The Hong Kong Polytechnic University

Department of Applied Biology and Chemical Technology

Metal Catalyzed Asymmetric [2+2+1] Cycloaddition Reactions

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A thesis submitted

in partial fulfillment of the requirements

for the degree of Master of Philosophy

(JULY 2008)

Certificate of originality

I hereby declare that this thesis is my own research work carried out since my registration at the Hong Kong Polytechnic University for the degree of Master of Philosophy in September, 2006, and that, to the best of my knowledge and belief, it reproduces no material previously published or neither written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

LEE HANG WAI

July, 2008

Abstract

"Metal Catalyzed Asymmetric [2+2+1] Cycloaddition Reactions"

Submitted by LEE HANG WAI

For the degree of Master of Philosophy

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Pauson-Khand-type reaction is a [2+2+1] carbonylative cycloaddition which was firstly reported in 1971. This is one of the most powerful synthetic tools to produce cyclopentenones which are known to be versatile building blocks for natural products, pharmaceuticals and fine chemicals.

Rhodium complex with chiral atropisomeric dipyidyl-diphosphine ligand, (*S*)-P-Phos was found to catalyze asymmetric Pauson-Khand-type reaction in aqueous medium to afford corresponding cyclopentenones in good yield and enantiomeric excess (up to 95% *ee*). Interestingly, a study on electronic effect of the enynes substrates revealed a correlation between the electronic property of the substrates and the *ee* of the cycloadducts in this reaction. A linear free energy relationship was observed from Hammett study.

Besides (*S*)-P-Phos, (*S*)-BisbenzodioxanPhos was also found to be highly effective in the coorperative processes of decarbonylation of aldehyde and subsequent enantioselective Pauson-Khand-type reaction in alcoholic medium. Good yield and enantiomeric excess (up to 96% *ee*) of the products were obtained under these reaction conditions.

Apart from rhodium metal precursor, iridium complex with (*S*)-BINAP was also effective in cascade decarbonylation of aldehyde and asymmetric

Pauson-Khand-type reaction. Although their reactivity was inferior to rhodium catalyzed asymmetric Pauson-Khand-type reaction, they afforded the corresponding cyclopentenones with excellent enantiomeric excess (up to 98% *ee*), which is the highest *ee* achieved so far for this reaction.

In addition to aldehyde as the CO source, we firstly found that formate esters were applicable as CO surrogate in Rh-catalyzed asymmetric Pauson-Khand-type reaction. Up to 94% *ee* cycloadducts were obtained.

Microwave assisted organic syntheses have received increasing attentions in recent decades. In order to shorten the reaction time of our carbonylative cycloaddition, we applied microwave heating to our catalysis. To our delights, the asymmetric Pauson-Khand-type reaction proceeded smoothly within an hour to generate good yield of the products.

Publications

1. Kwong, F. Y.*; Lee, H. W.; Qiu, L.; Lam, W. H.; Li, Y.M.; Kwong, H. L.; Chan, A. S. C.* *Adv. Synth. Catal.* **2005**, *347*, 1750-1754
2. Kwong, F. Y.*; Li, Y. M.; Lam, W. H.; Qiu, L.; Lee, H. W.; Yeung, C. H.; Chan, K. S.; Chan, A. S. C.* *Chem. Eur. J.* **2005**, *11*, 1-10
3. Kwong, F. Y.*; Lee, H. W.; Lam, W. H.; Qiu, L.; Chan, A. S. C.* *Tetrahedron Asymmetry* **2006**, *17*, 1238-1252
4. Lee, H. W.; Chan, A. S. C.*; Kwong, F. Y.* *Chem. Commun.* **2007**, 2633-2635
5. Lee, H. W.; Lee, L. N.; Chan, A. S. C.*; Kwong, F. Y.* *Eur. J. Org. Chem.* **2008,** 3403-3406
6. Lee, H. W.; Kwong, F. Y.*; Chan, A. S. C.* *Synlett.* **2008**, 1553-1556

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Abbreviation

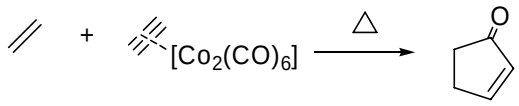
Ac	acetyl
Ad	adamantyl
Ar	aryl
BINAP	2, 2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-bi-2-naphthol (or 2,2′-dihydroxy-1,1′-binaphthyl)
Bn	benzyl
BSA	*N,O*-bis(trimethylsilyl)acetamide
Bu or *n*Bu	(primary) butyl
Bz	benzoyl
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
de	diastereomeric excess
DCE	1,2-dichloroethane
DCM	dichloromethane
Dppe	1,1’-bis-(diphenylphosphino)ethane
Dppp	1,1’-bis-(diphenylphosphino)propane
Dppb	1,1’-bis-(diphenylphosphino)butane
Dppf	1,1’-bis-(diphenylphosphino)ferrocene
DMF	dimethyl formamide
E^+	electrophile
Ee	enantiomeric excess
eq.	equivalent
Fur	furyl
GC	gas chromatography
h	hour
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
*i*Bu	isobutyl
ibuprofen	2-(4-isobutyl-phenyl)-propionic acid
*i*Pr	isopropyl
J	coupling constant (in Hertz)
L^*	chiral ligands
LDA	lithium diisopropylamide
L-DOPA	3,4-dihydroxy-L-phenylalanine
$[M]^+$	transition-metal pre-catalyst
Me	methyl
min	minute
MS	mass spectrometry
Ms	mesyl, methanesulfonyl
m/z	mass-to-charge ratio (in mass spectrometry)
Naph	naphthyl

NBD	norbornadiene
NMR	nuclear magnetic resonance
Nu-	nucleophile
Ph	phenyl
PKR	Pasuon-Khand (-type) reaction
P-Phos	2,2′,6,6′-tetramethoxy-4,4′-bis(diphenylphosphino)-3,3′-bipyridine
Pr	propyl
PS-DES	polystyrene-diethylsilyl
PS-Et	polystyrene-ethyl
PTC	phase transfer catalyst
py	pyridine
RT	room temperature
*s*Bu	secondary butyl
*t*Bu	tertiary butyl
THF	tetrahydrofuran
Tol	toluene
Ts	tosyl, toluenesulfonyl
Xyl	xylene
$[\alpha]_{D20}$	special optical rotation
σ_p	Hammett substituent constant
E_{TN}	normalized $E_T(30)$ solvent polarity

CHAPTER 1

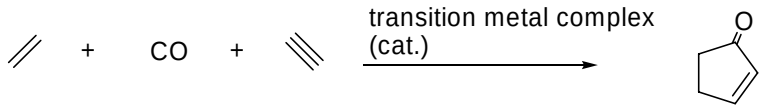
Introduction

Pauson and co-workers first prepared cyclopentenones by heating acetylene dicobalthexacarbonyl with ethylene [1] during their studies of cobalt-alkyne complexes in 1971 and hence the cobalt-mediated [2+2+1] cyclization of an alkyne, an alkene and carbon monoxide to cyclopentenone, are commonly called as Pauson-Khand reaction (PKR). (Scheme1)



(Scheme 1: Stoichiometric Pauson-Khand-type reaction)

At the very beginning, it is undesirable to process this cyclization in terms of cost and waste as stoichometric amounts of toxic and expensive transition-metal species was needed. In 1973, Pauson and co-workers reported the first example of catalytic cycloaddition with octacarbonyldicaobalt(0).[2] (Scheme 2)



(Scheme 2: Catalytic Pauson-Khand-type reaction)

Afterwards it was found that several other transition metal complexes such as Fe[3], Ru[4], Rh[5], Ir[6], Ni[7], Pd[8], Cr[9], Mo[10], W, Ti[11], Zr[12] and dual transition metals system[13] can catalyze this carbonylative cyclization.

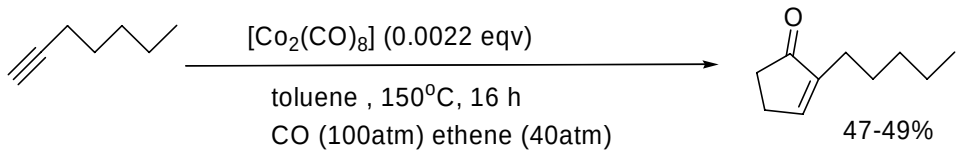
In the early study of an intermolecular reaction, symmetrical and active alkenes

such as norbornene and ethene were used. It was because four regioisomers would be obtained when an unsymmetrical alkyne and alkene were used and afterwards the intramolecular reaction was found to avoid the formation of regioisomers and to produce bicyclic cyclopentenone selectivity.[14]

1.1. Improvements to the PKR conditions

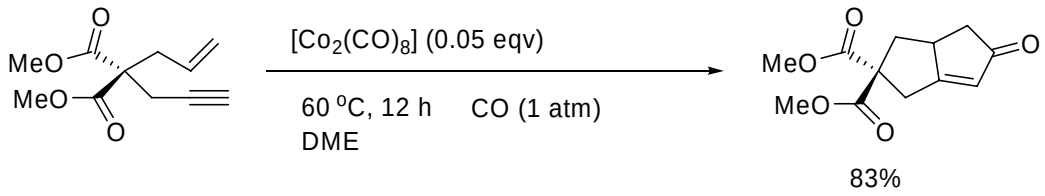
1.1.1. Lowering the amount of carbon monoxide

Following the work of Pauson and co-workers, Rautenstrauch *et al.* reported in 1990 that a high turnover number (TONs) was obtained by using nonconstrained alkenes, 0.0022 equivalents of $[Co_2(CO)_8]$ under very high practical pressures of carbon monoxide (100 atm) and ethane (40 atm).[15]



(Scheme 3: Pauson-Khand-type reaction under high pressure of carbon monoxide and ethene by Rautenstrauch *et al.*)

In 1996, with photoactivation of $[Co_2(CO)_8]$, Livinghouse and Pagenkopf first lowered the amount of carbon monoxide used to only 1 atm in PKR. Afterward they optimized the reaction conditions to lower the partial pressure of carbon monoxide to 1 atm by careful control of reaction temperature within a narrow range.[16]



(Scheme 4: Photoactivated Pauson-Khand-type reaction by Livinghouse *et al*.)

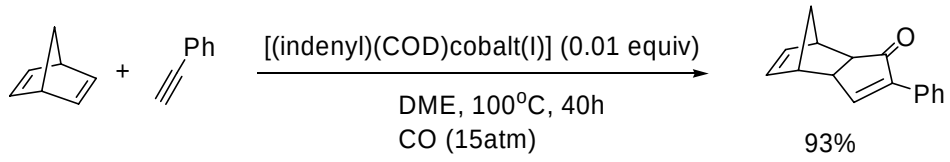
Through results of the thermal and photochemical PKR, Livinghouse and co-workers pointed out that the high purity of $[Co_2(CO)_8]$ is needed to ensure reproducible results and some additives can be introduced to stabilize the reaction intermediates in the PKR.

1.1.2. Employing additives to promote PKR

A wide range of compounds such as tertiary amine *N*-oxides, phosphines, phosphine oxides, dimethylsulfoxide (DMSO), hard Lewis bases have been employed as promoters or additives to improve the chemical yields of PKR. However tertiary amine *N*-oxides or DMSO were found ineffective to desired products in catalytic PKR[17] and it has been suggested that Co(0) species cannot be regenerated through out the reaction. Formation of cobalt clusters $[Co_4(CO)_{12}]$ is another impediment for the catalytic PKR as it was believed to be inert towards alkyne substrates.[18] Hence Pauson, Billington and co-workers introduced phosphines and phonsphine oxides as coligands to overcome the formation of inactive clusters in stoichiometric variants of PKR.[19]

1.1.3. Generating active cobalt(0) species in situ

As $[Co_2(CO)_8]$ is active towards PKR but easily decomposed, it is feasible to generate the active catalyst $[Co_2(CO)_8]$ *in situ* from Co(I), Co(II) precursors in the reaction to prevent decomposition, Chung *et al.* reported using [(indenyl)(COD)cobalt(I)] and carbon monoxide *in situ* to generate Co(0) catalyst. And it can perform both inter and intramolecular cyclizations between constrained alkenes and terminal alkynes to provide desired products in good yields.[20] However these reaction conditions required high pressure of carbon monoxide and were limited to the constrained alkenes.



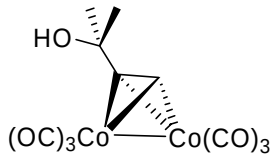
(Scheme 5: Intramolecular Pauson-Khand-type reaction between constrained alkenes and terminal alkynes by Chung *et al.*)

Later Lee and Chung reported using $[Co(acac)_2]$ and $NaBH_4$ to perform both inter and intramolecular PKR under high pressures of carbon monoxide. Although high pressure of carbon monoxide was required and the strong reducing agent may limit the range of compatible functional groups, it gave high TONs.[21] Afterward Rajesh and Periasamy reported the use of $CoBr_2$ and Zn *in situ* to generate active cobalt catalyst under 1 atm of carbon monoxide.[22] However limited scopes of substrates were converted and the turnover numbers

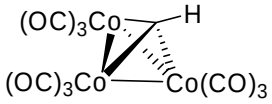
were still low.

1.1.4. Searching for the others active cobalt catalysts

As reported by several research groups, the $[Co_2(CO)_8]$ is hard to handle, it is highly toxic and ignites spontaneously upon contact with air. Hence it is urged to find out other active cobalt catalysts for PKR. Billington *et al.* attempted to catalyze PKR by ethyne-$[Co_2(CO)_6]$ complex under ethyne/CO atmosphere. However very low TONs and limited scope of substrates were resulted.[23] Livinghouse and Belenger employed another cobalt complex (**1**, scheme 6) for the simpler intramolecular substrates but it was not so active towards enynes and Et_3SiH was required to get good conversions.[24] Sugihara and Yamaguchi reported that air stable the alkylidyne nonacarbonyltricobalt clusters, methylidyne nonacarbonyltricobalt cluster (**2**, scheme 6) can catalyze both inter and intramolecular PKR under 7 atm of carbon monoxide.[25]



1



2

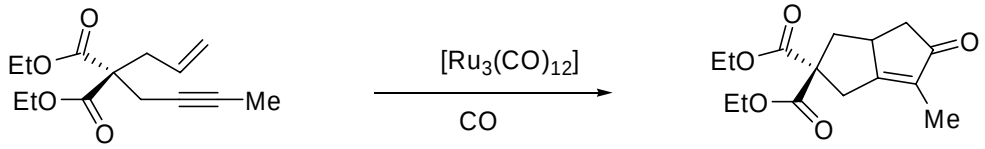
(Scheme 6)

The cobalt cluster $[Co_4(CO)_{12}]$ has been believed to be catalytically inactive towards PKR however Chung and Kim reported that it may establish equilibrium to form catalytic active cobalt cluster $[Co_2(CO)_8]$ under high pressure of carbon

monoxide. Indeed they utilized $[Co_4(CO)_{12}]$ successfully for both inter and intramolecular PKR.[26]

As mentioned before, PKR can be catalyzed by various kinds of transition metal, In 1997 Mitsudo[4(a)] and Murai[4(b)] independently reported the use of $[Ru_3(CO)_{12}]$ with different catalyst loading and solvent for cyclization. Murai showed that enyne with terminal alkyne group was poor for cycloaddition while no examples of enynes with terminal alkyne groups were included in Mitsudo's publication.

Table1: $[Ru_3(CO)_{12}]$-catalyzed Pauson-Khand-type reaction, Murai *et al.* and Mitsudo *et al.*)



Entry	$[Ru_3(CO)_{12}]$ [mol%]	T [°C]	t [h]	p (CO) [atm]	% yield
1[a]	2	160	20	10	86
2[b]	2	140	8	15	78

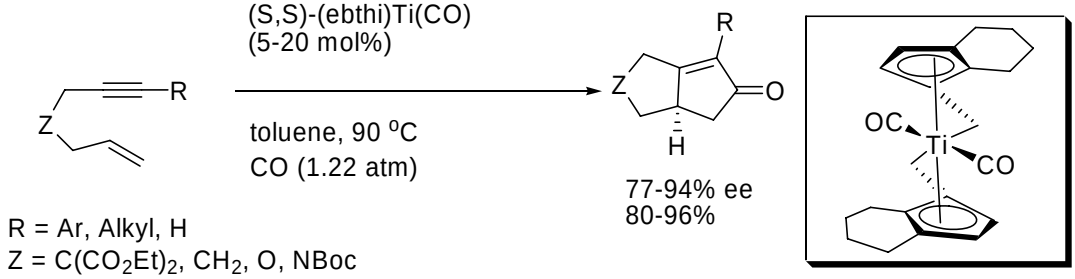
[a] In dioxane[4(b)], [b] In N,N-dimethylacetamide[4(a)]

Buchwald and co-workers demonstrated titanocene-mediated cyclization of enynes, in the presence of n-BuLi and triethylsiyl cyanides, commercially available and air stable $[Cp_2TiCl_2]$[11(d)] could be used in PKR. However the overall yields were still poor. Afterwards remarkable improvements were achieved by using $[Cp_2Ti(CO)_2]$[11(e)(f)] as catalyst for the cyclocarbonylation. It can catalyze cyclization of enynes under low pressures of carbon monoxide (1.22 atm).

1.2. Asymmetric Pauson-Khand-type Reactions

1.2.1. Titanium-catalyzed asymmetric Pauson-Khand-type Reactions

Starting from the works of Pauson and co-workers, PKR was studied intensively in recent decades however study of asymmetric PKR is rare. It is because most cases of PKR were generally carried under very harsh conditions such as high temperature and high pressure of carbon monoxide. The first asymmetric PKR had to wait until 1996, as chiral ligand would dissociate easily under high carbon monoxide pressure, Buchwald *et al.* reported using a chiral Ti complex that the metal center and chiral moiety were bonded in the σ-bond mode. This complex cyclized a range of enynes with high TONs under low pressure of carbon monoxide (Scheme 7). Furthermore it was also the first example of catalytic asymmetric PKR.

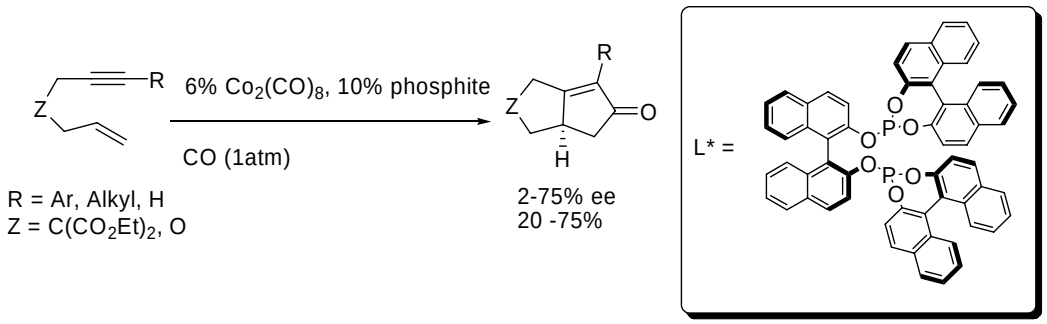


(Scheme 7: Titanium-catalyzed asymmetric Pauson-Khand-type reaction by Buchwald *et al.*)

1.2.2. Cobalt-catalyzed asymmetric Pauson-Khand-type Reactions

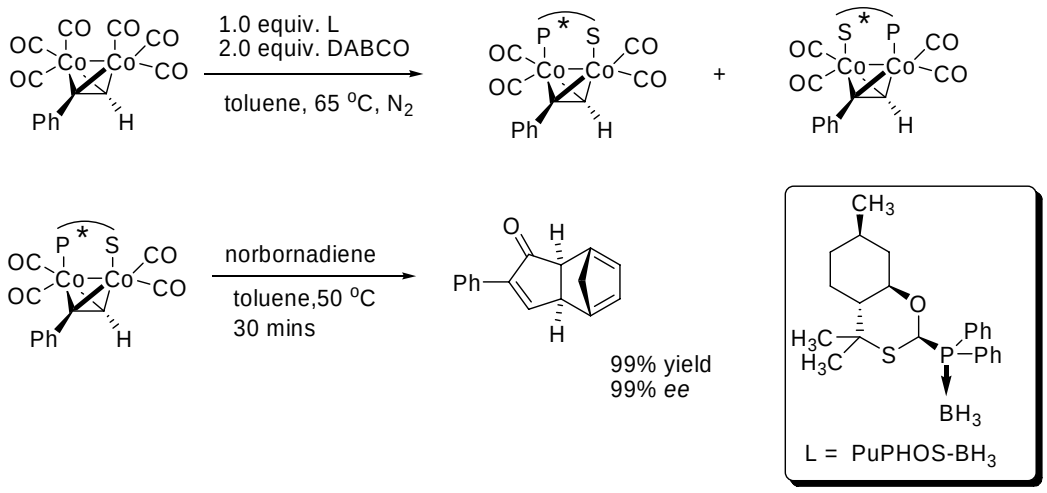
The first example of asymmetric cobalt-catalyzed PKR was reported by Hiroi

and co-workers.[27] They employed chiral biaryl phoshine ligand, (*S*)-BINAP to induce the high enantioselectivity. However high catalyst loading was needed and TONs were low. Later Buchwald and Sturla employed chiral biaryl phosphite on the cobalt-catalyzed PKR[28] (Scheme 8). The reaction conditions were optimized with respect to solvent, temperature and only 1 atm of carbon monoxide was needed to provide desired products in good *ee* values (75%).



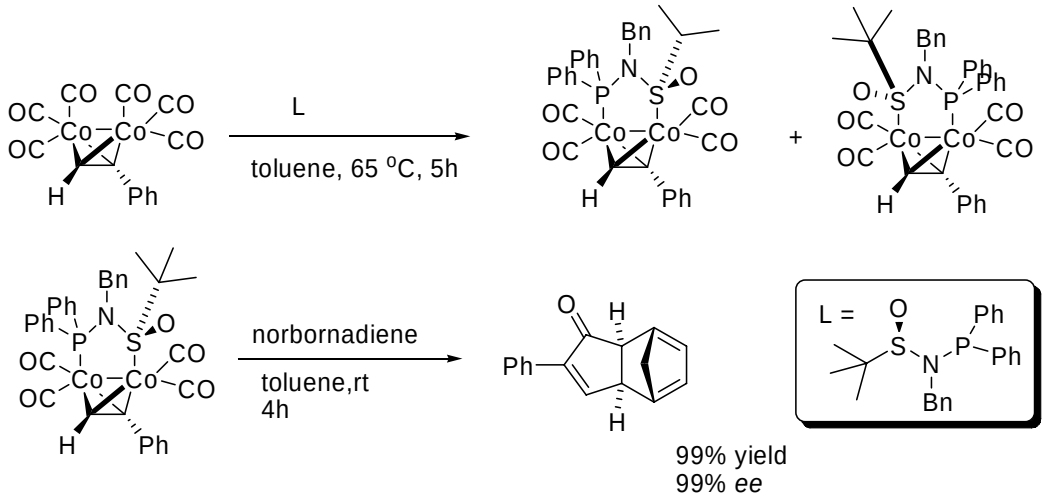
(Scheme 8: Cobalt-catalyzed asymmetric Pauson-Khand-type reaction by Buchwald *et al.*)

Not only chiral diphosphine and diphosphite ligand showed their effectiveness in PKR. In 2000, Verdaguer *et al.* reported that chiral bidentate (P, S) ligand[29] can catalyze asymmetric intermolecular PKR to provide cyclopentenones in excellent yields and *ee* values (up to 99% yield, 99 % *ee*)[29(a)] (scheme 9).



(Scheme 9: Asymmetric Pauson-Khand-type reaction of Co-PuPHOS complexes with norbornadiene by Verdaguer *et al.*)

Later the same group presented Co-PNSO complex catalyzed highly enantioselective asymmetric intermolecular PKR[30](scheme 10).



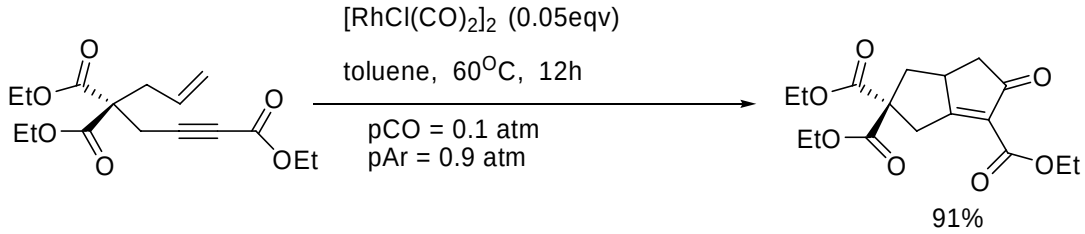
(Scheme 10: Asymmetric Pauson-Khand-type reaction of Co-PNSO complexes with norbornadiene by Verdaguer *et al.)*

However use of (P, S) ligand in asymmetric intramolecular PKR is sporadically studied.

1.2.3. Rhodium-catalyzed asymmetric Pauson-Khand-type reactions

1.2.3.1. Rhodium-catalyzed Pauson-Khand-type reaction under CO atmosphere

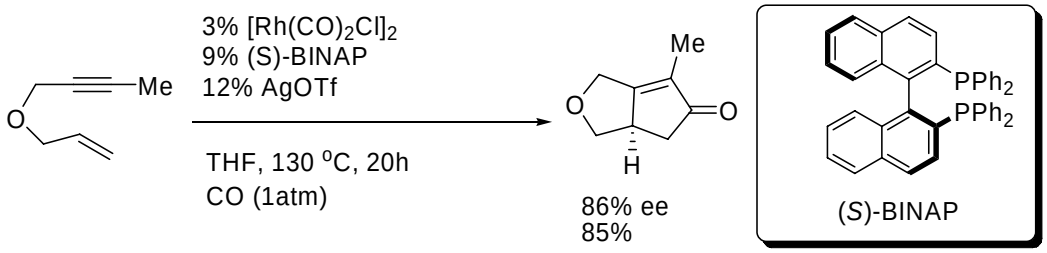
Following on the good results in cobalt-catalyzed PKR, several research groups moved their steps on rhodium-catalyzed PKR. In recent years, rhodium-catalyzed PKR have drawn much attention. Narasaka and co-workers employed 0.05 equivalents of $[RhCl(CO)_2]_2$ to catalyze the reaction under 1 atm of carbon monoxide.[5(a)] The performance of the catalyst was optimized later by replacing xylene with toluene and the partial pressure of carbon monoxide was decreased to 0.1 atm.[5(d)] This system was excellent for substrates containing electron deficient alkenes and alkynes. (Scheme 11)



(Scheme 11: Rhdoium-catalyzed Pauson-Khand-type reaction by Narasaka *et al.*)

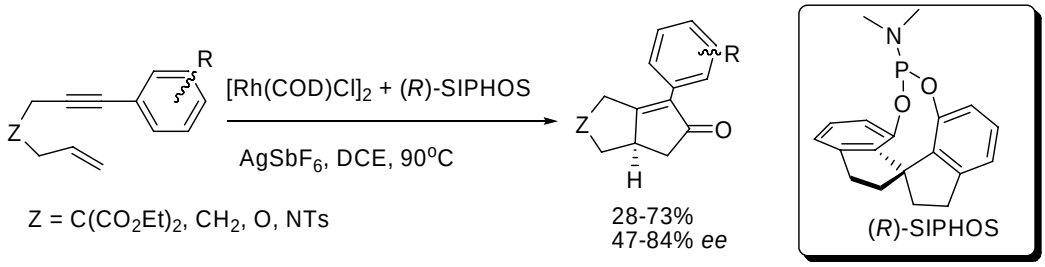
In 2000, Jeong reported a cationic Rh-catalyzed enantioselective PKR,[31] with the catalyst prepared *in situ* from $[RhCl(CO)_2]_2$ and BINAP by the addition of AgOTf (Scheme 12). They found out that PKR proceeded efficiently in toluene than in a coordinating solvent such as THF, however high enantioselective products can be only obtained in THF. Furthermore a silver salt such as AgOTf

was required for the initiation of the reaction in THF. Balancing of CO pressure was critical for the high enantioselectivity and high product yield. High CO pressure led to high product yield however better enantioselectivity was obtained under lower CO pressure environment.



(Scheme 12: Cationic rhodium-catalyzed asymmetric Pauon-khand-type reaction by Jeong *et al*.)

It is believed that chiral bidentate diphosphine ligand is necessary to achieve good enantioselectivities in asymmetric PKR however Zhou *et al.* employed Rh-SIPHOS complex to catalyze asymmetric PKR under 1 atm of carbon monoxide to obtain corresponding cyclopentenones in good *ee* values (Scheme 13).[32]

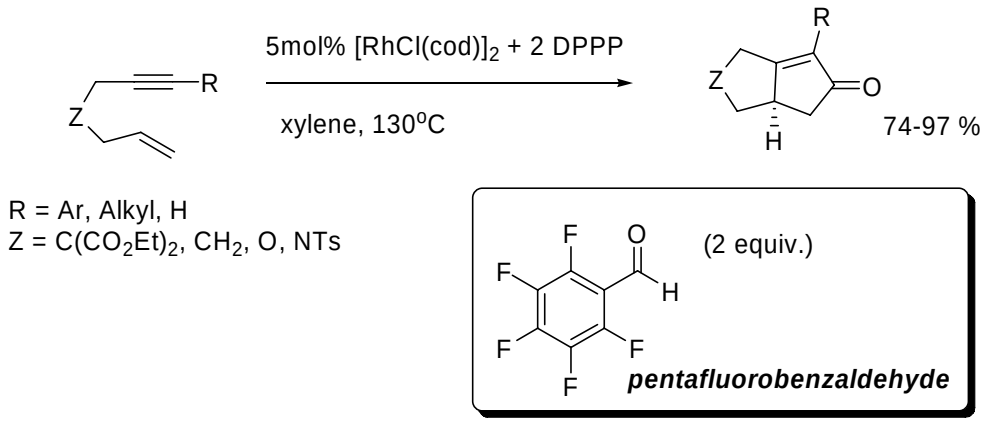


(Scheme 13: Rhodium-catalyzed enantioselective Pauson-khand-type reaction using (R)-SIPHOS by Zhou *et al.*)

1.2.3.2. <u>Rhodium-catalyzed Pauson-Khand-type reaction using aldehyde as CO source</u>

Carbon monoxide is a colourless, odorless but highly toxic gas. Therefore it is

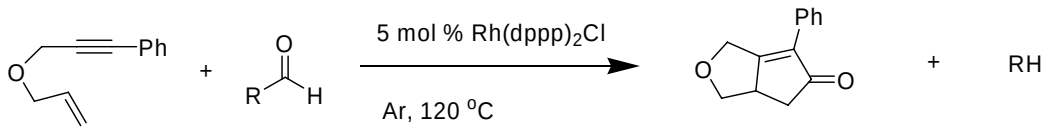
necessary to search for CO surrogate. Morimoto first utilized pentafluorobenzaldehye as a CO source (Scheme 14).[33]



(Scheme 14: Pasuon-Khand-type reaction using aldehyde as CO source by Morimoto *et al.*)

In the same period, Shibata also reported that the use of cinnamylaldehyde as a CO source.[34]

Table 2: Screening of aldehydes



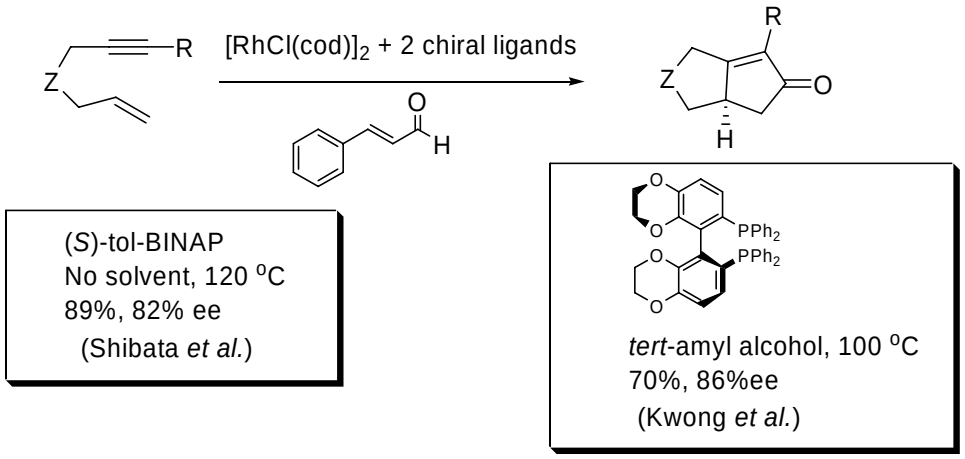
Entry	aldehyde (equiv.)	time / h	yield/ %
1	cinnamylaldehyde (20)	2	98
2	cinnamylaldehyde (5)	3	93
3	cinnamylaldehyde (1.2)	3	83
4 [b]	cinnamylaldehyde (1.2)	3	80
5 [c]	cinnamylaldehyde (20)	24	54
6	benzaldehyde (20)	3	87
7	benzaldehyde (1.2)	4	12
8	2-hexanal (20)	2	68
9	hexanal (20)	2	30

[a] Reaction was employed in a 0.3 mmol scale, and enone **2** was purified using preparatie TLC, except entry **4**.

[b] Reaction was employed in a 2.1 mmol scale, and enone **2** was purified by bulb-to-bulb distillation.

[c] Reaction was employed at 60 °C

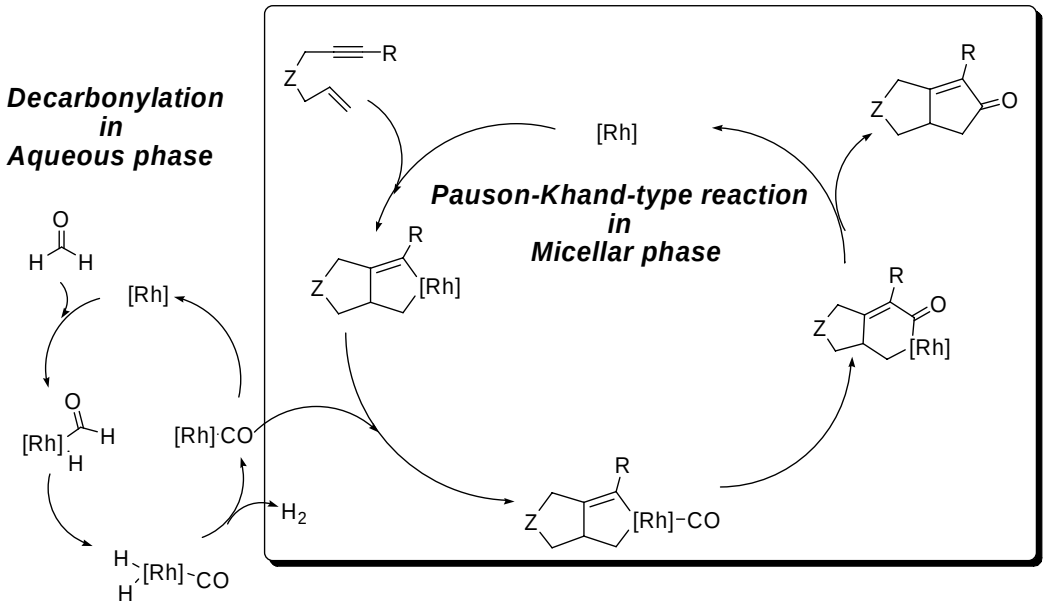
This catalytic system can be also applied for the enantioselective reaction using Rh-tol-BINAP under solevntless environment[35] and at the nearly same period of time Kwong *et al.* also demonstrated that Rh-BisbenzodioxanPhos complex can catalyze PKR in homogenous *tert*-amyl alcohol under milder reaction conditions (Scheme 15).[36]



(Scheme 15: Asymmetric Pauson-Khand-type reaction using cinnamyladehyde as CO sourrogate)

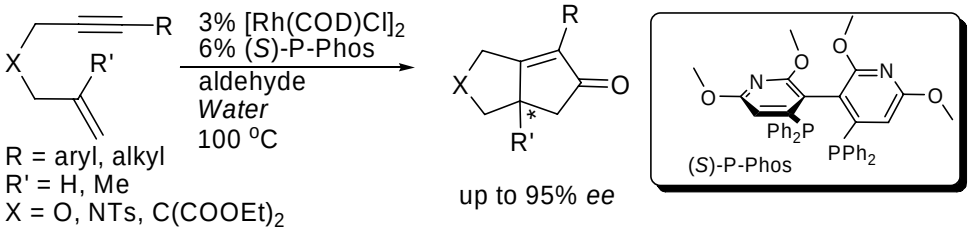
Although aldehydes were capable to be a CO source for PKR, side products from decarbonylation such as pentafluorobenze and styrene would be wasted. To minimize the side products, Morimoto and co-workers tried to employ formaldehyde as CO surrogate under aqueous conditions (Scheme 16).[37] With the combined use of hydrophobic DPPP [1,3-bis(diphenyl-phosphino)propane], hydrophilic TPPTS (triphenylphospholane-3,3',3''-trisuflonic acid trisodium salt) phosphines and a surfactant SDS (sodium dodecyl sulfate), they pointed out the importance of TPPTS as it is a water soluble phosphine and acts as the ligand instead of DPPP in water for decarbonylation as the CO source, formaldehyde is

highly soluble in water. As decarbonylation and carbonylation took place in different phase, they seldom interfered with each others so led to smooth and efficient reaction. Various 1,6-enynes were converted into corresponding cyclopentenones. With (s)-tol-BINAP instead of DPPP, this catalytic system can be applied to asymmetric PKR.



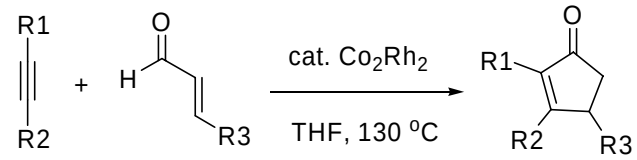
(Scheme 16: Proposed mechanism for Pauson-Khand-type reaction using formaldehyde as CO surrogate by Morimoto et al.)

Kwong *et al.* reported the asymmetric PKR in water by using (*S*)-P-Phos under mild conditions. They also first demonstrated the Hammett Plot relationship between the product *ee* values and the electronic properties of substrates (Scheme 17).[38]



(Scheme 17: Rhodium-catalyzed aqueous asymmetric Pauson-Khand-type reaction by Kwong *et al.*)

The most atom-economical reaction is that when the carbonyl and akene moiety on aldehyde reacted directly with an alkyne. Chung reported that the use of Co/Rh heterobimetallic nanoparticles derived from $Co_2Rh_2(CO)_{12}$ to catalyze reaction of an α,β-unsaturated aldehydes with alkynes to give desired cyclopentenones (Scheme 18).[39]



R1, R2 = Ph, Me, H
R3 = Ph, alkyl, TMS

(Scheme 18: Co_2Rh_2 catalyzed cyclization of an *α,β*-unsaturated aldehydes with alkynes by Chung *et al.*)

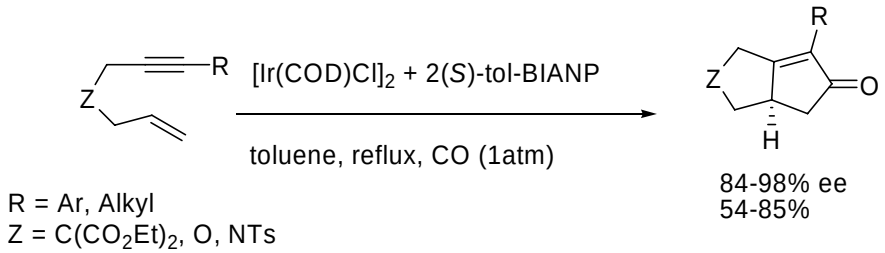
1.2.4. Iridium-catalyzed Pauson-Khand-type reactions

1.2.4.1. Iridium-catalyzed Pauson-Khand-type Reactions under CO atmosphere

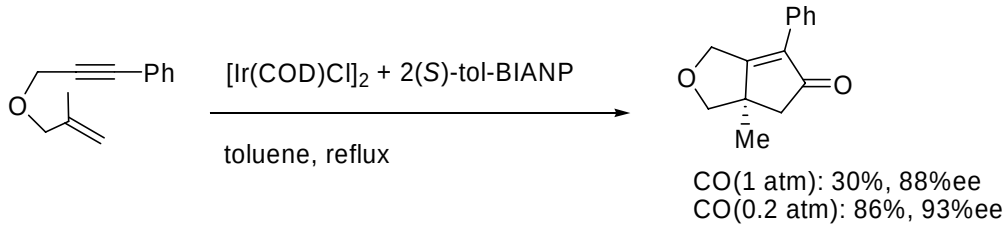
In the view of the interest in cobalt and rhodium-catalyzed PKR, it was natural that attention would be turned to iridium. In 2000 Shibata and Tagaki reported the first iridium-catalyzed asymmetric PKR by Ir-tol-BINAP complex which was prepared *in situ* from commercially available $[Ir(COD)Cl]_2$ and tol-BINAP to obtain desired cycloadducts in excellent *ee* values (Scheme 20).[40] Later Shibata *et al.* reported that higher yields and *ee* values can be obtained under lower partial pressure of carbon monoxide atmosphere (Scheme 21).[6(a)]

1.2.4.2. *Iridium-catalyzed Pauson-Khand-type Reactions under CO atmosphere*

Furthermore they also demonstrated cinnamylaldehyde can act as CO surrogate instead of carbon monoxide for the asymmetric Pauson-Khand-type transformation.

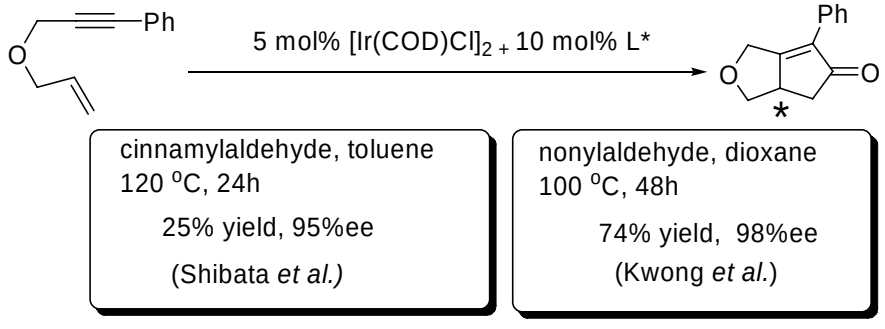


(Scheme 20: Asymmetric Pauson-Khand-type reaction under CO atmosphere by Shibata *et al.*)

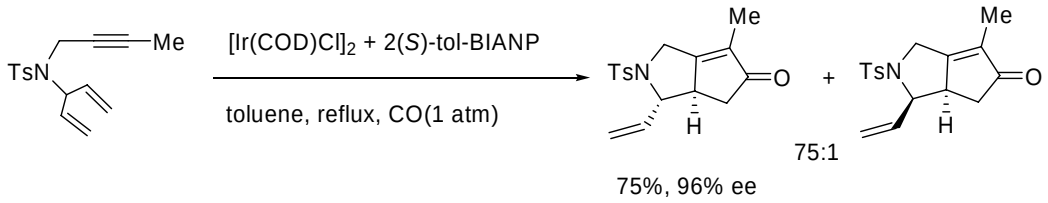


(Scheme 21: Asymmetric Pauson-Khand-type reaction under CO atmosphere by Shibata *et al.*)

Meanwhile Kwong *et al.* also reported that using Ir-BINAP complex to catalyze decarbonylation of aldehyde and asymmetric PKR to obtain cyclopentenones in excellent *ee* values (Scheme 22).[41] Jeong also employed the Ir-tol-BIANP complex in a highly enantio- and diasteroselective PKR to give vinyl-substiutied bicyclic cyclopentenones with two chiral centers (Scheme 23).

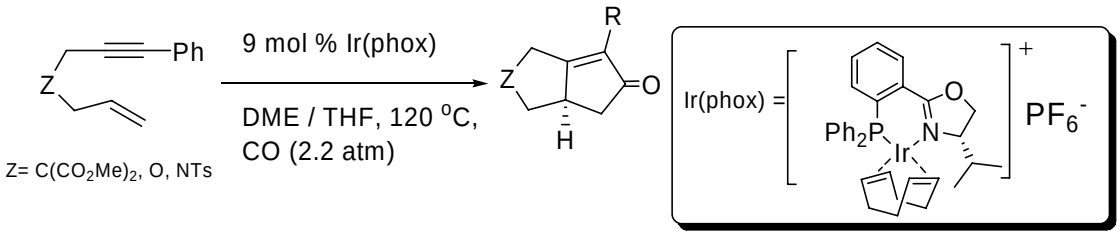


(Scheme 22: Decarbonlyation of aldehyde and cascade asymmetric Pasuon-Khand-type reaction by Kwong *et al*.)



(Scheme 23: Highly enantio- and diasteroselective Pauson-khand-type reaction with Ir-tol-BINAP catalysts by Jeong *et al.*)

Recently Pfaltz and co-workers reported using iridium and chiral phosphine-oxazolines (phox ligands) to catalyze intramolecular asymmetric PKR under carbon monoxide atmosphere. They also demonstrated that the influence of anion on the enantioselectivity and chemical yield. Best results were obtained by using relatively small and weakly coordinating anions such as BF_4, PF_6 and SbF_6 (Scheme 24).[42]

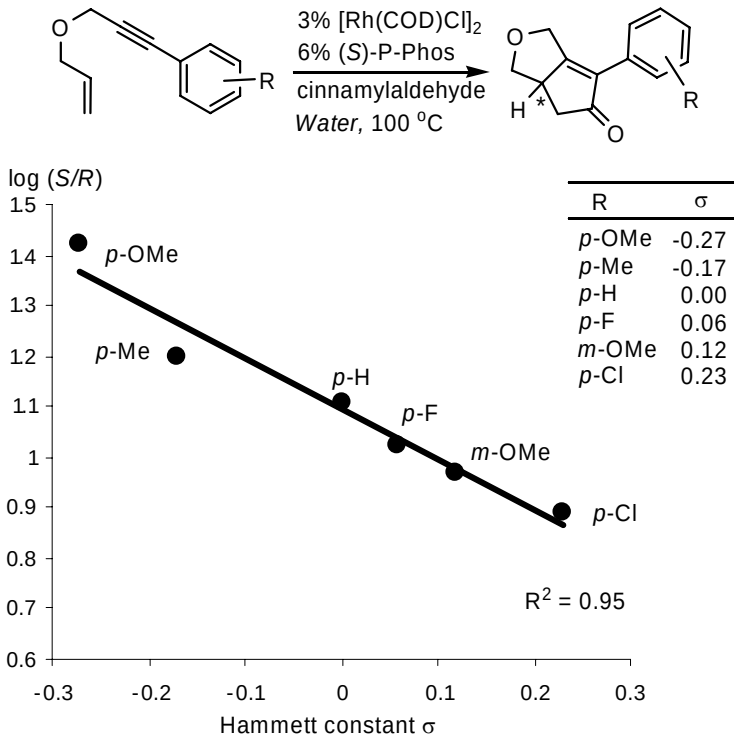


(Scheme 24: Enantioselective Pauson-Khand-type reaction with Ir(phox) catalysts by Pfaltz *et al.*)

1.3. Factors affect stereoselectivity

1.3.1. *Hammett plot relationship between enantioselectivity of PKR products and electronic properties of substrates*

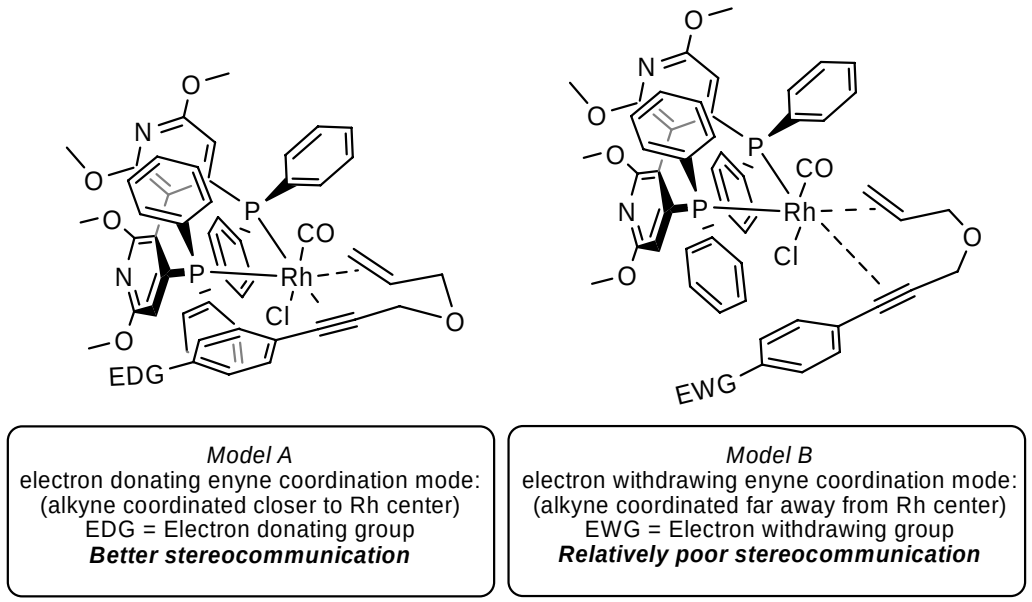
To further study the PKR, Kwong and co-workers performed an electronic effect investigation on the eyne. They showed the electron-donating aromatic enynes provided high enantioselectivity when electron-withdrawing substitiuents produced low enantioselective products. The enantioselectivity of products and electronic properties of substrates can be demonstrated from a Hammett Plot.



(Figure 1: Hammett Plot between enantioselectivity of products and electronic properties of substrates)

It showed that substrates with *para* and *meta* substitutions formed a linear free energy relation while *ortho*-substituted enynes was outside the trend as the steric

factor dominate the electronic factor in this case. The electronic effect can be accounted by stereochemical communication between the enyne and rhodium catalyst (Figure 2).



(Figure 2: Proposed stereochemical communication between enyne and rhodium catalysts)

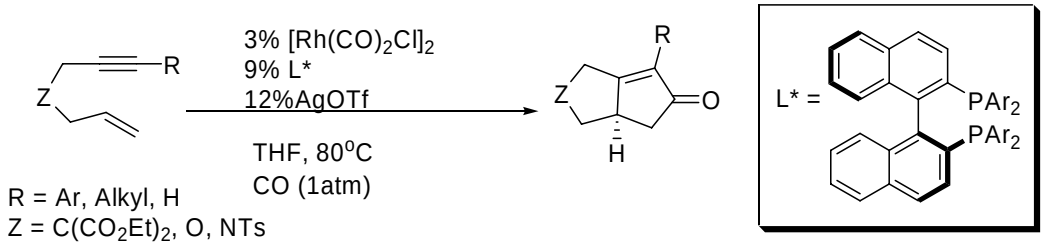
Electron-rich enyne (***A***) may coordinate more closely to the rhodium center through more π interaction, stereochemical communication was then improved and led to high enantioselectivity, vice versa electron-poor enyne (***B***) may coordinate far away from the metal so lower enantioselectivity was obtained.

1.3.2. *Electronic effect of ligands on stereoselectivity and reaction rate of PKR*

Electronic effect of ligands was believed to affect stereoselectivity in PKR. Recently, Genêt *et al.* and Jeong *et al.* reported electronic effect of ligands on stereoselectivity and reaction rate.[43] They reported that an electron-donating

ligand made the metal center more electron rich so that the π-back-bonding from metal to carbon monoxide became stronger and hence more energy was required for decarbonylation. Therefore electron-deficient ligand weakened the π-back-bonding so as to accelerate the decarbonylation. However the oxidative formation of metallacyclopentene, are accelerated by the electron-donating ligand. Hence ligands with different substitiuents on the phosphorus were screened (Table 4).

Table 4: Electronic effect of ligands with different substituents on phenyl group

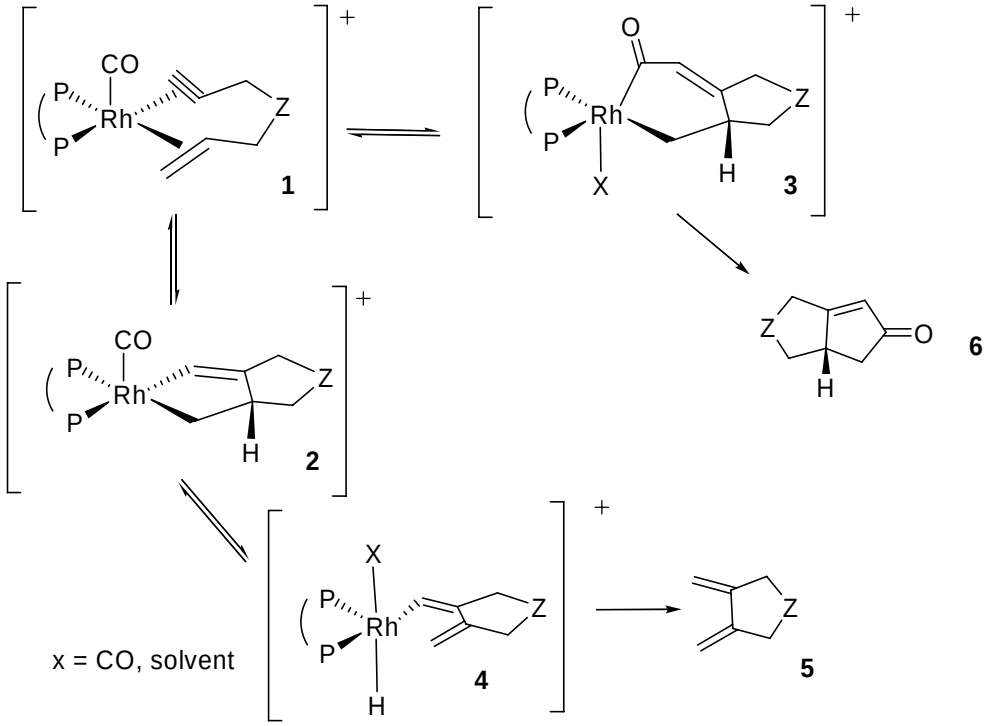


Entry	Ligand / L*	Substituents on phenyl group	^{31}P NMR δ ($CDCl_3$)
1	(S)-**L1**	Ar = 4-$MeOC_6H_4$	-16.9
2	(S)-**L2**	Ar = 4-MeC_6H_4	-15.8
3	(S)-**L3**	Ar = Ph	-14.4
4	(S)-**L4**	Ar = 4-$CF_3C_6H_4$	-13.8
5	(S)-**L5**	Ar = 3-$CF_3C_6H_4$	-13.7
6	(S)-**L6**	Ar=3,5-$Me_2C_6H_3$	-13.6

And they suggested that product yield was improved by using electron-donating ligand **L1** while enantiomeric excess can be improved by using electron-deficient ligand **L6** for the same substrate. Furthermore they also reported that the degree of enantioselectivity improvement was dependent on the substrate.

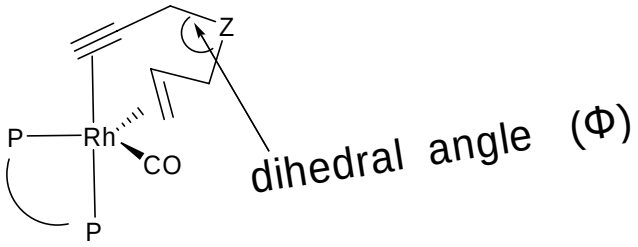
Tosylamino-tethered substrates were relatively insensitive to the electron character of ligand when oxygen-tethered substrates responded significantly. Malonate-tethered substrates did not show any trend as the electron character of ligand changed.

Malonate-tethered substrates were known to give worse yield and enantiomeric excess then tosylamino-tethered and oxygen-tethered substrates. It was believed that *β*-H elimination of metallacyclopentene would give diene side product (Scheme 25, complex **5)**.



(Scheme 25: Proposed mechanisms of Pauson-Khand-type reaction)

And the *β*-H elimination was influenced by the electron density of metal and the dihedral angle of enynes. The smaller dihedral angle of enynes would favour *β*-H elimination (Figure 3).



(Figure 3: Dihedral angle, Φ of enyne)

Malonate-tethered substrates had smaller dihedral angle (Φ) due to Thorpe-Ingold effect by the two ester groups and hence diene side product would be formed easier. Moreover the tighter binding of the electron-rich enynes would also make the dihedral angle (Φ) smaller and lead to lower yield but with improved enantiomeric excess as stereochemical communication increased.[38]

In the view of economic and environmental friendly processes, high priority should be given to the application and development of catalytic PKR to broaden the substrate scopes especially for the intermolecular systems as they are rare studied. Furthermore it is necessary to find out other CO sources in PKR instead of carbon monoxide as it is a highly toxic, odorless gas and difficult to handle in the reaction.

1.4. Summary on catalyst activity and average turnover number

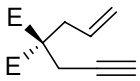
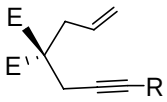
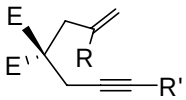
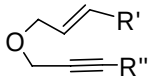
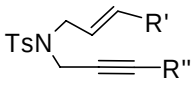
Table 5: Catalyst activity and practicability

Entry	Catalyst system	*p*(CO)[atm]	TON [a]	Cost	Sensitivity grade [b]
1	$[Rh(dppp)_2Cl]$	0	20	__	__
2	$[Rh(COD)Cl]_2$	0	10	High	1
3	$[Rh(CO)_2Cl]_2$	1	82	High	3
4	$[Cp_2Ti(CO)_2]$	1.22	19	High	4
5	$[Co_2(CO)_8]$ + R_3PS	1	16	Low	3
6	$[Co_2(CO)_7PPh_3]$	1.05	11	__	1
7	$[Co_2(CO)_8]$ + hv	1	10	Low	3
8	$[Co_2(CO)_8]$ + $CyNH_2$	1	10	Low	3
9	$[Co_2(CO)_8]$ + DME	7	50	Low	3
10	$[Co_3(CO)_9(\mu^3\text{-}CH)]$	7	17	__	2
11	$[Co_4(CO)_{12}]$	5	7	Medium	2
12	$[Co_4(CO)_{11}P(OPh)_3]$	5	7	__	1
13	$[Co(acac)_2]$+$NaBH_4$	30-40	100	Low	0
14	Indenyl cobalt(I)	15	97	__	0
15	$[Co_4(CO)_{12}]$	10	50	Medium	2
16	$[Ru_3(CO)_{12}]$	15	16	Medium	1

[a] TONs calculated with respect to the number of moles of Co, Ti, Rh, Ru in the catalyst

[b] 0 = stable, 4 = highly sensitive

Table 6: TONs observed with different metal-based complexes

Entry	Substrate	TON Co	TON Ti	TON Rh	TON Ru	TON Ir
1		12	4	14	8	—
2		10	18	20	13	4
3		10	19	7	12	—
4		2	18	14	12	4
5		10	16	16	15	4

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CHAPTER 2

Rhodium-BisbenzodioxanPhos complex-Catalyzed Enantioselectivity Pauson- Khand- Type Cyclization in Alcoholic Solvents

2.1. Introduction

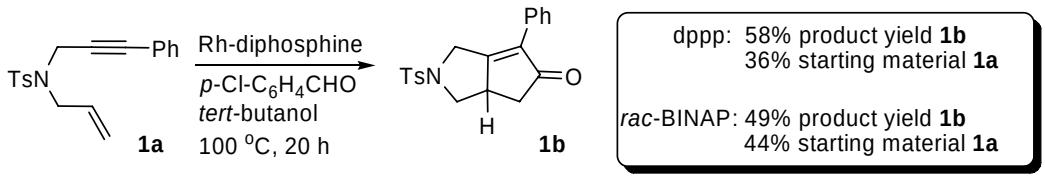
Following the good results of cobalt-catalyzed PKR, several research groups turned their attention on rhodium. In 1998, Narasaka *et al.* employed $[Rh(CO)_2Cl]_2$ to catalyze PKR between electron-deficient alkynes and alkenes under 1 atm of carbon monoxide to afford the corresponding cyclopentenones in good yield. In 2000, Jeong *et al.* reported that using $[Rh(CO)_2Cl]_2$ and (*S*)-BINAP in the presence of silver salt (e.g. AgOTf) under carbon monoxide atmosphere to afford chiral cyclopentenones with good to excellent *ee* values. (Ch 1, scheme 12) Although major improvements were achieved on PKR to enhance its product yields and enantiomeric excess, use of highly toxic carbon monoxide signifies a drawback to the PKR. Hence it is urgent to find out other CO surrogates to replace carbon monoxide in PKR.

Decarbonylation of aldehydes was first discovered by Tsuji and Ohno in 1965[1(a)] and a couple of years later a rhodium-catalyzed decarbonylation of aldehydes

was reported.[1(b)] Hence decarbonylation of carbonyl compounds (eg. aldehydes) as the CO surrogate may provide an attractive protocol for the PKR.[2,3,4] Later on two independent research groups (Kakiuchi/Morimoto)[2(d)] and Shibata[3(a)] offer a convenient "carbon monoxide" reagent for asymmetric carbonylation reactions. It is operational simply to run a reaction in a solventless reaction conditions or aid with a relatively non-toxic solvent medium. Shibata *et al.* used aldehyde as both CO source as well as the solvent medium in asymmetric PKR with good *ee*. However, no successful homogeneous catalytic asymmetric PKR systems that enable the use of relatively less toxic alcoholic solvents have been reported yet. Therefore I would like to catalyze the asymmetric PKR in less toxic alcoholic medium.

2.2. Results and discussion

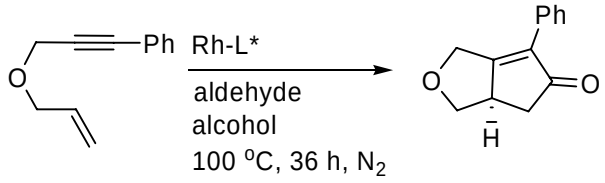
The feasibility of the Rh-catalyzed decarbonylation of aldehyde under alcoholic solvents was examined in the initial studies. The reaction of enyne **1a** and *para*-chlorobenzaldehyde in the presence of catalytic amount of $[Rh(COD)Cl]_2$ and dppp[5] (or *rac*-BINAP) in *tert*-butanol at 100 °C for 20 hours afforded the desired cyclopentenone **1b** in 58% yield according to GC analysis, along with 36% of unreacted **1a** (scheme 1).

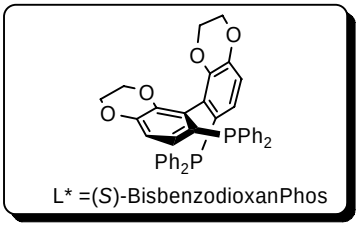


(Scheme 1: Initial results of decarbonylation of *para*-chlorobenzaldehyde and cascade PKR process)

The promising results showed the potential of catalytic decarbonylation in alcoholic medium. Next I would like to explore this reaction into asymmetric version to provide chiral cyclopentenones and hence different kinds of chiral ligands were subjected to the reaction (Table1).

Table1: Effects of ligand, solvent and aldehyde in enantioselective Pauson-Khand-type reaction in alcoholic medium.[a]





Entry	Ligand	Aldehyde	Solvent	%yield [b]	%*ee* [c]
1	(*S*)-BINAP	Benzaldehyde	t-BuOH	22	67
2	(*S*)-BisbenzodioxanPhos	Benzaldehyde	t-BuOH	58	81
3	(*S*)-BisbenzodioxanPhos	Benzaldehyde	t-amyl alcohol	70	86
4	(*S*)-BisbenzodioxanPhos	Benzaldehyde	n-BuOH	44	79
5	(*S*)-BisbenzodioxanPhos	*p*-OMe-benzaldehyde	t-amyl alcohol	12	33
6	(*S*)-BisbenzodioxanPhos	*p*-Cl-benzaldehyde	t-amyl alcohol	72	80
7	(*S*)-BisbenzodioxanPhos	*n*-nonylaldehyde	t-amyl alcohol	39	77
8	(*S*)-BisbenzodioxanPhos	cinnamylaldehyde	t-amyl alcohol	81	85
9	(*S*)-BINAP	cinnamylaldehyde	t-amyl alcohol	49	73
10	(*S*)-tol-BINAP	cinnamylaldehyde	t-amyl alcohol	66	78
11[d]	(*S*)-P-Phos	cinnamylaldehyde	t-amyl alcohol	79	84
12 [e]	(*R*,*R*)-Et-DuPhos	cinnamylaldehyde	t-amyl alcohol	5	n.d.

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (3 mol%), ligand (6 mol%), enyne (0.3 mmol), aldehyde (0.45 mmol) and magnetic stirrer-bar were charged to a screw-capped vial at RT. Unpurified solvent (0.2 mL, 1.5 M, prior bubbled with nitrogen for 2 mins) was added under nitrogen and the reaction was stirred at 100 °C for 36 hours.

[b] Isolated yield.

[c] Average of two runs from chiral HPLC analysis using Daicel Chiracel® AD-H columns (0.46 cm × 25 cm).

[d] (*S*)-P-Phos: (*S*)-2,2',6,6'- Tetramethoxy- 4,4'-bis(diphenylphosphano)- 3,3'-bipyridine.

[e] (*R*,*R*)-Et-DuPhos: (-)-1,2-Bis((2*R*,5*R*)-2,5-diethylphospholano)benzene.

2.2.1. Ligands screening

Several axially chiral ligands such as (*S*)-BINAP, (*S*)-tol-BINAP, (*S*)-P-Phos, (*S*)-BisbenzodioxanPhos[6] were screened (Table 1, entries 8-12), (*S*)-BINAP was found to give moderate yield and enantioselectivity of the PKR product when (*S*)-BisbenzodioxanPhos gave high yield and good enantioselectivity. The better results may due to better solubility of (S*)*-bisbenzodioxanPhos in alcoholic medium and hence provided a better homogenous reaction conditions for catalysis.

2.2.2. Solvents screening

To optimize the catalytic system, several alcohols were screened (Table 1, entries 2-4), branched alcohol were found to give better yield than that of aliphatic alcohol obtained and *tert*-amyl alcohol gave highest yields among the solvents. Unpurified bench grade (4L bottle) *tert*-amyl alcohol solvent gave the same good results as those obtained from using a purified solvent.

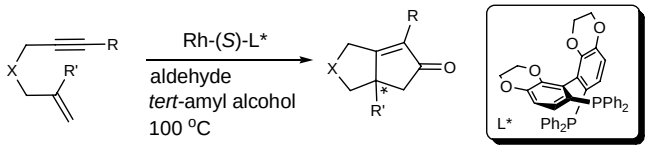
2.2.3. Electronic effects of aldehyde on decarbonylation

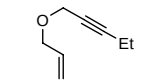
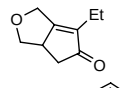
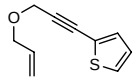
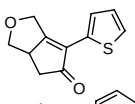
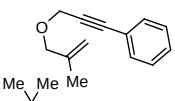
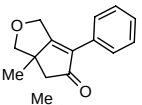
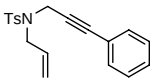
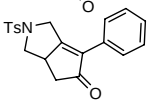
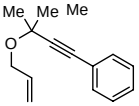
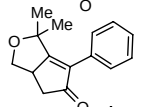
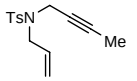
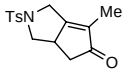
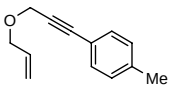
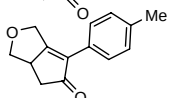
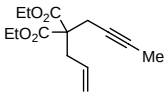
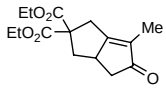
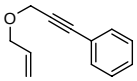
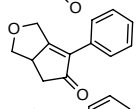
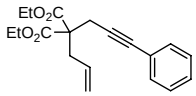
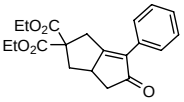
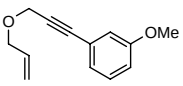
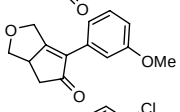
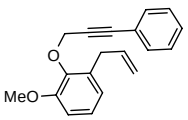
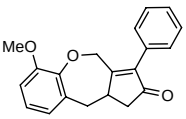
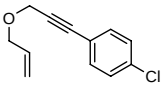
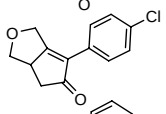
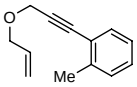
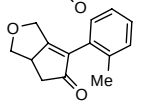
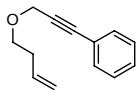
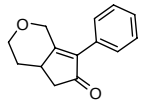
In order to increase the efficiency of the newly developed Rh-bisbenzodioxanPhos system, we examined different aldehydes as the CO surrogates (Table 1, entries 3, 5-8). The electrochemical nature of aromatic aldehydes was found to be responsible for both CO-transfer catalysis and

asymmetric carbonylative cyclization (Table 1, entries 3, 5 and 6). Electron-poor *p*-chlorobenzaldehyde can provide CO moiety more efficiently than the electron-rich *p*-methoxybenzaldehyde, which was supported by Hammett plot study for the decarbonylation of *para*-substituted benzaldehydes by Fristrup *et al.*[7] later. Aliphatic aldehyde gave the lowest product yield whereas α,β-unsaturated aldehyde gave the best results in terms of both yield and enantioselectivity (Table 1, entry 8) and it may due to its conjugated system to facilitate the CO donation. To further probe the effectiveness of the Rh-BisbenzodioxanPhos system, various oxygen-tethered 1,6-enynes for the enantioselective PKR was examined (Table 2).

2.2.4. Scope and limitation of Rhodium-BisbenzodioxanPhos catalyzed asymmetric Pauson-Khand-type reaction

Table 2: Rh-BisbenzodioxanPhos-catalyzed enantioselective Pauson-Khand-type cyclization in *tert*-amyl alcohol.[a]



entry	substrate	product	% yield[b]	%*ee*[c]	entry	substrate	product	% yield[b]	%*ee*[c]
1			61	96	9			trace	n.d.
2			69	91	10			94	80
3			78	91	11			97	88
4			83	89	12			90	77
5			81	85	13			91	69
6			79	70	14			trace	n.d.
7			72	49					
8			78	84	15			trace	n.d.

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (3 mol%), (*S*)-BisbenzodioxanPhos (6 mol%), enyne (0.3 mmol), cinnamaldehyde (0.45 mmol) and magnetic stirrer-bar were charged to a screw-capped vial at room temperature. Unpurified *tert*-amyl alcohol (0.2 mL, 1.5M, prior bubbled with nitrogen for 2 min) was added under N_2 and the reaction mixture was stirred at 100°C for 36h.

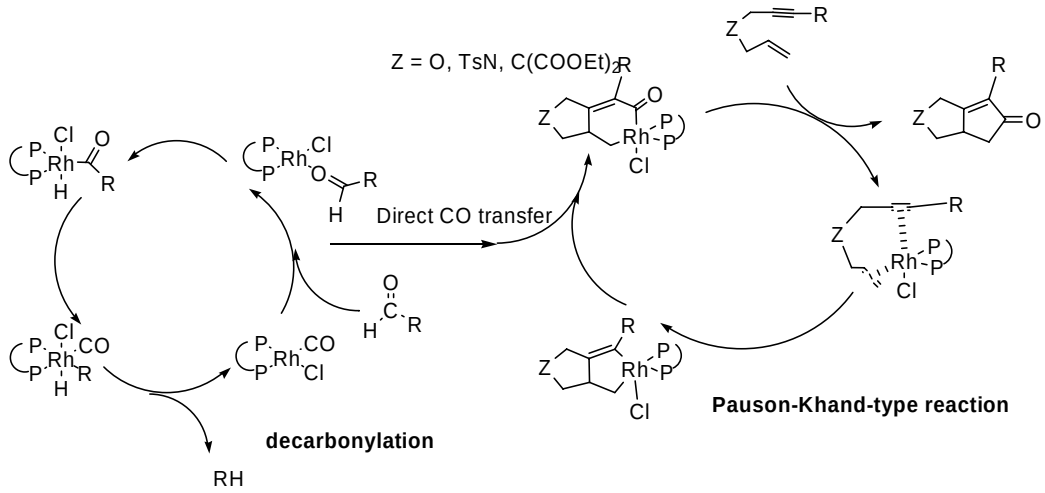
[b] Yield of isolated product.

[c] Determined by chiral HPLC analysis using Daicel Chiralcel® AD-H, AS-H, OD-H columns (0.46 x 25cm)

Alkyl-substituted alkynes gave excellent enantioselectivities (up to 96 %ee) of

the corresponding products (Table 2, entry 1). 1,1-Disubstituted alkene reacted smoothly to gave high enantioselectivity product (Table 2, entry 2). Various aromatic enynes were subjected to PKR (Table 2, entries 3-8) and interestingly electron-donating aromatic enynes gave higher enantioselectivity whereas electron-withdrawing aromatic enynes gave lower enantioselectiviy cycloadducts. However the Hammett Plot relationship between the electronic properties of the substrates and its cycloadducts *ee* values which suggested by Kwong *et al.* cannot be demonstrated in this catalytic system. Surprisingly sterically hindered *ortho*-substituted enyne can also give moderate yield and high *ee* (84 %*ee*) value (Table 2, entry 8). This catalytic condition can also applied to nitrogen-tethered and carbon-tethered enynes (Table 2, entries 10-13), excellent yields and high *ee* values were observed in substrates with alkyl substitution in stead of a phenyl group. This catalytic condition cannot provide cycloadduct with thiopheneyl-substituted substrate (Table 2, entry 9), it may probably due to the coordination of the thiophene moiety to the metal center which rendered the metal-complex coordinative saturated. Furthermore this catalytic system also cannot catalyze both 1,7 and 1,8-enynes (Table 2, entries 14,15)

2.2.5. Proposed mechanisms



(Scheme 2: Proposed mechanisms for Rh-catalyzed Pauson-Khand-type reaction and decarbonylation of aldehyde)

Aldehyde firstly approached the rhodium catalyst, followed by insertion, migration of CO and elimination to provide CO moiety and alkane. The CO moiety was then transferred to the metallacycle intermediate and enabled effective carbonylative coupling to form desired cyclopentenone. It was proposed that no free CO gas existed in the reaction

2.3. **Conclusion**

In summary, a homogeneous system was developed for the efficient decarbonylation of aldehyde and cascaded asymmetric Pauson-Khand-type cyclization in relatively non-toxic alcoholic medium. In the presence of axially chiral (*S*)-BisbenzodioxanPhos ligand, *O*-, *N*- and *C*-tethered cyclopentenones were obtained with good to excellent *ee*s in this cooperative dual catalysis. Interestingly, the electronic influence of the substrate was found to be responsible for the enantioselectivity of the product.

2.4. **Experimental section**

General procedures for asymmetric Pauson-Khand-type cyclization of various enynes: $[Rh(COD)Cl]_2$ (4.4 mg, 9.0 μmol), (*S*)-BisBenzodioxanPhos (11.5 mg, 18.0 μmol), aldehyde (0.45 mmol, 1.5 equivalents with respected to enyne) and Teflon-coated magnetic stirrer bar (3 mm × 10 mm) were charged to a Teflon-lined screw-capped vials on bench-top at room temperature with continuous stirring. Enynes (0.3 mmol) was then added. These vials were evacuated and backfilled with nitrogen (3 cycles), followed by the addition of unpurified *tert*-amyl alcohol (0.2 mL, 1.5 M, from bench grade 4L bottle, prior bubbled with nitrogen for 2 mins). The reaction mixtures were magnetically stirred in a preheated 100 °C (± 3 °C) oil bath for 36 hours (reaction times were unoptimized for each substrate). The vials were allowed to reach room temperature. Diethyl ether or ethyl acetate (~2 mL) was added. The crude reaction mixtures were directly purified by column chromatography on silica gel using hexane/ethyl acetate mixture as the eluent to afford chiral bicyclic cyclopentenones. The enantiomeric excess of the products were determined by chiral HPLC analysis using Chiralcel® columns..

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[5] Dppp:1,3-Bis(diphenylphosphano)propane; *rac*-BINAP: racemic-2,2’-Bis(diphenylphosphano)-1,1’-binaphthyl.

[6] (a) Pai, C.-C.; Li, Y.-M.; Zhou, Z.-Y.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 2789. (b) Genêt group named the ligand SYNPHOS®

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CHAPTER 3

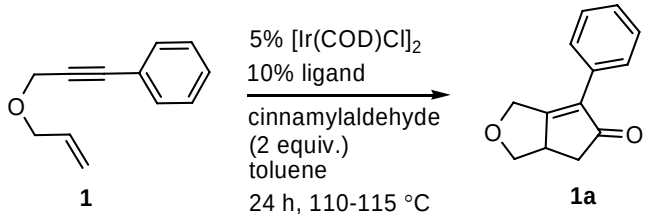
Iridium-Catalyzed Cascade Decarbonylation/Highly Enantioselective Pauson-Khand-type Cyclization Processes

3.1. Introduction

Rhodium-catalyzed asymmetric Pauson-Khand-type reaction had drew much attention in recent decade however the iridium-catalyzed enantioselective Pauson-Khand-type reaction remains only sporadically studied[1]. Apart from the rhodium catalyst, iridium complexes such as [Cp*$IrMe_2$(DMSO)] was realized can be effective in decarbonylation of aldehydes to give iridium-carbonyl complexes.[2] Hence I would like to explore the applicability of chiral iridium complex in the cooperative decarbonylation/ enantioselective cyclization sequential processes

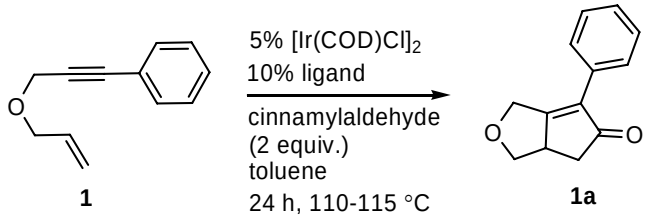
3.2. Results and discussion

To probe the feasibility of Ir-catalyzed cooperative decarbonylation/Pauson-Khand-type reaction were performed with $[Ir(COD)Cl]_2$ complex (Scheme 1).



(Scheme 1)

Table 1: Initial results on Ir-catalyzed decarbonylation of aldehyde and cascade Pauson-Khand-type reaction[a]



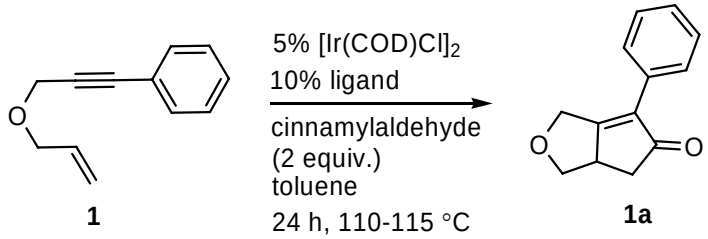
Entry	Ligand	Aldehyde	Solvent	Yield/%[b]
1	Nil	cinnamylaldehyde	toluene	11
2	PPh_3	cinnamylaldehyde	toluene	15
3	dppb	cinnamylaldehyde	toluene	49
4	rac-BINAP	cinnamylaldehyde	toluene	58

[a]Reaction conditions: 5 mol% $[Ir(COD)Cl]_2$, 10 mol% L, enyne **1** (0.3 mmol), cinnamyaldehyde (0.6 mmol) and toluene (4.0 mL) were stirred at 110-115 °C for 24 h under nitrogen atmosphere.
[b]Isolated yield.

Initial studies revealed that phosphine ligands were required for this catalytic transformation (Table 1, entry 1). Bidentate phosphines (e.g. dppb [3] and

rac-BINAP) provided significantly higher yield of the cyclopentenone **1a** then triphenylphosphine (Table 1, entries 2-4). Next I would like to explore the capability of the enantioselective version of this dual catalysis hence several commercially available chiral diphosine ligands were examined (Table 2).

Table 2: Effects of chiral phosphine ligands and solvents on Ir-catalyzed asymmetric Pauson-Khand-type cyclization.[a]



1 **1a**

Entry	Chiral ligand	Solvent	% yield [b]	% *ee* [c]
1	(*S*)-BINAP	toluene	42	94
2	(*S*)-xylyl-BINAP	toluene	41	92
3	(*S*)-P-Phos	toluene	39	90
4	(*S*)-xylyl-P-Phos	toluene	36	90
5	(*S*)-BisbenzodioxanPhos	toluene	41	92
6	(*R*)-PHANEPHOS	toluene	21	56
7 [d]	(*R,R*)-Et-Duphos	toluene	12	24
8 [d]	(*R,R*)-Me-Duphos	toluene	14	22
9 [d]	(*R,R*)-Et-Ferro-TANE	toluene	14	25
10 [e]	(*S*)-*N,N*-diMe-Monophos	toluene	21	67
11	(*S*)-BINAP	DMF	26	89
12	(*S*)-BINAP	dioxane	57	90
13	(*S*)-BINAP	DME	42	89
14	(*S*)-BINAP	THF	40	90
15	(*S*)-BINAP	[BMIM]NTf_2	11	81

[a] Reaction conditions: 5 mol% $[Ir(COD)Cl]_2$, 10 mol% L, enyne **1** (0.3 mmol), cinnamyaldehyde (0.6 mmol) and toluene (4.0 mL) were stirred at 110-115 °C for 48 h under nitrogen atmosphere.

[b] Isolated yield.

[c] *Ee* values were determined by chiral HPLC analysis using Daicel® Chiralcel AS column.

[d] A complex mixture of products were observed.

[e] 20 mol% ligand was used.

3.2.1. Ligands screening

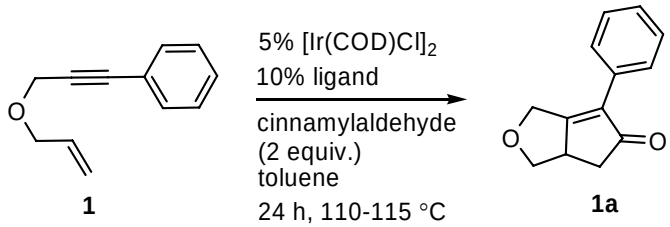
(*S*)-BINAP provided the best result among the ligands screened (Table 2, entry 1). The sterically more demanding (*S*)-xylyl-BINAP has no beneficial effect for this [2+2+1] reaction (Table 1, entry 2).[4] Both atropisomeric dipyridyldiphosphine (*S*)-P-Phos and (*S*)-BisbenzodioxanPhos gave slightly lower *ee* of the product (Table 1, entry 3-5). Phospholane-type chiral alkylphosphine Duphos and Ferro-TANE showed significantly lower *ee* and yield of the bicyclic cyclopentenone (Table 1, entry 7-9). Moderate *ee* and poor yield of the product were observed when monodentate phosphoramidite ligand (*S*)-Monophos was applied (Table 1, entry 10).

3.2.2. Solvents screening

In addition to the ligand screening, the solvent effect was investigated. Toluene as solvent provided the highest *ee* value of the product. We chose dioxane as solvent for our further study as it gave higher product yield with only slightly reduced enantioselectivity (Table 1, entry 12). Catalytic cooperative asymmetric Pauson-Khand-type reaction in ionic liquid remains unprecedented.[5] A good *ee* value but poor yield of the cyclopentenone product was observed when room temperature ionic liquid [BMIM]NTf_2 was used as solvent (Table 1, entry 15). However, initial attempt in recycling of the catalyst was unsuccessful.

3.2.3. Electronic effects of aldehyde on decarbonylation and enantioselective Pasuon-Khand-type reaction

Table 3: Aldehyde screening for Ir-catalyzed enantioselective Pauson-Khand-type cyclization.[a]



1 **1a**

Entry	Aldehyde	Equiv.	% yield [b]	% *ee* [c]
1	*trans*-cinnamylaldehyde	5	68	93
2	benzaldehyde	5	35	92
3	*p*-chlorobenzaldehyde	5	48	91
4	*p*-methoxybenzaldehyde	5	21	90
5	*n*-nonylaldehyde	5	74	94
6	2-pyridylmethylformate	5	30	80
7	*n*-nonylaldehyde	2	33	94
8	*n*-nonylaldehyde	10	48	93
9	*n*-nonylaldehyde	20	34	93

[a] Reaction conditions: 5 mol% $[Ir(COD)Cl]_2$, 10 mol% L, enyne **1** (0.3 mmol), cinnamyaldehyde (0.6 mmol) and toluene (4.0 mL) were stirred at 110-115 °C for 48 h under nitrogen atmosphere.

[b] Isolated yield.

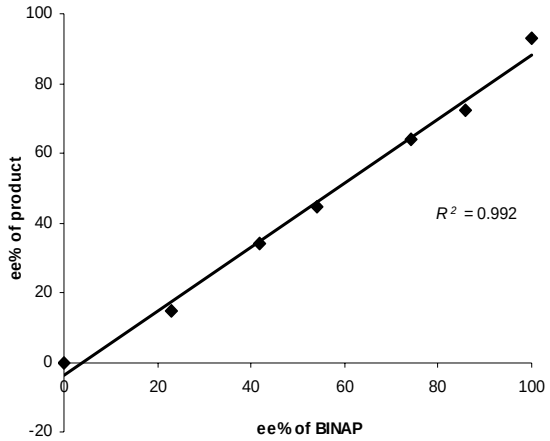
[c] *Ee* values were determined by chiral HPLC analysis using Daicel® Chiralcel AS column.

In order to increase the efficiency of the newly developed Ir-BINAP system, we examined different aldehydes as the CO surrogates (Table 3). α,β-Unsaturated *trans*-cinnamylaldehyde gave good results in terms of both yield and enantioselectivity (Table 2, entry 1). The electrochemical nature of aromatic aldehydes was found to be responsible for both CO-transfer catalysis and the enantioselective carbonylative cyclization[6](Table 3, entries 2-4). Electron-poor

p-chlorobenzaldehyde provided the CO moiety more effectively than the electron-rich *p*-methoxybenzaldehyde. The best aldehyde of choice was the *n*-nonylaldehyde (Table 3, entry 5). Notably, it was the first time that formate was shown to be capable for CO transfer in iridium-catalyzed enantioselective Pauson-Khand-type dual catalysis (Table 3, entry 6). Besides electronic effects of aldehyde, aldehyde loading was also found to be crucial to the product yield but the *ee* remained unaffected. The optimal yield was obtained when five equivalents of aldehyde were used. Interestingly, an addition of extra amount of aldehyde lowered the product yield.

3.2.4. Metal to ligand ratio screening

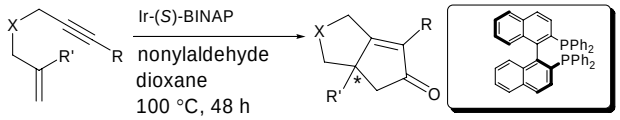
The relationship of metal to ligand ratio was also investigated. However no significant *ee* variations were observed when the ratio was varied from (*S*)-BINAP : Ir = 1:1 to 2:1. This result indicated that the catalytic complex with a ratio of (*S*)-BINAP : Ir = 1:1 would be involved for the catalytic reaction. To probe this question, the carbonylative cyclization of **1a** was performed using BINAP of varying *ee*. As shown in Figure 1, a linear correlation between the *ee* of the ligand and that of the product was observed, indicating that a 1:1 ligand-to-metal ratio is present in the catalytic complex.[7]

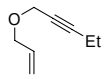
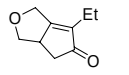
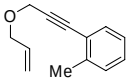
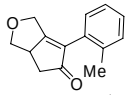
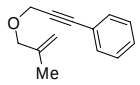
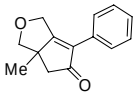
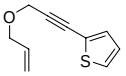
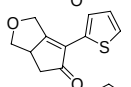
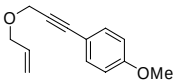
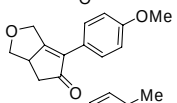
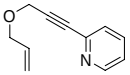
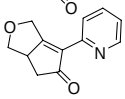
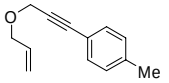
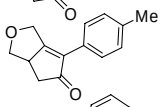
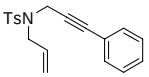
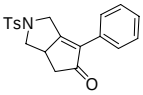
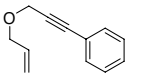
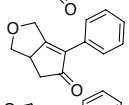
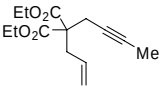
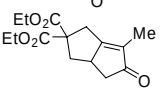
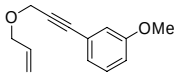
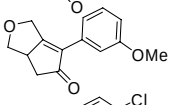
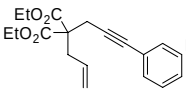
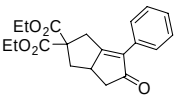
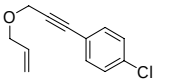
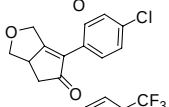
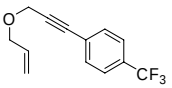
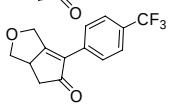
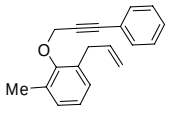
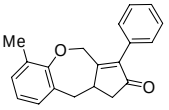

100
80
60
40
20
0
-20
0
20
40
60
80
100
ee% of product
ee% of BINAP
R^2 = 0.992

(Figure 1)

3.2.5. Scope and limitation of Ir-BINAP catalyzed asymmetric Pauson-Khand-type reaction

Table 4: Ir-BINAP catalyzed asymmetric Pauson-Khand-type cyclization of various enynes.[a]



entry	substrate	product	% yield[b]	%*ee*[c]	entry	substrate	product	% yield[b]	%*ee*[c]
1			69	95	9			trace	n.d.
2			41	96	10			trace	n.d.
3			76	94	11			trace	n.d.
4			75	95	12			31	95
5			74	94	13			39	90
6			24	94	14			35	90
7			60	98					
8			42	96	15[d]			trace	n.d.

[a] Reaction conditions: 5 mol% $[Ir(COD)Cl]_2$, 10 mol% L, enyne **1** (0.3 mmol), cinnamyaldehyde (0.6 mmol) and toluene (4.0 mL) were stirred at 100-105 °C for 48 h under nitrogen atmosphere.

[b] Isolated yield.

[c] *Ee* values were determined by chiral HPLC analysis using Daicel® Chiralcel AS column.

[d] 100 °C, 96 h; 120 °C, 72 h.

To test the effectiveness of the Ir-BINAP system, various oxygen-tethered 1,6-enynes were examined for the enantioselective Pauson-Khand-type cyclization (Table 4). Alkyl-substituted alkyne gave excellent enantioselectivity

(95% *ee*) of the corresponding product (Table 4, entry 1). Enyne with 1,1-disubstituted alkene reacted smoothly to give the chiral quaternary carbon center bicyclic cyclopentenone in good enantioselectivity (Table 4, entry 2). Remarkably, excellent enantioselectivity (98% *ee*) was attained for the reaction with *para*-chloro substituted enyne (Table 4, entry 7). To the best knowledge, this is the highest *ee* value reported so far for cascade iridium-catalyzed Pauson-Khand-type transformations. Various new aromatic enynes, which possessed different electronic properties were prepared and subjected to carbonylative cyclizations (Table 4, entries 3-8). Kwong *et al.* have reported an electronic effect in Rh-catalyzed asymmetric Pauson-Khand-type reaction.[6(a)] A linear free energy relationship in Hammett study was observed. Aromatic enyne with larger Hammett constant usually provided higher enantioselectivity of the cyclopentenone. In contrast, no significant electronic relationship between the enyne substrates and the *ee* of the bicyclic cyclopentenones was observed in the Ir-BINAP catalyzed carbonylative cyclization. Aromatic enynes with different electronic properties generally provided enantioselectivites greater than 94% *ee*. Although the electronic effect is insignificant, steric factor plays an important role. Sterically congested *ortho*-substituted enyne gave only a trace amount of product as indicated from GC analysis (Table 4, entry 9). The coordination of

hindered enyne to iridium metal center seemed to be problematic hence nearly no conversion was observed and a quantitative amount of starting material was recovered after the reaction. Heterocyclic enyne with pyridyl or thiophenyl moiety were also found to be unsuccessful (Table 4, entries 10-11). Presumably, the heteroatom bound to the metal center more tightly than π-interaction of enyne and rendered the metal complex coordinative saturated. The Ir-BINAP system was also applied to other nitrogen- and carbon-tethered enynes (Table 4, entries 12-14). Surprisingly, cycloadducts with excellent enantioselectivities were obtained (up to 95% *ee*). Besides this catalytic system was also attempted to convert 1,8-enyne into its corresponding cycloadducts, however, only a trace amount of product was observed from continuous GC-MS analysis after prolonged heating at higher temperature (120 °C)

3.3. **Conclusion**

In summary, Ir-diphosphine complex-catalyzed decarbonylation of aldehydes was successfully demonstrated. This versatile reaction was found to be a suitable cooperative partner in the sequential decarbonylation and highly enantioselective [2+2+1] carbonylative cyclization. Additionally, apart from aldehydes, initial result showed that formate was also capable as the CO source in Ir-catalyzed asymmetric carbonylative cyclization, which may provide an opportunity to use other readily available carbonyl compounds as CO surrogates in iridium catalysis. In the presence of easily accessible chiral Ir-BINAP catalyst and nonylaldehyde, various 1,6-enynes were transformed to optically active bicyclic cyclopentenones with excellent enantioselectivities that is generally higher than those obtained in rhodium-catalyzed asymmetric Pauson-Khand-type reaction.

3.4. Experimental section

General procedures for Ir-catalyzed asymmetric Pauson-Khand-type cyclization of various enynes: $[Ir(COD)Cl]_2$ (10.0 mg, 0.015 mmol), (*S*)-BINAP (18.9 mg, 0.03 mmol) and Teflon-coated magnetic stirrer bar (3 mm × 10 mm) were charged into a Rotaflo® (England) resealable screw-cap Schlenk flask on bench-top at RT. The flask was evacuated and backfilled with nitrogen (3 cycles). Anhydrous dioxane (3.0 mL) was added under nitrogen atmosphere with continuous stirring for 10 minutes. Distilled aldehyde (1.5 mmol, 5 equivalents with respected to enyne) and enynes (0.3 mmol) were added sequentially *via* micro-syringe. Additional dioxane (1.0 mL, total = 4.0 mL) was used to rinse the inner-wall of the Schlenk flask. The flask was resealed and the reaction mixtures were magnetically stirred in a preheated 100 °C (± 3 °C) oil bath for 48 hours (reaction times were unoptimized for each substrate). The flask was allowed to cool to RT. Diethyl ether or CH_2Cl_2 (~5 mL) was added (tiny amount of the aliquot was taken out for GC and TLC analysis) and then concentrated under reduced pressure. The crude reaction mixtures were directly purified by column chromatography on silica gel using hexane/ethyl acetate as the eluent to afford optically active bicyclic cyclopentenones. The enantiomer ratios were determined by chiral HPLC analysis.

References

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[2] Gómez, M.; Kisenyi, J. M.; Sunley, G. J.; Maitlis, P. M. *J. Organomet. Chem.* **1985**, *296*, 197

[3] Dppb: 1,3-Bis(diphenylphosphano)butane

[4] For a recent [2+2+2] carbocylization of enyne which used sterically hindered xyl-BINAP or xyl-P-Phos and has beneficial effects, see: Evans, P. A.; Lai, K. W.; Sawyer, J. R. *J. Am. Chem. Soc*. **2005**, *127*, 12466.

[5] For a pertinent review of ionic liquids, see: Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev*. **2002**, *102*, 3667.

[6] (a) Kwong, F. Y.; Li, Y.-M.; Lam, W. H.; Qiu, L.; Lee, H. W.; Chan, K. S.; Yeung, C.-H.; Chan, A. S. C. *Chem. Eur. J*. **2005**, *11*, 3872. (b) Kwong, F. Y.; Lee, H. W.; Lam, W. H.; Qiu, L.; Kwong, H. L.; Chan, A. S. C. *Adv. Synth. Catal*. **2005**, *347*, 1750. (c) Fristrup, P.; Krels, M.; Palmelund, A.; Norrby, P-O.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 5206

[7] For a discussion of nonlinear effects, see: (a) Girard, C.; Kagan, H. B. *Angew. Chem. Int. Ed.* **1998**, *37*, 2922. (b) Blackmond, D. G.. *Acc. Chem. Res*. **2000**, *33*, 402. (c) Kagan, H. B. *Adv. Synth. Catal.* **2001**, *343*, 227.

CHAPTER 4

Rh-Catalyzed Cooperative Decarbonylation and Asymmetric Pauson-Khand-type Cyclization Reactions using Formate as CO Surrogate

4.1. Introduction

Although major improvements on PKR conditions (such as temperature, catalyst loading and partial pressure of carbon monoxide required) have been achieved, the use of highly toxic carbon monoxide gas is still a concern. Hence there has been a considerable interest in the catalytic decarbonylation of carbonyl compounds to provide "CO" moiety for the PKR. In 2002, Kakiuchi/Morimoto[1] and Shibata[2] offered a convenient "carbon monoxide" reagent for asymmetric carbonylation reactions. Kwong *et al.* also utilized aldehyde as CO surrogate for the asymmetric PKR in both aqueous[3] and alcoholic[4] media to obtain optical active cyclopentenones with good yields and *ee* values. I believed that not only aldehyde can be CO source in PKR, it is possible to find out others carbonyl compounds that can provide CO moiety for the carbonylative cyclization.

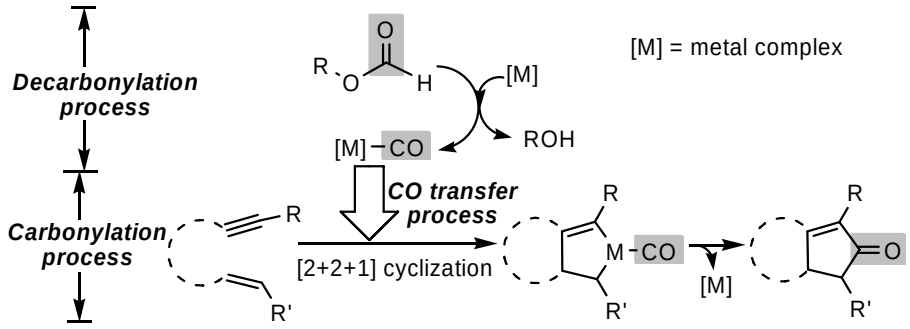
Chemistry of formate ester had drawn much attention in recent years. The conversion of methyl formate to methanol and carbon monoxide is particularly

desirable in the generation of easily handled CO moiety. However, drastic reaction conditions are usually employed (eg. >180 °C and/or >1 atm. pressure).[5] However Chung and co-workers demonstrated that decarbonylation of formates could be attained under mild reaction conditions (THF, 130 °C) with the suitable choice of metal complexes.[6]

During my study of Ir-catalyzed decarbonylation of aldehyde and cascade asymmetric Pauson-Khand-type reaction, formate ester can be decarbonylated and the CO moiety was successfully transferred for the carbonyative cyclization. Therefore I would like to examine the feasibility of cooperative decarbonylation of formate ester and Pauson-Khand-type transformation.

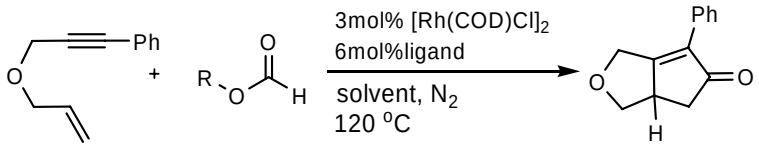
4.2. Results and discussion

Initial studies were focused on the feasibility of the Rh-catalyzed CO transfer process in alcoholic medium since the complimentary decarbonylation product of formate is ROH. 2-Pyridylmethyl formate was initially chosen to be the CO surrogate as its chelating property of pyridyl ring was supposed to assist the intramolecular RO(O)C–H oxidative addition, and thus facilitate the generation of [M]-CO species for the CO transfer hypothesis.(Scheme 1)



(Scheme 1: Pauson-Khand-type reaction using formate ester as CO surrogate)

Table 1: Investigations on catalytic cascade decarbonylation-PKR with formate as CO surrogate [a]



entry	R	ligand	solvent	%yield [b]
1	2-pyridylmethyl	dppe	*t*-amyl alcohol	23
2	2-pyridylmethyl	dppp	*t*-amyl alcohol	15
3	2-pyridylmethyl	dppf	*t*-amyl alcohol	33
4	2-pyridylmethyl	(±)-BINAP	*t*-amyl alcohol	38
5	2-pyridylmethyl	(±)-BINAP	dioxane	47
6	2-pyridylmethyl	(±)-BINAP	DMF	25
7	2-pyridylmethyl	(±)-BINAP	toluene	37
8	*n*-butyl	(±)-BINAP	dioxane	20
9	*t*-butyl	(±)-BINAP	dioxane	12
10	*n*-octyl	(±)-BINAP	dioxane	23
11	benzyl	(±)-BINAP	dioxane	42
12	benzyl [c]	(±)-BINAP	dioxane	18
13	benzyl [d]	(±)-BINAP	dioxane	20
14	benzyl [e]	(±)-BINAP	dioxane	40
15	*p*-Cl-benzyl	(±)-BINAP	dioxane	60

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (3 mol%), ligand (6 mol%), enyne (0.3 mmol), formate (1.5 mmol) and magnetic stirrer-bar were charged to a screw-capped vial at RT. Unpurified solvent (0.5mL bubbled with nitrogen for 2 mins) was added under nitrogen and the reaction was stirred at 120 °C for 36 hours.

[b] Isolated yield.

[c] formate (1 equiv., 0.3mmol) was used

[d] formate (1.5 equiv., 0.45mmol) was used

[e] formate (10 equiv., 3mmol) was used

4.2.1. Ligands and solvents screening

Bidentate diphosphine ligands were found to be suitable for the cascade process and the rigid binaphthyl scaffold gave a better cycloadduct yield (Table 1, entries 1-4). Solvent with different polarities were screened to test weather solvent

polarity may affect the rate of reaction however no significant observation was achieved and dioxane was the best solvent of choice among the solvents screened (Table1, entries 4-7).

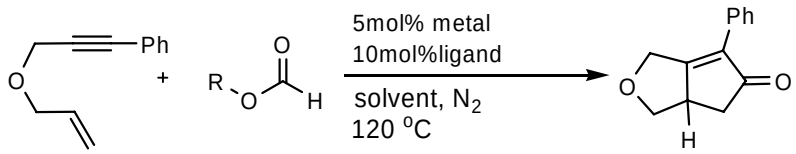
4.2.2. Electron effects of formate ester on decarbonylation

Commercially available alkyl formates were also investigated (Table 1, entries 8-15). Benzyl formate provided higher yield than other alkyl analogs. In order to further probe the efficacy of the formates, the electron-withdrawing *para*-chlorobenzyl formate donated a CO moiety more effectively (Table 1, entry 15). This is consistent with the general tendency for alkyl groups to migrate from acyl complexes leading to the formation of metal-carbonyls.[7] Besides the electronic property of benzylformate, amount of formate added also affected the product yield of cyclopentenones (Table 1, entries 11-14). Interestingly, for all formates examined, the catalyst abstracted a CO moiety from formates and transferred them to enyne, without hydroacylating the alkene and/or the alkyne portions of enyne as judged by GC-MS analysis.

Although 2-pyridylmethyl and *para*-chlorobenzyl formates afforded better yields of the cyclopentenone product, the inexpensive and commercially available benzyl formate as the CO source for further investigation. In fact, the electronic properties

of the substituted benzylformates did not affect the *ee* of the cyclopentenone products.

Table 2: Rhodium complex screening for catalytic cascade decarbonylation-PKR with formate as CO surrogate [a]



R = 2-pyridylmethyl

entry	Rh complex	ligand	solvent	%yield [b]
1	$[Rh(COD)Cl]_2$	(±)-BINAP	dioxane	35
2	$[Rh(COD)Cl]_2$ + $AgPF_6$ [c]	(±)-BINAP	dioxane	29
3	$[Rh(COD)_2]BF_4$	(±)-BINAP	dioxane	15
4	$[Ir(COD)Cl]_2$	(±)-BINAP	dioxane	30
5	$Ru_3(CO)_{12}$	(±)-BINAP	dioxane	15

[a] Reaction conditions: Metal complex (5 mol%), ligand (10 mol%), enyne (0.3 mmol), formate (1.5 mmol) and magnetic stirrer-bar were charged to a screw-capped vial at RT. Unpurified solvent (0.5mL bubbled with nitrogen for 2 mins) was added under nitrogen and the reaction was stirred at 120 °C for 36 hours.

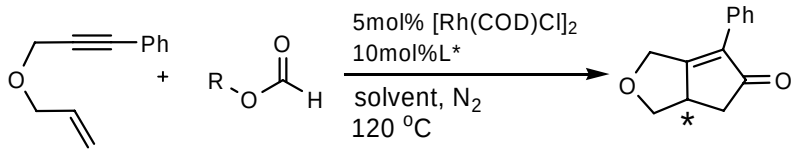
[b] Isolated yield.

[c] $[Rh(COD)Cl]_2$ (5mol%), $AgPF_6$ (20mol%), Ligand (10mol%)

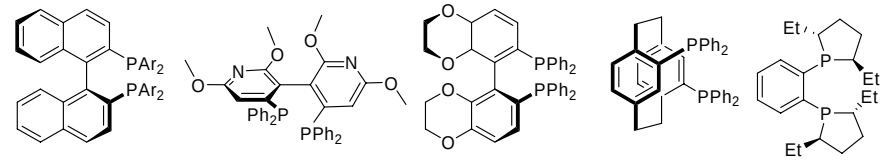
4.2.3. Metal precursors screening

Cationic $Rh(COD)_2BF_4$ and $[Rh(COD)Cl]_2/AgPF_6$ were inferior than that of neutral $[Rh(COD)Cl]_2$ in the cooperative process. When Ru and Ir complexes were applied for the cascade catalysis, CO transfer process from formate was also observed. However the effectiveness was inferior to that found from the Rh complexes. Hence neutral $[Rh(COD)Cl]_2$ was chosen as metal precursor for further optimization.

Table 3: investigations on chiral ligands on decarbonylation of formate and asymmetric PKR



R = 2-pyridylmethyl



Ar = Ph, (*S*)-BINAP
Ar = *p*-tol, (*S*)-*p*-tol-BINAP
Ar = 3,5-xylyl, (*S*)-xyl-BINAP

(*S*)-P-Phos

(*S*)-BisbenzodioxanPhos
(*S*)-SYNPHOS

(*R*)-PHANEPHOS

(*R*,*R*)-Et-Duphos

entry	ligand	solvent	%yield [b]	%*ee* [c]
1	(*S*)-BINAP	dioxane	45	70
2	(*S*)-tol-BINAP	dioxane	43	72
3	(*S*)-xyl-BINAP	dioxane	48	75
4	(*S*)-PPhos	dioxane	29	23
5	(*S*)-BisbenzodioxanPhos	dioxane	38	41
6	(*R*)-PHANPHOS	dioxane	trace	n.d.
7	(*R*,*R*)-Et-DuPhos	dioxane	33	10

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (5 mol%), ligand (10 mol%), enyne (0.3 mmol), formate (1.5 mmol) and magnetic stirrer-bar were charged to a screw-capped vial at RT. Unpurified solvent (0.5mL bubbled with nitrogen for 2 mins) was added under nitrogen and the reaction was stirred at 120 °C for 3 days.

[b] Isolated yield.

[c] Determined by chiral HPLC analysis using Daicel® AS-H, AD-H and OD-H columns

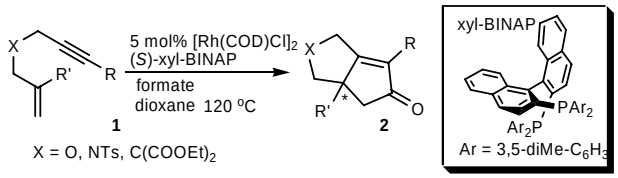
4.2.4. Effects of chiral ligands on product yield and enantiomeric excess

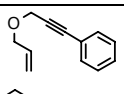
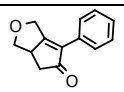
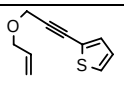
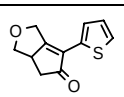
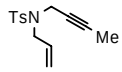
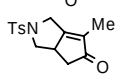
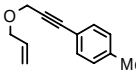
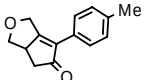
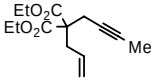
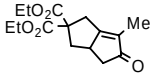
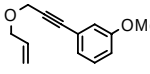
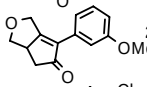
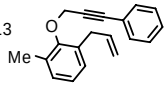
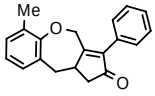
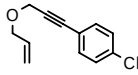
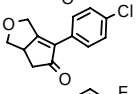
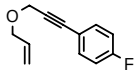
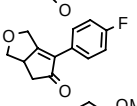
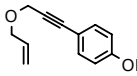
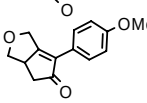
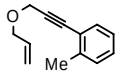
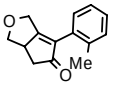
To explore this catalytic system into asymmetric version, various kind of chiral ligands were screened for purpose. BisbenzodioxanPhos/SYNPHOS and P-Phos afforded the desired cycloadduct in low enantioselectivities, 41% *ee* and 23% *ee*, respectively. However, the state-of-the-art BINAP class ligand showed

significant better product enantioselectivity. Among the enantiomerically pure BINAPs have examined, steric effect of the ligands improves the enantioselectivities of cycloadducts and the sterically demanding (*S*)-xyl-BINAP provided the best stereo-communication in the [2+2+1] cycloaddition (75% *ee*). Planar chiral (*R*)-PHANPHOS failed to convert the starting enyne into its cycloadduct. (*R*,*R*)-Et-DuPhos can catalyze the reaction but both product yield and %*ee* value were inferior to those obtained by axially chiral biaryldiphosphine ligands.

4.2.5. Scope and limitation of Rh-xyl-BINAP catalyzed asymmetric Pauson-Khand-type reaction

Table 4: Rh-catalyzed cascade decarbonylation asymmetric Pauson-Khand type reaction[a]



entry	substrate	product	% yield[b]	%*ee*[c]	entry	substrate	product	% yield[b]	%*ee*[c]
1	 **1a**	 **2a**	43	75	10	 **1j**	 **2j**	59	80
2	 R = Me, **1b**	 R = Me, **2b**	16	92	11	 **1k**	 **2k**	65	74
3	R = Et, **1c**	R = Et, **2c**	20	94					
4	 **1d**	 **2d**	44	81	12	 **1l**	 **2l**	40	86
5	 **1e**	 **2e**	37	84	13	 **1m**	 **2m**	trace	n.d.
6	 **1f**	 **2f**	65	84					
7	 **1g**	 **2g**	61	76					
8	 **1h**	 **2h**	58	77					
9	 **1i**	 **2i**	11	65					

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (5 mol%), ligand (10 mol%), enyne (0.3 mmol), formate (1.5 mmol) and magnetic stirrer-bar were charged to a screw-capped vial at RT. Unpurified solvent (0.5mL bubbled with nitrogen for 2 mins) was added under nitrogen and the reaction was stirred at 120 °C for 3 days

[b] Isolated yield.

[c] Determined by chiral HPLC analysis using Daicel® AS-H, AD-H and OD-H columns

To further test the effectiveness of the Rh-xyl-BINAP catalytic system, we studied a variety of oxygen-tethered 1,6-enynes for the enantioselective PKR (Table 4). Alkyl-substituted alkynes gave excellent enantioselectivities (94% *ee*) of the corresponding products (Table 4, entries 2-3). Various aromatic enynes, which

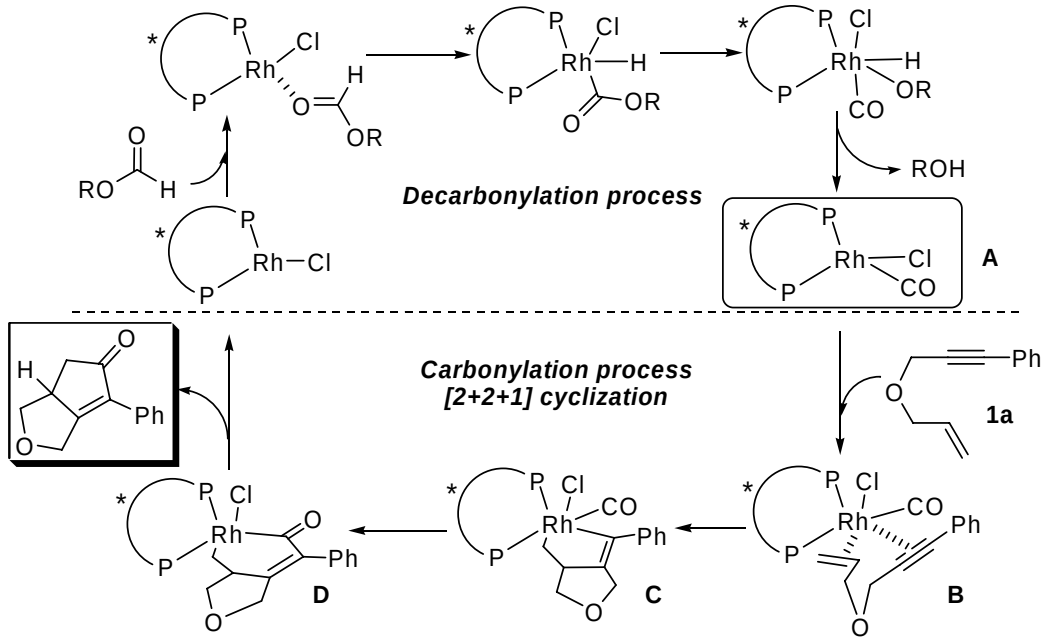
possessed different electronic properties were prepared and subjected to carbonylative cyclizations (Table 4, entries 5-8). The substituents on the enyne with different electronic natures apparently did not affect the *ee* of the carbonylative cycloadducts which is not similar to that observed in rhodium-catalyzed asymmetric PKR using aldehyde as CO source. Sterically hindered *ortho*-substituted aromatic enyne afforded low yield of the product presumably the *ortho*-methyl group hindered the coordination of yne moiety to the Rh center (Table 4, entry 9). Particularly noteworthy is that heterocyclic-substituted enyne was firstly successful transformed to its corresponding cyclopentenone (Table 4, entry 10).

These reaction conditions were also applied to other nitrogen- and carbon-tethered enynes (Table 4, entries 11-12). Moderate to good enanatioselectivies of the product were observed. However, when 1,8-enyne was applied in this cascade process, only trace amount of the desired product was obtained as judged by GC-MS analysis

4.2.6. Proposed mechanism

Figure 1 shows the suggested mechanism for Rh-catalyzed cascade decarbonylation–Pauson-Khand-type reaction. The coordination of formate followed by subsequent C-H oxidative addition generates the hydrido-Rh-acyl

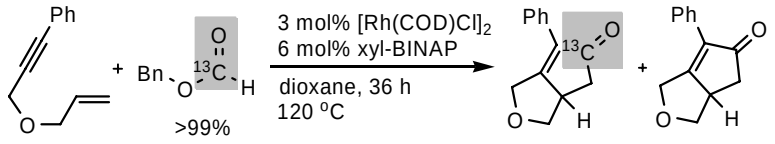
complex. After reductive elimination of ROH, the Rh carbonyl complex **A** is generated which presumably is the key intermediate of PKR. The carbonylation cycle starts from the coordination of enyne **1a** to complex **A** giving the Rh-enyne complex **B**. The chiral diphosphine ligand exerts stereo-induction to the coordinated enyne and finally gives the stereo-determining rhodacycle **C**. After insertion of CO moiety and reductive elimination of complex **D**, the desired cyclopentenone is obtained with the regenerated Rh(I) complex.



(Figure 1: Proposed mechanism for asymmetric PKR using formate as CO surrogate)

4.2.7. ^{13}C-Labeling experiment

In order to originate the CO transfer process, the ^{13}C-labeled benzyl formate (from benzyl alcohol and acetic anhydride with ^{13}C-labeled formic acid) was prepared for the decarbonylation–carbonylation sequence (Scheme 2).



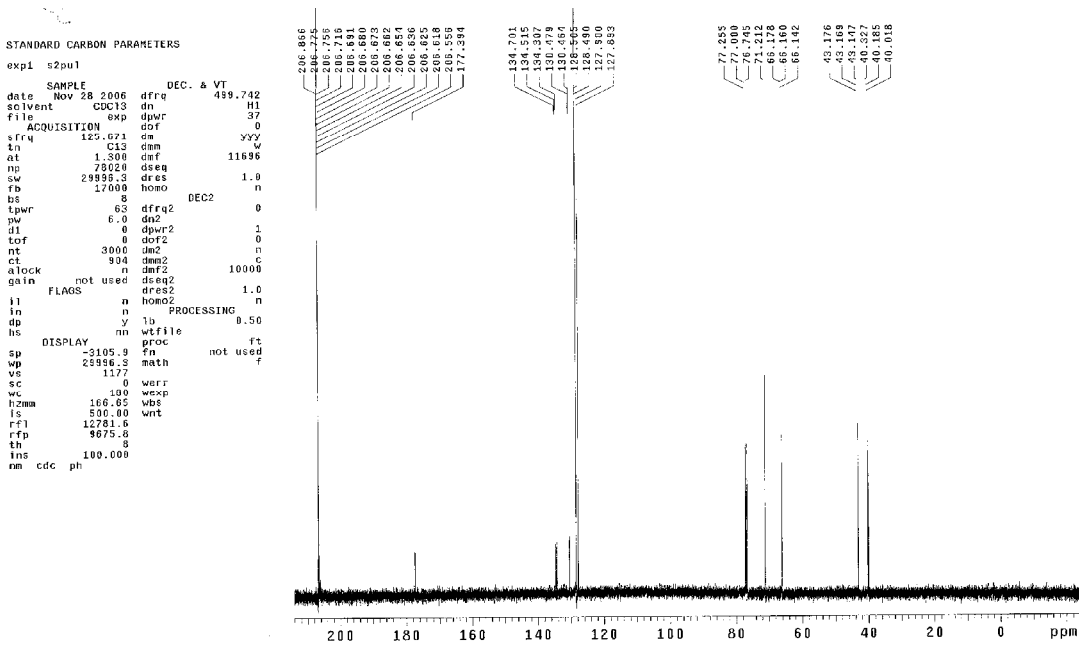
1a

under N_2 atmosphere:

^{13}C-2a : 2a
>99 : 1

(Scheme 2)

It is obvious that under the nitrogen atmosphere, over 99% of the corresponding ^{13}C-cyclopentenone was obtained as judged by NMR spectroscopy (Figure 2). These informative results show that the CO moiety for carbonylative coupling is mainly provided by the Rh-carbonyl complex **A** (Figure 1). Thus, it is feasible to apply formate as a convenient CO surrogate in direct CO transfer process



(Figure 2: ^{13}C NMR of ^{13}C-enriched 2-phenyl-7-oxabicyclo[3.3.0]oct-1-en-3-one)

4.3. Conclusion

In summary, formate was demonstrated its capability in replacing "external" gaseous carbon monoxide by transfer carbonylation using suitable Rh-diphosphine complexes. This versatile reaction was found to be a suitable cooperative partner in the cascade decarbonylation–Pauson-Khand-type cyclization. Notably, apart from the initial achiral synthesis, the asymmetric version of this dual catalysis has also been successfully achieved. Various 1,6-enynes were transformed to corresponding cyclopentenones in good enantioselectivities (up to 94% *ee*) in the presence of Rh-(*S*)-xyl-BINAP catalyst. ^{13}C-labeling experiments indicated that the CO moiety generated by the decarbonylation of formate is directly incorporated into carbonylative cyclization. To the best knowledge, it is the first example of asymmetric CO transfer carbonylation using formate ester as CO surrogate.

4.4. Experimental section

General procedures for asymmetric Pauson-Khand-type cyclization of various enynes: $[Rh(COD)Cl]_2$ (4.4 mg, 9.0 μmol), (*S*)-xyl-BINAP (16 mg, 18.0 μmol) and Teflon-coated magnetic stirrer bar (3 mm × 10 mm) were charged to a Teflon-lined screw-capped vials (or Schlenk flasks) on bench-top at room temperature. These vials were evacuated and backfilled with nitrogen (3 cycles), followed by the addition of anhydrous dioxane (0.5 mL) under nitrogen with continuous stirring for 30 mins. Enynes (0.3 mmol) and benzyl formate (1.5 mmol) were then added. The reaction mixtures were magnetically stirred at a preheated 120 °C (± 3 °C) oil bath for 3 days (reaction times were unoptimized for each substrate). The vials were allowed to reach room temperature. Diethyl ether or ethyl acetate (~2 mL) was added. The crude reaction mixtures were directly purified by column chromatography on silica gel using hexane/ethylacetate as the eluent to afford chiral bicyclic cyclopentenones. The enantiomeric excess of the products were determined by chiral HPLC analysis using Chiralcel® columns

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CHAPTER 5

Microwave-Assisted Rhodium Complex-Catalyzed Cascade Decarbonylation and Asymmetric Pauson-Khand-Type Cyclizations

5.1. Introduction

Microwave assisted organic synthesis (MAOS) drew much attractions in recent years, more than 2000 articles have been published since the first report on the use of microwave heating to accelerate reaction by the groups of Gedye and Giguere/Majetich in 1986[1,2]. There was small amount of publications about MAOS in the late 1980s and early 1990s because of the lack of controllability, reproducibility and couples with lack of basic understanding about dielectric heating. The risks associated with the flammability of organic solvents in microwave field, lack of control on the temperature and pressure produced during reaction led to slow down the development of MAOS. As our technology is becoming more advanced, scientists switched to use dedicated microwave instruments instead of modified domestic microwave in the late 1990s and publications increased dramatically.

It is believed that microwave not only able to (1) reduce chemical reaction time

but also can (2) reduce the side reaction, (3) increase product yield and (4) improve reproducibility.

5.2. Microwave theory

Microwave irradiation is electromagnetic irradiation in the frequency range of 0.3 to 300GHz. Almost all microwave reactors operate at a frequency of 2.45GHz (corresponds to a wavelength of 12.24cm) to avoid interference with telecommunication and cellular phone frequencies. Because energy of the microwave photon produced is only around 0.0016eV, even lower than the energy of Brownian motion so that it is too low to break chemical bonds and induce chemical reactions[3,4,5].

Microwave assisted organic synthesis is based on efficient heating of materials by microwave dielectric heating. It is dependent on the specific material such as solvent or reagent to absorb microwave energy and convert it into heat. If materials have dipole moment or ionic property, they will align in the applied electric field and oscillate with microwave frequency. As they are oscillated, energy will be loss in form of heat through molecular friction and dielectric loss. The amount of heat generated is directly related to ability of the matrix to align. If the dipole does not have enough time to realign, or reorients too fast with the applied field, no heating occurs[6].

The ability of substance to convert microwave irradiation into heat is commonly expressed as loss factor tanδ. tanδ = ε''/ε' where ε'' = dielectric loss which means the efficiency that electromagnetic radiation is converted to heat. ε' = dielectric constant which means the ability of molecules to be polarized by the electric field. And the loss factor of some common reagents was shown in Table 1.

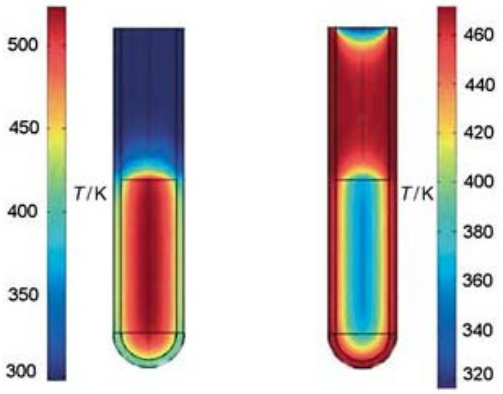
Table 1: Loss factors (tanδ) of different solvents[7]

solvent	tanδ	solvent	tanδ
Ethylene glycol	1.350	DMF	0.161
Ethanol	0.941	1,2-dichloroethane	0.127
DMSO	0.825	Water	0.123
2-propanol	0.799	Chlorobenzene	0.101
Formic acid	0.722	Chloroform	0.091
Methanol	0.659	Acetonitrile	0.062
Nitrobenzene	0.589	Ethylacetate	0.059
1-butanol	0.571	Acetone	0.054
2-butanol	0.447	Tetrahydrofuran	0.047
1,2-dichlorobenzene	0.280	dichloromethane	0.042
NMP	0.275	Toluene	0.040
Acetic acid	0.174	hexane	0.020

A high tanδ reaction medium is needed for efficient absorption and rapid heating. In general, solvents can be classified as high (tanδ > 0.5), medium (tanδ 0.1-0.5) and low microwave absorbing (tanδ < 0.1). Although a low tanδ solvent is not suitable for microwave irradiation, polar additives such as ionic liquids can be added to increase the absorbance level of the medium.

Organic synthesis is carried out by conductive heating with an external heat source such as oil bath, it is comparatively slow and inefficient method for

energy transfer as the transfer depends on the thermal conductivity of various materials such as containers, it causes temperature of reaction vessel being higher than that of reactants. Microwave irradiation transfers energy by direct coupling of microwave energy with the reactants and produces efficient internal heating within the reaction vessels. The differences can be shown in Figure 1.



(Figure 1: Differences in temperature profiles after 1min of MW irradiation (left) and treatment in oil bath (right). Microwave irradiation raises the temperature of the whole volume simultaneously (bulk heating) whereas in the oil-heated tube, reactants in contact with the vessel wall is heated up first)

Microwave effects are generally classified into thermal and non-thermal effects nowadays.

5.2.1. Thermal effects

It is mainly due to the superheating effect produced by microwave irradiation. Microwave heating can rapidly superheat methanol (tanδ = 0.659) up to 100^{o}C which is far above its boiling temperature in a sealed vessel. The superheat effect

is much more pronounced in some high tanδ solvents such as ionic liquid. And such rapid heating temperature profiles are very difficult to obtain by conventional heating. By simply applying the Arrhenius law $k=Ae^{-Ea/RT}$. Baghurst and Mingos demonstrated that the higher the reaction temperature, faster reaction rate was produced and the shorter reaction time was obtained. They reported that a transformation which required 68 days to reach 90% conversion at 27^{o}C can be obtained within 1.61 seconds under superheating at 227^{o}C. (Table 2, entry 1 versus entry 5)

Table 2: Relationship between temperature and time for a typical first order reaction

Entry	T/^{o}C	k/$^{s-1}$	Time/90% conversion
1	27	$1.55x10^{-7}$	68days
2	77	$4.76x10^{-5}$	13.4h
3	127	$3.49x10^{-2}$	11.4min
4	177	$9.86x10^{-2}$	23.4
5	227	1.43	1.61s

A = 4 x 10^{10} $mol^{-1}s^{-1}$, Ea = 100kjmol^{-1}

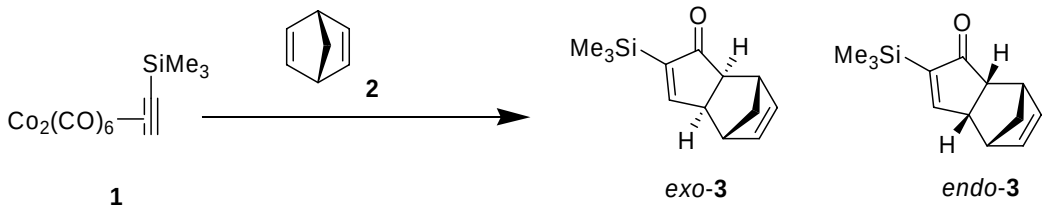
5.2.2. Non-thermal effects

Reaction rate enhancement sometimes cannot be explained by thermal effect and some scientists pointed out that the presence of an electric field leads to orientation effects of dipolar molecules and change the pre-exponential factor, A or activation energy, Ea in Arrhenius equation.[8] Although microwave effects

were classified into two main effects, they are still the subject of debate and controversy and extensive research will be needed to further investigate them and related phenomena.

5.3. Microwave assisted Pauson-Khand-type reactions

Evans *et al.* reported microwave-promoted Pauson-Khand reactions in 2002[9]. Trimethylsilylacetylene-dicobalthexacarbonyl complex (**1**) and norbornadiene (**2**) were put in sealed vessels to perform intermolecular PKR and various conditions were tested (scheme 1).



1 *exo*-**3** *endo*-**3**

(Scheme 1: Trimethylsilylacetylene-dicobalthexacarbonyl complex-catalyzed Pauson-Khand reaction under microwave irradiation by Evans *et al.*)

Table 1: Effect of solvents on the product yields and steroselectivities of PKR

Entry	Solvent	Temp./ ^{o}C	Time	%yield [c]	exo-3: endo-3 [d]
1 [a]	Toluene	90	5 min	97	95 : 5
2 [a]	DCE	90	20 min	98	> 95 : 5
3 [a]	DCE	120	200 s	93	> 95 : 5
4 [b]	DCE	180	100 s	91	95 : 5

[a] Method: 2 (5 equiv.) was added to a solution (0.25M) of 1

[b] Method: trimethylsiylacetylene (1 equiv.), cobalt octacarbonyl (0.5 equiv.) and 2 (5 equiv.) were dissolved in DCE (0.25M)

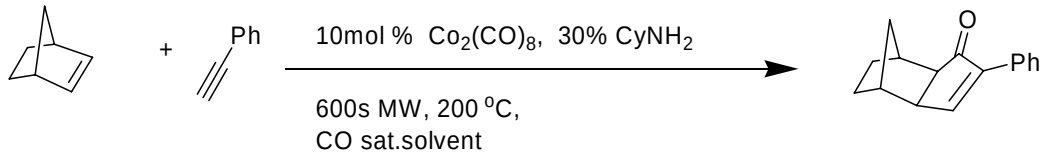
[c] Isolated yields

[d] Ratio determined by ^{1}H NMR spectroscopy

Toluene was tested to be the best solvent to give excellent yields of corresponding cyclopentenone (**3**) within only 5 minutes of microwave irradiation (Table1, entry1). However purification was very difficult because of the presence of norbornadiene derived by-products and *endo*-diastereoisomer.

Changing the toluene to 1,2-dichloroethane (DCE) increased the irradiation from 5 minutes to 20 minutes however less *endo*-diastereoisomers were produced so as to make purification easier (Table 1, entries 2,3). Toluene which has no dipole moment is known to be “transparent” to microwave energy, it means that toluene does not absorb microwave energy and hence reactants absorb microwave energy more efficiently. In the case of using DCE as solvent, it has dipole moment so that parts of the microwave energy will be absorbed and lost in solvent and hence reaction in DCE is less sensitive and clean than that in toluene. Furthermore the reaction time can be shortened by increasing temperature but concomitant pressure increases proved problematic.

Groth *et al.* reported cobalt-catalyzed Pauson-Khand reaction in CO saturated solvent under microwave irradiation[10] in 2002. They used 10 mol% of $Co_2(CO)_8$ with addition of cyclohexylamine, fivefold excess of norborene to phenylacetylene to produce cyclopentenone (scheme 2).



(Scheme 2: Co-catalyzed microwave promoted intermolecular Pauson-khand reaction in CO saturated solvent by Groth et al.)

Various solvents were screened, product yields increased as the polarity of solvents decreased and they concluded that non-polar solvents were

"transparent" to microwave irradiation so that energy can be transferred to the reactants easier (Table 2).

Table 2: Effect of solvents on product yields

Entry	Solvent	Dielectric constant	%yield [a]
1	DMSO	46.7	5
2	Acetonitrile	37.5	16
3	Dichloromethane	9.0	21
4	THF	7.6	38
5	1,2-dimethoxyethane	7.2	41
6	Diglyet [b]	5.7	44
7	Toluene	2.4	44
8	Toluene	2.4	43 [c]
9	Dioxane	2.2	41
10	Heptane	1.9	20

[a] Isolated yield

[b] Diethylene glycol diethyl ether

[c] No CO saturation

Interestingly, they observed the decomposition of cobalt catalyst at higher temperature, lowering the reaction temperature led to increased yields and the improvement was much more significant in microwave transparent solvent.

The cyclohexylamine additive was believed to replace carbon monoxide as a ligand and promoted additional ligand liberation by stabilizing the corresponding coordinative unsaturated complex so that later on the free site was able to coordinate with olefin to perform cycloaddition. Therefore concentration of cyclohexylamine should affect the product yields. And they demonstrated that using 20 mol% $Co_2(CO)_8$ and 1.2 equivalents of cyclohexylamine can afford the corresponding adducts in good yield (81%) within 5 minutes microwave

irradiation.

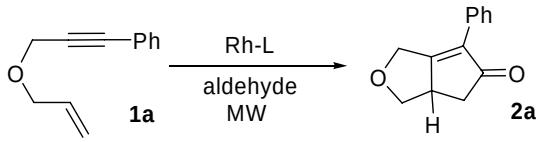
Although considerable interests were drawn to microwave assisted organic synthesis and enantioselective Pauson-Khand-type reaction in recent decades, the microwave-assisted catalytic enantioselective Pauson-Khand-type reaction is still sporadically studied. Hence I would like to examine the capability of microwave irradiation on asymmetric Pauson-Khand-type cyclizaition.

5.4. Results and discussion

5.4.1. Microwave-assisted decarbonylation of aldehyde and cascade asymmetric Pauson-Khand-type reaction

To examine the feasibility of decarbonylation of aldehdye under microwave irradiation to generate “CO” moiety for further carbonylative cyclization. Stoichiometric amount of $[Rh(COD)Cl]_2$/dppp complex with cinnamaldehyde were placed in the microwave reactor at 100 °C for 10 mins. Styrene (>90% from GC-MS, by decarbonylation of cinnamaldehyde) was observed. These preliminary results showed the potential of catalytic decarbonylation in microwave-assisted reaction conditions.

Table 1: Investigations on ligand and CO source effects in microwave-assisted cascade PKR[a]



Entry	Ligand	CO source	% yield [b]
1	Nil	cinnamylaldehyde	trace
2	dppe	cinnamylaldehyde	22
3	dppp	cinnamylaldehyde	75
4	dppp[c]	cinnamylaldehyde	83
5	dppf	cinnamylaldehyde	12
6	Ph_3P	cinnamylaldehyde	<5
7	dppp	CO gas [d]	15
8	dppp	*p*-Cl-benzaldehyde	44
9	dppp	benzaldehyde	55
10	dppp	*p*-OMe-benzaldyhde	48
11	dppp	*n*-nonylaldehyde	36

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (3 mol%), ligand (6 mol%), enyne (0.3 mmol), aldehyde (0.45 mmol) and *tert*-amyl alcohol (1.0 mL) were placed in MW-vials under nitrogen and the reaction were subjected at 120 °C for 45 mins under microwave-conditions.

[b] Isolated yield.

[c] $[Rh(COD)Cl]_2$ (3 mol%), ligand (6.6mol%) were used

[d] 1 atm pressure CO was applied.

5.4.1.1. Ligands screening

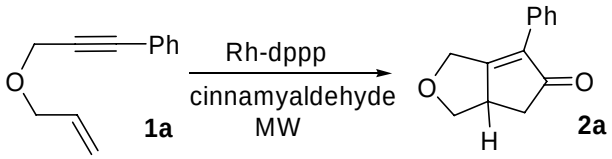
Followed the encouraging results of deacarbonylation of aldehyde, I would like to examine the feasibility of microwave-assisted Pasuon-Khand-type cyclization. Various kinds of commercially available phosphine ligands were subjected to the reaction and the oxygen-tethered enyne **1a** was chosen as the prototypical substrate (Table 1). Control experiment revealed that phosphine ligand was necessary for the successful tandem transformation (Table 1, entries 1-5). Diphosphine ligands (e.g. dppp) were found to be superior to monophosphine

ligand, PPh_3 (Table 1, entries 3 and 6).

5.4.1.2. Aldehydes screening

It is interesting to show that the CO surrogates (aldehydes) were even better than gaseous CO as the CO source in the microwave-assisted carbonylative reactions (Table 1, entries 7-11). α,β-Unsaturated aldehyde gave the best results (entry 3) which is similar to the results obtained by conventional heating[11]. Though the decarbonylation of aliphatic aldehyde was observed, the efficiency was inferior to that found in aromatic aldehydes (Table 1, entry 11).

Table 2: Effect of solvent on product yield



Entry	Solvent	% yield [b]
1	cyclohexane	43
2	toluene	67
3	dioxane	70
4	*tert*-amyl alcohol	75
5	acetonitrile	58
6	solventless	52

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (3 mol%), ligand (6 mol%), enyne (0.3 mmol), aldehyde (0.45 mmol) and solvent (1.0 mL) were placed in MW-vials under nitrogen and the reaction were subjected at 120 °C for 45 mins under microwave-conditions.

[b] Isolated yield.

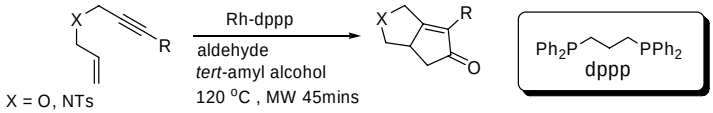
5.4.1.3. Solvents screening

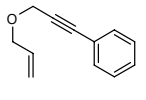
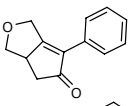
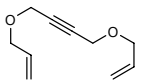
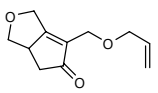
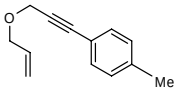
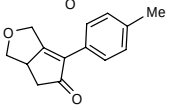
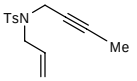
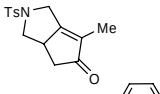
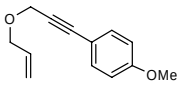
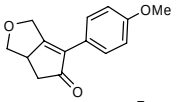
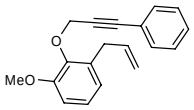
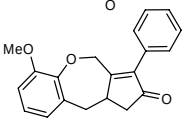
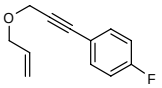
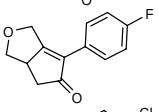
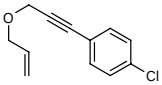
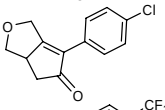
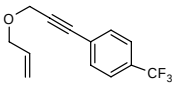
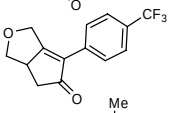
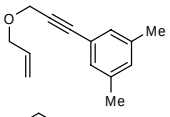
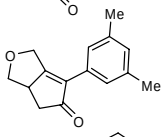
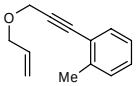
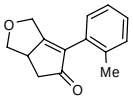
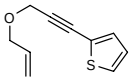
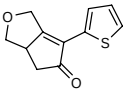
To further optimize the catalytic system, solvent with different polarities and loss factor (tanδ) were examined to see if their polarities affect the rate and yield of

reaction. However no significant differences were observed. Non-polar cyclohexane gave poor yield (Table 2, entry 1) when toluene, dioxane and acetonitrile gave moderate yields (Table 2, entries 2, 3 and 5). Branched *tert*-amyl alcohol gave the best yield among screened solvents (Table 2, entry 4). Interestingly, this catalytic system afforded desired cyclopentenone in moderate yield (Table 2, entry 6) under solventless condition and it is presumably due to the polar aldehyde can oscillate with the microwave irradiation and transfer the energy to the catalytic system.

5.4.1.4. Scope and limitation of substrates on Rh-dppp catalyzed decarbonylation of aldehyde and cascade PKR

Table 3: Microwave assisted Rh-catalyzed cascade Pauson-Khand-type reaction [a]



entry	substrate	product	% yield [b]	entry	substrate	product	% yield [b]
1			83	11 12 [c]			36 trace
2			81	13			34
3			85	14			trace
4			78				
5			87				
6			66				
7			78				
8			16				
9 10 [c]			73 trace				

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (3 mol%), ligand (6.6 mol%), enyne (0.3 mmol), cinnamaldehyde (0.45 mmol) and *tert*-amyl alcohol (1.0 mL) were placed in MW-vials under nitrogen and the reaction were subjected at 120 °C for 45 mins under microwave-conditions.

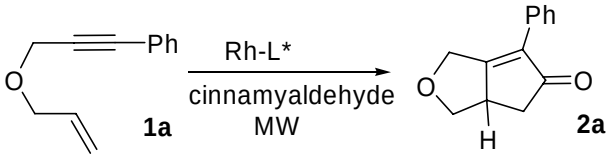
[b] Isolated yields.

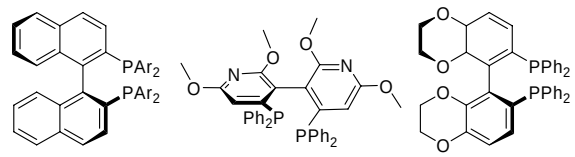
[c] Under conventional heating at 120 °C for 36 h.

To further probe the effectiveness of the microwave-assisted dual catalysis system. Various oxygen-tethered 1,6-enynes were subjected to the

Pauson-Khand-type cyclization (Table 3). Electronically different aromatic enynes were found to be compatible in these reaction conditions to furnish the corresponding cyclopentenones (Table 3, entries 1-7). Sterically hindered *ortho*-substituted aromatic enyne afforded low yield of the product presumably the *ortho*-methyl group hindered the coordination of yne moiety to the Rh center (Table 3, entry 8). Surprisingly, heterocyclic thiophenyl-enyne was firstly transformed to desired product under microwave-assisted conditions using aldehyde as CO surrogate (entry 9). In contrast, only trace amount of product was obtained under conventional oil-bath heating (Table 3, entry 10). Moreover, significant amount of substrate decomposition was observed from GC-MS analysis. Besides heterocyclic enyne, allyloxy-enyne was also first transformed to its desired cycloadducts (Table 3, entry 11). However 1,8-enyne was still unsuccessful in this transformation and ~80% of starting material was recovered (Table 3, entry 14).

Table 4: Investigations on chiral ligands on microwave assisted asymmetric PKR

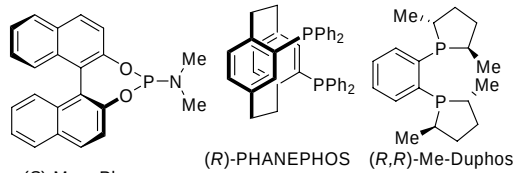




Ar = Ph, (*S*)-BINAP
Ar = *p*-tol, (*S*)-*p*-tol-BINAP
Ar = 3,5-xylyl, (*S*)-xyl-BINAP

(*S*)-P-Phos

(*S*)-BisbenzodioxanPhos
(*S*)-SYNPHOS



(*S*)-MonoPhos

(*R*)-PHANEPHOS

(*R*,*R*)-Me-Duphos

entry	ligand	% yield [b]	% *ee* [c]
1	(*S*)-BINAP	30	85
2	(*S*)-tol-BINAP	12	90
3	(*S*)-xyl-BINAP	trace	nd
4	(*R,R*)-Me-DuPhos	trace	nd
5	(*S*)-PHANEPHOS	trace	nd
6	(*S*)-PPhos	trace	nd
7	(*S*)-BisbenzodioxanPhos	63	86
8 [d]	(*S*)-MonoPhos	trace	nd

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (3 mol%), ligand (6.6 mol%), enyne (0.3 mmol), cinnamaldehyde (0.45 mmol) and *tert*-amyl alcohol (1.0 mL) were placed in MW-vials under nitrogen and the reaction were subjected at 100 °C for 45 mins under microwave-conditions.

[b] Isolated yields.

[c] Average of two runs from chiral HPLC analysis using Daicel Chiracel® AS-H and AD-H columns (0.46 cm × 25 cm).

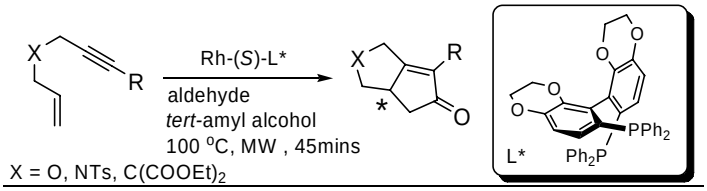
[d] $[Rh(COD)Cl]_2$ (3 mol%), (*S*)-MonoPhos (12 mol%) were used

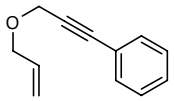
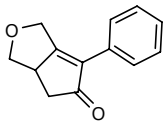
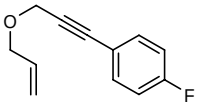
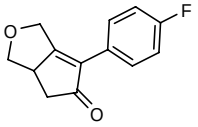
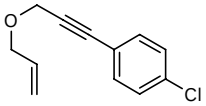
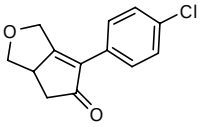
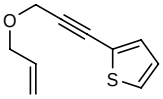
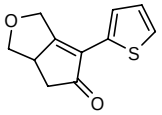
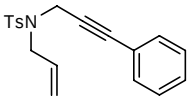
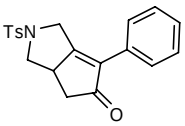
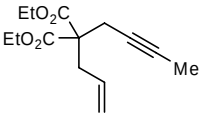
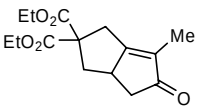
5.4.1.5. Effect of chiral ligands on product yields and enantiomeric excess

With promising results on achiral microwave assisted Pasuon-Khand-type reaction, it is nature to explore to the enantioselective version of this

transformation. Commonly use chiral phosphine ligands were examined in place of dppp (Table 4). (*S*)-BINAP and (*S*)-tol-BINAP can catalyze the cyclization to afford desired products, steric effect of ligands was crucial to increase the stereochemical communication to increase the enantioselectivities of the products (85% to 90%). (*S*)-PPhos, (*R*,*R*)-Me-DuPhos failed to catalyze the reaction to give the cycloadducts. Monodentate (*S*)-MonoPhos failed to afford the cyclopentenone which resembles to those results in conventional heating, chiral bidentate phosphine ligands generally gave better yields and %*ee* values in Pauson-Khand-type reaction. (*S*)-BisbenzodioxanPhos provided the best results in terms of product yield and enantioselectivity (63%, 86%*ee*) among those examined ligands.

Table 5: Microwave assisted asymmetric Rh-BisbenzodioxanPhos-catalyzed cascade Pauson-Khand-type reaction [a]



entry	substrate	product	% yield [b]	%*ee* [c]
1			73	89 85[d]
2			52	87
3			73	82 49 [d]
4			58	90
5			53	80 65 [d]
6			40	89 77 [d]

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (3 mol%), ligand (6.6 mol%), enyne (0.3 mmol), cinnamaldehyde (0.45 mmol) and *tert*-amyl alcohol (1.0 mL) were placed in MW-vials under nitrogen and the reaction were subjected at 100 °C for 45 mins under microwave-conditions.

[b] Isolated yields.

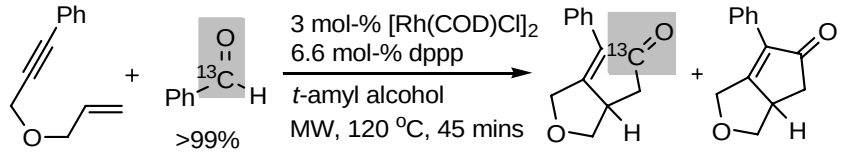
[c] Average of two runs from chiral HPLC analysis using Daicel Chiracel® AS-H and AD-H columns (0.46 cm × 25 cm).

[d] Reactions were performed under conventional heating at 100 °C for 36 h.

Electronically different aromatic enynes were subjected to the reaction and corresponding cyclopentenones were obtained in moderate yields and %*ee* values. Heteocyclic thiophenyl-enyne was first transformed to its optical active cycloadducts in good %ee value (up to 90%*ee*). Besides oxygen-tethered

substrates, nitrogen and ester-tethered substrates were also converted to their corresponding products in moderate to good %*ee* values. Surprisingly, microwave wave assisted asymmetric Pauson-Khand reaction generally provided cyclopentenones with better enantiomeric excess than those obtained in conventional heating.

5.4.1.6. ^{13}C-labeling experiment



1a

	^{13}C-2a : 2a
under N_2 atmosphere:	>99 : 1
under CO atmosphere:	>99 : 1

(Scheme 3: ^{13}C-labeling Rh-dppp catalyzed asymmetric PKR)

In order to originate the microwave-promoted CO transfer process, ^{13}C-labeled benzaldehyde was applied for the decarbonylation–carbonylation sequence (Scheme 3). When the reactions were placed either under the nitrogen or CO atmosphere, over 99% of the corresponding ^{13}C-cyclopentenone was obtained as judged by MS and NMR spectroscopy. These informative results indicated that the CO moiety for carbonylative coupling is mainly provided by the decarbonylation of aldehyde.

5.4.1.7. Conclusion

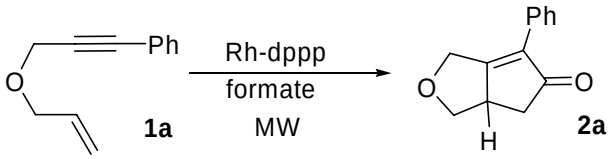
The first successful microwave-assisted cooperative decarbonylation of aldehyde and enantioselective Pauson-Khand-type cyclization was demonstrated. The microwave energy considerably increased the rate of reaction in both decarbonylation and carbonylative cyclization so that can shorten the reation time from 36 hours into 45 minutes. Substrate such as thienyl enyne significantly showed better yield in microwave conditions. Notably, the reaction conditions in this sequential process can be rendered enantioselectivity. Higher enantioselectivities were observed than conventional heating with product %*ee* up to 90%.

5.4.2. Microwave-assisted aqueous Pauson-Khand-type cycloaddition using formate as CO surrogate

Follow the promising results of catalytic decarbonylation of aldehyde and cooperative Pauson-Khand-type cycloaddition under microwave irradiation. I attempted to apply microwave irradiation to fasten the Pauson-Khand reaction using formate as CO surrogate as some drawbacks reported that it is not a considerable catalytic system in terms of reaction time.

Initial screenings were triggered to accomplish the cascade decabonylation-carbonylation sequence under an aqeuous medium in the presence of microwave energy. 1,3-Bis(diphenylphosphino)propane (dppp) showed the best result in both of the sequential processes. Hence the Rh-dppp complex was applied to further examine the efficiency of the condensed CO source (Table 1).

Table 1: Initial screening of aqueous PKR with formate esters as CO source [a]



Entry	Formate	Solvent	Temp./°C	% yield [b]
1[c]	benzyl	H_2O	130	33
2	benzyl	H_2O	130	45
3[d]	benzyl	H_2O	130	30
4	benzyl	H_2O	100	13
5	*p*-MeObenzyl	H_2O	130	35
6	*p*-Clbenzyl	H_2O	130	60
7	*p*-Clbenzyl	nil	130	trace
8	*p*-CF_3benzyl	H_2O	130	32

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (5 mol%), ligand (11 mol%), enyne (0.3 mmol), formate (1.5 mmol) and water (1.0 mL) were placed in MW-vials under nitrogen and the reaction were subjected at 130 °C for 50 mins under microwave irradiation.

[b] Isolated yield.

[c] benzyl formate (0.9 mmol) was used.

[d] Water (0.5 mL) was used

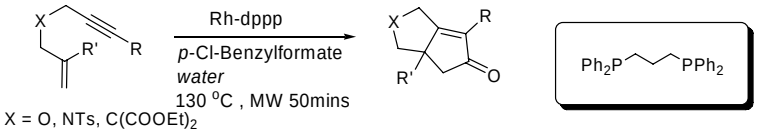
5.4.2.1. Electronic effects of formates on decarbonylation

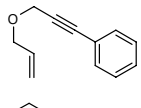
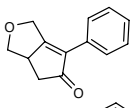
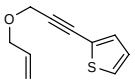
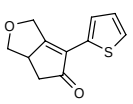
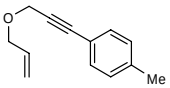
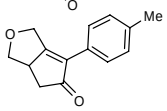
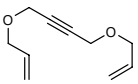
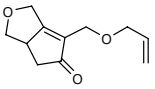
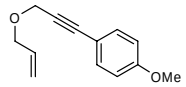
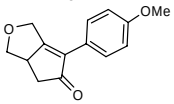
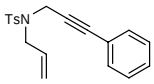
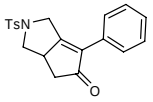
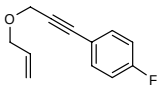
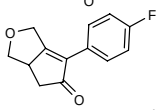
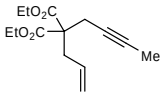
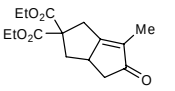
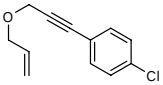
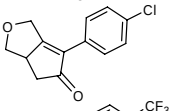
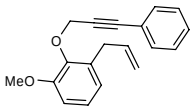
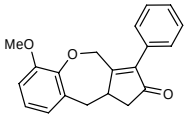
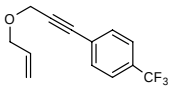
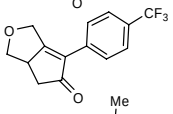
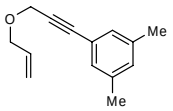
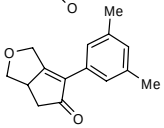
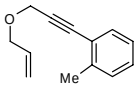
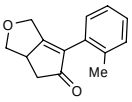
To demonstrate the electronic effect of formate on the decarbonylation, electronically different benzyl formates were prepared according to literature procedures [12] and subjected to the reaction. Electron-donating *para*-Methoxybenzyl formate can be decarbonylated to provide CO moiety for the carbonylatve cyclization but its product yield was inferior to the benzyl formate vice versa electron-withdrawing *para*-Chlorobenzyl formate provided the highest isolated yield (60%) of the desired product among screened formats

(entry 6). The reaction temperature at 130 °C was required to drive the tandem reaction successfully (entries 2 *vs*. 4). In the absence of water solvent, only a trace amount of the product was obtained (entries 6 *vs*. 7).

5.4.2.2. Scope and limitation of substrates on microwave-assisted aqueous Pauson-Khand-type reaction

Table 2: Rh-catalyzed aqueous PKR with formate esters as CO source [a]



entry	substrate	product	% yield[b]	entry	substrate	product	% yield[b]
1			60	11			72
2			43[c]	12			59[c]
3			70	13			trace
4			61[c]				
5			52	14			53
6			41	15			48
				16			40[c]
7			47	17			trace
8			27				
9			73				
10			20				

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (5 mol%), ligand (11 mol%), enyne (0.3 mmol), *p*-chlorobenzyl formate (1.5 mmol) and water (1.0 mL) were placed in MW-vials under nitrogen and the reactions were subjected at 130 °C for 50 mins under microwave irradiation.

[b] Isolated yield.

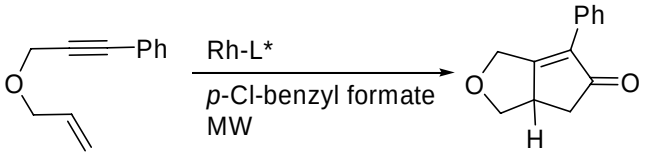
[c] Reactions performed under conventional heating (120°C, 3 days).

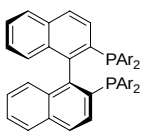
To investigate effectiveness of the microwave-assisted aqueous dual catalysis, we surveyed various oxygen-tethered 1,6-enynes for the Pauson-Khand-type

cycloaddition (Table 2). Substituted aromatic enynes were tolerable under these reaction conditions to furnish the corresponding cyclopentenones (Table 2, entries 1-9). Although no significant electronic effect of aromatic enyes on the product yield was observed, performances of electron-withdrawing aromatic enynes were generally inferior to electron-donating aromatic enynes (Table 2, entries 6-8). Sterically congested *ortho*-tolyl enyne afforded low yield of the product presumably the *ortho*-methyl group hindered the coordination of yne moiety to the metal center (Table 2, entry 10). Thiophenyl-enyne was successfully transformed to the desired product under aqueous microwave-assisted conditions (Table 2, entry 11). In contrast, only a trace amount of desired product was obtained under conventional oil-bath heating (Table 2, entry 12), along with significant amount of substrate decomposition as judged by GC-MS analysis. Dienyne and 1,8-enyne were unsuccessful in this transformation and ~80% of starting material were recovered (Table 2, entries 10 and 13). This catalytic system can be also applied to *N*- and *C*-tethered enynes and moderate cyclopentenones were obtained. (Table 2, entries 14-16)

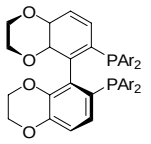
Furthermore this catalytic system can be also explore to the asymmetric Pasuon-Khand-type cyclization by changing dppp to chrial diphosphine ligands[13] (Table 3).

Table 3: Microwave-assisted asymmetric aqueous Pauson-Khand-type cyclization [a]

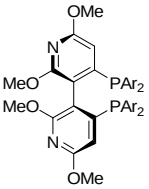




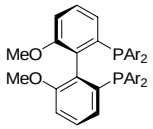
Ar = Ph, (*S*)-BINAP, **1**
Ar = *p*-tol, (*S*)-tol-BINAP, **2**
Ar = 3,5-xylyl, (*S*)-xylyl-BINAP, **3**



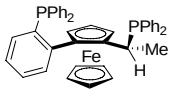
(*S*)-BisbenzodioxanPhos, **4**



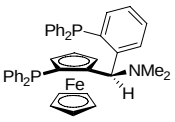
Ar = Ph, (*S*)-P-Phos, **5**
Ar = 3,5-xylyl, (*S*)-xylyl-P-Phos, **6**



Ar = Ph, (*S*)-MeO-BIPHEP, **7**
Ar = 3,5-Di-*t*-Bu-4-MeO-C_6H_2, (*S*)-**8**



Walphos, **9**



Taniaphos, **10**

entry	ligand, L*	yield/%[b]	*ee*/%
1	(*S*)-BINAP, **1**	23	89
2	(*S*)-tol-BINAP, **2**	30	89
3	(*S*)-xylyl-BINAP, **3**	32	87
4	(*S*)-BisBenzodioxanPhos, **4**	42	93
5	(*S*)-Phos, **5**	<5	60
6	(*S*)-xyl-PPhos, **6**	72	84
7	(*S*)-MeO-BIPHEP, **7**	55	91
8	(*S*)-**8**	27	98
9	(*R,R*)-Walphos, **9**	no rxn	n.d.
10	(*R,S*)-Taniaphos, **10**	no rxn	n.d.

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (5 mol%), L* (11 mol%), enyne (0.3 mmol), p-chlorobenzyl formate (1.5 mmol) and water (1.0 mL) were placed in MW-vials under nitrogen and the reaction were subjected at 130 °C for 50 mins under microwave-conditions.

[b] Isolated yield.

BINAPs provided good enantioselectivities, although poor yields were obtained (entries 1-3). BisbenzodioxanPhos[14] **4** (SYNPHOS)[15] showed better yield and enantioselectivity than BINAPs (entry 4). Xyl-PPhos[16] **6** gave the highest yield

of the cyclopentenone product (entry 6). The modified MeO-BIPHEP **8** furnished the product in excellent enantioselectivity (98%), which is the highest *ee* achieved so far for the *O*-tethered aromatic enyne (entry 8). Chiral ferrocenyl ligands such as Walphos **9** and Taniaphos **10** were found to be inferior in these aqueous cascade process (entries 9-10).

5.4.2.3. Conclusion

In summary, various kind of oxygen-, nitrogen- and carbon-tethered enynes were successfully transformed to their corresponding cyclopentenones. The decarbonylation of formate and cooperative carobnylative cyclization was successfully accelerated under microwave irradiation and the reaction time was shortened from 3 days to 50 minutes. Furthermore excellent product enantioselectivities (up to 98%) were obtained with axially chiral bidentate diphosphine ligand, (*S*)-xyl-PPhos.

5.4.2.4. Experimental Section

General procedures for Pauson-Khand-type cyclization of various enynes: $[Rh(COD)Cl]_2$ (7.4 mg, 15.0μmol), DPPP (13.6 mg, 33.0 μmol) were charged into the reaction vial on bench-top at room temperature. The reaction vial was then transferred to the dry box for being evacuated and backfilled with nitrogen (3 cycles). *p*-Cl-benzylformate (255 mg, 1.5 mmol, 5 equivalents with respected to enyne) was added under nitrogen atmosphere and the reaction mixture was stirred for 1 hour. Enynes (57mg, 0.3 mmol) and water (1.0 mL) were charged into the reaction vial. The vial was air-tighten by a special designed lid and transferred to the microwave oven. The reaction mixtures were heated to 130 °C by microwave irradiation with power of 500 watts for 50 minutes. The vials were allowed to reach room temperature. Diethyl ether or ethyl acetate (~2 mL) was added. The crude reaction mixtures were directly purified by column chromatography on silica gel using hexane/ethyl acetate as the eluent to afford chiral bicyclic cyclopentenones. For the asymmetric catalytic Pauson-Khand-type cyclization.. The enantiomeric excess of the products were determined by chiral HPLC analysis using Chiralcel® columns.

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CHAPTER 6

Summary

In conclusion, aldehyde and formate were found to be carbon monoxide surrogate for Pauson-Khand-type carbonylative cyclization process. With using biaryl diphoshine liagnd, BisbenzodioxanPhos (SYN-Phos), rhodium can decarbonylate aldehyde effectively in homogenous conditions to provide CO moiety for the carbonylative cyclization with enynes to provide cyclopentenones in good enantiomeric excess (% *ee*) values and chemical yields. Meanwhile rhodium-xyl-BINAP complex can also decarbonylate formate and transfer the CO moiety to the Pauson-Khand-type cyclization to provide cyclopentenones in moderate yields and good *ee* values however it takes quite long time to complete the reaction. To the best knowledge it is the first example of rhodium-catalyzed cooperative decarbonylation of formate and asymmetric Pauson-Khand-type cycloadditon.

Following the encouraging results of rhodium-catalyzed Pauson-Khand reaction, iridium was examined and iridium-BINAP complex was found to catalyze decarbonylation of aldehyde (*n*-nonylaldehyde) and cascade carbonylative cycloaddition, results in excellent *ee* values but the reactivity was lower than rhodium-catalyzed Pauson-Khand reaction.

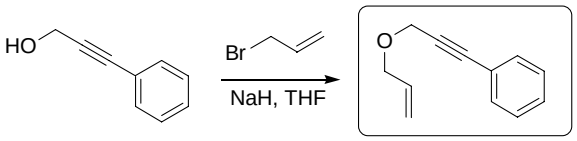
Although aldehyde and formate were found to substitute carbon monoxide for the Pauson-Khand reaction, it generally takes several days to complete the reaction (36 hours for aldehyde, 3 days for formate) and hence makes the cooperative decaronylation of carbonyl compounds and Pasuon-Khand-type cyclization become impractical and undesirable processes. Therefore microwave was attempted to accelerate the reactions and satisfactory results were obtained. Under microwave irradiation, both decarobonylation of aldehyde and formate/cascade asymmetric Pauson-Khand reaction can be completed within an hour to provide cycloadducts in moderate product yields and the enantioselectivies were retained.

Although the decarbonylation of carbonyl compounds now provides us an attractive protocol to generate safe CO sources for carbonylative reactions, examples of carbonylative cyclization between diynes, alkynals and allenes were rarely studied. It is generally believed that biaryl diphosphine ligands (such as BINAP, P-Phos and BisbenzodioxanPhos) were necessary to obtain good product yields and *ee* values in Pauson-Khand-type reaction. Recently P,S and P,N ligands were examined for the asymmetric Pauson-Khand reaction and it may be one of the developing areas in future.

Appendix

Preparation and characterization data of enyne substrates

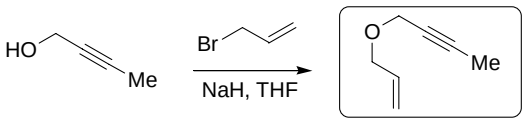
3-(Allyloxy)-1-phenyl-1-propyne[1]



General procedures of condensation of arylpropargyl alcohol with allyl bromide: To a solution of 3-phenyl-2-propyn-1-ol (5.28 g, 40 mmol) in freshly distilled THF (80 mL) was added NaH (1.44 g, 60 mmol, freshly pre-washed with dry hexane) portionwise under nitrogen atmosphere at 0 ºC. The white suspension was slowly warmed to room temperature and stirred for 2 hours. The reaction mixture was then cooled to 0 °C and allyl bromide (6.8 mL, 80 mmol) was added dropwise. After complete addition, the reaction was warmed to room temperature and further stirred for 2 hours. Water (~30 mL) was slowly added and the aqueous layer was extracted with diethyl ether (3 × ~100 mL). The combined organic layers were washed with water (~50 mL), brine (~50 mL) and dried over sodium sulfate. Solvent was removed by rotary evaporation and the light yellow crude product was purified by vacuum distillation (bp. 101-102 °C, 5 mmHg) to give title compound as a colorless liquid (6.53 g, 95% yield). R_f = 0.2

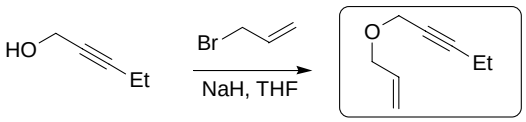
(hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30-7.43 (m, 5H), 6.02 (tdd, *J* = 17.0 Hz, 10.0 Hz, 5.5 Hz, 1H), 5.38 (dd, *J* = 17.0 Hz, 2.0 Hz, 1H), 5.27 (dd, *J* = 10.0 Hz, 2.0 Hz, 1H), 4.39 (s, 2H), 4.17 (dd, *J* = 5.5 Hz, 1.5 Hz, 2H); IR (neat, cm^{-1}) 3080, 3019, 2982, 2938, 2849, 2237, 1954, 1881, 1647, 1598, 1571, 1489, 1442, 1424, 1354, 1256, 1124, 1081, 1027, 991, 964, 925, 757, 691, 626, 549, 585, 538, 525; MS(EI) *m/z* (relative intensity) 172 (M^+, 20), 131 (100).

4-(Allyloxy)-2-butyne[2]



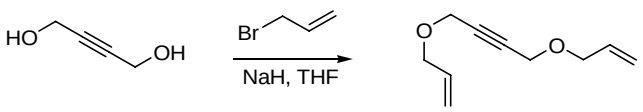
The general procedures of condensation of arylpropargyl alcohol with allyl bromide were followed: 2-Butyn-1-ol (4.0 g, 57.1 mmol), NaH (2.1 g, 87.5 mmol, prewashed with dry hexane), allyl bromide (9.7 mL, 115 mmol) and freshly distilled THF (200 mL) were used to obtain the title compound as colorless liquid (5.5 g, 88% yield). General procedure workup and purified by vac-transfer. R_f = 0.2 (hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.90 (tdd, *J* = 17.0 Hz, 10.0 Hz, 5.5 Hz, 1H), 5.28 (dd, *J* = 17.0 Hz, 2.0 Hz, 1H), 5.19 (dd, *J* = 10.0 Hz, 2.0 Hz, 1H), 4.10 (q, *J* = 2.5 Hz, 2H), 4.04 (d, *J* = 5.5 Hz, 2H), 1.85 (t, *J* = 2.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.1, 117.5, 82.3, 75.0, 70.4, 57.6, 3.5; MS(EI) *m/z* (relative intensity) 110 (M^+, 10), 69 (100).

5-(Allyloxy)-3-pentyne[2]



The general procedures of C-O bond formation were followed: 3-Pentyn-1-ol (4.2 g, 50 mmol), NaH (1.8 g, 75 mmol, prewashed with dry hexane), allyl bromide (8.5 mL, 100 mmol) and freshly distilled THF (150 mL) were used to obtain the title compound as a colorless liquid (5.3 g, 85% yield). Purification was conducted by distillation under reduced pressure (30-33 °C, 5 mmHg). R_f = 0.2 (hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.91 (tdd, *J* = 17.0 Hz, 10.0 Hz, 5.5 Hz, 1H), 5.31 (dd, *J* = 17.0 Hz, 2.0 Hz, 1H), 5.20 (dd, *J* = 10.0 Hz, 2.0 Hz, 1H), 4.12 (t, *J* = 2.5 Hz, 2H), 4.04 (d, *J* = 5.5 Hz, 2 H), 2.21-2.25 (m, 2H), 1.14 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 133.1, 117.6, 82.5, 75.1, 70.5, 57.7, 11.8, 9.5; IR (neat, cm^{-1}) 3078, 2978, 2938, 2851, 2289, 2223, 1649, 1454, 1424, 1357, 1316, 1137, 1084, 999, 926, 748, 650, 563; MS(EI) *m/z* (relative intensity) 125 (M^+, 15), 84 (100).

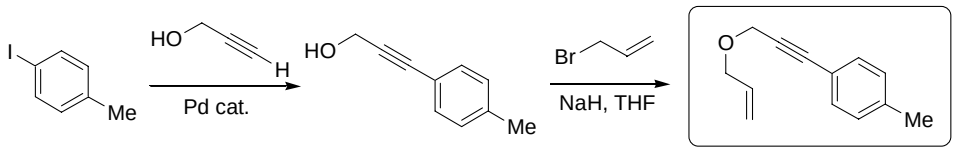
1,3-Diallyloxy-2-butyne



2-Butyne-1,4-diol (0.5 g, 6.0 mmol), NaH (288 mg, 12.0 mmol, prewashed with

dry hexane), allyl bromide (1.12 mL, 13.0 mmol) and freshly distilled THF (10 mL) were used to afford the desired product as a colourless liquid (1.16 g, 94% yield). Purification of crude product was conducted by filtered over a short silica pad followed by flash column chromatography on silica gel using hexane/ethyl acetate (2:1) as eluent. R_f = 0.5 (hexane/ethyl acetate = 2:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.90 (m, 2H), 5.30 (dt, *J* = 1.5 Hz, 17Hz, 2H), 5.21 (dt, *J* = 1.5 Hz, 10.5, 2H), 4.20 (d, *J* = 1.5 Hz, 4H), 4.05 (dd, *J* = 1.5 Hz, 6 Hz, 4H); MS(EI) *m/z* (relative intensity) 166 (M^+, 10), 107 (100);

3-(Allyloxy)-1-(4-methylphenyl)-1-propyne[3]



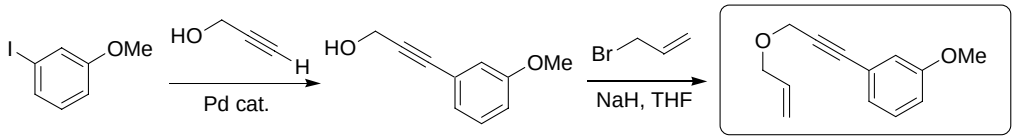
The procedure of Sonogashira coupling of propagyl alcohol with ArI were used: 4-Iodotoluene (10.9 g, 50 mmol), $Pd(PPh_3)_2Cl_2$ (3 mol%), CuI (6 mol%), piperidine (8.4 g, 100 mmol), propagyl alcohol (3.07 mL, 52 mmol) and freshly distilled toluene (50 mL) were charged into a round-bottom flask with Teflon inter-key under nitrogen. The resulting dark brown reaction mixture was stirred at 30-35 °C for 3 hours under nitrogen (ArI was completely consumed as judged by GC analysis). The 3-(4-methylphenyl)-2-propyn-1-ol[4] (5.26 g, 72% yield)

was afforded as a light brown solid. Purification was conducted by filtered the reaction mixture over a silica pad (5 cm × 5 cm), and purified by flash column chromatography on silica gel using dichloromethane as eluent. R_f = 0.5 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.49 (s, 2H), 3.23 (brs, 1H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.2, 131.3, 128.6, 119.3, 86.5, 85.3, 51.2, 21.0; MS(EI) *m/z* (relative intensity) 146 (M^+, 100); HRMS cald. for $C_{10}H_{10}O$ 146.07316, found 146.07311.

The general procedures of condensation of arylpropargyl alcohol with allyl bromide were followed: 3-(4-Methylphenyl)-2-propyn-1-ol[4] (1.46 g, 10 mmol), NaH (360 mg, 15 mmol, prewashed with dry hexane), allyl bromide (1.7 mL, 20 mmol) and freshly distilled THF (20 mL) were used to afford 3-(allyloxy)-1-(4-methylphenyl)-1-propyne as a light yellow liquid (1.78 g, 96% yield). Purification was conducted by distillation under reduced pressure (130-133 °C, 3 mmHg). R_f = 0.2 (hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.92-6.00 (m, 1H), 5.33 (dd, *J* = 17.0 Hz, 1.0 Hz, 1H), 5.23 (dd, *J* = 17.5 Hz, 1.0 Hz, 1H), 4.38 (s, 2H), 4.13 (d, *J* = 5.0 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.5, 137.4, 132.0, 128.8, 119.3, 115.1, 89.4, 85.5, 72.2, 57.4, 20.1; IR (neat, cm^{-1}) 3080,

3028, 2982, 2921, 2851, 2243, 1910, 1649, 1509, 1442, 1424, 1354, 1260, 1123, 1080, 991, 926, 817, 666, 558, 526; MS(EI) *m/z* (relative intensity) 186 (M^+, 15), 145 (100); HRMS cald. for $C_{13}H_{14}O$ 186.10447, found 186.10451.

3-(Allyloxy)-1-(3-methoxyphenyl)-1-propyne[3]

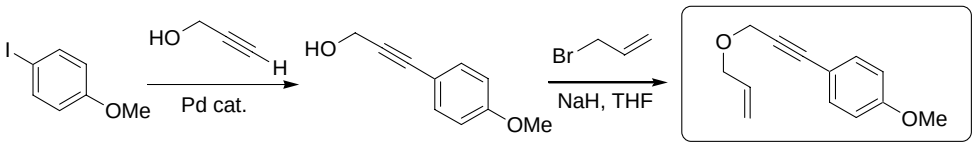


The general procedures for Sonogashira coupling of propagyl alcohol with ArI were used: 3-Iodoanisole (11.7 g, 50 mmol), $Pd(PPh_3)_2Cl_2$ (3 mol%), CuI (6 mol%), piperidine (8.4 g, 100 mmol), propagyl alcohol (3.07 mL, 52 mmol) and freshly distilled toluene (50 mL) were used to afford 3-(3-methoxyphenyl)-2-propyn-1-ol[5] (5.91 g, 73% yield) as a light yellow viscous liquid. Purification was conducted by filtered the reaction mixture over a silica pad (5 cm × 5 cm), and purified by flash column chromatography on silica gel using dichloromethane as eluent. R_f = 0.4 (dichloromethane); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.22 (t, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.97 (m, 1H), 6.89 (m, 1H), 4.50 (d, *J* = 6.5 Hz, 2H), 3.80 (s, 3H), 1.72 (t, *J* = 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.9, 131.1, 128.6, 119.6, 86.5, 85.3, 51.2, 44.8; MS(EI) *m/z* (relative intensity) 162 (M^+, 100); HRMS cald. for

$C_{10}H_{10}O_2$ 162.06808, found 162.06829.

The general procedures of condensation of arylpropargyl alcohol with allyl bromide were followed: 3-(3-Methoxyphenyl)-2-propyn-1-ol[5] (1.0 g, 6.2 mmol), NaH (223 mg, 9.3 mmol, prewashed with dry hexane), allyl bromide (1.05 mL, 12.4 mmol) and freshly distilled THF (10 mL) were used to afford 3-(allyloxy)-1-(3-methoxyphenyl)-1-propyne as a light yellow liquid (1.16 g, 94% yield). Purification of crude product was conducted by filtered over a short silica pad followed by flash column chromatography on silica gel using hexane/ethyl acetate (10:1) as eluent. R_f = 0.5 (hexane/ethyl acetate = 10:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.21 (t, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.96 (m, 1H), 6.89 (m, 1H), 5.94 (m, 1H), 5.32 (dd, *J* = 17.0 Hz, 1.0 Hz, 1H), 5.23 (dd, *J* = 17.5 Hz, 1.0 Hz, 1H), 4.37 (s, 2H), 4.13 (d, *J* = 5.0 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.7, 134.1, 133.2, 117.8, 114.7, 113.9, 86.2, 83.6, 70.6, 57.9, 55.2; IR (neat, cm^{-1}) 3077, 3004, 2939, 2911, 2840, 2228, 1644, 1600, 1572, 1483, 1419, 1353, 1318, 1289, 1204, 1165, 1124, 1046, 992, 927, 855, 784, 687, 584, 512; MS(EI) *m/z* (relative intensity) 202 (M^+, 10), 161 (100); HRMS cald. for $C_{13}H_{14}O_2$ 202.09938, found 202.09923.

3-(Allyloxy)-1-(4-methoxyphenyl)-1-propyne[6]

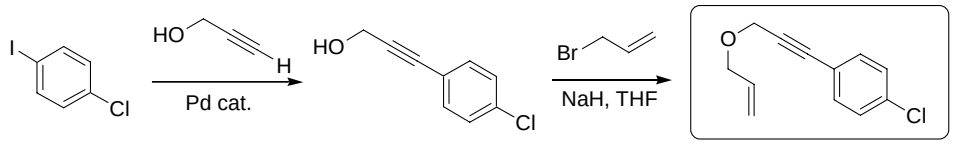


General procedure for Sonogashira coupling of propargyl alcohol with ArI: 4-Iodoanisole (11.7 g, 50 mmol), $Pd(PPh_3)_2Cl_2$ (3 mol%) and CuI (6 mol%) were dissolved in freshly distilled toluene (50 mL) under nitrogen at room temperature. Piperidine (8.4 g, 100 mmol) was added, followed by slow addition of propagyl alcohol (3.07 mL, 52 mmol) via syringe (*Caution*: exothermic reaction, when propagyl alcohol was added). The resulting dark brown reaction mixture was stirred at 30-35 °C for 3 hours under nitrogen (ArI was completely consumed as judged by GC analysis). The reaction was allowed to reach room temperature and the dark brown crude product was filtered over a silica pad (5 cm diameter × 5 cm height) and rinsed with dichloromethane (~200 mL). Solvent was removed by rotary evaporation to give a viscous brown liquid, which was purified by flash column chromatography on silica gel using dichloromethane as eluent to afford 3-(4-methoxyphenyl)-2-propyn-1-ol[7] as a yellow solid (6.07 g, 75% yield). R_f = 0.4 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 4.47 (d, *J* = 6.0 Hz), 3.81 (s, 2H),

1.75 (t, *J* = 5.5 Hz, 1H); ^{13}C NMR (CDCl3, 125 MHz) δ 138.8, 131.3, 128.8, 119.3, 86.5, 85.4, 51.2, 43.6; MS(EI) m/z (relative intensity) 162 (M+, 100).

The general procedures of condensation of arylpropargyl alcohol with allyl bromide were followed: 3-(4-Methoxyphenyl)-2-propyn-1-ol7 (1.0 g, 6.2 mmol), NaH (223 mg, 9.3 mmol, prewashed with dry hexane), allyl bromide (1.05 mL, 12.4 mmol) and freshly distilled THF (10 mL) were used to afford 3-(allyloxy)-1- (4-methoxyphenyl)-1-propyne as pale yellow liquid (1.18 g, 95% yield). Purification of crude product was conducted by filtered over a short silica pad followed by flash column chromatography on silica gel using hexane/ethyl acetate (10:1) as eluent. Rf = 0.5 (hexane/ethyl acetate = 10:1); 1H NMR (CDCl3, 500 MHz) δ 7.39 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 5.92-5.98 (m, 1H), 5.33 (dd, J = 17.0 Hz, 1.0 Hz, 1H), 5.23 (dd, J = 17.5 Hz, 1.0 Hz, 1H), 4.37 (s, 2H), 4.13 (d, J = 5.0 Hz, 2H), 3.81 (s, 3H); 13C NMR (CDCl3, 125 MHz) δ 159.7, 134.1, 133.2, 117.8, 114.7, 113.9, 86.2, 83.6, 70.6, 57.9, 55.2; IR (neat, cm-1) 3077, 3039, 3006, 2935, 2901, 2839, 2541, 2235, 2049, 1967, 1885, 1648, 1606, 1568, 1509, 1462, 1442, 1354, 1291, 1251, 1175, 1085, 1032, 927, 833, 800, 675, 567, 536, 417; MS(EI) m/z (relative intensity) 202 (M+, 10), 161 (100).

3-(Allyloxy)-1-(4-chlorophenyl)-1-propyne[3]

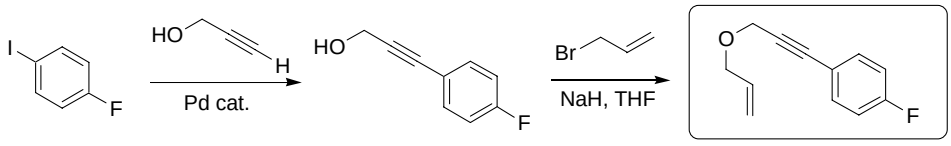


The general procedures for Sonogashira coupling of propagyl alcohol with ArI were used: 4-Chloroiodobenzene (11.9 g, 50 mmol), $Pd(PPh_3)_2Cl_2$ (3 mol%), CuI (6 mol%), piperidine (8.4 g, 100 mmol), propagyl alcohol (3.07 mL, 52 mmol) and freshly distilled toluene (50 mL) were used to afford 3-(4-chlorophenyl)-2-propyn-1-ol[8] (5.91 g, 73% yield) as a light yellow viscous liquid. Purification was conducted by filtered the reaction mixture over a silica pad (5 cm × 5 cm), and purified by flash column chromatography on silica gel using dichloromethane as eluent. R_f = 0.5 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 4.45 (s, 2H), 1.98 (brs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 133.2, 131.3, 128.2, 119.3, 86.5, 85.1, 51.2; MS(EI) *m/z* (relative intensity) 168 (M^+, 30), 166 (M^+, 100); HRMS cald. for C_9H_7ClO 166.01854, found 166.01850.

The general procedures of condensation of arylpropargyl alcohol with allyl bromide were followed: 3-(4-Chlorophenyl)-2-propyn-1-ol (1.67 g, 10 mmol), NaH (360 mg, 15 mmol, prewashed with dry hexane), allyl bromide (1.7 mL, 20 mmol) and freshly distilled THF (30 mL) were used to afford

3-(allyloxy)-1-(4-chlorophenyl)-1-propyne as a light yellow liquid (1.84 g, 89% yield). Purification of crude product was conducted by filtered over a short silica pad followed by flash column chromatography on silica gel using hexane/ethyl acetate (30:1) as eluent. R_f = 0.4 (hexane/ethyl acetate = 30:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 5.94 (tdd, *J* = 17.0 Hz, 10.0 Hz, 5.5 Hz, 1H), 5.34 (dd, *J* = 17.0 Hz, 1.0 Hz, 1H), 5.24 (dd, *J* = 17.5 Hz, 1.0 Hz, 1H), 4.36 (s, 2H), 4.12 (d, *J* = 6.0 Hz); IR (neat, cm^{-1}) 3078, 3011, 2980, 2939, 2850, 2243, 1895, 1644, 1583, 1488, 1353, 1260, 1124, 1089, 1015, 991, 927, 828, 753, 526; MS(EI) *m/z* (relative intensity) 208 (M^+, 10), 206 (M^+, 40); 167 (30), 165 (100); HRMS cald. for $C_{12}H_{11}ClO$ 206.04984, found 206.04989.

3-(Allyloxy)-1-(4-fluorophenyl)-1-propyne[3]



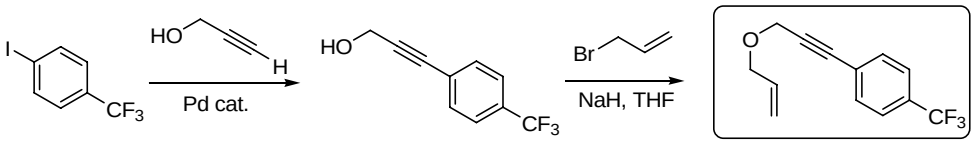
The general procedures for Sonogashira coupling of propagyl alcohol with ArI were used: 4-Iodoflurobenzene (11.1 g, 50 mmol), $Pd(PPh_3)_2Cl_2$ (3 mol%), CuI (6 mol%), piperidine (8.4 g, 100 mmol), propagyl alcohol (3.07 mL, 52 mmol) and freshly distilled toluene (50 mL) were used to afford

3-(4-fluorophenyl)-2-propyn-1-ol[9] (5.85 g, 78% yield) as light yellow viscous liquid. Purification was conducted by filtered the reaction mixture over a silica pad (5 cm × 5 cm), and purified by flash column chromatography on silica gel using dichloromethane as eluent. R_f = 0.5 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 4.78 (s, 2H), 2.69 (brs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.5, 161.5, 133.5 (d, J_{CF} = 8.3 Hz), 118.5 (d, J_{CF} = 3.0 Hz), 115.5 (d, J_{CF} = 22.1 Hz), 86.9, 84.5, 51.3; MS(EI) *m/z* (relative intensity) 150 (M^+, 100); HRMS cald. for C_9H_7FO 150.04809, found 150.04820.

The general procedures of condensation of arylpropargyl alcohol with allyl bromide were followed: 3-(4-Fluorophenyl)-2-propyn-1-ol[9] (1.5 g, 10 mmol), NaH (360 mg, 15 mmol, prewashed with dry hexane), allyl bromide (1.7 mL, 20 mmol) and freshly distilled THF (30 mL) were used to afford 3-(allyloxy)-1-(4-fluorophenyl)-1-propyne as colorless liquid (1.42 g, 75% yield). Purification was conducted by distillation under reduced pressure (89-90 °C, 2 mmHg). R_f = 0.2 (hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (d, *J* = 8.5 Hz, 2H), 7.00 (t, *J* = 8.5 Hz), 5.95 (tdd, *J* = 17.0 Hz, 10.0 Hz, 5.5 Hz, 1H), 5.34 (dd, *J* = 17.0 Hz, 1.0 Hz, 1H), 5.24 (dd, *J* = 17.5 Hz, 1.0 Hz, 1H), 4.36 (s, 2H), 4.13 (d, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.5, 161.6, 134.0, 133.6 (d, J_{CF}

= 8.4 Hz), 118.7, (d, J_{CF} = 3.0 Hz), 117.9, 115.5 (d, J_{CF} = 22.0 Hz), 85.1, 84.7, 70.7, 57.8; IR (neat, cm^{-1}) 3073, 3016, 2986, 2934, 2851, 2248, 1885, 1649, 1601, 1506, 1354, 1229, 1156, 1088, 992, 928, 837, 815, 563, 529; MS(EI) *m/z* (relative intensity) 190 (M^+, 10), 149 (100); HRMS cald. for $C_{12}H_{11}FO$ 190.07939, found 190.07923.

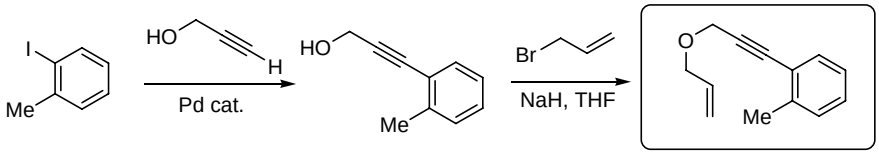
3-(Allyloxy)-1-(4-trifluoromethylphenyl)-1-propyne[10]



The general procedure for Sonogashira coupling of propargyl alcohol with ArI was used: 4-Trifluoromethyliodobenzene (13.6 g, 50 mmol), $Pd(PPh_3)_2Cl_2$ (3 mol %), CuI (6 mol %), piperidine (8.4 g, 100 mmol), propargyl alcohol (3.07 mL, 52 mmol), and freshly distilled toluene (50 mL) were used to afford 3-(4-trifluoromethylphenyl)-2-propyn-1-ol (7.50 g, 75% yield) as a light yellow solid. Purification was conducted by filtering the reaction mixture over a silica pad (5 cm × 5 cm), and purified by flash column chromatography on silica gel using dichloromethane as eluent. R_f = 0.5 (dichloromethane); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.56 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 4.52 (d, *J* = 6.0 Hz, 2H), 2.10 (t, *J* = 6.0 Hz, 1H); MS(EI) *m/z* (relative intensity) 200 (M^+, 100).

The general procedure of the condensation of arylpropargyl alcohol with allyl bromide was followed: 3-(4-Trifluoromethylphenyl)-2-propyn-1-ol (2.0 g, 10 mmol), NaH (360 mg, 15 mmol, pre-washed with dry hexane), allyl bromide (1.7 mL, 20 mmol), and freshly distilled THF (30 mL) were used to afford 3-(allyloxy)-1-(4-trifluoromethylphenyl)-1-propyne as a colorless liquid (1.82 g, 91% yield). Purification of the crude product was conducted by filtering over a short silica pad followed by flash column chromatography on silica gel using hexane/ethyl acetate (30:1) as eluent. R_f = 0.4 (hexane/ethyl acetate = 30:1); ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.56 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 5.37 – 5.97 (m, 1H), 5.35 (dd, J = 17.0, 1.0 Hz, 1H), 5.25 (dd, J = 17.5, 1.0 Hz, 1H), 4.39 (s, 2H), 4.13 (d, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ133.8, 131.9, 130.3 (q, J_{CF} = 32.3 Hz), 126.7, 125.2 (q, J_{CF} = 3.9 Hz), 124.9 (q, J_{CF} = 270.8 Hz), 118.2, 87.9, 85.0, 71.1, 57.9; IR (neat, cm^{-1}) 3078, 3016, 2986, 2939, 2853, 1921, 1649, 1615, 1567, 1521, 1441, 1406, 1325, 1259, 1171, 1018, 928, 843, 716, 598; MS(EI) *m/z* (relative intensity) 240 (M^+, 100); HRMS calcd for $C_{13}H_{11}F_3O$ 240.07620, found 240.07690.

3-(Allyloxy)-1-(2-methylphenyl)-1-propyne[3]

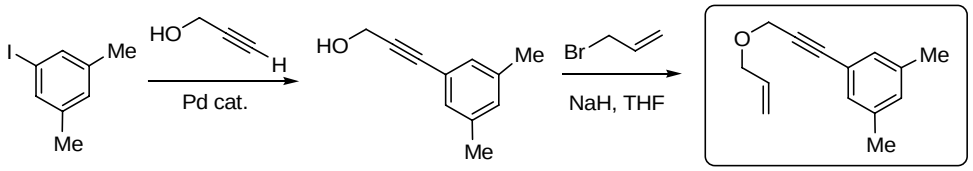


The general procedures for Sonogashira coupling of propagyl alcohol with ArI were used: 2-Iodotoluene (10.9 g, 50 mmol), $Pd(PPh_3)_2Cl_2$ (3 mol%), CuI (6 mol%), piperidine (8.4 g, 100 mmol), propagyl alcohol (3.07 mL, 52 mmol) and freshly distilled toluene (50 mL) were used to afford 3-(2-methylphenyl)-2-propyn-1-ol[5] (5.26 g, 72% yield) as a light brown solid. Purification was conducted by filtered the reaction mixture over a silica pad (5 cm × 5 cm), and purified by flash column chromatography on silica gel using dichloromethane as eluent. R_f = 0.5 (dichloromethane); Melting point: 43-44 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (d, J = 7.5 Hz, 1H), 7.11-7.24 (m, 3H), 4.54 (d, J = 6.0 Hz), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.2, 131.3, 128.6, 128.1, 119.3, 115.3, 86.5, 85.3, 51.2, 21.2; MS(EI) *m/z* (relative intensity) 146 (M^+, 100); HRMS cald. for $C_{10}H_{10}O$ 146.07316, found 146.07310.

The general procedures of condensation of arylpropargyl alcohol with allyl bromide were followed: 3-(2-Methylphenyl)-2-propyn-1-ol (1.46 g, 10 mmol), NaH (360 mg, 15 mmol, prewashed with dry hexane), allyl bromide (1.7 mL, 20 mmol) and freshly distilled THF (20 mL) were used to afford

3-(allyloxy)-1-(2-methylphenyl)-1-propyne as a light yellow liquid (1.73 g, 94% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43 (d, *J* = 8.0 Hz, 1H), 7.12-7.25 (m, 3H), 5.95-6.01 (m, 1H), 5.36 (dd, *J* = 17.0 Hz, 1.0 Hz, 1H), 5.27 (dd, *J* = 17.5 Hz, 1.0 Hz, 1H), 4.44 (s, 2H), 4.16 (d, *J* = 6.0 Hz), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.6, 137.4, 132.0, 128.8, 128.6, 119.6, 119.3, 115.1, 89.4, 85.5, 72.3, 57.4, 20.2; IR (neat, cm^{-1}) 3069, 3020, 2981, 2920, 2850, 2223, 1644, 1603, 1485, 1455, 1425, 1353, 1249, 1117, 1085, 926, 758, 716, 599, 452; HRMS cald. for $C_{13}H_{14}O$ 186.10447, found 186.10453.

3-(Allyloxy)-1-(3,5-dimethylphenyl)-1-propyne[11]

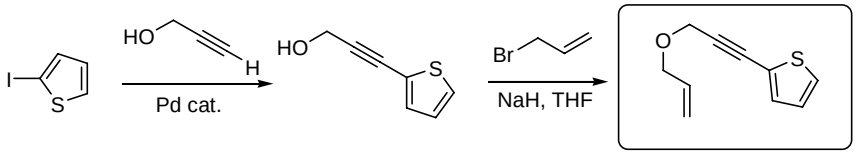


The general procedures for Sonogashira coupling of propagyl alcohol with ArI were used: 5-Iodo-*m*-xylene (2.85 g, 12 mmol), $Pd(PPh_3)_2Cl_2$ (3 mol%), CuI (6 mol%), Piperidine (1.72 g, 20 mmol), propagyl alcohol (0.62 mL, 10.5 mmol) and freshly distilled toluene (25 mL) were used to afford 3-(3,5-dimethylphenyl)- 2-propyn-1-ol (4.1 g, 54% yield) as a light brown solid. Purification was conducted by filtered the reaction mixture over a silica pad (5 cm × 5 cm), and further purified by flash column chromatography on silica gel

using dichloromethane as eluent. R_f = 0.5 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.07 (s, 2H), 6.96 (s, 1H), 4.48 (d, *J* = 5.5 Hz, 2H), 2.28 (s, 6H), 1.79 (t, *J* = 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ137.6, 130.1, 122, 86.5, 85.6, 77.3, 77.2, 77, 76.7, 51.1, 20.8.

The general procedures of condensation of arylpropargyl alcohol with allyl bromide were followed: 3-(3,5-dimethylphenyl)-2-propyn-1-ol (2g, 10 mmol), NaH (360 mg, 15 mmol, prewashed with dry hexane), allyl bromide (1.7 mL, 20 mmol) and freshly distilled THF (20 mL) were used to afford 3-(allyloxy)-1-(3,5-dimethylphenyl)-1-propyne as a light yellow liquid (1.73 g, 82% yield). urification was conducted by filtered the reaction mixture over a silica pad (5 cm × 5 cm), and purified by flash column chromatography on silica gel using dichloromethane as eluent. R_f = 0.4 (hexane/ethylacetate = 40:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.82 (s, 2H), 6.70 (s, 2H), 5.65-5.73 (m, 1H), 5.09 (dd, *J* = 18.5 Hz, 1.5 Hz, 1H), 4.98 (dd, *J* = 10.25 Hz, 1.0 Hz, 1H), 4.11 (s, 2H), 3.88 (d, *J* = 5.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.8, 134.1, 129.9, 122.2, 117.8, 86.575, 84.246, 76.9, 70.6, 57.9, 21.1

3-(Allyloxy)-1-(2-thiophenyl)-1-propyne

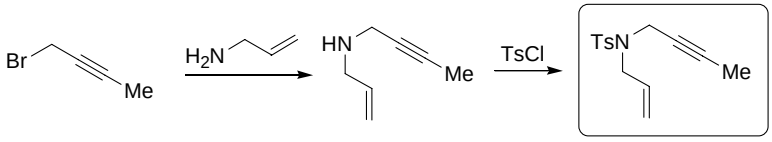


The general procedures for Sonogashira coupling of propagyl alcohol with ArI were used: 2-Iodothiophene (10.5 g, 50 mmol), $Pd(PPh_3)_2Cl_2$ (3 mol%), CuI (6 mol%), piperidine (8.4 g, 100 mmol), propagyl alcohol (3.07 mL, 52 mmol) and freshly distilled toluene (50 mL) were used to afford 3-(2-thiophenyl)-2-propyn-1-ol (5.03 g, 70% yield) as an orange-brown liquid. Purification was conducted by filtered the reaction mixture over a silica pad (5 cm × 5 cm), and purified by flash column chromatography on silica gel using dichloromethane as eluent. R_f = 0.4 (dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25 (d, 1H, *J* = 5.0 Hz), 7.21 (d, 1H, *J* = 3.5 Hz), 6.96 (t, 1H, *J* = 5.0 Hz), 4.50 (s, 2H), 2.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 132.7, 127.7, 127.2, 122.7, 91.5, 79.2, 51.8; MS(EI) *m/z* (relative intensity) 138 (M^+, 100), 121 (40), 109 (60).

The general procedures of condensation of arylpropargyl alcohol with allyl bromide were followed: 3-(2-thiophenyl)-2-propyn-1-ol (1.38 g, 10 mmol), NaH (360 mg, 15 mmol, prewashed with dry hexane), allyl bromide (1.7 mL, 20 mmol) and freshly distilled THF (20 mL) were used to afford

3-(allyloxy)-1-(2-thiophenyl)-1-propyne as a brown liquid (1.69 g, 91% yield). R_f = 0.2 (hexane/ethyl acetate = 100/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25 (d, 1H, *J* = 5.5 Hz), 7.22 (d, 1 H, *J* = 3.5 Hz), 6.97 (dd, 1H, *J* = 4.0 Hz, 5.0 Hz), 5.90-5.98 (m, 1H), 5.34 (dd, 1H, *J* = 1.0 Hz, 17.5 Hz), 5.24 (d, 1H, *J* = 9.5 Hz), 4.39 (s, 2H), 4.12 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 133.9, 132.4, 127.3, 126.9, 122.5, 117.9, 89.1, 79.5, 70.7, 57.9; IR (neat, cm^{-1}) 3108, 3079, 3011, 2982, 2937, 2847, 2220, 1649, 1518, 1425, 1356, 1263, 1245, 1190, 1124, 1021, 927, 848, 703, 669, 589, 508; MS(EI) *m/z* (relative intensity) 178 (M^+, 5), 149 (40), 135 (65), 121 (100); HRMS cald. for $C_{10}H_{10}OS$ 178.04524, found 178.04514.

_N_-Allyl-_N_-(2-butynyl)-4-tolylsulfonamide[3]



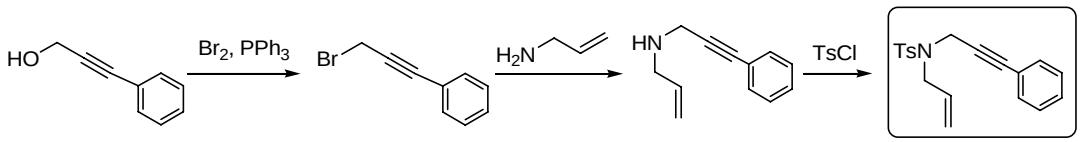
Allylamine (15.0 mL, 200 mmol) was charged into a 3-necked round bottom flask, followed by the addition of freshly distilled diethyl ether (50 mL) at room temperature under nitrogen. 1-Bromo-2-butyne (1.86 mL, 20 mmol) was added dropwise at 0 °C and the reaction mixtures were stirred at room temperature for 2 hours. The reaction was quenched with water and extracted with ethyl acetate

(3 × ~100 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The crude mixture was passed through a short silica pad (5 cm width × 10 cm height). Solvent was removed in *vacuo* and the *N*-allyl-*N*-(2-butynyl)amine product was used in next step without further purification.

To a mixture of *N*-allyl-*N*-(2-butynyl)amine (crude), triethylamine (4 mL), and dichloromethane (50 mL) was added a dichloromethane solution of *p*-toluenesulfonyl chloride (4 g, 22 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 2 hours. Water (~100 mL) was added to quench the reaction, and the aqueous phase was extracted with chloroform (2 × ~100 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Solvent was removed by rotary evaporation and the crude product was purified by column chromatography on silica gel using hexane/dichloromethane (4:1) to afford the title compound as a colorless liquid (2.30 g, 44% yield in two steps). R_f = 0.2 (hexane/dichloromethane = 4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (d, *J* = 7.5 Hz, 2H), 7.27 (d, *J* = 7.5 Hz, 2H), 5.67-5.73 (m, 1H), 5.25 (d, *J* = 17.0 Hz, 1H), 5.18 (d, *J* = 10.5 Hz, 1H), 3.98 (d, *J* = 2.0 Hz, 2H), 3.77 (d, *J* = 5.0 Hz, 2H), 2.39 (s, 3H), 1.51 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.5,

136.4, 132.4, 129.5, 128.1, 119.7, 81.8, 71.9, 49.2, 36.5, 21.7, 3.4; IR (neat, cm^{-1}) 3073, 3062, 2980, 2914, 2847, 2294, 2223, 1644, 1593, 1491, 1439, 1349, 1255, 1162, 1092, 1055, 899, 814, 735, 663, 572, 545; MS(EI) *m/z* (relative intensity) 263 (M^+, 5), 248 (10), 184 (40), 155 (60), 108 (100); HRMS cald. for $C_{14}H_{17}NO_2S$ 263.09800, found 263.09809.

_N_-Allyl-_N_-(3-phenyl-2-propynyl)-4-tolylsulfonamide[3]

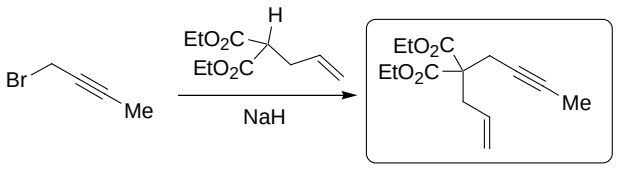


Triphenylphosphine (14.4 g, 55 mmol) was dissolved in dichloromethane (250 mL) at room temperature. Bromine (8.8 g, 2.82 mL, 55 mmol) was then added dropwise at 0 ^oC, and stirred for 30 min. 3-Phenyl-2-propyn-1-ol was added at 0 ^oC and the reaction mixture was left to stir for additional 1 hour. Hexane (~800 mL) was added and the white suspension was passed through a short silica pad (~5 cm wide × ~10 cm height) and washed with hexane. The crude product was concentrated and distilled under reduced pressure (88 – 90 ^oC, 1 mmHg) to afford 3-bromo-1-phenyl-1-propyne (9.01 g, 92% yield) as a light yellow liquid. R_f = 0.4 (hexane); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.44 – 7.46

(m, 2H), 7.32 – 7.36 (m, 3H), 4.17 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 132.1, 129.1, 128.6, 122.4, 87.0, 84.5, 15.6; MS(EI) *m/z* (relative intensity) 196 (M^+, 100), 194 (M^+, 100). Allylamine (4.0 mL, 53 mmol) was charged into a three-necked round-bottomed flask, followed by the addition of freshly distilled diethyl ether (10 mL) at room temperature under nitrogen. 3-Bromo-1-phenyl-1-propyne (1.0 g, 5.13 mmol) was added dropwise at 0 ^{o}C and the reaction mixtures stirred at room temperature for 2 h. The reaction was quenched with water and extracted with ethyl acetate (3 × ~50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The crude mixture was passed through a short silica pad (3 cm wide × 10 cm height). Solvent was removed in *vacuo* and the *N*-allyl-*N*- (3-phenyl-2-propynyl)amine product used in next step without further purification. To a mixture of *N*-allyl-*N*-(3-phenyl-2-propynyl)amine (crude), triethylamine (0.9 mL), and dichloromethane (5 mL) was added a dichloromethane solution (5 mL) of *p*-toluenesulfonyl chloride (967 mg, 5.07 mmol) at 0 ^{o}C. The reaction mixture was slowly warmed to room temperature and stirred for 2 h. Water (~50 mL) was added to quench the reaction, and the aqueous phase was extracted with chloroform (2 × ~50 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Solvent was removed by rotary

evaporation and the crude product was purified by column chromatography on silica gel using hexane/ dichloromethane (2:1) to afford the title compound as a white solid (1.39 g, 83% yield in two steps). R_f = 0.3 (hexane/dichloromethane = 2:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.22 – 7.28 (m, 5H), 7.06 (d, *J* = 7.0 Hz, 2H), 5.77 – 5.83 (m, 1H), 5.33 (d, *J* = 17.5 Hz, 1H), 5.26 (d, *J* = 10.0 Hz, 1H), 4.31 (s, 2H), 3.89 (d, *J* = 6.0 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.5, 135.9, 132.0, 131.4, 129.5, 128.3, 128.1, 127.7, 122.2, 119.9, 85.6, 81.6, 49.2, 36.7, 21.4; IR (neat, cm^{-1}) 2904, 1460, 1376, 723; MS(EI) *m/z* (relative intensity) 325 (M^+, 5), 222 (20), 170 (80), 142 (70), 115 (100).

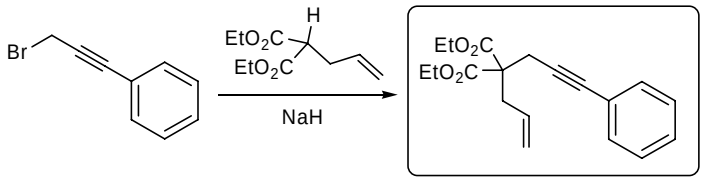
Diethyl 7-octen-2-yne-5,5-dicarboxylate[12]



Diethyl 1-butene-4,4-dicarboxylate (2.0 g, 10 mmol) was charged to a 3-necked round bottom flask followed by the addition of dry THF (30 mL) under nitrogen at room temperature. NaH (360 mg, 15 mmol, prewashed with dry hexane) was added protionwise to the reaction mixture at 0 °C and stirred for 2 hours. White suspension was observed. 1-Bromo-2-butyne (1.86 mL, 20 mmol) was then

added dropwise at 0 °C, and the reaction mixture was slowly warmed to room temperature with stirring for 3 hours. The reaction was quenched by water (~50 mL), and the aqueous phase was extracted by diethyl ether (3 × ~100 mL). The combined organic phase was washed with water, brine and dried over sodium sulfate. Solvent was removed by rotary evaporation, and the crude mixture was purified by distillation under reduced pressure to afford the title compound as a viscous colorless oil (2.31 g, 92% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.63 (m, 1H), 5.15 (d, *J* = 17.0 Hz, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 4H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.72 (q, *J* = 2.5 Hz, 2H), 1.75 (t, *J* = 2.5 Hz, 3H), 1.24 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.9, 131.8, 119.3, 78.6, 73.2, 61.3, 56.8, 36.3, 22.7, 13.9, 3.3; IR (neat, cm^{-1}) 3646, 3472, 3083, 2982, 2929, 2233, 1739, 1639, 1465, 1441, 1325, 1292, 1218, 1136, 1096, 1036, 912, 855, 661, 574; MS(EI) *m/z* (relative intensity) 252 (M^+, 20), 194 (100).

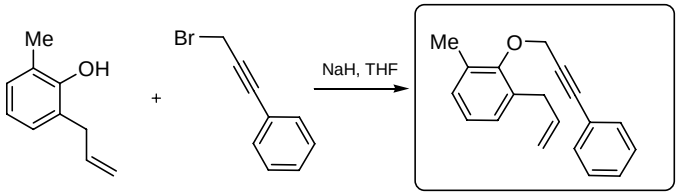
Diethyl 1-phenyl-6-hepten-1-yne-4,4-dicarboxylate[13]



Diethyl 1-butene-4,4-dicarboxylate (2.0 g, 10 mmol) was charged to a 3-necked round bottom flask followed by the addition of dry THF (30 mL) under nitrogen

at room temperature. NaH (360 mg, 15 mmol, prewashed with dry hexane) was added protionwise to the reaction mixture at 0 °C and stirred for 2 hours. White suspension was observed. 3-bromo-1-phenyl-1-propyne (3.9 mL, 20 mmol) was then added dropwise at 0 °C, and the reaction mixture was slowly warmed to room temperature with stirring for 3 hours. The reaction was quenched by water (~50 mL), and the aqueous phase was extracted by diethyl ether (3 × ~100 mL). The combined organic phase was washed with water, brine and dried over sodium sulfate. Solvent was removed by rotary evaporation, and the crude mixture was purified by distillation under reduced pressure to afford the title compound as a viscous colorless oil (2g, 80% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37-7.23 (m, 5H), 5.71-5.66 (m, 1H), 5.21 (d, *J* = 17.5 Hz, 1H), 5.14 (d, *J* = 9.0 Hz, 1H), 4.22 (q, *J* = 7.0 Hz, 4H), 3.01 (s, 2H), 2.86 (d, *J* = 7.5 Hz, 2H), 1.26 (t, *J* = 7 Hz, 6H)

3-Phenyl-1-(2-methyl-6-allyl-1-phenyoxy)propyne

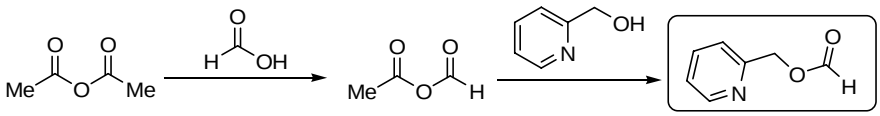


The general procedure for condensation was followed: viscous colorless liquid, R_f = 0.4 (hexane/ethyl acetate = 50/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ

7.43-7.45 (m, 2H), 7.31-7.33 (m, 3H), 7.00-7.09 (m, 3H), 5.98-6.05 (m, 1H), 5.08-5.13 (m, 2H), 4.74 (s, 2H), 3.55 (d, 2H, J = 7.0 Hz), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.3, 137.6, 133.6, 131.9, 131.7, 129.6, 128.8, 128.5, 128.3, 124.8, 122.8, 116.0, 87.0, 84.9, 61.5, 34.6, 16.9; IR (neat, cm^{-1}) 3078, 3062, 2975, 2914, 2852, 2233, 1639, 1539, 1485, 1465, 1364, 1256, 1184, 1086, 993, 906, 757, 691, 517; MS(EI) *m/z* (relative intensity) 178 (M^+, 5), 149 (40), 135 (65), 121 (100); HRMS cald. for $C_{19}H_{18}ONa$ 285.1255, found 285.1260.

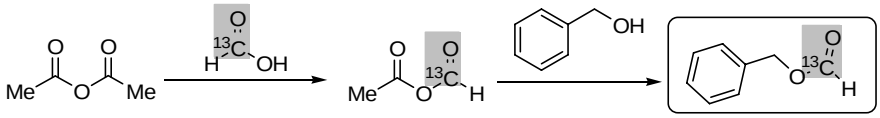
Preparation of pyridylmethyl formate and ^{13}C-labeled benzyl formate

2-Pyridylmethyl formate[14]



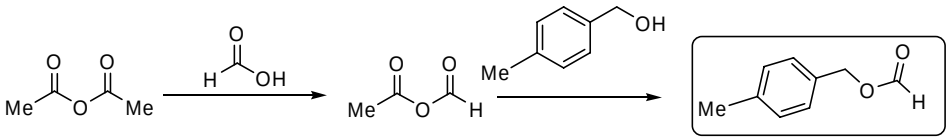
General procedure: To a stirring acetic anhydride (6.5 mL, 69 mmol) at 0 °C was added formic acid (2.6 mL, 99%, 69 mmol) dropwise. The reaction mixture was stirred at room temperature for 2 hours. The resulting formic acetic anhydride was cannulated to a stirring mixture of 2-pyridylmethanol (5 g, 46 mmol), $NaHCO_3$ (5.7 g, 69 mmol), and THF (25 mL). After stirring at RT for 1 hour, saturated aq. $NaHCO_3$ was added to the reaction mixture until gas evolution stopped. The resulting mixture was extracted with EtOAc (3 × ~50 mL). The organic layers were combined and washed with H_2O, saturated aq $NaHCO_3$, and brine, then were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel using 40% EtOAc in hexane as the eluent to give the desired product (6.1 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.0 Hz, 1H), 8.21 (s, 1H), 7.74 (dt, *J* = 1.5, 8.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.27 (dd, *J* = 5.0, 7.5 Hz, 1H), 5.3 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 154.8, 149.4, 136.9, 123.1, 121.9, 65.9.

^{13}C-Enriched benzyl formate



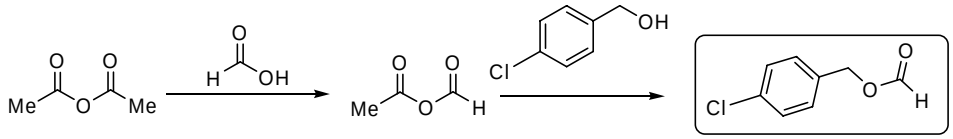
General procedures for the synthesis of 2-pyridylmethyl formate were used. Colorless liquid (90% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J_{CH} = 226.0 Hz, 1 H), 7.38-7.40 (m, 5 H), 5.22 (d, J = 3.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 135.1, 128.5, 128.3, 128.2, 65.5 (d, J_{CC} = 2.3 Hz); MS(EI) *m/z* (relative intensity) 137 (M^+, 80), 107 (40), 91 (100).

4-Methyl benzyl formate



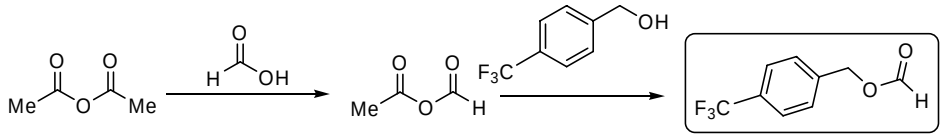
General procedures for the synthesis of 2-pyridylmethyl formate were used. Colorless liquid (90% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1 H), 7.28 (d, J = 7.5 Hz, 2 H), 7.19 (d, J = 7.5 Hz, 2 H), 5.17 (s, 2 H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 138.6, 129.5, 128.7, 65.9, 21.4

4-Chlorobenzyl formate



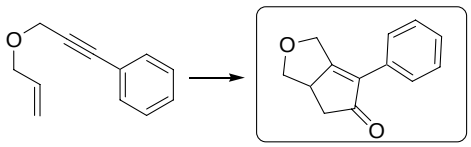
General procedures for the synthesis of 2-pyridylmethyl formate were used. Colorless liquid (85% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1 H), 7.34-7.25 (m, 4 H), 5.15 (s, 2 H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 138.6, 129.5, 128.7, 64.7

4-Trifluoromethyl benzyl formate



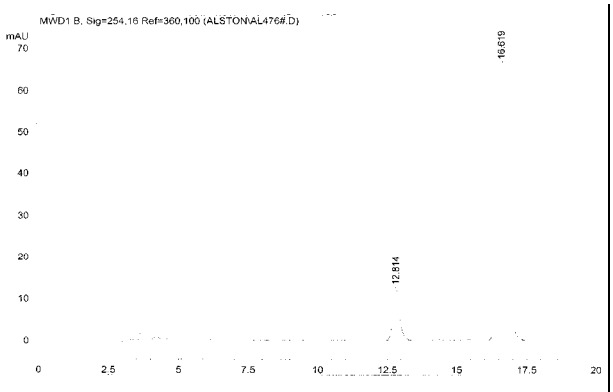
General procedures for the synthesis of 2-pyridylmethyl formate were used. Colorless liquid (87% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1 H), 7.64 (d, J = 8.5 Hz, 2 H), 7.49 (d, J = 8.5 Hz, 2H), 5.25 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 139.1, 130.5 (J_{CF} = 32.8Hz), 128.2, 125.7 (J_{CF} = 3.6Hz), 126.7 (J_{CF} = 269.5Hz), 64.6

Characterization data and HPLC chromatograms & conditions of PKR products



2-Phenyl-7-oxabicyclo[3.3.0]oct-1-en-3-one[15]

Purified by column chromatography (2 cm diameter × ~20 cm height) on silica gel using hexane/ethyl acetate (3:1) as eluent to obtain the title compound as light yellow oil. 43% yield; R_f = 0.3 (hexane/ethyl acetate = 2:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (d, *J* = 7.5 Hz, 2H), 7.39-7.42 (m, 2H), 7.33-7.37 (m, 1H), 4.93 (d, *J* = 16.5 Hz, 1H), 4.59 (d, *J* = 16.0 Hz, 1H), 4.38 (t, *J* = 8.0 Hz, 1H), 3.30-3.35 (m, 1H), 3.23 (dd, *J* = 8.0 Hz, 11.5 Hz, 1H), 2.85 (dd, *J* = 6.5 Hz, 18.5 Hz, 1H), 2.34 (dd, *J* = 4.0 Hz, 18.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.7, 177.3, 134.5, 130.5, 128.6, 128.5, 127.9, 71.2, 66.2, 43.2, 40.2; MS(EI) *m/z* (relative intensity) 200 (M^+, 70), 170 (40), 158 (50), 141 (100).



Chiral HPLC conditions

Column:	Chiralcel AD-H
Solvent:	Hex:IPA = 9:1
Flow rate:	1.0 mL/ min

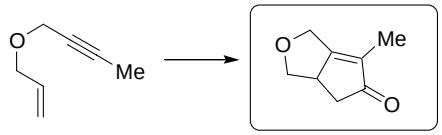
Signal 1: MWD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.814	BB	0.2523	206.90604	12.55115	12.3344
2	16.619	BB	0.3218	1470.56140	70.36609	87.6656
Totals :				1677.46744	82.91724	

Results obtained with enhanced integrator!

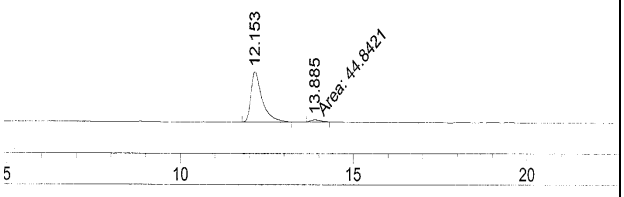
*** End of Report ***

UV lamp:	254 nm
Retention time:	12.8, 16.6 min



2-Methyl-7-oxabicyclo[3.3.0]oct-1-en-3-one[15]

Purified by column chromatography (2 cm diameter × ~15 cm height) on silica gel using hexane/ethyl acetate (3:1) as eluent to obtain the title compound as colorless oil. 16% yield; R_f = 0.3 (hexane/ethyl acetate = 2:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.54 (q, *J* = 15.0 Hz, 2H), 4.30-4.32 (m, 1H), 3.19-3.23 (m, 2H), 2.64-2.71 (dd, *J* = 5.5 Hz, 18.0 Hz, 1H), 2.09-2.17 (dd, *J* = 2.0 Hz, 18.0 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.0, 176.1, 132.6, 71.8, 64.7, 43.2, 38.6, 8.9; MS(EI) *m/z* (relative intensity) 138 (M^+, 100), 123 (60), 105 (30).



Chiral HPLC conditions

Column:	Chiralcel AS-H
Solvent:	Hex:IPA = 9:1
Flow rate:	1.0 mL/ min
UV lamp:	210 nm

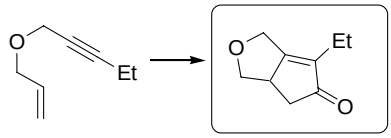
Signal 1: MWD1 E, Sig=210,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.153	BV	0.3366	1147.57092	50.22519	96.2394
2	13.885	MM	0.3436	44.84212	2.17515	3.7606
Totals :				1192.41305	52.40034	

Results obtained with enhanced integrator!

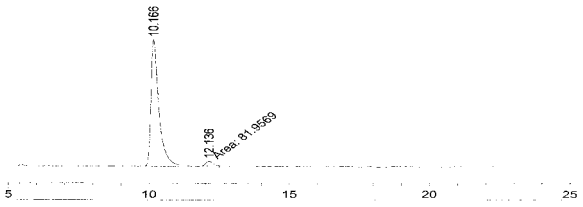
*** End of Report ***

Retention time:	12.2, 13.9 min



2-Ethyl-7-oxabicyclo[3.3.0]oct-1-en-3-one[12]

Purified by column chromatography (2 cm diameter × ~20 cm height) on silica gel using hexane/ethyl acetate (3:1) as eluent to obtain the title compound as colorless oil. 20% yield; R_f = 0.3 (hexane/ethyl acetate = 2:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.61 (q, *J* = 15.5 Hz, 2H), 4.30-4.34 (m, 1H), 3.19-3.23 (m, 2H), 2.64-2.71 (dd, *J* = 5.5 Hz, 18.0 Hz, 1H), 2.19-2.33 (m, 2H), 2.10-2.17 (dd, *J* = 2.5 Hz, 18.0 Hz, 1H), 1.12 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 208.0, 175.1, 138.6, 71.8, 64.8, 43.2, 38.6, 17.6, 16.3; MS(EI) *m/z* (relative intensity) 152 (M^+, 100), 123 (40), 105 (50).



Signal 1: MWD1 E, Sig=210,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.166	VB	0.2874	2619.79346	133.23909	96.9665
2	12.136	MM	0.2885	81.95692	4.73482	3.0335

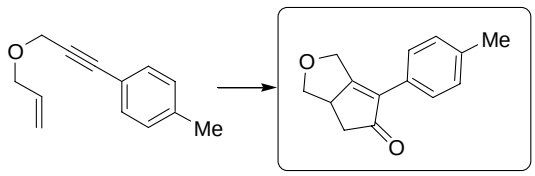
Totals : 2701.75038 137.97391

Results obtained with enhanced integrator!

*** End of Report ***

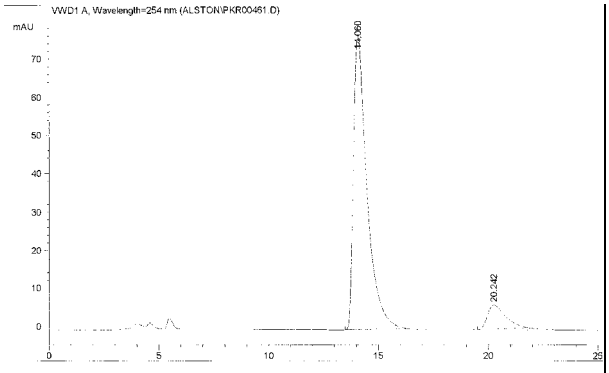
Chiral HPLC conditions

Column:	Chiralcel AS-H
Solvent:	Hex:IPA = 9:1
Flow rate:	1.0 mL/ min
UV lamp:	210 nm
Retention time:	10.2, 12.1 min



2-(4-Methylphenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one[3]

Purified by column chromatography (2 cm diameter × ~20 cm height) on silica gel using hexane/ethyl acetate (3:1) as eluent to obtain the title compound as white solid. 44% yield; R_f = 0.4 (hexane/ethyl acetate = 2:1); $[\alpha]^{25}_D$ = +55.9° (*c* = 0.10); Melting point: 49-51 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 1H), 4.93 (d, *J* = 16.0 Hz, 1H), 4.59 (d, *J* = 16.0 Hz, 1H), 4.37 (t, *J* = 7.5 Hz, 1H), 3.28-3.32 (m, 1H), 3.23 (dd, *J* = 8.0 Hz, 11.5 Hz, 1H), 2.84 (dd, *J* = 6.5 Hz, 17.5 Hz, 1H), 2.37 (s, 3H), 2.32 (dd, *J* = 3.5 Hz, 18.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.3, 175.2, 159.8, 134.1, 129.3, 123.2, 114.0, 71.3, 66.3, 43.1, 40.2, 23.8; IR (neat, cm^{-1}) 3020, 2397, 1747, 1511, 1419, 1215, 1040, 922, 756, 669; MS(EI) *m/z* (relative intensity) 214 (M^+, 100), 184 (30), 169 (40), 156 (45), 141 (70); HRMS cald. for $C_{14}H_{14}O_2$ 214.09938, found 214.09943.



Signal 1: VWD1 A, Wavelength=254 nm

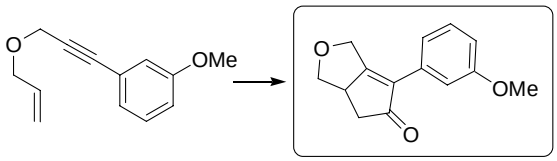
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.060	BB	0.6289	3264.54980	76.71992	90.5279
2	20.242	BB	0.8241	341.57483	6.08195	9.4721
Totals :				3606.12463	82.80187	

Results obtained with enhanced integrator!

*** End of Report ***

Chiral HPLC conditions

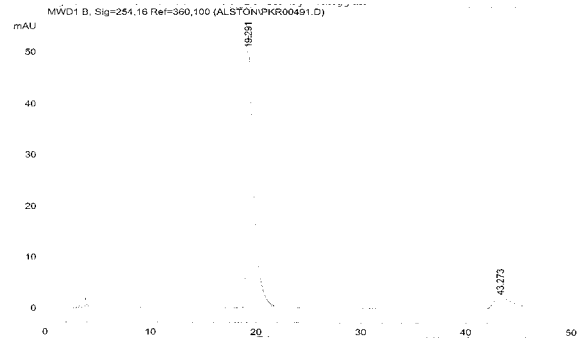
Column:	Chiralcel AS-H
Solvent:	Hex:IPA = 9:1
Flow rate:	1.0 mL/ min
UV lamp:	254 nm
Retention time:	14.1, 20.2 min



2-(3-Methoxyphenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one[3]

Purified by column chromatography (1.8 cm diameter × ~15 cm height) on silica gel using hexane/ethyl acetate (3:1) as eluent to obtain the title compound as light yellow viscous oil. 37% yield; R_f = 0.3 (hexane/ethyl acetate = 2:1); $[\alpha]^{25}_D$ = +21.4° (*c* = 0.011); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 (t, *J* = 7.5 Hz, 1H), 7.16 (s, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.90 (dd, *J* = 2.5 Hz, 8.0 Hz, 1H), 4.92 (d, *J* = 16.0 Hz, 1H), 4.59 (d, *J* = 16.0 Hz, 1H), 4.37 (t, *J* = 7.5 Hz, 1H), 3.82 (s, 3H), 3.29-3.33 (m, 1H), 3.23 (dd, *J* = 7.5 Hz, 11.5 Hz, 1H), 2.84 (dd, *J* = 6.5 Hz, 17.5

Hz, 1H), 2.33 (dd, J = 4.0 Hz, 17.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.7, 177.7, 159.6, 134.5, 131.8, 129.6, 120.5, 114.3, 113.4, 71.3, 66.3, 55.2, 43.3, 40.3; IR (neat, cm^{-1}) 3019, 2386, 1705, 1511, 1413, 1215, 1045, 1024, 922, 758, 669; MS(EI) *m/z* (relative intensity) 230 (M^+, 100), 213 (5), 199 (10), 185 (20), 171 (20), 159 (30); HRMS cald. for $C_{14}H_{14}O_3$ 230.09430, found 230.09422.



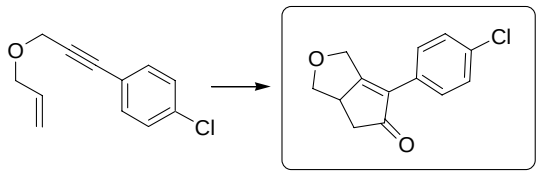
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.291	BB	0.6651	2439.30664	52.98916	92.1878
2	43.273	BB	1.2164	206.71307	1.99237	7.8122
Totals :				2646.01971	54.98152	

Results obtained with enhanced integrator!

*** End of Report ***

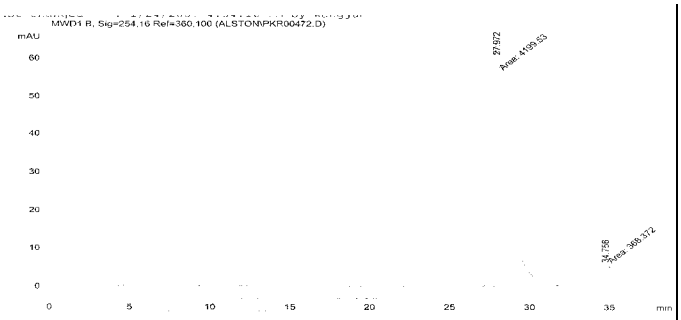
Chiral HPLC conditions

Column:	Chiralcel AS-H
Solvent:	Hex:IPA = 9:1
Flow rate:	1.0 mL/ min
UV lamp:	254 nm
Retention time:	19.3, 43.2 min



2-(4-Chlorophenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one[16]

Purified by column chromatography (1.8 cm diameter × ~15 cm height) on silica gel using hexane/ethyl acetate (3:1) as eluent to obtain the title compound as light yellow oil. 65% yield; R_f = 0.3 (hexane/ethyl acetate = 2:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (d, *J* = 9.0 Hz, 2H), 7.38 (d, *J* = 9.0 Hz, 1H), 4.92 (d, *J* = 16.0 Hz, 1H), 4.57 (d, *J* = 16.0 Hz, 1H), 4.38 (t, *J* = 8.0 Hz, 1H), 3.30-3.37 (m, 1H), 3.25 (dd, *J* = 7.5 Hz, 11.0 Hz, 1H), 2.85 (dd, *J* = 6.0 Hz, 18.0 Hz, 1H), 2.33 (dd, *J* = 3.5 Hz, 18.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.3, 175.1, 159.7, 134.0, 129.3, 123.3, 114.1, 71.1, 66.3, 43.2, 40.2; MS(EI) *m/z* (relative intensity) 236 (M^+, 20), 234 (M^+, 60), 204 (15), 192 (25), 169 (95), 141 (100).



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

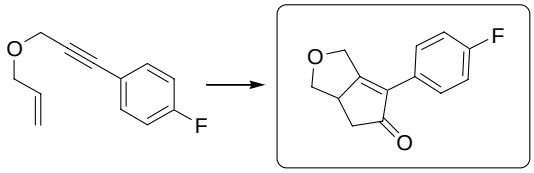
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.972	MM	1.1018	4199.52588	63.52272	91.9356
2	34.756	MM	1.1745	368.37219	5.22736	8.0644
Totals :				4567.89807	68.75008	

Results obtained with enhanced integrator!

*** End of Report ***

Chiral HPLC conditions

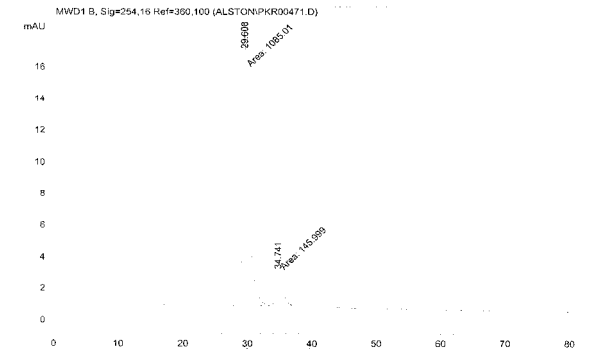
Column:	Chiralcel AS-H
Solvent:	Hex:IPA = 98:2
Flow rate:	1.0 mL/ min
UV lamp:	254 nm
Retention time:	28.0, 34.8 min



2-(4-Fluorophenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one[10]

Purified by column chromatography (1.8 cm diameter × ~15 cm height) on silica gel using hexane/ethyl acetate (3:1) as eluent to obtain the title compound as light yellow oil. 61% yield; R_f = 0.3 (hexane/ethyl acetate = 2:1); $[\alpha]^{25}_D$ = +0.7° (*c* = 0.0083); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (dd, *J* = 5.5 Hz, 8.0 Hz, 2H), 7.09 (t, *J* = 8.0 Hz, 2H), 4.91 (d, *J* = 16.5 Hz, 1H), 4.56 (d, *J* = 16.5 Hz, 1H),

4.37 (t, J = 7.5 Hz, 1H), 3.29-3.33 (m, 1H), 3.24 (dd, J = 7.5 Hz, 11.0 Hz, 1H), 2.84 (dd, J = 6.5 Hz, 18.0 Hz, 1H), 2.33 (dd, J = 3.5 Hz, 17.5 Hz, 1H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.1, 177.0, 161.7, 133.6, 129.8 (d, J_{CF} = 8.4 Hz), 126.7, 115.6 (d, J_{CF} = 22.0 Hz), 71.3, 66.2, 43.2, 40.1; IR (neat, cm^{-1}) 3021, 2392, 1701, 1506, 1215, 1029, 758, 669; MS(EI) *m/z* (relative intensity) 218 (M^+, 70), 188 (50), 176 (50), 159 (100), 146 (60); HRMS cald. for $C_{13}H_{11}FO_2$ 218.07431, found 218.07439.



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

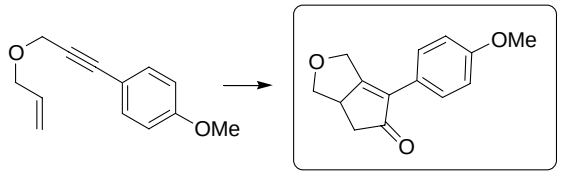
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.608	MM	1.0585	1085.00500	17.08397	88.1399
2	34.741	MM	1.1456	145.99861	2.12404	11.8601
Totals :				1231.00362	19.20801	

Results obtained with enhanced integrator!

*** End of Report ***

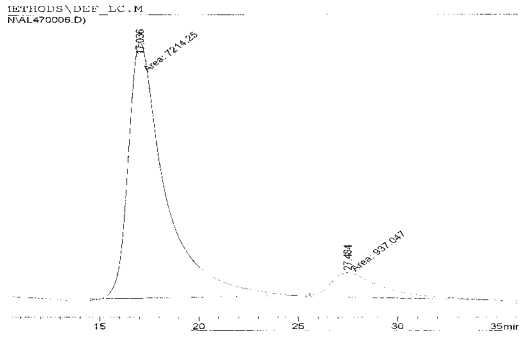
Chiral HPLC conditions

Column:	Chiralcel AS-H
Solvent:	Hex:IPA = 98:2
Flow rate:	1.0 mL/ min
UV lamp:	254 nm
Retention time:	29.6, 34.7 min



2-(4-Methoxyphenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one[16]

Purified by column chromatography (1.8 cm diameter × ~15 cm height) on silica gel using hexane/ethyl acetate (2:1) as eluent to obtain the title compound as light yellow solid. 58% yield; R_f = 0.2 (hexane/ethyl acetate = 2:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 1H), 4.89 (d, *J* = 16.0 Hz, 1H), 4.57 (d, *J* = 16.0 Hz, 1H), 4.35 (t, *J* = 8.0 Hz, 1H), 3.82 (s, 3H), 3.26-3.30 (m, 1H), 3.20 (dd, *J* = 7.5 Hz, 11.0 Hz, 1H), 2.81 (dd, *J* = 6.0 Hz, 17.5 Hz, 1H), 2.31 (dd, *J* = 3.0 Hz, 17.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.3, 175.2, 159.8, 134.1, 129.3, 123.2, 114.0, 71.3, 66.3, 55.2, 43.1, 40.2; MS(EI) *m/z* (relative intensity) 230 (M^+, 100), 201 (10), 189 (30), 172 (60).



Signal 1: VWD1 A, Wavelength=254 nm

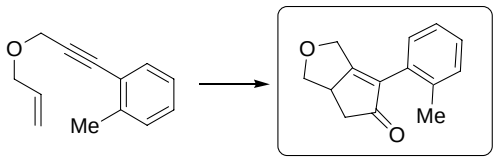
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	17.036	MM	2.1622	7214.25439	55.60995	88.5043
2	27.484	MM	2.9620	937.04688	5.27253	11.4957
Totals :				8151.30127	60.88247	

Results obtained with enhanced integrator!

*** End of Report ***

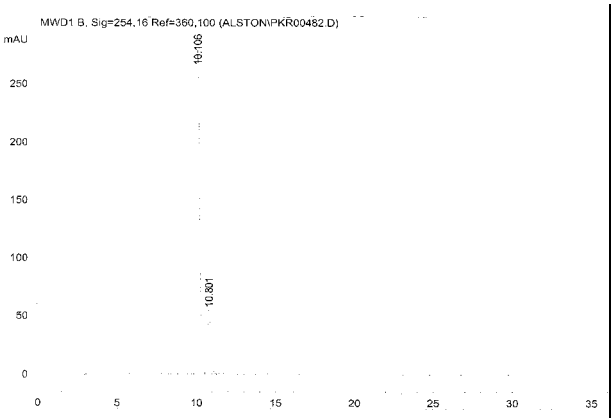
Chiral HPLC conditions

Column:	Chiralcel AS
Solvent:	Hex:IPA = 9:1
Flow rate:	1.0 mL/ min
UV lamp:	254 nm
Retention time:	17.0, 27.5 min



2-(2-Methylphenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one[3]

Purified by column chromatography (2 cm diameter × ~20 cm height) on silica gel using hexane/ethyl acetate (3:1) as eluent to obtain the title compound as colorless oil. 11% yield; R_f = 0.4 (hexane/ethyl acetate = 2:1); $[\alpha]^{25}_D$ = +39.1° (*c* = 0.12); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.19-7.29 (m, 3H), 7.10 (d, *J* = 7.5 Hz, 1H), 4.63 (d, *J* = 16.0 Hz, 1H), 4.42 (t, *J* = 7.5 Hz, 1H), 4.36 (d, *J* = 15.5 Hz, 1H), 3.38-3.42 (m, 1H), 3.34 (dd, *J* = 7.0 Hz, 11.0 Hz, 1H), 2.85 (dd, *J* = 5.5 Hz, 17.5 Hz, 1H), 2.35 (dd, *J* = 3.5 Hz, 17.5 Hz, 1H); 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.3, 175.2, 159.8, 134.1, 129.3, 128.9, 123.2, 114.0, 111.3, 71.3, 66.3, 43.1, 40.2, 23.8; IR (neat, cm^{-1}) 3021, 2397, 1737, 1510, 1419, 1215, 1043, 922, 758, 669; MS(EI) *m/z* (relative intensity) 214 (M^+, 100), 199 (5), 183 (40), 169 (50), 154 (30), 141 (70); HRMS cald. for $C_{14}H_{14}O_2$ 214.09938, found 214.09946.



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

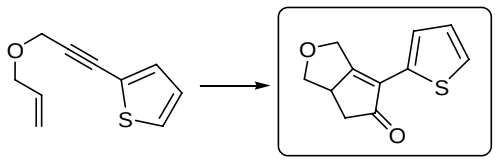
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.106	BV	0.2000	3619.47729	277.78891	82.6995
2	10.801	VB	0.2151	757.18298	54.16692	17.3005
Totals :				4376.66028	331.95583	

Results obtained with enhanced integrator!

*** End of Report ***

Chiral HPLC conditions

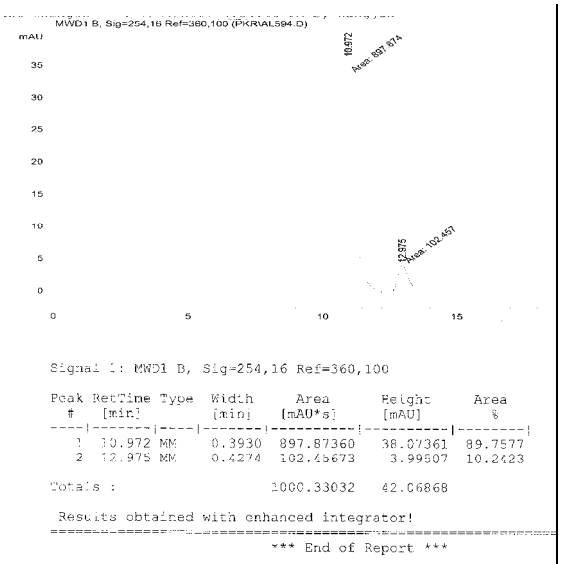
Column:	Chiralcel AD-H
Solvent:	Hex:IPA = 9:1
Flow rate:	1.0 mL/ min
UV lamp:	254 nm
Retention time:	10.1, 10.8 min



2-(2-Thiophenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one

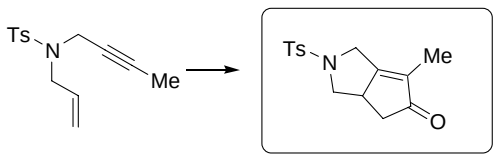
Purified by column chromatography (2 cm diameter × ~15 cm height) on silica gel using hexane/ethyl acetate (2:1) as eluent to obtain the title compound as yellow oil. 49% yield; R_f = 0.4 (hexane/ethyl acetate = 2:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 (d, *J* = 3.5 Hz, 1H), 7.41 (d, *J* = 5 Hz, 1H), 7.11 (dd, *J* = 3.5 Hz, 4.7Hz, 1H), 4.87 (d, *J* = 16.5 Hz, 1H), 4.72 (d, *J* = 16.5 Hz, 1H), 4.37 (t, *J* = 7.5 Hz, 1H) 3.36-3.33 (m, 1H), 3.25 (dd, *J* = 7.5 Hz, 11Hz, 4.7Hz, 1H), 2.84 (dd,

J = 6.5 Hz, 17.5 Hz, 1H), 2.31 (dd, J = 4 Hz, 17.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.4, 173.8, 132.2, 128.9, 127.4, 126.9, 126.6, 71.4, 66.3, 43.7, 39.4; MS(EI) *m/z* (relative intensity) 206 (M^+, 100), 176 (60), 164 (20). HRMS cald. for $C_{11}H_{10}O_2S$ 206.04015, found 206.04090.



Chiral HPLC conditions

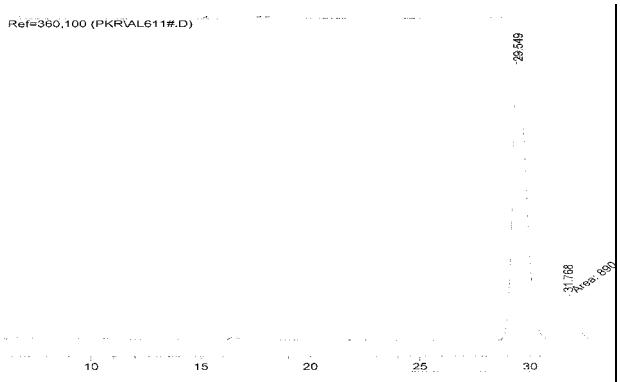
Column:	Chiralcel AS-H
Solvent:	Hex:IPA = 8:2
Flow rate:	1.0 mL/ min
UV lamp:	254 nm
Retention time:	11.0, 13.0 min



2-Methyl-7-[(4-methylphenyl)sulfonyl]-7-azabicyclo[3.3.0]oct-1-en-3-one[17]

Purified by column chromatography (2.0 cm diameter × ~15 cm height) on silica gel using hexane/ethyl acetate (2:1) as eluent to obtain the title compound as

white solid. 65% yield; R_f = 0.2 (hexane/ethyl acetate = 2:1); Melting point: 103-104 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 4.23 (d, *J* = 16.0 Hz, 1H), 3.96-4.00 (m, 2H), 2.96-3.06 (m, 1H), 2.54-2.62 (m, 2H), 2.44 (s, 3H), 2.03 (dd, *J* = 3.0 Hz, 17.5 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.3, 171.0, 144.0, 134.1, 133.9, 129.9, 127.4, 52.6, 46.7, 41.6, 39.2, 21.5, 8.8; MS(EI) *m/z* (relative intensity) 291 (M^+, 30), 263 (5), 155 (10), 136 (100).



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

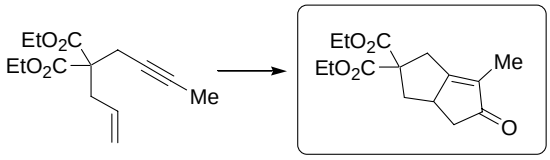
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.549	BB	0.6501	5998.62354	143.38464	87.0733
2	31.768	MM	0.6958	890.54547	21.33278	12.9267
Totals :				6889.16901	164.71743	

Results obtained with enhanced integrator!

*** End of Report ***

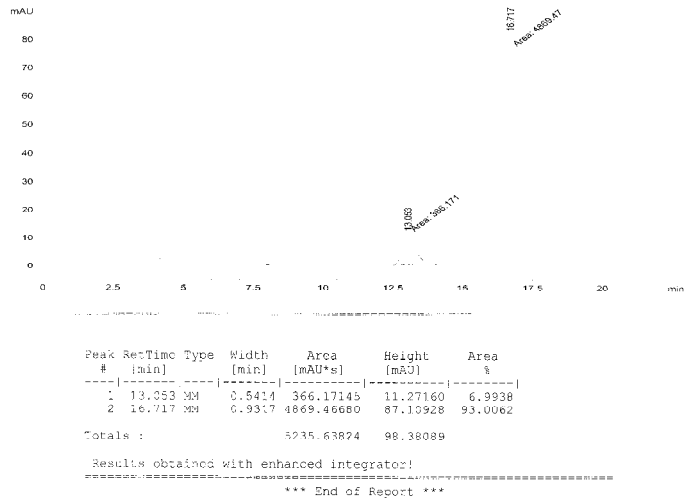
Chiral HPLC conditions

Column:	Chiralcel AD-H
Solvent:	Hex:IPA = 9:1
Flow rate:	1.0 mL/ min
UV lamp:	254 nm
Retention time:	29.5, 31.8 min



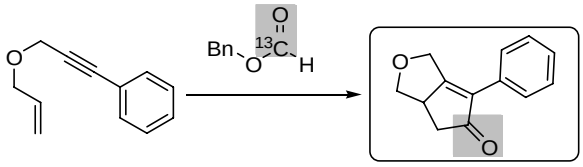
Diethyl 2-methyl-3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate[18]

Purified by column chromatography (2 cm diameter × ~20 cm height) on silica gel using hexane/ethyl acetate (4:1) as eluent to obtain the title compound as light yellow viscous oil. 40% yield; R_f = 0.3 (hexane/ethyl acetate = 4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.21 (q, *J* = 6.5 Hz, 2H), 4.17 (q, *J* = 6.5 Hz, 2H), 3.16 (q, *J* = 14.5 Hz, 2H), 2.94 (m, 1H), 2.74 (dd, *J* = 7.0 Hz, 12.5 Hz, 1H), 2.60 (dd, *J* = 6.0 Hz, 18.0 Hz, 1H), 2.04 (dd, *J* = 3.0 Hz, 18.5 Hz, 1H), 1.68 (s, 3H), 1.61 (t, *J* = 13.0 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 203.9, 177.7, 171.5, 170.9, 132.8, 61.9, 61.8, 60.8, 42.6, 41.3, 39.0, 33.9, 13.9 (overlapped), 8.4; MS(EI) *m/z* (relative intensity) 280 (M^+, 40), 235 (20), 206 (80), 178 (30), 133 (100).



Chiral HPLC conditions

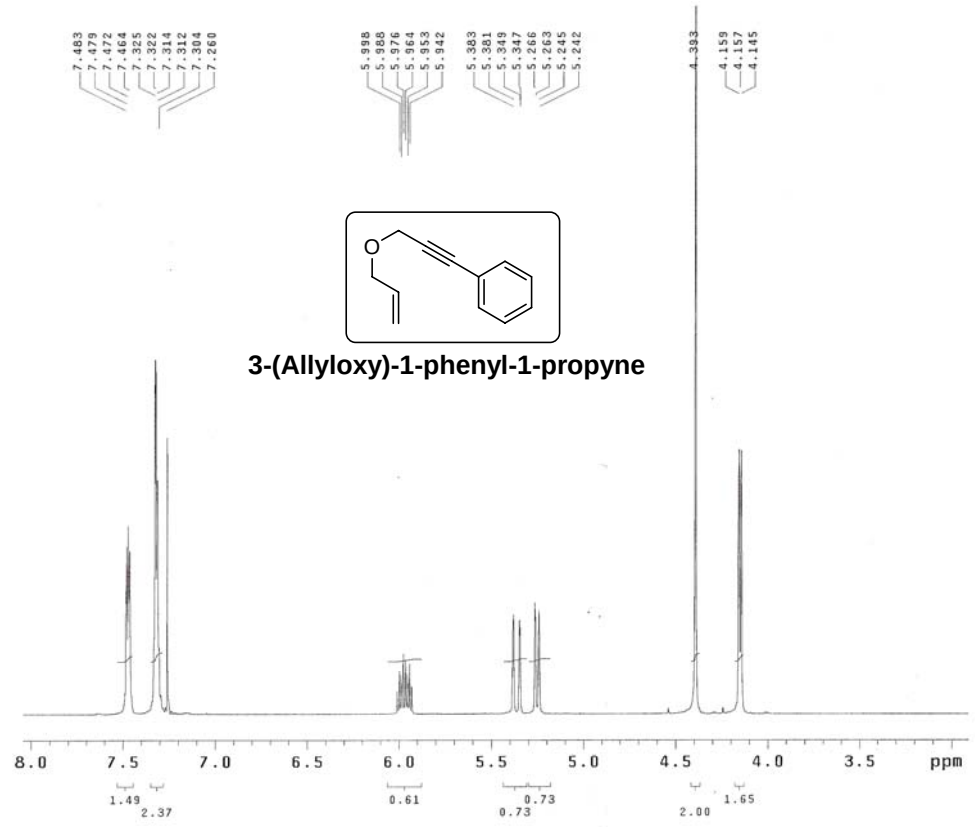
Column:	Chiralcel AS-H
Solvent:	Hex:IPA = 9:1
Flow rate:	1.0 mL/ min
UV lamp:	254 nm
Retention time:	13.1, 16.7 min



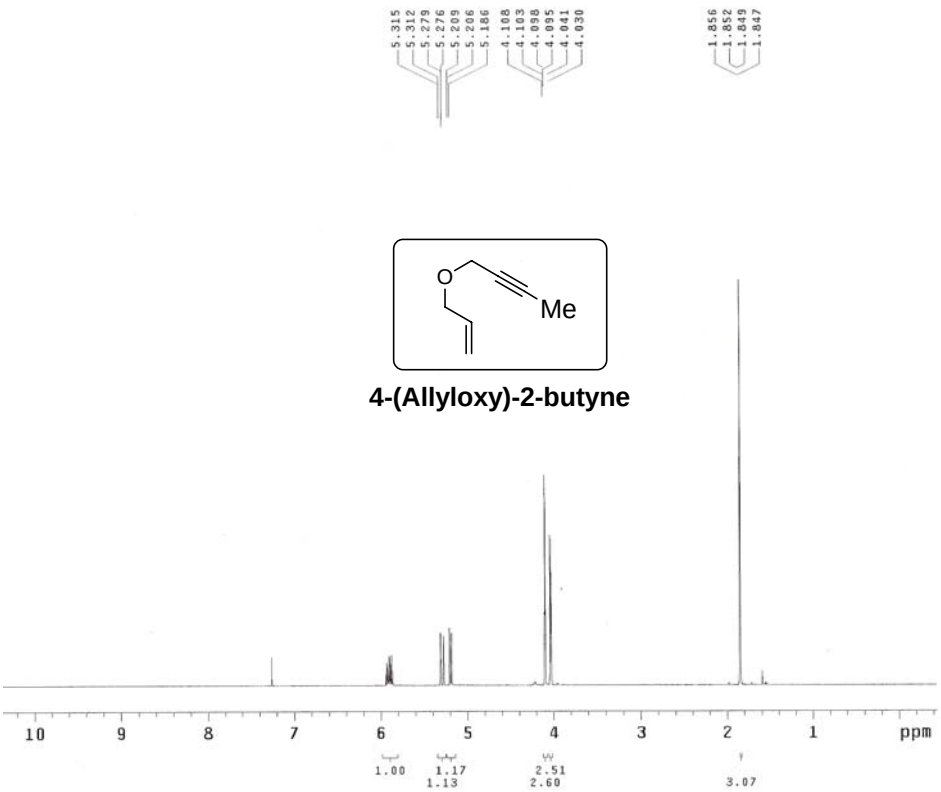
^{13}C-Enriched 2-phenyl-7-oxabicyclo[3.3.0]oct-1-en-3-one

General procedures of PKR were used except ^{13}C-enriched benzyl formate was added instead of original benzyl formate. Purified by column chromatography (2 cm diameter × ~20 cm height) on silica gel using hexane/ethyl acetate (3:1) as eluent to obtain the title compound as light yellow oil. >99% ^{13}C-labeled.

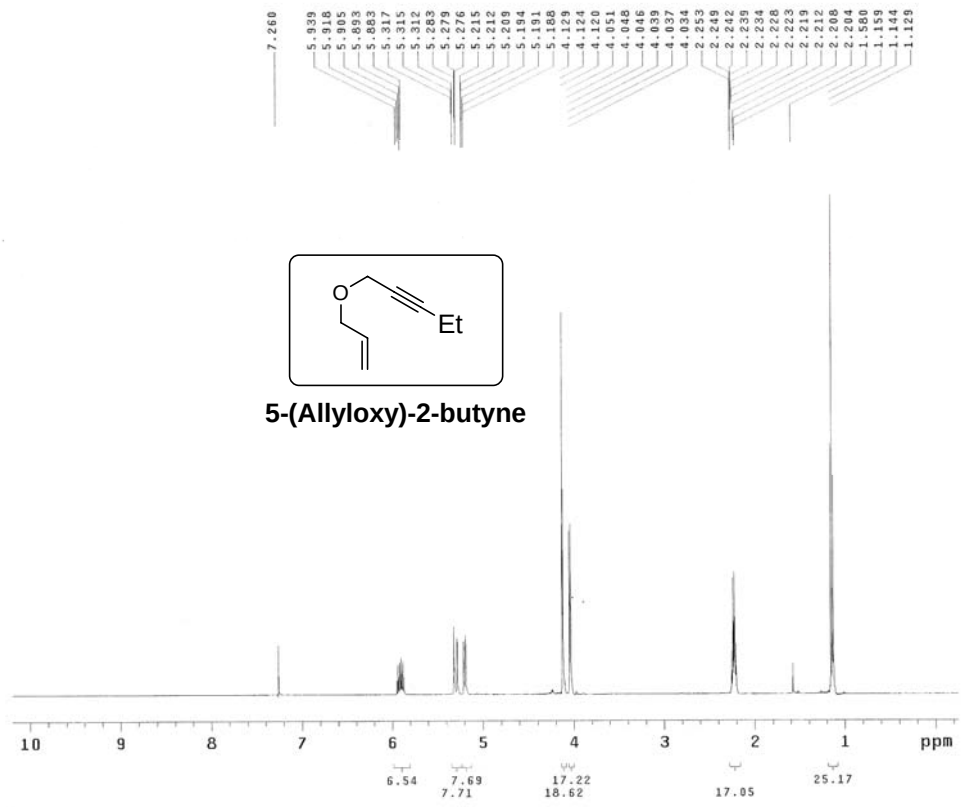
NMR spectra of enynes



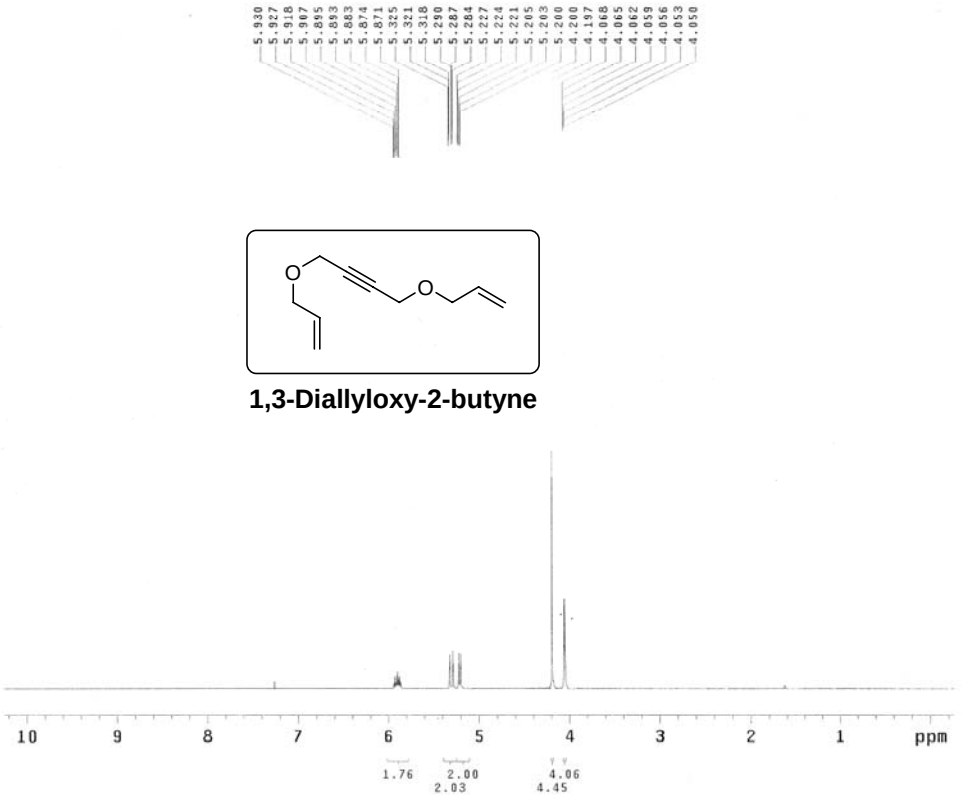
3-(Allyloxy)-1-phenyl-1-propyne



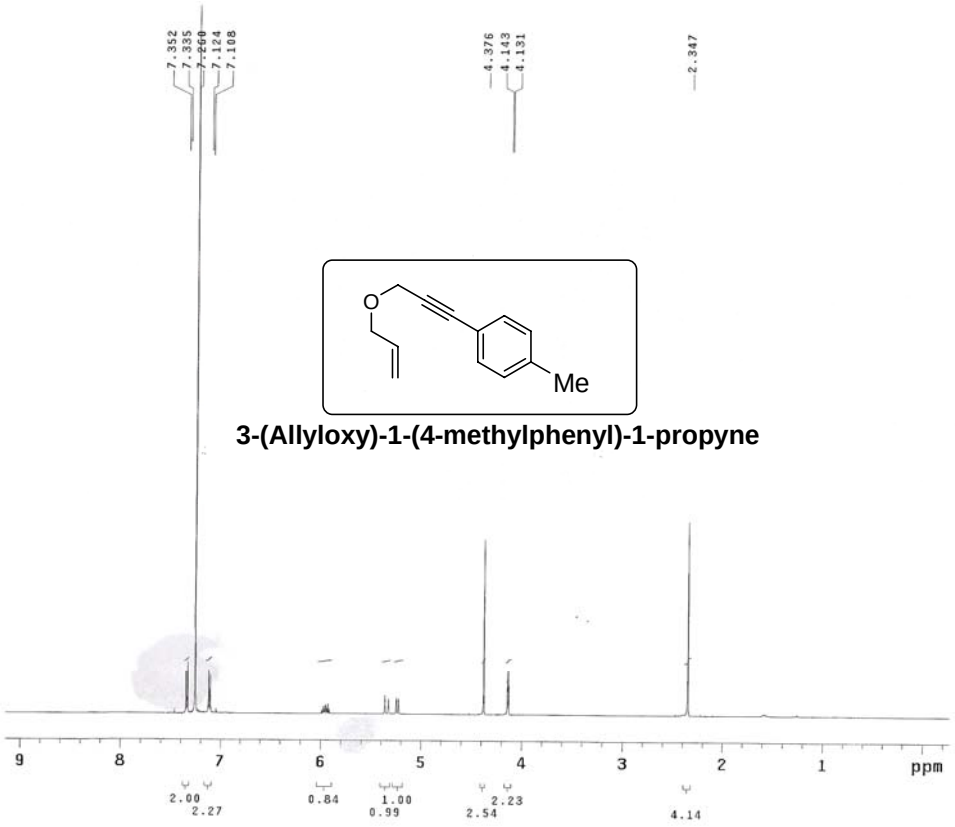
4-(Allyloxy)-2-butyne



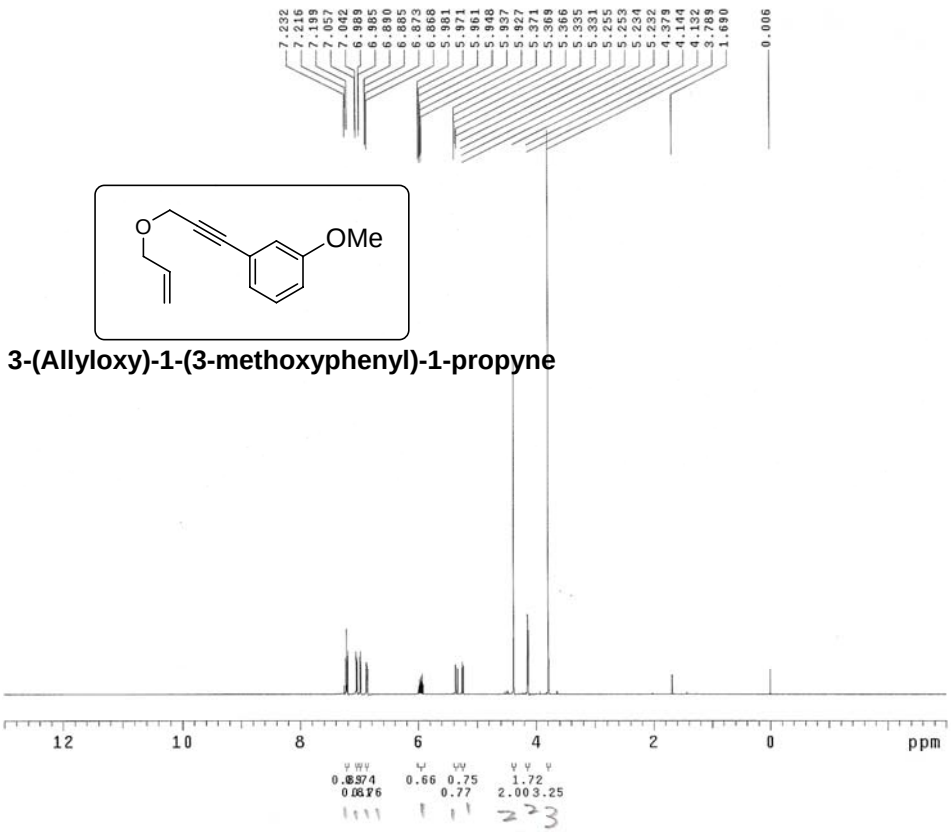
5-(Allyloxy)-2-butyne



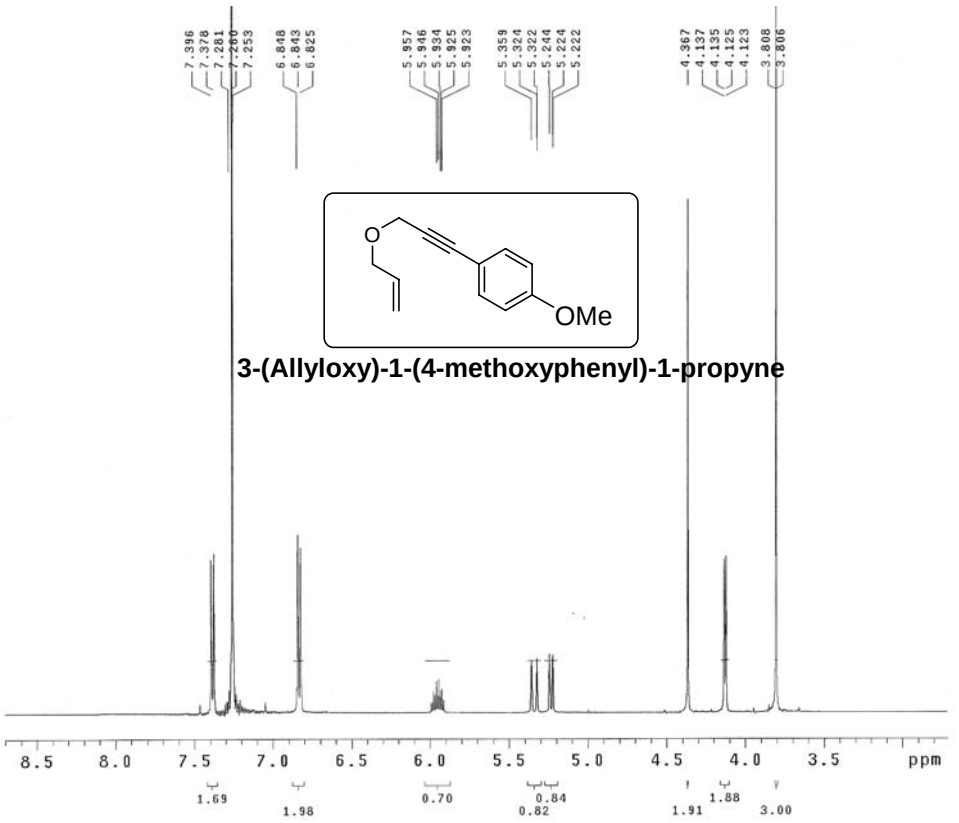
1,3-Diallyloxy-2-butyne



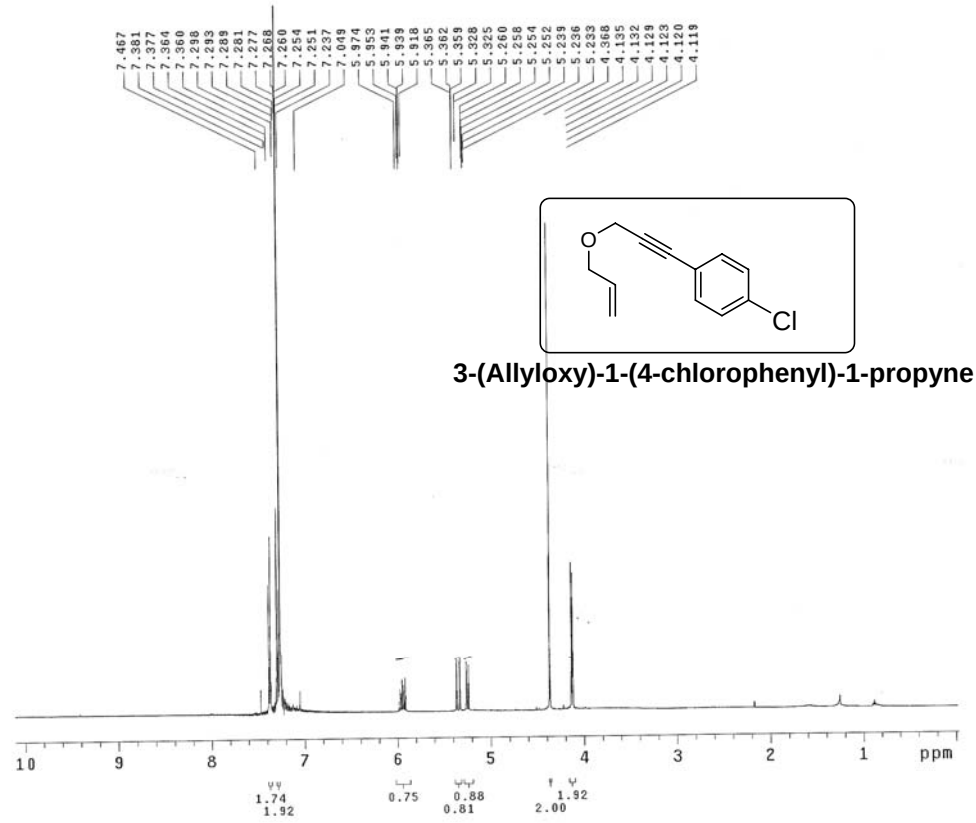
3-(Allyloxy)-1-(4-methylphenyl)-1-propyne



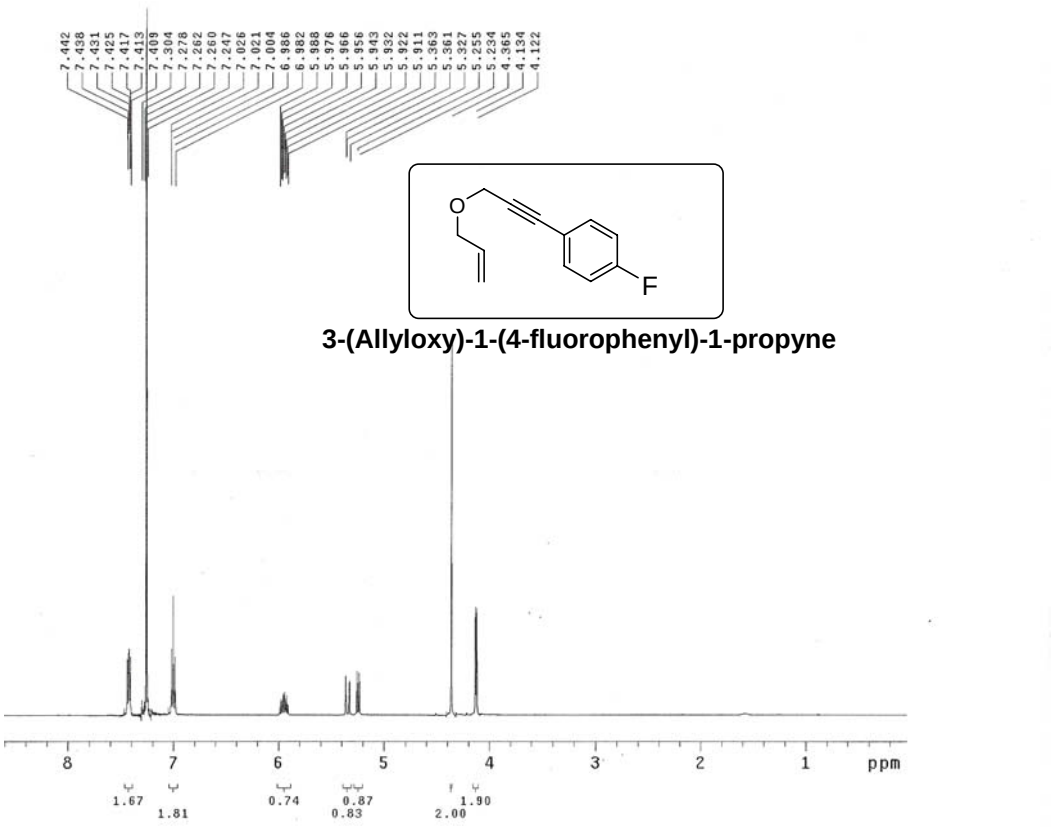
3-(Allyloxy)-1-(3-methoxyphenyl)-1-propyne



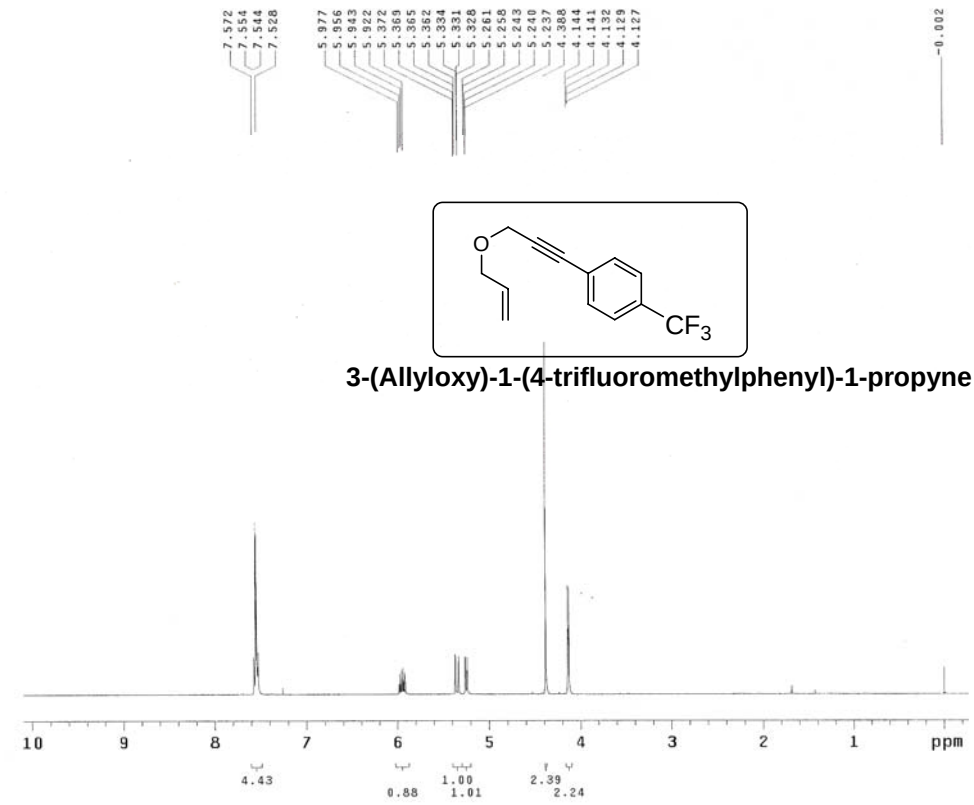
3-(Allyloxy)-1-(4-methoxyphenyl)-1-propyne



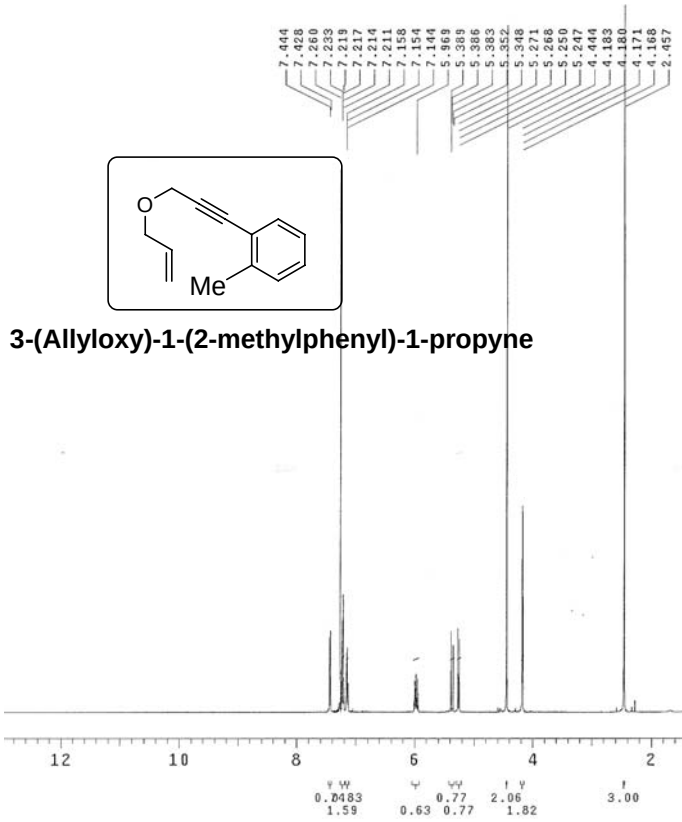
3-(Allyloxy)-1-(4-chlorophenyl)-1-propyne



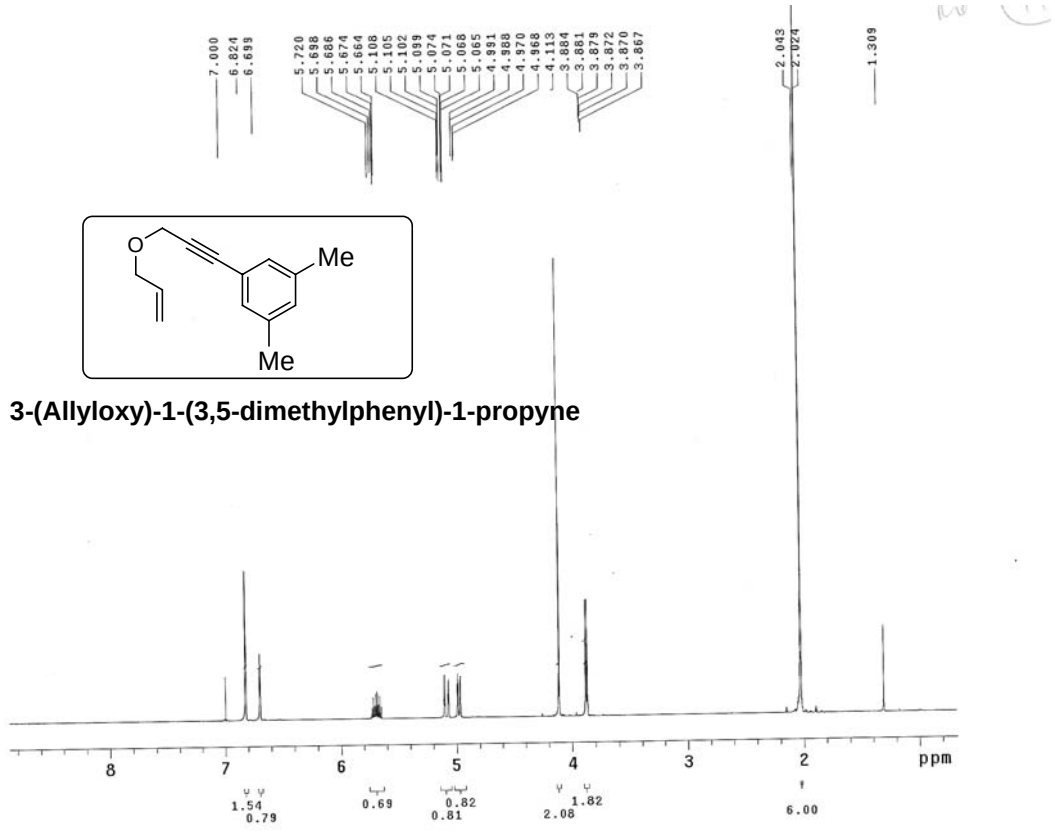
3-(Allyloxy)-1-(4-fluorophenyl)-1-propyne



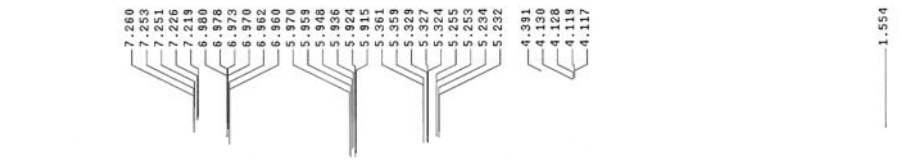
3-(Allyloxy)-1-(4-trifluoromethylphenyl)-1-propyne

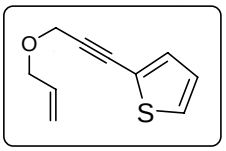


3-(Allyloxy)-1-(2-methylphenyl)-1-propyne

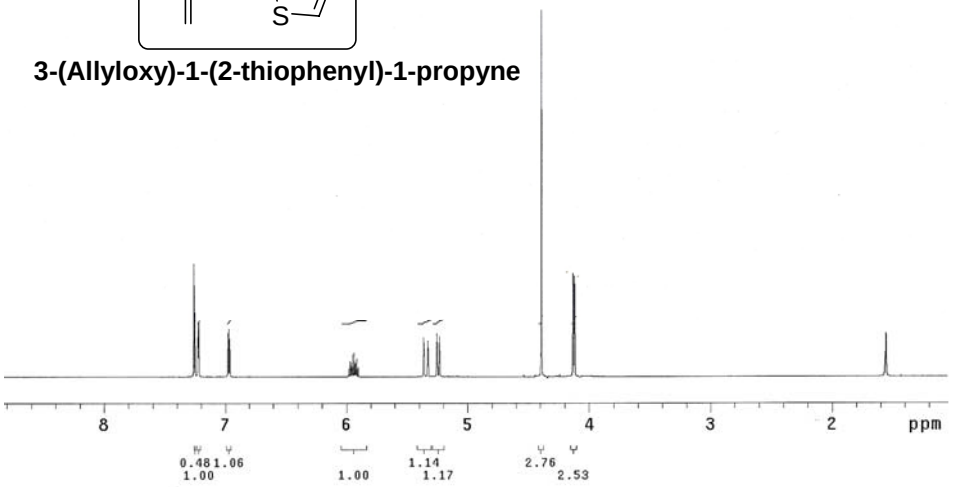


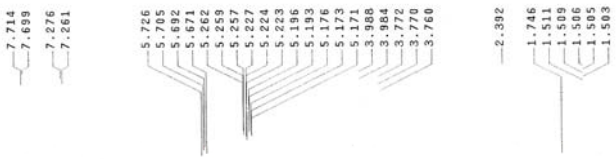
3-(Allyloxy)-1-(3,5-dimethylphenyl)-1-propyne

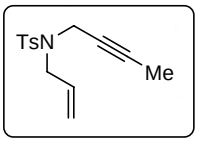




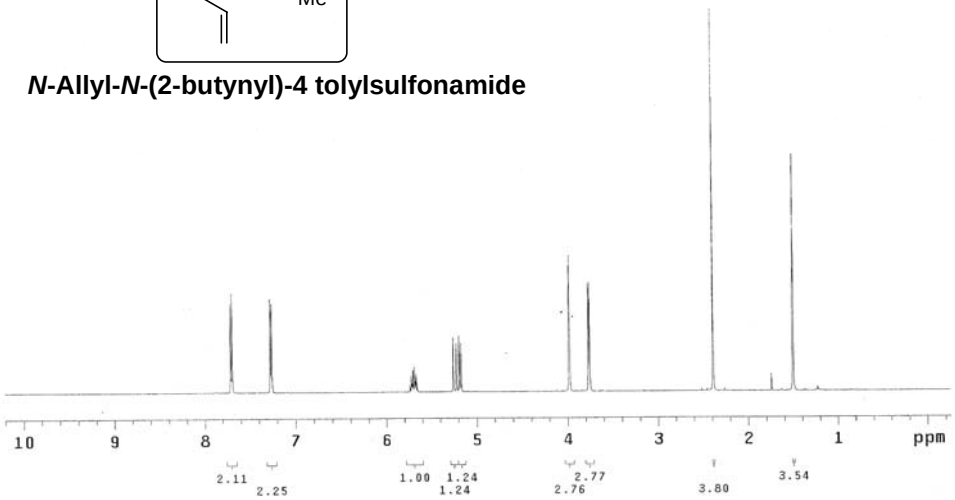
3-(Allyloxy)-1-(2-thiophenyl)-1-propyne

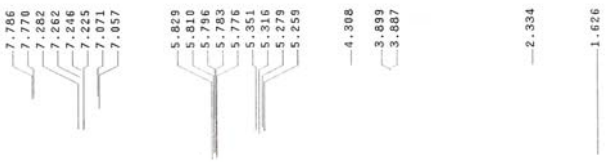


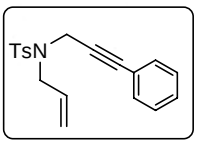




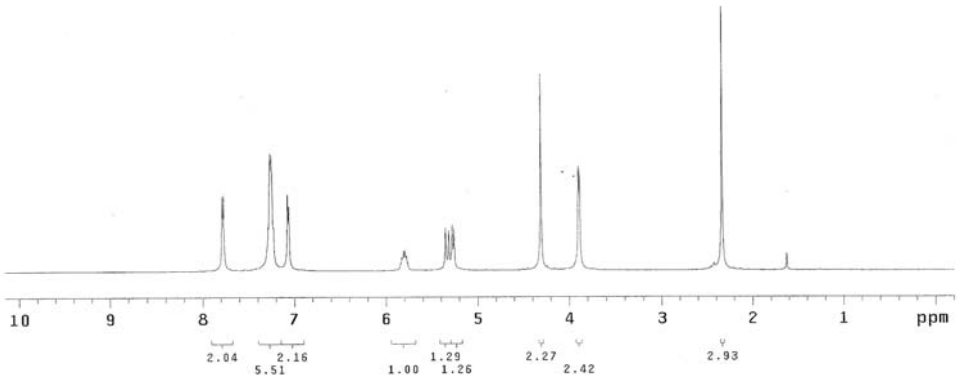
***N*-Allyl-*N*-(2-butynyl)-4 tolylsulfonamide**

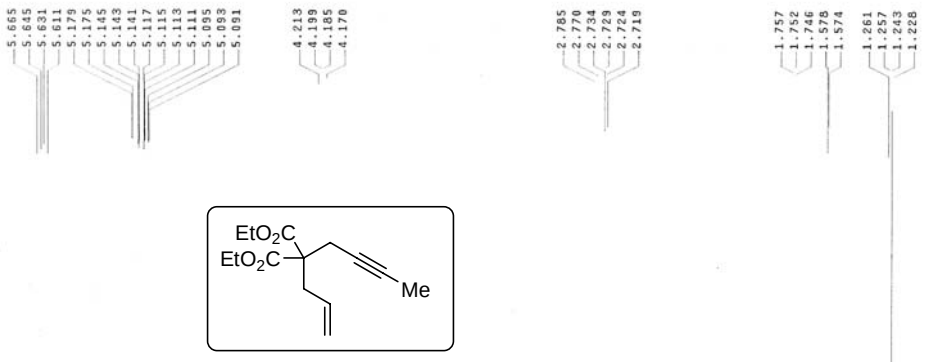




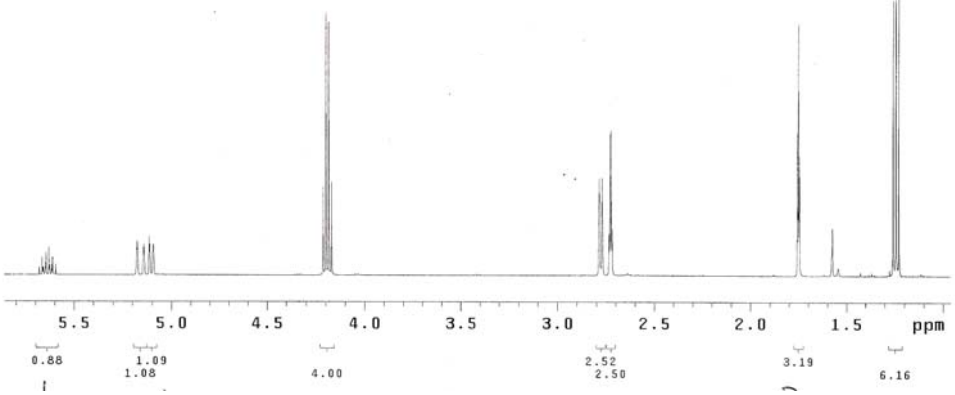


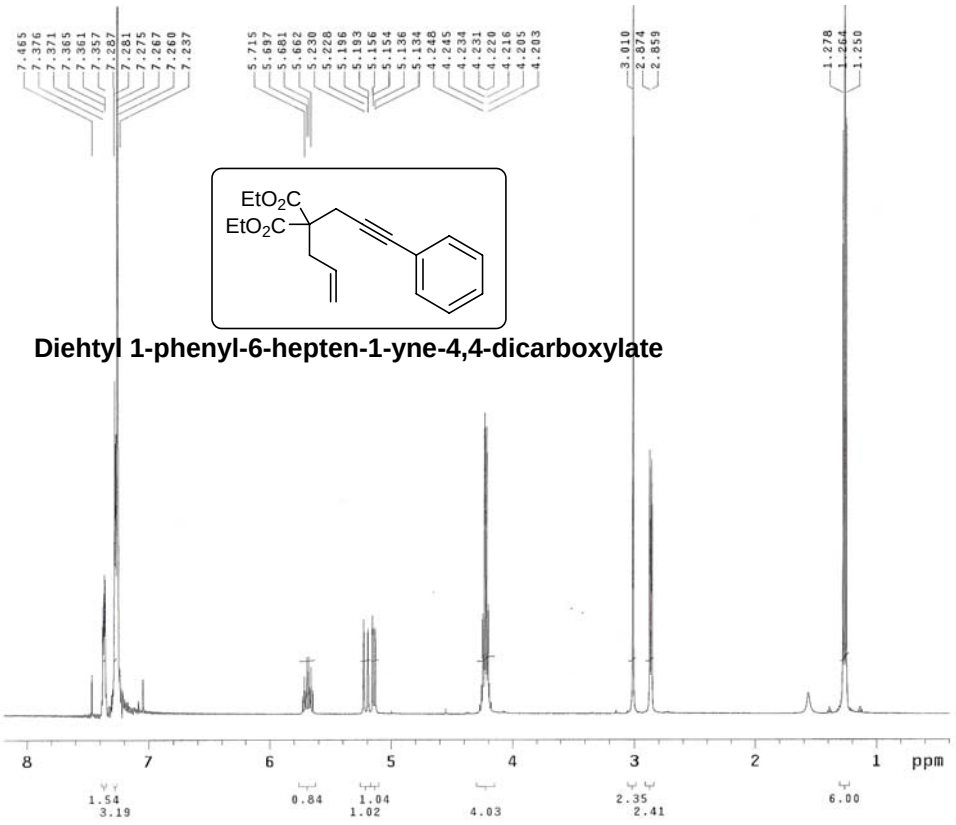
***N*-Allyl-*N*-(3-phenyl-2-propynyl)-4-tolylsulfonamide**



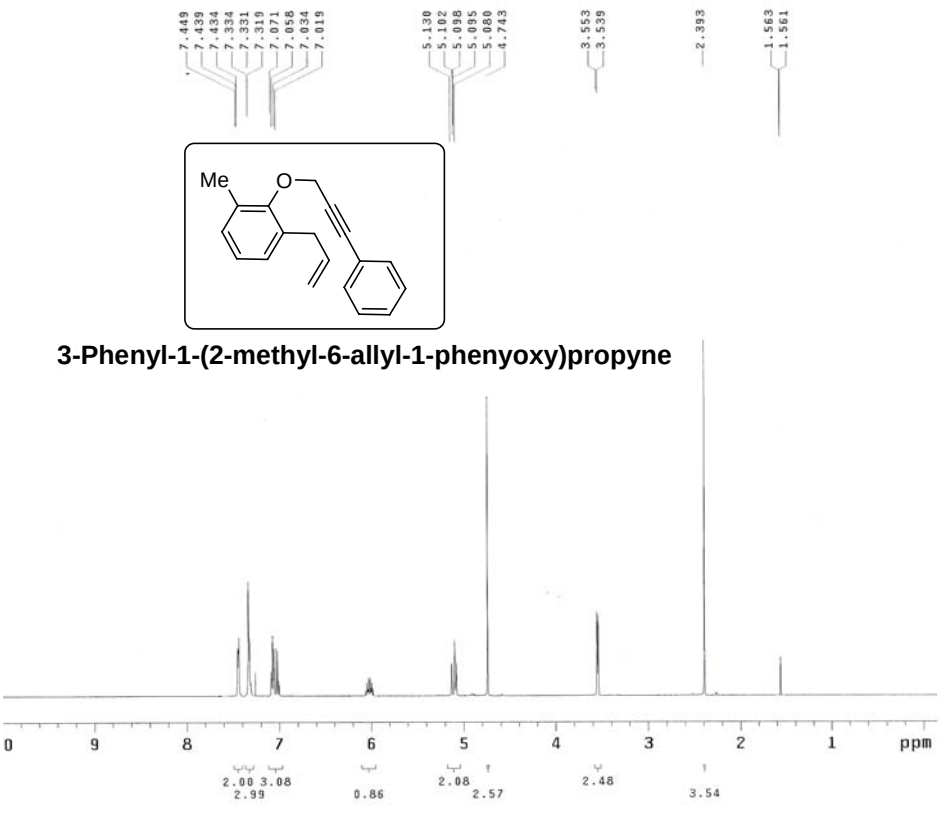


Diethyl 7-octen-2-yne-5,5-dicarboxylate



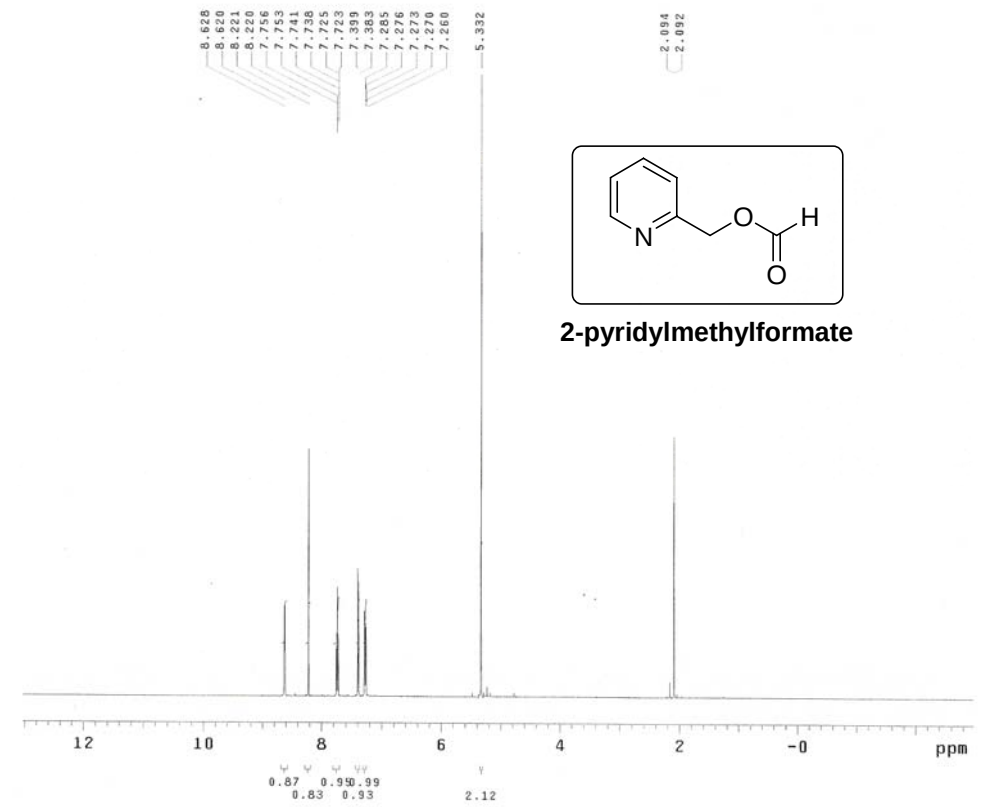


Diehtyl 1-phenyl-6-hepten-1-yne-4,4-dicarboxylate

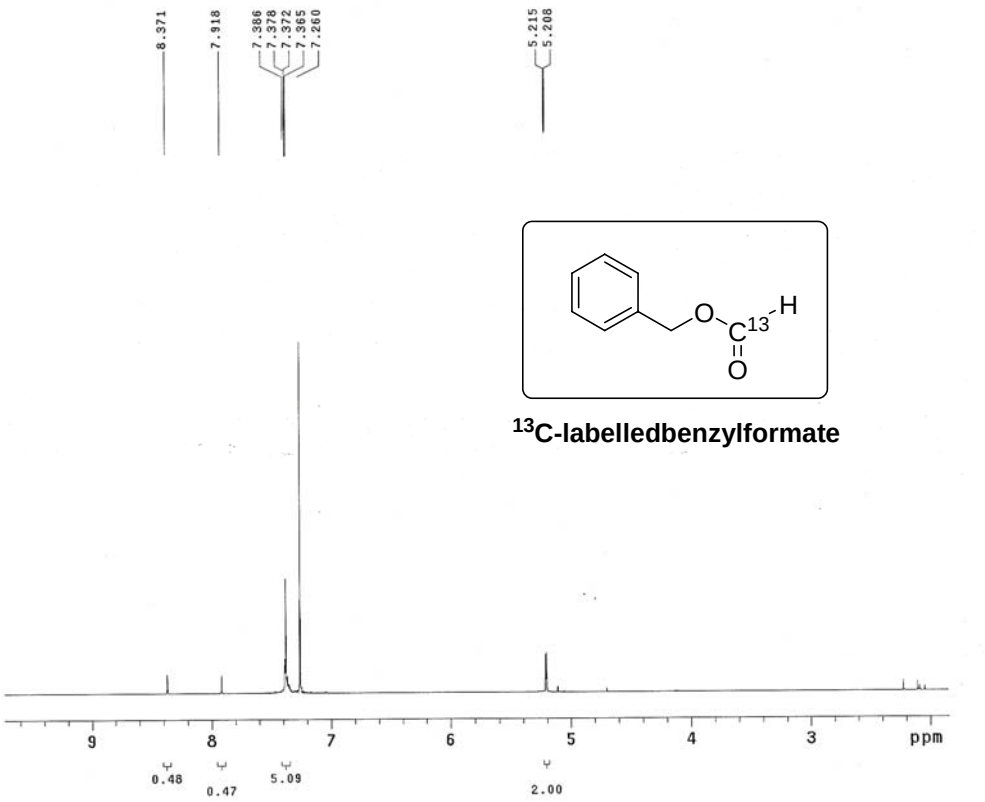


3-Phenyl-1-(2-methyl-6-allyl-1-phenyoxy)propyne

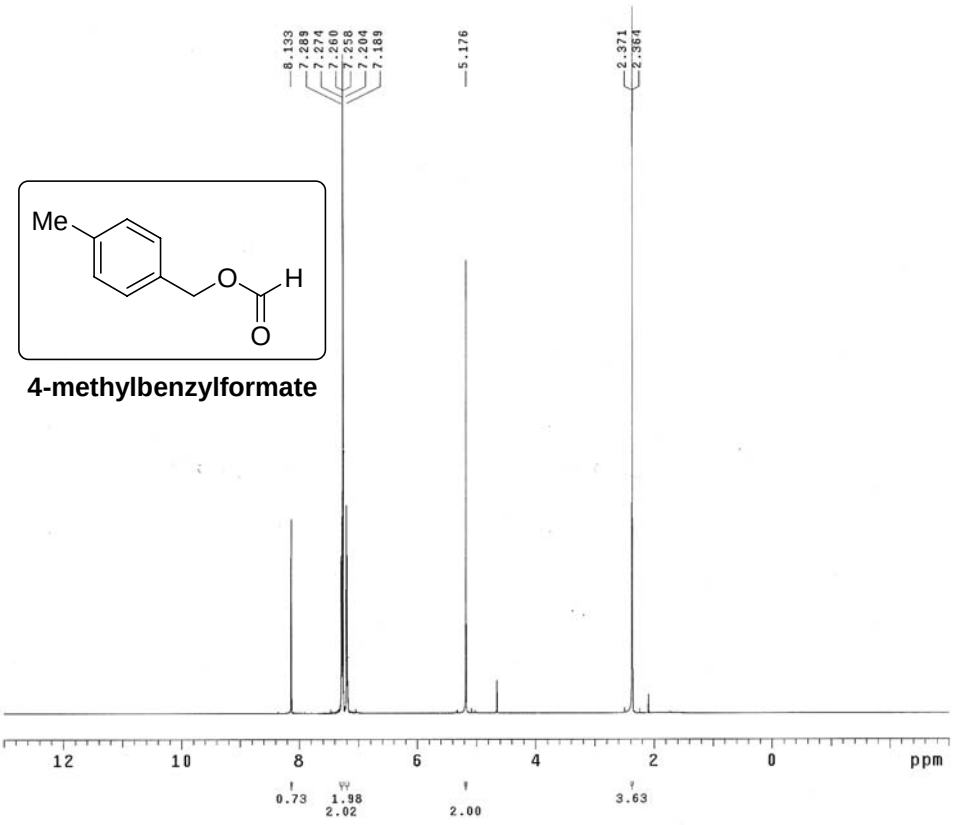
NMR Spectra of formates



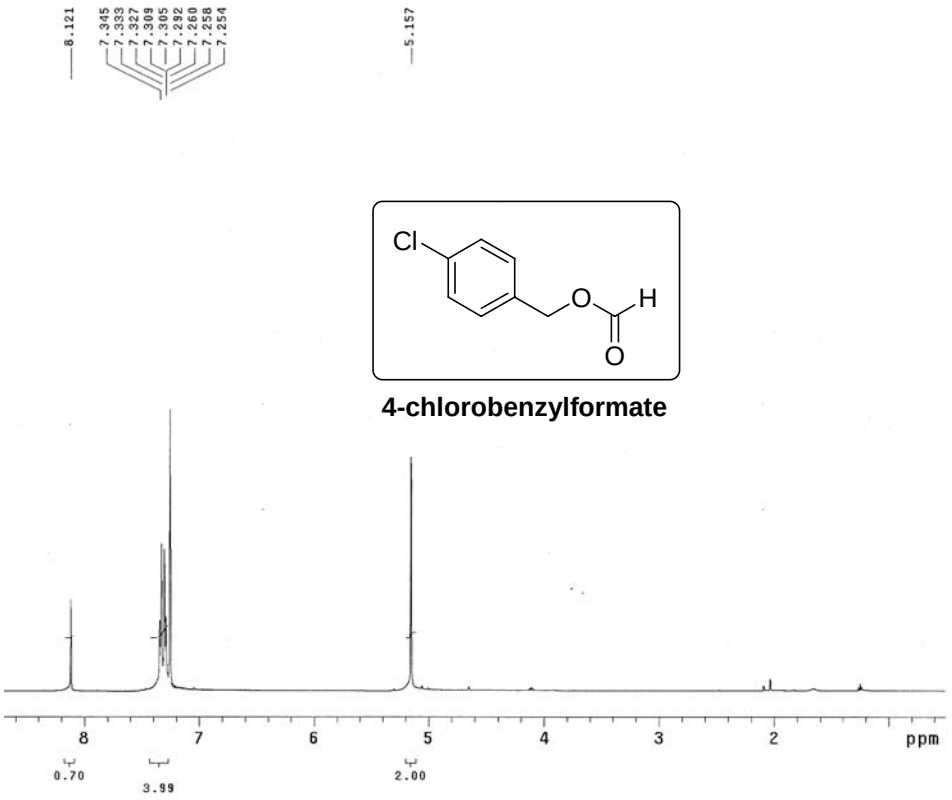
2-pyridylmethylformate



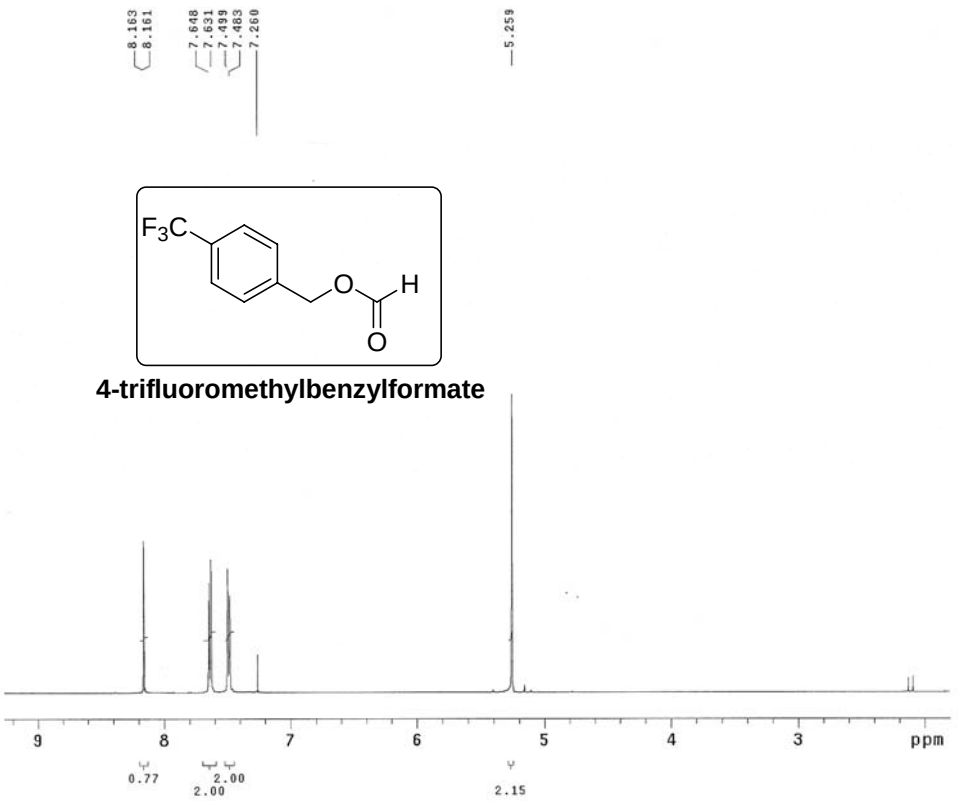
^{13}C-labelledbenzylformate



4-methylbenzylformate

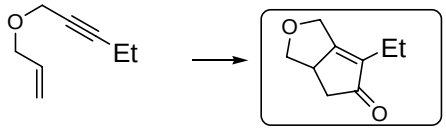


4-chlorobenzylformate

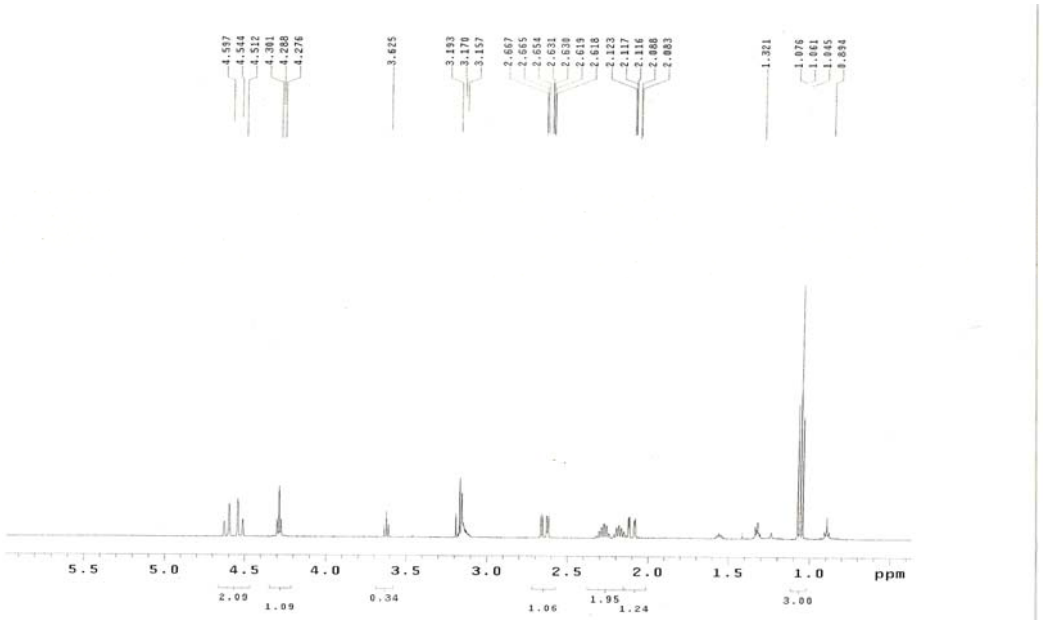


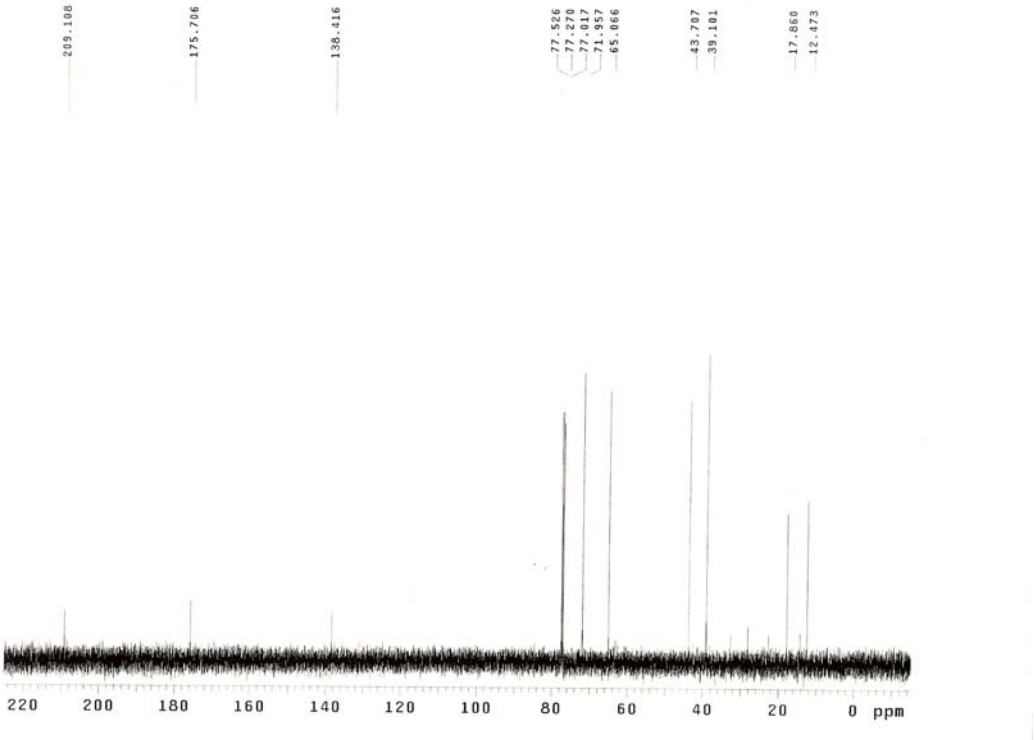
4-trifluoromethylbenzylformate

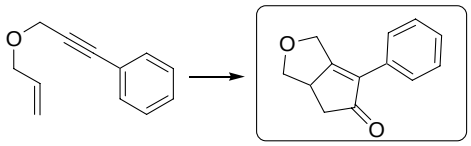
NMR spectra of cyclopentenones



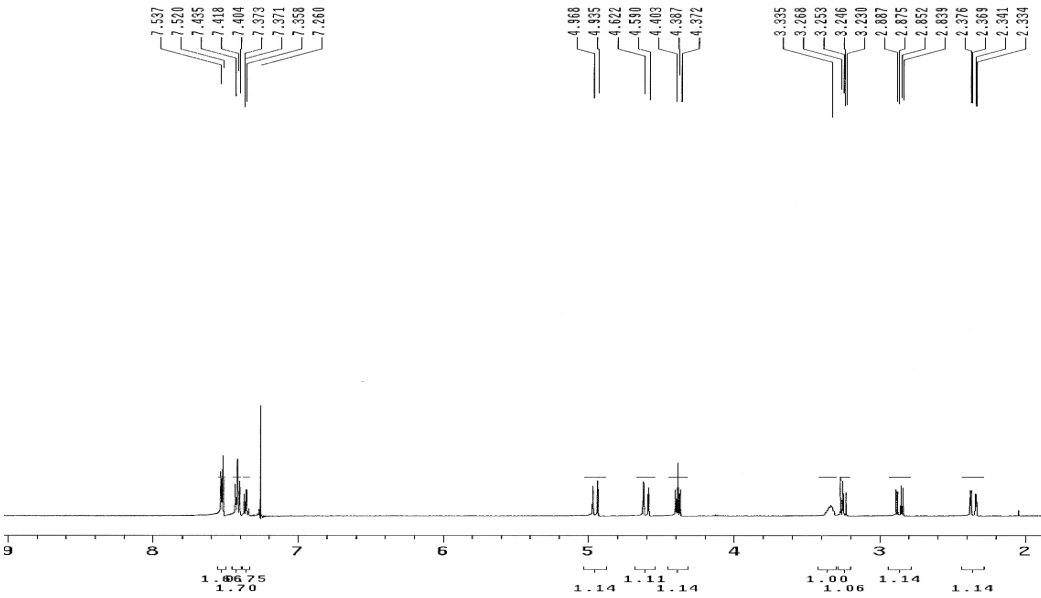
2-Ethyl-7-oxabicyclo[3.3.0]oct-1-en-3-one

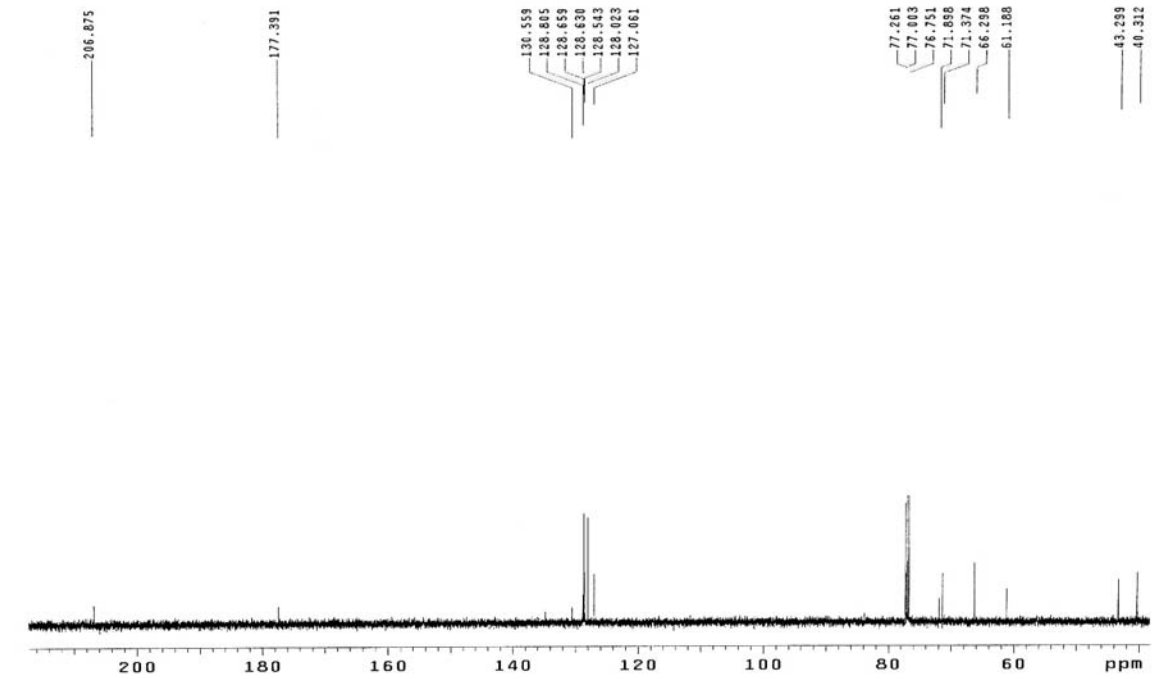


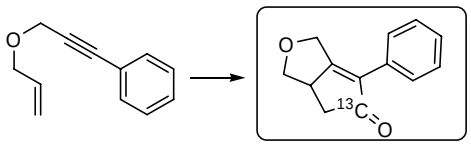




2-Phenyl-7-oxabicyclo[3.3.0]oct-1-en-3-one[19]





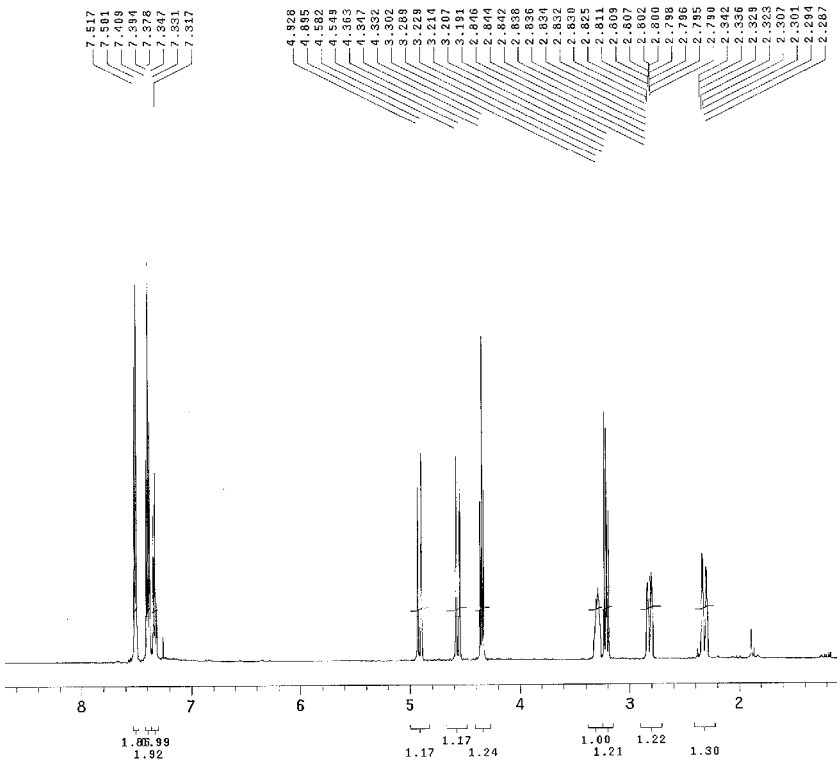


^{13}C-enriched 2-phenyl-7-oxabicyclo[3.3.0]oct-1-en-3-one

STANDARD PROTON PARAMETERS

exp1 s2pul

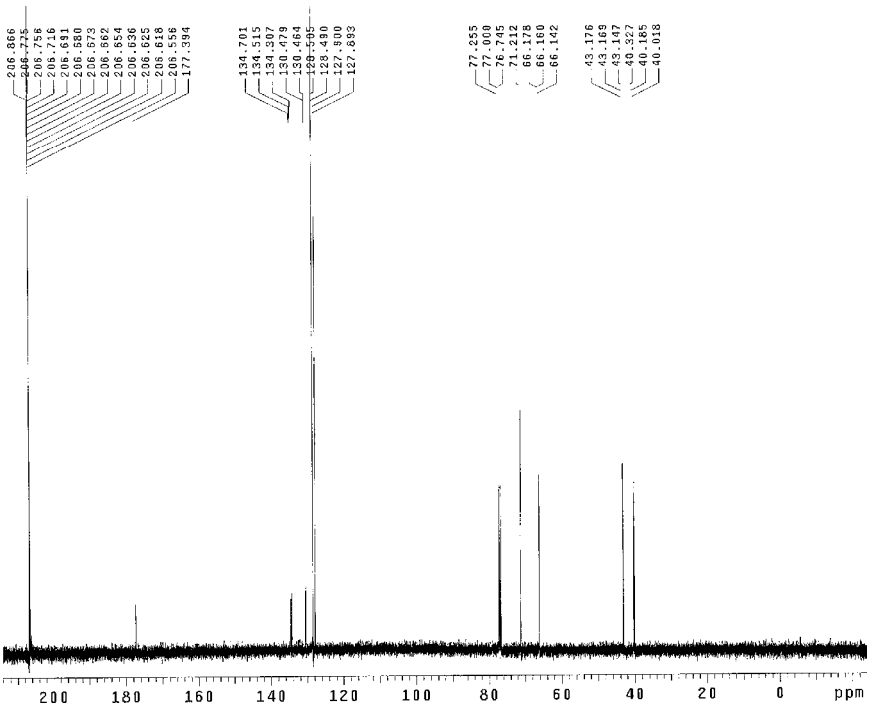
SAMPLE		DEC. & VT	
date	Nov 28 2006	dfrq	499.742
solvent	CDCl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	499.742	dm	nnn
tn	H1	dmm	c
at	1.892	dmf	200
np	30272	dseq	
sw	8000.0	dres	1.0
fb	4000	homo	n
bs	32	DEC2	
tpwr	57	dfrq2	0
pw	5.5	dn2	
d1	0	dpwr2	1
tof	0	dof2	0
nt	8	dm2	n
ct	8	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	PROCESSING	
dp	y	wtfile	
hs	nn	proc	ft
DISPLAY		fn	not used
sp	245.1	math	f
wp	4105.2		
vs	81	werr	
sc	0	wexp	
wc	180	wbs	
hzmm	22.81	wnt	wft
is	33.57		
rfl	5129.7		
rfp	3628.1		
th	7		
ins	1.000		
nm cdc ph			



STANDARD CARBON PARAMETERS

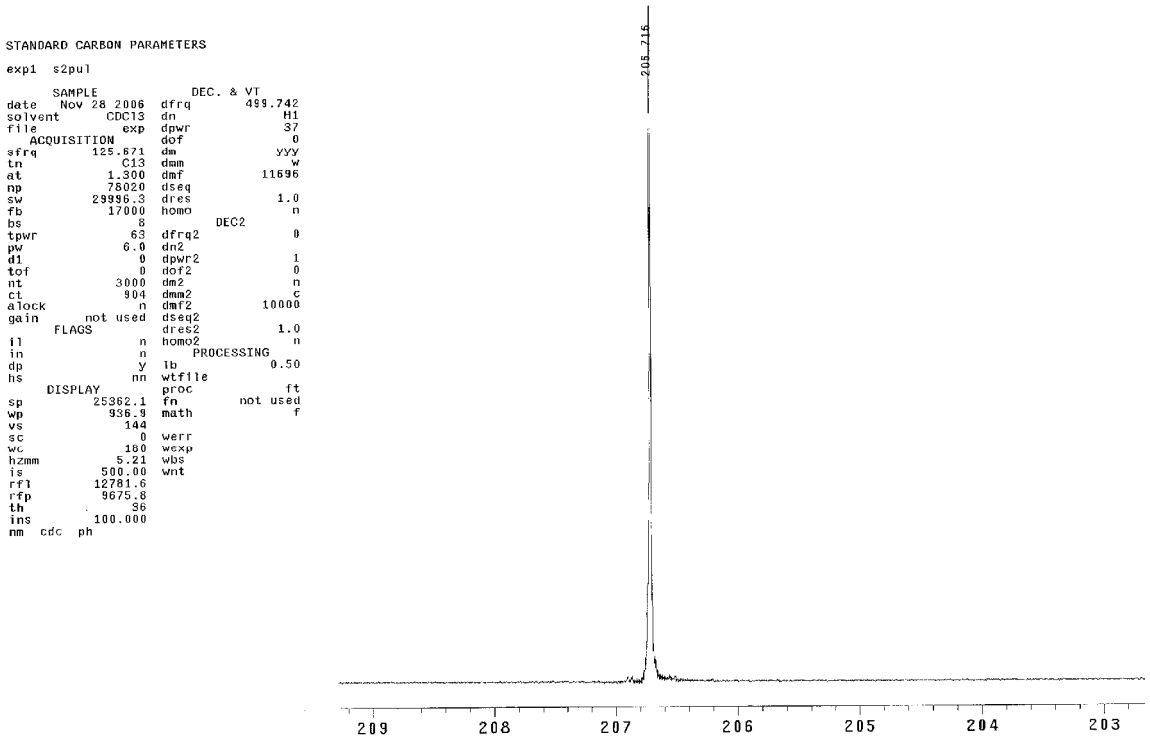
exp1 s2pul

SAMPLE		DEC. & VT	
date	Nov 28 2006	dfrq	499.742
solvent	CDCl3	dn	H1
file	exp	dpwr	37
ACQUISITION		dof	0
sfrq	125.671	dm	YYY
tn	C13	dmm	W
at	1.300	dmf	11686
np	78020	dseq	
sw	29996.3	dres	1.0
fb	17000	homo	n
bs	8	DEC2	
tpwr	63	dfrq2	0
pw	6.0	dn2	
d1	0	dpwr2	1
tof	0	dof2	0
nt	3000	dm2	n
ct	904	dmm2	c
alock	n	dmf2	10000
gain	not used	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	PROCESSING	
dp	y	lb	0.50
hs	nn	wtfile	
DISPLAY		proc	ft
sp	-3105.9	fn	not used
wp	29996.3	math	f
vs	1177		
sc	0	werr	
wc	100	wexp	
hzmm	166.85	wbs	
is	500.00	wnt	
rfl	12781.6		
rfp	9675.8		
th	8		
ins	100.000		
nm cdc ph			

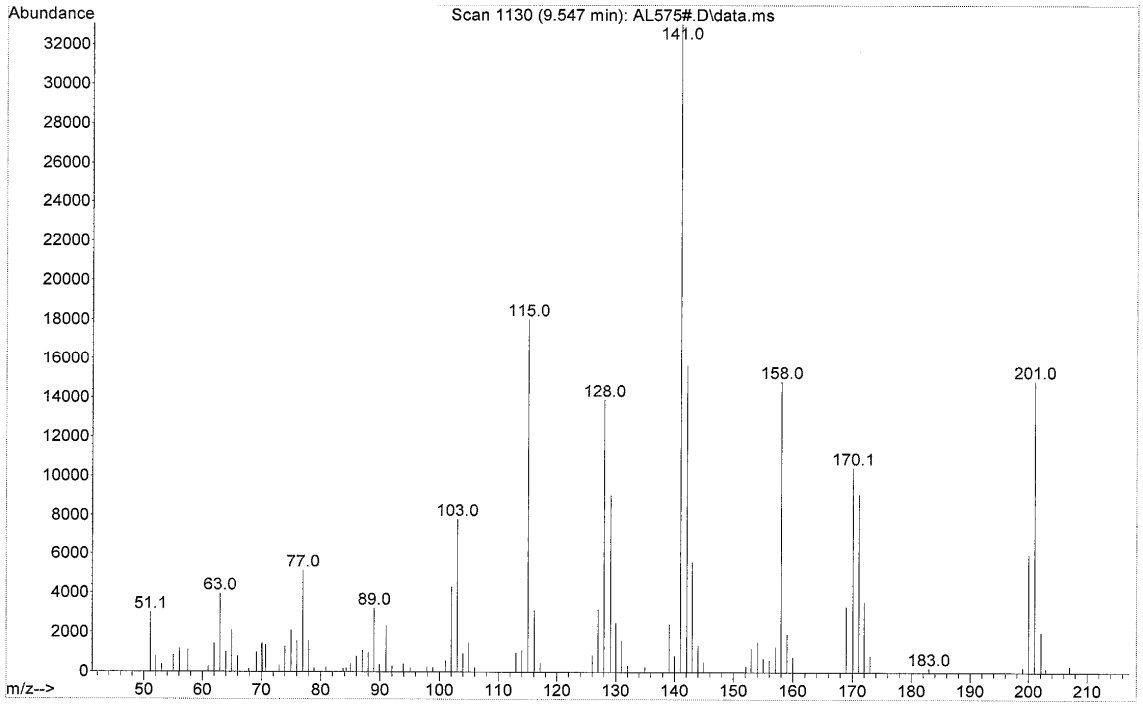


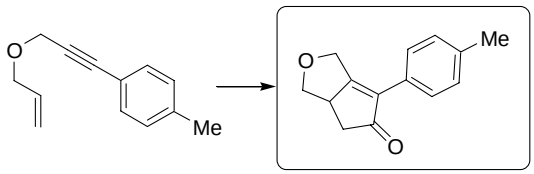
^{13}C NMR of ^{13}C-enriched 2-phenyl-7-oxabicyclo[3.3.0]oct-1-en-3-one

(enlarged labeled region)



Mass spectrum of ^{13}C-enriched 2-phenyl-7-oxabicyclo[3.3.0]oct-1-en-3-one



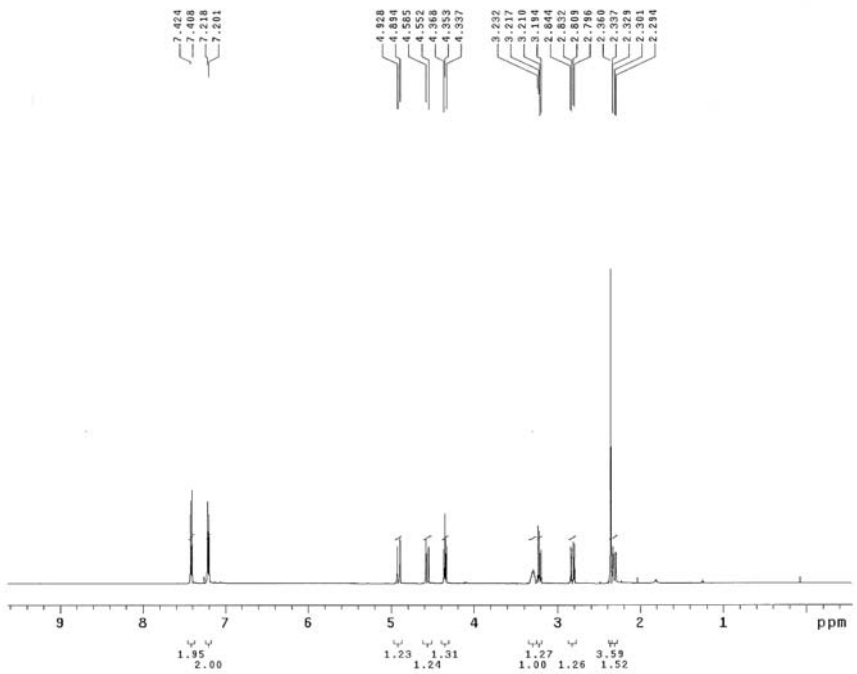


2-(4-Methylphenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one

STANDARD PROTON PARAMETERS

exp1 s2pul

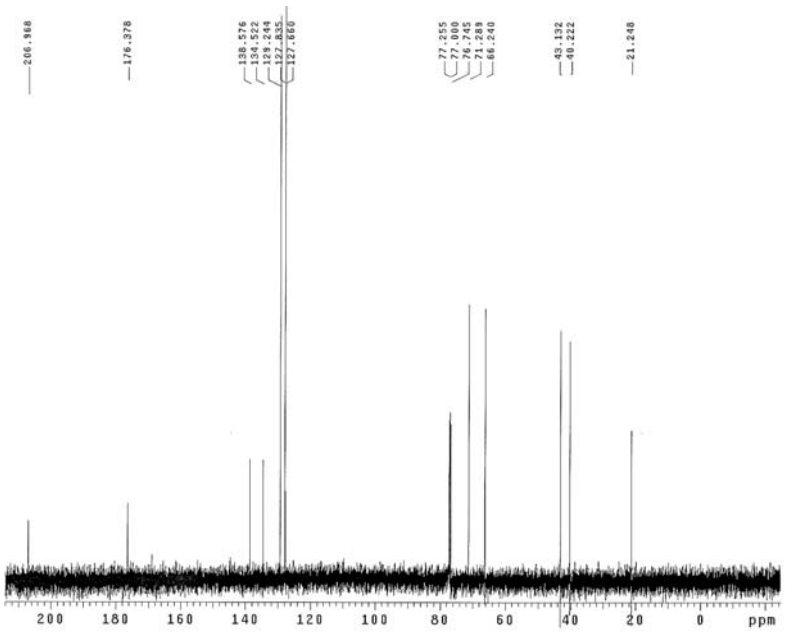
SAMPLE		DEC. & VT	
date	Mar 13 2007	dfrq	499.742
solvent	CDCl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	499.742	dm	nnn
tn	H1	dmm	c
at	1.892	dmf	200
np	30272	dseq	
sw	8000.0	dres	1.0
fb	4000	homo	n
bs	32	DEC2	
tpwr	57	dfrq2	0
pw	5.5	dn2	
d1	0	dpwr2	1
tof	0	dof2	0
nt	8	dm2	n
ct	8	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	PROCESSING	
dp	y	wtfile	
hs	nn	proc	ft
DISPLAY		fn	not used
sp	-273.5	math	f
wp	5088.7		
vs	72	werr	
sc	0	wexp	
wc	180	wbs	
hzmm	28.27	wnt	wft
is	33.57		
rf1	5130.7		
rfp	3628.1		
th	3		
ins	1.000		
nm cdc ph			

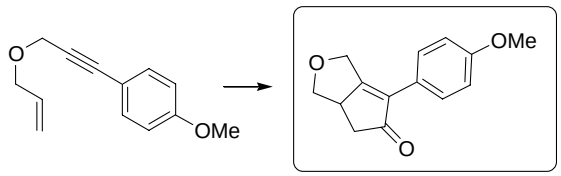


STANDARD CARBON PARAMETERS

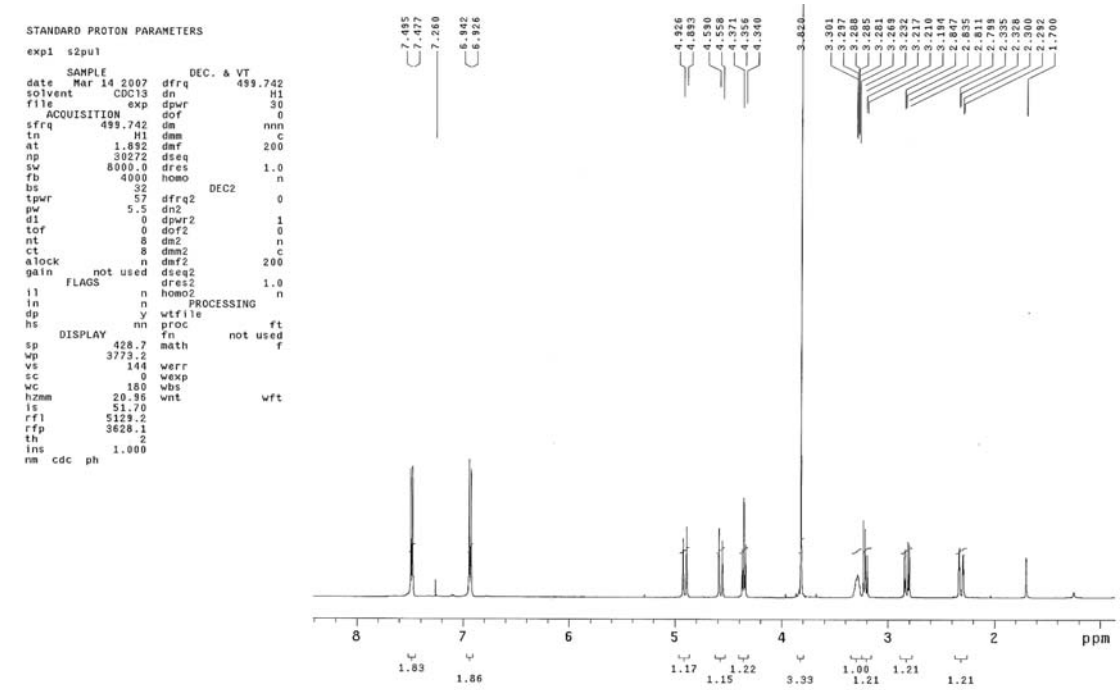
exp1 s2pul

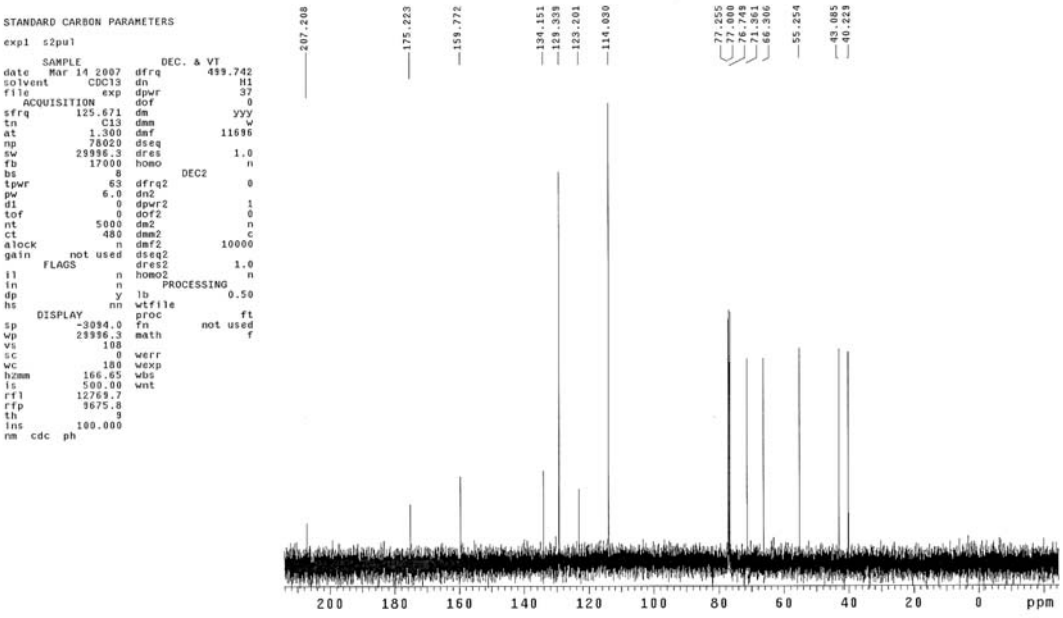
SAMPLE		DEC. & VT	
date	Mar 13 2007	dfrq	499.742
solvent	CDCl3	dn	H1
file	exp	dpwr	37
ACQUISITION		dof	0
sfrq	125.671	dm	yyy
tn	C13	dmm	w
at	1.300	dmf	11696
np	78020	dseq	
sw	29996.3	dres	1.0
fb	17000	homo	n
bs	8	DEC2	
tpwr	63	dfrq2	0
pw	6.0	dn2	
d1	0	dpwr2	1
tof	0	dof2	0
nt	5000	dm2	n
ct	232	dmm2	c
alock	n	dmf2	10000
gain	not used	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	PROCESSING	
dp	y	lb	0.50
hs	nn	wtfile	
DISPLAY		proc	ft
sp	-3100.4	fn	not used
wp	29996.3	math	f
vs	141		
sc	0	werr	
wc	180	wexp	
hzmm	166.65	wbs	
is	500.00	wnt	
rf1	12776.2		
rfp	9675.8		
th	10		
ins	100.000		
nm cdc ph			

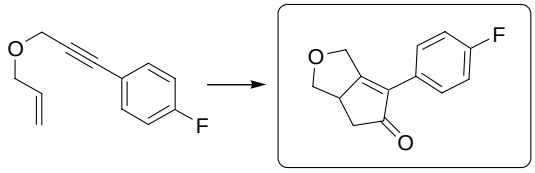




2-(4-Methoxyphenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one[20]





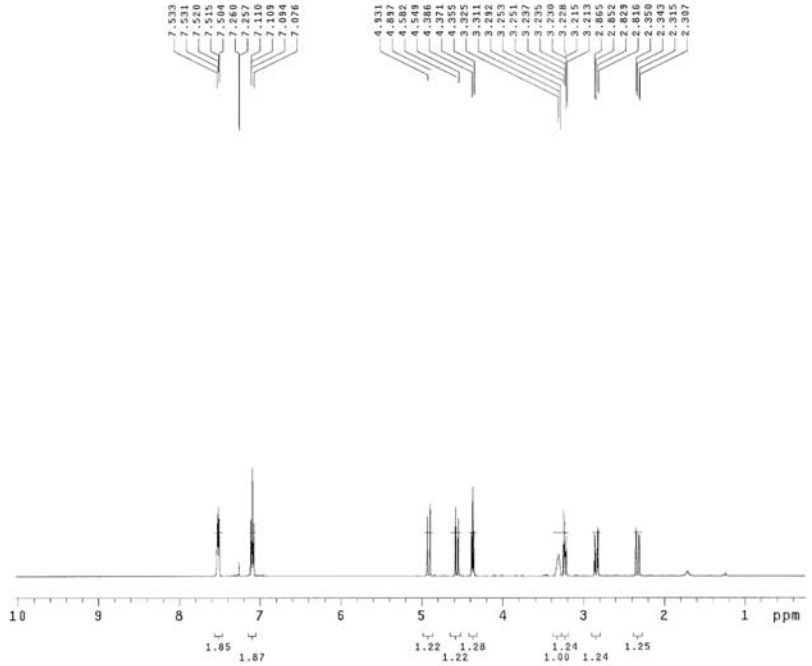


2-(4-Fluorophenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one

```
STANDARD PROTON PARAMETERS

expl  s2pul

      SAMPLE                DEC. & VT
date    Feb 21 2007  dfrq        499.742
solvent       CDCl3  dn              H1
file            exp  dpwr            30
   ACQUISITION       dof              0
sfrq        499.742  dm             nnn
tn               H1  dmm              c
at            1.892  dmf            200
np            30272  dseq
sw           8000.0  dres           1.0
fb             4000  homo             n
bs               32              DEC2
tpwr             57  dfrq2            0
pw              5.5  dn2
d1                0  dpwr2            1
tof               0  dof2             0
nt                8  dm2              n
ct                8  dmm2             c
alock             n  dmf2           200
gain      not used   dseq2
      FLAGS          dres2          1.0
il                n  homo2            n
in                n              PROCESSING
dp                y  wtfile
hs               nn  proc             ft
     DISPLAY         fn         not used
sp            125.0  math               f
wp           4884.1
vs               25  werr
sc                0  wexp
wc              180  wbs
hzmm          27.13  wnt              wft
is             1.05
rfl          5131.2
rfp          3628.1
th              2
lns          1.000
nm  cdc  ph
```



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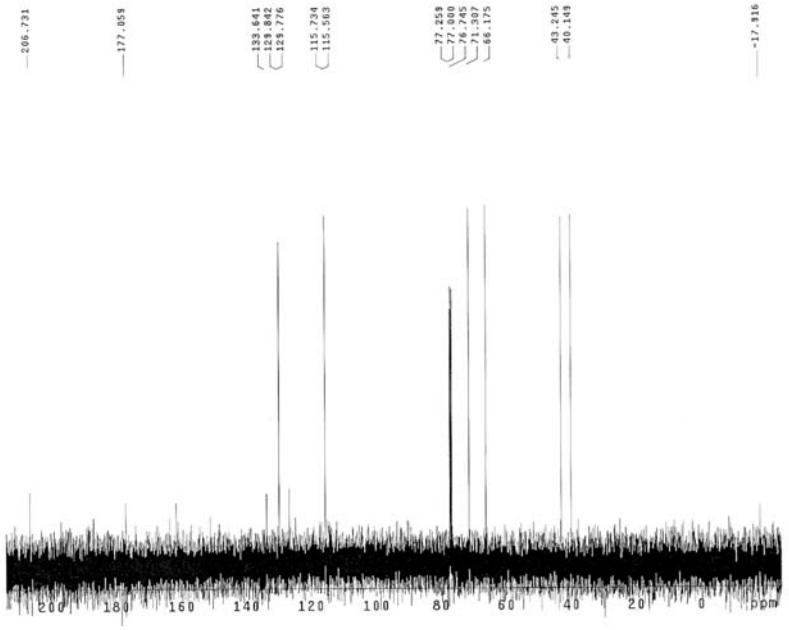
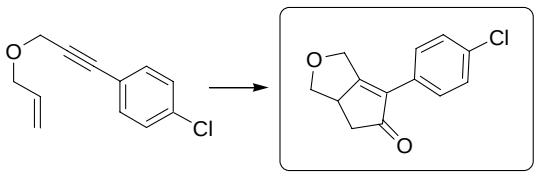
STANDARD CARBON PARAMETERS

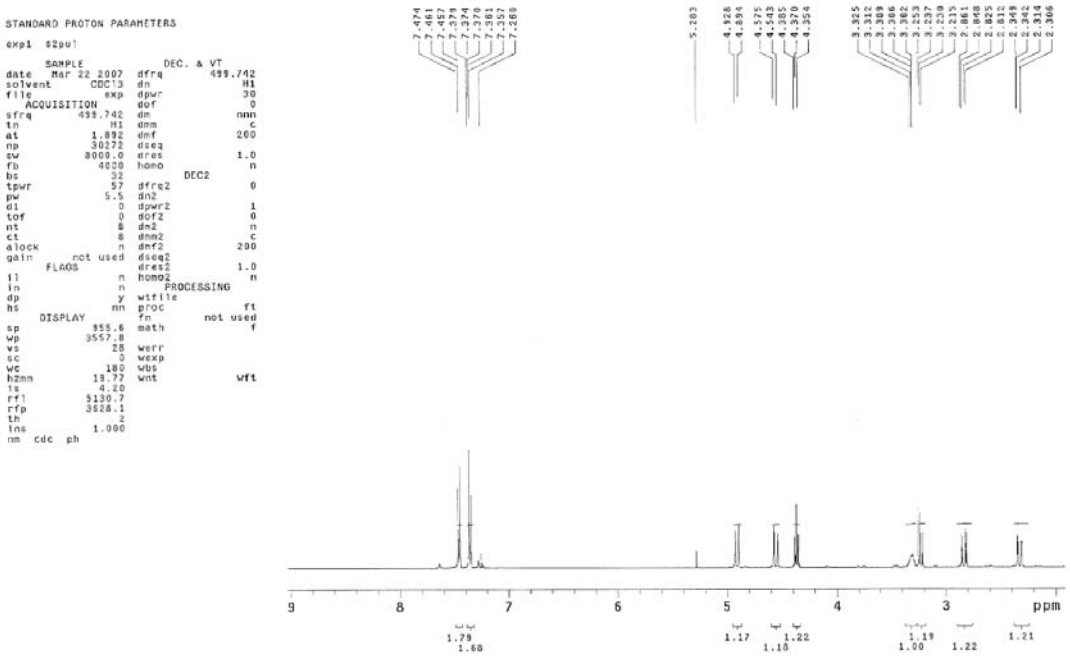
expl  s2pul

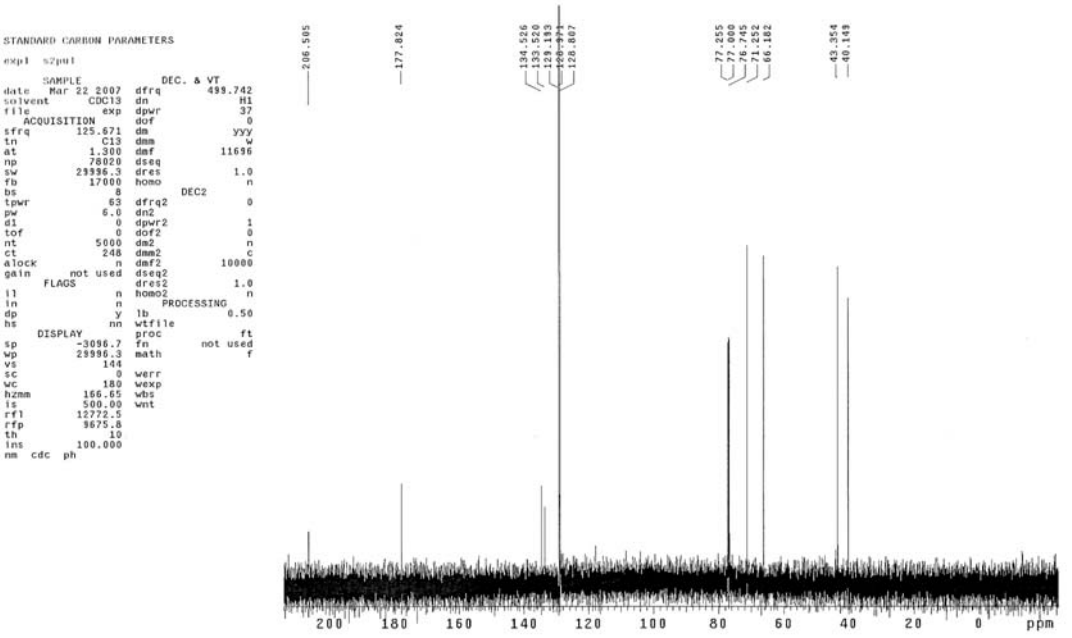
      SAMPLE                DEC. & VT
date    Mar 13 2007  dfrq        499.742
solvent       CDCl3  dn              H1
file            exp  dpwr            37
   ACQUISITION       dof              0
sfrq        125.671  dm             yyy
tn               C13  dmm              w
at             1.300  dmf          11696
np             78020  dseq
sw          29996.3   dres           1.0
fb             17000  homo             n
bs                8              DEC2
tpwr             63  dfrq2            0
pw              6.0  dn2
d1                0  dpwr2            1
tof               0  dof2             0
nt             5000  dm2              n
ct              160  dmm2             c
alock             n  dmf2         10000
gain      not used   dseq2
      FLAGS          dres2          1.0
il                n  homo2            n
in                n              PROCESSING
dp                y  lb             0.50
hs               nn  wtfile
     DISPLAY         proc             ft
sp          -3094.4  fn         not used
wp          29996.3  math               f
vs               85
sc                0  werr
wc              180  wexp
hzmm          166.65  wbs
is            500.00  wnt
rfl          12770.2
rfp           9675.8
th              13
lns          100.000
nm  cdc  ph
```

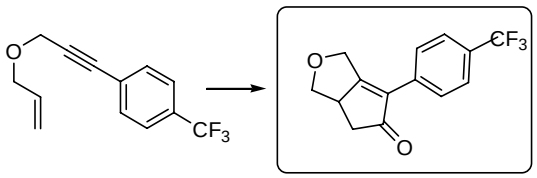




2-(4-Chlorophenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one





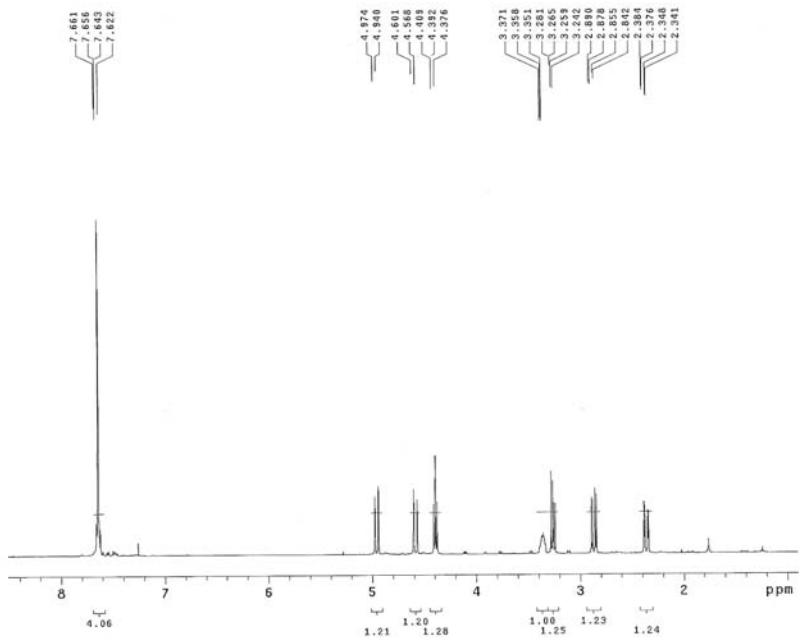


2-(4-Trifluoromethylphenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one

```
STANDARD PROTON PARAMETERS

expl  s2pul

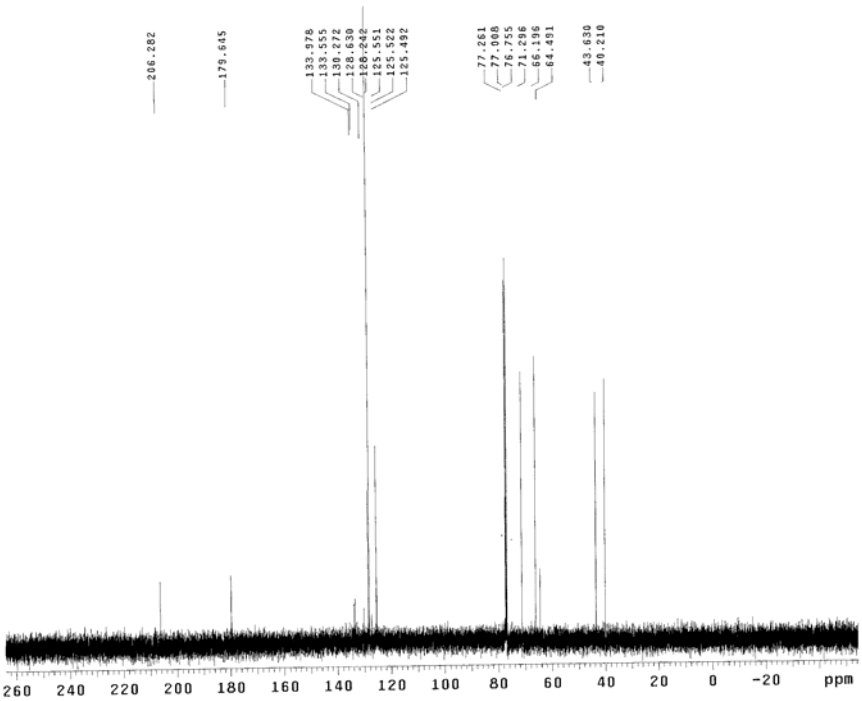
        SAMPLE                    DEC. & VT
date    Mar 22 2007   dfrq          499.742
solvent       CDCl3   dn                Hl
file            exp   dpwr              30
    ACQUISITION       dof                0
sfrq        499.742   dm               nnn
tn               Hl   dmm                c
at            1.892   dmf              200
np            30272   dseq
sw          8000.0    dres             1.0
fb            4000    homo               n
bs              32          DEC2
tpwr            57    dfrq2              0
pw             5.5    dn2
d1               0    dpwr2              1
tof              0    dof2               0
nt               8    dm2                n
ct               8    dmm2               c
alock            n    dmf2             200
gain      not used     dseq2
          FLAGS        dres2            1.0
il               n    homo2              n
in               n         PROCESSING
dp               y    wtfile
hs              nn    proc              ft
      DISPLAY         fn          not used
sp           448.7    math               f
wp          3805.9
vs               81   werr
sc               0    wexp
wc             180    wbs
hzmm         21.14    wnt              wft
is            1.05
rfl         5130.7
rfp         3628.1
th               3
ins          1.000
nm  cdc  ph
```

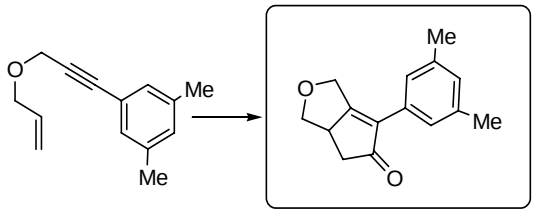



```
Std proton

expl  Carbon

        SAMPLE                    SPECIAL
date    Dec 19 2007   temp          not used
solvent       CDCl3   gain                30
file            exp   spin                20
    ACQUISITION       hst              0.008
sw          40000.0   pw90            17.000
at            1.300   alfa            10.000
np           104038         FLAGS
fb            22000   il                   n
bs                8   in                   n
d1            1.000   dp                   y
nt              500   hs                  nn
ct              304         PROCESSING
    TRANSMITTER       lb                0.50
tn               C13  fn          not used
sfrq        125.673         DISPLAY
tof          1255.0   sp             -6837.5
tpwr           61     wp             39999.4
pw            8.500   rfl            16514.9
      DECOUPLER       rfp             9676.8
dn                Hl  rp               -32.9
dof               0   lp               -357.8
dm              yyy         PLOT
dmm               w   wc                 180
dpwr             37   sc                   0
dmf           11368   vs               18756
                      th                   7
                      ai  cdc  ph
```



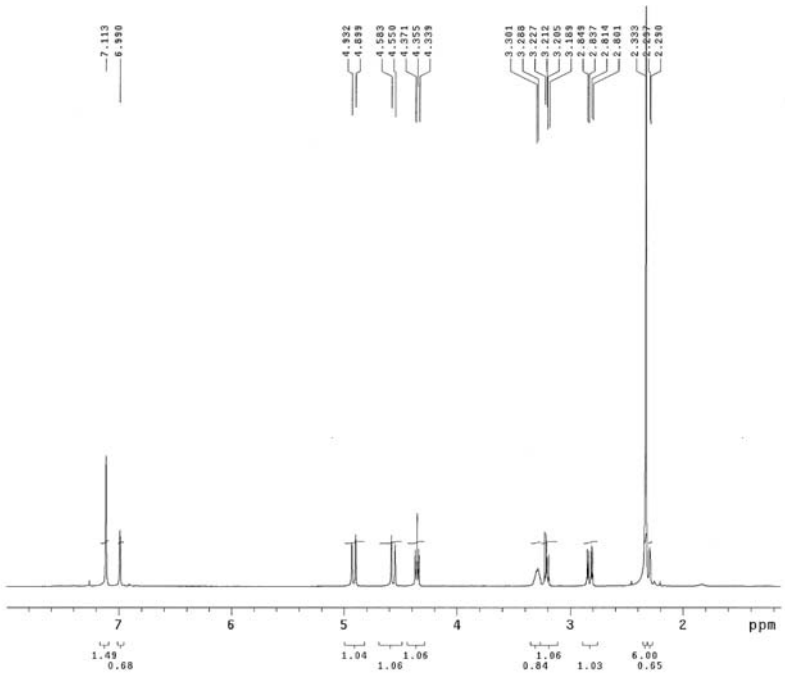


2-(3,5-Dimethylphenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one

STANDARD PROTON PARAMETERS

```
expl  s2pul

      SAMPLE                DEC. & VT
date   Mar 13 2007  dfrq          499.742
solvent       CDCl3  dn                H1
file            exp  dpwr              30
   ACQUISITION       dof                0
sfrq          499.742  dm               nnn
tn                H1  dmm                c
at             1.892  dmf              200
np             39272  dseq
sw            8000.0  dres             1.0
fb              4000  homo               n
bs                32       DEC2
tpwr              57  dfrq2              0
pw               5.5  dn2
d1                 0  dpwr2              1
tof                0  dof2               0
nt                 8  dm2                n
ct                 8  dmm2               c
alock              n  dmf2             200
gain       not used  dseq2
     FLAGS           dres2            1.0
il                 n  homo2             n
in                 n       PROCESSING
dp                 y  wtfile
hs                nn  proc               ft
    DISPLAY          fn           not used
sp             567.4  math                 f
wp            3428.4
vs               144  werr
sc                 0  wexp
wc               180  wbs
hzmm           19.05  wnt              wft
is             33.57
rfl          5130.7
rfp          3628.1
th                 1
ins            6.000
nm  cdc  ph
```



STANDARD CARBON PARAMETERS

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expl  s2pul

      SAMPLE                DEC. & VT
date   Mar 13 2007  dfrq          499.742
solvent       CDCl3  dn                H1
file            exp  dpwr              37
   ACQUISITION       dof                0
sfrq          125.671  dm               yyy
tn                C13  dmm                w
at             1.300  dmf            11696
np             78020  dseq
sw          29996.3  dres               1.0
fb            17000  homo                 n
bs                8       DEC2
tpwr              63  dfrq2              0
pw               6.0  dn2
d1                 0  dpwr2              1
tof                0  dof2               0
nt              5000  dm2                n
ct               240  dmm2               c
alock              n  dmf2           10000
gain       not used  dseq2
     FLAGS           dres2            1.0
il                 n  homo2             n
in                 n       PROCESSING
dp                 y  lb               0.50
hs                nn  wtfile
    DISPLAY          proc               ft
sp           -3101.3  fn           not used
wp          29996.3  math                 f
vs                83
sc                 0  werr
wc               180  wexp
hzmm          166.65  wbs
is            500.00  wnt
rfl          12777.1
rfp           9675.8
th                 6
ins          100.000
nm  cdc  ph
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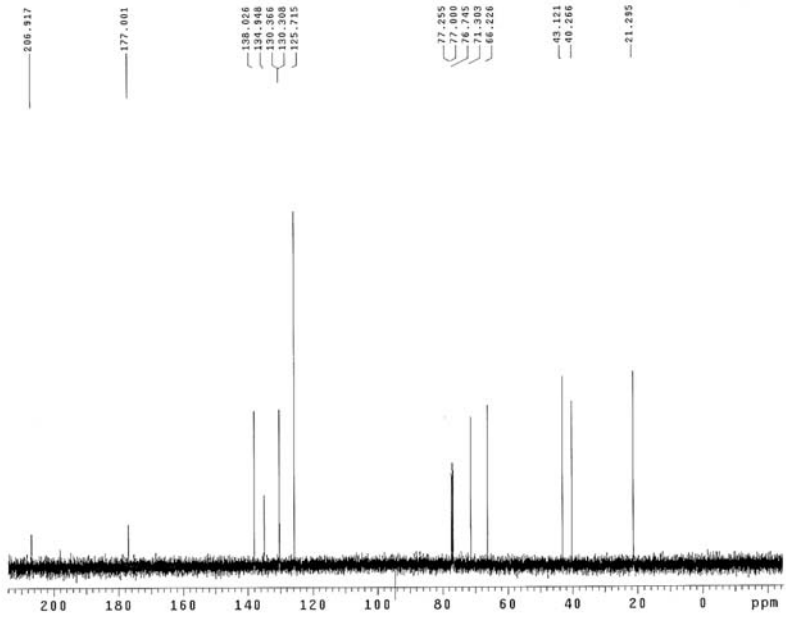
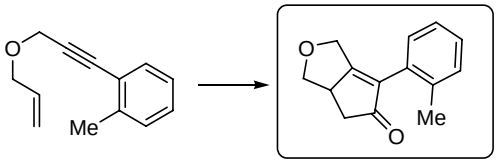
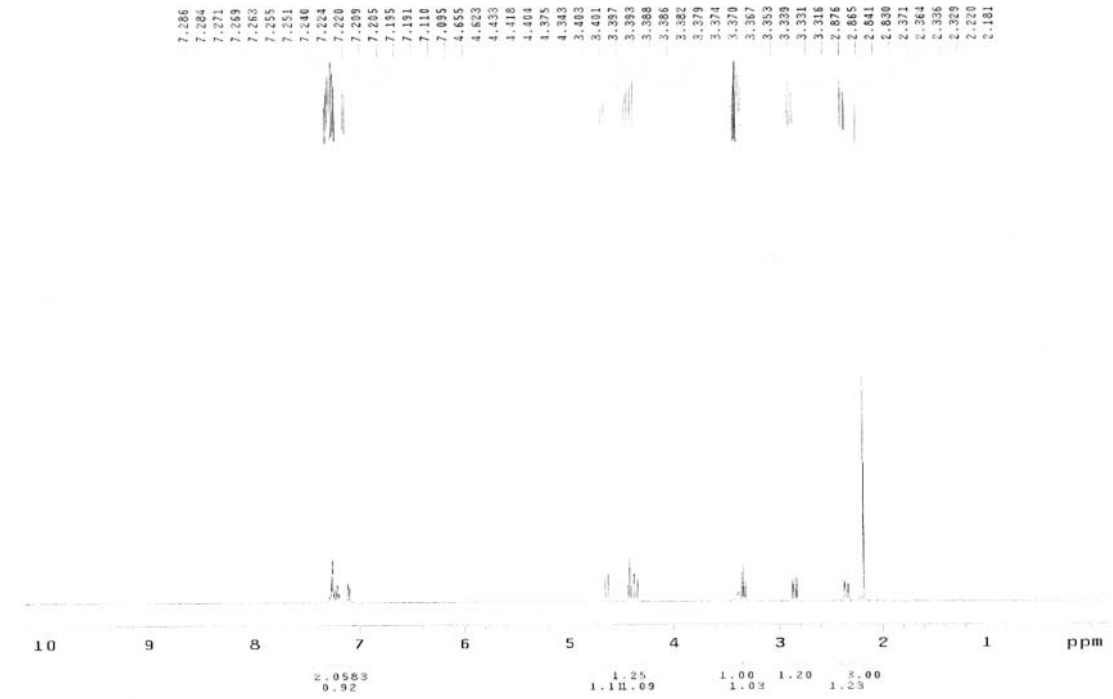
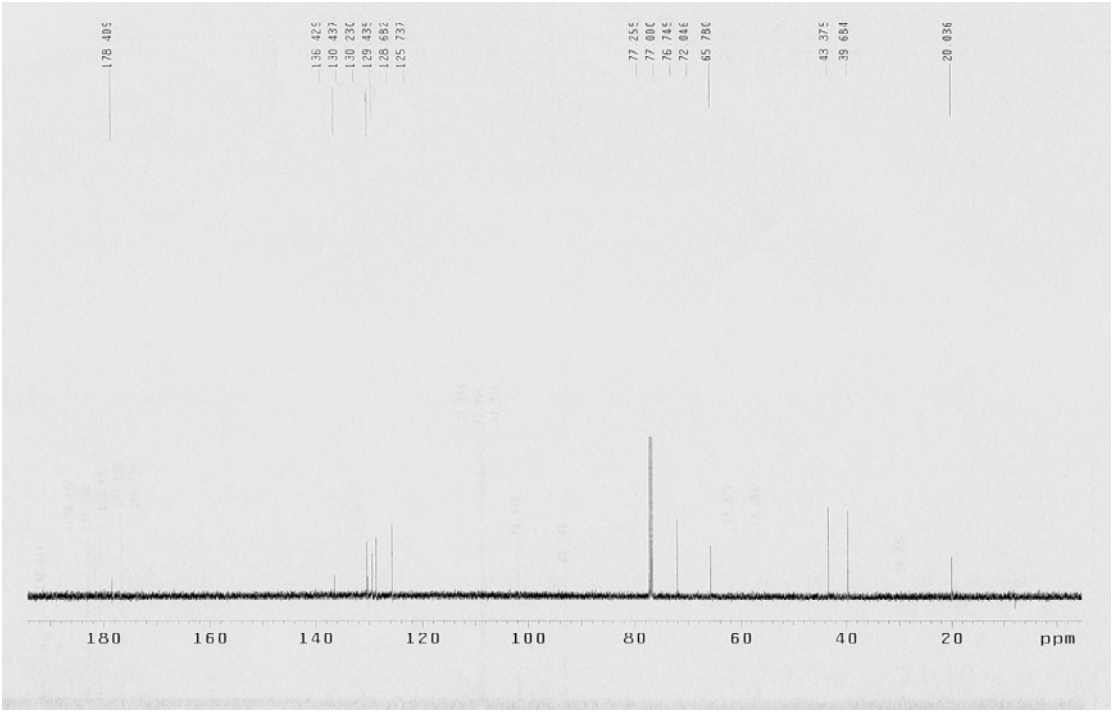
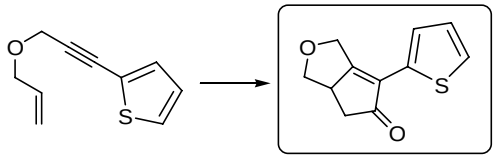




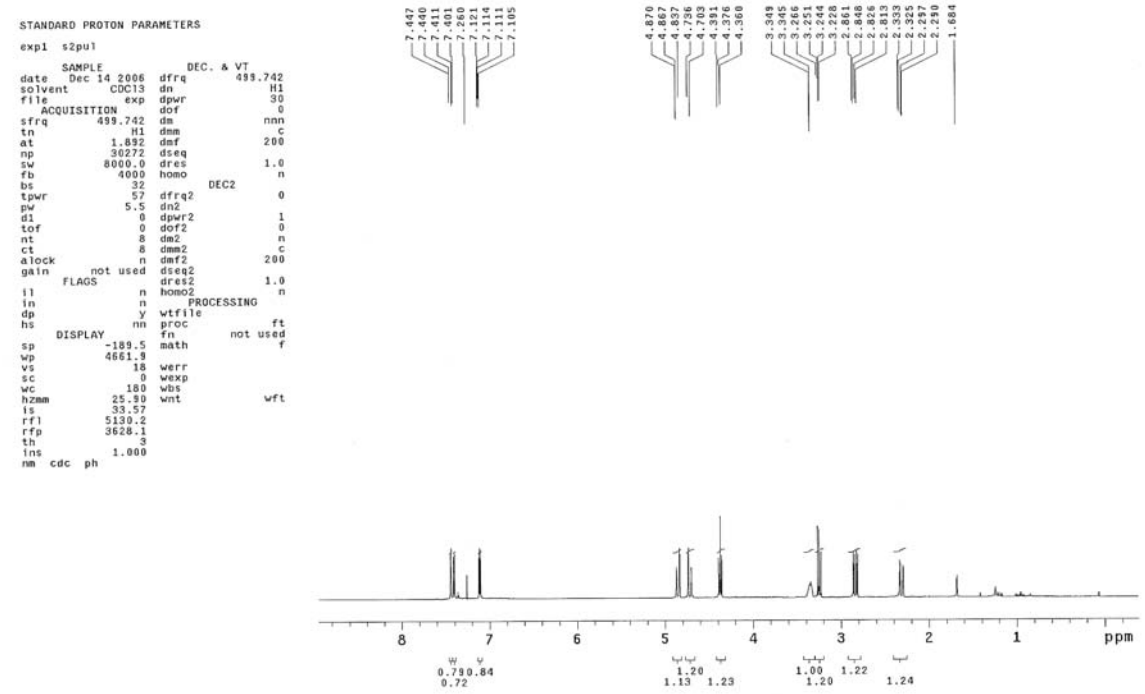
2-(2-Methylphenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one

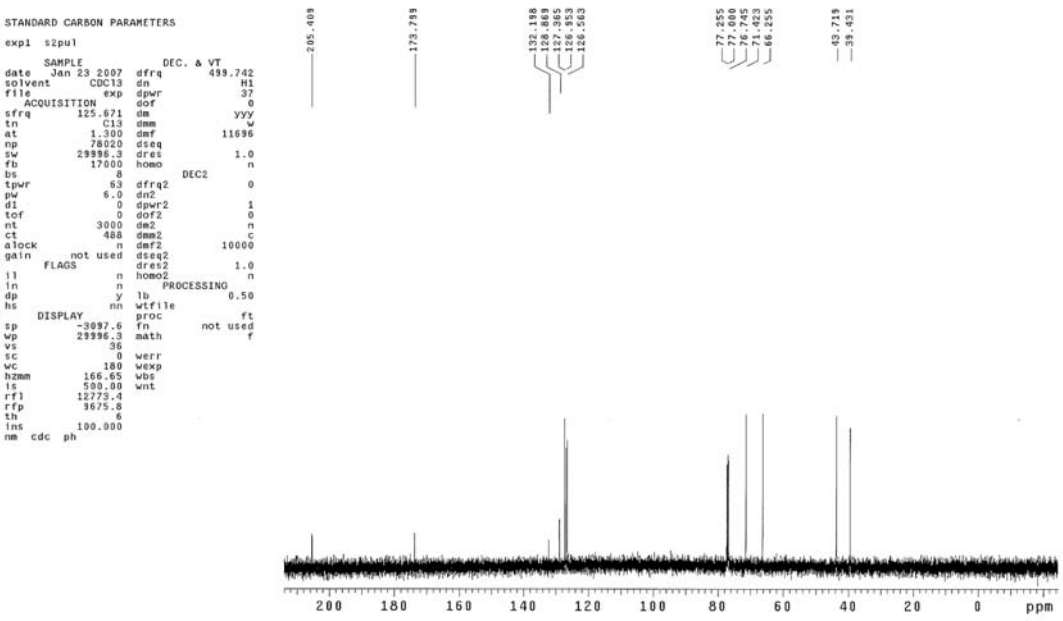


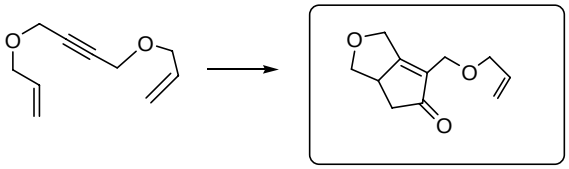




2-(2-Thiophenyl)-7-oxabicyclo[3.3.0]oct-1-en-3-one





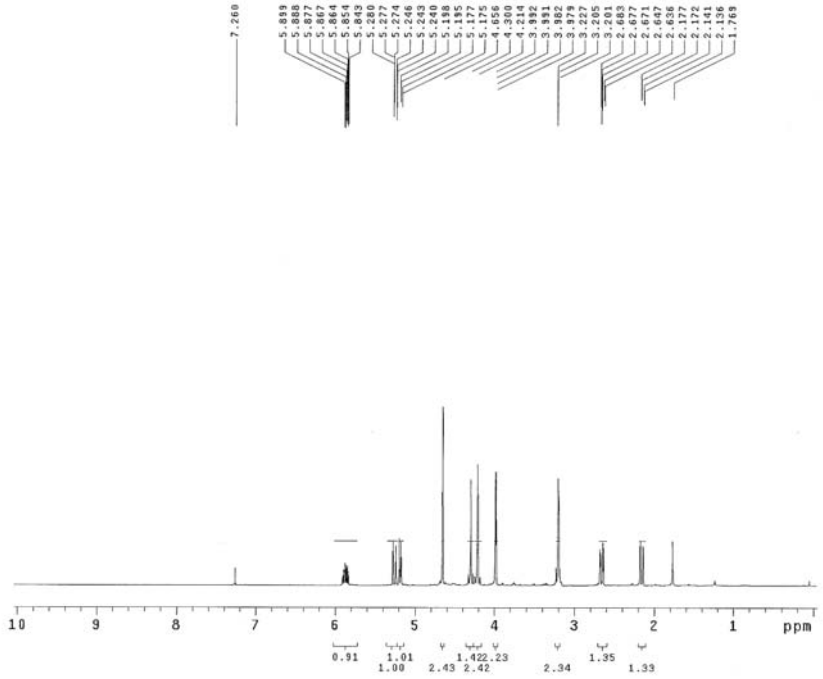


2-(allyloxy)-7-oxabicyclo[3.3.0]oct-1-en-3-one

STANDARD PROTON PARAMETERS

expl s2pul

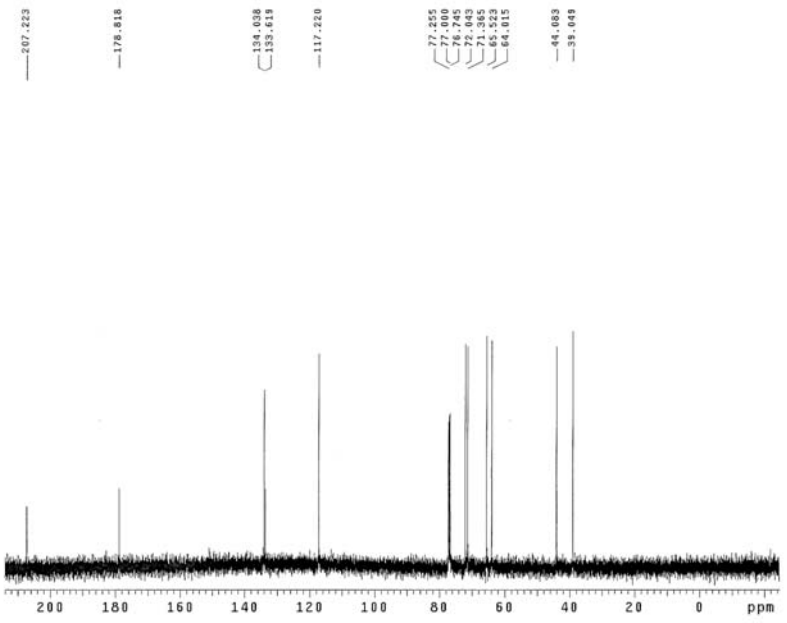
SAMPLE		DEC. & VT	
date	Mar 22 2007	dfrq	499.742
solvent	CDCl3	dn	H1
file	/export/home/~	dpwr	30
	alston/a1836H.fid	dof	0
ACQUISITION		dm	nnn
sfrq	499.742	dmm	c
tn	H1	dmf	200
at	1.892	dseq	
np	30272	dres	1.0
sw	8000.0	homo	n
fb	4000	DEC2	
bs	32	dfrq2	0
tpwr	57	dn2	
pw	5.5	dpwr2	1
d1	0	dof2	0
tof	0	dm2	n
nt	8	dmm2	c
ct	8	dmf2	200
alock	n	dseq2	
gain	not used	dres2	1.0
FLAGS		homo2	n
il	n	PROCESSING	
in	n	wtfile	
dp	y	proc	ft
hs	nn	fn	not used
DISPLAY		math	f
sp	-21.5	werr	
wp	5038.4	wexp	
vs	47	wbs	
sc	0	wnt	wft
wc	180		
hzmm	27.99		
is	9.45		
rfl	5130.2		
rfp	3628.1		
th	3		
ins	1.000		
al cdc ph			

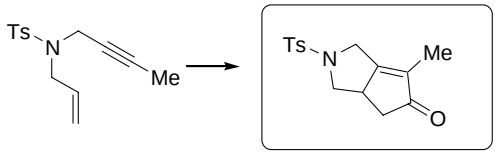


STANDARD CARBON PARAMETERS

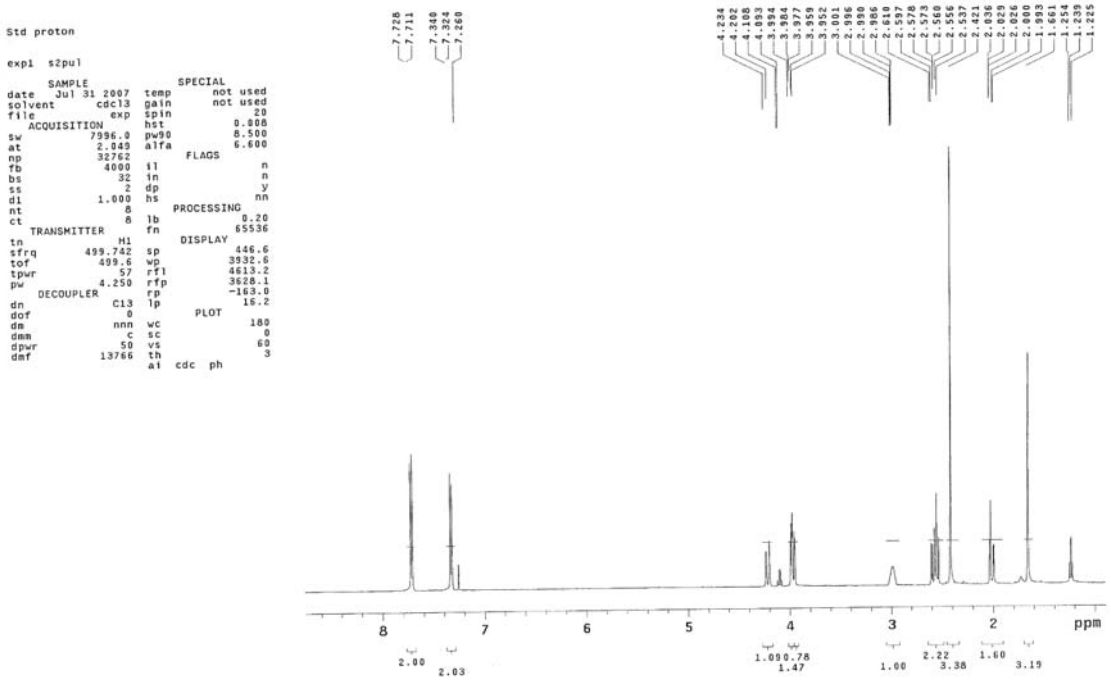
expl s2pul

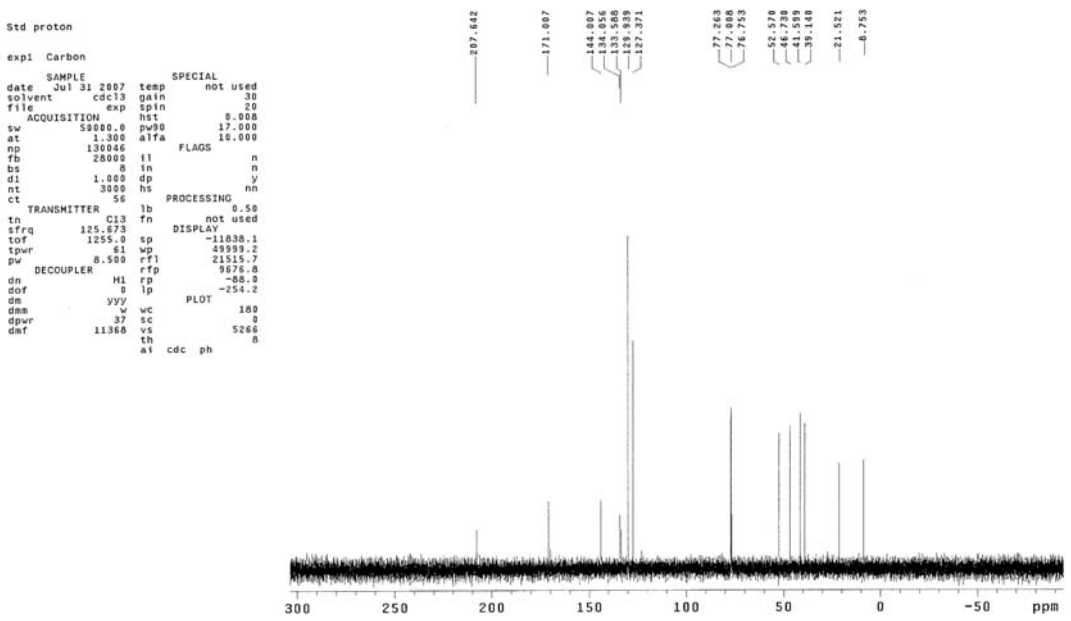
SAMPLE		DEC. & VT	
date	Mar 22 2007	dfrq	499.742
solvent	CDCl3	dn	H1
file	/export/home/~	dpwr	37
	alston/a1836C.fid	dof	0
ACQUISITION		dm	yyy
sfrq	125.671	dmm	w
tn	C13	dmf	11696
at	1.300	dseq	
np	78020	dres	1.0
sw	29996.3	homo	n
fb	17000	DEC2	
bs	8	dfrq2	0
tpwr	63	dn2	
pw	6.0	dpwr2	1
d1	0	dof2	0
tof	0	dm2	n
nt	5000	dmm2	c
ct	1680	dmf2	10000
alock	n	dseq2	
gain	not used	dres2	1.0
FLAGS		homo2	n
il	n	PROCESSING	
in	n	lb	0.50
dp	y	wtfile	
hs	nn	proc	ft
DISPLAY		fn	not used
sp	-3096.7	math	f
wp	29996.3	werr	
vs	1552	wexp	
sc	0	wbs	
wc	180	wnt	
hzmm	166.65		
is	500.00		
rfl	12772.5		
rfp	9675.8		
th	11		
ins	100.000		
al cdc ph			

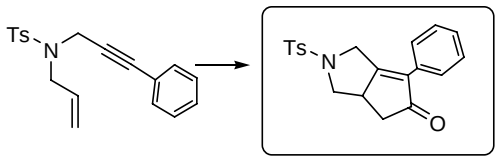




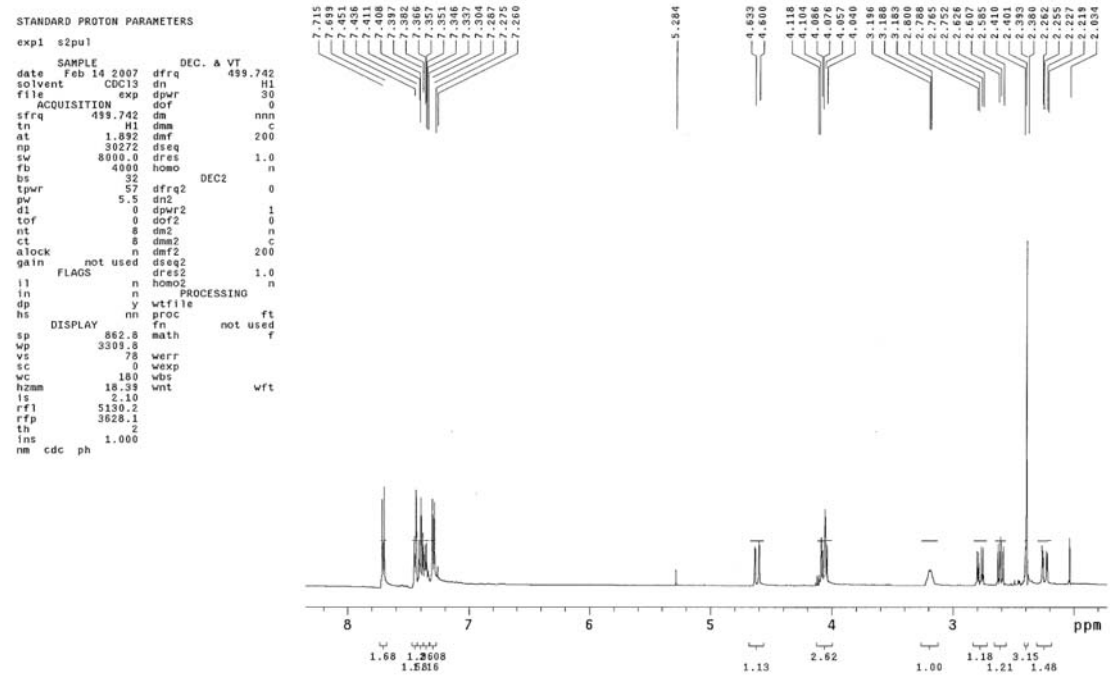
2-Methyl-7-[(4-methylphenyl)sulfonyl]-7-azabicyclo[3.3.0]oct-1-en-3-one[21]







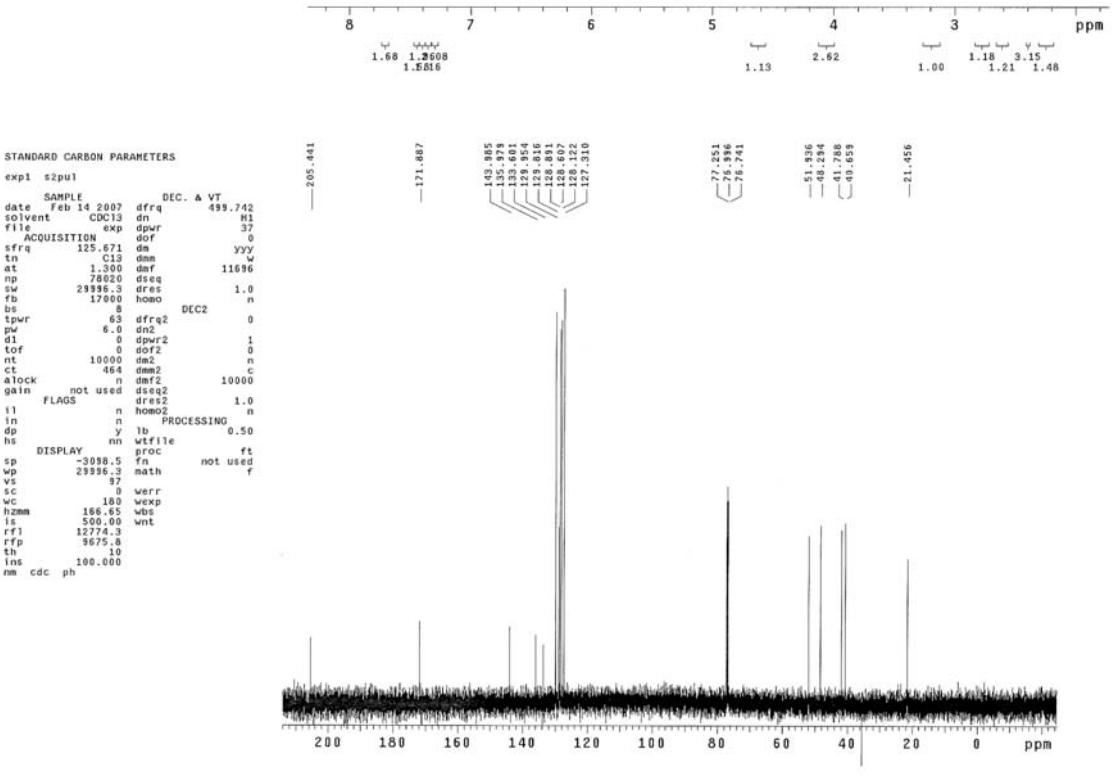
2-Phenyl-7-[(4-methylphenyl)sulfonyl]-7-azabicyclo[3.3.0]oct-1-en-3-one[21]



STANDARD PROTON PARAMETERS

exp1 s2pul

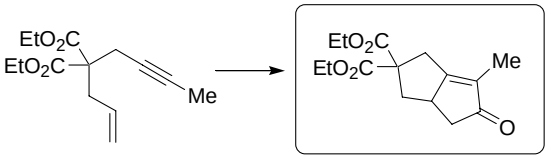
SAMPLE		DEC. & VT	
date	Feb 14 2007	dfrq	499.742
solvent	CDCl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	499.742	dm	nnn
tn	H1	dmm	c
at	1.892	dmf	200
np	30272	dseq	
sw	8000.0	dres	1.0
fb	4000	homo	n
bs	32	DEC2	
tpwr	57	dfrq2	0
pw	5.5	dn2	
d1	0	dpwr2	1
tof	0	dof2	0
nt	8	dm2	n
ct	8	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	PROCESSING	
dp	y	wtfile	
hs	nn	proc	ft
DISPLAY		fn	not used
sp	862.8	math	f
wp	3309.8	werr	
vs	78	wexp	
sc	0	wbs	
wc	180	wnt	wft
hzmm	18.39		
is	2.10		
rfl	5130.2		
rfp	3628.1		
th	2		
ins	1.000		
nm cdc ph			



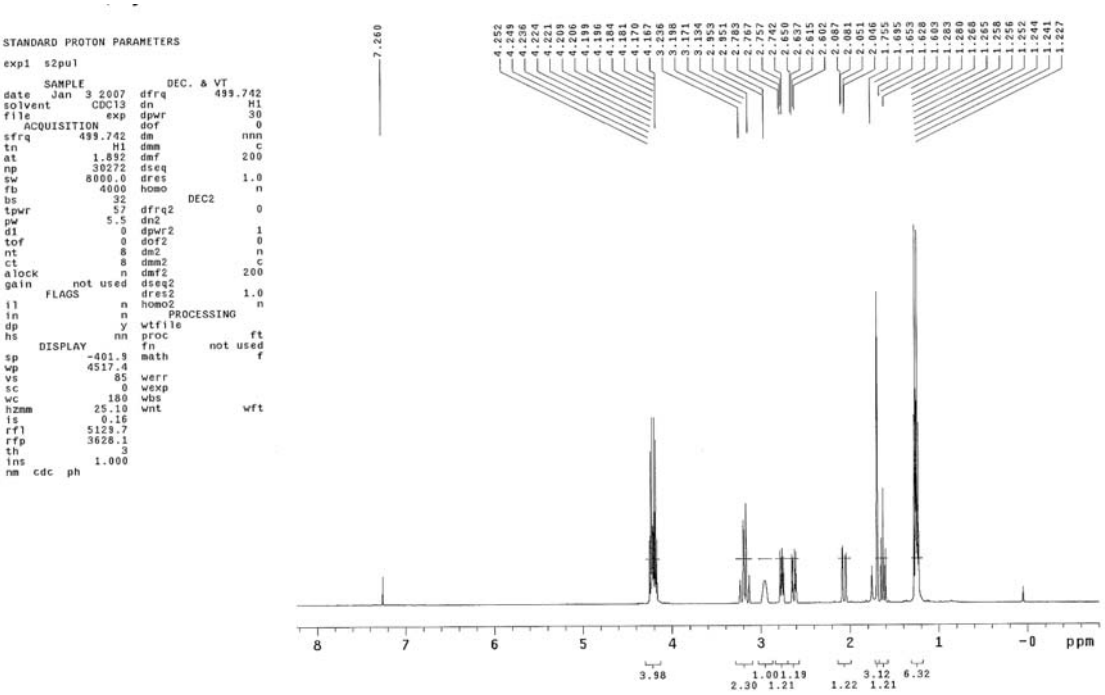
STANDARD CARBON PARAMETERS

exp1 s2pul

SAMPLE		DEC. & VT	
date	Feb 14 2007	dfrq	499.742
solvent	CDCl3	dn	H1
file	exp	dpwr	37
ACQUISITION		dof	0
sfrq	125.671	dm	yyy
tn	C13	dmm	w
at	1.300	dmf	11696
np	78020	dseq	
sw	29996.3	dres	1.0
fb	17000	homo	n
bs	8	DEC2	
tpwr	63	dfrq2	0
pw	6.0	dn2	
d1	0	dpwr2	1
tof	0	dof2	0
nt	10000	dm2	n
ct	464	dmm2	c
alock	n	dmf2	10000
gain	not used	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	PROCESSING	
dp	y	lb	0.50
hs	nn	wtfile	
DISPLAY		proc	ft
sp	-3098.5	fn	not used
wp	29996.3	math	f
vs	97		
sc	0	werr	
wc	180	wexp	
hzmm	166.65	wbs	
is	500.00	wnt	
rfl	12774.3		
rfp	9675.8		
th	10		
ins	100.000		
nm cdc ph			



Diethyl 2-methyl-3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate[22]



STANDARD PROTON PARAMETERS

expl s2pul

SAMPLE		DEC. & VT	
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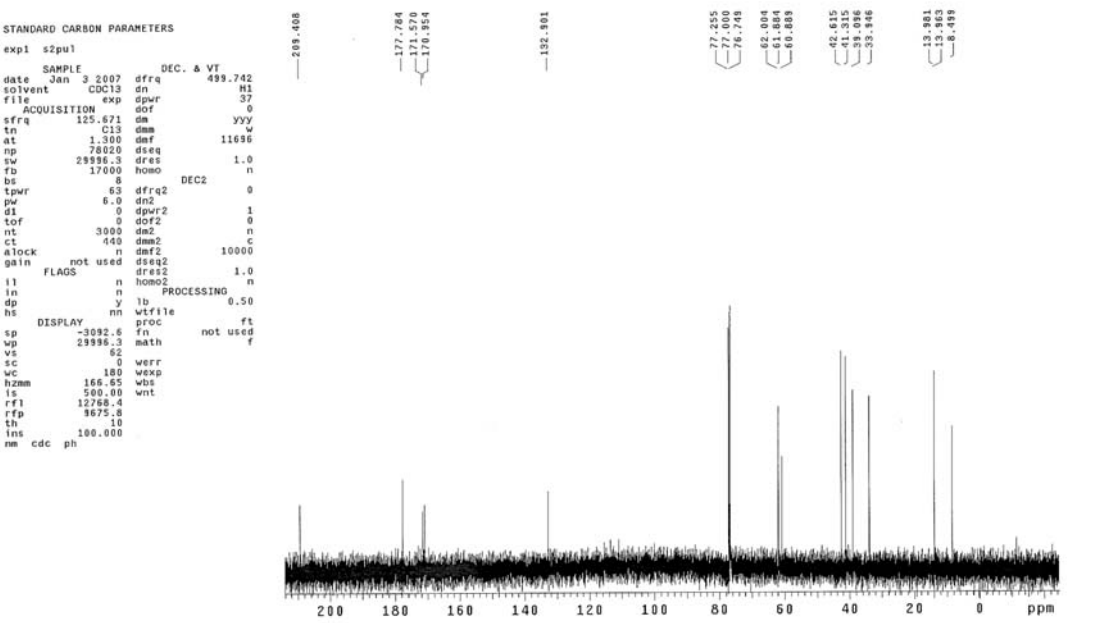
solvent	CDCl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	499.742	dm	nnn
tn	H1	dmm	c
at	1.892	dmf	200
np	30272	dseq	
sw	8000.0	dres	1.0
fb	4000	homo	n
bs	32	DEC2	
tpwr	57	dfrq2	0
pw	5.5	dn2	
d1	0	dpwr2	1
tof	0	dof2	0
nt	8	dm2	n
ct	8	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	PROCESSING	
dp	y	wtfile	
hs	nn	proc	ft
DISPLAY		fn	not used
sp	-401.9	math	f
wp	4517.4		
vs	85	werr	
sc	0	wexp	
wc	180	wbs	
hzmm	25.10	wnt	wft
is	0.16		
rfl	5129.7		
rfp	3628.1		
th	3		
ins	1.000		
nm cdc ph			



STANDARD CARBON PARAMETERS

expl s2pul

SAMPLE		DEC. & VT	
date	Jan 3 2007	dfrq	499.742
solvent	CDCl3	dn	H1
file	exp	dpwr	37
ACQUISITION		dof	0
sfrq	125.671	dm	yyy
tn	C13	dmm	w
at	1.300	dmf	11696
np	78020	dseq	
sw	29996.3	dres	1.0
fb	17000	homo	n
bs	8	DEC2	
tpwr	63	dfrq2	0
pw	6.0	dn2	
d1	0	dpwr2	1
tof	0	dof2	0
nt	3000	dm2	n
ct	440	dmm2	c
alock	n	dmf2	10000
gain	not used	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	PROCESSING	
dp	y	lb	0.50
hs	nn	wtfile	
DISPLAY		proc	ft
sp	-3092.6	fn	not used
wp	29996.3	math	f
vs	62		
sc	0	werr	
wc	180	wexp	
hzmm	166.65	wbs	
is	500.00	wnt	
rfl	12768.4		
rfp	3675.8		
th	10		
ins	100.000		
nm cdc ph			

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