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Part A: Design of new camphor-based hydrazide organocatalysts and their applications to enantioselective Friedel-Crafts alkylations.
Part B: The development of the palladium catalyzed addition of organoborates to alkynyl esters: Synthesis of trisubstituted olefins as single isomers.

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Part A

Design of new camphor-based hydrazide organocatalysts and their applications to enantioselective Friedel-Crafts alkylations

Part B

The development of the palladium catalyzed addition of organoborates to alkynyl esters: Synthesis of trisubstituted olefins as single isomers

Alexander Graham Bush

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Candidate	Supervisor
Alexander Graham Bush	Dr. William W. Ogilvie

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List of abbreviations

9-BBN	9-Borabicyclononane
Ac	Acetyl
AcOH	Acetic acid
Ala	Alanine
Ar	Aryl
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
br	Broad
Bu	Butyl
Bz	Benzoyl
calcd	Calculated
CAN	Ceric ammonium nitrate
Cy	cyclohexyl
d	Doublet
dba	Dibenzylideneacetone
DCE	1,2-dichloroethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
DFT	Density functional theory
DHDQ	Dihydroquinidine
DHQ	Dihydroquinine

DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dpephos	Bis(2-diphenylphosphinophenyl)ether
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppe	1,2-Bis(diphenylphosphino)ethane
dq	Doublet of quartets
dt	Doublet of triplets
E	Electrophile
ee	Enantiomeric excess
ent	Enantiomer
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
Equiv	Equivalents
Gly	Glycine
HIV	Human immunodeficiency virus
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
Hz	Hertz
Ind	*N*-methylindole
*i*Pr	Isopropyl
*i*PrOH	Isopropanol

IR	Infrared spectroscopy
m	Multiplet
M+	Molecular ion
Me	Methyl
MeOH	Methanol
min	Minutes
MS	Mass spectroscopy
*n*BuLi	*n*-butyl lithium
nd	Not determined
NMR	Nuclear magnetic resonance spectroscopy
*n*Pr	propyl
nOe	Nuclear Overhauser enhancement
NOESY	Nuclear Overhauser enhancement spectroscopy
Nuc	Nucleophile
OAc	Acetate; ethanoate
OMs	Mesylate; methanesulfonate
OPiv	Pivalate; 2,2-dimethylpropanoate
OTf	Triflate; trifluoromethanesulfonate
OTs	Tosylate; *para*-toluenesulfonate
O*t*Bu	*tert*-butoxide
Ph	Phenyl
PHAL	Phthalazine
Phe	Phenylalanine

pKa	Acid dissociation constant
q	Quartet
RNA	Ribonucleic acid
RT	Room temperature
s	Singlet
SOMO	Singly occupied molecular orbital
t	Triplet
*t*Bu	*tert*-butyl
TFA	2,2,2-Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Tol	4-tolyl
TfOH	Trifluoromethanesulfonic acid
TsOH	*para*-toluenesulfonic acid
XantPhos	Bis(diphenylphosphino)-9,9-dimethylxanthene

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First and foremost I would like to thank Bill. Thank you for taking a chance on a Math/Bio student who just loved chemistry. I have definitely learned a lot here and it's all thanks to you

I'd like to thank Alison Flynn. Alison, your help has been amazing. Don't worry, one day you'll find a TA who's almost as good as me. I'll see you on the field.

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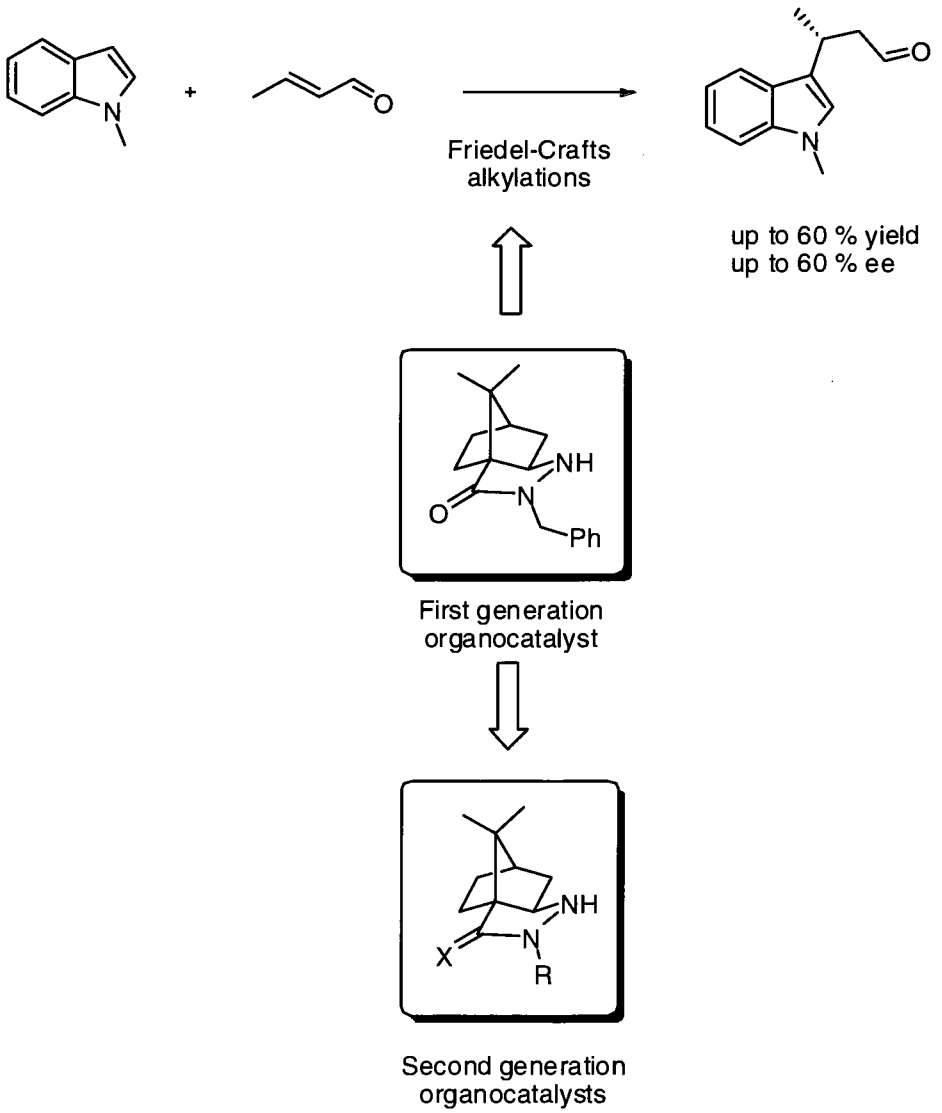
I would definitely like to thank my family. Without your love and support none of this would be possible. Laura, you have been such a great help to me. I can't begin to thank you enough.

Part A

Design of new hydrazide based organocatalysts and their applications to enantioselective Friedel-Crafts alkylations

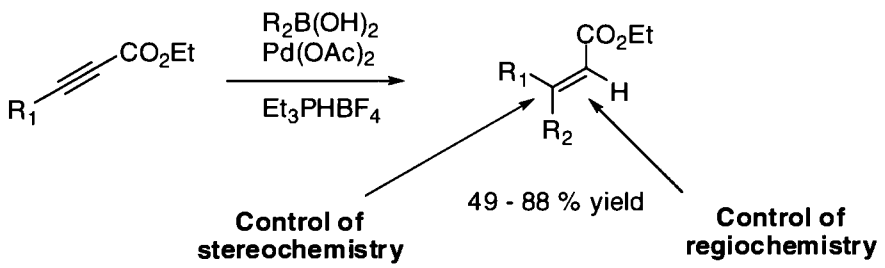
Abstract – Part A

Asymmetric synthesis is a growing field in synthetic and medicinal chemistry. Investigations into the use of organocatalysts to engender chirality into organic molecules is of particular interest. Herein we present the study of the efficiency of camphor-based hydrazide organocatalysts in the asymmetric Friedel-Crafts alkylations of *N*-methylindole with α,β-unsaturated aldehydes. In addition, the applicability of newly designed second-generation camphor-based hydrazide catalysts will be examined



Part B

The synthesis of trisubstituted olefins represents an intriguing target in organic chemistry. However, the stereocontrolled synthesis of trisubstituted olefins can prove to be difficult, as mixtures of isomers are often obtained. A new methodology is presented herein that allows for the synthesis of single isomer trisubstituted olefins by a palladium catalyzed reaction of alkynyl esters with aryl and vinyl boronic acids under mild reaction conditions by using the simple phosphine ligand Et_3P. The process provides α,β-unsaturated esters with complete control of the stereochemistry and regiochemistry at the newly formed the double bond.



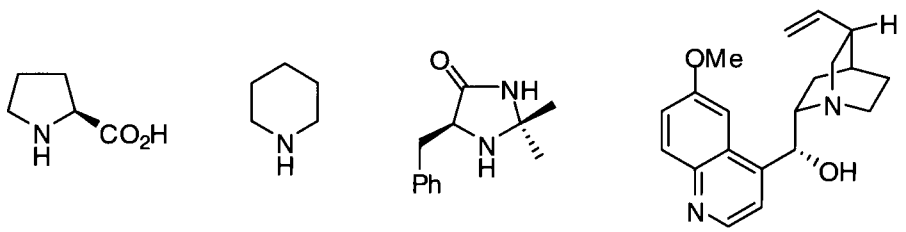
Chapter 1

1.1 Introduction

Catalysis is the process of increasing the rate of a reaction by adding a compound that is not consumed in the reaction. In organic chemistry, there are many types of catalysis. Typically, carbon-carbon bonds are formed either by using transition metal catalysis with elements such as palladium, rhodium or ruthenium, or with organocatalysts. The next section of this thesis (chapter 3) will focus on the use of palladium catalysts in carbon-carbon bond forming reactions. In this chapter, the focus will be on various organocatalytic reactions.

Organocatalysis involves the use of small organic molecules to facilitate various organic transformations. Some examples of organocatalysts are shown in figure 1.

Figure 1. Common organocatalysts.



1 **2** **3** **4**

There are many types of organocatalytic reactions. We will focus primarily on enamine[1] and iminium catalysis,[2] but other methods include the use of *N*-heterocyclic

[1] Mukherjee, S.; Yang, J.W.; Hoffmann, S.; List, B.; *Chem. Rev.* **2007**, *107*, 5471.

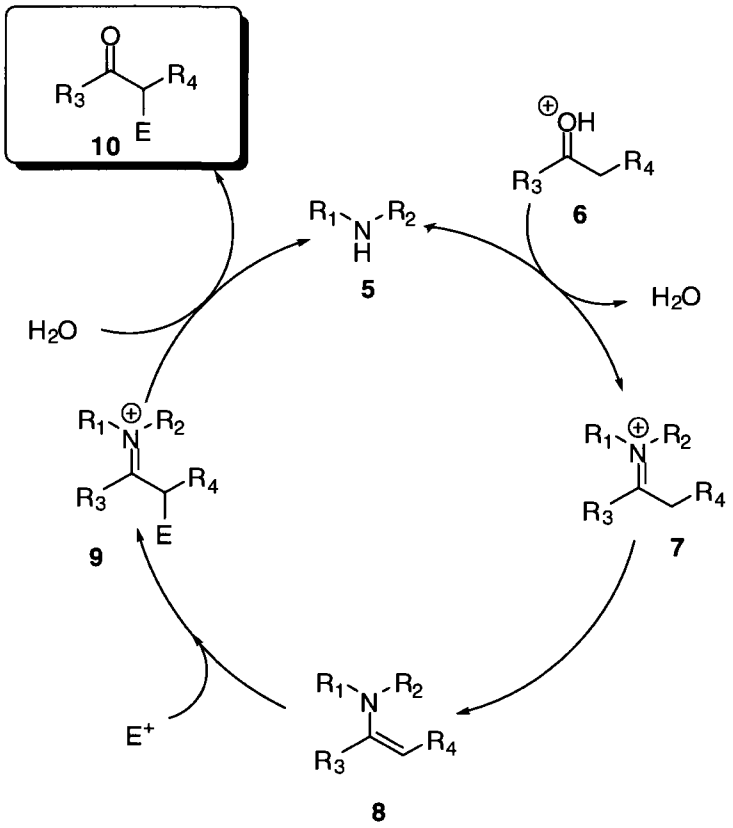
carbenes,[3] and chiral Brønsted acids.[4]

1.1.1 Discovery and development

One of the first uses of organocatalysis was enamine catalysis, which involves the formation of an enamine from the condensation of a ketone or an aldehyde with a secondary amine **5**. The enamine **8** then acts as a nucleophile to form a new carbon-carbon bond at the α-position to the enamine, forming iminium **9**. The formation of the enamine raises the energy of the HOMO of the nucleophile to increase the rate of the reaction. Hydrolysis of iminium **9** with water regenerates the secondary amine catalyst and liberates product **10** (scheme 1).

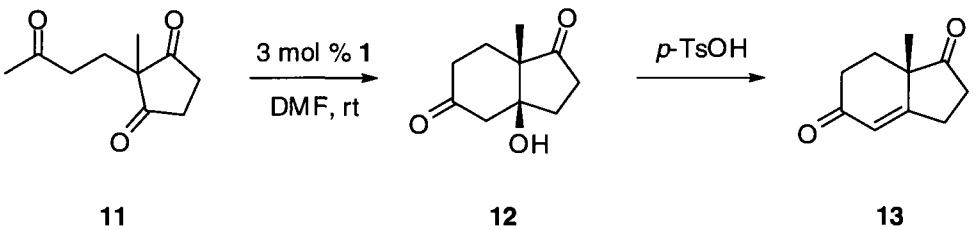
[2] Erkkilä, A.; Majander, I.; Pihko, P.M.; *Chem. Rev.* **2007**, *107*, 5416.
[3] Enders, D.; Niemeier, O.; Henseler, A.; *Chem. Rev.* **2007**, *107*, 5606.
[4] Doyle, A.G.; Jacobsen, E.N.; *Chem. Rev.* **2007**, *107*, 5713.

Scheme 1. Mechanisms of enamine catalysis



If the secondary amine catalyst is chiral, enantioselectivity in the reaction can be induced. This was first done with the use of (*L*)-proline **1** as the chiral catalyst in the Hajos-Parrish-Eder-Sauer-Wiechert reaction[5,6] shown in scheme 2.

Scheme 2. The Hajos-Parrish-Eder-Sauer-Wiechert reaction.



[5] Hajos, Z.G.; Parrish, D.R.; *J. Org. Chem.* **1974**, *39*, 1615.
[6] Eder, U.; Sauer, G.; Weichert, R.; *Angew. Chem. Int. Ed.* **1971**, *10*, 496.

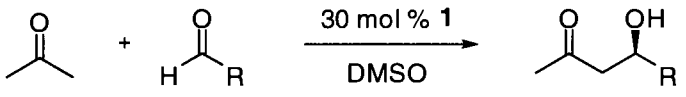
The reaction of substrate **11** with a catalytic amount of (*L*)-proline **1** afforded complete conversion to aldol product **12** in 93 % ee. Treatment of product **12** with *p*-toluenesulfonic acid resulted in the formation of elimination product **13** with no loss of enantiopurity.

1.1.2 Proline catalysis

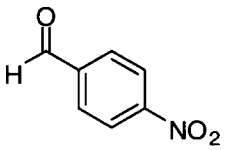
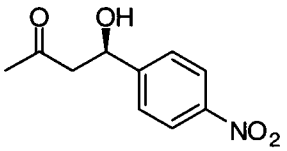
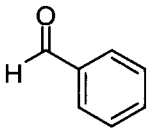
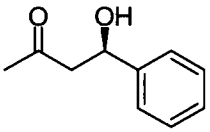
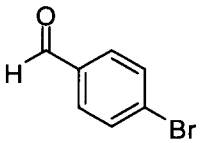
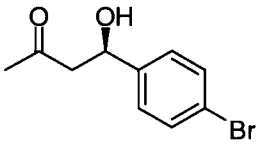
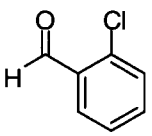
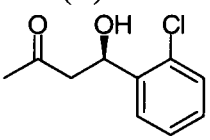
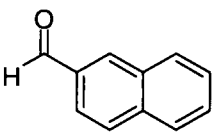
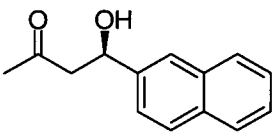
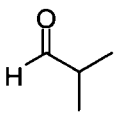
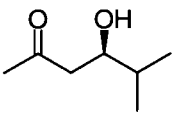
Despite the first use of (*L*)-proline as an organocatalyst in the 1970s, it was not until 2000 that methodology for organocatalysis was developed.[7] List and coworkers found that acetone would undergo an asymmetric aldol condensation with a wide variety of aldehydes to form chiral products as shown in table 1.

[7] List, B.; Lerner, R.A.; Barbas III, C.F.; *J. Am. Chem. Soc.* **2000**, *122*, 2395.

Table 1. The enantioselective synthesis of aldol products with (*L*)-proline as catalyst.



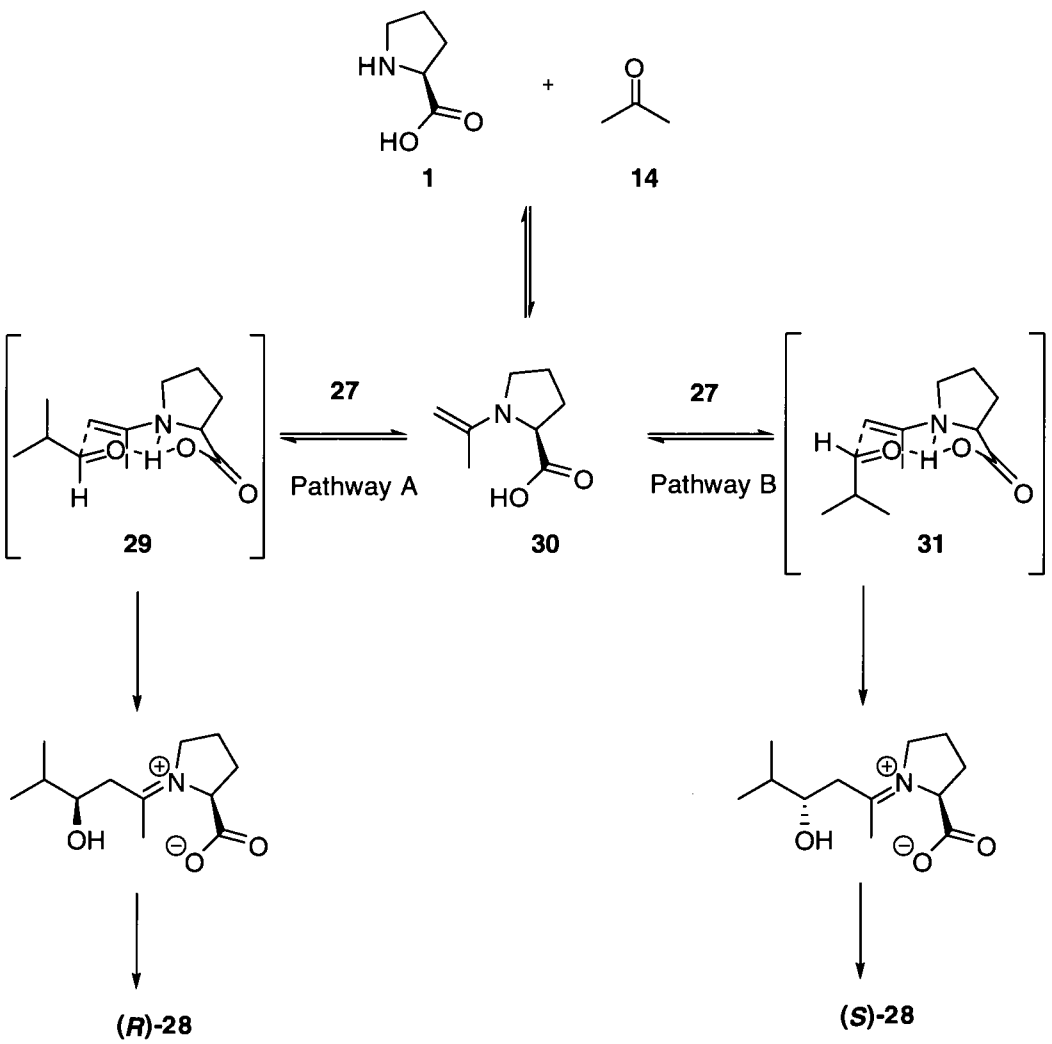
14 **15** **16**

Entry	Aldehyde	Product	Yield (%)	ee (%)
1	 **17**	 **(*R*)-18**	68	76
2	 **19**	 **(*R*)-20**	62	60
3	 **21**	 **(*R*)-22**	74	65
4	 **23**	 **(*R*)-24**	94	69
5	 **25**	 **(*R*)-26**	54	77
6	 **27**	 **(*R*)-28**	97	96

The condensation of acetone **14** with aryl aldehydes (entries 1 - 5) gave moderate enantioselectivity in the crossed-aldol products with the use of (*L*)-proline as an organocatalyst. List found that the use of isobutyraldehyde **27** could produce crossed-aldol product **28** in 97 % yield and 96 % ee. From this result, List was able to develop a

mechanism that could explain the observed enantioselectivity. It was proposed that the proline was acting as a "micro-aldolase." Aldolase is a natural enzyme that catalyzes aldol condensations in glycolysis asymmetrically. List hypothesized that the (*L*)-proline provided a means to bring the aldehyde near the reaction centre as shown in scheme 3.

Scheme 3. Proposed mechanisms of (*L*)-proline catalyzed aldol condensation

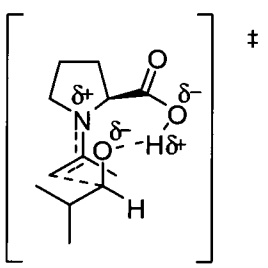


Condensation of (*L*)-proline **1** with acetone **14** will form enamine **30**. Once enamine **30** had formed, two diastereomeric pathways are available for an aldol process.

Enamine **30** can react with aldehyde **27** to form either (***R***)-**28** by pathway A or it can form (*S*)-**28** by pathway B. It was hypothesized by List and coworkers that this reaction proceeded through a six-membered chair-like transition state. When the reaction occurs via pathway B, transition state **31** develops a 1,3-diaxial interaction between the R-group of the aldehyde and the methyl of the enamine. This increases the energy of pathway B, disfavouring it relative to pathway A. However, if the reaction proceeds through transition state **29**, the 1,3-diaxial interactions are minimized, as the R-group of the aldehyde is located in the pseudo-equatorial position. This makes pathway A the favoured pathway and hence (***R***)-**28** the major product.

Further investigations into the mechanism of this reaction were performed by Houk and List.[8] By using computational methods, Houk was able to demonstrate that transition state **32** (figure 2) is the lowest energy transition state of the proline catalyzed aldol condensation.

Figure 2. The revised transition state of the aldol condensation.



32

In the proposed mechanism of the reaction, the hydrogen of the carboxylic acid moiety is being transferred to the newly formed alkoxide. Transition state **32** has

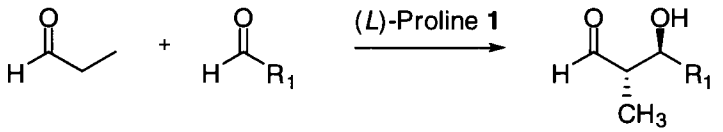
[8] Bahmanyar, S.; Houk, K.N.; Martin, H.J.; List, B. L.; *J. Am. Chem. Soc.* **2003**, *125*, 2475.

favourable H-bonding interactions between the partial positive charge on the hydrogen of the carbon adjacent to the nitrogen to the forming alkoxide, increasing the stability of this transition state.

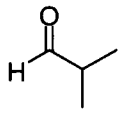
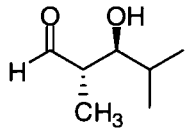
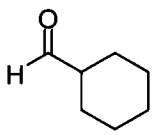
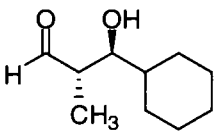
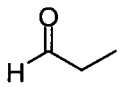
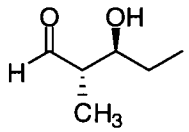
In 2002, the MacMillan group was able to expand the scope of the enantioselective aldol condensation by performing an organocatalytic aldol condensation with aldehydes,[9] in contrast to the previous results by List that required the use of ketone nucleophiles. In the cross-aldol condensation of two aldehydes, MacMillan was able to select one aldehyde to act as the electrophile and a second aldehyde to act as the nucleophile.

[9] Northrup, A.B.; MacMillan, D.W.C.; *J. Am. Chem. Soc.* **2002**, *124*, 6798.

Table 2. The aldol condensation of non-equivalent aldehydes.



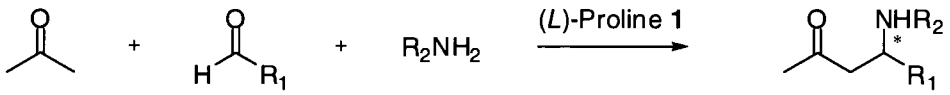
33 **15** **34**

Entry	Electrophile	Product	Yield (%)	*anti*:*syn*	ee (%)
1	 **27**	 **35**	82	24:1	99
2	 **36**	 **37**	87	14:1	99
3	 **33**	 **38**	80	4:1	99

In order to engender the cross condensation of non-equivalent aldehydes, the enamine nucleophile formed when **33** was added to a solution of (*L*)-proline catalyst **1**. Addition of the aldehyde electrophile **15** by syringe pump allowed formation of the desired cross product **34**. Enolate formation in the electrophile was minimized by employing aldehydes that are more sterically encumbered at the α-position. In all cases, the homodimerization of either aldehyde was suppressed.

Proline catalysis also found a use in the analogous Mannich reactions. In the Mannich reaction, an aldehyde would react with a primary amine to generate an imine, which would then react with an "enolate" nucleophile in either one or two steps to form new secondary amines (scheme 4).

Scheme 4. Organocatalytic Mannich reactions.



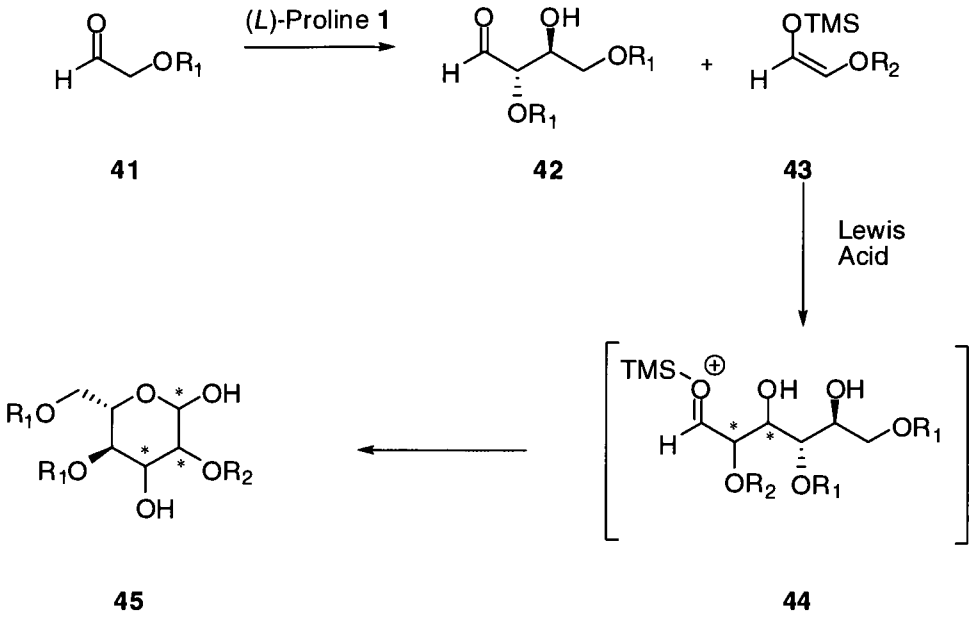
14 **15** **39** **40**

The imine electrophiles were formed by the reaction of aromatic aldehydes and *p*-anisidine. The Mannich reaction of acetone **14** with these newly formed imine electrophiles proceeded in moderate yield and high enantioselectivity at high pressures with 30 mol % proline catalyst **1** to produce the desired β-amino carbonyls.[10,11] The transition state of the Mannich reaction catalyzed by (*L*)-proline was thought to be similar to that of the aldol condensation.

Perhaps the most dramatic use of proline as an organocatalyst was the two step asymmetric synthesis of carbohydrates, present by the MacMillan group in 2004.[12] This two-step process involved aldehyde dimerization with (*L*)-proline to form an enantiopure product that was inert to further organocatalytic aldol reactions due to the increased size of the newly formed aldol product. This was followed by a Lewis acid-mediated aldol condensation to form an oxocarbenium which would cyclize to form one of four possible sugars (scheme 5).

[10] Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N.; *J. Am. Chem. Soc.* **2003**, *125*, 11208.
[11] List, B.; *J. Am. Chem. Soc.* **2000**, *122*, 9336.
[12] Northrup, A.B.; MacMillan, D.W.C; *Science* **2004**, *305*, 1752.

Scheme 5. The two-step enantioselective synthesis of carbohydrates.

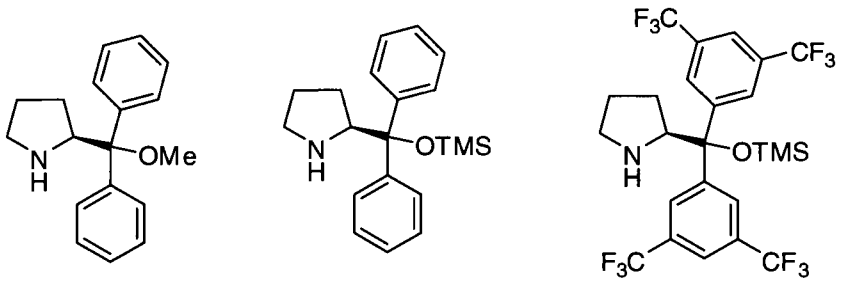


With this methodology, Northrup and coworkers were able to synthesize six different hexoses in good yields and excellent enantiocontrol, including glucose (73 %, 1:10 α:β, 95 % ee), mannose (80 % yield, >19:1 α:β, 95 % ee) and allose (89 % yield, >19:1 α:β, 95 % ee).

1.1.3 Proline-derived catalysts

Despite the examples shown above, proline has found limited use as an organocatalysts for reactions other than the aldol condensation. To increase the scope, the use of proline-derived pyrrolidine catalysts has been employed in organocatalytic reactions.

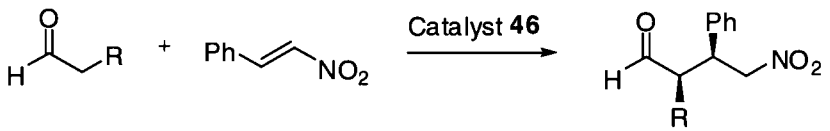
Figure 3. Pyrrolidine-derived organocatalysts.



46 **47** **48**

Pyrrolidine derived organocatalysts were first developed by the Hayashi group.[13,14] The versatility of these catalysts was explored in the 1,4-Michael reaction of aldehydes with nitroalkenes (table 3).

Table 3. The 1,4-Michael addition of aldehydes with nitroalkenes.



49 **50** **51**

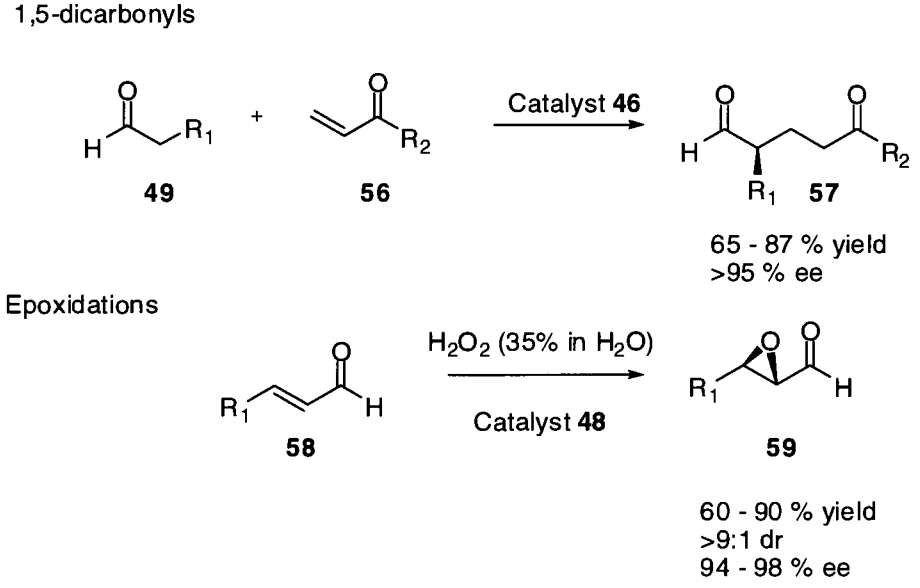
Entry	R	Product	Yield (%)	*syni:anti*	ee (%)
1	Me	**52**	85	94:6	99
2	*i*Pr	**53**	77	94:6	99
3	Et	**54**	66	93:7	99
4	*n*Pr	**55**	74	95:5	99

[13] Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H.; *Adv. Synth. Catal.* **2004**, *346*, 1435.
[14] Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M.; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.

The Hayshi group was able to affect the chiral synthesis of γ-nitro aldehydes with the use of pyrrolidine based organocatalyst via enamine catalysis. Similar reactions with other pyrrolidine based organocatalysts were explored by other groups.

The Gellman group was able to expand the applicability of pyrrolidine catalysis in 1,4-Michael additions by synthesizing chiral 1,5-dicarbonyl products by reacting aldehyde **49** with α,β-unsaturated ketones in the presence of catalyst **46**.[15] The Jørgensen group was able to use catalyst **48** for the enantioselective epoxidation of α,β-unsaturated aldehydes[16] and for the synthesis of α-fluorinated aldehydes with chiral catalyst **47** (scheme 6).[17]

Scheme 6. Reactions using pyrrolidine-based catalysts.

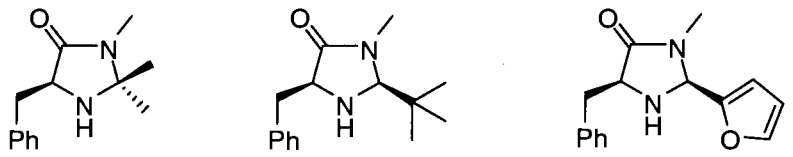


[15] Chi. Y.; Gellman, S.; *Org. Lett.* **2005**, *7*, 4253.
[16] Marigo, M.; Franzén, J.; Poulsen, T.B.; Zuang, W.; Jørgensen, K.A.; *J. Am Chem. Soc.* **2005**, *127*, 6964.
[17] Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K.A.; *Angew. Chem. Int. Ed.* **2005**, *44*, 3703.

1.1.4 Imidazolidinone catalysis

The use of organocatalysis in organic chemistry exploded with the development of the imidazolidinone catalyst family by the MacMillan group. The MacMillan group focused primarily on iminium catalysis. Contrary to enamine catalysis, in which the use of a chiral enamine nucleophile creates diastereomeric pathways that leads to enantioselectivity, iminium catalysis makes use of an α,β-unsaturated aldehyde to form a chiral iminium electrophile, creating two reaction pathways of different energy. The advent of imidazolidinone catalysts (figure 3) was important to the development of iminium catalysis, as both proline and pyrroldine catalysts cannot control the *E*/*Z* ratio of the isomers of the newly formed iminium.[18]

Figure 4. MacMillan imidazolidinone catalyst family.

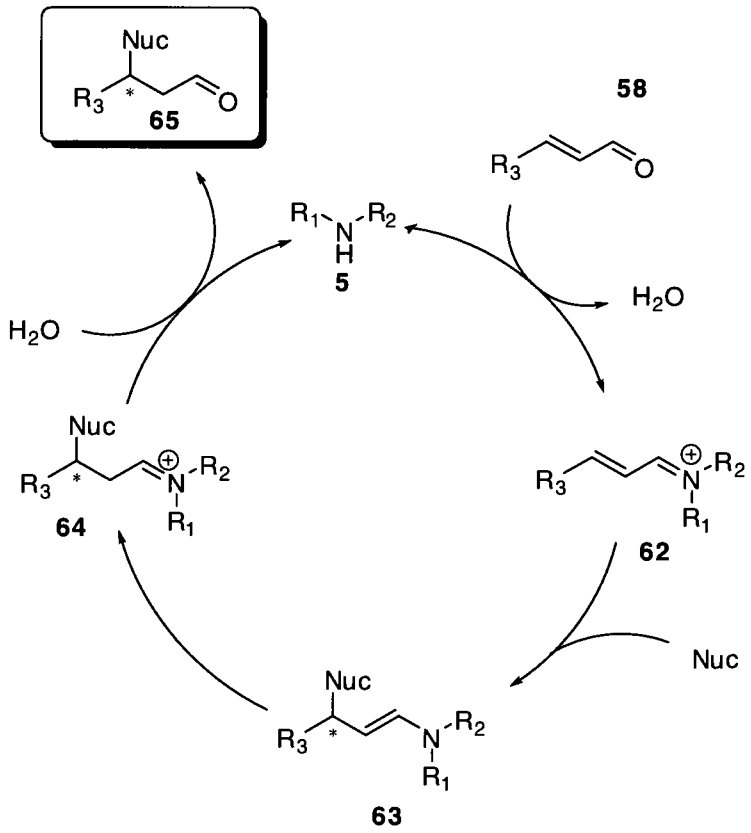


3 **60** **61**

The mechanism of iminium catalysis is shown in scheme 7. The chiral secondary amine reacts with the α,β-unsaturated aldehyde to form an iminium **62**. A 1,4-Michael addition of a suitable nucleophile, or a cycloaddition with an appropriate diene will create a new chiral centre at C3 of intermediate **63**. Tautomerization of the enamine reforms the iminium, which reacts with water to liberate the enantiopure product and regenerate the chiral catalyst.

[18] Kunz, R.K.; MacMillan, D.W.C; *J. Am. Chem. Soc.* **2005**, *127*, 3240.

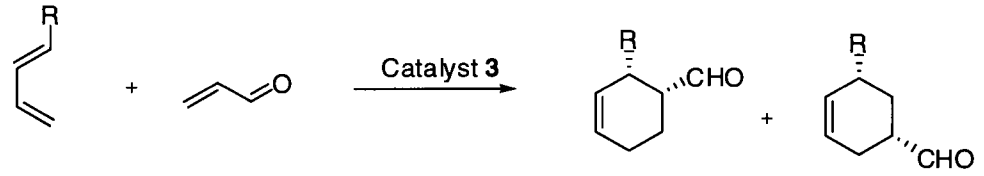
Scheme 7. The mechanism of iminium catalysis.



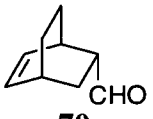
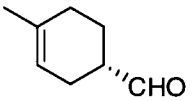
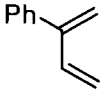
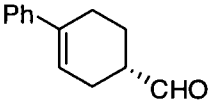
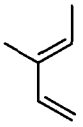
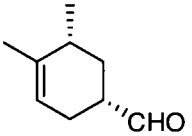
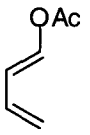
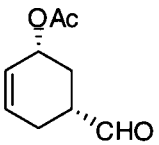
The first use of iminium organocatalysis with a member of the imidazolidinone catalyst family was with the asymmetric Diels-Alder reaction.[19] The reaction of a suitable diene with an aldehyde dienophile formed chiral products when catalyst **3** was used. Enantiomeric control in catalyst **3** is exerted by the benzyl group α to the carbonyl. It controls both the *E*/*Z* iminium selectivity and the top vs. bottom face approach of the diene.

[19] Ahrendt, K.A.; Borths, C.J.; MacMillan, D.W.C.; *J. Am. Chem. Soc.* **2000**, *122*, 4243.

Table 4. The enantioselective Diels-Alder reaction.



66 **67** *exo*-**68** *endo*-**68**

Entry	Diene	Product	Yield (%)	*exo*:*endo*	ee (%)
1	 **69**	 **70**	82	1:14	94
2	 **71**	 **72**	84		89
3	 **73**	 **74**	90		83
4	 **75**	 **76**	75	1:5	90
5	 **77**	 **78**	72	1:11	85

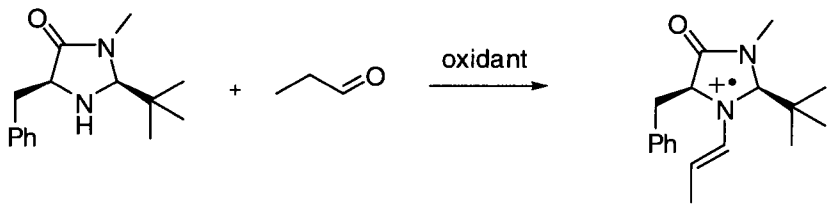
The Diels-Alder reaction of acrylaldehyde **67** with cyclohexadiene **69** afforded product **70** in 82 % yield and 94 % ee of the endo isomer (table 4, entry 1). Similar reactions of acrylaldehyde **67** with other dienes produced cyclohexene products in good yields with excellent enantioselectivity (table 4, entries 2 - 5).

The success of this reaction led to many other applications of imidazolidinone catalyst **3** and its derivatives **60** and **61** in organic reactions. By using these

organocatalysts, MacMillan was able to perform a wide variety of asymmetric organic reactions, as long as a carbonyl was present in the molecule. Some examples include the asymmetric transfer hydrogenation of cyclic enones,[20] Friedel-Crafts alkylations[21] and amine conjugate addition.[22]

Another highlight of the imidazolidinone catalyst is SOMO activation, also developed by the MacMillan group.[23] First shown in 2007,[23a] enamine formation with chiral catalyst **60** in the presence of a radical initiator would form a radical intermediate.[23b]

Scheme 8. The SOMO activation of propanal with catalyst **60**.



60 **32** **79**

DFT calculations showed that the 3π system would orient away from the bulky *tert*-butyl group and that the benzyl group would effectively shield the *Re* face of the radical cation. The radical cation was trapped with enol silyl ethers, which would approach from the exposed *Si* face of the molecule, generating chiral 1,4-dicarbonyls in good yields.

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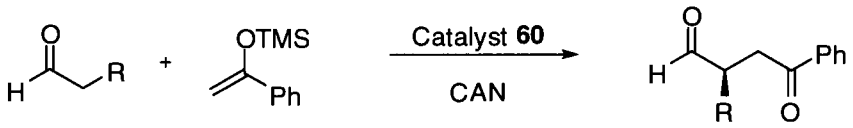
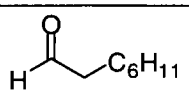
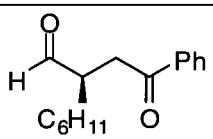
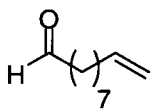
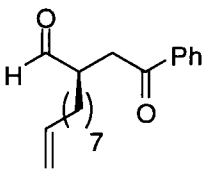
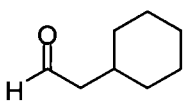
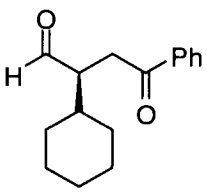
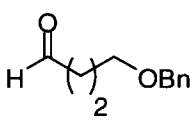
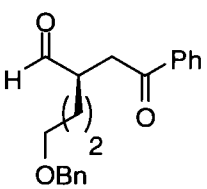
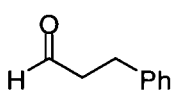
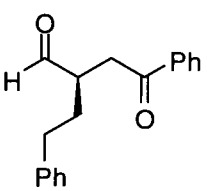
[20] Tuttle, J.B.; Ouellet, S.G.; MacMillan, D.W.C; *J. Am. Chem. Soc.* **2006**, *128*, 12662.
[21] Paras, N.A.; MacMillan, D.W.C.; *J. Am. Chem. Soc.* **2001**, *123*, 4370.
[22] Chen, Y.K.; Yoshida, D.; MacMillan, D.W.C; *J. Am. Chem. Soc.* **2006**, *128*, 9328.
[23] a) Beeson, T.D.; Mastracchio, A.; Hong, J.; Ashton, K.; MacMillan, D.W.C.; *Science* **2007**, *316*, 582; b) Jang, H.; Hong, D.; MacMillan, D.W.C.; *J. Am. Chem. Soc.* **2007**, *129*, 7004.; c) Kim, H.; MacMillan, D.W.C.; *J. Am. Chem. Soc.* **2008**, *130*, 398.

Table 5. The SOMO activation reaction of silyl enol ethers with aldehydes.



49 **80** **81**

Entry	Aldehyde	Product	Yield (%)	ee (%)
1	 **82**	 **83**	85	90
2	 **84**	 **85**	92	92
3	 **86**	 **87**	74	93
4	 **88**	 **89**	71	90
5	 **90**	 **91**	77	91

The organocatalytic SOMO activation showed a completely new approach to organocatalysis. It became possible to synthesize 1,4-dicarbonyls in good yields and with very high enantioselectivity. Organocatalysis was used to synthesize 1,3-dicarbonyls by a Claisen condensation; 1,5-dicarbonyls by the Michael reaction; and 1,4-dicarbonyls

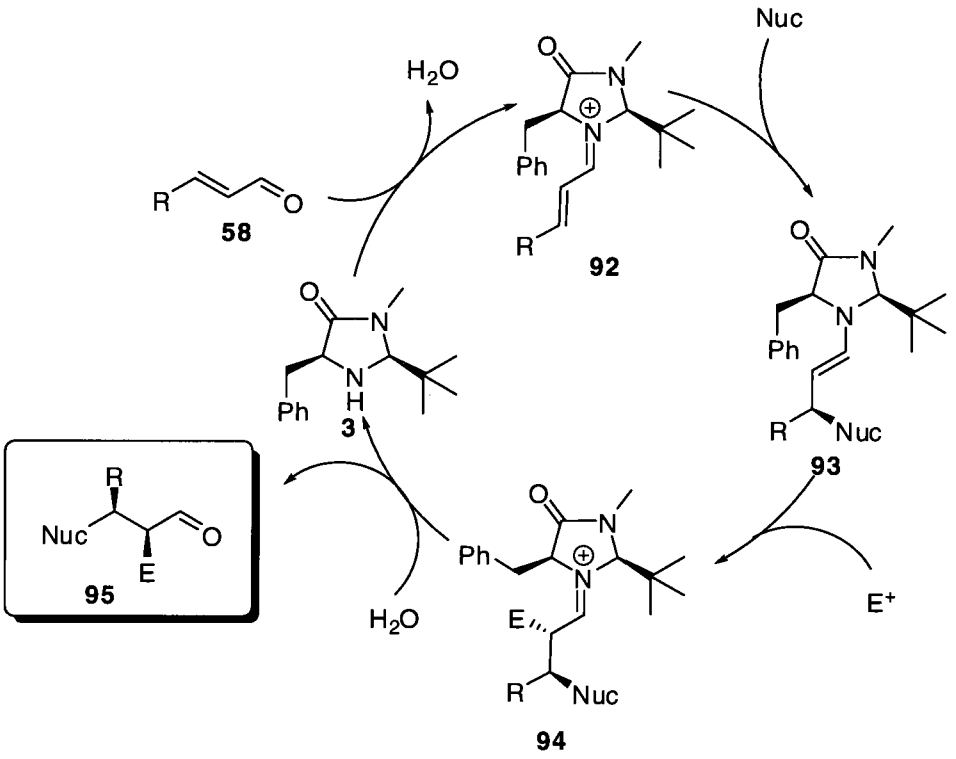
with SOMO activation. SOMO activation demonstrated the extensive scope of organocatalysis.

1.1.5 Cascade catalysis

Another application of organocatalysis was the one-pot cascade reaction involving two organocatalytic reactions, an enamine reaction and an iminium reaction. This was developed independently by the MacMillan group with the imidazolidinone catalyst **60**,[24] and by the Jørgensen group with the pyrrolidine-based catalyst **47**.[25] The cascade approach involved first iminium activation of an α,β-unsaturated aldehyde **58**, forming iminium **92**. This was followed by nucleophilic addition to generate an activated enamine **93**. Rather than quench with H^+ as was done with iminium catalysis (scheme 7), the addition of an appropriate electrophile would generate product **95** with two stereocentres in a one pot reaction (scheme 9).

[24] Huang, Y.; Walji, A.M.; Larsen, C.H.; MacMillan, D.W.C.; *J. Am. Chem. Soc.* **2005**, *127*, 15051.
[25] Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K.A.; *J. Am. Chem. Soc.* **2005**, *127*, 15710.

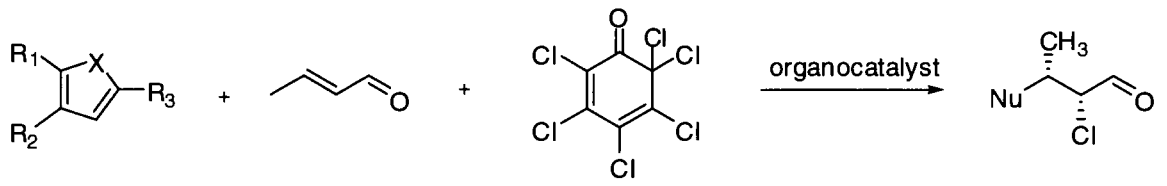
Scheme 9. The MacMillan cascade catalysis.



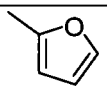
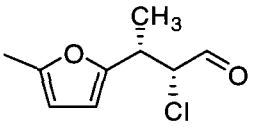
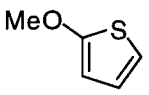
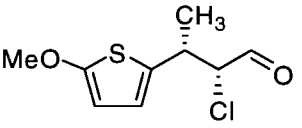
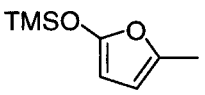
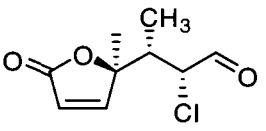
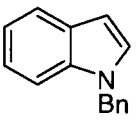
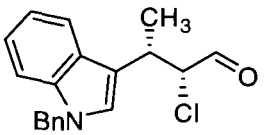
The use of a nucleophile and an electrophile that did not react together was a prerequisite for the organocascade catalysis reaction. It was found that quinone derivative **96**[26] was an adequate source of electrophilic chlorine, as it did not react with any of the aromatic heterocycles used as nucleophiles in table 6. The organocascade reaction proceeded as planned, generating many α-chloro Friedel-Crafts alkylation products.

[26] a) Wack, H.; Taggi, A.E.; Hafez, A.M.; Drury, W.J. III; Lectka, T.; *J. Am. Chem. Soc.* **2001,** *123,* 1531; b) Hafez, A.M.; Taggi, A.E.; Wack, H.; Esterbrook, J.; Lectka, T.; *Org. Lett.* **2001,** *3,* 2049.

Table 6. The MacMillan organo-cascade reaction.



96 **97** **98** **99**

Entry	Nucleophile	Product	Yield (%)	*syn:anti*	ee (%)
1	 **100**	 **101**	86	14:1	99
2	 **102**	 **103**	77	11:1	99
3	 **104**	 **105**	71	>25:1	>99
4	 **106**	 **107**	75	12:1	>99

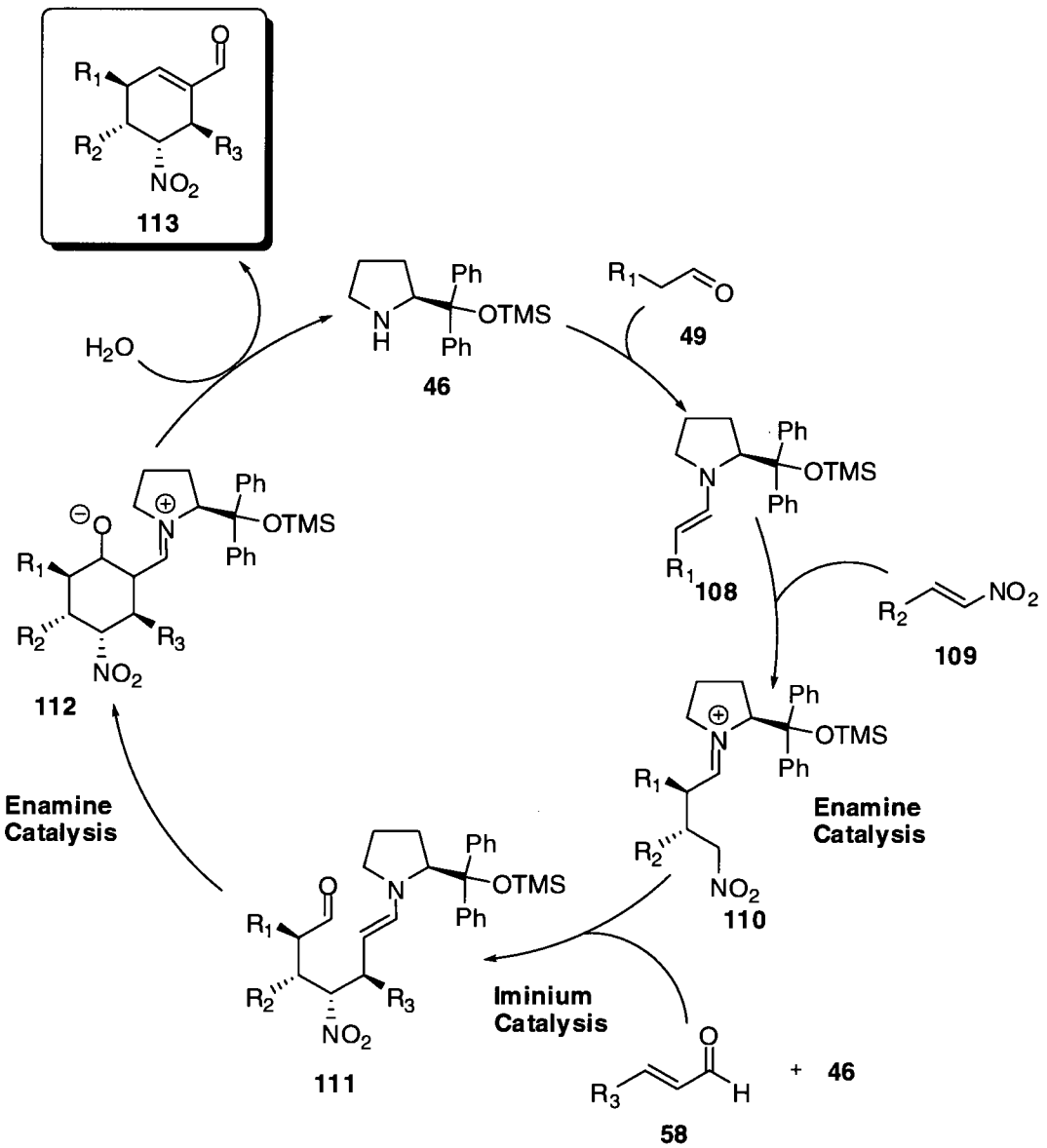
The organocatalytic cascade reaction was further improved by the Enders group in 2006.[27] They developed an efficient means to synthesize chiral cyclohexene derivatives with four stereogenic centres by a three component cascade reaction. Pyrrolidine based catalyst **46** was able to perform an enamine-iminium-enamine catalysis reaction generating the desired cyclohexene products through two Michael reactions and an aldol condensation. This cascade cycle is different than the MacMillan approach as

[27] Enders, D.; Hüttl, M.R.M.; Grondal, C.; Raabe, G.; *Nature*, **2006**, *441*, 861.

three different organocatalytic reactions are occurring in one pot as opposed to two reactions

.

Scheme 10. The triple cascade organocatalysis.



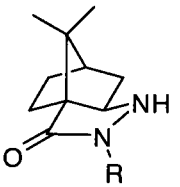
In the first step of the cascade reaction, catalyst **46** performs an enamine activation of an aldehyde to generate intermediate **108**, which then catalyzes the 1,4-

Michael reaction with nitroalkene **109**, forming two of the stereocentres enantioselectively. The newly formed product **110** then undergoes a second 1,4-Michael addition with an iminium activated α,β-unsaturated aldehyde **58** to form the remaining two stereocentres in product **111**. An enamine activated aldol reaction closes the ring, producing cyclohexane derivative **112**. This is followed by the elimination of water to generate the cyclohexene product **113** and regenerate catalyst **46**. The final product is much too sterically hindered to undergo condensation with catalyst **46**, preventing further reactions or polymerizations.

1.1.6 Previous work

In 2005, the Ogilvie group designed and developed a new camphor-based hydrazide organocatalyst (figure 4) for the use in the Diels-Alder cycloadditions.[28] The catalyst was designed with the intent to increase catalytic turnover and thus increase the overall efficiency of the reaction.

Figure 5. The Ogilvie group camphor-based hydrazide organocatalyst.



114

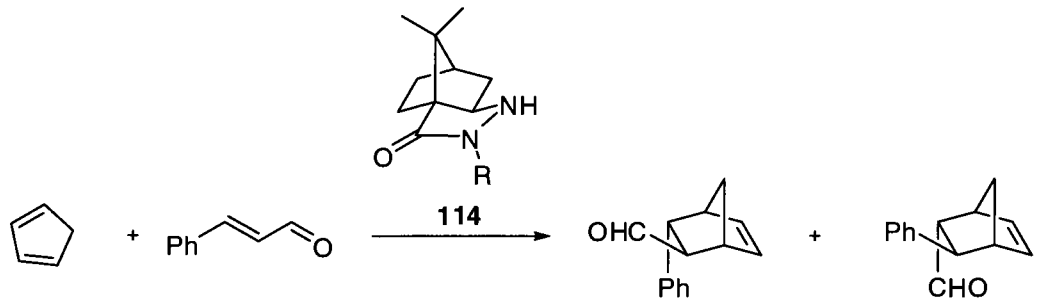
[28] Lemay, M.; Ogilvie, W.W.; *Org. Lett.* **2005**, *7*, 4141.

The idea behind the design was that the hydrazide would increase the nucleophilicity of the secondary nitrogen by virtue of the α-effect; an inductive donation of the lone pair on the tertiary nitrogen to the secondary nitrogen. The camphor-based skeleton was used to incorporate chirality into the product. The camphor moiety was also chosen because of the ease of synthesis of catalyst **114** (four steps from camphorsulfonic acid). The carbonyl in the five-membered ring is added to increase stability of the catalyst.

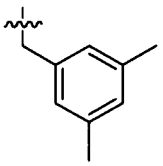
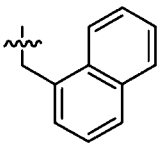
With the scaffold in mind, our laboratory set out to build and test a series of camphor-based hydrazide catalysts, to test their efficiency in the Diels-Alder reaction of cyclopentadiene **115** with (*E*)-cinnamaldehyde **116** (table 7).[29]

[29] Lemay, M.; Aumand, L.; Ogilvie, W.W.; *Adv. Synth. Catal.* **2007**, *349*, 441.

Table 7. Design of camphor-based hydrazide catalysts



115 **116** ***exo*-117** ***endo*-117**

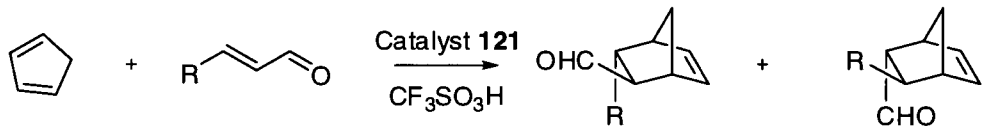
Entry	R	Acid co-catalyst	Yield (%)	*exo:endo*	*endo* ee (%)
1	H **118**	$HClO_4$	25	0.9:1	3
2	Me **119**	$HClO_4$	18	1.2:1	58
3	Ph **120**	$HClO_4$	25	1.1:1	60
4	Bn **121**	$HClO_4$	82	1.7:1	85
5	Bn **121**	CF_3SO_3H	96	1.9:1	88
6	 **122**	CF_3SO_3H	91	1.8:1	87
7	 **123**	$HClO_4$	82	1.7:1	74
8	*t*Bu **124**	CF_3SO_3H	32	1.1:1	7

After exploring the effects of the R group on the enantioselectivity of the reaction of cyclopentadiene with (*E*)-cinnamaldehyde, it was found that camphor-based hydrazide catalyst **121**, with trifluoromethanesulfonic acid as co-catalyst (entry 5), afforded Diels-Alder adducts *endo*-**117** and *exo*-**117** in the highest yield and the greatest ee. It was

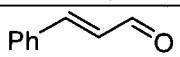
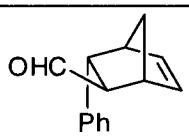
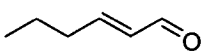
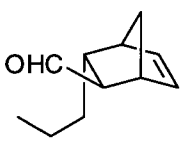
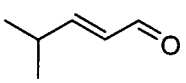
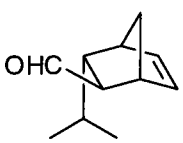
hypothesized that this was because the benzyl group was able to exert the most control in the formation of the *Z*-iminium over the *E*-iminium. Other organocatalysts with similar structural features to catalyst **121** afforded cyclohexene products in equally high enantioselectivity. Catalyst **121** became the first generation Ogilvie catalyst.

The scope of catalyst **121** was explored in the Diels-Alder reaction of cyclopentadiene **115** with α,β-unsaturated aldehydes, as shown in table 8.

Table 8. The Diels-Alder reaction use hydrazide-based catalyst **122.**



115 **58** *exo*-**125** *endo*-**125**

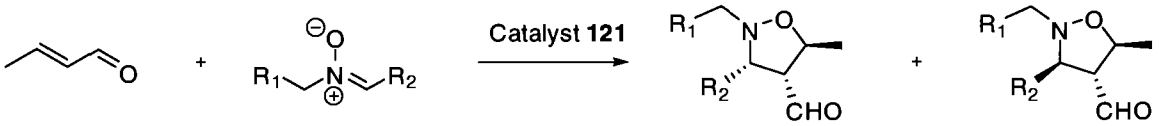
Entry	Aldehyde	Product	Yield (%)	*exo:endo*	*exo* ee (%)
1	 **116**	 **117**	96	1.9:1	90
2	 **126**	 **127**	83	1.6:1	81
3	 **128**	 **129**	84	2.6:1	85

Catalyst **121** afforded a variety of Diels-Alder adducts in good yields and with good enantioselectivity (table 8). A mechanistic investigation showed that the

conversion of aldehyde **58** to the iminium was very rapid, being complete in less than two hours.[30] Once the iminium had formed, it remained at a constant concentration until the amount of residual aldehyde **58** fell below the initial concentration of catalyst **121** (20 mol %). At this point, the concentration of iminium dropped smoothly and the conversion to product *endo*-**117** and *exo*-**117** reached a plateau.

Catalyst **121** also showed success in [3+2] cycloadditions of nitrones with α,β-unsaturated aldehydes to afford isoxazolidines.[31] By forming an iminium with crotonaldehyde **97**, catalyst **121** was able to exert enantiocontrol on the approach of nitrone **130** by creating two diastereomeric reaction pathways. This enantiocontrol allowed for the creation of products **131** with high ee and in good yields (scheme 11).

Scheme 11. The cycloaddition of crotonaldehyde with nitrones.



97 **130** *exo*-**131** *endo*-**131**

Catalyst **121** was successful in the [4+2] and [3+2] cycloadditions of iminium products. The camphor moiety of the catalyst was able to block the top-face approach of either the dienophile or the dipolarophile. The benzyl group ensured selectivity of the *Z*-iminium over the *E*-iminium. These combined factors contributed to the high enantioselectivity of cycloadditions with catalyst **121**.

[30] Lemay, M.; Ogilvie, W.W.; *J. Org. Chem.* **2006**, *71*, 4663.
[31] Lemay, M.; Trant, J.; Ogilvie, W.W.; *Tetrahedron* **2007**, *63*, 11644.

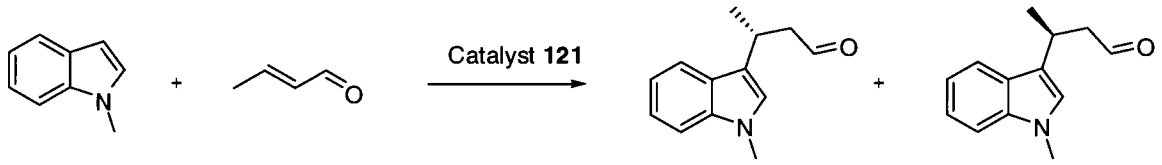
Chapter 2

2.1 Results and Discussion

2.1.1 Optimizations

Given the success of the Ogilvie group organocatalysts **121** in [4+2] and [3+2] cycloadditions, it was decided to explore its use in other possible reactions. The reaction that was targeted was the Friedel-Crafts alkylation of *N*-methylindole with crotonaldehyde.

Scheme 12. The Friedel-Crafts alkylation of *N*-methylindole with crotonaldehyde.

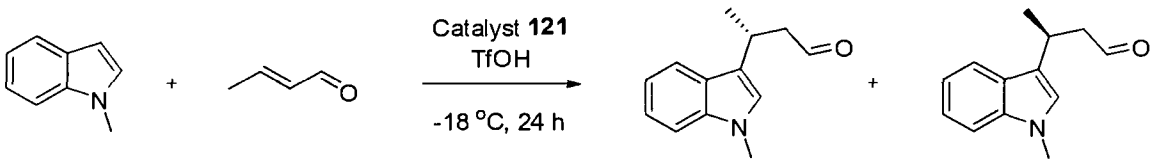


132 **97** **(*R*)-133** **(*S*)-133**

Literature precedent for this reaction existed as MacMillan and coworkers were able to synthesize product **(*R*)-133** in 82 % yield and 92 % ee with organocatalyst **60**.[32] The application of organocatalyst **121** to the Friedel-Crafts alkylation of *N*-methylindole was first explored by Ami Chin in the Ogilvie group. She performed an initial solvent investigation in an attempt to optimize the reaction.

[32] Austin, J.F.; MacMillan, D.W.C.; *J. Am. Chem. Soc.* **2002**, *124*, 1172.

Table 9. Solvent optimization of the Friedel-Crafts alkylation.



132 **97** **(*R*)-133** **(*S*)-133**

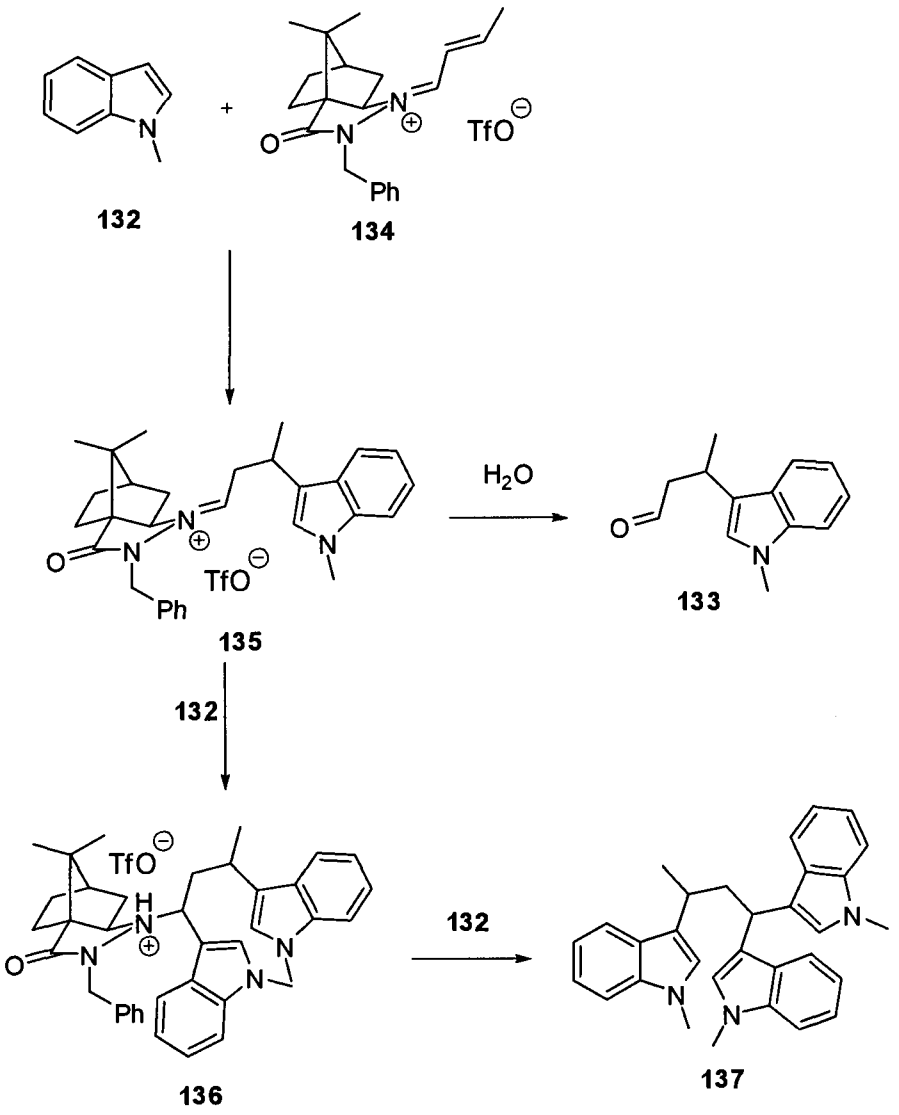
Entry[a]	Solvent	Yield (%)	ee (%)
1[b]	CH_2Cl_2:*i*PrOH	25	61
2[c]	THF:*i*PrOH	27	62
3[d]	CH_3NO_2:*i*PrOH	39	52

[a] 0.20 equiv of catalyst **121**, 0.16 equiv of TfOH, 3.0 equiv of crotonaldehyde, 85:15 solvent ratio, -18 °C, 24 h. [b] Reaction performed at -78 °C for 72 h. [c] Approx. 30 equiv. of H_2O was added. [d] Reaction performed at 23 °C for 4 h.

Although there was complete consumption of the *N*-methylindole, the products were afforded in poor yields, as shown in table 9. Analysis of all the products that were formed revealed the formation of tri-indole alkyl side product **137** (scheme 13).[33]

[33] a) Shi, M.; Cui, S.-C.; Li, Q.-J.; *Tetrahedron* **2004**, *60*, 6679; b) Ko, S.; Lin, C.; Tu, Z.; Wang, Y.-F., Wang, C.-C.; Yao, C.-F.; *Tet. Lett.* **2006**, *47*, 487.

Scheme 13. The appearance of tri-indole alkyl product.

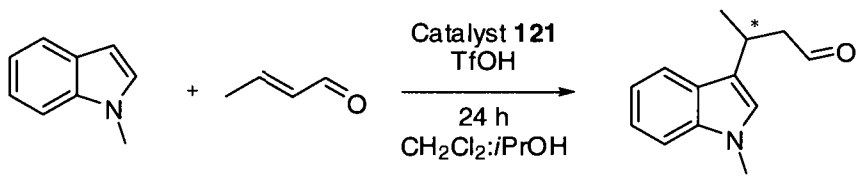


It was observed that once iminium **135** had formed after the reaction of indole **132** with iminium **134** it could undergo two different reaction pathways. Ideally, iminium **135** would be hydrolyzed by H_2O to form the desired alkyl-indole product **133**. However, iminium **135** could also react with a second equivalent of indole **132** via a 1,2-addition to form di-indole iminium **136**, which could react further with a third equivalent

of indole **132** to form tri-indole alkyl product **137** via elimination of hydrazide catalyst.[34] The goal of this project was to optimize the reaction of indole **132** with iminium **134** to maximize the yield of **133** in good enantioselectivity and minimize the formation of tri-indole alkyl product **137**.

The starting point of this project was the optimized conditions elucidated by MacMillan for the Friedel-Crafts alkylation of *N*-methylindole.[32] The first set of experiments was designed to explore the effect of temperature on the reaction of *N*-methylindole with crotonaldehyde.

Table 10. Optimization of the temperature of the Friedel-Crafts alkylation of indole.



132 **97** **133**

Entry[a]	Temperature (°C)	Yield **90** (%)	ee (%)[b]
1[c]	-78	25	61
2	-18	29	60
3	23	30	44

[a] 0.20 equiv of catalyst **121**, 0.16 equiv of TfOH, 10 equiv of crotonaldehyde, 85:15 CH_2Cl_2:*i*PrOH, 24 h. [b] % ee determined by chiral HPLC. [c] Reaction performed for 72 h.

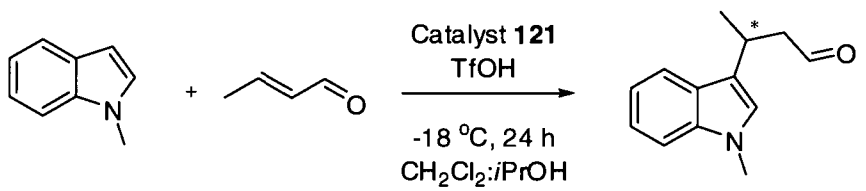
Under the initial reaction conditions, -78 °C in CH_2Cl_2:*i*PrOH for 72 hours (table 10, entry 1), the reaction afforded product **133** after three days in 25 % yield and 61 % ee. A similar yield was observed when the reaction was warmed to -18 °C, however, the reaction was complete in only 24 hours (entry 2). At room temperature product **133** was

[34] Gibbs, T.J.K.; Tomkinson, N.C.O.; *Org. Biomol. Chem.* **2005**, *3*, 4043.

isolated in comparable yield as at lower temperatures, albeit with lower enantioselectivity. The short reaction time and reasonable temperature led us to continue using -18 °C as the optimized temperature.

As water is required in the catalytic cycle to generate catalytic turnover, it was decided to explore the effect of stoichiometric amounts of water to the reaction to see if the yield could be increased.[30]

Table 11. The effect of water on the reactivity of *N*-methylindole with crotonaldehyde



132 **97** **133**

Entry[a]	Equiv. H_2O	Yield **133** (%)	ee (%)[b]
1	0	29	60
2	0.5	40	54
3	1	36	61
4	2	38	54
5	5	35	54

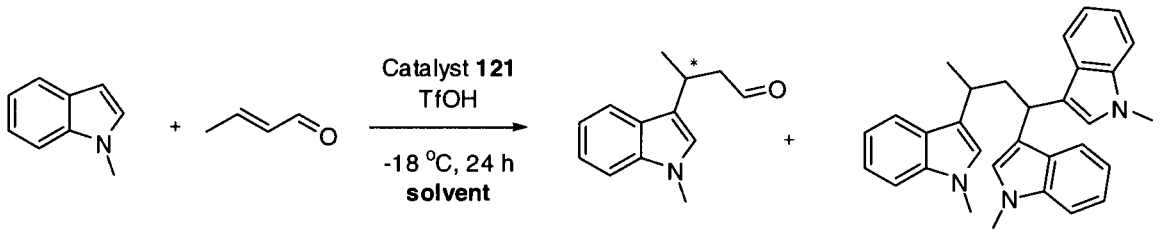
[a] 0.20 equiv of catalyst **121**, 0.16 equiv of TfOH, 10 equiv of crotonaldehyde, 85:15 CH_2Cl_2:*i*PrOH, -18 °C, 24 h. [b] % ee determined by chiral HPLC.

Since water was required to regenerate the catalyst in the catalytic cycle, it was unsurprising that the addition of 0.5 equivalents of water to the reaction increased the overall yield with a minimal effect on enantiopurity (table 11, entry 2). Doubling the amount of water maximized the enantioselectivity (**133** produced in 61 % ee of the *R*-enantiomer), however, the yield suffered slightly. A further increase to two equivalents of the water additive showed marginal change in yield but a slight drop in

enantioselectivity (entry 4). As shown in entry 5, a large excess of water (5 equivalents relative to *N*-methylindole **132**) resulted in a minor alteration of both yield and % ee.

Since the yield of alkyl indole **133** was comparable no matter how much water was added to the reaction, the use of one equivalent was chosen for further optimizations as it gave the highest enantioselectivity. We hypothesized that a more complete examination of the effects of solvent could result in an increase in yield and % ee.

Table 12. The effect of different solvent on the synthesis of alkyl-indole product **133**.



132 **97** **133** **137**

Entry[a]	Solvent	Yield **132** (%)[b]	Yield **137** (%)[c]	ee (%)[d]
1	CH_2Cl_2:*i*PrOH	36	nd	61
2	CH_3NO_2:*i*PrOH	26	70	13
3[e]	CH_3NO_2:H_2O	76	8	22
4	MeOH:H_2O	54	30	57
5	EtOH:H_2O	62	31	54
6	*i*PrOH:H_2O	45	40	nd
7[e]	H_2O	31	54	46
8	CF_3CH_2OH:H_2O	45	nd	17
9	CF_3CH_2OH	25	nd	33
10	DMSO	20	45	30
11	$CHONH_2$	10	25	60

[a] 0.20 equiv of catalyst **121**, 0.16 equiv of TfOH, 10 equiv of crotonaldehyde, 1 equiv of H_2O, -18 °C, 24h. [b] Isolated yield. [c] Yield determined by ^1H NMR. [d] % ee determined by chiral HPLC. [e] Reaction performed at room temperature for 1 h.

The choice of solvent had a large effect on the enantioselectivity of the reaction. An 85:15 mixture of dichloromethane:isopropanol afforded desired alkyl-indole product

133 in low yield and moderate enantioselectivity (table 12, entry 1). The yield of tri-indole alkyl product **137** was not determined. The use of nitromethane:isopropanol (85:15 mixture) was examined, giving product **133** in 26 % isolated yield and 13 % ee. It was observed that the remaining indole continued to react, forming the undesired tri-indole alkyl product **137** in 70 % yield. When the reaction was performed with H_2O as the co-solvent (entry 3) at room temperature, the yield of **133** was greatly increased to 76 %, and the yield of **137** suffered. Although this result was promising, the enantioselectivity of the reaction under these conditions was poor, affording product **133** in only 22 % ee as shown in entry 3.

The use of polar protic solvents was also explored. When a 3:1 mixture of MeOH:H_2O was employed (entry 4) some success was observed, as product **133** was isolated in 54 % yield and 57 % ee with a diminished yield of the undesired product **137**. When ethanol and water (3:1 mixture) were used as the solvent system, the reaction showed good conversion to the desired product **133** in good yield and good enantioselectivity (entry 5). The yield of the over-reacted product **137** was minimized with this solvent combination. To examine if this trend would continue, a 3:1 mixture of isopropanol:H_2O was examined. The use of this solvent combination produced Friedel-Crafts alkylation product **133** in 45 % yield and product **137** in 40 % yield. The enantiomeric excess was not determined for this solvent combination.

There has been recent literature precedents for the use of organic reactions in aqueous solvents, as H_2O can create artificially high concentrations by forcing the organic materials together.[30,35] When the reaction was performed with water as solvent,

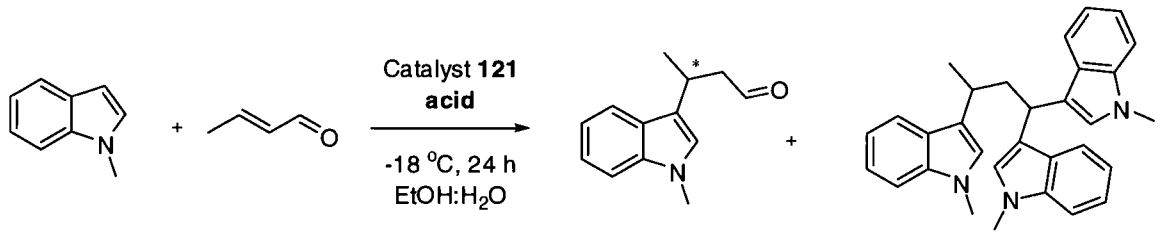
[35] a) Narayan, S.; Finn, M.G.; Fokin, V.V.; Kolb, H.C.; Sharpless, K.B.; *Angew. Chem. Int. Ed.* **2005**, *44*, 3275; b) Klijn, J.E.; Engberts, J.B.F.N.; *Nature* **2005**, *435*, 746.

product **133** was isolated in low yield (entry 7) with the majority of indole **132** reacting to form undesired product **137**. Moderate enantioselectivity was observed, however, with the *R*-enantiomer being favoured in a 73:27 ratio over the *S*-enantiomer.

The use of polar solvents appeared to have positive effects on the reaction of *N*-methylindole **132** with crotonaldehyde **97** as shown in entries 4 and 5, further polar solvents were therefore explored. As shown in entry 8, the use of a 3:1 mixture of 2,2,2-trifluoroethanol:H_2O was not as beneficial as the use of EtOH:H_2O, with product **132** isolated in 45 % yield and 17 % ee. When the reaction was performed under the same conditions with only a stoichiometric amount of H_2O added, the isolated yield of **132** suffered (entry 9). The use of polar, aprotic solvents showed poor reactivity, as shown in entries 10 and 11. When DMSO was employed as the solvent for the reaction, the yield of product **132** was poor (entry 10). Formamide as the choice of solvent gave poor reactivity overall, with low yields of both product **132** (10 %) and of side product **137** (25 %). However, formamide did show good enantioselectivity, generating the *R*-enantiomer of **132** in 60 % ee.

With the solvent optimization complete, it was hypothesized that a change in pKa of the co-catalyst might affect both the yield and the enantioselectivity, as it was possible that the acid was catalyzing the over-reaction of product **133** to tri-indole alkyl product **137**. In order to explore this hypothesis, the effect of different acids on the reactivity was explored.

Table 13. The effect of acid on the conversion to alkyl-indole **133**.



132 **97** **133** **137**

Entry[a]	Acid	Yield **133** (%)[b]	Yield **137** (%)[c]	ee (%)[d]
1	None	15	0	1
2[e]	TfOH	12	0	0
3	TfOH	62	31	54
4	$HClO_4$	11	nd	34
5	TFA	43	nd	nd
6	Boc-Gly-OH	36	52	2
7	Boc-Ala-OH	39	56	1
8	Boc-Phe-OH	22	77	5
9	Boc-(*D*)-Phe-OH	19	nd	6

[a] 0.20 equiv of catalyst **121**, 0.16 equiv of TfOH, 10 equiv of crotonaldehyde, -18 °C, 24h. [b] Isolated yield. [c] Yield determined by ^{1}H NMR. [d] % ee determined by chiral HPLC. [e] No organocatalyst was added.

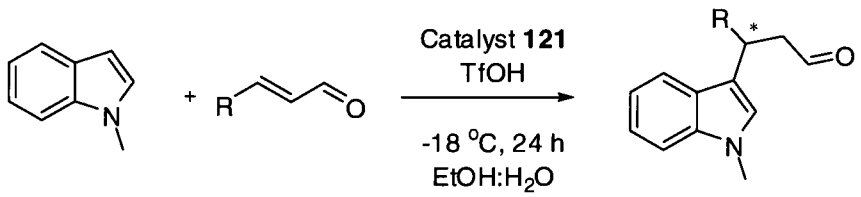
The use of an acid co-catalyst was required, as shown by table 13, entry 1, which afforded minimal yield of alkyl-indole product **133** when no acid was added. There was no appearance of tri-indole alkyl product **137** under these reaction conditions. In the absence a chiral organocatalyst, the reaction did not perform well, with product **133** isolated in 12 % yield as a racemic mixture. The use of a very strong acid (TfOH, entry 3) afforded a good yield of product **133** with good enantioselectivity. However, using a similarly strong acid ($HClO_4$) was less successful, generating low amounts of product **133** (entry 4). The use of trifluoroacetic acid did not prove effective in the reaction, as shown by entry 5.

The use of chiral amino acid co-catalysts was also attempted, as it had been shown that enantioselectivity could be improved with their use in some applications.[36] The first trial was made with an *N*-Boc protected glycine, an achiral amino acid, to see if reactivity would occur (entry 6). Under these conditions, product **133** was isolated as a racemic mixture in 36 % yield. An additional 52 % of *N*-methylindole **132** was converted to product **137**. The use of *N*-Boc protected (*L*)-alanine was ineffective (entry 7), generating product **133** in similar results to the reaction with glycine as co-catalyst. The *N*-Boc protected amino acids (*L*)-phenylalanine and (*D*)-phenylalanine were also submitted to the reaction conditions but to no avail (entries 7 and 8).

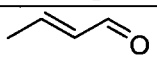
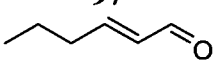
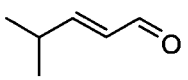
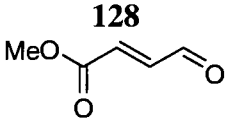
Given the results of the optimization of the reaction of crotonaldehyde with *N*-methylindole, it was decided to explore the scope of the reaction using the optimal conditions: a 3:1 mixture of EtOH:H_2O as this solvent system and TfOH as the acid co-catalyst, as these conditions maximized both the yield and enantiomeric excess of alkyl-indole **133** while minimizing the formation of tri-indole alkyl **137**. The scope of the reaction was examined by exploring different β-substitutions on the α,β-unsaturated aldehyde.

[36] a) Ibrahem, I.; Zou, W.; Xu, Y.; Córdova, A.; *Adv. Synth. Catal.* **2006**, *348*, 211; b) Dziedzic, P.; Zou, W.; Ibrahem, I.; Sundén, H.; Córdova, A.; *Tetrahedron Lett.* **2006**, *47*, 6657.

Table 14. Modifications to the electrophile



132 **58** **138**

Entry[a]	Electrophile	Product	Yield (%)[b]	ee (%)[c]
1	 **97**	**132**	62	54
2	 **126**	**137**	45	55
3	 **128**	**139**	48	65
4	 **140**	**141**	28	60

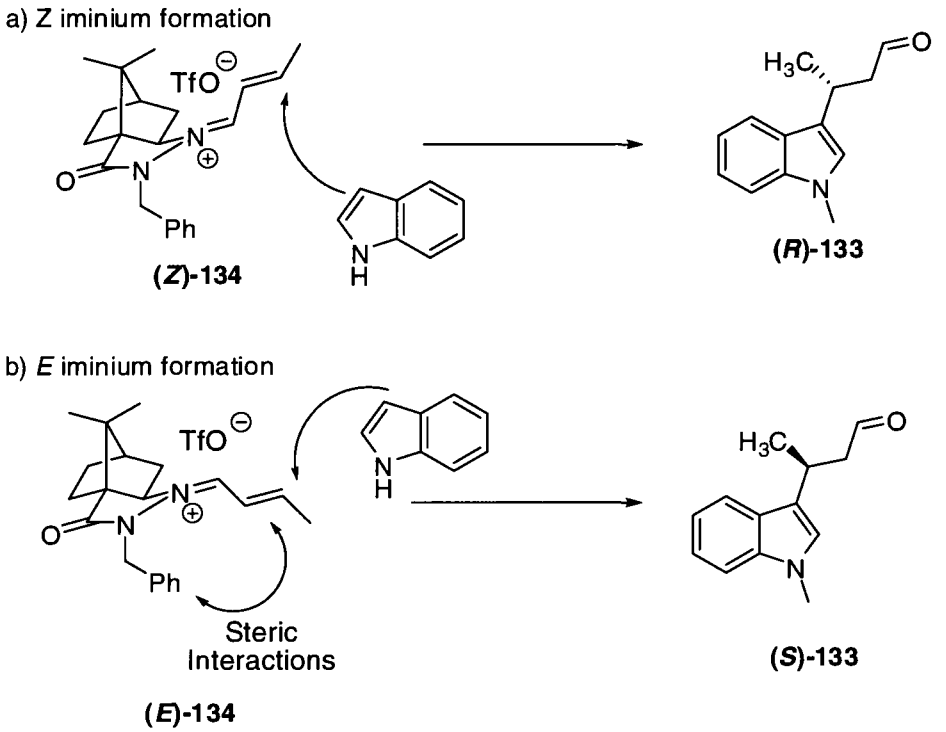
[a] 0.20 equiv of catalyst **121**, 0.16 equiv of TfOH, 10 equiv of crotonaldehyde, 3:1EtOH:H_2O-18 °C, 24h. [b] Isolated yield. [c] % ee determined by chiral HPLC.

The reaction tolerated different substituents at the β-position of the α,β-unsaturated aldehydes, as shown in table 14. The use of a longer alkyl chain on the aldehyde component, as shown with 2-hexenal **126**, generated product **138** in 45 % yield and 55 % ee (entry 2). Branching on the alkyl chain (5-methyl-2-pentenal **128**, entry 3) resulted in similar conversion as shown in entry 2, however, a small increase in enantioselectivity was observed, as product (***R***)-**139** was isolated in 65 % ee, suggesting that increased steric bulk at the reactive centre had an effect on facial selectivity. When aldehyde **140** was employed in the reaction mixture, the resulting product **141** was isolated with good enantioselectivity (60 % ee) but in poor yield (entry 4).

2.1.2 Modifications to the catalyst design

The second goal of this project was to design new hydrazide-based organocatalysts to explore their usefulness with the alkylation of *N*-methylindole. As the optimized conditions had been elucidated, the synthesis of new organocatalysts was carried out.

Scheme 14. How the *E*/*Z* ratio of iminium formation affects enantioselectivity.

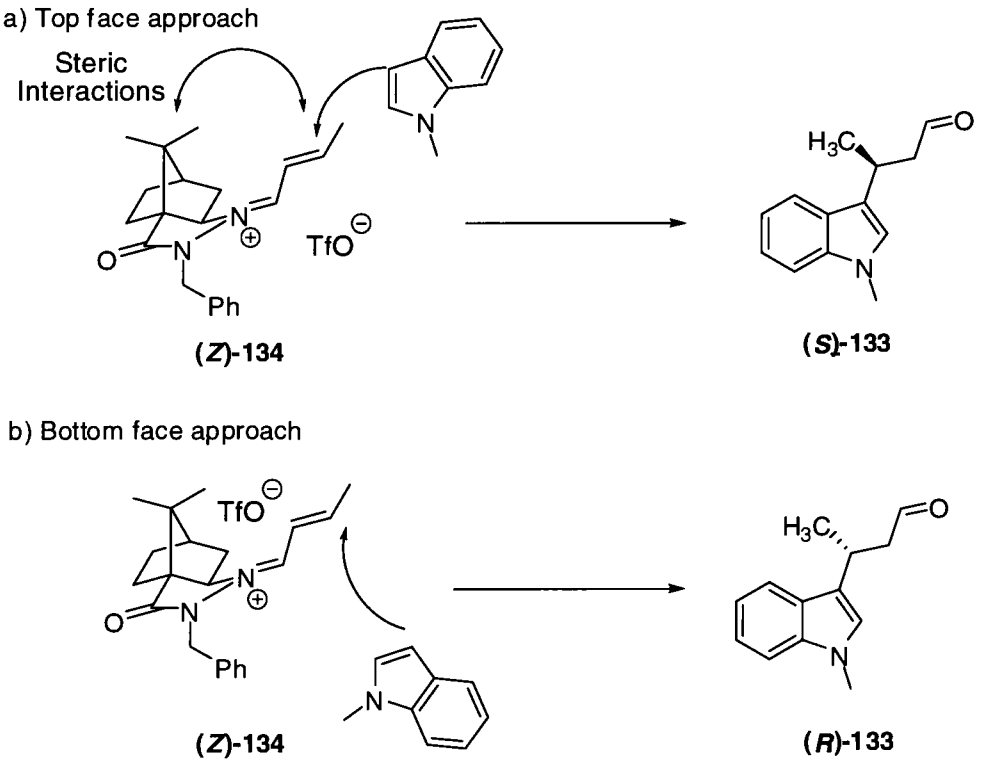


During the condensation of catalyst **121** with aldehyde **97** two possible iminium structures can be formed; the *Z* isomer **(*Z*)-134** shown in scheme 14a, or the *E* isomer **(*E*)-134** shown in scheme 14b. Approach of the nucleophile to these two isomers will result in the formation of either the *R* or the *S* enantiomer of product **133**. The function of the benzyl group attached to the amide nitrogen is to control the *E*/*Z* formation of

iminium **134**. Steric interactions between the benzyl group and the tail end of the α,β-unsaturated aldehyde are intended to prevent the formation of *E*-iminium **134**. This increases the population of **(*Z*)-134**, resulting in an increase in the selectivity for the *R*-enantiomer.

The newly designed organocatalyst must also be able to control top vs. bottom face approach of the nucleophile. Assuming only the *Z*-iminium is formed, approach of the nucleophile from either the top face (scheme 15a) or the bottom face (scheme 15b) will produce either the *S* or *R* enantiomers respectively.

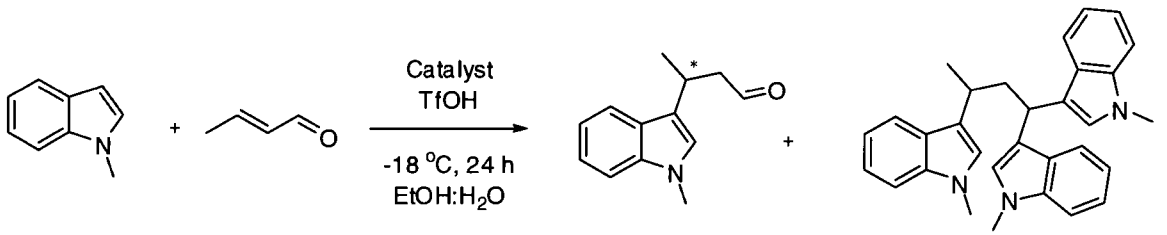
Scheme 15. The effect of top vs. bottom face approach of the nucleophile to the iminium on enantioselectivity.



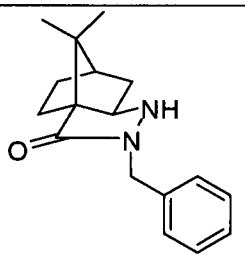
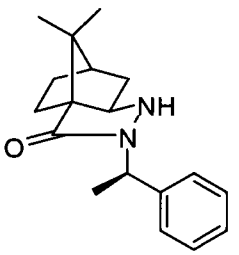
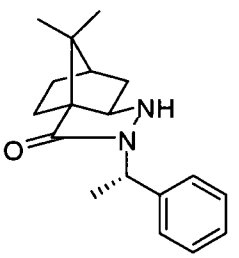
The geminal dimethyl groups are responsible for controlling the approach of the nucleophile. As the nucleophile approaches from the top face, steric interactions with the geminal dimethyl groups will prevent attack at the β-position of iminium. However, steric interactions are minimized as the nucleophile approaches from the bottom face of the iminium. This makes bottom-face approach the lower energy, more favoured pathway of the nucleophile.

Modifications to the catalyst design were made by replacing the benzyl group with other functional groups in order to increase the selectivity for the *Z*-iminium. No modifications were made to the geminal dimethyl groups in an effort to increase bottom-face approach over top-face approach due to the difficulty in synthesis of these products. The efficacy of newly designed catalysts was tested with the optimized conditions for the Friedel-Crafts alkylation of *N*-methylindole **132** with crotonaldehyde **97**.

Table 15. Modifications of the catalyst at the α-benzyl position.



132 **97** **133** **137**

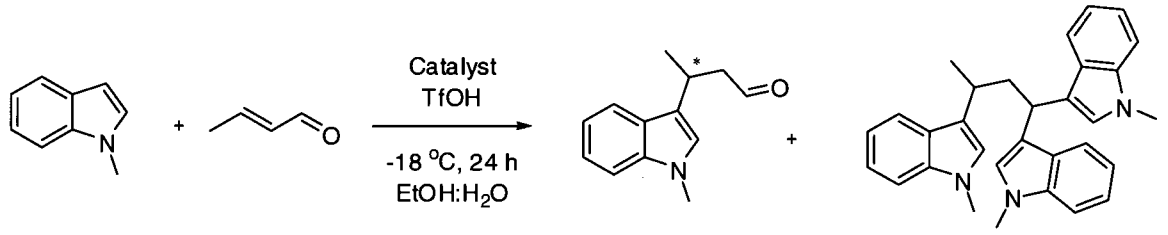
Entry[a]	Catalyst	Yield **133** (%)[b]	Yield **137** (%)[c]	ee (%)[d]
1	 **121**	62	31	54
2	 **142**	41	nd	12
3	 **143**	37	nd	48

[a] 0.20 equiv of organocatalyst, 0.16 equiv of TfOH, 10 equiv of crotonaldehyde, -18 °C, 24h. [b] Isolated yield. [c] Yield determined by ^{1}H NMR. [d] % ee determined by chiral HPLC.

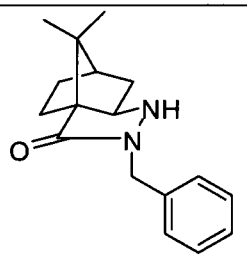
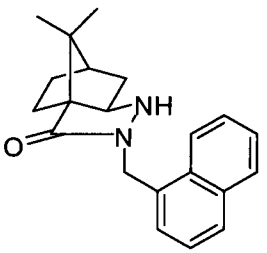
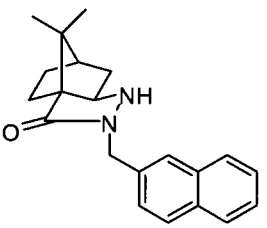
The first modification made to catalyst **121** was to introduce a methyl group to the α-position of the benzyl side-chain. The hypothesis was that a methyl group on the benzyl chain might lock the phenyl ring in place, increasing the *E/Z* iminium selectivity.

The use of the (*R*)-methyl substituted catalyst **142** (table 15, entry 2) showed diminished enantioselectivity, isolating product **133** in only 12 % ee, suggesting that this configuration locked the phenyl group away from iminium and could not control the stereochemistry of the iminium. Enantioselectivity was almost restored with the use of the (*S*)-methyl substituted catalyst **143**, as shown in entry 4. This indicated that the phenyl ring was in position to affect the *E*/*Z* selectivity. However, the lower enantioselectivity relative to the first generation catalyst (entry 2) suggested that some amount of free rotation was required in order to maximize formation of the *Z*-iminium.

Table 16. The effect of larger aromatic groups on catalyst activity in the Friedel-Crafts alkylation of *N*-methylindole.



132 **97** **133** **137**

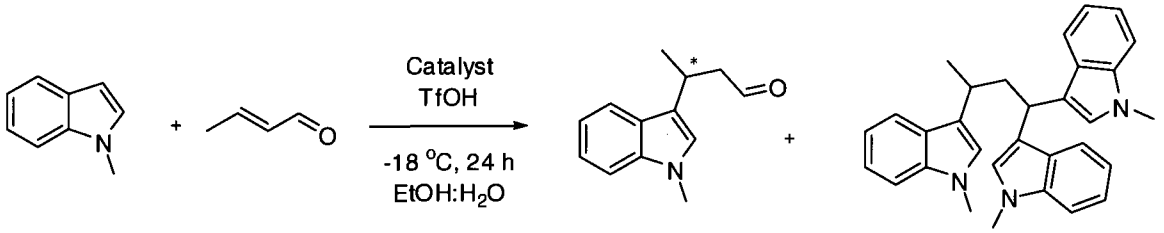
Entry[a]	Catalyst	Yield **133** (%)[b]	Yield **137** (%)[c]	ee (%)[d]
1	 **121**	62	31	54
2	 **122**	54	46	55
3	 **144**	30	51	38

[a] 0.20 equiv of organocatalyst, 0.16 equiv of TfOH, 10 equiv of crotonaldehyde, -18 °C, 24h. [b] Isolated yield. [c] Yield determined by ^{1}H NMR. [d] % ee determined by chiral HPLC.

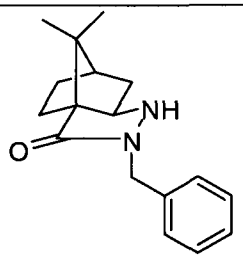
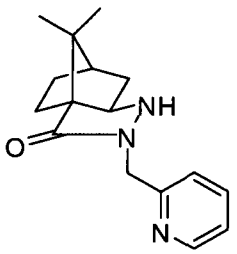
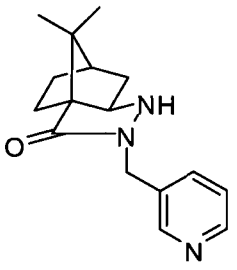
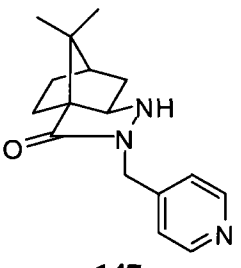
The second modification made to the first generation catalyst **121** was to increase the size of the benzyl side chain. The increased size of the aromatic group was explored

with catalysts **122** and **144** (table 16). The use of 1-naphthyl catalyst **122** (entry 2) showed very similar reactivity to the first generation catalyst (entry 1). The yield of the reaction was marginally lower and the enantiomeric excess was slightly higher. However, the isolated yield of side product **133** was greatly increased compared to when catalyst **121** was used. We hypothesized that 2-naphthyl catalyst **144** would show increased enantioselectivity, as the 2-naphthyl group had a very similar orientation in space as the benzyl group. Our hypothesis was rejected, as shown in entry 3, since increased enantioselectivity was not observed. Catalyst **143** afforded lower yield and lower enantioselectivity of product **133** as compared to catalyst **121**. As well, the yield of **137** was increased with this catalyst.

Table 17. The effect of replacing the phenyl group on the catalyst with a heterocycle.



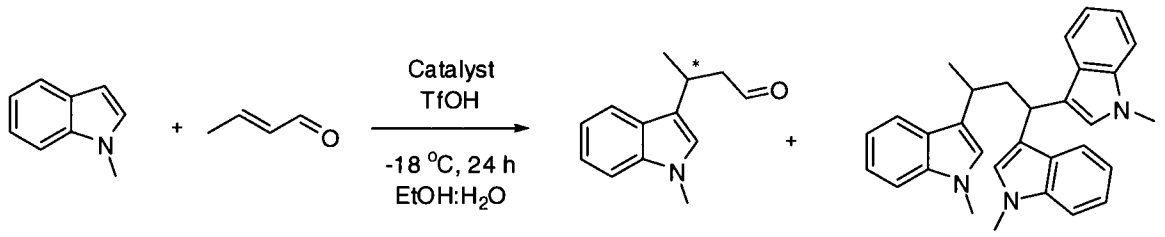
132 **97** **133** **137**

Entry[a]	Catalyst	Yield **133** (%)[b]	Yield **137** (%)[c]	ee (%)[d]
1	 **121**	62	31	54
2	 **145**	20	70	24
3	 **146**	41	59	56
4	 **147**	29	Trace	57

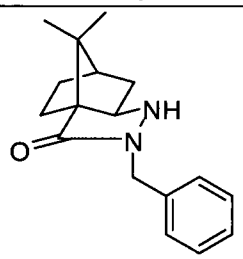
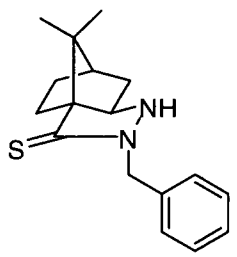
[a] 0.20 equiv of organocatalyst, 0.16 equiv of TfOH, 10 equiv of crotonaldehyde, -18 °C, 24h. [b] Isolated yield. [c] Yield determined by ^{1}H NMR. [d] % ee determined by chiral HPLC.

By replacing the phenyl group with a pyridine moiety, we hoped to increase the catalyst activity in the alkylation of *N*-methylindole **132**. The pyridinyl catalysts were obtained prepared from Mathieu Lemay during work on his PhD thesis.[31] The use of 2-pyridinyl catalyst **145** showed diminished enantioselectivity, affording product **133** in low yield and low ee (table 17, entry 2). Catalyst **146** showed similar reactivity to the first generation catalyst, affording product **133** in good ee (entry 3). However, the yield of product **133** suffered when this catalyst was used in the reaction. When 4-pyridinyl catalyst **147** was employed, the enantioselectivity was higher than that of the reaction with catalyst **121**, but the yield of the reaction was greatly lowered (29 %). It is interesting to note that with catalyst **147** only trace amounts of side-product **137** were detected.

Table 18. Comparison of thiohydrazides and hydrazide-based catalysts.



132 **97** **133** **137**

Entry[a]	Catalyst	Yield **133** (%)[b]	Yield **137** (%)[c]	ee (%)[d]
1	 **121**	62	31	54
2	 **148**	31	34	48

[a] 0.20 equiv of organocatalyst, 0.16 equiv of TfOH, 10 equiv of crotonaldehyde, -18 °C, 24h. [b] Isolated yield. [c] Yield determined by ^{1}H NMR. [d] % ee determined by chiral HPLC.

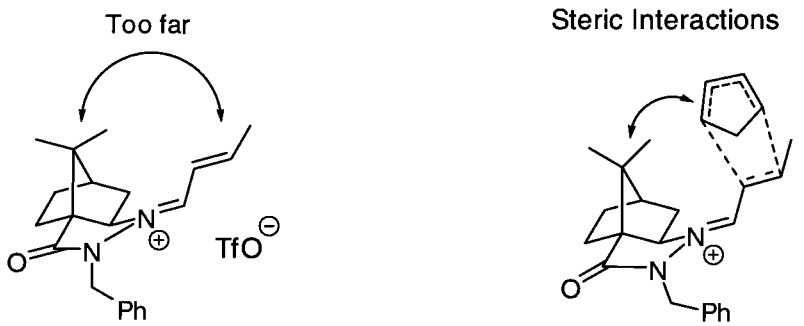
The final catalyst modification made was to change the hydrazide to a thiohydrazide by treating catalyst **121** with Lawesson's reagent[37] generating catalyst **148**. This new catalyst was inefficient in the transformation of **132** to product **133**, converting 31 % of the starting material to product in 48 % ee (table 18, entry 2).

[37] Jesberger, M.; Davis, T.P.; Barner, L.; *Synthesis* **2003**, 1929.

After testing many different catalyst scaffolds, it appeared that the first generation catalyst performed the best, achieving product **133** in 62 % yield and 54 % ee, with a minimal formation of side product **137**.

The efficacy of the Friedel-Crafts alkylation of *N*-methylindole with crotonaldehyde was moderate at best. High yields and high enantioselectivities were not observed. It appears that the *E*/*Z* iminium selectivity is adequately controlled with catalyst **121**, as no other catalyst designs demonstrated a significant increase in enantioselectivity. However, it is possible that catalyst **121** does not properly control the top vs. bottom-face approach of the nucleophile (figure 5).

Figure 6. The distance of the geminal dimethyl groups from the reaction centre.



It was possible that the geminal dimethyl groups are too far from the reaction centre at C3 of the iminium to have exerted enough steric bias to control the approach of the nucleophile. If this were the case, high enantioselectivity would not be possible, as the energy difference in the approach of the nucleophile from either the top or the bottom face of the molecule would not be enough to produce different enantiomers. The use of bulky alkyl or aryl groups at the geminal position could increase the enantiocontrol by increasing the overall steric bulk of the catalyst. This could be an interesting area for

further research. The catalyst does have enough steric bulk to exert steric hinderance at the C1 and C2 positions to control top vs. bottom face approach as shown in the case of the [4+2] or [3+2] cycloadditions, in which both C2 and C3 are involved in the reaction with the diene and good enantioselectivities are possible. This hints that catalyst **121** might be quite useful in enamine catalysis. The α-nitrogen could also serve to increase the nucleophilicity of the newly formed enamine, which could perhaps increase the reactivity.

Part B.

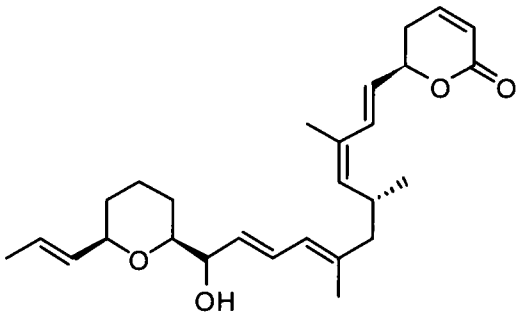
The development of the palladium catalyzed addition of organoborates to alkynyl esters: Synthesis of trisubstituted olefins as single isomers

Chapter 3

3.1 Introduction

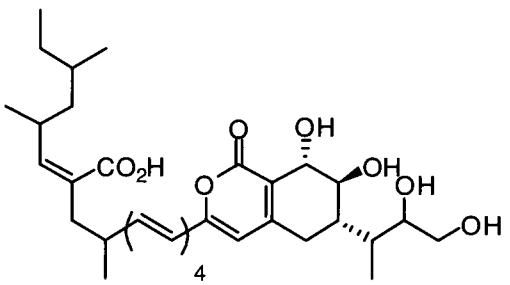
Trisubstituted olefins represent an important motif in organic chemistry and are ubiquitous in medicinal and natural products. The spatial orientation of the substituents around trisubstituted olefins is important to the functionality of the molecule. Ratjadone A **149** is a polyketide isolated from cultures of the myxobacterium *Sorangium cellulosum.*[38] It displays potent antifungal activity and significant cytotoxicity in certain mammalian cell lines.[39] Orevactaene **150** represents a trisubstituted polyene isolated from the bacterium *Epicocum nigrum* WC47880.[40] It is an HIV-1 *rev* response element antagonist that helps to prevent HIV RNA from exiting the nucleus and overwhelming the host's defenses.

Figure 7. Examples of natural products containing trisubstituted olefin.



Ratjadone A

149



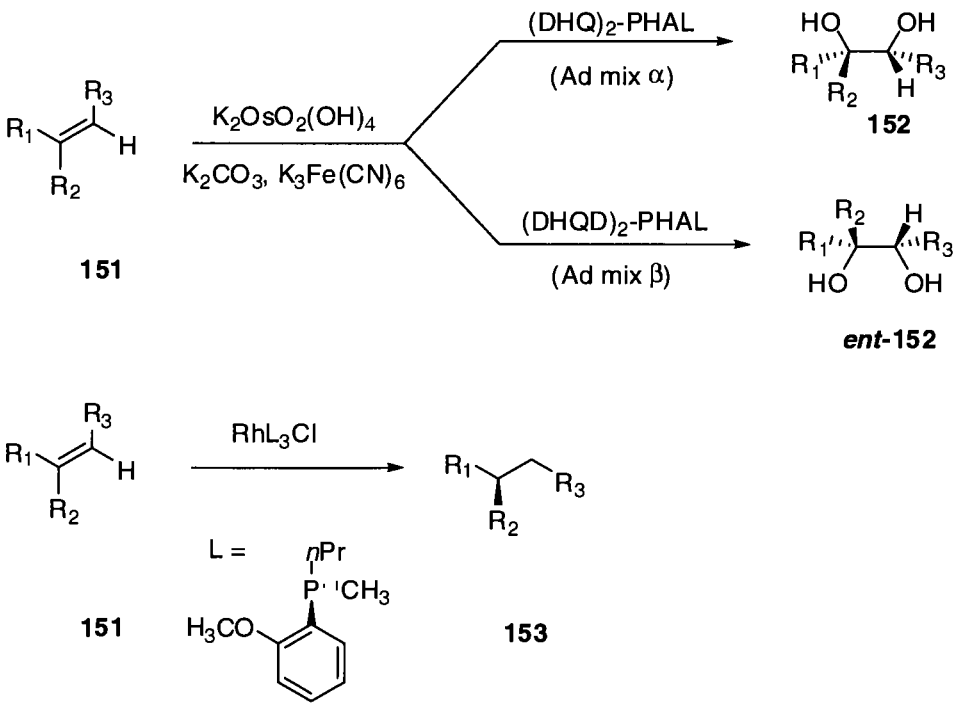
Orevactaene

150

[38] Williams, D.R.; Ihle, D.C.; Plummer, S.V.; *Org. Lett.* **2001**, *3,* 1383.
[39] Gerth, K.; Schummer, D.; Höfle, G.; Irschik, H.; Reichenbach, H.; *J. Antibiot.* **1995**, *48,* 973
[40] Organ, M.G.; Bilokin, Y.V.; Bratovanov, S.; *J. Org. Chem.* **2002**, *67,* 5176.

The importance of trisubstituted olefins extends beyond natural products, as they represent important starting materials and can be further functionalized to afford different organic substances. The Sharpless Dihydroxylation[41] takes a pre-existing trisubstituted olefin **151** and, using either Ad-mix-α or Ad-mix-β, can synthesize new chiral diol **152** or ***ent*-152** respectively. A second important reaction is the asymmetric hydrogenation of the alkene to the alkane developed by William Knowles.[42] Knowles showed that it was possible to successfully reduce alkene **151** to a chiral alkane **153** with the use of chiral phosphine ligand and rhodium (scheme 16). These reactions are very important since they can synthesize chiral products from achiral starting materials. Both chemists shared the Nobel Prize in 2001 for their work in asymmetric catalysis.

Scheme 16. Further reactions with trisubstituted olefin substrates



[41] Kolb, H.C.; Van Nieuwenhze, K.; Sharpless, K.B.; *Chem. Rev.* **1994**, *94*, 2483.
[42] a) Vineyard, B.D.; Knowles, W.S.; Sabacky, M.J.; Bachman, G.L.;Weinkauff, D.J.; *J. Am. Chem. Soc.* **1977**, *99*, 5946; b) Knowles, W.S.; *Acc. Chem. Res.* **1983**, *16*, 106.

3.2 Synthetic Strategies

3.2.1 Direct Approaches

The synthesis of trisubstituted olefins is not a new reaction. Direct approaches towards trisubstituted olefins involve the formation of the alkene via an elimination step. A common direct approach is the Wittig olefination developed by Georg Wittig,[43] for which he was awarded the Nobel Prize in 1979. The Wittig reaction involves the synthesis of an alkene from a carbonyl and a phosphine ylid. The carbonyl and the ylid undergo a formal [2+2] cyclization to form an oxaphosphetane intermediate which will then undergo a retro-[2+2] reaction to eliminate the desired alkene product and PPh_3O.

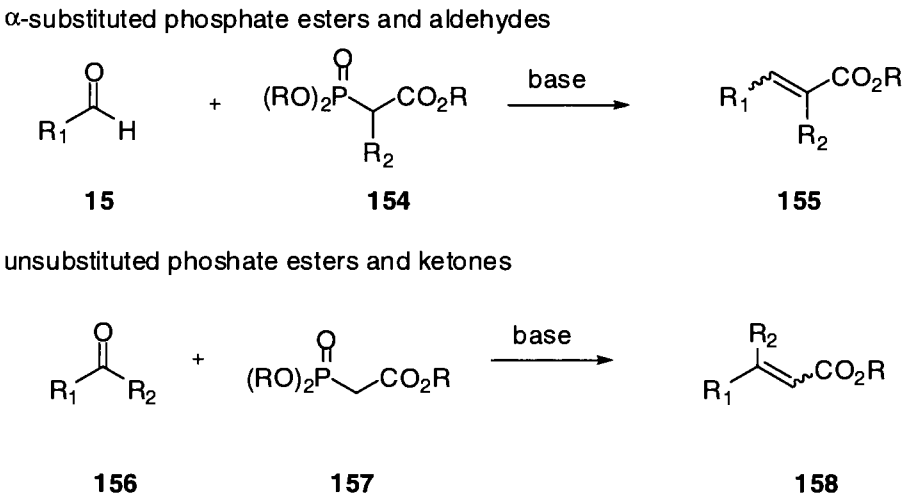
Although the Wittig olefination represents a powerful method to synthesize alkenes, it has some limitations. The ratio of isomers in the products can be difficult to control, generating a mixture of *E* and *Z*-alkenes. Sterically encumbered ketones react poorly under Wittig reaction conditions, limiting the scope of available trisubstituted olefin products. The Horner-Wadsworth-Emmons reaction represents an improvement on the Wittig olefination. It replaces the phosphonium ylid with phosphoryl-stabilized carbanions **154**.[44] In order to form trisubstituted olefins, α-substituted phosphates **154** can be reacted with aldehydes **15** to give α-substituted α,β-unsaturated esters **155**, or ketones **156** can be reacted with unsubstituted phosphates **157** to form β-substituted α,β-unsaturated esters **158** (scheme 17).

---

[43] a) Valentine Jr., D.H.; Hillhouse, J.H.; *Synthesis* **2003**, 317; b) Maryanoff, B.E., Reitz, A.B.; *Chem. Rev.* **1989**, *89*, 863.

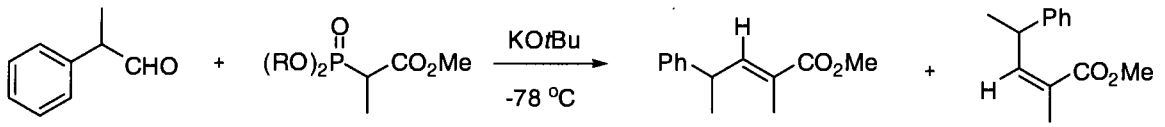
[44] a) Iorga, B.; Eymery, F.; Mouriès, V.; Savignac, P.; *Tetrahedron* **1998**, *54*, 14637; b) Wadsworth Jr., W.S.; *Org. React.* **1977**, *25*, 73.

Scheme 17. An overview of the Horner-Wadsworth-Emmons reaction.



We will first examine the use of α-substituted phosphates in order to form trisubstituted olefins stereoselectively. Control of stereochemistry can be exerted by using different phosphonate esters, as shown by scheme 18. When aldehyde **159** was reacted with the ethyl-phosphonate ester **160** trisubstituted olefin products **162** were obtained in a 5:95 ratio of *E:Z* isomers. However, when the reaction was performed with phosphate **161**, in which the ethyl group had been replaced by an isopropyl group, the stereoselectivity was reversed and trisubstituted olefin products were isolated in a 95:5 ratio favouring the **(*E*)-162** over **(*Z*)-162**.

Scheme 18. Stereocontrol of the formation of trisubstituted olefins using the Horner-Wadsworth-Emmons reaction.

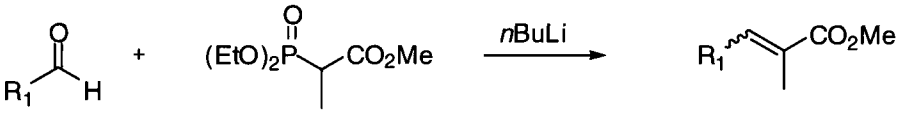


159		(*E*)-162	(*Z*)-162
	160 R = Et	5	95
	161 R = *i*Pr	95	5

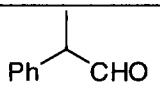
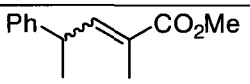
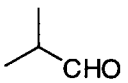
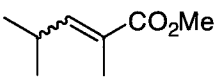
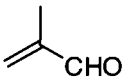
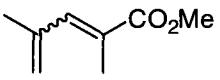
The stereochemistry of the olefin products can be controlled by varying the temperature of the reaction.[45] At low reaction temperatures, the reaction tends to favour one isomer. At higher temperatures, statistical mixtures of isomers are often observed, as equilibration of the oxaphosphetane intermediate is possible.

[45] Etemad-Moghadam, G.; Seyden-Penne, J. *Tetrahedron* **1984**, *40*, 5153.

Table 19. The effect of temperature on the *E:Z* ratio of trisubstituted olefins.



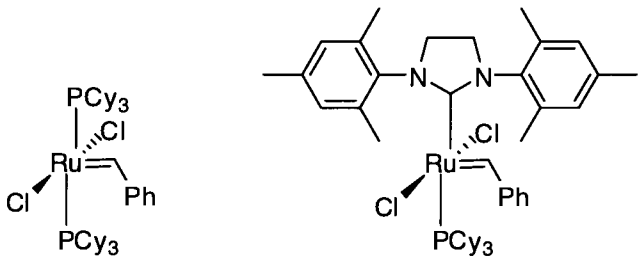
15 **160** **163**

Entry	Substrate	Product	Temperature (°C)	*E:Z* ratio
1			-78	5:95
2	**159**	**162**	0	46:54
3			-78	10:90
4	**164**	**165**	20	50:50
5			-78	65:35
6	**166**	**167**	20	90:10

When reacting aldehyde **159** with phosphonate **160** at -78 °C (table 19, entry 1), trisubstituted olefin product **162** is obtained as a 5:95 ratio of *E* and *Z* isomers. However, upon warming the reaction to 0 °C (entry 2), the stereoselectivity for the reaction was lost and the products were isolated in a 46:54 ratio of *E:Z* isomers. Similarly, the reaction of isobutyraldehyde **164** with phosphonate **160** at -78 °C (entry 3) gave good stereoselectivity, affording a 10:90 *E:*Z ratio of isomers of trisubstituted olefin product **165**; yet at room temperature (entry 4), there was no stereoselectivity in this reaction, as compound **165** was isolated as a 50:50 mixture of *E:Z* isomers. Low temperatures are not always required for excellent stereocontrol, as demonstrated by entry 5 and 6. Cooling the reaction of methacrylaldehyde **166** with phosphonate **160** resulted in the synthesis of olefin product **167** as a 65:35 mixture of *E* and *Z* isomers. Increased stereocontrol was observed when the reaction was performed at room temperature, giving product **167** as a 90:10 mixture favouring the *E* isomer over the *Z* isomer.

The Horner-Wadsworth-Emmons reaction can also synthesize trisubstituted olefins by reacting ketones with simple phosphonate esters (scheme 17). Under these reaction conditions, the production of the *E* isomer is favoured slightly.[46] The Horner-Wadsworth-Emmons reaction is not without its drawbacks. The synthesis of phosphonate esters can be difficult and single isomer products are rarely observed.

Figure 8. Grubbs first and second generation catalyst.



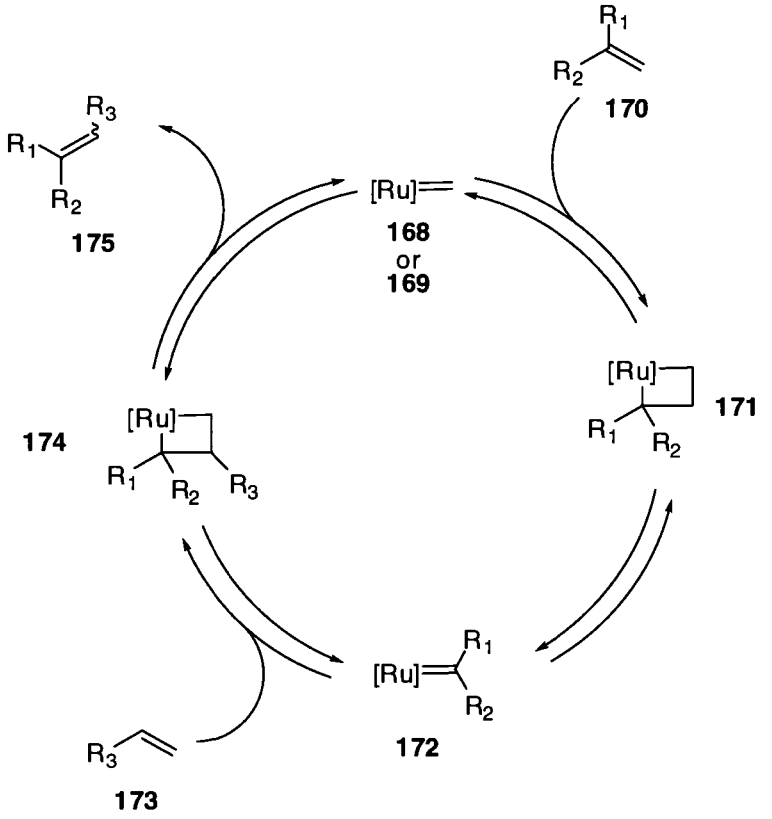
168 **169**

A more modern direct approach to the synthesis of trisubstituted olefins is olefin metathesis using ruthenium catalyst **168** or **169** shown in figure 7. This process was developed by R.H. Grubbs for which he won the Nobel Prize in 2005. The mechanism of olefin cross metathesis involves first the [2+2] cycloaddition of catalysts **168** or **169** with terminal alkene **170**.[47] This is followed by a retro-[2+2] cycloaddition reaction of intermediate **171** to generate ruthenium complex **172** and ethene gas. A second [2+2] cycloaddition with alkene **173** provides ruthenium cyclobutane intermediate **174**, which will perform a second retro-[2+2] cycloaddition to afford trisubstituted olefin **175** and

[46] a) Corey, E.J.; Kwiatkowski, G.T.; *J. Am. Chem. Soc.* **1968**, *90*, 6816; b) Corey, E.J.; Shulman, J.I.; *J. Org. Chem.* **1970**, *35*, 777.
[47] a) Nicolaou, K.C.; Bulger, P.G.; Sarlah, D.; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490; b) Grubbs, R.H.; *Tetrahedron* **2004**, *60*, 7117.

regenerate the ruthenium catalyst. If a 1,1-disubstituted olefin is reacted with a mono-substituted olefin using Grubbs catalysts **169** or **170** a trisubstituted olefin can be produced (scheme 19).

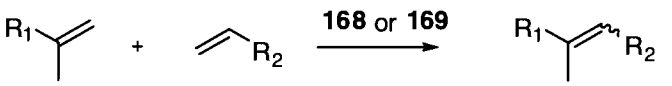
Scheme 19. Synthesis of trisubstituted alkenes by olefin cross metathesis.



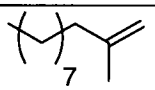
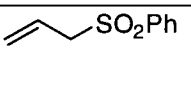
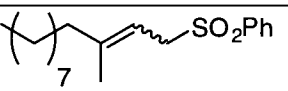
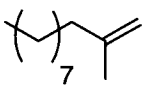
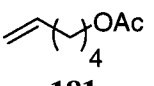
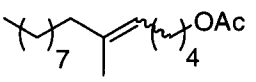
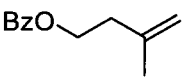
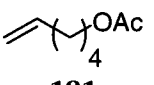
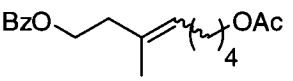
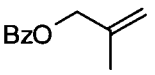
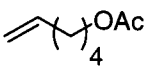
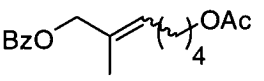
Olefin cross metathesis has seen limited use due to several problems that arise. Unlike ring-closing or ring-opening metathesis, it can be difficult to synthesize the desired olefin product due to the competing homometathesis reactions of alkenes **170** and **173.** However, some modifications can be made to the alkenes in order to suppress homometathesis. The use of 2-substituted olefins can suppress the formation of the tetrasubstituted homodimer product and favour the desired cross metathesis product.

Using a large excess of the 2-substituted olefin can ensure that the cross metathesis reaction goes to completion, as shown in table 2.[48] Control of the stereochemistry of olefin **175** can also be challenging, as the ratio of *E* to *Z* isomers depends upon the relative stereochemistry of intermediate **174**.

Table 20. Synthesis of trisubstituted olefins by olefin cross metathesis.



176 **173** **177**

Entry	R_1	R_2	Product	Yield (%)	*E:Z* ratio
1	 **176**	 **179**	 **180**	87	77:23
2	 **176**	 **181**	 **182**	60	70:30
3	 **183**	 **181**	 **184**	80	74:26
4	 **185**	 **181**	 **186**	81	80:20

Olefin cross methathesis with alkyl substituted 1,1-disubstituted olefins is a very powerful method to synthesize trisubstituted alkenes with the *E*-isomer favoured over the *Z*-isomer (table 2, entries 1 and 2). The reaction of functionalized 1,1-disubstituted olefins **183** and **185** with olefin **181** afforded trisubstituted olefins products **184** and **186** respectively in good yields, as shown in entries 4 and 5. Again, the *E* isomer is slightly

[48] Chatterjee, A.K.; Grubbs, R.H.; *Org. Lett.* **1999**, *1*, 1751.

favoured over the *Z* isomer because it is more energetically favourable to have the benzoyl containing side chain of the disubstituted alkene located *anti* to the acetyl carbon backbone of the monosubstituted alkene. In this spatial orientation, steric interactions between the two larger side chains are minimized. Under the reaction conditions no homometathesis product was observed.

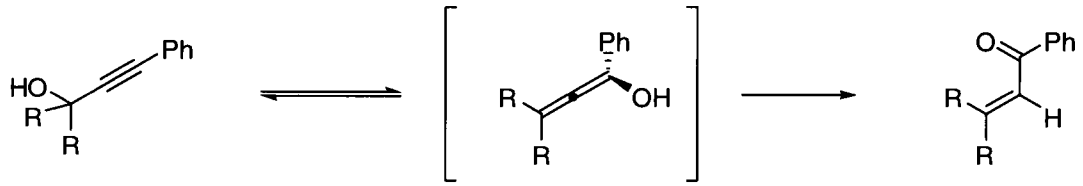
The synthesis of trisubstituted olefins by direct approaches rarely leads to single isomer products and mixtures are quite common. Direct synthetic approaches are by no means an exhaustive methodology in the formation of trisubstituted olefins. Indirect present an alternative procedure to generate trisubstituted olefins.

3.2.2 Indirect Approaches

Indirect approaches towards trisubstituted olefins involve modifying some existing functionality to form a new double bond and do not involve an elimination step. The Meyer-Schuster rearrangement represents an indirect methodology towards the synthesis of trisubstituted olefins by the isomerization of propargylic alcohols.[49] The mechanism of the Meyer-Schuster rearrangement is shown in scheme 20. A [1,3]-OH shift of alkyne **187** generates allene **188**, which will then collapse to form trisubstituted olefin **189**.

[49] Swaminathan, S.; Narayanan, K.V.; *Chem. Rev.* **1971**, *71*, 429.

Scheme 20. The mechanism of the Meyer-Schuster rearrangement.

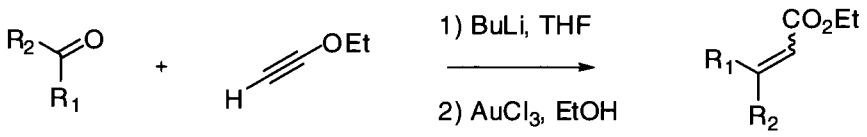


187 **188** **189**

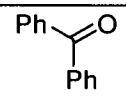
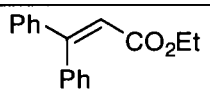
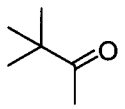
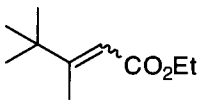
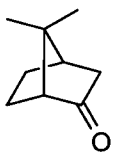
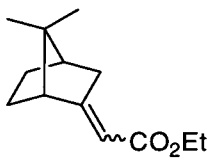
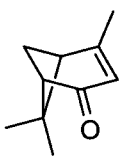
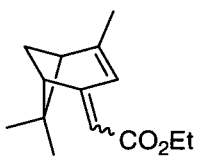
In 2006, Dudley and coworkers were able to employ the Meyer-Schuster rearrangement using a gold catalyst to form α,β-unsaturated trisubstituted olefins.[50] The required tertiary alcohol was formed by the reaction of an alkyne nucleophile with a ketone. Subsequent addition of a catalytic amount of $AuCl_3$ promoted the Meyer-Schuster rearrangement to afford the desired olefin product (table 21).

[50] Engel, D.A.; Dudley, G.B.; *Org. Lett.* **2006**, *8*, 4027.

Table 21. Application of the Meyer-Schuster rearrangement in the olefination of hindered ketones.



157 **190** **191**

Entry	Substrate	Product	Yield (%)	*E:Z* ratio
1	 **192**	 **193**	91	-
2	 **194**	 **195**	99	57:43
3	 **196**	 **197**	68	66:33
4	 **198**	 **199**	96	66:33

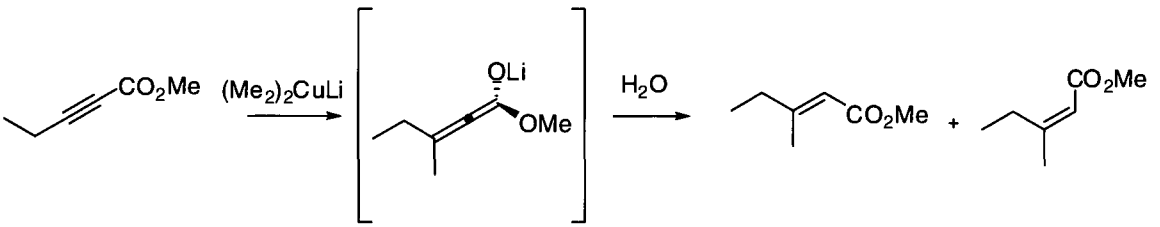
The use of symmetrical ketones afforded trisubstituted olefins in excellent yields (entry 1). Asymmetrical acyclic ketones afforded the corresponding trisubstituted olefin product in excellent yield as a 1.3:1 mixture of *E* and *Z*-isomers (entry 2). Cyclic ketones were tolerated under the reaction conditions as shown with camphor **196** (entry 3) and verbenone **198** (entry 4). Both products were isolated with a 2:1 preference for the *E* isomer over the *Z* isomer.

The poor stereoselectivity of the Meyer-Schuster rearrangement is a significant impediment to its use in the synthesis of trisubstituted olefins. However, alkynes represent a common foundation for the synthesis of trisubstituted olefins. At the end of the 1960s, Corey and coworkers developed a method to make trisubstituted olefins from alkynyl esters using organocuprates.[51] Corey reasoned that a soft nucleophile, in the form of a copper-lithium species, would undergo addition to the β-position of an α,β-unsaturated alkynyl ester to form a trisubstituted alkene.

Siddall and coworkers discovered similar chemistry while trying to synthesize insect hormones.[52] The effect of temperature and time on the yield and stereoselectivity of the reaction of alkyne **200** with dimethyl copper lithium salt was examined (table 4). The copper-lithium species would react to form intermediate allene **201**, which could be quenched with water at different temperatures to form trisubstituted olefin **202** as either the *E* or the *Z* isomer.

[51] Corey, E.J.; Katzenellenbogen, J.A.; *J. Am. Chem. Soc.* **1969**, *91*, 1851
[52] Siddall, J.B.; Biskup, M.; Fried, J.H.; *J. Am. Chem. Soc.* **1969**, *91*, 1853.

Table 22. The addition of organocopper-lithium salts to α,β-unsaturated alkynyl esters.



200 **201** **(*E*)-202** **(*Z*)-202**

Entry	Temperature (°C)	Time (min)	Yield (%)	*E:Z* ratio
1	0	5	35	39:61
2	0	360	44	38:62
3	-78	60	90	85:15
4	-78	2	93	92:8
5	-100	2	95	97:3

Performing the reaction at room temperature for 5 minutes afforded **202** in low yield, with a slight preference for the *Z*-isomer over the *E*-isomer (table 22, entry 1). The use of longer reaction times had a marginal effect on the yield and no effect on the *E:Z* ratio of products (entry 2). Stereoselectivity was observed when the reaction was performed at -78 °C for one hour (entry 3), affording product **202** in 90 % yield as an 85:15 mixture of isomers. It was noted that the selectivity for the *E* isomer could be improved dramatically by quenching the reaction after two minutes, a modification that produced a 92:8 mixture of isomers (entry 4). At extremely low temperatures and short reaction times (-100 °C for two minutes) **202** was isolated in a 97:3 *E:Z* ratio in 95 % overall yield.

The use of indirect methodologies has proven effective in the synthesis of single isomer trisubstituted olefins. However, in order to achieve these results, very low temperatures and sensitive reagents are required. As well, the scope of available trisubstituted olefins is limited to α,β-unsaturated esters. New methodologies involving

the modification of olefin templates have been developed to synthesize trisubstituted alkenes as single isomers.

3.2.3 Modification of olefin templates

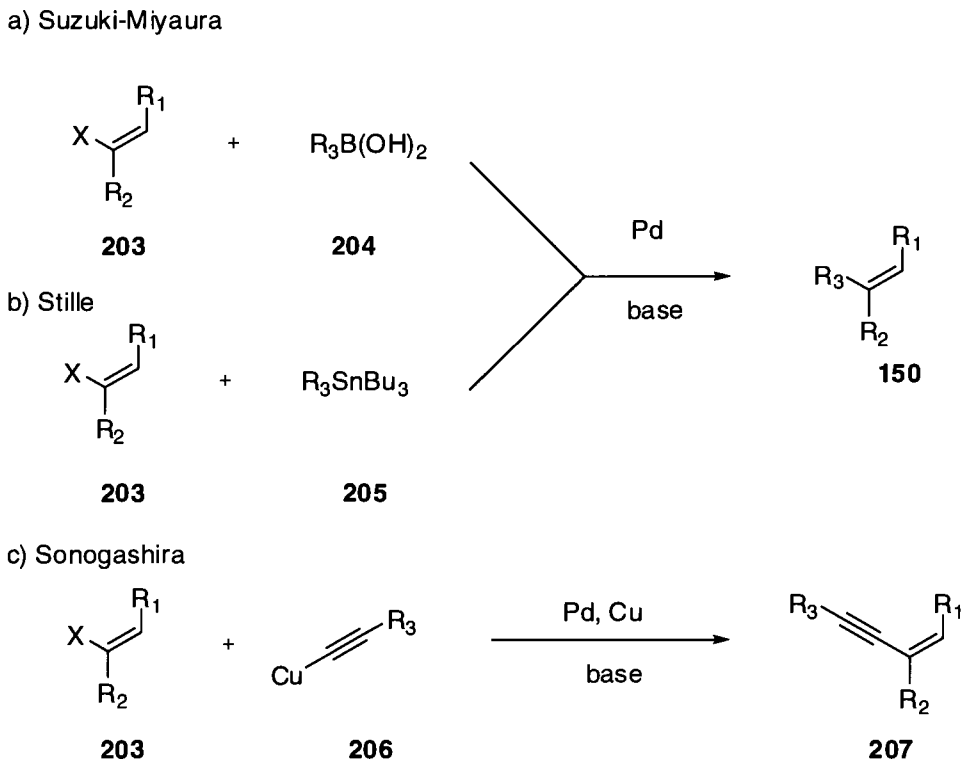
The modification of an olefin template represents a powerful methodology to synthesize trisubstituted olefin as single isomer products. Single isomers are obtained due to the stereochemical information already built into the template. Olefin templates are ubiquitous in cross-coupling reactions, such as the Suzuki-Miyaura,[53] the Sonogashira[54] and the Stille[55] reactions, which are often used to synthesize trisubstituted olefins.

The Suzuki-Miyaura cross-coupling reaction involves the prefunctionalization of an alkyl, aryl or vinyl group with a boronic acid or a trifluoroborate salt (scheme 21a). The Stille reaction preactivates an alkyl, aryl or vinyl group with a tin moiety (scheme 21b). The Sonogashira reaction makes use of terminal alkynes as cross-coupling reagents. The terminal hydrogen of the alkyne is deprotonated to form an alkynyl copper species, which can participate in the cross-coupling process. In each of the above reactions, the cross-coupling partner is always an aryl or vinyl halide. In order for the cross-coupling reaction to proceed, a catalytic amount of palladium is added.

---

[53] Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.
[54] Duncton, M.A.J.; Pattenden, G.J.; *J. Chem. Soc., Perkin Trans I,* **1999**, 1235.
[55] Chinchilla, R.; Nájera, C.; *Chem. Rev.* **2007**, *107*, 874.

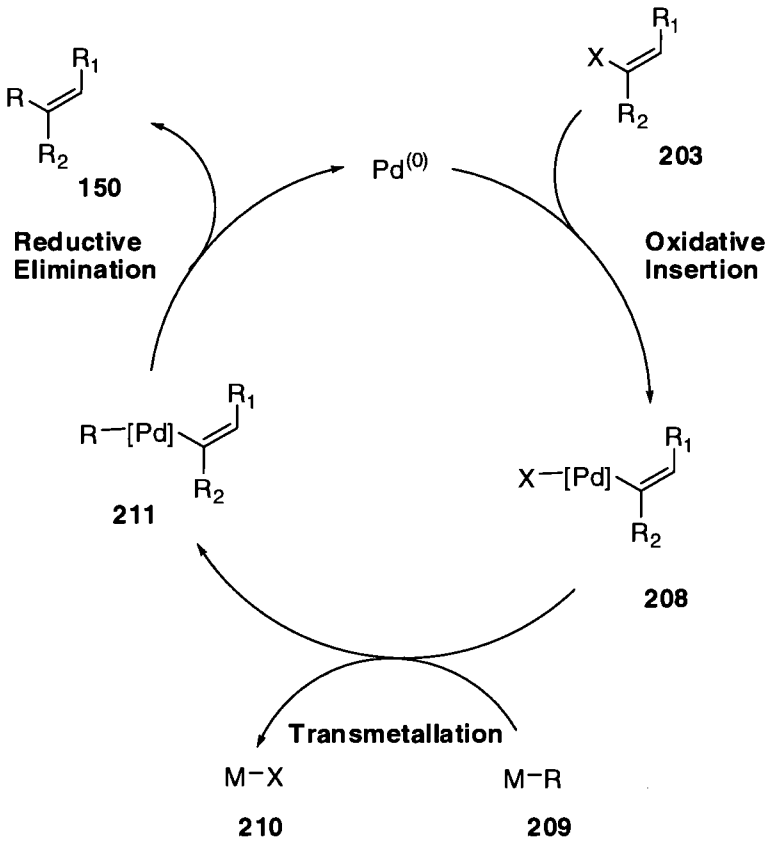
Scheme 21. The synthesis of trisubstituted olefins by palladium cross-coupling reactions.



X = OTf, OTs, OMs, I,Br, Cl
R_3 = Aryl, vinyl, alkyl

Palladium cross-coupling reactions follow a common mechanism. Palladium will undergo an oxidative insertion into the C-X bond of the vinyl halide **203** to form intermediate **208**. Transmetallation will exchange the halogen bound to the palladium with the carbon nucleophile **209** bound to a metal (boron, tin or copper). Finally, reductive elimination of intermediate **211** will regenerate the palladium catalyst and produce the desired trisubstituted olefin product **150** (scheme 22).

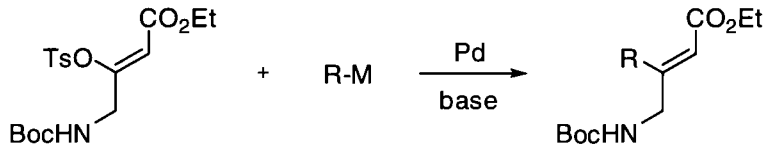
Scheme 22. The general mechanism of palladium cross-coupling reactions.



Steinhuebel and coworkers[56] examined the usefulness of enol tosylates as partners for various cross-coupling reactions. They were able to perform palladium catalyzed cross-coupling reactions with enol tosylates in good yields and isolated the products as single isomers as shown in table 23.

[56] Steinhuebel, D.; Baxter, J.M.; Palucki, M.; Davies, I.W.; *J. Org. Chem.* **2005**, *70*, 10124.

Table 23. Enol tosylates as coupling partners for palladium cross-coupling reactions.



212 **209** **213**

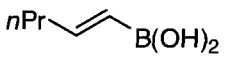
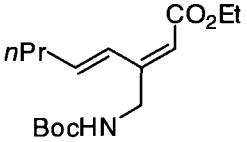
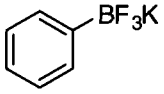
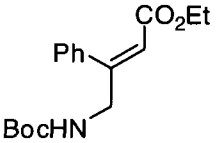
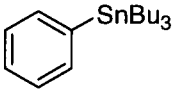
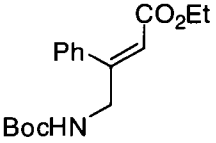
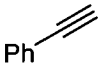
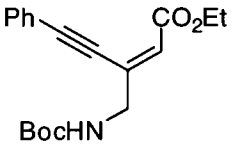
Entry	R-X	Product	Yield (%)
1	 **214**	 **215**	81
2	 **216**	 **217**	81
3	 **218**	 **217**	67
4	 **219**	 **220**	78

Table 23 presents a sample of the possible trisubstituted olefin products produced from a variety of palladium cross-coupling reactions. A Suzuki-Miyaura coupling of enol tosylate **212** with vinyl boronic acid **214** saw complete conversion to trisubstituted olefin **215** (entry 1). Coupling of substrate **212** with potassium phenyltrifluoroborate salt **216** under Suzuki-Miyaura conditions or with tributylphenylstannanne **218** under Stille conditions afforded the trisubstituted olefin **217** in 81 and 67 % yield respectively (entries 2 and 3). Sonogashira couplings were tolerated with enol tosylates, as shown in entry 4

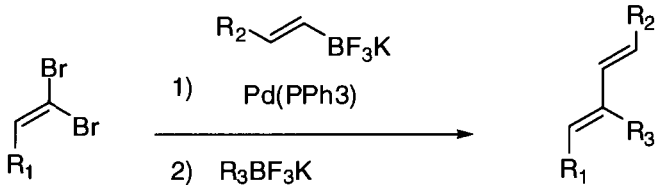
in which phenylacetylene **219** was coupled with enol tosylate **212** giving product **220** in 78 % yield. Under all cross-coupling reactions, a single isomer olefin product was observed.

Palladium cross-coupling reactions of olefin templates represent a convenient methodology for the synthesis of trisubstituted olefins as single isomers. However, the problem of stereoselectivity has not been entirely solved. The synthesis of the olefin template with the appropriate stereochemistry can be difficult as both *E* and *Z* isomers are possible.

In order to bypass this problem, the use of 1,1-dihaloalkenes in the synthesis of trisubstituted olefins has been developed (scheme 23). This is an attractive approach to trisubstituted olefins as there is no stereochemistry to control of the 1,1-dihaloalkenes. This completely eliminates the problem of stereoselectivity in the synthesis of trisubstituted olefins.

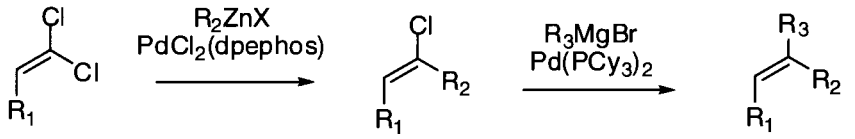
Scheme 23. The use of 1,1-dihaloalkenes towards the synthesis of trisubstituted olefins

Molander approach[58]



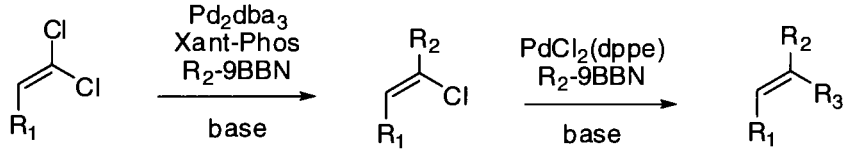
221 **222**

Negishi approach[59]



223 **(*E*)-224** **150**

Roulland approach[60]

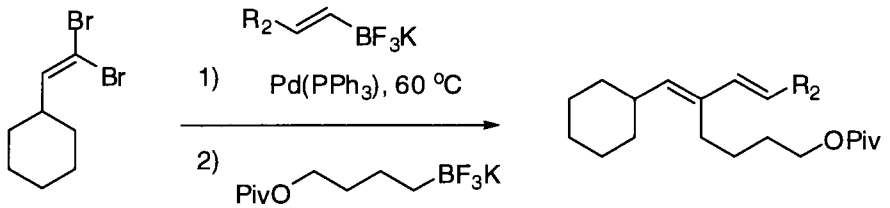


223 **(*Z*)-224** **150**

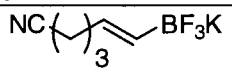
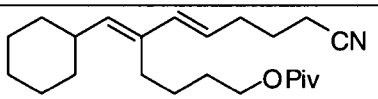
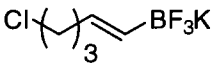
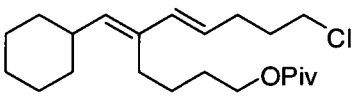
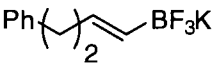
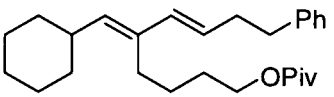
Three different approaches towards trisubstituted olefins, all involving 1,1-dihaloalkenes, have been developed in recent years. The first approach was developed by the Suzuki group[57] involving the selective addition to 1,1-dichloroalkenes. Further research was developed by Molander.[58] His research group showed that it was possible to synthesize trisubstituted olefins by a series of reactions performed in one pot (table 24).

[57] Minato, A.; Suzuki, K.; Tamao, K.; *J. Am. Chem. Soc.* **1987,** *109*, 1257.
[58] Molander, G.A.; Yokoyama, Y.; *J. Org. Chem.* **2006**, *71*, 2493.

Table 24. The synthesis of trisubstituted olefins using 1,1-dibromoalkenes.



225 **226** **227**

Entry	Vinyl trifluoroborate salt	Product	Yield (%)
1	 **228**	 **229**	91
2	 **230**	 **231**	90
3	 **232**	 **233**	90

The one pot synthesis of single isomer trisubstituted olefin products **229**, **231**, and **233** from 1,1-dibromoalkene **225** and trifluoroborates was complete in >90 % yield. To ensure the appropriate stereochemistry of the product, reactivity at the bromine located at the *trans* position was achieved by adding the vinyl trifluoroborate at 60 °C. A different alkyl trifluoroborate was then added and the reaction was heated to 80 °C to achieve the second coupling and thus the transformation into the observed trisubstituted olefin product.

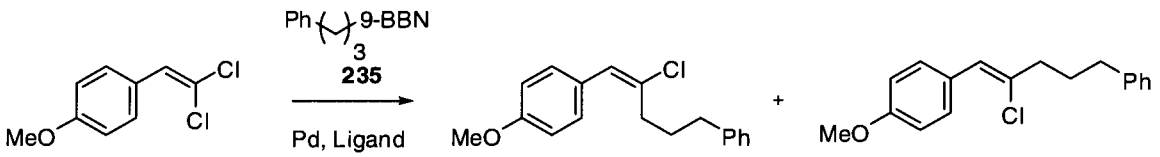
A second approach was developed by Negishi and coworkers[59] that made use of 1,1-dichloroalkenes and organozinc reagents in their efforts to synthesize trisubstituted olefins concurrently with Molander. By varying the amount of equivalents of reagents,

[59] Negishi, E.; Tan, Z.; *Angew. Chem. Int. Ed.* **2006**, *45*, 762.

stereoselectivity could be controlled. The reaction favoured addition at the chlorine group *cis* to the substituent (Scheme 23). Once the disubstituted alkylvinyl chloride had formed, further cross-coupling reactions were trivial and trisubstituted olefin products were obtained in good yields.

Roulland and coworkers built on the use of 1,1-dichloralkenes to synthesize trisubstituted olefins.[60] Selectivity at the chlorine *trans* to the substituent was achieved by modifying the ligand used in the reaction.

Table 25. Optimization of reaction at the *trans* chloride position.



234 **(*E*)-236** **(*Z*)-236**

Entry	Palladium	Ligand	Yield (%)	*E*:*Z* ratio
1	$PdCl_2(PPh_3)_2$		35	86:15
2	$PdCl_2$(dppf)		33	94:6
3	$PdCl_2$(dppp)		51	88:12
4	Pd_2dba_3	XantPhos	72	1:99

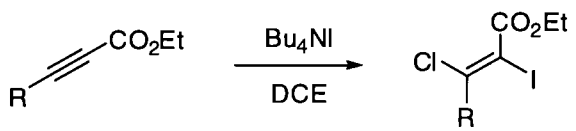
The reaction of substrate **234** with alkyl-9-BBN **235** in the presence of $PdCl_2(PPh_3)_2$ produced product **236** in 35 % yield. The reaction favoured the *E* isomer (table 7, entry 1). The use of $PdCl_2$(dppf) as a catalyst increased the formation of the *E* isomer, giving the products in a 94:6 ratio of *E* and *Z* isomers (entry 2). Performing the reaction with the bidentate catalyst $PdCl_2$(dppp) resulted in an increase in the yield of the

[60] Liron, F.; Fosse, C.; Pernolet, A.; Roulland, E.; *J. Org. Chem.* **2007**, *72*, 2220.

trisubstituted olefin **236** (entry 3) with a small change in stereoselectivity. Success was realized when the catalyst was changed to Pd_2dba_3 and XantPhos was used as a ligand. This reaction afforded the product in good yield while the formation of the *E*-isomer was almost completely suppressed (entry 4). Once **(*Z*)-236** was synthesized, further cross-coupling reactions were performed at the remaining chlorine position to afford trisubstituted alkene products in good yields as single isomers.

The Ogilvie group has also found success in the synthesis of trisubstituted olefins from alkene templates. Our laboratory discovered a novel way to synthesize (*E*)-β-chloro-α-iodo-α,β-unsaturated esters from alkynyl esters (scheme 24).[61]

Scheme 24. The synthesis of single isomer chloro-iodo alkene templates.

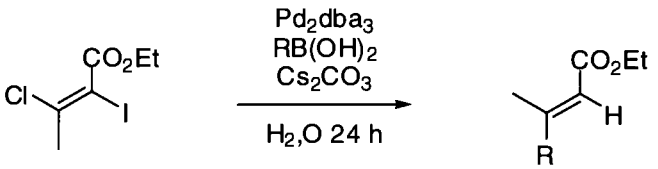


237 **238**

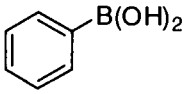
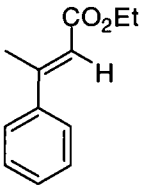
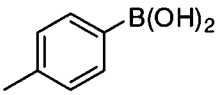
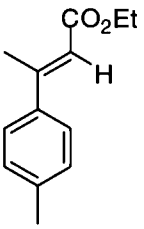
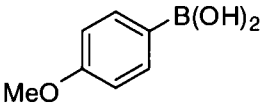
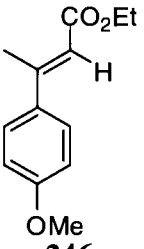
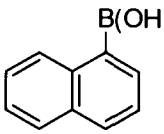
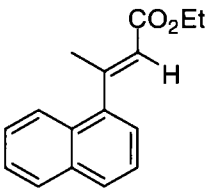
By reacting alkynyl esters **237** with tetrabutylammonium iodide in dichloroethane, single isomer chloro-iodo alkene templates **238** can be generated in good yields. These chloro-iodo alkene templates can be used to synthesize single isomer trisubstituted olefins by submitting them to Suzuki reaction conditions (table 26).[62]

[61] Ho, M.L.; Flynn, A.B.; Ogilvie, W.W.; *J. Org. Chem.* **2007**, *72*, 977.
[62] Simard-Mercier, J.; Jiang, J.L.; Ho, M.L.; Flynn, A.B.; Ogilvie, W.W.; *J. Org. Chem.* **2008**, *73*, 5899.

Table 26. The coupling of arylboronic acids with chloro-iodo alkene templates.



239 **240**

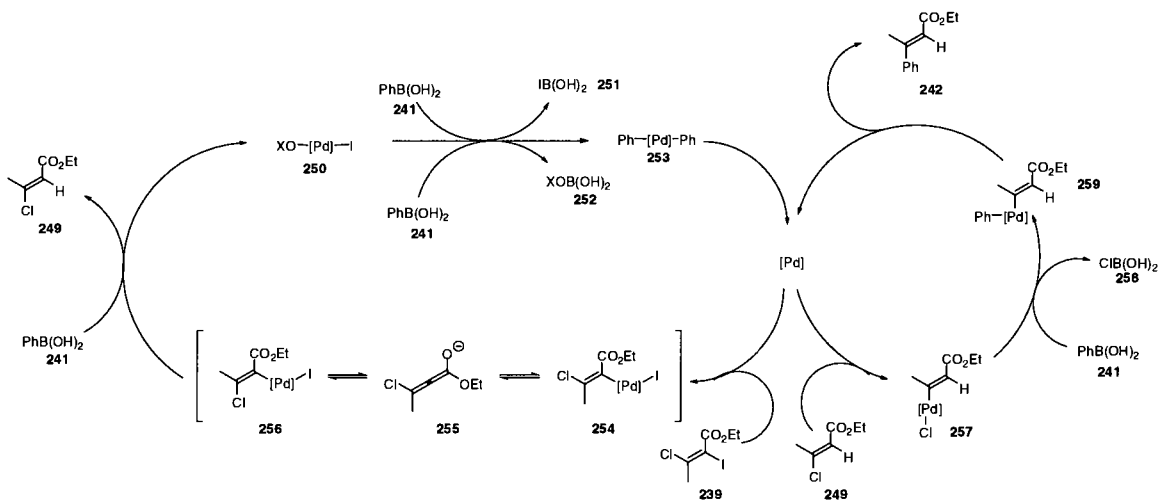
Entry	$RB(OH)_2$	Product	Yield (%)
1	 **241**	 **242**	99
2	 **243**	 **244**	76
3	 **245**	 **246**	83
4	 **247**	 **248**	96

The use of chloro-iodo alkene templates to synthesize trisubstituted olefin products was found to be broadly applicable. The newly formed α,β-unsaturated esters were isolated in 54 - 99 % yields. In all cases, *syn* addition of the boronic acid and the

hydrogen occurred, even though the olefin template had the iodine and the chlorine in an *anti* configuration. The aryl group of the boronic acid was added to the β-position, while the hydrogen, derived a proton in solution, always ended up on the α-position of the newly formed α,β-unsaturated ester.

To achieve the desired trisubstituted olefin products, it was hypothesized that this reaction proceeded by two interlocking catalytic cycles (scheme 25).

Scheme 25. The catalytic cycle for the synthesis of trisubstituted olefins from chloro-iodo alkene templates.



It was hypothesized that palladium would undergo oxidative insertion into the C-I bond of the chloro-iodo alkene template **239** to form carbopalladium product **254**. Once this happened, isomerization of the double bond via an allene intermediate **255** would form **256** with the appropriate olefin stereochemistry. It was hypothesized that alkene **256** would react more quickly with phenylboronic acid **241** to form chloro-alkene **249** than alkene **254** due to the presence of an increased dipole Protonation of the carbon-palladium bond with phenylboronic acid would generate the α-hydrogen alkenyl ester

249. Palladium could then re-insert into the C-Cl bond, which would continue through a normal Suzuki coupling mechanism to generate the trisubstituted olefin product with the observed regio- and stereochemistry.

Modification of an olefin template provides a synthetically useful strategy towards the synthesis of trisubstituted olefins. However, this is not necessarily the most efficient method in making trisubstituted alkenes. The modification process can create many waste byproducts and could take several synthetic steps to produce the olefin template starting material. Also, in the case of palladium cross-coupling reactions, the problem of stereocontrol is not always solved; it is merely moved to an earlier point in the synthetic sequence.

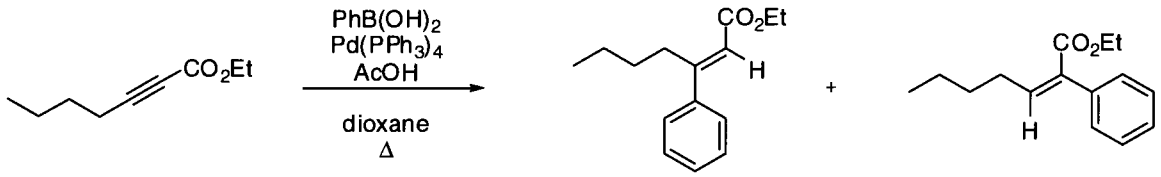
3.2.4 Synthesis of trisubstituted olefins from alkynes

The synthesis of trisubstituted olefins without any preactivation is an idealized goal in organic chemistry. By avoiding the activating boronic acids and vinyl halides, the amount of waste byproducts can be reduced, lowering the cost of the synthesis and increasing the ease of the reactions.

In 2003, Oh and coworkers demonstrated the synthesis of trisubstituted olefins from alkynyl esters with a variety of boronic acids.[63] Although preactivation of the nucleophile was still required, there was no necessity for activation of the electrophile. Trisubstituted olefin products were isolated in good yields and with excellent stereoselectivity as a mixture of regioisomers (scheme 26).

[63] Oh, C.H.; Jung, H.H.; Kim, K.S.; Kim, N.; *Angew. Chem. Int. Ed.* **2003**, *42*, 805.

Scheme 26. The synthesis of trisubstituted olefins from alkynyl esters.

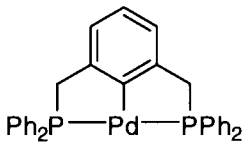


260 **261** **262**

The reaction was performed at high temperature under mild acid catalysis in order to achieve complete conversion of **260** to products **261** and **262**. However, the reaction was unable to produce single isomer products. Stereocontrol of the reaction was achieved as the hydride and aryl group were always added in a *syn* fashion; however, regioisomers **261** and **262** were isolated in an 80 % combined yield in a 4:1 ratio respectively.

In 2005, the Oh group was able to improve the regioselectivity of the reaction of alkynyl esters with boronic acids by using a palladium pincer-type ligand **263** (figure 8) and basic conditions.[64]

Figure 9. Palladium Pincer ligand.

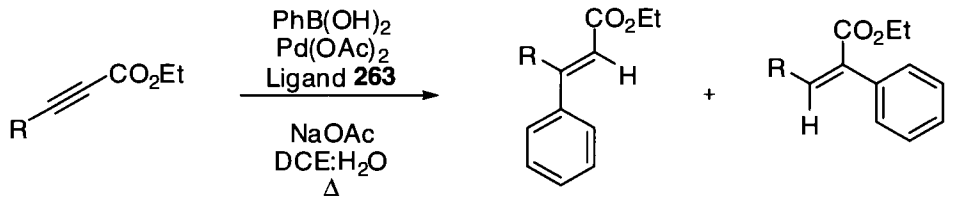


263

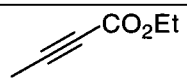
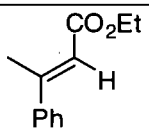
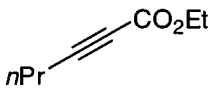
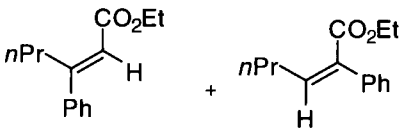
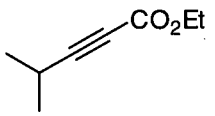
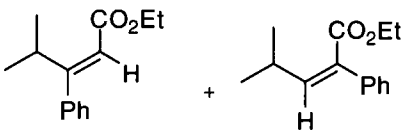
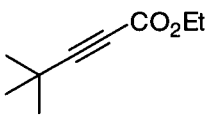
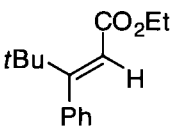
[64] Gupta, A.K.; Kim, K.S.; Oh, C.H.; *Syn. Lett.* **2005**, *3*, 457.

By using ligand **263** and 10 mol % of NaOAc, the conversion of alkynyl esters to trisubstituted olefins was completed in good yields with excellent regioselectivity. Complete regiocontrol was obtained in some cases (table 27).

Table 27. The reaction of alkynyl esters with phenylboronic acid.



237 **264** **265**

Entry	Substrate	Product	Yield (%)	Ratio
1	 **266**	 **242**	89	-
2	 **267**	 **268** + **269**	85	98:2
3	 **270**	 **271** + **272**	76	85:15
4	 **273**	 **274**	79	-

Oh and coworkers had limited success however, as single isomer trisubstituted olefins were synthesized in only two cases (entries 1 and 4). When other alkynyl esters were used, mixtures of regioisomers were obtained (entries 2 and 3). In all cases, the boronic acid and the hydrogen were added in a *syn* fashion.

Combining the previous work by Oh with some of the current work in our laboratory led to the hypothesis that trisubstituted olefins could be synthesized with complete control of the regiochemistry across the newly formed double bond and of the stereochemistry at the β-position of the newly formed alkenyl ester.

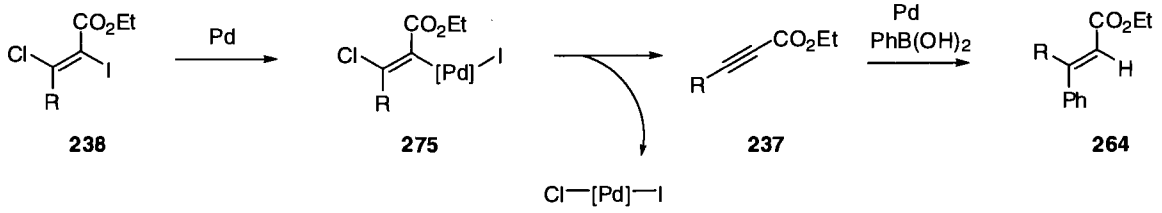
Chapter 4

4.1 Results and Discussion

4.1.1 Optimizations

In 2008, the Ogilvie group demonstrated the synthesis of trisubstituted olefins using (*E*)-β-chloro-α-iodo-α,β–unsaturated esters by cross coupling with organoboronic acids.[62] It was hypothesized that this reaction could occur through an alkynyl intermediate by the oxidative insertion of palladium into the C-I bond forming **275**. This would be followed by the elimination of a palladium iodo-chloro complex generating alkyne **237** which could then form the trisubstituted olefin product (scheme 27).

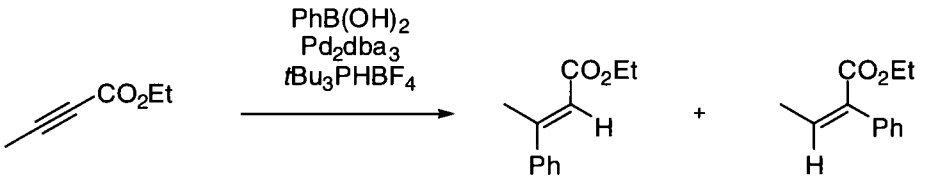
Scheme 27. Proposed mechanism for the synthesis of trisubstituted olefins from chloro-iodo alkene templates.



In order to investigate this possible mechanism, the corresponding alkyne **266** was submitted to the reaction conditions. Upon performing the condensation with **237** and phenylboronic acid (scheme 28), a 3:1 mixture of regioisomers **242** and **276** were obtained in 10 % yield. Under these control conditions the reaction was not

regioselective, suggesting that the reaction of (*E*)-β-chloro-α-iodo-α,β–unsaturated esters **238** did not proceed through alkynyl intermediate **237**. However, this did present an exciting opportunity for research. A new project was initiated with the goal of maximizing the yield of the reaction and suppressing the formation of one of the regioisomeric products.

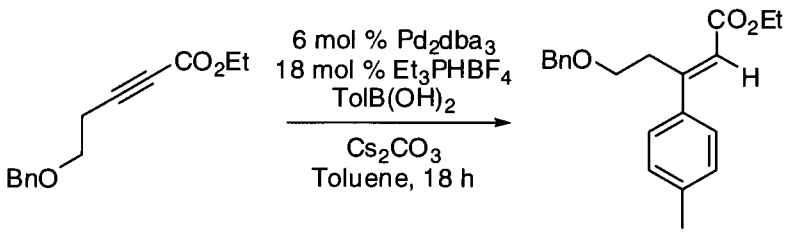
Scheme 28. The results of the mechanistic investigation.



266 **242** **276**

While attempting further reactions with the (*E*)-β-chloro-α-iodo-α,β–unsaturated esters, Pippa Payne, an undergraduate student in the Ogilvie lab, discovered that it was possible to synthesize single isomer trisubstituted olefin **278** from alkyne **277** with the use of a small phosphine ligand in 62 % isolated yield.

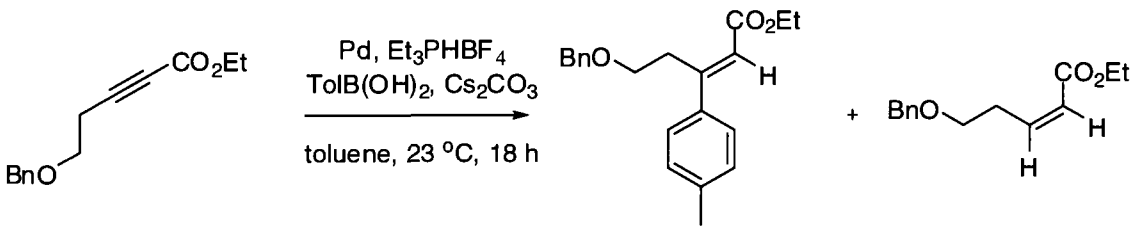
Scheme 29. The reaction of a substituted alkyne with 4-tolylboronic acid.



277 **278**

When ethyl 5-(benzyloxy)pent-2-ynoate **277** was reacted with 4-tolylboronic acid, using Pd_2dba_3 as a catalyst and $Et_3P{\cdot}HBF_4$ as ligand product **278** was isolated in 62 % yield as a single isomer with 30 % of the starting material recovered. This result indicated that regioselectivity was possible and that it might be dependent on the ligand used. It was our hope that we could convert the remaining unreacted starting material to a single isomer trisubstituted product. The first step in the optimization of the reaction was to find a suitable palladium source.

Table 28: Exploring various sources of palladium.



277 **278** **279**

Entry[a]	Pd source	Yield **278** (%)[b]	Yield **279** (%)[c]	RSM **277** (%)
1	Pd_2dba_3	50	17	0
2	$Pd(OAc)_2$	25	7	0
3[d]	$Pd(OAc)_2$	57	5	0

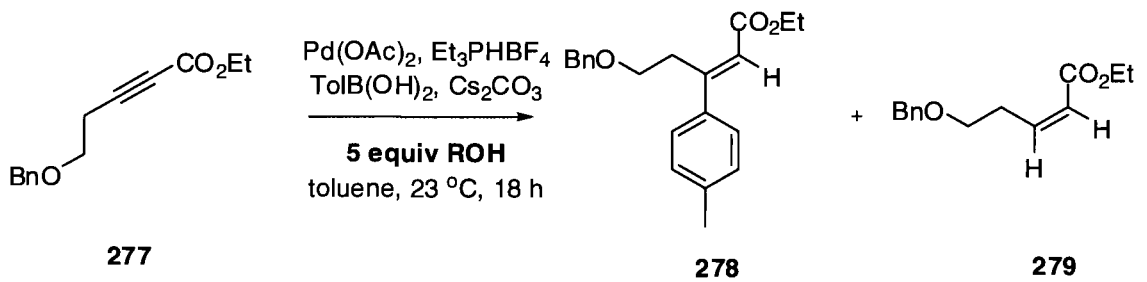
[a] Conditions: 0.06 equiv of Pd, 0.18 equiv of $Et_3P{\cdot}HBF_4$, 3.6 equiv of 4-MePhB(OH)_2, 3.7 equiv of Cs_2CO_3, toluene, 23 °C, 18 h. [b] Isolated yield. [c] Yield determined by ^1H NMR. [d] Reaction performed with 5 equivalents of H_2O added.

Initial attempts to repeat the reaction of alkyne **277** with 4-tolylboronic acid were unsuccessful, isolating trisubstituted olefin **278** in 50 % yield. A *cis*-alkene product **279** was also isolated from the reaction mixture in 17 % yield (table 28, entry 1). Changing the source of palladium from Pd_2dba_3 to $Pd(OAc)_2$ (entry 2), afforded product **278** in 25 % yield with an additional 7 % isolated yield of side-product **279**. It was observed that

the addition of five equivalents of water to the reaction (entry 3), gave product **278** in 57 % isolated yield together with olefin **279** in 5 % yield. It was decided to continue the optimization of the reaction using the conditions described in entry 3.

As the introduction of five equivalents of H_2O had increased the conversion of **277** to **278**, the effects of protic additives on the reactivity of alkyne **277** with 4-tolylboronic acid were investigated, as shown in table 29.

Table 29: The effect of protic additives to the reactivity of alkynyl esters.



277 **278** **279**

Entry[a]	R	Yield **278** (%)[b]	Yield **279** (%)[c]
1	H	57	5
2	*i*PrOH	52	8
3	3:1 *i*PrOH:H_2O	48	7

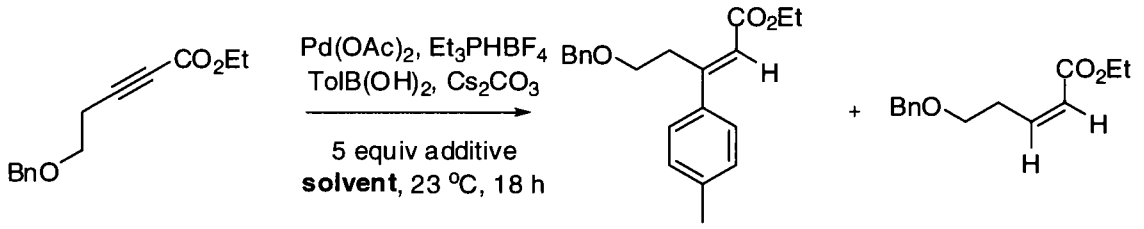
[a] Conditions: 0.06 equiv of $Pd(OAc)_2$, 0.18 equiv of $Et_3P{\cdot}HBF_4$, 3.6 equiv of 4-$MePhB(OH)_2$, 3.7 equiv of Cs_2CO_3, 5 equiv of additive, toluene, 23 °C, 18 h. [b] Isolated yield. [c] Yield determined by ^1H NMR.

The use of five equivalents of H_2O as an additive in the reaction afforded product **278** in moderate yield with minimal formation of undesired side-product **279** (table 29, entry 1). By using *i*PrOH as an additive (entry 2), a nominal change in the both the yield of trisubstituted olefin product **278** and of the *cis*-alkene product **279** was observed.

Finally, a 3:1 mixture of *i*PrOH:H_2O gave a slightly diminished yield, with only 48 % of olefin product **278** being observed together with 7 % of the *cis*-alkene **279** being isolated.

The addition of both *i*PrOH and H_2O was compatible with the reaction conditions, affording products **278** and **279** in comparable yields. As such, both additives were retained for further optimization investigations. The effect of different solvents on the conversion of the alkyne **277** to trisubstituted olefin products **278** was examined next.

Table 30. The effect of solvents on the formation of trisubstituted olefin products.



277 **278** **279**

Entry[a]	Additive	Solvent	Yield **278** (%)[b]	Yield **279** (%)[c]
1	H_2O	Toluene	57	5
2	H_2O	CH_2Cl_2	59	0
3	H_2O	EtOAc	38	5
4	H_2O	DMF	7	0
5	H_2O	$ClCH_2CH_2Cl$	34	2
6	H_2O	Benzene	25	3
7	*i*PrOH	Toluene	52	8
8	*i*PrOH	CH_2Cl_2	37	0
9	*i*PrOH	Dioxane	33	3
10	*i*PrOH	Benzene	33	3
11	*i*PrOH	THF	Trace	Trace

[a] Conditions: 0.06 equiv of $Pd(OAc)_2$, 0.18 equiv of $Et_3P{\cdot}HBF_4$, 3.6 equiv of 4-$MePhB(OH)_2$, 3.7 equiv of Cs_2CO_3, 5 equiv of additive, solvent, 23 °C, 18 h. [b] Isolated yield. [c] Yield determined by ^1H NMR.

The initial solvent investigations were performed with H_2O as an additive. When the reaction was performed with toluene as the solvent, as had been done in previous

reaction investigations, the trisubstituted olefin product **278** was isolated in 57 % yield together with 5 % yield of the *cis*-alkene side-product **279** (table 30, entry 1). By substituting dichloromethane for toluene, product **278** was isolated in 59 % yield with no appearance of the *cis*-alkene side product **279** (entry 2). When experiments were conducted in more polar solvents, the results were less promising. As shown in entry 3, the use of EtOAc as a solvent decreased the overall yield to 38 % of alkene **278** and 5 % of the alkene side product **279**. Performing the reaction in DMF was not as beneficial (entry 4) as the desired olefin product **278** was generated in 7 % yield with no *cis*-alkene **279** detected. The choice of 1,2-dichloroethane as a solvent for the reaction of alkyne **277** with 4-tolylboronic acid proved to be an unproductive as trisubstituted olefin product **278** was generated in only 34 % isolated yield, with trace amounts of *cis*-alkene product **279** observed by ^{1}H NMR (entry 5). The use of benzene also proved unproductive, as shown in entry 6, in which only 25 % isolated yield of the desired product **278** and 3 % isolated yield of the undesired olefin product **279** were isolated.

The reaction was also tested in different solvents with *i*PrOH as an additive, as shown in entries 7 - 11. The use of toluene as solvent afforded the trisubstituted olefin product **278** in 52 % isolated yield together with an 8 % isolated yield of the *cis*-alkene **279** (entry 7). Performing the reaction in dichloromethane instead of toluene as the solvent (entry 8) proved unsuccessful as the desired trisubstituted olefin product **278** was isolated in only 37 % yield. As with the case of H_2O as an additive (entry 2), he *cis*-alkene side product **279** was not detected. Similarly, when dioxane was employed as the solvent for the reaction, the yield of the trisubstituted olefin **278** suffered (entry 9). The use of benzene gave no improvement in the yield of **279**, generating 33 % product (entry

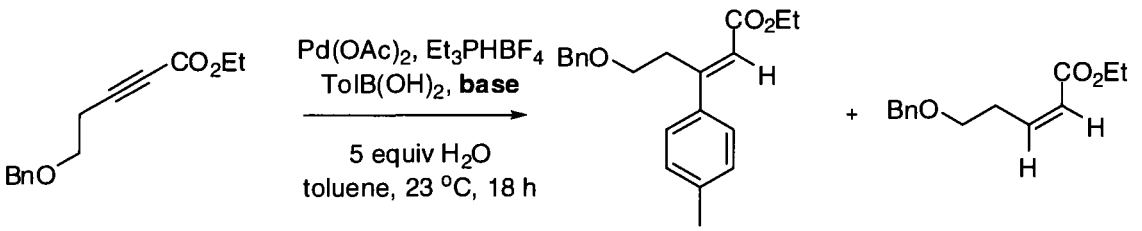
10). Lastly, when THF was employed as a solvent only a trace amount of product was evident by ^{1}H NMR (entry 11).

The use of *i*PrOH as an additive proved to be less effective than H_2O in all cases. The best result with *i*PrOH was achieved when toluene was used as solvent. However, even in this case, there was an increase in the proportion of the undesired *cis*-alkene **279** side product observed. Due to these observations, the use of *i*PrOH as an additive was abandoned and the use of H_2O retained.

The use of both dichloromethane and toluene as solvents was promising when H_2O was used as the additive, as both afforded product **278** in good yields and showed minimal formation of side product **279** (5 % and 0 % respectively). Further optimizations were carried out with the use of both solvents.

With our optimal solvents in hand, it was decided to explore the effect of a different collection of bases had on the reactivity of the alkynyl ester with the boronic acid.

Table 31: The effect of different bases on the reactivity of alkynes with boronic acids.



277 **278** **279**

Entry[a]	Base	Yield **278** (%)[b]	Yield **279** (%)[c]
1	Cs_2CO_3	57	5
2[d]	Cs_2CO_3	59	0
3	Na_2CO_3	36	7
4	K_2CO_3	60	9
5[d]	K_2CO_3	41	0
6	K_3PO_4	42	2
7	Et_3N	68	0
8[d]	Et_3N	60	2

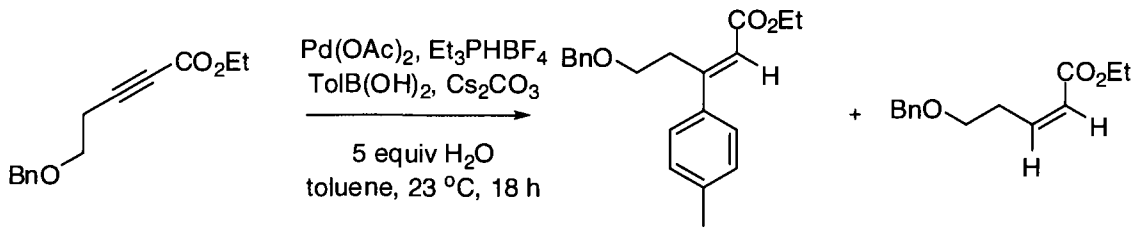
[a] Conditions: 0.06 equiv of $Pd(OAc)_2$, 0.18 equiv of $Et_3P{\cdot}HBF_4$, 3.6 equiv of 4-$MePhB(OH)_2$, 3.7 equiv of base, 5 equiv of H_2O, toluene, 23 °C, 18 h. [b] Isolated yield. [c] Yield determined by ^1H NMR. [d] CH_2Cl_2 was used as solvent.

The use of Cs_2CO_3 as the base for the reaction of **277** with 4-tolylboronic acid provided the starting point for our investigation. Its use in toluene (table 31, entry 1) afforded olefin **278** in moderate yield along with olefin **279** in low yield. Similarly, the use of Cs_2CO_3 in dichloromethane (entry 2) afforded olefin **278** in comparable yield as entry 1, but with no detection of olefin **279** by ^1H NMR. When Na_2CO_3 was employed as the base for the reaction in toluene (entry 3), the trisubstituted olefin product **278** was afforded in low yield, with a marginal increase in the amount of olefin **279** formed. The use of K_2CO_3 in toluene provided the olefin product in good yield (entry 4). However, there was an increase in the conversion of alkyne **277** to the *cis*-alkene **279**. When K_2CO_3 was tried in dichloromethane, the results were much less promising as only 41 % of the trisubstituted olefin product **278** isolated. However, there was no detection of side

product **279** by ^{1}H NMR under these reaction conditions (entry 5). As shown in entry 6, the use of K_3PO_4 gave the trisubstituted olefin product **278** in 42 % yield together with 2 % of the undesired *cis*-alkene **279** detected. When the inorganic base was replaced with an organic base, Et_3N (entry 7) in toluene, an observed yield of 68 % of the desired product **278** was observed, with no observed appearance of the undesired *cis*-alkene product **279**. The use Et_3N in dichloromethane was also examined (entry 8). It was found to be less efficient than the corresponding reaction in toluene, with product **278** obtained in 60 % yield.

Both Cs_2CO_3 and Et_3N proved to be promising bases for the reaction of alkynyl esters with boronic acids. It was decided to continue the optimization by examining the effect that modification of the equivalents of boronic acid would have on the reaction using both bases.

Table 32: The effect that equivalents of boronic acid had on reactivity.



277 **278** **279**

Entry[a]	Equiv 4-MePhB(OH)$_2$	Equiv of base	Yield **278** (%)[b]	Yield **279** (%)[c]
1	1.5	1.6	51	3
2	2	2.1	71	4
3[d]	2	2.1	40	0
4[e]	2	2.1	63	2
5	3.6	3.7	57	5
6	6	6.1	42	8
7	8	8.1	39	7

[a] Conditions: 0.06 equiv of $Pd(OAc)_2$, 0.18 equiv of $Et_3P{\cdot}HBF_4$, 5 equiv of H_2O, toluene, 23 °C, 18 h. [b] Isolated yield. [c] Yield determined by ^1H NMR. [d] CH_2Cl_2 was used as solvent. [e] Et_3N was used as base in place of Cs_2CO_3.

When the reaction was performed with 1.5 equivalents of boronic acid (table 32, entry 1) product **278** was generated in moderate yield with a minimal formation of side product **279**. A good yield of **278** was observed when the number of equivalents of boronic acid was increased to two (entry 2). When alkyne **277** was submitted to the reaction conditions in dichloromethane, trisubstituted olefin product **278** was isolated in low yield with no detection of product **279** by ^1H NMR (entry 3). The use of triethylamine as the base together with two equivalents of boronic acid afforded good yields of olefin product **278** (entry 4), although the reaction was less efficient than the corresponding reaction using Cs_2CO_3.

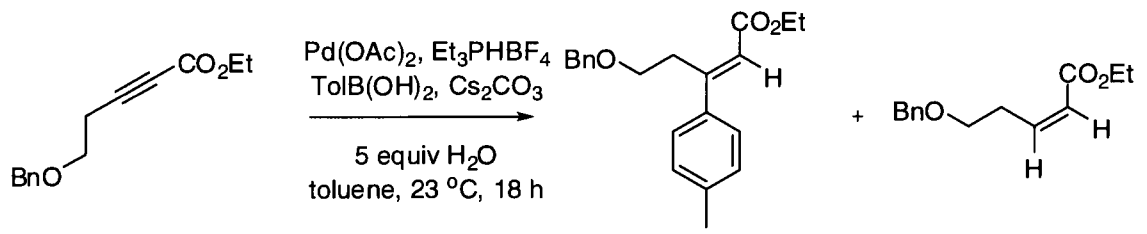
The use of 3.6 equivalents of boronic acid afforded the previously reported best results as shown in entry 5, giving product **278** in 57 % isolated yield with an additional 5

% yield of side product **279**. A further increase to six equivalents of boronic acid resulted in a much less effective reaction, affording a poor yield of trisubstituted olefin product **278** together with an increased yield of *cis*-alkene side product **279** (entry 6). This trend continued as the excess of boronic acid was increased to eight equivalents, generating only 39 % of alkene product **278** and 7 % of the side product **279** (entry 7).

The use of two equivalents of boronic acid in toluene with Cs_2CO_3 as the base proved to be the most effective conditions for this process. As both dichloromethane and triethylamine were less efficient than toluene and Cs_2CO_3 respectively, their use in the reaction was abandoned.

Further optimization experiments were performed by varying the ratio of the number of equivalents of boronic acid to base. The amount of boronic acid was held fixed at two equivalents and the number of equivalents of Cs_2CO_3 was varied as shown in table 33.

Table 33: The effect of varied base relative to boronic acid.



277 **278** **279**

Entry[a]	Equiv Cs_2CO_3	Yield **278** (%)[b]	Yield **279** (%)[c]
1	1.5	57	1
2	2.1	71	4
3	2.5	47	0
4	3.0	39	5
5[d]	4.0	31	4
6[e]	8.0	17	3

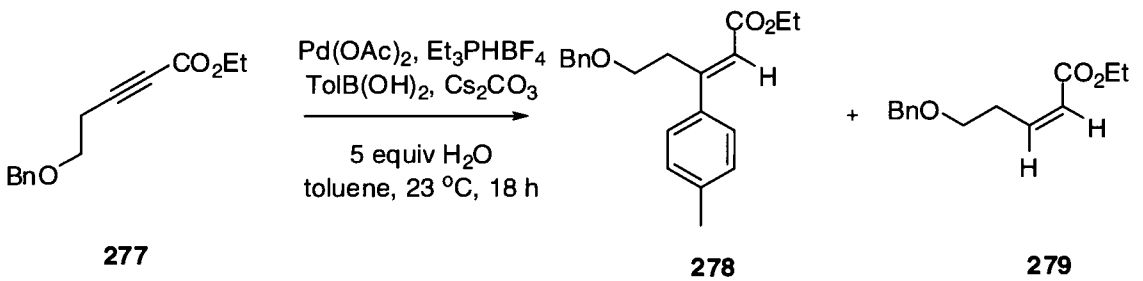
[a] Conditions: 0.06 equiv of $Pd(OAc)_2$, 0.18 equiv of $Et_3P{\cdot}HBF_4$, 2.0 equiv of 4-$MePhB(OH)_2$, 5 equiv of H_2O, toluene, 23 °C, 18 h. [b] Isolated yield. [c] Yield determined by ^1H NMR. [d] 17 % recovered starting material. [e] 4.0 equiv of 4-$MePhB(OH)_2$ was used.

When the reaction was performed under acidic conditions, by using 1.5 equivalents of Cs_2CO_3, the yield of **278** suffered (table 33, entry 1). When 2.1 equivalents of base was used, almost complete conversion of the alkyne **277** to the alkene **278** was observed (entry 2). A further increase in amount of base used to 2.5 equivalents saw the reaction perform less efficiently, with trisubstituted olefin product **278** isolated in 47 % yield, although there was no trace of olefin **279** in the ^1H NMR spectrum (entry 3). Employing three equivalents of Cs_2CO_3 produced a decreased yield of the desired product **278** (entry 4). This trend continued when 4.0 equivalents of base was used (entry 5), with the desired trisubstituted alkene product **278** being isolated in 31 % yield, although 17 % of the starting material was recovered. The use of an excess amount of base (entry 6)

resulted a 17 % isolated yield of trisubstituted alkene product **278** together with 3 % of the olefin side product.

When 2.1 equivalents of Cs_2CO_3 and 2.0 equivalents of boronic acid were used, the conversion of alkyne **277** to alkene **278** was synthetically useful, generating **278** in 71 % yield. Before examining the complete scope of the reaction, further optimization reactions were completed in order to examine the effect of concentration on reaction efficiency.

Table 34: The effect of concentration on the formation of trisubstituted olefins



277 **278** **279**

Entry[a]	Concentration **277** (M)	Yield **278** (%)[b]	Yield **279** (%)[c]
1	0.05	71	4
2	0.1	52	1
3	0.2	43	1
4	0.5	57	0

[a] Conditions: 0.06 equiv of $Pd(OAc)_2$, 0.18 equiv of $Et_3P{\cdot}HBF_4$, 2.0 equiv of 4-$MePhB(OH)_2$, 2.1 equiv of Cs_2CO_3, 5 equiv of H_2O, toluene, 23 °C, 18 h. [b] Isolated yield. [c] Yield determined by ^1H NMR.

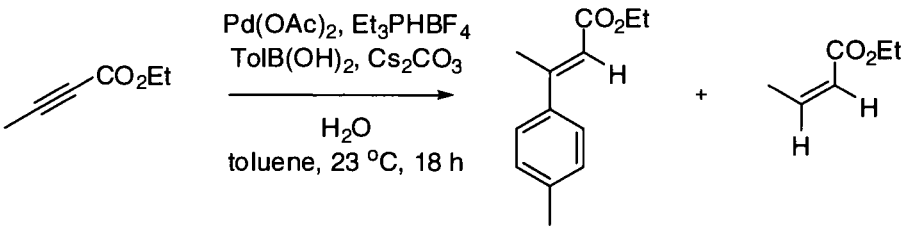
During the previous optimization reactions, the concentration of the alkyne was 0.05 M. At this concentration, the yield of the trisubstituted alkene **278** was 71 % and the yield of the undesired *cis*-alkene **279** was 4 % (table 34, entry 1). When the concentration of alkyne **277** was doubled to 0.1 M, the yield of the reaction decreased, with product **278** being isolated in 52 % yield (entry 2). This trend continued as the

concentration was increased. When the concentration of alkyne **277** was doubled again to 0.2 M the efficiency of the reaction suffered as trisubstituted olefin product **278** was isolated in 43 % yield with trace amounts of **279** being observed (entry 3). When the concentration of the reaction was increased to 0.5 M of alkyne **277** the desired trisubstituted alkyne was afforded in 57 % yield. No trace of side product **279** was observed by ^{1}H NMR at this concentration (entry 4). It was concluded that at lower concentrations the reaction proceeded more efficiently than at higher concentrations, generating high yields of the desired trisubstituted olefin product **278**. At low concentrations the yield of the undesired *cis*-alkene product **279** was greater than that at higher concentrations; however, this was balanced by the increased yield of trisubstituted olefin **278**.

At this point in the optimization of the addition of organoboronic acids to alkynoates, alkyne **277** was completely consumed over the course of the optimization reactions. While more alkyne **277** was being synthesized, further optimization experiments were performed with ethyl-2-butynoate **266**.

The amount of water being used in the reaction of an alkynyl ester with a boronic acid had yet to be optimized. The effect on the number of equivalents of water added to the reaction was explored in table 35.

Table 35: The effect of water on the formation of trisubstituted olefins.



266 **244** **280**

Entry[a]	Equiv H_2O	Yield **244** (%)[b]	Yield **280** (%)[c]
1	0	21	7
2	1	25	0
3	2	54	0
4	5	72	0
5	10	88	0
6	20	64	0

[a] Conditions: 0.06 equiv of $Pd(OAc)_2$, 0.18 equiv of $Et_3P{\cdot}HBF_4$, 2.0 equiv of 4-$MePhB(OH)_2$, 2.1 equiv of Cs_2CO_3, toluene, 23 °C, 18 h. [b] Isolated yield. [c] Yield determined by ^1H NMR.

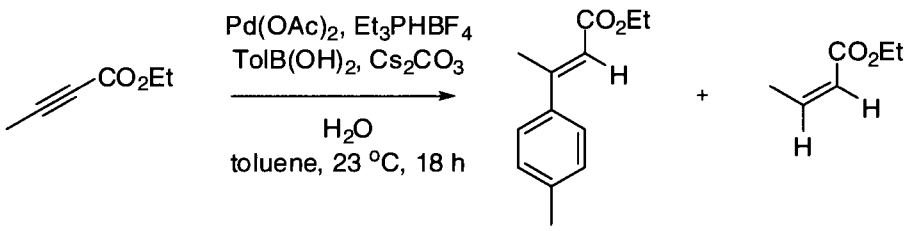
As had been shown in table 28, when no water was used as an additive, the reaction did not perform well, affording trisubstituted olefin product **244** in 21 % yield, with 7 % of *cis*-ethyl crotonate **280** being observed (table 35, entry 1). When one equivalent of water was added, very little change in synthesis of olefin **92** was observed, however, the presence of ethyl crotonate **280** was no longer detected by ^1H NMR (entry 2). Employing twice as much additive produced a marked improvement in the yield of the trisubstituted product **244** (entry 3), with no appearance of alkene **280**.

The use of five equivalents of H_2O caused the reactivity return to similar levels as with alkyne **277** as trisubstituted olefin product **244** was isolated in 72 % yield. Fortunately, the smaller alkyne showed no appearance of the *cis*-alkene product **280** (entry 4). A further increase in the amount of additive to ten equivalents (entry 5) gave the complete conversion of alkyne **266** to trisubstituted olefin **244** with no appearance of

alkene side product **280**. Ten equivalents of water proved to be the maximum that the reaction could tolerate, as shown in entry 6, when 20 equivalents of this additive was used. Under these conditions, the yield of trisubstituted olefin product **244** suffered, with the product being isolated in 64 % yield.

The amount of H_2O added had a drastic affect on the yield of this reaction. The optimal conversion of alkyne **266** to alkene **244** occurred when ten equivalents of water were added to the reaction. Before exploring the scope of the reaction, very low concentrations of alkyne **266** were examined.

Table 36: The effect of low concentration on the synthesis of trisubstituted olefins.



266 **244** **280**

Entry[a]	Concentration **266** (M)	Yield **244** (%)[b]	Yield **280** (%)[c]
1[d]	0.01	87	0
2	0.05	88	0
3	0.1	78	0

[a] Conditions: 0.06 equiv of $Pd(OAc)_2$, 0.18 equiv of $Et_3P{\cdot}HBF_4$, 2.0 equiv of 4-$MePhB(OH)_2$, 2.1 equiv of Cs_2CO_3, 10 equiv of H_2O, toluene, 23 °C, 18 h. [b] Isolated yield. [c] Yield determined by ^1H NMR. [d] Reaction time was four days.

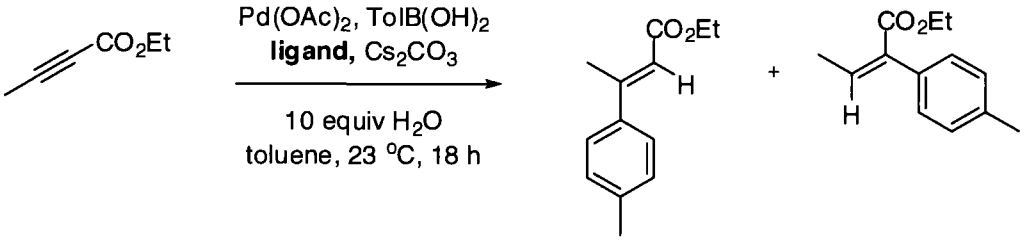
As had been shown with the alkyne **277** (table 34), a decrease in concentration of alkyne resulted in an increase in yield of alkene **244**. At the standard reaction condition of 0.05 M of alkyne, product **244** was isolated in 88 % yield (table 36, entry 2). When the concentration of alkyne was decreased to 0.01 M no increase in yield was observed,

with the trisubstituted olefin product being realized in 87 % yield (entry 1). However, at this low concentration, the reaction took four days to go to completion, instead of the usual 18 hours. The reaction was also performed at a concentration of 0.1 M of alkyne **266** (entry 3). At this concentration the olefin product **244** was isolated in 78 % yield, a minor decrease over the previous concentration. At all concentrations examined, no amount of *cis* olefin **280** was detected.

At 0.05 M, the complete conversion of alkyne **266** to olefin **244** was observed in a reasonable amount of time. At lower concentrations, the reaction was very slow and a minimal change in yield was observed. It was decided to continue the optimization at a concentration of 0.05 M of alkyne.

Although the use of Et_3P as a ligand gave single isomer trisubstituted olefin products in good yields, the effect of different phosphine ligands on the reaction of alkyne **266** with 4-tolylboronic acid was explored in an effort to improve the yield while still isolating a single isomer trisubstituted olefin product.

Table 37. Initial optimization of the synthesis of trisubstituted olefins from alkynyl esters.



266 **244** **281**

Entry[a]	Ligand	Yield (%)[b]	Ratio (**244**:**281**)[c]
1	tBu$_3$P·HBF$_4$	89	85:15
2	Cy$_3$P·HBF$_4$	86	95:5
3	Ph$_3$P	53	93:7
4	S-Phos	69	97:3
5	Dave-Phos	46	92:8
6	MetBu$_2$P·HBF$_4$	95	96:4
7	Me$_3$P·HBF$_4$	59	Only **244**
8	Et$_3$P·HBF$_4$	88	Only **244**

[a] Conditions: 0.06 equiv of Pd(OAc)$_2$, 0.18 equiv of ligand, 2.0 equiv of 4-MePhB(OH)$_2$, 2.1 equiv of Cs$_2$CO$_3$, 10 equiv of H$_2$O, toluene, 23 °C, 18 h. [b] Combined isolated yield of **244** and **281**. [c] Ratio determined by ^{1}H NMR.

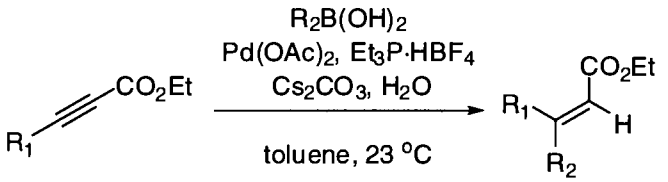
Employing tBu$_3$P·HBF$_4$ as a ligand resulted in an increase in yield (89 %) but a loss in regioselectivity, with the appearance of isomer **281** (table 19, entry 1). The use of bulky ligands such as Cy$_3$P gave high regioselectivity (19:1) together with good overall yields (entry 3). When PPh$_3$ was implemented as the ligand, the efficiency of the process suffered (entry 4). A reaction performed with S-Phos (entry 5) gave very good regioselectivity (97:3) but the overall yield was moderate. Similarly, the use of Dave-Phos (entry 6) resulted in a reaction with high regioselectivity, but poor yield. The application of smaller alkyl-substituted phosphine ligands produced success. As shown in entry 7, MetBu$_2$P worked quite well as a ligand, giving high yield (95 %) and excellent regioselectivity (24:1). By decreasing the size of the ligand slightly to Et$_3$P, we were able

to suppress the formation of **281**, isolated only product 5 in 88 % yield (entry 8). The smaller ligand, Me_3P (entry 9), also gave exclusive regioselectivity, however, the yield decreased to 59 %.

4.1.2 Scope and mechanism

As the conversion of alkyne **266** to trisubstituted olefin product **244** with use of $Et_3P{\cdot}HBF_4$ as the ligand gave a single isomer product, the scope of the reaction of alkynyl esters with aryl and vinyl boronic acids was explored in table 38 under the optimized reaction conditions.

Table 38. The formation of trisubstituted olefins from corresponding alkynyl esters and boronic acids.



85 **43**

Entry[a]	R_1	Substrate	R_2	Product	Yield[e] (%)
1	CH_3	**266**	4-MeC_6H_4	**244**	88
2	CH_3	**266**	3-MeC_6H_4	**282**	75
3	CH_3	**266**	2-MeC_6H_4	**283**	80
4	CH_3	**266**	C_6H_5	**242**	77
5	CH_3	**266**	4-$MeOC_6H_4$	**246**	67
6	CH_3	**266**	3-$MeOC_6H_4$	**284**	67
7[b]	CH_3	**266**	2-$MeOC_6H_4$	**285**	58
8	CH_3	**266**	4-FC_6H_4	**286**	58
9[b]	CH_3	**266**	4-$CH_3COC_6H_4$	**287**	49
10	CH_3	**266**	(*E*)-C_6H_4CHCH	**288**	51
11	CH_3	**266**	(*E*)-$C_6H_{13}CHCH$	**289**	86
12	CH_3	**266**	1-naphthyl	**248**	77
13	CH_3	**266**	2-naphthyl	**290**	78
14	CH_3	**266**	3-thiophene	**291**	56
15	C_6H_{12}	**292**	4-MeC_6H_4	**293**	77
16	C_6H_5	**294**	4-MeC_6H_4	**295**	66
17[c]	H	**296**	4-MeC_6H_4	**297**	10
18	$BnO(CH_2)_2$	**277**	4-MeC_6H_4	**278**	71
19	$TIPSO(CH_2)_4$	**298**	4-MeC_6H_4	**299**	68
20[d]	$Me(CH_2)_5$	**300**	4-MeC_6H_4	**301**	60
21[d]	C_6H_{12}	**302**	C_6H_5	**303**	55

[a] 0.06 equiv of Pd(OAc)2, 0.18 equiv of $Et_3P{\cdot}HBF_4$, 2.0 equiv of $R_2B(OH)_2$, 2.1 equiv of Cs_2CO_3, 10 equiv of H_2O, toluene, 23 °C, 18 h. [b] Me*t*$Bu_2P{\cdot}HBF_4$ was used in place of $Et_3P{\cdot}HBF_4$. [c] The methyl ester was used in place of the ethyl ester. [d] The Weinreb amide was used in place of the ester. [e] A single isomer was observed in every case.

Simple boronic acids worked well under the reaction conditions, affording trisubstituted olefins in good yields (table 38, entries 1 – 4). The presence of a strong electron-donating group on the boronic acid component had a minimal impact on the

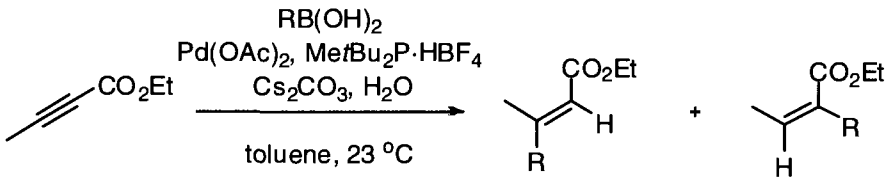
reactivity, regardless of whether the substitutent was in the *para-*, *meta-*, or *ortho-* positions (entries 5 – 7). Electron withdrawing groups were compatible with the process, giving the trisubstituted products in moderate yield (entries 8 and 9). Coupling with sp^2-hybridized partners, such as vinyl or styrenyl boronic acids, gave moderate to good yields, as shown in entry in entries 10 and 11. The steric bulk of the boronic acid did not affect the yield of the process, as shown in entries 12 and 13, in which the use of either 1- or 2-naphthylboronic acids afforded the respective addition products in good yields. Heterocyclic boronic acids were also tolerated, as shown by the result of entry 14, employing 3-thiophenylboronic acid. In all cases, no loss of olefin stereochemical information was observed and the products were isolated as single isomers.

Modification to the alkynyl starting material resulted in an efficient coupling, as shown in entry 15, in which a cyclohexyl substituted replaced the methyl substituted. It was possible to substitute the alkyne component with a phenyl group, a modification that produced the desired trisubstituted olefin as a single isomer (entry 16). In both of these cases, the newly introduced hydrogen and aryl ring were added *syn* to each other, indicating that the product stereochemistry was a consequence of mechanism and not of thermodynamics. Using methyl propriolate as a substrate did not provide useful amounts of product (entry 17). The presence of substituted alkyl chains was compatible with the reaction conditions, as shown in entries 18 and 19. Finally, the reaction proceeded with complete selectivity when the carboxylate moiety on the alkyne was replaced with a Weinreb amide (entries 20 and 21). In all cases, the products were isolated as single isomers.[65]

[65] The relative stereochemistry of all products was assigned by nOe networks.

In an effort to see if the isolated yield of the reaction could be improved, reaction of ethyl-2-butynoate with a series of boronic acids was performed using Me*t*Bu$_2$P·HBF$_4$ as ligand, due to the high yield and excellent regioselectivity observed in the initial optimization experiments.

Table 39. The formation of trisubstituted olefins from ethyl-2-butynoate and the corresponding boronic acid with Me*t*Bu$_2$P·HBF$_4$ as ligand.



266

	244	**281**
R = 4-MeC$_6$H$_4$	**244**	**281**
R = 4-MeOC$_6$H$_4$	**246**	**304**
R = 3-MeOC$_6$H$_4$	**284**	**305**
R = 4-FC$_6$H$_4$	**286**	**306**
R = (*E*)-C$_6$H$_4$CHCH	**288**	**307**
R = 1-naphthyl	**248**	**308**
R = 2-naphthyl	**290**	**309**
R = 3-thiophene	**291**	**310**

Entry[a]	R	Product	Yield (%)[b]	Ratio[c]
1	4-MeC$_6$H$_4$	**244 + 281**	95	96:4
2	4-MeOC$_6$H$_4$	**246 + 304**	87	94:6
3	3-MeOC$_6$H$_4$	**284 + 305**	82	92:8
4	4-FC$_6$H$_4$	**286 + 306**	78	95:5
5	(*E*)-C$_6$H$_4$CHCH	**288 + 307**	75	89:11
6	1-naphthyl	**248 + 308**	83	96:4
7	2-naphthyl	**290 + 309**	87	89:11
8	3-thiophene	**291 + 310**	82	93:7

[a] Conditions: 0.06 equiv of Pd(OAc)$_2$, 0.18 equiv of Me*t*Bu$_2$P·HBF$_4$, 2.0 equiv of RB(OH)$_2$, 2.1 equiv of Cs$_2$CO$_3$, 10 equiv of H$_2$O, toluene, 23 °C, 18 h. [b] Combined isolated yield. [c] Ratio determined by ^{1}H NMR.

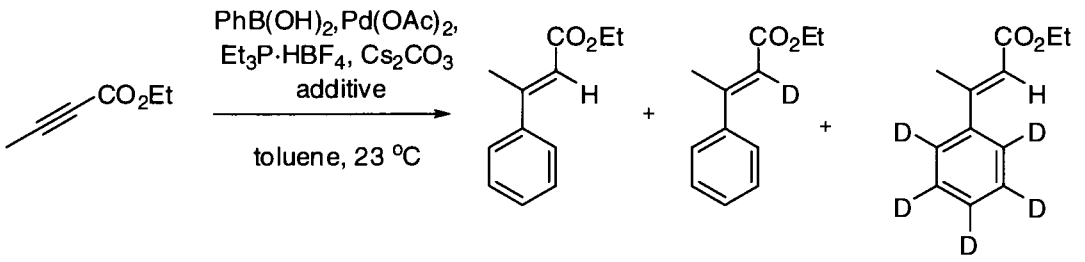
When ethyl-2-butynoate **266** was submitted to the optimized reaction conditions, replacing the ligand Et$_3$P·HBF$_4$ with Me*t*Bu$_2$P·HBF$_4$, an inseparable mixture of

trisubstituted olefin products **244** and regioisomer **281** was isolated as a 96:4 ratio in 95 % yield (table 39, entry 1). The reaction proceeded in equally high regioselectivity with strongly electron donating group at the *para-* and *meta-* positions, when a methoxy group was used as the substituent. Trisubstituted olefin products **246** & **304** and **284** & **305** were isolated in 87 % and 82 % combined yields as 94:6 and 92:8 ratios of isomers respectively (entries 2 and 3).

The reaction also proceeded smoothly with an electron withdrawing group at the *para*-position as shown in entry 4, giving a 95:5 mixture of isomers **286** & **306** in 78 % combined yield. Coupling with sp^2-partners proceeded efficiently, albeit in lower selectivity, as shown in entry 6 with styrenylboronic acid, which gave product **288** & **307** as an 89:11 mixture of isomers in 75% yield. Larger aromatic boronic acids gave good yield and good selectivity, as shown in entries 6 and 7 with the use of both 1- and 2-naphthylene. These resulted in combined yields of 83 % and 87 % respectively of trisubstituted olefin products **248** & **308** and **290** & **309**. However, 1-naphthylene gave a much better ratio of isomers (96:4), compared to 89:11 for 2-naphthylene (entries 7 and 8). The use of heterocycles with this methodology was shown to produce trisubstituted olefin products in good yields, as shown in entry 8 with 3-thiophene, which afforded a 93:7 mixture of isomer **291** & **310** in 82 % yield.

The yield of the reaction of ethyl-2-butynoate **266** with aryl boronic acids was improved when Me*t*Bu$_2$P·HBF$_4$ was employed as the ligand. However, the reaction was no longer regiospecific, as mixtures of isomers were obtained in most cases. An area for future research would be to try this reaction with the ligand Me$_2$*t*BuP·HBF$_4$ to determine if an increase in both regioselectivity and yield would be observed.

Table 40. The source of hydrogen during trisubstituted olefin formation from alkynes.



266 **242** **311** **312**

Entry[a]	Boronic Acid	Additive	Yield (%)	Ratio (**242**:**311**)
1	$PhB(OH)_2$	H_2O	77	100:0
2[b]	$PhB(OH)_2$	H_2O	64	100:0
3	$PhB(OH)_2$	D_2O	66	30:70
4[c]	$PhB(OH)_2$	D_2O	72	27:73
5	$PhB(OD)_2$[d]	H_2O	63	97:3
6	$PhB(OD)_2$[d]	D_2O	68	30:70
7	$PhB(pin)_2$	None	Trace	
8	$PhB(pin)_2$	H_2O	36	100:0
9	$PhB(pin)_2$	D_2O	30	40:60
10	$C_6D_5B(OH)_2$	H_2O	78	100:0[e]

[a] 0.06 equiv of $Pd(OAc)_2$, 0.18 equiv of $Et_3P{\cdot}HBF_4$, 2.0 equiv of $PhB(OH)_2$, 2.1 equiv of Cs_2CO_3, 10 equiv of additive, toluene, 23 °C, 18 h. [b] Reaction performed in C_6D_6. [c] 30 equiv of D_2O were added. [d] $PhB(OD)_2$ was 40 % atom D. [e] Ratio given is of product **312**:**311**.

In order to identify the hydrogen source, a series of isotope labeling experiments were done. Only product **242** was obtained when substrate **266** was coupled with $PhB(OH)_2$ in C_6D_6 indicating that the solvent was not the source of hydrogen (table 3, entry 2). Performing a reaction between alkyne **266** and phenylboronic acid in the presence of D_2O produced 70 % deuterium incorporation in the alkene (entry 3). Using an excess of D_2O (30 equiv) did not significantly increase the proportion of deuterated product **311**, as shown in entry 4. Replacing the boronic acid with the corresponding

deuterated boronic acid (40 % atom D) resulted in almost no deuterium incorporation (entry 5). These results suggested that H_2O or the boronic acid was the source of hydrogen. A qualitative deuterium isotope effect was operative, indicating that the hydrogen transfer was a rate limiting part of the process. Evidence supporting this is shown in entry 6, in which both the deuterated boronic acid (40 % atom D) and D_2O were added, affording only 70 % deuterium incorporation in the products.[66]

When the phenylboronic acid was replaced with its corresponding pinacol ester, the reaction did not proceed. However, when water was added to the mixture, a moderate yield of product **242** was noted (entries 7 and 8). Performing a coupling with the pinacol ester and D_2O, we observed 60 % deuterium incorporation in the product. The remaining 40 % (product **242**) could possibly have arisen from the $Et_3P{\cdot}HBF_4$ salt. As a final control experiment, we performed a reaction with $C_6D_5B(OH)_2$ and H_2O in order to see if the hydrogen could have been derived form a [1,4]-Pd shift onto the aryl group of the product as had been shown with similar rhodium catalyzed additions to alkynes.[67] No deuterium incorporation was observed under these conditions as only product **312** was isolated.

Based on these experiments and on previous results,[63,68,69] the following mechanism could be proposed (scheme 30). Palladium undergoes oxidative insertion in the OH bond of either the boronic acid or the water to form an initial H–[Pd]–OX species.[63,70] This step is suggested by the observation of an isotope effect for hydrogen

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[66] The initial ratio of H:D was 10:90

[67] a) Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M.; *J. Am. Chem. Soc.* **2001**, *123*, 9918; Lautens, M.; Yoshida, M.; *Org. Lett.* **2002**, *4*, 123.

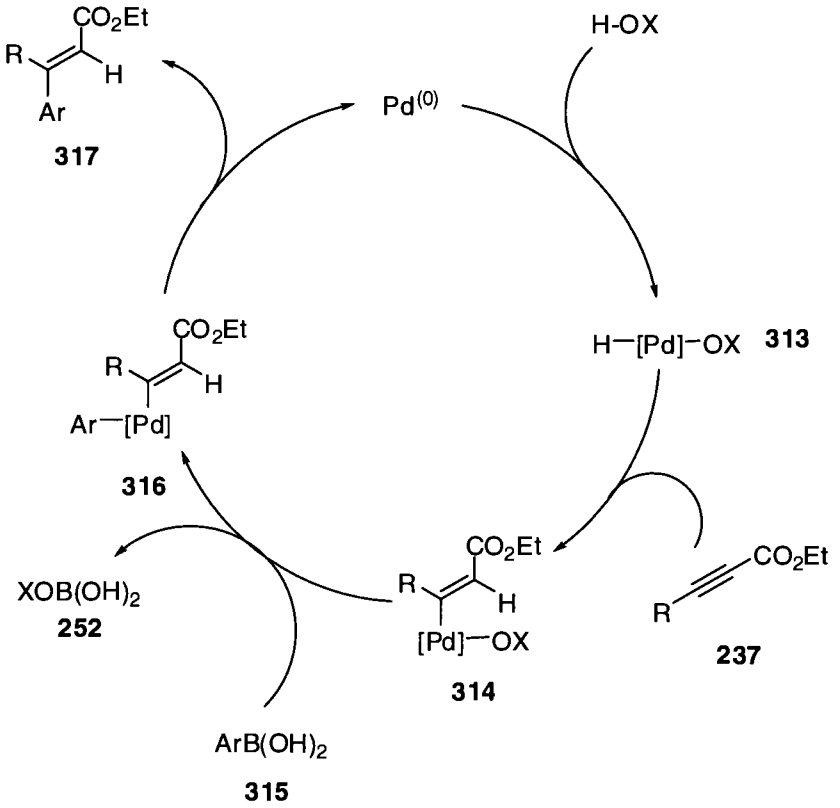
[68] Lindhardt, A.T.; Mantel, M.L.H.; Skrydstrup, T.; *Angew. Chem. Int. Ed.* **2008**, *120*, 2708.

[69] Ma, S.; Jiao, N.; Ye, L.; *Chem. Eur. J.* **2003**, *9*, 6049.

[70] Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A.; *J. Am. Chem. Soc.* **1985**, *107*, 972.

transfer and by the fact that pinacol boronic esters do not undergo the process in the absence of water. Following the oxidative insertion, there a *syn* carbopalladation into the triple bond of the alkynyl ester occurs, forming a palladium intermediate with the observed regio- and stereochemistry. Transmetallation of the arylboronic acid is followed by reductive elimination to regenerate the palladium catalyst and produce the final product.

Scheme 30. Proposed mechanism of addition of organoboronic acids to alkynyl esters.



Although the mechanism proposed in scheme 30 has literature precedent, there are some problems associated with it. The addition of palladium hydride species **313** to alkyne **237** does not follow the appropriate electronics of the alkyne. The partially

negative hydrogen should add to the partially positive β-carbon of the alkyne to form the regioisomer of intermediate **314**. However, this does not happen as the regioisomer of **317** is not observed. In addition, there is literature precedent for carbopalladation to add aryl groups to the β-position of α,β-unsaturated esters.[71] This mechanism also does not explain why small phosphine ligands provide single isomer products and larger phosphine ligands provide mixtures of isomers.

This leads us to speculate about a different mechanism for the addition of organoborates to alkynyl esters, shown in scheme 31. In this proposed mechanism, the small phosphine ligand would perform a 1,4-addition to the β-position of the alkynyl ester forming alkene **319** and **320** after protonation of allene intermediate **318**. This type of reaction is highly precedented in the Baylis-Hillman reaction.[72] Cross coupling reactions have previously been observed for related quaternary ammonium species[73] and the complete exchange of aryl rings between a phosphine species and palladium(II) complexes has been documented.[74]

Both intermediate **319** and **320** have the potential to enter the catalytic cycle. If this mechanism were to be proven accurate, intermediate **320** must not enter the catalytic cycle, since the corresponding product is not observed. This suggests that there exists equilibrium between **319**, **318**, and **320**. Intermediate **319** could potentially be more stable than **320** as the phosphonium group is aligned away from the ester functionality. However, when large R groups such as cyclohexy or phenyl are used, this argument loses some strength as it becomes a stericly bulky group. It is possible that intermediate **319** is

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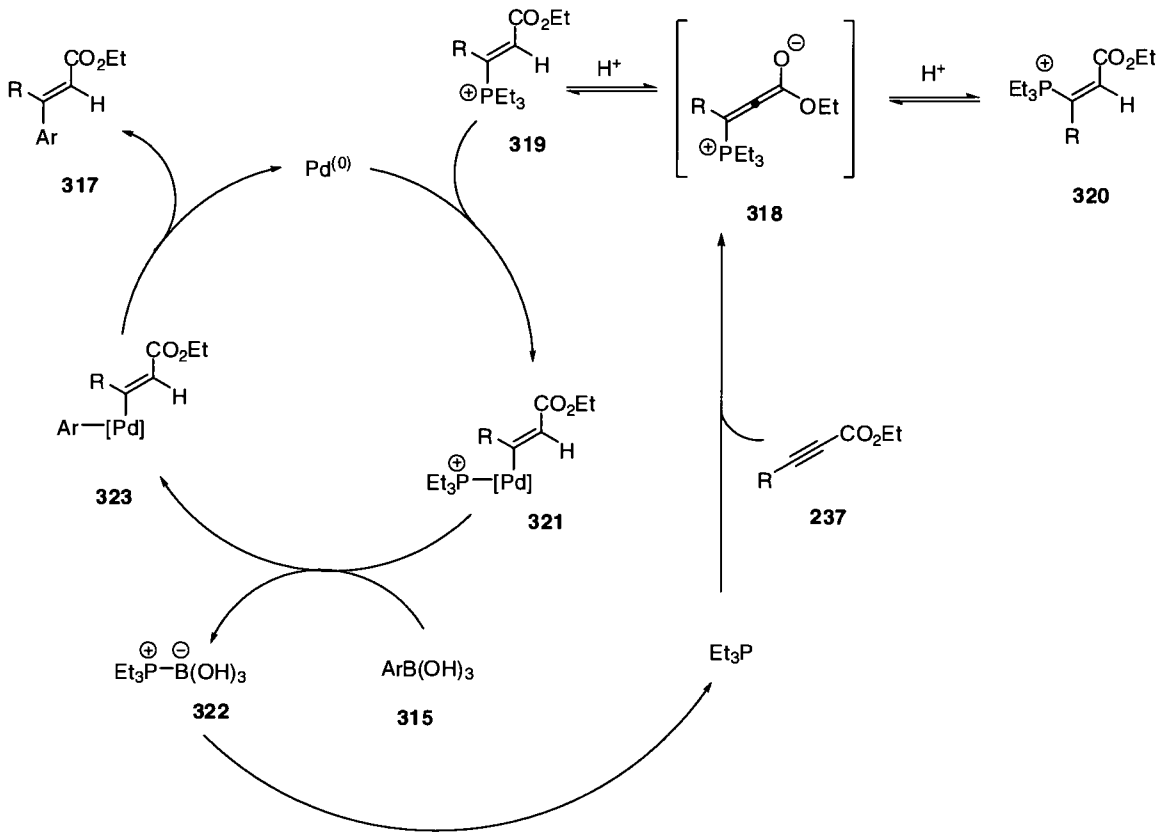
[71] Dieck, H.A.; Heck, R.F.; *J. Org. Chem.* **1975**, *40*, 1083.
[72] a) Trost, B.M.; Dake, G.R.; *J. Am. Chem. Soc.* **1997**, *119*, 7595; b) Trost, B.M.; Dake, G.R.; *J. Org. Chem.* **1997**, *62*, 5670.
[73] Blakey, S.B.; MacMillan, D.W.C.; *J. Am. Chem. Soc.* **2003**, *125*, 6046.
[74] Kong, K.C.; Cheng, C.H.; *J. Am. Chem. Soc.* **1991**, *113*, 6313.

more stable than intermediate **320** due to electronics, as the dipoles are eliminated in **319** and are aligned in **320**.

The reaction of **319** over **320** could also be explained by Curtin-Hammett kinetics.[71] It is possible that the equilibrium between **320** and **319** is very fast and it is the subsequent entry into the catalytic cycle that is slow. In the case of **320**, the phosphonium and ester group are adjacent to each other and in **319** the phosphonium and the ester group are aligned on opposite sides of the double bond. Intermediate **319** may therefore react faster as was shown in earlier examples.[57,58,60]

Once intermediate **319** has formed, oxidative insertion of palladium into the C-P bond could occur to form compound **321**. At this point, the transmetallation with the arylboronic acid would produce intermediate **323** which could reductively eliminate to regenerate the palladium catalyst and produce trisubstituted olefin product **317** with the observed regiochemistry.

Scheme 31. The speculated mechanism of the addition of organoborates to alkynyl esters.



Research into this mechanism is currently ungoing in our laboratory. ^{31}P NMR experiments along with investigations of the reaction trimethylphenylphosphonium with arylboronic acids are being used to elucidate this mechanism.

By using the sterically unencumbered phosphine ligand, Et_3P, we have been able to generate single isomer trisubstituted olefins from alkynyl esters in good yields by coupling with either aryl or vinyl boronic acids. The reactions proceeded well at room temperature under very mild conditions and, in all cases, produced the desired products as single isomers. Ligand size proved to be critical in this process as only small ligands such as Me_3P or Et_3P resulted in the production of single isomers. This new

methodology provides a convenient synthesis of trisubstituted olefins without the need to generate olefin templates.

Chapter 5

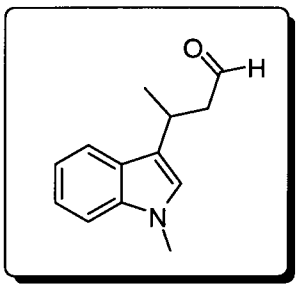
5.1 Experimental

5.1.1 General

Standard inert atmosphere techniques were employed in handling all air and moisture sensitive reagents. Reactions were monitored by thin layer chromatography (TLC) using commercial glass-backed silica gel sheets coated with silica gel 60 F_{254}. TLC spots were visualized under ultraviolet light or developed by heating after treatment with potassium permanganate. All reactions were performed in oven dried glassware. Solvents were distilled prior to use: THF over sodium/benzophenone; CH_2Cl_2 was distilled over calcium hydride; DMF was distilled over calcium hydride; Benzene was distilled over calcium hydride; Toluene was distilled over calcium hydride; Triethylamine was distilled over sodium hydride. (*E*)-crotonaldehyde was distilled prior to use. Commercially available reagents were obtained from Sigma-Aldrich, TCI America or Frontier Scientific and were used as is. Column chromatography was performed using silica gel 60 (230 - 400 mesh, Silicycle). ^{1}H NMR and ^{13}C NMR were recorded on Bruker AMX instruments at either 300 MHz and 75 MHz respectively or 400 MHz and 100 MHz respectively. Chemical shifts are reported in ppm δ units relatively to chloroform (7.26 ppm for ^{1}H NMR, 77.0 ppm for decoupled ^{13}C NMR) or acetone-d6 (2.05 ppm for ^{1}H NMR, 33.0 ppm for decoupled ^{13}C NMR) as internal standard. IR spectra were recorded as neat films on a sodium chloride cell with a Bomen Michaelson

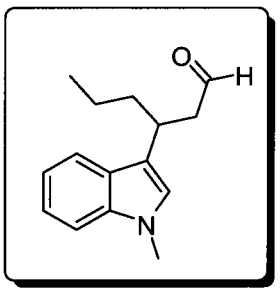
100 FTIR instrument. Mass spectra were recorded at the University of Ottawa Mass Spectrometry Centre. Chiral HPLC data was obtained on a Waters 2695 equipped with a Chiracel AD-H (4.6 x 250 mm) chiral column and a Waters PDA detector 2996. Room temperature refers to 23 °C.

5.1.2 Procedures for organocatalysis experiments



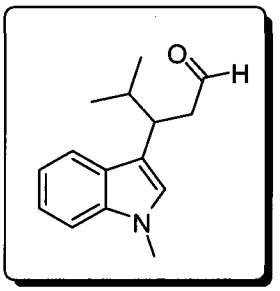
3-(1-Methyl-1*H*-indol-3-yl)butanal (133). To a flame dried 10 mL round bottom flask equipped with a Teflon-coated stir bar was added (*S*)-(+)-3-benzyl-10,10-dimethyl-3,4-diazatricyclo[5.2.1.01,5]decan-2-one **121** (10.6 mg, 0.04 mmol), 0.75 mL EtOH and 0.25 mL H_2O. Triflic acid (2.8 μL, 0.03 mmol) was added to the stirred solution, which was then cooled to -20 °C in an acetone-dry ice bath. Once cooled, freshly distilled (*E*)-crotonaldehyde (0.15 mL, 1.81 mmol) was added and the reaction was stirred at -20 °C. After 15 minutes, 1-methylindole (24.0 μL, 0.190 mmol) was added and the reaction was placed in the freezer for 24 hours at -18 °C. Once the reaction was complete by TLC, it was eluted through a plug of silica with ether. The crude product was purified by flash column chromatography (benzene) to afford the title compound[32] (23.3 mg, 62 %). To determine enantiomeric excess, the pure product was dissolved in 1 mL of EtOH and

$NaBH_4$ (200 mg, 5.30 mmol) was added. After stirring the reaction for 20 minutes, 2 mL saturated $NaHCO_3$ solution was added and the solution was stirred for another 10 minutes. Once complete by TLC, the reaction was diluted with 10 mL of dichloromethane and extracted three times with water, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting alcohol was subjected to chiral HPLC analysis using a Chiracel AD-H column and a solvent system of 3:97 *i*PrOH:Hexanes in a 35 minute run. The retention time for the *S* enantiomer was 26.99 minutes and that of the *R* enantiomer was 29.61 minutes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (d, J = 2.1, 2.1 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.32 – 7.21 (m, 2H), 7.12 (ddd, J = 1.5, 7.4, 8.1 Hz, 1H), 6.84 (s, 1H), 3.75 (s, 3H), 3.68 (dt, J = 6.9, 13.8 Hz, 1H), 2.88 (ddd, J = 2.7, 6.9, 16.2 Hz, 1H), 2.71 (ddd, J = 2.7, 6.9, 16.2 Hz, 1H), 1.44 (d, J = 7.2 Hz, 3H).

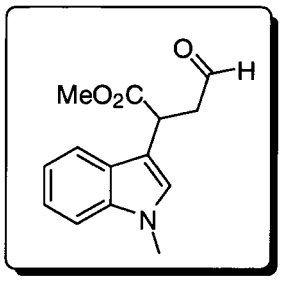


3-(1-Methyl-1*H*-indol-3-yl)hexanal (137) Prepared in a similar method to 3-(1-methyl-1*H*-indol-3-yl)hexanal **133** using (*E*)-hex-2-enal (0.230 mL, 2.00 mmol). The crude product was purified by flash chromatography (benzene) to give the title compound[32] (20.1 mg, 45 %). The aldehyde was converted to an alcohol following a similar procedure. The resulting alcohol was subjected to chiral HPLC analysis using a Chiracel AD-H column and a solvent system of 3:97 *i*PrOH:Hexanes in a 35 minute run. The

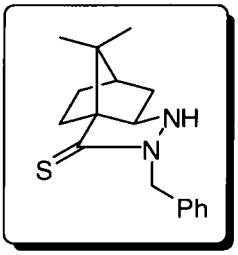
retention time for the *S* enantiomer was 25.11 minutes and that of the *R* enantiomer was 31.10 minutes: ^{1}H NMR (300 MHz, $CDCl_3$) 9.71 (dd, *J* = 2.1, 2.1 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.35-7.24 (m, 2H), 7.12 (ddd, *J* = 1.5, 7.2, 8.1 Hz, 1H), 6.87 (s, 1H), 3.76 (s, 3H), 3.55 (m, 1H), 2.83 (m, 2H), 1.79 (m, 2H), 1.34 (dt, *J* = 7.2, 22.8 Hz, 2H), 0.92 (dd, *J* = 7.2, 7.2 Hz, 3H).



4-Methyl-3-(1-methyl-1H-indol-3-yl)pentanal (138) Prepared in a similar method to 3-(1-methyl-1H-indol-3-yl)hexanal **133** using (*E*)-4-methylpent-2-enal (0.220 mL, 1.90 mmol). The crude product was purified by flash chromatography (benzene) to give the title compound[32] (20.9 mg, 48 %). The aldehyde was converted to an alcohol following a similar procedure. The resulting alcohol was subjected to chiral HPLC analysis using a Chiracel AD-H column and a solvent system of 3:97 *i*PrOH:Hexanes in a 60 minute run. The retention time for the *S* enantiomer was 28.76 minutes and that of the *R* enantiomer was 49.13 minutes: ^{1}H NMR (300 MHz, $CDCl_3$) 9.61 (dd, *J* = 2.4, 2.4 Hz, 1H), 7.63 (dt, *J* = 0.9, 8.1 Hz, 1H), 7.33 – 7.22 (m, 2H), 7.13 (ddd, *J* = 1.5, 6.9, 8.1 Hz, 1H), 6.82 (s, 1H), 3.75 (s, 3H), 3.40 (dt, *J* = 6.6, 7.8 Hz, 1H), 2.81 (d, *J* = 2.4 Hz, 1H); 2.79 (d, *J* = 2.4 Hz, 1H); 2.10 (ddd, *J* = 6.6, 13.2, 19.8 Hz, 1H), 0.96 (d, *J* = 2.1 Hz, 3H), 0.94 (d, *J* = 2.1 Hz, 3H).

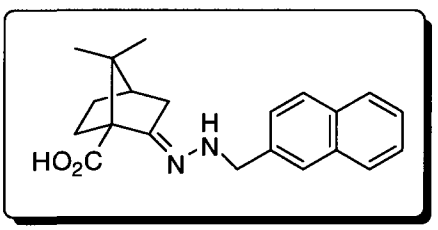


Methyl 2-(1-methyl-1H-indol-3-yl)-4-oxobutanoate (139) Prepared in a similar method to 3-(1-methyl-1H-indol-3-yl)hexanal **133** using (*E*)-ethyl 4-oxobut-2-enoate (0.220 mL, 1.83 mmol). The crude product was purified by flash chromatography (benzene) to give the title compound (13.1 mg, 28 %). The aldehyde was converted to an alcohol following a similar procedure. The resulting alcohol was subjected to chiral HPLC analysis using a Chiracel AD-H column and a solvent system of 3:97 *i*PrOH:Hexanes in a 120 minute run. The retention time for the *S* enantiomer was 103.42 minutes and that of the *R* enantiomer was 111.48 minutes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.33 – 7.23 (m, 2H), 7.15 (ddd, J = 1.2, 7.6, 7.8 Hz, 1H), 6.98 (s, 1H), 4.44 (dd, J = 5.4, 9.3 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.47 (dd, J = 9.3,18.6 Hz, 1H); 2.94 (dd, J = 5.1, 18.3 Hz, 1H).



(*S*)-(+)-3-Benzyl-10,10-dimethyl-3,4-diazatricyclo[5.2.1.0^{1,5}]decan-2-thione (148) To a flame dried 10 mL flask equipped with a Teflon-coated magnetic stir bar and a reflux condenser was added (*S*)-(+)-3-benzyl-10,10-dimethyl-3,4-

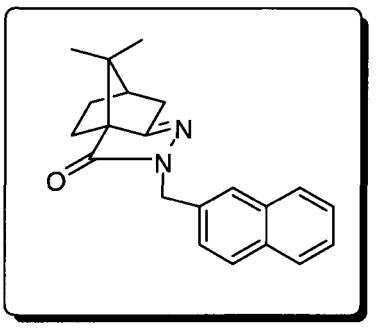
diazatricyclo[5.2.1.01,5]decan-2-one[28] **121** (112.4 mg, 0.4157 mmol) and Lawesson's Reagent (830.0 mg, 2.052 mmol) in 5 mL of toluene. The reaction was refluxed for 4 h until complete by TLC, at which point the crude product was purified by flash column chromatography (dichloromethane) to afford the title compound as a yellow solid (93.6 mg, 80 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 5H), 5.53 (d, J = 14.4 Hz, 1H), 4.71 (d, J = 14.4 Hz, 1H), 3.55 (dd, J = 4.4, 8.4 Hz, 1H), 2.35 (dt, J = 4.8, 4.8, 11.6 Hz, 1H), 2.13 – 2.07 (m, 1H), 2.00 – 1.89 (m, 2H), 1.68 (dd, J = 8.0 Hz, 12.8 Hz, 1H), 1.36 (ddd, J = 2.8, 8.8, 12.0 Hz, 1H), 1.27 – 1.20 (m, 2H), 1.15 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3 (C), 129.0 (CH), 128.8 (CH), 128.5 (CH), 69.2 (C), 65.7 (CH_2), 53.0 (C), 51.5 (CH), 47.1 (CH_2), 35.8 (CH), 31.3 (CH_3), 26.6 (CH_3), 20.8 (CH_2), 20.0 (CH_2); IR (neat) 1715, 1625 cm^{-1}; MS 286.1 (M+); HRMS calcd for $C_{17}H_{22}N_2S$ (M+) 286.1504, found 286.1492.



(*S*)-(+)-(*E*)-7,7-Dimethyl-2-(2-(naphthalen-2-ylmethyl)hydrazono)bicyclo[2.2.1]heptane-1-carboxylic acid (328). To a flame dried 25 mL flask equipped with a Teflon-coated magnetic stir bar was added (*S*)-(+)-ketopinic acid[75] (443.2 mg, 2.432 mmol) and 2-naphthylhydrazine (500.5 mg, 2.906 mmol). The reagents were dissolved in 10 mL dichloromethane and acetic acid (2.781 μL, 0.049 mmol) was added. The reaction was stirred for 24 h until complete by TLC. Once

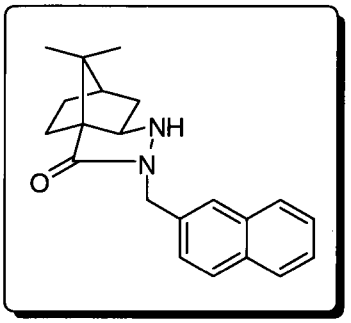
[75] Bartlett, P.D.; Knox, L.H.; *Organic Synthesis*; Wiley: New York, 1973, Collect. Vol. V, p.689.

complete, the solvent was removed *in vacuo* by azeotroping with toluene. The crude product was pure enough to continue to the next step.



(*S*)-(+)-(2-(Naphthalen-2-ylmethyl)-10,10-dimethyl-3,4-diazo-tricyclo[5.2.1.0^{1,5}]dec-4-en-2-one (329). To a flame dried 25 mL round bottom flask equipped with a Teflon-coated magnetic stir bar, a dean-stark apparatus and a condenser was added (*S*)-(+)-(*E*)-7,7-dimethyl-2-(2-(naphthalen-2-ylmethyl)hydrazono)bicyclo[2.2.1]heptane-1-carboxylic acid **328** (513.9 mg, 1.528 mmol) in 15 mL of mesitylene. The reaction was refluxed for 24 hours until complete by TLC. The pure product was obtained by flash column chromatography, eluting with 100 % hexanes to remove the mesitylene, followed by 30 % EtOAc in hexanes to afford the title compound as white crystals (282.6 mg, 39 % over two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.79 (m, 3H), 7.76 (s, 1H), 7.47 – 7.41 (m, 3H), 4.98 (d, *J* = 2.4 Hz, 2H), 2.55 (ddd, *J* = 3.2, 3.6, 17.2 Hz, 1H), 2.32 (dt, *J* = 4.4, 4.4, 12.0 Hz, 1H), 2.25 (t, *J* = 4.4 Hz, 1H), 2.18 – 2.05 (m, 2H), 1.69 (ddd, *J* = 4.4, 9.2, 13.6 Hz, 1H), 1.49 (ddd, *J* = 4.4, 9.6, 13.2 Hz, 1H), 1.24 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6 (C), 173.7 (C), 134.7 (C), 133.4 (C), 132.8 (C), 128.4 (CH), 127.9 (CH), 127.6 (CH), 126.9 (CH), 126.1 (CH), 125.9 (CH), 125.8 (CH), 63.8 (C), 49.9 (C), 49.3 (CH_2), 32.0 (CH), 27.0 (CH_3), 25.4 (CH_3), 19.2 (CH_2), 18.6 (CH_2); IR (neat)

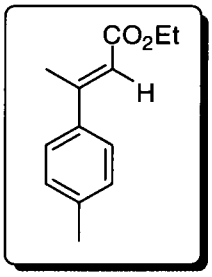
1694 cm^{-1}; MS 318.2 (M+); HRMS calcd for $C_{21}H_{22}N_2O$ (M+) 318.1732, found 318.1745.



(*S*)-(+)- (2-(Naphthalen-2-ylmethyl)-10,10-dimethyl-3,4-diazatricyclo[5.2.1.$0^{1,5}$]decan-2-one (144). To a flame dried 25 mL round bottom flask equipped with a Teflon-coated magnetic stir bar was added (*S*)-(+)-(2-(naphthalen-2-ylmethyl)-10,10-dimethyl-3,4-diazo-tricyclo[5.2.1.$0^{1,5}$]dec-4-en-2-one **329** (282.6 mg, 0.8875 mmol), 8 mL of methanol and 4 mL of glacial acetic acid. Sodium cyanoborohydride (557.7 mg, 8.875 mmol) was added in 4 portions over 1 h and the reaction was stirred overnight. Once complete by TLC, the reaction was quenched with 10 % HCl then extracted three times with dichloromethane. Solid NaOH pellets were was added to the combined aqueous phases and these were re-extracted three times with dichloromethane. The combined organic phases were then washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (30 % EtOAc in hexanes) to afford the title compound after purification by flash column chromatography (45 % EtOAc in petroleum ether) as white crystals (185.5 mg, 65 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.80 (m, 3H), 7.77 (s, 1H), 7.49 – 7.43 (m, 3H), 4.87 (d, J = 14.4 Hz, 1H), 4.67 (d, J = 14.4 Hz, 1H), 3.57 (dd, J = 4.8, 8.4 Hz, 1H), 2.22 (dt, J = 4.8, 4.8, 11.6, 1H), 2.05 – 2.00 (m, 1H), 1.97 – 1.87 (m, 2H), 1.66

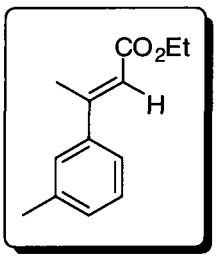
(dd, J = 8.4, 12.8 Hz, 1H), 1.35 (ddd, J = 2.4, 6.4, 8.8, 1H), 1.28 – 1.21 (m, 2H), 1.14 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (C), 133.4 (C), 133.3 (C), 132.9 (C), 128.7 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 126.3 (CH), 126.3 (CH), 126.1 (CH), 65.4 (CH_2), 58.5 (C), 51.3 (C), 48.3 (CH), 46.9 (CH_2), 36.2 (CH), 28.7 (CH_3), 26.7 (CH_3), 21.0 (CH_2), 20.4 (CH_2); IR (neat) 1671 cm^{-1}; MS 320.2 (M+); HRMS calcd for $C_{21}H_{24}N_2O$ (M+) 320.1889, found 320.1877.

5.1.3 Procedures for trisubstituted olefins experiments

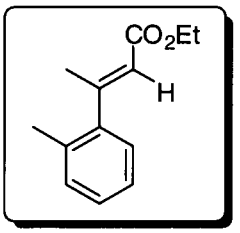


General Procedure for the preparation of trisubstituted alkenes. (*E*)-Ethyl-3-*p*-tolylbut-2-enoate (244) To a flame-dried 4 mL vial equipped with a teflon-coated stir bar were added $Pd(OAc)_2$ (4.80 mg, 0.007 mmol), $Et_3P{\cdot}HBF_4$ (4.10 mg, 0.020 mmol), 4-tolylboronic acid (29.9 mg, 0.220 mmol), Cs_2CO_3 (74.9 mg, 0.230 mmol) under a nitrogen atmosphere. Freshly distilled toluene was added (2.0 mL) followed by H_2O (20.0 μL, 1.10 mmol) and ethyl-2-butynoate (13.0 μL, 0.112 mmol). The solution was stirred for 18 h at room temperature, then diluted with Et_2O and extracted three times with H_2O. The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The pure product[62] (20.1 mg, 85%) was obtained as a clear oil by flash chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether): ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.48 – 7.45 (m, 2H), 7.24 – 7.22 (m, 2H), 6.12 (q, J =

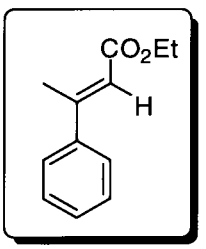
1.2 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 2.55 (d, J = 1.2 Hz, 3H), 2.35 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H).



. **(*E*)-Ethyl 3-*m*-tolylbut-2-enoate (282)** Prepared from ethyl-2-butynoate (13.0 μL, 0.112 mmol) and 3-tolylboronic acid (29.9 mg, 0.220 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colourless oil (17.2 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 3H), 7.19 – 7.16 (m, 1H), 6.13 (q, J = 1.2 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 2.57 (d, J = 1.2 Hz, 3H), 2.38 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9 (C), 155.7 (C), 142.2 (C), 138.1 (C), 129.7 (CH), 128.4 (CH), 127.0 (CH), 123.4 (CH), 116.9 (CH), 59.8 (CH_2), 21.4 (CH_3), 18.0 (CH_3), 14.3 (CH_3); IR (neat) 1712, 1631 cm^{-1}; MS 175.1 (M+ - CH_2CH_3); HRMS calcd for $C_{11}H_{11}O_2$ (M+ - CH_2CH_3) 175.0759, found 175.0754.

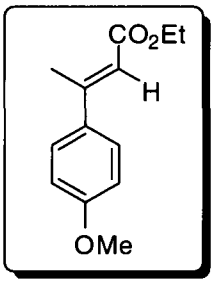


(*E*)-Ethyl 3-*o*-tolylbut-2-enoate (283) Prepared from ethyl-2-butynoate (13.0 μL, 0.112 mmol) and 2-tolylboronic acid (29.9 mg, 0.220 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colourless oil (18.3 mg, 80%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.13 (m, 3H), 7.06 – 7.04 (m, 1H), 5.74 (q, *J* = 1.6 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.43 (d, *J* = 1.6 Hz, 3H), 2.72 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6 (C), 158.2 (C), 143.9 (C), 133.9 (C), 130.4 (CH), 127.6 (CH), 127.1 (CH), 125.7 (CH), 119.4 (CH), 59.8 (CH_2), 20.8 (CH_3), 19.7 (CH_3), 14.3 (CH_3); IR (neat) 1715, 1635 cm^{-1}; MS 189.1 (M+ - CH_3); HRMS calcd for $C_{12}H_{13}O_2$ (M+ - CH_3) 189.0910, found 189.0902.

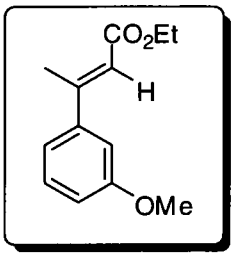


(*E*)-Ethyl-3-phenyl-2-enoate (242) Prepared from ethyl-2-butynoate (13.0 μL, 0.112 mmol) and phenylboronic acid (26.8 mg, 0.220 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound[62] after

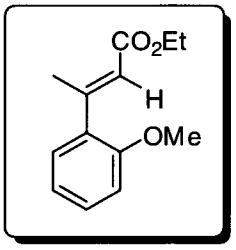
purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colourless oil (16.4 mg, 77%): ^1H NMR (400 MHz, Acetone-d_6) δ 7.58-7.55 (m, 2H), 7.42-7.40 (m, 3H), 6.13 (q, J = 1.3 Hz, 1H), 4.17 (q, J = 7.0 Hz, 2H), 2.56 (d, J = 1.4 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H).



(*E*)-Ethyl 3-(4-Methoxyphenyl)but-2-enoate (246) Prepared from ethyl-2-butynoate (13.0 μL, 0.112 mmol) and 4-methoxyphenylboronic acid (33.4 mg, 0.220 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound[62] after purification by flash column chromatography (2% Et_2O in petroleum ether followed by 5% Et_2O in petroleum ether) as a colourless oil (16.5 mg, 67%): ^1H NMR (400 MHz, Acetone-d_6) δ 7.57-7.53 (m, 2H), 6.98-6.96 (m, 2H), 6.11 (q, J = 1.2 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 2.55 (d, J = 1.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H).

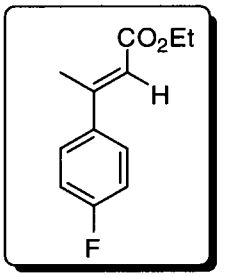


(*E*)-Ethyl 3-(3-Methoxyphenyl)but-2-enoate (284) Prepared from ethyl-2-butynoate (13.0 μL, 0.112 mmol) and 3-methoxyphenylboronic acid (33.4 mg, 0.220 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound[62] after purification by flash column chromatography (2% Et_2O in petroleum ether followed by 5% Et_2O in petroleum ether) as a colourless oil (16.5 mg, 67%): ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.33 (dd, J = 8.1, 0.3 Hz, 1H), 7.13 (ddd, J = 7.7, 1.7, 0.9 Hz, 1H), 7.09 (dd, J = 2.3, 0.3 Hz, 1H), 6.97 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 6.13 (q, J = 1.3 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 2.55 (d, J = 1.3 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H).

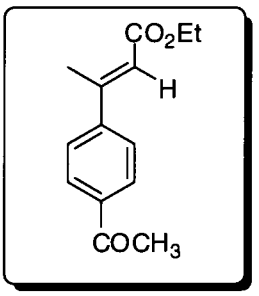


(*E*)-Ethyl 3-(2-Methoxyphenyl)but-2-enoate (285) Prepared from Ethyl-2-butynoate (13.0 μL, 0.112 mmol), 2-methoxyphenylboronic acid (33.4 mg, 0.220 mmol) and Me*t*Bu$_2$P·HBF$_4$ (5.00 mg, 0.020 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound[62] after purification by flash column chromatography (2% Et_2O in petroleum ether followed by 5% Et_2O in

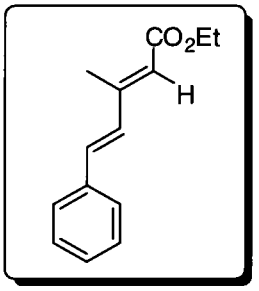
petroleum ether) as a colourless oil (14.3 mg, 58%): ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.35-7.31 (m, 1H), 6.97 (dd, J) 7.6, 1.6 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.97-6.93 (m, 1H), 5.82 (q, J =1.2 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 2.45 (d, J = 1.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H).



(*E*)-Ethyl 3-(4-fluorophenyl)but-2-enoate (286) Prepared from Ethyl-2-butynoate (13.0 μL, 0.112 mmol) and 4-Fluorophenylboronic acid (30.8 mg, 0.220 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound[62] after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colourless oil (13.5 mg, 58%): ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.66-7.63 (m, 2H), 7.21-7.16 (m, 2H), 6.12 (q, J = 1.2 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 2.56 (d, J = 1.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H).



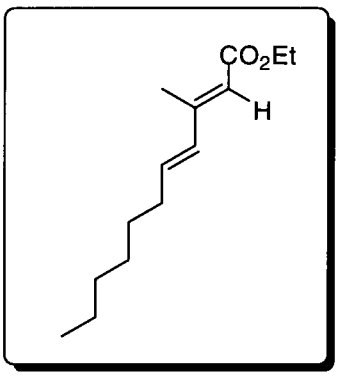
(*E*)-Ethyl 3-(4-acetylphenyl)but-2-enoate (287) Prepared from Ethyl-2-butynoate (13.0 μL, 0.112 mmol) and 4-acetylphenylboronic acid (30.8 mg, 0.220 mmol), and Me*t*Bu$_2$P·HBF$_4$ (5.00 mg, 0.020 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound[76] after purification by flash column chromatography (10% Et$_2$O in petroleum ether) as a colourless oil (12.7 mg, 49%): ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, *J* = 6.8 Hz, 2H), 7.70 (d, *J* = 6.4 Hz, 2H), 6.21 (q, *J* = 1.2 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.60 (s, 3H), 2.58 (d, *J* = 1.6 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H).



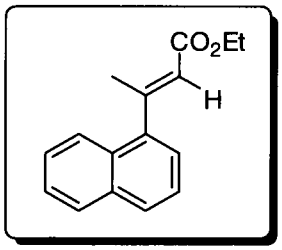
(2*E*,4*E*)-Ethyl 3-Methyl-5-phenylpenta-2,4-dienoate (288) Prepared from Ethyl-2-butynoate (13.0 μL, 0.112 mmol) and *trans*-Styrenylboronic acid (30.8 mg, 0.220 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound[62] after purification by flash column chromatography (100% petroleum ether followed by 5% Et$_2$O in petroleum ether) as a colourless oil (12.4 mg,

[76] Botella, L.; Najera, C.; *J. Org. Chem.* **2005**, *70*, 4360.

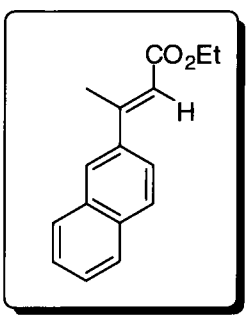
51%): ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.61-7.59 (m, 2H), 7.40-7.36 (m, 2H), 7.33-7.29 (m, 1H), 7.13-7.02 (m, 2H) 5.98 (s, 1H), 4.14 (q, J = 7.2 Hz, 2H), 2.40 (d, J = 1.3 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H).



(2*E*,4*E*)-Ethyl 3-methylundeca-2,4-dienoate (289) Prepared from Ethyl-2-butynoate (13.0 μL, 0.112 mmol) and 1-Octenylboronic acid (34.3 mg, 0.220 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colourless oil (21.1 mg, 86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (m, 2H), 5.69 (d, J = 1.2 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 2.26 (d, J = 1.2 Hz, 3H), 2.18 – 2.13 (m, 2H), 1.45 – 1.38 (m, 2H), 1.34 – 1.25 (m, 9H), 0.90 – 0.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (C), 152.7 (C), 137.5 (CH), 133.6 (CH), 117.5 (CH), 59.6 (CH_2), 33.0 (CH_2), 31.7 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 22.6 (CH_2), 14.3 (CH_3), 14.1 (CH_3), 13.8 (CH_3); IR (neat) 1713, 1637, 1613; MS 224.2 (M+); HRMS calcd for $C_{12}H_{19}O$ (M+ - C_2H_5O) 179.1436, found 179.1438

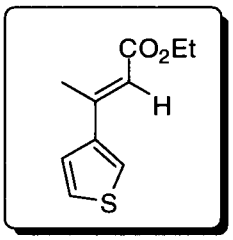


(*E*)-Ethyl 3-(naphthalen-1-yl)but-2-enoate (248) Prepared from Ethyl-2-butynoate (13.0 μL, 0.112 mmol) and Naphthylen-1-ylboronic acid (37.8 mg, 0.220 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound[62] after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colourless oil (20.7 mg, 77%): ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.95-7.87 (m, 3H), 7.56-7.47 (m, 3H), 7.34 (dd, J = 7.0, 1.1 Hz, 1H), 5.90 (q, J = 1.4 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.58 (d, J = 1.4 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H).

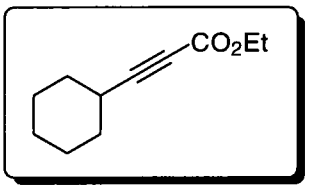


(*E*)-Ethyl 3-(naphthalen-2-yl)but-2-enoate (290) Prepared from Ethyl-2-butynoate (13.0 μL, 0.112 mmol) and Naphthylen-2-ylboronic acid (37.8 mg, 0.220

mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound[62] after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colourless oil (21.0 mg, 78%): ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.13 (d, J = 1.6 Hz, 1H), 8.00-7.91 (m, 3H), 7.72 (dd, J = 8.7, 2.0 Hz, 1H), 7.57-7.53 (m, 2H), 6.31 (dd, J = 2.6, 1.3 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.68 (d, J = 1.3 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H).

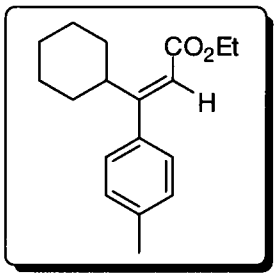


(*E*)-Ethyl 3-(thiophen-3-yl)but-2-enoate (291) Prepared from Ethyl-2-butynoate (13.0 μL, 0.112 mmol) and 3-Thiofuranylboronic acid (28.2 mg, 0.220 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colourless oil (12.3 mg, 56%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.48 (m, 1H), 7.32 – 7.31 (m, 2H), 6.23 (q, J = 1.6 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 2.57 (d, J = 1.6 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1 (C), 148.9 (C), 143.4 (C), 126.1 (CH), 125.2 (CH), 124.1 (CH), 115.3 (CH), 59.8 (CH_2), 17.2 (CH_3), 14.3 (CH_3); IR (neat) 1709, 1621 cm^{-1}; MS 196.1 (M+); HRMS calcd for $C_{10}H_{12}O_2S$ (M+) 196.0558, found 196.0558.

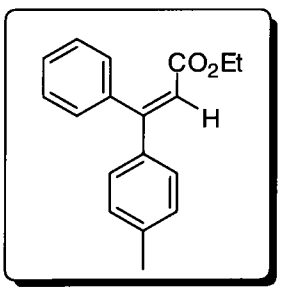


Ethyl 3-cyclohexylpropiolate (292) To an oven-dried 250 mL round bottom flask equipped with a Teflon coated stir bar was added commercially available Ethynylcyclohexane (0.90 mL, 6.9 mmol) in 65 mL freshly distilled THF. The solution was cooled to -78 °C and Butyl lithium (3.1 mL, 2.5 M) was added dropwise by syringe pump over 30 minutes, after which the solution was stirred at -78 °C for one hour. Ethyl chloroformate (1.33 mL, 13.5 mmol) in 5 mL THF was then added by syringe pump over 10 minutes. The reaction was warmed to room temperature and stirred for 3 hours, until complete by TLC. The reaction was quenched with the dropwise addition of 50 mL of 10 % HCl solution and was then extracted three times with EtOAc. The combined organic extracts were washed with $NaHCO_3$ and brine and dried over $MgSO_4$. The crude oil was purified by flash chromatograph (1 % Et_2O in hexanes, followed by 2 % Et_2O in hexanes, followed by 4 % Et_2O in hexanes) to afford the title compound[77] as a clear oil (967.2 mg, 76 %): ^1H NMR (300 MHz, $CDCl_3$) δ 4.23 (q, J = 7.2 Hz, 2H), 2.53 (m, 1H), 1.82-1.90 (m, 2H), 1.69 – 1.78 (m, 2H), 1.48 – 1.59 (m, 3H), 1.32 – 1.38 (m, 3H), 1.33 (t, J = 7.2 Hz, 3H).

[77] Liu,P.; Jordan, R.W.; Kibbee, S.P.; Goddard, J.D.; Tam, W.; *J. Org. Chem.* **2006,** *71,* 3793.

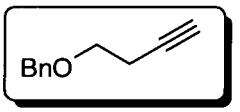


(*E*)-Ethyl 3-cyclohexyl-3-*p*-tolylacrylate (293) Prepared from Ethyl 3-cyclohexylpropiolate **292** (40.2 mg, 0.223 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colourless oil (46.7 mg, 77%): ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.19 – 7.17 (m, 2H), 7.12 – 7.10 (m, 2H), 5.60 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.81 – 3.74 (m, 1H), 2.33 (s, 3H), 1.75 – 1.62 (m, 5H), 1.41 – 1.23 (m, 8H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 168.3 (C), 167.3 (C), 140.3 (C), 139.0 (C), 130.3 (CH), 129.3 (CH), 120.1 (CH), 61.2 (CH_2), 42.3 (CH), 33.3 (CH_2), 28.2 (CH_2), 27.6 (CH_2), 22.1 (CH_3), 15.6 (CH_3); IR (neat) 1715, 1625 cm^{-1}; MS 272.2 (M+); HRMS calcd for $C_{17}H_{21}O_2$ (M+ - CH_3) 257.1542, found 257.1535.



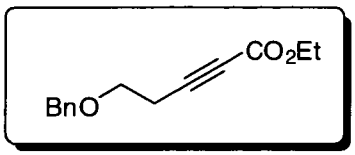
(*E*)-Ethyl 3-phenyl-3-*p*-tolylacrylate (294) Prepared from Ethyl 3-phenylpropiolate (38.8 mg, 0.223 mmol) using a procedure similar to that described for

(*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound[78] after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colourless oil (39.2 mg, 66%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.38 (m, 3H), 7.23 – 7.20 (m, 4H), 7.15 – 7.13 (m, 2H), 6.36 (s, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H).



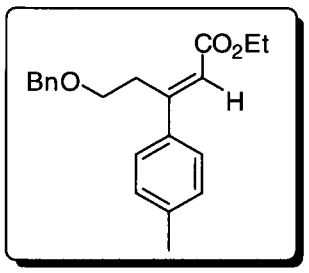
((But-3-ynyloxy)methyl)benzene (329) To an oven-dried 250 mL round bottom flask equipped with a Teflon coated stir bar was added 95 % Sodium hydride (505.3 mg, 21.05 mmol) and But-3-yn-1-ol (1.000 mL, 13.21 mmol) in 120 mL THF. After stirring the solution for 30 minutes, Benzyl bromide (2.400 mL, 20.07 mmol) was added and the reaction was stirred for 3 hours. Upon completion by TLC, 50 mL of H_2O was added to quench the excess Sodium hydride and the solution was extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$ then filtered and concentrated *in vacuo*. The crude oil was purified by flash chromatography (petroleum ether) to afford the title compound[79] as a clear oil (1460.0 mg, 69 %): ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.41 (m, 5H), 4.57 (s, 2H), 3.61 (t, *J* = 6.8 Hz, 2H), 2.51 (dt, *J* = 2.8 Hz, 6.8 Hz, 2H), 2.00 (t, *J* = 2.8 Hz, 1H).

[78] Calò, V.; Nacci, A.; Monopoli, A.; Lopez, L.; di Cosmo, A.; *Tetrahedron* **2001**, 57, 6071.
[79] Qin, D.-G.; Zha, H.-Y.; Yao, Z.-J.; *J. Org. Chem.* **2002**, *67*, 1038.

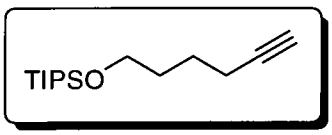


Ethyl 5-(benzyloxy)pent-2-ynoate (277) To an oven-dried 250 mL round bottom flask equipped with a Teflon-coated stir bar was added 50 mL of freshly-distilled THF and ((But-3-ynyloxy)methyl)benzene **329** (1460.0 mg, 9.119 mmol). The resulting solution was cooled to -78 °C and Butyl lithium (4.400 mL, 2.5 M) was added by syringe pump over 30 minutes. After all the Butyl lithium had been added, Ethyl chloroformate (1.330 mL, 13.48 mmol) in 25 mL THF was added by syringe pump over 30 minutes. After the addition of the Ethyl chloroformate was complete, the reaction was stirred for 2 h until complete disappearance of the alkyne was observed. Upon completion of the reaction, 50 mL of H_2O was added and the reaction was stirred for 15 minutes, after which the solution was poured into a separatory funnel and extract three times with ether. The combined organic layers were then dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The crude oil was purified by flash chromatography (10 % ether in petroleum ether) to afford the title compound[80] as a clear oil (1840.0 mg, 87 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.36 (m, 5H), 4.56 (s, 2H), 4.22 (q, J = 7.2 Hz, 2H), 3.64 (t, J = 6.8 Hz, 2H), 2.64 (t, J = 6.8 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H).

[80] Yadav, J.S.; Srihari, P.; *Tet. Asym.* **2004**, *15*, 81.

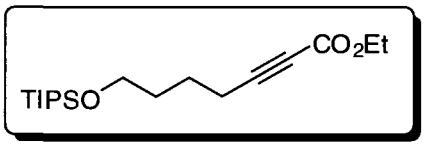


(*E*)-Ethyl 5-(benzyloxy)-3-*p*-tolylpent-2-enoate (278) Prepared from Ethyl 5-(benzyloxy)pent-2-ynoate **277** (26.4 mg, 0.112 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colourless oil (26.2 mg, 71%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.35 – 7.25 (m, 5H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.12 (s, 1H), 4.49 (s, 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.64 (t, *J* = 7.0 Hz, 2H), 3.45 (t, *J* = 7.0 Hz, 2H), 2.37 (s, 3H), 1.31 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (C), 156.8 (C), 139.1 (C), 138.5 (C), 138.2 (C), 129.2 (CH), 128.2 (CH), 127.5 (CH), 127.3 (CH), 126.7 (CH), 117.9 (CH), 72.6 (CH_2), 69.3 (CH_2), 59.9 (CH_2), 31.6 (CH_2), 21.2 (CH_3), 14.3 (CH_3); IR (neat) 1704, 1618 cm^{-1}; MS 279.1 (M+ - C_2H_5O); HRMS calcd for $C_{19}H_{19}O$ (M+ - C_2H_5O) 279.1385, found 279.1389.



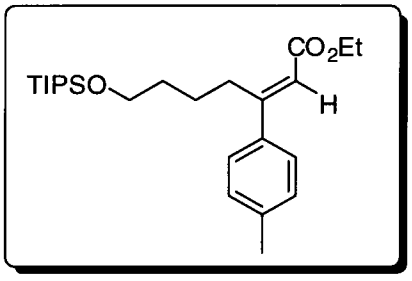
(Hex-5-ynyloxy)triisopropylsilane (330) To an oven-dried 100 mL round bottom flask equipped with a Teflon coated stir bar was added Hex-5-yn-1-ol (2.00 mL, 18.1

mmol) in 20 mL DMF followed by Imidazole (2.47 g, 36.3 mmol). After stirring the solution for two hours, Triisopropylsilyl chloride (5.80 mL, 27.2 mmol) was added and the reaction was stirred over night. Upon completion by TLC, the reaction was extracted three times with EtOAc. The combined organic extracts were washed with brine then dried over $MgSO_4$ and concentrated *in vacuo*. The crude oil was purified by flash chromatography (hexanes) to afford the title compound as a clear oil (4.62 g, 100 %): ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (t, J = 6.0 Hz, 2H), 2.20 – 2.25 (m, 2H), 1.93 – 1.95 (m, 1H), 1.63 – 1.65 (m, 4H), 1.01 – 1.15 (m, 24H).



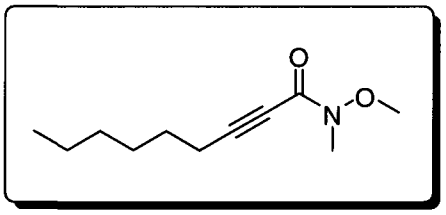
Ethyl 7-(triisopropylsilyloxy)hept-2-ynoate (298) To an oven-dried 250 mL round bottom flask equipped with a Teflon-coated stir bar was added 50 mL of freshly-distilled THF and (Hex-5-ynyloxy)triisopropylsilane **330** (4.91 g, 19.3 mmol). The resulting solution was cooled to -78 °C and Butyl lithium (9.20 mL, 2.50 M) was added by syringe pump over 10 minutes. After all the Butyl lithium had been added, Ethyl chloroformate (3.70 mL, 37.5 mmol) in 15 mL THF was added by syringe pump over 45 minutes. After complete addition of Ethyl chloroformate, the reaction was warmed to room temperature and stirred overnight. The reaction was quenched with 50 mL saturated NH_4Cl solution. The reaction was extracted three times with EtOAc and the combined organic layers were then dried over $MgSO_4$ and concentrated *in vacuo*. The crude oil was purified by flash chromatography (1 % ether in petroleum ether) to afford

the title compound as a clear oil (4.53 g, 72 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (q, *J* = 6.9 Hz, 2H), 3.71 (t, *J* = 6.0 Hz, 2H), 2.78 (t, *J* = 6.9 Hz, 2H), 1.62 – 1.73 (m, 4H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.02 – 1.11 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9 (C), 89.3 (C), 73.3 (C), 62.6 (CH_2), 61.7 (CH_2), 31.9 (CH_2), 24.2 (CH_2), 18.5 (CH_2), 18.0 (CH_3), 14.0 (CH), 11.9 (CH_3); IR (neat) 2239, 1714 cm^{-1}; MS 283.2 (M+ - C_3H_7); HRMS calcd for $C_{15}H_{27}O_3Si$ (M+ - C_3H_7) 283.1729, found 283.1739.



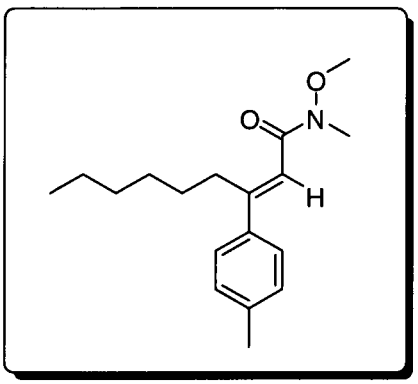
(*E*)-Ethyl 3-*p*-tolyl-5-(triisopropylsilyloxy)pent-2-enoate (299) Prepared from Ethyl 7-(triisopropylsilyloxy)pent-2-ynoate **298** (72.3 mg, 0.221 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colourless oil (62.9 mg, 68%): ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.03 (s, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.70 (t, *J* = 6.0 Hz, 2H), 3.18 (t, *J* = 7.6 Hz, 2H), 2.35 (s, 3H), 1.62 – 1.51 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.08 – 1.02 (m, 21H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 167.7 (C), 162.1 (C), 140.8 (C), 140.0 (C), 131.1 (CH), 128.4 (CH), 118.2 (CH), 64.7 (CH_2), 61.1 (CH_2), 34.6 (CH_2), 31.6 (CH_2), 27.1 (CH_2), 22.2 (CH_3), 19.4

(CH_3), 15.7 (CH_3), 13.7 (CH_3); IR (neat) 1714, 1622 cm^{-1}; MS 375.2 (M+ - C_3H_7); HRMS calcd for $C_{22}H_{35}O_3Si$ (M+ - C_3H_7) 375.2355, found 375.2346.

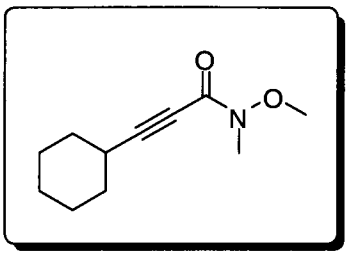


***N*-Methoxy-*N*-methylnon-2-ynamide (300)** To an oven-dried 250 mL round bottom flask equipped with a Teflon coated stir bar was added 1-Octyne (3.20 mL, 22.1 mmol) in 115 mL freshly distilled THF. The solution was cooled to -78 °C and Butyl lithium (9.70 mL, 2.5 M) was added via syringe pump over 30 minutes. After complete addition of the butyl lithium, Methoxy(methyl)carbamic chloride[81] (3.00 g, 24.3 mmol) was added by canula, rinsing the flask once with 10 mL THF, and the reaction was stirred for 60 minutes at -78 °C. After warming the reaction to room temperature and stirring overnight, the reaction was quenched with 50 mL 10 % HCl solution then extracted three times with EtOAc. The combined organic extracts were then washed with saturated $NaHCO_3$ followed by brine and then dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (5 % Et_2O in hexanes followed by 20 % Et_2O in hexanes) to afford the title compound[61] as a clear oil (3.01 g, 69 %): ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.23 (br s, 3H), 2.38 (t, J = 7.2 Hz, 2H), 1.52 – 1.64 (m, 2H), 1.36 – 1.47 (m, 2H), 1.27 – 1.32 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H).

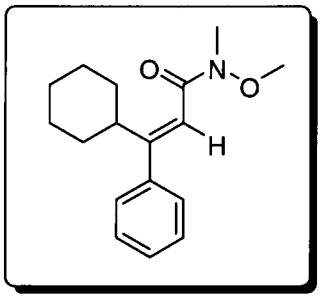
[81] Smith, A.B.; Beiger, J.J.; Davulcu, A.H.; Cox, J.M.; Lautens, M.; Taillier, C.; *Org. Syn.* **2005**, *82*, 147.



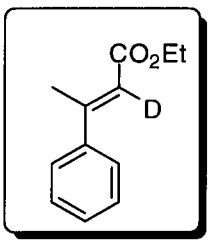
(*E*)-*N*-Methoxy-*N*-methyl-3-p-tolylnon-2-enamide (301) Prepared from *N*-Methoxy-*N*-methylnon-2-ynamide **300** (20.6 mg, 0.104 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound after purification by flash column chromatography (3% EtOAc in petroleum ether followed by 5% EtOAc in petroleum ether) as a colourless oil (18.0 mg, 60%): ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.40 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.49 (s, 1H), 3.72 (s, 3H), 3.18 (s, 3H), 3.06 (t, J = 7.2 Hz, 2H), 2.34 (s, 3H), 1.42 – 1.23 (m, 8H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 169.2 (C), 158.2 (C), 141.0 (C), 140.1 (C), 131.0 (CH), 128.4 (CH), 117.6 (CH), 62.8 (CH_2), 33.3 (CH_2), 32.0 (CH_2), 31.0 (CH_2), 30.7 (CH_2), 24.2 (CH_2), 22.1 (CH_3), 15.3 (CH_3); IR (neat) 1649; MS 229.2 (M+ - C_2H_6NO); HRMS calcd for $C_{16}H_{21}O$ (M+ - C_2H_6NO) 229.1587, found 229.1586.



3-Cyclohexyl-*N*-methoxy-*N*-methylpropiolamide (302). To an oven-dried 250 mL round bottom flask equipped with a Teflon coated stir bar was added Ethynylcyclohexane (0.35 mL, 2.7 mmol) in 25 mL freshly distilled THF. The solution was cooled to -78 °C and Butyl lithium (1.2 mL, 2.5 M) was added via syringe pump over 30 minutes. Upon stirring for 30 minutes, Methoxy(methyl)carbamic chloride (0.52 mL, 5.4 mmol) was added by canula, rinsing the flash once with 10 mL THF, and the reaction was stirred for 60 minutes at -78 °C. After warming the reaction to room temperature and stirring overnight, the reaction was quenched with 50 mL 10 % HCl solution then extracted three times with EtOAc. The combined organic extracts were then washed with saturated $NaHCO_3$ followed by brine and then dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatograph (1 % Et_2O in hexanes followed by 4 % Et_2O in hexanes) to afford the title compound as a clear oil (0.46 g, 94 %). ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.24 (s, 3H), 2.54 – 2.59 (m, 1H), 1.81 – 1.85 (m, 2H), 1.67 – 1.74 (m, 2H), 1.48 – 1.56 (m, 3H), 1.30 – 1.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 97.1 (C), 77.2 (CH_3), 73.1 (C), 61.8 (CH_3), 31.5 (CH_2), 29.0 (CH), 25.6 (CH_2), 24.5 (CH_2); IR (neat) 2932.8, 2855.6, 2231.6, 1643.4, 1380.3 968.1, 723.2 cm^{-1}; MS 195.1 (M+); HRMS calcd for $C_{11}H_{17}NO_2$ (M+) 195.1259, found 195.1259.

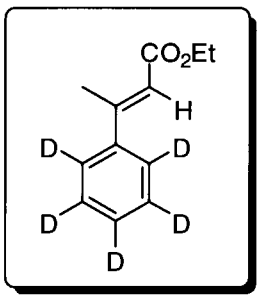


(*E*)-3-Cyclohexyl-*N*-methoxy-*N*-methyl-3-phenylacrylamide (303) Prepared from 3-Cyclohexyl-*N*-methoxy-*N*-methylpropiolamide **302** (22.5 mg, 0.115 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound as a colourless oil (17.2 mg, 55%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.35 (m, 3H), 7.18 – 7.21 (m, 2H), 6.07 (s, 1H), 3.67 (s, 3H), 3.25 (s, 3H), 1.61 – 1.77 (m, 5H), 1.33 – 1.43 (m, 2H), 1.19 – 1.29 (m, 3H), 1.02 – 1.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1 (C), 127.8 (CH), 127.6 (CH), 127.1 (CH), 117.4 (CH), 61.4 (CH_3), 40.8 (CH_3), 32.6 (CH_2), 31.7 (CH_2), 26.4 (CH_2), 26.0 (CH_2);); IR (neat) 1645 cm^{-1}; MS 273.2 (M+); HRMS calcd for $C_{15}H_{17}O$ (M+ - C_2H_6NO) 213.1279, found 213.1285.



(*E*)-Ethyl-3-phenyl-2-deuterobut-2-enoate (311) Prepared from Ethyl-2-butynoate (13.0 μL, 0.112 mmol) and Phenylboronic acid (26.8 mg, 0.22 mmol) and D_2O (20.0 mL, 1.10 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-

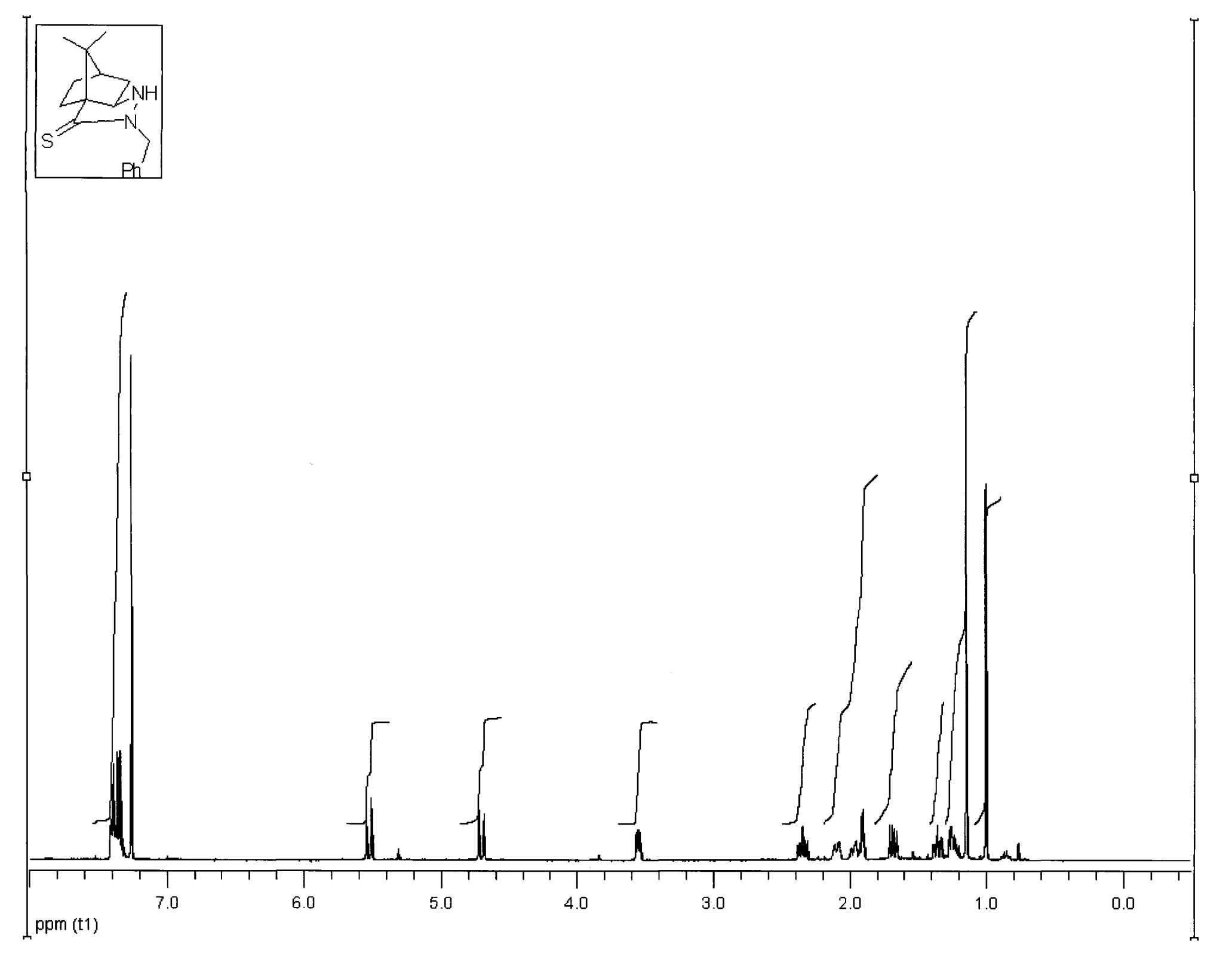
tolylbut-2-enoate that provided the title compound[62] after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colourless oil (16.4 mg, 77%): ^1H NMR (400 MHz, Acetone-d_6) δ 7.58 – 7.55 (m, 2H), 7.42 – 7.40 (m, 3H), 6.13 (q, J = 1.3 Hz, 0.3H), 4.17 (q, J = 7.0 Hz, 2H), 2.56 (d, J = 1.4 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H).



(*E*)-Ethyl-3-(pentadeuterophenyl)but-2-enoate (312) Prepared from Ethyl-2-butynoate (13.0 μL, 0.112 mmol) and Pentadeuterophenylboronic acid (27.9 mg, 0.22 mmol) using a procedure similar to that described for (*E*)-Ethyl-3-*p*-tolylbut-2-enoate that provided the title compound[62] after purification by flash column chromatography (100% petroleum ether followed by 5% Et_2O in petroleum ether) as a colourless oil (17.1 mg, 78%): ^1H NMR (400 MHz, Acetone-d_6) δ 6.14 (q, J = 1.4 Hz, 1H), 4.17 (q, J = 7.0 Hz, 2H), 2.56 (d, J = 1.4 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H).

Appendix

NMR Spectra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N
S
Ph
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6.0
5.0
4.0
3.0
2.0
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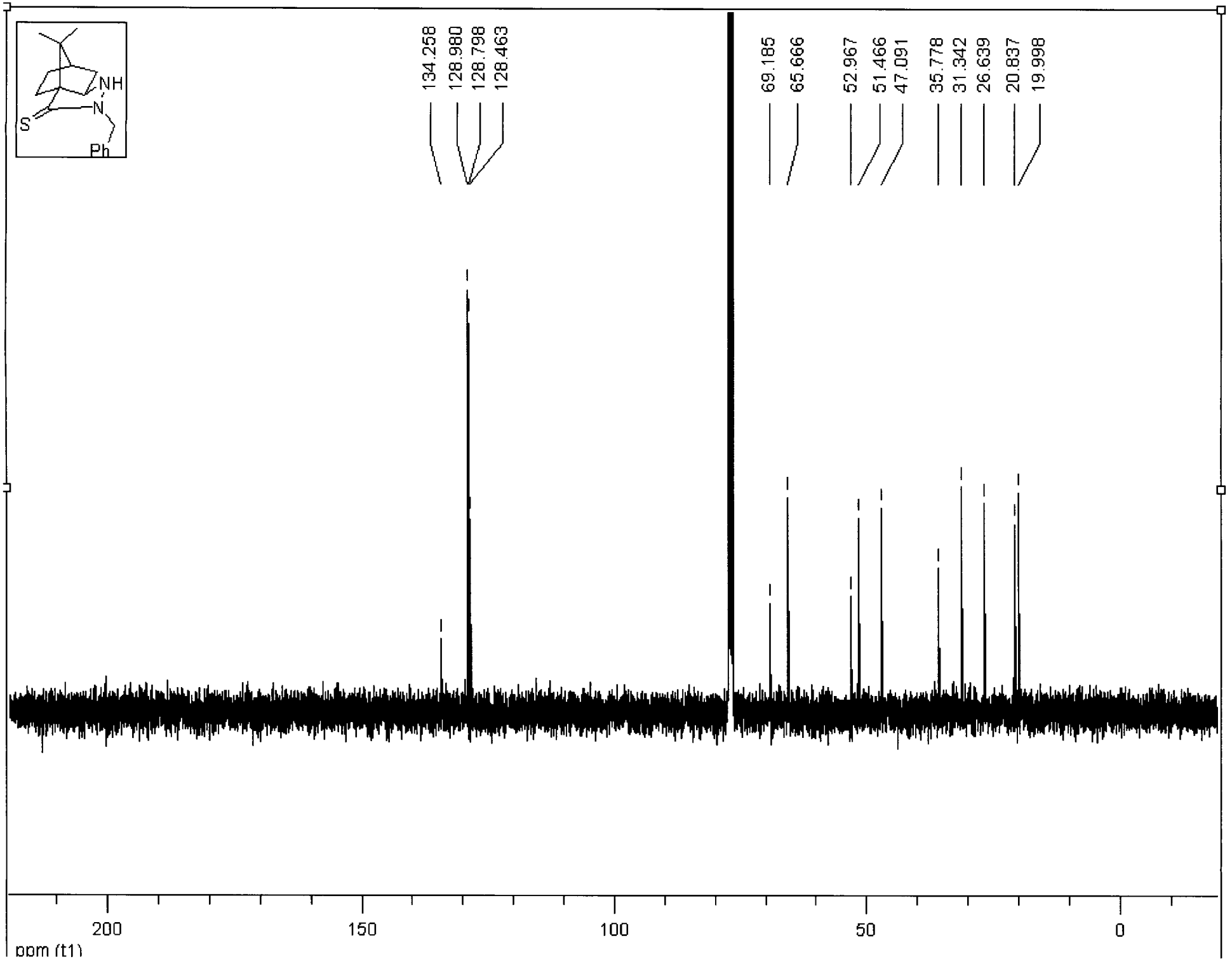
0.0
ppm (t1)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150
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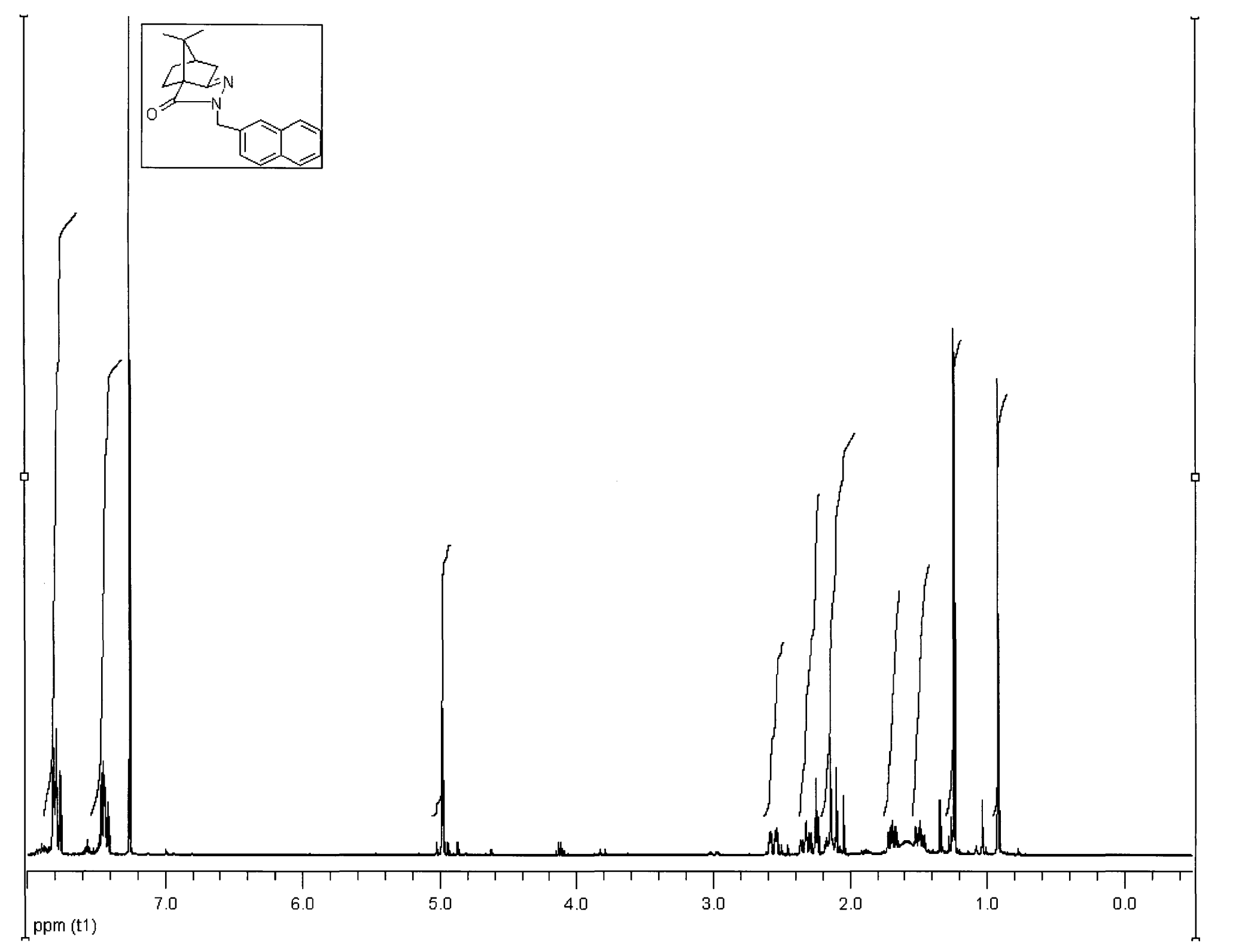
50
0
ppm (t1)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O
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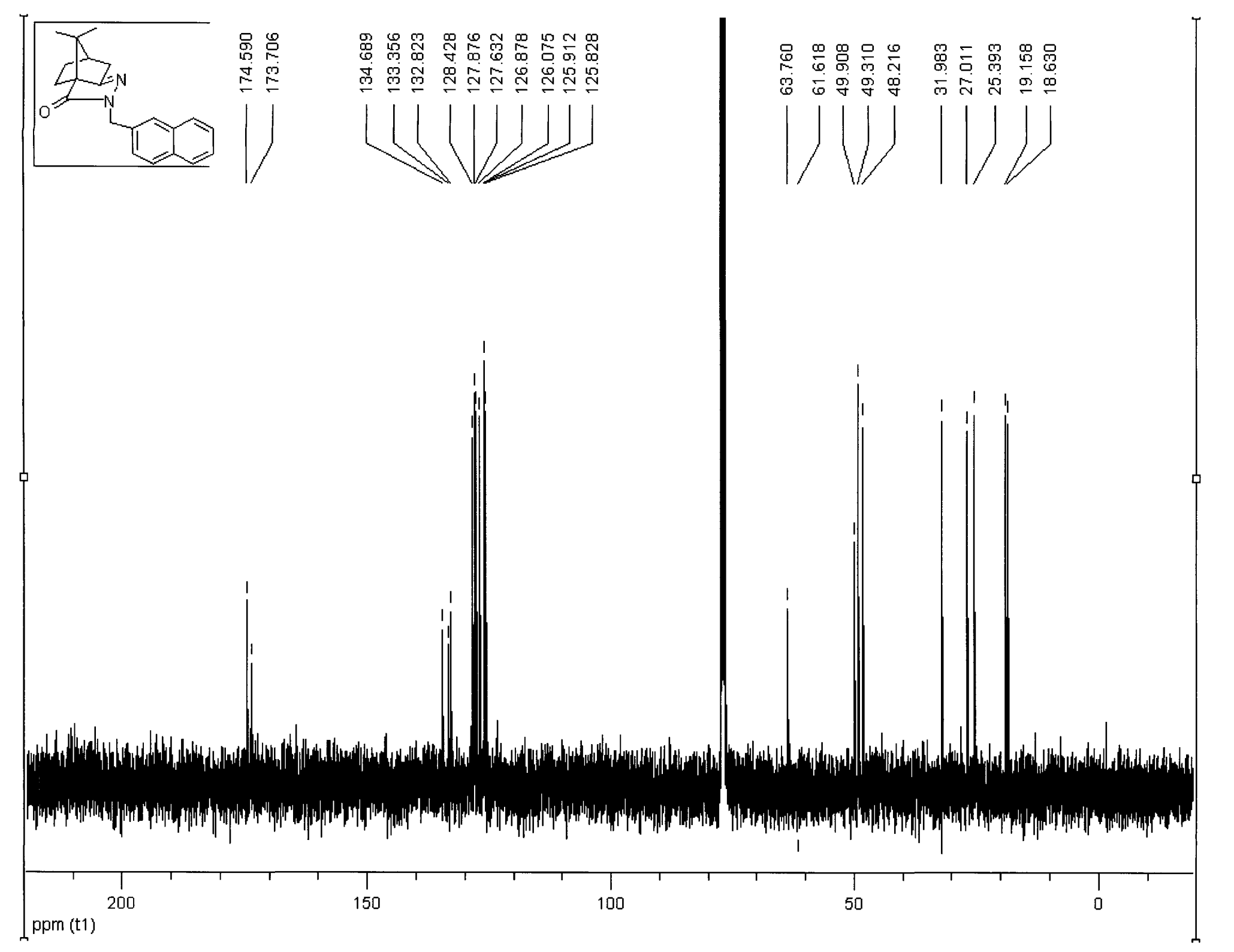
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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173.706
134.689
133.356
132.823
128.428
127.876
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61.618
49.908
49.310
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O
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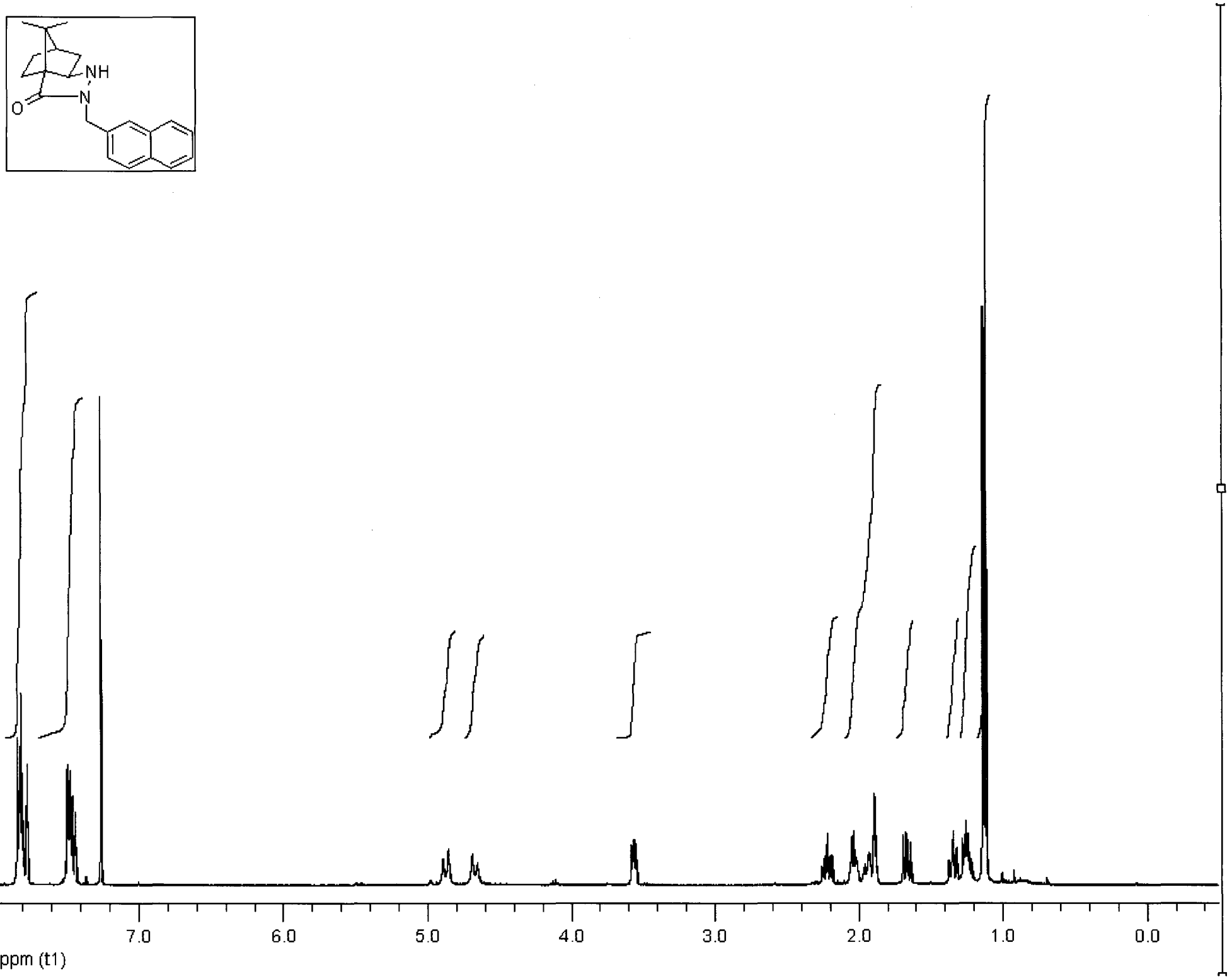
N
200
150
100
50
0
ppm (t1)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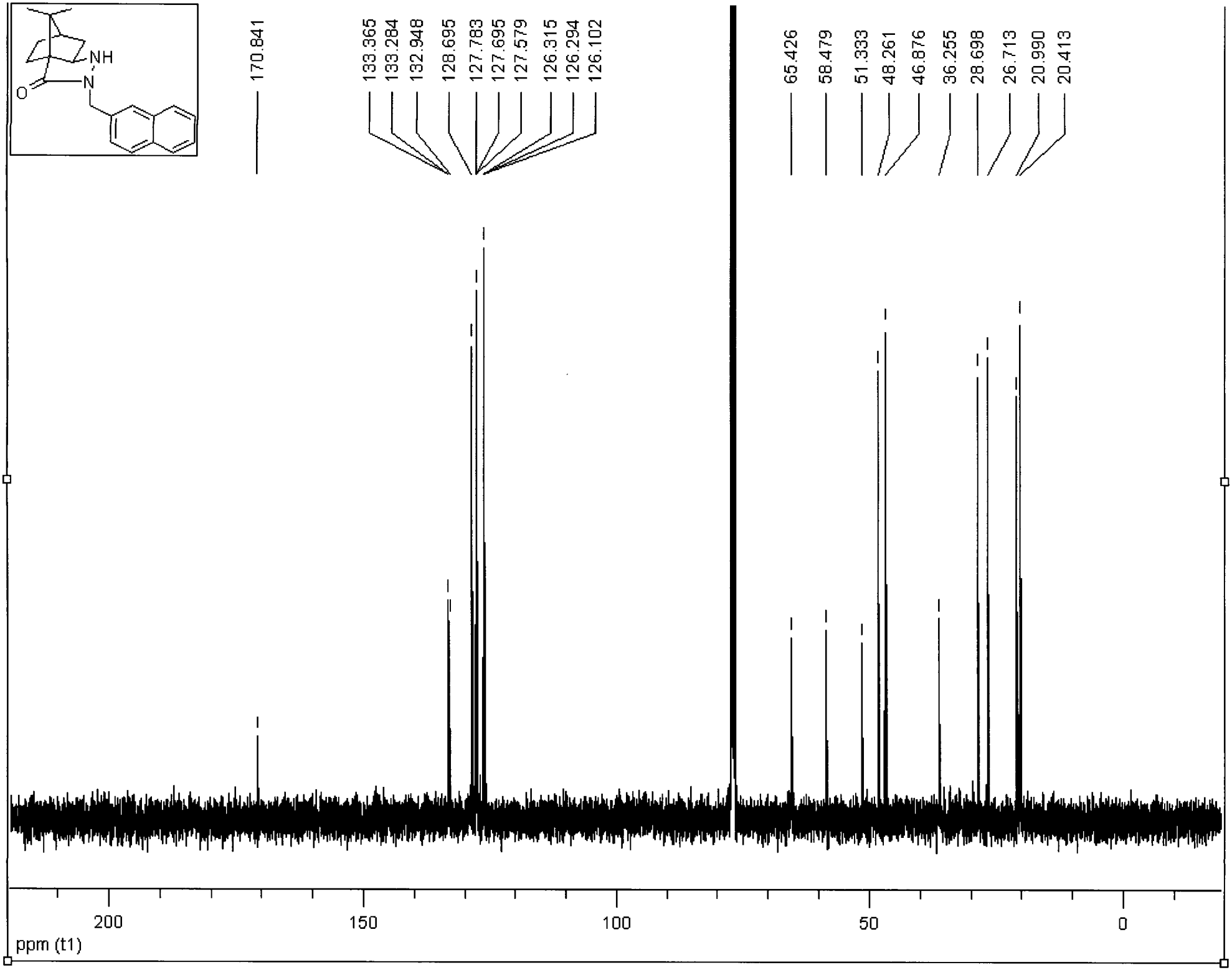
ppm (t1)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O
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133.284
132.948
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127.695
127.579
126.315
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65.426
58.479
51.333
48.261
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36.255
28.698
26.713
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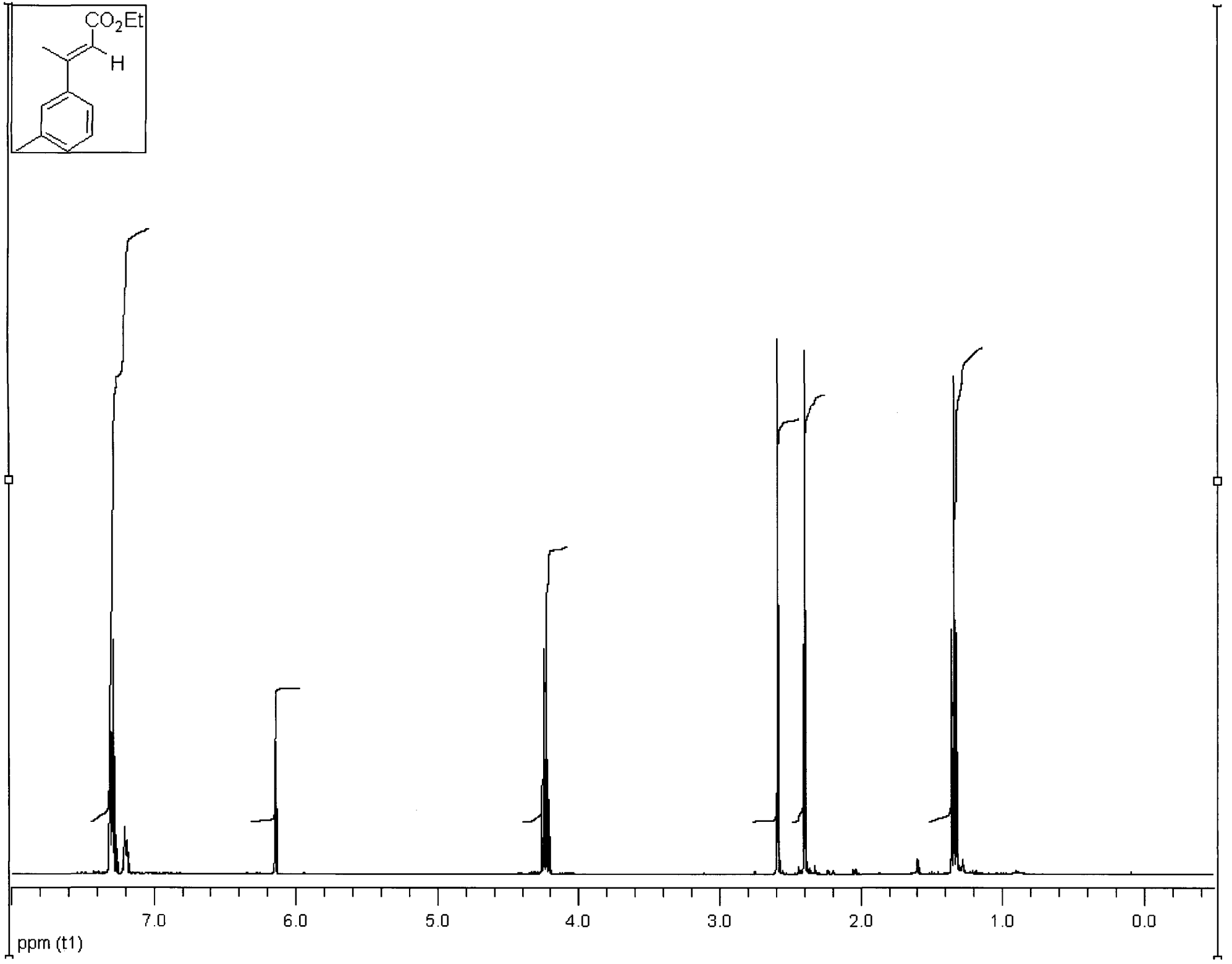
200
150
100
50
0
ppm (t1)


CO2Et
H
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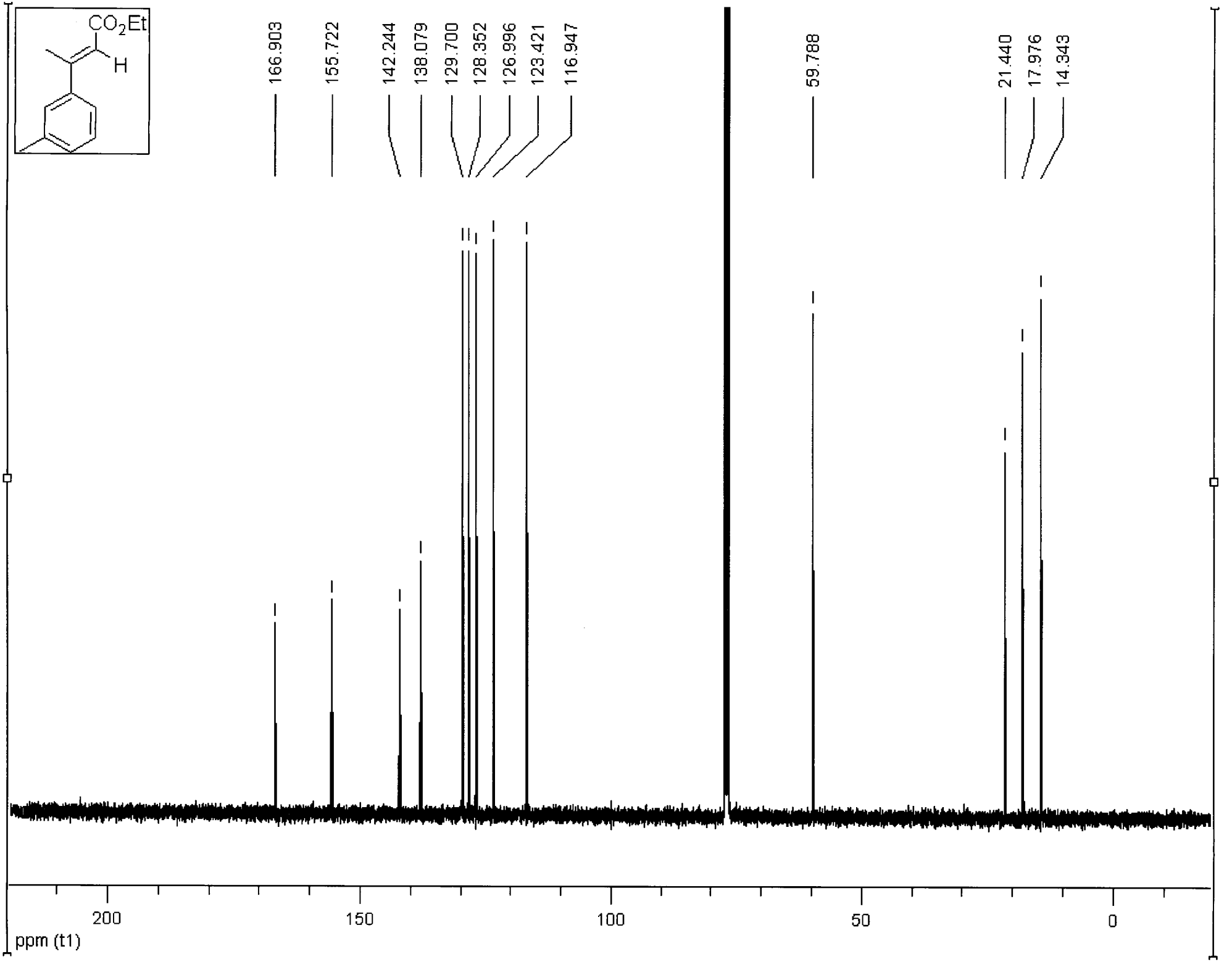
1.0
0.0
ppm (t1)


CO2Et
H
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138.079
129.700
128.352
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123.421
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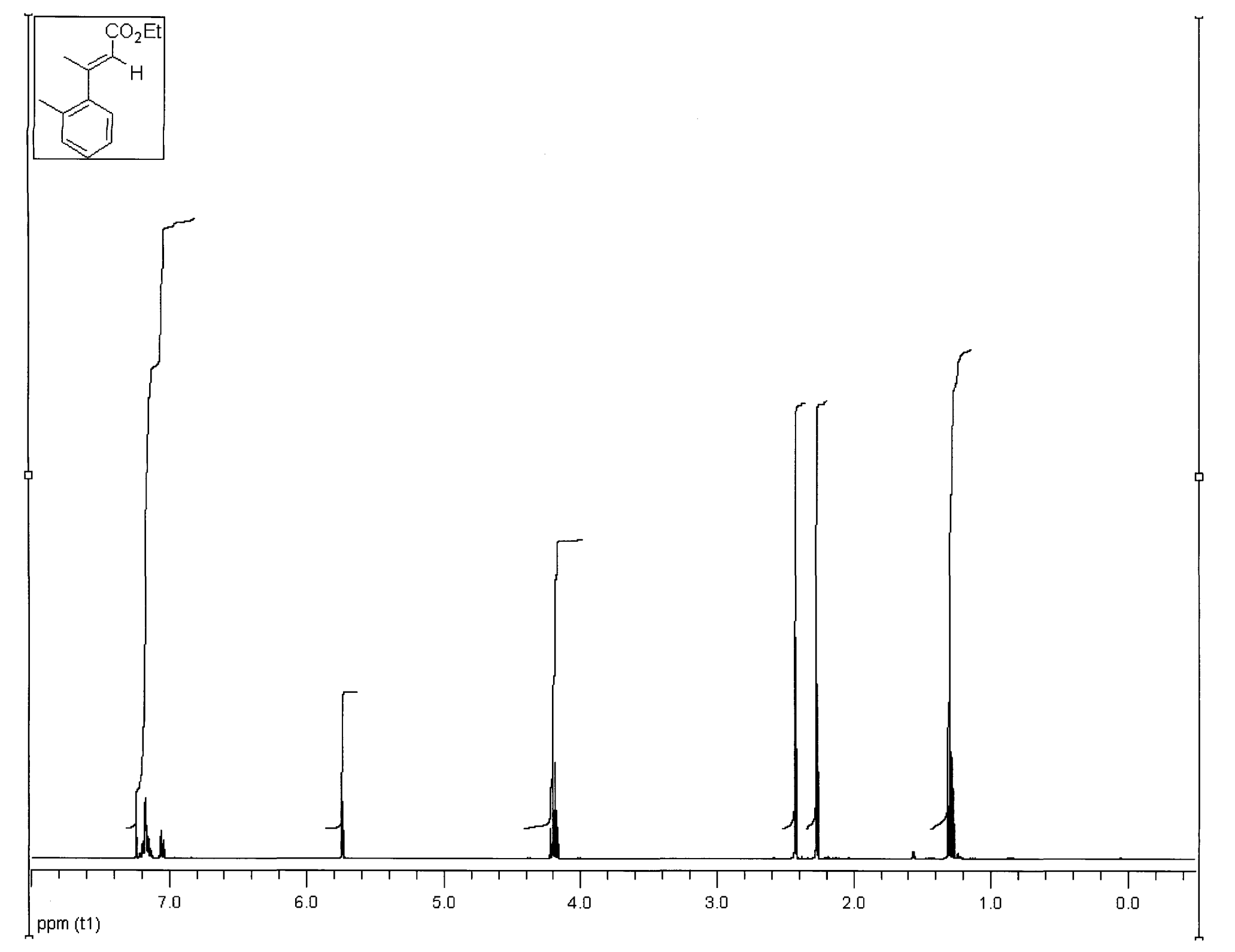
200
150
100
50
0
ppm (t1)


CO2Et
H
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5.0
4.0
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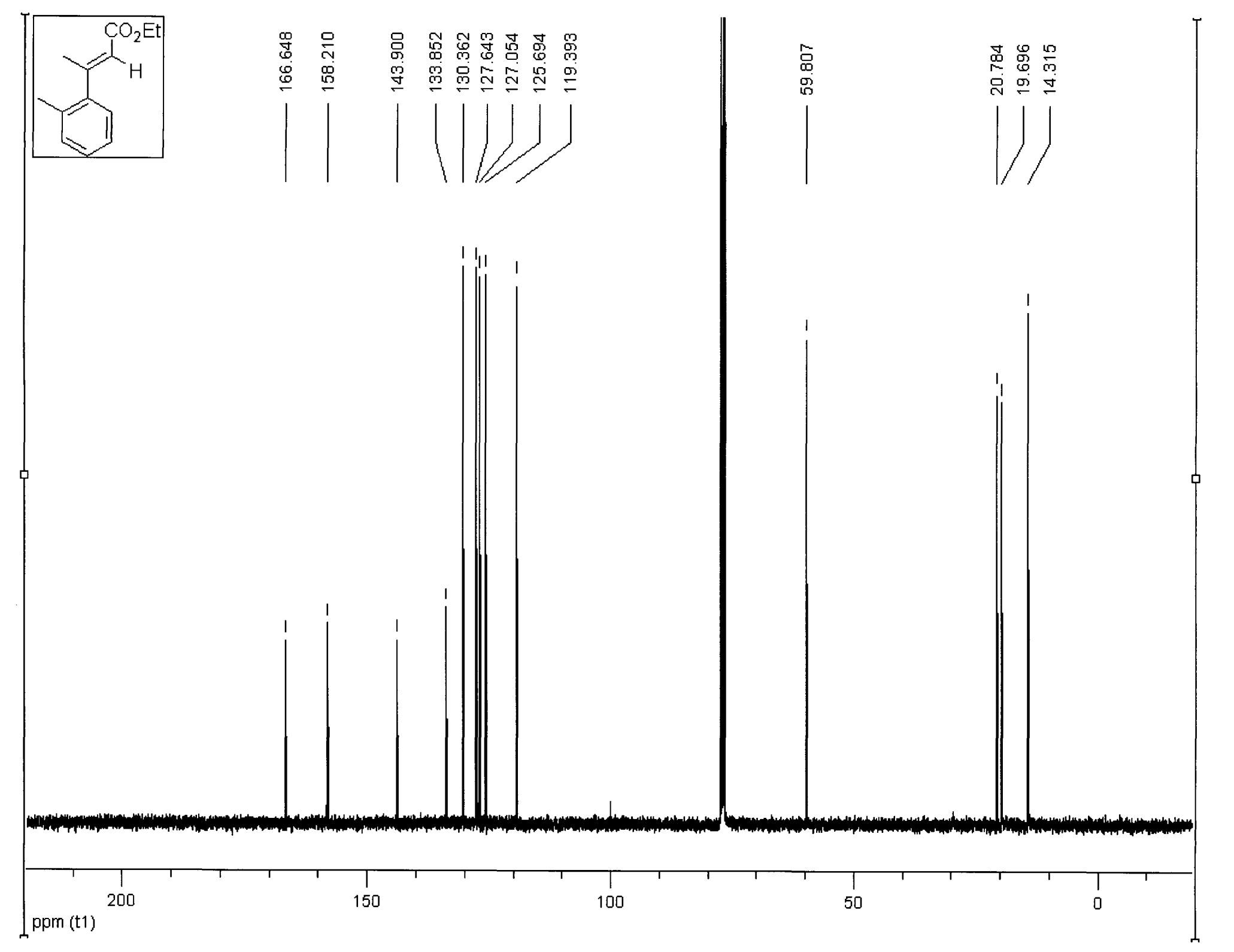
CO2Et
H
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127.054
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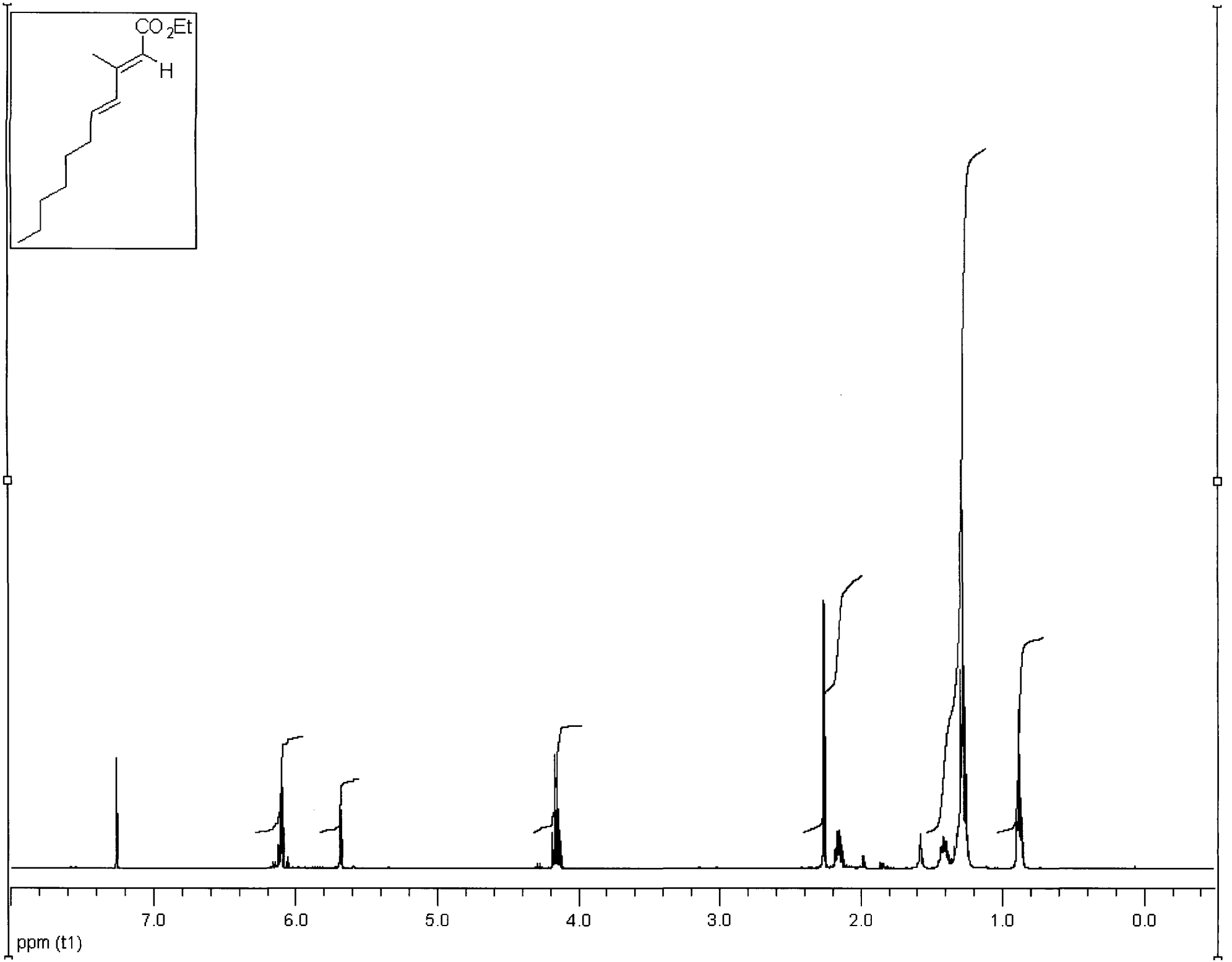
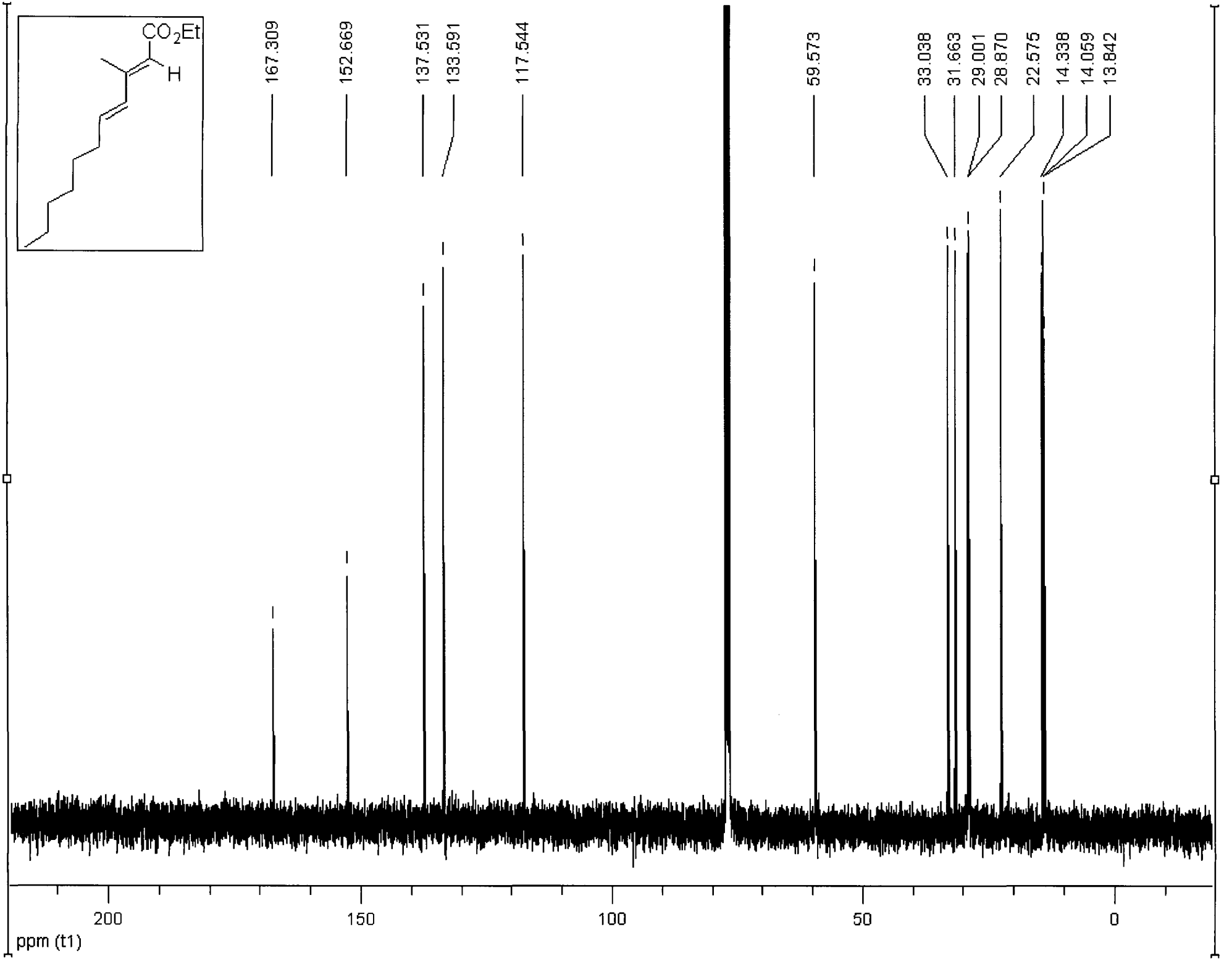
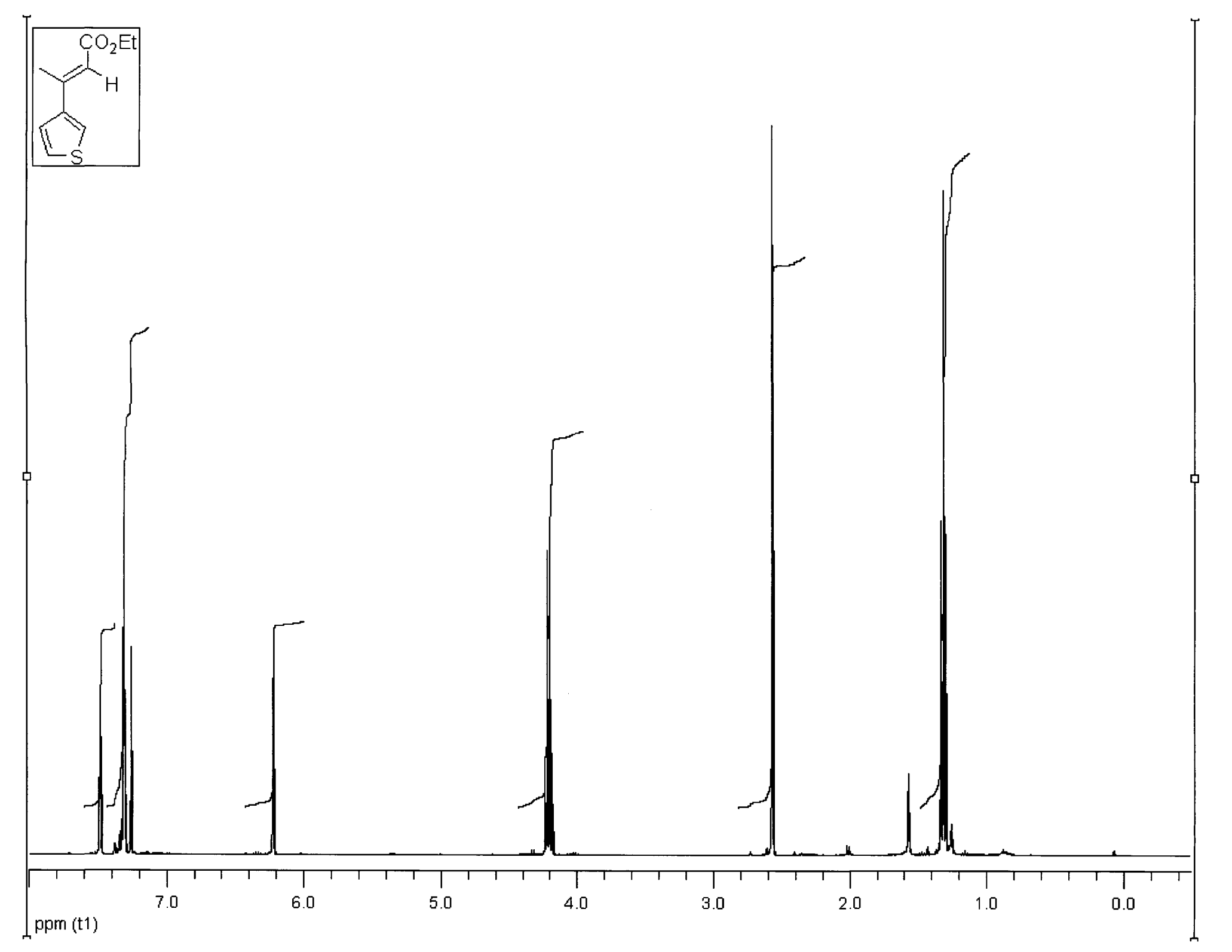
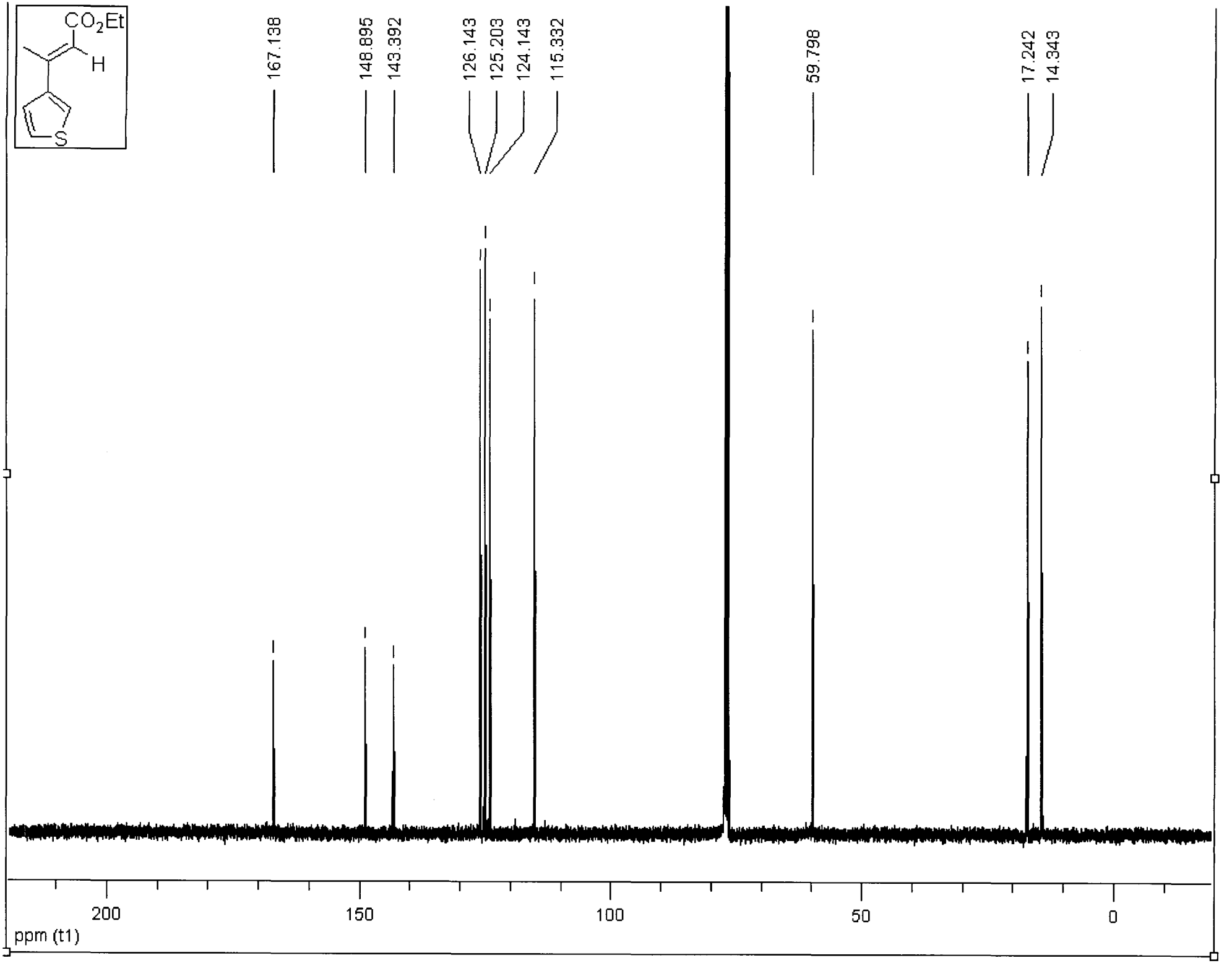
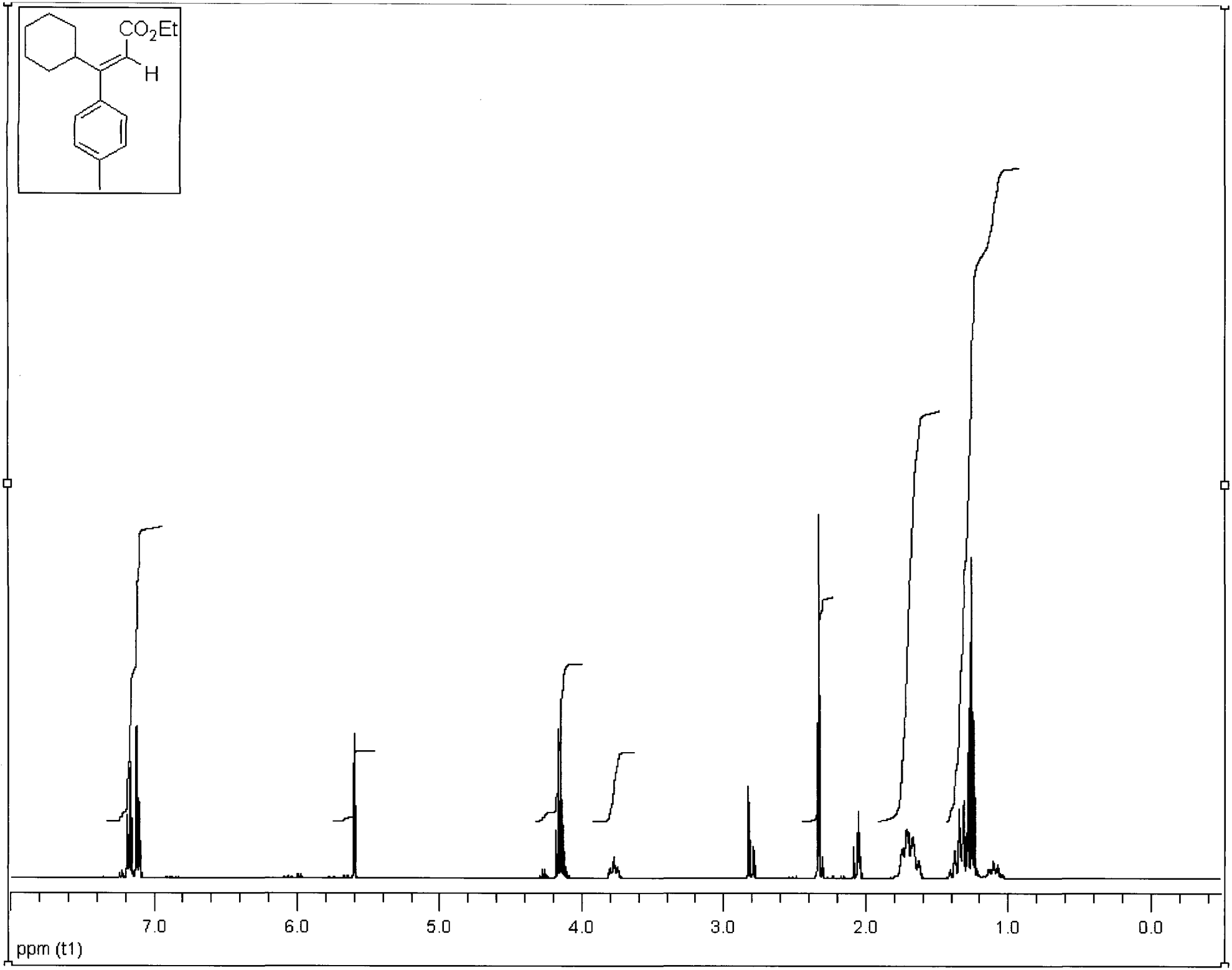
119.393
59.807
20.784
19.696
14.315
200
150
100
50
0
ppm (t1)

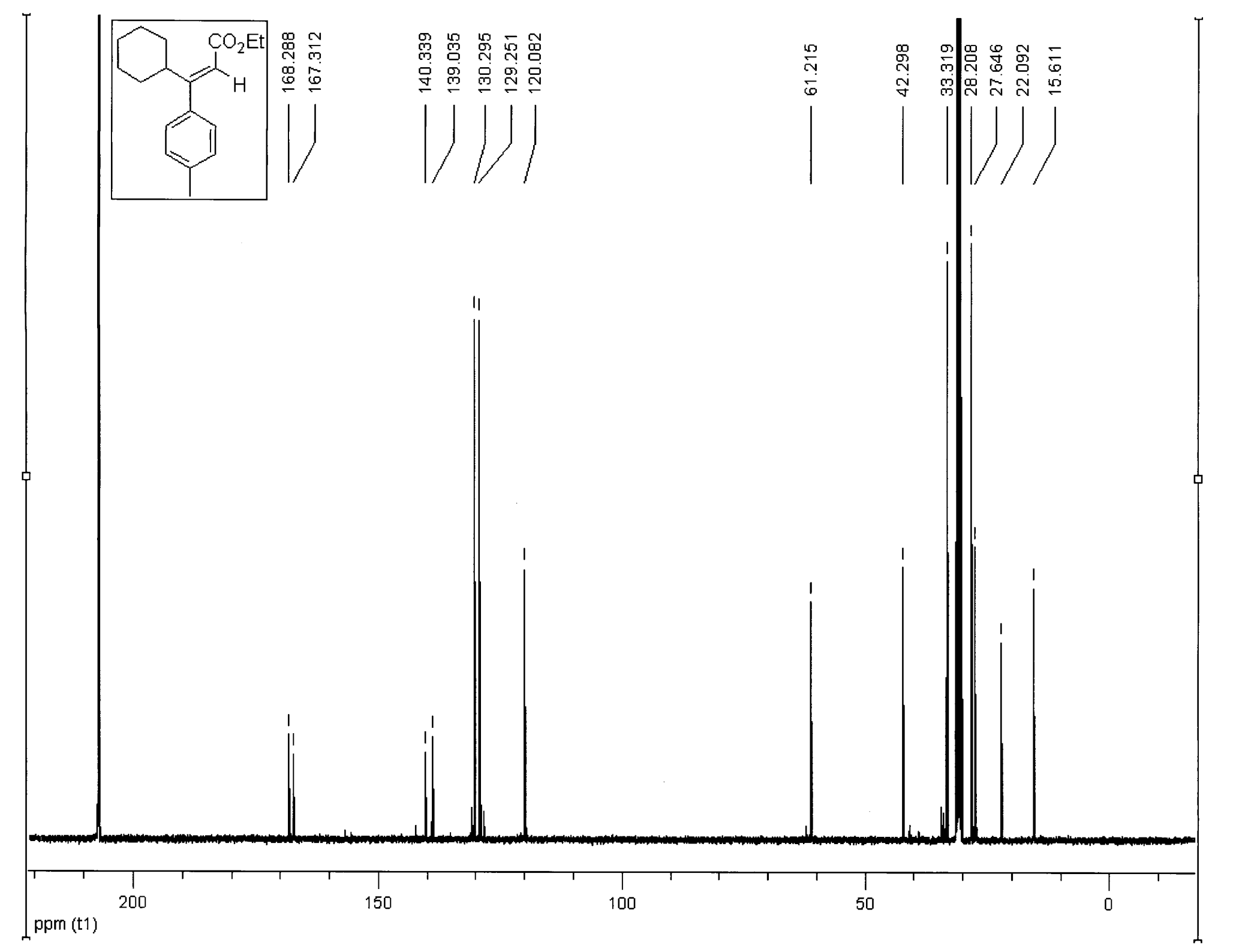

CO2Et
H
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

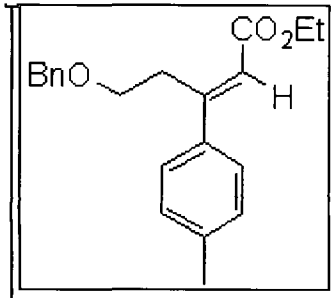

CO2Et
H
167.309
152.669
137.531
133.591
117.544
59.573
33.038
31.663
29.001
28.870
22.575
14.338
14.059
13.842
200
150
100
50
0
ppm (t1)

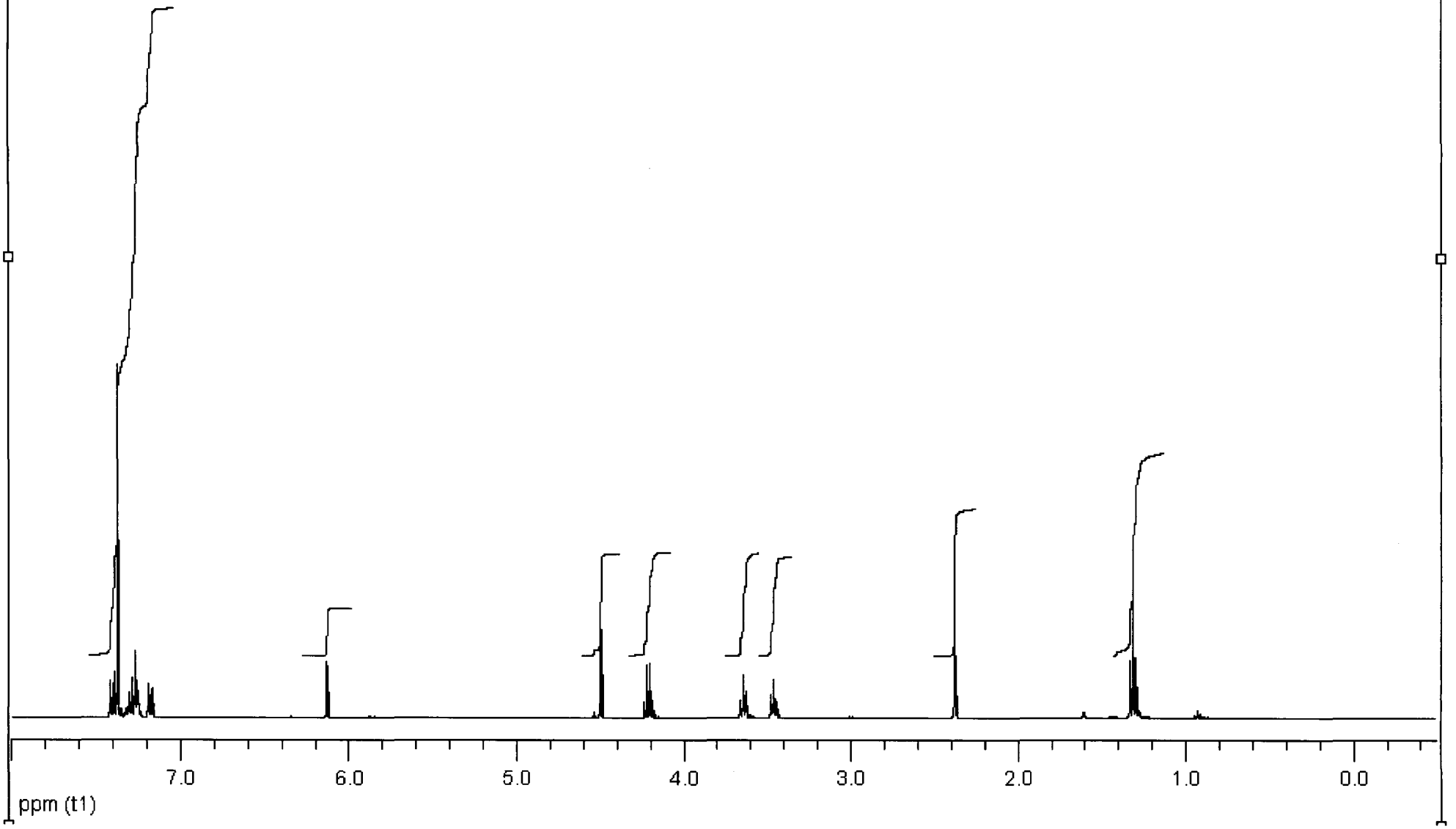

CO2Et
H
S
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

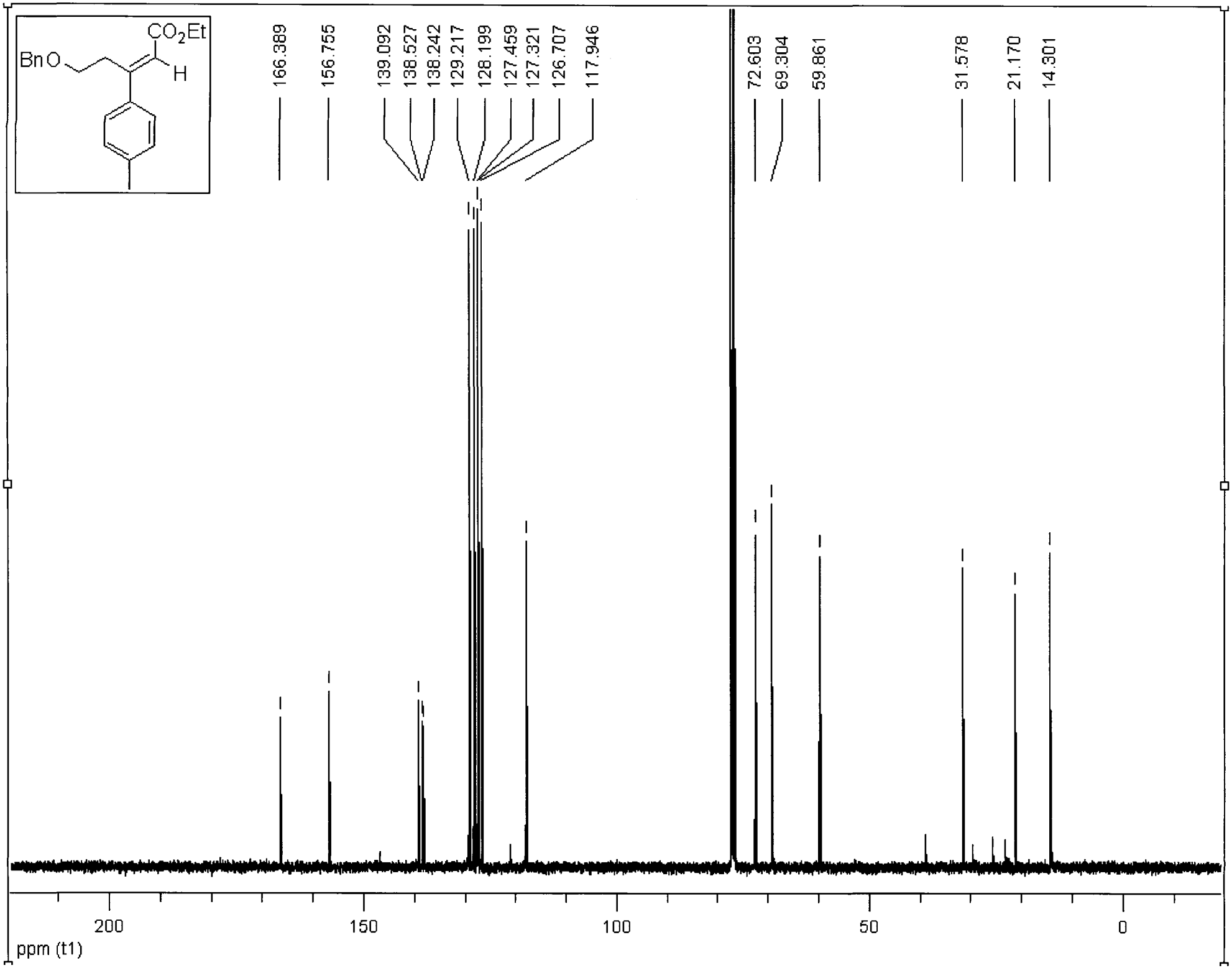

CO2Et
H
S
167.138
148.895
143.392
126.143
125.203
124.143
115.332
59.798
17.242
14.343
200
150
100
50
0
ppm (t1)

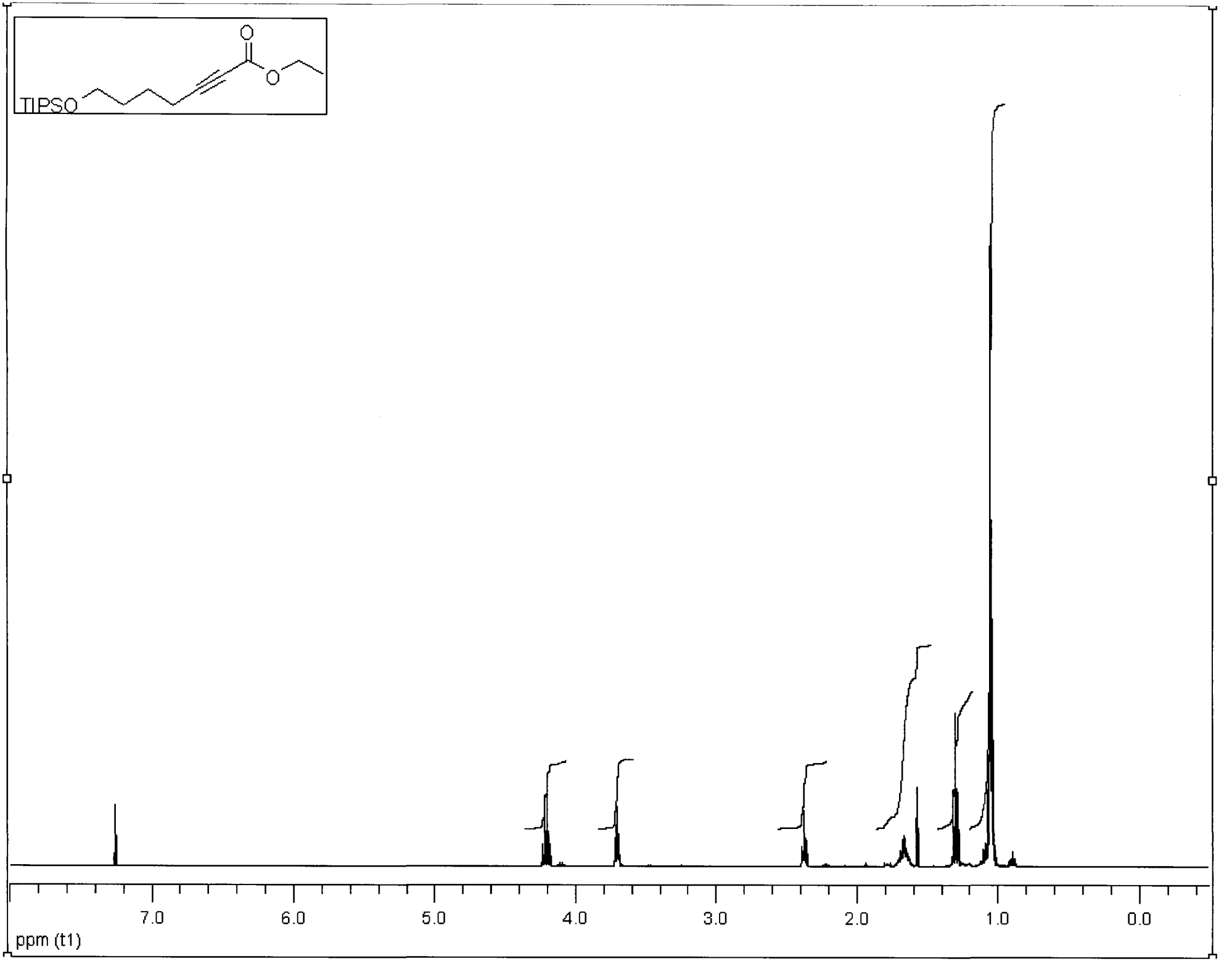

CO2Et
H
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

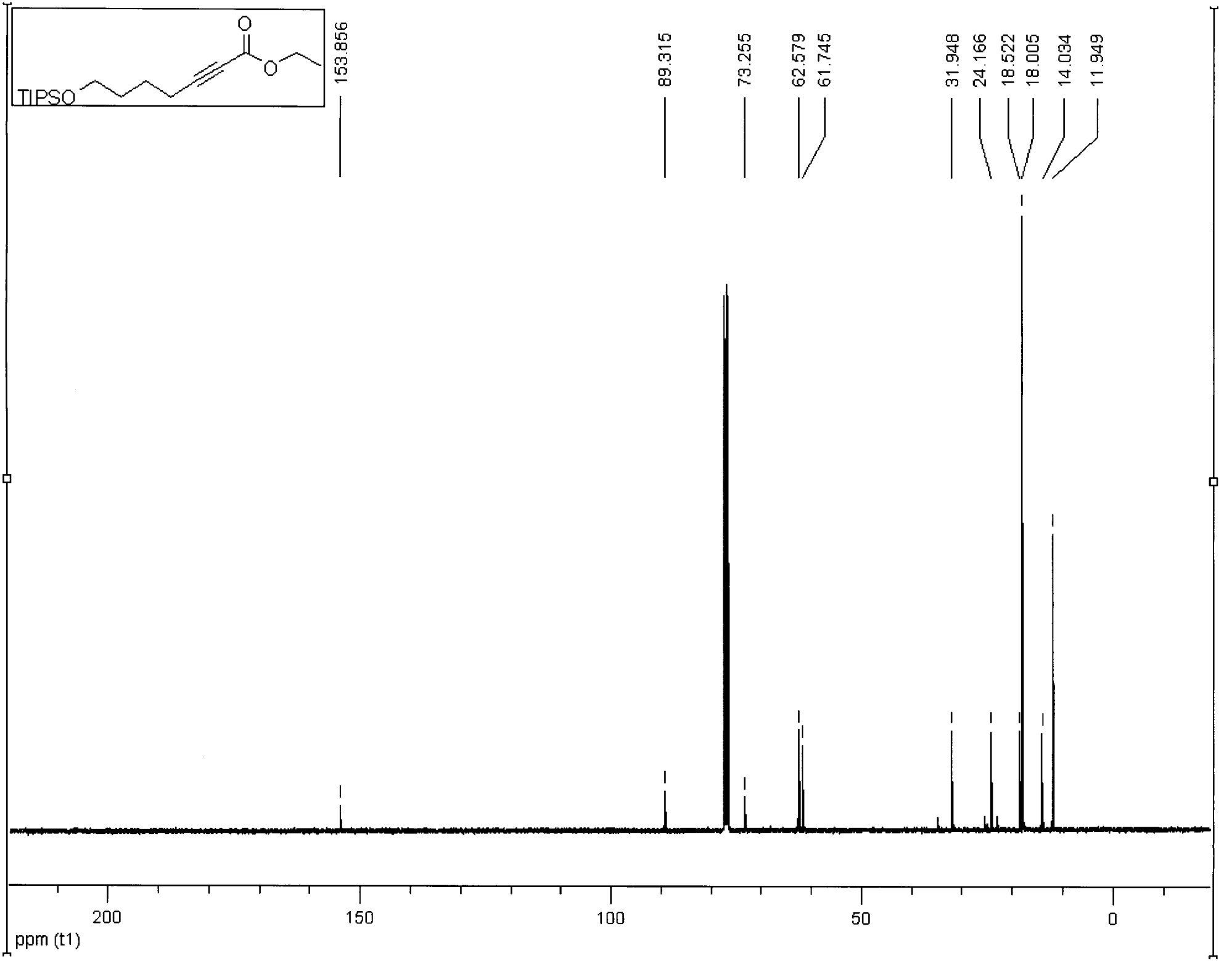

CO2Et
H
168.288
167.312
140.339
139.035
130.295
129.251
120.082
61.215
42.298
33.319
28.208
27.646
22.092
15.611
200
150
100
50
0
ppm (t1)

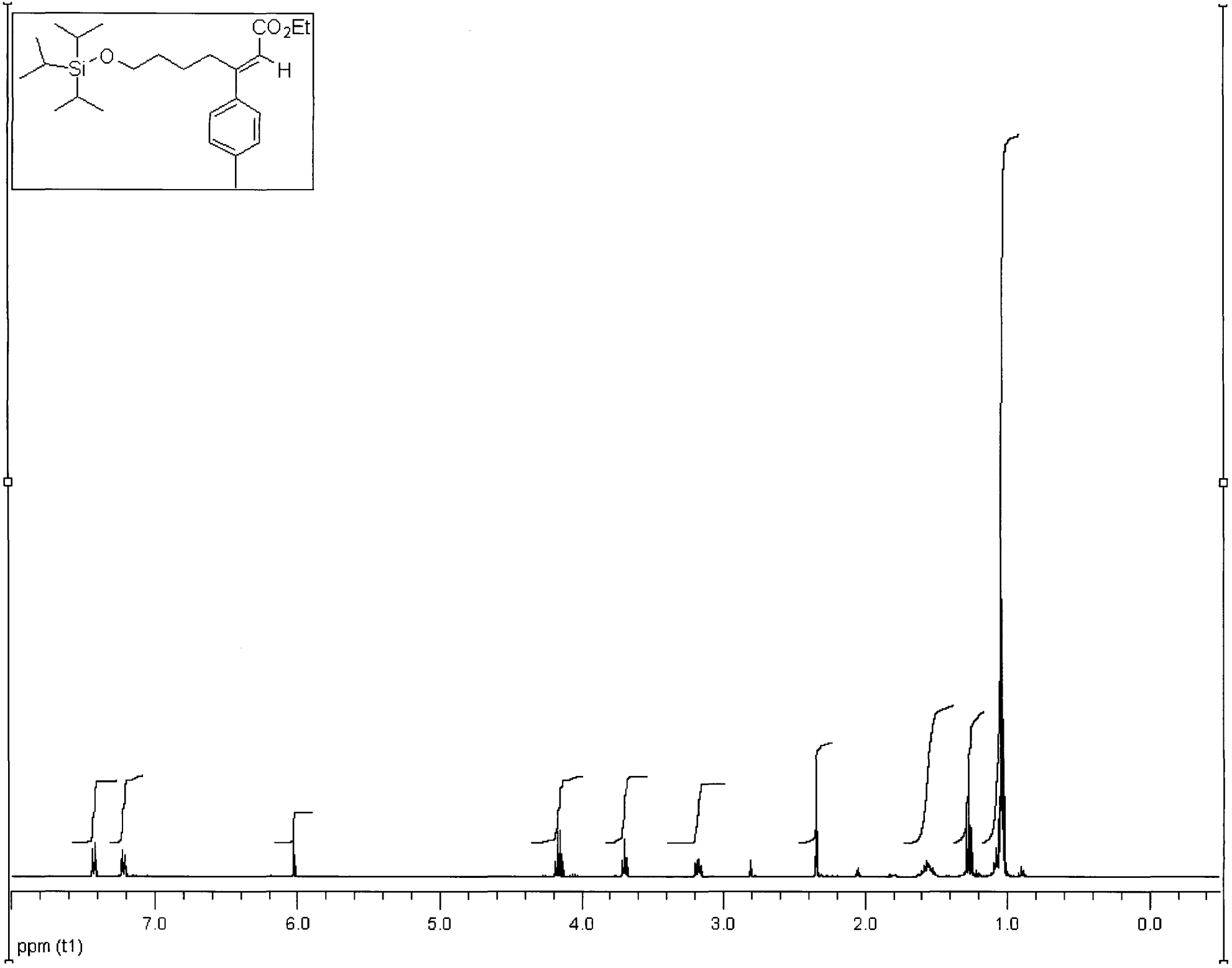

CO2Et
BnO
H

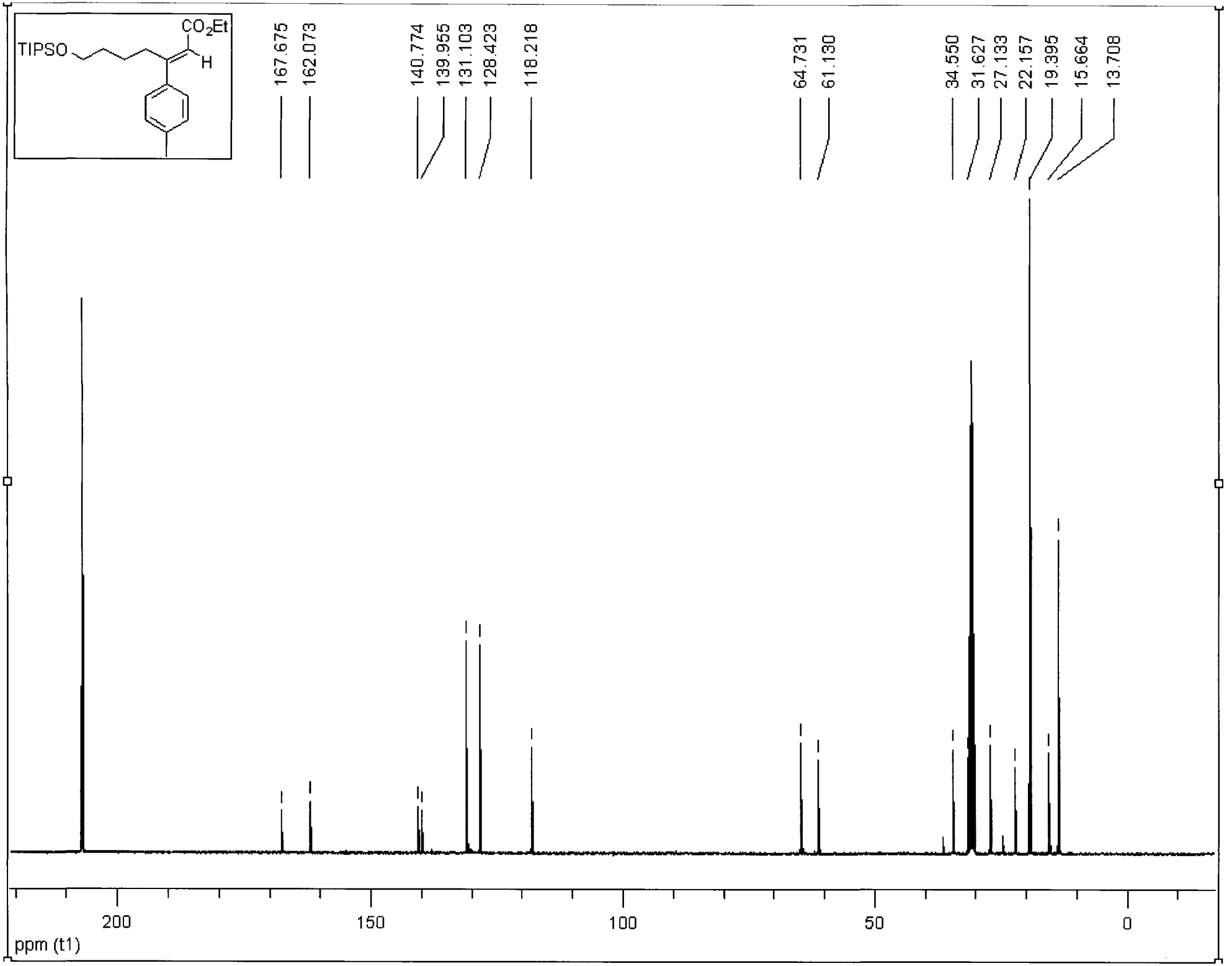

7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

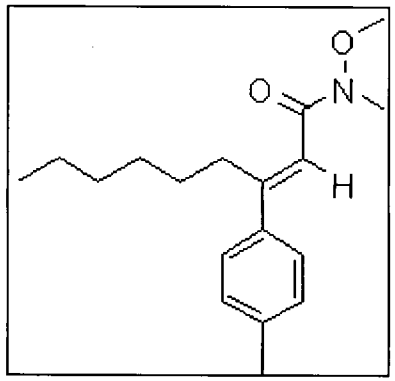

CO2Et
BnO
H
166.389
156.755
139.092
138.527
138.242
129.217
128.199
127.459
127.321
126.707
117.946
72.603
69.304
59.861
31.578
21.170
14.301
200
150
100
50
0
ppm (t1)

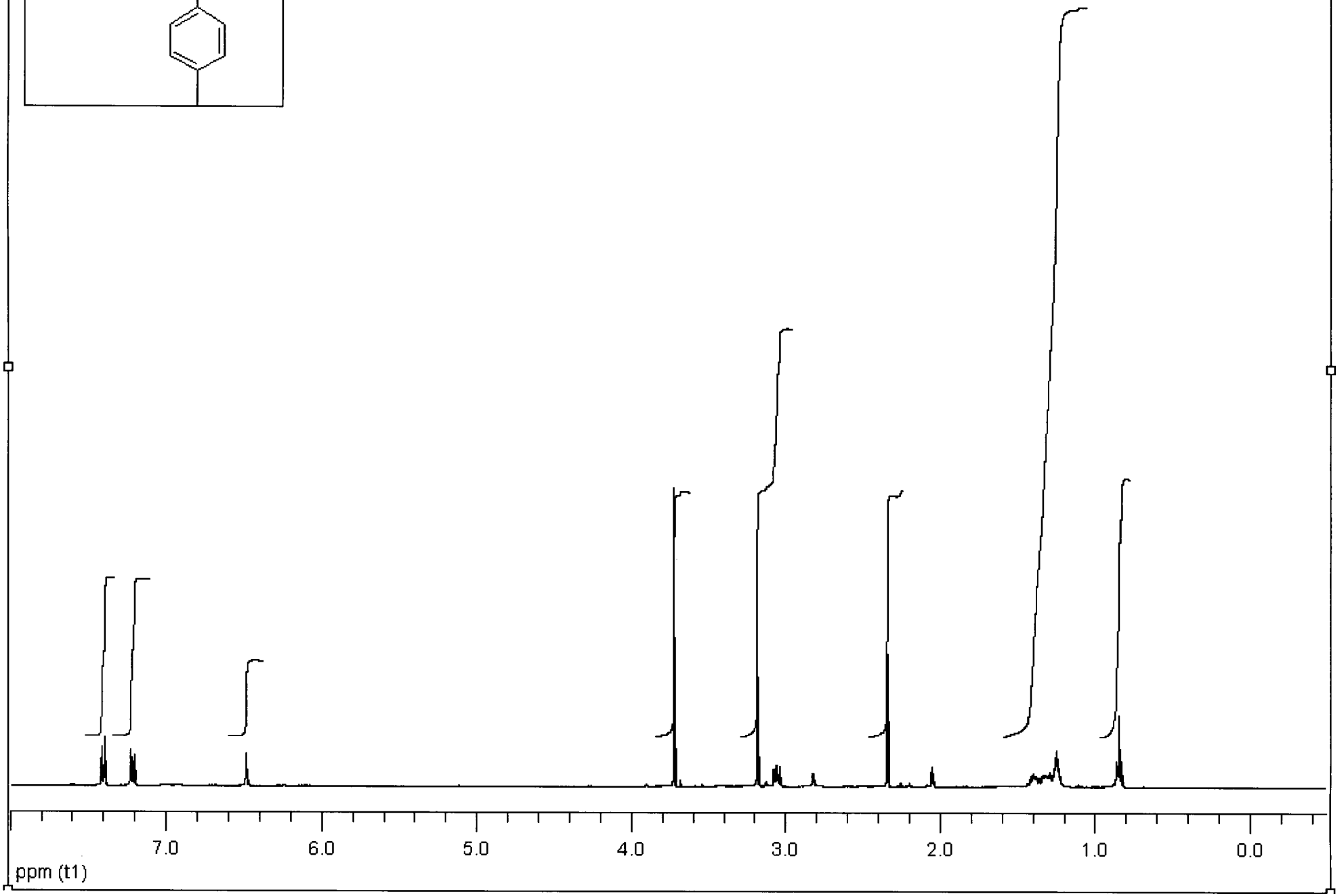

TIPSO
O
O
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

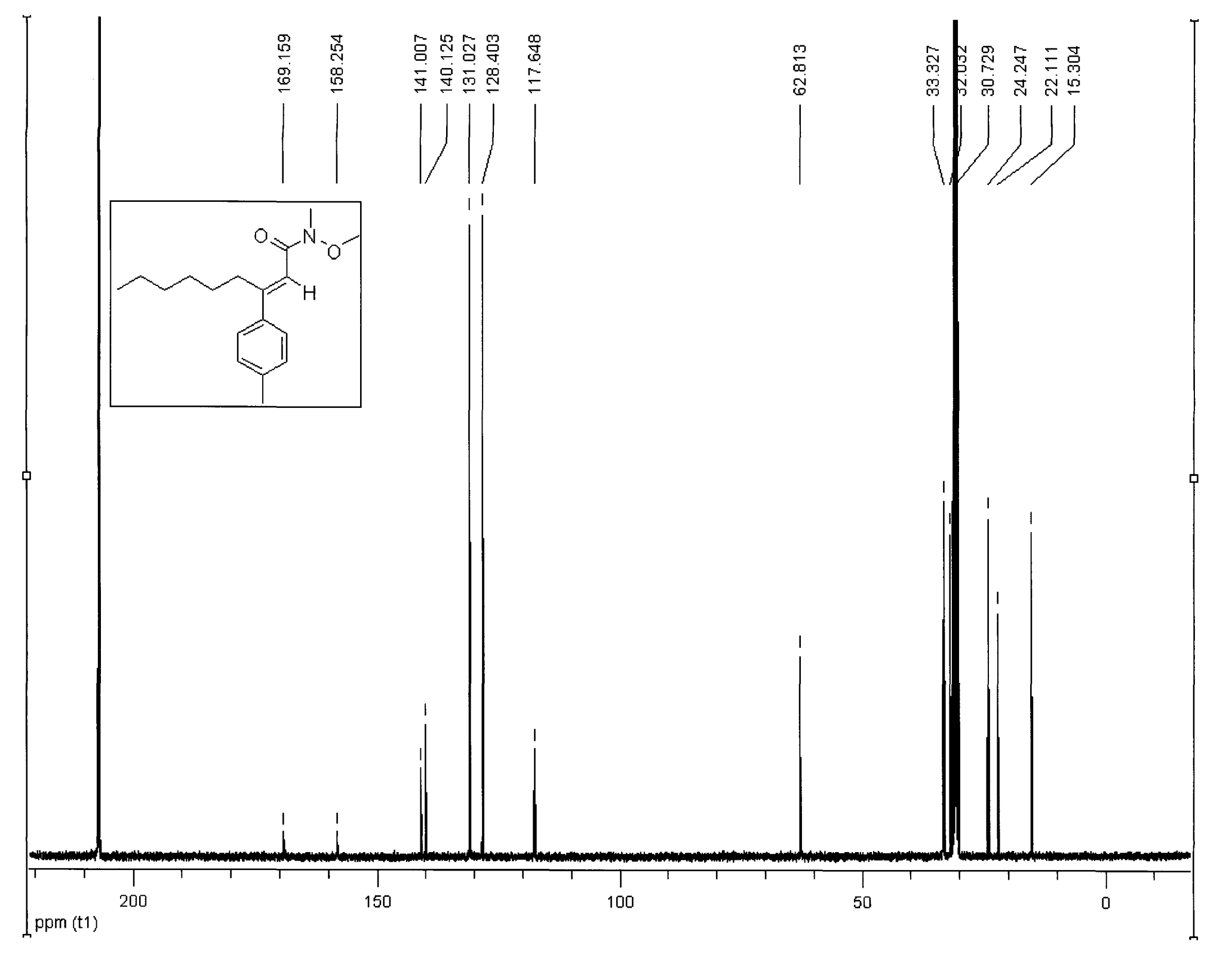

TIPSO
O
O
153.856
89.315
73.255
62.579
61.745
31.948
24.166
18.522
18.005
14.034
11.949
200
150
100
50
0
ppm (t1)

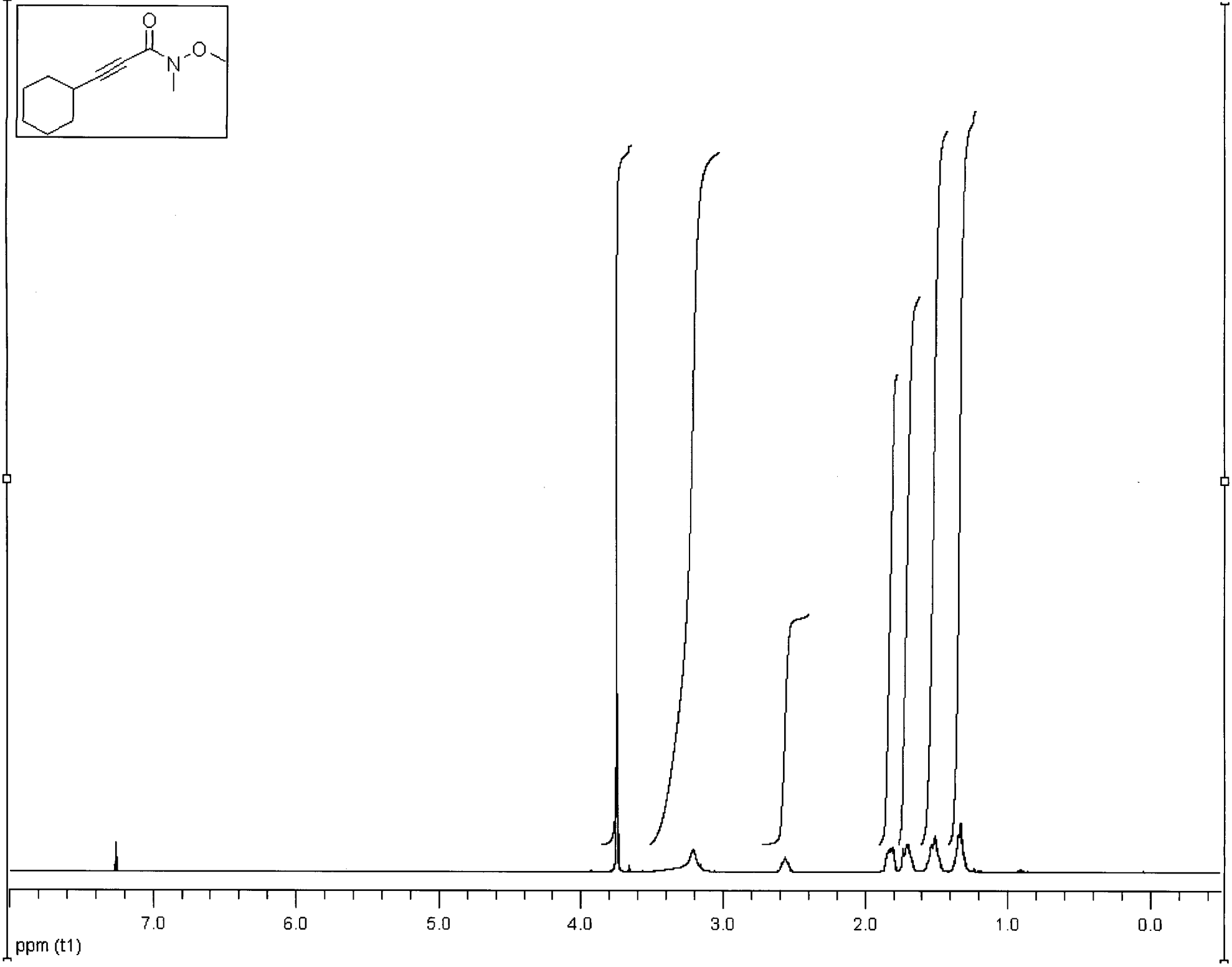

CO2Et
Si
O
H
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

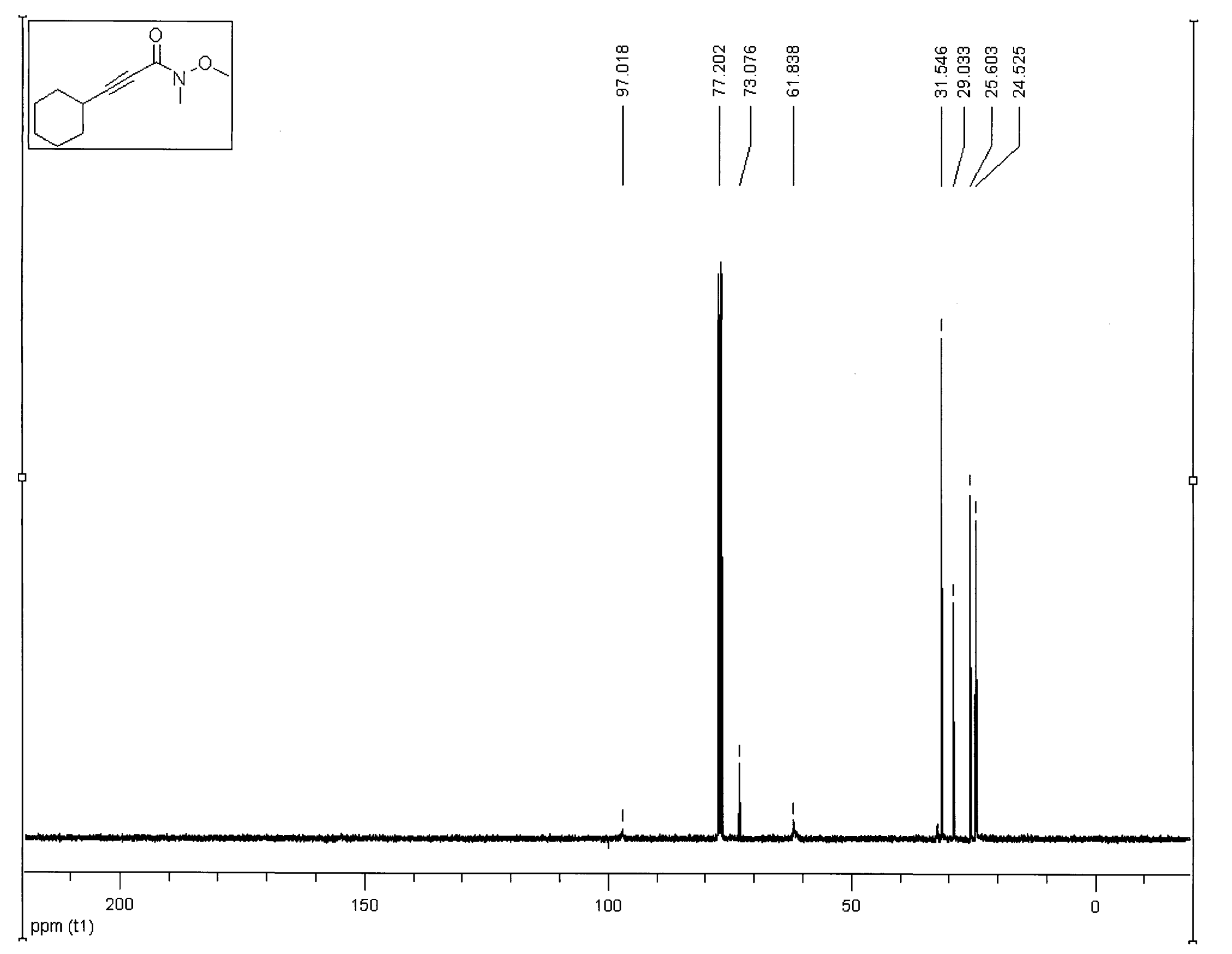

TIPSO
CO2Et
H
167.675
162.073
140.774
139.955
131.103
128.423
118.218
64.731
61.130
34.550
31.627
27.133
22.157
19.395
15.664
13.708
200
150
100
50
0
ppm (t1)

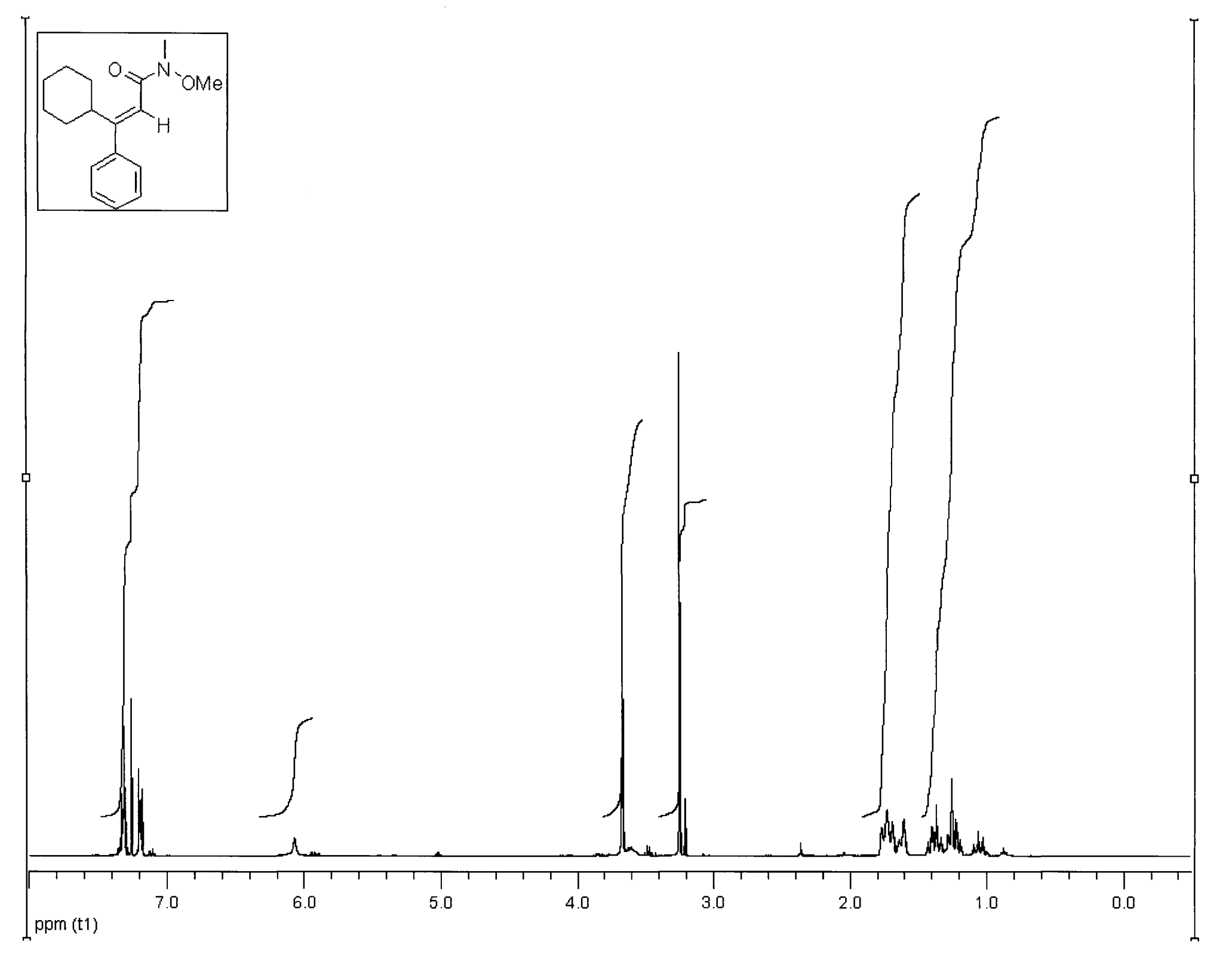

O
O
N
H

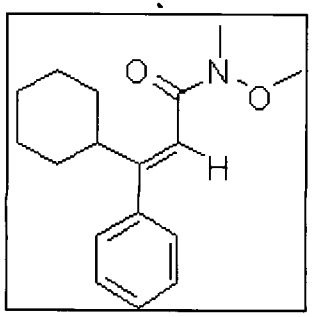

7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


169.159
158.254
141.007
140.125
131.027
128.403
117.648
62.813
33.327
32.052
30.729
24.247
22.111
15.304
O
N
O
H
200
150
100
50
0
ppm (t1)


O
N
O
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


97.018
77.202
73.076
61.838
31.546
29.033
25.603
24.525
200
150
100
50
0
ppm (t1)


O
N
OMe
H
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)



142.074
127.830
127.617
127.108
117.382
61.435
40.821
32.577
31.664
26.355
25.955
25.483

200
150
100
50
0
ppm (t1)