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To my family

Acknowledgments

I am deeply grateful to my supervisor, Professor Howard Alper, who has accompanied me through these years with his invaluable knowledge, guidance and encouragement. His patience and understanding allowed me to work in a very comfortable atmosphere.

I want to thank the School of Graduate Studies and Research at the University of Ottawa for providing me with a Tuition Fee Waiver, which made possible my stay in the University.

Thanks are owed to Dr. Corinne Bensimon for the X-ray analysis, Dr. Glenn Facey and Mr. Raj Capoor for NMR experiments, Dr. Clem Kazakoff for mass spectra and to all the faculty and staff members of the Department for their continuous disposition to help.

My stay in Dr. Alper's laboratories and in Ottawa would not have been so enjoyable without the presence of the numerous graduate students, postdoc fellows and visiting scientists, with whom I shared very good times and stimulating discussions. To all of them, my most sincere gratitude.

Special thanks to my close friends: Cristina Mateo, Abdelaziz Nait Ajjou, his beautiful wife Jamila, Raluca Aldea, Chitchamai Larksarp, Velaga Valli, Yew Beng Kang and Kanjai Khumtaveeporn for their encouragement and friendship.

Finally, I would like to thank my large family, who continuously supports me from the distance.

Abstract

This thesis describes the results obtained in the metal catalyzed carbonylation of aziridines, alkynyl oxiranes and α-allenic alcohols.

Aziridines undergo carbonylation and ring expansion when they are treated with catalytic amounts of $Co_2(CO)_8$ under 33 atm of carbon monoxide in ether solvents at 100 °C, to afford β-lactams in good to excellent yields. This reaction is applicable to aziridines containing alkyl or aryl groups at the ring carbons, and alkyl, aryl or acyl groups at the nitrogen atom. The reactions in most cases are regioselective, with carbon monoxide insertion occurring into the less substituted ring carbon-nitrogen bond. The carbonylation reaction is also stereoselective, giving *trans*-3,4-disubstituted β-lactams when *cis*-2,3-disubstituted aziridines are used, and vice versa. This stereoselectivity was mantained when fused bicyclic aziridines were subjected to carbonylation, affording the previously unknown *trans*-7-azabicyclo[4.2.0]octan-8-one derivatives. An X-ray study of one of these novel compounds reveals that the four membered ring contains structural features similar to those found in biologically active β-lactams, suggesting that these compounds might have considerable acylation power. The mechanism of the reaction involves nucleophilic ring opening of the aziridine ring by the in situ generated $Co(CO)_4^-$ anion. The carbonylation of aziridines is described in Chapter 2.

Palladium (0) complexes catalyze the carbonylation of alkynyl oxiranes to 5-hydroxy-2,3-dienoates in the presence of 20 atm of carbon monoxide and methanol as the solvent. The reaction takes place under mild conditions (room temperature, one to two hours for complete conversion.) The mechanism involves the formation of a zwitterionic σ-allenylpalladium complex. When the carbonylation reaction is effected on alkynyl oxiranemethanol derivatives, partially saturated furan-3-ol compounds are obtained. These compounds are presumably formed by spontaneous cyclization of a nonisolable allenediol intermediate. Hydrofuran derivatives containing an *exo* or *endo* double bond are obtained depending on the substitution

pattern of the initial epoxide. An interesting application of this reaction is the synthesis of a chiral furan-3-ol by carbonylation of a chiral epoxy alcohol obtained by Sharpless epoxidation. These results are described in Chapter 3.

Chapter 4 describes the carbonylation of α-allenic alcohols to α-vinylacrylic acids catalyzed by a novel cationic aquo hydride palladium complex. The reaction requires the presence of catalytic amounts of *p*-toluenesulphonic acid and 20 atm of carbon monoxide to take place. This complex generates a palladium (0) species *in situ*, which is the active catalyst. The formation of a π-allylpalladium complex would be a key step in this reaction.

Abbreviations

anal	analytical
atm	atmosphere
BOC	*tert*-butoxycarbonyl
br	broad
***n*-Bu**	*normal*-Butyl
t-Bu	*tert*-butyl
calcd	calculated
CI	chemical ionization
CTAB	cetyltrimethylammonium bromide
cod	1,5-cyclooctadiene
CSI	chlorosulfonyl isocyanate
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
DIPT	diisopropyl tartrate
DME	dimethoxyethane
DMF	dimethylformamide
dppb	diphenylphosphinebutane
dppp	diphenylphosphinepropane
dq	doublet of quartets
dt	doublet of triplets
ee	enantiomeric excess
EI	electron impact
Et	ethyl group
FT-IR	Fourier-transform infrared
g	grams
GC	gas chromatography
h	hours
Hz	Hertz
J	coupling constant, in Hz
L	ligand
LA	Lewis acid
LUMO	lowest unoccupied molecular orbital
M	metal

M	molar concentration, in mol/litre
MCPBA	*meta*-chloroperbenzoic acid
Me	methyl group
MeOH	methanol
min	minutes
ml	milliliters
mmol	millimols
mp	melting point
MS	mass spectrometry
NCS	N-chlorosuccinimide
NMR	Nuclear Magnetic Resonance
Nu^-	nucleophile
ORTEP	Oak Ridge thermal ellipsoid plot
Ph	phenyl group
ppm	parts per million
psi	pound per square inch
PTC	phase transfer catalysis
q	quartet
rt	room temperature
s	singlet
SET	Single Electron Transfer
t	triplet
T	temperature
TBDMS	*tert*-butyldimethylsilane
TBDPS	*tert*-butyldiphenylsilane
TBHP	*tert*-butyl hydroperoxide
THF	tetrahydrofuran
TLC	thin layer chromatography
TPAP	tetrapropylammonium perruthenate
Ts	*para*-toluenesulphonyl
***p*-TsOH**	*para*-toluenesulphonic acid

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Chapter 1

1 Introduction

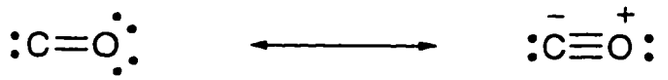
The carbonyl group is one of the more useful and versatile functionalities in organic chemistry. Its importance lies in the ability to undergo reactions with nucleophiles and electrophiles, as well as to affect the surroundings of the molecule by means of its polarity and capacity to stabilize adjacent carbanions. Oxidation of alcohols and interconversion of carbonyl group derivatives are widely used methods for the synthesis of carbonyl compounds. On the other hand, the synthesis of carbonyl compounds from non-oxygenated substrates is not trivial. It is in this area where carbon monoxide plays an important role for organic chemists. Although carbon monoxide can be incorporated into an organic molecule by anionic or radical mechanisms, the use of transition metal complexes in stoichiometric or catalytic quantities has become the most versatile methodology for carbonylation reactions[1].

The transition metal catalyzed carbonylation reaction covers a wide range of applications, from very important large scale industrial processes[2] (Monsanto process for the preparation of acetic acid from methanol, hydroformylation of propene, etc.) to the preparation of fine chemicals (ring expansion carbonylation[3], asymmetric carbonylation[1], etc.) It is not surprising then that major efforts are being pursued to develop better catalytic systems for known processes, and to explore new carbonylation reactions for the synthesis of potentially useful compounds.

1.1 The Carbon Monoxide Molecule

Carbon monoxide can be represented as two canonical forms, a "carbenelike" structure **1** in which the two atoms are linked by a double bond, and a "dinitrogenlike" form **2** which

contains a triple bond and positive and negative formal charges at the O and C respectively (Scheme 1). The canonical form on the right is the more important.



1 2

Scheme 1

The coordination chemistry of carbon monoxide can be better rationalized in terms of a molecular orbital basis. An energy level MO diagram is shown in Figure 1, in which the filled orbitals 3σ and $5\sigma^*$ are assigned to the lone pairs on O and C respectively[4]. $5\sigma^*$ is the HOMO and is slightly antibonding, and $2\pi^*$ is the LUMO.

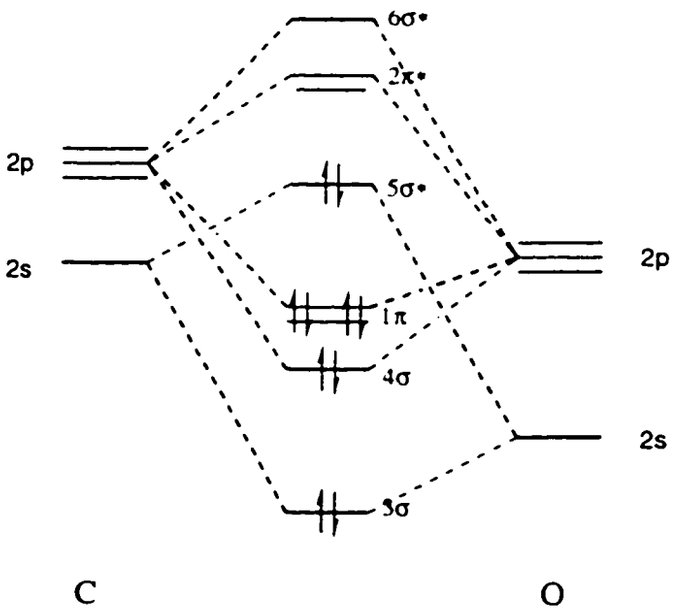


Figure 1

Transition metals containing filled or partially filled d orbitals which have the required symmetry and energy can coordinate carbon monoxide molecules. This type of bonding is synergistic, in which CO donates electron density from the weakly antibonding $5\sigma^*$ orbital and accepts electrons into the antibonding $2\pi^*$ orbital, resulting in the reduction of the order of the C–O bond (Figure 2).

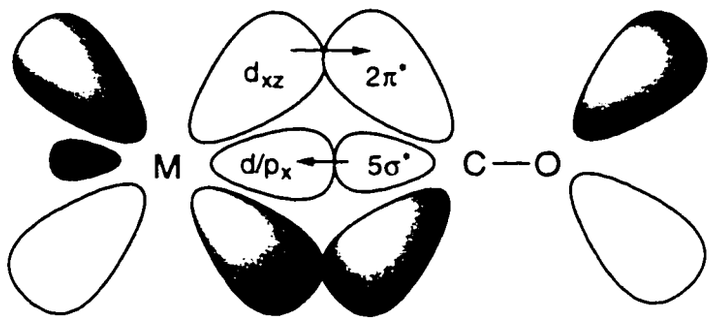
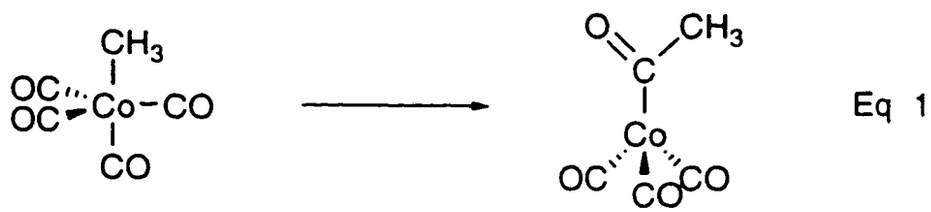


Figure 2

Coordination of carbon monoxide to transition metals induces the activation of this rather unreactive molecule. The most important reaction of coordinated carbon monoxide, which is extremely relevant to the carbonylation reactions, is the insertion into metal-carbon bonds in σ-alkyl, alkenyl and aryl metal complexes (Eq 1).

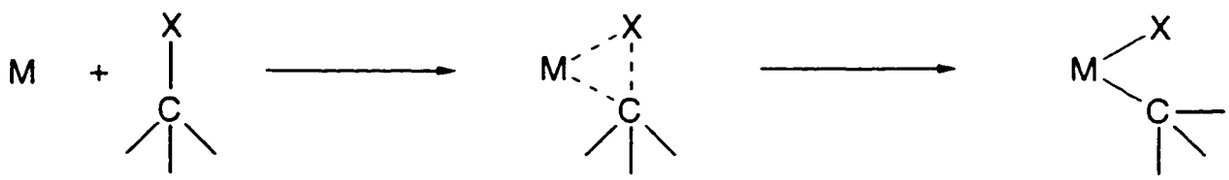


Eq 1

1.2 Carbonylation of organic compounds catalyzed by transition metal complexes

The wide variety of catalytic carbonylation reactions differ mostly in the way that the initial carbon-metal bond is formed, as well as in the type of decomposition reaction of the acyl-metal complex after the carbonyl insertion. The most common mechanisms for the formation of C–M bonds are oxidative addition, nucleophilic attack by the metal and insertion reactions[1].

i) *Oxidative addition*: Transition metals in low oxidation states can induce the cleavage of a σ-bond, forming a bond with each of the atoms involved (Scheme 2). During this process the metal increases its formal oxidation state, electronic configuration and coordination number by two units. Although the mechanism of this reaction depends on the metal and on the type of σ-bond, a concerted process in which the metal transfers electron density to the σ-antibonding orbital usually is believed to occur. The most common bonds that undergo oxidative addition are C–X (X= halogen), although C–O, C–C and C–H can react as well.



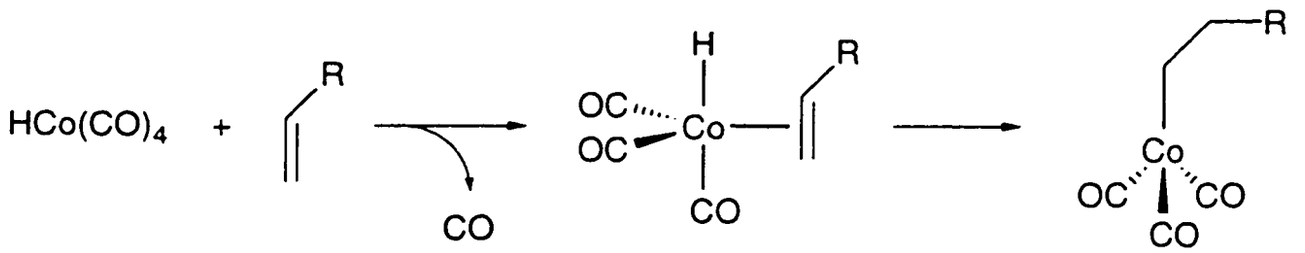
Scheme 2

ii) *Nucleophilic attack by the metal*: When the metal center is electronically saturated, oxidative addition cannot take place. Instead, the complex can act as a metal centered nucleophile (Scheme 3). When these complexes react with an electrophile the metal increases its oxidation

state, but keeps the 18 electron configuration. The most common electrophiles are alkyl halides, although other electrophiles such as epoxides are also reactive.

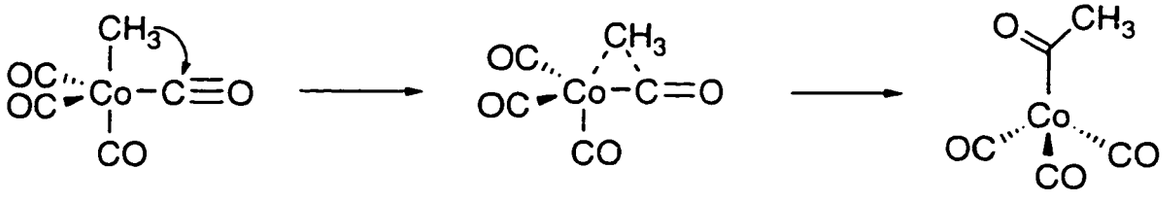
Scheme 3

iii) *Formation of C–M bond by insertion reaction*: Olefins can insert into M–H or M–C bonds, prior to coordination to the metal, to form a new M–C bond (Scheme 4). This insertion reaction has made possible the development of carbonylation reactions known as hydrocarboxylation and hydroesterification, which are widely used in industry.



Scheme 4

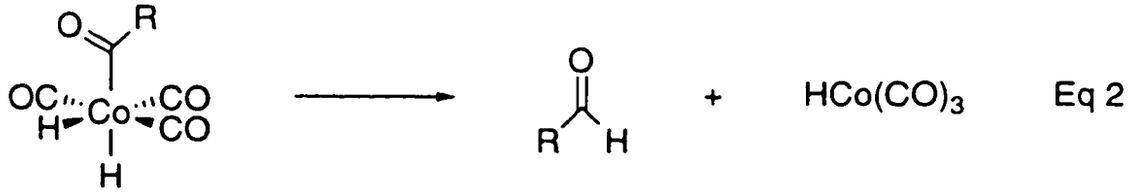
After the formation of the metal–carbon bond, carbon monoxide must insert to form an acyl–metal complex, such insertion requiring the alkyl and CO ligands to be in *cis* positions with respect to each other. The insertion reaction occurs with retention of configuration at the migrating carbon, as a consequence of the front-side attack during the concerted reaction[5] (Scheme 5).



Scheme 5

The formation of the acyl–metal complex is followed by its degradation to form the carbonylated product and regenerate the catalyst, which will start another catalytic cycle. There are several types of reactions that lead to the degradation of the intermediate. The most common are reductive elimination and reductive displacement[1].

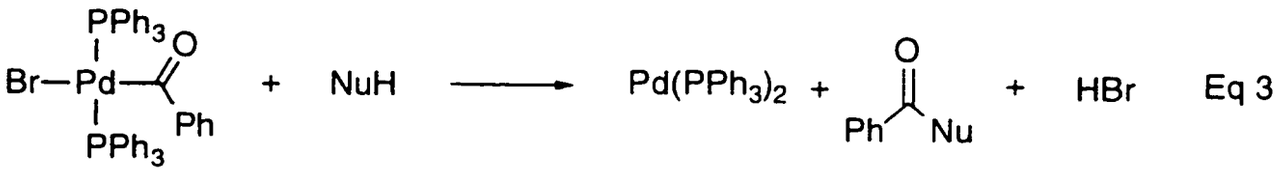
i) *Reductive elimination*: When the metal has two "one electron" ligands, a process can occur in which these two ligands are eliminated to form a bond between them (Eq 2). C–C and C–H bonds can be formed in this way. Usually a concerted elimination occurs, requiring the two ligands to be in a *cis* configuration. The metal decreases its formal oxidation state and coordination number by two units. As shown in equation 2, this is the product releasing step in hydroformylation reactions.



Eq 2

ii) *Reductive displacement*: When acyl–metal complexes are formed in the presence of nucleophiles, reductive cleavage of the C–M bond takes place giving carboxylic acid derivatives and the regenerated catalyst (Eq 3). This "product releasing step" takes place in most hydroesterification and hydrocarboxylation reactions. The mechanism of reductive

displacements varies with the system.



Eq 3

The existence of numerous types of carbonylation reactions arises from the different combination of the steps described above, and from the use of more than one organic substrate, what leads to the combination of two, three, four or more molecules in one step and with high selectivity.

1.3 Aims of research

Although a large number of catalytic systems have been developed for the carbonylation of a wide range of compounds, the search for the improvement of carbonylation technology continues, with the goal of increasing versatility to these very useful chemical transformations.

One of our objectives is to find catalytic systems for the carbonylation of three membered heterocycles. We centered our attention on aziridines and alkynyl epoxides. As noted in Chapter 2, the catalytic carbonylation of aziridines to β-lactams has been described several years ago, but these reactions are limited to a small range of aziridines. It was our intention to develop a system which is compatible with a larger number of aziridine derivatives, making possible the preparation of some useful and novel β-lactams.

In spite of the known reactivity of alkynyl epoxides with transition metal complexes, their carbonylation has not been reported. We envisioned that carbonylation of alkynyl epoxides would lead to the formation of potentially useful allenic esters. In Chapter 3 we show the results obtained in this project, including the unexpected formation of interesting five-membered oxygen heterocycles.

Finally, we wanted to study the reactivity of a new cationic aquo hydride palladium complex as a carbonylation catalyst. The use of this complex for the carbonylation of α-allenic alcohols is described in Chapter 4.

1.4 References

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Chapter 2

2 Carbonylation of aziridines to β-lactams

2.1 Introduction

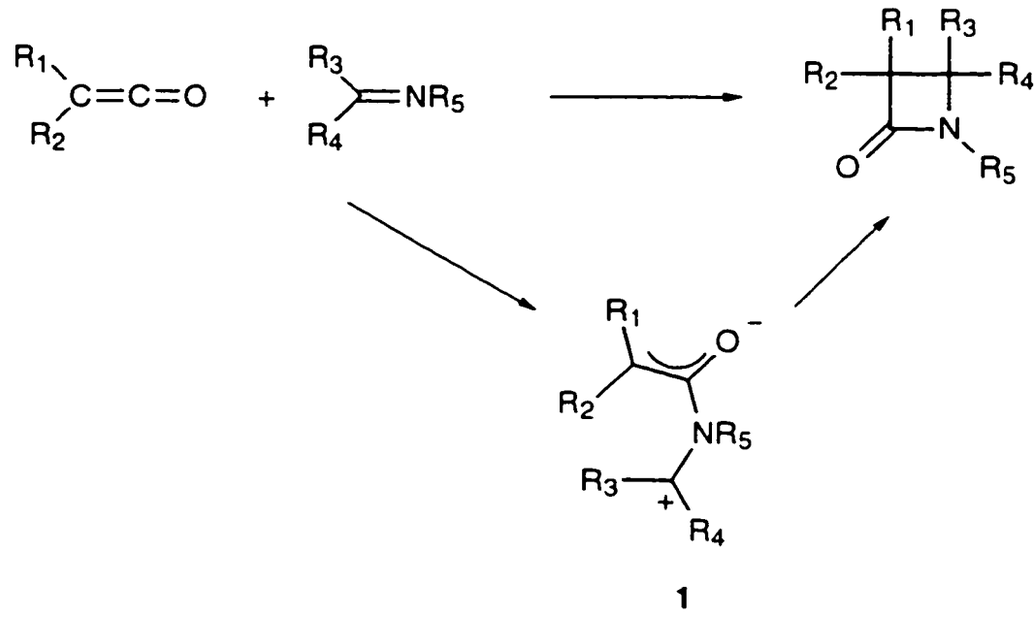
2.1.1 Synthesis of β-lactams

The discovery of the antibiotic activity of naturally occurring β-lactams has given an extraordinary impulse to the development of synthetic methods for the preparation of a wide range of β-lactams[1]. Furthermore, in the last years β-lactams have been considered as important synthetic intermediates. The most important contribution in this area has been provided by Ojima, with the development of the "β-lactam synthon method"[2].

There are many methods for the construction of the β-lactam ring, but the most versatile are those based on 2 + 2 cycloaddition and ring closure reactions[3]. Cycloaddition reactions between ketenes and imines are well known. The wide range of substituted ketenes (usually prepared *in situ*) and imines available allows the preparation of a large variety of β-lactam derivatives. Two mechanisms are proposed for this reaction (Scheme 1). A concerted 2 + 2 cycloaddition reaction, and the more accepted pathway, the formation of a dipolar intermediate **1** by nucleophilic attack of the imine to the sp carbon of the ketene, followed by a conrotatory electrocyclization to form the four membered ring.

Another very important route to β-lactams is the cycloaddition of isocyanates with alkenes. The most widely used isocyanate is chlorosulphonyl isocyanate (CSI, **2**), which due to its high reactivity, reacts with many types of alkenes. The resulting β-lactams can be reacted with sodium bisulphite/sodium bicarbonate to form the N-unsubstituted derivatives (Scheme

2).



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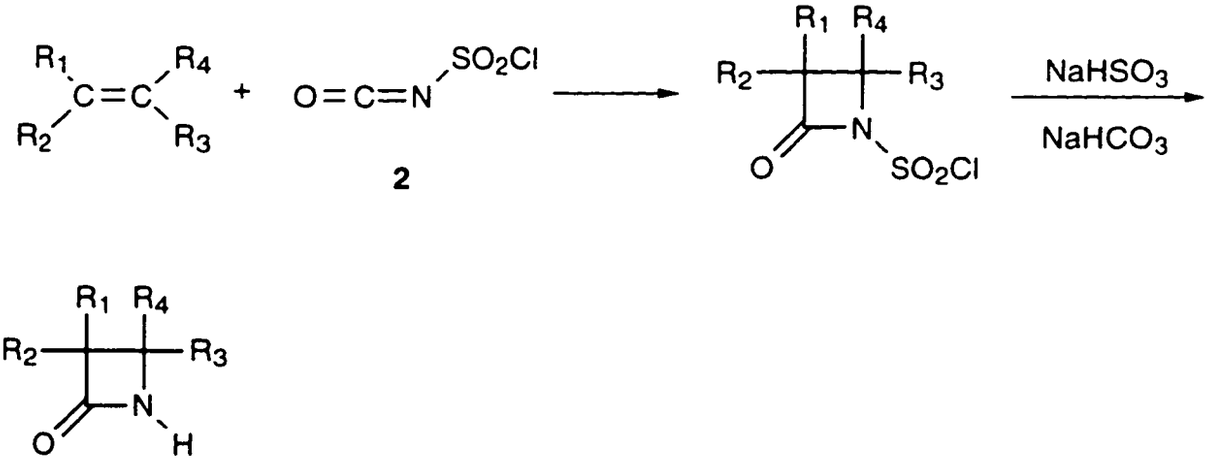
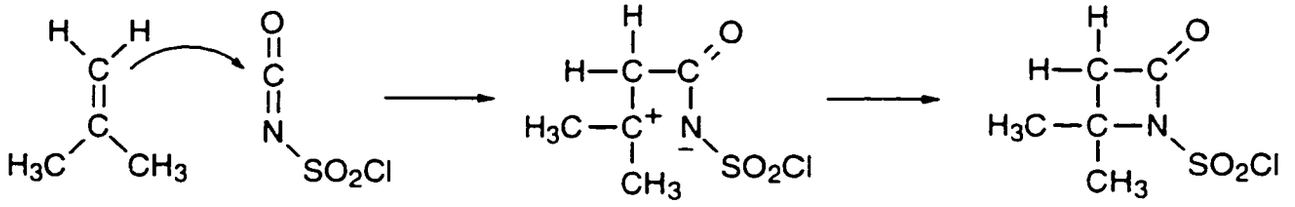
Scheme 1



Scheme 2

The mechanism proposed for this reaction is also a two step zwitterionic process, in which C–N bond formation is the fast step (Scheme 3). The ring closure step is significantly

faster than the rotational time about the developing carbonium ion, resulting in excellent stereoselectivity for the reaction. *Cis* olefins react with CSI to give exclusively *cis*-β-lactams, and *trans* olefins affords *trans* β-lactams. Other isocyanates can be used for the reaction, but they react mostly with electron rich olefins.



Scheme 3

The other widespread methodology for the synthesis of β-lactams is the ring closure of β-amino acids or their derivatives (Eq 1). A variety of activating agents have been used, such as acetic anhydride, acetyl chloride, thionyl chloride, sulphonyl chlorides, dicyclohexylcarbodiimide, triphenylphosphine/carbon tetrachloride, etc.

Eq 1

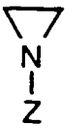
Ring closures forming N-C_4, C_2-C_3 and C_3-C_4 bonds have been developed as well and numerous other methodologies have been described in the literature including the carbonylation and ring expansion of aziridines[3b] (see section 2.1.5.4) which appears to be an attractive way to synthesize β-lactams. The research described in this chapter is focused on the carbonylation of aziridines catalyzed by $Co_2(CO)_8$, which affords monocyclic and novel strained bicyclic β-

lactams in good yields.

2.1.2 Chemistry of aziridines

The rich chemistry of aziridines is due mostly to the strain present in the three membered ring, which makes ring opening possible under relatively mild conditions. The presence of different substituents at nitrogen enables one to control the regio and stereochemistry of the reaction, and thus aziridines are important intermediates for stereoselective organic synthesis[4].

According to the nature of the substituent at nitrogen, aziridines can be divided in two main groups[5]: activated and nonactivated aziridines (Scheme 4). Activated aziridines contain electron withdrawing subtituents, which can stabilize, by conjugation, the negative charge formed at the nitrogen in the transition state of a nucleophilic ring opening reaction. The more common substituents are acyl, alkoxycarbonyl and sulphonyl groups. Nonactivated aziridines contain substituents such as H, alkyl or aryl groups on the nitrogen, and ring opening reactions usually occur under more drastic conditions, or in the presence of Bronsted or Lewis acids.



activated

Z= COR, CO_2R, SO_2R

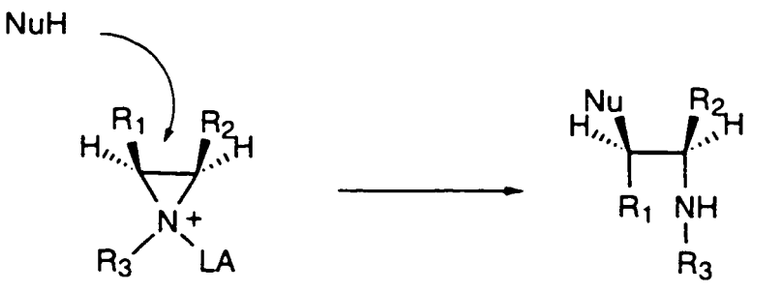
nonactivated

R= H, alkyl, aryl

Scheme 4

2.1.3 Acid catalyzed ring opening

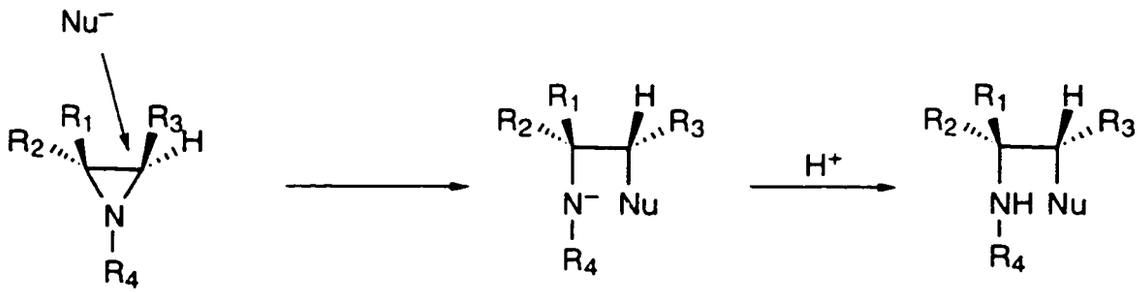
Bronsted and Lewis acid catalyzed ring opening reactions of aziridines usually occur by a bimolecular mechanism, with complete inversion of configuration at the reaction center. This suggests that a carbonium ion is not generated in the transition state of the reaction. The regiochemistry of the ring opening is determined by steric factors, or by the influence of electron releasing groups attached to the reacting carbon (Scheme 5).



Scheme 5

2.1.4 Nucleophilic ring opening of aziridines

Ring opening of aziridines initiated by nucleophiles are almost exclusively stereoselective, with inversion of configuration at the reacting carbon (Scheme 6). The nucleophile usually attacks the less substituted carbon, but this regioselectivity can be modified sometimes by using the appropriate reaction conditions. Activated aziridines undergo direct nucleophilic ring opening under relatively mild conditions. Unactivated aziridines require very strong nucleophiles or very drastic reaction conditions.



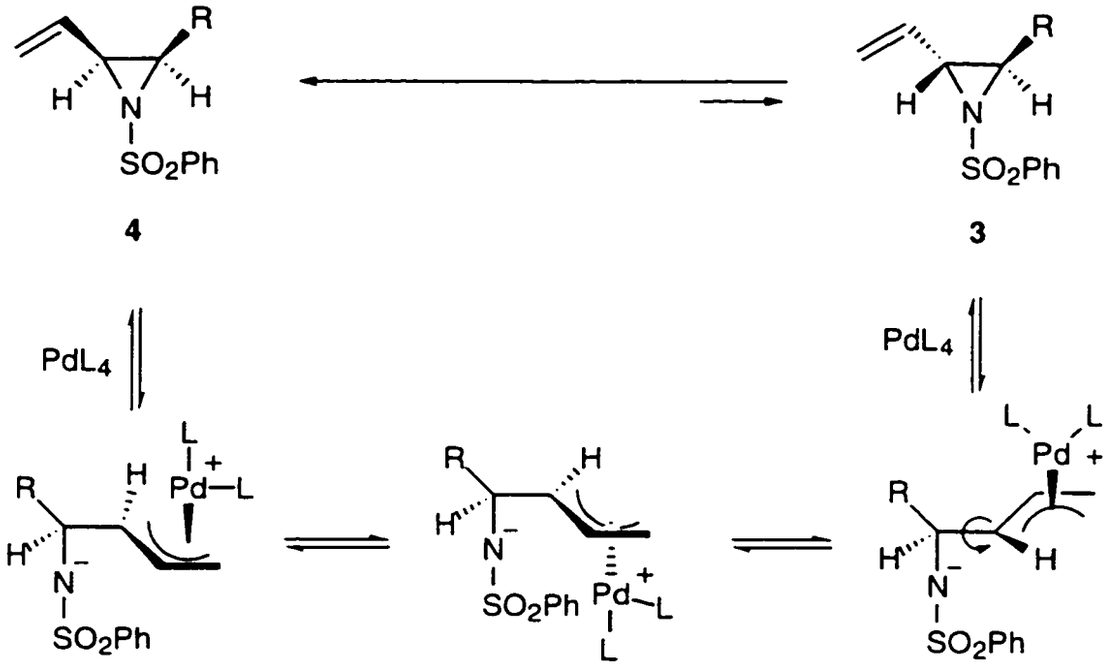
Scheme 6

2.1.5 Reactions of aziridines catalyzed by transition metal complexes

The coordinative ability of aziridines to transition metal complexes, together with their ring strain, suggests that these heterocycles might be easily activated by transition metals. Nevertheless, there are few reports of the reactions of aziridines catalyzed by transition metal complexes, such as isomerization, ring expansion, cycloaddition and carbonylation reactions[6-14].

2.1.5.1 *Cis-trans* isomerization of 2-vinylaziridines

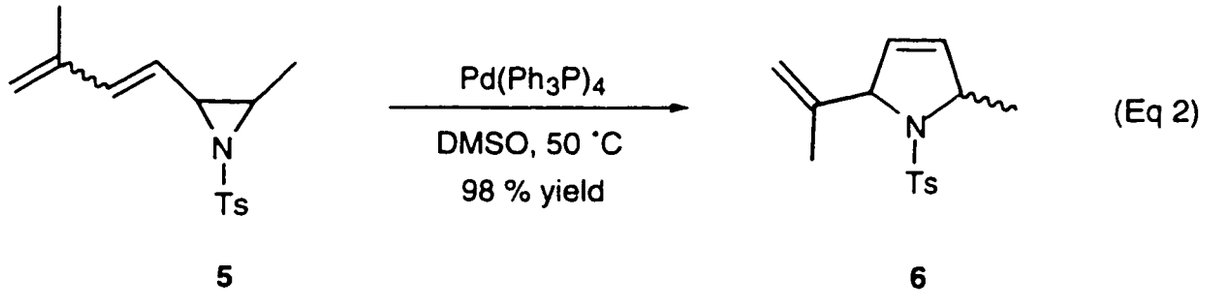
Isomerization of *trans* to *cis* N-tosyl-2-vinyl aziridine (**3** to **4**) can be carried out in the presence of catalytic amounts of Pd(0) complexes[6]. The equilibrium point depends on the substituents in the aziridine ring. Usually the *cis/trans* ratio lies at the point of equilibrium between 90:10 and 98:2. The isomerization takes place through a series of allylpalladium complexes in equilibrium (Scheme 7), formed by S_N2 attack of Pd(0) at the vinyl aziridine.



Scheme 7

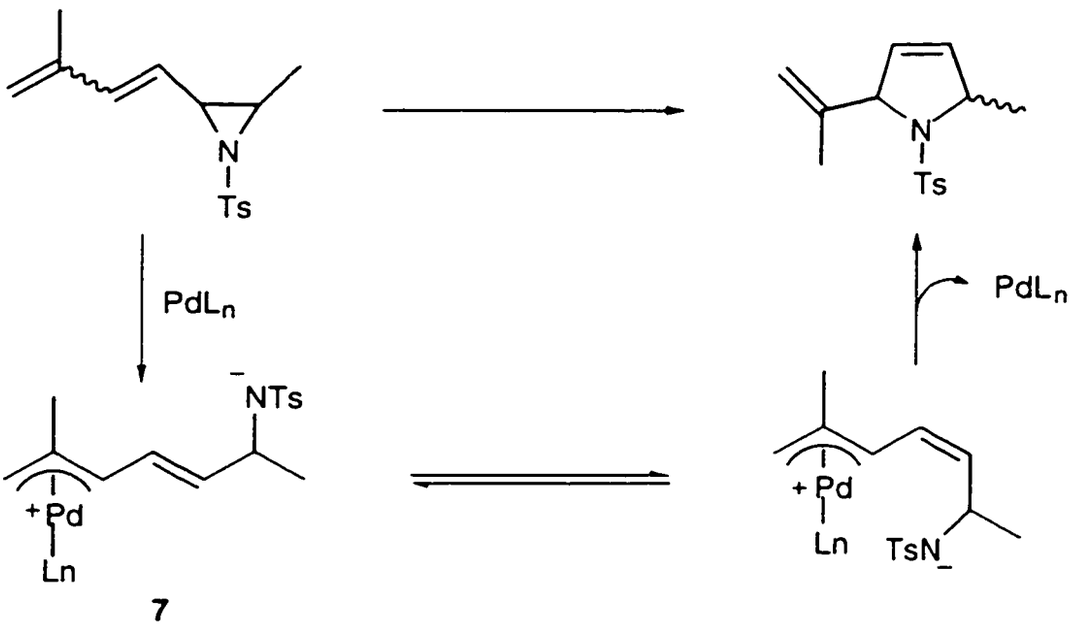
2.1.5.2 Ring expansion of 2-(1,3-butadienyl)aziridines to 2-ethenyl pyrrolines

Tetrakis(triphenylphosphine)palladium catalyzes the ring expansion isomerization of N-tosyl 2-(1,3-butadienyl)aziridines **5** to N-tosyl-2-ethenyl-3-pyrrolines[7] **6** (Eq 2). This reaction is similar to the vinylcyclopropane-cyclopentene isomerization reaction catalyzed by Pd (0) complexes[8].



(Eq 2)

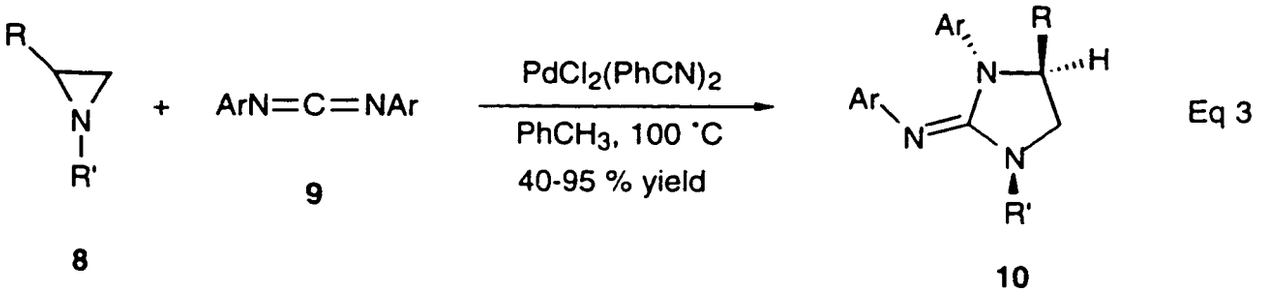
The presence of the 1,3-dienyl portion is necessary for the isomerization, since vinyl aziridine derivatives give a complex mixture of products under the same reaction conditions. The rearrangement might proceed through nucleophilic attack of $Pd^0(Ph_3P)_n$ to the diene, to form the zwitterionic allylpalladium intermediate **7**, which after ring closure forms the five membered heterocyclic product (Scheme 8). Seven membered heterocycles were not observed in the reaction mixture.



Scheme 8

2.1.5.3 Cycloaddition reactions of aziridines catalyzed by Pd (II) complexes

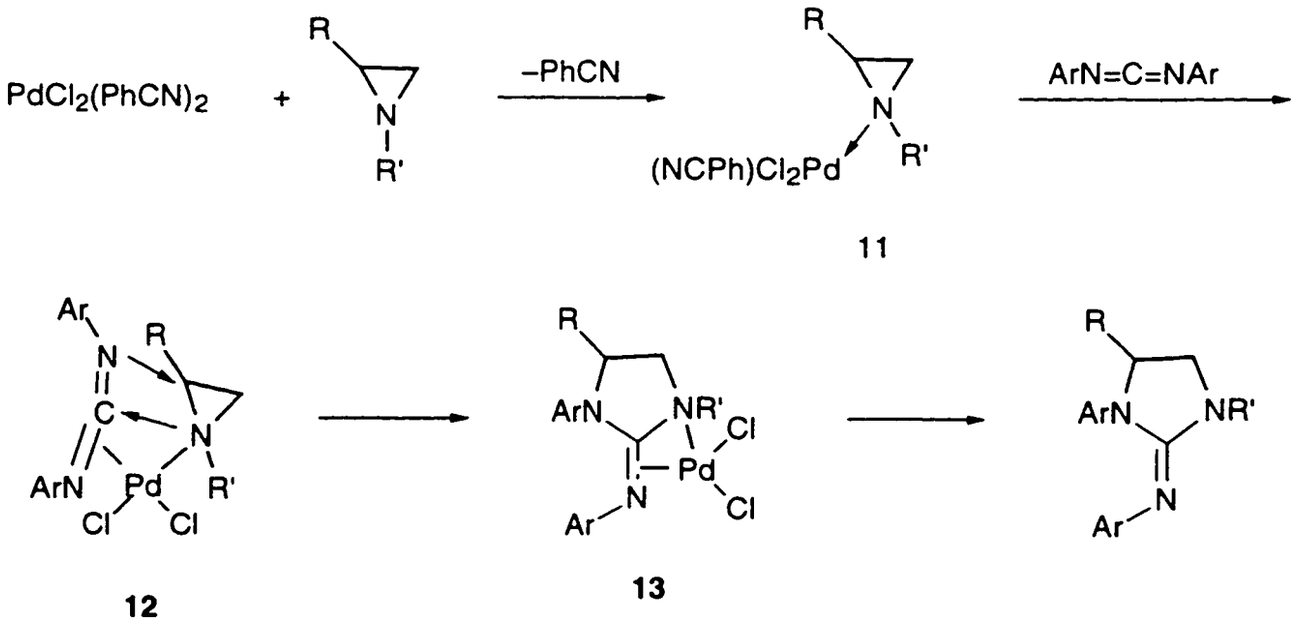
Aziridines **8** having aryl substituents at C_2 react with carbodiimides **9** in the presence of bis(benzonitrile)palladium chloride to form imidazolidenimines **10** in good yields[9] (Eq 3).



8 9 10 Eq 3

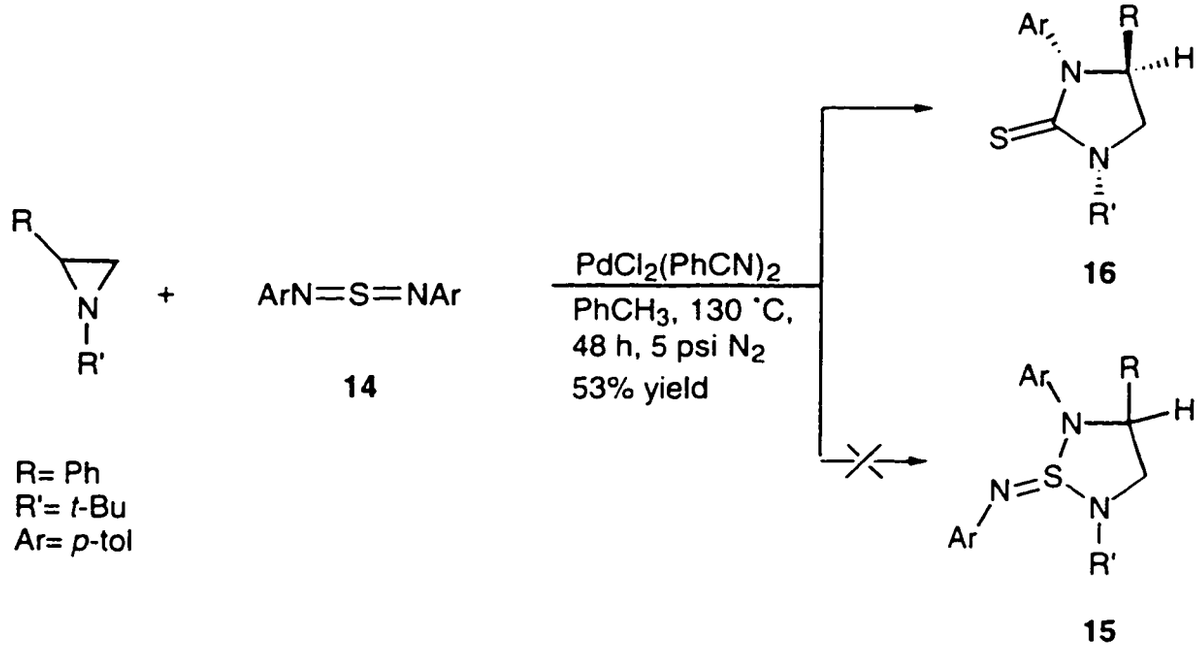
R= Ph, *p*-PhC_6H_4, *p*-BrC_6H_4
R'= *t*-Bu, 1-adamantyl
R''= Ph, *p*-tolyl

The reaction is regiospecific, with the cleavage of the more substituted ring carbon-nitrogen bond. The stereochemistry of the product is as shown in Eq 3, where the aryl group attached to the imine nitrogen is *syn* to the N-Ph portion of the five membered ring. A possible mechanism for this reaction is outlined in Scheme 9. Coordination of the aziridine to the Pd complex can form intermediate **11**, which would further coordinate to the carbodiimide to give **12**. Cycloaddition then would take place to form complex **13**, which would react with another aziridine molecule affording the product and to start a new catalytic cycle.



Scheme 9

Bis(benzonitrile)palladium dichloride also catalyzes the cycloaddition of **8** (R= Ph, R'= *t*-Bu) and di-*p*-tolylsulphurdiimides[10] **14**. In this case, the expected thiadiazolideneimine **15** was not formed. Surprisingly, imidazolidinethione **16** was obtained (Scheme 10). Note that the product has incorporated one extra carbon. As in the cycloaddition with carbodiimides, the more substituted ring carbon-nitrogen bond was cleaved.



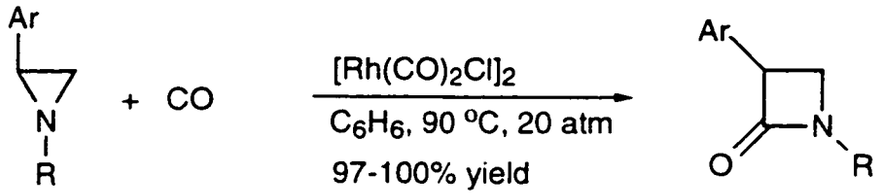
Scheme 10

Experiments using ^{13}C-labeled aziridine at C_3 showed that the extra carbon of the product comes from C_3 of a second aziridine molecule. No reaction mechanism was proposed for this unusual reaction.

2.1.5.4 Carbonylation with ring expansion of aziridines

The reaction of aziridines with carbon monoxide in the presence of transition metal catalysts is a recently developed method for the synthesis of β-lactams. Carbonylation with

ring expansion of aziridines can be carried out using $[Rh(CO)_2Cl]_2$ as the catalyst[11] (Eq 4).



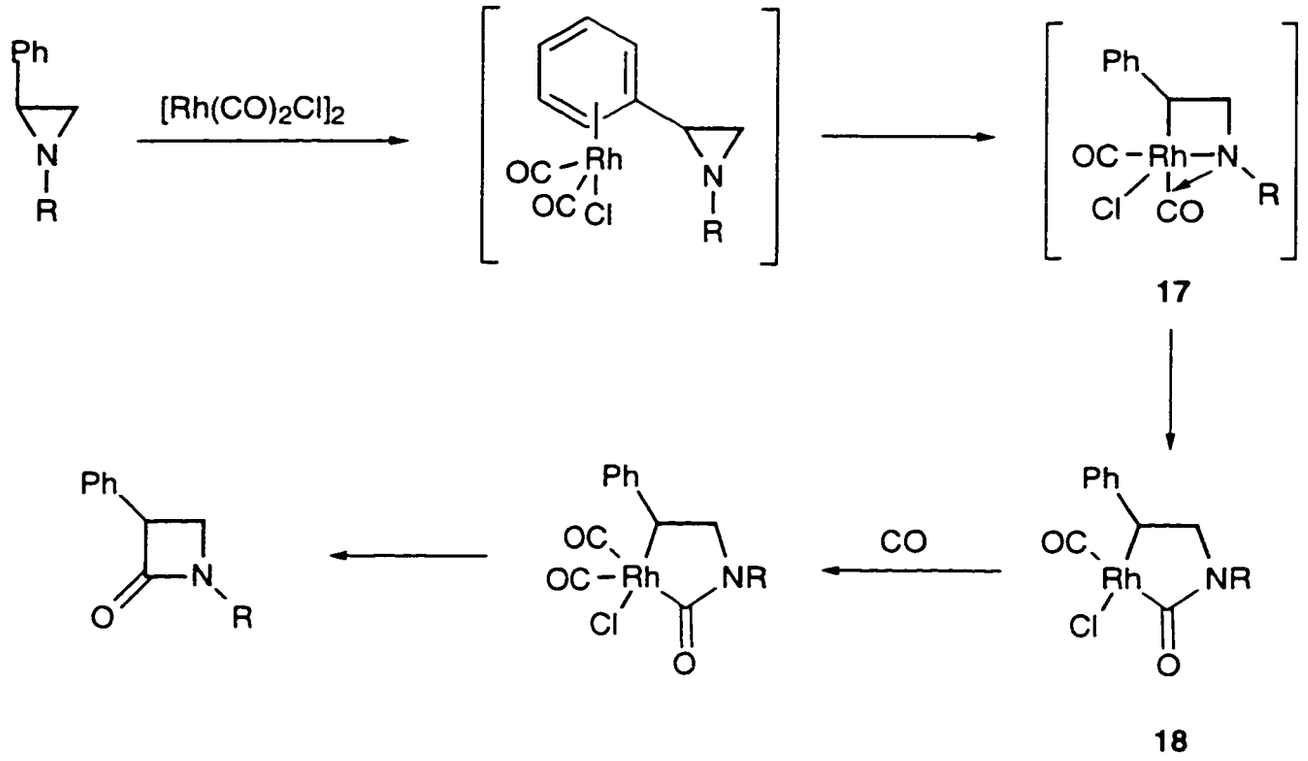
(Eq. 4)

Ar= Ph, *p*-PhC_6H_4, *p*-BrC_6H_4
R= *t*-Bu, 1-adamantyl

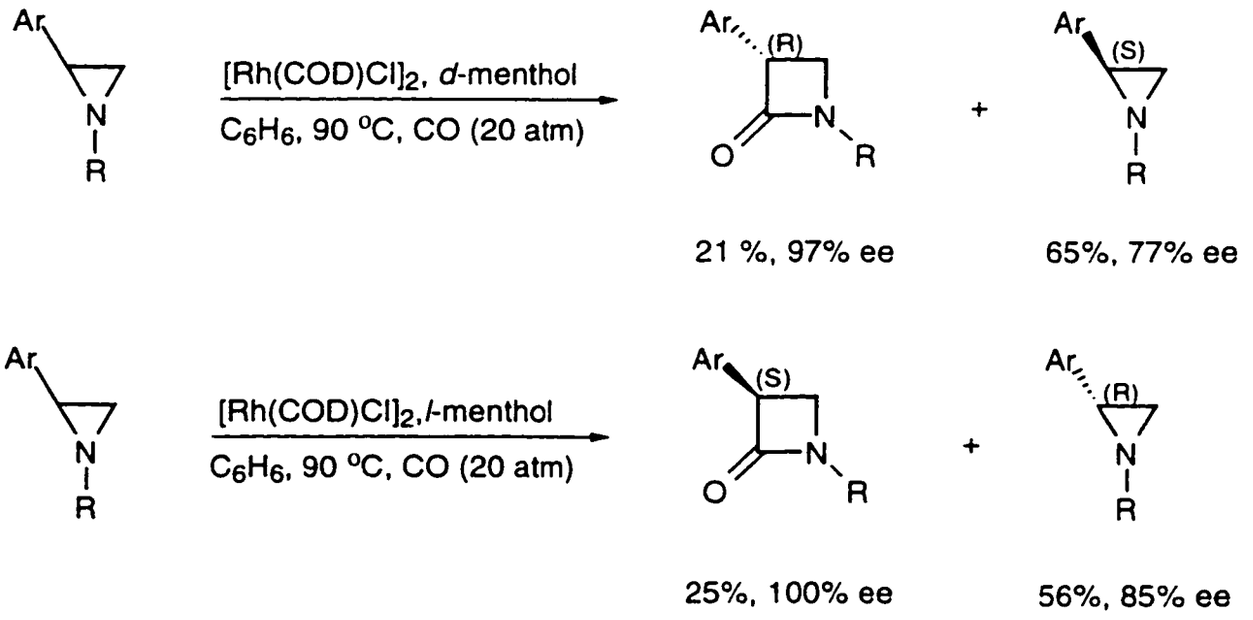
This reaction, which affords β-lactams in quantitative yields, is regiospecific, with carbonyl insertion occurring exclusively into the aryl bearing carbon-nitrogen bond. The process is stereospecific, proceeding with retention of stereochemistry of the substituents on the carbon atoms of the aziridine ring.

A possible mechanism for the carbonylation reaction (Scheme 11) would involve initial coordination of the aromatic ring to the rhodium catalyst, followed by the insertion of the metal into the aryl substituted carbon-nitrogen bond to form **17**. Carbon monoxide insertion into the Rh-N bond (**18**) and reductive elimination would afford the β-lactam.

A very interesting application of this reaction is for the kinetic resolution of aziridines. When the carbonylation reaction is carried out in the presence of optically pure *d* or *l* menthol, kinetic resolution of the aziridine takes place, and the lactam as well as the recovered aziridine are both obtained in high optical purity (Scheme 12).

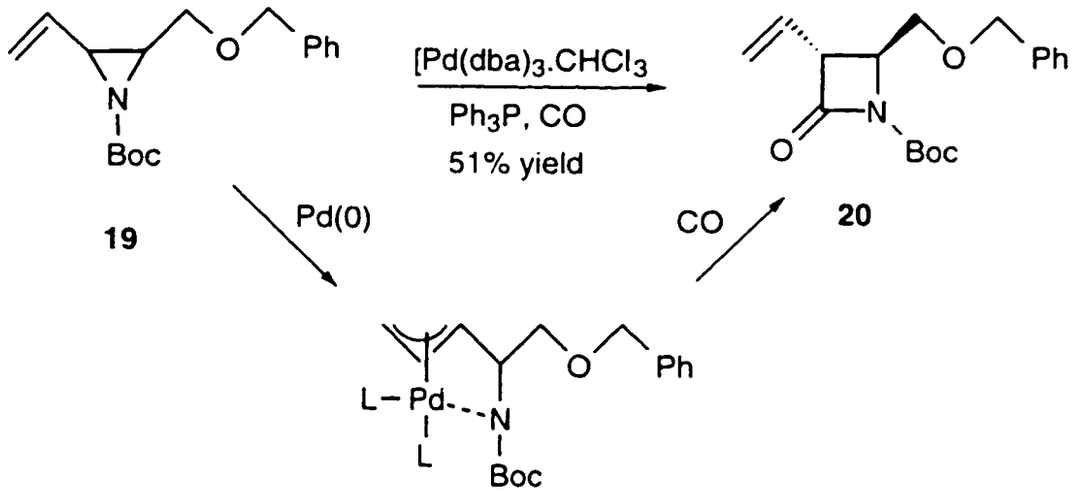


Scheme 11



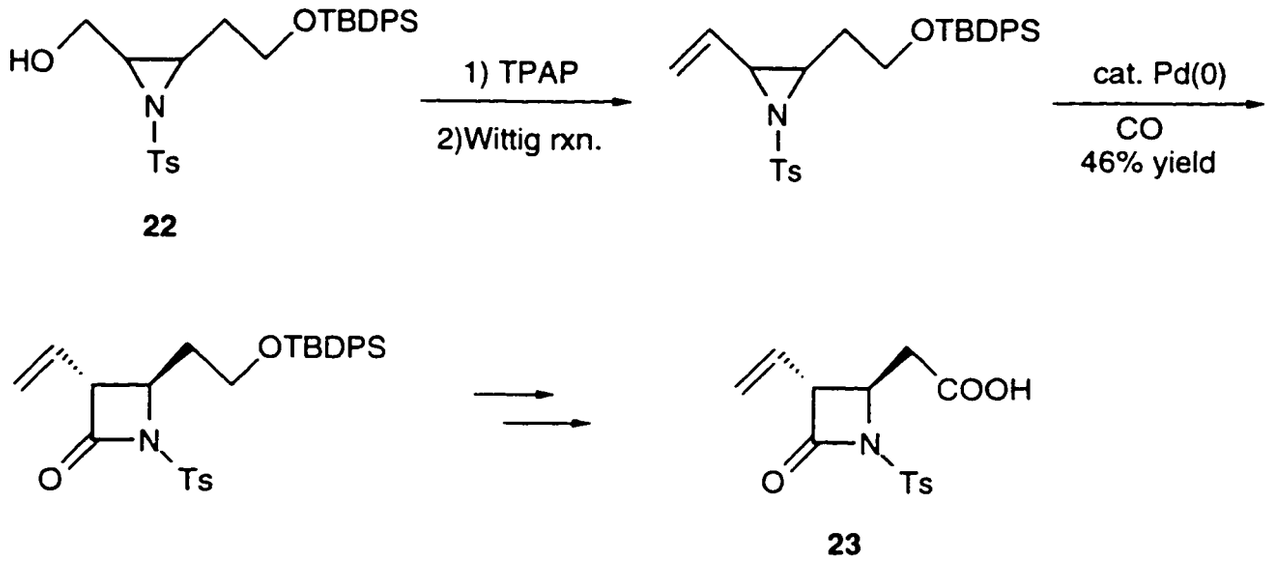
Scheme 12

2-Vinyl aziridine **19** can be converted into 3-vinyl β-lactam **20** by carbonylation catalyzed by [$Pd_2(dba)_3.CHCl_3$] in the presence of triphenylphosphine[12] (Scheme 13). The carbon monoxide insertion takes place into the vinyl bearing carbon-nitrogen bond. The *trans* β-lactam **20** was obtained as the only product.



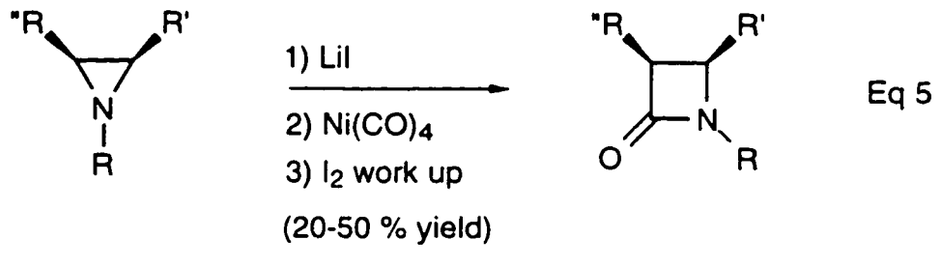
Scheme 13

The mechanism of the reaction involves the π-allylpalladium intermediate **21**, which after carbon monoxide insertion and elimination forms the β-lactam. This reaction was used as a key step in the enantioselective synthesis of **23** which is an important intermediate for the synthesis of carbapenem PS-5[13] (Scheme 14). This synthesis uses optically pure 2,3-aziridinoalcohol **22** derived from a Sharpless epoxidation.



Scheme 14

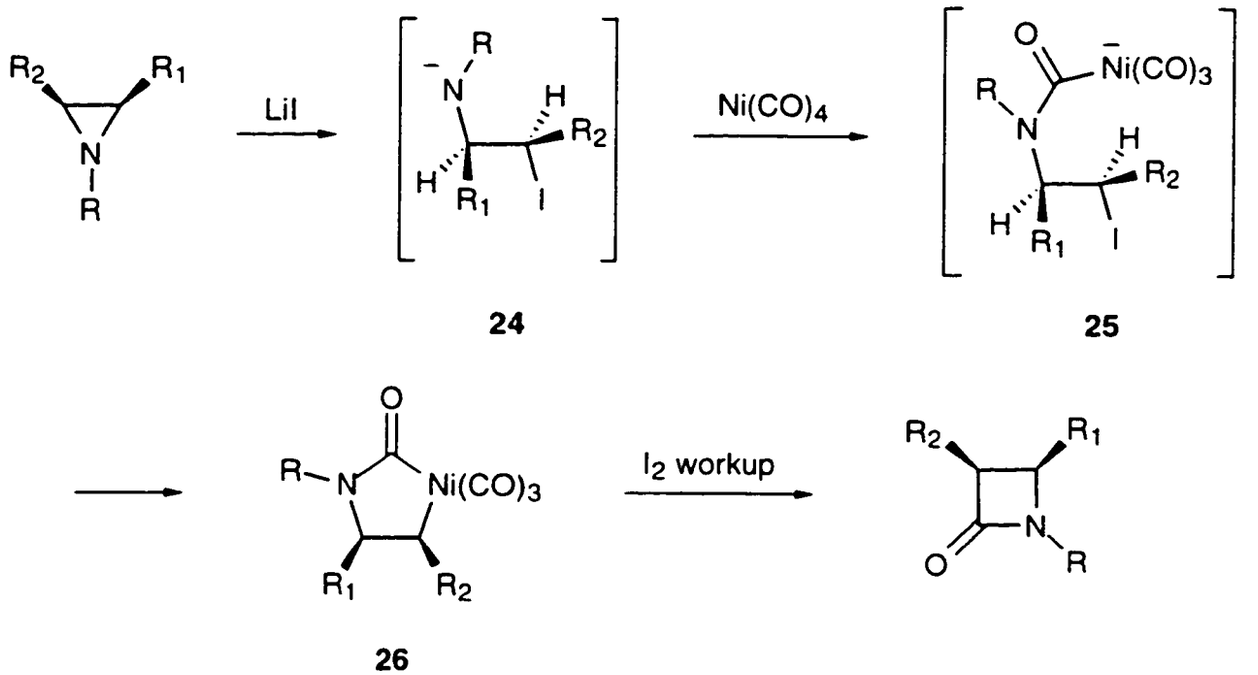
The two noted examples are limited to aziridines bearing activating groups (phenyl or vinyl) in the 2-position of the aziridine ring, which likely have a directive effect in the process. Carbonylation of unactivated aziridines is achieved by using tetracarbonylnickel as the carbonylation agent[14]. This reaction is not catalytic, since it uses an 11-fold amount of the very toxic $Ni(CO)_4$. The carbon monoxide insertion takes place into the less substituted ring carbon-nitrogen bond, with overall retention of configuration at the carbon. The aziridine is reacted first with lithium iodide, then with $Ni(CO)_4$ followed by workup with iodine (Eq 5).



Eq 5

R= CH_2Ph, $CH_2C_6H_4OCH_3$, C_6H_{13}, SO_2CH_3
R'= CH_3
R"= CH_3, H

A four step mechanism is proposed for this reaction (Scheme 15). The first step consists of an S_N2 ring opening of the aziridine by iodide, which occurs with inversion of configuration at the reactive center, to form the anionic intermediate **24**. The second step is the attack of the nitrogen anion at the carbonyl group of $Ni(CO)_4$ to form **25**. The subsequent nucleophilic attack of the nickel acylate on the alkyl halide occurs with inversion of configuration to give **26**, and finally the iodine induced reductive elimination affords the β-lactam.



Scheme 15

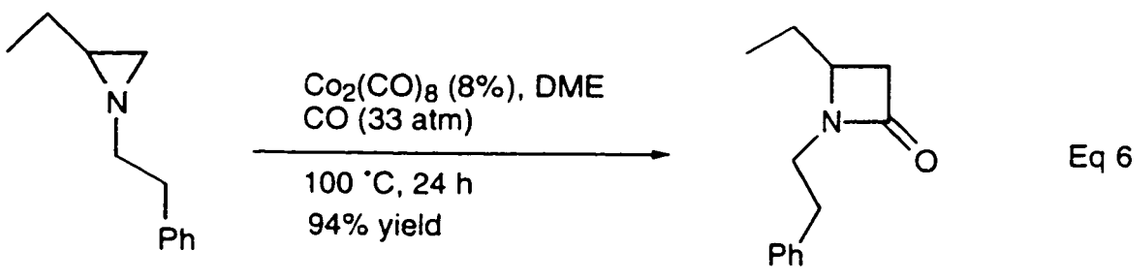
The carbonylation and ring expansion of aziridines to β-lactams catalyzed by Rh and Pd complexes present severe limitations. These reactions take place only when aryl groups (for the Rh system) or vinyl groups (Pd system) are attached to a carbon of the aziridine ring. A more general carbonylation reaction takes place when $Ni(CO)_4$ is used, but excess amounts of this very toxic compound are needed. Therefore we believed that it was highly desirable to develop a catalytic system that would allow us to apply the carbonylation reaction to a broader range of

aziridines. The goal of this research is to explore the catalytic activity of $Co_2(CO)_8$ for the carbonylation of different type of aziridines. $Co_2(CO)_8$ has shown to be of great utility for the carbonylation with ring expansion of other heterocycles[3b].

2.2 Results and discussion

2.2.1 Carbonylation of monocyclic aziridines

When aziridine **27a** is reacted with carbon monoxide in the presence of catalytic amounts of dicobalt octacarbonyl at 100 °C, β–lactam **28a** is obtained in 94% yield (Eq 6). Carbon monoxide insertion takes place exclusively at the less substituted ring carbon-nitrogen bond.



27a **28a** Eq 6

The optimization process for this reaction showed that DME and THF are suitable solvents. Less polar solvents, like benzene, decrease the reaction rate, and the conversion is complete only after 3 days, giving the β–lactam in low yield. More polar solvents like acetonitrile and dimethylformamide give complete conversion but the desired β–lactam is not formed. When less than 8 mol % of the catalyst is used, the conversion is not complete. At 100 °C it takes around 10 h for complete reaction of the aziridine. Nevertheless the reactions were run for 24 hours with all the aziridines to assure complete conversion. Carbon monoxide pressure lower than 500 psi gives the β–lactam in reduced yield.

The β–lactam products can be easily identified by their strong absorption in the IR spectra at around 1740 cm^{-1} and a carbonyl carbon signal between 167 and 171 ppm in the ^{13}C-NMR (Figure 1).

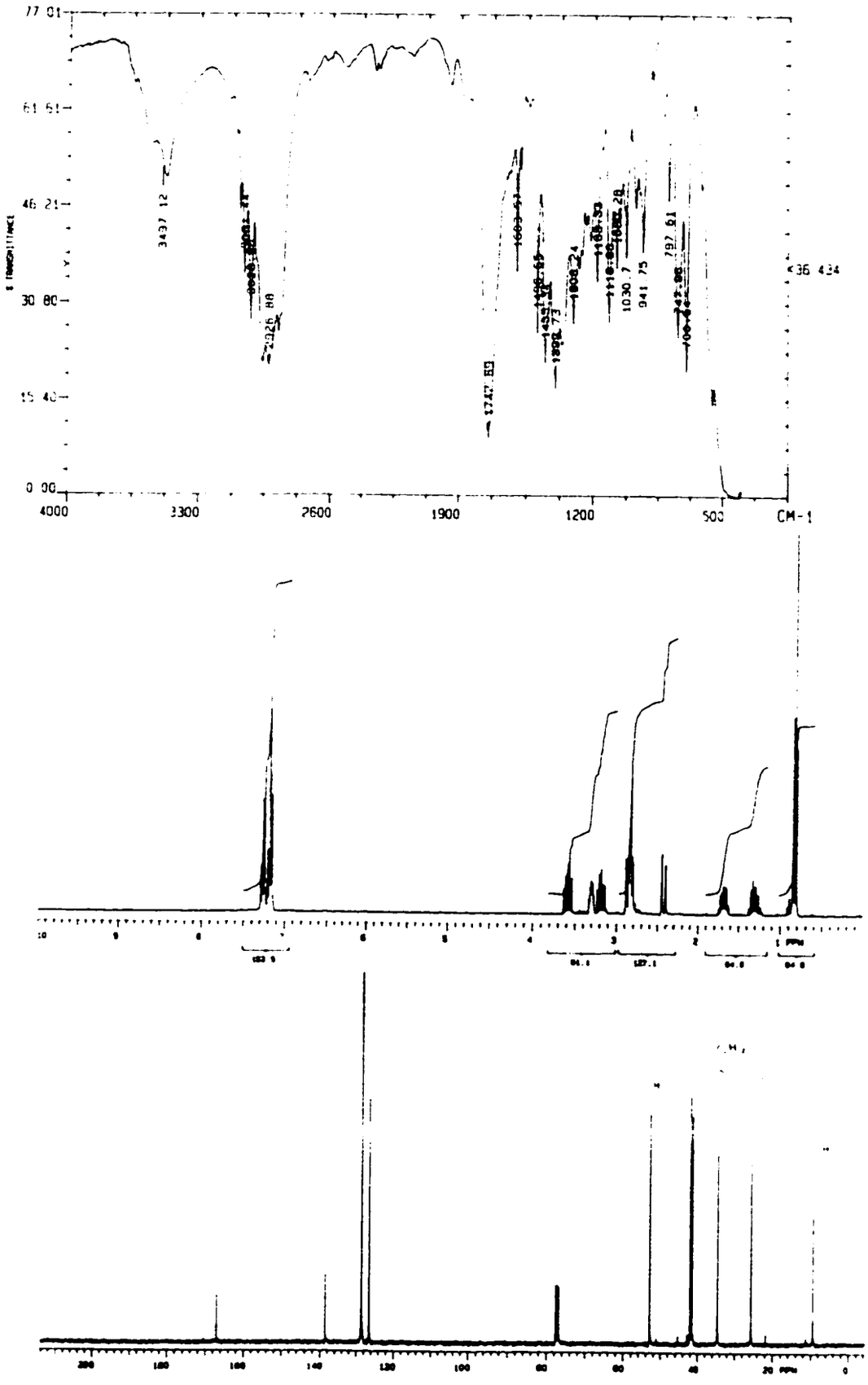
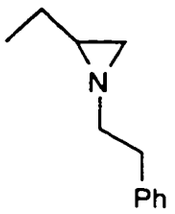
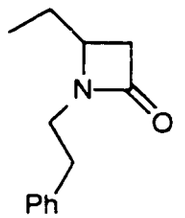
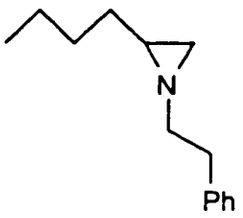
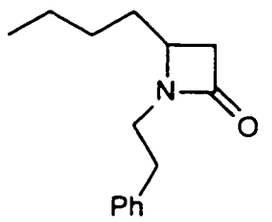
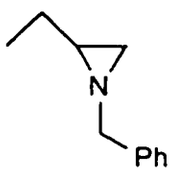
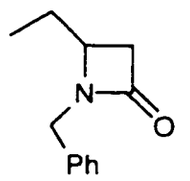
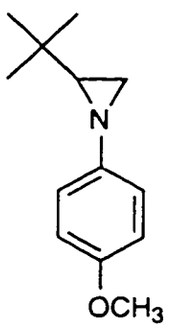
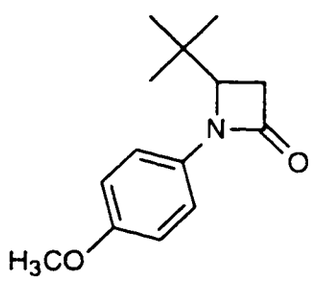
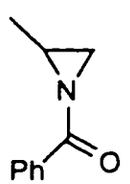
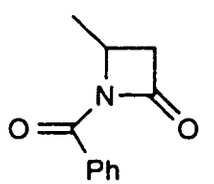
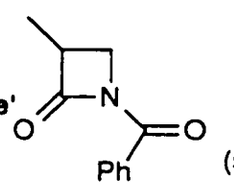
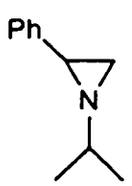
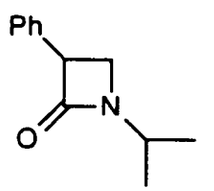


Figure 1: IR, ^{1}H-NMR and ^{13}C-NMR spectra of **28a**

Table 1: Carbonylation of 1,2-disubstituted aziridines

Substrate		product		Yield (%)
27a		**28a**		94
27b		**28b**		95
27c		**28c**		64
27d		**28d**		50
27e		**28e**	 + **28e'** 	92 (55:37)
27f		**28f**		42

Carbonylation of a series of 1,2-disubstituted aziridines was performed under the same reaction conditions. Table 1 shows that usually the carbon monoxide insertion occurs at the less substituted ring carbon-nitrogen bond. Exceptions are aziridine **27e**, which gives a mixture of two possible isomers, and aziridine **27f**, which undergoes insertion exclusively in the phenyl bearing carbon-nitrogen bond.

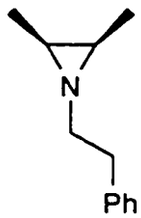
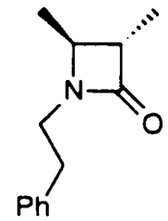
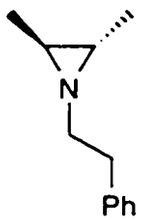
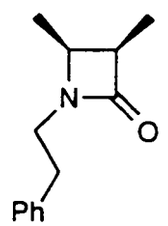
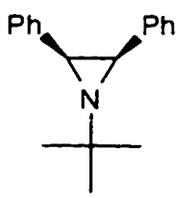
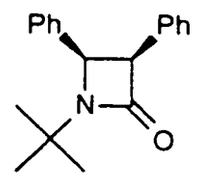
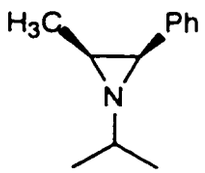
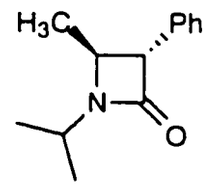
Excellent stereoselectivities are observed in the carbonylation of 1,2,3-trisubstituted aziridines (Table 2). For aziridines containing identical groups in positions 2 and 3 (**29a-29c**), carbon monoxide insertion occurs with inversion of configuration at the reacting carbon, i.e. starting from a *cis*-aziridine the product is a *trans*-β–lactam, and the *cis*-β–lactam is formed as the only product by use of a *trans*-aziridine. Reaction of **29d**, which contains two different substituents at positions 2 and 3, with $Co_2(CO)_8$ and CO, affords carbonylation only of the benzylic C-N bond, also with inversion of configuration.

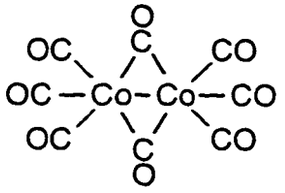
The regio and stereoselectivity of the carbonylation reaction suggests that the initial step is a S_N2 ring opening of the aziridine. This indicates that $Co_2(CO)_8$ is not the active catalyst, since it does not behave as a nucleophile. Therefore, the active catalyst must be formed *in situ*.

2.2.1.1 Chemistry of $Co_2(CO)_8$

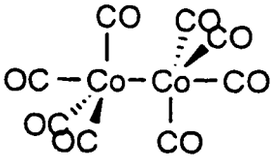
Octacarbonyl dicobalt is an orange crystalline solid which slowly loses carbon monoxide to form $[Co_4(CO)_{12}]$ and eventually cobalt metal[15]. It oxidizes on exposure to air to a purple Co (II) species. The crystal structure of $Co_2(CO)_8$ shows that in the solid state it contains two bridging carbonyl groups, and that the two cobalt atoms are connected by a single bond (Scheme 16).

Table 2: Carbonylation of 1,2,3-trisubstituted aziridines

	Substrate		product	Yield (%)
29a		**30a**		95
29b		**30b**		95
29c		**30c**		94
29d		**30d**		94



31



32

Scheme 16

In solution, structure **31** persists, but it is in equilibrium with the isomeric non bridged form **32**. The amount of the non bridged form increases with increasing temperature.

Octacarbonyl dicobalt reacts with bases such as phosphines, arsines and stibines under mild conditions to give disproportionation products **33** (Eq 7). This type of reaction occurs also with hard O or N bases.

$$Co_2(CO)_8 + nL \rightleftharpoons [Co(CO)_{5-n}L_n]^+[Co(CO)_4]^- + (n-1)CO \qquad \text{(Eq. 7)}$$

33

Studies on the disproportionation of $Co_2(CO)_8$ induced by nitrogen bases indicate that, in Eq 7, n can go from 1 to 5, depending on the reactivity of the ligands[16]. This reactivity is not significantly dependent on the nucleophilicity of the base. Instead, steric hindrance of the base seems to affect its ability to coordinate to the metal. In one extreme, tertiary amines like triethylamine have low reactivity, and just one molecule of triethylamine coordinates to the $Co_2(CO)_8$, to give the dinuclear complex **34** (Eq 8).

$$Co_2(CO)_8 + Et_3N \xrightarrow{CO} [Co_2(CO)_7NEt_3] \qquad \text{(Eq. 8)}$$

34

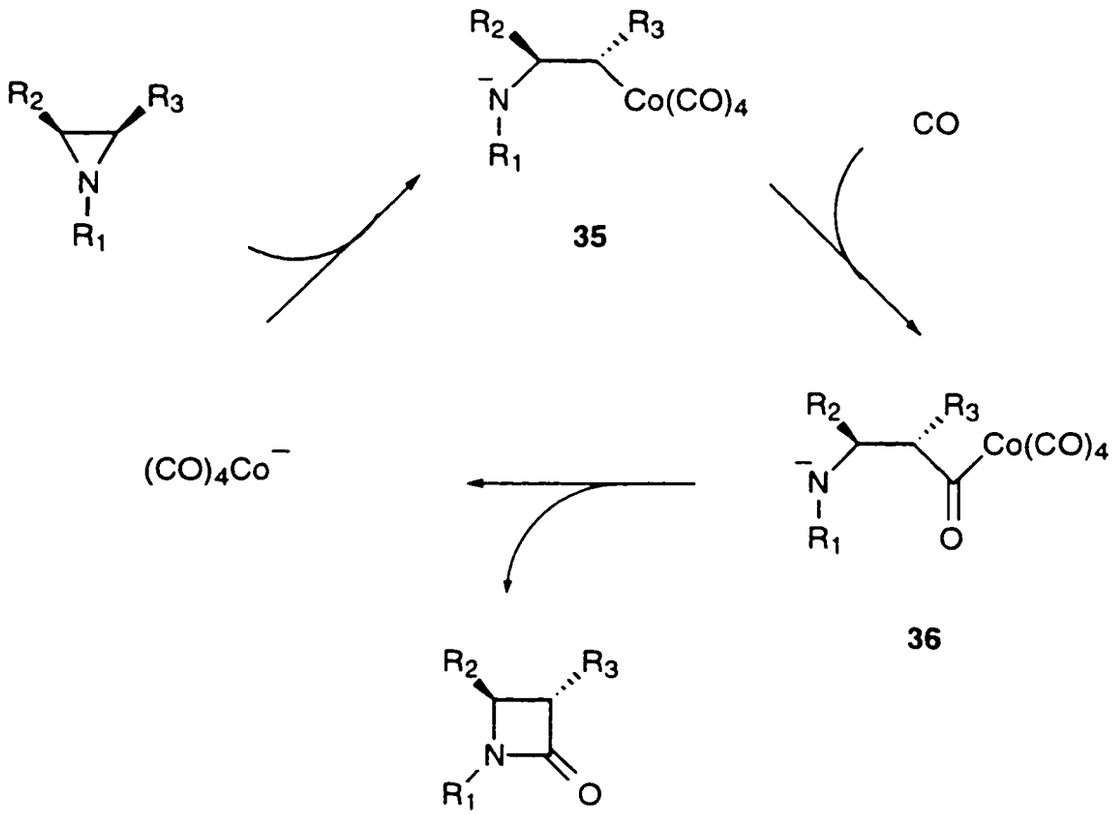
Coordination of just one ligand does not induce disproportionation of the dicobalt complex. But less hindered amines coordinate two or more ligands, decomposing the dinuclear complex and forming free tetracarbonylcobaltate anion. Although the reaction of aziridines with $Co_2(CO)_8$ has not been studied, we can assume that the small ring makes aziridines less bulky than acyclic tertiary amines, therefore two or more aziridine molecules might coordinate to the dinuclear complex, inducing the formation of the ionic pair **33** (Eq 7, L= aziridine). This is a very important step for our carbonylation reaction, because the $Co(CO)_4^-$ formed can act as the nucleophile for the ring cleavage of the aziridine.

Tetracarbonylcobaltate anion is known to be a nucleophile of moderate strength[17]. Its reaction with alkyl halides is a very useful method for the preparation of alkyl and acyl cobalt carbonyl complexes[15], and it has been used repeatedly as a catalyst for the carbonylation of alkyl halides, sulfates, sulfonates, etc. The anion is added as a salt, or is formed *in situ* by reduction of $Co_2(CO)_8$ or by reaction of the latter with NaOH. The development of phase transfer catalyzed carbonylation reactions using $Co_2(CO)_8$ and aqueous NaOH is especially significant[18].

2.2.1.2 Reaction mechanism

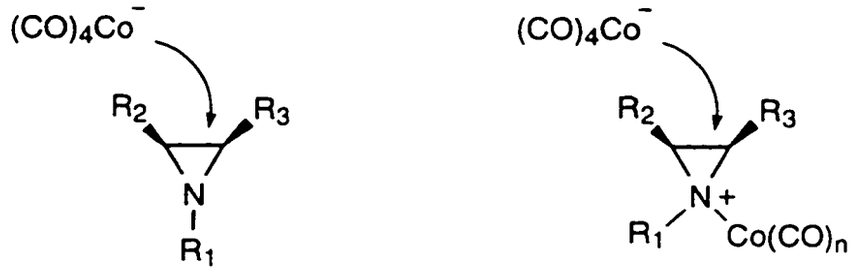
Reaction of an aziridine with $Co_2(CO)_8$ can give $Co(CO)_4^-$, which would be the active catalyst for the reaction (Scheme 17). Nucleophilic ring opening of the aziridine by tetracarbonylcobaltate would occur at the less substituted carbon of the aziridine, with inversion of configuration, to give **35**. Insertion of CO into the C-Co bond of **35** should proceed with retention of configuration to form **36**. Ring closure of the acyl complex **36** gives the β–lactam and regenerates the catalyst.

It is not clear whether the ring opening by $Co(CO)_4^-$ is induced in a free aziridine or in an aziridine coordinated to a cationic cobalt species (Scheme 17). It is important to note that the electrophilicity of the aziridine will be improved if it is coordinated to a metal.



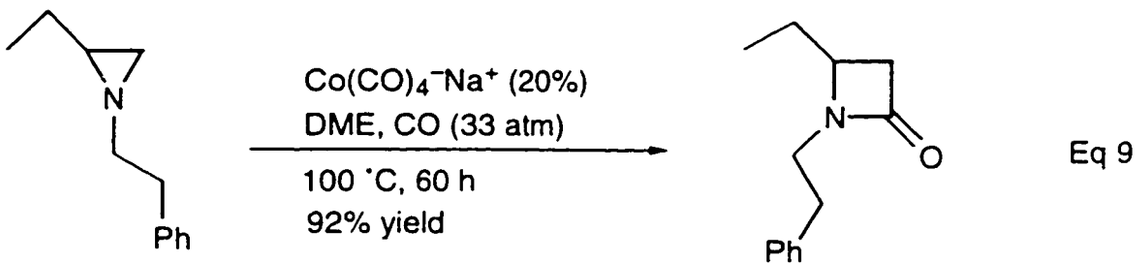
Scheme 17

If the reaction takes place by nucleophilic attack of $Co(CO)_4^-$ to a free aziridine, then the carbonylation reaction should occur using $Co(CO)_4^-Na^+$ as the catalyst. A reaction was carried out by using $Co(CO)_4^-Na^+$ in THF solution prepared by the reaction of $Co_2(CO)_8$ with NaOH powder in THF. The cobaltate anion was added in a 20 mol % ratio (Eq 9). The β–lactam was obtained in 92% yield, but after 60 h of reaction. This experiment confirms the participation of $Co(CO)_4^-$ in the reaction pathway. The lower rate of reaction could be due to the lower solvation of the Na^+ counterion, or to the lack of activation of the aziridine ring by Co^+.



37

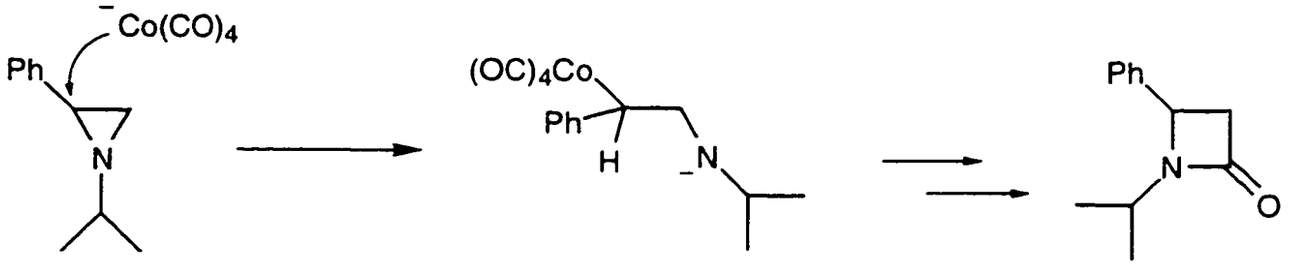
Scheme 18



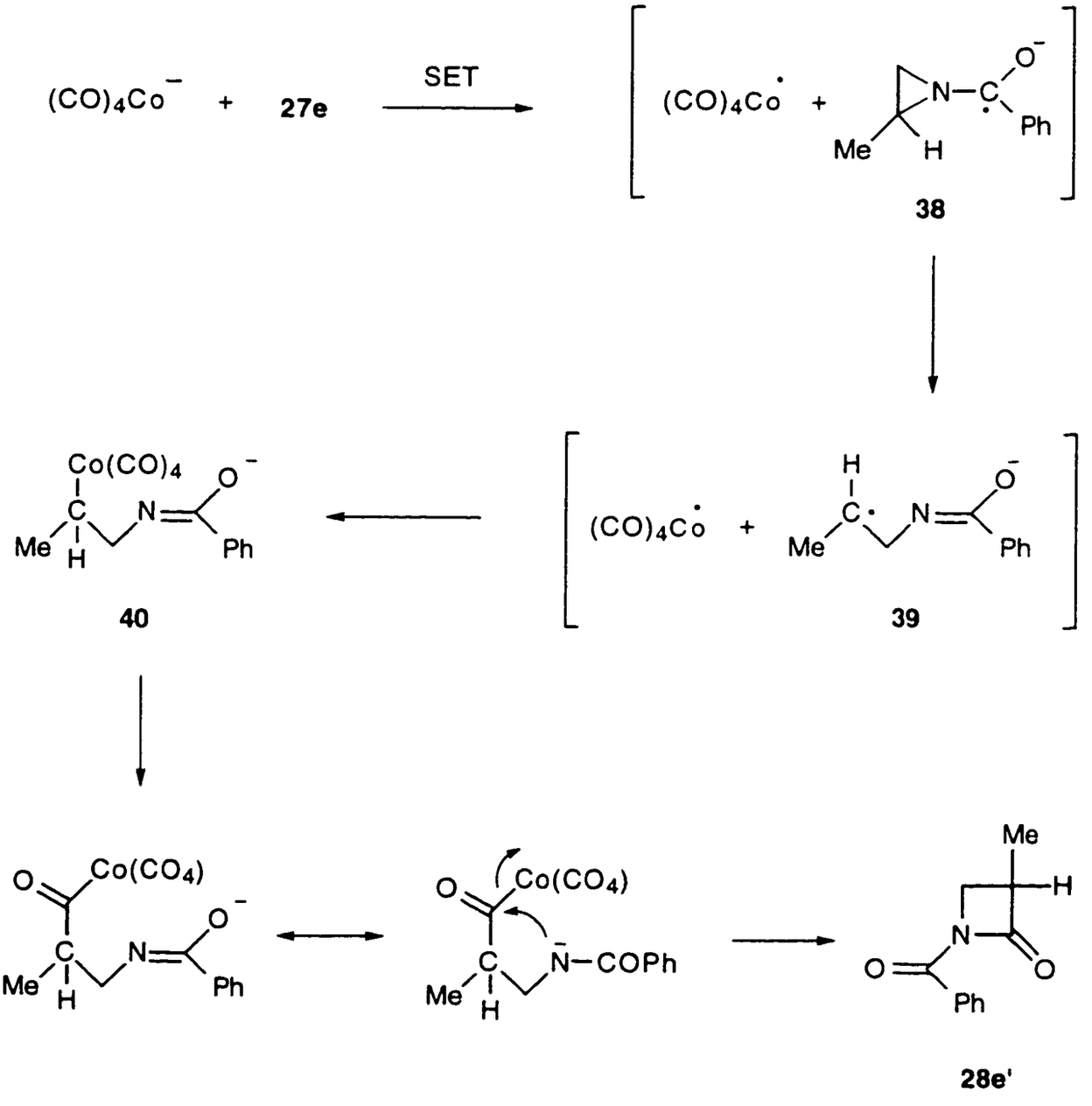
Eq 9

The mechanism outlined above explains the regio and stereoselectivity of the carbonylation reaction of most of the aziridines used. The 2-phenyl substituted aziridine **27f** undergoes carbonyl insertion into the more substituted ring carbon-nitrogen bond. Studies done on nucleophilic ring opening of 2-phenylaziridines[19] show that nucleophiles usually attack the C_2 of the aziridine ring, probably due to the delocalization of any partial charge formed at the benzylic carbon. Taking this into account, we think that the ring opening of **27f** takes place by a S_N2 mechanism as well, where the more reactive benzylic carbon-nitrogen bond is cleaved (Scheme 19). The inversion of configuration during the carbonylation of **29c** and **29d** supports this idea.

Use of 1-benzoyl-2-methylaziridine **27e** as the reactant gives a mixture of two isomers (**28e** and **28e'**) in good combined yield. The lower regioselectivity here can be explained by considering some studies done by Stamm *et al.*[20] regarding nucleophilic ring opening of aziridines. Usually this reaction, under neutral or basic conditions, proceeds via an S_N2 like



Scheme 19

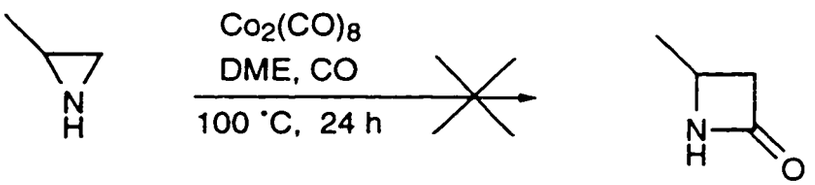


Scheme 20

mechanism. However, when there is a moderate activating group attached to the nitrogen atom, the nucleophile reacts at the most substituted carbon of the aziridine ring, with a single electron transfer mechanism proposed for the reaction. It is conceivable that a SET type mechanism (Scheme 20) is competing with the "normal" process (Scheme 17) in the reaction of $Co(CO)_4^-$ with **27e.** A ketyl radical anion (**38**) may be formed, which undergoes ring opening to a secondary radical (**39**). Radical combination with $(CO)_4Co^{\cdot}$ would afford (**40**) which is then convertible to **28e'**.

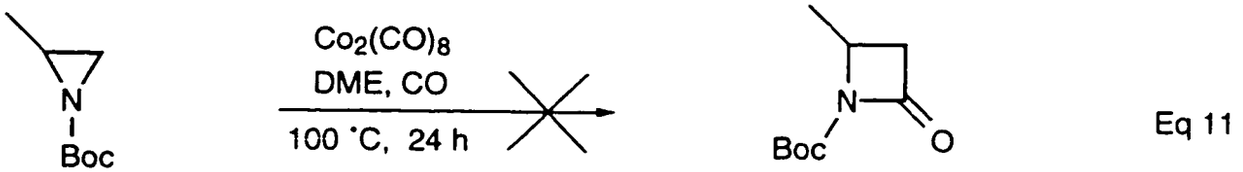
2.2.1.3 Carbonylation of N-protected aziridines

The preparation of N-unsubstituted β–lactams would be desirable because it would make possible further functionalization to more useful molecules. Unfortunately, treatment of the unsubstituted aziridine **41** with $Co_2(CO)_8$ and CO did not afford the expected β–lactam **42**. Although the conversion was complete, only polymeric material was recovered (Eq 10).



41 **42** Eq 10

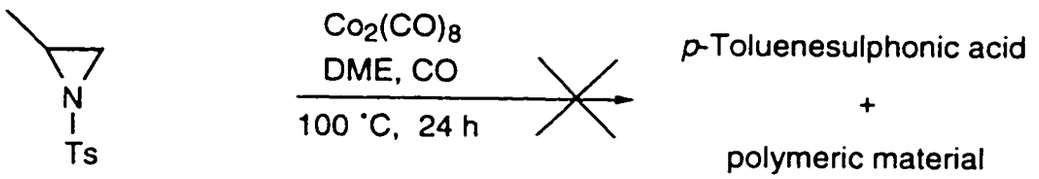
It was necessary then to perform the carbonylation reactions on aziridines containing removable groups at the nitrogen. Some of the more common protecting groups for β–lactams are *t*-butoxycarbonyl (Boc) and *p*-toluenesulphonyl (Ts). Carbonylation of compound **43** afforded only polymeric material, with no β–lactam **44** detected in the reaction mixture (Eq 11)



Eq 11

43 **44**

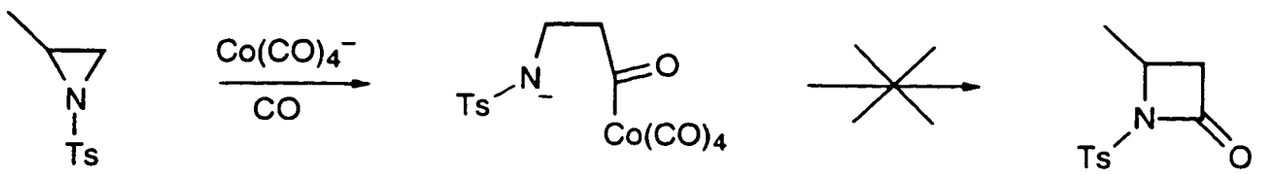
N-*p*-Toluenesulfonyl-2-methylaziridine **45** did not give the expected β–lactam either, with polymeric material and *p*-toluenesulphonic acid isolated from the rection (Eq 12).



Eq 12

45

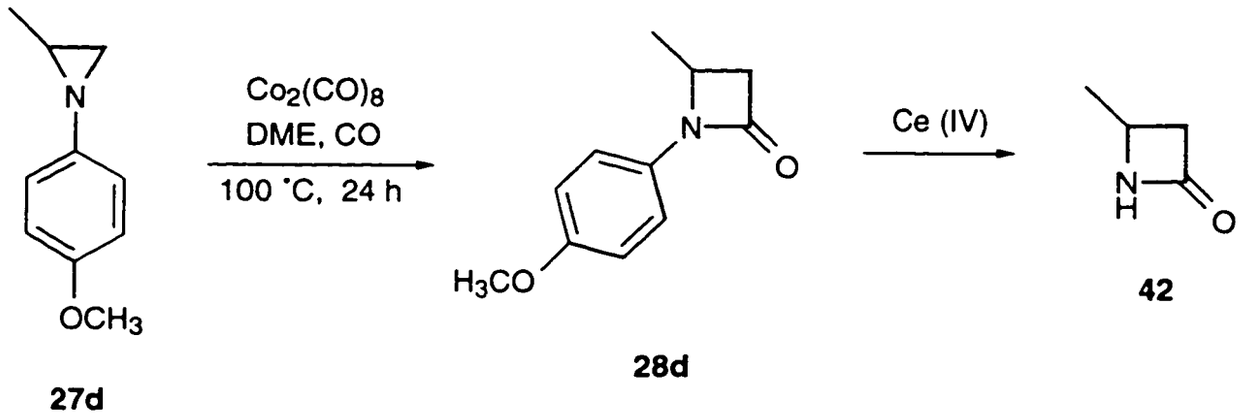
The reason for the failure of these reactions might be the presence of strong electron withdrawing substituents at the nitrogen. Although the ring opening should occur very easily, the negative charge in the anion **46** would be stabilized, and the nitrogen would not be nucleophilic enough to close the ring. In this case the reaction could take another course (Scheme 21).



46

Scheme 21

As it is shown in Table 1, 1-*p*-methoxyphenyl-2-*t*-butylaziridine (**27d**) gives a 50% yield of the β–lactam. The aryl group in the product can be removed by treatment with Ce (IV) salts[21] (Scheme 22), and in this way the N-unsubstituted β–lactam **42** can be obtained.



27d **28d** **42**

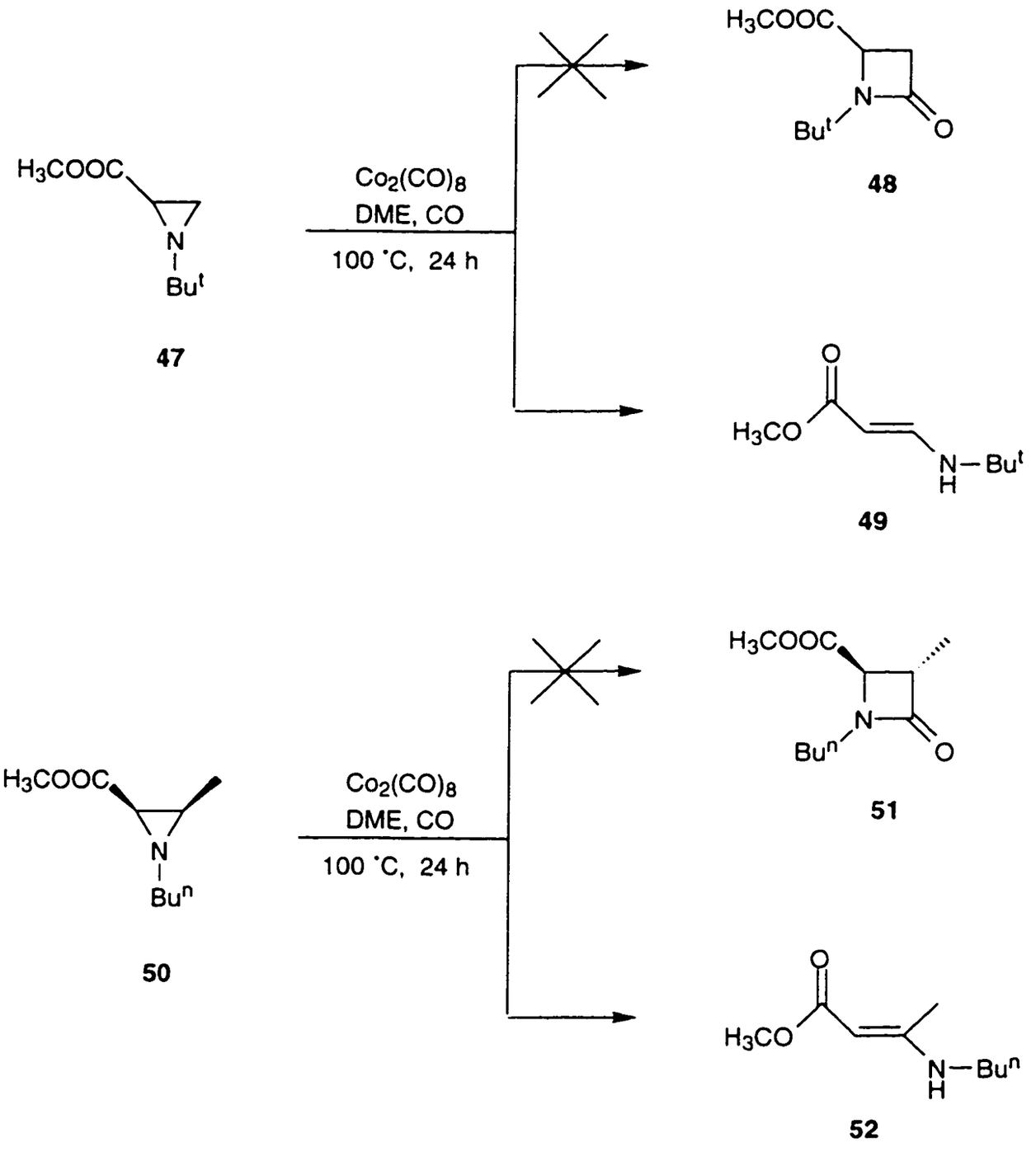
Scheme 22

2.2.1.4 Attempted carbonylation of aziridino-2-carboxylates

The presence of carboxylic acid groups attached to the sp^3 carbon bonded to nitrogen in the β–lactam ring is a very important requirement for the physiological activity of β–lactam antibiotics. It would be interesting to develop the synthesis of β–lactams bearing a carboxylate group at C_4 by carbonylation of aziridino 2-carboxylates.

Exposure of **47** and **50** to the carbonylation conditions did not afford the expected β–lactams **48** and **51**. After complete conversion, the isomerization products **49** and **52** respectively were observed in the reaction mixture (Scheme 23).

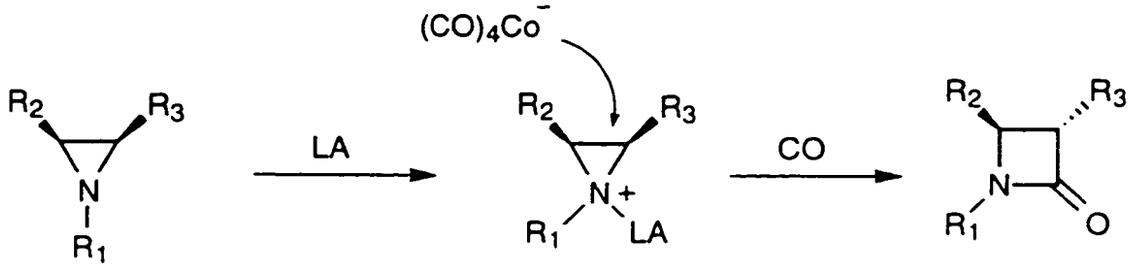
It is not clear how these products are formed. Control reactions show that **47** and **50** are stable at 100°C in DME solution. Reaction with $Co_2(CO)_8$ may induce elimination to the stable conjugated compounds **49** and **52** respectively before any carbonylation could occur.


H3COOC
N
But
47
Co2(CO)8
DME, CO
100 °C, 24 h
H3COOC
N
But
O
48
O
H3CO
N—But
H
49
H3COOC
N
Bun
O
51
H3COOC
N
Bun
50
Co2(CO)8
DME, CO
100 °C, 24 h
O
H3CO
N—Bun
H
52

Scheme 23

2.2.1.5 Carbonylation of aziridines using acids as co-catalysts

The apparent enhancement of the reactivity of the aziridines when they are coordinated to Co^+ suggested that it could be possible to carry out the carbonylation reaction in the presence of Lewis acids. The latter can activate the aziridine for the ring opening by forming a coordination complex of type **53** (Scheme 24).

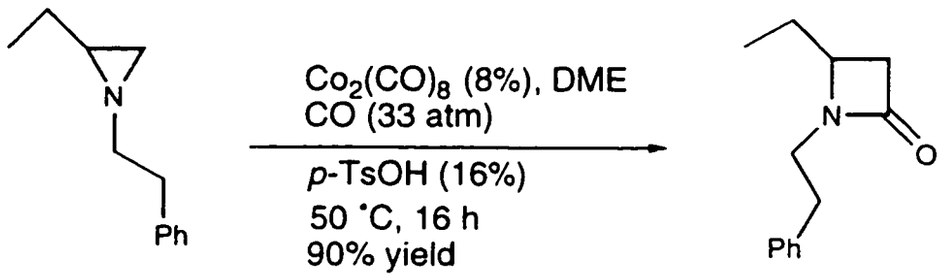


53

Scheme 24

Carbonylation in the presence of $BF_3.Et_2O$, $AlCl_3$ or $ZnCl_2$, either in catalytic or stoichiometric amounts, gave much lower yields of the β-lactam. But the reaction improved considerably when *p*-TsOH was added to the reaction in a 2/1 *p*-TsOH/$Co_2(CO)_8$ ratio. Carbonylation of **27a** at just 50 °C, with complete conversion of the aziridine after 16 h, gave a 90% yield of **28a** (Eq 13).

The protonation of the aziridine nitrogen by *p*-TsOH could be responsible for the improvement in reactivity.

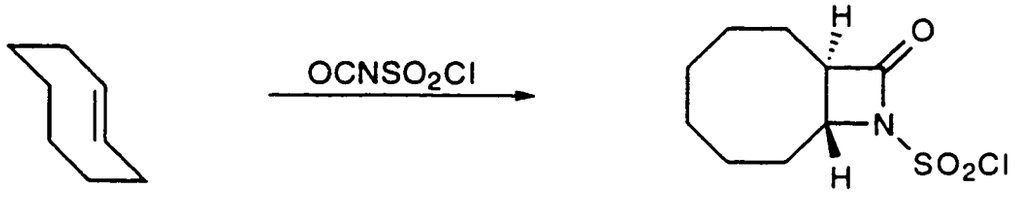


27a 28a Eq 13

2.2.2 Carbonylation of bicyclic aziridines

The stereoselective formation of *trans* β–lactams from *cis*-aziridines encouraged us to attempt the carbonylation of aziridines fused to cycloalkanes. Carbonylation of *cis* fused bicyclic aziridines allowed us to prepare *trans* fused β–lactams, compounds that were unknown before we performed these reactions.

Bicyclic β–lactams are usually prepared by cycloaddition of a cycloalkene and chlorosulfonylisocyanate[22] (Eq. 14). The stereochemistry of this reaction is such that one can only obtain the *trans* isomer if a *trans* cycloalkene is used as reactant. The smallest isolable *trans* cycloalkene is *trans*-cyclooctene (**54**), which has been used to prepare the β–lactam **55**[23] (Eq. 14).



54 **55** (Eq. 14)

Carbonylation of the *cis*-bicyclic aziridines **56a-56e** (7-azabicyclo[4.1.0]heptane

derivatives) affords the β–lactams **57a–57e.** While the yield of the *trans*- β–lactams is relatively low using DME as the solvent, it increased significantly when THF was the solvent for the reaction (e.g. 80 % yield for **57e** in THF, 35 % yield using DME, Table 3). Spectroscopic studies and X-ray analysis of **57e** confirm the *trans* configuration of the product.

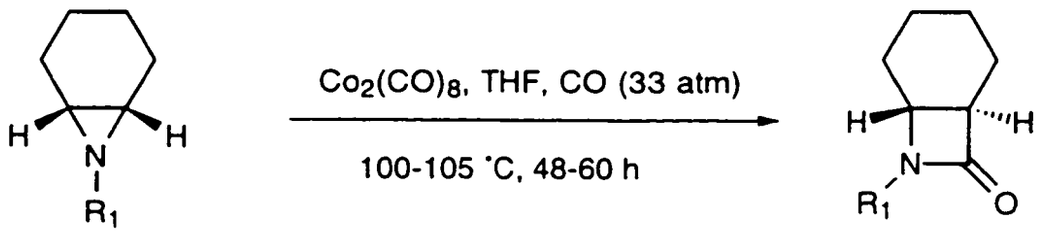
Temperature control is crucial to the success of these reactions, as it must be maintained between 100 and 105 °C. At T<100 °C the reaction is too slow, and at T>110 °C the decomposition of the product is faster than its formation, and no lactam can be isolated.

The β–lactams **56a** and **56c–56e** are white solids while **56b** is a liquid at room temperature. These compounds can be purified by preparative TLC, column chromatography or recrystallization from hexane. Suitable crystals of **57e** were easily obtained from hexane or mixtures of hexane and ether or methylene chloride and subjected to X-ray analysis. The ORTEP of **57e** (Figure 2) confirms the *trans* configuration for the β–lactam.

2.2.2.1 The bicyclo[4.2.0]octane system

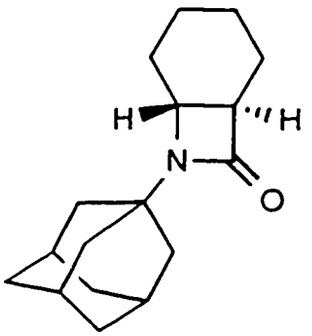
The *trans* fusion in bicyclo[4.2.0]octane compounds adds some strain to the molecule. *Trans*-bicyclo[4.2.0]octane and *trans*-7-azabicyclo[4.2.0]octane derivatives have been described in the literature. The X-ray structure[24] of compound **58** (Scheme 25) shows that the four member ring has a folded conformation, with bond torsion angles of about 25°. This conformation is not very different to the conformation of cyclobutane[25], what suggests that the strain in this ring system is not very high.

Table 3: Cobalt catalyzed carbonylation of bicyclic aziridines



56a-e **57a-e**

	R_1	product	isolated yield (%)
56a	$PhCH_2CH_2$	**57a**	44
56b	$PhCH_2$	**57b**	28
56c	cyclohexyl	**57c**	69
56d	$(CH_3)_3C$	**57d**	67
56e	1-adamantyl	**57e**	80



57e

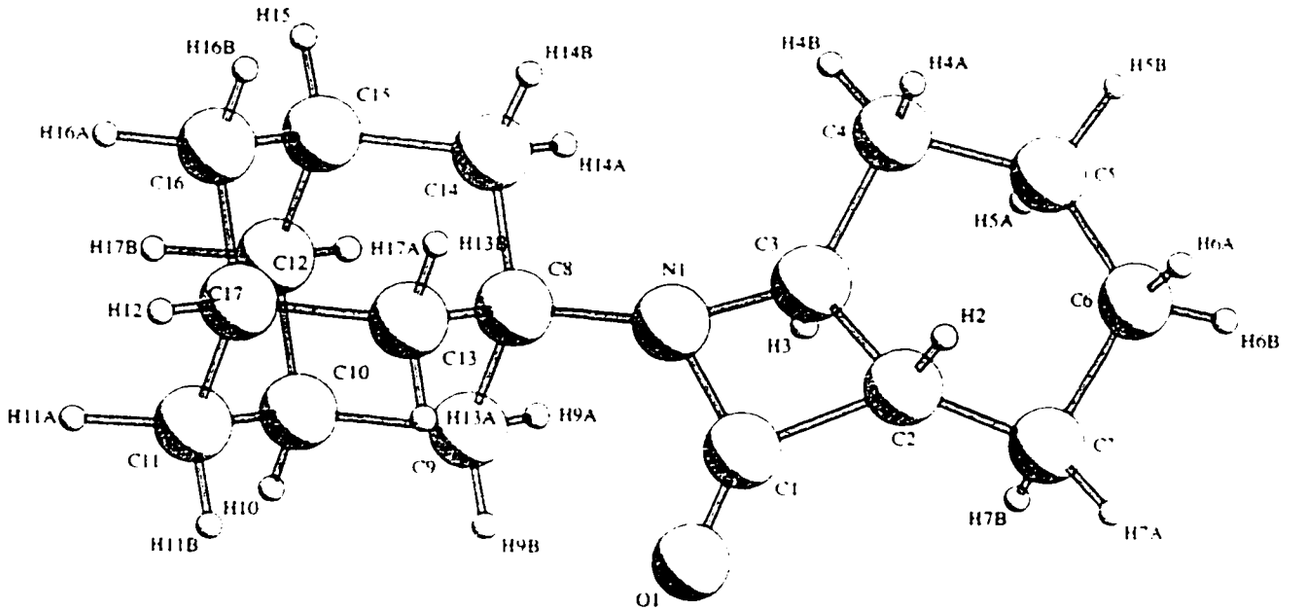
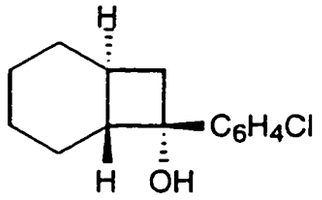
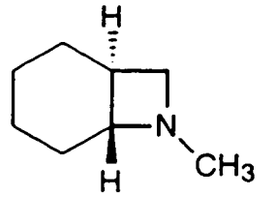


Figure 2: Structure of **57e**, showing the atom-labeling Scheme. Selected bond distances (Å): N1–C1, 1.395(4); N1–C3, 1.492(4); N1–C8, 1.456(3); C1–O1, 1.215(4); C1–C2, 1.531(4); C2–C3, 1.524(4). Selected bond angles (deg): C1–N1–C3, 91.25(20); C1–N1-C8, 127.09(23); C3–N1–C8, 127.59(22); N1–C1–C2, 90.62(21); C1–C2–C3, 85.08(20); N1–C1–O1, 131.8(3); C2–C1–O1, 137.6(3).



58

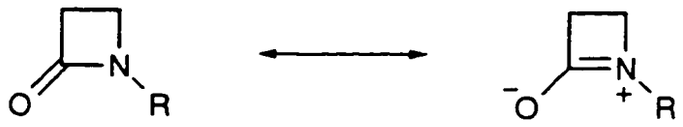


59

Scheme 25

7-Methyl-7-azabicyclo[4.2.0]octane **59** has also been synthesized[26]. Although there are no studies about its structure, we can assume that the four membered ring has a folded conformation like the monocyclic azetidines, since a planar structure would add strain to the molecule.

The favorable puckered conformation for the four membered rings in **58** and **59** will add strain energy in the case of β-lactams fused in a *trans* fashion to the cyclohexane ring. Usually, the four membered ring in unstrained β–lactams is essentially planar. In addition, the substituent at N lies in the same plane as the ring. These two structural features make possible an optimum amide resonance between the unpaired N electrons and the carbonyl group, resulting in a shorter OC–N bond and a longer C=O bond (Scheme 26).



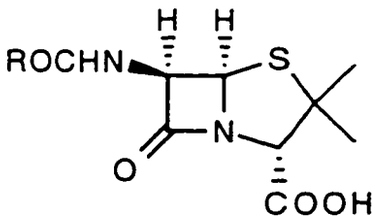
Scheme 26

The planar geometry can not be sustained in compound **57e**. The X-ray analysis of **57e** shows that the *trans* fusion of the rings adds considerable strain to the system. The N is out of the plane formed by the three carbons in the ring. The distance between the N and the plane is

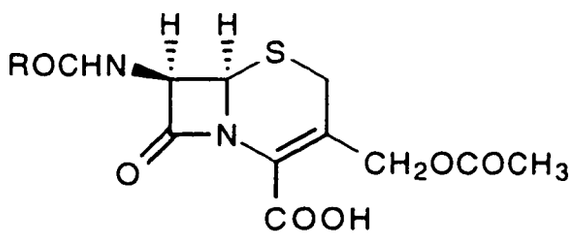
0.433 Å. The torsion angle in the four membered ring is 18.5°. In addition, the structure shows a pyramidal N, as reflected by the sum of bond angles about N (345.93°). The N-CO length bond (1.395 Å) is longer than the one present in unstrained systems. All these facts suggest the amide conjugation in the ring is considerably inhibited by the strain of the system.

It is worth to note that the carbonyl stretching absorptions in the IR spectra of compounds **57a-e** do not correspond with the expected values for strained β-lactams (>1750 cm^{-1}). Moreover, the absorption band for compound 57e is unusually low (1732 cm^{-1}). Bulky alkyl groups attached to the nitrogen seem to lower the carbonyl stretching frequency.

All the structural properties of **57e** are very important when compared with physiologically active β–lactams[1,27]. It is known that the activity of β–lactam antibiotics depends mainly on two factors: a) The presence of a carboxylic acid group attached to the carbon next to the nitrogen, which acts as a hook to bind the enzyme and to position the molecule so that the reaction can take place. b) The deviation from planarity of the four membered ring. It increases as the tension in the ring is higher, and it is absent when there is not enough strain in the cycle. The acylating power of penicillins **60** and cephalosporins **61** (Scheme 27) is due mainly to the strain present in the ring, which facilitates the cleavage of the amide bond by lowering the amide resonance.



60



61

Scheme 27

Table 4 shows comparative structural parameters of **57e**, penicillins, cephalosporins

and unstrained systems. The distance from the N to the plane formed by the other three members in the penicillin ring is quite similar to the one observed in **57e**. In addition, the N-CO bond is longer in the latter than the average in penicillins. Although cephalosporins seem to have lower ring strain, the presence of a leaving group in position 3 of the bicyclic system increases the reactivity of the amide function by stabilizing the ring opening product. The rest of the substituents usually modulate the antibiotic activity of the β-lactam. In the light of these structural similarities it is reasonable to believe that this class of bicyclic β–lactams could find application as acylating agents, and that appropriately substituted derivatives may exhibit significant physiological activity.

Table 4: Comparative structural parameters of different types of β–lactams.

	N-CO bond (Å)	distance between N and plane (Å)	sum of bond angles about N (°)
57e	1.395	0.433	345.93
Penicillins[a]	1.37[b]	0.4[b]	335-343
Cephalosporins[a]	1.38[b]	0.2[b]	343-351
Unstrained systems[a]	1.347[b]	~ 0	~ 360

a) Ref. 1. b) Average values.

2.3 Conclusions

A new method has been developed for the synthesis of β–lactams by the carbonylation of a wide range of aziridines, using $Co_2(CO)_8$, an economical catalyst. The yields are often excellent, and the reaction proceeds with inversion of configuration at the reacting carbon. In most cases the reaction begins by nucleophilic ring opening of the aziridine by *in situ* generated tetracarbonylcobaltate anion. Aziridines containing a moderately activating group at the nitrogen undergo carbonylation by initial ring opening via an SET mechanism. This alternative mechanism competes with the nucleophilic ring opening, and favors the carbonylation of the more substituted carbon-nitrogen bond.

A significant result of this research is the preparation of highly strained bicyclic β–lactams containing the *trans*-7-azabicyclo[4.2.0]octan-8-one nucleus. These new compounds present very interesting structural features that resemble those contained in biologically active *β*–lactams.

2.4 Experimental Section

2.4.1 General Comments

^{1}H- and ^{13}C-NMR spectra were recorded on Gemini 200, Varian XL 300 and Bruker AMX 500 NMR spectrometers. Infrared spectra were recorded on a BOMEM MB 100 FTIR spectrometer. Liquid samples were run neat, and solid samples were run as KBr pellets. A VG7070E spectrometer was used for mass spectra determinations. Elemental analyses were carried out by MHW Laboratories, Phoenix, AZ. or by our analytical laboratories at the University of Ottawa. Gas chromatography was carried out using a Varian 3400 chromatograph, fitted with a glass column packed with 1.5% OV-17 & 1.95% OV-210 on CHROMOSORB W HP 100/120 mesh.

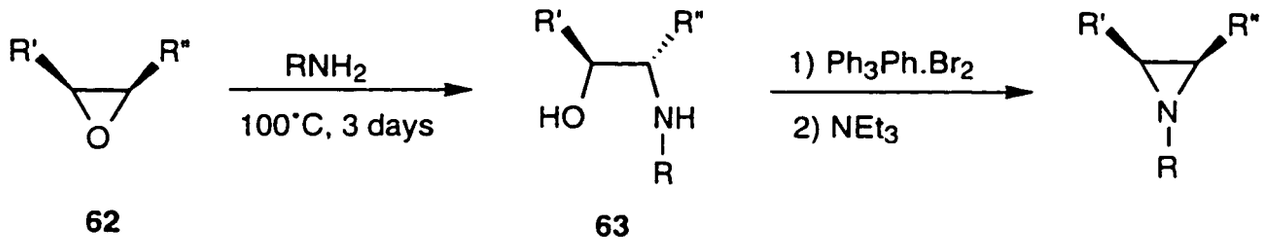
Chemicals were purchased from Aldrich, Lancaster, Fluka and Strem Chemicals, and were used as received unless otherwise noted. Solvents were purified and dried by standard methodologies[28].

High pressure reactions were conducted in stainless steal autoclaves with screw cap, provided by Parr instruments.

2.4.2 Synthesis of aziridines

Aziridines **27a-27c**, **27f**, **29a-29b**, **56a-56e** were synthesized following Scheme 28[29].

The epoxide **62** (20 mmol) was mixed with 4 eq of the amine in an autoclave. The mixture was heated to 100 °C and stirred for 3 days. After the reaction was brought to room temperature the excess amine was evaporated under vacum. The remaining oil was dissolved in hot hexane and crystallized at 0 °C. The amino alcohol **63** was separated by filtration.



62 63

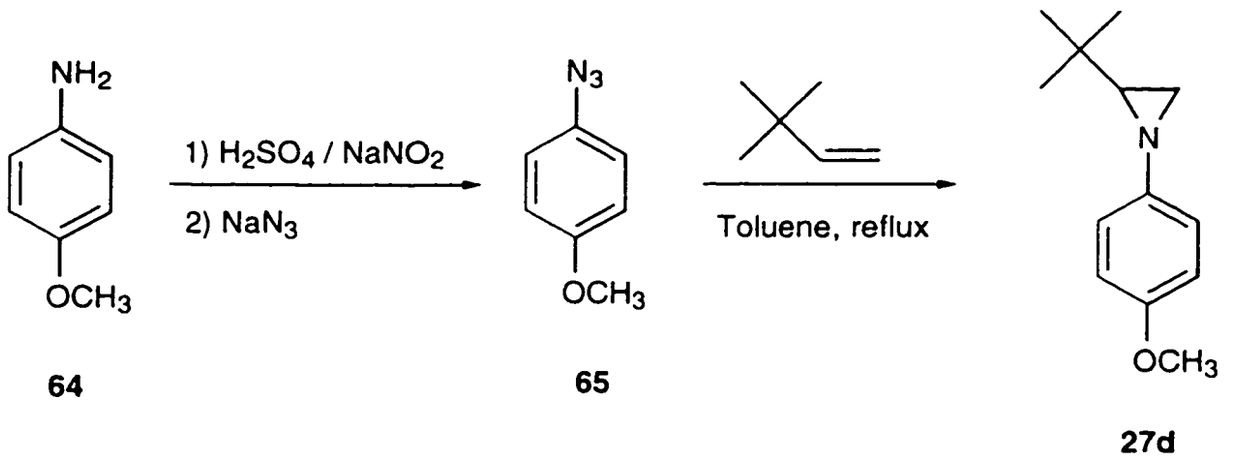
Scheme 28

When bulky amines were used (R= *t*-Bu, 1-adamantyl), the amminolysis was done by dissolving the epoxide and the amine[30] (1/1 ratio) in CH_2Cl_2, followed by the addition of 10 mol % of $Yb(OTf)_3$. The mixture was stirred overnight. The reaction mixture was then washed with distilled water and the organic phase was dried ($MgSO_4$). After evaporation of the solvent, the amino alcohol was recrystallized from hexane.

The ring closure of the amino alcohol was carried out as follows: To an ice cold solution of triphenylphosphine (7.2 g, 26.2 mmol) in 62 ml of acetonitrile, was added dropwise (under nitrogen atmosphere) a solution of bromine (1.45 ml, 26.2 mmol) in 21 ml of acetonitrile. The mixture was stirred for an additional 10 minutes. Then, the amino alcohol (25 mmol) was added in portions, followed by a solution of NEt_3 (7 ml, 50 mmol) in 9 ml of acetonitrile. The ice bath was removed and the solution was stirred overnight at room temperature. The solid formed was separated by filtration, and the filtrate was concentrated by rotary evaporation. The residue was extracted with 4 portions of 20 ml of hexane, and the combined hexane solution was concentrated to around 10 ml. The solution was filtered to remove triphenylphosphine oxide, and the filtrate was evaporated. All the aziridines were purified by bulb to bulb distillation.

Synthesis of aziridine 27d: It was prepared as outlined in Scheme 29[31]. Water (35 ml) was placed in a round bottom flask containing a magnetic stirrer. While stirring, sulphuric acid (6 ml) was added, followed by *p*-methoxyaniline **64** (4 g, 32.5 mmol). After the white solid

was formed, the flask was placed in an ice bath. A solution of sodium nitrite (3.6 g) in 20 ml of water was added dropwise during 10 minutes and the mixture was stirred for an additional 45 minutes. A solution of sodium azide (3.6 g) in 20 ml of water was added with vigorous stirring, and stirring was continued for another 40 minutes. A dark thick oil was formed. It was extracted with ether and the ethereal solution was dried ($MgSO_4$). After evaporation of the solvent, *p*-azidoanisole **65** was purified by column chromatography.



64 **65** **27d**

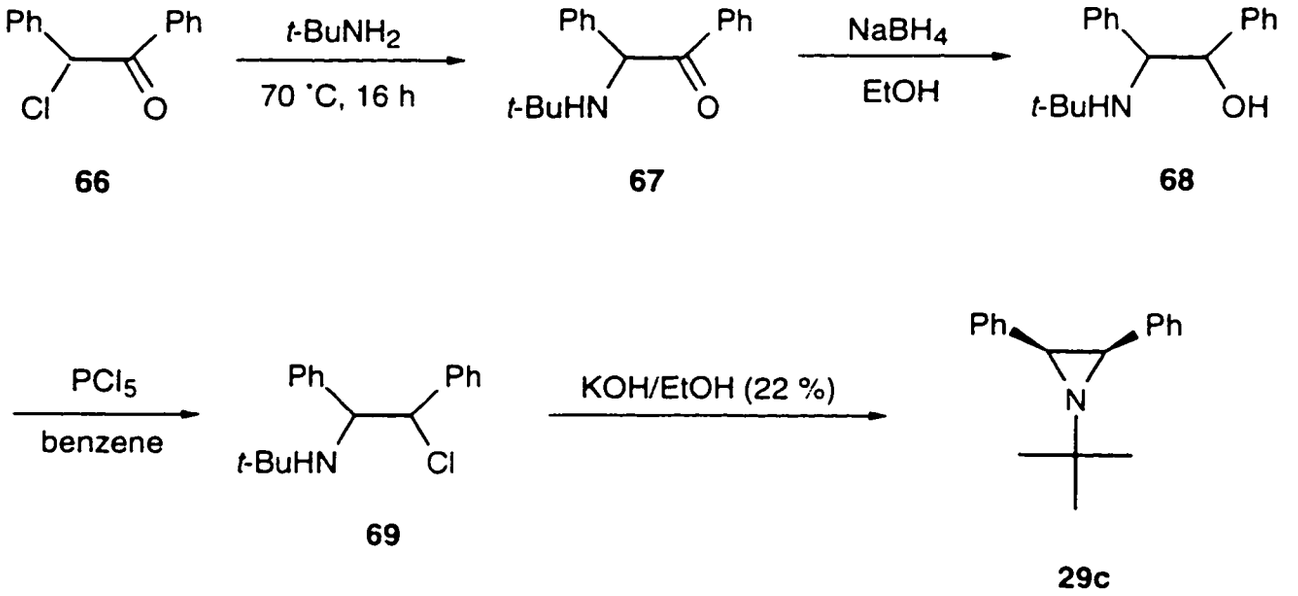
Scheme 29

p-Azidoanisole (**65**) (1 g, 6.71 mmol) and 3,3-dimethyl-1-butene (1.13 g, 13.4 mmol) were dissolved in 40 ml of toluene and the solution was placed in an autoclave. The mixture was heated to 130 °C with stirring for 48 hours. The reaction was cooled and the solvent evaporated. The resultant aziridine **27d** was purified by column chromatography.

Synthesis of aziridine 27e: This heterocycle was prepared by alkylation of 2-methylaziridine[14]. 2-Methylaziridine (1.4 ml, 20 mmol) and triethylamine (2.88 ml, 20 mmol) were dissolved in 30 ml of dry benzene. To the mixture was added, dropwise, a solution of benzoyl chloride (2.81 g, 20 mmol) in 25 ml of benzene. The reaction was stirred at room temperature for 5 hours. The triethylammonium chloride formed was separated by filtration.

The filtrate was concentrated. Bulb to bulb distillation of the crude gave 81 % yield of **27e**.

Synthesis of aziridine 29c: (Following Scheme 30)[32]. Desyl chloride (**66**) (10 g, 43.4 mmol) was mixed with *t*-butylamine (9.5 g, 130 mmol) and the mixture was heated at 70 °C overnight[33]. The crude reaction was dissolved in ether, washed 3 times with water and then dried ($MgSO_4$). The product **67** was isolated as the hydrochloride, in 36 % yield, by bubbling HCl through the solution.



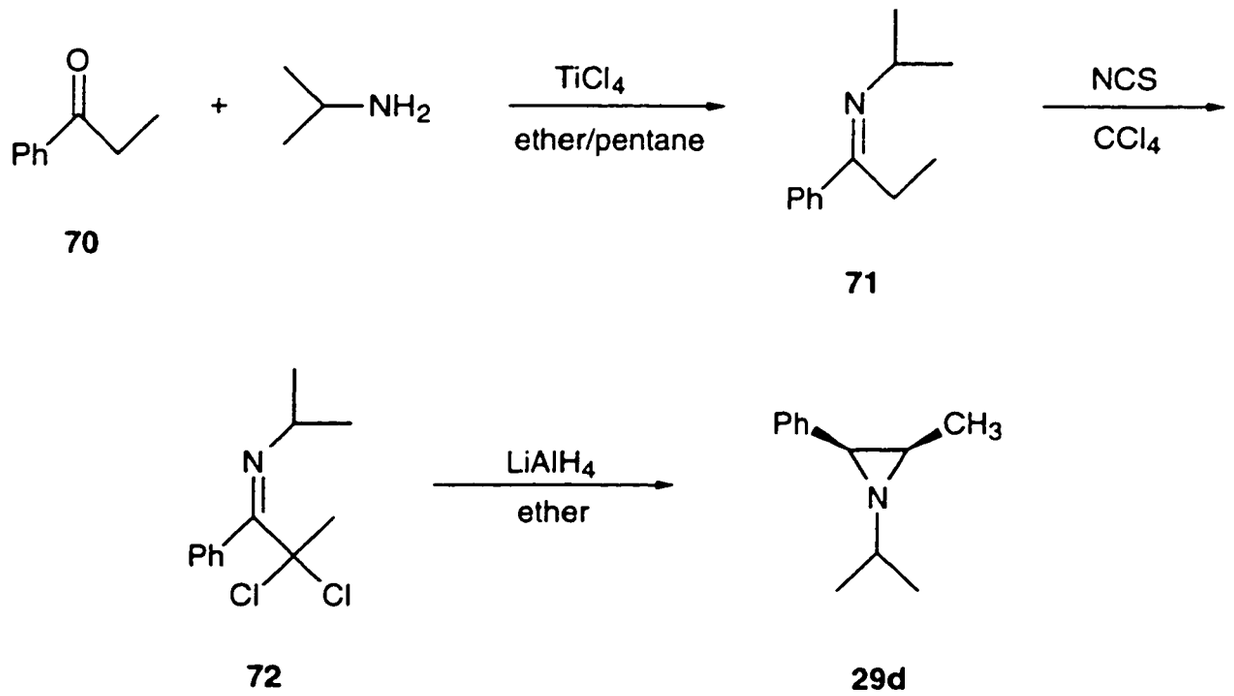
Scheme 30

The aminoketone **67** (3.94g, 12.9 mmol) was dissolved in 34 ml of dry ethanol[32]. A suspension of $NaBH_4$ in 15 ml of ethanol was added, and the mixture was refluxed for 3 hours. After cooling, it was poured into cold water and left in the fridge overnight. The white solid was filtered and recrystallized from ethanol to give the amino alcohol **68** in 54 % yield.

1,2-Diphenyl-2-(N-*t*-butylamino)ethanol (**68**) (1.87 g, 6.95 mmol) was dissolved in 10 ml of benzene[32]. Phosphorus pentachloride (1.6 g, 7.65 mmol) was added slowly to the stirred solution. The reaction was exothermic. The mixture was cooled and the solvent was

evaporated to obtain **69**. The product was used for the next step without purification. To **69** was added 40 ml of 22 % alcoholic potasium hydroxide. The reaction mixture was refluxed for 2 hours, then cooled and poured into 200 ml of water. The organic product was extracted with ether, the solution was dried ($MgSO_4$) and the solvent was evaporated. Bulb to bulb distillation gave the aziridine **29c**, which was collected as a white solid, in 52 % yield.

Synthesis of aziridine 29d: see Scheme 31. Propiophenone (**70**) (5.36 g, 40 mmol) and isopropylamine (7.08 g, 120 mmol) were dissolved in 25 ml of dry ether[34]. To this solution was added a solution of titanium tetrachloride (3.84 g, 20 mmol) over a period of 30 minutes. The mixture was stirred at room temperature for 1 hour, refluxed for 2 hours and then let stand overnight at room temperature. The solution was filtered, and the filtrate was concentrated. The residue was distilled under vacuum to give imine **71** in 45 % yield.



Scheme 31

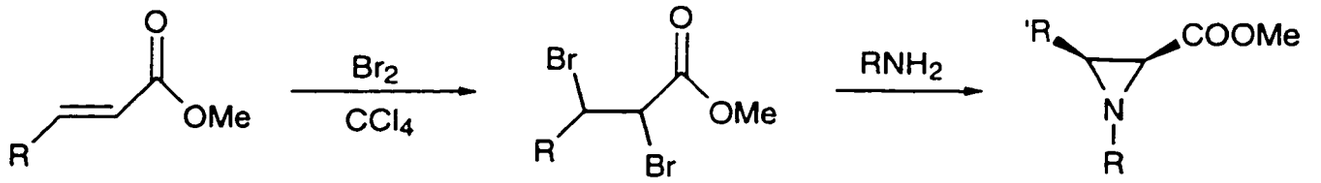
To a solution of imine **71** (3.15 g, 18 mmol) in carbon tetrachloride[35] (35 ml) was added N-chlorosuccinimide (5.3 g, 39.6 mmol), in portions, during 15 minutes. The reaction is slightly exothermic. The mixture was stirred at room temperature overnight, filtered and the filtrate was evaporated to give **72** in quantitative yield.

An ice cold suspension of $LiAlH_4$ (1.37 g, 36 mmol) in 35 ml of dry ether was treated dropwise with a solution of **72** (4.8 g, 18 mmol) in 35 ml of ether[36]. The reaction mixture was refluxed overnight, cooled and then slowly poured into cold water. The aqueous phase was washed with ether 3 times, and the combined ethereal extracts were dried ($MgSO_4$). Aziridine **29d** was purified by column chromatography; Yield: 32 % .

Synthesis of aziridine 43[37]: 2-Methylaziridine (1g, 17.5 mmol) was added to a 10 % solution of triethylamine in methanol[38] (26 ml). To this mixture was added di-*t*-butyldicarbonate (7.63 g, 35 mmol) with vigorous stirring. The mixture was heated for 1 h at 50 °C, cooled and the solvent was evaporated. The residue was treated with HCl (pH= 2), stirred for 10 minutes, and extracted with EtOAc, dried ($MgSO_4$) and filtered. After evaporation of the solvent, 1.01 g (37%) of the product was obtained.

Synthesis of aziridine 45[39]: To a mixture of 2-methylaziridine (1 ml, 13.89 mmol) and triethylamine (2.9 ml, 20.85 mmol) in 4 ml of methylene chloride at 0° to -10°C (methanol/ice bath) was added *p*-toluenesulphonyl chloride (3.24 g, 17 mmol) in portions during 10 minutes. The reaction mixture was stirred for an additional hour. To the mixture was added 40 ml of methylene chloride. The mixture was washed with cold water, followed by cold 10% HCl, saturated sodium bicarbonate and brine. The organic phase was dried ($MgSO_4$) and the solvent was evaporated. The aziridine was recrystallized from hexane (81% yield).

Synthesis of aziridines 48[40] and 51[41]: Prepared by the reaction of a primary amine with 2,3-dibromocarboxylic esters (Scheme 32).



73

74

R= *n*-bu, *t*-bu
R'= H, Me

Scheme 32

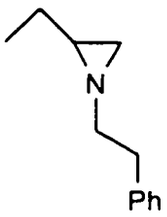
The bromination of the unsaturated esters **73** was effected by dropwise addition of Br_2 to an ice cold solution of the ester in carbon tetrachloride. The addition was continued until the color persisted. Evaporation of the solvent gave **74**, which was used for the next step without purification.

A solution of **74** (40 mmol) and the primary amine (120 mmol) in acetonitrile (200 ml) was refluxed for 20 hr[42]. After cooling the mixture was filtered and the filtrate was concentrated. The residue was extracted with ether, and the combined ethereal solution was concentrated. Bulb to bulb distillation gives the aziridine.

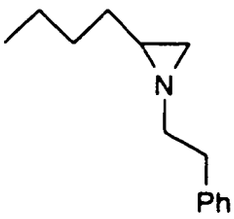
2.4.3 Synthesis of sodium tetracarbonylcobaltate

All the manipulations for this reaction were done in a glove bag full of nitrogen. Powdered sodium hydroxide[43] (470 mg, 11.5 mmol) was put in a round bottom flask, which was connected to a vacuum line for 15 minutes. The flask was charged with $Co_2(CO)_8$ (812 mg, 2.39 mmol, recrystallized from hexane). Very slowly, 20 ml of dry and deoxygenated THF was added. The mixture was stirred under nitrogen for 3 hours. A purple precipitate was formed. The mixture was filtered under nitrogen using Schlenk techniques. A light yellow solution was obtained. The determination of the concentration of the solution was made by

evaporation of a known volume of the solution, and the white solid remaining was weighed. The concentration was 0.084 M. The catalyst was kept in THF solution. An IR of the solution shows a characteristic metal carbonyl absorption at 1890 cm^{-1}.

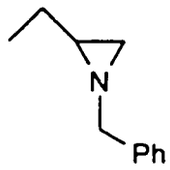


2-Ethyl-1-(2-phenylethyl)aziridine (27a): ^{1}H-NMR (300 MHz) δ= 0.99 ppm (t, 3H, J= 6.7 Hz, C*H*$_3$), 1.22 ppm (s, 1H) and 1.54 ppm (d, 1H, J= 3.2 Hz) (CHC*H*$_2$N), 1.38 ppm (q, 2H, J= 6.7 Hz, C*H*$_2$CH$_3$), 2.38 ppm (m, 1H) and 2.59 ppm (m, 1H) (C*H*$_2$N), 2.90 ppm (m, 2H, C*H*$_2$Ph), 7.25 ppm (m, 5H, Ph). ^{13}C-NMR: 12.2 (*C*H$_3$), 26.7 (*C*H$_2$CH$_3$), 34.3 (CH*C*H$_2$N), 37.1 (*C*H$_2$Ph), 41.9 (*C*H), 63.8 (*C*H$_2$N), 126.6, 128.9, 129.3 and 140.7 (Ph). MS: 175 (M^+). Anal. Calc. for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 81.84; H, 9.79; N, 7.92.

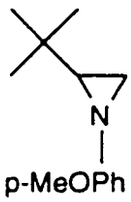


2-Butyl-1-(2-phenylethyl)aziridine (27b): ^{1}H-NMR (200 MHz) δ= 0.90 ppm (t, 3H, J= 6.9 Hz, C*H*$_3$), 1.18 ppm (s, 1H) and 1.51 ppm (d, 1H, J= 3.1 Hz) (CHC*H*$_2$N), 1.31 ppm (m, 7H, (C*H*$_2$)$_3$C*H*), , 2.48 ppm (m, 2H, C*H*$_2$N), 2.88 ppm (m, 2H, C*H*$_2$Ph), 7.24 ppm (m,

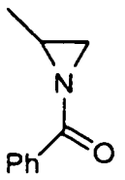
5H, Ph). ^{13}C-NMR: 14.7 (CH_3), 23.2 (CH_2), 30.3 (CH_2), 33.4 (CH_2), 34.5 ($CHCH_2N$), 37.1 (CH_2Ph), 40.4 (CH), 63.8 (CH_2N), 126.6, 128.9, 129.3 and 140.7 (Ph) ppm. MS: 203 (M^+). Anal. Calc. for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.41; H, 10.62; N, 6.80.



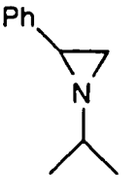
2-Ethyl-1-phenylmethylaziridine (27c)[44]: ^{1}H-NMR (200 MHz) δ= 0.89 ppm (t, 3H, J= 7.0 Hz, CH_3), 1.42 ppm (m, 4H) and 1.63 ppm (m, 1H) (CH_2CHCH_2), 3.32 ppm (d, 1H, J= 13.2 Hz) and 3.53 ppm (d, 1H, J= 13.2 Hz) (CH_2Ph), 7.3 ppm (m, 5H, Ph). ^{13}C-NMR: 12.1 (CH_3), 26.7 (CH_2CH_3), 34.4 (CH_2N), 41.9 (CH), 65.6 (CH_2Ph), 127.5, 128.7, 128.8 and 140.0 (Ph) ppm. MS: 161 (M^+).



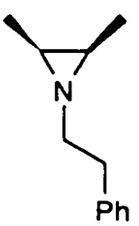
2-(1,1-Dimethylethyl)-1-(4-methoxyphenyl)aziridine (27d): ^{1}H-NMR (200 MHz) δ= 0.99 ppm (s, 9H, $(CH_3)_3C$), 1.81 ppm (d, 2H, J= 2.3 Hz, CH_2), 2.15 ppm (t, 1H, J= 2.3 Hz, CH), 3.74 ppm (s, 3H, OCH_3), 6.75 ppm (d, 2H, J= 8.9 Hz) and 6.90 ppm (d, 2H, J= 8.9 Hz) (Ph). ^{13}C-NMR: 26.8 ($(CH_3)_3C$), 30.3 ($(CH_3)_3C$), 30.5 (CH_2), 49.9 (CH), 55.5 (OCH_3), 114.1, 121.2, 149.1 and 154.8 (Ph) ppm. MS: 205 (M^+). Anal. Calc. for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.77; H, 9.01; N, 6.85.



1-Benzoyl-2-methylaziridine (27e)[14]: ^{1}H-NMR (200 MHz) δ= 1.40 ppm (d, 3H, J= 5.6 Hz, C*H*$_3$), 2.15 ppm (d, 1H, J= 3.1 Hz) and 2.57 ppm (m, 2H) (C*H*C*H*$_2$), 7.49 ppm (m, 3H) and 8.04 ppm (m, 2H) (Ph). ^{13}C-NMR: 17.7 (*C*H$_3$), 32.1 (*C*H$_2$), 34.5 (*C*H), 128.3, 129.0, 132.6 and 133.5 (Ph), 179.2 (*C*=O) ppm. IR (neat): 1672 (C=O) cm^{-1} MS: 161 (M$^+$).

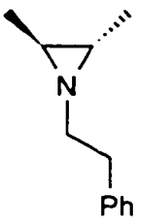


1-(1-Methylethyl)-2-phenylaziridine (27f)[45]: ^{1}H-NMR (200 MHz) δ= 1.08 ppm (d, 6H, J= 6.2 Hz, (C*H*$_3$)$_2$CH), 1.51 ppm (sept, 1H, J= 6.2 Hz, (CH$_3$)$_2$C*H*), 1.57 ppm (d, 1H, J= 6.6 Hz) and 1.79 ppm (d, 1H, J= 3.4 Hz) (C*H*$_2$), 2.24 ppm (dd, 1H, J= 6 and 3.4 Hz, C*H*), 7.2 ppm (m, 5H, Ph). ^{13}C-NMR: 22.4 (*C*H$_3$), 23.0 (*C*H$_3$), 37.2 (*C*H$_2$), 41.4 (*C*H), 62.5 ((CH$_3$)$_2$*C*H), 127.0, 127.3, 128.8 and 141.2 (Ph) ppm. MS: 161 (M$^+$).

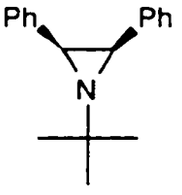


***cis*-2,3-Dimethyl-1-(2-phenylethyl)aziridine (29a)**: ^{1}H-NMR (200 MHz) δ= 1.05

ppm (d, 6H, J= 6.4 Hz, 2CH_3), 1.28 ppm (m, 2H, 2CH), 2.50 ppm (t, 2H, J= 8.5 Hz, CH_2N), 2.85 ppm (t, 2H, J= 8.5 Hz, CH_2Ph), 7.21 ppm (m, 5H, Ph). ^{13}C-NMR: 13.6 (CH_3), 37.2 (CH_2Ph), 39.3 (CH), 63.6 (CH_2N), 126.6, 128.9, 129.4 and 140.8 (Ph) ppm. MS: 175 (M^+). Anal. Calc. for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.34; H, 9.90; N, 7.98.

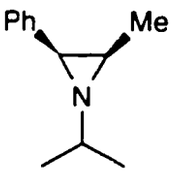


***trans*-2,3-Dimethyl-1-(2-phenylethyl)aziridine (29b):** ^{1}H-NMR (200 MHz) δ= 1.05 ppm (s, 4H, CH_3CH), 1.18 ppm (d, 3H, J= 6.4 Hz, CH_3), 1.72 ppm (dq, 1H, J= 6.4 and 2.2 Hz, CH), 2.55 ppm (m, 1H) and 2.85 ppm (m, 3H) (CH_2CH_2), 7.22 ppm (m, 5H, Ph). ^{13}C-NMR: 11.5 (CH_3), 19.0 (CH_3), 38.0, 39.1 and 42.4 (2CH and CH_2Ph), 54.4 (CH_2N), 126.6, 128.9, 129.4 and 141.0 (Ph) ppm. MS: 175 (M^+). Anal. Calc. for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.23; H, 9.95; N, 7.90.

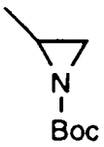


***cis*-1-(1,1-Dimethylethyl)-2,3-diphenylaziridine (29c)[32]:** White solid, mp: 96.5-97 °C. ^{1}H-NMR (200 MHz) δ= 1.21 ppm (s, 9H, C(CH_3)$_3$), 3.20 ppm (s, 2H, 2CH), 7.15 ppm (m, 10H, Ph). ^{13}C-NMR: 27.4 (C(CH_3)$_3$), 42.6 (2CH), 53.9 (C(CH$_3$)$_3$), 126.9, 128.1,

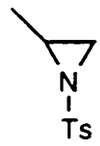
128.6 and 138.3 (Ph) ppm. MS: 251 (M^+).



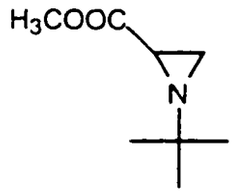
***cis*-3-Methyl-1-(1-methylethyl)-2-phenylaziridine (29d)**[36]: ^{1}H-NMR (200 MHz) δ= 0.81 ppm (d, 3H, J= 5.7 Hz, CH_3), 1.08 ppm (d, 3H, J= 6.2 Hz) and 1.09 ppm (d, 3H, J= 6.4 Hz, CH(CH_3)$_2$), 1.63 ppm (m, 2H, C*H*N and C*H*(CH$_3$)$_2$), 2.41 ppm (d, 1H, J= 6.8 Hz, C*H*Ph), 7.2 ppm (m, 5H, Ph). ^{13}C-NMR: 13.7 (*C*H$_3$), 21.9 (*C*H$_3$), 22.1 (*C*H$_3$), 40.5 (*C*HCH$_3$), 45.9 (*C*HPh), 61.3 (*C*HN), 126.4, 127.8, 127.9 and 138.0 (Ph) ppm. MS: 175 (M^+).



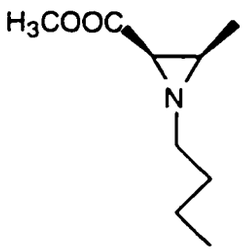
1-*t*-butoxycarbonyl-2-methylaziridine (43)[37]: ^{1}H-NMR (200 MHz) δ= 1.18 ppm (d, 3H, J= 5.7 Hz, CHCH_3), 1.40 ppm (s, 9H, C(CH_3)$_3$), 1.84 ppm (d, 1H, J= 3.7 Hz) and 2.18 ppm (d, 1H, J= 6.0 Hz) (CH_2), 2.39 ppm (m, 1H, C*H*CH$_3$). ^{13}C-NMR: 17.4 (*C*H$_3$), 27.9 (C(*C*H$_3$)$_3$), 32.5 (*C*H$_2$), 33.5 (*C*H), 80.9 (*C*(CH$_3$)$_3$), 162.4 (*C*=O) ppm. IR= 1718 cm^{-1} (C=O). MS: (CI) 158 (M^+ + 1).



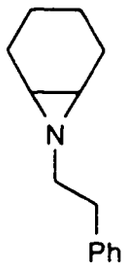
2-Methyl-1-*p*-toluenesulphonylaziridine (45)[39]: ^{1}H-NMR (200 MHz) δ= 1.24 ppm (d, 3H, J= 5.6 Hz, CHCH_3), 2.01 ppm (d, 1H, J= 4.7 Hz) and 2.60 ppm (d, 1H, J= 7.1 Hz) (CH_2), 2.43 ppm (s, 3H, CH_3Ar), 2.81 ppm (m, 1H, CHCH$_3$) 7.27 ppm (d, 2H, J= 8 Hz) and 7.81 ppm (d, 2H, J= 8 Hz). ^{13}C-NMR: 15.8 (*C*H$_3$), 20.6 (*C*H$_3$), 33.7 (*C*H$_2$), 34.8 (*C*H), 126.7, 128.7, 134.3 and 143.4 (Ph) ppm. IR= 1322, 1158 cm^{-1} (O=S=O). MS: 211 (M$^+$).



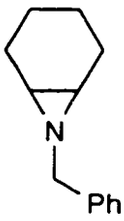
Methyl 1-(1,1-dimethylethyl)aziridine-2-carboxylic acid (48)[40]: ^{1}H-NMR (200 MHz) δ= 0.96 ppm (s, 9H, (C(CH_3)$_3$), 1.78 ppm (dd, 1H, J=) and 1.92 ppm (dd, 1H, J=) (CH_2), 2.22 ppm (dd, 1H, J= CHCO$_2$Me) 3.68 ppm (s, 3H, OCH_3). ^{13}C-NMR: 26.2 (C(*C*H$_3$)$_3$), 28.0 and 30.9 (*C*H$_2$*C*H), 52.2 (O*C*H$_3$), 53.8 (*C*N), 172.2 (*C*=O) ppm. IR (neat): 1745 (C=O) cm^{-1} MS: 157 (M$^+$).



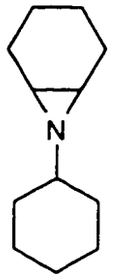
***cis*-Methyl 1-*n*-butyl-3-methylaziridine-2-carboxylic acid (51)**[41]: ^{1}H-NMR (200 MHz) δ= 0.83 ppm (t, 3H, J= 7.2 Hz, CH_2CH_3), 1.12 ppm (d, 3H, J= 5.6 Hz, $CHCH_3$), 1.25 ppm (m, 2H) and 1.45 ppm (m, 2H) $(CH_2)_2$, 1.72 ppm (m, 1H, $CHCH_3$) 1.97 ppm (d, 1H, J= 6.8 Hz, $CHCO_2Me$), 2.25 ppm (m, 2H, CH_2N), 3.65 ppm (s, 3H, OCH_3). ^{13}C-NMR: 13.8 (CH_3), 14.5 (CH_3), 20.9 (CH_2), 32.0 (CH_2), 42.3 and 43.1 (*C*HCH), 52.4 (OCH_3), 61.1 (CH_2N), 171.0 (*C*=O) ppm. IR (neat): 1748 (C=O) cm^{-1} MS: 171 (M^+).



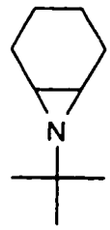
7-(2-Phenylethyl)-7-azabicyclo[4.1.0]heptane (56a)[46]: ^{1}H-NMR (200 MHz) δ= 1.26 ppm (m, 4H) and 1.73 ppm (m, 4H) $(CH_2)_4$, 1.42 ppm (m, 2H, 2*CH*), 2.46 ppm (t, 2H, J= 7.8 Hz, CH_2N), 2.86 ppm (t, 2H, J= 7.8 Hz, CH_2Ph), 7.24 ppm (m, 5H, Ph). ^{13}C-NMR: 20.6 ($2CH_2$), 24.5 ($2CH_2$), 36.5 (CH_2Ph), 38.3 (2*C*H), 63.2 (CH_2N), 125.9, 128.3, 128.8 and 140.4 (Ph) ppm. MS: 201 (M^+).



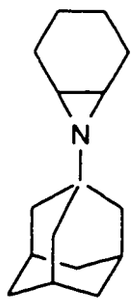
7-Phenylmethyl-7-azabicyclo[4.1.0]heptane (56b)[47]: ^{1}H-NMR (200 MHz) δ= 1.31 ppm (m, 4H), 1.83 ppm (m, 4H) (CH_2)$_4$, 1.63 ppm (m, 2H, 2C*H*), 3.48 ppm (s, 2H, CH_2Ph), 7.31 ppm (m, 5H, Ph). ^{13}C-NMR: 20.6 (2CH_2), 24.5 (2CH_2), 38.5 (2*C*H), 64.3 (*C*H$_2$Ph), 126.5, 127.4, 128.2 and 140.0 (Ph) ppm. MS: 187 (M$^+$).



7-cyclohexyl-7-azabicyclo[4.1.0]heptane (56c)[48]: ^{1}H-NMR (200 MHz) δ= 1.25 ppm (m, 13H) and 1.72 ppm (m, 8H) (9CH_2 and 3C*H*). ^{13}C-NMR: 20.6 (2CH_2), 24.8 (2CH_2), 25.1 (2CH_2), 26.1 (CH_2), 32.3 (2CH_2), 36.9 (2*C*H), 69.6 (*C*HN) ppm. MS: 179 (M$^+$).



7-(1,1-Dimethylethyl)-7-azabicyclo[4.1.0]heptane (56d): ^{1}H-NMR (200 MHz) δ= 0.91 ppm (s, 9H, C(C*H*$_3$)$_3$), 1.18 ppm (m, 2H), 1.35 ppm (m, 2H) and 1.65 ppm (m, 6H) ((C*H*$_2$)$_4$ and (C*H*)$_2$). ^{13}C-NMR: 20.6 (2*C*H$_2$), 25.0 (2*C*H$_2$), 26.6 (C(*C*H$_3$)$_3$), 30.1 (2*C*H), 52.8 (*C*(CH$_3$)$_3$) ppm. MS: 153 (M^+). HRMS calc. for $C_{10}H_{19}N$: 153.1517. Found: 153.1516.



7-(1-Adamantyl)-7-azabicyclo[4.1.0]heptane (56e): ^{1}H-NMR (200 MHz) δ= 1.13 ppm (m, 2H), 1.36 ppm (m, 2H), 1.48 ppm (m, 6H), 1.62 ppm (m, 10H), 1.87 ppm (m, 2H) and 2.02 ppm (m, 3H) (adamantyl, (C*H*$_2$)$_4$ and (C*H*)$_2$). ^{13}C-NMR: 20.6 (2*C*H$_2$), 25.3 (2*C*H$_2$), 28.0 (2*C*H), 29.6 (3*C*H), 36.9 (3*C*H$_2$), 40.4 (3*C*H$_2$), 52.4 (*C*N) ppm. MS: 231 (M^+). Anal. Calc. for $C_{16}H_{25}N$: C, 83.06; H, 10.89; N, 6.05. Found: C, 83.45; H, 10.61; N, 6.00.

2.4.4 Carbonylation reactions

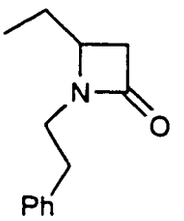
2.4.4.1 Carbonylation of monocyclic aziridines: The following is a typical procedure: 0.6 mmol of aziridine **27a**, 10 ml of dry and O_2 free DME, and 0.05 mmol of $Co_2(CO)_8$ (17.4 mg) were placed in a stainless steel autoclave equipped with a stirring bar. The autoclave was purged three times with carbon monoxide and then was charged with 500 psi of carbon monoxide. The reaction was placed in an oil bath at 100°C and stirred overnight. The autoclave was opened and left in contact with air for a few hours to induce decomposition of the catalyst. Addition of a small amount of ether accelerates the process. A precipitate was formed, the mixture was filtered through a small column packed with silica gel, using ether as the eluant, to give the β-lactam in high purity. For analytically pure β-lactam, the product was further purified by preparative TLC, using hexane/ethyl acetate 65/35 as the developer.

2.4.4.2 Carbonylation of bicyclic aziridines 57a-57e: 0.6 mmol of aziridine, 6 ml of dry and O_2 free THF, and 0.05 mmol of $Co_2(CO)_8$ (17.4 mg) were placed in a stainless steel autoclave equipped with a stirring bar. The autoclave was purged three times with carbon monoxide and then was charged with 500 psi of carbon monoxide. The reaction was placed in an oil bath at 100-105 °C. Conversion of **57a** and **57b** was complete after 60 h. In the case of **57c-57e**, 40 h was sufficient for complete reaction. Workup was similar to that described for monocyclic aziridines.

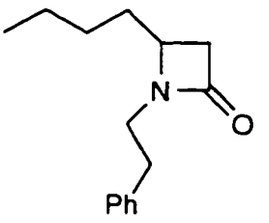
2.4.4.3 Carbonylation of aziridine 27a catalyzed by $Co(CO)_4Na$: It was carried out by mixing 0.6 mmol of the aziridine, 0.72 ml of the 0.084 M solution of $Co(CO)_4Na$ in THF, and 9 ml of DME. The reaction was pressurized with carbon monoxide to 500 psi and heated to 100°C for 60 h. Workup was carried out as usual giving 92% of **28a**.

2.4.4.4 Carbonylation of aziridine 27a using Lewis acids as co-catalysts: The same procedure was used as Section 2.4.3.1, but adding 8 mol % $BF_3.Et_2O$, Al_3Cl or $ZnCl_2$. Workup was carried out as usual.

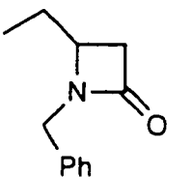
2.4.4.5 Carbonylation of aziridine 27a using *p*-TsOH as co-catalyst: The same procedure was used as Section 2.4.3.1, but adding 16 mol % *p*-TsOH. Workup was carried out as usual.



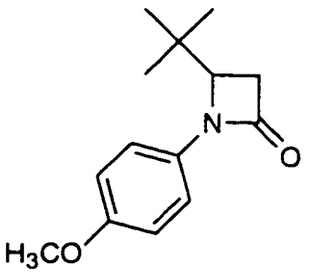
4-Ethyl-1-(2-phenylethyl)-2-azetidinone (28a): ^{1}H-NMR (300 MHz) δ= 0.84 ppm (t, 3H, J= 7.5 Hz, C*H*$_3$), 1.30 ppm (m, 1H) and 1.68 ppm (m, 1H) (C*H*$_2$CH$_3$), 2.42 ppm (dd, 1H, J= 2.0 and 14.4 Hz) and 2.84 ppm (m, 3H) (C*H*$_2$CO and C*H*$_2$Ph), 3.18 ppm (m, 1H) and 3.58 ppm (m, 1H) (C*H*$_2$N), 3.29 ppm (m, 1H, C*H*N), 7.21 ppm (m, 5H, Ph). ^{13}C-NMR: 9.25 (*C*H$_3$), 25.5 (*C*H$_2$CH$_3$), 34.5 (*C*H$_2$Ph), 41.4 and 41.9 (*C*H$_2$N and *C*H$_2$CO), 52.9 (*C*HN), 126.5, 128.5 and 138.6 (Ph), 167.0 (C=O) ppm. IR (neat): 1743 cm^{-1} (*C*=O). MS: 203 (M^+). Anal. Calc. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.84; H, 8.25; N, 7.01.



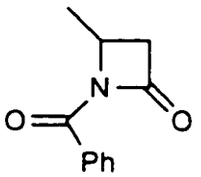
4-Butyl-1-(2-phenylethyl)-2-azetidinone (28b): ^{1}H-NMR (200 MHz) δ= 0.90 ppm (t, 3H, J= 6.8 Hz, C*H*$_3$), 1.28 ppm (m, 5H) and 1.70 ppm (m, 1H) (C*H*$_2$)$_3$, 2.47 ppm (dd, 1H, J= 2.2 and 14.3 Hz) and 2.92 ppm (m, 3H) (C*H*$_2$CO and C*H*$_2$Ph), 3.25 ppm (m, 1H) and 3.62 ppm (m, 1H) (C*H*$_2$N), 3.38 ppm (m, 1H, C*H*N), 7.28 ppm (m, 5H, Ph). ^{13}C-NMR: 14.6 (*C*H$_3$), 23.2 (*C*H$_2$), 28.2 (*C*H$_2$), 33.1 (*C*H$_2$), 35.3 (*C*H$_2$Ph), 42.6 and 42.7 (*C*H$_2$N and *C*H$_2$CO), 52.5 (*C*HN), 127.2, 129.2 and 139.3 (Ph), 167.7 (*C*=O) ppm. IR (neat): 1743 cm^{-1} (C=O). MS: 231 (M$^+$). Anal. Calc. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.69; H, 9.39; N, 5.98.



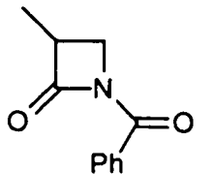
4-Ethyl-1-phenylmethyl-2-azetidinone (28c)[49]: ^{1}H-NMR (200 MHz) δ= 0.82 ppm (t, 3H, J= 7.5 Hz, C*H*$_3$), 1.40 ppm (m, 1H) and 1.73 ppm (m, 1H) (C*H*$_2$CH$_3$), 2.55 ppm (dd, 1H, J= 14.5 and 2 Hz) and 2.98 ppm (dd, 1H, J= 14.5 and 5 Hz) (C*H*$_2$CO), 3.39 ppm (m, 1H, C*H*N), 4.10 ppm (d, 1H, J= 14.5 Hz) and 4.60 ppm (d, 1H, J= 14.5 Hz) (C*H*$_2$Ph), 7.30 ppm (m, 5H, Ph). ^{13}C-NMR: 9.2 (*C*H$_3$), 25.6 (*C*H$_2$), 41.7 (*C*H$_2$CO), 44.6 (*C*H$_2$N), 52.5 (*C*HN), 127.6, 128.1, 128.7 and 136.1 (Ph), 167.2 (*C*=O) ppm. IR (neat): 1743 cm^{-1} (C=O). MS: 189 (M$^+$).



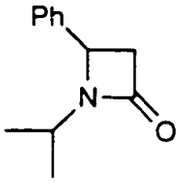
4-(1,1-Dimethylethyl)-1-(4-methoxyphenyl)-2-azetidinone (28d): White solid, mp: 89-90 °C. ^{1}H-NMR (200 MHz) δ= 0.93 ppm (s, 9H, C(C*H*$_3$)$_3$), 2.74 ppm (dd, 1H, J= 15.2 and 2.5 Hz) and 2.95 ppm (dd, 1H, J= 15.2 and 5.5 Hz) (C*H*$_2$), 3.76 ppm (s, 3H, OC*H*$_3$), 3.97 ppm (dd, 1H, J= 5.5 and 2.5 Hz, C*H*), 6.85 ppm (d, 2H, J= 9 Hz) and 7.23 ppm (d, 2H, J= 9 Hz) (Ph). ^{13}C-NMR: 26.7 (C(*C*H$_3$)$_3$), 34.6 (*C*(CH$_3$)$_3$), 38.7 (*C*H$_2$), 56.0 (O*C*H$_3$), 61.4 (*C*H), 114.7, 122.8, 131.6 and 157.3 (Ph), 166.3 (*C*=O) ppm. IR (KBr): 1730 cm^{-1} (C=O). MS: 233 (M$^+$). Anal. Calc. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.16; H, 8.43; N, 5.73.



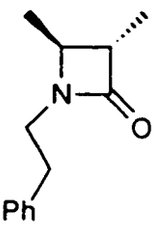
1-Benzoyl-4-methyl-2-azetidinone (28e)[50]: ^{1}H-NMR (200 MHz) δ= 1.31 ppm (d, 3H, J= 6.8 Hz, C*H*$_3$), 2.31 ppm (dd, 1H, J= 16.1 and 9.5 Hz) and 2.68 ppm (dd, 1H, J= 16.1 and 5.2 Hz) (C*H*$_2$), 3.91 ppm (m, 1H, C*H*), 7.38 ppm (m, 3H) and 7.94 ppm (m, 2H) (Ph). ^{13}C-NMR: 22.1 (*C*H$_3$), 35.8 (*C*H$_2$), 49.6 (*C*H), 128.2, 129.0, 131.0 and 132.3 (Ph), 153.0 (Ph*C*O), 166.7 (CH$_2$*C*O) ppm. IR (neat): 1671 (PhCO) and 1786 (CH$_2$CO) cm^{-1} . MS: 189 (M$^+$).



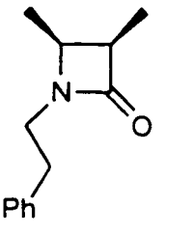
1-Benzoyl-3-methyl-2-azetidinone (28e')[50]: ^{1}H-NMR (200 MHz) δ= 1.24 ppm (d, 3H, J= 6.9 Hz, C*H*$_3$), 2.64 ppm (m, 1H, C*H*), 3.37 ppm (dd, 1H, J= 16.3 and 12.3 Hz) and 3.82 ppm (dd, 1H, J= 16.3 and 7.0 Hz) (C*H*$_2$), 7.38 ppm (m, 3H) and 7.94 ppm (m, 2H) (Ph). ^{13}C-NMR: 13.0 (*C*H$_3$), 33.9 (*C*H), 50.1 (*C*H$_2$), 128.1, 129.0, 131.0 and 132.3 (Ph), 154.5 (Ph*C*O), 170.1 (CH$_2$*C*O) ppm. IR (neat): 1671 (PhCO) and 1786 (CH$_2$CO) cm^{-1} (C=O). MS: 189 (M$^+$).



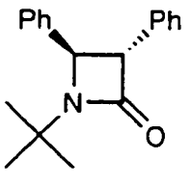
1-(1-Methylethyl)-3-phenyl-2-azetidinone (28f)[51]: ^{1}H-NMR (200 MHz) δ= 1.13 ppm (d, 3H, J= 6.8 Hz, C*H*$_3$), 1.15 ppm (d, 3H, J= 6.8 Hz, C*H*$_3$), 3.12 ppm (dd, 1H, J= 5.3 and 2.5 Hz) and 3.54 ppm (t, 1H, J= 5.5 Hz) (C*H*$_2$), 3.93 ppm (sept, 1H, J= 6.6 Hz, C*H*(CH$_3$)$_2$), 4.15 ppm (dd, 1H, J= 5.5 and 2.5 Hz, C*H*Ph), 7.2 ppm (m, 5H, Ph). ^{13}C-NMR: 20.9 (*C*H$_3$), 21.2 (*C*H$_3$), 43.9 (*C*H(CH$_3$)$_2$), 44.8 (*C*H$_2$N), 53.5 (*C*HPh), 127.9, 128.0, 129.4 and 136.6 (Ph), 168.1 (*C*=O) ppm. IR (neat): 1739 cm^{-1} (C=O). MS: 104 (M$^+$-65, PhCH=CH$_2$).



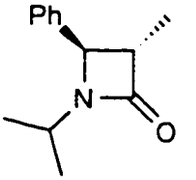
***trans*-3,4-Dimethyl-1-(2-phenylethyl)-2-azetidinone (30a)**: ^{1}H-NMR (200 MHz) δ= 1.18 ppm (d, 3H, J= 6.1 Hz, C*H*$_3$CHN), 1.20 ppm (d, 3H, J= 7.4 Hz, C*H*$_3$CHCO), 2.62 ppm (dq, 1H, J= 7.4 and 2.0 Hz, C*H*CO), 2.88 ppm (m, 2H, C*H*$_2$Ph), 3.06 ppm (dq, 1H, J= 6.1 and 2.0 Hz, C*H*N), 3.20 ppm (m, 1H) and 3.64 ppm (m, 1H) (C*H*$_2$N), 7.25 ppm (m, 5H, Ph). ^{13}C-NMR: 12.8 (*C*H$_3$), 17.5 (*C*H$_3$), 34.6 (*C*H$_2$Ph), 41.2 (*C*H$_2$N), 51.6 (*C*H$_2$CO), 56.0 (*C*HN), 126.6, 128.6, 138.7 and 138.7 (Ph), 170.4 (*C*=O) ppm. IR (neat): 1738 cm^{-1} (C=O). MS: 203 (M$^+$). HRMS calcd for $C_{13}H_{17}NO$: 203.1310. Found: 203.1325.



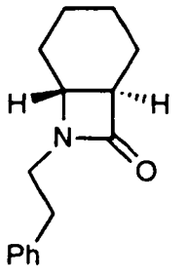
***cis*-3,4-Dimethyl-1-(2-phenylethyl)-2-azetidinone (30b)**: ^{1}H-NMR (500 MHz) δ= 1.03 ppm (d, 3H, J= 6.4 Hz, C*H*$_3$CHN), 1.09 ppm (d, 3H, J= 7.6 Hz, C*H*$_3$CHCO), 2.85 ppm (t, 2H, J= 7.4 Hz, C*H*$_2$Ph), 3.13 ppm (dq, 1H, J= 7.6 and 5.3 Hz, C*H*CO), 3.20 ppm (m, 1H) and 3.54 ppm (m, 2H) (C*H*NC*H*$_2$), 7.23 ppm (m, 5H, Ph). ^{13}C-NMR: 9.3 (*C*H$_3$), 14.0 (*C*H$_3$), 35.2 (*C*H$_2$Ph), 41.9 (*C*H$_2$N), 47.2 (*C*H$_2$CO), 51.7 (*C*HN), 127.1, 129.1, 129.2 and 139.4 (Ph), 171.6 (*C*=O) ppm. IR (neat): 1739 cm^{-1} (C=O). MS: 203 (M$^+$). Anal. Calc. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.44; H, 8.27; N, 7.11.



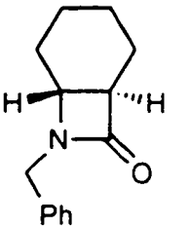
***trans*-1-(1,1-Dimethylethyl)-3,4-diphenyl-2-azetidinone (30c)**[52]: white solid, mp = 91-92 °C. ^{1}H-NMR (200 MHz) δ = 1.33 ppm (s, 9H, C(C*H*$_3$)$_3$), 3.98 ppm (d, 1H, J= 2.15 Hz, C*H*CO), 4.48 ppm (d, 1H, J= 2.15 Hz, C*H*N), 7.35 ppm (m, 10H, 2Ph). ^{13}C-NMR: 28.2 (C(*C*H$_3$)$_3$), 54.7 (*C*(CH$_3$)$_3$), 63.1 and 63.6 (N*C*H*C*HCO), 126.3, 127.2, 127.4, 128.3, 128.7, 128.8, 135.5 and 140.3 (2Ph), 168.4 (*C*=O) ppm. IR (KBr): 1745 cm^{-1} (C=O). MS (EI): 180 (M^{+} – 99, PhCH=CHPh). MS (CI): 280 (M+1).



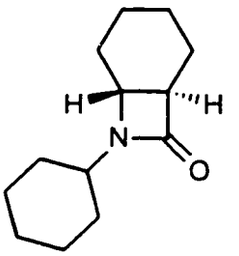
***trans*-4-Methyl-1-(1-methylethyl)-3-phenyl-2-azetidinone (30d)**: ^{1}H-NMR (200 MHz) δ= 1.18 ppm (d, 3H, J= 6.8 Hz) and 1.22 ppm (d, 3H, J= 6.8 Hz) (CH(C*H*$_3$)$_2$), 1.39 ppm (d, 3H, J= 6 Hz, C*H*$_3$CHN), 3.58 ppm (dd, 1H, J= 6 and 2.1 Hz, CH$_3$C*H*N), 3.66 ppm (d, 1H, J= 2.2 Hz, C*H*Ph), 3.85 ppm (sept, 1H, J= 6.8 Hz, C*H*(CH$_3$)$_2$), 7.2 ppm (m, 5H, Ph). ^{13}C-NMR: 20.8 (*C*H$_3$), 21.1 (*C*H$_3$), 22.5 (*C*H$_3$), 44.5 (*C*H(CH$_3$)$_2$), 56.5 (*C*HPh), 61.8 (*C*HN), 127.9, 129.4 and 136.3 (Ph) 167.6 (*C*=O) ppm. IR (neat): 1743 cm^{-1} (C=O). MS (EI): 118 (M^{+}-85, PhCH=CH$_2$CH$_3$). MS (CI): 204 (M+1). Anal. Calc. for C$_{13}$H$_{17}$NO: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.69; H, 8.52; N, 6.79.



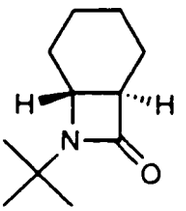
***trans*-7-(2-Phenylethyl)-7-azabicyclo[4.2.0]octan-8-one (57a):** White solid, mp: 69-70 °C. ^{1}H-NMR (500 MHz) δ= 1.33 ppm (m, 3H) and 1.78 ppm (m, 5H) (C*H*$_2$)$_4$, 2.55 ppm (m, 1H, C*H*CO), 2.80 ppm (m, 2H, C*H*$_2$Ph), 2.86 ppm (m, 1H, C*H*N), 3.19 ppm (m, 1H) and 3.60 ppm (m, 1H) (C*H*$_2$N), 7.23 ppm (m, 5H, Ph). ^{13}C-NMR: 25.5 (*C*H$_2$), 26.0 (*C*H$_2$), 26.8 (*C*H$_2$), 32.1 (*C*H$_2$), 35.9 (*C*H$_2$Ph), 44.7 (*C*H$_2$N), 57.8 (*C*HCO), 61.0 (*C*HN), 126.8, 128.5, 128.8 and 139.7 (Ph), 174.6 (*C*=O) ppm. IR (KBr): 1742 cm^{-1} (C=O). MS: 229 (M$^+$). HRMS calc. for $C_{15}H_{19}NO$: 229.1467. Found: 229.1460.



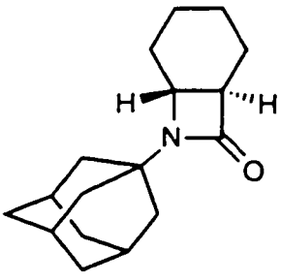
***trans*-7-Phenylmethyl-7-azabicyclo[4.2.0]octan-8-one (57b):** ^{1}H-NMR (200 MHz) δ= 1.12–1.88 ppm (m, 8H, (C*H*$_2$)$_4$), 2.58 ppm (m, 1H, C*H*CO), 2.78 ppm (m, 1H, C*H*N), 4.14 ppm (d, 1H, J= 14.5 Hz) and 4.31 ppm (d, 1H, J= 14.5 Hz) (C*H*$_2$Ph), 7.20 ppm (m, 5H, Ph). ^{13}C-NMR: 24.7 (*C*H$_2$), 25.5 (*C*H$_2$), 26.3 (*C*H$_2$), 31.3 (*C*H$_2$), 46.9 (*C*H$_2$N), 57.3 (*C*HCO), 59.4 (*C*HN), 127.4, 128.3, 128.6 and 136.7 (Ph), 174.0 (*C*=O) ppm. IR (neat): 1752 cm^{-1} (C=O). MS: 215 (M$^+$). HRMS calc. for $C_{14}H_{17}NO$: 215.1310. Found: 215.1330.



***trans*-7-cyclohexyl-7-azabicyclo[4.2.0]octan-8-one (57c):** White solid, mp: 43.5-44.5 °C. ^{1}H-NMR (200 MHz) δ= 1.0–2.1 ppm (m, 18H, (CH_2)$_5$ and (CH_2)$_4$), 2.57 ppm (m, 1H, C*H*CO), 3.07 ppm (m, 1H, C*H*N), 3.45 ppm (m, 1H, CH_{cy}).^{13}C-NMR: 24.8 (CH_2), 24.9 (CH_2), 25.0 (CH_2), 25.3 (CH_2), 25.4 (CH_2), 26.4 (CH_2), 30.7 (CH_2), 32.1 (CH_2), 32.5 (CH_2), 51.9 (CH_{cy}), 56.4 and 57.1 (*C*HCO and *C*HN), 173.0 (*C*=O) ppm. IR (KBr): 1738 cm^{-1} (C=O). MS: 207 (M^+). HRMS calc. for $C_{13}H_{21}NO$: 207.1623. Found: 207.1629.



***trans*-7-(1,1-Dimethylethyl)-7-azabicyclo[4.2.0]octan-8-one (57d):** White solid, mp: 57-58 °C. ^{1}H-NMR (200 MHz) δ= 1.29 ppm (s, 9H, C(CH_3)$_3$), 1.30–2.15 ppm (m, 8H, (CH_2)$_4$), 2.50 ppm (m, 1H, C*H*CO), 3.01 ppm (m, 1H, C*H*N). ^{13}C-NMR: 25.0 (CH_2), 25.2 (CH_2), 26.5 (CH_2), 27.7 (C(CH_3)$_3$), 33.2 (CH_2), 53.8 (*C*(CH_3)$_3$), 55.9 and 56.7 (*C*HCO and *C*HN), 173.0 (*C*=O) ppm. IR (KBr): 1735 cm^{-1} (C=O). MS: 181 (M^+). HRMS calc. for $C_{11}H_{19}NO$: 181.1467. Found: 181.1464.



***trans*-7-(1-Adamantyl)-7-azabicyclo[4.2.0]octan-8-one (57e):** White solid, mp: 122 °C (dec). ^{1}H-NMR (200 MHz) δ= 1.40–2.40 ppm (m, 23H, 1-adam. and C*H*$_2$)$_4$), 2.48 ppm (m, 1H, C*H*CO), 3.07 ppm (m, 1H, C*H*N). ^{13}C-NMR: 25.0 (*C*H$_2$), 25.3 (*C*H$_2$), 26.5 (*C*H$_2$), 29.1 (3*C*H), 33.5 (*C*H$_2$), 36.3 (3*C*H$_2$), 40.8 (3*C*H$_2$), 54.7, (*C*N) 55.8 (*C*HCO and *C*HN), 172.8 (*C*=O) ppm. IR (KBr): 1732 cm^{-1} (C=O). MS: 259 (M$^+$). HRMS calc. for $C_{17}H_{25}NO$: 259.1947. Found: 259.1936.

2.4.5 Single crystal diffraction study of 23b

Crystals of **23b** were obtained by layering a concentrated solution of **23b** in ether with hexane. One of the crystals having approximate dimensions of 0.2 x 0.05 x 0.1 mm was mounted on a glass capillary. All the measurements were made on a Rigaku diffractometer with Mo Kα radiation. Cell constants, and an orientation matrix for data collection, were obtained from least-squares refinement using the setting angles of 25 reflections in the range 40<θ<50 corresponded to a monoclinic cell with dimensions a= 13.904(6) Å, b= 6.385(3) Å, c= 15.793(9) Å, β= 91.43(6). For Z= 4 and FW= 259.39, the calculated density is 1.229 g/cm^3. Based on the systematic absences, the space group was determined to be P 21/n. The data was collected at a temperature of -145 °C using the ω-2θ scan technique to a maximun 2θ value of 49.9 degrees.

A total of 2595 reflections was collected. The unique set contains only 2486 reflections. The standards were measured after every 150 reflections. No crystal decay was noticed. The

data were corrected for Lorentz and polarisation effects[53]. No absorption correction was made.

The structure was solved by direct methods. All the atoms were refined anisotropically except for hydrogen atoms. The hydrogen atoms were found by difference Fourier map. The final cycle of full matrix least-squares refinement was based on 1825 observed reflections ($I>2.5\sigma(I)$) and 272 variable parameters. Weights based on counting statistics were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.220 and -0.220 e/a^3, respectively.

All the calculations were performed using the NRCVAX crystallographic software package[54].

EXPERIMENTAL DETAILS

Empirical formula	O1N1C17H25
Formula weight	259.39
Crystal shape	needle
Crystal dimensions (mm)	.2,.05,.1
Crystal system	monoclinic
No. Reflection used for unit cell dimension (2theta range)	25 40-50
Lattice parameters	a=13.904(6) b=6.385(3) c=15.793(9)
Space group	P 21/n
Z value	4
Dcalc (g.cm-3)	1.229
F(000)	568.18
mu (mm-1)	.07
No of reflection measured	2595
No of reflection unique	2486
No of reflection observed	1825
No of atoms	44
No of variables	272
Rf (sign refl)	.051
Rw (sign refl)	.051
Rf (all refl)	.077
Rw (all refl)	.068
Goodness of fit	1.98
Last difference fourier map	
max peak	.220
min peak	-.220

Table of Atomic Parameters x,y,z and Biso.
E.S.Ds. refer to the last digit printed.

	x	y	z	Biso
O1	-0.19148(15)	0.7430(3)	0.17551(13)	3.24(9)
N1	-0.13587(16)	1.0617(4)	0.11519(14)	2.22(9)
C1	-0.20141(21)	0.9061(4)	0.13660(17)	2.49(11)
C2	-0.28292(19)	1.0261(5)	0.09133(17)	2.31(11)
C3	-0.21544(19)	1.2137(4)	0.09793(16)	2.20(10)
C4	-0.22984(21)	1.3590(5)	0.02368(18)	2.69(11)
C5	-0.33541(21)	1.4325(5)	0.03235(19)	2.98(12)
C6	-0.41003(21)	1.2543(6)	0.04229(19)	3.25(13)
C7	-0.38509(21)	1.0884(5)	0.11051(18)	2.84(12)
C8	-0.04258(19)	1.1032(4)	0.15572(16)	2.02(10)
C9	-0.05151(20)	1.1332(4)	0.25159(17)	2.26(11)
C10	0.04678(20)	1.1779(5)	0.29209(17)	2.46(11)
C11	0.11587(21)	0.9956(5)	0.27628(19)	2.73(12)
C12	0.12497(20)	0.9646(5)	0.18017(19)	2.66(12)
C13	0.02634(20)	0.9201(4)	0.13949(17)	2.40(11)
C14	-0.00076(20)	1.3049(4)	0.11794(17)	2.34(11)
C15	0.09818(20)	1.3486(5)	0.15794(18)	2.54(11)
C16	0.16655(20)	1.1647(5)	0.14142(19)	2.91(12)
C17	0.08876(20)	1.3784(4)	0.25404(18)	2.55(12)
H2	-0.2893 (19)	0.974 (4)	0.0360 (17)	2.6 (6)
H3	-0.2287 (19)	1.296 (4)	0.1482 (16)	2.5 (6)
H4A	-0.2227 (20)	1.279 (5)	-0.0333 (18)	3.5 (7)
H4B	-0.1840 (20)	1.478 (5)	0.0272 (17)	3.0 (6)
H5A	-0.3337 (20)	1.533 (5)	0.0824 (18)	3.3 (7)
H5B	-0.3570 (22)	1.514 (5)	-0.0180 (19)	4.1 (8)
H6A	-0.4221 (21)	1.179 (5)	-0.0117 (19)	4.1 (7)
H6B	-0.4730 (22)	1.325 (5)	0.0516 (19)	4.4 (8)
H7A	-0.4335 (19)	0.964 (5)	0.1036 (17)	2.9 (6)
H7B	-0.3862 (21)	1.151 (5)	0.1683 (19)	3.9 (7)
H9A	-0.0945 (17)	1.253 (4)	0.2583 (15)	1.8 (5)
H9B	-0.0782 (19)	1.001 (5)	0.2722 (16)	2.6 (6)
H10	0.0405 (19)	1.194 (5)	0.3512 (17)	2.8 (6)
H11A	0.1852 (18)	1.021 (4)	0.3091 (16)	2.2 (6)
H11B	0.0874 (20)	0.867 (5)	0.3018 (17)	2.9 (6)
H12	0.1752 (18)	0.843 (4)	0.1727 (16)	2.3 (6)
H13A	-0.0003 (18)	0.790 (4)	0.1628 (16)	2.2 (6)
H13B	0.0329 (19)	0.900 (4)	0.0799 (16)	2.6 (6)
H14A	-0.0483 (17)	1.427 (4)	0.1285 (14)	1.5 (5)
H14B	0.0003 (19)	1.291 (5)	0.0558 (17)	2.9 (6)
H15	0.1261 (18)	1.478 (4)	0.1358 (16)	2.0 (6)
H16A	0.2323 (17)	1.198 (4)	0.1707 (15)	1.6 (5)
H16B	0.1727 (20)	1.141 (5)	0.0800 (18)	3.6 (7)
H17A	0.0422 (17)	1.498 (4)	0.2640 (15)	1.5 (5)
H17B	0.1596 (18)	1.406 (4)	0.2860 (16)	2.4 (6)

Biso is the Mean of the Principal Axes of the Thermal Ellipsoid

Table of u(i,j) or U values *100.
E.S.Ds. refer to the last digit printed

	u11(U)	u22	u33	u12	u13	u23
O1	4.26(12)	2.86(11)	5.18(13)	-0.63(10)	-0.19(10)	0.69(10)
N1	2.95(12)	2.45(12)	3.03(12)	-0.04(10)	0.39(10)	-0.05(10)
C1	3.84(16)	2.63(14)	3.00(14)	-0.28(13)	0.55(12)	-0.36(13)
C2	2.92(15)	3.18(15)	2.69(14)	-0.59(13)	0.42(12)	-0.21(12)
C3	3.11(14)	2.68(15)	2.61(13)	-0.10(13)	0.71(11)	0.02(12)
C4	3.58(16)	3.58(17)	3.06(15)	-0.31(14)	0.59(12)	0.42(13)
C5	3.64(16)	4.06(18)	3.64(16)	0.41(15)	0.21(13)	0.93(15)
C6	3.27(15)	5.11(20)	3.98(17)	0.23(15)	-0.02(13)	0.83(16)
C7	3.10(16)	4.16(18)	3.55(16)	-0.47(14)	0.47(12)	0.49(14)
C8	2.73(14)	2.28(14)	2.67(13)	0.09(12)	0.55(11)	-0.28(11)
C9	3.16(15)	2.70(14)	2.77(14)	0.17(12)	1.03(11)	-0.09(12)
C10	3.43(15)	3.29(15)	2.64(14)	0.21(13)	0.47(11)	-0.56(13)
C11	3.69(16)	2.92(16)	3.73(16)	0.11(14)	-0.22(13)	-0.04(14)
C12	3.12(15)	2.77(15)	4.25(17)	0.55(13)	0.68(13)	-0.96(13)
C13	3.60(16)	2.53(14)	3.00(14)	0.09(13)	0.57(12)	-0.55(12)
C14	3.73(15)	2.49(14)	2.72(14)	-0.11(13)	0.73(12)	-0.09(12)
C15	3.43(16)	2.63(15)	3.66(16)	-0.62(13)	1.14(13)	-0.07(13)
C16	2.81(15)	4.11(17)	4.19(17)	-0.28(14)	1.11(13)	-1.00(15)
C17	3.24(15)	2.53(15)	3.94(16)	0.14(13)	0.43(13)	-0.91(13)

Anisotropic Temperature Factors are of the form
Temp=-2*Pi*Pi*(h*h*u11*astar*astar+---+2*h*k*u12*astar*bstar+---)

Table of Atomic Bond Distances in Angstroms

O1-C1	1.215(4)	C9-H9A	0.98(3)
N1-C1	1.395(4)	C9-H9B	0.98(3)
N1-C3	1.492(4)	C10-C11	1.534(4)
N1-C8	1.456(3)	C10-C17	1.536(4)
C1-C2	1.531(4)	C10-H10	0.94(3)
C2-C3	1.524(4)	C11-C12	1.539(4)
C2-C7	1.513(4)	C11-H11A	1.10(3)
C2-H2	0.94(3)	C11-H11B	1.00(3)
C3-C4	1.505(4)	C12-C13	1.526(4)
C3-H3	0.97(3)	C12-C16	1.536(4)
C4-C5	1.550(4)	C12-H12	1.05(3)
C4-H4A	1.04(3)	C13-H13A	0.98(3)
C4-H4B	0.99(3)	C13-H13B	0.96(3)
C5-C6	1.550(5)	C14-C15	1.525(4)
C5-H5A	1.02(3)	C14-H14A	1.040(25)
C5-H5B	0.99(3)	C14-H14B	0.99(3)
C6-C7	1.544(4)	C15-C16	1.537(4)
C6-H6A	0.99(3)	C15-C17	1.539(4)
C6-H6B	1.00(3)	C15-H15	0.98(3)
C7-H7A	1.05(3)	C16-H16A	1.036(24)
C7-H7B	1.00(3)	C16-H16B	0.99(3)
C8-C9	1.534(4)	C17-H17A	1.015(25)
C8-C13	1.537(4)	C17-H17B	1.11(3)
C8-C14	1.540(4)	H6A-H6B	1.55(4)
C9-C10	1.521(4)		

Table of Atomic Bond Angles in Degrees

C1-N1-C3	91.25(20)	C10-C9-H9B	111.4(15)
C1-N1-C8	127.09(23)	H9A-C9-H9B	113.6(21)
C3-N1-C8	127.59(22)	C9-C10-C11	110.44(23)
O1-C1-N1	131.8(3)	C9-C10-C17	109.75(23)
O1-C1-C2	137.6(3)	C9-C10-H10	109.3(16)
N1-C1-C2	90.62(21)	C11-C10-C17	108.86(22)
C1-C2-C3	85.08(20)	C11-C10-H10	108.4(17)
C1-C2-C7	136.57(24)	C17-C10-H10	110.0(18)
C1-C2-H2	107.9(17)	C10-C11-C12	108.98(23)
C3-C2-C7	111.05(24)	C10-C11-H11A	111.0(14)
C3-C2-H2	112.9(17)	C10-C11-H11B	107.5(16)
C7-C2-H2	102.3(16)	C12-C11-H11A	113.1(13)
N1-C3-C2	87.33(20)	C12-C11-H11B	109.6(16)
N1-C3-C4	128.84(22)	H11A-C11-H11B	106.5(21)
N1-C3-H3	110.9(16)	C11-C12-C13	110.11(23)
C2-C3-C4	111.21(23)	C11-C12-C16	109.09(23)
C2-C3-H3	110.6(16)	C11-C12-H12	106.1(14)
C4-C3-H3	106.1(16)	C13-C12-C16	109.28(24)
C3-C4-C5	103.04(22)	C13-C12-H12	114.1(14)
C3-C4-H4A	111.0(17)	C16-C12-H12	108.1(14)
C3-C4-H4B	110.9(16)	C8-C13-C12	110.22(22)
C5-C4-H4A	109.6(16)	C8-C13-H13A	109.7(15)
C5-C4-H4B	111.7(16)	C8-C13-H13B	109.9(17)
H4A-C4-H4B	110.4(23)	C12-C13-H13A	110.0(15)
C4-C5-C6	115.1(3)	C12-C13-H13B	109.4(16)
C4-C5-H5A	104.8(16)	H13A-C13-H13B	107.5(22)
C4-C5-H5B	110.9(18)	C8-C14-C15	109.75(22)
C6-C5-H5A	112.7(16)	C8-C14-H14A	108.6(13)
C6-C5-H5B	106.1(18)	C8-C14-H14B	109.0(17)
H5A-C5-H5B	106(3)	C15-C14-H14A	111.5(13)
C5-C6-C7	115.78(24)	C15-C14-H14B	113.1(16)
C5-C6-H6A	111.6(18)	H14A-C14-H14B	104.7(21)
C5-C6-H6B	106.0(19)	C14-C15-C16	110.21(23)
C7-C6-H6A	107.5(19)	C14-C15-C17	109.46(22)
C7-C6-H6B	112.8(18)	C14-C15-H15	111.6(15)
H6A-C6-H6B	102(3)	C16-C15-C17	109.28(24)
C2-C7-C6	103.67(22)	C16-C15-H15	109.2(15)
C2-C7-H7A	112.6(15)	C17-C15-H15	107.0(15)
C2-C7-H7B	109.0(17)	C12-C16-C15	109.11(22)
C6-C7-H7A	108.4(15)	C12-C16-H16A	109.3(14)
C6-C7-H7B	110.7(18)	C12-C16-H16B	108.0(18)
H7A-C7-H7B	112.2(23)	C15-C16-H16A	108.0(14)
N1-C8-C9	111.31(21)	C15-C16-H16B	110.6(18)
N1-C8-C13	109.89(22)	H16A-C16-H16B	111.8(21)
N1-C8-C14	108.84(22)	C10-C17-C15	108.99(22)
C9-C8-C13	109.01(22)	C10-C17-H17A	108.4(14)
C9-C8-C14	108.58(21)	C10-C17-H17B	107.1(14)
C13-C8-C14	109.18(21)	C15-C17-H17A	108.4(13)
C8-C9-C10	110.14(21)	C15-C17-H17B	111.8(13)
C8-C9-H9A	105.6(14)	H17A-C17-H17B	112.0(20)
C8-C9-H9B	105.0(15)	C6-H6A-H6B	39.0(16)

C10-C9-H9A	110.7(15)	C6-H6B-H6A	38.6(16)

Torsion angles

C3	N1	C1	O1	-162.1(3)	C3	N1	C1	C2	18.4(2)
C8	N1	C1	O1	-20.7(2)	C8	N1	C1	C2	159.8(3)
C1	N1	C3	C2	-18.5(2)	C1	N1	C3	C4	-133.8(3)
C1	N1	C3	H3	92.5(16)	C8	N1	C3	C2	-159.6(3)
C8	N1	C3	C4	85.1(2)	C8	N1	C3	H3	-48.6(16)
C1	N1	C8	C9	-53.8(2)	C1	N1	C8	C13	67.0(2)
C1	N1	C8	C14	-173.5(3)	C3	N1	C8	C9	74.2(2)
C3	N1	C8	C13	-164.9(3)	C3	N1	C8	C14	-45.4(2)
O1	C1	C2	C3	162.5(4)	O1	C1	C2	C7	46.8(2)
O1	C1	C2	H2	-85.0(17)	N1	C1	C2	C3	-18.1(1)
N1	C1	C2	C7	-133.8(3)	N1	C1	C2	H2	94.4(17)
C1	C2	C3	N1	16.9(1)	C1	C2	C3	C4	147.8(3)
C1	C2	C3	H3	-94.5(16)	C7	C2	C3	N1	155.3(3)
C7	C2	C3	C4	-73.8(2)	C7	C2	C3	H3	43.9(16)
H2	C2	C3	N1	-90.5(17)	H2	C2	C3	C4	40.4(16)
H2	C2	C3	H3	158.1(23)	C1	C2	C7	C6	166.1(3)
C1	C2	C7	H7A	-76.9(15)	C1	C2	C7	H7B	48.2(17)
C3	C2	C7	C6	60.3(2)	C3	C2	C7	H7A	177.2(15)
C3	C2	C7	H7B	-57.6(17)	H2	C2	C7	C6	-60.4(16)
H2	C2	C7	H7A	56.6(22)	H2	C2	C7	H7B	-178.3(24)
N1	C3	C4	C5	166.8(3)	N1	C3	C4	H4A	49.6(16)
N1	C3	C4	H4B	-73.5(16)	C2	C3	C4	C5	62.4(2)
C2	C3	C4	H4A	-54.8(16)	C2	C3	C4	H4B	-177.9(17)
H3	C3	C4	C5	-57.9(16)	H3	C3	C4	H4A	-175.1(23)
H3	C3	C4	H4B	61.8(22)	C3	C4	C5	C6	-51.4(2)
C3	C4	C5	H5A	73.0(16)	C3	C4	C5	H5B	-171.9(18)
H4A	C4	C5	C6	66.9(16)	H4A	C4	C5	H5A	-168.8(23)
H4A	C4	C5	H5B	-53.7(24)	H4B	C4	C5	C6	-170.5(17)
H4B	C4	C5	H5A	-46.1(23)	H4B	C4	C5	H5B	69.0(24)
C4	C5	C6	C7	49.7(2)	C4	C5	C6	H6A	-73.6(18)
C4	C5	C6	H6B	175.7(19)	H5A	C5	C6	C7	-70.4(16)
H5A	C5	C6	H6A	166.3(24)	H5A	C5	C6	H6B	55.6(24)
H5B	C5	C6	C7	172.8(18)	H5B	C5	C6	H6A	49.5(25)
H5B	C5	C6	H6B	-61.2(26)	C5	C6	C7	C2	-49.8(2)
C5	C6	C7	H7A	-169.7(16)	C5	C6	C7	H7B	66.8(17)
H6A	C6	C7	C2	75.6(18)	H6A	C6	C7	H7A	-44.3(23)
H6A	C6	C7	H7B	-167.7(25)	H6B	C6	C7	C2	-172.3(19)
H6B	C6	C7	H7A	67.9(24)	H6B	C6	C7	H7B	-55.6(25)
C5	C6	H6A	H6B	-113.0(22)	C7	C6	H6A	H6B	119.1(23)
H6B	C6	H6A	H6B	0.0(22)	C5	C6	H6B	H6A	117.0(23)
C7	C6	H6B	H6A	-115.2(23)	H6A	C6	H6B	H6A	0.0(22)
N1	C8	C9	C10	-179.6(3)	N1	C8	C9	H9A	-60.0(14)
N1	C8	C9	H9B	60.3(16)	C13	C8	C9	C10	59.0(2)
C13	C8	C9	H9A	178.6(15)	C13	C8	C9	H9B	-61.1(16)
C14	C8	C9	C10	-59.8(2)	C14	C8	C9	H9A	59.7(14)
C14	C8	C9	H9B	-179.9(16)	N1	C8	C13	C12	178.8(3)
N1	C8	C13	H13A	-59.9(15)	N1	C8	C13	H13B	58.1(16)
C9	C8	C13	C12	-59.0(2)	C9	C8	C13	H13A	62.3(15)
C9	C8	C13	H13B	-179.7(16)	C14	C8	C13	C12	59.5(2)

C14	C8	C13	H13A	-179.2(15)	C14	C8	C13	H13B	-61.2(16)
N1	C8	C14	C15	-178.6(3)	N1	C8	C14	H14A	59.3(13)
N1	C8	C14	H14B	-54.2(16)	C9	C8	C14	C15	60.1(2)
C9	C8	C14	H14A	-62.0(13)	C9	C8	C14	H14B	-175.5(16)
C13	C8	C14	C15	-58.6(2)	C13	C8	C14	H14A	179.3(14)
C13	C8	C14	H14B	65.8(16)	C8	C9	C10	C11	-59.8(2)
C8	C9	C10	C17	60.2(2)	C8	C9	C10	H10	-179.0(17)
H9A	C9	C10	C11	-176.3(15)	H9A	C9	C10	C17	-56.2(14)
H9A	C9	C10	H10	64.5(22)	H9B	C9	C10	C11	56.3(16)
H9B	C9	C10	C17	176.3(16)	H9B	C9	C10	H10	-62.9(23)
C9	C10	C11	C12	58.9(2)	C9	C10	C11	H11A	-175.8(14)
C9	C10	C11	H11B	-59.8(16)	C17	C10	C11	C12	-61.6(2)
C17	C10	C11	H11A	63.6(14)	C17	C10	C11	H11B	179.7(16)
H10	C10	C11	C12	178.7(17)	H10	C10	C11	H11A	-56.1(21)
H10	C10	C11	H11B	60.0(23)	C9	C10	C17	C15	-59.6(2)
C9	C10	C17	H17A	58.2(14)	C9	C10	C17	H17B	179.2(14)
C11	C10	C17	C15	61.4(2)	C11	C10	C17	H17A	179.2(14)
C11	C10	C17	H17B	-59.8(14)	H10	C10	C17	C15	-179.9(17)
H10	C10	C17	H17A	-62.1(21)	H10	C10	C17	H17B	58.9(21)
C10	C11	C12	C13	-58.6(2)	C10	C11	C12	C16	61.3(2)
C10	C11	C12	H12	177.5(14)	H11A	C11	C12	C13	177.4(14)
H11A	C11	C12	C16	-62.7(14)	H11A	C11	C12	H12	53.5(19)
H11B	C11	C12	C13	58.8(16)	H11B	C11	C12	C16	178.7(16)
H11B	C11	C12	H12	-65.2(21)	C11	C12	C13	C8	59.4(2)
C11	C12	C13	H13A	-61.6(15)	C11	C12	C13	H13B	-179.6(16)
C16	C12	C13	C8	-60.4(2)	C16	C12	C13	H13A	178.5(15)
C16	C12	C13	H13B	60.6(16)	H12	C12	C13	C8	178.6(14)
H12	C12	C13	H13A	57.5(20)	H12	C12	C13	H13B	-60.4(21)
C11	C12	C16	C15	-60.6(2)	C11	C12	C16	H16A	57.4(13)
C11	C12	C16	H16B	179.2(17)	C13	C12	C16	C15	59.9(2)
C13	C12	C16	H16A	177.8(14)	C13	C12	C16	H16B	-60.4(17)
H12	C12	C16	C15	-175.5(15)	H12	C12	C16	H16A	-57.5(19)
H12	C12	C16	H16B	64.3(22)	C8	C14	C15	C16	59.5(2)
C8	C14	C15	C17	-60.7(2)	C8	C14	C15	H15	-179.0(15)
H14A	C14	C15	C16	179.8(14)	H14A	C14	C15	C17	59.6(13)
H14A	C14	C15	H15	-58.6(20)	H14B	C14	C15	C16	-62.5(16)
H14B	C14	C15	C17	177.3(16)	H14B	C14	C15	H15	59.0(22)
C14	C15	C16	C12	-59.9(2)	C14	C15	C16	H16A	-178.6(14)
C14	C15	C16	H16B	58.7(17)	C17	C15	C16	C12	60.4(2)
C17	C15	C16	H16A	-58.3(13)	C17	C15	C16	H16B	179.0(17)
H15	C15	C16	C12	177.2(15)	H15	C15	C16	H16A	58.4(20)
H15	C15	C16	H16B	-64.2(23)	C14	C15	C17	C10	60.0(2)
C14	C15	C17	H17A	-57.8(14)	C14	C15	C17	H17B	178.2(14)
C16	C15	C17	C10	-60.8(2)	C16	C15	C17	H17A	-178.6(14)
C16	C15	C17	H17B	57.4(14)	H15	C15	C17	C10	-179.0(15)
H15	C15	C17	H17A	63.2(20)	H15	C15	C17	H17B	-60.8(20)
C6	H6A	H6B	C6	0.0(3)					

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Chapter 3

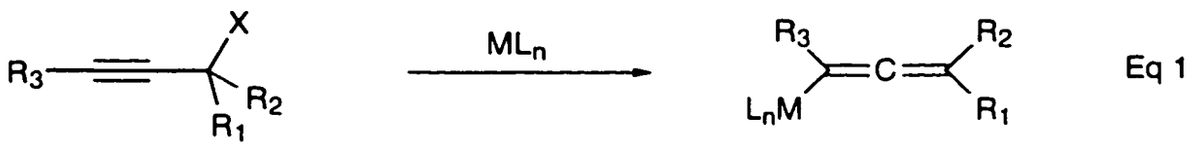
3 Carbonylation of alkynyl epoxides

3.1 Introduction

3.1.1 Chemistry of propargylic compounds

Allenic compounds were once thought to be very unstable species, due to the belief that such a cumulated system would be extremely reactive. As this idea lost favor, many naturally occurring and synthetic allenic compounds were characterized[1]. At present, the diversity of methods for their synthesis, and their unique reactivity and stereochemical properties, make allene derivatives very useful for organic synthesis.

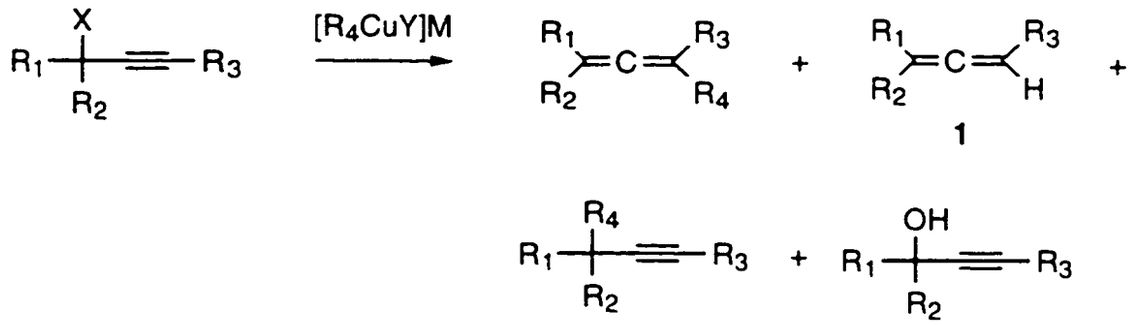
One of the most useful methodologies for the synthesis of allenes is by using propargylic compounds as starting materials. Propargylic compounds containing a suitable leaving group in the propargylic position undergo overall S_N2' reactions when they are treated with some organometallic reagents (Eq 1). Organocuprates, Grignard reagents and palladium (0) complexes are the most useful reagents for the preparation of allenes from propargylic compounds by this methodology[1b].



Eq 1

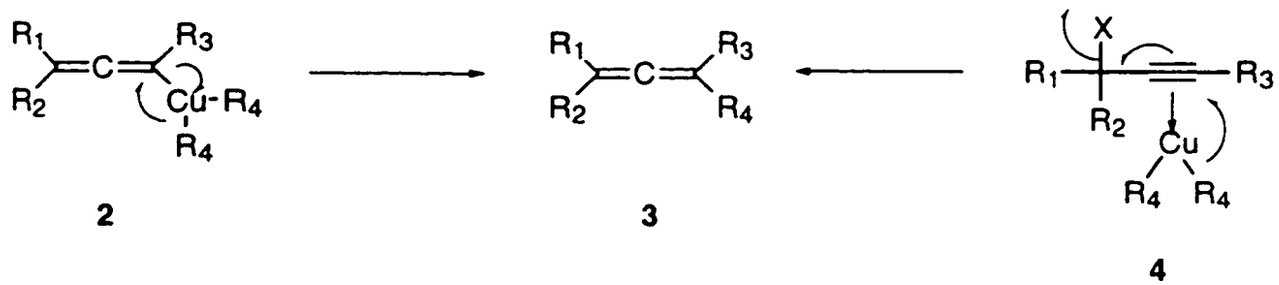
3.1.2 Reactions of propargylic compounds with organocopper reagents

1,3-Substitution reactions of propargylic substrates by organocopper reagents leads to the formation of a mixture of products[1b], as shown in Eq 2.



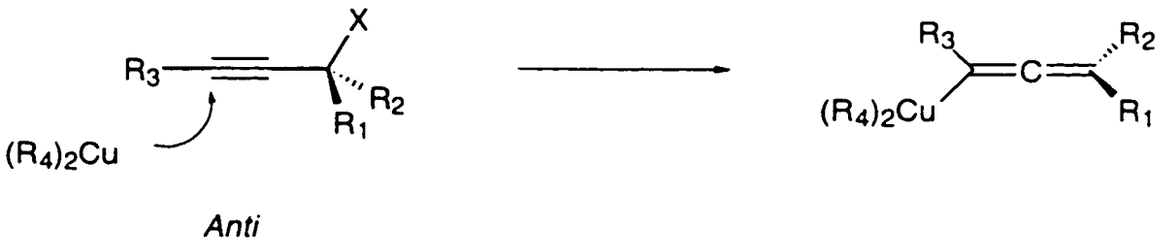
Eq 2

The product distribution can be manipulated by choosing the appropriate organocopper reagent, leaving group, steric bulk at either R_1 or R_3, solvent and temperature of the reaction. The mechanism of the reaction is believed to proceed via an S_N2' process with formation of a Cu (III) intermediate (**2**)[2], which after a 1,2-shift of the alkyl group results in the formation of (**3**) (Scheme 1). Launder[3a] and Pasto[3b] have proposed a π-complex such as **4** as the intermediate, but the formation of unsubstituted allenes **1** as a by-product supports **2** as the intermediate, since such reduction by-products are typical of Cu (III) compounds.



Scheme 1

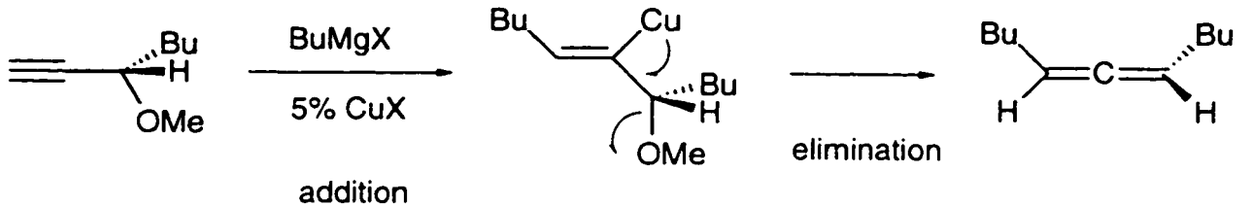
S_N2' reactions of propargylic compounds can give two different isomeric products, depending on whether the attack of the nucleophile is in the *syn* or *anti* fashion (Scheme 2). When a good leaving group is present in the propargylic position (OAc, OCOR, OSO_2R, OSOR, halogen, etc...), the allenic product results from *anti* attack of the alkyl copper reagent. But when poorer leaving groups are present, an overall *syn* process competes with the *anti* process. This phenomenon has been studied in some detail for reactions of propargylic ethers and epoxides[4]. The authors concluded that the overall syn product is formed by an *addition-elimination* mechanism (Scheme 3) or by isomerization of the *anti* product, instead of by a *syn* S_N2' mechanism. This reaction pathway is more favored when a Grignard reagent and catalytic amounts of Cu (I) salt are used, instead of stoichiometric amounts of the organocupric reagent. The *syn/anti* distribution ratio is strongly affected by the nature of the halide in the Grignard reagent. This is called the "halogen effect".



Anti

Syn

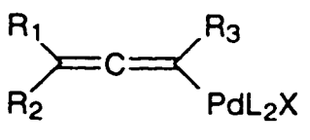
Scheme 2



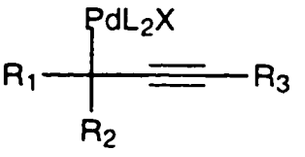
Scheme 3

3.1.3 Reactions of propargylic compounds with Pd(0) complexes

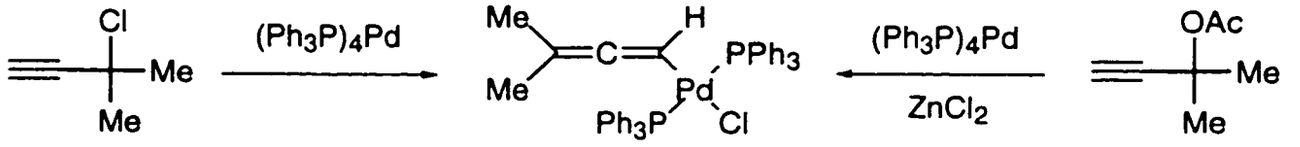
Propargylic compounds react with Pd(0) complexes in a S_N2' manner, to give σ-allenylpalladium complexes of the type **5**[5], analogous to the Cu (III) intermediates formed by reaction with organocuprates. This type of Pd intermediate can actually be isolated. For example, complex **9** has been prepared and characterized by reacting stoichiometric amounts of $(Ph_3P)_4Pd$ with propargylic chloride **7** and acetate **8**[6] (Scheme 4). When R is a bulky substituent, the propargyl-Pd compound **6** is sometimes formed, but only a few catalytic reactions involving **6** are known.



5



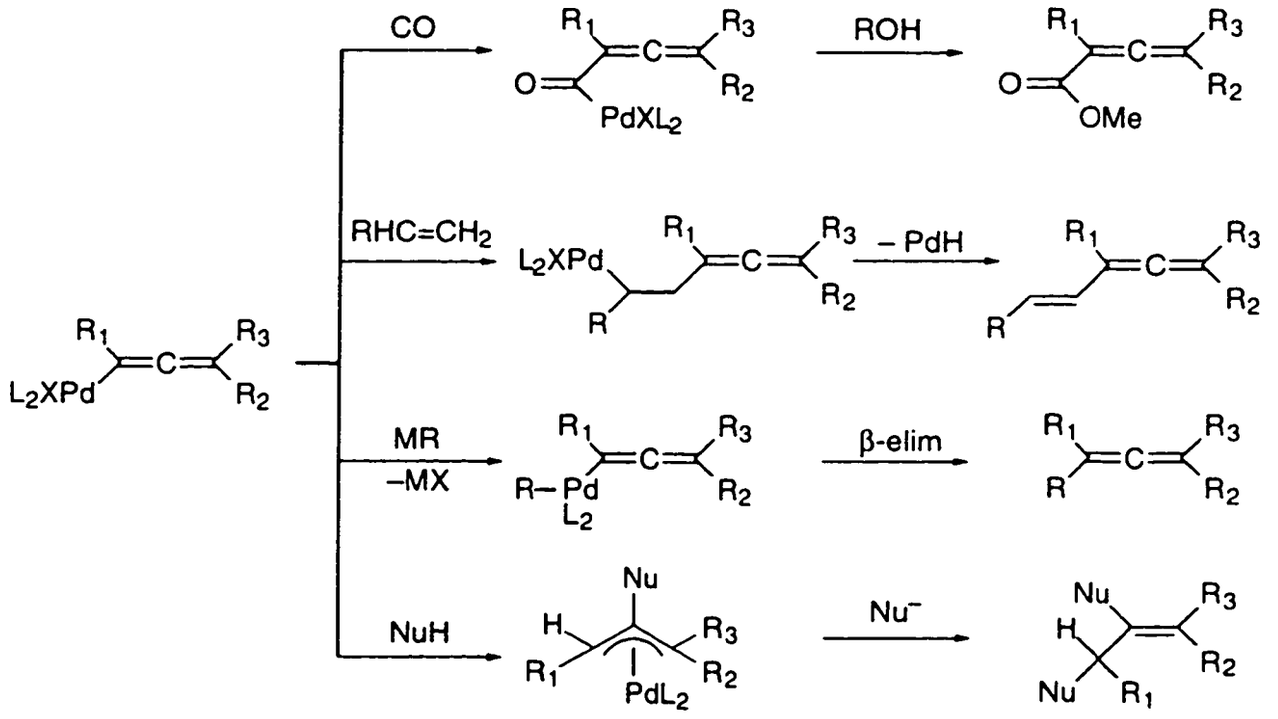
6



7 **9** **8**

Scheme 4

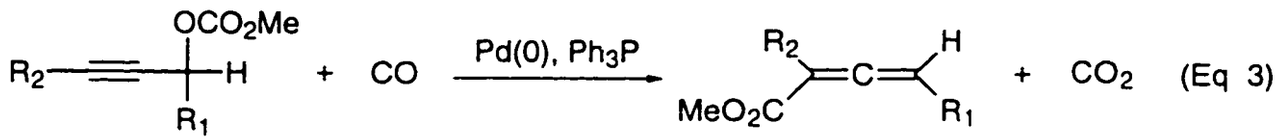
These σ-allenyl-Pd complexes can undergo 4 types of reactions (Scheme 5): a) insertion of carbon monoxide into the Pd-C bond: the acylpalladium complex formed reacts with alcohols to form 2,3-dienoates. b) insertion of an olefin into the Pd-C bond: the alkylpalladium complex gives vinylic allenes after β-hydrogen elimination. c) transmetallation reaction to form a dialkylpalladium complex, which after reductive elimination gives substituted allenes. d) reaction of soft nucleophiles at the central carbon of the allenyl group forming π-allylpalladium complexes, which are further attacked by nucleophiles. These reactions can be performed using catalytic amounts of the Pd(0) complex, what makes this a very useful method for the synthesis of allene derivatives.



Scheme 5

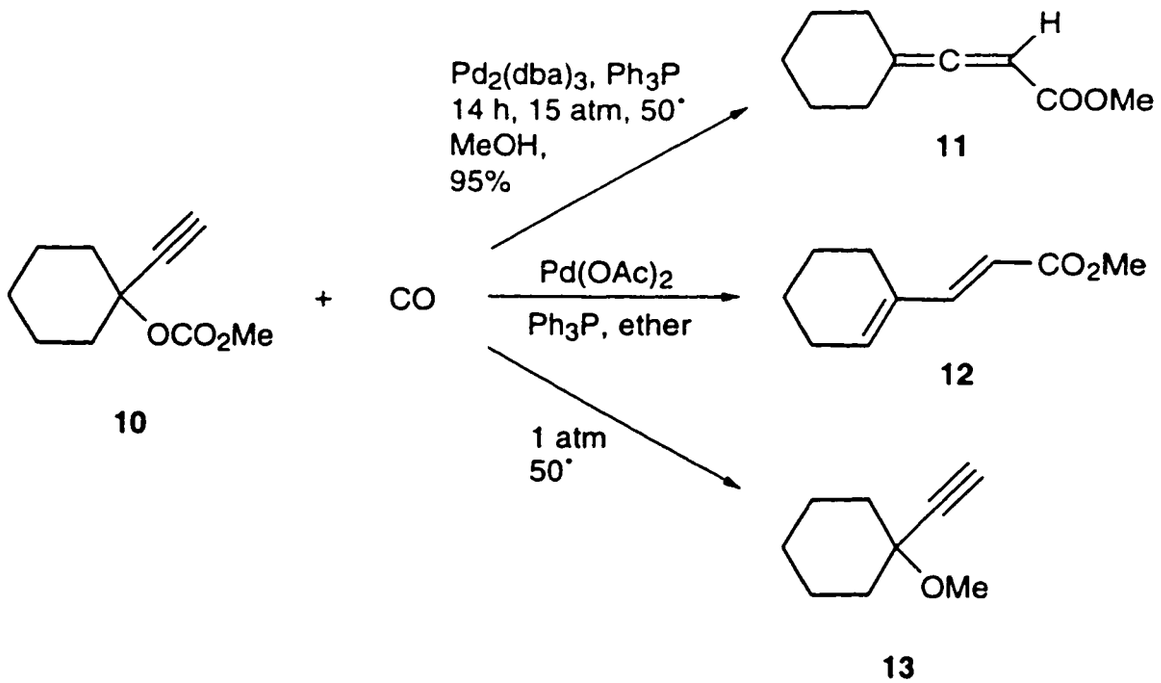
3.1.4 Carbonylation of propargylic compounds catalyzed by Pd(0) complexes

The carbonylation of propargylic compounds is a very practical method for the preparation of 2,3-dienoates. Most of the research has been done on propargylic carbonates[7]. The release of carbon dioxide is believed to be the driving force of this reaction, which occurs under quite mild reaction conditions (Eq 3).



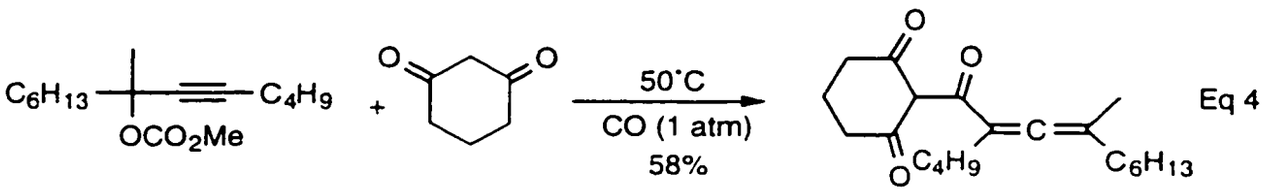
(Eq 3)

Carbonylation of **10** gives **11** in good yield. Depending on the reaction conditions, products **12** and **13** are also formed (Scheme 6). **12** is the product of the isomerization of the

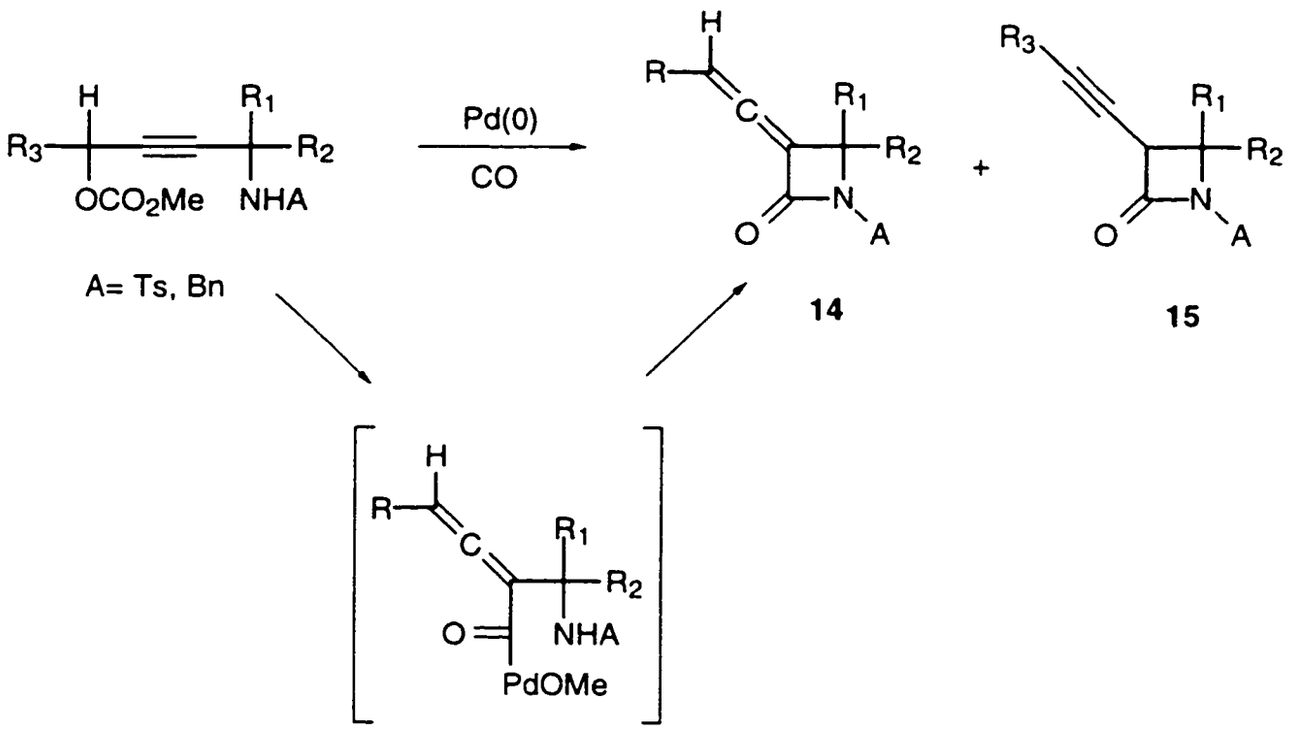


Scheme 6

2,3-dienoate **11**. The formation of **12** can be favored by changing the solvent of the reaction from methanol to ether, benzene or acetonitrile[8]. Also longer reaction times induce isomerization, presumably by the action of the Pd catalyst. **13** is formed by simple decarboxylation of the alkynyl carbonate. This side reaction becomes more important at low pressures of carbon monoxide.

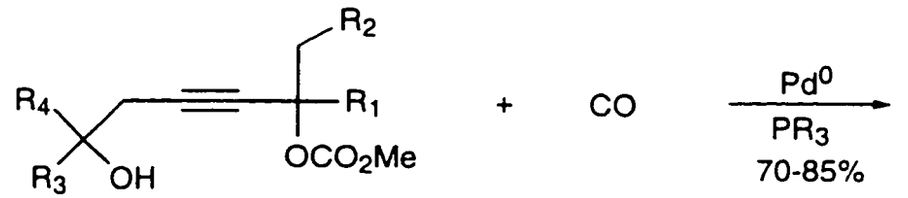


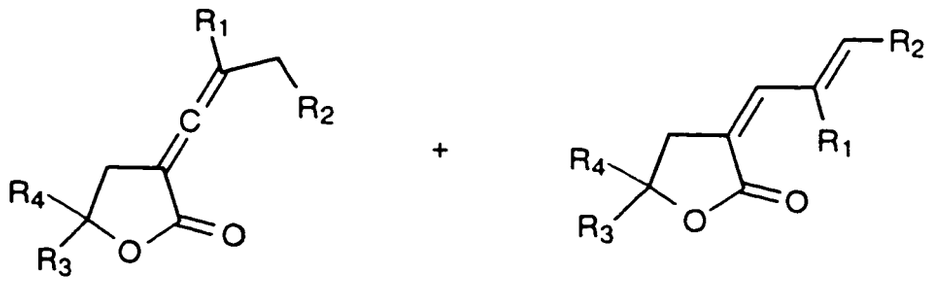
Eq 4



Scheme 7

When β-diketones are used as the nucleophiles, allenyl ketones are obtained[9]. These reactions must be performed in the presence of NaH, which generates the carbanion (Eq 4). β-Keto esters and malonates react in the same way. Synthesis of α-vinylidene β-lactams can be achieved by the carbonylation of 4-amino-2-alkynyl carbonates[10]. The β-lactam is formed by intramolecular nucleophilic attack of the amino group at the acylpalladium intermediate (Scheme 7). α-Alkynyl-β-lactams **15** are obtained as byproducts by isomerization of **14**. In the same way, α-vinylidene-γ-lactones are prepared by carbonylation of 5-hydroxy-2-alkynyl methyl carbonates[11] (Eq 5), with isomerization byproducts obtained again.

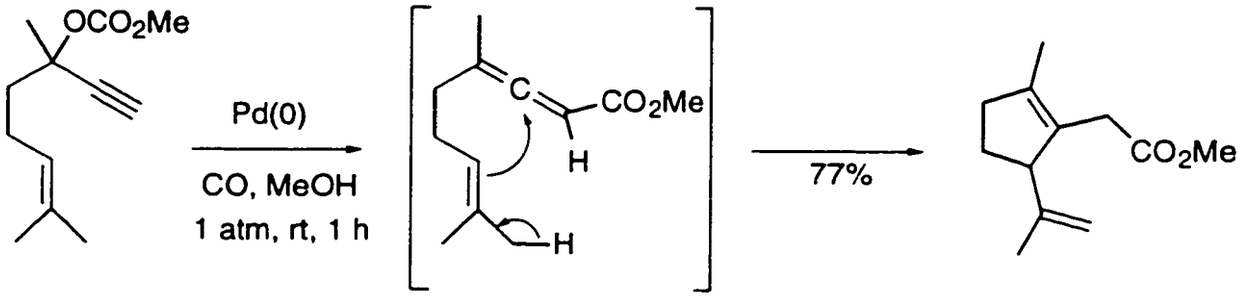




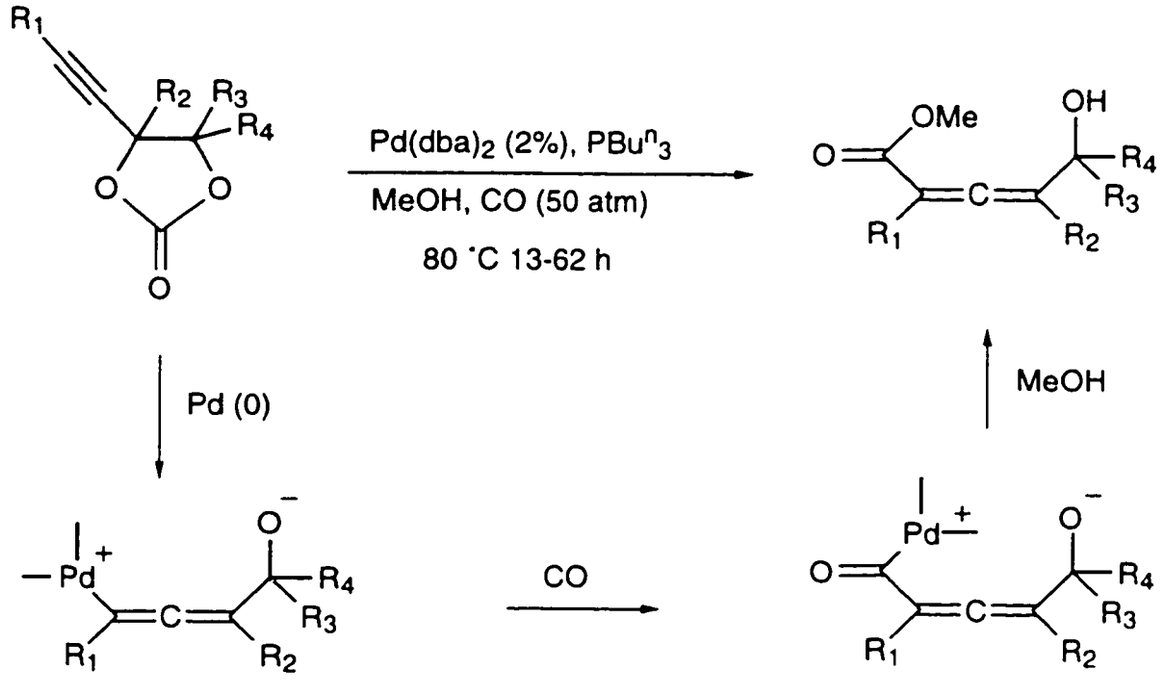
Eq 5

Propargylic carbonates containing double bonds in appropriate positions can undergo tandem carbonylation-cyclization reactions (Scheme 8).

Carbonylation of cyclic alkynyl carbonates under quite drastic conditions leads to the formation of highly functionalized allenic compounds[12]. In this case, a zwitterionic σ-allenylpalladium intermediate is formed (Scheme 9)



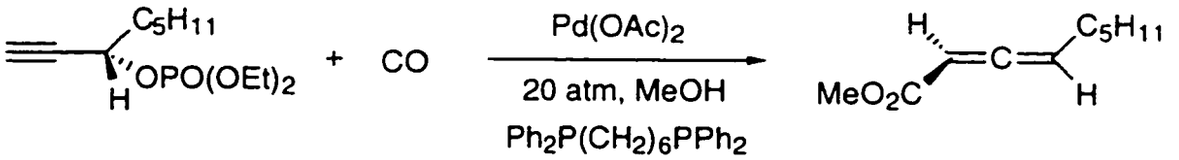
Scheme 8



Scheme 9

Although propargylic carbonates are the more reactive compounds, propargylic mesylates[13], acetates[14], phosphates[14] and halides[15a] have been used as substrates as well, giving the same type of 2,3-dienoate compounds. Carbonylation of propargylic amines requires the presence of *p*-toluenesulphonic acid[15b].

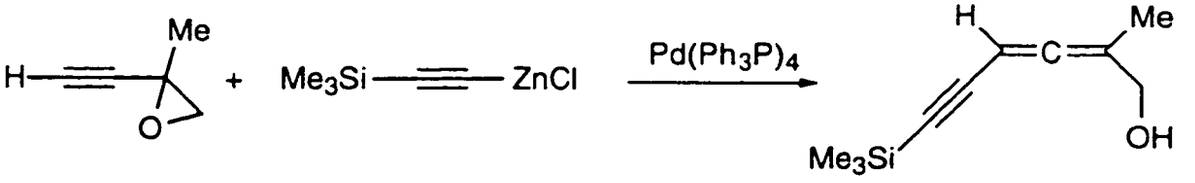
Regarding the stereochemistry of the reaction, chiral propargylic mesylates[13a] and phosphates[14b] have been used for carbonylation reactions. It was found that optically enriched allenes are obtained under the appropriate reaction conditions (Eq 6). The chiral allenic compound arises by *anti* S_N2' attack of Pd^0 to the propargylic compound.



Eq 6

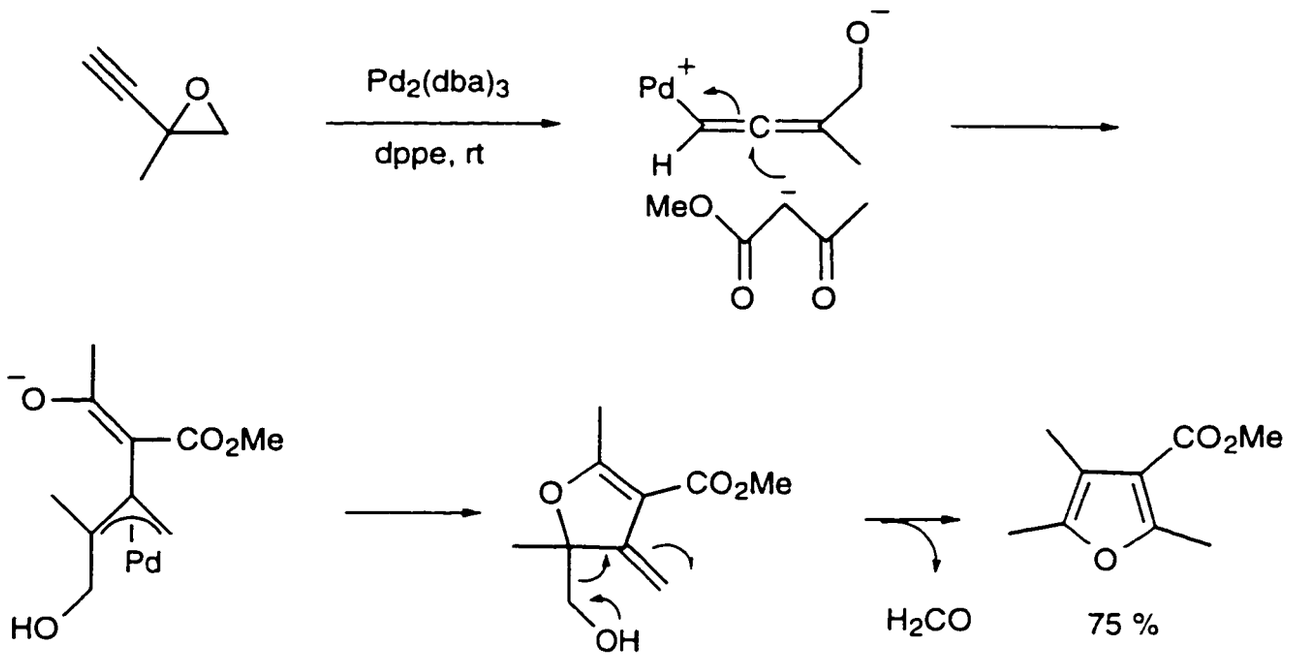
3.1.5 Reactions of alkynyloxiranes catalyzed by Pd(0) complexes

The oxirane ring in propargylic epoxides can be considered as a good leaving group due to the strain in the cycle. Having this in mind, some catalytic reactions of propargylic epoxides with Pd (0) complexes have been developed. Allenyl alkynes are prepared by the reaction of alkynyl oxiranes and zinc acetylides, in the presence of catalytic amounts of $(Ph_3P)_4Pd$. The reaction takes place by a transmetallation intermediate[16] (Eq 7).



Eq 7

Alkynyl oxiranes react with soft nucleophiles and a Pd(0) catalyst to afford furan derivatives[17]. The nucleophile attacks the central carbon of the σ-allenylpalladium intermediate to form a allyl-Pd complex. Intramolecular nucleophilic reaction and elimination of formaldehyde gives the final product (Scheme 10).



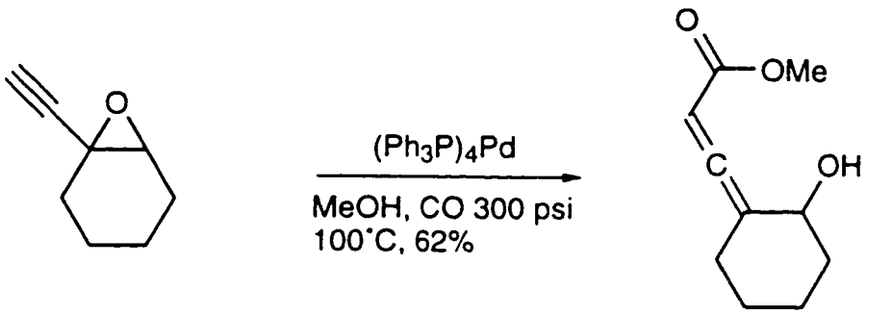
Scheme 10

Although alkynyl epoxides react easily with Pd (0) complexes, the carbonylation of these compounds has not been reported in the literature. The aim of this work is to explore the carbonylation of alkynyl epoxides, leading to the formation of highly functionalized allenes and to oxygen heterocycles.

3.2 Results and Discussion

3.2.1 Carbonylation of Alkynyl Epoxides

The initial experiments for the carbonylation of alkynyl epoxides were carried out at 100 °C, in the presence of $(Ph_3P)_4Pd$. The expected 5-hydroxy-2,3-pentadienoate **17** was obtained from substrate **16** in 62% yield (Eq 8).



16e **17e** Eq 8

The allenyl products can be easily identified by their IR and ^{13}C-NMR spectra. The IR spectrum shows absorption at ~ 3400 cm^{-1} (OH), 1960-1965 cm^{-1} (C=C=C stretching) and 1700-1720 cm^{-1} (C=O). ^{13}C-NMR spectroscopy shows signals at 205-210 ppm for the central allenyl carbon, and ~ 167 ppm for the carbonyl group. Figure 1 shows spectra corresponding to **17a**.

After optimization of the reaction conditions, we observed that the carbonylation reaction takes place under very mild conditions: 0.8 mmol of the alkynyl epoxide, 1 mol % of $(MePh_2P)_4Pd$, 10 ml of methanol, 300 psi of carbon monoxide, room temperature, 2 hours. Although longer reaction times do not affect the chemical yields, 2 hours are enough to reach full conversion of the epoxide. Methanol is the best solvent for the reaction.

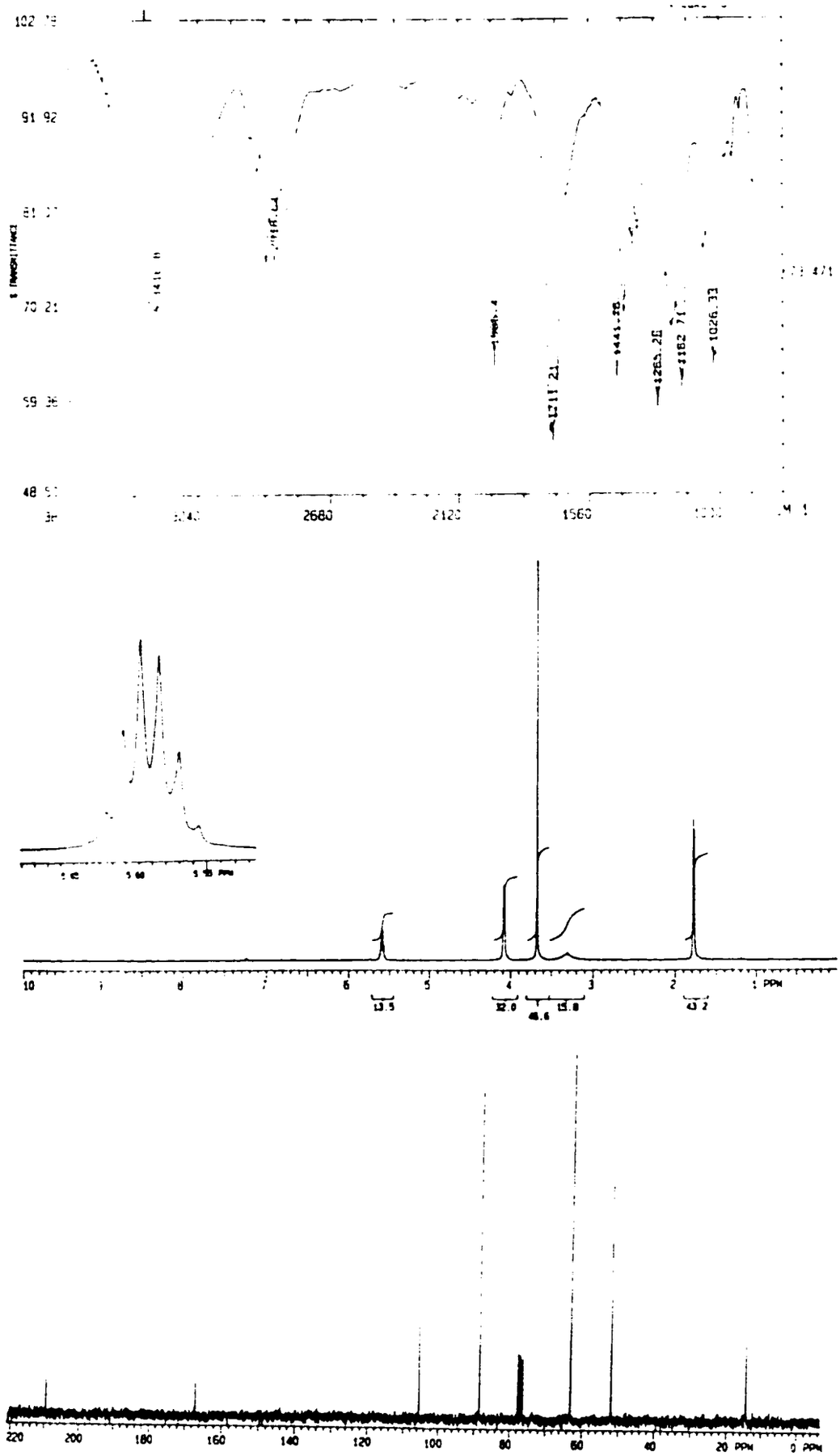
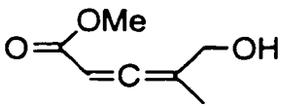
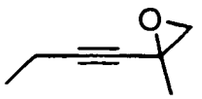
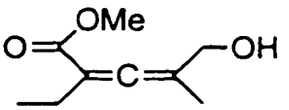
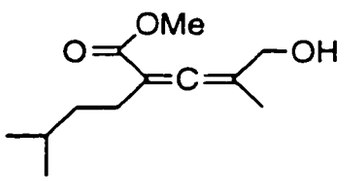
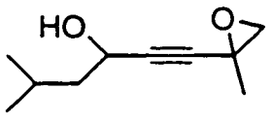
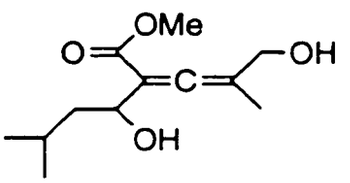
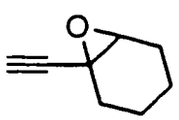
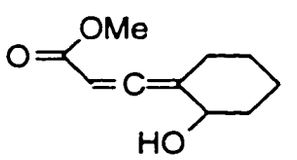
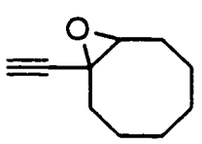
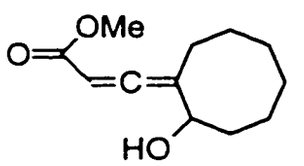


Figure 1: IR, ^{1}H-NMR and ^{13}C-NMR spectra of **17a**

Table 1: Carbonylation of alkynyl oxiranes catalyzed by $(MePh_2P)_4Pd$[a]

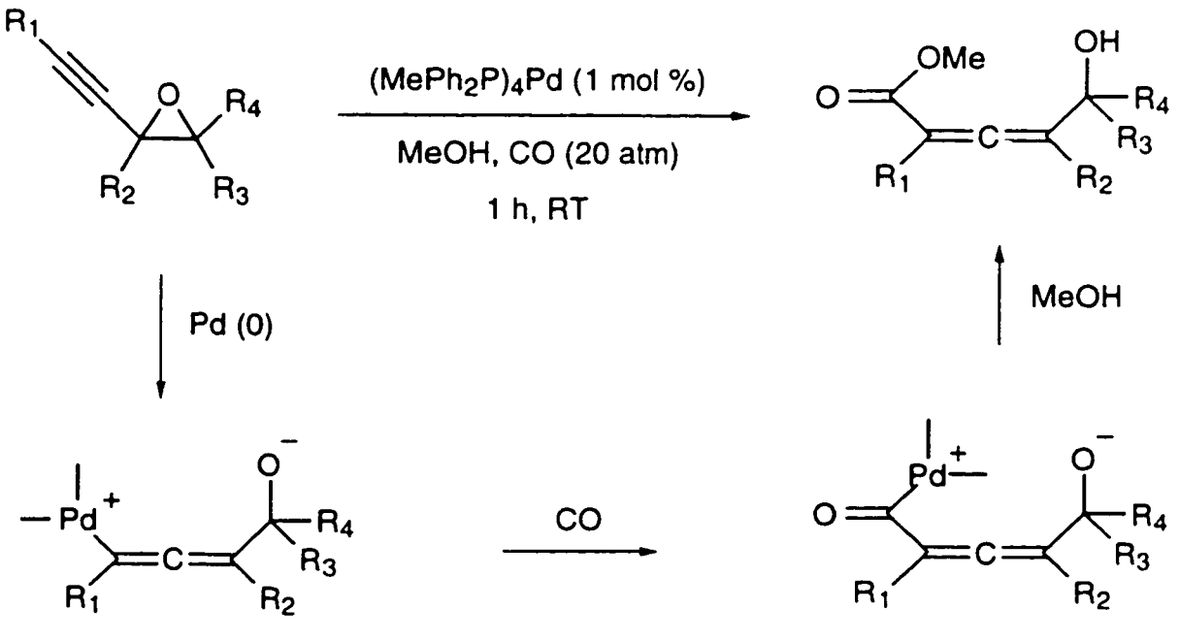
substrate		product		yield (%)
16a		**17a**		70
16b		**17b**		74
16c		**17c**		78
16d		**17d**		55
16e		**17e**		90
16f		**17f**		94

a) Reaction conditions: alkynyl epoxide, 0.8 mmol; $(MePh_2P)_4Pd$, 1 mol %; methanol, 10 ml; CO, 300 psi; rt, 2h.

When benzene or THF was used, in the presence of 0.5 ml of methanol, the conversion is very low and the desired allene was not detected in the reaction mixture, even when the reaction was carried out at 100 °C. Carbon monoxide pressure higher than 300 psi does not improve the yields. A decrease in the conversion is noted when the reaction is done under 200 psi of carbon monoxide.

Table 1 shows the results for the carbonylation of a series of alkynyl epoxides. Linear substrates (**16a-c**) give fine yields of hydroxymethyl allenyl esters. The yields are quite high for fused bicyclic epoxides (**16e-f**). A hydroxy derivative of an alkynyl epoxide (**16d**) gives a highly oxygenated allene in lower yields.

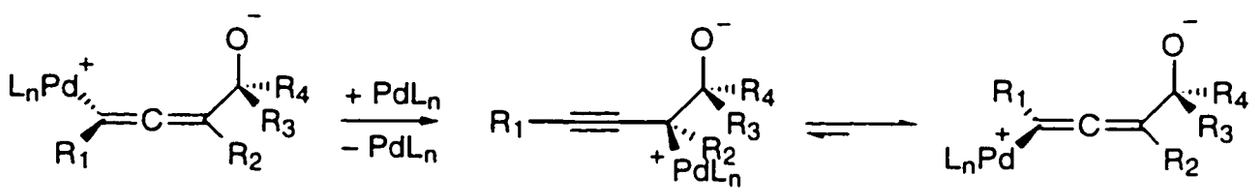
The mechanism of the reaction is probably the same as that proposed for the carbonylation of cyclic alkynyl carbonates[12] (Scheme 9). In that case, the driving force of the reaction might be the liberation of CO_2, while in the carbonylation of alkynyl oxiranes the driving force is the release of ring strain by opening the epoxide ring (Scheme 11). It is worth noting that the reaction conditions for the carbonylation of alkynyl oxiranes are much milder than those for the carbonylation of cyclic carbonates.



Scheme 11

The effect of different catalytic systems on the carbonylation of **16e** is shown in Table 2. Note that not only the yield of the reaction is affected, but also the diastereomeric ratio of the product. The highest yield is obtained by using the commercially available $(MePh_2P)_4Pd^0$ complex. Bidentate phosphine ligands improve the diastereoselectivity. DPPB and 1,5-bis(diphenylphosphino)pentane both give a 97/3 *anti/syn* ratio of **17e**.

Although we didn't determine the configuration of the major diastereomer, we can assume that the formation of the *anti* isomer is favored. Studies done on the carbonylation of chiral mesylates[13] and phosphates[14b] show that the Pd^0 complex reacts with the triple bond in a S_N2' manner. Any loss in stereoselectivity may be due to a racemization induced by the same Pd^0 catalyst. Nucleophilic attack of free Pd^0L_n at the σ-allenyl-Pd intermediate **18** in *anti* S_N2' fashion, followed by allenyl-propargyl rearrangement in the same plane would give the intermediate **19** (Scheme 12). This racemization could be minimized by decreasing the amount of catalyst and by using larger diphosphine ligands.



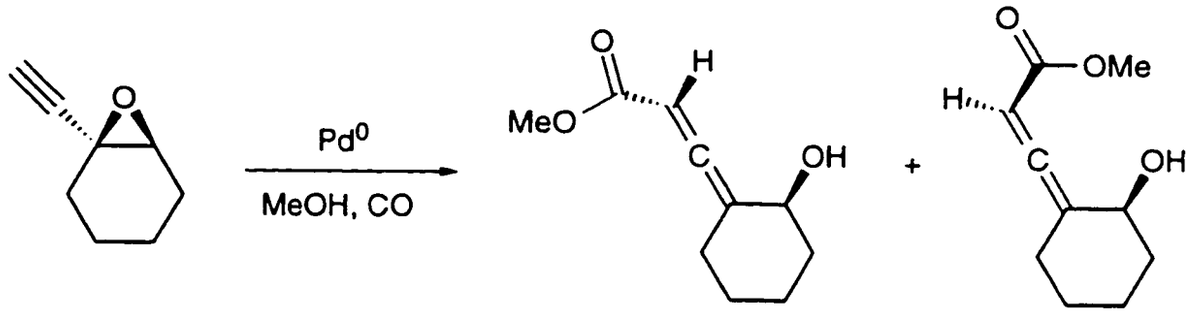
18 **19**

Scheme 12

3.2.2 Carbonylation of alkynyl oxiranemethanol derivatives

Following the same mechanism, the carbonylation of alkynyl oxiranemethanol derivative **20a** should lead to the formation of allenyl diol **22** (Eq 9). When alkynyl oxirane **20a** is reacted under the standard reaction conditions, the conversion is complete, but product

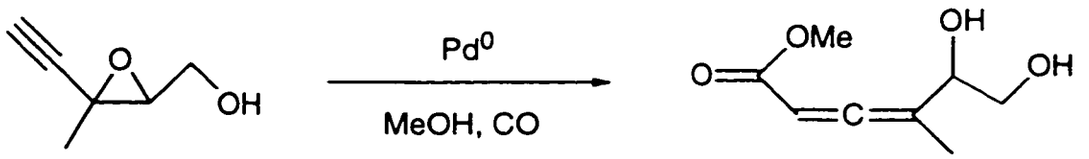
Table 2:Variation of diastereomeric ratio of **17e** with the catalytic system



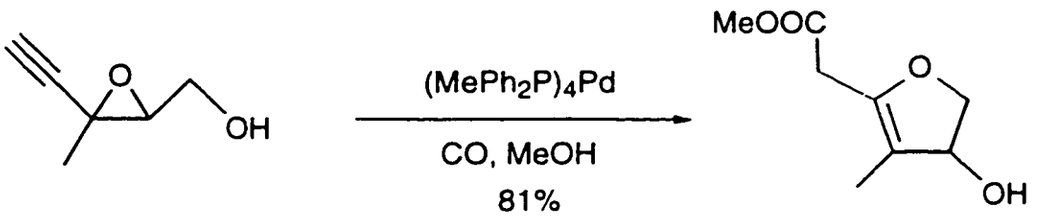
	Anti	*Syn*
Ligand or catalyst	yield (%)	*anti / syn*
------	0	-----
DPPP[a]	78	97/3
DPPB[a]	89	93/7
Ph_3P[b]	88	82/18
DPPPentane[a]	84	97/3
$(Ph_3P)_4Pd$[c]	84	88/12
$(MePh_2P)_4Pd$[c]	90	93/7

a) Reaction conditions: **16a**, 0.8 mmol; $Pd_2(dba)_3.CHCl_3$, 0.004 mmol; ligand, 0.008 mmol; MeOH, 10 ml; 24 h, rt. b) Using 0.016 mmol of Ph_3P. c) 0.008 mmol of catalyst and no added ligand.

22 was not found in the reaction mixture. Instead, the oxygen heterocycle **21a** was isolated in 81 % yield (Eq 10).



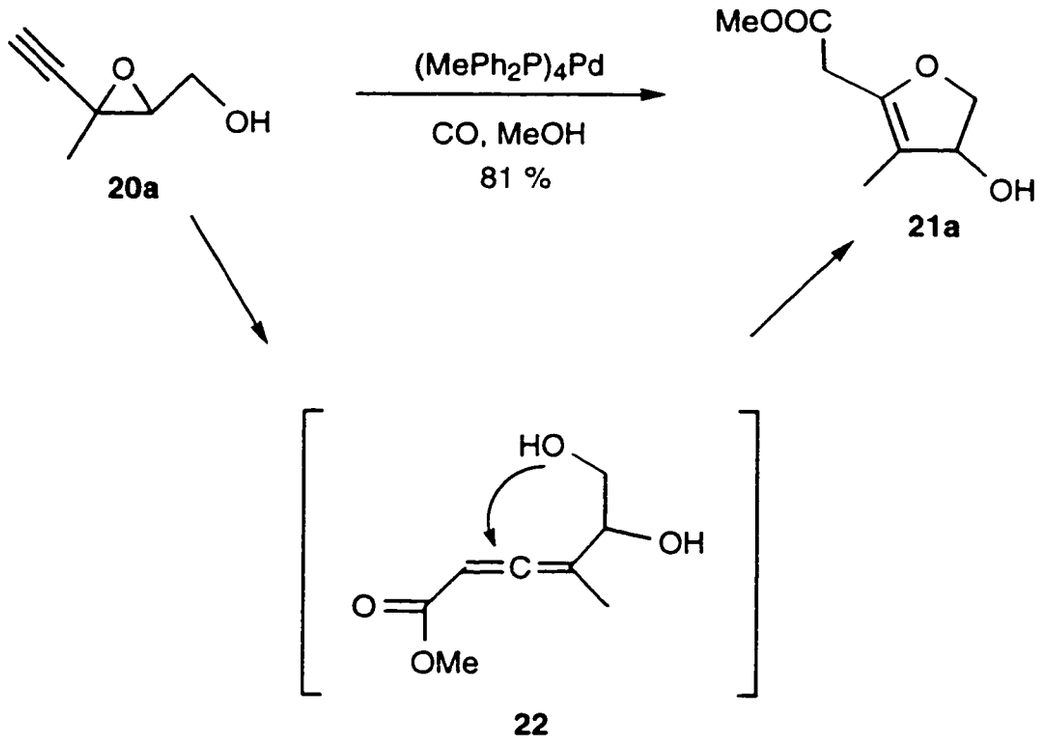
20a **22** Eq 9



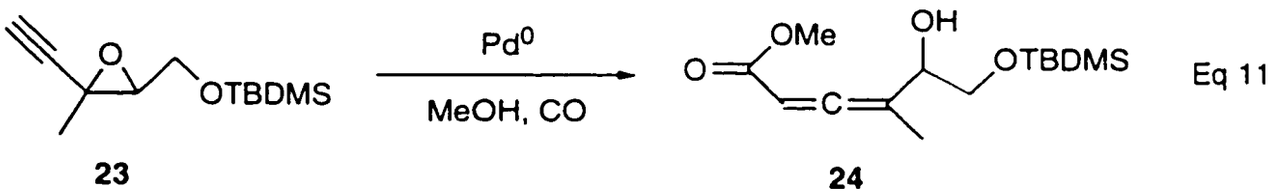
20a **21a** Eq 10

This result can be rationalized as a consequence of a 5-exo cyclization of the expected allenyl diol product under the reaction conditions (Scheme 13). Since the carbonylation reaction is carried out under neutral conditions, we can rule out an acid or basic catalysis. The formation of **21a** could be due to a Pd catalyzed cyclization of the diol, or by a spontaneous process.

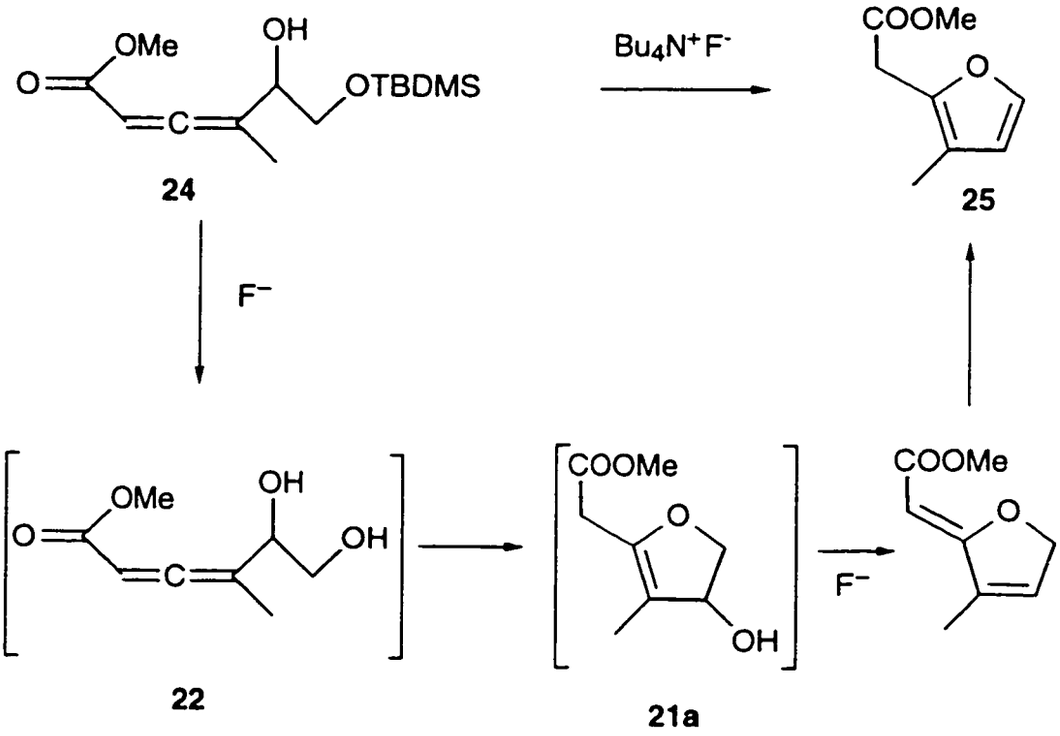
We attempted to isolate the diol intermediate by reacting the protected substrate as a silyl ether (**23**). The carbonylation reaction gave 47 % yield of the allene **24** (Eq 11).



Scheme 13



Deprotection of **24** with $Bu_4N^+F^-$ did not afford the expected diol, nor the dihydrofuranol derivative **21a**. Instead, the dehydration product of **21a** was isolated in 79 % yield. The basicity of F^- might induce the dehydration of **21a** to form the more stable aromatic compound **25** (Scheme 14).

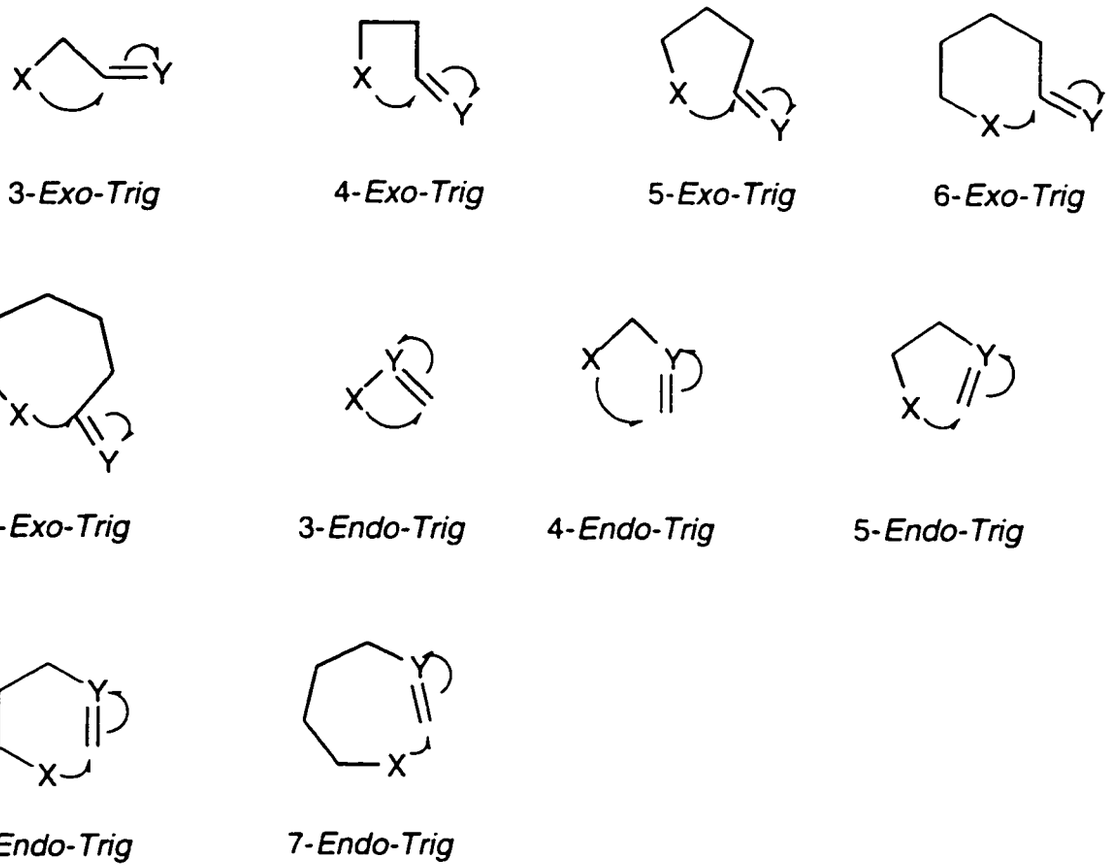


Scheme 14

This result suggests that the cyclization of the diol **22** during the carbonylation reaction occurs spontaneously, following Baldwin's rules for cyclization reactions.

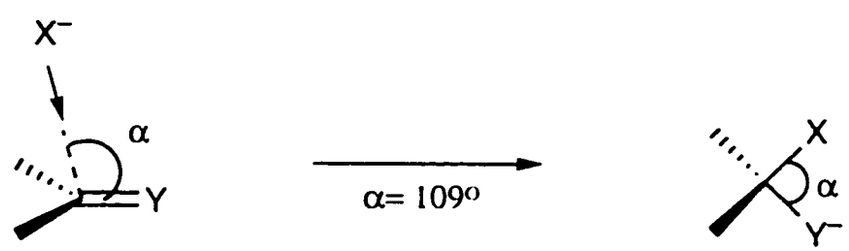
3.2.2.1 Baldwin Rules

In 1976, Baldwin outlined a set of simple rules predicting the relative facility of different ring closure reactions[18]. The physical bases of the rules lie in the stereochemical requirements of the transition state in the ring closure process. The nature and length of the linking chain, and the size of the ring formed, will determine whether the system can reach the required transition state geometry, without the need to consider distortions of bond angles and distances. These rules postulate that, for closures at sp^2 carbon atoms (trigonal case), the *exo* cyclization is favored for the formation of 3 to 7 membered rings, while the *endo* process is disfavored for 3 to 5 membered rings, and favored for 6 and 7 membered rings (Scheme 15)



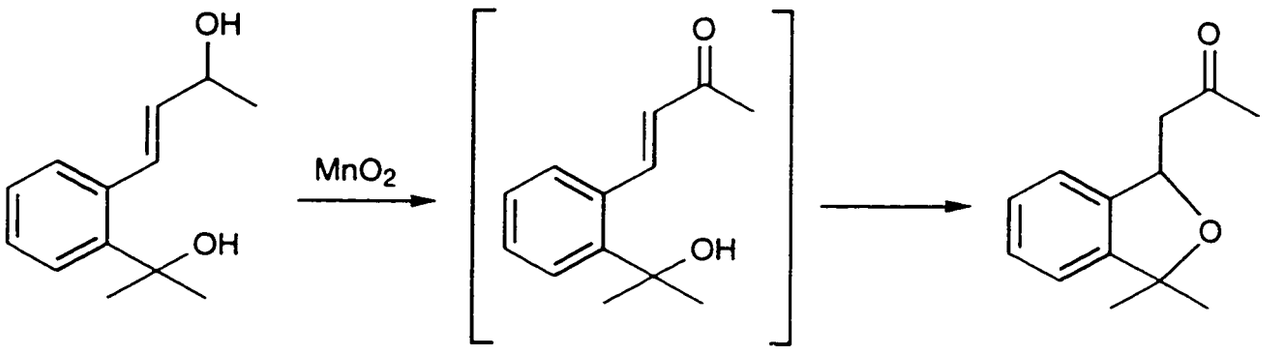
Scheme 15

For a trigonal ring closure to be favored, the three reacting atoms must maintain an angle $\alpha = 109^{\circ}$ during the reaction pathway. This angle is maintained between these atoms in the product (Scheme 16).



Scheme 16

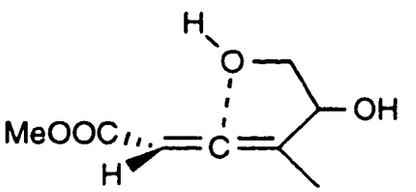
The case of conjugate addition of oxygen nucleophiles has been studied in some detail[19]. For 5-*exo-trig* systems, the cyclization is highly favored. When the secondary hydroxyl group in **26** is selectively oxidized, the hydroxy ketone **27** is not observed, since it cyclizes spontaneously to the isobenzofuran derivative **28** (Scheme 17).



26 **27** **28**

Scheme 17

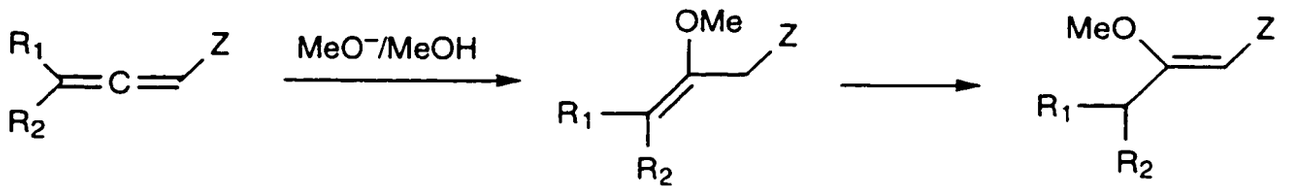
Although compounds containing allenic carboxylic esters have not been studied, from molecular models we reason that compound **22** can adopt a conformation favorable for the interaction of the hydroxy group with the π system of the α,β-unsaturation, which makes the cyclization very facile (Scheme 18).



Scheme 18

Table 3 shows the results for the carbonylation of several alkynyl oxiranemethanol derivatives. Note that, depending on the substitution pattern of the starting material, heterocycles containing *endo* or *exo* double bonds are obtained.

The preference for the formation of the *exo* or *endo* unsaturated products seems to be related to their thermodynamic stability. In fact, the intermolecular addition of oxygen nucleophiles to allenic compounds containing an electron acceptor group is well known[20]. The addition of MeOH to compound **29** gives **30** as the first product. But depending on the substitution pattern, this compound may isomerize to a more stable conjugated system **31** (Scheme 19)

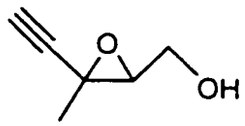
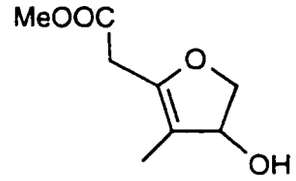
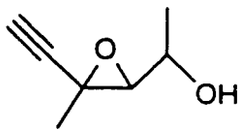
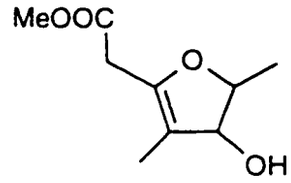
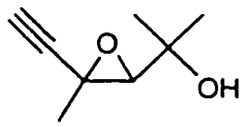
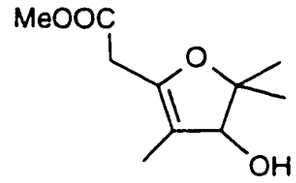
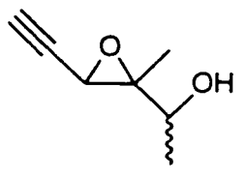
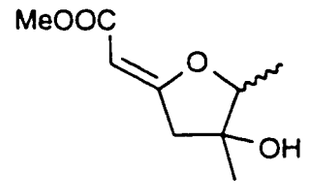
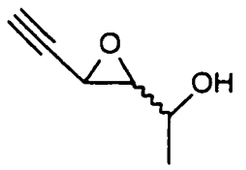
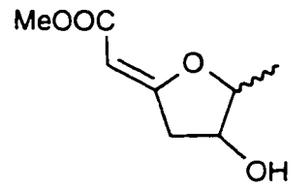
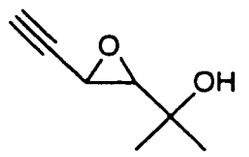
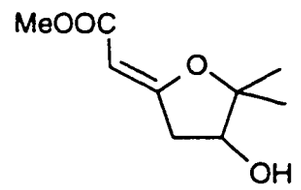


29 **30** **31**

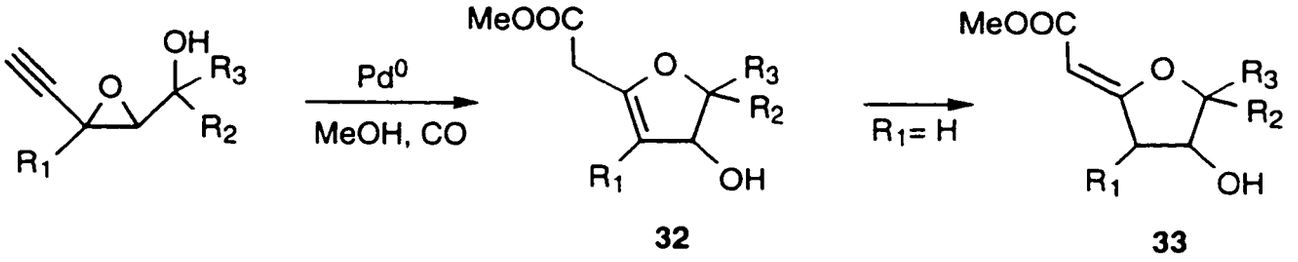
Scheme 19

In the carbonylation of alkynyl oxiranemethanol derivatives, the dihydrofuranol **32** is formed by a normal intramolecular Michael type addition (Scheme 20). When R_1= Me the product is stable and can be isolated. For R_1= H isomerization occurs to give a more stable α,β-unsaturated ester **33**. We have not determined wether the α,β–unsaturated esters have Z or E configuration. Nevertheless just one isomer is formed.

Table 3: Carbonylation of alkynyl oxiranemethanol derivatives[a]

Substrate		Product		Yield (%)
20a		**21a**		81 %
20b		**21b**		49%
20c		**21c**		91%
20d		**21d**		74%
20e		**21e**		30%
20f		**21f**		91%

a) Reaction conditions: alkynyl epoxide, 0.8 mmol; $(MePh_2P)_4Pd$, 1 mol %; methanol, 10 ml; CO, 300 psi; rt, 2h.

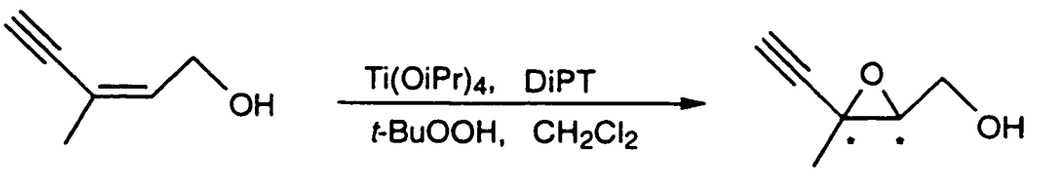


Scheme 20

The formation of one or the other isomer is very selective. In cases **20d** and **20e**, the synthesis of the starting epoxides gave mixtures of diastereomers, and this ratio is reflected in the *cis-trans* distribution in the heterocyclic product (**21e**: 64/36 *cis/trans*. **21d**: 59/41. We could not determine which one corresponds to *cis* or *trans*.).

3.2.2.2 Preparation of chiral heterocycles

The transformation of alkynyl oxiranemethanol compounds to 3,4-dihydrofuran-3-ol derivatives proceeds with loss of stereochemistry at C_3 of the starting material. According to the mechanism of the reaction, the stereochemistry at C_1 and C_2 should not be affected during the course of the reaction. The ease of synthesis of chiral alkynyl oxiranemethanol derivatives by Sharpless epoxidation[21] makes this carbonylation reaction a potential route for the preparation of chiral oxygen heterocycles. The asymmetric epoxidation of **34** to **35** was examined as a model system (Eq 12).



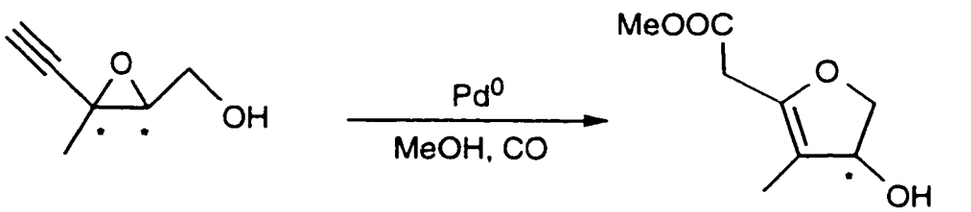
34 **35**

60 % ee

Eq 12

Unfortunately, the enantiomeric excess of **35**, measured by chiral GC (Figure 2), was only 47%. The reaction was repeated two times with the same result. After one recrystallization of **35** the ee improved to 60%. Further recrystallizations didn't increase the ee. A literature search shows that there is only one paper where the ee of the same compound obtained by Sharpless epoxidation is reported[22]. In that case, the enantiomeric excess is 60 %, the same value that we obtained.

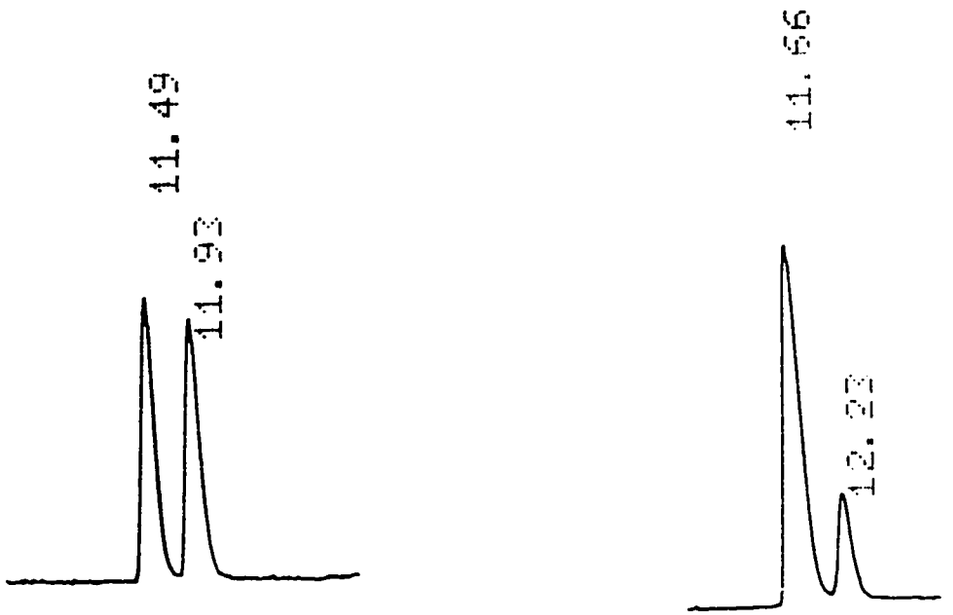
Carbonylation of **35** gave **36** in 79% yield (Eq 13). The ee was 55%, as determined by the use of an NMR chiral shift reagent (Figure 2). Chiral GC could not be used because **36** dehydrates upon injection into the column.



35 **36** Eq 13

60 % ee 55 % ee

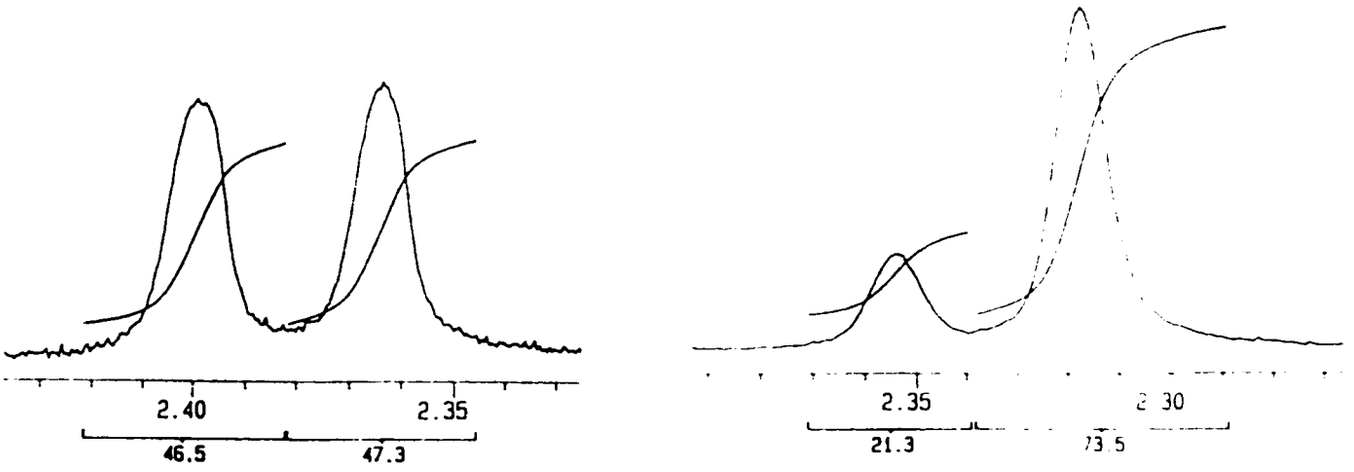
This result shows that the stereocentre at C_2 is unaffected by the reaction, therefore different chiral oxygen heterocycle derivatives can be synthesized in this way. It is well known that compounds of the type **36** can undergo highly diastereoselective hydrogenation[23] or epoxidation[24] reactions, since the OH group can act as a directing group. This would allow the preparation of tetrahydrofuran derivatives containing three chiral centers, the only chiral source being the Sharpless epoxidation reaction (Scheme 21).



PEAK#	AREA%	RT	AREA BC
1	49.89	11.49	21550 02
2	50.11	11.93	21645 03
TOTAL	100.		43195

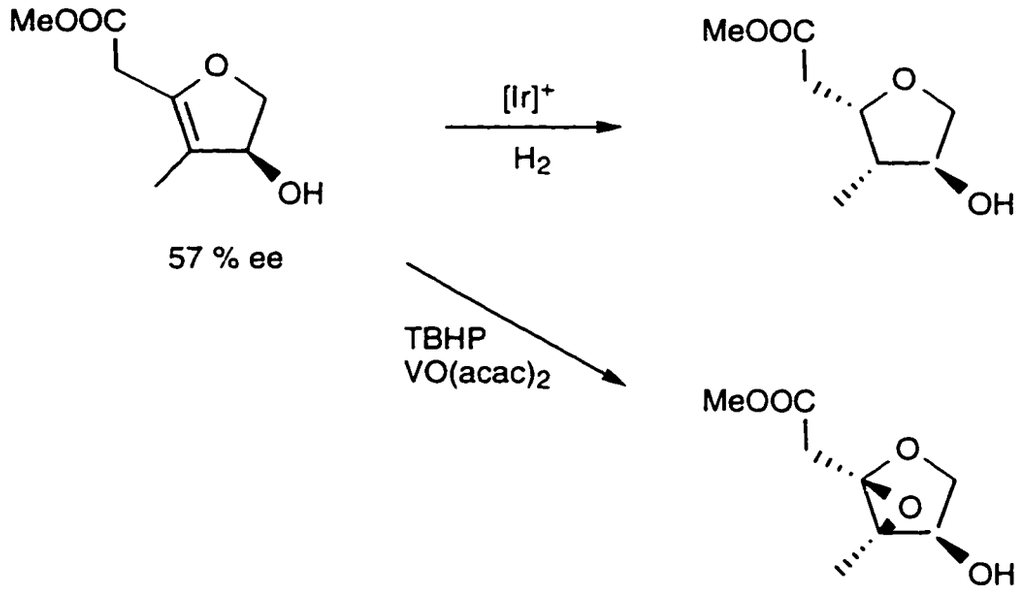
PEAK#	AREA%	RT	AREA BC
1	80.113	11.56	37076 02
2	19.887	13.01	9200 01
TOTAL	100.		46276

Enantiomeric excess determination of **35** by chiral GC.



Enantiomeric excess determination of **36** by ^{1}H-NMR

Figure 2: Determination of enantiomeric excess of **35** and **36** (The racemates are shown on the left side).



Scheme 21

3.3 Conclusions

The Pd(0) catalyzed carbonylation of alkynyl oxiranes affords 5-hydroxy-2,3-pentadienoates derivatives in good yields. The reaction starts with a S_N2' attack on the triple bond by a palladium (0) complex, forming a zwitterionic σ-allenylpalladium intermediate, which after carbon monoxide insertion and attack by methanol leads to the formation of the product. The diastereomeric ratio of the product is affected by the phosphine ligand with larger bidentate ligands favoring the formation of the *anti* products.

The carbonylation of alkynyl oxiranemethanol derivatives affords oxygen heterocyclic compounds. These compounds are formed by spontaneous intramolecular Michael type addition of the diol allenic intermediate, following Baldwin's cyclization rules. Depending on the substitution pattern of the starting epoxide, the heterocycle will contain an *endo* or *exo* carbon-carbon double bond. The use of enantiomerically enriched alkynyl oxiranemethanol leads to the preparation of an optically active 4,5-dihydrofuran-3-ol derivative.

3.4 Experimental Section

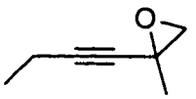
3.4.1 Synthesis of alkynyl oxiranes 16a-16f

The synthesis of alkynyl oxiranes was carried out by epoxidation of the corresponding enynes[4]. These precursors were purchased from Aldrich or Lancaster, and used as received. The enyne precursor of **16f** was prepared by dehydration of 1-ethynyl-1-cyclooctanol with $POCl_3$ in pyridine[4].

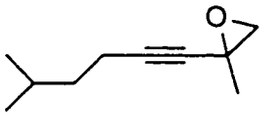
General procedure: To a solution of the enyne (26.2 mmol) in CH_2Cl_2 (17 ml) at 0 °C was added, in portions, 33 mmol of *m*-chloroperoxybenzoic acid. The reaction mixture was stirred for 15 minutes at 0 °C, then the ice bath was removed and the mixture was stirred for 2 hours at room temperature. 10% Sodium sulphite solution was slowly added until the mixture gave a negative test with starch-iodide paper. Saturated sodium bicarbonate solution was added, the aqueous phase discarded, and the organic phase was washed with sodium bicarbonate solution two times, then with distilled water (two times) and finally with brine. The organic phase was dried (magnesium sulphate), filtered, and the solvent was removed using a rotatory evaporator. The residue was distilled under vacuum, unless otherwise noted, to yield the desired alkynyl oxirane.

1-Ethynyl-1-methyloxirane[16] (16a): 12% yield. The low yield is probably due to the moderate solubility of **16a** in water. ^{1}H-NMR (200 MHz) δ = 1.53 ppm (3H, s, CH_3), 2.27 ppm (1H, s, -CC*H*), 2.72 ppm (1H, d, J = 5.6 Hz) and 3.01 ppm (1H, d, J = 5.6 Hz, CH_2).

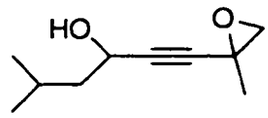
^{13}C-NMR: 22.6 (*C*H$_3$), 46.8 (*C*-CH$_3$), 55.1 (*C*H$_2$), 70.3 (H*C*C-), 83.1 (HC*C*-) ppm. IR (neat): 3277 (C*C*-*H*), 2119 (*C*C) cm^{-1} MS: 82 (M$^+$).



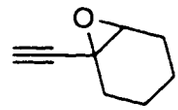
1-(But-1-ynyl)-1-methyloxirane (16b): 25% yield. ^{1}H-NMR (200 MHz) δ = 1.16 ppm (3H, t, J = 7.6 Hz, CH$_2$C*H*$_3$), 1.54 ppm (3H, s, C*H*$_3$), 2.22 ppm (2H, q, J = 7.6 Hz, C*H*$_2$CH$_3$), 2.73 ppm (1H, d, J = 5.5 Hz) and 2.98 ppm (1H, d, J = 5.5 Hz, OC*H*$_2$). ^{13}C-NMR: 12.2 (*C*H$_3$), 13.5 (*C*H$_3$), 23.3 (*C*H$_2$CH$_3$), 47.5 (*C*CH$_3$), 55.5 (O*C*H$_2$), 78.7 (CH$_2$*C*C), 84.3 (C*C*-C) ppm. IR (neat): 3243 (C*C*-*H*), 2210 (*C*C)cm^{-1} MS: 110 (M$^+$). HRMS calc. for C$_7$H$_{10}$O: 110.0732. Found: 110.0744.



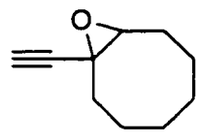
1-(5-Methylhex-1-ynyl)-1-methyloxirane (16c): 50% yield. ^{1}H-NMR (200 MHz) δ = 0.85 ppm (6H, d, J = 6.6 Hz, 2C*H*$_3$), 1.36 ppm (2H, q, J = 7.5 Hz, C*H*$_2$CH), 1.50 ppm (3H, s, C*H*$_3$), 1.61 ppm (1H, m, C*H*), 2.16 ppm (2H, t, J = 7.5 Hz, C*H*$_2$CC), 2.69 ppm (1H, d, J = 5.5 Hz) and 2.94 ppm (1H, d, J = 5.5 Hz, OC*H*$_2$). ^{13}C-NMR: 16.6 (*C*H$_3$), 22.1 (2*C*H$_3$), 23.3 (*C*H$_2$), 27.1 (*C*H$_2$), 37.3 (*C*H), 47.5 (*C*CH$_3$), 55.5 (O*C*H$_2$), 79.2 (CH$_2$*C*C), 83.1 (C*C*-C) ppm. IR (neat): 2231 (*C*C) cm^{-1} MS: 152 (M$^+$). Anal. Calc. for C$_{10}$H$_{16}$0: C, 78.90; H, 10.59. Found: C, 78.93; H, 10.98.



1-(3-Hydroxy-5-methylhex-1-ynyl)-1-methyloxirane (16d): 32% yield. ^{1}H-NMR (200 MHz) δ = 0.89 ppm (3H, d, J = 6.6 Hz, C*H*$_3$), 0.91 ppm (3H, d, J = 6.6 Hz, C*H*$_3$), 1.50 ppm (3H, s, C*H*$_3$), 1.50-1.86 ppm (4H, m, C*H*C*H*$_2$, O*H*), 2.73 ppm (1H, d, J = 5.5 Hz) and 2.98 ppm (1H, d, J = 5.5 Hz, OC*H*$_2$), 4.39 ppm (1H, t, J = 7.2 Hz, C*H*OH). ^{13}C-NMR: 22.3 (*C*H$_3$), 22.6 (*C*H$_3$), 22.9 (*C*H$_3$), 24.7 (*C*H$_2$), 46.6 (*C*H), 47.2 (*C*CH$_3$), 55.4 (O*C*H$_2$), 60.8 (O*C*H), 83.4 and 84.0 (*CC*) ppm. IR (neat): 3393 (*OH*) cm^{-1} MS: 168 (M$^+$). Anal. Calc. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.48; H, 9.85.



1-Ethynyl-1-oxabicyclo[4-1-0]heptane[4] (16e): 65% yield. ^{1}H-NMR (200 MHz) δ = 1.33 ppm (4H, m) and 1.98 ppm (4H, m, (C*H*$_2$)$_4$), 2.29 ppm (1H, s, CC*H*), 3.33 ppm (1H, m, OC*H*). ^{13}C-NMR: 18.8 (*C*H$_2$), 19.3 (*C*H$_2$), 24.0 (*C*H$_2$), 29.4 (*C*H$_2$), 49.8 (*C*--CC), 59.7 (O*C*H), 70.15 (C*C*H), 84.24 (*C*CH) ppm. IR (neat): 3230 (C*C*-*H*), 2110 (*CC*) cm^{-1} MS: 122 (M$^+$).



1-Ethynyl-1-oxabicyclo[6-1-0]nonane[26] (16f): 56% yield. ^{1}H-NMR (200 MHz) δ = 1.10–1.90 ppm (10H, m) and 2.16 ppm (2H, m, (C*H*$_2$)$_6$), 2.26 ppm (1H, s, CC*H*), 3.07

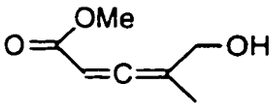
ppm (1H, dd, J = 10.6 and 4.4 Hz, OC*H*). ^{13}C-NMR: 25.1 (*C*H_2), 25.6 (*C*H_2), 26.0 (*C*H_2), 26.3 (*C*H_2), 26.9 (*C*H_2), 30.2 (*C*H_2), 53.3 (*C*--CC), 63.4 (O*C*H), 70.6 (C*C*H), 83.4 (*C*CH) ppm. IR (neat): 3280 (C*C-H*), 2116 (*CC*) cm^{-1} MS: 150 (M^+).

3.4.2 Carbonylation of alkynyl oxiranes 16a-f catalyzed by $(MePh_2P)_4Pd$

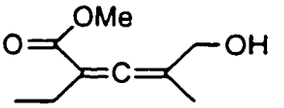
In a 45 ml stainless steel autoclave equipped with a magnetic stirring bar, 0.8 mmol of the alkynyl oxirane was mixed with 10 ml of dry, oxygen free methanol. To this solution was added 0.008 mmol of the catalyst. The autoclave was closed and purged twice with carbon monoxide by pressurizing to 100 psi and releasing the gas consecutively. Then the autoclave was pressurized to 300 psi of carbon monoxide, and the mixture was stirred for two hours at room temperature. The reaction was stopped, the gas was released and the solution was filtered through a short Florisil® column (silica gel and aluminum oxide slowly decompose the allene product). The solvent was removed by rotatory evaporation. Column chromatography of the crude mixture was performed by using Florisil® as the stationary phase and hexane/EtOAc 95/5 as the eluant. After 60 ml of the eluant was used, 80 ml of hexane/EtOAc 60/40 was passed through the column. Evaporation of this last fraction gave the desired product.

3.4.3 Carbonylation of 16a catalyzed by other systems

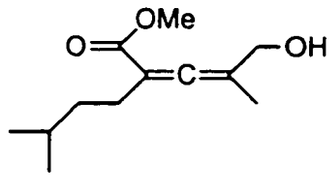
General procedure: 0.8 mmol of **16a**, 0.004 mmol of $Pd_2(dba)_3.CHCl_3$, 0.008 mmol of a bidentate phosphine ligand or 0.016 mmol of Ph_3P and 10 ml of methanol were placed in an autoclave. The autoclave was pressurized to 300 psi of carbon monoxide and the mixture was stirred for 24 h. The reaction was worked up as described before.



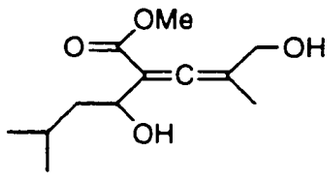
Methyl 5-hydroxy-4-methyl-2,3-pentadienoate (17a): 70% yield. ^{1}H-NMR (200 MHz) δ = 1.78 ppm (3H, d, J = 2.75 Hz, C*H*$_3$), 3.30 ppm (1H, br, O*H*), 3.67 ppm (3H, s, OC*H*$_3$), 4.08 ppm (2H, d J = 2.75 Hz, C*H*$_2$OH), 5.59 ppm (1H, sext, J = 2.75 Hz, C*H*). ^{13}C-NMR: 14.4 (*C*H$_3$), 52.0 (O*C*H$_3$), 63.0 (*C*H$_2$OH), 88.4 (H*C*=C=C), 105.5 (HC=C=*C*), 167.1 (*C*=O), 209.5 (C=*C*=C) ppm. IR (neat): 1712 (C=O), 1965 (C=C=C), 3417 (OH) cm^{-1} MS: 142 (M$^+$). HRMS calc. for $C_7H_{10}O_3$: 142.0630. Found: 142.0639.



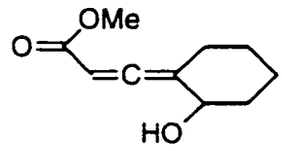
Methyl 2-ethyl-5-hydroxy-4-methyl-2,3-pentadienoate (17b): 74% yield. ^{1}H-NMR (200 MHz) δ = 1.01 ppm (3H, t, J = 7.4 Hz, CH$_2$C*H*$_3$), 1.83 ppm (3H, s, C*H*$_3$), 2.10 ppm (1H, br, O*H*), 2.24 ppm (2H, q, J = 7.4 Hz, C*H*$_2$CH$_3$), 3.72 ppm (3H, s, OC*H*$_3$), 4.14 ppm (2H, s, C*H*$_2$OH). ^{13}C-NMR: 12.5 (*C*H$_3$), 14.9 (*C*H$_3$), 21.9 (*C*H$_2$), 51.9 (O*C*H$_3$), 63.5 (*C*H$_2$OH), 103.1 and 105.4 (*C*=C=*C*), 168.2 (*C*=O), 206.1 (C=*C*=C) ppm. IR (neat): 1703 (C=O), 1960 (C=C=C), 3406 (OH) cm^{-1} MS: 170 (M$^+$). HRMS calc. for $C_9H_{14}O_3$: 170.0943. Found: 170.0935.



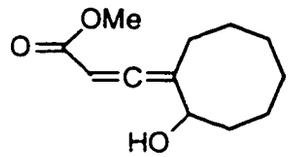
Methyl 2-(3-hydroxy-2-methylpropenylidene)-5-methylhexanoate (17c): 78% yield. ^{1}H-NMR (200 MHz) δ = 0.89 ppm (6H, d, J = 6.6 Hz, 2C*H*$_3$), 1.28 ppm (2H, q, J = 7.5 Hz, C*H*$_2$CH), 1.58 ppm (1H, m, C*H*), 1.81 ppm (4H, s, C*H*$_3$ and O*H*), 2.23 ppm (2H, t, J= 7.5 Hz, C*H*$_2$C), 3.72 ppm (3H, s, OC*H*$_3$), 4.12 ppm (2H, s, C*H*$_2$OH). ^{13}C-NMR: 15.0 (*C*H$_3$), 22.5 (2*C*H$_3$), 26.7 (*C*H$_2$), 27.5 (*C*H$_2$), 37.2 (*C*H), 52.1 (O*C*H$_3$), 63.7 (*C*H$_2$OH), 102.2 and 104.8 (*C*=C=*C*), 168.1 (*C*=O), 206.1 (C=*C*=C) ppm. IR (neat): 1705 (C=O), 1961 (C=C=C), 3409 (OH) cm^{-1}. MS: 212 (M$^+$). HRMS calc. for $C_{12}H_{20}O_3$: 212.1412. Found: 212.1408.



Methyl 2-(3-hydroxy-2-methylpropenylydene)-3-hydroxy-5-methylhexanoate (17d): 55% yield. ^{1}H-NMR (200 MHz) δ = 0.90 ppm (6H, d, J = 6.1 Hz, (C*H*$_3$)$_2$CH), 1.46 ppm (2H, m, C*H*$_2$CH), 1.75 ppm (1H, m, (CH$_3$)$_2$C*H*), 1.80 and 1.82 ppm (3H, 2s, C*H*$_3$), 3.10 ppm (1H, br, O*H*), 3.73 ppm (3H, s, OC*H*$_3$), 4.11 and 4.13 ppm (2H, 2s, C*H*$_2$OH), 4.43 and 4.52 (1H, 2dq, J= 8.1 and 5.5 Hz, C*H*OH). ^{13}C-NMR: 14.6 and 14.7 (*C*H$_3$), 21.9 and 22.1 (2*C*H$_3$), 22.9 and 23.0 (*C*H$_3$), 24.6 and 24.7 (*C*H$_2$), 44.7 and 44.8 (*C*H(CH$_3$)$_2$), 52.0 and 52.1 (O*C*H$_3$), 62.8 and 63.1 (*C*H$_2$OH), 67.0 and 68.4 (*C*HOH), 104.5, 105.8, 106.7 and 108.0 (*C*=C=*C*), 167.5 and 167.7 (*C*=O), 205.2 and 205.4 (C=*C*=C) ppm. IR (neat): 1705 (C=O), 1961 (C=C=C), 3370 (OH) cm^{-1} MS: 228 (M$^+$).



Methyl 3-(2-hydroxycyclohexylidene)-propenoate (17e): 90% yield. ^{1}H-NMR (200 MHz) δ = 1.10–2.20 ppm (7H, m) and 2.40 ppm (1H, m) (CH_2)$_4$, 2.90 ppm (1H, br, O*H*), 3.73 ppm (3H, s, OCH_3), 4.23 ppm (1H, m, C*H*OH), 5.73 ppm (1H, dt, J = 2.8 Hz and 1.1 Hz, CC*H*). ^{13}C-NMR: 23.2 (CH_2), 26.1 (CH_2), 28.7 (CH_2), 35.1 (CH_2), 51.9 (OCH_3), 68.7 (*C*HOH), 89.8 (H*C*=C=C), 112.4 (HC=C=*C*), 167.0 (*C*=O), 205.9 (C=*C*=C) ppm. IR (neat): 1721 (C=O), 1964 (C=C=C), 3405 (OH) cm^{-1} MS: 182 (M^+). HRMS calc. for $C_{10}H_{14}O_3$: 182.0943. Found: 182.0951.

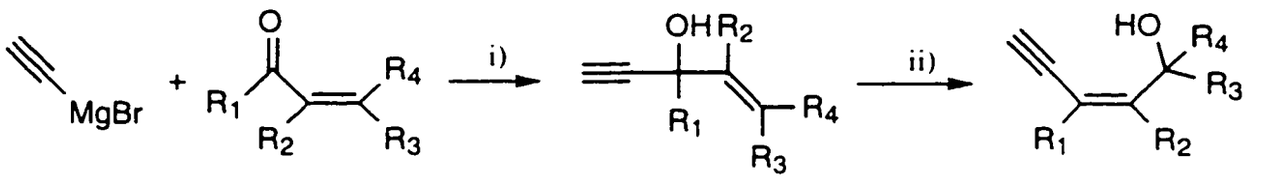


Metyhl 3-(2-hydroxycyclooctylidene)-propenoate (17f): 94% yield. ^{1}H-NMR (200 MHz) δ = 1.40–2.10 ppm (11H, m) and 2.31 ppm (2H, m) (CH_2)$_6$ and O*H*, 3.73 ppm (1H, s, OCH_3), 4.37 ppm (1H, m, C*H*OH), 5.66 ppm (1H, q, J = 1.6 Hz, CC*H*). ^{13}C-NMR: 22.6 (CH_2), 25.3 (CH_2), 25.4 (CH_2), 26.8 (CH_2), 28.4 (CH_2), 32.4 (CH_2), 51.9 (OCH_3), 71.9 (*C*HOH), 88.6 (H*C*=C=C), 113.1 (HC=C=*C*), 167.0 (*C*=O), 211.0 (C=*C*=C) ppm. IR (neat): 1720 (C=O), 1954 (C=C=C), 3423 (OH) cm^{-1} MS: 210 (M^+). HRMS calc. for $C_{12}H_{18}O_3$: 210.1256. Found: 210.1245.

3.4.4 Synthesis of alkynyl oxiranemethanol derivatives 20a-f

The preparation of **20a-f** was carried out by epoxidation of the corresponding alk-2-en-4-yn-1-ol precursors **37** by the same procedure used in section 3.4.2. With the exception of the precursor of **20a**, which was purchased from Aldrich, the unsaturated alcohols were prepared following Scheme 21[29].

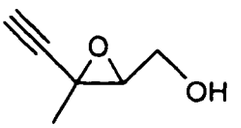
The *cis-trans* ratio could be determined by measuring the coupling constant between R_1 and R_2 for R_1= R_2= H, the chemical shift of the proton attached to the *sp* carbon and the proton chemical shift when R_3= H.



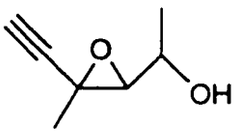
i) 1) ether 2) NH_4Cl
ii) H_2SO_4 (50%), ether

37

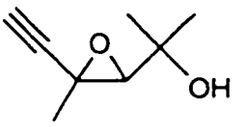
Scheme 21



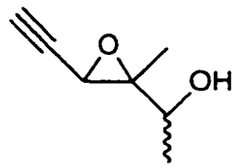
(2-Ethynyl-2-methyloxirane)methanol[22] **(20a):** 40% yield. ^{1}H-NMR (200 MHz) δ = 1.60 ppm (3H, s, C*H*$_3$), 2.15 ppm (1H, br, O*H*), 2.43 ppm (1H, s, CC*H*), 3.13 ppm (1H, dd, J = 6.0 and 4.8 Hz, C*H*), 3.81 ppm (1H, dd, J = 13.0 and 5.9 Hz) and 3.93 ppm (1H, dd, J = 13.0 and 4.9 Hz).^{13}C-NMR: 23.0 (*C*H$_3$), 51.5 (*C*CH$_3$), 62.3 (*C*H$_2$), 63.7 (*C*HO), 73.1 (C*C*H), 80.7 (*C*CH) ppm. IR (neat): 3214 (OH), 2118 (CC) cm^{-1} MS: 112 (M$^+$).



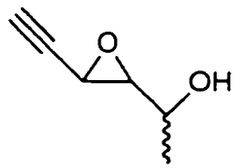
1-(2-Ethynyl-2-methyloxirane)ethanol (20b): 56% yield. ^{1}H-NMR (200 MHz) d = 1.30 ppm (3H, d, J = 6.2 Hz, C*H*$_3$CH), 1.54 ppm (3H, s, C*H*$_3$), 2.10 ppm (1H, br, O*H*), 2.38 ppm (1H, s, CC*H*), 2.81 ppm (1H, d, J = 8.0 Hz, OC*H*), 3.78 ppm (1H, dq, J = 8.0 and 6.2 Hz, C*H*OH).^{13}C-NMR: 18.1 (*C*H$_3$), 22.8 (*C*H$_3$), 51.3 (*C*CH$_3$), 67.7 and 67.9 (O*C*H, *C*HOH), 72.7 (C*C*H), 76.1 (*C*CH) ppm. IR (neat): 3405 (OH), 3285 (CC-H), 2121 (CC) cm^{-1} MS: EI: 109 (M^{+}– 17), CI: 127 (M^{+}+ 1). Anal. Calc. for $C_7H_{10}0_2$: C, 66.65; H, 7.99. Found: C, 66.38; H, 8.28.



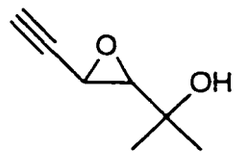
1-(2-Ethynyl-2-methyloxirane)-1-methylethanol (20c): 67% yield. ^{1}H-NMR (200 MHz) δ = 1.33 ppm (3H, s, C*H*$_3$), 1.35 ppm (3H, s, C*H*$_3$), 1.55 ppm (3H, s, C*H*$_3$), 2.19 ppm (1H, s, O*H*), 2.55 ppm (1H, s, CC*H*), 2.81 ppm (1H, s, OC*H*).^{13}C-NMR: 24.4 (*C*H$_3$), 25.5 (*C*H$_3$), 28.2 (*C*H$_3$), 50.2 (*C*CH$_3$), 68.1 (*C*OH), 70.7 (O*C*H), 75.9 (C*C*H), 81.0 (*C*CH) ppm. IR (neat): 3439 (OH), 3282 (CC-H), 2116 (CC) cm^{-1} MS: EI: 109 (M^{+}– 31). CI: 141 (M^{+}+ 1). Anal. Calc. for $C_8H_{12}0_2$: C, 68.55; H, 8.63. Found: C, 68.23; H, 8.51.



***cis* and *trans*-1-(2-Ethynyl-3-methyloxirane)ethanol (20d):** 60% yield. ^{1}H-NMR (200 MHz) δ = 1.23 ppm (3H, d, J= 6.2 Hz) and 1.25 ppm (3H, d, J= 6.2 Hz) (CHC*H*$_3$), 1.42 ppm (3H, s) and 1.43 ppm (3H, s) (C*H*$_3$), 2.02 ppm (2H, br, 2O*H*), 2.39 ppm (2H, m, 2CC*H*), 3.49 ppm (1H, d, J= 1.6 Hz) and 3.53 ppm (1H, d, J= 1.7 Hz) (OC*H*), 3.59 ppm (1H, q, J= 6.2 Hz) and 3.84 ppm (1H, q, J= 6.2 Hz) (C*H*OH) ^{13}C-NMR: 13.6 and 15.3 (*C*H$_3$), 18.4 and 19.0 (*C*H$_3$), 46.6 and 48.8 (O*C*H), 65.5 and 66.6 (*C*CH$_3$), 67.5 and 69.8 (*C*HOH), 74.2 and 74.3 (C*C*H), 78.8 and 78.9 (*C*CH) ppm. IR (neat): 3435 (OH), 3284 (CC-H), 2123 (CC) cm^{-1} MS: EI: 109 (M^+– 17), CI: 127 (M^++ 1).



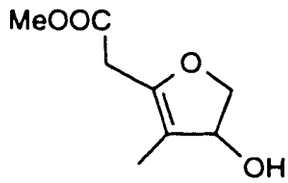
1-(2-Ethynyloxirane)-ethanol (20f): 46% yield. The epoxidation product was a mixture of three diastereomers, making the NMR spectra quite difficult to interpret. ^{1}H-NMR (200 MHz) δ = 1.27 ppm (m), 2.22 ppm (br), 2.33 and 2.37 ppm (2d), 2.99 ppm (dd, J = 7.9 and 4.1 Hz), 3.15 ppm (m), 3.35 ppm (t, J = 2.0), 3.41 ppm (m), 3.50 ppm (dd, J = 4.2 and 1.8 Hz), 3.72 ppm (m), 3.98 ppm (dq, J = 6.5 and 2.7 Hz).^{13}C-NMR: 18.3, 18.4, 19.8, 41.4, 43.0, 44.0, 61.4, 42.9, 63.4, 63.9, 66.1, 68.1, 72.5, 74.4, 79.5 ppm. IR (neat): 3411 (OH), 3287 (CC-H), 2124 (CC) cm^{-1} MS: EI: 95 (M^+– 17), CI: 113 (M^+ + 1). Anal. Calc. for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.25; H, 6.79.



1-(2-Ethynyloxirane)-1-methylethanol (20f): 51% yield. ^{1}H-NMR (200 MHz) δ = 1.25 ppm (3H, s, C*H*$_3$), 1.29 ppm (3H, s, C*H*$_3$), 1.70 ppm (1H, br, O*H*), 2.32 ppm (1H, d, J = 1.4 Hz, CC*H*), 3.10 ppm (1H, d, J = 2.3 Hz, C*H*C(CH$_3$)$_2$), 3.41 ppm (1H, dd, J = 2.3 and 1.4 Hz, CC-C*H*). ^{13}C-NMR: 24.8 (*C*H$_3$), 27.5 (*C*H$_3$), 42.2 (CC-*C*H), 65.9 (*C*HC(CH$_3$)$_2$), 67.4 (*C*OH), 72.5 (C*C*H), 79.9 (*C*CH) ppm. IR (neat): 3442 (OH), 3287 (CC-H), 2124 (CC) cm^{-1} MS: EI: 109 (M^{+}– 17), CI: 127 (M^{+}+ 1). Anal. Calc. for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.80; H, 8.30.

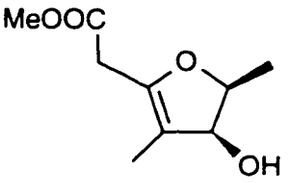
3.4.5 Carbonylation of alkynyloxirane methanol derivatives 20a-f

The carbonylation of **20a-f** and purification of the products were carried out by the same procedure described in section 3.4.3.

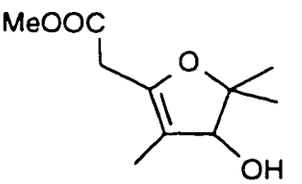


Methyl (4-hydroxy-3-methyl-4,5-dihydrofuran-2-yl)-acetate (21a): 81% yield. ^{1}H-NMR (200 MHz) δ = 1.72 ppm (3H, s, C*H*$_3$), 3.14 ppm (1H, d, J = 8 Hz, O*H*), 3.21 ppm (2H, s, C*H*$_2$CO$_2$Me), 3.72 ppm (3H, s, OC*H*$_3$), 4.18 ppm (1H, dd, J = 10.5 and 3.0 Hz) and 4.26 ppm (1H, dd, J = 10.5 and 6.9 Hz) (C*H*$_2$O), 4.71 ppm (1H, m, C*H*OH).^{13}C-NMR: 8.8 (*C*H$_3$), 32.0 (*C*H$_2$CO$_2$Me), 52.2 (OC*H*$_3$), 76.2 and 77.4 (OCH$_2$*C*HOH), 109.5

(CCH_3), 147.5 (CCH_2), 170.0 (C=O) ppm. IR (neat): 3400 (OH), 1727 (C=O) cm^{-1} MS: 154 (M^+). Anal. Calc. for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.94; H, 6.69.

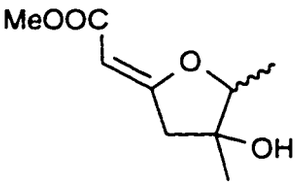


***cis*-Methyl (4-hydroxy-3,5-dimethyl-4,5-dihydrofuran-2-yl)-acetate (21b):** 49% yield. ^{1}H-NMR (200 MHz) δ = 1.32 ppm (3H, d, J = 7.2 Hz), 1.67 ppm (3H, s), 2.40 ppm (1H, br), 3.14 ppm (2H, s), 3.66 ppm (3H, s), 4.29 ppm (1H, quint, J = 7.2 Hz), 4.35 ppm (1H, d, J = 7.2 Hz).^{13}C-NMR: 9.3 (CH_3), 13.2 (CH_3), 32.0 (CH_2), 52.2 (OCH_3), 78.2 and 80.1 ($CHOH$,$CHCH_3$), 110.2 (CCH_3), 147.8 (CCH_2), 170.0 (C=O) ppm. IR (neat): 3415 (OH), 1726 (C=O) cm^{-1} MS: 186 (M^+). HRMS calc. for $C_9H_{14}O_4$: 186.0892. Found: 186.0897.



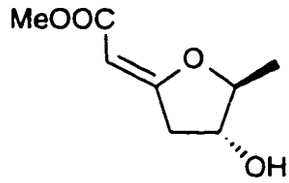
Methyl (4-hydroxy-3,5,5-trimethyl-4,5-dihydrofuran-2-yl)-acetate (21c): 91% yield. ^{1}H-NMR (200 MHz) δ = 1.22 ppm (3H, s, CH_3), 1.31 ppm (3H, s, CH_3), 1.67 ppm (3H, s, CH_3), 1.80 ppm (1H, br, OH), 3.12 ppm (2H, s, CH_2), 3.67 ppm (3H, s, OCH_3), 4.08 ppm (1H, d, J = 8.6 Hz, $CHOH$).^{13}C-NMR: 9.5 (CH_3), 20.6 (CH_3), 26.3 (CH_3), 32.3 (CH_2), 52.1 (OCH_3), 84.0 ($CHOH$), 85.2 ($C(CH_3)_2$), 108.3 (CCH_3), 146.7 (CCH_2), 169.9

(*C*=O) ppm. IR (neat): cm^{-1} MS: 200 (M^+). HRMS calc. for $C_{10}H_{16}O_4$: 200.1048. Found: 200.1047.

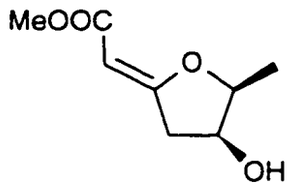


Methyl (4-hydroxy-4,5-dimethyltetrahydrofuran-2-ylydene)-acetate (21d): 74% yield (*cis* and *trans* mixture). a) ^{1}H-NMR (200 MHz) δ = 1.15 ppm (3H, d, J = 6.4 Hz, CHC*H*$_3$), 1.27 ppm (3H, s, C*H*$_3$), 3.00 ppm (1H, dd, J = 18.1 and 1.9 Hz) and 3.27 ppm (1H, dd, J = 18.1 and 1.6 Hz) (C*H*$_2$), 3.08 ppm (1H, br, O*H*), 3.58 ppm (3H, s, OC*H*$_3$), 4.32 ppm (1H, q, J = 6.4 Hz, C*H*CH$_3$), 5.24 ppm (1H, m, C*H*CO$_2$Me). ^{13}C-NMR: 16.1 (*C*H$_3$), 21.6 (*C*H$_3$), 44.8 (*C*H$_2$), 50.7 (O*C*H$_3$), 75.9 (*C*OH), 87.2 (*C*CH$_3$), 90.5 (*C*HCO$_2$Me), 169.2 (*C*=O), 174.4 (C=*C*O) ppm. IR (neat): 1642 (C=C), 1689 (C=O), 3429 (OH) cm^{-1} MS: 186 (M^+).

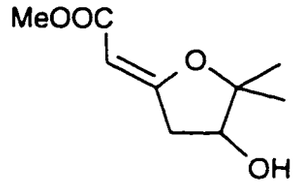
b) ^{1}H-NMR (200 MHz) δ = 1.28 ppm (3H, d, J = 6.4 Hz, CHC*H*$_3$), 1.32 ppm (3H, s, C*H*$_3$), 2.52 ppm (1H, br, O*H*), 2.83 ppm (1H, dd, J = 18.3 and 2.3 Hz) and 3.49 ppm (1H, dd, J = 18.3 and 1.1 Hz) (C*H*$_2$), 3.58 ppm (3H, s, OC*H*$_3$), 4.09 ppm (1H, q, J = 6.4 Hz, C*H*CH$_3$), 5.24 ppm (1H, m, C*H*CO$_2$Me). ^{13}C-NMR: 12.2 (*C*H$_3$), 22.9 (*C*H$_3$), 46.2 (*C*H$_2$), 50.7 (O*C*H$_3$), 77.2 (*C*OH), 86.2 (*C*CH$_3$), 90.3 (*C*HCO$_2$Me), 169.2 (*C*=O), 174.3 (C=*C*O) ppm. IR (neat): 1642 (C=C), 1689 (C=O), 3429 (OH) cm^{-1} MS: 186 (M^+). HRMS calc. for $C_9H_{14}O_4$: 186.0892. Found: 186.0888.



***trans*-Methyl (4-hydroxy-5-methyltetrahydrofuran-2-ylydene)-acetate (21e)-1:** 30% yield (*cis* and *trans* mixture). ^{1}H-NMR (200 MHz) δ = 1.24 ppm (3H, d, J = 6.2 Hz, C*H*$_3$), 1.77 ppm (1H, br, O*H*), 3.06 ppm (1H, ddd, J = 18.5, 5.13 and 2.2 Hz) and 3.50 ppm (1H, d, J = 18.5 Hz) (C*H*$_2$), 3.64 ppm (3H, s, OC*H*$_3$), 4.35 ppm (2H, m, C*H*CH$_3$ and C*H*OH), 5.33 ppm (1H, m, C*H*CO$_2$Me).^{13}C-NMR: 13.3 (*C*H$_3$), 41.1 (*C*H$_2$), 50.8 (O*C*H$_3$), 70.5 (*C*HOH), 83.3 (*C*HCH$_3$), 90.1 (*C*HCO$_2$Me), 169.3 (*C*=O), 174.7 (C=*C*O) ppm. IR (neat): 3439 (OH), 1680 (C=O), 1637 (C=C) cm^{-1} MS: 172 (M$^+$). Anal. Calc. for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.85; H, 6.76.



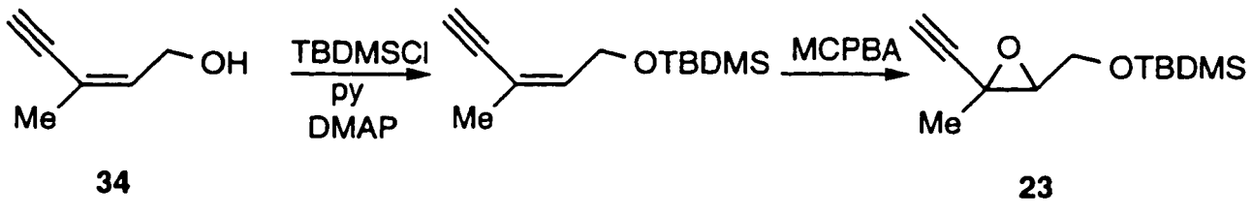
***Cis*-Methyl (4-hydroxy-5-methyltetrahydrofuran-2-ylydene)-acetate (21e)-2:** ^{1}H-NMR (200 MHz) δ = 1.24 ppm (3H, d, J = 6.6 Hz, C*H*$_3$), 2.07 ppm (1H, br, O*H*), 3.26 ppm (2H, dd, J = 4.2 and 1.7 Hz, C*H*$_2$), 3.64 ppm (3H, s, OC*H*$_3$), 4.18 ppm (1H, m, C*H*OH), 4.42 ppm (1H, dq, J = 6.6 and 2.2 Hz, C*H*CH$_3$), 5.33 ppm (1H, m, C*H*CO$_2$Me).^{13}C-NMR: 18.2 (*C*H$_3$), 39.1 (*C*H$_2$), 50.8 (O*C*H$_3$), 74.2 (*C*HOH), 86.3 (*C*HCH$_3$), 90.4 (*C*HCO$_2$Me), 169.3 (*C*=O), 174.5 (C=*C*O) ppm. IR (neat): 3439 (OH), 1680 (C=O), 1637 (C=C) cm^{-1} MS: 172 (M$^+$). Anal. Calc. for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.85; H, 6.76.



Methyl (4-hydroxy-5,5-dimethyltetrahydrofuran-2-ylydene)-acetate (21f): 91% yield. ^{1}H-NMR (200 MHz) δ = 1.24 ppm (3H, s, C*H*$_3$), 1.36 ppm (3H, s, C*H*$_3$), 2.92 ppm (1H, d, J = 4.8 Hz, O*H*), 3.29 ppm (2H, m, C*H*$_2$), 3.60 ppm (3H, s, OC*H*$_3$), 4.06 ppm (1H, q, J = 3.7 Hz, C*H*OH), 5.22 ppm (1H, t, J= 1.8 Hz, C*H*CO$_2$Me).^{13}C-NMR: 20.7 (*C*H$_3$), 25.6 (*C*H$_3$), 40.1 (*C*H$_2$), 50.8 (O*C*H$_3$), 74.7 (*C*HOH), 89.6 (*C*(CH$_3$)$_2$), 90.0 (*C*HCO$_2$Me), 169.4 (*C*=O), 174.1 (C=*C*O) ppm. IR (neat): 3436 (OH), 1695 (C=O), 1637 (C=C) cm^{-1} MS: 186 (M$^+$). HRMS calc. for $C_9H_{14}O_4$: 186.0892. Found: 186.0872.

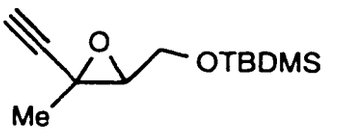
3.4.7 Synthesis and carbonylation of protected alkynyl oxiranemethanol 23

The preparation of **23** was carried out by protection of *trans*-3-methylpent-2-en-4-yn-1-ol (**34**) with *t*-butyldimethylsilyl chloride and epoxidation of the silyl ether by the same procedure as that described in section 3.4.2 (Scheme 22).



34 **23**

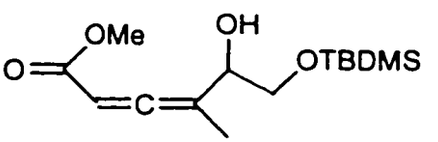
Scheme 22



1-(2-Ethynyl-2-methyloxirane)ethanol, *t*-butyldimethylsilyl ether[27] (23): 67% yield. ^{1}H-NMR (200 MHz) δ = 0.09 ppm (3H, s, $(CH_3)_2Si$), 0.89 ppm (9H, s, $C(CH_3)_3$), 1.55 ppm (3H, s, CH_3), 2.35 ppm (1H, s, CCH), 3.01 ppm (1H, t, J= 15.0 Hz, CH), 3.78 ppm (1H, dd, J = 11.2 and 5.0 Hz) and 3.89 ppm (1H, dd, J = 11.2 and 5.0 Hz)(CH_2).^{13}C-NMR: -5.2 ($(CH_3)_2Si$), 18.3 ($C(CH_3)_3$), 23.0 CH_3, 25.9 ($C(CH_3)_3$), 51.4 (CCH_3), 62.9 (CH_2), 64.2 (CH), 72.8 (CCH), 81.2 (CCH) ppm. IR (neat): 3287 (CC-H), 2123, (CC) cm^{-1} MS: 211 (M^+– 15).

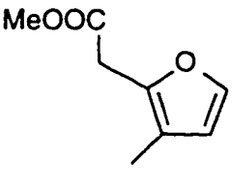
3.4.8 Deprotection of 24[30]

250 mg of **24** (0.78 mmol) were dissolved in 5 ml of THF and treated at 0 °C with tetra-n-butylammonium fluoride (2 eq) for five minutes. The mixture was stirred at room temperature for 40 min. The solvent was evaporated and the residue subjected to column chromatography on Florisil using hexane/EtOAc 95/5 as eluant.



Methyl 5,6-dihydroxy-4-methyl-2,3-hexadienoate mono *t*-butyldimethyl-silyl ether (24): 47% yield. ^{1}H-NMR (200 MHz) δ = 0.06 ppm (3H, s, $(CH_3)_2Si$), 0.88 ppm

(9H, s, $C(CH_3)_3$), 1.83 ppm (3H, d, J= 2.6 Hz, CH_3), 2.70 ppm (1H, br, O*H*), 3.58 ppm (1H, dd, J= 10.0 and 6.8 Hz) and 3.73 ppm (1H, dd, J = 10.0 and 3.9 Hz) (CH_2O), 3.70 ppm (3H, s, OCH_3), 4.18 ppm (1H, m, C*H*OH), 5.62 ppm (1H, quint, J= 2.6 Hz, C=C*H*). ^{13}C-NMR: -5.2 ($(CH_3)_2Si$), 14.6 (CH_3), 18.2 ($C(CH_3)_3$), 25.8 ($C(CH_3)_3$), 51.9 (OCH_3), 65.3 (CH_2), 71.7 (*C*HOH), 88.8 (C=C=*C*H), 104.6 (*C*=C=CH), 166.5 (*C*=O), 209.6 (C=*C*=CH) ppm. IR (neat): 3433 (OH), 1964 (C=C=C), 1715 (C=O) cm^{-1} MS: 286 (M^+). HRMS calc. for $C_{14}H_{26}O_4Si$: 286.16002. Found: 286.15683.



Methyl 2-(3-methylfuranyl)acetate[28] (25): ^{1}H-NMR (200 MHz) δ = 1.97 ppm (3H, s, CH_3), 3.60 ppm (2H, s, CH_2), 3.69 ppm (3H, s, OCH_3), 6.19 ppm (1H, d, J= 2.0 Hz, C*H*), 7.26 ppm (1H, d, J= 2.0 Hz, C*H*O).^{13}C-NMR: 9.7 (CH_3), 32.0 (CH_2), 52.2 (OCH_3), 113.0 (*C*H), 116.9 (CCH_3), 141.1 (O*C*H), 143.1 (CCH_2), 170.1 (*C*=O) ppm. IR (neat): 1741 (C=O) cm^{-1} MS: 154 (M^+).

3.4.9 Synthesis of 35

An oven dried 500 ml round bottom flask was equipped with a magnetic stirring bar, fitted with a rubber septum and flushed with nitrogen. The flask was charged with 400 ml of methylene chloride and 4 g of activated powdered molecular sieves (4Å). The flask was cooled to –23 °C using a CCl_4/dry ice bath. The following liquids were added in sequence by syringe while stirring at –23 °C: 11.88 ml (40 mmol) of titanium isopropoxide, 8.4 ml (40 mmol) of L-diisopropyltartrate; after stirring during 5 minutes, was added 4.16 ml (40 mmol) of *trans*-3-

methylpent-2-en-4-yn-1-ol and 14.6 ml (ca. 80 mmol) of an anhydrous decane solution of TBHP (5-6 M). The resulting solution was stored overnight in a freezer at –21 °C. Then the reaction flask was placed in a CCl_4/dry ice bath and 100 ml of 10% aqueous tartaric acid solution was added while stirring. The aqueous phase solidified. The cooling bath was removed after 30 minutes and the mixture was stirred for 2 hours. The aqueous phase was separated and the organic phase was treated with 10% sodium sulphite until a negative test with starch/iodide paper was obtained. The organic phase was washed with water, then with brine and dried with magnesium sulphate. After filtration and evaporation of the solvent, the residue was passed through a short silica gel column using hexane as eluant to separate the remaining decane. The epoxide was eluted from the column with ethyl acetate. After evaporation of the solvent, the product was distilled in a Kügelrhor apparatus, and was collected as a white solid. 1.47 gr (40% yield) of **35** were obtained. The enantiomeric excess was 47%. The enantiomeric excess was determined by capillary chiral GC, using a Lipodex E column, isothermal run at 90 °C, and 20 psi of the carrier gas (He) (see Figure 2). A small amount of hexane was added to the product, and benzene was added dropwise until all the solid dissolved. The flask was stored in a fridge for a few hours and the solid formed was filtered. The ee of the solid was 60%. After a second recrystallization the enantiomeric excess remained unchanged.

3.4.10 Enantiomeric excess determination of 36

Compound **21a** dehydrates upon injection in the GC. Therefore we determined the % ee by using the NMR chiral shift reagent (+)-$Eu(hfc)_3$ by examining the splitting of the singlet at 1.72 ppm corresponding to the vinylic methyl group (see Figure 2).

3.5 References

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Chapter 4

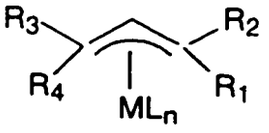
4 Carbonylation of α-allenic alcohols

4.1 Introduction

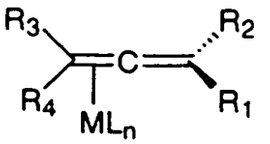
4.1.1 Chemistry of allenes

Reactions of allenes are often quite different from those of the alkenes, due to the presence of the cumulative bond. The development of many synthetic methods for the preparation of allenes makes possible the synthesis of a wide variety of allene derivatives. As a result, the chemistry of these compounds is being thoroughly studied, and many important applications for organic synthesis have been reported[1].

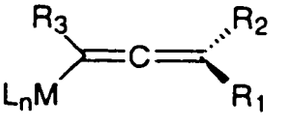
Usually, allenes react with transition metal complexes to form π-allyl **1**, π-η^2-allenyl **2** or σ-η^1-allenyl **3** complexes[2].



1



2



3

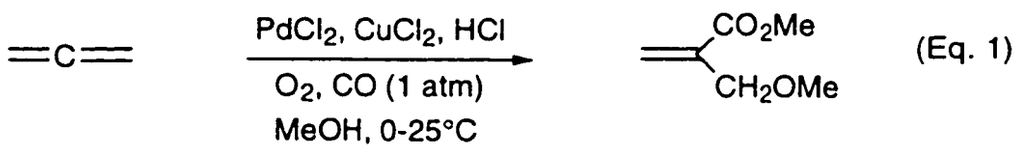
Scheme 1

These complexes have been proposed as intermediates in the transition metal catalyzed reactions of allenes. The transition metal catalyzed carbonylation of allenes enables one to prepare unsaturated carbonyl compounds, which are relevant from the industrial point of view.

4.1.2 Carbonylation of allenes catalyzed by transition metal complexes

During the 1960's several reports appeared on the homogeneous carbonylation and hydroesterification of allenes catalyzed by various metal complexes[3]. These reactions afford unsaturated carboxylic esters and acids in low to moderate yields, and usually require drastic conditions. Later on, much milder procedures were described for the carbonylation of allenes.

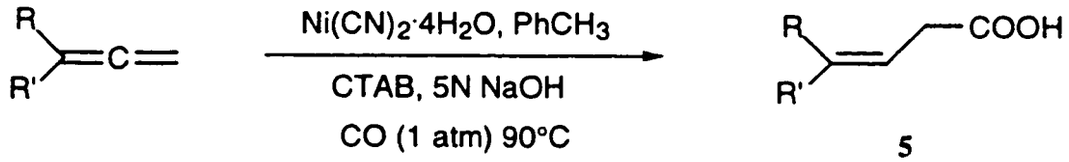
Allenes undergo alkoxy-alkoxycarbonylation to give 2-methoxymethylacrylates **4** in fine yields when treated with carbon monoxide, oxygen, palladium and copper (II) chloride and hydrochloric acid in methanol[4] (Eq 1).



(Eq. 1)

4

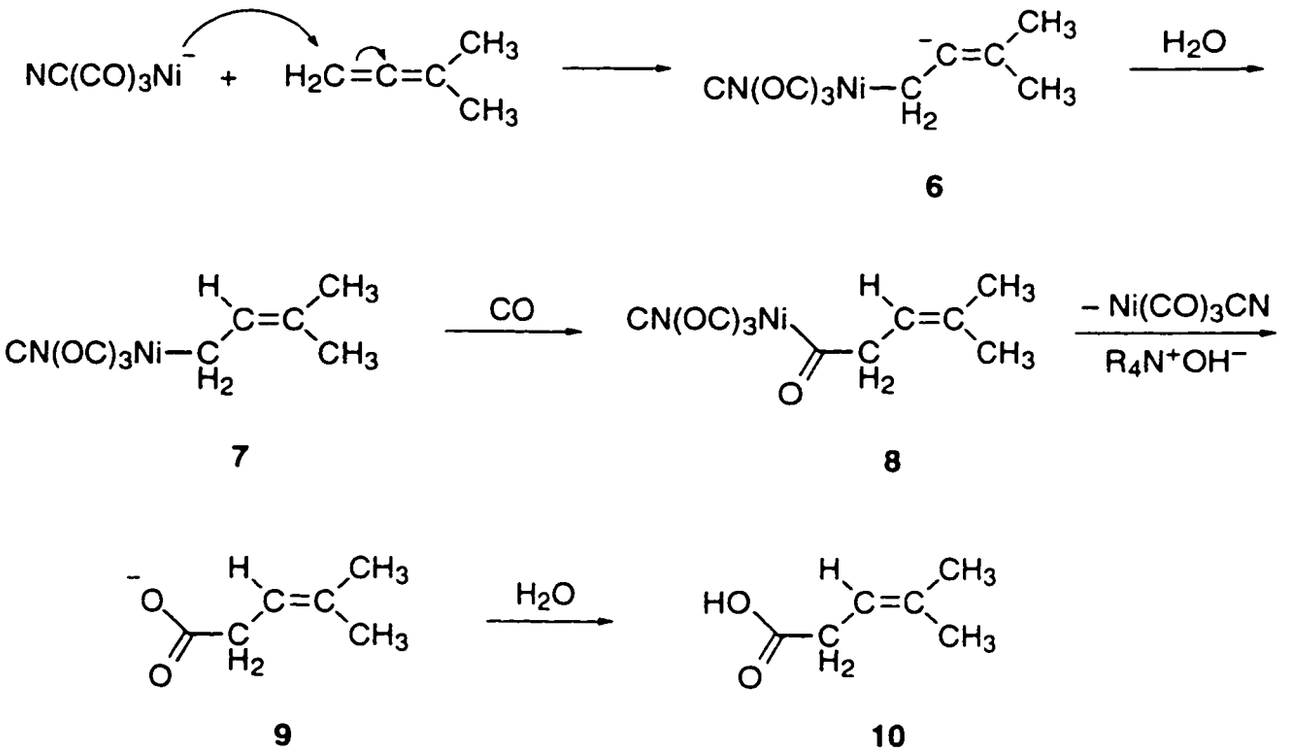
Very mild reaction conditions are used for the carbonylation of allenes under phase transfer catalysis. A nickel cyanide phase transfer system was developed for the regiospecific carboxylation of allenes to form unsaturated carboxylic acids (**5**)[5] (Eq 2).



(Eq. 2)

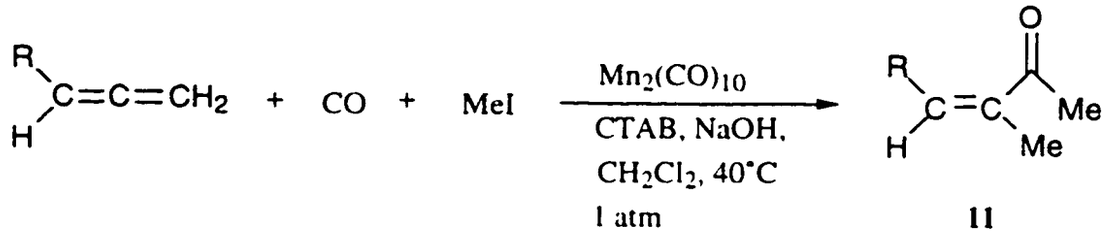
5

A possible mechanism for the reaction is shown in Scheme 2. Cyanotricarbonylnickelate anion, generated *in situ*, attacks the less substituted terminal carbon of the allene to form the vinyl carbanion **6**. In the presence of water the carbanion is protonated to give **7**. Carbon monoxide insertion affords the acylnickel intermediate **8**. Hydroxide induced cleavage of the C-Ni bond generates the anion **9**, which after protonation yields the β,γ-unsaturated carboxylic acid **10**.



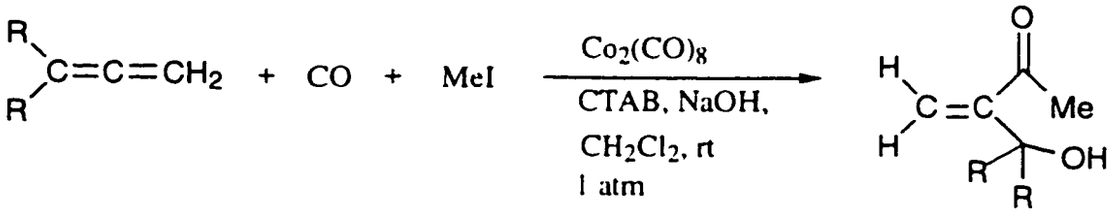
Scheme 2

The use of $Mn_2(CO)_{10}$ and $Co_2(CO)_8$ for the acylation of allenes under PTC conditions has also been developed. When $Mn_2(CO)_{10}$ is used as the catalyst[6], hydroacylation takes place, giving α,β-unsaturated ketones **11** as the product (Eq 3). If $Co_2(CO)_8$ is the catalyst[7], then hydroxyacylation occurs, and the product obtained is a hydroxy ketone (**12**) (Eq 4).



(Eq. 3)

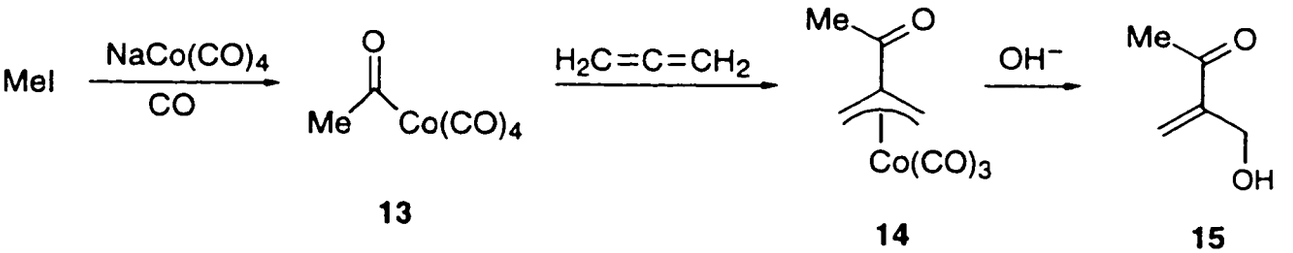
11



(Eq. 4)

12

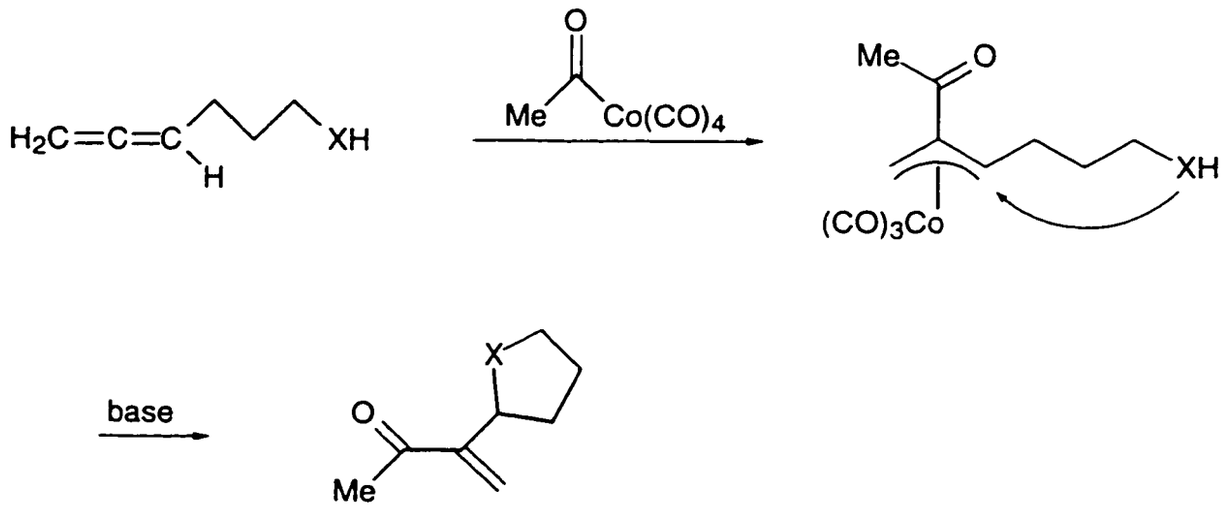
The mechanism proposed for the last reaction is shown in Scheme 3. Reaction of the *in situ* generated $Co(CO)_4^-Na^+$ with MeI and CO gives the acyl cobalt complex **13**. Insertion of the allene forms the allyl-Co complex **14**. Nucleophilic attack by OH^- affords **15**.



13 **14** **15**

Scheme 3

When the allenes bear tethered nucleophiles, intramolecular nucleophilic attack takes place, allowing the preparation of heterocyclic compounds[8] **16** (Scheme 4).

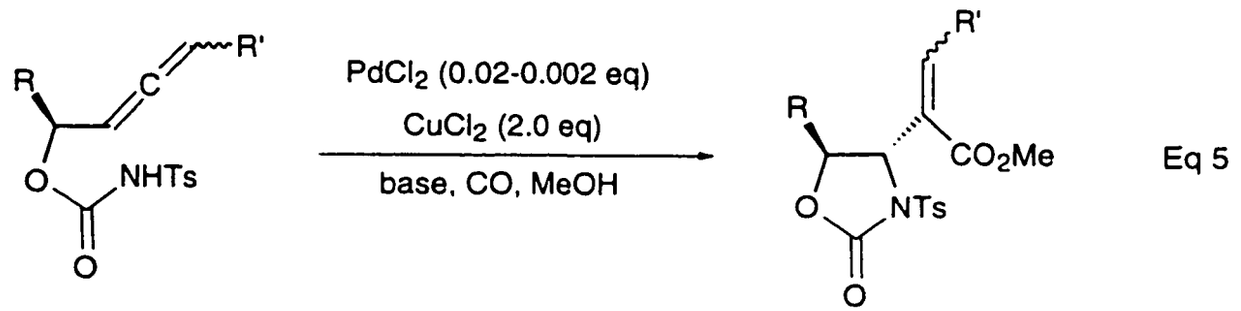


16

X= NTs, O, $CHNO_2$, $C(CO_2Me)_2$

Scheme 4

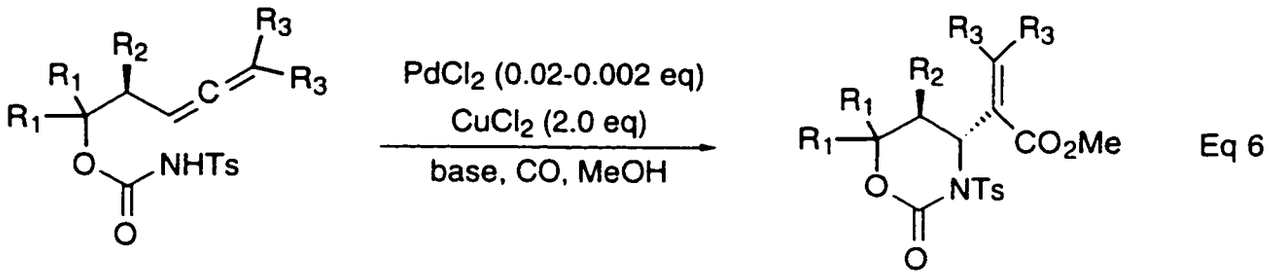
Five and six membered heterocycles **19** and **20** can be prepared by the aminocarbonylation of allenes **17** and **18** using the $PdCl_2/CuCl_2$ system, in the presence of base[9] (Eq 5 and 6).



Eq 5

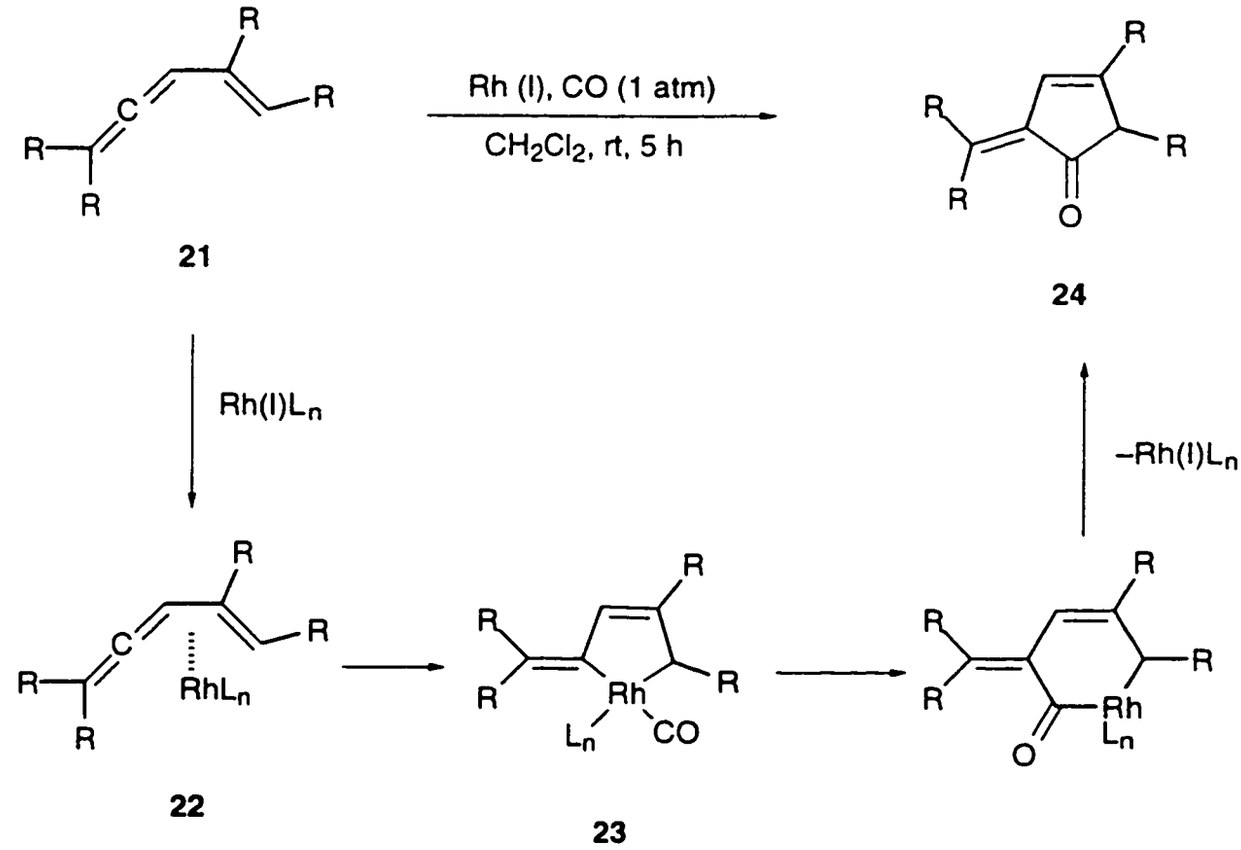
17

19



18 20 Eq 6

Vinyl allenes **21** undergo carbonylative [4+1] cycloaddition when treated with Rh (I) complexes and carbon monoxide[10]. The reaction involves the formation of a (η^4-vinylallene)Rh (I) intermediate **22** (Scheme 5). In the presence of carbon monoxide complex **22** forms a rhodacyclo-3-pentene intermediate **23**, which after carbonyl insertion and reductive elimination gives the unsaturated cyclopentanone **24**.

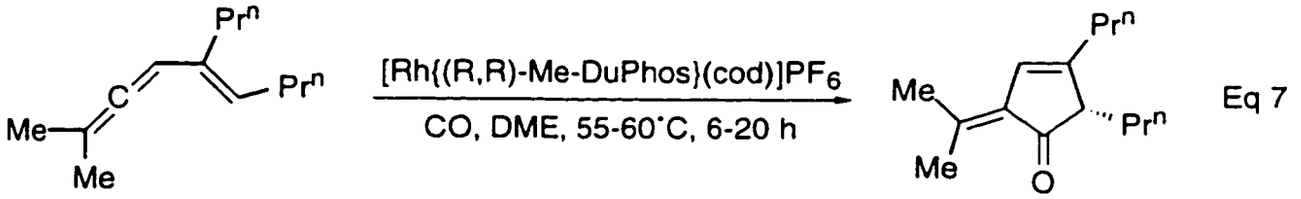


21 24

22 23

Scheme 5

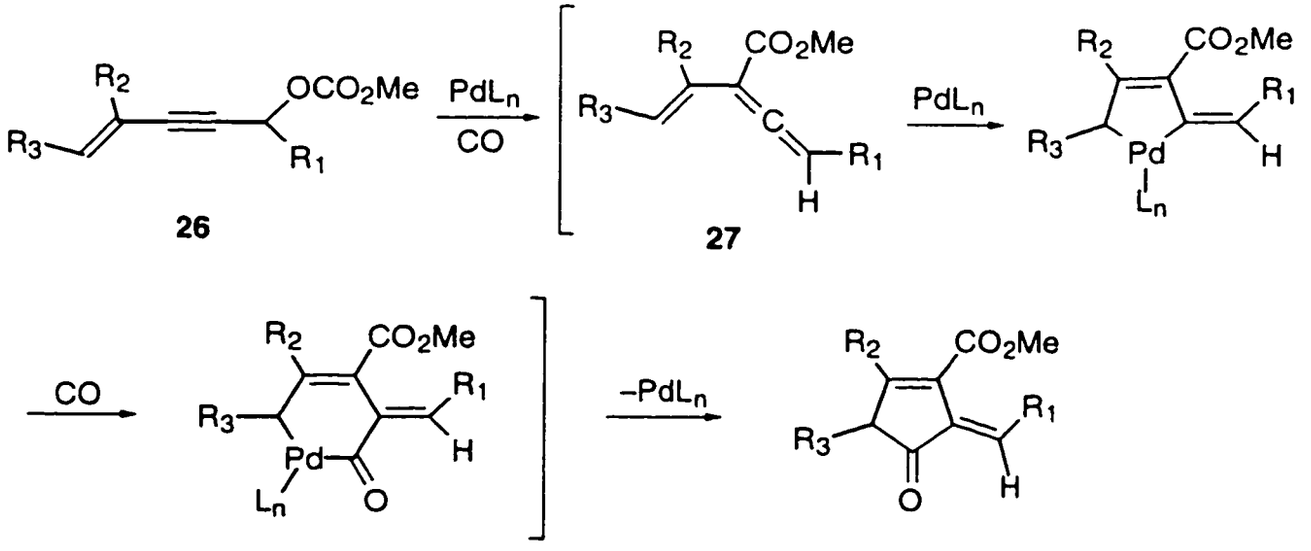
When the reaction is carried out in the presence of chiral phosphine ligands[11], asymmetric induction takes place and the cyclic ketone **25** is formed in moderate ee's (Eq 7).



Eq 7

25

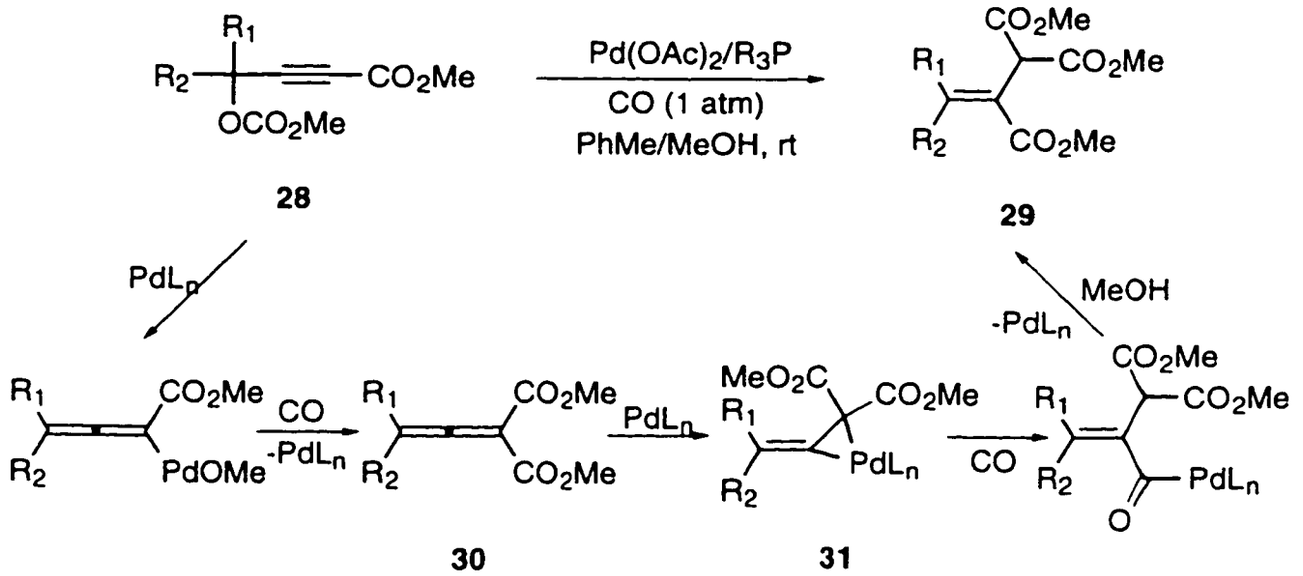
The same type of cyclic compounds are obtained by the double carbonylation of 4-ene-2-ynyl methyl carbonates[12] **26** (Scheme 6). The first carbonylation gives an α-allenyl β-vinyl ester **27**, which can not be isolated. This intermediate undergoes [4+1] cycloaddition with carbon monoxide catalyzed by the Pd(0) complex, following the same mechanism shown for the Rh (I) catalyst.



26 **27**

Scheme 6

Carbonylation of the allenyl intermediate **30** is believed to be responsible for the formation of triesters **29**, in the carbonylation of 1-substituted-3-methoxycarbonyl-2-propynyl methyl carbonates[13] (Scheme 7). A palladacyclopropane intermediate **31** is proposed as a key step in the reaction.

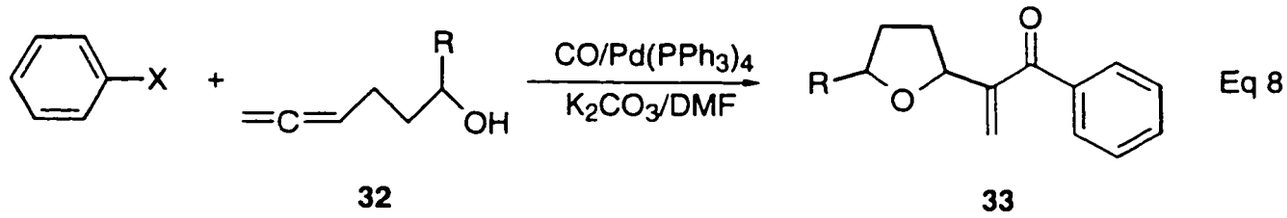


Scheme 7

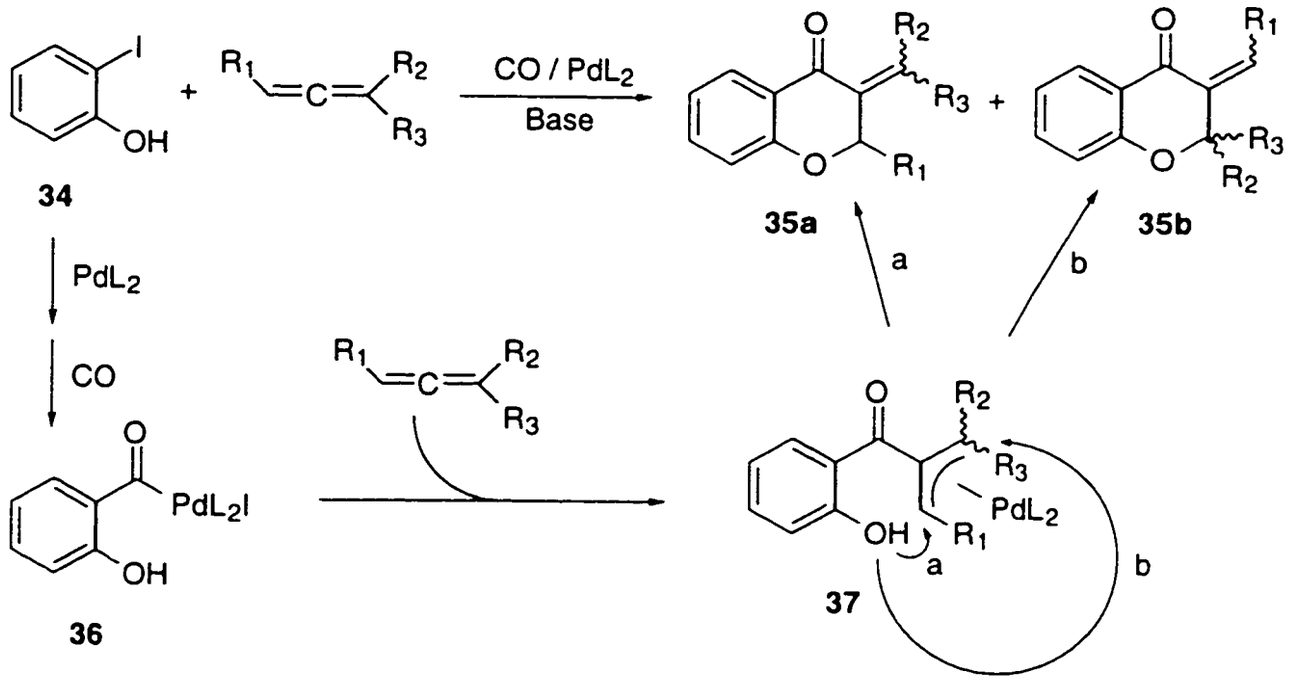
Oxidative addition of Pd(0) complexes into carbon-halogen bonds in the presence of carbon monoxide gives acylpalladium intermediates. If an allene is added to the reaction, it can easily insert into the acyl-Pd bond, affording unsaturated ketones. The reaction of aryl halides with carbon monoxide and γ-hydroxy allenes **32** gives heterocyclic unsaturated ketones[14] **33** (Eq 8).

Following the same protocol, the reaction of o-hydroxyiodobenzene **34** derivatives[15] with allenes affords 1-benzopyran-4-one compounds (**35a** and **35b**). The reaction probably follows the pathway shown in Scheme 8. Oxidative addition of the Pd(0) complex into the C-I

bond, followed by carbonyl insertion gives the aroylpalladium intermediate **36**. Reaction of the latter with the allene affords a π-allylpalladium complex **37**.



32 **33** Eq 8



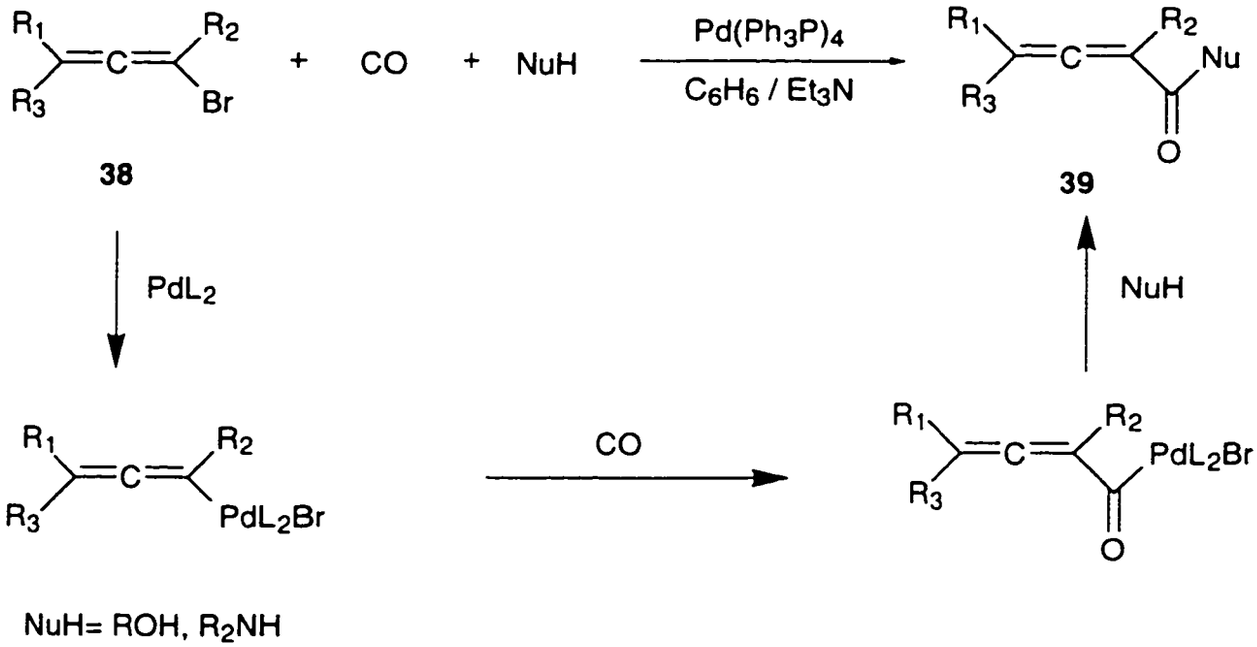
34 **35a** **35b** **36** **37**

Scheme 8

Intramolecular nucleophilic attack by the OH group to any of the allylic positions affords the product.

1-Bromoallenes **38** undergo carbonylation without modifying the cumulative double bonds[16]. Reaction with carbon monoxide catalyzed by a Pd complex in the presence of

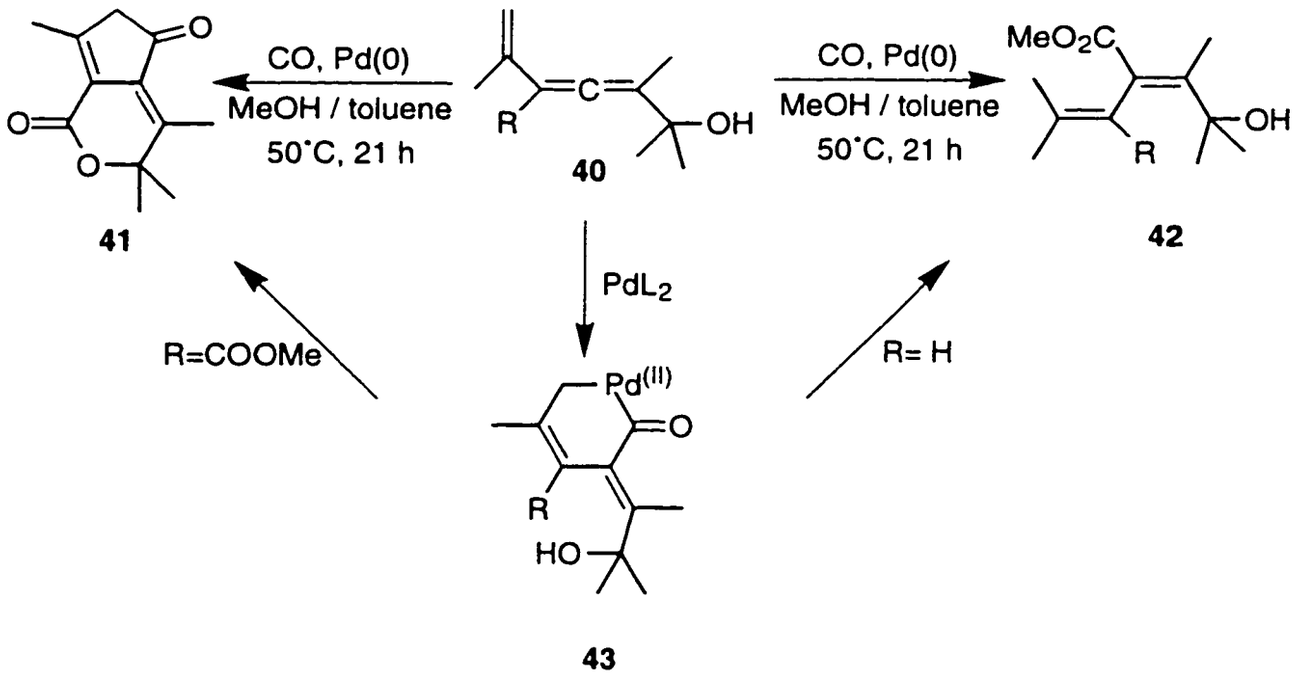
triethylamine affords α-allenic esters and amides **39** (Scheme 9). The reaction starts with an oxidative addition of the Pd(0) complex into the C-Br bond, followed by carbonyl insertion and attack by a nucleophile to form the product.



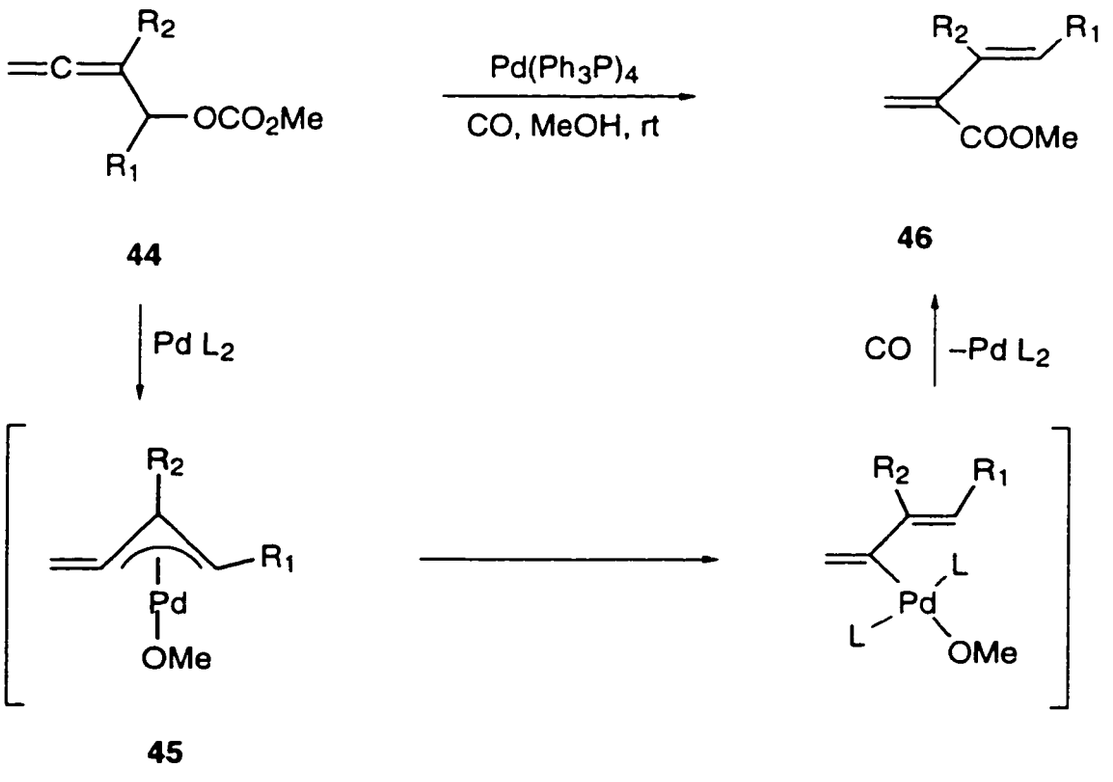
Scheme 9

α-Allenic alcohols containing a conjugated double bond (**40**) are carbonylated in the presence of a Pd (0) catalyst[17] (Scheme 10). Formation of intermediate **43** would take place, and depending on the substitution pattern of the substrate, the cyclic (**41**) or acyclic (**42**) products are formed.

Reaction of α-allenyl carbonates **44** with carbon monoxide catalyzed by Pd(0) complexes involves the S_N2' attack of Pd at the central carbon of the allene, the carbonate being the leaving group[18] (Scheme 11). The release of carbon dioxide is the driving force for the reaction. The allylpalladium compound **45**, where the allyl group is directly connected to the double bond, is proposed as the intermediate. Carbon monoxide insertion and reductive elimination gives the methyl 1,3-dien-2-carboxylate **46**.

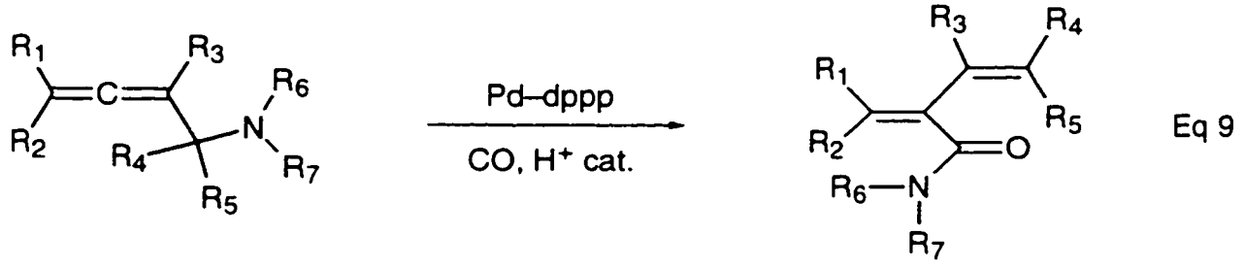


Scheme 10



Scheme 11

After the results shown in this chapter were obtained, the carbonylation of α-allenylamines **47** to α-vinylacrylic amides **48** was carried out using Pd-dppp and *p*-TsOH as the catalytic system[19] (Eq 9). The mechanism is also thought to involve an allyl-Pd intermediate of the type of **45**.

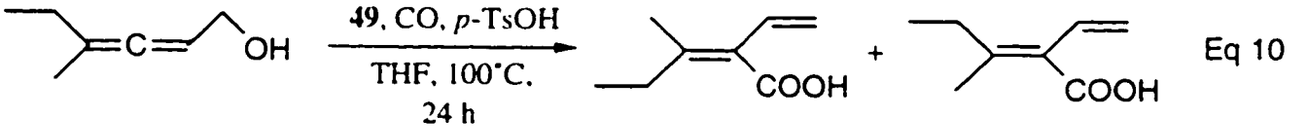


47 **48** Eq 9

The goal of this research was to explore the catalytic activity of a new cationic aquo hydride palladium complex[20], $[(Cy_3P)_2Pd(H_2O)(H)]^+BF_4^-$ (**49**), for the carbonylation of α-allenic alcohols. The presence of a hydride makes this complex interesting, since in many carbonylation reactions hydride complexes are proposed as intermediates.

4.2 Results and Discussion

Reaction of **50a** with carbon monoxide in THF, in the presence of $[(Cy_3P)_2Pd(H)(H_2O)]^+BF_4^-$ (**49**) and *p*-TsOH affords the carbonylated product **51a** (Eq 10). The reaction does not take place in the absence of *p*-TsOH. The optimized conditions of the reaction are as follows: α-allenic alcohol (1 mmol), **49** (10 mg, 0,012 mmol), *p*-TsOH (4.6 mg, 0.024 mmol), THF (5 ml), CO (300 psi), 100°C, 24 h.



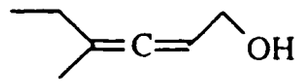
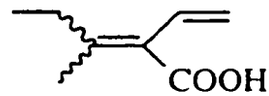
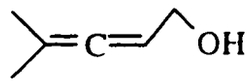
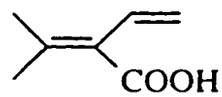
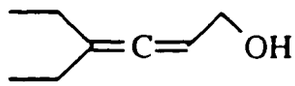
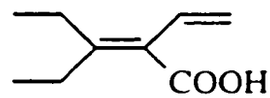
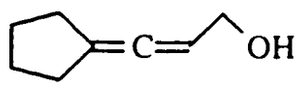
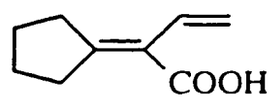
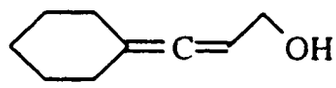
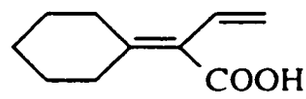
50a **Z-51a** **E-51a** Eq 10

A series of 4,4-disubstituted α-allenic alcohols (**50a-e**) were subjected to carbonylation under these conditions, and the results are shown in Table 1. The α-vinyl acrylic acids derivatives (**51a-e**) obtained can be easily identified by spectroscopic means (Figure 1): ^{1}H-NMR spectra show an ABX system between 5 and 7 ppm, corresponding to the three vinylic protons. A broad signal is also observed between 8 and 12 ppm, corresponding to the carboxylic proton. ^{13}C-NMR shows a signal near 176 ppm for the carbonyl carbon, and 4 vinylic carbons corresponding to the dienyl system. A broad O-H stretching absorption centered at around 3000 cm^{-1}, and a carbonyl stretching band around 1690 cm^{-1}, were observed in the infrared spectrum.

Carbonylation of **50a** gives a 1:1 mixture of the E and Z carboxylic acids. The lack of selectivity is due to the similarity in the bulkiness of the Me and Et groups. The selectivity is excellent when 4-monosubstituted allenic alcohols (**52a-d**) are subjected to carbonylation. Table 2 shows the results for these carbonylation reactions. In the four cases the E isomer is formed exclusively, and the yields are slightly higher than those shown in Table 1. The E / Z

Table 1

Conversion of 4,4-disubstituted α-allenic alcohols to 2-vinylacrylic acids catalyzed by **49**.

Substrates		Products		Isolated yield(%)
50a		**51a**		64
50b		**51b**		59
50c		**51c**		55
50d		**51d**		43
50e		**51e**		58

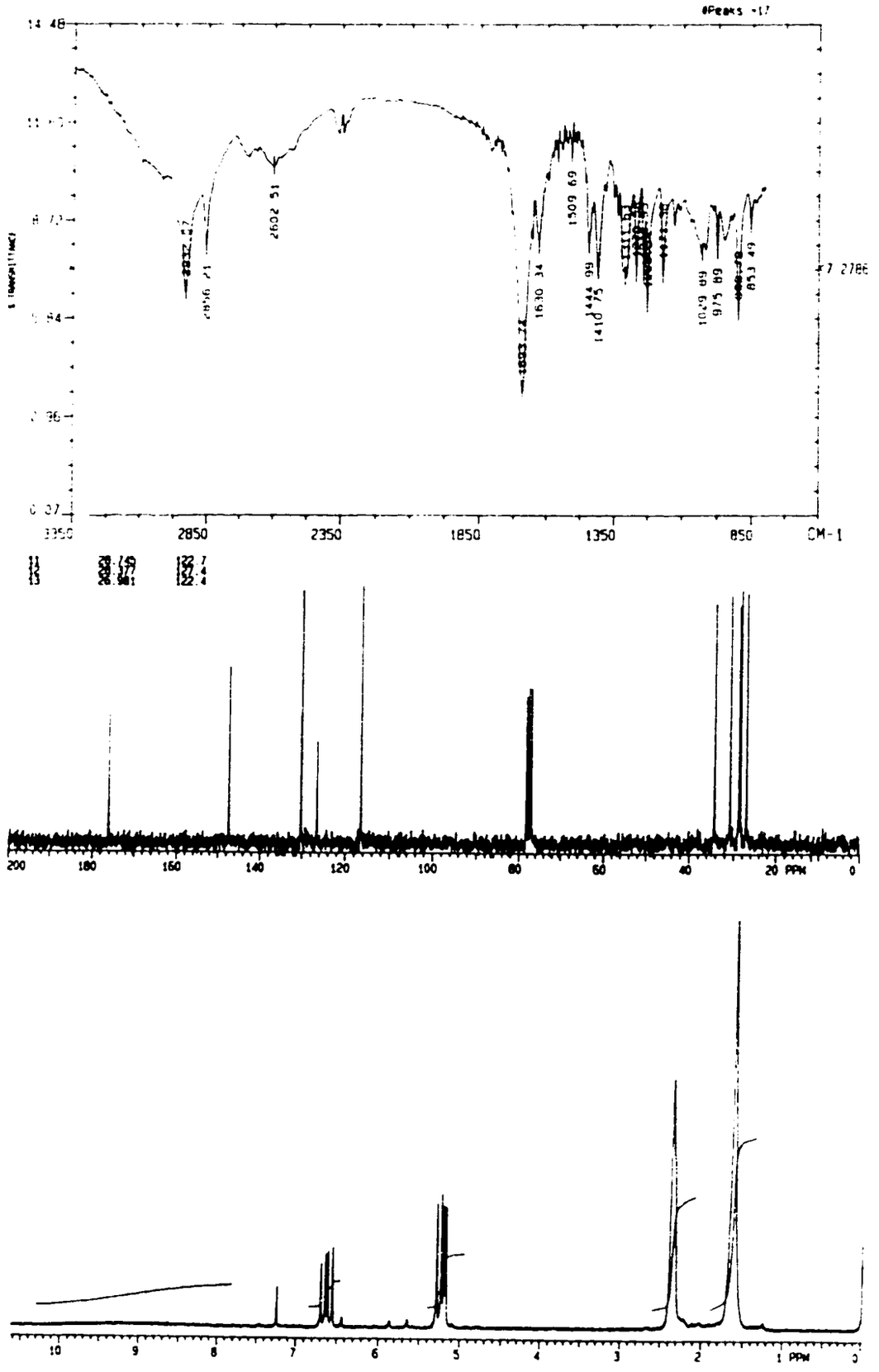
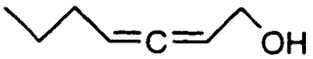
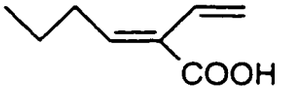
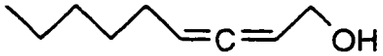
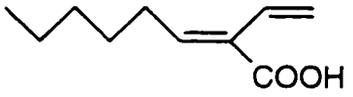
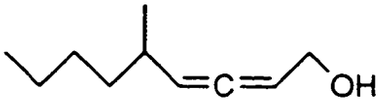
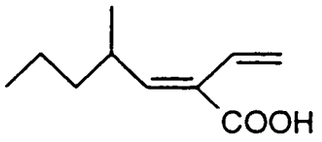
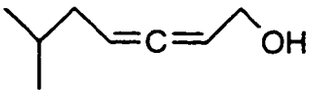
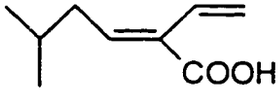


Figure 1: ^{1}H-NMR, ^{13}C-NMR and IR spectra of **50e**.

Table 2

Conversion of 4-monosubstituted α-allenic alcohols to 2-vinylacrylic acids catalyzed by **49**

Substrates		Products		Isolated yield(%)
52a		**53a**		61
52b		**53b**		74
52c		**53c**		72
52d		**53d**		64

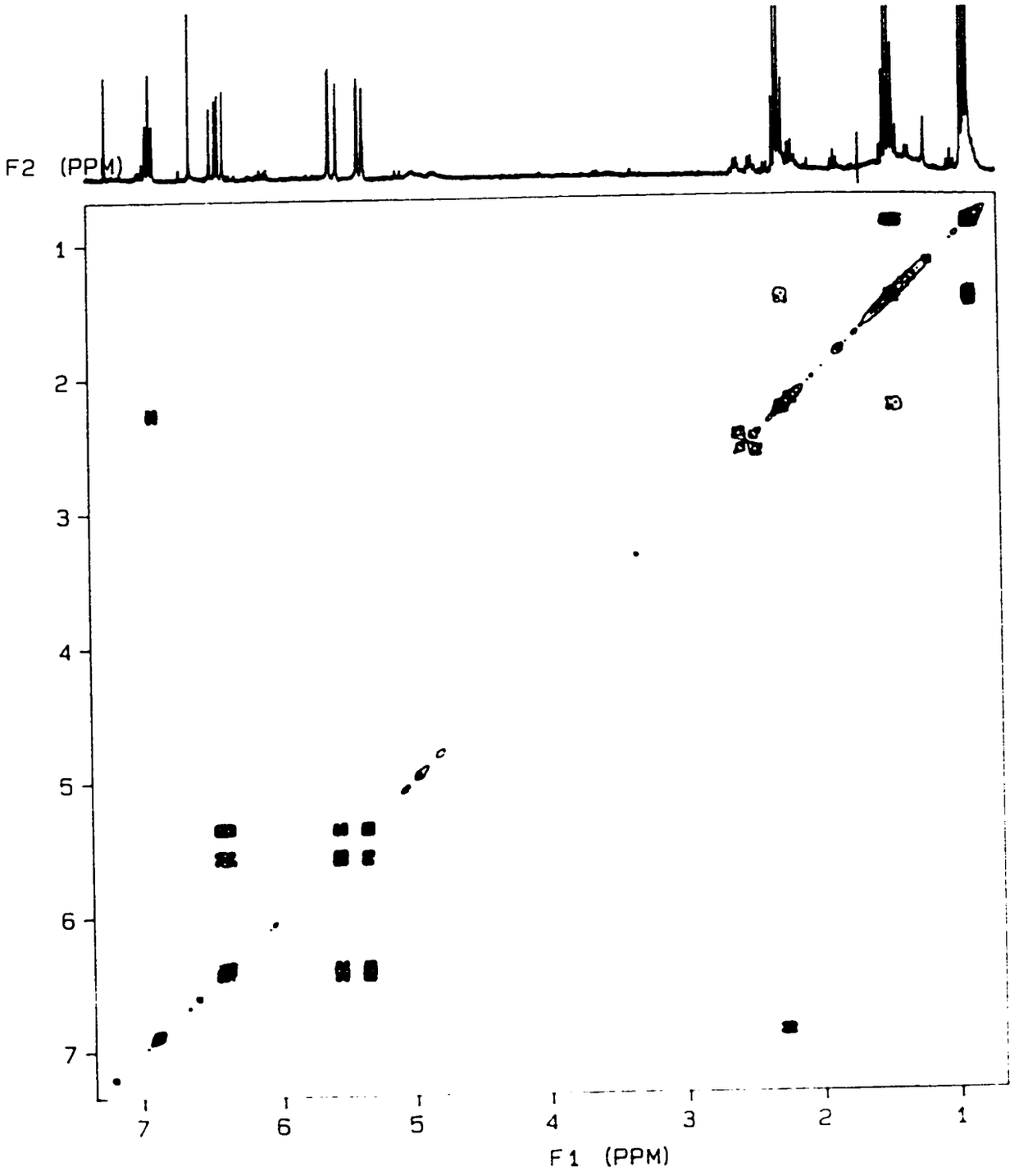
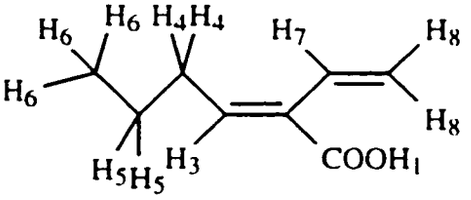


Figure 2: NOESY spectrum of **53a**.

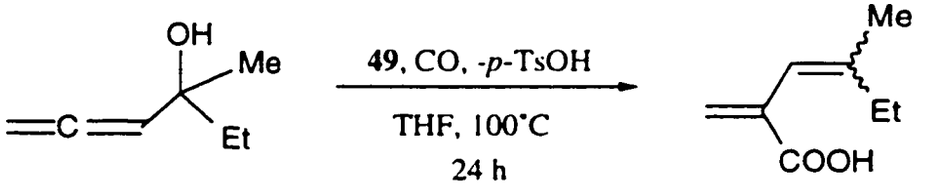
configuration was determined by an NOE experiment performed on compound **53a** (Figure 2). The spectrum shows NOE interaction between H-4 and H-7 (Scheme 12), and a lack of interaction between H-3 and H-7. These observations indicate that the E isomer is the product.



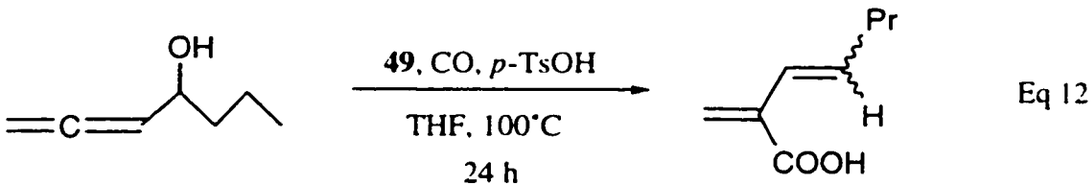
E-53a

Scheme 12

Allenic alcohols **54a** and **54b** did not give the expected carboxylic acids **55a** and **55b** under the same carbonylation conditions (Eq 11 and 12). Although the conversion is complete, the ^{1}H-NMR of the product shows a lack of vinylic protons, and the mass spectra indicates that polymeric material has been formed. The polymeric material obtained from **54a**, which was not fully characterized, presents in the ^{13}C-NMR spectrum peaks corresponding to carbonyl groups at 172.5, 177.2 and 182.2 ppm. The presence of carbonyl groups suggests that the polymerization took place after the carbonylation reaction.

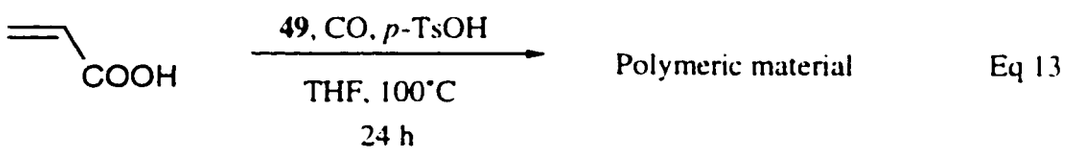


54a **55a** Eq 11



54b **55b** Eq 12

Compounds **55a** and **55b** are acrylic acid derivatives which have no substituents in the β-position. This might make them more prone to polymerization. To test this idea, acrylic acid (**56**) was exposed to the same carbonylation conditions, and the same type of polymerization took place (Eq 13).

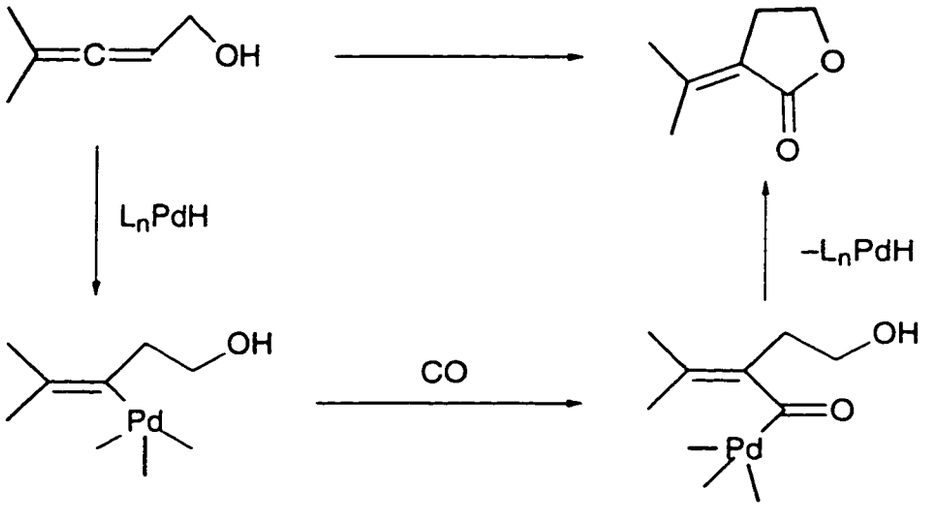


56 Eq 13

4.2.1 Mechanism of the carbonylation reaction

By using a Pd hydride complex as the catalyst for the carbonylation of α-allenic alcohols one can expect an initial addition to one of the double bonds, followed by carbonyl insertion and ring closure to form a lactone (Scheme 13).

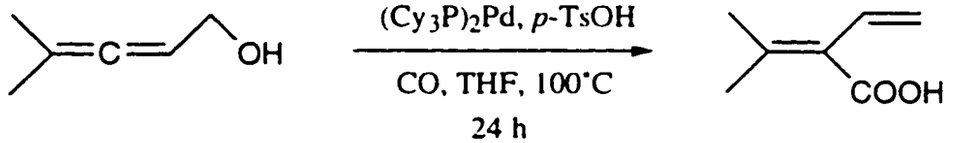
The unexpected scission of the C–O bond indicates that the Pd–H addition does not take place. Instead, an oxidative addition of palladium to the central carbon of the allene in an S_N2' manner, as proposed for allylic systems[21], seems a more plausible initial step (Eq 14). There are two requirements for this mechanism to be possible. First, the OH group must be converted *in situ* into a better leaving group. Second, the active catalytic species must be a palladium (0) complex, i.e. $(Cy_3P)_2Pd$ (**57**), which should also be formed *in situ*.



Scheme 13

Eq 14

To support the participation of **57** in this mechanism, the carbonylation reaction of **50b** was carried out using bis(tricyclohexylphosphine)palladium (0) as the catalyst, and the same product was obtained in 57 % yield (Eq 15).



50b **51b**

Eq 15

The necessary addition of *p*-TsOH to the reaction mixture could provide a means for the conversion of the C–OH group to an C–OH_2^+ group, facilitating the cleavage of the C–O bond.

4.2.2 Formation of $(Cy_3P)_2Pd$ *in situ*

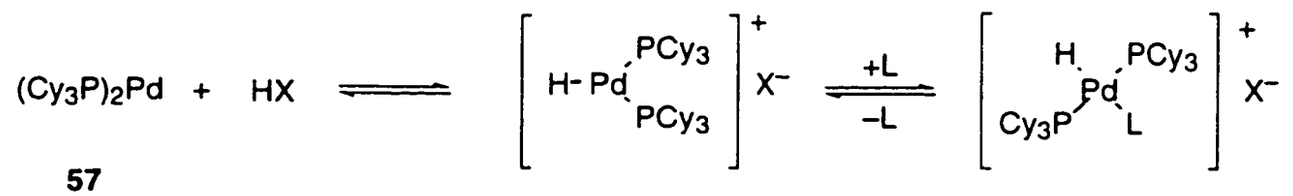
Cationic aquo hydride complex **49** is an air stable solid[20], synthesized by reaction of a toluene solution of $(Cy_3P)_2Pd$ with aqueous HBF_4 (Eq 16). The water ligand in **49a** can be replaced by stronger coordination agents by reacting **57** with pyridine or acetonitrile. Although in **49b** the BF_4^- anion can be successfully exchanged with $NaBPh_4$, any attempt to replace the BF_4^- in **49a** by a non-fluorinated anion resulted in fast decomposition to $(Cy_3P)_2Pd$.

$$(Cy_3P)_2Pd \quad + \quad HBF_4 \xrightarrow{\text{Toluene/X}} [(Cy_3P)_2Pd(H)(X)]^+BF_4^- \qquad \text{Eq 16}$$

57

X= H_2O (**49a**)
X= CH_3CN (**49b**)
X= py (**49c**)

The reaction can be depicted as an acid base equilibrium involving protonation of $(Cy_3P)_2Pd$ by HX (Scheme 14), where X is a non-coordinating ligand, followed by the coordination of a 2 electron ligand to the three coordinated hydride intermediate **58** to saturate the fourth coordination site around the metal.



58

Scheme 14

The position of the overall equilibrium is related to the acidity of the Pd–H bond, which in turn depends on the strength of the M–L bond. Ligands which can form strong bonds to palladium (L= CH_3CN, pyridine) would drive the equilibrium to the right, making the Pd–H bond less acidic and giving more stable complexes. Ligands which form weak bonds with palladium (ethers) increase the acidity of the Pd–H bond, giving unstable complexes. In fact, the cationic complex with L= ether could not be prepared. A special case is found when water is the ligand. Water coordinates weakly to palladium compounds, so it would fall in the same category as ethers for the formation of **49a**. Nevertheless, the formation of the aquo hydride palladium compound **49a** suggests that an additional stabilization factor must exist for this complex. This stabilization takes place by hydrogen–bonding of the water to the fluorine atoms in the counterion. This interaction is observed by X-ray crystallography, which shows two BF_4^- counterions acting as a bridge to two *trans*-$[(Cy_3P)_2Pd(H)(H_2O)]^+$ cations (Figure 3). The contact ion pair interactions are established by hydrogen-bonding between two F atoms of each BF_4^- and the oxygen atoms of the coordinated water molecule.

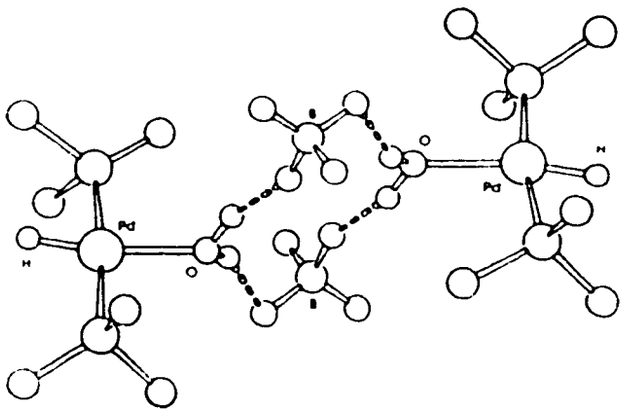
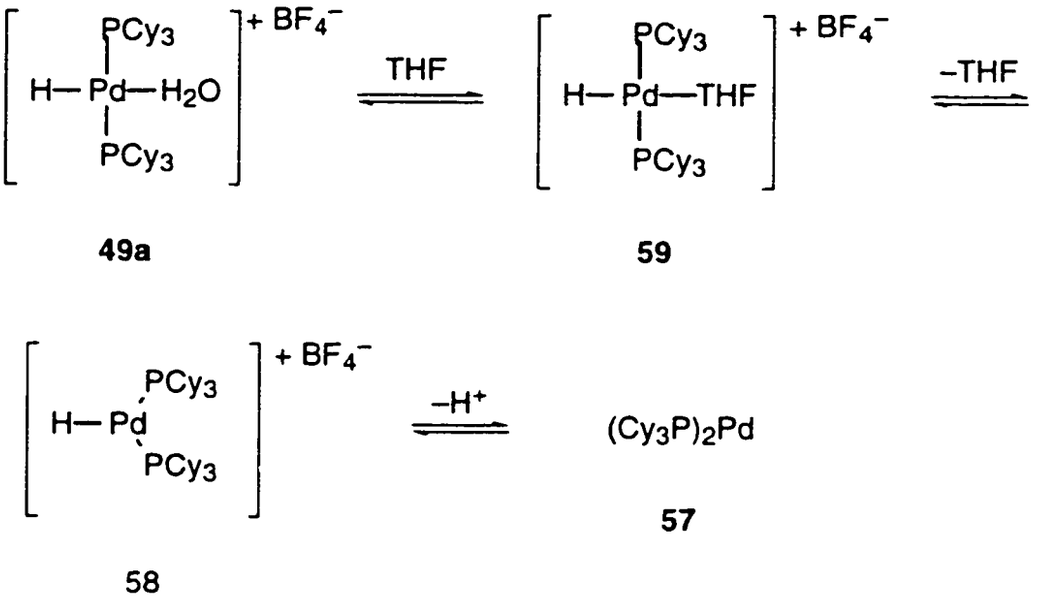


Figure 3

The stabilization of **49a** by hydrogen bonding to the counterion may explain why the complex with non-fluorinated counterions cannot be prepared, since hydrogen bonding can not exist in these molecules.

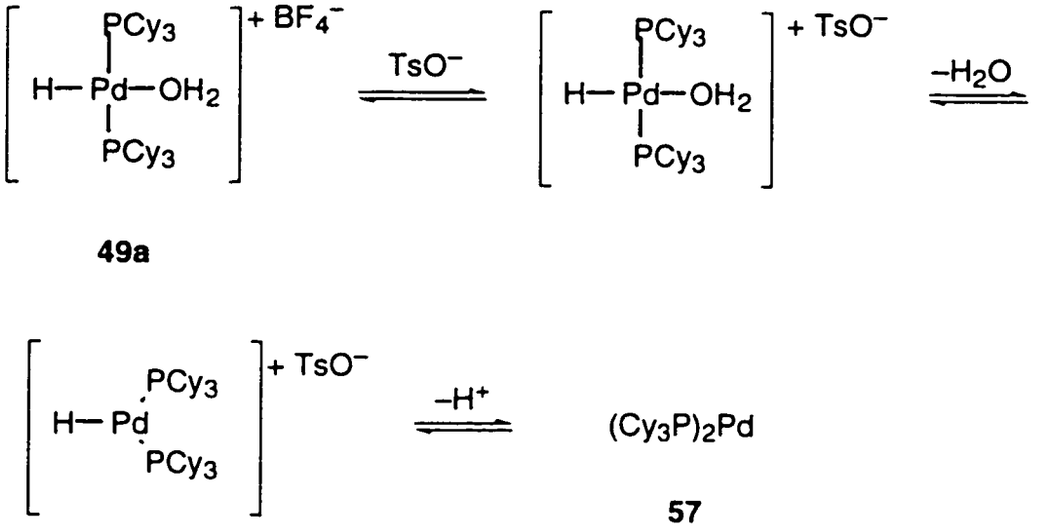
Knowing the factors that affect the stability of complex **49a**, we thought of two possible mechanisms for the formation of $(Cy_3P)_2Pd$ during the carbonylation reaction. a) Since the reaction is performed in THF a large excess of the solvent might induce the displacement of water from **49a** (Scheme 15). As described in the original paper[20], the THF complex **59** would not be stable, liberating $(Cy_3P)_2Pd$. Against this idea is the fact that when **49a** is dissolved in THF and treated with excess D_2O, there is almost no incorporation of D_2O in the complex, at least during the first 1 or 2 days of reaction. Only the hydride is exchanged with deuterium, suggesting that the equilibrium in Scheme 15 does not take place. Nevertheless we have to consider that this experiment was done at room temperature, while our carbonylation reaction is effected at 100°C.



Scheme 15

b) The presence of *p*-TsO^- anion can produce a change in the palladium complex. The tosylate anion may displace the F_4B^- as the counterion. If this happens, the stabilizing hydrogen bond between the oxygen and fluorine would disappear, inducing decoordination of water and formation of $(Cy_3P)_2Pd$ (Scheme 16). We must consider as well that the thermal stability of

complex **49a** has not been studied, and therefore we cannot rule out the formation of $(Cy_3P)_2Pd$ by a thermal reaction.

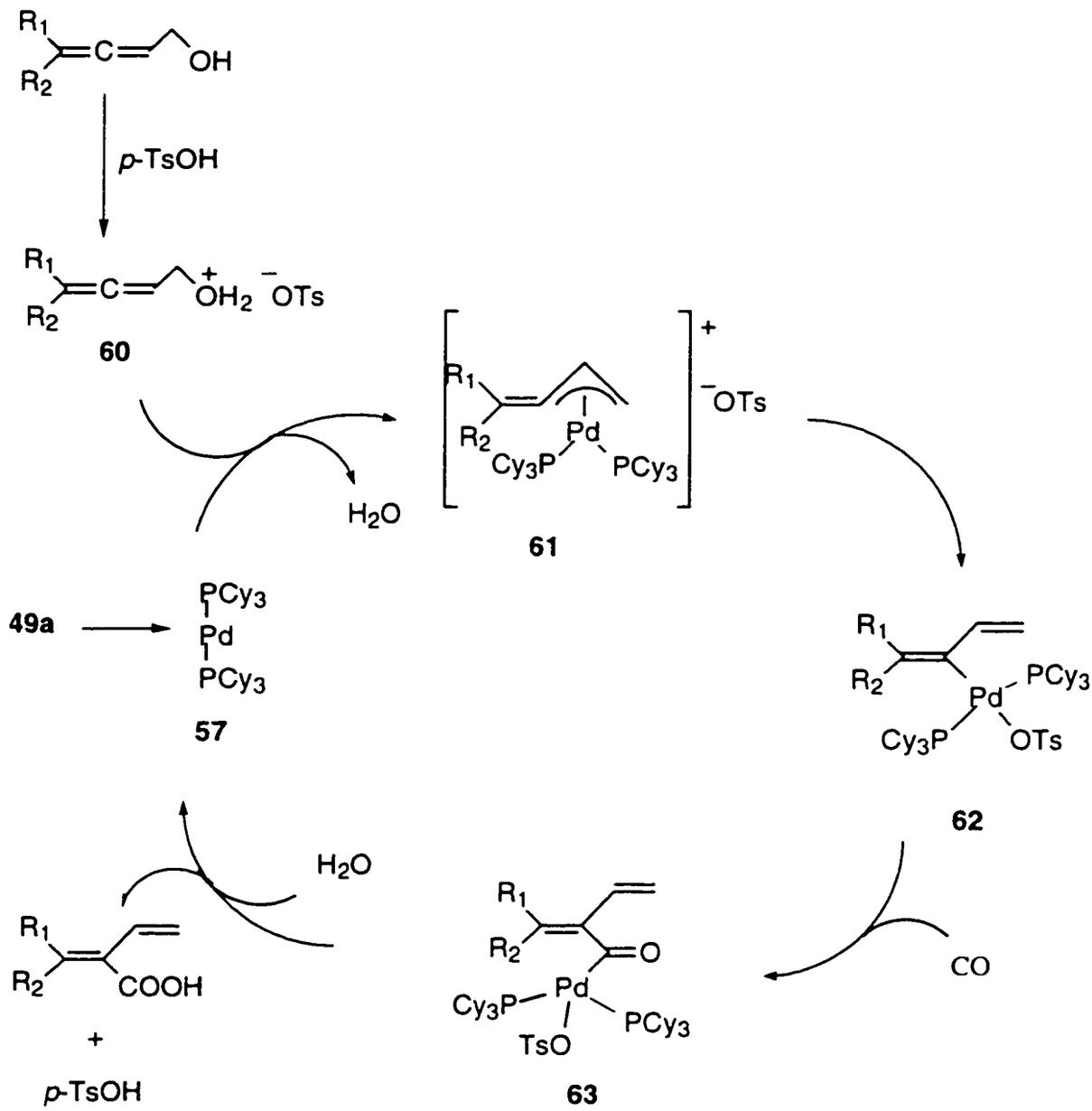


49a

Scheme 16

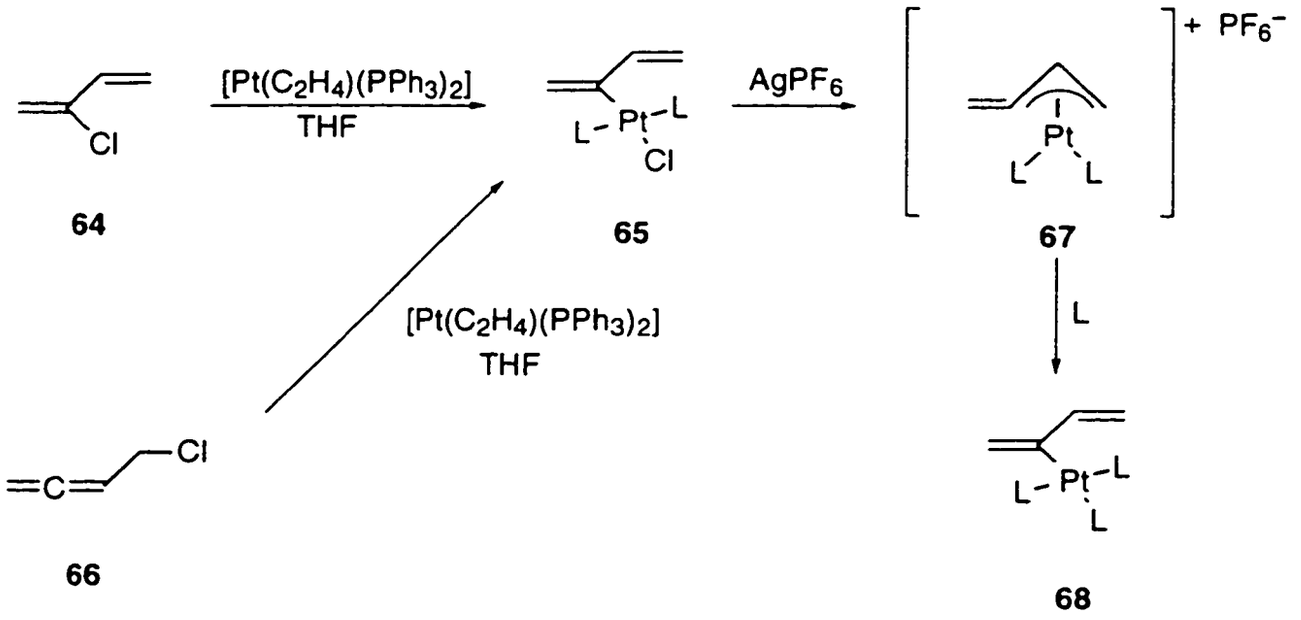
Knowing that $(Cy_3P)_2Pd$ is the active catalyst, we can formulate a reaction mechanism as outlined in Scheme 17. *p*-Toluenesulfonic acid can protonate the allenic alcohol to give **60**. Reaction of the latter with the Pd(0) complex **57** generated from **49a** would form the allyl palladium intermediate **61.** The formation of the conjugated diene would be the driving force for the conversion of the π to the σ-bonded complex **62**. Carbonyl migration may then occur forming the acyl complex **63** and acyl palladium hydrolysis will give the product and regenerate the Pd(0) species.

Intermediate **61**, where the π-allyl group is directly attached to the double bond, has been suggested for the reaction of allenyl esters and carbonates using Pd(0) catalysts[18]. Although Pd complexes of this type have not been isolated, analogous complexes of platinum have been synthesized and their reactivity has been studied[22]. These complexes have been prepared as shown in Scheme 18. Reaction of stoichiometric amounts of chloroprene **64** with a THF solution of $[Pt(C_2H_4)(PPh_3)_2]$ forms the 2-η^1-butadienylplatinum complex **65**. The


R1
R2
C
OH
p-TsOH
OH2
OTs
60
H2O
61
PCy3
Pd
Cy3P
49a
57
62
CO
63
TsO
COOH
+
p-TsOH

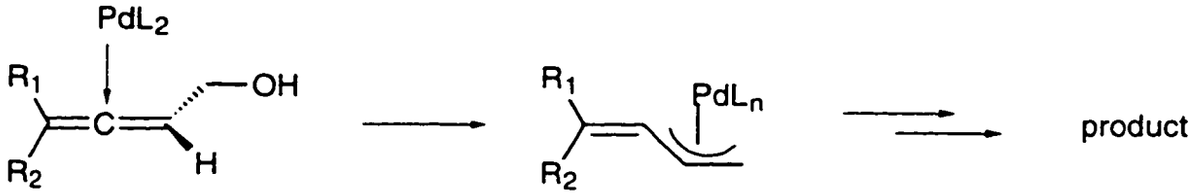
Scheme 17

same complex can be prepared by reacting 4-chloro-3-methylbuta-1,2-diene **66** with $[Pt(C_2H_4)(PPh_3)_2]$ in THF. Halide abstraction of **65** by $AgPF_6$ in CH_2Cl_2 leads to the formation of the yellow air stable crystalline cationic complex **67**. Reaction of **67** with triphenylphosphine leads to the formation of the 2-η^1-butadienyl platinum **68** complex in quantitative yield.



Scheme 18

The mechanism proposed accounts for the stereochemistry of the carbonylation reaction. $(Cy_3P)_2Pd$ approaches the central carbon of the allene from the direction of the smaller substituent at C-4, minimizing the steric repulsion (Scheme 19). The subsequent transformations occur with retention of configuration, to form the E-vinylacrylic acid.



$R_1 < R_2$

Scheme 19

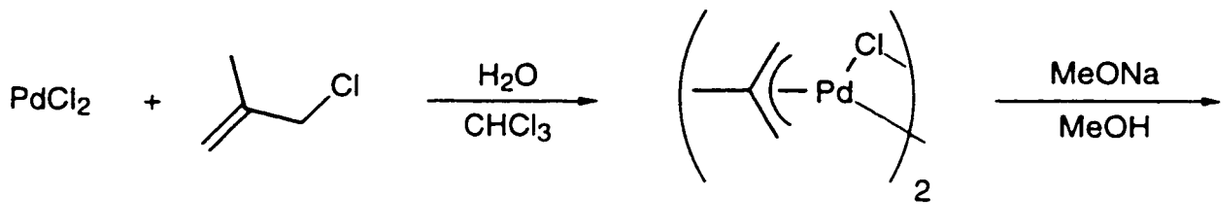
4.3 Conclusion

We found that $[(Cy_3P)_2Pd(H)(H_2O)]^+BF_4^-$ is a good catalyst for the carbonylation of allenic alcohols to 2-vinylacrylic acids. The reaction proceeds by attack of $(Cy_3P)_2Pd$ at the central carbon of the allene in an S_N2' fashion, with the probable formation of a η^3-butadienylpalladium complex intermediate. The reaction is stereospecific in cases where the allene has one substituent at C–4, giving exclusively the E-acrylic acid derivative. In addition, it is shown that **49a**, an air stable complex, can be used as a precursor of the very reactive bis(tricyclohexylphosphine)palladium (0) complex.

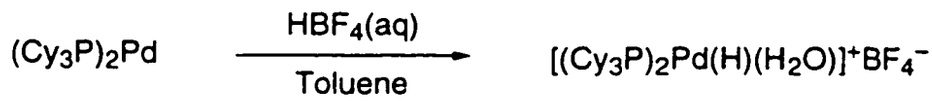
Experimental Section

4.4.1 Synthesis of *trans*-$[(Cy_3P)_2Pd(H)(H_2O)]^+BF_4^-$ (49a)

The preparation of **49a** was carried out following Scheme 20. $PdCl_2$ (730 mg, 4 mmol) and 3-chloro-2-methylpropene[23] (**63**) (392 mg, 4.4 mmol) were added to a flask containing degasified water (120 ml) and $CHCl_3$ (40 ml). The mixture was stirred vigorously while being gently refluxed under nitrogen for 15 h. The aqueous layer was separated and extracted with chloroform. The combined organic layers were dried ($MgSO_4$) and filtered. After concentration, 1.98 mmol (99 %) of **64** was isolated as a yellow crystalline solid.



63 **64**



57 **49a**

Scheme 20

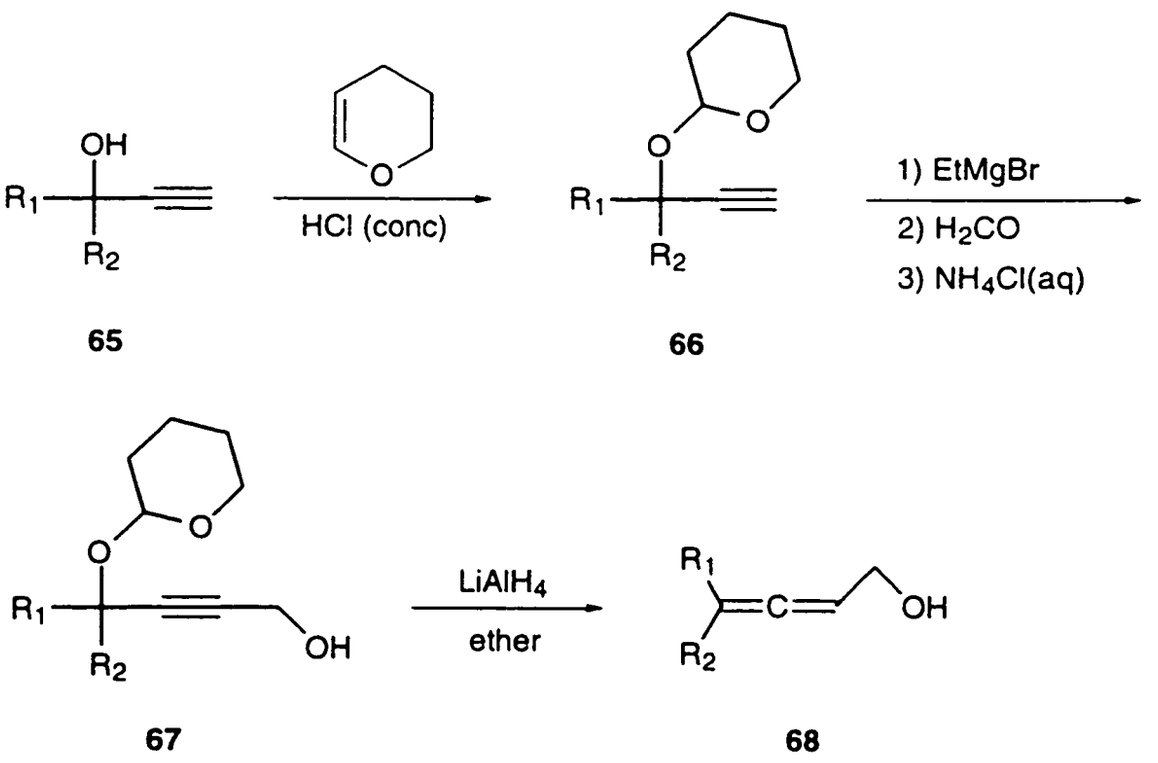
Complex **64** (1.02 g, 2.8 mmol) was suspended in 32 ml of methanol[24]. To the suspension was added MeONa (25 % wt, 1.55 ml, 6.72 mmol), followed by 75 ml of methanol. Tricyclohexylphosphine (4.71 g, 16.8 mmol) in 38 ml of toluene was then added. After 30 minutes a clear solid separated. The mixture was stirred for 24 hours. The white solid

was filtered (under nitrogen) and washed with methanol. The solid $(Cy_3P)_2Pd$ was dried under vacuum, and used for the following step without purification.

Complex **57** was dissolved in 20 ml of toluene[25]. To the solution was added aqueous (35 %) HBF_4 (1.15 ml, 5,6 mmol) and the mixture was stirred vigorously at room temperature for 24 hours. The solid formed was filtered and dried in vacuo. Complex **49a** was isolated in 61% overall yield.

4.4.2 Synthesis of α-allenic alcohols

α-Allenic alcohols were synthesized following Scheme 21. In a round bottom flask, alkynol **65** is mixed with dihydropyran[26] (1.1 eq). Two drops of concentrated hydrochloric acid are added and the mixture is stirred at room temperature overnight. The mixture is dried ($MgSO_4$) and the product **66** is purified by bulb to bulb distillation.

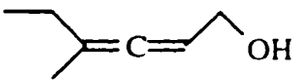


65 **66** **67** **68**

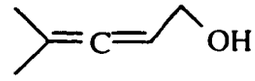
Scheme 21

To a solution of ethylmagnesium bromide (50 mmol) in 30 ml of ether is added dropwise a solution of **66** in 15 ml of ether. The reaction was stirred for three hours. Paraformaldehyde (2 g) contained in a flask connected to the reaction vessel was heated, and the gaseous formaldehyde was bubbled into the reaction mixture. After stirring for 50 minutes, saturated NH_4Cl (50 ml) was added slowly. The organic layer was separated and the aqueous phase was extracted twice with ether. The organic extracts were combined, washed with water and dried ($MgSO_4$). After filtration and evaporation of the solvent, **67** was distilled under vacuum.

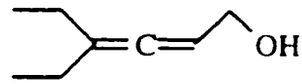
To a suspension of $LiAlH_4$ (0.733 g) in ether (32 ml) was added dropwise a solution of **67** (16 mmol) in ether (7 ml) so that a smooth reflux was maintained. After the addition was complete, the mixture was refluxed for 4 h. Cold water was slowly added until the solid turned white. The mixture was filtered and the filtrate was dried ($MgSO_4$). The ether was evaporated and the product **68** was purified by vacuum distillation.



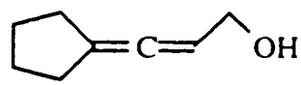
4-Methyl-2,3-hexadiene-1-ol[26] **(50a):** ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.95 ppm (3H, t, CH_2CH_3), 1.68 ppm (3H, dt, CH_3C), 1.74 ppm (1H, br, O*H*), 1.84 ppm (2H, dq, CH_2CH_3), 4.05 ppm (2H, d, CH_2OH), 5.29 ppm (1H, m, =C*H*). IR: 3320 (OH) and 1970 cm^{-1} (C=C=C).



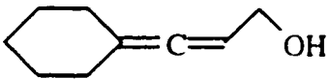
4-Methyl-2,3-pentadiene-1-ol[27] **(50b):** ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.67 ppm (6H, d, J= 1.6 Hz, 2C*H*$_3$), 3.60 ppm (1H, br, O*H*), 4.02 ppm (2H, d, J= 5.8 Hz C*H*$_2$OH), 5.14 ppm (1H, m, =C*H*). IR: 3345 (OH) and 1978 cm^{-1} (C=C=C).



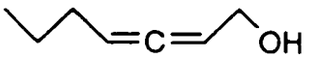
4-Ethyl-2,3-hexadiene-1-ol (50c): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.98 ppm (6H, t, J= 7.3 Hz, 2C*H*$_3$), 1.33 ppm (1H, t, J= 5.9 Hz, O*H*), 1.98 ppm (4H, dq, J= 7.3 and 3 Hz, 2C*H*$_3$), 4.07 ppm (2H, t, J= 5.7 Hz, C*H*$_2$OH), 5.40 ppm (1H, m, =C*H*). ^{13}C-NMR: δ 12.3 (*C*H$_3$), 25.5 (*C*H$_2$), 61.1 (*C*H$_2$OH), 94.0 (C=C=*C*H), 111.9 (*C*=C=CH) and 198.9 ppm (C=*C*=CH). IR: 3350 (OH) and 1972 cm^{-1} (C=C=C). MS: 126 (M$^+$)



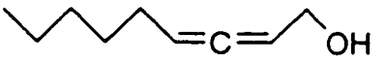
3-Cyclopentylidene-2-propen-1-ol (50d): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.54 ppm (1H, br, O*H*), 1.65 ppm (4H, m, 2C*H*$_2$), 2.35 ppm (4H, m, 2C*H*$_2$C=), 4.05 ppm (2H, d, J= 5.7 Hz, C*H*$_2$OH), 5.26 ppm (1H, m, =C*H*). IR: 3366 (OH) and 1968 cm^{-1} (C=C=C). MS: 124 (M$^+$).



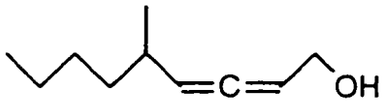
3-Cyclohexylidene-2-propen-1-ol[28] **(50e):** ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.50 ppm (7H, m, $(CH_2)_3$ and O*H*), 2.06 ppm (4H, m, $2CH_2C=$), 4.02 ppm (2H, d, J= 5.8 Hz, CH_2OH), 5.18 ppm (1H, m, =C*H*). IR: 3372 (OH) and 1969 cm^{-1} (C=C=C).



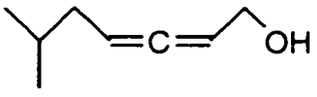
2,3-Heptadiene-1-ol[26] **(52a):** ^{1}H-NMR (200 MHz, $CDCl_3$): δ= 0.88 ppm (3H, d, J= 7.2 Hz, CH_3), 1.39 ppm (2H, sext, J= 7.3 Hz, CH_2CH_3), 1.60 ppm (1H, br, O*H*), 1.95 ppm (2H, m, $CH_2CH=$), 4.06 ppm (2H, dd, J= 5.7 and 3.3 Hz, CH_2OH), 5.26 ppm (2H, m, C*H*=C=C*H*). IR: 3325 (OH) and 1966 cm^{-1} (C=C=C).



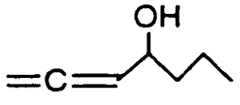
2,3-Nonadiene-1-ol[29] **(52b):** ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.88 ppm (3H, t, J= 7.2 Hz, CH_3), 1.35 ppm (7H, m, $(CH_2)_3CH_3$ and O*H*), 1.98 ppm (2H, m, CH_2=CH), 4.08 ppm (2H, dd, J= 5.7 and 3.2 Hz, CH_2OH), 5.30 ppm (2H, m, C*H*=C=C*H*). ^{13}C-NMR: δ 14.0 (CH_3), 22.5 (CH_2), 28.6 (CH_2), 28.8 (CH_2), 31.3 (CH_2), 60.8 (CH_2OH), 91.7 and 94.0 (*C*H=C=*C*H) and 202.9 ppm (C=*C*=CH). IR: 3360 (OH) and 1965 cm^{-1} (C=C=C).



5-Methyl-2,3-octadiene-1-ol (52c): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.87 ppm (3H, t, J= 6.5 Hz, CH_2CH_3), 0.98 ppm (3H, d, J= 6.8 Hz, $CHCH_3$), 1.30 ppm (5H, m, $(CH_2)_2$ and O*H*), 2.15 ppm (1H, m, $CHCH_3$), 4.09 ppm (2H, dd, J= 5.8 and 2.9 Hz, CH_2OH), 5.24 ppm (1H, m) and 5,34 ppm (1H, m) (*CH*=C=*CH*). ^{13}C-NMR: δ 14.1 (CH_3), 20.3 (CH_3), 20.4 (CH_2), 33.1 (CH_2), 39.6 (*C*H), 60.9 (CH_2OH), 92.3 and 99.8 (*C*H=C=*C*H) and 202.0 ppm (C=*C*=CH). IR: 3348 (OH) and 1968 cm^{-1} (C=C=C). MS: 154 (M^+).

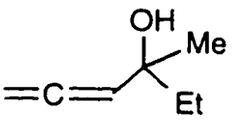


6-Methyl-2,3-heptadiene-1-ol[30] (52d): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.90 ppm (6H, d, J= 7.2 Hz, $CH(CH_3)_2$), 1.42 ppm (1H, br, O*H*), 1.64 ppm (1H, sept, J= 7.2 Hz, $CH(CH_3)_2$), 1.81 ppm (2H, m, $CH_2CH(CH_3)_2$), 4.08 ppm (2H, dd, J= 5.8 and 3.0 Hz, CH_2OH), 5.26 ppm (2H, m, *CH*=C=*CH*). ^{13}C-NMR: δ 22.1 ($2CH_3$), 28.4 (*C*H), 38.1 (CH_2), 60.8 (CH_2OH), 91.0 and 92.2 (*C*H=C=*C*H) and 203.6 ppm (C=*C*=CH). IR: 3354 (OH) and 1966 cm^{-1} (C=C=C).



1,2-Heptadiene-4-ol[26] (54a): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.90 ppm (3H, t, J= 7.3 Hz, CH_3), 1.43 ppm (4H, m, $(CH_2)_2$), 2.30 ppm (1H, br, O*H*), 4.15 ppm (1H, m, *C*HOH), 4.81 ppm (2H, dd, J= 5.8 and 3.0 Hz, $=CH_2$), 5.21 ppm (1H, q, J= 6.5 Hz, *CH*=C=CH_2).

^{13}C-NMR: δ 13.4 (CH_3), 18.1 (CH_2), 39.1 (CH_2), 69.0 ($CHOH$), 76.9 (C=CH_2), 94.3 (C=CH) and 206.5 ppm (HC=C=CH_2). IR: 3340 (OH) and 1962 cm^{-1} (C=C=C).



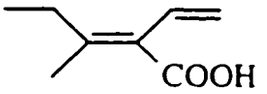
4-Methyl-1,2-hexadiene-4-ol[26] (54b): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.88 ppm (3H, t, J= 7.3 Hz, CH_2CH_3), 1.25 ppm (3H, s, CH_3), 1.56 ppm (2H, q, J= 7.3 Hz, CH_2CH_3), 1.71 ppm (1H, br, O*H*), 4.82 ppm (2H, d, J= 6.6 Hz, =CH_2), 5.21 ppm (1H, t, J= 6.6 Hz, CH=C=CH_2). ^{13}C-NMR: δ 8.4 (CH_3), 27.3 (CH_3), 35.4 (CH_2), 71.6 (COH), 78.3 (C=CH_2), 99.0 (C=CH) and 205.7 ppm (HC=C=CH_2). IR: 3375 (OH) and 1964 cm^{-1} (C=C=C).

4.4.3 Carbonylation of α-allenic alcohols catalyzed by 49a

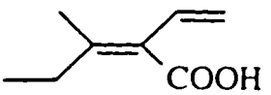
The following general procedure was used: a mixture of allenic alcohol (1 mmol), **49a** (10 mg, 0.012 mmol), *p*-TsOH (4.6 mg, 0.024 mmol) and THF (5 ml) was reacted in an autoclave at 20 atm of carbon monoxide for 24 h at 100°C. The reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was diluted with ether (20 ml) and extracted with 0.5 N NaOH (3x10 ml). The combined aqueous phase was acidified with 1N HCl and then extracted with ether (3 x 20 ml). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under low pressure to give the product.

4.4.4 Carbonylation of α-allenic alcohols catalyzed by $(Cy_3P)_2Pd$

The carbonylation reactions were effected using $(Cy_3P)_2Pd$ (0.012 mmol) instead of **49a**.

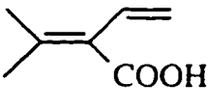


(E)-2-Ethenyl-3-methyl-2-pentenoic acid (E-51a): ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.03 ppm (3H, t, J= 7.6 Hz, CH_2CH_3) 1.93 ppm (3H, s, CH_3), 2.23 ppm (2H, q, J= 7.6 Hz, CH_2CH_3), 5.20 ppm (1H, dd, J_{cis}= 10.9, J_{gem}= 2.8 Hz, $CH=CH_2$), 5.23 ppm (1H, dd, J_{trans}= 17.6, J_{gem}= 2.8 Hz, $CH=CH_2$), 6.54 ppm (1H, dd, J= 17.6, 10.9 Hz, $CH=CH_2$), 9.8 ppm (1H, br, COOH). ^{13}C-NMR: δ 12.3 (CH_3CH_2), 20.6 (CH_3), 27.3 (CH_3CH_2), 115.9 ($CH=CH_2$), 128.1 (C-COOH), 129.9 ($CH=CH_2$), 145.0 (C=C-COOH) and 174.8 ppm (COOH). IR: 1695 cm^{-1} (C=O). MS: 140 (M^+). Anal. Calc. for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.38; H, 8.59.

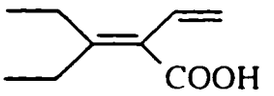


(Z)-2-Ethenyl-3-methyl-2-pentenoic acid (Z-51a): ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.05 ppm (3H, t, J= 7.6 Hz, CH_2CH_3) 1.84 ppm (3H, s, CH_3), 2.24 ppm (2H, q, J= 7.6 Hz, CH_2CH_3), 5.20 ppm (1H, dd, J_{cis}= 10.9, J_{gem}= 2.8 Hz, $CH=CH_2$), 5.23 pmm (1H, dd, J_{trans}= 17.6, J_{gem}= 2.8 Hz, $CH=CH_2$), 6.52 ppm (1H, dd, J= 17.6, 10.9 Hz, $CH=CH_2$), 9.8 ppm (1H, br, COOH). ^{13}C-NMR: δ 12.6 (CH_3CH_2), 17.7 (CH_3), 30.1 (CH_3CH_2), 115.9 ($CH=CH_2$), 128.2 (C-COOH), 130.4 ($CH=CH_2$), 145.7 (C=C-COOH), 174.8 ppm (COOH).

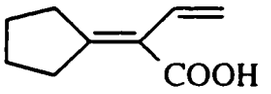
IR: 1695 cm^{-1} (C=O). MS: 140 (M^+). Anal. Calc. for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.38; H, 8.59.



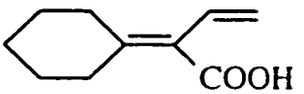
2-Ethenyl-3-methyl-2-butenoic acid (51b): ^{1}H-NMR (200 MHz,$CDCl_3$): δ 1.88 ppm (3H, s, C*H*$_3$), 1.98 ppm (3H, s, C*H*$_3$), 5.20 ppm (1H, dd, J_{cis}= 12, J_{gem}= 2 Hz, CH=C*H*$_2$), 5.25 ppm (1H, dd, J_{trans}= 17.4, J_{gem}= 2Hz, CH=C*H*$_2$), 6.5 ppm (1H, dd, J= 17.4, 12 Hz, C*H*=CH_2), 9.5 ppm (1H, br, COO*H*). ^{13}C-NMR: δ 21.5 (*C*H_3), 23.9 (*C*H_3), 116.7 (CH=*C*H_2), 129.1 (*C*-COOH), 131.0 (*C*H=CH_2), 141.8 (*C*-COOH), 175.3 ppm (*C*OOH). IR: 1694 cm^{-1} (C=O). MS: 126 (M^+).



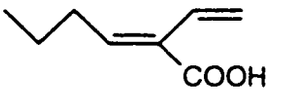
2-Ethenyl-3-ethyl-2-pentenoic acid (51c): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.05 ppm (3H, t, J= 7.6 Hz, CH_2C*H*$_3$), 1.07 ppm (3H, t, J= 7.6 Hz, CH_2C*H*$_3$), 2.24 ppm (4H, q, J= 7.6 Hz, (C*H*$_2$$CH_3$)$_2$), 5.20 ppm (1H, dd, J_{cis}= 11 Hz, J_{gem}= 0.9 Hz, CH=C*H*$_2$), 5.25 ppm (1H, dd, J_{trans}= 17.6 Hz, J_{gem}= 0.9 Hz, CH=C*H*$_2$), 6.56 ppm (1H, dd, J=17.5, 11.1 Hz, C*H*=CH_2), 8.6 ppm (1H, br, COO*H*). ^{13}C-NMR: δ 13.6 (*C*H_3), 13.7 (*C*H_3), 24.8 (*C*H_2), 28.4 (*C*H_2), 116.5 (CH=*C*H_2), 128.5 (*C*-COOH), 130.6 (*C*H=CH_2), 151.0 (*C*=C-COOH), 175.7 ppm (*C*OOH). IR: 1691 cm^{-1} (C=O).



2-Cyclopentyliden-3-butenoic acid (51d): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.7 ppm (4H, m, CH_2CH_2), 2.5 ppm (4H, m, $(CH_2)_2C=C$), 5.23 ppm (1H, dd, J_{cis}= 11.5 Hz, J_{gem}= 2 Hz, $CH=CH_2$), 5.42 ppm (1H, dd, J_{trans}= 17.5 Hz, J_{gem}= 2 Hz, $CH=CH_2$), 6.42 ppm (1H, dd, J= 17.5, 11.5 Hz, $CH=CH_2$), 10.6 ppm (1H, br, COOH). ^{13}C-NMR: δ 26.4, 27.1 $(CH_2)_2$, 34.6, 35.2 $((CH_2)_2C=C)$, 117.3 $(CH=CH_2)$, 123.4 (*C*-COOH), 132.5 $(CH=CH_2)$, 163.2 (*C*=C-COOH), 174.0 ppm (*C*OOH). IR: 1695 cm^{-1} (C=O).

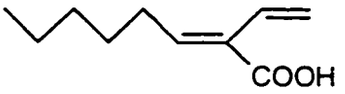


2-Cyclohexyliden-3-butenoic acid (51e): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.6 ppm (6H, m, $(CH_2)_3$), 2.3 ppm (4H, m, $(CH_2)_2C=C$), 5.17 ppm (1H, dd, J_{cis}= 12.2 Hz, J_{gem}= 0.8 Hz, $CH=CH_2$), 5.21 ppm (1H, dd, J_{trans}= 18.1 Hz, J_{gem}= 0.8 Hz, $CH=CH_2$), 6.60 ppm (1H, dd, J= 18.1, 12.2 Hz, $CH=CH_2$), 11.8 ppm (1H, br, COOH). ^{13}C-NMR: δ 26.5, 28.0, 28.2, 30.2, 33.8 $(CH_2)_5$, 115.9 $(CH=CH_2)$, 126.0 (*C*-COOH), 129.6 $(CH=CH_2)$, 146.7 (*C*=C-COOH), 175.5 ppm (*C*OOH). IR: 1694 cm^{-1} (C=O). MS: 166 (M^+). Anal. Calc. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.51; H, 8.41.

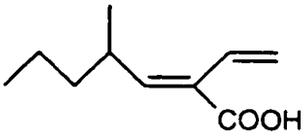


2-Ethenyl-2-hexenoic acid (53a): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.85 ppm (3H, t, J= 7.8 Hz, CH_3), 1.40 ppm (2H, m, CH_2CH_3), 2.20 ppm (2H, q, J= 7.8 Hz, $CH_2CH=C$), 5.28

ppm (1H, dd, J_{cis}= 11.5 Hz, J_{gem}= 2 Hz, CH=CH_2), 5.50 ppm (1H, dd, J_{trans}= 17.6 Hz, J_{gem}= 2 Hz, CH=CH_2), 6.35 ppm (1H, dd, J= 17.6, 11.5 Hz, CH=CH_2), 6.88 ppm (1H, t, J= 7.9 Hz, CH_2CH=C), 9.7 ppm (1H, br, COOH). ^{13}C-NMR: δ 14.5 (CH_3), 22.7 (CH_2CH_3), 31.6 (CH_2CH=C), 120.5 (CH=CH_2), 129.3 (CH=CH_2), 130.1 (C-COOH), 147.6 (CH=C-COOH), 173.4 ppm (COOH). IR: 1691 cm^{-1} (C=O). MS: 140 (M^+). HRMS calc. for $C_8H_{12}O_2$: 140.0837. Found: 140.0842.

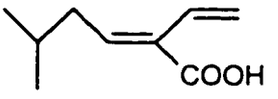


2-Ethenyl-2-octenoic acid (53b): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.9 ppm (3H, t, J= 8 Hz, CH_3), 1.40 ppm (6H, m, $(CH_2)_3CH_3$), 2.18 ppm (2H, q, J= 8.2 Hz, CH_2CH=C), 5.40 ppm (1H, dd, J_{cis}= 12 Hz, J_{gem}= 2 Hz, CH=CH_2), 5.62 ppm (1H, dd, J_{trans}= 18 Hz, J_{gem}= 2 Hz, CH=CH_2), 6.44 ppm (1H, dd, J= 18, 12 Hz, CH=CH_2), 6.92 ppm (1H, t, J= 8 Hz, CH_2CH=C), 11.0 ppm (1H, br, COOH). ^{13}C-NMR: δ 14.6 (CH_3), 23.1, 29.1, 29.6, 32.1 $(CH_2)_4$, 31.6 (CH_2CH=C), 120.5 (CH=CH_2), 129.2 (CH=CH_2), 129.9 (C-COOH), 147.9 (CH=C-COOH), 173.5 ppm (COOH). IR: 1693 cm^{-1} (C=O). MS: 168 (M^+).



2-Ethenyl-4-methyl-2-heptenoic acid (53c): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.9 ppm (3H, t, J= 7 Hz, CH_3CH_2), 1.0 ppm (3H, d, J= 7.2 Hz, CH_3CH), 1.3 ppm (4H, m, $(CH_2)_2CH_3$), 2.7 ppm (1H, m, CHCH$_3$), 5.35 ppm (1H, dd, J_{cis}= 11.5 Hz, J_{gem}= 2.3 Hz, CH=CH_2), 5.64 ppm (1H, dd, J_{trans}= 17.2 Hz, J_{gem}= 2.3 Hz, CH=CH_2), 6.43 ppm (1H, dd,

J= 17.2, 11.5 Hz, C*H*=CH_2), 6.63 ppm (1H, d, J= 10 Hz, CHC*H*=C), 8.5 ppm (1H, br, COO*H*). ^{13}C-NMR: δ 14.7 (*C*H_3), 20.7 (CH_3), 21.2, 33.4, (*C*H_2)$_2$, 39.6 (*C*H), 120.3 (CH=*C*H_2), 128.7 (*C*H=CH_2), 129.3 (*C*-COOH), 153.3 (*C*H=C-COOH), 173.5 ppm (*C*OOH). IR: 1692 cm^{-1} (C=O). MS: 168 (M^+).



2-Ethenyl-5-methyl-2-hexenoic acid (53d): ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.9 ppm (6H, d, J= 8 Hz, (C*H*$_3$)$_2$CH), 1.8 ppm (1H, m, C*H*), 2.23 ppm (2H, t, J= 8 Hz, C*H*$_2$), 5.38 ppm (1H, dd, J_{cis}= 12 Hz, J_{gem}= 2 Hz, CH=C*H*$_2$), 5.62 ppm (1H, dd, J_{trans}= 17 Hz, J_{gem}= 2 Hz, CH=C*H*$_2$), 6.55 ppm (1H, dd, J= 17, 12 Hz, C*H*=CH_2), 6.95 ppm (1H, t, J= 8 Hz, CH_2C*H*=C), 9.5 ppm (1H, br, COO*H*). ^{13}C-NMR: δ 23.1 (*C*H_3)$_2$, 29.2 (*C*H_2), 38.5 (*C*H), 120.6 (CH=*C*H_2), 129.3 (*C*H=CH_2), 130.5 (*C*-COOH), 146.8 (*C*H=C-COOH), 173.4 ppm (*C*OOH). IR: 1698 cm^{-1} (C=O).

4.5 References

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Claims to original research

1) Use of $Co_2(CO)_8$ as the catalyst for the regio and stereoselective carbonylation and ring expansion of aziridines to β–lactams.

2) Synthesis and X-ray characterization of the novel *trans*-7-azabicyclo[4.2.0]octan-2-one derivatives, compounds that present similar structural features as those contained in physiologically active bicyclic β-lactams.

3) Synthesis of methyl 5-hydroxy-2,3-pentadienoate derivatives by carbonylation of alkynyloxiranes catalyzed by palladium (0) complexes.

4) Synthesis of partially saturated furanols by carbonylation of alkynyl oxiranemethanol derivatives catalyzed by a palladium (0) complex.

5) Preparation of 2-vinylacrylic acids by carbonylation of α-allenic alcohols. Use of a novel cationic aquo hydride palladium complex as the precursor of the catalytically active bis-(tricyclohexylphosphine) palladium.

Publications

Piotti, M. E. and Alper H. "Regioselective and in Some Cases Stereoselective Carbonylation of α-Allenic Alcohols to α-Vinylacrylic Acids Catalyzed by a Cationic Palladium Complex." *J. Org. Chem.*, **1994**, *59*, 1956.

Piotti, M. E. and Alper, H. "Inversion of Stereochemistry in the $Co_2(CO)_8$ Catalyzed Carbonylation of Aziridines to β-Lactams. The First Synthesis of Highly Strained *trans*-Bicyclic β-Lactams."*J. Am. Chem. Soc.* **1996**, *118*, 111.

Piotti, M. E. and Alper, H. "Carbonylation of Alkynyl Epoxides: Synthesis of 5-hydroxy-2,3-dienoate esters and 2,3-dihydrofuran-3-ol derivatives." Submitted for publication to *J. Org. Chem.*

IMAGE EVALUATION
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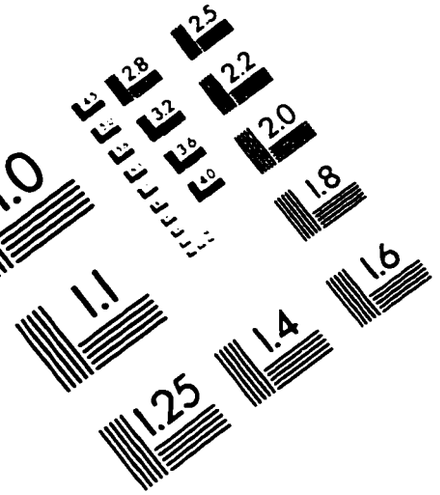

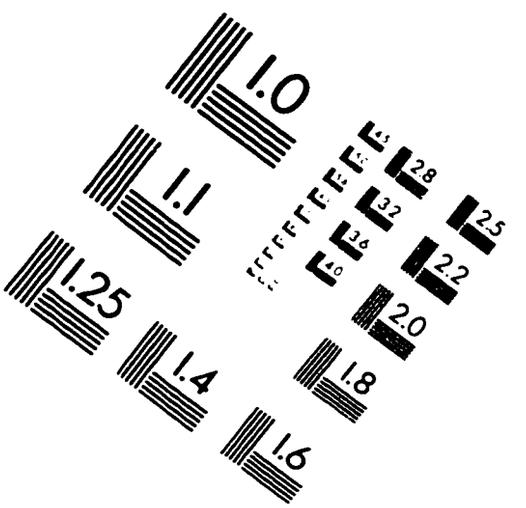

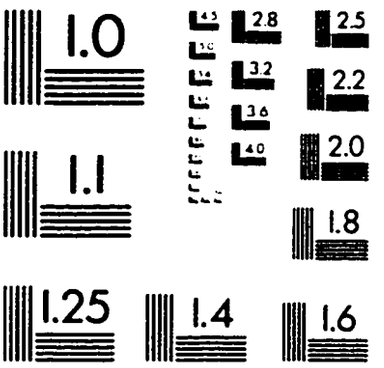

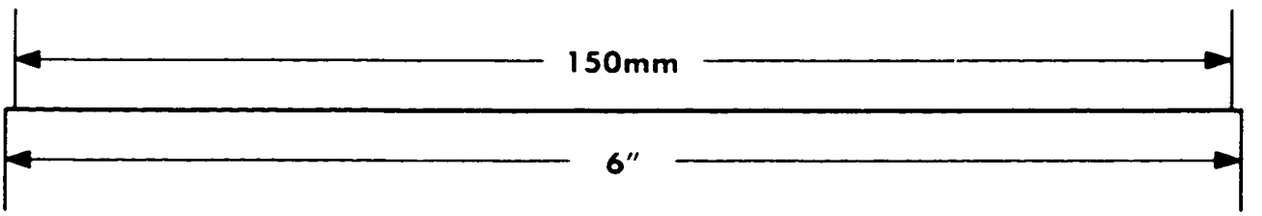

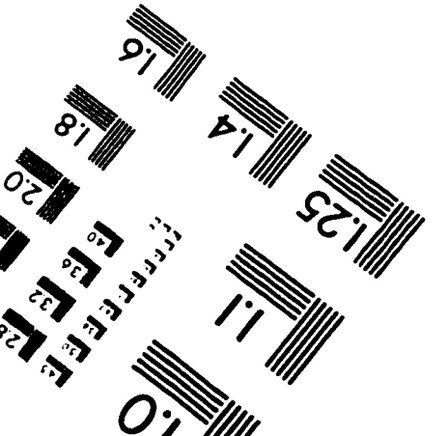

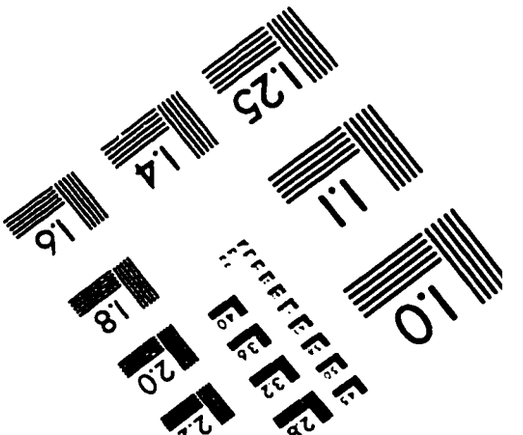

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