of experiment were conducted at various temperatures (40–102 ºC, table 2) in which different iron salts were screened for activity in this reaction. The first reaction tested was that of iron(II) acetate with styrene and diazo compound **4** in refluxing dichloromethane. At the end of the allotted time of reaction (12 h), only starting material was observed in the crude ^{1}H NMR. Iron(III) chloride was tested next as a possible catalyst in refluxing dichloroethane, but only polymerization of styrene could be observed by crude ^{1}H NMR (entry 2). Iron(II) iodide gave the same outcome (entry 3). It appears that these iron salts preferentially lead to the polymerization of the styrene at the higher temperature. The reaction with iron(II) acetate was revisited at this temperature, and it was observed that the cyclopropane product was formed in low yield (14%) and with 86 : 14 diastereomer ratio – much lower than the corresponding rhodium catalyzed reaction (entry 4). With

iron(II) sulfate, the formation of the cyclopropane products were also observed with slightly better yield (30%) (entry 5). From these studies, it was observed that increased reaction temperature and time gave better results. The temperature was therefore further increased to 102 ºC (refluxing trifluorotoluene) over a period of 12 hours. When the reaction with iron (III) chloride was conducted again under these new conditions, it was again observed that polymerization activity was predominant (entry 6). With iron(III) acetylacetonate, the cyclopropane products were formed with an increased yield of 63% and similar diastereoselectivity as before (d.r. = 76:24) (entry 7). The same was observed with various salts (entries 8-10). All of these reactions gave the cyclopropane products in higher yields (up to 92 %) and with similar diastereoselectivity (d.r. ~ 4 : 1). During these experiments, it was observed that many of the catalysts were not always completely, or even partially, dissolved in the solution during the reaction time. The results did not correlate well with these observations.

Scheme 10: Screen of iron salts in cyclopropanation reaction.



4 **6**

Table 2: Iron Salt Screen

Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)	dr
1	$Fe(OAc)_2$	CH_2Cl_2	40	--*	N/A*
2	$Fe(Cl)_3$	$C_2H_4Cl_2$	80	--*	N/A*
3	$Fe(I)_2$	$C_2H_4Cl_2$	80	--*	N/A*
4	$Fe(OAc)_2$	$C_2H_4Cl_2$	80	14	86 : 14
5	$Fe(SO_4)$	$C_2H_4Cl_2$	80	30	88 : 12
6	$Fe(Cl)_3$	$PhCF_3$	102	--*	N/A*
7	$Fe(acac)_3$	$PhCF_3$	102	63	76 : 24
8	$Fe(OAc)_2$	$PhCF_3$	102	81	79 : 21
9	$Fe(SO_4)$	$PhCF_3$	102	92	80 : 20
10	$Fe(O_2CCF_3)_2$	$PhCF_3$	102	69	79 : 21
11	None	$PhCF_3$	102	90	79 : 21

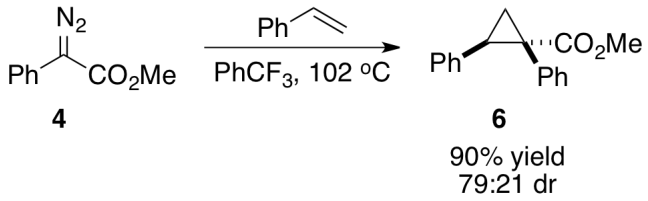
*Only styrene polymerization could be observed in crude ^1H NMR.

Due to the similar results, and an observed lack of solubility of many of the iron salts, a control experiment was conducted in which the iron salt was omitted (entry 11). The reaction still produced the cyclopropane products in high yields (90 % overall) and identical diastereoselectivity to the reactions conducted with iron-catalysts at this temperature. The reaction was furthermore repeated with new glassware and stir bar to make sure that no metal contaminants were present, again with similar results. It appears that a free carbene is generated under these reaction conditions, which undergoes cyclopropanation with styrene in a diastereoselective fashion. Since there are no detailed reports of the synthetic utility of such thermally generated carbenes from aryldiazoacetates, a systematic study was undertaken to understand the control elements of the selectivity as well as the scope of the reaction.

1.2.2 Scope of Free Carbene Cycloaddition

During exploratory studies on iron-catalysis, a control experiment was conducted in which methyl phenyldiazoacetate **4** was heated to reflux with styrene in trifluorotoluene over 12 h. Remarkably under theses conditions, a clean transformation was observed, generating the cyclopropane **6** in 90% yield in a 4 : 1 *E/Z* ratio (scheme 12). Although photochemically induced reactions of aryldiazoacetates have been described in the literature,[27-29] there are no reports of applying the thermally induced decomposition of such diazo compounds into synthetically useful reactions.

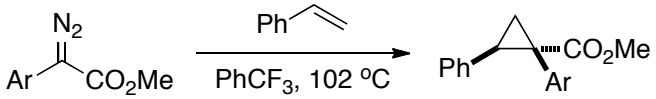
Scheme 11: Thermal cyclopropanation of styrene with **4.**



Theoretical studies have shown that the favored electronic structure of carbenes derived from aryldiazoacetates is dependent on the aryl substituent.[30] The singlet is favored when there is a donor substituent, such as *p*-methoxy group, while the triplet state is favored when there is an acceptor substituent such a *p*-nitro group. The cyclopropanation of a series of aryldiazoacetates was examined to see what impact the donor substituent would have on the reactivity (scheme 12, table 3). The reaction of the aryldiazoacetate in the presence of 5 equiv. of styrene in trifluorotoluene under reflux for 12 h was used as the standard reaction conditions. From this study it was observed that the diazos containing the more electron neutral and electron rich donor groups (**4**, **7-8**, and **11-12**) produced the cyclopropane products in higher yields (90-97%) and with high diastereoselectivity (≥93 : 7 dr) for the more electron rich diazo (**4**, **7-8**, and **10-11**). The diazos with the more

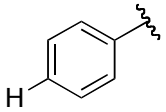
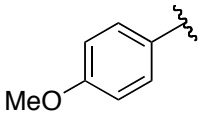
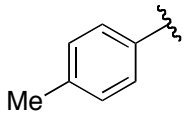
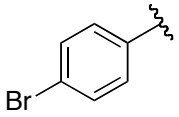
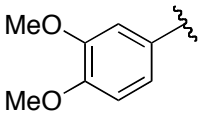
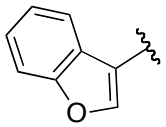
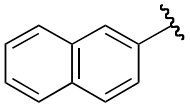
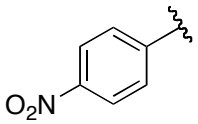
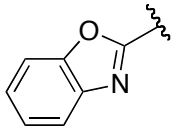
electron deficient donor group (**9**, **13** and **14**) produced the cyclopropane products in lower yields (76-57%), and moderate diastereoselectivity. The diastereoselectivity was almost non-existent for the cyclopropane derived from the *p*-nitro derivative **13** (56 : 44 dr). Many of the reactions were obtained in higher yields than the corresponding rhodium catalyzed reactions, although the diastereoselectivity was inferior and no opportunity exist for asymmetric induction. The reason for the marked difference in diastereoselectivity may be due to a change in the reacting electronic form of the carbene or may be due to an inherently more selective reaction by carbenes with a stronger donor substituent.

Scheme 12: Screen of different donor groups for thermal cyclopropanation reactions.



4, 7-14 **6, 15-22**

Table 3: Influence of diazo compound structure

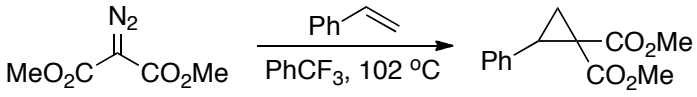
Compd	Ar	Yield (%)[a]	dr[b]
6		90	79 : 21
15		92	95 : 5
16		93	95 : 5
17		76	81 : 19
18		68	95 : 5
19		95	93 : 7
20		97	82 : 18
21		57	56 : 44
22		68	77 : 23

[a] Isolated yields. [b] From ^{1}H NMR of crude reaction mixture.

Recent studies have shown that the reactivity of metal carbenes is highly dependent on the nature of the carbenoid.[21] So, the thermal reactions of aryldiazoacetates were compared with other major classes of carbenes; the acceptor carbenes and the acceptor/acceptor carbenes. Reaction with methyl diazomalonate (**23**) produced the

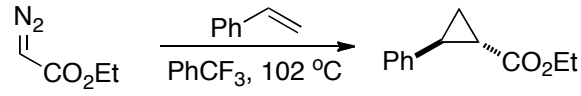
cyclopropane product (**24**) in 13% after 12 h because the conversion of **23** was slow under these reaction conditions (Scheme 13). The reaction with the more traditional carbene precursor, ethyldiazoacetate (**25**) produced the two cyclopropane products (**26**) in 90% yield and 67 : 33 dr (Scheme 14). The yield was comparable but the distereoselectivity was much lower than for those conducted with the aryldiazoacetate. The synthetic studies conducted up to now indicate that the thermal stability of the diazo compounds is structurally dependant, and that the diastereoselectivity is strongly related to the structure of the carbene.

Scheme 13: Thermal cyclopropanation of styrene with diazomalonate.



23 **24**
13% yield

Scheme 14: Thermal cyclopropanation of styrene with ethyl diazoacetate.

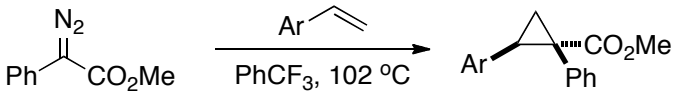


25 **26**
90% yield
67:33 dr

Next, it was studied whether the electronic nature of the alkene trap was influencing the reaction. A series of *p*-substitutes styrene derivatives were studied first (scheme 15, table 4). The cyclopropanes **27-28**, derived from electron-rich styrene derivatives, were obtained in 92% yield and again with moderate diastereoselectivity (≥76 : 24). This is comparable to what was observed for cyclopropane **6**. The diastereoselectivity (79 : 21) was also moderate in this case. The cyclopropanes **29-31** derived from the more electron deficient *p*-substituted styrene systems were obtained in yields ranging from 64-87%

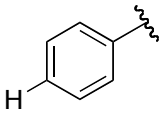
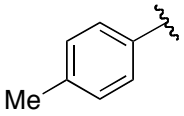
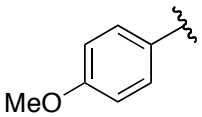
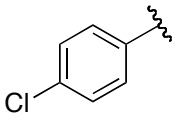
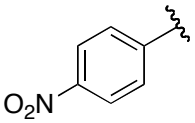
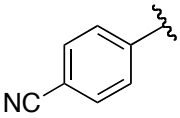
yield, although with similar diastereoselectivity to before. The lowest yield was obtained for the *p*-cyanostyrene (**31**), probably due to polymerization, that was observed, of the substrate under these thermal conditions (102 ^{o}C).

Scheme 15: Thermal cyclopropanation of electronically different styrenes.



4 **6, 27-31**

Table 4: Influence of styrene electronics on thermal cyclopropanation.

Compd	Ar	Yield (%)[a]	dr[b]
6		90	79 : 21
27		92	76 : 24
28		92	83 : 17
29		87	74 : 26
30		94	67 : 33
31		64	71 : 29

[a] Isolated yields. [b] From ^{1}H NMR of crude reaction mixture.

The same study as above was next repeated with methyl (4-methoxyphenyl)diazoacetate to see whether or not the high stereoselectivity observed for this diazo compound before

would be retained with the electronically different styrenes (scheme 16, table 5). The cyclopropanes (**32-33**) generated from the more electron rich styrene systems were obtained in yields ranging from 92-98 % and high diastereoselectivity (≥ 92 : 8 dr). When the reaction was carried out with *p*-chlorostyrene the cyclopropane product **34** was generated in a good 80% yield and with very high diastereoselectivity (95 : 5 dr). When the reaction was carried out with even more electron-deficient systems **34-36** the yield dropped dramatically (50-20%), but reactions were still very diastereoselective (≥92 : 8). This screen of various styrene derivatives with two electronically different diazo compounds has shown that the high diastereoselectivity is controlled by the electronic nature of the carbene, and the influence of the electronic nature of the alkene appears to be minor. However, very electron deficient alkenes give lower yields.

Scheme 16: Styrene screen with (4-methoxy)phenyldiazoacetate.

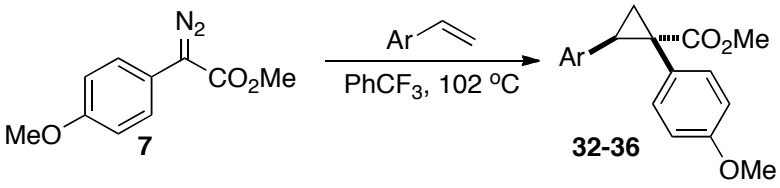
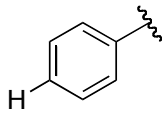
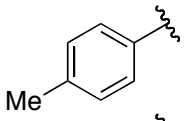
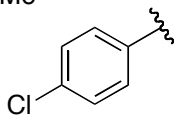
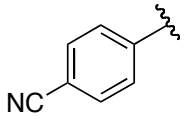
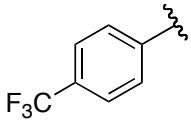


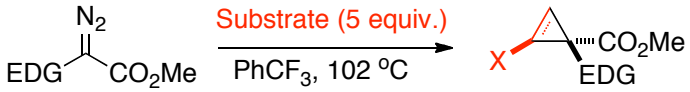
Table 5: Styrene screen with (4-methoxyphenyl)diazoacetate.

Compd	Ar	Yield (%)	dr
32		92	98 : 2
33		98	92 : 8
34		80	95 : 5
35		50	92 : 8
36		20	93 : 7

In continuation with the study on the influence the trapping agent, and to broaden the scope of the cycloaddition chemistry, various systems were studied next with electron-rich carbenes under the standard reaction conditions (Scheme 17, Chart 1). A moderately diastereoselective (86: 14 dr) reaction was observed when butyl vinyl ether was reacted with **7**, generating **38** in good combined yield of 85%. A cyclic vinyl ether, 1,2-dihydrofuran, afforded the corresponding cyclopropane **37** in ≥95: 5 dr and 71% yield. The reaction between diazo **10** and *cis*-β-methylstyrene afforded cyclopropane **39** in good 72% yield and diastereselectivity (92 : 8 dr). The high stereoselectivity lends support to a predominant singlet carbene mechanism of the reaction. Even *trans*-β-methylstyrene readily underwent cyclopropanation under these conditions to afford **40** in 62% yield and ≥95 : 5 dr. Cyclopropanation of *trans*-alkenes cannot be achieved under rhodium-catalyzed conditions unless the alkene is very electron-rich.[34] Using 1,2-

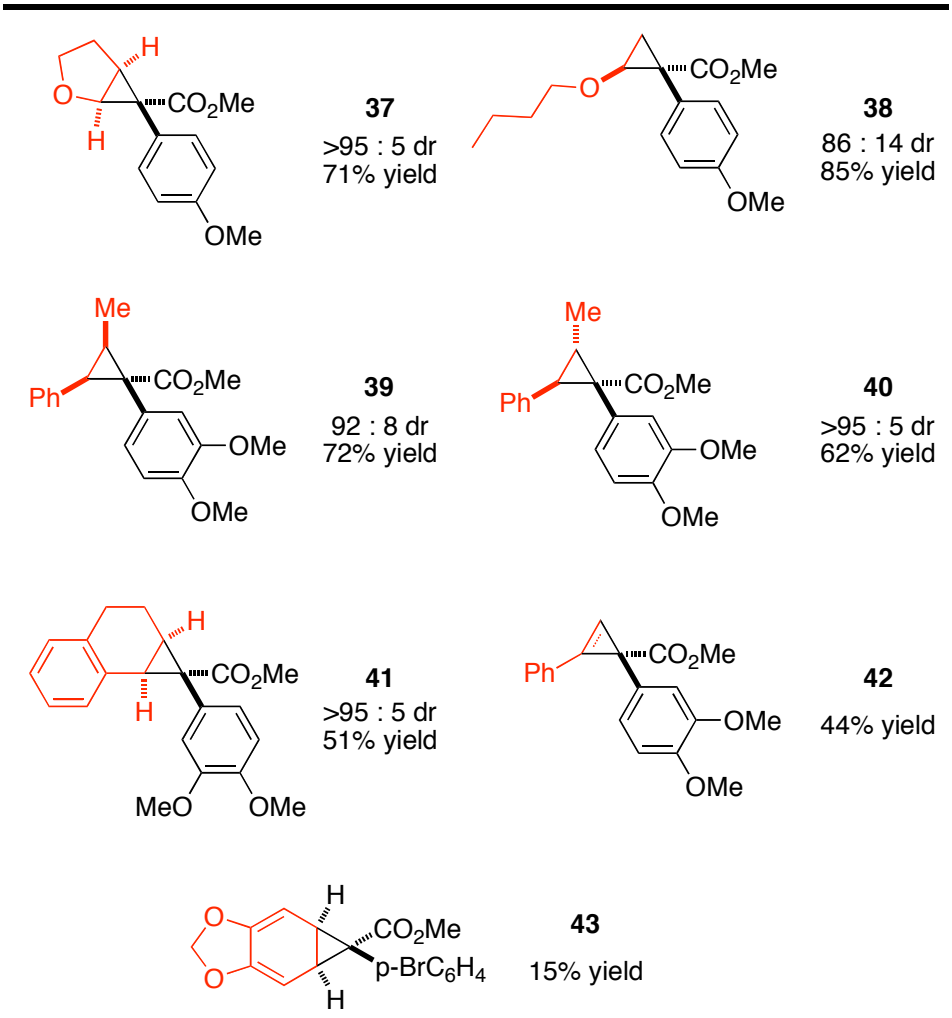
dihydronaphthalene as substrate with **10**, generated the cyclopropane **41** in 50 % yield and ≥95: 5 dr. A reaction was run with phenylacetylene and the cyclopropene **42** was generated in 44 % yield. A strange reaction occurred when benzo[1,3]dioxole was used as a substrate, this time with diazo **17**. Although not a clean reaction, product **43** was isolated in 15% yield. A cyclopropanation seems to have occurred on the electron-rich aromatic ring in spite of the presence of highly activated C–H bonds in this molecule. Although many of these reactions were fairly clean, lowered yields were observed in several cases. This may be attributed to product instability.

Scheme 17: Thermal cyclopropanation of various substrates with aryldiazoacetates.



7, 10 or **17** **37-43**

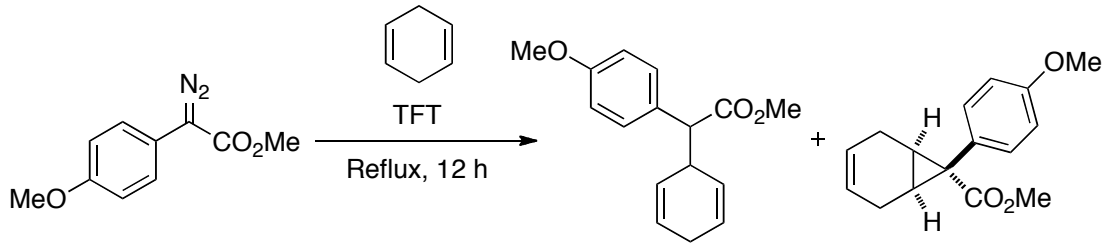
Chart 1: Exploration of the substrate scope for [2+1] cycloaddition.



An interesting observation is that no evidence for C–H insertion processes has been observed, even though many of the substrates have "activated" C–H bonds (α to heteroatom or allylic). A system that is highly activated for C–H insertion chemistry in metal-catalyzed reactions is 1,4-cyclohexadiene (scheme 18), which affords exclusively C–H insertion product into the methylene site. When methyl p-methoxyphenyldiazoacetate **7** was decomposed in the presence of an excess of 1,4-cyclohexadiene under the thermal reaction conditions, the C–H insertion product **44** was

observed in a 60 : 40 ratio with product of cyclopropanation of the double bond **45** in % yield. This shows that C–H insertions are possible with the free donor/acceptor carbenes, however, cyclopropanation appears to be more favorable as it is formed even for highly activated C–H bond containing substrates.

Scheme 18: Reaction with 1,4-cyclohexadiene.

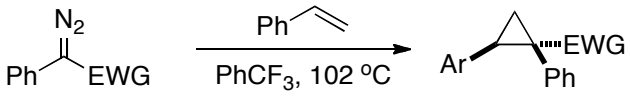


7 **44** **45**

60 : 40 ratio

Having established that the carbene donor group strongly influences the diasteroselectivity of the thermally generated cyclopropane products, next, the nature of the electron-withdrawing group on the carbene was studied briefly (scheme 19, table 6). When a phosphonate ester **46** was used as the electron-withdrawing group, the cyclopropane product **48** was generated in 97% yield, but with virtually no diastereoselectivity (52: 48 dr). Using a cyano- group as the acceptor, generated the cyclopropane **49** in 68% yield and again with no diastereoselectivity (50:50). These studies show that the acceptor group also plays a vital role in the stereoselectivity, and that an ester group is important to achieve high levels of diastereoselectivity.

Scheme 19: Thermal cyclopropanation with alternative EWGs.



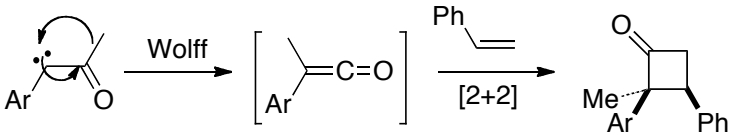
46-47 **48-49**

Table 6: Influence of EWG on thermal cyclopropanation.

Comp'd	EWG	Yield (%)	dr
48	$PO(OMe)_2$	97	52 : 48
49	CN	68	50 : 50

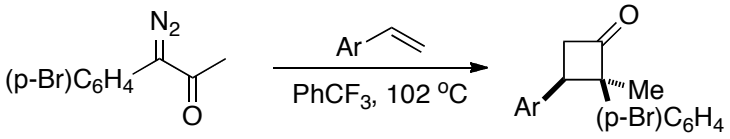
Attempts at extending the acceptor group to a methyl ketone resulted in a totally different reaction. Instead of the observed cyclopropanation chemistry, the carbenes derived from aryldiazoketones (**50**) underwent a Wolff-rearrangement to generate a ketene (**51**), followed by thermal [2+2]-cycloaddition with styrene (scheme 20). A series of styrene derivatives were reacted with diazoketone **53** to test the generality of the reaction. Electronically differentiated styrenes were tested in the reaction to produce cyclobutanones **54-57**. This proceeded in overall high yields (69-94%) and diastereoselectivities (≥90 : 10 dr). Only for the methoxy-substituted styrene was the diastereoselectivity >95 : 5. This represents a very practical and effective method for the generation of substituted cyclobutanones, since you only have to pre-mix the diazo compound with the alkene and heat the mixture to reflux for a few hours.

Scheme 20: Wolff rearrangement to a ketene, followed by a thermal [2+2]-cycloaddition.



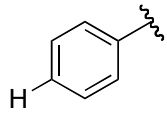
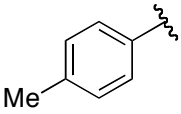
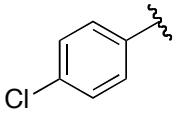
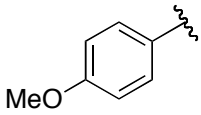
50 **51** **52**

Scheme 21: Thermal [2+2]-cycloaddition of diazoketone **53** with styrene.



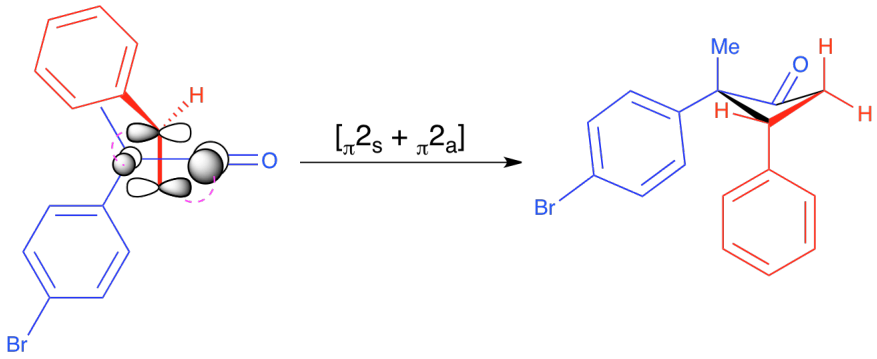
53 **54-57**

Table 7: Influence of styrene electronics on cyclobutanone formation.

Compd	Ar	Yield (%)	dr
54		69	91 : 9
55		91	90 : 10
56		94	90 : 10
57		71	>95 : 5

[2+2]-cycloaddtions between alkenes and ketenes is known, however, not with thermally generated ketenes from aryldiazoketones. In this case, the *syn*-diastereomer was formed preferentially, consistent with the concerted [$_{\pi}2_{s}+_{\pi}2_{a}$]-mechanism (scheme 22) and literature precedence.[1] The relative stereochemistry and structure of the major diastereomer was unambiguously proven with the elucidation of a crystal structure for the major diastereomer of cyclobutanone **54** (figure 9). The figure clearly shows the regioselectivity and *syn*-relationship between the aryl groups.

Scheme 22: The concerted [$_{\pi}2_s$+ $_{\pi}2_a$]-mechanism.



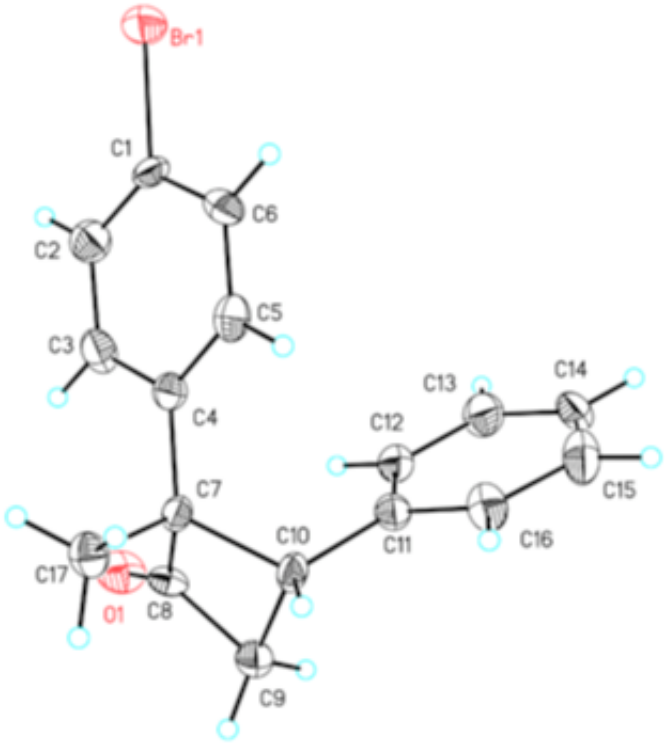
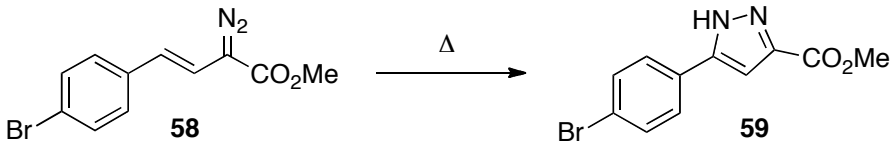


Figure 9: X-ray crystallographic structure of **54**.

Vinylcarbenoids derived from vinyldiazoacetates can also undergo very selective transformations under metal catalysis. Under thermal conditions, however, vinyldiazoacetates do not readily loose nitrogen to generate the corresponding vinylcarbene. They preferentially undergo 6π-electrocyclisation, followed by a [1,2]-hydrogen shift to form pyrazoles, as exemplified by vinyldiazo **58** forming **59** cleanly

(scheme 23).[35] Such diazo compounds were therefore not amenable to the thermal carbene chemistry that was observed for aryldiazoacetates.

Scheme 23: Pyrazole formation upon heating vinyldiazo compound.[35]



1.2.3 Mechanistic Studies of Free Carbene Generation

Hammett studies. To better understand the mechanism of the thermal cyclpropanations, a Hammett competition study was conducted. Styrene and other para- substitued styrene derivatives were combined in equal amounts and subjected to the thermal cyclopropanation by methyl p-methoxyphenyldiazoacetate (Scheme 24, table 8). The ratios of products were determined by ^{1}H NMR of the crude reaction mixtures and are given in table 8. When the data is plotted against σ^+ values obtained from literature reference,[36] there was poor correlation, however this gave the best result (Figure 10). Although the data is very scattered, the plot suggests a negative Hammett slope and therefore positive charge buildup in the transition state. The data was also plotted agains other substituent parameters, but this resulted in much worse correlations ($R^2 \sim 0.1$-0.4).[36] When the reactions were done in the past with rhodium carbenoids, there was a clear trend with a negative slope, which signified that there was a positive charge build up in the reaction and that a single mechanism is operating. The reason why a good trend is not observed is unclear, but may be because of two mechanisms acting in this chemistry – the cycloaddition may occur from both triplet and singlet states of the carbene.

Scheme 24: Competition studies.

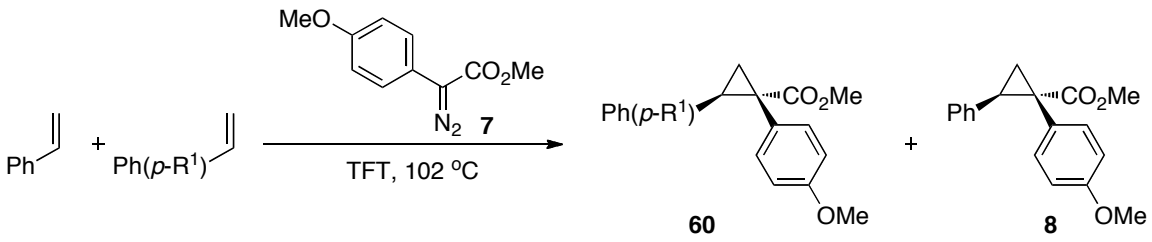


Table 8: Product ratios from competition studies.

R^1	Prod. Ratio (Ar/Ph)
-CN	1.05
$-CF_3$	0.48
-Cl	1.25
-H	1.00
-Me	0.95
-OMe	2.6

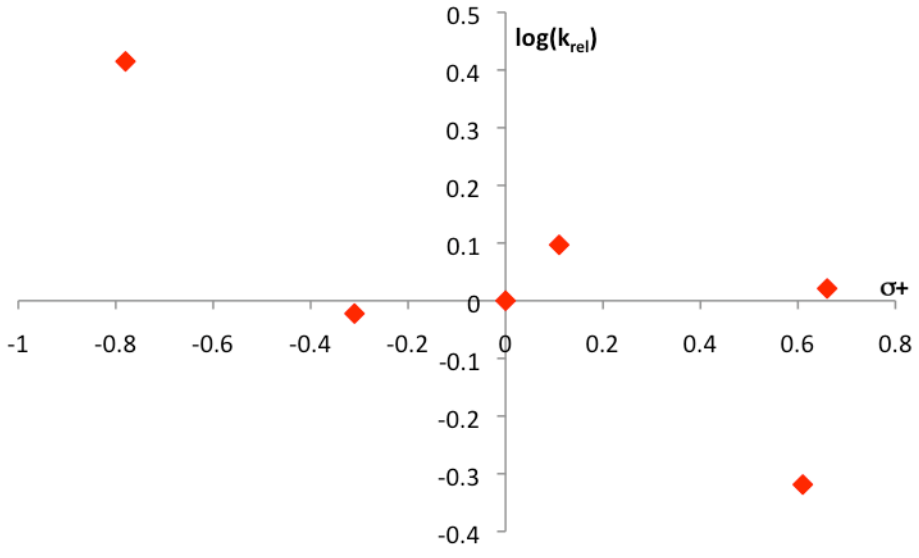


Figure 10: Hammett plot of free carbene cyclopropanation versus σ^+.[36]

Kinetic studies. The synthetic studies conducted thus far have indicated that the thermal stability of the diazo compound was structurally dependent. This issue was examined in more detail by conducting ReactIR studies on electronically differentiated aryldiazoacetates **4**, **7**, **13** and ethyl diazoacetate **25**. In the kinetics experiments, the diazo compound and styrene (5 equivalents) were combined in trifluorotoluene and then the reaction mixture was lowered into an oil bath kept at >130°C. The disappearance of diazo compound was monitored by tracking the $C{=}N_2$ stretch frequency (~2100 cm^{-1}). The experimental setup for these studies is shown in Figure 11.

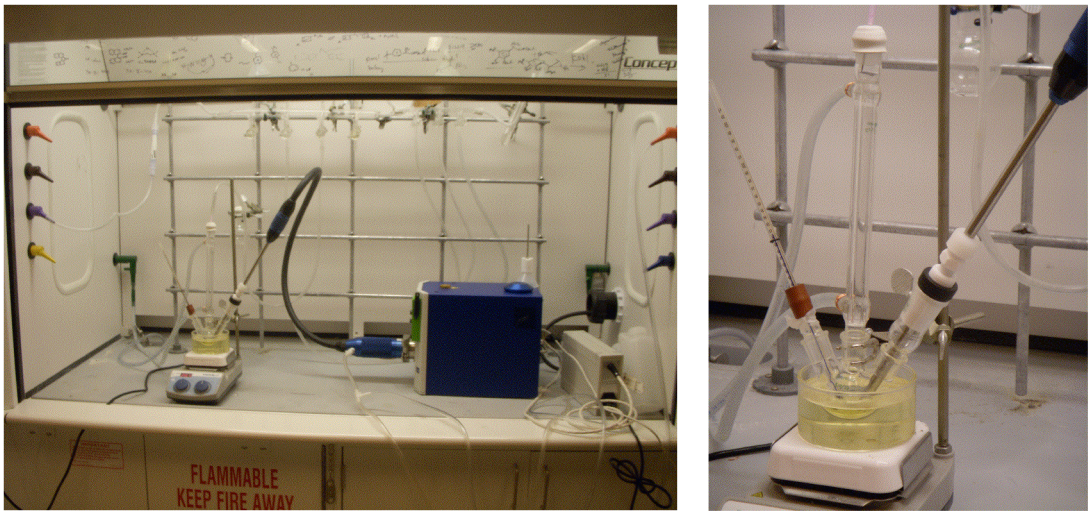


Figure 11: Experimental setup for kinetic studies.

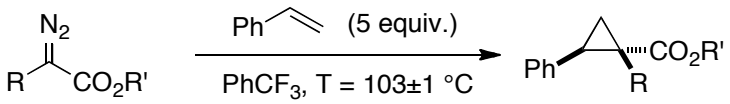
Figure 12 shows a conversion plot of the reaction progress over 1h. The initial data for **13** has a lot of noise, probably due to problems with solubility in the initial phase of the reaction. All the diazo compounds decomposed following first-order kinetics in trifluorotoluene at reflux. The decomposition reaction therefore follows the rate law given in Equation 1, where k_1 is the first-order rate constant. The first order rate constants

were found from linear regression analysis of plots of ln(ΔA) *vs* time, where the slope is equal to the rate constant (see Experimental Section).

$$\text{Rate} = k_1 [\text{diazo}] \qquad \text{(Eq. 1)}$$

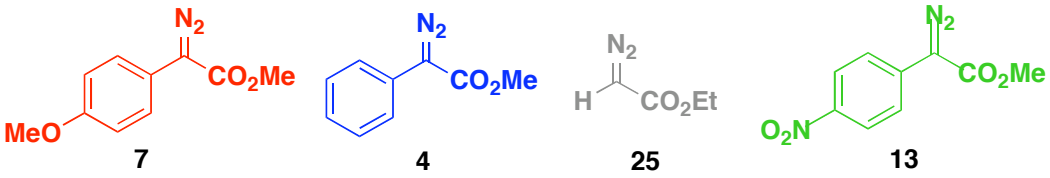
The rates of decomposition were very different, depending on the substituents (table 9). The nature of the aromatic substituent was profound; the *p*-methoxy derivative **7** had a half-life of 1.82 min, whereas the *p*-nitro derivative **13** had a half-life of ~5.2 h. Ethyl diazoacetate (**25**) displayed a half-life of ~1.6 h, inbetween the half-life of the unsubstituted aryl derivative **4** (21.7 min) and the *p*-nitro derivative **7**. Diazomalonate was the most stable and underwent negligible conversion over the 1 h period (not shown). These studies confirm the general opinion that acceptor groups stabilize diazo compounds. Furthermore, theses studies give valuable insight on why aryldiazoacetates are such useful precursors for metal carbenoid chemistry. The aryl group acts as a "donor" group, capable of stabilizing the electron deficient center of the carbene though *p*-donation. However, aryl groups are also σ-acceptors, and consequently, they do not greatly destabilize the diazo compound compared to ethyl diazoacetate except when a strongly electron donating group is present.

Scheme 25: Thermal cyclopropanation kinetics study.



4, 7, 13, 25 **6, 15, 26, 21**

Figure 12: Conversion vs time plot for cyclopropanation over 1h.



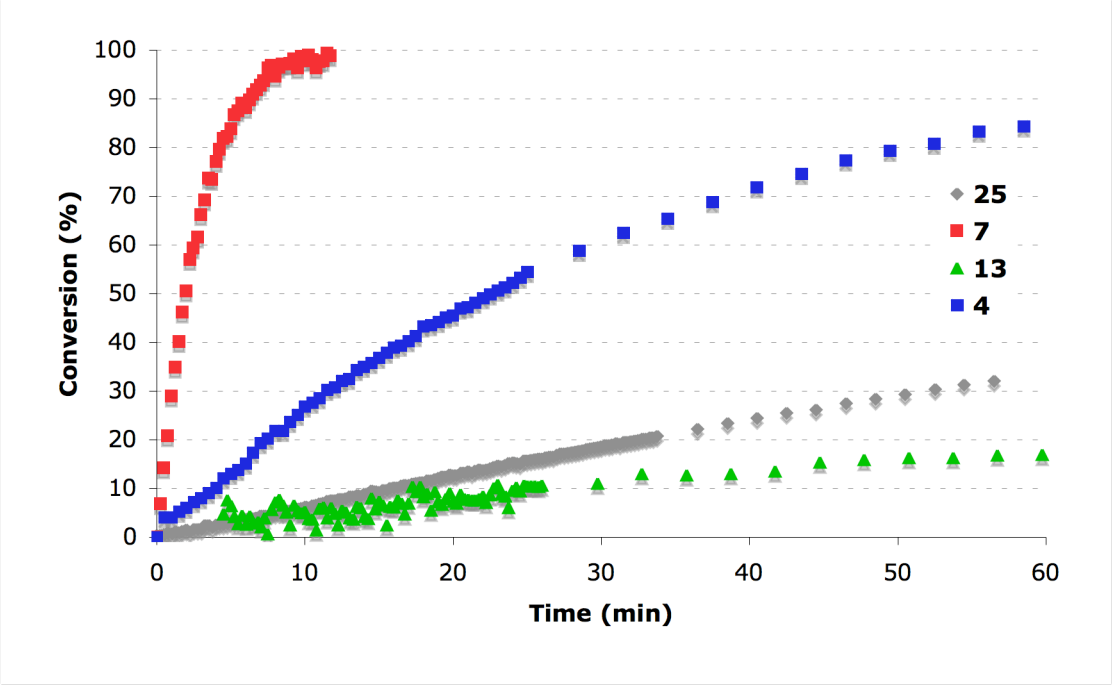
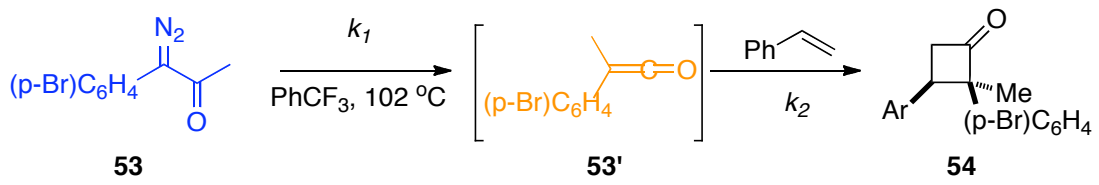


Table 9: First-order rate constants and half-lives from kinetic studies of thermal cyclopropanation.

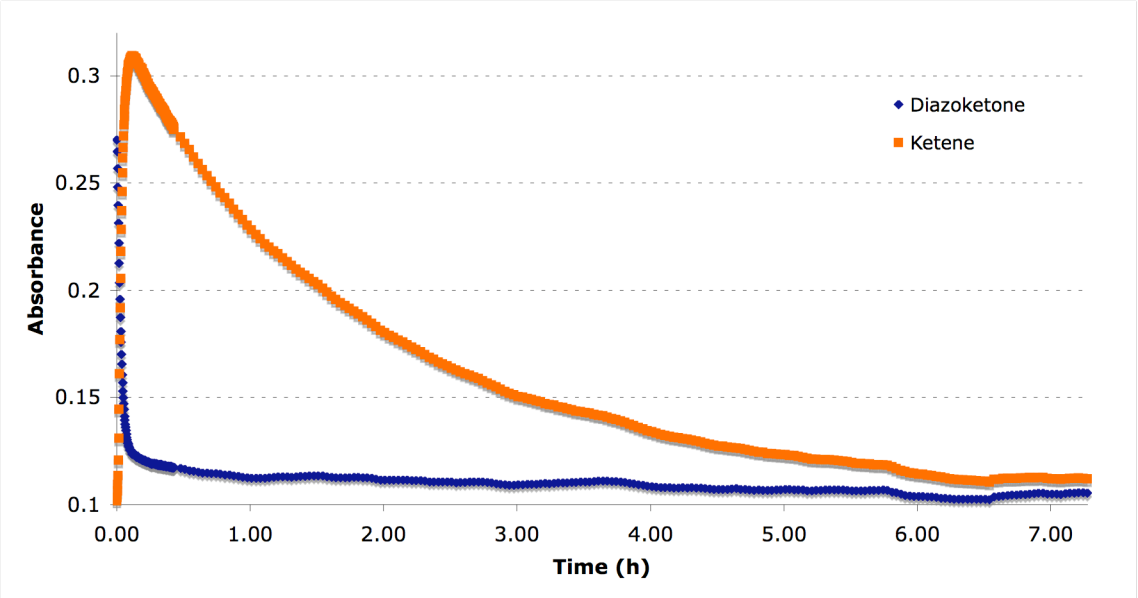
Entry	R =	Cmpd	k_1 (h^{-1})	$t_{1/2}$ (min)
1	(4-MeO)Ph	**7**	22.87 ± 0.03	1.82
2	Ph	**4**	1.92 ± 0.02	21.7
3	(4-NO_2)Ph	**13**	0.147 ± 0.009	310
4	H	**25**	0.422 ± 0.008	98.6
5	Ketone	**53**	26.99 ± 0.01	1.54

When studying the decomposition of the aryldiazoketone **53** under the thermal conditions using reactIR (Scheme 26), it also decomposed by first-order kinetics. The formation of the ketene intermediate **53'** was readily observed as the ketene C=C=O stretch frequency band appeared strongly as the diazo compound disappeared (figure 13a). The diazoketone decomposed even faster than methyl p-methoxyphenyldiazoacetate with a half-life of ~1.54 min (k_1). The ketene, however, was remarkably stable and underwent the [2+2] cycloaddition with styrene very slowly over a period of 8-9 h (Figure 13b). The pseudo first-order rate constant for this process was $k_2 = 0.622\ s^{-1}$.

Scheme 26: [2+2] cycloaddition with diazoketones.



a)



b)

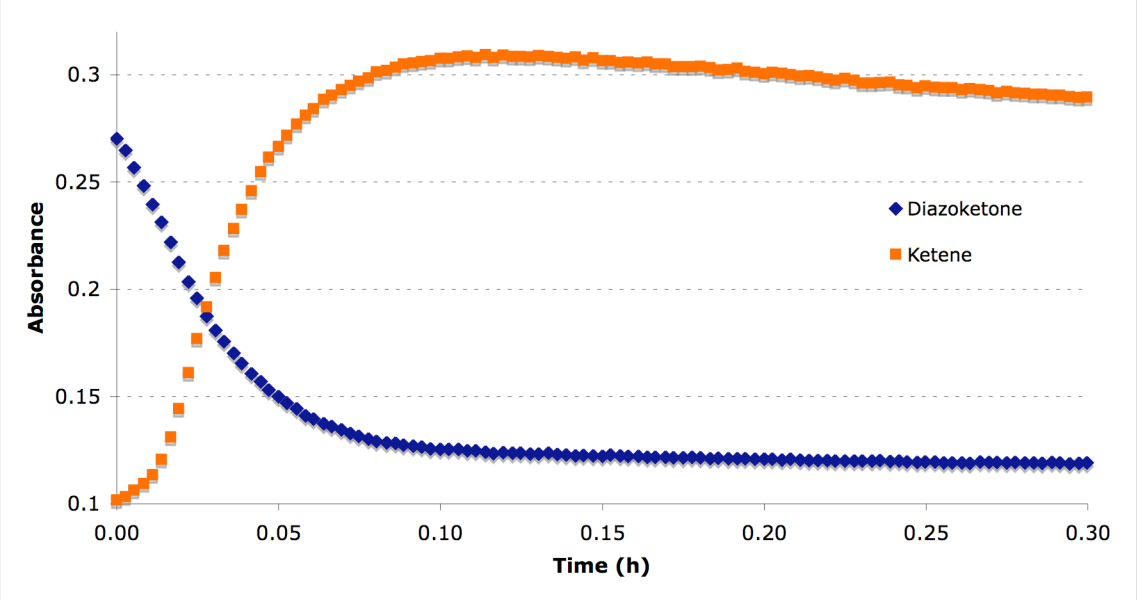


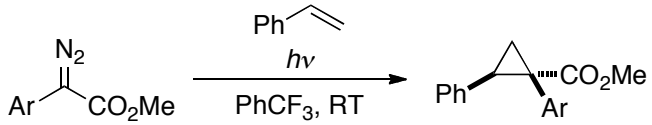
Figure 13: (a) Raw trace for decomposition of diazoketone **53**, formation of ketene intermediate and ketene decomposition. (b) Expanded view of initial 30 minutes.

1.2.4 Thermal *versus* Photochemical Carbene Generation

In order to understand the reactivity profile of the thermally generated donor/acceptor carbenes, a comparison study was initiated against the photochemically generated donor/acceptor carbenes. A series of aryl diazoacetates of differing electronics were subjected to UV light in a photochemical reactor with 5 equiv. of styrene at room temperature. In all three cases, the *cis* isomers were preferred over the *trans*. When the reaction was run with the electronically neutral methyl phenyldiazoacetate **4** the cyclpropane product (**6**) was isolated in 83% yield and 87 : 18 dr. This reaction was completed after approximately 10 h. This is comparable to what was observed by Tomioka et. al. (91 : 9 dr, 75% yield at 0°C).[27,29] Next, the reaction was run with the more electron rich methyl *p*-methoxyphenyldiazoactate which generated the

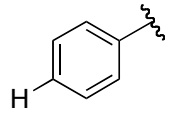
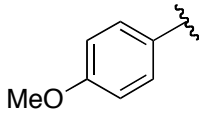
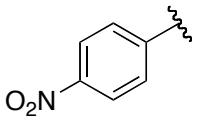
cyclopropane (**15**) in 82% yield and 96 : 4 dr. The reaction which was the most comparable to the thermal reaction was the one conducted with methyl *p*-nitrophenyldiazoacetate **13**, producing the cyclopropane **21** in 72% yield and 67 : 33 dr. This result is identical to that observed for the thermal reaction. The results are generally very similar to the thermal reactions but the diastereoselectivity appears to be slightly higher. This could be due the fact that these photolytic reactions are conducted at room temperature, and a lower temperature would most likely give higher selectivity. A major drawback of the photochemical method, however, was the much longer reaction times that were observed compared to the thermal reactions. These studies suggest that the carbenes generated from thermal and photolytic conditions are the same, and that the substituents determine the preferred spin state. This is consistent with the theoretical studies by Hadad et. al.[30]

Scheme 27: Photochemical cyclopropanation with aryldiazoacetates.



4, 7, 13 **6, 15, 21**

Table 10: Photolytic decompostion of arydiazoacetates in the presence of styrene.

Compd	Ar	Yield (%)	dr
6		83	87 : 13
15		82	96 : 4
21		72	67 : 33

1.3 Conclusions

In conclusion, we have demonstrated that free carbenes derived from a variety of aryldiazo compounds can be generated thermally in refluxing trifluorotoluene. In the presence of alkenes, these carbenes can undergo highly diastereoselective cyclopropanations in moderate to excellent yields if the aryl group is electron rich. Aryldiazoketones undergo a Wolff rearrangement to form ketenes under the thermal conditions, which participate in [2+2] cycloaddition chemistry with styrene substrates present. Kinetic studies have demonstrated that electron-withdrawing groups on the aryl group stabilizes the diazo compound as ~100-fold reactivity difference was observed between nitro and methoxy-substituted aryldiazo compounds

Chapter 2

Ylide Chemistry of Thermally Generated Donor/Acceptor-Carbenes

2.1 Introduction

2.1.1 Ylide Chemistry with Carbenes

If a singlet carbene is generated in close proximity to a nucleophilic functionality, bonding may occur to result in an ylide (Figure 14).[1,37,38] Ylide formation with carbenes is well known and many examples exist of how this has been utilized to promote further chemical transformations, such as dipolar cycloadditions, insertions, rearrangements and cascades.[37,38] Synthetic utility of ylide formation with carbenes has mainly been developed for metal carbene processes, and this type of chemistry has been utilized in the synthesis of complex natural products.[38]

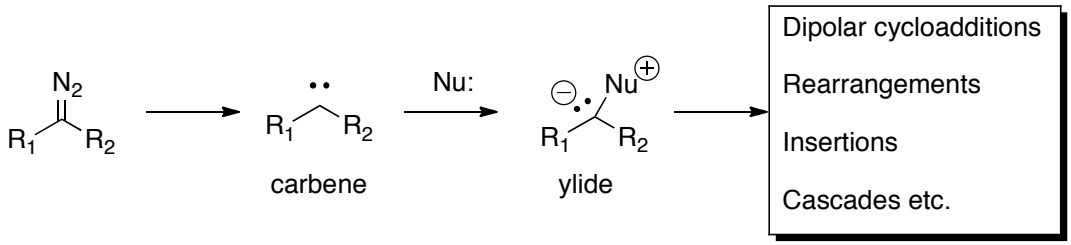


Figure 14: Ylide formation with carbenes.

2.1.2 N-H Insertion Chemistry

The insertion of a carbene or carbenoid into an N–H bond is a potentially powerful process for C–N bond formation.[39-46] Reactions between N–H containing substrates and metal carbenes, generated from catalytic decomposition of diazo compounds with rhodium,[43-47] copper,[40,48,49] ruthenium,[50] silver[48] and iron,[51,52] have been reported to give carbene N–H insertion products. If the diazo compound is an α-diazocarbonyl compound, the N–H insertion product is a direct precursor to α-amino acids (Figure 15) – extremely important building blocks of peptides, other natural compounds and pharmaceuticals.[53] The N–H insertion reactions of diazocarbonyl compounds has attracted much attention as it provides a general and convergent route to both proteinogenic and unusual non-proteinogenic amino acids.[40] Although powerful synthetic techniques already exist for the formation of such structures, these often require at least four steps to give the target amino acid starting from expensive reagents.[40] The N–H insertion of α-diazocarbonyls has furthermore been utilized for the synthesis of many heterocycles, such as penicillins and other β-lactams, oxazoles, indoles, imidazolones, pyrazinones and pyrazines.[40,41,43-45,47]

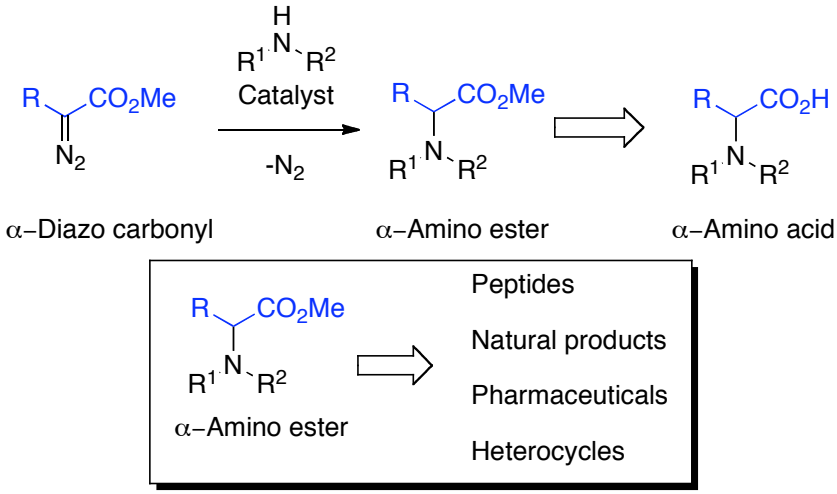


Figure 15: Carbene N–H insertion with diazocarbonyls as direct and convergent approach to α-amino esters.

$Rh_2(OAc)_4$ and other dirhodium catalysts can form Lewis acid/base complexes with many amines.[54] The decomposition of diazo compounds to generate the reactive carbenoids can therefore be strongly or completely inhibited.[54] Rhodium(II)-catalyzed carbene insertions into N–H bonds is therefore often limited to N–H substrates that are sterically hindered or electronically modulated.[44,48,49] For example, in refluxing benzene, the decomposition of dimethyl diazomalonate **23** by $Rh_2(OAc)_4$, in the presence of a variety of bulky secondary amines, can afford hindered tertiary amine diesters in moderate to good yields (Scheme 28, Chart 2). [55] If the amine was too bulky, however, such as for di-*tert*-butylamine, the corresponding N–H insertion product could not be detected under these conditions.[55]

Scheme 28: Rhodium-catalyzed N–H insertion with diazomalonate.[55]

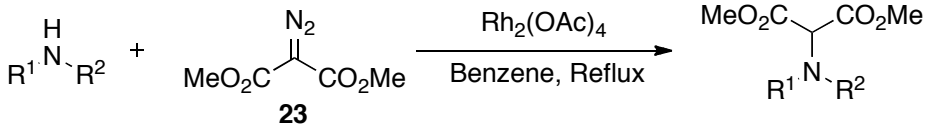
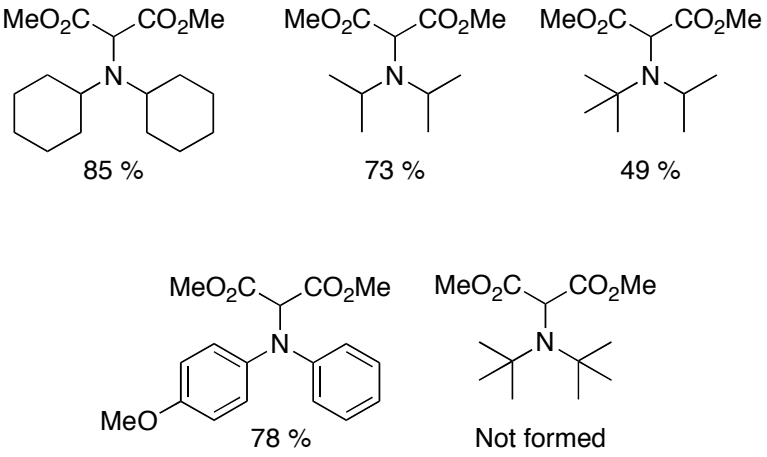


Chart 2: N–H insertions with **23**.[55]



Copper has emerged as the only metal compatible with a wider array of N–H substrates in the N–H insertion chemistry.[31,40,56-58] For example, many unhindered secondary amines and anilines were amenable to N–H insertion when a copper tris(2-pyridyl)amine complex, [Cu(TPN)(THF)]BAr'$_4$, was used as catalyst and ethyl diazoacetate as the carbenoid source (Scheme 2).[58] Some of the highest yields reported for catalytic N–H insertion were achieved for this combination.

Scheme 29: Copper-catalyzed N–H insertion.[58]

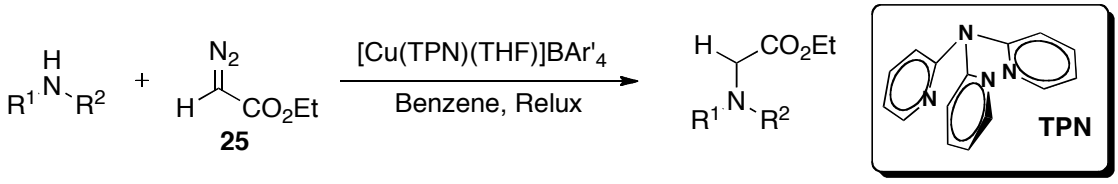
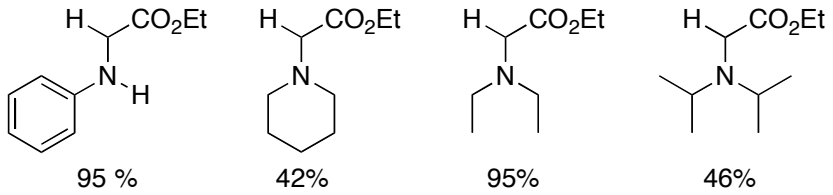


Chart 3: N–H insertion products with **25.**[58]

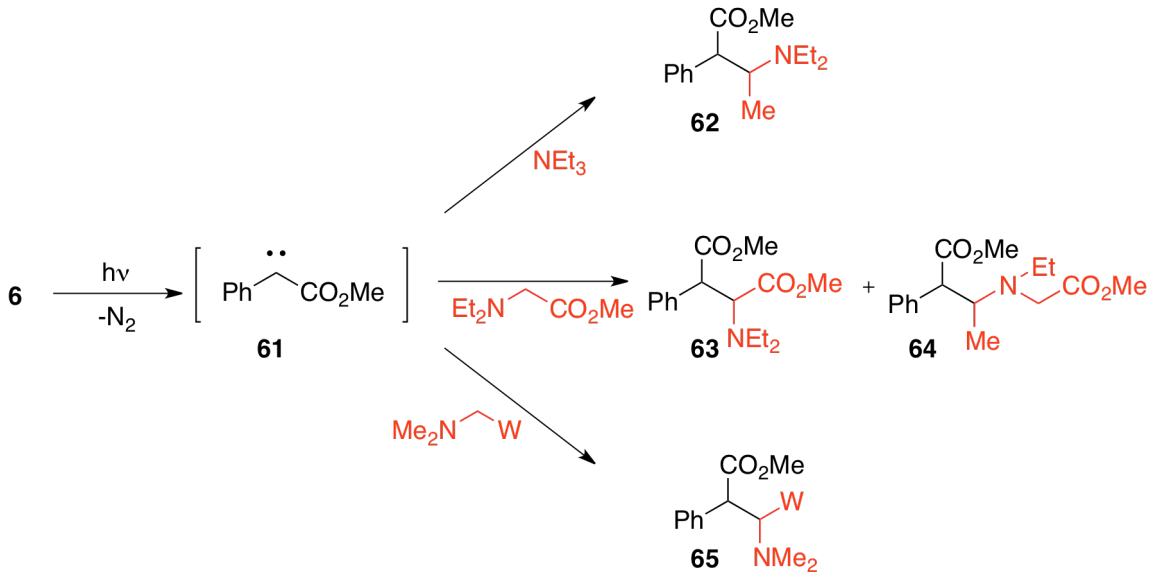


2.1.3 Ylide chemistry of Free Carbenes from Aryldiazoacetates

The insertion of carbenes into C–H bonds is an attractive transformation that has received much attention in the chemical community since the initial discovery by Meerwein, Rathjen and Werner.[59] Even though this reaction is commonly observed with carbenes, its development into a synthetically useful process has been hampered by lack of selectivity and low yields.[16,17,37] However, Tomioka and co-workers discovered that when insertions occur in substrates containing heteroatoms, for example ethers and amines, a slight preference exists for insertion into the C–H bonds alpha to the heteroatom.[27] When carbene **61** was generated photolytically from diazo compound **6** in triethylamine, the reaction afforded the alpha-insertion product 1-methoxycarbonyl-2-diethylamino-1-phenylpropane **62** (Scheme 30).[27] In the presence of N,N-diethylglycine methyl ester, succinate was obtained as the major product **63** in 42% yield, along with a small amount of phenylpropane **64** (13.8 % yield). The reaction with N,N-dimethylgycine ester resulted in the exclusive formation of **65** in 81 % yield. No C–H insertion product was observed in this case. These results were indicative of a reaction taking place through a triplet carbene, since radicals are stabilized by capto-dative substituents.[27] It was suggested that, in the ylide intermediate, the methylene protons are highly acidic due to the adjacent

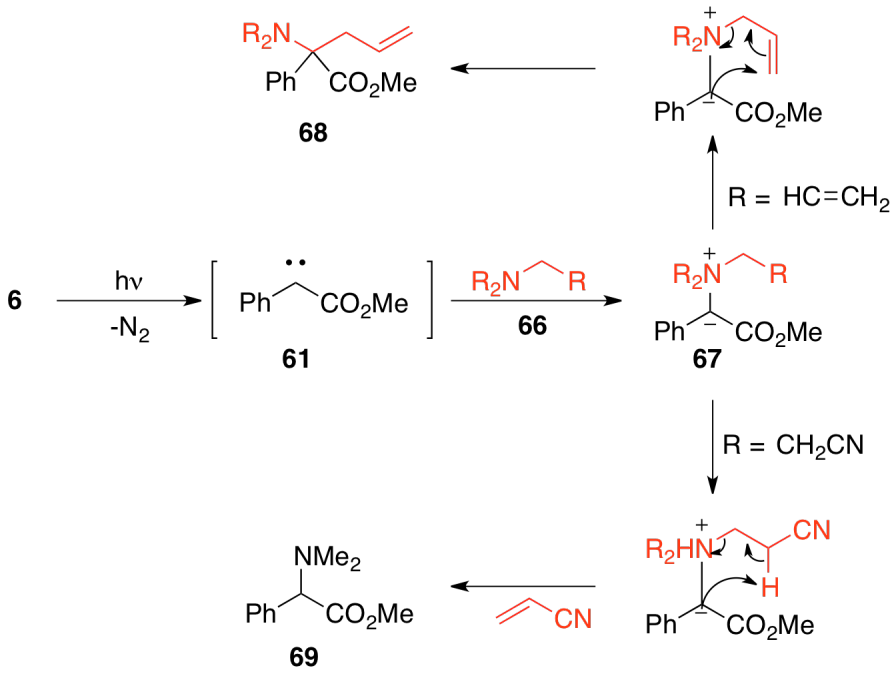
positively charged nitrogen, and can therefore undergo a 1,3-proton shift to generate a secondary ylide, which in turn undergoes a Stevens-rearrangement. This sequence would give the observed formal C–H insertion product **65**. The regioselectivity in the proton shift is due to the higher acidity of the methylene protons flanked by only an electron-withdrawing group. [27]

Scheme 30 Ylide chemistry of photochemically generated carbene **61**.[27]



Additional experiments were conducted, for example the reaction between carbene **61** and allylamine **66**. This reaction afforded the quarternary alpha-amino product **68**, presumably *via* aza-ylide formation followed by a [2,3]-sigmatropic rearrangement.[27] The analogous reaction with cyanoethylamine, produced **69** exclusively. Here, an elimination of the intermediate aza-ylide is believed to occur. A main conclusion from this work was that C–H bonds can be formally activated by carbenes containing capto-dative substituents, resulting in the formation of a new C–C bond.[27]

Scheme 31 Ylide rearrangements.[27]



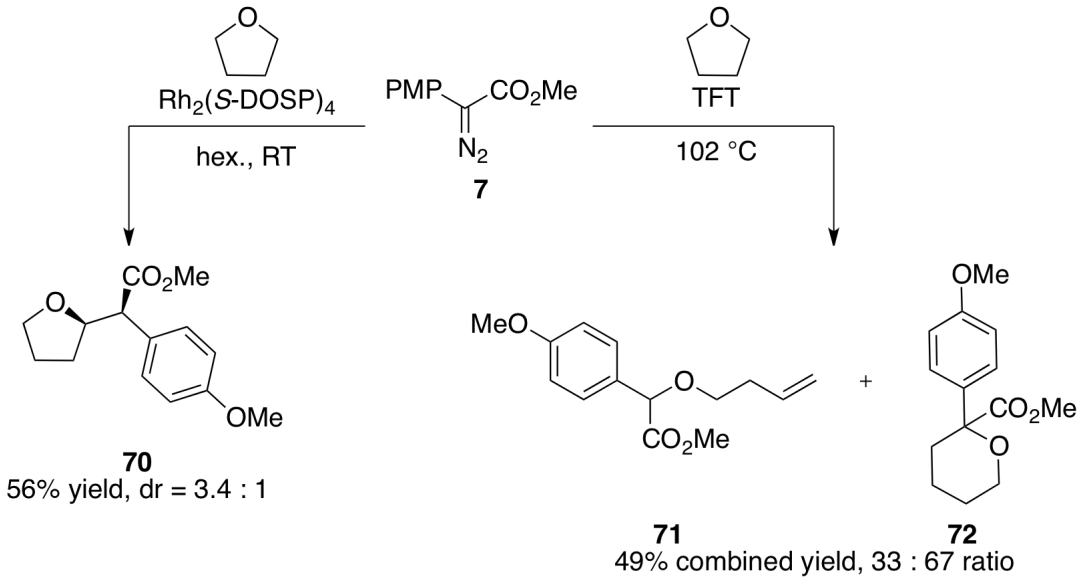
This chapter describes an investigation of reactions where ylides can be formed between free carbenes derived from the thermal decomposition of aryldiazoactates and oxygen and nitrogen containing substrates. The observations of efficient aza-ylide formation between certain amines and photochemically generated donor/acceptor carbenes from aryldiazoacetates,[27-29,60,61] provide a clue for what type of reactivity can expected when aryldiazoacetates are decomposed in the presence of ylide-forming substrates through the thermal carbene formation protocol developed in Chapter 1. The formation of N–H insertion products through this technique will also be explored in light of the potential utility of such structures as discussed in section 2.1.2. The thermal approach to N–H insertion would be a metal-free process and could potentially be more general with respect to the structures of the diazo carbonyl and the N–H substrate.

2.2 Results and Discussion

2.2.1 Initial Explorations

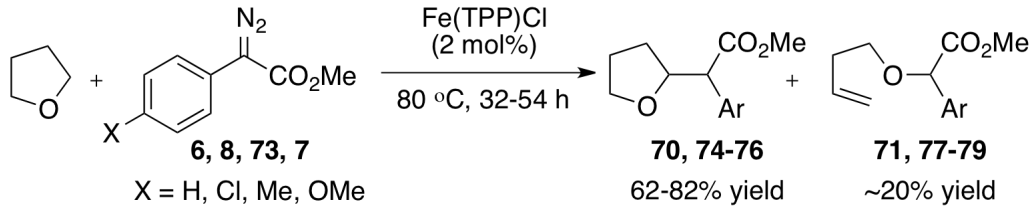
In order to study whether the thermally generated carbenes would undergo ylide or C–H insertion processes, it was decided to investigate THF as a substrate. This was compared to the rhodium-catalyzed process.[62] When **7** was decomposed by Rh(II)-catalyst in the presence of THF, the C–H insertion product **70** was observed in 56% yield and 3.4 : 1 dr, consistent with previous reports.[62] However, when the diazo compound was decomposed thermally in the presence of THF, two new products **71** and **72** were produced in a 33 : 67 ratio and 49% combined yields. **71** is derived from a β-elimination of an intermediate oxa-ylide, whereas **72** presumably comes from ring-expansion of the same intermediate. These results show that oxa-ylide formation can occur with these carbenes and further be elaborated to products.

Scheme 32: Rhodium-catalyzed and free carbene reactions with THF.



The elimination/ring-opening product **71** has been previously reported by Woo and co-workers.[63] This was observed as a by-product in iron-porphyrin catalyzed decomposition of aryldiazoacetates in the presence of THF (Scheme 33). However, these reactions were conducted over an extended period of time (32-54h) and at elevated temperature (80 °C). In light of other results presented, it is likely that iron-catalysis does occur in this chemistry, however, the results presented in chapter 1 and above suggest that background reactions from thermal decomposition of the diazo compounds may be significant at these temperatures.

Scheme 33: Reported iron-catalyzed transformation by Woo.[63]



The observed ylide reactivity through oxa-ylides led to a brief investigation of other oxygen containing compounds (Table 11). Reaction between **71** and the four-membered analog of THF led to the ring-expansion product **80** in 46% yield. Similar reactivity was observed with the 3,3-dimethylsubstituted ring, which also gave 46% yield of the ring-expansion product **81**. The reaction was also tested with the *p*-bromo substituted diazo compound **9**, which gave a large improvement in selectivity with an 81% isolated product **82**. It appears that this diazo compound may be optimum for this chemistry. A similar observation was made in rhodium carbenoid chemistry by Dr. Jaemoon Yang,[64,65] who discovered small amounts of ring-expansion products in the metal catalyzed chemistry as well. The use of 2-methyltetrahydrofuran led to elimination product **83** in a low 38% yield. In this case, elimination of the ylide has occured on the methyl group. By

conducting the thermal reaction in the presence of ethylene glycol, the O–H insertion product **84** was observed in 74% yield along with a small amount of the corresponding cyclization product. These studies demonstrate that oxa-ylide formation can be effective with the thermally generated carbenes from aryldiazoacetates. However, the yields were generally moderate.

Scheme 34: Thermal generation of oxa-ylides.

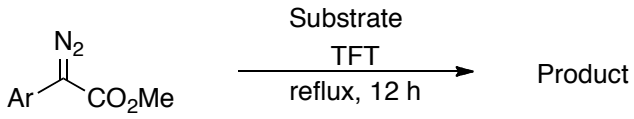
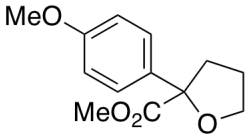
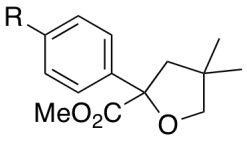
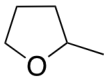
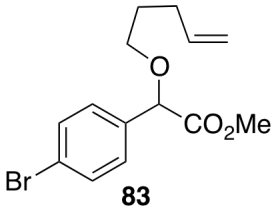
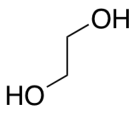
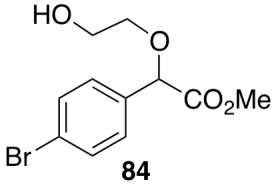


Table 11: Preliminary oxa-ylide studies.

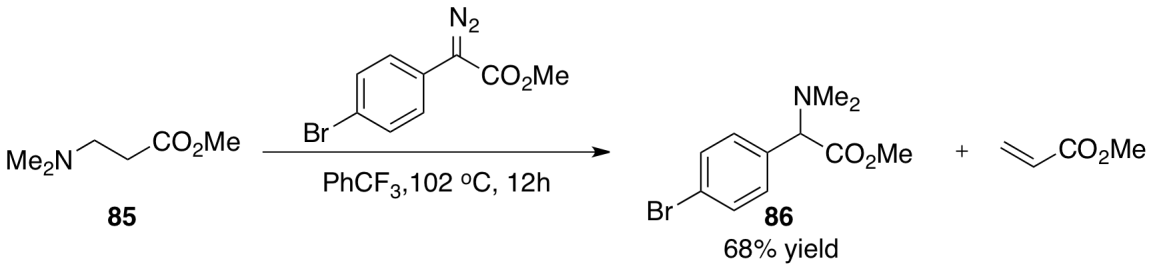
Entry	Substrate	Product	Yield
1		 **80**	46%
2			R = OMe 46% **81** Br 81% **82** With Rh(II)-catalyst[a]: R = OMe 5% Br 32%
3		 **83**	38%
4[b]		 **84**	74%

[a]Conditions : Rh_2(S-DOSP)$_4$, Hex, -50 °C. [b]A small amount of cyclization was also observed.

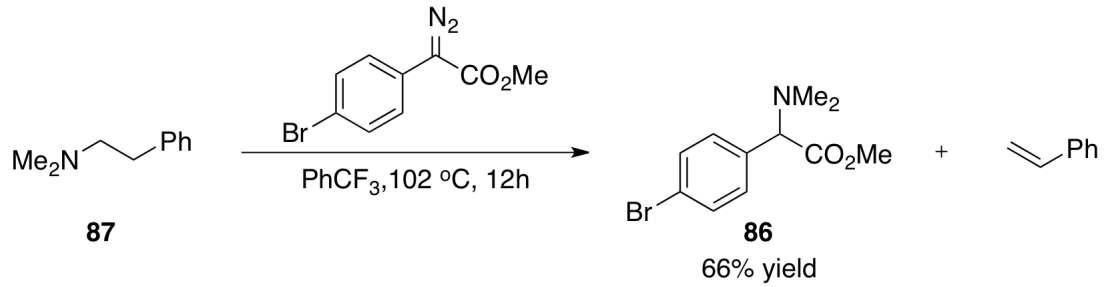
Studies were next conducted to examine whether a substrate similar to that reported by Tomioka et. al. would undergo aza-ylide formation under the thermal conditions. The carbene was generated, using the thermal conditions developed herein, from **9** in the presence of methyl 3-(dimethylamino)propionate **85**. The reaction gave rise to alpha-amino ester **86** in 68% yield along with methyl acrylate (Scheme 87). The same reaction with *N,N*-Dimethyl phenethylamine **87** yielded the identical product **86** in a comparable

yield of 66%. Here was also observed that styrene was produced. The observations of methyl acrylate and styrene in the crude reaction mixtures support the mechanism proposed by Tomioka.[27] These results show that aza-ylide formation can effectively take place under the thermal conditions.

Scheme 35: ylide formation/elimination with **85**.

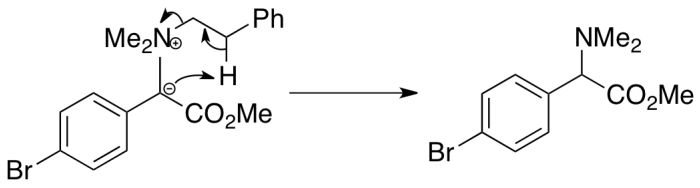


Scheme 36: ylide formation/elimination with **87**.



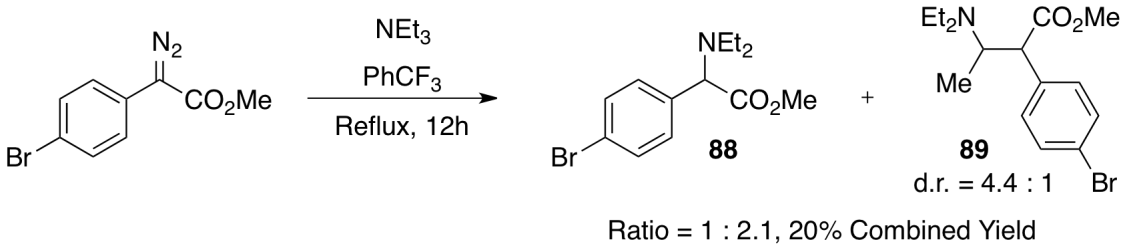
The reaction is envisioned as proceeding according to what was described previously (Scheme 37). First, the aza-ylide is generated, followed by a 1,3-proton shift generating the secondary ylide, which undergoes the Stevens rearrangement to give rise to the observed alpha-amino ester (Scheme 6).[27] Alternatively, the elimination can be a concerted process from the aza-ylide. The results indicate that the thermal aza-ylide formation can be utilized to generate α-amino esters in a metal-free process.

Scheme 37: Elimination from the aza-ylide.



As part of the intitial studies of ylide formation, it was desired to re-investigate the reaction with triethylamine, initially reported by Tamioka et. al. for photochemically generated carbene.[27] They reported a formal C–H insertion process alpha to the nitrogen, presumably trough the aza-ylide, followed by proton shift and a Stevens rearrangement.[27] When the reaction was conducted with thermally generated carbene from **9**, the C–H insertion product was observed in a 4.4 : 1 dr as the major product. The minor product was **88** formed in a 1 : 2.1 ratio with **89** and 20% combined yield (scheme 38). This result indicates that C–H insertion processes may not be very effective with thermally generated carbenes from aryldiazoacetates.

Scheme 38: Reaction with triethylamine.[27]

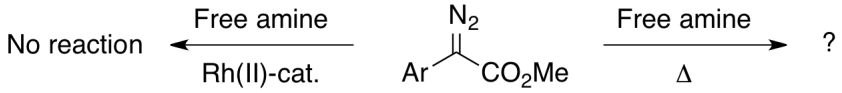


2.2.2 Thermal N–H Insertion Chemistry through Aza-ylides

The initial studies strongly indicated that alpha-amino esters could be generated from aza-ylides formed between carbenes and amines. Alpha-amino esters are direct precursors to alpha-amino acids, as discussed in the introduction to this chapter, and their

synthesis is therefore of great interest to the chemical community.[40] It was therefore decided to study the generality of the aza-ylide formation through reactions with free amines containing N–H bonds. It was anticipated that the aza-ylide would undergo proton transfer to generate the formal N–H insertion products – α-amino esters. Many of the standard metal-catalyzed processes of diazo compounds are not compatible with many amines as they can strongly bind to the metal catalyst and therefore can have detrimental effects on reactivity. The structures compatible with metal-catalysis are usually anilines or amines with suitable electron-withdrawing protecting groups or bulky substituents.[43,48,55] To study the possibility of N–H insertion with free carbenes, a variety of amines were subjected to reactions with thermally generated carbenes derived from aryldiazoacetates.

Scheme 39: Metal catalyzed versus free carbene reactions with free amines.



The studies on N–H substrates began with **90**, a primary amine which contains a dimetyl acetal group. The N–H insertion occurred readily in this system. Interestingly, neither ylide reactivity nor C–H insertion chemistry were observed with the acetal group. This suggests that the aza ylide formation is very favorable, even in the presence of other potentially reactive groups. In the cyclopropanation chemistry described before, the electron density of the aryl group substituted on the carbene had a large influence on the reaction outcome. This electronic effect was also tested in the N–H insertion reaction with substrate **90** in order to investigate if similar trends existed for the aza-ylide chemistry (Scheme 40, Table 12). The reactions between amine **90** and a series of *p*-

substituted aryldiazo compounds were conducted under the standard reaction conditions which generated the formal N–H insertion products. The best yields were obtained with *p*-bromo-substituted diazo compound **9** (80%), whereas only 69% yield was obtained with the electron-neutral substituent **4**. The acceptor (CF_3) group on the diazo compound **91** led to strongly diminished 40% yields. The bromo-compound appeared to be superior also in this chemistry, and was consequently chosen as the standard diazo compound for further studies.

Scheme 40: Diazo Structure Screening.

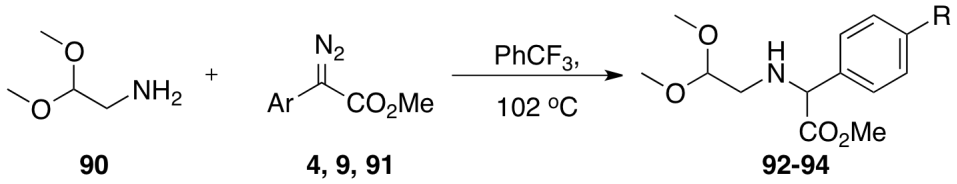
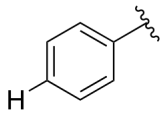
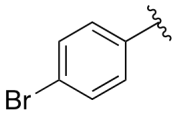
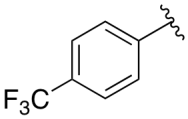


Table 12: Aryl Diazo Structure Screen.

Compd	Ar	Yield (%)
92		69
93		80
94		40

Having established the optimum diazo compound for this chemistry, and that the reactions appears general, the substrate scope was studied next with a variety of primary amines and anilines (Chart 5). The first reaction was conducted with *tert*-butylamine and diazo compound **9**. This generated the N–H insertion product **98** in a good yield of 61%.

This reaction demonstrated that the N–H insertion process is feasible and that steric bulk around the amine structure is tolerated. The reaction with 4-benzylpiperidine furnished the N–H insertion product **103** exclusively in a 70 % isolated yield. This reaction demonstrates that the aza-ylide formation is a good control element for selectivity in free-carbene reactions, since no C–H insertion or radical reactions were observed at the tertiary or benzylic C–H sites of the substrate. The reaction also worked well with an electron-rich aniline derivative **97** in 75% yield. Again, no reaction with the electron-rich aromatic system or the methoxy group suggests a strong preference for aza-ylide formation. In general, the anilines readily underwent the N–H insertion reaction with ortho, meta- or para substitutents. Ortho-methoxyaniline gave N–H insertion product **96** in 54% yield, somewhat less selective than the para-substituted analogue, which gave 75% yield of **97**. *Meta*-trifluoromethyl aniline afforded insertion product **95** in 75% yield as well, so both electron-donating and withdrawing substituents on the aniline ring are tolerated. The aniline system can be extended to napthyl yielding the N–H insertion product **102** in a moderately good yield of 64%. The low yields may be attributed to product instability during chromatography and the reaction conditions. A range of aliphatic amines were also compatible with the chemistry, namely ethers and even electron-rich phenyl groups. Cyclohexylamine and *tert*-butylamine were also good substrates. With these results, the scope of N–H insertion chemistry has been broadened beyond what is currently possible with metal-catalyzed transformations.

Chart 4: Substrate scope for N–H insertion reaction.

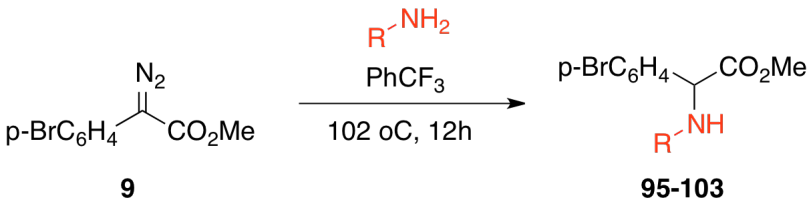
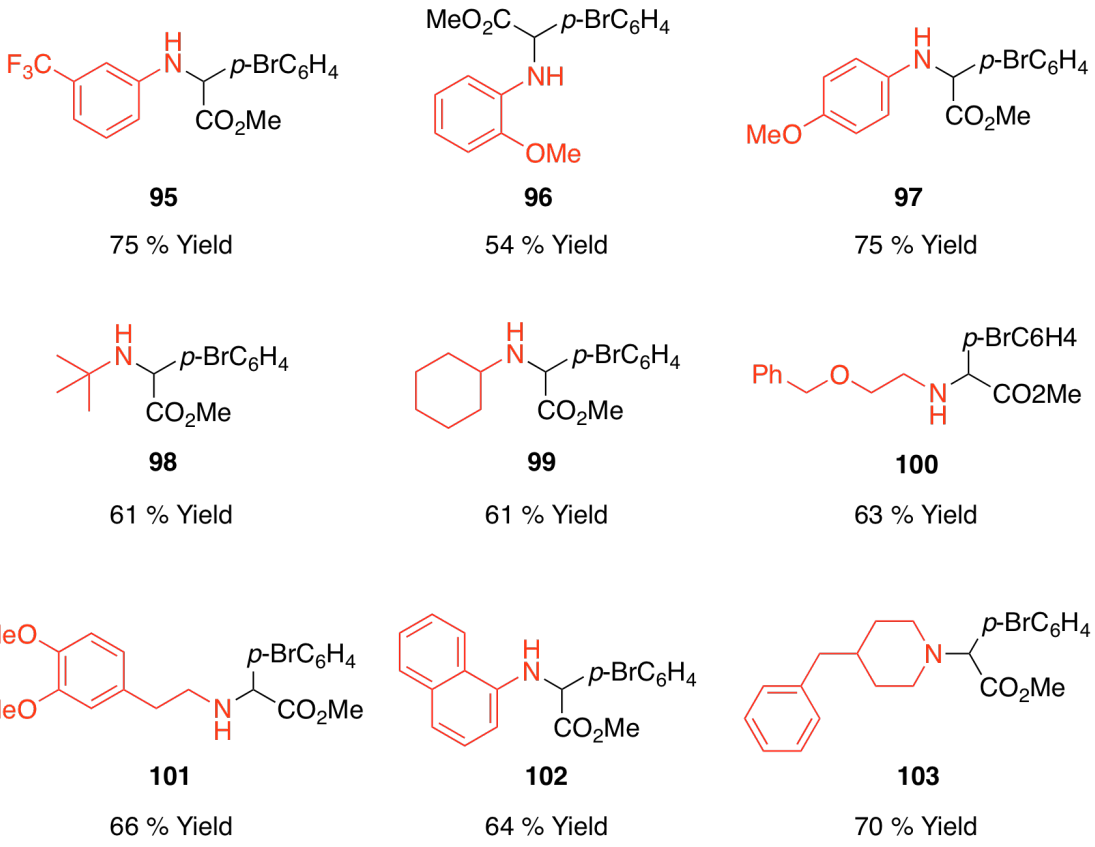


Chart 5: Scope of N–H insertion chemistry.



Heteroaromatic compounds are incredibly important in pharmaceutical research. The thermal NH insertion chemistry was therefore also tested in the presence of heterocycles (Scheme 41, Chart 6). A variety of substituted pyridines **105-108** readily underwent the NH insertion. Even when the heterocycle was an isoxazole, the reaction was effective.

Scheme 41: N–H insertions with heterocyclic amines and anilines.

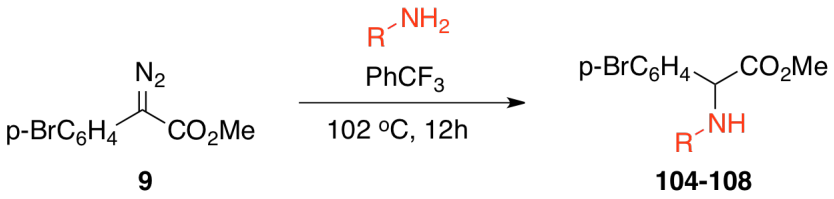
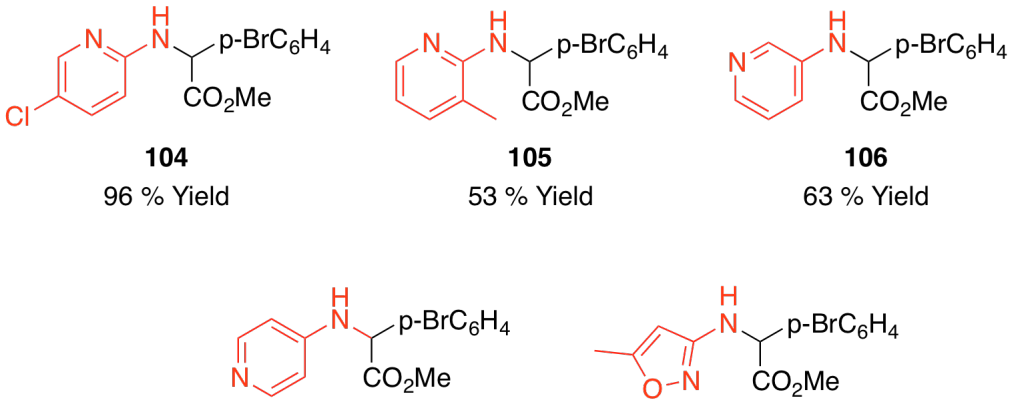


Chart 6: Heterocyclic N–H insertion products.



A variety of secondary cyclic amines, which also contains oxygen moieties, were subjected to the standard reaction conditions as shown in Scheme 42, Chart 7. Interestingly, even in the presence of a primary free hydroxy group, the N–H insertion process was strongly preferred. Also the presence of a tertiary C–H bond was tolerated as no product of C–H insertion processes was observed. Reactions with 2-(piperidin-4-yl)ethanol gave 54% isolated yield of the corresponding N–H insertion product **111**. Piperidine and piperazine both gave N–H insertion (**109-110)** as well in 64-74% yields. A ketal protected substrate also underwent the NH insertion reaction in (**112**) 78% yield, without any observed oxygen-ylide reactivity. These results demonstrate readily that aza

ylide formation is a highly favorable process with the free carbene derived from diazo compound **9** and that, even in the presence of oxygen moieties and activated tertiary C–H bonds, the selectivity is high.

Scheme 42: N–H insertions with secondary cyclic amines.

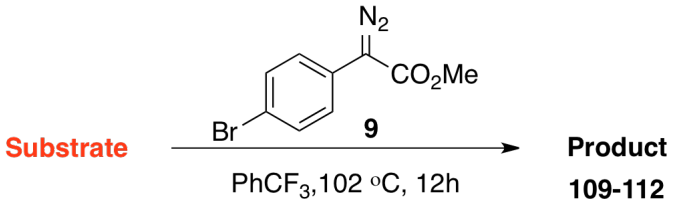
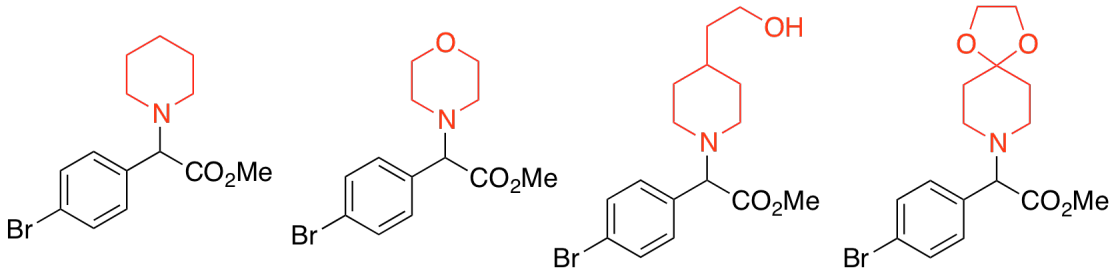


Chart 7: Products of N–H insertion of cyclic amines.



109
64% yield

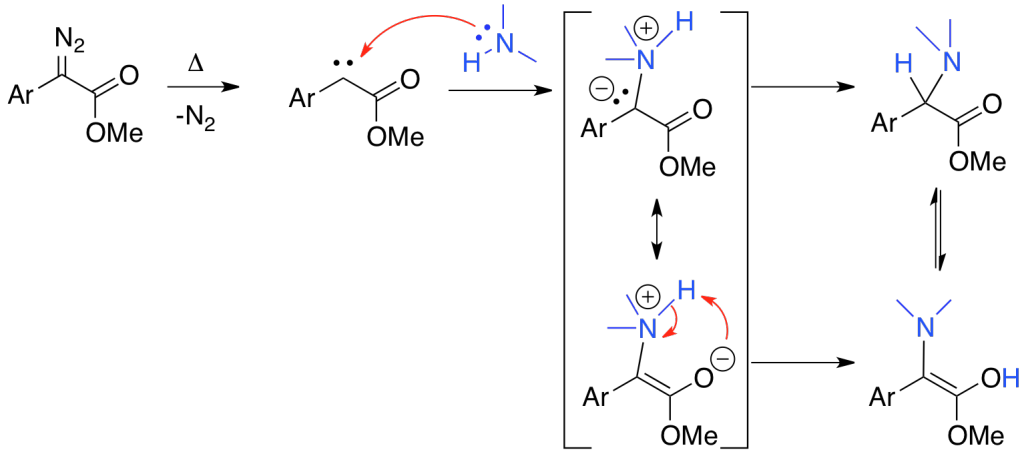
110
74% yield

111
54% yield

112
78% yield

The mechanism of the N–H insertion is believed to involve an aza-ylide intermediate formed through addition of the amine to the carbene in the singlet state (Scheme 43). The ylide could undergo a proton 1,2-shift to directly give the product, or proton transfer to form the enamine enol, which can tautomerize to the observed product.

Scheme 43: Mechanistic explanation for N–H insertion chemistry.

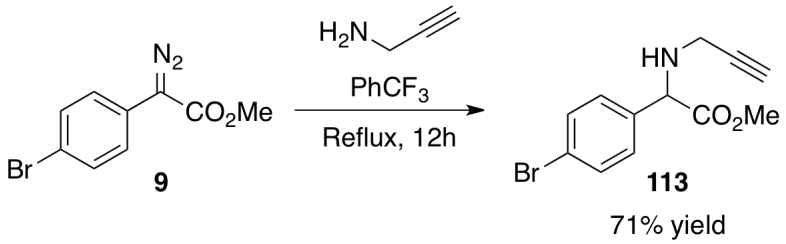


2.2.3 N–H Insertion vs Rearrangement Chemistry

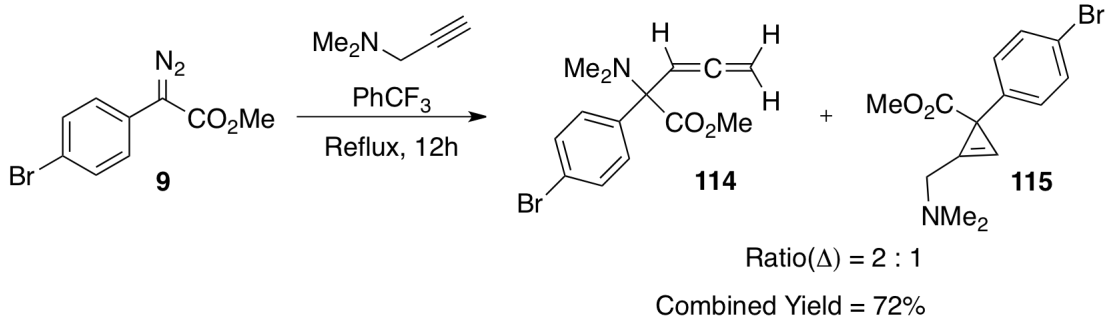
An important competing reaction in the aza-ylide chemistry is the possibility of certain systems to undergo rearrangement chemistry rather than the N–H insertion.[27,66] Based on the result of Tomioka, where an allylic amine underwent aza-ylide formation followed by a [2,3]-sigmatropic rearrangement,[27] it was expected that a propargylic amine could undergo either insertion or rearrangement reaction. In the presence of thermally generated carbene from *p*-bromo diazo compound **9**, propargyl amine effectively underwent N–H insertion to generate **113** in 71% yield. The N–H insertion process appears to be much faster than sigmatropic rearrangement from the aza-ylide. When the amino group was switched to a dimethylamino group, the reaction produced two products **114** and **115** in a 2 : 1 ratio in 72% overall yield. **114** is the product of a [2,3]-sigmatropic rearrangement of the intermediate aza-ylide, whereas cyclopropene **115** is the product of a [2+1] cycloaddition onto the triple bond. Although the selectivity was not high for the propargylic amine substrate in this reaction, the alpha- amino ester is a precursor to a highly unusual, un-natural amino acid with a quaternary stereocenter and an allenyl

substituent. This method could therefore potentially give access to a variety of exotic amino acid precursors.

Scheme 44: N–H insertion with propargylamine.

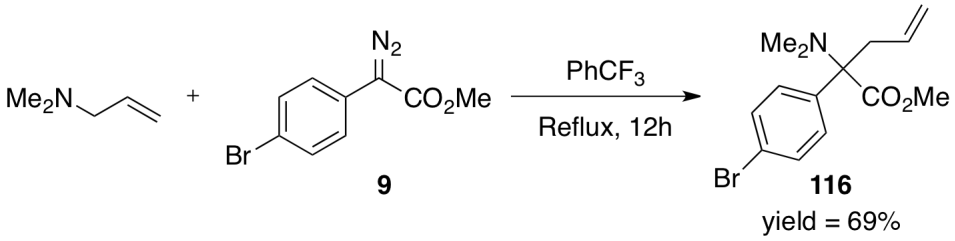


Scheme 45: Reaction with dimethyl propargylamine.



In order to investigate the scope of the rearrangement chemistry, and to improve selectivity, dimethyl allylamine was tested as a substrate. When subjected to the standard reaction conditions with diazo **9,** the rearrangement product **116** was isolated in 69% yield (Scheme 46). Cycloaddition was not observed in this case. To re-investigate the influence of the diazo compound electronics on this particular chemistry, several para-substituted aryldiazoacetates **4, 8-9** were tested in this reaction and it was demonstrated that the para-bromo diazo compound was again the optimal also for this chemistry (Scheme 47, table 13). The exact reason for the success of the bromo-substituted carbene in the ylide chemistry is unclear.

Scheme 46: Reaction with dimethyl allylamine



Scheme 47: Sigmatropic rearangement.

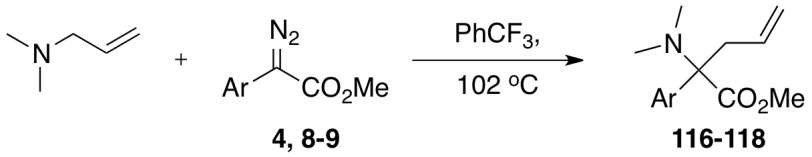
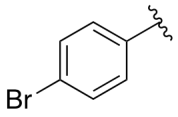
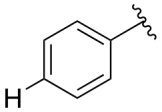
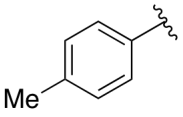


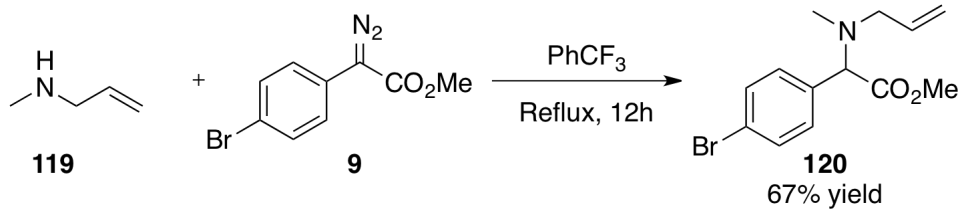
Table 13: Aryldiazo screen for [2,3]-sigmatropic rearrangement.

Compd	Ar	Yield (%)
116		69
117		24
118		53

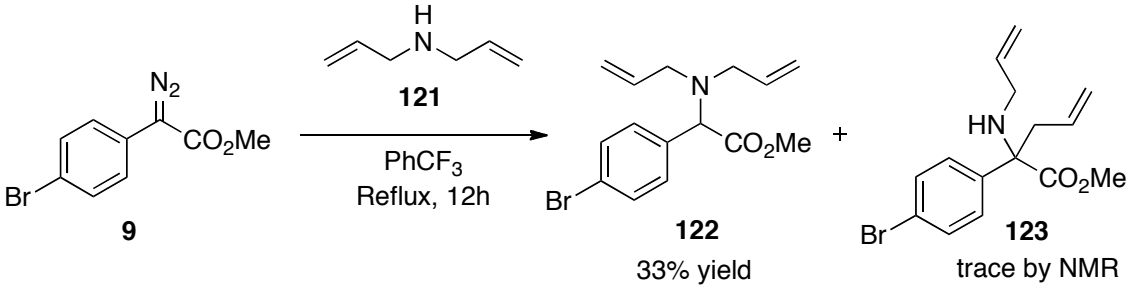
To test the competition between N–H insertion and rearrangement chemistry, a reaction was carried out between the standard diazo compound **9** and substrate **119**. This substrate has an N–H bond as well as an allylic amine moiety. Only the N–H insertion product **120** could be observed in 67% isolated yield and none of the rearranged product. Clearly the N–H insertion process is very favored compared to the rearrangement. When the amine substrate **121** had two allylic amine moieties, and one N–H bond, the reaction still went

in favor of the N–H insertion product **122**, but a minor amount of rearrangement product **123** was observed by NMR. The N–H insertion product was isolated in 33% yield.

Scheme 48: N–H insertion vs [2,3]-sigmatropic rearrangment.



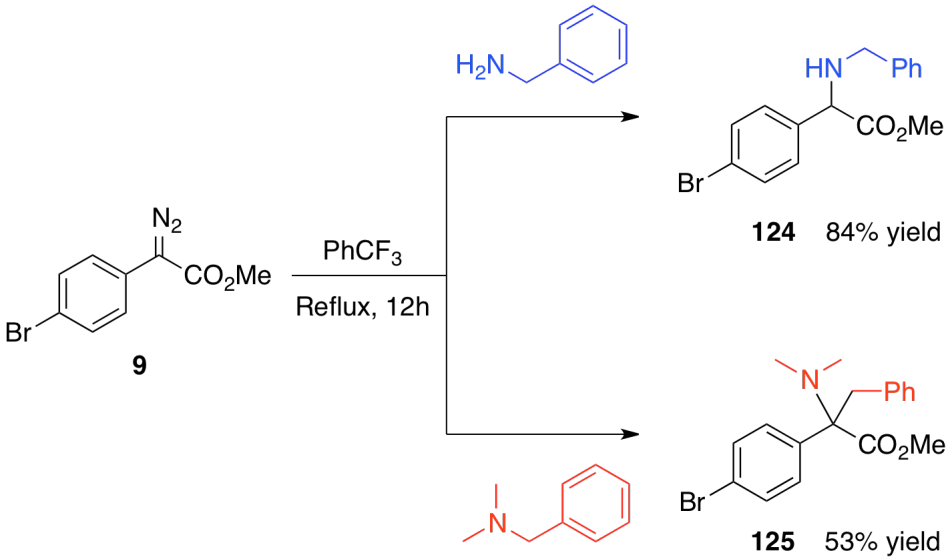
Scheme 49: Bis-allylic amine reaction.



From the studies above, it is clear that the substituents on the amine are of great importance for the reaction outcome. If an N–H bond is present, it appears very likely that the carbene undergoes insertion into this bond. However, if there are no N–H bonds, the systems still undergo the aza-ylide formation, but must find other reaction pathways than just proton transfer. In oxygen ylide chemistry of metal carbenoids, it is known that [1,2]-shifts may also occur in addition to [2,3]-sigmatropic rearrangements if the ylide is formed with a benzylic hydroxyl group.[23] It was decided to test whether this type of chemistry is possible in the context of the thermally generated donor/acceptor carbenes and free amines. When the standard reaction conditions were applied with benzyl amine as the substrate, the N–H insertion product **124** was observed exclusively in 84% isolated yield. However, considering the dramatic effects of amine substituents observed in the

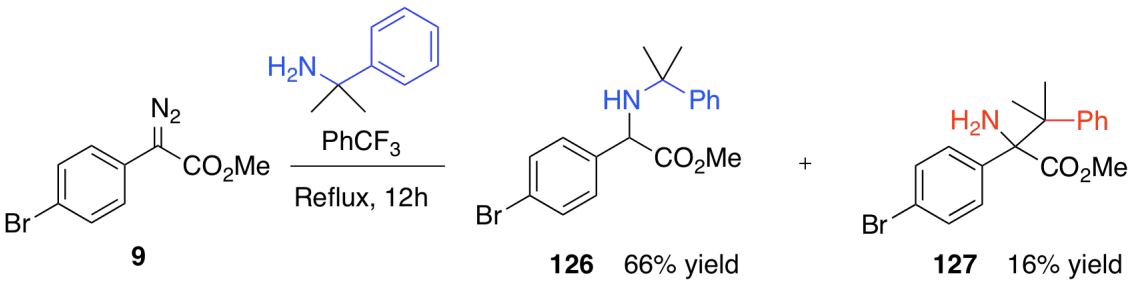
allylic amine chemistry, it was decided to also test the dimethyl benzyl amine. As expected, the aza ylide was also formed in this case, but the system underwent a [1,2]-carbon shift to produce the α-amino ester **125** in 53% isolated yield. This product is an unusual α-arylated phenylalanine derivative. Such structural amino-acid analogues may be difficult to obtain through other methods.

Scheme 50: Substrate structure influence on reaction path.



When a primary gem-dimethyl amine was used, a mixture of the two mechanisms occurred to produce **126** and **127** in a 6.8: 1 ratio with overall 82% yield. These studies demonstrate that N–H insertion versus rearrangement chemistry can be controlled through appropriate modifications of the amine substrate. Highly unusual amino esters can be generated through this methodology which can be used to synthesize the amino acids in a direct fashion.

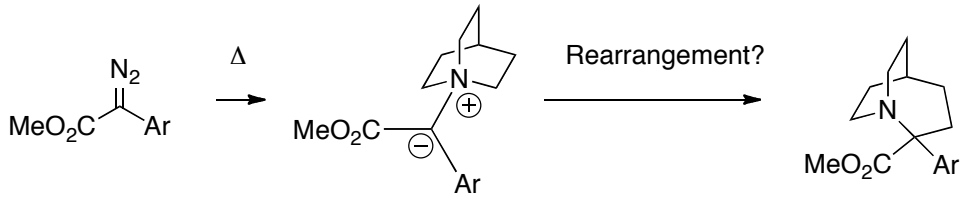
Scheme 51: Reaction with substituted benzylic amine.



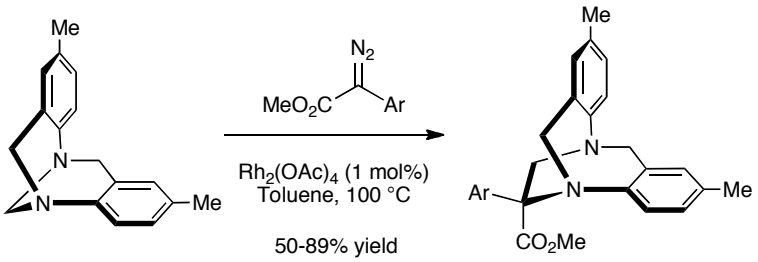
2.3 Future Directions

A possible application of the selective aza-ylide formation observed with the free carbenes described in this chapter is functionalization of complex N-containing molecules. The aza-ylide formation is particularly selective, even in the presence of many other functional groups, and can therefore direct the functionalization. The ylide could potentially undergo selective rearrangements (Scheme 52). A range of N-containing important molecules could be amenable to this, such as tropanes and other alkaloids. An example recently appeared in the literature, where Lacour and co-workers utilized aryldiazo compounds to form aza-ylides with Tröger bases, which selectively rearranged from methano to ethano-bridged Tröger bases (Scheme 53).[67] It was reported to be a rhodium-catalyzed reaction in toluene at 100 °C. Although no control reaction was reported without the catalyst present, the studies presented in this dissertation strongly suggest that a significant thermal background reaction would be occuring, particularly considering the very high reaction temperature. This study demonstrates that the concept is viable and potentially applicable to complex molecule functionalization. A further advantage is that the thermal route would eliminate the need for a metal catalyst in this chemistry.

Scheme 52: Proposed ylide formation with N-containing substrates and rearrangement.



Scheme 53: Synthesis of ethano-bridged Tröger bases.[67]



2.4 Conclusions

In this chapter, it has been demonstrated that thermally generated carbenes from aryldiazoacetates readily undergo ylide formation with oxygen or nitrogen-containing substrates. Particularly selective reactions can be achieved in N–H insertion chemistry with a wide variety of primary and secondary amines to produce a range of unusual α-amino esters – valuable precursors to amino acids. In contrast to the many reported catalytic N–H insertions, this process occurs metal-free. If allylic or propargylic tertiary amines are used as substrates, the intermediate aza-ylide can undergo a [2,3]-sigmatropic rearrangement to produce very unusual amino esters with an α-quaternary center. With benzylic tertiary amines, a [1,2]-shift can occur from the aza-ylide to generate α-aryl phenylalanine derivatives.

Chapter 3

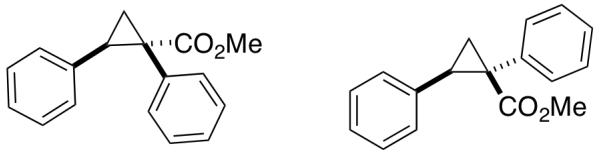
Experimental Section

3.1 General Considerations

All reactions were conducted in flame-dried glassware under an inert atmosphere of dry argon. All reagents were used as received from commercial suppliers, unless otherwise stated. Liquid substrates were filtered through a plug of silica before use. Solvents were obtained from solvent purifier systems and were degassed by bubbling argon through the solvent for 10-20 min prior to use. Flash chromatography was performed on silica gel (230-400 mesh). Thin layer chromatography (TLC) was performed on aluminium backed plates, pre-coated with silica gel (0.25 mm, 60 F_{254}) which were developed using standard visualizing agents: UV fluorescence (254 nm), phosphomolybdic acid/Δ or ninhydrin/Δ. ^{1}H NMR spectra were recorded on Varian Nuclear Magnetic Resonance spectrometers at 600, 500, 400 or 300 MHz. Tetramethylsilane (TMS) was used as internal standard (δ = 0.00) and data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = multiplet, and br = broad), integration and coupling constants in Hz. ^{13}C NMR spectra were recorded at 150, 125, 100 or 75 MHz. The solvent was used as internal standard ($CDCl_3$ δ =77.0) and spectra were obtained with complete proton decoupling. Infrared (IR) spectra were aquired using a Thermo Scientific Nicolet iS10 FTIR spectrometer and the wavenumbers are reported in reciprocal centimeters (cm^{-1}). Diastereomeric and product ratios were determined by integration of the ^{1}H NMR spectra of crude reaction mixtures.

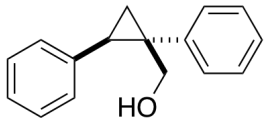
3.2 Procedures And Characterization Data

General procedure for thermal cyclopropanation reactions: To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added the alkene (5.0 - 10.0 equiv.) and dry trifluorotoluene (4-5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. The diazo compound was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. A ^{1}H NMR spectrum was aquired of the crude material to determine the product and diastereomeric ratios shown with the characterization data. The residue was then purified by flash column chromatography (SiO_2, pentane/diethyl ether mixtures) to yield the products.



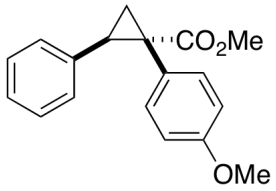
Methyl 1,2-diphenylcyclopropanecarboxylate (6): To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added the styrene (0.67 mL, 5.70 mmol, 5 equiv.) and dry trifluorotoluene (2 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl phenyldiazoacetate (200 mg, 1.14 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a

period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **6a+6b** (239 mg, 0.95 mmol, 83 % overall yield) in a 84:16 ratio of **6a:6b**. Flash column conditions: 12:1 pentane/Et_2O. Products obtained as clear oils. Data for **6a**: R_f = 0.32 (5:1 Pentane/ Et_2O); ^1H NMR (400 MHz, $CDCl_3$): δ 7.11-7.09 (m, 3H), 7.03-7.00 (m, 5H), 6.76-6.74 (m, 2H), 3.63 (s, 3H), 3.11 (dd, 1H, *J*=7.0, 9.5 Hz), 2.13 (dd, 1H, *J*=5.0, 9.5 Hz), 1.86 (dd, 1H, *J*=5.0, 7.0 Hz). Consistent with previously reported results.[68]



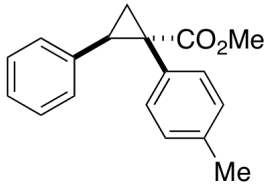
(1,2-diphenylcyclopropyl)methanol (6c): The minor diastereomer from the above cyclopropantion was isolated after reduction of of cyclopropane **6b**. To an oven dried 25 mL round-bottom flask charged with a stir bar under a constant stream of argon gas, was added the LAH (113.9 mg, 3.0 mmol, 1.5 eq) and dry THF (2 mL). The flask was sealed with a rubber septum and placed in an ice bath (0 ^oC). To the vigorously stirring solution was added the cyclopropane mixture (**6a+6b**) (50 mg, 0.2 mmol, 1 eq) dissolved in dry THF (2 mL) dropwise over a period of 10 minutes. The reaction was allowed to warm slowly to ambient temperature and left to stir under argon for 2 hours. Then TLC analysis showed that reaction was complete, it was then quenched with Rochelle's salt (2 mL). The reaction was left to stir overnight at ambient temperature and under argon. The clear solution with a white precipitate floating inside was diluted with EtOAc and filtered through a pad of celite. The solution was reduced in *vacuo*. Flash column conditions: 3:1 pentane/Et_2O). The reduced products **6c +6d** (40 mg, 0.18 mmol, 90 %)

were obtained as a clear oil. Data for **6b**: Rf = 0.34 (1:1 Pentane/E_2O); ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.51-7.41 (m, 2H), 7.40-7.33 (m, 6H), 7.30-7.24 (m, 2H), 3.55-3.52 (m, 2H), 2.59 (dd, 1H, J_S = 6.0 Hz, J_L = 12.0 Hz, OH), 1.47 (dd, 1H, J_S = 6.0 Hz 6.0, J_L = 6.0 Hz), 1.42 (dd, 1H, J_S = 6.0, J_L = 12.0 Hz), 1.11 (dd, 1H, J_S = 6.0, J_L = 6.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.5, 137.8, 128.9, 128.9, 128.6, 128.5, 126.7, 126.5, 66.9, 34.5, 29.8, 15.5; IR (film neat): 3228, 1495, 1042, 697; HRMS- m/z 207.11679 ($C_{16}H_{14}$ requires 207.11683).

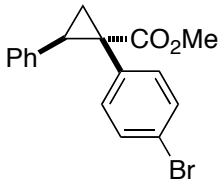


Methyl 1-(4-methoxyphenyl)-2-phenylcyclopropanecarboxylate (15). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added styrene (1.11 mL, 9.70 mmol, 10 equiv.) and dry trifluorotoluene (4 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl 2-diazo-2-(4-methoxyphenyl)acetate (200 mg, 0.97 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo* to afford **15a+15b** (252 mg, 0.82 mmol, 92 % overall yield) in a 98 : 2 ratio of **15a**:**15b**. Flash column conditions: 10/1 pentane/Et_2O. Products obtained as yellow oil. Data for **15a**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.11 (m, 3 H), 6.98 (m, 2 H),

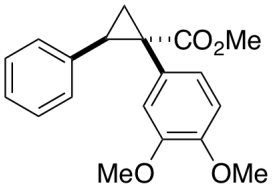
6.82 (m, 2 H), 6.71 (m, 2 H), 3.75 (s, 3 H), 3.69 (s, 3 H), 3.13 (dd, J = 7.5, 9.0 Hz, 1 H), 2.17 (dd, J = 5.0, 9.0 Hz, 1 H), 1.87 (dd, J = 5.0, 7.5 Hz, 1 H). Consistent with previously reported results.[69]



Methyl 2-phenyl-1-(*p*-tolyl)cyclopropanecarboxylate (16). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added styrene (1.2 mL, 10.5 mmol, 10 equiv.) and dry trifluorotoluene (4 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl 2-diazo-2-(4-methylphenyl)acetate (200 mg, 1.05 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **16a+16b** (260 mg, 0.98 mmol, 93 % overall yield) in a 95: 5 ratio of **16a:16b**. Flash column conditions: 10/1 pentane/Et_2O. Products obtained as light yellow oil. Data for **16a**: R_f = 0.33 (5:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.13-7.05 (m, 3H), 6.95 (d, 2H, J = 8 Hz), 6.92 (d, 2H, J = 8 Hz), 6.83-6.75 (m, 2H), 3.61 (s, 3H), 3.10 (t, 1H, J = 8 Hz), 2.25 (s, 3H), 2.13 (dd, 1H, J_S = 4 Hz, J_L = 12 Hz), 1.86 (dd, 1H, J_S = 4 Hz, J_L = 8 Hz). Consistent with previously reported results.[69]

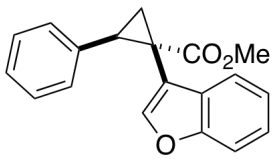


Methyl 1-(4-bromophenyl)-2-phenylcyclopropanecarboxylate (17). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added styrene (0.4 mL, 3.9 mmol, 5 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl 2-diazo-2-(4-bromophenyl)acetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **17a+17b** (196 mg, 0.59 mmol, 76 % combined yield) in a 81 : 19 dr of **17a:17b**. Flash column conditions: 9/1 pentane/Et_2O. Data for major isomer **17a**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24 (d, *J* = 8.5 Hz, 2 H), 7.08 (m, 3 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 6.77 (m, 2 H), 3.64 (s, 3 H), 3.12 (dd, *J* = 7.5, 9.0 Hz, 1 H), 2.13 (dd, *J* = 5.0, 9.0 Hz, 1 H), 1.84 (dd, *J* = 5.0, 7.0 Hz, 1 H). Consistent with reported data.[69]



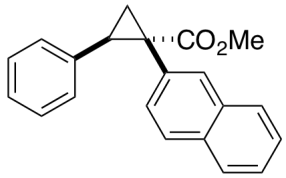
Methyl 1-(3,4-dimethoxyphenyl)-2-phenylcyclopropanecarboxylate (18). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added styrene (0.97 mL,

8.47 mmol, 10 equiv.) and dry trifluorotoluene (4 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl 3,4-dimethoxyphenyldiazoacetate (200 mg, 0.85 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Products obtained as clear oils. **18a+18b** (180 mg, 0.58 mmol, 68 % overall yield) 95 : 5 ratio of **18a:18b** from crude ^{1}H NMR. Flash column conditions: 3/1 pentane/Et_2O. Data for **18a**: R_f = 0.24 (1:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.12-7.02 (m, 3H), 6.84-6.74 (m, 2H), 6.68 (d, 2H, J = 1.2 Hz), 6.36 (s, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 3.55 (s, 3H), 3.08 (dd, 1H, J_S = 7.2 Hz, J_L = 9.2 Hz), 2.13 (dd, 1H, J_S = 4.8 Hz, J_L = 9.2 Hz), 1.83 (dd, 1H, J_S = 4.8 Hz, J_L = 7.2 Hz. Consistent with reported data.[70]



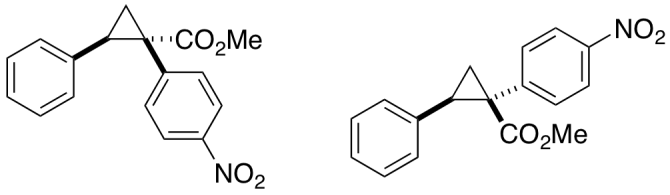
Methyl 1-(benzofuran-3-yl)-2-phenylcyclopropanecarboxylate (19): To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added styrene (1.07 mL, 9.30 mmol, 10 equiv.) and dry trifluorotoluene (2 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl 2-(benzofuran-3-yl)-2-diazoacetate (200 mg, 0.93 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously

stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **19** (257 mg, 0.88 mmol, 95 % overall yield) as a mixture of diastereomers in a ratio of 93 : 7. Products obtained as yellow oil. Flash column conditions: silica gel, 10:1 pentane/Et_2O. Data for major isomer **19**: R_f = 0.50 (1:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.61 (d, 1H, J = 5.2 Hz), 7.55 (d, 1H, J = 5.6 Hz), 7.40 (t, 1H, J = 4.8 Hz), 7.34 (t, 1H, J = 4.8 Hz), 7.30-7.26 (m, 4H), 7.22-7.18 (m, 2H), 3.96 (s, 3H), 3.46 (t, J = 6 Hz), 2.41 (dq, 1H, J_S = 0.8 J_L = 3.2 Hz), 2.16-2.08 (m, 1H). Consistent with reported data.[71]



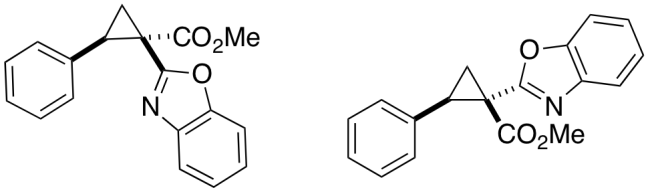
Methyl 1-(naphthalen-2-yl)-2-phenylcyclopropanecarboxylate (20). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added styrene (0.86 mL, 7.50 mmol, 10 equiv.) and dry trifluorotoluene (2 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 °C) under an atmosphere of dry argon. Methyl 2-diazo-2-(naphthalen-2-yl)acetate (200 mg, 0.75 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was

removed in *vacuo*. Product obtained as clear oil. **20** (220 mg, 0.73 mmol, 97 % overall yield) of 82 : 18 diastereomer mixture from crude ^{1}H NMR. Flash column conditions: 10/1 pentane/Et_2O. Data for **20**: R_f = 0.28 (5:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.96-7.80 (m, 1H), 7.76-7.66 (m, 2H), 7.64-7.50 (m, 2H), 7.44-7.36 (m, 2H), 7.20-6.94 (m, 4H), 6.86-6.74 (m, 2H), 3.64 (s, 3H), 3.18 (dd, 1H, J_S = 7.6, J_L = 9.6 Hz), 2.22 (dd, 1H, J_S = 4.8, J_L = 9.2 Hz), 2.01 (dd, 1H, J_S = 5.2, J_L = 7.6 Hz). Consistent with reported data.[68]



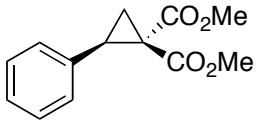
Methyl 1-(4-nitrophenyl)-2-phenylcyclopropanecarboxylate (21). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added styrene (0.52 mL, 4.50 mmol, 5.0 equiv.), Methyl 2-diazo-2-(4-nitrophenyl)acetate (200 mg, 0.90 mmol, 1.0 equiv.), and dry trifluorotoluene (7 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^oC) under an atmosphere of dry argon. The reaction mixture was left to stir at reflux for 12 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Products obtained as yellow solid. **21a+21b** (152 mg, 0.51 mmol, 57 % overall yield) 56 : 44 ratio of **21a:21b** from crude ^{1}H NMR. **21a**: R_f = 0.44 (1:1 Pentane/Et_2O). 1H NMR (400 MHz; CDCl3) δ 7.98 (d, 2H, J = 8.8 Hz), 7.19 (d, 2H, J = 8.8 Hz), 7.12-7.06 (m, 3H), 6.82-6.75 (m, 2H), 3.68 (s, 3H), 3.21 (dd, 1H, J = 7.6, 9.2 Hz), 2.22 (dd, 1H, J = 5.2, 9.2 Hz), 1.96 (dd, 1H, J = 5.2, 7.6 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.1, 142.9, 133, 128.1, 127.2, 123.1, 53.1, 37.1, 33.8, 20.2; IR (film:

neat): 1719, 1517, 1347, 1255, 1162; HRMS-APCI m/z 298.10719 (M+H requires 298.10738); **21b**: R_f = 0.37 (1:1 Pentane/Et_2O); 1H NMR (400 MHz; CDCl3) δ 8.23 (d, 2H, J = 9.2 Hz), 7.67 (d, J = 8.8 Hz2H,), 7.38-7.24 (m, 5H,), 3.32 (s, 3H,), 2.89 (dd, J = 8.0, 9.2 Hz1H,), 2.45 (dd, J = 5.6, 7.6 Hz1H,), 1.68 (dd, J = 5.2, 9.2 Hz1H,); 13C NMR (100 MHz, $CDCl_3$) δ 169.8, 147.4, 147.1, 135.4, 131.1, 128.9, 128.2, 127.2, 123.6, 52.2, 37.6, 33.7, 18.6; IR (film: neat): 2922, 1723, 1599, 1517, 1347, 1163, 1105; HRMS-APCI m/z 298.10725 ($C_{17}H_{16}NO_4$ requires 298.10738).



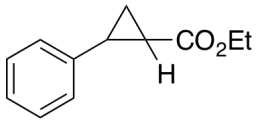
Methyl 1-(benzo[*d*]oxazol-2-yl)-2-phenylcyclopropanecarboxylate (22). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added styrene (0.53 mL, 4.60 mmol, 5.0 equiv.) and dry trifluorotoluene (4 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^oC) under an atmosphere of dry argon. Methyl 2-(benzo[*d*]oxazol-2-yl)-2-diazoacetate (200 mg, 0.92 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Products obtained **22a+22b** (183 mg, 0.62 mmol, 68 % overall yield). 77 : 23 ratio of **22a:22b** from crude ^1H NMR. Flash column conditions: 5:1 to 1:1 pentane/Et_2O. Data for **22a**: Rf = 0.49 (2:1 Pentane/EtOAc); ^1H NMR (500 MHz; $CDCl_3$)

δ 7.64-7.58 (m, 1H), 7.35-7.27 (m, 1H), 7.25-7.19 (m, 2H), 7.10-6.90 (m, 5H), 3.77 (s, 3H), 3.39 (dd, 1H, J_S = 8.0 Hz, J_L = 9.2 Hz), 2.58 (dd, 1H, J_S = 4.8 Hz, J_L = 7.6 Hz), 2.21 (dd, 1H, J_S = 5.2 Hz, J_L = 9.2 Hz). Consistent with reported data.[72] **22b**: R_f = 0.45 (5:1 Pentane/Et_2O); ^1H NMR (400 MHz; $CDCl_3$) δ 7.76-7.70 (m, 1H), 7.57-7.51 (m, 1H), 7.39-7.27 (m, 7H), 3.58 (t, 1H, J = 8.8 Hz), 3.44 (s, 3H), 2.52 (dd, 1H, J_S = 5.6 Hz, J_L = 8.4 Hz), 1.96 (dd, 1H, J_S = 5.2 Hz, J_L = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 164.1, 151.0, 140.9, 134.4, 129.1, 128.2, 127.5, 125.0, 124.4, 119.9, 110.6, 52.5, 33.8, 20.2; IR (film: neat): 2951, 1736, 1567, 1454, 1315, 1241, 1165; HRMS-APCI m/z 294.11234 (M+H requires 294.11247).

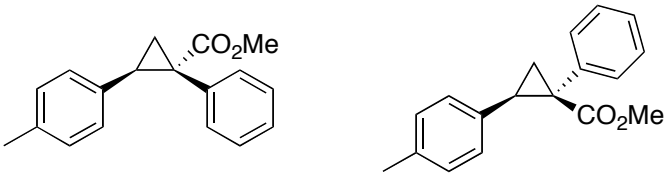


Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (24). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added the styrene (1.4 mL, 12.6 mmol, 10 equiv.) and dry trifluorotoluene (2 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^oC) under an atmosphere of dry argon. Methyl diazomalonate (200 mg, 1.26 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Products obtained as clear oils. Flash column conditions: 5/1 pentane/Et_2O. Data for **24**: R_f = 0.41 (1:1 Pentane/Et_2O); ^1H NMR (400 MHz; $CDCl_3$) δ 7.45-7.15 (m, 5H), 3.79 (s, 3H), 3.36 (s,

3H), 3.23 (t, 1H, J = 8.8 Hz), 2.20 (dd, 1H, J_S = 5.2, J_L = 8.0 Hz), 1.75 (dd, 1H, J_S =5.2, J_L = 9.2 Hz). Consistent with previously reported data.[22]

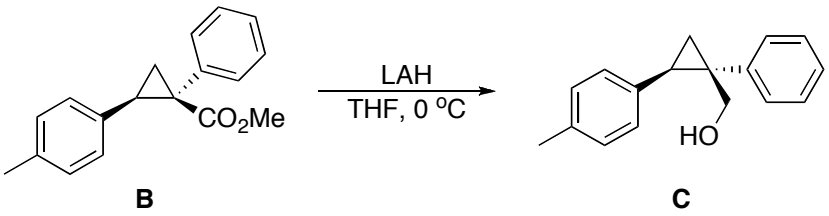


Ethyl 2β-phenylcyclopropane-1α-carboxylate and Ethyl 2β-phenylcyclopropane-1β-carboxylate (26). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added styrene (1.00 mL, 8.80 mmol, 10.0 equiv.) and dry trifluorotoluene (4 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Ethyl diazoacetate (100 mg, 0.88 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Products obtained as clear oils. **26a+26b** (151 mg, 0.79 mmol, 90 % overall yield). 67 : 33 ratio of **26a:26b** from crude. ^{1}H NMR. Flash column conditions: 5:1 pentane/Et_2O. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.08 (m, 10H), 4.32-4.11 (q, 2H, J = 6.0 Hz), 3.92-3.81 (q, 2H, J = 6.0 Hz), 2.64-2.47 (m, 2H), 2.13-2.02 (m, 1H), 1.95-1.86 (m, 1H), 1.76-1.56 (m, 2H), 1.39-1.22 (m, 2H), 1.30-1.24 (t, 3H, J = 6.0 Hz), 1.01-0.93 (t, 3H, J = 6.0 Hz). Consistent with previously reported results.[22]

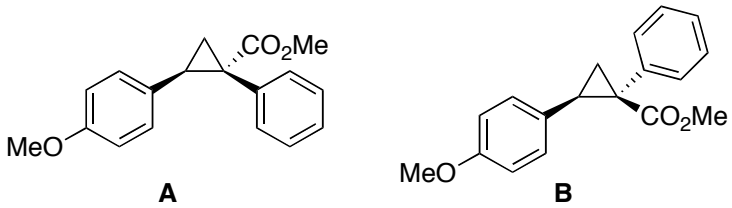


A **B**

Methyl 2β-(4-methylphenyl)-1β-phenylcyclopropane-1α-carboxylate (27). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 4-methylstyrene (1.5 mL, 11.4 mmol, 10 equiv.) and dry trifluorotoluene (2 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl phenyldiazoacetate (200 mg, 1.14 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **27a+27b** (279.6 mg, 1.05 mmol, 92 % overall yield) in a 76 : 24 ratio of **27a:27b**. Flash column conditions: 10/1 pentane/Et_2O. Products obtained as clear oils. Data for **27a**: R_f = 0.32 (5:1 Pentane/ Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.17-7.12 (m, 3H), 7.07-7.01 (m, 2H), 6.86 (d, 2H, J = 7.26 Hz), 6.65 (d, 2H, J = 8 Hz), 3.66 (s, 3H), 3.07 (dd, 1H, J_S = 7.6, J_L = 9.6 Hz), 2.21 (s, 3H), 2.12 (dd, 1H, J_S = 4.8, J_L = 9.6 Hz), 1.83 (dd, 1H, J_S = 5.2, J_L = 7.6 Hz). Consistent with previously published data.[62] Data for **27b**: R_f = 0.38 (5:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.53-7.47 (m, 2H), 7.40-7.33 (m, 2H), 7.32-7.26 (m, 1H), 7.26-7.20 (m, 2H), 7.12 (d, 2H, J = 7.6 Hz), 3.32 (s, 3H), 2.83 (t, 1H, J = 8.4 Hz), 2.33 (s, 3H), 2.31 (dd, 1H, J_S = 4.8, J_L = 7.6 Hz), 1.59 (dd, 1H, J_S = 5.2 Hz, J_L = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 140.4, 136.3, 133.4, 130.2, 128.8, 128.7, 128.3, 127.3, 52.0, 38.0, 33.0, 21.1, 18.4. Fully characterized in its reduced form **27c**.

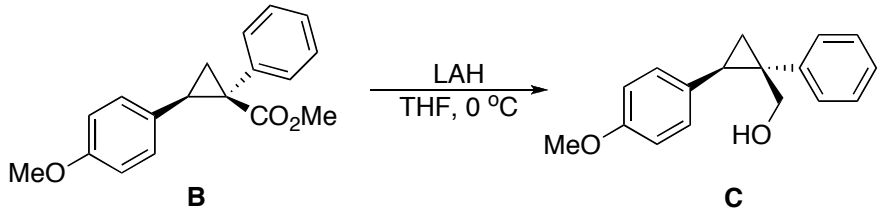


Data for **27c**: R_f = 0.26 (3:1 Hexane/EtOAc); ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.50 (d, 2H, *J* = 7.2 Hz), 7.38 (t, 2H, *J* = 7.8 Hz), 7.28 (m, 3H), 7.16 (d, 2H, J = 7.8 Hz), 3.59 (dd, 1H, J_S = 7.8 Hz, J_L = 12.0 Hz), 3.53 (dd, 1H, J_S = 5.4 Hz, J_L = 12.0 Hz), 2.55 (t, 1H, *J* = 7.8 Hz), 2.36 (s, 3H), 1.45 (t, 1H, *J* = 5.4 Hz), 1.39 (dd, 1H, J_S = 5.4 Hz, J_L = 8.4 Hz), 1.15 (bt, 1H, *J* = 6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.6, 136.1, 134.7, 129.2, 128.9, 128.7, 128.5, 126.6, 66.9, 34.4, 29.4, 21.0, 15.5; IR (film neat): 3223, 1516, 1446, 1041; HRMS- m/z 221.13238 ($C_{17}H_{17}$ requires 221.13248).



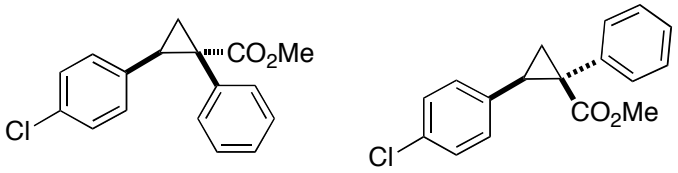
Methyl 2-(4-methoxyphenyl)-1-phenylcyclopropanecarboxylate (28). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 4-methoxystyrene (1.530 g, 11.4 mmol, 10 equiv.) and dry trifluorotoluene (2 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 °C) under an atmosphere of dry argon. Methyl phenyldiazoacetate (200 mg, 1.14 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed *in vacuo* and

gave **28a+28b** (297 mg, 1.05 mmol, 92 % overall yield) in a ratio of 83 : 17 **28a:28b**. Products obtained as clear oils. Flash column conditions: 10/1 pentane/Et_2O. Data for **28a**: R_f = 0.21 (5:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.34-7.26 (m, 1H), 7.16-7.10 (m, 2H), 7.06-7.69 (m, 2H), 6.68 (d, 2H, J = 8.8 Hz), 6.60 (d, 2H, J = 8.8 Hz), 3.70 (s, 3H), 3.66 (s, 3H), 3.06 (dd, 1H, J_S = 7.2 Hz, J_L = 9.2 Hz), 2.12 (dd, 1H, J_S = 4.8 Hz, J_L = 9.2 Hz), 1.80 (dd, 1H, J_S = 4.8 Hz, J_L = 7.2 Hz). Consistent with reported data.[62] Data for **28b**: R_f = 0.39 (5:1 Pentane/Et_2O); ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.52-7.46 (m, 2H), 7.40-7.32 (m, 2H), 7.32-7.26 (m, 1H), 7.06-6.98 (m, 2H), 6.86 (d, 2H, J = 8.8 Hz,), 3.80 (s, 3H), 3.33 (s, 3H), 2.81 (t, 1H, J = 8.4 Hz), 2.29 (dd, 1H, J_S = 5.2, J_L = 7.6 Hz), 1.59 (dd, 1H, J_S = 4.8, J_L =8.8 Hz). To enable isolation of the minor diastereomer, the mixture was reduced with LAH. The resulting alcohol was characterized below as **28c**.



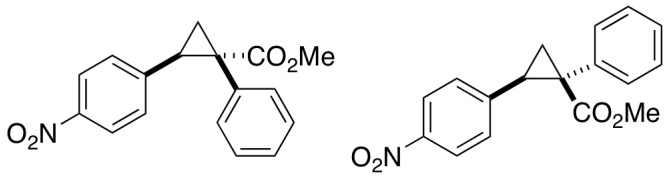
B **C**

(2-(4-methoxyphenyl)-1-phenylcyclopropyl)methanol (**28c)**: R_f = 0.47 (1:1 Hexane/EtOAc); ^{1}H NMR (600 MHz; $CDCl_3$): δ 7.47 (d, 2H, J = 7.8 Hz), 7.35 (t, 2H, J = 7.2 Hz), 7.28 (d, 2H, J = 8.4 Hz), 7.25 (t, 1H, J = 7.2 Hz), 6.87 (d, 2H, J = 8.4 Hz), 3.80 (s, 3H), 3.56 (dd, 1H, J_S = 12.0, J_L = 7.2 Hz), 3.51 (dd, 1H, J_S = 12.0, J_L = 4.2 Hz), 2.51 (t, 1H, J = 7.8 Hz), 6.40-1.35 (m, 2H), 1.13 (t, 1H, J = 6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.3, 143.6, 129.9, 129.8, 128.9, 128.5, 126.6, 113.9, 66.9, 52.3, 34.2, 29.0, 15.7; IR (film): 3223, 1514, 1242, 1301, 833; HRMS-APCI m/z 237.12734 (M-H_2O requires 237.12739).



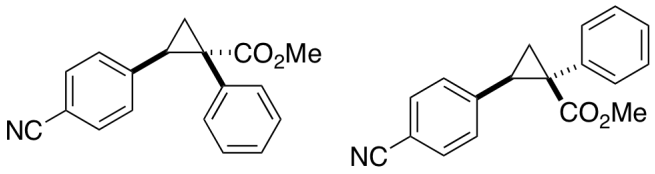
Methyl 2-(4-chlorophenyl)-1-phenylcyclopropanecarboxylate (29). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added *p*-chloro styrene (1.5 mL, 11.4 mmol, 10 equiv.) and dry trifluorotoluene (2 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl phenyldiazoacetate (200 mg, 1.14 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Products obtained as yellow oils. **29a+29b** (285.3 mg, 0.99 mmol, 87 % overall yield) 74 : 26 ratio of **29a:29b** from crude ^{1}H NMR. Flash column conditions: 5/1 pentane/Et_2O. Data for **29a**: R_f = 0.29 (5:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.18-7.10 (m, 3H), 7.06-6.96 (m, 4H), 6.68 (d, 2H, J = 8.4 Hz), 3.66 (s, 3H), 6.14 (dd, 1H, J_S = 7.2 Hz, J_L = 9.2 Hz), 2.14 (dd, 1H, J_S = 5.2 Hz, J_L = 9.6 Hz), 1.82 (dd, 1H, J_S = 4.8 Hz, J_L = 7.2 Hz). Consistent with reported data.[62] Data for **29b**: R_f = 0.41 (5:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.52-7.47 (m, 2H), 7.41-7.35 (m, 2H), 7.34-7.30 (m, 1H), 7.30 (s, 4H), 3.45 (s, 3H), 2.82 (dd, 1H J_S = 7.6 Hz, J_L = 9.2 Hz), 2.31 (dd, 1H, J_S = 5.2 Hz, J_L = 7.2 Hz), 1.64 (dd, 1H, J_S = 5.2 Hz, J_L = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 139.9, 135.0, 132.6, 130.3, 130.1, 128.3, 128.2, 127.4, 52.1, 38.2, 32.5, 18.5; IR

(film): 2950, 1723, 1493, 1306, 1209, 1162, 834; HRMS-APCI m/z 287.08339 (M+H requires 287.08333);



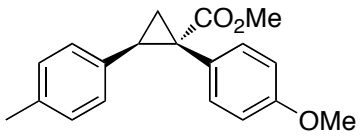
Methyl 2-(4-nitrophenyl)-1-phenylcyclopropanecarboxylate (30). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added *p*-nitrostyrene (1.70 g, 11.4 mmol, 10.0 equiv.) and dry trifluorotoluene (2 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl phenyldiazoacetate (200 mg, 1.14 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Products obtained as yellow oils. **30a+30b** (320 mg, 1.08 mmol, 94 % overall yield) 68 : 32 ratio of **30a:30b** from crude ^{1}H NMR. Flash column conditions: 10/1 pentane/Et_2O. Data for **30a**: R_f = 0.30; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.91 (d, 2H, J = 8.8 Hz), 7.22-7.10 (m, 3H), 7.06-6.96 (m, 2H), 6.88 (d, 2H, J = 8.8 Hz), 3.68 (s, 3H), 3.20 (dd, 1H, J_S = 6.8 Hz, J_L = 8.8 Hz), 2.24 (dd, 1H, J_S = 5.2 Hz, J_L = 9.2 Hz), 1.96 (dd, 1H, J_S = 5.2 Hz, J_L = 7.2 Hz). Consistent with published data.[62] Data for **30b**: R_f = 0.32 (2:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.20 (d, 2H, J = 8.8 Hz), 7.53 (d, 2H, J = 8.8 Hz), 7.51-7.43 (m, 2H), 7.41-7.33 (m, 2H), 7.33-7.30 (m, 1H), 3.35 (s, 3H), 2.91 (t, 1H, J = 8 Hz), 2.40 (dd, 1H, J_S = 5.2 Hz, J_L = 7.6 Hz), 1.76 (dd, 1H, J_S = 5.2 Hz, J_L = 8.8 Hz); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 170.5, 146.8, 144.4, 139.3, 130.8, 129.9, 128.5, 127.7, 123.3, 52.3, 38.9, 32.9, 19.0; IR (neat): 2951, 1721, 1599, 1515, 1211, 1163, 854; HRMS-APCI m/z 298.10741 (M+1 requires 298.10738).

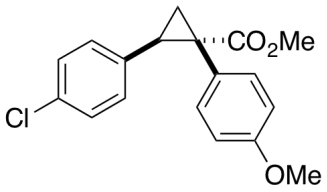


Methyl 2-(4-cyanophenyl)-1-phenylcyclopropanecarboxylate (31). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added *p*-cyanostyrene (1.44 g, 11.4 mmol, 10.0 equiv.) and dry trifluorotoluene (2 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^oC) under an atmosphere of dry argon. Methyl phenyldiazoacetate (200 mg, 1.14 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Products obtained as clear oils. **31a+31b** (202 mg, 0.73 mmol, 64 % overall yield). 71 : 29 ratio of **31a:31b** from crude ^1H NMR. Flash column conditions: 10:1 pentane/Et_2O. Data for **31a**: R_f = 0.30; ^1H NMR (400 MHz; $CDCl_3$) δ 7.33 (d, 2H, J = 8.8 Hz), 7.22-7.12 (m, 3H), 7.02-6.94 (m, 2H), 6.83 (d, 2H, J = 8.4 Hz), 3.67 (s, 3H), 3.14 (dd, 1H, J_S = 7.2 Hz, J_L = 9.2 Hz), 2.21 (dd, 1H, J_S = 4.8 Hz, J_L = 9.2 Hz), 1.91 (dd, 1H, J_S = 5.2 Hz, J_L = 7.2 Hz). Consistent with reported data.[62] Data for **31b**: R_f = 0.28 (2:1 Pentane/Et_2O); ^1H NMR (400 MHz; $CDCl_3$) δ 7.62 (d, 2H, J = 8.4 Hz), 7.52-7.42 (m, 4H), 7.42-7.34 (m, 2H), 7.20-7.10 (m, 1H), 3.34 (s, 3H), 2.87 (t, 1H, J = 8.0 Hz), 2.36 (dd, 1H, J_S = 5.2 Hz,

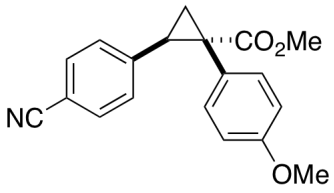
J_L = 7.6 Hz), 1.71 (dd, 1H, J_S = 5.2 Hz, J_L = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 142.2, 139.4, 131.8, 130.0, 129.8, 128.4, 127.6, 118.9, 110.6, 52.2, 38.7, 33.0, 18.7; IR (film): 2227, 1722, 1608, 1307, 1212, 1162, 844; HRMS- m/z 278.11759 (M+H requires 278.11756).



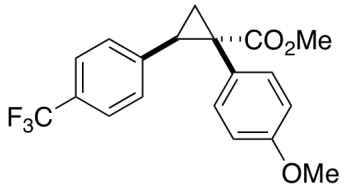
Methyl 1-(4-methoxyphenyl)-2-(*p*-tolyl)cyclopropanecarboxylate (33). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 4-methylstyrene (1.28 mL, 9.70 mmol, 10 equiv.) and dry trifluorotoluene (2 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl 2-diazo-2-(4-methoxyphenyl)acetate (200 mg, 0.97 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **33** (256 mg, 0.86 mmol, 98 % overall yield) in a 92 : 8 diastereomeric ratio. Flash column conditions: 10/1 pentane/Et_2O. Products obtained as light yellow oil. Data for major isomer **33**: ^{1}H NMR (500 MHz; $CDCl_3$) δ 6.93 (d, 2H, J = 8.5 Hz), 6.87 (d, 2H, J = 8 Hz), 6.66 (dd, 4H, J_L = 8.5 Hz, J_S = 8.0 Hz), 3.71 (s, 3H), 3.64 (s, 3H), 3.02 (dd, 1H, J_L = 9.0 Hz, J_S = 7.0 Hz), 2.20 (s, 3H), 2.09 (dd, 1H, J_L = 9.0 Hz, J_S = 5.0 Hz), 1.77 (dd, 1H, J_L = 7.0 Hz, J_S = 5.0 Hz). Consistent with reported data.[62]



Methyl 2-(4-chlorophenyl)-1-(4-methoxyphenyl)cyclopropanecarboxylate (34). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 4-chlorostyrene (1.24 mL, 9.70 mmol, 10 equiv.) and dry trifluorotoluene (2 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl 2-diazo-2-(4-methoxyphenyl)acetate (200 mg, 0.97 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo* to afford **34** (245 mg, 0.77 mmol, 80 % overall yield) in a 95 : 5 diastereomeric ratio. Flash column conditions: 10/1 pentane/Et_2O. Products obtained as yellow oil. Data for major isomer **34**: ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.03 (d, 2H, J = 8.5 Hz), 6.92 (d, 2H, J = 8.5 Hz), 6.68 (d, 4H, J = 8.5 Hz), 3.72 (s, 3H), 3.65 (s, 3H), 3.03 (dd, 1H, J_L = 9.0 Hz, J_S = 7.0 Hz), 2.12 (dd, 1H, J_L = 9.0 Hz, J_S = 5.0 Hz), 1.76 (dd, 1H, J_L = 7.0 Hz, J_S = 5.0 Hz). Consistent with reported data.[62]

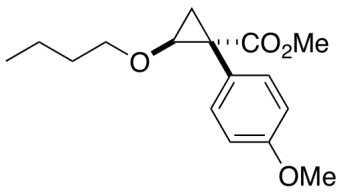


Methyl 2-(4-cyanophenyl)-1-(4-methoxyphenyl)cyclopropanecarboxylate (35). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added *p*-cyano styrene (629 mg, 4.85 mmol, 5.0 equiv.) and dry trifluorotoluene (2 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl 2-diazo-2-(4-methoxyphenyl)acetate (200 mg, 0.97 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Products obtained as clear oil **35** (150 mg, 0.49 mmol, 50 % overall yield) in 92 : 8 diastereomeric ratio from crude ^{1}H NMR. Flash column conditions: 10/1 pentane/Et_2O. Data for major isomer **35**: R_f = 0.19 (5:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.33 (d, 2H, J = 8.4 Hz), 6.88 (d, 2H, J = 8.8 Hz), 6.82 (d, 2H, J = 8.4 Hz), 6.66 (d, 2H, J = 8.4 Hz), 3.72 (s, 3H), 3.65 (s, 3H), 3.08 (dd, 1H, J_S = 7.2 Hz, J_L = 8.8 Hz), 2.20-2.10 (m, 1H), 1.83 (dd, 1H, J_S = 5.2 Hz, J_L = 7.2 Hz). Consistent with reported data.[62]



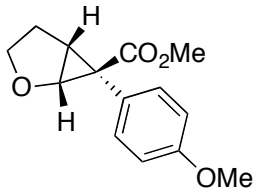
Methyl1-(4-methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)cyclopropanecarboxylate (36). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added *p*-trifluoromethyl styrene (0.72 mL, 4.85 mmol, 5.0 equiv.) and dry trifluorotoluene (2 mL).

The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl 2-diazo-2-(4-methoxyphenyl)acetate (200 mg, 0.97 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Products obtained as clear oils **36** (68 mg, 0.19 mmol, 20 % overall yield) in 93 : 7 diastereomeric ratio of from crude ^{1}H NMR. Flash column conditions: 5/1 pentane/Et_2O. Data for major isomer **36**: R_f = 0.54 (1:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.32 (d, 2H, J = 8 Hz), 6.92 (d, 2H, J = 8.8 Hz), 6.85 (d, 2H, J = 8 Hz), 6.69 (d, 2H, J = 8.8 Hz), 3.74 (s, 3H), 3.67 (s, 3H), 3.11 (dd, 1H, J_S = 7.2 Hz, J_L = 9.2 Hz), 2.17 (dd, 1H, J_S = 5.2 Hz, J_L = 9.2 Hz), 1.84 (dd, 1H, J_S = 7.2 Hz, J_L = 5.2 Hz). Consistent with reported data.[62]



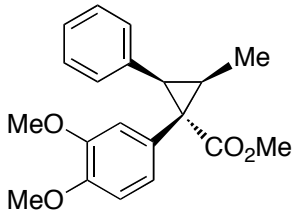
Methyl 2-butoxy-1-(4-methoxyphenyl)cyclopropanecarboxylate (38). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added butyl vinyl ether (0.63 mL, 4.85 mmol, 5.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl 2-diazo-2-(4-methoxyphenyl)acetate (206.2 mg, 0.97 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in

a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Product **38** (229 mg, 0.82 mmol, 85 % yield). Flash column conditions: 5:1 pentane/Et_2O. R_f = 0.23 (5:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.26 (d, 2H, J = 8.8 Hz), 6.86 (d, 2H, J = 8.8 Hz), 3.88 (dd, 1H, J_S = 4.4, J_L = 6.8 Hz), 3.81 (s, 3H), 3.63 (s, 3H), 3.59-3.44 (m, 2H), 1.76 (dd, 1H, J_S = 5.6, J_L = 6.8 Hz), 1.57 (dd, 1H, J_S = 4.8, J_L = 5.6 Hz), 1.42-1.24 (m, 2H), 1.13 (sext, 2H, J = 7.2 Hz), 0.79 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 158.6, 132.5, 126.3, 113.3, 70.9, 65.0, 55.2, 52.3, 34.3, 31.4, 21.2, 19.0, 13.6; IR (film: neat): 2955, 1713, 1516, 1433, 1245, 1177, 1086. HRMS- m/z 279.15928 ($C_{16}H_{23}O_4$ requires 279.15909).



Methyl 6-(4-methoxyphenyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (37). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 2,3-dihydrofuran (0.73 mL, 9.70 mmol, 10.0 equiv.) and dry trifluorotoluene (2 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl 2-diazo-2-(4-methoxyphenyl)acetate (200 mg, 0.97 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a

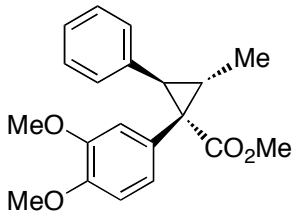
period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained product **37** (172 mg, 0.69 mmol, 71 % yield). Flash column conditions: 10:1 pentane/Et_2O. Rf = 0.1 (5:1 Pentane/Et_2O); ^1H NMR (400 MHz; $CDCl_3$) δ 7.24 (d, 2H, *J* = 8.8 Hz), 6.90 (d, 2H, *J* = 8.4 Hz), 4.47 (d, 1H, *J* = 5.2 Hz), 3.82 (s, 3H), 3.82-3.74 (m, 1H), 3.57 (s, 3H), 2.61 (t, 1H, *J* = 8 Hz), 2.44 (q, 1H, *J* = 16 Hz), 2.18-2.30 (m, 1H), 1.78-1.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 158.9, 132.4, 124.0, 113.9, 70.1, 70.0, 55.1, 52.3, 37.2, 32.2, 32.4, 26.1; IR (film: neat): 1706, 1611, 1514, 1241, 1093, 1033; HRMS- m/z 248.10457 ($C_{14}H_{16}O_4$ requires 248.10431).



Methyl 1-(3,4-dimethoxyphenyl)-2-methyl-3-phenylcyclopropanecarboxylate (40).

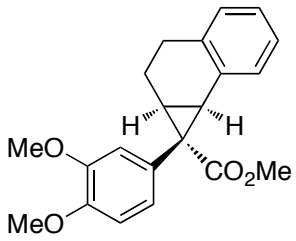
To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added *cis*-β-methylstyrene (5.0 equiv.) and dry trifluorotoluene (4 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^oC) under an atmosphere of dry argon. Methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate (208.1 mg, 0.88 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 1 h. After the addition, the reaction mixture was left to stir at reflux for additional 2 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was

removed in *vacuo*. Obtained product **40** (205.7 mg, 0.69 mmol, 72 % yield). Data for **40**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (t, 3H, J = 3.2 Hz), 6.86-6.83 (m, 2H), 6.80 (d, 1H, J = 8.4 Hz), 6.66 (dd, J_S = 8.4 Hz, J_L = 2.0 Hz, 1H), 6.42 (d, 1H, J = 1.6 Hz), 3.88 (s, 3H), 3.63 (s, 3H), 3.57 (s, 3H), 3.08 (d, 1H, J = 10.4 Hz), 2.37 (dq, 1H, J = 10.4, 6.8 Hz), 1.29 (d, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 175.7, 147.9, 136.4, 130.4, 127.5, 126.0, 125.3, 124.5, 116.4, 110.4, 55.5, 52.7, 37.6, 36.6, 28.0, 11.0; IR (film): 2951, 1713, 1517, 1232, 1027, 729, 700; HRMS-p-APCI m/z 327.15905 (M+H requires 327.15909).



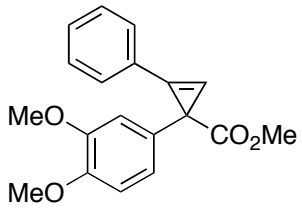
Methyl 1-(3,4-dimethoxyphenyl)-2-methyl-3-phenylcyclopropanecarboxylate (39). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added *trans*-β-methylstyrene (0.550 mL, 5.0 equiv.) and dry trifluorotoluene (4 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate (196.3 mg, 0.83 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 1 h. After the addition, the reaction mixture was left to stir at reflux for additional 2 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Product **39** (164.8 mg, 0.50 mmol, 61 % yield) was obtained after flash column chromatography. Data for **39**: ^{1}H NMR (600 MHz; $CDCl_3$): δ 7.07-7.03 (m,

3H), 6.78 (d, 2H, J = 7.2 Hz), 6.68 (bs, 2H), 6.30 (s, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 3.55 (s, 3H), 3.05 (d, 1H, J = 7 Hz), 2.21 (qu, 1H, J = 7 Hz), 1.46 (d, 3H, J = 7 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.5, 147.9, 147.7, 137.1, 128.8, 127.9, 127.7, 126.0, 123.7, 114.6, 110.3, 55.6, 52.4, 43.0, 37.6, 27.7, 12.9; IR (film): 2951, 1716, 1516, 1247, 1161, 1027, 697; HRMS-p-APCI m/z 327.15902 (M+H requires 327.15909).

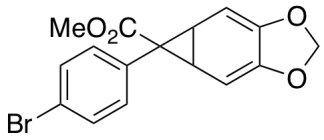


Methyl1-(3,4-dimethoxyphenyl)-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*] naphthalene - 1-carboxylate (41). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added dihydronaphthalene (570 microL, 567.7 mg, 4.36 mmol, 5.0 equiv.), 3,4-Dimethoxydiazo (205.8 mg, 0.87 mmol, 1.0 equiv.) and dry trifluorotoluene (10 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. The reaction mixture was left to stir at reflux for additional 12 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Product **41** (148.4 mg, 0.44 mmol, 51% yield) was obtained after flash column chromatography. Data for **41**: ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.44 (d, 1H, J = 8 Hz), 7.15 (t, 1H, J = 8 Hz), 7.05 (t, 1H, J = 8 Hz), 6.73 (d, 1H, J = 8 Hz), 6.68 (bs, 2H), 6.23 (bs, 1H), 3.79 (s, 3H), 3.63 (s, 3H), 3.37 (bs, 3H), 3.02 (d, J = 8 Hz1H), 2.56 (dd, J_S = 4.0 Hz, J_L = 8.0 Hz1H), 2.19-2.10 (m, 2H), 2.00-1.94 (m, 1H), 1.09-1.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.1, 173.9, 173.0, 147.7, 135.4, 133.0, 129.8, 128.4, 126.7, 126.2, 125.6, 123.0, 113.9, 110.6, 55.4, 55.2, 52.5, 38.5, 31.0, 28.4, 25.1, 17.9; IR (film): 2930,

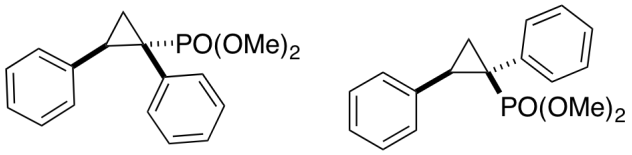
1712, 1516, 1238, 1138, 1027, 758; HRMS-p-APCI m/z 339.15899 ($C_{21}H_{23}O_4$ requires 339.15909).



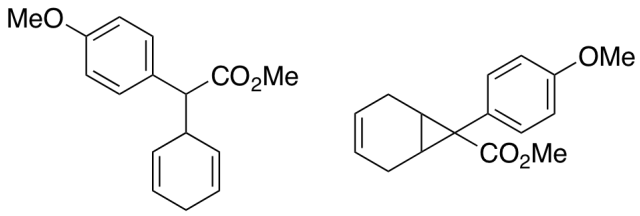
Methyl 1-(3,4-dimethoxyphenyl)-2-phenylcycloprop-2-enecarboxylate (42). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added phenylacetylene (0.470 mL, 5.0 equiv.) and dry trifluorotoluene (4 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate (203.1 mg, 0.86 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 1 h. After the addition, the reaction mixture was left to stir at reflux for additional 2 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained product **42** (117.4 mg, 44 % yield) after flash column chromatography. Data for **42**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (dd, 2H, J_S = 1.6 Hz, J_L = 6.4 Hz,), 7.46-7.40 (m, 3H), 7.21 (s, 1H), 6.97 (d, 1H, J = 1.6 Hz), 6.92 (dd, 1H, J_S = 1.6 Hz, J_L = 8.4 Hz), 6.79 (d, 1H, J = 8.4 Hz), 3.85 (s, 3H), 3.84 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 175.1, 148.4, 147.7, 133.5, 129.9, 129.8, 128.8, 125.4, 120.3, 117.4, 111.7, 110.8, 100.4, 55.8, 52.2, 33.1; IR (film): 2950, 1716, 1513, 1247, 1140, 1025, 699; HRMS-p-APCI m/z 311.12769 (M+H requires 311.12779).



Methyl 5-(4-bromophenyl)-5,5a-dihydro-4aH cyclopropa[4,5]benzo [1,2d] [1,3] dioxole-5-carboxylate (43). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added benzo[*d*][1,3]dioxole (0.40 mL, 3.90 mmol, 5.0 equiv.) and dry trifluorotoluene (4 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. 1-(4-bromophenyl)-1-diazopropan-2-one (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Product **43** (40 mg, 0.11 mmol, 15 % yield). Rf = 0.30 (1:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.34 (dt, 2H, J_S = 2.80 Hz, J_L = 8.80 Hz), 7.03 (dt, 2H, J_S = 2.40 Hz, J_L = 8.80 Hz), 5.48 (ABX system, 2H, J_S = 2.0 Hz, J_L = 4.0 Hz), 5.36 (d, 1H, J = 1.2 Hz), 5.15 (d, 1H, J = 0.8 Hz), 3.62 (s, 3H), 3.44-3.37 (AB (dd), 2H, J_S = 2.4 Hz, J_L = 4.40 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5 (C), 146.7 (C), 134.7 (CH), 132.4 (CH), 130.5 (C), 120.9 (C), 98.8 (CH2), 96.0 (CH), 52.9 (CH3), 46.0 (CH), 30.8 (CH); HRMS- m/z 349.007 ($C_{16}H_{14}BrO_4$ requires 349.00726).



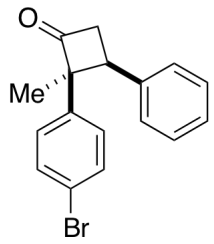
Dimethyl (1,2-diphenylcyclopropyl)phosphonate (48). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added styrene (0.50 mL, 4.40 mmol, 5.0 equiv.) and dry trifluorotoluene (4 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Dimethyl (diazo(phenyl)methyl)phosphonate (200 mg, 0.88 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Data for **48a**: ^{1}H NMR (400 MHz, $CDCl_3$): 7.14-7.10 (m, 2H), 7.07-7.04 (m, 6H), 6.76-6.73 (m, 2H), 3.75 (d, 3H, J = 12.0 Hz), 3.69 (d, 3H, J = 12.0 Hz), 3.02 (ddd, 1H, J = 6.4, 8.8, 16.0 Hz), 2.07 (ddd, 1H, J = 2.0, 7.2, 16.4 Hz), 1.74 (ddd, 1H, J = 5.6, 6.8, 12.4 Hz). Consistent with previously reported data.[73] Data for **48b**: ^{1}H NMR (400 MHz, $CDCl_3$): 7.60-7.56 (m, 2H), 7.52 (d, 2H, J = 7.2 Hz), 7.38-7.34 (m, 4H), 7.31-7.23 (m, 2H), 3.28 (d, 3H, J = 11.2 Hz), 3.23 (d, 3H, J = 11.2 Hz), 2.66 (dt, 1H, J_S = 8.0 Hz, J_L = 12 Hz), 2.19 (ddd, 1H, J = 5.2, 7.6, 16.8 Hz), 1.70 (td, 1H, J_S = 4.8 Hz, J_L = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7 (d, J = 3.1 Hz), 136.6 (d, J = 6.1 Hz), 130.8 (d, J = 3.4 Hz), 129.7, 128.4 (d, J = 1.9 Hz), 127.8, 127.3 (d, J = 2.3 Hz), 126.7, 52.6 (m), 52.2 (m), 31.0, 30.5 (d, J = 190 Hz), 16.0; IR (neat film): 2951, 1601, 1492, 1447, 1267, 1235, 1023; HRMS-posAPCI: m/z 303.11448 (M+H requires 303.11446).



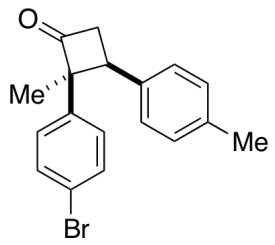
44 **45**

Mixture of Methyl 2-(cyclohexa-2,5-dien-1-yl)-2-(4-methoxyphenyl)acetate (44) and Methyl 7-(4-methoxyphenyl)bicyclo[4.1.0]hept-3-ene-7-carboxylate (45). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 1,4-cyclohexadiene (5.0 mL, 54.5 mmol, 52.85 equiv.) and dry trifluorotoluene (4-5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl 2-diazo-2-(4-methoxyphenyl)acetate (200 mg, 0.97 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained products **44** and **45** (245 mg, 0.95 mmol, 98 % yield) were formed in a ratio of (60:40). Flash column conditions: 10:1 pentane/Et_2O. **44:** R_f = 0.4 (5:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.25 (d, 2H, *J* = 8.8 Hz), 6.86 (d, 2H, *J* = 8.4 Hz), 5.84-5.74 (m, 1H), 5.74-5.62 (m, 2H), 5.34-5.22 (m, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.50-3.39 (m, 1H), 3.36 (d, 1H, *J* = 10.4 Hz), 2.66-2.56 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.7, 158.8, 129.6, 128.7, 126.7, 126.2, 125.9, 125.8, 113.9, 57.4, 55.2, 51.9, 38.5, 26.4; IR (film: neat): 3031, 2898, 1702, 1609, 1514, 1243, 1208; HRMS- m/z 259.13281 (259.13287 requires M+1). Data for **45:** Rf = 0.29 (5:1 Pentane/Et_2O); ^{1}H

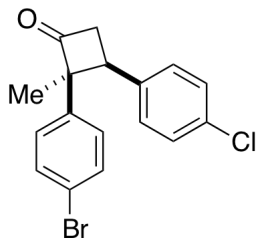
NMR (400 MHz; $CDCl_3$) δ 7.12 (d, 2H, J = 8.8 Hz), 6.82 (d, 2H, J = 9.2 Hz), 5.08-4.98 (m, 2H), 3.79 (s, 3H), 3.56 (s, 3H), 2.60-2.44 (m, 2H), 2.44-2.32 (m, 2H), 2.16-2.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 158.4, 130.9, 126.3, 123.2, 113.3, 55.0, 52.4, 32.5, 25.0, 21.0; IR (film neat): 3030, 2898, 1702, 1513, 1242; HRMS- m/z 259.13281 ($C_{16}H_{19}O_3$ requires 259.13287).



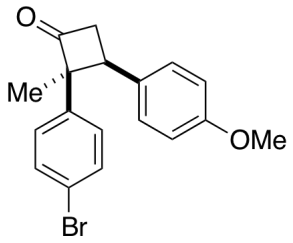
2-(4-bromophenyl)-2-methyl-3-phenylcyclobutanone (54). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added styrene (0.48 mL, 4.20 mmol, 5.0 equiv.) and dry trifluorotoluene (4 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^oC) under an atmosphere of dry argon. 1-(4-bromo phenyl)-1-diazopropan-2-one (200 mg, 0.84 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained product **54** (183 mg, 0.58 mmol, 69 % yield). Flash column conditions: 5:1 pentane/Et_2O. Rf = 0.31 (5:1 Pentane/Et_2O); ^1H NMR (400 MHz; $CDCl_3$) δ 7.24-7.08 (m, 5H), 6.91 (dd, 2H, J_S = 2.0 Hz, J_L = 7.6 Hz), 6.76 (dt, 2H, J_S = 2.8 Hz, J_L = 8.4 Hz), 3.68-3.54 (m, 2H), 3.31 (dd, 1H, J_S = 6.8 Hz, J_L =17.2 Hz), 1.68 (s, 3H). Consistent with reported data.[74]



2-(4-bromophenyl)-2-methyl-3-(*p*-tolyl)cyclobutanone (55). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 4-methylstyrene (0.55 mL, 4.20 mmol, 5.0 equiv.) and dry trifluorotoluene (4 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. 1-(4-bromophenyl)-1-diazopropan-2-one (200 mg, 0.84 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained product **55** (252 mg, 0.77 mmol, 91% yield). Flash column conditions: 5:1 pentane/Et_2O. R_f = 0.31 (5:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.19 (dt, 2H, J_S = 2.8 Hz, J_L = 11.6 Hz), 6.95 (dt, 2H, J = 8 Hz), 6.86-6.70 (m, 4H), 3.63-3.50 (m, 2H), 3.26 (dd, 1H, J_S = 6.0 Hz, J_L = 16.4 Hz), 2.25 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1 (C), 138.6 (C), 136.6 (C), 136.3 (C), 131.0 (CH), 128.9 (CH), 128.6 (CH), 127.9 (CH), 120.4 (C), 72.0 (C), 49.9 (CH), 43.8 (CH), 27.0 (CH), 20.9 (CH); IR (film neat): 2922, 1774, 1489, 1009; HRMS- m/z 329.05355 ($C_{18}H_{18}BrO$ requires 329.05347).



2-(4-bromophenyl)-3-(4-chlorophenyl)-2-methylcyclobutanone (56). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 4-chlorostyrene (0.50 mL, 4.20 mmol, 5.0 equiv.) and dry trifluorotoluene (4 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. 1-(4-bromophenyl)-1-diazopropan-2-one (200 mg, 0.84 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained product **56** (277 mg, 0.79 mmol, 94 % yield). Flash column conditions: 5:1 pentane/Et_2O. Rf = 0.22 (5:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.22 (dt, 2H, J_S = 2.4 Hz, J_L = 8.8 Hz), 7.12 (dt, 2H, J_S = 2.4 Hz, J_L = 8.4 Hz), 6.83 (dt, 2H, J_S = 2.8 Hz, J_L = 8.4 Hz), 6.77 (dt, 2H, J_S = 2.8 Hz, J_L = 8.4 Hz), 3.64-3.56 (m, 2H), 3.27-3.19 (m, 1H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 138.4, 138.1, 132.5, 131.3, 128.5, 128.4, 120.7, 72.3, 50.0, 43.6, 26.9; IR (film neat): 2963, 1775, 1491, 1009; HRMS: m/z (APCI) 371 (M+Na).



2-(4-bromophenyl)-3-(4-methoxyphenyl)-2-methylcyclobutanone (57). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 4-methoxystyrene (0.56 mL, 4.20 mmol, 5.0 equiv.) and dry trifluorotoluene (4 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. 1-(4-bromophenyl)-1-diazopropan-2-one (200 mg, 0.84 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained product **57** (206 mg, 0.60 mmol, 71% yield). Flash column conditions: 5:1 pentane/Et_2O. Data for **57**: Rf = 0.22 (5:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.20 (dt, 2H, J = 8.8 Hz), 6.81 (dt, 2H, J = 8.8 Hz), 6.76 (dt, 2H, J_S = 2.8 Hz, J_L=8.4 Hz), 6.68 (dt, 2H, J_S = 2.8 Hz, J_L=8.8 Hz), 3.72 (s, 3H), 3.64-3.48 (m, 2H), 3.24 (dd, 1H, J_S = 5.6 Hz, J_L = 15.6 Hz), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2, 158.2, 138.5, 131.1, 129.0, 128.6, 120.4, 113.6, 72.0, 55.1, 49.9, 43.4, 26.8; IR (film neat): 2960, 2835, 1774, 1513, 1247, 1009; HRMS- m/z 345.04838 ($C_{18}H_{18}BrO_2$ requires 345.04847).

Hammett studies of free-carbene cyclopropanation: To an oven dried round-bottom flask under an inert and dry argon-atmosphere, was added substituted styrene (5.0 equiv.) and styrene (5.0 equiv.), and dry trifluorotoluene (5.0 mL). Methyl 2-diazo-2-(4-methoxyphenyl)acetate (0.49 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4.0 mL) and added to the former solution, drop-wise over 3 h at reflux (~102 °C). The mixture was allowed to stir for further 9 h at reflux after addition. The oil bath was then removed and reaction was allowed to cool down to ambient temperature before the solvent was removed *in vacuo*. The ratio of cyclopropane products was obtained from the crude ^{1}H NMR spectrum. The obtained product ratios are summarized in Table 14.

Scheme 54: Hammett Study

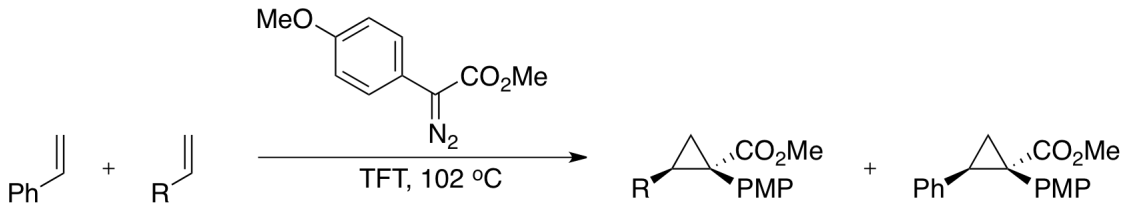


Table 14: Product ratios obtained in competition studies.

R^1	Prod. Ratio (Ar/Ph)
-CN	1.05
-CF_3	0.48
-Cl	1.25
-H	1.00
-Me	0.95
-OMe	2.6

Experimental procedure for kinetic studies of thermal decomposition of diazo compounds. The experimental setup and data analysis were carried out with the assistance of Dr. Jørn Hansen. The kinetic experiments were carried out with a Mettler Toledo ReactIR™ 45m instrument equipped with a 9.5mm x 12" AgX 1.5m SiComp probe, monitoring the disappearance of diazo compound ($\nu_{C=N=N}$ ~ 2100 cm^{-1}). To a dry 25 mL three-neck round-bottom flask fitted with a condenser, a thermometer and the ReactIR probe was added the diazo compound (1.0 mmol, 1.0 equiv.), styrene (5 mmol, 5 equiv.) and dry trifluorotoluene (5 mL) under an inert Ar-atmosphere. The react-IR recording was commenced and a baseline of 4.0 min was collected under vigorous stirring, after which the solution was lowered into an oil bath kept at >130°C. The internal temperature of the reaction mixture reached the boiling point (103±1 °C) within ~40 seconds. All the kinetic traces displayed characteristics of first-order kinetics and were treated according to conventional analysis.[10] The rate is proportional to the diazoacetate concentration according to Equation 1:

$$\text{Rate} = k_1[\text{diazo}] \qquad \text{(Eq. 1)}$$

The first-order rate constant, k_1, can be extracted from regression analysis of a plot of ln[A(t) – A(inf)] *vs* time (h), where:

A(t) = Absorbance at time t.

A(inf) = Absorbance at infinity, estimated from absorbance at 10 half-times (99.9% completed reaction) or 4 half-times (93.75% completed reaction).

The data was processed in Microsoft Excel 2004, and is summarized in Table 15 with corresponding R^2-values. The raw-data traces and kinetic plots are shown below. Error bars are based on standard deviations obtained from the least-squares regression analysis. The % conversion *versus* time plots were also generated from the reactIR raw-data. The percent conversion was estimated from the following formula:

$$\%\text{Conversion} = (|A(0)-A(t)|/|A(0)-A(\text{inf})|)*100\% \qquad \text{(Eq. 2)}$$

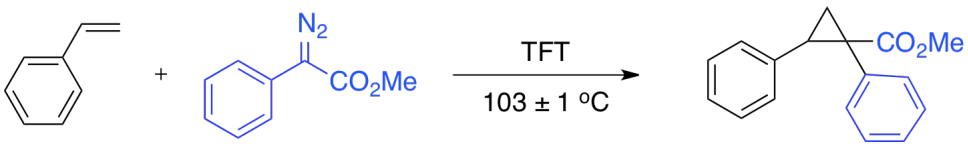
where A(t) and A(inf) are as defined in Equation 1, and:

A(0) = Initial absorbance before reaction was started.

Table 15: Summary of linear regression parameters and estimated A(inf).

Entry	Slope	St.dev.	R^2	A(inf)	Species
1	1.92	0.02	0.999	0.1178	**4** (H)
2	22.87	0.03	0.998	0.1176	**7** (OMe)
3	0.147	0.009	0.992	0.1109	**13** (NO_2)
4	0.42	0.01	0.999	0.1095	**25** (EDA)
5	26.99	0.01	0.998	0.1067	**53** (ketone)
6	0.622	0.002	0.994	0.1067	**53'** (ketene)

Scheme 55: Kinetic study of cyclopropanation with **4** and styrene.



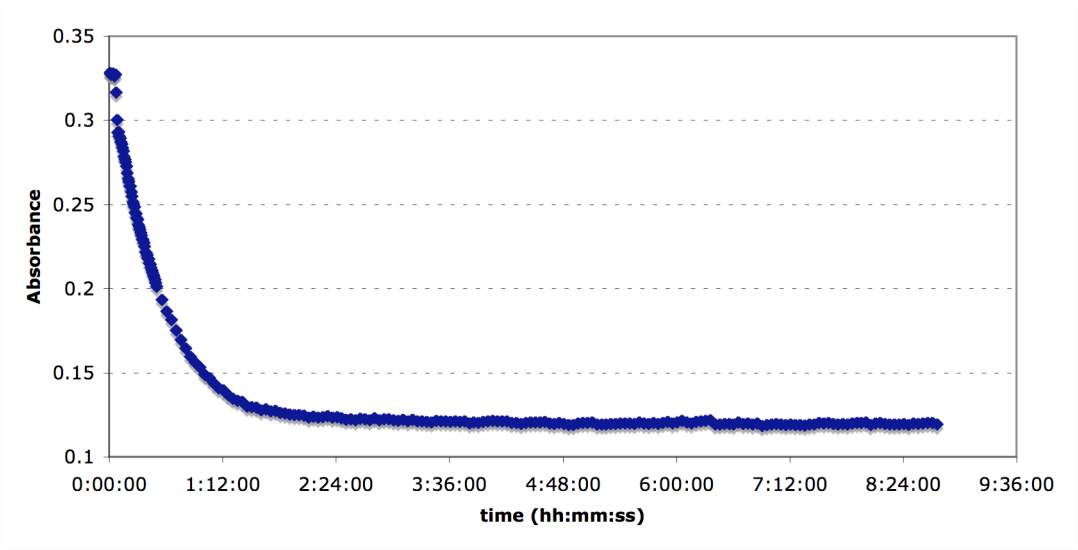


Figure 16: Raw data trace for kinetic studies of diazo **4**.

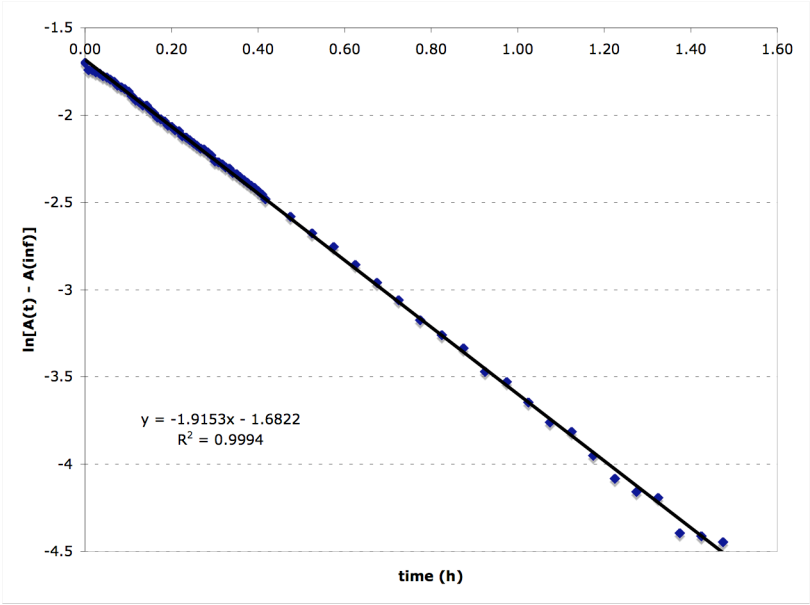
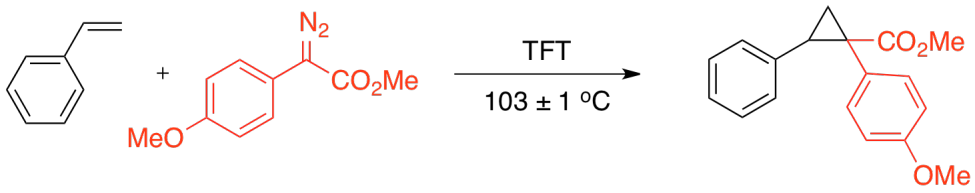


Figure 17: Semi-logaritmic plot and linear regression to determine rate constant for decomposition of **4**. The time axis is arbitrary.

Scheme 56: Kinetic data for cyclopropantaion of styrene with *p*-methoxy phenyldiazoacetate **7**.



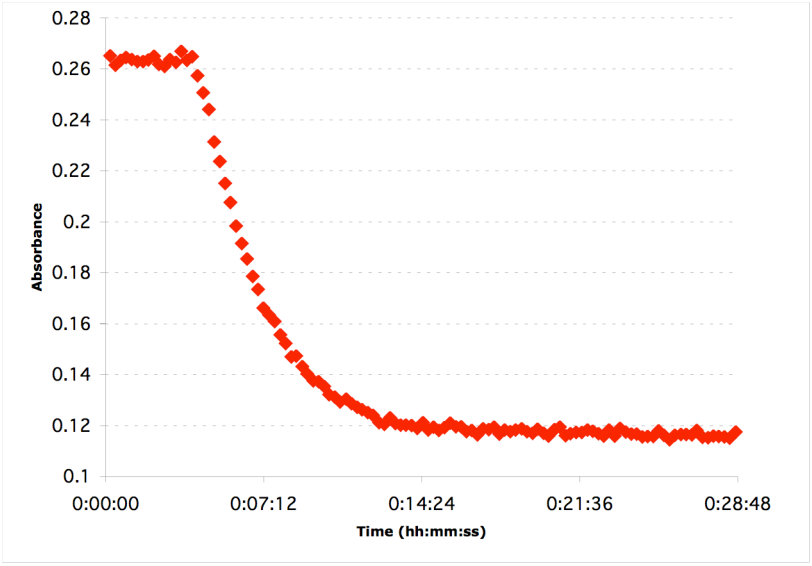


Figure 18: Raw data for **7**.

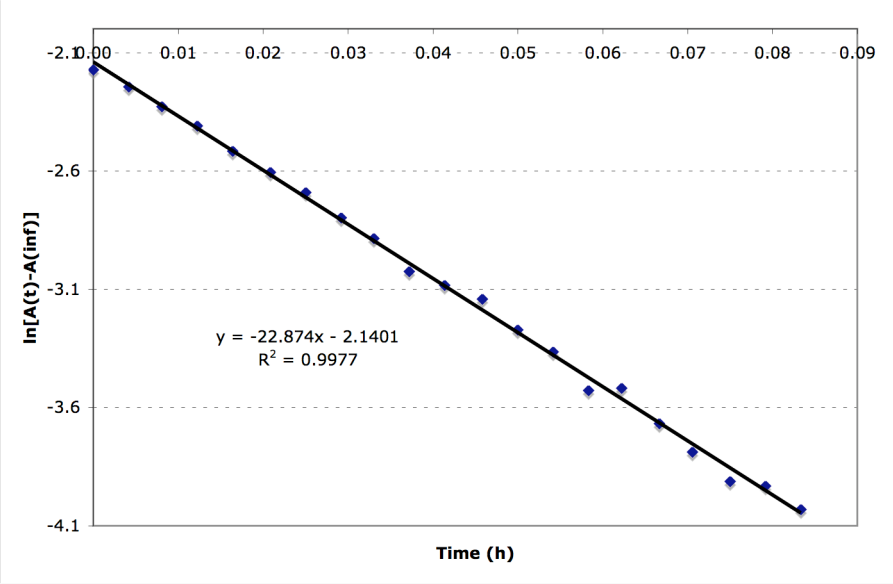
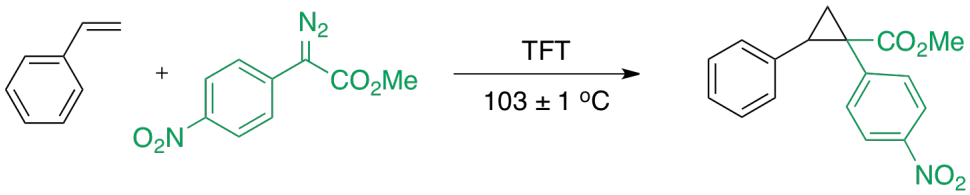


Figure 19: Semi-logaritmic plot and linear regression to determine rate constant for decomposition of **7**. The time axis is arbitrary.

Scheme 57: Kinetic data for the cyclopropanation of styrene with *p*-nitro phenyldiazoacetate **13**.



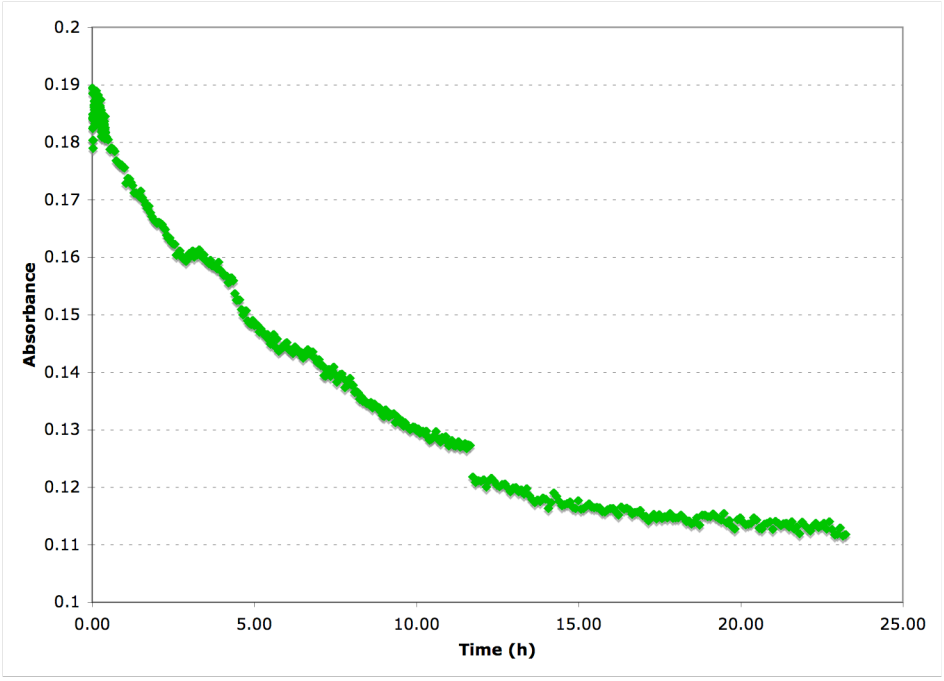


Figure 20: Raw data for **13**. Variations occured due to baseline fluctuations at 3-5 h and 6-8 h. Break-point at ~12 h occured as a result of addition of more solvent to the reaction mixture.

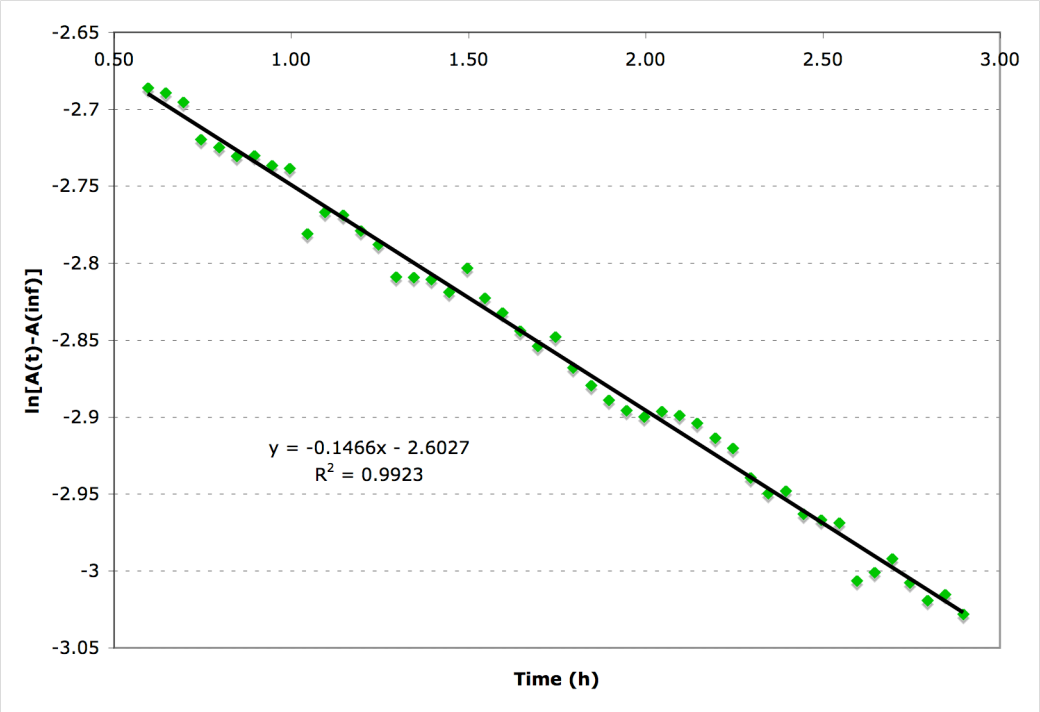
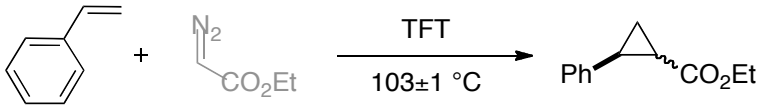


Figure 21: Semi-logaritmic plot for **13** and linear regression**.** The time axis is arbitrary.

Scheme 58: Kinetic data for cyclopropanation of styrene with ethyl dizaoacetate **25**.



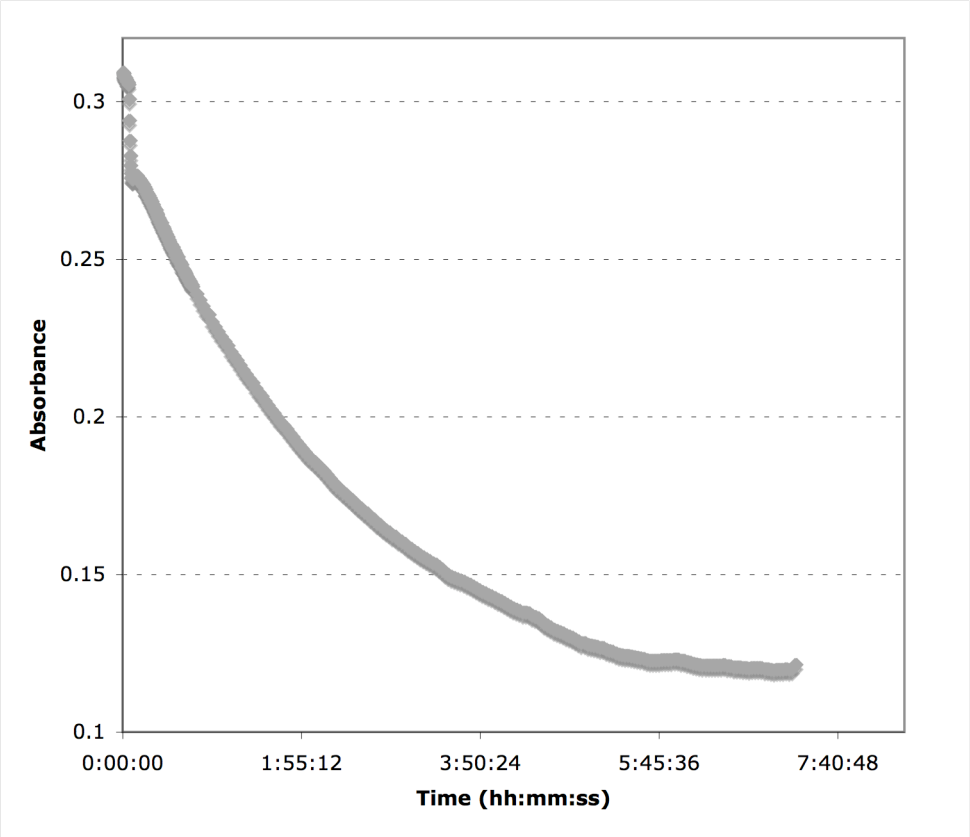


Figure 22: Raw data for **25**.

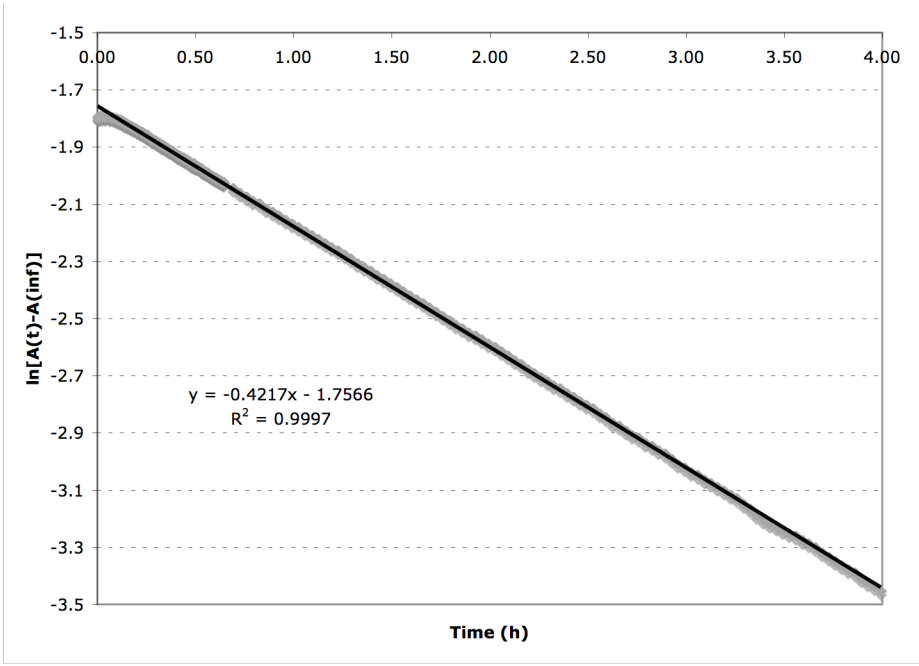
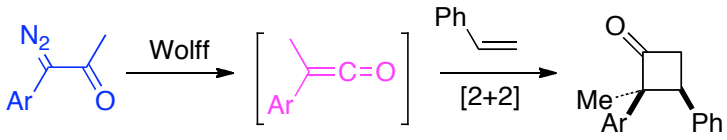


Figure 23: Semi-logaritmic plot for **25** and linear regression. The time axis is arbitrary.

Scheme 59: [2+2] cycloaddition with diazoketones.



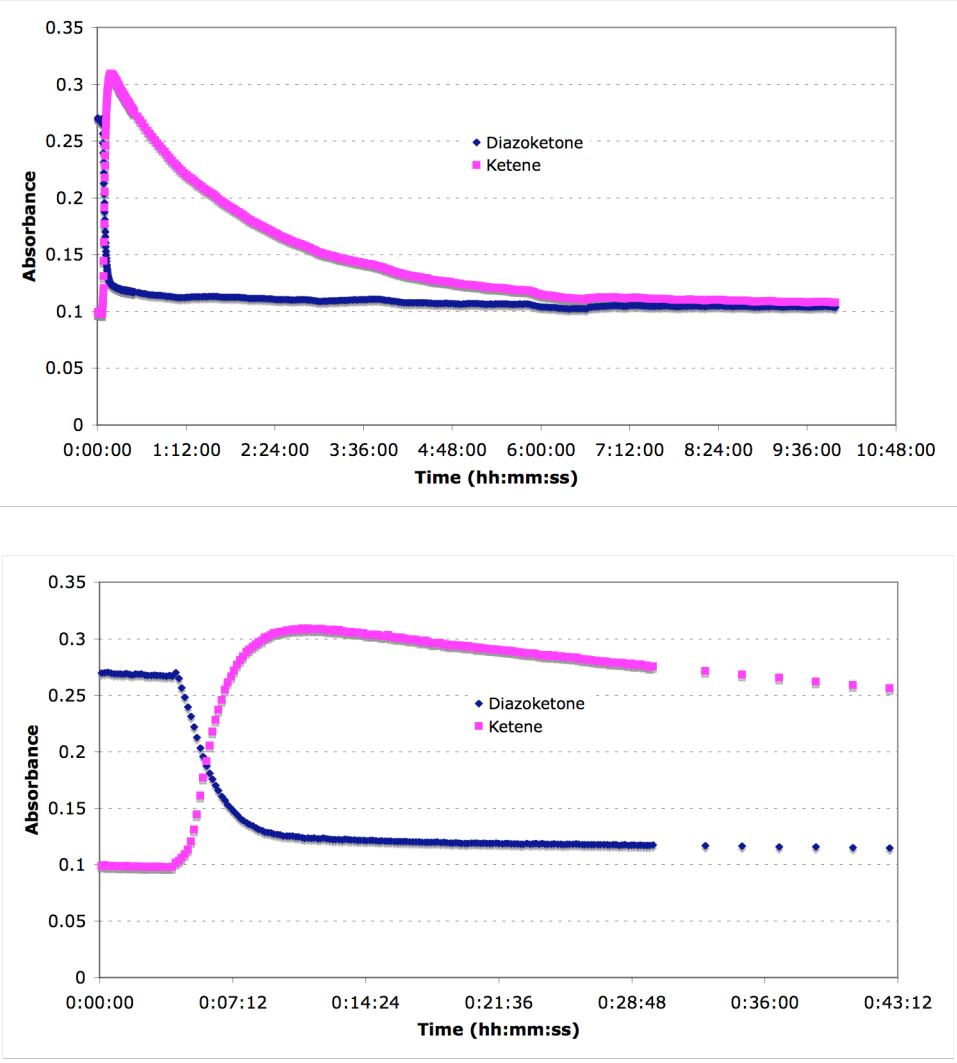


Figure 24: (a) Raw trace for decomposition of diazoketone **53**, formation of ketene intermediate and ketene decomposition. (b) Expanded view of initial 43 minutes.

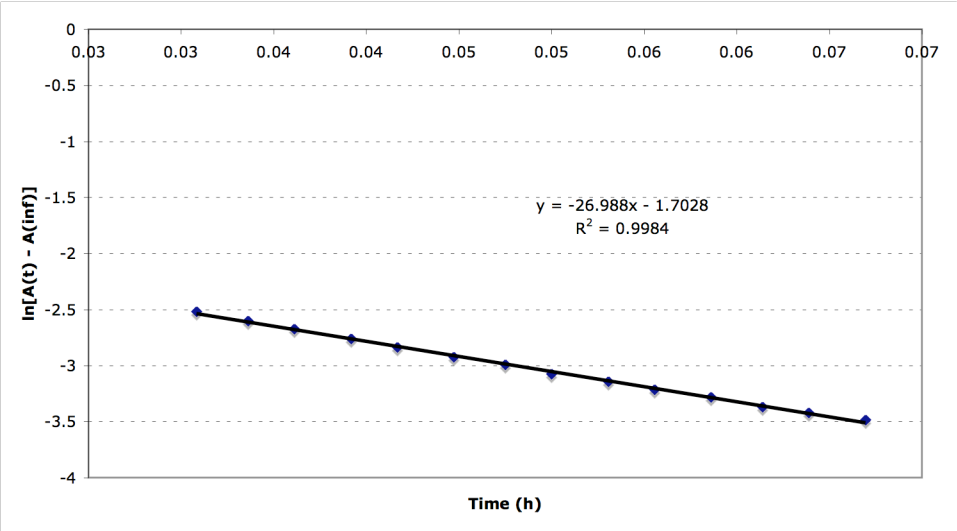


Figure 25: Semi-ln plot for diazoketone and linear regression. The time axis is arbitrary

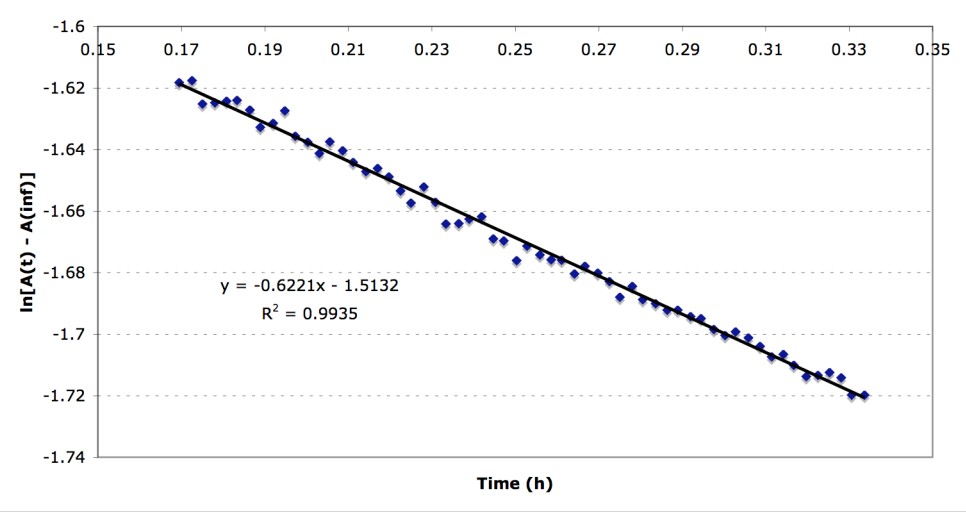
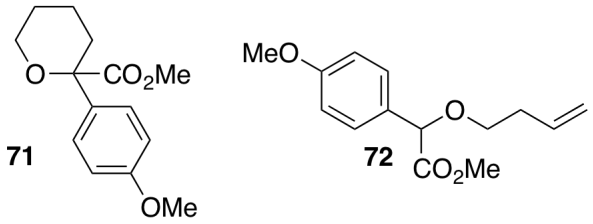
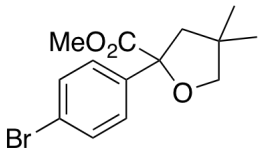


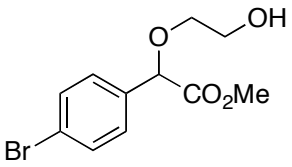
Figure 26: Semi-ln plot and linear regression for determination of pseudo first-order rate constant for ketene trapping. The time axis is arbitrary.



Methyl 2-(4-methoxyphenyl)tetrahydro-2*H*-pyran-2-carboxylate (71) and Methyl 2-(but-3-en-1-yloxy)-2-(4-methoxyphenyl)acetate (72). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added tetrahydrofuran (0.79 mL, 9.70 mmol, 10.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl 2-diazo-2-(4-methoxyphenyl)acetate (200 mg, 0.97 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained products **71** and **72** (118 mg, 0.47 mmol, 49 % yield) were formed in a ratio of (67:33). Flash column conditions: 5:1 to 3:1 pentane/Et_2O. Data for **71:** ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.44 (d, 2H, J = 8.8 Hz), 6.88 (d, 2H, J = 8.8 Hz), 3.98-3.88 (m, 1H), 3.82-3.70 (m, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 2.45 (m, 1H), 1.85 (m, 1H), 1.81-1.70 (m, 1H), 1.60 (m, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 173.3, 159.0, 132.9, 126.5, 113.7, 80.3, 64.8, 55.2, 52.4, 33.3, 25.0, 20.6; IR (film: neat): 2946, 1727, 1608, 1510, 1239, 1176. Data for **72:** ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.37 (d, 2H, J = 8.4 Hz), 6.89 (d, 2H, J = 8.8 Hz), 5.88-5.74 (m, 1H), 5.14-5.00 (m, 2H), 4.84 (s, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.60-3.40 (m, 2H), 2.50-2.32 (m, 2H); Consistent with reported data.[63]

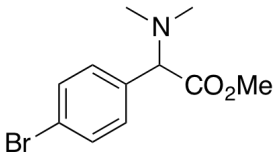


Methyl 2-(4-bromophenyl)-4,4-dimethyltetrahydrofuran-2-carboxylate (82). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 3,3-dimethyloxetane (0.40 mL, 3.92 mmol, 5.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (~102 ^{o}C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Ring expansion product **82** (197 mg, 0.63 mmol, 81 % yield) was isolated as a clear yellow oil. Flash column conditions: 5:1 pentane/Et_2O. Data for **82**: R_f = 0.29 (5:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.46 (dt, 2H, J_S = 2.0 Hz, J_L = 8.8 Hz), 7.42 (dt, 2H, J_S = 2.0 Hz, J_L = 9.2 Hz), 3.79-3.74 (m, 1H), 3.72-3.69 (m, 1H), 3.70 (s, 3H), 2.79 (d, 1H, J = 12.8 Hz), 2.07 (d, 1H, J = 13.2 Hz), 1.11 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3 (C), 141.4 (C), 131.3 (CH), 127.0 (CH), 121.6 (C), 87.2 (C), 80.7 (CH_2), 52.9 (CH_3), 51.8 (CH_2), 40.0 (C), 26.3 (CH_3), 25.9 (CH_3); IR (film $CDCl_3$): 2955, 2870, 1731, 1248, 1057, 1009; HRMS- m/z 313.04358 (313.04338 requires M+1).

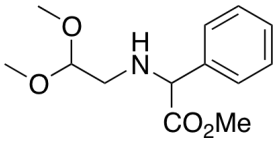


Methyl 2-(4-bromophenyl)-2-(2-hydroxyethoxy)acetate (84). Data for **84**: ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.50 (d, 2H, J = 8.4 Hz), 7.33 (d, 2H, J = 8.4 Hz), 4.89 (s, 1H), 3.81-3.79 (m, 2H,), 3.72 (s, 3H), 3.67-3.63 (m, 2H), 2.59 (t, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171, 135, 131.7, 128.7, 122.8, 80.2, 71.2, 61.4, 52.4; IR (film): 3459 (OH), 2951, 1736, 1487, 1210, 1069, 1011; HRMS-pAPCI m/z 289.00708 ($C_{11}H_{14}O_4Br$ requires 289.007).

General procedure for thermal N–H insertion reactions: To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added the amine (2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 °C) under an atmosphere of dry argon. The diazo compound was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. A ^{1}H NMR spectrum was aquired of the crude material to determine the product and diastereomeric ratios shown with the characterization data. The residue was then purified by flash column chromatography (SiO_2,) to yield the product(s).

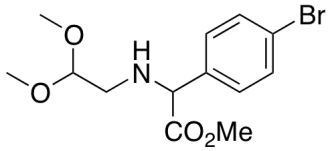


Methyl 2-(4-bromophenyl)-2-(dimethylamino)acetate (86). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added N,N-Dimethylphenethylamine (0.65 mL, 3.90 mmol, 5.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 °C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **86** (140 mg, 0.51 mmol, 66 % overall yield). Flash column conditions: 5:1, 3:1, 2:1, 1:1 Pentane/Et_2O + 0.5%NEt_3 and finally column was flushed with 100 % Et_2O. Products obtained as clear yellow oil. Data for **86**: R_f = 1.5 (1:1 Pentane/Et_2O); ^1H NMR (400 MHz; $CDCl_3$) δ 7.48 (d, 2H, J = 8 Hz), 7.32 (d, 2H, J = 8 Hz), 3.84 (s, 1H), 3.70 (s, 3H), 2.24 (s, 6H). Consistent with reported data.[28]



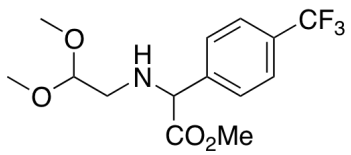
Methyl 2-((2,2-dimethoxyethyl)amino)-2-phenylacetate (92). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 2,2-dimethoxyethylamine (0.25 mL, 2.28 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then

equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 °C) under an atmosphere of dry argon. Methyl 2-diazo-2-phenylacetate (200 mg, 1.14 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **92** (199 mg, 0.79 mmol, 69 % overall yield). Flash column conditions: 3:1 Pentane/EtOAc + 0.5%NEt_3. Products obtained as yellow oil. R_f = 0.22 (2:1 Pentane/EtOAc); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.40-7.26 (m, 5H), 4.48 (t, 1H, J = 5.6 Hz), 4.40 (s, 1H), 3.67 (s, 3H), 3.36 (s, 3H), 3.33 (s, 3H), 2.72 (dd, 1H, J_S = 6.0 Hz, J_L = 12.0 Hz), 2.62 (dd, 1H, J_S = 5.2 Hz, J_L =12.0 Hz), 2.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 137.8, 128.5, 128.0, 127.3, 103.7, 65.2, 53.7, 53.5, 52.0; IR (film neat): 2832, 1735, 1128, 1057; HRMS-pos-ESI m/z 254.13872 ($C_{13}H_{20}NO_4$ requires 254.13868).



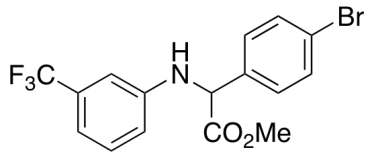
Methyl 2-(4-bromophenyl)-2-((2,2-dimethoxyethyl)amino)acetate (93). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 2,2-dimethoxyethylamine (0.17 mL, 1.56 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^{o}C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4

mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **93** (199 mg, 0.63 mmol, 80 % yield). Flash column conditions: 2:1 Pentane/EtOAc + 0.5%NEt_3. Products obtained as light brown oil. Data for **93**: R_f = 0.33 (2:1 EtOAc/Pentane + 0.5% NEt_3); Rf = 0.33; ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.47 (d, 2H, J = 8.4 Hz), 7.27 (d, 2H, J = 8.4 Hz), 4.46 (t, 1H, J = 4.8 Hz), 4.37 (s, 1H), 3.69 (s, 3H), 3.37 (s, 3H), 3.34 (s, 3H), 2.70 (dd, 1H, J_S = 6.0 Hz, J_L = 12.0 Hz), 2.60 (dd, 1H, J_S = 5.4 Hz, J_L = 12.0 Hz), 2.17 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 136.9, 131.7, 129.1, 122.0, 103.7, 64.6, 53.9, 53.7, 52.3, 48.7; IR (film neat): 2832, 1736, 1128, 1069, 1011; HRMS-pos-ESI m/z 332.04913 ($C_{13}H_{19}BrNO_4$ requires 332.0492).



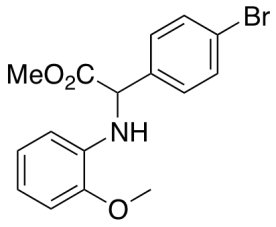
Methyl 2-((2,2-dimethoxyethyl)amino)-2-(4-(trifluoromethyl)phenyl)acetate (94). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 2,2-dimethoxyethylamine (0.18 mL, 0.64 mmol, 2.0 equiv.). and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 °C) under an atmosphere of dry argon. Methyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate (200 mg, 0.82 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period

of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **94** (106 mg, 0.33 mmol, 40 % overall yield). Flash column conditions: 2:1 Pentane/EtOAc +0.5% NEt_3. Products obtained as yellow oil. Data for **94**: R_f = 0.18 (2:1 Pentane/EtOAc); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.61 (d, 2H, J = 8.4 Hz), 7.52 (d, 2H, J = 8.0 Hz), 4.52-4.44 (m, 2H), 3.71 (s, 3H), 3.38 (s, 3H), 3.35 (s, 3H), 2.73 (dd, 1H, J_S = 6.0, J_L = 12.0 Hz), 2.61 (dd, 1H, J_S = 4.8 Hz, J_L = 12.0 Hz), 2.24 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 142.0, 130.3, 127.9, 125.6, 124.0, 103.8, 64.9, 54.0, 53.8, 52.4, 48.9; IR (film neat): 2835, 1739, 1324, 1120, 1065; HRMS-pos-ESI m/z 322.12599 ($C_{14}H_{18}F_3NO_4$ requires 322.12607);



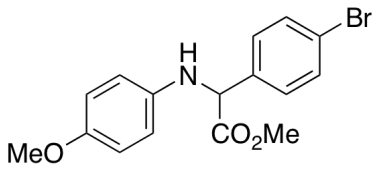
Methyl 2-(4-bromophenyl)-2-((3-(trifluoromethyl)phenyl)amino)acetate (95). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 3-(trifluoromethyl)aniline (0.19 mL, 1.56 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^{o}C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient

temperature. The solvent was removed in *vacuo*. Obtained **95** (227 mg, 0.58 mmol, 75 % overall yield). Flash column conditions: 9:1 pentane/Et_2O +0.5% NEt_3. Products obtained as yellow oil. Data for **95**: ^1H NMR (400 MHz; $CDCl_3$) δ 7.49-744 (m, 3H), 7.36 (d, 2H, J = 8.8 Hz), 7.18 (t, 1H, J = 7.6 Hz), 6.70 (t, 1H, J = 7.2 Hz), 6.34 (d, 1H, J = 8.4 Hz), 5.87 (bs, 1H), 5.08 (d, 1H, J = 4.8 Hz), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 143.0, 136.2, 133.2, 132.4, 129.0, 127.0, 125.3, 122.8, 117.3, 114.6, 113.0, 59.7, 53.4; IR (film neat): 3438, 1742, 1615, 1098, 1033; HRMS-pos-ESI m/z 388.01543 ($C_{16}H_{14}O_2NBrF_3$ requires 388.01545).



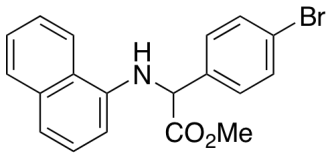
Methyl 2-(4-bromophenyl)-2-((2-methoxyphenyl)amino)acetate (96). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^oC) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **96** (150 mg, 0.43 mmol, 55 % overall yield). Flash column conditions: 9:1 pentane/Et_2O +0.5% NEt_3. Products obtained

as yellow oil. R_f = 0.54 (1:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.47 (d, 2H, J = 8.4 Hz), 7.38 (d, 2H, J = 8.4 Hz), 6.78 (dd, 1H, J_S = 2.0 Hz, J_L =8.0 Hz), 6.76-6.62 (m, 2H), 6.27 (dd, 1H, J_S = 1.6 Hz, J_L = 7.2 Hz), 5.50 (d, 1H, J = 5.2 Hz), 5.03 (d, 1H, J = 6 Hz), 3.89 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 147.0, 136.9, 135.5, 131.9, 128.9, 122.2, 121.0, 117.6, 110.7, 109.6, 60.1, 55.4, 52.8; IR (film neat): 3420, 1739, 1603, 1511, 1223; HRMS-pos-ESI m/z 350.03876 ($C_{16}H_{17}BrNO_3$ requires 350.03863).

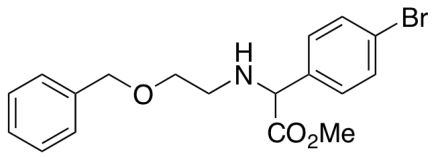


Methyl 2-(4-bromophenyl)-2-((4-methoxyphenyl)amino)acetate (97). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 4-methoxyaniline (0.192 g, 1.56 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^{o}C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. R_f = 0.58 (1% DCM/NEt_3); ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.46 (d, 2H, *J* = 7.8 Hz), 7.36 (d, 2H, *J* = 8.4 Hz), 6.70 (d, 2H, *J* = 8.4 Hz), 6.48 (d, 2H, *J* = 9.6 Hz), 4.96 (d, 1H, *J* = 5.4 Hz), 4.72 (d, 1H, *J* = 5.4 Hz), 3.70 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 152.5, 139.7, 136.9, 131.9, 128.9, 122.1, 114.8, 114.7,

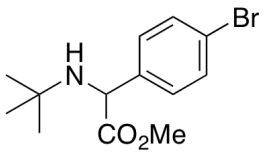
60.9, 55.5, 52.8; IR (film neat): 3397, 1736, 1511, 1236, 1011; HRMS-pos-ESI m/z 350.03852 ($C_{16}H_{17}BrNO_3$ requires 350.03863);



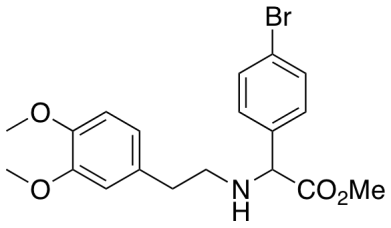
Methyl 2-(4-bromophenyl)-2-(naphthalen-1-ylamino)acetate (102). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added naphthalen-1-amine (223 mg, 1.56 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^{o}C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **102** (186 mg, 0.50 mmol, 64 % overall yield). Flash column conditions: 3:1 Pentane/EtOAc+1.0 % NEt_3. Products obtained as red solid. R_f = 0.59 (1:1 Pentane/EtOAc+1% NEt_3); ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.01 (d, 1H, J = 8.4 Hz), 7.78 (dd, 1H, J_S = 1.2 Hz, J_L= 7.8 Hz), 7.54-7.40 (m, 6H), 7.23 (d, 1H, J = 7.8 Hz), 7.17 (t, 1H, J = 7.2 Hz), 6.25 (d, 1H, J = 7.2 Hz), 5.81 (d, 1H, J = 4.8 Hz), 5.19 (d, 1H, J = 5.4 Hz), 3.78 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 140.5, 136.4, 134.2, 132.0, 128.9, 128.7, 126.2, 125.9, 125.1, 123.4, 122.3, 120.0, 118.3, 105.6, 60.2, 53.1; IR (film neat): 3425, 3058, 1736, 1582, 1478, 1010, 767; HRMS-pos-ESI m/z 370.0444 ($C_{19}H_{16}BrNO_2$ requires 370.04372).



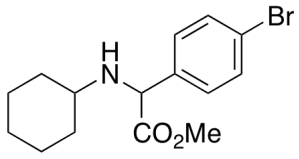
Methyl 2-((2-(benzyloxy)ethyl)amino)-2-(4-bromophenyl)acetate (100). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 2-(benzyloxy)-ethylamine (0.236 g, 1.56 mmol, 2.0 equiv.) and dry trifluorotoluene (4 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^{o}C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **100** (186 mg, 0.49 mmol, 63 % overall yield). Flash column conditions: 5:1 pentane/Et_2O +0.5% Net_3. Products obtained as clear oil. R_f = 0.21 (5:1 Pentane/Et_2O +0.5% NEt_3); ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.45 (dt, 2H, J_S = 2.4 Hz, J_L = 8.4 Hz), 7.35-7.30 (m, 4H), 7.29-7.24 (m, 3H), 4.50 (s, 2H), 4.37 (s, 1H), 3.65 (s, 3H), 3.62-3.54 (m, 2H), 2.88-2.74 (m, 1H), 2.76-2.64 (m, 1H), 2.37 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 138.0, 137.0, 131.6, 129.2, 128.2, 127.5, 121.9, 72.9, 69.4, 64.7, 52.2, 46.9; IR (film neat): 2856, 1736, 1487, 1089, 1010; HRMS-pos-ESI m/z 378.07001 ($C_{18}H_{21}BrNO_3$ requires 378.06993).



Methyl 2-(4-bromophenyl)-2-(tert-butylamino)acetate (98). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added tert-butylamine (0.16 mL, 1.56 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^{o}C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **98** (144 mg, 0.48 mmol, 61 % overall yield). Flash column conditions: (5 : 1 Pentane/Et_2O +1.0 % NEt_3). Products obtained as clear oil. Data for **98:** R_f = 0.33 (5:1 Pentane/Et_2O + 1% NEt_3); ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.44 (d, 2H, *J* = 8.4 Hz), 7.30 (d, 2H, *J* = 8.4 Hz), 4.44 (s, 1H), 3.69 (s, 3H), 2.07 (s, 1H), 1.08 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.9, 139.8, 131.6, 129.0, 121.5, 59.0, 52.5, 51.3, 29.4; IR (film neat): 2360, 1732, 1485, 1161, 1011; HRMS-pos- ESI m/z 300.05929 ($C_{13}H_{19}BrNO_2$ requires 300.05937).

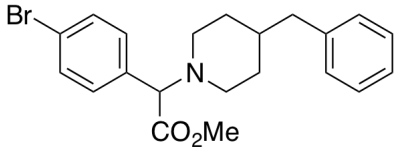


Methyl 2-(4-bromophenyl)-2-((3,4-dimethoxyphenethyl)amino)acetate (101). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 3,4-dimethoxyphenylamine (0.26 mL, 1.56 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 °C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **101** (210 mg, 0.51 mmol, 66 % overall yield). Flash column conditions: 9 : 1 Pentane/Et_2O +0.5 % NEt_3. Products obtained as a orange oil. Data for **101**: ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.45 (dt, 2H, J_S = 2.4 Hz, J_L = 8.4 Hz), 7.20 (dt, 2H, J_S = 2.4 Hz, J_L = 8.4 Hz), 6.79 (d, 1H, J = 7.6 Hz), 6.75-6.65 (m, 2H), 4.33 (s, 1H), 3.85 (d, 6H, J = 2.4 Hz), 3.66 (s, 3H), 2.86-2.66 (m, 4H), 2.01 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 148.9, 147.5, 137.1, 132.0, 131.7, 129.1, 122.0, 120.5, 111.8, 111.3, 64.8, 55.8, 52.3, 48.9, 35.8; IR (film neat): 2950, 1735, 1514, 1234, 1139; HRMS- m/z 408.08183 ($C_{19}H_{23}O_4NBr$ requires 408.08048).



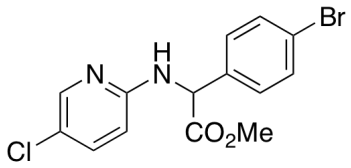
Methyl 2-(4-bromophenyl)-2-(cyclohexylamino)acetate (99). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added cyclohexylamine (0.18 mL, 1.56 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a

reflux condenser, placed in an oil bath and heated to reflux (102 °C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **99** (150 mg, 0.46 mmol, 59 % overall yield). Flash column conditions: 10 : 1 Pentane/EtOAc +0.5 % NEt_3. Products obtained as a bright orange oil. Data for **99**: R_f = 0.24 (5:1 Pentane/Et_2O + 1% NEt_3); ^1H NMR (600 MHz; $CDCl_3$) δ 7.46 (d, 2H, J = 8.4 Hz), 7.26 (d, 2H, J = 8.4 Hz), 4.49 (s, 1H), 3.68 (s, 3H), 2.38-2.28 (m, 1H), 2.00 (s, 1H), 1.84 (d, 1H, J = 11.4 Hz), 1.79 (d, 1H, J = 12 Hz), 1.74-1.64 (m, 2H), 3.15 (bd, 1H, J = 10.8 Hz), 1.29-1.05 (m, 5H,); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.5, 137.8, 131.7, 129.0, 121.8, 61.7, 54.3, 52.3, 33.5, 33.1, 25.9, 24.7; IR (film neat): 2925, 2852, 1735, 1486, 1166, 1011; HRMS-pos-ESI m/z 326.07495 ($C_{15}H_{21}BrNO_2$ requires 326.07502).



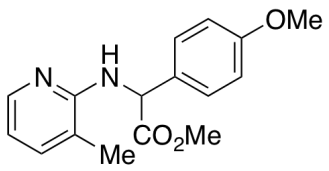
Methyl 2-(4-benzylpiperidin-1-yl)-2-(4-bromophenyl)acetate (103). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 4-benzylpiperidine (0.28 mL, 1.56 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^oC) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a

syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **103** (220 mg, 0.55 mmol, 70 % overall yield). Flash column conditions: 5 : 1 Pentane/Et_2O +1.0 % NEt_3. Products obtained as a white solid. Data for **103:** R_f = 0.34 (1% DCM/NEt_3); ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.44 (d, 2H, J = 8.4 Hz), 7.30 (d, 2H, J = 7.8 Hz), 7.24 (d, 2H, J = 7.8 Hz), 7.16 (t, 1H, J = 7.2 Hz), 7.10 (d, 2H, J = 6.6 Hz), 3.93 (s, 1H), 3.66 (s, 3H), 2.89 (dd, 1H, J_S = 1.8 Hz, J_L = 11.4 Hz), 2.68 (dd, 1H, J_S = 1.8 Hz, J_L = 11.4 Hz), 2.52 (d, 2H, J = 7.2 Hz), 2.05 (td, 1H, J_S = 2.4 Hz, J_L = 12.0 Hz), 1.79 (td, 1H, J_S = 1.2 Hz, J_L = 10.8 Hz), 1.62 (dt, 1H, J_S = 3.0 Hz, J_L = 12.6 Hz), 1.59-1.46 (m, 2H), 1.39 (qd, 1H, J_S = 4.2 Hz, J_L = 12.0 Hz), 1.31 (qd, 1H, J_S = 3.6 Hz, J_L =12.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 140.4, 135.3, 131.6, 130.3, 129.0, 128.1, 122.2, 73.8, 52.0, 51.8, 51.3, 43.0, 37.7, 31.8; IR (film neat): 2919, 1737, 1487, 1163, 907, 728; HRMS-pos-ESI m/z 402.10605 ($C_{21}H_{25}BrNO_2$ requires 402.10632).



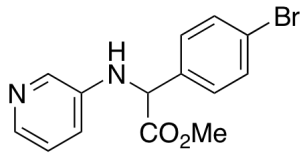
Methyl 2-(4-bromophenyl)-2-((5-chloropyridin-2-yl)amino)acetate (104). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 5-chloropyridin-2-amine (201 mg, 1.56 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^oC) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg,

0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **104** (217 mg, 0.75 mmol, 96 % overall yield). Flash column conditions: 5 : 1 Pentane/Et_2O +1.0 % NEt_3. Products obtained as a white solid. R_f = 0.46 (DCM + 1% NEt_3); ^1H NMR (600 MHz; $CDCl_3$) δ 8.00 (d, 1H, *J* = 2.4 Hz), 7.46 (d, 2H, *J* = 9.0 Hz), 7.33 (d, 2H, *J* = 8.4 Hz), 7.31 (dd, 1H, *J* = 6.0 Hz), 6.36 (d, 1H, *J* = 8.4 Hz), 5.61 (d, 1H, *J* = 6.6 Hz), 5.50 (d, 1H, *J* = 6.6 Hz), 3.72 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 154.8, 146.3, 137.2, 136.4, 132.0, 129.1, 122.4, 121.1, 109.3, 58.0, 52.9; IR (film neat): 3395, 1738, 1596, 1483; HRMS-pos-ESI m/z 354.98417 ($C_{14}H_{13}BrClN_2O_2$ requires 354.98434).



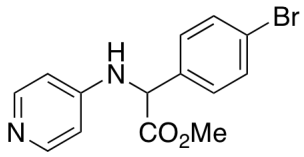
Methyl 2-(4-methoxyphenyl)-2-((3-methylpyridin-2-yl)amino)acetate (105). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 2-amino-3-picoline (0.24 mL, 2.38 mmol, 2.4 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^oC) under an atmosphere of dry argon. Methyl 2-diazo-2-(4-methoxyphenyl)acetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction

mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **105** (151 mg, 0.53 mmol, 53 % overall yield). Flash column conditions: 3:1 Pentane/EtOAc + 0.5% NEt_3. Product obtained as light brown oil. Data for **105**: R_f = 0.39 (2:1 EtOAc/Pentane + 0.5% NEt_3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.97 (dd, 1H, J_S = 1.2 Hz, J_L = 5.2 Hz), 7.42 (dt, 2H, J_S = 2.8 Hz, J_L =8.8 Hz), 7.22 (dq, 1H, J_S = 0.8 Hz, J_L = 5.6 Hz), 6.89 (dt, 2H, J_S = 3.2 Hz, J_L = 8.8 Hz), 6.55 (dd, 1H, J_S = 5.2 Hz, J_L = 7.6 Hz), 5.71 (d, 1H, J = 6.8 Hz), 4.94 (d, 1H, J = 6.4 Hz), 3.79 (s, 3H), 3.72 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 159.5, 155.3, 145.2, 136.9, 129.7, 128.7, 116.9, 114.2, 113.7, 57.8, 55.2, 52.4, 16.8; IR (film neat): 3438, 2952, 1735, 1598, 1466, 1246, 1171; HRMS-pos-ESI m/z 287.13887 ($C_{16}H_{19}N_2O_3$ requires 287.13902).



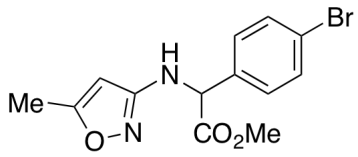
Methyl 2-(4-bromophenyl)-2-(pyridin-3-ylamino)acetate (106). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 3-aminopyridine (0.147 g, 1.56 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 °C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*.

Obtained **106** (158 mg, 0.49 mmol, 63 % overall yield). Flash column conditions: EtOAc/NEt_3 0.5%. Products obtained as orange oil. R_f = 0.41 (3% EtOAc/NEt_3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.00 (d, 1H, J = 2.8 Hz), 7.96 (dd, 1H, J_S = 1.2 Hz, J_L = 4.8 Hz), 7.48 (dt, 2H, J_S = 2.0 Hz, J_L = 8.4 Hz), 7.36 (dt, 2H, J_S = 2.4 Hz, J_L = 8.0 Hz), 7.00 (dd, 1H, J_S = 4.8, J_L = 8.0 Hz), 6.73 (dq, 1H, J_S = 1.2 Hz, J_L = 8.4 Hz), 5.20 (d, 1H, J = 5.2 Hz), 5.02 (d, 1H, J = 5.6 Hz), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 141.4, 139.6, 136.3, 135.7, 132.1, 128.8, 123.5, 122.5, 119.3, 59.5, 53.1; IR (film neat): 3388, 1736, 1588, 1483, 1251, 1010; HRMS-pos-ESI m/z 321.02368 ($C_{14}H_{14}BrN_2O_2$ requires 321.02332).



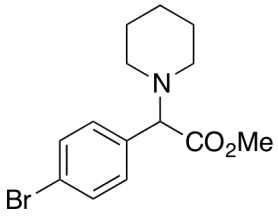
Methyl 2-(4-bromophenyl)-2-(pyridin-4-ylamino)acetate (107). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 4-aminopyridine (0.147 g, 1.56 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^{o}C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **107** (153 mg, 0.48 mmol, 61 % overall yield). Flash column conditions: DCM/NEt_3 3.0%. R_f = 0.41 (3% EtOAc/NEt_3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.17 (d,

2H, J = 6.4 Hz), 7.50 (dt, 2H, J_S = 2.0 Hz, J_L = 8.4 Hz), 6.36 (dd, 2H, J_S = 1.2 Hz, J_L = 4.4 Hz), 5.54 (d, 1H, J = 5.2 Hz), 5.06 (d, 1H, J = 5.6 Hz), 3.76 (s, 3H); IR (film neat): 1740, 1600, 1516, 1207; HRMS-pos-ESI m/z 321.0238 ($C_{14}H_{14}BrN_2O_2$ requires 321.02332);

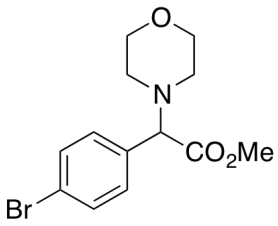


Methyl 2-(4-bromophenyl)-2-((5-methylisoxazol-3-yl)amino)acetate (108). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 3-amino-5-methylisoxazole (0.153 g, 1.56 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^oC) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **108** (175 mg, 0.54 mmol, 69 % overall yield). Flash column conditions: DCM/NEt_3 3.0%. Products obtained as a red solid. R_f = 0.30 (1:1 Pentane/EtOAc + 1% NEt_3); ^1H NMR (600 MHz; $CDCl_3$): δ 7.47 (dt, 2H, J_S = 1.8 Hz, J_L = 7.8 Hz), 7.33 (dt, 2H, J_S = 1.8 Hz, J_L = 9.0 Hz), 5.50 (s, 1H), 5.22 (d, 1H, J = 6.6 Hz), 5.09 (d, 1H, J = 6.6 Hz), 3.73 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 169.1, 162.6, 136.1, 131.9, 129.0, 122.5, 93.3, 59.3, 53.0,

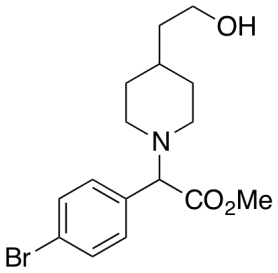
12.4; IR (film neat): 3382, 1739, 1625, 1536, 1011; HRMS-pos-ESI m/z 325.01822 ($C_{13}H_{13}BrN_2O_3$ requires 325.01823).



Methyl 2-(4-bromophenyl)-2-(piperidin-1-yl)acetate (109). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added piperidine (0.39 mL, 3.90 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 °C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **109** (156 mg, 0.50 mmol, 64 % overall yield). Flash column conditions: 5 : 1 Pentane/Et_2O +1.0 % NEt_3. Products obtained as a clear oil. Data for **109**: R_f = 0.33 (1% DCM/NEt_3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.46 (d, 2H, J = 8.4 Hz), 7.33 (d, 2H, J = 8.4 Hz), 3.94 (s, 1H), 3.68 (s, 3H), 2.44-2.29 (m, 4H), 1.58 (qu, 4H, J = 6.0 Hz), 1.49-1.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 135.3, 131.5, 130.3, 132.0, 74.1, 52.2, 51.8, 25.6, 24.1; IR (film neat): 2935, 1736, 1161, 1011; HRMS-pos-ESI m/z 312.05925 ($C_{14}H_{19}BrNO_2$ requires 312.05937).

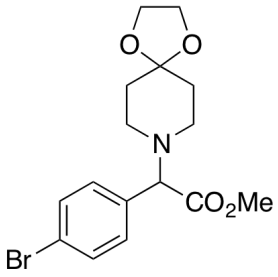


Methyl 2-(4-bromophenyl)-2-morpholinoacetate (110). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added morpholine (0.14 mL, 1.56 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 °C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **110** (182 mg, 0.58 mmol, 74 % overall yield). Flash column conditions: 10:1 Pentane/Et_2O +0.5 % NEt_3. Products obtained as clear yellow oil. Data for **110**: R_f = 0.23 (1:1 Pentane/Et_2O + 0.5% NEt_3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.48 (d, 2H, *J* = 8.8 Hz), 7.33 (d, 2H, *J* = 8.4 Hz), 3.94 (s, 1H), 3.72 (t, 4H, *J* = 4.4 Hz), 3.69 (s, 3H), 2.45-2.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 134.4, 131.8, 130.5, 122.6, 73.7, 66.7, 52.2, 51.5; IR (film neat): 2953, 1745, 1487, 1116, 1023; HRMS-pos-ESI m/z 314.03857 ($C_{13}H_{17}BrNO_3$ requires 314.03863);



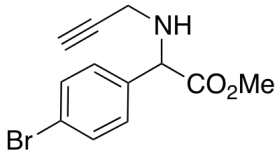
Methyl 2-(4-bromophenyl)-2-(4-(2-hydroxyethyl)piperidin-1-yl)acetate (111). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 4-piperidine ethanol (0.202 g, 1.56 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^{o}C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **111** (150 mg, 0.42 mmol, 54 % overall yield). Flash column conditions: 5 : 1 Pentane/Et_2O +1.0 % NEt_3. Products obtained as a clear oil. Data for **111**: R_f = 0.31 (5% DCM/NEt3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.46 (d, 2H, J = 8.4 Hz), 7.32 (d, 2H, J = 8.4 Hz), 3.93 (s, 1H), 3.68 (s, 3H), 3.70-3.64 (m, 1H), 2.91 (dd, 1H, J_S = 2.0 Hz, J_L = 11.2 Hz), 2.69 (dd, 1H, J_S = 2.0 Hz, J_L = 11.2 Hz), 2.63 (q, 1H, J_S = 6.8 Hz, J_L = 13.6 Hz), 2.10 (td, 1H, J_S = 2.4 Hz, J_L = 11.2 Hz), 1.84 (td, 1H, J_S = 2.4 Hz, J_L = 11.6 Hz), 1.69 (bd, 1H, J = 12.4 Hz), 1.61 (bd, 1H, J = 12.8 Hz), 1.56-1.18 (m, 5H), 1.08 (t, 1H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 135.2, 131.6, 130.3, 122.2,

73.9, 60.2, 52.0, 51.9, 51.3, 45.9, 39.2, 32.1, 32.0; IR (film neat): 3366, 2924, 1736, 1487, 1163, 1011; HRMS-pos-ESI m/z 356.08541 ($C_{16}H_{23}BrNO_3$ requires 356.08558).

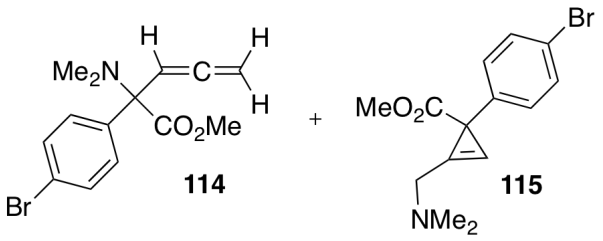


Methyl 2-(4-bromophenyl)-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)acetate (112). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 1,4-dioxa-8-azaspiro[4.5]decane (0.50 mL, 3.90 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^{o}C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **112** (228 mg, 0.62 mmol, 78 % overall yield). Flash column conditions: 5 : 1 Pentane/Et_2O +1.0 % NEt_3. Products obtained as a clear oil. Data for **112**: R_f = 0.34 (3% DCM/NEt_3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.47 (d, 2H, J = 8.4 Hz), 7.32 (d, 2H, J = 8.4 Hz), 4.01 (s, 1H), 3.93 (s, 4H), 3.69 (s, 3H), 2.51 (bt, 4H, J = 5.2 Hz), 1.75 (t, 4H, J = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 135.3, 131.8, 130.3, 122.4, 106.9, 73.1, 64.2, 52.1, 49.2, 34.7; IR (film

neat): 2954, 1736, 1087, 1011; HRMS-pos-ESI m/z 370.06466 ($C_{16}H_{21}BrNO_4$ requires 370.06485).

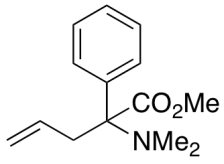


Methyl 2-(4-bromophenyl)-2-(prop-2-yn-1-ylamino)acetate (113). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added propargylamine (0.25 mL, 3.90 mmol, 5.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 °C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **113** (156 mg, 0.71 mmol, 71 % overall yield). Flash column conditions: 5:1 Pentane/Et_2O. Products obtained as clear yellow oil. Data for **113**: R_f = 0.32 (5:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.45 (d, 2H, J = 8.4 Hz), 7.26 (d, 2H, J = 8.4 Hz), 4.58 (s, 1H), 3.66 (s, 3H), 3.44 (dd, 1H, J_S = 2.4 Hz, J_L = 16.8 Hz), 3.20 (dd, 1H, J_S = 2.4 Hz, J_L = 17.2 Hz), 2.30-2.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3 (C), 136.2 (C), 131.8 (CH), 129.6 (CH), 122.3 (C), 80.8 (C), 72.3 (CH), 62.7 (CH), 52.4 (CH_3), 35.6 (CH_2); IR (film neat): 3293, 1733, 1487, 1205, 1010; HRMS-pos-ESI m/z 282.1241 ($C_{12}H_{13}$ $BrNO_2$ requires 282.01242).



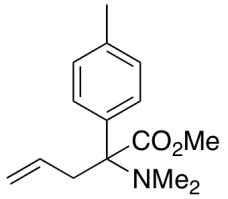
Methyl 2-(4-bromophenyl)-2-(dimethylamino)penta-3,4-dienoate (114) and Methyl 1-(4-bromophenyl)-2-((dimethylamino)methyl)cycloprop-2-enecarboxylate (115). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 3-dimethylamino-1-propyne (0.42 mL, 3.90 mmol, 5.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^{o}C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **114** and **115** (175 mg, 0.56 mmol, 72 % overall yield). Crude ratio 2:1, **114**:**115**. Flash column conditions: 5:1 Pentane/Et_2O +0.5 % NEt_3. Products obtained as yellow oil. Data for **114**: R_f = 0.43 (1:1 Pentane/Et2O + 0.5 %NEt_3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.46 (d, 2H, J = 9.2 Hz), 7.43 (d, 2H, J = 9.2 Hz), 5.63 (t, 1H, J = 6.8 Hz), 4.84 (dd, 2H, J_S = 1.2 Hz, J_L = 6.8 Hz), 3.69 (s, 3H), 2.27 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.9 (C), 171.6 (C), 138.3 (C), 131.1 (CH_2), 130.0 (CH_2), 121.8 (C), 88.5 (CH), 77.6 (C), 74.4 (CH_2), 52.4 (CH_3), 40.0 (CH_3); IR (film neat): 2948, 1730, 1215, 1009, 830; HRMS-pos-ESI m/z 310.04368 ($C_{14}H_{17}BrNO_2$ requires 310.04372); Data for **115**: R_f = 0.50 (1:1 Pentane/Et_2O); ^{1}H

NMR (600 MHz; $CDCl_3$) δ 7.46 (dt, 2H, J_S = 1.8 Hz, J_L = 8.4 Hz), 7.35 (dt, 2H, J_S = 1.8 Hz, J_L = 9.0 Hz), 3.80 (s, 3H), 2.98 (dd, 1H, J_S = 2.4 Hz, J_L = 17.4 Hz), 2.89 (dd, 1H, J_S = 2.4 Hz, J_L = 17.4 Hz), 2.34 (s, 6H), 1.93 (t, 1H, J = 3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 138.8, 130.8, 129.7, 121.6, 79.9, 72.9, 71.7, 51.6, 40.4, 28.4; IR (film neat): 3297, 2951, 1724, 1226; HRMS-pos-ESI m/z 310.04375 ($C_{14}H_{17}BrNO_2$ requires 310.04372)

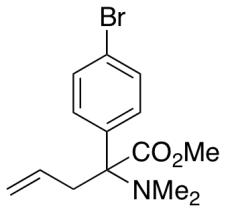


Methyl 2-(dimethylamino)-2-phenylpent-4-enoate (117). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added N,N-Dimethylallylamine (0.26 mL, 2.28 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^{o}C) under an atmosphere of dry argon. Methyl 2-diazo-2-phenylacetate (200 mg, 1.14 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **117** (63 mg, 0.27 mmol, 24 % overall yield). Flash column conditions: 5:1 Pentane/Et_2O +0.5 % NEt_3. Products obtained as yellow oil. Data for **117**: R_f = 0.20 (5:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.37-7.20 (m, 5H), 5.55 (dddd, 1H, J = 6.8, 4.0, 10.4, 20.8 Hz), 4.96-4.84 (m, 2H), 3.79 (s, 3H), 2.85 (tdd, 1H, J = 1.2, 7.6, 14.4 Hz), 2.78 (tdd, 1H, J = 1.2, 6.4, 14.4 Hz), 2.31 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (C), 139.5 (C), 133.5 (C), 128.0 (CH), 127.5 (CH), 127.0 (CH), 117.7 (CH), 74.0

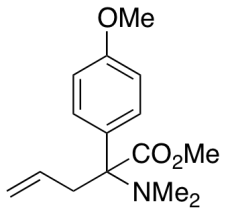
(C), 51.1 (CH_3), 42.3 (CH_2), 40.3 (CH_3); IR (film neat): 2790, 1721, 1447, 1205, 703; HRMS-pos-ESI m/z 234.14871 ($C_{14}H_{20}NO_2$ requires 234.14886).



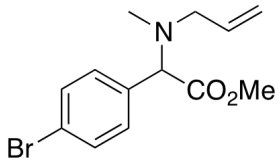
Methyl 2-(dimethylamino)-2-(p-tolyl)pent-4-enoate (118). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added N,N-Dimethylallylamine (0.24 mL, 1.94 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^oC) under an atmosphere of dry argon. Methyl 2-diazo-2-(*p*-tolyl)acetate (200 mg, 1.05 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **118** (138 mg, 0.56 mmol, 53 % overall yield). Flash column conditions: 5:1 Pentane/Et_2O +0.5 % NEt_3. Products obtained as yellow oil. Data for **118**: R_f = 0.29 (5:1 Pentane/Et_2O); ^1H NMR (400 MHz; $CDCl_3$) δ 7.18 (d, 2H, *J* = 8.4 Hz), 7.12 (d, 2H, *J* = 8.4 Hz), 5.57 (dddd, 1H, *J* = 6.8, 7.2, 10.0, 16.8 Hz), 4.96-4.88 (m, 2H), 3.77 (s, 3H), 2.82-2.81 (m, 1H), 2.81-2.73 (m, 1H), 2.33 (s, 3H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C), 136.6 (C), 136.3 (C), 133.5 (CH), 128.2 (CH), 127.8 (CH), 117.5 (CH2), 73.7 (C), 51.0 (CH3), 42.1 (CH2), 40.2 (CH3), 20.9 (CH3); IR (film neat): 2789, 1721, 1433, 1204; HRMS-pos-ESI m/z 248.16436 ($C_{15}H_{22}NO_2$ requires 248.16451).



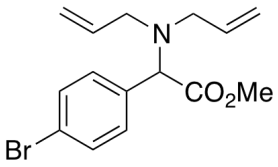
Methyl 2-(4-bromophenyl)-2-(dimethylamino)pent-4-enoate (116). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added N,N-Dimethylallylamine (0.45 mL, 3.90 mmol, 5.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^{o}C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **116** (168 mg, 0.54 mmol, 69 % overall yield). Flash column conditions: 5:1 Pentane/Et_2O +0.5 % NEt_3. Products obtained as yellow oil. Data for **116**: R_f = 0.38 (5:1 Pentane/Et2O + 1% NEt_3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.41 (d, 2H, J = 8.8 Hz), 7.20 (d, 2H, J = 8.4 Hz), 5.48 (dddd, 1H, J = 7.2, 7.2, 10.4, 17.2 Hz), 4.91 (dd, 1H, J_S = 1.2 Hz, J_L = 10.4 Hz), 4.85 (dd, 1H, J_S = 1.2 Hz, J_L = 20.4 Hz), 3.76 (s, 3H), 2.78 (dd, 1H, J_S = 7.6 Hz, J_L = 14.8 Hz), 2.71 (dd, 1H, J_S = 7.2 Hz, J_L = 14.8 Hz), 2.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.7 (C), 80.1 (C), 79.8 (CH), 79.7 (CH), 79.6 (CH), 79.2 (CH_2), 79.1 (C), 76.8 (C), 75.7 (CH_3), 75.3 (CH_2), 75.1 (CH_3); IR (film neat): 2790, 1721, 1204, 1007; HRMS-pos-ESI m/z 312.05937 ($C_{14}H_{19}BrNO_2$ requires 312.05929).



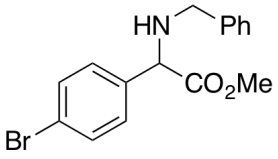
Methyl 2-(dimethylamino)-2-(4-methoxyphenyl)pent-4-enoate. To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added N,N-Dimethylallylamine (0.22 mL, 1.94 mmol, 2.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 °C) under an atmosphere of dry argon. Methyl 2-diazo-2-(4-methoxyphenyl)acetate (200 mg, 0.97 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Flash column conditions: 5:1 Pentane/Et_2O +0.5 % NEt_3. Products obtained as yellow oil. Data: R_f = 0.51 (1:1 Pentane/Et_2O + 0.5% NEt_3); ^1H NMR (400 MHz; $CDCl_3$) δ 7.23 (d, 2H, *J* = 9.2 Hz), 6.85 (d, 2H, *J* = 8.8 Hz), 5.56 (dddd, 1H, *J* = 7.2, 6.8, 10.4, 17.2 Hz), 5.00-4.88 (m, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 2.88-2.72 (m, 2H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C), 158.4 (C), 133.6 (CH), 131.4 (C), 129.1 (CH), 117.6 (CH2), 112.8 (CH), 73.4 (C), 55.1 (CH3), 51.0 (CH3), 42.2 (CH), 40.2 (CH3); IR (film neat): 2950, 1720, 1510, 1247, 828; HRMS-pos-ESI m/z 264.15935 ($C_{15}H_{22}NO_3$ requires 264.15942).



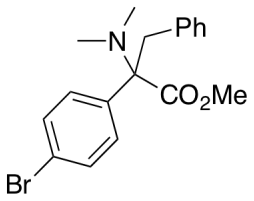
Methyl 2-(allyl(methyl)amino)-2-(4-bromophenyl)acetate (120). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added N-allylmethylamine (0.200 mL, 2.10 mmol, 2.1 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 °C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (255.1 mg, 1.0 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **120** (199.5 mg, 67% yield). Flash column conditions: 9:1 to 5:1 Pentane/Et_2O. Product obtained as clear oil. Data for **120**: R_f = 0.29 (1:5 Et_2O/Hexanes); ^1H NMR (600 MHz; $CDCl_3$) δ 7.48 (dt, 2H, J_S = 2.4 Hz, J_L = 8.4 Hz), 7.30 (dt, 2H, J_S = 2.4 Hz, J_L = 8.4 Hz), 5.84 (1H), 5.15 (dm, 2H, J = 11.4 Hz), (s, 1H), 3.70 (s, 3H), 3.11 (dd, 1H, J_S = 6.6 Hz, J_L = 13.8 Hz), 2.98 (dd, 1H, J_S = 6.6 Hz, J_L = 13.8 Hz), 2.24 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 135.3, 134.7, 131.6, 130.4, 122.3, 118.1, 71.4, 57.6, 52.0, 39.2; IR (film): 2950, 2792, 1736, 1487, 1162, 1011; m/z (pos-ESI) 300 (100%), 298 (95%, M+H); HRMS-pos-ESI m/z 298.04368 ($C_{13}H_{17}O_2NBr$ requires 298.04372);



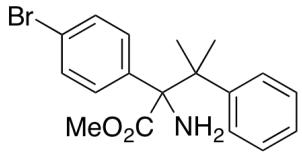
Methyl 2-(4-bromophenyl)-2-(diallylamino)acetate (122). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added diallylamine (0.260 mL, 2.11 mmol, 2.1 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 °C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (253.4 mg, 0.99 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained product **122** (96.3 mg, 33% yield). Flash column conditions: 5:1 Pentane/Et_2O. Product obtained as colourless oil. Data for **122**: ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.47 (dt, 2H, J_S = 2.8 Hz, J_L = 8.4 Hz), 7.26 (dm, 2H, J = 8.4 Hz), 5.80 (dddd, 2H, J = 17.2, 10.4, 7.2, 6.0 Hz), 5.18 (m, 1H), 5.15 (m, 2H), 5.13 (m, 1H), 4.55 (s, 1H), 3.72 (s, 3H), 3.19 (d, 4H, J = 6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.1, 135.7, 135.3, 131.5, 130.3, 121.9, 117.8, 67.0, 53.1, 51.7; IR (film): 3077, 2950, 1736, 1488, 1158, 1011, 920; m/z (pos-APCI) 326 (100%), 324 (99%, M+H); HRMS-pos-APCI m/z 324.05933 ($C_{15}H_{18}O_2NBr$+H requires 324.05937).



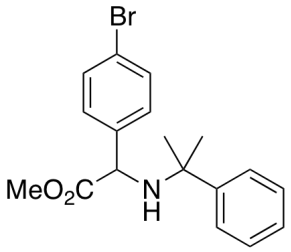
Methyl 2-(benzylamino)-2-(4-bromophenyl)acetate (124). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added benzylamine (0.43 mL, 3.90 mmol, 5.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^{o}C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **124** (220 mg, 0.66 mmol, 84 % overall yield). Flash column conditions: 5:1 Pentane/Et_2O +0.5 % NEt_3. Products obtained as clear oil. Data for **124**: R_f = 0.33 (DCM + 1% NEt_3); 1H NMR (400 MHz; $CDCl_3$) δ 7.48 (dt, 2H, J_S = 2.0 Hz, J_L = 8.8 Hz), 7.36-7.20 (m, 7H), 4.35 (s, 1H), 3.76-3.63 (m, 2H), 3.68 (s, 3H), 2.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 139.1, 137.0, 131.7, 129.2, 128.1, 122.0, 63.5, 52.2, 51.1; IR (film neat): 2950, 1735, 1168, 1010; HRMS-pos-ESI m/z 334.04354 ($C_{16}H_{17}BrNO_2$ requires 334.04372).



Methyl 2-(4-bromophenyl)-2-(dimethylamino)-3-phenylpropanoate (125). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added N,N-dimethylbenzylamine (0.59 mL, 3.90 mmol, 5.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^{o}C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added dropwise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **125** (151 mg, 0.42 mmol, 53 % overall yield). Flash column conditions: 5:1 Pentane/Et_2O +0.5 % NEt_3. Products obtained as clear oil. Data for **125**: R_f = 0.36 (5:1 Pentane/Et_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.24 (d, 2H, *J* = 8.8 Hz), 7.12-7.00 (m, 3H), 6.94 (d, 2H, *J* = 8.8 Hz), 6.66-6.60 (m, 2H), 3.81 (s, 3H), 3.63 (d, 1H, *J* = 12.8 Hz), 2.88 (d, 1H, *J* = 13.2 Hz), 2.36 (s, 6H); ^{13}C NMR (100 MHz, CDCl3) δ 169.5 (C), 138.6 (C), 136.5 (C), 130.6 (CH), 130.4 (CH), 130.0 (CH), 127.5 (CH), 126.2 (CH), 120.7 (C), 75.3 (C), 50.8 (CH3), 44.2 (CH2), 40.5 (CH3); IR (film neat): 2791, 1721, 1486, 1193, 1006, 699; HRMS-pos-ESI m/z 362.07497 ($C_{18}H_{21}BrNO_2$ requires 362.07502).



Methyl 2-amino-2-(4-bromophenyl)-3-methyl-3-phenylbutanoate (127). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 2-phenylpropan-2-amine (0.527 g, 3.90 mmol, 5.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 °C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed *in vacuo*. Obtained **127** (44 mg, 0.12 mmol, 16 % overall yield). Flash column conditions: 10:1 Pentane/Et_2O +0.5 % NEt_3. Products obtained as clear yellow oil. Data for **127**: R_f = 0.45 (1% DCM/NEt_3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.62 (dt, 2H, J_S = 2.0 Hz, J_L = 8.8 Hz), 7.42 (dt, 2H, J_S = 2.0 Hz, J_L = 8.8 Hz), 7.35-7.18 (m, 5H), 3.57 (s, 3H), 1.71 (s, 2H), 1.56 (s, 3H), 2.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 144.7, 138.7, 130.3, 130.2, 128.1, 127.6, 126.6, 121.8, 69.3, 52.1, 45.6, 25.4, 24.8; IR (film neat): 2948, 1723, 1217, 1009; HRMS-pos-ESI m/z 362.07502 ($C_{18}H_{21}BrNO_2$ requires 362.0749).



Methyl 2-(4-bromophenyl)-2-((2-phenylpropan-2-yl)amino)acetate (126). To an oven dried 25 mL round-bottom flask, charged with a stir bar, was added 2-phenylpropan-2-amine (0.527 g, 3.90 mmol, 5.0 equiv.) and dry trifluorotoluene (5 mL). The flask was then equipped with a reflux condenser, placed in an oil bath and heated to reflux (102 ^{o}C) under an atmosphere of dry argon. Methyl 2-(4-bromophenyl)-2-diazoacetate (200 mg, 0.78 mmol, 1.0 equiv.) was dissolved in dry trifluorotoluene (4 mL) and taken up in a syringe. The diazo solution was added drop-wise via syringe pump addition to the vigorously stirring solution at reflux over a period of 3 h. After the addition, the reaction mixture was left to stir at reflux for additional 9 h. Then, the oil bath was removed and the reaction flask was allowed to cool down to ambient temperature. The solvent was removed in *vacuo*. Obtained **126** (186 mg, 0.51 mmol, 66 % overall yield). Flash column conditions: 10:1 Pentane/Et_2O +0.5 % NEt_3. Products obtained as yellow oil. Data for **126**: R_f = 0.49 (1% DCM/NEt_3); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.45-7.36 (m, 4H), 7.33-7.25 (m, 2H), 7.25-7.17 (m, 1H), 7.20 (d, 2H, J = 8.0 Hz), 4.05 (s, 1H), 3.57 (s, 3H), 2.67 (s, 1H), 1.47 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 147.0, 139.5, 131.5, 129.0, 128.2, 126.5, 126.0, 121.4, 59.7, 57.0, 52.4, 30.6, 29.1; IR (film neat): 2970, 1734, 1164, 765; HRMS-pos-ESI m/z 362.07483 ($C_{18}H_{21}BrNO_2$ requires 362.07502).

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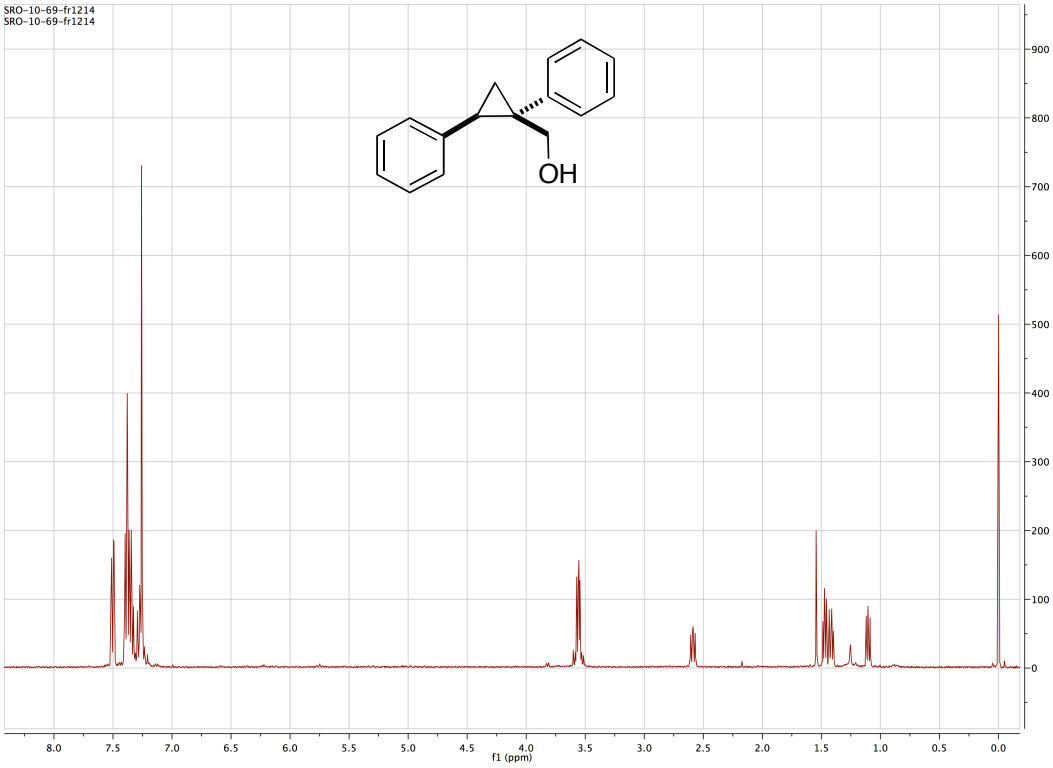
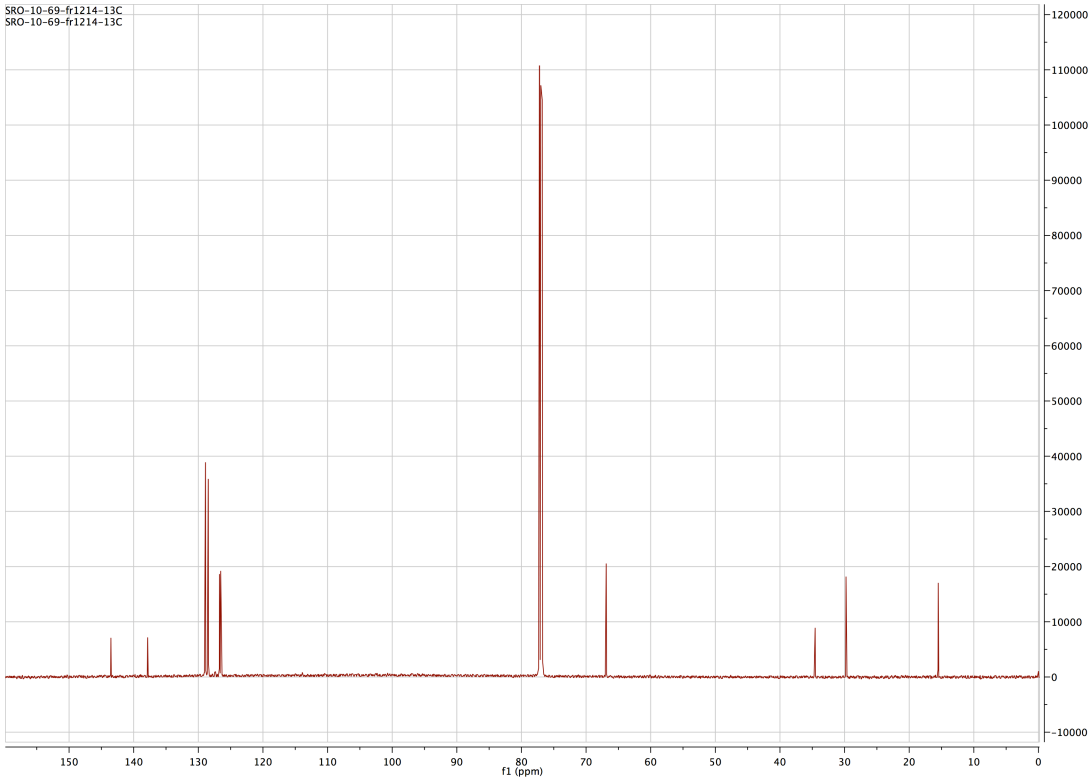
Appendix 1:

^{1}H and ^{13}C NMR Data for New Compounds

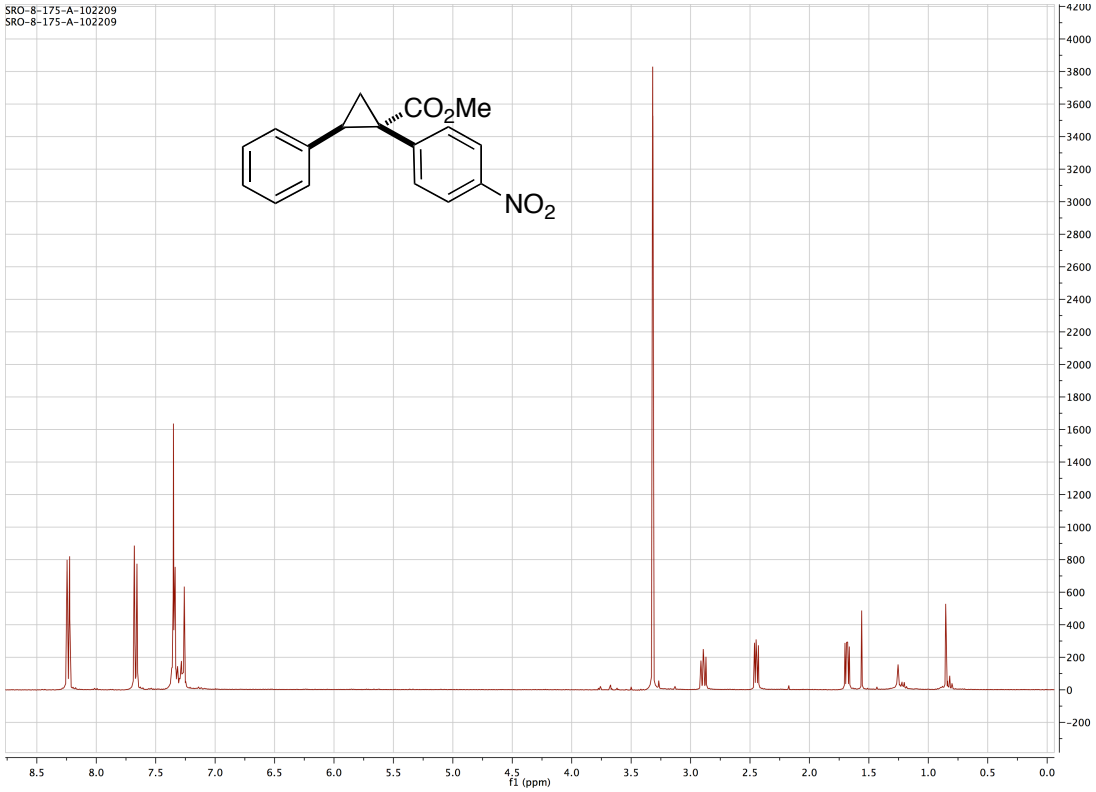
400 MHz, $CDCl_3$



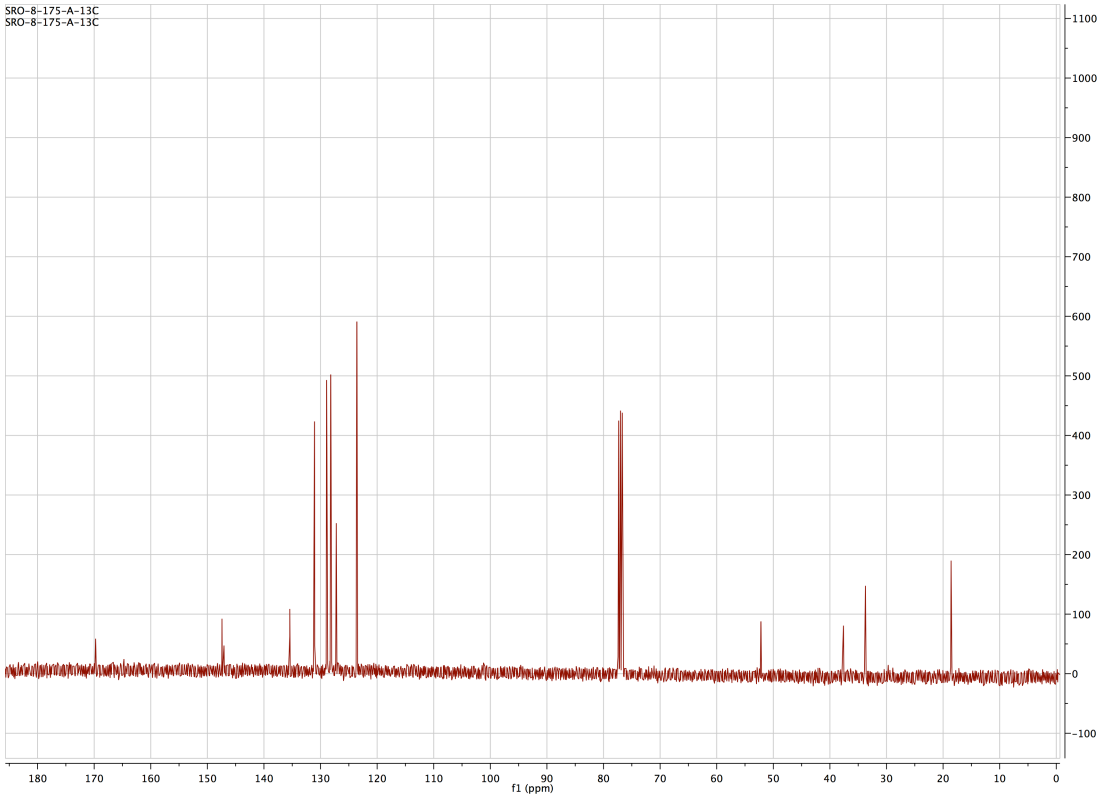
150 MHz, $CDCl_3$



400 MHz, $CDCl_3$



100 MHz, $CDCl_3$



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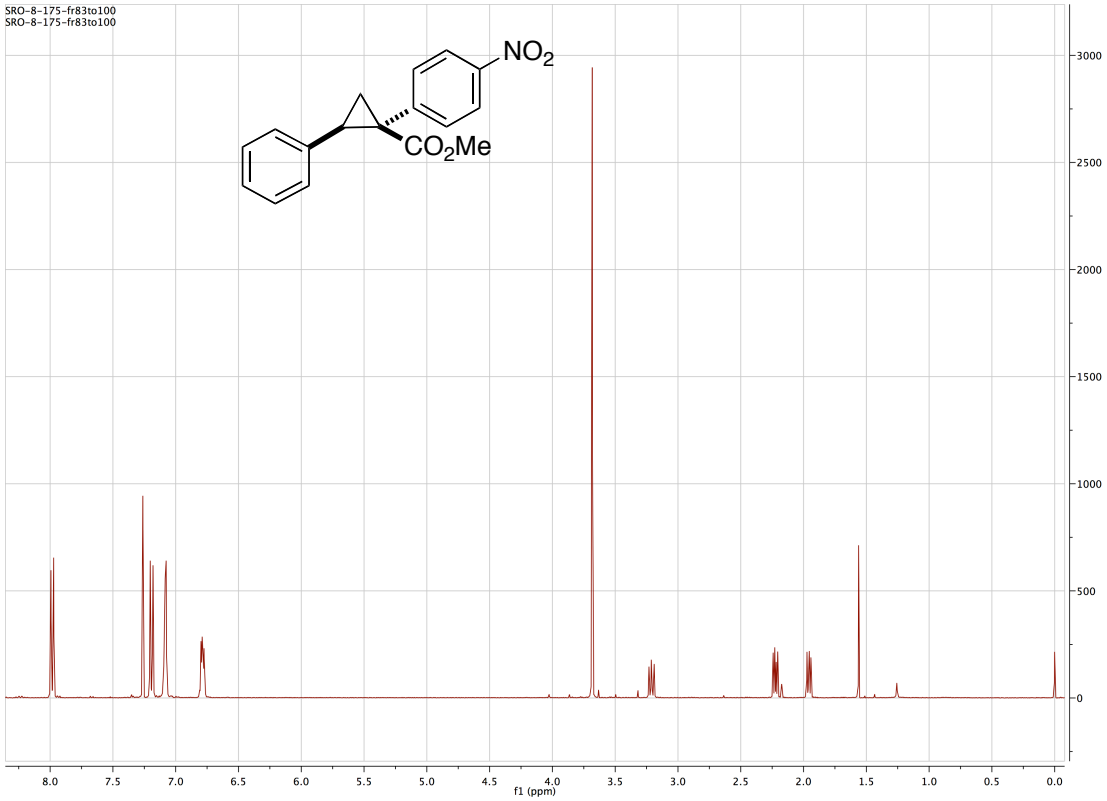

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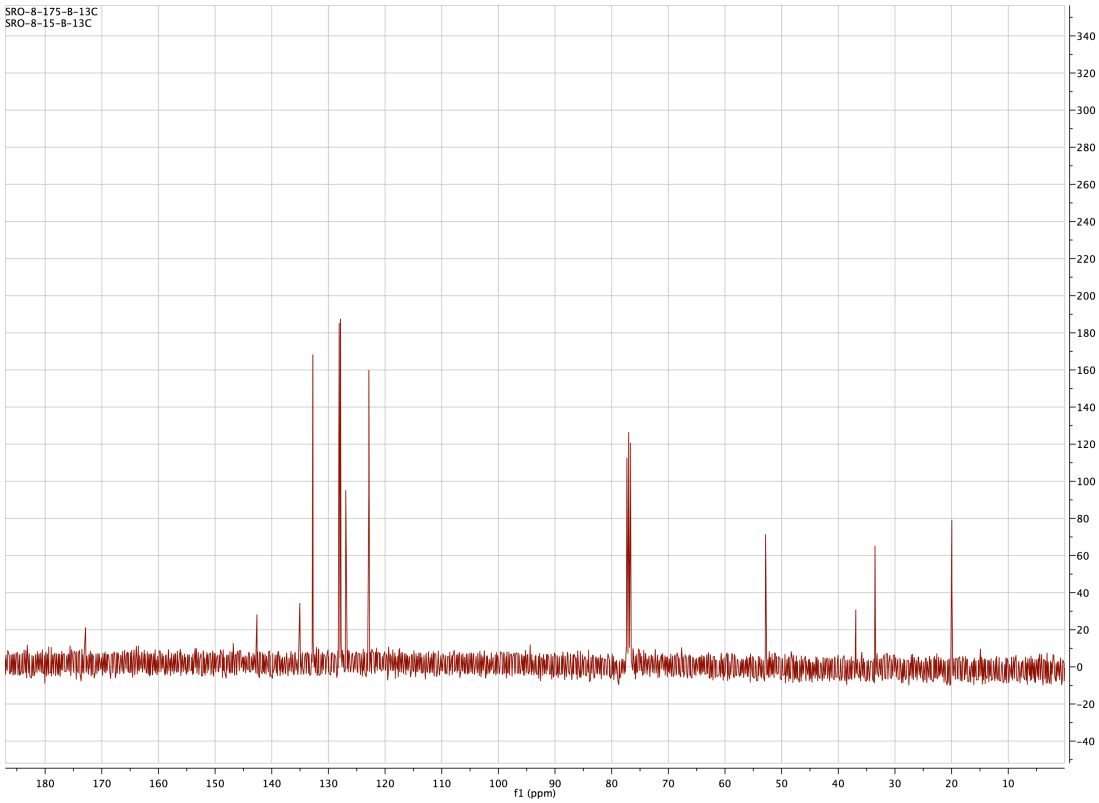

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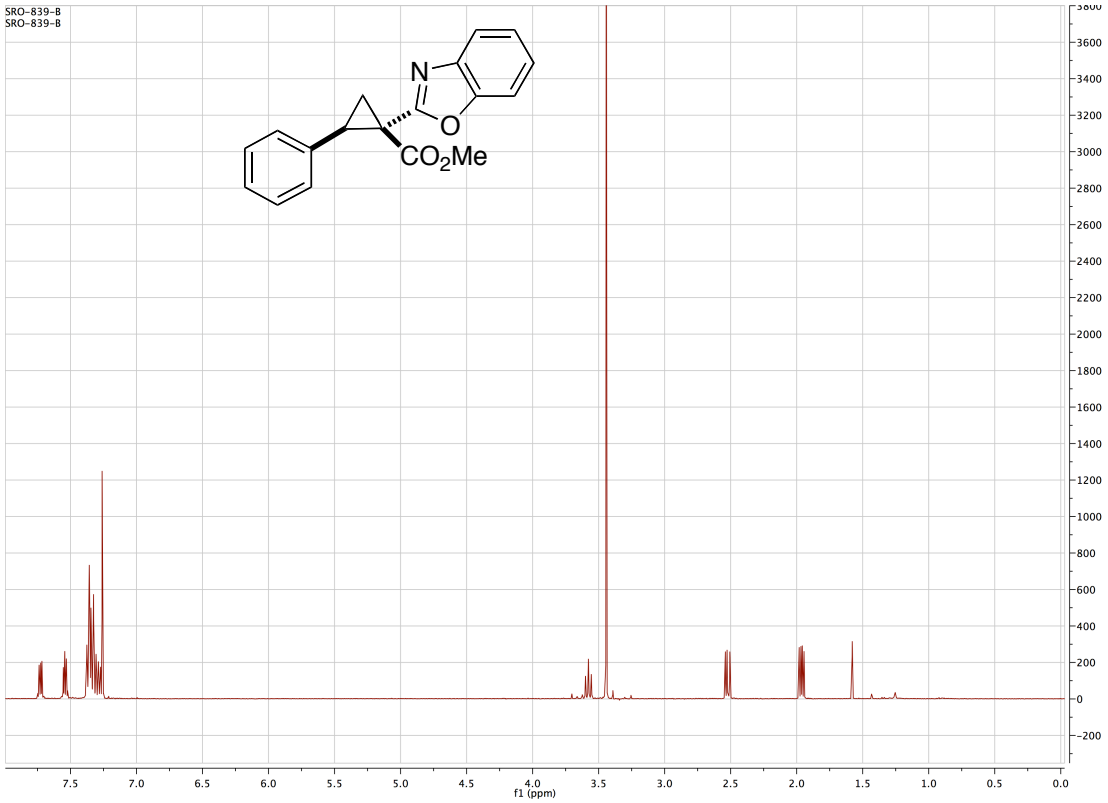
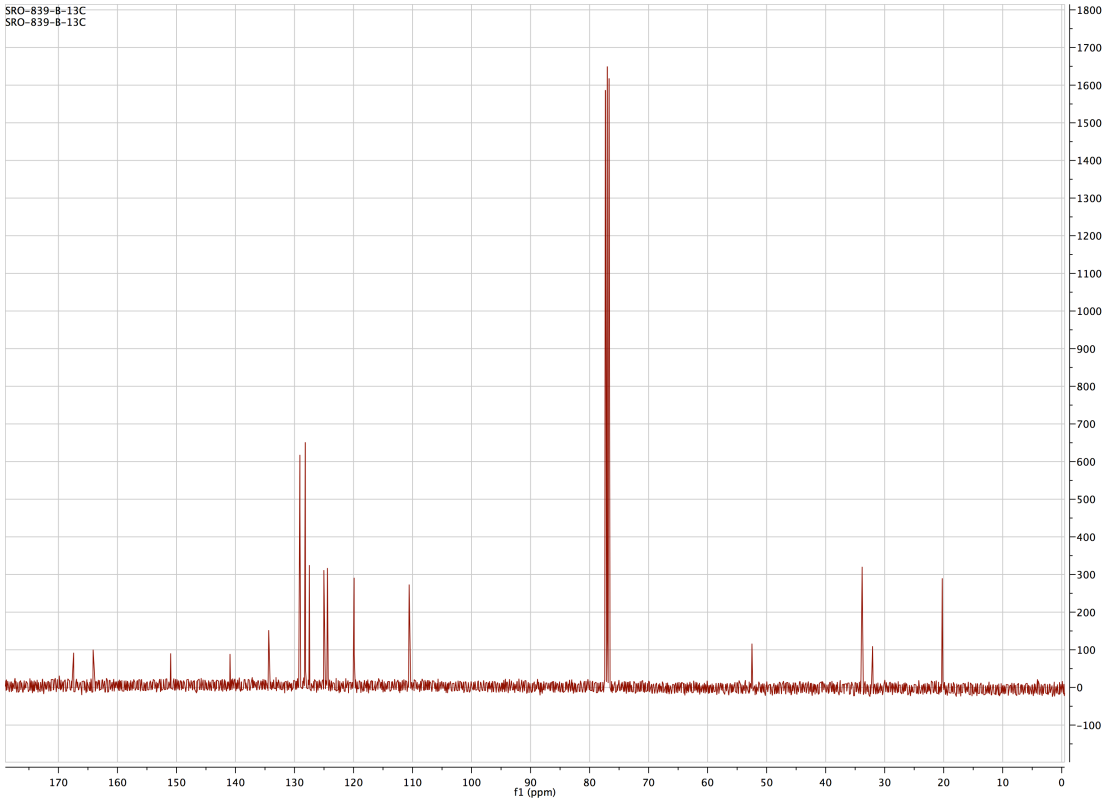
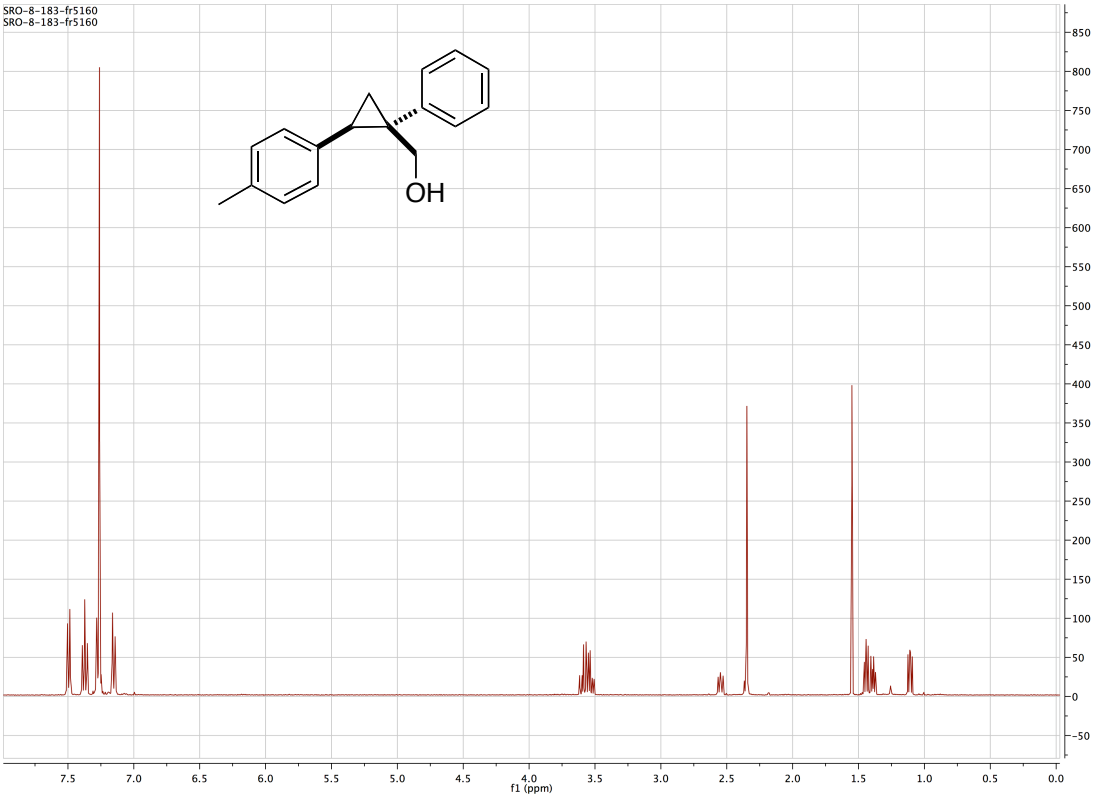


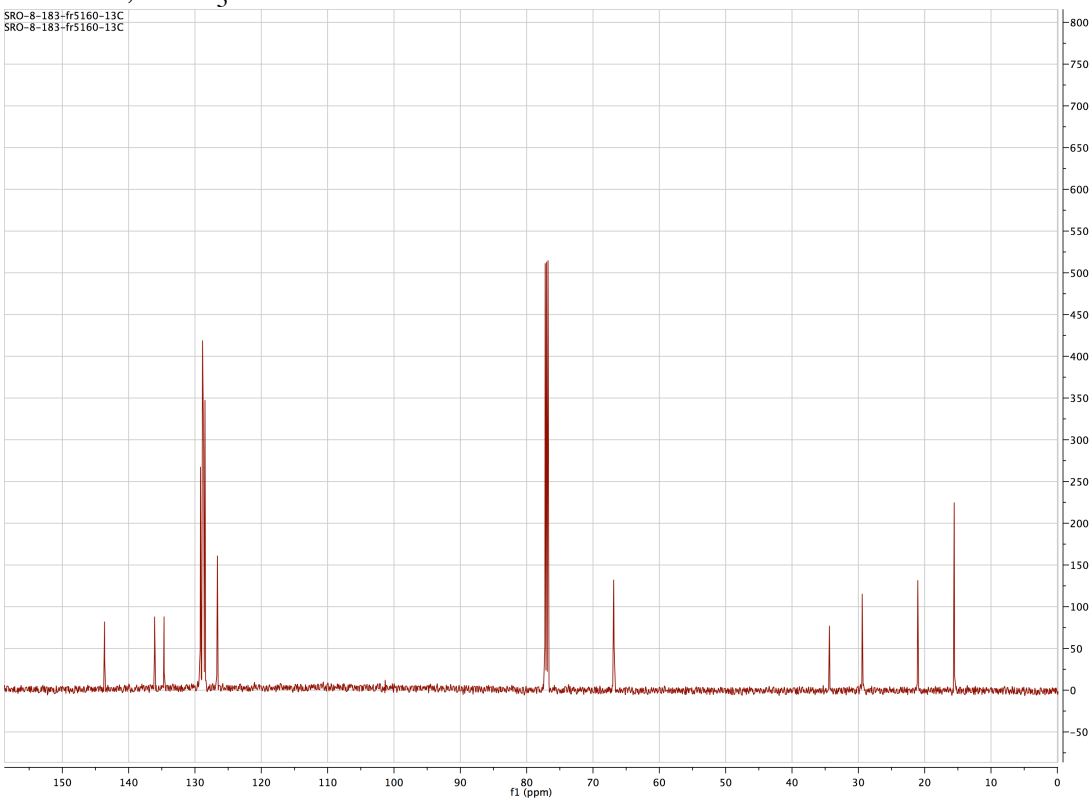
100 MHz, $CDCl_3$



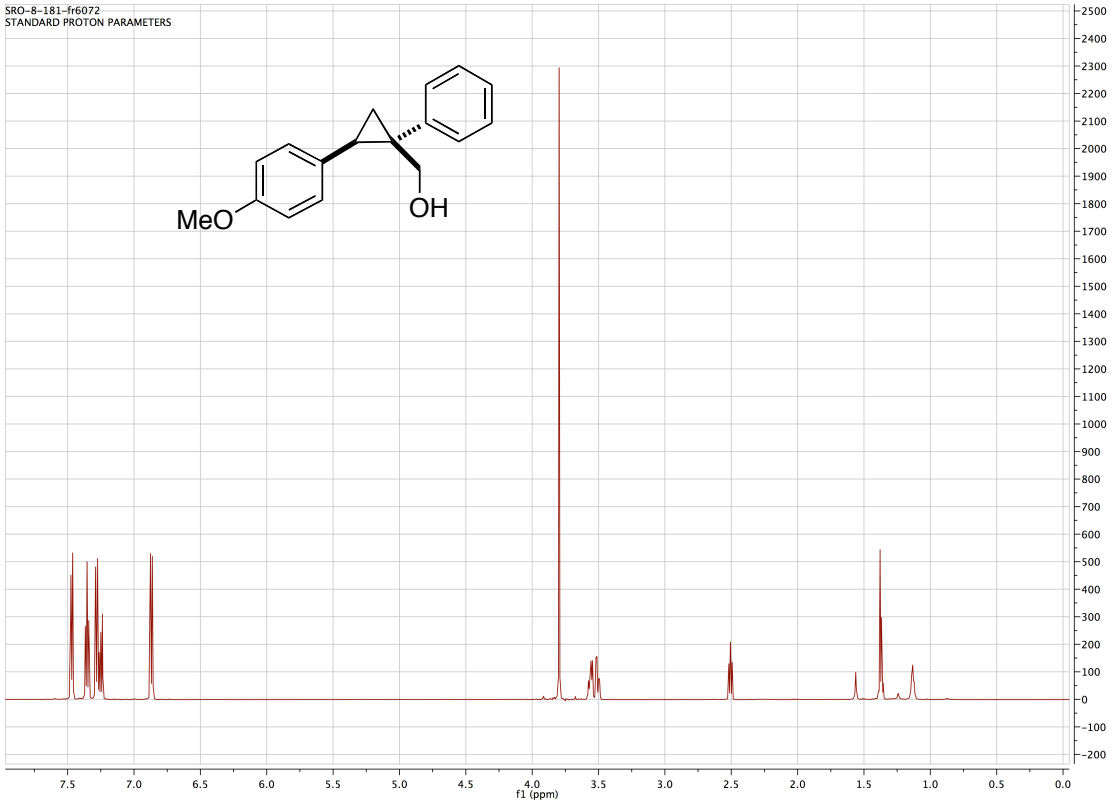
600 MHz, $CDCl_3$



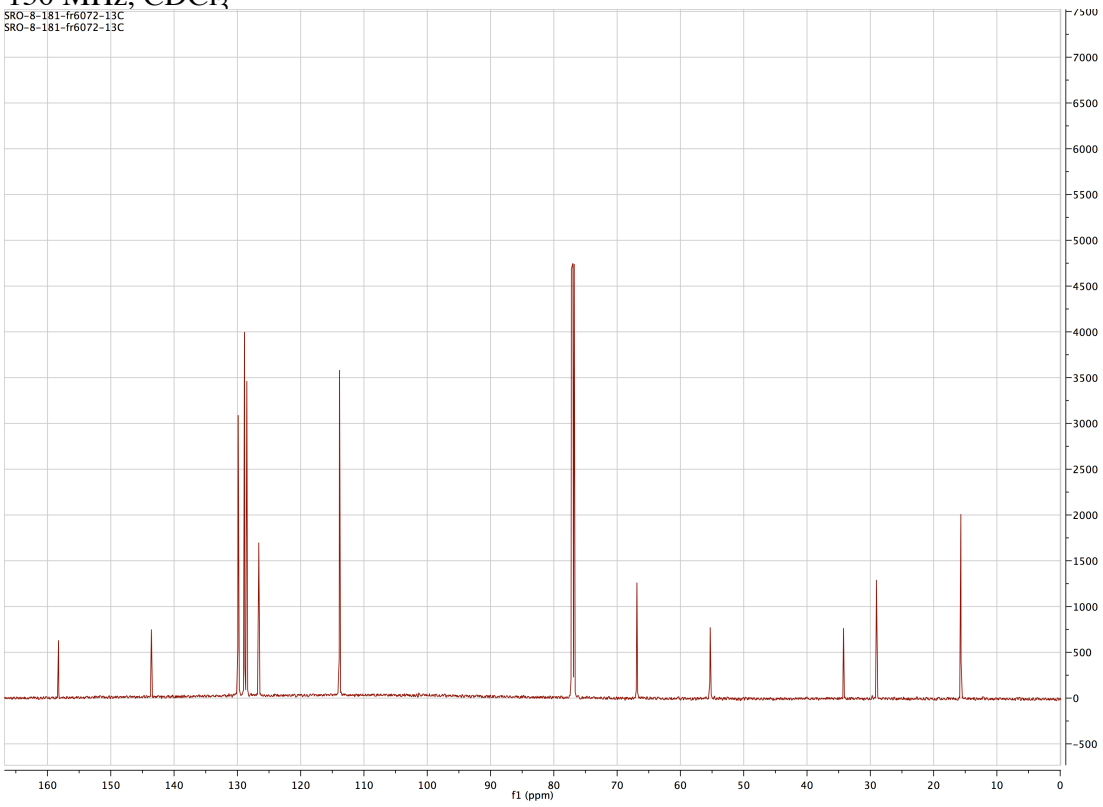
150 MHz, $CDCl_3$



600 MHz, $CDCl_3$



150 MHz, $CDCl_3$



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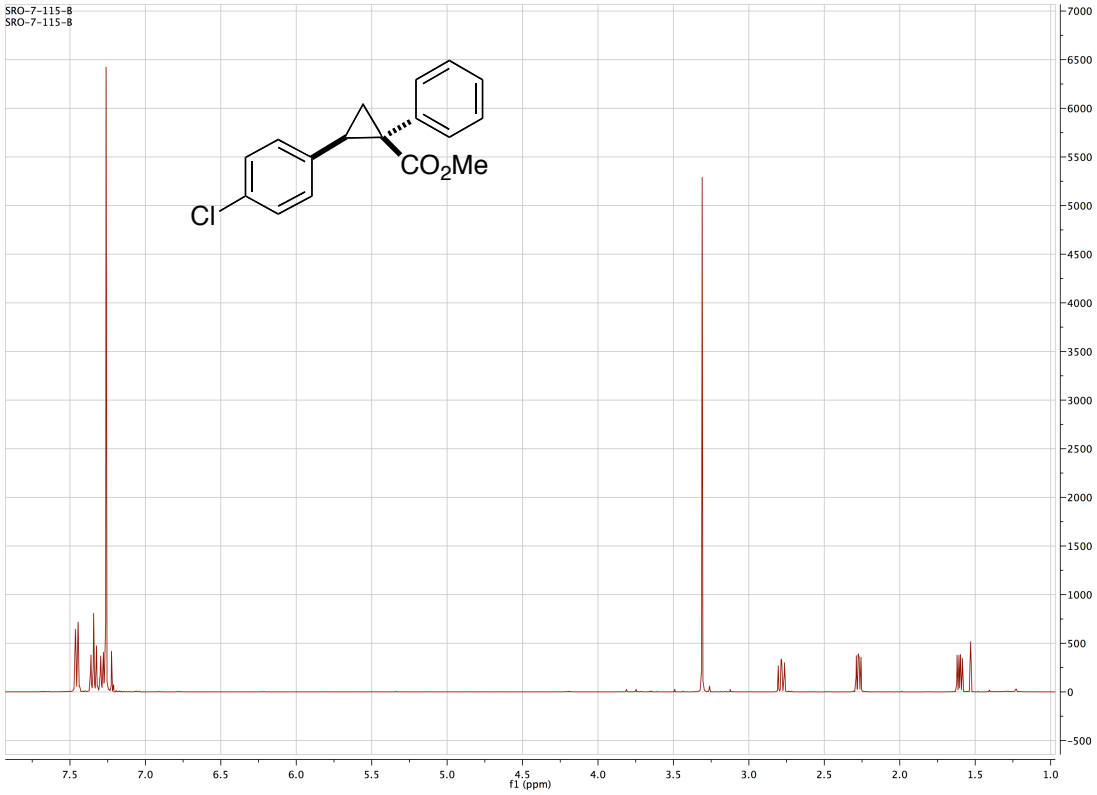
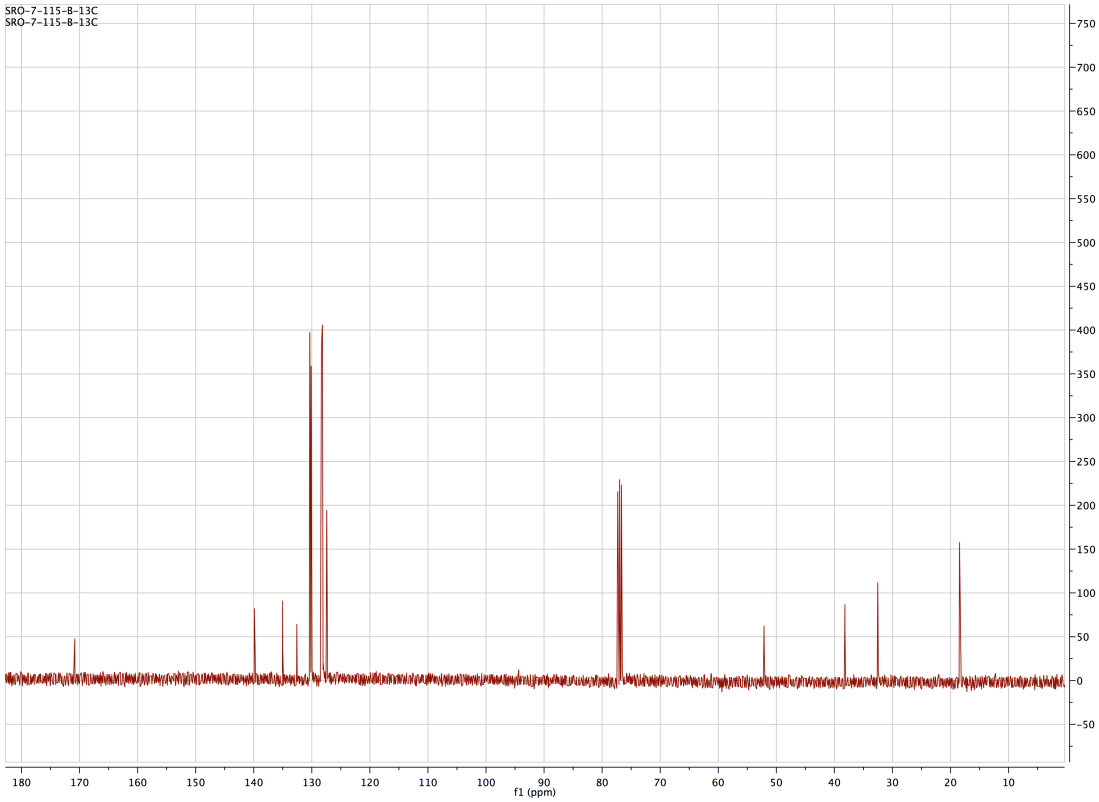


100 MHz, $CDCl_3$



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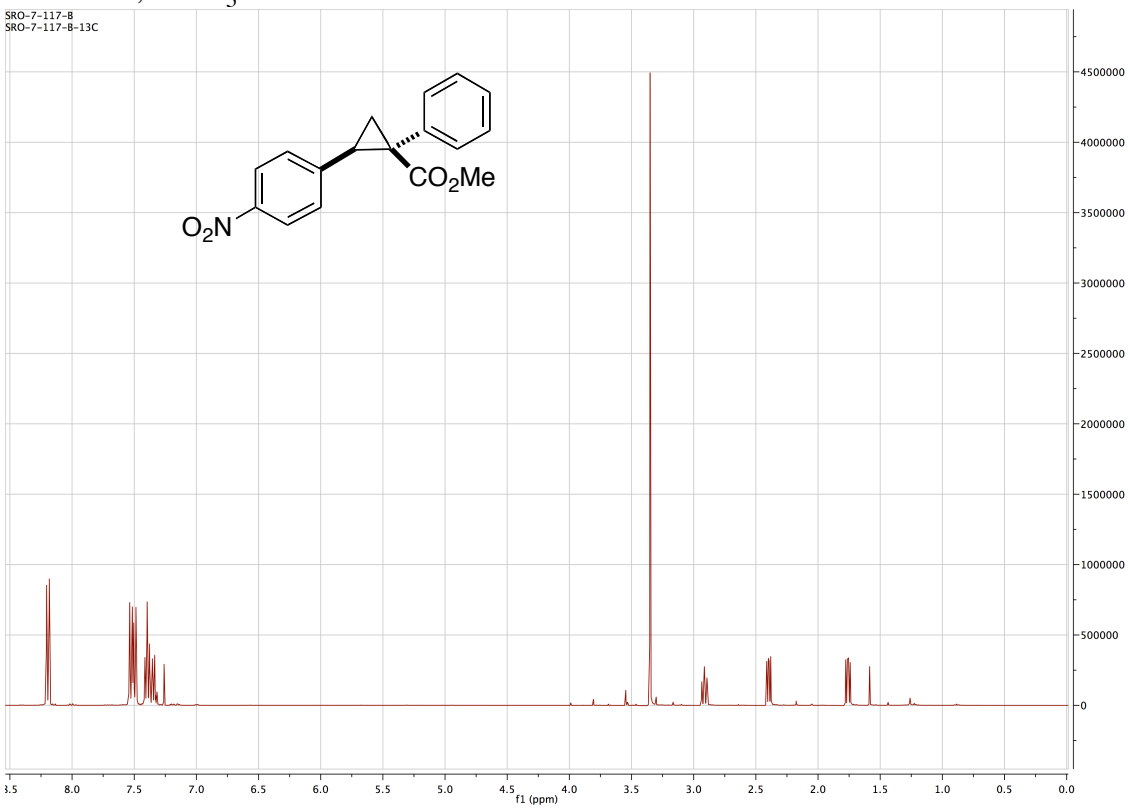
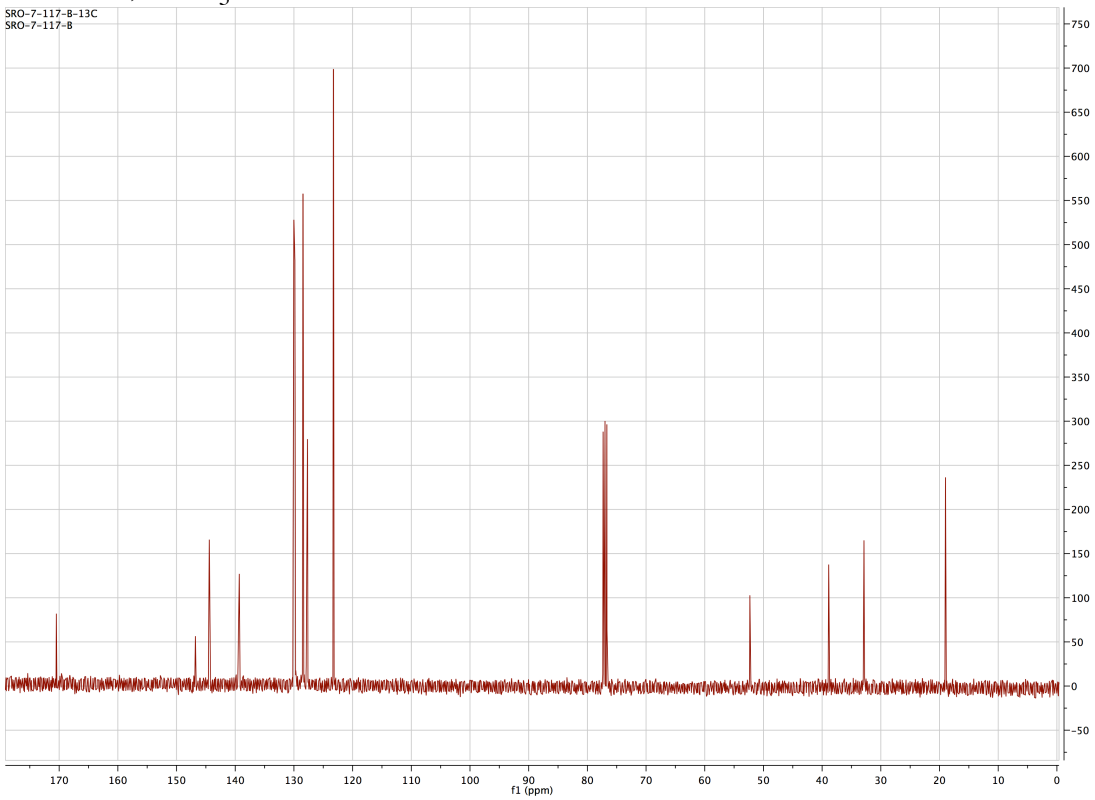


100 MHz, $CDCl_3$



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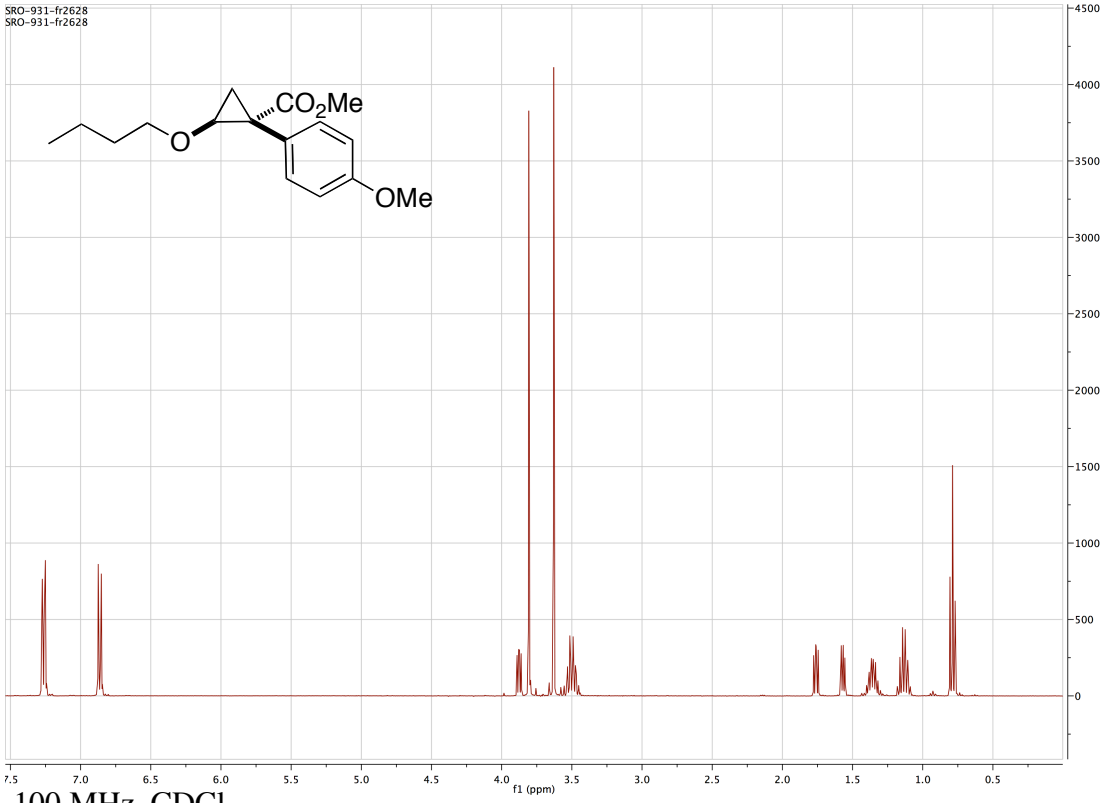

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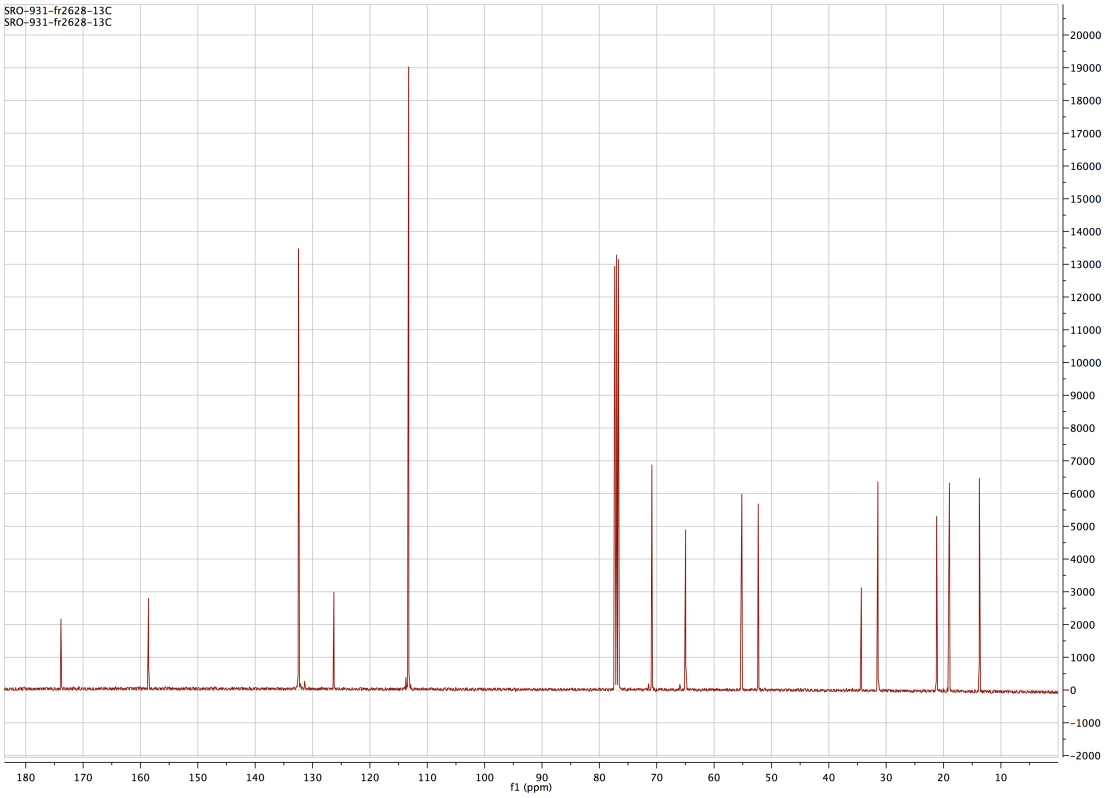

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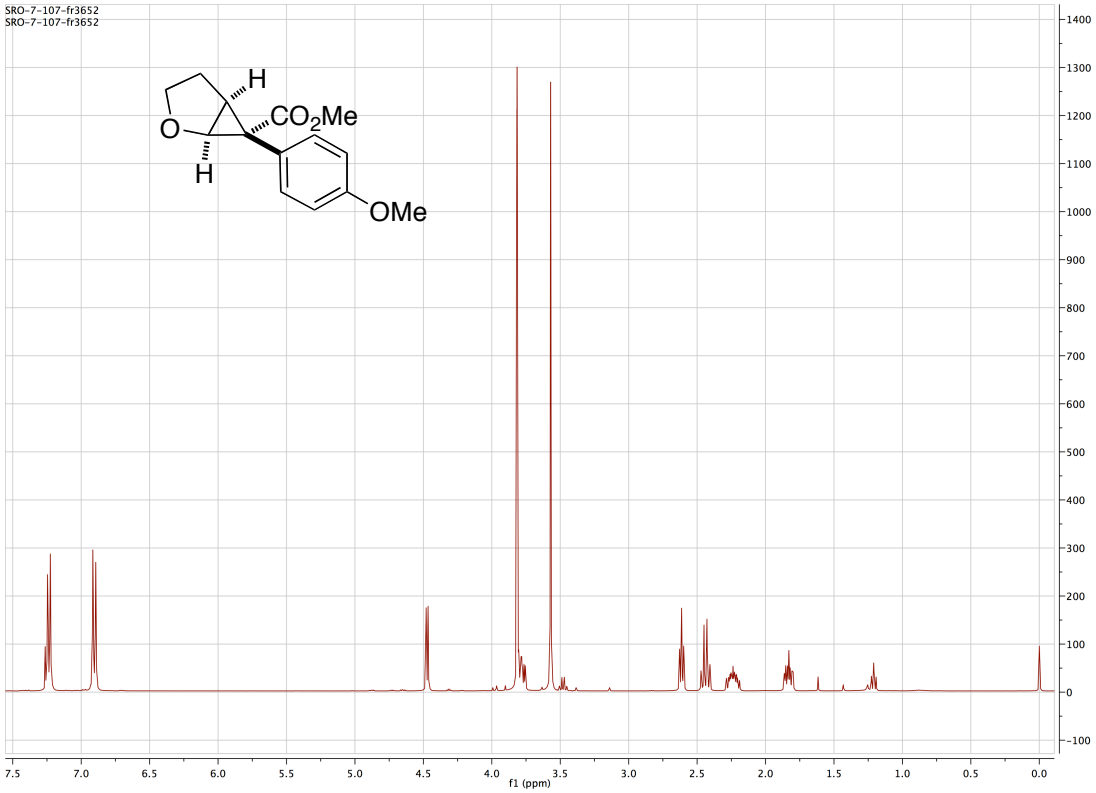

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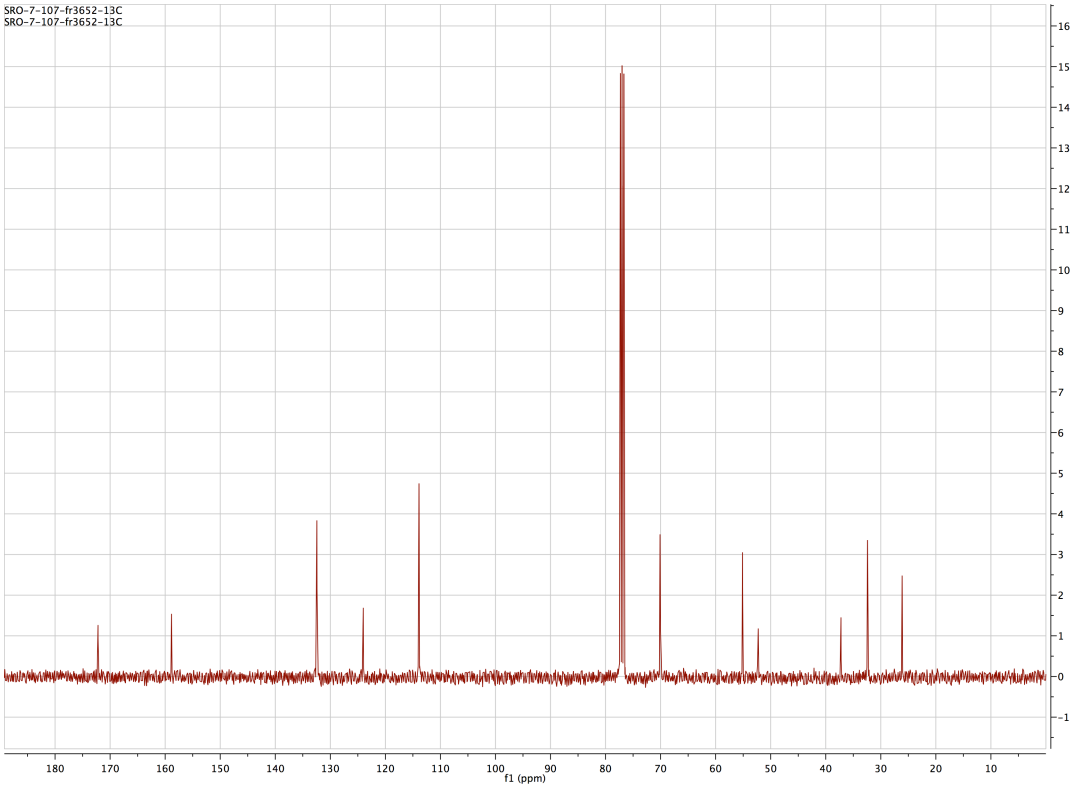

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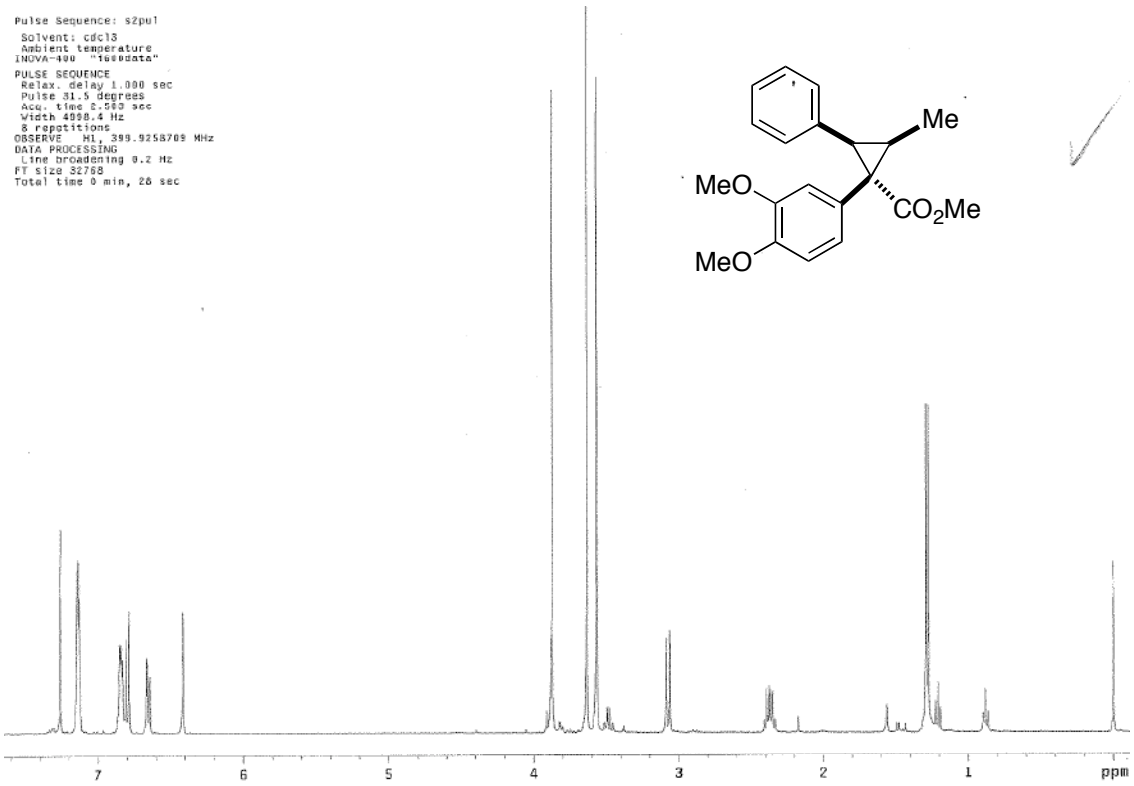
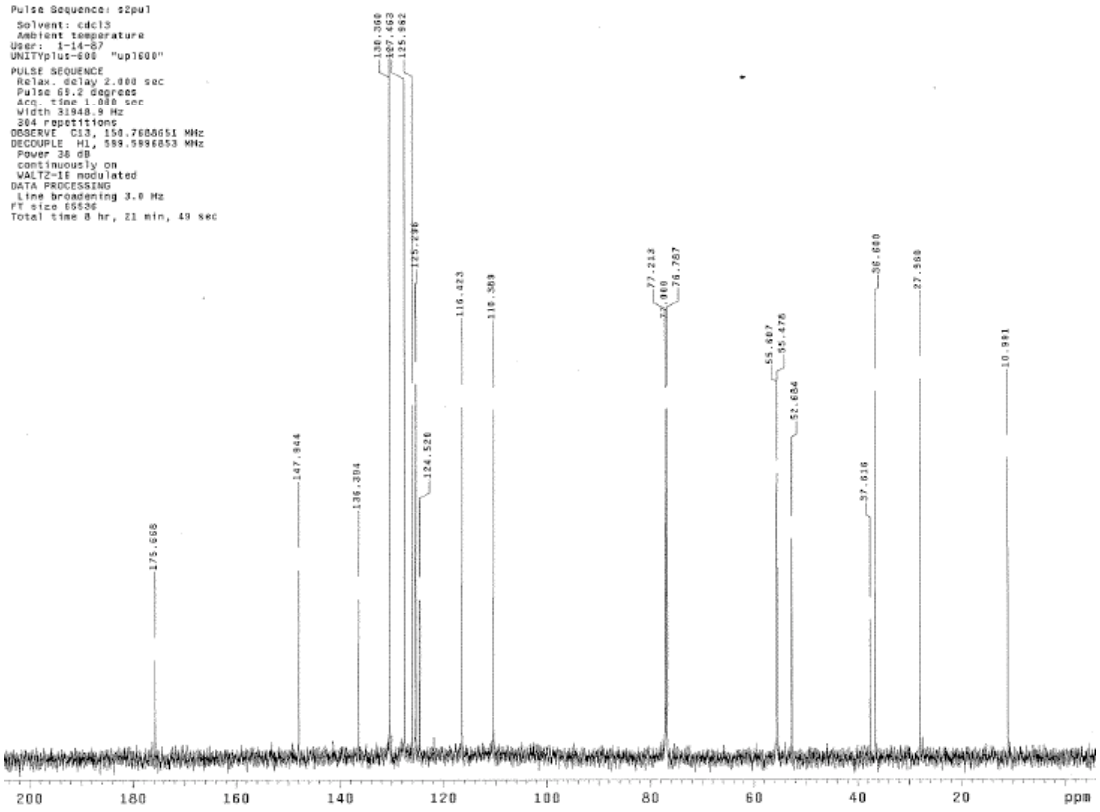


150 MHz, $CDCl_3$



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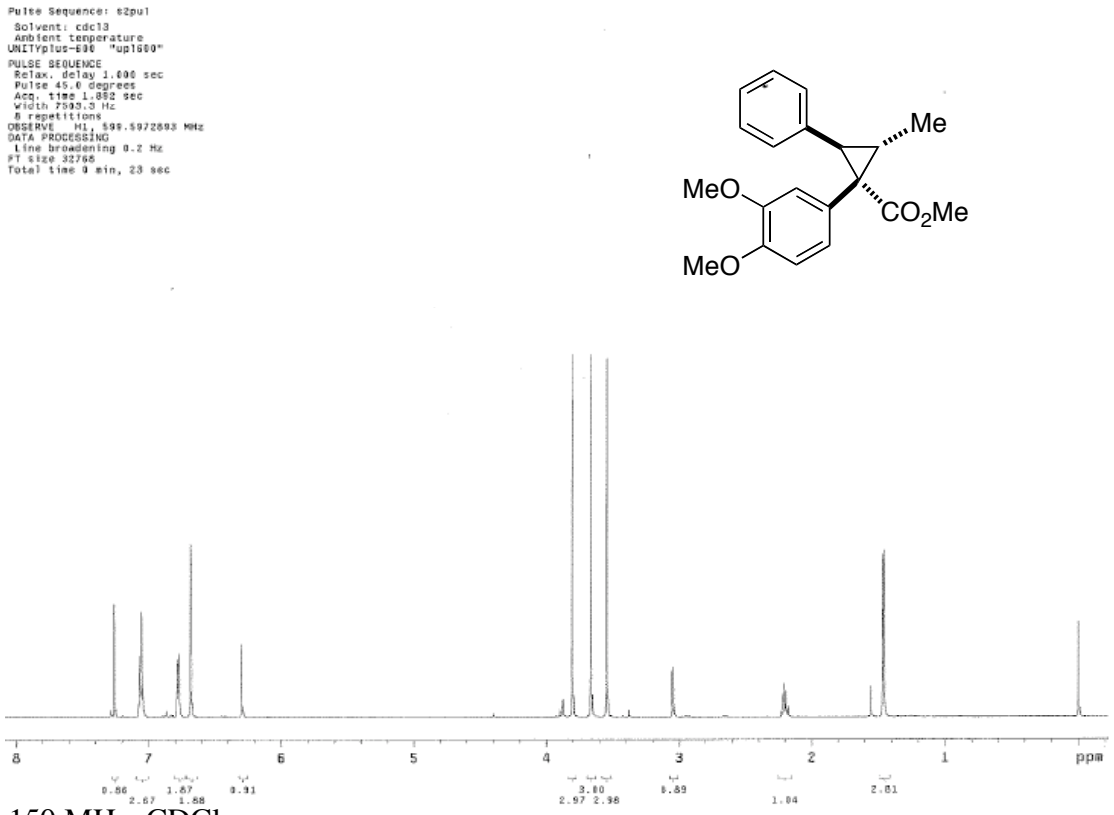
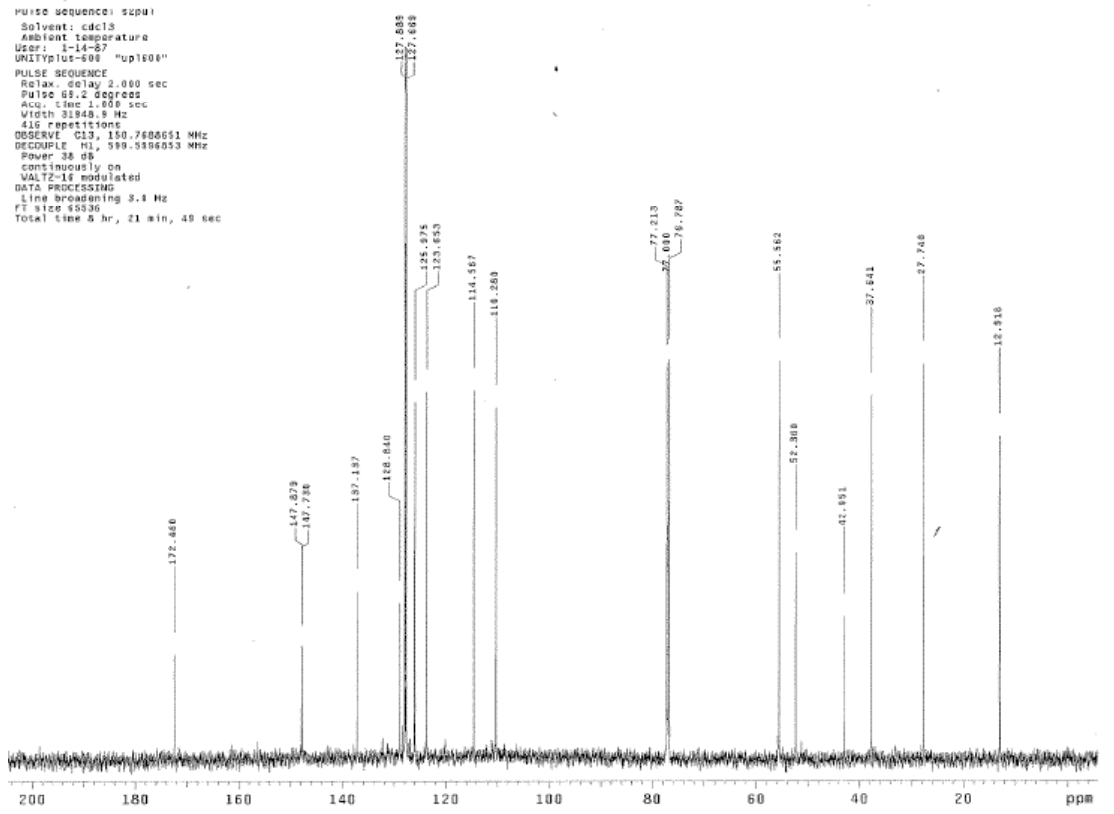
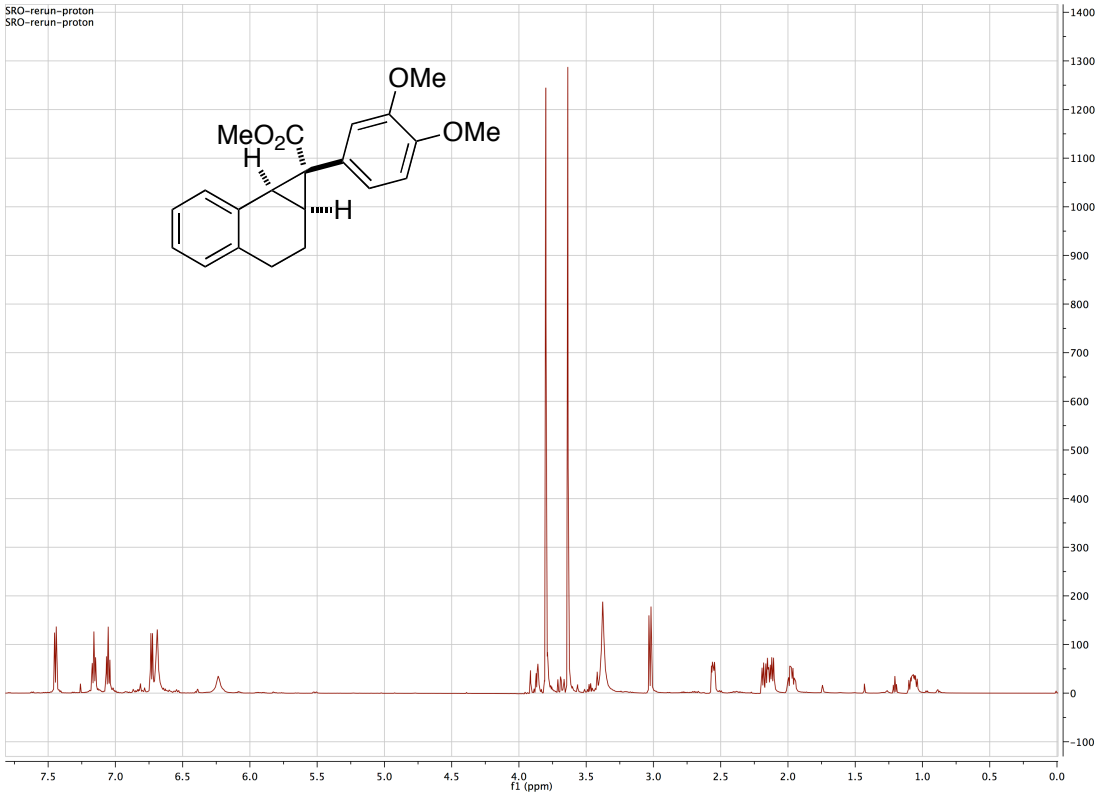


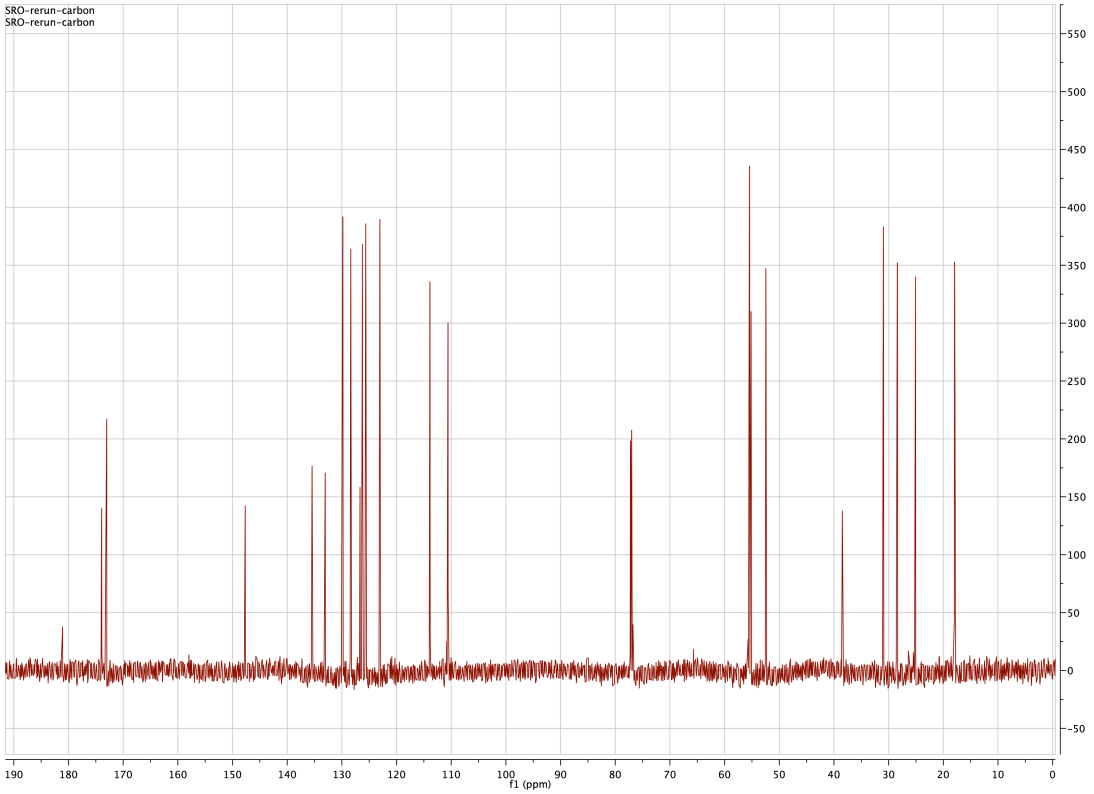
150 MHz, $CDCl_3$



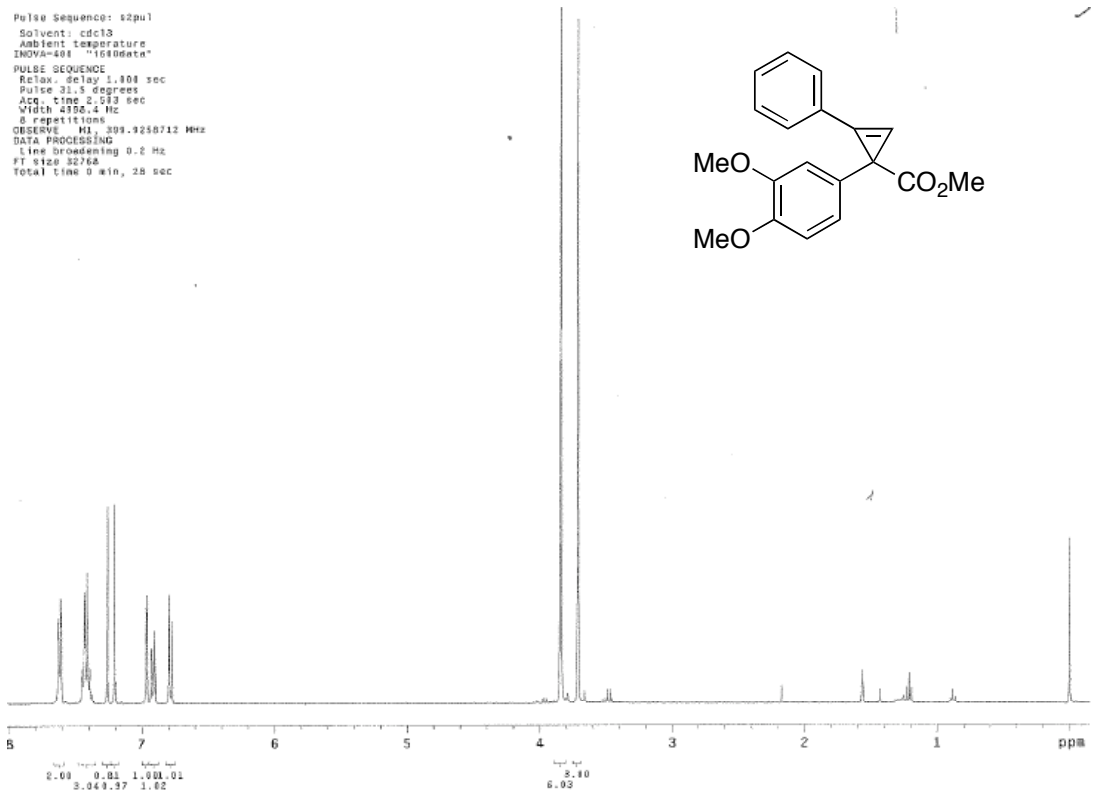
400 MHz, $CDCl_3$



100 MHz, $CDCl_3$



600 MHz, $CDCl_3$



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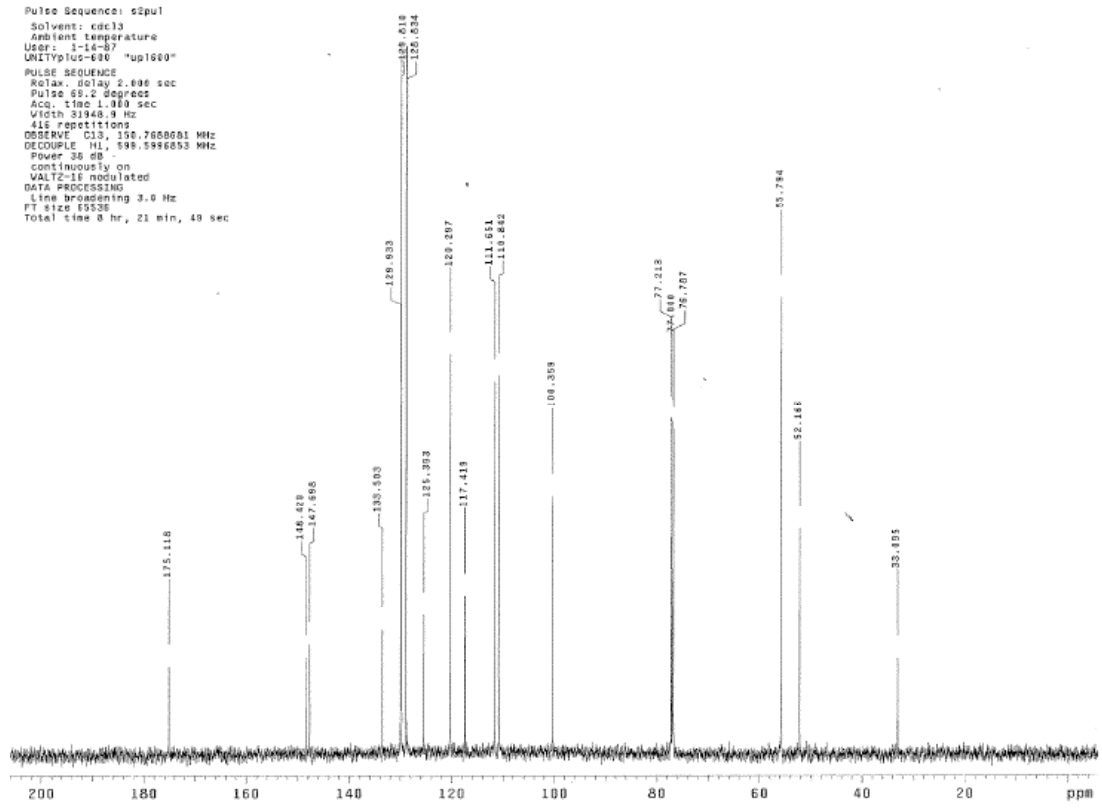
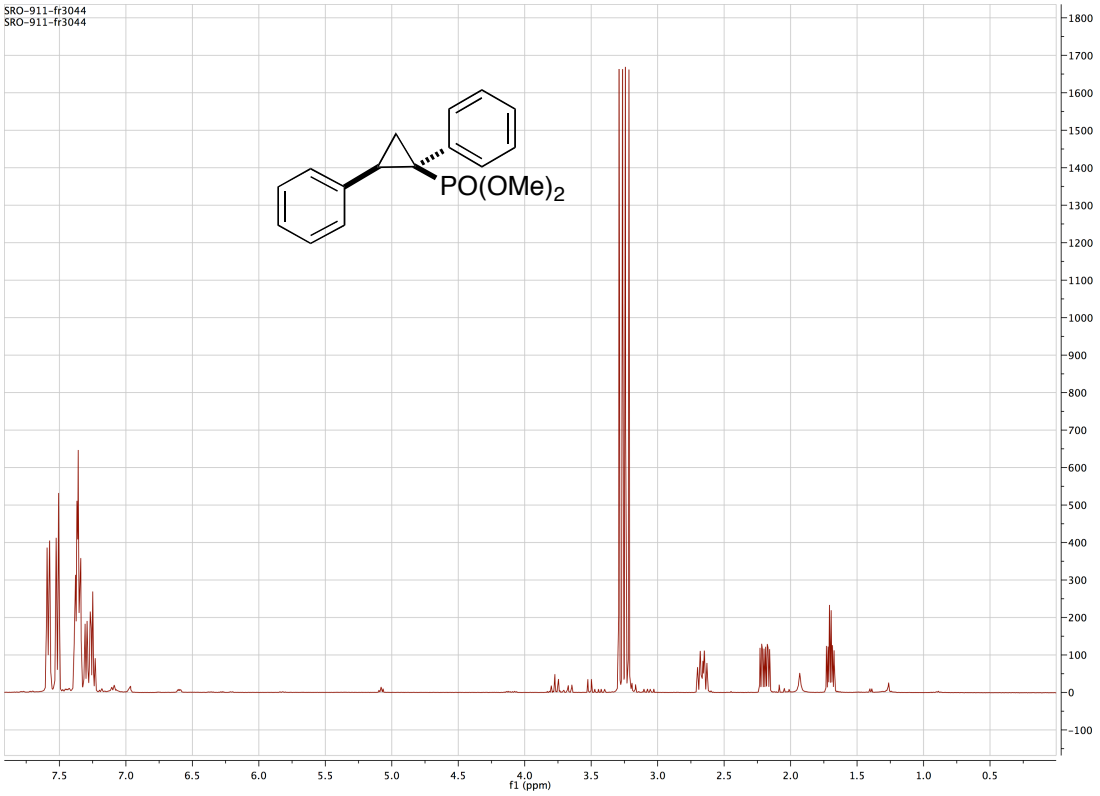
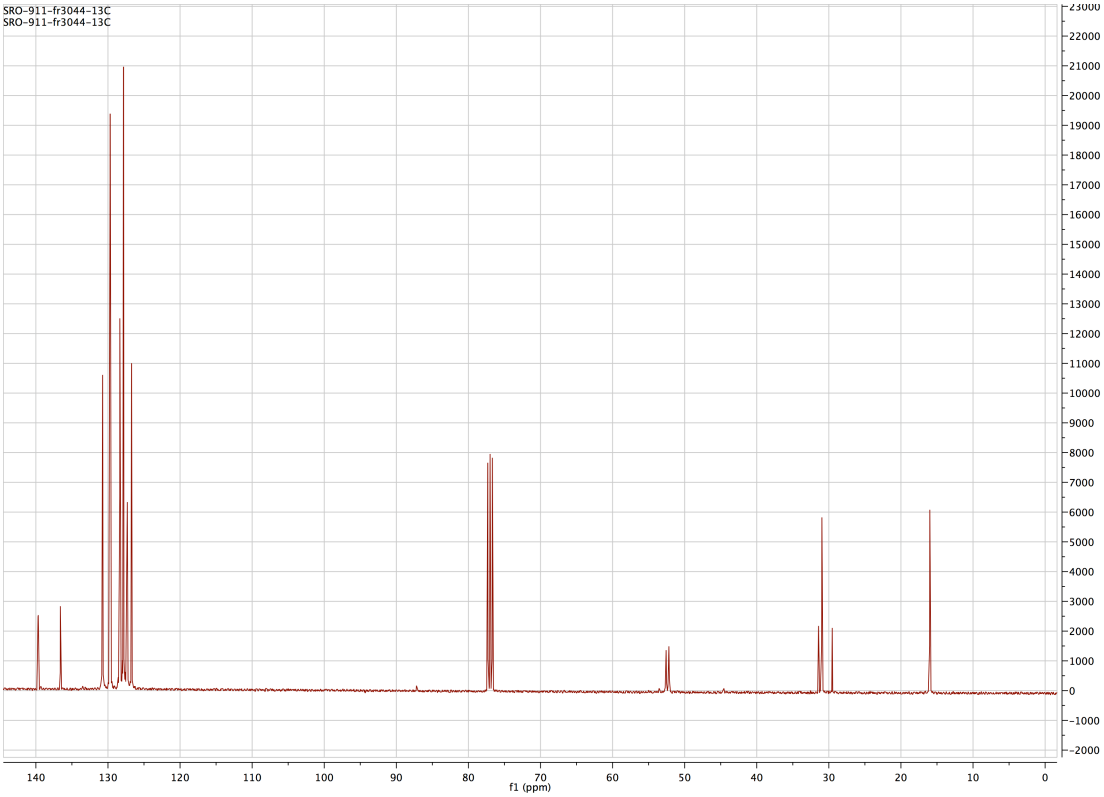


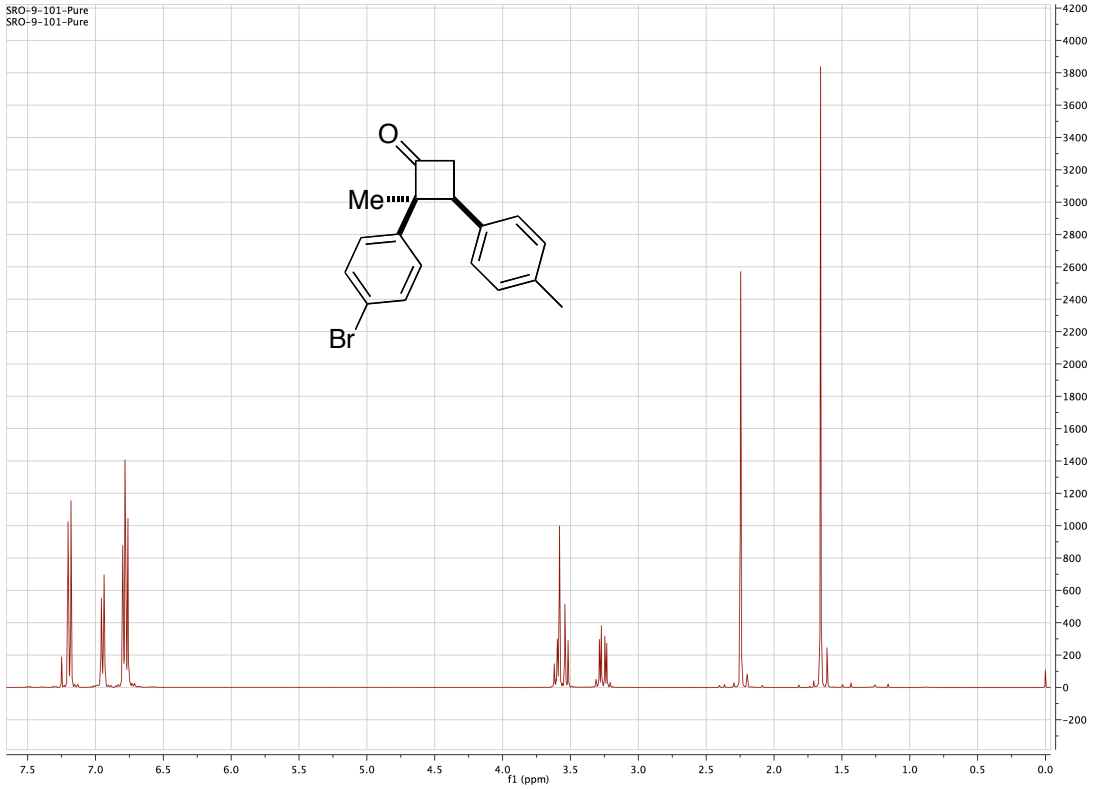
400 MHz, $CDCl_3$



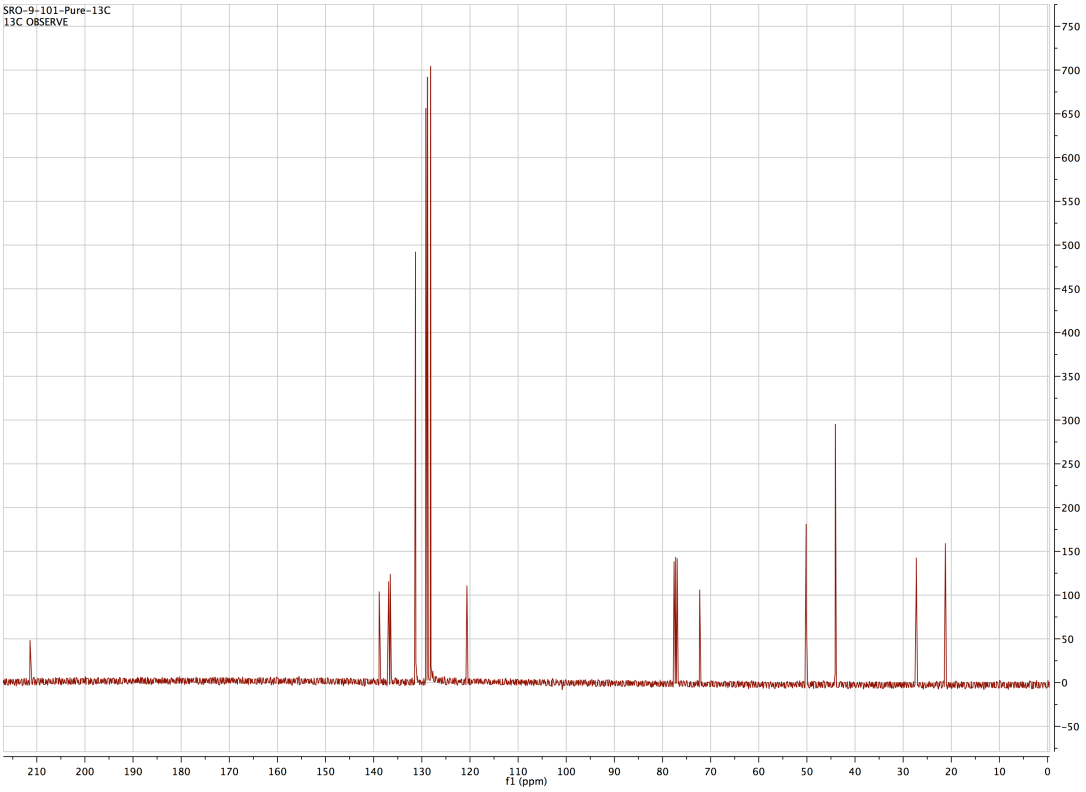
100 MHz, $CDCl_3$



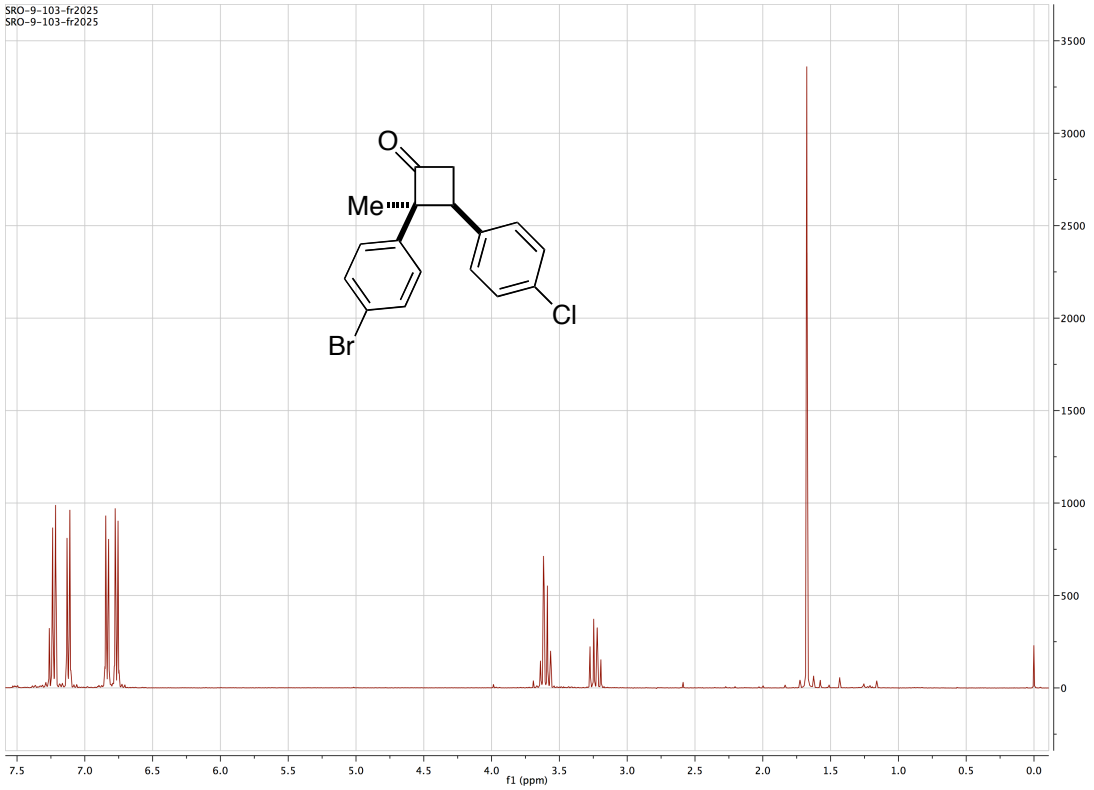
400 MHz, $CDCl_3$



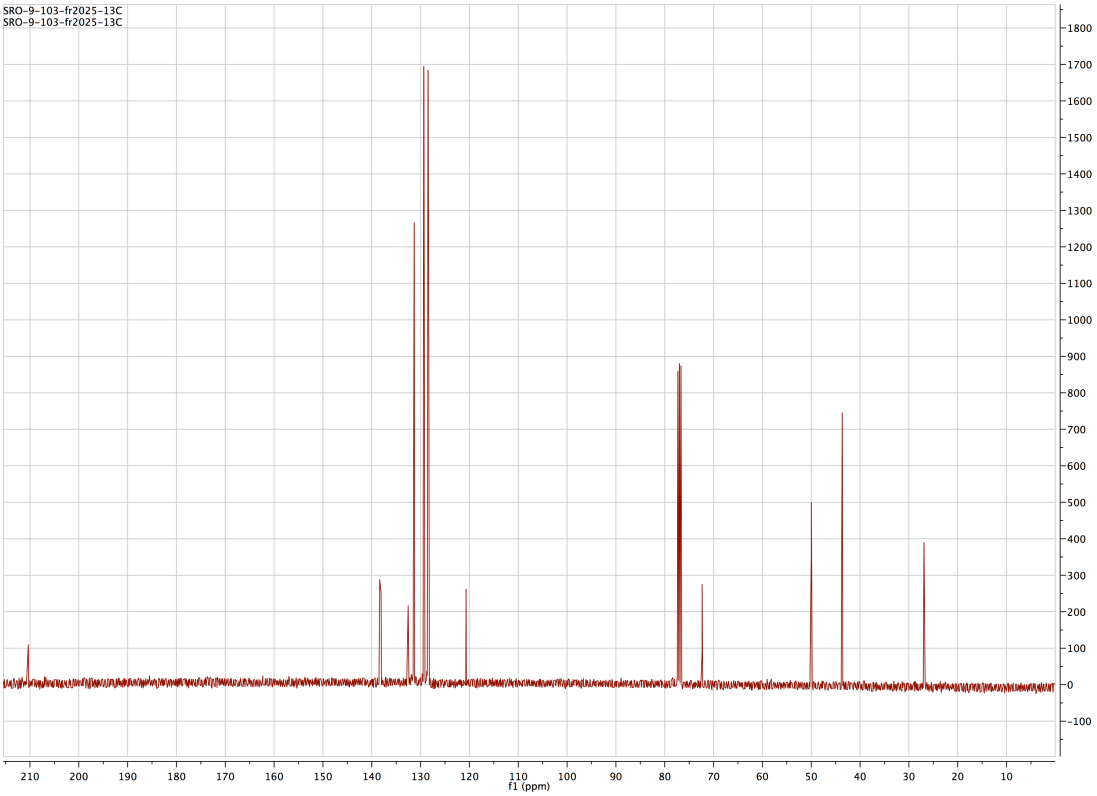
100 MHz, $CDCl_3$



400 MHz, $CDCl_3$



100 MHz, $CDCl_3$



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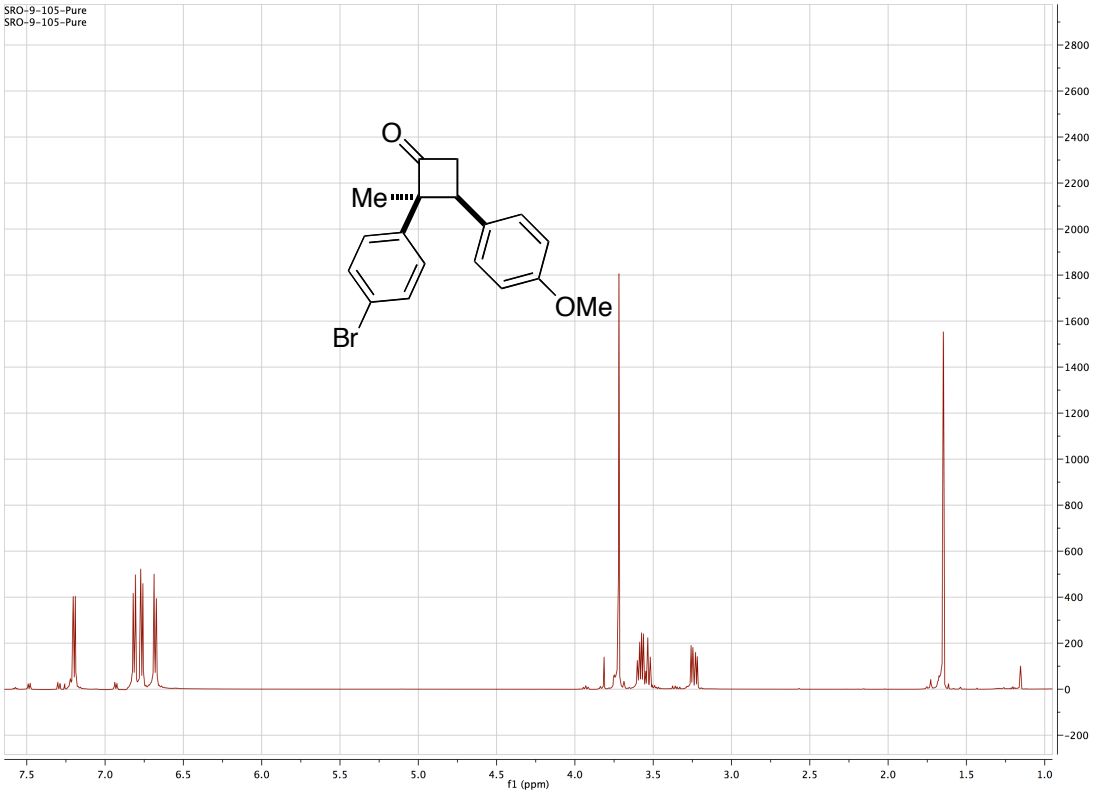
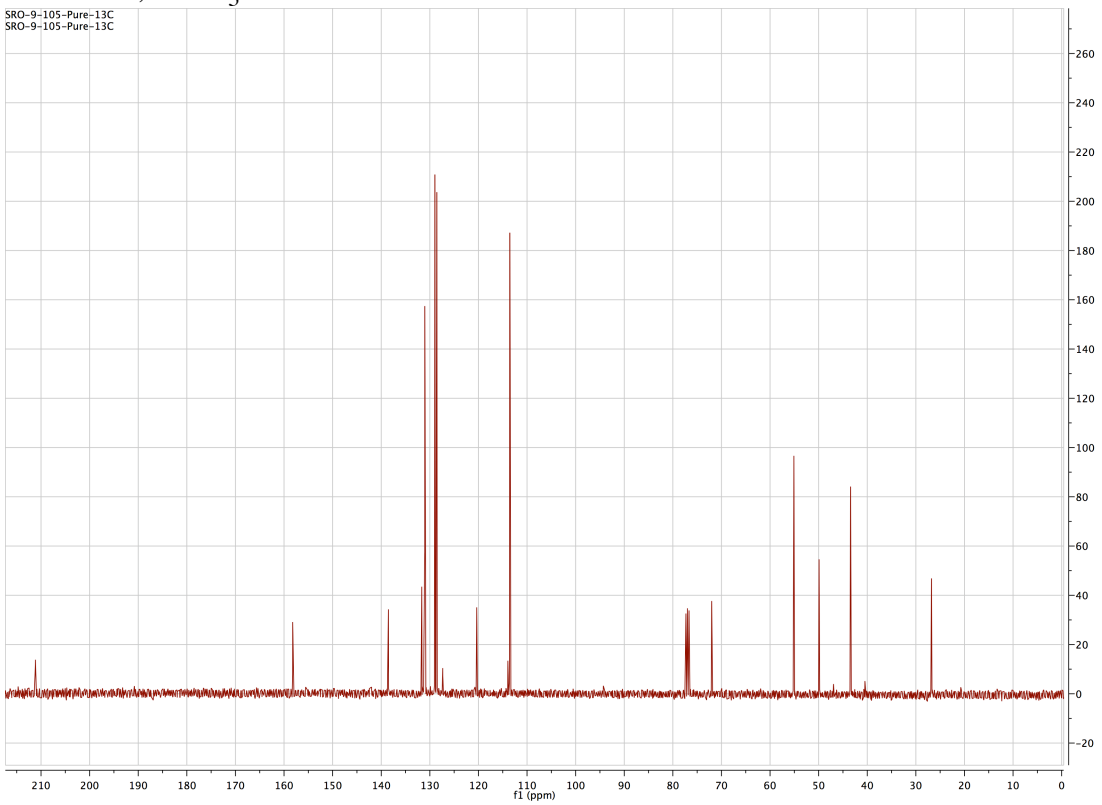
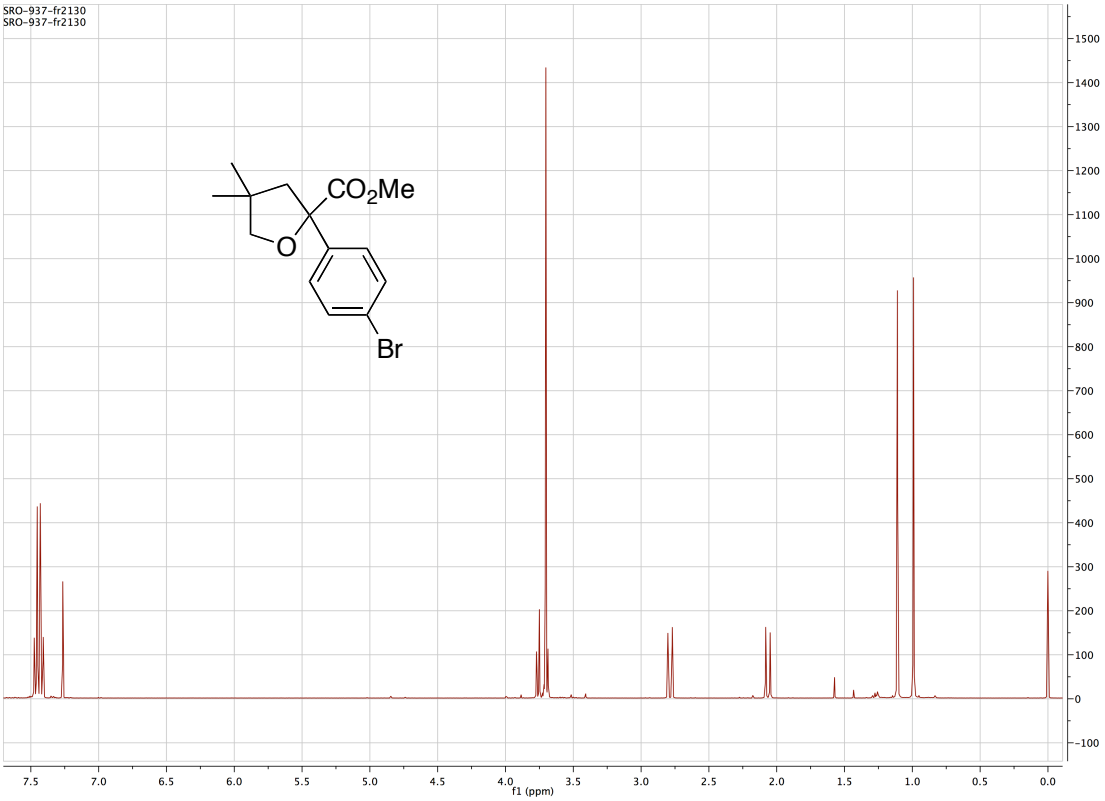


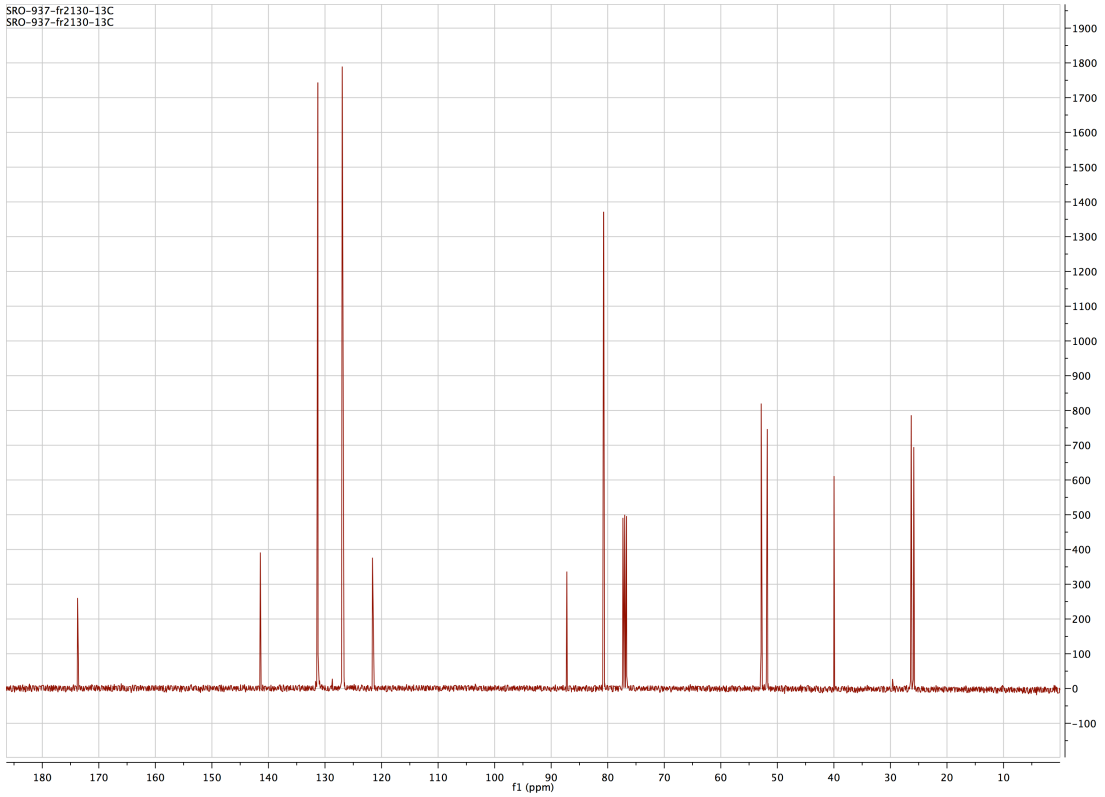
100 MHz, $CDCl_3$



400 MHz, $CDCl_3$



100 MHz, $CDCl_3$



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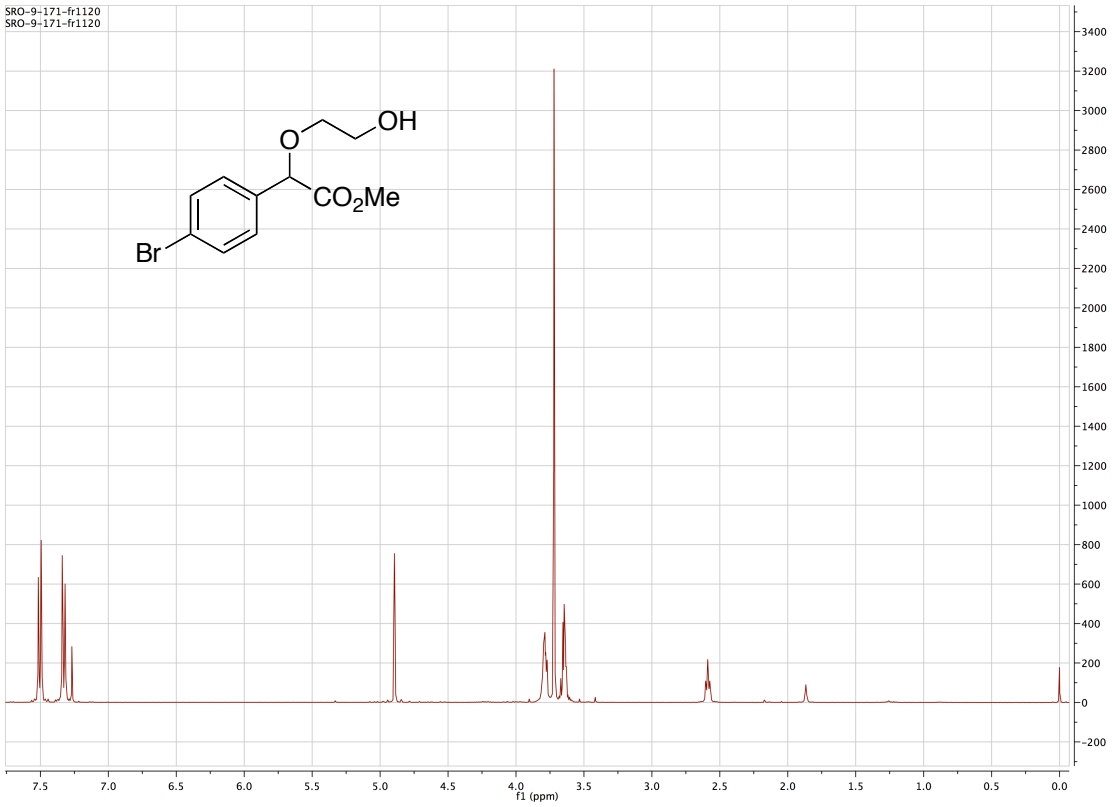
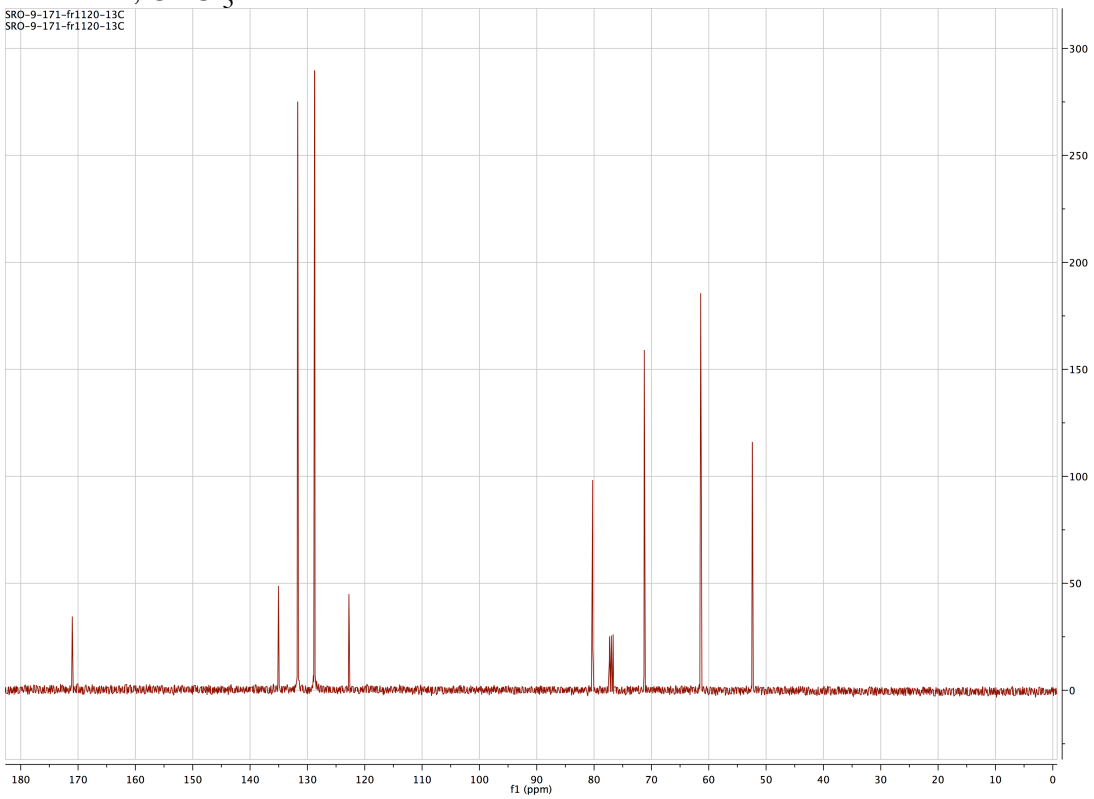
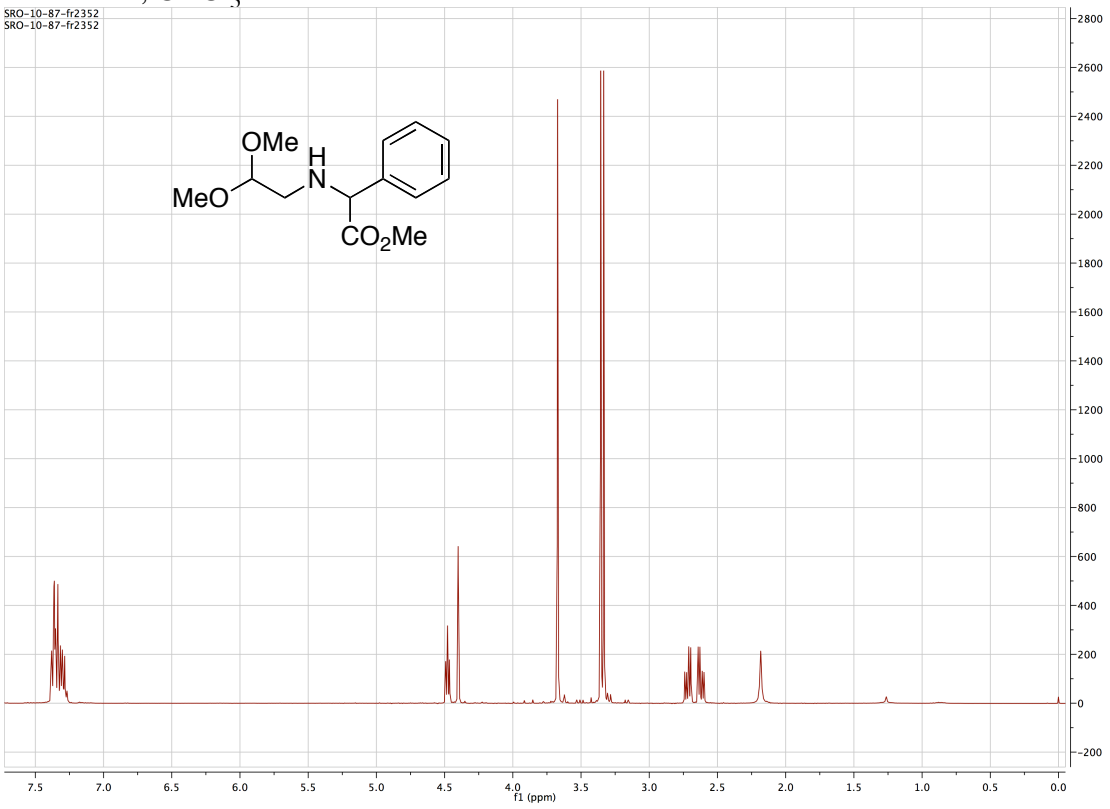


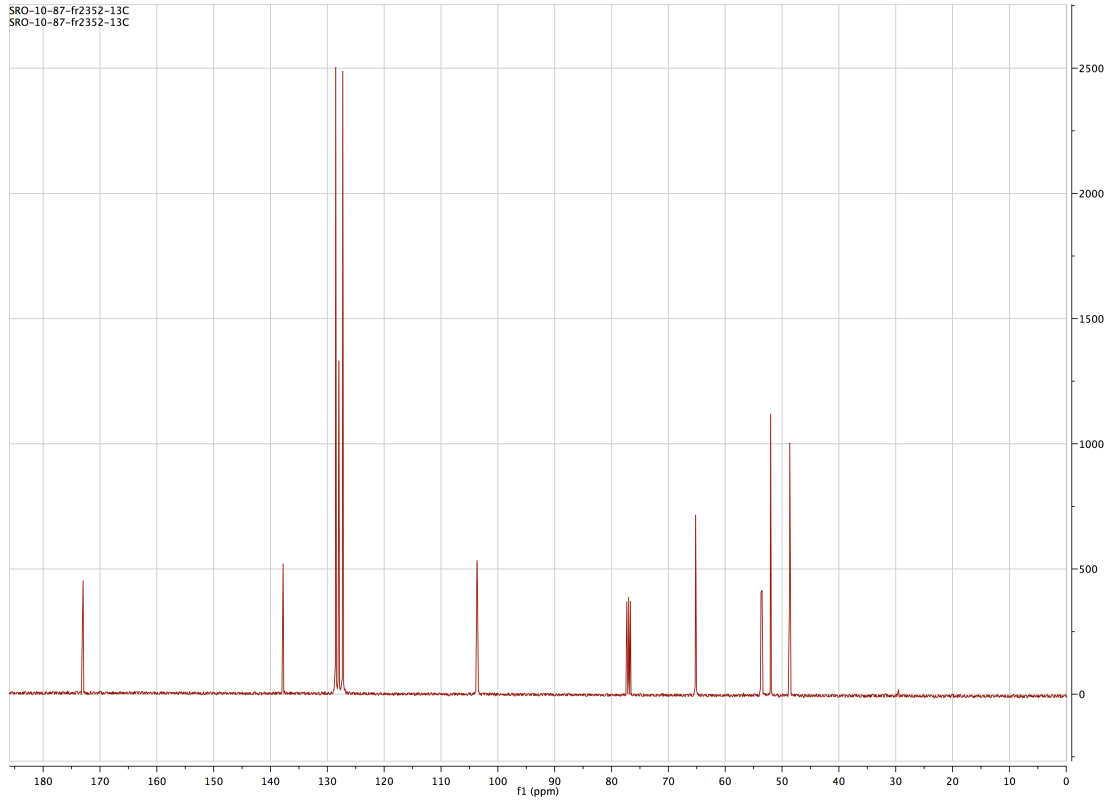
100 MHz, $CDCl_3$



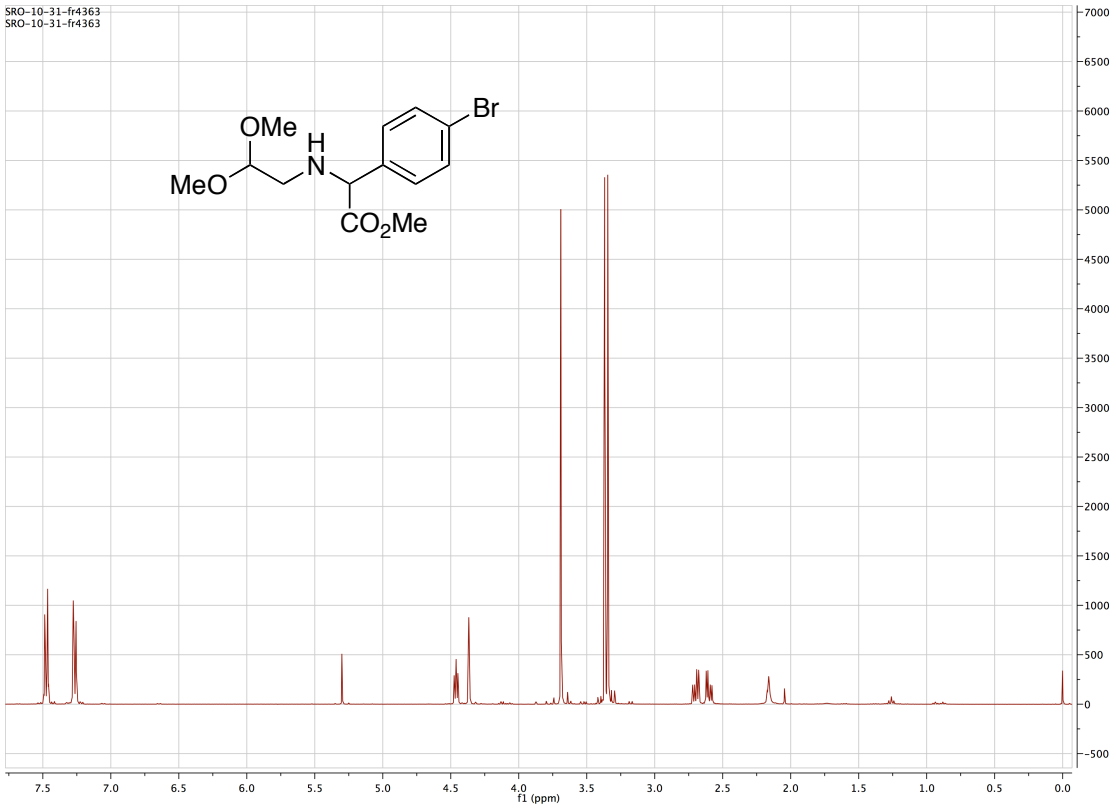
400 MHz, $CDCl_3$



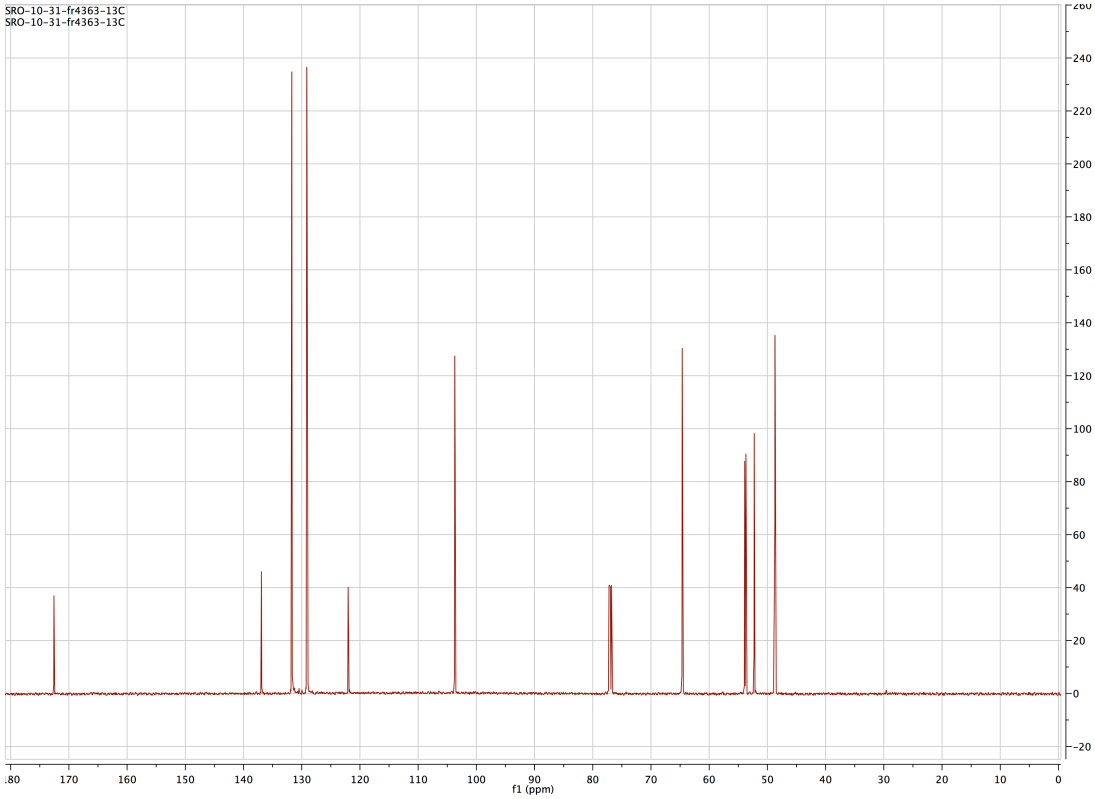
100 MHz, $CDCl_3$



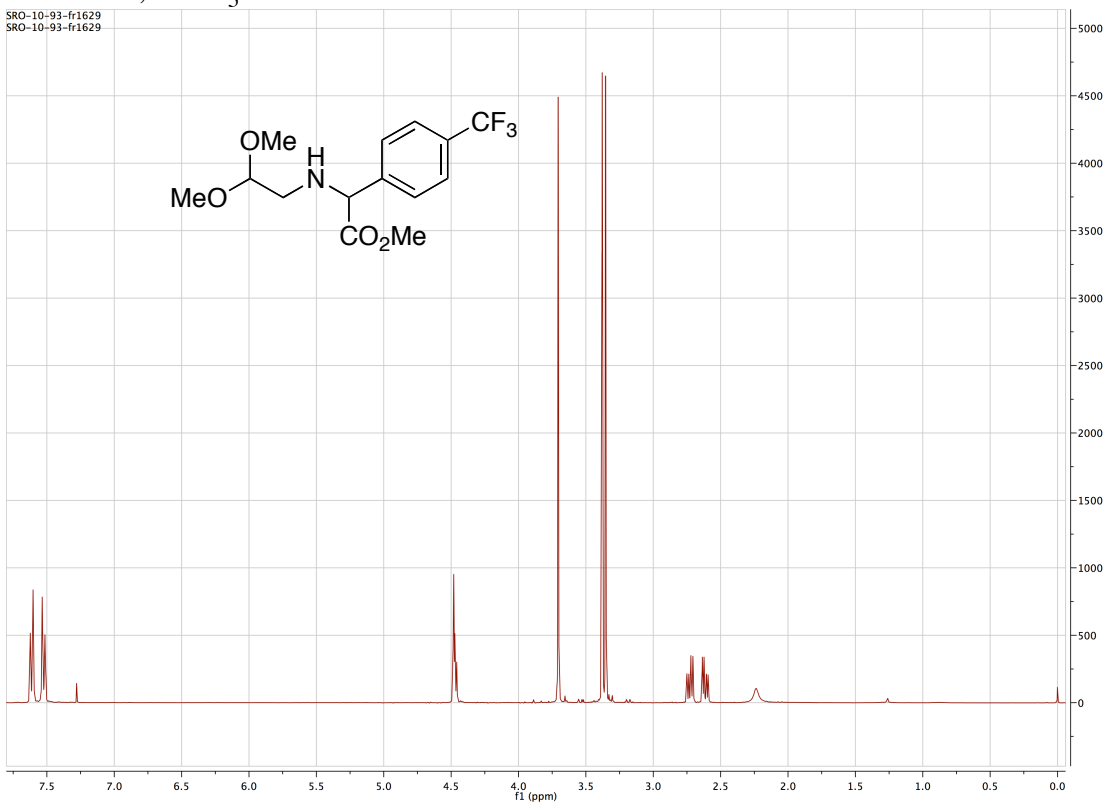
600 MHz, $CDCl_3$



150 MHz, $CDCl_3$



400 MHz, $CDCl_3$



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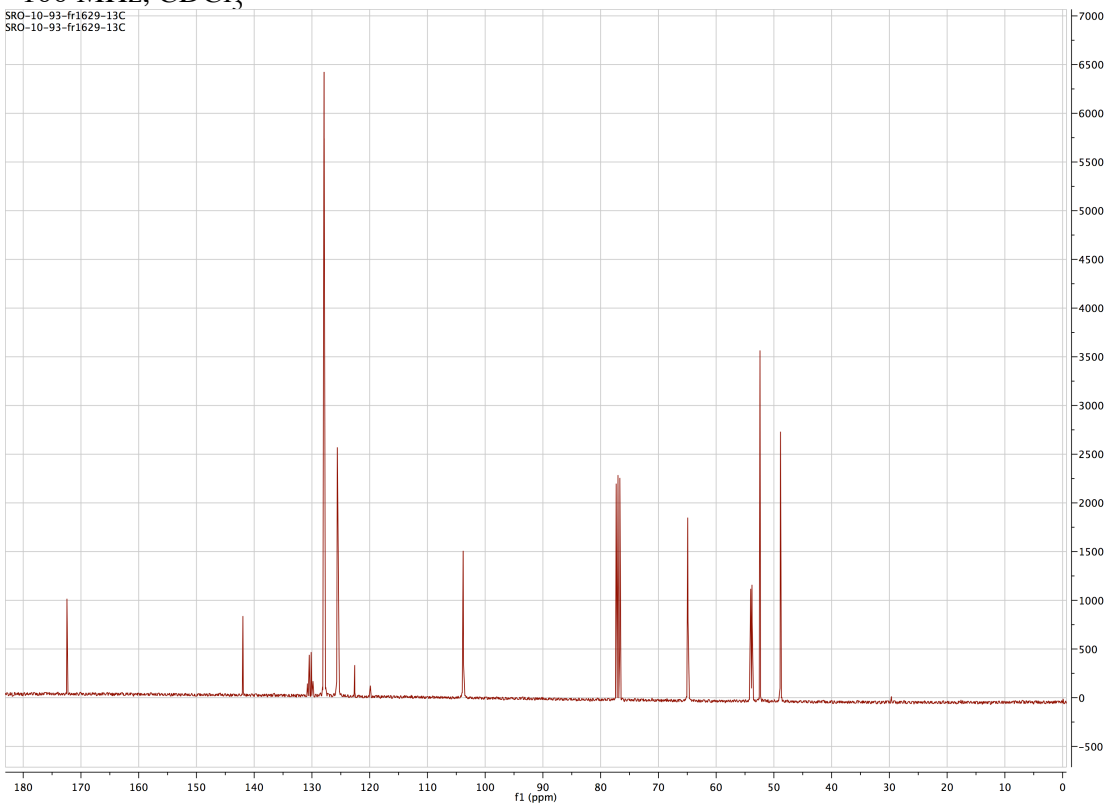

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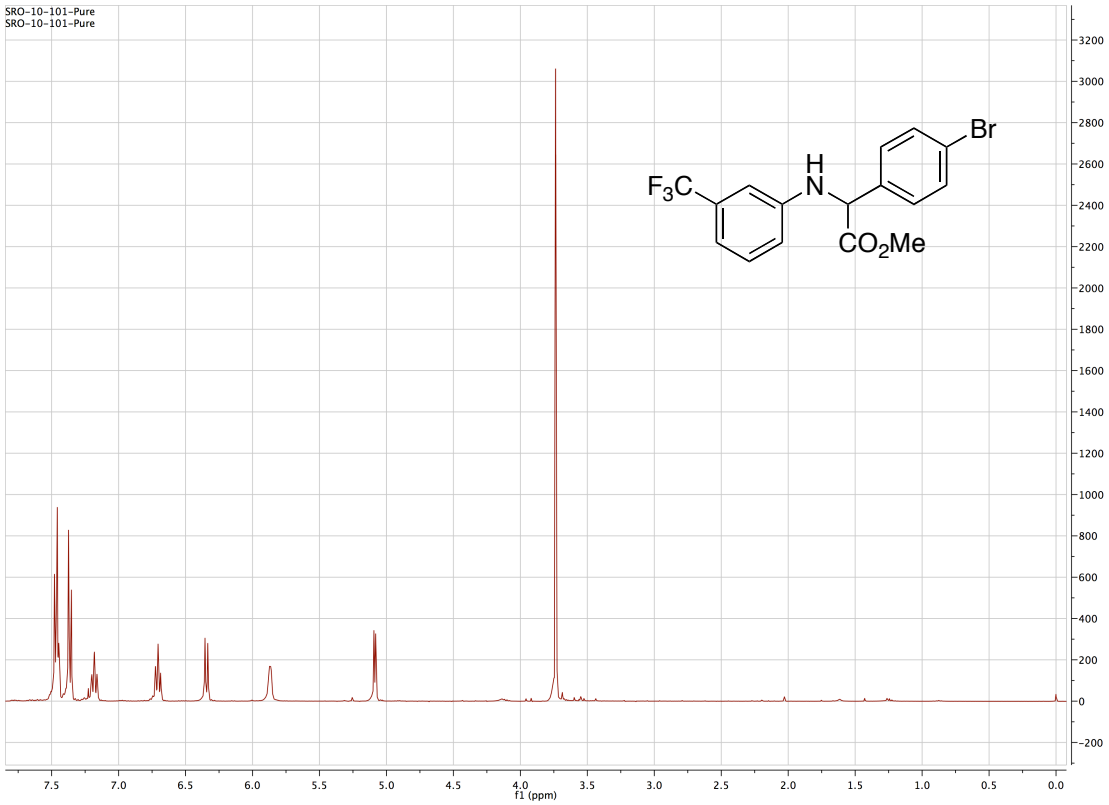

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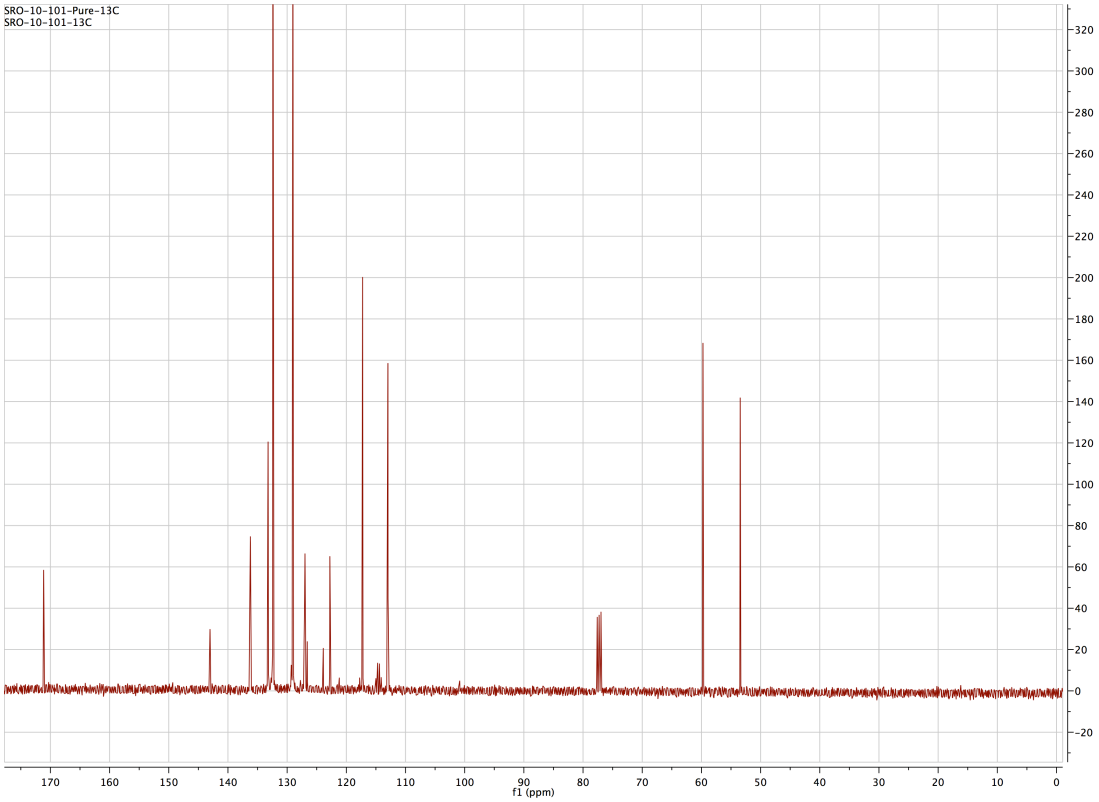
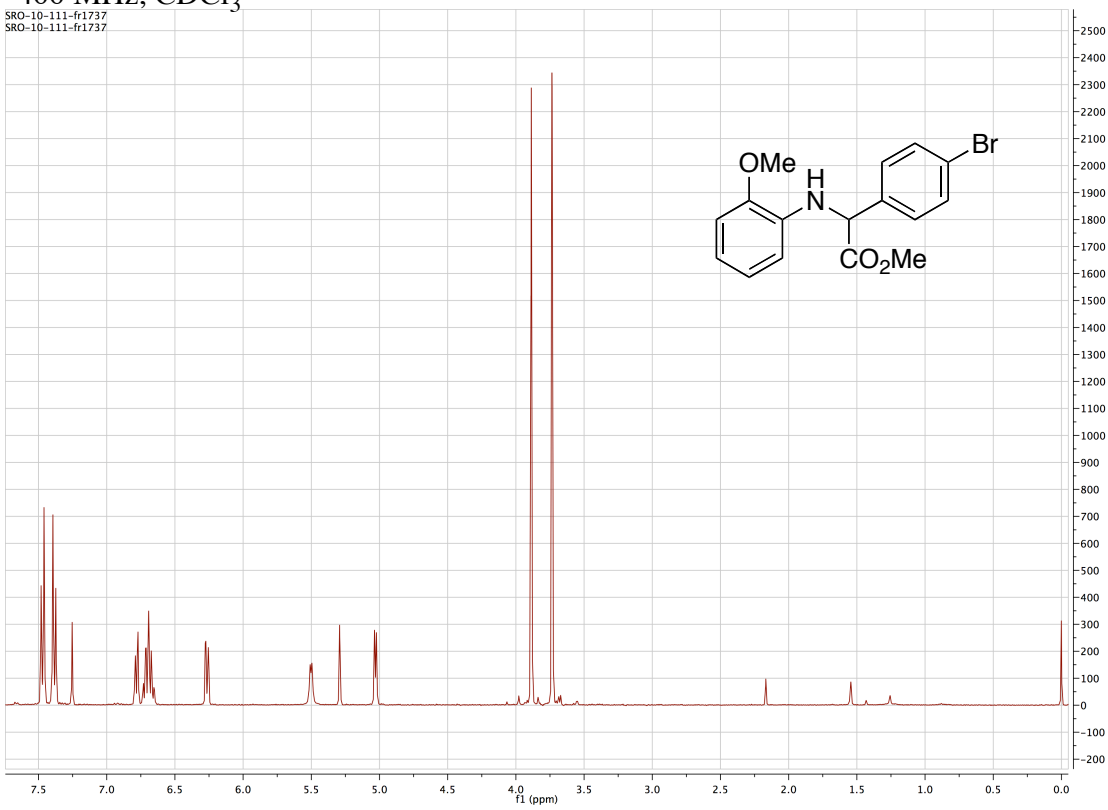
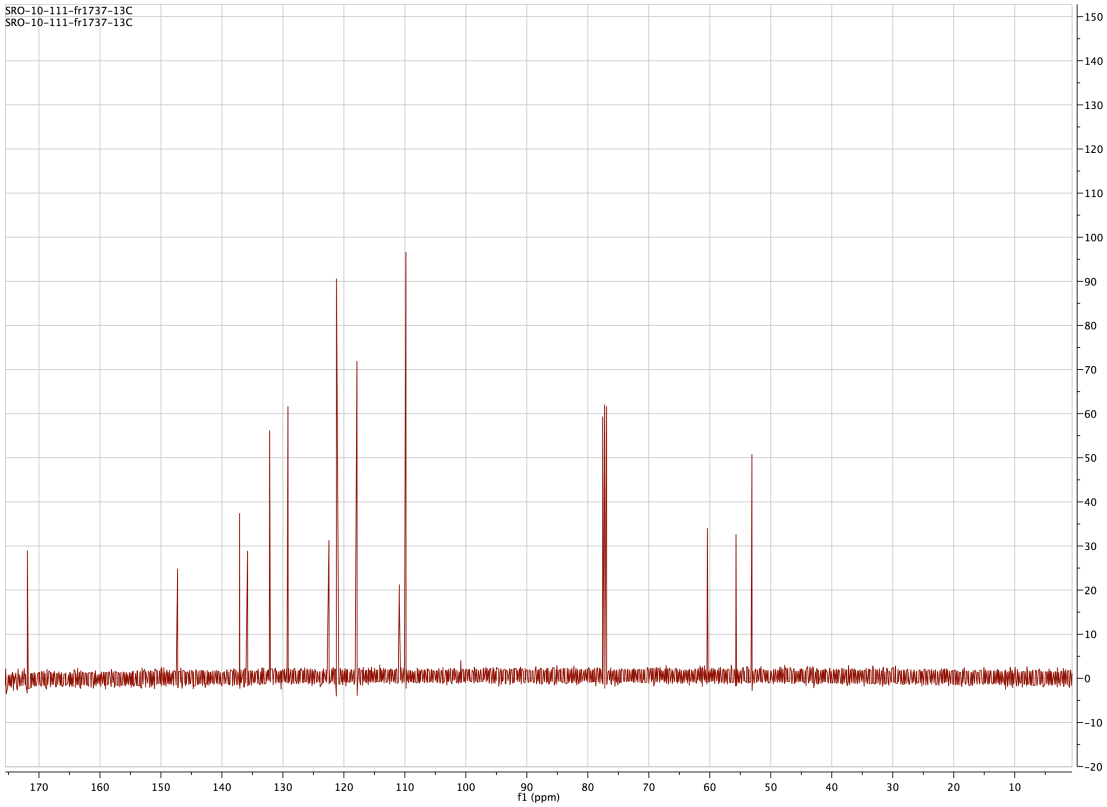


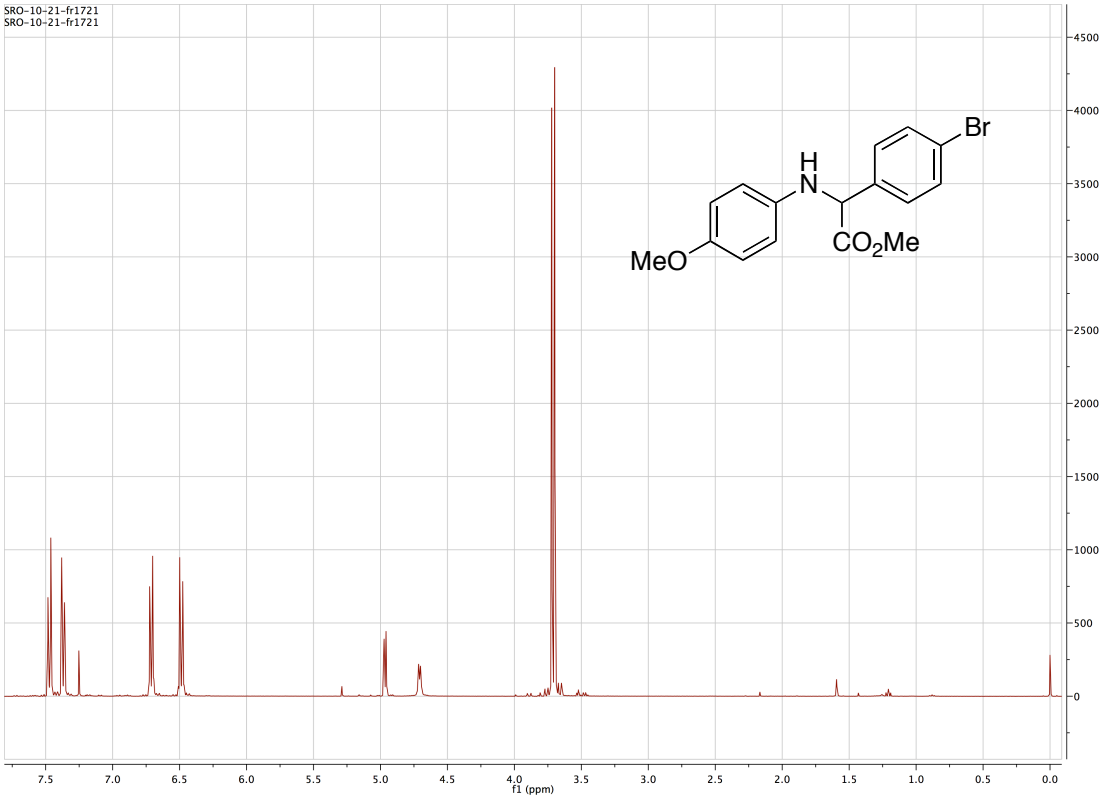
400 MHz, $CDCl_3$



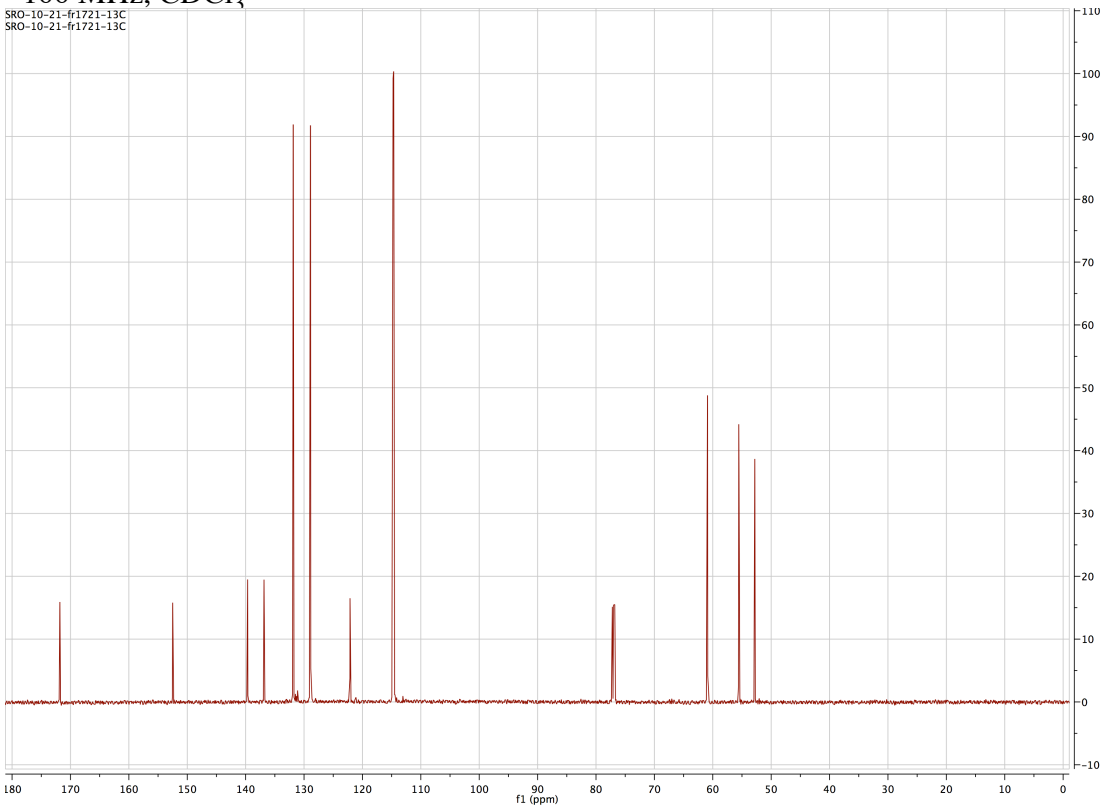
100 MHz, $CDCl_3$



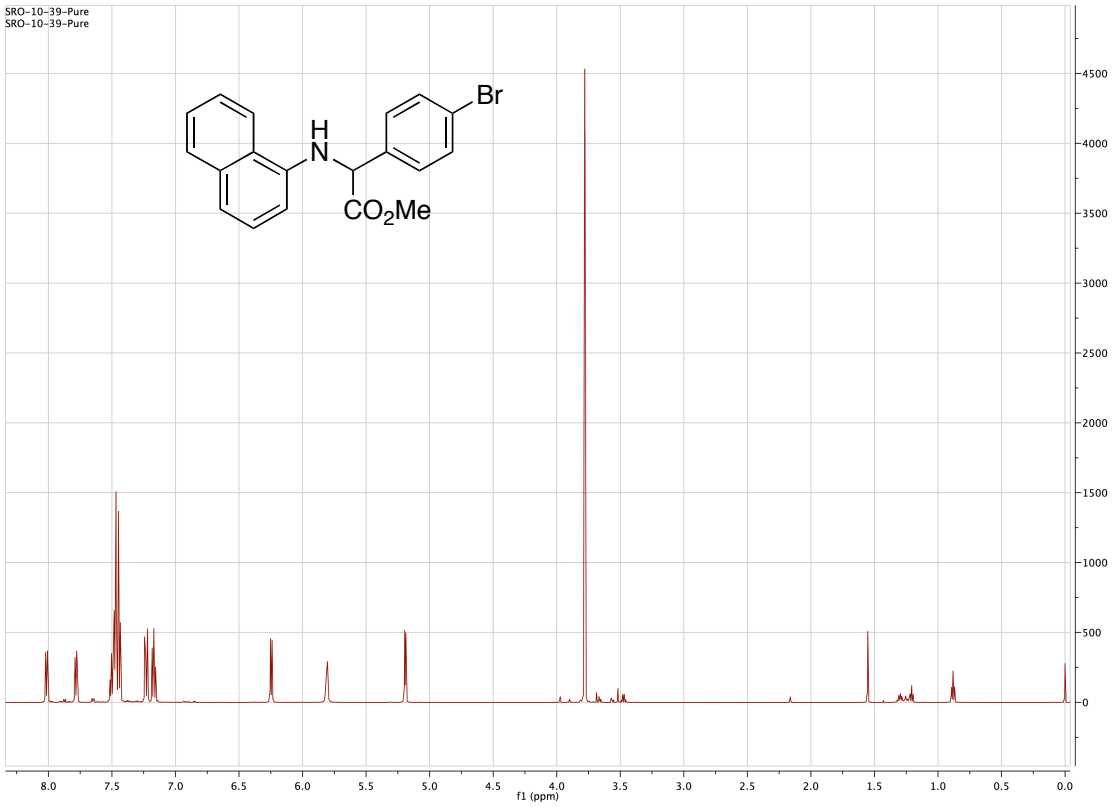
400 MHz, $CDCl_3$



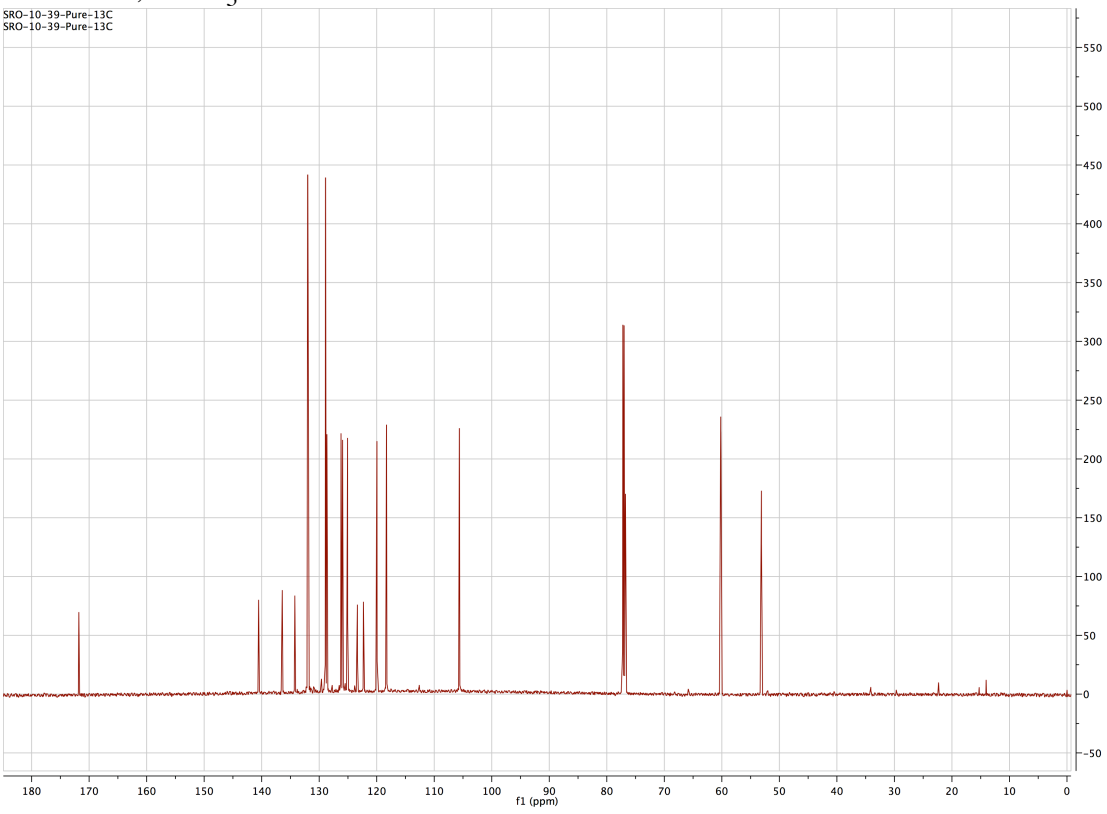
100 MHz, $CDCl_3$



600 MHz, $CDCl_3$



150 MHz, $CDCl_3$



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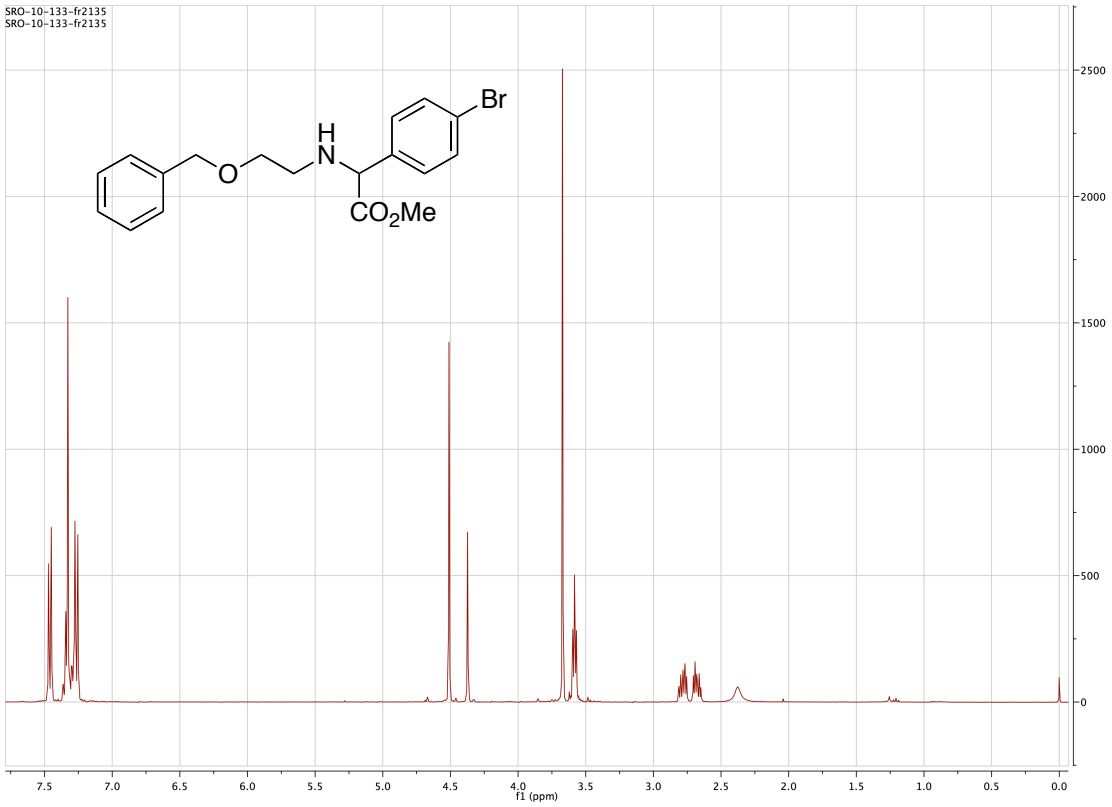

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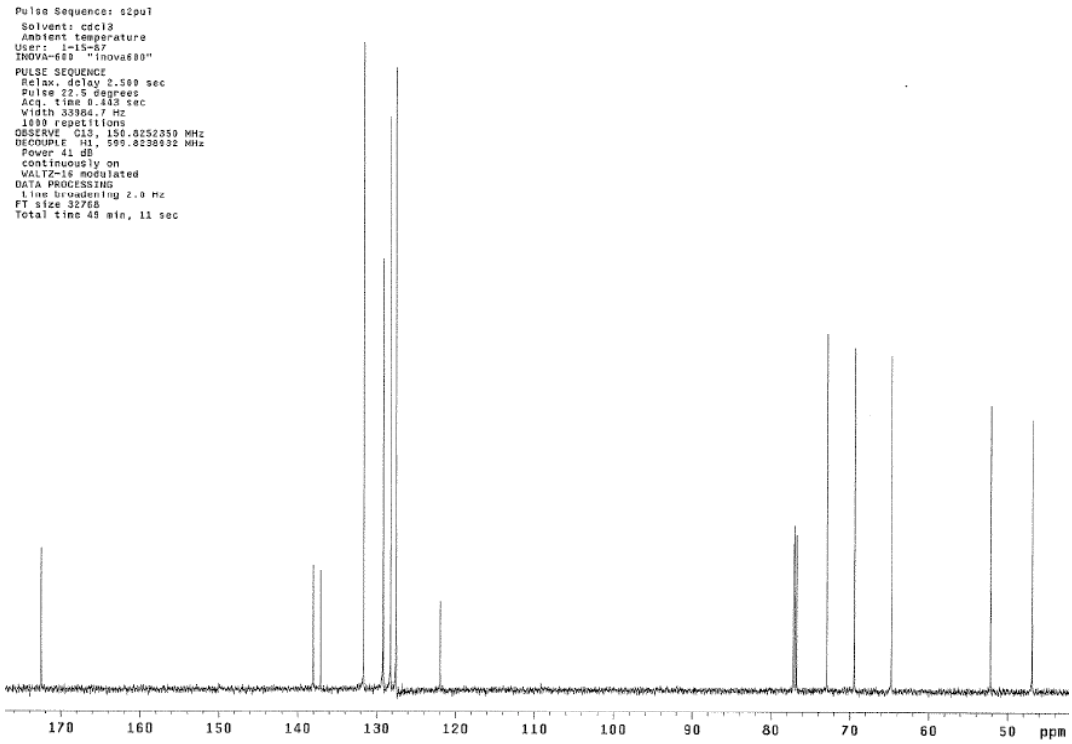

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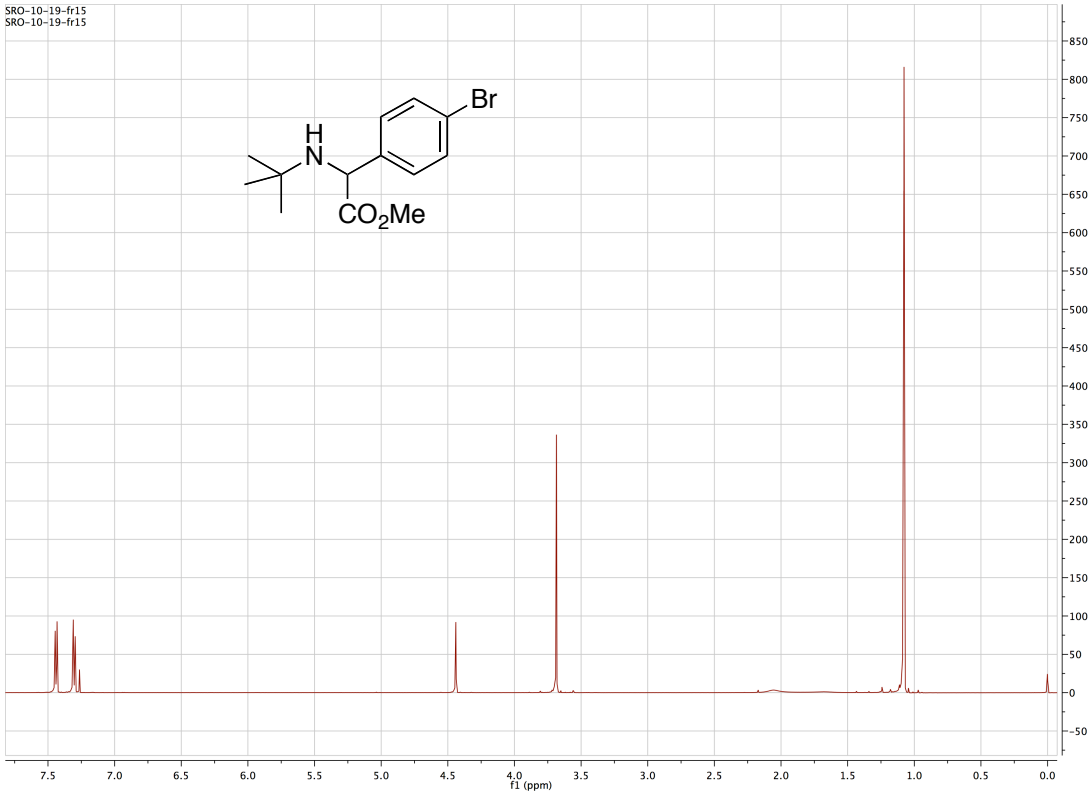

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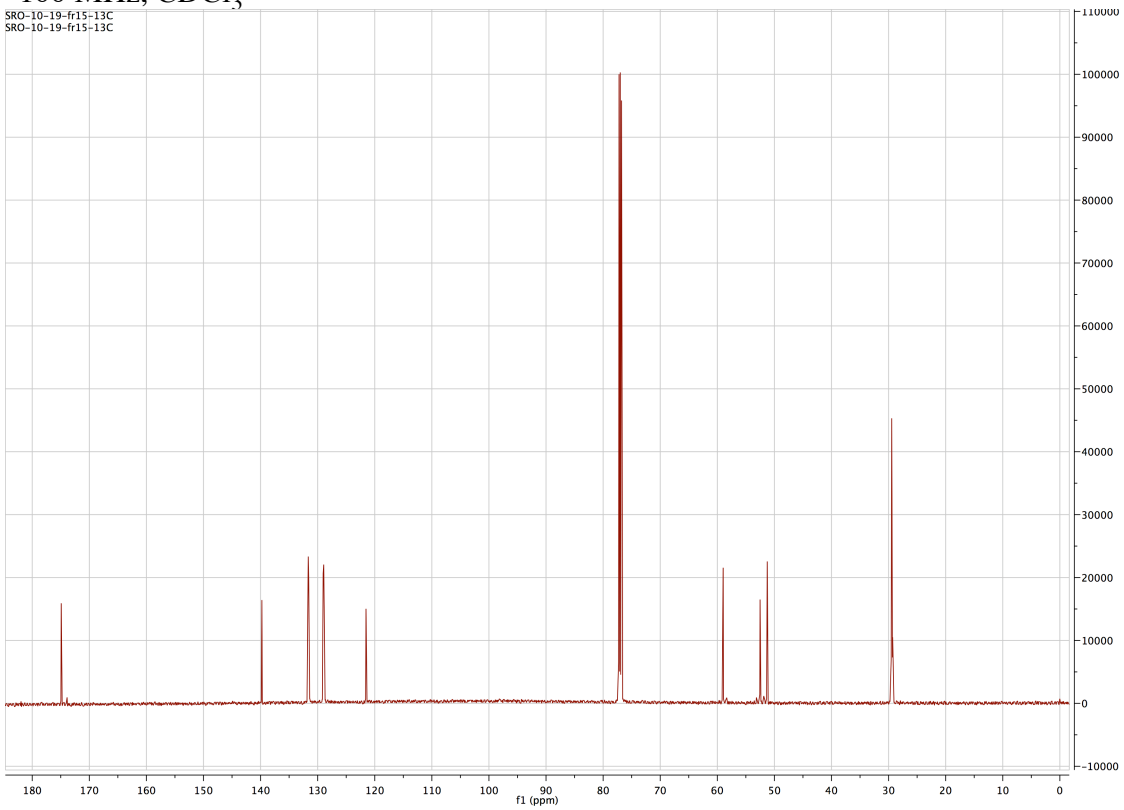

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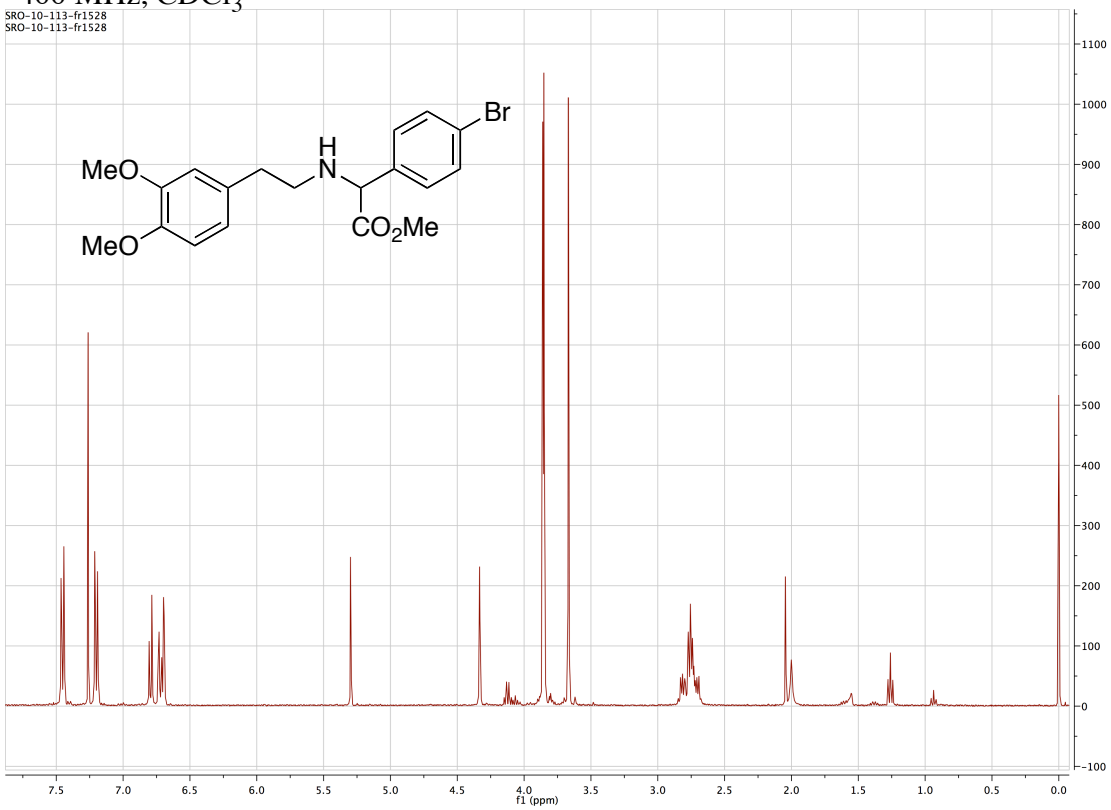

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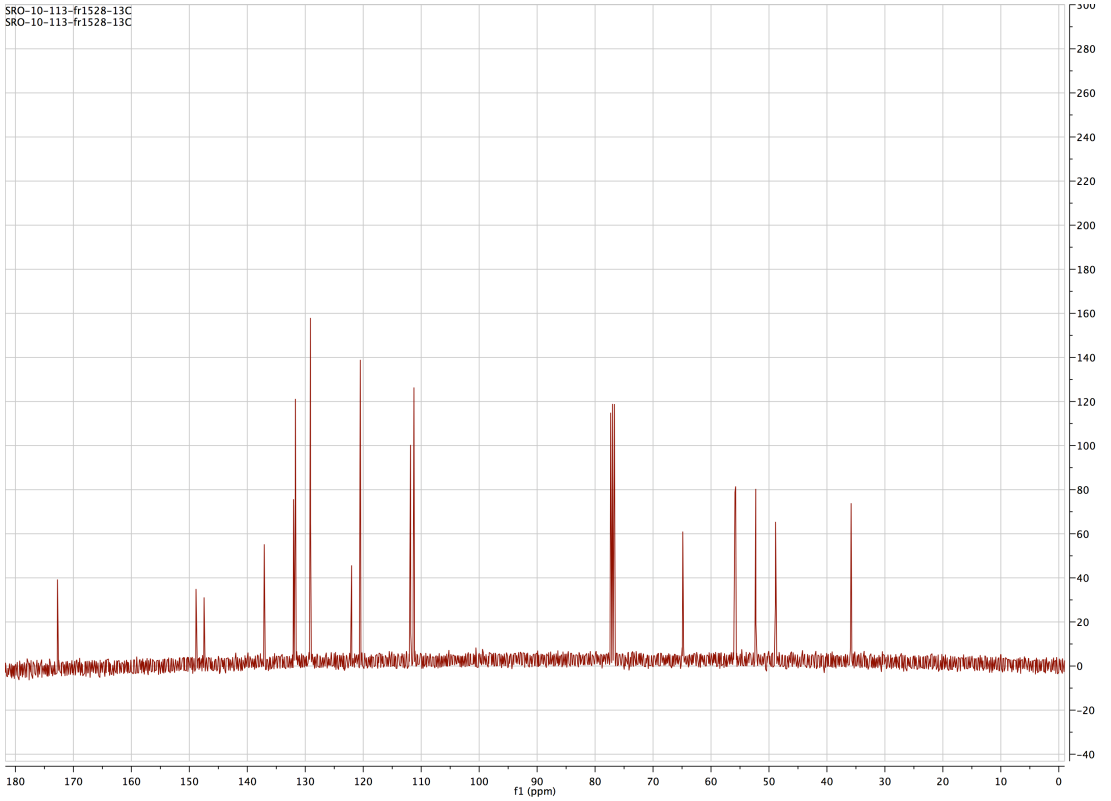

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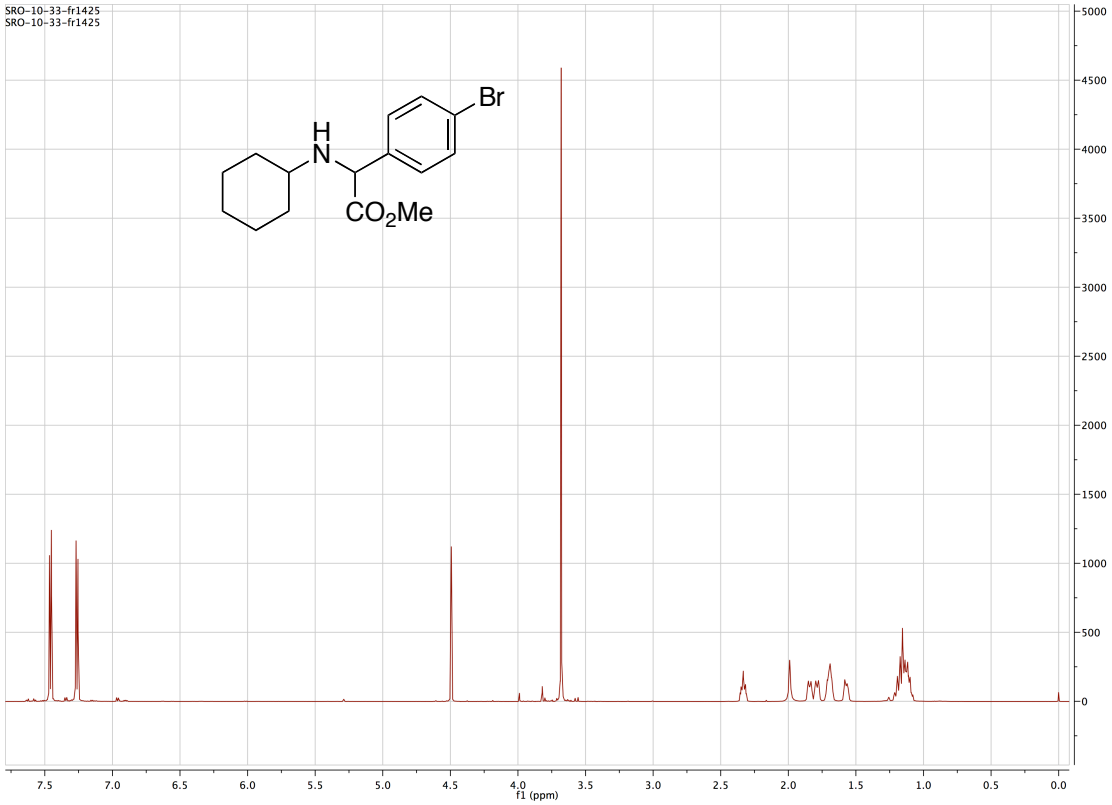

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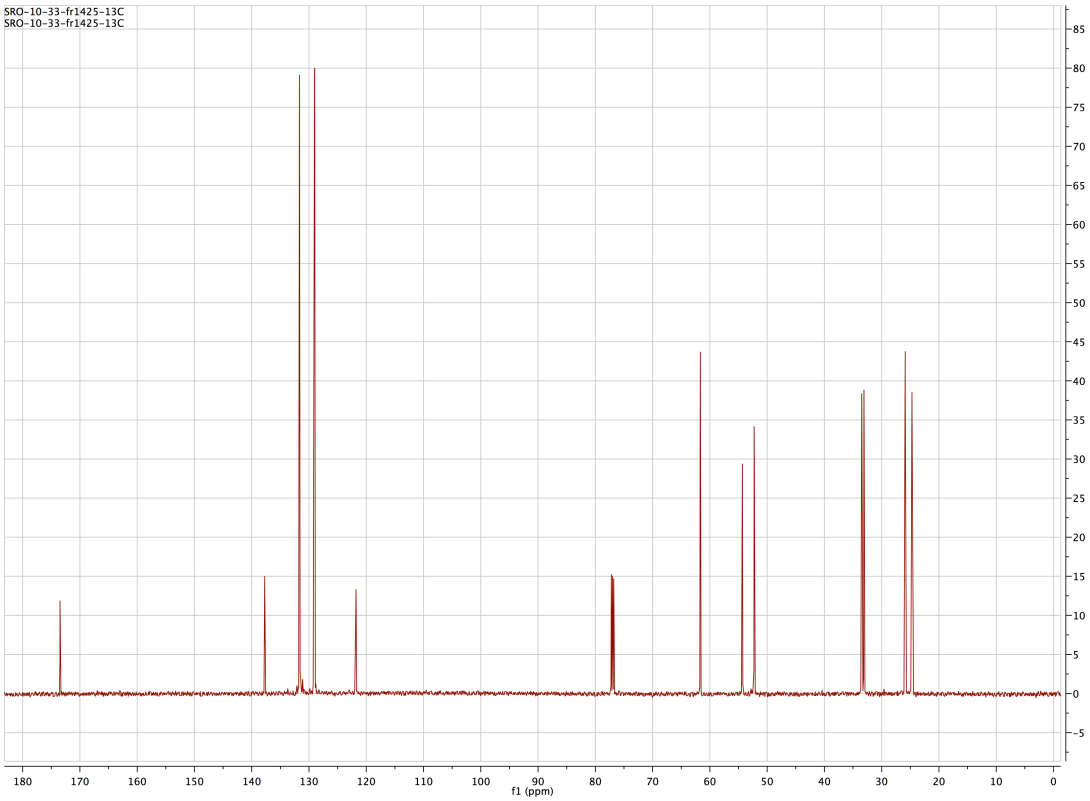

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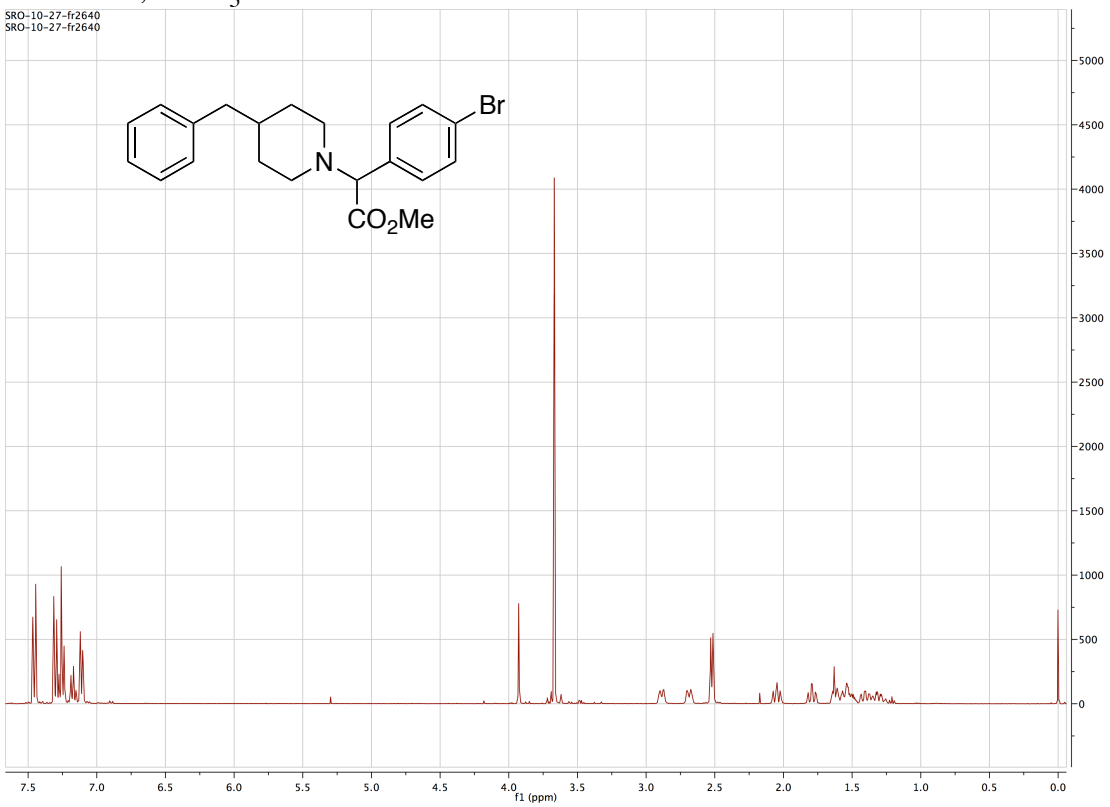

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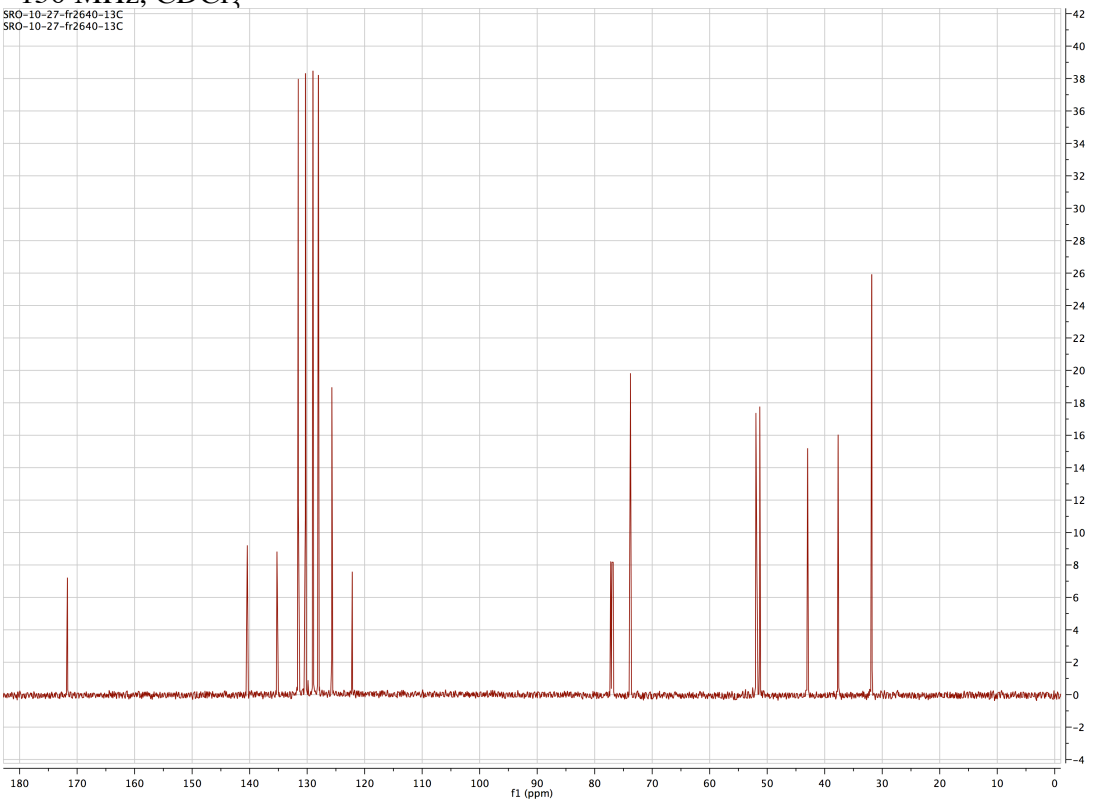

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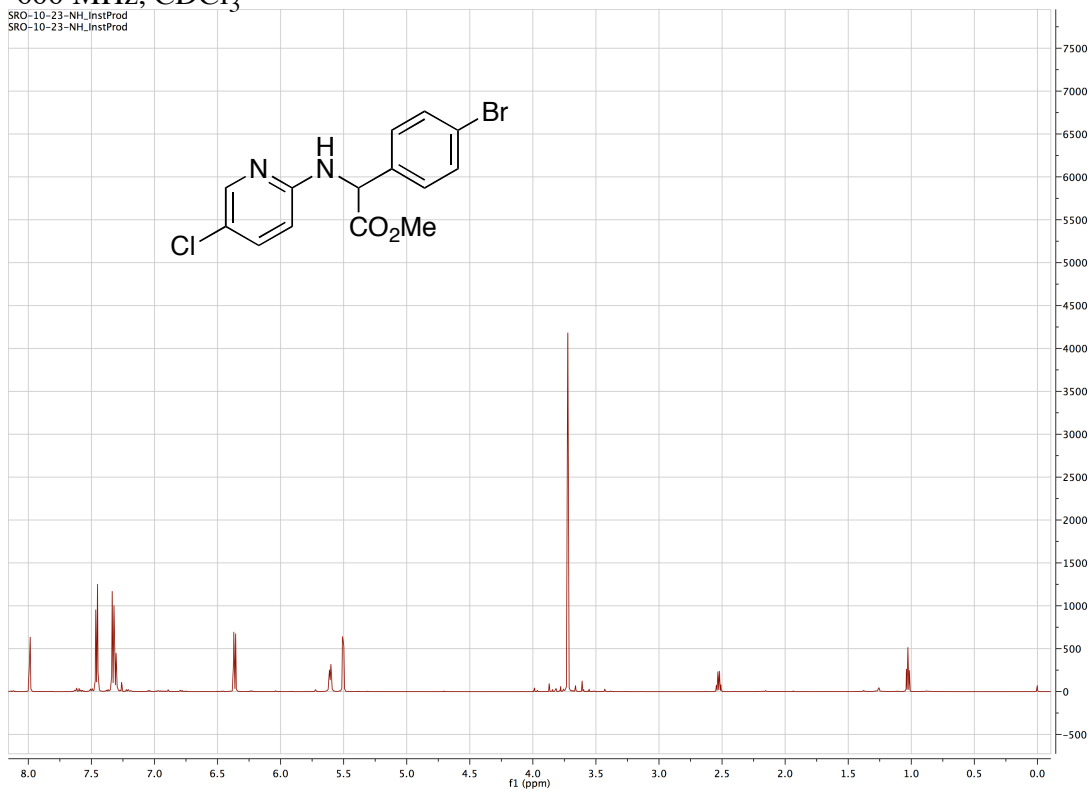

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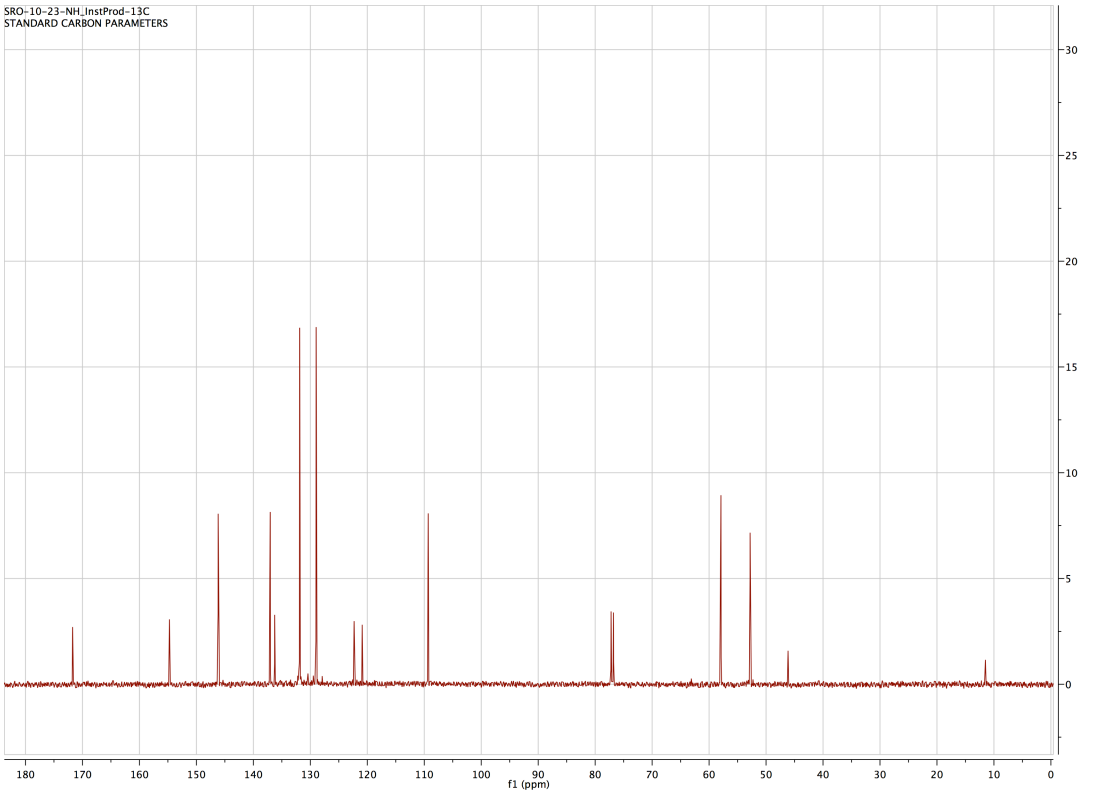

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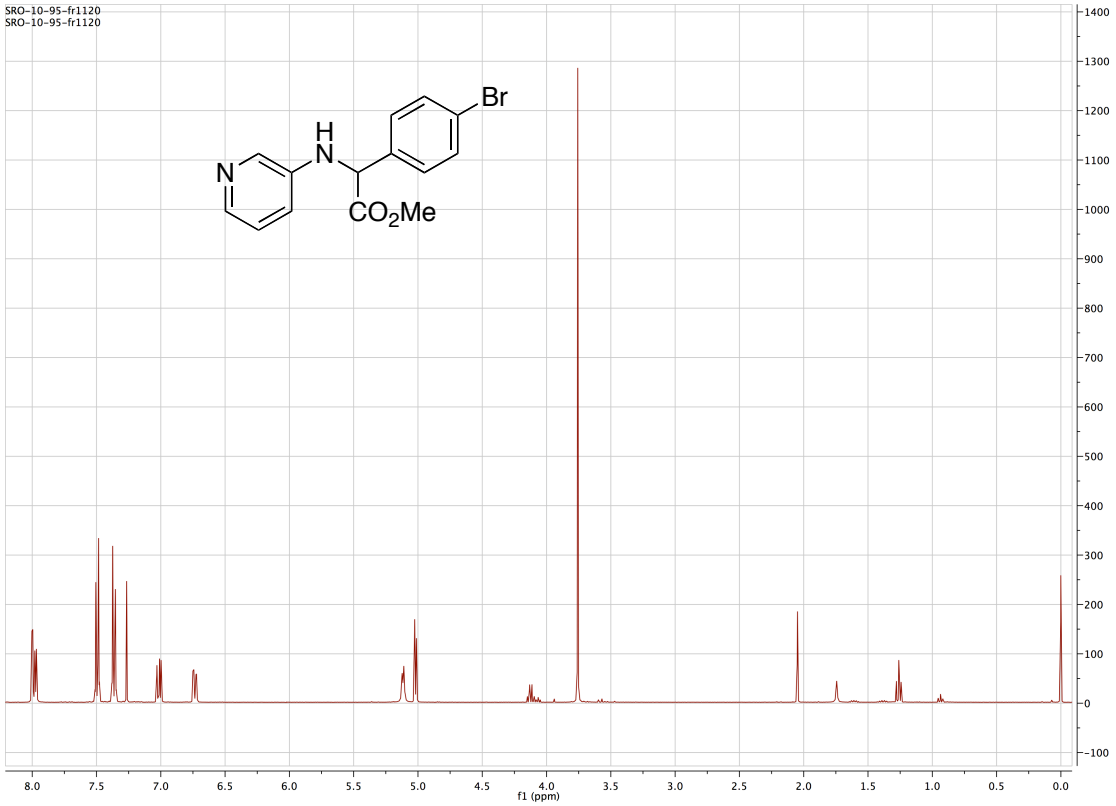

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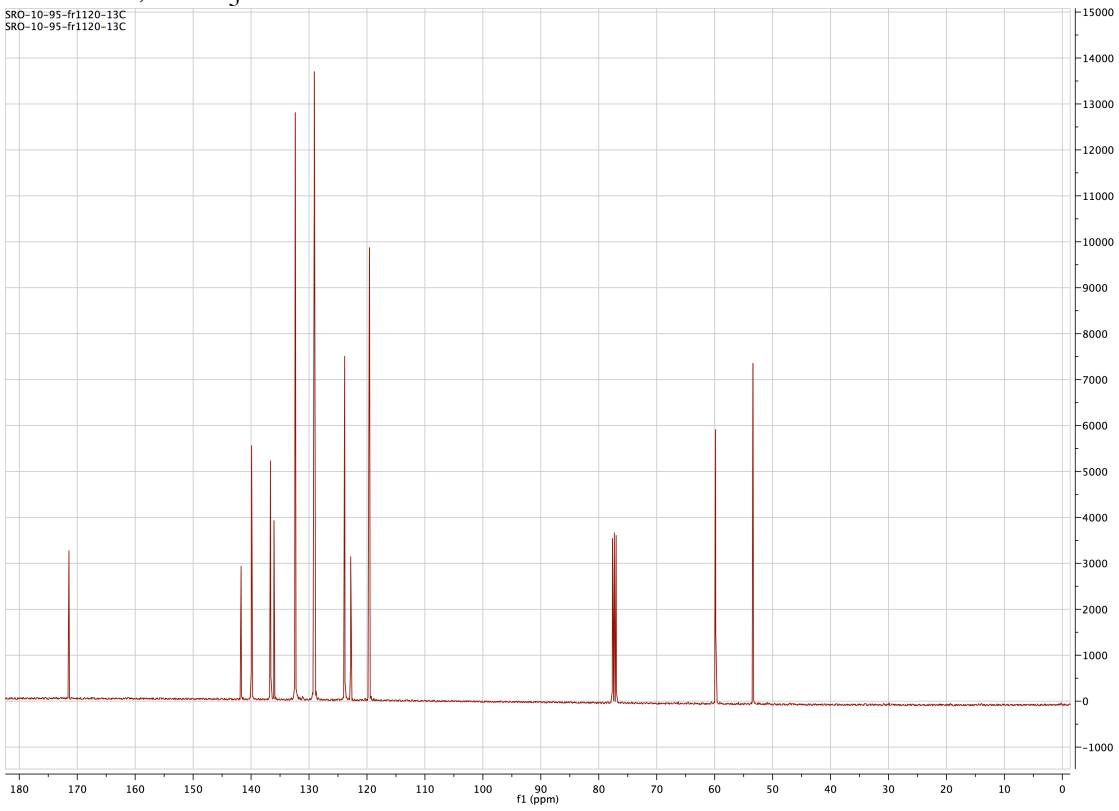

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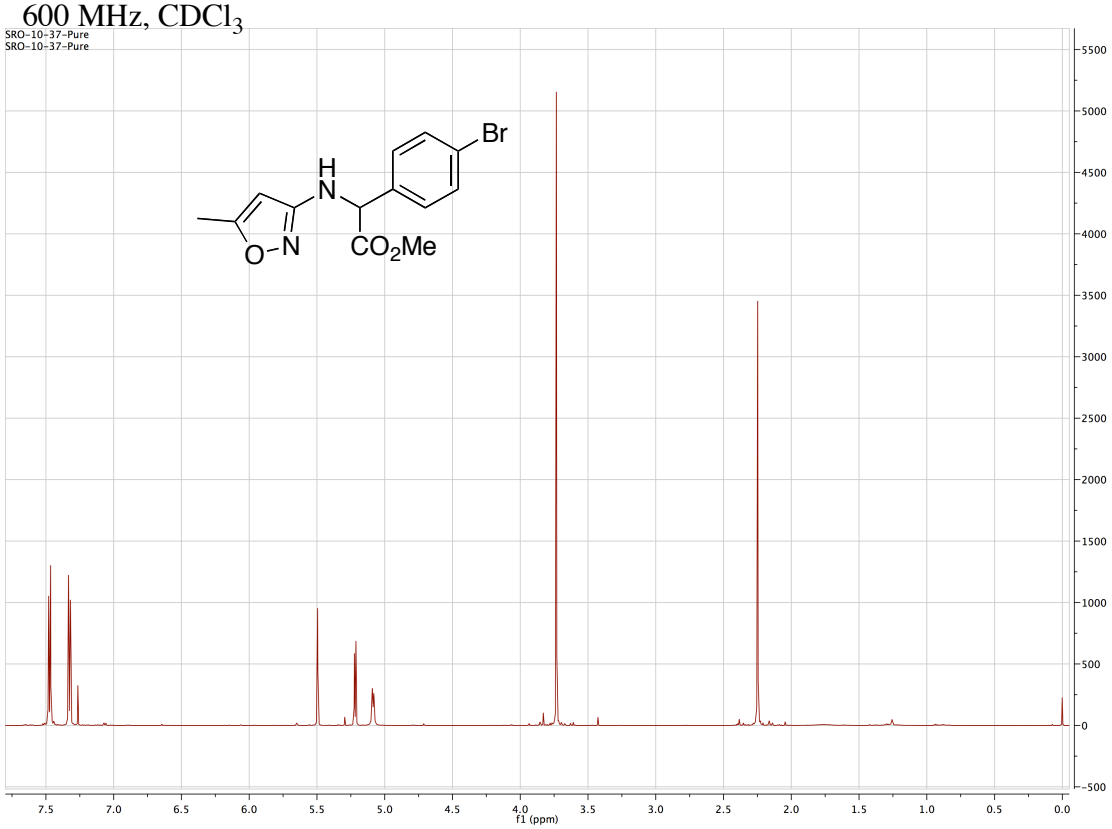

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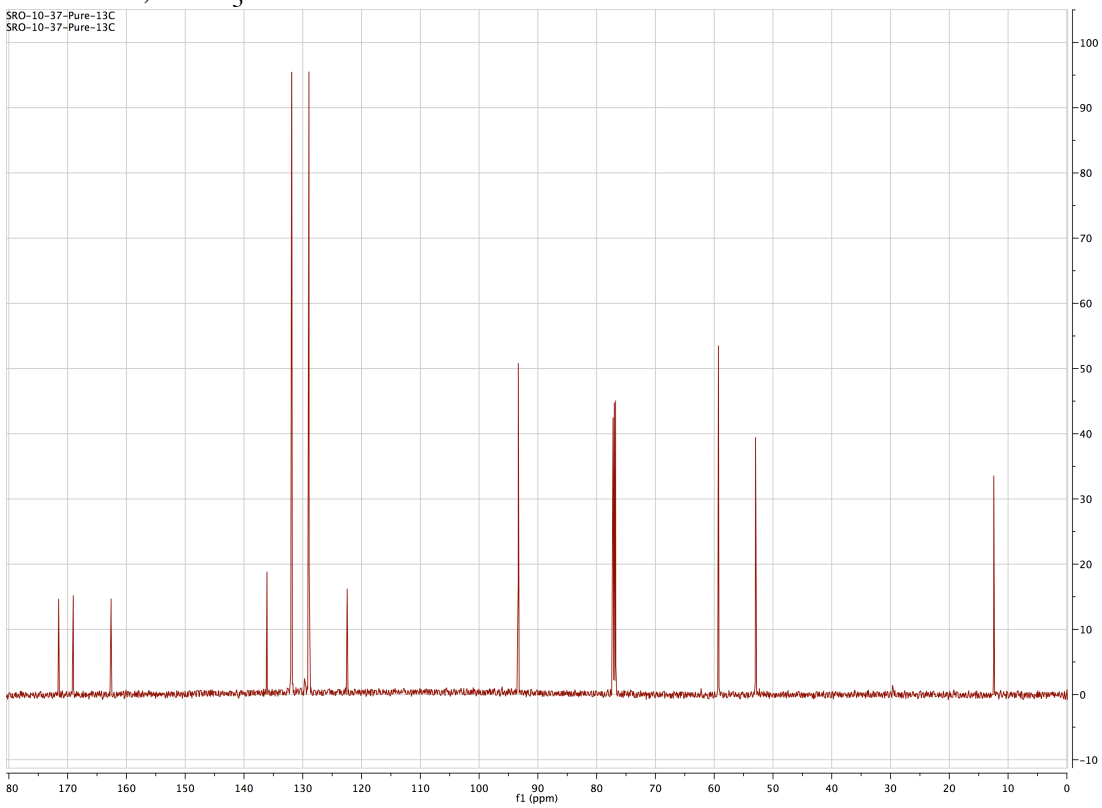

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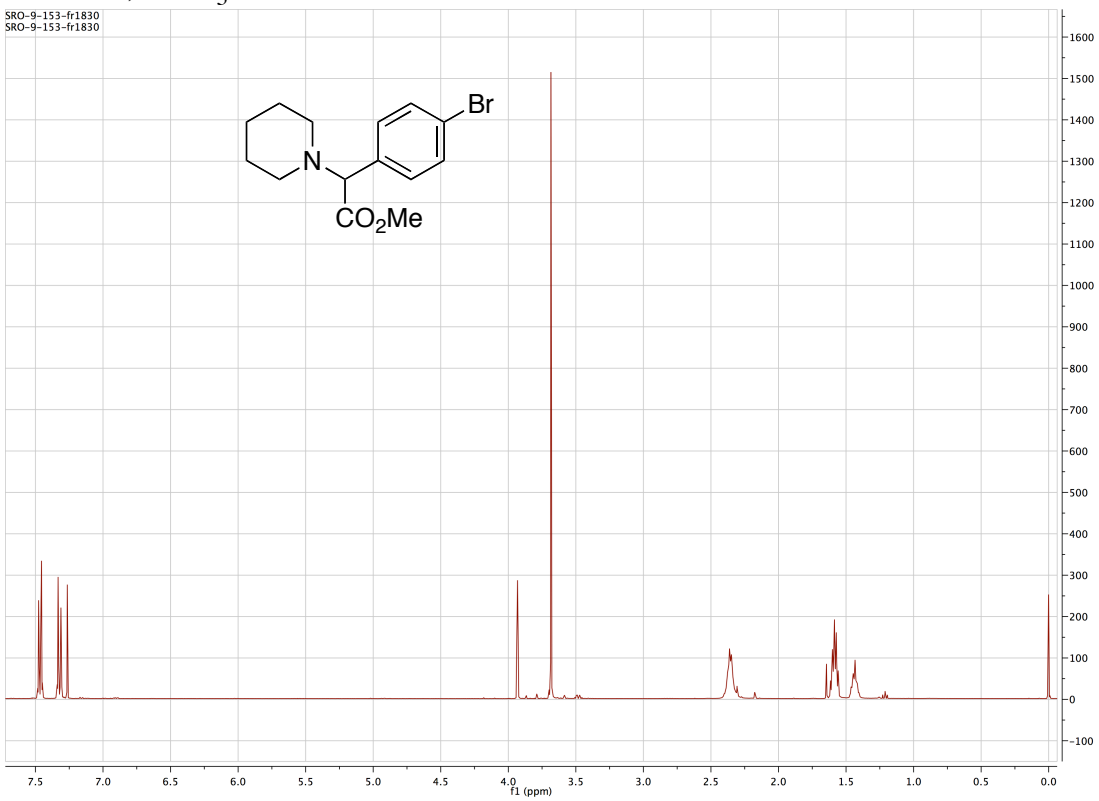
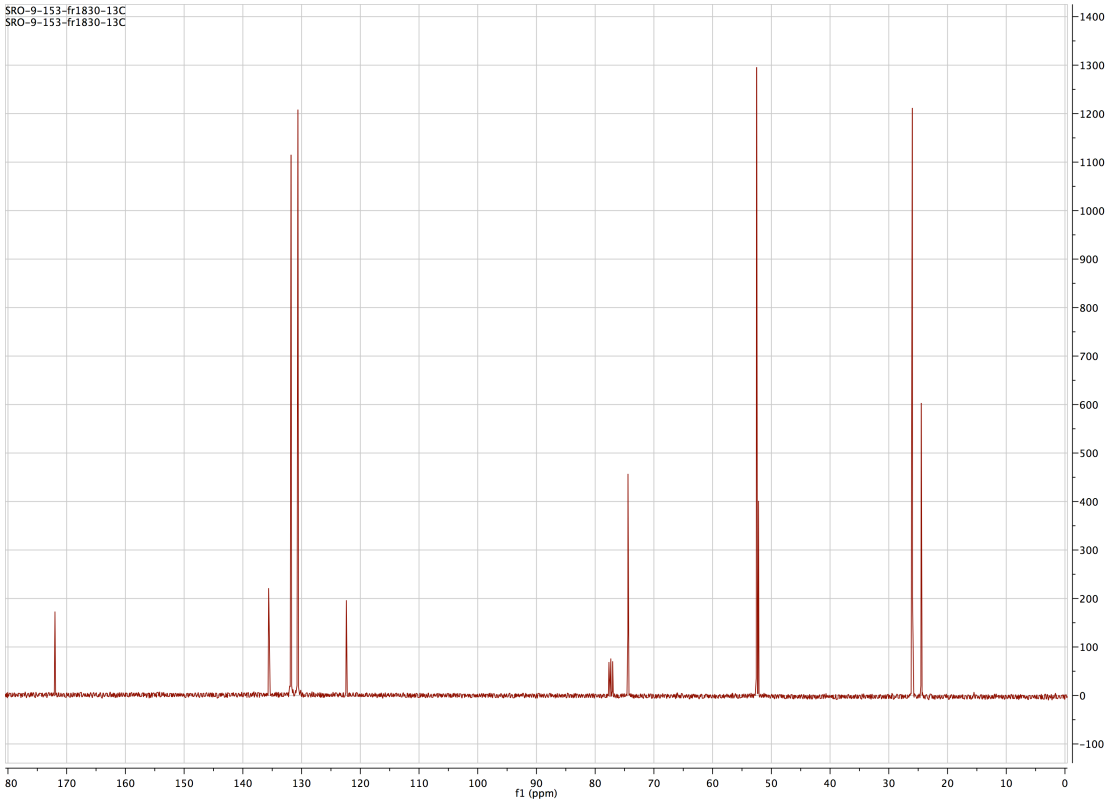


100 MHz, $CDCl_3$



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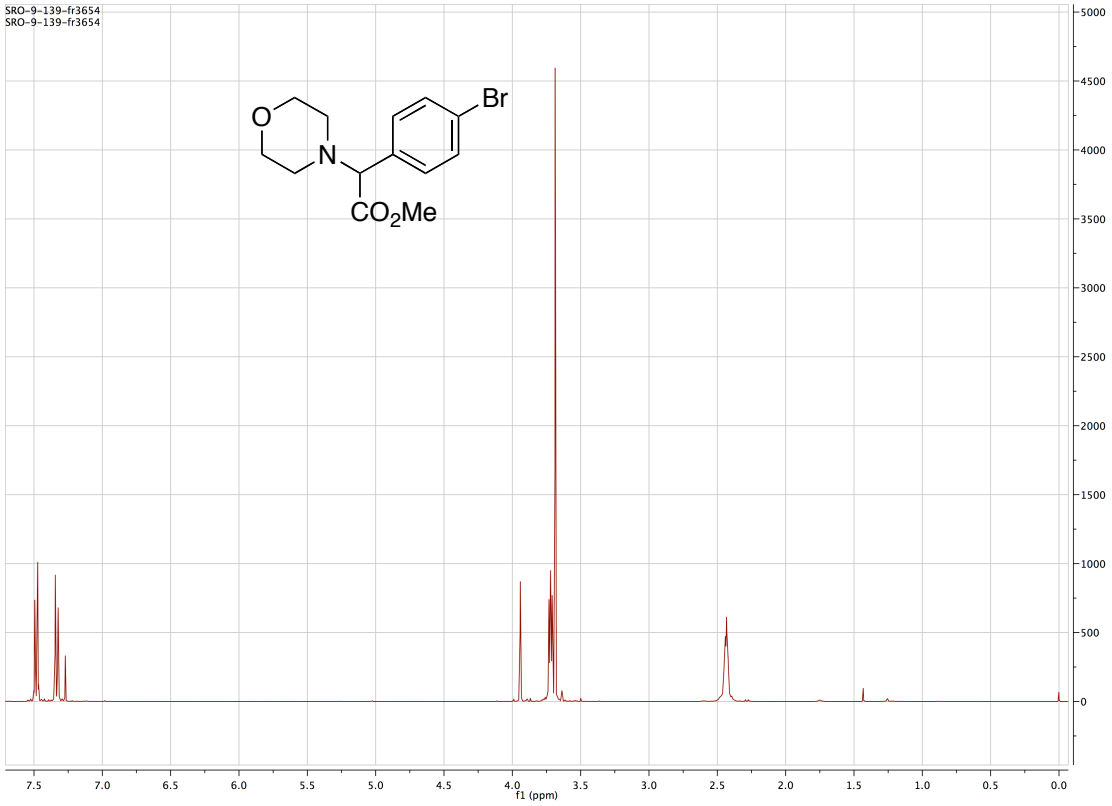

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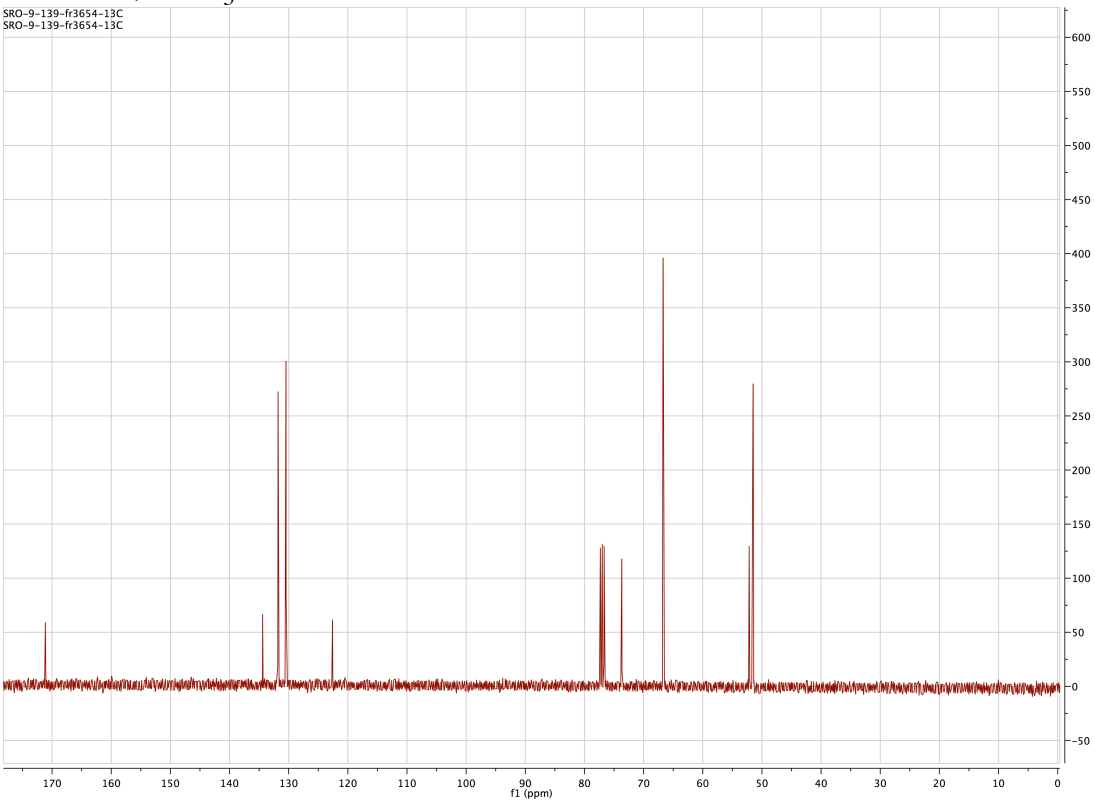

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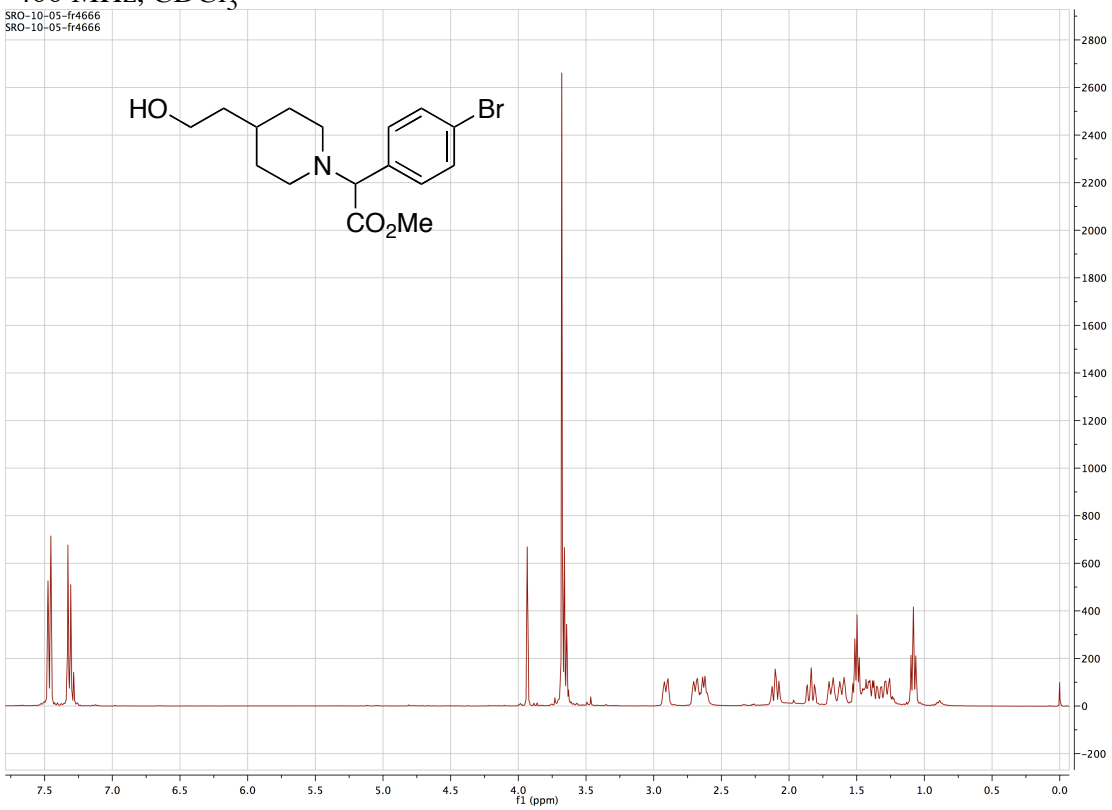

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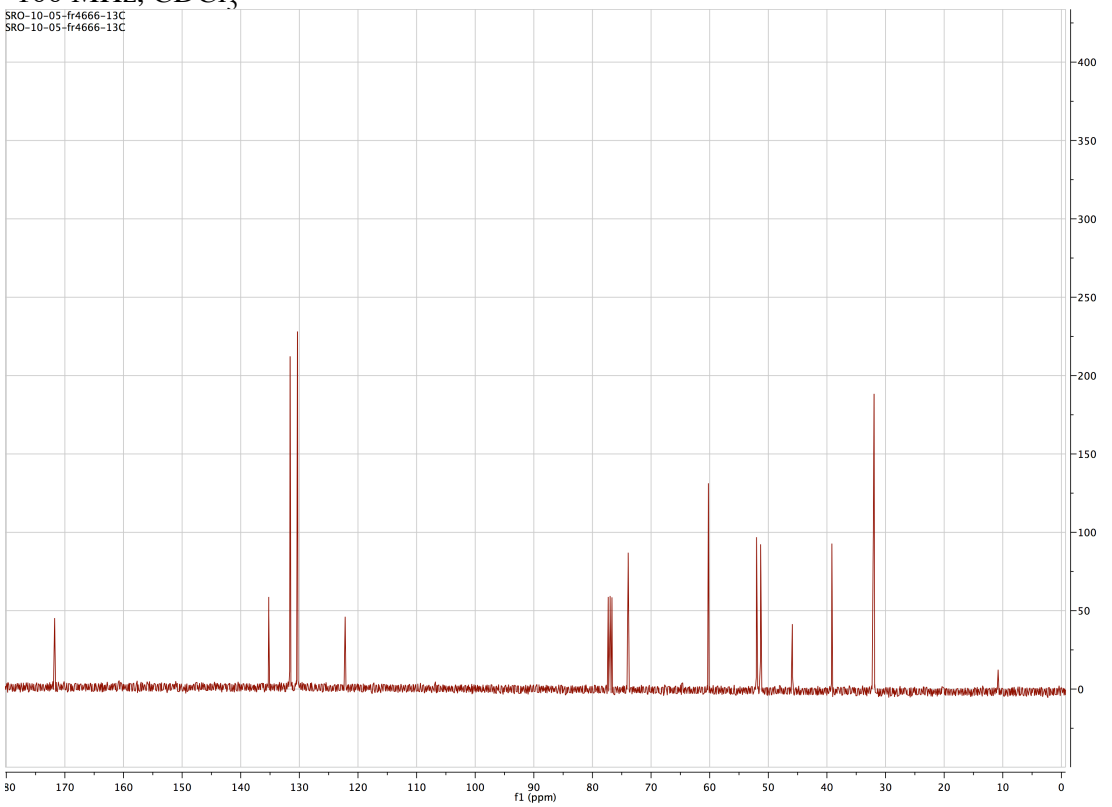

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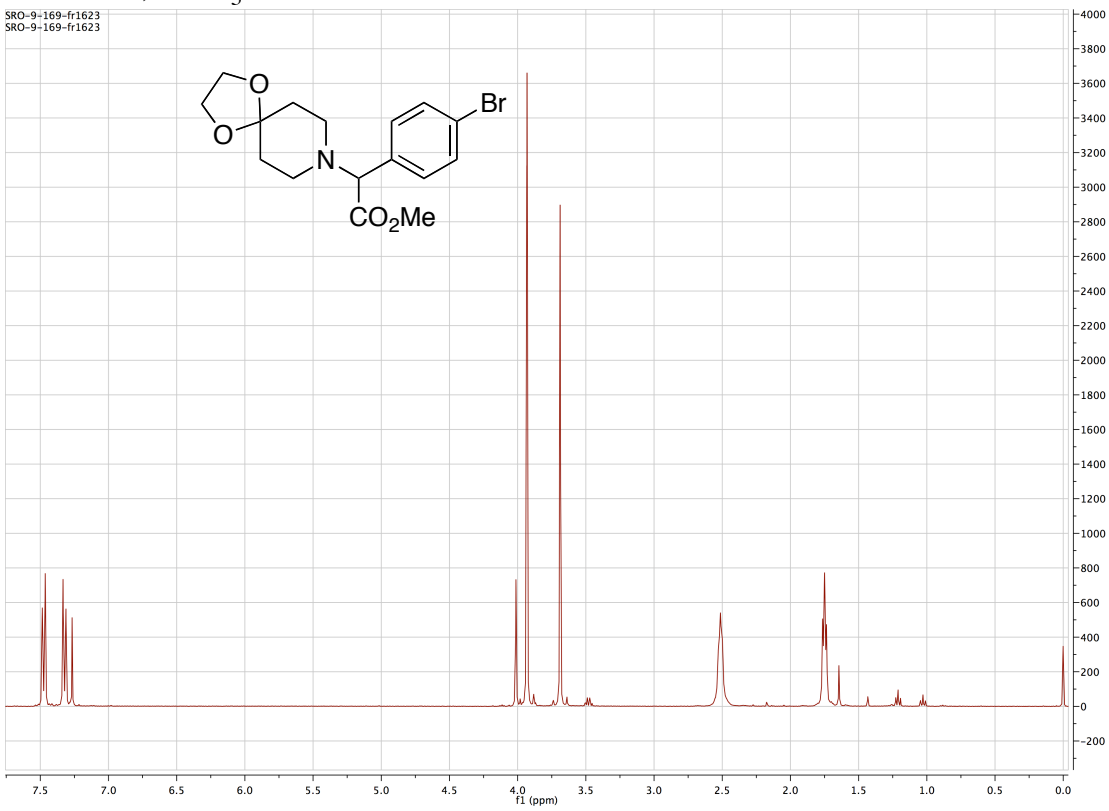

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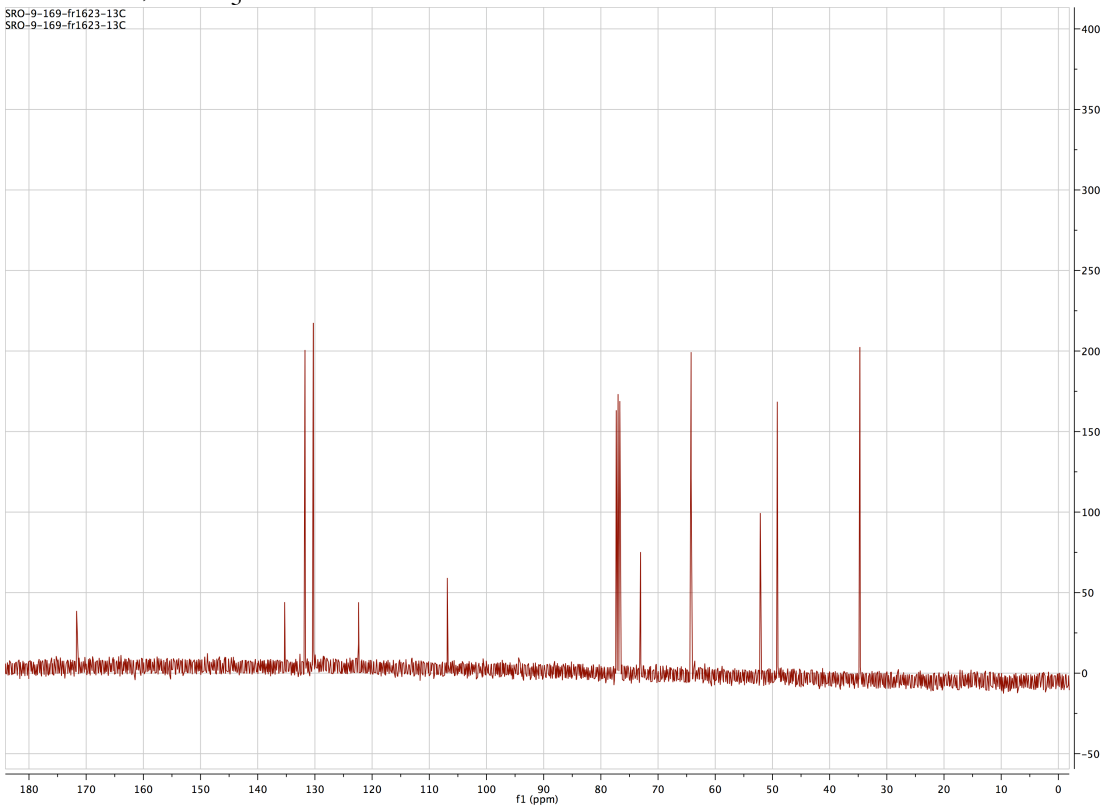

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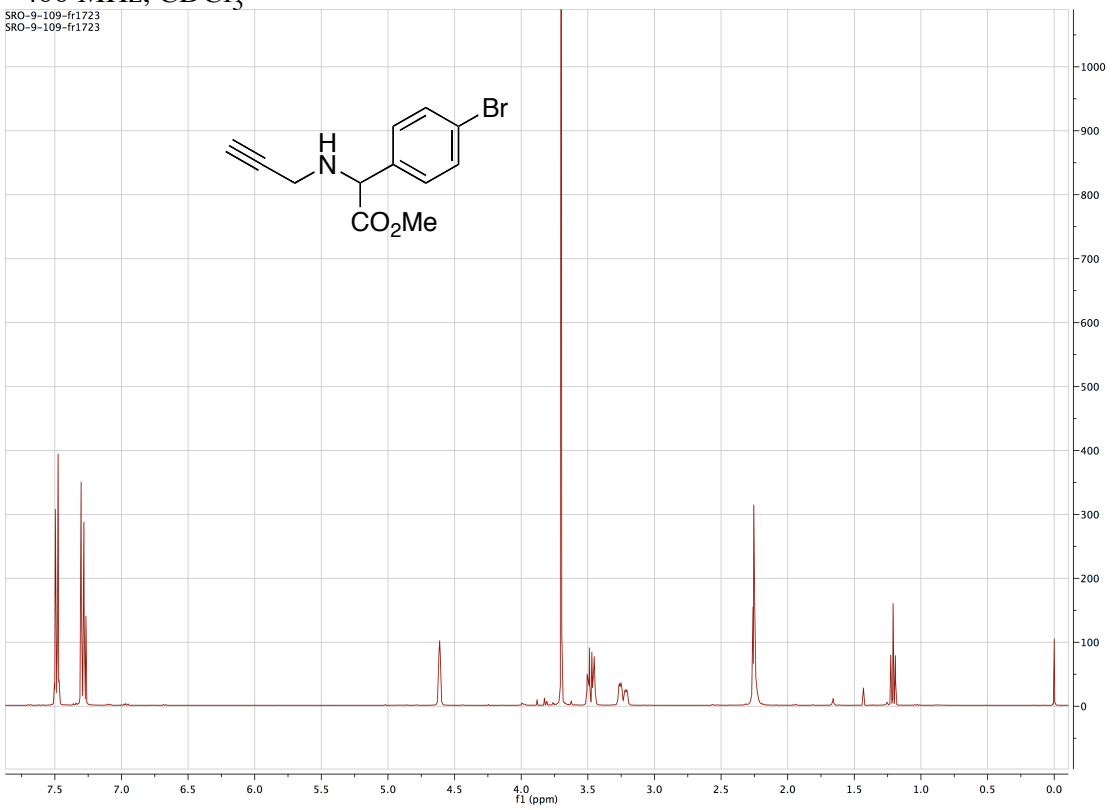

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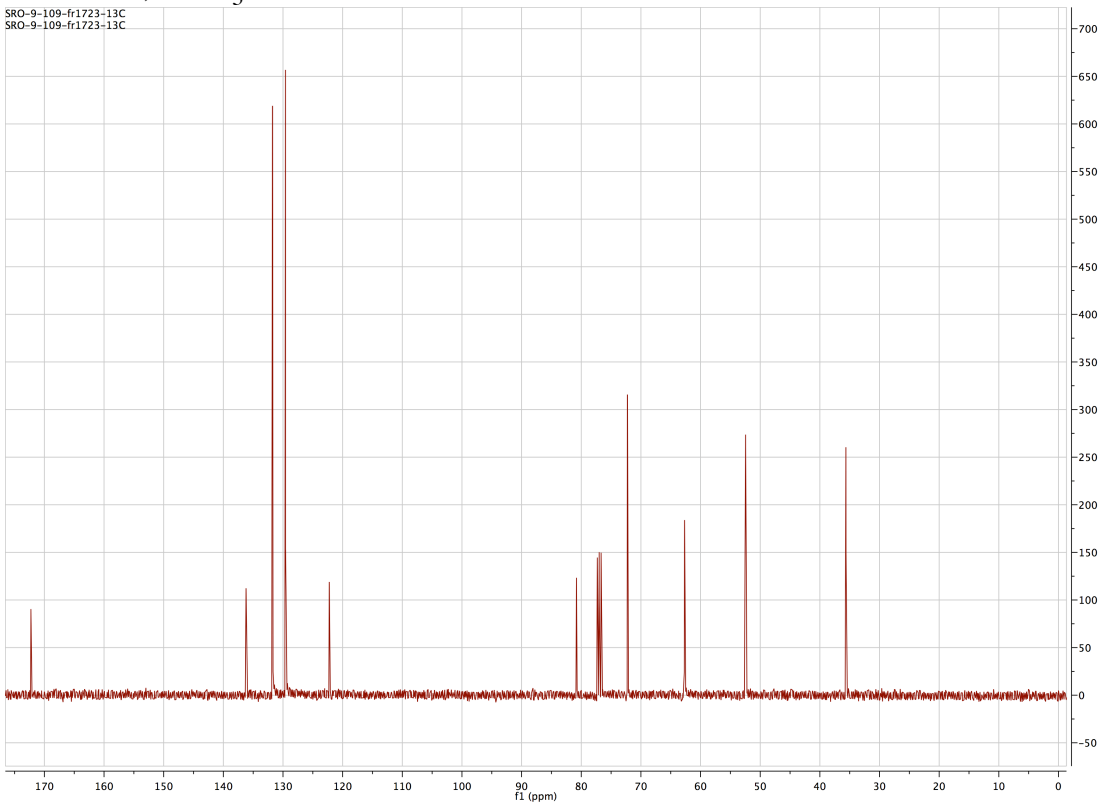

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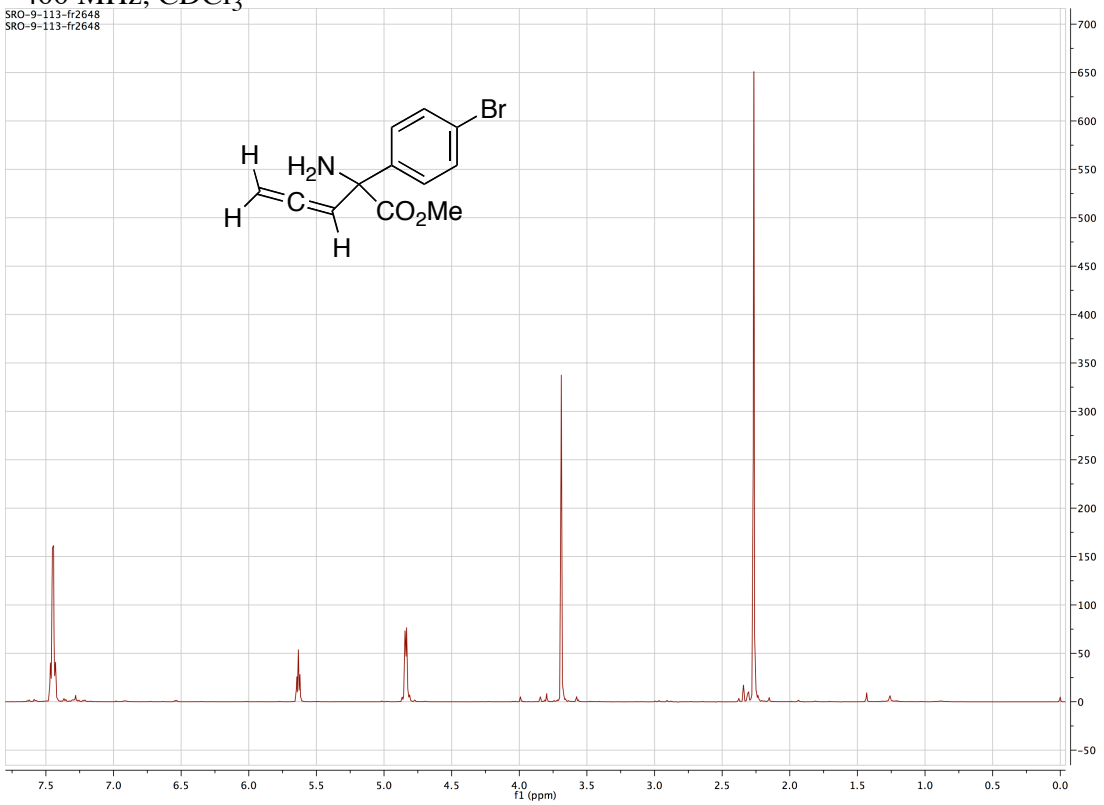
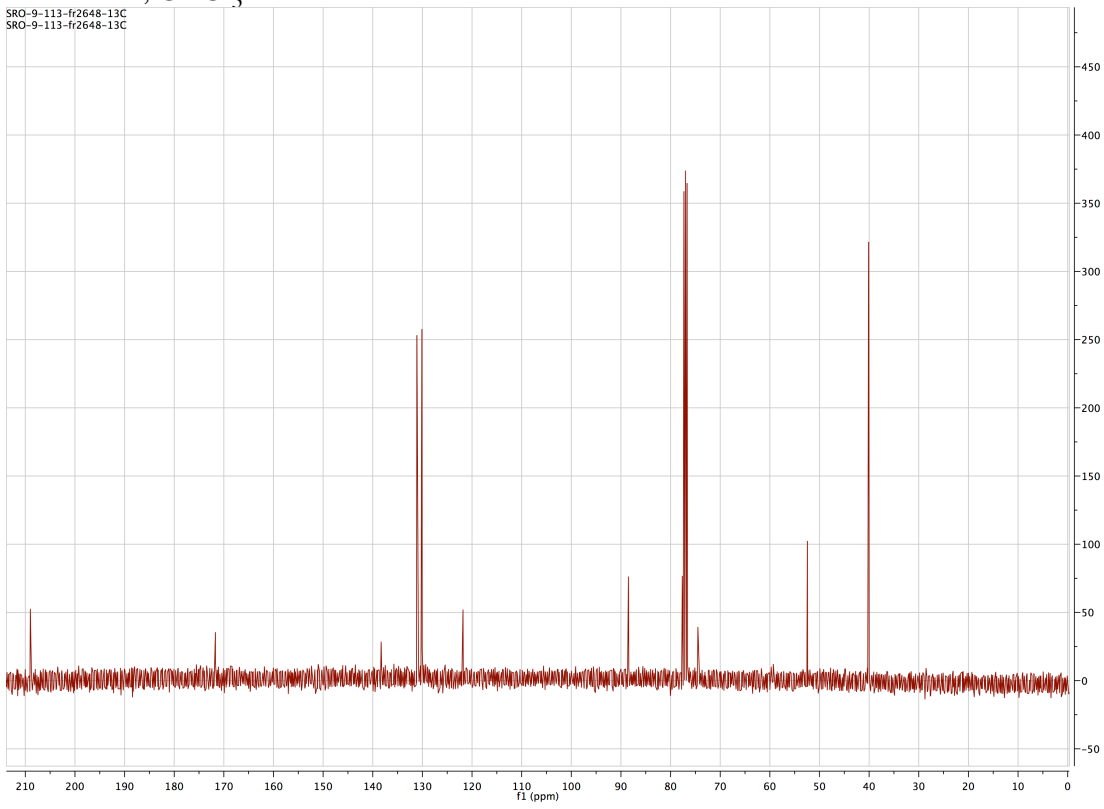
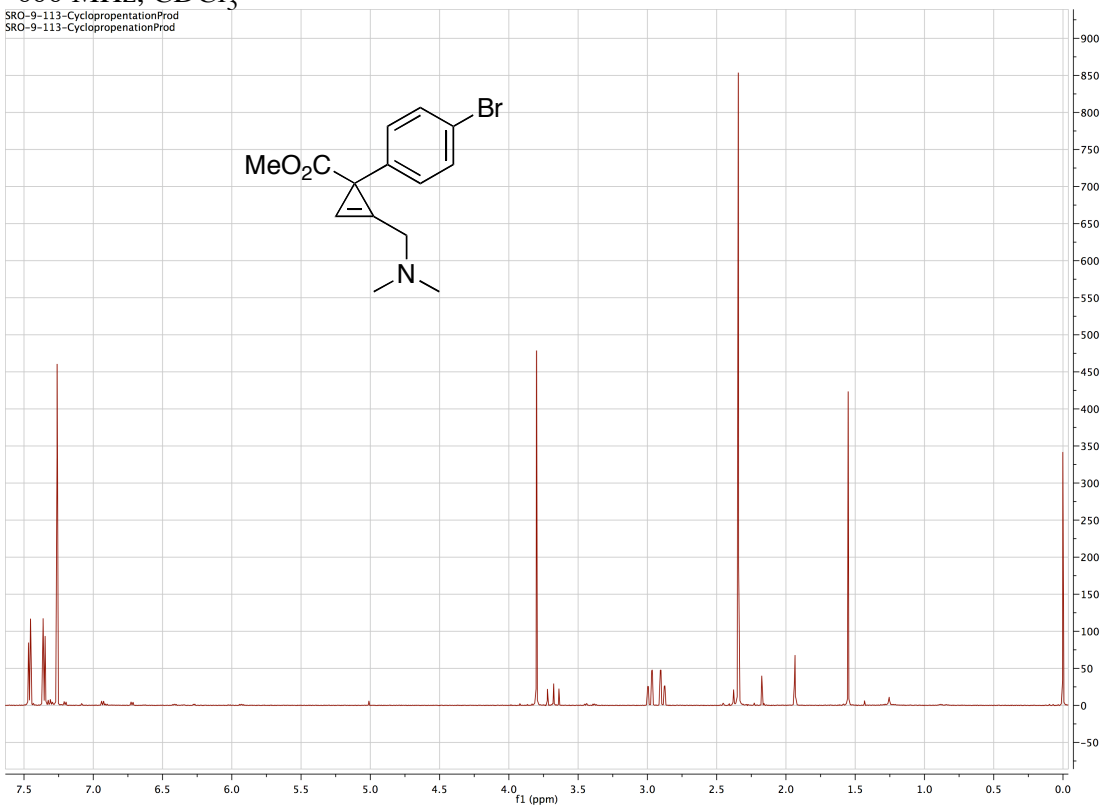


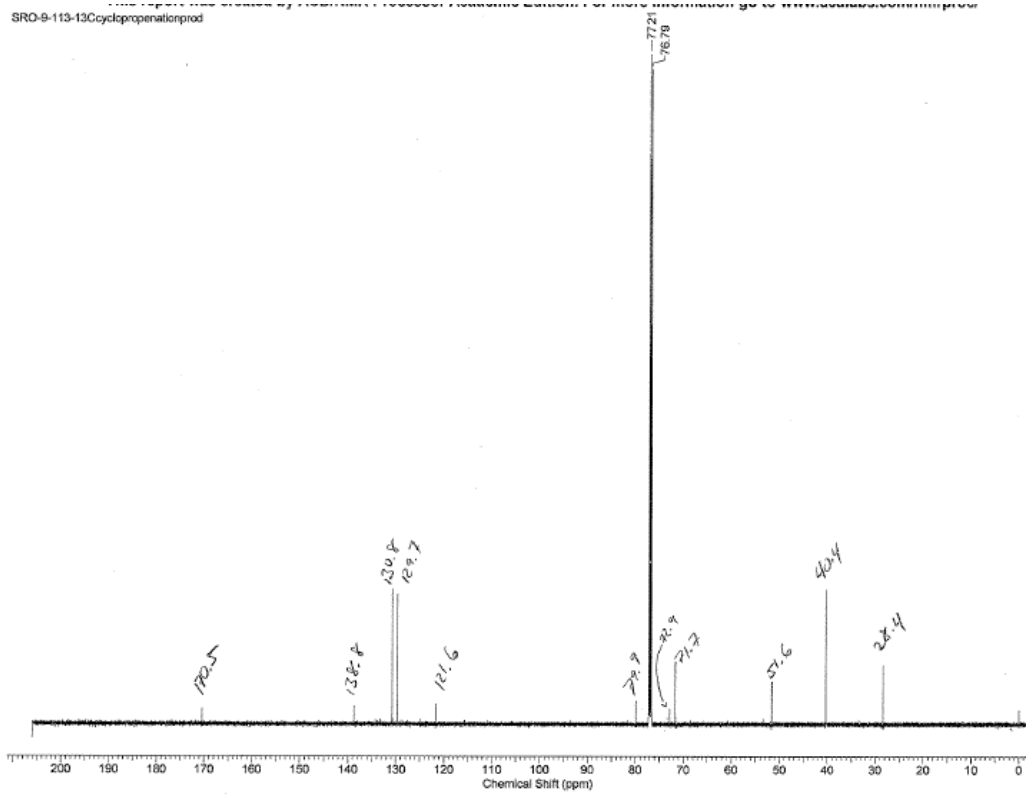
150 MHz, $CDCl_3$



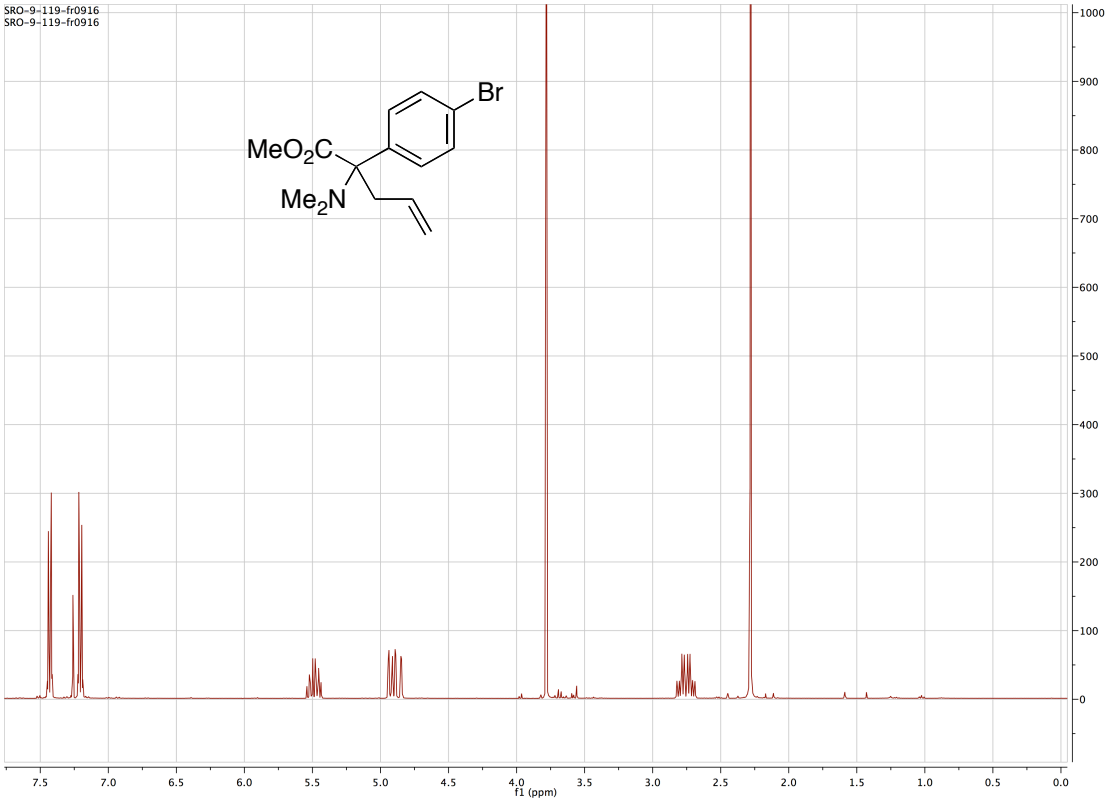
600 MHz, $CDCl_3$



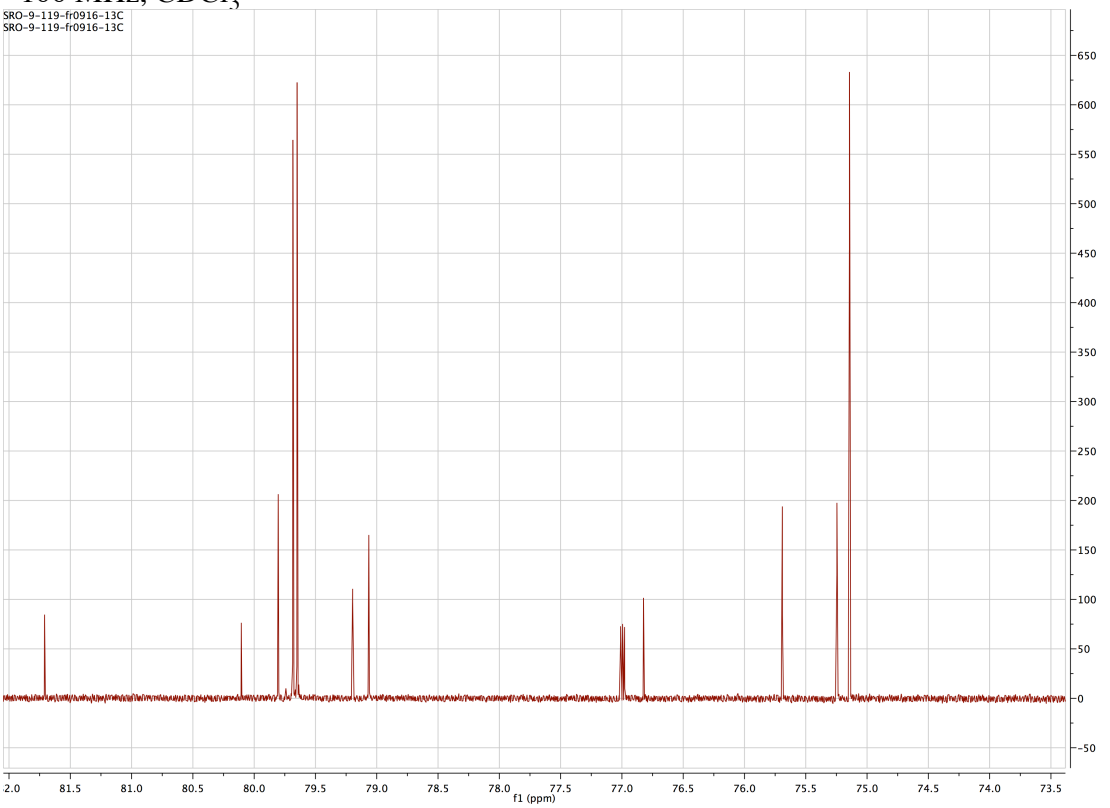
150 MHz, $CDCl_3$



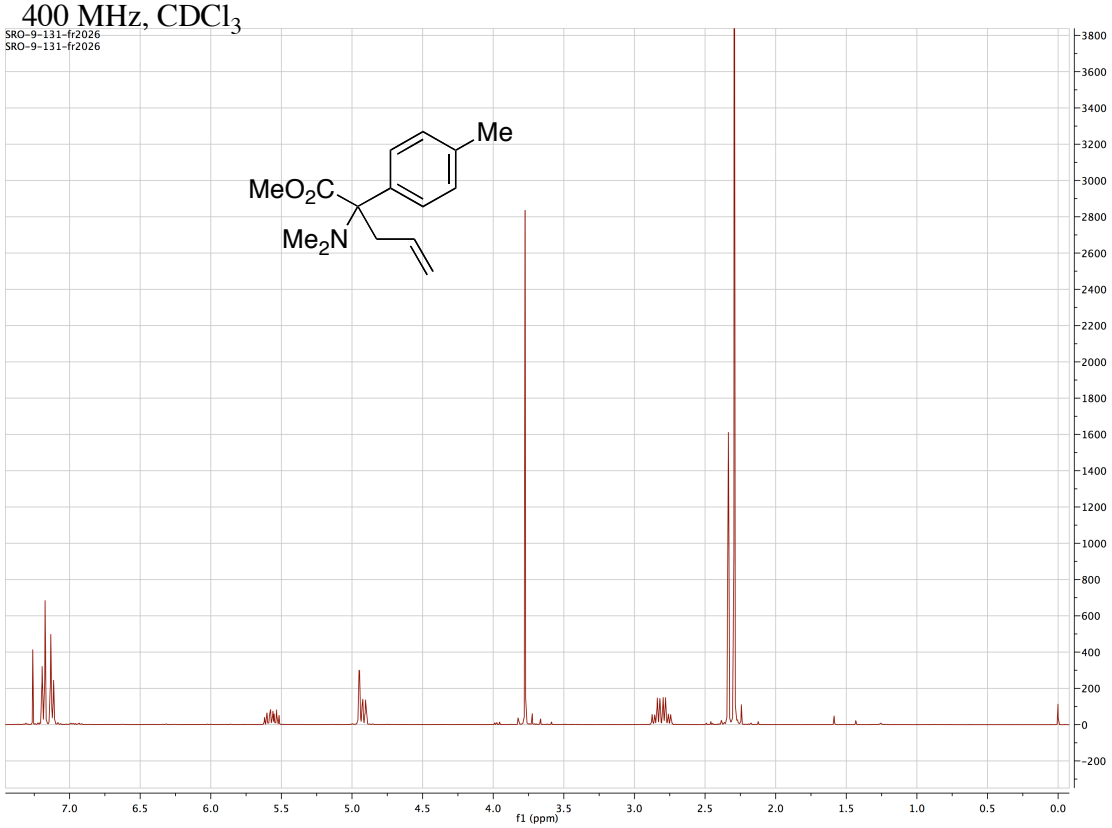
400 MHz, $CDCl_3$



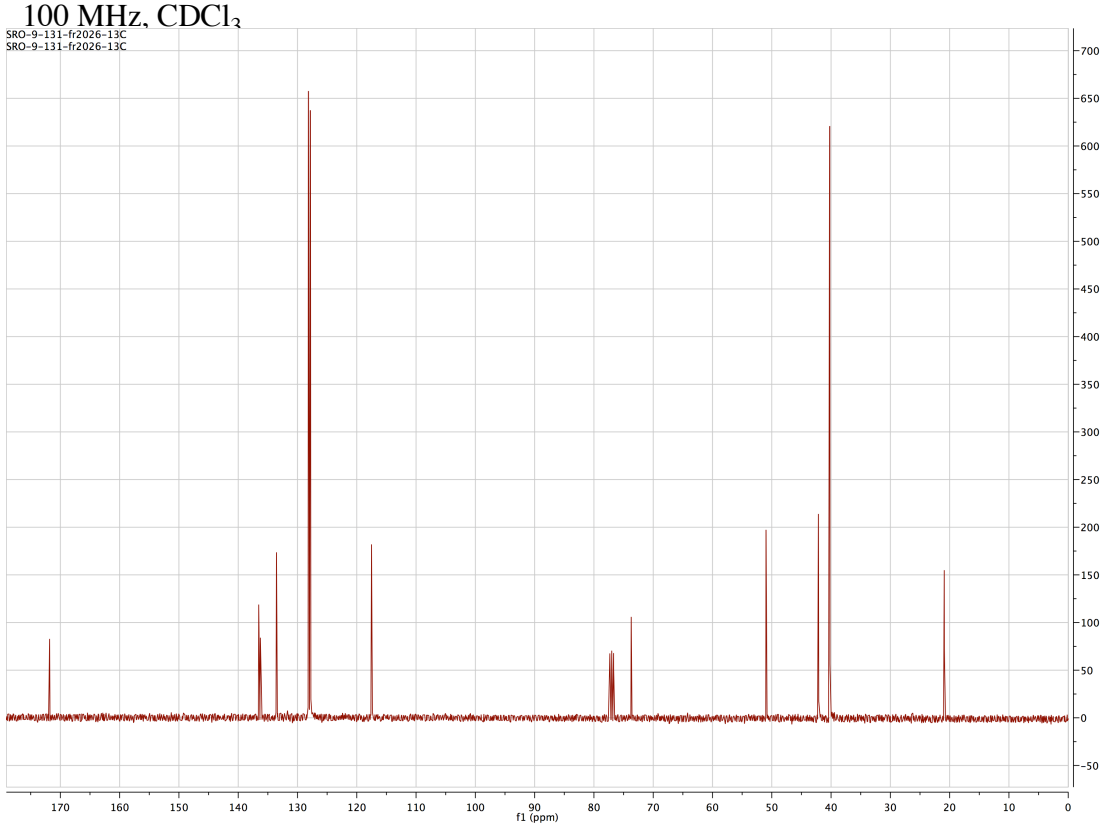
100 MHz, $CDCl_3$



400 MHz, $CDCl_3$



100 MHz, $CDCl_3$



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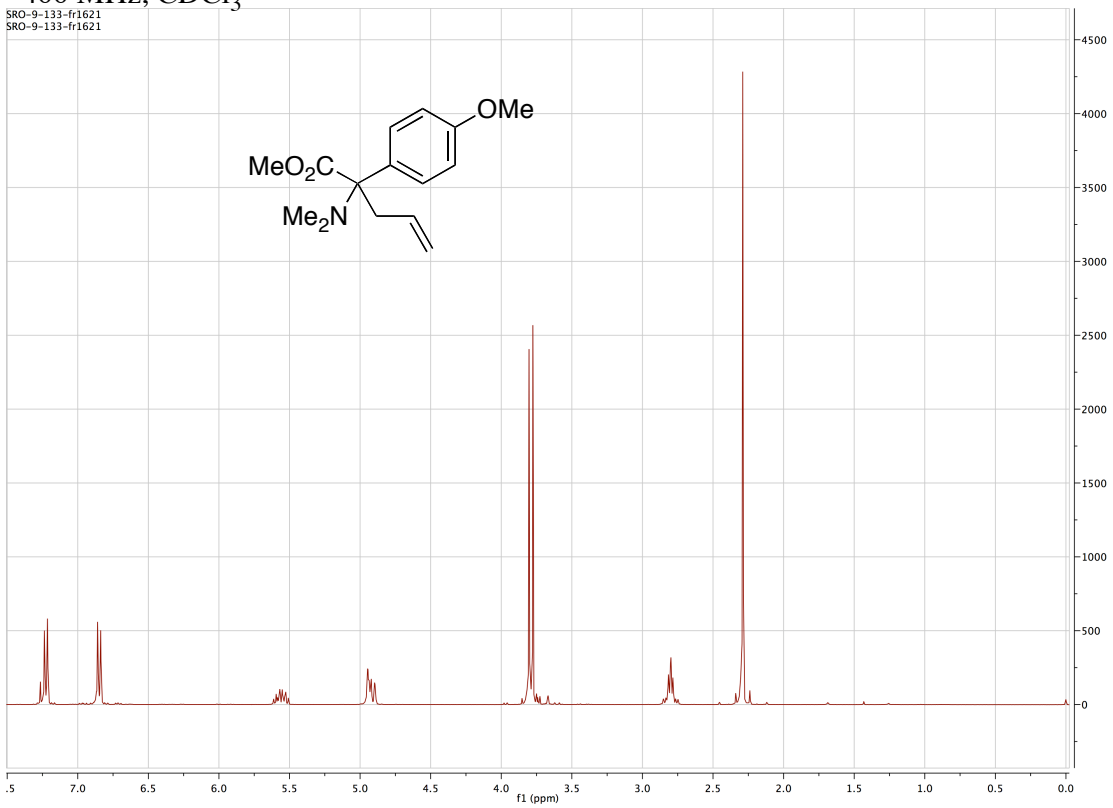
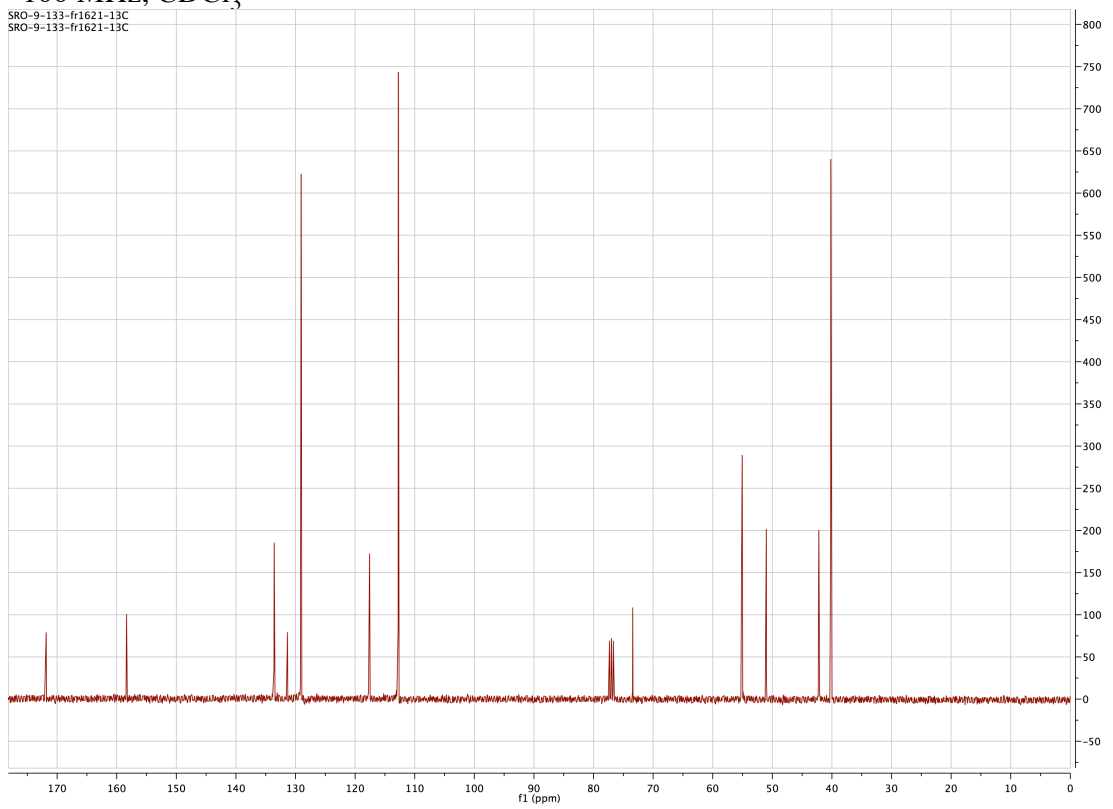
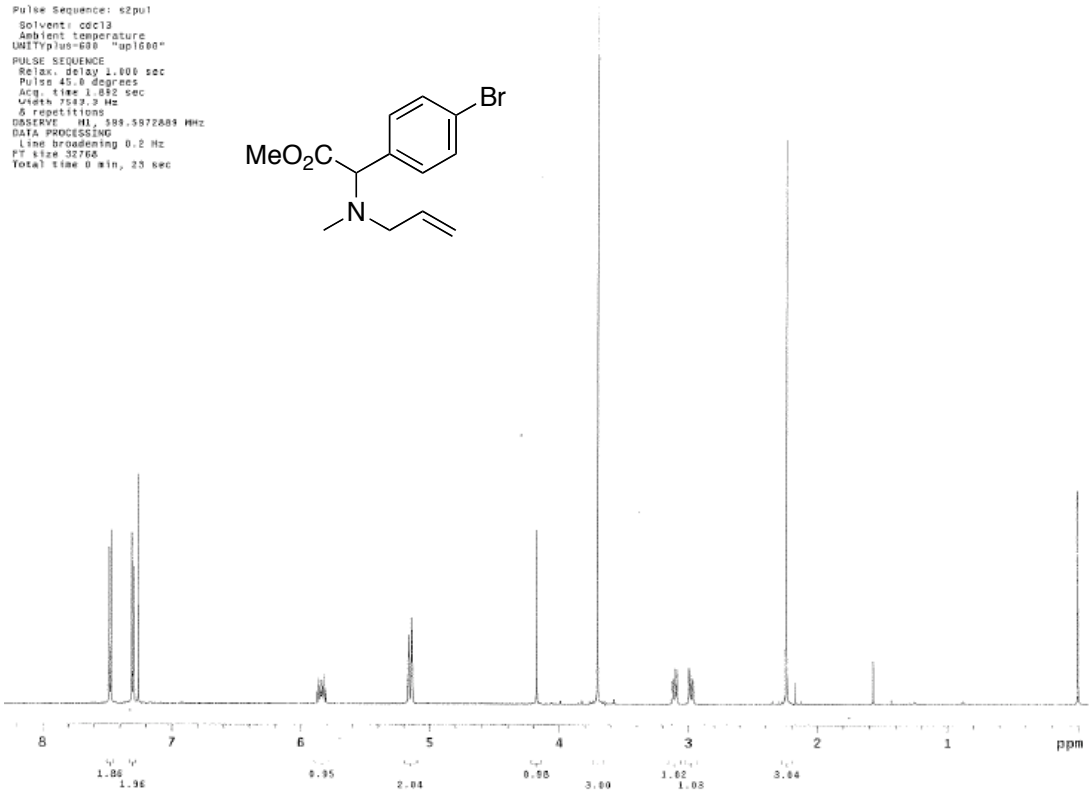


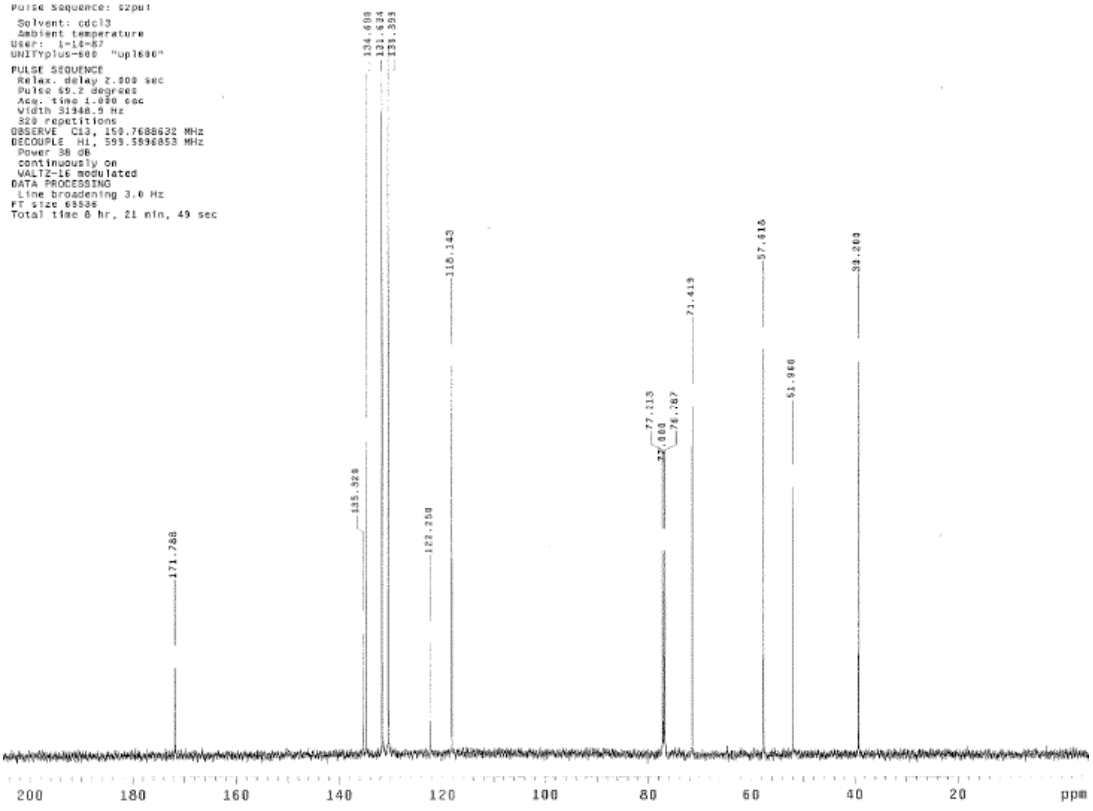
100 MHz, $CDCl_3$



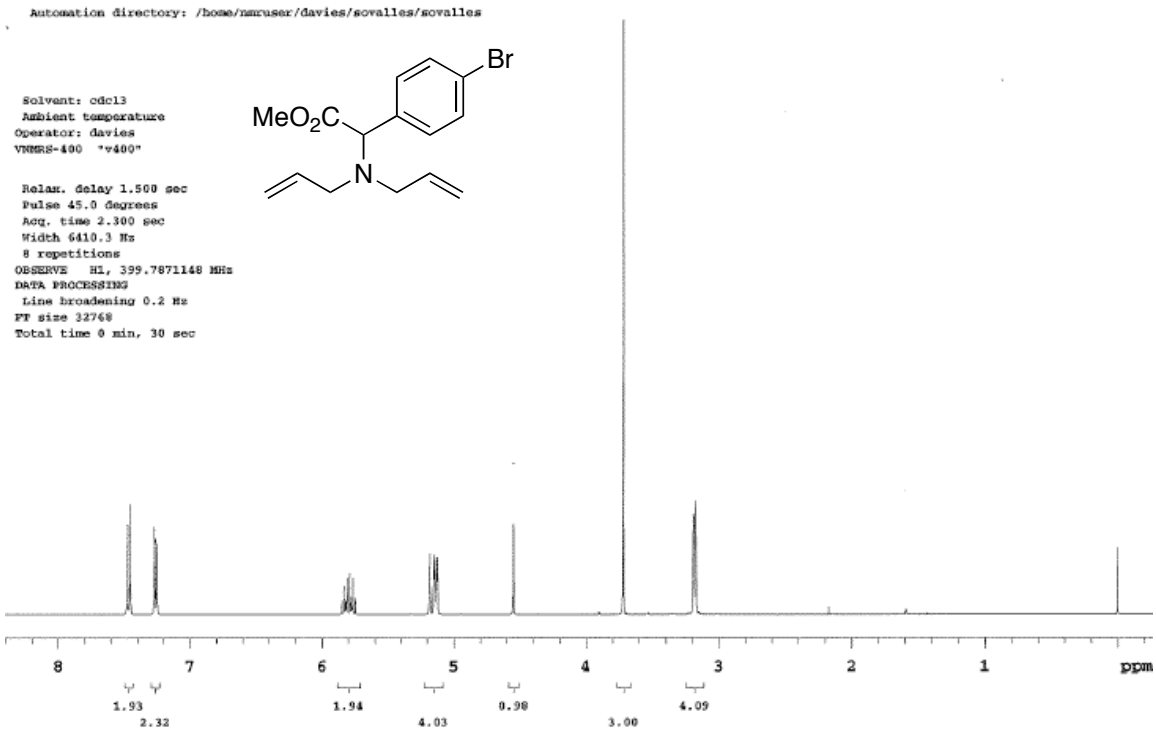
600 MHz, $CDCl_3$



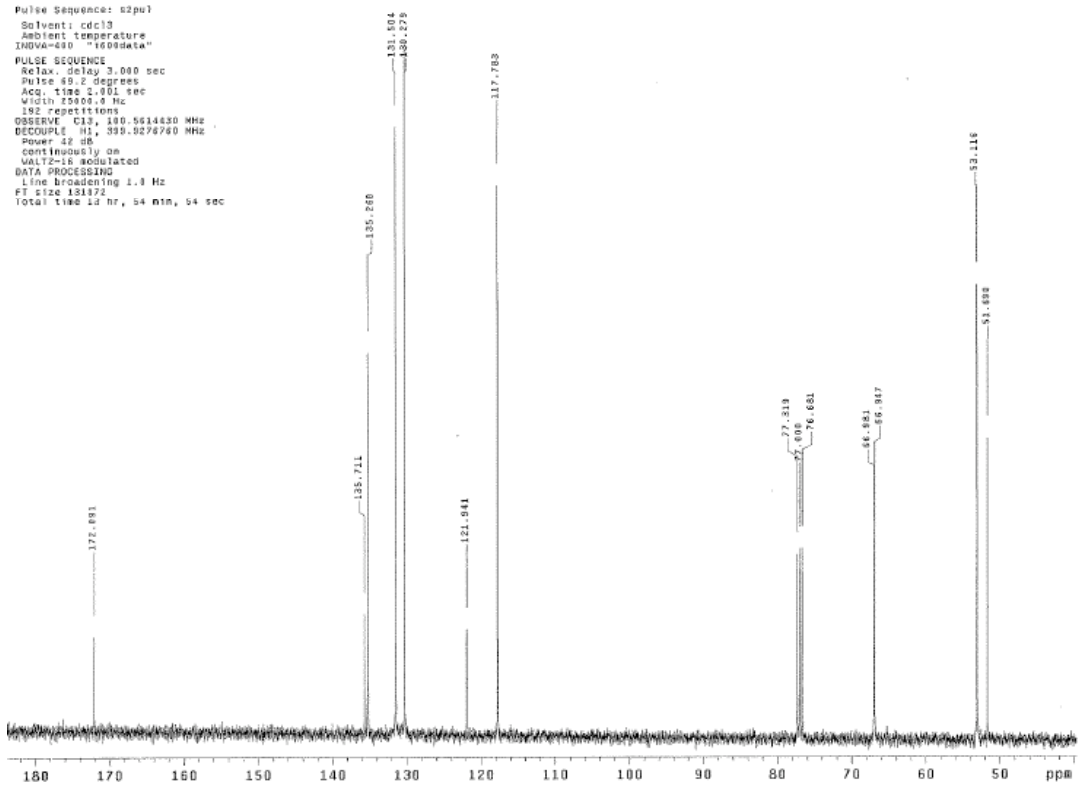
150 MHz, $CDCl_3$



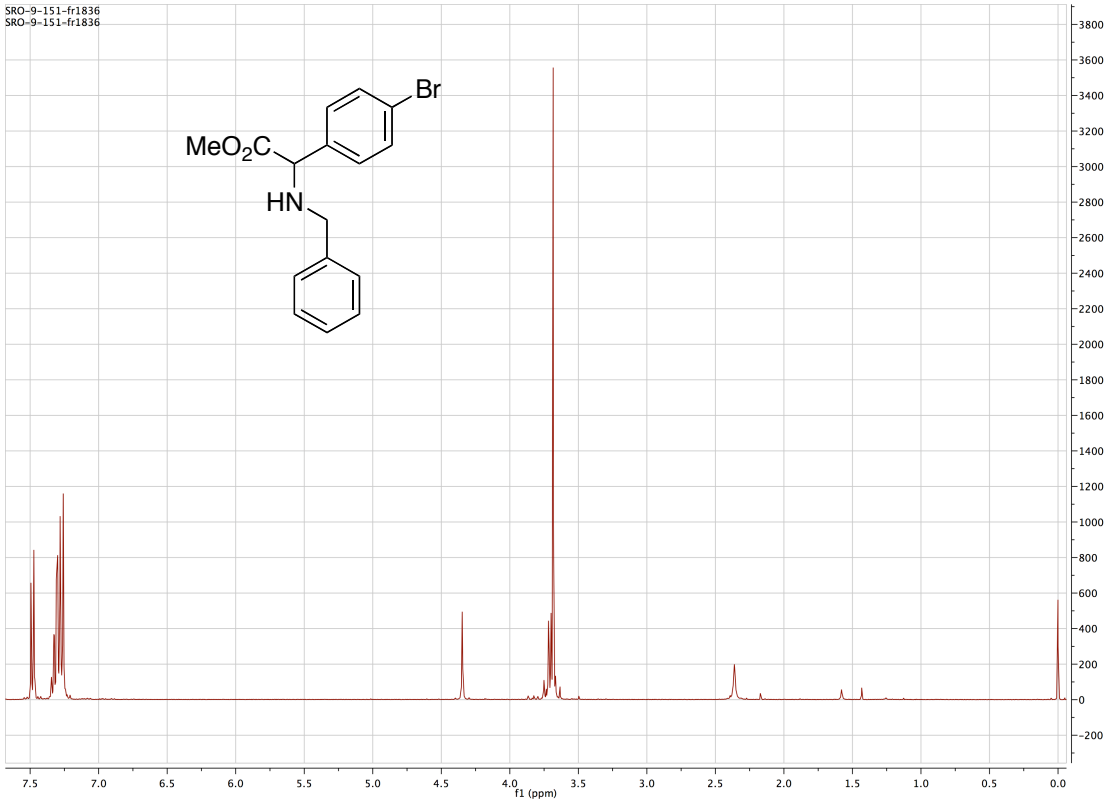
400 MHz, $CDCl_3$



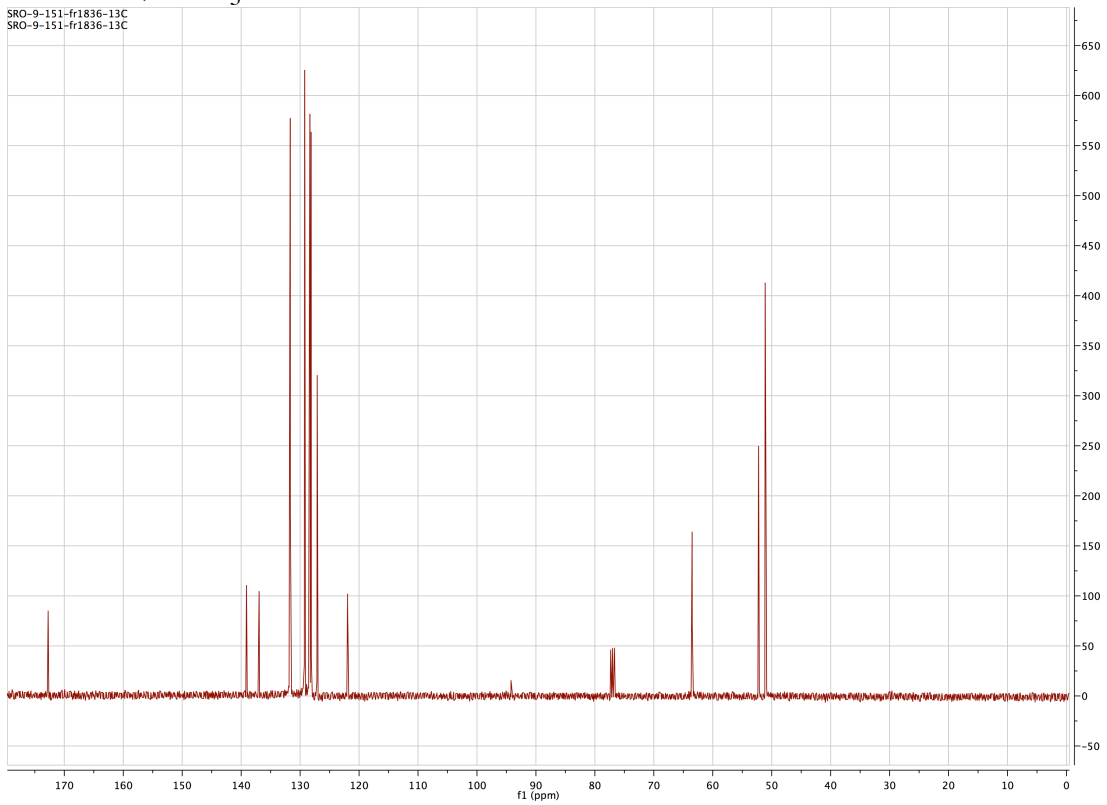
100 MHz, $CDCl_3$



400 MHz, $CDCl_3$



100 MHz, $CDCl_3$



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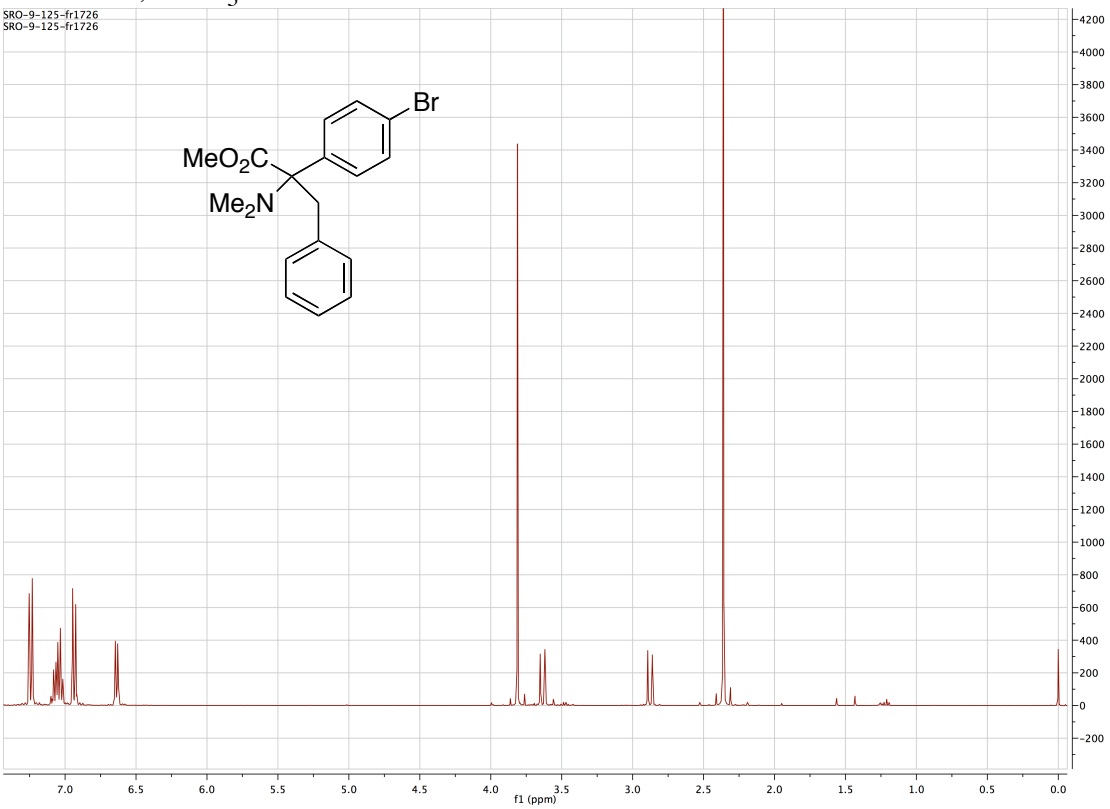
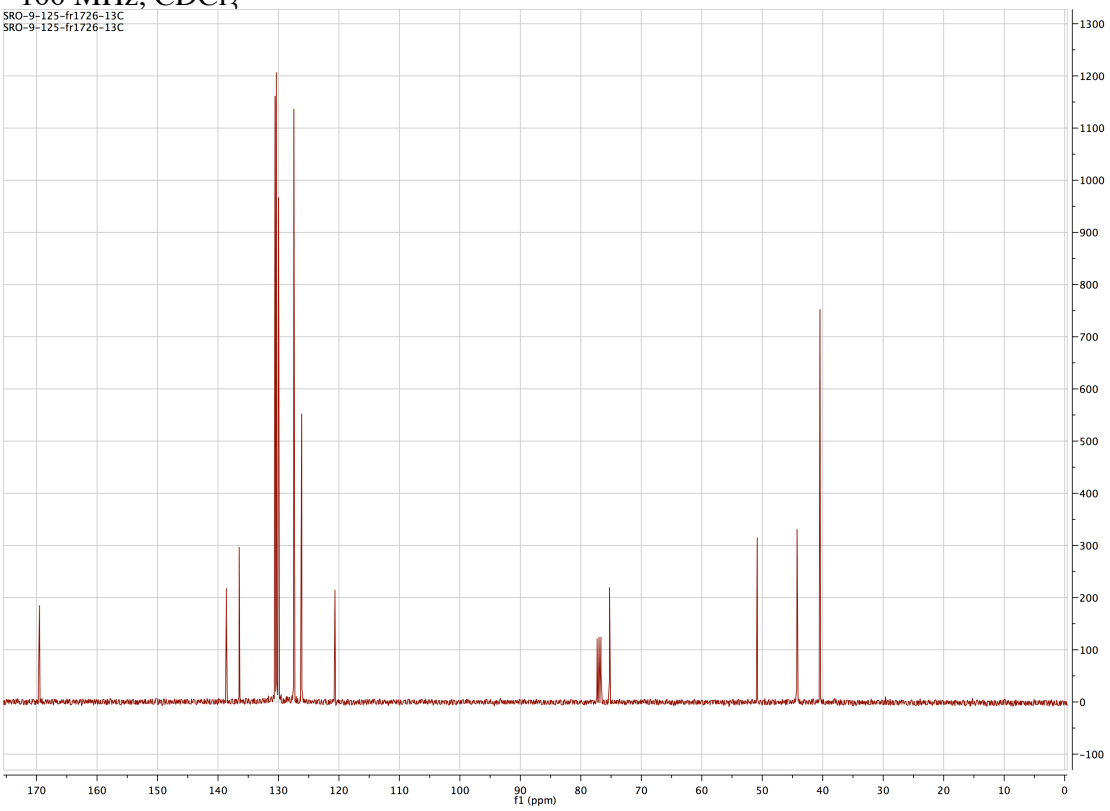


100 MHz, $CDCl_3$



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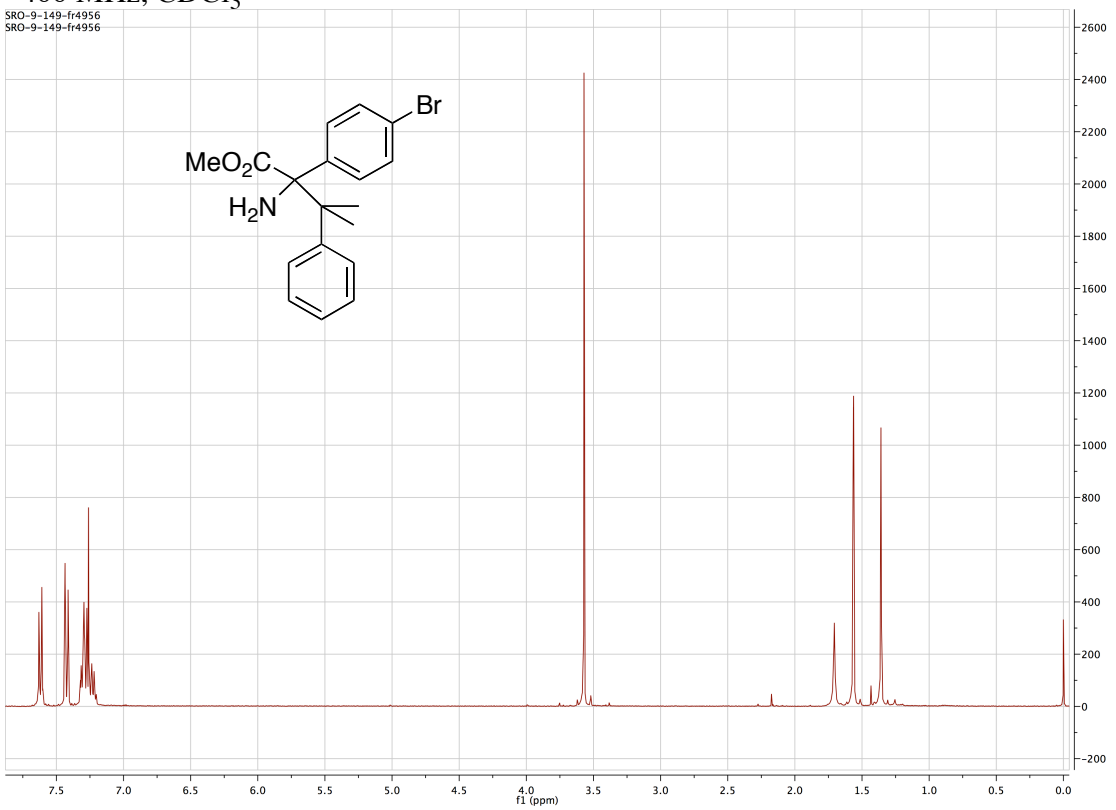

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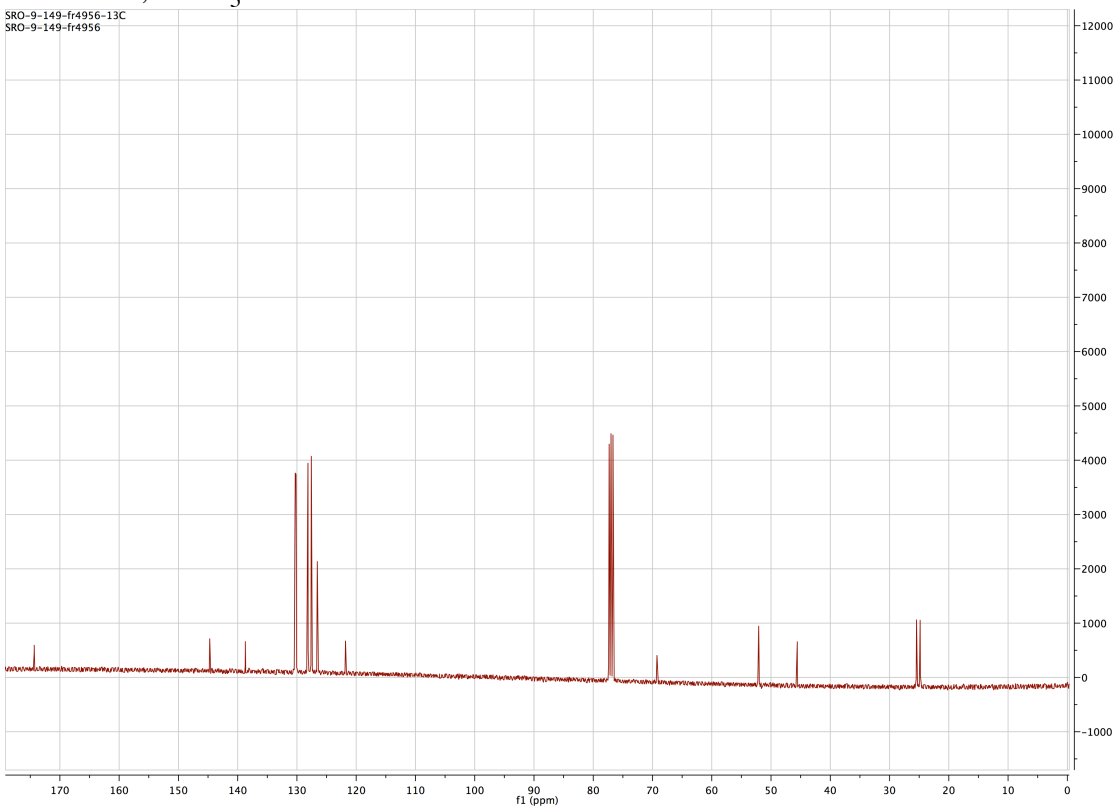
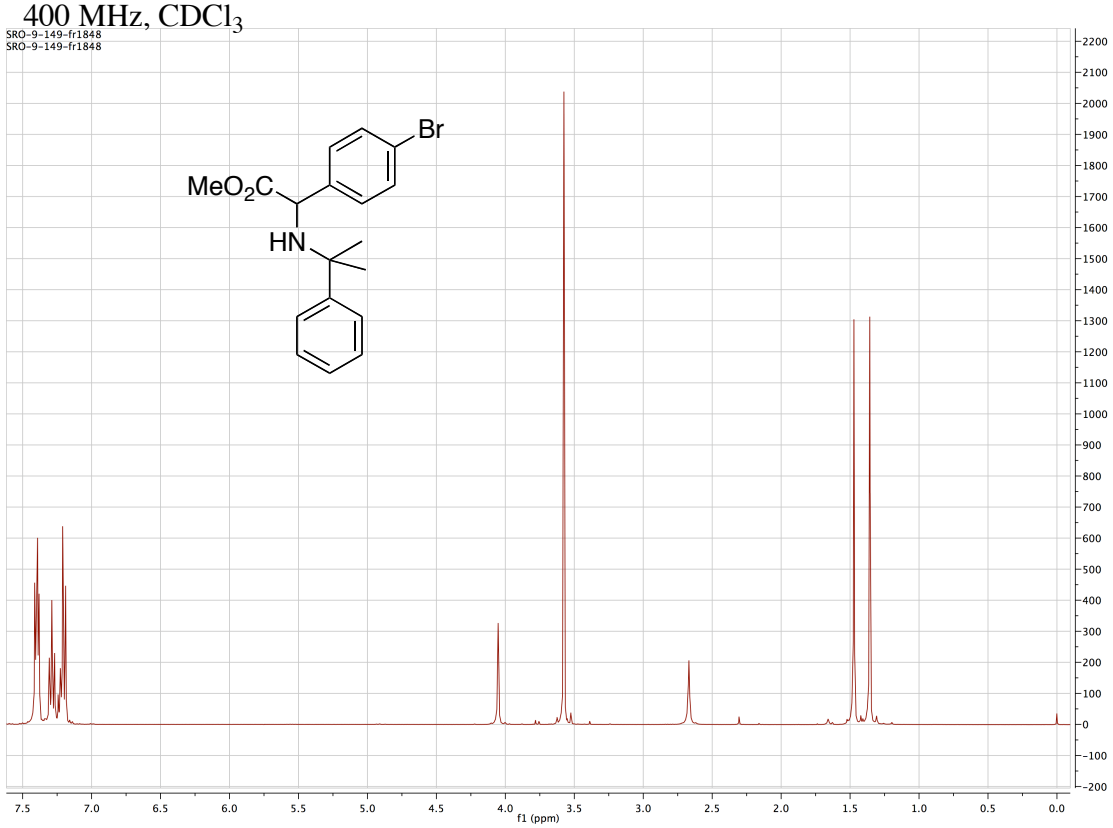
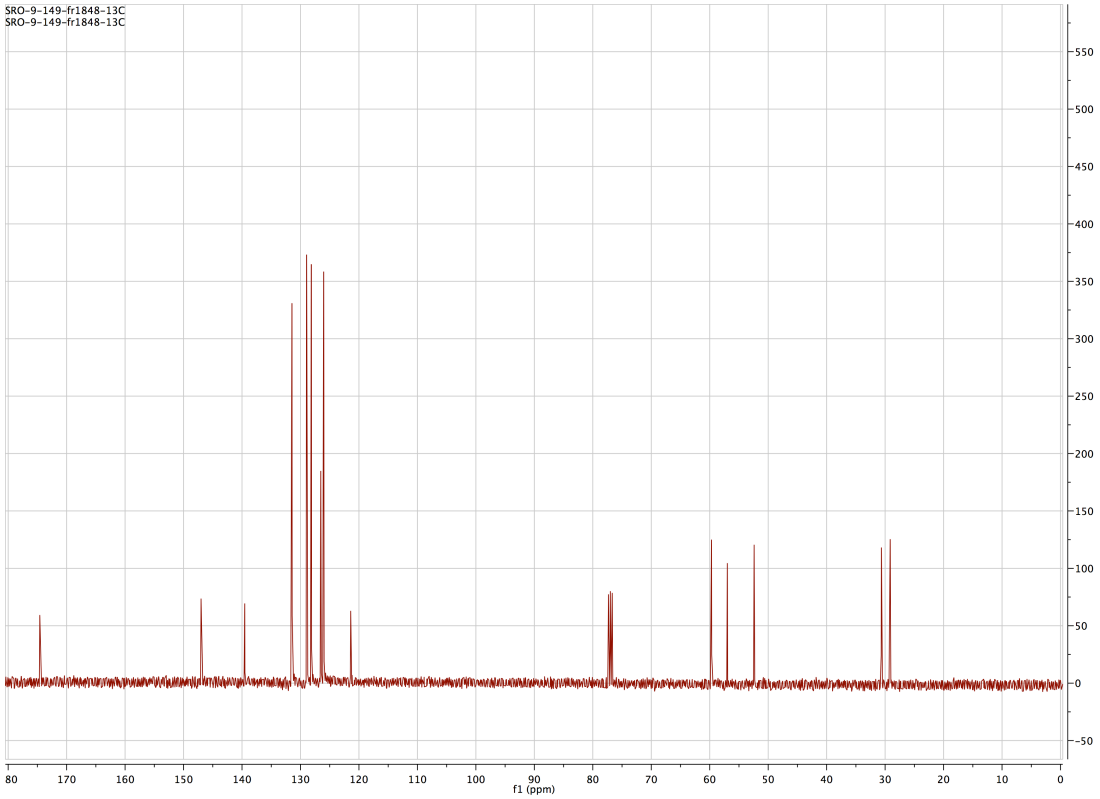


400 MHz, $CDCl_3$



100 MHz, $CDCl_3$



Appendix 2: X-Ray Crystallography of Compound 54

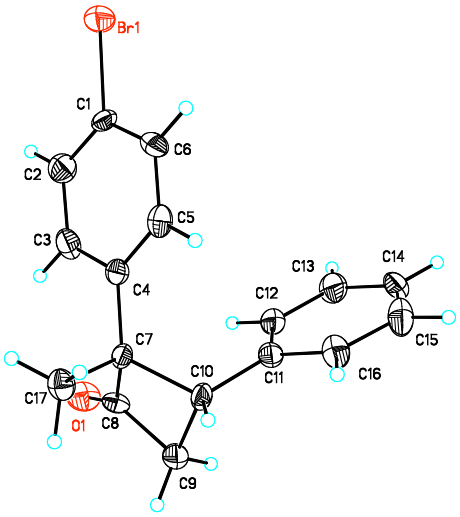


Table A1. Crystal data and structure refinement for sro_999t.

Identification code	sro_999t	
Empirical formula	C17 H15 Br O	
Formula weight	315.20	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 18.9697(9) Å	a= 90°.
b = 6.1032(3) Å	b= 95.162(3)°.	
c = 12.0780(6) Å	g = 90°.	
Volume	1392.67(12) $Å^3$	
Z	4	
Density (calculated)	1.503 Mg/m^3	
Absorption coefficient	3.918 mm^{-1}	
F(000)	640	
Crystal size	0.39 x 0.12 x 0.08 mm^3	
Theta range for data collection	5.69 to 69.64°.	
Index ranges	-22<=h<=0, -7<=k<=0, -14<=l<=14	
Reflections collected	1354	

Independent reflections	1354 [R(int) = 0.0000]
Completeness to theta = 69.64°	93.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7471 and 0.3131
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1354 / 1 / 172
Goodness-of-fit on F^2	1.137
Final R indices [I>2sigma(I)]	R1 = 0.0589, wR2 = 0.1853
R indices (all data)	R1 = 0.0677, wR2 = 0.2174
Absolute structure parameter	0.02(7)
Largest diff. peak and hole	1.238 and -1.273 e.$Å^{-3}$

Table A2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for sro_999t. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

x	y	z	U(eq)	
Br(1)	804(1)	3616(2)	6035(1)	38(1)
C(1)	1809(4)	3760(20)	6324(7)	26(2)
C(2)	2148(6)	5594(19)	6032(9)	34(2)
C(3)	2888(6)	5739(18)	6297(8)	32(2)
C(4)	3251(5)	4082(15)	6860(7)	25(2)
C(5)	2886(6)	2174(17)	7110(8)	28(2)
C(6)	2173(5)	2014(17)	6865(8)	28(2)
C(7)	4043(5)	4262(16)	7117(7)	23(2)
C(8)	4371(5)	6448(15)	7463(8)	23(2)
C(9)	4898(6)	5440(20)	8337(8)	35(2)
C(10)	4421(5)	3313(18)	8246(7)	25(2)
C(11)	3984(5)	3033(15)	9220(7)	26(2)
C(12)	3537(6)	4650(20)	9558(8)	33(2)
C(13)	3153(6)	4360(20)	10478(9)	37(2)
C(14)	3223(6)	2410(20)	11070(9)	37(2)
C(15)	3662(7)	810(20)	10756(9)	40(2)
C(16)	4029(6)	1087(18)	9818(8)	33(2)
C(17)	4412(5)	3330(17)	6121(7)	28(2)
O(1)	4229(4)	8343(13)	7225(7)	38(2)

Table A3. Bond lengths [Å] and angles [°] for sro_999t.

Br(1)-C(1)	1.909(8)
C(1)-C(2)	1.354(17)
C(1)-C(6)	1.398(16)
C(2)-C(3)	1.415(16)
C(2)-H(2A)	0.9500
C(3)-C(4)	1.369(15)
C(3)-H(3A)	0.9500
C(4)-C(5)	1.401(13)
C(4)-C(7)	1.510(13)
C(5)-C(6)	1.363(15)
C(5)-H(5A)	0.9500
C(6)-H(6A)	0.9500
C(7)-C(8)	1.516(13)
C(7)-C(17)	1.554(11)
C(7)-C(10)	1.592(11)
C(8)-O(1)	1.216(13)
C(8)-C(9)	1.516(15)
C(9)-C(10)	1.582(16)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.508(10)
C(10)-H(10A)	1.0000
C(11)-C(12)	1.388(15)
C(11)-C(16)	1.389(14)
C(12)-C(13)	1.393(14)
C(12)-H(12A)	0.9500
C(13)-C(14)	1.391(18)
C(13)-H(13A)	0.9500
C(14)-C(15)	1.358(18)
C(14)-H(14A)	0.9500
C(15)-C(16)	1.392(15)
C(15)-H(15A)	0.9500
C(16)-H(16A)	0.9500

C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800

C(2)-C(1)-C(6)	121.7(8)
C(2)-C(1)-Br(1)	118.6(9)
C(6)-C(1)-Br(1)	119.6(8)
C(1)-C(2)-C(3)	118.5(10)
C(1)-C(2)-H(2A)	120.7
C(3)-C(2)-H(2A)	120.7
C(4)-C(3)-C(2)	120.7(9)
C(4)-C(3)-H(3A)	119.7
C(2)-C(3)-H(3A)	119.7
C(3)-C(4)-C(5)	119.0(9)
C(3)-C(4)-C(7)	119.6(8)
C(5)-C(4)-C(7)	121.1(9)
C(6)-C(5)-C(4)	120.8(9)
C(6)-C(5)-H(5A)	119.6
C(4)-C(5)-H(5A)	119.6
C(5)-C(6)-C(1)	119.1(9)
C(5)-C(6)-H(6A)	120.5
C(1)-C(6)-H(6A)	120.5
C(4)-C(7)-C(8)	119.8(8)
C(4)-C(7)-C(17)	108.9(7)
C(8)-C(7)-C(17)	109.5(7)
C(4)-C(7)-C(10)	120.9(7)
C(8)-C(7)-C(10)	86.6(7)
C(17)-C(7)-C(10)	109.3(7)
O(1)-C(8)-C(7)	134.0(9)
O(1)-C(8)-C(9)	131.9(10)
C(7)-C(8)-C(9)	93.7(8)
C(8)-C(9)-C(10)	87.0(7)
C(8)-C(9)-H(9A)	114.2
C(10)-C(9)-H(9A)	114.2
C(8)-C(9)-H(9B)	114.2

C(10)-C(9)-H(9B)	114.2
H(9A)-C(9)-H(9B)	111.3
C(11)-C(10)-C(9)	113.0(8)
C(11)-C(10)-C(7)	118.2(8)
C(9)-C(10)-C(7)	88.3(7)
C(11)-C(10)-H(10A)	111.8
C(9)-C(10)-H(10A)	111.8
C(7)-C(10)-H(10A)	111.8
C(12)-C(11)-C(16)	117.8(9)
C(12)-C(11)-C(10)	122.8(9)
C(16)-C(11)-C(10)	119.3(9)
C(11)-C(12)-C(13)	121.4(11)
C(11)-C(12)-H(12A)	119.3
C(13)-C(12)-H(12A)	119.3
C(14)-C(13)-C(12)	119.1(11)
C(14)-C(13)-H(13A)	120.4
C(12)-C(13)-H(13A)	120.4
C(15)-C(14)-C(13)	120.3(9)
C(15)-C(14)-H(14A)	119.9
C(13)-C(14)-H(14A)	119.9
C(14)-C(15)-C(16)	120.4(11)
C(14)-C(15)-H(15A)	119.8
C(16)-C(15)-H(15A)	119.8
C(11)-C(16)-C(15)	120.9(11)
C(11)-C(16)-H(16A)	119.5
C(15)-C(16)-H(16A)	119.5
C(7)-C(17)-H(17A)	109.5
C(7)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(7)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table A4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for sro_999t. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}	
Br(1)	24(1)	48(1)	40(1)	7(1)	1(1)	-1(1)
C(1)	15(3)	42(5)	20(3)	-1(5)	-2(3)	2(5)
C(2)	33(6)	36(5)	33(5)	4(4)	2(4)	2(5)
C(3)	32(5)	35(5)	30(5)	8(4)	10(4)	1(5)
C(4)	26(5)	34(6)	16(4)	-4(3)	4(3)	-4(4)
C(5)	36(6)	24(4)	25(5)	5(3)	3(4)	3(4)
C(6)	25(5)	28(4)	33(5)	3(4)	6(4)	-7(4)
C(7)	20(4)	35(5)	16(4)	4(3)	3(3)	7(3)
C(8)	17(4)	21(4)	31(5)	-2(4)	6(4)	0(3)
C(9)	28(5)	49(6)	27(5)	4(5)	-1(4)	-13(5)
C(10)	25(4)	31(6)	20(3)	9(4)	2(3)	8(4)
C(11)	26(5)	29(5)	22(4)	-1(3)	0(4)	-8(4)
C(12)	27(5)	45(6)	25(4)	6(4)	3(4)	1(5)
C(13)	36(6)	52(6)	25(5)	-3(4)	6(4)	2(5)
C(14)	33(6)	53(7)	26(5)	6(5)	7(5)	-12(5)
C(15)	54(7)	39(6)	27(4)	5(4)	5(5)	-5(5)
C(16)	40(6)	31(5)	28(4)	1(4)	4(4)	-3(4)
C(17)	32(4)	26(5)	26(4)	-2(4)	7(3)	4(4)
O(1)	37(4)	23(4)	52(4)	2(4)	2(3)	-4(3)

Table A5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for sro_999t.

x	y	z	U(eq)	
H(2A)	1894	6758	5658	41
H(3A)	3136	7000	6082	38
H(5A)	3140	977	7455	34
H(6A)	1926	735	7059	34
H(9A)	4918	6177	9070	42
H(9B)	5378	5235	8091	42
H(10A)	4705	1971	8116	30
H(12A)	3491	5988	9154	39
H(13A)	2848	5487	10697	45
H(14A)	2963	2193	11697	45
H(15A)	3718	-498	11178	48
H(16A)	4314	-74	9583	40
H(17A)	4178	3900	5424	42
H(17B)	4382	1727	6122	42
H(17C)	4911	3776	6188	42

Table A6. Torsion angles [°] for sro_999t.

C(6)-C(1)-C(2)-C(3)	-0.7(14)
Br(1)-C(1)-C(2)-C(3)	176.9(7)
C(1)-C(2)-C(3)-C(4)	-1.5(15)
C(2)-C(3)-C(4)-C(5)	3.9(14)
C(2)-C(3)-C(4)-C(7)	179.1(8)
C(3)-C(4)-C(5)-C(6)	-4.2(13)
C(7)-C(4)-C(5)-C(6)	-179.3(9)
C(4)-C(5)-C(6)-C(1)	2.1(14)
C(2)-C(1)-C(6)-C(5)	0.4(14)
Br(1)-C(1)-C(6)-C(5)	-177.2(7)
C(3)-C(4)-C(7)-C(8)	39.2(12)
C(5)-C(4)-C(7)-C(8)	-145.7(8)
C(3)-C(4)-C(7)-C(17)	-87.8(10)
C(5)-C(4)-C(7)-C(17)	87.3(10)
C(3)-C(4)-C(7)-C(10)	144.6(9)
C(5)-C(4)-C(7)-C(10)	-40.4(12)
C(4)-C(7)-C(8)-O(1)	-33.4(14)
C(17)-C(7)-C(8)-O(1)	93.3(12)
C(10)-C(7)-C(8)-O(1)	-157.4(11)
C(4)-C(7)-C(8)-C(9)	140.0(8)
C(17)-C(7)-C(8)-C(9)	-93.3(8)
C(10)-C(7)-C(8)-C(9)	16.0(7)
O(1)-C(8)-C(9)-C(10)	157.5(10)
C(7)-C(8)-C(9)-C(10)	-16.1(7)
C(8)-C(9)-C(10)-C(11)	-104.8(8)
C(8)-C(9)-C(10)-C(7)	15.3(7)
C(4)-C(7)-C(10)-C(11)	-23.0(14)
C(8)-C(7)-C(10)-C(11)	100.0(9)
C(17)-C(7)-C(10)-C(11)	-150.5(9)
C(4)-C(7)-C(10)-C(9)	-138.3(9)
C(8)-C(7)-C(10)-C(9)	-15.3(7)
C(17)-C(7)-C(10)-C(9)	94.2(9)
C(9)-C(10)-C(11)-C(12)	53.9(14)

C(7)-C(10)-C(11)-C(12)	-47.2(15)
C(9)-C(10)-C(11)-C(16)	-125.7(10)
C(7)-C(10)-C(11)-C(16)	133.3(10)
C(16)-C(11)-C(12)-C(13)	1.1(17)
C(10)-C(11)-C(12)-C(13)	-178.4(10)
C(11)-C(12)-C(13)-C(14)	0.2(18)
C(12)-C(13)-C(14)-C(15)	0.2(18)
C(13)-C(14)-C(15)-C(16)	-2.0(19)
C(12)-C(11)-C(16)-C(15)	-2.9(16)
C(10)-C(11)-C(16)-C(15)	176.7(11)
C(14)-C(15)-C(16)-C(11)	3.4(19)

Symmetry transformations used to generate equivalent atoms: