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UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

TO GOD AND MY PARENTS

ABSTRACT

A study has been made of cycloaddition reactions of 3- and 4-membered ring nitrogen-containing heterocycles with heterocumulenes in the presence of Pd(II) catalyst. Bis(benzonitrile)palladium dichloride, $Pd(PhCN)_2Cl_2$, smoothly catalyzes the completely regioselective reactions of 1,2-disubstituted aziridines with N,N-diarylcarbodiimides to give imidazolidinimines in high yield. Similar cycloaddition reactions involving 1,2,3-trisubstituted aziridines and heterocumulenes (carbodiimides, isocyanates and isothiocyanates) provide regio- and stereospecific routes to imidazolinimines, imidazolidinones, and thiazolidinimines.

$Pd(PhCN)_2Cl_2$-catalyzed cycloaddition reactions of chiral, optically active 1,2-disubstituted aziridines with heterocumulenes proceed with retention of configuration affording the corresponding five-membered ring heterocycles in high yield and in optically pure form. The study of the reaction of aziridines with N,N-diarylsulfurdiimide in the presence of a Pd(II) catalyst resulted in the discovery of a new and unusual cyclization furnishing imidazolidinethiones. Cycloaddition reactions of azetidines with heterocumulenes (carbodiimides and isothiocyanates) are also catalyzed by $Pd(PhCN)_2Cl_2$ and afford tetrahydropyridin-2-imines and tetrahydro-1,3-thiazine-2-imines, respectively, in a regio- and stereospecific manner in excellent yield.

On the basis of results obtained, including spectroscopic studies and X-ray analysis, a mechanism has been proposed for the cycloaddition reactions of the N-heterocycles with heterocumulenes.

A bis(azetidine)palladium complex was isolated and shown to be catalytically active for the reaction of azetidines with heterocumulenes. Numerous heterocyclic compoounds have been prepared for the first time, some of them having the potential for pharmacological activity.

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ABBREVIATIONS

BCR	bifunctional conjunctive reagent
***n*-Bu**	*n*-butyl group
***t*-Bu**	*t*-butyl group
1,5-COD	1,5-cycooctadiene
COSY	shift correlation spectroscopy
***m*-CPBA**	*m*-chloroperbenzoic acid
d	doublet
dba	dibenzylidene acetone, $(PhCH=CH)_2CO$
dd	doublet of doublets
dm	doublet of multiplets
DEPT	distortionless enhancement by polarization transfer
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
E	entgegen
Et	ethyl group
FT-IR	Fourier-transform infrared
GC	gas chromatography
Eu(fod)3	tris(1,1,2,2,3,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium (III)
Eu(hfc)3	tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato], europium (III)
HMPA	hexamethylphosphoric triamide
hn	photolysis
IR	infrared spectroscopy

J	coupling constant, in Hz
L	ligand
Me	methyl group
MS	mass spectrometry
NMR	nuclear magnetic resonance
Nu^-	nucleophile
ORTEP	Oak Ridge thermal ellipsoid plot
Ph	phenyl group
ppm	parts per million, 10^{-6}
psi	pounds per square inch
P.T. agent	phase transfer agent
PTC	phase transfer catalysis
q	quartet
t	triplet
TMM	trimethylenemethane
TOPP	tris(o-phenylphenyl)phosphite
Yb(fod)3	tris(1,1,2,2,3,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)ytterbium (III)
Z	zusammen

CHAPTER 1

INTRODUCTION

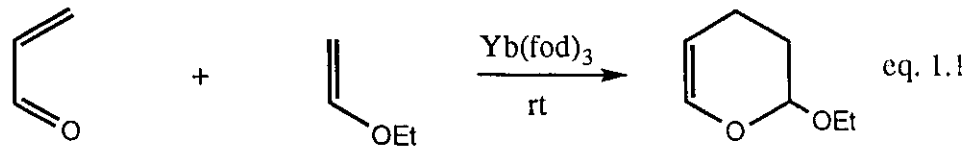
1.1 SELECTED TRANSITION METAL CATALYZED CYCLOADDITION REACTIONS.

The cycloaddition reaction is one of the most useful methods for the formation of cyclic compounds. For example, the Diels-Alder reaction (discovered in 1928[1]), i.e. the [4+2] cycloaddition of a diene and a dienophile, has become one of the most powerful carbon-carbon bond forming processes in organic chemistry. The last comprehensive survey of the Diels-Alder reaction was in 1991.[2] Since then, substantial gains in insight and methodology have been accomplished together with a body of creative and conceptually new applications in organic synthesis.

Cycloaddition reactions are concerted reactions. Also, any particular cycloaddition reaction is either thermally induced or photo induced, but not both.

Recent efforts have demonstrated that introduction of a metal catalyst can increase the yield and selectivity for cycloaddition under mild conditions. For instance, the [4+2] cycloaddition of simple α,β-unsaturated carbonyl compounds generally proceed only under vigorous thermal reaction conditions (150-250 °C) even when electron-rich dienophiles are employed.[3-8] Dimerization and

polymerization products are obtained as by-products. However, the reaction of α,β-unsaturated carbonyl compounds such as acrolein with ethyl vinyl ether in the presence of a transition metal catalyst ($Yb(fod)_3$) affords 2-ethoxy-3,4-dihydro-1,2-pyran in 80% yield at room temperature (eq. 1.1).[9, 10]



eq. 1.1

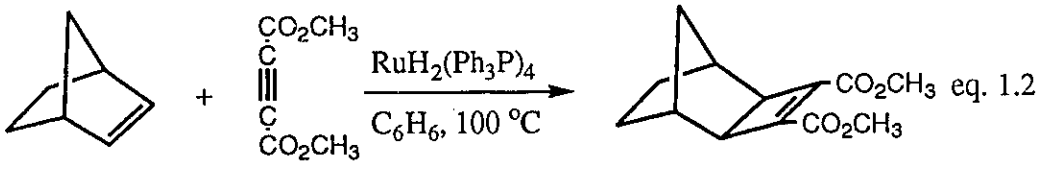
Transition metal complexes which are used as catalysts for cycloaddition reactions include those of iron, ruthenium, cobalt, rhodium, nickel, palladium, copper, europium and ytterbium.[11] One unique advantage of these transition metal-catalyzed reactions is the ability to modulate the selectivity of the cycloaddition by the judicious selection of the metal and its ancillary ligands. Most transition metal complexes used for cycloaddition reactions are either commercially available or readily prepared.[11] In most cases, these transition metal-catalyzed reactions require only routine oxygen- and moisture-free laboratory techniques.

In view of the extensive literature on cycloaddition reactions,[11, 12] this section will be limited to transition metal catalyzed cycloaddition processes that involve two components.

1.1.1 [2+2] CYCLOADDITION REACTIONS

The two plus two cycloaddition reaction of olefins is a valuable route to cyclobutane derivatives. The reaction is formally a thermally forbidden process[13], and the reaction is usually achieved photochemically.

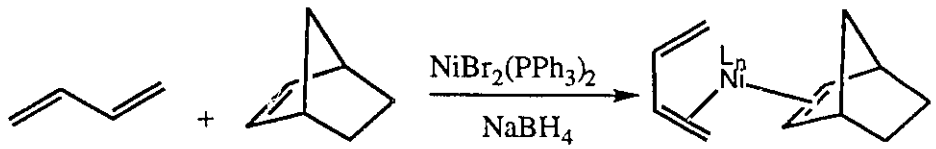
The photo-induced [2+2] cycloaddition of bicyclo[2,2,1]hept-2-ene (norbornene) with dimethyl acetylenedicarboxylate is an inefficient reaction (yield < 10%).[14] However, in the presence of a catalytic amount of $RuH_2(PPh_3)_4$, norbornene **1.1** readily reacts with an equimolar amount of dimethylacetylenedicarboxylate **1.2** in benzene at 100 °C to give the corresponding [2+2] cross-adduct dimethyl exo-tricyclo[4,2,1,0]non-3-ene-3,4-dicarboxylate **1.3** in 87% yield (eq. 1.2)[15].



eq. 1.2

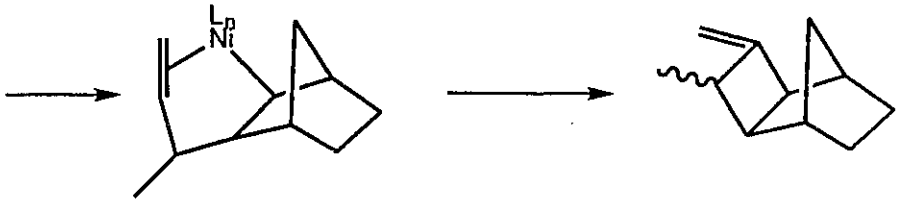
1.1 **1.2** **1.3**

Also, the Ni(II) catalyzed [2+2] cycloaddition of butadiene **1.4** with norbornene **1.1** gives the four-membered cross-coupling product **1.7** in 60% yield (eq. 1.3).[16]



1.4 **1.1** **1.5**

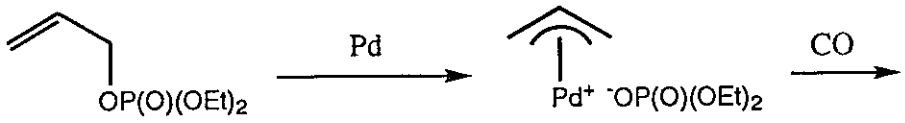
eq. 1.3



1.6 **1.7**

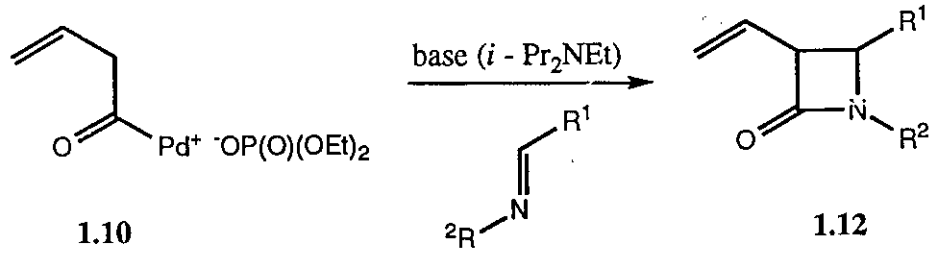
Kiji[17] suggested that the active species of the coupling reaction of **1.4** with **1.1** catalyzed by $NiBr_2(PPh_3)_2$ and $NaBH_4$ is a nickel hydride such as $HNiBr(PPh_3)_2$, and that the reaction proceeds through a π-nickel intermediate **1.5**. The π-nickel intermediate thus generated couples with a strained olefin coordinated to nickel to form an intermediate **1.6** which subsequently undergoes β-elimination to give the four-membered cross-coupling adducts **1.7**.

Another interesting example of a transition metal catalyzed [2+2] cycloaddition is the synthesis of β-lactam derivatives by palladium-catalyzed carbonylative [2+2] cycloaddition. The allyl diethyl phosphate **1.8** reacts with imines under CO pressure (30 atm) in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (2 mol%), PPh_3 (8 mol%) and amine (2 equiv) in THF (70 °C, 5 hours) to give β-lactams in 47-86% yield (eq. 1.4).[18]



1.8 **1.9**

eq. 1.4



1.10 **1.11** **1.12**

The phosphate **1.8** is known to undergo carbonylation *via* the π-allylpalladium complex **1.9**.[19, 20] The intermediate **1.10** contains acidic protons α to carbonyl which could be abstracted by a base.[21] The ketene or carbanion so formed can add to the imine **1.11** to give the lactam **1.12**. This approach, which has the advantage in that there is no need for acid or acid chloride, complements ketene-imine cycloaddition reactions.[22]

1.1.2 [3+2] CYCLOADDITION REACTIONS

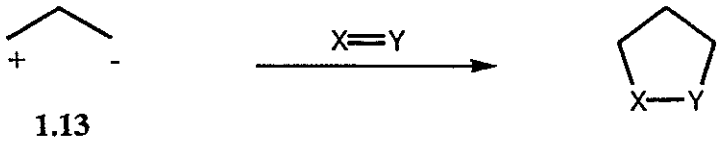
Five-membered ring systems are found in a large number of natural products and some are theoretically interesting molecules.[23] The development of methodologies for the construction of these systems has thus become a subject of great interest and intense effort for synthetic chemists.[24]

One particularly attractive approach to a five-membered ring is the [3+2] cycloaddition reaction. This reaction involves coupling of a three-carbon 4π unit directly with a two-carbon 2π unit, forming two C-C bonds in one operation. The net result is the rapid and efficient construction of complex cyclic structures from simple building blocks.

The main research efforts in transition metal catalyzed [3+2] cycloaddition can be catagorized into the development of two classes of C_3 synthons : dimethylenemethane and trimethylenemethane.

1.1.2.1 THE DIMETHYLENEMETHANE SYNTHONS

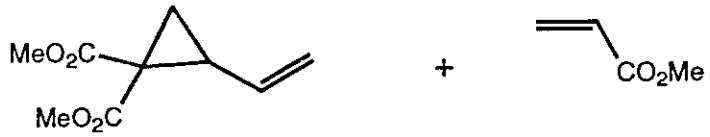
A [3+2] cycloaddition involving a dimethylenemethane **1.13** and an unsaturated receptor is depicted in equation 1.5.



1.13

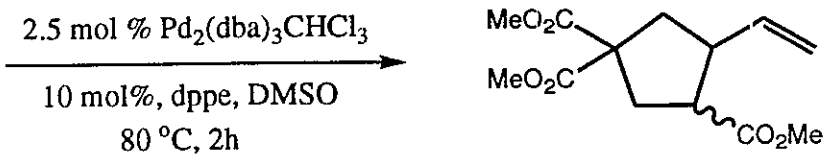
eq. 1.5

Tsuji and coworkers have developed a palladium-catalyzed cycloaddition reaction using electron-deficient vinylcyclopropanes.[24, 25] Thus, vinylcyclopropane **1.15** undergoes smooth cyclization with methyl acrylate in the presence of a palladium catalyst to give vinylcyclopentane **1.16** as a mixture of diastereoisomers (eq. 1.6).[24]



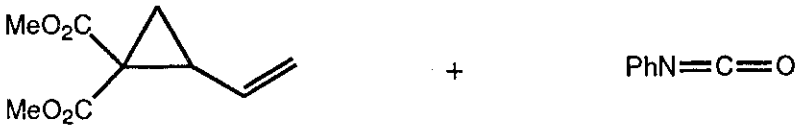
1.15

eq. 1.6



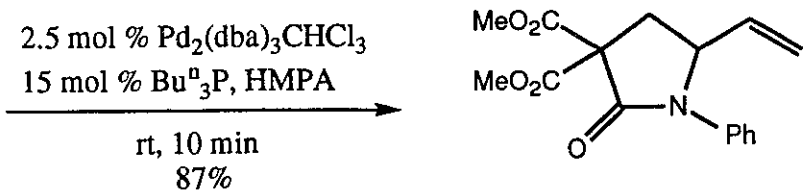
1.16

The zwitterionic π-allylpalladium complex, formed by treatment of the activated vinylcyclopropane **1.15** with a Pd(0) complex as a catalyst, also reacts with phenyl isocyanate (or diphenylketene) to form the five-membered cycloaddition product **1.17** in good yield (eq. 1.7).[25]



1.15

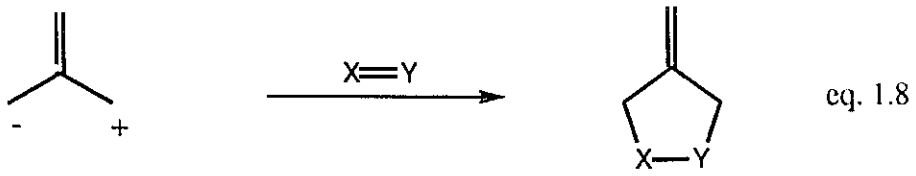
eq. 1.7



1.17

1.1.2.2 THE TRIMETHYLENEMETHANE SYNTHONS

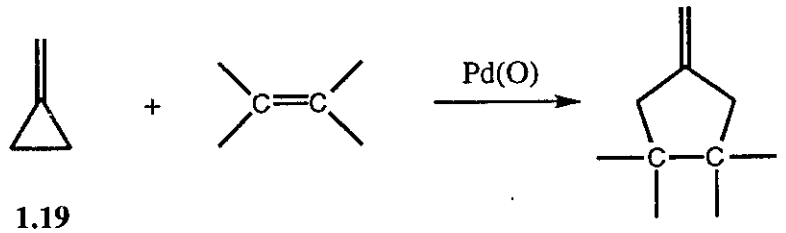
Trimethylenemethane (TMM ; **1.18**) represents a very useful synthon in the [3+2] cycloaddition approach to cyclopentanoids. In addition to contributing the three-carbon unit necessary for the ring formation, it also generates a methylene moiety useful for further synthetic elaboration (eq. 1.8). For example, the exocyclic alkene can be cleaved to generate a ketone carbonyl, or it can be transformed into a methyl group or a gem-dimethyl unit.



eq. 1.8

1.18

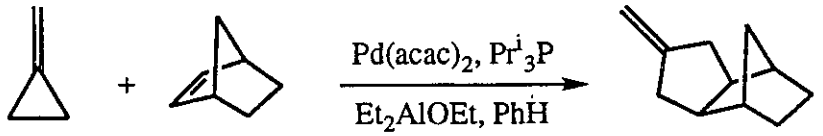
Methylenecyclopropane **1.19**, and its substituted derivatives, have been shown to function as TMM equivalents in the presence of a transition metal catalyst. Palladium(0) catalysts promote exclusive distal ring-opening cycloaddition of **1.19** with alkenes (eq. 1.9). The reaction is normally performed in an autoclave at elevated temperature in benzene or THF. The most effective catalyst system is a 1:1 mixture of a palladium(0) species and a hindered trialkylphosphine ligand, e.g. $^{i}Pr_3P$.[26] A thermally stable complex, such as bis(dibenzylideneacetone)palladium, can be employed as a source of Pd(0). The catalyst can also be generated by the *in situ* reduction of Pd(II) salts, e.g. $Pd(acac)_2$ + Et_2AlOEt, although (η^3-allyl)CpPd functions as a catalyst without any external reducing agent.[26]



eq. 1.9

1.19

A variety of alkenes can participate in the cycloaddition. Simple alkenes such as ethylene and allene will react to form methylenecyclopentane adducts. Facile cycloaddition reactions with strained alkanes are also observed.[27, 28] For example, norbornene reacts smoothly with methylenecyclopropane **1.19** to give only the exo adduct **1.20** in good yield (eq. 1.10).

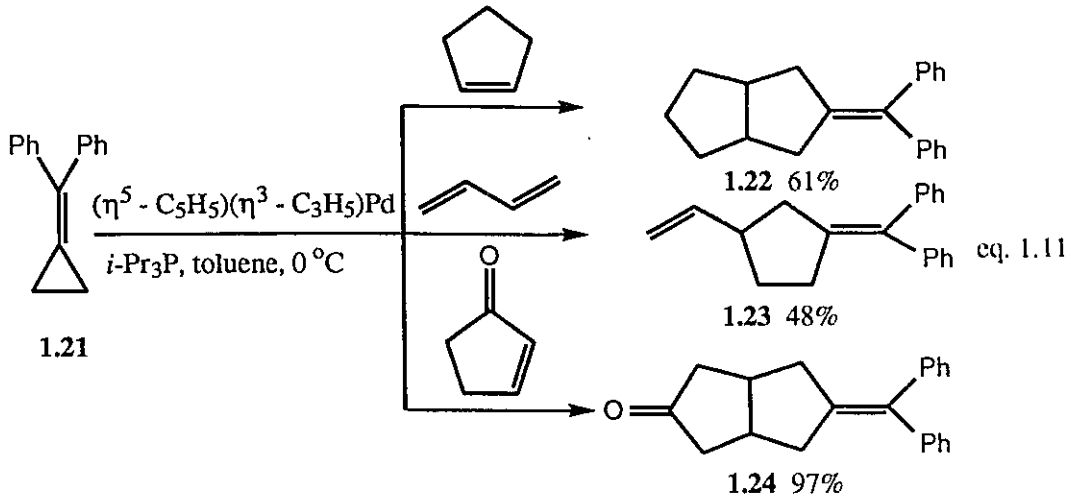


eq. 1.10

1.19 **1.1** **1.20**

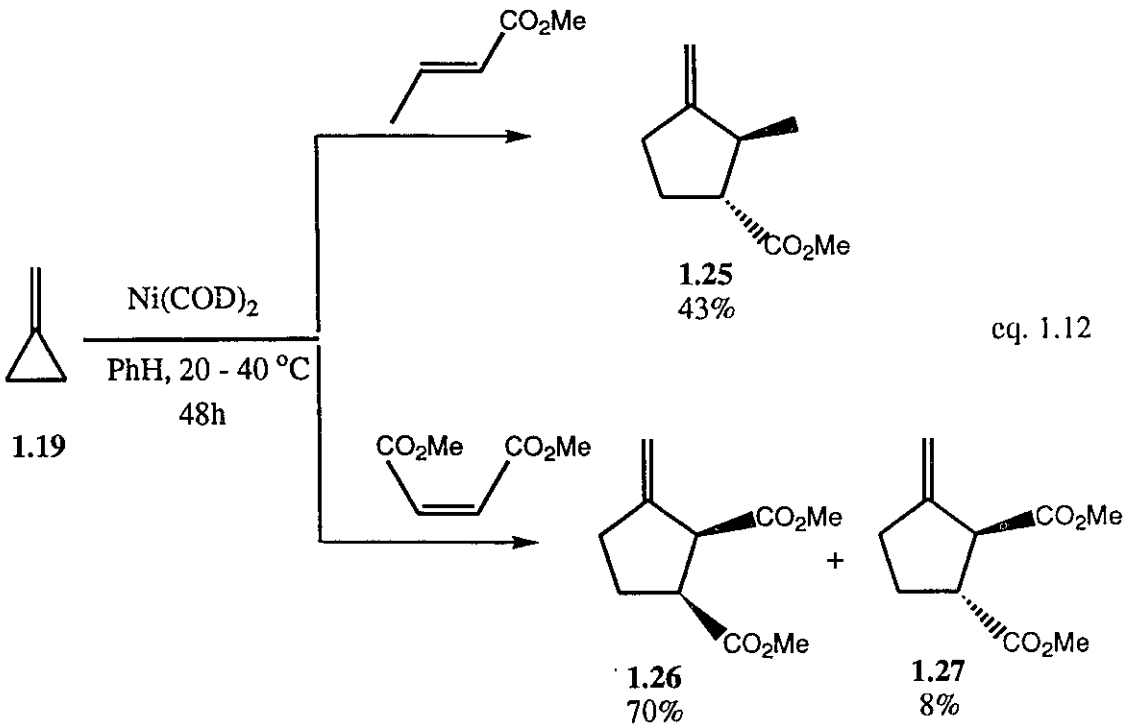
The palladium-catalyzed cycloaddition of substituted methylenecyclopropanes also proceeds *via* distal ring-opening. There is a propensity to form alkylidenecyclopentane adducts, regardless of the location of the substituent.

Diphenylmethylenecyclopropane **1.21** reacts faster than methylenecyclopropane **1.19** with cyclopentane, 1,3-butadiene or 2-cyclopentenone (eq. 1.11).[29]



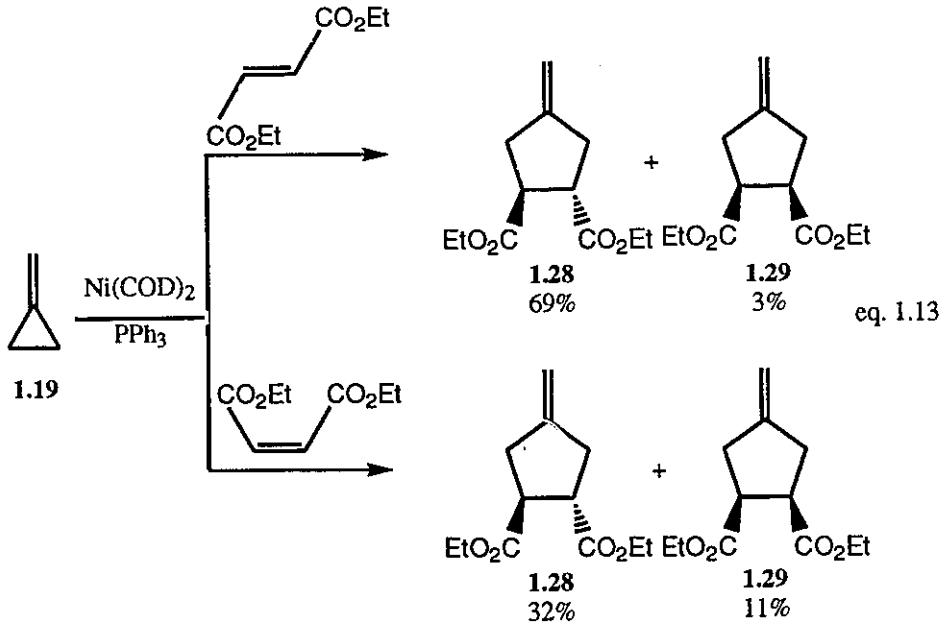
eq. 1.11

The reactions of methylenecyclopropane **1.19** with a Ni(0) catalyst are very sensitive to the nature of the ancillary ligands and that of the reacting alkene. A nickel catalyst, such as $Ni(COD)_2$ produces proximal ring-opening adducts with high stereospecificity (eq. 1.12).[30, 31]



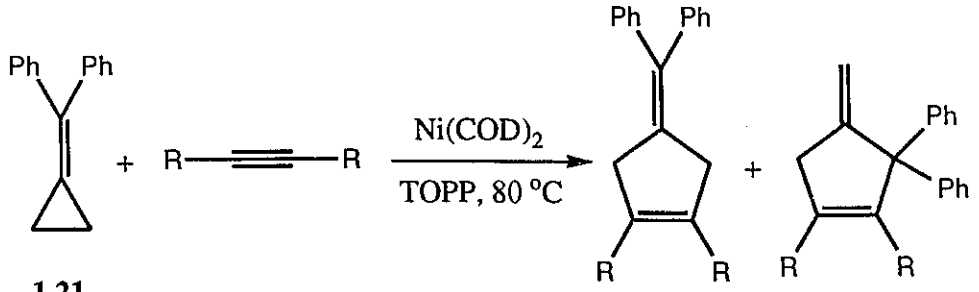
eq. 1.12

Reactions with phosphine- or phosphite-modified catalysts, e.g. $Ni(COD)_2$ + PPh_3, show lower stereospecificity and require higher reaction temperatures. In the case of fumarate and maleate this catalyst system promotes only distal ring-opening cycloaddition (eq. 1.13).[32]



eq. 1.13

The use of alkynes in transition metal catalyzed reactions is often complicated by their tendency to undergo cyclotrimerization and tetramerization. Thus, it is useful to note that phosphite-modified catalysts, $Ni(COD)_2$ / tris(*o*-phenylphenyl)phosphite (TOPP), promotes codimerization of an alkyne with diphenylmethylenecyclopropane.[33] Both electron-rich and electron-poor alkynes participate in cycloaddition with moderate regioselectivity (eq. 1.14).

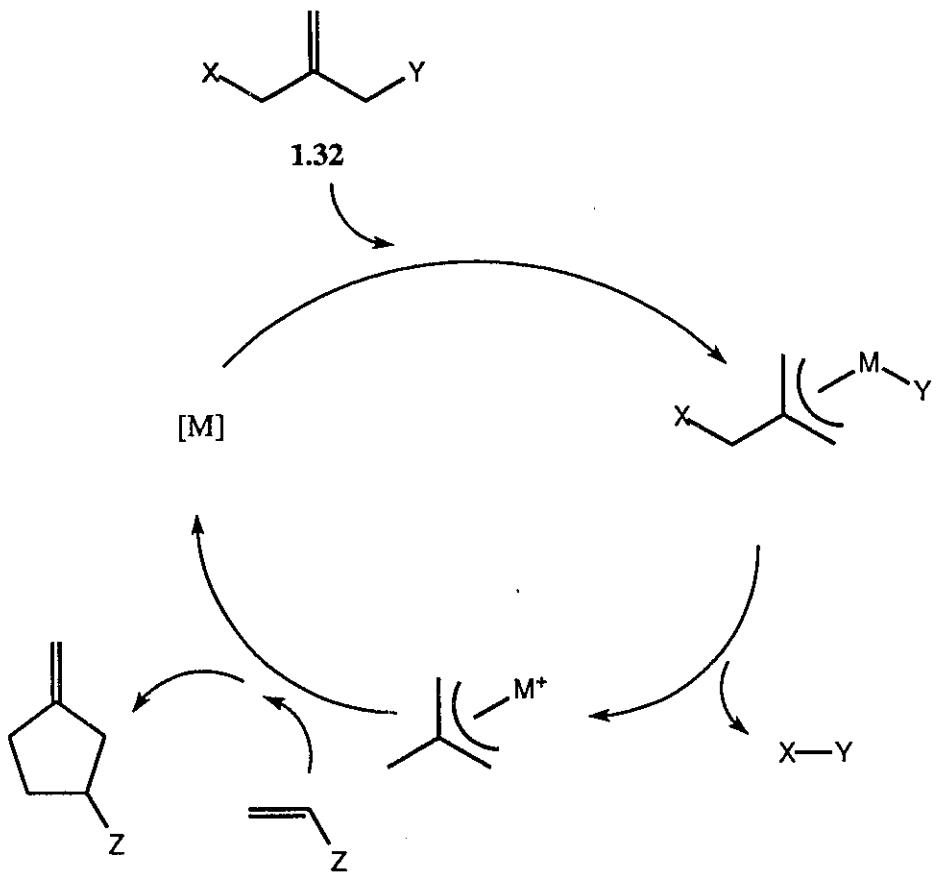


eq. 1.14

1.21

	1.30	**1.31**
R = Me	6%	89%
CH_2OSiMe_3	49%	37%
Me_3Si	34%	37%
Me_3Si, CO_2Me	63%	-

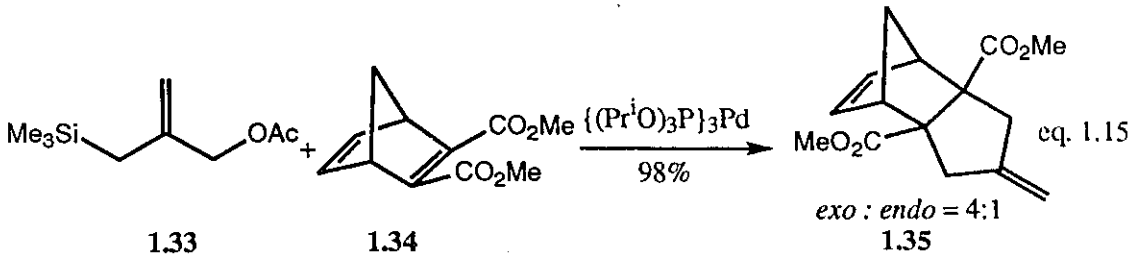
Bifunctional conjunctive reagents (BCRs), such as a 1,3-substituted 2-methylenepropane **1.32**, can serve as effective trimethylene-methane synthons *via* transition metal catalysis. In this case, the transition metal complex can promote the elimination of the elements X-Y from **1.32** to form a coordinated trimethylene-methane synthon species. Cyclization of this intermediate with an alkene thus produces the methylenecyclopropane product and also regenerates the catalyst (Scheme 1.1).[34]



Scheme 1.1

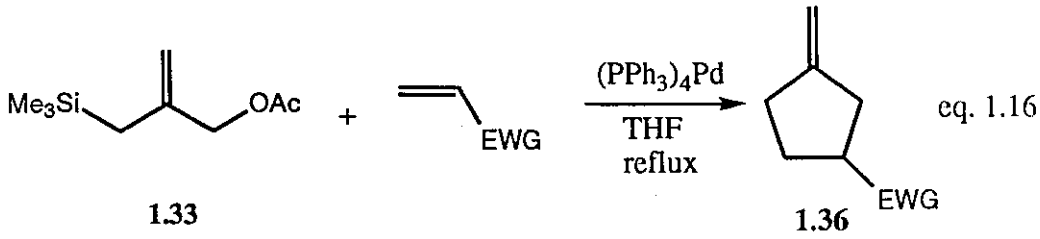
The use of BCR methodology for the trimethylenemethane synthon was first demonstrated by Trost and Chan using a Pd(0) catalyst and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **1.33** as the bifunctional prototype.[36, 37] The Pd(0)-catalyzed [3+2] cycloaddition reactions of **1.33** exhibit very different selectivities from those of the corresponding methylenecyclopropane codimerizations. One major distinction is the chemoselectivity : only electron-deficient alkenes will react to form methylenecyclopentane. The nucleophilic nature of this trimethylenemethane synthon is

indicated by the exclusive annulation of the electron-poor double bond of 2,3-dimethoxycarbonylnorbornadiene (eq. 1.15).[35]



1.33 1.34 1.35

The cycloaddition is normally performed by heating a solution of the silylacetate with an electron-deficient alkene in the presence of 0.1-9 mol% of a palladium catalyst in an appropriate solvent, such as THF, toluene, DME, DMF or acetonitrile.[37] The commercially available (PPh3)4Pd is a good catalyst for this reaction (eq. 1.16).[36]



1.33 1.36

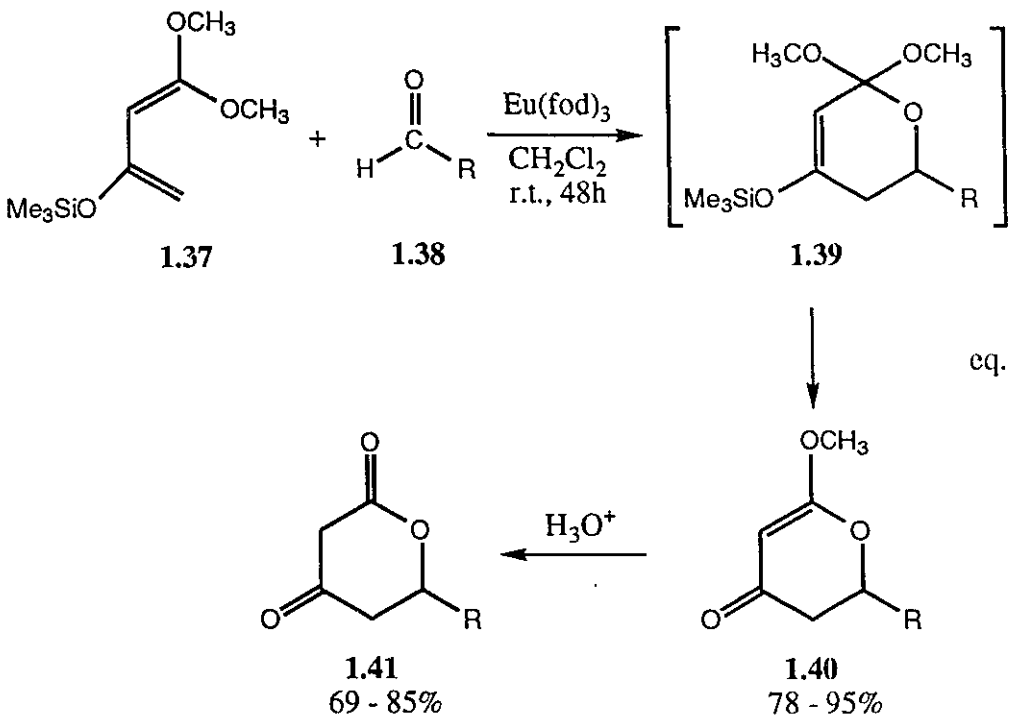
EWG = CO_2Me	68%
= COMe	30%
= CN	35%

A wide range of alkenes possessing a ketone, ester, cyano, sulfoxide or sulfone function have been shown to react under the

noted conditions.[35] Thus, this annulation procedure is compatible with many reactive functional groups, with even a broader scope of reactivity than the methylenecyclopropane codimerization.

1.1.3 [4+2] CYCLOADDITION REACTIONS

The Diels-Alder reaction, the best known [4+2] cycloaddition reaction, is a symmetry-allowed process, and therefore readily occurs in the absence of UV-irradiation and catalysts.[12] For this reason, only a limited number of examples of transition metal-catalyzed Diels-Alder ([4+2] cycloaddition) reactions are known.[37] Of particular interest is the application of lanthanide shift reagents as mild Lewis acids.[37-39] Because the [4+2] cycloaddition of simple α,β-unsaturated carbonyl compounds needs vigorous reaction conditions which require heating the solutions in sealed tubes at high temperature, the reactions give yields ranging from poor to fair.[40-42] Compared to these non-catalytic [4+2] cycloaddition reactions, lanthanide-catalyzed cycloadditions occur under mild reaction conditions and give high yields of products. For example, Castellino and co-workers reported the preparation of β-oxo-δ-lactones **1.41** by the $Eu(fod)_3$ catalyzed [4+2] cycloaddition reaction between aldehydes **1.38** and bis-1,1-dimethoxy-3-trimethylsiloxy-1,3-butadiene **1.37** (eq. 1.17).[38] The reaction occured at room temperature to give β-oxo-δ-lactones **1.41** in 69-87% yield.



1.37 **1.38** **1.39**

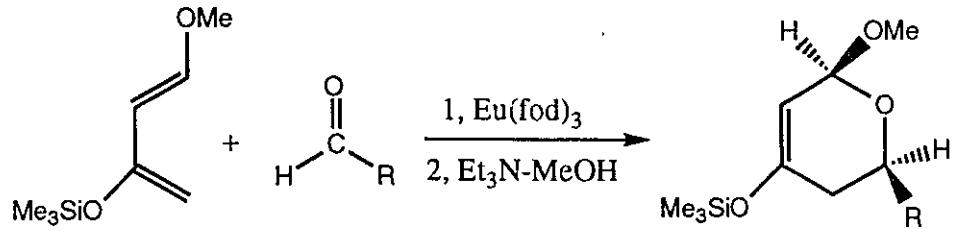
eq. 1.17

1.41
69 - 85%

1.40
78 - 95%

(R = $-CO_2CH_3$, $-C_6H_5$, $-CH(CH_3)_2$)

Danishefsky and co-workers have also demonstrated the utility of lanthanide catalysts in the hetero-Diels-Alder reaction between siloxydiene **1.42** and various aldehydes **1.43** (eq. 1.18).[39]



1.42 **1.43**

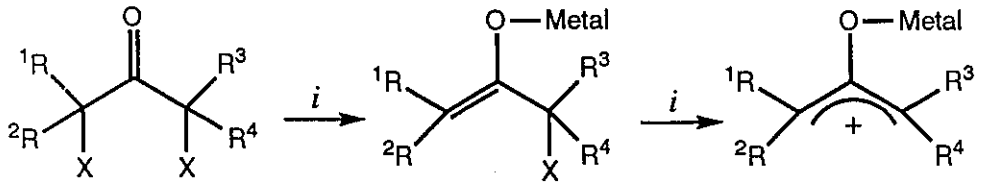
1.44
82-94%

eq. 1.18

(R = $-C_6H_5$, 2-furyl, *trans*-styryl)

1.1.4 [4+3] CYCLOADDITION REACTIONS

Seven-membered ring carbocycles are an important class of organic compounds that are of practical and theoretical interest. Before discovery of the [4+3] cycloaddition reaction, methods for preparing seven-membered carbocycles were limited to enlargement of six-membered rings in some cyclization reactions.[43] Recently, various routes to reactive three-carbon species (allylic cations) have been developed and therefore [4+3] cycloadditions using these species have come to be widely investigated. The most common reactive three carbon units (allylic cations) for [4+2] cycloadditions are 2-oxylallyl cations **1.47** usually prepared by the reaction of α, α'-dihalo ketones **1.45** with reducing agents (eq. 1.19). Initially, halogenated metal enolates of type **1.46** are formed and oxyallyl cations **1.47** are then generated by subsequent elimination of halide ion.



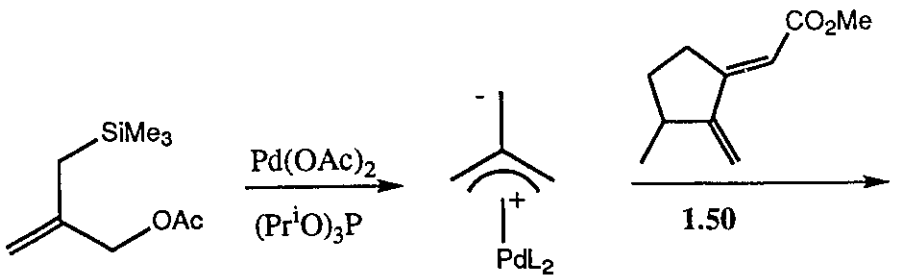
eq. 1.19

1.45 **1.46** **1.47**

X = Cl, Br

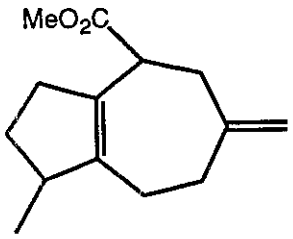
i = Cu/NaI[44], $Zn/B(OEt)_3$[45], Zn-Cu/DME[46], Fe_2CO_9[47], NaI/Me_2CO or MeCN[48]

Few examples of transition metal catalyzed [4+3] cycloaddition reactions have been reported in the literature. Recently, Trost demonstrated the [4+3] cycloaddition of trimethylenemethane fragments by palladium-catalyzed reaction of 2-(trimethylsilylmethyl)allyl acetate **1.48** with an electron-deficient diene[49, 50] to give the methylenecycloheptane **1.51**. These interesting reagents have been reviewed by Trost.[50]



1.48 **1.49** **1.50**

eq. 1.20

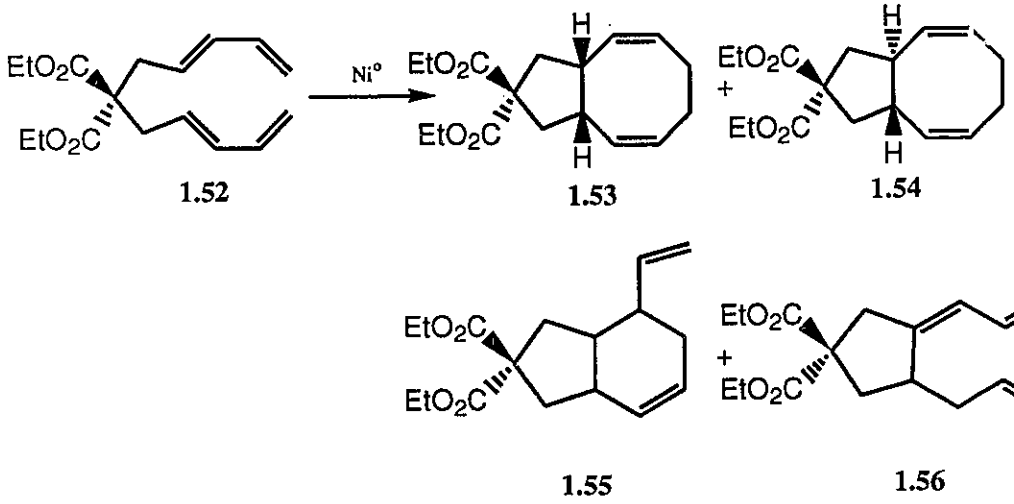


1.51

1.1.5 [4+4] CYCLOADDITION REACTIONS

The [4+4] cycloaddition reaction is one of the simplest methods for the formation of the eight-membered rings. However, [4+4] cycloaddition reactions are generally photo induced transformations,

[51, 52] which are characterized by relatively low yields of products and the formation of many kinds of different photochemical byproducts. [53-55] Therefore, direct application of this cycloaddition method to natural product synthesis is rare. The use of transition metal catalysts for [4+4] cycloaddition reactions has resulted in a number of useful advantages in the synthetic application of these cycloaddition reactions. For instance, treatment of tetraene **1.52** in toluene at 60 ^{0}C with 11 mol% $Ni(COD)_2$ and 33 mol% PPh_3 gave cyclooctadienes **1.53** and **1.54** (19 : 1, respectively) in 70 % yield. The products of six-membered ring formation **1.55** and of β-hydride elimination **1.56** were also obtained in 2.6 % and 12 % yields respectively (eq. 1.21). [56, 57]



1.52 **1.53** **1.54**

eq. 1.21

1.55 **1.56**

Even though examples of this type of reaction are limited, the above serve as models for fundamentally new approaches to several structural classes including taxanes, ophibolins, and fusicoccins. [58-60]

1.2 CYCLOADDITION REACTIONS OF 3- AND 4-MEMBERED RING HETEROCYCLES AND HETEROCUMULENES

The analysis of literature data on transition metal-catalyzed cycloaddition reactions clearly shows that they represent a powerful and versatile tool in organic synthesis, which enables one to obtain a large variety of cyclic products. As previously noted, strained-ring carbocyclic molecules (e. g. cyclopropanes) are also able to serve as participants in cycloadditon reactions (see Section 1.1.2) leading to heterocyclic products. Similar reactions involving small-ring heterocycles are of interest since they may provide a convenient one-step route to both known and novel heterocyclic systems containing two or more heteroatoms.

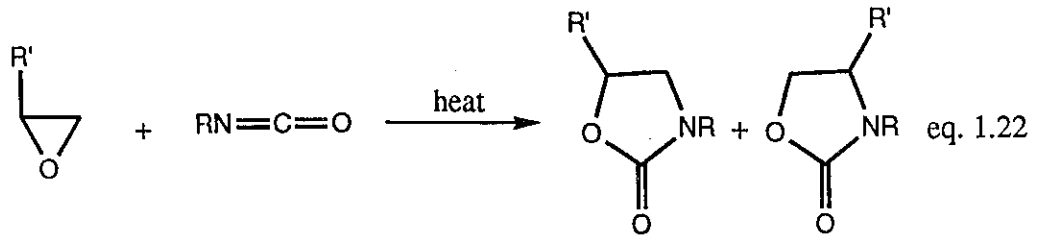
This section describes cycloaddition reactions of N-, O-, and S-containing 3- and 4-membered ring heterocycles with heterocumulenes.

1.2.1 CYCLOADDITION REACTIONS OF 3-MEMBERED RING HETEROCYCLES AND HETEROCUMULENES

Oxiranes and Thiiranes

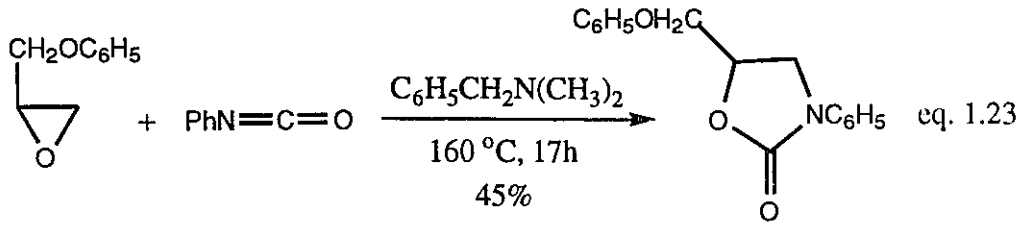
The chemical behaviour of oxiranes is governed by two factors: the strain in the ring and the basicity of the ring.[61] The extent to which these two factors contribute to the reactivity, either separately or jointly, can be assessed from the results of the chemical behaviour of the heterocycles.

In particular, cycloaddition reactions of oxiranes with heterocumulenes usually occur by the heterolytic cleavage of the C-O bond of the oxirane ring. For example, the 1,3-cycloaddition of organic isocyanates to oxiranes affording 2-oxazolidinones has been extensively studied because of the potential biological activity of 2-oxazolidones.[62] Non-catalytic cycloaddition reactions of unsymmetrical epoxides **1.57** with isocyanates **1.58** usually occurred under relatively vigorous reaction conditions (reaction temperature ca. 150 °C or higher) and gave not only 4-substituted 2-oxazolidinone **1.59**, but also 5-substituted 2-oxazolidinone **1.60** (eq. 1.22).[63-66]



1.57 **1.58** **1.59** **1.60**

Better yields and regioselectivities can be achieved by the introduction of catalysts. Phenylglycidyl ether **1.61** reacts with phenyl isocyanate **1.62** in the presence of a catalytic quantity of benzyldimethylamine to selectively form the 1 : 1 cyclic adduct, 5-phenoxylmethyl-3-phenyloxazolidin-2-one **1.63** in 45 % yield (eq. 1.23).[67] Yields for this type of reaction can be improved by

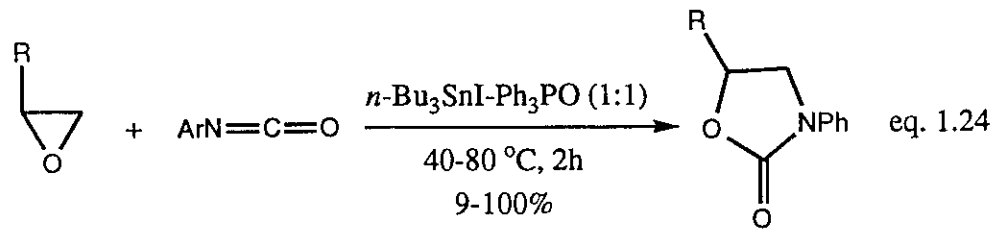


eq. 1.23

1.61 **1.62** **1.63**

the use of hydrocarbon-soluble adduct of lithium bromide and tributylphosphine oxide. [68, 69]

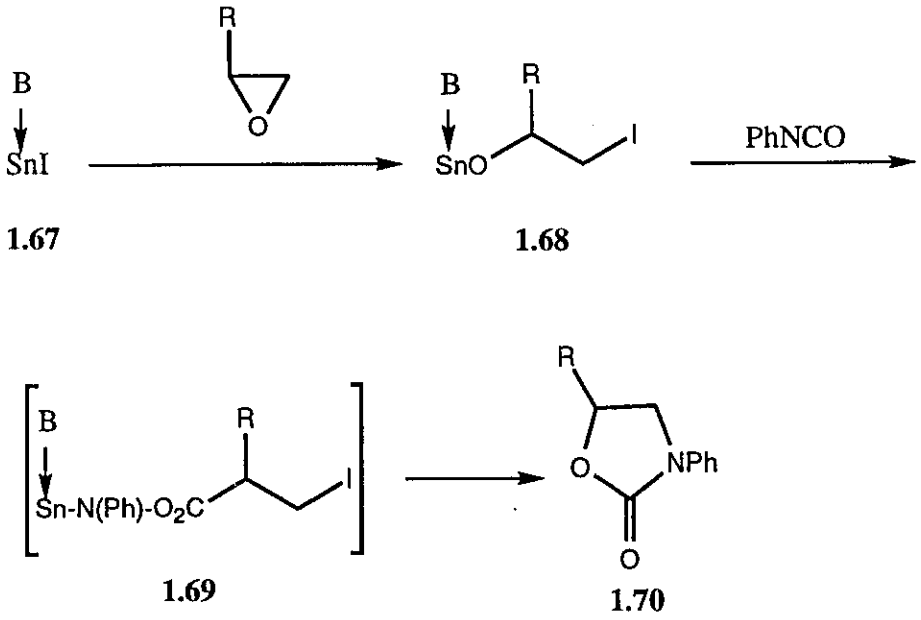
Shibata and coworkers have reported that organotin halide - Lewis base complexes are good catalysts for the cycloaddition of phenylisocyanate with oxiranes and afford good yields of 2-oxazolidinones under mild and neutral conditions. The catalysts are sufficiently active that reaction of PhNCO with oxiranes gave a variety of 2-oxazolidinones without appreciable trimerization of phenylisocyanate (eq. 1.24). [70]



1.64 **1.65** **1.66**

(R = CH_3, C_2H_5, C_2H_4Cl, C_6H_5, CH_2=$CHCH_2OCH_2$, $C_6H_5OCH_2$, Ar = Ph)

The following mechanism for this reaction was proposed by Shibata (Scheme 1.2).



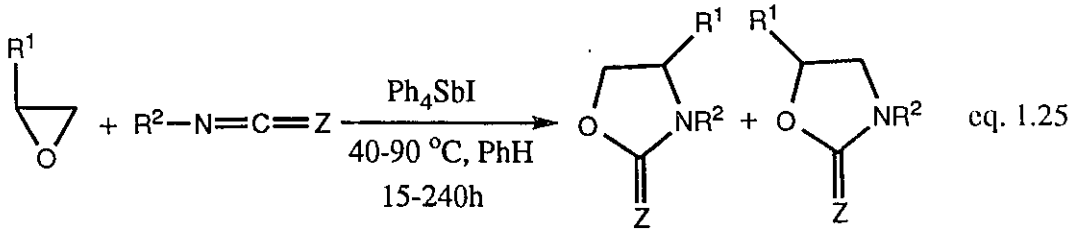
1.67 **1.68**

1.69 **1.70**

B = Ph_3PO

Scheme 1.2

Under mild conditions tetraphenylstibonium iodide catalyzed cycloaddition of oxiranes with isocyanates or carbodiimides afforded 3,4-disubstituted oxazolidin-2-ones (**1.71** or **1.72**) in 53 - 100 % yields and oxazolidin-2-imines (**1.73** or **1.74**) in 48 - 100 % yields respectively (eq. 1.26).[71] Also a catalytic amount of Ph_4SbI



eq. 1.25

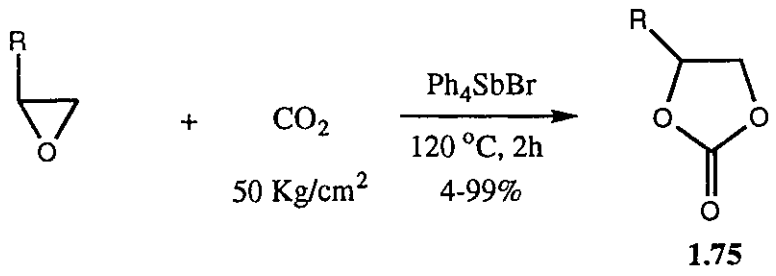
Z = O **1.71** **1.72**

Z = N-R^3 **1.73** **1.74**

(R^1 = CH_3, C_2H_5, C_6H_5, $C_6H_5OCH_2$, $CH_3CO_2CH_2$, CH_2=$CHCH_2OCH_2$, CH_2=CH, R^2 = C_6H_5, *p*-ClC_6H_4, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *n*-C_4H_9, CH_2=$CHCH_2$, R^3 = C_6H_5, *n*-C_4H_9)

promoted the cycloadditon of dialkylketenes with oxiranes to give γ-lactones and cyclic ketene acetals in 42 - 100 % yields.[72]

Oxiranes also react with carbon dioxide in the presence of Lewis acid catalysts such as organoantimony compounds, to form cyclic carbonates **1.75** in good yield (eq. 1.26).[73, 74]



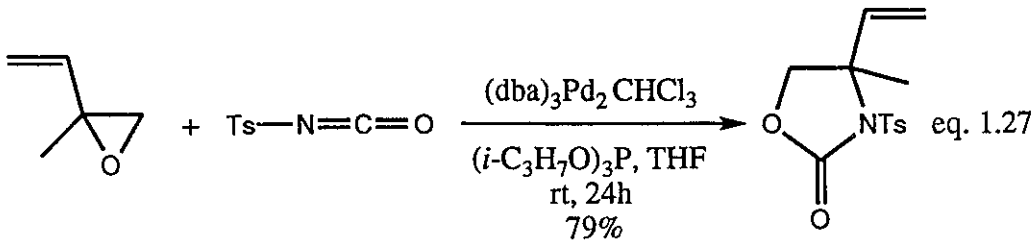
eq. 1.26

1.75

(R = H, CH_3, CH_2Cl, C_6H_5)

The cycloaddition of CO_2 and oxiranes was significantly improved when a mixture of zinc chloride and tetrabutylammonium iodide ($ZnCl_2$ / nBu_4NI = 0.2 : 0.4) was used as the catalyst system at ambient temperature and pressure.[75]

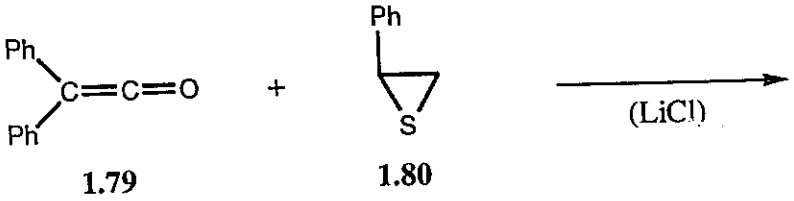
Vinyl oxazolidin-2-ones were synthesized by palladium(0)-catalyzed cycloaddition of vinyl oxiranes and isocyanates. 2-Methyl-2-vinyloxirane reacts with *p*-toluenesulfonyl isocyanate in the presence of $(dba)_3Pd_2.CHCl_3$ (1 mol %), and triisopropyl phosphite (1.2 mole %) in THF (room temperature, 24 h) to give the oxazolidin-2-one in 79 % yield (eq. 1.27).[76]



eq. 1.27

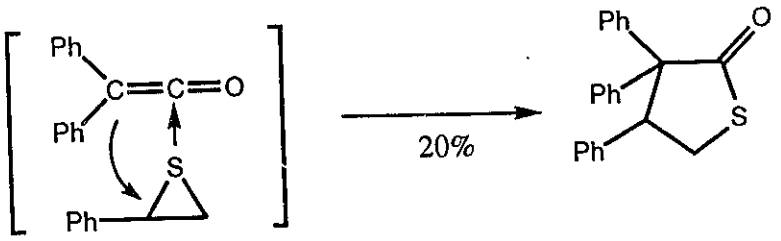
1.76 **1.77** **1.78**

There are some examples of cycloaddition reaction of thiiranes with heterocumulenes. The reaction of diphenylketene **1.79** with phenylthiirane **1.80** with (or without) the addition of LiCl as the catalyst results in the isolation of 2,3,3-triphenyl-γ-thiolactone (eq. 1.28).[77]



1.79 **1.80**

eq. 1.28

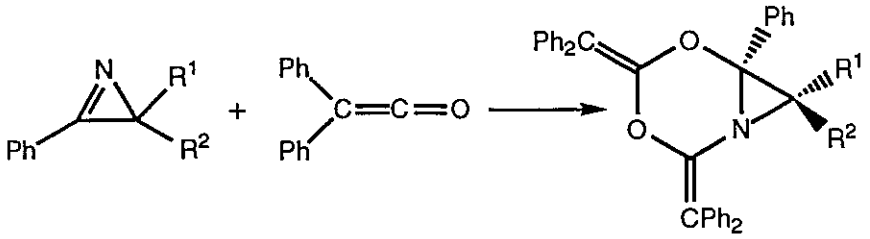


1.81 **1.82**

Interestingly, in the reactions of diphenylketene with chloromethylthiirane, ethoxymethylthiirane, or the parent thiirane, a γ-thiolactone was not isolated; rather, only polymeric materials were produced.

2H-Azirines

Hassner and coworkers reported that 2H-azirines **1.83** react with diphenylketene **1.79** to form the 1 : 2 adducts **1.84** (eq. 1.29) [78-80]

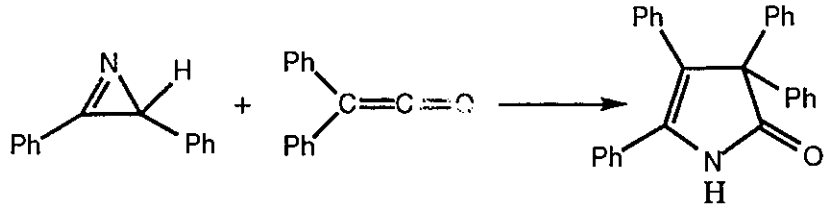


eq. 1.29

1.83 **1.79** **1.84**

(R^1 = H, CH_3, R^2 = H, CH_3)

However, 2,3-diphenyl-2H-azirine **1.85** reacted with diphenylketene to give a 1 : 1 adduct **1.86** (eq. 1.30).

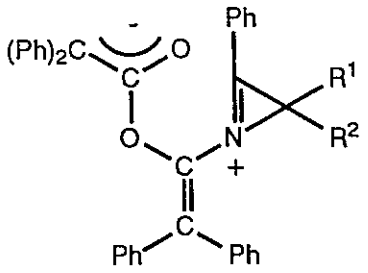


eq. 1.30

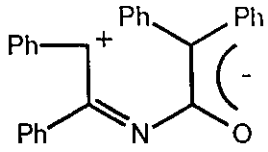
1.85 **1.79** **1.86**

In the previous case, the formation of **1.84** proceeds via the intermediacy of a reactive azirinium ion **1.87**. The 1 : 1 adduct **1.86**

observed in the case of 2,3-diphenyl-2H-azirine **1.86** was interpreted as resulting from the intermediate **1.88**, where the presence of the 3-phenyl substituent in the azirine stabilizes the cationic site resulting in the initial monoaddition to ketene.

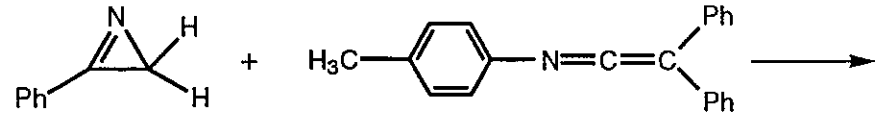


1.87

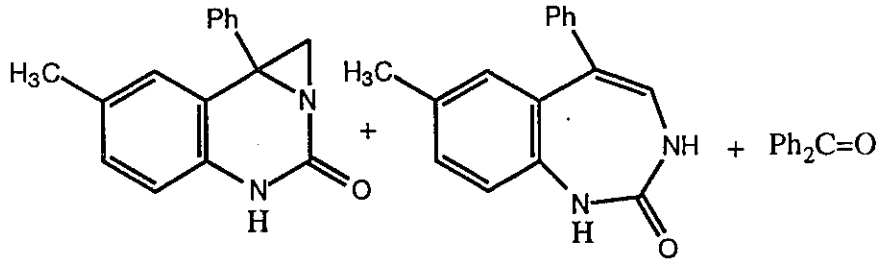


1.88

Ketenimine **1.90** reacts with 2-phenyl-2H-azirine **1.89** in refluxing benzene to give a mixture of the bicyclic aziridine **1.91** (15 %), the benzodiazepinone **1.92** (15 %), and benzophenone **1.93** [81] The benzodiazepinone **1.92** is a secondary product of this reaction and is produced from the thermal rearrangement of **1.91** (eq. 1.31).



1.89 **1.90**

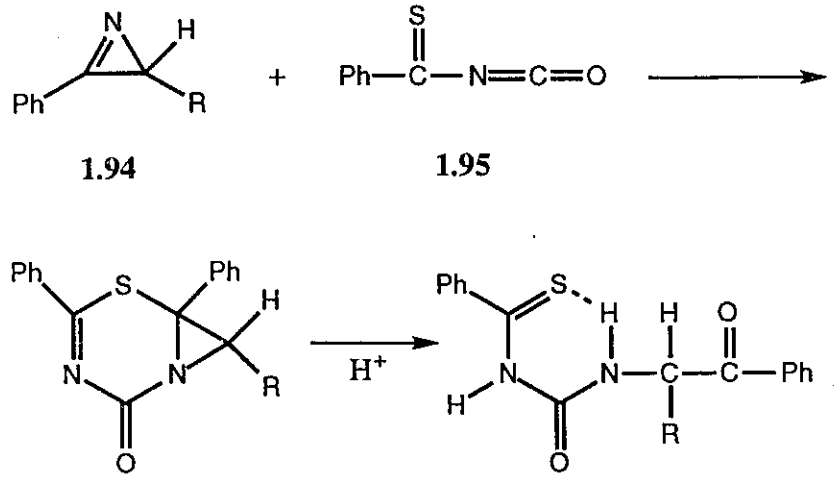


eq. 1.31

1.91 **1.92** **1.93**

Heterocumulenes containing a carbonyl or related unsaturation adjacent to the cumulative bonds usually possess high reactivity, and Nair and Kim first described the interesting reactions of 2H-azirines with such isocyanates.[82, 83]

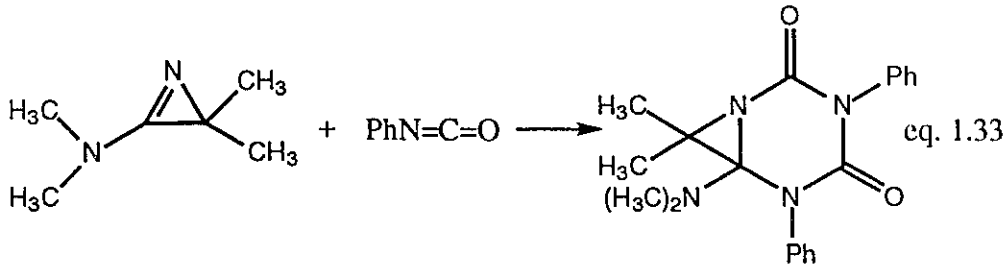
Thiobenzoyl isocyanate **1.95** can be generated from 2-phenylthiazoline-4,5-dione by thermal extrusion of carbon monoxide. Isocyanate **1.95**, prepared in situ, adds stereospecifically and regiospecifically at room temperature to give bicyclic aziridines **1.96** in high yields.[82, 83] The aziridines **1.96** undergo facile acid-catalyzed hydrolysis to the urea **1.97** providing excellent evidence for the regiospecificity of these cycloadditions (eq. 1.32).



eq. 1.32

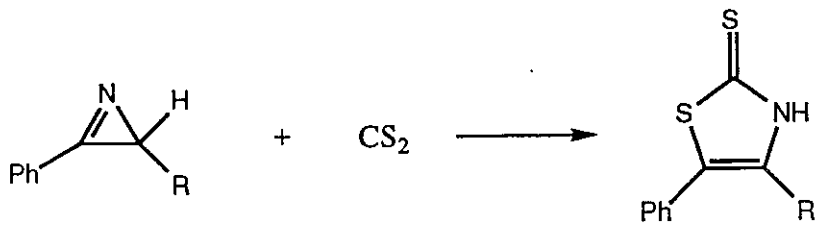
The behavior of benzoyl isocyanate toward 2H-azirines paralleled those observed with thiobenzoyl isocyanate, and consequently [4+2] cycloadducts were isolated.[83] Benzoyl isothiocyanate and 2-pyridyl isothiocyanate reacts with 2H-azirines in a [2+2] fashion across the C=S bond to form thiazoles as the final products.[83, 84]

Simple aryl isocyanates, while unreactive toward 2-aryl-2H-azirines, do undergo cycloaddition with 2-amino-2H-azirine to give the 2 : 1 adduct (eq. 1.33). [85, 86]



1.98 **1.99** eq. 1.33

Carbon disulfide is a simple heterocumulene, and most of its reactions proceed from initial nucleophilic attack on the central carbon.[87] For example, 2-phenyl-2H-azirine **1.94** (R = H) and 3-methyl-2-phenyl-2H-azirine **1.94** (R = CH_3) react with carbon disulfide in a sealed tube at 100 °C to give the thiazoles **1.100**. These products are the result of regiospecific cycloaddition of CS_2 to the π bond of the 2H-azirines (eq. 1.34).[88] In general, cycloaddition



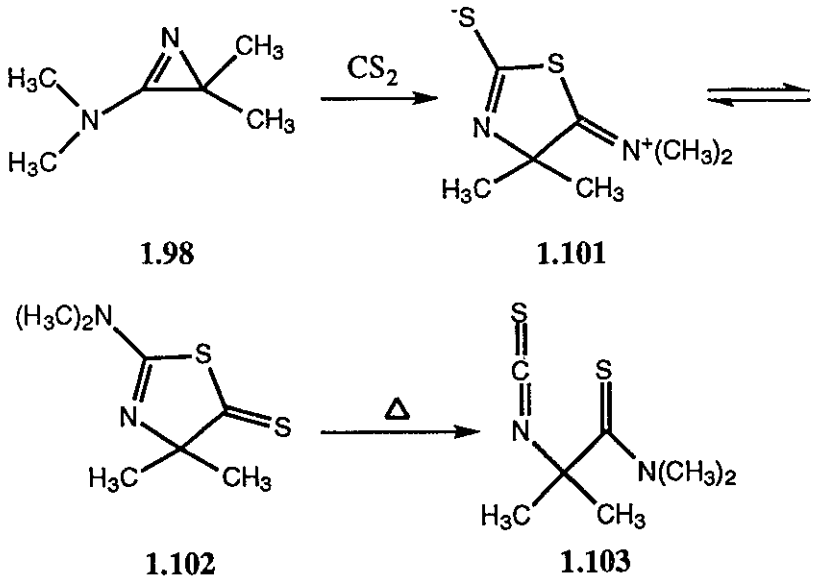
eq. 1.34

1.94 **1.100**

(R = H, CH_3)

of 2-phenyl-2H-azirine with heterocumulenes containing the C=S bond proceeds through a dipolar transition state where the ability of sulfur to stabilize the negative charge results in a lower energy pathway to the cycloadducts.

2-Amino-2H-azirines react differently with carbon disulfide. For instance, 2-dimethylamino-3,3-dimethyl-2H-azirine **1.98** reacts smoothly with carbon disulfide to give crystals that have the dipolar structure **1.101**. In solution, the isomeric form **1.102** is the predominant structure. Thermolysis of the adduct leads to **1.103** in high yield (eq. 1.35). [89, 90]



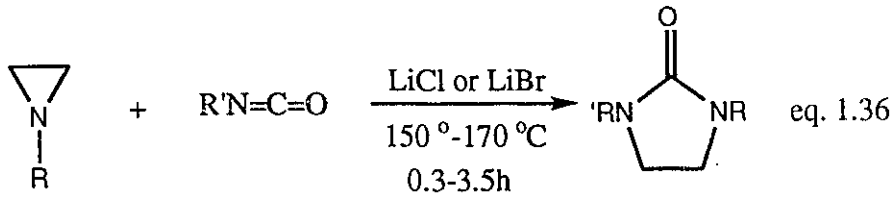
1.98 **1.101**

eq. 1.35

1.102 **1.103**

Aziridines

The ring opening of aziridines usually occurs by acid, catalysis or nucleophilic addition.[91] For example, aziridines bearing strong electron-accepting groups (Ar, CN, RCO, RSO_2, etc.) on nitrogen undergo direct nucleophilic ring opening. The aziridines that do not bear such substituents require very strong nucleophiles or vigorous reaction conditions for ring opening. For instance, the reactions of N-substituted aziridines **1.104** with isocyanate **1.105**, in the presence of a catalytic amount of a lithium halide such as LiCl or LiBr, at 150-170 °C affords imidazolidinones (eq. 1.36). [92]

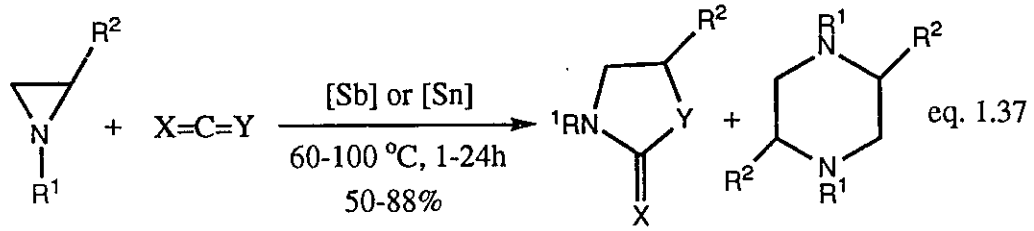


1.104 **1.105** **1.106** eq. 1.36

(R = benzyl, *p*-nitrophenyl, ethoxycarbonyl, R' = Ph, benzoyl, *p*-tosyl, cyclohexyl)

However, in the presence of catalytic amounts of organoantimony(V) halides such as Ph_4SbI, Ph_4SbBr, Ph_4SbBr_2 and Ph_4SbCl_2, the cycloaddition of aziridines **1.107** with heterocumulenes **1.108** (phenyl isocyanate, carbon disulfide and

carbon dioxide) selectively give ring-expanded cycloadducts **1.109** by α-cleavage of the aziridine rings under mild reaction conditions (eq. 1.37). [93, 94]



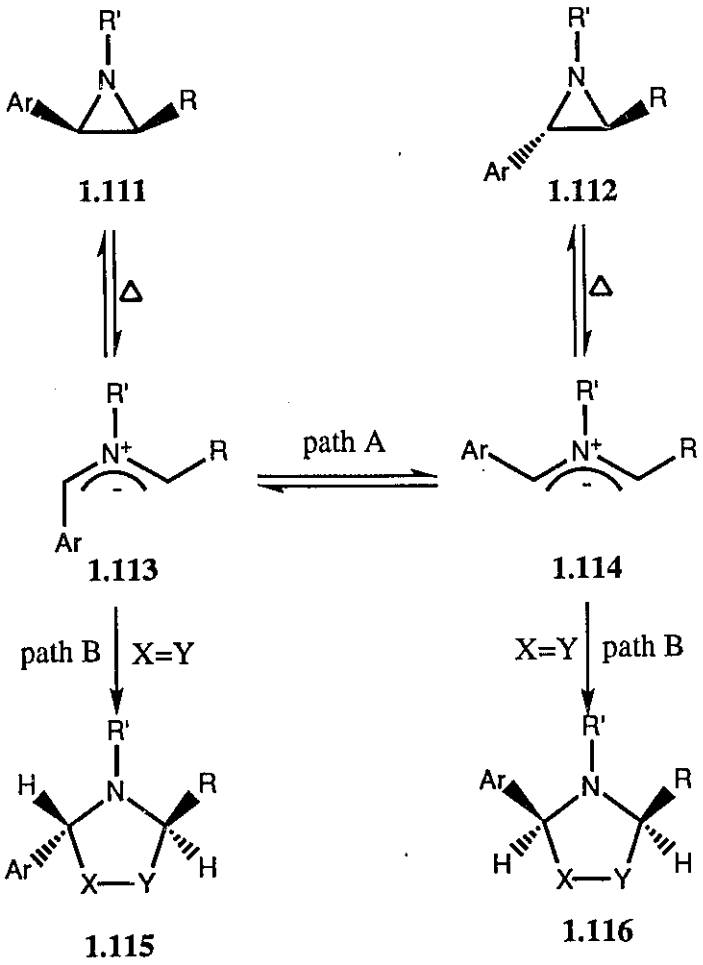
1.107 **1.108** **1.109** **1.110** eq. 1.37

(R^1 = Ph, *n*-Bu, R^2 = H, Me, Et)

When tributyltin iodide (nBu_3SnI) was used as a catalyst, dimers of aziridines were also obtained as by-products. These results can be explained by considering the relative Lewis acid strengths of antimony halides and organotin halides. Due to the higher Lewis acidities of organotin halides compared to organoantimony halides, the interaction between organotin catalysts and aziridines is stronger than that between organoantimony halides and aziridines. Thus, organotin halides as Lewis acids activate aziridines to dimerization. In contrast, organoantimony halides could not activate aziridines themselves and selectively promote the cycloaddition by α-cleavage of aziridine rings.

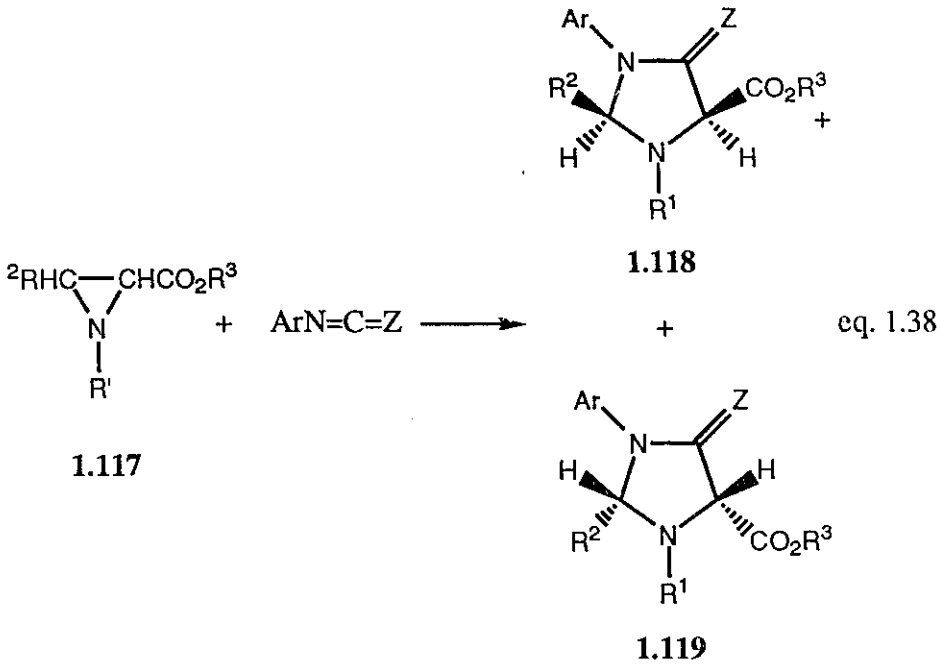
The thermal process of ring cleavage of trisubstituted aziridines involves stereospecific, conrotatory ring opening. [95] Thus, trisubstituted aziridines **1.111** and **1.112** would be expected to yield the azomethine ylides **1.113** and **1.114**, respectively. The ylides can either equilibrate and ring close back to the aziridines (path A) or, in the presence of an unsaturated substrate, undergo cycloaddition reaction to form five-membered ring heterocycles (path B-Scheme 1.3). [96]

Isocyanates [97] or isothiocyanates [98] also react with 2-alkoxycarbonylaziridines **1.117**, which are potential azomethine ylides, to produce five-membered ring heterocycles **1.118** and **1.119** (eq. 1.38).



(R' = C_6H_{11}, *i*-C_3H_7, R = CH_3O_2C, Ar = *p*-$C_6H_5C_6H_4$)

Scheme 1.3



(R^1 = Ph, C_6H_{11}, $(CH_2)CH$, R^2 = Ph, CO_2CH_3, R^3 = CH_3, C_2H_5, Ar = *m*-ClC_6H_4, *p*-$NO_2C_6H_4$, Z = O, S)

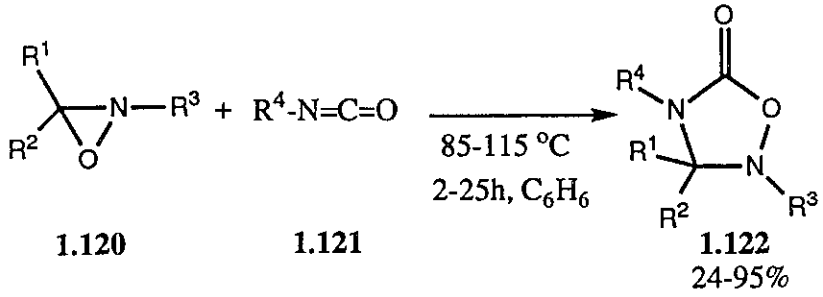
The reactions usually proceed in a nonstereospecific way, because the cycloaddition to heterocumulenes competes with the equilibration process. [99]

Oxaziridines and Diaziridines

Reactions of oxaziridines with heterocumulenes are quite different from those of oxiranes, aziridines, 2H-azirines or thiiranes. For example, treatment of 2-ethyl-3-phenyloxaziridine with diphenylketene gave a mixture of products, the major ones being an

oxazolidinone derivative (38% yield) and benzaldehyde (59% yield).

Reaction of oxaziridines **1.120** with isocyanates **1.121** gave the 1 : 1 cycloadduct **1 122** (eq. 1.39). [100]



1.120 **1.121** **1.122** 24-95%

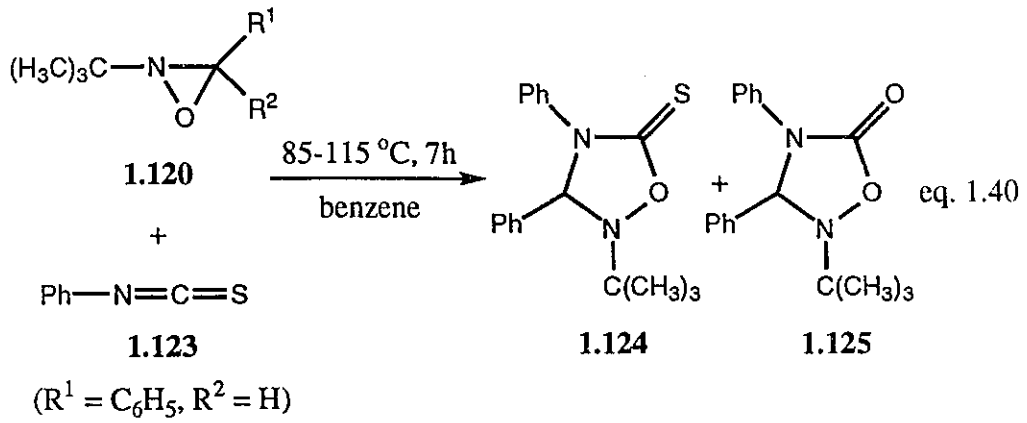
eq. 1.39

($R^1 = C_6H_5$, $R^2 = H$, $R^3 = n\text{-}C_4H_9$, $i\text{-}C_3H_7$, $t\text{-}C_4H_9$, COC_6H_5, $R^4 = C_6H_5$, $n\text{-}C_4H_9$)

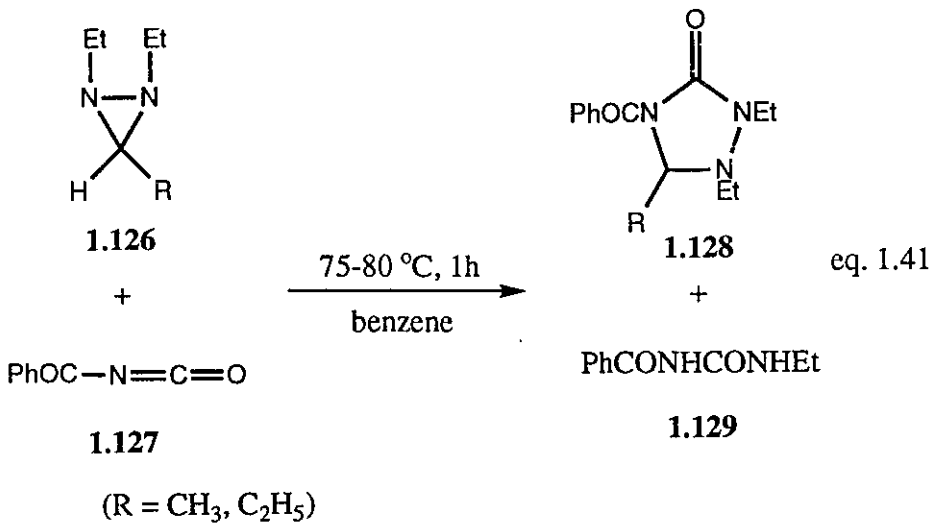
Diphenylcarbodiimide reacted rather differently to yield hexahydrotriazine derivatives or guanidines, depending upon the substitution at the oxaziridine carbon. [100] These reactions can be classified into two types, those initiated by the nucleophilic attack of a nitrogen atom of an oxaziridine to a centre atom of a heterocumulene and others initiated by the oxygen atom. The reaction with the ketene belongs to the former and the reaction with isocyanates to the latter. Both types were observed in the reactions with carbodiimide.

Keteneimines reacted similarly, the heterocycle formed initially was thermally labile and rearranged or decomposed.[101] Phenylisothiocyanate **1.123** also reacts with oxaziridines to give the

1 : 1 cycloadduct, oxadiazolidinethione **1.124**, in good yield with a small amount of oxadiazolidinone **1.125** (eq. 1.40). [102]



Reactions of diaziridines with diphenylketene are different from those of other three-membered ring heterocycles. For example, 1,2,3-trialkyldiaziridines reacted with diphenylketene in refluxing benzene to give the 1 : 2 adducts, N-alkyl-N-(1-alkylamino-2-alkyl-3-oxo-4,4-diphenylbut-1-en-1-yl) diphenylacetamides in 6-53 % yields. [103, 104] On the other hand, 1,2-dialkyldiaziridines and diphenylketene form azetidinones in approximately 25 % yields. [105] However, reaction of 1,2,3-trialkyldiaziridines **1.126** with benzoyl isocyanate **1.127** afforded triazolidinones **1.128** (30 - 44 %) and N-ethyl-N-benzoylurea **1.129** in 18 - 39 % yields (eq. 1.41). [104] This seems to be the first example of a cycloaddition reaction of diaziridine.



eq. 1.41

1.2.2 CYCLOADDITION REACTIONS OF 4-MEMBERED RING HETEROCYCLES AND HETERCUMULENES

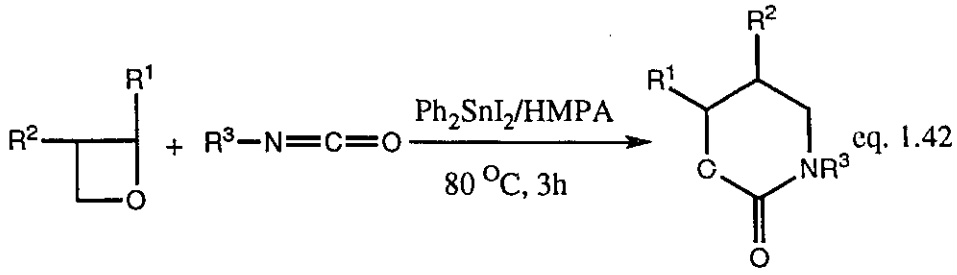
Oxetanes

Oxetanes shows many of the reactions of the more familiar oxiranes, though usually with a lower degree of reactivity as might be expected from the reduced ring strain.

Thermal decomposition of oxetanes proceeds at elevated temperatures, usually in the range of 300 - 450 °C, to give an alkene and a carbonyl compound in practically quantitative yield. [106] Oxetanes also undergo ring cleavage by electrophilic or nucleophilic reagents.

Cycloadditions of heterocumulenes with three-membered ring heterocycles are conveniently used for the synthesis of five-membered ring heterocycles. Cycloaddition with four-membered ring

heterocycles would also be a useful method for the preparation of six-membered ring heterocycles. Few examples of cycloaddition reactions of oxetanes with heterocumulenes have been reported,[107] one of which is the reaction of oxetanes **1.130** with isocyanates **1.131**, using diphenyltin diiodide with hexamethylphosphoric triamide (HMPA) as a catalyst (eq. 1.42). [108, 109]

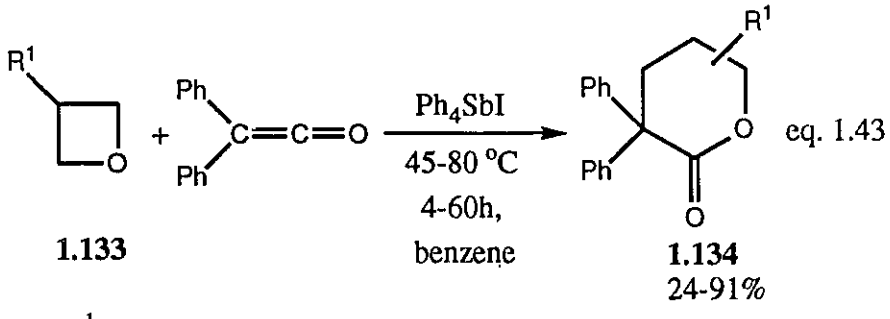


eq. 1.42

1.130 **1.131** **1.132**
63-100%

(R^1 = H, Me, R^2 = H, Me, R^3 = *n*-Bu, Ph, *p*-tolyl, *p*-ClC_6H_4)

The cycloaddition of oxetanes **1.133** with diphenylketene can be accelerated by catalytic amounts of Ph_4SbI yielding δ-lactones **1.134** in good yields (eq. 1.43). [110]

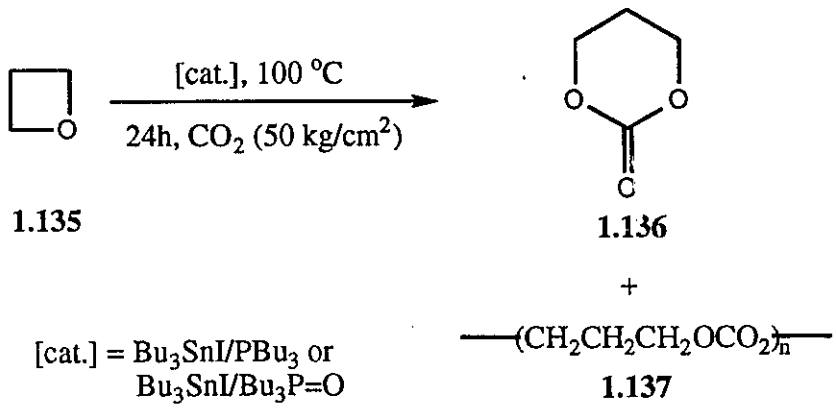


eq. 1.43

1.133 **1.134**
24-91%

(R^1 = H, Ph)

Complexes of tributyltin iodide with tributyl phosphine or tributyl phosphine oxide catalyze the addition of carbon dioxide to oxetane **1.135**, giving trimethylene carbonate **1.136** and poly(trimethylene carbonate) **1.137**. The choice of a ligand is crucial. All the complexes with Bu_3P gave polycarbonate, but the combination of Bu_3SbI with $Bu_3P{=}O$ yielded trimethylene carbonate exclusively in good yields (eq. 1.44). [111, 112]



eq. 1.44

1.3 AIMS OF RESEARCH

Analysis of the results on cycloaddition reactions of three- and four-membered ring heterocycles and heterocumulenes published to date, clearly shows that they represent a useful tool in organic synthesis, enabling one to obtain a large variety of heterocyclic products. Nevertheless, many of these processes are handicapped by

disadvantages such as severe reaction conditions, moderate yields and selectivities. Only a few of these types of cycloaddition reactions are catalytic and there are almost no studies on transition metal catalyzed reactions of heterocycles with heterocumulenes. The purpose of this research was to explore the chemistry of the transition metal catalyzed cycloaddition reactions of aziridine and azetidine based heterocycles with heterocumulenes. A variety of reaction conditions employing a number of transition metal catalysts were to be examined.

The developement of new synthetic methods for the preparation of heterocyclic compounds was anticipated with the achievement of high regio- and stereoselectivity. The role of the transition metal catalyst was also investigated by the isolation and characterization of catalytically active intermediates.

CHAPTER 2

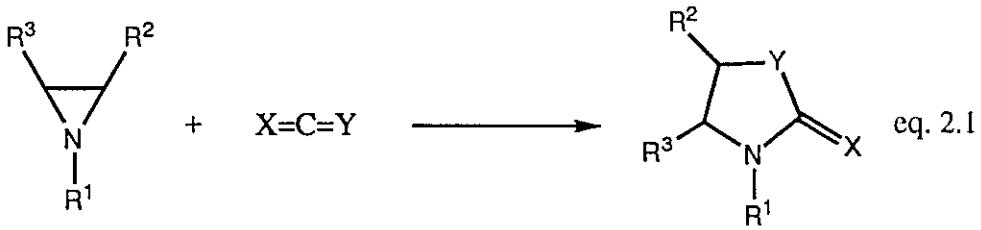
REGIOSPECIFIC AND STEREOSPECIFIC PALLADIUM-CATALYZED CYCLOADDITION OF AZIRIDINES AND HETEROCUMULENES

2.1 INTRODUCTION

Cycloaddition reactions involving 3-membered ring heterocycles and heterocumulenes have received a great deal of attention (see section 1.2.1). Owing to their high reactivity, oxiranes, thiranes, 2H-azirines, aziridines, oxaziridines and diaziridines readily react with a large variety of heterocumulenes (RNCO, RNCS, RNCNR, RCCO, CO_2, CS_2 etc.) and furnish diverse heterocycles (mostly 5-membered ring), which in some cases cannot be obtained by other methods. However, many of these processes are handicapped by disadvantages such as severe reaction conditions, moderate yields and selectivities. Just a few of the known transformations are catalytic and there are almost no studies on transition metal catalyzed reactions of heterocycles with heterocumulenes.

Among various 3-membered ring heterocyclic compounds, aziridine derivatives appear to be the most suitable candidates for investigation. Unlike S- and O- containing heterocycles, there are much more possibilities for variations in the structure of the starting materials by introducing different substituents at the nitrogen atom.

Since there are numerous β-amino alcohols available, one has easy access to various substituted aziridines and therefore can easily change steric factors and/or electronic characteristics of the substrates. In addition, 1,2-di- and 1,2,3-trisubstituted aziridines with known stereochemistry are available,[113] which is also important from a synthetic and mechanistic point of view. Besides, should reactions of aziridines with heterocumulenes of type X=C=Y (X = N-R or O, Y = N-R or S) occur, they might provide a convenient route to five-membered ring heterocycles such as imidazolidines and thiazolidines (eq 2.1). The latter are known to be pharmaceutically important since many derivatives of these heterocycles are biologically active. [114]



eq. 2.1

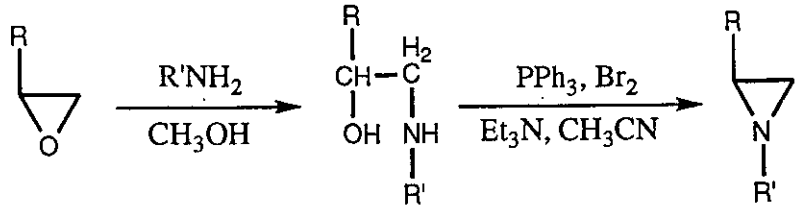
Based on the above considerations, we have studied the reactions of various 1,2-di- and 1,2,3-trisubstituted aziridines with carbodiimides, aryl isocyanates and aryl isothiocyanates in the presence of transition metal catalysts (mostly Pd(II) complex). In addition, cycloadditon reactions involving optically active 1,2-disubstituted aziridines with heterocumulenes have been also investigated. The results of this study are described below.

2.2 RESULTS AND DISCUSSION

2.2.1 SYNTHESIS OF STARTING MATERIALS

2.2.1.1 AZIRIDINES

A number of 1-alkyl-2-arylaziridines **2.3** were prepared by the cyclization of corresponding amino alcohols **2.2** The latter are readily available from the reaction of 2-substituted oxiranes **2.1** with primary amines (eq. 2.2).[115]

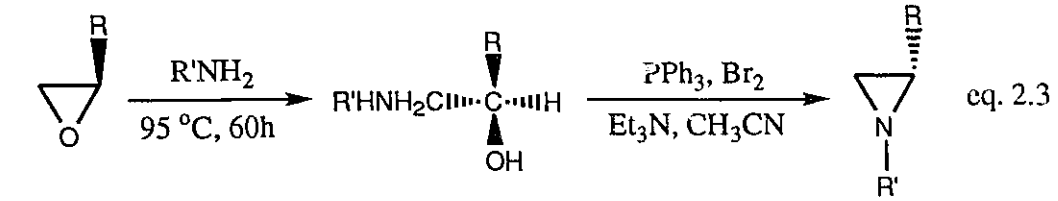


2.1 **2.2** **2.3** eq. 2.2

(R = Ph, *p*-BrC_6H_4, *p*-PhC_6H_4, R' = *n*-C_4H_9, $C(CH_3)_3$, 1-adamantyl)

Using a similar procedure, (S)- and (R)-1-adamantyl-2-phenylaziridines (**2.6** or **2.9**, R = Ph, R' = 1-adamantyl) were prepared by treatment of (R)- or (S)-2-phenyloxirane (**2.4** and **2.7**) with 1-aminoadamantane, followed by the reaction of the corresponding amino alcohols (**2.5** and **2.8**) with bromine and

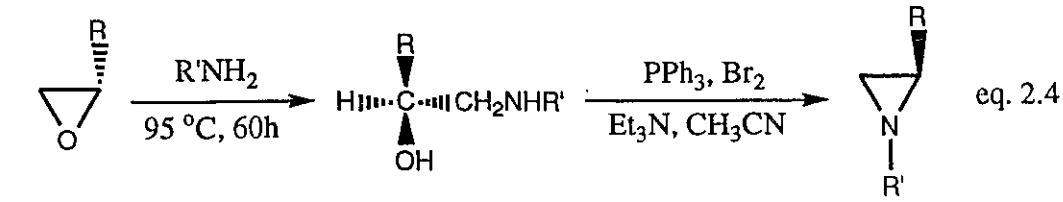
triphenylphosphine. Previously unknown (S)- and (R)-1-*n*-butyl-2-phenylaziridines (**2.6** or **2.9**, R = Ph, R' = *n*-butyl) were synthesized in the same manner from (R)- and (S)-2-phenyloxirane (eq. 2.3, 2.4).[116]



eq. 2.3

(R)-(-)-**2.4** (R)-(-)-**2.5** 62-65% (S)-(+)-**2.6** 60-94%

(R = Ph, R' = *n*-C_4H_9, 1-adamantyl)

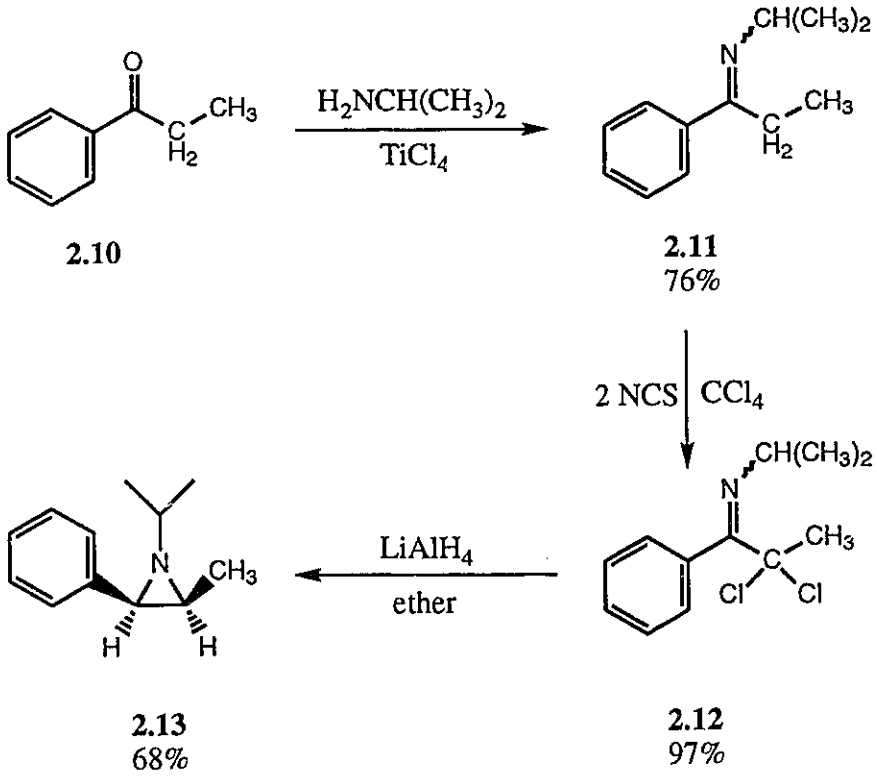


eq. 2.4

(S)-(+)-**2.7** (S)-(+)-**2.8** 64-69% (R)-(-)-**2.9** 61-95%

(R = Ph, R' = *n*-C_4H_9, 1-adamantyl)

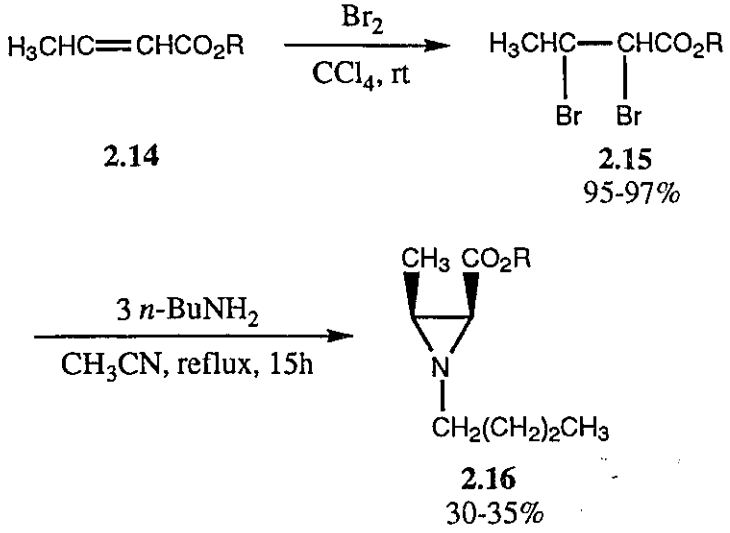
cis-1-Isopropyl-3-methyl-2-phenylaziridine **2.13** was prepared from propiophenone **2.10** by using known methodology (eq. 2.5). Reaction of **2.10** with isopropylamine and a catalytic amount of titanium tetrachloride afforded Schiff base **2.11** in 76% yield.[117] Treatment of latter the with N-chlorosuccinimide in carbon tetrachloride gave compound **2.12** in quantitative yield.[118] Reductive cyclization of chlorinated imine **2.12** with $LiAlH_4$ in ether gave aziridine **2.13** in 68% yield.[119]



eq. 2.5

Previously unknown *cis*-1-*n*-butyl-2-carboalkoxy-3-methylaziridines **2.16** were obtained by the reaction of *n*-butylamine (3 equiv.) with alkyl 2,3-dibromocrotonates **2.15** which in turn were synthesized by the bromination of alkyl crotonates **2.14** (eq. 2.6).

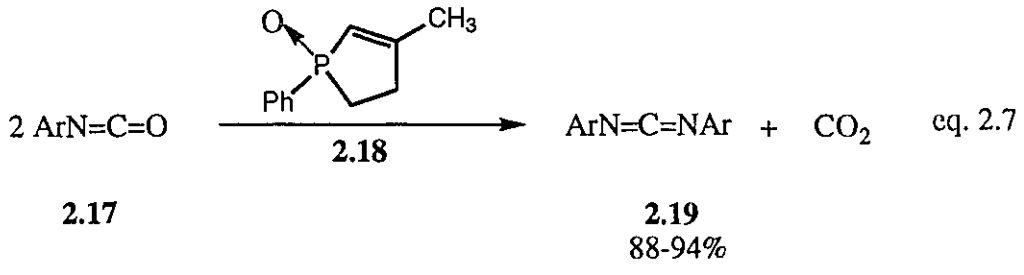
All the aziridines obtained were characterized by ^{1}H and ^{13}C NMR spectra as well as by IR and mass spectra. The purity of new compounds was also confirmed by elemental analysis (see experimental section 5.2.1)



(R = CH_3, C_2H_5)

2.2.1.2 CARBODIIMIDES

Diarylcarbodiimides were prepared from the corresponding aryl isocyanates in the presence of a catalytic amount of 3-methyl-1-phenylphospholene-1-oxide (**2.18**) as described in the literature (eq. 2.7).[120]



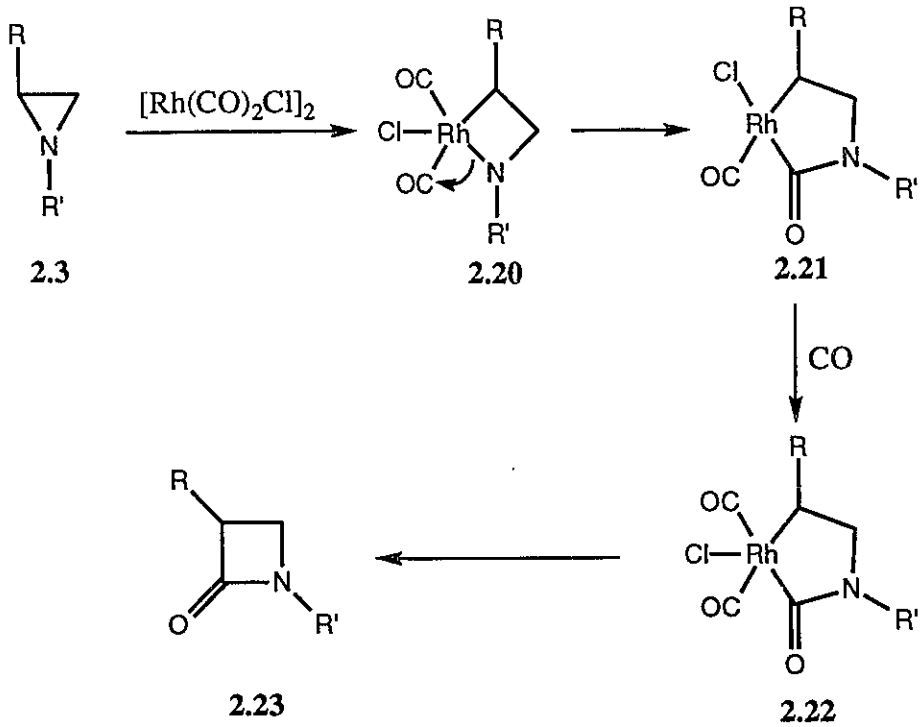
(Ar = Ph, *p*-$CH_3C_6H_4$, *p*-ClC_6H_4)

2.2.2 PALLADIUM-CATALYZED CYCLOADDITION OF 1,2-DISUBSTITUTED AZIRIDINES AND CARBODIIMIDES

In 1983, Alper and co-workers discovered a direct regiospecific, Rh(I)-catalyzed carbonylation and ring expansion of aziridines to form β-lactams.[121]

A possible mechanism involves initial oxidative addition at the more substituted C-N bond of the aziridine **2.3** to give an azametallocyclobutane **2.20**. Subsequent insertion of CO followed by reductive elimination would give the β-lactam **2.23** (Scheme 2.1).

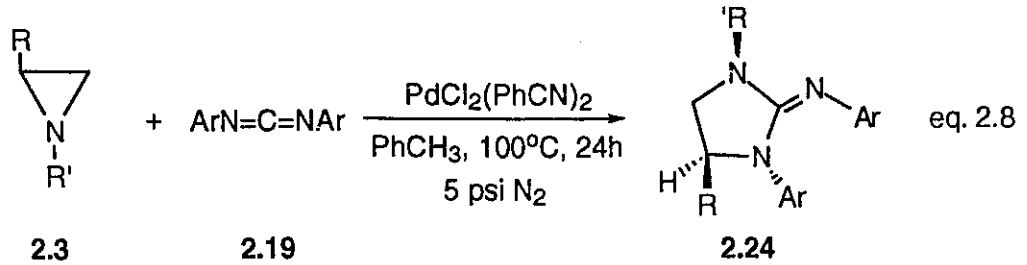
Scheme 2.1



2.3 **2.20** **2.21** **2.22** **2.23**

It seemed conceivable that heterocumulenes such as carbodiimides would also cycloadd to the C-N bond of aziridine under this Rh(I)-catalytic system. In order to determine whether such a process could occur, the reaction of 1-*tert*-butyl-2-phenylaziridine with diphenylcarbodiimide (**2.19**, Ar = Ph) in the presence of $[Rh(CO)_2Cl]_2$ was investigated under various conditions. All the attempts of the cycloaddition were unsuccessful. From these results we can conclude that the cycloaddition reaction mechanism differs from that of Rh(I)-catalyzed carbonylation. The above reaction was further studied using other transition metal complexes: $Co_2(CO)_8$, $IrCl(CO)(PPh_3)_2$, $Ni(COD)_2$, $Ni(CO)_2(PPh_3)_2$, $Pd(dba)_2$, $Pd(PPh_3)_4$, $(PPh_3)_2PdCl_2$, $Pd(OAc)_2$, $Pd(CH_3CN)_4(BF_4)_2$, $Ru_3(CO)_{12}$, $Mo(CO)_6$. Under various reaction conditions, no cycloaddition reaction was observed (usually recovery of aziridine or polymerization of carbodiimide took place).

However, if bis(benzonitrile)palladium dichloride is used as the catalyst, then clean cycloaddition reaction occurs at 100 °C. Thus, 1-*tert*-butyl-2-phenylaziridine (**2.3**, R = Ph, R' = $C(CH_3)_3$) and diphenylcarbodiimide (**2.19**, Ar = Ph) react readily affording the imidazolidinimine **2.24** (R = Ph, R' = $C(CH_3)_3$, Ar = Ph) in an isolated yield of 95 % (eq. 2.8).



eq. 2.8

2.3 **2.19** **2.24**

The optimum ratio of **2.3**/ **2.19**/palladium catalyst used was 10 : 10 : 1. The reaction is sensitive to the nature of nitrile ligand in the palladium catalyst. Use of acetonitrile, which is more basic than benzonitrile, as the nitrile ligand in the palladium catalyst, in the reaction of the aziridine with diphenylcarbodiimide, afforded **2.24** (R = Ph, R' = $C(CH_3)_3$, Ar = Ph) in only 48 % yield. The $(PhCN)_2PdCl_2$ - catalyzed cycloaddition reaction was effected using different aziridines and either diphenyl or di-*p*-tolylcarbodiimide affording imidazolidinimines **2.24** in 40-95 % yields (see Table 2.1).

The palladium(II)-catalyzed process proceeds in a regiospecific manner, with the aziridine reacting by cleavage of the more substituted ring carbon-nitrogen bond. The structure of **2.24** was elucidated on the basis of spectral data (see experimental section 5.2.3) as well as an X-ray analysis of **2.24** (R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = Ph). The imine stretching absorption of **2.24** occurred in the infrared spectrum at 1638-1645 cm^{-1}. An abundant molecular ion peak appeared in the mass spectrum of all of the products. The proton and carbon magnetic resonance spectra were consistent with the assigned structure, one characteristic signal being that of the imine carbon which appeared at δ 151.73-152.36 ppm. Note that the three heterocyclic ring protons usually appear as a doublet of doublets and two triplets, the latter probably a result of overlapping doublets in each case.

TABLE 2.1 Reaction of 1,2-Disubstituted aziridines with Carbodiimides Catalyzed by $(PhCN)_2PdCl_2$[a]

R	R'	Ar	Yield of 2.24[b] (%)
Ph	$C(CH_3)_3$	Ph	95
Ph	$C(CH_3)_3$	*p*-tolyl	80
Ph	1-adamantyl	Ph	94
Ph	1-adamantyl	*p*-tolyl	61
p-PhC_6H_4	$C(CH_3)_3$	Ph	72
p-PhC_6H_4	$C(CH_3)_3$	*p*-tolyl	62
p-PhC_6H_4	1-adamantyl	Ph	71
p-PhC_6H_4	1-adamantyl	*p*-tolyl	40
p-BrC_6H_4	$C(CH_3)_3$	Ph	90
p-BrC_6H_4	$C(CH_3)_3$	*p*-tolyl	78
Ph	*n*-C_4H_9	Ph	86

[a] Reaction Conditions: aziridine (1.0 mmol), carbodiimide (1.0 mmol), $(PhCN)_2PdCl_2$ (0.1 mmol), $PhCH_3$ (7.0 mL), 100 °C, 24h, 5 psi N_2. [b]Isolated yield of pure materials.

The structure of **2.24** (R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = Ph) in the solid state shows some interesting features. There are two different molecules in the asymmetric unit (data collection information, atomic coordinates and selected interatomic distances and angles are listed in Tables 5.2.1-5.2.7). Views of the two different molecules (denoted as **2.24** (1) and **2.24** (2)) are given in Figure 2.1 and 2.2 The difference between the two can be seen by

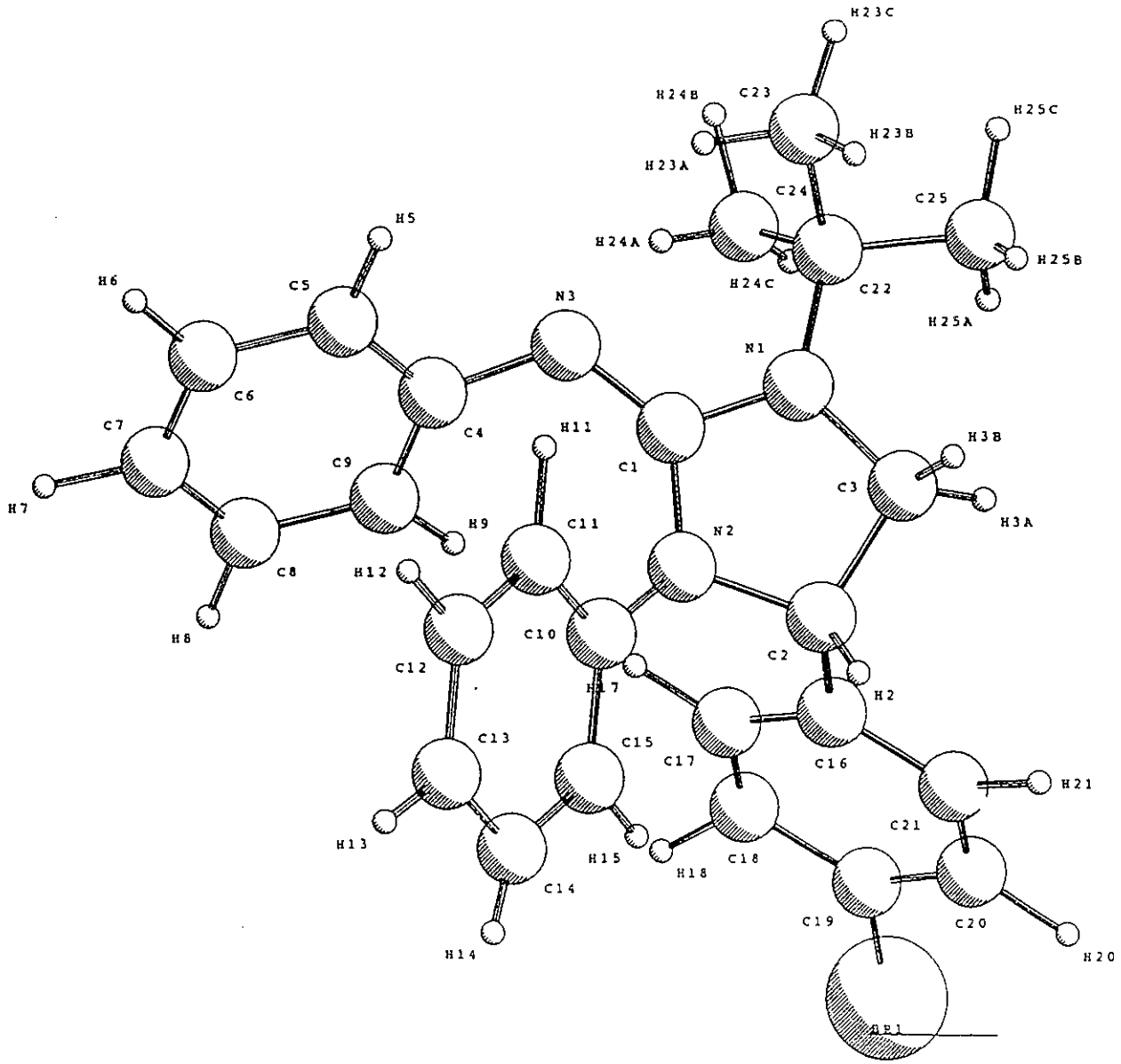


Figure 2.1. View of 2.24 (R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = Ph (molecule 1)) **showing the atom numbering scheme.**

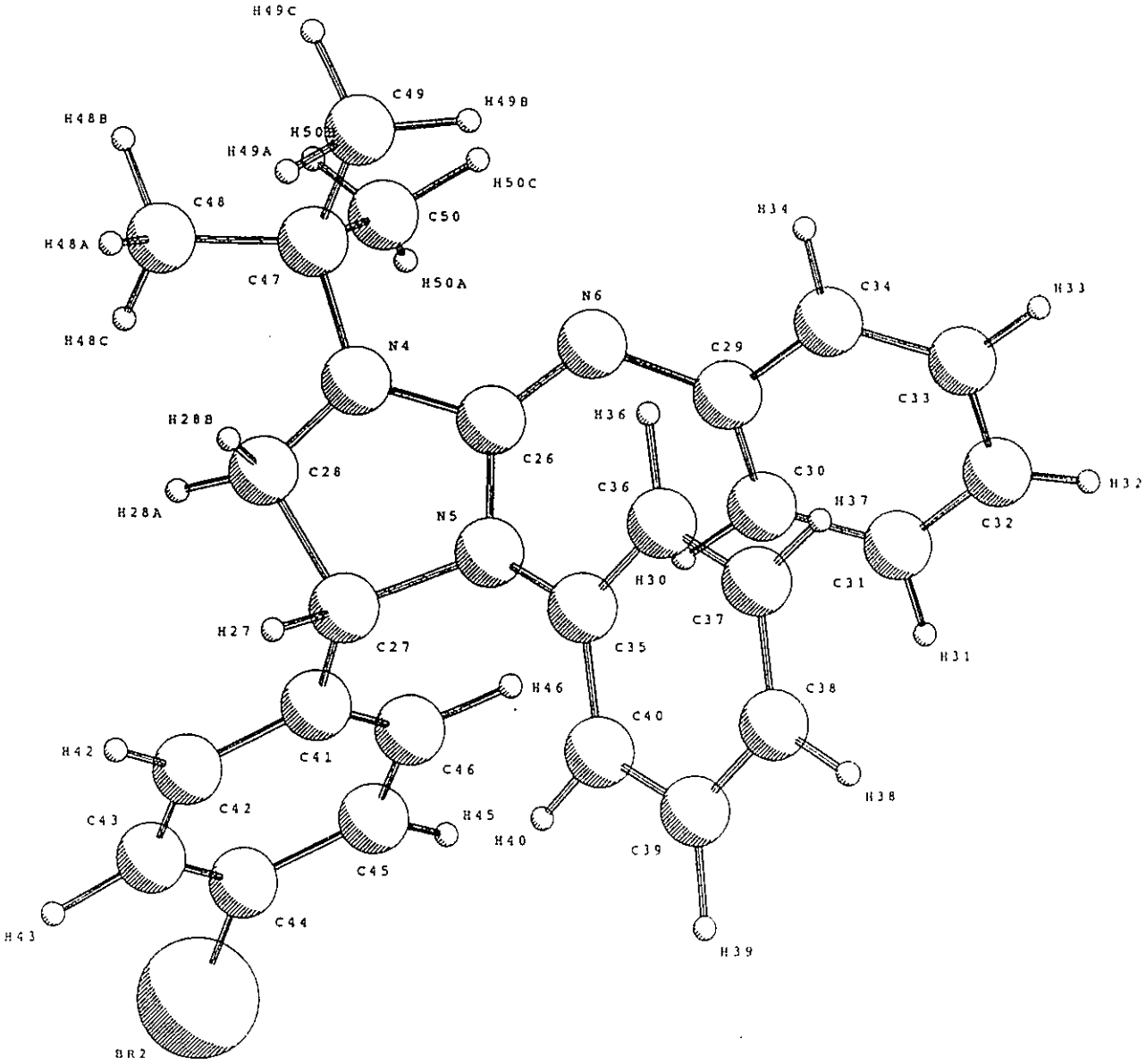


Figure 2.2. View of 2.24 (R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = Ph (molecule 2)) **showing the atom numbering scheme.**

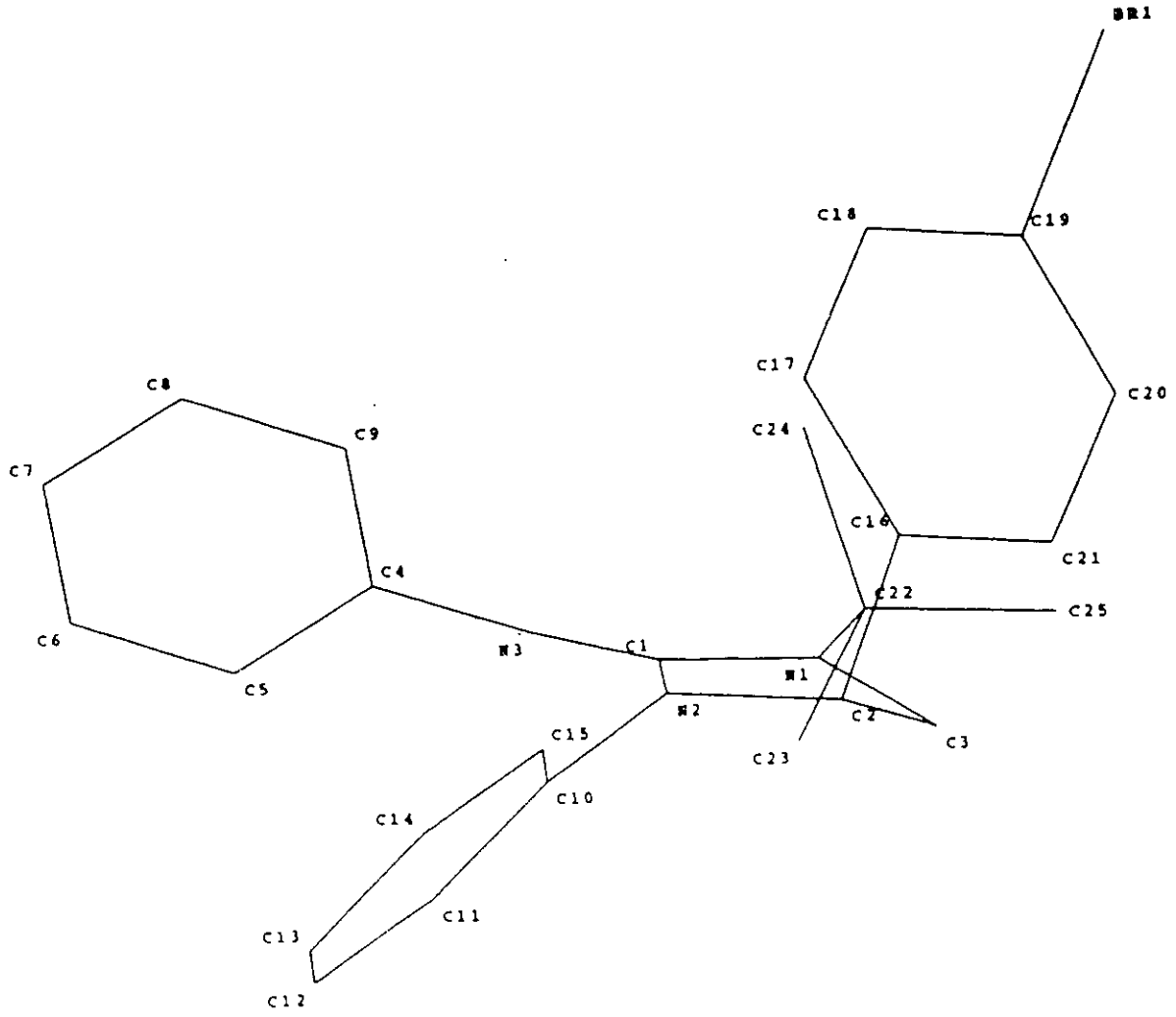


Figure 2.3. Representation of 2.24 (R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = Ph (molecule 1)) **showing the relationship between substituent groups.**

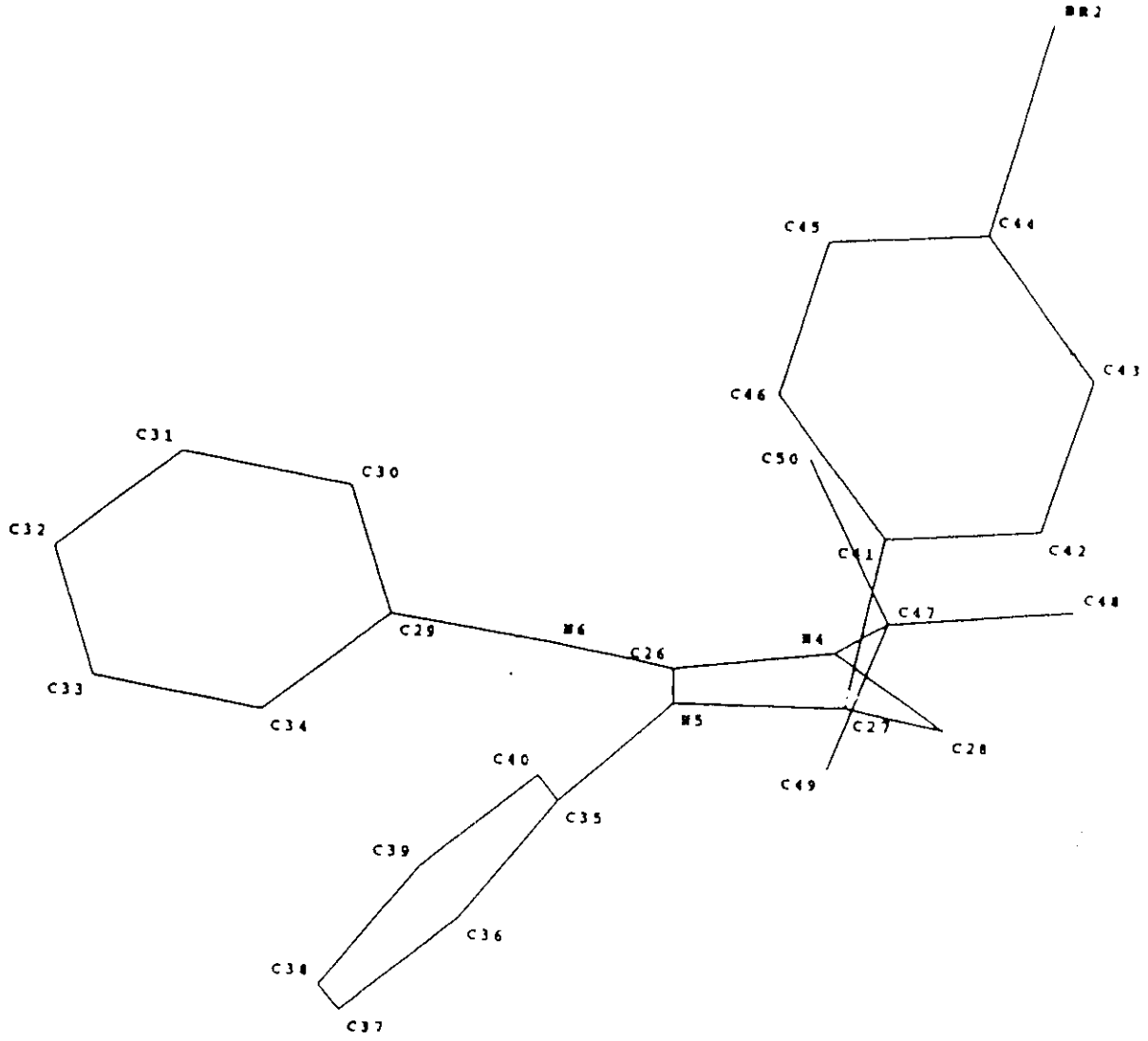
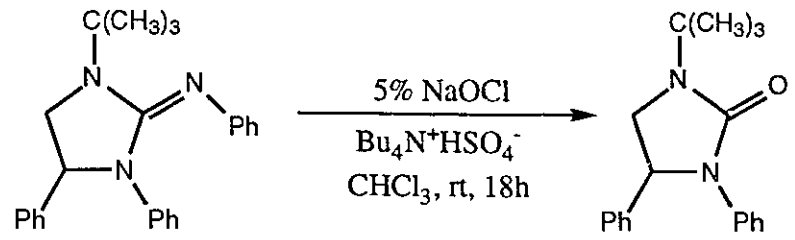


Figure 2.4. Representation of 2.24 (R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = Ph (molecule 2)) **showing the relationship between substituent groups.**

examination of Figures 2.3 and 2.4 which reveal that the torsion angles are not the same, especially when one considers the position of the *tert*-butyl group with respect to the *p*-bromophenyl unit. Specifically, the torsion angle for C(47)N(4)C(26)N(6) is 81.53° in molecule **2.24** (2) compared with the torsion angle of -51.76° for the same series of atoms in **2.24** (1). Similarly, the value is 54.35° for C(47)N(4)N(5)C(35) in **2.24** (2) while the torsion angle is -78.33° for corresponding atoms in **2.24** (1). The phenyl group, attached to the imine nitrogen, is located anti to the N-$C(CH_3)_3$ unit (or syn to the N-Ph portion of the five-membered ring). The *p*-bromophenyl substituent is in *trans* relationship with respect to the phenyl group attached to the saturated nitrogen atom and *cis* with respect to the *tert*-butyl group in both molecules. As expected, the carbon-nitrogen double bond is shorter (1.282 Å) than the two single C-N bonds involving the same carbon atom in each molecule. The bond distances of the latter are not equivalent, and this is reflected in the different NCN bond angles.

The imidazolidinimine **2.24** (R = Ar = Ph, R' = $C(CH_3)_3$) can be hydrolyzed to the imidazolidinone **2.25** by treatment with 1N HCl in toluene but the yield is only 5 %. However, use of sodium hypochlorite as the reagent, under phase transfer catalysis conditions, gave **2.25** in 57 % yield (eq. 2.9).



2.24 **2.25** 57%

eq. 2.9

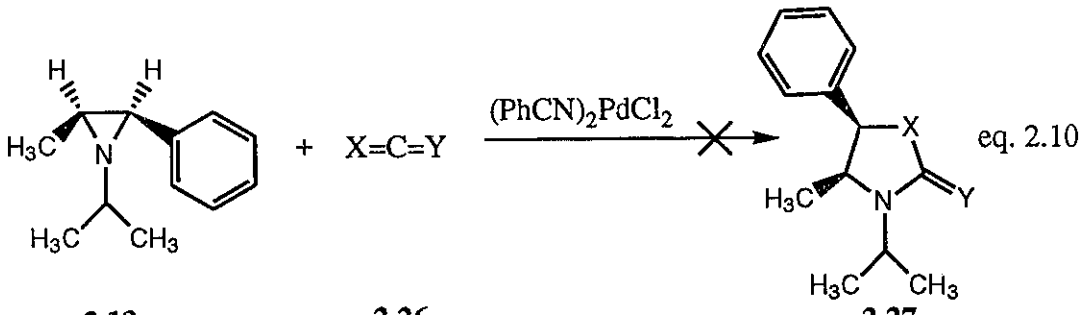
In conclusion, bis(benzonitrile)palladium dichloride is an effective catalyst for the cycloaddition reaction of 1,2-disubstitued aziridines with carbodiimides to form imidazolidinimines in good to excellent yields. The process is a regiospecific one, involving cleavage of the more substituted ring carbon-nitrogen bond. It has been also found that imidazolidinimine can be oxidatively hydrolyzed to the corresponding imidazolidine-2-one using sodium hypochlorite under phase transfer catalysis conditions.

2.2.3 PALLADIUM-CATALYZED CYCLOADDITION OF 1,2,3-TRISUBSTITUTED AZIRIDINES AND HETEROCUMULENES

The non-catalytic thermal cycloaddition reaction of 1,2,3-trisubstituted aziridines with heterocumulenes occurs *via* azomethine ylide intermediates which are produced by the thermal cleavage of carbon-carbon bond of aziridine rings (see section 1.3.1). The ylides can easily equilibrate between *cis-* and *trans-* isomer and undergo cycloaddition reaction in the presence of heterocumulenes to form

five-membered ring heterocycles. Usually the cycloaddition to heterocumulenes competes with the equilibration process. For this reason, the cycloaddition reaction usually proceeds in a non-stereospecific way. To our knowledge, there is no example of a stereospecific cycloaddition reaction of 1,2,3-trisubstituted aziridines with heterocumulenes.

Taking into account the results of the palladium(II)-catalyzed reaction of 1,2-disubstituted aziridines with carbodiimides, which regiospecifically gave imidazolidinimines in high yield, we have undertaken the investigation of palladium-catalyzed cycloaddition of 1,2,3-trisubstituted aziridines with heterocumulenes. Treatment of *cis*-1-isopropyl-3-methyl-2-phenylaziridine **2.13** with heterocumulenes such as diphenylcarbodiimide, phenyl isocyanate or *p*-chlorophenyl isothiocyanate under various reaction conditions, using catalytic quantities of bis(benzonitrile)palladium(II) dichloride resulted in the recovery of aziridine **2.13** (eq. 2.10).

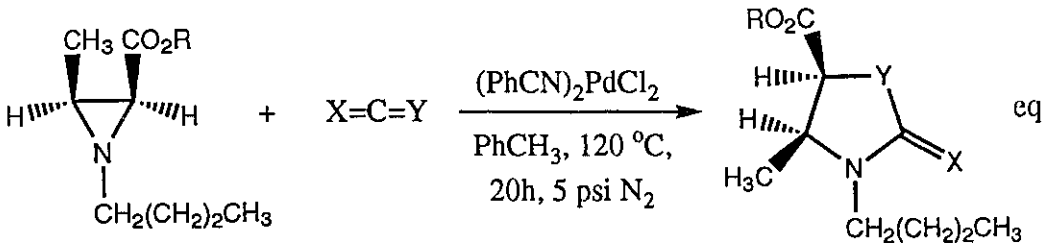


2.13 **2.26** **2.27**

(X = PhN, O, *p*-ClC_6H_4N, Y = PhN, S)

eq. 2.10

This can be explained by the steric effect of the bulky substituents. N-Isopropyl and 2-phenyl groups of **2.13** obviously reduce dramatically its ability to complex with palladium. The complexation of aziridine *via* ligand exchange is probably an essential step in the Pd-catalyzed cycloaddition reactions. For this reason, a study was carried out using aziridines substituted by a less bulky group, such as *cis*-1-*n*-butyl-2-carboalkoxy-3-methylaziridines **2.16.** Indeed, when aziridine (**2.16**, R = CH_3) was reacted with *p*-chlorophenyl isocyanate in toluene at 120 °C, for 20h in the presence of a catalytic amount of bis(benzonitrile)palladium dichloride (10 mol %), then a clean cycloaddition reaction occurred yielding *cis*-1-*n*-butyl-3-*p*-chlorophenyl-4-carbomethoxy-5-methyl-imidazolidin-2-one (**2.28**, R = CH_3, X = O, Y = *p*-ClC_6H_4N) in 80 % yield (eq. 2.11). The reaction is both regio- and stereospecific, the cycloaddition occurring with retention of configuration of the carbon centers bearing the substituent groups. In other words, *cis*-**2.16** (R = CH_3) affords *cis*-**2.28** (R = CH_3, X = O, Y = *p*-ClC_6H_4N). The configuration of the 4,5-protons of the imidazolidine ring follows from the coupling constant (J = 8.0 Hz) characteristic of *cis* -vicinal proton coupling.[122]



2.16 **2.26** **2.28** eq. 2.11

Phenyl isocyanate reacted with aziridine **2.16** (R = CH_3) in a similar fashion and afforded **2.28** (R = CH_3, X = O, Y = *p*-ClC_6H_4N) in 72 % yield. These results allowed us to assume that some other heterocumulenes would also be able to react with aziridines **2.16** in the presence of $(PhCN)_2PdCl_2$ giving rise to the corresponding five-membered ring heterocycles. The results of these studies are summarized in Table 2.2.

TABLE 2.2 Reaction of 1,2,3-Trisubstituted aziridines with Heterocumulenes Catalyzed by $(PhCN)_2PdCl_2$[a]

R	X	Y	Yield of **2.28**[b] (%)
CH_3	C_6H_5N	C_6H_5N	60
CH_3	O	C_6H_5N	72
CH_3	O	*p*-ClC_6H_4N	80
C_2H_5	O	*p*-ClC_6H_4N	86
CH_3	*p*-ClC_6H_4N	S	70
CH_3	*p*-$NO_2C_6H_4N$	S	72
C_2H_5	*p*-ClC_6H_4N	S	75

[a] Reaction Conditions: aziridine (1.0 mmol), heterocumulene (1.0 mmol), $(PhCN)_2PdCl_2$ (0.1 mmol), $PhCH_3$ (2.0 mL), 120 °C, 20h, 5 psi N_2. [b]Isolated yield of pure materials.

Indeed, both diphenylcarbodiimide and aryl isothiocyanates smoothly cycloadd to aziridines **2.16** and furnish imidazolidinimines and imidazolidinethiones **2.28** in fair yields. All the compounds **2.28** are new. They were isolated from the reaction mixtures as viscous liquids by preparative TLC and characterized by ^{1}H and ^{13}C NMR, IR, MS and elemental analysis, (see Experimental section 5.2.6).

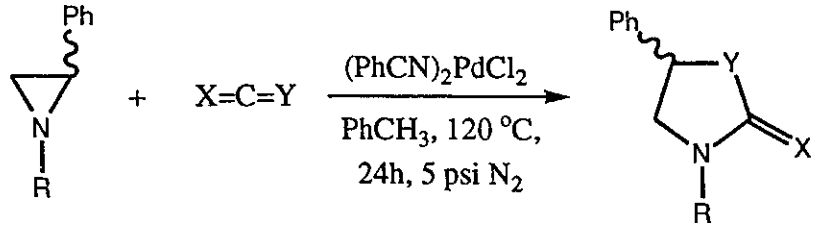
In conclusion, we have shown that Pd(II)-catalyzed reactions of 1,2,3-trisubstituted aziridines with heterocumulenes provide simple and efficient route to five-membered ring heterocycles such as imidazolidinones, imidazolidinimines and thiazolidinimines. These reactions occur both regio- and stereospecifically with the retention of the configuration of substituents in the aziridine ring.

2.2.4 ENANTIOSPECIFIC PALLADIUM-CATALYZED CYCLOADDITION OF AZIRIDINES AND HETEROCUMULENES

To acquire additional information concerning the scope and limitation of the Pd(II)-catalyzed cycloaddition reaction of aziridines and heterocumulenes, we also examined reactions of chiral, optically active, 1,2-disubstituted aziridines with carbodiimides, isocyanates and isothiocyanates. It is well-known that only one of a pair of enantiomers is usually pharmacologically active, the others being inactive or even having detrimental effect. The enantiospecific synthesis of chiral molecules of biological interest is an important problem which has received a great deal of attention within last

years.[127] To our knowledge, there are no examples in the literature on enantiospecific cycloaddition reactions involving heterocycles and heterocumulenes. Also, a study of the stereochemistry of Pd(II)-catalyzed reactions of optically pure aziridines with heterocumulenes can provide valuable additional information from a mechanistic perspective.

In order to determine the enantioselectivity of the cycloaddition reaction, several known, and new optically pure aziridines were prepared from commercially available enantiomers of 2-phenyloxirane (see experimental section 5.2.1) and then studied in cycloaddition reactions. The palladium(II)-catalyzed cycloaddition reaction of (S)-(+)-*n*-butyl-2-phenylaziridine **2.6** (R = *n*-C_4H_9) with phenyl isocyanate **2.26** (X = O, Y = PhN) gave (+)-1-*n*-butyl-3,4-diphenylimidazolidin-2-one **2.29** (R = *n*-C_4H_9, X = O, Y = PhN) ($[\alpha]^{23}_D$ +31.7° (*c* 5.4, $CHCl_3$)) in 82% yield. Similarly, (-)-enantiomer **2.30** (R = *n*-C_4H_9, X = O, Y = PhN) ($[\alpha]^{23}_D$ -31.0° (*c* 5.0, $CHCl_3$)) was obtained in 81% yield when (R)-(-)-*n*-butyl-2-phenylaziridine **2.9** (R = *n*-C_4H_9) was treated with phenyl isocyanate (eq. 2.12). The imidazolidin-2-ones obtained were characterized by ^1H and ^{13}C NMR spectra as well as by IR, mass spectra and elemental analysis (see experimental section 5.2.7).



eq. 2.12

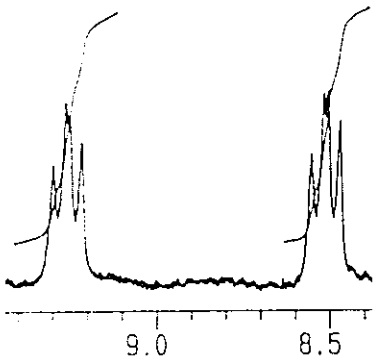
(S)-(+)-**2.6** **2.26** (+)-**2.29**

(R)-(-)-**2.9** (-)-**2.30**

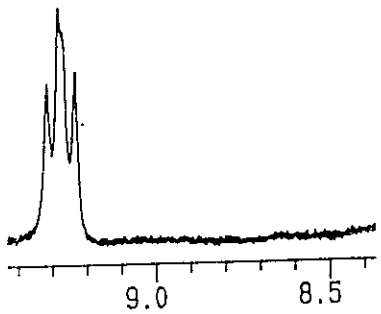
(R = *n*-C_4H_9, X = O, Y = Ph)

To determine the optical purities of products (+)-**2.29** and (-)-**2.30**, the protons attached to the chiral carbons at position 4 in imidazolidin-2-ones were resolved by ^1H NMR using Eu(hfc)3 as the chiral shift regent (see Figure 2.5). The europium resolved ^1H NMR spectra clearly show that the products obtained by cycloaddition reaction are optically pure.

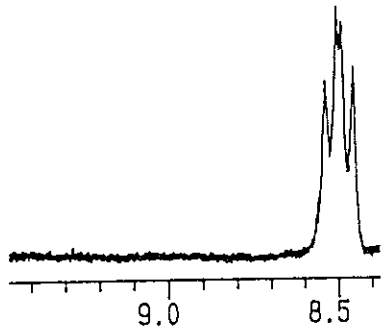
The absolute configuration of the asymmetric carbon in (+)-1-*n*-butyl-3-*p*-chlorophenyl-4-phenylimidazolidin-2-one **2.29** (R = *n*-C4H9, X = O, Y = *p*-ClC6H4N) which was prepared by reaction of (S)-(+)-1-*n*-butyl-2-phenylaziridine with *p*-chlorophenyl isocyanate, was determined by single-crystal X-ray analysis (see Figure 2.6 for ORTEP diagram). The chiral center has the (S)-configuration. These results unequivocally demonstrate that palladium(II)-catalyzed cycloaddition reactions of aziridines with heterocumulenes occur enantiospecifically and with retention of the configuration of the asymmetric centre.



(a) racemate



(b) (+)-enantiomer (**2.29**)



(c) (-)-enantiomer (**2.30**)

Figure 2.5 **Eu(hfc)3 resolved ^{1}H NMR spectra of 1-*n*-butyl-3,4-diphenylimidazolidin-2-one** (a-racemate, b-(+)-enantiomer (2.29), c-(-)-enantiomer (**2.30**)).

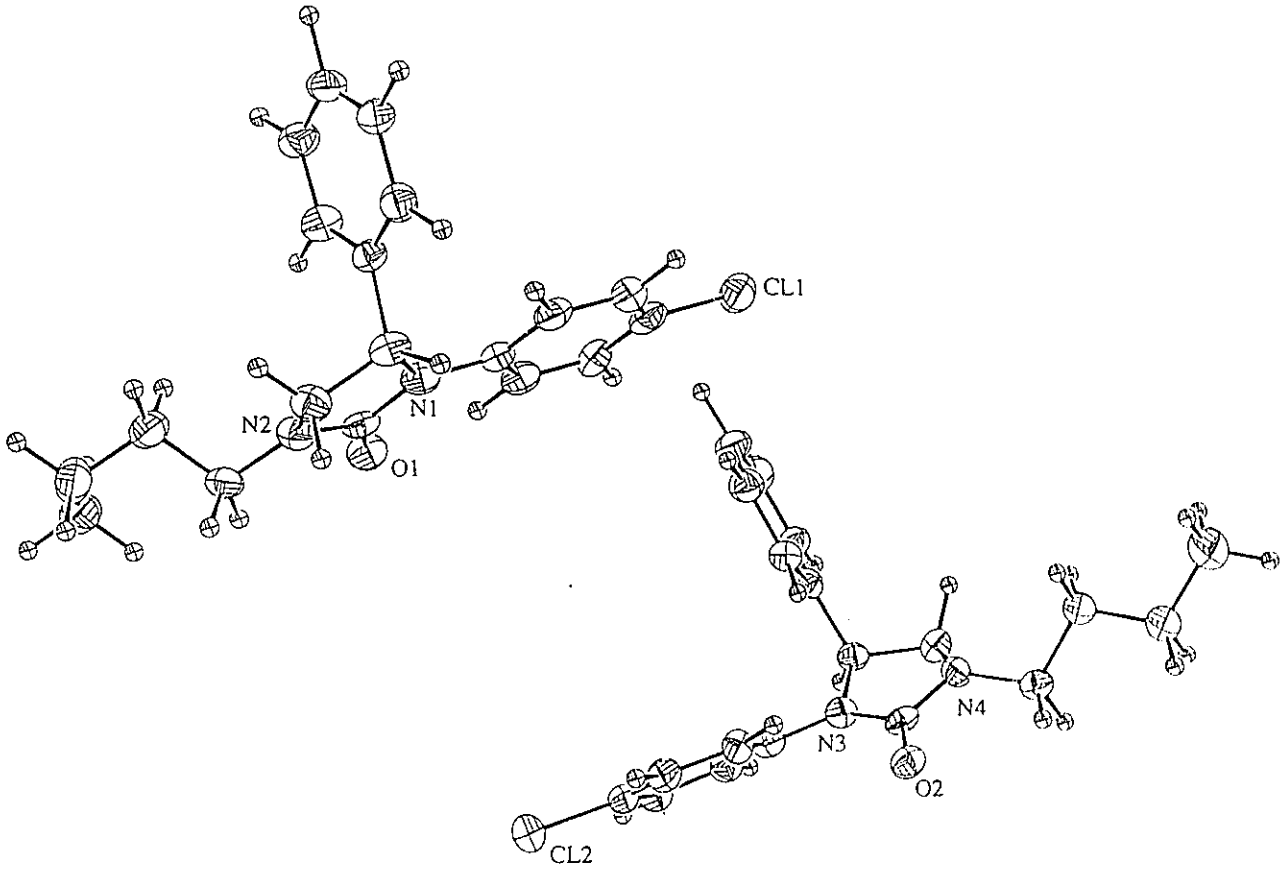
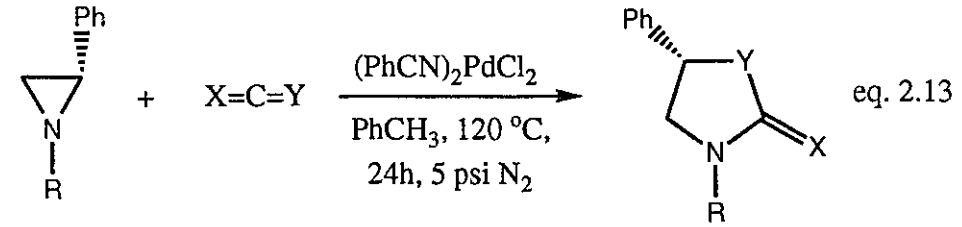


Figure 2.6 View of (S)-(+)-2.29 (R = *n*-C_4H_9, X = O, Y = *p*-ClC_6H_4N) **showing the atom numbering scheme.**

Various optically pure aziridines react with heterocumulenes to give the corresponding five-membered ring heterocycles in high yields (eq. 2.13 and 2.14). The results are summarized in Tables 2.3 and 2.4.



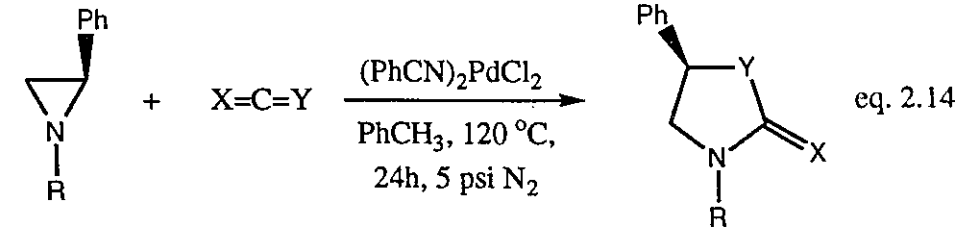
eq. 2.13

(S)-(+)-**2.6** **2.26** (S)-(+)-**2.29**

TABLE 2.3 Reaction of (S)-(+)-1-Alkyl-2-phenylaziridines with Heterocumulenes Catalyzed by $(PhCN)_2PdCl_2$[a]

R	X	Y	Yield of (S)-(+)-**2.29**[b] (%)
n-C4H9	*p*-ClC6H4N	*p*-ClC6H4N	90
n-C4H9	O	C6H5N	82
n-C4H9	O	*p*-ClC6H4N	87
1-adamantyl	C6H5N	S	85
1-adamantyl	*p*-ClC6H4N	S	83

[a] Reaction Conditions: aziridine (1.0 mmol), heterocumulene (1.0 mmol), $(PhCN)_2PdCl_2$ (0.1 mmol), $PhCH_3$ (2.0 mL), 120 °C, 24h, 5 psi N_2. [b]Isolated yield of pure materials.



eq. 2.14

(R)-(-)-**2.9** **2.26** (R)-(-)-**2.30**

TABLE 2.4 Reaction of (R)-(-)-1-Alkyl-2-phenylaziridines with Heterocumulenes Catalyzed by $(PhCN)_2PdCl_2$[a]

R	X	Y	Yield of (R)-(-)-**2.30**[b] (%)
n-C4H9	*p*-ClC6H4N	*p*-ClC6H4N	88
n-C4H9	O	C6H5N	81
n-C4H9	O	*p*-ClC6H4N	84
1-adamantyl	C6H5N	S	82
1-adamantyl	*p*-ClC6H4N	S	80

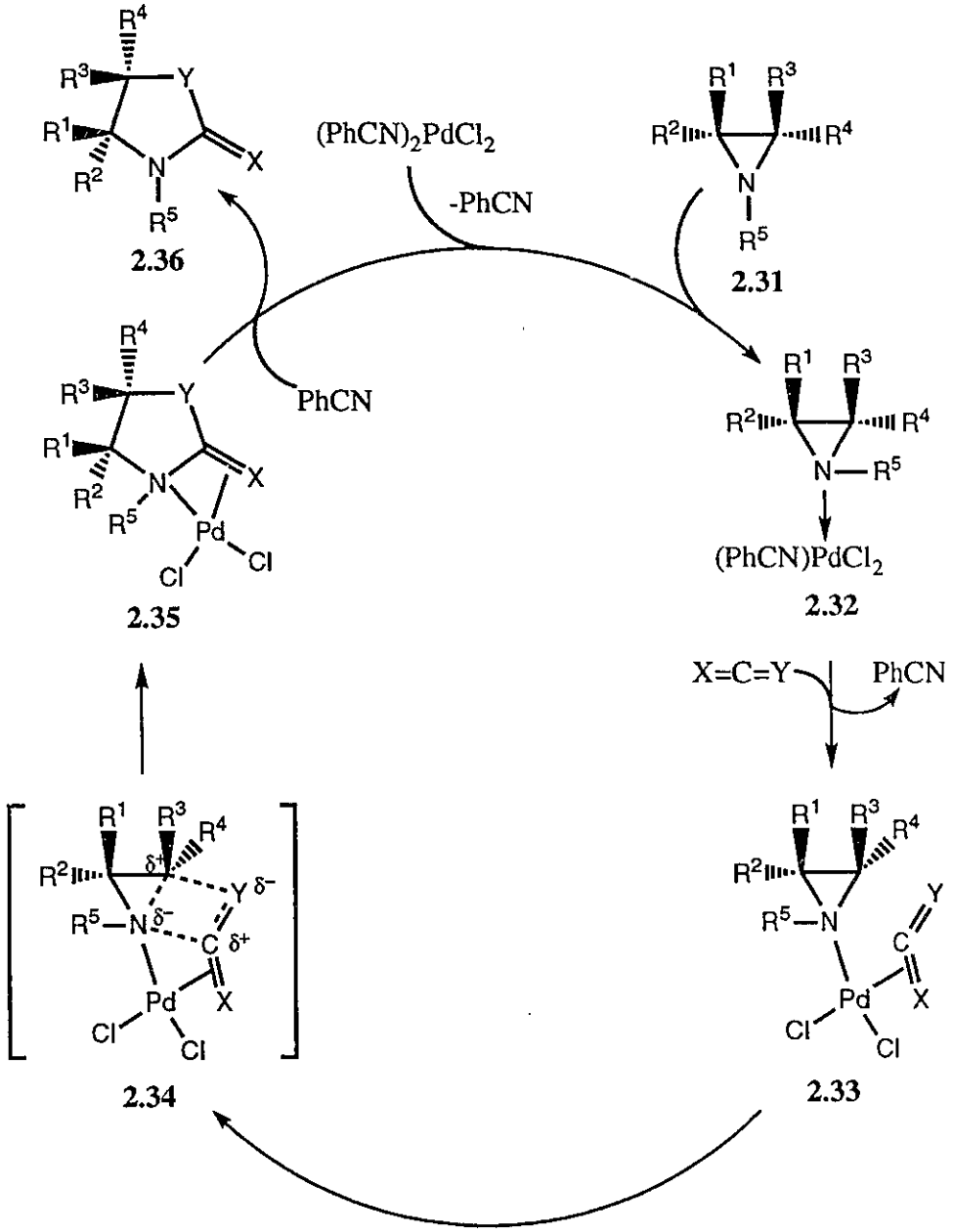
[a] Reaction Conditions: aziridine (1.0 mmol), heterocumulene (1.0 mmol), $(PhCN)_2PdCl_2$ (0.1 mmol), $PhCH_3$ (2.0 mL), 120 °C, 24h, 5 psi N_2. [b]Isolated yield of pure materials.

Based on the results obtained, a possible pathway for the palladium-catalyzed cycloaddition reaction is proposed in Scheme 2.2. Reaction of $(PhCN)_2PdCl_2$ with the aziridine may afford the N-

donor ligand complex **2.32**. Reaction of the latter with the heterocumulene can form **2.33**, in which there is π-complexation of one of the double bonds of the heterocumulene to palladium.[128] The same intermediate **2.33** can result by complexation of the heterocumulene to Pd followed by the aziridine. It is also conceivable that the η-lone pair, rather than π-electrons of the heterocumulene participate in bonding to palladium. Cycloaddition of the aziridine to the uncomplexed double bond of the heterocumulene, ligand may occur *via* a four-membered transition state **2.34** to give **2.35**. Therefore, the cycloaddition proceeds with retention of stereochemistry of the carbon centers bearing the substituent groups. Reaction of the latter with additional benzonitrile (dissociated from $(PhCN)_2PdCl_2$) and aziridine could afford the corresponding five-membered ring heterocycle **2.36** and regenerate **2.32**.

In conclusion, the reaction of substituted aziridines with heterocumulenes are readily catalyzed by bis(benzonitrile)palladium dichloride affording the corresponding cycloaddition products in high yields, regio-, stereo-, and enantiospecifically.

Scheme 2.2


(PhCN)2PdCl2
-PhCN
PhCN
2.36
2.31
2.35
2.32
(PhCN)PdCl2
X=C=Y
PhCN
2.34
2.33

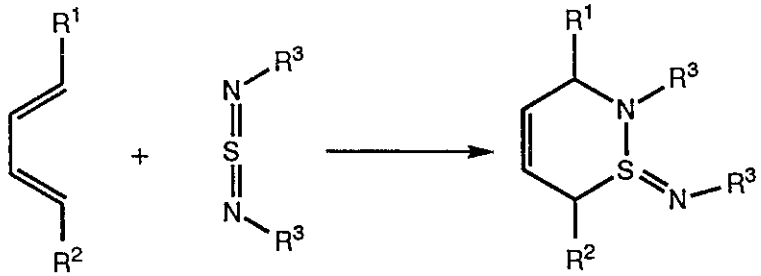
CHAPTER 3

NOVEL PALLADIUM(II)-CATALYZED CYCLIZATION OF AZIRIDINES AND SULFUR DIIMIDES

3.1 INTRODUCTION

Sulfur diimides are formally considered to be the diimides derived from sulfur dioxide. Thus, the same relationship observed for the imides of carbon dioxide (carbodiimides and isocyanates) could be expected.

The synthesis and reactivity of sulfur diimides have been widely studied, particularly for Diels-Alder cycloaddition reactions.[130, 131] Various electron-deficient sulfur diimides (employed as the heterodienophiles) such as bis(arylsulfonyl)-[132, 133], bis(alkoxycarbonyl)-[134], or bis(*p*-nitrobenzoyl)sulfur diimides **3.2**[135] readily react with dienes **3.1** to form 1,2-thiazine derivatives **3.3** (eq. 3.1).

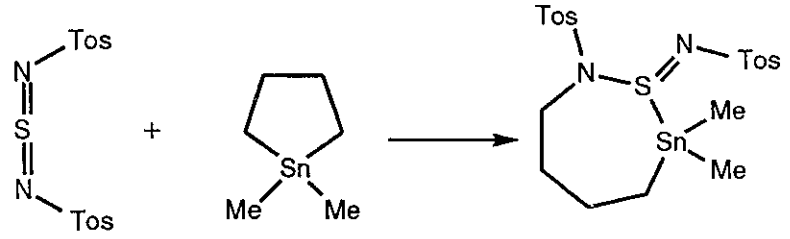


3.1 **3.2** **3.3**

eq. 3.1

($R^1 = R^2 = H, CH_3, R^3 = C_6H_5SO_2, p\text{-}CH_3C_6H_4SO_2, p\text{-}ClC_6H_4SO_2, CO_2Et, p\text{-}NO_2C_6H_4CO$)

Unlike other heterocumulenes, sulfur diimides have rarely been used in cycloaddition reactions with heterocycles. To our knowledge, the only published example is the addition of 1,3-di-*p*-tosylsulfur diimide **3.4** to 1,1-dimethylstannolane **3.5** (eq. 3.2).[136]



eq. 3.2

3.4 **3.5** **3.6**

Therefore, investigations concerning the reaction of sulfur diimides with heterocycles could be a topic of great interest. It may also be possible to find new synthetic pathways to new heterocyclic compounds.

This chapter describes the results of the study of bis(benzonitrile)palladium dichloride catalyzed cyclization reaction of aziridines with sulfur diimides which resulted in the discovery of novel and unusual transformation.

3.2 RESULTS AND DISCUSSION

3.2.1 SYNTHESIS OF STARTING MATERIALS

3.2.1.1 AZIRIDINES

A variety of aziridines were prepared according to literature procedures (see section 2.2.1). [115]

3.2.1.2 SULFUR DIIMIDES

One of the known common methods for the preparation of symmetrically substituted sulfur diimides **3.7** involves the reaction of SCl_2 with RNH_2 usually with benzene or ether as the solvent and with pyridine or NEt_3 as added base. Aliphatic, aromatic and heterocyclic derivatives **3.7** have been prepared in this way (eq. 3.3). [137-141] The structure of possible intermediates in this reaction

$$RNH_2 + SCl_2 \longrightarrow [\text{R-NH-SCl, R-N=S or other}] \qquad \text{eq. 3.3}$$

$$\xrightarrow{+\,RNH_2} \underset{\textbf{3.7}}{RN{=}S{=}NR}$$

is still uncertain. Also, the reaction conditions influence strongly the selectivities for final products and yields and selectivities are quite

low. For these reasons, the synthesis of sulfur diimides by reaction of SCl_2 with primary amines was found to be unsuitable. Therefore, aryl sulfur diimides **3.11** were prepared by the reaction of N-phenylsulfonylimidosulfurous chloride **3.8** with arylamines. Reaction of **3.8** with 3 equiv. of arylamine **3.9** in benzene at room temperature for 3 h, gave N-phenylsulfonyl-N'-arylsulfurous diimide **3.10** in quantitative yield. Subsequent reaction of **3.10** with arylamine in benzene at room temperature for 3-4 days afforded aryl sulfur diimides **3.11** in good yields (eq. 3.4). [142, 143]

$$\underset{\textbf{3.8}}{PhSO_2N{=}SCl_2} + \underset{\textbf{3.9}}{3ArNH_2} \xrightarrow[\text{rt, 3h}]{\text{benzene}}$$

eq. 3.4

$$\underset{\textbf{3.10}}{PhSO_2N{=}S{=}NAr} \xrightarrow[\text{benzene, rt, 3-4 days}]{ArNH_2} \underset{\textbf{3.11}}{ArN{=}S{=}NAr}$$

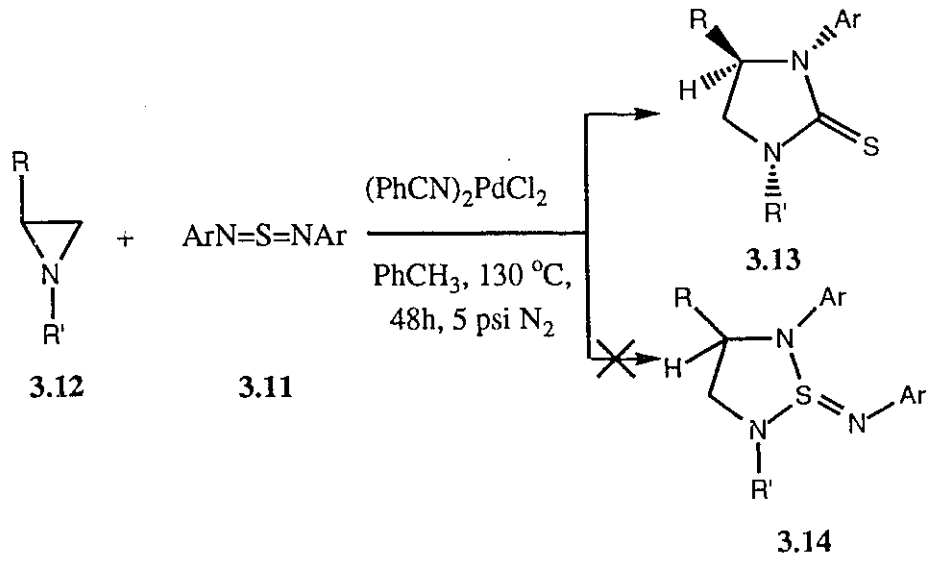
(Ar = Ph, *p*-tolyl)

3.2.2 THE NEW CATALYTIC CYCLIZATION REACTION

It was anticipated that replacement of the heterocumulene carbon of diarylcarbodiimide by a sulfur atom (i.e., sulfur diimide **3.11**) in the palladium-catalyzed reaction would result in the formation of a thiadiazolidinimine (**3.14**, in Scheme 3.1). The latter compound was not obtained in the reaction. A remarkable cyclization process occurred instead. Specifically, treatment of 1-

tert-butyl-2-phenylaziridine (**3.12**, R = Ph, R' = $C(CH_3)_3$) with di-*p*-tolylsulfur diimide (**3.11**, Ar = *p*-$CH_3(C_6H_4)$) in toluene at 130 °C, using bis(benzonitrile)palladium dichloride as the catalyst, afforded the imidazolidinethione (**3.13**, Ar = *p*-$CH_3C_6H_4$, R = Ph, R' = $C(CH_3)_3$) in 53 % yield of pure material.

Scheme 3.1



3.12 **3.11** **3.13** **3.14**

The ratio of aziridine to sulfur diimide to palladium catalyst used was 20 : 10 : 1.0. The reaction is sensitive to the ratio of aziridine **3.12** and sulfur diimide **3.11**. When the ratio of aziridine **3.12** (R = Ph, R' = $C(CH_3)_3$) and sulfur diimide **3.11** (Ar = *p*-tosyl) was 1 : 1, the yield decreased to 36 %.

A study was made to determine the influence of temperature on the reaction yields. The results in Table 3.1 demonstrate the sensitivity of the cyclization process to the reaction temperature. At

relatively low temperature (80 °C) no reaction was observed. The reaction became noticeable at 100 °C giving 4 % of product in 48 hours. The highest yield (53 %) was obtained when the reaction was run at 130 °C.

Table 3.1 Effect of Temperature on $(PhCN)_2PdCl_2$-Catalyzed Reaction of Aziridine (R = Ph, R' = $C(CH_3)_3$) with Sulfur Diimide (Ar = *p*-tolyl)[a]

T, °C	reaction time, h	aziridine convsn, (%)	yield of **3.13**[b] (%)
80	48	0	0
100	48	10	4
115	48	35	16
130	24	67	34
130	48	100	53
145	48	100	50

[a] Reaction conditions: aziridine (2.0 mmol), sulfur diimide (1.0 mmol), $(PhCN)_2PdCl_2$ (0.1 mmol), $PhCH_3$ (3.0 mL), 5 psi N_2.

[b] Isolated yield of pure materials.

The effect of solvent on the cyclization reaction was also examined. The reaction of **3.12** (R = Ph, R' = $C(CH_3)_3$), with **3.11** (Ar = *p*-tolyl), was carried out in toluene, benzene, THF and acetonitrile (see Table 3.2). The yields of **3.13** were similar when using aromatic

solvents, whereas in THF and acetonitrile the yields were much lower.

Table 3.2 Effect of Solvent on $(PhCN)_2PdCl_2$-Catalyzed Reaction of Aziridine (R = Ph, R' = $C(CH_3)_3$) with Sulfur Diimide (Ar = *p*-tolyl)[a]

solvent	aziridine convsn, (%)	yield of **3.13**[b] (%)
C_6H_6	100	52
$PhCH_3$	100	53
THF	23	10
CH_3CN	45	21

[a] Reaction conditions: aziridine (2.0 mmol), sulfur diimide (1.0 mmol), $(PhCN)_2PdCl_2$ (0.1 m mol), solvent (3.0 mL), 130 °C, 48h, 5 psi N_2. [b] Isolated yield of pure materials.

The bis(benzonitrile)palladium dichloride catalyzed cyclization reaction was effected using different aziridines and either diphenyl or di-*p*-tolylsulfur diimide, affording imidazolidinethiones **3.13** in 52 - 70 % yields (see Table 3.3). In all of these reactions the aziridine experiences cleavage of the more substituted ring carbon - nitrogen bond. The 2-imidazolidinethiones **3.13** were identified by means of spectral data (see Experimental Section) as well as an X-ray analysis of **3.13** (R = Ph, R' = $C(CH_3)_3$, Ar = *p*-$CH_3C_6H_4$). The thiocarbonyl

stretching frequency of **3.13** occurred in the infrared spectrum at 1241 - 1251 cm^{-1},[144] and the thiocarbonyl carbon occurred at δ 182.00 - 183.16 in the ^{13}C-NMR spectrum.[145]

Table 3.3 Reaction of Aziridines with Sulfur Diimides Catalyzed by $(PhCN)_2PdCl_2$[a]

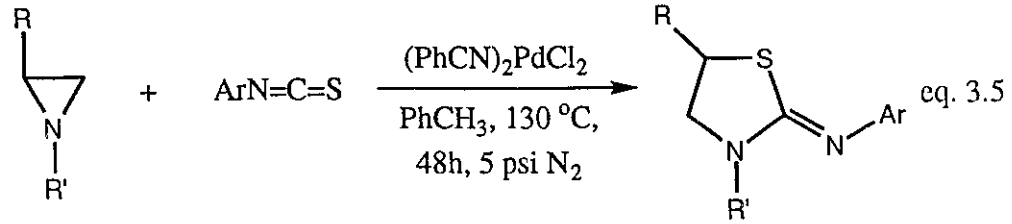
R	R'	Ar	Yield of **3.13**[b] (%)
Ph	$C(CH_3)_3$	*p*-tolyl	53
Ph	*n*-C_4H_9	*p*-tolyl	52
Ph	1-adamantyl	Ph	52
Ph	1-adamantyl	*p*-tolyl	56
p-BrC_6H_4	$C(CH_3)_3$	Ph	60
p-BrC_6H_4	$C(CH_3)_3$	*p*-tolyl	58
p-PhC_6H_4	1-adamantyl	Ph	70
p-PhC_6H_4	1-adamantyl	*p*-tolyl	68
p-PhC_6H_4	$C(CH_3)_3$	Ph	60

[a] Reaction conditions: aziridine (2.0 mmol), sulfur diimide (1.0 mmol), $(PhCN)_2PdCl_2$ (0.1 mmol), $PhCH_3$ (3.0 mL), 130 °C, 48h, 5 psi N_2. [b] Isolated yield of pure materials.

Two doublets of doublets and a triplet (i.e., two overlapping doublets) were normally observed for the ring protons of **3.13** in the ^1H NMR. The mass spectra displayed molecular ion peaks in all cases. An X-ray structure determination revealed that the phenyl

substituent of **3.13** (R = Ph, R' = $C(CH_3)_3$, Ar = *p*-$CH_3C_6H_4$) was *trans* to both of the substituents (*p*-$CH_3C_6H_4$, $C(CH_3)_3$) attached to the nitrogen atoms. An ORTEP drawing is presented in Figure 3.1.

How does this remarkable cyclization reaction occur? One can consider the formation of **3.13** by a formal [3+2] cycloaddition of an *in situ* generated aryl isothiocyanate **3.15** and aziridine **3.12**. However, treatment of 1-(1-adamantyl)-2-phenylaziridine (**3.12**, R = Ph, R' = 1-adamantyl) with phenyl isothiocyanate (**3.15**, Ar = Ph) under the same reaction conditions as in Scheme 3.1 gave the thiazolidinimine **3.16** in 85. % isolated yield, and no imidazolidinethione **3.13** was detected in the reaction (eq 3.5).



3.12 **3.15** **3.16**

eq. 3.5

(R = Ph, R' = 1-adamantyl, Ar = Ph)

The result is analogous to the organoantimony halide catalyzed cycloaddition of aziridines with phenyl isothiocyanate.[105] Therefore, the imidazolidinethiones **3.13** do not originate from the

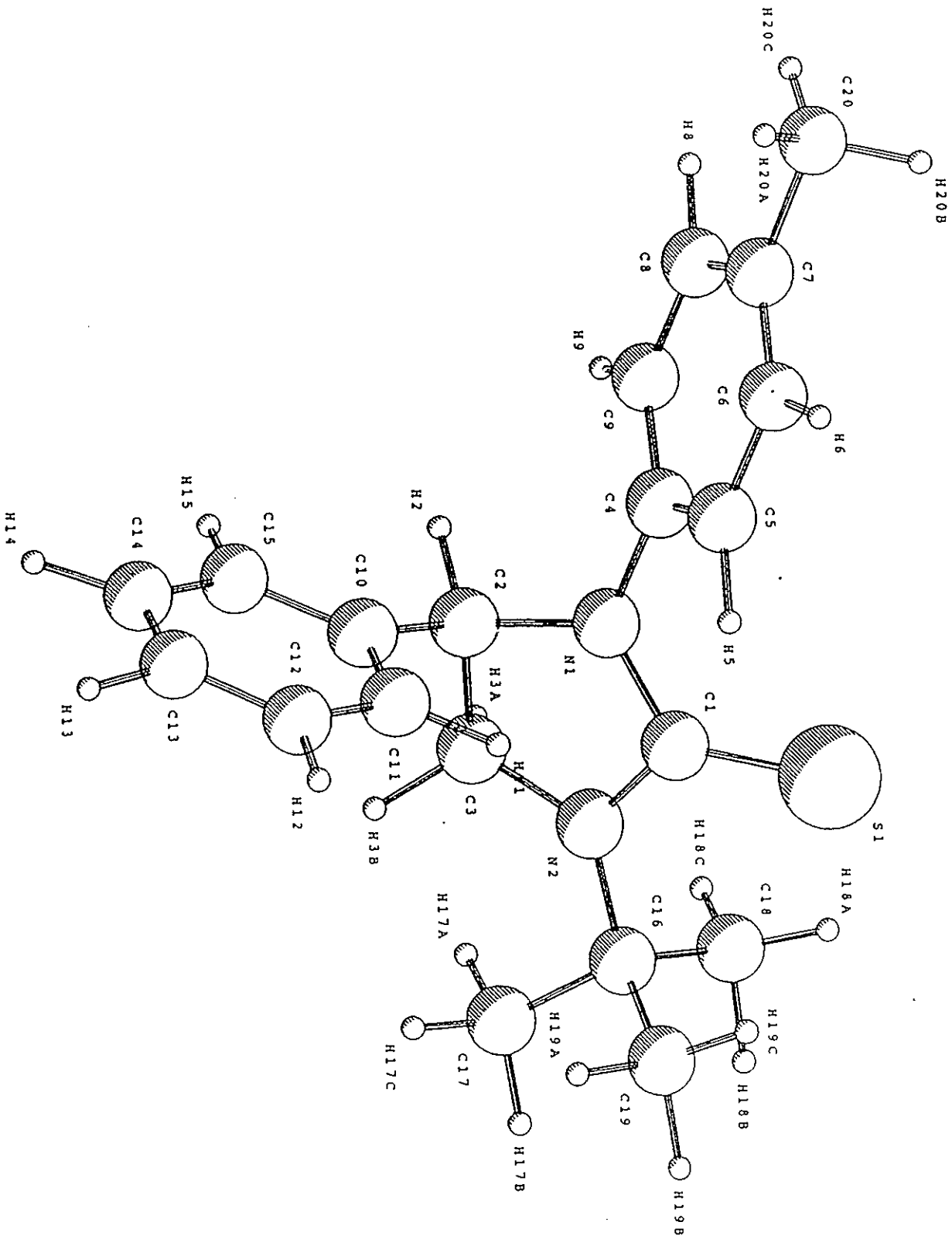
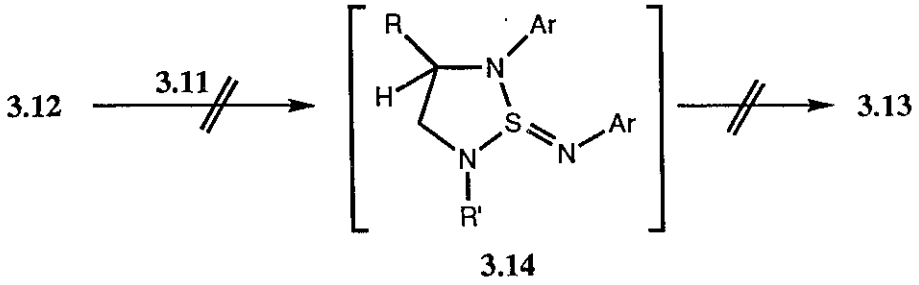


Figure 3.1 View of **3.13** (R = Ph, R' = $C(CH_3)_3$, Ar = p-$CH_3C_6H_4$) showing the atom numbering scheme.

cycloaddition reaction of aziridines and *in situ* generated aryl isothiocyanates.

Another possible route to **3.13** might be the cycloaddition of sulfur diimide **3.11** to aziridine **3.12** resulting in the intermediate **3.14** followed by its subsequent transformation to imidazolidinethione **3.13** (Scheme 3.2).

Scheme 3.2



3.14

(R = Ph, R' = *t*-butyl, Ar = *p*-tolyl)

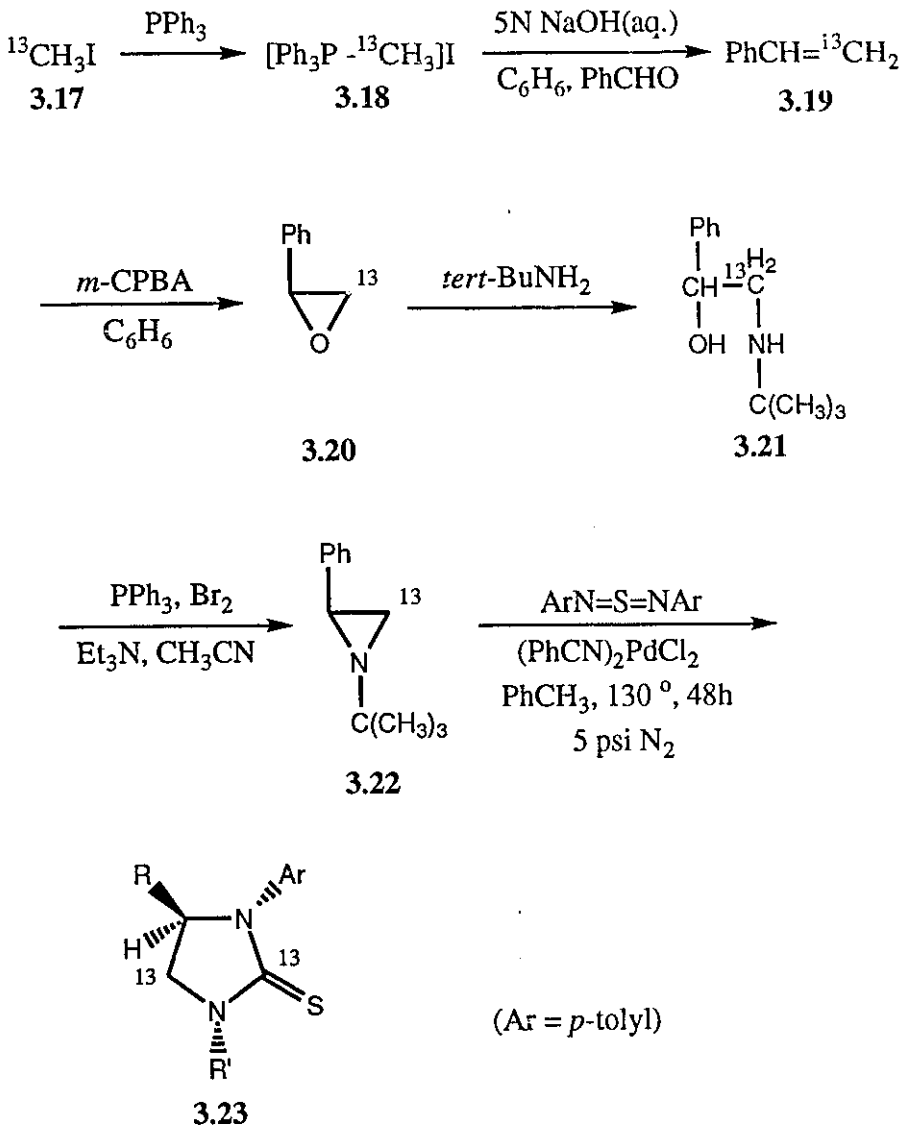
However, careful analysis of reaction mixtures obtained under various reaction conditions did not show even trace amounts of a thiadiazolidinimine **3.14.** Therefore, this reaction pathway appears to be improbable.

Several experiments were then undertaken to probe the source of the carbon in the thiocarbonyl group of **3.13**. The benzonitrile ligand is an unlikely source of the thiocarbonyl carbon, since use of excess benzonitrile (equimolar with respect to **3.12**) in the reaction of **3.12** and **3.11** resulted in a lower yield of **3.13** [e.g., 1, R = Ph, R'

= $C(CH_3)_3$, reacted with **3.11**, Ar = *p*-$CH_3C_6H_4$, to give **3.13** in 5 % yield]. The methyl group of the solvent, toluene, is not incorporated in the product, since similar product yields were obtained in benzene or toluene, using the conditions described above (see Table 3.2). It seemed conceivable that the thiocarbonyl carbon of **3.13** derived from a second molecule of the reactant aziridine **3.12**, with the ring carbons (i.e., at the 2- or 3-position) being the likely candidates. In order to address this possibility, 1-*tert*-butyl-2-phenyl[3-^{13}C]aziridine **3.22** was prepared from [^{13}C]iodomethane **3.17**. Treatment of [^{13}C]iodomethane **3.17** with triphenylphosphine afforded labeled methyltriphenylphosphonium iodide **3.18** in 96 % yield.[146] Reaction of the latter with benzaldehyde in the presence of 5 N aqueous sodium hydroxide in benzene gave the labeled styrene ($PhCH=^{13}CH_2$, **3.19**) in 42 % GC yield. [147] The benzene solution of **3.19**, containing Ph_3PO as a byproduct, was reacted *in situ* with *m*-chloroperbenzoic acid to give 2-phenyl-[3-^{13}C]oxirane **3.20** in 52 % isolated yield. [148] Subsequent reaction of the labeled oxirane **3.20** with *tert*-butylamine, followed by treatment with bromine/PPh_3 and Et_3N in acetonitrile, gave labeled aziridine **3.22** in 66 % yield.[149] When **3.22** was treated with di-*p*-tolylsulfur diimide (**3.11**, Ar = *p*-$CH_3C_6H_4$) using conditions identical to those for the unlabeled reaction [$Pd(PhCN)_2$, $PhCH_3$, 130 °C, 48h], ^{13}C-labeled imidazolidinethione **3.23** was obtained in 52 % yield (Scheme 3.3).

The ^{13}C NMR spectrum of **3.23** clearly shows that the product contains ^{13}C at the 2- and 5-positions (δ 183.17 (^{13}C=S) and δ 54.46 ($^{13}CH_2$), respectively) (Figure 3.2). The mass spectrum gave an intense molecular ion peak at *m/e* 326. Therefore, the ^{13}C-

Scheme 3.3



3.17 **3.18** **3.19** **3.20** **3.21** **3.22** **3.23**

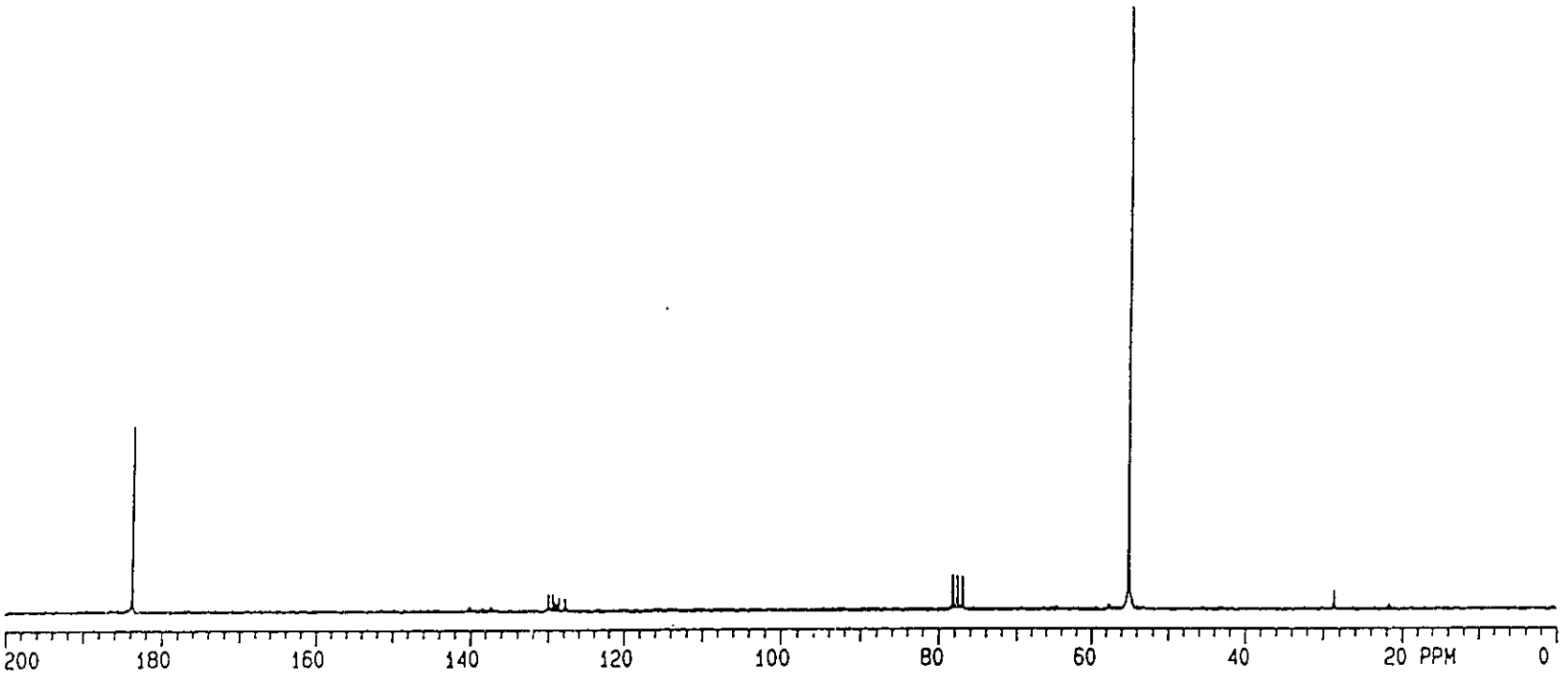
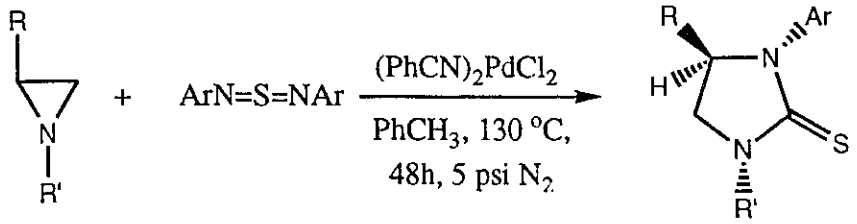


Figure 3.2 ^{13}C-NMR spectrum of **3.23**

labeling experiment demonstrated that the source of the new carbon atom in **3.13** is the CH_2 group of the reactant aziridine **3.12**.

Some additional information relevant to the reaction was obtained by analysis of the products accompanying the cycloaddition of **3.12** and **3.11** (eq. 3.6).



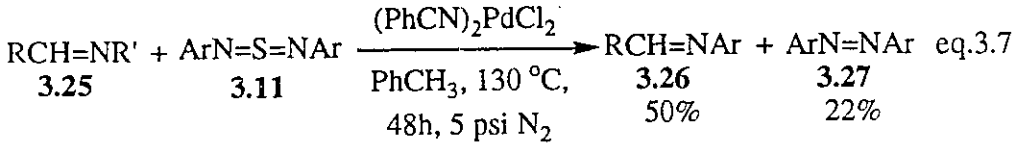
3.12 **3.11** **3.13** 60%

eq.3.6

+ $ArNH_2$ **3.24** 58% + RCH=NR' **3.25** 15% + RCH=NAr **3.26** 45%

(R = *p*-$C_6H_5C_6H_4$, R' = $C(CH_3)_3$, Ar = *p*-tolyl)

The primary arylamine **3.24** and two imines **3.25** and **3.26** were also isolated when **3.12** (R = *p*-$C_6H_5C_6H_4$, R' = $C(CH_3)_3$) was treated with **3.11** (Ar = *p*-tosyl) to give **3.12** under the standard conditions. The yield of amine **3.24** (originally part of the sulfur diimide **3.11**) was almost the same as that of the imidazolidinethione **3.13**. The yield of the imine **3.25**, which results from formal loss of methylene from the aziridine **3.12**, was 15 %. Imine **3.26**, isolated in 45 % yield, may arise from an exchange reaction between **3.25** and **3.11**.



eq.3.7

(R = *p*-$C_6H_5C_6H_4$, R' = $C(CH_3)_3$, Ar = *p*-tolyl)

Some evidence for the latter reaction was obtained by treating the imine **3.25** with the sulfur diimide **3.11** in the presence of $PdCl_2(PhCN)_2$, which afforded a mixture of imine **3.26** (50 %) and azoarene **3.27** (22 % yield) (eq 3.7). Any azoarene **3.27**, formed by treatment of **3.12** with **3.11** (eq. 3.6) could react with a palladoazacyclobutane, to give **3.24** and **3.26**. This would explain the generation of any traces of **3.27** in the reaction leading to **3.12** (eq 3.6). This rationale assumes occurence of a metathesis pathway for the production of the imidazolidinethione.

In conclusion, bis(benzonitrile)palladium dichloride is an effective catalyst for the reaction of aziridines with sulfur diimides. This unique cyclization reaction affords 2-imidazolidinethiones in good yields. Palladium(II)-catalyzed reaction of aziridine with phenylisothiocyanate results in the formation of thiazolidinimine in high yield.

CHAPTER 4

REGIOSPECIFIC AND STEREOSPECIFIC PALLADIUM-CATALYZED CYCLOADDITION OF AZETIDINES AND HETEROCUMULENES

4.1 INTRODUCTION

The cycloaddition reaction of three-membered ring heterocycles with heterocumulenes is a useful method for the formation of five membered-ring heterocycles (see Section 1.2.1, Chapter 2 and Chapter 3). In principle, six-membered ring heterocycles can be synthesized by cycloaddition of four-membered ring heterocycles and heterocumulenes. Few examples of cycloaddition reactions of four-membered ring heterocycles (oxetanes) with heterocumulenes have been reported (see Section 1.2.2). There are no examples of the cycloaddition of azetidines and heterocumulenes. This may be due, in part, to the lower ring strain of the azetidine compared with the aziridine ring system. Consequently, ring cleavage of an azetidine occurs much less readily than that of an aziridine.[150]

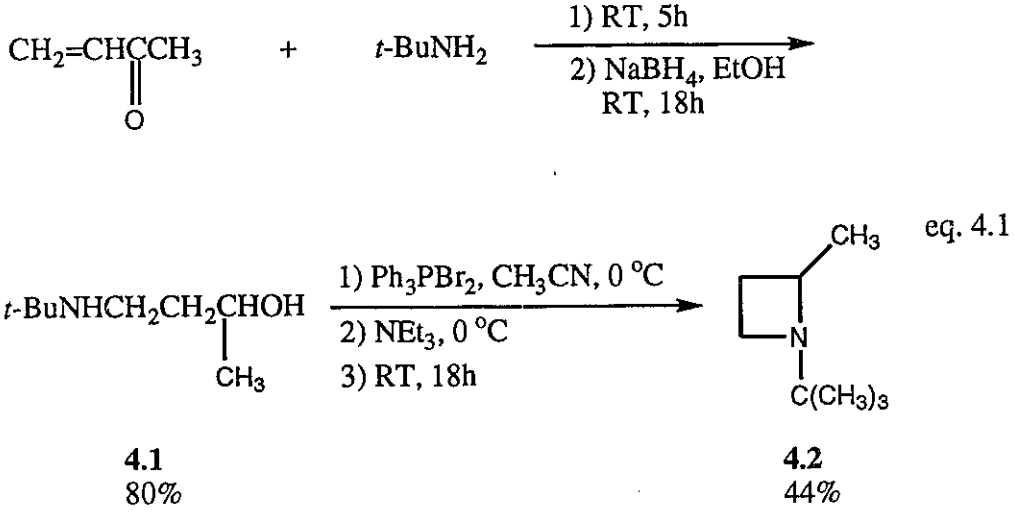
The present chapter describes our results for palladium-catalyzed cycloaddition reactions of azetidines with heterocumulenes.

4.2 RESULTS AND DISCUSSION

4.2.1 SYNTHESIS OF AZETIDINES

The most important method of azetidine synthesis is cyclization of open-chain compounds, most generally by formation of the C-N bond.[151]

In order to study the palladium-catalyzed cycloaddition reaction of azetidines with heterocumulenes, we prepared three representative derivatives of these heterocycles: 1-*tert*-butyl-2-methylazetidine (**4.2**), 1-alkyl-2-carboalkoxyazetidines (**4.4**) and *trans*-1-n-butyl-2-carbomethoxy-4-methylazetidine (**4.6**).



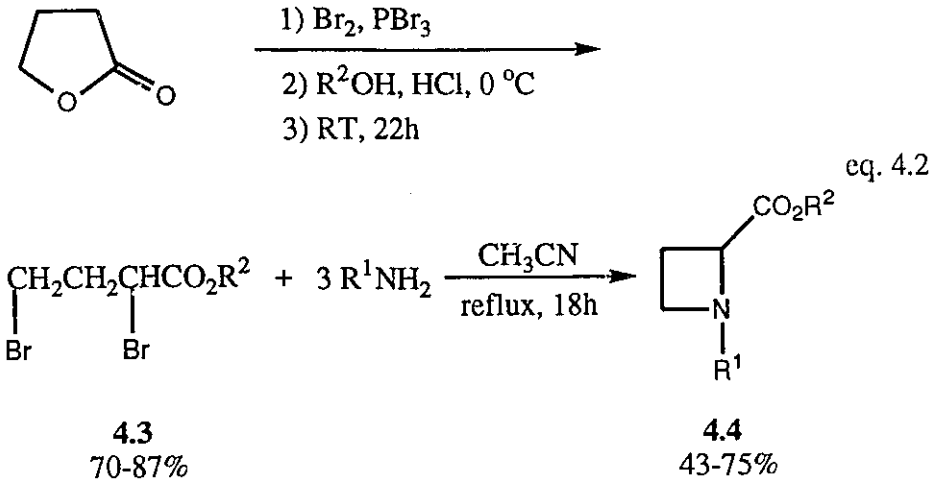
eq. 4.1

4.1
80%

4.2
44%

1-*tert*-Butyl-2-methylazetidine **4.2** was synthesized by the cyclization of 4-*tert*-butylamino-2-butanol **4.1** which can be made by reduction of the amino ketone obtained by addition of *tert*-butylamine to methyl vinyl ketone (eq. 4.1).[152]

Four 1-alkyl-2-carboalkoxyazetidines (**4.4**, R^1 = $C(CH_3)_3$, C_6H_{11}, R^2 = CH_3, $C_6H_5CH_2$) were prepared by the reaction of three molar equivalents of primary amines with α,γ-dibromobutyrate derivatives **4.3** which can be synthesized by bromination and subsequent esterification of γ-butyrolactone (eq. 4.2).[153, 154]



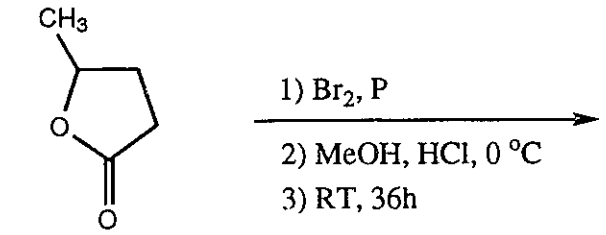
eq. 4.2

4.3
70-87%

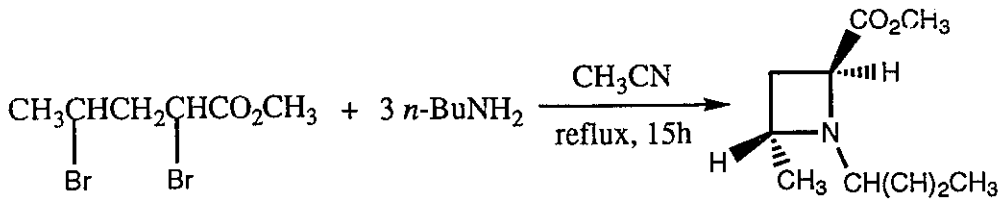
4.4
43-75%

Using a similar procedure, previously unknown *trans*-1-n-butyl-2-carbomethoxy-4-methylazetidine **4.6** was prepared by the

reaction of methyl α, γ-dibromovalerate **4.5** with *n*-butylamine (eq. 4.3).[155]



eq. 4.3



4.5
58%

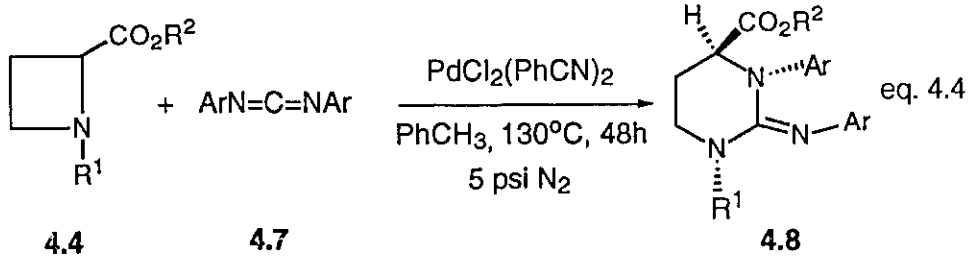
4.6
30%

4.2.2 PALLADIUM-CATALYZED CYCLOADDITION OF 1,2-DI- AND 1,2,4-TRISUBSTITUTED AZETIDINES AND CARBODIIMIDES

An investigation of the reaction of azetidines with carbodiimides was carried out using palladium complexes. Bis(dibenzylideneacetone)palladium(0), bis(triphenylphosphine)palladium(II) dichloride, palladium(II) acetate, tetrakis(triphenylphosphine)palladium(0), palladium(II) trifloroacetate, tetrakis(acetonitrile)palladium(II) tetrafloroborate,

bis(benzonitrile)palladium(II) dichloride and bis(acetonitrile)palladium(II) dichloride were all unable to catalyze the reaction of 1-*tert*-butyl-2-methylazetidine with diphenylcarbodiimide. No reaction occurred, even at high temperature (180 °C). The lack of reactivity of 1-*tert*-butyl-2-methylazetine may have been a result of the electron-releasing effect of the 2-methyl substituent. Therefore, a study was undertaken using a more electron-withdrawing group substituted azetidine such as 1-*tert*-butyl-2-carbomethoxyazetidine. The results are summarized in Table 4.1.

First, 1-*tert*-butyl-2-carbomethoxyazetidine (**4.4**, R^1 = $C(CH_3)_3$, R^2 = CH_3) was reacted with an equimolar amount of di-*p*-chlorophenylcarbodiimide **4.7** in toluene at different temperatures, using bis(benzonitrile)palladium dichloride (10 mol %) as the catalyst. No reaction ocurred at 90 °C. An increase of the reaction temperature resulted in the formation of **4.8** (Ar = *p*-ClC_6H_4, R^1 = $C(CH_3)_3$, R^2 = CH_3). The yield of **4.8** increased with the elevation of the temperature and reached its maximum (95%) at 130 °C (eq. 4.4).



eq. 4.4

4.4 **4.7** **4.8**

Table 4.1 Reaction of Azetidine (4.4, R^1 = $C(CH_3)_3$, R^2 = CH_3) with Di-*p*-tolylcarbodiimide under Various Reaction Conditions[a]

solvent	T, °C	reaction time, h	yield of 4.8[b] (%)
$PhCH_3$	90	48	0
$PhCH_3$	100	48	12
$PhCH_3$	120	48	60
$PhCH_3$	130	48	95
$PhCH_3$	130	24	56
$PhCH_3$	130	48	62[c]
$PhCH_3$	130	48	82[d]
$PhCH_3$	140	48	90
benzene	130	48	92
DMF	130	48	0
DMSO	130	48	0
THF	130	48	21
CH_3CN	130	48	30

[a]Reaction Conditions: azetidine (1.0 mmol), carbodiimide (1.0 mmol), $(PhCN)_2PdCl_2$ (0.1 mmol), solvent (3.0 mL), 5 psi N_2. [b] Isolated yield of pure materials. [c] Ratio of azetidine/carbodiimide/$(PhCN)_2PdCl_2$ = 20/20/1. [d]Ratio of azetidine/carbodiimide/$(PhCN)_2PdCl_2$ = 5/5/1.

At higher temperature (140 °C), the yield is lower due to the decomposition of **4.8**. Other solvents such as benzene, DMF, DMSO, THF, acetonitrile were found to be less effective than toluene. The optimum molar ratio of azetidine to carbodiimide to bis(benzonitrile)palladium dichloride was 10 : 10 : 1.0.

It is also interesting to note that no reaction occurred if dichlorobis(triphenylphosphine)palladium(II) was used as the catalyst. Furthermore, addition of 2 equivalents of triphenylphosphine to the $(PhCN)_2PdCl_2$ catalyzed system, resulted in complete inhibition of the reaction. Finally use of acetonitrile as the nitrile ligand in the palladium catalyst (instead of PhCN) afforded **4.8** in only 36% yield.

These results can be rationalized by consideration of the bond strength between the palladium metal center and its ligand. Triphenylphosphine in $(PPh_3)_2PdCl_2$ is firmly bound and benzonitrile in $(PhCN)_2PdCl_2$ is labile.[156] Indeed, even the IR spectrum of a freshly prepared bis(benzonitrile)palladium dichloride solution (irrespective of solvent) shows two bands (v C≡N at 2230 and 2290 cm^{-1}) due to both free and complexed PhCN and are of comparable intensity.[157] The acetonitrile ligand in $(MeCN)_2PdCl_2$ is more basic than benzonitrile ligand of $(PhCN)_2PdCl_2$.[156] Therefore, $(PhCN)_2PdCl_2$ should react in a more facile manner than $(MeCN)_2PdCl_2$ with azetidines to give N-donor ligand complexes which are active species for the cycloaddition reaction.[158, 159]

The bis(benzonitrile)palladium dichloride catalyzed cycloaddition reaction was effected using a variety of azetidines and carbodiimides, producing tetrahydropyrimidin-2-imines **4.8** in 64-97% yield (see Table 4.2). In all of these reactions the azetidines undergo selective cleavage of the more substituted ring carbon-nitrogen bond.

TABLE 4.2 Reaction of Azetidines with Carbodiimides Catalyzed by $(PhCN)_2PdCl_2$[a]

Ar	R^1	R^2	Yield of **4.8**[b] (%)
Ph	$C(CH_3)_3$	CH_3	92
Ph	$C(CH_3)_3$	$C_6H_5CH_2$	94
p-tolyl	$C(CH_3)_3$	$C_6H_5CH_2$	64
p-ClC_6H_4	C_6H_{11}	CH_3	88
p-ClC_6H_4	$C(CH_3)_3$	CH_3	95
p-ClC_6H_4	$C(CH_3)_3$	$C_6H_5CH_2$	97

[a] Reaction Conditions: azetidine (1.0 mmol), carbodiimide (1.0 mmol), $(PhCN)_2PdCl_2$ (0.1 mmol), $PhCH_3$ (3.0 mL), 130 °C, 48h, 5 psi N_2. [b]Isolated yield of pure materials.

The tetrahydropyrimidin-2-imines **4.8**, were identified by means of spectral data (see Section 5.4) and an X-ray analysis of one product. The imine and carbonyl stretching absorption bands of **4.8** occurred in the infrared spectrum at 1606-1623 cm^{-1} and 1736-1744 cm^{-1}, respectively.[160] The signals for the imine and carbonyl carbon appeared at δ 150.84-151.69 and δ 172.22-172.91, respectively in the ^{13}C NMR spectra, and molecular ion peaks were observed in the mass spectra of **4.8**.[161] An X-ray structure determination revealed that the phenyl substituent of **4.8** (R^1 = $C(CH_3)_3$, R^2 = $CH_2C_6H_5$, Ar = Ph) was *trans* to both of the substituents ($O_2CCH_2C_6H_5$, $C(CH_3)_3$). An ORTEP drawing is presented in Figure 4.1.

The stereochemistry of the cycloaddition reaction is important for understanding the reaction mechanism as well as for the design of biologically active tetrahydropyrimidine derivatives.[162] The reaction of *trans*-1-*n*-butyl-2-carbomethoxy-4-methylazetidine **4.6** with di-*p*-chlorophenylcarbodiimide **4.7** in toluene at 140 °C, for 48h, using bis(benzonitrile)palladium dichloride as the catalyst, gave *trans*-1-*n*-butyl-3-*p*-chlorophenyl-4-carbomethoxy-6-methyl-3,4,5,6-tetrahydropyrimidin-2(1H)-*p*-chlorophenylimine **4.9** in 55% yield (eq 4.5). Compound **4.9** was identified by means of spectral data (see Experimental Section) as well as X-ray analysis. An ORTEP drawing is presented in Figure 4.2.

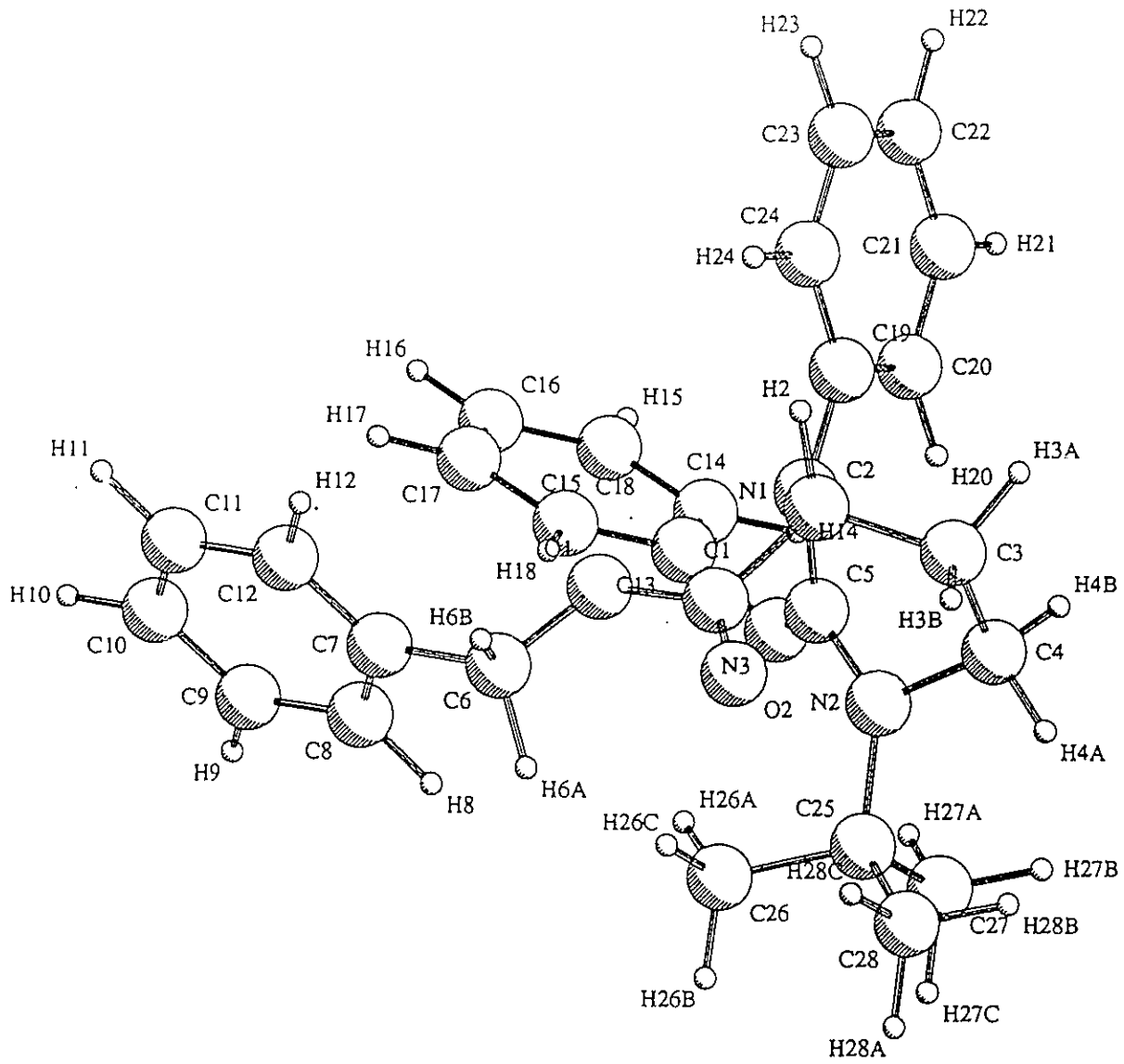
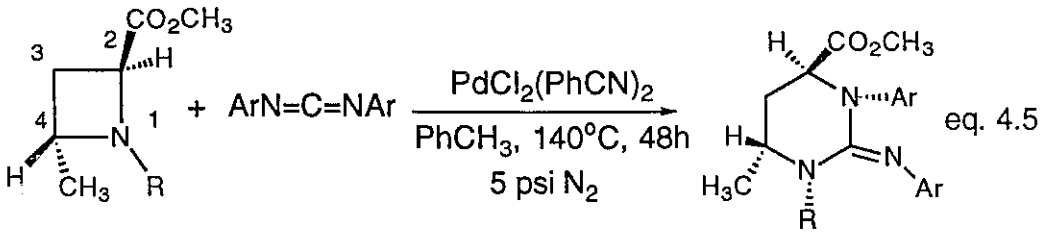


Figure 4.1. View of **4.8** (R^1 = $C(CH_3)_3$, R^2 = $CH_2C_6H_5$, Ar = Ph) showing the atom numbering scheme.

As in the case of 1,2-disubstituted azetidine, the reaction proceeds by cleavage of only the N-C_2 bond (i.e. the N-C_4 bond is unaffected). The cycloaddition also occurs with retention



eq. 4.5

4.6 **4.7** **4.9**

(R=*n*-Bu, Ar=*p*-ClC_6H_4)

of configuration of the carbon centers bearing the substituent groups. However, *trans*-1-*tert*-butyl-2-carbomethoxy-4-methylazetidine did not give any cycloaddition product under identical reaction conditions. This result can be explained by the probable slow rate of the formation of a palladium-azetidine N-donor ligand complex. Because of the steric hindrance caused by the bulky N-*tert*-butyl group, the formation of the N-donor ligand complex between the azetidine and $(PhCN)_2PdCl_2$ is much less efficient than in the case of *trans*-1-*n*-butyl-2-carbomethoxy-4-methylazetidine **4.6**.

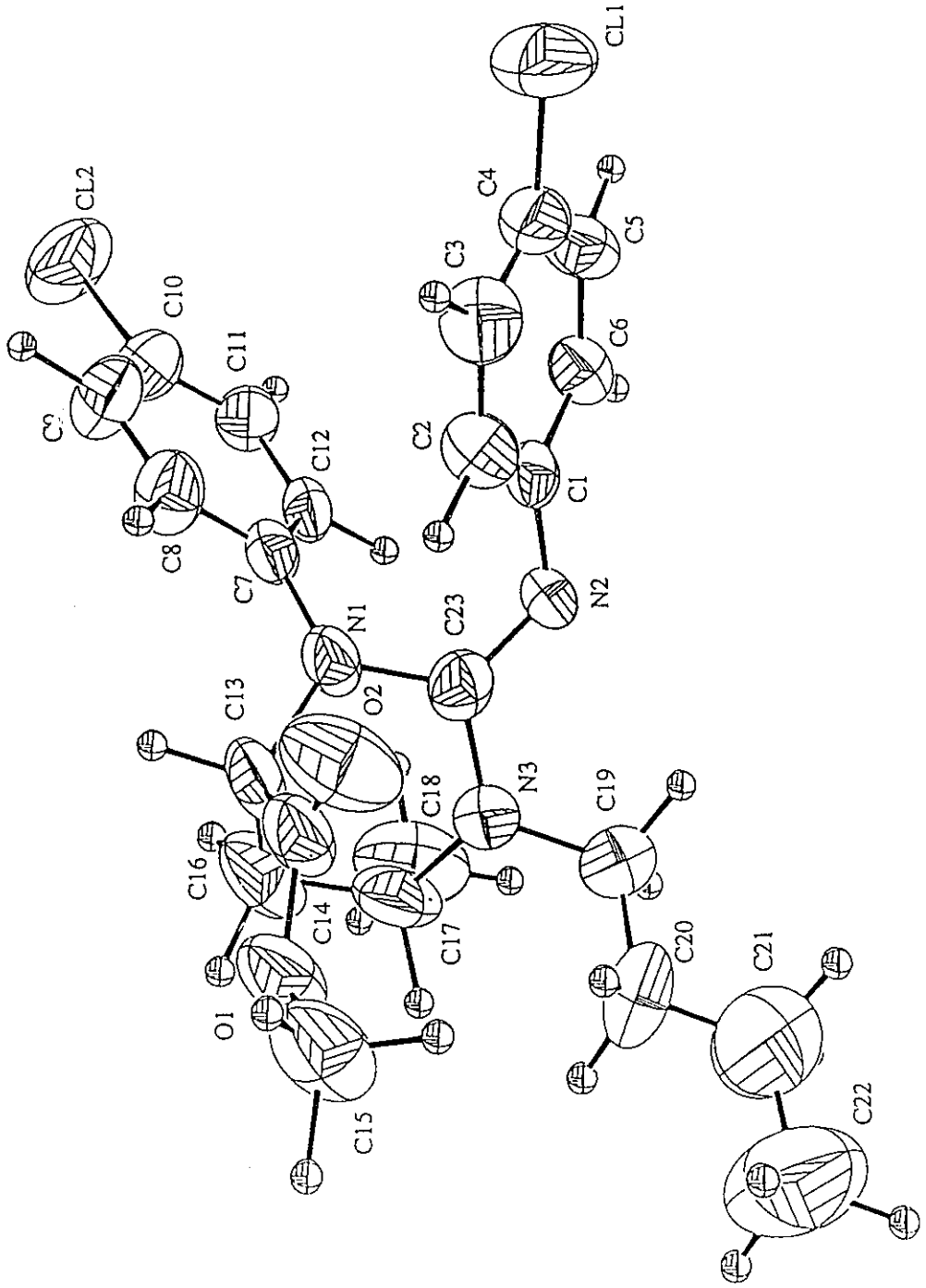


Figure 4.2. View of 4.9 (R^1 = n-C_4H_9, R^2 = CH_3, R^3 = CH_3, Ar = p-ClC_6H_4) showing the atom numbering scheme.

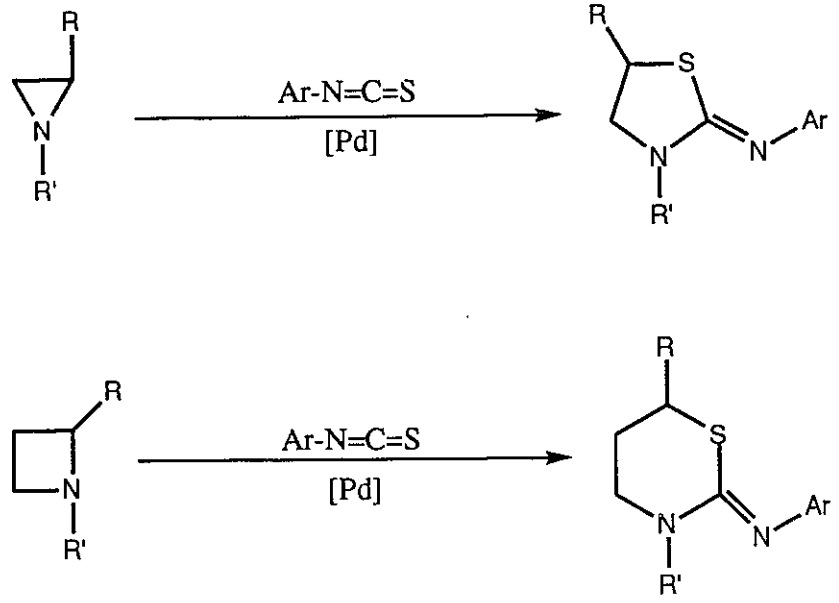
Thus, palladium(II)-catalyzed cycloaddition of 1,2-disubstituted azetidines with carbodiimides results in excellent yields of tetrahydropyrimidin-2-imines. Similar reaction involving 1,2,4-trisubstituted azetidine occurs stereospecifically with retention of configuration of the carbon centres bearing the substituent groups.

The chemistry described above represents the first examples of the transition metal-catalyzed synthesis of pyrimidinimine derivatives from azetidines and carbodiimides. It allows us to assume that reactions of azetidines with heterocumulenes in the presence of a Pd(II) catalyst would give rise to new six-membered ring heterocycles. The results of this study are described in the next section.

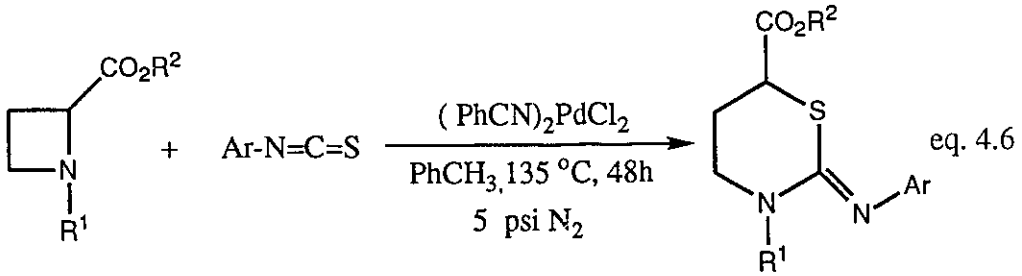
4.2.3 PALLADIUM-CATALYZED CYCLOADDITION OF 1,2-DISUBSTITUTED AZETIDINES AND ISOTHIOCYANATES

Taking into account the results for the cycloaddition reactions of 1,2-disubstituted aziridines and aryl isothiocyanates which gave thiazolidinimines in high yields with both regio- and stereospecificity (see Chapter 2 and 3), we have undertaken the study of similar cycloadditions involving 1,2-disubstituted azetidines. If aziridines and azetidines behave similarly, we could expect the formation of 1,3-thiazine derivatives (Scheme 4.1).

Scheme 4.1



Indeed, when 1-*tert*-butyl-2-carbomethoxyazetidine (**4.4**, R^1 = $C(CH_3)_3$, R^2 = CH_3) was reacted with an equimolar amount of *p*-chlorophenyl isothiocyanate **4.10** in toluene at 135°C, using bis(benzonitrile)palladium dichloride (10 mol %) as the catalyst, the tetrahydro-1,3-thiazine-2-imine **4.11** (Ar = *p*-ClC_6H_4, R^1 = $C(CH_3)_3$, R^2 = CH_3) was formed in 90% yield (eq 4.6).



eq. 4.6

4.4 **4.10** **4.11**

The optimized reaction conditions and results are presented in Table 4.3.

TABLE 4.3 Reaction of Azetidines with Isothiocyanates Catalyzed by $(PhCN)_2PdCl_2$[a]

Ar	R^1	R^2	Yield of **4.11**[b] (%)
Ph	$C(CH_3)_3$	$C_6H_5CH_2$	82
p-ClC_6H_4	$C(CH_3)_3$	CH_3	90
p-ClC_6H_4	$C(CH_3)_3$	$C_6H_5CH_2$	93
p-$NO_2C_6H_4$	$C(CH_3)_3$	$C_6H_5CH_2$	98
p-$NO_2C_6H_4$	C_6H_{11}	CH_3	85
p-$NO_2C_6H_4$	$C(CH_3)_3$	CH_3	92
p-$NO_2C_6H_4$	1-adamantyl	CH_3	89

[a] Reaction Conditions: azetidine (1.0 mmol), isothiocyanate (1.0 mmol), $(PhCN)_2PdCl_2$ (0.1 mmol), $PhCH_3$ (2.0 mL), 135 °C, 48h, 5 psi N_2. [b]Isolated yield of pure materials.

Cycloaddition of aryl isothiocyanate to the azetidine (**4.4**, R^1 = $C(CH_3)_3$, R^2 = CH_3) occurs exclusively into the nitrogen-carbon bond of **4.4** bearing alkoxycarbonyl substituent at position 2.

It should be mentioned that 1-*tert*-butyl-2-methylazetidine did not react with aryl isothiocyanate under similar reaction conditions.

It is also interesting to note that the four-membered ring of the azetidine catalytically cycloadds to the carbon-sulfur double bond, whereas in the case of a carbodiimide, cycloaddition to the central nitrogen - carbon double bond predominates. This result is similar to what we have observed in the reaction of aziridines with aryl isothiocyanates (see section 3.2.2).

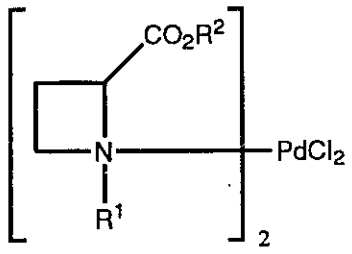
All tetrahydro-1,3-thiazine-2-imines **4.11** are new compounds. The structure of the tetrahydro-1,3-thiazine-2-imines **4.11** was determined by spectroscopic data, i.e., IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis (see section 5.4). The imine and carbonyl stretching absorption bands of **4.11** are observed in the IR spectrum at 1602-1612 cm^{-1} and 1732-1739 cm^{-1}, respectively.[160] The resonance signals for the imine and carbonyl carbon appeared at δ 153.92-157.26 and δ 171.60-172.26 ppm respectively in the ^{13}C NMR spectra, and molecular ion peaks were found in the mass spectra of **4.11**.[161]

As anticipated, azetidines smoothly react with aryl isothiocyanates in the presence of bis(benzonitrile)palladium dichloride affording previously unknown 1,3-thiazine-2-imines in excellent yields and regiospecifically.

4.2.4 ISOLATION AND CHARACTERIZATION OF A CATALYTICALLY ACTIVE INTERMEDIATE DICHLORO BIS(1-*tert*-BUTYL-2-CARBOMETHOXY AZETIDINE)PALLADIUM(II), AND A POSSIBLE MECHANISM FOR THE CYCLOADDITION REACTION

While carrying out the reaction of 1,2-disubstituted azetidines with heterocumulenes, the palladium(II) catalyst was added to the solution of other reagents in toluene at room temperature. In all cases, the addition of bis(benzonitrile)palladium dichloride caused the precipitation of solid material which dissolved upon heating the mixture to the reaction temperature. It was assumed that the solid product which forms at room temperature may perform an important function in the cycloaddition.

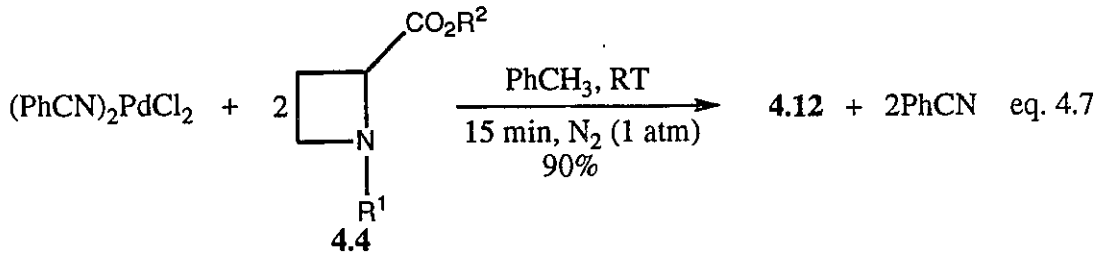
When a catalytic amount (10 molar %) of $(PhCN)_2PdCl_2$ was added to an equimolar mixture of azetidine (**4.4**, $R^1 = C(CH_3)_3$, $R^2 = CH_3$) and aryl isothiocyanates or carbodiimides at room temperature, a dark-brown powder was isolated in almost quantitative yield (based on palladium). According to elemental analysis data, the product consisted of dichloro bis(1-*tert*-butyl-2-carbomethoxy- azetidine)palladium(II) **4.12**. It was also characterized by IR and FAB-MS (see section **5.4**).[163, 164]



4.12

($R^1 = C(CH_3)_3$, $R^2 = CH_3$)

The same complex **4.12** then, was synthesized readily in high yield by a stoichiometric reaction of azetidine (**4.4**, R^1 = $C(CH_3)_3$, R^2 = CH_3) with $(PhCN)_2PdCl_2$ in toluene at room temperature (eq. 4.7).

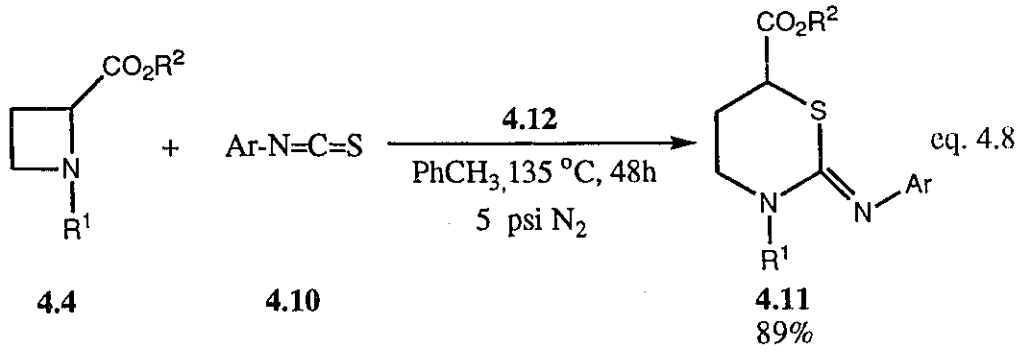


4.4

($R^1 = C(CH_3)_3$, $R^2 = CH_3$)

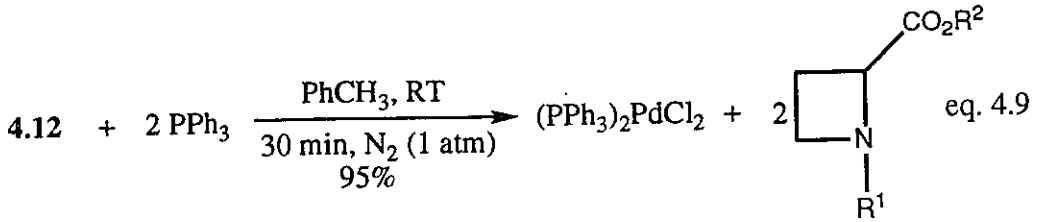
Compound **4.12** is air stable and insoluble in common organic solvents. It does dissolve in both DMF and DMSO, but unfortunately these solvents also cause the decomposition of **4.12**. Consequently, we were unable to record an NMR spectrum. Taking into account the

ease of formation of **4.12**, it is believed that this complex is a genuine catalyst for the cycloaddition reaction. Indeed, the reaction of 1-*tert*-butyl-2-carbomethoxyazetidine (**4.4**, R^1 = $C(CH_3)_3$, R^2 = CH_3) with *p*-chlorophenyl isothiocyanate (**4.10**, Ar = *p*-ClC_6H_4) carried out under optimum conditions in the presence of 10 mol % of **4.12** afforded the same cycloaddition product, tetrahydro-1,3-thiazine-2-imine (**4.11**, R^1 = $C(CH_3)_3$, R^2 = CH_3, Ar = *p*-ClC_6H_4), which was formed when using $(PhCN)_2PdCl_2$ (eq. 4.8). The yield of **4.11** (89 %) was also the same as in the case of $(PhCN)_2PdCl_2$ (90 %).



4.4 **4.10** **4.11** 89%

The azetidine ligands in complex **4.12** were easily replaced by triphenylphosphine giving rise to the known bis(triphenylphosphine)palladium dichloride and a free azetidine ligand (eq. 4.9 , see also section 5.4).



eq. 4.9

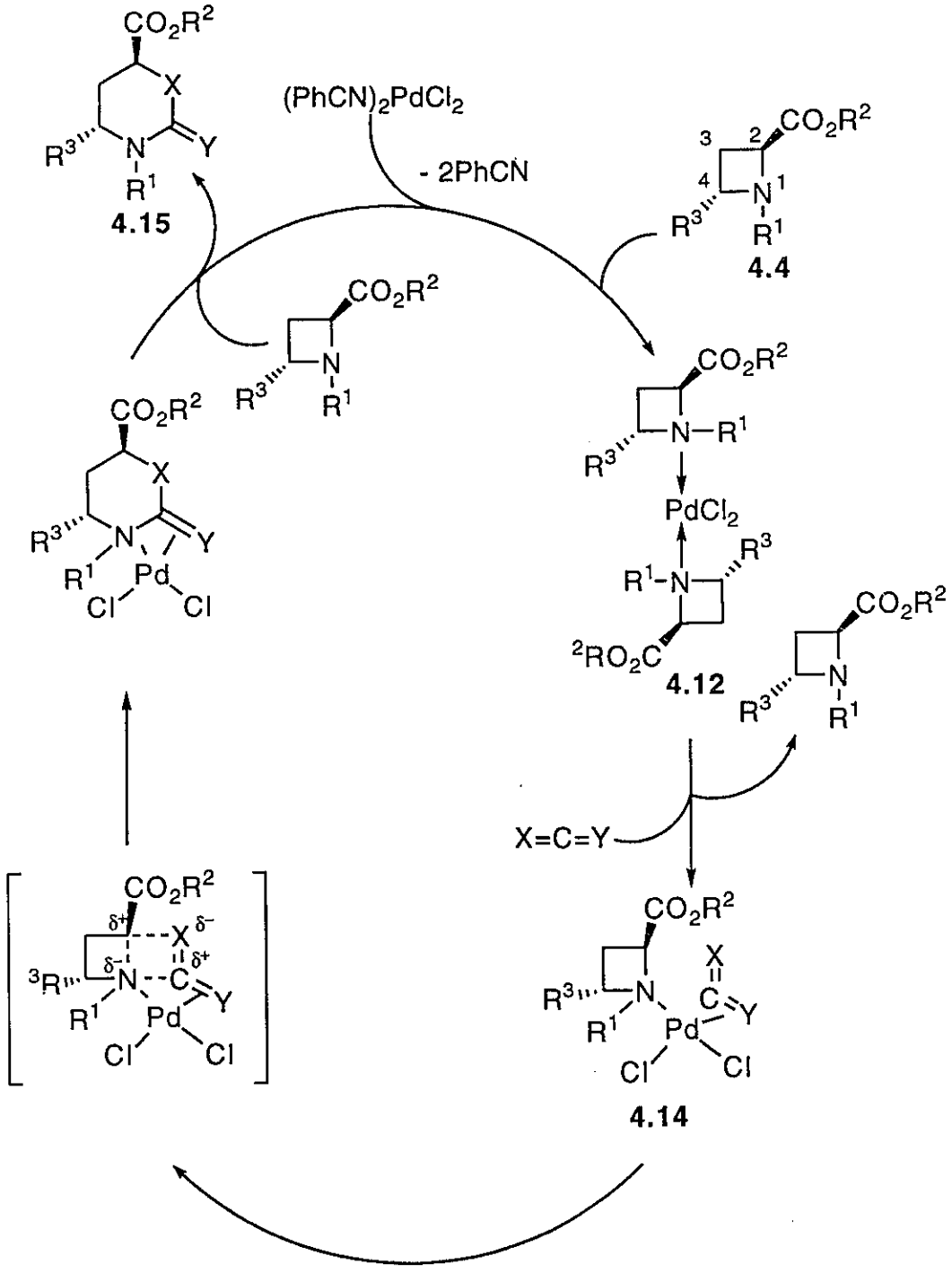
($R^1 = C(CH_3)_3$, $R^2 = CH_3$)

These data explain why $(PPh_3)_2PdCl_2$ is inactive for cycloaddition as well as why the reaction is inhibited by triphenylphosphine (see section 4.2.2). It should be also noted that the failure to perform the cycloaddition in DMF and DMSO can probably be explained by the instability of **4.12** in these solvents.

On the basis of the results obtained from the study of the catalytically active intermediate **4.12**, a possible pathway for the palladium-catalyzed cycloaddition reaction is outlined in Scheme 4.2, which mimics that of the aziridine reactions (see Scheme 2.2). Reaction of $(PhCN)_2PdCl_2$ with the two molar equivalents of azetidine affords the palladium-azetidine N-donor ligand complex **4.12**. Reaction of the latter with the heterocumulene can form **4.14**, in which there is π-complexation of one of the double bonds of heterocumulene to palladium.[128] This complex is by the same type as **2.33** (Scheme 2.2) and the subsequent conversion to **4.15** follow the same route as that for **2.36**.

In conclusion, the reaction of substituted azetidines with heterocumulenes (carbodiimides and isothiocyanates) are smoothly catalyzed by bis(benzonitrile)palladium dichloride affording the corresponding cycloaddition products in excellent yields, regio- and stereospecifically. It has been shown that this reaction occurs *via* a bis(azetidine)palladium(II) dichloride intermediate.

Scheme 4.2



CHAPTER 5

EXPERIMENTAL

5.1 GENERAL COMMENTS

Bruker AMX 500, Varian XL 300 and Gemini 200 NMR spectrometer were used for recording ^{1}H, ^{13}C and ^{31}P spectra. ^{1}H and ^{13}C chemical shifts are reported in ppm and referenced to residual protons in the deuterated solvents (7.24 ppm for $CDCl_3$). ^{31}P NMR chemical shifts are reported in ppm relative to the external standard (85 % H_3PO_4). Chemical shifts reported upfield of zero are defined as negative.

A Bomem MB100 FT-IR spectrometer, interfaced to NEC 286 computer was used with Bomem version 1.45 Michelson series software for all infrared analyses. The samples were run neat, as nujol mulls, in solution or as KBr pellets.

A VG7070E spectrometer was used for mass spectral determinations. The energy of ionization was 70 eV. For complex mixtures, the mass spectrometer was coupled to a gas chromatograph for GC-MS analysis.

A Fisher-Johns melting point apparatus was used and the uncorrected values are reported.

Varian 3300 and Hewlett Packard chromatographs were used for GC analyses. Both instruments were equipped with flame ionization detectors and packed columns containing OV-101 and 1.5

% OV-17 + 1.95 % OV-210 on Chromosorb W-HP (100-200 mesh), respectively.

A Perkin-Elmer 241 polarimeter was used for measuring optical rotations.

A standard vacuum line equipped with a two stage Edwards pump was used for handling air and moisture sensitive materials.

Fischer and Porter glass autoclaves were used for all reactions. For experiments at elevated temperatures, a silicone oil bath was used.

The palladium catalysts were prepared according to literature procedures.[123]. Organic solvents were dried, purified and distilled as described in the literature.[124].

Elemental analyses were carried out by MHW Laboratories, Phoenix, AZ.

5.2 EXPERIMENTAL FOR CHAPTER 2

5.2.1 SYNTHESIS OF AZIRIDINES

5.2.1.1 1-ALKYL-2-ARYLAZIRIDINES

Different 1-alkyl-2-arylaziridines were prepared according to the methods of Okada, Ichimura and Sudo[115]. Some characteristic data of aziridines are presented below.

1-*tert*-Butyl-2-phenylaziridine (**2.3**, R = Ph, R' = $C(CH_3)_3$)

58% yield; bp 40-42 °C/0.5 mmHg (lit.[115] bp 120 °C/20 mmHg); ^1H NMR ($CDCl_3$) δ 1.10 (s, 9H, $C(CH_3)_3$), 1.52 (d, 1H, *J* = 2.0 Hz), 1.90 (d, 1H, *J* = 6.0 Hz), 2.61 (dd, 1H, CHPh, *J* = 2.0, 6.0 Hz), 7.17-7.32 (m, 5H, Ph); MS (*m/e*) 175 $[M]^+$.

1-*n*-Butyl-2-phenylaziridine (**2.3**, R = Ph, R' = *n*-C_4H_9)

60% yield; bp 69-71 °C/0.6 mmHg (lit.[115] bp 80-81 °C/1.0 mmHg); ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, CH_3, *J* = 7.2 Hz), 1.35 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 1.65 (d, 1H, *J* = 6.4 Hz), 1.87 (d, 1H, *J* = 3.4 Hz), 2.27 (dd, 1H, CHPh, *J* = 3.4, 6.4 Hz), 7.12-7.35 (m, 5H, Ph); MS (*m/e*) 175 $[M]^+$.

1-*tert*-Butyl-2-(*p*-bromophenyl)aziridine (**2.3**, R = *p*-BrC_6H_4, R' = $C(CH_3)_3$)

65% yield; mp 34-35 °C; (lit.[116] mp 32-34 °C); ^1H NMR ($CDCl_3$) δ 1.05 (s, 9H, $C(CH_3)_3$), 1.55 (d, 1H, *J* = 3.0 Hz), 1.87 (d, 1H, *J* = 6.4 Hz), 2.65 (dd, 1H, CHPh, *J* = 3.0, 6.4 Hz), 7.13-7.39 (m, 4H, Ph); MS (*m/e*) 253 $[M]^+$, 255 $[M + 2]^+$.

1-*tert*-Butyl-2-(*p*-biphenyl)aziridine (**2.3**, R = *p*-PhC_6H_4, R' = $C(CH_3)_3$)

58% yield; mp 80-81 °C; (lit.[116] mp 80-82 °C); ^1H NMR ($CDCl_3$) δ 1.03 (s, 9H, $C(CH_3)_3$), 1.62 (d, 1H, *J* = 3.0 Hz), 1.90 (d, 1H, *J* = 6.2 Hz), 2.65 (dd, 1H, CHAr, *J* = 3.0, 6.2 Hz), 7.17-7.62 (m, 9H, aromatic ring protons); MS (*m/e*) 251 $[M]^+$.

1-(1-Adamantyl)-2-phenylaziridine (**2.3**, R = Ph, R' = 1-adamantyl)

92 % yield; mp 161-162 °C (lit.[116] mp 161-162 °C); ^{1}H NMR ($CDCl_3$) δ 1.51-2.22 (m, 17 H, adamantyl and CH_2), 2.81 (dd, 1 H, CHPh, *J* = 3.0, 6.4 Hz), 7.12-7.40 (m, 5 H, Ph); MS (*m/e*) 253 $[M]^+$.

1-(1-Adamantyl)-2-(*p*-biphenyl)aziridine (**2.3**, R = *p*-PhC_6H_4, R' = 1-adamantyl)

76 % yield; mp 104-105 °C; (lit.[116] mp 104-106 °C); ^{1}H NMR ($CDCl_3$) δ 1.55-2.17 (m, 17 H, adamantyl and CH_2), 2.92 (dd, 1 H, CHAr, *J* = 3.0, 6.4 Hz), 7.20-7.62 (m, 9 H, aromatic ring protons); MS (*m/e*) 329 $[M]^+$.

5.2.1.2 SYNTHESIS OF (S)-1-*n*-BUTYL-2-PHENYLAZIRIDINE (**2.9**, R = Ph, R' = *n*-C_4H_9).[116]

(a) CONVERSION OF (R)-PHENYLOXIRANE TO (R)-2-PHENYL-2-(*n*-BUTYLAMINO)-1-ETHANOL.

A mixture of 5 mL (43.7 mmol) of (R)-phenyloxirane (Fluka) and 17.3 mL (175 mmol) of n-butylamine was stirred in an autoclave for 60 h at 95 °C. After evaporation of excess n-butylamine, the residue solid was crystallized from hexane to give 5.3 g (62 %) of white amino alcohol, mp 60-61 °C (lit.[115] mp 58-59 °C); $[\alpha]^{23}_D$ -56.1° (*c* 3.8, $CHCl_3$); IR ($CHCl_3$) ν OH,NH 3600, 3400-3300

cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (t, 3H, CH_3, J = 7.2 Hz), 1.25 (m, 4H, CH_2), 2.05 (m, 5H, CH_2 and NH), 4.60 (dd, 1H, CHPh, J = 3.8, 8.8 Hz), 7.15-7.37 (m, 5H, Ph); MS (*m/e*) 193 $[M]^+$.

(b) CYCLIZATION OF (R)-1-PHENYL-2-(*n*-BUTYLAMINO)-1-ETHANOL. (2.8, R= Ph, R' = *n*-C_4H_9)

To an ice-cold solution of 4.42 g (16.8 mmol) of triphenylphosphine in 25 mL of acetonitrile (N_2 atmosphere) was added drop-by-drop, an ice-cold solution of 2.7 g (16.8 mmol) of bromine in 10 mL of acetonitrile. To the resulting red solution was slowly added 3.25 g (16.8 mmol) of the β-amino alcohol, followed by drop-by-drop addition of 5.11 g (50.5 mmol) of distilled triethylamine in 10 mL of acetonitrile (all done at 0 °C). The reaction mixture was then stirred at ambient temperature for 20 min, triethylamine hydrobromide (7.07 g, 77 %) was filtered, and the filtrate was concentrated by rotary evaporation. The residue was treated with hexane (5 x 20 mL), concentrated to 10 mL, and then filtered to remove triphenylphosphine oxide, and the filtrate was evaporated. Aziridine **2.9** (R' = *n*-C_4H_9) was obtained by distillation at 80-81 °C/1.0 mmHg: yield 60 %; $[\alpha]^{23}_D$ +140.5° (*c* 4.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, CH_3, J = 7.2 Hz), 1.35 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 1.65 (d, 1H, J = 6.4 Hz), 1.87 (d, 1H, J = 3.4 Hz), 2.27 (dd, 1H, CHPh, J = 3.4, 6.4 Hz), 7.12-7.35 (m, 5H, Ph); MS (*m/e*) 175 $[M]^+$. Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.37; H, 9.63; N, 8.21.

5.2.1.3 SYNTHESIS OF (R)-1-*n*-BUTYL-2-PHENYLAZIRIDINE (**2.6**, R = Ph, R' = *n*-C4H9).[116]

Aziridine **2.6** (R' = *n*-C4H9) was prepared by treatment of (S)-phenyloxirane (Fluka) with n-butylamine, followed by reaction of the resultant amino alcohol with bromine and triphenylphosphine. Both reactions were run in an identical manner to that described for the preparation of **2.9** (R' = *n*-C4H9) and gave **2.6** (R' = *n*-C4H9) in 40 % overall yield, $[\alpha]^{23}D$ -139.9 ^{o} (*c* 4.2, $CHCl_3$). Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.21; H, 9.72; N, 7.97.

5.2.1.4 SYNTHESIS OF (S)-1-(1-ADAMANTYL)-2-PHENYLAZIRIDINE (**2.9**, R = Ph, R' = 1-adamantyl).[116]

(a) CONVERSION OF (R)-PHENYLOXIRANE TO (R)-1-PHENYL-2-((1-ADAMANTYL)AMINO)-1-ETHANOL.

A mixture of 5 mL (43.7 mmol) of (R)-phenyloxirane and 6.60 g (43.7 mmol) of 1-aminoadamantane in methanol (30 mL) was refluxed for 5 h. The cooled solution was filtered, the filtrate was evaporated, and the crude product was crystallized from hexane affording the amino alcohol in 65 % yield, mp 109-110 ^{o}C (lit.[116] mp 108-110 ^{o}C); $[\alpha]^{23}D$ -57.0^{o} (*c* 1.22, $CHCl_3$); IR ($CHCl_3$) ν OH, NH 3600, 3400-3300 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.62-2.03 (m, 15 H, adamantyl

protons), 2.40-2.80 (m, 4H, CH_2, NH, OH), 4.52 (1 H, CHOH), 7.18-7.45 (m, 5 H, Ph); MS (*m/e*) 271 $[M]^+$.

(b) CYCLIZATION OF (R)-1-PHENYL-2-((1-ADAMANTYL)AMINO)-1-ETHANOL (2.8, R = Ph, R' = 1-adamantyl).

The reaction was effected in the same manner as that described for the preparation of **2.9** (R' = *n*-C_4H_9) with the following modification of the workup procedure: instead of distilling the product, it was crystallized from ether / ethanol affording 2.9 (R' = 1-adamantyl), mp 161-162 °C, in 94 % yield. $[\alpha]^{23}_D$ +108.9° (*c* 4.32, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.51-2.22 (m, 17 H, adamantyl and CH_2), 2.72 (dd, 1 H, CHPh), 7.12-7.40 (m, 5 H, Ph); MS (*m/e*) 253 $[M]^+$.

5.2.1.5 SYNTHESIS OF (R)-1-(1-ADAMANTYL)-2-PHENYLAZIRIDINE (2.6, R = Ph, R' = 1-adamentyl).[116]

Aziridine **2.6** was prepared by treatment of (S)-phenyloxirane with 1-aminoadamantane, followed by reaction of the formed amino alcohol with bromine and triphenylphosphine. The two-step sequence, identical with that described for the preparation of **2.9** (R' = 1-adamantyl) from (R)-phenyloxirane, afforded **2.6** (R' = 1-adamantyl) in 66 % overall yield, $[\alpha]^{23}_D$ -109.2° (*c* 4.56, $CHCl_3$).

5.2.1.6 SYNTHESIS OF *cis*-1-ISOPROPYL-3-METHYL-2-PHENYLAZIRIDINE

Aziridine **2.13** was prepared according to the literature method.[116-119] Some characteristic data of the aziridine are presented below.

68% yield; bp 61-62 °C/0.6 mmHg (lit.[116] bp 54-56 °C/0.4 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 3H, CH_3, J = 5.8 Hz), 1.09, 1.12 (each d, 6H $(C\underline{H}_3)_2CH$, J = 6.2 Hz), 1.65 (m, 2H, $C\underline{H}CH_3$ ring, $C\underline{H}(CH)_2$), 2.42 (d, 1H, CHPh, J = 6.8 Hz), 7.15-7.40 (m, 5H, Ph); MS (*m/e*) 175 $[M]^+$.

5.2.1.7 SYNTHESIS OF *cis*-1-*n*-BUTYL-2-CARBOALKOXY-3-METHYLAZIRIDINES

(a) *cis*-1-*n*-BUTYL-2-CARBOMETHOXY-3-METHYLAZIRIDINE (**2.16**, R = CH_3)

A solution of 39.0g (0.15 mol) of methyl α,β-dibromomethylcrotonate and 33.0g (0.45 mol) of n-butylamine in 600mL of acetonitrile was refluxed for 15 hours. The mixture was diluted with ether (250 mL), filtered, and the solvent evaporated. The residue was extracted with ether (350 mL) and the extract exposed to a stream of hydrogen chloride gas for 5 minutes. The ether was decanted and the residual syrup was dissolved in 35 mL of water. The aqueous solution was washed twice with ether

(discarded), 250 mL of ether added, and solid sodium bicarbonate added to neutrality. The ether layer was separated, the aqueous layer washed with three 70 mL portions of ether, and the combined extracts dried over magnesium sulfate. Careful vacuum fractional distillation of the crude product through a 30-cm Vigreux column gave 9.0g (35%) of **2.16** (R = CH_3) as a colorless oil: b.p. 52-55 °C (0.4 mmHg); IR ($CDCl_3$) ν (C=O) 1748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (t, 3H, CH_3, *J* = 7.2 Hz), 1.12 (d, 3H, CH_3, *J* = 5.6 Hz), 1.25 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 1.72 (m, 1H, CH, ring), 1.97 (d, 1H, $CHCO_2$, *J* = 6.8 Hz), 2.25 (m, 2H, CH_2N), 3,65 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 13.79, 14.54 (CH_3), 20.94, 31.99 (CH_2), 42.30, 43.09 (CH, ring), 52.39 (CO_2CH_3), 61.12 (CH_2N), 170.98 (C=O); MS (*m/e*) 171 $[M]^+$. Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01;N, 8.18. Found: C, 63.10; H, 9.97; N, 8.12.

(b) *cis*-1-*n*-BUTYL-2-CARBOETHOXY-3-METHYLAZIRIDINE (2.16, R = C_2H_5)

Aziridine **2.16** (R = C_2H_5) was prepared by treatment of ethyl 2,3-dibromocrotonate with n-butylamine. The procedure, identical with that described above for the preparation of **2.16** (R = CH_3) from methyl 2,3-dibromocrotonate, afforded **2.16** (R = C_2H_5) in 30% overall yield. b.p. 51-54 °C (0.5 mmHg); IR ($CDCl_3$) ν (C=O) 1746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.67 (t, 3H, CH_3, *J* = 7.2 Hz), 1.03 (d, 3H, CH_3, *J* = 5.6 Hz), 1.05 (t, 3H, CH_3, *J* = 7.0 Hz), 1.11 (m, 2H, CH_2), 1.35 (m, 2H, CH_2), 1.57 (m, 1H, CH, ring), 1.82 (d, 1H, $CHCO_2$, *J* = 6.8 Hz), 2.10 (m, 2H, CH_2N), 3,95 (m, 2H, CO_2CH_2); ^{13}C NMR ($CDCl_3$) δ 13.65, 14.51,

14.81 (CH_3), 20.91, 31.97 (CH_2), 42.17, 43.15 (CH, ring), 61.11 (CO_2CH_2), 61.21 (CH_2N), 170.42 (C=O); MS (*m/e*) 185 $[M]^+$. Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34;N, 7.56. Found: C, 64.76; H, 10.27; N, 7.39.

5.2.2 SYNTHESIS OF DIARYL CARBODIIMIDES

(a) Diphenylcarbodiimide (2.19, Ar = Ph)[120]

Phenyl isocyanate (5.4 g, 4.5 mmol) was pipetted into 5.0 mL of dry benzene under nitrogen. 3-Methyl-1-phenylphospholene-1-oxide (2.5 mmol, 20 mg) was added and the solution was heated to 50 °C with stirring. Evolution of carbon dioxide was vigorous. Heating and stirring were continued for 2.5 hr., at which point gas evolution was slow. Solvent was removed under reduced pressure and the residue was vacuum distilled to yield 4.11 g (94 %) of an oil, bp 119-121 °C (0.40-0.45 mmHg)

(b) 4,4'-Ditolylcarbodiimide (2.19, Ar = *p*-tolyl)[120]

p-Tolyl isocyanate (10.0 g, 75 mmol) was diluted with 15 mL of xylene and refluxed. 3-Methyl-1-phenylphospholene-1-oxide was added and the mixture was refluxed for 4 hours. Carbon dioxide was evolved in copious quantities during this period. The reaction mixture was distilled. After removal of xylene, the boiling point rose sharply to 165 °C (2.4 mmHg) at which temperature 7.3 g (88 %) of ditolylcarbodiimide melting at 56.6-57.5 °C was obtained.

(c) **Bis-(*p*-chlorophenyl)-carbodiimide**, (**2.19**, Ar = *p*-ClC_6H_4)[120]

A mixture of 5.0 g (3.2 mmol) of *p*-chlorophenyl isocyanate and 6.0 mg of 3-methyl-1-phenylphospholene-1-oxide was allowed to stand at room temperature in a vacuum dessicator for about 2 hr. The evolution of carbon dioxide was brisk and the liquid soon turned to a mass of crystals. Without purification, this material (4.23 g, 99 %) melted at 54-56 °C, leaving a trace of high-melting crystalline residue. For purification, 0.2 g of the product was dissolved in isooctane and filtered free of insoluble matter. The filtrate was evaporated to dryness to give 0.18 g (91 %) recovery of a crystalline product which melted sharply at 56-57 °C.

5.2.3 GENERAL PROCEDURE FOR THE PALLADIUM-CATALYZED CYCLOADDITION REACTION OF 1,2-DISUBSTITUTED AZIRIDINES AND CARBODIIMIDES

A mixture of aziridine (1.0 mmol), carbodiimide (1.0 mmol), and bis(benzonitrile)palladium dichloride (0.038g, 0.10 mmol) in toluene (7.0 mL) was heated with stirring in a glass autoclave for 24h, at 100 °C (oil bath temperature) under a slight pressure of nitrogen (5 psi). After being cooled to room temperature, the autoclave was opened and the brown homogeneous solution was filtered through Celite. The filtrate was concentrated by rotary evaporation, and the crude product was purified by silica gel thin-

layer chromatography using 25:1 toluene/acetonitrile as the developer. Melting points, IR, NMR, MS and analytical data for **2.** are as follows:

1-*tert*-Butyl-3,4-diphenylimidazolidine-2-phenylimine (**2.24**, R = Ph, R' = $C(CH_3)_3$, Ar = Ph)

95% yield; mp 88-90 °C; IR ν (C=N) 1641 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (s, 9H, $C(CH_3)_3$), 3.31 (dd, 1H, CH_2, J = 7.8, 8.7 Hz), 3.89 (t, 1H, CH_2, J = 8.5 Hz), 4.53 (t, 1H, CHPh, J = 7.9 Hz), 6.45-7.43 (m, 15H, Ph); ^{13}C NMR ($CDCl_3$) δ 27.14 (CH_3), 51.83 (CH_2), 54.36 ($C(CH_3)_3$), 65.66 (CHPh), 119.27, 122.17, 124.62, 125.56, 127.76, 128.01, 128.80, 128.91 (CH-aromatic), 142.14, 143.54, 149.67 (quaternary aromatic carbons), 152.13 (C=N); MS (*m/e*) 369 $[M]^+$. Anal. Calcd for $C_{25}H_{27}N_3$: C, 81.26; H, 7.37; N, 11.37. Found: C, 80.82; H, 7.39; N, 11.35.

1-*tert*-Butyl-4-phenyl-3-*p*-tolylimidazolidine-2-*p*-tolylimine (**2.24**, R = Ph, R' = $C(CH_3)_3$, Ar = *p*-tolyl)

80% yield; mp 103-105 °C; IR ν (C=N) 1644 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (s, 9H, $C(CH_3)_3$), 2.06 (s, 3H, CH_3), 3.29 (dd, 1H, CH_2, J = 8.0, 8.8 Hz), 3.88 (t, 1H, CH_2, J = 8.3 Hz), 4.52 (t, 1H, CHPh, J = 7.9 Hz), 6.50-7.44 (m, 13H, aromatic ring protons); ^{13}C NMR ($CDCl_3$) δ 20.36, 20.59 (p-$CH_3C_6H_4$), 27.15 (CH_3), 51.82 (CH_2), 54.30 ($C(CH_3)_3$), 65.87 (CHPh), 122.01, 125.52, 127.27, 127.95, 128.24, 128.56, 128.71, 134.10, 141.25, 142.24, 147.03 (aromatic), 152.27 (C=N); MS (*m/e*) 397 $[M]^+$. Anal. Calcd for $C_{27}H_{31}N_3$: C, 81.57; H, 7.86; N, 10.57. Found: C, 81.65; H, 7.67; N, 10.23.

1-(1-Adamantyl)-3,4-diphenylimidazolidine-2-phenylimine (**2.24**, R = Ph, R' = 1-adamantyl, Ar = Ph)

94% yield; mp 120-121 °C; IR ν (C=N) 1639 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66-2.52 (m, 15H, adamantyl), 3.42 (dd, 1H, CH_2, J = 7.4, 8.7 Hz), 3.94 (t, 1H, CH_2, J = 8.6 Hz), 4.51 (t, 1H, CHPh, J = 7.7 Hz), 6.48-7.48 (m, 15H, Ph); ^{13}C NMR ($CDCl_3$) δ 29.89, 36.67, 39.42 (CH, CH_2-adamantyl), 50.88 (CH_2), 55.46 (C-adamantyl), 65.87 (CHPh), 119.28, 122.39, 124.63, 125.49, 127.22, 127.93, 128.16, 128.97, 142.47, 143.76, 149.89 (aromatic carbons), 151.77 (C=N); MS (*m/e*) 447 $[M]^+$. Anal. Calcd for $C_{31}H_{33}N_3$: C, 83.18; H, 7.43; N, 9.39. Found: C, 82.88; H, 7.54; N, 9.45.

1-(1-Adamantyl)-4-phenyl-3-*p*-tolylimidazolidine-2-*p*-tolylimine (**2.24**, R = Ph, R' = 1-adamantyl, Ar = *p*-tolyl)

61% yield; mp 151-153 °C; IR ν (C=N) 1641 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59-2.45 (m, 15H, adamantyl), 2.03 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 3.32 (dd, 1H, CH_2, J = 8.0, 8.6 Hz), 3.84 (t, 1H, CH_2, J = 8.6 Hz), 4.47 (t, 1H, CHPh, J = 8.1 Hz), 6.45-7.42 (m, 13H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 20.39, 20.59 (p-$CH_3C_6H_4$), 29.66, 36.54, 39.08 (CH, CH_2-adamantyl), 65.96 (CHPh), 120.92, 121.92, 125.30, 127.16, 127.90, 128.24, 128.54, 128.70, 133.99, 141.31, 142.42, 147.11 (aromatic carbons), 152.02 (C=N); MS (*m/e*) 475 $[M]^+$. Anal. Calcd for $C_{33}H_{37}N_3$: C, 83.32; H, 7.84; N, 8.83. Found: C, 83.22; H, 7.94; N, 8.85.

1-*tert*-Butyl-4-*p*-biphenyl-3-phenylimidazolidine-2-phenylimine (**2.24**, R = *p*-PhC_6H_4, R' = $C(CH_3)_3$, Ar = Ph)

72% yield; mp 108-109 °C; IR ν (C=N) 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (s, 9H, $C(CH_3)_3$), 3.43 (dd, 1H, CH_2, *J* = 7.7, 8.1 Hz), 3.98 (t, 1H, CH_2, *J* = 8.4 Hz), 4.64 (t, 1H, CHAr, *J* = 7.8 Hz), 6.51-7.69 (m, 19H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 27.27 (CH_3), 51.85 (CH_2), 54.43 ($C(CH_3)_3$), 65.44 (CHAr), 119.41, 122.35, 124.71,125.60, 127.14, 127.56, 127.67, 127.85, 128.13, 128.93, 140.68, 141.02, 141.26, 143.63, 149.72 (aromatic carbons), 151.99 (C=N); MS (*m/e*) 445 $[M]^+$. Anal. Calcd for $C_{31}H_{31}N_3$: C, 83.56; H, 7.01; N, 9.43. Found: C, 83.14; H, 6.94; N, 9.40.

1-*tert*-Butyl-4-*p*-biphenyl-3-*p*-tolylimidazolidine-2-*p*-tolylimine (**2.24**, R = *p*-PhC_6H_4, R' = $C(CH_3)_3$, Ar = *p*-tolyl)

62% yield; mp 133-135 °C; IR ν (C=N) 1644 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (s, 9H, $C(CH_3)_3$), 2.14 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.40 (dd, 1H, CH_2, *J* = 7.5, 9.2 Hz), 3.96 (t, 1H, CH_2, *J* = 8.4 Hz), 4.63 (t, 1H, CHAr, *J* = 8.0 Hz), 6.63-7.70 (m, 17H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 20.36, 20.56 (p-$CH_3C_6H_4$), 27.14 (CH_3), 51.82 (CH_2), 54.34 ($C(CH_3)_3$), 65.58 (CHAr), 122.01, 125.55, 127.08, 127.44, 127.70, 128.27, 128.62, 128.84, 134.16, 140. 67, 140.87, 141.23, 146.99 (aromatic carbons), 152.36 (C=N); MS (*m/e*) 473 $[M]^+$. Anal. Calcd for $C_{33}H_{35}N_3$: C, 83.68; H, 7.45; N, 8.87. Found: C, 83.79; H, 7.41; N, 8.66.

1-(1-Adamantyl)-4-*p*-biphenyl-3-phenylimidazolidine-2-phenylimine (**2.24**, R = *p*-PhC_6H_4, R' = 1-adamantyl, Ar = Ph)

71% yield; mp 165-166 °C; IR ν (C=N) 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70-2.61 (m, 15H, adamantyl), 3.51 (dd, 1H, CH_2, *J* = 7.5, 8.3 Hz), 4.01 (t, 1H, CH_2, *J* = 8.6 Hz), 4.67 (t, 1H, CHAr, *J* = 7.7 Hz), 6.57-7.74 (m, 19H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 29.77, 36.63, 39.24 (CH, CH_2-adamantyl), 50.82 (CH_2), 55.49 (C-adamantyl), 65.53 (CHAr), 119.31, 122.38, 124.64, 125.48, 127.20, 127.63, 127.95, 128.19, 129.01, 140.73, 141.00, 141.51, 143.73, 149.86 (aromatic carbons), 151.73 (C=N); MS (*m/e*) 523 $[M]^+$. Anal. Calcd for $C_{37}H_{37}N_3$: C, 84.85; H, 7.12; N, 8.02. Found: C, 84.52; H, 7.17; N, 7.79.

1-(1-Adamantyl)-4-*p*-biphenyl-3-*p*-tolylimidazolidine-2-*p*-tolylimine (**2.24**, R = *p*-PhC_6H_4, R' = 1-adamantyl, Ar = *p*-tolyl)

40% yield; mp 195-197 °C; IR ν (C=N) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53-2.40 (m, 15H, adamantyl), 2.01 (s, 3H, CH_3), 3.35 (dd, 1H, CH_2, *J* = 7.5, 8.5 Hz), 3.80 (t, 1H, CH_2, *J* = 8.7 Hz), 4.52 (t, 1H, CHAr, *J* = 7.6 Hz), 6.52-7.60 (m, 17H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 20.39, 20.58 (p-$CH_3C_6H_4$), 29.67, 36.54, 39.10 (CH, CH_2-adamantyl), 50.72 (CH_2), 55.37 (C-adamantyl), 65.68 (CHAr), 121.98, 125.33, 127.10, 127.44, 127.61, 128.31, 128.63, 128.88, 134.03, 140.71, 140.80, 141.32, 141.45, 147.08 (aromatic carbons), 151.97 (C=N); MS (*m/e*) 551 $[M]^+$. Anal. Calcd for $C_{39}H_{41}N_3$: C, 84.89; H, 7.49; N, 7.62. Found: C, 85.06; H, 7.12; N, 7.30.

1-*tert*-Butyl-4-*p*-bromophenyl-3-phenylimidazolidine-2-phenylimine (**2.24**, R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = Ph)

90% yield; mp 143-145 °C; IR ν (C=N) 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52 (s, 9H, $C(CH_3)_3$), 3.27 (dd, 1H, CH_2, *J* = 7.5, 8.9 Hz), 3.91 (t, 1H, CH_2, *J* = 8.6 Hz), 4.51 (t, 1H, CHAr, *J* = 7.8 Hz), 6.44-7.53 (m, 14H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 27.11 (CH_3), 51.59 (CH_2), 54.40 ($C(CH_3)_3$), 65.11 (CHAr), 119.43, 121.91, 122.21, 124.85, 125.64, 127.77, 128.11, 131.95, 141.07, 143.30, 149.43 (aromatic carbons), 151.75 (C=N); MS (*m/e*) 449, 447 $[M]^+$. Anal. Calcd for $C_{25}H_{26}BrN_3$: C, 66.96; H, 5.95; N, 9.37. Found: C, 66.80; H, 5.92; N, 9.30.

1-*tert*-Butyl-4-*p*-bromophenyl-3-*p*-tolylimidazolidine-2-*p*-tolylimine (**2.24**, *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = *p*-tolyl)

78% yield; mp 166-168 °C; IR ν (C=N) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (s, 9H, $C(CH_3)_3$), 2.03 (s,3H, CH_3), 2.05 (s,3H, CH_3), 3.19 (dd, 1H, CH_2, *J* = 8.0, 8.4 Hz), 3.82 (t, 1H, CH_2, *J* = 8.4 Hz), 4.44 (t, 1H, CHAr, *J* = 8.0 Hz), 6.41-7.50 (m, 12H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 20.42, 20.61 (p-$CH_3C_6H_5$), 27.15 (CH_3), 51.63 (CH_2), 54.37 ($C(CH_3)_3$), 65.34 (CHAr), 121.84, 122.02, 125.66, 128.31, 128.71, 129.04, 131.89, 134.42, 141.01, 141.16, 146.83 (aromatic carbons), 152.07 (C=N); MS (*m/e*) 475, 477 $[M]^+$. Anal. Calcd for $C_{27}H_{30}BrN_3$: C, 68.06; H, 6.35; N, 8.38. Found: C, 68.34; H, 6.04; N, 8.85.

1-*n*-Butyl-3,4-diphenylimidazolidine-2-phenylimine (2.24, R = Ph, R' = *n*-C_4H_9, Ar = Ph)

95% yield; mp 35-36 °C; IR ν (C=N) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, CH_3), 1.29 (q, 2H, CH_2CH_3), 1.54 (m, 2H, $CH_2CH_2CH_3$), 3.29 (m, 3H, NCH_2 and one H of CH_2 (ring)), 3.94 (t, 1H, CH_2, ring, J = 8.8 Hz), 4.80 (dd, 1H, CHPh, J = 6.2,8.5 Hz), 6.58-7.43 (m, 15H, aromatic); ^{13}C NMR ($CDCl_3$) δ 13.94 (CH_3), 20.06, 29.20 ($CH_2CH_2CH_3$), 46.08 (NCH_2) 54.22 (CH_2 ring), 64.61 (CHPh), 120.07, 122.41, 124.11, 124.16, 126.73, 128.04, 128.10, 128.93, 141.98, 142.07, 149.15 (aromatic carbons), 151.91 (C=N); MS (*m/e*) 369 $[M]^+$. Anal. Calcd for $C_{25}H_{27}N_3$: C, 81.26; H, 7.37; N, 11.37. Found: C, 81.04; H, 7.05; N, 11.55.

5.2.4 HYDROLYSIS OF IMIDAZOLIDENIMINE (2.24, R = Ph, R' = $C(CH_3)_3$, Ar = Ph)

A mixture of the imidzolidenimine (0.092 g, 0.25 mmol), 5 % NaOCl (2.0 mL) and tetra-n-butylammonium hydrogen sulfate (0.017 g, 0.05 mmol) in chloroform (2.0 mL) was stirred for 18 h at room temperature under nitrogen. The organic phase was separated, washed with water, dried ($MgSO_4$), and concentrated by rotary evaporation. The crude product was purified by silica gel thin-layer chromatography using 25 : 1 toluene / acetonitrile as the developer affording **2.25** in 57 % yield: IR ν(CO) 1676 cm^{-1}, ^1H NMR ($CDCl_3$) d

1.46 (s, 9H, $C(CH_3)_3$), 3.37 (t, 1H, CH_2), 3.87 (t, 1H, CH_2), 5.33 (t, 1H, CHPh), 6.90-7.55 (m, 10H, Ph); MS (*m/e*) 294 $[M]^+$.

5.2.5 X-RAY ANALYSIS (2.24, R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = Ph)

A plate crystal of $C_{25}H_{26}BrN_3$ was mounted on a glass capillary, and all measurements were made on a Rigaku diffractometer with MoKα radiation. Cell dimensions and the orientation matrix were obtained from least-square refinement using the setting angles of 25 reflections in the range $30^o < 2\theta < 47$ corresponding to a triclinic cell with dimensions given in Table 5.1. For Z = 4 and FW = 448.40, the calculated density was 1.326 g / cm^3. The space group was determined to be P^{-1}. The data was collected at 22 ^oC using the $\omega - 2\theta$ scan technique to a maximum 2θ value of 47, and the data were collected for Lorentz and polarization effects. [11]

The structure was solved by direct methods. All of the atoms with the exception of hydrogen were refined anisotropically. The final cycle of full matrix least-square refinement was based on 2679 observed reflections ($I > 2.5\sigma(I)$) and 316 variable parameters. All calculations were performed using the NRC VAX crystallographic software package. [12]

TABLE 5.2.1 CRYSTAL DATA COLLECTION AND REFINEMENT INFORMATION FOR COMPOUND 2.24 (R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = Ph)

formula	$C_{25}H_{26}BrN_3$
cryst. system	triclinic
space group	P^{-1}
a, Å	12.953 (4)
b, Å	18.216 (10)
c, Å	10.121 (10)
α, deg	99.36 (7)
β, deg	91.084 (6)
γ, deg	72.50 (3)
V, Å^3	2247.0
FW	448.40
cryst size, mm	0.30 × 0.30 × 0.30 mm
d(calcd), g cm^{-3}	1.326
total no. of reflns	7003
unique reflns	6660
obsd reflns[b]	2679
no. of variables	316
final R_F[c]	0.072[d]
final R_{WF}[c]	0.031[d]
final GOF	3.54[d]

TABLE 5.2.2 ATOMIC PARAMETERS X, Y, Z AND B_{iso} FOR 2.24

(R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = Ph) (molecule 1)

	x	*y*	*z*	B_{iso}
Br1	0.009 77 (12)	0.565 50 (9)	0.366 09 (15)	6.63 (10)
N1	0.3361 (7)	0.8240 (4)	0.2656 (7)	4.0 (6)
N2	0.4340 (6)	0.7254 (4)	0.3617 (7)	3.0 (5)
N3	0.4128 (6)	0.8592 (4)	0.4677 (7)	3.2 (6)
C1	0.3970 (8)	0.8064 (5)	0.3748 (9)	2.8 (7)
C2	0.3866 (8)	0.6912 (5)	0.2446 (9)	3.4 (7)
C3	0.3493 (8)	0.7560 (6)	0.1643 (9)	3.6 (7)
C22	0.2733 (8)	0.9033 (5)	0.2491 (9)	3.6 (7)
C23	0.3469 (9)	0.9530 (6)	0.2319 (11)	7.0 (10)
C24	0.1942 (9)	0.9426 (7)	0.3629 (10)	7.3 (9)
C25	0.2094 (10)	0.9043 (6)	0.1190 (11)	7.4 (10)
C4	0.4487 (6)	0.8443 (4)	0.5941 (4)	2.9 (3)
C5	0.5294 (6)	0.8757 (4)	0.6470 (8)	3.8 (3)
C6	0.5616 (5)	0.8694 (4)	0.7781 (8)	4.4 (3)
C7	0.5132 (6)	0.8316 (4)	0.8562 (4)	5.4 (3)
C8	0.4324 (6)	0.8003 (4)	0.8033 (8)	5.4 (3)
C9	0.4002 (4)	0.8066 (4)	0.6723 (8)	4.0 (3)
C10	0.5327 (5)	0.6807 (4)	0.4108 (6)	2.7 (3)
C11	0.6214 (7)	0.7089 (3)	0.4347 (6)	4.1 (3)
C12	0.7166 (5)	0.6624 (5)	0.4821 (7)	5.1 (3)
C13	0.7230 (5)	0.5878 (5)	0.5056 (6)	6.2 (3)
C14	0.6343 (8)	0.5596 (3)	0.4816 (7)	5.5 (3)
C15	0.5392 (6)	0.6061 (5)	0.4342 (7)	4.4 (3)
C16	0.2957 (4)	0.6597 (4)	0.2793 (8)	3.2 (3)
C17	0.2456 (6)	0.6787 (3)	0.4063 (6)	4.1 (3)
C18	0.1601 (6)	0.6505 (4)	0.4312 (5)	4.8 (3)
C19	0.1247 (4)	0.6035 (4)	0.3291 (9)	4.4 (3)
C20	0.1748 (6)	0.5845 (3)	0.2021 (7)	4.7 (3)
C21	0.2603 (6)	0.6126 (4)	0.1772 (5)	4.2 (3)

TABLE 5.2.3 ATOMIC BONDS IN ANGSTROMS OF 2.24 (R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = Ph) (molecule 1)

Br(1)–C(19)	1.886 (8)	C(5)–H(5)	1.077 (8)
N(1)–C(1)	1.369 (11)	C(6)–C(7)	1.395 (12)
N(1)–C(3)	1.444 (12)	C(6)–H(6)	1.080 (7)
N(1)–C(22)	1.464 (12)	C(7)–C(8)	1.395 (12)
N(2)–C(1)	1.392 (12)	C(7)–H(7)	1.122 (5)
N(2)–C(2)	1.461 (12)	C(8)–C(9)	1.395 (11)
N(2)–C(10)	1.424 (9)	C(8)–H(8)	1.083 (8)
N(3)–C(1)	1.294 (11)	C(9)–H(9)	1.089 (7)
N(3)–C(4)	1.393 (9)	C(10)–C(11)	1.395 (12)
C(2)–C(3)	1.496 (13)	C(10)–C(15)	1.395 (12)
C(2)–C(16)	1.525 (12)	C(11)–C(12)	1.395 (10)
C(2)–H(2)	1.065 (9)	C(11)–H(11)	1.082 (6)
C(3)–H(3A)	1.099 (10)	C(12)–C(13)	1.395 (13)
C(3)–H(3B)	1.094 (9)	C(12)–H(12)	1.077 (8)
C(22)–C(23)	1.529 (14)	C(13)–C(14)	1.395 (13)
C(22)–C(24)	1.491 (14)	C(13)–H(13)	1.104 (6)
C(22)–C(25)	1.542 (14)	C(14)–C(15)	1.395 (10)
C(23)–H(23A)	0.99 (7)	C(14)–H(14)	0.90 (8)
C(23)–H(23B)	1.135 (12)	C(15)–H(15)	1.066 (9)
C(23)–H(23C)	1.033 (10)	C(16)–C(17)	1.395 (10)
C(24)–H(24B)	1.121 (12)	C(16)–C(21)	1.395 (10)
C(24)–H(24C)	1.057 (11)	C(17)–C(18)	1.395 (12)
C(25)–H(25A)	1.070 (12)	C(17)–C(17)	1.066 (7)
C(25)–H(25B)	0.71 (6)	C(18)–C(19)	1.395 (10)
C(25)–H(25C)	1.061 (11)	C(18)–H(18)	1.05 (6)
C(4)–C(5)	1.395 (11)	C(19)–C(20)	1.395 (11)
C(4)–C(9)	1.395 (11)	C(20)–C(21)	1.395 (12)
C(5)–C(6)	1.395 (11)	C(20)–H(20)	1.111 (7)
		C(21)–H(21)	1.097 (5)

TABLE 5.2.4 ATOMIC ANGLES IN DEGREES OF 2.24 (R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = Ph) (molecule 1)

C(1)-N(1)-C(3)	111.7 (7)	C(7)-C(6)-H(6)	120.3 (7)
C(1)-N(1)-C(22)	123.8 (7)	C(6)-C(7)-C(8)	120.0 (6)
C(3)-N(1)-C(22)	124.3 (7)	C(6)-C(7)-H(7)	120.1 (8)
C(1)-N(2)-C(2)	109.5 (7)	C(8)-C(7)-H(7)	119.9 (7)
C(1)-N(2)-C(10)	126.0 (7)	C(7)-C(8)-C(9)	120.0 (7)
C(2)-N(2)-C(10)	119.6 (7)	C(7)-C(8)-H(8)	119.9 (7)
C(1)-N(3)-C(4)	123.1 (7)	C(9)-C(8)-H(8)	120.1 (7)
N(1)-C(1)-N(2)	107.0 (7)	C(4)-C(9)-C(8)	120.0 (6)
N(1)-C(1)-N(3)	122.8 (8)	C(4)-C(9)-H(9)	118.9 (7)
N(2)-C(1)-N(3)	130.2 (8)	C(8)-C(9)-H(9)	120.6 (8)
N(2)-C(2)-C(3)	103.7 (7)	N(2)-C(10)-C(11)	122.3 (7)
N(2)-C(2)-C(16)	113.6 (7)	N(2)-C(10)-C(15)	117.7 (7)
N(2)-C(2)-H(2)	109.7 (8)	C(11)-C(10)-C(15)	120.0 (6)
C(3)-C(2)-C(16)	112.8 (8)	C(10)-C(11)-C(12)	120.0 (7)
C(3)-C(2)-H(2)	108.6 (8)	C(10)-C(11)-H(11)	120.3 (7)
C(16)-C(2)-H(2)	108.1 (7)	C(12)-C(11)-H(11)	119.7 (9)
N(1)-C(3)-C(2)	101.9 (7)	C(11)-C(12)-C(13)	120.0 (7)
N(1)-C(3)-H(3A)	113.7 (8)	C(11)-C(12)-H(12)	119.5 (9)
N(1)-C(3)-H(3B)	111.8 (8)	C(13)-C(12)-H(12)	120.5 (6)
C(2)-C(3)-H(3A)	110.7 (8)	C(12)-C(13)-C(14)	120.0 (6)
C(2)-C(3)-H(3B)	111.7 (8)	C(12)-C(13)-H(13)	115.5 (7)
H(3A)-C(3)-H(3B)	107.0 (7)	C(14)-C(13)-H(13)	124.5 (8)
N(1)-C(22)-C(23)	111.5 (8)	C(13)-C(14)-C(15)	120.0 (7)
N(1)-C(22)-C(24)	112.1 (8)	C(13)-C(14)-H(14)	93 (5)

N(1)-C(22)-C(25)	111.9 (8)
C(23)-C(22)-C(24)	109.9 (8)
C(23)-C(22)-C(25)	103.4 (8)
C(24)-C(22)-C(25)	107.7 (9)
C(22)-C(23)-H(23A)	96 (4)
C(22)-C(23)-H(23B)	110.1 (9)
C(22)-C(23)-H(23C)	117.7 (10)
H(23A)-C(23)-H(23B)	107 (4)
H(23A)-C(23)-H(23C)	115 (4)
H(23B)-C(23)-H(23C)	108.7 (9)
C(22)-C(24)-H(24A)	95 (4)
C(22)-C(24)-H(24B)	111.9 (10)
C(22)-C(24)-H(24C)	115.5 (9)
H(24A)-C(24)-H(24B)	87 (4)
H(24A)-C(24)-H(24C)	135 (5)
H(24B)-C(24)-H(24C)	108.1 (9)
C(22)-C(25)-H(25A)	102.8 (9)
C(22)-C(25)-H(25B)	104 (5)
C(22)-C(25)-H(25C)	108.2 (9)
H(25A)-C(25)-H(25B)	116 (5)
H(25A)-C(25)-H(25C)	108.8 (10)
H(25B)-C(25)-H(25C)	115 (5)
N(3)-C(4)-C(5)	117.1 (7)
N(3)-C(4)-C(9)	122.6 (7)
C(5)-C(4)-C(9)	120.0 (6)
C(4)-C(5)-C(6)	120.0 (7)
C(4)-C(5)-H(5)	119.7 (7)
C(6)-C(5)-H(5)	120.3 (7)
C(5)-C(6)-C(7)	120.0 (7)
C(5)-C(6)-H(6)	119.7 (8)
C(15)-C(14)-H(14)	145 (5)
C(10)-C(15)-C(14)	120.0 (7)
C(10)-C(15)-H(15)	120.8 (6)
C(14)-C(15)-H(15)	119.2 (8)
C(2)-C(16)-C(17)	122.4 (7)
C(2)-C(16)-C(21)	117.5 (7)
C(17)-C(16)-C(21)	120.0 (7)
C(16)-C(17)-C(18)	120.0 (6)
C(16)-C(17)-H(17)	119.9 (7)
C(18)-C(17)-H(17)	120.1 (6)
C(17)-C(18)-C(19)	120.0 (6)
C(17)-C(18)-H(18)	121 (4)
C(19)-C(18)-H(18)	113 (4)
Br(1)-C(19)-C(18)	119.1 (6)
Br(1)-C(19)-C(20)	120.9 (6)
C(18)-C(19)-C(20)	120.0 (7)
C(19)-C(20)-C(21)	120.0 (6)
C(19)-C(20)-H(20)	118.8 (7)
C(21)-C(20)-H(20)	121.1 (6)
C(16)-C(21)-C(20)	120.0 (6)
C(16)-C(21)-H(21)	122.9 (8)
C(20)-C(21)-H(21)	117.1 (6)

TABLE 5.2.5 ATOMIC PARAMETERS X, Y, Z AND B_{iso} FOR 2.24

(R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = Ph) (molecule 2)

	x	*y*	*z*	B_{iso}
Br2	−0.495 52 (12)	0.567 63 (9)	0.862 75 (15)	6.80 (10)
N4	−0.1849 (7)	0.8290 (4)	1.1311 (7)	3.9 (6)
N5	−0.0783 (6)	0.7334 (4)	0.9814 (7)	2.9 (5)
N6	−0.1124 (7)	0.8679 (4)	0.9545 (7)	4.5 (7)
C26	−0.1210 (8)	0.8137 (5)	1.0160 (9)	3.1 (7)
C27	−0.1173 (8)	0.6915 (5)	1.0773 (8)	3.2 (7)
C28	−0.1578 (8)	0.7605 (6)	1.1946 (9)	3.4 (7)
C47	−0.2415 (8)	0.9090 (5)	1.2043 (9)	3.8 (7)
C48	−0.3039 (9)	0.9027 (6)	1.3225 (9)	5.5 (8)
C49	−0.1598 (9)	0.9520 (6)	1.2489 (10)	6.8 (9)
C50	−0.3164 (9)	0.9533 (6)	1.1108 (10)	6.3 (9)
C29	−0.0710 (6)	0.8528 (4)	0.8214 (5)	3.4 (3)
C30	−0.1129 (5)	0.8111 (4)	0.7175 (9)	4.1 (3)
C31	−0.0761 (6)	0.8033 (4)	0.5858 (7)	5.2 (3)
C32	0.0026 (7)	0.8372 (4)	0.5580 (5)	5.7 (3)
C33	0.0446 (5)	0.8789 (4)	0.6619 (9)	4.6 (3)
C34	0.0078 (6)	0.8867 (3)	0.7936 (7)	4.4 (3)
C35	0.0217 (4)	0.6943 (4)	0.9163 (6)	3.8 (3)
C36	0.1037 (7)	0.7295 (3)	0.9171 (6)	3.9 (3)
C37	0.2017 (5)	0.6893 (5)	0.8480 (7)	5.1 (4)
C38	0.2177 (5)	0.6140 (5)	0.7780 (6)	5.4 (3)
C39	0.1356 (7)	0.5789 (3)	0.7772 (6)	5.5 (3)
C40	0.0376 (6)	0.6191 (5)	0.8464 (7)	4.4 (3)
C41	−0.2090 (4)	0.6613 (4)	1.0165 (8)	3.0 (3)
C42	−0.2486 (6)	0.6185 (4)	1.0944 (5)	4.1 (3)
C43	−0.3336 (6)	0.5897 (3)	1.0493 (8)	4.7 (3)
C44	−0.3790 (4)	0.6037 (4)	0.9263 (8)	4.2 (3)
C45	−0.3395 (6)	0.6465 (4)	0.8484 (5)	4.8 (3)
C46	−0.2545 (6)	0.6753 (3)	0.8935 (7)	4.5 (3)

TABLE 5.2.6 ATOMIC BONDS IN ANGSTROMS OF 2.24 (R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = Ph) (molecule 2)

Br(2)–C(44)	1.883 (7)	C(30)–H(30)	1.078 (7)
N(4)–C(26)	1.383 (12)	C(31)–C(32)	1.395 (13)
N(4)–C(28)	1.443 (12)	C(31)–H(31)	1.088 (7)
N(4)–C(47)	1.496 (12)	C(32–C(33)	1.395 (11)
N(5)–C(26)	1.386 (11)	C(32)–H(32)	0.98 (7)
N(5)–C(27)	1.507 (11)	C(33–C(34)	1.395 (12)
N(5)–C(35)	1.394 (9)	C(33)–H(33)	1.072 (8)
N(6)–C(26)	1.282 (12)	C(34)–H(34)	1.087 (7)
N(6)–C(29)	1.413 (9)	C(35)–C(36)	1.395 (11)
C(27)–C(28)	1.551 (13)	C(35)–C(40)	1.395 (11)
C(27)–C(41)	1.534 (12)	C(36)–C(37)	1.395 (10)
C(27)–H(27)	1.30 (6)	C(36)–H(36)	1.079 (5)
C(28)–H(28A)	1.072 (10)	C(37)–C(38)	1.395 (11)
C(28)–H(28B)	1.18 (7)	C(37)–H(37)	1.069 (9)
C(47)–C(48)	1.495 (14)	C(38)–C(39)	1.395 (12)
C(47)–C(49)	1.518 (14)	C(38)–H(38)	1.099 (5)
C(47)–C(50)	1.494 (14)	C(39)–C(40)	1.395 (10)
C(48)–H(48A)	1.18 (6)	C(39)–H(39)	1.123 (5)
C(48)–H(48B)	1.077 (10)	C(40)–H(40)	1.080 (9)
C(48)–H(48C)	1.122 (11)	C(41)–C(42)	1.395 (11)
C(49)–H(49A)	1.09 (6)	C(41)–C(46)	1.395 (11)
C(49)–H(49B)	1.069 (11)	C(42)–C(43)	1.395 (12)
C(49)–H(49C)	1.069 (10)	C(42)–H(42)	1.083 (5)
C(50)–H(50A)	0.70 (7)	C(43)–C(44)	1.395 (11)
C(50)–H(50B)	1.127 (11)	C(43)–H(43)	1.102 (8)
C(50)–H(50C)	1.063 (11)	C(44)–C(45)	1.395 (12)
C(29)–C(30)	1.395 (10)	C(45)–C(46)	1.395 (12)
C(29)–C(34)	1.395 (12)	C(45)–H(45)	1.110 (6)
C(30)–C(31)	1.395 (12)	C(46)–H(46)	1.075 (8)

TABLE 5.2.7 ATOMIC ANGLES IN DEGREES OF 2.24 (R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = Ph) (molecule 2)

C(26)–N(4)–C(28)	109.2 (7)	C(30)–C(31)–H(31)	120.3 (8)
C(26)–N(4)–C(47)	124.5 (7)	C(32)–C(31)–H(31)	119.7 (6)
C(28)–N(4)–C(47)	122.8 (7)	C(31)–C(32)–C(33)	120.0 (6)
C(26)–N(5)–C(27)	111.4 (7)	C(31)–C(32)–H(32)	115 (4)
C(26)–N(5)–C(35)	125.4 (7)	C(33)–C(32)–H(32	120 (4)
C(27)–N(5)–C(35)	116.5 (7)	C(32)–C(33)–C(34)	120.0 (7)
C(26)–N(6)–C(29)	122.5 (8)	C(32)–C(33)–H(33)	119.3 (8)
N(4)–C(26)–N(5)	108.0 (7)	C(34)–C(33)–H(33)	120.6 (7)
N(4)–C(26)–N(6)	122.3 (8)	C(29)–C(34)–C(33)	120.0 (6)
N(5)–C(26)–N(6)	129.6 (8)	C(29)–C(34)–H(34)	121.3 (6)
N(5)–C(27)–C(28)	98.8 (7)	C(33)–C(34)–H(34)	118.6 (7)
N(5)–C(27)–C(41)	110.4 (7)	N(5)–C(35)–C(36)	121.6 (6)
N(5)–C(27)–H(27)	126 (3)	N(5)–C(35)–C(40)	118.4 (7)
C(28)–C(27)–C(41)	112.5 (7)	C(36)–C(35)–C(40)	120.0 (5)
C(28)–C(27)–H(27)	86.0 (24)	C(35)–C(36)–C(37)	120.0 (6)
C(41)–C(27)–H(27)	116 (3)	C(35)–C(36)–C(37)	120.0 (6)
N(4)–C(28)–C(27)	104.3 (7)	C(35)–C(36)–H(36)	120.1 (7)
N(4)–C(28)–H(28A)	107.4 (8)	C(37)–C(36)–H(36)	119.9 (8)
N(4)–C(28)–H(28B)	118 (3)	C(36)–C(37)–C(38)	120.0 (7)
C(27)–C(28)–H(28A)	106.2 (8)	C(36)–C(37)–H(37)	122.4 (7)
C(27)–C(28)–H(28B)	107 (3)	C(38)–C(37)–H(37)	117.6 (6)
H(28A)–C(28)–H(28B)	111 (3)	C(37)–C(38)–C(39)	120.0 (5)
N(4)–C(47)–C(48)	109.4 (8)	C(37)–C(38)–H(38)	121.2 (7)
N(4)–C(47)–C(49)	110.2 (8)	C(39)–C(38)–H(38)	118.8 (7)
N(4)–C(47)–C(50)	108.5 (7)	C(38)–C(39)–C(40)	120.0 (6)
		C(38)–C(39)–H(39)	118.8 (7)

C(48)-C(47)-C(49)	110.5 (8)		
C(48)-C(47)-C(50)	110.1 (9)	C(40)-C(39)-H(39)	121.1 (8)
C(49)-C(47)-C(50)	108.1 (8)	C(35)-C(40)-C(39)	120.0 (7)
C(47)-C(48)-H(48A)	108 (3)	C(35)-C(40)-H(40)	120.4 (6)
C(47)-C(48)-H(48B)	113.7 (9)	C(39)-C(40)-H(40)	119.6 (7)
C(47)-C(48)-H(48C)	112.2 (8)	C(27)-C(41)-C(42)	115.5 (7)
H(48A)-C(48)-H(48B)	101 (3)	C(27)-C(41)-C(46)	124.5 (7)
H(48A)-C(48)-H(48C)	114 (3)	C(42)-C(41)-C(46)	120.0 (6)
H(48B)-C(48)-H(48C)	106.6 (9)	C(41)-C(42)-C(43)	120.0 (6)
C(47)-C(49)-H(49A)	89 (4)	C(41)-C(42)-H(42)	120.1 (7)
C(47)-C(49)-H(49B)	114.2 (9)	C(43)-C(42)-H(42)	119.9 (7)
C(47)-C(49)-H(49C)	112.5 (9)	C(42)-C(43)-C(44)	120.0 (7)
H(49A)-C(49)-H(49B)	127 (4)	C(42)-C(43)-H(43)	121.2 (7)
H(49A)-C(49)-H(49C)	99 (4)	C(44)-C(43)-H(43)	118.7 (7)
H(49B)-C(49)-H(49C)	111.2 (10)	Br(2)-C(44)-C(43)	121.5 (6)
C(47)-C(50)-H(50A)	130 (5)	Br(2)-C(44)-C(45)	118.5 (6)
C(47)-C(50)-H(50B)	111.7 (8)	C(43)-C(44)-C(45)	120.0 (7)
C(47)-C(50)-H(50C)	117.1 (10)	C(44)-C(45)-C(46)	120.0 (6)
H(50A)-C(50)-H(50B)	91 (5)	C(44)-C(45)-H(45)	120.0 (7)
H(50A)-C(50)-H(50C)	94 (5)	C(46)-C(45)-H(45)	119.9 (7)
H(50B)-C(50)-H(50C)	107.2 (9)	C(41)-C(46)-C(45)	120.0 (7)
N(6)-C(29)-C(30)	121.9 (8)	C(41)-C(46)-H(46)	117.9 (7)
N(6)-C(29)-C(34)	117.9 (6)	C(45)-C(46)-H(46)	121.9 (7)
C(30)-C(29)-C(34)	120.0 (6)		
C(29)-C(30)-C(31)	120.0 (7)		
C(29)-C(30)-H(30)	119.2 (8)		
C(31)-C(30)-H(30)	120.6 (7)		
C(30)-C(31)-C(32)	120.0 (6)		

5.2.6 GENERAL PROCEDURE FOR THE PALLADIUM-CATALYZED CYCLOADDITION REACTION OF 1,2,3-TRISUBSTITUTED AZIRIDINES AND HETEROCUMULENES

A mixture of aziridine (1.0 mmol), heterocumulene (1.0 mmol), and bis(benzonitrile)palladium dichloride (0.038g, 0.10 mmol) in toluene (2.0 mL) was heated with stirring in a glass autoclave for 20h, at 120 °C (oil bath temperature) under a slight pressure of nitrogen (5 psi). After being cooled to room temperature, the autoclave was opened and the red-brown homogeneous solution was filtered through Celite. The filtrate was concentrated by rotary evaporation, and the crude product was purified by silica gel thin-layer chromatography using 10:1 toluene/acetonitrile as the developer. Melting points, IR, NMR, MS and analytical data for **2.28** are as follows:

***cis*-1-*n*-Butyl-4-carbomethoxy-5-methyl-3-phenylimidazolidine-2-phenylimine** (**2.28**, R=CH_3, X = C_6H_5N, Y = C_6H_5N)

60 % yield; viscous oil; IR ν(C=N) 1648 and ν(C=O) 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, CH_3, J = 7.2 Hz), 1.25 (d, 3H, CH_3, J = 6.4 Hz), 1.23 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 3.10 (m, 1H, NCH_2), 3.55 (m, 1H, NCH_2), 3.73 (s, 3H, CO_2CH_3), 4.12 (m, 1H, CH ring), 4.51 (d, 1H, $CHCO_2$, J = 8.6 Hz), 6.52-7.30 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.56, 15.03 (CH_3), 20.68, 29.17, 43.15 (CH_2), 52.74 (CH_3CO_2), 53.29 (CH), 67.35 ($CHCO_2$), 120.98, 122.83, 123.98, 124.83, 128.63, 128.82 (CH-aromatic), 141.19, 148.71 (

quaternary aromatic carbons), 150.67 (C=N), 170.86 (C=O); MS (*m/e*) 365 $[M]^+$. Anal. Calcd for $C_{22}H_{27}N_3O_2$: C, 72.30; H, 7.45; N, 11.50. Found: C, 72.38; H, 7.41; N, 11.35.

***cis*-1-*n*-Butyl-4-carbomethoxy-5-methyl-3-phenylimidazolidin-2-one (2.28, R=CH_3, X = O, Y = C_6H_5N)**

72% yield; viscous oil; IR ν(C=O) 1687 and 1752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3H, CH_3, *J* = 7.2 Hz), 1.06 (d, 3H, CH_3, *J* = 6.4 Hz), 1.23 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 3.04 (m, 1H, NCH_2), 3.55 (m, 1H, NCH_2), 3.67 (s, 3H, CO_2CH_3), 3.95 (m, 1H, CH ring), 4.79 (d, 1H, $CHCO_2$, *J* = 8.2 Hz), 6.52 - 7.30 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.51, 14.55 (CH_3), 20.65, 29.48, 42.74 (CH_2), 52.89 (CH_3CO_2), 54.11 (CH), 78.49 ($CHCO_2$), 122.88, 124.14, 129.06 (CH-aromatic), 147.39 (quaternary aromatic carbons), 152.25, 168.77 (C=O); MS (*m/e*) 290 $[M]^+$. Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.30; H, 7.52; N, 9.61.

***cis*-1-*n*-Butyl-4-carbomethoxy-5-methyl-3-(*p*-chlorophenyl)imidazolidin-2-one (2.28, R=CH_3, X = O, Y = *p*-ClC_6H_4N)**

80% yield; viscous oil; IR ν(C=O) 1680 and 1753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (t, 3H, CH_3, *J* = 7.0 Hz), 1.05 (d, 3H, CH_3, *J* = 6.2 Hz), 1.25 (m, 2H, CH_2), 1.46 (m, 2H, CH_2), 3.01 (m, 1H, NCH_2), 3.45 (m, 1H, NCH_2), 3.66 (s, 3H, CO_2CH_3), 3.95 (m, 1H, CH ring), 4.80 (d, 1H, $CHCO_2$, *J* = 8.0 Hz), 6.85-7.10 (m, 4H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.49, 16.29 (CH_3), 20.65, 29.47, 42.66 (CH_2), 52.94 (CH_3CO_2), 54.04 (CH), 77.47 ($CHCO_2$), 125.48, 128.96 (CH-

aromatic), 127.55, 146.59 (quaternary aromatic carbons), 152.25, 168.72 (C=O); MS (*m/e*) 323 $[M]^+$, 325 $[M + 2]^+$. Anal. Calcd for $C_{16}H_{21}ClN_2O_3$: C, 59.17; H, 6.52; N, 8.62. Found: C, 59.49; H, 6.81; N, 8.46.

***cis*-1-*n*-Butyl-4-carboethoxy-5-methyl-3-(*p*-chlorophenyl)imidazolidin-2-one (2.28**, R=C_2H_5, X = O, Y = *p*-ClC_6H_4N)

86% yield; viscous oil; IR ν(C=0) 1681 and 1749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (t, 3H, CH_3, *J* = 7.0 Hz), 1.04 (d, 3H, CH_3, *J* = 6.6 Hz), 1.12 (t, 3H, CH_3, *J* = 7.1 Hz), 1.23 (m, 2H, CH_2), 1.40 (m, 2H, CH_2), 2.90 (m, 1H, NCH_2), 3.35 (m, 1H, NCH_2), 3.82 (m, 1H, CH ring), 4.06 (q, 2H, CO_2CH_2, J = 7.0), 4.80 (d, 1H, $CHCO_2$, J = 8.4 Hz), 6.80-7.05 (m, 4H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.37, 14.44, 14.70 (CH_3), 20.60, 29.47, 42.55, (CH_2), 53.96 (CH), 62.16 (CH_2CO_2), 77.30 ($CHCO_2$), 125.52, 128.81 (CH-aromatic), 127.18, 146.97 (quaternary aromatic carbons), 152.33, 168.17 (C=O); MS (*m/e*) 338 $[M]^+$, 340 $[M + 2]^+$. Anal. Calcd for $C_{17}H_{23}ClN_2O_3$: C, 60.26 ; H, 6.84 ; N, 8.27. Found: C, 60.11; H, 7.08; N, 8.63.

***cis*-3-*n*-Butyl-5-carbomethoxy-4-methylthiazolidine-2-(*p*-chlorophenyl)imine (2.28**, R=CH_3, X = *p*-ClC_6H_4N, Y = S)

70% yield; viscous oil; IR ν(C=N) 1622 and ν(C=O) 1742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (t, 3H, CH_3, *J* = 7.1 Hz), 1.12 (d, 3H, CH_3, *J* = 6.2 Hz), 1.25 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 2.92 (m, 1H, NCH_2), 3.62 (s, 3H, CO_2CH_3), 3.70 (m, 1H, NCH_2), 4.00 (m, 1H, CH ring), 4.27 (d, 1H, $CHCO_2$, *J* = 6.6 Hz), 6.40-7.10 (m, 4H, aromatic protons);

^{13}C NMR ($CDCl_3$) δ 13.67, 14.52 (CH_3), 20.76, 30.01, 44.59 (CH_2), 50.70 (CH), 53.39 (CH_3CO_2), 58.25 ($CHCO_2$), 124.11, 129.39 (CH-aromatic), 128.78, 150.80 (quaternary aromatic carbons), 157.29, 169.20 (C=O); MS (*m/e*) 340 $[M]^+$, 342 $[M + 2]^+$. Anal. Calcd for $C_{16}H_{21}ClN_2O_3S$: C, 56.37; H, 6.21; N, 8.22. Found: C, 56.02; H, 6.15; N, 8.29.

***cis*-3-*n*-Butyl-5-carbomethoxy-4-methylthiazolidine-2-(*p*-nitrorophenyl)imine (2.28**, R=CH_3, X = *p*-$NO_2C_6H_4N$, Y = S)

72% yield; viscous oil; IR ν(C=N) 1621 and ν(C=O) 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (t, 3H, CH_3, *J* = 7.0 Hz), 1.13 (d, 3H, CH_3, *J* = 5.4 Hz), 1.21 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 2.95 (m, 1H, NCH_2), 3.60 (s, 3H, CO_2CH_3), 3.65 (m, 1H, NCH_2), 4.05 (m, 1H, CH ring), 4.30 (d, 1H, $CHCO_2$, *J* = 5.4 Hz), 6.80-7.95 (m, 4H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 13.82, 14.45 (CH_3), 20.71, 30.07, 44.75 (CH_2), 50.92 (CH), 53.55 (CH_3CO_2), 58.48 ($CHCO_2$), 123.11, 125.43 (CH-aromatic), 143.54, 157.52 (quaternary aromatic carbons), 158.34, 168.87 (C=O); MS (*m/e*) 351 $[M]^+$. Anal. Calcd for $C_{16}H_{21}N_3O_4S$: C, 54.69; H, 6.02; N, 11.96. Found: C, 54.28; H, 5.81; N, 12.32.

***cis*-3-*n*-Butyl-5-carboethoxy-4-methylthiazolidine-2-(*p*-chlorophenyl)imine (2.28**, R=C_2H_5, X = *p*-ClC_6H_4N, Y = S)

75% yield; viscous oil; IR ν(C=N) 1622 and ν(C=O) 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (t, 3H, CH_3, *J* = 7.0 Hz), 1.10 (d, 3H, CH_3, *J* = 7.0 Hz), 1.12 (t, 3H, CH_3, *J* = 7.2 Hz), 1.20 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 3.59 (m, 1H, NCH_2), 3.70 (m, 1H, NCH_2), 3.92 (m, 1H, CH ring), 4.05 (q, 2H, CO_2CH_2, J = 7.0), 4.25 (d, 1H, $CHCO_2$, J = 6.6 Hz), 6.65-

7.10 (m, 4H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 13.52, 14.51, 14.69 (CH_3), 20.75, 30.13, 44.52, (CH_2), 50.92 (CH), 58.20 ($CHCO_2$), 62.56 (CH_2CO_2), 124.10, 129.31 (CH-aromatic), 128.57, 151.00 (quaternary aromatic carbons), 157.25, 168.63 (C=O); MS (*m/e*) 354 $[M]^+$, 356 $[M + 2]^+$. Anal. Calcd for $C_{17}H_{23}ClN_2O_2S$: C, 57.54 ; H, 6.53 ; N, 7.89. Found: C, 57.47; H, 6.39; N, 7.70.

5.2.7 GENERAL PROCEDURE FOR THE PALLADIUM-CATALYZED ENANTIOSPECIFIC CYCLOADDITION REACTION OF AZIRIDINES AND HETEROCUMULENES

A mixture of aziridine (1.0 mmol), heterocumulene (1.0 mmol), and bis(benzonitrile)palladium dichloride (0.038g, 0.10 mmol) in toluene (2.0 mL) was heated with stirring in a glass autoclave for 24h, at 120 °C (oil bath temperature) under a slight pressure of nitrogen (5 psi). After being cooled to room temperature, the autoclave was opened and the red-brown homogeneous solution was filtered through Celite. The filtrate was concentrated by rotary evaporation, and the crude product was purified by silica gel thin-layer chromatography using 10:1 toluene/acetonitrile as the developer. Melting points, IR, NMR, MS and analytical data for **2.29** and **2.30** are as follows:

(S)-(+)-1-*n*-Butyl-3-*p*-chlorophenyl-4-phenylimidazolidine-2-*p*-chlorophenylimine (**2.29**, R = *n*-C_4H_9, X = *p*-ClC_6H_4N, Y = *p*-ClC_6H_4N)

90% yield; mp 35-36 °C; $[\alpha]^{23}_D$ +285.1° (*c* 3.9, $CHCl_3$); IR ν (C=N) 1641 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (t, 3H, CH_3, *J* = 7.4 Hz), 1.20 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 3.20 (m, 3H, NCH_2 and one H of CH_2 (ring)), 3.83 (t, 1H, CH_2, ring, *J* = 9.0 Hz), 4.80 (dd, 1H, CHPh, *J* = 6.4, 8.4 Hz), 6.58-7.43 (m, 13H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.55 (CH_3), 20.67, 29.73 (CH_2), 46.71 (NCH_2) 54.80 (CH_2 ring), 65.04 (CHPh), 124.15, 126.06, 127.35, 128.72, 128.94, 129.45, 129.70 (aromatic carbons), 125.64, 130.30, 141.05, 141.71, 148.46 (quaternary aromatic carbons), 152.52 (C=N); MS (*m/e*) 437 $[M]^+$, 439 $[M + 2]^+$, 441 $[M + 4]^+$. Anal. Calcd for $C_{25}H_{25}Cl_2N_3$: C, 68.49; H, 5.75; N, 9.58. Found: C, 68.51; H, 5.83; N, 9.67.

(S)-(+)-1-*n*-Butyl-3,4-diphenylimidazolidin-2-one (**2.29**, R = *n*-C_4H_9, X = O, Y = C_6H_5N)

82% yield; mp 67-68 °C; $[\alpha]^{23}_D$ +31.7° (*c* 5.4, $CHCl_3$); IR ν (C=O) 1699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (t, 3H, CH_3, *J* = 7.4 Hz), 1.23 (m, 2H, CH_2), 1.42 (m, 2H, CH_2), 3.10 (dd, 1H, CH_2, ring, *J* = 5.8, 8.6 Hz), 3.22 (t, 1H, CH_2, ring, *J* = 6.8 Hz), 5.09 (dd, 1H, CHPh, *J* = 5.8, 9.3 Hz), 6.77-7.63 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.45 (CH_3), 20.56, 30.12 (CH_2), 44.04 (NCH_2) 51.89 (CH_2 ring), 58.00 (CHPh), 120.08, 123.15, 126.60, 128.58, 129.12, 129.64 (aromatic carbons), 140.21, 141.42 (quaternary aromatic carbons), 158.78 (C=N); MS

(*m/e*) 294 $[M]^+$. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.54; N, 9.51. Found: C, 77.58; H, 7.53; N, 9.75.

(S)-(+)-1-*n*-Butyl-3-*p*-chlorophenyl-4-phenylimidazolidin-2-one (**2.29**, R = *n*-C_4H_9, X = O, Y = *p*-ClC_6H_4N)

87% yield; mp 90-91 °C; $[\alpha]^{23}_D$ +30.8° (*c* 5.3, $CHCl_3$); IR ν (C=O) 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (t, 3H, CH_3, *J* = 7.2 Hz), 1.21 (m, 2H, CH_2), 1.35 (m, 2H, CH_2), 3.09 (dd, 1H, CH_2, ring, *J* = 5.7, 8.8 Hz), 3.74 (t, 1H, CH_2, ring, *J* = 6.8 Hz), 5.03 (dd, 1H, CHPh, *J* = 5.7, 9.1 Hz), 6.97-7.42 (m, 9H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.41 (CH_3), 20.57, 30.11 (CH_2), 44.13 (NCH_2) 51.91 (CH_2 ring), 58.14 (CHPh), 121.29, 126.58, 128.85, 129.12, 129.81 (aromatic carbons), 128.20, 138.69, 140.83 (quaternary aromatic carbons), 158.56 (C=O); MS (*m/e*) 328 $[M]^+$, 330 $[M + 2]^+$. Anal. Calcd for $C_{19}H_{21}ClN_2O$: C, 69.40; H, 6.44; N, 8.52. Found: C, 69.06; H, 6.73; N, 8.73.

(S)-(+)-3-(1-Adamantyl)-5-phenylthiazolidine-2-phenylimine (**2.29**, R = 1-adamantyl, X = C_6H_5N, Y = S)

85 % yield mp 133-134 °C; $[\alpha]^{23}_D$ +32.1° (*c* 2.4, $CHCl_3$); IR ν (C=N) 1619 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.66-2.50 (m, 15H, adamantyl protons), 3.67 (dd, 1H, *J* = 8.2 and 9.7 Hz, CH_2), 4.01 (dd, 1H, *J* = 6.6 and 9.7 Hz, CH_2), 4.55 (m, 1H, CHPh), 6.95-7.46 (m, 10H, aromatic ring protons); ^{13}C NMR ($CDCl_3$) δ 30.73, 37.27, 40.29 (secondary and tertiary adamantyl carbons), 46.51 (CHPh), 56.57 (CH_2), 58.94 (quaternary carbon of adamantyl group), 122.53, 123.27, 128.17,

128.62, 129.37, 129.43 (CH-aromatic), 140.13, 153.26 (quaternary carbons of Ph), 156.75 (C=N); MS (*m/e*) 388 $[M]^+$. Anal. Calcd for $C_{25}H_{28}N_2S$: C, 77.23; H, 7.26; N, 7.21. Found: C, 77.28; H, 6.99; N, 7.14.

(S)-(+)-3-(1-Adamantyl)-5-phenylthiazolidine-2-(*p*-chlorophenyl)imine (**2.29**, R = 1-adamantyl, X = *p*-ClC_6H_4N, Y = S)

83% yield mp 159-160 °C; $[\alpha]^{23}_D$ +45.0° (*c* 3.0, $CHCl_3$); IR ν (C=N) 1610 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.66-2.50 (m, 15H, adamantyl protons), 3.67 (dd, 1H, *J* = 8.2 and 9.7 Hz, CH_2), 4.01 (dd, 1H, *J* = 6.6 and 9.7 Hz, CH_2), 4.55 (m, 1H, CHPh), 6.95-7.46 (m, 10H, aromatic ring protons); ^{13}C NMR ($CDCl_3$) δ 30.64, 37.16, 40.24 (secondary and tertiary adamantyl carbons), 46.50 (CHPh), 56.59 (CH_2), 59.05 (quaternary carbon of adamantyl group), 123.87, 128.07, 128.68, 129.37 (CH-aromatic), 128.22, 139.89, 151.71 (quaternary carbons of Ph), 157.19 (C=N); MS (*m/e*) 422 $[M]^+$, 424 $[M + 2]^+$. Anal. Calcd for $C_{25}H_{27}ClN_2S$: C, 70.98; H, 6.43; N, 6.62. Found: C, 71.35; H, 6.66; N, 6.41.

(R)-(-)-1-*n*-Butyl-3-*p*-chlorophenyl-4-phenylimidazolidine-2-*p*-chlorophenylimine (**2.30**, R = *n*-C_4H_9, X = *p*-ClC_6H_4N, Y = *p*-ClC_6H_4N)

88% yield; mp 35-36 °C; $[\alpha]^{23}_D$ -284.9° (*c* 3.5, $CHCl_3$). Anal. Calcd for $C_{25}H_{25}Cl_2N_3$: C, 68.49; H, 5.75; N, 9.58. Found: C, 68.60; H, 5.71; N, 9.53.

(R)-(-)-1-*n*-Butyl-3,4-diphenylimidazolidin-2-one (2.30, R = *n*-C_4H_9, X = O, Y = C_6H_5N)

81% yield; mp 67-68 °C; $[\alpha]^{23}_D$ -31.0° (*c* 5.0, $CHCl_3$). Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.54; N, 9.51. Found: C, 77.48; H, 7.48; N, 9.80.

(R)-(-)-1-*n*-Butyl-3-*p*-chlorophenyl-4-phenylimidazolidin-2-one (2.30, R = *n*-C_4H_9, X = O, Y = *p*-ClC_6H_4N)

84% yield; mp 90-91 °C; $[\alpha]^{23}_D$ -30.1° (*c* 5.2, $CHCl_3$). Anal. Calcd for $C_{19}H_{21}ClN_2O$: C, 69.40; H, 6.44; N, 8.52. Found: C, 68.97; H, 6.33; N, 8.75.

(R)-(-)-3-(1-Adamantyl)-5-phenylthiazolidine-2-phenylimine (2.30, R = 1-adamantyl, X = C_6H_5N, Y = S)

82 % yield mp 133-134 °C; $[\alpha]^{23}_D$ -31.8° (*c* 2.3, $CHCl_3$). Anal. Calcd for $C_{25}H_{28}N_2S$: C, 77.23; H, 7.26; N, 7.21. Found: C, 76.92; H, 7.47; N, 7.28.

(R)-(-)-3-(1-Adamantyl)-5-phenylthiazolidine-2-(*p*-chlorophenyl)imine (**2.30**, R = 1-adamantyl, X = *p*-ClC_6H_4N, Y = S)

80 % yield mp 159-160 °C; $[\alpha]^{23}_D$ -44.7° (*c* 2.0, $CHCl_3$). Anal. Calcd for $C_{25}H_{27}ClN_2S$: C, 70.98; H, 6.43; N, 6.62. Found: C, 71.04; H, 6.21; N, 6.97.

The IR, NMR, and mass spectral results of compounds (S)-**2.30** are identical to those obtained for the corresponding (R)-**2.29** (see above).

5.2.8 X-RAY ANALYSIS ((S)-(+)-**2.29**, R = *n*-C_4H_9, X = O, Y = *p*-ClC_6H_4N)

A plate crystal of $C_{19}H_{21}ClN_2O$ was mounted on a glass capillary, and all measurements were made on a Rigaku diffractometer with MoK_α radiation. Cell dimensions and orientation matrix were obtained from least-square refinement using the setting angles of 25 reflections in the range $40° < 2\theta < 45°$, corresponding to an orthorhombic cell with dimensions given in the supplementary material. For Z = 4 and FW = 328.84, the calculated density is 1.284 g/cm^3. The space group was determined to be P21. The data were collected at -140 °C using the ω - 2θ scan technique to a maximum 2θ value of 44.9, and the data were corrected for Lorentz and polarization effects. [125]

The structure was solved by direct methods. All of the atoms with the exception of hydrogen were refined anisotropically. The final cycle of full-matrix least-square refinement was based on 4280 observed reflections ($I > 2.5\sigma(I)$) and 415 variable parameters.

The absolute structure was determined with the approach developed by LePage et al [129] and applied as follows: the structure solution allowed the 100 most sensitive Bijvoet pairs to be found by utility Bijvoet. Seventy-three individual indications for the hand ponited one way and twenty-seven the other way, giving a robust probability of 2×10^{-6} of having the wrong hand. Refinement of eta was also done to confirm the hand. A value of +0.981 was obtained, confirming the hand of the molecule.

All calculations were performed using the NRC VAX crystallographic software package. [126]

Crystal data collection and refinement information of (S)-(+)-**2.29** (R = Ph, X = O, Y = *p*-ClC_6H_4N) are listed in Table 5.2.8. The atomic parameter x, y, z and B_{iso} of (S)-(+)-**2.29** are in Table 5.2.9. Table 5.2.10 and 5.2.11 will show the interatomic distances (in angstroms) and angles (in degrees) of (S)-(+)-**2.29** respectively.

TABLE 5.2.8 CRYSTAL DATA COLLECTION AND REFINEMENT INFORMATION FOR COMPOUND (S)-(+)-2.29 (R = *n*-C_4H_9, X = O, Y = *p*-ClC_6H_4N)

Empirical formula	Cl1O1N2C19H21
Formula weight	328.84
Crystal shape	cube
Crystal dimensions (mm)	.2,.2,.2
Crystal system	monoclinic
No. Reflection used for unit cell dimension (2theta range)	25 40-45
Lattice parameters	a=6.037(6) b=18.123(6) c=15.625(5) beta=95.91(7)
Space group	P 21
Z value	4
Dcalc (g.cm-3)	1.284
F(000)	695.89
mu (mm-1)	.23
No of reflection measured	8063
No of reflection unique	4460
No of reflection observed	4280
No of atoms	88
No of variables	415
Rf (sign refl)	.041
Rw (sign refl)	.056
Rf (all refl)	.045
Rw (all refl)	.056
Goodness of fit	3.42
Last difference fourier map	
max peak	0.320
min peak	-0.280

TABLE 5.2.9 ATOMIC PARAMETERS X, Y, Z AND B_{iso} FOR (S)-(+)-2.29 (R = *n*-C_4H_9, X = O, Y = *p*-ClC_6H_4N)

	x	y	z	Biso
CL1	0.20966(23)	0.32019	0.14545(8)	3.98(6)
CL2	-0.09730(21)	0.65614(8)	0.62925(8)	3.50(6)
O1	0.0063 (5)	0.69224(21)	0.17379(21)	3.24(15)
O2	0.3810 (5)	0.31904(19)	0.68687(19)	2.78(14)
N1	0.3199 (6)	0.64434(24)	0.11609(23)	2.65(17)
N2	0.2775 (6)	0.76535(24)	0.1255 (3)	2.98(17)
N3	0.0123 (6)	0.33082(22)	0.63027(23)	2.37(16)
N4	0.1729 (6)	0.22122(22)	0.62869(24)	2.43(16)
C1	0.1831 (7)	0.7006 (3)	0.1419 (3)	2.67(22)
C2	0.5021 (8)	0.7574 (3)	0.1000 (3)	3.10(21)
C3	0.5098 (7)	0.6750 (3)	0.0758 (3)	2.74(22)
C4	0.4882 (7)	0.6640 (3)	-0.0211 (3)	2.46(19)
C5	0.6678 (8)	0.6369 (3)	-0.0605 (3)	3.04(21)
C6	0.6511 (8)	0.6305 (3)	-0.1497 (3)	3.25(23)
C7	0.4611 (9)	0.6496 (3)	-0.1992 (3)	3.39(23)
C8	0.2789 (8)	0.6769 (3)	-0.1600 (3)	3.46(23)
C9	0.2936 (7)	0.6825 (3)	-0.0707 (3)	3.08(23)
C10	0.2837 (7)	0.5677 (3)	0.1221 (3)	2.47(21)
C11	0.4457 (8)	0.5193 (3)	0.0978 (3)	2.94(22)
C12	0.4207 (8)	0.4437 (3)	0.1051 (3)	3.01(23)
C13	0.2333 (8)	0.4157 (3)	0.1371 (3)	3.15(22)
C14	0.0693 (8)	0.4623 (3)	0.1606 (3)	2.98(21)
C15	0.0927 (8)	0.5384 (3)	0.1535 (3)	2.97(21)
C16	0.1886 (8)	0.8362 (3)	0.1492 (3)	3.03(21)
C17	0.0961 (9)	0.8807 (3)	0.0711 (3)	3.53(24)
C18	0.0066 (10)	0.9564 (3)	0.0952 (4)	4.3 (3)
C19	-0.2155 (10)	0.9521 (4)	0.1326 (4)	4.7 (3)
C20	0.2075 (7)	0.2936 (3)	0.6525 (3)	2.32(20)
C21	-0.1606 (7)	0.2835 (3)	0.5866 (3)	2.32(19)
C22	-0.0610 (8)	0.2065 (3)	0.6065 (3)	2.75(20)
C23	-0.2048 (7)	0.29945(25)	0.4912 (3)	2.25(18)
C24	-0.4093 (8)	0.2801 (3)	0.4493 (3)	2.79(20)
C25	-0.4532 (8)	0.2916 (3)	0.3608 (3)	3.36(23)
C26	-0.2920 (8)	0.3224 (3)	0.3147 (3)	3.46(23)
C27	-0.0869 (8)	0.3425 (3)	0.3563 (3)	3.23(22)
C28	-0.0430 (7)	0.3310 (3)	0.4452 (3)	2.58(20)
C29	-0.0089 (7)	0.4091 (3)	0.6325 (3)	2.43(20)
C30	0.1627 (7)	0.4556 (3)	0.6118 (3)	2.57(20)
C31	0.1342 (7)	0.5308 (3)	0.6115 (3)	2.76(21)
C32	-0.0639 (8)	0.5607 (3)	0.6310 (3)	2.51(21)
C33	-0.2368 (7)	0.5156 (3)	0.6516 (3)	2.77(21)
C34	-0.2100 (7)	0.4402 (3)	0.6511 (3)	2.58(20)
C35	0.3180 (8)	0.1628 (3)	0.6682 (3)	2.83(21)
C36	0.3667 (8)	0.1028 (3)	0.6046 (3)	3.19(22)
C37	0.4976 (9)	0.0404 (3)	0.6486 (3)	3.71(24)
C38	0.5656 (11)	-0.0179 (4)	0.5862 (4)	5.3 (3)
H2A	0.538	0.794	0.048	4.1
H2B	0.634	0.772	0.155	4.1
H3	0.673	0.649	0.106	3.5

H5	0.832	0.621	-0.020	4.3
H6	0.799	0.609	-0.182	4.5
H7	0.447	0.643	-0.273	4.5
H8	0.122	0.694	0.199	4.4
H9	0.153	0.706	-0.041	3.7
H11	0.595	0.542	0.068	4.4
H12	0.547	0.403	0.086	3.9
H14	-0.079	0.438	0.189	4.4
H15	-0.038	0.577	0.173	3.6
H16A	0.059	0.828	0.192	4.3
H16B	0.322	0.869	0.185	4.3
H17A	-0.042	0.850	0.035	4.9
H17B	0.223	0.888	0.026	4.9
H18A	0.130	0.982	0.141	5.3
H18B	-0.012	0.992	0.037	5.3
H19C	-0.279	1.006	0.150	5.9
H19A	-0.348	0.928	0.086	5.9
H19B	-0.207	0.918	0.190	5.9
H24	-0.534	0.254	0.488	3.9
H21	-0.317	0.288	0.617	2.9
H22A	-0.088	0.171	0.549	3.7
H22B	-0.138	0.179	0.658	3.7
H25	-0.627	0.277	0.326	5.2
H26	-0.331	0.333	0.244	4.4
H27	0.038	0.366	0.318	4.6
H28	0.130	0.348	0.481	3.8
H30	0.319	0.429	0.595	3.6
H31	0.273	0.569	0.594	4.5
H33	-0.396	0.541	0.669	3.9
H34	-0.354	0.404	0.671	3.6
H35A	0.483	0.188	0.695	3.8
H35B	0.251	0.138	0.724	3.8
H36A	0.208	0.081	0.575	4.4
H36B	0.455	0.126	0.553	4.4
H37A	0.653	0.064	0.686	4.9
H37B	0.406	0.014	0.698	4.9
H38C	0.667	-0.061	0.618	6.0
H38A	0.421	-0.040	0.551	6.0
H38B	0.668	0.010	0.540	6.0

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

TABLE 5.2.10 ATOMIC BONDS IN ANGSTROMS OF (S)-(+)-2.29 (R = *n*-C_4H_9, X = O, Y = *p*-ClC_6H_4N)

C11-C13	1.749(5)	C17-H17A	1.110(5)
C12-C32	1.741(5)	C17-H17B	1.101(5)
O1-C1	1.233(5)	C18-C19	1.519(9)
O2-C20	1.217(5)	C18-H18A	1.083(6)
N1-C1	1.397(6)	C18-H18B	1.110(6)
N1-C3	1.472(6)	C19-H19C	1.100(6)
N1-C10	1.410(7)	C19-H19A	1.112(6)
N2-C1	1.341(7)	C19-H19B	1.094(6)
N2-C2	1.459(6)	C21-C22	1.539(7)
N2-C16	1.454(7)	C21-C23	1.515(6)
N3-C20	1.371(6)	C21-H21	1.104(4)
N3-C21	1.464(6)	C22-H22A	1.105(5)
N3-C29	1.425(6)	C22-H22B	1.085(5)
N4-C20	1.374(6)	C23-C24	1.382(6)
N4-C22	1.444(6)	C23-C28	1.393(6)
N4-C35	1.469(6)	C24-C25	1.396(7)
C2-C3	1.542(7)	C24-H24	1.124(5)
C2-H2A	1.091(5)	C25-C26	1.386(7)
C2-H2B	1.145(5)	C25-H25	1.162(5)
C3-C4	1.521(6)	C26-C27	1.386(7)
C3-H3	1.149(5)	C26-H26	1.126(5)
C4-C5	1.390(6)	C27-C28	1.402(7)
C4-C9	1.380(6)	C27-H27	1.096(5)
C5-C6	1.391(7)	C28-H28	1.170(5)
C5-H5	1.152(5)	C29-C30	1.399(7)
C6-C7	1.361(7)	C29-C34	1.396(7)
C6-H6	1.136(5)	C30-C31	1.374(7)
C7-C8	1.403(7)	C30-H30	1.111(5)
C7-H7	1.151(5)	C31-C32	1.375(7)
C8-C9	1.394(7)	C31-H31	1.147(5)
C8-H8	1.119(5)	C32-C33	1.390(7)
C9-H9	1.092(5)	C33-C34	1.376(7)
C10-C11	1.396(7)	C33-H33	1.118(5)
C10-C15	1.403(7)	C34-H34	1.162(5)
C11-C12	1.385(8)	C35-C36	1.521(7)
C11-H11	1.129(5)	C35-H35A	1.133(5)
C12-C13	1.380(7)	C35-H35B	1.096(5)
C12-H12	1.123(5)	C36-C37	1.504(7)
C13-C14	1.380(7)	C36-H36A	1.096(5)
C14-C15	1.391(8)	C36-H36B	1.091(5)
C14-H14	1.126(5)	C37-C38	1.523(8)
C15-H15	1.126(5)	C37-H37A	1.139(6)
C16-C17	1.520(7)	C37-H37B	1.097(5)
C16-H16A	1.091(5)	C38-H38C	1.078(7)
C16-H16B	1.106(5)	C38-H38A	1.059(7)
C17-C18	1.535(8)	C38-H38B	1.112(6)

TABLE 5.2.11 ATOMIC ANGLES IN DEGREES OF (S)-(+)-2.29

(R = *n*-C_4H_9, X = O, Y = *p*-ClC_6H_4N)

C1-N1-C3	110.9(4)	C18-C19-H19C	113.3(5)
C1-N1-C10	126.8(4)	C18-C19-H19A	112.0(5)
C3-N1-C10	122.2(4)	C18-C19-H19B	112.1(5)
C1-N2-C2	113.0(4)	H19C-C19-H19A	105.7(5)
C1-N2-C16	123.3(4)	H19C-C19-H19B	107.0(5)
C2-N2-C16	122.3(4)	H19A-C19-H19B	106.2(6)
C20-N3-C21	112.5(4)	O2-C20-N3	127.1(5)
C20-N3-C29	124.1(4)	O2-C20-N4	125.5(4)
C21-N3-C29	122.2(4)	N3-C20-N4	107.3(4)
C20-N4-C22	111.0(4)	N3-C21-C22	101.0(3)
C20-N4-C35	120.5(4)	N3-C21-C23	113.1(4)
C22-N4-C35	119.6(4)	N3-C21-H21	110.7(4)
O1-C1-N1	126.1(5)	C22-C21-C23	113.4(4)
O1-C1-N2	125.9(5)	C22-C21-H21	108.3(4)
N1-C1-N2	107.9(4)	C23-C21-H21	109.9(4)
N2-C2-C3	102.4(4)	N4-C22-C21	103.5(4)
N2-C2-H2A	114.0(4)	N4-C22-H22A	111.1(4)
N2-C2-H2B	111.3(4)	N4-C22-H22B	113.1(4)
C3-C2-H2A	113.0(4)	C21-C22-H22A	109.8(4)
C3-C2-H2B	112.3(4)	C21-C22-H22B	112.1(4)
H2A-C2-H2B	104.1(4)	H22A-C22-H22B	107.2(4)
N1-C3-C2	102.5(4)	C21-C23-C24	118.4(4)
N1-C3-C4	112.7(4)	C21-C23-C28	121.6(4)
N1-C3-H3	110.0(4)	C24-C23-C28	120.0(4)
C2-C3-C4	111.7(4)	C23-C24-C25	120.0(4)
C2-C3-H3	110.4(4)	C23-C24-H24	118.0(4)
C4-C3-H3	109.5(4)	C25-C24-H24	121.9(4)
C3-C4-C5	119.8(4)	C24-C25-C26	120.1(4)
C3-C4-C9	120.5(4)	C24-C25-H25	120.1(4)
C5-C4-C9	119.7(4)	C26-C25-H25	119.7(5)
C4-C5-C6	119.6(4)	C25-C26-C27	120.2(4)
C4-C5-H5	120.5(4)	C25-C26-H26	119.5(4)
C6-C5-H5	119.9(4)	C27-C26-H26	120.2(5)
C5-C6-C7	121.2(5)	C26-C27-C28	119.6(4)
C5-C6-H6	119.3(5)	C26-C27-H27	118.5(4)
C7-C6-H6	119.4(4)	C28-C27-H27	121.9(5)
C6-C7-C8	119.6(4)	C23-C28-C27	120.0(4)
C6-C7-H7	120.9(5)	C23-C28-H28	120.2(4)
C8-C7-H7	119.5(5)	C27-C28-H28	119.8(4)
C7-C8-C9	119.4(5)	N3-C29-C30	121.6(4)
C7-C8-H8	121.2(5)	N3-C29-C34	119.3(4)
C9-C8-H8	119.3(5)	C30-C29-C34	119.0(4)
C4-C9-C8	120.4(4)	C29-C30-C31	120.2(4)
C4-C9-H9	120.9(4)	C29-C30-H30	117.7(4)
C8-C9-H9	118.5(4)	C31-C30-H30	122.2(4)
N1-C10-C11	118.9(4)	C30-C31-C32	120.2(4)
N1-C10-C15	122.3(4)	C30-C31-H31	120.8(4)
C11-C10-C15	118.8(5)	C32-C31-H31	119.0(5)
C10-C11-C12	120.9(4)	C12-C32-C31	119.4(4)
C10-C11-H11	119.8(5)	C12-C32-C33	119.9(4)
C12-C11-H11	119.2(4)	C31-C32-C33	120.7(4)

C11-C12-C13	119.6(5)	C32-C33-C34	119.4(4)
C11-C12-H12	122.9(4)	C32-C33-H33	119.8(5)
C13-C12-H12	117.5(5)	C34-C33-H33	120.8(4)
C11-C13-C12	119.6(4)	C29-C34-C33	120.5(4)
C11-C13-C14	119.8(4)	C29-C34-H34	121.1(4)
C12-C13-C14	120.6(5)	C33-C34-H34	118.3(4)
C13-C14-C15	120.3(4)	N4-C35-C36	112.8(4)
C13-C14-H14	119.4(5)	N4-C35-H35A	109.2(4)
C15-C14-H14	120.2(5)	N4-C35-H35B	112.3(4)
C10-C15-C14	119.8(5)	C36-C35-H35A	107.7(4)
C10-C15-H15	118.8(5)	C36-C35-H35B	109.9(4)
C14-C15-H15	121.4(4)	H35A-C35-H35B	104.6(4)
N2-C16-C17	112.3(4)	C35-C36-C37	111.5(4)
N2-C16-H16A	110.1(4)	C35-C36-H36A	108.2(4)
N2-C16-H16B	109.3(4)	C35-C36-H36B	110.4(4)
C17-C16-H16A	109.8(4)	C37-C36-H36A	108.7(5)
C17-C16-H16B	108.5(4)	C37-C36-H36B	110.4(4)
H16A-C16-H16B	106.8(4)	H36A-C36-H36B	107.5(4)
C16-C17-C18	112.7(4)	C36-C37-C38	113.1(4)
C16-C17-H17A	109.5(5)	C36-C37-H37A	108.7(5)
C16-C17-H17B	110.5(4)	C36-C37-H37B	111.4(4)
C18-C17-H17A	108.0(4)	C38-C37-H37A	109.4(5)
C18-C17-H17B	110.0(5)	C38-C37-H37B	109.7(5)
H17A-C17-H17B	105.8(4)	H37A-C37-H37B	104.1(4)
C17-C18-C19	113.4(5)	C37-C38-H38C	112.2(5)
C17-C18-H18A	108.1(5)	C37-C38-H38A	109.3(5)
C17-C18-H18B	109.4(5)	C37-C38-H38B	108.0(5)
C19-C18-H18A	109.8(5)	H38C-C38-H38A	111.3(6)
C19-C18-H18B	109.0(5)	H38C-C38-H38B	107.3(6)
H18A-C18-H18B	107.0(5)	H38A-C38-H38B	108.6(5)

TABLE 5.2.12 BIVOET (BEST MEASURABLE BIJVOET DIFFERENCES) OF (S)-(+)-2.29 (R = *n*-C4H9, X = O, Y = *p*-ClC6H4N)

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This routine selects reflections for which the Bijvoet difference is
  MOST significant, i.e. (Fc+ - Fc-)/Sigma(Fo) is largest.
If Fo- is available (Fc+ - Fc-) is compared to (Fo+ - Fo-).
Before running the routine Structure Factors must be calculated with :--
 (1) A refined structure
 (2) The dispersion flag "Yes" for all atoms
 (3) An ETA parameter of 1.0.
If this has not been done, abort the run by requesting 0 reflections.
%
```

	h	k	l	Fc+		Fc-	Del/Sig	Fo+		Fo-	Sense
1	1	1	0	20.490	>	19.712	15.707	20.397	>	19.923	+
2	1	3	3	26.525	>	25.574	14.056	26.946	>	26.810	+
3	0	4	3	16.125	<	16.945	-12.023	16.228	<	17.609	+
4	-1	2	1	64.837	>	64.252	11.289	62.577	>	62.401	+
5	1	1	4	67.412	>	66.715	10.279	65.637	<	65.948	-
6	-1	3	2	90.205	<	90.783	-9.885	86.983	<	89.144	+
7	1	2	2	36.795	<	37.369	-9.855	36.172	<	37.644	+
8	0	5	2	19.106	>	18.507	8.859	19.792	>	19.604	+
9	1	6	0	45.461	>	44.860	8.372	43.639	<	44.537	-
10	1	3	2	39.540	<	40.037	-8.085	38.347	<	40.313	+
11	1	6	5	22.333	>	21.637	7.379	23.124	<	23.788	-
12	-1	2	7	32.853	>	32.233	7.278	32.754	>	32.535	+
13	1	7	0	26.520	<	27.107	-7.272	25.737	<	27.405	+
14	1	3	7	31.760	>	31.084	7.074	32.088	<	32.653	-
15	-1	2	5	24.119	>	23.608	7.004	24.381	>	24.134	+
16	0	7	5	17.113	<	17.784	-6.988	17.614	<	18.818	+
17	1	1	6	32.238	<	32.834	-6.980	32.962	<	33.791	+
18	1	2	4	32.889	<	33.381	-6.951	31.432	<	33.005	+
19	2	1	0	9.151	<	9.757	-6.853	8.040	<	8.545	+
20	-1	5	5	23.022	<	23.581	-6.725	23.502	<	25.021	+
21	-2	4	2	33.095	<	33.611	-6.67[illegible]	30.887	<	32.449	+
22	-1	3	3	40.726	>	40.317	6.[illegible]0	41.781	<	42.276	-
23	-1	4	2	101.188	>	100.782	6.469	97.989	<	99.255	-
24	1	5	0	28.177	<	28.614	-6.442	26.592	<	27.912	+
25	-1	6	3	19.826	<	20.341	-6.400	19.207	<	20.419	+
26	-2	6	3	4.995	>	4.154	6.395	6.639	>	5.726	+
27	-1	1	1	87.130	<	87.440	-6.392	83.282	<	83.723	+
28	2	2	4	21.505	<	22.103	-6.366	21.275	<	22.779	+
29	1	7	4	21.577	<	22.160	-6.215	21.380	<	23.047	+
30	-1	3	1	17.224	<	17.597	-6.167	17.147	<	17.916	+
31	1	1	1	26.180	>	25.862	6.164	25.636	<	26.057	-
32	-1	4	1	36.041	<	36.399	-5.761	34.947	<	35.900	+
33	1	6	1	19.034	>	18.595	5.676	18.964	<	18.968	-
34	1	2	0	55.592	>	55.305	5.597	53.344	<	54.175	-
35	1	4	6	13.702	<	14.266	-5.581	14.227	<	15.051	+
36	-1	2	6	17.546	<	17.997	-5.398	17.415	<	18.267	+
37	0	2	3	16.678	<	16.991	-5.288	15.938	<	16.555	+
38	1	5	1	46.981	<	47.340	-5.277	45.175	<	47.235	+
39	-1	9	2	26.489	<	26.991	-5.207	25.917	<	27.465	+
40	0	7	1	30.564	<	30.958	-5.205	30.783	<	32.224	+
41	2	3	3	20.280	>	19.808	5.204	18.371	<	19.057	-

42	1	7	1	29.402	<	29.820	-5.182	28.260	<	30.199	+
43	-2	1	4	17.231	<	17.661	-5.163	15.146	<	15.420	+
44	-1	8	1	18.193	>	17.721	5.149	18.298	<	18.487	-
45	1	5	4	28.118	<	28.533	-5.063	28.585	<	30.158	+
46	0	6	8	15.407	<	15.969	-4.970	15.907	<	17.318	+
47	-1	6	4	61.158	>	60.765	4.958	61.049	<	62.513	-
48	-1	2	2	68.879	<	69.149	-4.933	67.882	<	69.216	+
49	1	2	1	38.379	<	38.643	-4.897	36.698	<	38.313	+
50	0	2	4	6.121	<	6.541	-4.887	8.051	<	8.824	+
51	-1	4	7	21.976	<	22.431	-4.864	22.766	<	23.857	+
52	-2	4	10	15.429	<	16.060	-4.861	14.788	<	16.225	+
53	-1	2	3	14.408	>	14.089	4.816	14.695	<	14.696	-
54	-3	4	1	43.198	>	42.766	4.729	43.349	<	45.066	-
55	-3	1	3	7.046	>	6.383	4.647	6.779	>	5.879	+
56	-1	5	6	21.769	>	21.347	4.642	20.486	<	20.783	-
57	-1	5	9	21.341	<	21.864	-4.630	21.349	<	22.837	+
58	-1	1	6	48.179	<	48.528	-4.623	49.218	<	50.214	+
59	0	10	3	7.685	<	8.311	-4.587	8.026	<	9.077	+
60	0	1	1	30.835	<	30.993	-4.576	10.528	<	17.190	+
61	1	1	8	42.603	>	42.153	4.528	42.437	<	42.643	-
62	-2	4	6	39.990	<	40.399	-4.527	39.888	<	41.746	+
63	-1	6	5	18.903	<	19.310	-4.510	19.243	<	20.540	+
64	-1	3	6	44.584	<	44.940	-4.500	43.644	<	45.151	+
65	1	4	5	10.346	<	10.787	-4.444	10.400	<	11.177	+
66	-1	8	3	50.514	<	50.904	-4.429	51.027	<	53.439	+
67	2	1	6	15.651	>	15.170	4.397	15.986	>	15.520	+
68	1	2	8	35.618	<	36.058	-4.386	34.817	<	35.743	+
69	1	1	10	19.845	<	20.384	-4.347	20.012	<	20.743	+
70	-1	1	7	10.616	<	11.061	-4.311	11.515	<	11.904	+
71	-1	6	1	28.075	<	28.391	-4.307	26.909	<	28.112	+
72	1	5	3	33.842	<	34.163	-4.273	33.538	<	35.147	+
73	-1	4	5	25.766	>	25.432	4.267	26.028	<	26.344	-
74	1	3	11	9.465	>	8.802	4.238	10.351	>	9.519	+
75	-1	1	2	61.019	<	61.240	-4.233	59.732	<	60.390	+
76	3	6	2	4.162	<	4.829	-4.205	5.448	<	6.507	+
77	1	12	5	20.320	>	19.787	4.187	20.174	<	21.115	-
78	-4	4	5	22.123	>	21.616	4.182	21.515	<	22.317	-
79	0	4	0	18.592	>	18.251	4.143	16.650	>	16.473	+
80	-1	3	7	11.813	>	11.388	4.137	12.869	>	12.483	+
81	0	2	1	33.845	>	33.677	4.101	33.398	<	33.879	-
82	2	5	4	13.505	<	13.942	-4.093	13.504	<	14.696	+
83	0	8	1	7.742	>	7.245	4.070	7.310	>	7.034	+
84	0	3	4	20.087	>	19.799	4.063	20.122	<	20.403	-
85	-2	3	7	10.073	>	9.588	4.051	10.710	>	10.185	+
86	-3	3	2	3.309	<	3.820	-4.009	4.173	<	5.012	+
87	1	8	0	55.564	>	55.227	3.965	55.679	<	57.855	-
88	1	7	2	32.760	>	32.443	3.847	33.506	<	34.556	-
89	0	4	4	17.625	>	17.351	3.763	17.129	<	17.264	-
90	-1	7	9	3.067	<	3.622	-3.737	3.464	<	4.077	+
91	1	1	2	61.831	<	62.038	-3.733	58.455	<	60.300	+
92	-1	10	1	14.587	<	15.001	-3.732	14.512	<	15.525	+
93	1	6	9	22.678	>	22.227	3.728	21.877	<	22.661	-
94	2	5	6	13.887	<	14.315	-3.728	15.109	<	16.184	+
95	1	3	4	33.766	>	33.497	3.690	33.560	<	34.444	-

96	2	7	6	12.211	<	12.691	-3.685	12.390	<	13.728	+
97	1	2	6	3.302	<	3.878	-3.674	5.257	<	6.011	+
98	-1	4	3	40.902	<	41.147	-3.665	42.442	<	43.698	+
99	-1	7	5	7.739	<	8.245	-3.646	6.356	<	7.301	+
100	0	8	3	25.359	>	25.035	3.620	25.311	<	25.900	-

Out of 100 TOTAL measurements, (Fo+ - Fo-) has the SAME sign as (Fc+ - Fc-) in 73 cases and the OPPOSITE sign in 27 cases.

Cumulative Binomial Distribution

The Absolute Structure of the Model is CONFIRMED
Based on 100 Measurements, 73 of which Support the Model
The Probability that the Above Statement is WRONG is 0.2346E-05

5.3 EXPERIMENTAL FOR CHAPTER 3

5.3.1 SYNTHESIS OF DIARYL SULFUR DIIMIDES

5.3.1.1 SYNTHESIS OF N-PHENYLSULFONYL-N'-PHENYLSULFUROUS DIIMIDE

A solution of 0.06 mole (5.6g) of aniline in 200 mL of benzene was added slowly with cooling to a solution of 0.02 mole (5.2g) of N-phenylsulfonylimidosulfurous chloride in 50 mL of benzene. The mixture was left at room temperature until the separation of a precipitate had ceased (3h), and this was then filtered off in vacuum and the residue was crystallized from a mixture of benzene and petroleum ether. The yield was 96 % (5.4g), m.p. 94-95 ^{o}C.[142]

5.3.1.2 SYNTHESIS OF DIPHENYL SULFUR DIIMIDE

To a solution of 0.01 mole (0.93g) of aniline in 10 mL of benzene was added a solution of 0.01 mole (2.8g) of N-phenylsulfonyl-N'-phenylsulfurous diimide in 10 mL of benzene. The mixture was left at room temperature for 3 days. The precipitate of benzenesulfonamide was filtered off with suction. The filtrate was concentrated by rotary evaporation. Diphenyl sulfur diimide was obtained by distillation at 106-108 ^{o}C/0.2 mmHg (lit.[142] bp 123-124 ^{o}C/0.6 mmHg): yield 87 %; IR ν (N=S=N) 1171, 1269

cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.65 - 7.70 (m, 10H, aromatic ring protons); MS (*m/e*) 214 $[M]^+$.

5.3.1.3 SYNTHESIS OF DI-*p*-TOLYL SULFUR DIIMIDE

The reaction was effected in the same manner as that described for the preparation of diphenyl sulfur diimide with the following modification of the work-up procedure : instead of distilling the product, it was crystallized from petroleum ether affording di-*p*-tolyl sulfur diimide, mp 47-48 °C (lit.[142] mp 47-48 °C), in 89 % yield. IR ν (N=S=N) 1174, 1267 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H, CH_3), 7.06-7.41 (m, 8H, aromatic ring protons); MS (*m/e*) 242 $[M]^+$.

5.3.2 GENERAL PROCEDURE FOR THE PALLADIUM-CATALYZED CYCLIZATION REACTION OF AZIRIDINES AND SULFUR DIIMIDES.

A mixture of aziridine (2.0 mmol), sulfur diimide (1.0 mmol), and bis(benzonitrile)palladium dichloride (0.038g, 0.1 mmol) in toluene (3.0 mL) was heated with stirring in a glass autoclave for 48h at 130 °C (oil bath temperature) under a slight pressure of nitrogen (5 psi). After being cooled to room temperature, the autoclave was opened and the red-brown homogeneous solution was filtered through Celite. The filtrate was concentrated by rotary evaporation, and the crude product was purified by silica gel thin-

layer chromatography using 10 : 1 toluene / acetonitrile as the developer.

Yields (based on sulfur diimide) melting points IR, NMR, MS, and either high-resolution mass spectra (HRMS) determination or analytical data for **3.13** are as follows :

1-*tert*-Butyl-3-*p*-tolyl-4-phenyl-2-imidazolidinethione (**3.13**, R = Ph, R' = $C(CH_3)_3$, Ar = *p*-tolyl)

53% yield; mp 203-204 °C; IR ν (C=S) 1242 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52 (s, 9H, $C(CH_3)_3$), 2.22 (s, 3H, CH_3), 3.66 (dd, 1H, *J* = 8.4, 9.9 Hz), 4.17 (t, 1H, *J* = 9.9 Hz), 4.95 (dd, 1H, *J* = 8.4, 9.9 Hz), 7.01-7.26 (m, 9H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 21.26 (p-$CH_3C_6H_4$), 28.05 (CH_3), 54.48 (CH_2), 57.07 ($C(CH_3)_3$), 64.36 (CHAr), 127.23, 128.03, 128.48, 128.85, 129.40 (CH-aromatic), 136.70, 137.79, 139.59 (quaternary aromatic carbons), 183.00 (C=S); MS (*m/e*) 324 $[M]^+$; HRMS (*m/e*) 324.1643 (Calcd for $C_{20}H_{24}N_2S$, 324.1660).

1-*n*-Butyl-3-*p*-tolyl-4-phenyl-2-imidazolidinethione (**3.13**, R = Ph, R' = n-C_4H_9, Ar = *p*-tolyl)

52% yield; mp 109-110 °C; IR ν (C=S) 1251 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H, CH_3), 1.38 (q, 2H, CH_2CH_3), 1.63 (m, 2H, $CH_2CH_2CH_3$), 2.22 (s, 3H, CH_3), 3.71 (m, 3H, NCH_2 and one H of CH_2 (ring)), 4.08 (t, 1H, CH_2, ring, *J* = 10.0 Hz), 5.11 (dd, 1H, CHPh, *J* = 7.6, 10.0 Hz), 6.99-7.30 (m, 9H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.03 (CH_3), 20.10, 29.25 ($CH_2CH_2CH_3$), 21.12 (CH_3) 47.62 (NCH_2) 55.58 (CH_2 ring), 64.61 (CHPh), 127.17, 128.54, 128.59, 129.01, 129.40 (CH-aromatic), 136.57, 137,46, 139.66 (quaternary aromatic

carbons), 182.60 (C=S); MS (*m/e*) 324 $[M]^+$. Anal. Calcd for $C_{22}H_{24}N_2S$: C, 74.03; H, 7.45; N, 8.63. Found: C, 73.86; H, 7.36; N, 8.58.

1-(1-Adamantyl)-3-phenyl-4-phenyl-2-imidazolidinethione (**3.13**, R = Ph, R' = 1-adamantyl, Ar = Ph)

52% yield; mp 215-216 °C; IR ν (C=S) 1244 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61-2.60 (m, 15H, adamantyl protons), 3.68 (dd, 1H, CH_2, *J* = 8.2, 10.0 Hz), 4.18 (t, 1H, *J* = 10.0 Hz), 4.60 (dd, 1H, J = 8.2, 10.0 Hz), 7.10-7.25 (m, 10H, aromatic ring protons); ^{13}C NMR ($CDCl_3$) δ 29.93, 36.27, 39.34 (secondary and tertiary adamantyl carbons), 53.53 (CH_2), 58.34 (quaternary carbon of adamantyl group), 64.27 (CHPh), 126.80, 127.14, 128.21, 128.43, 128.53, 128.83 (CH-aromatic), 139.50, 140.26 (quaternary carbons of Ph) 182.01 (C=S); MS (*m/e*) 388 $[M]^+$. Anal. Calcd for $C_{25}H_{28}N_2S$: C, 77.27; H, 7.26; N, 7.21. Found: C, 77.08; H, 7.19; N, 7.14.

1-(1-Adamantyl)-3-*p*-tolyl-4-phenyl-2-imidazolidinethione (**3.13**, R = Ph, R' = 1-adamantyl, Ar = *p*-tolyl)

56% yield; mp 217-218 °C; IR ν (C=S) 1246 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59-2.52 (m, 15H, adamantyl protons), 2.21 (s, 3H, CH_3) 3.67 (dd, 1H, CH_2, *J* = 8.2, 10.0 Hz), 4.16 (t, 1H, *J* = 10.0 Hz), 4.92 (dd, 1H, J = 8.2, 10.0 Hz), 6.96-7.25 (m, 9H, aromatic ring protons); ^{13}C NMR ($CDCl_3$) δ 21.14 (p-$CH_3C_6H_4$) 29.94, 36.27, 39.36 (secondary and tertiary adamantyl carbons), 53.51 (CH_2), 58.27 (quaternary carbon of adamantyl group), 64.37 (CHPh), 127.20, 128.08, 128.40, 128.80, 129.33 (CH-aromatic), 136.58, 137.69, 139.65 (quaternary carbons of

Ph) 182.22 (C=S); MS (*m/e*) 402 $[M]^+$. Anal. Calcd for $C_{26}H_{30}N_2S$: C, 77.57; H, 7.51; N, 6.96. Found: C, 77.73; H, 7.46; N, 6.90.

1-*tert*-Butyl-3-phenyl-4-*p*-bromophenyl-2-imidazolidinethione (**3.13**, R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = Ph)

60% yield; mp 153-154 °C; IR ν (C=S) 1246 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67 (s, 9H, $C(CH_3)_3$), 3.60 (dd, 1H, *J* = 8.4, 9.9 Hz), 4.17 (t, 1H, *J* = 9.9 Hz), 4.97 (dd, 1H, *J* = 8.4, 9.9 Hz), 7.09-7.43 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 28.02 (CH_3), 54.27 (CH_2), 57.21 ($C(CH_3)_3$), 63.58 (CHAr), 127.01, 128.03, 128.72, 128.85, 132.06 (CH-aromatic), 122.45, 138.45, 140.16 (quaternary aromatic carbons), 182.86 (C=S); MS (*m/e*) 389 $[M]^+$ and 391 $[M + 2]^+$. Anal. Calcd for $C_{19}H_{21}BrN_2S$: C, 58.61; H, 5.44; N, 7.20. Found: C, 58.86; H, 6.01; N, 6.65.

1-*tert*-Butyl-3-*p*-tolyl-4-*p*-bromophenyl-2-imidazolidinethione (**3.13**, R = *p*-BrC_6H_4, R' = $C(CH_3)_3$, Ar = *p*-tolyl)

58% yield; mp 175-176 °C; IR ν (C=S) 1241 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66 (s, 9H, $C(CH_3)_3$), 2.22 (s, 3H, CH_3), 3.58 (dd, 1H, J = 8.2, 10.0 Hz), 4.15 (t, 1H, *J* = 10.0 Hz), 4.92 (dd, 1H, *J* = 8.2, 10.0 Hz), 7.01-7.41 (m, 8H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 21.15 (p-$CH_3C_6H_4$) 28.03 (CH_3), 54.23 (CH_2), 57.13 ($C(CH_3)_3$), 63.67 (CHAr), 127.88, 128.90, 129.47, 132.01 (CH-aromatic), 122.39, 136.79, 137.59, 138.59 (quaternary aromatic carbons), 183.07 (C=S); MS (*m/e*) 403 $[M]^+$ and 405 $[M + 2]^+$. Anal. Calcd for $C_{20}H_{23}BrN_2S$: C, 59.55; H, 5.75; N, 6.94. Found: C, 59.21; H, 5.82; N, 6.81.

1-(1-Adamantyl)-3-phenyl-4-biphenyl-2-imidazolidinethione (**3.13**, R = *p*-PhC_6H_4, R' = 1-adamantyl, Ar = Ph)

70% yield; mp 211-212 °C; IR ν (C=S) 1245 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69-2.55 (m, 15H, adamantyl protons), 3.71 (dd, 1H, CH_2, *J* = 8.4, 10.0 Hz), 4.20 (t, 1H, *J* = 10.0 Hz), 5.02 (dd, 1H, *J* = 8.4, 10.0 Hz), 7.14-7.71 (m, 14H, aromatic ring protons); ^{13}C NMR ($CDCl_3$) δ 30.04, 36.37, 39.41 (secondary and tertiary adamantyl carbons), 53.59 (CH_2), 58.41 (quaternary carbon of adamantyl group), 63.96 (CHPh), 127.03, 127.40, 127.55, 127.64, 128.26, 128.63, 128.89, 129.09 (CH-aromatic), 138.59, 140.28, 140.43, 141.24 (quaternary carbons of Ph) 182.02 (C=S); MS (*m/e*) 464 $[M]^+$. Anal. Calcd for $C_{31}H_{32}N_2S$: C, 80.13; H, 6.94; N, 6.03. Found: C, 80.06; H, 7.03; N, 5.82.

1-(1-Adamantyl)-3-*p*-tolyl-4-biphenyl-2-imidazolidinethione (**3.13**, R = *p*-PhC_6H_4, R' = 1-adamantyl, Ar = *p*-tolyl)

68% yield; mp 142-143 °C; IR ν (C=S) 1245 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69-2.62 (m, 15H, adamantyl protons), 2.23 (s, 3H, CH_3) 3.70 (dd, 1H, CH_2, *J* = 8.4, 9.8 Hz), 4.19 (t, 1H, *J* = 9.8 Hz), 4.98 (dd, 1H, *J* = 8.4, 9.8 Hz), 7.04-7.97 (m, 13H, aromatic ring protons); ^{13}C NMR ($CDCl_3$) δ 21.12 (p-$CH_3C_6H_4$) 30.03, 36.37, 39.43 (secondary and tertiary adamantyl carbons), 53.57 (CH_2), 58.34 (quaternary carbon of adamantyl group), 64.10 (CHPh), 127.02, 127.52, 127.69, 128.14, 128.87, 129.09, 129.43 (CH-aromatic), 136.63, 137.81, 140.30, 141.22 (quaternary carbons of aromatic group) 182.28 (C=S); MS

(*m/e*) 478 $[M]^+$. Anal. Calcd for $C_{32}H_{34}N_2S$: C, 80.29; H, 7.16; N, 5.85. Found: C, 80.50; H, 7.85; N, 5.35.

1-*tert*-Butyl-3-*p*-tolyl-4-biphenyl-2-imidazolidinethione (**3.13**, R = *p*-PhC_6H_4, R' = $C(CH_3)_3$, Ar = *p*-tolyl)

60% yield; mp 183-184 °C; IR ν (C=S) 1243 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (s, 9H, $C(CH_3)_3$), 2.23 (s, 3H, CH_3), 3.68 (dd, 1H, *J* = 8.4, 9.9 Hz), 4.19 (t, 1H, *J* = 9.9 Hz), 4.95 (dd, 1H, *J* = 8.4, 9.9 Hz), 7.04-7.58 (m,13H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 21.18 (p-$CH_3C_6H_4$), 28.09 (CH_3), 54.49 (CH_2), 57.13 ($C(CH_3)_3$), 64.08 (CHAr), 127.00, 127.53, 127.67, 128.05, 128.84, 129.46, 129.74 (CH-aromatic), 136.74, 137.87, 138.51, 140.26, 141.28 (quaternary aromatic carbons), 183.16 (C=S); MS (*m/e*) 400 $[M]^+$; HRMS (m/e) 400.1987 (Calcd for $C_{26}H_{28}N_2S$, 400.1972).

5.3.3 PROCEDURE FOR THE PALLADIUM-CATALYZED CYCLOADDITION REACTION OF 1-(1-ADAMANTYL)-2-PHENYLAZIRIDINE AND PHENYL ISOTHIOCYANATE.

A mixture of aziridine (**3.12**, 1.0 mmol), phenyl isothiocyanate (**3.15**, 1.0 mmol), and bis(benzonitrile)palladium dichloride (0.038g, 0.10 mmol) in toluene (3.0 mL) was heated with stirring in a glass autoclave, for 48h at 130 °C (oil bath temperature) under a slight pressure of nitrogen (5 psi). The workup procedure was the same as described in the general procedure for the palladium-catalyzed cyclization reaction of

aziridines and sulfur diimides. The isolated yield of **3.16** was 0.33 g: 85 % yield mp 133-134 °C; IR ν (C=N) 1619 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 1.66 - 2.50 (m, 15H, adamantyl protons), 3.67 (dd, 1H, *J* = 8.2 and 9.7 Hz, CH_2), 4.01 (dd, 1H, *J* = 6.6 and 9.7 Hz, CH_2), 4.55 (m, 1H, CHPh), 6.95-7.46 (m, 10H, aromatic ring protons); ^{13}C NMR ($CDCl_3$) δ 30.73, 37.27, 40.29 (secondary and tertiary adamantyl carbons), 46.51 (CHPh), 56.57 (CH_2), 58.94 (quaternary carbon of adamantyl group), 122.53, 123.27, 128.17, 128.62, 129.37, 129.43 (CH-aromatic), 140.13, 153.26 (quaternary carbons of Ph), 156.75 (C=N); MS (*m/e*) 388 $[M]^+$. Anal. Calcd for $C_{25}H_{28}N_2S$: C, 77.23; H, 7.26; N, 7.21. Found: C, 77.08; H, 7.15; N, 7.50.

5.3.4 SYNTHESIS OF 1-*tert*-BUTYL-2-PHENYL[3-^{13}C]AZIRIDINE (3.22).

5.3.4.1 METHYL [^{13}C]TRIPHENYLPHOSPHONIUM IODIDE (3.18).

A solution containing 9.4g (36.0 mmol) of triphenylphosphine dissolved in dry benzene (6.0 mL) was placed in a pressure bottle, the bottle was cooled in an ice bath, and 5.0g (36.0 mmol) of [^{13}C]methyl iodide was added. The bottle was sealed, allowed to stand at room temperature for 2 days, and then reopened. The white solid was collected by filtration with the aid of about 100 mL of hot benzene and was dried in a vacuum at 100 °C over phosphorous pentoxide. The yield was 13.9g (96 %), mp 183-184 °C.

5.3.4.2 2-PHENYL[3-^{13}C]OXIRANE (3.20).

A heterogeneous mixture of benzaldehyde (1.83g, 17.2 mmol) , methy[^{13}C]triphenylphosphonium iodide (13.9g, 34.3 mmol), benzene (34 mL), and 5 N aqueous sodium hydroxide (102 mL) was stirred for 24h at 40 °C. The reaction mixture was extracted with benzene (3 x 25 mL), the alkali was removed by washing with water, and the benzene solution was dried ($MgSO_4$) and filtered. The yield of 1-phenyl[2-^{13}C]ethene was 42 % (GC yield, using n-undecane as internal standard). The benzene solution (also containing Ph_3PO as a byproduct) was used for subsequent epoxidation.

To the benzene solution was added 7.6 g (22.0 mmol) of *m*-chloroperbenzoic acid (50 %). The mixture was kept at 0 °C for 40 h and was shaken frequently during the first hour. The formed *m*-chlorobenzoic acid was removed from the benzene solution by shaking with an excess of 10 % aqueous sodium hydroxide, and the alkali was removed by washing with water. The benzene layer was dried ($MgSO_4$) and evaporated, and the residue was diluted *in vacuo* to give 0.91 g (52 %) of oxirane: bp 38 - 40 °C / 1 mmHg; ^{1}H NMR ($CDCl_3$) d 2.78 (ddd, 1H, J = 2.5, 5.8, and 176.0 Hz, $^{13}CH_2$), 3.12 (ddd, 1H, J = 4.1, 5.8, and 178.0 Hz, $^{13}CH_2$), 3.83 (m, 1H, CHPh), 7.26 - 7.43 (m, 5H, Ph); MS (*m/e*) 121 $[M]^+$.

5.3.4.3 1-PHENYL-2-(*tert*-BUTYLAMINO)[2-^{13}C]-ETHANOL (3.21).

A mixture of 0.91g (7.5 mmol) of 2-phenyl[3-^{13}C]oxirane and 2.74g (37.5 mmol) of *tert*-butylamine was stirred in an autoclave

for 60h at 95 °C. After evaporation of excess *tert*-butylamine, the residual solid was crystallized from hexane to give 1.03g (71 %) of the white amino alcohol: mp 85 - 86 °C; IR ($CHCl_3$) $\nu_{OH,\ NH}$ 3600, 3400 - 3300 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 9H, $C(CH_3)_3$) 2.26 - 3.15 (m, 4H, $^{13}CH_2$, NH, OH), 4.55 (m, 1H, CHOH), 7.28 (m 5H, Ph); MS (*m/e*) 194 $[M]^+$.

5.3.4.4 1-*tert*-BUTYL-2-PHENYL[3-^{13}C]AZIRIDINE (3.22).

To an ice-cold solution of 1.40g (5.3 mmol) of triphenylphosphine in 12 mL of acetonitrile (N_2 atomsphere) was added, drop-by-drop, an ice-cold solution of 0.85 g (5.3 mmol) of bromine in 3.5 mL of acetonitrile. To the resulting red solution was slowly added 1.03g (5.3 mmol) of the β-amino alcohol, followed by drop-by-drop addition of 1.62g (16.0 mmol) of distilled triethylamine in 3.5 mL of acetonitrile (all done at 0 °C). The reaction mixture was then stirred at ambient temperature for 20 min, triethylamine hydrobromide (2.24g, 77 %) was filtered, and the filtrate was concentrated by rotary evaporation. The residue was treated with hexane (6 x 15 mL), concentrated to 7 mL, and then filtered to remove triphenyl phosphine oxide, and the filtrate was evaporated. The aziridine was obtained in 66 % yield by distillation at 40 °C (0.5 mm Hg): ^1H NMR ($CDCl_3$) δ 1.06 (s, 9H, $C(CH_3)_3$), 1.66 (ddd, 1H, J = 0.8, 3.0, and $J\ ^{13}C\text{-}^1H$ = 176.0 Hz, $^{13}CH_2$), 1.91 (ddd, 1H, J = 0.8, 6.4, and $J\ ^{13}C\text{-}^1H$ = 162.0 Hz, $^{13}CH_2$), 2.64 (m, 1H, CHPh), 7.20 - 7.37 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 27.20 (CH_3), 30.55 ($^{13}CH_2$, intense signal), 34.30 ($C(CH_3)_3$), 51.83 (CHPh),

127.20, 128.78 (CH-aromatic), 128.95 (quaternary aromatic carbon); MS (*m/e*) 176 $[M]^+$.

5.3.5 PROCEDURE FOR THE PALLADIUM-CATALYZED CYCLIZATION REACTION OF 1-*tert*-BUTYL-2-PHENYL[3-^{13}C]AZIRIDINE AND 1,3-DI-*p*-TOLYL SULFUR DIIMDE.

The reaction procedure was the same as that described in the general procedure for the palladium-catalyzed cycloaddition reaction of aziridines and sulfur diimides. The isolated yield of the pure product **3.23** was 52 % : mp 203 - 204 ^oC; IR ν (^{13}C=S) 1214 cm^{-1}, ^1H NMR ($CDCl_3$) d 1.69 (s, 9H, $C(CH_3)_3$), 2.23 (s, 3H, CH_3), 3.66 (doublet of multiplets, 1H, $J^{13}C-^1H$ = 144.0 Hz, $^{13}CH_2$), 4.19 (doublet of multiplets, 1H, $J^{13}C-^1H$ = 146.0 Hz, $^{13}CH_2$), 4.96 (m, 1H, CHPh), 7.02-7.35 (m, 9H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 21.16 (p-$CH_3C_6H_4$), 28.06 (CH_3), 54.46 ($^{13}CH_2$, intense signal), 57.07 ($C(CH_3)_3$), 64.23 (CHAr), 127.25, 128.04, 128.49, 128.87, 129.40 (CH-aromatic), 137.69, 137.85, 139.60 (quaternary aromatic carbons), 183.17 (^{13}C=S, intense signal); MS (*m/e*) 326 $[M]^+$.

5.3.6 REACTION OF N-*p*-PHENYLBENZYLIDENE-*tert*-BUTYLAMINE WITH 1,3-DI-*p*-TOLYL SULFUR DIIMIDE.

A mixture of imine (1.0 mmol), sulfur diimide (1.0 mmol), and bis(benzonitrile)palladium dichloride (0.038g, 0.1. mmol) in toluene (3.0 mL) was heated with stirring in a glass autoclave for

48 h at 130 °C (oil bath temperature) under a slight pressure of nitrogen (5 psi). After being cooled to room temperature, the autoclave was opened and the dark-red homogenous solution was filtered through Celite. The work-up procedure was the same as that described in the general procedure for the palladium-catalyzed cyclization reaction of aziridines and sulfur diimides. The isolated yield of imine **3.26** was 50 %; mp 127 - 128 °C; IR ν (C=N) 1621 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28 (s, 3H, CH_3), 7.06-7.91 (m, 13H, aromatic ring protons), 8.42 (s, 1H, CH=N); MS (*m/e*) 2.71 $[M]^+$. The isolated yield of di-*p*-tolyldiazene **3.27** was 22 %; mp 137 - 138 °C; IR ν (N=N) 1501 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H, CH_3), 7.22-7.85 (m, 8H, aromatic ring protons); MS (*m/e*) 210 $[M]^+$.

5.3.7 X-RAY ANALYSIS FOR 3.13 (R = Ph, R' = $C(CH_3)_3$, Ar = *p*-$CH_3C_6H_4$)

A plate crystal of $C_{20}H_{24}N_2S$ was mounted on a glass capillary, and all measurements were made on a Rigaku diffractometer with $MoK\alpha$ radiation. Cell dimensions and orientation matrix were obtained from least-square refinement using the setting angles of 25 reflections in the range $40° < 2\theta < 47°$, corresponding to an orthorhombic cell with dimensions given in the supplementary material. For Z = 4 and FW = 324.48, the calculated density is 1.147 g/cm^3. The space group was determined to be $P2_12_12$. The data were collected at 21 °C using the ω - 2θ scan technique to a maximum 2θ value of 47, and the data were corrected for Lorentz and polarization effects. [125]

The structure was solved by direct methods. All of the atoms with the exception of hydrogen were refined anisotropically. The final cycle of full-matrix least-square refinement was based on 789 observed reflections ($I > 2.5\sigma(I)$) and 185 variable parameters. All calculations were performed using the NRC VAX crystallographic software package. [126]

Crystal data collection and refinement information of **3.13** (R = Ph, R' = $C(CH_3)_3$, Ar = p-$CH_3C_6H_4$) are listed in Table 5.3.1. The atomic parameter x, y, z and B_{iso} of **3.13** are in Table 5.3.2. Table 5.3.3 and 5.3.4 will show the interatomic distances (in angstroms) and angles (in degrees) of **3.13** respectively.

TABLE 5.3.1 CRYSTAL DATA COLLECTION AND REFINEMENT INFORMATION FOR COMPOUND 3.13 (R = Ph, R' = $C(CH_3)_3$, Ar = p-$CH_3C_6H_4$)

Empirical formula	SN2C20H24
Formula weight	324.48
Crystal shape	PLATE
Crystal dimensions	.2,.2,.2
Crystal system	ORTHOROMBIC
No. Reflection used for unit cell dimension (2theta range)	25 40,47
Lattice parameters	a=11.622(4) b=17.259(6) c=9.371(3)
Space group	P 212121
Z value	4
Dcalc	1.147
F(000)	696.63
mu	.17
No of reflection measured	1585
No of reflection unique	1585
No of reflection observed	789
No of atoms	47
No of variables	185
Rf (sign refl)	.073
Rw (sign refl)	.043
Rf (all refl)	.151
Rw (all refl)	.044
Goodness of fit	3.58
Last difference fourier map	
max peak	.460
min peak	-.270

TABLE 5.3.2 ATOMIC PARAMETERS X, Y, Z AND B_{iso} FOR 3.13

(R = Ph, R' = $C(CH_3)_3$, Ar = p-$CH_3C_6H_4$)

	x	y	z	Biso
S1	0.0708(3)	0.45788(20)	0.1384(3)	5.45(15)
N1	0.1047(9)	0.5227 (5)	-0.1186(10)	4.9 (5)
N2	0.0970(9)	0.3964 (5)	-0.1273(10)	4.8 (5)
C1	0.0922(10)	0.4555 (6)	-0.0353(12)	4.4 (5)
C2	0.1147(13)	0.5061 (7)	-0.2748(13)	5.2 (6)
C3	0.1349(16)	0.4187 (8)	-0.2672(15)	6.9 (8)
C16	0.0963(11)	0.3128 (6)	-0.0864(15)	5.2 (6)
C17	0.1009(22)	0.2614 (7)	-0.2174(19)	10.2 (13)
C18	0.1985(16)	0.2936 (9)	0.006 (3)	10.1 (12)
C19	-0.0146(15)	0.2934 (9)	-0.012 (3)	10.1 (12)
C20	0.1336(17)	0.8393 (8)	0.0798(20)	8.5 (10)
H2	0.187	0.538	-0.322	6.1
H3A	0.226	0.406	-0.286	6.9
H3B	0.087	0.389	-0.355	6.9
H5	-0.047	0.590	0.053	6.7
H6	-0.039	0.726	0.141	6.5
H8	0.276	0.760	-0.089	7.5
H9	0.268	0.625	-0.176	5.8
H11	-0.114	0.514	-0.177	5.8
H12	-0.288	0.539	-0.322	7.9
H13	-0.270	0.569	-0.579	9.5
H14	-0.078	0.575	-0.692	8.1
H15	0.097	0.551	-0.547	6.6
H17C	0.031	0.274	-0.292	9.7
H17A	0.182	0.270	-0.277	9.7
H17B	0.097	0.199	-0.193	9.7
H18C	0.282	0.299	-0.048	10.9
H18A	0.202	0.313	0.109	10.9
H18B	0.200	0.222	0.024	10.9
H19C	-0.031	0.325	0.083	10.7
H19A	-0.091	0.305	-0.085	10.7
H19B	-0.024	0.230	0.014	10.7
H20C	0.209	0.857	0.034	8.9
H20A	0.058	0.866	0.045	8.9
H20B	0.138	0.834	0.195	8.9
C4	0.1089(10)	0.6020 (6)	-0.0658(11)	4.0 (5)
C5	0.0239(12)	0.6296 (7)	0.0232(14)	5.2 (6)
C6	0.0335(14)	0.7082 (7)	0.0720(17)	6.7 (8)
C7	0.1213(14)	0.7542 (8)	0.0304(15)	6.1 (7)
C8	0.2062(14)	0.7236 (7)	-0.0612(19)	6.9 (8)
C9	0.2013(10)	0.6476 (7)	-0.1099(15)	4.9 (6)
C10	0.0048(10)	0.5299 (6)	-0.3536(13)	4.5 (5)
C11	-0.1049(13)	0.5285 (7)	-0.2900(14)	5.9 (7)
C12	-0.2030(15)	0.5440 (8)	-0.3686(19)	7.7 (9)
C13	-0.1928(16)	0.5645 (10)	-0.5074(20)	8.7 (10)
C14	-0.0853(17)	0.5660 (8)	-0.5753(14)	7.6 (9)
C15	0.0167(14)	0.5485 (8)	-0.4970(13)	6.3 (7)

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

TABLE 5.3.3 ATOMIC BONDS IN ANGSTROMS OF 3.13 (R = Ph, R' = $C(CH_3)_3$, Ar = p-$CH_3C_6H_4$)

S(1)-C(1)	1.648(11)	C(20)-H(20A)	1.041(18)
N(1)-C(1)	1.405(14)	C(20)-H(20B)	1.080(19)
N(1)-C(2)	1.497(15)	C(20)-C(7)	1.546(20)
N(1)-C(4)	1.457(14)	H(5)-C(5)	1.105(13)
N(2)-C(1)	1.337(13)	H(6)-C(6)	1.101(16)
N(2)-C(3)	1.435(18)	H(8)-C(8)	1.063(14)
N(2)-C(16)	1.493(14)	H(9)-C(9)	1.062(12)
C(2)-C(3)	1.528(18)	H(11)-C(11)	1.087(13)
C(2)-H(2)	1.096(13)	H(12)-C(12)	1.086(17)
C(2)-C(10)	1.532(19)	H(13)-C(13)	1.126(18)
C(3)-H(3A)	1.102(17)	H(14)-C(14)	1.106(14)
C(3)-H(3B)	1.116(15)	H(15)-C(15)	1.043(15)
C(16)-C(17)	1.515(20)	C(4)-C(5)	1.378(17)
C(16)-C(18)	1.505(22)	C(4)-C(9)	1.392(16)
C(16)-C(19)	1.501(21)	C(5)-C(6)	1.436(17)
C(17)-H(17C)	1.096(23)	C(6)-C(7)	1.351(22)
C(17)-H(17A)	1.107(24)	C(7)-C(8)	1.410(22)
C(17)-H(17B)	1.101(14)	C(8)-C(9)	1.391(17)
C(18)-H(18C)	1.096(22)	C(10)-C(11)	1.407(19)
C(18)-H(18A)	1.029(22)	C(10)-C(15)	1.388(18)
C(18)-H(18B)	1.243(16)	C(11)-C(12)	1.384(22)
C(19)-H(19C)	1.066(21)	C(12)-C(13)	1.35(3)
C(19)-H(19A)	1.139(22)	C(13)-C(14)	1.40(3)
C(19)-H(19B)	1.119(15)	C(14)-C(15)	1.426(23)
C(20)-H(20C)	1.022(20)		

TABLE 5.3.4 ATOMIC ANGLES IN DEGREES OF 3.13 (R = Ph, R' = $C(CH_3)_3$, Ar = p-$CH_3C_6H_4$)

C(1)-N(1)-C(2)	113.1(8)	H(19A)-C(19)-H(19B)	102.7(14)
C(1)-N(1)-C(4)	126.2(9)	H(20C)-C(20)-H(20A)	117.5(16)
C(2)-N(1)-C(4)	120.7(9)	H(20C)-C(20)-H(20B)	114.0(17)
C(1)-N(2)-C(3)	113.4(9)	H(20C)-C(20)-C(7)	103.7(14)
C(1)-N(2)-C(16)	124.9(10)	H(20A)-C(20)-H(20B)	112.5(17)
C(3)-N(2)-C(16)	119.7(10)	H(20A)-C(20)-C(7)	104.2(14)
S(1)-C(1)-N(1)	122.9(8)	H(20B)-C(20)-C(7)	102.7(12)
S(1)-C(1)-N(2)	131.5(9)	N(1)-C(4)-C(5)	120.4(10)
N(1)-C(1)-N(2)	105.5(9)	N(1)-C(4)-C(9)	117.1(10)
N(1)-C(2)-C(3)	99.0(10)	C(5)-C(4)-C(9)	122.5(11)
N(1)-C(2)-H(2)	111.2(11)	H(5)-C(5)-C(4)	118.6(10)
N(1)-C(2)-C(10)	110.8(10)	H(5)-C(5)-C(6)	123.8(12)
C(3)-C(2)-H(2)	113.1(12)	C(4)-C(5)-C(6)	117.6(12)
C(3)-C(2)-C(10)	114.6(11)	H(6)-C(6)-C(5)	112.6(13)
H(2)-C(2)-C(10)	108.0(10)	H(6)-C(6)-C(7)	125.9(12)
N(2)-C(3)-C(2)	105.1(10)	C(5)-C(6)-C(7)	121.5(14)
N(2)-C(3)-H(3A)	113.1(13)	C(20)-C(7)-C(6)	122.8(14)
N(2)-C(3)-H(3B)	113.8(14)	C(20)-C(7)-C(8)	118.2(14)
C(2)-C(3)-H(3A)	109.8(13)	C(6)-C(7)-C(8)	119.0(12)
C(2)-C(3)-H(3B)	109.8(12)	H(8)-C(8)-C(7)	117.2(12)
H(3A)-C(3)-H(3B)	105.3(11)	H(8)-C(8)-C(9)	121.1(14)
N(2)-C(16)-C(17)	110.9(11)	C(7)-C(8)-C(9)	121.6(13)
N(2)-C(16)-C(18)	110.8(11)	H(9)-C(9)-C(4)	121.9(11)
N(2)-C(16)-C(19)	109.9(11)	H(9)-C(9)-C(8)	120.2(12)
C(17)-C(16)-C(18)	108.0(14)	C(4)-C(9)-C(8)	117.8(12)
C(17)-C(16)-C(19)	105.9(14)	C(2)-C(10)-C(11)	123.1(11)
C(18)-C(16)-C(19)	111.3(15)	C(2)-C(10)-C(15)	116.5(11)
C(16)-C(17)-H(17C)	112.4(14)	C(11)-C(10)-C(15)	120.3(13)
C(16)-C(17)-H(17A)	111.0(16)	H(11)-C(11)-C(10)	120.2(13)
C(16)-C(17)-H(17B)	113.8(14)	H(11)-C(11)-C(12)	118.7(14)
H(17C)-C(17)-H(17A)	106.4(15)	C(10)-C(11)-C(12)	121.2(13)
H(17C)-C(17)-H(17B)	106.8(17)	H(12)-C(12)-C(11)	121.6(16)
H(17A)-C(17)-H(17B)	106.0(15)	H(12)-C(12)-C(13)	119.0(16)
C(16)-C(18)-H(18C)	114.5(18)	C(11)-C(12)-C(13)	119.4(16)
C(16)-C(18)-H(18A)	119.7(16)	H(13)-C(13)-C(12)	121.7(18)
C(16)-C(18)-H(18B)	108.0(13)	H(13)-C(13)-C(14)	115.9(16)
H(18C)-C(18)-H(18A)	112.1(16)	C(12)-C(13)-C(14)	121.2(16)
H(18C)-C(18)-H(18B)	97.7(13)	H(14)-C(14)-C(13)	121.5(16)
H(18A)-C(18)-H(18B)	101.4(17)	H(14)-C(14)-C(15)	118.1(16)
C(16)-C(19)-H(19C)	114.9(14)	C(13)-C(14)-C(15)	120.2(13)
C(16)-C(19)-H(19A)	110.8(17)	H(15)-C(15)-C(10)	122.1(14)
C(16)-C(19)-H(19B)	113.7(14)	H(15)-C(15)-C(14)	120.2(12)
H(19C)-C(19)-H(19A)	106.2(15)	C(10)-C(15)-C(14)	117.7(13)
H(19C)-C(19)-H(19B)	107.6(18)		

5.4 EXPERIMENTAL FOR CHAPTER 4

5.4.1 SYNTHESIS OF AZETIDINES

5.4.1.1 1-*tert*-BUTYL-2-METHYLAZETIDINE (4.2)

1-*tert*-Butyl-2-methylazetidine was prepared in 44 % yield by the cyclization of 4-*tert*-butylamino-2-butanol **4.1** following the procedure of Freeman and Mondron (see section 4.2.1).[152]

bp = 125-127 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 9H, $(CH_3)_3C$), 1.10 (d, 3H, CH_3CH), 1.43-2.00 (m, 2H, CH_2 ring), 2.73-3.03 (m, 2H, CH_2N), 3.32 (m, 1H, CHN); MS (*m/e*) 127 $[M]^+$.

5.4.1.2 1-ALKYL-2-CARBOALKOXYAZETIDINES (4.4)

Different 1-alkyl-2-carboalkoxyazetidines were prepared according to the methods of Cromwell and Rodeboaugh (see section 4.2.1).[153-155] Some characteristic data of azetidines are presented below:

1-*tert*-Butyl-2-carbomethoxyazetidine (**4.4**, R^1 = $C(CH_3)_3$, R^2 = CH_3)

75% yield; bp 41-42 °C/0.8 mmHg (lit.[153] bp 55-56 °C/2.0 mmHg); IR ($CHCl_3$) ν (C=O) 1725 and 1753 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 9H, $C(CH_3)_3$), 2.05 (m, 2H, CH_2 ring), 3.02 (m, 2H, CH_2 ring), 3.58 (s, 3H, CH_3), 4.30 (t, 1H, $CHCO_2$, J = 8.0 Hz); MS (*m/e*) 171 $[M]^+$

1-*tert*-Butyl-2-carbobenoxyazetidine (**4.4**, R^1 = $C(CH_3)_3$, R^2 = $C_6H_5CH_2$)

73% yield; bp 105-106 °C/0.3 mmHg (lit.[153] bp 118-119 °C/0.65 mmHg); IR ($CHCl_3$) ν (C=O) 1727 and 1753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 9H, $C(CH_3)_3$), 2.15 (m, 2H, CH_2 ring), 3.12 (m, 2H, CH_2 ring), 3.92 (t, 1H, $CHCO_2$, *J* = 8.1 Hz), 5.10 (m, 2H, CO_2CH_2), 7.25 (m, 5H, aromatic protons); MS (*m/e*) 247 $[M]^+$

1-Cyclohexyl-2-carbomethoxyazetidine (**4.4**, R^1 = C_6H_{11}, R^2 = CH_3)

56% yield; bp 80-81 °C/0.6 mmHg (lit.[153] bp 95-97 °C/2.0 mmHg); IR ($CHCl_3$) ν (C=O) 1727 and 1754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 and 1.90 (m, 11H, cyclohexyl), 2.82 (m, 2H, CH_2 ring), 3.35 (m, 2H, CH_2 ring), 3.62 (t, 1H, $CHCO_2$, *J* = 8.0 Hz), 3.68 (s, 3H, CH_3); MS (*m/e*) 197 $[M]^+$

1-(1-Adamantyl)-2-carbomethoxyazetidine (**4.4**, R^1 = 1-adamantyl, R^2 = CH_3)

43% yield; bp 145-148 °C/0.3 mmHg (lit.[154] bp 131-135 °C/0.2 mmHg); IR ($CHCl_3$) ν (C=O) 1729 and 1754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36-2.10 (m, 15H, adanantyl protons), 2.15 (m, 2H, CH_2 ring), 3.05 (m, 1H, CH_2 ring), 3.25 (m, 1H, CH_2 ring), 3.65 (s, 3H, CH_3), 4.02 (t, 1H, $CHCO_2$, *J* = 8.4 Hz); MS (*m/e*) 249 $[M]^+$

5.4.1.3 SYNTHESIS OF *trans*-1-*n*-BUTYL-2-CARBOMETHOXY-4-METHYLAZETIDINE (4.6)

A solution of 27.5g (0.1 mol) of methyl α,γ-dibromovalerate and 21.9g (0.3 mol) of n-butylamine in 300mL of acetonitrile was refluxed for 15 hours. The mixture was diluted with ether (150 mL), filtered and the solvent was evaporated. The residue was extracted with ether (250 mL) and the extract exposed to a stream of hydrogen chloride gas for 5 minutes. The ether was decanted and the residual syrup was dissolved in 25 mL of water. The aqueous solution was washed twice with ether (discarded), 150 mL of ether was added, and solid sodium bicarbonate added to neutrality. The ether layer was separated, the aqueous layer was washed with three 50 mL portions of ether, and the combined extracts dried over magnesium sulfate. Careful vacuum fractional distillation of the crude product through a 30-cm Vigreux column gave 5.49g (30%) of **4.6** as a colorless oil: b.p. 45-50 ^{o}C (0.5 mmHg); IR ($CDCl_3$) ν (C=O) 1743 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3H, CH_3, J = 7.0 HZ), 1.14 (d, 3H, CH_3, J = 6.0 Hz), 1,28 (m, 4H, CH_2CH_2), 1.82 (m, 1H, CH_2 ring), 2.30 (m, 1H, CH_2 ring), 2.45 (m, 2H, CH_2N), 2.95 (m, 1H, CH), 3.34 (t, 1H, $CHCO_2$, J = 8.4 Hz), 3,65 (s, 3H, methoxy); ^{13}C NMR ($CDCl_3$) δ 14.48 (CH_3), 21.19 (CH_2), 22.83 (CH_3), 29.79 (CH_2 ring), 30.16 (CH_2), 52.32 (CO_2CH_3), 58.98 (CH_2N), 59.48 (CH), 62.75 ($CHCO_2$), 174.02 (C=O); MS (*m/e*) 185 $[M]^{+}$. Anal. Calcd for $C_{10}H_{19}O_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 65.04; H, 10.34; N, 8.04.

5.4.2 GENERAL PROCEDURE FOR THE PALLADIUM-CATALYZED CYCLOADDITION REACTION OF AZETIDINES AND CARBODIIMIDES

A mixture of azetidine (1.0 mmol), carbodiimide (1.0 mmol), and bis(benzonitrile)palladium dichloride (0.038g, 0.10 mmol) in toluene (2.0 mL) was heated with stirring in a glass autoclave for 48h, at 130 °C (oil bath temperature) under a slight pressure of nitrogen (5 psi). After being cooled to room temperature, the autoclave was opened and the red-brown homogeneous solution was filtered through Celite. The filtrate was concentrated by rotary evaporation, and the crude product was purified by silica gel thin-layer chromatography using 1:1 chloroform/acetonitrile as the developer. Melting points, IR, NMR, MS and analytical data for **4.** are as follows:

1-*tert*-Butyl-3-phenyl-4-carbomethoxy-3,4,5,6-tetrahydropyrimidin-2(1H)-phenylimine (**4.8**, R^1 = $C(CH_3)_3$, R^2 = CH_3, Ar = Ph)

92% yield; viscous oil; IR ν (C=N) 1619 cm-1, ν (C=O) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9H, $C(CH_3)_3$), 2.26 (m, 1H, CH_2), 2.57 (m, 1H, CH_2), 3.08 (m, 1H, CH_2N), 3.52 (m, 1H, CH_2N), 3.81 (s, 3H, CH_3), 4.07 (dd, 1H, $CHCO_2$, *J* = 2.3 and 7.7 Hz), 6.39-6.62 (m, 1H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 28.40 (CH_3), 29.84 (CH_2), 38.56 (CH_2N), 52.47 (CH_3), 56.11 ($C(CH_3)_3$), 61.44 ($CHCO_2$), 119.37, 121.66, 123.60, 124.44, 127.71, 128.33 (CH-aromatic), 145.03, 149.53, (quaternary aromatic carbons), 150.84 (C=N), 172.77 (C=O); MS (*m/e*) 365 $[M]^+$.

Anal. Calcd for $C_{22}H_{27}N_3O_2$: C, 72.29; H, 7.45; N, 11.50. Found: C, 71.90; H, 7.55; N, 11.24.

1-*tert*-Butyl-3-phenyl-4-carbobenzoxy-3,4,5,6-tetrahydropyrimidin-2(1H)-phenylimine (**4.8**, $R^1 = C(CH_3)_3$, $R^2 = CH_2C_6H_5$, Ar = C_6H_5)

94%; mp 69-70 °C; IR ν (C=N) 1619 cm^{-1}, ν (C=O) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H, $C(CH_3)_3$), 2.23 (m, 1H, CH_2), 2.69 (m, 1H, CH_2), 3.17 (m, 1H, CH_2), 3.61 (m, 1H, CH_2), 4.17 (dd, 1H, $CHCO_2$, *J* = 2.4 and 7.6 Hz), 5.32 (dd, 2H, CH_2Ph, *J* = 12.0 and 35.6 Hz), 6.58-7.48 (m, 15H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 29.07 (CH_3), 30.25 (CH_2), 39.28 (CH_2N), 56.77 ($C(CH_3)_3$), 62.37 ($CHCO_2$), 68.34 (CH_2Ph), 119.89, 122.45, 124.30, 125.27, 128.31, 129.01, 129.35, 129.43, 129.64 (CH-aromatic), 135.98, 145.91 150.30 (quaternary aromatic carbons), 151.35 (C=N), 172.70 (C=O); MS (*m/e*) 441 $[M]^+$. Anal. Calcd for $C_{28}H_{31}N_3O_2$: C, 76.16; H, 7.08; N, 9.52. Found: C, 76.56; H, 7.31; N, 9.10.

1-*tert*-Butyl-3-*p*-tolyl-4-carbobenzoxy-3,4,5,6-tetrahydropyrimidin-2(1H)-*p*-tolylimine (**4.8**, $R^1 = C(CH_3)_3$, $R^2 = CH_2C_6H_5$, Ar = *p*-$CH_3C_6H_4$)

64% yield; mp 77-78 °C; IR ν (C=N) 1623 cm^{-1}, ν (C=O) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H, $C(CH_3)_3$), 2.10 (s, 3H, p-$CH_3C_6H_4$), 2.16 (s, 3H, p-$CH_3C_6H_4$), 2.35 (m, 1H, CH_2), 2.66 (m, 1H, CH_2), 3.15 (m, 1H, CH_2), 3.62 (m, 1H, CH_2), 4.16 (dd, 1H, $CHCO_2$, *J* = 2.2 and 7.4 Hz), 5.35 (dd, 2H, CH_2Ph, *J* = 12.0 and 35.6 Hz), 6.56-7.54, (m, 13H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 21.31, 21.36 (p-

$CH_3C_6H_4$), 29.07 (CH_3), 30.08 (CH_2), 39.20 (CH_2N) 56.63 ($C(CH_3)_3$), 62.58 ($CHCO_2$), 68.22 (CH_2Ph), 122.15, 125.04, 128.85, 129.27, 129.39, 129.51, 129.58 (CH-aromatic), 128.70, 133.69, 136.06, 143.48, 147.69 (quaternary aromatic carbons), 151.37 (C=N), 172.82 (C=O); MS (*m/e*) 469 $[M]^+$. Anal. Calcd for $C_{30}H_{35}N_3O_2$: C, 76.73; H, 7.51; N, 8.95. Found: C, 76.40; H, 7.51; N, 8.86.

1-*tert*-Butyl-3-*p*-chlorophenyl-4-carbobenzoxy-3,4,5,6-tetrahydropyrimidin-2(1H)-*p*-chlorophenylimine (**4.8**, R^1 = $C(CH_3)_3$, R^2 = CH_2Ph, Ar = *p*-ClC_6H_4)

97% yield; mp 123-124 °C; IR ν (C=N) 1613 cm^{-1}, ν (C=O) 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 9H, $C(CH_3)_3$), 2.31 (m, 1H, CH_2), 2.64 (m, 1H, CH_2), 3.11 (m, 1H, CH_2), 3.56 (m, 1H, CH_2), 4.08 (dd, 1H, $CHCO_2$, *J* = 2.5 and 7.7 Hz), 5.27 (dd, 2H, CH_2Ph, *J* = 30.0 Hz), 6.46-7.47 (m, 13H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 28.96 (CH_3), 30.17 (CH_2), 39.29 (CH_2N), 57.08 ($C(CH_3)_3$), 62.17 ($CHCO_2$), 68.50 (CH_2Ph), 123.43, 126.27, 128.33, 129.18, 129.45, 129.47, 129.65 (CH-aromatic), 124.95, 129.78, 135.60, 144.26, 148.56 (quaternary aromatic carbons), 151.69 (C=N), 172.22 (C=O); MS (*m/e*) 509 $[M]^+$, 511 $[M + 2]^+$, 513 $[M + 4]^+$. Anal. Calcd for $C_{28}H_{29}Cl_2N_3O_2$: C, 65.88; H, 5.73; N, 8.23. Found: C, 65.87; H, 5.62; N, 7.98.

1-Cyclohexyl-3-*p*-chlorophenyl-4-carbomethoxy-3,4,5,6-tetrahydropyrimidin-2(1H)-*p*-chlorophenylimine (**4.8**, R^1 = C_6H_{11}, R^2 = CH_3, Ar = *p*-ClC_6H_4)

88% yield; mp 181-182 °C; IR ν (C=N) 1606 cm^{-1}, ν (C=O) 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92-2.11 (m, 10H, CH_2 of cyclohexyl), 2.31

(m, 2H, CH_2 ring), 3.25 (m, 2H, CH_2N), 4.10 (dd, 1H, $CHCO_2$, J = 4.8 and 6.5 Hz), 4.42 (m, 1H, CHN), 6.50-6.98 (m, 8H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.36, 28.12, 30.64 (CH_2 of cyclohexyl), 30.87 (CH_2 ring), 37.77 (CH_2N), 53.19 (CH_3), 55.98 (CHN), 61.89 (CH), 124.18, 125.85, 128.32, 129.12 (CH-aromatic), 124.85, 129.65, 144.94, 149.91 (quaternary aromatic carbons), 151.24 (C=N), 172.55 (C=O); MS (*m/e*) 459 $[M]^+$, 461 $[M + 2]^+$, 463 $[M + 4]^+$. Anal. Calcd for $C_{24}H_{27}N_3O_2Cl_2$: C, 62.61; H, 5.91; N, 9.13. Found: C, 62.41; H, 5.91; N, 8.93.

1-*tert*-Butyl-3-*p*-chlorophenyl-4-carbomethoxy-3,4,5,6-tetrahydropyrimidin-2(1H)-*p*-chlorophenylimine (**4.8**, R^1 = $C(CH_3)_3$, R^2 = CH_3, Ar = *p*-ClC_6H_4)

95% yield; mp 116-117 °C; IR ν (C=N) 1614 cm^{-1}, ν (C=O) 1741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 9H, $C(CH_3)_3$), 2.27 (m, 1H, CH_2), 2.60 (m, 1H, CH_2), 3.09 (m, 1H, CH_2N), 3.54 (m, 1H, CH_2N), 3.84 (s, 3H, CH_3), 4.05 (dd, 1H, $CHCO_2$, J = 2.6 and 7.8 Hz), 6.55-6.90 (m, 8H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 28.95 (CH_3), 30.38 (CH_2), 39.23 (CH_2N), 53.14 (CH_3), 56.91 ($C(CH_3)_3$), 61.89 ($CHCO_2$), 123.38, 126.05, 128.38, 129.14 (CH-aromatic), 124.93, 129.52, 144.22, 148.83 (quaternary aromatic carbons), 151.53 (C=N), 172.91 (C=O); MS (*m/e*) 433 $[M]^+$, 435 $[M + 2]^+$, 437 $[M + 4]^+$. Anal. Calcd for $C_{22}H_{25}Cl_2N_3O_2$: C, 60.83; H, 5.80; N, 9.67. Found: C, 60.58; H, 5.77; N; 9.50.

5.4.3 PROCEDURE FOR THE PALLADIUM-CATALYZED CYCLOADDITION REACTION OF *trans*-1-*n*-BUTYL-2-CARBOMETHOXY-4-METHYLAZETIDINE WITH 1,3-DICHLOROPHENYLCARBODIIMIDE.

A mixture of azetidine (1.0 mmol), carbodiimide (1.0 mmol), and bis(benzonitrile)palladium dichloride (0.076g, 0.20 mmol) in toluene (3.0 mL) was heated with stirring in a glass autoclave for 48h, 140 °C (oil bath temperature) under a slight pressure of nitrogen (5 psi). The workup procedure was the same as that described in the general procedure for the palladium-catalyzed cycloaddition reaction of azetidines and carbodiimides. The isolated yield of **4.9** was 0.25g: 55% yield; mp 98-99 °C; IR ν (C=N) 1607 cm^{-1}, ν (C=O) 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, CH_3), 1.25 (m, 2H, CH_2), 1.30 (d, 3H, CH_3, J = 6.4 Hz), 1.45 (m, 2H, CH_2), 1.98 (m, 1H, CH_2), 2.65 (m, 1H, CH_2), 2.68 (m, 1H, CH_2, ring), 3.61 (m, 1H, CH), 3.84 (s, 3H, CH_3), 3.95 (m, 1H, CH_2 ring), 4.04 (dd, 1H, $CHCO_2$, J = 3.7 and 5.7 Hz), 6.55-6.98 (m, 8H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.56 (CH_3), 20.60 (CH_2), 22.03 (CH_3), 30.49 (CH_2), 35.06 (CH_2N), 47.56 (CH_2 ring), 49.69 (CH), 53.26 (CH_3), 61.77 ($CHCO_2$), 123.87, 126.02, 128.46, 129.27 (CH-aromatic), 125.09, 129.90, 144.17, 149.58 (quaternary aromatic carbons), 150.79 (C=N), 172.36 (C=O); MS (*m/e*) 447 $[M]^+$, 449 $[M + 2]^+$, 451 $[M + 4]^+$. Anal. Calcd for $C_{23}H_{27}Cl_2N_3O_2$: C,61.61; H, 6.07; N, 9.37. Found: C, 61.41; H, 6.55; N, 9.29.

5.4.4 X-RAY ANALYSIS FOR **4.8** (R^1 = $C(CH_3)_3$, R^2 = $CH_2C_6H_5$, Ar = Ph)

A plate crystal of $C_{28}H_{31}N_3O_2$ was mounted on a glass capillary, and all measurements were made on a Rigaku diffractometer obtained from least-squares refinement using the setting angles of 25 reflections in the range $40^o < 2\theta < 45^o$ corresponding to a monoclinic cell with dimensions given in the supplementary material. For Z = 8 and FW = 441.57, the calculated density is 1.230 g/cm^3. The space group was determined to be P 21/n. The data were collected at -110 ^oC using the ω - 2θ scan technique to a maximum 2θ value 44.9, and the data were corrected for Lorentz and polarization effects.[125]

The structure was solved by direct methods. All of the atoms with the exception of hydrogen were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 2772 observed reflections ($I > 2.5\sigma$ (I)) and 263 variable parameters. All calculations were performed using the NRC VAX crystallographic software package.[126]

Crystal data collection and refinement information of **4.8** (R^1 = $C(CH_3)_3$, R^2 = $CH_2C_6H_5$, Ar = Ph) are listed in Table 5.4.1. The atomic parameter x, y, z and B_{iso} of **4.8** are in Table 5.4.2. Table 5.4.3 and 5.4.4 will show the interatomic distances (in angstroms) and angles (in degrees) of **4.8** respectively.

TABLE 5.4.1 CRYSTAL DATA COLLECTION AND REFINEMENT INFORMATION FOR COMPOUND 4.8 ($R^1 = C(CH_3)_3$, $R^2 = CH_2C_6H_5$, Ar = Ph)

Empirical formula	O2N3C28H31
Formula weight	441.57
Crystal shape	plate
Crystal dimensions (mm)	.2,.1,.3
Crystal system	orthorombic
No. Reflection used for unit cell dimension (2theta range)	25 40-45
Lattice parameters	a=16.292(13) b=21.058(10) c=13.905(11)
Space group	P cab
Z value	8
Dcalc (g.cm-3)	1.230
F(000)	1888.67
mu (mm-1)	.07
No of reflection measured	2772
No of reflection unique	2772
No of reflection observed	1879
No of atoms	64
No of variables	263
Rf (sign refl)	.059
Rw (sign refl)	.039
Rf (all refl)	.116
Rw (all refl)	.040
Goodness of fit	3.51
Last difference fourier map	
max peak	.260
min peak	-.270

TABLE 5.4.2 ATOMIC PARAMETERS X, Y, Z AND B_{iso} FOR 4.8

(R^1 = $C(CH_3)_3$, R^2 = $CH_2C_6H_5$, Ar = Ph)

	x	y	z	Biso
O1	0.18398(20)	0.33272(15)	0.13607(22)	2.57(17)
O2	0.24013(21)	0.25649(16)	0.04405(24)	3.51(19)
N1	0.03857(23)	0.32080(17)	0.0385 (3)	2.05(21)
N2	0.05055(25)	0.21402(18)	0.0762 (3)	2.46(22)
N3	-0.03674(24)	0.27734(17)	0.1719 (3)	2.25(21)
C1	0.1860 (3)	0.29448(23)	0.0578 (4)	2.6 (3)
C2	0.1164 (3)	0.30721(23)	-0.0124 (3)	2.3 (3)
C3	0.1046 (3)	0.25119(25)	-0.0821 (3)	2.7 (3)
C4	0.0500 (3)	0.20240(24)	-0.0301 (3)	3.0 (3)
C5	0.0128 (3)	0.27129(22)	0.1021 (3)	2.3 (3)
C6	0.2534 (3)	0.32515(23)	0.2004 (4)	3.2 (3)
C25	0.0594 (3)	0.16072(23)	0.1465 (3)	2.5 (3)
C26	0.0930 (3)	0.18709(23)	0.2416 (4)	2.9 (3)
C27	-0.0221 (3)	0.12679(24)	0.1633 (4)	3.7 (3)
C28	0.1236 (3)	0.11401(25)	0.1085 (4)	3.9 (3)
H2	0.133	0.350	-0.056	3.5
H3A	0.077	0.266	-0.148	4.3
H3B	0.164	0.230	-0.097	4.3
H4A	0.072	0.155	-0.044	4.4
H4B	-0.013	0.206	-0.057	4.4
H6A	0.258	0.276	0.224	4.5
H6B	0.311	0.337	0.164	4.5
H8	0.164	0.301	0.361	4.7
H9	0.144	0.371	0.502	6.0
H10	0.209	0.477	0.506	6.0
H11	0.294	0.513	0.369	5.8
H12	0.314	0.443	0.228	5.0
H14	-0.185	0.320	0.208	4.0
H15	-0.221	0.415	0.302	4.8
H16	-0.112	0.487	0.360	4.7
H17	0.034	0.464	0.324	4.3
H18	0.070	0.368	0.230	3.9
H20	-0.125	0.308	0.034	3.6
H21	-0.224	0.382	-0.040	4.3
H22	-0.175	0.479	-0.121	4.4
H23	-0.026	0.503	-0.127	4.3
H24	0.073	0.429	-0.053	3.9
H26C	0.151	0.212	0.228	4.4
H26A	0.050	0.222	0.270	4.4
H26B	0.102	0.150	0.292	4.4
H27C	-0.015	0.088	0.214	5.5
H27A	-0.068	0.160	0.190	5.5
H27B	-0.044	0.107	0.096	5.5
H28C	0.182	0.138	0.097	5.3
H28A	0.134	0.075	0.158	5.3
H28B	0.104	0.094	0.040	5.3
C7	0.24028(22)	0.36736(16)	0.28552(21)	2.6 (3)
C8	0.19201(20)	0.34703(14)	0.3625 (3)	3.4 (3)
C9	0.18059(19)	0.38649(21)	0.44193(22)	4.7 (4)

C10	0.21744(25)	0.44626(18)	0.44447(23)	4.6 (3)
C11	0.26570(24)	0.46659(12)	0.3675 (3)	4.2 (3)
C12	0.27712(20)	0.42714(18)	0.28806(23)	3.7 (3)
C13	-0.05487(22)	0.33723(12)	0.21343(20)	2.3 (3)
C14	-0.13690(18)	0.35086(15)	0.23349(24)	2.8 (3)
C15	-0.15716(15)	0.40493(17)	0.28636(25)	3.3 (3)
C16	-0.09540(24)	0.44538(12)	0.31917(21)	3.3 (3)
C17	-0.01337(20)	0.43175(15)	0.29911(23)	3.0 (3)
C18	0.00689(14)	0.37768(17)	0.24623(24)	2.6 (3)
C19	-0.01982(18)	0.36323(14)	-0.00494(22)	2.1 (3)
C20	-0.10371(21)	0.35022(12)	-0.00083(22)	2.5 (3)
C21	-0.15972(14)	0.39190(17)	-0.04293(24)	2.9 (3)
C22	-0.13185(20)	0.44661(15)	-0.08914(22)	3.1 (3)
C23	-0.04796(23)	0.45962(12)	-0.09325(21)	2.9 (3)
C24	0.00805(15)	0.41794(16)	-0.05115(24)	2.4 (3)

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

TABLE 5.4.3 ATOMIC BONDS IN ANGSTROMS OF 4.8 (R^1 = $C(CH_3)_3$, R^2 = $CH_2C_6H_5$, Ar = Ph)

O1-C1	1.355(6)	H8-C8	1.070(3)
O1-C6	1.451(6)	H9-C9	1.077(3)
O2-C1	1.206(6)	H10-C10	1.087(3)
N1-C2	1.480(6)	H11-C11	1.090(3)
N1-C5	1.430(6)	H12-C12	1.083(3)
N1-C19	1.438(5)	H14-C14	1.083(3)
N2-C4	1.499(6)	H15-C15	1.085(3)
N2-C5	1.401(6)	H16-C16	1.083(3)
N2-C25	1.495(6)	H17-C17	1.078(3)
N3-C5	1.269(6)	H18-C18	1.075(3)
N3-C13	1.418(5)	H20-C20	1.077(3)
C1-C2	1.519(7)	H21-C21	1.0756(25)
C2-C3	1.539(7)	H22-C22	1.079(3)
C2-H2	1.113(5)	H23-C23	1.083(3)
C3-C4	1.540(7)	H24-C24	1.085(3)
C3-H3A	1.071(5)	C7-C8	1.395(5)
C3-H3B	1.091(5)	C7-C12	1.395(5)
C4-H4A	1.087(5)	C8-C9	1.395(5)
C4-H4B	1.092(5)	C9-C10	1.395(6)
C6-H6A	1.096(5)	C10-C11	1.395(5)
C6-H6B	1.092(5)	C11-C12	1.395(5)
C6-C7	1.496(6)	C13-C14	1.395(5)
C25-C26	1.537(7)	C13-C18	1.395(4)
C25-C27	1.526(7)	C14-C15	1.395(5)
C25-C28	1.530(7)	C15-C16	1.395(5)
C26-H26C	1.091(5)	C16-C17	1.395(5)
C26-H26A	1.090(5)	C17-C18	1.395(5)
C26-H26B	1.062(5)	C19-C20	1.395(5)
C27-H27C	1.085(5)	C19-C24	1.395(4)
C27-H27A	1.082(6)	C20-C21	1.395(4)
C27-H27B	1.092(5)	C21-C22	1.395(5)
C28-H28C	1.098(6)	C22-C23	1.395(5)
C28-H28A	1.080(5)	C23-C24	1.395(4)
C28-H28B	1.088(5)		

TABLE 5.4.4 ATOMIC ANGLES IN DEGREES OF 4.8 (R^1 = $C(CH_3)_3$, R^2 = $CH_2C_6H_5$, Ar = Ph)

C1-O1-C6	114.3(4)	C25-C28-H28B	110.3(4)
C2-N1-C5	114.0(4)	H28C-C28-H28A	108.1(5)
C2-N1-C19	119.1(3)	H28C-C28-H28B	107.6(5)
C5-N1-C19	121.2(4)	H28A-C28-H28B	108.9(5)
C4-N2-C5	113.0(4)	C6-C7-C8	120.3(3)
C4-N2-C25	121.5(4)	C6-C7-C12	119.6(3)
C5-N2-C25	121.4(4)	C8-C7-C12	120.0(3)
C5-N3-C13	122.2(4)	H8-C8-C7	120.2(3)
O1-C1-O2	122.6(4)	H8-C8-C9	119.8(3)
O1-C1-C2	113.1(4)	C7-C8-C9	120.0(3)
O2-C1-C2	124.1(4)	H9-C9-C8	120.6(4)
N1-C2-C1	111.5(4)	H9-C9-C10	119.4(3)
N1-C2-C3	110.0(4)	C8-C9-C10	120.0(3)
N1-C2-H2	108.0(4)	H10-C10-C9	120.4(3)
C1-C2-C3	111.2(4)	H10-C10-C11	119.6(3)
C1-C2-H2	108.1(4)	C9-C10-C11	120.0(3)
C3-C2-H2	107.9(4)	H11-C11-C10	119.9(3)
C2-C3-C4	106.7(4)	H11-C11-C12	120.1(4)
C2-C3-H3A	111.2(4)	C10-C11-C12	120.0(3)
C2-C3-H3B	109.1(4)	H12-C12-C7	120.5(3)
C4-C3-H3A	111.1(4)	H12-C12-C11	119.5(3)
C4-C3-H3B	109.4(4)	C7-C12-C11	120.0(3)
H3A-C3-H3B	109.3(4)	N3-C13-C14	117.6(3)
N2-C4-C3	110.5(4)	N3-C13-C18	121.7(3)
N2-C4-H4A	109.3(4)	C14-C13-C18	120.0(3)
N2-C4-H4B	109.6(4)	H14-C14-C13	119.9(3)
C3-C4-H4A	110.2(4)	H14-C14-C15	120.1(3)
C3-C4-H4B	109.2(4)	C13-C14-C15	120.0(3)
H4A-C4-H4B	108.1(4)	H15-C15-C14	119.7(3)
N1-C5-N2	109.9(4)	H15-C15-C16	120.3(3)
N1-C5-N3	125.9(4)	C14-C15-C16	120.0(3)
N2-C5-N3	124.2(4)	H16-C16-C15	119.4(3)
O1-C6-H6A	110.2(4)	H16-C16-C17	120.6(3)
O1-C6-H6B	110.7(4)	C15-C16-C17	120.0(3)
O1-C6-C7	108.1(4)	H17-C17-C16	119.4(3)
H6A-C6-H6B	107.4(4)	H17-C17-C18	120.6(3)
H6A-C6-C7	109.8(4)	C16-C17-C18	120.0(3)
H6B-C6-C7	110.5(4)	H18-C18-C13	120.3(3)
N2-C25-C26	109.0(4)	H18-C18-C17	119.7(3)
N2-C25-C27	111.6(4)	C13-C18-C17	120.0(3)
N2-C25-C28	108.8(4)	N1-C19-C20	120.6(3)
C26-C25-C27	110.4(4)	N1-C19-C24	119.4(3)
C26-C25-C28	106.6(4)	C20-C19-C24	120.0(3)
C27-C25-C28	110.3(4)	H20-C20-C19	120.0(3)
C25-C26-H26C	109.1(4)	H20-C20-C21	120.0(3)

C25-C27-H27B	109.6(4)	H23-C23-C22	120.3(3)
H27C-C27-H27A	109.0(5)	H23-C23-C24	119.6(3)
H27C-C27-H27B	108.3(4)	C22-C23-C24	120.0(3)
H27A-C27-H27B	108.5(5)	H24-C24-C19	119.9(3)
C25-C28-H28C	110.4(4)	H24-C24-C23	120.1(3)
C25-C28-H28A	111.4(4)	C19-C24-C23	120.0(3)
C25-C26-H26A	108.9(4)	C19-C20-C21	120.0(3)
C25-C26-H26B	110.8(4)	H21-C21-C20	120.2(3)
H26C-C26-H26A	107.9(4)	H21-C21-C22	119.8(3)
H26C-C26-H26B	110.0(4)	C20-C21-C22	120.0(3)
H26A-C26-H26B	110.1(5)	H22-C22-C21	120.4(3)
C25-C27-H27C	110.7(4)	H22-C22-C23	119.6(3)
C25-C27-H27A	110.7(4)	C21-C22-C23	120.0(3)

5.4.5 X-RAY ANALYSIS FOR 4.9 ($R^1 = n\text{-}C_4H_9$, $R^2 = CH_3$, $R^3 = CH_3$, $Ar = p\text{-}ClC_6H_4$)

A plate crystal of $C_{23}H_{27}Cl_2N_3O_2$ was mounted on a glass capillary, and all measurements were made on a Rigaku diffractometer obtained from least-squares refinement using the setting angles of 25 reflections in the range $40^o < 2\theta < 50^o$ corresponding to a monoclinic cell with dimensions given in the supplementary material. For Z = 4 and FW = 451.35, the calculated density is 1.252 g/cm^3. The space group was determined to be P cab. The data were collected at 20 ^oC using the ω - 2θ scan technique to a maximum 2θ value 49.9, and the data were corrected for Lorentz and polarization effects.[125]

The structure was solved by direct methods. All of the atoms with the exception of hydrogen were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 2069 observed reflections ($I > 2.5\sigma$ (I)) and 272 variable parameters. All calculations were performed using the NRC VAX crystallographic software package.[126]

Crystal data collection and refinement information of **4.9** (R^1 = n-C_4H_9, $R^2 = CH_3$, $R^3 = CH_3$, Ar = p-ClC_6H_4) are listed in Table 5.4.5. The atomic parameter x, y, z and B_{iso} of **4.9** are in Table 5.4.6. Table 5.4.7 and 5.4.8 will show the interatomic distances (in angstroms) and angles (in degrees) of **4.9** respectively.

TABLE 5.4.5 CRYSTAL DATA COLLECTION AND REFINEMENT INFORMATION FOR COMPOUND 4.9 (R^1 = n-C_4H_9, R^2 = CH_3, R^3 = CH_3, Ar = p-ClC_6H_4)

Empirical formula	C12N2O2C25H20
Formula weight	451.35
Crystal shape	cube
Crystal dimensions (mm)	.2,.2,.2
Crystal system	monoclinic
No. Reflection used for unit cell dimension (2theta range)	25 40-50
Lattice parameters	a=12.987(3) b=14.456(6) c=13.695(5) beta=111.363(22)
Space group	P 21/n
Z value	4
Dcalc (g.cm-3)	1.252
F(000)	935.87
mu (mm-1)	0.29
No of reflection measured No of reflection unique No of reflection observed No of atoms	3881 3686 2069 57
No of variables	272
Rf (sign refl)	.068
Rw (sign refl)	.044

Rf (all refl)	.146
Rw (all refl)	.045
Goodness of fit	3.76
Last difference fourier map	
max peak	.390
min peak	-.370

TABLE 5.4.6 ATOMIC PARAMETERS X, Y, Z AND B_{iso} FOR 4.9

(R^1 = n-C_4H_9, R^2 = CH_3, R^3 = CH_3, Ar = p-ClC_6H_4)

	x	y	z	Biso
CL1	0.01287(13)	0.18342(12)	0.99567(14)	8.78(12)
CL2	0.47743(14)	-0.08389(11)	1.36196(12)	8.24(11)
O1	0.7126 (3)	0.43599(21)	1.1542 (3)	6.82(21)
O2	0.5332 (3)	0.41434(24)	1.1224 (3)	8.3 (3)
N1	0.5646 (3)	0.22516(24)	1.1196 (3)	4.48(22)
N2	0.4438 (3)	0.19874(23)	0.94233(25)	3.71(19)
N3	0.6214 (3)	0.2582 (3)	0.9829 (3)	4.69(23)
C1	0.3485 (3)	0.1931 (3)	0.9675 (3)	3.63(24)
C2	0.3156 (4)	0.2605 (3)	1.0216 (3)	4.6 (3)
C3	0.2140 (4)	0.2569 (3)	1.0319 (4)	5.5 (3)
C4	0.1443 (4)	0.1835 (4)	0.9880 (3)	5.2 (3)
C5	0.1749 (4)	0.1146 (3)	0.9373 (4)	5.2 (3)
C6	0.2760 (4)	0.1185 (3)	0.9253 (3)	4.2 (3)
C7	0.5356 (3)	0.1510 (3)	1.1728 (3)	3.9 (3)
C8	0.5138 (4)	0.1693 (3)	1.2633 (3)	5.3 (3)
C9	0.4938 (4)	0.0972 (3)	1.3204 (4)	5.8 (3)
C10	0.4946 (4)	0.0075 (3)	1.2855 (3)	5.1 (3)
C11	0.5118 (4)	-0.0111 (3)	1.1950 (3)	4.3 (3)
C12	0.5324 (3)	0.0604 (3)	1.1388 (3)	3.8 (3)
C13	0.6580 (4)	0.2850 (3)	1.1787 (3)	5.3 (3)
C14	0.6246 (4)	0.3852 (3)	1.1470 (3)	5.5 (3)
C15	0.6903 (5)	0.5316 (4)	1.1260 (4)	8.4 (4)
C16	0.7599 (4)	0.2517 (3)	1.1631 (4)	6.8 (3)
C17	0.7377 (4)	0.2359 (4)	1.0463 (4)	6.2 (3)
C18	0.7665 (5)	0.1380 (4)	1.0250 (5)	8.7 (4)
C19	0.5963 (4)	0.2826 (4)	0.8742 (4)	7.0 (4)
C20	0.6402 (5)	0.3813 (4)	0.8640 (4)	9.0 (4)
C21	0.6164 (7)	0.4104 (5)	0.7636 (5)	14.0 (6)
C22	0.6611 (6)	0.5002 (6)	0.7492 (6)	15.4 (7)
C23	0.5376 (4)	0.2243 (3)	1.0116 (3)	4.1 (3)
H2	0.371	0.319	1.054	5.3
H3	0.189	0.311	1.076	6.0
H5	0.120	0.054	0.909	5.5
H6	0.301	0.063	0.884	4.5
H8	0.509	0.242	1.288	5.7
H9	0.475	0.109	1.392	6.5
H11	0.509	-0.083	1.168	4.8
H12	0.545	0.046	1.066	4.0
H13	0.672	0.278	1.264	5.4
H15C	0.767	0.570	1.133	8.1
H15A	0.635	0.540	1.043	8.1
H15B	0.653	0.568	1.174	8.1
H16A	0.826	0.302	1.195	6.8
H16B	0.789	0.187	1.206	6.8
H17	0.793	0.283	1.025	6.5
H18C	0.748	0.132	0.937	9.5
H18A	0.850	0.121	1.063	9.5
H18B	0.713	0.089	1.042	9.5
H17A	0.654	0.234	0.835	7.1

H19B	0.507	0.283	0.829	7.1
H20A	0.731	0.382	0.902	8.8
H20B	0.608	0.432	0.904	8.8
H21A	0.643	0.360	0.714	13.2
H21B	0.523	0.414	0.718	13.2
H22C	0.640	0.526	0.669	13.8
H22A	0.632	0.556	0.790	13.8
H22B	0.752	0.501	0.786	13.8

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

TABLE 5.4.7 ATOMIC BONDS IN ANGSTROMS OF 4.9 (R^1 = n-C_4H_9, R^2 = CH_3, R^3 = CH_3, Ar = p-ClC_6H_4)

Cl1-C4	1.747(4)	C11-C12	1.372(6)
C12-C10	1.750(5)	C11-H11	1.094(4)
O1-C14	1.331(6)	C12-H12	1.089(4)
O1-C15	1.436(6)	C13-C14	1.530(7)
O2-C14	1.187(6)	C13-C16	1.495(7)
N1-C7	1.422(5)	C13-H13	1.124(4)
N1-C13	1.469(5)	C15-H15C	1.115(5)
N1-C23	1.391(5)	C15-H15A	1.105(5)
N2-C1	1.403(5)	C15-H15B	1.084(6)
N2-C23	1.295(5)	C16-C17	1.535(7)
N3-C17	1.478(6)	C16-H16A	1.091(5)
N3-C19	1.446(6)	C16-H16B	1.098(5)
N3-C23	1.375(5)	C17-C18	1.519(8)
C1-C2	1.383(6)	C17-H17	1.102(5)
C1-C6	1.410(6)	C18-H18C	1.142(6)
C2-C3	1.378(6)	C18-H18A	1.053(6)
C2-H2	1.097(5)	C18-H18B	1.077(6)
C3-C4	1.383(7)	C19-C20	1.562(8)
C3-H3	1.106(5)	C19-H19A	1.100(6)
C4-C5	1.354(7)	C19-H19B	1.094(5)
C5-C6	1.383(6)	C20-C21	1.362(8)
C5-H5	1.103(5)	C20-H20A	1.105(6)
C6-H6	1.093(4)	C20-H20B	1.078(6)
C7-C8	1.394(6)	C21-C22	1.465(10)
C7-C12	1.385(6)	C21-H21A	1.133(8)
C8-C9	1.383(7)	C21-H21B	1.141(8)
C8-H8	1.107(5)	C22-H22C	1.099(7)
C9-C10	1.384(7)	C22-H22A	1.121(9)
C9-H9	1.111(4)	C22-H22B	1.098(8)
C10-C11	1.364(6)		

TABLE 5.4.8 ATOMIC ANGLES IN DEGREES OF 4.9 (R^1 = n-C_4H_9, R^2 = CH_3, R^3 = CH_3, Ar = p-ClC_6H_4)

C14-O1-C15	115.3(4)	O2-C14-C13	124.6(4)
C7-N1-C13	118.8(3)	O1-C15-H15C	111.7(4)
C7-N1-C23	121.8(3)	O1-C15-H15A	112.1(4)
C13-N1-C23	115.4(3)	O1-C15-H15B	113.3(5)
C1-N2-C23	121.0(3)	H15C-C15-H15A	105.2(5)
C17-N3-C19	117.2(4)	H15C-C15-H15B	106.7(4)
C17-N3-C23	120.0(4)	H15A-C15-H15B	107.4(5)
C19-N3-C23	118.4(4)	C13-C16-C17	110.9(4)
N2-C1-C2	124.2(4)	C13-C16-H16A	109.4(4)
N2-C1-C6	117.5(4)	C13-C16-H16B	110.4(4)
C2-C1-C6	117.9(4)	C17-C16-H16A	110.0(4)
C1-C2-C3	121.5(4)	C17-C16-H16B	108.8(4)
C1-C2-H2	118.6(4)	H16A-C16-H16B	107.3(4)
C3-C2-H2	119.9(4)	N3-C17-C16	110.2(4)
C2-C3-C4	119.0(4)	N3-C17-C18	111.1(4)
C2-C3-H3	120.9(4)	N3-C17-H17	109.4(4)
C4-C3-H3	120.1(4)	C16-C17-C18	111.9(4)
C11-C4-C3	118.3(4)	C16-C17-H17	107.1(4)
C11-C4-C5	120.4(4)	C18-C17-H17	107.1(4)
C3-C4-C5	121.3(4)	C17-C18-H18C	107.7(5)
C4-C5-C6	120.0(4)	C17-C18-H18A	114.0(5)
C4-C5-H5	119.3(4)	C17-C18-H18B	110.7(4)
C6-C5-H5	120.6(4)	H18C-C18-H18A	106.8(5)
C1-C6-C5	120.3(4)	H18C-C18-H18B	105.2(5)
C1-C6-H6	119.2(4)	H18A-C18-H18B	111.8(5)
C5-C6-H6	120.5(4)	N3-C19-C20	111.2(4)
N1-C7-C8	119.3(4)	N3-C19-H19A	111.6(5)
N1-C7-C12	121.5(4)	N3-C19-H19B	112.1(4)
C8-C7-C12	119.2(4)	C20-C19-H19A	107.7(4)
C7-C8-C9	120.1(4)	C20-C19-H19B	107.0(5)
C7-C8-H8	120.1(4)	H19A-C19-H19B	106.9(4)
C9-C8-H8	119.8(4)	C19-C20-C21	114.6(5)
C8-C9-C10	118.9(4)	C19-C20-H20A	109.4(5)
C8-C9-H9	122.2(4)	C19-C20-H20B	110.5(4)
C10-C9-H9	118.8(4)	C21-C20-H20A	106.1(5)
C12-C10-C9	118.8(3)	C21-C20-H20B	108.2(6)
C12-C10-C11	119.6(4)	H20A-C20-H20B	107.7(5)
C9-C10-C11	121.5(4)	C20-C21-C22	117.0(6)
C10-C11-C12	119.5(4)	C20-C21-H21A	113.3(7)
C10-C11-H11	119.5(4)	C20-C21-H21B	111.7(6)
C12-C11-H11	121.0(4)	C22-C21-H21A	105.6(6)
C7-C12-C11	120.7(4)	C22-C21-H21B	106.1(7)
C7-C12-H12	119.4(4)	H21A-C21-H21B	101.7(5)
C11-C12-H12	119.9(4)	C21-C22-H22C	117.8(7)
N1-C13-C14	108.0(3)	C21-C22-H22A	110.0(6)

5.4.6 GENERAL PROCEDURE FOR THE PALLADIUM-CATALYZED CYCLOADDITION REACTION OF AZETIDINES AND ISOTHIOCYANATES

A mixture of azetidine (1.0 mmol), isothiocyanate (1.0 mmol), and bis(benzonitrile)palladium dichloride (0.038g, 0.10 mmol) in toluene (3.0 mL) was heated with stirring in a glass autoclave for 48h, at 135 °C (oil bath temperature) under a slight pressure of nitrogen (5 psi). After being cooled to room temperature, the autoclave was opened and the red-brown homogeneous solution was filtered through Celite. The filtrate was concentrated by rotary evaporation, and the crude product was purified by silica gel thin-layer chromatography using 1:1 chloroform/toluene as the developer. Melting points, IR, NMR, MS and analytical data for **4.11** are as follows:

3-*tert*-Butyl-6-carbobenzoxy-3,4,5,6-tetrahydro-1,3-thiazine-2-phenylimine (4.11, R^1 = $C(CH_3)_3$, R^2 = $CH_2C_6H_5$, Ar = Ph)

82% yield; oil; IR ($CHCl_3$) ν (C=N) 1612 cm^{-1}, ν (C=O) 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (s, 9H, $C(CH_3)_3$), 2.23 (m, 1H, CH_2 ring), 2.50 (m, 1H, CH_2 ring), 3.41 (m, 1H, CH_2N), 3.55 (m, 1H, CH_2N), 3.88 (dd, 1H, $CHCO_2$, J = 5.4 and 8.2 Hz), 5.23 (dd, 2H, $CH_2C_6H_5$, J = 12.3 and 14.1 Hz), 7.23-7.43 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 29.04 (CH_3), 29.81 (CH_2), 42.98 (CH_2N), 44.04 ($CHCO_2$), 59.11 ($C(CH_3)_3$), 68.15 ($CH_2C_6H_5$), 122.50, 123.25, 129.06, 129.15, 129.35, 129.50 (CH-aromatic), 136.12, 150.26 (quaternary aromatic carbons),

153.92 (C=N), 171.95 (C=O); MS (*m/e*) 382 $[M]^+$. Anal. Calcd for $C_{22}H_{26}N_2O_2S$: C, 69.08; H, 6.85; N, 7.32. Found: C, 69.25; H, 6.42; N, 7.32.

3-*tert*-Butyl-6-carbomethoxy-3,4,5,6-tetrahydro-1,3-thiazine-2-*p*-chlorophenylimine (4.11, $R^1 = C(CH_3)_3$, $R^2 = CH_3$, Ar = *p*-ClC_6H_4)

90% yield; oil; IR ($CHCl_3$) ν (C=N) 1606 cm^{-1}, ν (C=O) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H, $C(CH_3)_3$), 2.30 (m, 2H, CH_2 ring), 3.41 (m, 2H, CH_2N), 3.69 (s, 3H, CH_3), 3.81 (dd, 1H, $CHCO_2$, *J* = 6.1 and 8.1 Hz), 6.70-7.20 (m, 4H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 28.91 (CH_3), 29.87 (CH_2), 42.92 (CH_2N), 43.98 ($CHCO_2$), 53.39 (CH_3), 59.27 ($C(CH_3)_3$), 123.69, 129.38 (CH-aromatic), 128.17, 148.69 (quaternary aromatic carbons), 154.24 (C=N), 172.26 (C=O); MS (*m/e*) 340 $[M]^+$, 342 $[M + 2]^+$. Anal. Calcd for $C_{16}H_{21}ClN_2O_2S$: C, 56.38, H, 6.21; N, 8.22. Found: C, 56.81; H, 6.18; N, 8.32.

3-*tert*-Butyl-6-carbobenzoxy-3,4,5,6-tetrahydro-1,3-thiazine-2-*p*-chlorophenylimine (4.11, $R^1 = C(CH_3)_3$, $R^2 = CH_2C_6H_5$, Ar = *p*-ClC_6H_4)

93% yield; oil; IR ($CHCl_3$) ν (C=N) 1606 cm^{-1}, ν (C=O) 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9H, $C(CH_3)_3$), 2.22 (m, 1H, CH_2), 2.43 (m, 1H, CH_2), 3.42 (m, 2H, CH_2N), 3.84 (dd, 1H, $CHCO_2$, *J* = 5.4 and 8.4 Hz), 5.15 (dd, 2H, $CH_2C_6H_5$, *J* = 12.2 and 15.0 Hz),6.66-7.36 (m, 9H, aromatic protons) ^{13}C NMR ($CDCl_3$) δ 28.92 (CH_3), 29.72 (CH_2), 42.95 (CH_2N), 43.99 ($CHCO_2$), 59.23 ($C(CH_3)_3$), 68.19 ($CH_2C_6H_5$), 123.74, 129.13, 129.18, 129.28, 129.37 (CH-aromatic), 128.14, 135.87,

148.70 (quaternary aromatic carbons), 154.24 (C=N), 171.77 (C=O); MS (*m/e*) 416 $[M]^+$, 418 $[M + 2]^+$. Anal. Calcd for $C_{22}H_{25}ClN_2O_2S$: C, 63.37; H, 6.04; N, 6.72. Found: C, 63.50; H, 5.98; N, 6.80.

3-*tert*-Butyl-6-carbobenzoxy-3,4,5,6-tetrahydro-1,3-thiazine-2-*p*-nitrophenylimine (**4.11**, $R^1 = C(CH_3)_3$, $R^2 = CH_2C_6H_5$, Ar = *p*-$NO_2C_6H_4$)

98% yield; oil; IR ($CHCl_3$) ν (C=N) 1606 cm^{-1}, ν (C=O) 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H, $C(CH_3)_3$), 2.23 (m, 1H, CH_2), 2.42 (m, 1H, CH_2), 3.37 (m, 1H, CH_2N), 3.55 (m, 1H, CH_2N), 3.87 (dd, 1H, $CHCO_2$, *J* = 5.2 and 8.8 Hz), 5.15 (dd, 1H, $CH_2C_6H_5$, *J* = 12.1 and 16.9 Hz), 6.74-8.05 (m, 9H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 28.95 (CH_3), 29.67 (CH_2), 43.36 (CH_2N), 43.93 ($CHCO_2$), 59.93 ($C(CH_3)_3$), 68.30 ($CH_2C_6H_5$), 122.72, 125.52, 129.21, 129.32 (CH-aromatic), 135.78, 142.98, 154.33 (quaternary aromatic carbons), 156.48 (C=N), 171.60 (C=O); MS (*m/e*) 427 $[M]^+$. Anal. Calcd for $C_{22}H_{25}N_3O_4S$: C, 61.81; H, 5.89; N, 9.83. Found: C, 62.00; H, 5.74; N, 9.91.

3-Cyclohexyl-6-carbomethoxy-3,4,5,6-tetrahydro-1,3-thiazine-2-*p*-nitrophenylimine (**4.11**, $R^1 = C_6H_{11}$, $R^2 = CH_3$, Ar = *p*-$NO_2C_6H_4$)

85% yield; oil; IR ($CHCl_3$) ν (C=N) 1602 cm^{-1}, ν (C=O) 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95-1.91 (m, 10H, CH_2 of cyclohexyl),2.26 (m, 2H, CH_2 ring), 3.35 (m, 2H, CH_2N), 3.68 (s, 3H, CH_3), 3.91 (t, 1H, $CHCO_2$, *J* = 7.1 Hz), 4.56 (m, 1H, CHN), 6.83-8.09 (m, 4H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 26.19, 26.32, 28.30 (CH_2 of cyclohexyl), 30.38 (CH_2 ring), 40.65 (CH_2N), 43.34 (CHN), 53.51 (CH_3), 56.76 ($CHCO_2$), 123.54,

125.41 (CH-aromatic), 143.04, 150.83 (quateranry aromatic carbons), 157.26 (C=N), 171.63 (C=O); MS (*m/e*) 377 $[M]^+$. Anal. Calcd for $C_{11}H_{23}N_3O_4S$: C, 57.28; H, 6.14; N, 11.13. Found: C, 57.63; H, 5.79; N, 11.16.

3-*tert*-Butyl-6-carbomethoxy-3,4,5,6-tetrahydro-1,3-thiazine-2-*p*-nitrophenylimine (4.11, R^1 = $C(CH_3)_3$, R^2 = CH_3, Ar = *p*-$NO_2C_6H_4$)

92% yield; oil; IR ($CHCl_3$) ν (C=N) 1610 cm^{-1}, ν (C=O) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H, $C(CH_3)_3$), 2.27 (m, 2H, CH_2 ring), 3.48 (m, 2H, CH_2N), 3.72 (s, 3H, CH_3), 3.82 (dd, 1H, $CHCO_2$, *J* = 5.7 and 8.5 Hz), 6.79-8.07 (m, 4H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 28.92 (CH_3), 29.75 (CH_2), 43.31 (CH_2N), 43.90 ($CHCO_2$), 53.45 (CH_3), 59.95 ($C(CH_3)_3$), 122.66, 125.50 (CH-aromatic), 142.94, 154.16 (quaternary aromatic carbons), 156.54 (C=N), 172.08 (C=O); MS (*m/e*) 351 $[M]^+$. Anal. Calcd for $C_{16}H_{21}N_3O_4S$: C, 54.69; H, 6.02; N, 11.96. Found: C, 54.55; H, 6.10; N, 11.84.

3-(1-Adamantyl)-6-carbomethoxy-3,4,5,6-tetrahydro-1,3-thiazine-2-*p*-nitrophenylimine (4.11, R^1 = 1-adamantyl, R^2 = CH_3, Ar = *p*-$NO_2C_6H_4$)

89% yield; mp 126-127 °C; IR ($CHCl_3$) ν (C=N) 1608 cm^{-1}, ν (C=O) 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52-2.20 (m, 15H, 1-adamantyl), 2.25 (m, 2H, CH_2 ring), 3.35 (m, 1H, CH_2N), 3.55 (m, 1H, CH_2N), 3.65 (s, 3H, CH_3), 3.81 (m, 1H, $CHCO_2$), 6.80-8.05 (m, 4H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 30.07, 30.68, 36.87 (CH, CH_2-adamantyl), 40.67 (CH_2 ring), 42.03 (CH_2N), 44.03 ($CHCO_2$), 53.44 (CH_3), 61.38 (C-

adamantyl), 122.69, 125.49 (CH-aromatic), 142.81, 154.16 (quaternary aromatic carbons), 156.47 (C=N), 172.24 (C=O); MS (*m/e*) 429 $[M]^+$. Anal. Calcd for $C_{22}H_{27}N_3O_4S$: C, 61.52; H, 6.34; N, 9.78. Found: C, 61.81; H, 6.32; N, 9.62.

5.4.7 SYNTHESIS OF DICHLOROBIS(1-*tert*-BUTYL-2-CARBOMETHOXYAZETIDINE)PALLADIUM(II)

To a solution of 1.5 g (3.9 mmol) of bis(benzonitrile)palladium dichloride in 20 mL of toluene (N_2 atomosphere) was added drop-by-drop, a solution of 1.3 g (7.8 mmol) of 1-*tert*-butyl-2-carbomethoxyazetidine in 5 mL of toluene. The reaction mixture was then stirred at ambient temperature for 15 min. The product, a dark-brown precipitate, was removed by filtration and washed with petroleum ether. The yield was 90% (1.8g): IR (KBr pellet) ν (Pd-Cl) 342 cm^{-1}, 352 cm^{-1} and ν (C=O) 1752 cm^{-1} ; FAB-MS (*m/e*) 517-527 $[MH]^+$. Anal. Calcd for $C_{18}H_{34}Cl_2N_2O_4Pd$: C, 41.59; H, 6.59; N, 5.39. Found: C, 41.38; H, 6.43; N, 5.35.

5.4.8 PROCEDURE FOR DICHLOROBIS(1-*tert*-BUTYL-2-CARBOMETHOXYAZETIDINE)PALLADIUM(II) CATALYZED CYCLOADDITION REACTION OF 1-*tert*-BUTYL-2-CARBOMETHOXYAZETIDINE AND *P*-CHLOROPHENYL ISOTHIOCYANATE

A mixture of azetidine (1.0 mmol), isothiocyanate (1.0 mmol), and bis(1-*tert*-butyl-2-carbomethoxyazetidine)palladium dichloride

(0.052g, 0.10 mmol) in toluene (2.0 mL) was heated with stirring in a glass autoclave for 48h, at 135 °C (oil bath temperature) under a slight pressure of nitrogen (5 psi). The workup procedure was the same as that described in the general procedure for the palladium-catalyzed cycloaddition reaction of azetidines and isothiocyanates. The isolated yield of **4.11** was 0.30g: 89 % yield.

5.4.9 REACTION OF DICHLOROBIS(1-*tert*-BUTYL-2-CARBOMETHOXYAZETIDINE)PALLADIUM(II) WITH TRIPHENYLPHOSPHINE

To a solution of 1.05 g (4.0 mmol) of triphenylphosphine in 10 mL of toluene (N_2 atomosphere) was slowly added of 1.04g, (2.0 mmol) of bis(1-*tert*-butyl-2-carbomethoxyazetidine)palladium dichloride. The reaction mixture was then stirred at ambient temperature for 30 min. The product, bis(triphenylphosphine)palladium dichloride (yellow precipitation), was removed by filtration and washed with petroleum ether. The yield was 95% (1.3 g): The complex was found identical (^{31}P NMR ($CDCl_3$) δ 23.3 (s)) with an authentic sample.

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CONCLUSIONS

Palladium(II) catalyzed cycloaddition reactions of three- and four-membered nitrogen-containing heterocycles with heterocumulenes has been explored. 1,2-Disubstituted aziridines react regioselectively with diarylcarbodiimides in the presence of a catalytic amount of bis(benzonitrile)palladium dichloride to give imidazolidinimines in high yield. Cycloaddition reactions of 1,2,3-trisubstituted aziridines with heterocumulenes (carbodiimides, isocyanates and isothiocyanates) resulted in the discovery of the first example of transition metal catalyzed regio- and stereospecific routes to imidazolinimines, imidazolidinones, and thiazolidinimines.

Cycloaddition reactions of chiral, optically active 1,2-disubstituted aziridines with heterocumulenes proceed with retention of configuration affording the corresponding five-membered ring heterocycles in high yield and in optically pure form. The reaction of aziridines with sulfur diimides in the presence of a Pd(II) catalyst provided a new and unusual pathway to imidazolidinethiones. Four-membered ring heterocycles (azetidines) also reacted with heterocumulenes (carbodiimides and isothiocyanates) in the presence of $Pd(PhCN)_2Cl_2$ to afford tetrahydropyridin-2-imines and tetrahydro-1,3-thiazine-2-imines, respectively, in a regio- and stereospecific manner in excellent yield.

A catalytically active intermediate, bis(azetidine)palladium dichloride, was isolated and characterized. Numerous new heterocyclic compoounds have been prepared, some of them having the potential for pharmacological activity.

CLAIMS TO ORIGINAL RESEARCH

1. Regiospecific palladium(II)-catalyzed synthesis of imidazolidinimines by the cycloaddition reaction of 1,2-disubstituted aziridines and carbodiimides.

2. Palladium(II)-catalyzed cycloaddition reactions of 1,2,3-trisubstituted aziridines and heterocumulenes (carbodiimides, isocyanates and isothiocyanates). Regio- and stereospecific route to imidazolidinimines, imidazolidinones and thiazolidinimines.

3. Enantiospecific palladium(II)-catalyzed cycloaddition reactions of optically pure aziridines and heterocumulenes.

4. Discovery of novel and unusal cyclization reactions of aziridines and sulfur diimides in the presence of a palladium(II) catalyst, affording imidazolinethiones.

5. Regio- and stereospecific palladium(II)-catalyzed cycloaddition reactions of azetidines and carbodiimides. Highly efficient method for the preparation of tetrahydropyrimidin-2-imines.

6. Palladium(II)-catalyzed cycloaddition reactions of azetidines and isothiocyanates. Regiospecific synthesis of tetrahydro-1,3-thiazine-2-imines.

7. Isolation and characterization of dichloro bis(1-*tert*-butyl-2-carbomethoxyazetidine)palladium(II), a catalytically active intermediate in cycloaddition reactions of azetidines with heterocumulenes.