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I wish to express my most sincere appreciation and deepest gratitude to Professor H. Alper under whose supervision this research was conducted. This work could not have been successful without his great encouragement, excellent guidance and criticism.

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I am deeply grateful to my husband, Ranjan for his patience, support and understanding throughout the period of this study and for many tedious hours of proof reading, and to my parents, my family and my friends for their help, encouragement and good wishes during these years in Canada.

Ottawa, Canada
January, 1984

Chulangani Mahatantila

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ABBREVIATIONS

IR	- Infrared
NMR	- Nuclear Magnetic Resonance
s	- singlet
d	- doublet
dd	- doublet of doublets
t	- triplet
q	- quartet
m	- multiplet
br	- broad
MS	- Mass Spectra
mp	- melting point
bp	- boiling point
atm	- atmosphere
psi	- pounds per square inch
r.temp.	- room temperature
PTC	- phase transfer catalysis
hr	- hour
acac	- acetylacetonate

ABSTRACT

Novel metal complexed induced reactions of azirines provide simple and convenient synthetic approaches to heterocyclic systems. Palladium (0) catalyzed carbonylation reactions of azirines under homogeneous and heterogeneous reaction conditions, as well as molybdenum hexacarbonyl induced reactions of azirines in the presence of carbanions are described. Various reagents and conditions employed for carrying out these different reactions are presented in three sections.

The use of soluble palladium (0) catalysts for the carbonylation of azirines results in the novel syntheses of two important classes of compounds. The reaction course is dependent on the nature of the ligands attached to the metal. Tetrakis(triphenylphosphine)palladium (0) catalyzes the conversion of azirines to β-lactams, while vinyl isocyanates are formed in a regiospecific reaction using bis(dibenzylideneacetone)palladium (0) as the catalyst. A mechanism is proposed for these reactions.

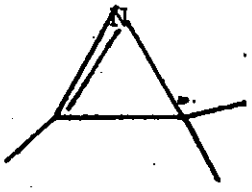
2-Styrylindoles were obtained in modest yields by the exposure of azirines to carbon monoxide, a palladium (0) catalyst, sodium hydroxide, benzene as the organic phase and benzyltriethylammonium chloride as the phase transfer agent. The reaction is sensitive to the atmosphere used.

Molybdenum hexacarbonyl induced reaction of azirines in the presence of carbanions results in a novel and stereospecific imide synthesis. The reaction is sensitive to the atmosphere used. Molybdenum hexacarbonyl induced reaction of azirine with ethyl diethyl malonate anion yielded an imino diester, a coupled product and a pyrrolinone instead of an imide.

CHAPTER 1

1. Introduction

The azirine ring system is a three membered heterocycle containing one nitrogen atom and one double bond. There are two isomeric azirines (1 and 2) which have been designated by Chemical Abstracts and "The Ring Index"[1], as 2H and 1H-azirine, respectively. More frequently a system of nomenclature that designates the position of the double bond has been used. Under this system compounds (1) and (2) are named as 1-azirine and 2-azirine respectively.



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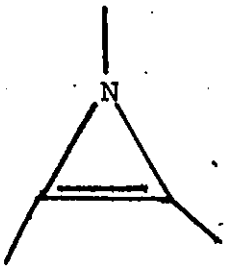


2

Although a number of 1-azirines have been synthesized and examined for their reactivity towards various reagents, there are no authentic examples of the isomeric 2-azirines as yet, in spite of several synthetic attempts.[2-6] Their instability is due not only to large bond-angle strain

inherent in any unsaturated 3-membered ring, but also to the overlap of the nitrogen lone-pair of electrons with the carbon-carbon double bond, a situation which gives rise to a destabilizing anti-aromatic 4π - electron system.

1-azirines are highly desirable synthetic reagents, due to high reactivity and relative ease of preparation. One can take advantage of the following features within their structure,

(i) high ring strain;

(ii) reactivity of the π bond - availability for cycloaddition reactions;

(iii) reactivity of the C = N bond towards electrophiles;

(iv) basicity of nitrogen-availability of the lone pair of electrons for protonation and complexation with metals.

1.2 Reactions of 1-Azirines

1.2.1. Photolytic and thermolytic reactions.

1.2.2. Reactions with electrophilic reagents.

1.2.3. Reactions with nucleophilic reagents.

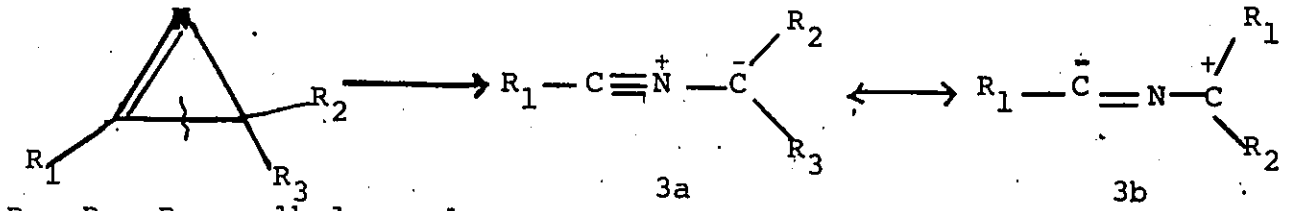
1.2.4. Cycloaddition reactions.

1.2.5. Metal promoted reactions.

1.2.6. Miscellaneous reactions.

1.2.1. Photolytic and thermolytic reactions

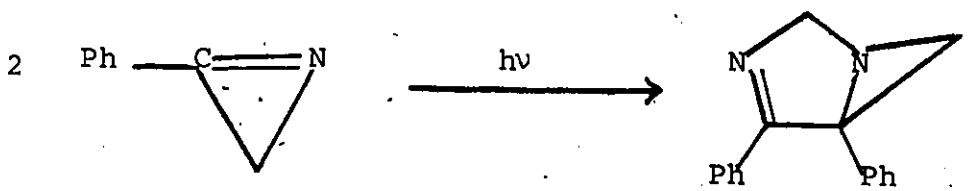
The photochemical decomposition and rearrangement of 1-azirines has aroused much interest in the last decade for the mechanistic and synthetic aspects of this branch of chemistry.[7,8] It has been demonstrated that, on photolysis 1-azirines undergo irreversible ring opening via C-C bond cleavage to 1,3 dipolar nitrile ylides (3a)<—>(3b) as intermediates, the latter readily undergo inter or intra-



3a 3b

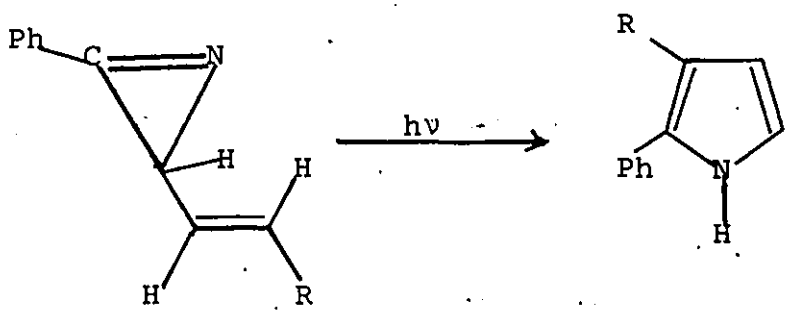
R_1, R_2, R_3 - alkyl, aryl

molecular 1,3 dipolar cycloaddition with a wide variety of dipolarophiles. Thus, the photolysis of 2-phenyl-1-azirine (4) affords diazabicyclohexene (5), by the intermolecular cycloaddition of the initially formed nitrile ylide intermediate (3) to a second molecule of azirine.[9]



4 5

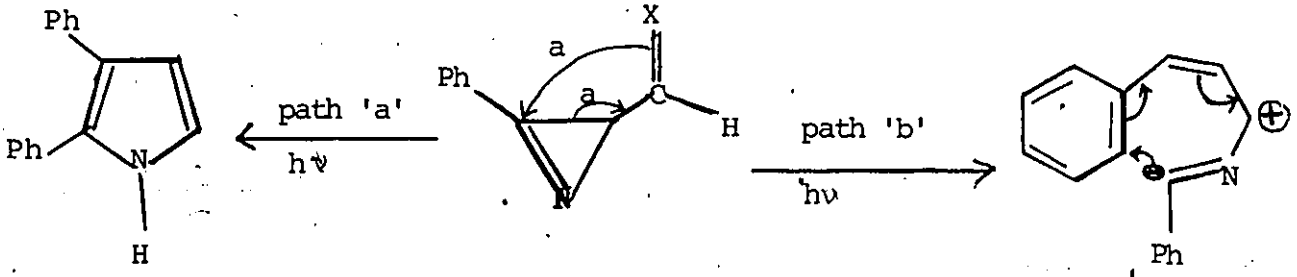
Many examples of intramolecular photocyclization also has been reported,[10,11] which involved the nitrile ylides derived from 1-azirines. For example, pyrroles (7) have been obtained on irradiation of 3-vinyl-1-azirine (6) as expected by intramolecular cyclization.



6 7

R = CN, CHO, COOMe

Of interest is the trans-styrylazirine (8) which gave 2,3 diphenyl pyrrole (9) according to path 'a' in contrast to its *cis* isomer which experienced ring expansion to the benzazepine[10] (10) [path 'b'].



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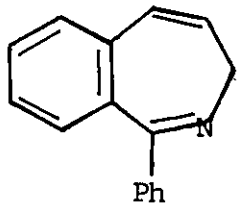
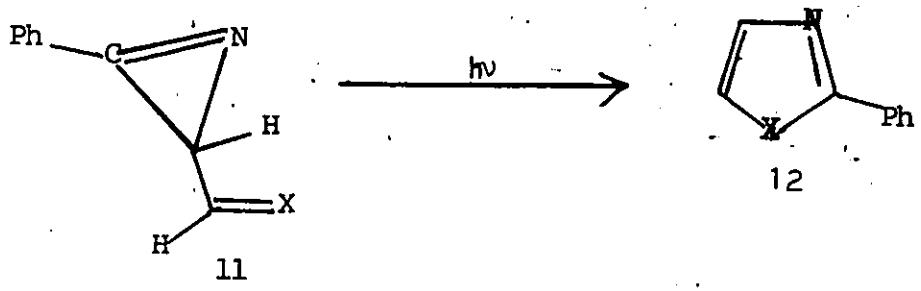


10

X = CHPh

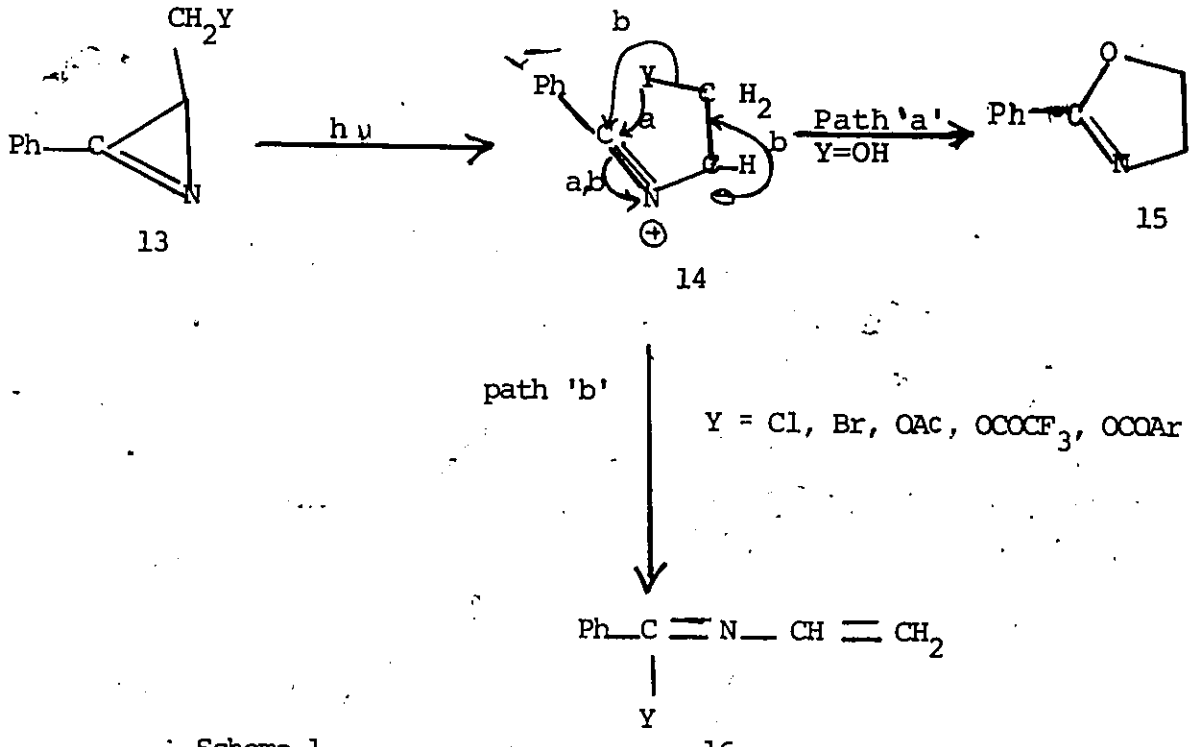
Similarly imidazole (12a) and oxazole (12b) has been obtained from compound (11) on photolysis via nitrile ylides.[12,13]



11 12

a, X = N—Ph b, X = O

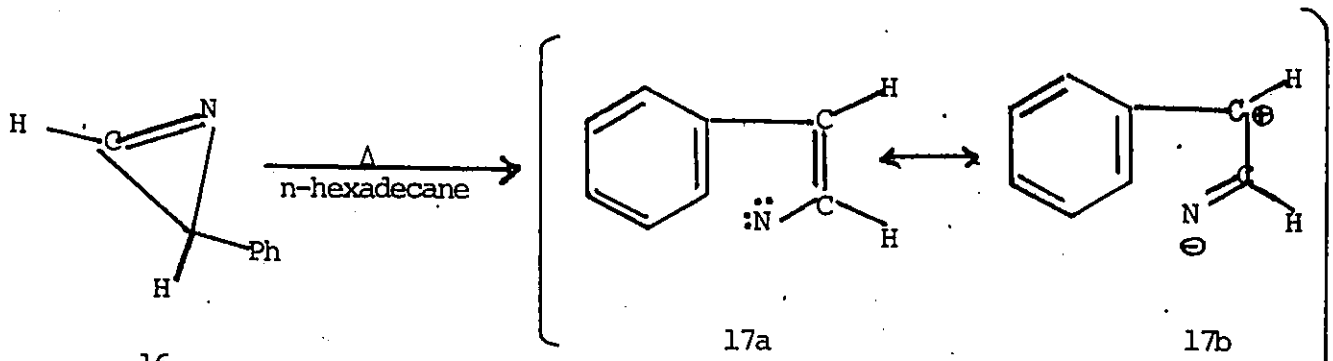
Photolysis of 3-hydroxymethyl-1-azirine (13) gave oxazoline(15) by proton transfer from the nitrile ylide intermediate (14) [Scheme 1; path 'a']. However, if 'Y' is a good leaving group, then 1-substituted 2-azabutadienes (16) were obtained [Scheme 1; path 'b'] by rearrangement [1,4 substituent shift].[9]



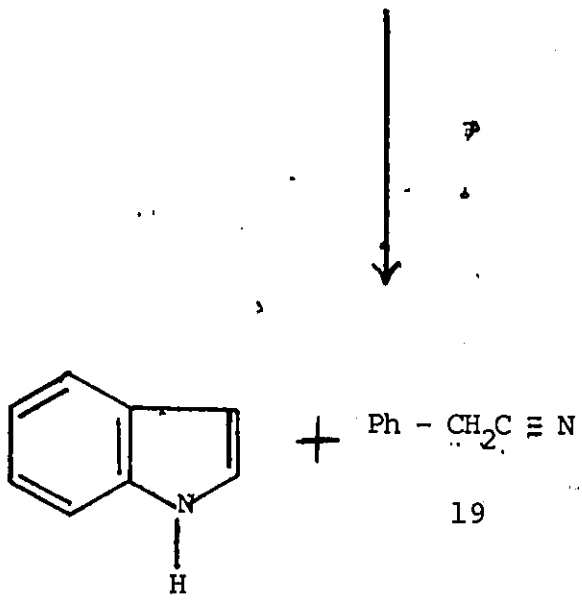
13 14 15 16

Scheme 1

In contrast to the photolysis, the thermochemistry of 1-azirines generally involves C-N rather than C-C bond cleavage. On thermolysis, 3-phenyl-1-azirine (16) gave an equimolar mixture of indoles (18) and phenyl acetonitrile (19) by rearrangement.[14] This result could be rationalized in terms of an equilibrium between azirine (16) and the corresponding transient vinyl nitrene (17), because the formation of (18) and (19) could be explained by intramolecular reactions of the vinyl nitrene (17).

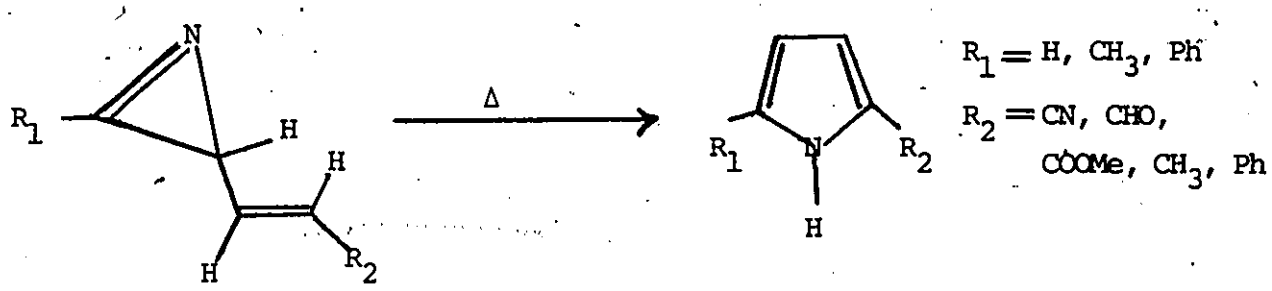


16 17a 17b



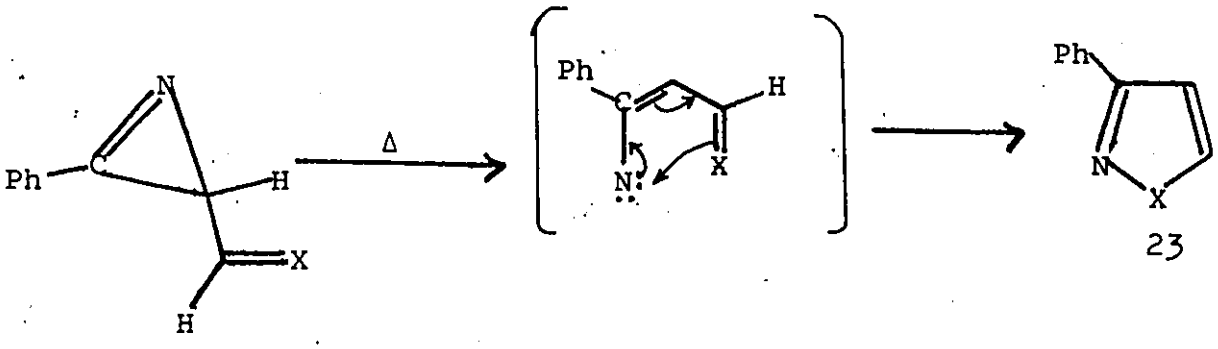
18 19

In the presence of a suitably positioned unsaturated side-chain, attack by the intermediate nitrene at the multiple bond leads to a series of heterocycles isomeric with those obtained photochemically. For example, pyrroles (21) have been obtained from the 1-azirines (20) on thermolysis, by intramolecular cyclization.[12,15]



20 21

Similarly, isoxazole (23a) and pyrazole (23b) were formed on thermolysis of compound (22).



22 23

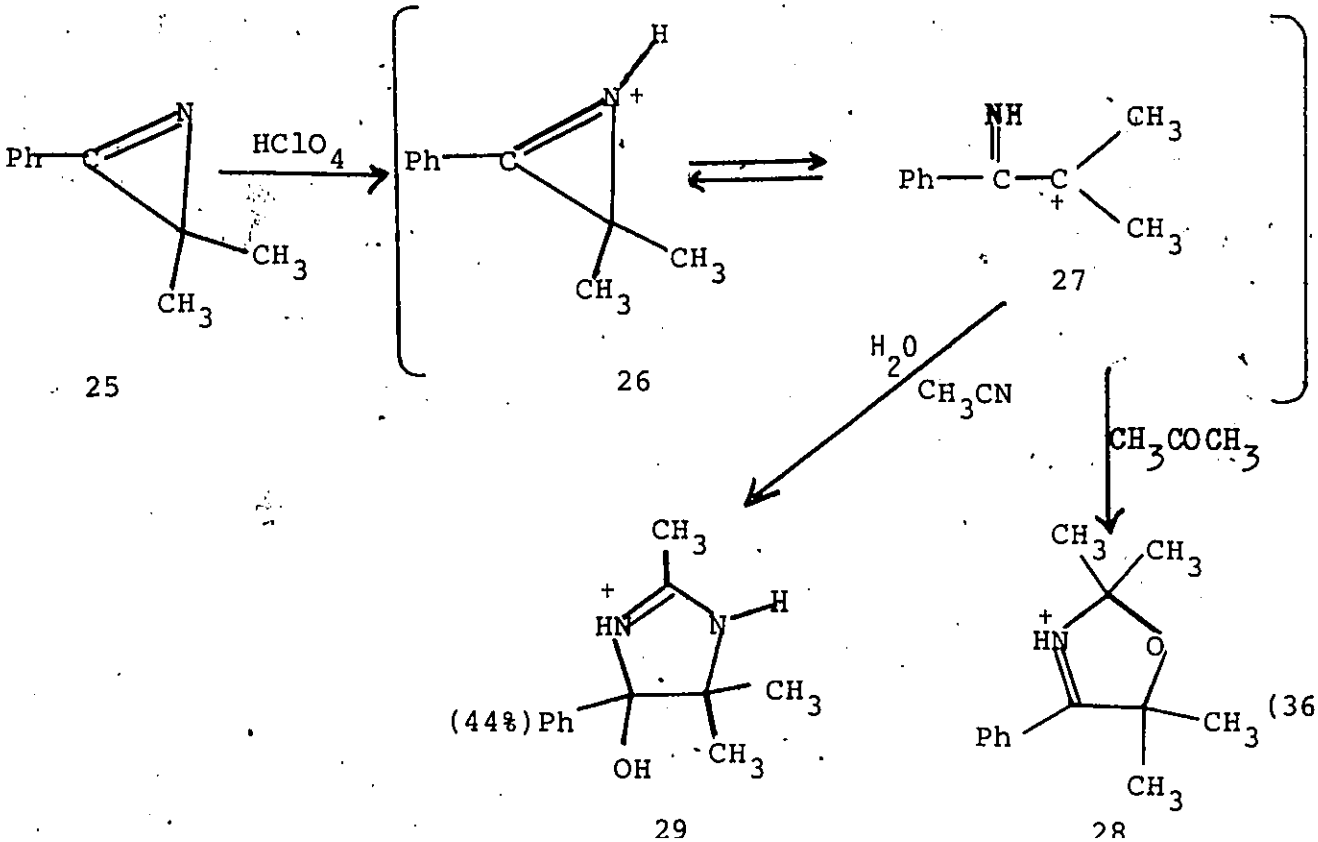
a, X=O b, X=N-Ph

This type of thermal ring expansion is believed to involve participation of a vinyl nitrene intermediate resulting from C-N bond cleavage of 1-azirines.[12,15,16]

1.2.2. Reactions with electrophilic reagents

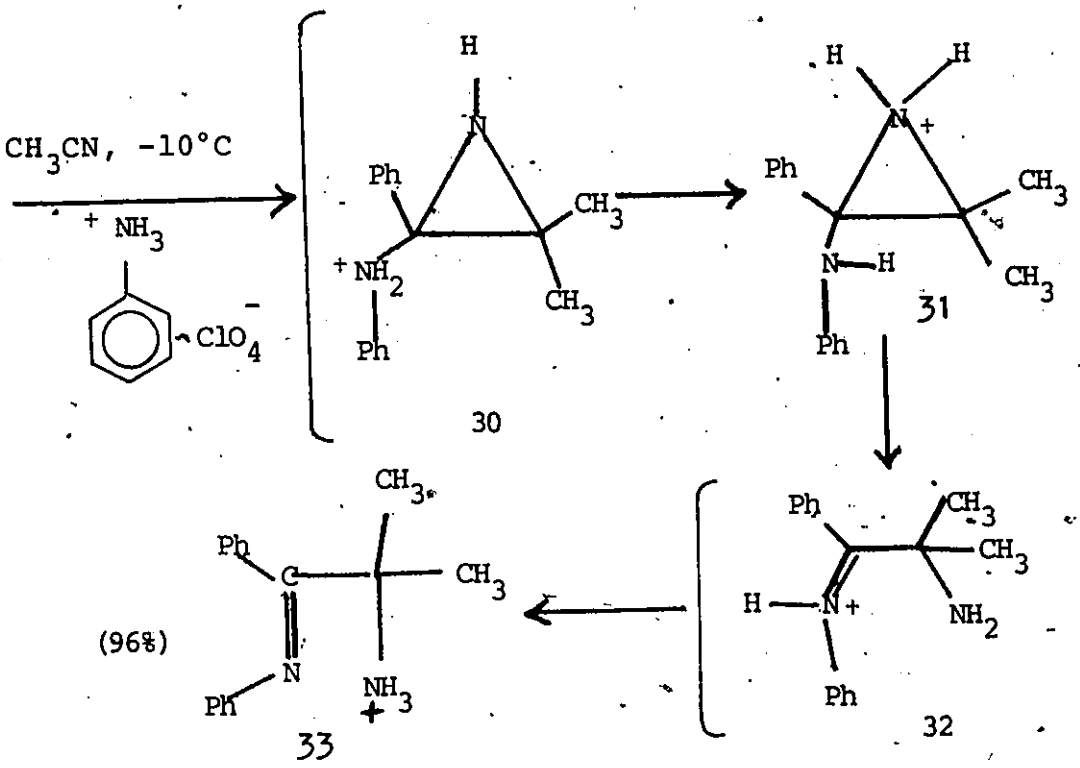
1-Azirines are very nonbasic due to the large degree of s character in the orbital containing the lone pair of electrons on the nitrogen.[17] They are insoluble in dilute HCl, but soluble with slow decomposition in concentrated acid.[18]

The anhydrous perchloric acid catalyzed reactions of 3,3-dimethyl-2-phenyl-1-azirine (25) with acetone, acetonitrile and aniline have been studied[19,20].

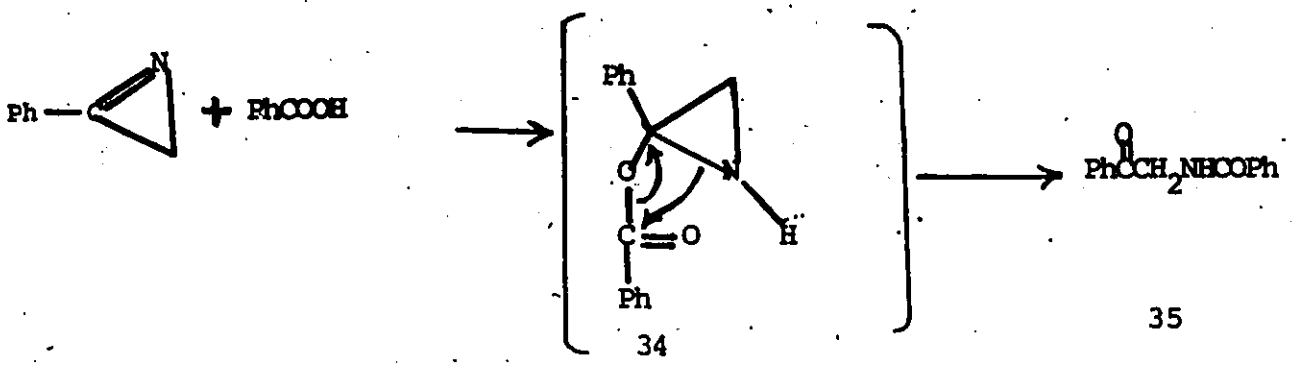


25 26 27 29 28

Protonated azirine ring (26) is believed to ring open to resonance stabilized cation (27), which then adds to the carbon-oxygen double bond or carbon-nitrogen triple bond to give (28) and (29) respectively. Similarly, the α-ammonioisobutyrophenone anil perchlorate (33) was obtained when azirine (25) was treated with anilinium perchlorate[20] in acetonitrile. The reaction has been postulated to proceed through aziridine (30), which rearranges to (32) [via 31].

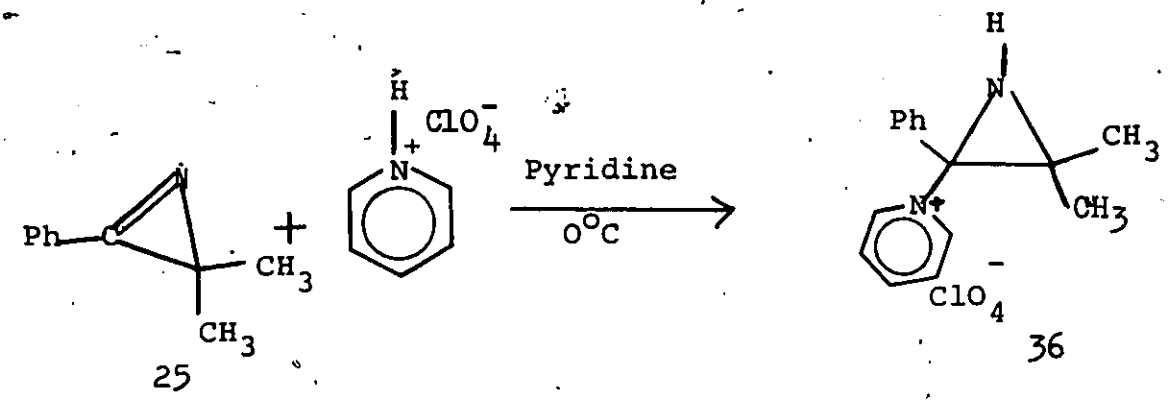


Reaction of 2-phenyl-1-azirine with benzoic acid resulted in the formation of N-benzoylphenacylamine (35).[21] Aziridine (34), believed to be an intermediate in this reaction, could then rearrange to (35).



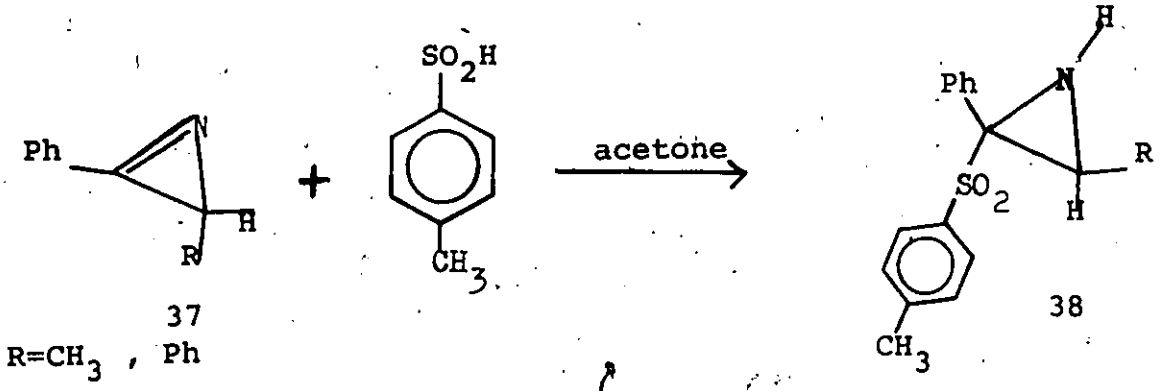
34 35

The addition of some acids to 1-azirines does not result in destruction of the 3-membered ring. For example, aziridine (36) has been obtained by Leonard and Zwanenburg, when 1-azirine (25) was treated with pyridinium perchlorate in pyridine.[19]



25 36

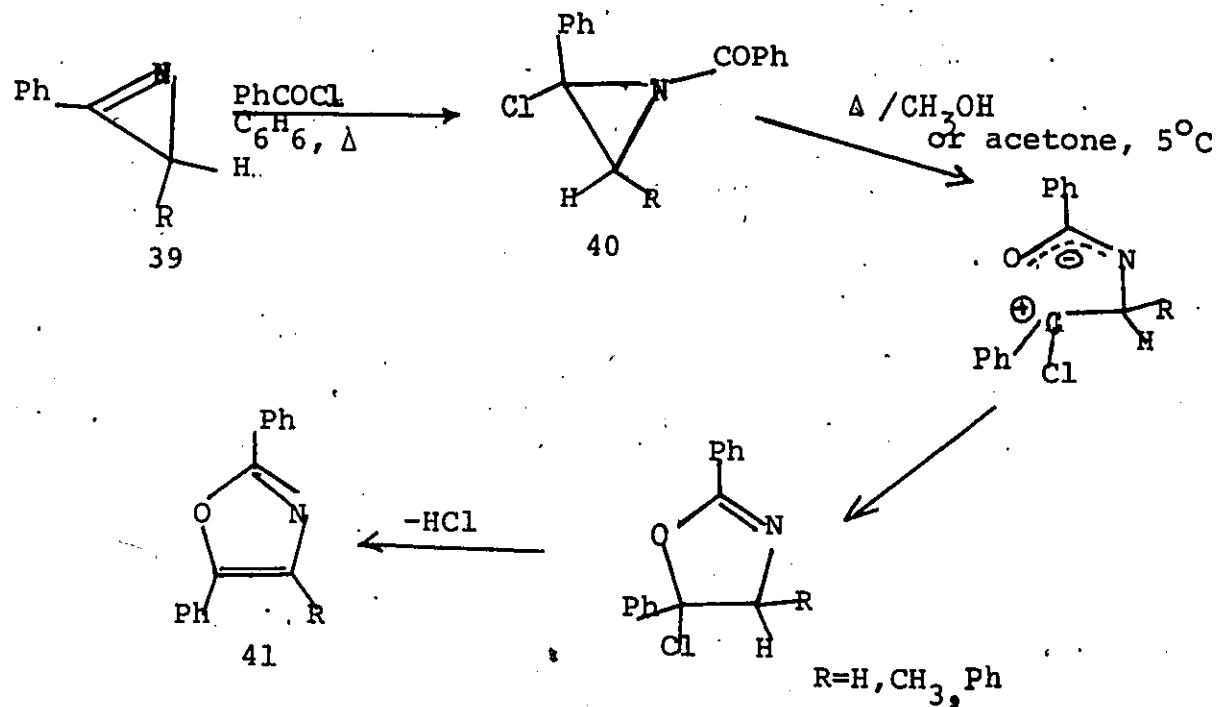
Similarly, addition of p-toluenesulfinic acid to 1-azirines (37) readily seems to give the sulfonyl aziridines (38).



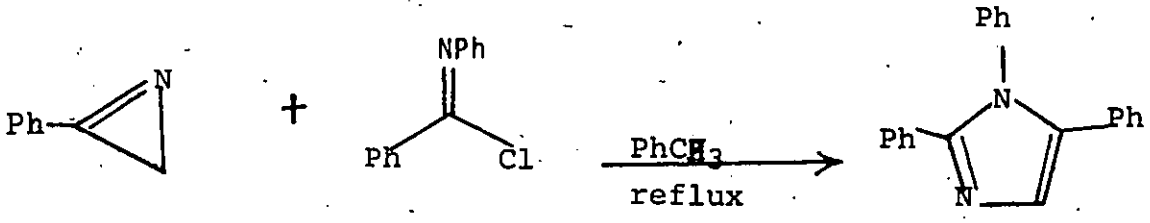
37
R=CH_3 , Ph

38

When reagents such as acid chlorides were reacted with 1-azirines (39) N-benzoyl-2-chloro aziridines (40)were obtained.[22] These were converted to oxazoles (41) in polar solvents or by heating. Similarly, acid anhydrides also were reported[21] to give oxazoles when heated with 1-azirines in benzene.

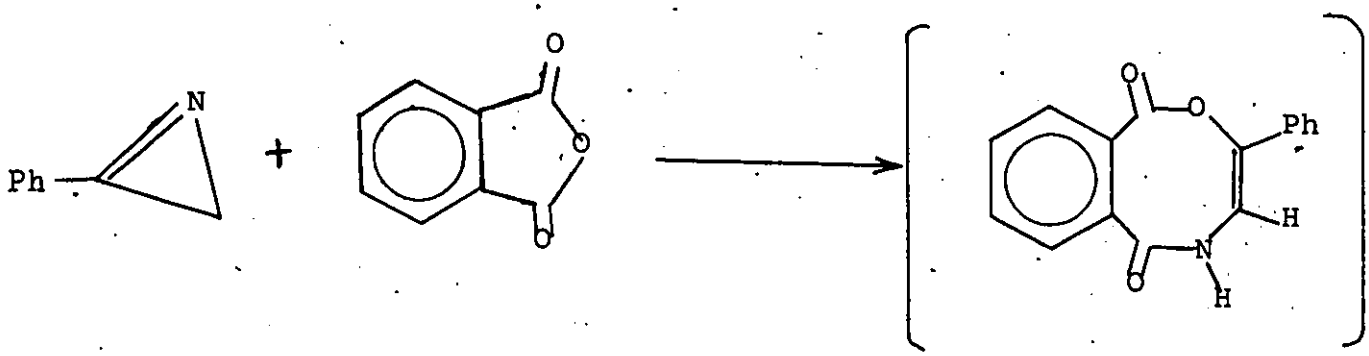


When N-phenylbenzimidoyl chloride was treated with 2-phenyl-1-azirine, 1,2,5 triphenylimidazole (42) was obtained as expected.[21]



42

However, ketoamide (44) was formed rather than the oxazole, when 2-phenyl-1-azirine was reacted with phthalic anhydride, presumably via hydrolysis of the initially formed 8-membered intermediate (43).[21] Similarly, maleic anhydride gave N-phenacylmaleinmonoamide.



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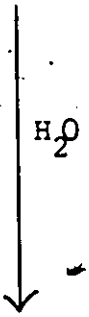
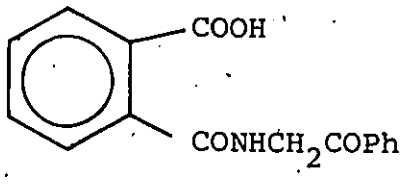
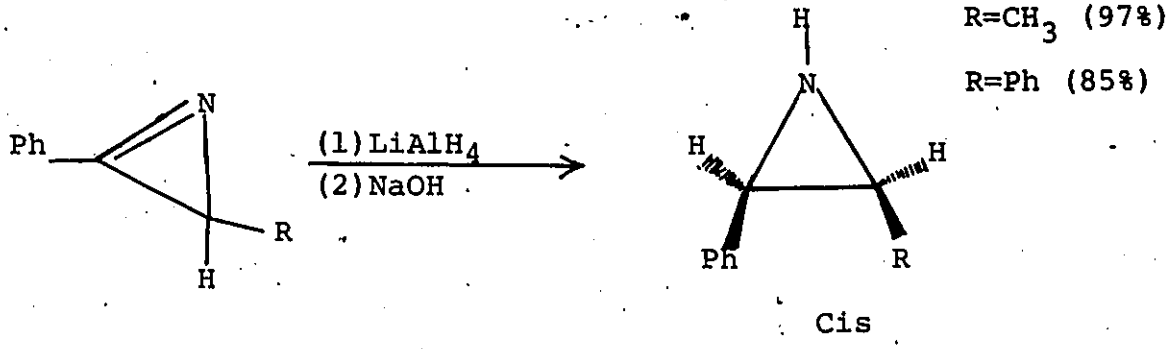




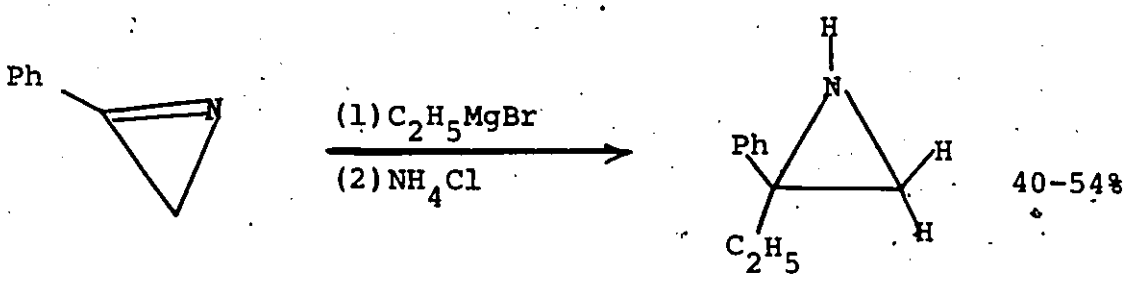
44

1.2.3. Reactions with nucleophilic Reagents

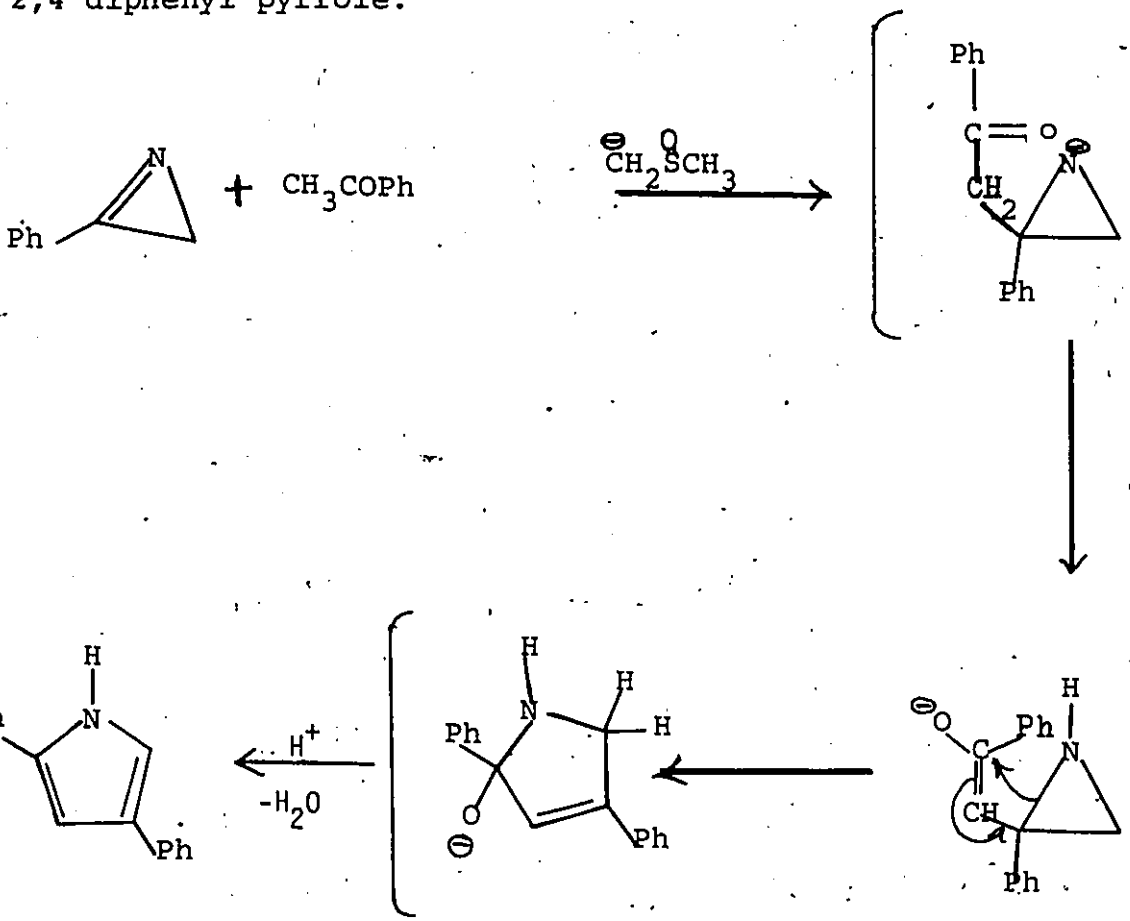
Addition of nucleophiles to the C=N of 1-azirines has reported to occur readily and stereospecifically from the least hindered side of the molecule.[17,23,24] Several 1-azirines have been reduced to aziridines with $LiAlH_4$. The reaction usually proceeds in high yield and is stereospecific.[25,26] This has therefore provided a useful synthesis of cis-1,2-disubstituted aziridines. The reaction of 1-azirines with sodium borohydride also has been reported to give aziridines.[24]



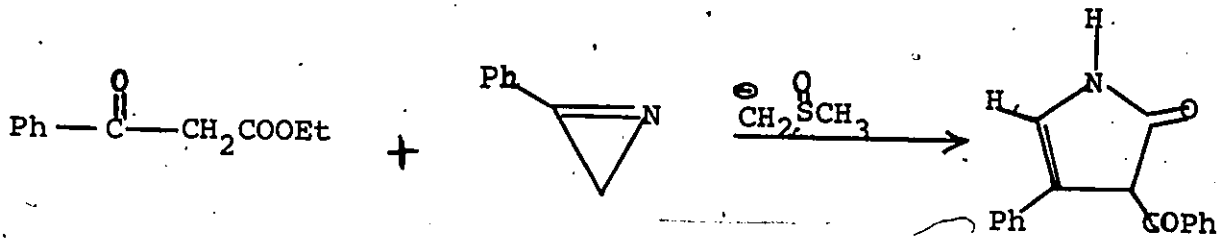
Grignard reagents have been shown to react with 1-azirines to give aziridines.[18,22,27] This is analogous to the stereospecific reduction of azirines to aziridines by $LiAlH_4$. The attack of the Grignard reagent has been shown to occur stereospecifically from the less sterically hindered side of the azirine.[28]



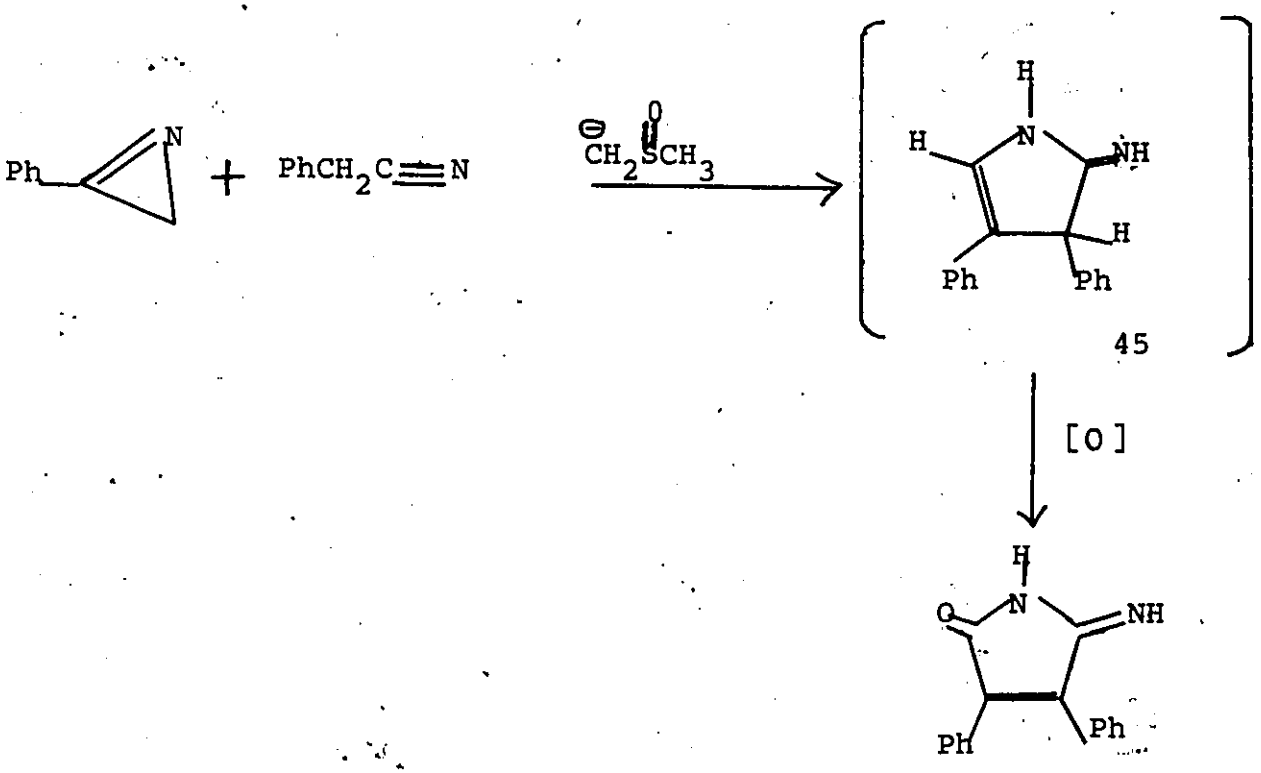
A variety of carbanions have been added to 1-azirines. Reaction of 2-phenyl-1-azirine with acetophenone in the presence of dimethylsulfinyl carbanion afforded 2,4 diphenyl pyrrole.[21]



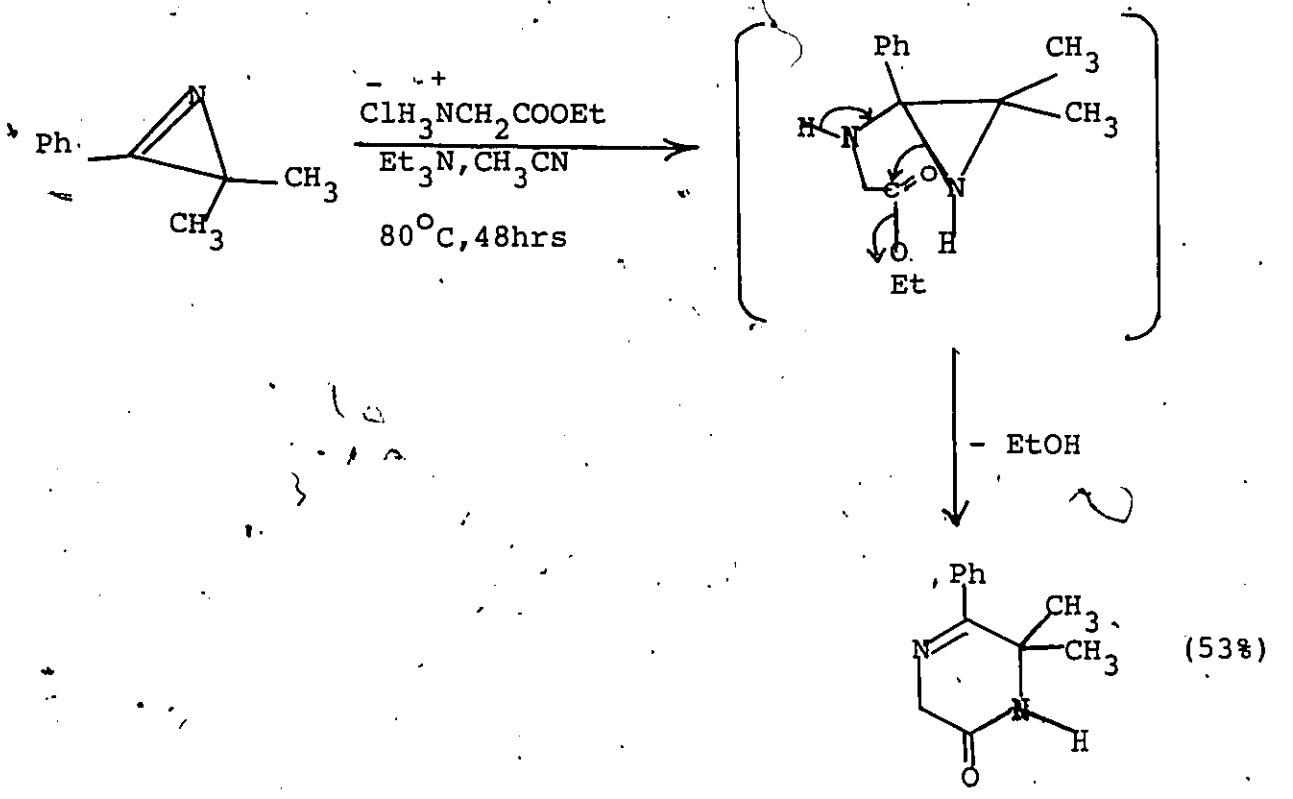
Similarly, ethyl benzoylacetate has yielded 3-benzoyl-4-phenyl-2-oxopyrroline by reaction with 2-phenyl-1-azirine in the presence of dimethylsulfinyl carbanion.[21]

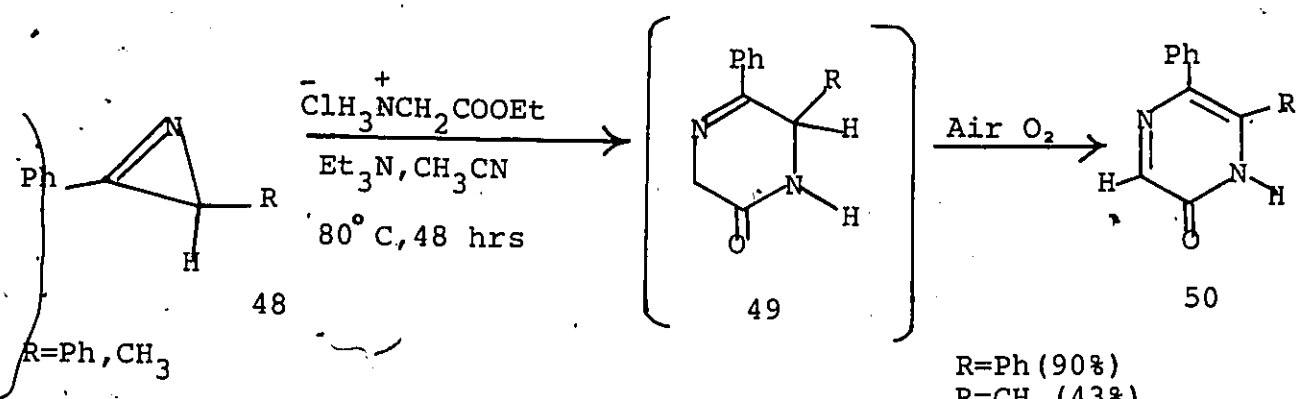


3,4-Diphenyl-2-oxo-5-iminopyrroline (46) has been obtained under similar conditions with benzyl cyanide. Probably the iminopyrroline (45) was formed initially and then oxidized by air to (46).[21]

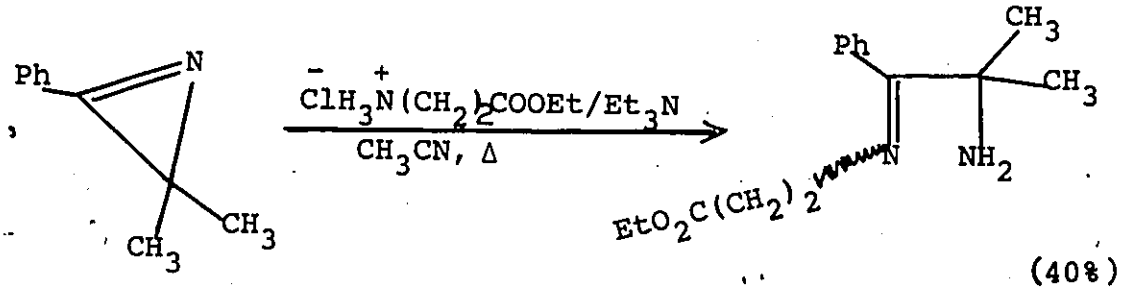


Recently nucleophilic addition of α-amino esters or α-hydroxy esters to 1-azirines was reported.[29] For example, treatment of 3,3- dimethyl-2-phenyl-1-azirine with glycine ethyl ester hydrochloride in the presence of Et_3N in CH_3CN gave dihydropyrazinone (47) in 53% yield. Similarly, with 1-azirines (48) pyrazinones (50) have been isolated, probably by air oxidation of the initially formed dihydropyrazinone (49). But product (51) has been obtained





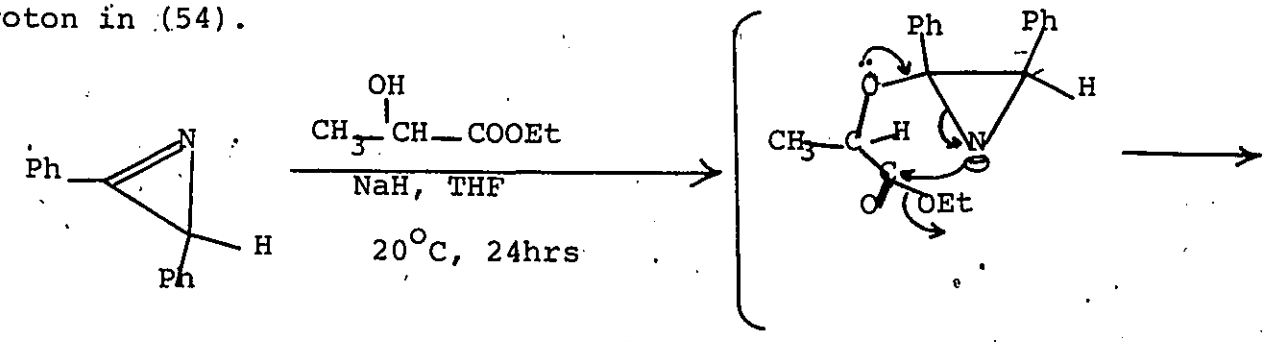
instead of a heterocycle when 3,3 -dimethyl-2-phenyl-1-azirine was treated with β-alanine ethyl ester hydrochloride.

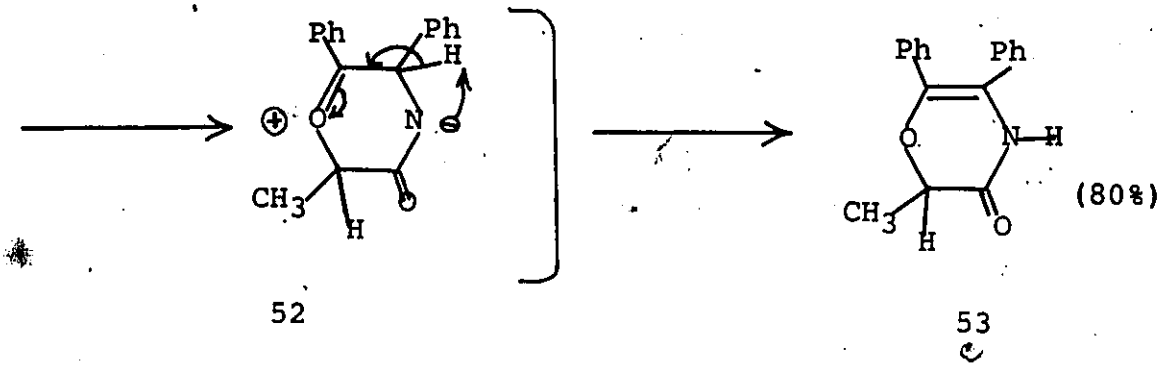


(40%)

51

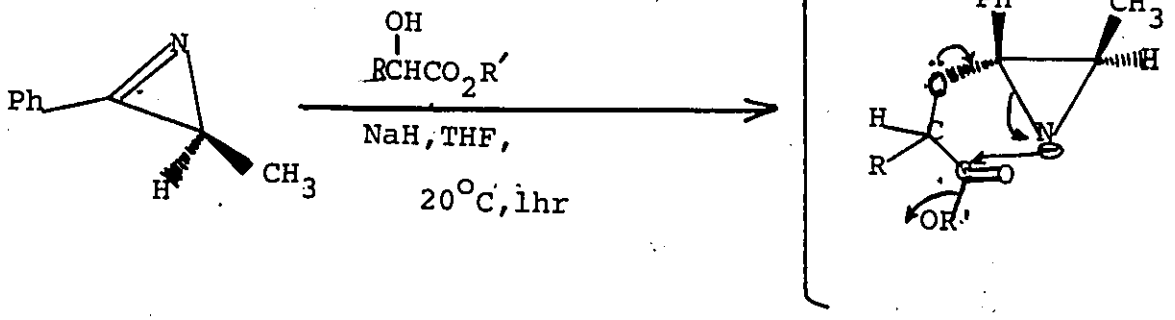
Nucleophilic addition of ethyl lactate to 2,3-diphenyl-1-azirine in the presence of NaH in THF gave (53) in a similar manner to α -amino esters. But a different result was observed when 3-methyl-2-phenyl-1-azirine was reacted with 0.50 mole of ethyl lactate or methyl mandelate. Heterocycle (55) was the only product formed in this reaction by condensation of 2 molecules of azirines with 1 molecule of α -hydroxy ester. When the above reaction was carried out using an equimolar amount of ethyl lactate, product (55) was formed as the major product with small amount of (56). But in the 2,3-diphenyl-1-azirine reaction, the analogous product of (55) was not formed. This may be due to more mobility of the benzylic proton in (52) than the aliphatic proton in (54).

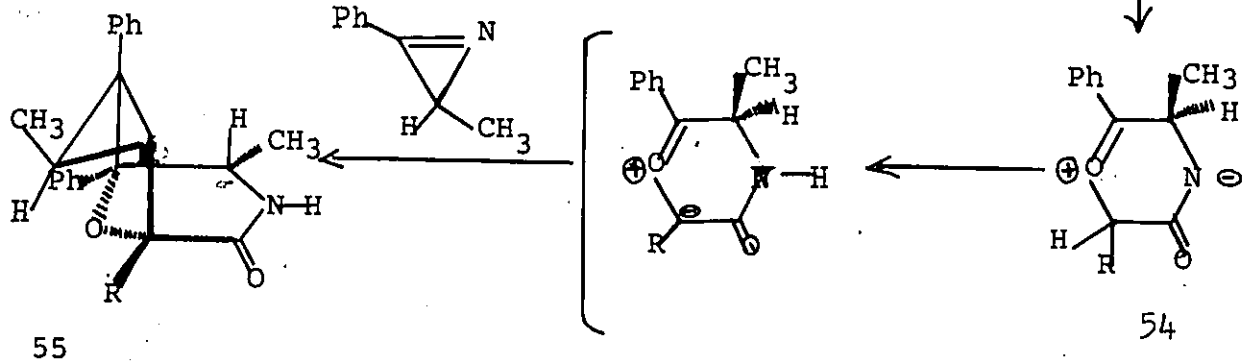




52

53 (80%)



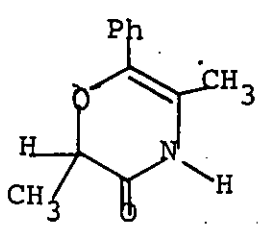


54

55

R=CH_3 (86%)

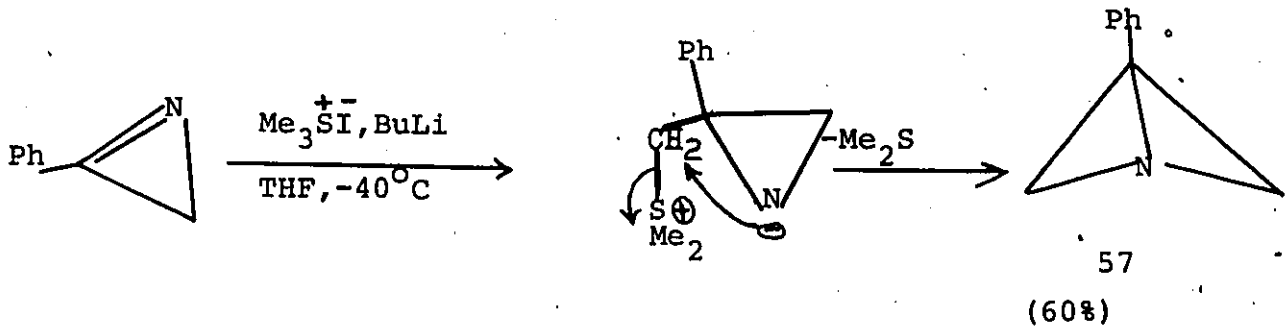
R=Ph (76%)



(10%)

56

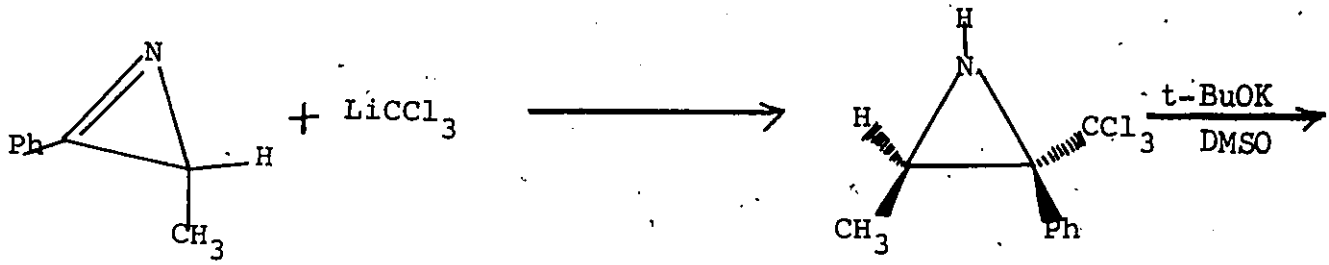
The first example of the 1-azabicyclo[1.1.0]butane ring system (57) has been obtained,[30] When 2-phenyl-1-azirine was treated with dimethylsulphonium methylide.



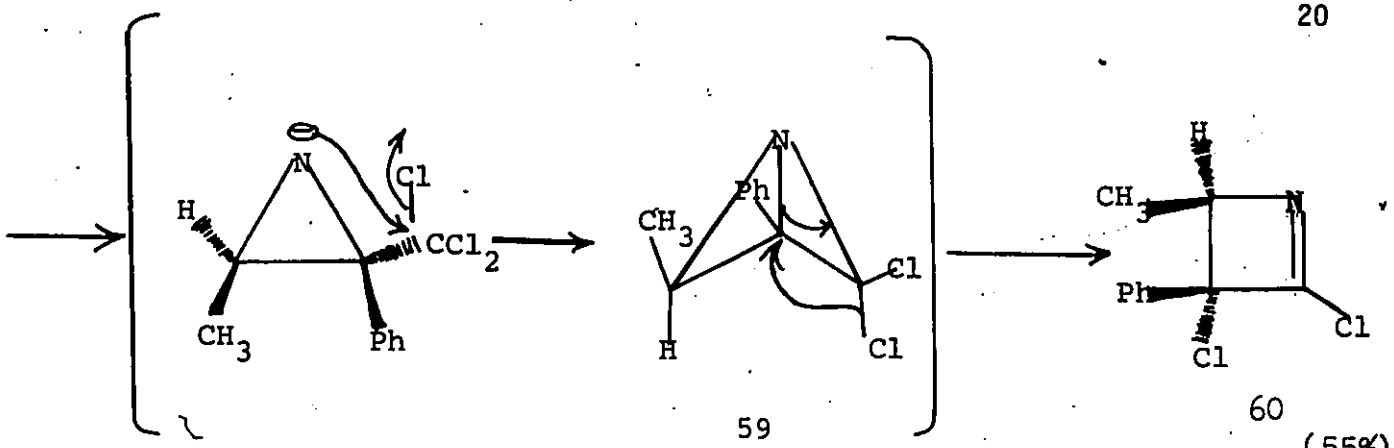
57

(60%)

Other attempts to prepare azabicyclobutane by addition of dichlorocarbenes to 1-azirines has given only N-vinylimines. However, adduct (58) has been obtained[31] by the reaction of 3-methyl-2-phenyl-1-azirine with trichloromethyl lithium. Attempted ring closure of (58) to an azabicyclobutane (59) has lead to isolation of the 4-membered ring azetine (60), which has suggested that the bicyclic compound (59) might be an intermediate in this reaction.



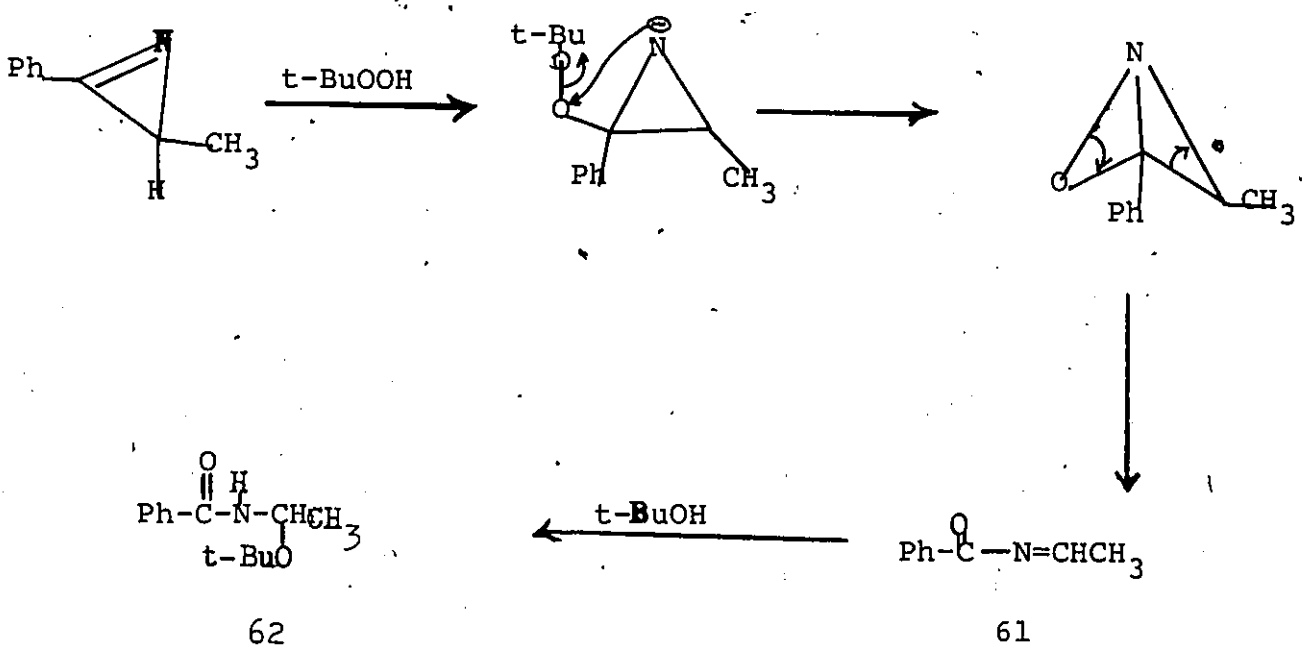
58



59

60 (55%)

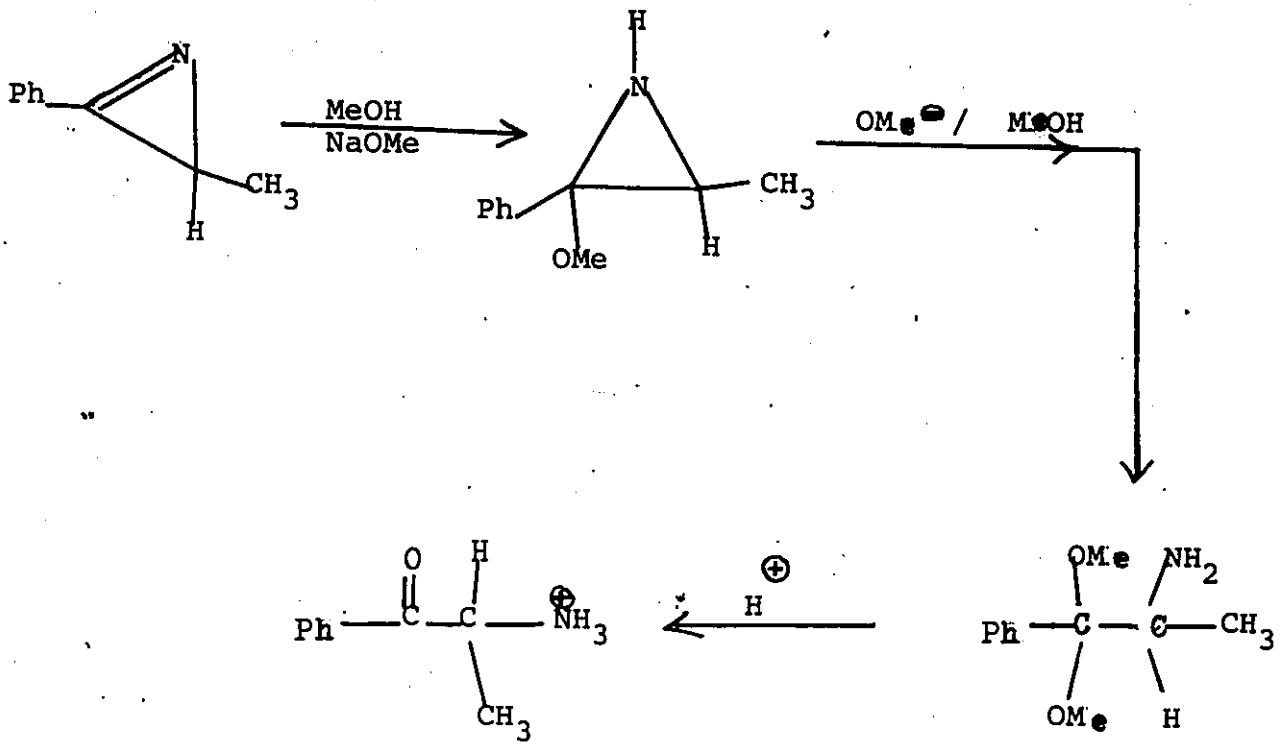
Attempted epoxidation of azirines to produce oxazabicyclobutanes have been unsuccessful thus far. The acylimine (61) or its alcohol addition product (62) have been isolated when t-butylhydroperoxide was employed.[23]



62

61

Aminoketones and acetals could be obtained by treatment of 1-azirines with methanol containing a catalytic amount of sodium methoxide.[32]



1.2.4. Cycloaddition Reactions

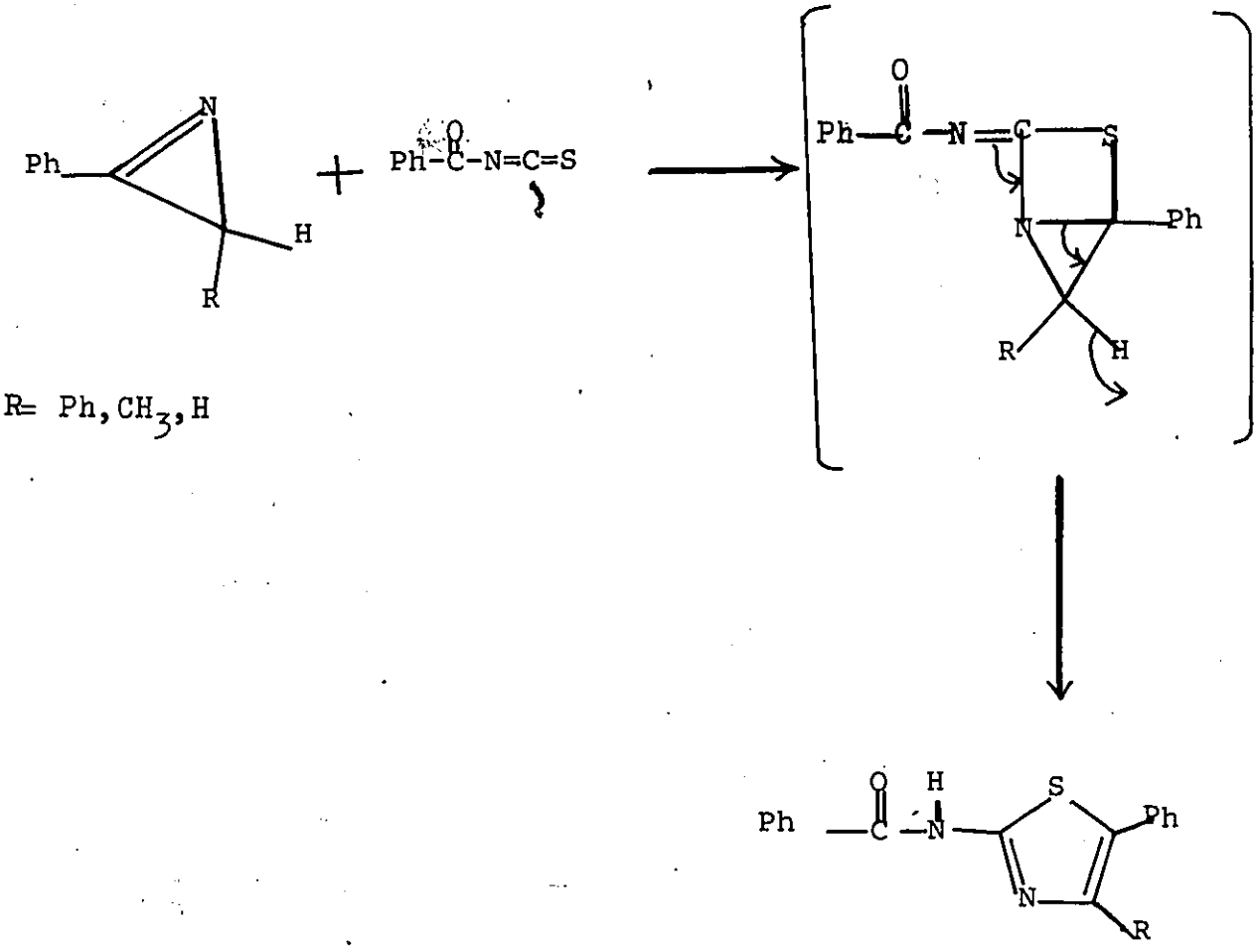
To effect cycloadditions under suitable reaction conditions, advantage can be taken of the inherent reactivity of the rigid carbon-nitrogen double bond of 1-azirines. These cycloaddition reactions are potentially valuable routes for the preparation of unusual heterocyclic compounds.

A. Thermal cycloaddition reactions (2 + 1) cycloaddition

The successful synthesis of azabicyclobutane (57) which was mentioned before is an example of a (2 + 1) cycloaddition reaction.

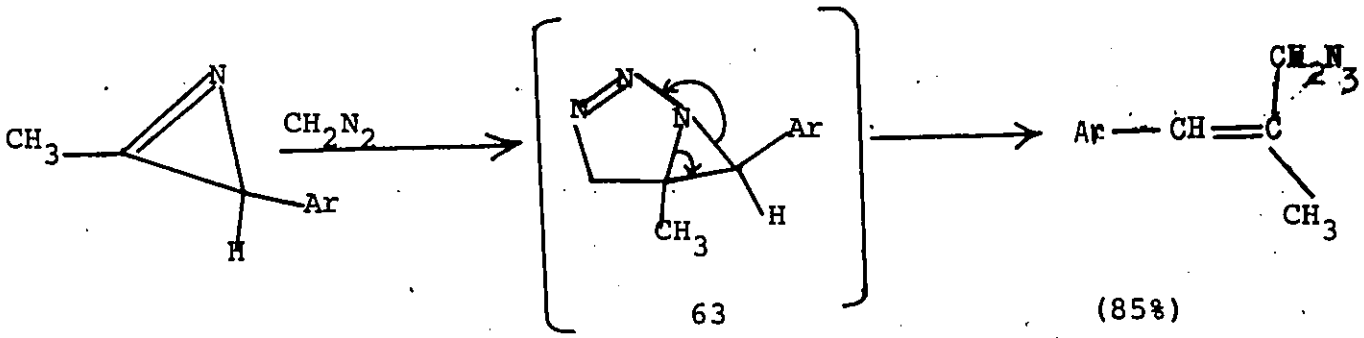
(2 + 2) cycloaddition

It has been shown that for the synthesis of heterocyclic compounds, 1-azirines are extremely useful precursors and could be incorporated into compounds containing desirable functions. A class of reactive reagents that can enter into complex heterocyclic systems through cycloadditions with azirines are heterocumulenes. For example, thiazoles were obtained as products by (2 + 2) cycloaddition when benzoyl isothiocyanate was reacted with 1-azirines.[33] Another heterocumulene , CS_2, also has been reported to add in a (2 + 2) fashion across its C = S bond to give thiazole.[34]

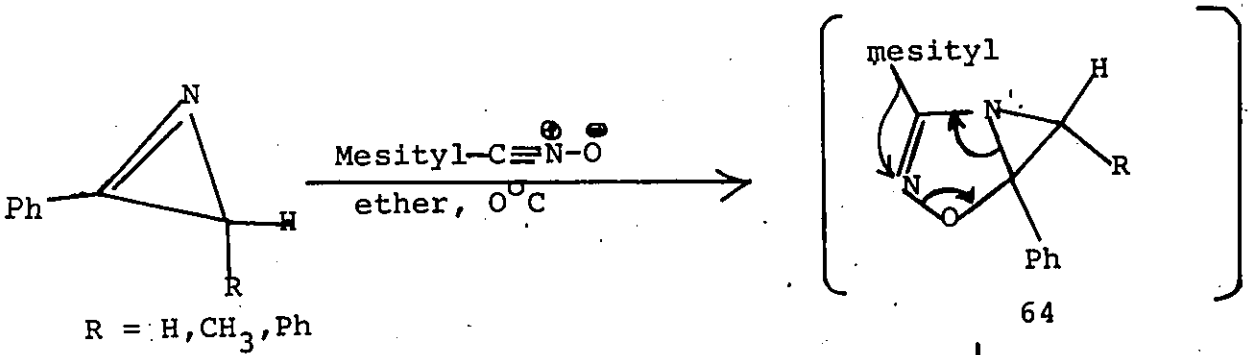


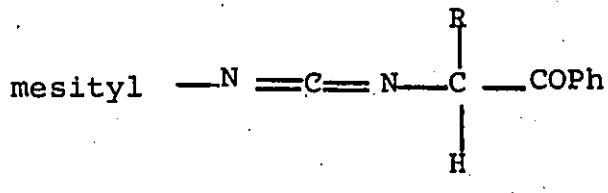
(2 + 3) cycloaddition

Addition of diazomethane to 1-azirine was the first example of this type of reaction.[35,36] The allyl azide which was obtained could arise from the initially formed triazoline cycloadduct (63).



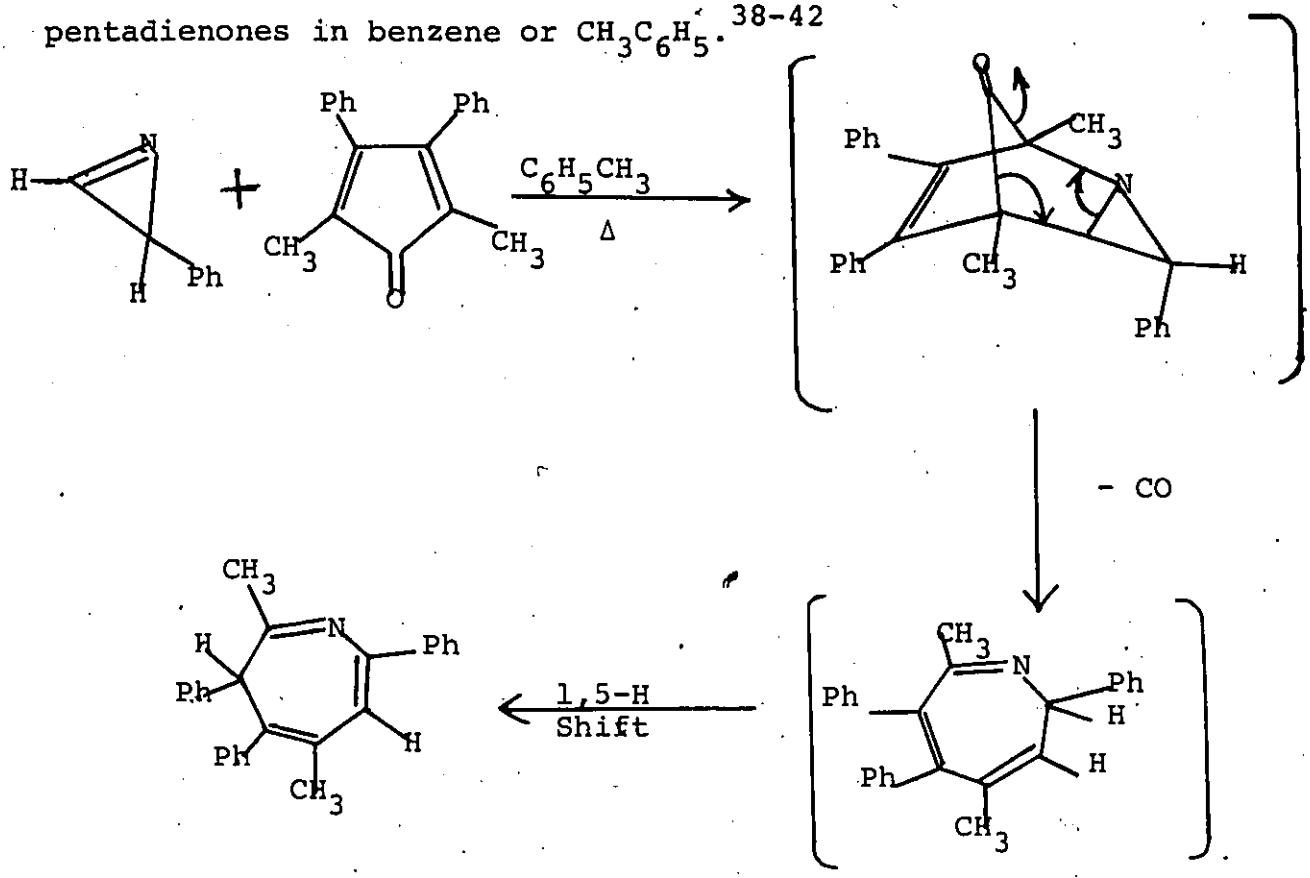
Similarly, reaction of mesityl nitrile oxide with 1-azirines gave carbodiimides via an initially formed 1,3 dipolar cycloadduct (64).[37]



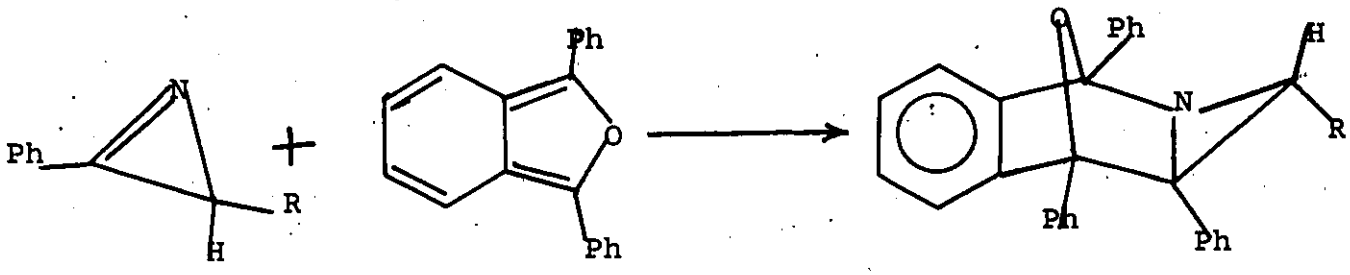


(2 + 4) cycloaddition

During the past several years, the formation of various heterocyclic compounds using 1-azirines as dienophiles has been reported. For example, 3H-azepines were obtained when 1-azirines were refluxed with cyclopentadienones in benzene or $CH_3C_6H_5$.[38-42]



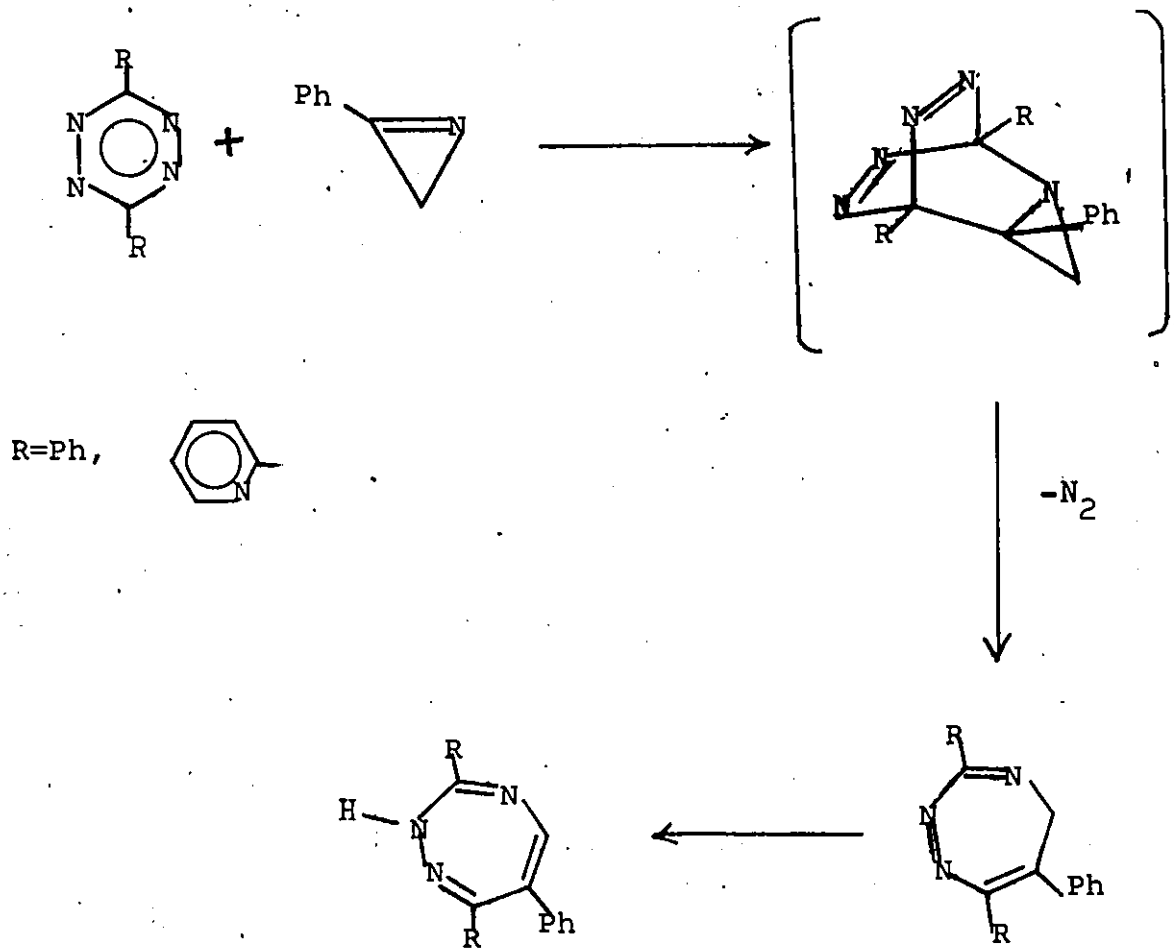
When the cycloaddition reaction of isobenzofuran with 1-azirines were carried out the exo cycloadducts (65) were isolated.[43]



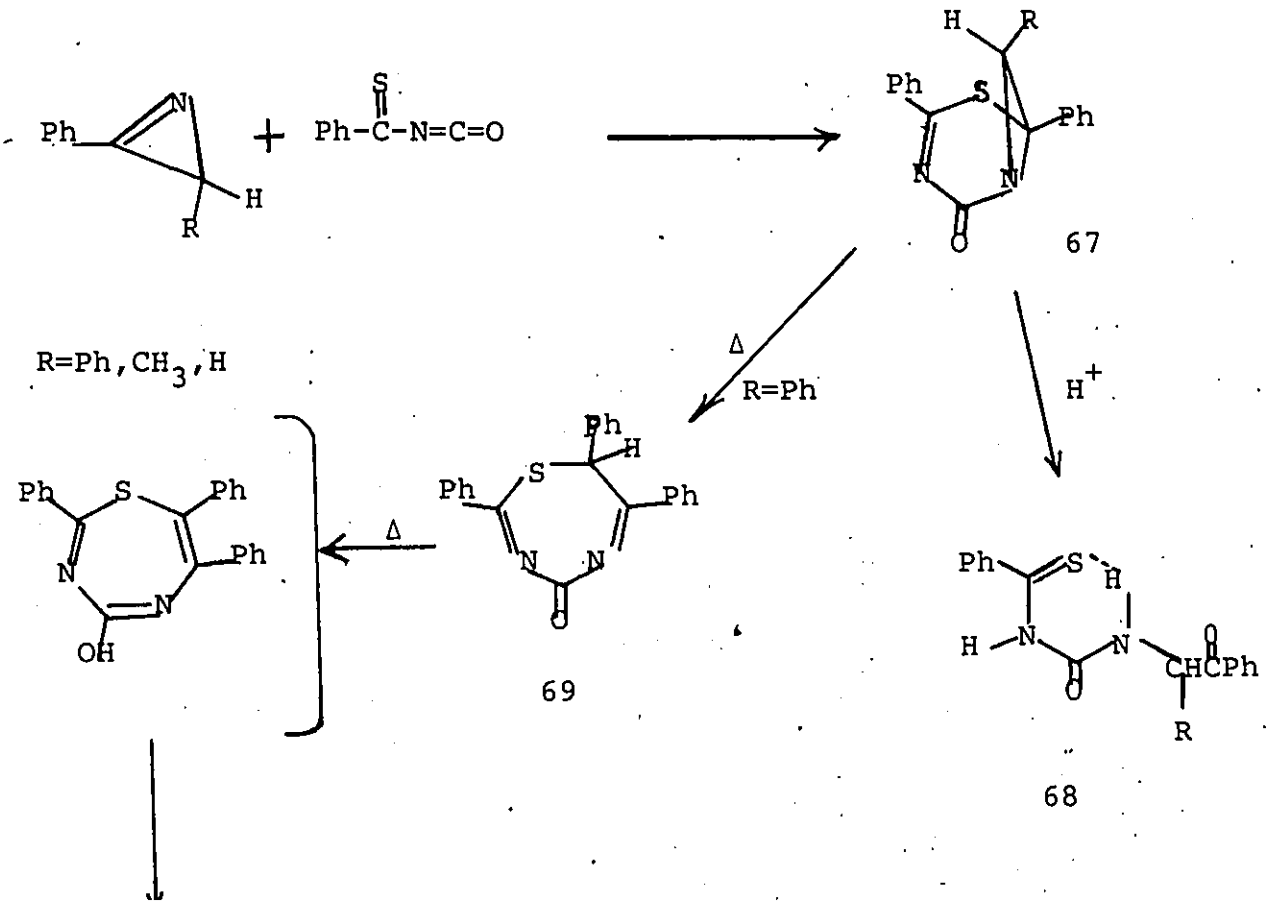
65

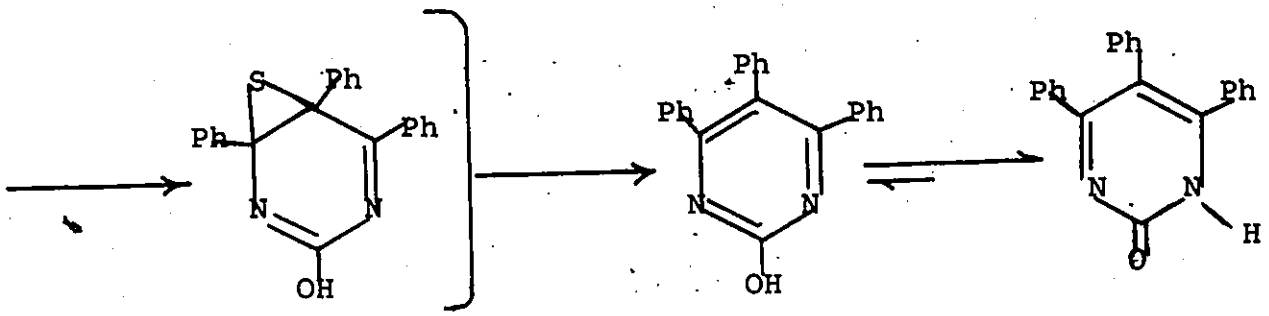
R=Ph,H

Diels-Alder reaction of 1-azirines with the diene components of tetrazines occurs to give triazepines (66) with the loss of nitrogen. Further thermolysis leads to a variety of other heterocycles, including pyrimidines, triazoles, pyrazoles.[44]



Heterocumulenes containing a carbonyl or related unsaturation adjacent to the cumulative bonds are usually very reactive, and thus thiobenzoyl isocyanate and benzoyl isocyanate are excellent compounds for cycloaddition with 1-azirines. When thiobenzoyl isocyanate was reacted with 1-azirines at room temperature, cis bicyclic aziridines (67) were obtained by stereospecific and regiospecific addition.[33,45] Acid catalyzed hydrolysis of the latter gave the urea (68). Thiadiazepinone (69) has been obtained when the cycloadduct (67) (R = Ph) was subjected to thermolysis,[prolonged thermolysis gave the pyrimidone (70)]. The behaviour of benzoyl isocyanate paralleled that of thiobenzoyl isocyanate and (4 + 2) cycloadducts have been isolated.[33]

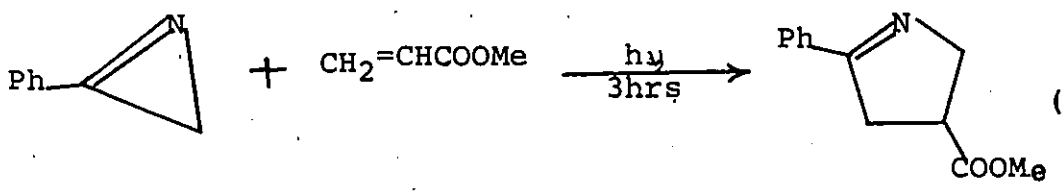




70

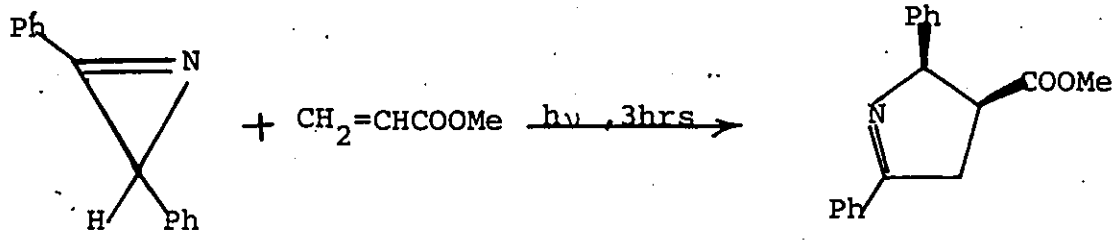
B. Photochemical cycloaddition reactions

As mentioned earlier, the photolysis of 1-azirines leads to irreversible carbon-carbon single bond cleavage of the ring and generation of nitrile ylides (3). The latter readily undergo inter or intramolecular 1,3 dipolar cycloadditions with a wide variety of dipolarophiles to form 5-membered heterocyclic compounds. Several electron deficient olefins have been reported to give Δ^1- pyrrolines regiospecifically on photolysis with 1-azirines.[46,47] For example, 2-phenyl-4-carbomethoxy- Δ^1-pyrroline has been obtained on irradiation of a solution of 2-phenyl-1-azirine in excess methyl acrylate.

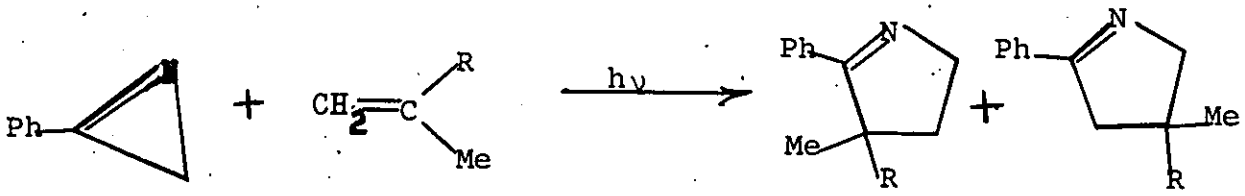


(80%).

Similarly, photolysis of 2,3-diphenyl-1-azirine with methyl acrylate afforded 2,5-diphenyl-cis-4-methoxy-carbonyl-Δ^1-pyrroline as a single photoadduct.



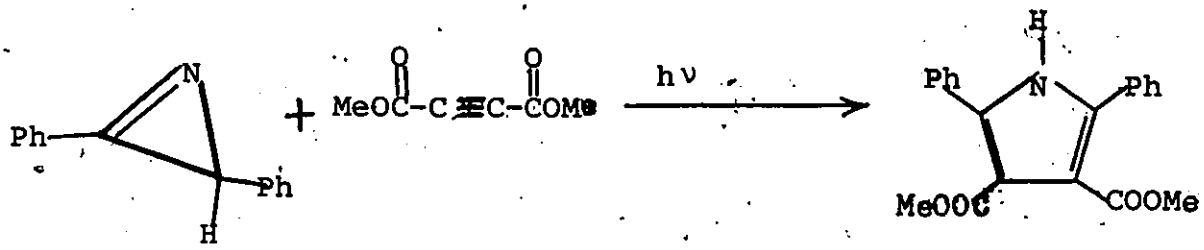
Interestingly, two major products (71) and (72) have been obtained on photolysis of 2-phenyl-1-azirine with methylmethacrylate. Similar results were obtained with methacrylonitrile too.



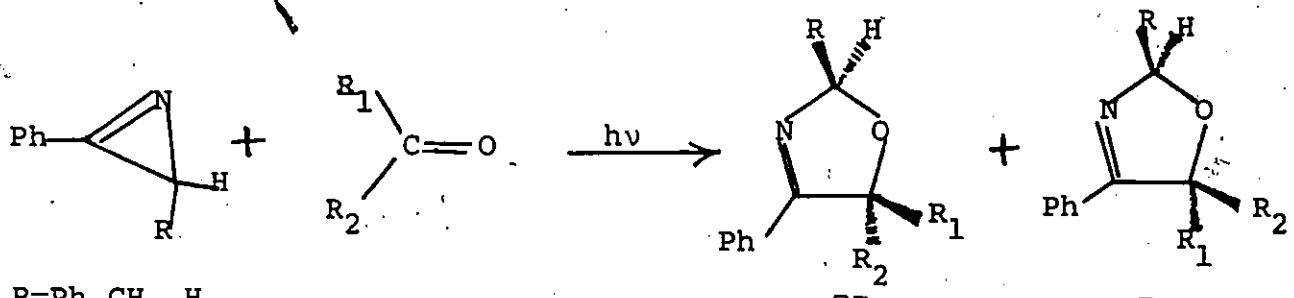
R=COOMe, CN

71 72

Photolysis of 2,3-diphenyl-1-azirine with dimethyl acetylenedicarboxylate afforded 2,5-diphenyl-3,4-dicarbomethoxy pyrrole.



The photochemical reactions of 1-azirines with carbon-oxygen and carbon-sulfur double bonds also has been extensively studied. The stereoisomeric oxazolines (73) and (74) have been obtained exclusively with complete regiospecificity, on photochemical addition of 1-azirines to the carbonyl group of aldehydes,[48,49,50] ketones[50,51,52] and esters.[51,53,54]



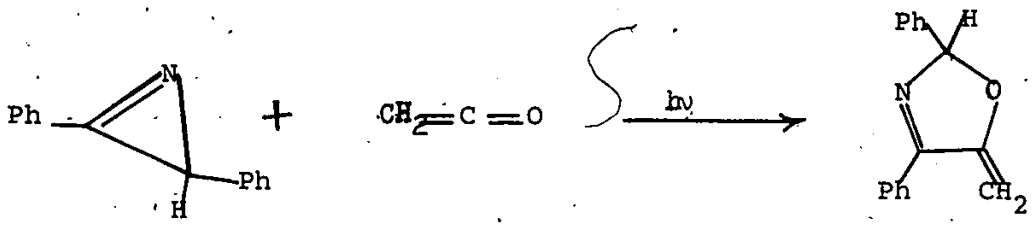
R=Ph,CH_3,H
R_1=alkyl, aryl

R_2= H,alkyl, OEt

73

74

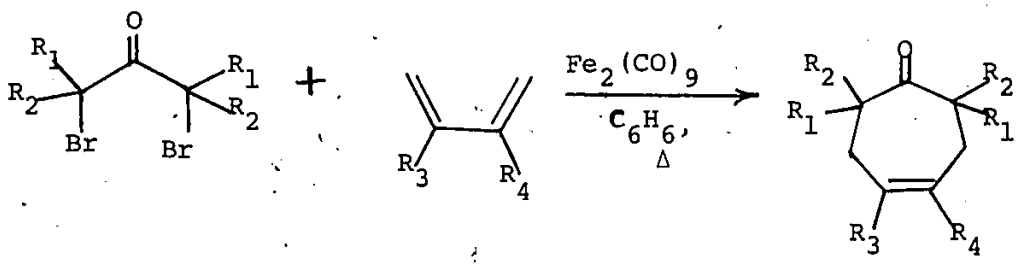
The photochemical addition of some heterocumulenes has also been studied.[55,56] Oxazoline (75) has been isolated on irradiation of 2,3-diphenyl-1-azirine in benzene in the presence of ketene. Similar results were obtained when 1-azirines were irradiated with diphenylketene.



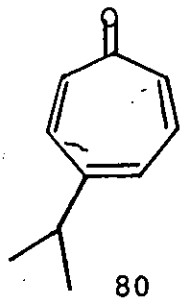
75

1.2.5 Metal Promoted Reactions

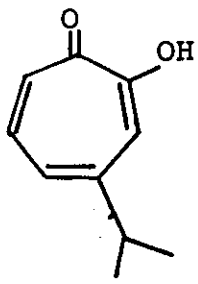
Transition metal carbonyls can effect a number of useful reactions in organic chemistry.[64] For example, cyclocoupling of α, α'-dibromo ketones with olefins or dienes in the presence of diiron enneacarbonyl is one interesting transformation.[65] Thus, substituted 4-cycloheptenones have been produced in fair to excellent yields by reaction of a number of open chain dienes with tertiary or secondary



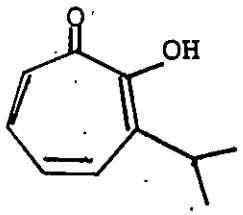
α,α'-dihaloketones. This reaction provides a very facile entry into seven membered ring systems which are normally both difficult and cumbersome to synthesize. This chemistry has offered the most direct route to a number of natural products containing seven-membered rings. For example, nezukone (80), β - thujaplicin (81) and α -thujaplicin (82) could be synthesized from the cycloadducts of furans.[66]



80

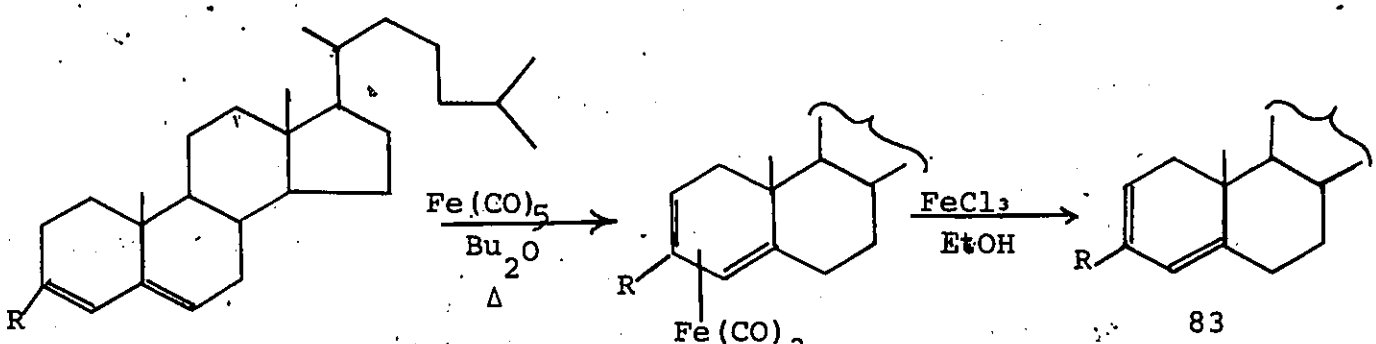


81



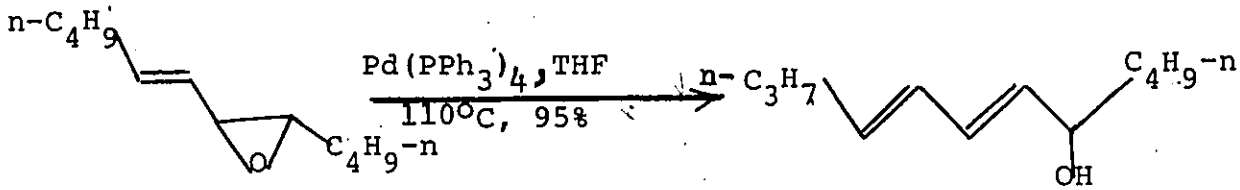
82

Isomerization of cholesta-3,5-dienes[67] with $Fe(CO)_5$ in refluxing dibutyl ether is another metal carbonyl induced reaction. Decomplexation with $FeCl_3$ in ethanol has given the cisoid isomer in good yield. The driving force for the isomerization is the necessity of the diene to possess a cisoid conformation in order for complex formation to take place. This reaction sequence has provided for the synthesis of compounds not readily available by other means (e.g. 83, R = OCH_3).



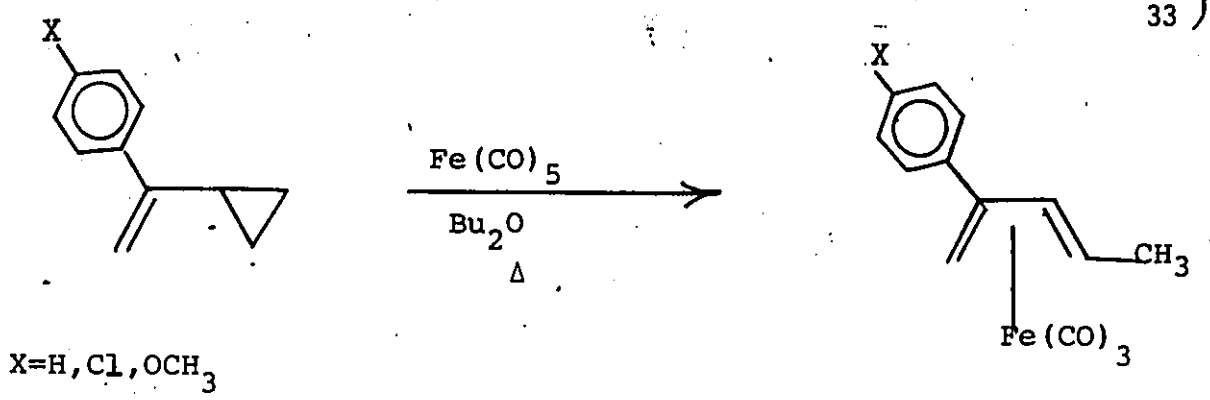
R=H, CH_3, OMe, C_6H_5

There also has been considerable interest in recent years in the use of transition metal organometallic complexes for the cleavage of strained ring compounds.[68] For example, tetrakis (triphenylphosphine) palladium (0) can catalyze the conversion of vinyl epoxides to either allylic alcohols (e.g. 84 → 85) or β,γ-unsaturated ketones, depending on the nature of the organic reactant.[69]



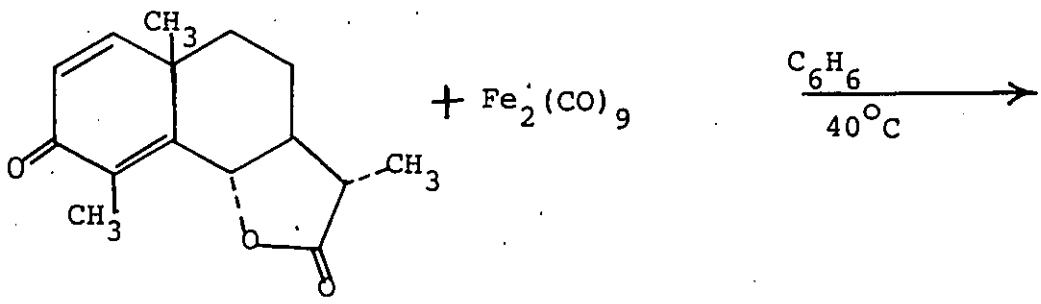
84 85

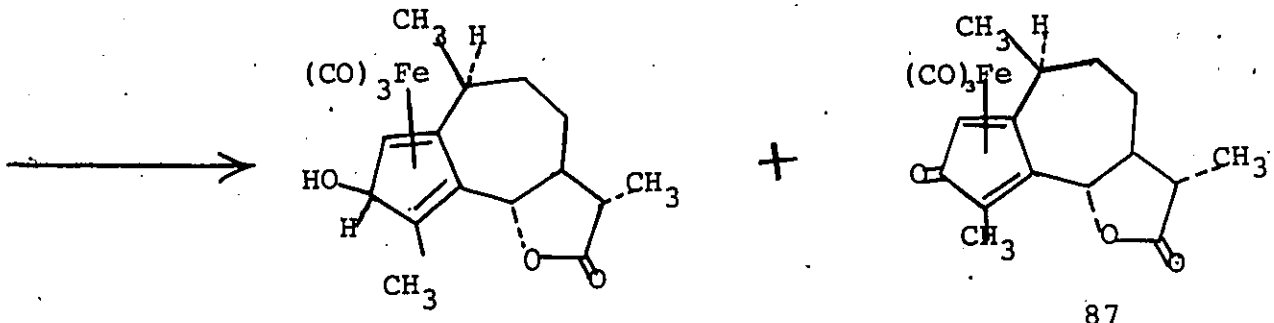
Vinyl cyclopropanes activated by the presence of a 2-aryl group, with $Fe(CO)_5$ have been reported to give the iron tricarbonyl complex of the highly reactive 2-aryl-1,3-trans pentadiene.[70]



X=H,Cl,OCH_3

As mentioned earlier, azirines undergo carbon-carbon bond cleavage on photolysis, while thermolytic ring opening of these 3-membered unsaturated heterocycles usually occurs by cleavage of the carbon-nitrogen bond.[12] It is also known that under nonphotolytic conditions metal carbonyls can effect photolytic type reactions of organic substrates. For example, the reaction of santonin with $Fe_2(CO)_9$ [71] leads to iron tricarbonyl complexes (86) and (87). The organic ligand of (87) is the product isolated as a dimer on solid state irradiation of santonin. Thus, $Fe_2(CO)_9$ could effect a rearrangement which previously was only observed under photolytic conditions.

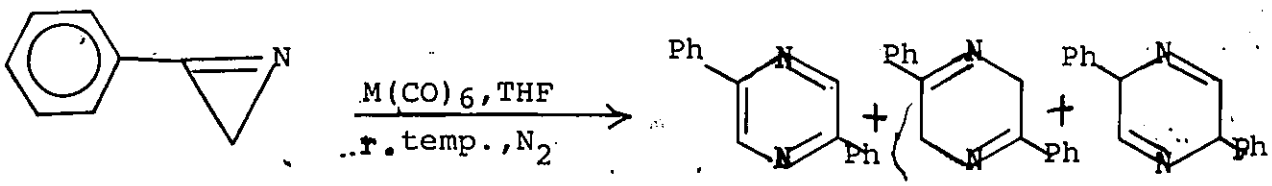




86 87

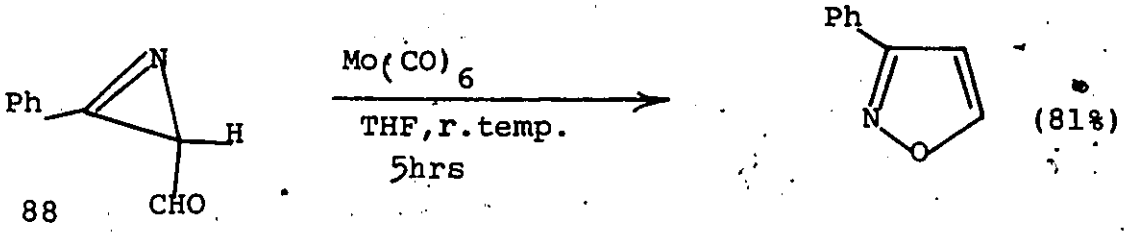
On the basis of these results it seemed interesting to find out whether metal carbonyls could induce cleavage of azirines in a synthetically useful manner to provide simple and convenient synthetic approaches to heterocyclic systems and/or to form novel organometallic complexes. It was also important to learn whether such anticipated organometallic reactions would take place by carbon-carbon or carbon-nitrogen bond cleavage of the azirine ring.

In 1975 Alper and co-workers[72] carried out the group 6 metal carbonyls [$M(CO)_6$; M = W, Cr, Mo] induced reaction of 1-azirines in THF at room temperature, which gave 2,5-diphenylpyrazines usually as the major product, with isomeric 2,5-diaryl-3,6-dihydropyrazine and 3,6-diphenyl-3,6-dihydropyrazine as the by products.



M=Cr,W,Mo

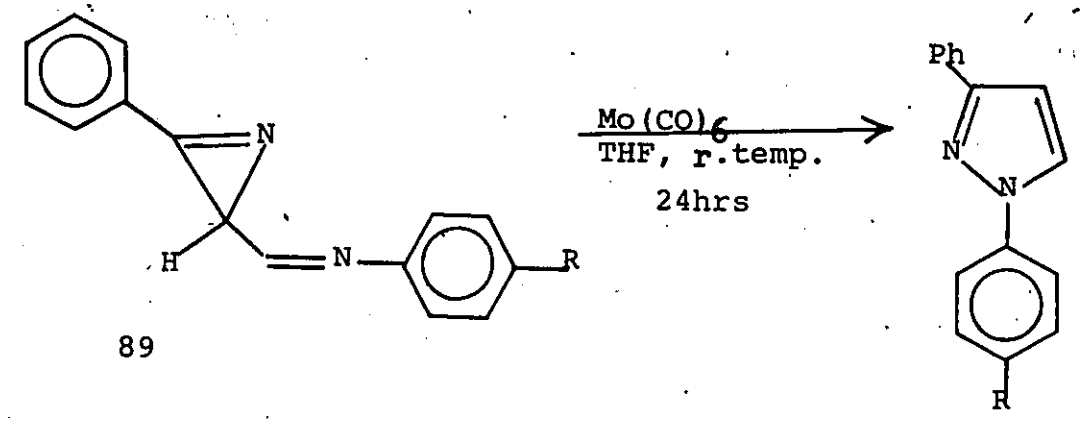
A study of the reaction of 2-phenyl-3-substituted-1-azirines having substituents which are capable of participating in intramolecular cycloaddition reactions has also been undertaken in the presence of molybdenum hexacarbonyl, since the nature of the products formed in such cycloaddition reactions would be able to provide evidence regarding the site of cleavage of the azirine ring. For example, 3-phenylisoxazole was obtained,[73] when 3-formyl-2-phenyl-1-azirine (88) was treated with $Mo(CO)_6$ in THF at room temperature. Previously, 3-phenylisoxazole was obtained in 80% yield by thermolysis of 1-azirine (88) in toluene at 200°C in a sealed tube for 3 days[12].



88 (81%)

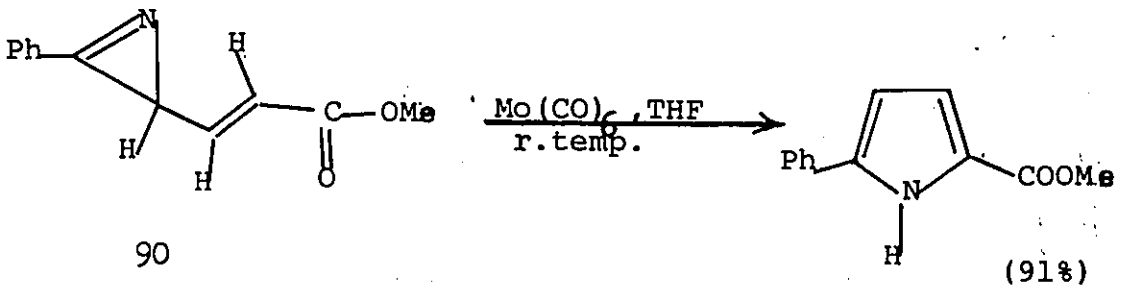
Similar treatment of N-arylimines (89), readily prepared from (88) with the appropriate aniline in the presence of p-toluenesulfonic acid or molecular sieves resulted in the formation of 1-aryl-3-phenylpyrazoles in 67-96% yield.

Application of the reaction to (E) 2-phenyl-1-azirine-3-acrylate (90) afforded 2-phenyl-5-carbomethoxypyrrole in 91% yield and (Z) 2-phenyl-3- (2,3 diphenyl-2H azirine-2-yl) acrylophenone (91) afforded mixtures of pyrroles and a 1,3-oxazepine[79] mixtures. Similar results were obtained with diiron enneacarbonyl[81].



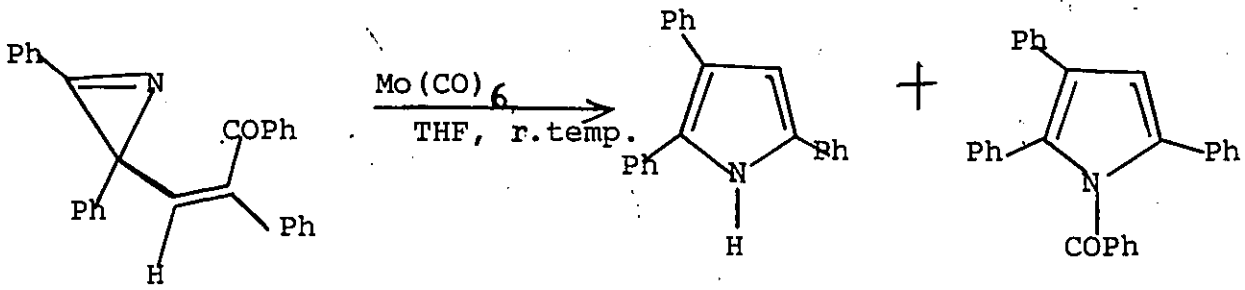
89

R=H, Cl, CH_3, OCH_3

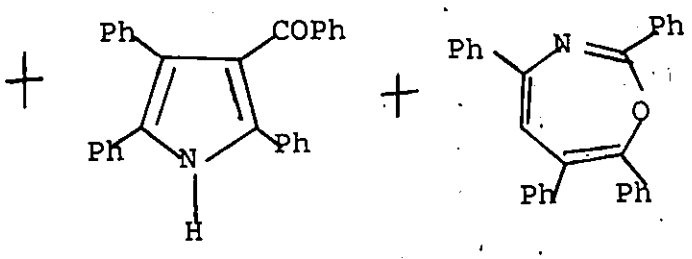


90

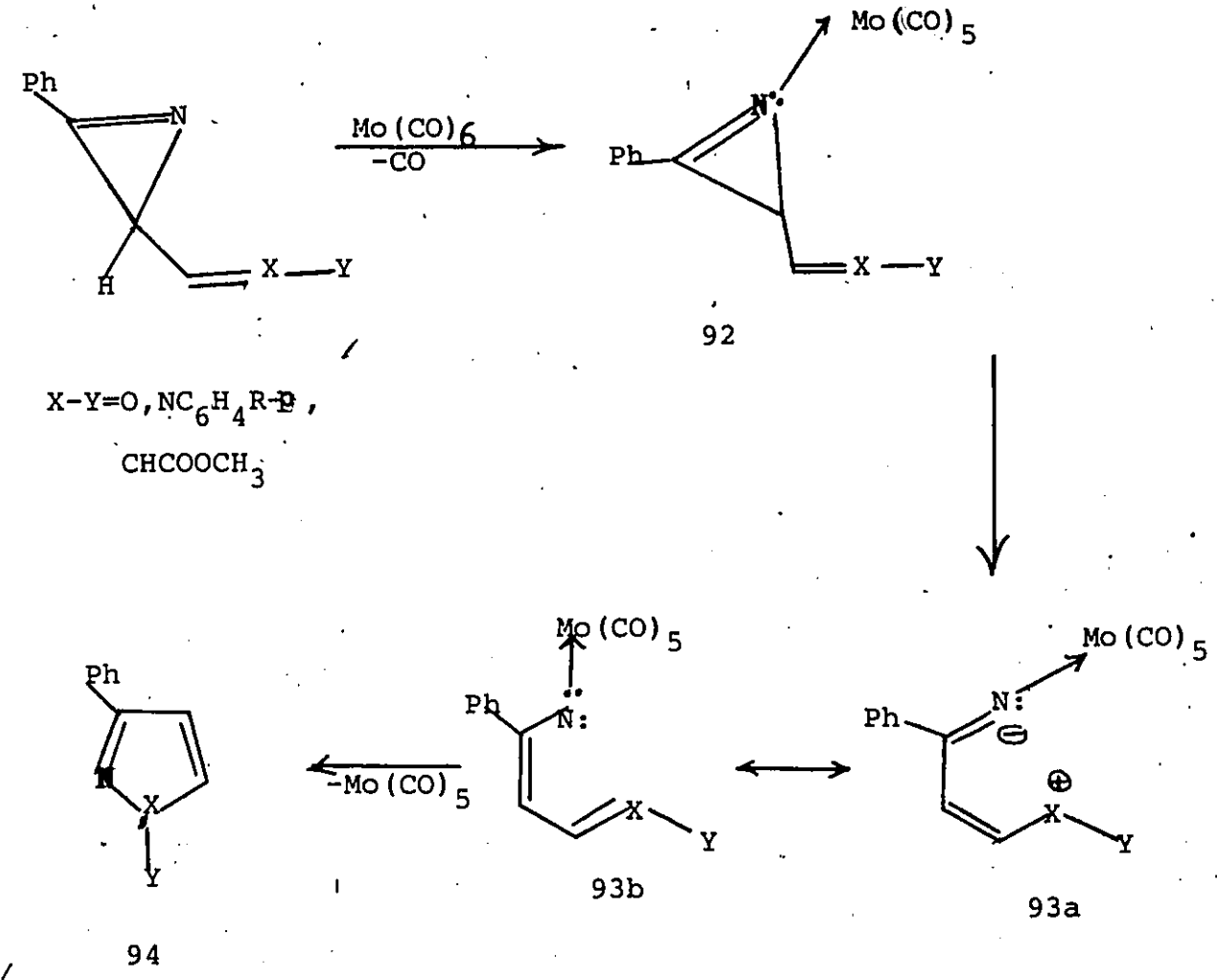
(91%)



91

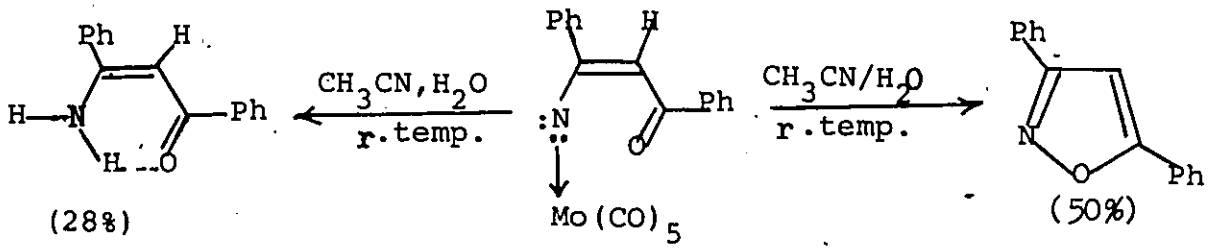


These results showed that $Mo(CO)_6$ effects C-N, rather than C-C bond cleavage of the azirine ring possibly via complex (92) [Scheme 2], since the products obtained in these reactions correspond to those formed by thermolysis rather than photolysis of 1-azirines.[12] The charged separated structure (93a) is a significant contributor to the resonance hybrid of (93) and is stabilized by electron-donating groups attached to X (e.g., Y= p-$CH_3OC_6H_4$). The heterocycle (94) would afford by the ring closure of (93).



SCHEME 2

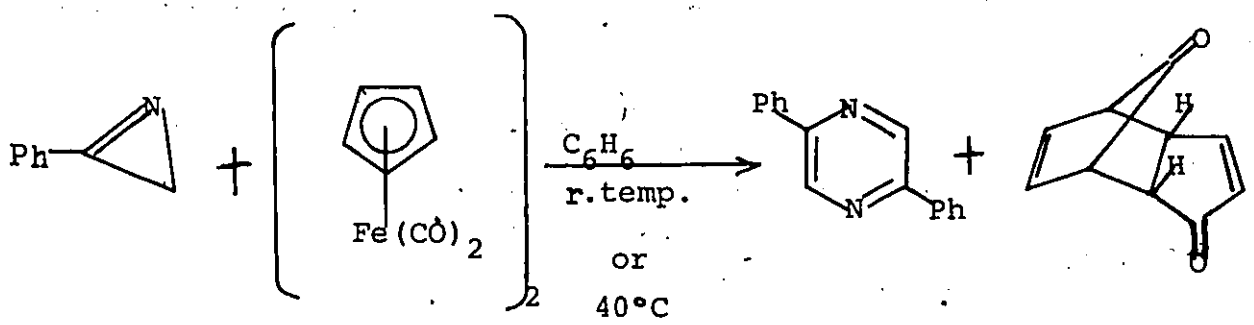
Recently, support for a nitrene intermediate has come from work by Nitta's group,[74] who carried out the reaction of 3-benzoyl-2-phenyl-1-azirine with an equivalent amount of $Mo(CO)_6$ in acetonitrile containing an equimolar quantity of water. In the presence of water the postulated nitrene complex collapses to isoxazole and β-aminoenone in 50% and 28% yields respectively.



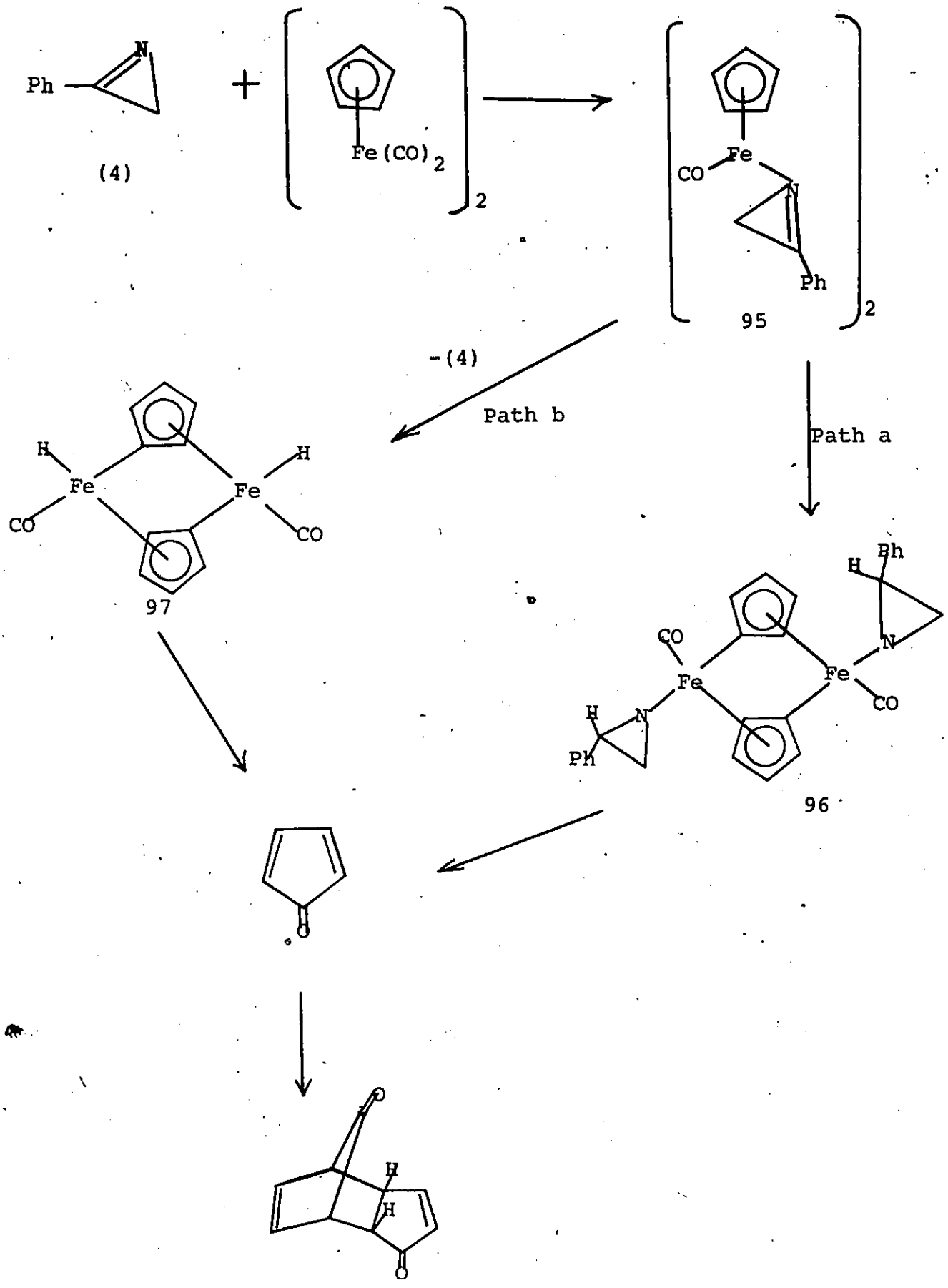
Similar results have been obtained by Nitta's[75] group on photoirradiation of 3-benzoyl-2-phenyl-1-azirine with a stoichiometric amount of $Fe(CO)_5$ in moist acetonitrile. Isoxazole and β-aminoenone were obtained in yields of 43% and 39% respectively. However, under similar conditions photoirradiation of 3-benzoyl-2-phenyl-1-azirine in the absence of $Fe(CO)_5$ gave the isoxazole in 27% yield with the isolation of the unreacted azirine in 69% yield. Furthermore, when the above reaction was carried out at 50°C in the presence of $Fe_2(CO)_9$, the same two products, isoxazole (31%) and β-aminoenone (57%) were isolated.

2H-Pyrrole has been obtained in low yields (5-20%) by molybdenum hexacarbonyl induced intermolecular cycloaddition of 3,3-dimethyl-2-phenyl-1-azirine with acetylene carboxylates.[76] In the absence of the alkyne, pyrazines or dihydropyrazines were formed. A substituted pyrrole has been isolated from 2,3-diphenyl-1-azirine where there is a H atom on the saturated carbon atom. The formation of the latter and 2H-pyrrole could be rationalized on the basis of cleavage of the carbon-nitrogen double bond of 1-azirine.

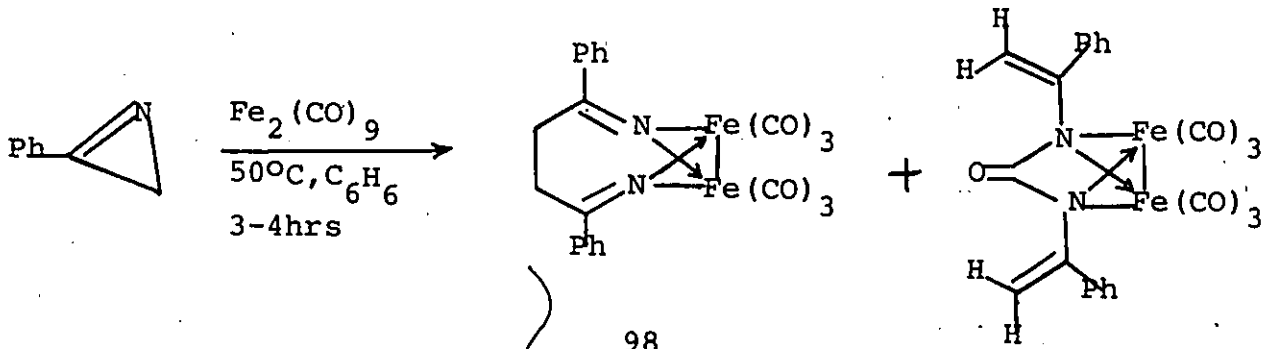
The use of silver perchlorate[77] is another metal induced process for converting azirines into pyrazines. Metallic silver has been obtained as a by-product in that reaction. Reaction of cyclopentadienyliron dicarbonyl dimer, $[CpFe(CO)_2]_2$, with 1-azirines also have formed pyrazines with the dimer of cyclopentadienone, [1,8-diketo-4,7-methano-3a,4,7,7a-tetrahydroindene], obtained in as high as 38% yield.[78]

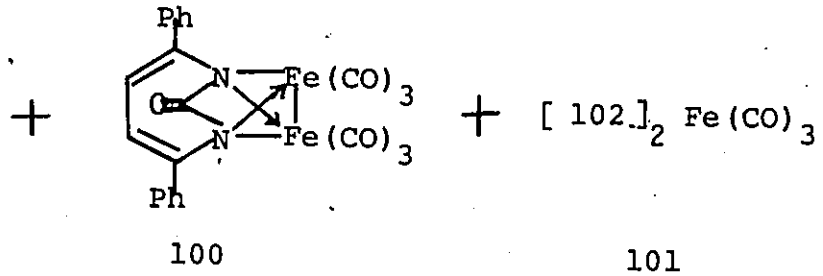


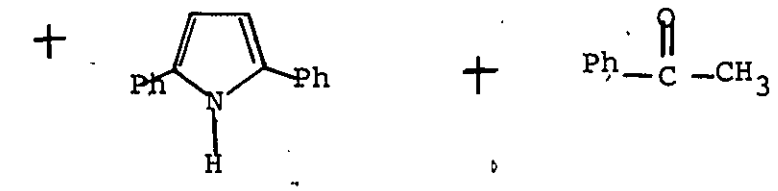
A similar reaction using 3-formyl-2-phenyl-1-azirine as the substrate afforded 3-phenylisoxazole in 84% yield. These results indicate that as group VI metal carbonyls, the iron carbonyl dimer behaves in an analogous manner towards 1-azirines. The formation of cyclopentadienone has been proposed to occur via initial CO displacement by azirine from $[Cp_2(CO)_2Fe]_2$, to give (95) [Scheme 3], which on metalation with hydrogen transfer to the azirine possibly via an iron hydride intermediate would form (96). Oxidative cleavage of (96) in which each iron atom is π-complexed to one cyclopentadienyl ring and σ-bonded to another would give cyclopentadienone. The latter would be readily dimerized to cyclopentadienone (path a). Metalation of (95) by loss of azirine to give (97) (path b), which could then collapse to cyclopentadienone also has been suggested as another possible path. In this reaction cyclopentadienone was not formed prior to work-up.


Ph
N
(4)
Fe(CO)2
2
CO
Fe
N
Ph
95
2
-(4)
Path b
Path a
H
Fe
Fe
H
CO
CO
97
Ph
H
N
CO
Fe
Fe
CO
H
N
Ph
96
O
H
H
O

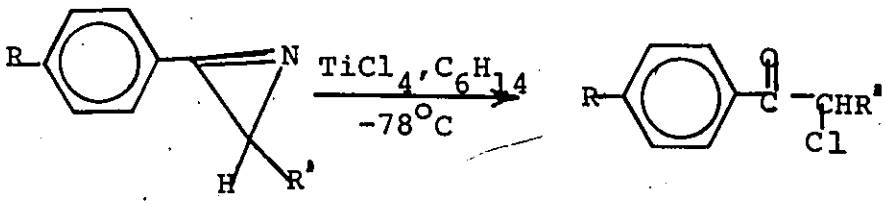
In 1976, it was reported[80] that 1-azirines react with diiron enneacarbonyl in benzene, probably via cleavage of the carbon-nitrogen single bond to give several interesting organometallic complexes (98-101) as well as pyrroles (102) and ketones (103). None, however, were formed in high yields.



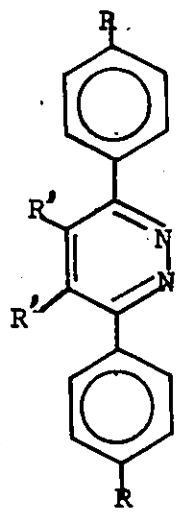




α -Chloro ketones (104) and pyridazines (105) have been obtained in modest yields with small amounts of 2,5-diphenylpyrazine (106) and monoketone (107), when 1-azirines were treated with twice the molar amount of $TiCl_4$ in hexane at -78°C.[73] Even at -78°C, these reactions were reported to be exothermic. No heterocycle has been detected when a methyl group was at the saturated carbon atom of the 1-azirine ring. The α-chloro ketone (104) was found to be the major product formed in all cases except 2-phenyl-1-azirine, where the pyridazine was obtained as the major product.

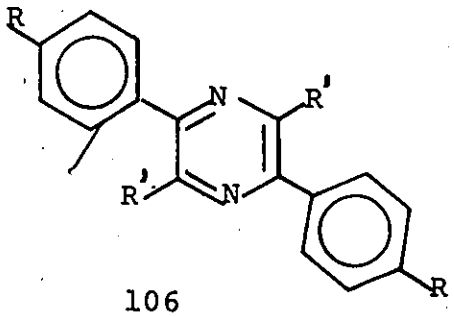


104



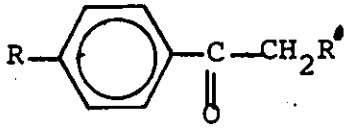
105

R=H, CH_3, Br
R'=H, CH_3



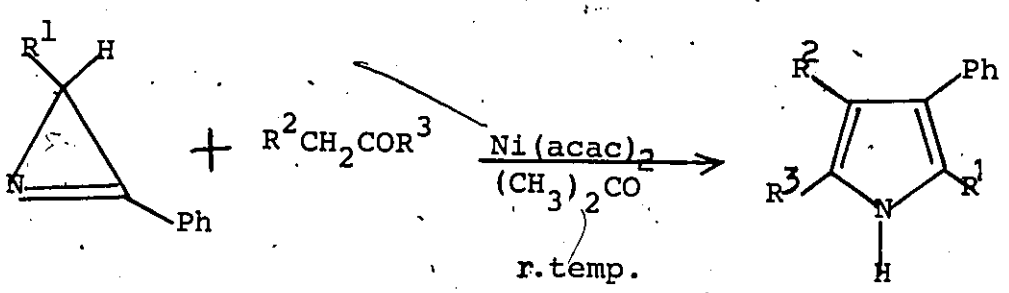
106

+



107

Nickel (II) catalyzed reaction of 1-azirines with activated ketones has been reported to give pyrroles in quantitative yield at room temperature.[82] This catalyst has proven to be advantageous, since the synthesis is free from side reactions.

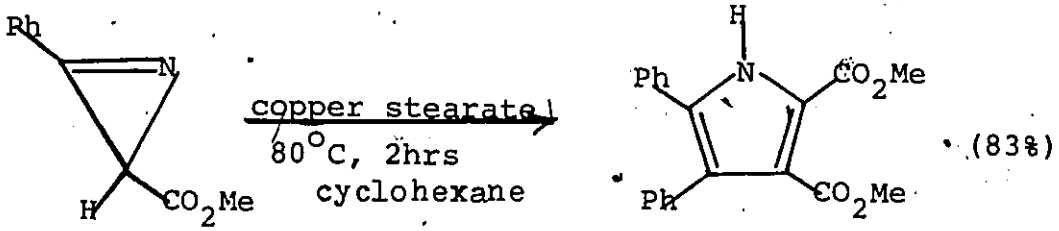


R^1 = H, CH_3, C_6H_5

R^2 = $-COCH_3$, -CN, $-\overset{O}{\overset{\|}{C}}-CH_2$

R^3 = $-CH_3$, C_6H_5, $-CH_2-\overset{(CH_3)_2}{\overset{|}{C}}$

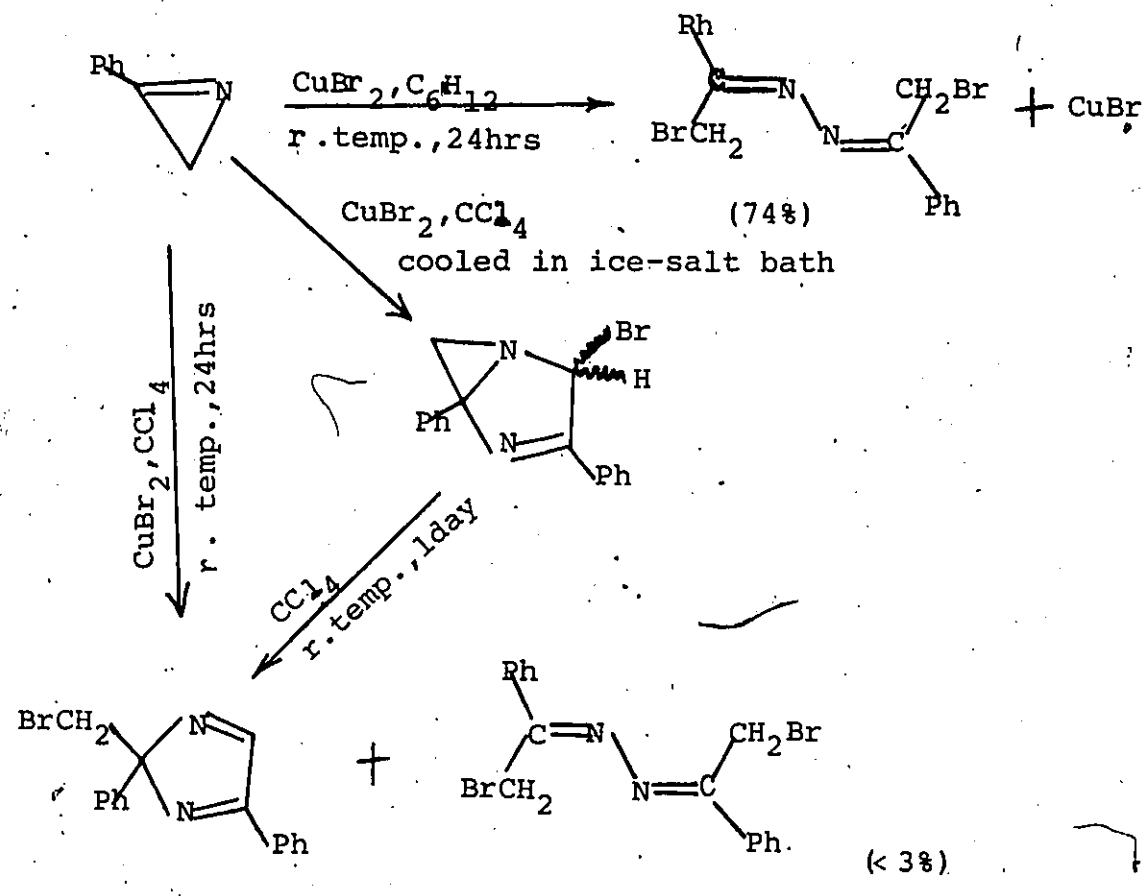
The pyrrole (109) was obtained in 83% yield by treatment of azirine ester (108) with copper stearate at 80°C in cyclohexane.[83]



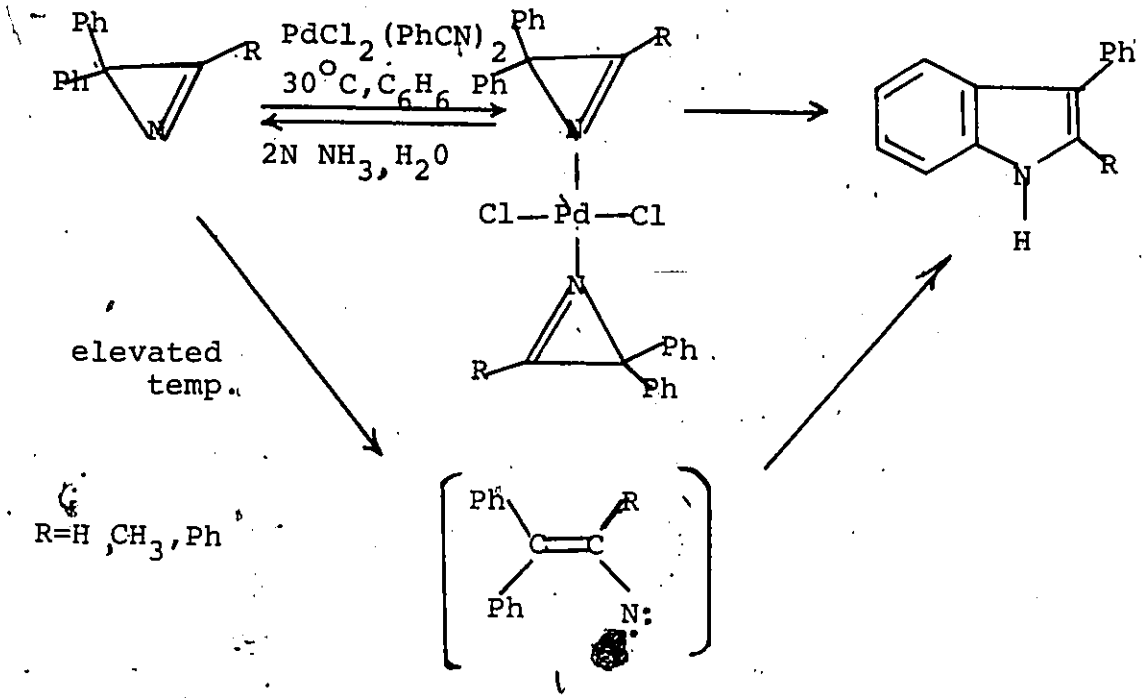
(83%)

108 109

On the other hand Cu(II) bromide promoted reaction of 2-phenyl-1-azirine under mild conditions has given 2 types of dimeric bromo compounds depending on the solvents used.[84] ω-Bromoacetophenone azine was obtained at room temperature in cyclohexane, while 2-bromomethyl-2,4-diphenyl-2H-imidazole was formed in CCl_4. When the latter was carried out by cooling in an ice-salt bath an isomeric 2-bromo-3,5-diphenyl-1,4-diazabicyclo [3.1.0] hex-3-ene was obtained. This was transformed to 2-bromomethyl-2,4-diphenyl-2H-imidazole by allowing it to stand in CCl_4 at room temperature for 1 day.



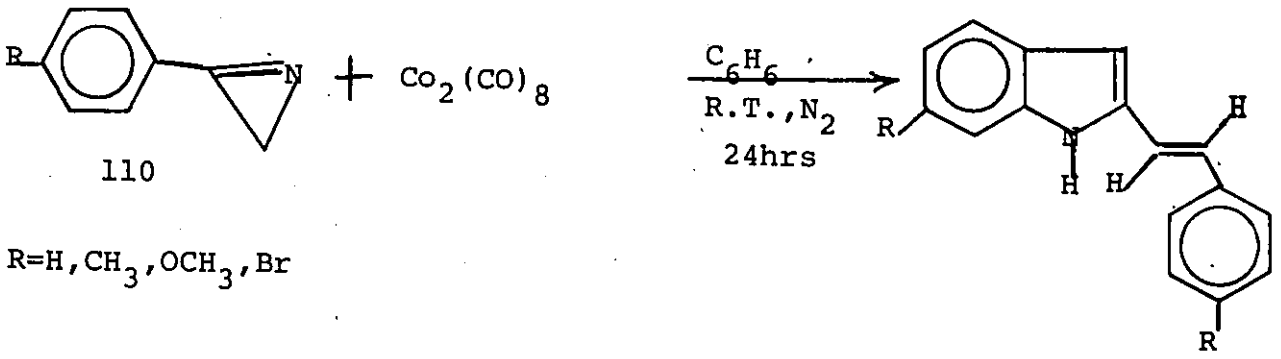
It was reported that dichlorobis (benzonitrile) palladium (II) catalyzed reaction of 1-azirines having a phenyl group at the saturated carbon atom of the ring has given indoles quantitatively.[85] The same indoles were isolated by thermolysis of these 1-azirines.



Evidence for the intermediacy of bis (azirine) palladium dichloride complexes in these reactions has been obtained using 2-equivalents of a variety of 1-azirines.[85,86] Indoles have been also isolated quantitatively upon stirring these bis (azirine) palladium dichloride intermediates in benzene at room temperature,[85] indicating the above assumption to be correct. Stable bis (amino azirine) zinc dibromide complexes were obtained by the reaction of 2-dimethylamino-

3,3-dimethyl-1-azirine or 2(N-methylanilino)-3,3-dimethyl-1-azirine with $ZnBr_2$ in a 1:1 mixture of $CH_3CN:CH_2Cl_2$ at room temperature.[87] By X-ray analysis, the structures of the zinc and the related bis (azirine) cobalt dichloride complexes have been confirmed.[68C,88]

2-Styrylindoles, which are useful intermediates in alkaloid synthesis have been obtained in good yields by the reaction of 1-azirines (110) with dicobalt octacarbonyl in benzene at room temperature.[89] Since 2-substituted indoles are not as readily accessible as 3-substituted indoles,[90] this reaction represents a simple and convenient approach to such heterocycles.



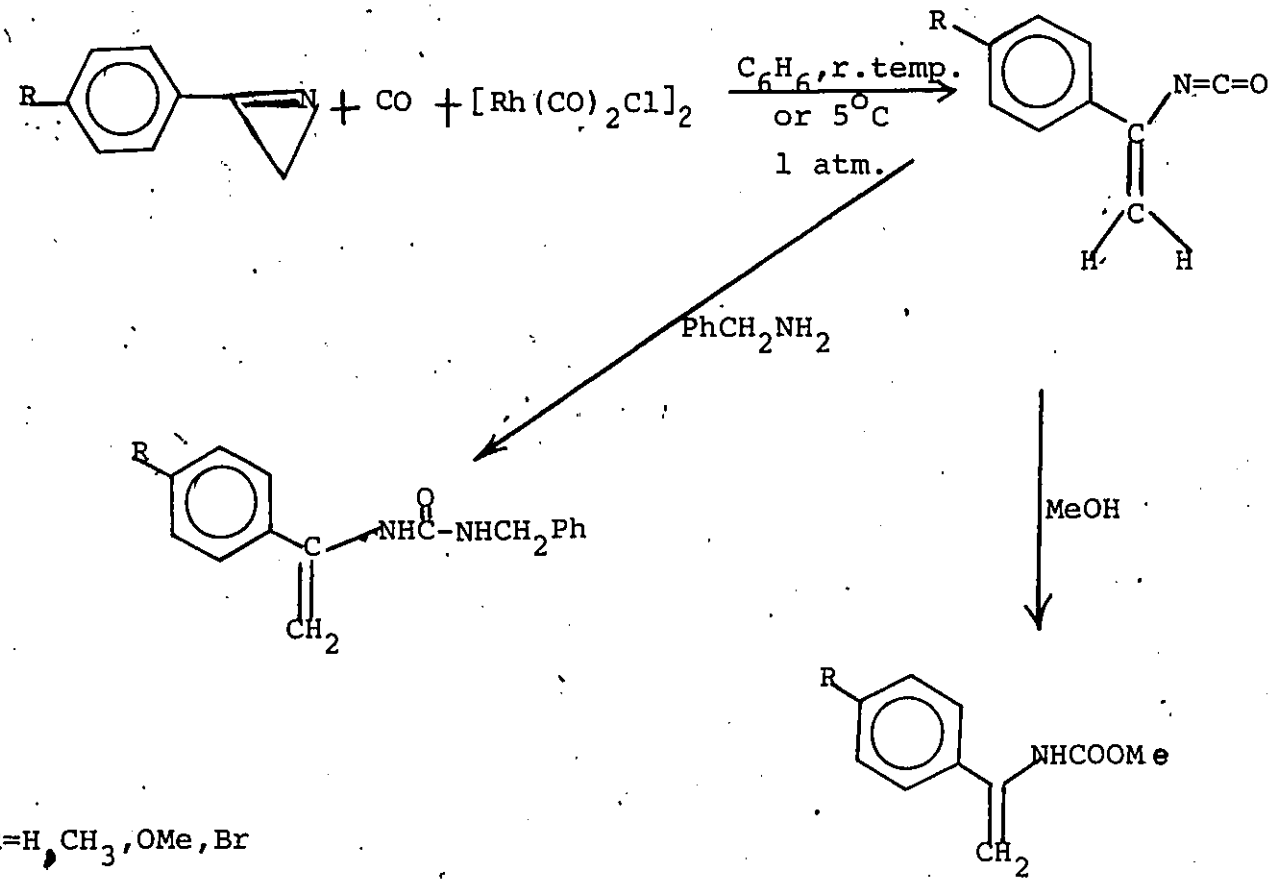
110

R=H, CH_3, OCH_3, Br

The same transformation has been realized using (110) either with a catalytic amount of chlorodicarbonylrhodium (I) dimer $[Rh(CO)_2Cl]_2$ or chlorocarbonylbis (triphenylphosphine) rhodium (I), $[(PPh_3)_2RH(CO)Cl]$, in benzene at room temperature.[91] This rhodium reaction has displayed.

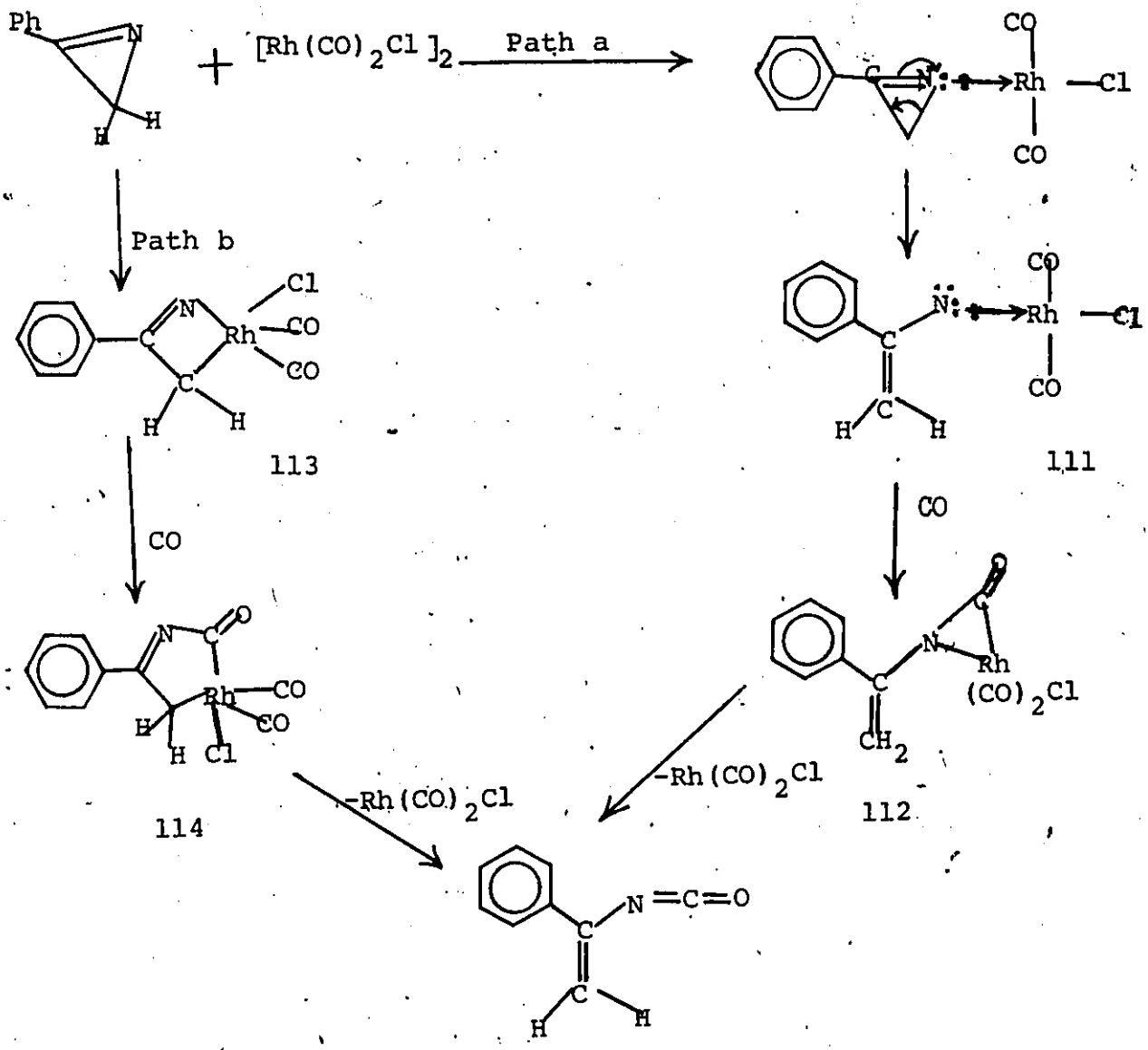
an interesting concentration dependence, since 2,5 diphenyl pyrroles were formed using a 2:1 molar ratio of 1-azirine to rhodium (I) complex, i.e. as a stoichiometric process.

Furthermore, this rhodium (I) reaction was carried out in the presence of carbon monoxide in order to trap the intermediates in the reaction, as well as to realize useful organic synthesis. From this carbonylation reaction vinyl isocyanates have been isolated.[92] The isocyanates were either isolated as such or as ureas or carbamates by exposure of the products to amine or alcohol, respectively.



R=H, CH_3, OMe, Br

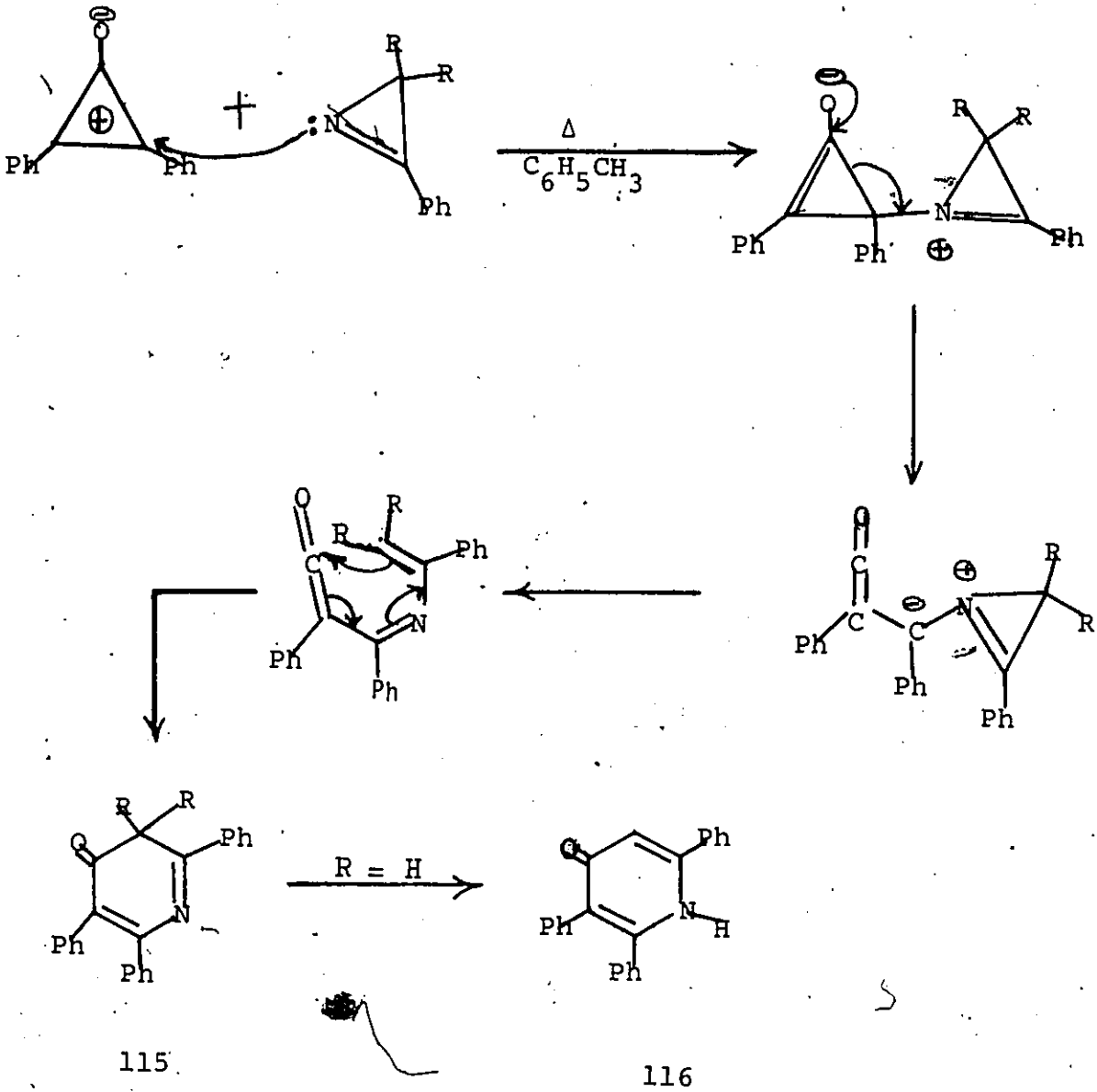
Vinyl isocyanates may have arisen from a vinyl nitrene complex (111) [Scheme 4, path a]. Ligand migration (112) followed by decomplexation would afford the isocyanate. Metallocycles were also suggested as possible intermediates in these reactions (path b). The rhodium (III) complex (113) could form by the oxidative addition of 1-azirines to the rhodium (I) complex, which on ligand migration (114), followed by decomplexation would afford the isocyanates.



Scheme 4

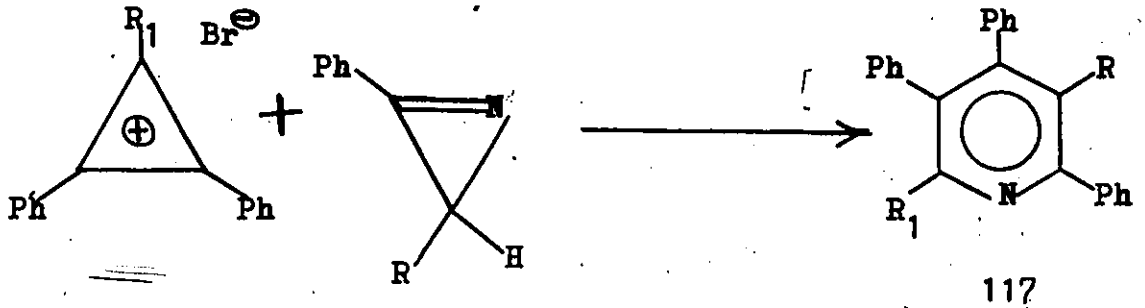
1.2.6. Miscellaneous reactions

1-Azirines have shown to be sufficiently nucleophilic to react with diphenylcyclopropenone to give 4-pyridones (116) in good yields.[57] When R = CH_3 the geminally substituted pyridone (115) was isolated.



115 116

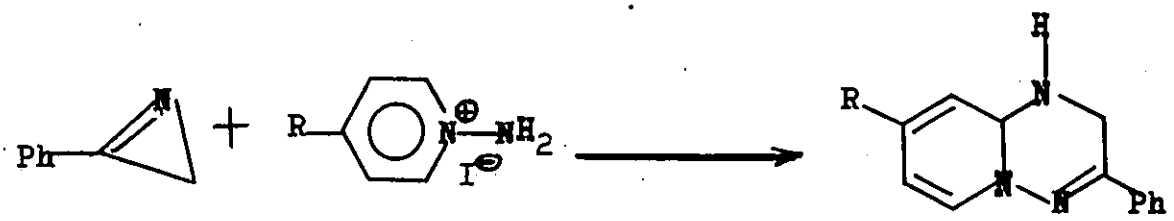
The addition of cyclopropenyl cations to 1-azirines has been reported[58] to give pyridine derivatives (117).



117

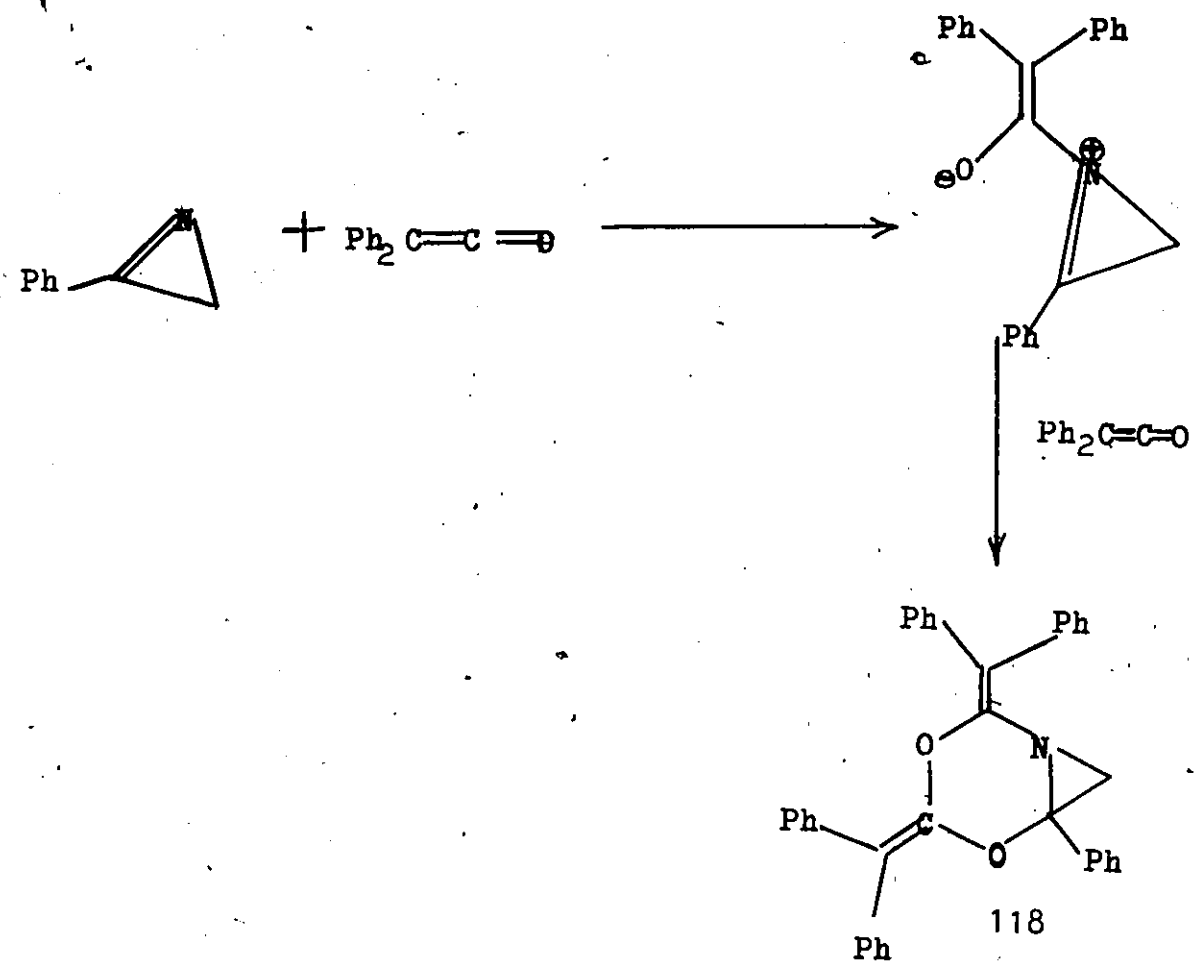
R_1=H, Ph R=H, CH_3, Ph

Reaction of 2-phenyl-1-azirine with pyridinium-N-imine hydroiodide in the presence of base gave bicyclic triazine derivatives in good yields.[59,60]



R= H, CH_3

Ketenes were also reported to be attacked by 1-azirines. But in this case 2:1 adducts (118) were formed.[61]



118

In contrast to lithium aluminum hydride, the catalytic hydrogenation by palladium or Raney nickel surprisingly resulted in reduction of the C-N bond rather than the double bond to give unstable imines.[3,62,63]

CHAPTER II

Aims of Research

$Pd(dba)_2$ Catalyzed carbonylation of azirines

Azirines undergo a variety of interesting and useful ring cleavage reactions in the presence of organometallic compounds [68c]. In 1979 Sakakibara and Alper investigated the carbonylation of azirines in the presence of Rh(I) complexes [e.g., $[Rh(CO)_2Cl]_2$]. Vinyl isocyanates, which are useful compounds in polymer chemistry, were obtained from this carbonylation reaction. Some disadvantages in this reaction are that the reaction is neither catalytic nor regiospecific. In a number of palladium(0) catalyzed reactions given in literature, palladium complexes behaves as nucleophiles. Palladium is more nucleophilic than rhodium, but $Pd(C_6H_5CH=CHCOCH=CHC_6H_5)_2$, [bis(dibenzylideneacetone)palladium(0), $Pd(dba)_2$], containing ligands with acceptor groups acts more like rhodium. Therefore our aim was to see if we could obtain the vinyl isocyanates in high yields by carbonylation of azirines using catalytic amounts of $Pd(dba)_2$.

Catalytic homogeneous carbonylation of azirines by $Pd(PPh_3)_4$

When the $Pd(dba)_2$ catalyzed carbonylation of azirines gave vinyl isocyanates in very high yields, we planned to examine the effect of other Pd(0) complexes also in this reaction. Since $Pd(dba)_2$ contains acceptor bidentate ligands, it seemed interesting to learn what would happen if one used Pd(0) complexes with donor ligands like tetrakis(triphenylphosphine)palladium(0), $Pd(PPh_3)_4$, in the latter reaction. Our aim was to determine whether $Pd(PPh_3)_4$ catalyzed carbonylation of azirines would give vinyl isocyanates like $Pd(dba)_2$ or whether if one would be able to ring expand the azirine to a four-membered ring heterocycle and thus realize the synthesis of β-lactam derivatives, an important class of compounds.

Pd(0) Catalyzed reactions of azirines under heterogeneous conditions

Palladium (0) catalyzed carbonylation of azirines under homogeneous conditions resulted in novel synthesis of two important classes of compounds. Tetrakis—(triphenylphosphine)palladium(0) catalyzed the conversion of azirines to β-lactams, while vinyl isocyanates are formed in a regiospecific manner using bis(dibenzylideneacetone)—palladium(0) as the catalyst. It seemed of interest therefore to learn whether Pd(0) catalyzed carbonylation of

azirines effected under phase transfer conditions would afford the same (β-lactam, vinyl isocyanate) or different products than the homogeneous reactions.

$Mo(CO)_6$ induced reactions of azirines with carbanions

The reaction of azirines with nucleophilic reagents has been investigated in some detail.[24] A question which arises is whether the presence of metal complexes can promote synthetically useful transformations under such conditions. Azirines are convertible to pyrazines, isoxazoles, pyrazoles, or pyrroles on exposure to $Mo(CO)_6$ and other Group 6 metal carbonyls[73]. Since it is believed that the initial step in the azirine-$Mo(CO)_6$ reaction is the formation of a nitrogen donor ligand complex [azirine$Mo(CO)_5$] and since in such a complex the carbon-nitrogen double bond would be more susceptible to nucleophilic addition[73], it was decided to investigate the molybdenum hexacarbonyl induced reaction of azirines with carbanions derived from β-dicarbonyl compounds.

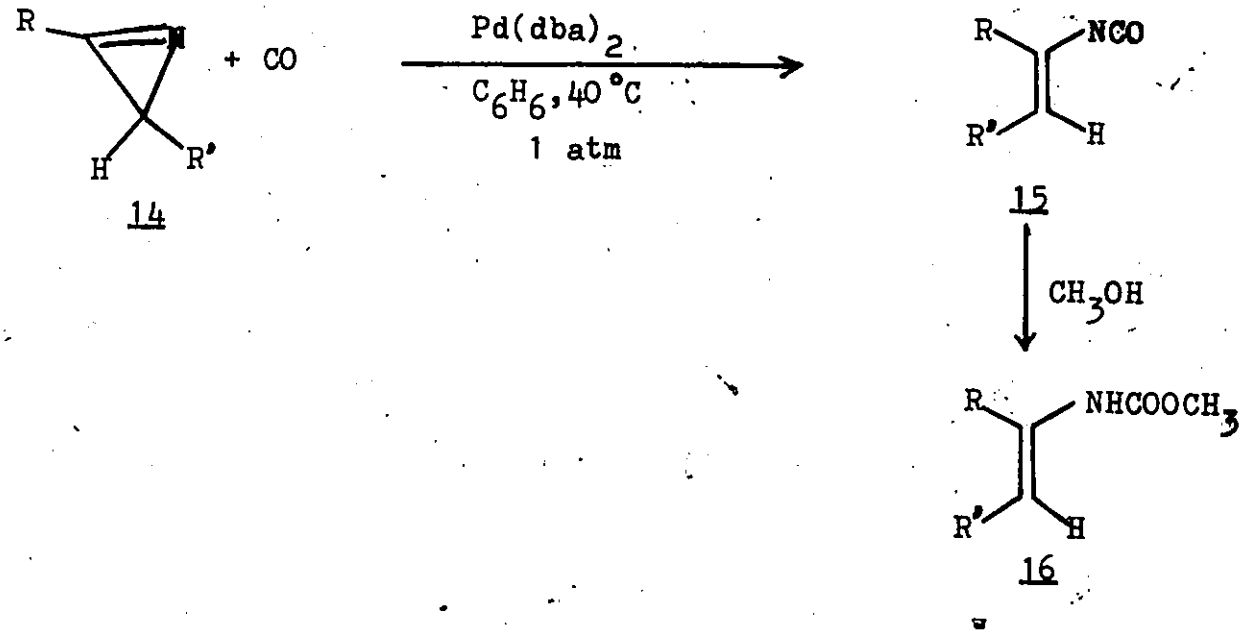
CHAPTER III

3. Results and Discussion

3.1. Palladium (0) catalyzed carbonylation of azirines under homogeneous conditions

The chemistry of azirines has been extensively investigated in recent years[7,24]. The metal complex catalyzed ring opening of azirines has led to the development of several interesting and useful reaction processes[68c]. In 1979, Sakakibara and Alper initiated a study of metal complex catalyzed carbonylation of azirines using soluble metal complexes, in order to trap the intermediates in reactions effected under a nitrogen atmosphere. Furthermore, it was hoped that one could ring-expand the azirine to a four-membered ring heterocycle and thus realize the synthesis of β-lactam derivatives, an important class of compounds. Although carbonylation of azirines did occur by the use of stoichiometric quantities of a rhodium(I) compound(e.g,chlorodicarbonylrhodium(I) dimer), the ring-opened vinyl isocyanates were obtained and not any heterocyclic compounds[92].It was anticipated that carbonylation of azirines in the presence of $Pd(dba)_2$ [dba= dibenzylideneacetone] would also lead to vinyl isocyanates, since $Pd(dba)_2$,containing an acceptor bidentate ligand would act more like rhodium. Therefore a study was made of

the reaction of the bis(dibenzylideneacetone)palladium(0) catalyzed carbonylation of azirines.



Carbonylation of an azirine (14) with a catalytic amount of $Pd(dba)_2$ in benzene afforded the vinyl isocyanates as anticipated. This metal-catalyzed azirine carbonylation reaction proved to be an exceedingly clean one leading to vinyl isocyanates (15) in high yields. Product characterization was made either on the vinyl isocyanate itself or on the carbamate ester (16), formed by simple addition of methanol to (15). The yields (77-99%) and reaction times are listed in Table 1. Spectral data are given in Table 2.

When one compares the $Pd(dba)_2$ reaction with the Rh(I) reaction, a serious disadvantage in the latter

is its stoichiometric nature whereas the $Pd(dba)_2$ reaction is catalytic; also the yields of (15) and (16) are consistently higher with $Pd(dba)_2$ than with $[Rh(CO)_2Cl]_2$[92]. When we used 3-methyl-2-phenyl-1-azirine only one isomer, (E)-1-phenyl-1-propenyl isocyanate (15, R= C_6H_5, R′ =CH_3), was obtained in quantitative yield. The nuclear magnetic resonance spectrum of (E)-1-phenyl-1-propenyl isocyanate (15, R=C_6H_5, R′ =CH_3); ^1H NMR($CDCl_3$), 1.67 (d,3H,CH_3,J=8Hz), 5.63(q,1H,CH=),7.33(s,5H,C_6H_5) agrees well with data reported for the same compound (i.e., the E isomer) synthesized by an independent route[93]. The latter was converted to carbamate ester (16, R=C_6H_5, R′ =CH_3) on treatment with methanol. No Z isomer of (15) or (16) was detected. In contrast, the Rh(I) reaction is not regiospecific[94].

Table 1: Yields for the carbamate ester (16)

(16) , R , R′	Reaction Time, hr	Yield %
p-$CH_3C_6H_4$,H	29	83
C_6H_5 ,H	48[a]	77[b]
p-ClC_6H_4 ,H	overnight	99
p-BrC_6H_4,H	overnight	96
C_6H_5 ,CH_3	overnight	98

[a] When Pd(o-MeOdba)$_2$ was used the reaction time was 4 days and with Pd(o-Medba)$_2$ the reaction time was 6 days.

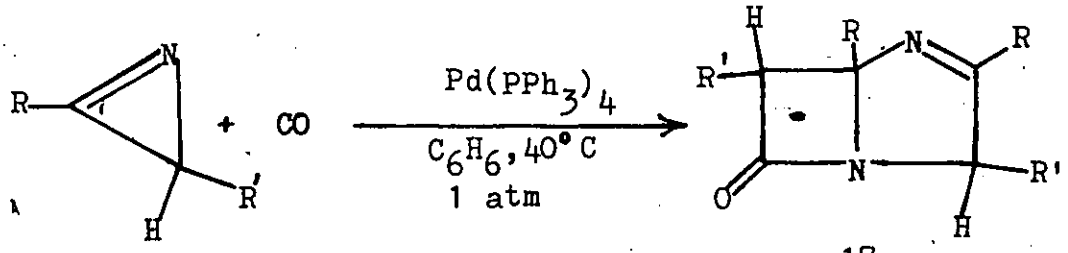
[b] When Pd(o-MeOdba)$_2$ was used the yield was 80% and with Pd(o-Medba)$_2$ the yield was 77%.

TABLE. 2: Pertinent Spectral Data for (16).

(16), R, R'	IR[a], cm^{-1}			^1H NMR [b], δ, ppm	MS, m/e
	ν_{NCO} (15)	ν_{NH}	ν_{CO}		
p-$CH_3C_6H_4$, H	2285	3400	1735	2.28 (s, 3H, CH_3) 3.63 (s, 3H, $COOCH_3$), 4.92, 5.57 (s each, 2H, CH_2=), 6.60 (s (br), 1H, NH), 7.12, 7.30 (d each, 4H, J=9Hz, aromatic protons)	191
C_6H_5, H	2260	3415	1740	3.65 (s, 3H, $COOCH_3$), 4.97, 5.63 (s each, 2H, CH_2=), 6.80 (s (br), 1H, NH), 7.10-7.60 (m, 5H, aromatic protons)	177
p-ClC_6H_4, H		3400	1735	3.69 (s, 3H, $COOCH_3$), 4.95, 5.55 (s each, 2H, CH_2=), 6.50 (s (br), 1H, NH), 7.25-7.55 (m, 4H, aromatic protons)	
p-BrC_6H_4, H	2270	3397	1735	3.68 (s, 3H, $COOCH_3$), 4.94, 5.53 (s each, 2H, CH_2=), 6.60 (s (br), 1H, NH), 7.23, 7.43 (d each, 4H, J=9 Hz, aromatic protons)	256
C_6H_5, CH_3	2260	3400	1728	1.68 (d, 3H, J=8Hz, CH_3), 3.65 (s, 3H, $COOCH_3$) 5.99 (q, 1H, CH=), 7.27 (s, 5H, aromatic protons)	

[a] $CHCl_3$ solution. [b] $CDCl_3$ with Me_4Si as internal standard.

Since the carbonylation of azirines in the presence of $Pd(dba)_2$ containing acceptor bidentate ligand lead to the vinyl isocyanates (15), it seemed interesting to learn whether Pd(0) complexes with donor ligands like $Pd(PPh_3)_4$ also would afford vinyl isocyanates (15) or different products than the $Pd(dba)_2$ catalyzed reaction. Therefore a study of the carbonylation reaction of azirines catalyzed by $Pd(PPh_3)_4$ in benzene was carried out. Much more interesting results were obtained with the $Pd(PPh_3)_4$ catalyst since the bicyclic β-lactam (17) was obtained by insertion of carbon monoxide and cycloaddition. This homogeneous process occurred under mild conditions (1 atm, 40°C) using a 10:1 ratio of (14)/$Pd(PPh_3)_4$. The yields, melting points and analytical data for (17) are listed in Table 3, and pertinent spectral data are given in Table 4. The structure of the product was determined from analytical and spectral data. A single-crystal X-ray determination of 17 (R=p-$CH_3C_6H_4$, R' =H) was also made.



14 17

TABLE 3: Yields, Melting Points and Analytical Data for (17)

17, R, R′	Yield %	mp, °C	Anal. [Calcd (found)] [a]		
			% C	%H	%N
p-$CH_3C_6H_4$, H	50	109-111	78.59(78.51)	6.25(6.33)	9.65(9.47)
Ph , H	40	144-146	77.84(77.87)	5.38(5.44)	10.68(10.79)
p-ClC_6H_4, H	37	40-42	61.63(61.73)	3.65(3.66)	8.45(7.86)
p-BrC_6H_4, H	55	145.5-147.0	48.58(48.71)	2.88(2.74)	6.67(6.63)
Ph, CH_3	2.5	oil	78.59(78.45)	6.25(6.14)	9.65(9.06)
4-$(CH_3)_2C_6H_3$, H	49	oil	—	—	—

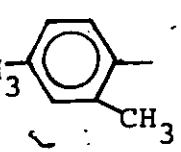
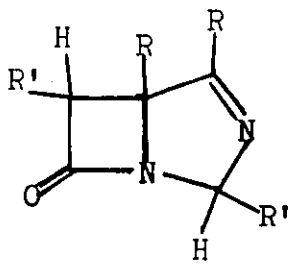
[a] No Elemental analyses were done on the β-lactam 17 (R=  , R′=H).

TABLE 4: Pertinent Spectral Data for (17)

17, R, R′	IR,[a] ν_{CO} cm^{-1}	NMR[b], δ, ppm		MS, m/e
		^1H	^{13}C	
p-$CH_3C_6H_4$, H	1780	2.35(s,6H,CH_3 protons),3.55(s, 2H,CH_2),3.95,5.00(d each,2H, CH_2,J=16Hz),7.05-7.90(m,8H, aromatic protons)	21.11(CH_3),21.54(CH_3),53.23(CH_2), 55.97(CH_2),92.66(>C-N), 125.53, 128.34, 128.78, 129.17,129.48,136.90 137.96,142.42 (aromatic carbons), 170.19 (CO), 179.37 (CN)	290
Ph, H	1780	3.59(s,2H,CH_2),4.00,5.10(d each, 2H,CH_2,J=16Hz),7.20-7.90(m,10H, aromatic protons)	53.46(CH_2),56.09(CH_2),92.91(>C-N), 125.57,128.40,128.59,131.44,131.98, 139.68 (aromatic carbons),170.50 (CO), 179.21(CN)	262
p-ClC_6H_4,H	1780	3.53(s,2H,CH_2),3.93,5.30(d each, 2H,CH_2,J=16Hz),7.20-7.90(m,8H, aromatic protons)	53.71(CH_2,56.01(CH_2),92.64(>C-N), 127.07,128.83,129.23,129.71,134.37, 138.04,138.41(aromatic carbons), 169.75 (CO),178.71(CN)	
p-BrC_6H_4,H	1783	3.53(s,2H,CH_2),3.92,4.98(d each, 2H,CH_2,J=16Hz),7.30-7.80(m, 8H,aromatic protons)	53.63(CH_2),55.95(CH_2),92.68(>C-N), 127.35,129.82,130.12,131.79,132.19, 135.46 (aromatic carbons),169.87 (CO), 178.66(CN)	420
Ph,CH_3	1763	1.35,1.62(dd each,6H,methyl protons),3.78(m,1H,CH),4.63 (m,1H,CH),7.08-7.78(m,10H, aromatic protons)		290
,4-$(CH_3)_2C_6H_3$,H	1773	2.30(s,6H,CH_3protons),2.52,2.60 (seach,6H,CH_3 protons),3.53(s,2H, CH_2),4.05,5.03(d each,2H,CH_2, J=16Hz),6.85-7.50(m,6H, aromatic protons)		318

[a] $CHCl_3$ solution. [b] $CDCl_3$ with Me_4Si as internal standard. ^{13}C assignments made with the aid of fully and partially decoupled spectra.

The appearance of a carbonyl stretching band at 1763-1783 cm^{-1} ($CHCl_3$) in the infrared spectrum was consistent with the presence of a β-lactam ring in (17). In the proton magnetic resonance spectra of 17 (R=aryl, R′ = H), the two methylene groups displayed different magnetic properties, the methylene protons of the four-membered ring gave a singlet (δ 3.53-3.59) whereas the methylene protons of the five-membered ring appeared as two doublets (δ 3.92-4.00, δ 4.98-5.30, J=16Hz). The methylene carbons of 17 (R=aryl,R′=H) occurred at δ 53.23-56.09 in the carbon magnetic resonance spectra, and the carbon at the ring junction appeared at δ 92.64-92.91. By comparison with shifts for the analogous carbon in related penam systems[95], the signal at δ 169.75-170.50 was assigned to the carbonyl carbon of the β-lactam. The unsaturated carbon of the imidazoline ring gave a signal at δ 178.66-179.37. All the mass spectra displayed a molecular ion peak, and the primary fragmentation was the extrusion of carbon monoxide.



18

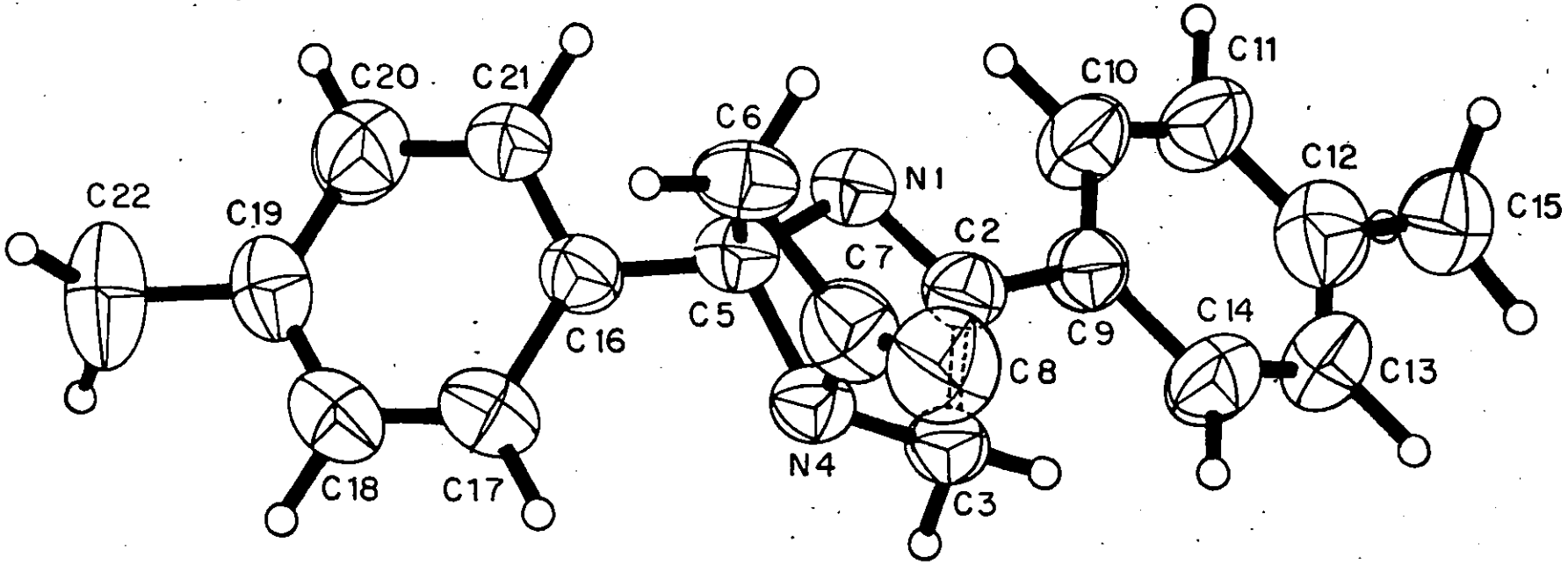


Figure 1. Molecular structure of 17, R=p-$CH_3C_6H_4$,R'=H , as determined by X-ray crystallography. Pertinent X-ray data[96] for 17, R=p-$CH_3C_6H_4$, R'=H;monoclinic,$P2_1/a$, a=19.176(2), b=5.745(1), c=15.144(2) A°; β =109.82(2)°,V=1569.5 $A°^3$, Z=4, D_m=1.22(1), D_x=1.229 g/cm^3 , Ni-filtered CuKα , λ ($K\alpha_1$)=1.54056, λ($K\alpha_2$)=1.54439 A°, μ (CuKα)=5.70 cm^{-1} ,F(000)=616, T=296 K, R=0.046 for 1467 observed reflexions.

Although structure (17) could be assigned on the basis of the spectral data, isomers such as (18) could not be ruled out. Consequently, an X-ray analysis of 17(R=p-$CH_3C_6H_4$,R′=H) was undertaken to unambiguously establish the structure[96]. The study has identified the product as (17).

The structure given in Figure 1, shows the

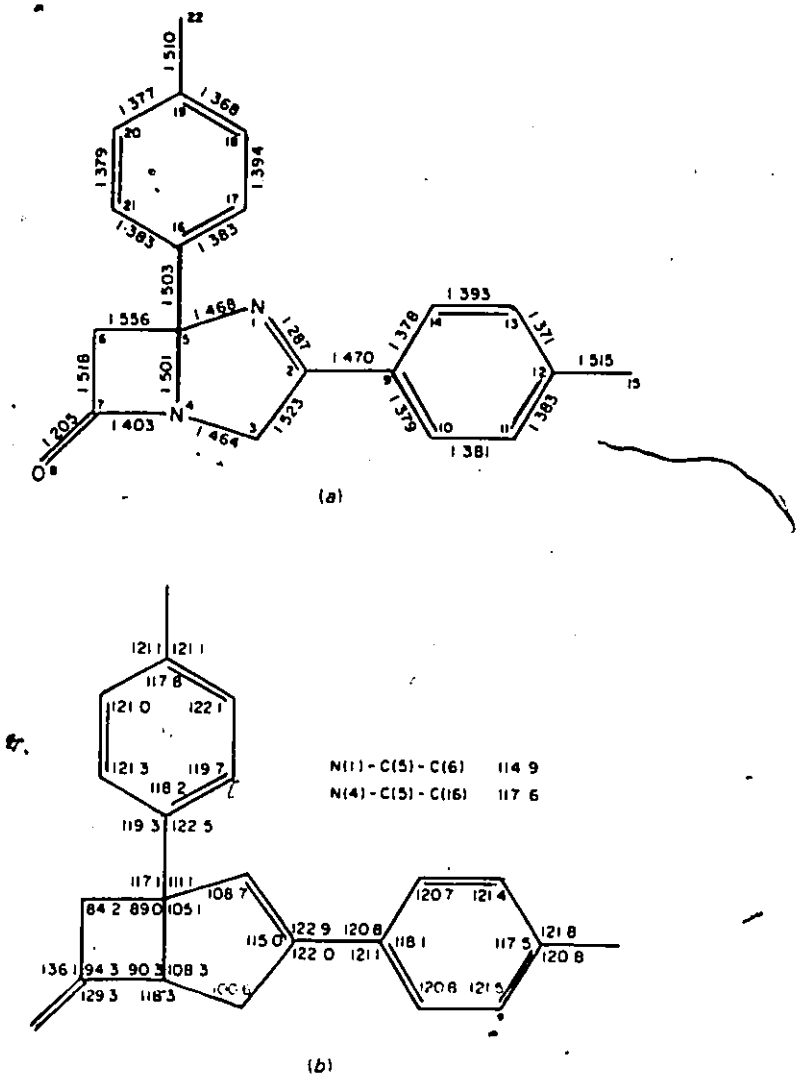


Figure 2. (a) Bond lengths (Å). e.s.d.'s =0.004-0.005 Å ; (b) Bond angles (°). e.s.d.'s = 0.2-0.3°.

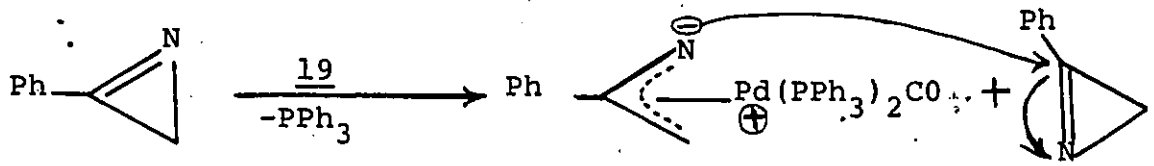
interesting geometry of the β-lactam with respect to the five-membered ring, and the bond lengths and angles are shown in Figure 2.

First we proposed, as a working hypothesis, a mechanism to account for the formation of (17) from (14) as outlined in scheme 5 (illustrated for 2-phenyl-1-azirine). Substitution of a phosphine ligand of the catalyst by carbon monoxide would give (19). The latter may then effect carbon-nitrogen bond cleavage of the azirine, affording the azaallyl complex (20). In a number of important palladium-catalyzed reactions π-allyl complexes have been suggested as intermediates [97,98]. Intermolecular reaction of (20) with another molecule of 2-phenyl-1-azirine would produce (21), which would afford the bicyclic system (22) by cyclization and decomplexation. Insertion of palladium into a carbon-nitrogen bond of (22) or oxidative addition would give (23), which on ligand migration and decomplexation or reductive elimination would afford the β-lactam (17) and regenerate the catalyst.

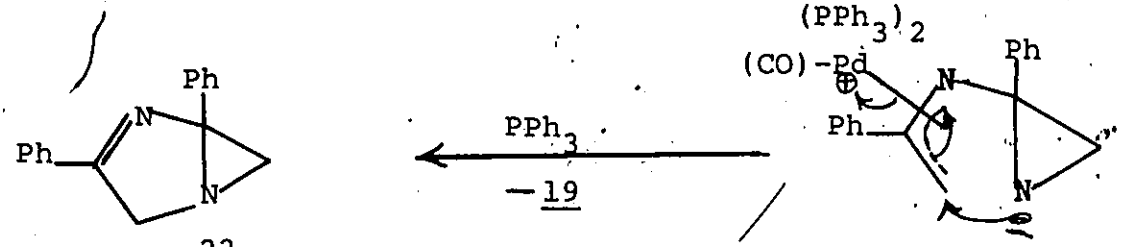
$$Pd(PPh_3)_4 \rightleftharpoons Pd(PPh_3)_3 + PPh_3$$

$$Pd(PPh_3)_3 + CO \longrightarrow Pd(PPh_3)_3CO$$

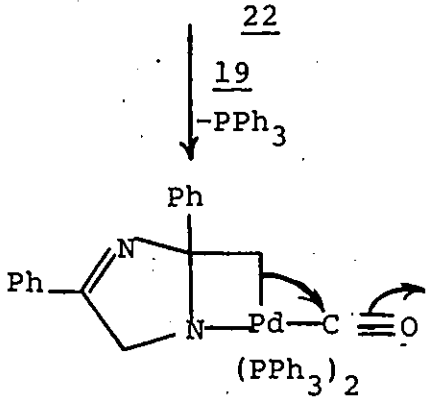
19



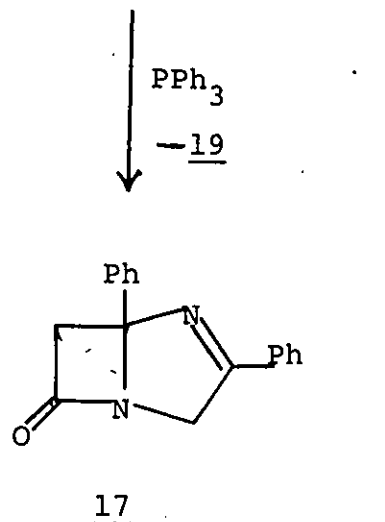
20



21 22



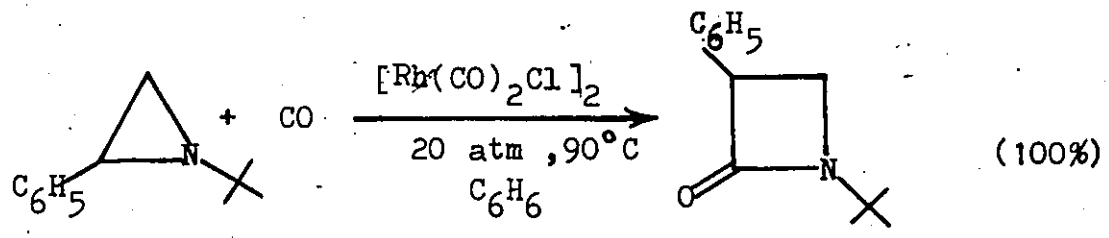
23 24



17

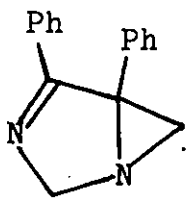
Scheme 5.

If (22) was an intermediate then one would expect the $Pd(PPh_3)_4$ to promote the carbonylation of an aziridine to a β-lactam. However, no reaction occurred when N-n-butyl-2-phenylaziridine (10) was exposed to carbon monoxide and $Pd(PPh_3)_4$. Recently it has been reported[99] that β-lactams could be obtained from Rh(I) catalyzed carbonylation of aziridines under pressure of carbon monoxide at elevated temperature.



(100%)

In addition, the photodimer (11)[106] of 2-phenyl-1-azirine is an isomer of (22), and it also failed to undergo carbonylation under conditions described for 14 (R = Ph, R' = H). These results provide evidence against the intermediacy of (22) in the carbonylation reaction.

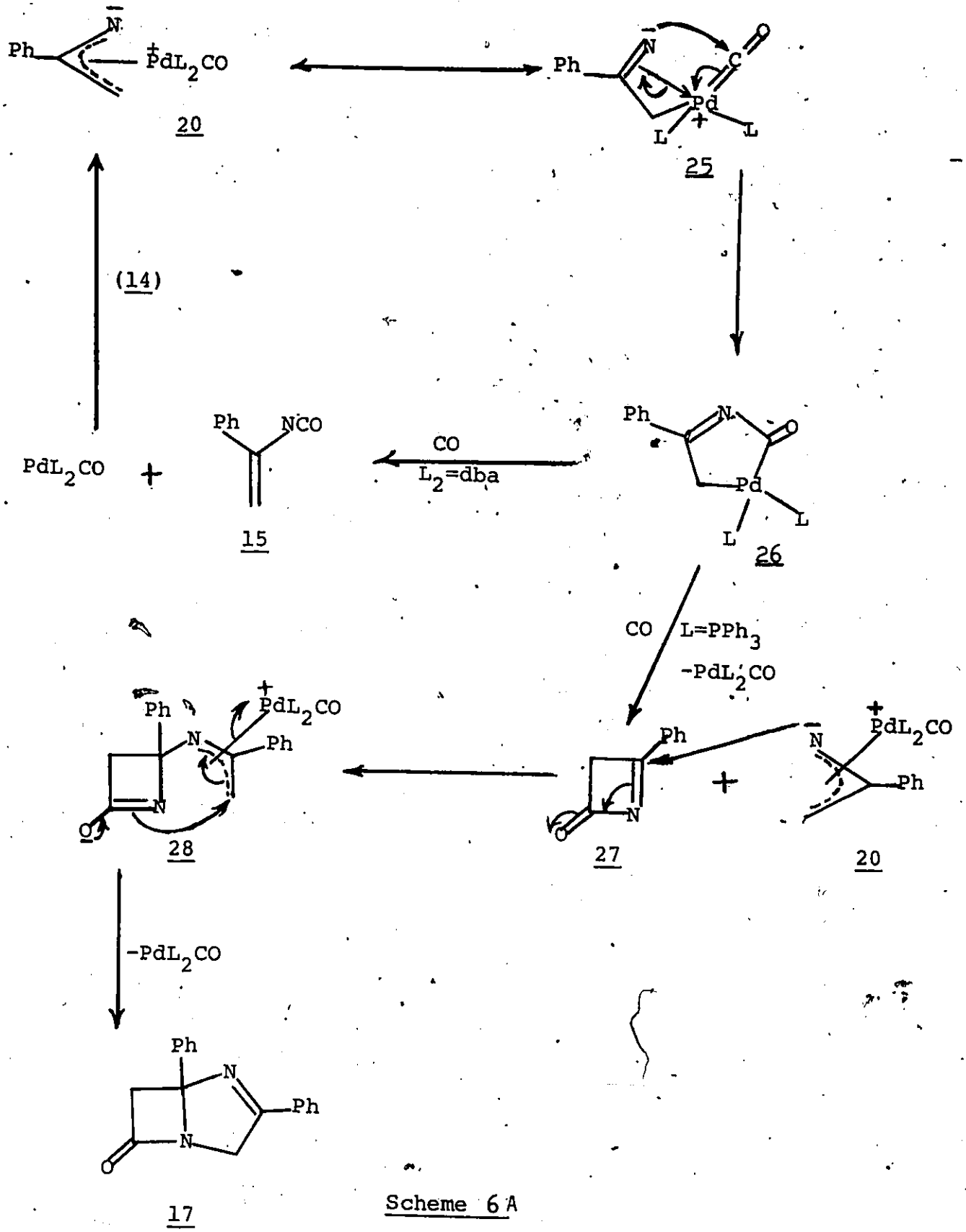


11

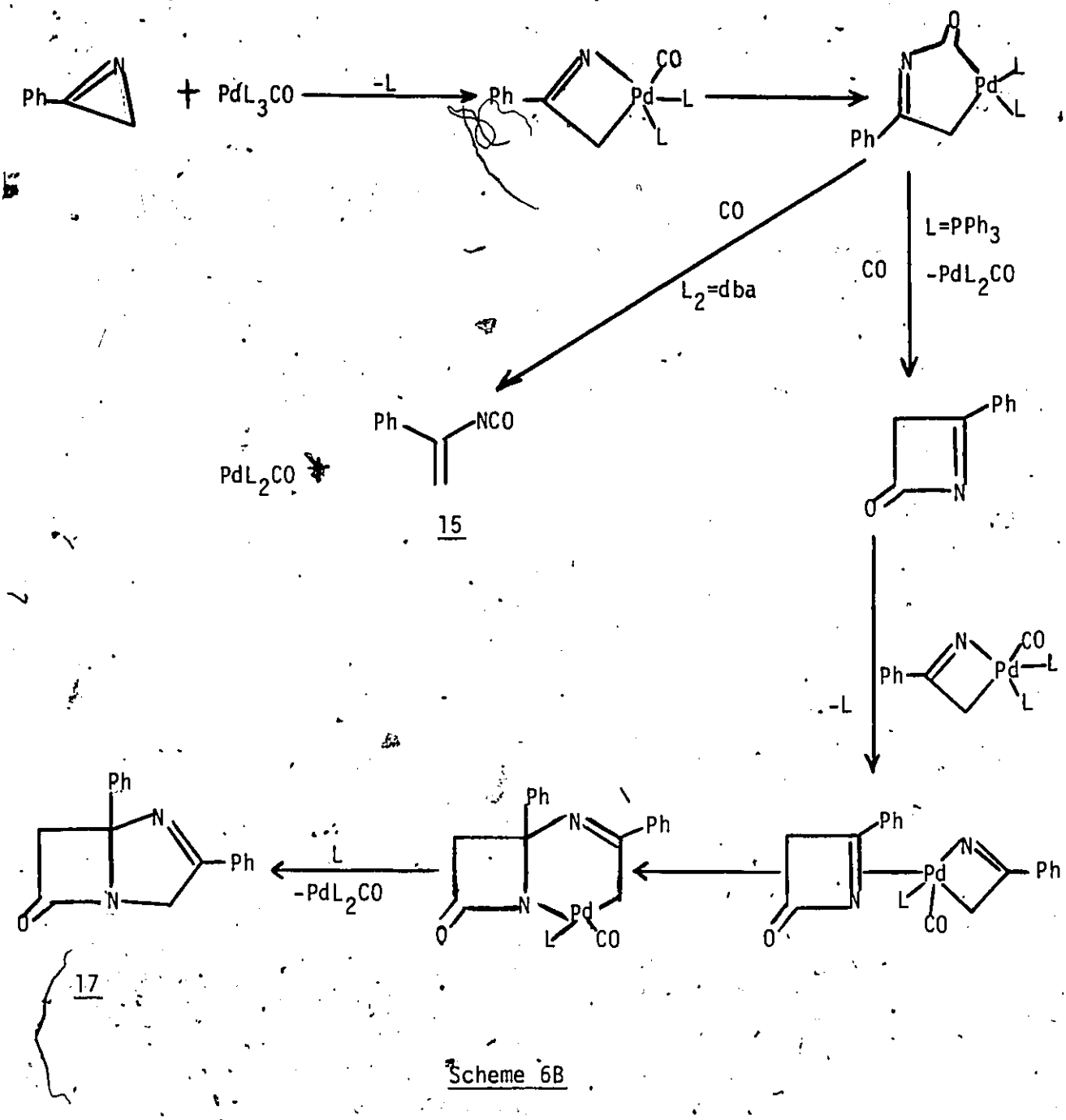
What is remarkable about the results described above is the complete selectivity exhibited by the palladium catalysts. While $Pd(PPh_3)_4$ catalyzes the conversion of azirines to β-lactams (17) with no vinyl isocyanate (15) product being detected, compound (15) is the only product obtained when $Pd(dba)_2$ is used as the catalyst.

How can one rationalize the formation of β-lactams and vinyl isocyanates in these reactions? It is conceivable that both products arise via a common intermediate (Scheme 6A); illustrated for 14, R= C_6H_5, R'=H). Structure (25) is a contributor to the resonance hybrid of (20). Intramolecular cyclization of (25) would afford (26). Decomplexation of the palladocycle can occur in one of two ways. For L_2=dba, elimination of Pd(dba)CO occurs in the presence of carbon monoxide to give the vinyl isocyanate (15). Reaction of the palladium species with azirine will regenerate (20). For L=PPh_3, reductive elimination takes place to give the azetinone (27) and $Pd(PPh_3)_2CO$, the latter again forming (20) on treatment with additional azirine (14). Nucleophilic addition of (20) to (27) would afford (28) which on ring closure and elimination of $Pd(PPh_3)_2CO$ would give the β-lactam (17).

An alternative mechanism involving metallocycle intermediates is outlined in Scheme 6B, for the formation of vinyl isocyanates (15) and β-lactams (17).


Ph
N
PdL2CO
20
Ph
N
C
O
Pd
L
L
25
(14)
PdL2CO
+
Ph
NCO
15
CO
L2=dba
Ph
N
O
Pd
L
L
26
CO
L=PPh3
-PdL2CO
Ph
PdL2CO
N
Ph
N
O
28
Ph
N
Ph
N
27
+
N
PdL2CO
Ph
20
-PdL2CO
Ph
N
Ph
N
O
17

Scheme 6 A



Scheme 6B

The $Pd(PPh_3)_4$ catalyzed carbonylation reaction of 1-azirine seemed to be inhibited by the substitution on the 3-position of the ring. No reaction occurred when

3-formyl-2-phenyl-1-azirine or 3-(dimethoxymethyl)-2-phenyl-1-azirine or 3-methyl-3-allyl-2-phenyl-1-azirine was exposed to carbon monoxide and $Pd(PPh_3)_4$, and 3-methyl-2-phenyl-1-azirine also gave a very low yield of β-lactam 17 ($R=C_6H_5$, $R=CH_3$).

The effect of other factors such as added ligands, polar solvents and hydrogen on the $Pd(PPh_3)_4$ catalyzed carbonylation reaction always resulted in reduced yields of the β-lactam (17). For example when the $Pd(PPh_3)_4$ catalyzed carbonylation of 2-phenyl-1-azirine was run in the dipolar aprotic solvent, N,N-dimethylacetamide, β-lactam (17) was formed in 16% yield. The latter reaction was also carried out in the presence of added ligands, such as 2,2'-bipyridyl, N,N,N',N'-tetramethylethylenediamine (TMEDA), maleic anhydride and allyl acetate in order to generate a new catalyst in situ by replacement of PPh_3 by the added ligands. Such catalytic species might be able to improve the yield of the reaction and/or change the reaction course. For example, the carbonylation of (1) by $Pd(PPh_3)_4$:2,2'-bipyridyl (1:1) or $Pd(PPh_3)_4$: TMEDA(1:1) or $Pd(PPh_3)_4$: TMEDA (1:2) or $Pd(PPh_3)_4$: maleic anhydride (1:3) gave β-lactam 17 ($R=C_6H_5$, $R'=H$) in 29%, 28%, 31% and 16% yields respectively. Similarly, the carbonylation reaction of (1) by $Pd(PPh_3)_4$ in the presence

of allyl acetate [$Pd(PPh_3)_4$: allyl acetate (1:1)] gave 33-36% of β-lactam 17 (R = C_6H_5, R' = H). But the $Pd(dba)_2$ catalyzed carbonylation reaction in the presence of allyl acetate did not show any reaction after 3 days. This may be due to the formation of a $(CH_2CHCH_2)Pd^+(dba)OAc^-$ complex in situ with the allyl acetate, which can inhibit the carbonylation reaction of azirine. But, in the case of $Pd(PPh_3)_4$, this type of complex formation must be very low, since the yield of β-lactam was only slightly reduced in the presence of allyl acetate. The carbonylation reaction was carried out using synthesis gas (1:1 CO/H_2) to see the effect of hydrogen on this reaction. β-Lactam 17 (R=C_6H_5, R'=H) was isolated in 25% yield in the latter reaction with 4.5% yield of 4,5-diphenylpyrimidine [^1H NMR($CDCl_3$), δ 7.40-8.96 (m,12H, aromatic protons + pyrimidine protons); MS(m/e), 232 [M^+].

The use of other Pd(0) complexes as catalysts on the carbonylation reaction of azirine was also examined. Replacement of two triphenylphosphine ligands of $Pd(PPh_3)_4$ by a dimethyl acetylenedicarboxylate ligand [i.e., $(PPh_3)_2(CH_3O_2CC{\equiv}CCO_2CH_3)Pd(0)$] resulted in β-lactam formation but in somewhat slightly lower yield (35%) than in the case of $Pd(PPh_3)_4$ (using 2-phenyl-1-azirine). The use of a bidentate donor ligand such as 1,2-bis(diphenylphosphino) ethane (i.e., $Pd(dpe)_2$) instead of triphenylphosphine

resulted in the complete inhibition of the reaction. Also tried were Pd(II) complexes in the carbonylation reaction of azirines. When one uses $Pd(CH_3CO_2)_2$ and di-μ-chlorobis (η^3-propenyl)dipalladium(II) , 6 and 4 fractions respectively were isolated, none of which was identified successfully. However, when the carbonylation reaction of 2-phenyl-1-azirine was effected with di- μ-chlorobis(η^3-propenyl)dipalladium(II) in the presence of triphenylphosphine ligand [Pd(II): PPh_3 (1:3)] , bicyclic β -lactam 17 (R=C_6H_5,R'=H) was isolated in 15% yield and 11% of 2,5-diphenylpyrazine was also formed. This may be due to the in situ formation of $Pd(PPh_3)_n$. Similarly, when the carbonylation reaction of 2-phenyl-1-azirine was carried out with $Pd(dba)_2$ in the presence of PPh_3, β-lactam was obtained instead of vinyl isocyanate, due to in situ generation of $Pd(PPh_3)_n$. When we use $Pd(dba)_2$: PPh_3 (1:30) the reaction was very slow and β-lactam 17 (R=C_6H_5,R'=H) was obtained in 27% yield, whereas with $Pd(dba)_2$:PPh_3 (1:3), latter was obtained in 35% yield and the reaction was very much faster. When there is a large excess of PPh_3 in the reaction mixture, the formation of $Pd(PPh_3)_{n-1}CO$ is very slow, because the equilibrium between $Pd(PPh_3)_n$ and $Pd(PPh_3)_{n-1}$ lies more towards $Pd(PPh_3)_n$ as shown below.

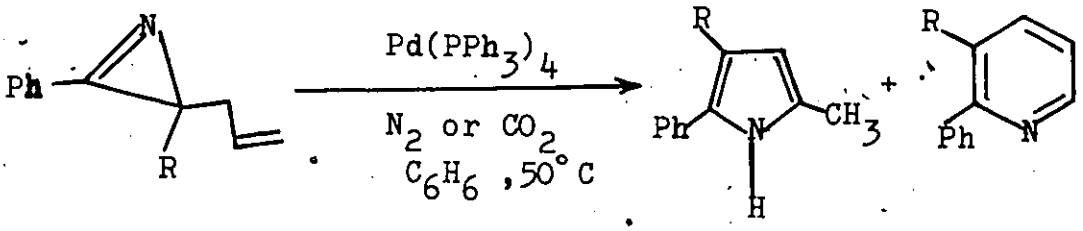
$$Pd(dba)_2 + n\ PPh_3 \longrightarrow Pd(PPh_3)_n + 2\ \text{'dba'}$$

$$Pd(PPh_3)_n \rightleftharpoons Pd(PPh_3)_{n-1} + PPh_3$$

$$Pd(PPh_3)_{n-1} + CO \longrightarrow Pd(PPh_3)_{n-1}CO$$

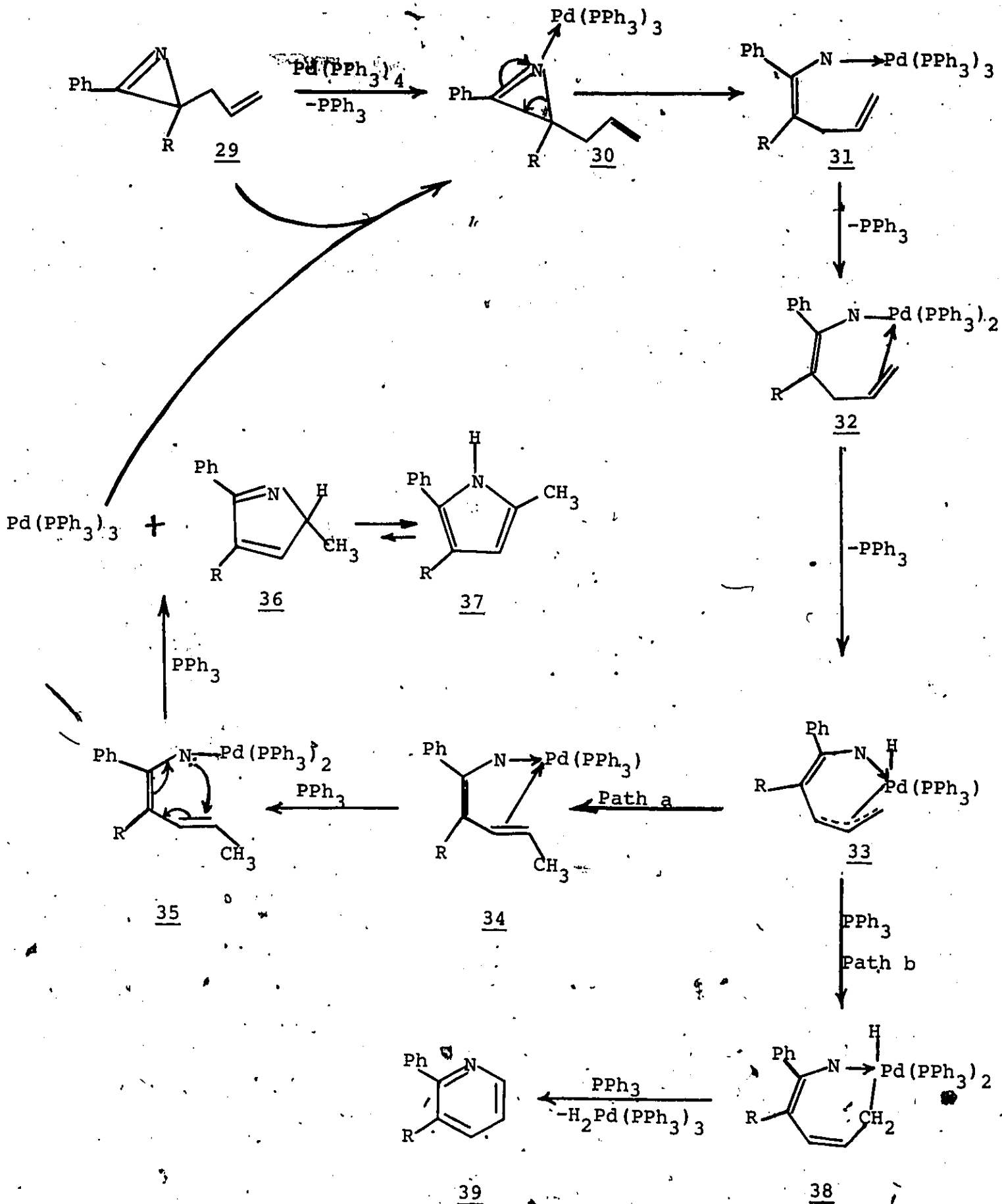
When nickel [$Ni(PPh_3)_4$] and platinum [$Pt(PPh_3)_4$] analogues of $Pd(PPh_3)_4$ were used, they were ineffective as catalysts for the azirine carbonylation reaction. Starting material was recovered in both cases.

The $Pd(PPh_3)_4$ catalyzed reaction of azirine under a nitrogen atmosphere gave 7 fractions, none of which were identified successfully. Recently it was reported[111] that tetrakis(triphenylphosphine)palladium(0) catalyzed the conversion of 3-allyl-1-azirines to pyridines and pyrroles, under nitrogen or carbon dioxide atmosphere. This reaction is sensitive to the atmosphere in which it is conducted, as well as to the pressure. Under elevated pressure (24.5 atm) the yield of pyrrole increased.



$R=CH_3$, $-CH_2CH=CH_2$

The mechanism which has been proposed for the formation of pyridines and pyrroles from allyl azirines, involves a common intermediate (33) [Scheme 7]. As in the other metal carbonyl catalyzed reactions of 1-azirines, a nitrene palladium complex (31) would form by


Ph
N
R
29
Pd(PPh3)4
-PPh3
Pd(PPh3)3
30
31
-PPh3
32
Pd(PPh3)2
-PPh3
33
Path a
Path b
PPh3
34
35
36
37
38
39
-H2Pd(PPh3)3
CH3
CH2
H

complexation (30) and cleavage of the carbon-nitrogen single bond. Unlike simple nitrene metal complexes, compound (31) has an allylic group. Binding of this double bond of the allylic unit to palladium may give (32). By allylic hydrogen abstraction, palladium hydride (33) may form, which could react by two pathways to give pyrroles and pyridines. Transformation of the hydride to the least substituted terminal carbon of the allyl unit would give (34) [path a] and with PPh_3, (35) and which on cyclization and decomplexation would afford (36) and $Pd(PPh_3)_3$. Compound (30) could be regenerated completing the cycle by the reaction of $Pd(PPh_3)_3$ with another molecule of azirine (29), while (36) would readily isomerize to the pyrrole (37).

Instead of hydrogen transfer from palladium to the least substituted terminal carbon of the allylic unit (33 $\longrightarrow$ 34), (33) could undergo $\pi \rightarrow \sigma$ allyl conversion in the presence of PPh_3 to give (38) [path b]. The pyridine (39) and $Pd(PPh_3)_2H_2$ would result from (38) by dehydrogenation and elimination. Addition of PPh_3 to $H_2Pd(PPh_3)_2$ would regenerate $Pd(PPh_3)_3$ with the elimination of H_2. It is also possible that (38) would eliminate $Pd(PPh_3)_3$ and H_2 directly in the presence of PPh_3.

Once some variations on the general procedure of $Pd(PPh_3)_4$ catalyzed carbonylation of azirines were done, we tried to trap the proposed dipolar azaallyl intermediate

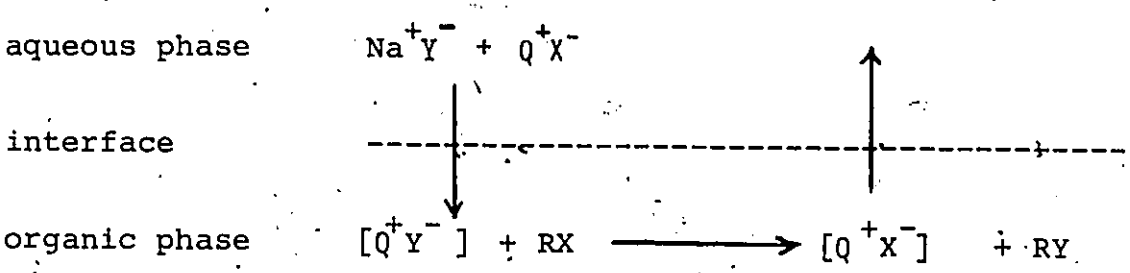
(20) in the latter reaction with various dipolarophiles. In all cases it was not successful. For example, when dimethyl fumarate and dimethyl maleate were used only β-lactams(17) were obtained with 2-phenyl-1-azirine or 2-(2',4'-dimethylphenyl)-1-azirine as reactants (i.e., no cycloaddition products were isolated). When dimethyl acetylenedicarboxylate was used 4 products were obtained with 2-phenyl-1-azirine, none of which was identified successfully. Similar results were obtained with 2-(2',4'-dimethylphenyl)-1-azirine.

Diels-Alder reactions were also attempted with various dienophiles on the resulting vinyl isocyanates(15) of $Pd(dba)_2$ catalyzed carbonylation reaction of azirines. This was also unsuccessful. When the resultant vinyl isocyanate 15 ($R=C_6H_5, R'=H$) was allowed to reflux with dimethyl acetylenedicarboxylate and dimethyl maleate in benzene only the unreacted vinyl isocyanate 15 ($R=C_6H_5, R'=H$) and esters were isolated after several days.

3.2. Palladium (0) catalyzed reactions of azirines under heterogeneous conditions

The use of phase-transfer catalysis as a preparative method in organic synthesis has grown rapidly during the past eighteen years [112,113]. These reactions are carried out in an aqueous base-organic two-phase system with an ammonium or phosphonium salt, or crown ether as the catalyst. Some of the advantages of phase-transfer catalytic processes include the ability to carry out the reactions efficiently and under mild conditions. The method also saves on expensive anhydrous aprotic solvents, and aqueous NaOH is used instead of alkali metal alkoxides. The workup is also usually simple.

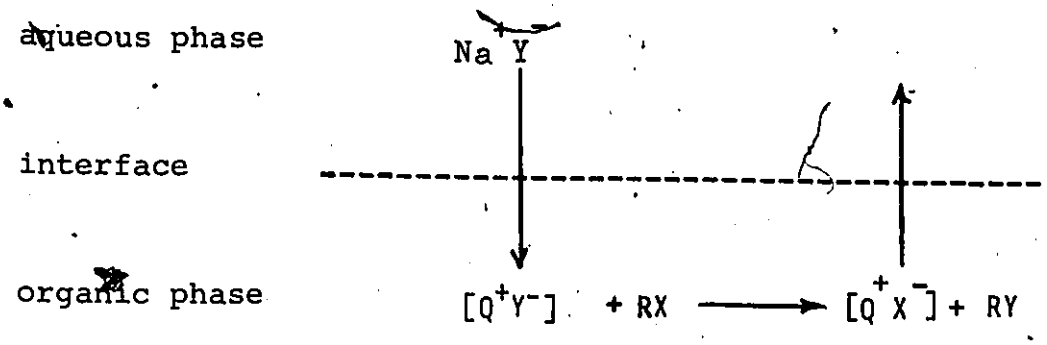
A liquid-liquid phase-transfer catalyzed nucleophilic substitution reaction is illustrated in Scheme 8. Here Q^+ is an ammonium or phosphonium salt cation and Y^- is assumed to be more lipophilic than X^-. The catalyst cation Q^+ migrates with the anion Y^- from the aqueous phase into the organic phase, where the weakly solvated ion pair reacts with RX to give RY and $[Q^+X^-]$, which is



Scheme 8

then transported to the aqueous phase.

However, the mechanism shown in Scheme 9 applies when highly lipophilic catalyst cations are used. According to this mechanism Q^+ will stay in the organic phase and only the anions are transferred across the interface.



Scheme 9

Crown ethers have also been of great use as catalysts in solid-liquid phase transfer reactions. The high rate of the latter reaction in comparison to the reaction in the absence of crown ethers is mainly due to the fact that crown ethers can bind to the cation of a salt and solvate the salt in the organic phase, thereby increasing the nucleophilicity of the anion.

Transition metal complexes catalyzed phase-transfer catalysis is also reported to be a useful method for effecting a variety of valuable synthetic transformations[112]. Examples include the regiospecific cobalt

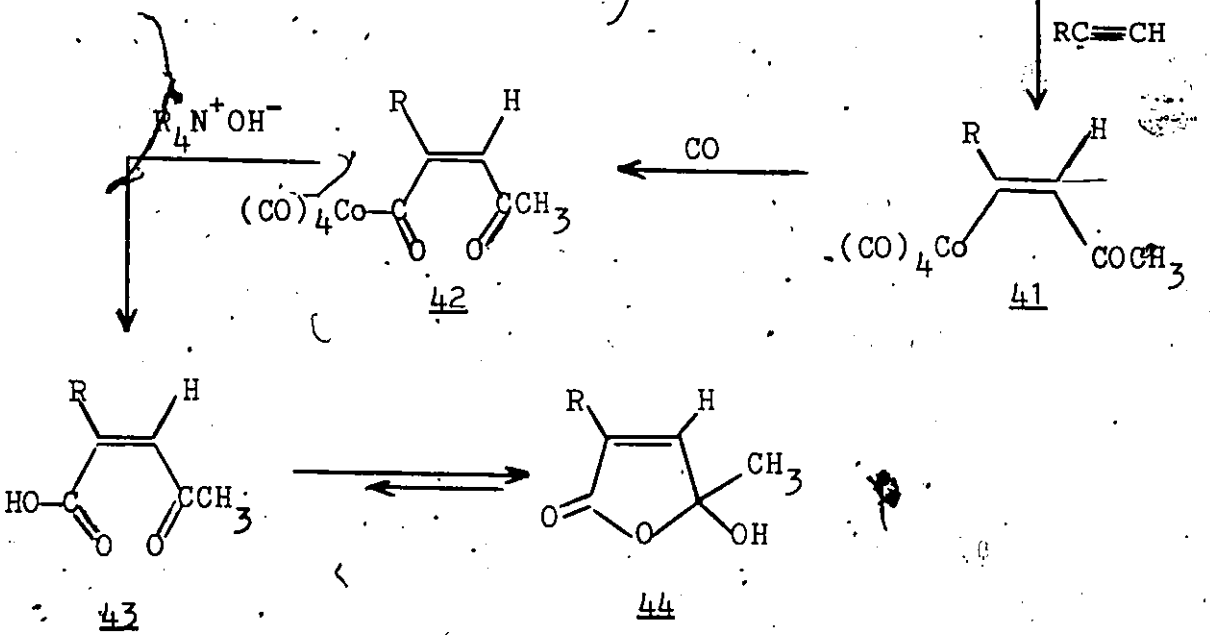
octacarbonyl catalyzed synthesis of butenolides (44) from alkynes[114] (Scheme 10) and the palladium(0) induced conversion of vinylic dibromides to diynes, diacids or monoacids depending on the nature of the unsaturated halide, and the reaction conditions[115]. The former

aqueous $R_4N^+X^- + Na^+OH^- \rightleftharpoons R_4N^+OH^- + Na^+X^-$

organic $32\ R_4N^+OH^- + 11Co_2(CO)_8 \longrightarrow 20R_4N^+Co(CO)_4^- + 6[R_4N]_2CO_3 + 16H_2O + 2Co^{+2} + 2CO_3^{-2}$

aqueous $2Co^{+2} + 8OH^- \longrightarrow 2\ Co(OH)_4^{-2}$

organic $CH_3I \xrightarrow{Co(CO)_4^-} CH_3Co(CO)_4 \xrightarrow{CO} CH_3C(=O)Co(CO)_4$ (40)



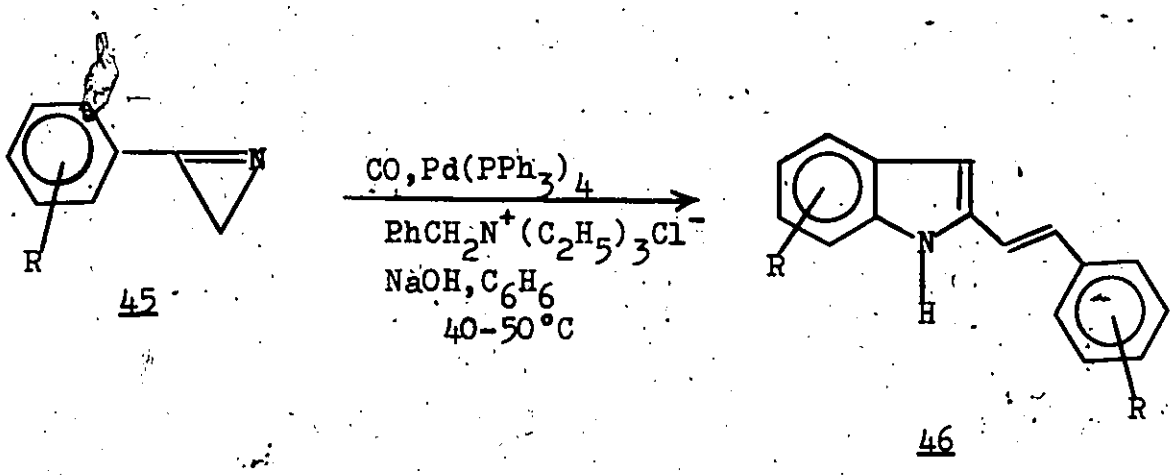
reaction may proceed by disproportionation of $Co_2(CO)_8$ by base to generate $Co(CO)_4^-$ anion which then reacts with CH_3I to give $CH_3Co(CO)_4$. Carbonylation of the latter may generate acetylcobalt tetracarbonyl (40) which can add to the alkyne giving a vinylcobalt complex (41). Carbonylation of (41) would give (42) which may undergo metal-carbon bond cleavage by base to produce the unsaturated keto acid (43), which is the chain tautomer of the cyclic lactone (44).

It seemed of interest therefore to learn whether the palladium(0) catalyzed carbonylation of azirines, effected under phase transfer conditions, would afford the same (15, 17) or different products than the homogeneous reactions. Therefore we investigated the latter reaction.

Treatment of 2-phenyl-1-azirine (45, R=H) with carbon monoxide, 50% NaOH, benzene as the organic phase, benzyltriethylammonium chloride as the phase transfer catalyst, and tetrakis(triphenylphosphine)palladium(0) [10/1 ratio of 45 / $Pd(PPh_3)_4$] as the metal catalyst, at 45°C for 1.5hr, afforded 2-styrylindole (46, R=H) in 29% yield. Product yields, reaction times and the phase transfer catalyst used are given in Table 5. Spectral data are listed in Table 6.

When the reaction was effected under a nitrogen instead of carbon monoxide atmosphere, no reaction took place, although the reaction should, in principle, proceed under such conditions since there is no CO insertion in the product formed. However, when carbon dioxide was used as the reaction atmosphere, the indole was obtained in 19% yield. The indole (46) is not formed in the absence of palladium(0) catalyst, but in the presence of CO.

In the absence of the phase transfer catalyst, the conversion of azirines to indoles does occur (i.e., as a biphasic process), but in lower yield (18%). Certain phase transfer catalysts such as dodecyltrimethylammonium chloride and tetrabutylammonium hydrogen sulfate were used instead of benzyltriethylammomium chloride in order to see whether any improvement could be made to the reaction. In both cases the yield did not improve. The concentration of base has some influence on the reaction since (46, R=H) was formed in 25% yield using more dilute sodium hydroxide (5N). When water was used as the aqueous phase the yield dropped to 11% with β-lactam (17, R=C_6H_5, R'=H) and acetophenone formed in 38% and 10% yields respectively. The use of potassium carbonate as the base afforded the β-lactam (17, R=C_6H_5, R'=H) in 35% yield, with 46 (R=H) formed in 5% yield. These two cases were the only instances where β-lactam (17) was formed.



45 46

The yield of 46 (R = C_6H_5) was decreased when the proportion of palladium(0) was increased [i.e., 5/1 ratio of 45 / Pd(0)]. Bis[bis(1,2-diphenylphosphino)-ethane]palladium(0) ,[$Pd(dpe)_2$] , was a less useful catalyst than $Pd(PPh_3)_4$, while with bis(dibenzylideneacetone)palladium(0), $Pd(dba)_2$, no indole was obtained. The use of the Pd(II) catalyst, palladium acetate gave 41% yield of acetophenone from 2-phenyl-1-azirine, and no indole was isolated. The substitution of other organic solvents for benzene such as t-amyl alcohol gave no indole and hexane gave a poor yield of 46 (R = H , 13%). Pressure of (350 psi) also inhibited the conversion of (45) to (46). A dimer [47; MS(m/e)234] and a trimer [48; MS(m/e) 351] of 2-phenyl-1-azirine were isolated in 19% and 13% yields respectively from the above reaction. The structures of the two products were not determined successfully.

When the phase transfer reaction was carried out in the presence of $Co_2(CO)_8$ [i.e., 1/1 ratio of

$Co_2(CO)_8$ / $Pd(PPh_3)_4$] as a bimetallic process the product yield again decreased.

Modest yields of styrylindoles were also obtained from 2-(4'-methylphenyl)-, and 2-(4'-methoxyphenyl)- as well as from 2-(2'-methylphenyl)- and 2-(2',4'-dimethylphenyl)-1-azirine. Since 2 molecules of (45) are required to form indole (46), a question arises as to the fate of the second nitrogen atom. No nitrogen containing species was isolated as a by-product. It is possible to consider that the nitrogen ends up as ammonium hydroxide. Previously styrylindoles have been obtained in high yields from homogeneous cobalt(0)[89] or rhodium(I)[91] reaction with azirines under a nitrogen atmosphere. Under a carbon monoxide atmosphere, as in the case of $Pd(dba)_2$, vinyl isocyanates (15) are formed[92].

TABLE 5: Products, Reaction Times, Temperatures and Yields for the Pd(Ø) and Phase Transfer Catalyzed Reactions of Azirines[a]

Azirine (45)	Reaction Time, hr	Temp. °C	$R_4N^+X^-$ [b]	Product	Yield %
2-Phenyl-1-azirine	1.5	45	A	2-Styrylindole	29
	18	40	-	2-Styrylindole	18
	2.5	50	B	2-Styrylindole	20
	2.5	50	C	2-Styrylindole	6
				Acetophenone	5
	2.5	50	A	2-Styrylindole	18[c]
				Acetophenone	12
	18	50	A	2-Styrylindole	13[d]
				Acetophenone	3
	2.5	45	A	2-Styrylindole	25[e]
	2.75	50	A	2-Styrylindole	11[f]
				Acetophenone	10
				β -Lactam (17, R=C_6H_5, R'=H)	38

TABLE 5: (Cont'd)

Azirine (45)	Reaction time, hr	Temp. °C	$R_4N^+X^-$ [b]	Product	Yield %
2-Phenyl-1-azirine	3	50	A	2-Styrylindole	5[g]
				β-Lactam (17, R=C_6H_5, R'=H)	35
	overnight	RT	A	2-Styrylindole	18[h]
				Acetophenone	4
	3.5	50	A	2-Styrylindole	19[i]
2-(4'-Methylphenyl)-1-azirine	2.5	50	A	2-p-Methylstyryl-6-methylindole	19
2-(4'-Methoxyphenyl)-1-azirine	18	50	A	2-p-Methoxystyryl-6-methoxyindole	15
				p-Methoxyacetophenone	23
2-(2'-Methylphenyl)-1-azirine	2.5	50	A	2-o-Methylstyryl-4-methylindole	9
				o-Methylacetophenone	19
2-(2',4'-Dimethylphenyl)-1-azirine	2.5	50	A	2-(2',4'-Dimethylstyryl)-4,6-dimethylindole	6
				2,4-Dimethylacetophenone	20

TABLE 5: (Cont'd)

[a] Reaction using $Pd(PPh_3)_4$, CO, 50% NaOH, C_6H_6.

[b] A = $PhCH_2N(C_2H_5)_3^+Cl^-$; B = $(C_4H_9)_4N^+HSO_4^-$; C = $C_{12}H_{25}N(CH_3)_3^+Cl^-$

[c] Using 5:1 ratio of 45: $Pd(PPh_3)_4$

[d] Using hexane as the organic phase.

[e] Using 5N NaOH.

[f] Using H_2O instead of NaOH.

[g] Using K_2CO_3 as the base.

[h] Using 1:1 ratio of $Pd(PPh_3)_4$: $Co_2(CO)_8$.

[i] Under a CO_2 atmosphere.

TABLE 6: Pertinent Spectral Data for Styrylindoles (46)

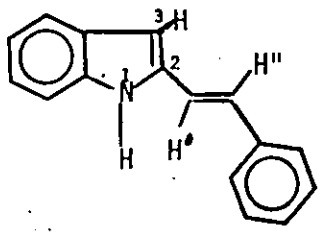
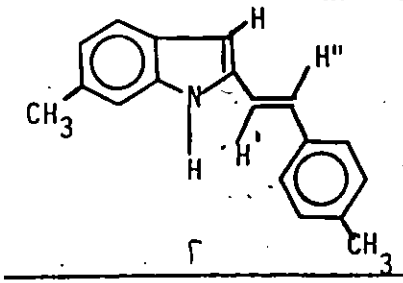
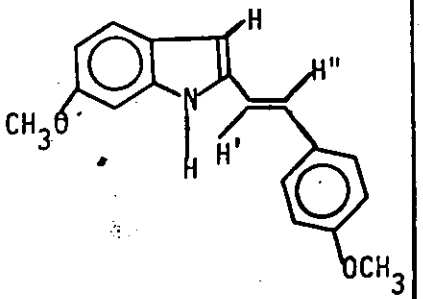
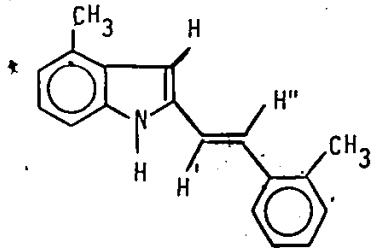
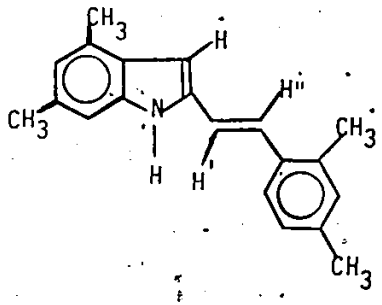
Products	IR[a], ν_{NH}, cm^{-1}	MS, m/e	NMR[b], δ, ppm	
			^1H	^{13}C
	3495	219	6.80(s(br),1H,C_3-H),7.00-7.70 (m,12H, aromatic protons,H', H″ ,NH)	103.97(C_3-H),115.75,123.90 (CH',CH"), 125.22, 125.78, 126.50, 126.69, 128.46, 128.54, 128.73, 128.94, 130.26, 132.54 (aromatic carbons
	3380	247	6.67(s(br), 1H,C_3-H),6.90-7.90 (m,10H, aromatic protons,H', H″ ,NH) 2.33 (s(br), 6H, CH_3 protons)	
	3460	279	3.80(s(br),6H,OCH_3 protons) 6.35(s(br), 1H, C_3-H) 6.60-8.20(m,10H, aromatic protons, H' ,H″ ,NH)	

TABLE 6: (Cont'd)

Products	IR[a] ν_{NH}, cm^{-1}	MS, m/e	NMR[b], δ, ppm ^1H	NMR[b], δ, ppm ^{13}C
	3495	247	2.44,2.53(s each, 6H,CH_3 protons), 6.46(s(br),1H,C_3-H),6.80-8.00 (m,10H, aromatic protons, H′,H″ , NH)	
	3350	275	2.16-2.44(m,12H,CH_3 protons), 6.50(s(br),1H,C_3-H),6.75-7.80 (m,8H,aromatic protons, H′,H″ , NH)	

[a] $CHCl_3$ solution. [b] $CDCl_3$ with Me_4Si as internal standard. ^{13}C assignments made with the aid of fully and partially decoupled spectra.

The acetophenone and substituted acetophenones were identified by comparing NMR, IR spectra to those of authentic samples.

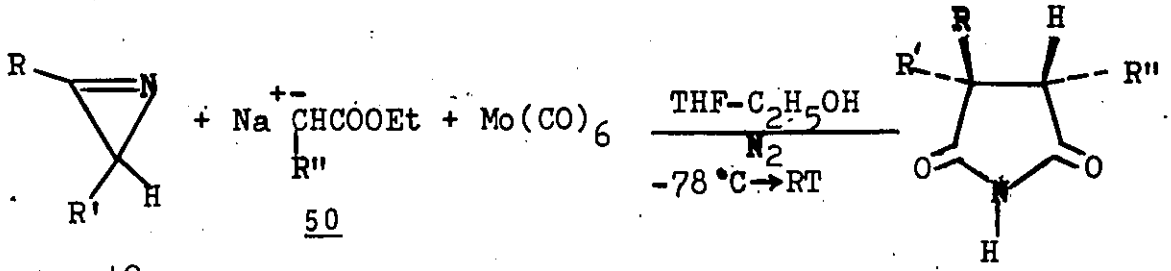
3.3. $Mo(CO)_6$ Induced Reactions of Azirines with Carbanions

In heterocyclic synthesis, transition metal complexes have played an important role as reagents and as catalysts in the last decade[116]. For example, pyrazines, isoxazoles, pyrazoles or pyrroles are obtained on exposure of azirines to molybdenum and other Group VI metal carbonyls[73], indoles using cobalt octacarbonyl[89], and bicyclic β-lactams (17) with tetrakis(triphenylphosphine)-palladium(0) and carbon monoxide.

The reaction of nucleophilic reagents with azirines has been investigated in considerable detail.[24] A question which arises is whether under such conditions the presence of metal complexes can promote synthetically useful transformations. Therefore it was decided to investigate the molybdenum hexacarbonyl induced reaction of azirines with carbanions derived from β-dicarbonyl compounds.

The reaction of sodium diethyl malonate [50, R'' =COOEt - generated from NaOEt and diethyl malonate in ethanol-tetrahydrofuran(THF)] with molybdenum hexacarbonyl at 50 °C, and then with 2-phenyl-1-azirine (49,R=Ph,R'=H) in THF at -78 °C (allowed to warm to room temperature), afforded the imide 51 (R=Ph,R'=H,R'' =COOEt) in 46% yield. The reaction was carried out using equimolar amounts of (49) and $Mo(CO)_6$ with 1.5 equivalents of (50). From spectral data and by an

X-ray crystal structure determination it was shown that this reaction is a stereospecific



49 51

one with the two substituent groups (R and R") of (51) in a trans relationship. The band at 3410 cm^{-1} in the infrared spectrum ($CHCl_3$) is due to an N-H stretching absorption. In the proton magnetic resonance spectrum, the two methine protons of 51 (R=C_6H_5,R'=H,R" =COOEt) gave two doublet signals at δ 3.80 and 4.42, while those for the carbon atoms bearing these hydrogens occurred at δ 51.02 and 56.21 in the carbon magnetic resonance spectrum. The structure given in Figure 3, shows the interesting geometry of the imide 51(R=C_6H_5,R'=H,R" =COOEt) with two substituent groups in a trans relationship as determined by X-ray crystallography. The selected bond lengths and bond angles are shown in Figure 4.

A variety of other azirines including 49 [R=p-BrC_6H_4,p-$CH_3C_6H_4$,o-$CH_3C_6H_4$,p-ClC_6H_4; R' = H, R" = COOEt], undergo this novel and interesting reaction to give the disubstituted imides in 27-68% yield. The product yields, reaction times, melting points and analytical data

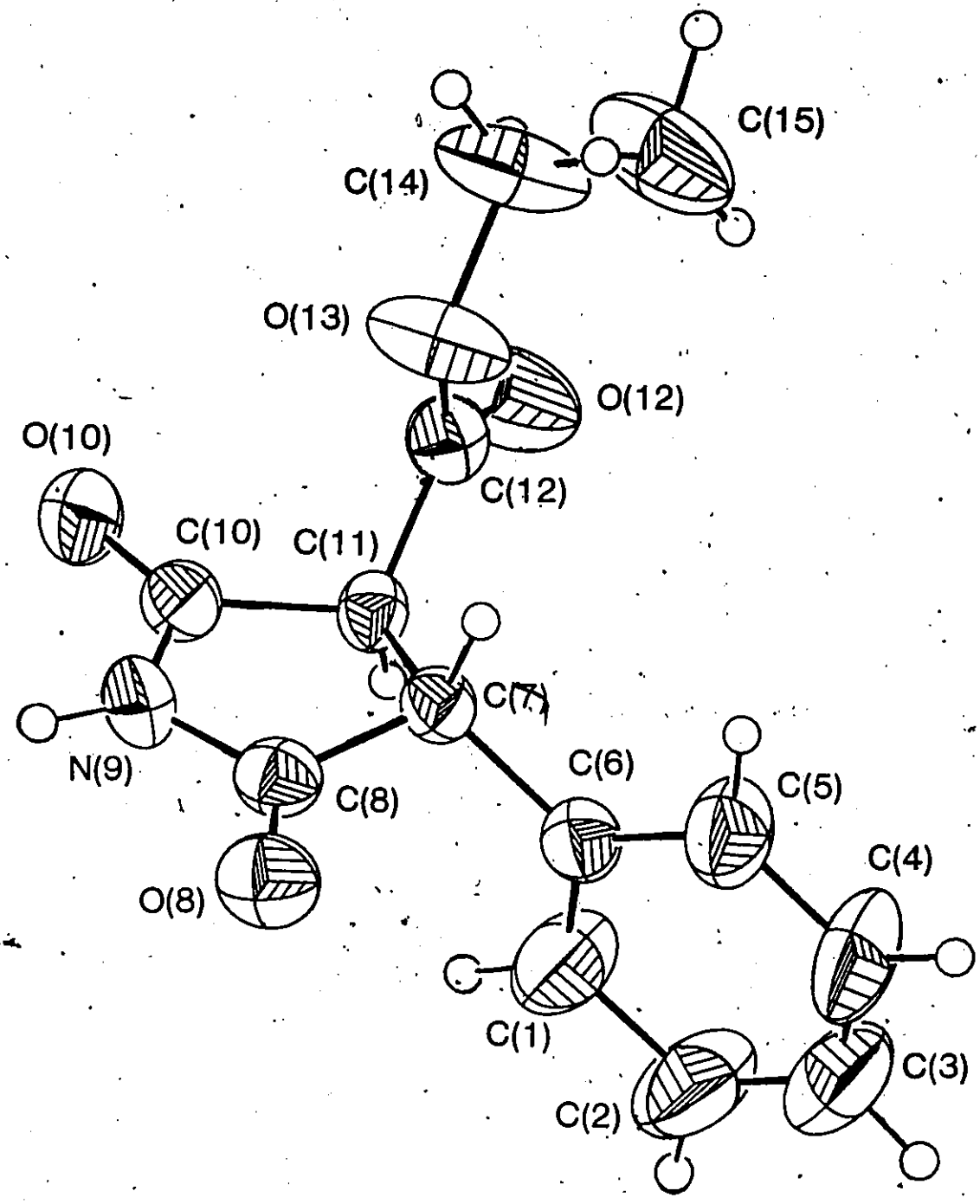


Figure 3. Molecular structure of 5ℓ, R=C_6H_5,R'=H, R"=COOEt, as determined by X-ray crystallography. Pertinent X-data for 5ℓ, R=C_6H_5 ,R'=H, R"=COOEt; monoclinic,$P2_1/n$,a=15.286(3), b=5.377(2), c=16.218(4)Å ; β=109.72(2)°, ρ_{calcd}(Z=4)=1.309gcm^{-3} ,graphite-monochromatized MoKα , λ($K\alpha_1$)=0.70930, λ($K\alpha_2$)=0.71359Å,R_1=0.046 ,R_2=0.055 for 1130 observed reflections.

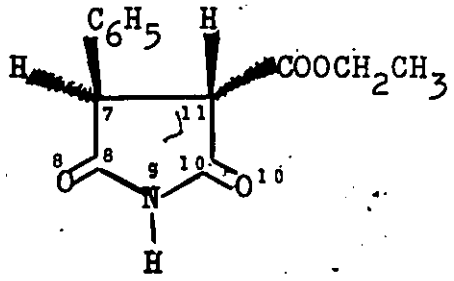


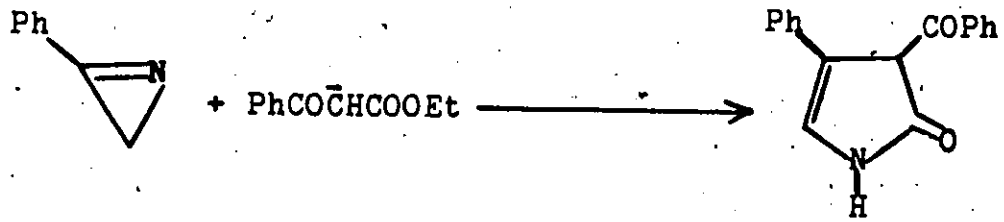
Figure 4. (a) Selected bond lengths (Å),e.s.d.'s=0.005Å :
C(7)-C(8),1.513;C(8)-N(9),1.388;N(9)-C(10),
1.357; C(10)-C(11), 1.519;C(11)-C(7),1.533;
C(8)-O(8), 1.209; C(10)-O(10), 1.219.

(b) Selected bond angles(deg.),e.s.d.'s=0.3° :
C(11)-C(7)-C(8), 103.8; C(7)-C(8)-N(9),107.7;
C(8)-N(9)-C(10), 114.0; N(9)-C(10)-C(11), 108.0;
C(10)-C(11)-C(7), 104.6.

are given in Table 7. Spectral data are listed in Table 8. The imide 51 ($R=C_6H_5, R'=CH_3, R''$ =COOEt) was obtained in 74% yield in the case of 3-methyl-2-phenyl-1-azirine (49, $R=Ph, R'=CH_3$). Other carbanions, derived from ethyl benzoylacetate (50, R'' =COPh) and ethyl cyanoacetate (50, R'' = CN), could also be used.

It should be noted that in the absence of $Mo(CO)_6$ this reaction does occur, but in significantly lower yield. The reverse addition [i.e., dropwise addition of 50 (R'' =COOEt) to a mixture of 49 (R=Ph, R'=H) and $Mo(CO)_6$ in THF] also gave imide in lower yield (32-33%). When the reaction was carried out in a carbon monoxide instead of a nitrogen atmosphere, a significant inhibition of the above reaction was observed.

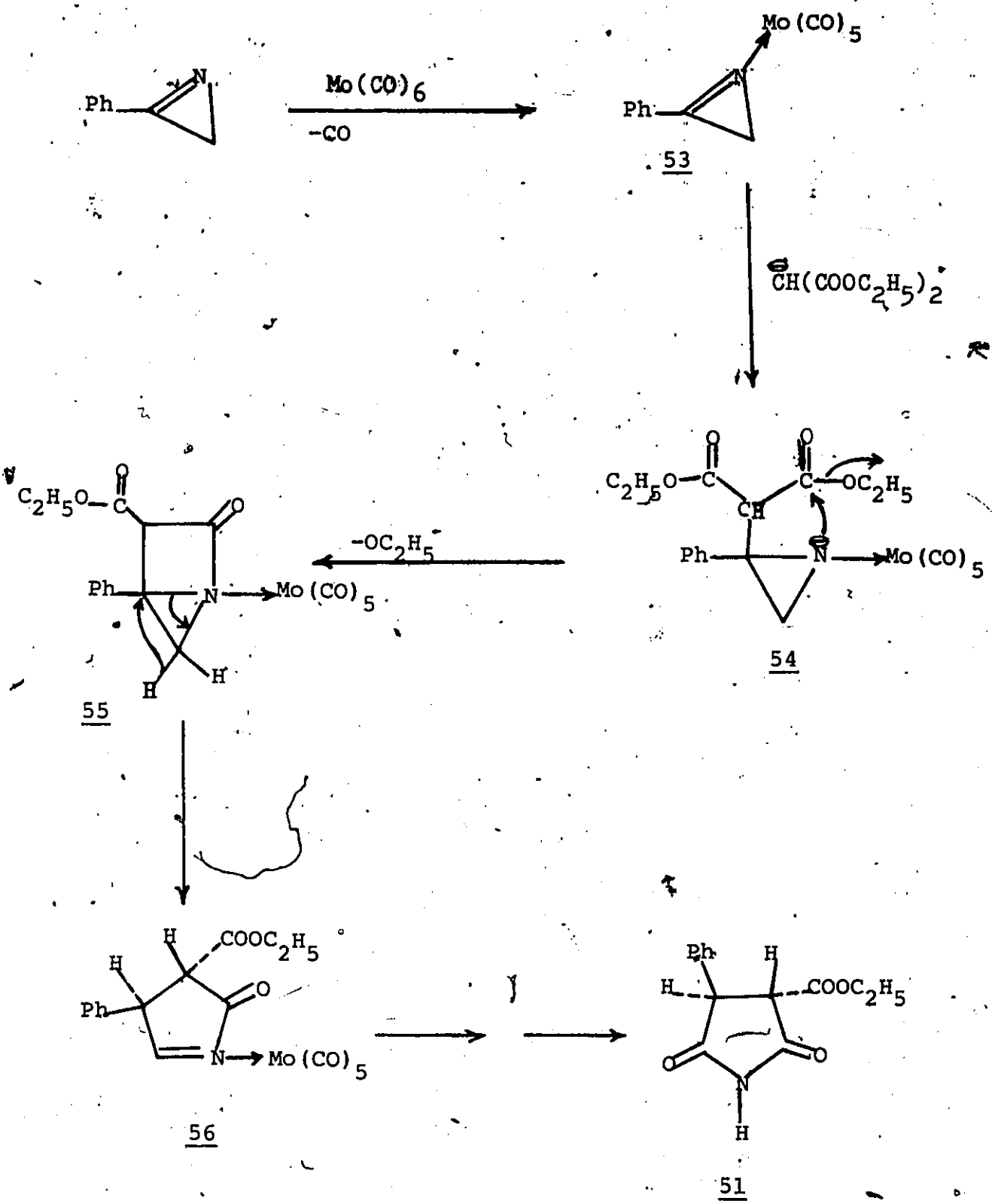
In 1967, Sato and co-workers[121] reported the isolation of 3-benzcyl-4-phenyl-4-pyrrolin-2-one (52) from the reaction of 2-phenyl-1-azirine with (50, R''=COPh), generated from ethyl benzoylacetate and methylsulfinyl carbanion in dimethylsulfoxide. Compound (52) was not isolated when the reaction was carried out in THF-ethanol, in the presence or absence of $Mo(CO)_6$ (i.e., the blank reaction). In addition imide 51 ($R=C_6H_5, R'=H, R''$=COPh) was not obtained from compound (52) on overnight exposure to $Mo(CO)_6$ in THF at room temperature.



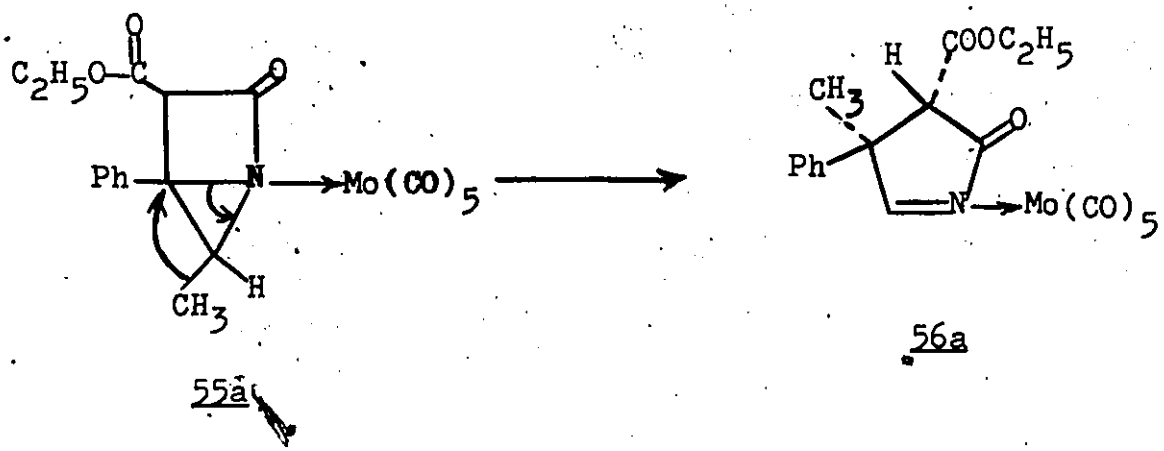
52

A possible mechanism for the conversion of azirines to imides with carbanions in the presence of $Mo(CO)_6$ is outlined in Scheme 11 [illustrated for 2-phenyl-1-azirine and diethyl malonate anion]. Initial complexation of the molybdenum with the lone pair of electrons on the nitrogen atom would give (53), which could react with the carbanion to give (54). The bicyclic β-lactam (55) would arise by intramolecular cyclization of (54), accompanied by elimination of ethoxide ion. The 5-membered heterocyclic ring complex (56) can be obtained from (55) by hydrogen migration and ring cleavage. Conversion of (56) to (51) may take place by oxidation during workup or alternatively via hydration [note that excess 99% ethanol is used in the generation of the carbanion (50)] of (56) followed by dehydrogenation. The yields of imides (51) were significantly enhanced when the reaction was effected in the presence of $Mo(CO)_6$, and this is probably due to the complexation pathway described above.

In the case of 3-methyl-2-phenyl-1-azirine (49), the CH_3 group in bicyclic β-lactam (55a) migrates in preference to the H atom to afford the 5- membered heterocyclic complex(56a).


Ph
Mo(CO)6
-CO
Mo(CO)5
53
CH(COOC2H5)2
C2H5O
OC2H5
CH
Ph
Mo(CO)5
54
-OC2H5
55
COOC2H5
56
51

Scheme 11

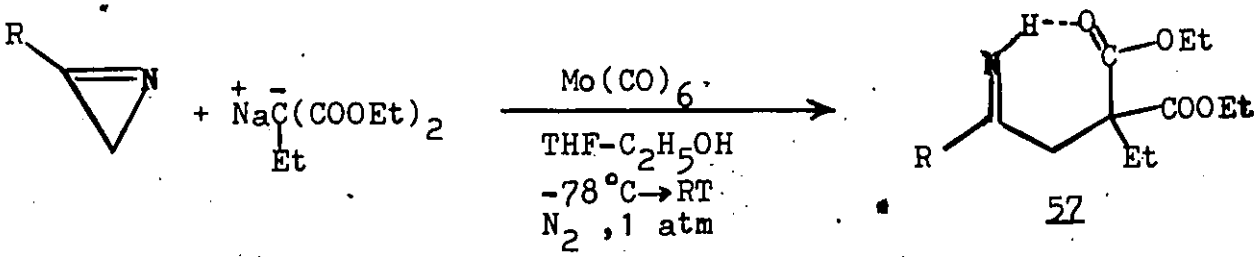


55a

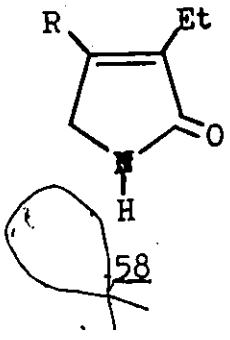
56a

When ethyl acetoacetate anion was used instead of diethyl malonate anion, 7 products were isolated, and none of them was characterized successfully. Similarly, when α-(p-toluene sulfonyl) acetate anion was used only starting ester and several unidentified products were isolated.

When molybdenum hexacarbonyl induced reaction of 2-phenyl-1-azirine was effected in the presence of ethyl diethyl malonate anion, different results were observed. An imino diester, a coupled product (57) and a 3-pyrrolinone (58) were obtained. Product yields, melting points, reaction times and analytical results are given in Table 9. Spectral data are listed in Table 10.



57



58

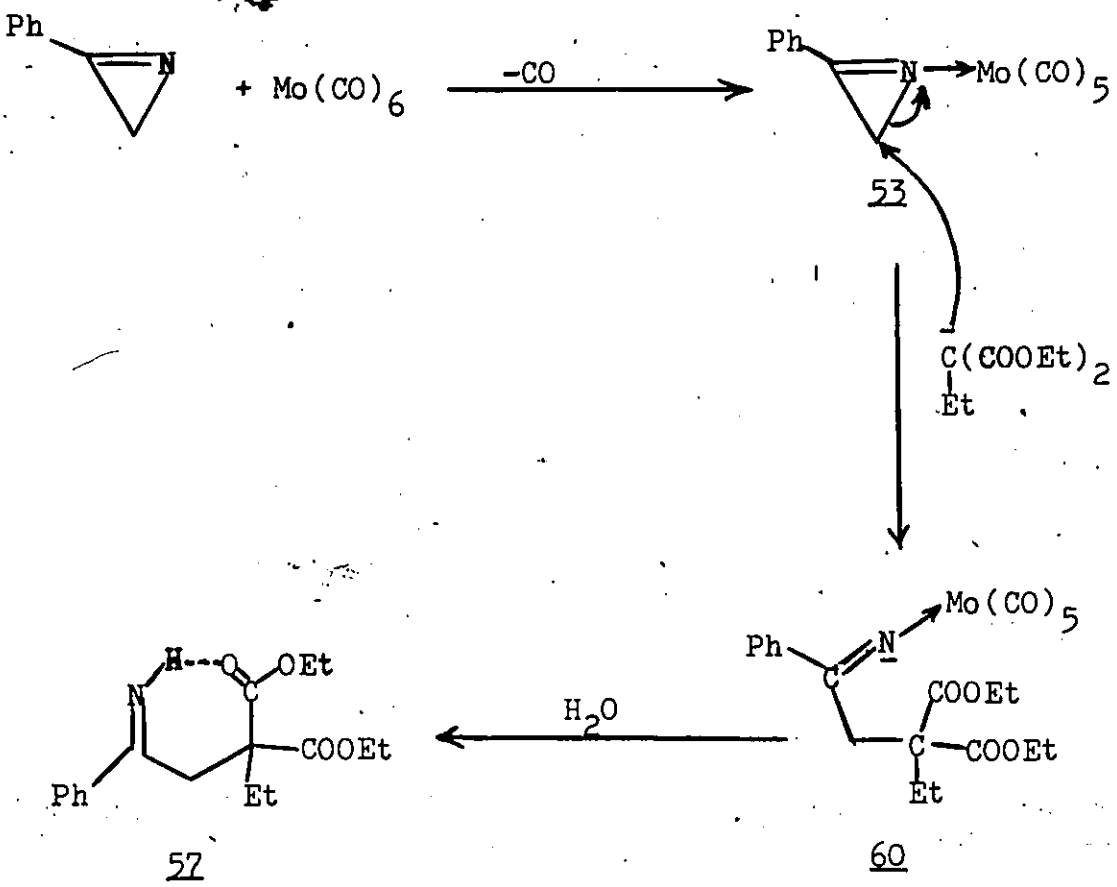
R = Ph, p-$CH_3C_6H_4$

The infrared spectrum ($CHCl_3$) of (57,R=C_6H_5) displayed an N-H stretching absorption at 3450 cm^{-1}. The two ester methylene groups and methyl groups showed two multiplets between δ 3.60-4.20 and δ 0.92-1.35 respectively in the proton magnetic resonance spectrum ($CDCl_3$). These two ester methylene groups showed two signals at δ60.34 and 60.92 in the carbon magnetic resonance spectrum. These spectral results indicate that these two ester groups are not equivalent. In the carbon magnetic resonance spectrum (in $CDCl_3$), there are 4 signals for quarternary sp^2 carbon atoms at δ 136.78, 139.87, 156.26 and 170.04 assigned to the aromatic quarternary carbon atom, the hydrogen bonded carbonyl carbon, the imine carbon, and the other ester carbonyl carbon respectively. The signal for the quarternary sp^3 carbon atom was hidden among the $CDCl_3$ peaks, but in CCl_4 it occurred at δ 61.76 in the carbon magnetic resonance spectrum. The mass spectrum showed the molecular ion peak. The same type of coupled product was also obtained with 2-(4'-methylphenyl)-1-azirine.

The 3-ethyl-4-(p-methylphenyl)-3-pyrrolin-2-one (58) obtained from the reaction of 2-(4'-methylphenyl)-1-azirine and ethyl diethyl malonate anion showed an N-H stretching band at 3465 cm^{-1} in the infrared spectrum ($CHCl_3$). The methylene proton of 58(R=p-$CH_3C_6H_4$) gave a singlet signal at δ 4.14 in the proton magnetic resonance

spectrum ($CDCl_3$) and the signal for this carbon atom occurred at δ 48.33 in the carbon magnetic resonance spectrum. The signal at δ 176.14 was assigned to the carbonyl carbon and the two unsaturated carbons of the pyrrolinone ring gave signals at δ 139.01 and 149.01. The mass spectrum showed the molecular ion peak.

A possible mechanism for the conversion of azirines to the imino diesters (57), is outlined in Scheme 12 [illustrated for 2-phenyl-1-azirine].



Scheme 12

Initial co-ordination of the nitrogen lone pair to the molybdenum as mentioned earlier would give 53 [Scheme 12]. When the attacking carbanion is very bulky it will attack at the less sterically hindered carbon atom on the ring. Therefore attack of the ethyl diethyl malonate anion could occur at the methylene group of the azirine ring, which could then undergo ring opening to give complex (60). During the workup (60) may be converted to (57).

Other metal complexes such as $Co_2(CO)_8$, [Rh(1,5-hexadiene)Cl]$_2$, $Pd(dpe)_2$, $Pd(PPh_3)_4$ and $RuCl_2(PPh_3)_3$ were also used instead of $Mo(CO)_6$ in the reaction of 2-phenyl-1-azirine with diethyl malonate carbanion in order to determine if any improvement could be made to the latter reaction. The different metal complexes used, reaction times and product yields are given in Table 11. In all cases the yields decreased when compared with $Mo(CO)_6$. When a

stoichiometric amount of $Co_2(CO)_8$ was used instead of $Mo(CO)_6$, 9% of imide 51 ($R=C_6H_5, R'=H, R''=COOEt$) was obtained, whereas with a catalytic amount of $Co_2(CO)_8$, 16% of imide 51 ($R=C_6H_5, R'=H, R''=COOEt$) was obtained. These results show that all these complexes are inhibiting the above reaction.

TABLE 7: Yields, Reaction Times, Melting Points and Analytical Data for Imides (51)[a]

Product 51,R,R',R"	Yield, %	Melting point, °C	Reaction time, hr	Anal.[calcd(found)] % C	% H	% N
Ph,H',COOEt	46[b]	100-102	2	63.15(62.86)	5.30(5.50)	5.66(5.57)
p-BrC_6H_4,H', COOEt	52	94-96	2	47.85(47.93)	3.68(3.82)	4.29(3.97)
p-$CH_3OC_6H_4$,H', COOEt	59	101-103	3	60.65(60.64)	5.42(5.45)	5.05(5.05)
p-$CH_3C_6H_4$,H', COOEt	68	oily	3	64.36(64.44)	5.75(5.79)	5.36(5.36)
o-$CH_3C_6H_4$,H', COOEt	41	89-91	3	64.36(64.51)	5.75(5.62)	5.36(5.13)
p-ClC_6H_4,H',COOEt	27	oily	3	55.32(55.63)	4.26(4.38)	4.96(4.46)
C_6H_5,CH_3,COOEt	74	179-182	overnight	64.36(64.48)	5.75(5.82)	5.36(5.37)
C_6H_5, H, COPh	29[c]	143-145	3	73.12(72.86)	4.66(4.86)	5.01(4.63)

TABLE 7: (Cont'd)

Product 51,R,R',R"	Yield,%	Melting point,°C	Reaction time,hr	Anal.[Calcd.(found)]		
				%C	%H	%N
p-BrC_6H_4,H,COPh	35	174-177	3	56.82(56.65)	3.34(3.49)	3.90(3.72)
C_6H_5,H',CN	23		4			

[a] Reaction using $Mo(CO)_6$: 49: 50 (1:1:1.5) in THF-ethanol under a N_2 atmosphere.

[b] Reaction in the absence of $Mo(CO)_6$ gave 21-23% yield of 51 (R=Ph,R'=H, R"=COOEt).

[c] Reaction in the absence of $Mo(CO)_6$ gave 10% yield of 51 (R=Ph, R'=H,R"=COPh).

TABLE 8: Pertinent Spectral Data for Imides (51)

51, R, R', R"	IR[a], cm^{-1} ν_{NH}	IR[a], cm^{-1} ν_{CO}	NMR[b], δ, ppm ^1H	NMR[b], δ, ppm ^{13}C	MS, m/e
C_6H_5, H', COOEt	3410	1735	1.30 (t, 3H, CH_3, J=7Hz), 4.20 (q, 2H, CH_2, J=7Hz), 3.80 (d, 1H, CH, J=6Hz), 4.42 (d, 1H, CH', J=6Hz), 7.30 (s (br), 5H, aromatic protons), 9.43 (s (br), 1H, NH)	176.25 (CO), 171.20 (CO), 166.79 (CO), 135.06 (quarternary aromatic carbon), 129.38, 128.47, 127.79 (aromatic carbons), 62.88 (CH_2), 56.21 (CH), 51.02 (CH), 14.08 (CH_3)	247 $[M]^+$ 202 $[M-OEt]^+$ 174 $[M-COOEt]^+$
p-BrC_6H_4, H', COOEt	3410	1735	1.30 (t, 3H, CH_3, J=7Hz), 3.80 (d, 1H, CH, J=6Hz), 4.43 (d, 1H, CH', J=6Hz), 4.23 (q, 2H, CH_2, J=7Hz), 7.10 (d, 2H, aromatic protons, J=8Hz), 7.43 (d, 2H, aromatic protons, J=8Hz), 9.30 (s (br), 1H, NH)		327, 325, $[M]^+$, 254, 252 $[M-COOEt]^+$
p-$CH_3C_6H_4$, H', COOEt	3410	1730	1.30 (t, 3H, CH_3, J=7Hz), 2.33 (s, 3H, CH_3), 3.81 (d, 1H, CH, J=6Hz) 4.40 (d, 1H, CH', J=6Hz), 4.20 (q, 2H, CH_2, J=7Hz), 7.11 (s, 4H, aromatic protons), 9.00 (s (br), 1H, NH)	176.66 (CO), 171.44 (CO), 166.85 (CO), 138.29, 132.06 (quarternary aromatic carbons), 130.00, 129.27 (aromatic carbons), 62.81 (CH_2), 56.27 (CH), 50.72 (CH), 21.11 (CH_3), 14.07 (CH_3)	261 $[M]^+$ 188 $[M-COOEt]^+$
p-$CH_3OC_6H_4$, H', COOEt	3410	1730	1.30 (t, 3H, CH_3, J=7Hz), 3.76 (s, 3H, OCH_3), 3.83 (d, 1H, CH, J=6Hz), 4.41 (d, 1H, CH', J=6Hz), 4.23 (q, 2H, CH_2, J=7Hz), 6.86 (d, 2H, aromatic protons, J=8Hz), 7.20 (d, 2H, aromatic protons, J=8Hz), 9.50 (s (br), 1H, NH)		277 $[M]^+$ 204 $[M-COOEt]^+$

TABLE 8: (Contn'd)

51,R,R',R"	IR[a], cm^{-1}		NMR[b], δ, ppm		MS, m/e
	ν_{NH}	ν_{CO}	^1H	^{13}C	
o-$CH_3C_6H_4$,H',COOEt	3420	1733	1.30(t,3H,CH_3,J=7Hz),2.33(s,3H CH_3),3.73(d,1H,CH,J=6Hz),4.20 (q,2H,CH_2,J=7Hz),4.64(d,1H, CH',J=6Hz),7.20(m,4H,aromatic protons),9.20(s(br),1H,NH)		261 $[M]^+$ 188 $[M-COOEt]^+$
p-ClC_6H_4,H',COOEt	3415	1735	1.30(t,3H,CH_3,J=7Hz),3.83(d, 1H,CH,J=6Hz),4.23(q,2H,CH_2, J=7Hz),4.46(d,1H,CH',J=6Hz), 7.13(d,2H,aromatic protons, J=8Hz),7.35(d,2H,aromatic protons,J=8Hz),8.50(s(br), 1H,NH)		281,283 $[M]^+$, 208,210 $[M-COOEt]^+$
C_6H_5,CH_3,COOEt	3300[c]	1725[c]	[d] 1.16(t,3H,CH_3,J=7Hz),1.48(s, 3H,CH_3),4.25(q,2H,CH_2,J=7Hz), 4.15(s,1H,CH),6.00(s(br),1H, NH),7.33-7.80(m,5H,aromatic protons)	[e] 14.15(CH_3),25.01(CH_3), 51.00(CH),62.38(CH_2), 88.61 (-C≡),124.00, 129.42,132.39,131.09 (aromatic carbons), 164.14(CO),169.07(CO), 164.93 (CO)	261[f] $[M]^+$ 246 $[M-CH_3]^+$ 188 $[M-COOEt]^+$
p-BrC_6H_4,H,COPh	3400	1687 (COPh) 1730	4.66(d,1H,CH,J=5Hz), 4.83(d,1H,CH,J=5Hz), 6.90-8.10(m,9H,aromatic protons),8.80(s(br),1H,NH)		357,359 $[M]^+$, 252,254 $[M-COPh]^+$

TABLE 8 : (Contn'd)

51, R, R', R''	IR[a], cm^{-1}		NMR[b], δ, ppm		MS, m/e
	ν_{NH}	ν_{CO}	^1H	^{13}C	
C_6H_5, H, COPh	3400	1688 (COPh) 1733	4.70(d,1H,CH,J=5.5Hz), 4.86(d,1H,CH,J=5.5Hz), 7.10-8.15(m,10H,aromatic protons), 9.20(s (br),1H,NH)	50.39(CH),58.87(CH),127.89, 128.32,128.52,128.79,129.37, 129.48,129.86,134.42(aromatic carbons),172.39 (CO),177.28(CO),191.80(CO)	279[M]$^+$ 174[M-COPh]$^+$
C_6H_5, H', CN	3400	[f]1738	3.89(d,1H,CH,J=7Hz),4.30 (d,1H,CH',J=7Hz),7.15-7.70 (m,5H,aromatic protons), 9.15(s (br),1H,NH)		200[M]$^+$ 129[M-CONHCO]$^+$

[a] $CHCl_3$ solution. [b] $CDCl_3$ with Me_4Si as internal standard. ^{13}C assignments made with the aid of fully and partially decoupled spectra. [c] In nujol. [d] DMSO with Me_4Si as internal standard. [e] MeOH with Me_4Si as internal standard. [f] IR($CDCl_3$) $\nu_{C\equiv N}$ 2228 cm^{-1}.

TABLE 9: The $Mo(CO)_6$ induced reaction of azirines in the presence of ethyl diethyl malonate anion

Azirine	Reaction time, hr	Products	Yield, %	Anal. [calcd (found)]			Melting points, °C
				% C	%H	%N	
2-phenyl-1-azirine	overnight	57 (R=C_6H_5)	13				oily
		58 (R=C_6H_5)	31	76.98(77.08)	7.00(6.83)	7.48(7.30)	147-149
2-(4'-methyl-phenyl)-1-azirine	overnight	57 (R=p-$CH_3C_6H_4$)	15				oily
		58 (R=p-$CH_3C_6H_4$)	17				183-185

TABLE 10 : Pertinent spectral data for the products of $Mo(CO)_6$ induced reaction of azirines in the presence of ethyl diethyl malonate anion

Product	IR[a], cm^{-1}		NMR[b], δ, ppm		MS, m/e
	ν_{NH}	ν_{CO}	^1H	^{13}C	
57 ($R=C_6H_5$)	3450	1710 (br)	0.83 (t, 3H, CH_3, J=7Hz), 0.97-1.35 (m, 6H, CH_3 protons), 2.55 (q, 2H, CH_2, J=2Hz), 3.60-4.20 (m, 6H, CH_2 protons), 4.56 (s (br), 1H, NH), 7.23 (s (br), 5H, aromatic protons)	13.48 (CH_3), 14.55 (CH_3), 23.68 (CH_2), 42.56 (CH_2), 60.34 (CH_2O), 60.92 (CH_2O), 127.60, 127.92, 128.23, 136.39 (aromatic carbons), 139.87 (CO), 156.26 (CN), 170.04 (CO)	305 $[M]^+$ 259 $[M-C_2H_5OH]^+$
				[c] 13.32 (CH_3), 14.50 (CH_3), 23.35 (CH_2), 42.24 (CH_2), 59.34 (CH_2O), 60.11 (CH_2O), 61.76 (>C), 126.97, 127.72, 128.62, 135.99 (aromatic carbons), 139.11 (CO), 155.07 (CN), 168.60 (CO)	
57 ($R=p\text{-}CH_3C_6H_4$)	3440	1710 (br)	0.70-1.40 (m, 9H, CH_3 protons), 2.20-2.70 (m, 5H, CH_3+CH_2), 3.60-4.20 (m, 6H, CH_2 protons), 4.57 (s (br), 1H, NH), 7.30 (s (br) 4H, aromatic protons)		319 $[M]^+$ 273 $[M-C_2H_5OH]^+$
58 ($R=C_6H_5$)	3460	1688	1.20 (t, 3H, CH_3, J=7Hz), 2.50 (q, 2H, CH_2, J=7Hz), 4.20 (s, 2H, CH_2), 7.43 (s, 5H, aromatic protons) 8.26 (s (br), 1H, NH)		187 $[M]^+$ 186 $[M-H]^+$ 158 $[M-C_2H_5]^+$
58 ($R=p\text{-}CH_3C_6H_4$)	3465	1690	1.19 (t, 3H, CH_3, J=7Hz), 2.40 (m, 5H, CH_3+CH_2), 4.14 (s, 2H, CH_2), 7.24 (s, 4H, aromatic protons) 8.00 (s (br), 1H, NH)	13.04 (CH_3), 17.67 (CH_2), 21.30 (CH_3 attached to aromatic carbon), 48.33 (CH_2), 127.14, 129.57, 130.94, 134.32 (aromatic carbons), 139.01, 149.01 (>C=), 176.14 (CO)	201 $[M]^+$ 200 $[M-H]^+$ 186 $[M-CH_3]^+$ 172 $[M-C_2H_5]^+$

[a] $CHCl_3$ solution. [b] $CDCl_3$ with Me_4Si as internal standard. ^{13}C assignments made with the aid of fully and partially decoupled spectra. [c] CCl_4 with Me_3Si as internal standard.

TABLE 11: Yields and reaction times for metal induced reactions of azirine 47 ($R=C_6H_5$, $R'=H$) with diethyl malonate anion

Metal Complex[a]	Reaction time, hr	Yield, %[b]
$Pd(PPh_3)_4$	3	19
$Pd(dpe)_2$	2	14
$[Rh(1,5\text{-hexadiene})Cl]_2$	2	5
$RuCl_2(PPh_3)_3$	2	9
$Co_2(CO)_8$	2.5	16

[a] catalytic amount of the metal complex was used. [i.e., 47: metal complex (10:1)]

[b] 51 ($R=C_6H_5$, $R'=H$)

Since it is well known that imides can be ring opened under a variety of conditions, the above described process, can be used as sources of a variety of useful acyclic compounds. The acid hydrolysis (2-6N HCl) of 51 ($R=C_6H_5$, $R'=H$, $R''=COOEt$) and 51 ($R=C_6H_5$, $R'=H$, $R''=COPh$) gave $C_6H_5CH(COOH)CH_2COOH$ and $C_6H_5CH(COOH)CH_2COPh$ respectively. Therefore hydrolysis and decarboxylation occurred instead of giving the expected $C_6H_5CH(COOH)CH(COOH)COOEt$ and $C_6H_5CH(COOH)CH$—$(COOH)COPh$.

CHAPTER IV

4. Experimental

General Data

Melting point determinations were made by using a Fisher-Johns apparatus and are uncorrected. Infrared spectra were obtained by use of a Unicam SP-1100 spectrometer equipped with a calibration standard. Mass spectra were determined on an AEI MS902 or VG7070-E spectrometer. Varian T60 and HA100 spectrometers were used for proton magnetic resonance determinations, and carbon magnetic resonance spectra were recorded in the fully and partially decoupled modes with a Varian FT-80 spectrometer. Elemental analyses were carried out by Canadian Microanalytical Service, Vancouver, Canada. X-ray analyses were carried out by Dr. F.R. Ahmed of the National Research Council, Ottawa, and by Dr. F.W.B. Einstein and Dr. A.C. Willis, Simon Fraser University.

Silica gel was used for column and for thin layer chromatography. Solvents were purified and dried by standard methods. The reactions were carried out under carbon monoxide or nitrogen atmosphere unless otherwise stated.

Tetrakis(triphenylphosphine)palladium(0) was either purchased from Aldrich Chemical Co. or synthesized following the procedure of Coulson [108]. Tetrakis(triphenylphosphine)platinum(0), dicobalt octacarbonyl, dichlorotris(triphenylphosphine)ruthenium(II), and tetrakis(triphenylphosphine)nickel(0) were obtained from Strem Chemicals, Inc., Palladium acetate was obtained from Alfa Chemicals. Dr. T. Izumi kindly donated bis [bis (1,2 - diphenylphosphine) ethane] palladium (0) and 3-methyl-3-allyl-2-phenyl-1-azirine. 3-(Dimethoxymethyl)-2-phenyl-1-azirine was a gift from Prof. H. Alper. Molybdenum hexacarbonyl was purchased from Pressure Chemical Co., Chloro (1,5-hexadiene) rhodium (I) dimer was a gift from K. Januszkiewicz.

All phase transfer catalysts, and saturated and unsaturated esters were commercially available and were used as received.

4.1 Palladium (0) catalyzed reactions under homogeneous conditions

4.1.1 Preparation of azirine compounds

The azirines were prepared following literature procedures [100,101,102,103]. The styrenes were commercially available and were used as received.

2-Phenyl-1-azirine (1)[100]

Bromine (80 g, 0.50 mol) in 100 ml of CCl_4 was added slowly to a solution of styrene (52.1 g, 0.50 mol) in 400 ml of CCl_4, at 15-20°C. After the addition was complete the CCl_4 was removed on a rotary evaporator and the remaining residue of crystalline 1,2-dibromostyrene was dissolved in 750 ml of dimethyl sulfoxide. To this solution was added 49 g (0.75 mol) of NaN_3 at 15-20°C (N_2 atmosphere). The mixture was allowed to stir for 24 hr at 24-26°C, and cooled to 12°C and was treated with 20 g (0.5 mol) of NaOH in 20 ml of H_2O. The solution was stirred for 24 hrs at 24-26°C, and was poured into 2 ℓ of a 2% aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined extracts were washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated to yield crude 1-azidostyrene as a red oil. ^1H NMR (CCl_4), δ 4.82 (d,H, J = 2.1 Hz), 5.27 (d, 1H, J = 2.1 Hz) and 7.1 - 7.6 (m, 5H, aromatic protons).

The oil was diluted with 200 ml of hexane and passed through a column of neutral alumina (200g) using an additional 800 ml of the same solvent as eluant. The eluate was

evaporated and the residual pale yellow oil was dissolved in toluene (1.2 ℓ) and was refluxed until the evolution of nitrogen ceased (1.5-2 hr). Removal of the solvent and the distillation of the crude product gave 30 g (51%) of (1) as a pale yellow liquid. bp. 63-64.5°C (3mm); ^{1}H NMR(CCl_4), δ 1.56 (s, 2H, CH_2), 7.4-7.9 (m, 5H, aromatic protons); IR (neat) 1740 cm^{-1} (C=N).

2-(4'-Methylphenyl)-1-azirine (2)[100]

Azirine (2) was prepared on a 0.083 mole scale as described for (1) using 4-methylstyrene. The mixture was stirred for 60 hrs after the addition of 3.33 g (0.083 mol) of NaOH pellets. The usual workup followed by distillation gave 6.27 g (58%) of (2) as a pale yellow liquid. bp. 75-77°C (5 mm); ^{1}H NMR ($CDCl_3$), δ 1.7 (s, 2H, CH_2), 2.4 (s, 3H, CH_3), 7.2-7.8 (Sym. A_2B_2 pattern, 4H, aromatic protons).

2-(4'-Bromophenyl)-1-azirine (3)[100]

Azirine (3) was prepared on a 0.05 mole scale as described for (2) starting with 4-bromostyrene. The usual workup was followed by sublimation under reduced pressure to give

3.9 g (40%) of (3) as pale yellow crystals. mp. 73-75°C; ^{1}H NMR ($CDCl_3$), δ 1.8 (s, 2H, CH_2), 7.1 (s, 4H, aromatic protons).

2-(4'-Chlorophenyl)-1-azirine (4)[100]

Azirine (4) was prepared as described for (2) on a 0.083 mol scale starting with 4-chlorostyrene. Distillation gave 5.19 g (55%) of (4) as a light yellow solid.. bp. 87-89°C (3 mm); ^{1}H NMR ($CDCl_3$), δ 1.66 (s, 2H, CH_2), 7.36-7.83 (Sym. A_2B_2 pattern, 4H, aromatic protons).

3-Methyl-2-phenyl-1-azirine (5)[101]

To a slurry of 7.5 g (0.125 mol) of NaN_3 in 50 ml of CH_3CN, cooled in a methanol-ice cold bath, was added ICl [9.15 g, 0.057 mol] in a small amount of CH_3CN over a period of 10-20 min.. After stirring for a further 5-10 min, 5.9 g (0.05 mol) of trans-β-methylstyrene was added and the mixture was allowed to warmup to room temperature and stirred for 21 hrs. The red brown slurry was poured into 125 ml of water and was extracted with ether (125 ml × 3). The combined ether extracts were washed with 75 ml of 5% sodium thiosulfate leaving a colourless ethereal solution. This solution was washed with 450 ml of water in 4 portions and dried over

$MgSO_4$. Removal of ether in vacuo at room temperature gave bright red 1-azido-2-iodo-1-phenyl propane. ^1H NMR ($CDCl_3$), δ 1.76 (d, 3H, CH_3, J = 6.5Hz), 4.20 (m, 1H, CHI), 4.63 (d, 1H, CHN_3, J = 6 Hz), 7-7.3 (s (br), 5H, aromatic protons).

The iodo azide [9.6 g, 0.060 mol] was dissolved in 125 ml of dry ether, cooled in an ice bath, and 6.75 g (20% excess) of KOBu-t was added. The mixture was stirred for 22 hrs at room temperature and then washed twice with 250 ml of H_2O. The ethereal solution was dried over $MgSO_4$, filtered and ether was removed in vacuo. The resultant crude unsaturated azide, cis-1-azido-1-phenyl-1-propene, was dissolved in 24 ml of hexane and passed through 40 g of neutral alumina, using 96 ml of hexane as eluant. The eluate was evaporated to yield a yellow oil. This was dissolved in 75 ml of toluene and was refluxed for 2 hrs. Removal of the solvent and distillation of the crude product gave 3.15 g (40%) of (5) as a pale yellow liquid. bp. 55-60°C (0.5 - 1mm); ^1H NMR (CCl_4), δ 7.2-8.0 (m, 5H, aromatic protons), 2.27 (q, 1H, CH, J = 5Hz), 1.35 (d, 3H, CH_3, J = 5 Hz).

3-Formyl-2-phenyl-1-azirine (7)[102, 103]

Cinnamaldehyde dimethyl acetal was prepared[102] by stirring a mixture of trans-cinnamaldehyde (26.4 g, 0.020 mol), trimethyl orthoformate (40 g, 0.42 mol) and p-toluenesulfonic acid monohydrate (1 g, 0.005 mol) in CH_3OH (180ml) at room temperature for 24 hrs. Removal of the alcohol followed by distillation of the residue gave 31.13 g (87%) cinnamaldehyde dimethyl acetal. bp. 75-77°C (0.15 mm).

To 29 g (0.45 mol) of NaN_3 in 175 ml of CH_3CN was added 32 g (0.2 mol) of ICl dropwise for 15-20 min. at 0°C. The reaction mixture was allowed to stir for an additional 15 min. and 31 g (0.17 mol) of cinnamaldehyde dimethyl acetal was then added over a period of 15-20 min. at 0-5°C. The solution was stirred for 12 hr at room temperature, poured into 200 ml of H_2O, and extracted with ether (200 ml × 3). The combined ether extracts were washed successively with 5% aqueous $Na_2S_2O_3$ (275 ml) and H_2O (375 ml), dried over $MgSO_4$, filtered and removal of the solvent using a rotary evaporator gave 1-azido -3,3-dimethoxy-2-iodo-1-phenyl propane as a dark oil. This oil was dissolved in 575 ml of dry ether and 24 g (0.21 mol) of KOBu-t was added (10-15 min), at -5° - 0°C. After stirring at 0°C for additional 5 hr,

the mixture was washed with water, dried over $MgSO_4$, filtered, and the solvent was removed using a rotary evaporator. The resultant crude 1-azido-3,3-dimethoxy-1-phenyl-1-propene was dissolved in 385 ml of $CHCl_3$ and refluxed for 12 hr. Removal of the solvent and distillation gave 15.13 g (0.080 mol) of 3-(dimethoxymethyl)-2-phenyl -1-azirine as a light yellow liquid. bp. 80-83°C (0.15 -0.2 mm). This material was dissolved in dioxane (160 ml) and 2% acetic acid (235 ml), and was heated at 85°C for 45 min. The reaction mixture was rapidly cooled to 0°C and extracted with ether. The combined ether extracts were washed successively with aqueous 5% $NaHCO_3$ (160 ml) and saturated aqueous NaCl (160 ml). The ether layer was dried over $MgSO_4$, filtered and removal of the solvent gave a brown oil which was allowed to stand in the refrigerator to induce crystallization. Since no crystals were formed, hexane was added, the solution was filtered and on removal of hexane 2.85 g (25%) of (7) was obtained as off white crystals. mp. 46-48°C; ^1H NMR ($CDCl_3$), δ 2.86 (d, 1H, CH, J = 6 Hz), 7.46 - 8.00 (m, 5H, aromatic protons), 8.90 (d, 1H, CHO, J = 6Hz)

2-(2',4'-Dimethylphenyl)-1-azirine (6)

Azirine (6) was prepared as described for (2) on a 0.1 mole scale starting from 2,4-dimethylstyrene. Distillation gave 4.79 g (33%) of (6) as a colourless liquid. bp. 88-91°C (5 mm); ^{1}H NMR ($CDCl_3$), δ 1.60 (s, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 6.9-7.8 (m, 3H, aromatic protons).

2-(2'-Methylphenyl)-1-azirine (8)

Azirine (8) was prepared as described for (2) on a 0.083 mole scale starting from 2-methylstyrene. Distillation gave 5.44 g (50%) of (8) as a colourless liquid. bp. 40-45°C (0.025 - .075 mm); ^{1}H NMR ($CDCl_3$), δ 1.66 (s, 2H, CH_2), 2.70 (s, 3H, CH_3); 7.13 - 7.86 (m, 4H, aromatic protons).

2-(4'-methoxyphenyl)-1-azirine (9)

Azirine (9) was prepared as described for (1) on a 0.063 mole scale starting from 4-methoxystyrene. Distillation gave 5.99 g (53%) of (9) as a pale yellow liquid, which readily solidified. bp. 75-77°C (0.5 mm); ^{1}H NMR ($CDCl_3$), δ 1.70 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 6.90 - 7.86 (sym. A_2B_2 pattern, 4H, aromatic protons).

4.1.2. Preparation of N-n-butyl-2-phenyl aziridine (10)[104,105].

To 29.3g(0.40 mol) of boiling n-butylamine, 24.5g (0.20 mol) of styrene oxide was added over a period of 1.5-2hrs. The solution was refluxed for a further 2hrs. Distillation afforded the crude product which on recrystallization from hexane gave 17.94g (46%) of β-butylamino-α-phenethyl alcohol as white crystals. mp. 58-59°C. The latter (13.5g, 0.07 mol) was ice cooled and was treated dropwise with 4.4ml (0.07 mol) of chlorosulfonic acid over a period of 45 min. After the addition, the solid mass was heated in an oil bath at slightly less than 150°C for 1.5 hr at reduced pressure (15-20 mm). The resulting ester was dissolved in H_2O (35 ml) and was treated with 30g of KOH in 30ml of H_2O. The mixture was heated on a steam bath for 30 min., cooled to room temperature and then extracted with ether (100mlx4). The combined ether layers were washed with water, dried over $MgSO_4$. Removal of the solvent and distillation of the residue gave 3.1g (25%) of (10) as a pale yellow liquid. bp. 35°C (0.2mm); ^1H NMR ($CDCl_3$), δ 7.13 (s,5H, aromatic protons), 0.8-2.5 (m,12H, $(CH_2)_3CH_3$ and three ring protons); MS(m/e) 175, 160, 132, 118, 91, 77.

4.1.3. Preparation of 4,5-diphenyl-1,3-diazabicyclo [3.1.0] hex-3-ene (11) [106]

2-Phenyl-1-azirine (0.5g, 4.27 mmol) in benzene (400ml) was irradiated for 5hrs using a Rayonet Photochemical Reactor (2537 Å). Removal of the solvent on a rotary evaporator gave a brown oil, which was treated with cold hexane and the hexane soluble portion was separated. Removal of the solvent using a rotary evaporator gave 0.207g (41%) of (11) as a yellow oil. ^{1}H NMR ($CDCl_3$), δ 1.68(s,1H), 3.00(s,1H), 4.90(d,1H,J=16Hz),5.30 (d,1H,J= 16Hz), 7.1-7.7 (m,10H,aromatic protons).

4.1.4. Preparation of palladium complexes

Bis(dibenzylideneacetone)palladium(0) [107] -Pd(dba)$_2$

To a solution of benzaldehyde (21.2g,0.20 mole) in EtOH(40ml) was added NaOH(5.12g,0.128 mole) in H_2O(40ml). To this mixture acetone (5.8g,0.10mole) was added dropwise for 30 min. A yellow precipitate was obtained. Recrystallization from EtOH gave 12g(51%) of dibenzylideneacetone.

A mixture of $PdCl_2$ (1.05g,5.90 mmol) and NaCl(0.69g,118 mmol) in MeOH (50ml) was stirred at room temperature for 24 hr. The mixture was filtered and was treated with sodium acetate (3.9g,47.5 mmol) and excess dibenzylideneacetone (4.6g,19.6 mmol) at 45° C. The

reaction mixture was stirred for 4hr during which a brown precipitate was formed and then allowed to cool to room temperature to complete the precipitation. The precipitate was filtered, washed successively with water and acetone and dried in vacuo to give 3.498g (100%) of $Pd(dba)_2$ as a purplish brown powder. mp. 145-153°C (decomp.).

Bis(di-o-methoxybenzylideneacetone)palladium(0) —$Pd(o\text{-}MeOdba)_2$

This black complex was prepared as described for $Pd(dba)_2$ using o-anisaldehyde instead of benzaldehyde. Yield: 3.82g(93%).mp.122-125°C(decomp.).

Bis(di-o-methylbenzylideneacetone)palladium(0)—$Pd(o\text{-}Medba)_2$

This reddish brown complex was prepared as described for $Pd(dba)_2$ using o-tolualdehyde instead of benzaldehyde. Yield: 1.482g(94%). mp. 125-133°C(decomp.).

Tetrakis(triphenylphosphine)palladium(0)[108] — $Pd(PPh_3)_4$

A mixture of $PdCl_2$ (o.886g,5.0 mmol) and PPh_3 (6.552g,25.0 mmol) in dimethyl sulfoxide (60ml) was heated under a N_2 atmosphere at 160°C until the solution became clear. The oil bath was removed and $NH_2NH_2.H_2O$ (1.01g, 0.020 mol) was added rapidly from a syringe. A vigorous reaction took place with evolution of nitrogen. The dark

solution was allowed to cool to room temperature. When it was cooling yellow flakes began to form. This solid was filtered under N_2 and was washed successively with ethanol and then with ether. The product was dried by passing a slow stream of N_2 through the funnel to give 5.48g(95%) of $Pd(PPh_3)_4$ as bright yellow flakes. mp. 99-106°C(decomp.).

(Dimethyl acetylenedicarboxylate)bis(triphenylphosphine)-palladium (0) [109]

A solution of $Pd(PPh_3)_4$(1.059g,0.918 mmol) in CH_2Cl_2 (10ml) [N_2 atmosphere] was cooled in an ice-bath and was treated dropwise with dimethyl acetylenedicarboxylate(0.846g, 6.0 mmol) in CH_2Cl_2 (10 ml). After the addition, the ice-bath was removed and the solution was stirred at room temperature for 1 hr, MeOH (15ml) was added, and removal of the solvent gave the crude product. Recrystallization from methanol afforded 0.298g (42%) of (dimethyl acetylenedicarboxylate)bis(triphenylphosphine)-Pd(0) as off white crystals. mp. 128-130°C (decomp.).

Di-μ-chloro bis (π^3-propenyl) dipalladium(II) [110]

$PdCl_2$ (1.812g, 0.010 mol) was heated at 100°C in 105 ml of 50% (v/v) aqueous acetic acid for 15 min. The insoluble material was filtered off and allyl chloride

(6.0ml) was added to the filtrate, and the mixture was heated at 60° C for 1hr. The pale yellow solution was treated with CH_2Cl_2 (60ml x 3) and the combined CH_2Cl_2 extracts were washed with water (60mlx6). After drying over $MgSO_4$, and removing of the solvent, a yellow solid was obtained. Recrystallization from MeOH gave 1.08 g (58%) of the π-allyl palladium complex as yellow crystals. ^1H NMR ($CDCl_3$), δ 5.16-5.85 (m,2H,2CH),4.11(d,4H,J=6.5Hz), 3.20 (d,4H,J=12Hz).

4.1.5. General procedure for the $Pd(dba)_2$ catalyzed carbonylation of azirines

To 50ml of dry C_6H_6, $Pd(dba)_2$ (0.12-0.47 mmol) and azirine (1.2-4.7 mmol) was added at 40°C under a CO atmosphere. The reaction was followed by thin layer chromatography and when complete, the reaction mixture was concentrated by using a rotary evaporator. The resulting crude residue was worked up in the following manner for various azirines to obtain pure carbamate ester (16). Product yields and reaction times are listed in Table 1. Spectral data are given in Table 2.

The vinyl isocyanate (15) can be isolated by distillation of the filtrate obtained by the treatment of the crude residue with (20-80ml) hexane[93].

2-Phenyl-1-azirine (1)

The reaction was carried out using (0.545g, 4.7 mmol) of (1). The resulting crude residue was treated with 80 ml of hexane and filtered. To the filtrate, 12ml of absolute MeOH was added and the mixture was stirred for 2.5 hrs at room temperature. After removal of the solvent by rotary evaporation, 0.634g (77%) of the carbamate ester was formed as an orange coloured oil.

2-(4-methylphenyl)-1-azirine (2)

The reaction was carried out using 0.247g (1.90 mmol) of (2). The resulting crude residue was treated with 20ml of hexane, and filtered. To the filtrate 10 ml of absolute CH_3OH was added and the solution was stirred for 2.5 hrs at room temperature. After removal of hexane-methanol by rotary evaporation 0.298g (83%) of carbamate ester was isolated as a thick orange oil.

2-(4-Bromophenyl)-1-azirine (3)

The reaction was carried out using 0.236g (1.20 mmol) of (3). The resulting crude residue was treated with 50 ml of hexane and filtered. To the filtrate 10 ml of absolute MeOH was added and the mixture was stirred at room temperature for 2.5 hrs. Removal of the

solvent by rotary evaporation gave 0.297g(97%) of the carbamate ester as a yellow oil.

2-(4'-chlorophenyl)-1-azirine (4)

The reaction was carried out using 0.255g (1.7 mmol) of (4). The resulting crude residue was treated with 30ml of hexane and filtered. To the filtrate 20ml of absolute MeOH was added and the solution was stirred for 2.5 hrs at room temperature. Removal of the solvent by rotary evaporation gave 0.351g (99%) of carbamate ester as a thick orange yellow oil.

3-Methyl-2-phenyl-1-azirine (5)

The reaction was carried out using 0.20g (1.50 mmol) of (5). The resulting crude residue was treated with 20ml of hexane and filtered. To the filtrate 20ml of absolute CH_3OH was added and the reaction mixture was stirred for 2.5 hrs at room temprature. Removal of the solvent by rotary evaporation gave 0.288g (98%) of carbamate ester as a thick yellow oil.

Isolation of (E)-$C_6H_5C(NCO)CHCH_3$

The reaction was carried out using 0.078g (0.60 mmol) of (5). The resulting crude residue was treated with 10 ml of hexane and filtered. Removal of the

solvent by rotary evaporation gave a quantitative yield of isocyanate as a pale yellow oil. IR($CHCl_3$) ν_{NCO}2260 cm^{-1}; ^1H NMR($CDCl_3$), δ 1.67 (d,3H,CH_3,J=8Hz),5.63 (q,1H,CH), 7.33 (s,5H, aromatic protons).

A few reactions were carried out on 2-phenyl-1-azirine with variation on the general procedure.

$Pd(dba)_2$ with substituents on the 'dba' ligand

$Pd(o\text{-}MeOdba)_2$

The reaction was effected in a manner identical with that described for the $Pd(dba)_2$ reaction, except for the change in the catalyst. The filtrate was treated with 25ml of absolute MeOH and stirred for 2.5 hrs at room temperature. Removal of the solvent by rotary evaporation gave 0.606g (80%) of carbamate ester (16,R=C_6H_5,R'=H) as an orange yellow oil.

$Pd(o\text{-}Medba)_2$

The reaction was effected in a manner identical with that described for the $Pd(dba)_2$ reaction, except for the change in the catalyst. The resulting crude residue was treated with 60ml of hexane and filtered. To the filtrate 25ml of absolute MeOH was added and the solution was stirred at room temperature for 2.5 hr. Removal of the solvent by rotary evaporation gave 0.588g (77%) of carbamate ester (16,R=C_6H_5,R'=H) as an orange yellow oil.

Reaction with $Pd(dba)_2$ in the presence of allyl acetate

To 40ml of dry C_6H_6, (0.43mmol) $Pd(dba)_2$ and allyl acetate (0.43 mmol) were added and the mixture was stirred under a N_2 atmosphere at room temperature for 2hrs. To this mixture azirine (1) (4.3 mmol) was added and the mixture was stirred at 40° C for 3 days under a carbon monoxide atmosphere. Starting material was recovered quantitatively.

4.1.6. General procedure for the $Pd(PPh_3)_4$ catalyzed carbonylation of azirines

A mixture of dry benzene (50ml), $Pd(PPh_3)_4$ (1 mmol), and azirine (10 mmol) was stirred under a CO atmosphere at 40°C. The reaction was followed by thin layer chromatography and when complete (usually overnight) the reaction mixture was concentrated by using a rotary evaporator. The resulting crude residue was dissolved in a small amount of benzene and coated on a small amount of silica gel. This was added on top of a silica gel column and eluted in the following manner using different solvent systems for the various bicyclic β-lactams (17). The yields, melting points and analytical data for (17) are given in Table 3. Spectral data are listed in Table 4.

2-Phenyl-1-azirine (1)

The reaction was carried out using (0.661g, 5.65 mmol) of (1). Elution with C_6H_6-$CHCl_3$ and $CHCl_3$ gave 0.297g (40%) of bicyclic β-lactam as a pale yellow solid. Recrystallization from hot hexane gave the pure off white crystalline product.

2-(4'-Methylphenyl)-1-azirine (2)

The reaction was carried out using (1.01g, 7.7 mmol) of (2). Elution with C_6H_6-$CHCl_3$ and $CHCl_3$ gave 0.563g (50%) of bicyclic β-lactam as a pale green solid. Recrystallization from hot hexane gave pure yellow green needle like crystals. A single crystal X-ray structure determination was also made of this compound.

2-(4'-Bromophenyl)-1-azirine (3)

The reaction was carried out using (1.00g, 5.1 mmol) of (3). Elution with C_6H_6-$CHCl_3$ gave 0.59g (55%) of bicyclic β-lactam as a pale yellow solid. Recrystallization from hot hexane gave pure off white crystals.

2-(4'-Chlorophenyl)-1-azirine (4)

The reaction was carried out using (0.190g, 1.26 mmol) of (4). Elution with 1:4 ether: hexane gave 0.077g (37%) of bicyclic β-lactam as a yellow solid.

Analytically pure material was obtained by passing a hexane solution of the compound through a small column using hexane: ether (5:1) as the eluant.

3-Methyl-2-phenyl-1-azirine (5)

The reaction was carried out using (1.022g, 7.8 mmol) of (5). The reaction was followed by thin layer chromatography. After 2 days since there was still unreacted azirine left; more $Pd(PPh_3)_4$ (0.96 mmol) was added to the reaction mixture. After 1.5 days the reaction was stopped and worked up in the usual manner. Elution with C_6H_6-$CHCl_3$ gave 0.029 g (2.5%) of analytically pure bicyclic β-lactam as an orange yellow oil.

2-(2',4'-Dimethylphenyl)-1-azirine (6)

The reaction was carried out using (0.503g,3.5 mmol) of (6). Elution with ether: hexane (1:4) gave 0.292g (49%) of bicyclic β-lactam as an orange-yellow oil.

3-Formyl-2-phenyl-1-azirine (7)

The reaction was carried out using (0.505g, 3.50 mmol) of (7). After 5 days the thin layer chromatography showed that there were no new products formed. The starting azirine (7) was recovered quantitatively.

3-(Dimethoxymethyl)-2-phenyl-1-azirine (12)

The reaction was carried out using (1.00g, 5.2 mmol) of (12). The reaction was followed by thin layer chromatography. After 1 day the starting material was still present. Therefore more $Pd(PPh_3)_4$ (0.52 mmol) was added to the reaction mixture. After another 3 days the starting material (12) was recovered quantitatively.

3-Methyl-3-allyl-2-phenyl-1-azirine (13)

The reaction was carried out using (1.064g, 5.8 mmol) of (13). After 3 days thin layer chromatography showed that there were no new products formed. The starting azirine (13) was recovered quantitatively.

Once the general procedure of $Pd(PPh_3)_4$ catalyzed carbonylation of azirines were established, some variations were made to determine if improvement could be made to the reaction and also to see the effect of other factors such as added ligands, polar solvents, and hydrogen on the reaction.

Carbonylation of 2-phenyl-1-azirine (1) catalyzed by $Pd(PPh_3)_4$ in N,N-dimethylacetamide

The general procedure was applied to the $Pd(PPh_3)_4$ (0.21 mmol) catalyzed carbonylation of (1) (2.18 mmol) in N,N-dimethylacetamide (50ml) instead of C_6H_6.

When the reaction was complete the mixture was treated with 20ml of absolute MeOH and stirred for 1hr and then poured into excess H_2O. The solution was extracted with ether and the combined ether extracts were washed successively 4-5 times with water, dried over $MgSO_4$, filtered and concentrated. The crude residue was chromatographed on a silica gel column and elution with 1:4 ether:hexane gave 0.036g (16%) of the bicyclic β-lactam as pale yellow crystals.

Reaction of 2-phenyl-1-azirine with 1:1 CO/H_2 catalyzed by $Pd(PPh_3)_4$

A 1:1 carbon monoxide-hydrogen gas mixture was bubbled through a C_6H_6(50ml) solution containing (1) (0.531g, 4.54 mmol) and $Pd(PPh_3)_4$ (0.58 mmol). Column chromatographic work-up (1:4 ether: hexane) gave 0.15g (25%) of bicyclic β-lactam and 0.024g (4.5%) of 4,5-diphenylpyrimidine.

$Pd(PPh_3)_4$ catalyzed carbonylation of 2-phenyl-1-azirine in the presence of added ligands

2,2'-Bipyridyl

To a mixture of 0.254g(0.220 mmol) of $Pd(PPh_3)_4$ and 0.037g (0.24 mmol) of 2,2'-bipyridyl in C_6H_6 (50ml) was added (1) (0.263g, 2.25 mmol). The reaction mixture was stirred overnight at 40°C under a carbon monoxide

atmosphere. Workup by silica gel chromatography [ether: hexane (1:4)] gave 0.0866g (29%) of bicyclic β-lactam.

$Pd(PPh_3)_4$/N,N,N',N'-Tetramethyl Ethylene Diamine [TMEDA] — (1:1)

To a mixture of 0.491g (0.426 mmol) of $Pd(PPh_3)_4$ and 0.502g(0.437 mmol) of TMEDA in benzene (50ml) was added 2-phenyl-1-azirine [0.502g, 4.29 mmol]. The reaction mixture was stirred overnight at 40°C. Workup by silica gel column chromatography [ether: hexane (1:4)] gave 0.155g (28%) of bicyclic β-lactam.

$Pd(PPh_3)_4$: TMEDA (1:2)

The reaction was effected in a manner identical to the above reaction except using double the amount of TMEDA used, [$Pd(PPh_3)_4$: 1: TMEDA (1:10:2)] to give 0.173g (31%) of bicyclic β-lactam.

Maleic Anhydride

A mixture of 0.494g (0.43 mmol) of $Pd(PPh_3)_4$ and 0.127g (1.29 mmol) of maleic anhydride was stirred for 15 min. under a CO atmosphere at 40°C. To this 0.503g (4.3 mmol) of (1) was added and the mixture was stirred overnight. Conventional work-up gave 0.088g (16%) of bicyclic β-lactam.

Allyl Acetate

A mixture of 0.496g (0.43 mmol) of $Pd(PPh_3)_4$ and 0.043g (0.43 mmol) of allyl acetate in benzene (40 ml) was stirred at room temperature under a nitrogen atmosphere for 2hr. To this mixture was added 0.503g (4.29 mmol) of (1), the atmosphere was changed to carbon monoxide, and the solution was stirred overnight at 40°C. Workup as usual gave 0.203g (36%) of bicyclic β-lactam.

When the above reaction was effected under a carbon monoxide atmosphere from the beginning 0.187g (33%) of bicyclic β-lactam was obtained.

$Pd(PPh_3)_4$ Catalyzed reaction of 2-phenyl-1-azirine under a nitrogen atmosphere.

A mixture of 0.985g (0.853 mmol) of $Pd(PPh_3)_4$ and 1.007g(8.6 mmol) of (1) was stirred for 2 days at 40°C under a nitrogen atmosphere. Workup by column chromatography with ether: hexane, ether gave 7 fractions. None of them were identified successfully.

Carbonylation reaction of 2-phenyl-1-azirine catalyzed by other palladium complexes

(Dimethyl acetylenedicarboxylate)bis(triphenylphosphine)-palladium (0)

A mixture of (dimethyl acetylenedicarboxylate)-bis(triphenylphosphine)palladium(0) complex (0.337g,

0.436 mmol) and 2-phenyl-1-azirine (0.51g, 4.36 mmol) in benzene (50ml) was stirred overnight under a carbon monoxide atmosphere at 40°C. Workup as usual gave 0.198g (35%) of bicyclic β-lactam.

Bis[bis(1,2-diphenylphosphino)ethane]palladium (0)- $Pd(dpe)_2$

A mixture of 0.385g (0.43 mmol) of $Pd(dpe)_2$ and 0.515g (4.4 mmol) of (1) in benzene (50ml) was stirred under a carbon monoxide atmosphere at 40°C. After 1 day the temperature was increased to 60 °C and the mixture was stirred overnight. Thin layer chromatography and an infrared spectrum of the crude residue showed that there were no new products formed and that unreacted starting material is still present.

The above reaction was also carried out in THF instead of C_6H_6, at 40°C for 4 days. Thin layer chromatography showed that there were no new products formed. Starting azirine (1) was isolated quantitatively.

$(CH_3COO)_2Pd(II)$

A mixture of 0.228g(1.02 mmol) of $(CH_3COO)_2Pd$ and 1.018g (8.7 mmol) of (1) in C_6H_6 (60ml) was stirred for overnight at room temperature under a carbon monoxide atmosphere. Workup by silica gel chromatography [benzene,

ether:hexane and ether] gave 6 fractions, none of which was identified successfully.

Di-μ-chlorobis(η^3-propenyl)dipalladium (II)

A mixture of the π-allyl palladium (II) complex (0.16g, 0.436 mmol) and 2-phenyl-1-azirine (0.503g, 4.3 mmol) in benzene (50ml) was stirred overnight at 40°C under carbon monoxide. Workup by column chromatography [ether: hexane, ether] gave 4 fractions, none of which was identified successfully.

Di-μ-Chlorobis(η^3-propenyl)dipalladium(II): PPh_3 (1:3)

To a mixture of PPh_3 (0.338g, 1.29 mmol) and Pd(II) catalyst (0.162g,0.442 mmol) in benzene (50ml) was added 2-phenyl-1- azirine (0.503g, 4.3 mmol) and the mixture was stirred overnight at 40°C under a carbon monoxide atmosphere. Workup by column chromatography [ether:hexane (1:3)] gave 0.053 g (11%) of 2,5-diphenylpyrazine and 0.084 g (15%) of bicyclic β-lactam.

$Pd(dba)_2$: PPh_3 (1:30)

To a mixture of 0.25g(0.43 mmol) of $Pd(dba)_2$ and 3.36g(12.8 mmol) of PPh_3 in benzene (40ml) was added 2-phenyl-1-azirine (0.501g, 4.28 mmol) and the mixture was stirred at 40°C for 4 days under a carbon monoxide

atmosphere. An infrared spectrum of the crude residue showed that isocyanate was not present. Elution with ether: hexane (1:4) gave 0.151g (27%) of bicyclic β-lactam.

$Pd(dba)_2$: PPh_3 (1:3)

To a mixture of 0.34g (1.296 mmol) of PPh_3 and 0.249g (0.433 mmol) of $Pd(dba)_2$ in C_6H_6 (40ml) was added 2-phenyl-1-azirine (0.4997g, 4.27 mmol) and the solution was stirred at 40°C overnight under a carbon monoxide atmosphere. An infrared spectrum of the crude residue showed that the isocyanate peak is not present. Elution with ether: hexane (1:9) gave 0.198g (35%) of bicyclic β-lactam.

Attempted carbonylation of 2-phenyl-1-azirine using other catalysts

$Pt(PPh_3)_4$

The reaction was effected in a manner identical with that described for $Pd(PPh_3)_4$ reaction. After 2 days the starting azirine (1) was recovered quantitatively.

$Ni(PPh_3)_4$

The reaction was effected in a manner identical with that described for $Pd(PPh_3)_4$ reaction except for a

change in the catalyst. After 1 week the starting azirine (1) was recovered quantitatively.

Reaction of N-n-butyl-2-phenyl aziridine(10) with CO and $Pd(PPh_3)_4$

The aziridine (10) (0.602g, 3.44 mmol-) and $Pd(PPh_3)_4$ (0.403g, 0.349 mmol) in benzene (50ml) were stirred under an atmosphere of carbon monoxide at 40°C for 2 days. Workup gave recovered starting material.

Reaction of 4,5-diphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene (11) with CO and $Pd(PPh_3)_4$

Starting material was recovered when a mixture of (11) (0.207g, 0.884 mmol) and $Pd(PPh_3)_4$ (0.117g, 0.102 mmol) in benzene (50ml) was exposed to CO for 2 days at 40°C.

Once some variations on the general procedure of $Pd(PPh_3)_4$ catalyzed carbonylation of azirines were done we tried to trap the proposed dipolar azaallyl intermediate (20) in the latter reaction with various dipolarophiles.

Attempted $Pd(PPh_3)_4$ catalyzed cycloaddition reactions of azirines in the presence of CO

Cycloaddition reaction of 2-phenyl-1-azirine with dimethyl maleate

To a mixture of $Pd(PPh_3)_4$ (0.522g, 0.452 mmol) and dimethyl maleate (1.14g, 7.9 mmol) in C_6H_6 (50ml) was added 2-phenyl-1-azirine (0.533g, 4.55 mmol) and the solution was stirred at room temperature under a carbon monoxide atmosphere. After 1 day the temperature was increased to 40 °C and stirring was continued overnight. Workup by column chromatography using, as eluant, ether: hexane with increasing proportions of ether. Elution with ether: hexane (1:4) gave 0.245g (41%) of bicyclic β-lactam.

Similarly β-lactams were obtained when dimethyl fumarate was used instead of dimethyl maleate and also 2-(2',4'-dimethylphenyl)-1-azirine was used instead of 2-phenyl-1-azirine in the above reaction.

Cycloaddition reaction of 2-phenyl-1-azirine with dimethyl acetylenedicarboxylate

A mixture of dimethyl acetylenedicarboxylate (0.608g,4.28 mmol) and $Pd(PPh_3)_4$ (0.494g, 0.428 mmol) in benzene (40ml) was stirred at room temperature for 0.5hr under a carbon monoxide atmosphere. To this was added 2-phenyl-1-azirine (0.4995g, 4.27 mmol) and the reaction

mixture was stirred for 1 day at room temperature and then at 40°C for 27 hrs. Workup gave 4 unidentified products.

The same results were observed when 2-(2',4'-dimethylphenyl)-1-azirine was used instead of 2-phenyl-1-azirine in the above reaction.

Once the general procedure for the $Pd(dba)_2$ catalyzed carbonylation of azirines was established we also tried to do Diels-Alder cycloaddition reaction on the resulting vinyl isocyanates with various dienophiles.

Reaction of 2-(4'-chlorophenyl)-1-azirine and $Pd(dba)_2$ in the presence of dimethyl acetylenedicarboxylate

To 40 ml of dry C_6H_6 was added $Pd(dba)_2$ (0.246g, 0.42 mmol) and dimethyl acetylenedicarboxylate (0.606g, 4.27 mmol) and the solution was stirred at room temperature for 0.5hr under a CO atmosphere. To this was added 2-(4'-chlorophenyl)-1-azirine (0.648g, 4.27 mmol) in C_6H_6(5ml) and stirring was continued at room temperature for 1 day and at 40°C for 4 days. The solvent was removed on a rotary evaporator. An infrared spectrum of the resultant crude residue showed that an isocyanate peak is not present. Workup gave 3 compounds which could not be identified.

Reaction of 2-phenyl-1-azirine and $Pd(dba)_2$ with dimethyl acetylenedicarboxylate

A mixture of $Pd(dba)_2$ (0.247g, 0.43 mmol), 2-phenyl-1-azirine (0.5g, 4.3 mmol) and benzene (40ml) was

stirred under a carbon monoxide atmosphere at 43°C for 6hrs. Then dimethyl acetylenedicarboxylate (0.609g, 4.3 mmol) was added. The reaction was followed by thin layer chromatography. After 2 days the reaction mixture was refluxed for 17hr. The solvent was removed on a rotary evaporator. An infrared spectrum of the resultant crude residue showed the presence of isocyanate. Therefore, the residue was treated with 80ml of hexane, filtered and concentrated on a rotary evaporator. The NMR and IR spectra of the resulting crude oil showed the presence of a mixture of vinyl isocyanate and unreacted dimethyl acetylenedicarboxylate. The latter was again dissolved in 40ml of benzene and dimethyl maleate (0.61g, 4.3 mmol) was added and refluxed under a CO atmosphere for 2.5 days. The solvent was removed on a rotary evaporator .NMR and IR spectra of the resulting crude showed that there was no reaction.

4.2. Palladium(0) Catalyzed Reactions Of Azirines Under Heterogeneous Conditions

General procedure

A mixture of benzyltriethylammonium chloride (0.10g) in 50% NaOH (15ml) and palladium(0) catalyst (0.34-0.43 mmol) in benzene (15ml) was stirred for 1hr at 40-50°C, under a carbon monoxide atmosphere. To this mixture was added, dropwise (1hr), the azirine (3.4-4.3 mmol)

in benzene (5ml). The reaction was followed by thin layer chromatography and, when complete, was extracted with ether. The organic layer was washed with water, dried over $MgSO_4$, concentrated and chromatographed on silica gel Styrylindoles were obtained from the aqueous phase by acidification with HCl followed by extraction with ether. Product yields, reaction times and the phase transfer catalyst used are given in Table 5. Spectral data are listed in Table 6.

Once the $Pd(PPh_3)_4$ catalyzed reaction of azirines under heterogeneous conditions was established some variations were made to determine if improvements could be made to the reaction. In these reactions 2-phenyl-1-azirine (1) was used as the substrate.

Reaction under a nitrogen atmosphere

The reaction was effected in a manner identical with that described for the general procedure, except in an atmosphere of nitrogen instead of carbon monoxide. Workup was effected as mentioned in the general procedure.

Reaction under a carbon dioxide atmosphere

The reaction was effected in a manner identical with that described for the general procedure except in an atmosphere of carbon dioxide instead of carbon monoxide.

Here, work-up by extraction of the aqueous phase after acidification did not give any indole. The organic layer was placed on a silica gel column. Elution with ether: hexane (1:5) gave 0.088g (19%) of 2-styrylindole.

Reaction without $Pd(PPh_3)_4$

The reaction was effected in a manner identical with that described for the general procedure, except in the absence of $Pd(PPh_3)_4$ catalyst. Extraction of the aqueous phase after acidification did not give indole. The organic layer was placed on a silica gel column. Elution with (1:4) ether: hexane gave 0.097g (19%) of a dimer(47) of 2-phenyl-1-azirine(1). The structure was not determined successfully. ^1H NMR ($CDCl_3$), δ 6.75(d,J=3Hz), 6.9-7.8(m); MS (m/e) 234; IR ν_{N-H} ($CHCl_3$) 3375 cm^{-1}.

Reaction using (5:1) 2-phenyl-1-azirine: $Pd(PPh_3)_4$

The reaction was effected in a manner identical with that described for the general procedure except using double the amount of $Pd(PPh_3)_4$ [i.e., 5/1 ratio of (1) / $Pd(PPh_3)_4$]. Extraction of the aqueous phase after acidification gave 0.085g (18%) of 2-styrylindole. Column chromatography [(1:9) ether: hexane] of the organic layer gave 0.062g (12%) of acetophenone.

Reaction without a phase transfer catalyst

The reaction was effected in a manner identical with that described for the general procedure except in the absence of a phase transfer catalyst. Extraction of the aqueous phase after acidification gave 0.084g (18%) of 2-styrylindole. Column chromatography of the organic layer on a silica gel column [(1:5) ether: hexane] gave 0.033g (6.5%) of a dimer (47) of 2-phenyl-1-azirine.

Using tetrabutylammonium hydrogen sulfate, [$Bu_4N^+HSO_4^-$] as the phase transfer catalyst

The reaction was effected in a manner identical with that described for the general procedure except using tetrabutylammonium hydrogen sulfate as the phase transfer catalyst. Extraction of the aqueous phase after acidification gave 0.095g (20%) of 2-styrylindole.

Using dodecyltrimethylammonium chloride as the phase transfer catalyst

The reaction was effected in a manner identical with that described for the general procedure except using dodecyltrimethylammonium chloride as the phase transfer catalyst. Extraction of the aqueous phase after acidification gave 0.029g (6%) of 2-styrylindole. Acetophenone [0.028g; 5%] was obtained on workup of the organic phase.

Using 5N NaOH

The reaction was effected in a manner identical with that described for the general procedure except using 5N NaOH instead of 50% NaOH. Extraction of the aqueous phase after acidification gave 0.115g (25%) of 2-styrylindole. Column chromatographic work-up of the organic phase gave small amounts of unidentified compounds.

Using H_2O

The general procedure was used except that distilled water instead of 50% NaOH was used as the aqueous phase. Extraction of the aqueous phase after acidification did not give any indole. Column chromatography of the organic layer [ether: hexane] gave 0.053g (10%) of acetophenone, followed by 0.053g (11%) of 2-styrylindole and 0.213g (38%) of bicyclic β-lactam.

Reaction with K_2CO_3

A mixture of benzyltriethylammonium chloride (0.1g, 0.44 mmol), K_2CO_3 (1.214g,8.798 mmol) and $Pd(PPh_3)_4$ (0.494g,0.43 mmol) in benzene(45ml) was heated at 50°C for 5hr, in a carbon monoxide atmosphere. To this 2-phenyl-1-azirine(0.5g,4.28 mmol) in benzene(5ml) was added dropwise (1hr). When the reaction was complete water (50ml) was added and the usual work-up afforded 0.195g(35%) of bicyclic

β-lactam and 0.023g(5%) of 2-styrylindole.

Using hexane as the organic phase

The reaction was effected in a manner identical with that described for the general procedure except using hexane instead of benzene as the organic phase. $Pd(PPh_3)_4$ was introduced by dissolving in 3ml of C_6H_6. Workup as usual gave 0.06g (13%) of 2-styrylindole and 0.01g (2%) acetophenone.

Using $Pd(PPh_3)_4/Co_2(CO)_8$ (1:1)

A mixture of benzyltriethylammonium chloride (0.10g, 0.44 mmol) in 50% NaOH (15ml) and $Pd(PPh_3)_4$ (0.493g, 0.43 mmol) in benzene (15ml) was stirred under a carbon monoxide atmosphere at 40°C for 1hr. The solution was cooled to room temperature, $Co_2(CO)_8$ (0.152g, 0.44 mmol) was added, and stirring continued for 0.5hr at room temperature. To this mixture 2-phenyl-1-azirine [0.502g,4.3 mmol] in C_6H_6 (5ml) was added dropwise(1hr), and the reaction mixture was stirred overnight. Workup as usual gave 0.086g (18%) of 2-styrylindole and 0.02g (4%) of acetophenone.

Reaction under CO pressure

A mixture of benzyltriethylammonium chloride (0.10g,0.44 mmol) in 50% NaOH (15ml) and $Pd(PPh_3)_4$

(0.493g,0.43 mmol) in benzene (15ml) was stirred under a carbon monoxide atmosphere at 40°C for 2hrs. This mixture was transferred to a titanium bomb and 2-phenyl-1-azirine (0.504g,4.3 mmol) in benzene (5ml) was added. To this mixture a carbon monoxide pressure of 350 psi was introduced and then the reaction mixture was heated overnight with stirring at 40-45°C. Conventional workup gave no indole, but gave 0.097g (19%) of a dimer (47) of 2-phenyl-1-azirine and then 0.065g (13%) of a trimer (48) of the latter. The structures of the two products were not determined successfully.

Dimer (47) - MS(m/e) 234, IR ν_{N-H} ($CHCl_3$) 3375 cm^{-1}.

Trimer (48) - MS(m/e) 351, IR ν_{N-H} ($CHCl_3$) 3310 cm^{-1}.

Using $Pd(dba)_2$ as the Pd(0) catalyst

The reaction was effected in a manner identical with that described for the general procedure except using $Pd(dba)_2$ instead of $Pd(PPh_3)_4$. Work-up as usual did not give indole but gave 0.069g (13%) of acetophenone.

Using $Pd(dpe)_2$ as the Pd(0) catalyst

The reaction was effected in a manner identical with that described for the general procedure using $Pd(dpe)_2$ and 5N NaOH instead of $Pd(PPh_3)_4$ and 50% NaOH respectively. $Pd(dpe)_2$ was introduced by dissolving in CH_2Cl_2 (3ml). Extraction of the aqueous phase after

acidification gave trace amounts of 2-styrylindole. Workup of the organic phase afforded 0.026g (5%) of acetophenone and 0.056g (12%) of 2-styrylindole.

Using $Pd(dpe)_2$ and 2-(4'-methylphenyl)-1-azirine

The reaction was effected in a manner identical to the reaction of $Pd(dpe)_2$ with 2-phenyl-1-azirine, using 2-(4'-methylphenyl)-1-azirine instead of 2-phenyl-1-azirine. $Pd(dpe)_2$ was introduced to the reaction mixture by dissolving it in CH_2Cl_2 (3ml). Column chromatographic work-up with ether: hexane (1:8) gave 0.079g(15%) of 2-p-methylacetophenone and 0.029g (6%) of 2p-methylstyryl-6-methylindole.

Using $Pd(CH_3COO)_2$ as the metal catalyst

The reaction was effected in a manner identical with that described for the general procedure except using $Pd(CH_3COO)_2$ instead of $Pd(PPh_3)_4$. Standard work-up gave 0.208g (41%) of acetophenone.

4.3. $Mo(CO)_6$ Induced Reactions Of Azirines With Carbanions

General Procedure

To a solution of NaOEt, prepared from the reaction of Na(4-7 mmol) in 99% ethanol (5ml), $CH_2(COOEt)_2$ (4-7 mmol)

in THF(10ml) was added and the solution was heated at 50°C under a nitrogen atmosphere. After 4hrs, 25ml of THF was added and stirring was continued for 0.5hr. To this mixture, $Mo(CO)_6$ (2.7-4.7 mmol) in THF(5ml) was added. After 0.5hr the mixture was cooled to -78°C and azirine (2.7-4.7 mmol) in THF(5ml) was added dropwise (1hr). The dropping funnel was washed with 5ml of THF and the THF was added to the solution. The mixture was then allowed to warm up to room temperature and stirring was continued until reaction was complete (followed by thin layer chromatography). The reaction mixture was added to distilled water, extracted with ether, dried over $MgSO_4$ and concentrated to give the crude imides. The pure imides were isolated by column chromatography on silica gel. Product yields, reaction times, melting points and analytical data are given in Table 7. Spectral data are listed in Table 8. Work-up in the individual cases was as follows:

2-Phenyl-1-azirine (1)

Elution with ether: hexane (3:2) gave 0.476-0.483g (45-46%) of imide (51, R=Ph,R'=H,R''=COOEt) as a thick pale yellow oil, which crystallized after a few weeks, as transparent crystals. A single-crystal X-ray determination was also made.

2-(4'-methylphenyl)-1-azirine (2)

Elution with ether: hexane (3:2) gave 0.678g (68%) of imide (51, R=p-$CH_3C_6H_4$, R'=H, R"=COOEt) as a thick pale yellow oil.

2-(4'-Bromophenyl)-1-azirine (3)

Elution with ether: hexane (3:2) gave 0.433g (52%) of imide (51, R=p-BrC_6H_4, R'=H, R"=COOEt) as a pale yellow oil, which crystallized as transparent crystals after a few weeks.

2-(4'-Chlorophenyl)-1-azirine (4)

Elution with ether: hexane (3:2) gave 0.291g (27%) of imide (51, R=p-ClC_6H_4, R'=H, R"=COOEt) as a thick yellow oil.

3-Methyl-2-phenyl-1-azirine (5)

Elution with ether gave 0.74g (74%) of imide (51, R=C_6H_5, R'=CH_3, R"=COOEt) as a white solid. Recrystallization from ethanol gave white needle like crystals.

2-(2'-methylphenyl)-1-azirine (8)

Elution with ether: hexane (3:2) gave 0.41g (41%) of imide (51, R=o-$CH_3C_6H_4$, R'=H, R"=COOEt) as an off white oil. This was purified further by using thin layer

chromatography with ether: hexane (1:1) as the developing solvent. A white thick oil was obtained which crystallized after a few weeks, as white crystals.

2-(4'-methoxyphenyl)-1-azirine (9)

Elution with ether: hexane (3:2) gave 0.56g (59%) of imide (51, R=p-$CH_3OC_6H_4$,R'=H, R"=COOEt), as a pale yellow oil, which gradually formed white crystals.

Once the $Mo(CO)_6$ induced reaction of azirines with diethyl malonate carbanion was established some variations were made to improve the reaction. In these reactions 2-phenyl-1-azirine (1) was used as the substrate unless otherwise mentioned.

Blank Test

The blank tests were carried out in a manner identical to the general procedure except in the absence of $Mo(CO)_6$. Workup was done as usual . Elution with ether: hexane (3:2) gave 0.22-0.24g (21-23%) of imide (51,R=C_6H_5, R'=H,R"=COOEt) as a pale yellow oil.

Reverse reaction

To 35ml of dry THF , $Mo(CO)_6$ (4.7mmol) and azirine (4.7 mmol) were added. The mixture was cooled at once to -78°C and stirred under a nitrogen atmosphere for 12-15 min. To this mixture, sodium diethyl malonate (7 mmol)

in THF (10ml) was added dropwise(1hr). The mixture was allowed to warm up to room temperature. When the reaction was complete, the usual workup was effected giving 0.337g (32%) of imide (51, R=C_6H_5, R'=H, R"=COOEt).

Under a CO atmosphere with catalytic amount of $Mo(CO)_6$

To a solution of NaOEt, prepared from (7 mmol) of Na in 99% ethanol (5ml), diethyl malonate (7 mmol) in THF (10ml) was added and the mixture was heated at 50°C under a nitrogen atmosphere. After 4hrs, 25ml of dry THF was added and the mixture was stirred for 30 min. To this solution $Mo(CO)_6$ (0.470 mmol) in THF (5ml) was added, and after 15 min the nitrogen atmosphere was changed to carbon monoxide. After 15 min, the mixture was cooled to -78°C and azirine (4.7 mmol) in THF (5ml) was added dropwise (1hr). The solution was allowed to warm up to room temperature, and then stirred overnight. Workup by column chromatography [ether: hexane (3:2)] gave a heavy oily impure material. This was again used on a short silica gel column. Elution with ether: hexane (2:3) afforded 0.023g (2%) of imide (51, R=C_6H_5, R'=H, R"=COOEt).

Reaction under a CO atmosphere with a stoichiometric amount of $Mo(CO)_6$

The reaction was effected in a manner identical with that described for the reaction under a CO atmosphere

with a catalytic amount of $Mo(CO)_6$, except using a stoichiometric quantity (4.7 mmol) of $Mo(CO)_6$. After overnight reaction, workup as usual gave 0.155g (15%) of imide (51,R=C_6H_5,R'=H,R"=COOEt).

Once some variations were made on the $Mo(CO)_6$ induced reaction of azirines with diethyl malonate anion, other carbanions were also used for this reaction. Product yields, reaction times, melting points and analytical data are given in Table 9. Spectral data are listed in Table 10.

Reaction of 2-phenyl-1-azirine with ethyl benzoyl malonate anion in the presence of $Mo(CO)_6$

The reaction was effected in a manner identical with that described for the general procedure, except using ethyl benzoyl malonate instead of diethyl malonate. Column chromatographic work-up [ether: hexane (1:1)] gave 0.346g (29%) of imide (51,R=C_6H_5,R'=H,R"=COC_6H_5), as a pale yellow oil, which crystallized as white crystals after a few weeks.

Reaction of 2-phenyl-1-azirine with ethyl benzoyl malonate anion in the absence of $Mo(CO)_6$

The reaction was effected in a manner identical with that described for the general procedure using ethyl benzoyl malonate instead of diethyl malonate, in the

absence of $Mo(CO)_6$. After overnight, workup as usual gave 0.12g (10%) of imide (51, R=C_6H_5, R'=H, R"=COC_6H_5).

Reaction of 2-(4'-bromophenyl)-1-azirine with ethyl benzoyl malonate anion in the presence of $Mo(CO)_6$

The reaction was effected in a manner identical with that described for the general procedure, except using ethyl benzoyl malonate instead of diethyl malonate. Column chromatographic workup with ether: hexane (1:1) gave 0.321g (35%) of imide (51, R=p-BrC_6H_4, R'=H, R"=COC_6H_5) as a pale yellow oil, which crystallized as white crystals after a few weeks.

Reaction of 2-phenyl-1-azirine with ethyl acetoacetate anion in the presence of $Mo(CO)_6$

The reaction was effected in a manner identical with that described for the general procedure, except using ethyl acetoacetate instead of diethyl malonate. Workup by column chromatography gave 7 fractions, none of them was identified successfully.

Reaction of 2-phenyl-1-azirine with ethyl α- (p-toluene sulfonyl) acetate anion in the presence of $Mo(CO)_6$

The reaction was effected in a manner identical with that described for the general procedure, except using ethyl α-(p-toluene sulfonyl) acetate instead of

diethyl malonate. Only starting ester and several unidentified products resulted on workup.

Reaction of 2-phenyl-1-azirine with ethyl cyanoacetate anion in the presence of $Mo(CO)_6$

The reaction was effected in a manner identical with that described for the general procedure except using ethyl cyanoacetate instead of diethyl malonate. When the reaction was completed, column chromatographic workup (ether: hexane) gave 4 fractions, none of which were successfully identified.

Reaction of 2-phenyl-1-azirine in the presence of $Mo(CO)_6$ with ethyl cyanoacetate anion generated by NaH

NaH (7 mmol) was added to 20ml of dry THF and the solution was stirred for 0.5hr under a nitrogen atmosphere. To this was added ethyl cyanoacetate (7 mmol) in THF (10ml). After 30 min, $Mo(CO)_6$ (4.7 mmol) in THF (5ml) was added, and the solution was stirred for a further 30 min. After cooling to -78°C azirine (1) in THF (5ml) was added dropwise (1hr). The mixture was allowed to warm up to room temperature and when the reaction was completed, the reaction was worked up as usual. Elution with (3:2) ether: hexane gave 0.19g (23%) of crude imide (51, R= C_6H_5, R'=H, R"=CN) as an orange coloured oil. Further purification was attempted by preparative thin layer chromatography

using (1:1) ether: hexane as the developing solvent. It was not successful since some other impurity was moving with the product. Other solvent systems were also tried on small thin layer chromatography plates, but they were also not very successful. Mass and infrared spectra agrees with the imide formulation (51). ^1H NMR spectrum showed that some other impurity is also present. Analytical results did not agree with the calculated values.

$Mo(CO)_6$ induced reaction of 2-phenyl-1-azirine with ethyl α-(p-toluene sulfonyl) acetate anion generated by NaH

The reaction was effected in a manner identical with that described for the reaction of ethyl cyanoacetate anion generated by NaH, except using ethyl α-(p-toluene sulfonyl) acetate. When the reaction was completed, workup by column chromatography gave 3 major fractions. The second one was the unreacted ester, and the other two fractions were not identified successfully.

$Mo(CO)_6$ induced reaction of 2-phenyl-1-azirine with ethyl diethyl malonate anion

The reaction was effected in a manner identical with that described for the general procedure, except using ethyl diethyl malonate instead of diethyl malonate. When the reaction was complete, the reaction was worked up by

column chromatography. Elution with ether: hexane (1:8) gave 0.174g (13%) of coupling product (57,R=C_6H_5) as a light yellow oil, and elution with ether: hexane (1:1) gave 0.246g (31%) of 3-ethyl-4-phenyl-3-pyrrolin-2-one (58) as an off white solid. The pyrrolinone (58,R=C_6H_5) was further purified by preparative thin layer chromatography using ether: hexane (3:4) as the developing solvent. The product was obtained as a pure white powder.

$Mo(CO)_6$ induced reaction of 2-(4-methylphenyl)-1-azirine with ethyl diethyl malonate anion

The reaction was effected in a manner identical with that described for the general procedure except using ethyl diethyl malonate instead of diethyl malonate. When the reaction was completed, workup was effected by column chromatography. Elution with ether: hexane (1:8) gave 0.187g (15%) of coupling product (57,R=p-$CH_3C_6H_4$) as a pale yellow oil and elution with (1:1) ether: hexane gave 0.128g (17%) of 3-ethyl-4-(p-methylphenyl)-3-pyrrolin-2-one(58) as a light yellow solid. The pyrrolinone (58,R=p-$CH_3C_6H_4$) was further purified by preparative thin layer chromatography using ether: hexane (3:4) as the developing system. The product was obtained as a pure white powder.

Reaction of 3-benzoyl-4-phenyl-4-pyrrolin -2-one (52) in the presence of $Mo(CO)_6$

3-Benzoyl-4-phenyl-4-pyrrolin -2-one (52) was prepared according to the literature procedure[111].

Preparation of 3-benzoyl-4-phenyl-4-pyrrolin -2-one (52)

To NaH (0.204g,0.009 mole) under a nitrogen atmosphere was added dimethyl sulfoxide (12.5ml). After stirring for 0.5 hr, ethyl benzoylacetate (1.9g, 0.01 mole) and 2-phenyl-1-azirine (1.15g, 0.01 mole) were added and stirring was continued overnight at room temperature. This mixture was added to water and acidified with HCl, but no precipitate was formed. Attempted extraction with ether gave a yellow precipitate which was filtered and washed successively with water and ether. Drying and concentration gave 0.322g (14%) of (52) as an off white powder. mp.184-187°C, Lit mp. 188-189°C; MS (m/e) 263 $[M]^+$; IR ($CDCl_3$) 3458 cm^{-1}(N-H), 1700 cm^{-1}(lactam >C=0), 1665 cm^{-1} (COPh).

Reaction of (52) with $Mo(CO)_6$

Molybdenum hexacarbonyl (0.6 mmol) in dry THF (40ml) was heated at 50°C under a nitrogen atmosphere. After 0.5hr, this solution was cooled to -78°C and compound (52) (0.6 mmol) in $CHCl_3$(5ml) was added dropwise (1hr).

The mixture was allowed to warm up to room temperature and reaction was followed by thin layer chromatography. After 1 day (according to TLC) there was no imide (51, R=C_6H_5, R'=H, R"=COPh) formed. The solvent was removed on a rotary evaporator and used the crude residue on a silica gel column. Elution with ether: hexane gradually increasing the amount of ether gave mainly 2 fractions. None of them were identified successfully. But no imide (51, R=C_6H_5, R'=H, R"=COPh) was isolated.

Reaction of 2-phenyl-1-azirine with carbanions in the presence of other catalysts

With a catalytic amount of $Co_2(CO)_8$, $Pd(PPh_3)_4$, $Pd(dpe)_2$, $RuCl_2(PPh_3)_4$ or, [Rh(1,5-hexadiene)Cl]$_2$

The reaction was effected in a manner identical with that described for the general procedure except using a catalytic amount of the above species. When the reaction was completed the reaction was worked-up as usual. The catalyst used, product yields and reaction times are given in Table 11.

With a stoichiometric amount of $Co_2(CO)_8$

The reaction was effected in a manner identical with that described for the general procedure except using $Co_2(CO)_8$ instead of $Mo(CO)_6$. The reaction once completed was worked up as usual.

Acid Hydrolysis of imides

Hydrolysis of (51, R=C_6H_5, R'=H, R''=COOEt) using 2N HCl

Imide (51, R=C_6H_5, R'=H, R''=COOEt) (0.8 mmol) was refluxed overnight in 2N HCl (25ml). The mixture was extracted with ether, the ether extracts were washed with water, dried ($MgSO_4$) and concentrated to give 0.137g (89%) of $C_6H_5CH(COOH)CH_2COOH$. ^1H NMR (DMSO) δ 2.55 (q,1H), 3.1 (q,1H), 3.9 (q,1H), 9.3 (s,2H,COOH), 7.15 (br., 5H, aromatic protons); MS (m/e) [TMS derivative of the acid], 338 $[M]^+$, 323 $[M-CH_3]^+$, 248 $[M-6CH_3]^+$, 147 $[HSi_2Me_6]^+$, 73 $[SiMe_3]^+$.

Hydrolysis of (51, R=C_6H_5, R'=H, R''=COOEt) using 0.5N HCl

Imide (51, R=C_6H_5, R'=H, R''=COOEt) (0.4 mmol) in 0.5N HCl (25 ml) was stirred overnight at room temperature. Workup as mentioned above gave starting material with trace amounts of $C_6H_5CH(COOH)CH_2COOH$.

Hydrolysis of (51, R=C_6H_5, R'=H, R''=COPh) using 2N HCl

Imide (51, R=C_6H_5, R'=H, R''=COPh) (0.14 mmol) in 2N HCl (25ml) was refluxed overnight. Workup as mentioned before gave mainly recovered starting material.

Hydrolysis of (51, R=C_6H_5, R'=H, R"=COPh)using 6N HCl

Imide (51, R=C_6H_5, R'=H, R"=COPh) (0.14mmol) in 6N HCl (25ml) was refluxed for 24hr . Workup as mentioned before gave 0.032g (88%) of $C_6H_5CH(COOH)CH_2COC_6H_5$. ^1H NMR ($CDCl_3$) , δ 3.28(q,1H) , 4.06(q,1H), 4.35(q,1H) , 7.30-8.30 (m,10H, aromatic protons) ,8.55 (br.,1H,COOH); MS(m/e) [TMS derivative of the acid], 326 $[M]^+$, 311 $[M-CH_3]^+$, 281 $[M-3CH_3]^+$, 236 $[M-HOSiMe_3]^+$, 105 $[COPh]^+$, 73 $[SiMe_3]^+$.

CHAPTER V

5. Summary

5.1. Conclusions

In conclusion, metal complexes can catalyze or promote some interesting and useful transformations including the synthesis of β-lactams, vinyl isocyanates and imides. The $Pd(PPh_3)_4$ and $Pd(dba)_2$ are highly selective catalysts for the novel synthesis of β-lactams and vinyl isocyanates, respectively. These two classes of compounds are of considerable importance in medicinal (β-lactams) and polymer (vinyl isocyanates) chemistry. β-Lactams are an important class of antibiotics, and there has been great interest in recent years in the synthesis of hetero(e.g.,aza[117], oxa[118]) as well as carbon (e.g.,thienamycin[119]) analogues of penicillin. The remarkable ligand effects observed in this investigation are rather unusual in homogeneous catalysis. Use of mild conditions and the simplicity in the workup of the reactions are other important features of these reactions.

Styrylindoles are obtained by palladium(0) and phase-transfer catalyzed reactions of azirines. Neither β-lactams, nor vinyl isocyanates were detected in any of these Pd(0) catalyzed heterogeneous reactions. When compared to the homogeneous process, this different behavior may be due to

the generation of anionic palladium complexes under phase transfer catalysis[115].

Molybdenum hexacarbonyl can induce or promote the remarkable conversion of azirines and carbanions (e.g., $R''CH_2$-COOEt, R''= COOEt, COPh, CN) to imides. The reaction is completely stereospecific. The described process would constitute to a simple and convenient entry into acyclic compounds of defined stereochemistry (e.g., succinic acids), since it is well known that imides can be ring opened under a variety of conditions. Trans-3,4-disubstituted pyrrolidines[120] could be obtained by hydride reduction of the above mentioned imides. Azirines are converted to an imino diester and a 3-pyrrolinone by molybdenum hexacarbonyl induced reaction in the presence of ethyl diethyl malonate anion.

5.2. Claims to Original Research

- Catalytic homogeneous carbonylation of azirines to vinyl isocyanates by bis(dibenzylideneacetone)-palladium(0).

- Catalytic homogeneous carbonylation of azirines to β-lactams by tetrakis(triphenylphosphine)-palladium(0).

- Palladium(0) and phase-transfer catalyzed conversion of azirines to styrylindoles.

- Novel and stereospecific imide synthesis by molybdenum hexacarbonyl induced reactions of azirines with carbanions of β-dicarbonyl compounds.

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