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Thivisa Rajagopal
AUTEUR DE LA THÈSE / AUTHOR OF THESIS

M.Sc. (Chemistry)
GRADE / DEGREE

Department of Chemistry
FACULTÉ, ÉCOLE, DÉPARTEMENT / FACULTY, SCHOOL, DEPARTMENT

Synthesis of Single Isomer Trisubstituted Olefins from B-Chloro-a-iodo-a, B-Unsaturated Esters and Alkynyl Esters

TITRE DE LA THÈSE / TITLE OF THESIS

W. Ogilvie
DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR

CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR

R. Ben

C. Boddy

Gary W. Slater
Le Doyen de la Faculté des études supérieures et postdoctorales / Dean of the Faculty of Graduate and Postdoctoral Studies

Synthesis of Single Isomer Trisubstituted Olefins from β-chloro-α-iodo-α, β-Unsaturated Esters and Alkynyl Esters

by

Thivisa Rajagopal

A thesis submitted to the School of Graduate Studies and Research

In Partial Fulfillment of the Requirements for the Degree of Master of Science

Ottawa-Carleton Chemistry Institute

Department of Chemistry

University of Ottawa

Ottawa, Ontario, Canada

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Candidate

Thivisa Rajagopal

Supervisor

Dr. William W. Ogilvie

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List of Abbreviations

9-BBN	9-borabicylco[3.3.1]nonane
Ac	Acetyl
AcOH	Acetic Acid
Ar	Aryl
Bn	Benzyl
Boc	tert-butyloxycarbonyl
br	broad
Bu	Butyl
Bz	Benzoyl
CI	Chemical Ionization
Cy	Cylcohexyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
DIPEA	diisopropylethylamine
DMAP	N,N-dimethylaminopyridine
DMF	N, N-dimethylformamide
DMSO	Dimethylsulfoxide

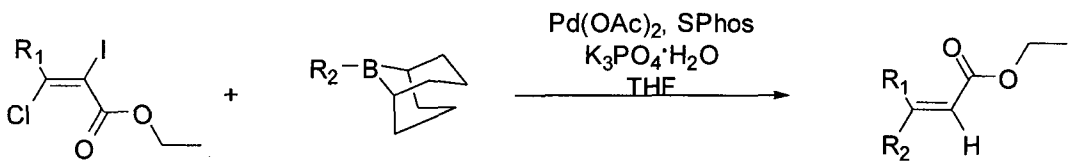
dpephos	Bis(2-diphenylphosphinophenyl)ether
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppb	1,4- Bis(diphenylphosphino)butane
dppp	1,3- Bis(diphenylphosphino)propane
dppe	1,2- Bis(diphenylphosphino)ethane
dppm	1,1- Bis(diphenylphosphino)methane
dt	Doublet of triplets
dq	Doublet of quartets
E	Electrophile
EI	Electron Impact Ionization
ent	Enantiomer
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
Equiv	Equivalents
HIV	Human Immunideficiency Virus
HOMO	Highest Occupied Molecular Orbital
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
*i*Pr	Isopropyl
*i*PrOH	Isopropanol
IR	Infrared spectroscopy
m	multiplet
M^+	Molecular ion

Me	Methyl
MeLi	Methyl lithium
MeOH	Methanol
min	Minutes
MS	Mass Spectroscopy
*n*BuLi	*n*-butyl lithium
NMR	Nuclear magnetic resonance spectroscopy
*n*Pr	propyl
nOe	Nuclear Overhauser enhancement spectroscopy
NOESY	Nuclear Overhauser Effect 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
q	quartet
RNA	Ribonucleic acid
r.t.	room temperature
s	singlet
SDS	Sodium dodecyl sulfate
SOMO	Singly Occupied Molecular Orbital

SPHOS	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
T	Temperature
t	triplet
*t*Bu	*tert*-butyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Tol	4-tolyl
TsOH	para-toluenesulfonic acid
Ts_2O	para-toluenesulfonic anhydride
XantPhos	Bis(diphenylphosphino)-9,9-dimethylxanthene

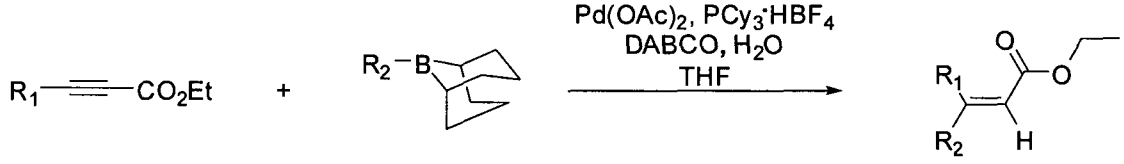
Abstract

A convenient method to synthesize regiospecific and stereoselective trisubstituted olefins bearing three substitutents with various functionalities is disclosed. A unique olefin template such as (E)-β-chloro-α-iodo-α,β-unsaturated esters cross-couple with 9-alkyl-9-BBN to produce single isomer trisubstituted olefins using palladium-catalyzed Suzuki-Miyaura cross-coupling reaction. This methodology can be further expanded to introduce various alkyl groups at the β-position. The mechanism is somewhat unusual as it involves two catalytic cycles with an allenoate intermediate to explain the observed stereochemistry and protonolysis of that intermediate produces the key product, (E)-β-chloro-α,β-unsaturated ester. The protonolysis is mediated by the presence of H_2O in the inorganic base, $K_3PO_4 \cdot H_2O$.



Similarly, another method has been developed to synthesize trisubstituted olefins using the alkynyl ester and 9-alkyl-9-BBN. This process also has a broad scope to introduce various alkyl groups at the β-position. The mechanism currently proposed involves an oxidation of palladium to form H-[Pd]-OH species. This was confirmed

based on the importance of water in the catalytic system and the isotopic experiments also confirmed the olefinic hydrogen at the α-position arises from the water itself. Following the formation of H-[Pd]-OH, syn carbopalladation to the alkynyl ester creates the hydroxyl palladium vinyl intermediate. However, this mechanism does not explain the observed stereochemistry. A more detailed study is required regarding this mechanism.



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buddy whom I didn't need to share my glasswares with that was just great. It was always great to have you in our lab and I really enjoyed your crazy dream conversations! Please promise me that you will eat and not starve yourself for chemistry. Zhu Zhu, you have been a great help and I hope you have enjoyed you stay in Canada.

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Chapter 1

1.1 Introduction

Synthesis of trisubstituted olefin bearing three substituents with various functionalities represents a challenging task in organic synthesis. This structural moiety is found in a wide variety of medicinal and natural products. Callystatin A[1] **1** is a novel polyketide isolated from the marine sponge, *Callyspongia truncata*. It exhibits potent *in vitro* cytotoxicity against KB cancer cell lines. Ratjadone[2] **2** arises from the Leptomycin family and is similar to Callystain A. It is extracted from a *Sorangium cellulosum* strain and displays potent *in vitro* antifungal activity and significant cytotoxicity in mammalian cell lines. Apoptolidan[3] **3**, is a macrolide from *Nocardiopsis sp.* It is a specific apoptosis inducer in transformed cells expressing oncogenes, which suggest a potential use as an anticancer agent to treat certain types of tumours. Stipiamide[4] **4** patented as Phenalamid A_1 represents a trisubstituted polyene isolated from *Myxococcus stipitatus*. It is an insecticidal antibiotic, anti-HIV, and multidrug resistance (MDR) reversal agent. Orevactaene[5] **5** isolated from *Epicoccum nigrum* WC47880, is a novel oxopolyene. It is a binding inhibitor for the HIV-1 REV protein to

[1] (a) Kobayashi, M.; Higuchi, K.; Murakami, N.; Tajima, H.; Aoki, S.; *Tetrahedron Lett.* **1997**, 38, 2859. (b) Crimmins, M. T.; King, B. W.; *J. Am. Chem. Soc.* **1998**, 120, 9084.

[2] (a) Williams, D. R.; Ihle, D. C.; Plummer, S. V.; *Org. Lett.* **2001**, 3, 1383. (b) Gerth, K.; Schummer, D.; Hofle, G.; Irschik, H.; Reichenbach, H.; *J. Antibiot.* **1995**, 48, 973.

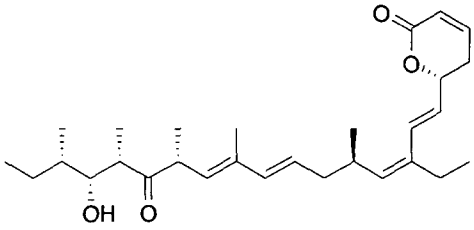
[3] Hayakawa, Y.; Kim, J. W.; Adachi, H.; Shin-ya, K.; Fujita, K.; Seto, H.; *J. Am. Chem. Soc.* **1998**, 120, 3524.

[4] (a) Kim, Y. J.; Furihata, K.; Yamanaka, S.; Fudo, R.; Seto, H.; *J. Antibiot.* **1991**, 44, 553. (b) Andrus, M. B.; Lepore, S. D.; *J. Am. Chem. Soc.* **1997**, 119, 2327.

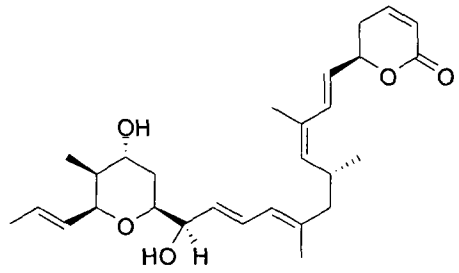
[5] (a) Organ, M. G.; Bilokin, Y. V.; Bratovanov, S.; *J. Org. Chem.* **2002**, 67, 5176.

REV response element (RRE). As a result, it deregulates the accumulation of viral mRNA in the nuclei of the infected cells which decreases the production of structural protein and terminates HIV virus replication.

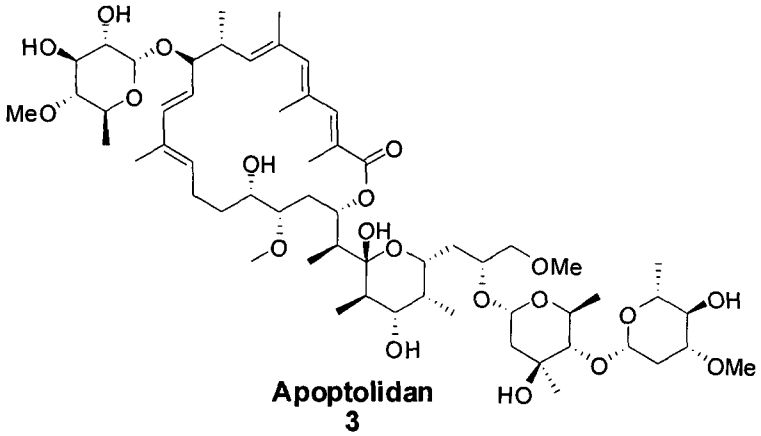
Figure 1. Examples of natural products containing trisubstituted olefin.



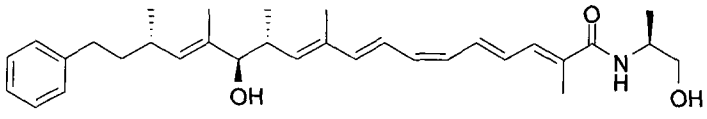
Callystatin A
1



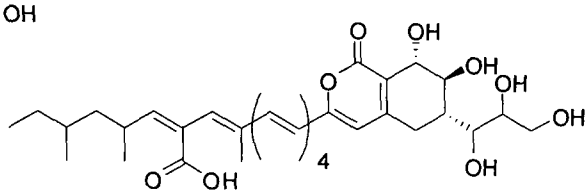
Ratjadone A
2



Apoptolidan
3



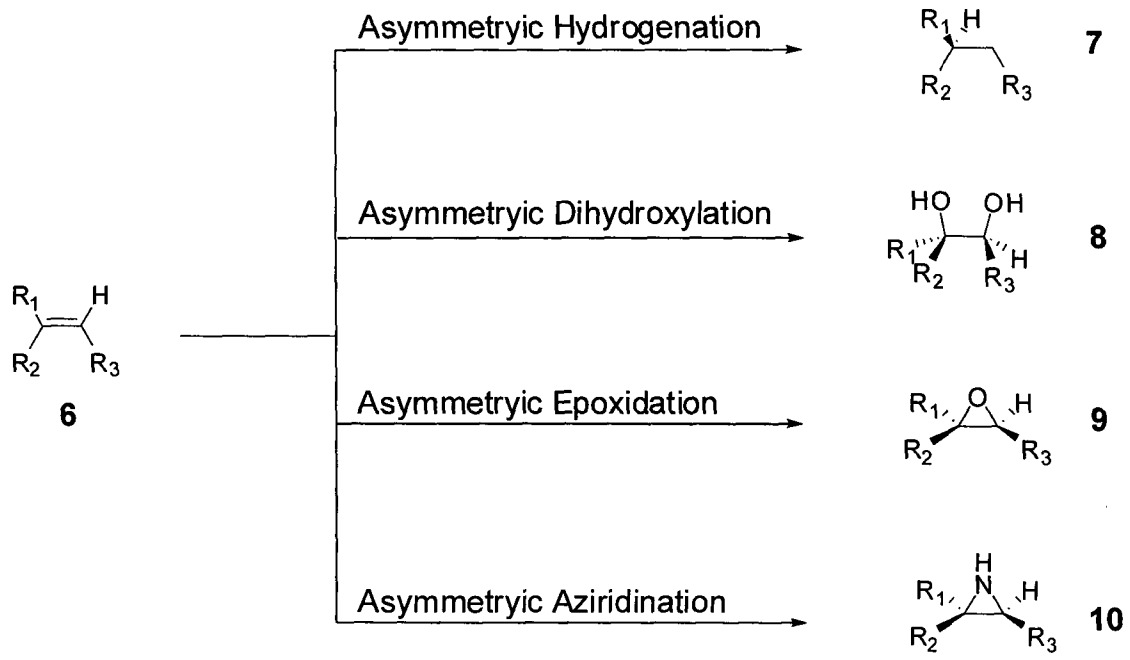
Stipiamide
4



Orevactaene
5

Though trisubstituted olefins constitute important functionalities in medicinal and natural products, their importance is further expanded as they represent key starting materials for chemical transformations that afford different organic substances. Asymmertric reactions such as hydroxylation, hydrogenation, epoxidation, aziridination and other processes convert stereodefined trisubstituted olefins into compounds containing asymmetric stereogenic sp_3-hybridized centers (Scheme 1). These reactions are very significant as they can synthesize chiral products from achiral building blocks.

Scheme 1. Asymmetric reactions with trisubstituted olefin substrates



The challenge to synthesize trisubstituted olefins in a regio- and stereospecific way arises in the field of organic synthesis after recognizing the significance of the trisubstituted olefin in both natural products and toward its involvement in asymmertric reactions.

The traditional direct approaches to synthesize trisubstitttuted olefins are the Wittig and Horner-Wadsworth-Emmons reaction. Although these reactions are simple, convenient and powerful, the control over stereochemistry is difficult as both *E* and *Z* isomers of the olefins are often produced. To resolve this problem chemists have explored successful indirect methods such as the carbometalation of alkynes and the manipulation of existing olefin templates via known cross-coupling reactions. Trisubstituted olefins can be synthesized via simple reactions such as ynolate chemistry, elimination, cycloadditions, sigmatrophic reactions, and by olefin metathesis. The creators of olefin metathesis, Y. Chauvi, R. Grubbs, and R. Schrock received the Nobel Prize in Chemistry in 2005. Each of these methods is well studied and thus examples of the published work will be thoroughly discussed below. As a start, we will begin to look at the traditional synthesis of trisubstituted olefins.

1.2 Olefination of Carbonyls

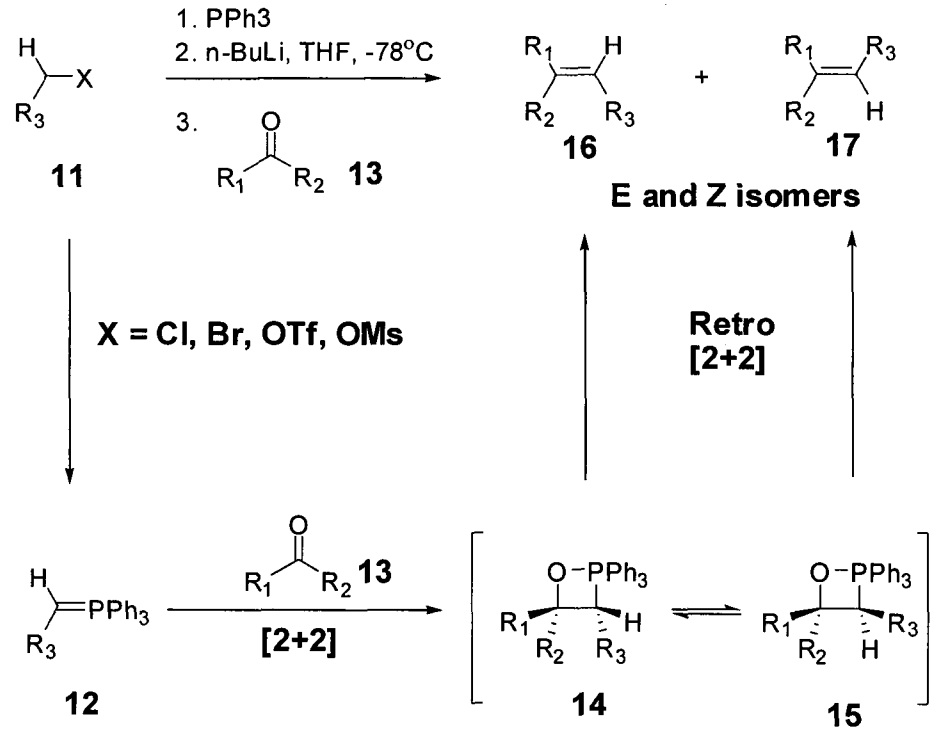
Trisubstituted olefins containing three different functionalities can be obtained by carbonyl olefination. One of the most common examples of carbonyl olefination is the traditional Witting reaction. The Wittig reaction[6] was discovered by George Wittig in 1952 and he was awarded the Nobel Prize in Chemistry in 1979. It is a very simple, efficient and convenient route to synthesize trisubstituted olefins from phosphonium ylides and aldehydes or ketones. The mechanism involves the treatment of alkyl halide **11** with triphenylphosphine to form the alkyl phosphonium salt via simple bimolecular substitution reaction. This material is deprotonated by *n*-butyllithium in THF at -78°C to afford the phosphonium ylide **12**. The ylide **12** and the corresponding aldehyde or ketone **13** undergo a formal [2+2] cycloaddition to produce 1,2-oxaphosphetane intermediates such as **14** which is in equilibrium with **15** . Following a retro [2+2] cycloaddition of the intermediates **14** and **15**, to the formation of both *E* and *Z* isomers such as **16** and **17** respectively follows (Scheme 2).

Though the Wittig olefination represents a powerful method to synthesize trisubstituted alkenes, it has some limitations. The ratio of isomers in the products can be difficult to control and mixtures of *E* and *Z*-alkenes are obtained. It has however been shown that the reaction of "stabilized" ylides with aldehydes predominantly favours the *E*-trisubstituted olefin. On the contrary, the reaction of "non stabilized" ylides with aldehydes favours the *Z*-olefin. Furthermore, the Wittig reaction of sterically

[6] Maryanoff, B. E.; Reitz, A. B.; *Chem Rev.* **1989**, 89, 863.

encumbered ketones with phosphonium ylides often does not work and shows poor stereoselectivity. The inability to control the stereochemistry of the olefin and the shortage of available ketone substrates limits the synthesis of trisubstituted olefins with various functionalities.

Scheme 2. Traditional Wittig Olefination produces mixtures of isomers

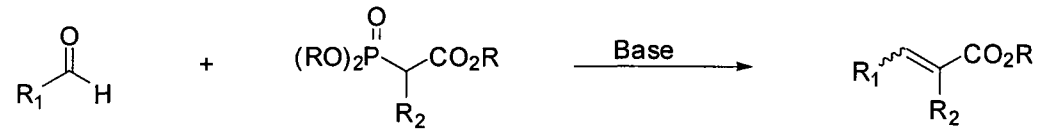


To account for the limitations associated with the Wittig reaction, it was later modified by Leopold Horner in 1958. A more thorough definition of the reaction was illustrated by William S. Wadsworth and William D. Emmons. The modified version of the Wittig reaction was named after the discoverers and called the Horner-Wadsworth-

Emmons reaction[7]. It represents an improvement of the Wittig Olefination. This reaction replaces the phosphinum ylides with more nucleophilic and basic phosphoryl-stabilized carbanions. The trisubstituted olefins can be obtained by employing two types of phosphate esters with aldehydes or ketones under Horner-Wadsworth-Emmons reactions. Alpha-substituted phosphate esters such as **19** react with aldehydes such as **18** to give α-substituted-α,β-unsaturated esters **20**. Ketones such as **21** react with unsubstituted phosphate esters such as **22** to form β-substituted-α,β-unsaturated esters **23** in the presence of a strong base such as sodium hydride (Scheme 3).

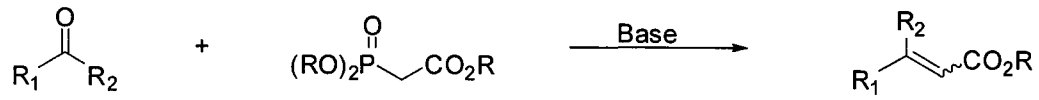
Scheme 3. Horner-Wadsworth-Emmons reactions produce trisubstituted olefin by employing two types of phosphate esters with aldehydes and ketones

(a) α-substituted phosphate esters and aldehydes



18 **19** **20**

(a) Unsubstituted phosphate esters and ketones

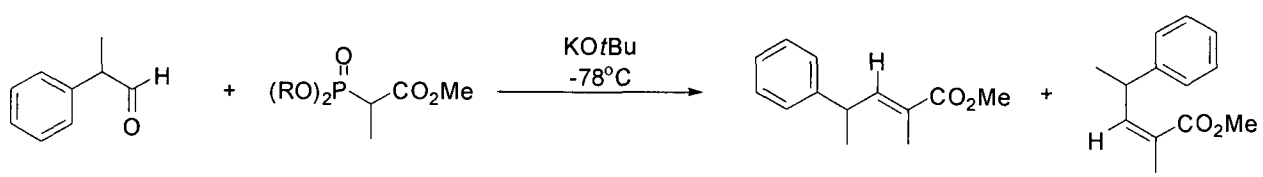


21 **22** **23**

[7] Iorga, B.; Eymery, F.; Mouries, V.; Savignac, P.; *Tetrahedron*. **1998**, 54, 14637.

Unlike the Wittig reaction, the Horner-Wadsworth-Emmons reaction shows good control over the stereoselectivity of the produced trisubstituted olefins by varying the steric bulk of the α-substituted phosphate ester and the temperature of the reaction. At first we will examine the α-substituted phosphates to form trisubstituted olefins stereoselectively (Scheme 4). Subjecting an aldehyde like **24** with ethyl-phosphate ester **25** gave trisubstituted olefin products **27** and **28** in a 5:95 ratio of *E*:*Z* isomers. In contrast, replacing the ethyl group with a more sterically hindered isopropyl-phosphate ester **26** dramatically reversed the results of the reaction. In the latter case, the *E* isomer was predominantly favoured over the *Z* isomer in a ratio of 95:5. It is evident from these results, the stereochemistry of the trisubstituted olefins can be controlled by using different phosphate esters.

Scheme 4. Stereochemistry of the Trisubstituted olefins are controlled by different phosphate esters



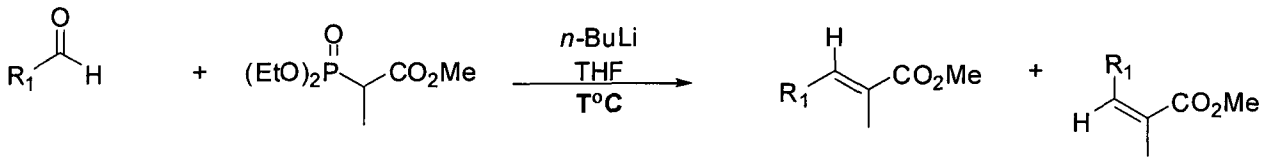
24		**(E)-27**	**(Z)-28**
	25 R= Et	5	95
	26 R= *i*Pr	95	5

The effect of temperature on the synthesis of stereoselective trisubstituted olefins via the Horner-Wadsworth-Emmons reaction was investigated[8]. The study involved the reaction of various aldehydes with α-substituted phosphate esters in the presence of *n*-butyllithium in THF at two different temperatures (Table 1).

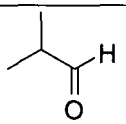
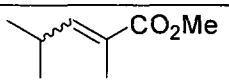
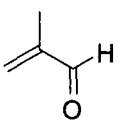
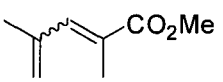
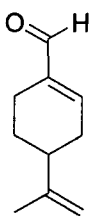
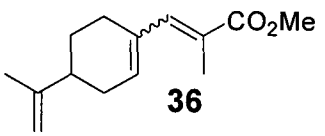
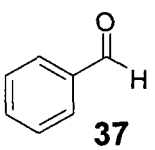
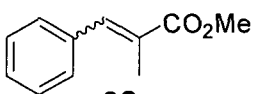
A simple alkyl aldehyde such as isobutyraldehye **31** reacted with ethyl-phosphate ester **25** to form *Z* olefin **32** at lower temperature (Table 1, Entry 1). By warming the reaction to room temperature the stereoselectivity of the desired olefin dropped dramatically to afford mixtures of *E* and *Z* isomers of **32** in equal proportion (Entry 2). Employing α-substituted α,β-unsaturated aldehydes such as methacrylaldehyde **33** produced the olefin product **34** as a 65:35 mixture of *E* and *Z* isomers at -78°C (Entry 3). It is interesting to note that by warming the temperature to 20°C the stereoselectivity rapidly increased to favour the *E*-olefin product **34** in a 90:10 ratio of *E*:*Z* isomers (Entry 4). This result was directly opposite to the results obtained in Entry 1 at lower temperature. Subjecting a more hindered alkyl aldehyde such as **35** showed no reaction at lower temperatures (Entry 5). Nonetheless, at room temperature the reaction efficiently converted the aldehyde to the *E* isomer as the major olefin product **36** (Entry 6). At last, an aromatic aldehyde such as benzaldehyde **37** showed no dependence on the temperature as the product **38** was formed in a 95:5 ratio of *E*:*Z* isomers. Only the *E*-isomer was more favourable in both reaction conditions.

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

Table 1. The effect of temperature on the stereoselectivity of the trisubstituted olefin[8]



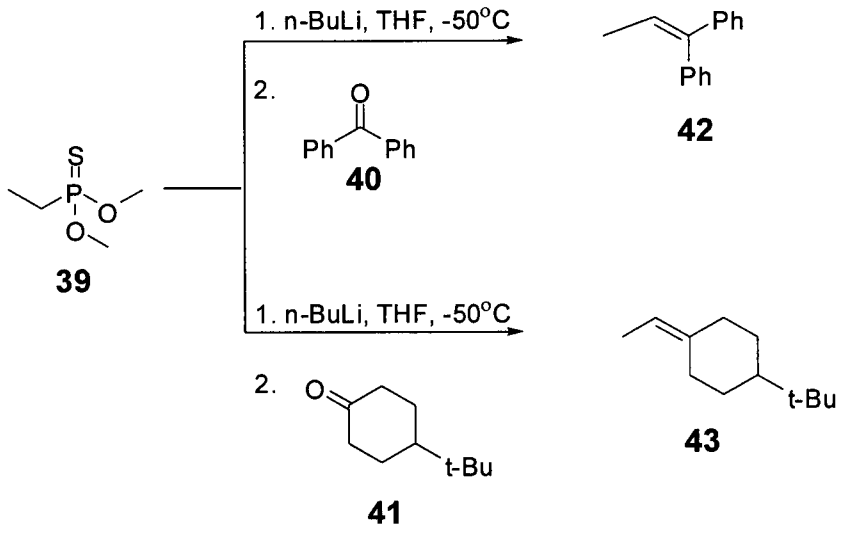
18 **25** **(*E*)-29** **(*Z*)-30**

Entry	Substrate	Product	Temperature	*E*:*Z* ratio
1			-78°C	10:90
2	**31**	**32**	20°C	50:50
3			-78°C	65:35
4	**33**	**34**	20°C	90:10
5			-78°C	-
6	**35**	**36**	20°C	90:10
7			-78°C	95:5
8	**37**	**38**	20°C	95:5

Furthermore, ketones play an important role in introducing various functionalities onto the trisubstituted olefin. Wittig reactions with sterically encumbered ketones and phosphonium ylides are very slow and show poor stereoselectivity. Hence, in 1966, Corey and Kwiatkowski[9] developed a new reagent called O, O'-dialkyl-α-lithioalkylphosphonothioate esters to replace the phosphate esters employed in Horner-Wadsworth-Emmons reaction. The phosphonothioate esters **39** were treated with *n*-butyllithium in THF at -50°C to form the phosphonium ylides which reacted with symmetric hindered ketones such as **40** or **41** to afford the geminally symmetrical trisubstituted olefins **42** and **43** respectively (Scheme 5). Though this reaction introduced different substituents around the trisubstituted olefin it did not solve the inherent issue of stereoselectivity. It cleverly bypassed the problem by the use of symmetric ketones. Thus, the need for a method capable of the efficient synthesis of differentially trisubstituted alkenes remains.

[9] Corey, E. J.; Kwiatkowski, G. T.; *J. Am. Chem. Soc.* **1966**, 88, 5654. (b) Corey, E. J.; Kwiatkowski, G. T.; *J. Am. Chem. Soc.* **1968**, 90, 6816

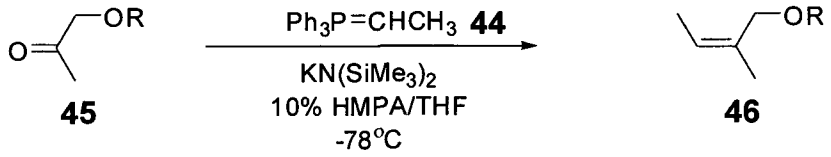
Scheme 5. Synthesis of geminally symmetrical Trisubstituted olefins from Phosphonothioate esters



In 1980, Still and coworkers[10] illustrated a direct route to synthesize *Z*-trisubstituted protected alcohols via a lithium free Wittig reaction. Treatment of simple "non stabilized' phosphonium ylides **44** with acyclic α-alkoxy ketones **45** led to the production of protected trisubstituted allylic alcohols **46** with high, yet not absolute, selectivity for the *Z* stereoisomers. A wide variety of trisubstituted olefins were synthesized by varying the protecting group of the α-alkoxy ketones. Selected examples of this work are demonstrated in Table 2. As summarized below, selectivity for the *Z* isomer was observed to be the highest with the tetrahydropyranyl group (THP) in hexamethyl disilazide basic solvent (Table 2, Entry 1).

[10] Sreekumar, C.; Darst, K. P.; Still, W. C.; *J. Org. Chem.* **1980**, 45, 4260.

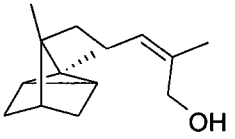
Table 2. Stereospecific synthesis of *Z*-trisubstituted olefin from α-alkoxy ketones[10]



Entry	R	Z:E ratio
1	THP	41:1
2	CMe_2OMe	30:1
3	CPh_3	18:1
4	$SiMe_3$-tBu	14:1
5	CH_2Ph	12:1

In addition, limitations to the reaction were evaluated by employing substituted phosphonium ylides and α-alkoxy ketones. The alkyl substituted ylides underwent efficient conversion to *Z*-olefins as long as the carbon β to the phosphorous remained unbranched. However, substitution of the carbonyl partner had its limits. Substitution at the α-carbon of an α-alkoxy ketone greatly improved the stereoselectivty while α' substitution tended to diminish the stereoselectivity. These findings were useful in synthesizing sesquiterpene α-santalol **47** (Figure 2) in an 85% yield with 99% stereoisomeric purity. Though the findings of Still and coworkers showed improvement toward the development of stereoselective Wittig and Horner-Wadsworth-Emmons reactions, complete stereoselectivity was not achieved.

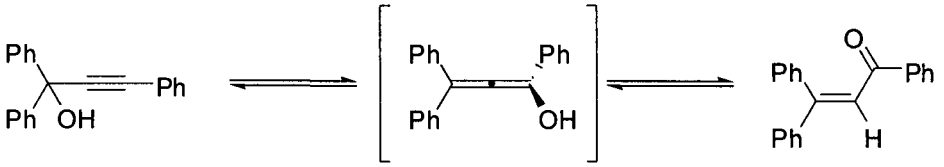
Figure 2. An example of *Z*-trisubstituted olefin synthesized from α-alkoxy ketones



Sesquiterpene α-santalol
47

Recently, Dudley and coworkers[11] reported an olefination of sterically hindered ketones to form trisubstituted olefins with carnonyl functionalities via a Meyer-Schuster rearrangement. The Meyer-Schuster rearrangement is not a well known reaction, but it is a powerful rearrangement with complete atom economy. The mechanism involved a 1,3-shift of the hydroxyl moiety of the propargyl alcohol **48** followed by the tautomerization of the allenol intermediate **49** to produce the desired carbonyl olefin product **50** (Scheme 6).

Scheme 6. Mechanism of Meyer-Schuster Rearrangement



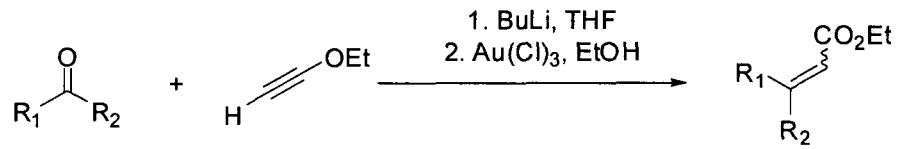
48 **49** **50**

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

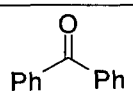
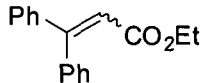
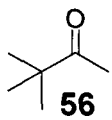
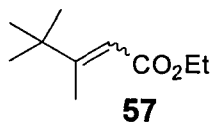
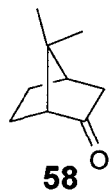
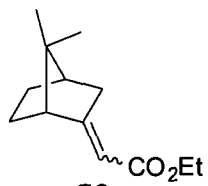
The α,β-unsaturated ester carbonyl compounds were synthesized in a two step sequence. As a first step, propargyl alcohols were prepared by the addition of terminal acetylide nucleophiles to the carbonyl compounds which underwent a Meyer-Schuster rearrangement that was catalyzed by gold (III) chloride, $AuCl_3$. The $AuCl_3$ emerged as the preferred choice of catalyst since late transition metal Lewis acids have high affinity for acetylenic π-bonds. The alkynophilicity of the gold catalyst proved to be advantageous to improve the Meyer-Schuster rearrangement reaction. Therefore, sterically encumbered ketones such as **51** were converted to propargyl alcohols upon the nucleophilc addition of acteylenes **52** followed by a Meyer-Schuster rearrangement to produce α,β-unsaturated ester carbonyl compounds **53**. Selected examples of this reaction are illustrated in Table 3.

Subjecting a sterically hindered and symmetric ketone such as benzophenone **54** to this process produced the desired trisubstituted olefin **55** in excellent yield (Table 3, Entry 1). Whereas the asymmetrical acyclic ketone **56** afforded the α,β-unsaturated ester carbonyl compound **57** in 99% yield as a 1.3:1 mixture of *E* and *Z* isomers (Entry 2). Finally, the cyclic ketone **58** generated the corresponding trisubstituted olefin **59** in moderate yield with a 2:1 preference for the *E* isomer over the *Z* isomer.

Table 3. Sterically encumbered ketones synthesize α,β-unsaturated ester carbonyl compounds via a Meyer-Schuster rearrangement[11]



51 **52** **53**

Entry	Substrate	Product	Yield (%)	E:Z ratio
1	 **54**	 **55**	91	-
2	 **56**	 **57**	99	57:33
3	 **58**	 **59**	68	66:33

Although the Meyer-Schuster rearrangement has a broad scope to utilize sterically encumbered ketones in the synthesis of trisubstituted olefins containing carbonyl functionalities, it requires high catalyst loading (20 mol %) to achieve efficient olefin conversions. Additionally the results obtained in Table 3 shows the poor stereoselectivty associated with Meyer-Schuster rearrangement.

Both the Wittig and Horner-Wadsworth-Emmons reactions remain the most powerful methods to synthesize trisubstituted olefins. However, their inability to control the stereochemistry of the olefins led to the development of modified Wittig and Horner-Wadsworth-Emmons reaction by Corey, Still, and Dudley. The latter reactions lacked the ability to incorporate the desired stereochemistry of the trisubstituted olefin with various functionalities. Thus, new methods have been developed to tackle the stereoselective synthesis of trisubstituted olefins. In the next chapter we will explore the synthesis of trisubstituted olefins by modifying olefin templates.

1.3 Modification to existing Olefin Templates

Modifying an existing olefin template built with stereochemical information is an alternative to the olefination of carbonyls to synthesize stereoselective trisubstituted olefins. Construction of these olefin templates with pre-included stereochemistry is a difficult challenge in organic synthesis. Hence, the types of templates that can be synthesized are limited which diminishes the scope of this method to make olefins.

Olefin templates are often employed in cross-coupling reactions such as the Suzuki-Miyaura[12], the Sonogashira[13], and the Stille[14] reactions to synthesize trisubstituted olefins with various functional groups. The Suzuki-Miyaura cross-coupling reaction preactivates an alkyl, alkenyl, or aryl group with boronic acid or trifluoroborate, or 9-BBN as the nucleophile. The Stille reaction involves the prefunctionalization of an alkynyl, vinyl, aryl, or alkyl group with a stannane moiety. A drawback with Stille reaction is the toxicity of the stannane compound. The Sonogashira reaction employs a terminal alkyne which is deprotonated to form an alkynyl copper species that is involved in the cross-coupling reaction. In all three cross-coupling reactions, aryl or vinyl halides or sulfonates are used as the electrophilic coupling partner and the reaction is catalyzed by the presence of palladium.

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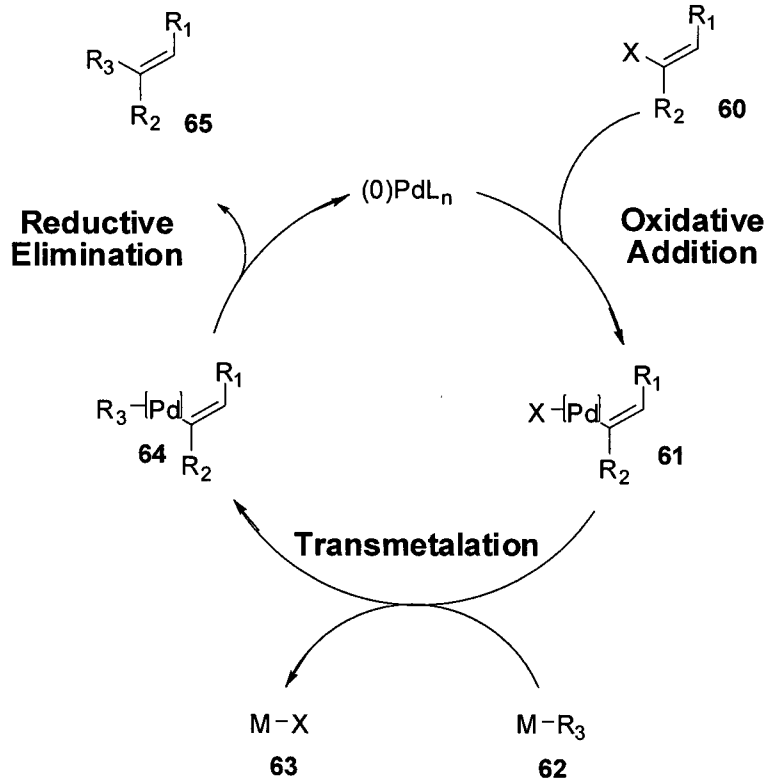
[12] (a) Suzuki, A.; *J. Organometallic Chem.* **1999**, 576, 147. (b) Miyaura, N.; Suzuki, A.; *Chem. Rev.* **1995**, 95, 2457.

[13] Chinchilla, R.; Najera, C.; *Chem Rev.* **2007,** 107, 874.

[14] Duncton, M. A. J.; Pattenden, G. J.; *J. Chem. Soc. Perkin Trans I.* **1999**, 1235.

A general mechanism for the synthesis of trisubstituted olefins via a palladium catalyzed cross-coupling reaction is shown in scheme 7. Palladium undergoes oxidative insertion into the C-X bond of the vinyl halide **60** to form vinyl palladium halide intermediate **61.** Transmetalation allows the transfer of the carbon nucleophile **62** bond to the metal (boron, tin, copper) to form the second vinyl palladium intermediate **64** and metal halide **63**. Reductive elimination generates the desired tristubtituted olefin **65** and regenerates the palladium catalyst to repeat the catalytic cycle.

Scheme 7. General mechanism for the palladium catalyzed cross-coupling reaction



Recently, Steinhuebel and coworkers[15] demonstrated the synthesis of trisubstituted olefins via palladium catalyzed Suzuki-Miyaura, Sonagashira, and Stille cross-coupling reactions using enol tosylates as the effective electrophilic coupling partner. The (*E*)- or (*Z*)-enol tosylates were easily prepared in high isomeric purity by the enolization of the corresponding ketone followed by treatment with Ts_2O. The cross coupling reaction between the (*Z*)-enol tosylate **66** and the respective nucleophilic coupling partner **67** generated the desired trisubstituted olefin **68** as single isomers. Selective examples are shown in Table 4.

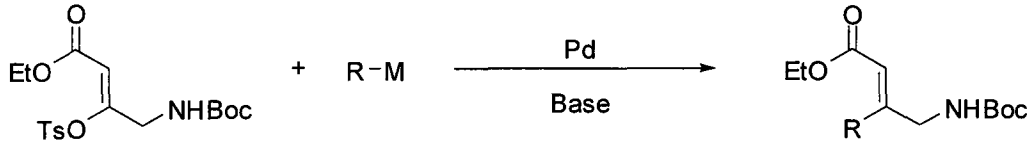
The trans-vinyl boronic acid **69** underwent effective Suzuki-Miyaura cross-coupling with enol tosylate **66** to yield the corresponding trisubstituted α,β-unsaturated ester **70** in good yield (Table 4, Entry 1). Replacing the boronic acid with a more robust, stable and nucleophilic trifluoroborate derivative such as the potassium phenyltrifluoroborate salt **71** gave good reactivity to produce the desired product **72** in a good yield comparable to that of the reaction with boronic acid (Entry 2). A Stille cross-coupling reaction of tributylphenyltin **73** with (*Z*)-enol tosylate **66** gave the desired ester **72** in 67% yield (Entry 3). Whereas the reaction of enol tosylate **66** with phenylacetylene **74** under Sonogashira cross-coupling reaction conditions provided the desired enyne **75** in 78% yield (Entry 4). Under all cross-coupling reactions, a single isomer olefin product was observed.

Palladium catalyzed cross-coupling reactions are efficient methods to synthesize stereoselective trisubstituted olefins and as evident from the examples provided in

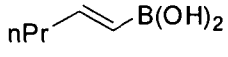
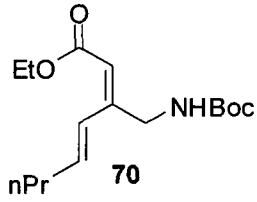
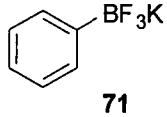
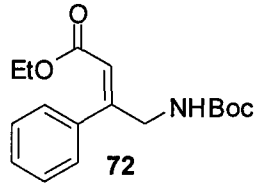
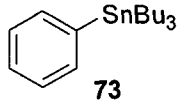
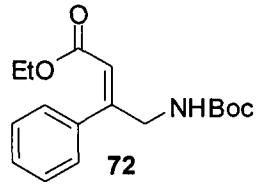
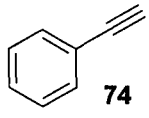
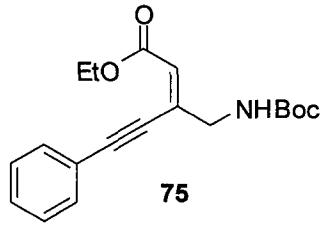
[15] Steinhuebel, D.; Baxter, J. M.; Palucki, M.; Davies, I. W.; *J. Org. Chem.* **2005**, 70, 10124.

Table 4 by Steinhuebel and coworkers. One difficulty in synthesizing the olefin templates was that they could be obtained as *E* and *Z* isomers. As a result the control over the stereoselectivity of the trisubstituted olefins remained unresolved.

Table 4. Synthesis of Trisubstituted Olefin via Pd-catalyzed cross-coupling reactions[15]

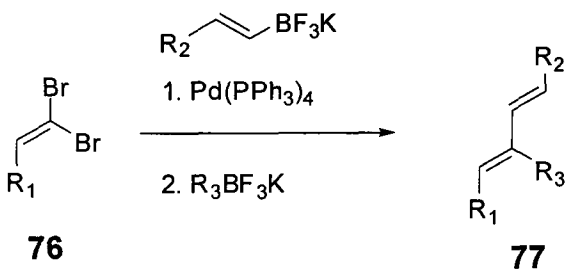


66 **67** **68**

Entry	R–M	Product	Yield (%)
1	 **69**	 **70**	81
2	 **71**	 **72**	81
3	 **73**	 **72**	67
4	 **74**	 **75**	78

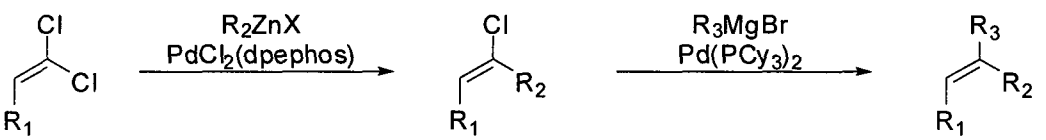
Scheme 8. Synthesis of trisubstituted olefins from 1,1-dihalogenated alkene templates

(a) Molander approach



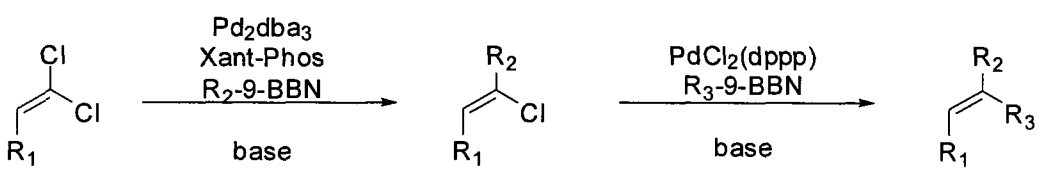
76 **77**

(b) Negishi approach



78 **79** **80**

(c) Roulland approach

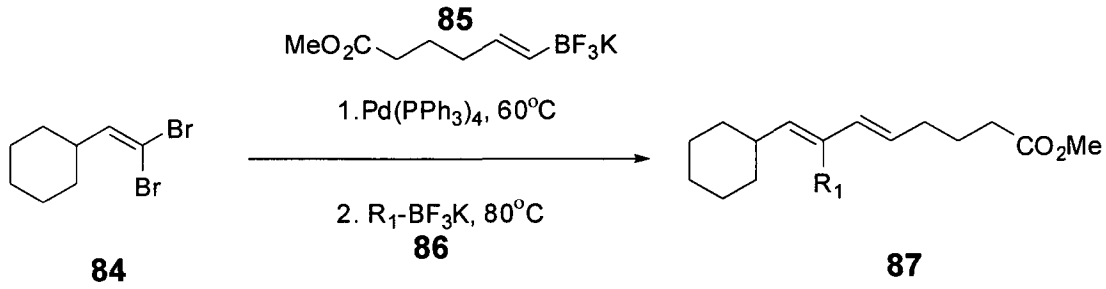


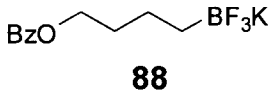
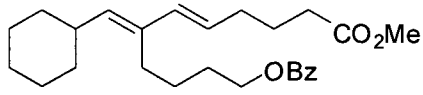
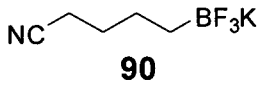
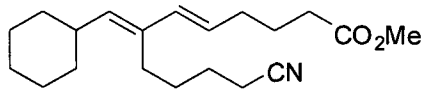
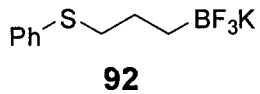
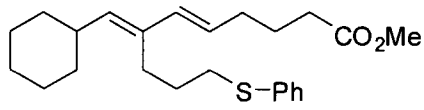
81 **82** **83**

In order to eliminate the problem of stereoselectivity in the synthesis of trisubstituted olefins, 1,1 and 1,2 dihalogenated species were developed and used as templates to synthesize olefins via cross-coupling reactions. First we will evaluate the

recent synthesis of trisubstituted olefins from 1,1-dihalogenated alkene templates (Scheme 8).

Table 5. Synthesis of stereoselective trisubstituted olefins from 1,1-dibromoalkenes[16]



Entry	R_1-BF_3K	Product	Yield (%)
1	 **88**	 **89**	90
2	 **90**	 **91**	89
3	 **92**	 **93**	90

Molander[16] has recently reported a successful one pot synthesis of single isomer trisubstituted olefins. This is achieved by reacting 1,1-dibromoalkene **84** with a variety of alkenyl and alkyltrifluoroborates in a stepwise addition in the presence of $Pd(PPh_3)_4$.

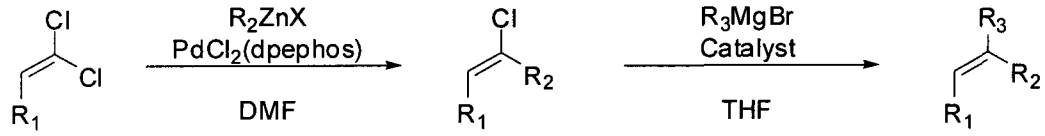
[16] Molander, G. A.; Yokoyama, Y.; *J. Org. Chem.* **2006**, 71, 2493.

In order to ensure the correct geometry of the product, the reactivity of the bromine located at the trans position was controlled by adding vinyl trifluoroborate **85** at 60°C. While the second coupling of alkyl trifluoroborate **86** was preceded at much higher temperature, 80°C, to obtain the desired product. In each case the trisubstituted olefins **89**, **91** and **93** were observed as single isomer in excellent yield (Table 5).

Negishi[17] developed the palladium catalyzed stepwise alkylation of 1,1-dichloroalkenes **78** to synthesize trisubstituted olefins as single isomers. The first alkylation used an organozinc reagent to generate monochlorinated product **79** which was followed by the treatment of Grignard reagent to afford the disubstituted product **80** (Table 6). The double addition products were observed in all cases in the first alkylation step. The use of bidentate ligands such as DPPP and DPEPHOS successfully suppressed the formation of the side product. An additive such as N-methylimidazole (NMI) was also required to eliminate the observed double addition product in the first step. Under Negishi's reaction conditions only 1,1-dichloroalkenes produced the trisubstituted olefin with stereoselectivity while with the 1,1,-dibromoalkenes the selectivity was diminished. In the case of 1,1-dibromoalkenes template the first alkylation was stereoselective while the addition of Grignard reagents gave ratios of *E* and *Z* isomers.

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

Table 6. Synthesis of stereoselective trisubstituted olefins from 1,1-dichloroalkenes[17]



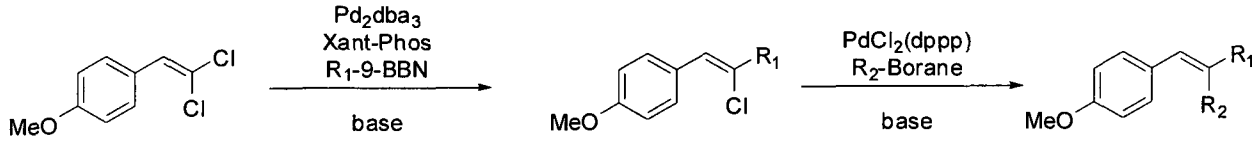
78 **79** **80**

Entry	R_1	R_2	Catalyst	R_3	Overall Yield (%)
1	Ph	*n*-oct	$NiCl_2(dppp)$	Me	88
2	*n*-hex	*n*-oct	$Pd(tBu_3P)_2$	Me	76
3	$TBSOCH(Me)CH_2$	Me	$Pd(Cy_3P)_2$	*n*-oct	81
4	$TBSOCH(Me)CH_2$	Me	$Pd(Cy_3P)_2$	Ph	75
5	$TBSOCH(Me)CH_2$	Me	$Pd(Cy_3P)_2$	4-F-Ph	75

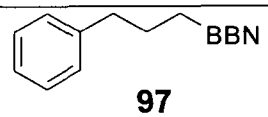
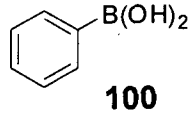
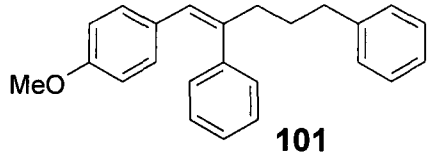
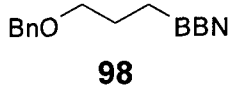
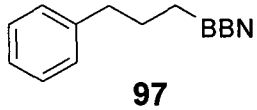
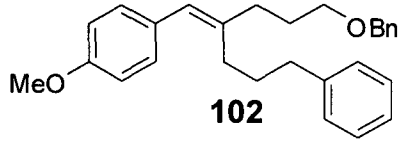
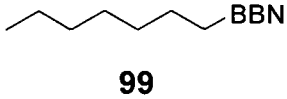
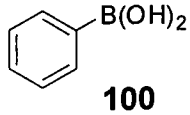
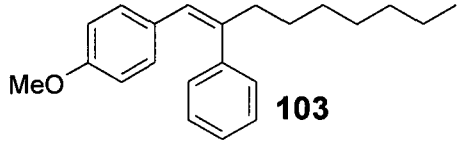
Roulland[18] and coworkers built on the use of 1,1-dichloroalkenes to synthesize stereoselective trisubstituted olefins with 9-alkyl-9-BBN reagents. The first alkylation was selectively carried out at the chlorine trans to the substituent by using a bidendate ligand with large bite angle such as XantPhos. The use of XantPhos also suppressed the formation of the bisubstituted product and produced the *Z*-chloroalkenes in excellent yields. The second alkylation was achieved with a $PdCl_2(dppp)$ catalyst to generate the trisubstituted olefins in good yields as single isomers (Table 7).

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

Table 7. Palladium catalyzed cross-coupling to 1,1-dichloroalkenes[18]



94 **95** **96**

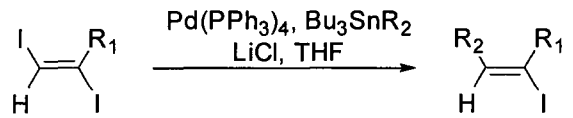
Entry	R_1-9-BBN	R_2-Borane	Product	Yield (%)
1	 **97**	 **100**	 **101**	76
2	 **98**	 **97**	 **102**	76
3	 **99**	 **100**	 **103**	71

Similarly the use of 1,2-dihalogenated olefin templates were exploited by Hénaff and Whiting[19]. They were very successful in producing both the *E* and *Z* isomers of their diiodoalkene olefin templates. Treatment of alkyne with ICl and NaI produced the thermodynamic (*E*)-diiodoalkene at room temperature. Yet the treatment of alkyne with ICl and Et_4NI produced the (*Z*)-diiodoalkene at -78°C. The use of (*E*)-diiodoalkenes **104** mono-coupled selectively at the less hindered iodine atom under Stille reaction

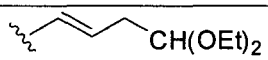
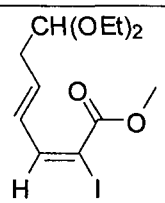
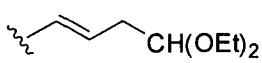
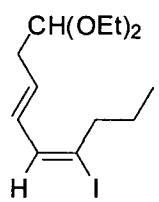
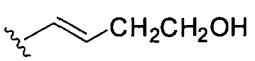
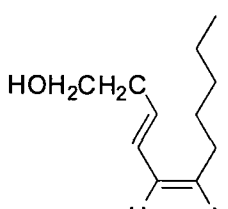
[19] Hénaff, N.; Whiting, A.; *J. Chem. Soc. Perkin Trans. I.* **2000**, 395.

conditions to produce the monoiodide products **105** in moderate yields (Table 8). Disappointingly the group did not report a subsequent cross coupling to the iodine at the α-position. However, they observed a clean double addition to both iodides to generate trisubstituted trienes in 50% yield under similar Stille reaction conditions.

Table 8. Synthesis of trisubstituted olefins from 1,2-dihalogenated olefin templates[19]

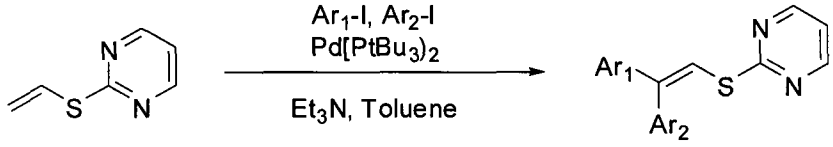


104 **105**

Entry	R_1	R_2	Product	Yield (%)
1	CO_2Me	 **106**	 **108**	61
2	C_3H_7	 **106**	 **109**	46
3	C_5H_{11}	 **107**	 **110**	32

Recently, Itami and Yoshida[20] reported a new olefin template that was unique and different from all the classical olefin templates discussed previously. This olefin template contained an ethylene derivative substituted by a directing heteroatom such as sulfur which was further added to a 2-pyrimidyl group to enhance the reactivity of the reaction. The π-component installed at the β-C-H bond of the vinyl 2-pyrimidyl sulfide **111** underwent Mizoroki-Heck reaction catalyzed by Pd using P*t*Bu$_3$ as a ligand. They were successful in introducing two different aryl groups at the β-position of the vinyl sulphide to synthesize trisubstituted olefins **112** as single isomers in one pot in excellent yields (Scheme 9).

Scheme 9. Vinyl 2-pyrimidyl sulfide as olefin template to synthesize trisubstituted olefins via Mizoroki-Heck reaction



111 **112** **85-95%**

In conclusion, the stereoselective synthesis of trisubstituted olefins via the modification of an existing template built in with a specific stereochemistry is a powerful method of generating trisubstituted olefins compared to the olefination of carbonyls. However the challenge in utilizing the olefin template is the synthesis and isolation of the template as a single isomer. Once synthesized the template to undergoes various

[20] Itami, K.; Mineno, M.; Muraoka, N.; Yoshida, J.; *J. Am. Chem. Soc.* **2004**, 126, 11778.

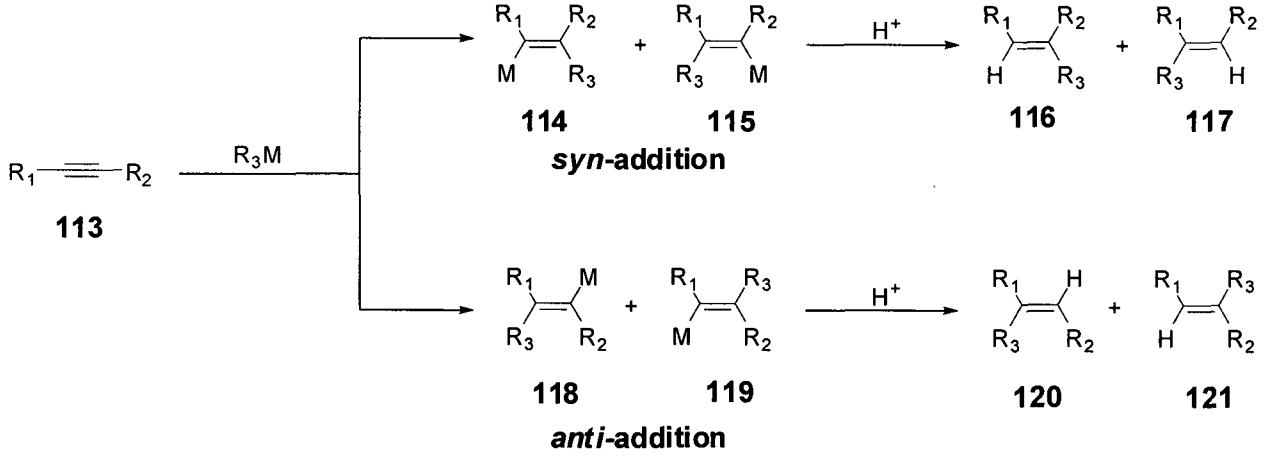
cross-coupling reactions to introduce a variety of functionalities around the trisubstituted olefins. Another way to control the stereochemistry of these processes is by employing 1,1- or 1, 2-dihalogenated olefin templates. One of the problems associated with 1,1-dihalogenated templates is the preference of one halogen over the other. Molander, Negishi, and Roulland have explored different conditions to ensure stepwise additions in one pot to produce trisubstituted olefins in excellent yields. Subsequently, the use of 1,2-dihalogenated olefin templates reported by Hénaff and Whiting produced mono- and biscoupled products under Stille reaction conditions. This group was unable to perform stepwise additions to introduce different substituents around the double bond.

Overall the synthesis of olefin templates remains a challenge in organic synthesis. Our group has succeeded in synthesizing an olefin template containing two different halogens which can efficiently undergo various cross-coupling reactions to produce a variety of trisubstituted olefins. This will be elaborated in chapter 2.

1.4 Carbometalation of Alkynes

The carbometaltion of alkynes is a widely-used tool in organic synthesis. This strategy involves the addition of organometallic compounds across triple bonds, controlling both regio- and chemoselectivity, to synthesize a variety of products including trisubstituted olefins[21]. One of the challenges associated with this method is achieving good regioselectivity. Depending on the nature of the alkyne substrate, the addition of the organometallic reagent can occur via either *syn* or *anti* pathways. These two possibilities lead to the potential production of four different regioisomers (Scheme 10). Regioselectivity control can be obtained by using the electronic effects of various substituents, by chelation control, or by employing steric effects.

Scheme 10. Two different routes available to product formation in carbometalation of alkynes

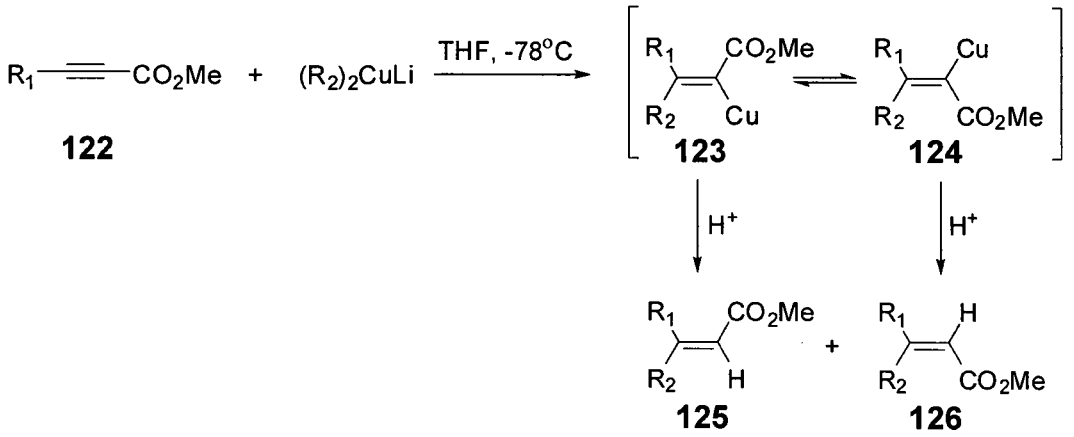


[21] Normant, J. F.; Alexakis, A.; *Synthesis.* **1981**, 841.

There are many examples of the carbometalation of alkynes providing trisubstituted olefins employing various transition metals; only, selected examples will be explored herein.

In 1969, Corey and Katzenellenbogen[22] illustrated the synthesis of trisubstituted olefins **125** and **126** via the conjugate addition of dialkylcopper-lithium reagents to α,β-acetylenic esters **122**. The regioselectivity of the reaction was controlled by the temperature and the solvent employed in the system. When the reaction was performed in THF at -78°C the *syn* product **125** was formed favourably in a 99.8:0.2 *syn*:*anti* selectivity with 95% isolated yield. However, in a different solvent and at elevated temperature the *anti* product **126** was favoured due to the equilibration of vinylic cuprates **123** and **124**. Thus quenching the reaction with acid at -78°C was done to avoid the isomerization and the desired trisubstituted olefin **125** was produced in high isomeric ratios (Scheme 11).

Scheme 11. Carbocupration of alkynes to produce trisubstituted olefins



[22] Corey, E. J.; Katzenellenbogen, J. A.; *J. Am. Chem. Soc.* **1969**, 91, 1851.

Siddall and coworkers[23] developed similar chemistry while trying to synthesize an insect hormone. Subjecting an alkynyl ester with a dimethylcopper-lithium reagent that underwent conjugate addition to add a methyl group at the β-position of the ester and form the allene intermediate, which was quenched by water to produce the (*E*)-trisubstituted olefin at an extremely low temperature and shorter reaction time (-100°C for two minutes).

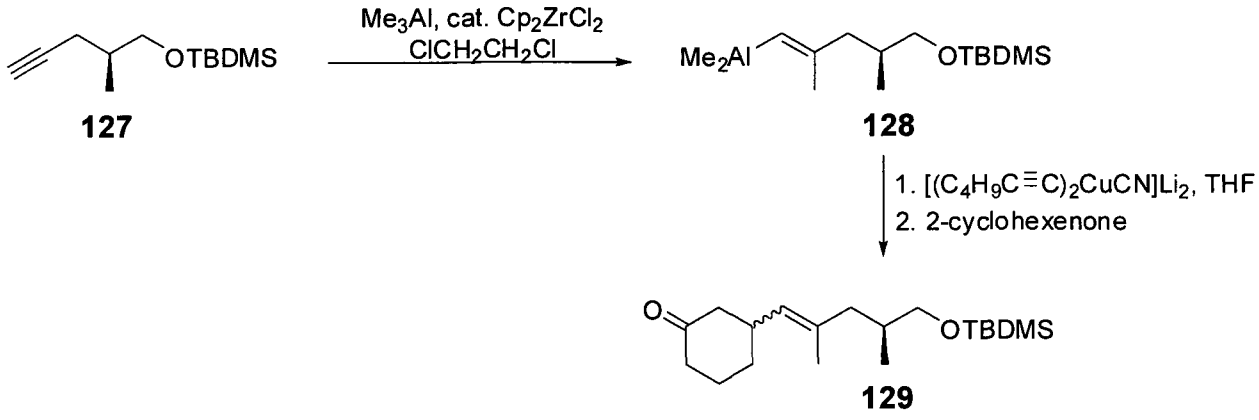
Wipf and coworkers[24] reported an improved synthetic strategy for the *in situ* preparation of vinyl cuprates from alkynes which were then used to prepare trisubstituted olefins. The first step involved the preparation of vinyl alanes **128** via the carboalumination of alkynes **127** using three equivalents of trimethylaluminum and a catalytic amount of Cp_2ZrCl_2. Treatment of the crude vinyl alanes with bis-alkynyl-copper complex,[$(C_4H_9C{\equiv}C)_2CuCN]Li_2$ allowed the transmetalation and the formation of the cuprate. The addition of 2-cyclohexenone led to the formation of trisubstituted olefin such as **129** in 92% yield. Both the transmetalation and 1,4-conjugate addition of the alkenyl substituent occurred rapidly at -23°C. This process had a broad tolerance for functional groups such as alcohols, silylethers, sulfides, halogens, alkenes, and arenes (Scheme 12).

---

[23] Siddall, J. B.; Biskup, M.; Fried, J. H.; *J. Am. Chem. Soc.* **1969**, 91, 1853.

[24] Wipf, P.; Smitrovich, J. H.; Moon, C.-W.; *J. Org. Chem.* **1992**, 57, 3178.

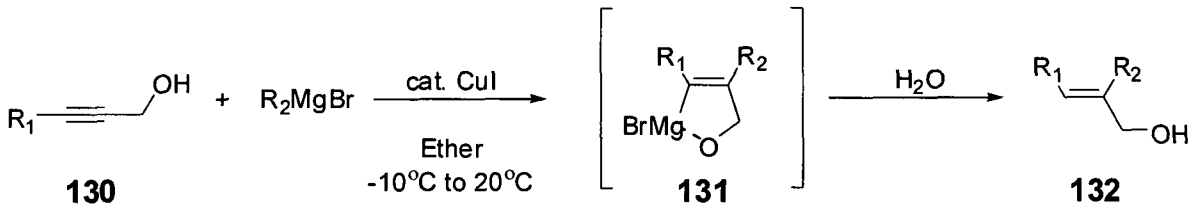
Scheme 12. In situ preparation of trisubstituted olefins via vinyl cuprates of alkynes



Negishi[25] showed that Grignard reagents could be employed to add alkyl groups across the triple bond of propargyl alcohols to synthesize trisubstituted olefins regio- and stereoselectively. The addition of the alkyl group could occur via a *syn-* or *anti* pathway: however, the addition was exclusively controlled by the substituents on the alcoholic carbon. The alcohol group had the ability to chelate with the magnesium metal leading to the intermediate **131** and thereby favouring *anti* addition of the alkyl group to the alkyne. If the alcohol carbon was substituted as in the case of secondary or tertiary alcohols, the steric effect interfered with the chelation between the alcohol oxygen and the magnesium metal: hence, mixtures of isomers were produced. As a result, a primary propargyl alchohol such as **130** added allylmagnesium bromide in an *anti* fashion in the presence of catalytic amount of CuI to generate the exocyclic olefin **132** as a single isomer (Scheme 13).

[25] Negishi, E.-i.; Zhang, Y.; Cederbaum, F. E.; Webb, M. B.; *J. Org. Chem.* **1986**, 51, 4080.

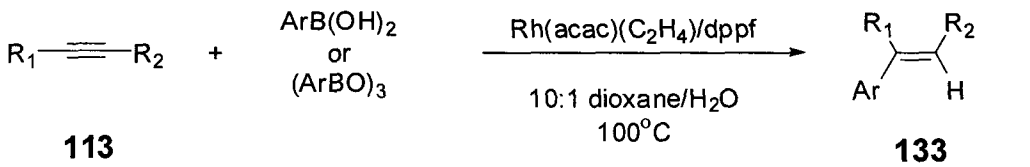
Scheme 13. Carbometalation of propargyl alcohols with Grignard reagents



130 **131** **132**

In 2001, Hayashi[26] developed a bisphosphine-rhodium catalyzed hydroarylation of alkynes in aqueous solvent to synthesize single isomer trisubstituted olefins. This process allowed the utilization of symmetric and non-symmetrical alkynes with arylboronic acids or boroxines. Non-symmetrical alkynes carried a directing group in the form of an ester or phosphonate. The alkyne **113** reacted with arylboronic acid with high syn-selectivity with respect to the aryl group and the hydrogen to produce (*E*)-trisubstituted olefin such as **133** in good yields (Scheme 14).

Scheme 14.Rhodium-catalyzed hydroarylation of alkynes produce trisubstituted olefins



113

133
31-95% yield

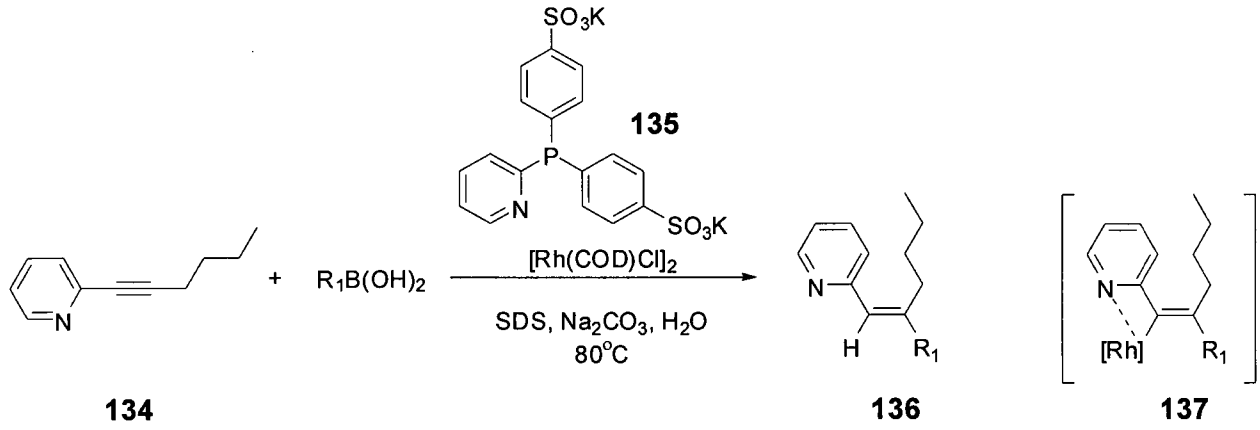
R_1 = Alkyl
R_2 = Alkyl, CO_2Me, $P(O)OEt_2$

[26] Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M.; *J. Am. Chem. Soc.* **2001**, 123, 9918.

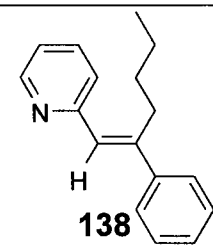
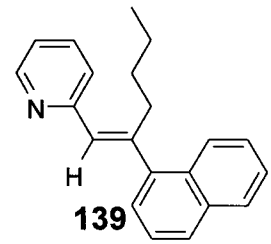
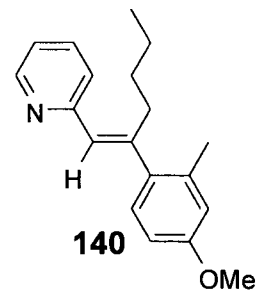
Later, Lautens and Yoshida[27] elaborated the rhodium-catalyzed hydroarylation of alkynes in water to produce trisubstituted olefins regiospecifically. In this reaction, the addition of arylboronic acids to alkynyl heteroaromatic compounds **134** successfully proceeded in the presence of a rhodium catalyst and pyridine-substituted-water soluble ligand such as **135**. Optimization of the base (Na_2CO_3) and the addition of a surfactant such as sodium dodecyl sulphate (SDS) was required at warm temperatures (Table 9). The high regioselectivity observed in each case was explained by intermediate **137** that presumably arose by chelation between the alkenylrhodium complex and pyridine substituent connected to the alkyne.

[27] Lautens, M.; Yoshida, M.; *Org. Lett.* **2002**, 4, 123.

Table 9. Rhodium catalyzed reactions of arylboronic acid to alkynyl pyridine[27]



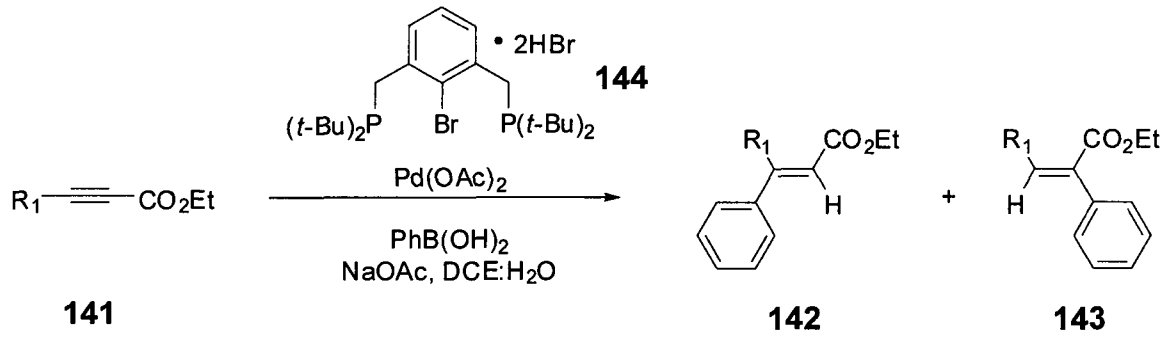
134 136 137

Entry	R_1	Product	Yield (%)
1	Ph	 **138**	51
2	1-Napthyl	 **139**	72
3	4-MeO-2-MePh	 **140**	83

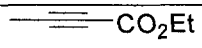
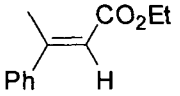
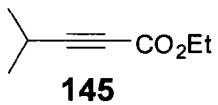
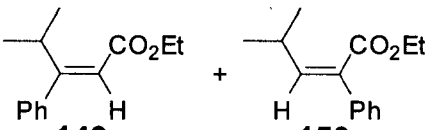
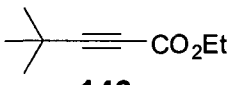
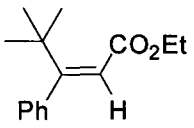
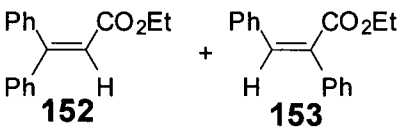
Oh and coworkers[28] illustrated a hydroarylation and hydroalkenylation of alkynyl esters that could be achieved via a palladium catalyzed Suzuki-Miyaura cross-coupling reaction. Treatment of alkynyl ester **141** and aryl boronic acid with a catalytic amount of $Pd(PPh_3)_4$ and stoichiometric amount of acetic acid afforded the products **142** and **143** in good yields, but with poor regioselectivity. The reaction proceeded with *syn* addition of the aryl group and the hydrogen across the triple bond. However, these reactions required higher temperatures (50°C). Later, the group improved the regioselectivity by employing bidendate phosphine ligand with an aromatic ring spacer such as **144** in combination with $Pd(OAc)_2$ in 1:1 ratio under basic conditions (10% NaOAc) in aqueous ethylene dichloride (DCE: H_2O 20:1). However, under these conditions only few trisubstituted olefins were observed as single isomers (Table 10, Entries 1 and 3) while others existed as mixtures of isomers (Entries 2 and 4).

[28] (a) Oh, C. H.; Jung, H. H.; Kim, H. S.; Kim, N.; *Angew. Chem. Int. Ed.* **2003**, 42, 805. (b) Gupta, A. K.; Kim, K. S.; Oh, C. H.; *Syn. Lett.* **2005**, 3, 457.

Table 10.Suzuki-Miyaura cross-coupling of various alkynyl esters with phenylboronic acid[28]



141 142 143

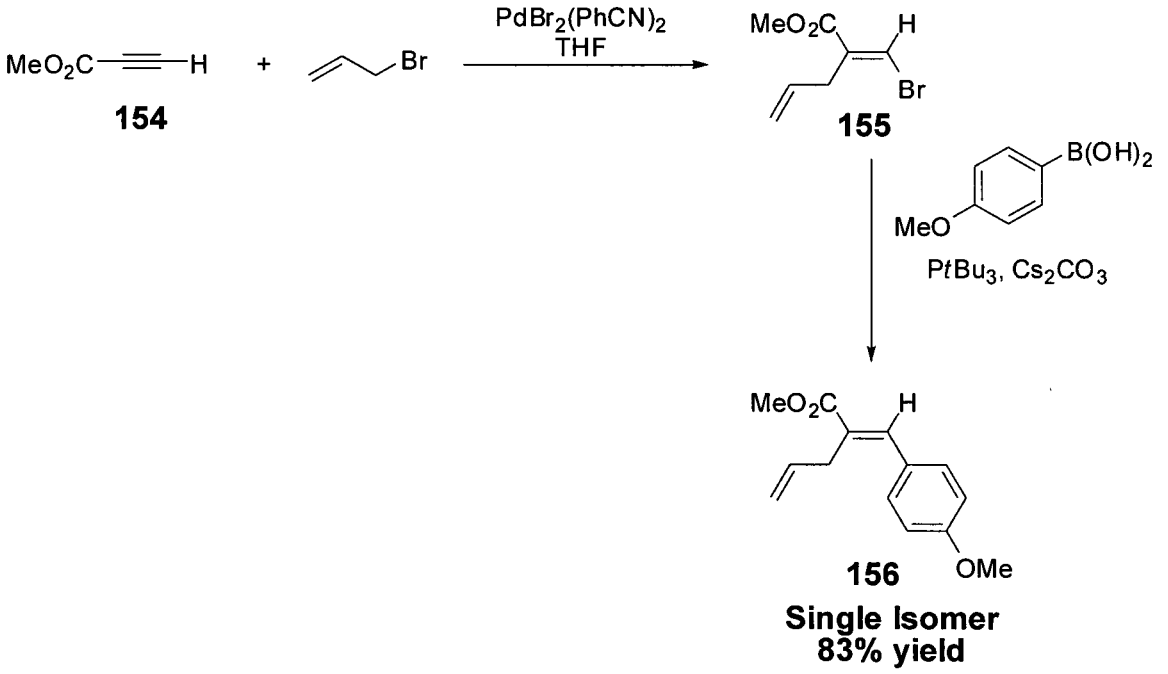
Entry	Substrate	Product	Yield (%)	E:Z raito
1	 **144**	 **148**	89	-
2	 **145**	 **149** + **150**	76	85:15
3	 **146**	 **151**	79	-
4	 **147**	 **152** + **153**	92	83:17

Thadani and Rawal[29] developed a one pot synthesis to produce trisubstituted olefins via haloallylation followed by a Suzuki cross coupling reaction sequence using

[29] Thadani, A. N.; Rawal, V. H.; *Org. Lett.* **2002**, 4, 4317.

the same palladium catalyst. An alkyne such as **154** was exposed to an allylic bromide in the presence of Pd(II) catalyst [$PdBr_2(PhCN)_2$] to generate the haloallylation product **155** which was used *in situ* to perform a Suzuki cross-coupling reaction with an arylboronic acid affording the desired trisubstituted olefin **156** in 83% yield. An additive such tert-butylphosphine ($PtBu_3$) was employed in the Suzuki coupling step to convert the initial catalyst $PdBr_2(PhCN)_2$ to $PdBr_2(PtBu_3)_2$, which presumably reduced *in situ* to a catalytically active Pd(0) species. (Scheme 15).

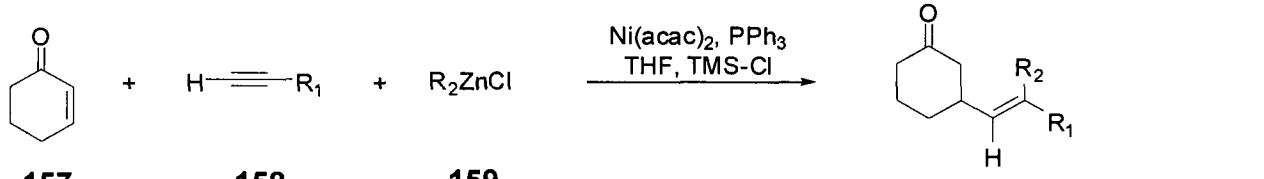
Scheme 15. Trisubstituted olefins via one-pot tandem bromoallylation/Suzuki cross-coupling of alkynes



Nickel catalyzed carbometalations of alkynes have advantages compared to those mediated by palladium. Nickel has a lower cost, is air stable and shows improved

reactivity. In 1995, Ikeda and Sato[30] developed a new nickel-catalyzed tandem coupling of cyclic enones and mono-substituted alkynes using an organozinc reagent to synthesize stereoselective trisubstituted olefins. A triphenylphosphine ligand was essential in the catalytic system to obtain the desired coupling products. The regioselectivity was dependant on the enone and the alkyne that was employed. Though the reaction was efficient it had somewhat limited scope (Scheme 16).

Scheme 16. Nickel-catalyzed tandem coupling of three-component



157 **158** **159**

160 R1 = n-hexyl, R2 = Me (89%)
161 R1 = TMS, R2 = Me (69%)

The carbometalation of alkynes is a widely-used tool to synthesize stereodefined trisubstituted olefins. It is a powerful method compared to the modification of existing olefin templates and is an alternative to the olefination of carbonyls. There are many explored metal catalyzed carbometalations of alkynes to introduce aryl and alkenyl groups. Our group has developed a new method to introduce alkyl groups to alkynes *via* a palladium catalyzed Suzuki cross-coupling reaction which will be focused on Chapter 4.

[30] (a) Ikeda, S.-i.; Sato, Y.; *J. Am. Chem. Soc.* **1994**, 116, 5975. (b) Ikeda, S.-i; Yamamoto, H.; Kondo, K.; Sato, Y.; *Organometallics*. **1995**, 14, 5015.

Chapter 2

2.1 Results and Discussion

Synthesis of Single Isomer of Trisubstituted Olefin from β-Chloro-α-Iodo-α,β-Unsaturated Ester

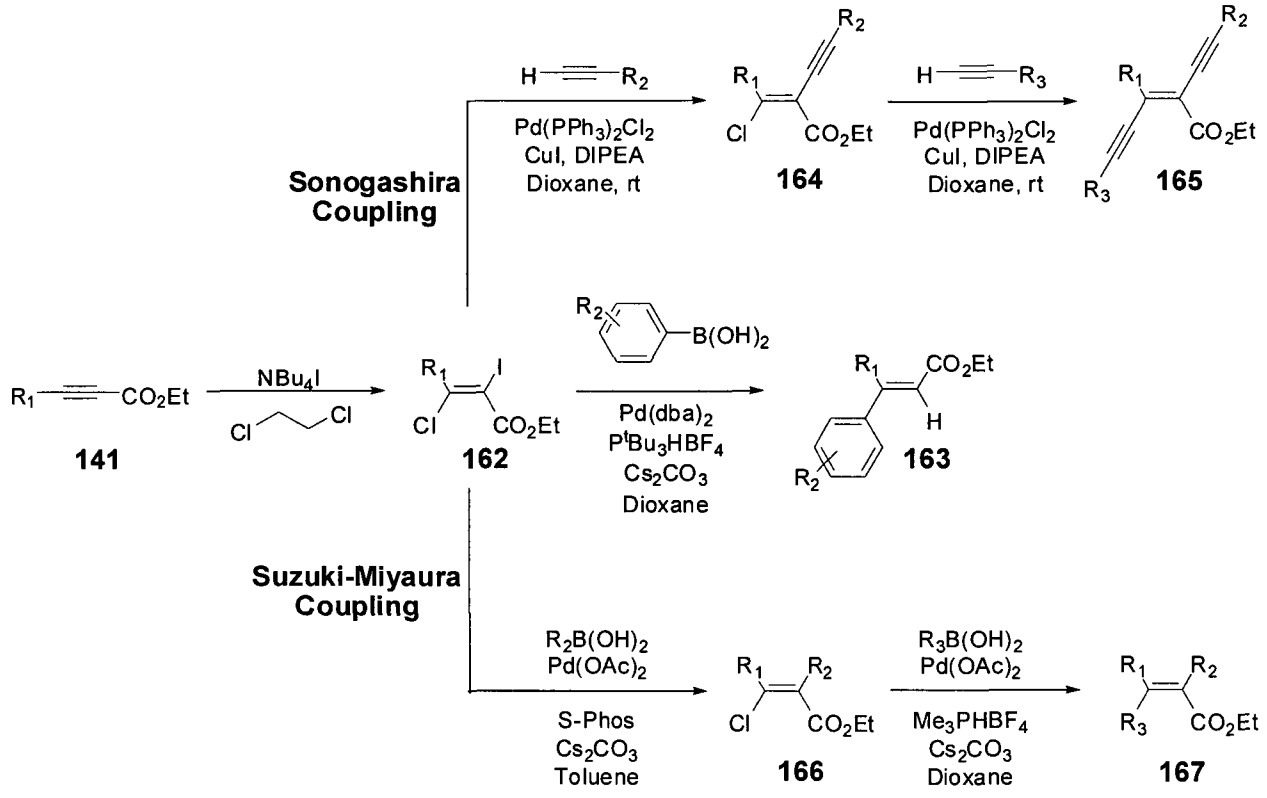
2.1.1 Previous Work

The main focus of research of the Ogilvie group for the past few years has been the synthesis of trisubstituted olefins. The path toward trisubstituted olefins began with the preparation of β-Chloro-α-Iodo-α,β-Unsaturated Ester[31] olefin template. This olefin template was very distinct from other templates employed in a typical cross coupling reaction. The key feature was the two different halogens that are present that are susceptible to undergo both Suzuki-Miyaura[32] and Sonogashira[33] cross coupling reactions.

[31] Ho, M. L.; Flynn, A. B.; Ogilvie, W. W. *J. Org. Chem.* **2007**, 72, 977.

[32] Simard-Mercier, J.; Jiang, J. L.; Ho, M. L.; Flynn, A. B.; Ogilvie, W.W.; *J. Org. Chem.* **2008**, 73, 5899.
[33] Lemay, A. B.; Vulic, K. S.; Ogilvie, W. W.; *J. Org. Chem.* **2006**, 71, 3615.

Scheme 17. Previous synthesis of Trisubstituted Olefins in the Ogilvie Group



An alkynyl ester **141** was subjected to tetrabutylammonium iodide in refluxing DCE to produce a single isomer β-Chloro-α-Iodo-α,β-Unsaturated Ester, **162**. The following unsaturated ester was employed in Suzuki-Miyaura cross coupling reactions with arylboronic acids to form trisubstituted olefins such as **163**. Further, it was illustrated that both tri- and tetrasubstituted[34] olefins could be synthesized via either Sonogashira cross coupling to form **164** and **165** or Suzuki-Miyaura reactions to form **166** and **167**. Overall all the possibilities have been explored in our lab except the alkyl Suzuki-Miyaura cross coupling reactions to produce trisubstituted olefins with β-Chloro-

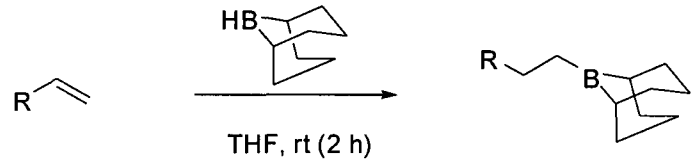
[34] Simard-Mercier, J.; Flynn, A. B.; Ogilvie, W.W.; *Tetrahedron*. **2008**, 64, 5472.

α-Iodo-α,β-unsaturated ester olefin template (Scheme 17). Olefins bearing alkyl substituents are very rarely synthesized though they play an important moiety in medicinal and natural products.

2.1.2 Discovery of the Reaction

The initial study aimed at developing an alkyl-Suzuki coupling reaction of our olefin template was performed as part of a Ph.D thesis by Dr. A. Flynn[35]. At first, the 9-alkyl-9-BBN reagents **169** were generated via the hydroboration of terminal alkenes **168** with 9-BBN (Scheme 18) which was immediately used in the cross coupling with β-Chloro-α-Iodo-α,β-unsaturated ester olefin template.

Scheme 18. Preparation of 9-alkyl-9-BBN reagents at room temperature



168 **169**

R = $CH_3(CH_2)_5$, $BzO(CH_2)_3$, $BnO(CH_2)_3$, $TIPSO(CH_2)_3$, $BzO(CH_2)_2CH_3$

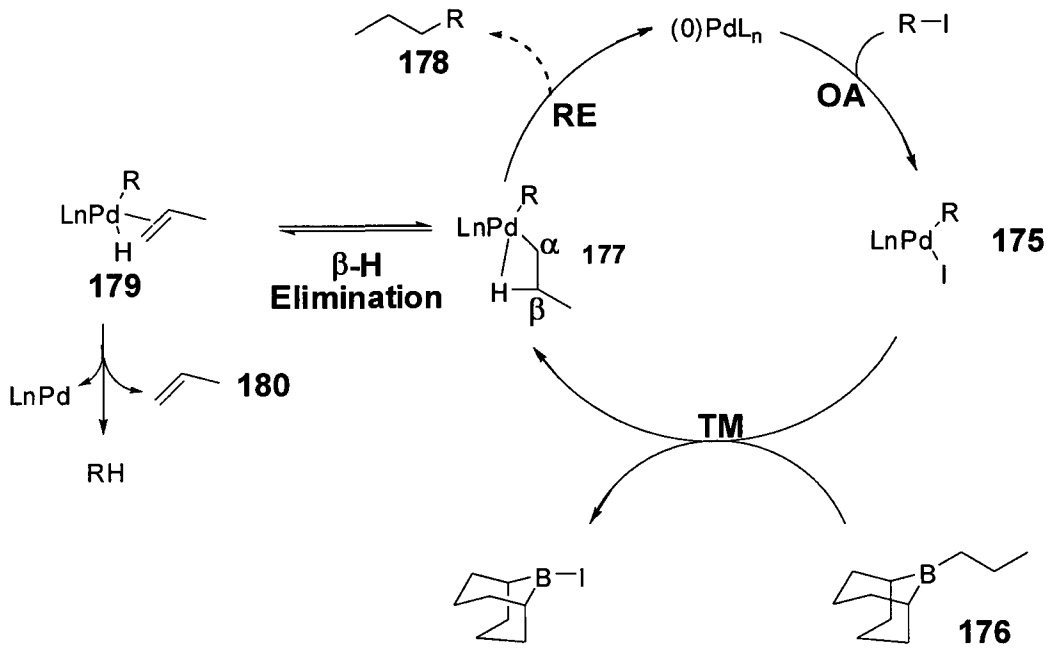
The alkyl-Suzuki coupling reaction between olefin template **170** and 9-octyl-9-BBN was first attempted using $PdCl_2$(dppf) as the catalyst and K_3PO_4 as the base in THF at room temperature. These conditions returned primarily the starting material **170**, however GC-MS analysis suggested the formation of compound **172** (Entry 1, Table 11). The possible explanation for the presence of product **172** would implicate β-

[35] Flynn, A. B. Ph.D. Thesis, **2007**.

hydride elimination at the α-position of the borane reagent. The β-H elimination would be in competition with reductive elimination in a typical alkyl-Suzuki coupling.

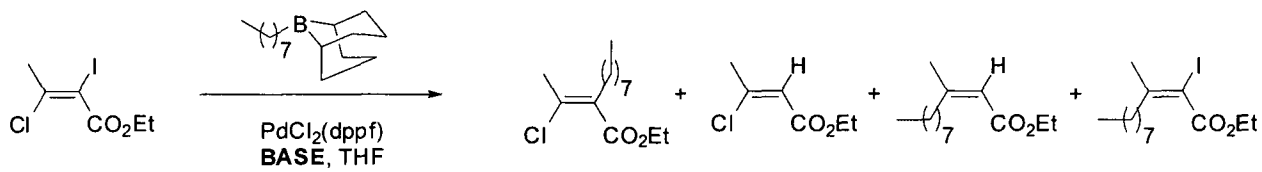
The alkyl-Suzuki reaction often suffers from decreased yields or unwanted side products due to β-hydride elimination (Scheme 19). Following the transmetalation step (TM), if the palladium possesses an empty coordination site, the β-C-H bond that is *cis* to the metal will occupy that vacant site as in **177**. This association readily promotes β-H elimination. This β-hydride elimination from the original alkyl moiety leads to the formation of palladium hydride and an olefin such as **179**. Dissociation of the alkene **180** and reductive elimination of RH regenerates the palladium (0) catalyst. The β-hydride elimination process is in competition with the desired reductive elimination process that would give product **178**.

Scheme 19. β-H elimination is competitive with reductive elimination



In a continuation of the initial screening, heating the reaction under same condition produced a trace amount of the desired product **171** as evidenced by GC-MS (Entry 2, Table 11). However, it was very difficult to separate this compound from the unreacted starting material. Addition of H_2O to the reaction medium resulted also in the formation of a trace amount of **171** (Entry 3). Therefore, the base was replaced with $K_3PO_4 \cdot H_2O$ and the resulting mixture was refluxed over 48 h which resulted in the formation of product **173** in 27% yield (Entry 4). This product (**173**) was isolated as a mixture of isomers (4:1).

Table 11. Initial studies toward the development of an alkyl-Suzuki coupling reaction with an olefin template



170 | **171 Desired Product** | **172** | **173 Observed Product** | **174 Never Observed**

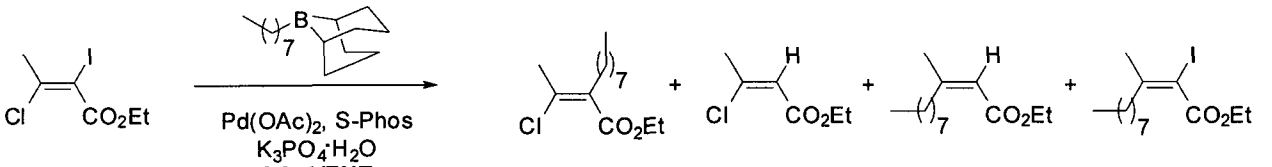
Entry	Base	Temp	Time	GC-MS Result
1	K_3PO_4	r.t.	3 h	**170**, trace **172**
2	K_3PO_4	reflux	3 h	trace **171**
3	K_3PO_4/H_2O (3M)[a]	reflux	3 h	trace **171**
4[c]	$K_3PO_4 \cdot H_2O$ (3M)[a]	reflux	48 h	27% **173**[b], trace **172**

[a] A 3M K_3PO_4 solution was prepared in H_2O and was sparged for 1 hour with N_2. The solution was added to the reaction mixture via syringe such that 3 equivalents of the base were employed. The 9-octyl-9-BBN solution was added last. [b] Obtained as a 4:1 mixture of isomers. [c] 3 equiv of 9-octyl-9-BBN were employed.

In an effort to eliminate the formation of product **173**, which arises from a side reaction β-hydride elimination, the DPPF ligand was replaced with S-Phos. This bulky and strongly electron donating ligand has been highly successful for many different cross-coupling reactions. The first reaction was performed with $Pd(OAc)_2$, and $K_3PO_4 \cdot H_2O$ in THF at reflux (Entry 1, Table 12). Surprisingly, instead of eliminating the side product, these reaction conditions increased the yield of **173** to 30% (2:1 mixture of isomers). At room temperature the yield increased to 38% for **173** (Entry 2).

Furthermore, employing DMF as the solvent at 85°C slightly improved the yield of **173** to 47% along with a trace amount of the stereoisomer (Entry 3).

Table 12. Analysis of S-Phos as a ligand for the alkyl-Suzuki reaction



170 | **171 Desired Product** | **172** | **173 Observed Product** | **174 Never Observed**

Entry	Solvent	Temp	Result (Z:E)
1	THF	reflux	30% **173** (2:1)
2	THF	r.t.	38% **173** (3:1)
3	DMF	85°C	47% **173** (13:1)

Dr. A. Flynn was unsuccessful in synthesizing the desired product **171**, which would have led to the formation of both tri and tetra-alkylsubstituted olefins; nonetheless, our lab was very ecstatic about the formation of product **173**. In this compound, an alkyl-suzuki reaction was observed at the β-position to produce a trisubstituted olefin which provided an exciting opportunity for new research. However, this product was difficult to separate from the non-polar substrate when 9-octyl-9-BBN was used as a coupling partner. Therefore, to begin the optimization study, the reaction of an alkyl reagent bearing a protected alcohol functionality was explored.

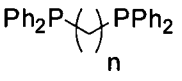
2.1.3 Optimizations

A new project was initiated with the goal to optimize the reaction conditions, maximize the yield and analyze the mechanism behind the formation of the trisubstituted olefin **173**. Initial studies toward the synthesis of trisubstituted olefins from β-Chloro-α-Iodo-α,β-unsaturated ester began with the aim to identify a suitable ligand for cross-coupling. The first experiment employed an unsaturated ester **170** with a polar 9-alkyl-9-BBN coupling partner **181** using $Pd(OAc)_2$ as the catalyst, $K_3PO_4 \cdot H_2O$ as the base and THF as the solvent at room temperature.

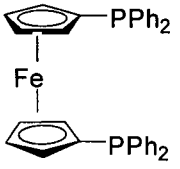
A variety of monodentate phosphine ligands (structures are shown in Figure 3) were screened (Table 13). A bulky and strongly electrondonating S-Phos ligand proved to be highly successful for our alkyl-suzuki cross-coupling reaction giving an 86% yield for the process (Entry 1). Similarly, the use of Davephos resulted in only a moderate yield of olefin **182** (60%, Entry 2). Employing larger alkyl-substituted ligands such as Cy_3P, $^tBu_2MeP$, and Et_3P worked quite well in the reaction (Entries 3-5). On the other hand, the use of smaller alkyl substituted ligands such as Me_3P suppressed the formation of **182** to 6% (Entry 6). Sterically hindered PPh_3 provided a slightly improved yield of 39% (Entry 7).

Among the bidentate phosphine ligands (structures are shown in Figure 3), Xantphos, Diphos (DPPE) and DPPB each gave a reasonable yield of product **182**, delivering 36, 31 and 21% respectively (Entries 8-9 and 11). The use of DPPF and DPPM provided very poor yields of the desired product (Entries 10 and 13). Finally, the use of DPPP as the ligand resulted in decomposition of the starting material **170** (Entry 12).

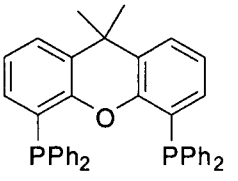
Figure 3. Structures of ligands used in ligand scan



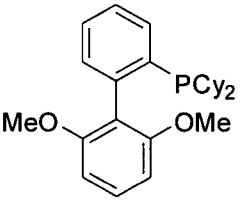
DPPM: n = 1
DPPE: n = 2
DPPP: n = 3
DPPB: n = 4



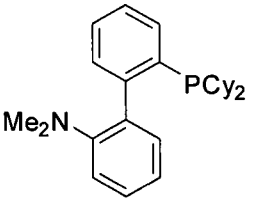
DPPF



XANTPHOS

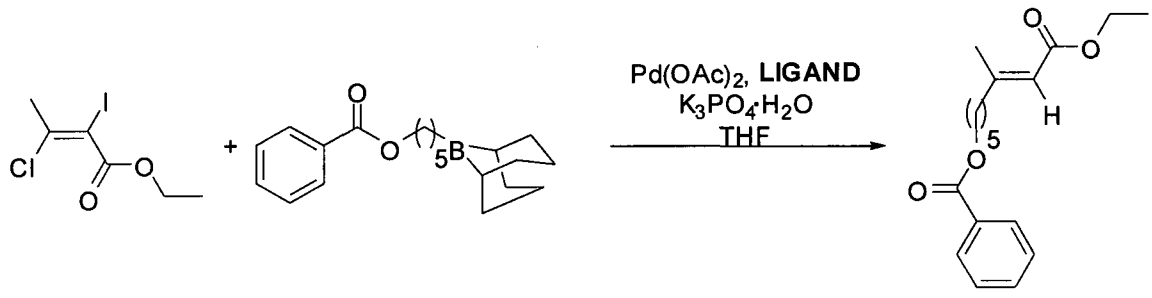


S-PHOS



DAVE-PHOS

Table 13. Determining a suitable ligand for alkyl-suzuki reaction



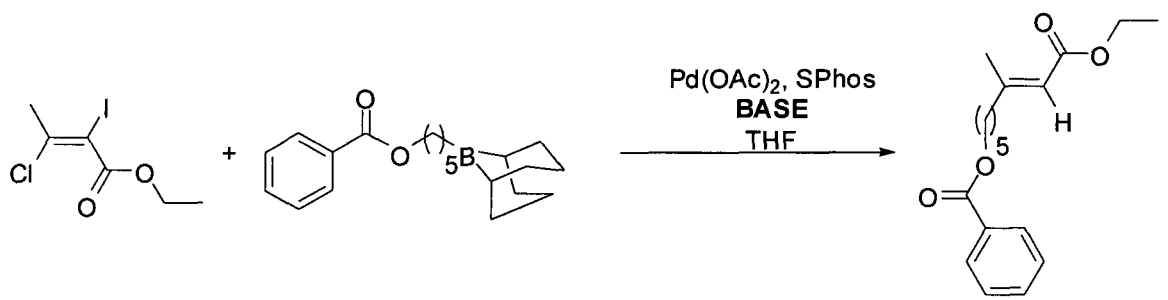
170 **181** **182**

Entry [a]	LIGAND	Yield (%)[b]
1	**SPhos**	**86**
2	Davephos	60
3	$PCy_3 \cdot HBF_4$	61
4	$P^tBu_2Me \cdot HBF_4$	79
5	$PEt_3 \cdot HBF_4$	60
6	$PMe_3 \cdot HBF_4$	6
7	PPh_3	39
8	Xantphos	36
9	Diphos	31
10	DPPF	8
11	DPPB	21
12	DPPP	Decomposition
13	DPPM	3

[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.10 equiv of LIGAND, 3.0 equiv of $K_3PO_4 \cdot H_2O$, 3.0 equiv of 5-(9-borabicyclo[3.3.1]nonan-9-yl)pentyl benzoate, THF (0.09M), 23°C, 18 h. [b] Isolated yield.

With S-Phos identified as an optimal ligand, it was decided to explore the influence of different bases on the reactivity of unsaturated esters with 9-alkyl-9-BBN. Employing the family of potassium phosphate bases resulted in a very low yield or decomposition (Entries 1-3, Table 14). Switching to the carbonate family, K_2CO_3 (Entry 4) showed decomposition while Cs_2CO_3 provided a low yield of the desired product (21%, Entry 5). Among the amine bases, Et_3N (Entry 6) and DABCO (Entry 7) resulted in decomposition of the starting material whereas DIPEA provided no reaction (Entry 8).

Table 14. Influence of different bases on the reactivity of unsaturated esters with 9-alkyl-9-BBN



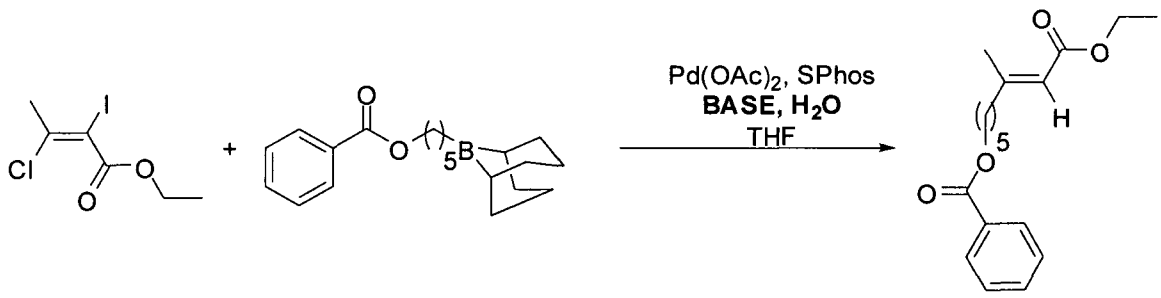
170 **181** **182**

Entry[a]	BASE	Yield (%)[b]
1	K_3PO_4	3
2	K_2HPO_4	4
3	KH_2PO_4	Decomposition
4	K_2CO_3	Decomposition
5	Cs_2CO_3	21
6	Et_3N	Decomposition
7	DABCO	Decomposition
8	Et*i*Pr$_2$N	No rxn

[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.10 equiv of SPhos, 3.0 equiv of BASE, 3.0 equiv of 5-(9-borabicyclo[3.3.1]nonan-9-yl)pentyl benzoate, THF (0.09M), 23°C, 18 h. [b] Isolated yield.

Since using $K_3PO_4 \cdot H_2O$ as a base worked very beautifully during the initial ligand screening, the importance of water was suggested, and therefore the influence of base was re-evaluated in the presence of water (Table 15).

Table 15. Influence of different bases re-evaluated in the presence of H_2O



170 **181** **182**

Entry[a]	BASE	Yield (%)[b]
1	K_3PO_4	52
2	K_2HPO_4	11
3	KH_2PO_4	5
4	K_2CO_3	65
5	Cs_2CO_3	78
6	Et_3N	No rxn
7	Et*i*Pr_2N	No rxn
8	DABCO	3
9[c]	**K_3PO_4•H_2O**	**86**

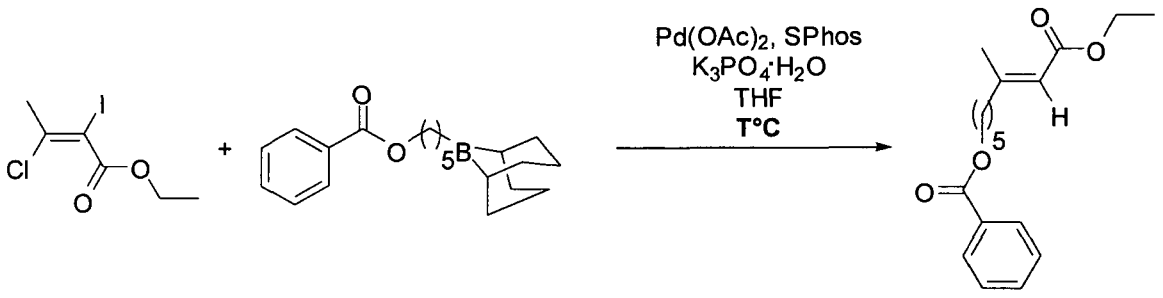
[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.10 equiv of SPhos, 3.0 equiv of BASE, 3.0 equiv of H_2O, 3.0 equiv of 5-(9-borabicyclo[3.3.1]nonan-9-yl)pentyl benzoate, THF (0.09M), 23°C, 18 h. [b] Isolated yield. [c] No additional H_2O is added.

The use of K_3PO_4 as the base for the reaction of **170** and 9-alkyl-9-BBN **181** in the presence of water dramatically increased the yield of product **182** from 3% (Entry 1, Table 14; no water) to 52% (Entry 1, Table 15). Both potassium phosphate monobasic

and dibasic were ineffective as bases and each barely produced the product **182** (Entries 2 -3). However it was a big improvement from the observed decomposition in the absence of water. We found that both K_2CO_3 (65%) and Cs_2CO_3 (78%) worked the best among all the bases to provide **182** in good yields (Entries 4-5). The addition of water to the three amine bases had no effect since the results remained the same (Entries 6-8). Therefore, both $K_3PO_4 \cdot H_2O$ and Cs_2CO_3 proved to be promising bases for the reaction, but $K_3PO_4 \cdot H_2O$ remained the optimal base.

It was decided to continue the optimization with the reaction conditions in Entry 9 (Table 15) to study the suitable temperature to convert **170** to **182**. Performing the reaction at room temperature proved most favorable giving **182** in 86% yield (Entry 1, Table 16). Heating the reaction in an oil bath at 40°C overnight greatly diminished the yield with only 6% of product **182** being observed (Entry 2). Reflux conditions resulted in the decomposition of **170** (Entry 4). Shortening the reaction time at 40°C to 4 hours resulted in recovery of the starting material **170** (Entry 3). While cooling the reaction to 0°C did not afford any reaction (Entry 5).

Table 16. Temperature Study



170 **181** **182**

Entry[a]	T(°C)	Yield (%)[b]
1	**rt**	**86**
2	40	6
3[c]	40	No rxn
4	Reflux	Decomposition
5	0	No rxn

[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.10 equiv of SPhos, 3.0 equiv of $K_3PO_4 \cdot H_2O$, 3.0 equiv of 5-(9-borabicyclo[3.3.1]nonan-9-yl)pentyl benzoate, THF (0.09M), 23°C, 18 h. [b] Isolated yield. [c] Reaction heated for 4 h.

The boron sources that were known to be efficient for hydroboration with terminal alkenes in the alkyl-Suzuki reaction were next investigated. Three partially substituted borane reagents such as 9-borabicyclo [3.3.1] nonane (9-BBN), 1,3,2-benzodioxaborole (catecholborane) and pinacolborane were analyzed. 9-BBN[36,37,38] is the only commercially available dialkylborane due to its favorable physical properties and unusual stability at room temperature. It is exceptionally stable toward

[36] Brown, H. C.; Mandal, A. K.; Kulkarni, S. U.; *J. Org. Chem.* **1977**, 42, 1392.
[37] Brown, H. C.; Liotta, R.; Scouten, C. G. *J. Am. Chem. Soc.* **1976**, 98, 5297.
[38] Brown, H. C.; Knights, E. F. *J. Am. Chem. Soc.* **1968**, 90, 5281.

disproportionation and is a highly regioselective hydroborating agent. The hydroboration of terminal alkenes with 9-BBN occurs very rapidly at room temperature (2 h) using one to one stoichiometry (Scheme 18). An alkyl-Suzuki cross-coupling between the unsaturated ester **170** and 9-alkyl-9-BBN **181** efficiently produced the desired product **182** in excellent yield (Entry 1, Table 17).

Hydroborations of terminal alkenes with catecholborane are extremely slow at room temperature, but sufficiently rapid at high temperatures (100°C). Conversely, at 120°C hydroboration with catecholborane[39,40] does not proceed due to the decomposition of the hydroborating agent at this elevated temperature. Therefore, a 10% excess of catecholborane effectively and regioselectively underwent hydroboration with a terminal alkene to generate alkylcatecholborane at 100°C in 2 h which was immediately employed into the alkyl-Suzuki coupling. Disappointingly no reaction was observed (Entry 2). Similarly refluxing reaction did no improvement (Entry 3).

Pinacolborane[41], a stable hydroborating agent at 25°C underwent hydroboration with the terminal alkene at milder conditions (50°C for 48 h) than catecholborane did to provide the pinacol alkylboronate which was purified by flash chromatography. Employing this reagent in the cross-coupling resulted in no reaction (Entry 4). In addition, both *n*-butyl boronic acid and *n*-butyltrifluoroborate were employed in the alkyl-Suzuki cross coupling reaction as the boron source and it was unsuccessful in producing *n*-butyl substitution at the β-position.

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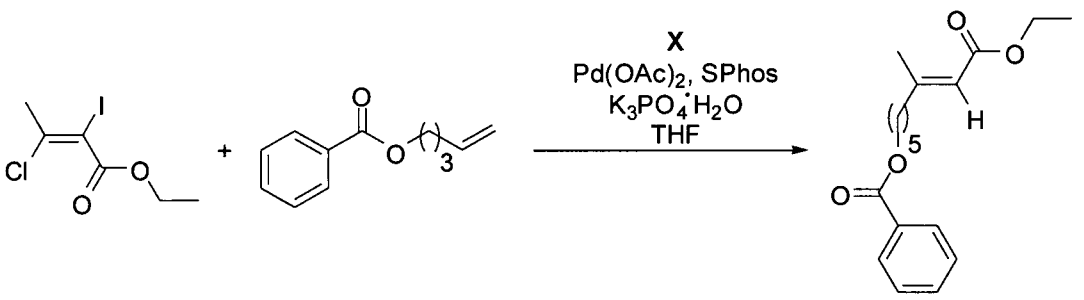
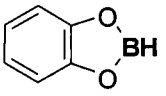
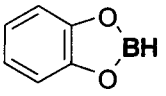
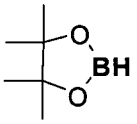
[39] Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1971**, 93, 1816.
[40] Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, 97, 5249.
[41] Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, 52, 3482.

Table 17. Investigating Boron sources that are efficient hydroborating agents for terminal alkenes in alkyl-Suzuki



170 **183** **182**

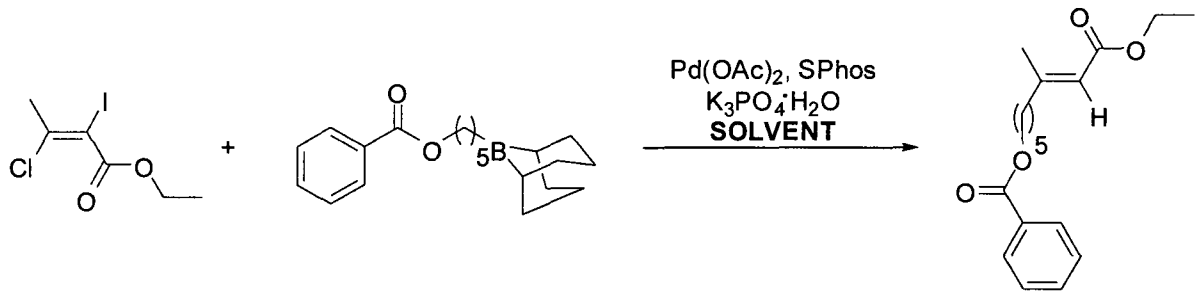
Entry [a]	X	Yield (%)[b]
1		86
2		No rxn
3[c]		No rxn
4		No rxn

[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.10 equiv of SPhos, 3.0 equiv of $K_3PO_4 \cdot H_2O$, 3.0 equiv of **X**-5-pentyl benzoate, THF (0.09M), 23°C, 18 h. [b] Isolated yield. [c] Reaction refluxed for 4 h.

Once 9-BBN was chosen as the optimal borane source, the effect of solvents on the conversion of unsaturated ester **170** to trisubstituted olefin **182** was examined. When the reaction was performed with THF as the solvent, the trisubstituted olefin **182** was isolated in 86% yield (Entry 1, Table 18). The use of a polar aprotic solvent such

as acetonitrile decreased the overall yield to 31% (Entry 2). When conducting the experiment with a nonpolar solvent such as benzene, the results were less promising as the reaction gave only a 26% yield of the product **182** (Entry 3). Hence, THF remained the solvent of choice for further optimization studies.

Table 18. Solvent Effect



170 **181** **182**

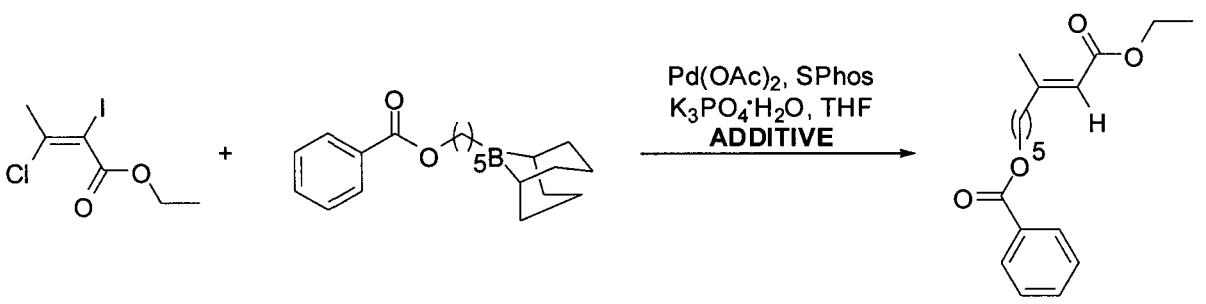
Entry[a]	**SOLVENT**	Yield (%)[b]
1	THF	86
2	Acetonitrile	31
3	Benzene	26

[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.10 equiv of SPhos, 3.0 equiv of $K_3PO_4 \cdot H_2O$, 3.0 equiv of 5-(9-borabicyclo[3.3.1]nonan-9-yl)pentyl benzoate, 23°C, 18 h. [b] Isolated yield.

The effects of protic additives on the reactivity of unsaturated ester **170** and 9-alkyl-9-BBN **181** were tested as shown in Table 19. Adding an additional 3 equivalents of H_2O to the reaction which contained H_2O in the form of potassium phosphate hydrate

afforded the desired product **182** in 73% yield (Table 19, Entry 2). By using *i*PrOH[42] as an additive, the formation of trisubstituted olefin **182** slightly suffered giving a 48% yield (Entry 3). The polar protic solvent *i*PrOH plays an additional role to finely suspend the inorganic bases in large scale reactions. Although, our reactions were performed at small scale, it was important to dissolve the entire inorganic base, $K_3PO_4 \cdot H_2O$, to push the reaction toward completion, and for that purpose *i*PrOH was employed. A dramatic decrease in the yield of the desired product **182** was observed suggests an alcohol was not necessary to dissolve inorganic bases in a small scale reaction.

Table 19. Presence of an Additive



170 **181** **182**

Entry[a]	ADDITIVE	Yield (%)[b]
1	-	86
2	H_2O	73
4	iPrOH	48

[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.10 equiv of SPhos, 3.0 equiv of $K_3PO_4 \cdot H_2O$, 3.0 equiv of 5-(9-borabicyclo[3.3.1]nonan-9-yl)pentyl benzoate, 3.0 equiv of **ADDITIVE**, THF (0.09M), 23°C, 18 h. [b] Isolated yield.

[42] Brock, S.; Hose, D. R.J.; Moseley, J. D.; Parker, A. J.; Patel, I.; Williams, A.J. *Org. Process Res. Dev.* **2008**, 12, 496.

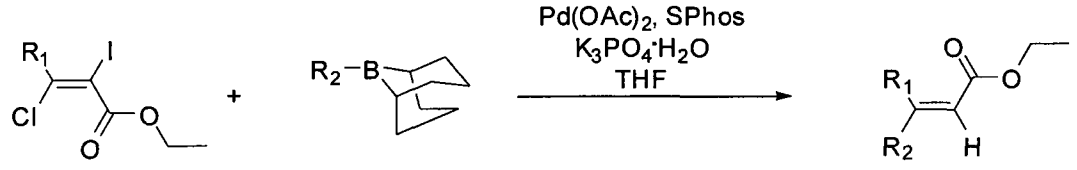
2.1.3 Scope and Mechanism

The scope of the reaction of β-chloro-α-iodo-α,β-unsaturated esters with 9-alkyl-BBN was next investigated. Results are summarized in Table 20.

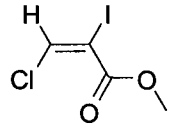
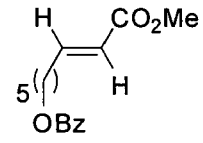
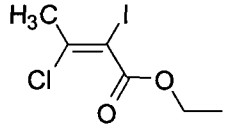
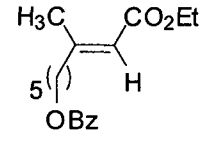
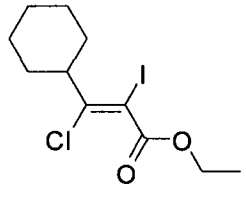
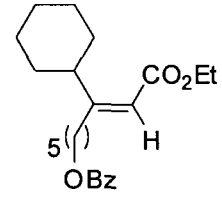
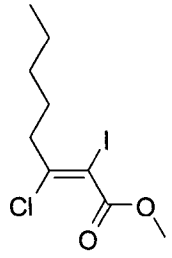
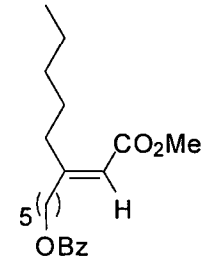
A very simple methyl substitution (Table 20, Entry 2) at the β position of the Cl-I olefin template provided a reaction that gave the best yield of product **182** (86%). Switching the methyl group to a smaller substituent such as hydrogen (Entry 1) decreased the yield to 30%. Branched substituents such as a cyclohexyl (Entry 3) produced a moderate yield (46%) of the corresponding product. Substituted alkyl chains were compatible with the reaction conditions as shown in entries 4 and 5. Changing the ethyl ester to methyl ester of the olefin template did not affect the overall reaction as was evident from entries 1 and 4.

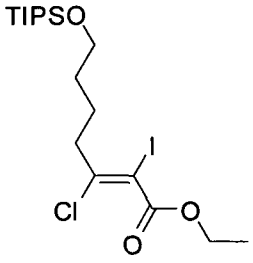
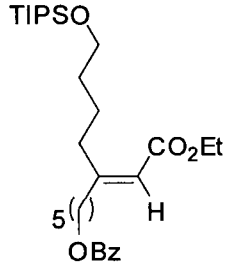
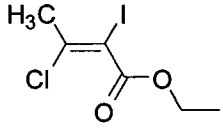
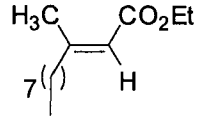
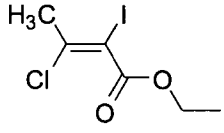
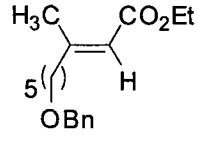
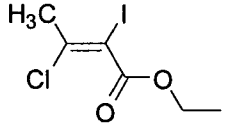
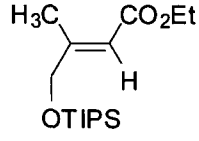
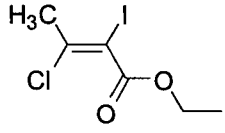
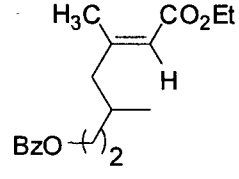
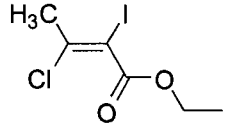
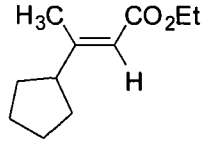
On the other hand, subjecting various alkenes to 9-BBN produced 9-alkyl-9-BBN reagents, which were used to cross couple to the olefin template **170** under optimized conditions. The use of a straight alkyl chain such as octene (Entry 6) produced the desired product with an excellent yield (82%). Employing a benzyloxy protected alkene (Entry 7) resulted in a very good yield (73%), similar to that benzoyloxy protected alkene (Entry 2). A more bulky triisopropylsilyloxy protected alkene decreased the yield slightly to 60% (Entry 8).

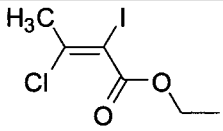
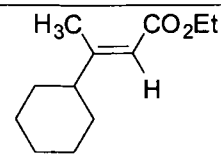
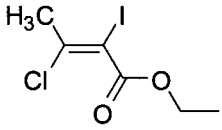
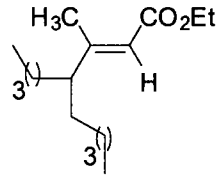
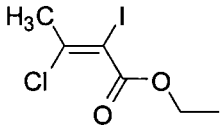
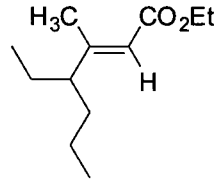
Table 20. Investigating various β-chloro-α-iodo olefins and 9-alkyl-9-BBN reagents



184 **185** **186**

Entry[a]	R_1	Substrate	R_2	Product	Yield (%)
1[b]	H	 **187**	$BzO(CH_2)_5$	 **191**	30
2	CH_3	 **170**	$BzO(CH_2)_5$	 **182**	86
3	C_6H_{12}	 **188**	$BzO(CH_2)_5$	 **192**	46
4[b]	$CH_3(CH_2)_4$	 **189**	$BzO(CH_2)_5$	 **193**	74

5	$TIPSO(CH_2)_4$	 **190**	$BzO(CH_2)_5$	 **194**	66
6	CH_3	 **170**	$CH_3(CH_2)_7$	 **195**	82
7	CH_3	 **170**	$BnO(CH_2)_5$	 **196**	73
8	CH_3	 **170**	$TIPSO(CH_2)_5$	 **197**	60
9	CH_3	 **170**	$BzO(CH_2)_3CHCH_3$	 **198**	76
10	CH_3	 **170**	Cyclopentene	 **199**	-

11	CH_3	 **170**	Cyclohexene	 **200**	-
12	CH_3	 **170**	trans-5-decene	 **201**	-
13	CH_3	 **170**	cis-3-hexene	 **202**	-

[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.10 equiv of SPhos, 3.0 equiv of $K_3PO_4 \cdot H_2O$, 3.0 equiv of R_2-9-BBN, THF (0.09M), 23°C, 18 h. [b] The methyl ester was used in place of the ethyl ester.

In general, branching near the double bond decreases the rate of hydroboration significantly compared to straight chain alkene. Surprisingly, an α-methyl substituent increased the rate of hydroboration with 9-BBN over that of the parent alkene, in spite of the steric hindrance. As a result, a benzoyloxy protected terminal alkene with a methyl substituent at the 2-position (Entry 9) was employed and worked beautifully in the subsequent cross-coupling regardless of the steric hindrance of the double bond to provide a good yield of the desired product (76%)[37]. The inductive effect of the α-methyl substituent increases the electron availability in the double bond, thereby favoring the hydroboration reaction.

This result suggested that 9-BBN was insensitive to the steric requirement of the alkenes. The terminal alkene, pent-4-en-1-ol was blocked with different protecting groups, which did not alter the coupling to the borane reagent nor to the olefin template as the alkoxy group was far away from the double bond. All protected alkoxy terminal alkenes underwent efficient hydroboration with 9-BBN within 2 h at room temperature. In all cases, the products were isolated as single isomers[43].

To explore the variety of alkenes that could couple to 9-BBN, internal alkenes such as cyclic olefins and cis and trans isomers were tested[37,38,44]. Internal olefins were less reactive than terminal alkenes. If only one side of the internal olefin was branched, then the rate of hydroboration of 9-BBN was only moderately reduced. As the hydroboration was regioselective and followed an anti-markovnikov addition, 9-BBN reacted exclusively at the less hindered side of the substituted double bond. If both sides of the double bond were branched, the rate of 9-BBN hydroboration dropped sharply. Cyclic olefins such as cyclopentene, cycloheptene, and cyclooctene showed higher reactivity toward 9-BBN at room temperature for 2 h due to highly strained double bonds. Whereas, cyclohexene, containing a less strained double bond was less reactive and underwent sluggish hydroboration at room temperature over 24 h. Conducting the cross coupling between the unsaturated ester **170** and 9-cyclopentyl- and 9-cyclohexyl-9-BBN derivatives did not give productive reactions (Entries 10 and 11).

---

[43] The relative stereochemistry of all products was assigned by nOe networks of the desired and the isomerized products.

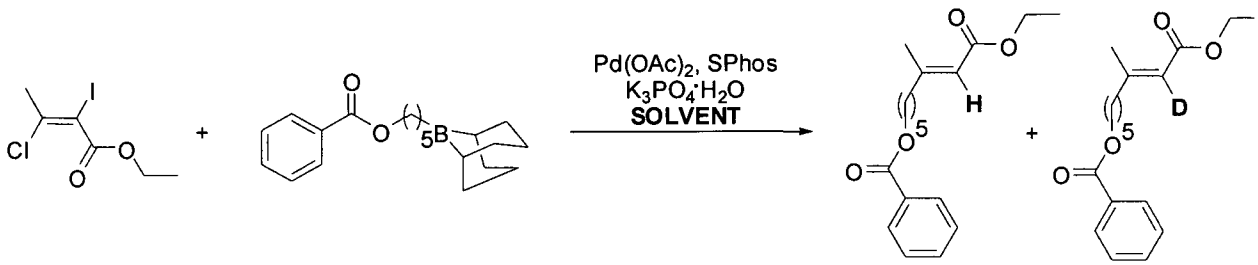
[44] Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, 96, 7765.

Cis and *trans* isomeric alkenes often underwent a selective hydroboration with a specific hydroborating agent. The trans alkenes underwent hydroboration with 9-BBN at a rate considerably faster than that of the corresponding *cis* alkenes[37]. This rule holds true for isomers containing highly branched alkyl groups. The precise reason for such specific reactivity with 9-BBN is not clear[37]. Hence, implementing trans-5-decene and *cis*-3-hexene to couple with 9-BBN over 24 h at 25°C followed by the cross coupling with the unsaturated ester **170** suppressed the overall reaction (Entries 12 and 13). Overall, the internal alkenes were not as successful as the terminal alkenes toward the alkyl cross-coupling with the unsaturated ester **170**.

Expanding the scope of the reaction to introduce a variety of alkyl substituents at the β-position of the β-chloro-α-iodo-α,β-unsaturated ester **170** generated a diversity of trisubstituted olefins. The next challenge was to reveal the mechanism behind the formation of the single isomeric trisubstituted olefins.

Unveiling the mechanism involved identifying the source of hydrogen that arose at the α-position of the desired product **182**. A series of isotopic labeling experiments were performed to determine the hydrogen source. The substrate **170** was coupled with 9-alkyl-9-BBN **181** in deuterated benzene (C_6D_6), a reaction that produced only product **182** indicating that the solvent was not the source of hydrogen (Entry 2, Table 21).

Table 21. Impact on the Solvent



170 **181** **182** **203**

Entry[a]	SOLVENT	Yield (%)[b]	
		182	**203**
1	Benzene	26	0
2	Benzene-d6	23	0

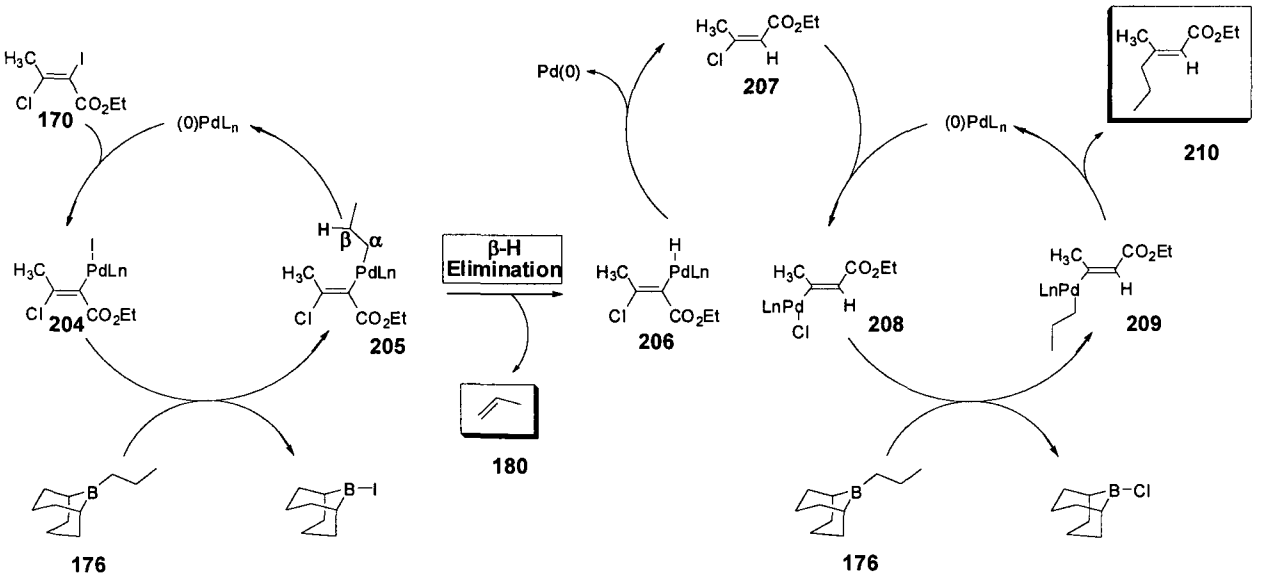
[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.10 equiv of SPhos, 3.0 equiv of $K_3PO_4 \cdot H_2O$, 3.0 equiv of 5-(9-borabicyclo[3.3.1]nonan-9-yl)pentyl benzoate, 23°C, 18 h. [b] Isolated yield.

As mentioned earlier, in an alkyl-Suzuki cross coupling reaction, the β-hydride elimination process is in competition with the desired reductive elimination process (Scheme 19)[12]. Consequently it was hypothesized that the unique olefinic hydrogen comes from a β-hydride elimination of the alkyl moiety that was employed as a coupling partner in the alkyl-Suzuki reaction. This hypothesis leads to a mechanism which involves two catalytic cycles (Scheme 20).

In the first catalytic cycle, palladium undergoes oxidative insertion between C-I bond of the olefin **170** to form the intermediate **204**. Transmetalation replaces the alkyl moiety on the palladium with iodide to give **205**. Instead of undergoing reductive elimination of **205** in the normal alkyl Suzuki cross-coupling, which would lead to the

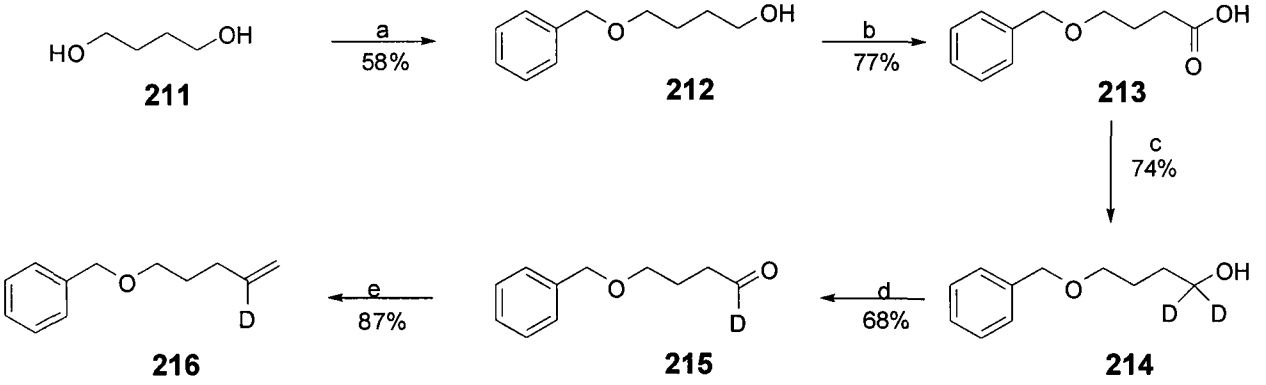
alkyl group introduced at the α-position, intermediate **205** undergoes β-H elimination to form the palladium hydride intermediate **206**. A reductive elimination would result in a product **207** in which the hydrogen is now at the α-position. Since the chlorine remains on the β position, the system continues through the second catalytic cycle to insert the alkyl group into the β position followed by reductive elimination to give **210**. This proposed mechanism did not account for the observed stereochemistry of the product. Yet at this point the main goal was to determine the origin of the hydrogen at the α-position and possibly explain the mechanism of the reaction and the stereochemistry of the products.

Scheme 20. The β-H Elimination from the Alkyl group is the Hydride source



To support this hypothesis, ((4-deuteropent-4-enyloxy)methyl)benzene **216** was synthesized incorporating a deuterium at the β-position of the double bond (Scheme 21). 1,4-butanediol was selectively monoprotected using benzyl bromide[45] to provide **212** which was carefully oxidized to carboxylic acid **213** in good yield[46]. The acid was reduced to an alcohol introducing two deuterium atoms by using sodium borodeuteride to give alcohol **214**[47]. The deuterated alcohol underwent Swern oxidation to produce the aldehyde **215** which was immediately subjected to a Wittig reaction to generate the olefin **216** containing a deuterium at the β-position.

Scheme 21. Preparation of D-Olefin



(a) Bn-Br, NaH, Bu_4NI, THF/DMSO (b) TEMPO, Na_3PO_4, $NaClO_2$/NaOCl, MeCN (c) 1. Ethylchloroformate and Et_3N; 2. $NaBD_4$, MeOH, THF (d) Oxalyl-Cl, DMSO, Et_3N, DCM (e) $MePPh_3Br$, NaHMDS, THF

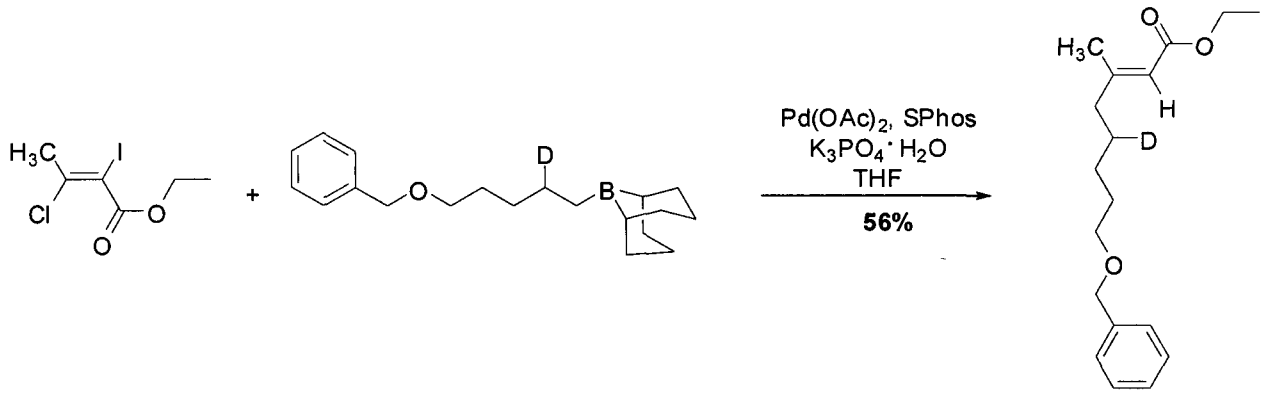
[45] Schomaker, J. M.; Pulgam, V. R.; Borhan, B.; *J. Am. Chem. Soc.* **2004**, 126, 13600.

[46] Zhao, M. M.; Li, J.; Mano, E.; Song, Z. J.; Tschaen, D. M.; *Organic Syntheses.* **2005**, 81, 195.

[47] Soai, K.; Yokoyama, S.; Mochida, K.; *Synth Commun.* **1987**, 17, 647.

The deuterated olefin **216** underwent hydroboration with 9-BBN to create the coupling partner **217**. Following an alkyl-Suzuki cross coupling reaction with the olefin template **170** we detected only the formation of product **218** (Scheme 22). The incorporated deuterium remained on the same carbon as its initial placement as shown in scheme 22, product **218**.

Scheme 7. An alkyl-Suzuki cross coupling between unsaturated ester and d-terminal olefin form an unexpected product

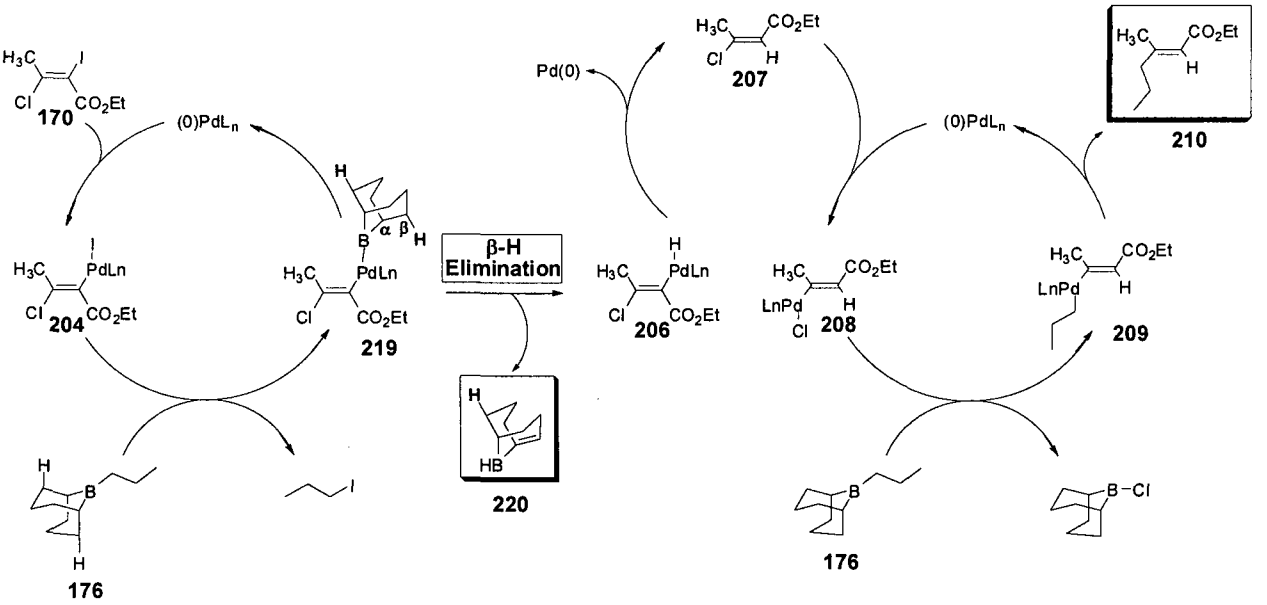


170 **217** **218**

The previous experiment indicates that a β-hydride elimination from the alkyl moiety of the boron reagent was not the hydrogen source. This result led to a more thrilling hypothesis: β-H elimination of the 9-BBN group was the source of the olefinic hydrogen. Proving that was the hardest challenge of this project.

The β-hydride elimination of 9-BBN involves a very similar mechanism to the one described above that also incorporates two catalytic cycles (Scheme 23). The first catalytic cycle involves an oxidative insertion of palladium into the C-I bond of the unsaturated ester **170**. Transmetalation replaces the boron of the 9-BBN with iodide to form the intermediate **219**, which undergoes β-H elimination to form an undesired product **220** and palladium hydride intermediate **206**. Subsequent reductive elimination of **206** would result in the hydride product **207**. The remaining chlorine atom further proceeds through an alkyl-Suzuki process to produce the observed product **210**.

Scheme 23. The β-H Elimination from 9-BBN is the H Source



To test the second hypothesis the synthesis of deuterated-9-BBN was required, which proved to be the most difficult aspect of this project. Though d-9-BBN was commercially available, it was packaged in a large quantity and was very expensive. Since our reactions were performed at a much smaller scale, commercially available d-9-BBN was not practical to purchase.

Therefore, we decided to synthesize our own d-9-BBN starting from BD_3-THF and cyclooctadiene. However, purchasing a good quality sample of the air sensitive BD_3-THF became extremely difficult due to inappropriate packaging of the material. Hence, we needed to take one step back in synthesizing d-9-BBN and prepare BD_3 from scratch, a task which became a complex process.

Brown has done extensive studies toward the synthesis of both diborane gas[48] and partially substituted borane reagents such as 9-BBN. The group of Robert Todd[49] has recently modified the procedure described by Brown to generate deuterated diborane gas using boron trifluoride as a Lewis acid in glyme. After many trials and errors a practical apparatus to synthesize BD_3-THF was designed (Figure 4) as this was more appropriate to be used in the laboratory fumehood. This was a huge advantage compared to Brown's complex setup.

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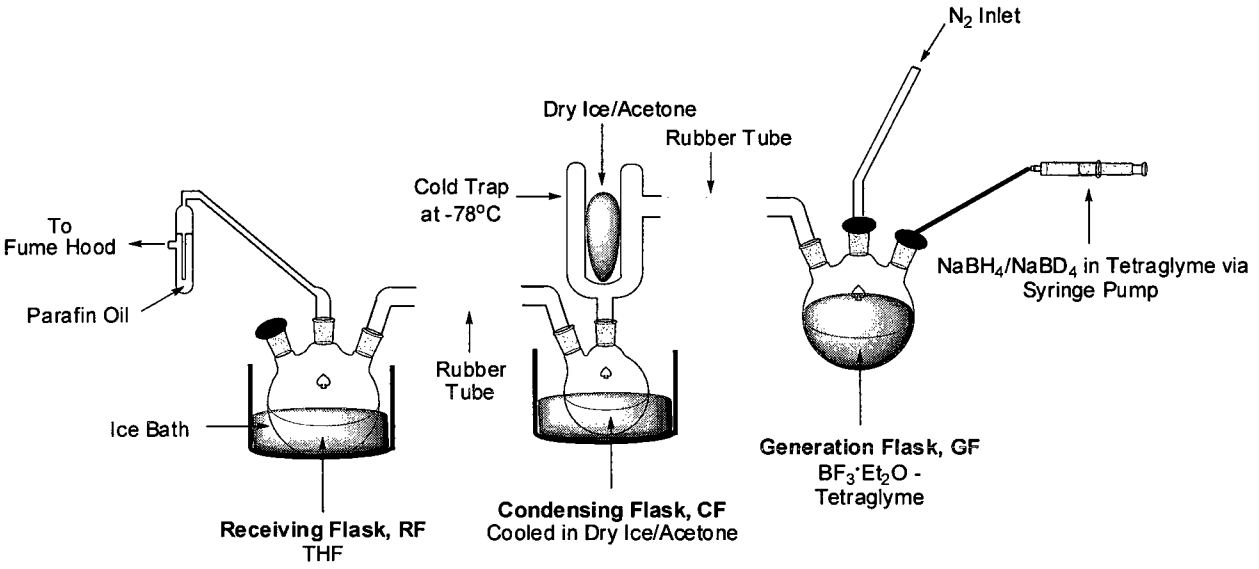
[48] (a) Brown, H.C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. "Organic Syntheses via Boranes"; Wiley-Interscience: New York, 1975. (b) Brown, H. C.; Mandal, A. K.; Yoon, N. M.; Singaram, B.; Schwier, J. R.; Jadhav, P. K. *J. Org. Chem.* **1982**, 47, 5069. (c) Kanth, J. V. B.; Brown, H. C. *Inorg. Chem.* **2000**, 39, 1795. (d) Schlesinger, H. I.; Brown, H. C.; Abraham, B.; Davidson, N.; Finholt, A. E.; Lad, R. A.; Knight, J.; Schwartz, A. M. *This Journal*, **1952**, 74, 191. (d) Schlesinger, H. I.; Burg, A. B. *This Journal*, **1931**, 53, 4321.

[49] (a) Todd, R. C.; Hossain, M. M.; Josyula, K. V.; Gao, P.; Kuo, J.; Tan, C. T. *Tetrahedron Lett.* **2007**, 48, 2335. (b) U.S. Patent No. 0 197 695 to Potyen, M. C.; Josyula, K. V. B.; Gao, P.; Hewitt, C. D.; Todd, R., which issued on **August 23, 2007.**

Figure 4. All-glass apparatus for the preparation of Borane solution



Our setup involved the use of two 100 mL 3-neck round bottom flasks and one 250 mL round bottom flask as the Condensing Flask (CF). The two 100 mL round bottom flasks were used as the Generation (GF) and Receiving Flasks respectively. Each flask was joined to one another by glass tubing using a 90° bend and adapter and a small piece of rubber tube which was oven-dried 24 h prior to the experiment. The cold trap was joined to the Condensing Flask and both were maintained at -78°C continuously using dry ice and acetone. The receiving flask was cooled in an ice-bath to trap the diborane gas in THF. The entire process was carried out under a nitrogen atmosphere. Dry nitrogen enters continuously through the Generation Flask and passes through the Receiving Flask before exiting through the bubbler containing parafin oil (Figure 4).

Once the apparatus was assembled as shown in Figure 4 the entire system was flame dried under vacuum (vacuum needle injected through the Receiving Flask septa) and left under nitrogen atmosphere. An anhydrous tetraglyme (26.0 mL, 3.0 A° MS) weighed into an oven dried 50 mL round bottom flask and purged under N_2. A 13.0 mL of the purged tetraglyme was added to the Generation Flask equipped with the Teflon stir bar followed by an addition of freshly distilled BF_3•Et_2O (6.4 mL, 51.54 mmol) and stirred at room temperature for 30 minutes. The system was concentrated *in vacuo* twice from the Receiving Flask for 30 minute interval to remove the Et_2O. To a separate oven dried 25 mL round bottom flask equipped with Teflon stir bar $NaBH_4$ or $NaBD_4$ (1.5 g, 39.65 mmol) and 13.0 mL of purged anhydrous tetraglyme were added and stirred in a hot water bath for 30 minutes under nitrogen atmosphere. The resulting solution was added to the Generation Flask via syringe pump over 3 h at room temperature. The solution continued to stir for additional 1 h at room temperature and the product was collected during that period as a solution in THF in the Receiving Flask which was cooled in an ice bath. The products BH_3- and BD_3-THF was immediately carried onto the formation of 9-BBN or d-9-BBN.

Modifying the application of Todd's literature conditions to our setup, we succeeded in generating both BH_3-THF and BD_3-THF without a stabilizer as described above. Often commercial BH_3-THF is stabilized by $NaBH_4$ or hindered amines such as N-isopropyl-N-methyl-t-butylamine. The presence of $NaBH_4$ as a stabilizer in commercial borane solutions suppressed the formation of 9-BBN[49]. Its absence was one of the key elements required for the successful synthesis of 9-BBN and d-9-BBN.

The direct synthesis of 9-borabicyclo [3.3.1] nonane or 9-BBN was explored in detail by Brown[50], Soderquist[51], and that of d-9-BBN by Midland[52]. Hydroboration of 1,5-cyclooctadiene (COD) with an equimolar amount of BH_3-THF yields 1,4- and 1,5-isomeric organoborane species (Scheme 24)[44]. This is evident from the oxidation of the following organoborane intermediate with alkaline hydrogen peroxide which generates cis-1,5- and cis-1,4-cyclooctanediol in the ratio 72:28. The 1,5-isomer **224** has two six-membered rings fused to form a boron bridge which is more thermodynamically stable than the 1,4-isomer **223**, which has a seven-membered ring fused to a five-membered ring. Thus, a complete isomerization of the 1,4-isomeric adduct **223** to the desired 1,5-adduct **224** can be achieved under milder conditions. Refluxing the reaction containing both isomers at 65°C for a 1.5 h period in THF as the solvent leads to the direct formation of 9-BBN (1,5-adduct) which exists as a dimer (**225**) in both solution and solid states.

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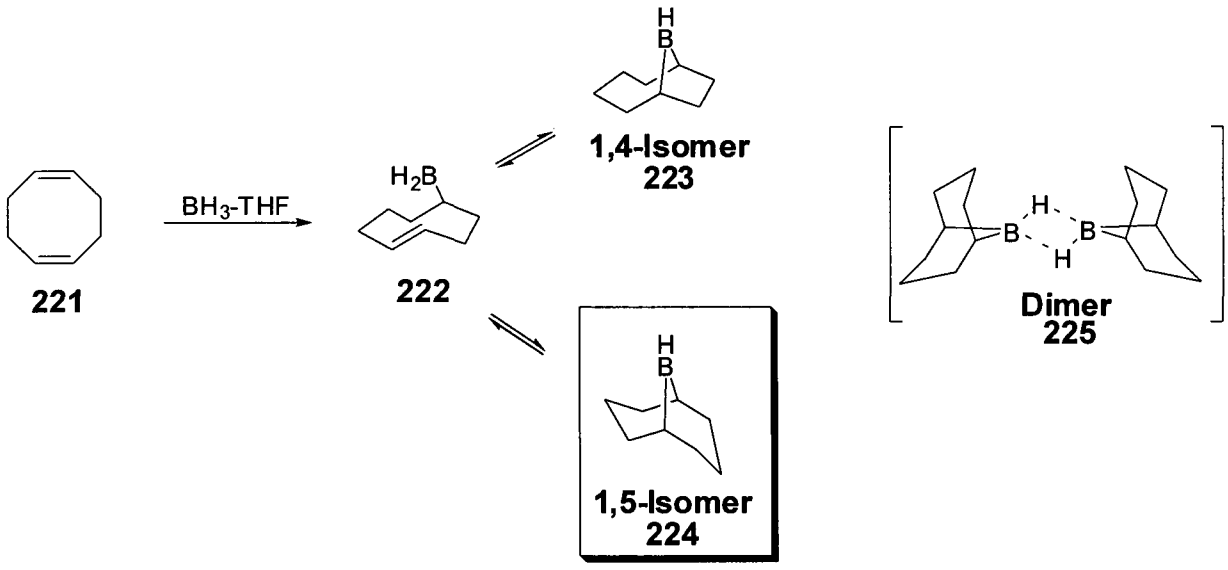
[50] (a) Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, 90, 5280. (b) Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, 96, 7765. (c) Brown, H. C.; Soderquist, J. A. *J. Org. Chem.* **1980**, 45, 846. (d) Brown, H. C.; Kanth, J. V. B.; Zaidlewicz, M. *Tetrahedron*, **1999**, 55, 5991.

[51] (a) Soderquist, J. A. *J. Org. Chem.* **1981**, 46, 4599. (b) Soderquist, J. A.; Negron, A. *Organic Syntheses.* **1992**, 70, 169.

[52] Midland, M. M.; Greer, S. *Synthesis.* **1978**, 845.

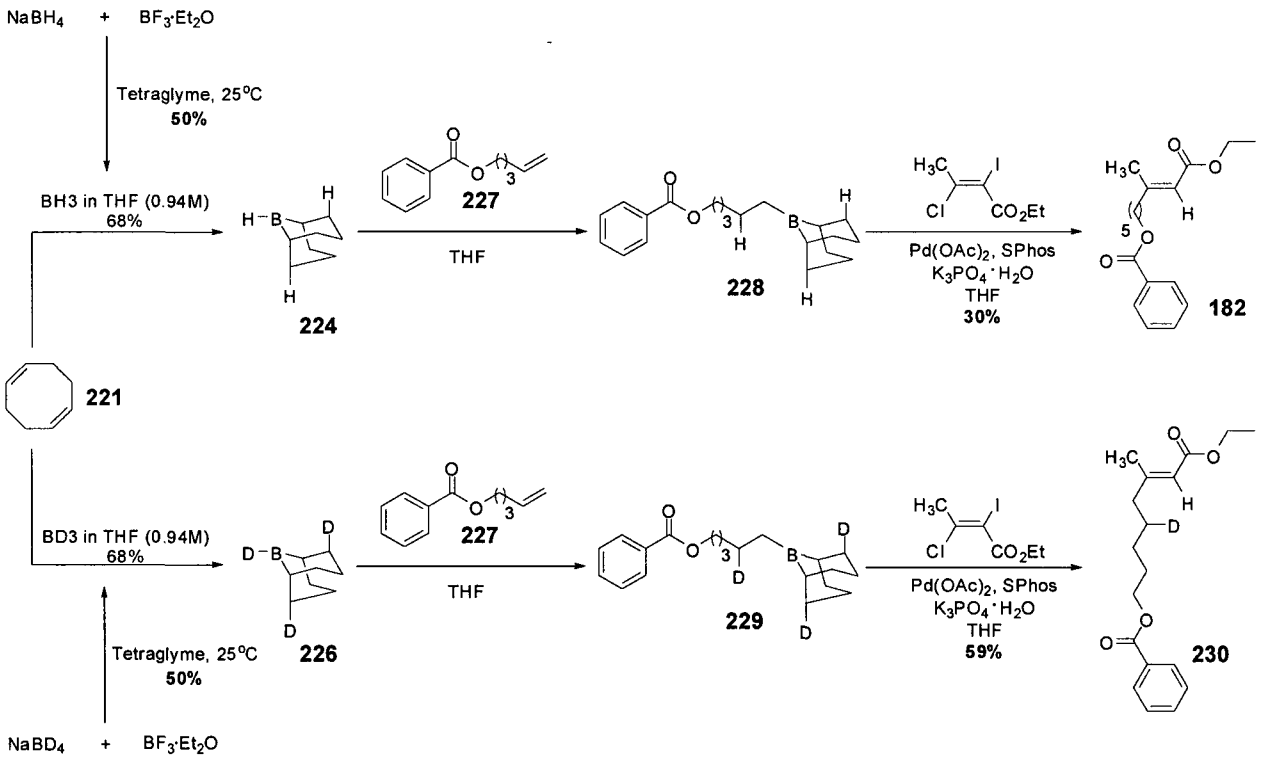
Scheme 24. Hydroboration of COD with BH_3-THF produces isomeric organoborane species



As a test reaction, Midland's procedure was directly followed employing our home-made BH_3-THF to produce 9-BBN **224** which was immediately used to hydroborate olefin **227** to form 9-alkyl-9-BBN **228** this was employed in an alkyl-Suzuki cross coupling reaction to create the desired trisubstituted olefin **182** in 30% yield. The NMR of the product was very clean and identical to that produced by employing commercial 9-BBN. This illustrates the quality of the home-made BH_3-THF and 9-BBN in THF. Performing the same sequence with home-made BD_3-THF led to the production of d-9-BBN **226** which was immediately used to hydroborate olefin **227** to form d-alkyl-9-BBN **229** and subsequent cross coupling provided the product **230** in 59% yield. Again our level of excitement dropped deeply. Observing the same product **230** from both d-olefin **216** and d-9-BBN **226** experiments confirmed that β-H elimination

was clearly not the source of hydrogen (Scheme 25). These experiments also showed that β-H elimination was not competing with the reductive elimination in this alkyl-Suzuki cross coupling reaction toward the trisubstituted olefin.

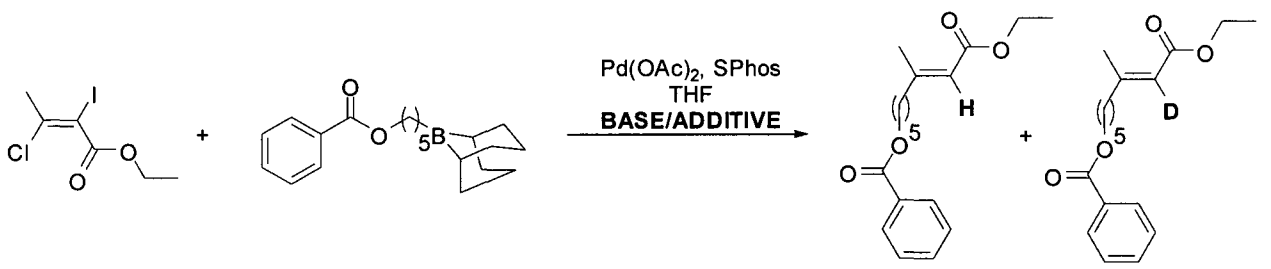
Scheme 25. Preparation of 9-BBN, d-9-BBN and the unexpected result



Neither the solvent nor a β-H elimination from the alkyl boron moiety, nor 9-BBN proved to be the source of hydrogen observed in the desired product **182**. Re-analyzing the optimized reaction conditions pointed out the presence of water in the form of a hydrate with the inorganic base, K_3PO_4. The possibility was then examined whether this could be a possible source of hydrogen. Earlier in the project, the addition of 3

equivalents H_2O to the reaction mixture gave no significance increase in the yield (Entry 1, Table 22). Replacing this with D_2O resulted in the product **182** with no incorporation of deuterium at the α-position (Entry 2). This reaction was now repeated using the following inorganic base, $K_3PO_4 \cdot D_2O$ (Entry 3). By dissolving the inorganic base $K_3PO_4 \cdot H_2O$ in D_2O and stirring for 1 h then removing the water under vacuum, we prepared $K_3PO_4 \cdot D_2O$. The use of this reagent in our reaction gave product **203** showing *44% deuterium incorporation at the α-position and confirmed that the source of the* hydrogen was the water of hydration present in the inorganic base $K_3PO_4 \cdot H_2O$. The low yield observed in Entry 3 was attributed to the disruption in the classical procedure.

Table 22 . Presence of H_2O



170 **181** **182** **203**

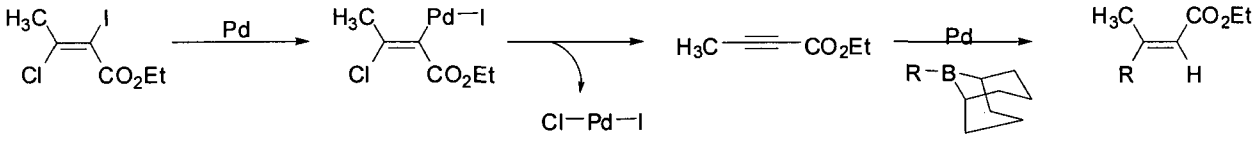
Entry[a]	Base	Yield (%)[c]	
		182	**203**
1	$K_3PO_4•H_2O/H_2O$	73	0
2	$K_3PO_4•H_2O/D_2O$	85	0
3[b]	$K_3PO_4•H_2O/D_2O$	34	22

[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.10 equiv of SPhos, 3.0 equiv of $K_3PO_4•H_2O$, 3.0 equiv of 5-(9-borabicyclo[3.3.1]nonan-9-yl)pentyl benzoate, 3.0 equiv of H_2O/D_2O, THF (0.09M), 23°C, 18 h. [b] $K_3PO_4•H_2O$ was dissolved in 0.3 mL of D_2O and stirred for 1 h at rt. Benzene was added and concentrated *in vacuo* to remove H_2O and form $K_3PO_4•D_2O$ salt. [c] Isolated yield.

Once the source of olefinic hydrogen was determined, the next focus turned toward elucidating the mechanism. It was intriguing to observe the configuration of the single isomer trisubstituted olefin **182** was "inverted" with respect to the starting substrate **170**. This meant the alkyl moiety and hydrogen were introduced in a *syn* fashion, which led to the consideration of a mechanism involving an alkyne intermediate. An alkyne intermediate would explain the stereoselectivity observed in our reaction (Scheme 26). This could have occurred through an initial oxidative

insertion of palladium into the C-I bond of the unsaturated ester **170** forming **204**. Followed by the reductive elimination of palladium iodo-chloro complex generate an alkynl ester such as **231**. The alkynyl ester would then suffer palladium catalyzed alkyl addition, followed by hydrogen transfer from the water of hydration present in the inorganic base $K_3PO_4 \cdot H_2O$ to form the observed trisubstituted olefin **232**.

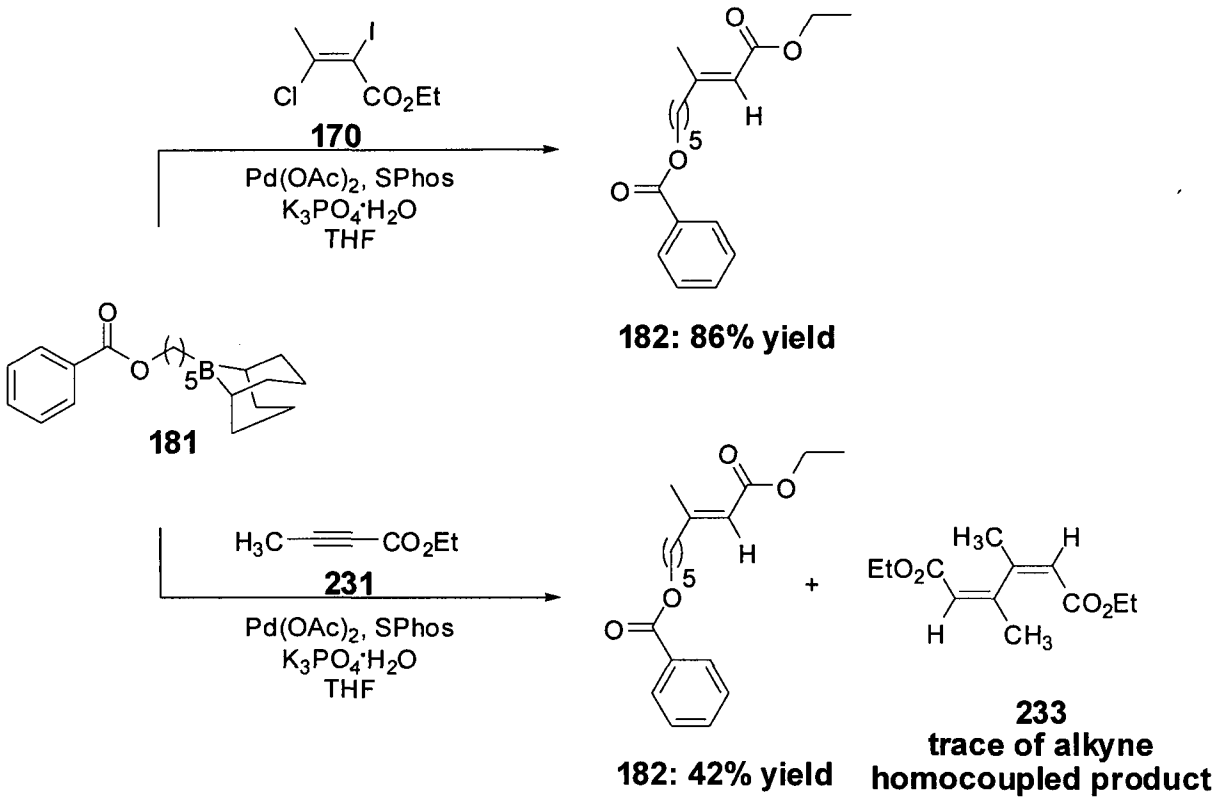
Scheme 26. Possibility of the mechanism involving an Alkynyl Intermediate



170 **204** **231** **232**

In order to verify this possible mechanism, alkyne **231** was subjected to cross-coupling under the optimized conditions. Performing an alkyl-Suzuki cross coupling between alkyne **231** and 9-alkyl-9-BBN **181**, the desired olefin **182** was obtained in very low yield (42%) together with an alkyne homocoupled product **233** (Scheme 27). An alkyl-Suzuki reaction between the unsaturated ester **170** and 9-alkyl-9-BBN **181** generated only the desired olefin **182** both regio- and stereoselectively without the presence of any side products. As a result, it was suggested that the reaction of β-chloro-α-iodo-α,β-unsaturated esters **184** may not proceed through an alkynyl intermediate. However, this controlled experiment presented an exciting research opportunity to synthesize trisubstituted olefins from alkynes via an alkyl-Suzuki cross coupling reaction from alkynyl esters which will be encountered in the next chapter.

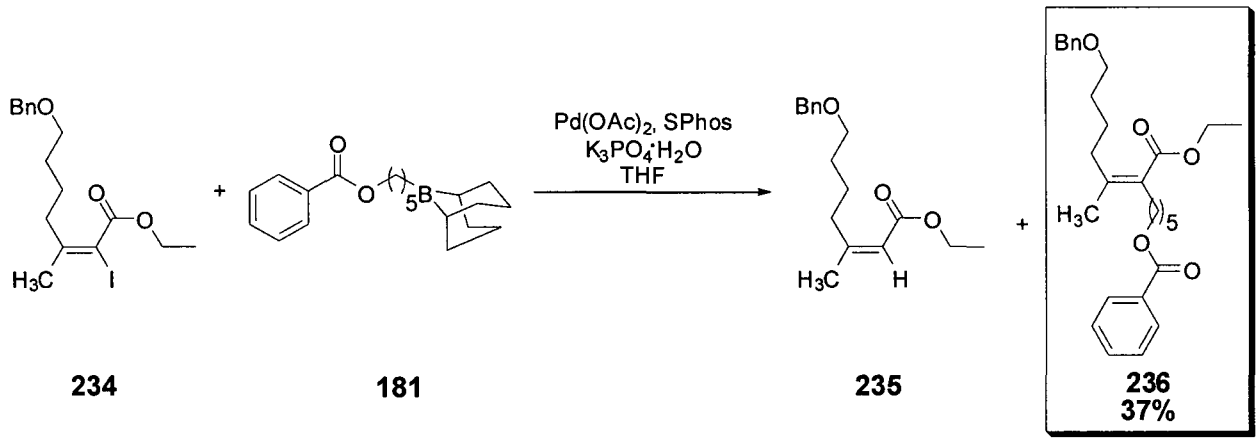
Scheme 27. Rule out Alkynyl Intermediate after observing Alkyne Homocoupled Product



Eliminating alkynes such as **231** as reaction intermediates indicated that the process must involve sequential replacement of the halogens during palladium catalyzed couplings. Previous experiments with β-chloro-α-iodo-α, β-unsaturated esters had shown that the iodide was always replaced first during related cross-coupling reactions[33]. Hence, experiments were performed to elucidate the order of substitution in the current process, by subjecting possible reaction intermediates to the reaction conditions. If the chloride atom at the β-position of the unsaturated ester **170** was replaced first, then iodide **234** should be converted to **235** (Scheme 28). When (E)-α-

iodo-α, β-unsaturated ester **234** was subjected to 9-alkyl-9-BBN **181**under the reaction conditions, only tetrasubstituted olefin product **236** was observed in 37% yield. The formation of the tetrasubstituted product **236** instead of the expected trisubstituted derivative **235**, suggested that **234** could not be a reaction intermediate and that the iodide was the first to be displaced when substrate such as **170** were coupled with 9-alkyl-9-BBN under the present conditions.

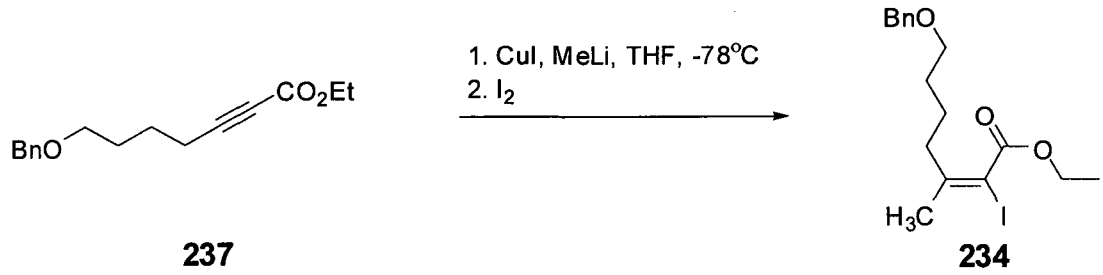
Scheme 28. Cross-Coupling at the α position and absence of Unique Hydrogen



The intermediate **234** was prepared by following the procedure developed by Klein and coworkers[53]. The first step involved the addition of copper iodide and methyl lithium in THF at -78°C. Then the precursor **237** was transferred and the mixture was stirred for additional 1 h. Finally, following the addition of iodine the reaction mixture was cooled to 0°C and stirred for an additional 2 h to isolate the intermediate **234** in 68% yield after purification procedure (Scheme 29).

[53] Klein, J.; Levene, R.; *J. Chem. Soc. Perkin Trans 2.* **1973**, 1971.

Scheme 29. Preparation of intermediate **234**



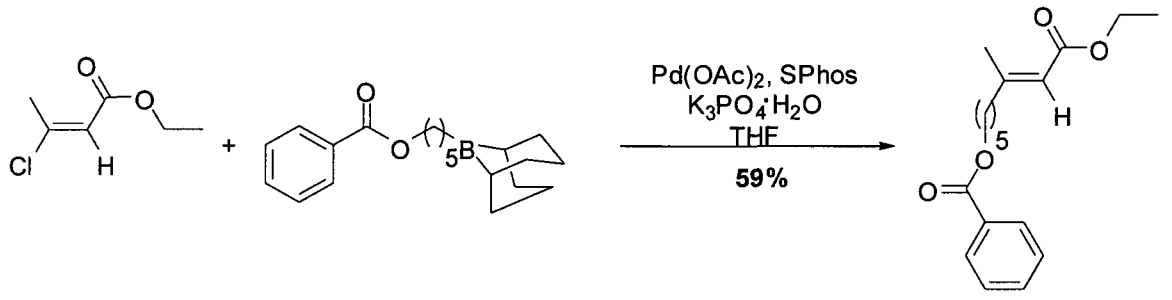
237 **234**

The previous experiments conclude the first step of the trisubstituted olefin formation was the replacement of the iodide by the hydrogen from the water present in the inorganic base, $K_3PO_4 \cdot H_2O$. This suggested the intermediate β-chloro-α, β-unsaturated esters (**207** or **238**)[54] thus formed must be cleanly converted to the desired product **182**. Treatment of *cis*-chloride **207** to the reaction conditions produced the expected trisubstituted olefin **182** in 59% yield as a single isomer. When the *trans*-chloride **238** was employed the olefin **239** was generated in slightly low yield of 51%. The observed olefin **239** was the stereoisomer of the desired olefin **182**. The fact that **207** was efficiently converted to **182** in higher yield compared to **238** suggested that this intermediate was implicated in the catalytic cycle more favourably to produce the thermodynamically more stable (E)-trisubstituted olefin **182**. Moreover, it was very interesting to note that the configuration of the final olefin products **182** and **239** were not altered from the starting substrates **207** and **238**. These results indicated that the

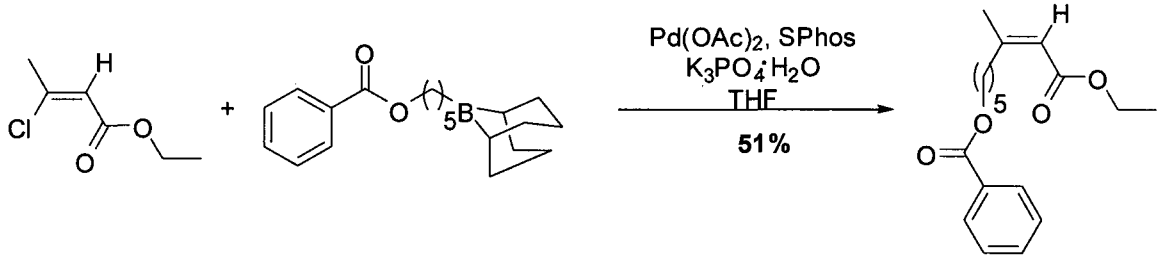
[54] (a) Hatch, L. F.; Perry, R. H.; *J. Am. Chem. Soc.* **1955**, 77, 1136. (b) Jones, D. E.; Morris, R. O.; Vernon, C. A.; White, R. F. M.; *J. Chem. Soc.* **1960**, 2349. (c) Conrow, R. E.; Marshall, J. A.; *Synthetic Commun.* **1981**, 11, 419.

observed inversion in stereochemistry in the final trisubstituted olefin **182** must occur during the replacement of the iodide with the hydrogen (Scheme 30).

Scheme 30. β-chloro-α, β-unsaturated esters (**207** and **238**) as plausible intermediates in an alkyl-Suzuki cross-coupling reaction



207 **181** **182**

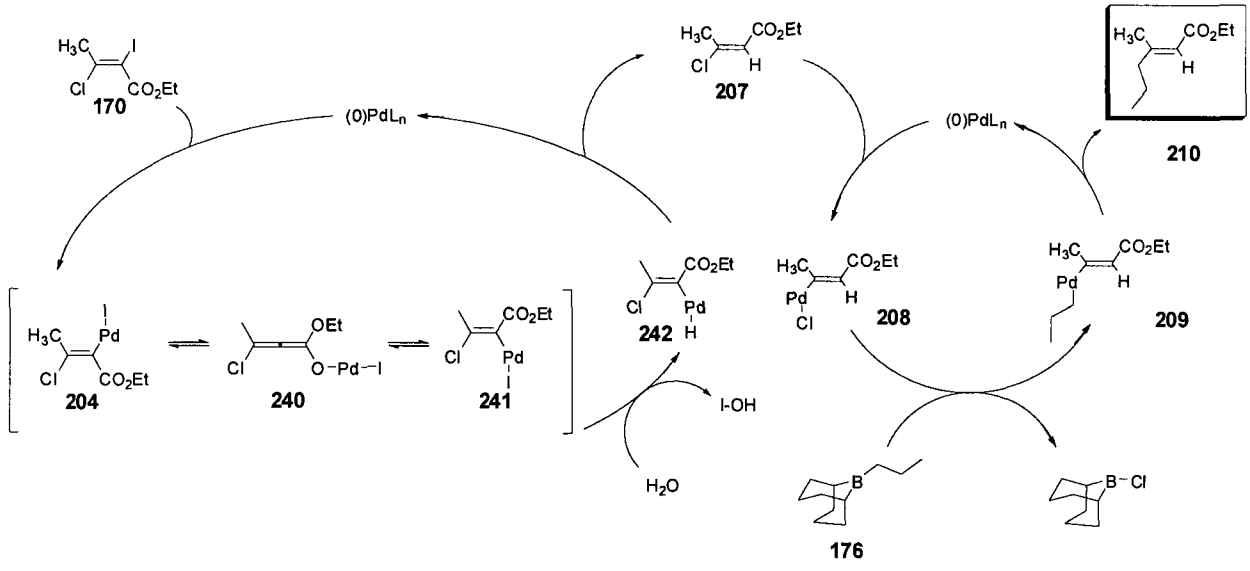


238 **181** **239**

Based on the source of the olefinic hydrogen in the key reaction product **182** and the stereochemical experiments performed, plausible mechanism involving two catalytic cycles was proposed that accounts for the formation of one single trisubstituted isomer **182** from the Suzuki reaction of (*E*)-β-chloro-α-iodo-α,β-unsaturated ester **170** (Scheme 31). The first step involves oxidative addition of the palladium into the C-I bond of the

unsaturated ester **170** to form (*E*)-alkenyl Pd^{II} species **204**. This species is expected to be in equilibrium with palladium allenoate **240** and the isomeric (*Z*)-alkenyl Pd^{II} complex **241**. A protonolysis step involving the H_2O additive would form the palladium-hydride intermediate **242**. The following reductive elimination re-generates the Pd^0 catalyst while expelling the (*E*)-β-chloro-α,β-unsaturated ester **207** which is the entry point for the second catalytic cycle. The unsaturated ester **207** efficiently undergoes alkyl-Suzuki cross coupling to covert to the desired trisubstituted olefin **210**. The conversion of **207** into **210** suggests intermediates such as **207** were implicated in the cycle and not the isomeric chloride **238**.

Scheme 31. Proposed Catalytic Cycle

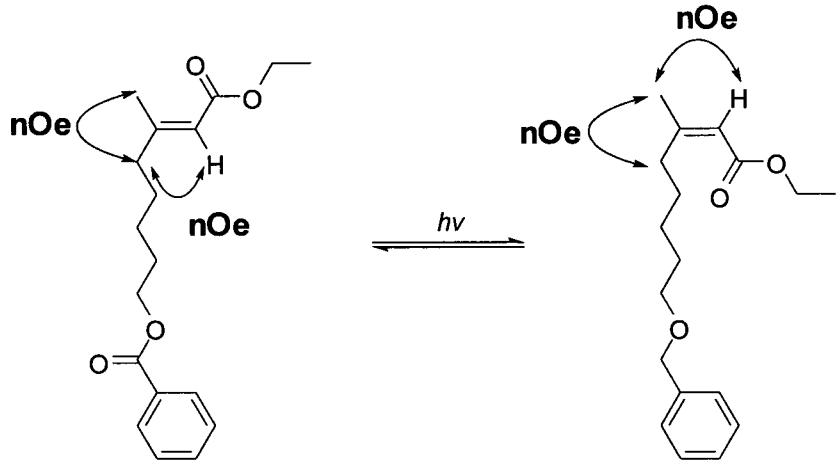


2.1.4 Structure Determination

An alkyl-Suzuki cross coupling between β-chloro-α-iodo-α,β-unsaturated ester **170** and 9-alkyl-9-BBN **181** using $Pd(OAc)_2$ as the catalyst, S-Phos as the ligand, $K_3PO_4 \cdot H_2O$ as the base, and THF as the solvent produced the trisubstituted olefin **182** as a single isomer indicating that the process exerted control over both stereochemistry and regioselectivity.

The stereochemistry of the observed trisubstituted olefin **182** was confirmed by analyzing NOE interactions obtained for both the desired product **182** and its photoisomerized olefin **239** as shown in scheme 32. In order to achieve this isomerization, UV light with a wavelength of approximately 210 nm was required. Such light does not pass through normal glass nor quartz test tubes. Employing a sensitizer such as p-xylene to carry out the reaction resulted in unwanted side products after overnight exposure. However, reducing the reaction time and removing the sensitizer resulted in a successful isomerization. The desired olefin **182** was dissolved in freshly distilled DCM in a quartz tube and the solution was photolyzed using a UV lamp (λ = 300 and 254 nm) for 4 h to produce the other isomeric olefin **239**.

Scheme 32. Elucidating the stereochemistry of the trisubstituted olefin



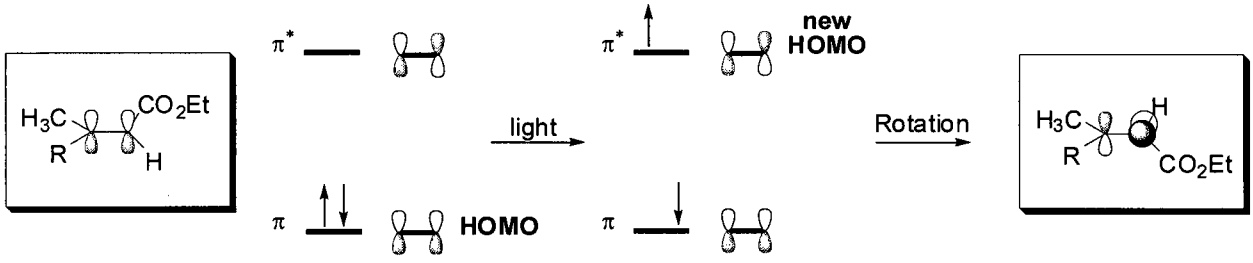
181 **239**

Photochemical *cis*-*trans* isomerization[55] of the alkene played a very important role in elucidating the stereochemistry of the products. *Cis* and *trans* isomers show a different absorption maxima; hence the relative amount of light absorbed by the *cis* and *trans* isomers at a given wavelength will not be identical. As a result, the isomerization of one isomer will occur faster than the other and its concentration will diminish until a photostationary state is reached in which the rate of *trans* to *cis* isomerization is equal to the rate of *cis* to *trans* isomerization.

[55] Carey, F. A.; Sundberg, R. J., *Advanced Organic Chemistry*, 5th ed., Springer-Verlag, New York, 2007, pp. 1081.

Isomerization occurs when an alkene absorbs a photon, promoting an electron from the π to the π* orbital. The resulting species then undergoes rotation to an excited state in which the sp^2 carbons are twisted 90° with respect to one another. The following perpendicular rearrangement is thought to be the minimum-energy geometry that reduces the electron repulsion between the somo orbitals. Continued rotation allows the possibility to return to either the *cis* or *trans* ground states (Figure 5).

Figure 5. Photochemical isomerization of alkenes

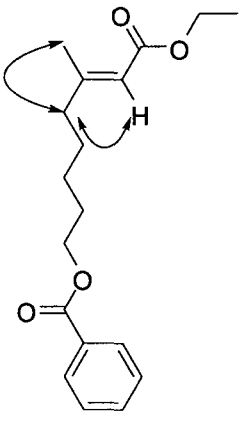
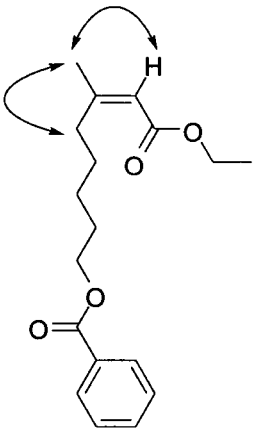
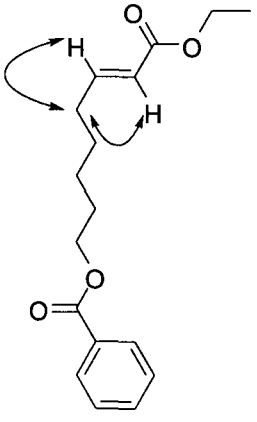


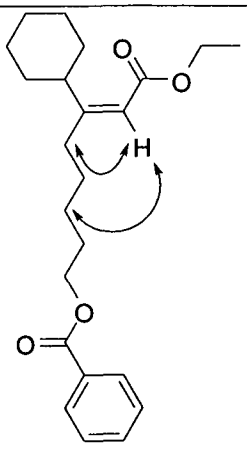
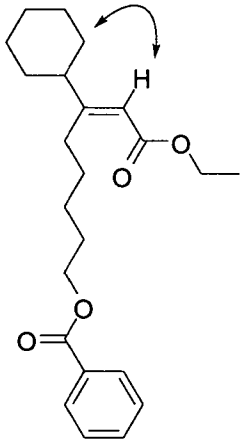
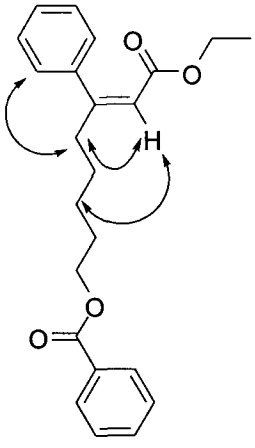
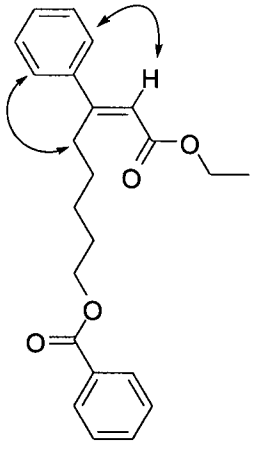
The key reaction product **182** displayed an NOE interaction between the methyl group on the olefin and the CH_2 group of the alkyl substituent as shown. In addition, interaction was noted between the alkyl CH_2 group and the olefinic hydrogen. The photoisomerized product **239** displayed a key enhancement between the terminal methyl group and the olefinic hydrogen. These NOE interactions would be possible only if the 9-alkyl-9-BBN couples at the β position and gave a product in which this group was *syn* to the olefinic hydrogen. The regiochemistry of product **182** was inferred by the magnitude of the long range coupling constant between the olefinic hydrogen

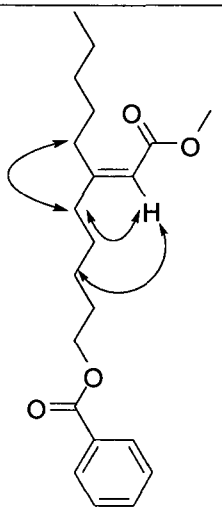
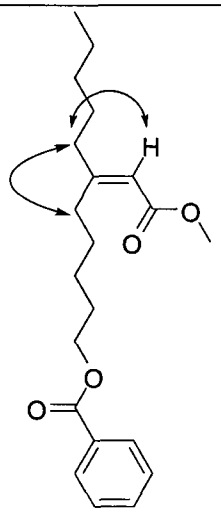
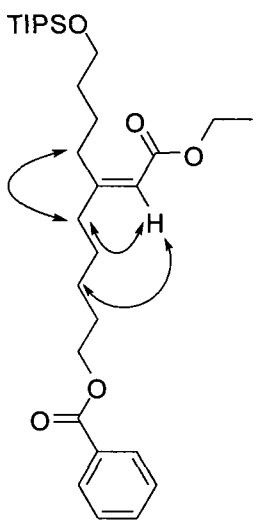
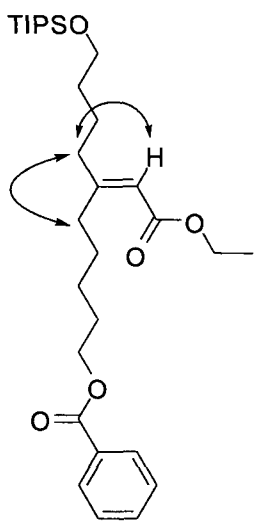
and the methyl group of both isomers **182** (1.2 Hz) and **239** (0.8 Hz). Hence, the network of NOE enhancements leads to one true possibility of the stereochemistry of product **182** and that is the 9-alkyl-9-BBN couples at the β position for both products and the stereochemistry is *E* as shown.

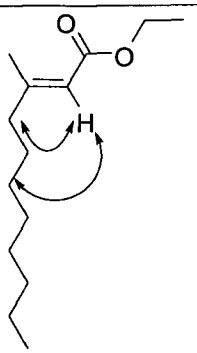
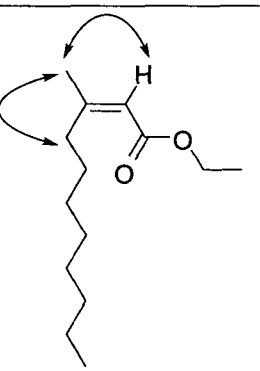
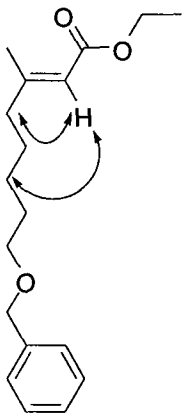
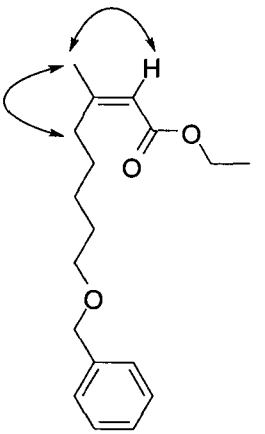
The desired trisubstituted olefin (*E*)-**182** and photoisomerized olefin (*Z*)-**239** are observed as inseparable mixtures of isomers in 1:1 ratio. The product **182** is thermodynamically more stable as the two largest substituents across the double bond are in opposite orientation, thus reduce the steric hindrance seen in the isomerized olefin **239**.

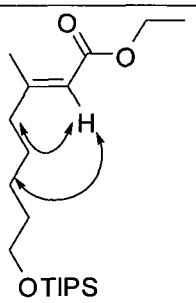
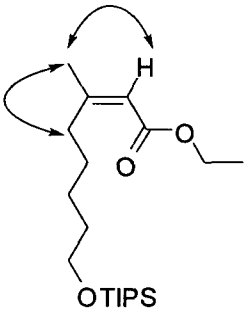
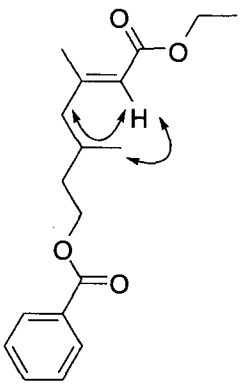
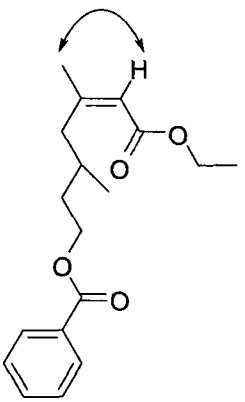
Table 23. Proof of stereoselectivity using nOe analysis

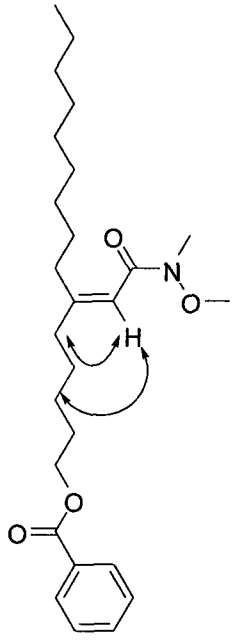
Original Isomer	Isomer
(E)  **182**	(Z)  **239**
(E)  **191**	
(Z)	(E)

 **192**	 **243**
(Z)  **244**	**(E)**  **245**
(E)	**(Z)**

 **193**	 **246**
(Z)	**(E)**
 **194**	 **247**
(E)	**(Z)**

 **195**	 **248**
(E)	**(Z)**
 **196**	 **249**
(E)	**(Z)**

 **197**	 **250**
(E)  **198**	**(Z)**  **251**
(E)	



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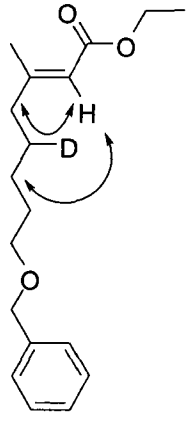
(E)



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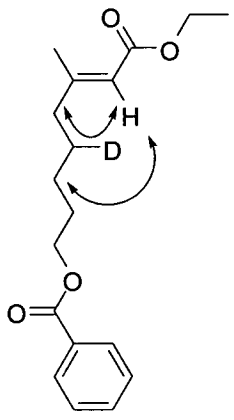
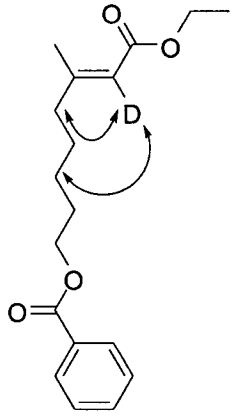
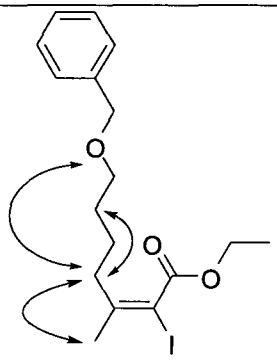
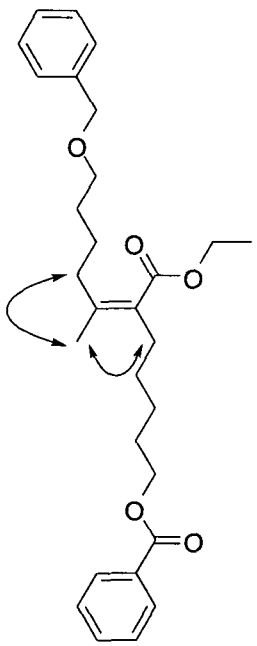
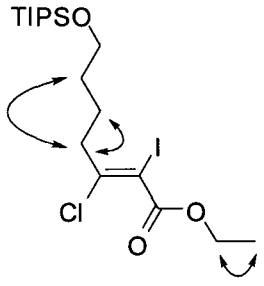
(E)  **230**	
(E)  **203**	
(E)	

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

 **190**	

Chapter 3

3.1 Conclusions

In summary, a regiospecific and stereoselective palladium-catalyzed cross-coupling reaction of 9-alkyl-9-BBN onto (*E*)-β-chloro-α-iodo-α,β-unsaturated esters has been developed to produce single isomer trisubstituted olefins in excellent yields. This methodology can be further expanded to introduce various alkyl groups at the β-position. The mechanism is somewhat unusual as it involves two catalytic cycles with an allenoate intermediate to elucidate the observed stereochemistry and protonolysis of that intermediate to produce the key product, (*E*)-β-chloro-α,β-unsaturated ester. The protonolysis is mediated by the presence of H_2O in the inorganic base, $K_3PO_4 \cdot H_2O$. The (*E*)-β-chloro-α,β-unsaturated ester intermediate rapidly undergo stereoselective alkyl-Suzuki coupling to deliver the final trisubstituted olefin product as a single isomers.

Chapter 4

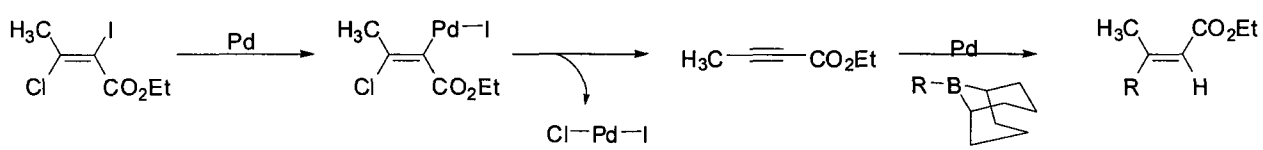
4.1 Results and Discussion

Synthesis of Single Isomer Trisubstituted Olefins from Alkynyl Esters

4.1.1 Discovery of the Reaction

During the mechanistic investigation of the formation of trisubstituted olefins from (*E*)-β-chloro-α-iodo-α,β-unsaturated esters, it was suggested that this process might involve an alkyne intermediate (Scheme 26).

Scheme 26. Possibility of the mechanism involving an Alkynyl Intermediate

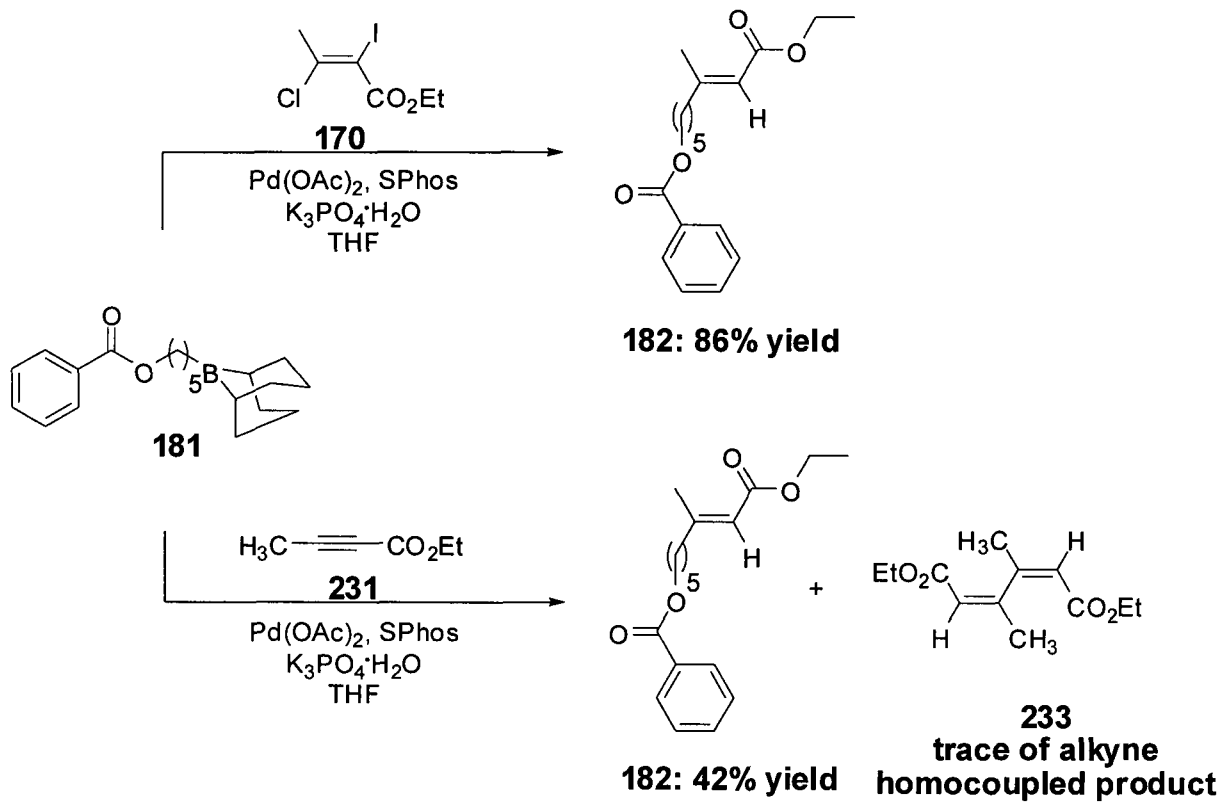


170 **204** **231** **232**

To test this, an alkynyl ester **231** was subjected to an alkyl-Suzuki cross coupling with 9-alkyl-9-BBN **181** under our optimized conditions (Scheme 27). This reaction produced the desired trisubstituted olefin **182** in moderate yield (42%) together with a small amount of alkyne homocoupled side product **233**. Conversely, an alkyl-Suzuki cross coupling between the unsaturated ester **170** and 9-alkyl-9-BBN **181** under similar

conditions afforded the single isomer trisubstituted olefin **182** in excellent yield. The presence of the product arising from homocoupling of the alkynyl ester ruled out the possibility of an alkyne intermediate in the formation of trisubstituted olefins from (*E*)-β-chloro-α-iodo-α,β-unsaturated esters.

Scheme 27. A new project emerge following Alkynyl intermediate elimination in the mechanistic study



Though these results were carried out as part of the mechanistic study, a new synthetic project emerged out of it. These results indicated that trisubstituted olefins could also be synthesized from simple alkyne templates.

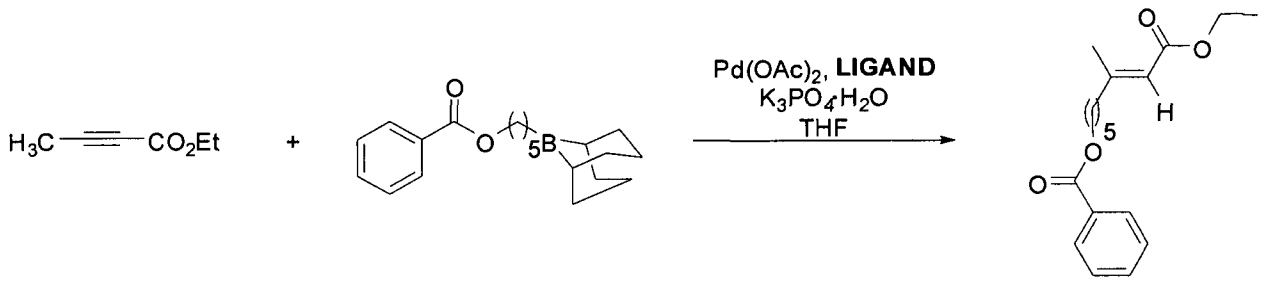
4.1.2 Optimizations

To establish an efficient cross coupling between the alkynyl ester **231** and 9-alkyl-9-BBN **181**, maximizing the yield of the desired trisubstituted olefin **182** and minimizing the formation of the alkyne homocoupled side product, an optimization study was initiated.

As the first step, the effect of the ligand used in the reaction was analyzed beginning with the biphenyl S-Phos ligand (Table 24, Entry 1). This experiment afforded the desired material in moderate yield. Correspondingly, employing a monodentate phosphine ligand such as Davephos resulted in a decreased yield (30%) (Entry 2). The use of bidentate phosphine ligands such as Diphos (DPPE) and Xantphos suppressed the overall reaction (Entries 3 and 4). When DPPF and DPPB were employed as the ligand, the efficiency of the process greatly improved to provide 62 and 58% yields respectively (Entries 5 and 6). However, the bidentate phosphine ligands with shorter lengths, DPPP and DPPM proved to be ineffective ligands affording low yields of product **182** (Entries 7 and 8).

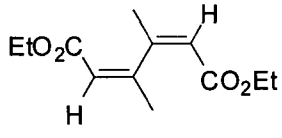
Employing alkyl-substituted bulky phosphine ligands such as Cy_3P dramatically improved the reactivity and afforded the desired olefin **182** in the highest yield of 75% (Entry 9). The use of tBu$_3$P as a ligand resulted in a reaction with moderate yield (50%) (Entry 10). The application of smaller alkyl-substituted phosphine ligands produced success. As shown in Entry 11, MetBu$_2$P worked quite well as a ligand, giving a good yield (69%) of the trisubstituted olefin product. By decreasing the size of the ligand slightly by using Et_3P, the desired trisubstituted olefin **182** was isolated in 49% yield (Entry 12). In all cases only a trace of the alkyne homocoupled product **233** was observed.

Table 24. Analyzing the Ligand



231 **181** **182**

Entry[a]	LIGAND	Yield (%)[b]
1	SPhos	42
2	Davephos	30
3	Diphos	18
4	Xantphos	3
5	DPPF	62
6	DPPB	58
7	DPPP	23
8	DPPM	33
9	**PCy_3•HBF_4**	**75**
10	$PtBu_3$•HBF_4	50
11	$PtBu_2Me$•HBF_4	69
12	PEt_3•HBF_4	49

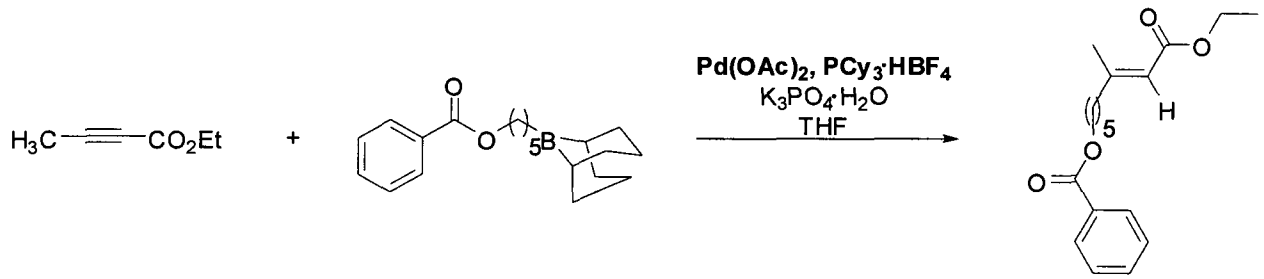
[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.10 equiv of LIGAND, 3.0 equiv of K_3PO_4•H_2O, 3.0 equiv of 5-(9-borabicyclo[3.3.1]nonan-9-yl)pentyl benzoate, THF (0.09M), 23°C, 18 h. [b] Isolated yield. **NOTE:** Trace amount of alkyne homocoupled product was observed in all cases, 

.

Though an optimal ligand was determined, the side product was not completely eliminated through such ligand screening. Hence, a further optimization was pursued by investigating the ratio of the metal to the ligand employed in the catalyst system.

Originally the reaction was performed using a 1:2 ratio of catalyst to ligand. At this ratio, the alkynyl ester **231** was successfully converted to the trisubstituted olefin **182** in good yield (75%), but a small amount of the side product **233** was also observed (Table 25, Entry 2). When the amount of ligand employed was reduced to equal the amount of the catalyst in the system (1:1), the efficiency of the reaction suffered as the trisubstituted olefin product **182** was isolated in only 53% yield together with a trace amount of **233** (Entry 1). Tripling the amount of ligand with respect to the palladium (1:3), gave the desired trisubstituted alkene **182** in 71% yield with no trace of side product **233** observed by TLC (Entry 3). It was concluded that in the presence of excess ligand the reaction proceeded more efficiently than at lower ligand loading, affording good yields of the desired trisubstituted olefin product **182**.

Table 25. Eliminating the Side Product



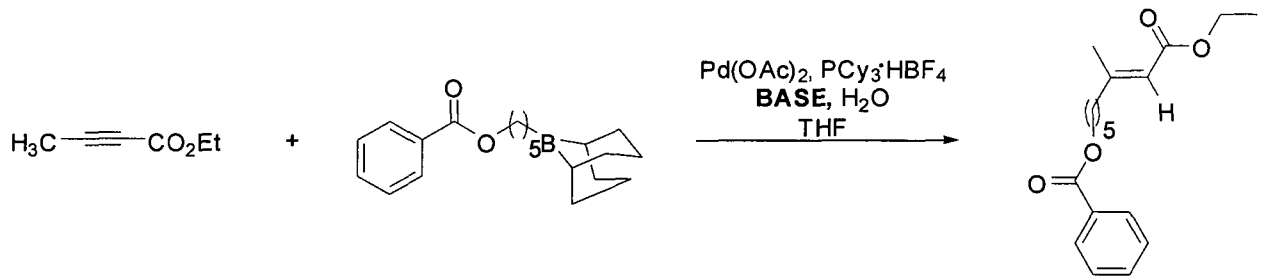
231 **181** **182**

Entry[a]	$Pd(OAc)_2$:PCy_3•HBF_4	Yield (%)[b]
1	1:1	53
2	1:2	75
3[c]	1:3	71

[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.10 equiv of PCy_3•HBF_4, 3.0 equiv of K_3PO_4•H_2O, 3.0 equiv of 5-(9-borabicyclo[3.3.1]nonan-9-yl)pentyl benzoate, THF (0.09M), 23°C, 18 h. [b] Isolated yield. [c] Only the desired product was observed without any presence of the side product.

Although the use of $Pd(OAc)_2$ as the catalyst and $Cy_3P \cdot HBF_4$ as the optimal ligand in 1:3 ratio gave a single isomer trisubstituted olefin product in good yields (71%), the effect of different bases on the reaction of alkynyl ester **231** with 9-alkyl-9-BBN **181** was investigated in an effort to improve the yield while still isolating a single isomer trisubstituted olefin product.

Table26. Investigating the Base



231 **181** **182**

Entry[a]	BASE	Yield (%)[b]
1	$K_3PO_4 \cdot H_2O$	71
2	K_3PO_4	70
3	K_2HPO_4	72
4	KH_2PO_4	68
5	Cs_2CO_3	68
6	Na_2CO_3	63
7	K_2CO_3	69
8	Et_3N	76
9	DIPEA	79
10	**DABCO**	**90**

[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.15 equiv of $PCy_3 \cdot HBF_4$, 3.0 equiv of BASE, 3.0 equiv of H_2O, 3.0 equiv of 5-(9-borabicyclo[3.3.1]nonan-9-yl)pentyl benzoate, THF (0.09M), 23°C, 18 h. [b] Isolated yield.

The use of an inorganic base such as $K_3PO_4 \cdot H_2O$ for the reaction of alkynyl ester **231** with 9-alkyl-9-BBN **181** provided the starting point for our investigation. Its use in THF afforded the desired olefin **182** in good yield (Table 26, Entry 1). Previously we

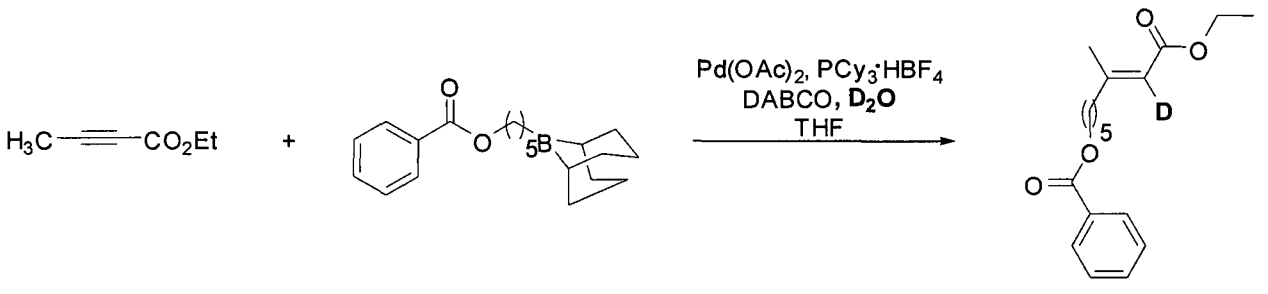
had found that the presence of water in the reaction medium dramatically improved the cross-coupling. Throughout the subsequent investigation an additional 3 equivalent of H_2O was employed to facilitate each reaction. It was predicted that the H_2O was the source of the olefinic hydrogen present at the α-position of the trisubstituted olefin **182**. The family of potassium phosphates such as K_3PO_4, K_2HPO_4, KH_2PO_4 were screened and we found yields comparable to entry 1 (Entries 2-4). Similarly, the use of Cs_2CO_3 afforded the olefin **182** in a yield 68% (Entry 5). When Na_2CO_3 was employed as the base, the alkyne **231** was converted to an alkene **182** in lower yield (63%) (Entry 6). Using K_2CO_3 as the base gave a slightly increased yield of the olefin product **182** (Entry 7). Replacing the inorganic base with an unhindered organic base, Et_3N resulted in a dramatic increase in the yield of the trisubstituted olefin product (76%) (Entry 8). The use of a hindered amine, DIPEA or N, N-diisopropylethyl amine, proved very promising for the alkyl-Suzuki cross coupling reaction of alkynyl ester and 9-alkyl-9-BBN (Entry 9). However, an excellent yield of trisubstituted olefin **182** (90%) was observed when a bicyclic diamine such as DABCO or 1,4-diazobicyclo[2.2.2]octane was employed (Entry 10).

Overall DABCO proved to be the most promising base for the reaction of alkynyl esters with 9-alkyl-9-BBN reagents. At this point, we decided not to further continue the optimization. Hence, the borane reagents, temperature, and time were not further examined. An alkyl-Suzuki cross coupling reaction of (*E*)-β-chloro-α-iodo-α,β-unsaturated esters or alkynyl esters efficiently produced the desired single isomer trisubstituted olefin in high yield by employing 9-BBN as the boron source at room temperature over 18 h period of time.

In the previous reaction in which the trisubstituted olefins such as **182** were generated from (E)-β-chloro-α-iodo-α,β-unsaturated esters it was found that the olefinic hydrogen α to the ester arose from the H_2O present in the inorganic base, $K_3PO_4 \cdot H_2O$. Synthesis of the same olefin product from the alkynyl ester required the addition of extra amounts of H_2O to facilitate the reaction when the base was not a hydrated salt (Table 26). Therefore, it was predicted that the source of the olefinic hydrogen at this arose from the added water. To examine this hypothesis deuterium labeling experiments were conducted.

Subjecting alkyne **231** to cross coupling with 9-alkyl-9-BBN **181** using $Pd(OAc)_2$ as the catalyst, $Cy_3P \cdot HBF_4$ as the ligand, and DABCO as the base in THF at room temperature for 18 h in the presence of 3 equivalent of deuterium oxide afforded the olefin product **203** with 40% deuterium incorporation at the α-position (Scheme 33). This result showed that the source of olefinic hydrogen was the H_2O as was observed previously.

Scheme 33. Source of Unique Hydrogen is H_2O



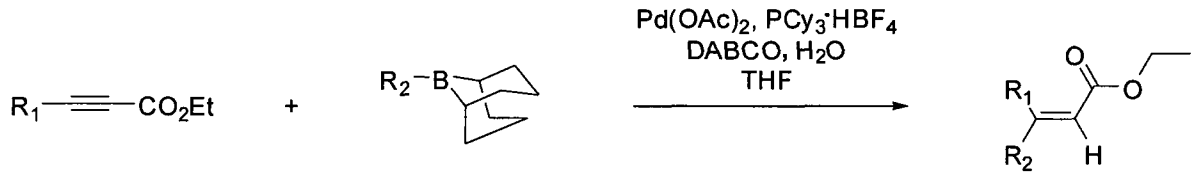
231 **181** **203**

4.1.3 Scope of the reaction

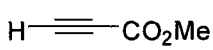
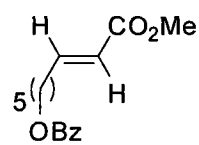
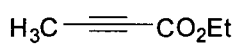
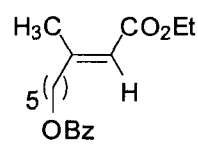
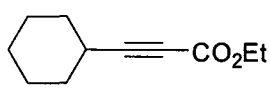
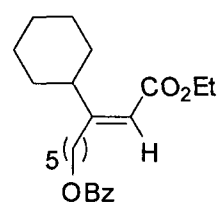
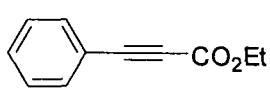
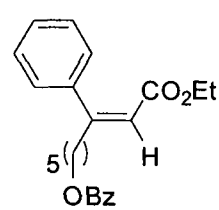
As the conversion of the alkynyl ester into a single isomer trisubstituted olefin was a great success, the scope of the reaction with various alkynyl esters such as **141** and 9-alkyl-9-BBN reagents such as **185** was explored as shown in table 27.

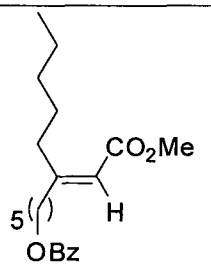
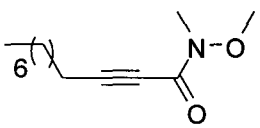
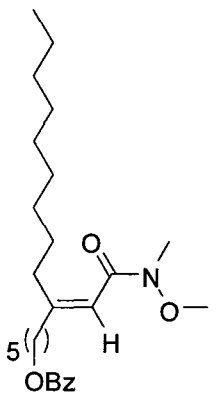
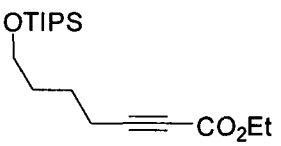
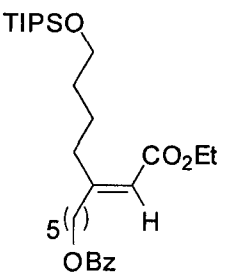
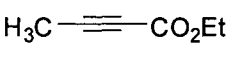
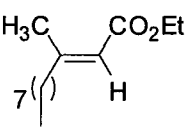
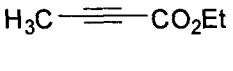
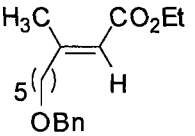
A methyl substituted alkynyl ester, ethyl but-2-ynoate **231** was cross coupled to benzoyl protected terminal alkene **181** to afford the trisubstituted olefin **182** in 90% yield (Table 27, Entry 2). Using methyl propiolate **253** as a substrate did not provide useful amounts of the desired product **191** (Entry 1). When the methyl substituted alkynyl ester was replaced by the branched cyclohexyl substituent, the efficiency of the cross coupling was reduced to afford a moderate yield (41%) of product **192** (Entry 3). By modifying the alkynyl component by adding a phenyl group, the desired olefin product **244** was isolated in excellent yield (80%) (Entry 4). The presence of long alkyl chains was compatible with the reaction conditions as shown in Entry 5. However, replacing the carboxylate moiety with a Weinreb amide slightly lowered the yield to 57% (Entry 6). The performance of the reaction suffered somewhat when an alkoxy substituted alkyl chain component of the alkyne was employed (Entry 7). Based on the results observed in Entries 1 and 5, we could not conclude that replacing the ethyl ester with methyl ester on the alkyne had a significant impact toward the production of the olefin products **191** and **193** respectively.

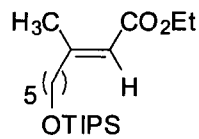
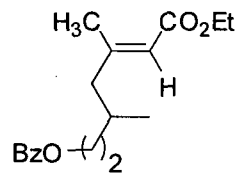
Table 27. Exploring various alkynyl and 9-alkyl-9-BBN reagents



141 **185** **186**

Entry[a]	R_1	Substrate	R_2	Product	Yield (%)
1[b]	H	 **154**	$BzO(CH_2)_5$	 **191**	7
2	CH_3	 **231**	$BzO(CH_2)_5$	 **182**	90
3	C_6H_{12}	 **253**	$BzO(CH_2)_5$	 **192**	41
4	C_6H_6	 **254**	$BzO(CH_2)_5$	 **244**	80

5[b]	$CH_3(CH_2)_4$	 **255**	$BzO(CH_2)_5$	 **193**	74
6[c]	$CH_3(CH_2)_8$	 **256**	$BzO(CH_2)_5$	 **252**	57
7	$TIPSO(CH_2)_4$	 **257**	$BzO(CH_2)_5$	 **194**	55
8	CH_3	 **231**	$CH_3(CH_2)_7$	 **195**	79
9	CH_3	 **231**	$BnO(CH_2)_5$		72

				196	
10	CH_3	H_3C—≡—CO_2Et **231**	$TIPSO(CH_2)_5$	 **197**	87
11	CH_3	H_3C—≡—CO_2Et **231**	$BzO(CH_2)_3C$ HCH_3	 **198**	80

[a] Conditions: 0.05 equiv of $Pd(OAc)_2$, 0.15 equiv of $PCy_3 \cdot HBF_4$, 3.0 equiv of DABCO, 3.0 equiv of H_2O, 3.0 equiv of R_2-9-BBN, THF (0.09M), 23°C, 18 h. [b] The methyl ester was used in place of the ethyl ester. [c] The weinreb amide was used in place of the ethyl ester.

Alkynes often underwent hydroboration with hydroborating agents[56]. When an internal alkynes such as ethyl but-2-ynoate **231** was employed as the substrate for alkyl-Suzuki it was predicted that it could compete with a terminal alkene in the reaction system for hydroboration with 9-BBN. Hence it could affect the overall efficiency of the reaction.

In general, terminal alkyne was competitive for monohydroboration much faster than an internal alkyne. Consequently, clean hydroboration of terminal alkynes of 9-BBN can be achieved at 0°C in THF over 18 h in 2:1 ratio whereas an internal alkyne

[56] Brown, H. C.; Scouten, C. G.; Liotta, R. *J. Am. Chem. Soc.* **1979**, 101, 96.

required between 6 to 12 h at 25°C in THF in 1:1 ratio to afford B-alkenyl-9-BBN derivatives. Hydroboration proceeds regiospecifically to place the boron at the terminal position of the 1-alkyne. In contrast, hydroboration of unsymmetrical internal alkynes produces a mixture of regioisomers.

To avoid a competitive hydroboration between the alkyne and alkene substrates involved in this specific cross coupling, the terminal alkenes were subjected to hydroboration with 9-BBN in 1:1 ratio at 25°C for 2 h in THF in a vial, this solution was then added to a second reaction vial containing the unsymmetrical internal alkyne substrate to perform the cross coupling. Such careful handling produced successful alkyl-Suzuki cross coupling reactions between ethyl but-2-ynoate and various terminal alkenes with 9-BBN and produced the trisubstituted olefin products in excellent yields.

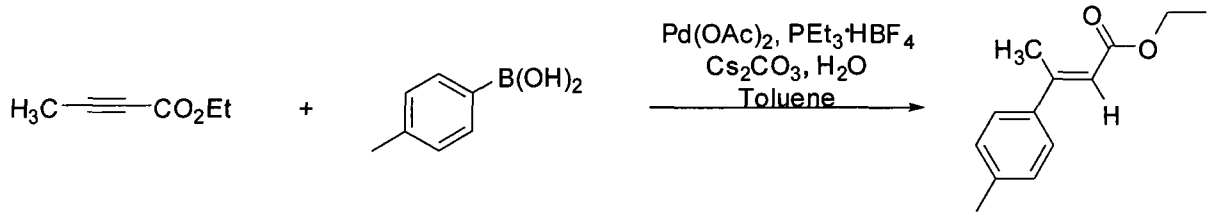
The incorporation of a straight alkyl chain such as octene (Entry 8) resulted in the production of the desired product **195** with an excellent yield (79%). Employing a benzyloxy protected alkene (Entry 9) resulted in a very good yield (72%) similar to that benzoyloxy protected alkene (Entry 2). A more bulky triisopropylsilyloxy protected alkene was compatible with the optimized conditions and the olefin product **197** was isolated with 87% yield (Entry 10). When an α-methyl substituted terminal alkene (Entry 11) was used a promising cross coupling was observed that gave an 80% yield.

4.1.4. Mechanistic Study

The alkyl-Suzuki cross coupling reaction between an alkynyl ester and 9-alkyl-9-BBN was successfully developed using an increase in the size of the phosphine ligand. Thus $Cy_3P{\cdot}HBF_4$ and a hindered bicyclic amine base, DABCO, in the presence of additional amount of H_2O was found to be optimal compared to the alkyl-Suzuki reaction with the unsaturated ester.

A similar case was observed during a different project that was ongoing in the lab. A Suzuki cross-coupling reaction was used to efficiently synthesize a single isomer trisubstituted olefin **259** from an alkynyl ester **231** and aryl boronic acid **258** employing $Pd(OAc)_2$ as the catalyst, $Et_3P{\cdot}HBF_4$ as a smaller phosphine ligand, Cs_2CO_3 as the base in toluene (Scheme 34)[57].

Scheme 34. The formation of trisubstitued olefin from alkynyl ester and arylboronic acid



231 **258** **259**

[57] Bush, A. G.; Jiang, J. J.; Payne, P. R.; Ogilvie, W. *Tetrahedron*. **2009**, 65, 8502.

There are three key similarities observed between the two cross-coupling reactions. In both cases the reaction does not proceed in the absence of H_2O. The arylboronic acid or 9-alkyl-9-BBN and the hydrogen add across the triple bond in a *syn* fashion to introduce the olefinic hydrogen at the α-position and the aryl or alkyl moiety at the β-position. The use of both small and large monodentate phosphine ligands such as $Et_3P{\cdot}HBF_4$ and $Cy_3P{\cdot}HBF_4$ efficiently catalyzed the cross-coupling to produce trisubstituted olefins as single isomers in good yields. In order to speculate the involved mechanism, the role of the phosphine ligand must be thoroughly analyzed.

It is interesting to note that in our Suzuki cross-coupling reaction the partially negative hydrogen from the water adds to the partially negative α-position of the alkynyl ester instead of the partially positive β-position. A Michael or 1,4-addition can insert a nucleophile at the β-position of the alkynyl ester. However, Trost's[58] group has proposed a new and remarkable reaction to introduce a nucleophile at the α-position of alkynoates which is mediated by triphenylphosphine (PPh_3) in acid-base catalyst system. The triphenylphosphine acted as the "nucleophilic trigger" when submitted to an alkynoates **260** underwent a Michael addition forming a vinylphosphonium intermediate **261** which was activated towards addition of a nucleophile to the α-position forming an ylide type species **262**. Following a hydrogen transfer and loss of the phosphine ligand the olefin **263** is generated (Scheme 35).

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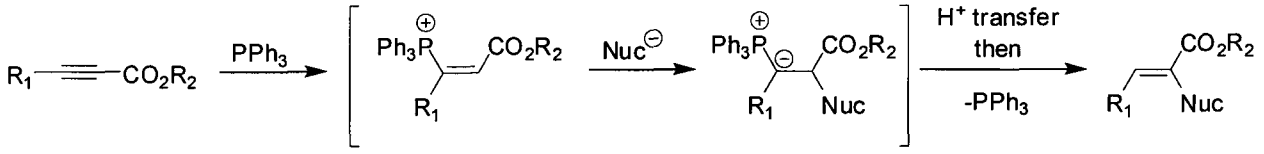
[58] (a) Trost, B. M.; Dake, G. R.; *J. Am. Chem. Soc.* **1997**, 119, 7595; (b) Trost, B. M.; Dake, G. R.; *J. Org. Chem.* **1997**, 62, 5670; (c) Trost, B. M.; Li, C-J.; *J. Am. Chem. Soc.* **1994**, 116, 3167; (d) Trost, B. M.; Li, C-J.; *J. Am. Chem. Soc.* **1994**, 116, 10819; (e) Trost, B. M.; Fleming, I.; Semmelhack, M. F.; In *Comprehensive Organic Synthesis*. Pergamon Press: Oxford, **1991**, 4, Chapter 1.1, pp1-67.

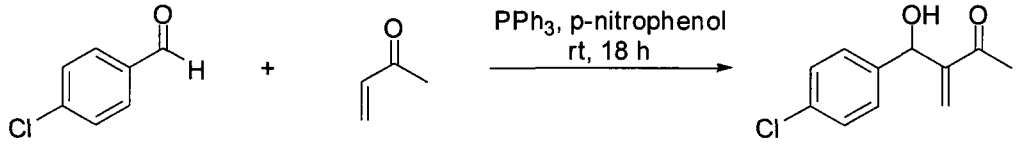
Scheme 35. Nucleophilic α-addition to Alkynoates



260 **261** **262** **263**

The vinylphosphonium intermediate **261** is highly precedented in the Morita-Baylis-Hillman (MBH) reaction[59]. A traditional Baylis-Hillman reaction of aldehydes with methyl vinyl ketones (MVK) is promoted by a Lewis base such as triphenylphosphine together with a Bronsted acid as a proton source. Shi and Liu[60] have recently reported the Morita-Baylis-Hillman reaction of *p*-chlorobenzaldehyde **264** with MVK **265** in the presence of a catalytic amount of weak Bronsted acid, *p*-nitrophenol, promoted by the Lewsis base PPh_3 in THF to effectively produce the corresponding alcohol **266** (Scheme 36).

Scheme 36. Traditional Baylis-Hillman reaction of *p*-chlorobenzaldehyde and MVK



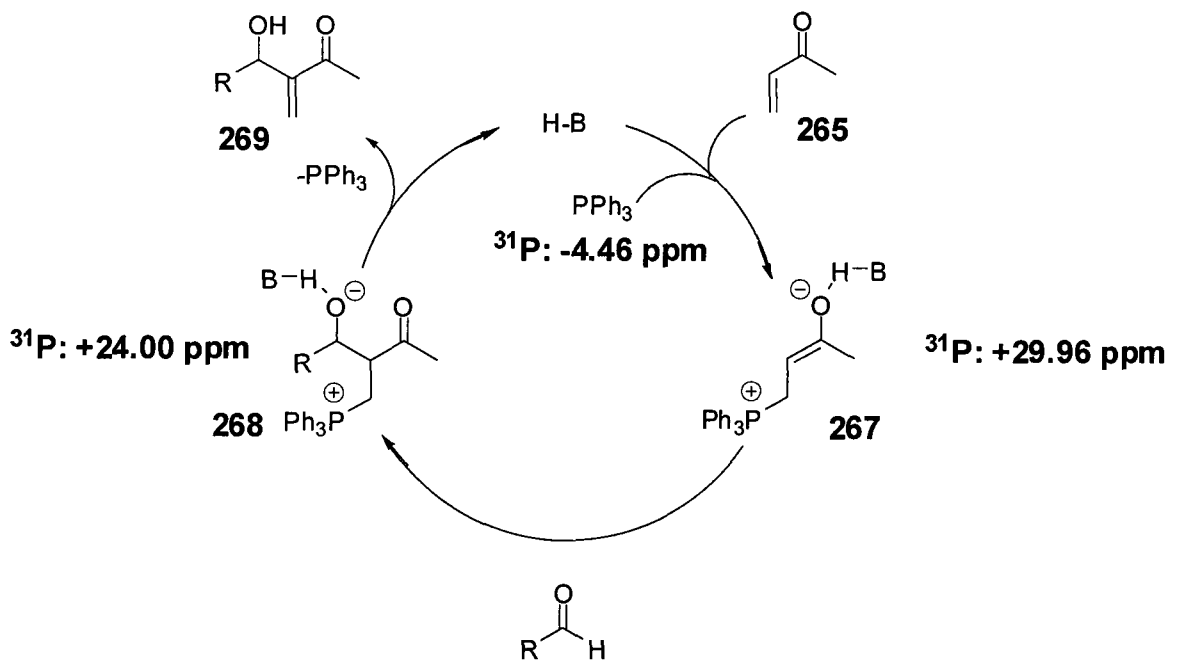
264 **265** **266**

[59] McDougal, N. T.; Schaus, S. E.; *J. Am. Chem. Soc.* **2003**, 125, 12094.

[60] (a) Shi, M.; Liu, Y-H.; *Org. Biomol. Chem.* **2006**, 4, 1486; (b) Shi, M.; Chen, L-H.; Li, C-Q.; *J. Am. Chem. Soc.* **2005**, 127, 3790.

The mechanism of this reaction involves 1,4-addition of PPh_3 onto MVK to form phosphonium enolate **267** which is further stabilized by the weak Bronsted acid via hydrogen bonding. This stabilization drives the reaction forward and accelerates the rate of the reaction. The phophonium enolate intermediate undergoes an aldol reaction with the corresponding aldehyde to form the second phosphonium **268** intermediate. Following a deprotonation the Morita-Baylis-Hillman adduct **269** is generated while regenerating the Lewis base (Scheme 37).

Scheme 37. A plausible mechanism for the Morita-Baylis-Hillman reaction of aldehydes with MVK co-catalyzed by PPh_3 and phenol (Bronsted acid)

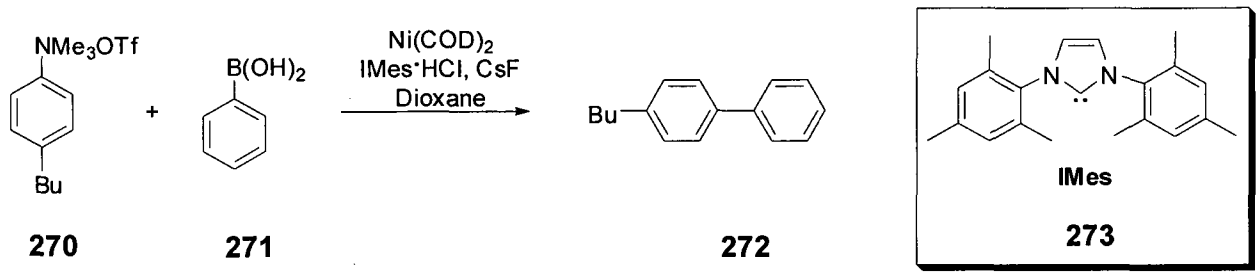


This mechanistic study has been investigated by ^{31}P NMR. A spectrum of the first phosphonium enolate intermediate **267** in the presence of Bronsted acid shows a peak at +29.96 ppm which corresponds to an alkyl(triphenyl)phosphonium ion. However, in the absence of the Bronsted acid, signals at both +29.96 and -4.46 ppm appear which indicates a free PPh_3 in the solution. This means that the phosphonium enolate formed *in situ* exists in equilibrium with free PPh_3. Following the aldol reaction a new signal at +24.00 ppm is seen along with the resonance at +29.96. The new signal indicated the presence of the second phosphonium enolate intermediate **268**.

The vinyl- or alkylphosphonium intermediates are very similar to ammonium salts which are utilized as electrophilic coupling partners in Suzuki cross-couplings with arylboronic acids to form carbon-carbon bonds. MacMillan[61] was the first to report a Suzuki cross-couplings of aryltrimethylammounium triflate **270** with arylboronic acid **271** catalyzed by Ni(0)·IMes in the presence of the mild base CsF which produced the biphenyl product **272** in excellent yield (Scheme 38). The scope of this reaction was extensively expanded to a wide range of boronic acids that incorporate electron donating groups and electron withdrawing groups at the ortho, meta, and para positions. Moreover, when the boron source was substituted with both boronate esters or alkenylboranes, the reaction gratifyingly produced the desired product.

[61] Blakey, S. B.; MacMillan, D. W. C.; *J. Am. Chem. Soc.* **2003**, 125, 6046

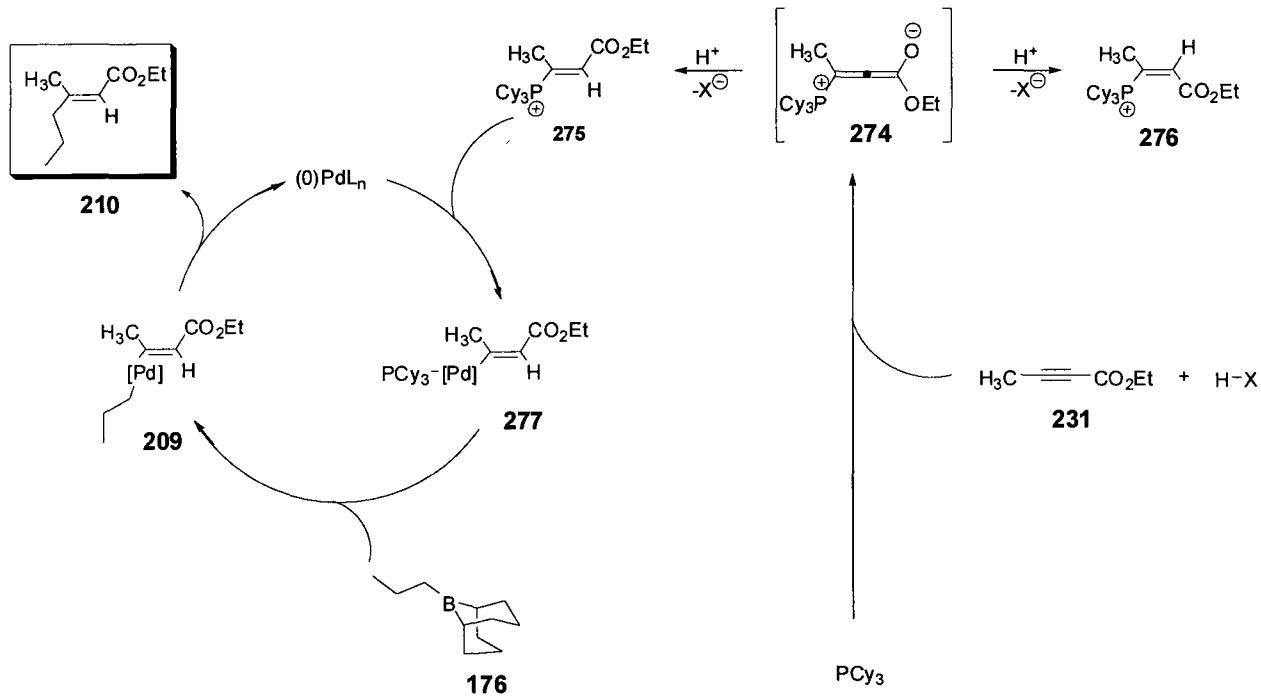
Scheme 38. *Trialkylammonium Salts function as Suzuki Cross-Coupling partner*



270 **271** **272** **273**

Following the literature precedent on the formation of a vinylphosphonium intermediate, it was suggested that the alkyl-Suzuki cross-coupling between alkynyl esters and 9-alkyl-9-BBN reagents could involve a similar intermediate as this reaction contained Cy_3P. This intermediate could be produced via a Baylis-Hillman type reaction. This preactivated intermediate would undergo protonation to allow a potentially nucleophilic hydride from the water to insert at the α-position. The vinylphosphonium intermediate is comparable to the aryltrimethylammonium triflate. Therefore, a phosphonium salt can act as the electrophilic partner and enter an alkyl-Suzuki cross coupling catalytic cycle to form the desired trisubstituted olefin. Hence, based on these speculations the following catalytic cycle was proposed (Scheme 39).

Scheme 39. Possible Catalytic Cycle for alkyl-Suzuki cross-coupling between alkynyl ester and 9-alkyl-9-BBN



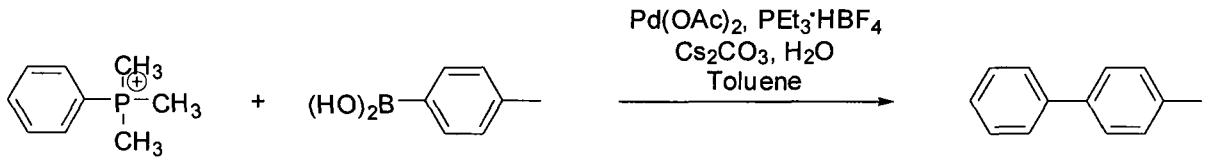
A Cy_3P ligand could undergo 1, 4-addition to the alkynyl ester **231** at the β-position to form allene phosphonium intermediate **274**. Protonation of **274** leads to both regioisomers of vinyltricyclophosphonium adducts **275** and **276**. The most reactive intermediate **275** could undergo oxidative insertion of palladium into the C-P bond to form compound **277**. Transmetalation with 9-alkyl-9-BBN replaces the alkyl moiety with Cy_3P from the palladium to produce the intermediate **209**. Reductive elimination generates the palladium catalyst and produces a trisubstituted olefin **210** with the observed regiochemistry.

In order to support the proposed mechanism as shown in Scheme 39, an evidence that vinyl(tricylco)phosphonium intermediate **275** could exist was mandatory. If the intermediate **275** was present then by submitting a commercially available phosphonium salt such as aryltrimethylphosphonium iodide as an electrophilic coupling partner should undergo a Suzuki cross-coupling with an arylboronic acid to produce the biphenyl product.

Performing a Suzuki cross-coupling reaction between phosphonium salt **278** and arylboronic acid **258** under optimized conditions did not produce the desired biphenyl product **279** at room temperature (Table 28, Entry 1). Refluxing the reaction for 1 h and slowly warming to 25°C with continuous monitoring of biphenyl product formation via TLC over 4 days showed no result (Entry 2). Finally refluxing for 36 h also resulted in no reaction (Entry 3).

A Suzuki cross-coupling reaction between a phosphonium salt and an arylboronic acid proved unsuccessful when palladium was employed as the catalyst under our reaction conditions. However, this reaction could have a broad scope and could emerge as a new protocol to synthesize carbon-carbon bond if it was successfully optimized.

Table 28. Suzuki Cross Coupling between Aryltrimethylphosphonium salt and Arylboronic Acid



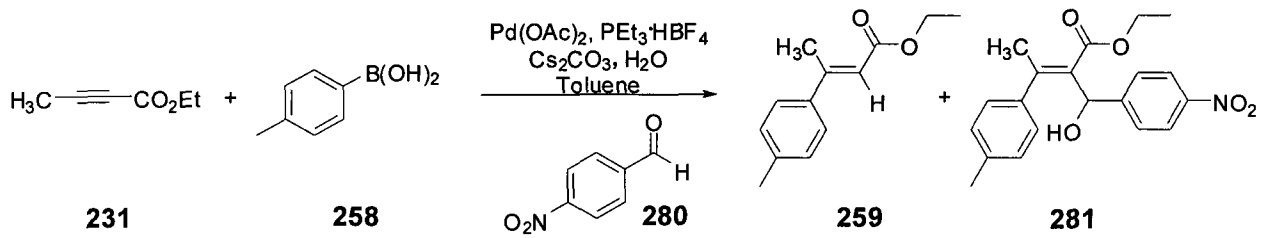
278 **258** **279**

Entry[a]	Condition	Yield (%)
1	r.t (18 h)	No rxn
2	reflux (1h) and r.t (96 h)	No rxn
3	Reflux (>36 h)	No rxn

[a] Conditions: 0.06 equiv of $Pd(OAc)_2$, 0.18 equiv of $PEt_3 \cdot HBF_4$, 2.0 equiv of $MePhB(OH)_2$, 2.1 equiv of Cs_2CO_3, 10.0 equiv of H_2O, THF (0.09M).

Our first attempt to prove the existence of phosphonium intermediate failed. Secondly, we suggested that the phosphonium intermediate could arise from a traditional Baylis-Hillman reaction. To test this hypothesis we submitted alkynyl ester **231** and arylboronic acid **258** under the optimized reaction conditions in the presence of *p*-nitrobenzaldehye **280** (Scheme 40). It was expected under these conditions that we might observe the formation of both the trisubstituted olefin **259** and the tetrasubstituted alcohol product **281**. If the product **281** is formed via a vinylphosphonium intermediate then it would prove our mechanism involves a Baylis-Hillman type process.

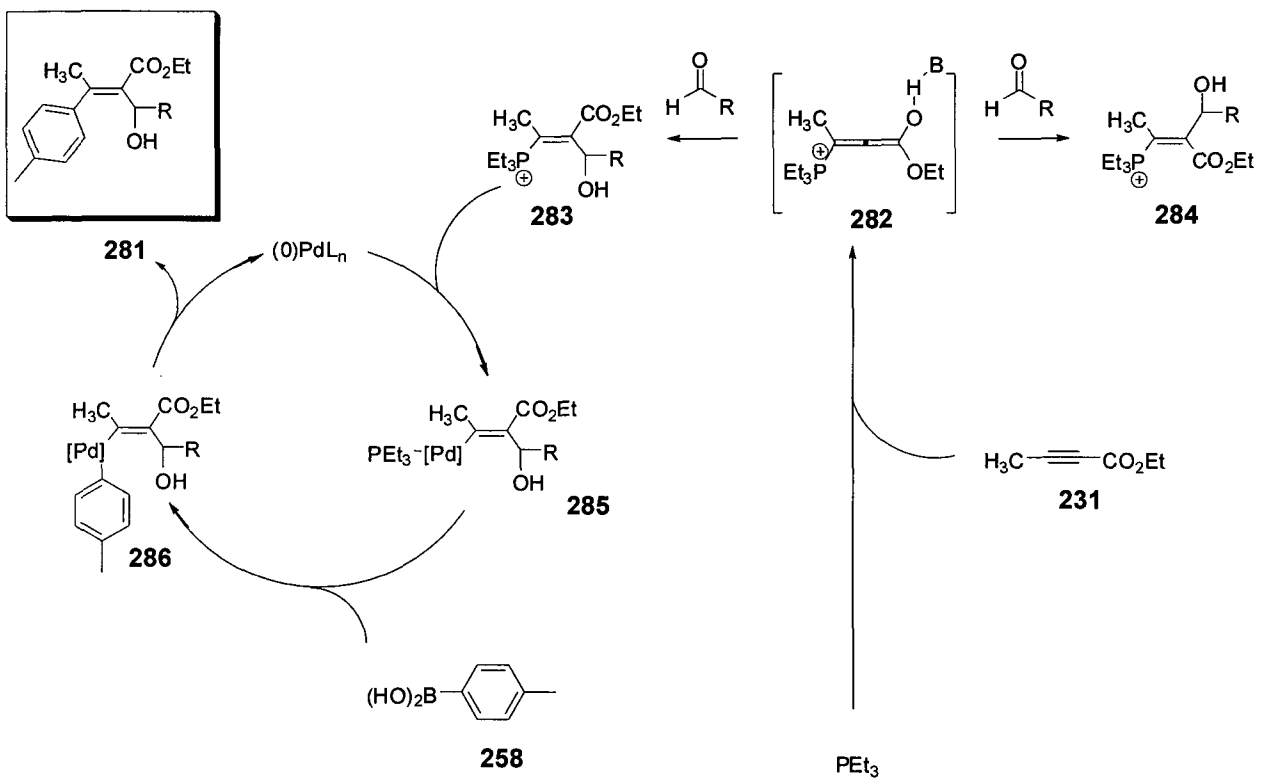
Scheme 40. Alkynyl ester underwent both Suzuki cross-coupling and Baylis-Hillman reaction



231 **258** **280** **259** **281**

To explain the formation of product **281**, the previously proposed mechanism (Scheme 39) was modified as illustrated in Scheme 41. Triethylphosphine adds to the alkynyl ester **231** in a 1,4-fashion to create the first phosphonium allenoate intermediate **282** which is further stabilized by the boronic acid present in the reaction system. This extra stabilization would accelerate the aldol reaction with the corresponding aldehyde to form both isomeric vinylphosphonium aldol products **283** and **284**. The intermediate **283** corresponds to the stereochemistry of the desired trisubstituted olefin **259** and enters into the Suzuki cross-coupling catalytic cycle. An oxidative addition inserts the palladium between the C-P bond to form the species **285**. Transmetalation with arylboronic acid **258** leads to intermediate **286**. Finally reductive elimination provides the desired product **281** and regenerates the palladium catalyst.

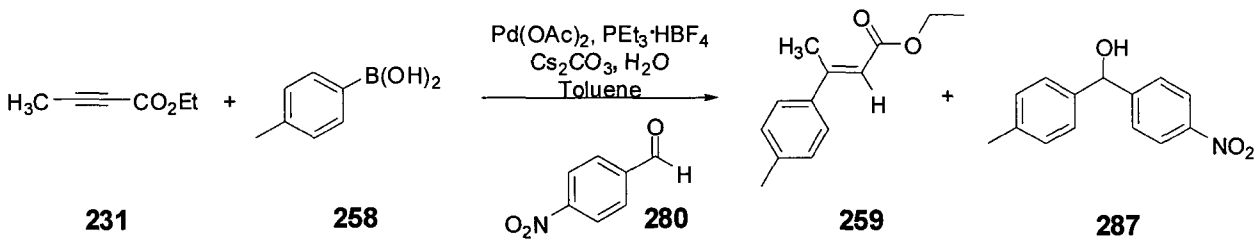
Scheme 41. Alkynyl Ester with arylboronic acid involves Baylis-Hillman followed by Suzuki cross-coupling Mechanism



The reaction with excess of alkynyl ester and arylboronic acid in the presence of an aldehyde was monitored by TLC at room temperature overnight. This reaction produced the trisubstituted olefin **259**, but the desired product **281** was not isolated. However, a trace amount of the unexpected secondary alcohol **287** was observed. Presumably the undesired product **287** arose from the 1,2-addition of the arylboronic acid to the aldehyde mediated by the palladium (0) complexes in the presence of a

base. Such reactions are successfully optimized and precedented in the literature[62] (Scheme 42).

Scheme 42. Suzuki cross-coupling between alkynyl ester and arylboronic acid in the presence of an aldehyde results in an undesired secondary alcohol



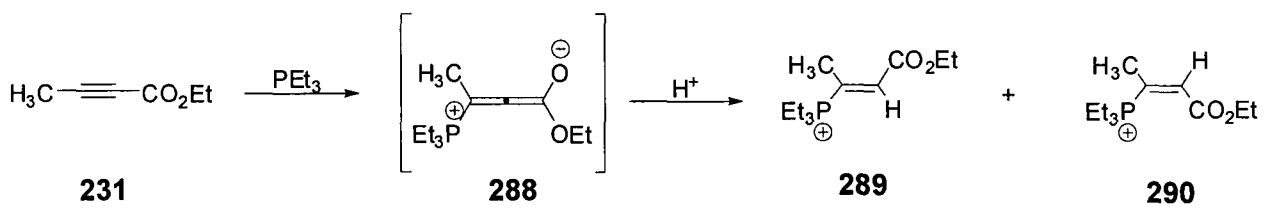
231 **258** **280** **259** **287**

Our aim to prove the existence of the vinylphosphonium intermediate in the formation of alkynyl esters from cross-coupling to arylboronic acids or 9-alkyl-9-BBN via Baylis-Hillman reaction was unsuccessful. Hence, in order to get more mechanistic insight into these phosphine catalyzed systems, we carried out a ^{31}P NMR study which was performed in a NMR tube capped with rubber septa under nitrogen atmosphere. We carried out ^{31}P NMR spectroscopic measurements (in C_6D_6) of triethylphosphine Et_3P in the presence of H_2O, Cs_2CO_3, alkynyl ester, and arylboronic acid. The spectrum of $PEt_3 \cdot HBF_4$ with H_2O (molar ratio = 1 : 5) showed a signal at +23.1 ppm which corresponds to the protonated phosphine. Addition of Cs_2CO_3 (2.0 equivalents) resulted in deprotonation of the phosphonium salt to form free PEt_3 which showed a signal at -19.6 ppm. Introduction of alkynyl ester **231** (1.0 equivalent) produced two additional

[62] Yamamoto, T.; Ohta, T.; Ito, Y. *Org. Lett.* **2005**, 7, 4153.

signals at 43.4 and 37.9 ppm which were assigned to the isomeric vinylphosphonium intermediates such as **289** and **290** (Scheme 43)[63]. The ^{31}P NMR spectrum of the observed intermediates was shown in Figure 5. It was important to note that the signal at -19.6 ppm for free PEt_3 was observed with the presence of alkynyl ester. This observation indicated that vinylphosphonium intermediates that are formed in equilibrium with the free PEt_3. Finally the arylboronic acid (2.0 equivalent) was introduced to the NMR tube and as a result the signal at 43.4 ppm disappeard (Figure 6). These results allowed us to conclude that the signal at 43.4 ppm corresponded to the intermediate **289** which underwent a Suzuki cross coupling reaction with the arylboronic acid. Whereas the intermediate **290** relies with the signal observed at 37.9 ppm.

Scheme 43. Plausible vinylphosphonium intermediates



231 **288** **289** **290**

In order to confirm the observed results, we decide to repeat the ^{31}P NMR study with triphenylphosphine, PPh_3. PPh_3 has been widely explored in Baylis-Hillman reaction and thus its use was precedent in literature. Our ^{31}P NMR chemical shifts could be easily compared to the literature values to confirm our observed results. We

[63] Xu, Z.; Lu, X.; *J. Org. Chem.* **1998**, 63, 5031.

carried out ^{31}P NMR spectroscopic measurements (in $CDCl_3$, referenced to 85% H_3PO_4) of the Lewis base PPh_3, and H_2O (molar ration = 1 : 5) which showed a signal at -4.9 ppm which corresponded to the free PPh_3. No phosphonium salt was detected as predicted from the PEt_3 case. Therefore, the addition of Cs_2CO_3 produced the same signal. Adding an excess of alkynyl ester (10.0 equivalents) generated two additional signal at 43.6 and 28.7 ppm along with the free PPh_3 signal. These two signals were very similar to the ones that were observed with PEt_3.

Figure 5 ^{31}P NMR spectrum of PEt_3, H_2O, Cs_2CO_3 and alkynyl ester in C_6D_6

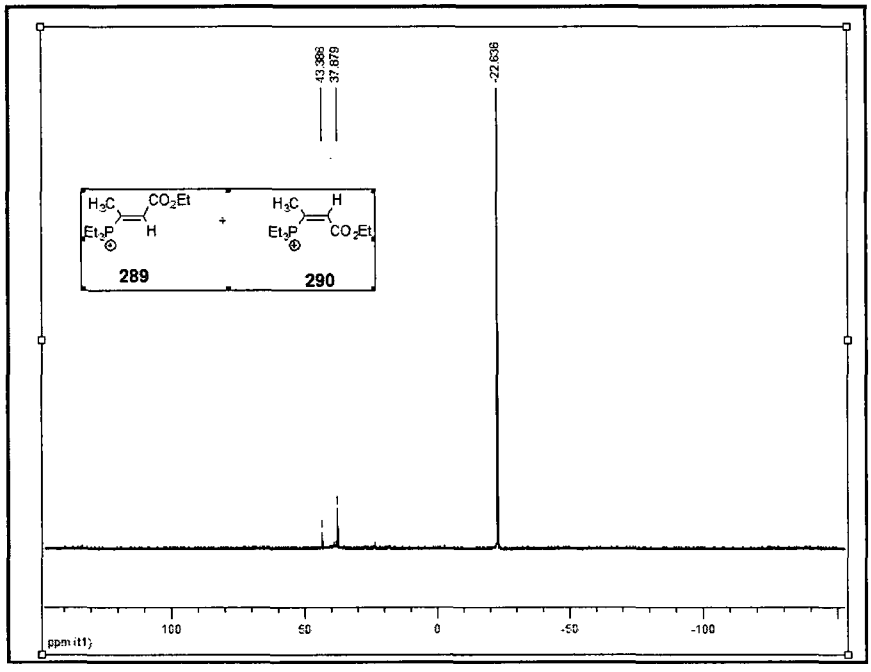
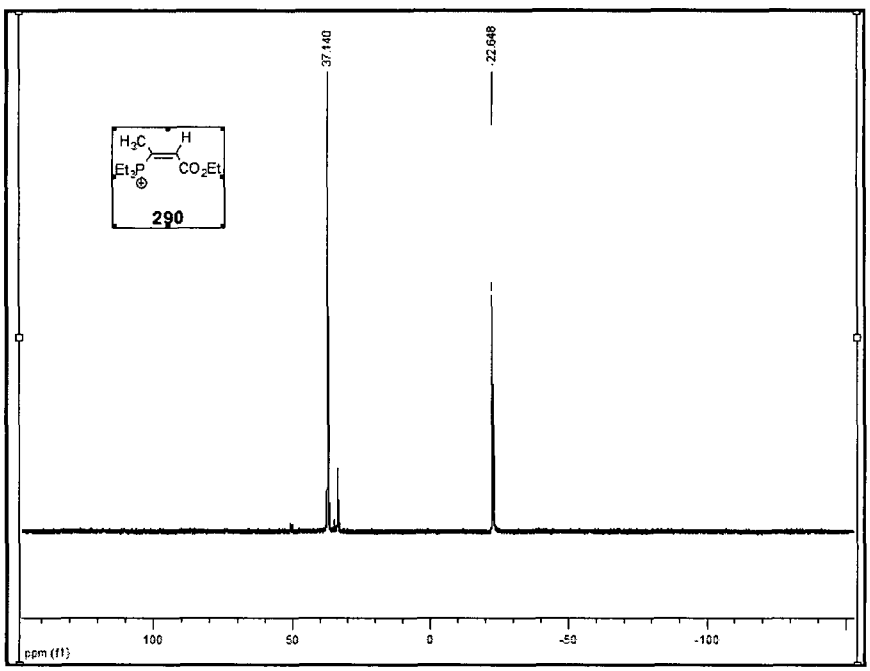


Figure 6. ^{31}P NMR spectrum of PEt_3, H_2O, Cs_2CO_3, alkynyl ester and arylboronic acid in C_6D_6



In the literature it is reported that vinyl(triphenyl)phosphonium ion displays a ^{31}P NMR resonance between 11.7 and 27.5 ppm[64]. Our observed signals for the PPh_3 experiments are not in that range of chemical shift. In consequence, the signal at 43.6 and 28.7 ppm did not correspond to the vinylphosphonium intermediates such as **275** and **276** as depicted in the mechanism (scheme 39). Arylboronic acid (2.0 equivalent s) was added to the NMR tube and the ^{31}P NMR showed the same two signals at 43.6 and 28.5 ppm. Repeating the experiment without the presence of alkynyl ester gave signals at 43.6 and -4.9 ppm. The last two results suggest that our mechanism does not

[64] Hinkle, R. J.; Stang, P. J.; Kowalski, M. H.; *J. Org. Chem.* **1990**, 55, 5033.

involve a vinylphosphonium intermediate. The ^{31}P NMR signal at 43.6 ppm corresponds to phosphorous oxidation to form triphenylphosphine oxide[65].

Neither the alkyl-Suzuki or Suzuki cross-coupling reaction between alkynyl ester and 9-alkyl-9-BBN or arylboronic acid seems to involve a vinylphosphonium intermediate as previously proposed. This reaction does not proceed in the absence of water. The olefinic hydrogen at the α-position of the desired trisubstituted olefin arises from the water as has been proven by the isotopic experiments. Based on these experiments and the previous results[28,66,67], the following mechanism could be proposed (Scheme 44). Palladium undergoes oxidative insertion into the OH bond of the water to form an initial H-[Pd]-OH species. Following the oxidative insertion, there is a *syn* carbopalladation into the triple bond of the alkynyl ester which forms a palladium intermediate **291** with the observed regio- and stereochemistry. Transmetalation of the 9-allkyl-9-BBN is followed by the reductive elimination generates the palladium catalyst and produces the desired trisubstituted olefin **210** as the final product.

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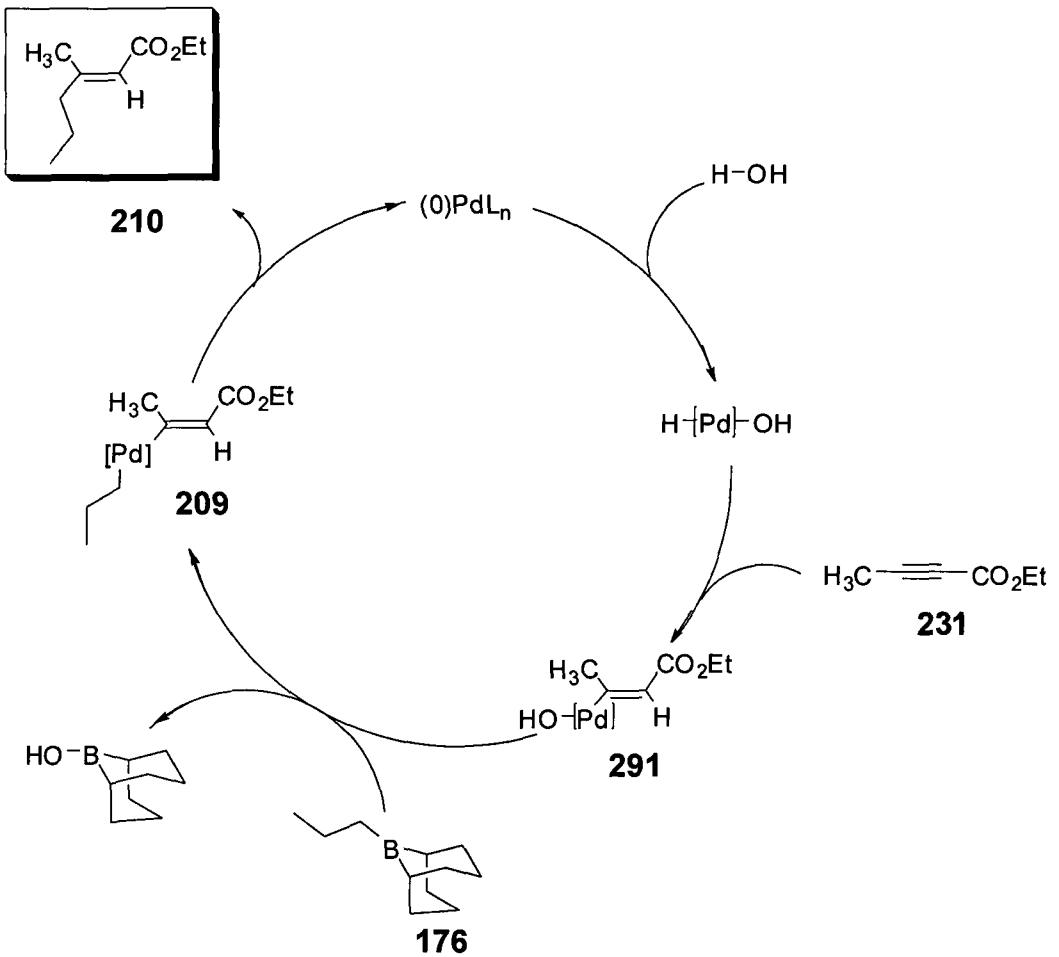
[65] Kayser, M. M.; Hatt, K. L.; *Can. J. Chem.* **1991**, 69, 1929.

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

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

Scheme 44. Possible mechanism for the addition of 9-alkyl9-BBN to alkynyl esters



Though this mechanism has literature precedent[28,66,67] it is associated with few problems. It does not explain why the negative hydrogen adds to the partially negative α-position of the alkynyl ester and what favors the transfer of the alkyl moiety to the partially positive β-position. Neither has it provided an explanation for the observed regio- and stereochemistry. As a result, a new mechanism must be investigated to explain the addition of 9-alkyl-9-BBN or arylboronic acid to the alkynyl esters.

Chapter 5

5.1 Conclusion

In conclusion, a regiospecific and stereoselective palladium-catalyzed cross-coupling reaction of 9-alkyl-9-BBN onto alkynyl esters has been developed to produce single isomer trisubstituted olefins in excellent yields. The scope of this reaction was broadly explored to introduce various alkyl groups at the β-position. Initially we proposed a mechanism that involved a vinylphosphonium intermediate which was formed when phosphine adds to an alkynyl ester via a 1, 4-addition. This hypothesis was proved wrong based on the ^{31}P NMR study which only showed a signal at 43.6 ppm which corresponds to phosphine oxide. The current mechanism proposed involves the oxidation of palladium to form H-[Pd]-OH species. This was confirmed based on the importance of water in the catalytic system and the isotopic experiments which confirm the olefinic hydrogen at the α-position arises from the water itself. Following the formation of H-[Pd]-OH, syn carbopalladation to the alkynyl ester creates the hydroxyl palladium vinyl intermediate. This mechanism does not explain the observed regio- and stereochemistry of the observed trisubstituted olefin. Hence, a new study to investigate the mechanism is required. Overall, the alkynyl ester intermediate rapidly undergoes stereoselective alkyl-Suzuki coupling to deliver the final trisubstituted olefin product as single isomers.

Claims to Original Research

1. Developed a method for the regioselective and stereospecific synthesis of trisubstituted olefins as single isomers from β-chloro-α-iodo-α, β-unsaturated esters.

2. Developed a method for the regioselective and stereospecific synthesis of trisubstituted olefins as single isomers from alkynyl esters.

3. Prepared and characterized 23 trisubstituted olefin derivatives.

4. Proved the stereo- and regiochemistry of the synthesis of trisubstituted olefins by isomerization techniques and NMR analysis.

5. Investigated in details the mechanism of trisubstituted olefins coupling reactions of β-chloro-α-iodo-α, β-unsaturated esters and alkynyl esters.

Presentations

1. "Revealing the mechanism of the trisubstituted olefins" Poster presented at Québec/Ontario Minisymposium in Synthetic and Bioorganic Chemistry, Montreal, QC, November 2008
2. "Mystery behind the mechanism of trisubstituted olefins" Poster presented at Synthesis Day, Ottawa, ON, June 2008
3. "Beginning of the mechanistic studies of the synthesis of trisubstituted alkenes via alkyl Suzuki coupling" Poster presented at Ottawa-Carleton Chemistry Institute Day, Ottawa, ON, May 2008
4. "Novel synthesis of substituted olefins via alkyl suzuki cross-coupling reactions" Poster presented at Québec/Ontario Minisymposium in Synthetic and Bioorganic Chemistry, Montreal, QC, November 2007

Chapter 6

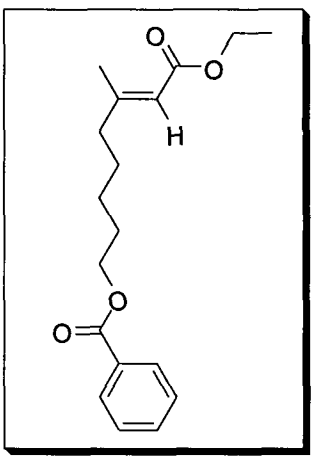
6.1 Experimental

6.1.1 General Experimental Procedure

Reactions were performed in an oven- or flame-dried round bottom flasks or vials under nitrogen atomosphere and equipped with a Teflon-coated stir bar and a rubber septum or a screw cap with a specialized septa. All solvents were freshly distilled prior to use: THF over sodium/benzophenone; Dichloromethane, benzene, dioxane, toluene, DMF, and triethylamine over calcium hydride. Reagents were purchased from Sigma-Aldrich, Lancaster, Strem Chemical, TCI America, and Frontier Scientific. Reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F_{254} pre-coated 0.25 mm thick aluminum plates. TLCs were visualized using ultraviolet light or developed by heating after treatment with potassium permanganate. Products were purified using flash chromatography on silica gel 60 (230-400 mesh). Solvents were evaporated on rotary evaporators.

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance instruments at 300 MHz and 400 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 or 33.0 ppm for decoupled ^{13}C NMR) as internal standard. Infrared spectra were recorded as neat films on a sodium chloride cell with Bomem

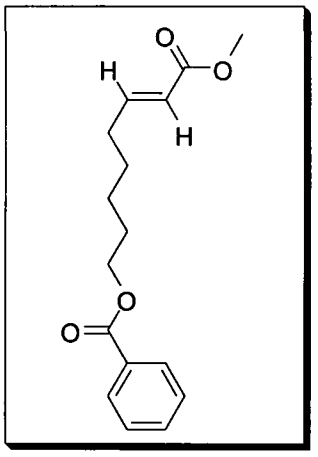
Michaelson 100 FTR spectrometer. Mass spectra were obtained using a Kratos IIH instrument using either CI or EI ionization techniques.



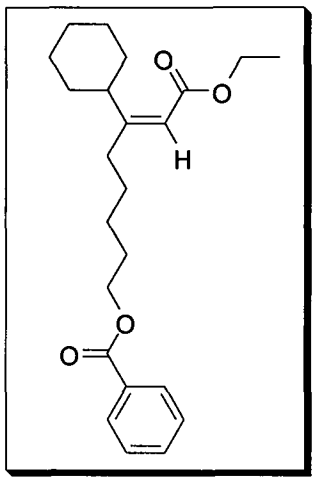
General Procedure for the Preparation of Trisubstituted Alkenes from (2E)-3-chloro-2-iodo-2-alkenoates. (6E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate (182). To an oven dried vial equipped with a teflon-coated stir bar were added $Pd(OAc)_2$ (6.1 mg, 0.0091 mmol), S-Phos (7.5 mg, 0.0182 mmol), and $K_3PO_4 \cdot H_2O$ (125 mg, 0.546 mmol) under a nitrogen atmosphere. Freshly distilled THF was added (1.0 mL) followed by a solution of (2E)-ethyl 3-chloro-2-iodobut-2-enoate (50 mg, 0.182 mmol) in THF (1 mL). To a second oven dried vial equipped with a teflon-coated stir bar were added pent-4-enyl benzoate (104 mg, 0.546 mmol) and 9-borabicyclo[3.3.1]nonane (0.5M solution in THF, 1.10 mL, 0.546 mmol) and the resulting mixture was stirred at room temperature for 2 h. The alkyl-9-BBN solution was transferred to the first vial via canula and the mixture was stirred for 18 h at room temperature. The solution was 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 (48 mg, 86%)

was obtained as a yellow oil by flash chromatography (2% EtOAc in hexane): ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.03 – 8.01 (m, 2H), 7.66 – 7.61 (m, 1H), 7.54 – 7.49 (m, 2H), 5.68 (q, J = 1.2 Hz, 1H), 4.32 (t, J = 6.4 Hz, 2H), 4.08 (q, J = 7.2 Hz, 2H), 2.22 (td, J = 1.2, 7.6 Hz, 2H), 2.15 (d, J = 1.2 Hz, 3H), 1.82 (p, J = 6.4 Hz, 2H), 1.64 – 1.47 (m, 4H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 167.8 (C), 167.7 (C), 161.4 (C), 134.8 (CH), 132.4 (C), 131.1 (CH), 130.4 (CH), 117.4 (CH), 66.4 (CH_2), 60.7 (CH_2), 42.1 (CH_2), 30.2 (CH_2), 28.7 (CH_2), 27.3 (CH_2), 19.6 (CH_3), 15.6 (CH_3); IR (neat) 1718, 1648 cm^{-1}; MS 304.2 (M^+); HRMS calcd for $C_{18}H_{24}O_4$ 304.1675, found 304.1659.

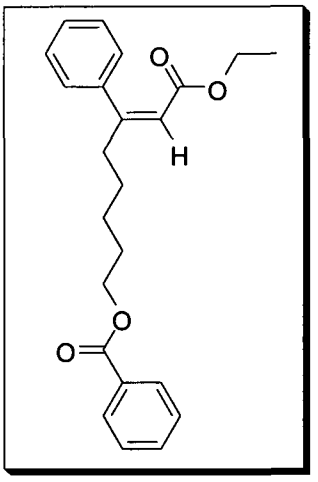
General Procedure for the Preparation of Trisubstituted Alkenes from Alkynyl Esters. (6E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate (182). To an oven dried vial equipped with a teflon-coated stir bar were added $Pd(OAc)_2$ (6.6 mg, 0.0098 mmol), PCy_3•HBF_4 (10.8 mg, 0.0293 mmol), and DABCO (66 mg, 0.586 mmol) under nitrogen atmosphere. Freshly distilled THF was added (1.0 mL) followed by H_2O (10.5 µL, 0.586 mmol) and a solution of ethyl but-2-ynoate (22 mg, 0.195 mmol in 1 mL THF). To a second oven dried vial equipped with a teflon-coated stir bar were added pent-4-enyl benzoate (111 mg, 0.586 mmol) and 9-borabicyclo[3.3.1]nonane (0.5M solution in THF, 1.20 mL, 0.586 mmol) and the resulting solution was stirred at room temperature for 2 h. The alkyl-9-BBN solution was transferred to the first vial via canula and the resulting mixture was stirred for 18 h at room temperature. The solution was 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 (54 mg, 90%) was obtained as a yellow oil by flash chromatography (2% EtOAc in hexane).



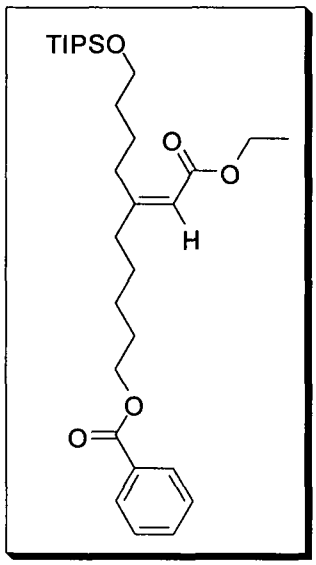
(6E)-8-methoxy-8-oxooct-6-enyl benzoate (191). Prepared from (2E)-ethyl 3-chloro-2-iodoacrylate (57 mg, 0.230 mmol) or methyl propiolate (16 mg, 0.194 mmol) using procedures similar to those described for (6E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (19.1 mg, 30% from (2E)-ethyl 3-chloro-2-iodoacrylate): ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.04 – 8.01 (m, 2H), 7.66 – 7.61 (m, 1H), 7.53 – 7.49 (m, 2H), 6.33 (dt, J = 11.2, 7.6 Hz, 1H), 5.79 (dt, *J* = 11.2, 1.6 Hz, 1H), 4.32 (t, *J* = 6.4 Hz, 2H), 3.65 (s, 3H), 2.70 (dq, *J*= 14.4, 2.0 Hz, 2H), 1.84 – 1.77 (m, 2H), 1.56 – 1.48 (m, 4H); ^{13}C NMR (400MHz, Acetone-d_6) δ 167.9 (C), 167.8 (C), 151.9 (CH), 134.8 (CH), 132.5 (C), 131.1 (CH), 130.4 (CH), 121.2 (CH), 66.4 (CH_2), 52.1 (CH_3), 30.3 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 27.2 (CH_2); IR (neat) 1713, 1637 cm^{-1}; MS 245.1 (M^+ -OCH_3); HRMS calcd for $C_{15}H_{17}O_3$ (M^+ -OCH_3) 245.1178, found 245.1154.



(6Z)-6-cyclohexyl-8-ethoxy-8-oxoocto-6-enyl benzoate (192). Prepared from (2E)-ethyl 3-chloro-3-cyclohexyl-2-iodoacrylate (50 mg, 0.146 mmol) or ethyl 3-cyclohexylpropiolate (34 mg, 0.191 mmol) using procedures similar to those described for (6E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (25 mg, 46% from (2E)-ethyl 3-chloro-3-cyclohexyl-2-iodoacrylate): ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.04 – 8.02 (m, 2H), 7.66 – 7.61 (m, 1H), 7.53 – 7.49 (m, 2H), 5.59 (br, 1H), 4.33 (t, *J* = 6.4 Hz, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.68 (tt, *J* = 11.6, 3.6 Hz, 1H), 2.22 (t, *J* = 6.4 Hz, 2H), 1.87 – 1.26 (m, 16H), 1.22 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 169.7 (C), 167.7 (C), 167.6 (C), 134.8 (CH), 132.5 (C), 131.1 (CH), 130.4 (CH), 116.2 (CH), 66.4 (CH_2), 60.8 (CH_2), 42.3 (CH), 34.7 (CH_2), 32.7 (CH_2), 30.3 (CH_2), 29.9 (CH_2), 28.2 (CH_2), 27.7 (CH_2), 15.6 (CH_3); IR (neat) 1717, 1633 cm^{-1}; MS 327.2 (M+ - OCH_2CH_3); HRMS calcd for $C_{21}H_{27}O_3$ (M^+ -OCH_2CH_3) 327.1955, found 327.1933.

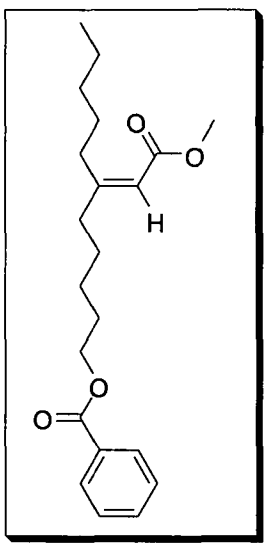


(6Z)-8-ethoxy-8-oxo-6-phenyloct-6-enyl benzoate (244). Prepared from ethyl 3-phenylpropiolate (34 mg, 0.194 mmol) using procedures similar to those described for (6E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (57 mg, 80%): ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.03 – 8.00 (m, 2H), 7.65 – 7.61 (m, 1H), 7.53 – 7.49 (m, 2H), 7.34 – 7.28 (m, 3H), 7.21 – 7.17 (m, 2H), 5.92 (t, J = 0.8 Hz, 1H), 4.28 (t, J = 6.4 Hz, 2H), 3.91 (q, J = 7.2 Hz, 2H), 2.54 (td, J = 0.8, 7.6 Hz, 2H), 1.76 (p, J = 6.4 Hz, 2H), 1.54 – 1.41 (m, 4H), 1.01 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 167.7 (C), 167.0 (C), 160.4 (C), 142.0 (C), 134.8 (CH), 132.5 (C), 131.1 (CH), 130.4 (CH), 129.5 (CH), 129.2 (CH), 119.3 (CH), 66.4 (CH_2), 60.9 (CH_2), 41.6 (CH_2), 30.2 (CH_2), 28.8 (CH_2), 27.2 (CH_2), 15.3 (CH_3); IR (neat) 1715 cm^{-1} ; MS 321.1 (M+ -OCH_2CH_3); HRMS calcd for $C_{21}H_{21}O_3$ (M^+ -OCH_2CH_3) 321.1485, found 321.1439.



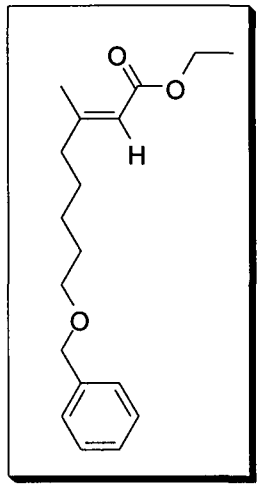
(6Z)-6-(2-ethoxy-2-oxoethylidene)-10-(triisopropylsilyloxy)decyl benzoate (194). Prepared from (2E)-ethyl 3-chloro-2-iodo-7-(triisipropylsilyloxy)hept-2-enoate (50 mg, 0.103 mmol) or ethyl 7-(triisopropylsilyloxy)hept-2-ynoate (52 mg, 0.158 mmol) using procedures similar to those described for (E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (35 mg, 66% from (2E)-ethyl 3-chloro-2-iodo-7-(triisipropylsilyloxy)hept-2-enoate): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 – 8.02 (m, 2H), 7.59 – 7.53 (m, 1H), 7.47 – 7.41 (m, 2H), 5.64 (s, 1H), 4.32 (t, *J* = 6.6 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.69 (t, J = 6.0 Hz, 2H), 2.63 (t, J = 7.5 Hz, 2H), 2.18 (t, J = 6.9 Hz, 2H), 1.79 (p, J = 6.9 Hz, 2H), 1.58 – 1.43 (m, 8H), 1.27 (t, J = 7.2 Hz, 3H), 1.04 (m, 21H); ^{31}C NMR (300 MHz, $CDCl_3$) δ 166.6 (C), 166.5 (C), 163.9 (C), 132.8 (CH), 130.4 (C), 129.5 (CH), 128.3 (CH), 115.6 (CH), 64.9 (CH_2), 63.1 (CH_2), 59.5 (CH_2), 38.1 (CH_2), 33.1 (CH_2), 31.7 (CH_2), 28.6 (CH_2), 27.3 (CH_2), 25.8 (CH_2), 24.9 (CH_2), 18.0 (CH_3), 14.3

(CH_3), 11.9 (CH); IR (neat) 1716, 1720 cm^{-1}; MS 475.3 (M+ -$CH(CH_3)_2$); HRMS calcd for $C_{27}H_{43}O_5Si$ (M^+ -$CH(CH_3)_2$) 475.2874, found 475.2909.



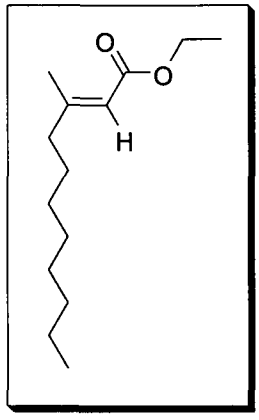
(6E)-6-(2-methoxy-2-oxoethylidene)undecyl benzoate (193). Prepared from (2E)-methyl 3-chloro-2-iodooct-2-enoate (53 mg, 0.168 mmol) or methyl oct-2-ynoate (30 mg, 0.197 mmol) using procedures similar to those described for (6E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (43mg, 74% from (2E)-methyl 3-chloro-2-iodooct-2-enoate): ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 – 8.02 (m, 2H), 7.58 – 7.53 (m, 1H), 7.46 – 7.42 (m, 2H), 5.63 (s, 1H), 4.32 (t, J = 6.8 Hz, 2H), 3.67 (s, 3H), 2.59 (td, J = 7.6, 2.0 Hz, 2H), 2.17 (td, J = 7.6, 0.8 Hz, 2H), 1.79 (p, J = 6.8 Hz, 2H), 1.59 – 1.41 (m, 8H), 1.35 – 1.30 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.9 (C), 166.6 (C), 164.8 (C), 132.8 (CH), 130.4 (C), 129.5 (CH), 128.3 (CH), 114.8 (CH), 64.8 (CH_2), 50.8 (CH_3), 38.2 (CH_2), 32.1 (CH_2), 32.0 (CH_2), 28.6 (CH_2), 28.4 (CH_2), 27.3 (CH_2), 25.8 (CH_2), 22.5 (CH_2), 14.0 (CH_3); IR (neat) 1712,

1701 cm^{-1}; MS 315.2 (M^+ -OCH_3); HRMS calcd for $C_{20}H_{27}O_3$ (M^+ -OCH_3) 315.1955, found 315.1953.

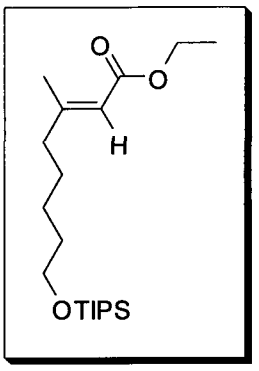


(2E)-ethyl 8-(benzyloxy)-3-methyloct-2-enoate (196). Prepared from (2E)-ethyl 3-chloro-2-iodobut-2-enoate (50 mg, 0.182 mmol) or ethyl but-2-ynoate (20 mg, 0.182 mmol) and ((pent-4-enyloxy)methyl)benzene (96 mg, 0.546 mmol) using procedures similar to those described for (6E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (39 mg, 73% from (2E)-ethyl 3-chloro-2-iodobut-2-enoate): ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.34 – 7.24 (m, 5H), 5.66 (q, J = 1.2 Hz, 1H), 4.48 (s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.47 (t, J = 6.4 Hz, 2H), 2.18 (td, J = 7.6, 0.9 Hz, 2H), 2.14 (d, J = 1.2 Hz, 3H), 1.66 – 1.59 (m, 2H), 1.55 – 1.48 (m, 2H), 1.43 – 1.36 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 167.8 (C), 161.6 (C), 141.1 (C), 130.0 (CH), 129.2 (CH), 129.1 (CH), 117.3 (CH), 74.2 (CH_2), 71.7 (CH_2), 60.7 (CH_2), 42.3 (CH_2), 31.3 (CH_2), 28.9 (CH_2). 27.6 (CH_2), 19.6 (CH_3), 15.6

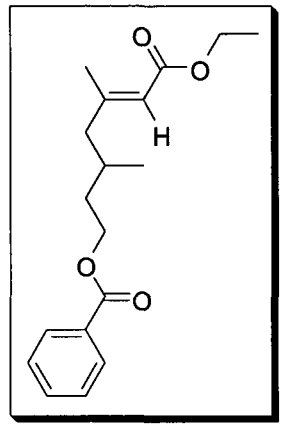
(CH_3); IR (neat) 1634 cm^{-1}; MS 245.2 (M^+ -OCH_2CH_3); HRMS calcd for $C_{16}H_{21}O_2$ (M^+ -OCH_2CH_3) 245.1536, found 245.1574.



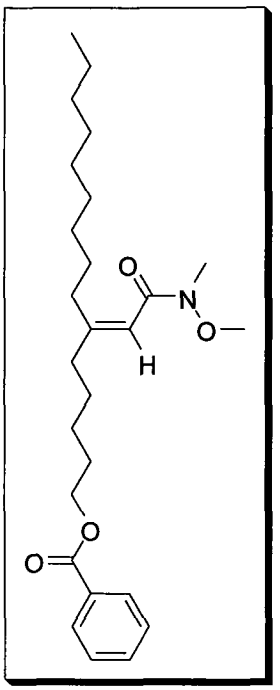
(2E)-ethyl 3-methylundec-2-enoate (195). Prepared from (2E)-ethyl 3-chloro-2-iodobut-2-enoate (50 mg, 0.182 mmol) or ethyl but-2-ynoate (20 mg, 0.182 mmol) and octene (61 mg, 0.546 mmol) using procedures similar to those described for (6E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate that provided the title compound after purification by flash chromatography (1% EtOAc in hexane) as a colorless oil (34 mg, 82% from (2E)-ethyl 3-chloro-2-iodobut-2-enoate): ^1H NMR (400 MHz, Acetone-d_6) δ 5.65 (q, J = 1.2 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 2.17 (td, J = 7.2, 1.2 Hz, 2H), 2.14 (d, J = 1.2 Hz, 3H), 1.53 -1.26 (m, 12H), 1.22 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 167.8 (C), 161.7 (C), 117.2 (CH), 60.7 (CH_2), 42.3 (CH_2), 33.6 (CH_2), 31.1 (CH_2), 30.9 (CH_2), 30.9 (CH_2), 29.2 (CH_2), 24.3 (CH_2), 19.6 (CH_3), 15.6 (CH_3), 15.3 (CH_3); IR (neat) 1637 cm^{-1}; MS 226.2 (M^+); HRMS calcd for $C_{14}H_{26}O_2$ (M^+) 226.1933, found 226.1904.



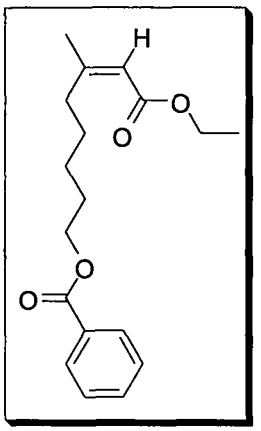
(2E)-ethyl 3-methyl-8-(triisopropylsilyloxy)oct-2-enoate (197). Prepared from (2E)-ethyl 3-chloro-2-iodobut-2-enoate (50 mg, 0.182 mmol) or ethyl but-2-ynoate (20 mg, 0.182 mmol) and triisopropyl(pent-4-enyloxy)silane (115 mg, 0.546 mmol) using procedures similar to those described for (6E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (56 mg, 86% from ethyl but-2-ynoate): ^{1}H NMR (300 MHz, Acetone-d_6) δ 5.66 (q, J = 1.2 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.74 (t, J = 6.0 Hz, 2H), 2.19 (t, J = 7.2 Hz, 2H), 2.14 (d, J = 1.2 Hz, 3H), 1.62 – 1.38 (m, 6H), 1.22 (t, J = 7.2 Hz, 3H), 1.09 – 1.06 (m, 21H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 167.8 (C), 161.5 (C), 117.3 (CH), 64.9 (CH_2), 60.7 (CH_2), 42.3 (CH_2), 34.5 (CH_2), 28.9 (CH_2), 27.2 (CH_2), 19.6 (CH_3), 19.4 (CH), 15.7 (CH_3), 13.7 (CH_3); IR (neat) 1645 cm^{-1}; MS 313.2 (M^+ - $CH(CH_3)_2$); HRMS calcd for $C_{17}H_{33}O_3Si$ (M^+-$CH(CH_3)_2$) 313.2193, found 313.2181.



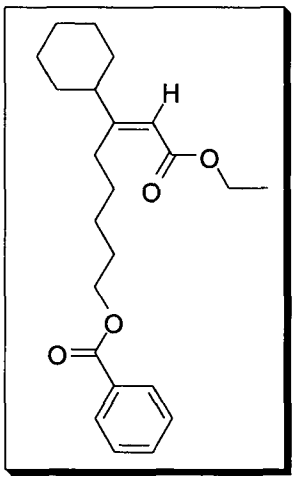
(5E)-7-ethoxy-3,5-dimethyl-7-oxohept-5-enyl benzoate (198). Prepared from (2E)-ethyl 3-chloro-2-iodobut-2-enoate (50 mg, 0.182 mmol) or ethyl but-2-ynoate (20 mg, 0.182 mmol) and 3-methylbut-3-enyl benzoate (104 mg, 0.546 mmol) using procedures similar to those described for (6E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (44 mg, 80% from ethyl but-2-ynoate): ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.05 – 8.02 (m, 2H), 7.66 – 7.61 (m, 1H), 7.54 – 7.49 (m, 2H), 5.70 (q, J = 1.2 Hz, 1H), 4.44 – 4.34 (m, 2H), 4.09 (q, J = 7.2 Hz, 2H), 2.32 – 2.28 (m, 1H), 2.15 (d, J = 1.2 Hz, 3H), 2.09 (dd, J = 1.2, 8.0 Hz, 1H), 1.87 – 1.79 (m, 1H), 1.65 – 1.57 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H), 0.97 (d, J = 6.4 Hz, 3H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 167.7 (C), 167.6 (C), 160.0 (C), 134.8 (CH), 132.4 (C), 131.1 (CH), 130.4 (CH), 118.9 (CH), 64.6 (CH_2), 60.8 (CH_2), 49.9 (CH_2), 37.1 (CH_2), 29.8 (CH), 20.7 (CH_3), 19.5 (CH_3), 15.6 (CH_3); IR (neat) 1645 cm^{-1}; MS 259.1 (M^+ -OCH_2CH_3); HRMS calcd for $C_{16}H_{19}O_3$ (M^+ -OCH_2CH_3) 259.1329, found 259.1359.



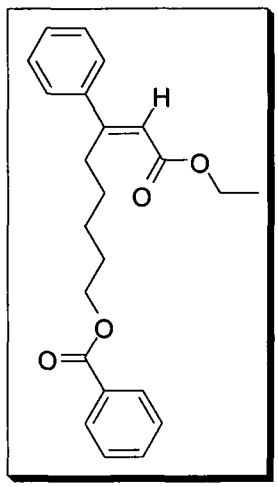
(6E)-6-(2-(methoxy(methyl)amino)-2-oxoethylidene)pentadecyl benzoate (252). Prepared from N-methoxy-N-methyldodec-2-ynamide (41 mg, 0.182 mmol) using procedures similar to those described for (6E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate that provided the title compound after purification by flash chromatography (10% EtOAc in hexane) as a colorless oil (43 mg, 57%): ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.04 – 8.01 (m, 2H), 7.66 – 7.61 (m, 1H), 7.53 – 7.49 (m, 2H), 6.15 (s, 1H), 4.33 (t, J = 6.4 Hz, 2H), 3.66 (s, 3H), 3.11 (s, 3H), 2.58 (t, J = 8.0 Hz, 2H), 2.23 (td, J = 8.0, 1.2 Hz, 2H), 1.87 – 1.27 (m, 20H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 169.3 (C), 167.7 (C), 161.3 (C), 134.8 (CH), 132.4 (C), 131.1 (CH), 130.4 (CH), 116.1 (CH), 71.7 (CH_3), 66.4 (CH_2), 62.7 (CH_3), 39.7 (CH_2), 33.9 (CH_2), 33.4 (CH_2), 33.3 (CH_2), 31.3 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 29.2 (CH_2), 28.2 (CH_2), 27.5 (CH_2), 24.3 (CH_2), 23.8 (CH_2), 15.3 (CH_3); IR (neat) 1670 and 1715 cm^{-1}; MS 431.3 (M^+); HRMS calcd for 431.3036 (M^+) 431. 3025.



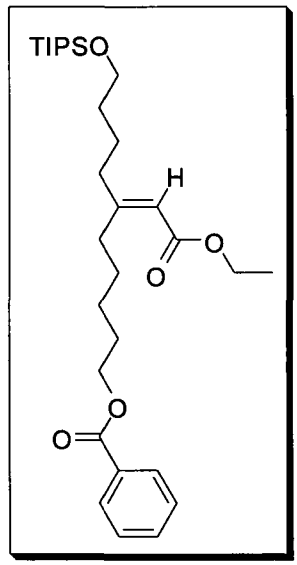
General Procedure for the Preparation of Isomeric Trisubstituted Alkenes. (6Z)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate (239). A solution of (6E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate (25 mg, 0.082 mmol) in CH_2Cl_2 (2 mL) was photolyzed using a UV lamp (λ = 300 and 254 nm) for 4 h. The CH_2Cl_2 was removed *in vacuo* followed by flash chromatography (2% EtOAc in hexane) to afford an inseparable mixture of E and Z isomers (E:Z = 1:1). ^{1}H NMR (Z isomer, 400 MHz, Acetone-d_6) δ 8.04 – 8.01 (m, 2H), 7.66 – 7.61 (m, 1H), 7.53 – 7.49 (m, 2H), 5.66 (q, *J* = 0.8 Hz, 1H), 4.32 (t, *J* = 6.4 Hz, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 7.2 Hz, 2H), 1.91 (d, *J* = 1.6 Hz, 3H), 1.85 – 1.78 (m, 2H), 1.64 – 1.47 (m, 4H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (Z isomer, 400 MHz, Acetone-d_6) δ 167.8 (C), 167.4 (C), 161.9 (C), 134.8 (CH), 132.5 (C), 131.1 (CH), 130.4 (CH), 117.9 (CH), 66.4 (CH_2), 60.7 (CH_2), 34.5 (CH_2) , 30.2 (CH_2), 29.4 (CH_2), 27.8 (CH_2), 26.0 (CH_3), 15.6 (CH_3); IR (neat) 1710 cm^{-1}; MS 259.1 (M^+ - OCH_2CH_3); HRMS calcd for $C_{16}H_{19}O_3$ (M^+-OCH_2CH_3) 259.1329, found 259.1329.



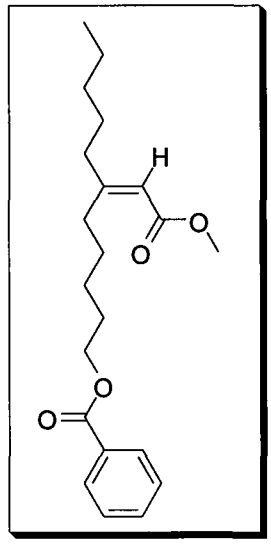
(6E)-6-cyclohexyl-8-ethoxy-8-oxoocto-6-enyl benzoate (243). Prepared from (6Z)-6-cyclohexyl-8-ethoxy-8-oxoocto-6-enyl benzoate (9.2 mg, 0.025 mmol) using the same procedure described above for compound **239**. The product was obtained as an inseparable mixture of E and Z isomers (E:Z = 1:0.77). ^{1}H NMR (E isomer, 400 MHz, Acetone-d_6) δ 8.04 – 8.02 (m, 2H), 7.66 – 7.61 (m, 1H), 7.53 – 7.49 (m, 2H), 5.61 (s, 1H), 4.35 – 4.28 (m, 2H), 4.11 – 4.03 (m, 1H), 2.27 – 2.13 (m, 2H), 1.87 – 1.26 (m, 16H), 1.22 (t, J = 6.8 Hz, 3H); ^{13}C NMR (E isomer, 400 MHz, Acetone-d_6) δ 169.7 (C), 167.7 (C), 167.6 (C), 134.8 (CH), 132.5 (C), 131.1 (CH), 130.4 (CH), 115.6 (CH), 66.4 (CH_2), 61.7 (CH_2), 47.5 (CH), 34.0 (CH_2), 32.6 (CH_2), 29.4 (CH_2), 28.5 (CH_2), 28.2 (CH_2), 27.8 (CH_2), 15.5 (CH_3); IR (neat) 1717, 1633 cm^{-1}; MS 327.2 (M+ - OCH_2CH_3); HRMS calcd for $C_{21}H_{27}O_3$ (M^+ -OCH_2CH_3) 327.1955, found 327.1933.



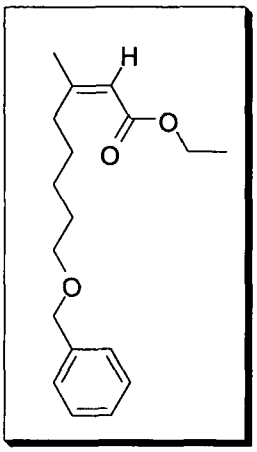
(6E)-8-ethoxy-8-oxo-6-phenyloct-6-enyl benzoate (245). Prepared from (6Z)-8-ethoxy-8-oxo-6-phenyloct-6-enyl benzoate (25 mg, 0.062 mmol) using the same procedure described above for compound **239**. The product was obtained as an inseparable mixture of E and Z isomers (E:Z = 0.56:1). ^{1}H NMR (E isomer, 400 MHz, Acetone-d_6) δ 8.05 – 7.99 (m, 2H), 7.66 – 7.61 (m, 1H), 7.53 – 7.49 (m, 2H), 7.34 – 7.17 (m, 5H), 5.68 (t, J = 7.2 Hz, 1H), 4.24 (t, J = 6.4 Hz, 2H), 3.99 (q, J = 7.2 Hz, 2H), 2.09 (t, J = 7.6 Hz, 2H), 1.79 – 1.67 (m, 2H), 1.58 – 1.41 (m, 4H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR (E isomer, 400 MHz, Acetone-d_6) δ 172.5 (C), 167.7 (C), 141.9 (C), 136.5 (C), 134.8 (CH), 132.9 (CH), 132.5 (C), 131.1 (CH), 130.3 (CH), 129.9 (CH), 128.7 (CH), 127.8 (CH), 66.3 (CH_2), 61.7 (CH_2), 46.1 (CH_2), 30.2 (CH_2), 29.9 (CH_2), 27.9 (CH_2), 15.4 (CH_3); IR (neat) 1715 cm^{-1} ; MS 321.1 (M+ -OCH_2CH_3); HRMS calcd for $C_{21}H_{21}O_3$ (M^+ - OCH_2CH_3) 321.1485, found 321.1439.



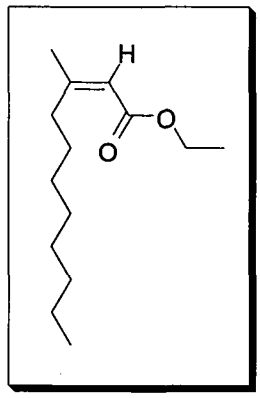
(6E)-6-(2-ethoxy-2-oxoethylidene)-10-(triisopropylsilyloxy)decylbenzoate (247). Prepared from (6Z)-6-(2-ethoxy-2-oxoethylidene)-10-(triisopropylsilyloxy)decyl benzoate (25 mg, 0.048 mmol) using the same procedure described above for compound **239**. The product was obtained as an inseparable mixture of E and Z isomers (E:Z = 2.83:1). ^{1}H NMR (E isomer, 400 MHz, $CDCl_3$) δ 8.05 – 8.03 (m, 2H), 7.58 – 7.53 (m, 1H), 7.46 – 7.42 (m, 2H), 5.39 – 5.30 (m, 1H), 4.31 (t, *J* = 6.6 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 3.04 (d, *J* = 5.2 Hz, 1H), 2.98 (d, *J* = 2.0 Hz, 1H), 2.63 (t, *J* = 7.5 Hz, 2H), 2.13 (t, *J* = 6.9 Hz, 2H), 1.82 – 1.74 (m, 2H), 1.62 – 1.21 (m, 8H), 1.04 (m, 21H); ^{31}C NMR (400 MHz, $CDCl_3$) δ 166.6 (C), 166.5 (C), 163.9 (C), 132.8 (CH), 130.4 (C), 129.5 (CH), 128.3 (CH), 115.5 (CH), 65.0 (CH_2), 62.8 (CH_2), 60.5 (CH_2), 38.1 (CH_2), 30.1 (CH_2), 29.7 (CH_2), 28.4 (CH_2), 27.7 (CH_2), 26.1 (CH_2), 23.9 (CH_2), 18.0 (CH_3), 14.2 (CH_3), 11.9 (CH); IR (neat) 1716, 1720 cm^{-1}; MS 475.3 (M+ - $CH(CH_3)_2$); HRMS calcd for $C_{27}H_{43}O_5Si$ (M^+ -$CH(CH_3)_2$) 475.2874, found 475.2909.



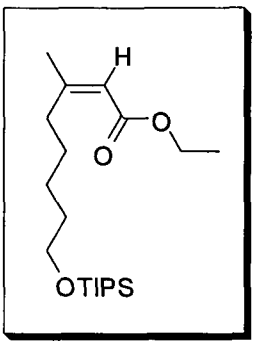
(6Z)-6-(2-methoxy-2-oxoethylidene)undecyl benzoate (246). Prepared from (6E)-6-(2-methoxy-2-oxoethylidene)undecyl benzoate (25 mg, 0.072 mmol) using the same procedure described above for compound **239**. The product was obtained as an inseparable mixture of E and Z isomers (E:Z = 2.83:1). ^{1}H NMR (Z isomer, 400 MHz, $CDCl_3$) δ 8.06 – 8.03 (m, 2H), 7.58 – 7.53 (m, 1H), 7.46 – 7.42 (m, 2H), 5.64 (s, 1H), 4.32 (t, *J* = 6.8 Hz, 2H), 3.67 (s, 3H), 2.59 (td, *J* = 8.0, 2.0 Hz, 2H), 2.17 (td, *J* = 7.6, 0.8 Hz, 2H), 1.79 (p, *J* = 6.8 Hz, 2H), 1.59 – 1.41 (m, 8H), 1.35 – 1.30 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.8 (C), 166.9 (C), 166.6 (C), 136.4 (C), 132.8 (CH), 129.5 (CH), 128.3 (CH), 114.8 (CH), 64.8 (CH_2), 50.8 (CH_3), 38.3 (CH_2), 32.1 (CH_2), 32.0 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 27.3 (CH_2), 26.3 (CH_2), 22.5 (CH_2), 13.9 (CH_3); IR (neat) 1712, 1701 cm^{-1}; MS 315.2 (M^+ -OCH_3); HRMS calcd for $C_{20}H_{27}O_3$ (M^+ - OCH_3) 315.1955, found 315.1953.



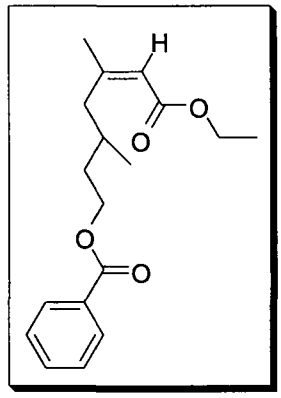
(2Z)-ethyl 8-(benzyloxy)-3-methyloct-2-enoate (249). Prepared from (2E)-ethyl 8-(benzyloxy)-3-methyloct-2-enoate (25 mg, 0.086 mmol) using the same procedure described above for compound **239**. The product was obtained as an inseparable mixture of E and Z isomers (E:Z = 1.05:1). ^{1}H NMR (Z isomer, 400 MHz, Acetone-d_6) δ 7.34 – 7.24 (m, 5H), 5.65 (q, J = 0.8 Hz, 1H), 4.48 (s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.47 (t, J = 6.4 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H), 1.89 (d, J = 1.6 Hz, 3H), 1.66 – 1.59 (m, 2H), 1.55 – 1.48 (m, 2H), 1.43 – 1.36 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 167.4 (C), 162.1 (C), 141.1 (C), 130.0 (CH), 129.2 (CH), 129.0 (CH), 117.8 (CH), 74.2 (CH_2), 71.8 (CH_2), 60.7 (CH_2), 34.7 (CH_2), 31.3 (CH_2), 29.7 (CH_2), 28.0 (CH_2). 26.0 (CH_3), 15.6 (CH_3); IR (neat) 1634 cm^{-1}; MS 245.2 (M^+ -OCH_2CH_3); HRMS calcd for $C_{16}H_{21}O_2$ (M^+ -OCH_2CH_3) 245.1536, found 245.1574.



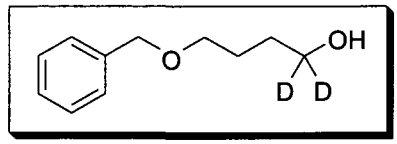
(2Z)-ethyl 3-methylundec-2-enoate (248). Prepared from (2E)-ethyl 3-methylundec-2-enoate (25 mg, 0.110 mmol) using the same procedure described above for compound **239**. The product was obtained as an inseparable mixture of E and Z isomers (E:Z = 1.05:1). ^{1}H NMR (Z isomer, 400 MHz, Acetone-d_6) δ 5.64 (br, 1H), 4.09 (q, J = 7.2 Hz, 2H), 2.64 (t, J = 7.6 Hz, 2H), 1.89 (d, J = 1.6 Hz, 3H), 1.51 -1.29 (m, 12H), 1.22 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 167.4 (C), 162.2 (C), 117.7 (CH), 60.7 (CH_2), 34.7 (CH_2), 33.6 (CH_2), 31.1 (CH_2), 30.9 (CH_2), 29.9 (CH_2), 26.0 (CH_2), 24.3 (CH_2), 19.6 (CH_3), 15.6 (CH_3), 15.3 (CH_3); IR (neat) 1637 cm^{-1}; MS 226.2 (M^+); HRMS calcd for $C_{14}H_{26}O_2$ (M^+) 226.1933, found 226.1904.



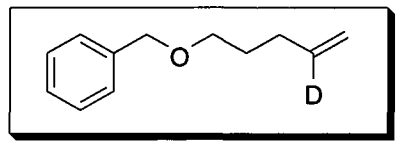
(2Z)-ethyl 3-methyl-8-(triisopropylsilyloxy)oct-2-enoate (250). Prepared from (2E)-ethyl 3-methyl-8-(triisopropylsilyloxy)oct-2-enoate (25 mg, 0.070 mmol) using the same procedure described above for compound **239**. The product was obtained as an inseparable mixture of E and Z isomers (E:Z = 1.50:1). ^{1}H NMR (Z isomer, 400 MHz, Acetone-d_6) δ 5.65 (q, J = 0.8 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.74 (t, J = 6.0 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H), 1.90 (d, J = 1.6 Hz, 3H), 1.62 – 1.38 (m, 6H), 1.22 (t, J = 7.2 Hz, 3H), 1.09 – 1.06 (m, 21H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 167.4 (C), 162.1 (C), 117.8 (CH), 65.0 (CH_2), 60.7 (CH_2), 34.7 (CH_2), 34.6 (CH_2), 29.7 (CH_2), 27.7 (CH_2), 26.1 (CH_3), 19.4 (CH), 15.7 (CH_3), 13.7 (CH_3); IR (neat) 1645 cm^{-1}; MS 313.2 (M^+ - $CH(CH_3)_2$); HRMS calcd for $C_{17}H_{33}O_3Si$ (M^+- $CH(CH_3)_2$) 313.2193, found 313.2181.



(5Z)-7-ethoxy-3,5-dimethyl-7-oxohept-5-enyl benzoate (251). Prepared from (5E)-7-ethoxy-3,5-dimethyl-7-oxohept-5-enyl benzoate (25 mg, 0.070 mmol) using the same procedure described above for compound **239**. The product was obtained as an inseparable mixture of E and Z isomers (E:Z = 1.23:1). ^{1}H NMR (Z isomer, 400 MHz, Acetone-d_6) δ 8.05 – 8.02 (m, 2H), 7.66 – 7.61 (m, 1H), 7.54 – 7.49 (m, 2H), 5.75 (br, 1H), 4.44 – 4.34 (m, 2H), 4.09 (q, *J* = 7.2 Hz, 2H), 2.73 (t, J = 7.2 Hz, 1H), 1.91 (d, *J* = 1.6 Hz, 3H), 2.09 (dd, *J* = 1.2, 8.0 Hz, 1H), 1.87 – 1.79 (m, 1H), 1.65 – 1.57 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 167.7 (C), 167.6 (C), 160.0 (C), 134.8 (2CH), 132.4 (C), 131.1 (CH), 130.4 (2CH), 119.4 (CH), 64.6 (CH_2), 60.8 (CH_2), 49.9 (CH_2), 37.1 (CH_2), 29.8 (CH), 20.7 (CH_3), 19.5 (CH_3), 15.6 (CH_3); IR (neat) 1645 cm^{-1}; MS 259.1 (M^+ -OCH_2CH_3); HRMS calcd for $C_{16}H_{19}O_3$ (M^+ -OCH_2CH_3) 259.1329, found 259.1359.

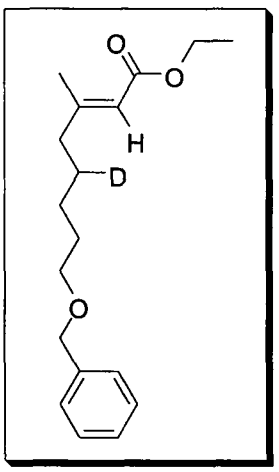


4-(benzyloxy)-1,1-dideuterobutan-1-ol (214). To a mixture of 4-(benzyloxy)butanoic acid (1.00 g, 5.15 mmol), THF (14.0 mL) and triethylamine (1.44 mL, 10.30 mmol) was added ethyl chloroformate (0.74 mL, 7.72 mmol) over a period of 5 min at 0°C. After stirring for an additional 2 ½ hr at the same temperature, the mixture was filtered with suction, and the cake was washed with THF (3 x 2 mL). Sodium borodeuteride (1.08 g, 25.75 mmol) was added to the filtrate in three intervals. Then, methanol (3.0 mL) was added dropwise to the mixture over a period of 1 h at 0°C. The resulting mixture was quenched with 1M HCl, the organic layer extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The pure product (0.69 g, 74%) was obtained as an oil by flash chromatography (25% EtOAc in hexane): ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H), 4.53 (s, 2H), 3.65 (t, J = 6.0 Hz, 2H), 3.53 (t, J = 5.6 Hz, 2H; 71% D incorporation), 2.15 (br, 1H), 1.76 – 1.66 (m, 4H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 141.1 (C), 130.0 (CH), 129.2 (CH), 129.0 (CH), 74.2 (CH_2), 71.9 (CH_2), 69.1 (CH_2), 28.1 (CH_2), 27.2 (CH_2); IR (neat) 3435 cm^{-1}; MS 182.1 (M^+); HRMS calcd for $C_{11}H_{14}D_2O_2$ (M^+) 182.1276, found 182.1248.



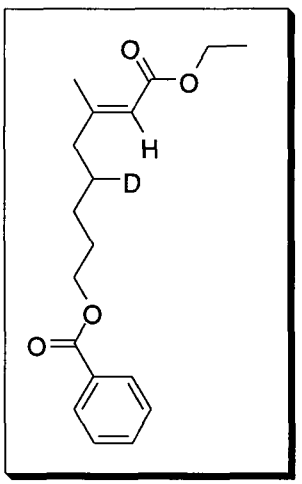
((4-deuteropent-4-enyloxy)methyl)benzene (216). To a solution of oxalyl chloride (0.47 mL, 5.56 mmol) in DCM (28.0 mL) was added dimethyl sulfoxide (0.39 mL, 5.56 mmol) at -78°C and after stirring for 30 min, a solution of 4-(benzyloxy)-1,1-dideuterobutan-1-ol (0.51 g, 2.78 mmol) in DCM (14.0 mL) was added dropwise over a period of 30 minutes. To the resulting mixture triethylamine (2.0 mL, 14.0 mmol) was added dropwise and stirring was continued for an additional 1h. The reaction was warmed to room temperature and the organic phase was extracted with Et_2O. The organic layer was washed with H_2O, 10% HCl, $NaHCO_3$, brine, dried over anhydrous $MgSO_4$., filtered, and concentrated *in vacuo*. The pure 4-(benzyloxy)-1-deuterobutanal (0.34 g, 68%) was obtained by flash chromatography (10% EtOAc in hexane) and was immediately dissolved in THF (9.5 mL). This solution was added dropwise over 30 min to a reaction mixuture containing NaHMDS (0.56 g, 3.04 mmol), $MePPh_3Br$ (1.15 g, 3.23 mmol), and THF (32 mL) at -78°C. The reaction was stirred for an additional 30 min at the same temperature, then warmed to room temperature, and stirred overnight. Quenched with saturated NH_4Cl, the organic phase was extracted with Et_2O, washed with brine, dried over anhydrous MgSO4, filtered, and concentrated *in vacuo*. The resulting product was redissolved in 5% Et_2O:Petroleum Ether and stirred for 30 min. The desired product was obtained by mini flash chromatography using a frit funnel (5% Et_2O:Petroleum Ether) (0.29 g, 87%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H), 5.03 – 5.00 (m, 1H), 4.96 - 4.95 (m, 1H), 4.51 (s, 2H), 3.49 (t, J = 6.8 Hz, 2H), 2.15 (t, J

= 7.6 Hz, 2H), 1.75 – 1.68 (m, 2H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 141.1 (C), 130.0 (CH), 129.2 (CH), 129.1 (CH), 115.8 (CH_2), 74.2 (CH_2), 71.9 (CH_2), 32.0 (CH_2), 30.8 (CH_2); IR (neat) 1625 cm^{-1}; MS 177.1 (M^+); HRMS calcd for $C_{12}H_{15}DO$ (M^+) 177.1264, found 177.1264.



(2E)-ethyl-8-(benzyloxy)-5-deutero-3-methyloct-2-enoate (218). Prepared from (2E)-ethyl 3-chloro-2-iodobut-2-enoate (50 mg, 0.182 mmol) and ((4-deuteropent-4-enyloxy)methyl)benzene (97 mg, 0.546 mmol) using procedures similar to those described for (6E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (30 mg, 56%): ^1H NMR (400 MHz, Acetone-d_6) δ 7.35 – 7.24 (m, 5H), 5.66 (q, J = 1.2 Hz, 1H), 4.48 (s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.47 (t, J = 6.4 Hz, 2H), 2.17 (d, J = 7.6, 2H), 2.14 (d, J = 1.2 Hz, 3H), 1.65 – 1.58 (m, 2H), 1.54 – 1.46 (m, 1H), 1.42 – 1.36 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 167.8 (C), 161.6 (C), 141.1 (C), 130.0 (CH), 129.2 (CH), 129.1 (CH), 117.3 (CH), 74.2 (CH_2), 71.7 (CH_2), 60.7 (CH_2), 42.2 (CH_2), 31.2 (CH_2), 28.7 (CHD), 27.5 (CH_2), 19.6 (CH_3), 15.6

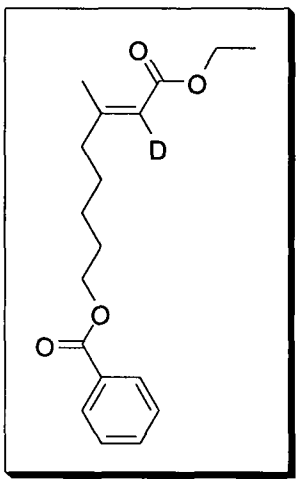
(CH_3); IR (neat) 1715 cm^{-1}; MS 246.2 (M^+ -OCH_2CH_3); HRMS calcd for $C_{16}H_{20}DO_2$ (M^+ -OCH_2CH_3) 246.1599, found 246.1596.



(6E)-4-deutero-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate (230).

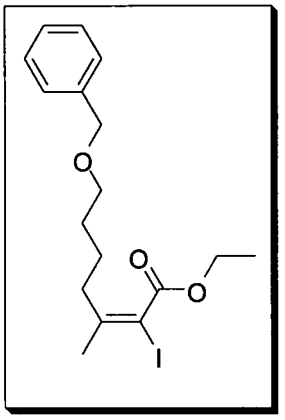
Prepared from (2E)-ethyl 3-chloro-2-iodobut-2-enoate (50 mg, 0.182 mmol), pent-4-enyl benzoate (104 mg, 0.546 mmol) and d-9-borabicyclo[3.3.1]nonane (0.5M solution in THF) (1.11 mL, 0.546 mmol) using procedures similar to those described for (6E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a yellow oil (33 mg, 59%): ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.03 – 8.01 (m, 2H), 7.66 – 7.61 (m, 1H), 7.54 – 7.49 (m, 2H), 5.68 (q, J = 1.2 Hz, 1H), 4.32 (t, J = 6.4 Hz, 2H), 4.08 (q, J = 7.2 Hz, 2H), 2.22 (d, J = 7.6 Hz, 2H), 2.15 (d, J = 1.2 Hz, 3H), 1.82 (p, J = 6.4 Hz, 2H), 1.64 – 1.47 (m, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 167.8 (C), 167.7 (C), 161.4 (C), 134.8 (CH), 132.5 (C), 131.1 (CH), 130.4 (CH), 117.3 (CH), 67.4 (CH_2), 60.7 (CH_2), 42.0 (CH_2), 30.2 (CH_2), 28.5 (CHD), 27.2 (CH_2), 19.6 (CH_3), 16.6

(CH_3); IR (neat) 1713, 1701 cm^{-1}; MS 305.2 (M^+); HRMS calcd for $C_{18}H_{22}DO_4$ 305.1737, found 305.1724.



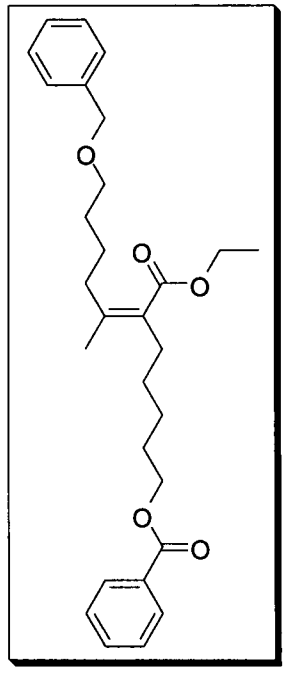
(6E)-7-deutero-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate (203).

Prepared from (2E)-ethyl 3-chloro-2-iodobut-2-enoate (50 mg, 0.182 mmol), pent-4-enyl benzoate (104 mg, 0.546 mmol) and D_2O (10 µL, 0.546 mmol) using procedures similar to those described for (6E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (28.3 mg, 51%): ^1H NMR (400 MHz, Acetone-d_6) (H:D : 1:0.67) δ 8.03 – 8.01 (m, 2H), 7.66 – 7.61 (m, 1H), 7.54 – 7.49 (m, 2H), 5.68 (q, J = 1.2 Hz, 0.6H), 4.32 (t, J = 6.4 Hz, 2H), 4.08 (q, J = 7.2 Hz, 2H), 2.22 (td, J = 1.2, 7.6 Hz, 2H), 2.15 (d, J = 1.2 Hz, 3H), 1.82 (p, J = 6.4 Hz, 2H), 1.64 – 1.47 (m, 4H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, Acetone-d_6) δ 167.78(C), 167.7 (C), 161.3 (C), 134.7 (CH), 132.4 (C), 131.1 (CH), 130.3 (CH), 117.3 (CH), 66.4 (CH_2), 60.7 (CH_2), 42.1 (CH_2), 30.2 (CH_2), 28.7 (CH_2), 27.3 (CH_2), 19.5 (CH_3), 15.6 (CH_3); IR (neat) 1713, 1648 cm^{-1}; MS 305.2 (M^+ -OCH_2CH_3); HRMS calcd for $C_{16}H_{18}DO_3$ (M^+ -OCH_2CH_3) 260.1391, found 260.1374.



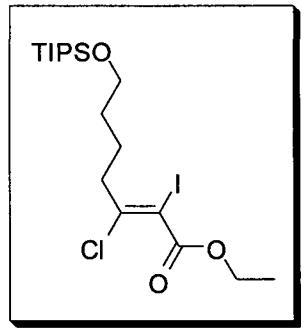
(2E)-ethyl 7-(benzyloxy)-2-iodo-3-methylhept-2-enoate (234). To an oven dried 100 mL round bottom flask (rbf) equipped with teflon coated stir bar were added CuI (0.37 g, 1.93 mmol) and freshly distilled THF (15.0 mL) followed by freshly titrated MeLi (1.0 M solution in Et_2O) (3.84 mL, 3.84 mmol) under nitrogen atmosphere. The reaction mixture was cooled to -78°C. A solution of ethyl 7-(benzyloxy)hep-2-ynoate (0.5 g, 1.92 mmol) in THF (5.0 mL) was transferred to the 100 mL rbf via canula and continued to stir at the same temperature for 1 h. Following the addition of I_2 (1.46 g, 5.76 mmol), the reaction mixture was cooled to 0°C and stirred for an additional 2 h. The reaction was quenched with NH_4Cl, the organic layer was extracted twice with Et_2O, once with EtOAc, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The pure product (0.52 g, 68%) was obtained by flash chromatography (2% Et_2O in hexane): ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 5H), 4.49 (s, 2H), 4.22 (q, J = 7.2 Hz, 2H), 3.47 (t, J = 6.0 Hz, 2H), 2.46 (t, J = 7.2 Hz, 2H), 2.04 (s, 3H), 1.64 – 1.57 (m, 4H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.7 (C), 153.9 (C), 138.5 (C), 128.4 (CH), 127.6 (CH), 127.5 (CH), 72.9 (CH_2), 69.9 (CH_2), 61.8 (CH_2),

36.3 (CH_2), 29.4 (CH_2), 29.1 (CH_3), 24.9 (CH_2), 14.0 (CH_3); IR (neat) 1709 cm^{-1}; MS 402.1 (M^+); HRMS calcd for $C_{17}H_{23}O_3I$ (M^+) 402.0692, found 402.0701.



(6Z)-11-(benzyloxy)-6-(ethoxycarbonyl)-7-methylundec-6-enyl benzoate (236). Prepared from (2E)-ethyl 7-(benzyloxy)-2-iodo-3-methylhept-2-enoate (50 mg, 0.124 mmol) and pent-4-enyl benzoate (141 mg, 0.744 mmol) using procedures similar to those described for (6E)-8-ethoxy-6-methyl-8-oxoocto-6-enyl benzoate that provided the title compound after purification by flash chromatography (2% EtOAc in hexane) as a colorless oil (18.4 mg, 35%): ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 - 8.02 (m, 2H), 7.58 – 7.52 (m, 1H), 7.46 – 7.41 (m, 2H), 7.34 – 7.27 (m, 5H), 4.49 (s, 2H), 4.31 (t, J = 6.6 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 3.47 (t, J = 6.3 Hz, 2H), 2.27 (t, J = 7.8 Hz, 4H), 1.77 (s, 3H), 1.67 – 1.39 (m, 10H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.9 (C), 166.6 (C), 144.2 (C), 138.6 (C), 132.8 (CH), 130.5 (C), 129.5 (CH), 128.4 (C), 128.3

(CH), 128.2 (CH), 127.6 (CH), 127.4 (CH), 72.9 (CH_2), 70.3 (CH_2), 64.9 (CH_2), 59.9 (CH_2), 36.2 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 25.9 (CH_2), 25.0 (CH_2), 19.2 (CH_3), 14.3 (CH_3); IR (neat) 1717, 1698 cm^{-1}; MS 421.2 (M^+ -OCH_2CH_3); HRMS calcd for $C_{27}H_{33}O_4$ (M^+ -OCH_2CH_3) 421.2373, found 421.2369.



(E)-ethyl 3-chloro-2-iodo-7-(triisopropylsilyloxy)hept-2-enoate (190). To an oven-dried 100 mL round bottom flask equipped with Teflon coated stir bar was added ethyl 7-(triisopropylsilyloxy)hept-2-ynoate (1.05 g, 3.22 mmol) in 32 mL DCE followed by BU_4NI (3.6 g, 9.67 mmol). The solution was refluxed for 72 hours. Upon completion by TLC, the reaction was washed with sodium bisulfite (2X), sodium bicarbonate (3X), and brine. The organic phase was extracted with EtOAc then dried over $MgSO_4$ and concentrated in *vacuo*. The crude oil was purified by flash chromatography (1% Et_2O: hexane) to afford the title compound as a clear oil (0.7 g, 43%): ^1H NMR (300 MHz, $CDCl_3$) δ 4.28 (q, J = 6.9 Hz, 2H), 3.72 (t, J = 6.3 Hz, 2H), 2.72 (t, J = 7.2 Hz, 2H), 1.76 – 1.57 (m, 4H), 1.33 (t, J = 7.2 Hz, 3H), 1.07 – 1.03 (m, 21H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.0 (C), 138.9 (C), 80.3 (C), 62.8 (CH_2), 62.4 (CH_2), 41.4 (CH_2), 31.8 (CH_2),

23.3 (CH_2), 18.1 (CH_3), 13.9 (CH), 12.0 (CH_3); IR (neat) 1732 cm^{-1}; MS 445.0 (M^+ - $CH(CH_3)_2$); HRMS calcd for $C_{15}H_{27}ClIO_3Si$ (M^+ -$CH(CH_3)_2$) 445.0457, found 445.0483.

BH_3 in THF. The apparatus is assembled in a fume hood as illustrated in Figure 4. Once assembled the entire system is flame dried under vacuum (vacuum needle in the Receiving Flask, RF) and left under nitrogen atmosphere. An anhydrous tetraglyme (26.0 mL, 3.0 A° MS) weighed into an oven dried 50 mL round bottom flask and purged under N_2. A 13.0 mL of the purged tetraglyme was added to a three neck round bottom flask equipped with the Teflon stir bar (Generation Flask, GF) followed by an addition of freshly distilled BF_3•Et_2O (6.4 mL, 51.54 mmol) and stirred at room temperature for 30 minutes. The system was vacummed twice from the RF for 30 minute interval to remove the Et_2O. To a separate oven dried 25 mL round bottom flask equipped with Teflon stir bar NaBH4 (1.5 g, 39.65 mmol) and 13.0 mL of purged anhydrous tetraglyme were added and stirred in a hot bath for 30 minutes under nitrogen atmosphere. The resulting solution was added to GF via syringe pump over 3 h at room temperature. The solution continued to stir for additional 1 h at rt and the product was collected during that period as a solution in THF in the RF which was cooled in an ice bath. The cold trap and the condensing flask were continuously maintained at -78°C (Dry Ice/Acetone). The product was immediately carried onto the formation of 9-BBN.

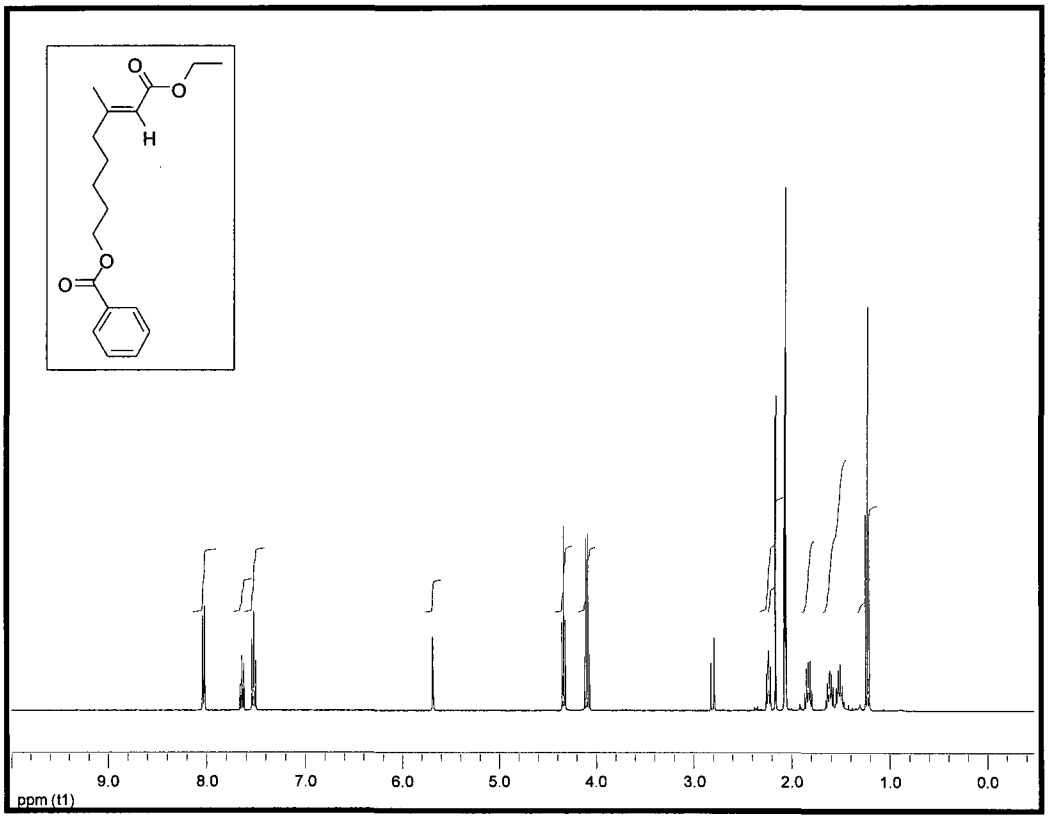
BD_3 in THF. Prepared from the procedure similar to that described for BH_3 in THF using $NaBD_4$. The product was immediately carried onto the formation of d-9-BBN.

9-Borabicyclo[3.3.1]nonane. An oven-dried 25 mL two neck round bottom flask equipped with a teflon coated stir bar was joined with the condenser, flame dried, and under nitrogen atmosphere was cooled to an ice bath. BH_3-THF (0.94M in THF) (5.2 mL, 4.892 mmol) was added to the round bottom flask followed by 1,5-cyclooctadiene (0.6 mL, 4.892 mmol) via syringe pump over 20 minutes. The resulting solution was immediately refluxed for 1.5 h. At the end of reflux the clear solution was cooled to room temperature and concentrated *in vacuo* to remove 50% of the solvent which results in the formation of precipitate. The flask was slowly warmed in a hot water bath to re-dissolve majority of the precipitate. Then the solution was slowly cooled to room temperature following an ice bath to obtain the product as white precipitate. The remaining solvent decanted via canula transfer. The white precipitate was washed with 0.34 mL of distilled pentane and the solvent decanted via canula transfer. The pure 9-borabicyclo[3.3.1]nonane was obtained after concentrated in vacuo which was dissolved in 6.6 mL of THF to make 0.5 M of 9-BBN in THF.

d-9-Borabicyclo[3.3.1]nonane. Prepared from the procedure similar to that described for 9-borabicyclo[3.3.1]nonane using BD_3 in THF.

Appendix

NMR Spectra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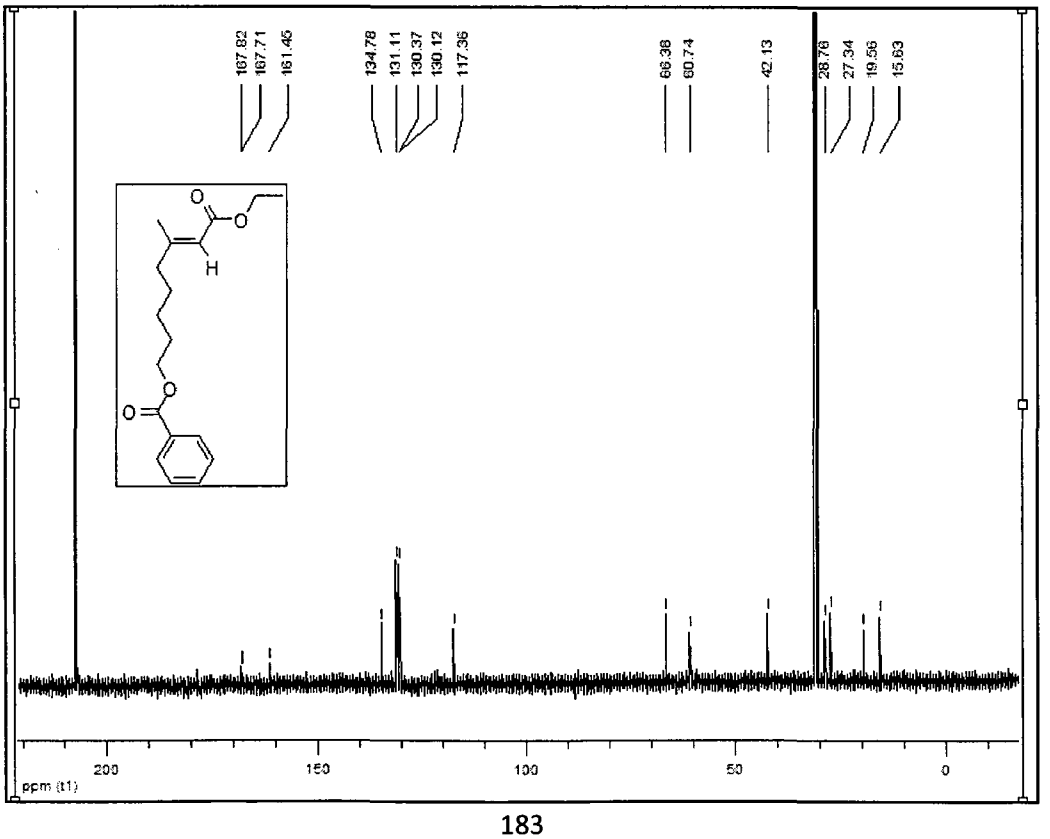
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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167.71
161.45
134.78
131.11
130.37
130.12
117.36
66.36
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42.13
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27.34
19.56
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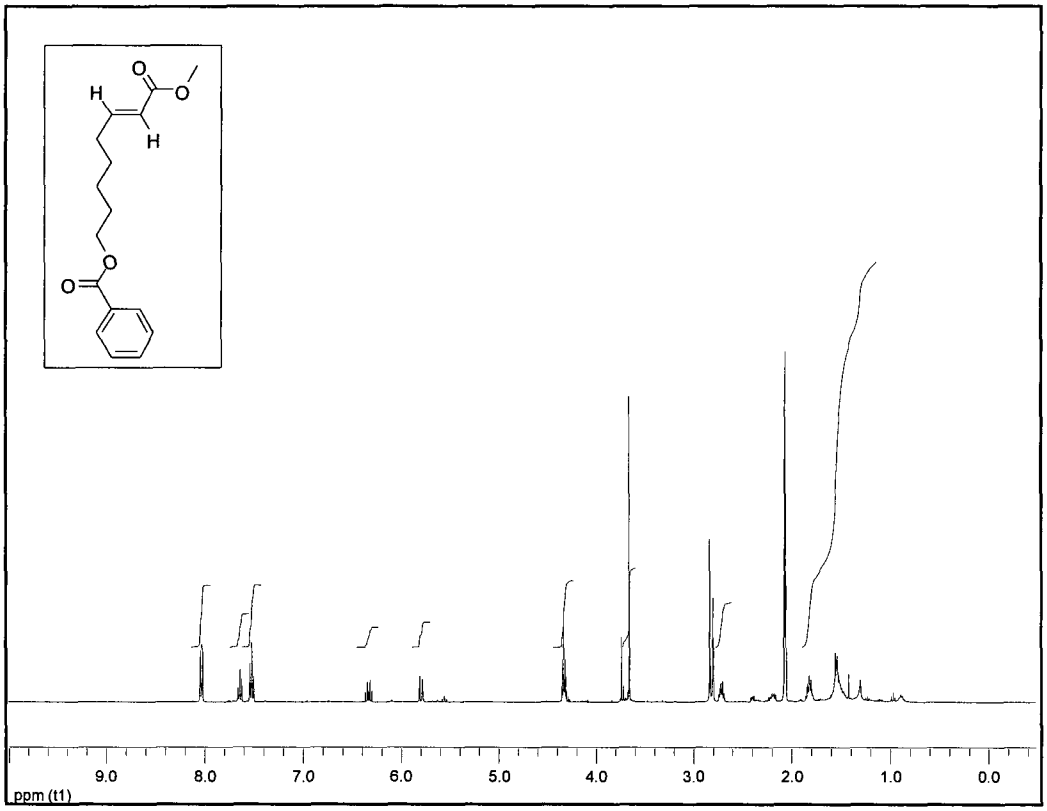
200
150
100
50
0
ppm (t1)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2.0
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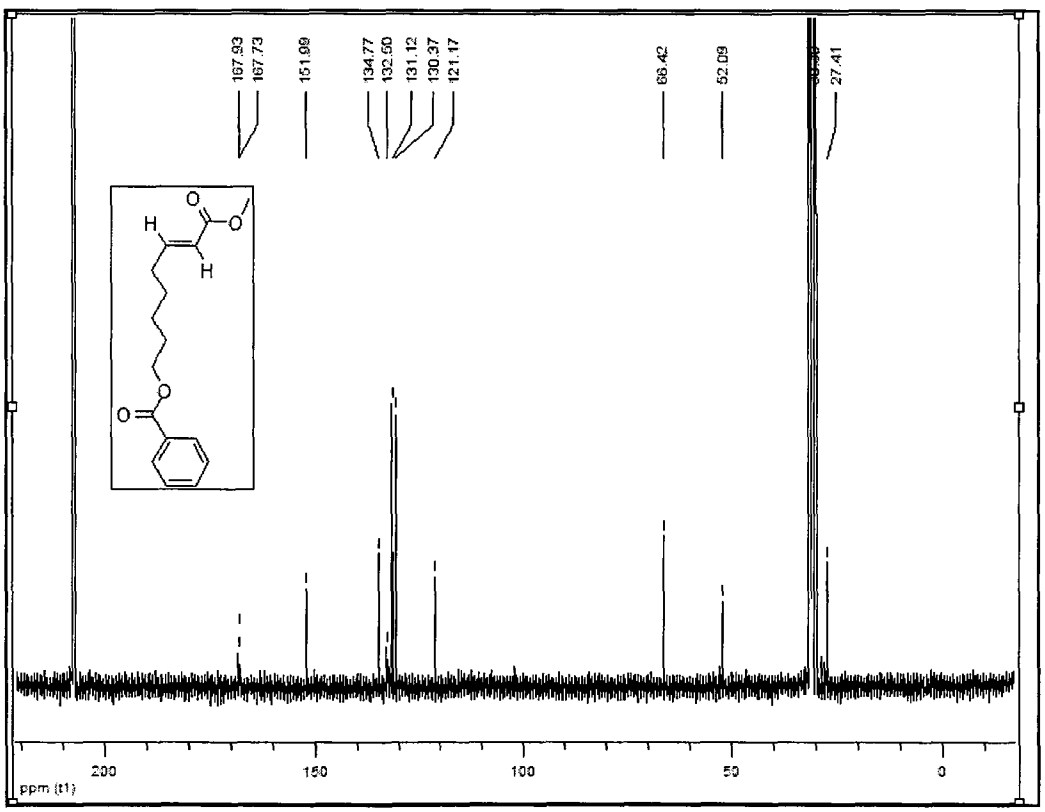
0.0
ppm (t1)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167.73
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121.17
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52.09
27.41
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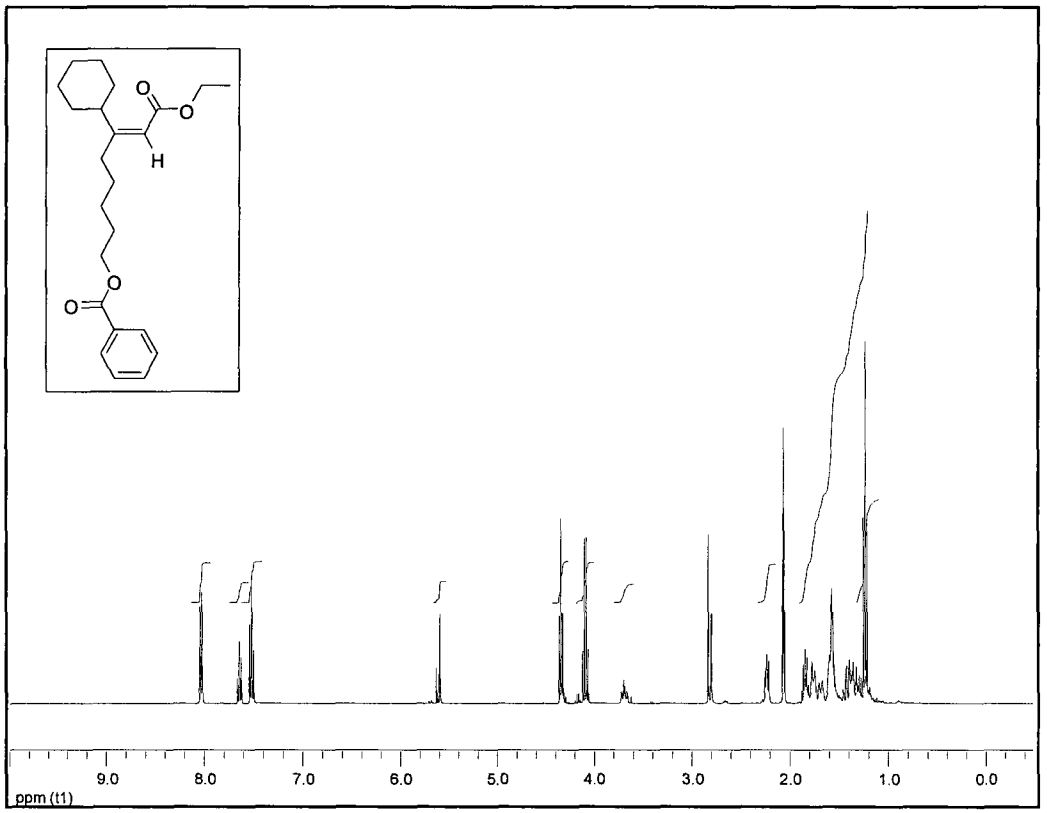
ppm (t1)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O
H
O
O
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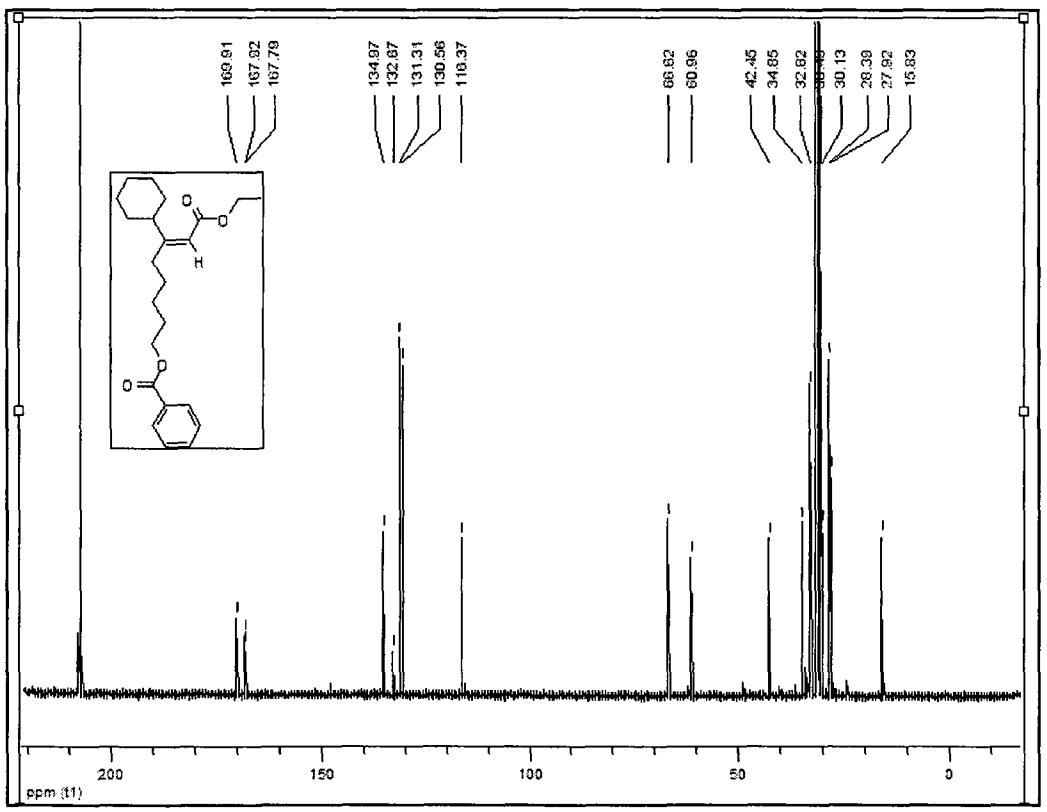
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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167.79
134.97
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131.31
130.56
118.37
66.82
60.96
42.45
34.85
32.82
30.13
29.39
27.92
15.83
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H
O
O
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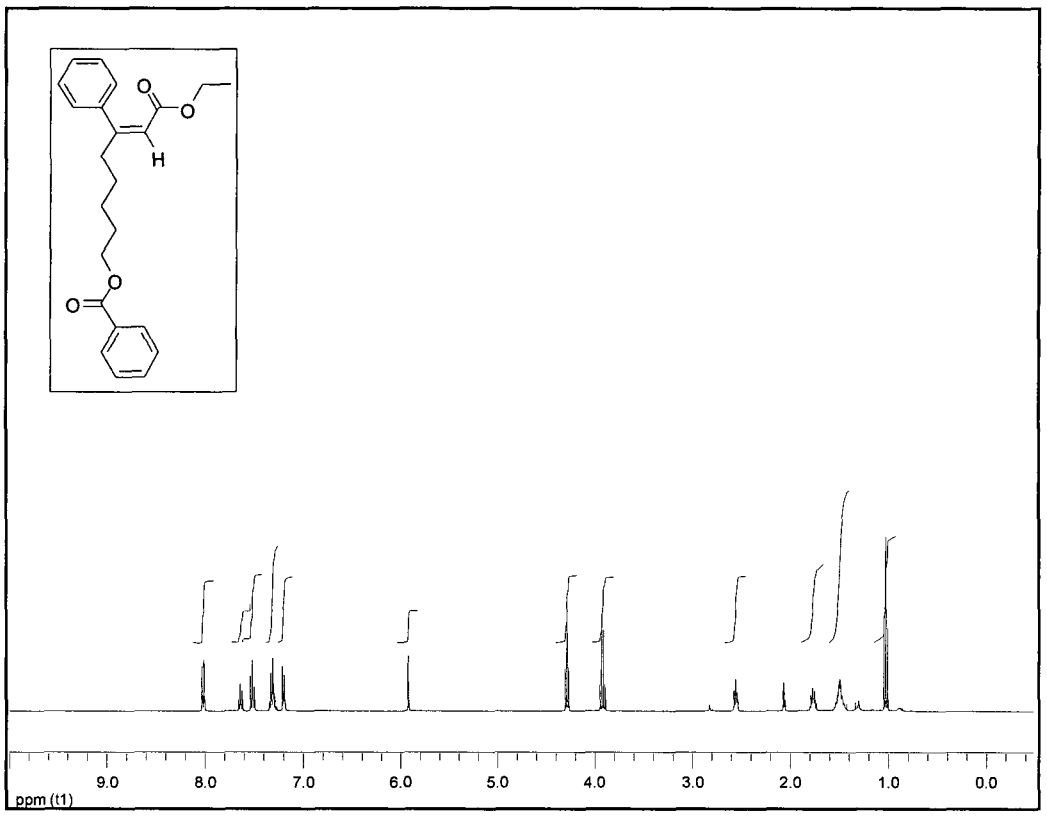
100
50
0
ppm (t1)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2.0
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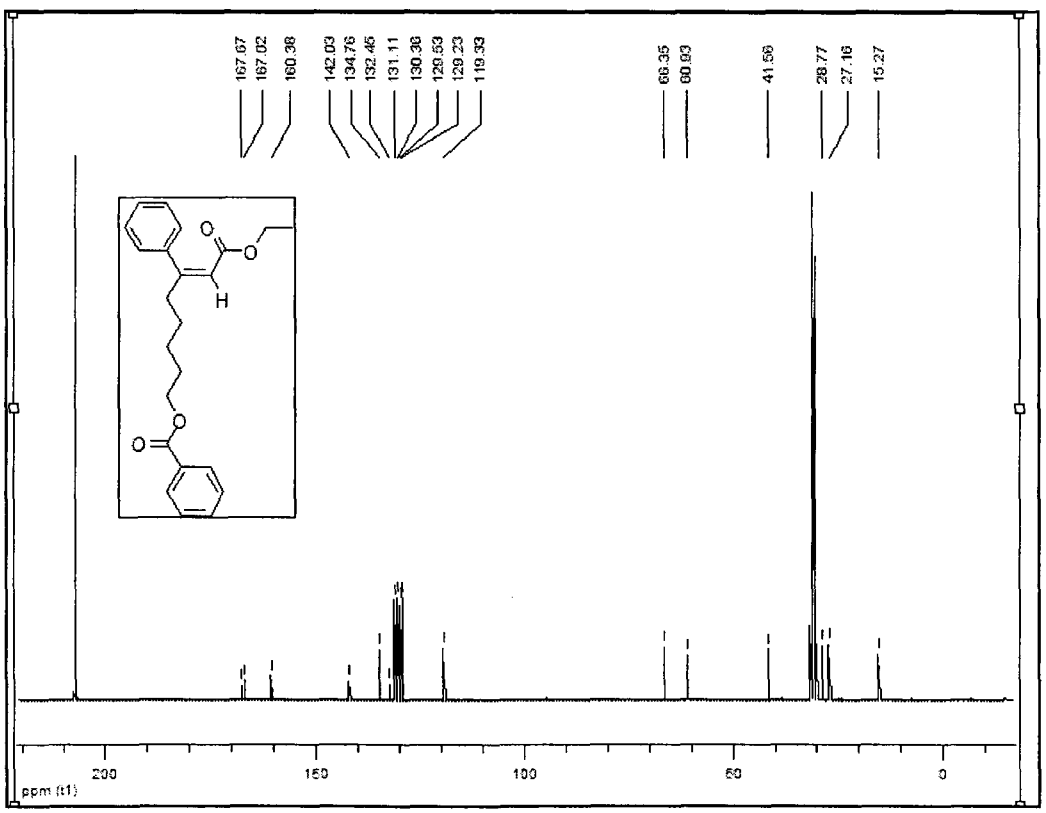
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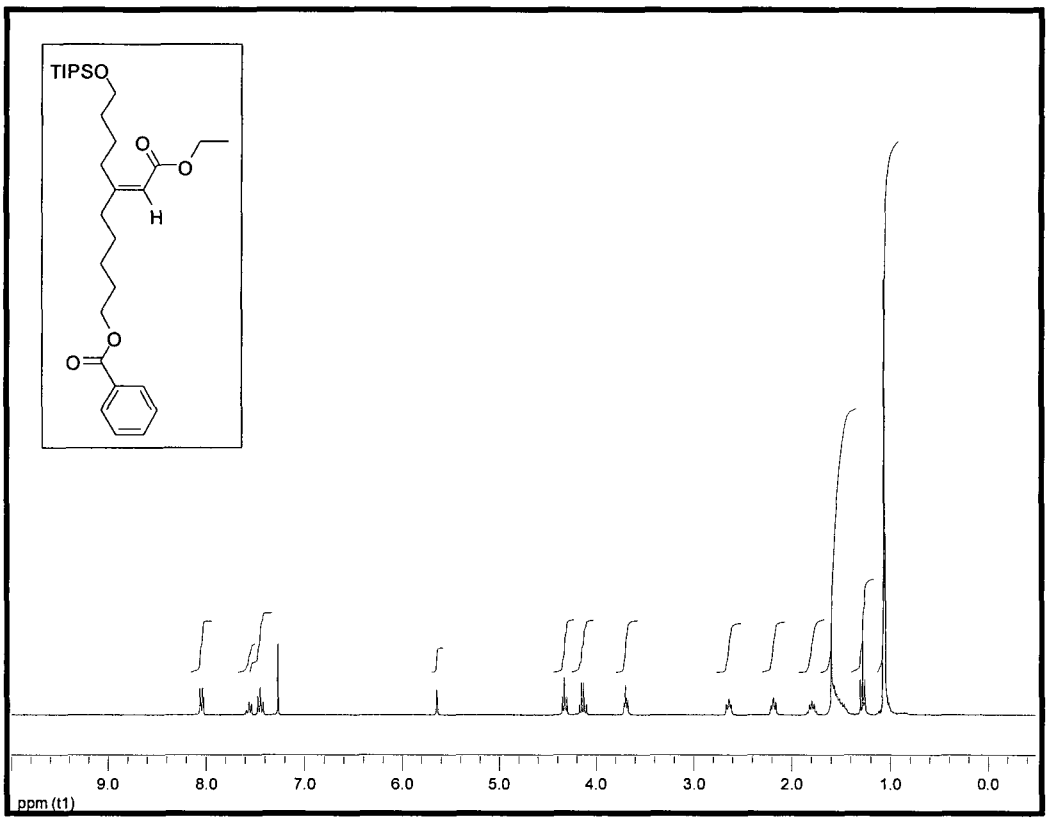
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H
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4.0
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2.0
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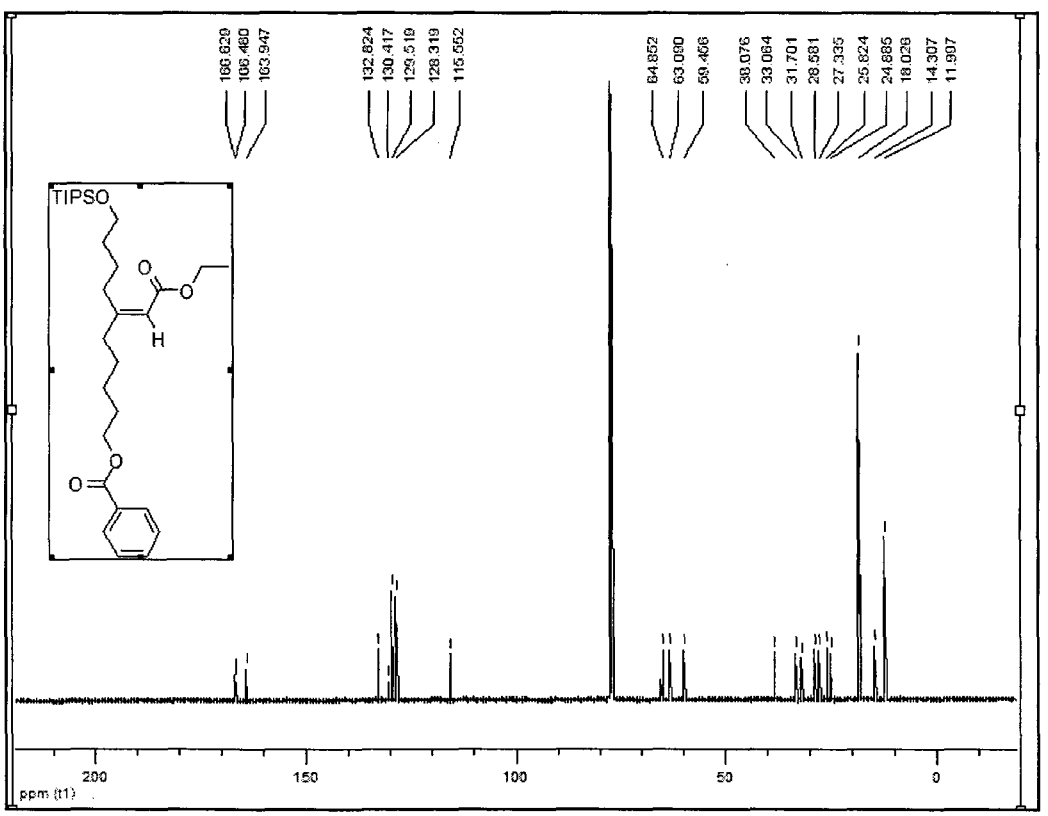
0.0
ppm (t1)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128.319
115.552
64.852
63.090
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38.076
33.084
31.701
28.581
27.335
25.824
24.885
18.026
14.307
11.907
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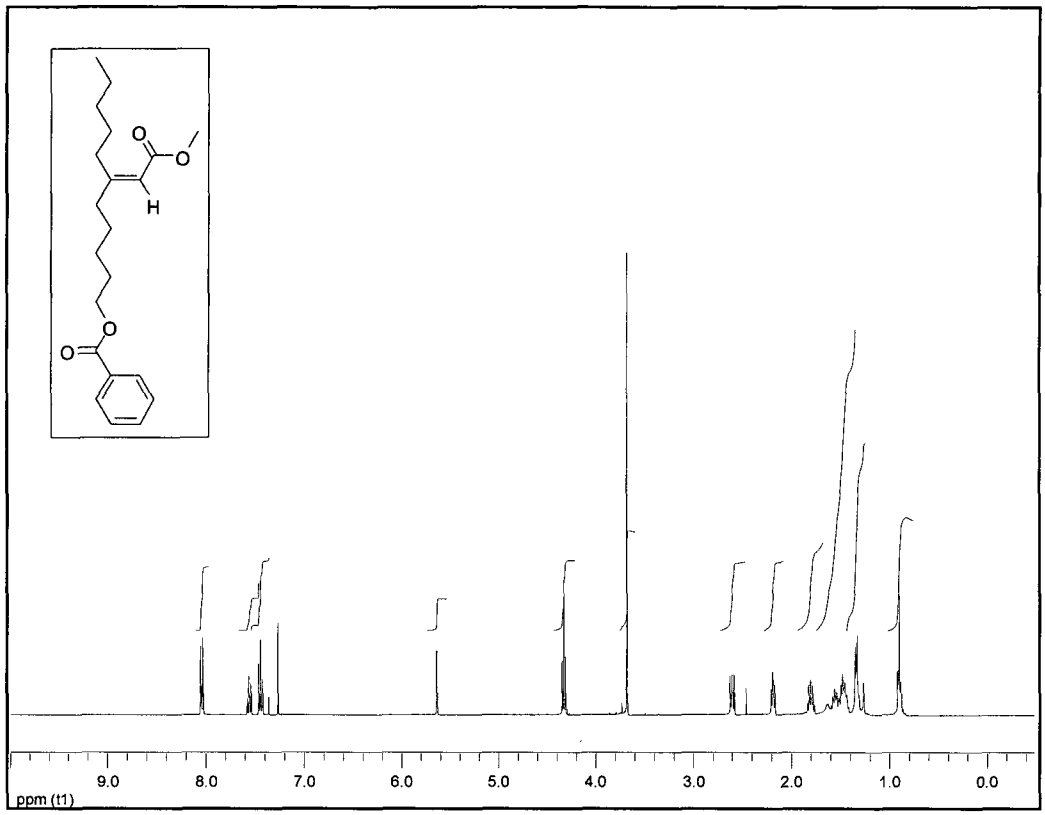
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5.0
4.0
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2.0
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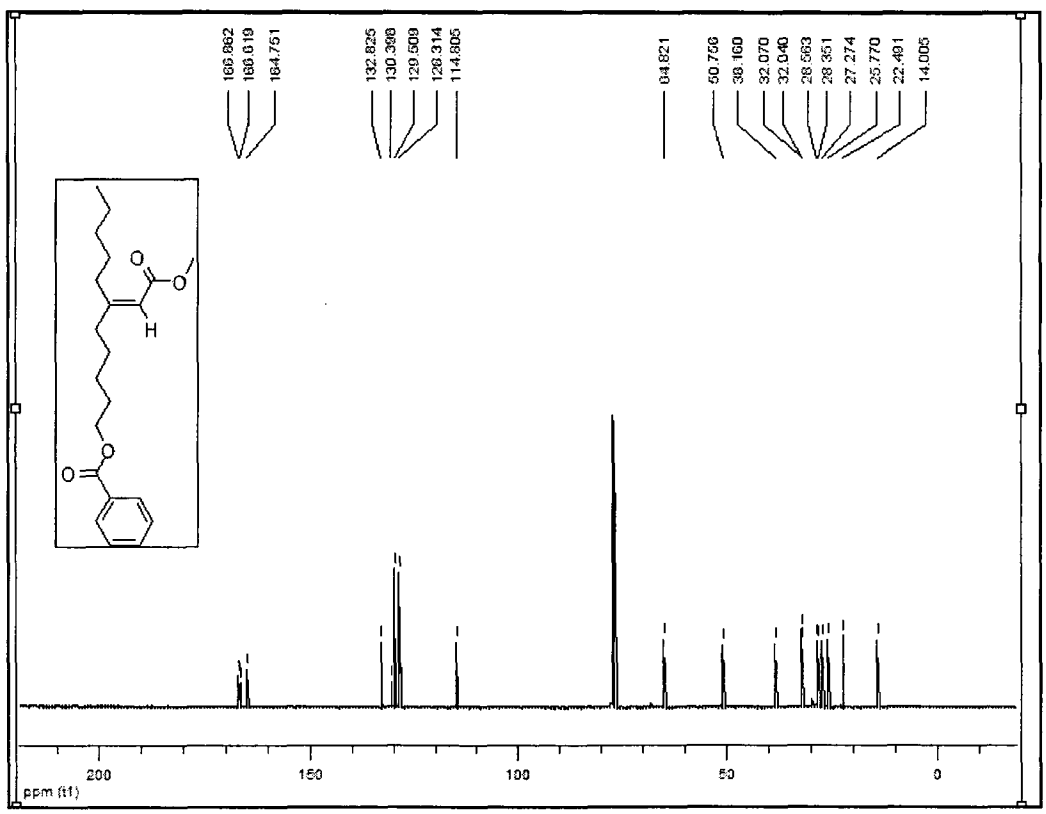
ppm (t1)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28.563
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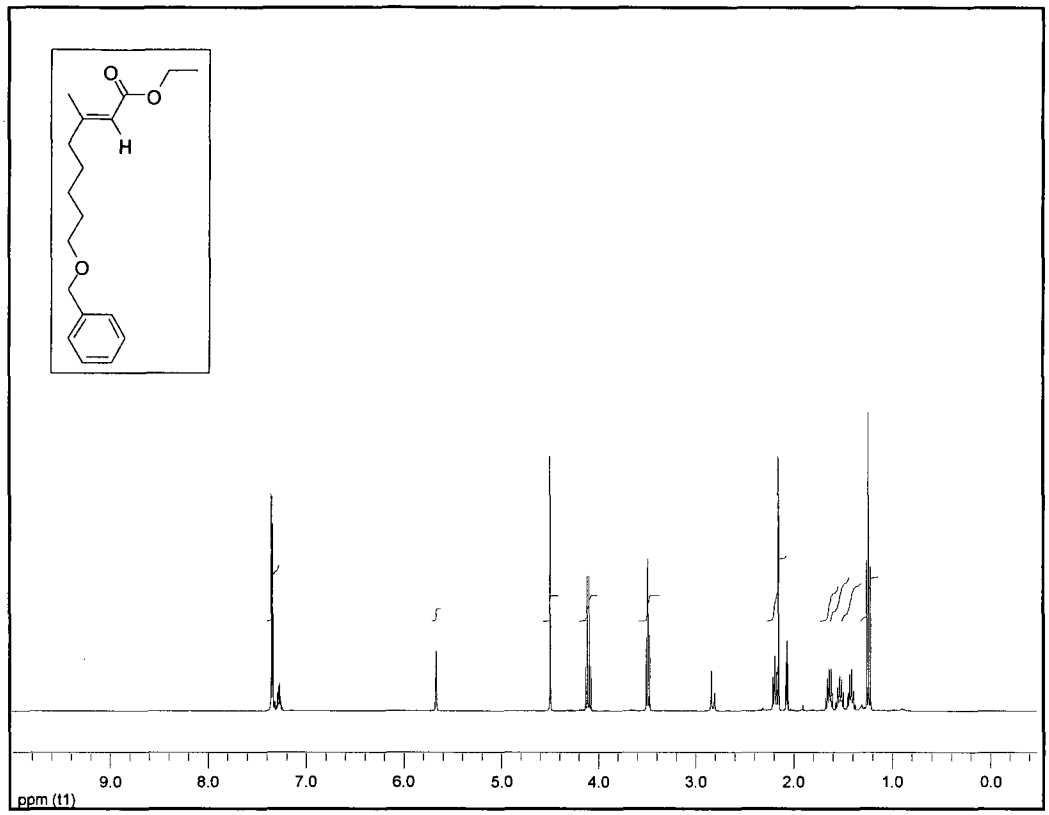
ppm (t1)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4.0
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2.0
1.0
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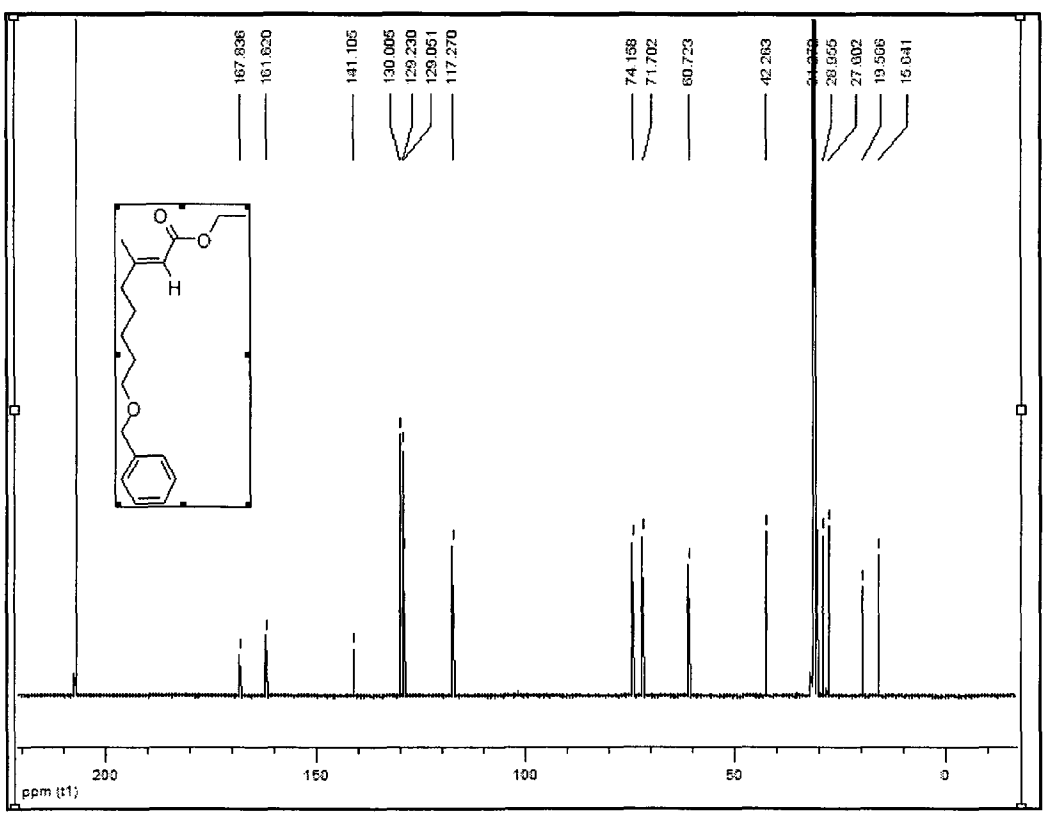
ppm (t1)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129.051
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50
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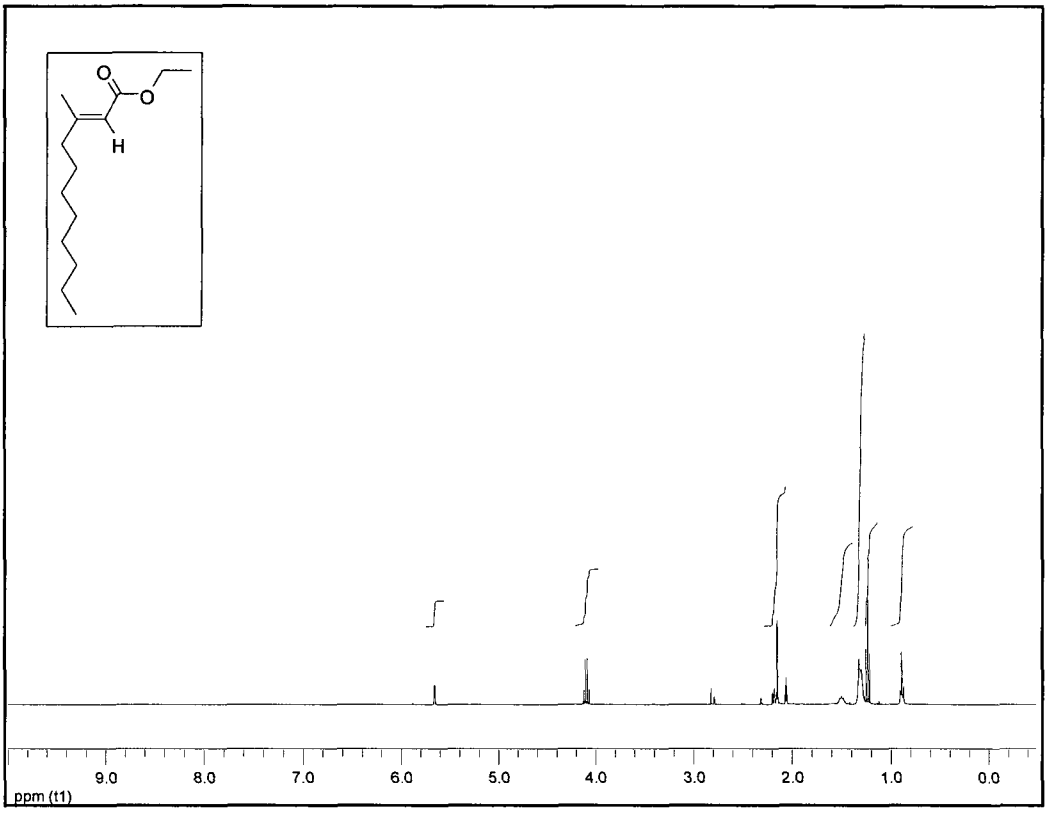
ppm (t1)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5.0
4.0
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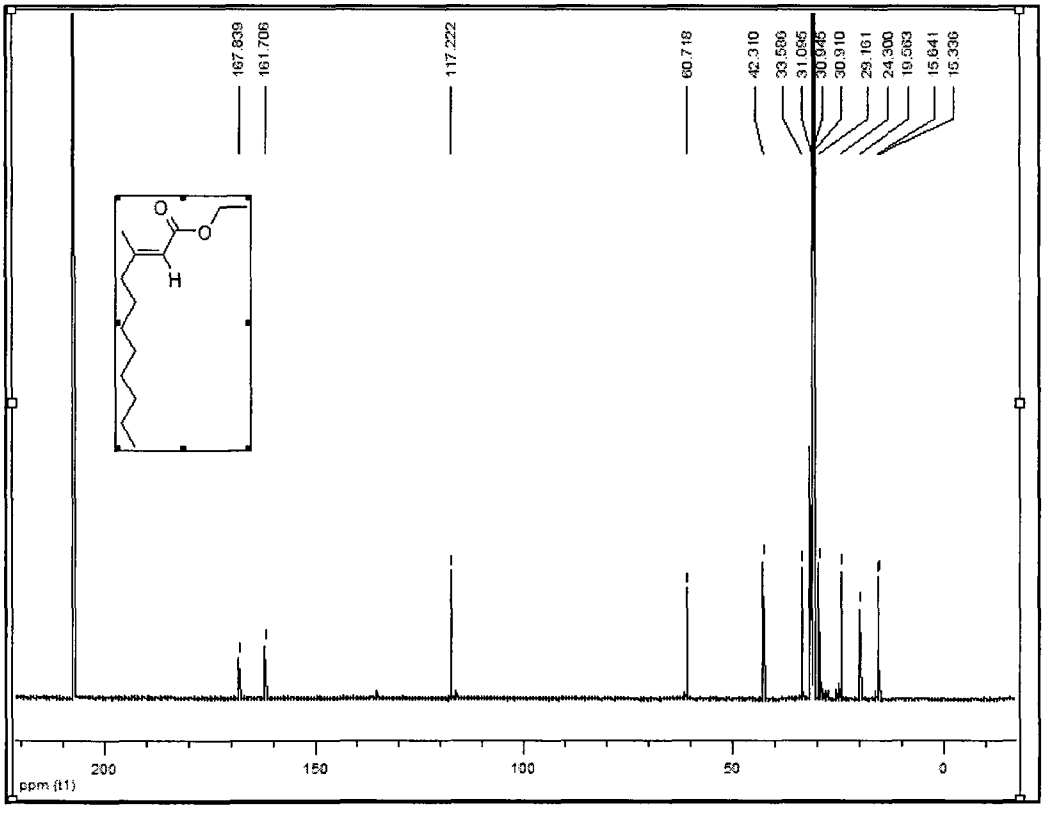
2.0
1.0
0.0
ppm (t1)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31.095
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15.336
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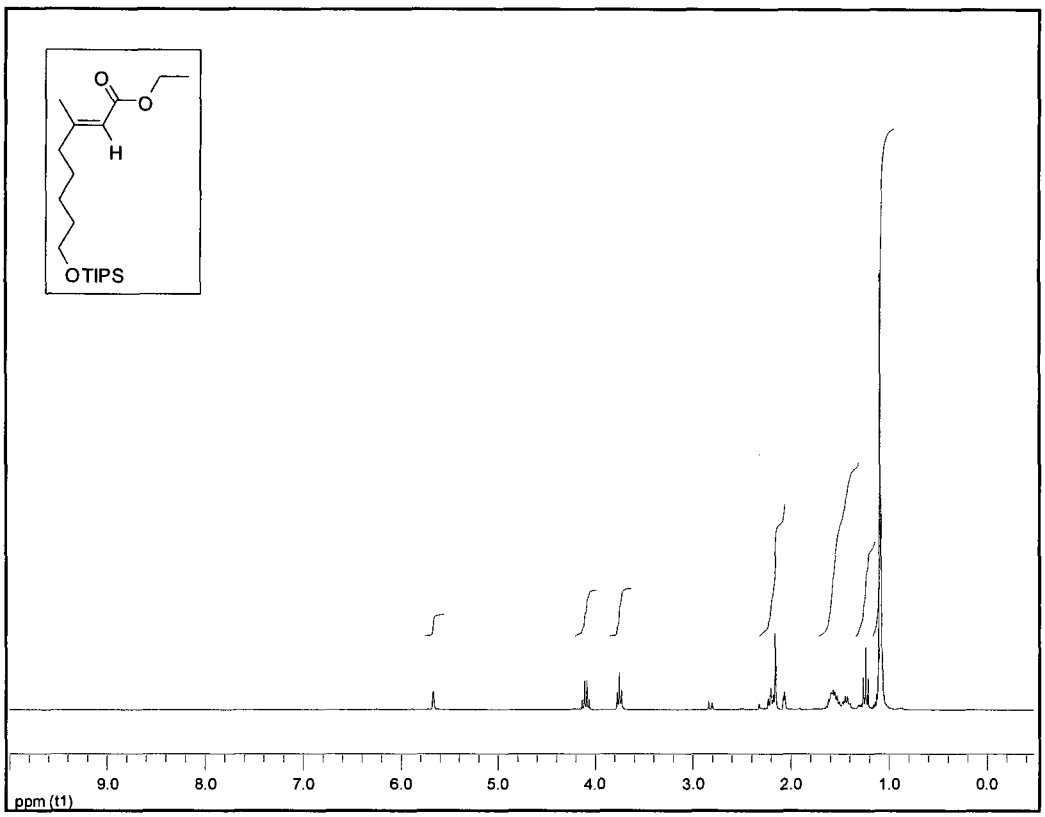
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O
H
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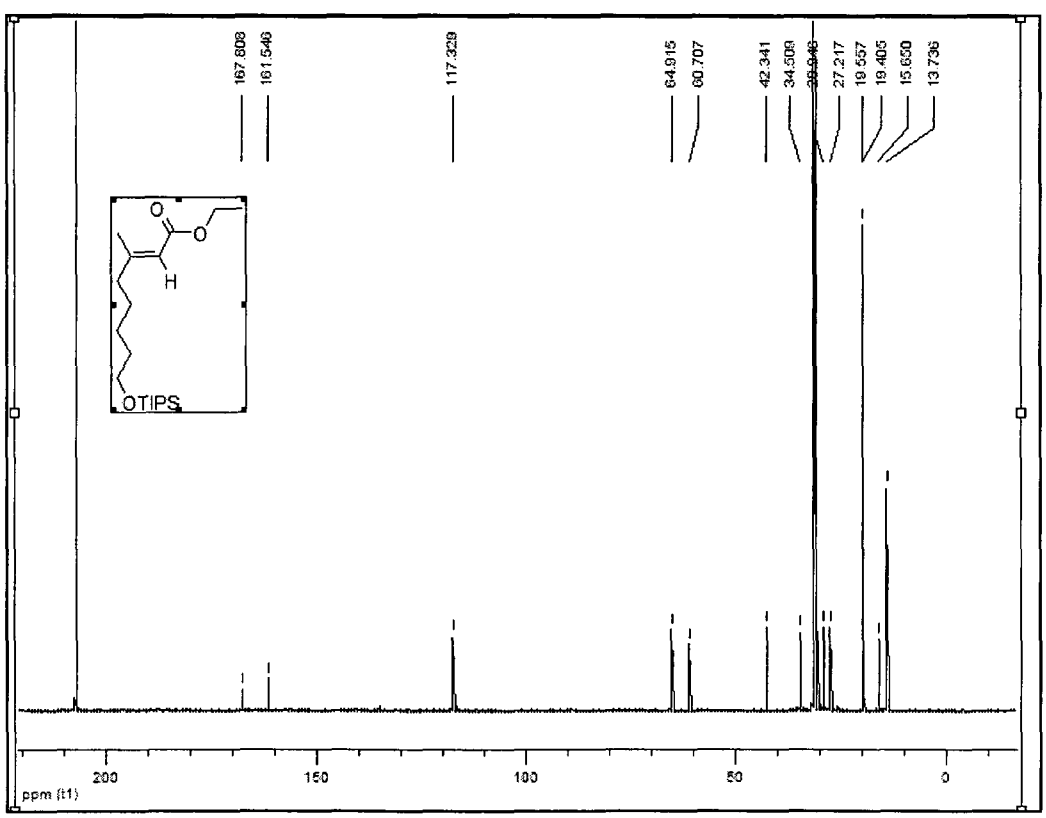
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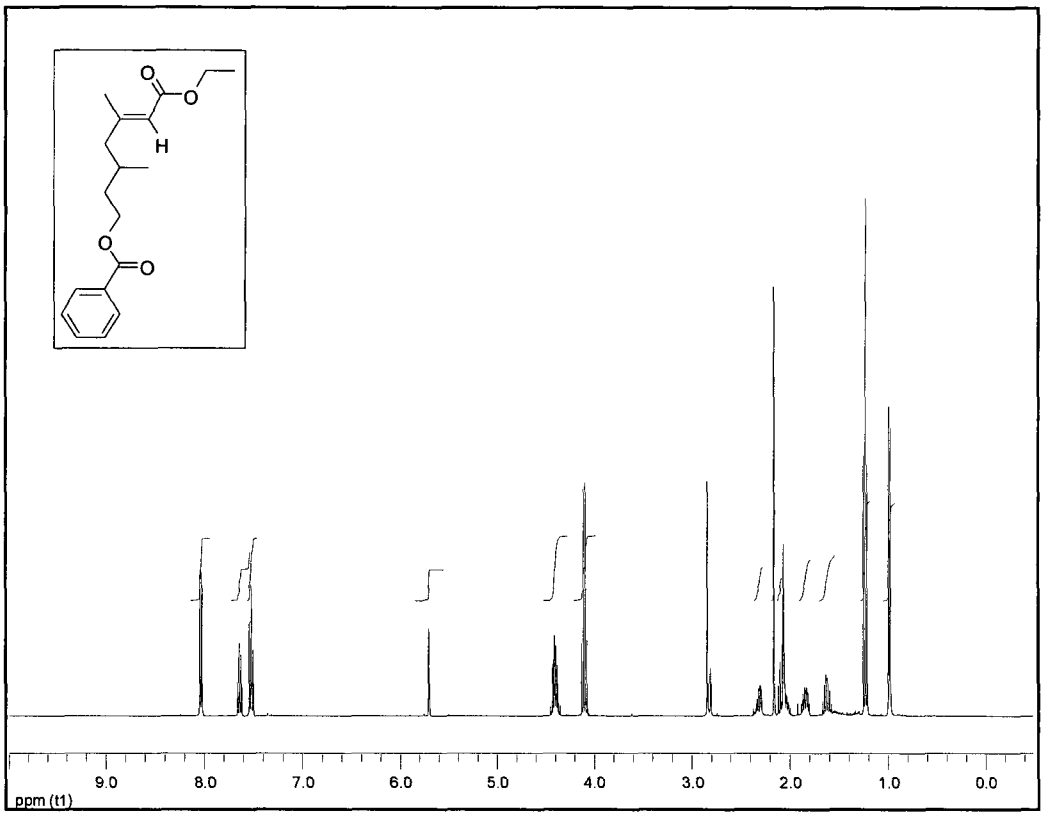
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H
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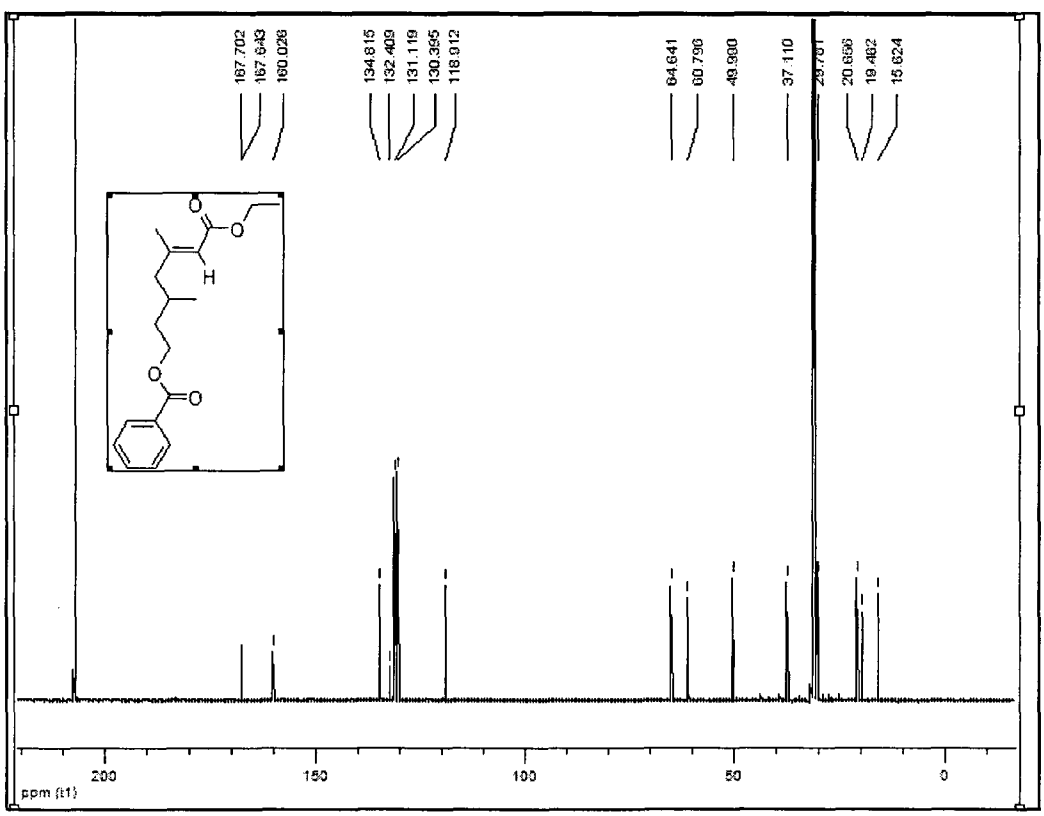
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H
O
O
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50
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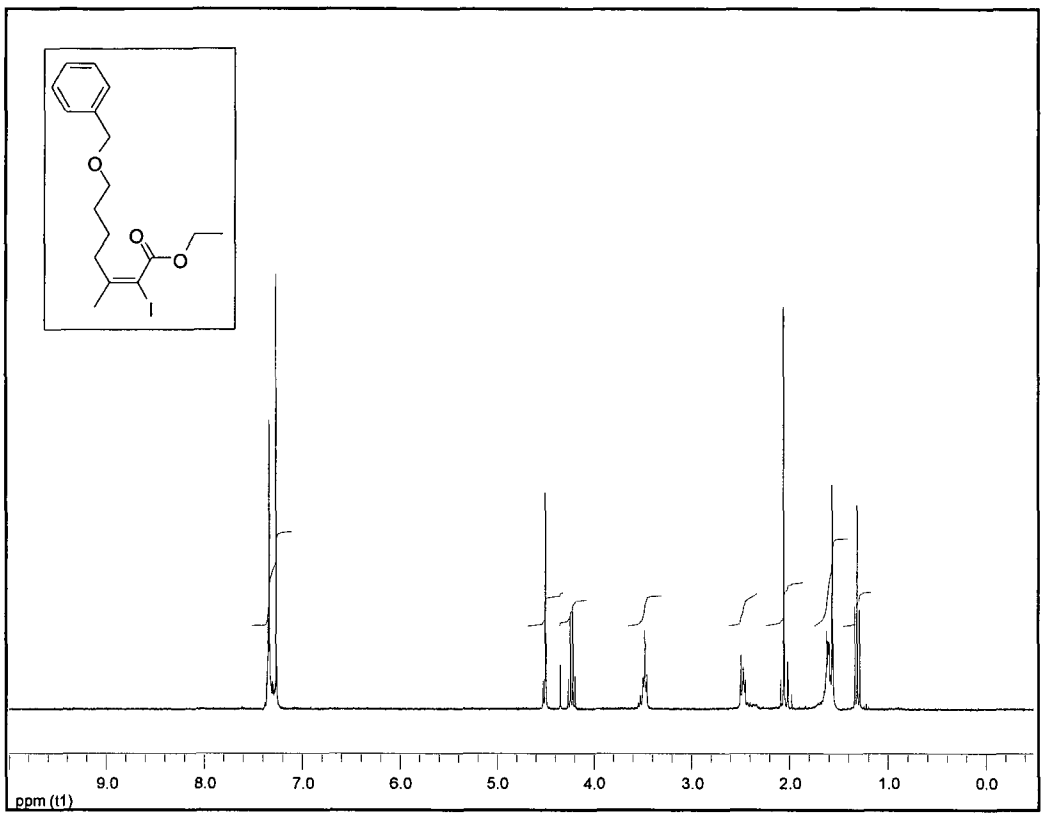
ppm (t1)


O
O
O
I
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8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
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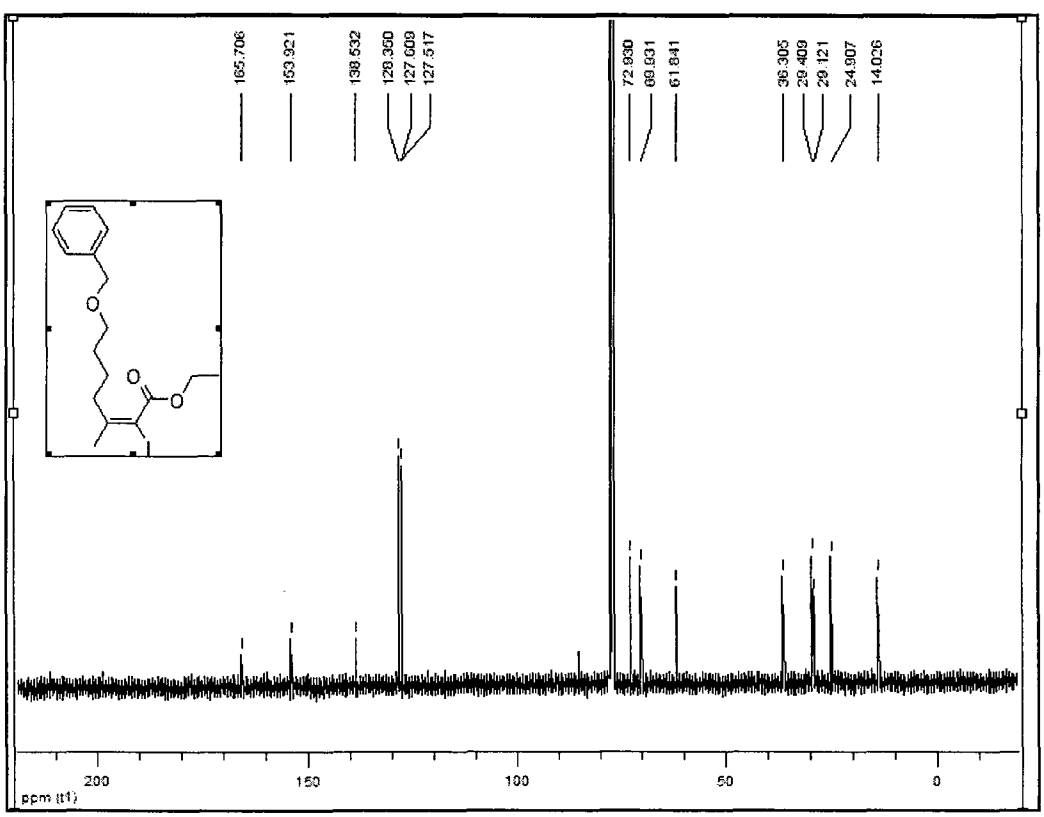
ppm (t1)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O
O
I
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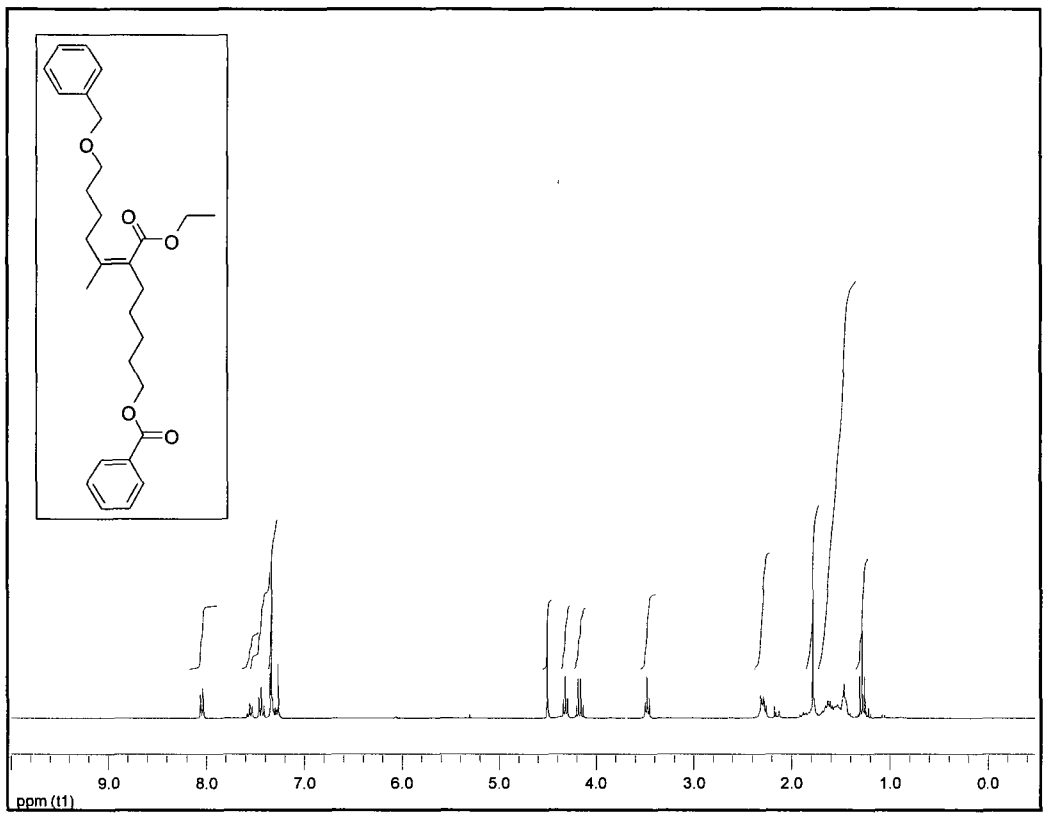
ppm (t1)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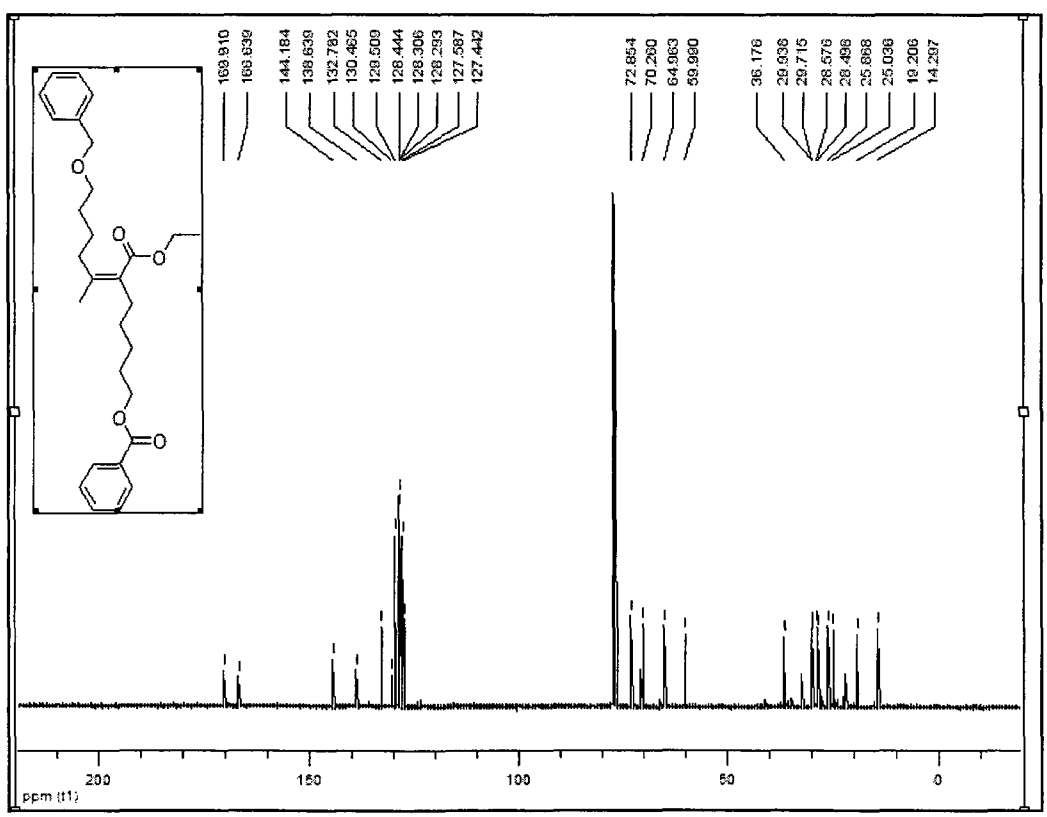
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127.442
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70.260
64.963
59.990
36.176
29.936
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28.496
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50
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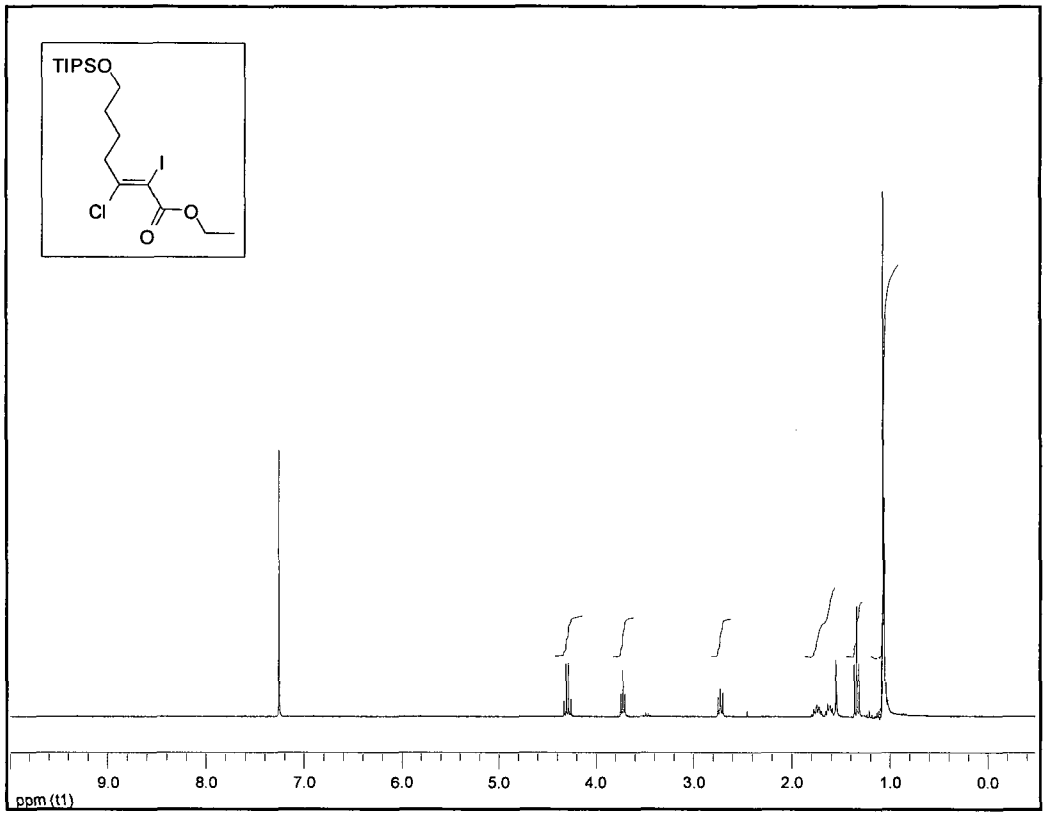
ppm (t1)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Cl
O
O
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5.0
4.0
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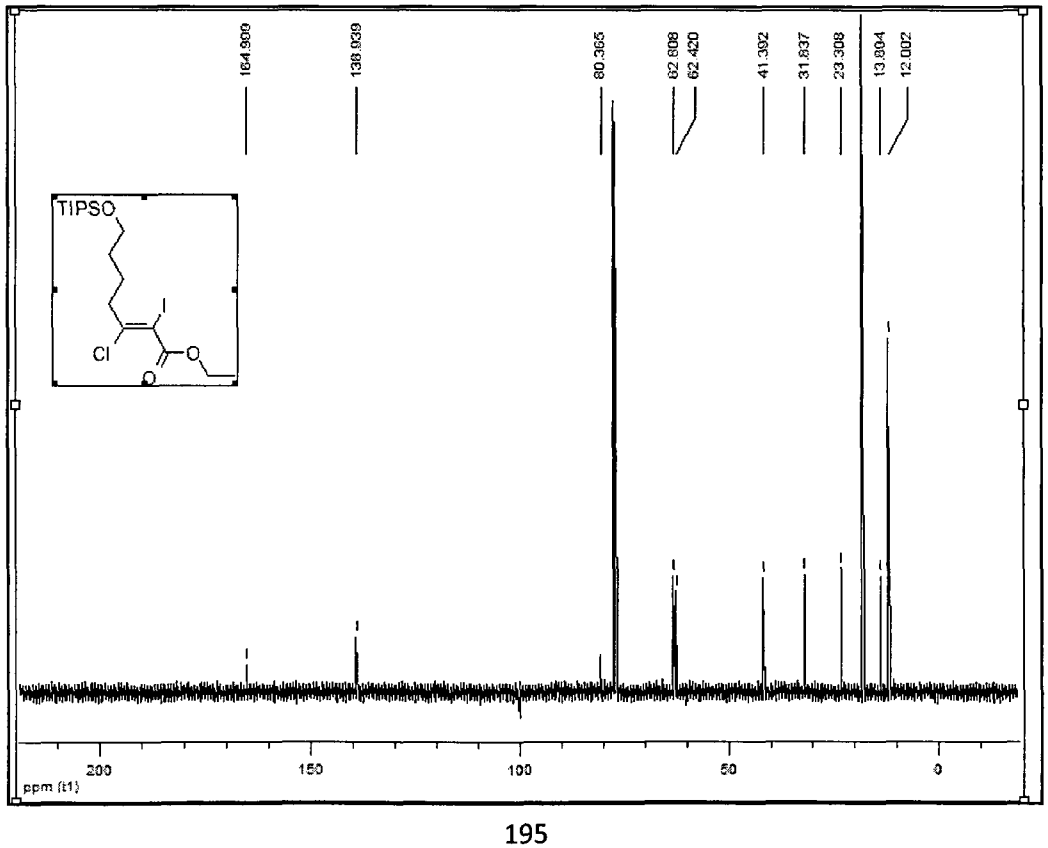
0.0
ppm (t1)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O
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100
50
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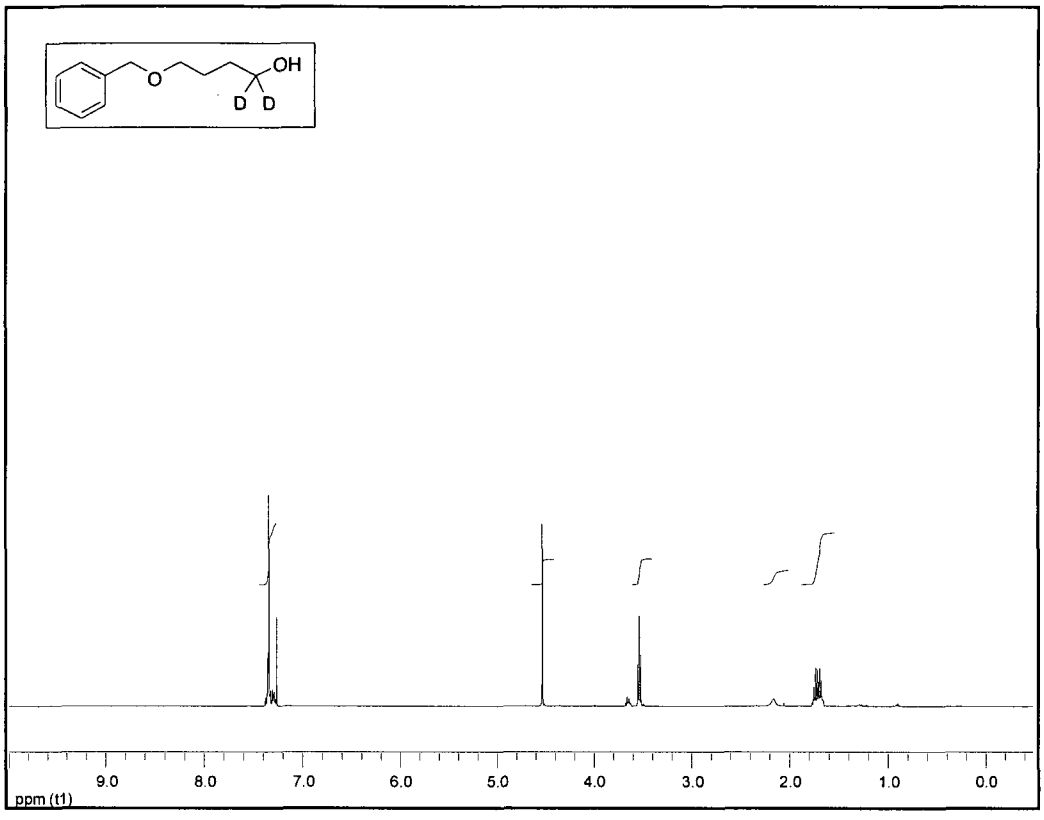
ppm (t1)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D D
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6.0
5.0
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3.0
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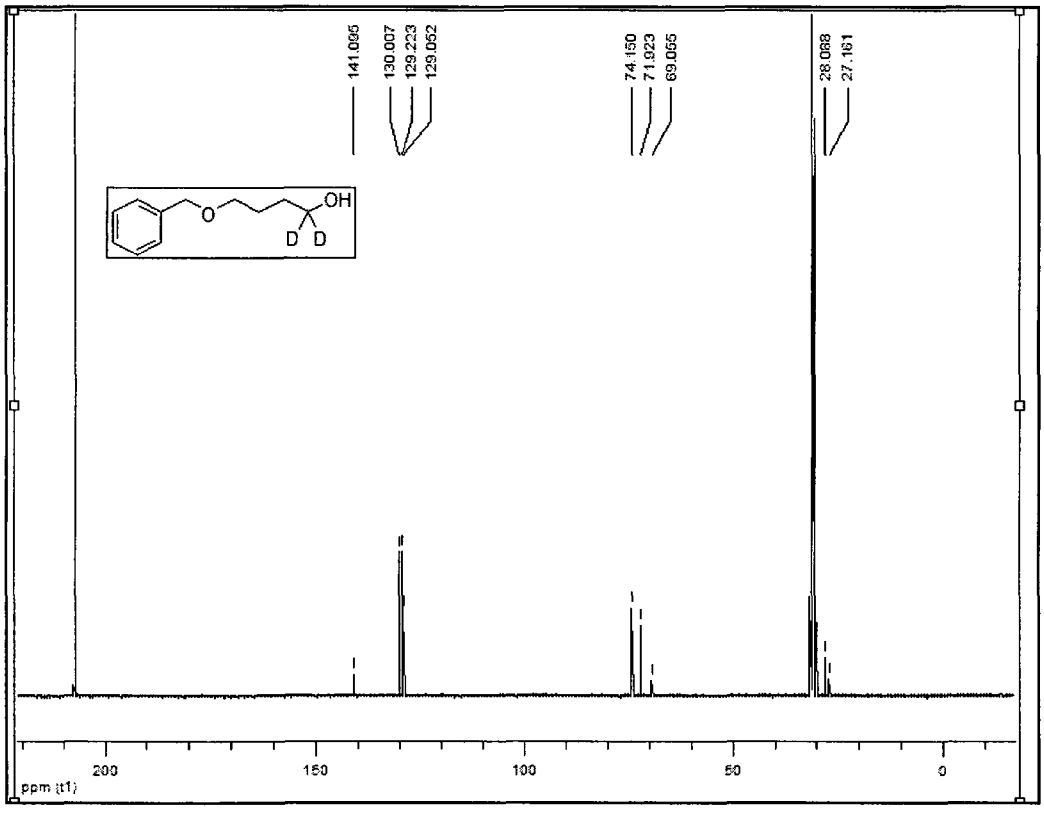
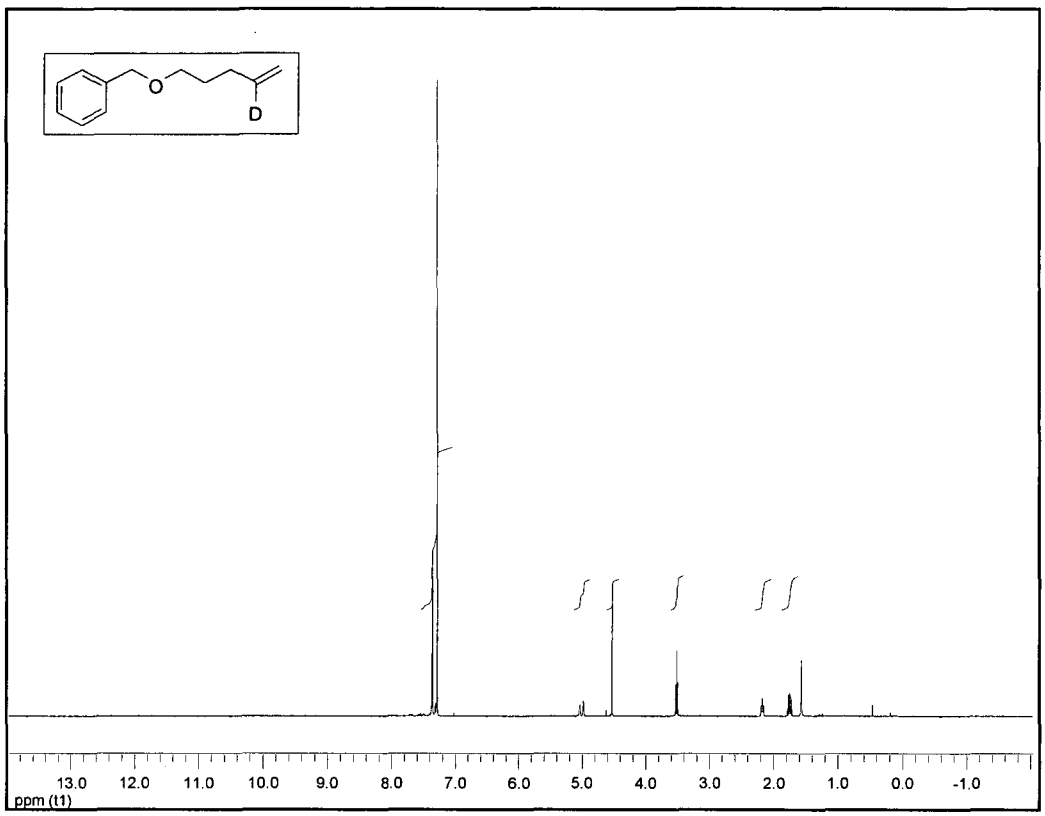
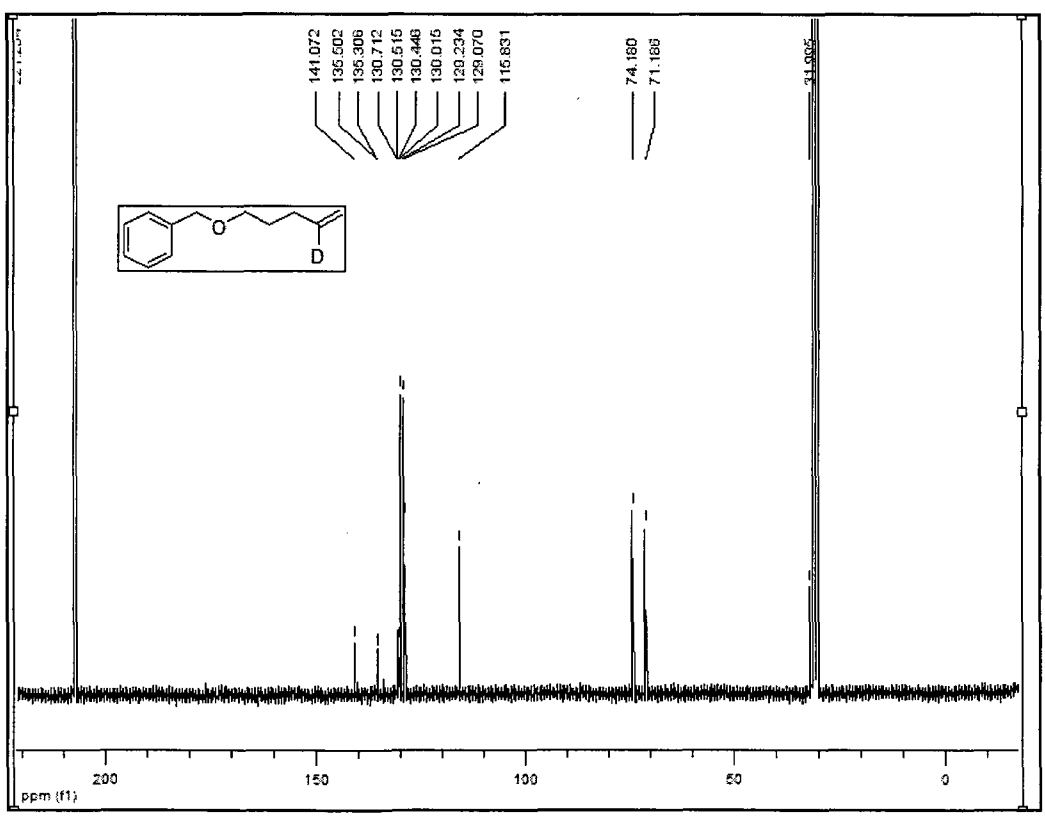
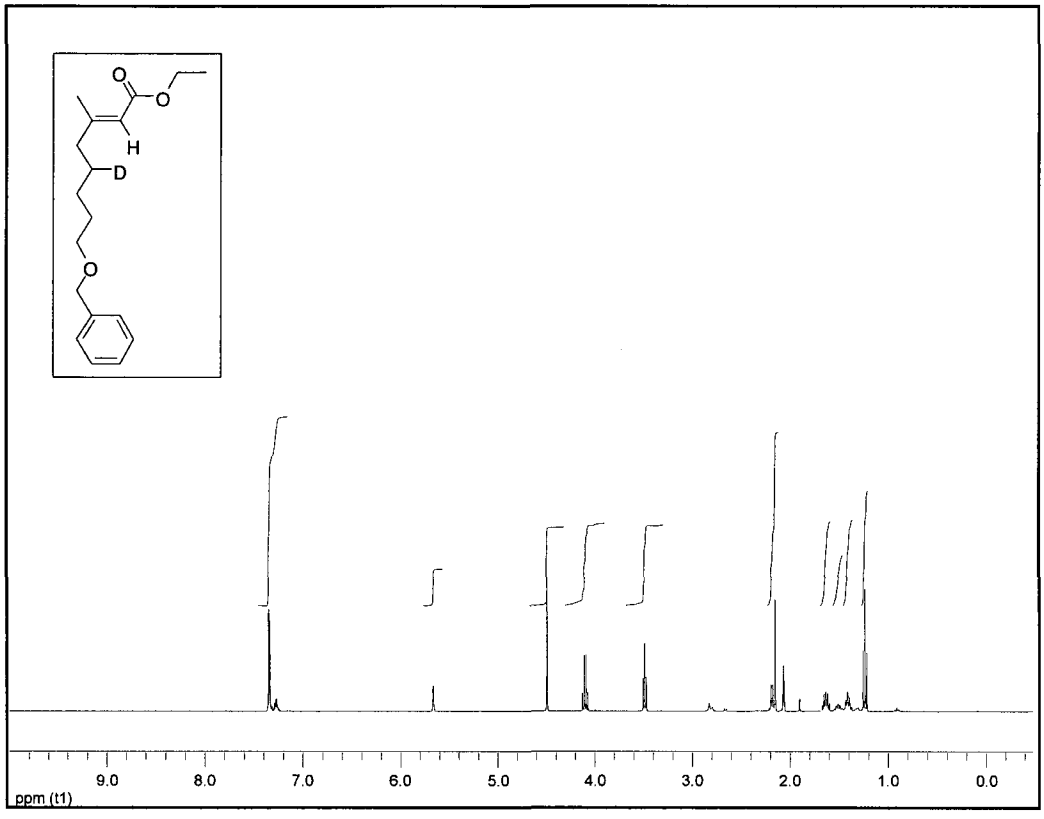
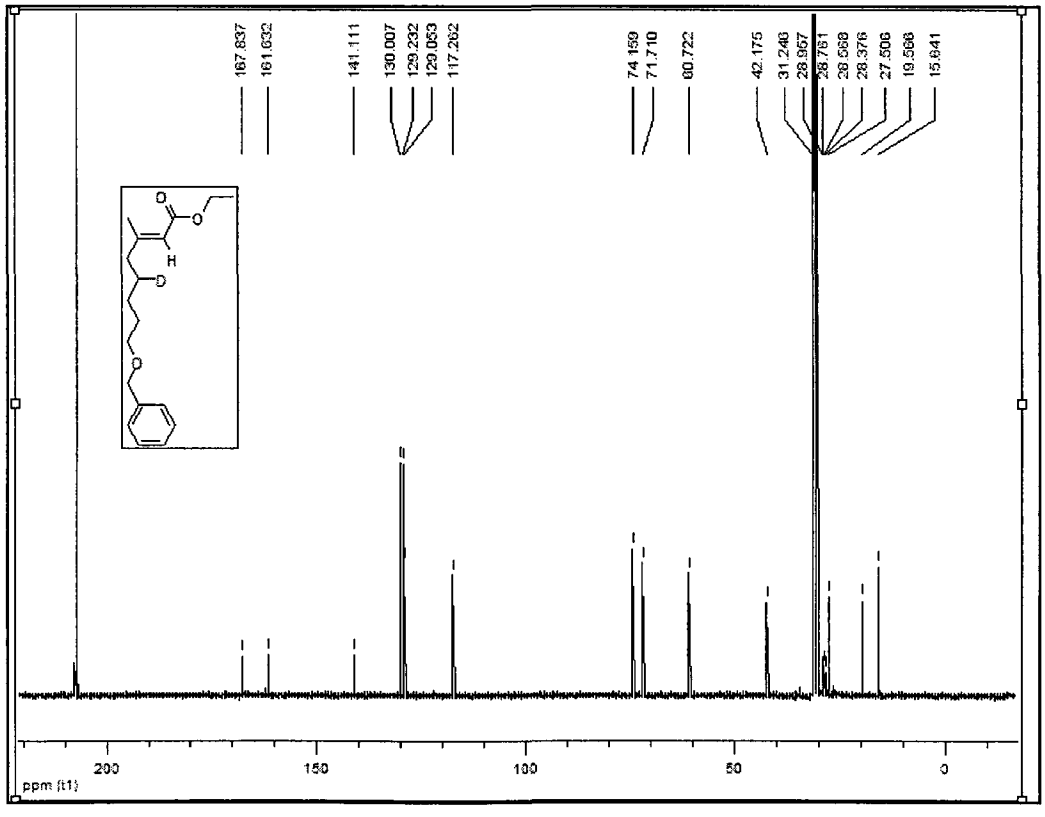
1.0
0.0
ppm (t1)

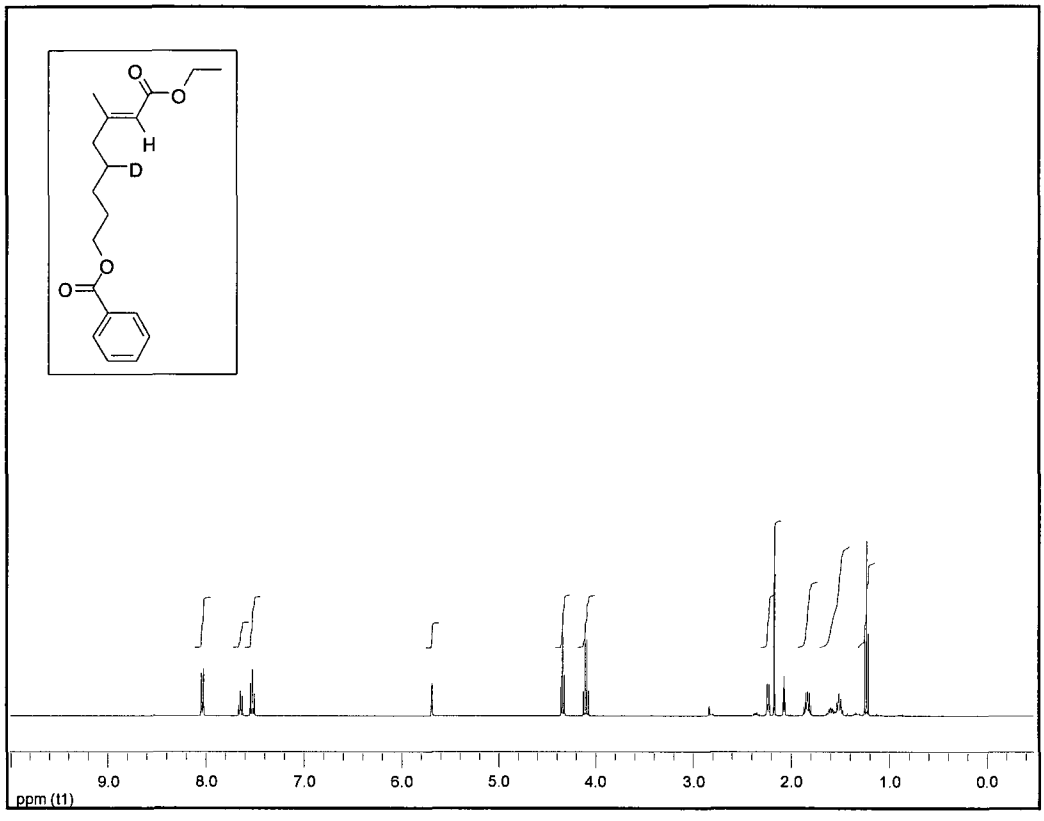

141.096
130.007
129.223
129.052
74.150
71.923
69.055
28.088
27.161
OH
D D
200
150
100
50
0
ppm (t1)

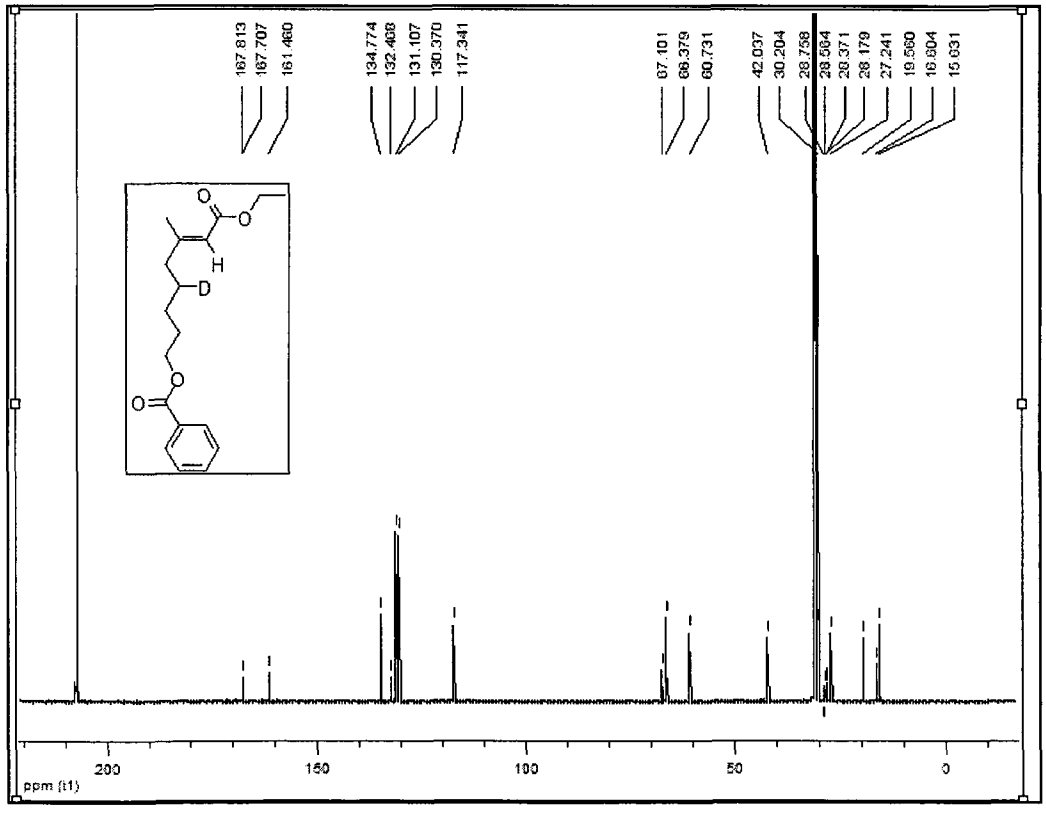

O
D
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
ppm (t1)

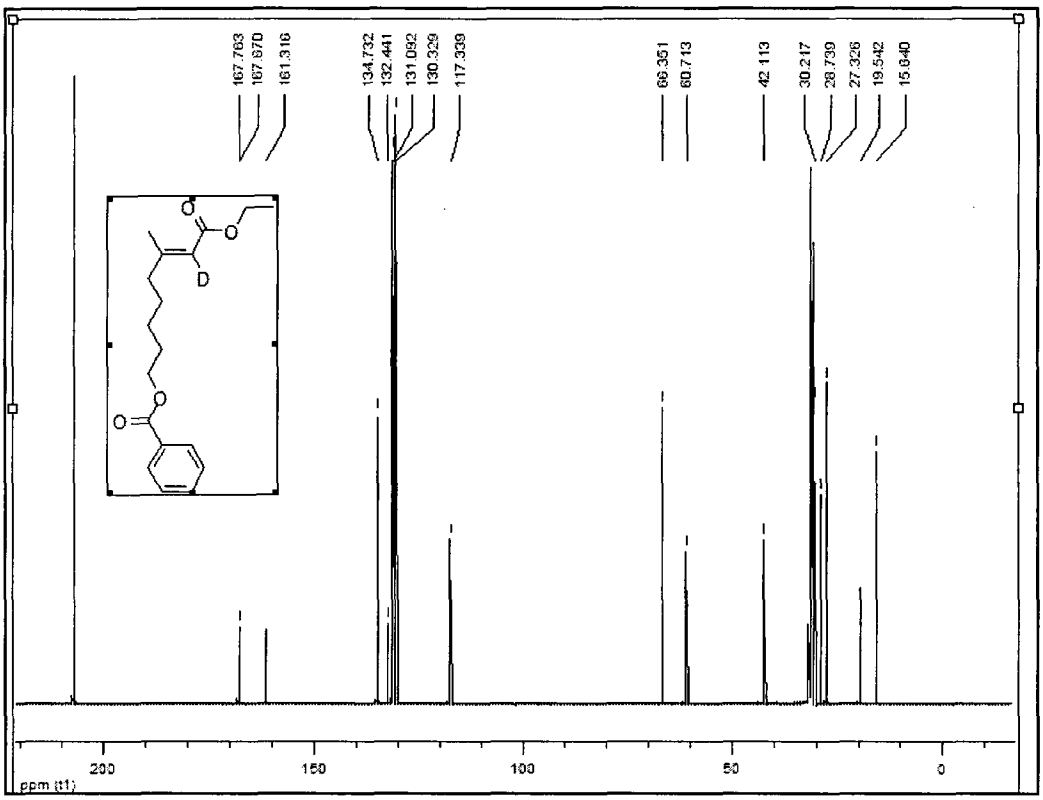

141.072
135.502
135.306
130.712
130.515
130.446
130.015
129.234
129.070
115.831
74.180
71.186
O
D
200
150
100
50
0
ppm (f1)

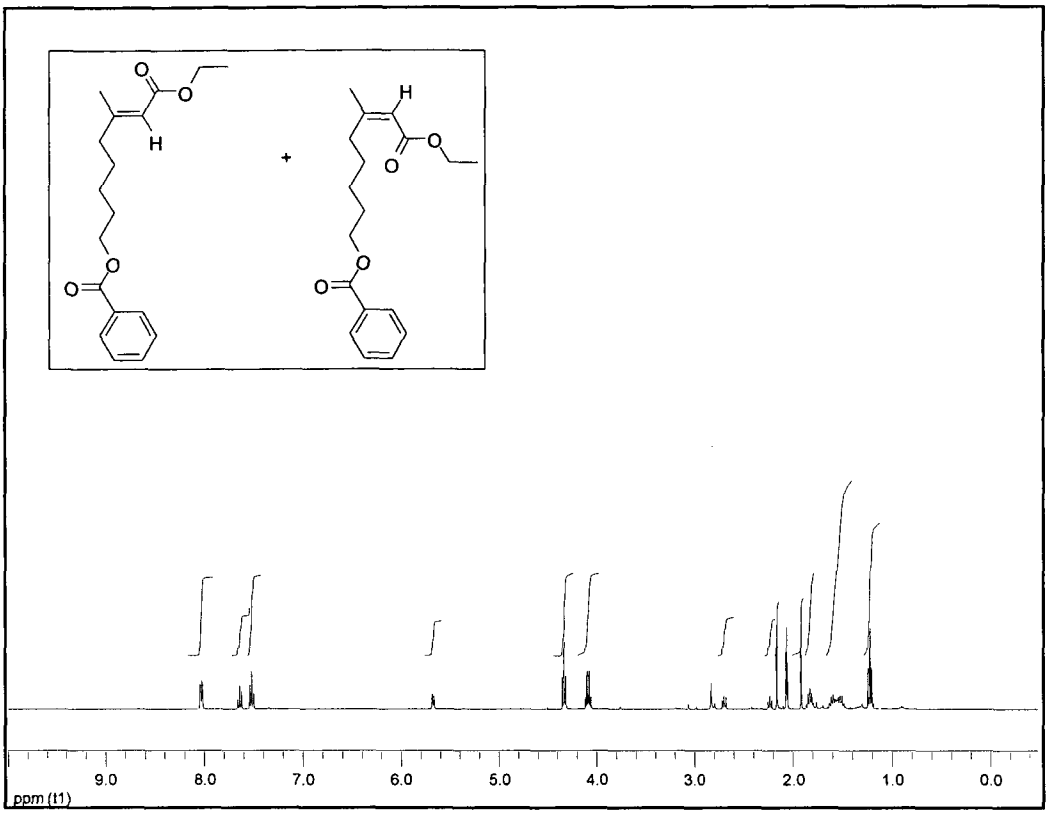

O
O
H
D
O
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

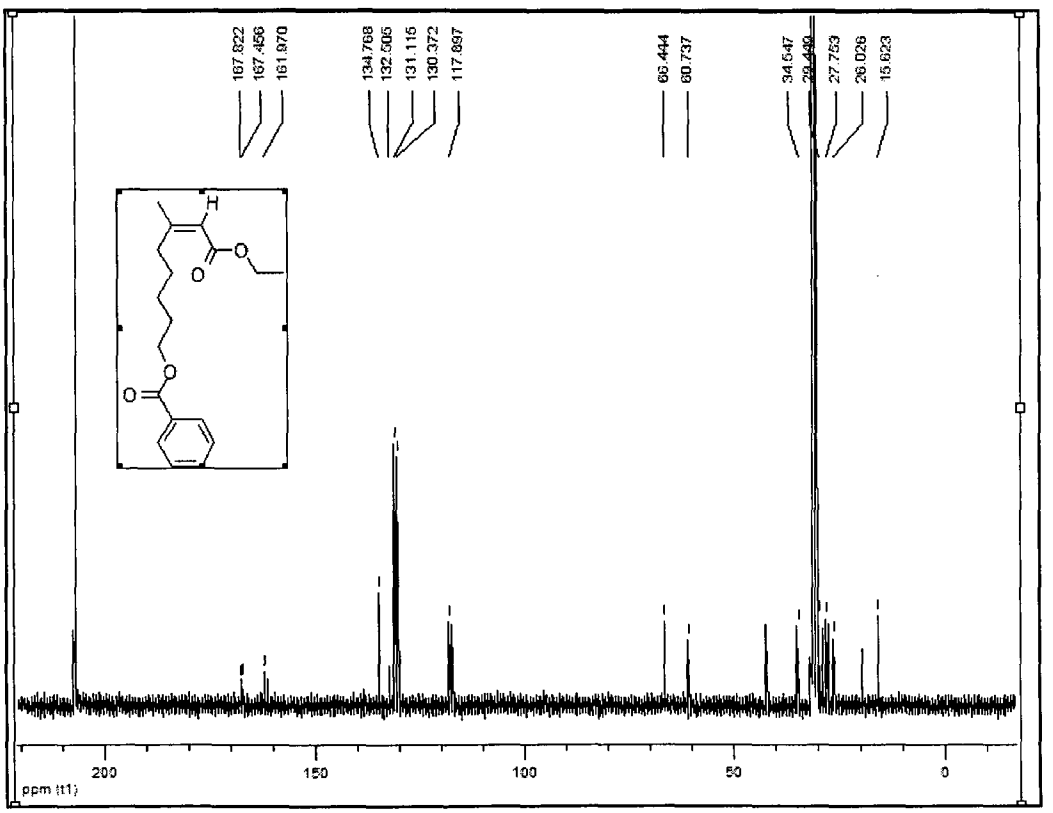

167.837
161.632
141.111
130.007
129.232
129.053
117.262
74.159
71.710
60.722
42.175
31.248
28.967
28.761
28.568
28.376
27.506
19.568
15.941
O
O
H
D
O
200
150
100
50
0
ppm (t1)

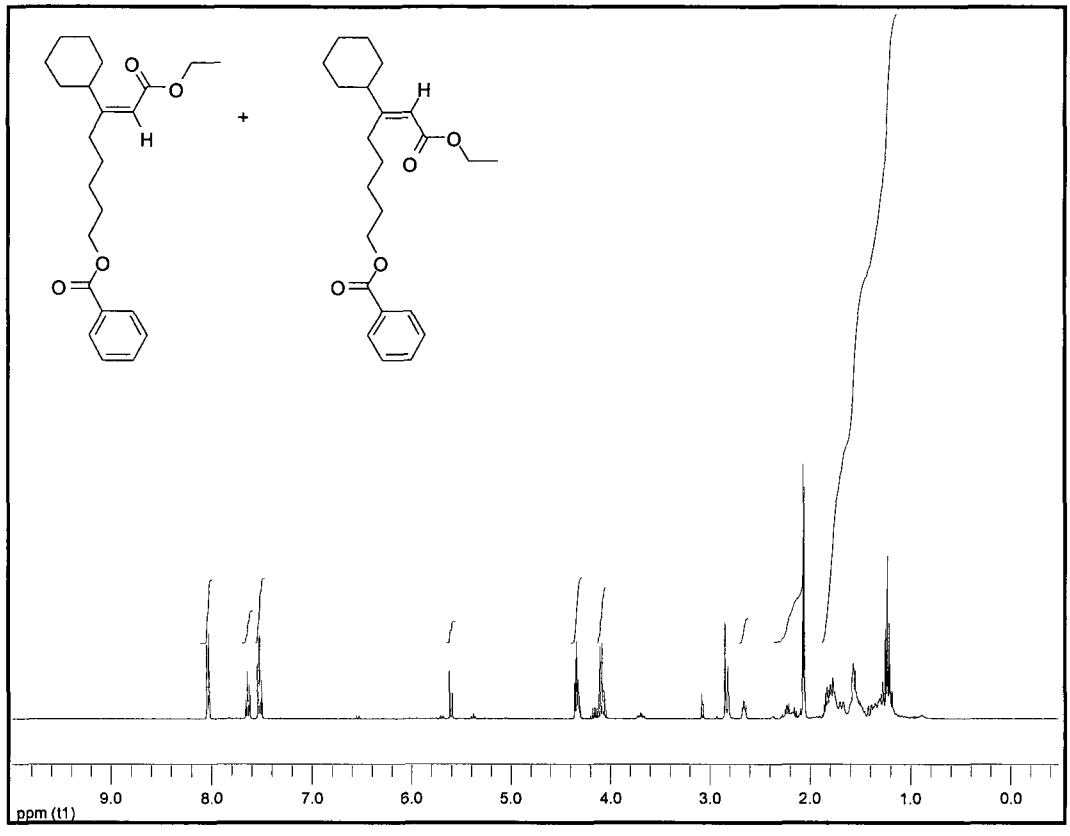

O
O
H
D
O
O
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

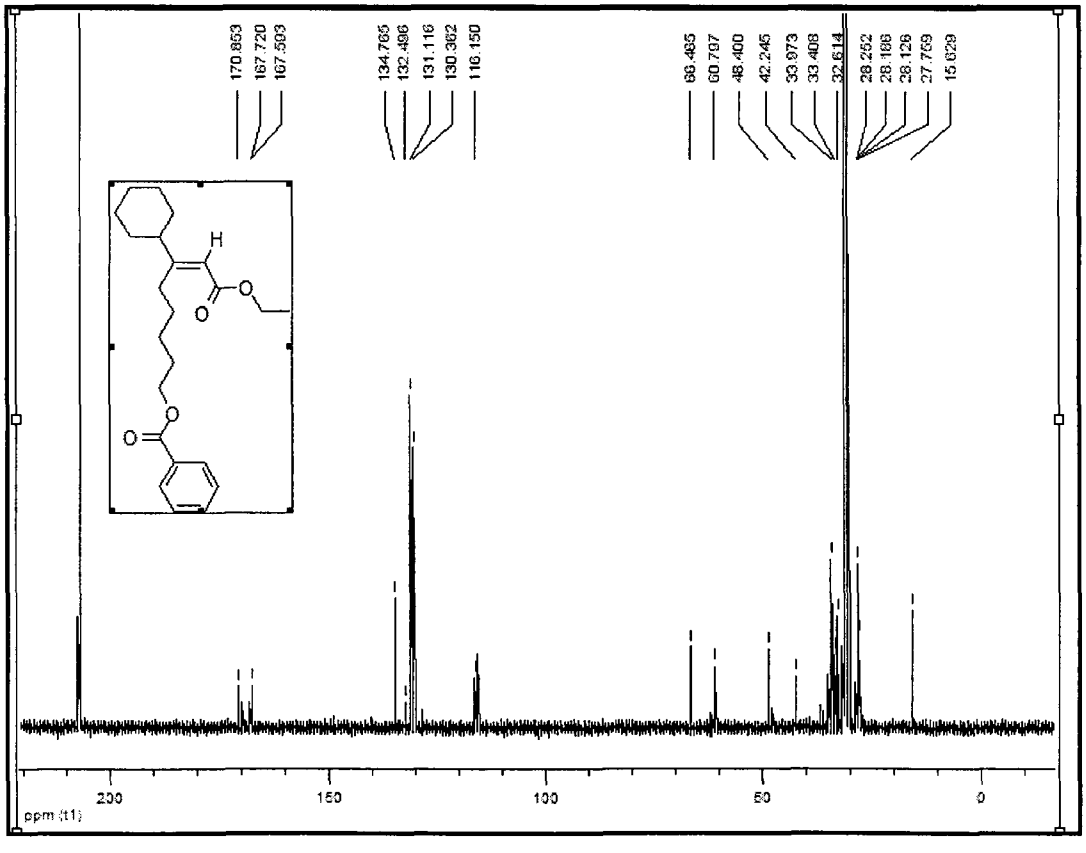

167.813
167.707
161.460
134.774
132.408
131.107
130.370
117.341
97.101
68.379
60.731
42.037
30.204
28.758
28.584
28.371
28.179
27.241
19.560
16.804
15.031
O
O
H
D
O
O
200
150
100
50
0
ppm (t1)

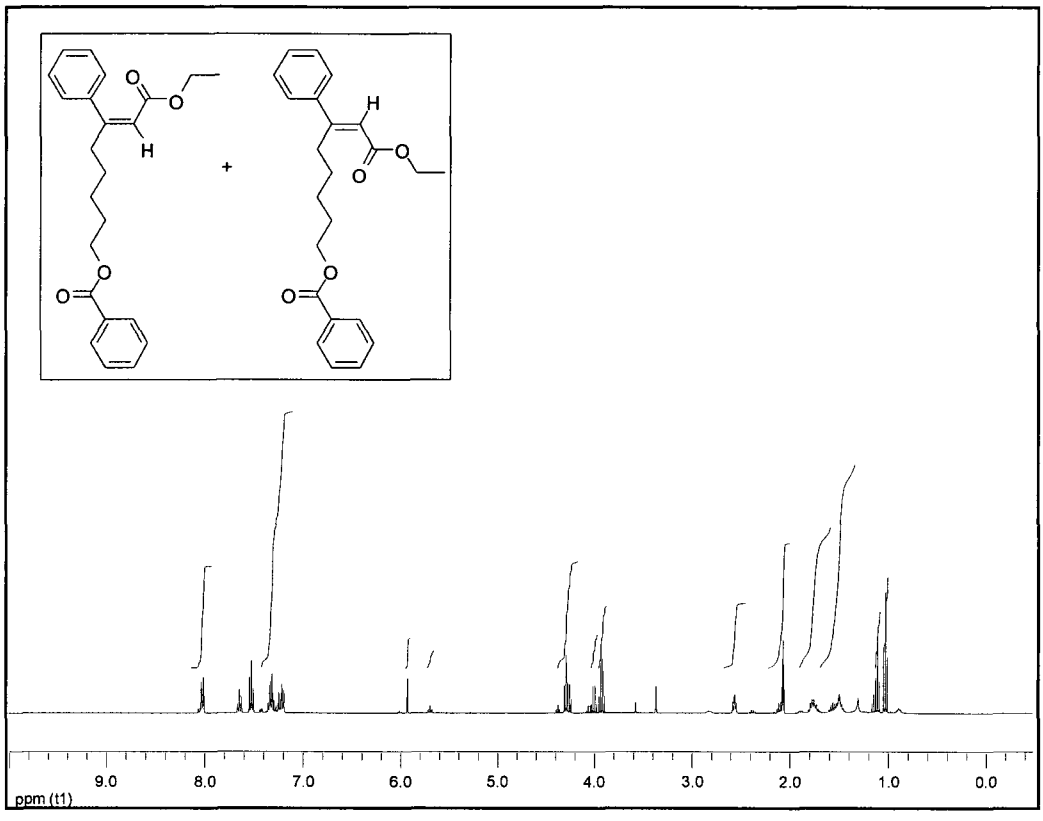

167.763
167.670
161.316
134.732
132.441
131.092
130.329
117.339
66.351
60.713
42.113
30.217
28.739
27.326
19.542
15.040
O
O
D
O
O
200
150
100
50
0
ppm (t1)

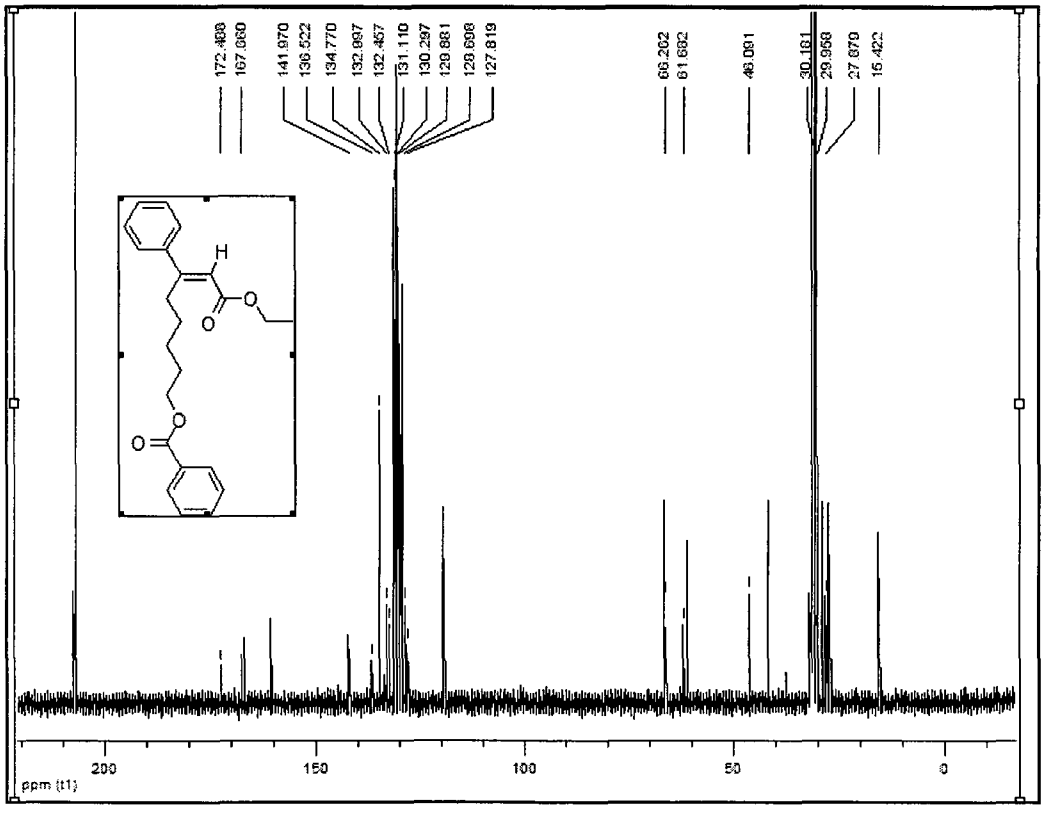

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

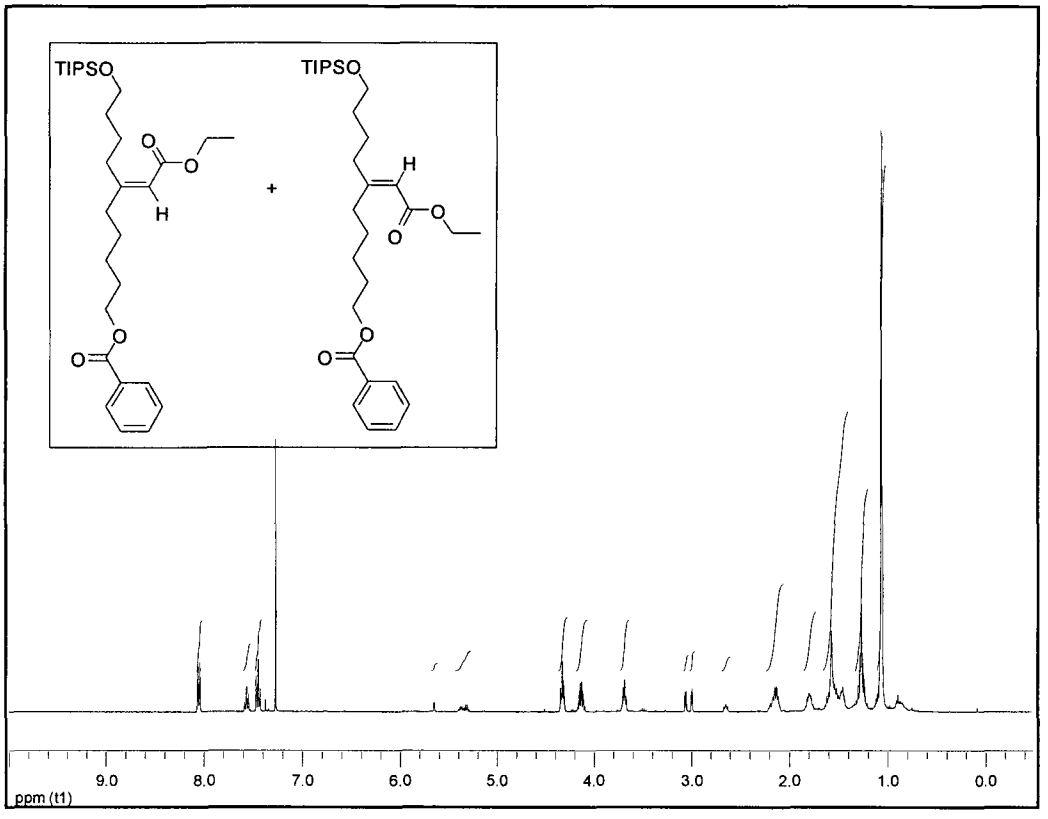

167.822
167.456
161.970
134.768
132.505
131.115
130.372
117.897
66.444
60.737
34.547
29.489
27.753
26.026
15.623
200
150
100
50
0
ppm (t1)

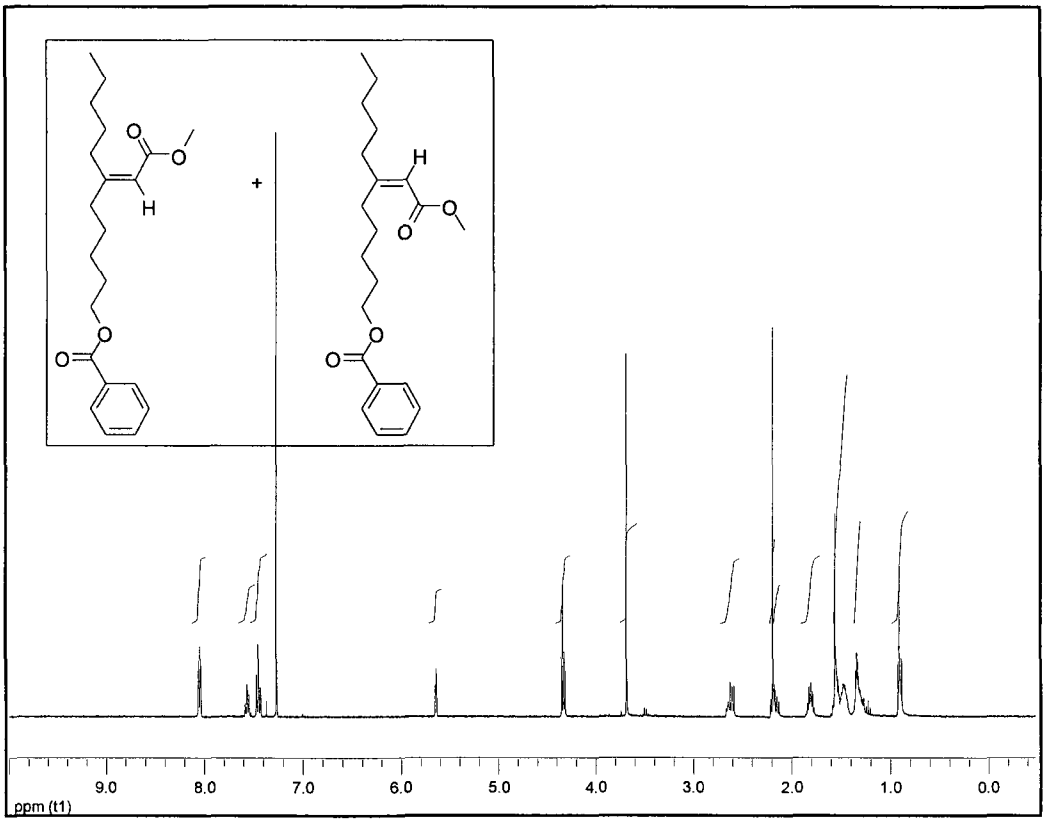

ppm (t1)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

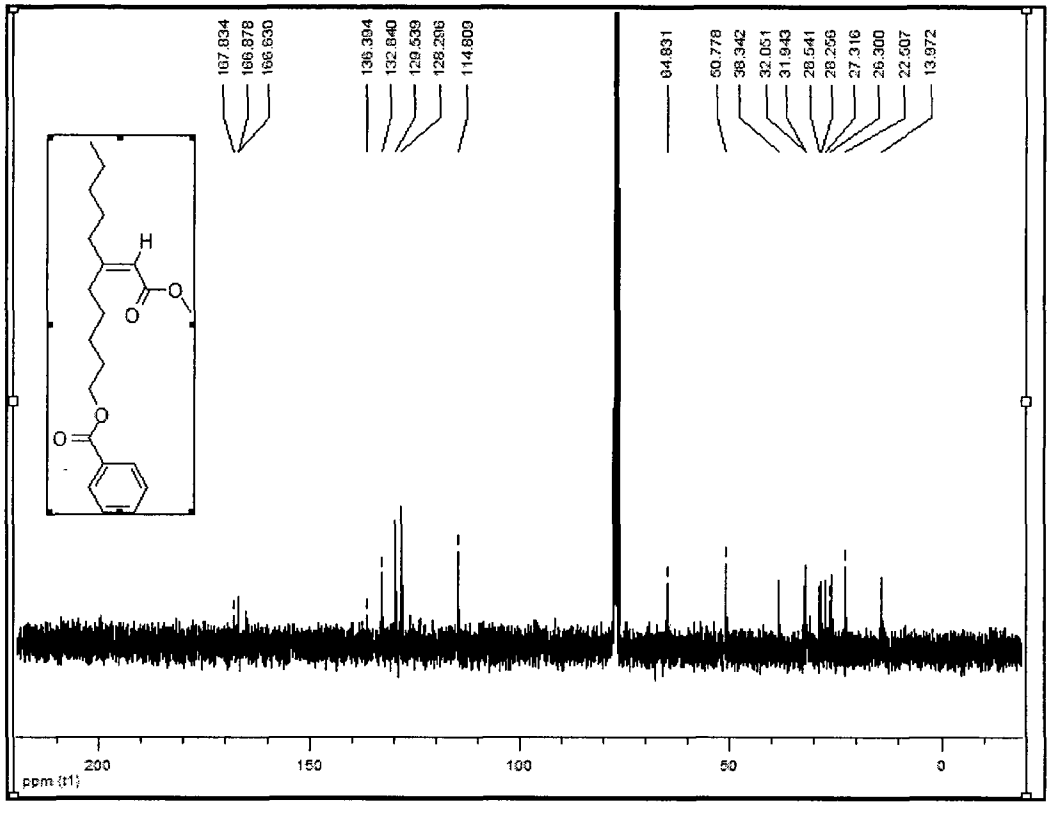

170.853
167.720
167.593
134.765
132.496
131.116
130.362
116.150
68.485
60.797
48.400
42.245
33.973
33.408
32.614
29.252
28.186
28.126
27.759
15.629
ppm (t1)
200
150
100
50
0

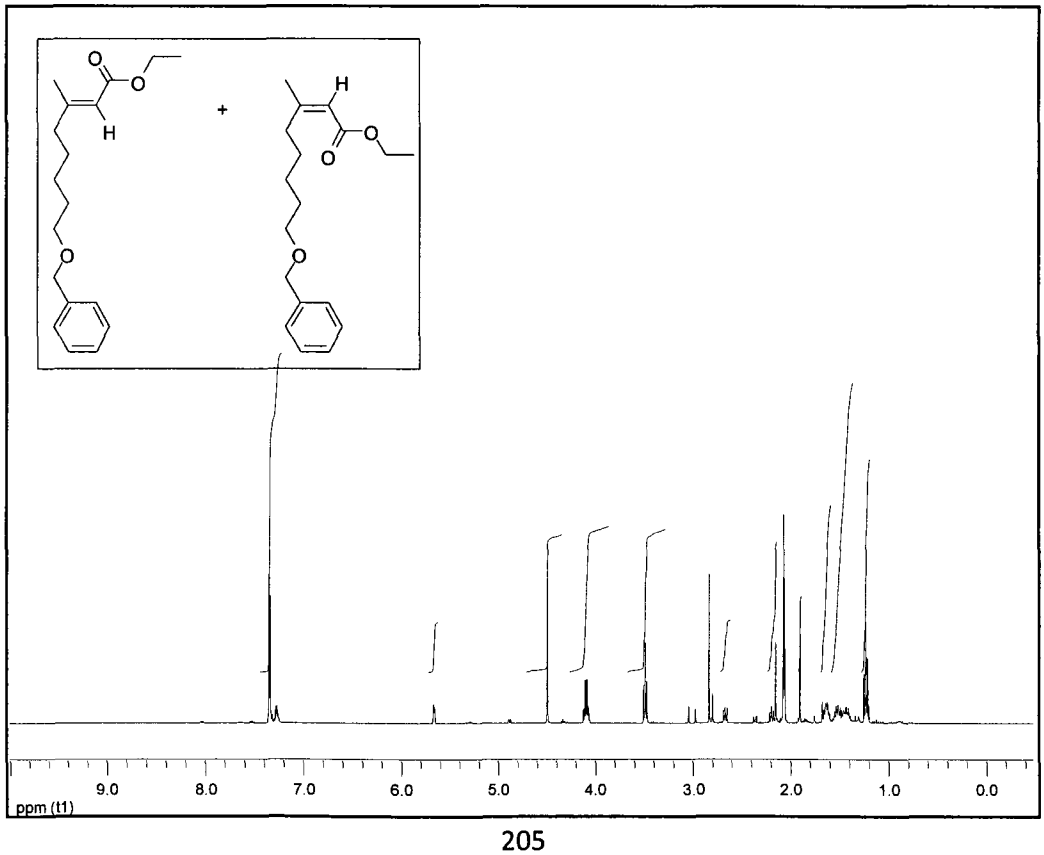

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

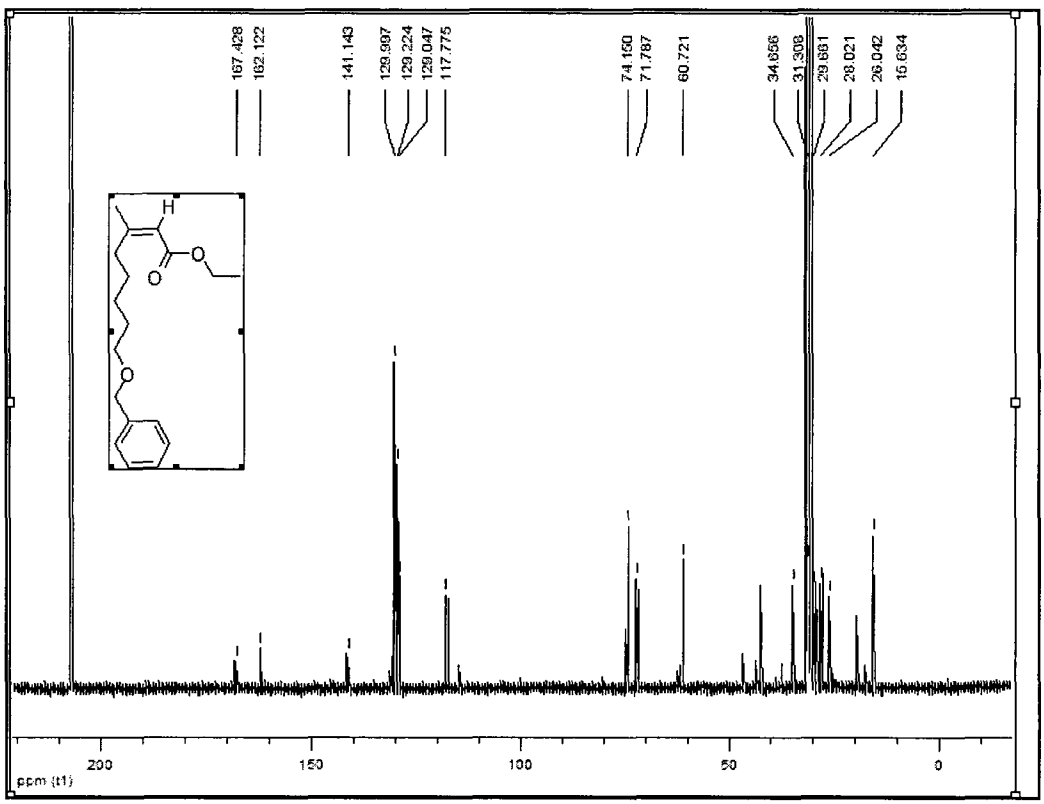

172.488
167.060
141.970
136.522
134.770
132.997
132.457
131.110
130.297
129.881
128.606
127.819
66.262
61.692
46.061
30.181
29.956
27.879
15.422
200
150
100
50
0
ppm (t1)

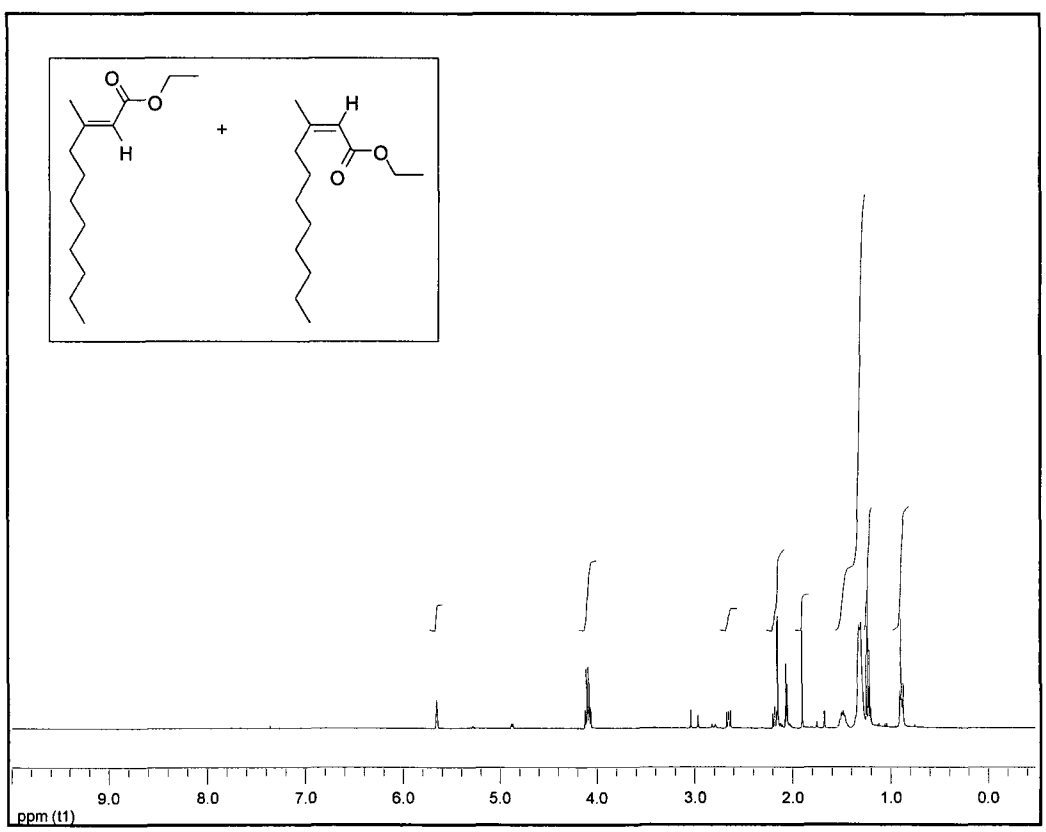

TIPSO
TIPSO
O
O
H
+
H
O
O
O
O
O
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

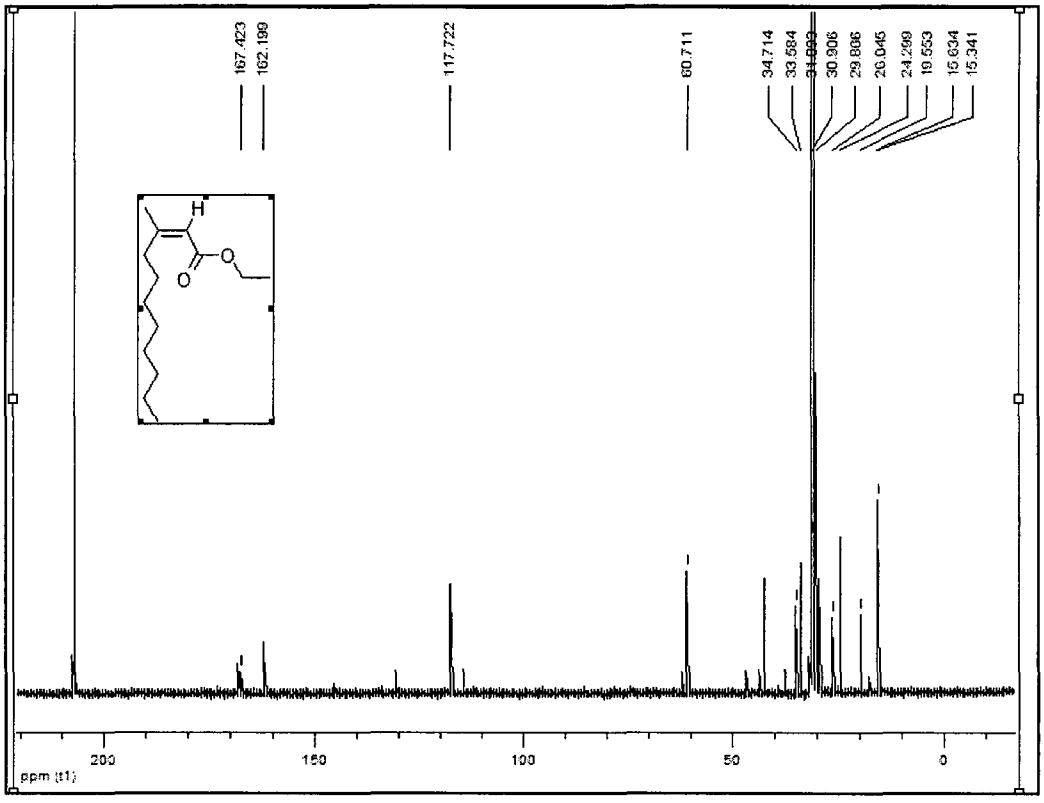

O
O
H
+
H
O
O
O
O
O
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

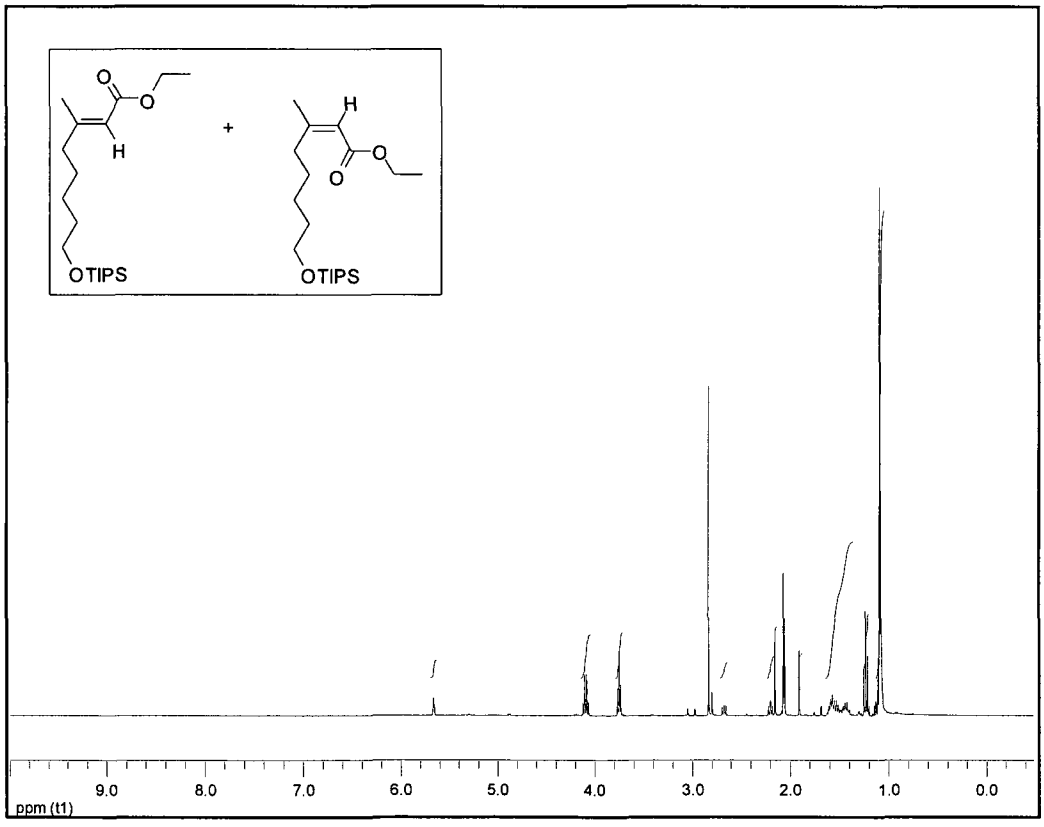

167.834
166.878
166.636
136.394
132.840
129.539
128.296
114.809
64.831
50.778
38.342
32.051
31.943
28.541
28.256
27.316
26.300
22.507
13.972
200
150
100
50
0
ppm (t1)

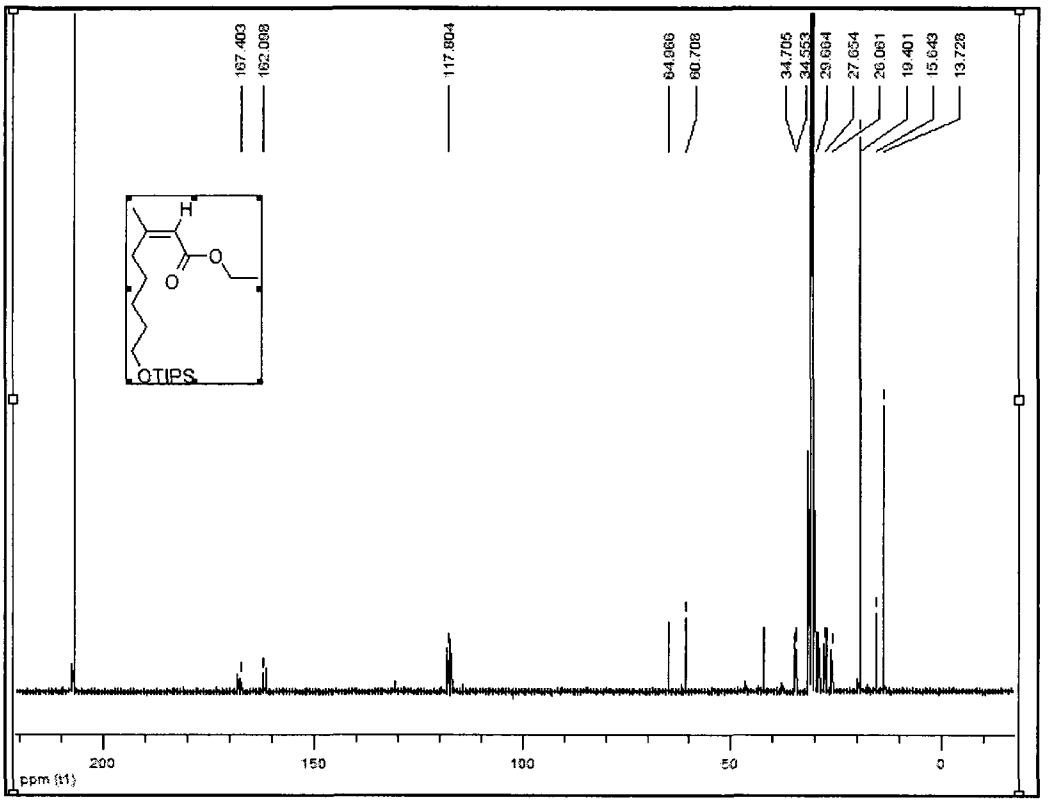

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

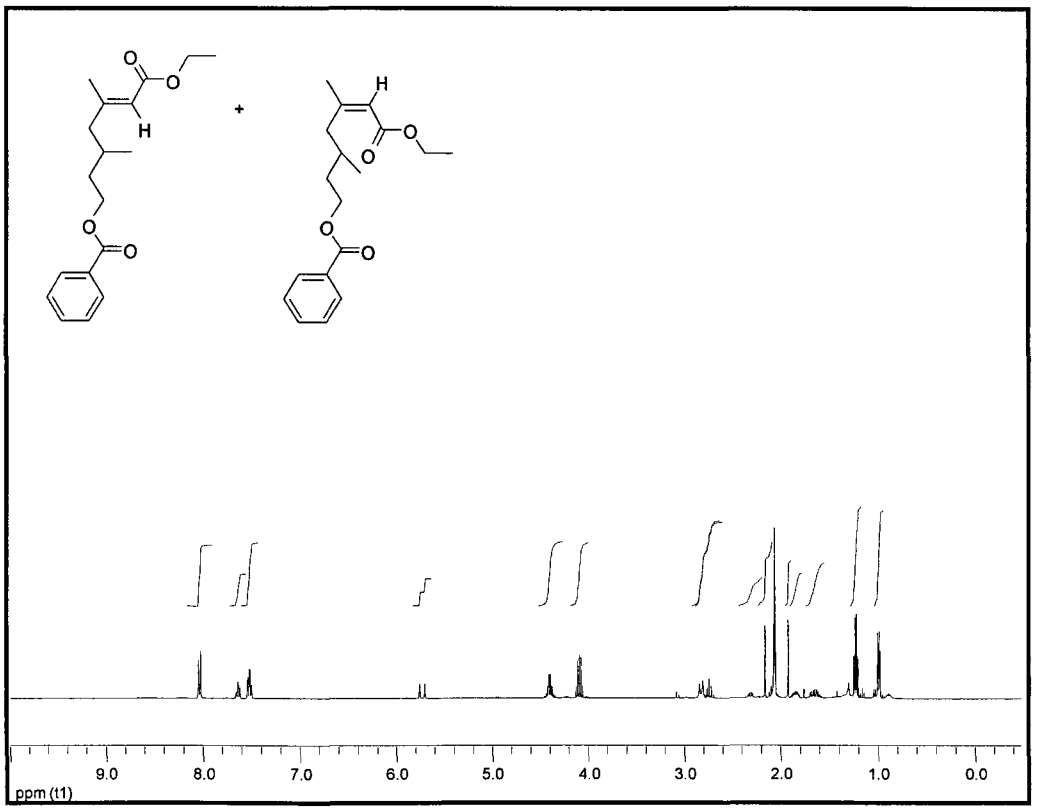

167.428
162.122
141.143
129.997
129.224
129.047
117.775
74.150
71.787
60.721
34.856
31.308
29.681
28.021
26.042
16.634
200
150
100
50
0
ppm (t1)

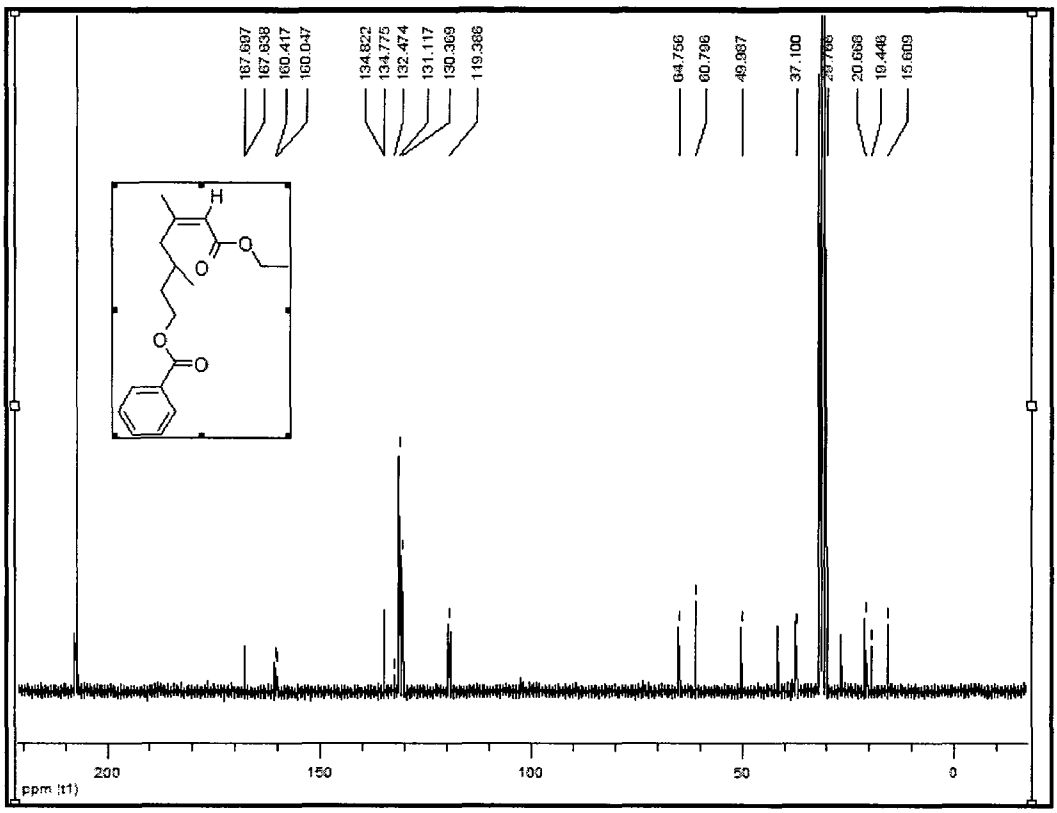

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


167.423
162.199
117.722
60.711
34.714
33.584
31.883
30.906
29.896
26.045
24.299
19.553
15.634
15.341
200
150
100
50
0
ppm (t1)


OTIPS
OTIPS
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


167.403
162.098
117.804
64.966
60.708
34.705
34.553
29.664
27.654
26.061
19.401
15.643
13.728
OTIPS
200
150
100
50
0
ppm (t1)


9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


167.697
167.638
160.417
160.047
134.822
134.775
132.474
131.117
130.369
119.386
64.756
60.796
49.987
37.100
29.766
20.666
19.446
15.609
H
O
O
O
O
200
150
100
50
0
ppm (t1)