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TABLE OF CONTENTS

CHAPTER 2

PALLADIUM(0) CATALYZED ASYMMETRIC CYCLOADDITION OF 2-VINYLOXIRANES WITH HETEROCUMULENES: A ROUTE TO HIGHLY ENANTIOSELECTIVE SYNTHESIS OF 4-VINYL-1,3-OXAZOLIDINE DERIVATIVES. **38**

Abstract

A study of heterocyclic formation by cycloaddition reactions has been made utilizing 2-vinyloxiranes, 2-vinyloxetanes, *o*-iodophenols and *o*-iodoanilines with heterocumulenes in the presence of a palladium catalyst. Cycloaddition reactions of 2-vinyloxiranes with carbodiimides using $Pd_2(dba)_3 \cdot CHCl_3$ and TolBINAP in THF, at ambient temperature, afforded 4-vinyl-1, 3-oxazolidin-2-imines in 70–99% yields and in up to 95% ee. The stereoselectivity is strongly influenced by the structure of the chiral phosphine ligands and substrates as well as by the reaction conditions. Reaction of 2-vinyloxiranes with isocyanates using the same catalyst system afforded 4-vinyl-1, 3-oxazolidin-2-ones in high yields but no greater than 50% ee under identical conditions.

The cycloaddition reactions of 2-vinyloxiranes with unsymmetrical carbodiimides catalyzed by palladium(0) complexes gave two isomers of 4-vinyl-1, 3-oxazolidin-2-imine derivatives in excellent total isolated yields. Highly enantioselective cycloadducts (up to > 99% ee) were formed by using TolBINAP as the chiral phosphine ligand, in THF at ambient temperatures.

4-Vinyl-1, 3-oxazine-2-imines were obtained in fine yields by the reaction of 2-vinyloxetanes with carbodiimides catalyzed by $Pd_2(dba)_3 \cdot CHCl_3$ and bidentate phosphine ligands (dppe or dppp). When isocyanates were utilized in the reaction, moderate to good yields of 4-vinyl-1, 3-oxazine-2-ones were achieved. Palladium catalyzed cycloaddition of fused-bicyclic vinyloxetanes with heterocumulenes

proceeds in a highly stereoselective fashion affording only the *cis*-3-aza-1-oxo-9-vinyl[4.4.0]decane derivatives.

Benzo[*e*]-1,3-oxazin-2-imine-4-ones were synthesized regioselectively by cyclocarbonylation of *o*-iodophenols with carbodiimides in the presence of a catalytic amount of palladium catalyst and 1,4-bis (diphenylphosphino) butane under CO pressure. Product yields are dependent on the nature of the substrate, catalyst, solvent, and base as well as phosphine ligand. Benzo[*e*]-1,3-oxazin-2,4-diones were obtained in good-excellent yields using the same procedure, and a 1:2 ratio of *o*-iodophenol: isocyanate. Pyrido[3,2-*e*]-1,3-oxazin-4-ones were isolated in fine yield using 2-hydroxy-3-iodopyridine.

A catalyst system comprising palladium acetate-bidentate phosphine is effective for the cyclocarbonylation of *o*-iodoanilines with heterocumulenes to give the corresponding 4(3*H*)-quinazolin-4-one derivatives in good yields. Utilizing *o*-iodoanilines with isocyanates, carbodiimides and ketenimines for the reaction afforded 2,4-(1*H*,3*H*)-quinazolinediones, 2-amino-4(3*H*)-quinazolinones and 2-alkyl-4(3*H*)-quinazolinones, respectively.

In the last Chapter, a study on the one-pot reaction of *o*-iodoanilines with acid chlorides and carbon monoxide showed that in the presence of a palladium catalyst and a base, the pharmaceutically important compounds, 2-substituted-4*H*-3,1-benzoxazin-4-ones, could be isolated in high yields.

Acknowledgements

I would like to express my deep gratitude to my supervisor Prof. H. Alper for his invaluable and generous guidance and support to me in many ways throughout all the past years in Ottawa. His excellent supervision, understanding and encouragement are gratefully acknowledged.

My family has always been a great support for everything in my life and I would like to thank my parents and sisters for their love and never ending support and always encourage me to do my best for my study.

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My thanks also go to all the friends that I have met in Ottawa during the past years whom I do not have enough space to mention their names. Their friendships and support made my time in Canada an unforgettable experience.

One thing that I will never forget is that on the first week of my study in Ottawa. I told Dr.Alper that I did not have any experience in doing this type of chemistry before coming to Ottawa, he said that everything is not difficult to learn if I will not put my courage away. I found that is true.

List of Abbreviations

Anal	Analytical
Atm	atmosphere
br	broad
***n*-Bu**	*normal*-butyl
***t*-Bu**	*tert*-butyl
calcd	calculated
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	Dimethyl sulfoxide
dppb	1,2-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,2-bis(diphenylphosphino)propane
ee	enantiomeric excess
Et	Ethyl
FT-IR	Fourier transform infrared
g	Grams
GC	Gas chromatography
h	Hours
Hz	Hertz
J	Coupling constant, in Hertz
L	Ligand
m	Multiplet
M	Metal

M	Molar concentration, in mol/litre
Me	Methyl
min	Minutes
mL	Millilitres
mmol	Millimoles
mp	Melting point
MS	Mass spectrometry
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
OAc	Acetate anion (CH_3COO^-)
ORTEP	Oak Ridge Thermal Ellipsoid Plot
Ph	Phenyl
ppm	Parts per million
psi	Pound per square inch
q	Quartet
rt	Room temperature
s	Singlet
t	Triplet
T	Temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography

List of Figures

List of Tables

Chapter 1

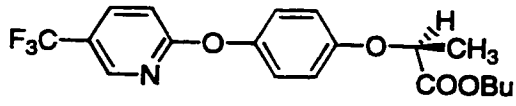
1.1 Introduction

Heterocyclic compounds are commonly found in nature and are important as key components in a number of biological processes.[1] For example, nucleic acids, which are derivatives of the pyrimidine and purine ring systems, are essential to the mechanism of replication. Chlorophyll and heme are porphyrin derivatives required for plant photosynthesis. Essential diet ingredients such as thiamin (vitamin B_1), riboflavin (vitamin B_2), pyridoxol (vitamin B_6), nicotinamide (vitamin B_3), and ascorbic acid (vitamin C) are heterocyclic compounds.

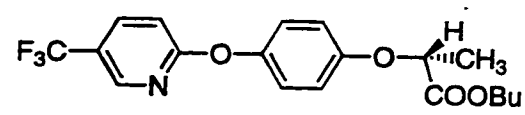
There are many pharmacologically active heterocyclic compounds that are currently in clinical use. Some of these are natural products, for example antibiotics such as penicillin, cephalosporin, and alkaloids (e.g. morphine, codeine, vinblastine, reserpine). However, the large majority of heterocycles are synthetic, and some have found use as, for example, anticancer agents, analgesics, antibiotics, and vasopressors. There are also a large number of synthetic heterocyclic compounds with other important practical applications including dyestuffs, polymers, solvents, antioxidants etc.

Natural products often occur in very small quantities and therefore difficult to isolate. By performing syntheses in the laboratory, one can provide a solution to

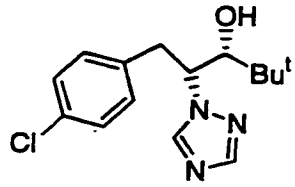
overcome a problem. Most naturally occurring medicinal heterocyclic compounds exist in optically active form.[2] Receptor sites in biological systems are also optically active and can distinguish between two enantiomers of a specific molecule. Even though the differences in the configuration of two enantiomers may be small, the biological properties may be significantly different. For example, (*R*)-fluazifob butyl has herbicidal activity whereas the (*S*)-isomer is inactive; (*2R,3R*)-paclobutrzol is a fungicide but (*2S,3S*)-isomer is a plant growth regulator; (*S*)-warfarin is 5-6 fold more potent than the (*R*)-isomer in vivo.



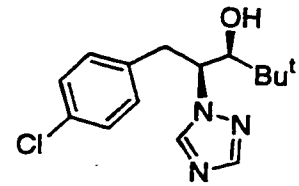
(S)-Fluazifop butyl
inactive



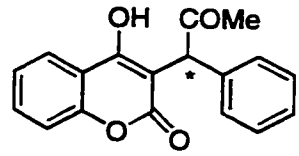
(*R*)-Fluazifop butyl
herbicide



(*2R, 3R*)-Paclobutrazol
fungicide



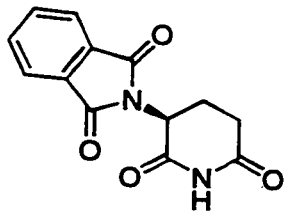
(*2S, 3S*)-Paclobutrazol
plant growth regulator



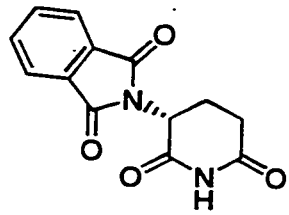
Warfarin

Thalidomide is a heterocyclic compound which contains an asymmetric center. In the early 1960s it was used therapeutically as a sedative and hypnotic.[3] The drug was administered in the racemic form. Although the drug appeared to be effective, its use by

pregnant women caused fetal deaths, neonatal deaths, and congenital malformations. The teratogenicity has subsequently found to be a property of only the (*S*)-enantiomer. Today, in the pharmaceutical industry, more than half of the drugs available on the market are chiral, and roughly half of those were sold as a single enantiomer. In this regard, the development of stereoselective approaches to optically active products would be a significant contribution to organic synthesis.



(*S*)-Thalidomide



(*R*)-Thalidomide

1.2 Palladium-catalyzed heterocyclic formation reactions

Transition metals offer the opportunity to create a new type of reactivity from which more efficient strategies may evolve.[4] Moreover, there is a growing interest in transition metal catalyzed organic reactions as a tool for selective organic synthesis. Among the metals that are widely used, palladium has found widespread application in many reactions.[5] There are several features that make reactions involving Pd particularly useful and versatile in organic synthesis. Palladium provides possibilities of carbon-carbon and carbon-heteroatom (e. g. N, O, S, P) bond formation. Pd-catalyzed reactions can often be carried out without protection of sensitive functional groups such as NH or

OH. Palladium reagents are not very sensitive to oxygen or moisture. In addition, high chemo– and stereoselective syntheses of heterocycles in a single reaction can be promoted by utilizing palladium reagents.

1.2.1 Fundamental reactions of palladium compounds

1.2.1.1 Oxidative addition reactions

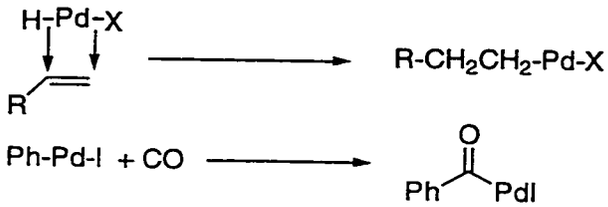
An oxidative addition is the addition of a molecule X-Y to Pd(0) with cleavage of its covalent bond and the formation of two new bonds (eq 1). The formal oxidation state of Pd(0) increases to Pd(II). A number of different covalent bonds are capable of oxidative addition to Pd(0), including C-X, H-X (X = halogen), C-O, H-H, Si-H, N-H, O-H, S-H, M-H, M-M (M = main group metals), and even some C-C bonds. Oxidative addition is usually the first step of a palladium-catalyzed reaction.

$$X{-}Y + Pd(0) \xrightarrow{\text{Oxidative addition}} X{-}Pd(II){-}Y \qquad \text{(eq 1)}$$

1.2.1.2 Insertion reaction

The insertion reaction in palladium chemistry is understood as the migration of a one-electron ligand from Pd to an unsaturated ligand. The insertion takes place in two ways: (a) α, β, (or 1, 2) insertion exemplified by the migration of a hydride ligand from

Pd to a coordinated alkene to form an alkyl palladium complex (eq 2); (b) α, α (or 1, 1) insertion –e.g. CO is a representative species for α, α-insertion, from which acyl palladium results by insertion of CO into the C-Pd bond of an acylpalladium iodide –note that mechanistically, this is a ligand migration process (eq 3).

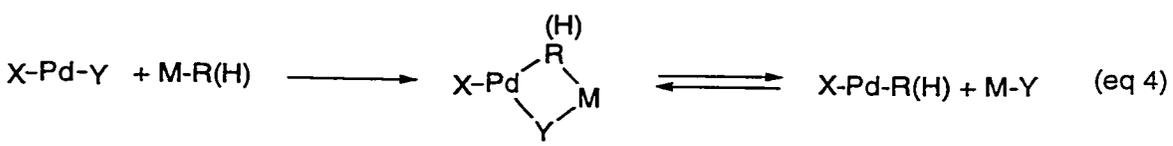


(eq 2)

(eq 3)

1.2.1.3 Transmetallation reaction

M-R and M-H (M = main group metal such as Mg, Zn, B, Al, Sn, Si, and Hg) react with X-Pd-Y in which an organic group (R) or hydride is transferred to Pd by ligand exchange reaction of Y with R or H (eq 4).



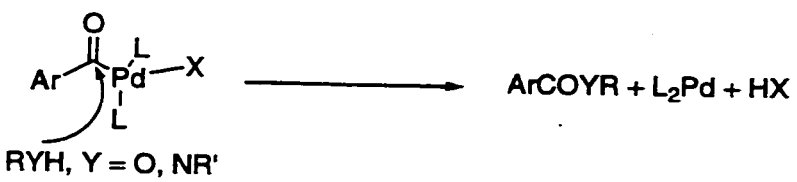
(eq 4)

1.2.1.4 Nucleophilic attack on ligands coordinated to palladium

The reaction of nucleophiles with unsaturated and coordinated ligands is one of the most useful processes for organic synthesis. Unsaturated organic compounds such as carbon monoxide, alkenes, alkynes, and arenes are electron rich, and are quite unreactive

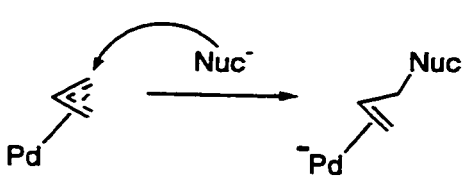
toward nucleophiles. However, complexation to electron deficient palladium enhances their susceptibility.

Nucleophilic cleavage of palladium-carbon σ-bonds is a process of interest, since it is involved in freeing an organic substrate from the metal. Many acyl-palladium complexes undergo direct cleavage by alcohol or amine (eq 5).



(eq 5)

Nucleophilic addition at a π-unsaturated ligand of a palladium complex provides a variety of useful functionalized organic compounds. For example nucleophilic attack on a η^3-allyl palladium complex usually occurs from the face opposite to the metal (eq 6).



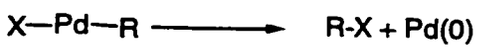
(eq 6)

1.2.1.5 Termination step

1.2.1.5.1 Reductive elimination reaction

This reaction is the reverse of the oxidative addition reaction. It is known that the ligands to be eliminated must be *cis*-to each other in the palladium complex, or must

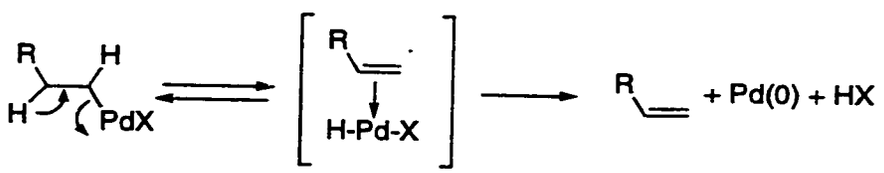
rearrange to *cis*, if they are *trans*, and the coupling of the two eliminated groups result in the formation of the products (eq 7). By means of reductive elimination, Pd(II) is reduced to Pd(0). A catalytic reaction is therefore possible by effecting the reaction with a small amount of a palladium complex. The regenerated Pd(0) can undergo oxidative addition and start another catalytic cycle.



(eq 7)

1.2.1.5.2 β-Hydride elimination

Another termination pathway is syn-elimination of hydrogen β to Pd in alkylpalladium complexes, forming a Pd hydride and an alkene. The insertion of an alkene into Pd-hydride and the elimination of β-hydrogen are reversible processes (eq 8).



(eq 8)

1.2.2 Applications of palladium complexes as catalysts for the formation of heterocycles.

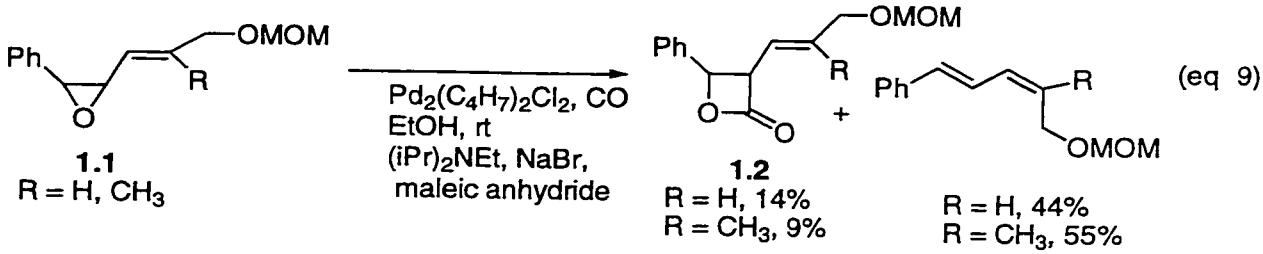
Numerous heterocyclic compounds have been prepared by utilizing a palladium complex as the catalyst. A unique advantage of palladium-catalyzed reactions is the ability to modulate selectivity for ring formation. Reducing the number of steps in the preparation of useful heterocycles can be achieved as well as good stereocontrol. The reaction can be performed under milder reaction conditions when compared with conventional methods. Moreover, the palladium catalyst provides accessibility to some heterocycles that cannot be synthesized by other methods. In this section, the two palladium-catalyzed methods for the preparation of heterocycles; ring expansion and cyclization reactions from non-cyclic substrates, will be discussed.

1.2.2.1 Palladium catalyzed ring expansion reactions.

The cycloaddition and ring expansion reaction is one of the most useful methods for the formation of heterocyclic compounds. The substrates for this reaction usually are small-ring heterocycles such as oxiranes, oxetanes, aziridines, azetidines, 2*H*-azirines, oxaziridines and diaziridines. Transition metal-catalyzed ring expansion reactions involving small-ring heterocycles are of interest since they may provide a convenient one-step route to both known and novel heterocyclic systems some of which may be biologically active.[6]

Epoxides appear to be the most widely used substrates for the palladium-catalyzed cycloaddition ring expansion reactions because the palladium aids ring opening of these substrates.

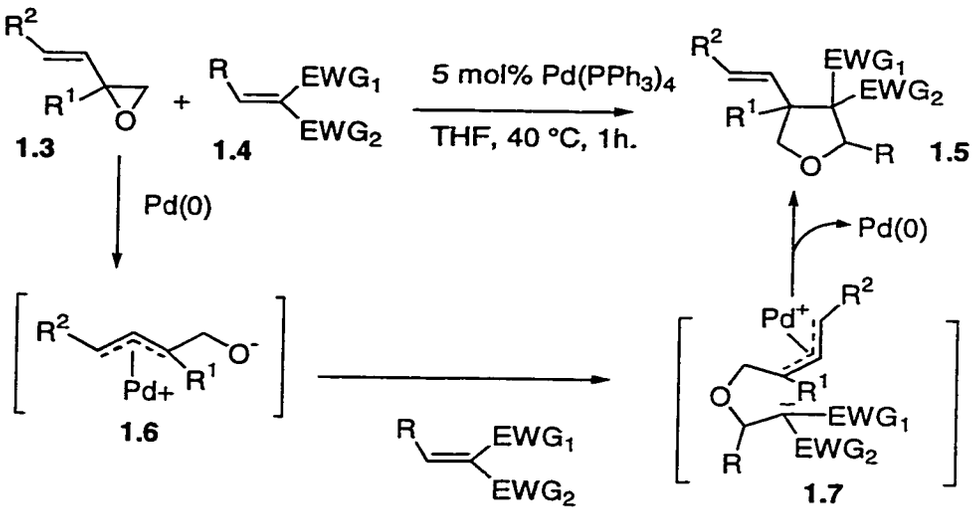
Palladium-catalyzed carbonylation and ring expansion of the 2-vinyloxirane **1.1** to the β–lactone **1.2**, has been reported to occur selectively between the O-C_2 bond (eq 9). However, the yield of **1.2** was low with the corresponding dienes formed as the major product.[7]



(eq 9)

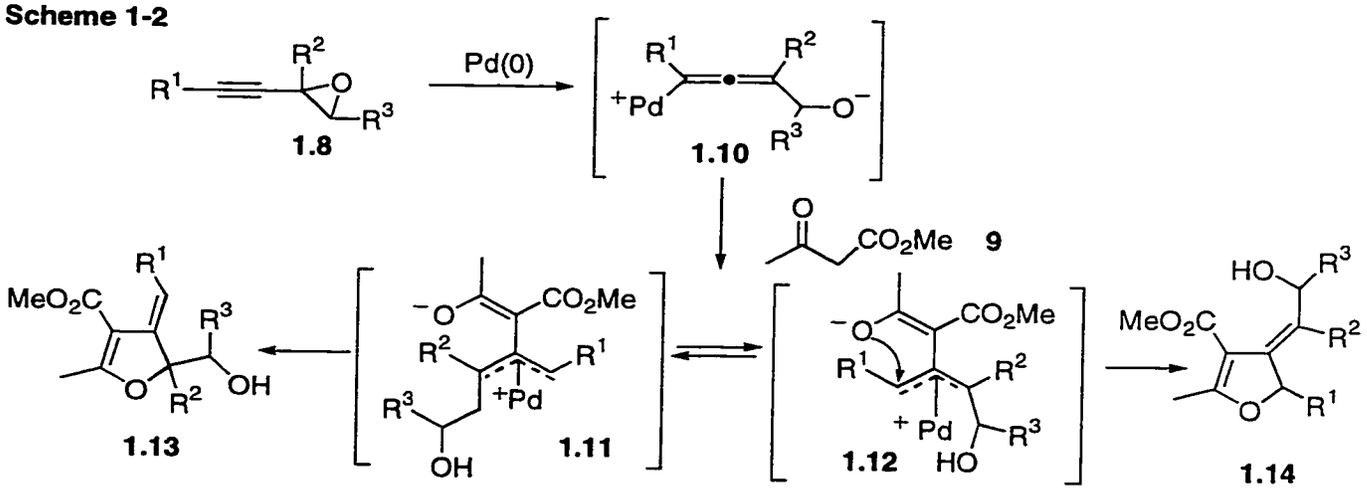
The reaction of activated olefins (**1.4**) with 2-vinyloxiranes (**1.3**) in the presence of a catalytic amount of $Pd(PPh_3)_4$ in THF at 40 °C gave the corresponding [3+2] cycloadducts–tetrahydrofuran derivatives (**1.5**) in good yields (Scheme 1–1).[8] This cycloaddition reaction proceeds only with olefins containing two electron-withdrawing groups, as Michael addition of the oxygen anion of the π–allyl palladium complex **1.6** occurs to the activated olefin to give intermediate **1.7**. The latter then undergo intramolecular nucleophilic attack at the π–allyl palladium moiety to give **1.5**.

Scheme 1-1



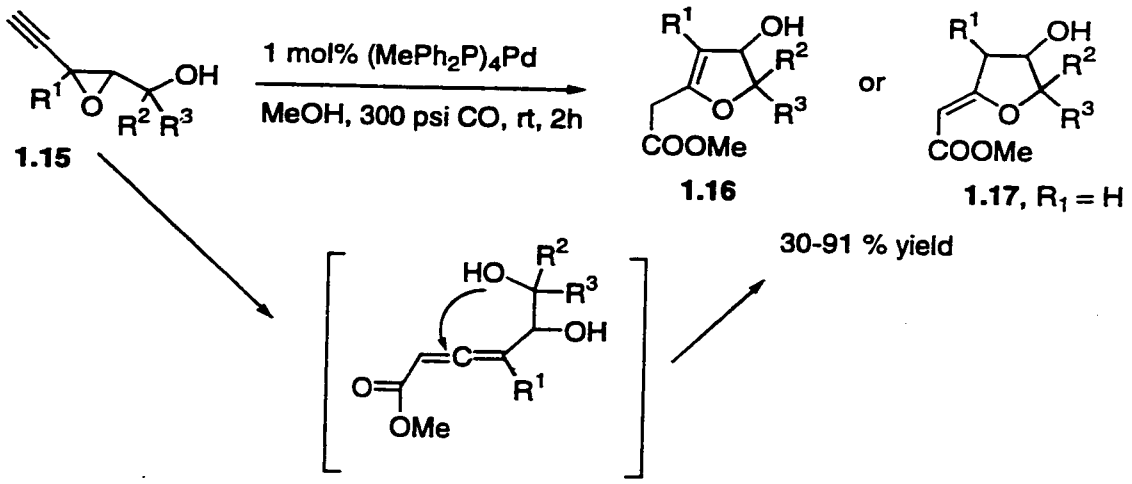
2-(1-Alkynyl)oxiranes (**1.8**) undergo palladium-catalyzed furan formation with soft nucleophiles such as **1.9**. The reaction of Pd(0) with **1.8** may generate the allenylpalladium complex **1.10**, which further reacts with **1.9** to form two types of π–allylpalladium complexes **1.11** and **1.12**. The enolate oxygen attacks at the more substituted carbon of the π–allylpalladium complexes to give furan **1.13**, when R^2 is not hydrogen (Scheme 1–2).[9]

Scheme 1-2



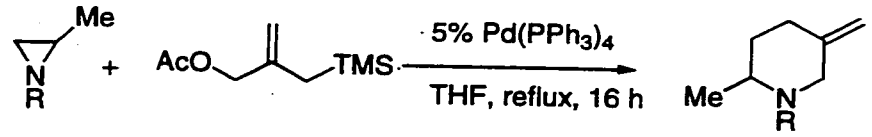
4,5-Dihydrofuran-3-ol derivatives (**1.16** or **1.17**) were obtained stereoselectively in 30-91% yields from the palladium-catalyzed carbonylation of alkynyl oxiranemethanol compounds (**1.15**).[10] The cyclization is believed to proceed via intramolecular Michael type addition of the diol to an allenic intermediate resulting from palladium-catalyzed ring opening and carbonylation of **1.15** (Scheme 1–3).

Scheme 1-3



Aziridine derivatives have been one of the most suitable class of reactants for the formation of other heterocyclic compounds. The variation in structure of the starting materials is possible by introducing different substituents at the nitrogen atom. In addition, 1,2-di and 1,2,3-trisubstituted aziridines with known stereochemistry are available and hence the stereoselective syntheses of optically active heterocycles are accessible.

Activated aziridines (**1.18**) undergo formal [3+3] cycloaddition with an allylic acetate (**1.19**), in the presence of a Pd(0) catalyst, to give the corresponding piperidines (**1.20**) in high yields (eq 10).[11]



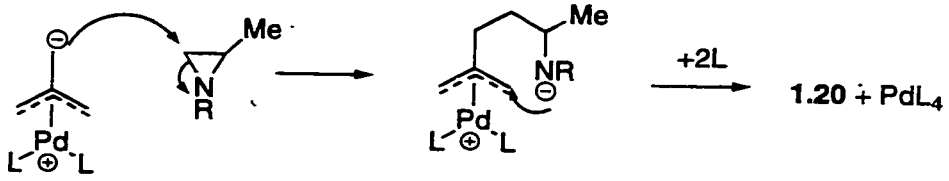
1.18 **1.19** **1.20**

R = $SO_2C_6H_4Me$-*p* 75 %
= $COC_6H_4NO_2$-*p* 71 %

(eq 10)

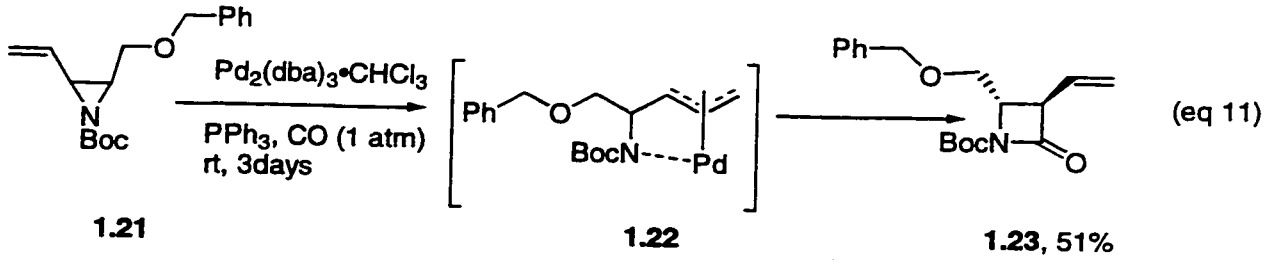
The reaction may take place by addition of a zwitterionic palladium complex to the aziridine, followed by an intramolecular ring closure (Scheme 1–4). Excellent regioselectivity, with reaction at the less hindered carbon atom, is observed in this process.

Scheme 1-4



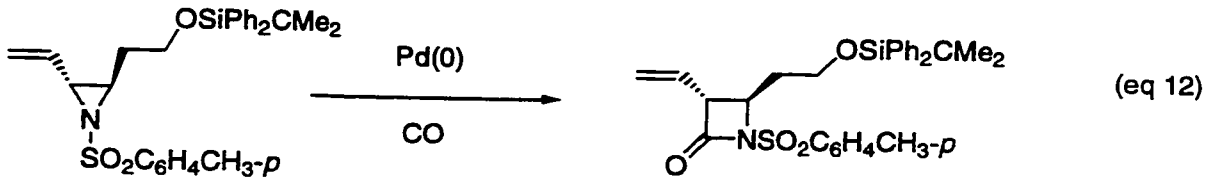
Optically pure *trans*-β-lactam **1.23** was prepared in moderate yield by palladium-catalyzed carbonylation of a 3:1 mixture of of the *cis* and *trans* isomers of 2-vinylaziridine (**1.21**) (eq 11).[12] The transformation may involve the formation of a

π–allyl palladium complex **1.22** followed by carbon monoxide insertion and reductive elimination.



1.21 **1.22** **1.23**, 51% (eq 11)

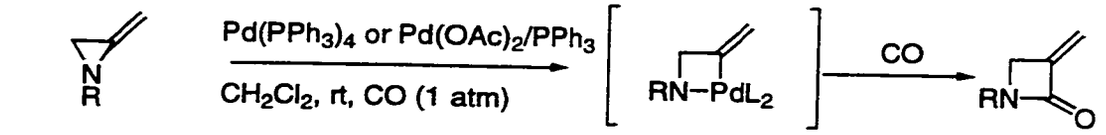
A similar strategy was applied for the formation of optically active β-lactam **1.25**, the key intermediate for the synthesis of carbapenem antibiotics, by treatment of optically pure *trans*-2-vinylaziridine (**1.24**) with Pd(0) catalyst under a carbon monoxide atmosphere.[13] The product was obtained with retention of configuration (eq 12).



1.24 **1.25** (eq 12)

Regioselective synthesis of α-methylene-β-lactams (**1.28**) by a homogeneous palladium-catalyzed ring expansion-carbonylation reaction of methyleneaziridines (**1.26**) was reported by Alper and Hamel.[14] $Pd(PPh_3)_4$ or $Pd(OAc)_2/PPh_3$ were effective catalysts for this transformation, but $Pd(dba)_2$ or palladium-1,2-bis(diphenylphosphino)ethane (dppe) complex did not catalyze this reaction. It was

demonstrated that the reaction proceeds via the generation of a vinylpalladium species, **1.27**, followed by CO insertion and subsequent reductive elimination (eq 13).



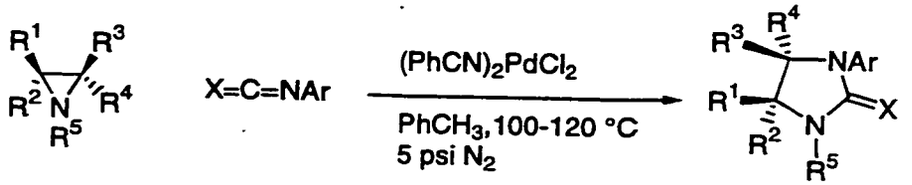
(eq 13)

1.26
R = alkyl, $(CH_2)_3OCH_3$, $CH_2CH(OCH_3)_2$

1.27

1.28, 55-83%

Cycloaddition of aziridines (**1.29**) with isocyanates (**1.30**) or carbodiimides (**1.31**) in the presence of catalytic quantities of $(PhCN)_2PdCl_2$ as the catalyst resulted in the formation of imidazolidine derivatives (**1.32**) in good to excellent yields (eq 14).[15]



(eq 14)

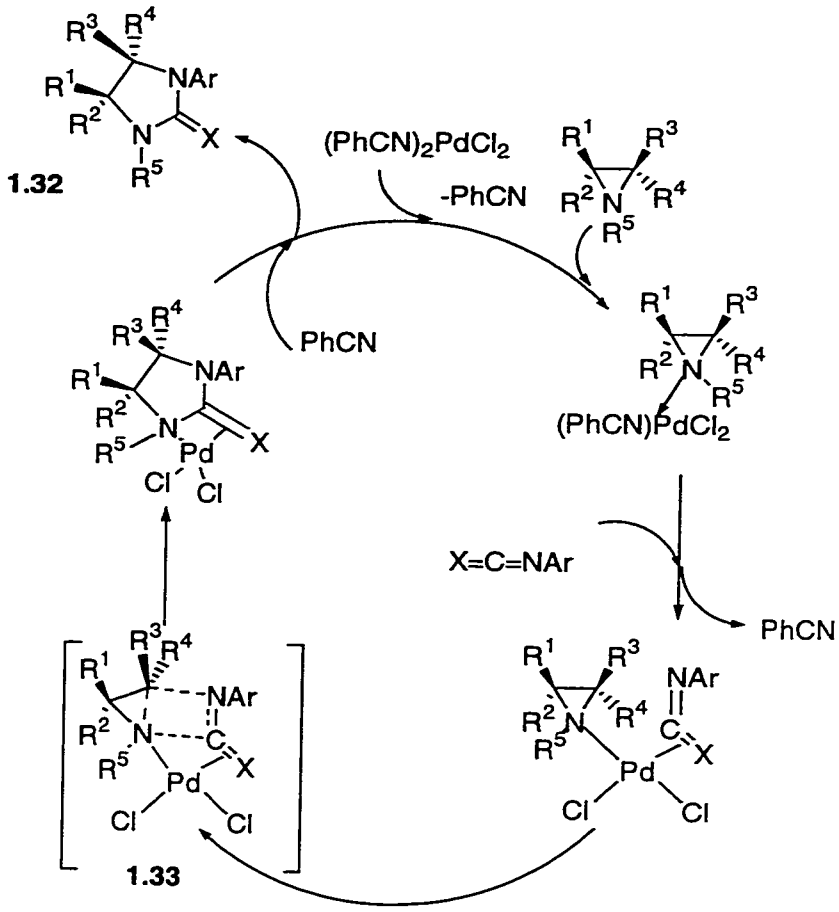
1.29

1.30, X =O,
1.31, X = NAr

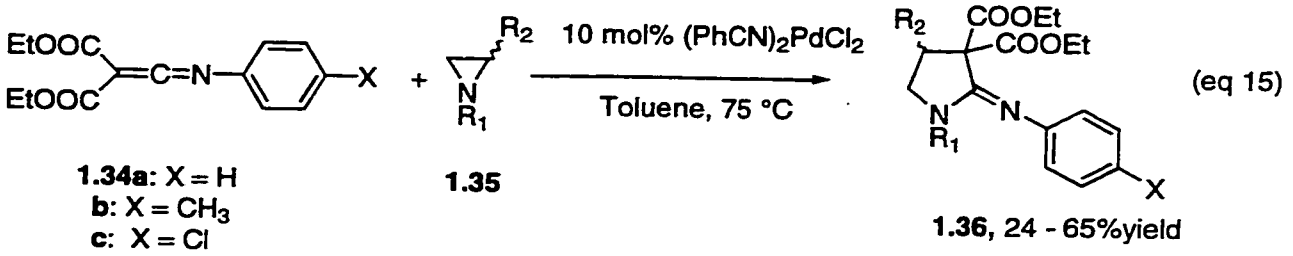
1.32, 40-95 %yields

The reaction is both regio- and stereospecific and the cycloaddition occurs with retention of stereochemistry at the heterocyclic carbon centers bearing the substituent groups. For instance, *cis*-**1.29** afforded only optically pure *cis*-**1.32**. The cyclization pathway is shown in Scheme 1–5. It is conceivable that the retention of stereochemistry is the result of the formation of a four-membered transition state (**1.33**) to give **1.32**.

Scheme 1-5



Treatment of dicarbethoxyketenimines (**1.34**) with 2-substituted aziridines (**1.35**) in toluene at 75 °C in the presence of 10 mol% $(PhCN)_2PdCl_2$ afforded iminopyrrolidines (**1.36**) in 24-65% isolated yields (eq 15).[16] Aziridines underwent selective cleavage of the bond between nitrogen and the substituted carbon (C-2), and the cycloaddition occurs across the C-C double bond of a ketenimine. Retention of stereochemistry during cycloaddition was observed in the reaction using (*S*)-1-*t*-butyl-2-phenylaziridine, (*S*)-**1.35,** with ketenimine **1.34a**, under the same reaction conditions (eq 16).

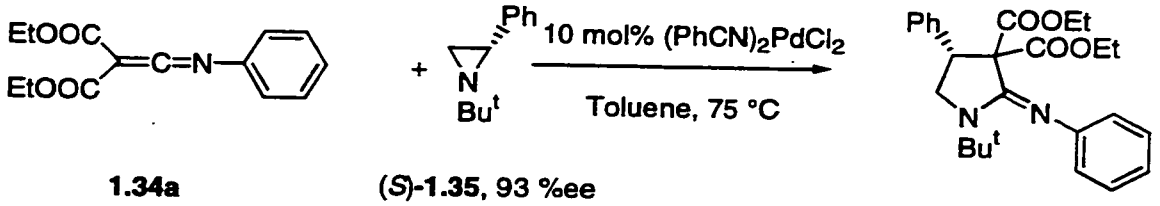


1.34a: X = H
b: X = CH_3
c: X = Cl

1.35

1.36, 24 - 65%yield

(eq 15)



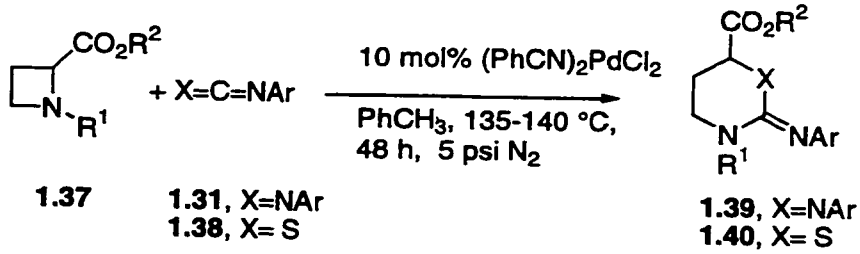
1.34a

(*S*)-**1.35**, 93 %ee

(*S*)-**1.36**, 93 %ee

(eq 16)

Azetidines (**1.37**) react regioselectively with carbodiimides (**1.31**) or isothiocyanates (**1.38**) in the presence of bis(benzonitrile)palladium dichloride to form tetrahydropyrimidin-2-imines (**1.39**) and tetrahydro-1,3-thiazin-2-imines (**1.40**) respectively (eq 17).[17]



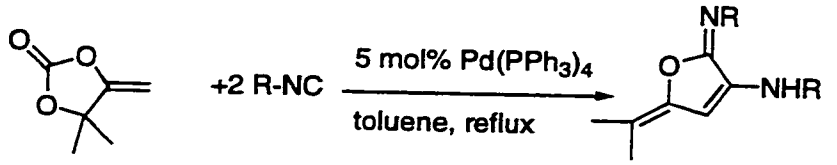
1.37

1.31, X=NAr
1.38, X= S

1.39, X=NAr
1.40, X= S

(eq 17)

When isonitriles were used in reaction with 5,5-dimethyl-4-methylene-1,3-dioxolane-2-one (**1.41**) in the presence of 5 mol% of $Pd(PPh_3)_4$ in toluene at 110 °C, 5-isopropylidene-2,5-dihydrofurans (**1.42**) were obtained in 26-54% yields (eq 18).[18]



(eq 18)

1.41

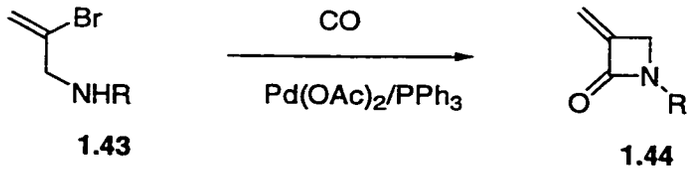
1. 42
26%, R = *t*-Bu
49%, R = 2,6-xylyl
54%, R = 2,6-diethylphenyl

1.2.2.2 Palladium-catalyzed transformation of non-cyclic substrates to heterocyclic compounds.

The application of Pd(0) and Pd(II) complexes for the synthesis of heterocycles from non-cyclic substrates has made remarkable progress in recent years. The advantages of using acyclic rather than cyclic substrate include stability, availability, and ease of preparation. A variety of functionalized non–cyclic compounds have been shown to undergo palladium-catalyzed heterocyclic formation. In general the substrates that can be used for this process should contain functional groups capable of oxidative addition or coordination to palladium including alkenes, alkynes, allenes, alcohols, amines, as well as organic halides.

The synthesis of β-lactams has attracted widespread interest for many years.[19] Palladium-mediated synthesis of β-lactams has been the subject of a large number of investigations. As mentioned above, they can be synthesized by palladium-assisted ring expansion reactions. Non-cyclic substrates were utilized in the formation of β-lactams as

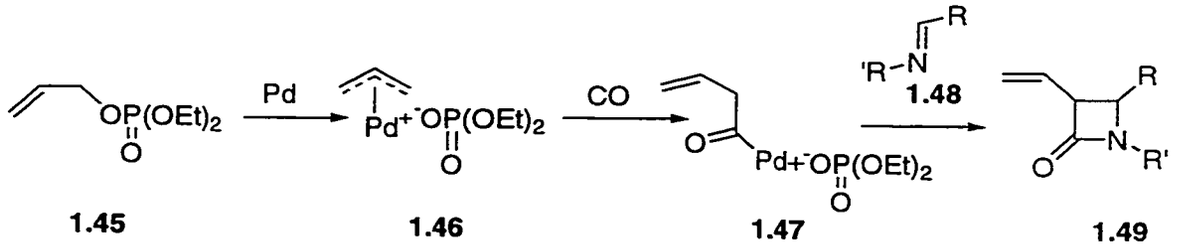
well. For example, the palladium acetate catalyzed carbonylation of amino vinyl halides **1.43** provides a convenient synthesis of β-lactams (**1.44**) (eq 19).[20]



1.43 **1.44** (eq 19)

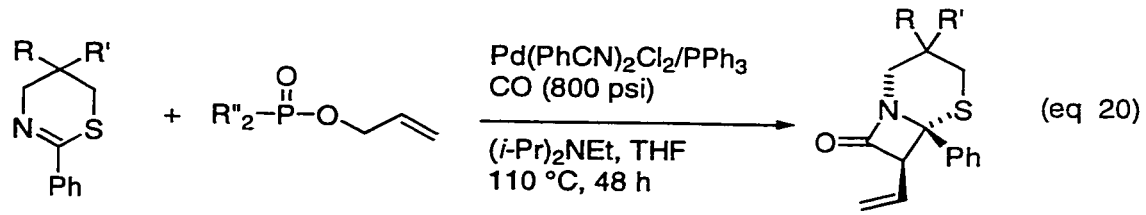
Torii's group reported the palladium-catalyzed carbonylation of allyl diethyl phosphates **1.45** and cycloaddition with imines **1.48**, for the construction of β-lactams **1.49**.[21] The reaction involves the cationic π-allylpalladium intermediate **1.46** formed by palladium-catalyzed carbonylation of allyl phosphate. The acyl palladium intermediate **1.47** then adds to imines to form **1.49** (Scheme 1–6). The stereoselectivity of this reaction depends on the nature of the imine, e.g. imines conjugated with carbonyls such as ketones selectively give *cis*-β-lactams, whereas imines unconjugated with a carbonyl group lead to *trans*-β-lactams.

Scheme 1-6



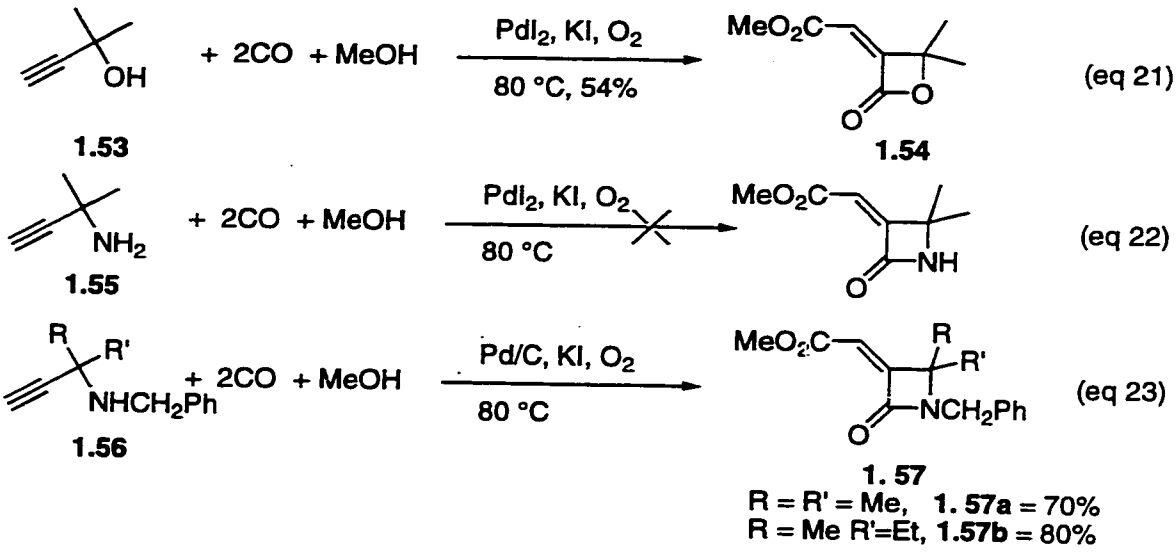
1.45 **1.46** **1.47** **1.49**

Alper and Zhou[22] described the synthesis of bicyclic β-lactams (**1.52**) via the carbonylative coupling and cyclization reaction of 2-aryl-1,3-thiazine **1.50** with allyl phosphate **1.51**, catalyzed by $Pd(PhCN)_2Cl_2$ using *N,N*-diisopropylethylamine as a base in THF. The transformation is stereospecific with aryl and vinyl groups on the β-lactams ring being *cis* to each other (eq 20).

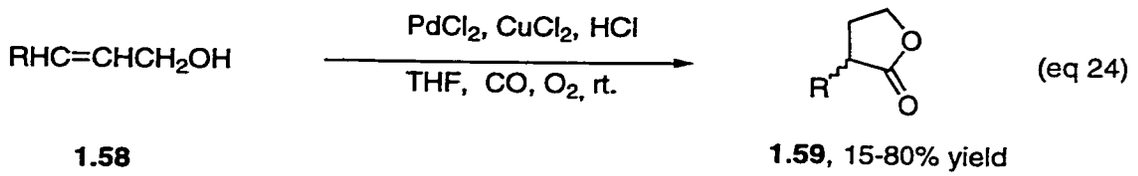


1.50 **1.51** **1.52**, 32-78% yields (eq 20)

α-Methylene-β-lactone **1.54** was obtained when 2-methyl-3-butyn-2-ol (**1.53**) was carbonylated in methanol using PdI_2 under an oxygen atmosphere (eq 21).[23] However, replacing **1.53** with the corresponding primary amine **1.55** under the same reaction conditions did not give the expected β–lactams (eq 22). The reaction proceeded to form β–lactams **1.57** when *N*-benzyl-2-propynylamines (**1.56**) were used.[24] The reaction occurs not only with PdI_2-KI but also with KI and palladium on carbon (eq 23).



Treatment of allylic alcohols (**1.58**) with carbon monoxide, $PdCl_2$, $CuCl_2$, HCl and oxygen in THF at room temperature gave γ–butyrolactones **1.59** in moderate yields.[25] Utilizing poly-L-leucine as an added chiral ligand in the reaction of 2-buten-1-ol gave up to 61%ee of α–methyl-γ–butyrolactone (eq 24).[26] In addition up to 83%ee of β–substituted-γ–butyrolactones (**1.61**) were isolated in good yields from the asymmetric cyclocarbonylation of allylic alcohols (**1.60**) using $Pd_2(dba)_3 \cdot CHCl_3$ and (–)-BPPM catalyst system in CH_2Cl_2 (eq 25).[27] Optically pure lactone was often formed on recrystallization.

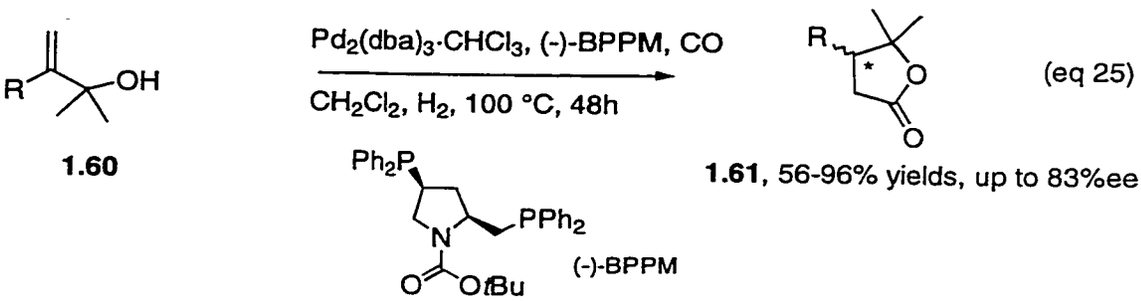


(eq 24)

1.58

1.59, 15-80% yield

(+)-Poly-L-leucine, 49% yield, 61%ee

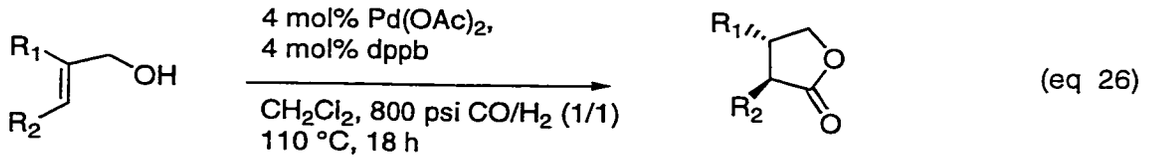


(eq 25)

1.60

1.61, 56-96% yields, up to 83%ee

Recently, a method was reported for the preparation of α,β-substituted–γ-butyrolactones **1.63** in good yields, by reaction of β,γ–substituted allylic alcohols **1.62** with carbon monoxide in the presence of catalytic quantities of $Pd(OAc)_2$ and dppb (eq 26).[28] In most cases, this transformation occurred stereospecifically since (*E*)-allylic alcohols were exclusively converted to the *trans*-lactones. The presence of hydrogen is essential for the formation of active palladium hydride complex to initiate the catalytic cycle, since without hydrogen no lactone was obtained.



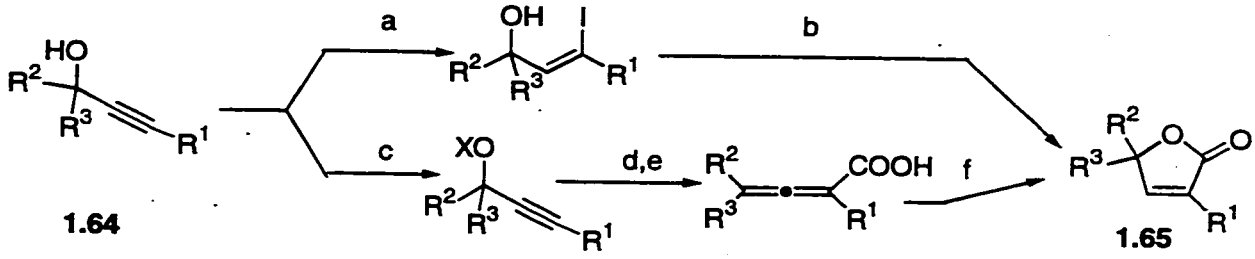
(eq 26)

1.62

1.63, 42-85 % yield

2(5*H*)-Furanones, or butenolides **1.65**, comprises a structural moiety found in biologically active natural products. They can be prepared by palladium-assisted reactions, –e.g. propargylic alcohol **1.64** was first converted to an iodoallyl alcohol by treatment with $LiAlH_4/I_2$, followed by cyclocarbonylation to the butenolide using $Pd(PPh_3)_2Cl_2/K_2CO_3$ under 2 atm of CO.[29] Another approach is to first derivatize propargyl alcohol as its ester, phosphonate ester or other derivative, and then subject it to $Pd(PPh_3)_4$-catalyzed carbonylation in the presence of methanol followed by hydrolysis to give the corresponding 2,3-dienoic acid. The latter was subsequently transformed to butenolides by using a protonic or a Lewis acid such as Ag^+ ion (Scheme 1–7).[30]

Scheme 1-7

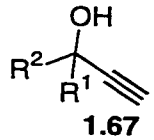


X = mesylate, phosphonate, etc.

(a) (1) $LiAlH_4$, (2) I_2; (b) $Pd(PPh_3)_2Cl_2/K_2CO_3$, CO (2 atm); (c) Mesyl chloride or diethyl chlorophosphate, base; (d) $Pd(PPh_3)_4$, CO, MeOH; (e) LiOH or BCl_3; (f) H^+ or Ag^+

Alper and co-workers[31] developed a one step synthesis of 2(5*H*)-furanones from propargylic alcohols. For example, the cyclocarbonylation of terminal propargylic alcohols (**1.67**) using $Pd(dba)_2$-dppb in DME at 150 °C for 48h (eq 27). Terminal as well as internal alkynols (**1.69**) were regio- and stereoselectively transformed to the corresponding 5,5-disubstituted-2(5*H*)-furanones (**1.70**) by performing the reaction using

a $Pd_2(dba)_3 \bullet CHCl_3$/phosphine ligand catalyst system under CO/H_2 pressure in CH_2Cl_2 (eq 28).[32] In addition, 4-thio-2(5*H*)-furanones (**1.72**) were prepared by the palladium-catalyzed thiocarbonylation of propagylic alcohols with thiols[33] or diaryl disulfides[34] and carbon monoxide (eq 29).

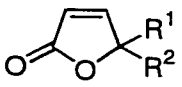


1.67

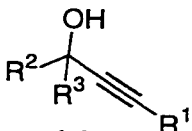
+CO
20 atm

$Pd(dba)_2$, dppb

DME, 150 °C, 48h



1.68, 60-80% yield (eq 27)



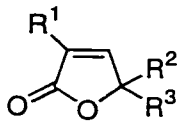
1.69

+CO 600 psi

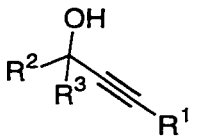
+H_2 200 psi

$Pd_2(dba)_3 \cdot CHCl_3$, dppb

CH_2Cl_2, 95 °C, 36h



1.70, 67-98% yield (eq 28)



1.71

+R^4SH or $(R^4S)_2$

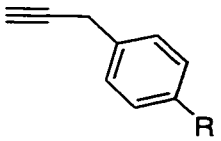
+CO 600 psi

$Pd(PPh_3)_4$

DME, 110 °C, 48h

1.72, 67-88% yield (eq 29)

Reaction of 3-aryl-1-propynes (**1.73**) with iodoarenes or acid chlorides and carbon monoxide in the presence of $Pd(OAc)_2$ and PPh_3 gave (*E*)-arylidenebutenolides (**1.74**) in 33-88% isolated yields (eq 30).[35]

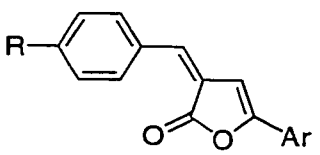


1.73

+ArI +CO 300-1200 psi

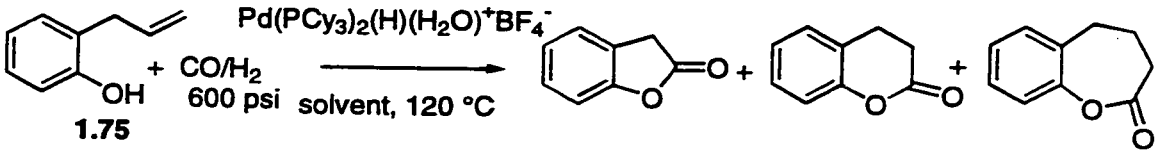
$Pd(OAc)_2$, PPh_3

C_6H_5, Et_3N, 110 °C, 12-24h



1.74, 33-88% yields (eq 30)

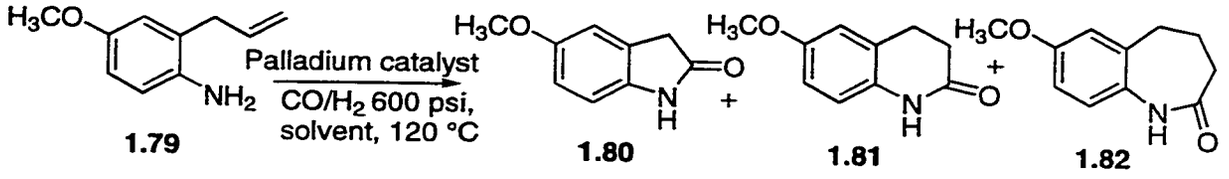
2-Allylphenols (**1.75**) react with carbon monoxide and hydrogen in the presence of catalytic quantities of a cationic palladium(II) complex $[(PCy_3)_2Pd(H)(H_2O)]^+BF_4^-$ or $Pd(OAc)_2$, and dppb, affording a mixture of five- (**1.76**), six- (**1.77**) and seven-membered lactones (**1.78**) in excellent yields. Changing the reaction condition affects the product distribution ratio. For example, performing the reaction in toluene under a 1:1 ratio of CO and H_2, afforded the seven-membered lactone as the major product. The five-membered lactone was formed as the principal product when the reaction was run under a 1:5 ratio of CO:H_2 in CH_2Cl_2 whereas the six-membered lactone was the major product when conducting the reaction in CH_2Cl_2 under 5:1 ratio of CO:H_2 (eq 31).[36] A similar effect was also observed in the cyclocarbonylation of **1.75** catalyzed by palladium-montmorillonite.[37]



(eq 31)

solvent	$CO:H_2$ ratio	yield(%)	**1.76**	**1.77**	**1.78**
toluene	1:1	93	1	7	92
CH_2Cl_2	1:5	98	76	18	6
CH_2Cl_2	5:1	48	14	70	16

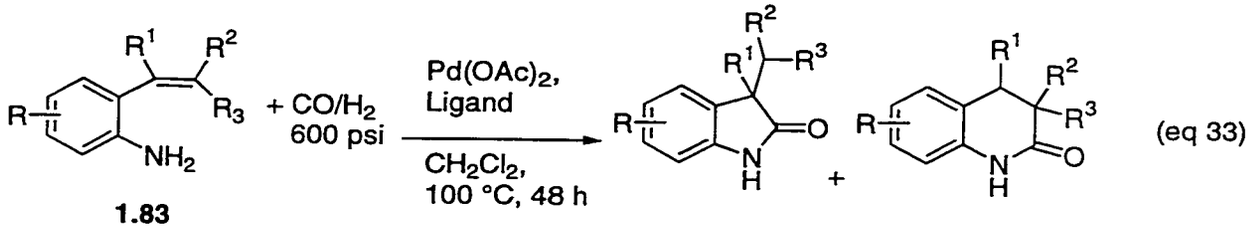
Similar solvent effects were observed when 2-allylanilines (**1.79**) were treated with CO and H_2, and the Pd catalyst (eq 32).



(eq 32)

Pd (cat)	ligand	solvent	$CO:H_2$ ratio	yield(%)	**1.80**	**1.81**	**1.82**
$Pd(OAc)_2$	PPh_3	CH_2Cl_2	5:1	90	6	91	3
$Pd(OAc)_2$	dppb	CH_2Cl_2	1:5	97	4	20	76
$Pd(PCy_3)_2(H)(H_2O)^+BF_4^-$	dppb	toluene	1:1	85	50	20	30

Palladium-catalyzed reaction of 2-aminostyrene (**1.83**) with CO and H_2 provided five and six-membered ring lactams **1.84** and **1.85** in good yields. The product distribution depends on the phosphine ligand and the ratio of $CO:H_2$ (eq 33).

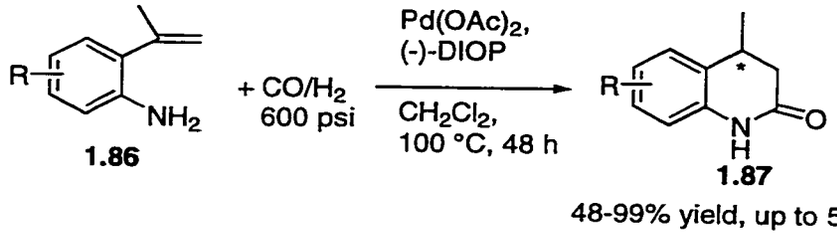


1.83

(eq 33)

Ligand	$CO:H_2$ ratio	yield(%)	**1.84**	**1.85**
dppb	1:0	62	25	75
PCy_3	5:1	95	100	0

Application of the $Pd(OAc)_2$/(−)DIOP to the reaction of 2-(1-methylvinyl)anilines (**1.86**) under 600 psi of a 5:1 ratio of $CO:H_2$ in CH_2Cl_2 at 100 °C for 48 h, gave optically active six-membered lactams **1.87** in up to 54% ee, and in excellent isolated yields (eq 34).[38]

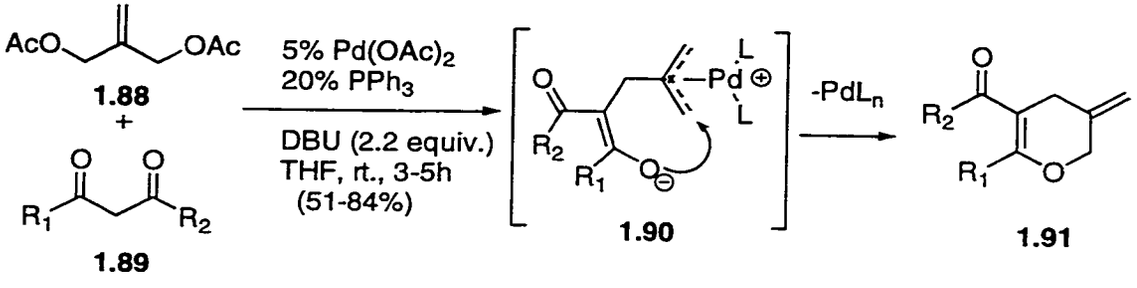


1.86 1.87

48-99% yield, up to 54% ee

(eq 34)

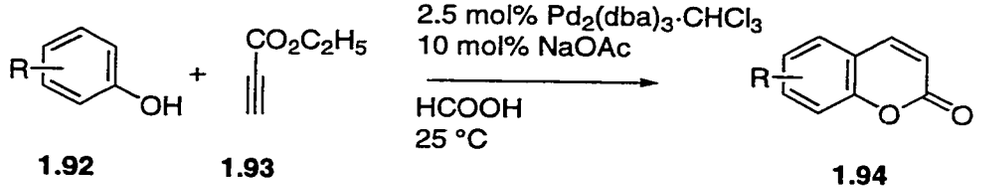
The π-allyl palladium complex derived from **1.88** reacts with the carbanion generated from **1.89** to form intermediate **1.90**, and then palladium-mediated intramolecular O-alkylation takes place affording **1.91** (eq 35).[39]



1.88 + 1.89 1.90 1.91

(eq 35)

A method for the preparation of coumarins **1.94** was attained by the palladium-catalyzed reaction of phenols **1.92** with ethylpropynoate **1.93** (eq 36).[40] The reaction proceeds to give the coumarin products when formic acid was introduced in the reaction. Since the reaction is initiated by a hydropalladation, the formation of HPdX (X = OCOH, OAr) appears likely.

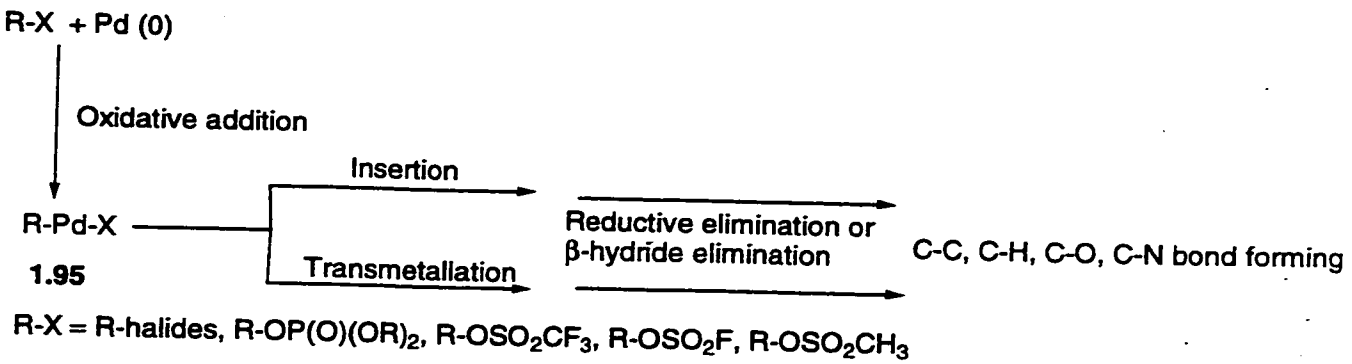


1.92 1.93 1.94

(eq 36)

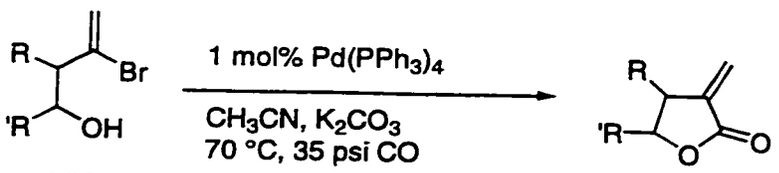
Palladium-catalyzed heterocyclization reactions of organic halides or pseudo-halides with unsaturated substrates such as alkynes, alkenes, 1,2- and 1,3-dienes have been extensively developed in the past decade.[5a,41] Both inter– and intramolecular coupling reactions were reported. The initial step for this type of reaction involves oxidative addition of organic halides to Pd(0) to form complexes **1.95** which have a Pd–C σ-bond. Two types of transformation of the intermediates are possible: insertion and transmetallation. Unsaturated compounds such as alkynes, alkenes, conjugated dienes and carbon monoxide undergo insertion into Pd-C bond. Cyclization is achieved by reductive elimination of C-C, C-H, C-O or C-N (Scheme 1–8).

Scheme1-8

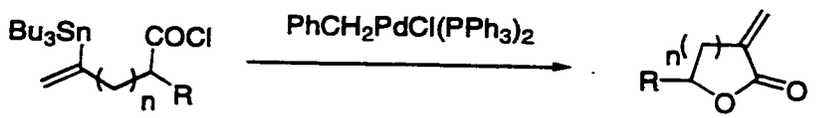


Stille and co-workers[42] reported the high yield formation of α–methylene-γ-lactones (**1.97**), some of which have interesting biological activities, by palladium-catalyzed carbonylation of vinylhalides (**1.96**) derived from epoxides in acetonitrile in the presence of K_2CO_3 at 70 °C (eq 37). The solvent has an effect on the reaction, since no-carbonylation product was observed when THF was used as the solvent. Another approach to obtain five- and six-membered α–methylene-γ-lactones (**1.99**) was reported

by Baldwin and co-workers from the coupling reaction of acid chloride with alkenyltin functionalities **1.98** (eq 38).[43]

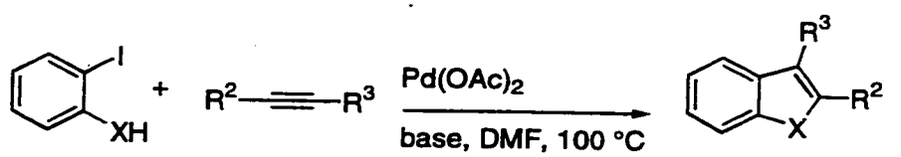


1.96 **1.97**, 58-93% yields (eq 37)



1.98, n =1, 2 **1.99**, n =1, 2, 50-90 %yields (eq 38)

Indoles (**1.103**, X = NH, NR) and benzofurans (**1.104**, X = O) can be synthesized by palladium-catalyzed heteroannulation of acetylenic compounds (**1.102**) with *o*-iodoanilines (**1.100**) or *o*-iodophenols (**1.101**).[44] For terminal alkynes, better results were observed in the presence of a co-catalyst such as CuI, LiI and LiCl.

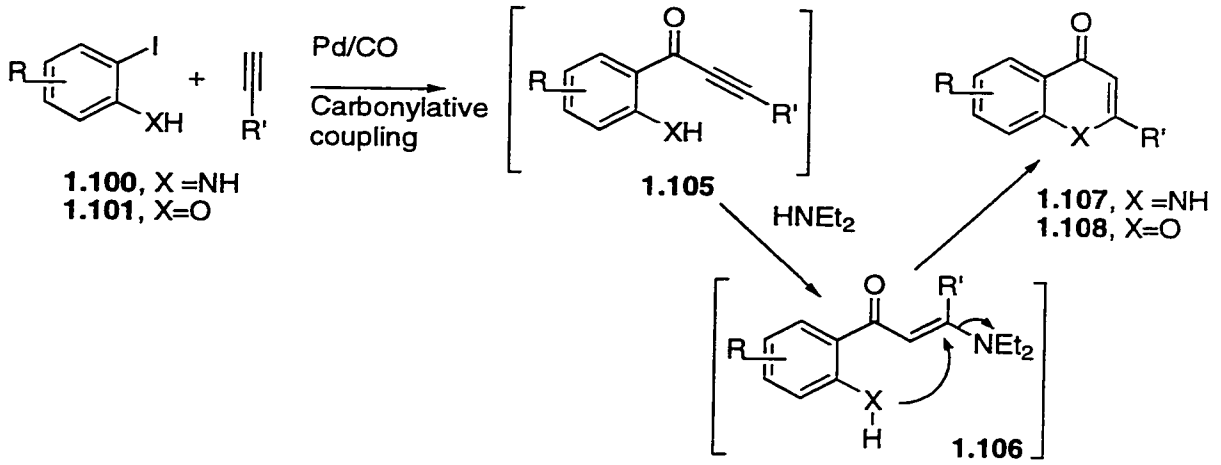


1.100, X = NH, NR^1 **1.102** **1.103**, X = NH, NR^1
1.101, X = O **1.104**, X = O (eq 39)

Torii, Kalinin and Ortar[45] separately reported the preparation of 4-quinolones (**1.107**) and chromone (**1.108**) by palladium-catalyzed intermolecular cyclocarbonylation of terminal alkynes with *o*-iodoanilines (**1.100**) or *o*-iodophenols (**1.101**) respectively.

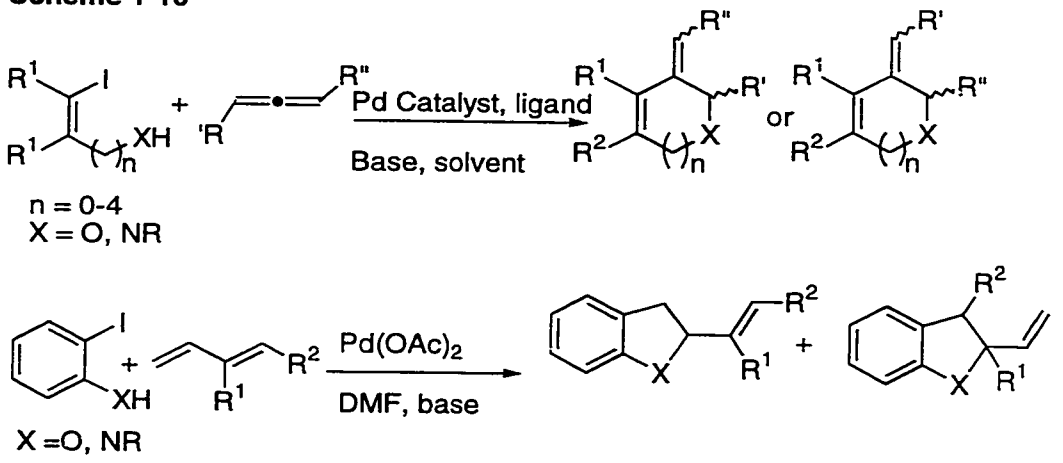
The cyclization is believed to proceed by addition-substitution, with acetylenic ketone intermediates (**1.105**) and the subsequent formation of β-aminovinyl ketone (**1.106**) in the presence of a secondary amine (Scheme 1–9).

Scheme 1-9



Utilizing 1,2-[46] and 1,3-dienes[47] for heteroannulation with organic halides affords heterocycles (Scheme 1–10).

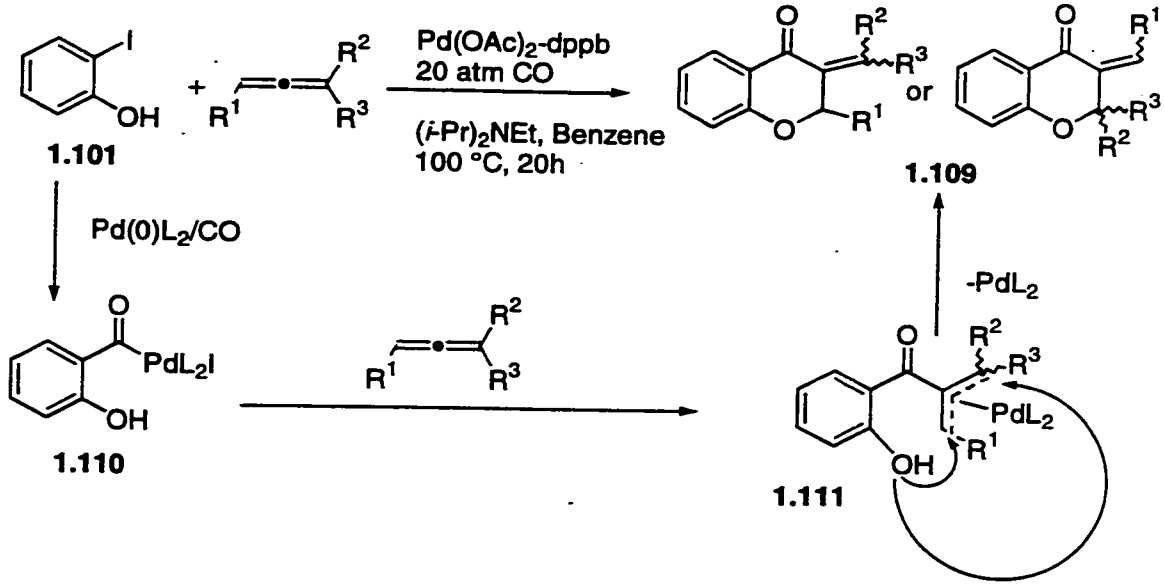
Scheme 1-10



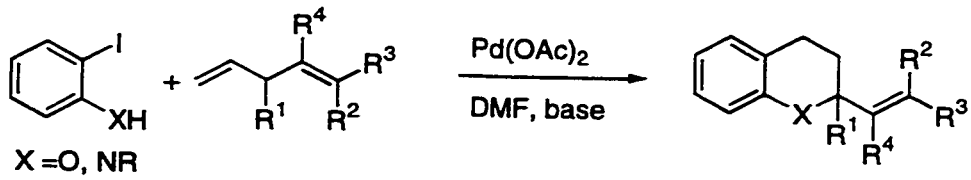
The reactions proceed through π-allyl palladium intermediates, generated by palladium intermediates from addition of haloarenes or haloalkenes to the dienes followed by nucleophilic addition.

Treatment of *o*-iodophenols (**1.101**) with allenes using a catalyst system consisting of $Pd(OAc)_2$-dppb in the presence of $(i\text{-Pr})_2NEt$ in benzene at 100 °C under 20 atm CO resulted in the formation of 4*H*-benzopyran-4-ones (**1.109**).[48] The reaction may occur by addition of an initially generated aroylpalladium intermediate **1.110** to the allenyl unit of allenes to form a π-allyl palladium complex **1.111**, which then undergoes nucleophilic attack by the hydroxyl group to give the products (Scheme 1–11).

Scheme 1-11



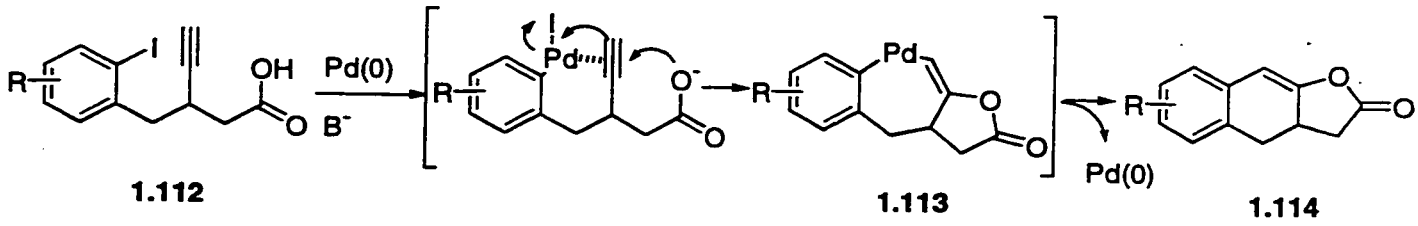
Larock and co-workers reported the use of 1,4-dienes in reaction with iodoarenes with $Pd(OAc)_2$ as the catalyst to form 6-membered ring heterocycles in high yields (eq 40).[49]



(eq 40)

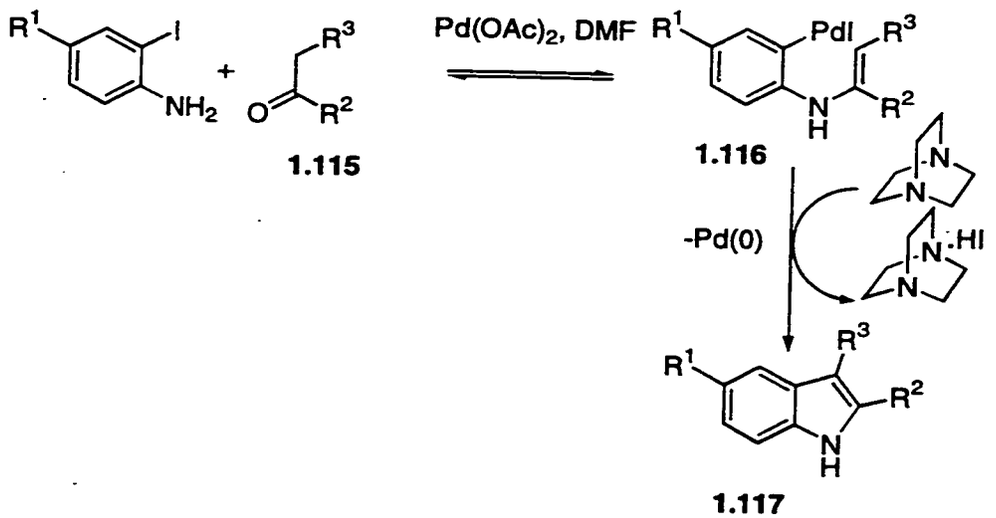
γ-Arylidenebutyrolactones (**1.114**) were obtained in good yields by the palladium-mediated intramolecular cyclization of pentynoic acids containing iodoaryl substituents (**1.112**).[50] The reaction proceeds via intramolecular nucleophilic attack by the carboxylate anion on the σ-aryl palladium-coordinated carbon-carbon triple bond. Reductive elimination of intermediate (**1.113**) leads to the exocyclic enol lactones with regeneration of the catalyst (Scheme 1–12).

Scheme 1-12



Another pathway which was reported for the formation of indole derivatives **1.117** by palladium-catalyzed annulation of *o*-iodoanilines with ketones (**1.115**) is shown in Scheme 1–13.[51] The reaction likely proceeds by the generation of an enamine (**1.116**), and subsequent intramolecular Heck reaction. High product yields were obtained when 3 equivalents of DABCO was used as the base.

Scheme 1-13



1.3 Aims of research

As mentioned in section 1.2 palladium complexes have been shown to be useful catalyst for the synthesis of a wide variety of heterocyclic compounds.

Stereoselective formation of 4-vinyl-1,3-oxazolidin-2-ones from 2-vinyloxiranes and isocyanates catalyzed by palladium complexes was reported.[52] However, to our knowledge, there are no examples of the synthesis of 1,3-oxazolidin-2-imines in high enantiomeric excess by the cycloaddition of oxiranes to carbodiimides. We, therefore, decided to explore the asymmetric cycloaddition of 2-vinyloxiranes with carbodiimides and isocyanates utilizing commercially available chiral phosphine ligands. Since two regioisomers could be obtained when unsymmetrical carbodiimides were used in the palladium-catalyzed cycloaddition reaction with 2-vinyloxirane, a study was initiated on

the regioselective and stereoselective cyclization of a variety of unsymmetrical carbodiimides with 2-vinyloxiranes in the presence of a palladium catalyst.

2-Vinyloxetanes were shown to undergo palladium-catalyzed ring opening in the presence of a hard nucleophile to yield allylic alcohols.[53] We envisioned that 2-vinyloxetanes could be used in the palladium–catalyzed cycloaddition reaction with heterocumulenes to form interesting six-membered ring heterocycles. The diastereoselectivity of the reaction was investigated using bicyclic-2-vinyloxetanes.

1,3-Benzoxazine-4-ones, 1,3-quinazoline-4-ones are known to have interesting biological activities. The formation of the products could be accessible by the palladium promoted carbonylation and cyclization of *o*-iodophenols or *o*-iodoaniline with heterocumulenes. We therefore intend to develop a system, which makes possible the formation of these potentially useful compounds.

Finally, the pharmaceutically interesting 3,1-benzoxazin-4-one derivatives have attracted attention in the past. We would like to investigate the reaction of *o*-iodoanilines with acid chlorides under carbon monoxide pressure in the presence of a catalytic amount of a palladium complex that would provide a simple route to the desired products.

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Chapter 2

Palladium(0) Catalyzed Asymmetric Cycloaddition of 2-Vinyloxiranes with Heterocumulenes: A Route to Highly Enantioselective Synthesis of 4-Vinyl-1,3-oxazolidine Derivatives.

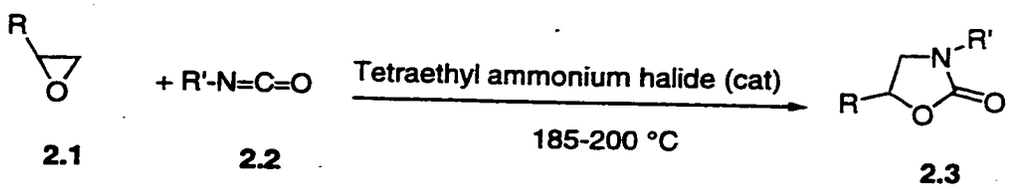
2.1 Introduction

2.1.1 1,3-oxazolidine derivatives

1,3-Oxazolidine derivatives are an important class of heterocyclic compounds found in a large number of molecules possessing medicinal activities including drugs against typhoid,[1,2], salmonella-type infections,[3-5] and respiratory diseases[6] in poultry. 1,3-Oxazolidin-2-ones have potent antibacterial activity against gram-positive organisms, [7-11] and also are β_3-adrenoceptor agonists,[12] as well as antitumor and antiviral,[13] neuroleptic,[14] and antihyperlipidemic agents.[15] The preparation of 1,3-oxazolidine derivatives has been extensively developed.[16] The most general synthetic methods are often utilizing β–amino alcohols, β–haloamines, β–haloalcohols and epoxides.

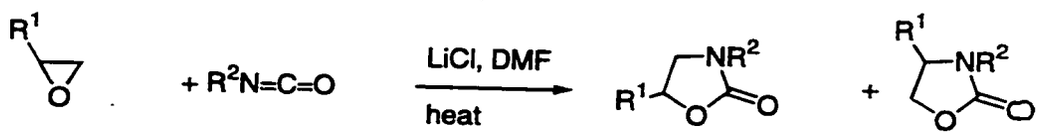
Much research has been done on the reaction of epoxides with heterocumulenes to form 1,3-oxazolidines. For instance, Speranza and Peppel[17] reported the preparation of 1,3-oxazolidin-2-ones (**2.3**) by the reaction of epoxides (**2.1**) with isocyanates (**2.2**) in the presence of a catalytic amount of tetraethylammonium halides at 185-200 °C (eq 1). Ring opening of

the epoxides assisted by halide ion, occurred at the less substituted O-C bond followed by addition of the oxygen anion to the isocyanate and ring closure to give the product.



2.1 **2.2** **2.3** (eq 1)

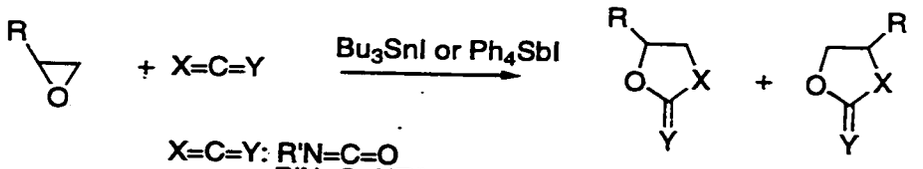
N-substituted-2-oxazolidinones have been prepared from isocyanates and epoxides in refluxing DMF (reaction temperature *ca.* 150 °C or greater) with lithium chloride as the catalyst (eq 2).[18-20] Although the major products are 5-substituted-2-oxazolidones (**2.6**), 4-substituted isomers (**2.7**) were also formed.



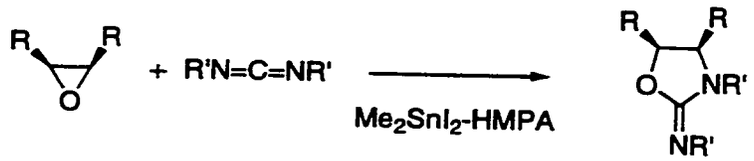
2.4 **2.5** **2.6**, major **2.7**, minor (eq 2)

Organotin halides-Lewis base complexes[21] and organoantimony halides[22,23] were utilized for the cycloaddition reaction of heterocumulenes with oxiranes affording a variety of 2-oxazolidine derivatives in good yields (eq 3). Selective α-cleavage of oxiranes was observed in the case of tetraphenylstibonium iodide whereas major products bearing a substituent at C-5 (resulting from β-cleavage) were obtained in the case of tin halides. Utilizing enantiomeric pure disubstituted oxiranes in the cycloaddition reaction with

heterocumulenes catalyzed by a dialkyltin diiodide–HMPA complex, resulting in the cyclized products with retention of the configuration (eq 4).[24]

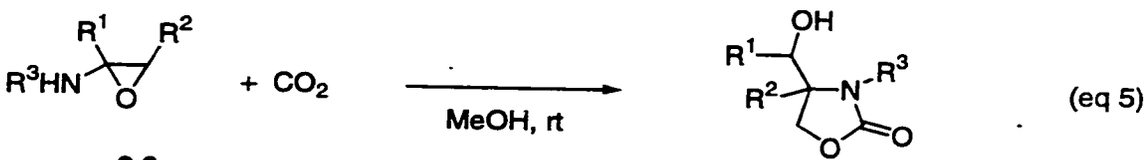


(eq 3)



(eq 4)

Toda's group reported the preparation of 5-substituted-2-oxazolidin-2-ones (**2.9**) in high yields by the reaction of 2-aminomethyloxiranes (**2.8**) with carbon dioxide in MeOH at room temperature for 2h (eq 5).[25] The reaction proceeded in a stereospecific manner (i.e. *cis*-**2.8** gives *anti*-**2.9**, and *trans*-**2.8** affords *syn*-**2.9**.

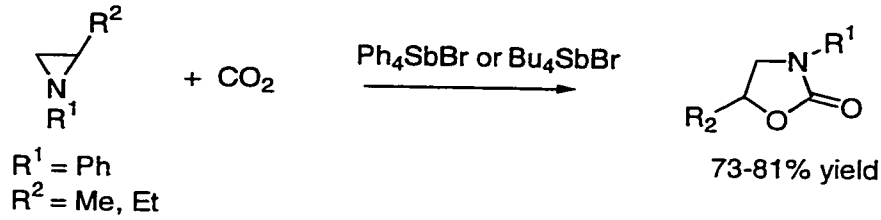


2.8
R^1 = H, CH_3
R^2 = H, CH_3, Ph
R^3 = *t*-butyl, CH_3, Pr, C_2H_4Ph

2.9, 51-94% yield

(eq 5)

Not only can epoxides be used for the synthesis of 1,3-oxazolidin-2-one, as moderate yields were also obtained by using organoantimony halide catalysts such as Ph_4SbBr and Bu_4SbBr in the cycloaddition of aziridines with carbon dioxide (eq 6).[26]



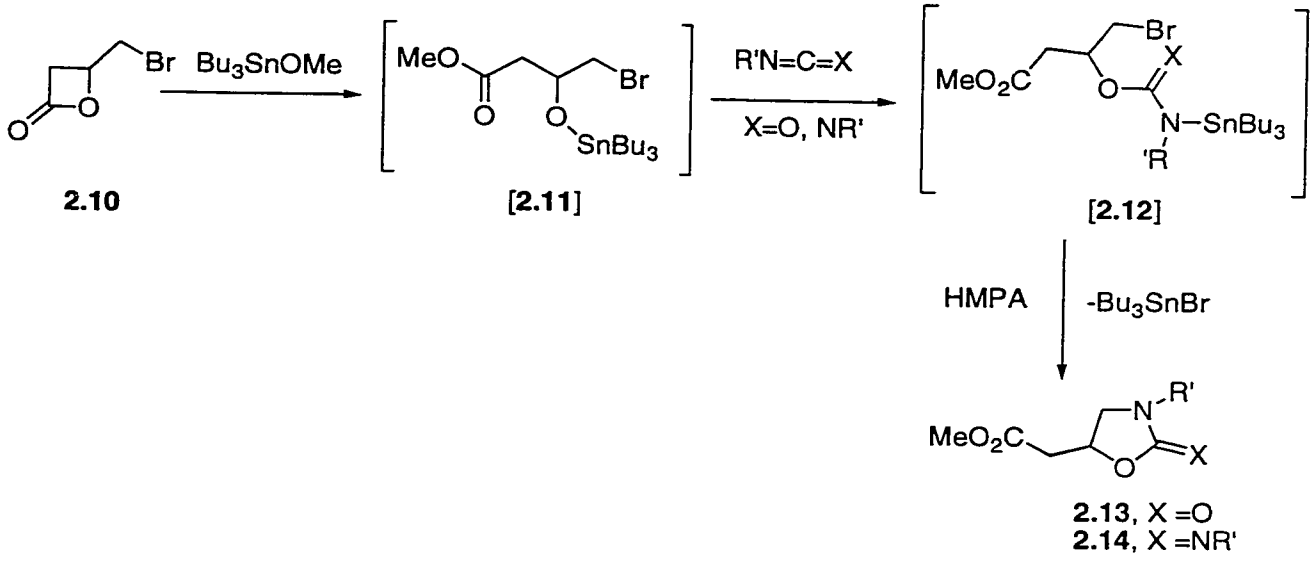
R^1 = Ph
R^2 = Me, Et

73-81% yield

(eq 6)

An organotin alkoxide reagent was utilized to promote the regioselective cleavage of a β-lactone ring (**2.10**) at the acyl-oxygen bond to form intermediate **2.11**. The latter subsequently reacts with isocyanates or carbodiimides to give **2.12**, which on addition of HMPA cyclizes to the 1,3-oxazolidin-2-one (**2.13**) and 1,3-oxazolidin-2-imine (**2.14**) respectively (Scheme 2–1).[27]

Scheme 2-1



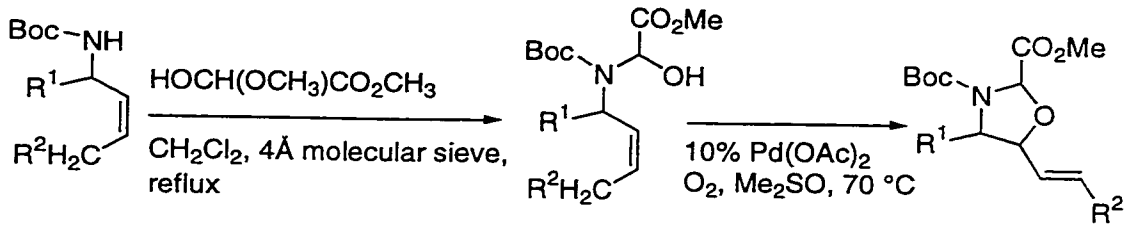
2.10 **[2.11]** **[2.12]**

2.13, X =O
2.14, X =NR'

Palladium-catalyzed cycloaddition reactions have been considered to be versatile tools for constructing heterocycles in organic synthesis (Chapter 1). In this context, a number of studies on the synthetic application of palladium-catalyzed cycloaddition to prepare 1,3-oxazolidine derivatives have been undertaken. Several types of starting materials were employed as well as the reaction conditions were optimized to maximize yields.

Palladium (II)-catalyzed oxidative cyclization of the adducts of *N*-protected allylic amines with methyl glyoxylate (**2.15**) in the presence of molecular oxygen resulted in the formation of 5-alkenyl oxazolidines in high yields (Scheme 2–2).[28] The reaction proceeds well without the need of a co-oxidant such as $Cu(OAc)_2$, if DMSO was used as the solvent.

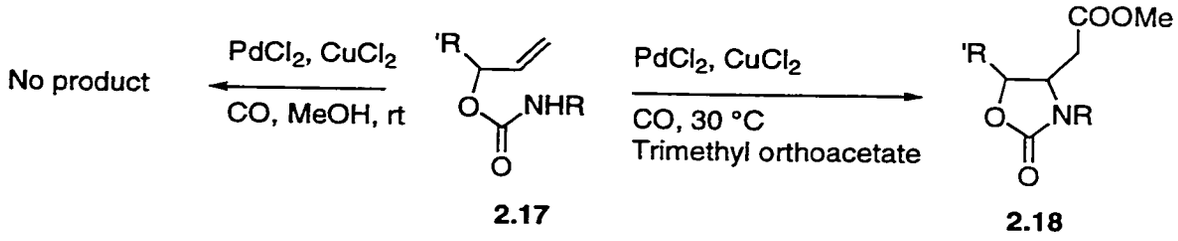
Scheme 2-2



2.15 **2.16**

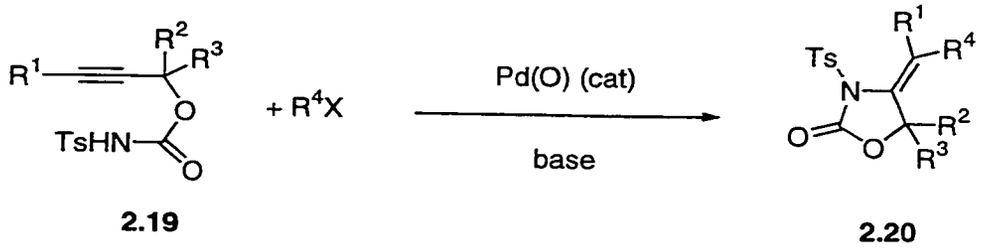
Harayama et al.[29] demonstrated that *endo*-carbamate **2.17** smoothly undergoes palladium(II)-catalyzed intramolecular aminocarbonylation to give 1,3-oxazolidin-2-ones (**2.18**). The additives in this reaction are crucial. No desired product was observed under reaction conditions utilizing palladium (II) chloride, copper (II) chloride and 1 atm of carbon monoxide in methanol at room temperature. However, when trimethyl orthoacetate (MOA) was used instead of methanol, the reaction effected at 30 °C, the 1,3-oxazolidin-2-one derivative was obtained in good yield. MOA promoted the reaction by serving as a base both

to generate the conjugated base of the carbamate, and as an HCl scavenger (eq 7). Moreover, the formation of the conjugate base enhances the nucleophilicity of the nitrogen nucleophile.



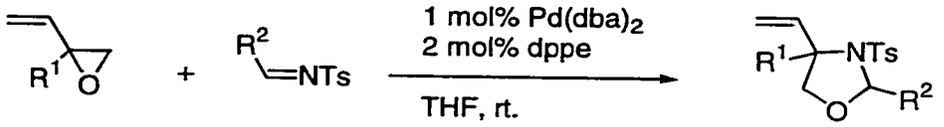
(eq 7)

Acardi[30] and Balme and co-workers[31] separately reported the cyclization-coupling reactions of propagyl tosylcarbamate (**2.19**) with aryl iodide/vinyl triflate in the presence of base and a catalytic amount of a palladium (0)-phosphine complex to form (*E*)-4-arylidene or 4-alkylidene-3-tosyloxazolidin-2-one (**2.20**) in a regio- and stereoselective manner (eq 8).



(eq 8)

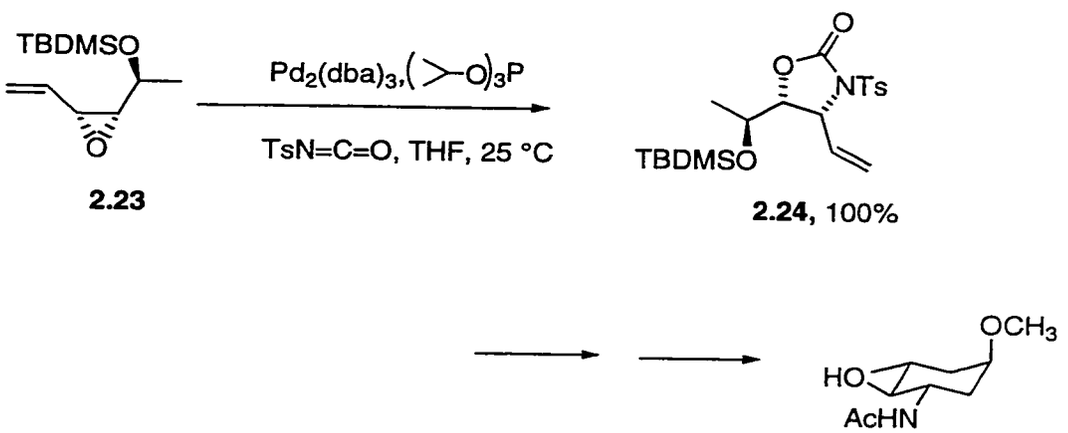
Palladium-catalyzed intermolecular reaction of imines (**2.21**) with 2-vinyloxiranes gives the regioselective [3+2] cycloaddition products, **2.22** in good to excellent yields (eq 9).[32] The reaction proceeds via nucleophilic addition of an oxygen anion, which is generated by the reaction of 2-vinyloxiranes with palladium, to an imine. This reaction is accomplished only by using activated tosyl imines, whereas, other imines such as those containing methyl, phenyl and phosphinoyl gave no products.



(eq 9)

The stereoselective synthesis of oxazolidin-2-one derivatives has attracted attention as important chiral building blocks for the synthesis of optically active natural products. The palladium mediated formation of stereo-pure oxazolidines has been demonstrated to be superior to other methods due to the applicability to a wide range of substrates in a predictable fashion. For example, 4-vinyloxazolidin-2-one (**2.24**), an intermediate in the synthesis of (–)–*N*–acetyl-*O*-methylacosamine (**2.25**), was prepared in a regio- and stereoselective manner by reaction of 2-vinyloxiranes (**2.23**) with isocyanates in the presence of $Pd_2(dba)_3$-triisopropylphosphite (Scheme 2–3).[33-35]

Scheme 2- 3



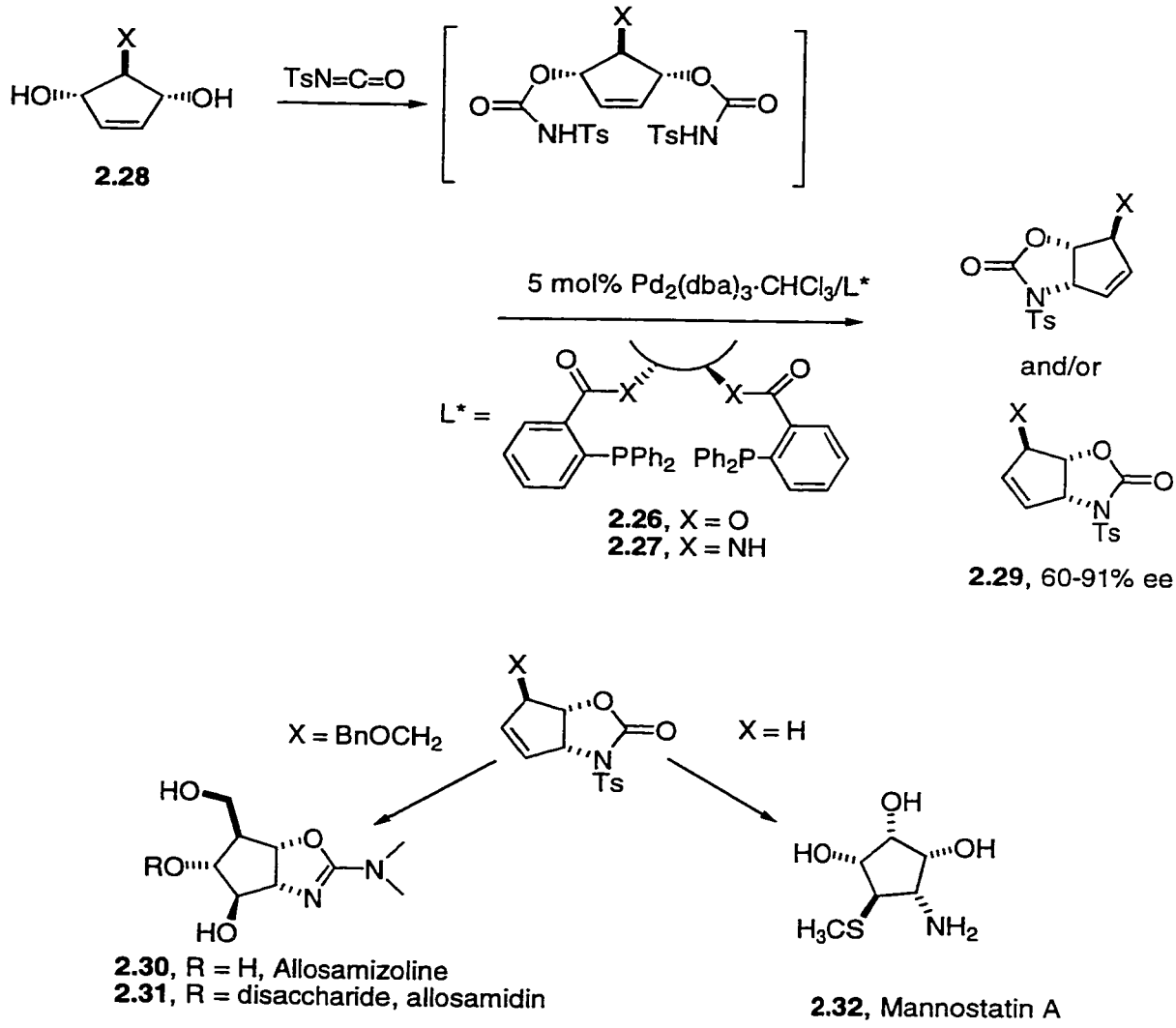
2.23

2.24, 100%

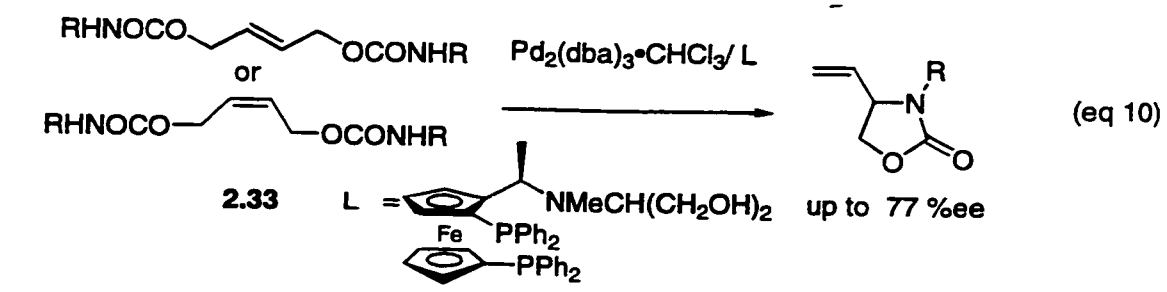
2.25, (-)-*N*-acetyl-*O*-methylacosamine

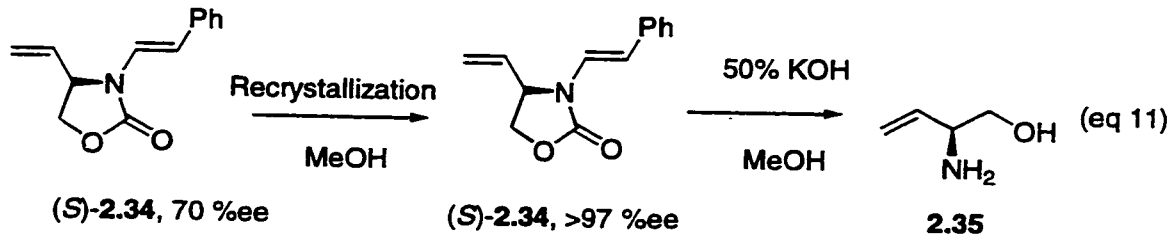
Trost and co-workers[36-39] designed a series of 2-(diphenylphosphino)benzoic acid (**2.26**) or 2-(diphenyphosphino)aniline (**2.27**) based ligands to use in the diastereoselective synthesis of **2.29,** the precursor to glycosidase inhibitors such as allosamizoline (**2.30**), allosamidin (**2.31**) and mannostatin A (**2.32**) from a diol (**2.28**) and *p*-toluenesulfonylisocyanate (Scheme 2–4).

Scheme 2-4



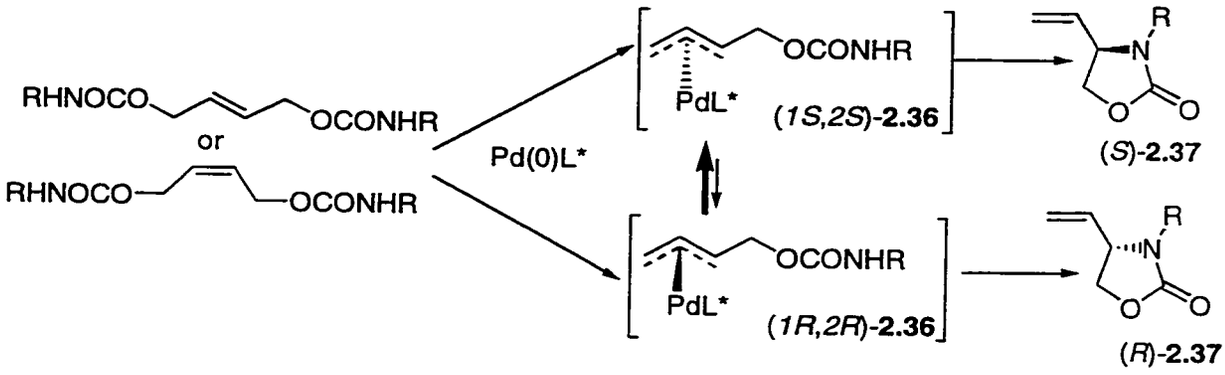
Optically active (up to 77% ee) 4-vinyl-2-oxazolidin-2-ones were prepared by the asymmetric cyclization of (*E*) or (*Z*)-2-butenylene dicarbamates (**2.33**) catalyzed by chiral ferrocenylphosphine-palladium complexes (eq 10).[40] The resulting products were converted to enantiomerically pure 2-amino-3-butenols by alkaline hydrolysis (eq 11). The latter is an important chiral building block for the synthesis of a number of natural products.[41,42]





The cyclization probably proceeds via a π–allylpalladium complex (**2.36**) bearing a carbamoyloxymethyl substituent as a key intermediate (Scheme 2–5). The interconversion of (1*S*,2*S*)-**2.36** and (1*R*,2*R*)-**2.36** via a π-σ-π mechanism is faster than the cyclization and therefore the stereochemical outcome of the cyclization is related mainly to the equilibrium ratio of the diastereomeric complexes.

Scheme 2-5



2.1.2 Aim of the research

To date, no example has been reported of the synthesis of 1,3-oxazolidin-2-imines in high enantiomeric excess by the cycloaddition of oxiranes with carbodiimides. We envisioned that a variety of chiral 1,3-oxazolidin-2-imine derivatives could be prepared by the reaction of 2-vinyloxiranes with carbodiimides in the presence of a palladium-chiral phosphine ligand catalyst system.

The question arises as to the degree of regioselectivity of the cycloaddition reaction of *unsymmetrical* carbodiimides with 2-vinyloxiranes –i.e. is there any preference for one of the two possible 4-vinyl-1,3-oxazolidin-2-imines? Therefore, an investigation was made on the regioselectivity of the palladium-catalyzed cycloaddition reaction of 2-vinyloxiranes with unsymmetrical carbodiimides.

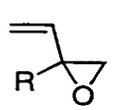
In this chapter a highly enantioselective method for the synthesis of 1,3-oxazolidine derivatives is described by the palladium-bidentate chiral ligand complex-catalyzed cycloaddition of heterocumulenes with 2-vinyloxiranes.

2.2. Results and discussion

2.2.1 Cycloaddition reaction of 2-vinyloxiranes with heteroculmulenes catalyzed by palladium complex and achiral phosphine ligand.

2.2.1.1 Cycloaddition reaction of 2-vinyloxiranes with isocyanates and symmetrical carbodiimides.

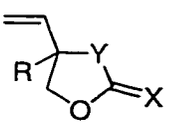
We initially performed this reaction using an achiral-Pd(0) catalyst such as $Pd(PPh_3)_4$ to examine the feasibility of the cycloaddition pathway for obtaining optically active oxazolidine derivatives from 2-vinyloxirane with heterocumulenes such as isocyanates or symmetrical carbodiimides. This reaction was successfully carried out by treatment of 2-vinyloxirane **2.38** (R= H or CH_3) with isocyanate **2.39** or symmetrical carbodiimide **2.40** in the presence of $Pd(PPh_3)_4$ (3 mol%) and triphenylphosphine (6 mol%) in anhydrous THF at room temperature for 15 h under nitrogen a atmosphere (eq 12).



2.38a, R =H
2.38b, R =CH_3

\+ X=C=Y

3 mol% $Pd(PPh_3)_4$
6 mol% PPh_3
THF, 15 h, rt, N_2



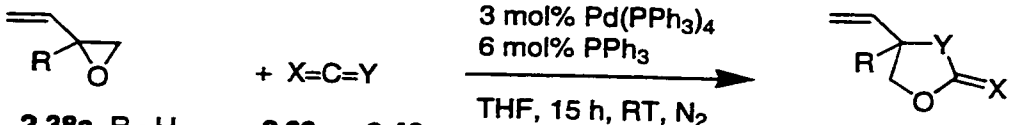
2.39, X =O, Y = NR'
2.40, X = Y = NR'

2.41, X = O, Y =NR'
2.42, X = Y = NR'

(eq 12)

In this manner 4-vinyl-1,3-oxazolidin-2-one **2.41** (X=O, Y= NR′) or 4-vinyl-1,3-oxazolidin-2-imine **2.42** (X = Y = NR′) were formed regioselectively and in 90-98 % yield (Table 2-1). This reaction required 3 mol% of $Pd(PPh_3)_4$ and 2 equivalents of triphenylphosphine relative to Pd. Reduced amounts of $Pd(PPh_3)_4$ or no additional PPh_3, resulted in lower product yields.

Table 2-1 Cycloadducts Obtained from the Reaction of 2-Vinyloxiranes (2.38) with Heterocumulenes, 2.39 or 2.40 in the Presence of $Pd(PPh_3)_4$ and PPh_3.[a]



2.38a, R =H
2.38b, R =CH_3

2.39 or **2.40**

2.41, X = O, Y =NR'
2.42, X = Y = NR'

entry	2.38	heterocumulene (2.39 or 2.40)	Products	Isolated yield (%)[b]
1	**2.38a**	$C_6H_5N=C=O$, **2.39a**	**2.41a**	90
2	**2.38a**	*p*-$ClC_6H_4N=C=O$, **2.39b**	**2.41b**	98
3	**2.38a**	*p*-$BrC_6H_4N=C=O$, **2.39c**	**2.41c**	95
4	**2.38b**	*p*-$ClC_6H_4N=C=O$, **2.39b**	**2.41d**	94
5	**2.38a**	$C_6H_5N=C=NC_6H_5$, **2.40a**	**2.42a**	98
6	**2.38a**	*p*-$ClC_6H_4N=C=NC_6H_4$*p*-Cl, **2.40b**	**2.42b**	96
7	**2.38b**	*p*-$CH_3C_6H_4N=C=NC_6H_4$*p*-CH_3, **2.40c**	**2.42j**	90

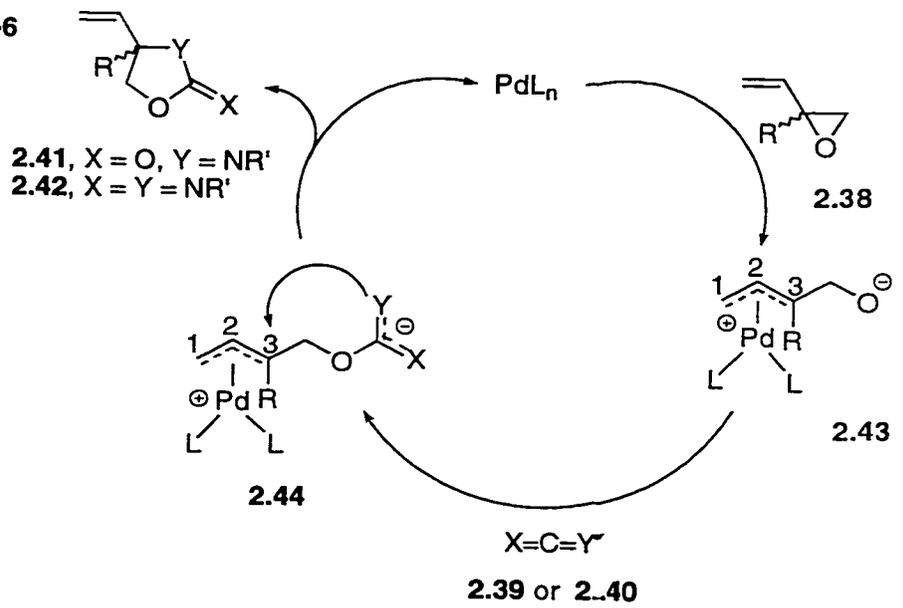
[a] Reaction conditions: 2-vinyloxirane (**2.38**, 1.5 mmol), heterocumulene (**2.39** or **2.40**, 1.0 mmol), $Pd(PPh_3)_4$ (0.03 mmol), PPh_3 (0.06 mmol), THF (3 mL), room temperture, 15 h, N_2 atmosphere.
[b] Purified by preparative TLC.

Attempts to perform the reaction of *p*-nitrophenyl isocyanate and bis(*p*-nitrophenyl) carbodiimide with 2-vinyloxirane (**2.38a**) failed to give the desired products, possibly because of the poor electrophilicity of the carbon center. No cyclization product was observed by reactions of **2.38a** with phenyl isothiocyanate or *p*-chlorophenyl isothiocyanate which were conducted in the same manner.

2.2.1.2 A possible reaction mechanism for the cycloaddition reaction.

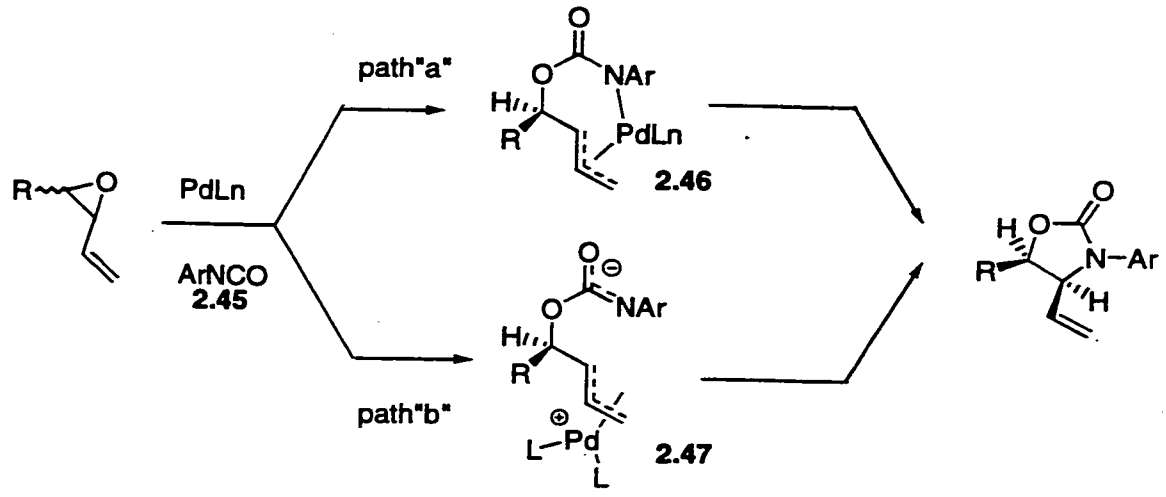
The cycloaddition may proceed via a zwitterionic π-allyl palladium intermediate (**2.43**) containing alkoxide anion generated by oxidative addition of vinyloxirane **2.38** to a palladium (0) species[43-50,36,51] followed by reaction with the heterocumulene resulting in the formation of the intermediate (**2.44**). The attack of nitrogen nucleophile on the C-3 carbon of **2.44** generates the five-membered heterocyclic product (Scheme 2–6).

Scheme 2-6



The mechanism of Pd(0) catalyzed formation of oxazolidin-2-ones from 2-vinyloxiranes was studied by Trost and Hurnaus using the reaction of carvone epoxide **2.48** and **2.49** with 2-methoxynaphthyl-1,1-isocyanate **2.45**.[34] Two pathways for the cyclization process may be possible. Path "a" in which nitrogen initially coordinates to the palladium in the intermediate π-allyl palladium complex **2.46**, and this species then collapses to product, whereas, or the formation of intermediate **2.47** by path "b" (Scheme 2–7).

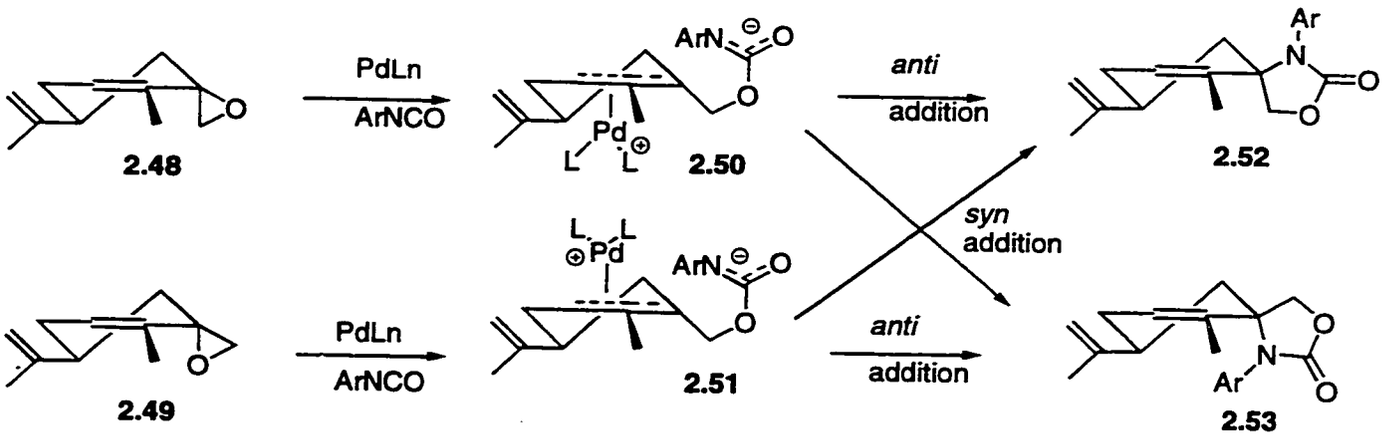
Scheme 2-7



Since palladium initiated ionization has been established to proceed with inversion of configuration, the diastereomeric π-allyl palladium complexes **2.50** and **2.51** should be generated. Attack *anti* (path "b") to palladium creates the product of overall retention of configuration (i.e. **2.50**→**2.52** and **2.51**→**2.53**); while, attack *syn* (path "a") to palladium forms the product of overall inversion of configuration (i.e. **2.50**→**2.53** and **2.51**→**2.52**) (scheme 2–8). The results revealed that net retention of configuration was obtained. Therefore, path

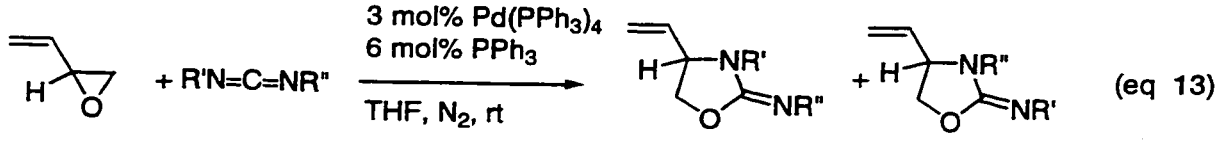
"b" is likely here. This type of pathway should also be applicable to the reaction of vinyloxiranes with carbodiimides in the synthesis if oxazolidin-2-imines.

Scheme 2-8



2.2.1.3 Cycloaddition reaction of 2-vinyloxiranes with unsymmetrical carbodiimides

As previously described for the cycloaddition reaction of 2-vinyloxiranes with isocyanate or symmetrical carbodiimides, 3 mol% of $Pd(PPh_3)_4$ and 6 mol% of PPh_3 were required for the process. Cycloaddition reactions of 2-vinyloxirane with unsymmetrical carbodiimides were carried out in the same manner providing good to excellent isolated yields of the products. The reactions were performed by treatment of 2-vinyloxirane **2.38a** with unsymmetrical carbodiimides **2.54** in the presence of $Pd(PPh_3)_4$ and 2 equivalents of triphenylphosphine relative to palladium, in dried THF at room temperature, until full conversion of carbodiimide was detected (monitored by IR) (eq 13).



(eq 13)

2.38a **2.54** **2.55** **2.56**

Two products (4-vinyl-1,3-oxazolidin-2-imines), **2.55** and **2.56,** were formed using carbodiimides containing alkyl and aryl substituents. The products were isolated in pure form (by preparative TLC) in a total yield of 79-96 % (Table 2-2). It is noteworthy that one of the two five-membered ring heterocycles was always obtained as the major product (**2.55**) and it is less polar than its isomer (**2.56**). The ratios of **2.55** to **2.56** were usually determined by gas chromatography of the reaction mixture after complete conversion of the carbodiimide. The ratio of the pure products obtained after isolation was also similar to the GC ratio.

Nuclear magnetic resonance (^{1}H, ^{13}C) spectra indicated that two products were formed from unsymmetrical diaryl carbodiimides (entries 10 and 11) but the ratio could not be determined, and the products were inseparable by GC or TLC.

Table 2-2 Cycloaddition Reactions of 2-Vinyloxirane (2.38a) with Unsymmetrical Carbodiimides (2.54) in the Presence of $Pd(PPh_3)_4$ and PPh_3.[a]

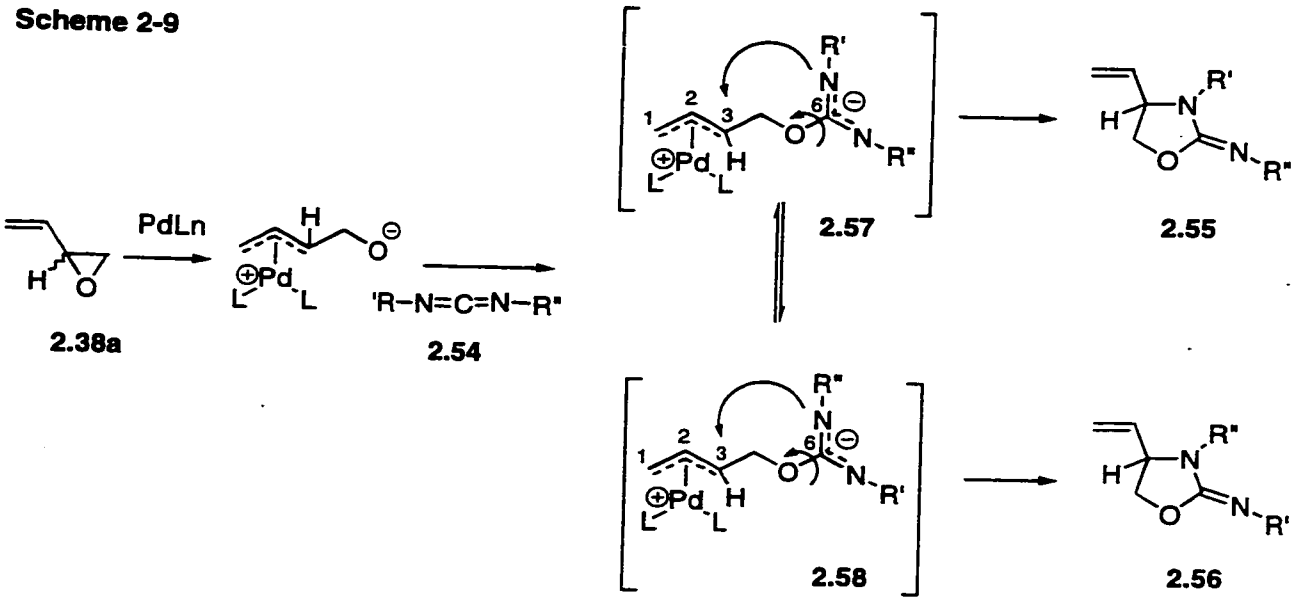
Entry	Carbodiimide (2.54)	Reaction time (h)	Ratio of 2.55:2.56[b]	Isolated yield (2.55+2.56) (%)[c]
1	$H_5C_6N{=}C{=}NC_6H_{11}$, **2.54a**	12	2.4:1	84
2	$H_5C_6N{=}C{=}N\text{-}^nC_4H_9$, **2.54b**	12	2:1	82
3	$H_5C_6N{=}C{=}N\text{-}^tC_4H_9$, **2.54c**	24	1.4:1	84
4	*p*-$H_3COH_4C_6N{=}C{=}NC_6H_{11}$, **2.54d**	12	2:1	81
5	*p*-$ClH_4C_6N{=}C{=}N\text{-}^nC_4H_9$, **2.54e**	12	2:1	84
6	*p*-$FH_4C_6N{=}C{=}NC_6H_{11}$, **2.54f**	12	2:1	90
7	*2,6*-$(H_3C)_2H_3C_6N{=}C{=}NC_6H_{11}$, **2.54g**	15	4:1	96
8	*p*-$H_3CH_4C_6N{=}C{=}NC_2H_5$, **2.54h**	12	2:1	82
9	*2,6*-$(H_3C)_2H_3C_6N{=}C{=}N^nC_4H_9$, **2.54i**	15	4.5:1	79
10	*p*-$ClH_4C_6N{=}C{=}N\text{-}^nC_6H_5$, **2.54j**	15	nd[d]	81
11	*p*-$H_3CH_4C_6N{=}C{=}NC_6H_5$, **2.54k**	15	nd[d]	94

[a] Reaction conditions: 2-vinyloxirane, **2.38a** (1.5 mmol), carbodiimide **2.54** (1.0 mmol), $Pd(PPh_3)_4$ (0.03 mmol), PPh_3 (0.06 mmol), THF (5 mL), room temperature, N_2 atmosphere, [b] Determined by GC. [c] Purified by preparative TLC. [d] The two isomers could not be separated by GC or TLC.

2.2.1.4 The reaction mechanism for the formation of two products from the reaction of 2-vinyloxiranes with unsymmetrical carbodiimides

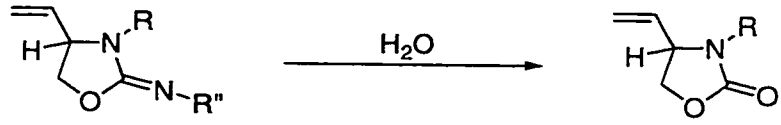
The cycloaddition reaction may proceed via zwitterionic π-allyl palladium intermediates **2.57** and **2.58** (similar to that in the reaction of 2-vinyloxiranes with symmetrical carbodiimides) formed by oxidative addition of **2.38** to a palladium (0) species followed by reaction with the unsymmetrical carbodiimide resulting in formation of intermediates **2.57** and **2.58**. Rotation about the C-6 carbon of **2.57** and **2.58** (Scheme 2–9) enables two types of intramolecular ring closure to occur, by either of the nitrogen nucleophiles of **2.57** and **2.58** at the C-3 carbon to give the five-membered ring, 4-vinyl-1, 3-oxazolidine-2-imines derivatives, **2.55** and **2.56**, respectively.

Scheme 2-9



2.2.1.5. Determination of the structure of the major product from the palladium-catalyzed cycloaddition reaction of 2-vinyloxiranes with unsymmetrical carbodiimides.

Since there are two possible structures for the major products from alkylarylcarbodiimides (**2.54**), one with the aryl group attached to the nitrogen of the oxazolidine ring and the other with the alkyl group attached to the heterocyclic nitrogen, the structure of the major products need to be determined. Attempts to hydrolyse 4-vinyl-1,3-oxazolidin-2-imines[21] (major product) to 4-vinyl-1,3-oxazolidin-2-ones (eq 14) led to only partial conversion.



2.55

(eq 14)

Therefore, a single-crystal X-ray determination was made to establish the structure of the major product of entry 7 (Table 2-2). The result shows that the structure of the major product (**2.55g**) of this cycloaddition reaction is the 4-vinyl-1,3-oxazolidin-2-imine, which contains a cyclohexyl group attached to the heterocyclic ring nitrogen (Figure 2-1). Comparison of the spectral data of the major and minor products from each reaction to those obtained from entry 7 reveals that the major product formed (**2.55**) is the isomer with the alkyl group attached to the nitrogen of the ring. This may be due to the fact that the nucleophilicities of anionic nitrogen containing alkyl substituents is higher than that bearing an aryl group substituent.

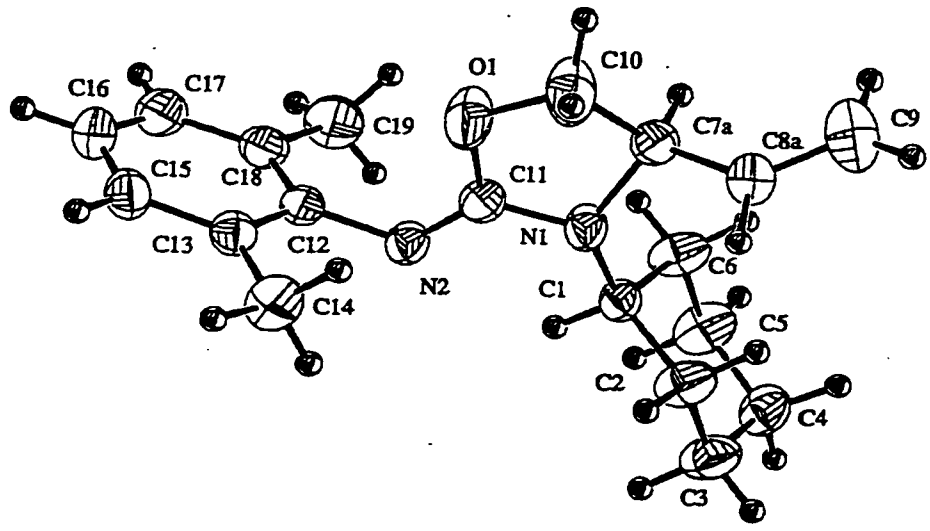
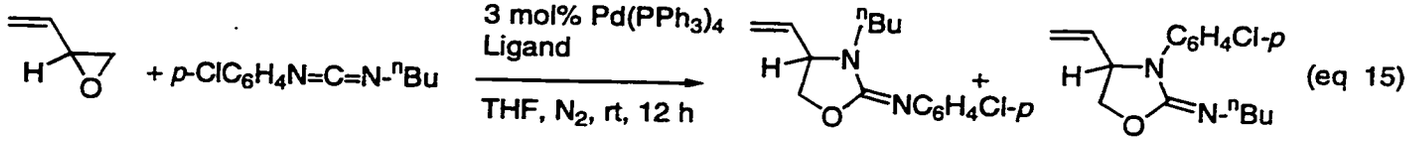


Figure 2-1 X-ray structure of the major product (2.55g) obtained from entry 7, Table 2-2.

Attempts to improve the regioselectivity of this reaction by introducing a more bulky alkyl group (R′), such as *tert*-butyl or cyclohexyl, on one nitrogen atom of the carbodiimides proved to be ineffective (entries 1-3). Using carbodiimides bearing phenyl rings (R″) which contain a substituent at the *para*-position also did not enhance the regioselectivity of the reactions (entries 4-6). Furthermore, the reaction temperature did not affect the regioselectivity of the reaction. Similar results were obtained when performing the reaction (entry 1) either at higher (80 °C, 2 h) or lower (5 °C, 24 h) reaction temperatures.

Using other phosphine ligands in the cycloaddition reaction such as tricyclohexylphosphine, dppp or dppb shows no effect on the selectivity. The product ratios of the **2.55** to **2.56** of the reaction (entry 5), by using tricyclohexylphosphine, dppp and dppb were 1.6:1, 1:1 and 0.8: 1 respectively (eq 15).



(eq 15)

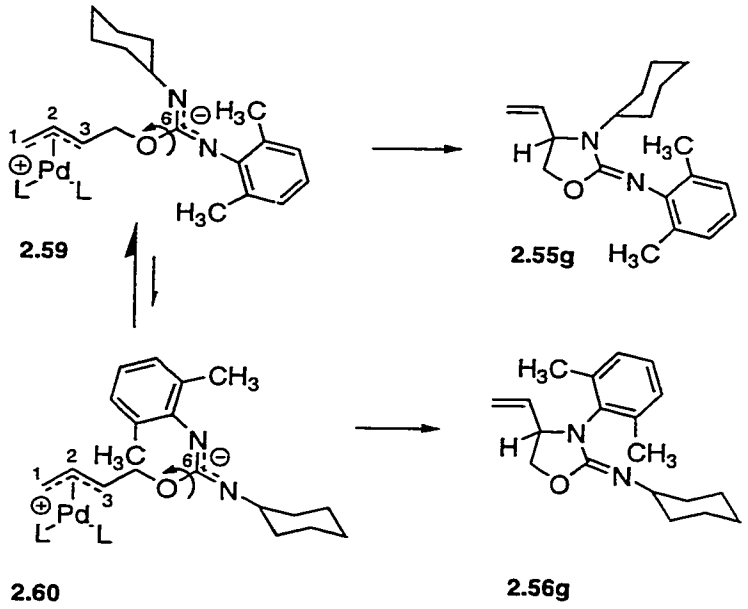
2.38a **2.54e** **2.55e** **2.56e**

Ligand	Ratio of **2.55e : 2.56e**
PPh_3 (6 mol%)	2:1
$P(Cy)_3$ (6 mol%)	1.6:1
dppp (3 mol%)	1:1
dppb (3mol%)	0.8:1

2.2.1.6. Postulated mechanism for the formation of the major isomers from the reaction of 2-vinyloxiranes with unsymmetrical carbodiimides.

The greater selectivity resulted using carbodiimides containing a phenyl ring with *ortho* substituents (entries 7 and 9), is possibly due to steric hindrance of the *ortho* substituents on the phenyl ring during rotation about C-6 of the intermediates. Therefore, it can be reasoned that intermediate **2.59** is preferred to **2.60** prior to intramolecular nucleophilic attack at C-3 (Scheme 2–10) and thus isomer **2.55g** is generated as the major product. A greater rate of cyclization of **2.59** than **2.60**, would lead to **2.55g** as the primary product.

Scheme 2-10



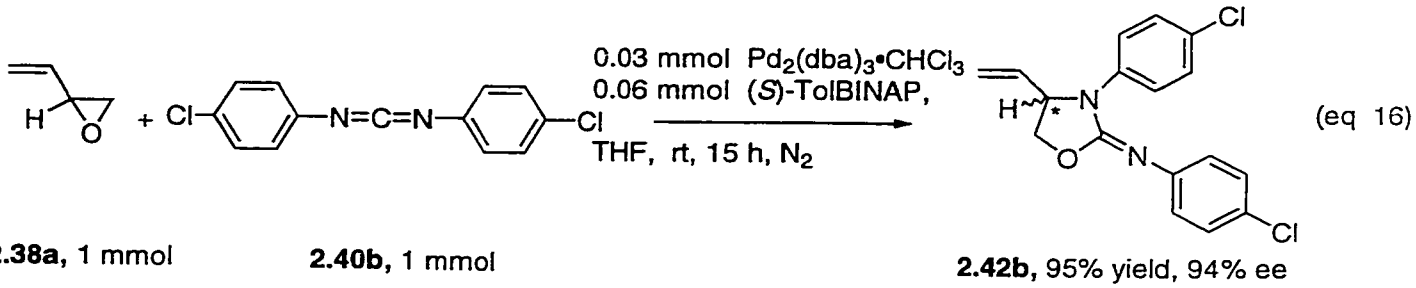
2.2.2. Cycloaddition reaction of 2-vinyloxiranes with heteroculmulene catalyzed by palladium complex and chiral phosphine ligand.

The oxazolidine products contain a chiral center at C-4 position, that is a result of the attack of nitrogen nucleophile on C-3 of the intermediate. Asymmetric induction could be achieved by introducing a chiral phosphine ligand in the cycloaddition reaction. Success in the achievement of a high degree of asymmetric induction depends on the choice of the appropriate combination of metal and chiral ligands as well as reaction conditions. The examples of enantioselective palladium-catalyzed reactions for the formation of oxazolidine derivatives were discussed earlier in section 2.1.1. However, there are no reports on the asymmetric formation of the palladium-catalyzed cycloaddition reactions of 2-vinyloxiranes with carbodiimides to form oxazolidin-2-imines was described. We therefore investigated the

factors that influence the stereoselective of the cycloaddition reaction such as type of the chiral ligands, the reaction temperature and the nature of the substrates.

2.2.2.1 Palladium-catalyzed asymmetric cycloaddition reactions of 2-vinyloxiranes with isocyanate or symmetrical carbodiimides.

We started our investigation by performing the cycloaddition reaction of **2.38a** (R=H, 1.5 mmol) and **2.40e** (X= Y = *p*-ClC_6H_4N, 1.0 mmol) in THF in the presence of $Pd_2(dba)_3$•$CHCl_3$ (0.03 mmol) and (*S*)-TolBINAP[52] (0.06 mmol). After 15 h of the reaction at room temperature under an inert atmosphere *N*, 3-di(*p*-chlorophenyl)-4-vinyl-1,3-oxazolidin-2-imine **2.42b** was isolated in 95% yield and in 94 % ee as determined by chiral HPLC (Chiracel OD)(eq 16).

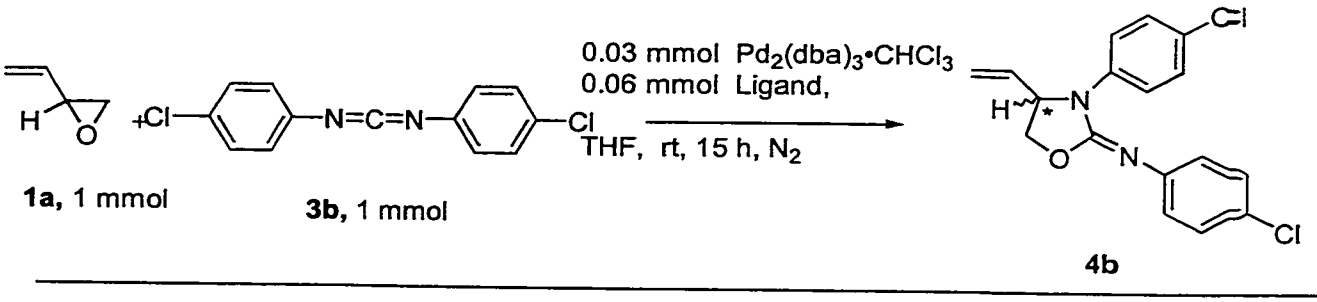


(eq 16)

2.38a, 1 mmol **2.40b**, 1 mmol **2.42b**, 95% yield, 94% ee

Other commercially available chiral ligands such as (–)DIOP[53] (94% yield, 20% ee), (–)-MeDUPHOS,[54] (87% yield, 45 %ee), (*R*, *R*)-NORPHOS,[55] (95% yield, 6% ee), (*R*)-PROPHOS,[56] (96% yield, 3% ee) were less effective in terms of asymmetric induction whereas (*R*)-BINAP[57] (93% yield, 94% ee) gave essentially the same yield and %ee as that obtained by using (*S*)-TolBINAP but of course providing the other enantiomer (Table 2-3).

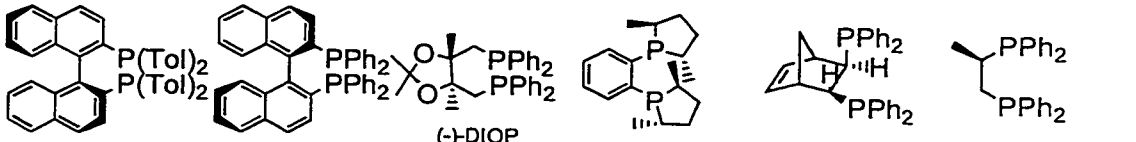
Table 2-3 Palladium-Catalyzed Asymmetric Cycloaddition of 2-Vinyloxirane (2.38a) and Bis(*p*-chlorophenyl)carbodiimide (2.40b) Using Various Chiral Phosphine Ligands.



1a, 1 mmol **3b**, 1 mmol **4b**

Ligand	Isolated yield of **5b**[a]	%ee[b]	$[\alpha]^{22}_D$ in $CHCl_3$
(*S*)-TolBINAP	95	94	+38.7 (*c* 5.04)
(-)-DIOP	94	20	-7.1 (*c* 5.14)
(-)-MeDuPHOS	87	45	-18.2 (*c* 5.03)
(*R,R*)-NORPHOS	95	6	-2.0 (*c* 5.04)
(*R*)-PROPHOS	96	3	-0.5 (*c* 5.04)
(*R*)-BINAP	93	94	-38.7 (*c* 5.07)

[a] Purified by preparative TLC. [b] Determined by HPLC (chiral OD, 15% *i*-PrOH in hexane).



(*S*)-TolBINAP (*R*)-BINAP (-)-DIOP (-)-MeDUPHOS (*R,R*)-NORPHOS (*R*)-PROPHOS

2.2.2.2 Enantiomeric excess and absolute configuration determination.

Enantiomeric excess of **2.42b** was determined by using HPLC on a Chriracel OD column using 15% isopropanol in *n*-hexane as the mobile phase. The chromatographic separation of racemic **2.42b,** on the chiral stationary phase produced a chromatogram with two peaks for the two enantiomers in a 1:1 ratio (Figure 2-2a). The chromatogram of **2.42b,** obtained by cyclization utilizing Pd/(*S*)-TolBINAP, showed a signal due to the predominant enantiomer with retention time corresponding to that of the first eluted enantiomer (Figure 2-2b).

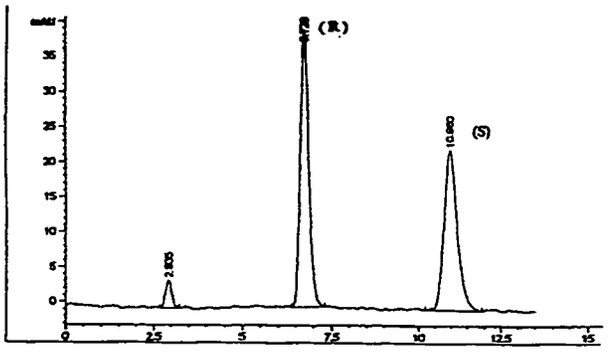


Figure 2-2a

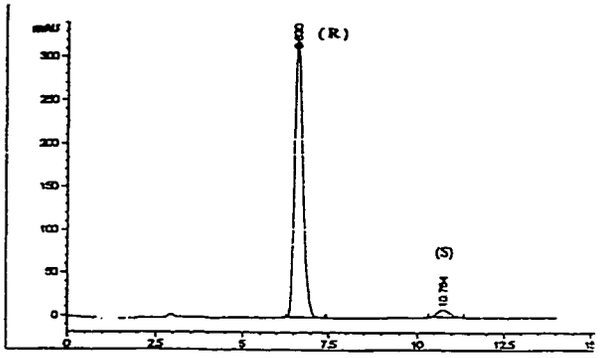


Figure 2-2b

Figure 2-2 Chromatograms shows the resolution of racemic **2.42b** (**Figure 2-2a**) and 94 %ee **2.42b** (**Figure 2-2b**) on chiral HPLC (Chiral OD, 15% *i*PrOH in hexane).

Absolute configuration of the major enantiomer was determined by utilizing single crystal X-ray diffraction analysis. The sample of *N*, 3-di(*p*-chlorophenyl)-4-vinyl-1,3-oxazolidin-2-imine, **2.42b**, can be readily obtained in purified form by preparative silica gel TLC followed by preparative HPLC. A single crystal of **2.42b** was obtained by using solvent layering technique. X-ray diffraction analysis of crystal of **2.42b** revealed it to possess (*R*) configuration. The molecular diagram of **2.42b** is shown in Figure 2-3.

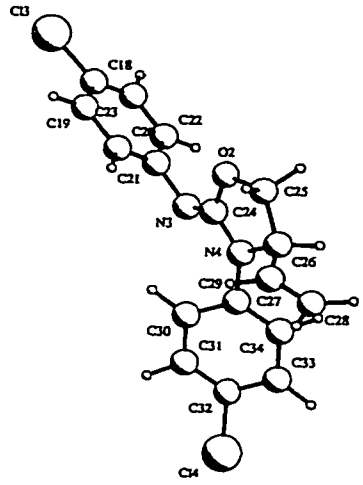
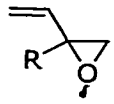


Figure 2-3 The molecular diagram of X-ray structure of 2.42b.

A series of other 4-vinyl-1,3-oxazolidines (eq 17) were similarly synthesized usually in high optical purity, by Pd(0)-TolBINAP catalyst which was generated in *situ* by reaction of 3 mol% of $Pd_2(dba)_3 \bullet CHCl_3$ with 2 equivalent of the bidentate ligand relative to palladium. The reaction mixtures were stirred in dry THF (under nitrogen) at room temperature until the full conversion of the heterocumulenes was observed (monitored by IR). The yields of the isolated products are shown in Table 2-4.

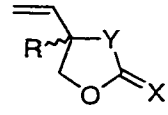


2.38
a: R =H
b: R =CH_3

+ X=C=Y

2.39 or **2.40**
2.39a: X = O, Y = C_6H_4N
2.39b: X =O, Y = *p*-ClC_6H_4N
2.39c: X =O, Y = *p*-BrC_6H_4N
2.40a: X = Y = C_6H_4N
2.40b: X = Y = *p*-ClC_6H_4N
2.40c: X = Y = *p*-$CH_3C_6H_4N$
2.40d: X = Y = *p*-BrC_6H_4N
2.40e: X = Y = *p*-$CH_3OC_6H_4N$
2.40f: X = Y = *o*-$CH_3C_6H_4N$
2.40g: X = Y = 1-Naphthyl

3 mol%$Pd_2(dba)_3 \bullet CHCl_3$
6 mol% TolBINAP
THF, N_2



(eq 17)

2.41, X = O, Y = N-R'
2.42, X = Y = N-R"

Table 2-4 Asymmetric Cycloaddition of 2-Vinyloxiranes 2.38 with Isocyanates 2.39 or Symmetrical Carbodiimides 2.40 in the Presence of $Pd_2(dba)_3$·$CHCl_3$-TolBINAP as the Catalyst.[a]

Entry	2.38	2.39 or 2.40	TolBINAP[b]	products	yield(%)[c]	ee(%)[d]	$[\alpha]^{22}_D$ in $CHCl_3$
1	**2.38a**	**2.40a**	*S*	**2.42a**	98	93	+26.2 (*c* 5.04)
2	**2.38a**	**2.40b**	*S*	**2.42b**	95	94	+38.7 (*c* 5.04)
3	**2.38a**	**2.40c**	*S*	**2.42c**	98	93	+38.5 (*c* 5.11)
4	**2.38a**	**2.40d**	*S*	**2.42d**	84	94	+34.5 (*c* 1.99)
5	**2.38a**	**2.40e**	*S*	**2.42e**	88	88	+31.7 (*c* 2.99)
6	**2.38a**	**2.40f**	*S*	**2.42f**	98	84	+32.8 (*c* 5.03)
7	**2.38a**	**2.40f**	*R*	**2.42f**	98	88	-33.5 (*c* 5.26)
8	**2.38a**	**2.40g**	*R*	**2.42g**	60	89	-31.4 (*c* 4.08)
9	**2.38b**	**2.40a**	*R*	**2.42h**	87	91	-22.1 (*c* 2.80)
10	**2.38b**	**2.40b**	*S*	**2.42i**	98	69	+10.4 (*c* 5.17)
11	**2.38b**	**2.40c**	*S*	**2.42j**	63	84	+18.1 (*c* 2.26)
12	**2.38b**	**2.40e**	*S*	**2.42k**	98	75	+11.6 (*c* 2.06)
13	**2.38a**	**2.39b**	*R*	**2.41b**	94	43	-1.72 (*c* 4.66)
14	**2.38a**	**2.39c**	*S*	**2.41c**	99	49	+1.43 (*c* 3.49)

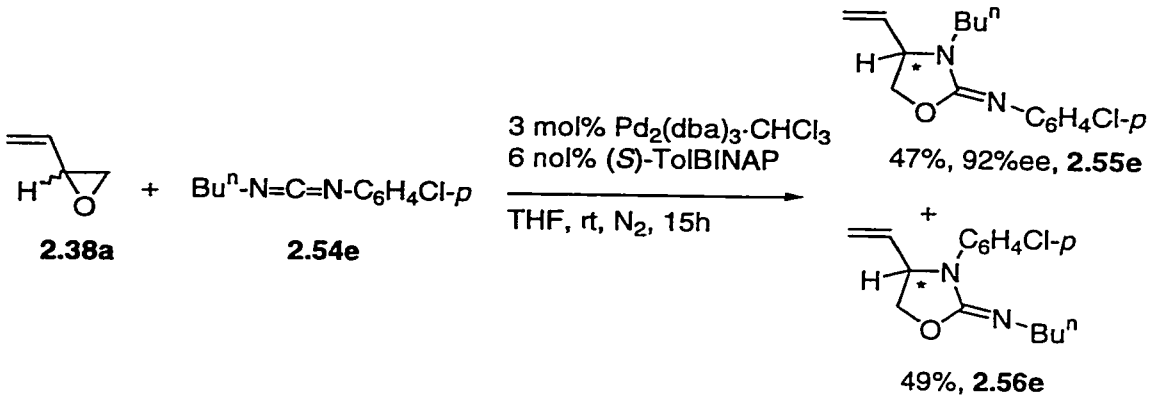
[a] Reaction conditions: **2.38** (1.5 mmol); **2.39** or **2.40** (1 mmol); $Pd_2(dba)_3$·$CHCl_3$ (0.03 mmol); Ligand (0.06 mmol);THF (5mL); room temperature, 15 h (unless otherwise noted), N_2 atmosphere. [b] yield of isolated product after silica gel TLC. [c] Determined by HPLC analysis using Chiracel OD, 15% *i*-PrOH in n-hexane. [d] Absolute configuration of major enantiomer is (*R*)-**2.42b** (see Figure 2-3). [e] Reaction time was 17 h. [f] Reaction time was 3days.

Attempts to improve the enantioselectivity of this reaction by introducing an *ortho* substituent such as a methyl group (Table 2-4, entries 6 and 7) on the phenyl ring of carbodiimides proved to be ineffective. The increased steric hindrance resulted in lower enantioselectivity. A naphthyl substituent on nitrogen nucleophile also failed to improve the optical yield of the product (entry 8).

2-Vinyloxirane (**2.38b**) having a methyl group at 2-position (entries 9–12) also provided products in lower %ee compared to that obtained from 2-vinyloxirane **2.38a** (R=H). Moreover, the cyclization proceeded at the lower rate.

2.2.2.3 Palladium-catalyzed asymmetric cycloaddition reaction of 2-vinyloxiranes with unsymmetrical carbodiimides (2.54) using TolBINAP ligand.

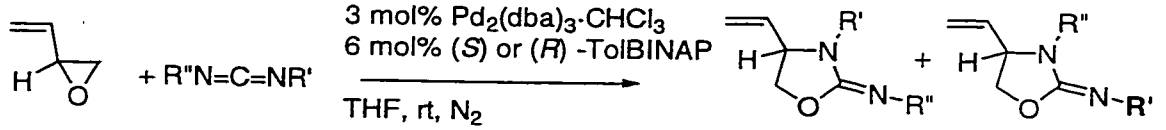
As previously noted, the cycloaddition reactions of 2-vinyloxiranes with symmetrical carbodiimides gave the highest enantioselectivities when TolBINAP was used as the chiral ligand. Impressive results were also realized in the asymmetric cycloaddition reaction of 2-vinyloxirane with unsymmetrical carbodiimides. We initially performed this reaction by using 1.5 mmol of **2.38a** and 1 mmol of **2.54e** (R′ = n-butyl, R″ = *p*-Cl-C_6H_4) in the presence of $Pd_2(dba)_3$•$CHCl_3$ (0.03 mmol) and (*S*)-TolBINAP (0.06 mmol) for 15 h in THF at room temperature (nitrogen atmosphere). After reaction, *N*-(*p*-chlorophenyl)-3-(*n*-butyl)-4-vinyl-1,3-oxazolidin-2-imine **2.55e** and *N*-(*n*-butyl)-3-*p*-chlorophenyl-4-vinyl-1,3-oxazolidin-2-imine **2.56e** were obtained in 96% isolated yield (**2.55e+2.56e**), with **2.55e** in 92 %ee (eq 18). The % enantiomeric excess of **2.55e** was determined by chiral HPLC using a Chiracel OD column and 15% *i*-PrOH in hexane as the eluant. The enantiomers of **2.56e** could not be resolved by the same column.



2.38a **2.54e** (eq 18)

The asymmetric cycloaddition of unsymmetrical carbodiimides (**2.54**) with 2-vinyloxirane (**2.38**) were successfully carried out by using the Pd(0)-TolBINAP catalyst system in THF and the results are summarized in Table 2-5. The catalyst was generated *in situ* by reaction of 3 mol% $Pd_2(dba)_3 \bullet CHCl_3$ with 2 equivalents of (*S*)-or (*R*)-TolBINAP relative to palladium. The reaction mixtures were stirred under an inert atmosphere at room temperature until the conversion of the carbodiimides was complete (monitored by IR). Remarkable results for the asymmetric induction were observed by employing carbodiimides **2.54** containing quite bulky alkyl substituents such as cyclohexyl [entries 1 (>99% ee of **2.55a**) and 4 (>99% ee of **2.55f**)] and *tert*-butyl [entry 2 (> 99% ee of **2.55c**)]. The enantiomers of each regioisomer of **2.55** were resolved by using HPLC with a chiral column (Chiracel OD) and a single signal was observed (using the same column and conditions) in the determination of the % enantiomeric excess of products from entries 1, 2 and 4. In addition, moderate to good enantiomeric selectivities were obtained from entries 3 (92-93% ee of **2.55e**), 5 (88% ee of **2.55i**) and 6 (94% ee of **2.55g**). When both substituents on the carbodiimides are of considerable effective steric bulk, the yield of the products are appreciably lower (entries 2, 5 and 6).

Table 2-5 Asymmetric Cycloadditions of 2-Vinyloxirane (2.38a) with Unsymmetrical Carbodiimides (2.54) in the Presence of $Pd_2(dba)_3.CHCl_3$-(*S*)-or (*R*)-TolBINAP.[a]



2.38a **2.54** **2.55** 2.56

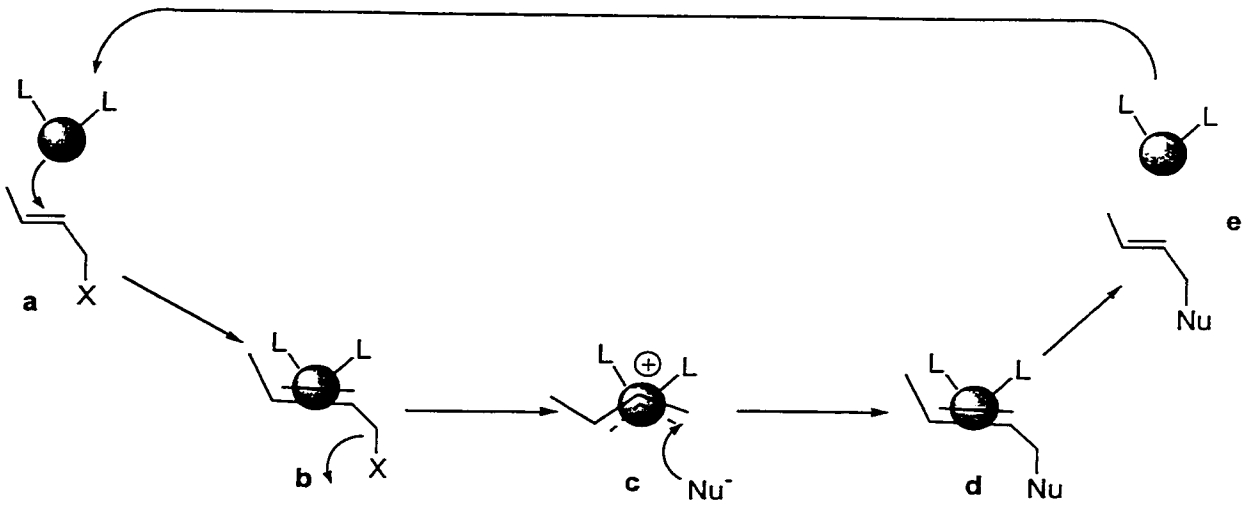
Entry	Carbodiimide, **2.54** **R"N=C=NR'**	Reaction time	Ratio of **2.55:2.56**[b]	Isolated yield of **2.55+2.56** (%)	%ee of **2.55**[d]	$[\alpha]^{22}_D$ of **2.55** in $CHCl_3$
1	$H_5C_6N=C=NC_6H_{11}$, **2.54a**	15h	4:1	94	>99	+18.9 (*c*, 2.74)[e]
2	$H_5C_6N=C=N^tC_4H_9$, **2.54c**	4 days	9:1	58	>99	+45.1 (*c*, 5.30)[e]
3	*p*-$ClH_5C_6N=C=N^nC_4H_9$, **2.54e**	15h	1:1	96	93	-75.8 (*c*, 5.15)[f]
4	*p*-$FH_4C_6N=C=NC_6H_{11}$, **2.54f**	15h	2:1	87	>99	-22.9 (*c*, 3.80)[f]
5	**2.54f**	15h	2:1	96	97	+21.9 (*c*, 2.74)[e]
6	2,6-$(CH_3)_2H_3C_6N=C=NC_6H_{11}$, **2.54g**	36h	3.5:1	55	88	+70.5 (*c*, 2.06)[e]
7	2,6-$(CH_3)_2H_3C_6N=C=NC_4H_9$, **2.54i**	36h	4:1	69	94	+27.9 (*c*, 1.80)[e]

[a] Reaction conditions : refer to the Experimental Section for the general procedure for the asymmetric cycloaddition. [b] Determined by GC. [c] Isolated by preparative TLC. [d] Enantiomeric excess determined by HPLC using a Chiracel OD column. [e] using (*S*)-TolBINAP. [f] using (*R*)-TolBINAP.

2.2.2.4 A possible Mechanism to Account for the Enantioselectivity of the reaction.

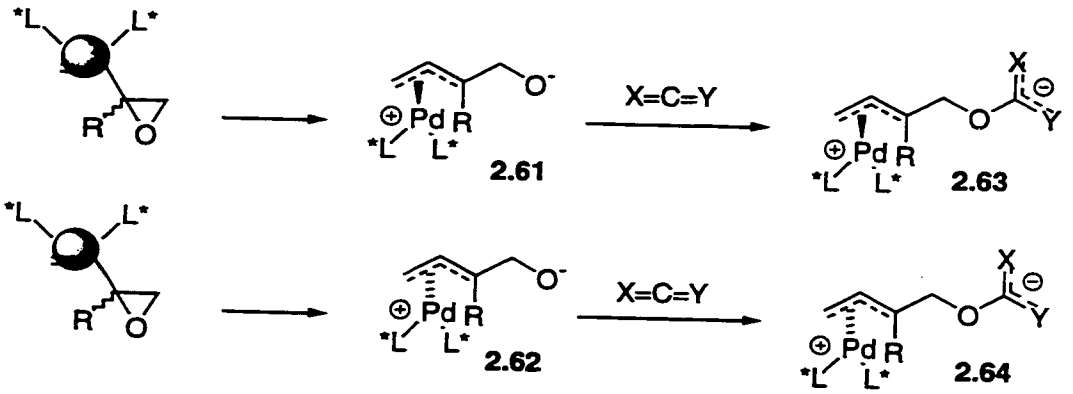
The general catalytic cycle for the enantiodiscrimination in palladium-catalyzed allylic addition by soft nucleophiles is composed of five primary steps (Scheme 2–11).[36,37] Theses steps are (a) metal-olefin complexation, (b) ionization, (c) enantioface discrimination of the π-allyl complex, (d) nucleophilic attack at the enantiotopic termini, and (e) decomplexation of the metal from the olefinic product.

Scheme 2-11



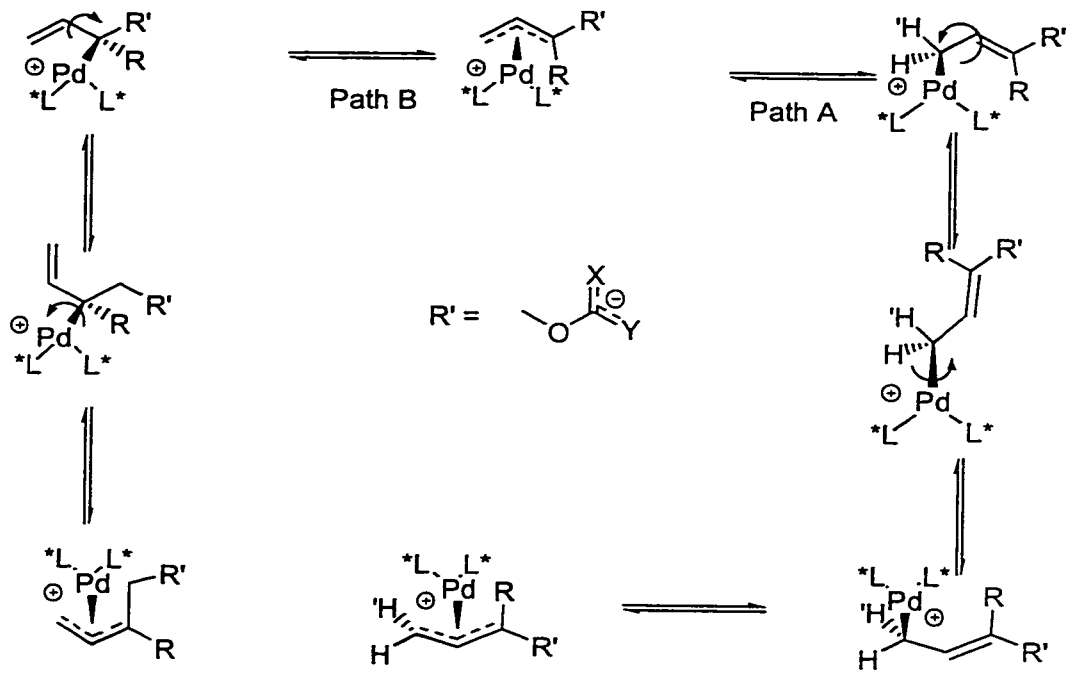
When a racemic 2-vinyloxiranes as the substrate, palladium catalyst can complex to the olefin part by either side, therefore, intermediates **2.61** and **2.62** would be formed after ionization step. The reaction of **2.61** and **2.62** with heterocumulenes resulted in the formation of π-allyl palladium intermediates **2.63** and **2.64** respectively (Scheme 2–12).

Scheme 2-12



• The π-allylic intermediates contain only the substitution at the 3-position of the coordinated π-allyl which can rapidly racemize via an η^3–η^1–η^3 (π–σ–π) mechanism.[46,50,58-64] The racemization process is shown in Scheme 2–13. Both σ–π intermediates are capable of inverting the olefin-face coordination by rotation about the carbon-carbon single bonds, but the two intermediates give two difference results. Path A involves inversion at the C-1 position with retention of *syn*-disposition of the R′ portion. Path B involves transfer R′ group to an anti-disposition but the chiral center retains its absolute configuration. Rearrangement via the more substituted end (path B) is slower than path A, since the former process involves the formation of a palladium-tertiary carbon bond, which should be disfavored, compared to the latter.[48,49,65-71] Enantioselection will be dictated by which face of the allylic fragment that the transition metal presents to the nucleophile.[51,72]

Scheme 2-13



The magnitude of steric interaction between nucleophile and allylic fragment could lead to the high stereoselectivity in the reaction. There are a number of studies showing the influence of the chiral ligand in a bond forming on the opposite of the allylic "plane" that separates the ligand and the trajectory of the nucleophile (Figure 2-4).[45,49,73-79]

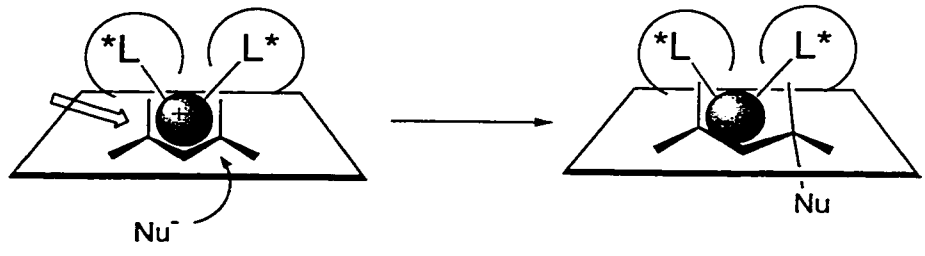
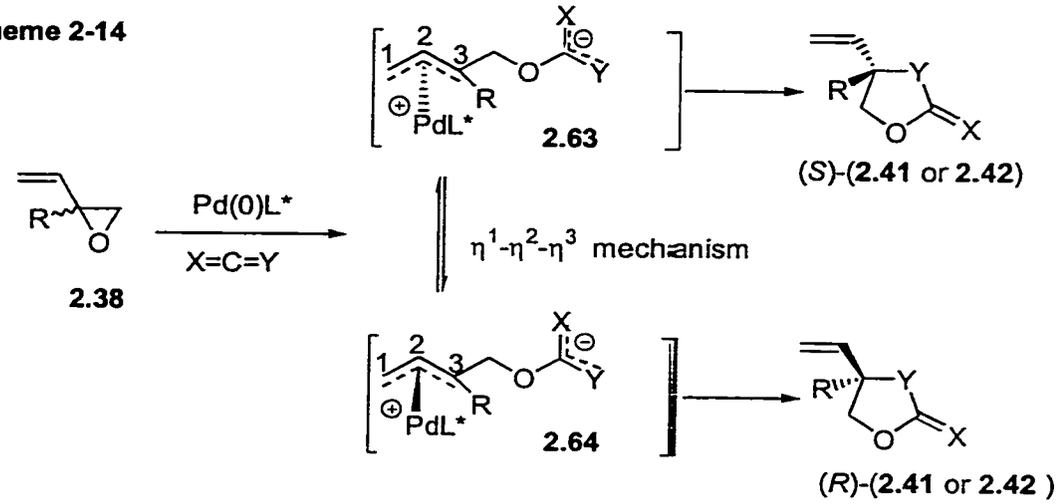


Figure 2-4 Steric interaction during nucleophilic addition.

In general high degree of asymmetric induction found in the cycloaddition reaction of 2-vinyloxirane with heterocumulenes can be explained by the pathway outlined in Scheme 2–14. Oxidative addition of a chiral phosphine palladium complex to racemic vinyloxirane **2.38** followed by heterocumulene interception affords the diastereomeric, π-allyl palladium complexes **2.63** and **2.64**. Attack of the nitrogen nucleophile (X=Y=NAr) at the C-3 carbon from the side opposite to palladium of **2.63** and **2.64** give the corresponding (*S*) and (*R*)-oxazolidine derivatives respectively.

The enantiodetermination step in this asymmetric cycloaddition is presumed to be the nucleophillic addition step since the asymmetric cyclization reactions of 2-butenylenedicarbamate in the presence of chiral phosphine ligands/Pd(0)[40] are believed to proceed via similar intermediates indicating that the interconversion between π-allyl palladium complexes **2.63** and **2.64** occurs via an η^3-η^1-η^3 mechanism[19] and is much faster than attack of the nitrogen nucleophile in the cyclization step (Scheme 2–14). Thus, one of the two intermediate complexes (**2.63** and **2.64**) reacts faster in the cyclization process than the other and consequently gives the major enantiomer. In the case of using (*S*)-TolBINAP as the chiral ligand, intermediate complex **2.64** reacts at a greater rate affording the (*R*)-enantiomer as a major product.

Scheme 2-14



4-Vinyl-1,3-oxazolidin-2-ones **2.41b** and **2.41d** (Table 2-4, entries 13 and 14) were obtained from reaction with isocyanates by employing an identical procedure to that used with carbodiimides. The %ee of these products is appreciably lower than those derived from carbodiimides which may suggest that TolBINAP has less influence in the steric interaction in the enantiodeterminating step.

The results from Tables 2-4 indicate that cycloaddition reactions of vinyloxirane to carbodiimides are influenced by not only the ligands, but also the structure of the reaction partners. In reaction with 2-vinyloxiranes, carbodiimides provide greater steric interaction between the substituent on nitrogen nucleophile of **2.63/2.64** and the substituent on the chiral phosphine ligands comparison with reaction using isocyanates, consequently, high % ee's resulted in using carbodiimides than isocyanates (See Figure 2-5).

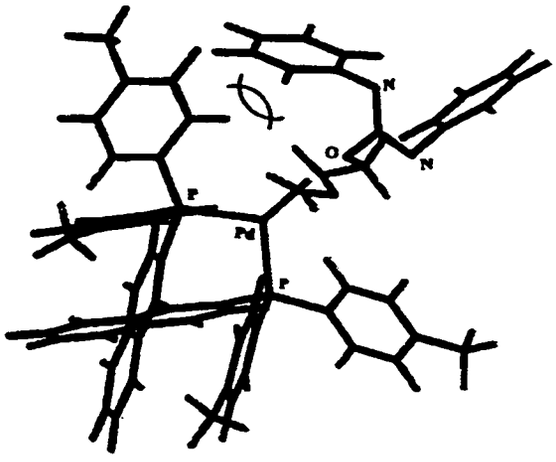


Figure 2-5a

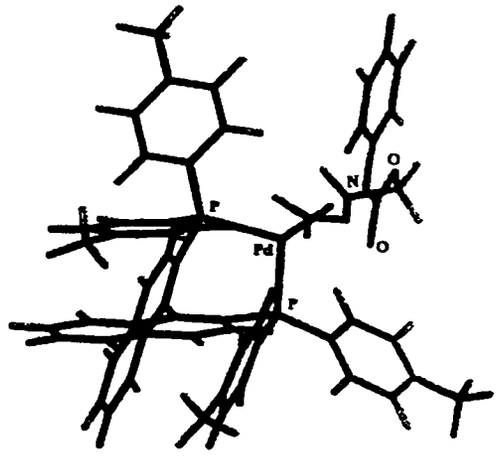
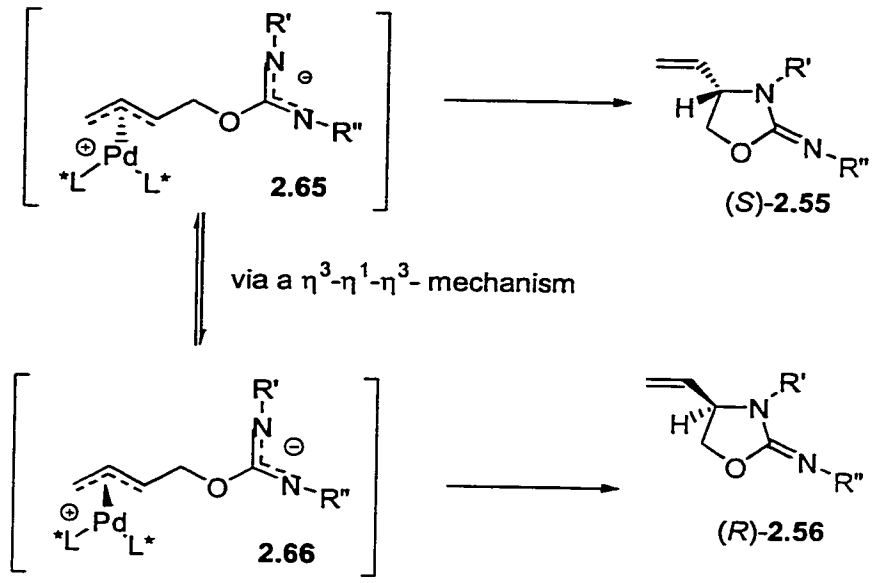


Figure 2-5b

Figure 2-5 Steric repulsion between the substituent on the nucleophilic nitrogen atom of the diphenylcarbodiimide unit and *p*-tolyl portion of the chiral phosphine ligand (Figure 2-5a). This repulsion has a strong influence on the stereoselectivity compared to that of phenyl isocyanate with the same chiral phosphine (Figure 2-5b).

The high %ee (upto > 99% ee), observed in the case of using unsymmetrical carbodiimides, could be accounted for by the pathway described for the symmetrical carbodiimides. A high degree of asymmetric induction presumably results from the kinetic enantioselection in the π-facial exchange step, reinforced by the steric interaction of bulky alkyl substitutents (such as cyclohexyl and *tert*-butyl) with chiral phosphine ligand during the cyclization step. Consequently, one of the intermediates reacts significantly faster than the other and thus accounts for the high enantomeric excess. In the experiment using (*S*)-TolBINAP as an added chiral ligand, intermedate (**2.66**) reacts at a greater rate than (**2.65**) and affords solely the (*R*)-enantiomer (Scheme 2–15).

Scheme 2-15



The assignment of absolute stereochemistry of the products obtained from the reaction of 2-vinyloxiranes with unsymmetrical carbodiimides was based on comparison of the sign of $[\alpha]^{22}_{D}$ with 4-vinyl-1,3-oxazolidin-2-imine products obtained previously from the reaction of 2-vinyloxiranes with symmetrical carbodiimides, and where the absolute configuration was based on crystallographic data. All (*R*)-enantiomers were eluted first from the chiral column.

2.2.2.5 Effect of reaction temperature on the enantioselectivity of the cycloaddition reaction.

It is known that the reaction temperature can have a pronounced effect on the enantioselectivity of a reaction.[80-82] To examine the dependence of the % ee on temperature,

vinyloxirane **2.38a** (R=H) was used in reaction with diphenylcarbodiimide **2.40a** or bis(*p*-chlorophenyl)carbodiimide **2.40b** affording the cycloadducts **2.42a** and **2.42b** respectively. Table 2-6 summarizes the effect of temperature on the asymmetric induction in the cycloaddition reaction.

Table 2-6 Effect of Temperature on the Pd-catalyzed Asymmetric Cycloaddition of 2-Vinyloxirane (2.38a) with Diphenylcarbodiimde (2.40a) or Bis(*p*-chlorophenyl) carbodiimide (2.40b) [a].

Reaction temperature (°C)	Reaction time (h)	2.42a			2.42b		
		yield(%)[b]	ee(%)[c]	$[\alpha]^{22}_D$ in $CHCl_3$	yield(%)[b]	ee(%)[c]	$[\alpha]^{22}_D$ in $CHCl_3$
100	1	93	90	+24.8 (*c* 5.05)	90	90	+35.0 (*c* 5.04)
80	2	95	90	+24.9 (*c* 5.01)	92	91	+35.2 (*c* 5.10)
rt[d]	15	98	93	+26.2 (*c* 5.04)	95	94	+38.7 (*c* 5.04)
10[e]	24	96	94	+26.8 (*c* 5.03)	85	94	+38.8 (*c* 5.00)
5[e]	36	98	91	+25.6 (*c* 5.04)	96	92	+36.0 (*c* 5.03)

[a] Refer to the Experimental Section for general procedure for determination of the effect of temperature on the cycloaddition reaction. [b] Isolated yield by preparative TLC.
[c] Enantiomeric excess determined by HPLC using Chiracel OD coulumn. [d] Approximately 22 °C.
[e] The reaction was performed in a Schlenk tube (N_2 atmosphere) inside a cold room.

2.3 Experimental Section

2.3.1 General comments

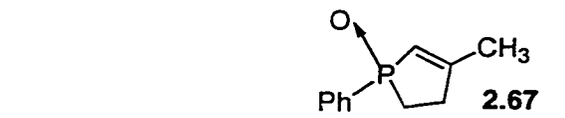
All NMR spectra were recorded using 200 and 300 MHz instruments. Infrared spectra were recorded on a Fourier transform spectrometer and are reported in wavenumbers (cm^{-1}). Mass spectra were obtained on a VG 7070E spectrometer. Optical rotations were measured using polarimeter at 22 °C. Melting points were measured on a Fisher-John apparatus and are uncorrected.

Enantomeric resolutions were achieved using a Hewlett Packard HPLC series II 1090 instrument equipped with an automatic injector, diode array detector monitoring at 220 nm. A Chiracel OD column was used with 85:15, n-hexane:2-propanol mixture was used as the mobile phase at a flow rate of 1 mL/min (oven temperature 30 °C).

2-Vinyloxiranes (**2.38a-b**) and $Pd(PPh_3)_4$ were purchased from Aldrich and were used as received. $Pd_2(dba)_3 \cdot CHCl_3$ was prepared according to literature procedures.[83] The organic solvents were dried and distilled prior to use.

2.3.2 Preparation of symmetrical carbodiimides (2.40a-g).

Diarylcarbodiimides were prepared refluxing the corresponding arylisocyanates in benzene in the presence of a catalytic amount of 3-methyl-1-phenylphospholene-1-oxide (**2.67**) as described in the literature (eq 19).[84]

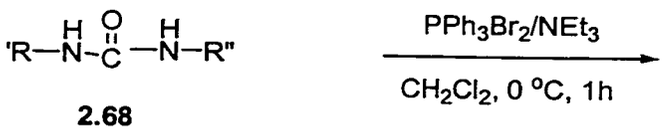


(eq 19)

Ar = Ph, *p*-Tolyl, *o*-Tolyl, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$NO_2C_6H_4$, *p*-$CH_3OC_6H_4$

2.3.3 Synthesis of unsymmetrical carbodiimides 2.54a-k.

Carbodiimides **2.54a-k** were prepared according to literature procedures[85] by dehydration of the appropriate urea (eq 20).



(eq 20)

The substituted urea (**2.68** ,8 mmol) was added portionwise during 60 min to a stirred suspension of bromotriphenylphosphonium bromide (10 mmol) and triethylamine (20 mmol) in dichloromethane (15 mL) at 0 °C. The resulting mixture was then washed with water and dried with anhydrous sodium sulfate. Evaporation of the solvent gave crude carbodiimide (**2.54**) which was distilled at reduced pressure to yield the desired unsymmetrical carbodiimide (**2.54**).

***N*-Cyclohexyl-*N'*-(phenyl)carbodiimide (2.54a)** (R'=C_6H_{11}, R"= C_6H_5): oily liquid; IR (C=N) 2116 cm^{-1}; ^{1}H-NMR($CDCl_3$ 200 MHz) δ = 1.20-2.20 (m, 10 H, CH_2-cyclohexyl), 3.45-

3.54 (m, 1H, C*H*-cyclohexyl), 7.05-7.39 (m, 5H, aromatic protons) ^{13}C-NMR ($CDCl_3$ 50 MHz) 24.34, 25.30, 34.91 (CH_2-cyclohexyl), 56.61 (C*H*-cyclohexyl), 123.31, 124.47, 129.30 (**C**H-aromatic ring), 136.01 (quaternary aromatic carbon), 140.88 (N=**C**=N) ppm.; MS (*m/e*) 200 $[M]^+$, HRMS Calcd for $C_{13}H_{16}N_2$: 200.1313 Found 200.1291.

***N*-(*n*-Butyl)-*N'*-(phenyl)carbodiimide (2.54b)** (R'= C_4H_9, R"= C_6H_5) : oily liquid; IR (C=N) 2134 cm^{-1}; ^{1}H-NMR($CDCl_3$ 200 MHz) δ = 0.98 (t, 3H, CH_3CH$_2$), 1.48-1.55 (m, 2H, CH$_3$CH_2), 1.60-1.75 (m, 2H, CH$_3$CH$_2$CH_2), 3.47 (t, 2 H, CH_2-N), 7.02-7.40 (m, 5H, aromatic protons); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 13.53 (**C**H$_3$CH$_2$), 19.91 (CH$_3$CH$_2$), 33.34 (CH$_3$CH$_2$CH$_2$), 46.47 (**C**H$_2$-N), 123.40, 124.48, 129.28 (**C**H-aromatic ring), 134.02 (quaternary aromatic carbon), 140.71 (N=**C**=N) ppm.; MS (m/e) 174 $[M]^+$, HRMS Calcd for $C_{11}H_{14}N_2$: 174.1157 Found 174.1164.

***N*-(*t*-Butyl)-*N'*-(phenyl)carbodiimide (2.54c)** (R'= C_4H_9, R"= C_6H_5) : oily liquid; IR (C=N) 2122 cm^{-1}; ^{1}H-NMR($CDCl_3$ 200 MHz) δ = 1.40 (s, 9 H, C(CH_3)$_3$), 7.02-7.36 (m, 5H, C*H*-aromatic protons) ; ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 31.57 (C(CH$_3$)$_3$), 57.34 (**C**(CH$_3$)$_3$), 123.24, 124.58, 129.34 (**C**H-aromatic ring), 134.02 (quaternary aromatic carbon), 140.90 (N=**C**=N) ppm.; MS (m/e) 174 $[M]^+$, HRMS Calcd for $C_{11}H_{14}N_2$: 174.1157 Found 174.1164.

***N*-Cyclohexyl-*N'*-(*p*-methoxyphenyl)carbodiimide (2.54d)** (R'= C_6H_{11}, R"= *p*-OCH$_3$-C$_6$H$_4$): oily liquid; IR (C=N) 2110 cm^{-1}; ^{1}H-NMR ($CDCl_3$ 200 MHz) δ = 1.28-2.10 (m, 10H CH_2-cyclohexyl), 3.48 (m, 1H, C*H*-cyclohexyl), 3.80 (s, 3H, *p*-CH_3OC$_6$H$_4$), 6.80-7.10 (m, 4H), C*H*-aromatic ring) ; ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 25.02, 25.95, 35.57 (**C**H$_2$-cyclohexyl), 56.09 (*p*-**C**H$_3$OC$_6$H$_4$), 57.24 (**C**H-cyclohexyl), 115.20, 124.78 (**C**H-aromatic ring), 128.99, 132.58 (quaternary aromatic carbons), 157.30 (N=**C**=N) ppm.; MS (m/e) 230 $[M]^+$, HRMS Calcd for $C_{14}H_{18}N_2O$: 230.1419 Found 230.1402.

***N*-(*n*-Butyl)-*N'*-(*p*-chlorophenyl)carbodiimide (2.54e)** (R'= C_4H_9, R"= *p*-Cl-C_6H_5): oily liquid; IR (C=N) 2138 cm^{-1}; ^{1}H-NMR($CDCl_3$ 200 MHz) δ = 0.93 (t, 3H, J = 7.4 Hz, C*H*$_3$CH$_2$), 1.32-1.52 (m, 2H, CH$_3$C*H*$_2$), 1.55-1.72 (m, 2H, CH$_3$CH$_2$C*H*$_2$), 3.40 (t, 2H, *J* = 6.7 Hz, C*H*$_2$-N), 6.96 (d, 2H, *J* = 8.5 Hz, C*H*-aromatic ring), 7.23 (d, 2H, *J* = 8.5 Hz, C*H*-aromatic ring); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 13.51 (**C**H$_3$CH$_2$), 19.90 (CH$_3$**C**H$_2$), 33.31 (CH$_3$CH$_2$**C**H$_2$), 46.43 (**C**H$_2$-N), 124.57, 129.32 (**C**H-aromatic ring), 129.61, 134.50 (quaternary aromatic carbons), 139.52 (N=**C**=N) ppm.; MS (m/e) 208 $[M]^+$, HRMS Calcd for $C_{14}H_{18}N_2O$: 208.0767 Found 208.0756.

***N*-Cyclohexyl-*N'*-(*p*-fluorophenyl)carbodiimide (2.54f)** (R'= C_6H_{11}, R"= *p*-F-C_6H_5): oily liquid; IR (C=N) 2131 cm^{-1}; ^{1}H-NMR ($CDCl_3$ 200 MHz) δ = 1.20-2.20 (m, 10H, C*H*$_2$-cyclohexyl), 3.30-3.48 (m, 1H, C*H*-cyclohexyl), 7.05-7.39 (m, 4H, C*H*-aromatic protons); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 24.32, 25.27, 34.89 (**C**H$_2$-cyclohexyl), 56.60 (**C**H-cyclohexyl), 115.84, 116.15, 124.35 (**C**H-aromatic ring), 136.79 (quaternary aromatic carbon), 158.12 (N=**C**=N), 161.34 (**C**-F) ppm.; MS (m/e) 218 $[M]^+$, HRMS Calcd for $C_{13}H_{15}FN_2$: 218.1219 Found 218.1229.

***N*-Cyclohexyl-*N'*-(2, 6-dimethylphenyl)carbodiimide (2.54g)** (R'= C_6H_{11}, R"= 2, 6-(CH$_3$)$_2$-C_6H_3): oily liquid; IR (C=N) 2128 cm^{-1}; ^{1}H-NMR($CDCl_3$ 200 MHz) δ = 1.23-2.10 (m, 10H, C*H*$_2$-cyclohexyl), 2.45 (s, 6H, 2,6-(C*H*$_3$)$_2$-C_6H_3), 3.30-3.48 (m, 1H, C*H*-cyclohexyl), 6.89-7.04 (m, 3H, aromatic protons); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 18.99, 24.47, 25.38 (**C**H$_2$-cyclohexyl), 34.62 (2,6-(**C**H$_3$)$_2$-C_6H_3), 56.15 (**C**H-cyclohexyl), 123.93, 128.03 (**C**H-aromatic ring), 132.25, 136.95 (quaternary aromatic carbon), 159.78 (N=**C**=N) ppm. MS (m/e) 228 $[M]^+$, HRMS Calcd for $C_{15}H_{20}N_2$: 228.1626 Found 228.1637.

***N*-Ethyl-*N'*-(*p*-tolyl)carbodiimide (2.54h)** (R'= C_2H_5, R"= *p*-$CH_3C_6H_4$): oily liquid; IR (C=N) 2132 cm^{-1}; ^{1}H-NMR ($CDCl_3$ 200 MHz) δ = 1.35 (t, 3H, CH_3CH_2), 2.32 (s, 3H, *p*-$CH_3C_6H_4$), 3.48 (q, 2H, CH_3CH_2), 6.98-7.15 (m, 4H, aromatic protons); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 16.97 (CH_3CH_2), 20.88 (*p*-$CH_3C_6H_4$), 41.86 (CH_3CH_2), 123.17, 129.89 (CH-aromatic ring), 134.32 (quaternary aromatic carbon), (N=C=N) ppm. MS (m/e) 160 $[M]^+$, HRMS Calcd for $C_{10}H_{12}N_2$: 160.1000 Found 160.1012.

***N*-*n*-Butyl-*N'*-(2,6-dimethylphenyl)carbodiimide (2.54i)** (R'= C_4H_9, R"= 2,6-$(CH_3)_2C_6H_3$): oily liquid; IR (C=N) 2147 cm^{-1}; ^{1}H-NMR ($CDCl_3$ 200 MHz) δ = 0.94 (t, 3H, *J* = 7.2 Hz, CH_3CH_2), 1.40-1.53 (m, 2H, $CH_3CH_2CH_2$), 1.55-1.72 (m, 2H, $CH_3CH_2CH_2$), 2.40 (s, 6H, 2,6-$(CH_3)_2C_6H_3$), 3.36 (t, 2H, *J* = 6.7 Hz, CH_2-N), 6.94-7.02 (m, 3H, aromatic protons); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 13.60 ($CH_3CH_2CH_2$), 18.89 ($CH_3CH_2CH_2$), 20.02 ($CH_3CH_2CH_2$), 33.19 (2,6-$(CH_3)_2C_6H_3$), 46.47 (CH_2-N), 123.99, 128.07 (CH-aromatic rings), 128.20, 132.16, 136.96 ppm. MS (m/e) 202 $[M]^+$, HRMS Calcd for $C_{13}H_{18}N_2$: 202.1470 Found 202.1441.

***N*-Phenyl-*N'*-(*p*-chlorophenyl)carbodiimide (2.54j)** (R'= C_6H_5, R"= *p*-ClC_6H_4): IR (C=N) 2140 cm^{-1}; ^{1}H-NMR($CDCl_3$ 200 MHz) δ = 7.01-7.45 (m, 9H, aromatic protons); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 124.17, 124.26, 125.33, 125.42, 125.58, 125.83, 129.49, 129.55, 129.61 (CH-aromatic rings), 138.39 (N=C=N) ppm MS (m/e) 228 $[M]^+$, HRMS Calcd for $C_{13}H_9ClN_2$: 228.0454 Found 228.0478.

***N*-Phenyl-*N'*-*p*-tolyl-carbodiimide (2.54k)** (R'= C_6H_5, R"= *p*-$CH_3C_6H_4$) : IR (C=N) 2128 cm^{-1}; ^{1}H-NMR($CDCl_3$ 200 MHz) δ = 2.35 (s, 3H, *p*-$CH_3C_6H_4$), 7.01-7.39 (m, 9H, aromatic protons); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 20.97 (*p*-$CH_3C_6H_4$), 123.95, 124.17, 125.50, 129.49, 130.05, 133.58, 133.84, 135.42, 138.71 (N=C=N) ppm MS (m/e) 208 $[M]^+$, HRMS Calcd for $C_{14}H_{12}N_2$: 208.1000 Found 208.0985.

2.3.4 General procedure for the cycloaddition reaction of vinyloxiranes with isocyanates or carbodiimides catalyzed by palladium-achiral phosphine complex.

A mixture of $Pd(PPh_3)_4$ (0.03 mmol), PPh_3 (0.06 mmol) and THF (3 mL) was stirred at room temperature for 30 min. 2-Vinyloxirane (**2.38,** 1.5 mmol) and 1 mmol of heterocumulene (**2.39** or **2.40**) were added, and the mixture was stirred under nitrogen for 15 h at room temperature. The light yellow homogeneous solution was then concentrated by rotary evaporation and the residue was purified by silica gel TLC using 1:1 pentane/ether as the developer.

***N*-Phenyl-4-vinyl-1,3-oxazolidin-2-one (2.41a)[23,40]:** (R = H, X = O, Y = C_6H_5N): mp = 55-56 °C; IR (C=O) 1753 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 200 MHz) 4.15 (dd, 1H, J = 8.6 and 6.0 Hz, C*H*$_2$–O), 4.60 (dd, 1H, J = 8.6 and 8.6 Hz, C*H*$_2$–O), 4.66-4.77 (m, 1H, C*H*–N), 5.11-5.24 (m, 2H, C*H*$_2$=CH), 5.53-5.71 (m, 1H, CH$_2$=C*H*), 7.10-7.50 (m, 5H, aromatic protons); ^{13}C–NMR ($CDCl_3$, 50 MHz) 59.73 (**C**H–N), 67.66 (**C**H$_2$–O), 129.84 (**C**H$_2$=CH), 121.86, 125.32, 129.43 (CH-aromatic ring), 135.25 (CH$_2$=**C**H), 137.69 (quaternary aromatic carbon), 156.22 (**C**=O); MS (*m/e*) 189 $[M]^+$.

***N*-(*p*-Chlorophenyl)-4-vinyl-1,3-oxazolidin-2-one (2.41b):** (R = H, X = O, Y = *p*-ClC_6H_4N) : mp = 45-46 °C; IR (C=O) 1754 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 200 MHz) 3.98 (dd, 1H, J = 8.6 and 6.2 Hz, C*H*$_2$–O), 4.47 (dd, 1H, J = 8.6 and 8.6 Hz, C*H*$_2$–O), 4.70-4.81 (m, 1H, C*H*–N), 5.19-5.30 (m, 2H, C*H*$_2$=CH), 5.625.75 (m, 1H, CH$_2$=C*H*), 7.15-7.40 (m, 4H, aromatic protons); ^{13}C–NMR ($CDCl_3$, 50 MHz) 59.78 (**C**H–N), 67.70 (**C**H$_2$–O), 121.30 (**C**H$_2$=CH), 122.0, 129.67, (CH-aromatic ring) 134.87 (CH$_2$=**C**H), 130.40, 136.29 (quaternary aromatic

carbons), 155.98 (C=O); MS (*m/e*) 223 $[M]^+$, 225 $[M+2]^+$. Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26 Found: C, 58.93; H, 4.18; N, 6.55.

***N*-(*p*-Chlorophenyl)-4-methyl-4-vinyl-1,3-oxazolidin-2-one (2.41c)** : (R = CH_3, X = O, Y = *p*-ClC_6H_4N) : mp = 75-76 °C; IR (C=O) 1752 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 200 MHz) 1.42 (s, 3H, C*H*$_3$), 4.20 (d, 1H, *J* = 8.5 Hz, C*H*$_2$–O), 4.23 (d, 1H, *J* = 8.5 Hz, C*H*$_2$–O), 5.25 (d, 2H, *J* = 17.4 Hz, C*H*$_2$=CH), 5.35 (d, 2H, *J* = 10.6 Hz, C*H*$_2$=CH), 6.05 (dd, 1H, *J* = 10.6 and 10.6 Hz, CH$_2$=C*H*), 7.20-7.40 (m, 4H, aromatic protons); ^{13}C–NMR ($CDCl_3$, 50 MHz) 21.73 (CH_3), 64.18 ((CH$_3$)C–N), 74.84 (CH_2–O), 118.11 (CH_2=CH), 128.57, 129.67 (CH-aromatic ring), 133.06, 134.66 (quaternary aromatic carbons), 139.75 (CH_2=CH), 156.92 (C=O); MS (*m/e*) 237 $[M]^+$, 239 $[M+2]^+$. Anal. Calcd for $C_{12}H_{12}ClNO_2$: C, 60.64; H, 5.09; N, 5.89 Found: C, 6.32; H, 4.88; N, 6.01.

***N*-(*p*-Bromophenyl)-4-vinyl-1,3-oxazolidin-2-one (2.41d):** (R = H, X = O, Y = *p*-BrC_6H_4N) : mp = 68-69 °C; IR (C=O) 1753 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 200 MHz) 3.99 (dd, 1H, *J* = 8.6 and 6.0 Hz, C*H*$_2$–O), 4.49 (dd, 1H, *J* = 8.6 and 8.6 Hz, C*H*$_2$–O), 4.70-4.81 (m, 1H, C*H*–N), 5.21-5.31 (m, 2H, C*H*$_2$=CH), 5.59-5.76 (m, 1H, CH$_2$=C*H*), 7.20-7.40 (m, 4H, aromatic protons); ^{13}C–NMR ($CDCl_3$, 50 MHz) 59.74 (CH–N), 67.71 (CH_2–O), 121.38 (CH_2=CH), 123.26, 132.41 (CH-aromatic ring), 134.85 (CH_2=CH), 118.24, 136.79 (quaternary aromatic carbons), 155.92 (C=O); MS (*m/e*) 267 $[M]^+$, 269 $[M+2]^+$. Anal. Calcd for $C_{11}H_{10}BrNO_2$: C, 49.28; H, 3.76; N, 5.22 Found: C, 49.25; H, 3.76; N, 5.31.

***N*, 3-Di(phenyl)-4-vinyl-1,3-oxazolidin-2-imine (2.42a):** (R = H, X = C_6H_4N, Y = C_6H_4N) : mp = 58-59 °C; IR (C=N) 1678 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 200 MHz) 4.06 (dd, 1H, *J* = 8.3 and 5.9 Hz, C*H*$_2$–O), 4.45 (dd, 1H, *J* = 8.3 and 8.3 Hz, C*H*$_2$–O), 4.68-4.78 (m, 1H, C*H*–N), 5.35-5.46 (m, 2H, C*H*$_2$=CH), 5.76-5.94 (m, 1H, CH$_2$=C*H*), 7.10-7.75 (m, 8H, aromatic

protons); ^{13}C–NMR ($CDCl_3$, 50 MHz) 61.07 (**C**H–N), 70.02 (**C**H_2–O), 120.60 (**C**H_2=CH), 122.60, 123.22, 124.23, 124.63, 129.36, 129.44 (CH-aromatic ring), 135.69 (CH$_2$=**C**H), 139.39, 148.28 (quaternary aromatic carbons), 150.65 (**C**=N); MS (*m/e*) 264 $[M]^+$.

***N*, 3-Di(*p*-chlorophenyl)-4-vinyl-1,3-oxazolidin-2-imine (2.42b)** (R = H, X = *p*-ClC_6H_4N, Y = *p*-ClC_6H_4N): mp = 95-96 °C; IR (C=N) 1677 cm^{-1}, ^{1}H–NMR ($CDCl_3$, 200 MHz) 4.07 (dd, 1H, *J* = 8.3 and 6.0 Hz, C*H*$_2$–O), 4.45 (dd, 1H, *J* = 8.3 and 8.3 Hz, C*H*$_2$–O), 4.67-4.78 (m, 1H, C*H*–N), 5.31-5.40 (m, 2H, C*H*$_2$=CH), 5.68-5.86 (m, 1H, CH$_2$=C*H*), 7.00-7.75 (m, 8H, aromatic protons); ^{13}C–NMR ($CDCl_3$, 50 MHz) 61.17 (**C**H–N), 70.05 (**C**H_2–O), 121.22 (**C**H_2=CH), 123.92, 125.40, 129.15, 129.36 (CH-aromatic ring), 128.19, 129.92, 137.49, 146.28, (quaternary aromatic carbons), 134.98 (CH$_2$=**C**H), 150.62 (**C**=N); MS (*m/e*) 332 $[M]^+$, 336 $[M+2]^+$. Anal. Calcd for $C_{17}H_{14}Cl_2N_2O$: C, 61.28; H, 4.23; N, 8.41 Found: C, 61.43; H, 4.05; N, 8.38.

***N*, 3-Di(*p*-tolyl)-4-methyl-4-vinyl-1,3-oxazolidin-2-imine (2.42h)** (R= CH_3, X = *p*-$CH_3C_6H_4N$, Y = *p*-$CH_3C_6H_4N$): mp = 136-137 °C; IR (C=N) 1672 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 200 MHz) 1.37 (s, 3H, (C*H*$_3$)C–N), 2.20 (s, 3H, *p*-C*H*$_3$C$_6$H$_4$N), 2.27 (s, 3H, *p*-C*H*$_3$C$_6$H$_4$N), 4.12 (d, 1H, *J* = 8.2 Hz, C*H*$_2$–O), 4.27 (d, 1H, *J* = 8.2 Hz, C*H*$_2$–O), 5.15 (d, 1H, *J* = 17.4 Hz, C*H*$_2$=CH), 5.22 (d, 1H, *J* = 10.6 Hz, C*H*$_2$=CH), 6.00 (dd, 1H, *J* = 17.4 and 10.6 Hz, CH$_2$=C*H*), 6.80-7.30 (m, 8H, aromatic protons); ^{13}C–NMR ($CDCl_3$, 50 MHz) 20.67 ((**C**H$_3$)C–N), 20.81 (*p*-**C**H$_3$C$_6$H$_4$N), 21.05 (*p*-**C**H$_3$C$_6$H$_4$N), 64.05 ((CH$_3$)**C**–N), 76.21 (**C**H$_2$–O), 116.86 (**C**H$_2$=CH), 123.23, 127.91, 128.94, 129.46 (CH-aromatic ring), 131.53, 133.77, 136.47, 144.59 (quaternary aromatic carbons), 139.69 (CH$_2$=**C**H), 152.09 (**C**=N); MS (*m/e*) 306 $[M]^+$, Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.13; H, 7.26; N, 9.12.

2.3.5 General procedure for the cycloaddition reaction of vinyloxiranes with unsymmetrical carbodiimides catalyzed by palladium-achiral phosphine complex.

A mixture of $Pd(PPh_3)_4$ (0.03 mmol), PPh_3 (0.06 mmol) and THF (3 mL) was stirred under nitrogen at room temperature for 30 min. Vinyloxirane **2.38** (1.5 mmol) and unsymmetrical carbodiimide **2.54** (1 mmol) were added to the solution. The mixture was then stirred under nitrogen at room temperature until the conversion of the carbodiimide was complete (monitored by the shift of the IR-absorption of the C=N band in the free carbodiimide (~ 2100 cm^{-1}) to that of the oxazolidine (1670-1690 cm^{-1}). The light yellow homogeneous solution was then concentrated by rotary evaporation and the residue was purified by silica gel TLC using pentane/ether mixture as the developer.

***N*-Phenyl-3-cyclohexyl-4-vinyl-1,3-oxazolidin-2-imine (2.55a)** (R = H, R′ = C_6H_{11}, R″= C_6H_5); IR (C=N) 1675 cm^{-1}; ^{1}H-NMR ($CDCl_3$ 200 MHz) δ 0.95-2.05 (m, 10H, C*H*$_2$-cyclohexyl), 3.75-3.98 (m, 2H, C*H*-cyclohexyl and C*H*$_2$–O), 4.20-4.38 (m, 2H, C*H*$_2$–O and C*H*–N), 5.18–5.34 (m, 2H, C*H*$_2$=CH), 5.75-5.93 (m, 1H, C*H*$_2$=CH), 6.90-7.35 (m, 5H, aromatic protons); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 25.61, 25.82, 25.94, 29.55, 31.69 (CH_2-cyclohexyl), 54.30 (CH-cyclohexyl), 58.38 (CH–N), 69.54 (CH_2–O), 118.15 (CH_2=CH), 121.74, 123.37, 128.35 (CH-aromatic ring), 138.16 (CH_2=CH), 148.13 (quaternary aromatic carbon),152.38 (C=N) ppm.; MS (*m/e*) 270 $[M]^+$, Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36 Found: C, 75.53; H, 8.37; N, 10.38.

***N*-Cyclohexyl-3-phenyl-4-vinyl-1,3-oxazolidin-2-imine (2.56a)** (R = H, R′ = C_6H_{11}, R″= C_6H_{15}): oily liquid; IR (C=N) 1673 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.10-2.00 (m, 10H, C*H*$_2$-cyclohexyl), 3.40-3.59 (m, 1H, C*H*-cyclohexyl) 4.03 (dd, 1H, *J* = 8.1 and 4.7 Hz, C*H*$_2$–O),

4.42 (dd, 1H, J = 8.1 and 8.1 Hz, CH_2–O), 4.65 (m, 1H, CH–N), 5.25-5.39 (m, 2H, CH_2=CH), 5.76-5.93 (m, 1H, CH$_2$=CH), 6.95-7.70 (m, 5H, CH-aromatic); ^{13}C-NMR ($CDCl_3$ 75MHz) δ 25.56, 25.89, 29.45, 31.66, (CH_2-cyclohexyl), 54.18 (CH-cyclohexyl), 58.27 (CH–N), 69.42 (CH_2–O), 118.01 (CH_2=CH), 113.64, 123.96, 141.25 (CH-aromatic ring), 138.17 (CH_2=CH), 152.29 (quaternary aromatic carbon), 154.53 (C=N) ppm.; MS (*m/e*) 270 $[M]^+$, HRMS. Calcd for $C_{17}H_{22}N_2O$: 270.1732 Found: 270.1725.

***N*-Phenyl-3-(*n*-butyl)-4-vinyl-1,3-oxazolidin-2-imine (2.55b)** (R = H, R′ = C_4H_9, R″= C_6H_5): oily liquid; IR (C=N) 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, CH_3CH$_2$), 1.28-1.65 (m, 4H, CH$_3$CH_2CH_2), 3.02-3.17 (m, 2H, CH_2–N), 3.99 (dd, 1H, J = 8.0 and 7.2 Hz, CH_2–O), 4.23 (dd, 1H, J = 15.6 and 7.7 Hz, CH–N), 4.45 (dd, 1H, J = 8.0 and 8.0 Hz, CH_2–O), 5.30-5.42 (m, 2H, CH_2=CH), 5.65-5.82 (m, 1H, CH$_2$=CH), 6.90-7.30 (m, 5H, CH-aromatic); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 13.89 (CH_3CH_2), 20.06 (CH_3CH_2), 28.91 ($CH_3CH_2CH_2$), 42.52 (CH_2–N), 60.25 (CH–N), 69.27 (CH_2–O), 120.57 (CH_2=CH), 121.89, 123.40, 128.43 (CH-aromatic), 135.23 (CH_2=CH), 147.94 (quaternary aromatic carbon), 152.64 (C=N) ppm.; MS (*m/e*) 244 $[M]^+$, HRMS. Calcd for $C_{15}H_{20}N_2O$: 244.1576 Found: 244.1567.

***N*-(*n*-Butyl)-3-phenyl-4-vinyl-1,3-oxazolidin-2-imine (2.56b)** (R = H, R′ = C_4H_9, R″= C_6H_5): oily liquid; IR (C=N) 1697 cm^{-1}; ^{1}H-NMR ($CDCl_3$ 200 MHz) δ 0.94 (t, 3H, CH_3CH$_2$), 1.26-1.63 (m, 4H, CH$_3$CH_2CH_2), 3.24-3.34 (m, 2H, CH_2–N), 4.02 (dd, 1H, J = 8.1 and 5.4 Hz, CH_2–O), 4.45 (m, 1H, CH_2–O), 4.66 (m, 1H, CH–N), 5.25-5.40 (m, 2H, CH_2=CH), 5.70-5.90 (m, 1H, CH$_2$=CH), 6.97-7.04 (m, 1H, CH-aromatic), 7.25-7.35 (m, 2H, CH-aromatic), 7.54-7.59 (m, 2H, CH-aromatic); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 14.04 (CH_3CH_2), 20.66 ($CH_3CH_2CH_2$), 33.84 ($CH_3CH_2CH_2$), 46.47 (CH_2CH_2–N), 60.31 (CH–N), 68.62 (CH_2–O), 119.07 (CH_2=CH), 120.74, 122.74, 128.48 (CH-aromatic), 135.53 (CH_2=CH), 139.48

(quaternary aromatic carbon), 150.01 (C=N) ppm.; MS (*m/e*) 244 $[M]^+$, HRMS. Calcd for $C_{15}H_{20}N_2O$: 244.1576 Found: 244.1587.

***N*-Phenyl-3-(*t*-butyl)-4-vinyl-1,3-oxazolidin-2-imine (2.55c)** (R = H, R′ = C_4H_9, R″= C_6H_5): oily liquid; IR (C=N) 1670 cm^{-1}; ^1H NMR ($CDCl_3$ 200 MHz) δ 1.53 (s, 9H, $C(CH_3)_3$), 3.86-3.90 (m, 1H, CH_2–O), 4.18-4.39 (m, 2H, CH_2–O and CH–N), 5.17-5.30 (m, 2H, CH_2=CH), 5.92-6.11 (m, 1H, CH_2=CH), 6.88-7.04 (m, 3H, CH-aromatic) 7.17-7.27 (m, 2H, CH-aromatic); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 28.04 ($C(CH_3)_3$), 54.33 ($C(CH_3)_3$), 59.56 (CH–N), 69.58 (CH_2–O), 116.83 (CH_2=CH), 121.44, 123.25, 128.32 (CH-aromatic), 138.82 (CH_2=CH), 148.39 (quaternary aromatic carbon), 149.98 (C=N) ppm.; MS (*m/e*) 244 $[M]^+$, HRMS. Calcd for $C_{15}H_{20}N_2O$: 244.1576 Found: 244.1575.

***N*-(*t*-Butyl)-3-phenyl-4-vinyl-1,3-oxazolidin-2-imine (2.56c)** (R = H, R′ = C_4H_9, R″= C_6H_5): oily liquid; IR (C=N) 1695 cm^{-1}; ^1H-NMR ($CDCl_3$ 200 MHz) δ 1.30 (s, 9H, $C(CH_3)_3$), 4.00 (dd, 1H, *J* = 8.0 and 4.6 Hz, CH_2–O), 4.39 (dd, 1H, 1H, *J* = 8.0 and 8.0 Hz, CH_2–O), 4.53-4.65 (m, 1H, CH–N), 5.24-5.38 (m, 2H, CH_2=CH), 5.74-5.90 (m, 1H, CH_2=CH), 6.92-7.00 (m, 1H, CH-aromatic), 7.22-7.30 (m, 2H, CH-aromatic), 7.60-7.67 (m, 2H, CH-aromatic); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 30.68 ($C(CH_3)_3$), 52.31 ($C(CH_3)_3$), 59.11 (CH–N), 68.46 (CH_2–O), 118.46 (CH_2=CH), 119.81, 121.94, 128.20 (CH-aromatic), 135.87 (CH_2=CH), 140.09 (quaternary aromatic carbon), 146.74 (C=N) ppm.; MS (*m/e*) 244 $[M]^+$, HRMS. Calcd for $C_{15}H_{20}N_2O$: 244.1576 Found: 244.1577.

***N*-(*p*-Methoxyphenyl)-3-cyclohexyl-4-vinyl-1,3-oxazolidin-2-imine (2.55d)** (R = H, R′ = C_6H_{11}, R″= *p*-$(CH_3O)C_6H_4$): oily liquid; IR (C=N) 1672 cm^{-1}; ^1H NMR ($CDCl_3$ 200 MHz) δ 0.95-2.00 (m, 10H, CH_2-cyclohexyl), 3.67-3.92 (m, 4H, *p*-$(CH_3O)C_6H_4$ and CH_2–O), 4.22-4.36 (m, 2H, CH_2–O and CH–N), 5.28 (d, 1H, *J* =14.3 Hz, CH_2=CH), 5.31 (d, 1H, *J* = 21.5

Hz, C*H*$_2$=CH), 5.75-5.93 (m, 1H, CH$_2$=C*H*), 6.75-7.03 (m, 4H, C*H*-aromatic) ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 25.68, 25.87, 26.00, 29.58, 31.80 (**C**H$_2$-cyclohexyl), 54.31 (**C**H-cyclohexyl), 55.41 (*p*-(**C**H$_3$O)C$_6$H$_4$), 58.42 (**C**H–N), 69.55 (**C**H$_2$–O), 113.78, 124.05 (**C**H-aromatic), 118.11 (**C**H$_2$=CH), 138.11 (CH$_2$=**C**H), 141.35, 152.45 (quaternary aromatic carbon), 154.66 (**C**=N) ppm.; MS (*m/e*) 300 $[M]^+$, 299 $[M-1]^+$ HRMS. Calcd for $C_{18}H_{24}N_2O_2$: 300.1838 Found: 300.1851.

***N*-Cyclohexyl-3-*p*-methoxyphenyl-4-vinyl-1,3-oxazolidin-2-imine (2.56d)** (R = H, R′ = C_6H_{11}, R″= *p*-(CH$_3$O)C$_6$H$_4$): oily liquid; IR (C=N) 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 1.10-1.85 (m, 10H, C*H*$_2$-cyclohexyl), 3.35-3.50 (m, 1H, C*H*-cyclohexyl), 3.78 (s, 3H, *p*-(C*H*$_3$O)C$_6$H$_4$), 3.99 (dd, 1H, *J* = 7.9 and 5.6 Hz, C*H*$_2$–O), 4.41 (dd, 1H, *J* = 7.9 and 7.9 Hz, C*H*$_2$–O), 4.45-4.55 (m, 1H, C*H*–N), 5.23 (d, 1H, *J* = 4.4 Hz, C*H*$_2$=CH), 5.29 (d, 1H, *J* = 11.3 Hz, C*H*$_2$=CH), 5.70-5.87 (m, 1H, CH$_2$=C*H*), 6.80-6.90 (m, 2H, CH-aromatic), 7.40-7.45 (m, 2H, CH-aromatic); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 25.21, 25.94, 34.88, 34.94 (**C**H$_2$-cyclohexyl), 55.10 (**C**H-cyclohexyl), 55.34 (*p*-(**C**H$_3$O)C$_6$H$_4$), 61.25 (**C**H–N), 68.56 (**C**H$_2$–O), 113.80 (**C**H$_2$=CH), 119.04, 123.12 (**C**H-aromatic), 133.02, 149.49 (quaternary aromatic carbons), 135.93 (CH$_2$=CH), 155.45 (**C**=N) ppm.; MS (*m/e*) 300 $[M]^+$, HRMS. Calcd for $C_{18}H_{24}N_2O_2$: 300.1838 Found: 300.1818.

***N*-(*p*-Chlorophenyl)-3-(*n*-butyl)-4-vinyl-1,3-oxazolidin-2-imine (2.55e)** (R = H, R′ = C_4H_9, R″= *p*-Cl-C$_6$H$_4$): IR (C=N) 1673 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 0.95 (t, 3H, C*H*$_3$CH$_2$), 1.25-1.65 (m, 4H, CH$_3$C*H*$_2$C*H*$_2$), 3.02-3.16 (m, 1H, CH$_2$C*H*$_2$–N), 3.41-3.56 (m, 1H, CH$_2$C*H*$_2$–N), 3.91 (dd, 1H, *J* = 8.1 and 8.1 Hz, C*H*$_2$–O), 4.09-4.20 (m, 1H, C*H*–N), 4.38 (dd, 1H, *J* = 8.0 and 8.0 Hz, C*H*$_2$–O), 5.26-5.39 (m, 2H, C*H*$_2$=CH), 5.61-5.78 (m, 1H, CH$_2$=C*H*), 6.90-7.20 (m, 4H, C*H*-aromatic); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 13.77 (**C**H$_3$CH$_2$), 19.19 (CH$_3$**C**H$_2$CH$_2$),

28.81 ($CH_3CH_2CH_2$), 42.35 (CH_2CH_2–N), 60.09 (CH–N), 69.27 (CH_2–O), 120.67 (CH_2=CH), 124.70, 128.22, (CH-aromatic), 134.86 (CH_2=CH), 126.55, 146.55 (quaternary aromatic carbons), 152.83 (C=N) ppm.; MS (*m/e*) 244 $[M]^+$, HRMS. Calcd for $C_{15}H_{19}ClN_2O$: 278.1186 Found: 278.1193.

***N*-(*n*-Butyl)-3-(*p*-chlorophenyl)-4-vinyl-1,3-oxazolidin-2-imine (2.56e)** (R = H, R′ = C_4H_9, R″= *p*-ClC_6H_4): oily liquid; IR (C=N) 1698 cm^{-1}; ^1H NMR ($CDCl_3$ 200 MHz) δ 0.98 (t, 3H, CH_3CH_2), 1.20-1.62 (m, 4H, $CH_3CH_2CH_2$), 3.28 (m, 2H, CH_2CH_2–N), 4.01 (dd, 1H, *J* = 8.0 and 5.3 Hz, CH_2–O), 4.40 (dd, 1H, *J* = 8.0 and 8.0 Hz, CH_2–O) 4.62-4.68 (m, 1H, CH–N), 5.20-5.31 (m, 2H, CH_2=CH), 5.63-5.80 (m, 1H, CH_2=CH), 7.18-7.68 (m, 4H, CH-aromatic); ^{13}C-NMR ($CDCl_3$ 50 MHZ) δ 14.03 (CH_3CH_2), 20.66 ($CH_3CH_2CH_2$), 33.78 ($CH_3CH_2CH_2$), 46.43 (CH_2CH_2–N), 60.30 (CH–N), 68.70 (CH_2–O), 119.51 (CH_2=CH), 121.98, 128.30, 130.15 (CH-aromatic), 135.12 (CH_2=CH), 127.62, 137.98 (quaternary aromatic carbons), 149.87 (C=N) ppm.; MS (*m/e*) 278 $[M]^+$, HRMS. Calcd for $C_{15}H_{19}ClN_2O$: 278.1186 Found: 278.1185.

***N*-(*p*-Fluorophenyl)-3-cyclohexyl-4-vinyl-1,3-oxazolidin-2-imine (2.55f)** (R = H, R′ = C_6H_{11}, R″= *p*-FC_6H_4); IR (C=N) 1667 cm^{-1}; ^1H NMR ($CDCl_3$ 200 MHz) δ 0.95-2.10 (m, 10H, CH_2-cyclohexyl), 3.74-3.95 (m, 2H, CH-cyclohexyl and CH_2–O), 4.23-4.37 (m, 2H, CH_2–O and CH–N), 5.22 (d, 1H, *J* = 9.9 Hz, CH_2=CH), 5.31 (d, 1H, *J* = 17.1 Hz, CH_2=CH), 5.78-5.84 (m, 1H, CH_2=CH), 6.82-7.05 (m, 4H, CH-aromatic); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 25.60, 25.82, 25.94, 29.59, 31.72 (CH_2-cyclohexyl), 54.32 (CH-cyclohexyl), 58.41 (CH–N), 69.64 (CH_2–O), 118.32 (CH_2=CH), 114.61, 115.06, 124.46 (CH-aromatic), 138.03 (CH_2=CH), 144.03, 155.92 (quaternary aromatic carbons), 152.67 (C=N) ppm.; MS (*m/e*) 288 $[M]^+$, HRMS. Calcd for $C_{17}H_{21}FN_2O$: 288.1638 Found: 288.1645.

***N*-Cyclohexyl-3-(*p*-fluorophenyl)-4-vinyl-1,3-oxazolidin-2-imine (2.56f)** (R = H, R′ = C_6H_{11}, R″= *p*-FC_6H_4); oily liquid; IR (C=N) 1698 cm^{-1}; ^{1}H-NMR ($CDCl_3$ 200 MHz) δ 1.10-1.95 (m, 10H, C*H*$_2$-cyclohexyl), 3.45-3.55 (m, 1H, C*H*-cyclohexyl), 4.02 (dd, 1H, *J* = 7.9 and 7.9 Hz, C*H*$_2$–O), 4.44 (dd, 1H, *J* = 7.9 and 7.9 Hz, C*H*$_2$–O), 4.51-4.65 (m, 1H, C*H*–N), 5.25-5.36 (m, 2H, C*H*$_2$=CH), 5.72-5.89 (m, 1H, CH$_2$=C*H*), 6.95-7.04 (m, 2H, C*H*-aromatic), 7.51-7.60 (m, 2H, C*H*-aromatic); ^{13}C-NMR ($CDCl_3$ 75 MHz) δ 25.03, 25.87, 34.76, 34.85 (**C**H$_2$-cyclohexyl), 54.98 (**C**H-cyclohexyl), 60.50 (**C**H–N), 68.44 (**C**H$_2$–O), 119.06 (**C**H$_2$=CH), 114.74, 115.03, 122.13, 122.23 (**C**H-aromatic), 135.48 (CH$_2$=**C**H), 148.72, 159.87 (quaternary aromatic carbons), 156.67 (**C**=N) ppm.; MS (*m/e*) 288 $[M]^+$, HRMS. Calcd for $C_{17}H_{21}N_2O$: 288.1638 Found: 288.1624.

***N*-[(2,6-dimethyl)phenyl]-3-cyclohexyl-4-vinyl-1,3-oxazolidin-2-imine (2.55g)** (R = H, R′ = C_6H_{11}, R″= 2,6-$(CH_3)_2C_6H_3$); IR (C=N) 1689 cm^{-1}; ^{1}H-NMR ($CDCl_3$ 200 MHz) δ 1.07-2.10 (m, 10H, C*H*$_2$-cyclohexyl), 2.14 (s, 6H, 2,6-(C*H*$_3$)$_2$C$_6$H$_3$), 3.70-3.87 (m, 2H, C*H*-cyclohexyl and C*H*$_2$–O), 4.15-4.33 (m, 2H, C*H*$_2$–O and C*H*–N), 5.15-5.35 (m, 2H, C*H*$_2$=CH), 5.74-5.92 (m, 1H, CH$_2$=C*H*), 7.05 (m, 3H, CH-aromatic); ^{13}C-NMR ($CDCl_3$ 50 MHz) δ 18.42, 25.65, 25.92, 25.98, 29.79, 31.26 (**C**H$_2$-cyclohexyl), 54.50 (**C**H-cyclohexyl), 58.94 (**C**H–N), 69.25 (**C**H$_2$–O), 118.19 (**C**H$_2$=CH), 121.90, 127.30 (**C**H-aromatic), 129.82, 146.00 (quaternary aromatic carbons), 138.08 (CH$_2$=**C**H), 150.49 (**C**=N) ppm.; MS (*m/e*) 298 $[M]^+$, Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39 Found: C, 76.33; H, 9.01; N, 9.36.

***N*-Cyclohexyl-3-[(2,6-dimethyl)phenyl]-4-vinyl-1,3-oxazolidin-2-imine (2.56g)**; (R = H, R′ = C_6H_{11}, R″= 2,6-$(CH_3)_2C_6H_3$); IR (C=N) 1691 cm^{-1}; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 1.00-1.80 (m, 10H; C*H*$_2$-cyclohexyl), 2.22 (s, 3H, 2,6-(C*H*$_3$)$_2$C$_6$H$_3$), 2.64, (s, 3H, 2,6-(C*H*$_3$)$_2$C$_6$H$_3$), 3.33-3.40 (m, 1H, C*H*-cyclohexyl), 4.01-4.10 (m, 1H, C*H*$_2$–O), 4.38-4.56 (m, 1H, C*H*$_2$–O), 5.00-

5.09 (m, 2H, C*H*$_2$=CH), 5.61-5.66 (m, 1H, CH$_2$=C*H*), 7.0-7.25 (m, 3H, C*H*-aromatic); ^{13}C-NMR ($CDCl_3$ 75 MHz) δ 18.55, 19.09 (2,6-(**C**H$_3$)$_2$C$_6$H$_3$), 25.49, 25.76, 34.94, 35.10 (**C**H$_2$-cyclohexyl), 55.32 (**C**H-cyclohexyl), 61.97 (**C**H–N), 69.36 (**C**H$_2$–O), 120.34 (**C**H$_2$=CH), 127.45, 128.45, 128.63 (**C**H-aromatic), 135.08, 136.62, 138.48 (quaternary aromatic carbons), 134.50 (CH$_2$=**C**H), 149.74 (**C**=N) ppm.; MS (*m/e*) 298 [M]$^+$, HRMS. Calcd for $C_{19}H_{26}N_2O$: 298.2045 Found: 298.2066.

***N*-*p*-Tolyl-3-ethyl-4-vinyl-1,3-oxazolidin-2-imine (2.55h)** (R = H, R′ = C_2H_5, R″= *p*-CH_3-C_6H_4): oily liquid; IR (C=N) 1679 cm^{-1}; ^{1}H NMR ($CDCl_3$)δ 1.17 (t, 3H), 2.27 (s, 3H), 3.19 (m, 1H), 3.57 (m, 1H), 3.89 (m, 1H), 4.16 (dd, 1H, *J*= 15.9 and 7.9 Hz), 4.36 (dd, 1H, *J* = 7.9 and 7.9 Hz), 5.35 (m, 2H), 5.71 (m, 1H), 6.92-7.24 (m, 4H) ^{13}C NMR $CDCl_3$ δ 11.67, 20.71, 37.35, 42.52, 60.25, 69.27, 120.57, 121.89, 123.40, 128.43, 135.23, 147.94, 152.64 ppm.; MS (*m/e*) 230 [M]$^+$, HRMS. Calcd for $C_{14}H_{18}N_2O$: 230.1419 Found: 230.1429.

***N*-Ethyl-3-*p*-tolyl-4-vinyl-1,3-oxazolidin-2-imine (2.56h)** (R = H, R′ = C_2H_5, R″= *p*-CH_3-C_6H_4): oily liquid; IR (C=N) 1692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3H), 2.29 (s, 3H), 3.30 (m, 2H), 4.03 (m, 1H), 4.48 (m, 1H), 4.62 (m, 1H), 5.28 (m, 2H), 5.78 (m, 1H), 7.14-7.40 (m, 4H) ^{13}C NMR $CDCl_3$ δ 15.81, 19.76, 40.09, 59.92, 69.71, 119.42, 121.89, 129.19, 135.60, 129.94, 130.53, 151.90 ppm.; MS (*m/e*) 230 [M]$^+$, HRMS. Calcd for $C_{14}H_{18}N_2O$: 230.1419 Found: 230.1424.

***N*-[(2,6-Dimethyl)phenyl]-3-*n*-butyl-4-vinyl-1,3-oxazolidin-2-imine (2.55i)** (R = H, R′ = C_4H_9, R″= 2, 6-$(CH_3)_2$-C_6H_3); IR (C=N) 1694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3H), 1.34-1.69 (m, 4H), 2.13 (s, 6H), 3.14 (m, 1H), 3.55 (m, 1H), 3.84 (dd, 1H, *J*= 7.7 and 6.6 Hz), 4.24 (m, 2H), 5.38 (m, 2H), 5.69 (m, 1H), 6.77-7.26 (m, 3H); ^{13}C NMR $CDCl_3$ 14.70, 19.12, 20.93, 20.93, 32.36, 42.32, 63.71, 75.86, 117.45, 122.65, 128.03, 140.02, 130.60, 146.66, 151.51

ppm.; MS (*m/e*) 272 $[M]^+$, Anal. Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28 Found: C, 74.94; H, 9.09; N, 10.29.

***N*-*n*-Butyl-3-[(2,6-dimethyl)phenyl]-4-vinyl-1,3-oxazolidin-2-imine (2.56i)** (R = H, R′ = C_4H_9, R″= 2, 6-$(CH_3)_2$-C_6H_3); IR (C=N) 1699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.34 (m, 4H), 2.22 (s, 3H), 2.27 (s, 3H), 3.18 (m, 2H), 4.09 (m, 1H), 4.56 (m, 2H), 5.03 (d, 1H, J = 1.28 Hz), 5.10 (d, 1H, J = 4.03 Hz), 5.69 (m, 1H), 7.05 (m, 3H); ^{13}C NMR $CDCl_3$ δ 14.04, 18.44, 18.97, 20.56, 34.00, 42.44, 61.98, 69.43, 120.43, 127.62, 128.55, 134.47, 134.82, 136.56, 138.43, 151.24 ppm.; MS (*m/e*) 272 $[M]^+$, HRMS. Calcd for $C_{17}H_{24}N_2O$: 272.1889 Found: 272.1891.

2.3.6 General Procedure for the Asymmetric Palladium-Catalyzed Cycloaddition Reaction of Vinyloxirane with Heterocumulenes (2.39, 2.40 and 2.54).

A mixture of $Pd_2(dba)_3$•$CHCl_3$ (0.03 mmol), chiral phosphine ligand (0.06 mmol) and THF was stirred at room temperature for 30 min. The vinyloxirane (1.5 mmol) and heterocumulene (1.0 mmol) were then added, the mixture was stirred under nitrogen at either room temperature or at 10 °C, until the conversion of the the heterocumulenes was completed (as monitored by IR-absorption band of carbodiimide C=N group at approximately 2100 cm^{-1} was shifted to the region of 1670 cm^{-1} -or the absorption band of the isocyanate C=O group at about 2200 cm^{-1} was replaced by one at approximately 1750 cm^{-1}). After the reaction was complete, the orange brown solution was subjected to rotary evaporation, and the residue was purified by preparative silica gel TLC. The purified product was re-chromatographed on preparative HPLC in order to eliminate the rest of the chiral phosphine ligand. The

enantiomeric excess was calculated according to the area under the peak of chromatogram obtained from programming analytical HPLC integrator.

***N*, 3-Di(*p*-tolyl)-4-vinyl-1,3-oxazolidin-2-imine (2.42c):** (R = H, X = *p*-$CH_3C_6H_4N$, Y = *p*-$CH_3C_6H_4N$): mp = 102-103 °C; IR (C=N) 1679 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 200 MHz) 2.21 (s, 3H, *p*-$CH_3C_6H_4N$), 2.24 (s, 3H, *p*-$CH_3C_6H_4N$), 3.99 (dd, 1H, J = 8.3 and 6.4 Hz, CH_2–O), 4.44 (dd, 1H, J = 8.3 and 8.3 Hz, CH_2–O), 4.62-4.73 (m, 1H, C*H*–N), 5.16-5.32 (m, 2H, CH_2=CH), 5.65-5.83 (m, 1H, CH_2=C*H*), 6.85-7.42 (m, 8H, aromatic protons); ^{13}CNMR ($CDCl_3$, 50 MHz) 21.52 (*p*-$CH_3C_6H_4N$), 61.57 (CH–N), 69.89 (CH_2–O), 120.65 (CH_2=CH), 123.08, 123.73, 129.73, 129.93 (CH-aromatic ring), 135.79 (CH_2=CH), 132.19, 134.41, 136.62, 145.50 (quaternary aromatic carbons), 150.81 (C=N); MS (*m/e*) 292 $[M]^+$, Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.86; H, 6.84; N, 9.54.

***N*, 3-Di(*p*-bromophenyl)-4-vinyl-1,3-oxazolidin-2-imine (2.42d):** (R = H, X = *p*-BrC_6H_4N, Y = *p*-BrC_6H_4N): mp = 98-99 °C; IR (C=N) 1675 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 200 MHz) 4.05 (dd, 1H, J = 8.0 and 6.3 Hz, CH_2–O), 4.49 (dd, 1H, J = 8.0 and 8.0 Hz, CH_2–O), 4.65-4.76 (m, 1H, C*H*–N), 5.26-5.36 (m, 2H, CH_2=CH), 5.65-5.82 (m, 1H, CH_2=C*H*), 6.83-7.52 (m, 8 H, aromatic protons); ^{13}C–NMR ($CDCl_3$) 60.40 (CH–N), 69.36 (CH_2–O), 120.53 (CH_2=CH), 123.49, 125.12, 131.39, 131.62 (CH-aromatic ring), 134.29 (CH_2=CH), 115.31, 117.03, 137.27, 145.99 (quaternary aromatic carbons), 149.77 (C=N); MS (*m/e*) 422 $[M]^{+\cdot}$ 424 $[M+2]^+$. Anal. Calcd for $C_{17}H_{14}N_2OBr$: C, 48.37; H, 3.34; N, 6.64 Found: C, 48.38; H, 3.06; N, 6.59.

***N*, 3-Di(*p*-methoxyphenyl)-4-vinyl-1,3-oxazolidin-2-imine (2.42e):** (R = H, X = *p*-$CH_3OC_6H_4N$, Y = *p*-$CH_3OC_6H_4N$): mp = 65-66 °C; IR (C=N) 1678 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 200 MHz) 3.67 (s, 3H, *p*-$CH_3OC_6H_4N$), 3.69 (s, 3H, *p*-$CH_3OC_6H_4N$), 3.97 (dd, 1H, J = 8.0 and 6.6 Hz, CH_2–O), 4.42 (dd, 1H, J = 8.0 and 8.0 Hz, CH_2–O), 4.51-4.62 (m, 1H, CH–N), 5.16 (d, 1H, J = 3.7 Hz, CH_2=CH), 5.25 (d, 1H, J = 10.7 Hz, CH_2=CH), 5.61-5.78 (m, 1H, CH_2=CH), 6.69-7.39 (m, 8H, aromatic protons); ^{13}C–NMR ($CDCl_3$, 50 MHz) 55.21 (*p*-$CH_3OC_6H_4N$), 61.31 (CH–N), 69.09 (CH_2–O), 120.03 (CH_2=CH), 113.57, 113.84, 123.98, 124.58 (CH-aromatic ring), 134.96 (CH_2=CH), 131.40, 140.51, 150.46, 154.80 (quaternary aromatic carbons), 156.37 (C=N); MS (*m/e*) 324 $[M]^+$, Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.67; H, 5.99; N, 8.64.

***N*, 3-Diphenyl-4-methyl-4-vinyl-1,3-oxazolidin-2-imine (2.42f):** (R = CH_3, X = C_6H_5N, Y = C_6H_5N): mp = 82-83 °C; IR (C=N) 1677 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 200 MHz) 1.38 (s, 3H, (CH_3)C–N), 4.05 (d, 1H, J = 8.2 Hz, CH_2–O), 4.17 (d, 1H, J = 8.2 Hz, CH_2–O), 5.16 (d, 1H, J = 13.7 Hz, CH_2=CH), 5.22 (d, 1H, J = 6.8 Hz, CH_2=CH), 6.00 (dd, 1H, J = 17.3 and 10.6 Hz, CH_2=CH), 6.80-7.40 (m, 10H, aromatic protons); ^{13}C–NMR ($CDCl_3$, 50 MHz) 20.72 ((CH_3)C–N), 64.07 ((CH_3)C–N), 76.24 (CH_2–O), 116.86 (CH_2=CH), 122.23, 123.43, 126.03, 127.48, 128.37, 128.72 (CH-aromatic ring), 139.64 (CH_2=CH), 136.84, 147.52 (quaternary aromatic carbons), 151.57 (C=N); MS (*m/e*) 278 $[M]^+$. Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.07. Found: C, 77.29; H, 6.25; N,.10.01.

***N*, 3-Di(*p*-chlorophenyl)-4-methyl-4-vinyl-1,3-oxazolidin-2-imine (2.42g) :** (R = CH_3, X = *p*- ClC_6H_4N, Y = *p*- ClC_6H_4N): mp = 97-98 °C; IR (C=N) 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) 1.39 (s, 3H, (CH_3)C–N), 4.07 (d, 1H, J = 8.3 Hz, CH_2–O), 4.20 (d, 1H, J = 8.3 Hz, CH_2–O), 5.18 (d, 1H, J = 17.4 Hz, CH_2=CH), 5.26 (d, 1H, J = 10.6 Hz, CH_2=CH),

5.98 (dd, 1H, J = 17.4 and 10.6 Hz, CH_2=C*H*), 6.91 (d, 1H, J = 17.4 Hz, aromatic protons), 7.11 (d, 1H, J = 17.4 Hz, aromatic protons), 7.27 (s, 4H, aromatic protons); ^{13}C–NMR ($CDCl_3$, 50 MHz) 20.50 ((CH_3)C–N), 64.17 ((CH_3)C–N), 76.40 (CH_2–O), 117.5 (CH_2=CH), 124.77, 128.39, 128.78, 128.99 (CH-aromatic ring), 139.04 (CH_2=CH), 127.44, 132.02, 135.06, 145.70 (quaternary aromatic carbons), 151.70 (C=N), MS (*m/e*) 346 $[M]^+$, 348 $[M+2]^+$ Anal. Calcd for $C_{18}H_{16}Cl_2N_2O$: C, 62.26; H, 4.64; N, 8.07. Found: C, 62.18; H, 4.47; N, 7.85.

***N*, 3-Di(*p*-methoxyphenyl)-4-methyl-4-vinyl-1,3-oxazolidin-2-imine (2.42i):** (R = CH_3, X = *p*-$CH_3OC_6H_4N$, Y = *p*-$CH_3OC_6H_4N$): mp = 60-61 °C; IR (C=N) 1677 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 200 MHz) 1.34 (s, 3H, (C*H*$_3$)C–N), 3.68 (s, 3H, *p*-C*H*$_3OC_6H_4N$), 3.72 (s, 3H, *p*-C*H*$_3OC_6H_4N$), 4.05 (d, 1H, J = 8.2 Hz, C*H*$_2$–O), 4.17 (d, J = 8.2 Hz, C*H*$_2$–O), 5.11 (d, 1H, J = 17.4 Hz, C*H*$_2$=CH), 5.19 (d, 1H, J = 10.6 Hz, C*H*$_2$=CH), 5.99 (dd, 1H, J = 17.4 and 10.6 Hz, CH_2=C*H*), 6.69-7.23 (m, 8H, aromatic protons); ^{13}C–NMR ($CDCl_3$, 50 MHz) 20.62 ((CH_3)C–N), 55.33 (*p*-$CH_3OC_6H_4N$), 63.85 ((CH_3)C–N), 75.96 (CH_2–O), 116.79 (CH_2=CH), 113.61, 114.07, 124.16, 129.85 (CH-aromatic ring), 139.56 (CH_2=CH), 129.23, 140.77, 152.12 154.82, (quaternary aromatic carbons), 158.21 (C=N); MS (*m/e*) 338 $[M]^+$, Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 70.93; H, 6.53; N, 8.33.

***N*, 3-Di(*o*-tolyl)-4-vinyl-1,3-oxazolidin-2-imine (2.42j):** (R = H, X = *o*-$CH_3C_6H_4N$, Y = *o*-$CH_3C_6H_4N$): mp = 68-69 °C; IR (C=N) 1688 cm^{-1}; ^{1}H–NMR ($CDCl_3$, 200 MHz) 2.09 (s, 3H, *o*-C*H*$_3C_6H_4N$), 2.36 (s, 3H, *o*-C*H*$_3C_6H_4N$), 3.98-4.14 (m, 1H, C*H*$_2$–O), 4.44-4.63 (m, 2H, C*H*$_2$–O and C*H*–N), 5.07-5.19 (m, 2H, C*H*$_2$=CH), 5.60-5.77 (m, 1H, CH_2=C*H*) 6.77-7.27 (m, 8H, aromatic protons); ^{13}C–NMR ($CDCl_3$, 50 MHz) 18.34 (*o*-$CH_3C_6H_4N$), 63.16 (CH–N), 69.65 (CH_2–O), 121.06 (CH_2=CH), 122.29, 122.71, 125.76, 126.66, 127.65, 129.81, 131.16 (CH-aromatic ring), 134.38 (CH_2=CH), 130.54, 136.49, 137.08, 146.66 (quaternary aromatic

carbons), 150.34 (C=N); MS (*m/e*) 292 $[M]^+$, Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.19; H, 6.84; N, 9.54.

***N*, 3-Di(α-naphthyl)-4-vinyl-1,3-oxazolidin-2-imine (2.42k):** (R = H, X = 1-naphthyl, Y= 1-naphthyl): mp = 172-173 °C; IR (C=N) 1676 cm^{-1}; ^1H–NMR ($CDCl_3$, 200 MHz) 4.20 (dd, 1H, J = 7.6 and 7.6 Hz, C*H*$_2$–O), 4.65-4.72 (m, 2H, C*H*$_2$–O and C*H*–N), 4.95-5.12 (m, 2H, C*H*$_2$=CH), 5.69-5.87 (m, 1H, CH_2=C*H*), 7.00-8.60 (m, 14H, aromatic protons); ^{13}C–NMR ($CDCl_3$, 50 MHz) 63.84 (CH–N), 70.08 (CH_2–O), 122.21 (CH_2=CH), 121.24, 123.25, 124.39, 124.56,125.40, 125.63, 126.26, 126.48, 127.51, 128.41, 128.64, 129.33 (CH-naphthyl ring), 134.27 (CH_2=CH), 123.30, 134.15, 134.78, 144.0 (quaternary aromatic carbons), 152.06 (C=N); MS (*m/e*) 364 $[M]^+$, 365 $[M+1]^+$. Anal. Calcd for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69. Found: C, 82.03; H, 5.25; N, 7.80.

2.3.7 General Procedure for Determination the Effect of Temperature on the Asymmetric Induction of the palladium-catalyzed Cycloaddition of vinyloxiranes with heterocumulenes.

A mixture of $Pd_2(dba)_3$•$CHCl_3$ (0.03 mmol), (*S*)-TolBINAP (0.06 mmol) and 3 mL THF was stirred at room temperature for 30 min. 2-Vinyloxirane **2.38a** (1.5 mmol) and carbodiimide **2.40d** or **2.40e** (1 mmol) were added, the mixture was then stirred under nitrogen atmosphere at a given temperature (see Table 2-6 for the reaction time and temperature in each case). The reaction was then concentrated by rotary evaporation and the crude product was purified by silica gel TLC using 1:1 n-pentane/ether as the developer.

2.3.8 Single Crystal X-ray Diffraction Study of 2.42b.

Crystals of **2.42b** were obtained by purification using preparative TLC, preparative HPLC and recrystalization from methanolic solution. One of the crystals having proximate dimension of 0.2, 0.2, 0.2 mm was mounted on a glass capillary. All the measurements were made on a Siemens CCD diffractometer with Mo Kα radiation. Cell constants and an orientation matrix for data collection, were obtained from least-squares refinement using the setting angles of 5734 reflections in the range $3° < 2\theta < 57°$ corresponded to a monoclinic cell with dimension $a = 9.7465(4)$ Å, $b = 13.0803(6)$ Å, $c = 12.8570(6)$ Å and $\beta = 103.015(1)$. For Z = 4 and FW = 333.21, the calculated density is 1.386 g/cm^3. Based on the systematic absences, the space group was determined to be $P21$. The data was collected at −100 °C using ω–2θ scan technique to a maximum 2θ value of 57 °.

A total of 11377 reflections were collected. The unique set contained only 7678 reflections. The data was corrected for Lorentz and polarization effects.[86] Absorption correction was made. The minimum and maximum transmission factors are 0.542–1.000.

The structure was solved by direct methods. All the atoms were refined anisotropically except the hydrogen. The hydrogen atoms were found by differences Fourier map. The final cycle of full matrix least-squares refinement was based on 4430 observed reflections ($I > 2.5\sigma(I)$) and 398 variable parameters. Weights based on counting statistics were used. The maximum and minimum peak on the final differences Fourier map corresponded to 0.450 and –0.300 e/a^3, respectively.

The absolute structure was determined by refinement of the η parameter with the Rogers Schemes, giving a value of 1.0177(0.1001), showing that we have the good hand.

All the calculations were performed using the NRCVAX crystallographic software package.[87]

Table 2-7 Crystal data and structure refinement for 2.42b.

Empirical formula	$C_{17}H_{14}N_2OCl_2$
Formula weight	333.21
Wavelength	0.70930 Å
Crystal shape	cube
Crystal system, space group	Monoclinic, P21
Unit cell dimensions	a = 9.7465 (4) Å,
	b = 13.0803 (6) Å,
	c = 12.8570 (6) Å,
Z value	4
Z, calculated density	1.386 mg/m^3
Absorption coefficient	0.41 mm^{-1}
F (000)	689.26
Crystal size	0.2 x 0.2 x 0.2 mm
Theta range for data collection	3.00 to 57.00 °

Intensity data were collected for Lorentz and polarization effect.

Limiting indices	$-13 \leq h \leq 12, -17 \leq k \leq 17, -17 \leq l \leq 17$
Reflections collected/unique	11377/7678 [R (int) = 0.017]
The weight modifier K in KFo^2	0.000100

Absorption correction was made, the minimum and maximum transmission factors are 0.542 and 1.000

Final R indices [I > 2 sigma (I)]	RF = 0.050, Rw = 0.053
R indices (all data)	RF = 0.064, Rw = 0.059
Goodness of fit on F^2	1.82
The maximum shift/sigma ratio	0.091
Secondary ext. coefficient	0.0949 micron
The highest peak and the deepest hole	0.450 and –0.300 Å^{-3}

Table 2-8 Atomic parameters x, y, z and Biso for **2.42b**.
E. S. Ds. Refer to the last digit printed.

	x	y	z	Biso
C13	0.42806(13)	0.12926(10)	0.41495(9)	7.32(6)
C14	-0.30618(11)	0.37225(8)	-0.44312(8)	5.33(5)
C11	0.31325(12)	-0.36429	0.93599(9)	6.10(5)
C12	-0.44711(12)	-0.11052(8)	0.09101(8)	6.39(5)
O1	0.0169 (3)	0.06889(16)	0.49772(18)	4.45(12)
O2	-0.0251 (3)	-0.06180(18)	0.00049(20)	4.79(12)
N1	0.1139 (3)	-0.01438(20)	0.64944(23)	3.99(13)
N2	-0.0724 (3)	-0.09303(20)	0.52298(22)	3.88(13)
N3	0.0537 (3)	0.10210(21)	-0.01736(23)	4.34(14)
N4	-0.1258 (3)	0.02746(21)	-0.14382(22)	4.41(15)
C1	0.2557 (3)	-0.2645 (3)	0.8533 (3)	3.90(17)
C2	0.2106 (4)	-0.2805 (3)	0.7410 (3)	4.78(21)
C3	0.1633 (4)	-0.1977 (3)	0.6774 (3)	3.70(17)
C4	0.1525 (3)	-0.09986(24)	0.7149 (3)	3.49(15)
C5	0.1955 (4)	-0.0859 (3)	0.8271 (3)	4.83(19)
C6	0.2430 (4)	-0.1686 (3)	0.8927 (3)	4.36(18)
C7	0.2060 (4)	0.0741 (3)	0.6478 (3)	5.57(20)
C8	0.2739 (5)	0.1244 (3)	0.7462 (4)	7.1 (3)
C9	0.4067 (6)	0.1389 (4)	0.7807 (4)	8.8 (3)
C10	0.1143 (4)	0.1404 (3)	0.5650 (3)	5.50(21)
C11	0.0126 (4)	-0.0179 (3)	0.5550 (3)	3.89(16)
C12	-0.1640 (4)	-0.0872 (3)	0.4210 (3)	3.80(15)
C13	-0.3060 (4)	-0.0940 (3)	0.4075 (3)	4.93(20)
C14	-0.3935 (4)	-0.1006 (3)	0.3035 (3)	5.44(21)
C15	-0.3346 (4)	-0.1011 (3)	0.2179 (3)	4.58(17)
C16	-0.1928 (4)	-0.0925 (3)	0.2280 (3)	4.85(20)
C17	-0.1103 (4)	-0.0877 (3)	0.3282 (3)	4.44(17)
C18	0.3214 (4)	0.1133 (3)	0.2872 (3)	5.00(19)
C19	0.1791 (4)	0.1030 (3)	0.2787 (3)	5.37(21)
C20	0.0873 (4)	0.0938 (3)	0.1759 (3)	4.36(18)
C21	0.1415 (3)	0.10036(23)	0.0867 (3)	3.29(15)
C22	0.2876 (4)	0.1129 (3)	0.0980 (3)	4.66(19)
C23	0.3762 (4)	0.1185 (3)	0.1974 (4)	5.64(21)
C24	-0.0280 (4)	0.03085(25)	-0.0490 (3)	3.61(16)
C25	-0.1196 (4)	-0.1315 (3)	-0.0638 (3)	5.39(19)
C26	-0.1874 (4)	-0.0745 (3)	-0.1677 (3)	4.85(18)
C27	-0.3437 (4)	-0.0774 (3)	-0.1909 (3)	5.34(21)
C28	-0.4212 (5)	-0.1238 (4)	-0.2767 (4)	8.1 (3)
C29	-0.1682 (4)	0.11102(25)	-0.2166 (3)	3.75(16)
C30	-0.1605 (4)	0.2126 (3)	-0.1727 (3)	4.37(19)
C31	-0.2042 (4)	0.2900 (3)	-0.2468 (3)	4.01(17)
C32	-0.2445 (4)	0.2704 (3)	-0.3517 (3)	4.16(17)
C33	-0.2538 (4)	0.1719 (3)	-0.3955 (3)	4.57(18)
C34	-0.2079 (4)	0.0929 (3)	-0.3219 (3)	3.78(16)
H2	0.214	-0.356	0.707	5.6
H3	0.131	-0.210	0.592	4.4
H5	0.191	-0.011	0.861	5.6
H6	0.272	-0.156	0.978	5.0
H7	0.290	0.047	0.612	6.1
H8	0.208	0.152	0.797	7.4

H9a	0.428	0.177	0.857	9.0
H9b	0.486	0.116	0.739	9.0
H10a	0.058	0.196	0.601	6.2
H10b	0.178	0.179	0.519	6.2
H13	-0.353	-0.094	0.476	5.6
H14	-0.506	-0.106	0.293	6.0
H16	-0.147	-0.089	0.159	5.7
H17	0.003	-0.085	0.338	5.1
H19	0.137	0.102	0.350	6.0
H20	-0.024	0.083	0.168	5.1
H22	0.331	0.117	0.028	5.4
H23	0.488	0.127	0.205	6.3
H25a	-0.063	-0.198	-0.082	5.8
H25b	-0.199	-0.155	-0.022	5.8
H26	-0.151	-0.109	-0.233	5.4
H27	-0.397	-0.041	-0.136	6.1
H28a	-0.532	-0.116	-0.277	8.2
H28b	-0.380	-0.162	-0.337	8.2
H30	-0.123	0.228	-0.088	5.1
H31	-0.206	0.368	-0.219	4.7
H33	-0.293	0.158	-0.480	5.4
H34	-0.205	0.016	-0.351	4.6

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

Table 2-9 u (i, j) or U values ×100 for **2.42b**. E. S. Ds. Refer to the last digit printed.

	u11(U)	u22	u33	u12	u13	u23
C13	8.65(8)	10.40(9)	7.09(8)	-2.01(8)	-1.71(7)	-0.38(7)
C14	6.48(7)	8.09(7)	5.42(6)	1.01(6)	0.74(5)	1.81(5)
C11	8.23(8)	7.51(7)	6.89(7)	0.90(6)	0.55(6)	1.78(6)
C12	7.43(7)	9.11(8)	5.89(6)	-1.94(6)	-2.42(6)	0.68(6)
O1	7.31(17)	4.05(13)	4.88(14)	-0.71(13)	-0.03(14)	0.58(11)
O2	5.89(17)	5.44(15)	6.16(16)	-0.21(13)	-0.15(14)	-0.40(12)
N1	5.32(19)	3.63(16)	5.62(19)	-0.42(14)	-0.02(16)	-0.24(13)
N2	5.07(18)	4.68(17)	4.77(17)	-0.22(15)	0.67(15)	-0.35(14)
N3	5.29(19)	5.18(18)	5.23(19)	-1.41(15)	-0.46(16)	0.39(14)
N4	7.57(23)	4.58(17)	4.01(17)	-0.54(16)	0.01(17)	-0.37(13)
C1	2.76(18)	6.27(24)	5.39(24)	-0.20(17)	0.11(17)	-0.28(18)
C2	8.0 (3)	3.94(21)	6.5 (3)	-0.19(21)	2.07(24)	-0.02(18)
C3	4.64(22)	5.73(22)	3.53(19)	-0.36(19)	0.58(17)	-0.92(16)
C4	2.71(17)	4.87(21)	4.98(20)	-1.22(16)	-0.62(15)	-1.15(16)
C5	7.7 (3)	5.38(22)	5.04(22)	-1.24(22)	0.91(22)	-1.57(18)
C6	4.31(23)	9.0 (3)	2.59(18)	-0.25(21)	-0.68(17)	-0.37(18)
C7	6.9 (3)	5.93(25)	7.3 (3)	-1.58(23)	-0.63(24)	0.64(21)
C8	10.7 (4)	5.11(25)	9.5 (4)	-0.8 (3)	-1.3 (3)	0.09(23)
C9	10.6 (4)	7.2 (3)	13.2 (5)	-3.8 (3)	-2.5 (4)	1.1 (3)
C10	7.9 (3)	4.46(22)	8.0 (3)	-0.70(22)	0.8 (3)	-0.29(20)
C11	4.56(21)	4.95(21)	5.32(22)	0.06(18)	1.25(18)	-0.68(17)
C12	4.27(20)	3.99(19)	5.75(22)	0.56(17)	0.23(18)	0.36(16)
C13	3.77(21)	7.0 (3)	7.6 (3)	-0.58(21)	0.64(21)	-0.49(22)
C14	4.79(24)	9.1 (3)	6.0 (3)	-1.42(24)	-0.35(20)	-0.75(23)
C15	4.65(22)	5.84(24)	5.44(22)	-1.71(20)	-1.97(18)	0.98(18)
C16	7.8 (3)	6.20(25)	4.56(22)	-0.43(23)	1.65(21)	0.27(19)
C17	3.41(20)	6.69(25)	6.37(25)	-0.52(19)	0.28(19)	-0.29(20)
C18	6.6 (3)	5.86(25)	6.0 (3)	-0.26(22)	0.37(22)	-0.38(19)
C19	4.91(24)	9.3 (3)	5.49(25)	-1.19(23)	-0.19(21)	-0.08(22)
C20	3.93(21)	6.64(25)	5.63(23)	-0.42(19)	0.30(19)	0.09(19)
C21	4.08(19)	3.36(18)	4.84(20)	0.32(16)	0.50(17)	-0.52(15)
C22	6.2 (3)	7.7 (3)	3.70(20)	0.34(22)	0.88(19)	-0.93(18)
C23	4.75(23)	8.1 (3)	8.2 (3)	-0.37(23)	0.71(23)	0.38(24)
C24	5.34(22)	3.95(19)	4.26(20)	0.39(17)	0.71(18)	0.18(16)
C25	7.2 (3)	5.28(23)	6.7 (3)	-1.74(22)	-1.14(23)	-0.27(19)
C26	6.8 (3)	4.36(21)	6.34(25)	-1.31(21)	-0.56(22)	-0.38(18)
C27	6.4 (3)	5.11(22)	8.5 (3)	-0.40(22)	1.05(24)	-0.07(21)
C28	8.4 (3)	8.8 (3)	10.8 (4)	-1.9 (3)	-3.6 (3)	0.3 (3)
C29	5.14(22)	4.88(21)	4.37(20)	0.97(18)	1.39(18)	0.81(16)
C30	7.0 (3)	4.19(20)	5.10(23)	0.63(20)	0.73(21)	-0.15(17)
C31	4.78(22)	5.91(23)	4.13(21)	0.62(19)	0.17(18)	-0.72(17)
C32	5.77(24)	5.94(22)	4.35(22)	0.75(20)	1.63(19)	1.47(18)
C33	5.95(24)	5.40(23)	6.2 (3)	-0.42(20)	1.67(21)	-0.65(19)
C34	4.17(20)	5.43(21)	4.73(21)	0.26(18)	0.92(18)	0.23(17)

Table 2-10 Atomic bond angles for **2.42b** in degree.

C10-O1-C11	107.9(3)	C15-C16-H16	121.4(3)
C24-O2-C25	110.8(3)	C17-C16-H16	120.9(4)
C4-N1-C7	123.8(3)	C12-C17-C16	123.4(3)
C4-N1-C11	122.9(3)	C12-C17-H17	117.9(3)
C7-N1-C11	109.4(3)	C16-C17-H17	118.7(4)
C11-N2-C12	118.8(3)	C13-C18-C19	117.6(3)
C21-N3-C24	120.5(3)	C13-C18-C23	121.4(3)
C24-N4-C26	112.7(3)	C19-C18-C23	120.9(4)
C24-N4-C29	126.5(3)	C18-C19-C20	119.6(4)
C26-N4-C29	120.7(3)	C18-C19-H19	120.1(3)
C11-C1-C2	120.2(3)	C20-C19-H19	120.3(3)
C11-C1-C6	121.1(3)	C19-C20-C21	119.5(3)
C2-C1-C6	118.5(3)	C19-C20-H20	120.3(4)
C1-C2-C3	118.2(3)	C21-C20-H20	120.3(3)
C1-C2-H2	121.1(3)	N3-C21-C20	121.8(3)
C3-C2-H2	120.8(3)	N3-C21-C22	118.5(3)
C2-C3-C4	124.4(3)	C20-C21-C22	119.5(3)
C2-C3-H3	117.7(3)	C21-C22-C23	120.7(4)
C4-C3-H3	117.9(3)	C21-C22-H22	119.8(3)
N1-C4-C3	124.2(3)	C23-C22-H22	119.5(4)
N1-C4-C5	119.1(3)	C18-C23-C22	119.7(4)
C3-C4-C5	116.5(3)	C18-C23-H23	120.0(4)
C4-C5-C6	120.0(3)	C22-C23-H23	120.3(4)
C4-C5-H5	119.9(3)	O2-C24-N3	124.9(3)
C6-C5-H5	120.1(3)	O2-C24-N4	108.9(3)
C1-C6-C5	122.4(3)	N3-C24-N4	125.9(3)
C1-C6-H6	119.2(3)	O2-C25-C26	106.8(3)
C5-C6-H6	118.4(3)	O2-C25-H25a	110.3(3)
N1-C7-C8	120.4(4)	O2-C25-H25b	110.0(3)
N1-C7-C10	101.4(3)	C26-C25-H25a	110.0(3)
N1-C7-H7	105.7(3)	C26-C25-H25b	110.4(3)
C8-C7-C10	116.0(3)	H25a-C25-H25b	109.5(3)
C8-C7-H7	106.1(4)	N4-C26-C25	100.5(3)
C10-C7-H7	106.0(4)	N4-C26-C27	114.7(3)
C7-C8-C9	126.6(5)	N4-C26-H26	110.4(3)
C7-C8-H8	117.6(4)	C25-C26-C27	112.4(3)
C9-C8-H8	115.8(5)	C25-C26-H26	108.9(3)
C8-C9-H9a	110.6(6)	C27-C26-H26	109.5(3)
C8-C9-H9b	124.2(5)	C26-C27-C28	122.8(4)
H9a-C9-H9b	125.3(4)	C26-C27-H27	118.7(3)
O1-C10-C7	104.6(3)	C28-C27-H27	118.5(4)
O1-C10-H10a	111.2(3)	C27-C28-H28a	109.6(5)
O1-C10-H10b	110.4(3)	C27-C28-H28b	125.2(5)
C7-C10-H10a	111.2(4)	H28a-C28-H28b	125.3(4)
C7-C10-H10b	109.9(4)	N4-C29-C30	117.7(3)
H10a-C10-H10b	109.5(3)	N4-C29-C34	119.8(3)
O1-C11-N1	110.2(3)	C30-C29-C34	122.4(3)
O1-C11-N2	123.9(3)	C29-C30-C31	115.0(3)
N1-C11-N2	125.9(3)	C29-C30-H30	122.5(3)
N2-C12-C13	121.8(3)	C31-C30-H30	122.5(3)
N2-C12-C17	120.6(3)	C30-C31-C32	121.7(3)
C13-C12-C17	117.0(3)	C30-C31-H31	119.1(3)
C12-C13-C14	120.2(4)	C32-C31-H31	119.2(3)
C12-C13-H13	120.3(3)	C14-C32-C31	119.8(3)
C14-C13-H13	119.5(3)	C14-C32-C33	116.0(3)
C13-C14-C15	119.6(3)	C31-C32-C33	123.9(3)
C13-C14-H14	120.2(4)	C32-C33-C34	115.0(3)
C15-C14-H14	120.2(3)	C32-C33-H33	122.2(3)
C12-C15-C14	117.9(3)	C34-C33-H33	122.8(3)
C12-C15-C16	120.2(3)	C29-C34-C33	121.8(3)
C14-C15-C16	121.9(3)	C29-C34-H34	119.3(3)
C15-C16-C17	117.7(3)	C33-C34-H34	118.9(3)

Table 2-11 Atomic bond distances for **2.42b** in degree.

C13-C18	1.747(4)	C12-C17	1.407(5)
C14-C32	1.789(3)	C13-C14	1.417(5)
C11-C1	1.698(4)	C13-H13	1.080(4)
C12-C15	1.753(3)	C14-C15	1.351(6)
O1-C10	1.468(4)	C14-H14	1.080(4)
O1-C11	1.359(4)	C15-C16	1.364(6)
O2-C24	1.366(4)	C16-C17	1.358(5)
O2-C25	1.421(4)	C16-H16	1.080(4)
N1-C4	1.399(4)	C17-H17	1.080(3)
N1-C7	1.468(5)	C18-C19	1.373(6)
N1-C11	1.382(4)	C18-C23	1.378(6)
N2-C11	1.292(4)	C19-C20	1.425(5)
N2-C12	1.412(4)	C19-H19	1.080(4)
N3-C21	1.416(4)	C20-C21	1.369(5)
N3-C24	1.234(4)	C20-H20	1.080(3)
N4-C24	1.369(4)	C21-C22	1.408(5)
N4-C26	1.467(4)	C22-C23	1.374(5)
N4-C29	1.437(4)	C22-H22	1.080(4)
C1-C2	1.426(5)	C23-H23	1.080(4)
C1-C6	1.368(5)	C25-C26	1.543(5)
C2-C3	1.373(5)	C25-H25a	1.080(4)
C2-H2	1.080(4)	C25-H25b	1.080(5)
C3-C4	1.379(5)	C26-C27	1.485(6)
C3-H3	1.080(3)	C26-H26	1.080(4)
C4-C5	1.420(5)	C27-C28	1.335(6)
C5-C6	1.386(5)	C27-H27	1.080(4)
C5-H5	1.080(4)	C28-H28a	1.080(6)
C6-H6	1.080(3)	C28-H28b	1.080(6)
C7-C8	1.448(6)	C29-C30	1.439(5)
C7-C10	1.501(6)	C29-C34	1.343(5)
C7-H7	1.080(5)	C30-C31	1.389(5)
C8-C9	1.284(7)	C30-H30	1.080(4)
C8-H8	1.080(6)	C31-C32	1.342(5)
C9-H9a	1.080(6)	C31-H31	1.080(3)
C9-H9b	1.080(7)	C32-C33	1.402(5)
C10-H10a	1.080(4)	C33-C34	1.404(5)
C10-H10b	1.080(4)	C33-H33	1.080(4)
C12-C13	1.359(5)	C34-H34	1.080(3)

Table 2-12 Torsion angles for **2.42b.**

C11	O1	C10	C7	21.2(4)	C11	O1	C10	H10a	-98.9(6)
C11	O1	C10	H10b	139.4(7)	C10	O1	C11	N1	-8.0(3)
C10	O1	C11	N2	173.5(6)	C25	O2	C24	N3	-171.7(7)
C25	O2	C24	N4	2.2(3)	C24	O2	C25	C26	1.3(3)
C24	O2	C25	H25a	120.7(7)	C24	O2	C25	H25b	-118.5(7)
C7	N1	C4	C3	-117.6(6)	C7	N1	C4	C5	56.7(4)
C11	N1	C4	C3	37.8(4)	C11	N1	C4	C5	-147.9(6)
C4	N1	C7	C8	-50.8(5)	C4	N1	C7	C10	179.6(7)
C4	N1	C7	H7	69.2(5)	C11	N1	C7	C8	150.9(7)
C11	N1	C7	C10	21.3(4)	C11	N1	C7	H7	-89.1(6)
C4	N1	C11	O1	-167.5(6)	C4	N1	C11	N2	10.9(3)
C7	N1	C11	O1	-9.0(3)	C7	N1	C11	N2	169.4(7)
C12	N2	C11	O1	2.2(3)	C12	N2	C11	N1	-176.0(6)
C11	N2	C12	C13	-122.4(6)	C11	N2	C12	C17	66.1(5)
C24	N3	C21	C20	-58.7(5)	C24	N3	C21	C22	125.8(6)
C21	N3	C24	O2	-12.9(3)	C21	N3	C24	N4	174.3(7)
C26	N4	C24	O2	-5.0(3)	C26	N4	C24	N3	168.8(7)
C29	N4	C24	O2	175.5(7)	C29	N4	C24	N3	-10.7(3)
C24	N4	C26	C25	5.4(3)	C24	N4	C26	C27	126.2(7)
C24	N4	C26	H26	-109.4(6)	C29	N4	C26	C25	-175.1(7)
C29	N4	C26	C27	-54.2(4)	C29	N4	C26	H26	70.1(5)
C24	N4	C29	C30	-29.3(4)	C24	N4	C29	C34	148.2(7)
C26	N4	C29	C30	151.3(6)	C26	N4	C29	C34	-31.3(4)
C11	C1	C2	C3	179.2(7)	C11	C1	C2	H2	-1.06(17)
C6	C1	C2	C3	3.3(3)	C6	C1	C2	H2	-177.0(8)
C11	C1	C6	C5	-179.6(7)	C11	C1	C6	H6	0.84(16)
C2	C1	C6	C5	-3.7(4)	C2	C1	C6	H6	176.8(8)
C1	C2	C3	C4	-1.9(3)	C1	C2	C3	H3	178.7(8)
H2	C2	C3	C4	178.4(8)	H2	C2	C3	H3	-1.038(8)
C2	C3	C4	N1	175.2(7)	C2	C3	C4	C5	0.8(4)
H3	C3	C4	N1	-5.36(21)	H3	C3	C4	C5	-179.8(7)
N1	C4	C5	C6	-175.8(7)	N1	C4	C5	H5	4.64(21)
C3	C4	C5	C6	-1.0(3)	C3	C4	C5	H5	179.4(8)
C4	C5	C6	C1	2.6(3)	C4	C5	C6	H6	-177.9(8)
H5	C5	C6	C1	-177.8(8)	H5	C5	C6	H6	1.727(14)
N1	C7	C8	C9	123.5(8)	N1	C7	C8	H8	-55.5(5)
C10	C7	C8	C9	-113.7(8)	C10	C7	C8	H8	67.3(6)
H7	C7	C8	C9	3.8(4)	H7	C7	C8	H8	-175.3(11)
N1	C7	C10	O1	-24.9(3)	N1	C7	C10	H10a	95.2(7)
N1	C7	C10	H10b	-143.4(8)	C8	C7	C10	O1	-157.3(8)
C8	C7	C10	H10a	-37.1(4)	C8	C7	C10	H10b	84.3(7)
H7	C7	C10	O1	85.2(6)	H7	C7	C10	H10a	-154.6(10)
H7	C7	C10	H10b	-33.3(3)	C7	C8	C9	H9a	-179.2(11)
C7	C8	C9	H9b	1.0(3)	H8	C8	C9	H9a	-0.1(13)
H8	C8	C9	H9b	-180.0(12)	N2	C12	C13	C14	-172.1(7)
N2	C12	C13	H13	8.46(21)	C17	C12	C13	C14	-0.4(4)
C17	C12	C13	H13	-179.8(8)	N2	C12	C17	C16	173.3(7)
N2	C12	C17	H17	-6.46(21)	C13	C12	C17	C16	1.4(4)
C13	C12	C17	H17	-178.3(8)	C12	C13	C14	C15	0.7(3)

C12	C13	C14	H14	-179.8(9)	H13	C13	C14	C15	-179.9(9)
H13	C13	C14	H14	-0.415(3)	C13	C14	C15	C12	179.5(7)
C13	C14	C15	C16	-2.0(4)	H14	C14	C15	C12	-0.05(18)
H14	C14	C15	C16	178.5(9)	C12	C15	C16	C17	-178.6(7)
C12	C15	C16	H16	2.17(18)	C14	C15	C16	C17	2.9(4)
C14	C15	C16	H16	-176.4(8)	C15	C16	C17	C12	-2.6(3)
C15	C16	C17	H17	177.1(9)	H16	C16	C17	C12	176.6(8)
H16	C16	C17	H17	-3.63(3)	C13	C18	C19	C20	177.6(7)
C13	C18	C19	H19	-2.74(20)	C23	C18	C19	C20	2.4(4)
C23	C18	C19	H19	-177.9(9)	C13	C18	C23	C22	-175.3(7)
C13	C18	C23	H23	4.82(20)	C19	C18	C23	C22	-0.3(4)
C19	C18	C23	H23	179.8(9)	C18	C19	C20	C21	-3.2(3)
C18	C19	C20	H20	177.6(9)	H19	C19	C20	C21	177.1(9)
H19	C19	C20	H20	-2.058(17)	C19	C20	C21	N3	-173.5(7)
C19	C20	C21	C22	1.9(4)	H20	C20	C21	N3	5.64(21)
H20	C20	C21	C22	-178.9(8)	N3	C21	C22	C23	175.7(7)
N3	C21	C22	H22	-4.99(21)	C20	C21	C22	C23	0.1(4)
C20	C21	C22	H22	179.4(8)	C21	C22	C23	C18	-1.0(3)
C21	C22	C23	H23	178.9(9)	H22	C22	C23	C18	179.8(9)
H22	C22	C23	H23	-0.381(3)	O2	C25	C26	N4	-3.82(25)
O2	C25	C26	C27	-126.3(7)	O2	C25	C26	H26	112.2(7)
H25a	C25	C26	N4	-123.4(7)	H25a	C25	C26	C27	114.1(7)
H25a	C25	C26	H26	-7.47(6)	H25b	C25	C26	N4	115.7(7)
H25b	C25	C26	C27	-6.8(3)	H25b	C25	C26	H26	-128.3(9)
N4	C26	C27	C28	129.8(8)	N4	C26	C27	H27	-50.9(4)
C25	C26	C27	C28	-116.2(7)	C25	C26	C27	H27	63.1(5)
H26	C26	C27	C28	5.0(4)	H26	C26	C27	H27	-175.7(10)
C26	C27	C28	H28a	179.8(10)	C26	C27	C28	H28b	-0.8(3)
H27	C27	C28	H28a	0.478(5)	H27	C27	C28	H28b	179.9(11)
N4	C29	C30	C31	-179.4(7)	N4	C29	C30	H30	0.64(22)
C34	C29	C30	C31	3.3(3)	C34	C29	C30	H30	-176.7(8)
N4	C29	C34	C33	178.2(7)	N4	C29	C34	H34	-1.58(22)
C30	C29	C34	C33	-4.5(3)	C30	C29	C34	H34	175.7(8)
C29	C30	C31	C32	-2.7(3)	C29	C30	C31	H31	177.0(8)
H30	C30	C31	C32	177.2(8)	H30	C30	C31	H31	-3.014(23)
C30	C31	C32	C14	177.6(6)	C30	C31	C32	C33	3.6(3)
H31	C31	C32	C14	-2.13(18)	H31	C31	C32	C33	-176.2(8)
C14	C32	C33	C34	-178.6(7)	C14	C32	C33	H33	1.37(18)
C31	C32	C33	C34	-4.3(3)	C31	C32	C33	H33	175.6(8)
C32	C33	C34	C29	4.7(3)	C32	C33	C34	H34	-175.5(8)
H33	C33	C34	C29	-175.2(8)	H33	C33	C34	H34	4.57(3)

2.3.9 Single Crystal X-ray Diffraction Study of 2.55g.

Crystals of **2.55g** were obtained by purification using preparative TLC, preparative HPLC and recrystallization from an ether-hexane solution. One of the crystals having a proximate dimension of 0.2, 0.2, 0.2 mm was mounted on a glass capillary. All measurements were made on a Siemens SMART diffractometer using the omega scan mode. Cell dimensions and an orientation matrix for data collection, were obtained from least-squares refinement using the setting angles of 8192 reflections in the range $3° < 2\theta < 57°$, and corresponded to a monoclinic cell with dimensions a = 13.0399(2) Å, b = 16.4639(2) Å, c =17.2130(2) Å, β = 109.273(1). For Z = 4 and FW = 596.85, the calculated density is 1.136 g/cm^3. Based on the systematic absences, the space group was determined to be $P21$. The data was collected at −100 °C using ω–2θ scan technique to a maximum 2θ value of 57°.

A total of 23988 reflections were collected. The unique set contained only 8855 reflections. The final cycle of full matrix least-squares refinement was based on 5999 observed reflections ($I > 2.5\sigma(I)$) and 398 variable parameters. Weights based on counting statistics were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.300 and - 0.400 e/a^3, respectively.

All the calculations were performed using the NRCVAX crystallographic software package.[87]

Table 2-13 Crystal data and structure refinement for 2.55g.

Empirical formula	$C_{38}H_{52}N_4O_2$
Formula weight	596.85
Wavelength	0.70930 Å
Crystal system, space group	Monoclinic, P21/n
Unit cell dimensions	a = 13.0399 (2) Å,
	b = 16.4639 (2) Å,
	c = 17.2130 (2) Å,
Volume	3488.31 (8) $Å^3$
Z, calculated density	1.136 mg/m^3
Absorption coefficient	0.07 mm^{-1}
F (000)	1296.68
Crystal size	0.2 x 0.2 x 0.2 mm
Theta range for data collection	3.00 to 57.00 °

Intensity data were collected on a Siemens SMART diffractometer, using the omega scan mode (0.3 ° scans).

The last least squares cycle was calculated with 104 atoms, 626 parameters and 5987 out of 8855 reflections.

The weight modifier K in Kfo^2	0.00250
Limiting indices	$-17 \leq h \leq 16, 0 \leq k \leq 22, 0 \leq 1 \leq 23$
Reflections collected/unique	23988/8855 [R (int) = 0.011]
Absorption correction	none
Final R indices [I > 2 sigma (I)]	RF = 0.056, Rw = 0.066, GoF = 2.39
R indices (all data)	RF = 0.079, Rw = 0.071
The maximum shift/sigma ratio	0.858
Secondary ext. coefficient	73.1346
The highest peak and the deepest hole	0.400 and –0.300 $Å^{-3}$

Table 2-14 Atomic parameters x, y, z and Biso for **2.55g**. E. S. Ds. Refer to the last digit printed.

	x	y	z	Biso
O1	0.53746(12)	0.33367(8)	0.25166(11)	5.47(9)
O2	0.43516(10)	0.77272(10)	0.16831(7)	4.91(8)
N1	0.67557(11)	0.38478(9)	0.21845(9)	3.09(7)
N2	0.54431(11)	0.47257(8)	0.23917(9)	2.85(6)
N3	0.26096(11)	0.73704(10)	0.11627(8)	3.46(7)
N4	0.36579(11)	0.74482(9)	0.02938(8)	2.78(6)
C1	0.74999(13)	0.44992(10)	0.21359(11)	2.91(8)
C2	0.77588(15)	0.44757(13)	0.13408(11)	4.01(9)
C3	0.84683(16)	0.52003(14)	0.12935(12)	4.43(10)
C4	0.90009(15)	0.52300(13)	0.20274(12)	3.90(9)
C5	0.92549(17)	0.52287(14)	0.28268(12)	4.50(10)
C6	0.85406(16)	0.45060(13)	0.28766(11)	3.89(9)
C7a	0.71093(24)	0.30129(17)	0.24543(17)	2.95(13)
C7b	0.6890 (4)	0.3007 (3)	0.2025 (4)	4.9 (3)
C8a	0.74818(23)	0.25572(18)	0.18095(17)	2.94(12)
C8b	0.7792 (5)	0.2553 (3)	0.2270 (4)	5.1 (3)
C9	0.83074(17)	0.20514(14)	0.20370(15)	5.10(11)
C10	0.59800(19)	0.26544(13)	0.23653(18)	5.75(15)
C11	0.58326(13)	0.40297(10)	0.23599(10)	2.82(7)
C12	0.44578(14)	0.47787(10)	0.25718(10)	2.68(7)
C13	0.34497(14)	0.46746(10)	0.19498(10)	2.89(8)
C14	0.34009(16)	0.44770(13)	0.10893(11)	3.86(9)
C15	0.25055(14)	0.47428(11)	0.21526(11)	3.47(9)
C16	0.25395(16)	0.49184(13)	0.29363(12)	4.09(9)
C17	0.35255(17)	0.50505(13)	0.35398(11)	4.00(9)
C18	0.45020(15)	0.49819(11)	0.33717(11)	3.26(8)
C19	0.55858(18)	0.50950(14)	0.40309(12)	4.64(11)
C20	0.15696(13)	0.72520(11)	0.05027(9)	2.90(7)
C21	0.07375(16)	0.78991(12)	0.05151(12)	3.86(9)
C22	-0.03016(16)	0.77911(12)	-0.02188(12)	4.24(9)
C23	-0.07687(14)	0.69504(13)	-0.02277(12)	3.89(9)
C24	0.00559(15)	0.63045(12)	-0.02232(12)	3.92(9)
C25	0.11116(15)	0.64081(12)	0.05056(11)	3.55(8)
C26a	0.2770 (4)	0.7256 (4)	0.2035 (3)	4.7 (3)
C26b	0.27186(24)	0.76594(19)	0.19993(16)	3.13(13)
C27a	0.2117 (5)	0.7464 (5)	0.2439 (3)	6.2 (3)
C27b	0.23893(24)	0.69606(17)	0.24806(15)	2.71(12)
C28	0.17624(16)	0.71308(14)	0.29453(11)	4.13(10)
C29	0.39548(18)	0.76757(21)	0.23674(12)	7.12(17)
C30	0.35397(13)	0.75063(11)	0.09899(10)	2.81(7)
C31	0.46962(13)	0.76325(10)	0.02365(9)	2.52(7)
C32	0.48885(14)	0.84154(11)	0.00037(10)	2.91(8)
C33	0.40293(16)	0.90566(12)	-0.01302(13)	4.07(10)
C34	0.58908(15)	0.85857(11)	-0.00879(11)	3.45(8)
C35	0.66807(15)	0.79933(13)	0.00486(11)	3.61(9)
C36	0.64760(14)	0.72201(12)	0.02669(11)	3.37(8)
C37	0.54832(14)	0.70205(11)	0.03574(10)	2.90(8)
C38	0.52557(16)	0.61747(12)	0.05792(13)	4.17(9)
H1	0.7102 (15)	0.5009 (11)	0.2156 (10)	4.2 (4)
H2a	0.7070 (16)	0.4470 (13)	0.0888 (12)	5.5 (5)

H2b	0.8191 (15)	0.3937 (12)	0.1361 (11)	5.2 (5)
H3a	0.8638 (17)	0.5189 (13)	0.0796 (12)	6.0 (5)
H3b	0.8031 (16)	0.5743 (13)	0.1253 (12)	5.9 (5)
H4a	0.9912 (15)	0.5735 (11)	0.1972 (11)	4.6 (4)
H4b	0.9947 (15)	0.4731 (11)	0.2003 (10)	4.4 (4)
H5a	0.9911 (18)	0.5219 (14)	0.3310 (13)	7.0 (6)
H5b	0.8805 (17)	0.5755 (13)	0.2814 (12)	5.8 (5)
H6a	0.8355 (15)	0.4511 (12)	0.3371 (11)	5.0 (5)
H6b	0.8967 (17)	0.3962 (13)	0.2907 (12)	6.5 (6)
H9a	0.843 (3)	0.1786 (23)	0.1586 (21)	14.5 (11)
H9b	0.8778 (25)	0.1950 (19)	0.2636 (16)	10.5 (8)
H10a	0.6123 (19)	0.2271 (14)	0.2802 (13)	7.0 (6)
H10b	0.5536 (19)	0.2371 (15)	0.1853 (13)	7.6 (6)
H14a	0.3636 (16)	0.4861 (14)	0.0904 (13)	6.6 (6)
H14b	0.2644 (18)	0.4434 (13)	0.0714 (13)	6.3 (5)
H14c	0.3686 (17)	0.3920 (13)	0.1039 (12)	5.9 (5)
H15	0.1799 (15)	0.4675 (11)	0.1722 (11)	4.3 (4)
H16	0.1845 (15)	0.4978 (12)	0.3078 (11)	4.5 (4)
H17	0.3571 (16)	0.5173 (12)	0.4100 (11)	4.9 (5)
H19a	0.5531 (19)	0.5373 (15)	0.4518 (14)	7.9 (6)
H19b	0.6114 (17)	0.5411 (13)	0.3844 (12)	6.3 (5)
H19c	0.5969 (19)	0.4563 (14)	0.4205 (14)	7.4 (6)
H20	0.1738 (14)	0.7304 (10)	-0.0011 (10)	3.7 (4)
H21a	0.1037 (17)	0.8455 (13)	0.0480 (12)	6.0 (5)
H21b	0.0547 (16)	0.7866 (12)	0.1031 (11)	5.5 (5)
H22a	-0.0838 (17)	0.8219 (13)	-0.0184 (12)	5.8 (5)
H22b	-0.0103 (16)	0.7897 (12)	-0.0749 (11)	5.1 (5)
H23a	-0.1452 (15)	0.6872 (11)	-0.0707 (10)	4.4 (4)
H23b	-0.0977 (16)	0.6868 (12)	0.0292 (12)	5.6 (5)
H24a	-0.0233 (16)	0.5761 (12)	-0.0223 (12)	5.4 (5)
H24b	0.0237 (14)	0.6341 (11)	-0.0740 (10)	4.1 (4)
H25a	0.1643 (16)	0.6014 (12)	0.0472 (12)	5.3 (5)
H25b	0.0984 (15)	0.6331 (12)	0.1035 (11)	4.8 (4)
H28a	0.1503 (24)	0.7597 (18)	0.3004 (17)	10.2 (8)
H28b	0.1683 (21)	0.6645 (16)	0.3240 (15)	8.7 (7)
H29a	0.4131 (19)	0.8189 (15)	0.2688 (13)	7.2 (6)
H29b	0.4372 (24)	0.7226 (19)	0.2754 (17)	11.5 (9)
H33a	0.4230 (16)	0.9537 (12)	-0.0370 (11)	5.3 (5)
H33b	0.3901 (18)	0.9173 (13)	0.0378 (13)	6.7 (6)
H33c	0.3321 (18)	0.8856 (14)	-0.0488 (13)	6.6 (6)
H34	0.6004 (14)	0.9112 (10)	-0.0259 (10)	3.7 (4)
H35	0.7394 (15)	0.8144 (11)	0.0010 (10)	4.0 (4)
H36	0.7038 (15)	0.6787 (11)	0.0378 (11)	4.5 (4)
H38a	0.4576 (18)	0.5996 (13)	0.0208 (13)	6.3 (5)
H38b	0.5823 (20)	0.5794 (15)	0.0581 (15)	8.0 (6)
H38c	0.5193 (18)	0.6120 (13)	0.1137 (13)	6.3 (5)
H7a	0.768	0.297	0.306	3.6
H8a	0.705	0.266	0.117	3.5
H27b	0.266	0.636	0.244	3.5
H26b	0.233	0.821	0.203	4.1
H26a	0.293	0.660	0.216	5.5
H27a	0.184	0.811	0.231	6.7
H7b	0.655	0.293	0.137	6.0
H8b	0.820	0.267	0.291	6.1

Table 2-15 u (i., j) or U values ×100 for **2.55g**. E.S. Ds. Refer to the last digit printed.

	u11(U)	u22	u33	u12	u13	u23
O1	5.60(9)	3.06(7)	14.20(14)	-0.15(6)	6.09(10)	0.54(8)
O2	3.07(7)	12.50(14)	2.89(6)	-1.49(8)	0.74(5)	-1.36(7)
N1	3.35(8)	3.30(8)	5.43(9)	-0.12(6)	1.92(7)	0.03(7)
N2	3.36(8)	3.36(8)	4.39(8)	-0.23(6)	1.65(6)	0.09(6)
N3	2.76(8)	7.77(12)	2.57(7)	-0.96(7)	0.82(6)	-0.30(7)
N4	2.89(7)	4.75(9)	2.94(7)	-0.62(6)	0.99(6)	-0.20(6)
C1	2.96(9)	3.46(9)	4.94(10)	-0.02(7)	1.70(8)	0.51(8)
C2	4.02(11)	7.07(14)	3.63(10)	-1.35(10)	0.56(8)	0.68(10)
C3	4.51(12)	7.32(15)	5.00(11)	-1.10(11)	1.57(9)	1.53(11)
C4	3.52(10)	5.67(13)	5.89(12)	-0.88(9)	1.88(9)	-0.01(10)
C5	5.10(12)	6.73(14)	5.00(11)	-2.38(11)	1.30(10)	-1.04(10)
C6	5.01(12)	6.07(13)	3.50(10)	-1.81(10)	1.11(8)	-0.23(9)
C7a	4.25(17)	3.22(15)	3.98(15)	0.10(13)	1.70(13)	-0.03(13)
C7b	4.8 (3)	3.6 (3)	11.3 (5)	-0.32(23)	4.2 (3)	-0.5 (3)
C8a	3.42(16)	3.94(16)	3.45(14)	-0.10(13)	0.62(12)	-0.97(13)
C8b	6.2 (4)	4.5 (3)	9.8 (4)	0.8 (3)	3.9 (3)	1.2 (3)
C9	4.48(12)	5.89(14)	8.64(16)	0.51(10)	1.67(12)	-1.66(12)
C10	5.81(14)	3.41(11)	14.38(24)	-0.08(10)	5.67(16)	-0.13(13)
C11	3.14(9)	3.48(9)	4.15(9)	-0.54(7)	1.26(7)	0.05(8)
C12	3.61(9)	2.64(8)	4.20(9)	0.12(7)	1.66(8)	0.27(7)
C13	3.62(10)	3.14(9)	4.32(9)	-0.06(7)	1.44(8)	0.03(8)
C14	4.44(11)	5.78(12)	4.22(10)	-0.81(9)	1.13(9)	-0.82(9)
C15	3.51(10)	4.23(10)	5.47(11)	0.36(8)	1.51(9)	0.26(9)
C16	4.49(11)	5.49(13)	6.18(12)	1.11(10)	2.62(10)	0.68(10)
C17	6.14(13)	5.27(12)	4.49(11)	1.22(10)	2.73(10)	0.29(9)
C18	4.62(11)	3.82(10)	3.98(9)	0.43(8)	1.47(8)	0.41(8)
C19	5.71(13)	7.27(15)	4.03(11)	0.12(11)	0.80(10)	-0.17(10)
C20	2.62(8)	5.59(12)	2.70(8)	-0.47(8)	0.73(7)	0.04(8)
C21	4.54(11)	4.15(11)	5.11(11)	0.03(9)	0.40(9)	0.14(9)
C22	3.78(11)	5.05(12)	6.23(13)	0.82(9)	0.22(9)	0.57(10)
C23	2.76(9)	6.39(13)	5.27(11)	-0.26(9)	0.81(8)	0.33(10)
C24	4.00(11)	4.72(11)	5.25(11)	-0.62(9)	0.27(9)	-0.58(9)
C25	3.66(10)	4.40(11)	4.68(10)	0.72(8)	0.39(8)	-0.39(9)
C26a	2.72(24)	12.5 (5)	2.54(22)	-0.7 (3)	0.59(18)	-0.8 (3)
C26b	3.93(16)	5.23(19)	2.83(14)	-1.07(14)	1.22(12)	-0.18(13)
C27a	6.0 (4)	13.2 (6)	3.7 (3)	-2.6 (4)	0.9 (3)	-0.9 (3)
C27b	4.23(16)	3.59(15)	2.51(13)	0.98(13)	1.15(12)	0.21(12)
C28	4.80(12)	6.98(14)	4.12(10)	-0.17(10)	1.73(9)	0.02(10)
C29	3.73(12)	20.0 (3)	3.38(11)	-2.25(16)	1.26(9)	-1.96(15)
C30	2.60(8)	4.66(10)	3.07(8)	-0.23(7)	0.47(7)	0.01(8)
C31	2.85(8)	4.20(10)	2.49(8)	-0.42(7)	0.83(6)	-0.41(7)
C32	3.65(10)	4.02(10)	3.47(9)	-0.20(8)	1.30(7)	-0.48(8)
C33	4.80(12)	4.02(11)	6.91(13)	0.16(9)	2.29(10)	0.23(10)
C34	4.54(11)	4.30(11)	4.79(10)	-0.92(9)	2.24(9)	-0.15(9)
C35	3.53(10)	6.23(13)	4.53(10)	-0.69(9)	2.08(8)	-0.66(9)
C36	3.36(10)	5.40(12)	4.14(10)	0.46(8)	1.37(8)	-0.52(9)
C37	3.45(9)	4.23(10)	3.13(8)	-0.04(8)	0.82(7)	-0.29(8)
C38	4.75(12)	4.55(12)	6.16(12)	0.25(9)	1.27(10)	0.67(10)

Table 2-16 Torsion angle of **2.55g**.

C11	O1	C10	C7a	23.4(3)	C11	O1	C10	H10a	135. (3)
C11	O1	C10	H10b	-108. (3)	C10	O1	C11	N1	-5.2(3)
C10	O1	C11	N2	175.9(5)	C30	O2	C29	C26b	-18.2(3)
C30	O2	C29	H29a	-131. (3)	C30	O2	C29	H29b	110. (4)
C29	O2	C30	N3	4.9(3)	C29	O2	C30	N4	-175.9(5)
C7a	N1	C1	C2	83.3(4)	C7a	N1	C1	C6	-41.9(3)
C7a	N1	C1	H1	-158.2(21)	C11	N1	C1	C2	-127.9(4)
C11	N1	C1	C6	106.9(4)	C11	N1	C1	H1	-9.3(21)
C1	N1	C7a	C8a	-71.2(4)	C1	N1	C7a	C10	-180.0(6)
C1	N1	C7a	H7a	59.6(4)	C11	N1	C7a	C8a	137.3(6)
C11	N1	C7a	C10	28.6(3)	C11	N1	C7a	H7a	-91.8(5)
C1	N1	C11	O1	-169.3(4)	C1	N1	C11	N2	9.51(20)
C7a	N1	C11	O1	-16.6(3)	C7a	N1	C11	N2	162.2(5)
C12	N2	C11	O1	-2.30(20)	C12	N2	C11	N1	179.0(4)
C11	N2	C12	C13	-82.6(3)	C11	N2	C12	C18	100.8(4)
C26b	N3	C20	C21	36.5(3)	C26b	N3	C20	C25	-89.2(4)
C26b	N3	C20	H20	154.0(22)	C30	N3	C20	C21	-119.0(4)
C30	N3	C20	C25	115.2(4)	C30	N3	C20	H20	-1.5(22)
C20	N3	C26b	C27b	74.7(4)	C20	N3	C26b	C29	-178.5(6)
C20	N3	C26b	H26b	-55.3(4)	C30	N3	C26b	C27b	-127.7(6)
C30	N3	C26b	C29	-20.8(3)	C30	N3	C26b	H26b	102.4(6)
C20	N3	C30	O2	169.7(4)	C20	N3	C30	N4	-9.42(20)
C26b	N3	C30	O2	11.2(3)	C26b	N3	C30	N4	-167.9(5)
C31	N4	C30	O2	-0.24(19)	C31	N4	C30	N3	178.8(4)
C30	N4	C31	C32	-95.0(4)	C30	N4	C31	C37	89.2(4)
N1	C1	C2	C3	176.1(5)	N1	C1	C2	H2a	52. (3)
N1	C1	C2	H2b	-63.1(23)	C6	C1	C2	C3	-57.9(3)
C6	C1	C2	H2a	178. (3)	C6	C1	C2	H2b	62.9(23)
H1	C1	C2	C3	60.3(21)	H1	C1	C2	H2a	-64. (3)
H1	C1	C2	H2b	-179. (3)	N1	C1	C6	C5	-176.3(5)
N1	C1	C6	H6a	-50. (3)	N1	C1	C6	H6b	62. (3)
C2	C1	C6	C5	57.5(3)	C2	C1	C6	H6a	-176. (3)
C2	C1	C6	H6b	-65. (3)	H1	C1	C6	C5	-61.8(21)
H1	C1	C6	H6a	65. (3)	H1	C1	C6	H6b	176. (3)
C1	C2	C3	C4	56.7(3)	C1	C2	C3	H3a	180. (3)
C1	C2	C3	H3b	-64.5(25)	H2a	C2	C3	C4	177. (3)
H2a	C2	C3	H3a	-60. (4)	H2a	C2	C3	H3b	56. (4)
H2b	C2	C3	C4	-61.9(23)	H2b	C2	C3	H3a	61. (4)
H2b	C2	C3	H3b	177. (3)	C2	C3	C4	C5	-55.1(3)
C2	C3	C4	H4a	-177. (3)	C2	C3	C4	H4b	64.5(22)
H3a	C3	C4	C5	-178. (3)	H3a	C3	C4	H4a	60. (4)
H3a	C3	C4	H4b	-59. (4)	H3b	C3	C4	C5	66.1(25)
H3b	C3	C4	H4a	-56. (3)	H3b	C3	C4	H4b	-174. (3)
C3	C4	C5	C6	54.6(3)	C3	C4	C5	H5a	176. (3)
C3	C4	C5	H5b	-62.5(25)	H4a	C4	C5	C6	175. (3)
H4a	C4	C5	H5a	-63. (4)	H4a	C4	C5	H5b	58. (3)
H4b	C4	C5	C6	-64.5(22)	H4b	C4	C5	H5a	57. (4)
H4b	C4	C5	H5b	178. (3)	C4	C5	C6	C1	-55.8(3)
C4	C5	C6	H6a	-178. (3)	C4	C5	C6	H6b	67. (3)

H5a	C5	C6	C1	180. (3)	H5a	C5	C6	H6a	58. (4)
H5a	C5	C6	H6b	-58. (4)	H5b	C5	C6	C1	59.7(25)
H5b	C5	C6	H6a	-63. (4)	H5b	C5	C6	H6b	-178. (4)
N1	C7a	C8a	C9	143.4(7)	N1	C7a	C8a	H8a	-36.6(3)
C10	C7a	C8a	C9	-112.7(7)	C10	C7a	C8a	H8a	67.3(5)
H7a	C7a	C8a	C9	12.0(3)	H7a	C7a	C8a	H8a	-168.0(9)
N1	C7a	C10	O1	-30.11(25)	N1	C7a	C10	H10a	-146. (3)
N1	C7a	C10	H10b	95. (3)	C8a	C7a	C10	O1	-143.9(7)
C8a	C7a	C10	H10a	100. (3)	C8a	C7a	C10	H10b	-19. (3)
H7a	C7a	C10	O1	91.3(6)	H7a	C7a	C10	H10a	-24. (3)
H7a	C7a	C10	H10b	-144. (3)	C7a	C8a	C9	H9a	175. (4)
C7a	C8a	C9	H9b	-3. (4)	H8a	C8a	C9	H9a	-5. (4)
H8a	C8a	C9	H9b	177. (4)	N2	C12	C13	C14	1.86(20)
N2	C12	C13	C15	-179.1(5)	C18	C12	C13	C14	178.3(5)
C18	C12	C13	C15	-2.59(23)	N2	C12	C18	C17	178.7(5)
N2	C12	C18	C19	-3.28(22)	C13	C12	C18	C17	2.12(24)
C13	C12	C18	C19	-179.8(5)	C12	C13	C14	H14a	-50. (3)
C12	C13	C14	H14b	-179. (3)	C12	C13	C14	H14c	67. (3)
C15	C13	C14	H14a	131. (3)	C15	C13	C14	H14b	2. (3)
C15	C13	C14	H14c	-112. (3)	C12	C13	C15	C16	0.82(24)
C12	C13	C15	H15	-179.3(25)	C14	C13	C15	C16	179.9(5)
C14	C13	C15	H15	-0.3(24)	C13	C15	C16	C17	1.41(24)
C13	C15	C16	H16	178. (3)	H15	C15	C16	C17	-178. (3)
H15	C15	C16	H16	-2. (3)	C15	C16	C17	C18	-1.90(23)
C15	C16	C17	H17	179. (3)	H16	C16	C17	C18	-179. (3)
H16	C16	C17	H17	2. (4)	C16	C17	C18	C12	0.13(24)
C16	C17	C18	C19	-177.9(5)	H17	C17	C18	C12	179. (3)
H17	C17	C18	C19	1. (3)	C12	C18	C19	H19a	162. (3)
C12	C18	C19	H19b	44. (3)	C12	C18	C19	H19c	-71. (3)
C17	C18	C19	H19a	-20. (3)	C17	C18	C19	H19b	-138. (3)
C17	C18	C19	H19c	107. (3)	C18	C19	H19a	H19b	-125. (4)
H19b	C19	H19a	H19b	0. (3)	H19c	C19	H19a	H19b	108. (5)
C18	C19	H19b	H19a	122. (4)	C18	C19	H19b	H19c	-122. (4)
H19a	C19	H19b	H19a	0. (4)	H19a	C19	H19b	H19c	115. (5)
H19c	C19	H19b	H19a	-115. (5)	H19c	C19	H19b	H19c	0. (4)
C18	C19	H19c	H19b	124. (4)	H19a	C19	H19c	H19b	-110. (6)
H19b	C19	H19c	H19b	0. (3)	N3	C20	C21	C22	175.8(5)
N3	C20	C21	H21a	54. (3)	N3	C20	C21	H21b	-62.8(25)
C25	C20	C21	C22	-57.6(3)	C25	C20	C21	H21a	-179. (3)
C25	C20	C21	H21b	63.7(25)	H20	C20	C21	C22	60.3(22)
H20	C20	C21	H21a	-61. (3)	H20	C20	C21	H21b	-178. (3)
N3	C20	C25	C24	-177.0(5)	N3	C20	C25	H25a	-57. (3)
N3	C20	C25	H25b	59.1(25)	C21	C20	C25	C24	56.7(3)
C21	C20	C25	H25a	177. (3)	C21	C20	C25	H25b	-67.3(25)
H20	C20	C25	C24	-61.8(22)	H20	C20	C25	H25a	58. (3)
H20	C20	C25	H25b	174. (3)	C20	C21	C22	C23	57.0(3)
C20	C21	C22	H22a	-180. (3)	C20	C21	C22	H22b	-64.1(23)
H21a	C21	C22	C23	177. (3)	H21a	C21	C22	H22a	-60. (4)
H21a	C21	C22	H22b	56. (4)	H21b	C21	C22	C23	-65.4(25)
H21b	C21	C22	H22a	58. (4)	H21b	C21	C22	H22b	174. (3)
C21	C22	C23	C24	-56.2(3)	C21	C22	C23	H23a	-179.9(24)
C21	C22	C23	H23b	62.9(25)	H22a	C22	C23	C24	-178. (3)
H22a	C22	C23	H23a	58. (4)	H22a	C22	C23	H23b	-59. (4)
H22b	C22	C23	C24	62.8(23)	H22b	C22	C23	H23a	-61. (3)

H22b	C22	C23	H23b	-178. (3)
C22	C23	C24	H24a	180. (3)
H23a	C23	C24	C25	-179.4(24)
H23a	C23	C24	H24b	62. (3)
H23b	C23	C24	H24a	60. (4)
C23	C24	C25	C20	-55.7(3)
C23	C24	C25	H25b	64.6(25)
H24a	C24	C25	H25a	61. (4)
H24b	C24	C25	C20	64.4(23)
H24b	C24	C25	H25b	-175. (3)
N3	C26b	C27b	H27b	42.7(3)
C29	C26b	C27b	H27b	-61.3(5)
H26b	C26b	C27b	H27b	173.4(9)
N3	C26b	C29	H29a	138. (3)
C27b	C26b	C29	O2	134.0(7)
C27b	C26b	C29	H29b	13. (4)
H26b	C26b	C29	H29a	14. (3)
C26b	C27b	C28	H28a	2. (4)
H27b	C27b	C28	H28a	-178. (4)
N4	C31	C32	C33	3.62(21)
C37	C31	C32	C33	179.3(5)
N4	C31	C37	C36	177.7(5)
C32	C31	C37	C36	2.10(22)
C31	C32	C33	H33a	-169. (3)
C31	C32	C33	H33c	-50. (3)
C34	C32	C33	H33b	-115. (3)
C31	C32	C34	C35	0.03(22)
C33	C32	C34	C35	179.1(5)
C32	C34	C35	C36	0.95(23)
H34	C34	C35	C36	-176.6(24)
C34	C35	C36	C37	-0.41(23)
H35	C35	C36	C37	178.4(24)
C35	C36	C37	C31	-1.10(22)
H36	C36	C37	C31	178.2(24)
C31	C37	C38	H38a	50. (3)
C31	C37	C38	H38c	-69. (3)
C36	C37	C38	H38b	-7. (3)
C37	C38	H38b	H38c	123. (4)
H38c	C38	H38b	H38c	0. (3)
H38a	C38	H38c	H38b	117. (5)
C19	H19a	H19b	C19	0.0(4)
C19	H19b	H19c	C19	0.0(4)
C38	H38b	H38c	C38	0.0(4)

C22	C23	C24	C25	55.7(3)
C22	C23	C24	H24b	-63.3(23)
H23a	C23	C24	H24a	-55. (4)
H23b	C23	C24	C25	-64.4(25)
H23b	C23	C24	H24b	177. (3)
C23	C24	C25	H25a	-174. (3)
H24a	C24	C25	C20	179. (3)
H24a	C24	C25	H25b	-61. (4)
H24b	C24	C25	H25a	-54. (3)
N3	C26b	C27b	C28	-137.3(7)
C29	C26b	C27b	C28	118.7(7)
H26b	C26b	C27b	C28	-6.58(22)
N3	C26b	C29	O2	22.67(23)
N3	C26b	C29	H29b	-99. (4)
C27b	C26b	C29	H29a	-111. (3)
H26b	C26b	C29	O2	-101.1(7)
H26b	C26b	C29	H29b	138. (4)
C26b	C27b	C28	H28b	-177. (4)
H27b	C27b	C28	H28b	3. (3)
N4	C31	C32	C34	-177.3(5)
C37	C31	C32	C34	-1.58(22)
N4	C31	C37	C38	-2.18(21)
C32	C31	C37	C38	-177.8(5)
C31	C32	C33	H33b	64. (3)
C34	C32	C33	H33a	12. (3)
C34	C32	C33	H33c	131. (3)
C31	C32	C34	H34	177.7(24)
C33	C32	C34	H34	-3.3(23)
C32	C34	C35	H35	-177.9(24)
H34	C34	C35	H35	5. (3)
C34	C35	C36	H36	-179.7(24)
H35	C35	C36	H36	-1. (3)
C35	C36	C37	C38	178.8(5)
H36	C36	C37	C38	-1.9(23)
C31	C37	C38	H38b	173. (3)
C36	C37	C38	H38a	-130. (3)
C36	C37	C38	H38c	111. (3)
H38a	C38	H38b	H38c	-114. (5)
C37	C38	H38c	H38b	-123. (4)
H38b	C38	H38c	H38b	0. (4)
C19	H19a	H19b	H19c	-41. (4)
H19a	H19b	H19c	C19	37. (3)

Table 2-17 Atomic Bond Distances in Angstroms of **2.55g**.

O1-C10	1.444(3)	C17-H17	0.95(3)
O1-C11	1.353(3)	C18-C19	1.501(4)
O2-C29	1.442(3)	C19-H19a	0.94(3)
O2-C30	1.358(3)	C19-H19b	0.97(3)
N1-C1	1.468(3)	C19-H19c	1.02(3)
N1-C7a	1.480(4)	C20-C21	1.526(4)
N1-C11	1.370(3)	C20-C25	1.515(4)
N2-C11	1.263(3)	C20-H20	1.007(24)
N2-C12	1.422(3)	C21-C22	1.533(4)
N3-C20	1.466(3)	C21-H21a	0.98(3)
N3-C26b	1.482(4)	C21-H21b	1.01(3)
N3-C30	1.364(3)	C22-C23	1.512(4)
N4-C30	1.258(3)	C22-H22a	1.02(3)
N4-C31	1.423(3)	C22-H22b	1.08(3)
C1-C2	1.516(4)	C23-C24	1.511(4)
C1-C6	1.529(3)	C23-H23a	1.01(3)
C1-H1	1.002(23)	C23-H23b	1.03(3)
C2-C3	1.529(4)	C24-C25	1.539(3)
C2-H2a	0.94(3)	C24-H24a	0.97(3)
C2-H2b	1.06(3)	C24-H24b	1.02(3)
C3-C4	1.512(4)	C25-H25a	0.97(3)
C3-H3a	0.96(3)	C25-H25b	1.00(3)
C3-H3b	1.06(3)	C26b-C27b	1.559(6)
C4-C5	1.513(4)	C26b-C29	1.528(5)
C4-H4a	1.02(3)	C26b-H26b	1.080(4)
C4-H4b	1.04(3)	C27b-C28	1.355(5)
C5-C6	1.537(4)	C27b-H27b	1.080(4)
C5-H5a	0.98(3)	C28-H28a	0.92(4)
C5-H5b	1.09(3)	C28-H28b	0.96(4)
C6-H6a	0.99(3)	C29-H29a	0.95(3)
C6-H6b	1.04(3)	C29-H29b	1.05(4)
C7a-C8a	1.548(5)	C31-C32	1.401(3)
C7a-C10	1.555(5)	C31-C37	1.401(3)
C7a-H7a	1.080(4)	C32-C33	1.503(4)
C8a-C9	1.319(5)	C32-C34	1.398(3)
C8a-H8a	1.080(4)	C33-H33a	0.94(3)
C9-H9a	0.96(5)	C33-H33b	1.01(3)
C9-H9b	1.02(4)	C33-H33c	1.01(3)
C10-H10a	0.94(3)	C34-C35	1.379(4)
C10-H10b	1.01(3)	C34-H34	0.937(24)
C12-C13	1.405(3)	C35-C36	1.378(4)
C12-C18	1.399(3)	C35-H35	0.983(25)
C13-C14	1.496(4)	C36-C37	1.398(3)
C13-C15	1.394(3)	C36-H36	1.02(3)
C14-H14a	0.98(3)	C37-C38	1.499(4)
C14-H14b	0.99(3)	C38-H38a	0.94(3)
C14-H14c	1.03(3)	C38-H38b	0.96(3)
C15-C16	1.365(4)	C38-H38c	1.01(3)
C15-H15	0.96(3)		
C16-C17	1.376(4)		
C16-H16	0.97(3)		
C17-C18	1.403(4)		
N1-C7b	1.437(7)	C26a-C27a	1.328(11)
N3-C26a	1.463(6)	C26a-H26a	1.080(9)
C7b-C8b	1.337(10)	C27a-C28	1.261(9)
C7b-C10	1.609(7)	C27a-H28a	1.47(4)
C7b-H7b	1.080(9)	C27a-H27a	1.080(11)
C8b-C9	1.228(8)		

Table 2-18 Atomic angles in degree of **2.55g**.

C10-O1-C11	108.49(19)	H19b-C19-H19c	100(3)
C29-O2-C30	108.44(19)	N3-C20-C21	112.08(20)
C1-N1-C7a	123.65(22)	N3-C20-C25	112.38(20)
C1-N1-C11	119.79(19)	N3-C20-H20	105.1(14)
C7a-N1-C11	110.05(22)	C21-C20-C25	110.96(19)
C11-N2-C12	118.01(19)	C21-C20-H20	108.4(14)
C20-N3-C26b	124.25(22)	C25-C20-H20	107.6(14)
C20-N3-C30	120.92(18)	C20-C21-C22	110.27(22)
C26b-N3-C30	110.87(21)	C20-C21-H21a	108.1(17)
C30-N4-C31	117.83(18)	C20-C21-H21b	111.1(16)
N1-C1-C2	112.33(20)	C22-C21-H21a	111.2(17)
N1-C1-C6	112.03(20)	C22-C21-H21b	109.3(15)
N1-C1-H1	104.7(13)	H21a-C21-H21b	106.8(23)
C2-C1-C6	110.60(19)	C21-C22-C23	110.83(22)
C2-C1-H1	109.4(13)	C21-C22-H22a	109.1(16)
C6-C1-H1	107.5(13)	C21-C22-H22b	107.4(14)
C1-C2-C3	110.16(23)	C23-C22-H22a	111.8(17)
C1-C2-H2a	107.2(17)	C23-C22-H22b	110.7(15)
C1-C2-H2b	107.3(14)	H22a-C22-H22b	106.8(22)
C3-C2-H2a	113.8(18)	C22-C23-C24	111.23(21)
C3-C2-H2b	110.9(14)	C22-C23-H23a	112.2(15)
H2a-C2-H2b	107.2(23)	C22-C23-H23b	109.5(16)
C2-C3-C4	111.68(22)	C24-C23-H23a	109.9(15)
C2-C3-H3a	110.7(18)	C24-C23-H23b	107.9(16)
C2-C3-H3b	109.4(16)	H23a-C23-H23b	105.9(21)
C4-C3-H3a	110.1(18)	C23-C24-C25	111.54(22)
C4-C3-H3b	109.3(16)	C23-C24-H24a	112.2(17)
H3a-C3-H3b	105.4(24)	C23-C24-H24b	109.5(14)
C3-C4-C5	111.31(21)	C25-C24-H24a	110.0(17)
C3-C4-H4a	108.6(15)	C25-C24-H24b	107.6(14)
C3-C4-H4b	108.1(14)	H24a-C24-H24b	105.8(22)
C5-C4-H4a	110.5(15)	C20-C25-C24	110.19(20)
C5-C4-H4b	109.0(14)	C20-C25-H25a	107.6(17)
H4a-C4-H4b	109.3(21)	C20-C25-H25b	107.3(16)
C4-C5-C6	111.51(22)	C24-C25-H25a	110.0(16)
C4-C5-H5a	113.0(18)	C24-C25-H25b	113.4(15)
C4-C5-H5b	105.5(15)	H25a-C25-H25b	108.1(22)
C6-C5-H5a	107.7(19)	N3-C26b-C27b	108.4(3)
C6-C5-H5b	108.1(16)	N3-C26b-C29	98.9(3)
H5a-C5-H5b	111.0(24)	N3-C26b-H26b	115.7(3)
C1-C6-C5	110.14(22)	C27b-C26b-C29	102.9(3)
C1-C6-H6a	107.9(16)	C27b-C26b-H26b	114.3(3)
C1-C6-H6b	110.9(16)	C29-C26b-H26b	114.9(4)
C5-C6-H6a	115.2(16)	C26b-C27b-C28	118.6(3)
C5-C6-H6b	110.1(16)	C26b-C27b-H27b	120.7(3)
H6a-C6-H6b	102.5(23)	C28-C27b-H27b	120.7(3)
N1-C7a-C8a	110.9(3)	C27b-C28-H28a	125.4(24)
N1-C7a-C10	97.3(3)	C27b-C28-H28b	107.5(22)
N1-C7a-H7a	115.0(3)	H28a-C28-H28b	127(3)
C8a-C7a-C10	104.6(3)	O2-C29-C26b	106.17(23)
C8a-C7a-H7a	113.8(3)	O2-C29-H29a	108.9(20)

C10-C7a-H7a	113.7(3)
C7a-C8a-C9	120.2(3)
C7a-C8a-H8a	119.9(3)
C9-C8a-H8a	119.9(4)
C8a-C9-H9a	117(3)
C8a-C9-H9b	124.4(24)
H9a-C9-H9b	118(4)
O1-C10-C7a	104.26(24)
O1-C10-H10a	110.2(19)
O1-C10-H10b	110.6(19)
C7a-C10-H10a	104.4(19)
C7a-C10-H10b	120.7(18)
H10a-C10-H10b	106(3)
O1-C11-N1	109.72(20)
O1-C11-N2	123.18(21)
N1-C11-N2	127.09(21)
N2-C12-C13	120.63(20)
N2-C12-C18	118.90(21)
C13-C12-C18	120.37(21)
C12-C13-C14	120.46(21)
C12-C13-C15	118.75(22)
C14-C13-C15	120.79(22)
C13-C14-H14a	111.3(18)
C13-C14-H14b	111.4(17)
C13-C14-H14c	113.1(17)
H14a-C14-H14b	114.1(25)
H14a-C14-H14c	104(3)
H14b-C14-H14c	102.0(25)
C13-C15-C16	121.38(23)
C13-C15-H15	120.0(15)
C16-C15-H15	118.7(15)
C15-C16-C17	119.85(23)
C15-C16-H16	119.4(16)
C17-C16-H16	120.6(16)
C16-C17-C18	121.20(24)
C16-C17-H17	121.6(17)
C18-C17-H17	117.2(17)
C12-C18-C17	118.38(23)
C12-C18-C19	119.75(23)
C17-C18-C19	121.84(23)
C18-C19-H19a	111.4(21)
C18-C19-H19b	115.3(17)
C18-C19-H19c	113.4(19)
H19a-C19-H19b	104(3)
H19a-C19-H19c	111(3)
C7b-N1-C11	115.5(3)
C26a-N3-C30	114.4(3)
N1-C7b-C8b	128.2(7)
N1-C7b-C10	96.7(4)
N1-C7b-H7b	106.6(6)
C8b-C7b-C10	110.4(6)
C8b-C7b-H7b	107.8(7)
C10-C7b-H7b	104.7(5)
C7b-C8b-C9	140.7(9)

O2-C29-H29b	107.6(22)
C26b-C29-H29a	105.1(20)
C26b-C29-H29b	118.9(22)
H29a-C29-H29b	109(3)
O2-C30-N3	110.08(19)
O2-C30-N4	123.54(20)
N3-C30-N4	126.37(20)
N4-C31-C32	118.65(20)
N4-C31-C37	120.18(21)
C32-C31-C37	121.02(20)
C31-C32-C33	119.86(21)
C31-C32-C34	118.56(22)
C33-C32-C34	121.58(22)
C32-C33-H33a	110.6(17)
C32-C33-H33b	109.8(17)
C32-C33-H33c	110.5(18)
H33a-C33-H33b	113.7(24)
H33a-C33-H33c	107.8(25)
H33b-C33-H33c	104.2(24)
C32-C34-C35	120.92(23)
C32-C34-H34	118.7(15)
C35-C34-H34	120.3(15)
C34-C35-C36	120.01(22)
C34-C35-H35	118.9(15)
C36-C35-H35	121.1(15)
C35-C36-C37	121.14(23)
C35-C36-H36	120.0(15)
C37-C36-H36	118.9(15)
C31-C37-C36	118.32(22)
C31-C37-C38	120.69(21)
C36-C37-C38	120.99(22)
C37-C38-H38a	109.1(18)
C37-C38-H38b	112.6(19)
C37-C38-H38c	113.7(18)
H38a-C38-H38b	110(3)
H38a-C38-H38c	106.6(25)
H38b-C38-H38c	103(3)

N3-C26a-C29	95.6(4)
N3-C26a-H26a	106.7(5)
C27a-C26a-C29	112.5(6)
C27a-C26a-H26a	108.4(7)
C29-C26a-H26a	105.0(5)
C26a-C27a-C28	131.3(10)
C26a-C27a-H27a	114.3(8)
C28-C27a-H27a	114.3(7)
C27a-C28-H28a	83.4(25)

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Chapter 3

Synthesis of Tetrahydro-1,3-Oxazine Derivatives by Palladium Catalyzed Cycloaddition of Vinyloxetanes with Heterocumulenes; Completely Stereoselective Synthesis of Bicyclic 1,3-Oxazines.

3.1 Introduction

3.1.1 Tetrahydro-1,3-oxazine Derivatives

Tetrahydro-1, 3-oxazine consists of a ring of four carbon atoms, one oxygen and one nitrogen atom; the two heteroatoms are in the 1,3-positions (Figure 3-1).

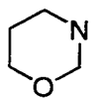
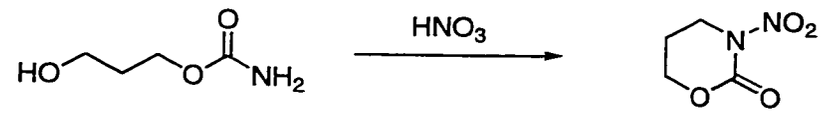


Figure 3-1 Common structure of tetrahydro-1,3-oxazines.

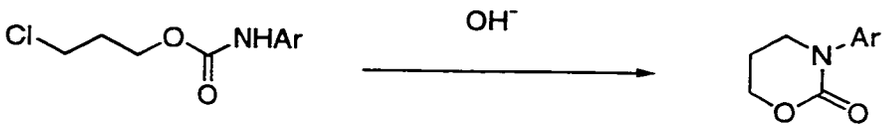
The synthesis of tetrahydro-1,3-oxazines has attracted attention in the past because of their potential as antibiotics,[1-4] antitumor agents,[5-7] analgesics,[8,9] sedatives,[10,11] neuroleptics[12] and anticonvulsants.[13] There are a number of known methods for the preparation of tetrahydro-1,3 oxazine derivatives.[14-18]

The introductory section of this chapter focuses only on the synthetic procedures for the formation of 2-oxo- and 2-iminotetrahydro-1,3-oxazine derivatives.

The first preparation of 2-oxotetrahydro-1,3-oxazines was performed by the cyclization reaction of a hydroxy carbamate ester (**3.1**) in nitric acid (eq 1).[14] *N*-Arylcarbamates (**3.3**) of γ-halogenopropanols can also be cyclized to *N*-aryltetrahydro-1,3-oxazin-2-one derivatives (**3.4**) under basic conditions (eq 2).[19-21]

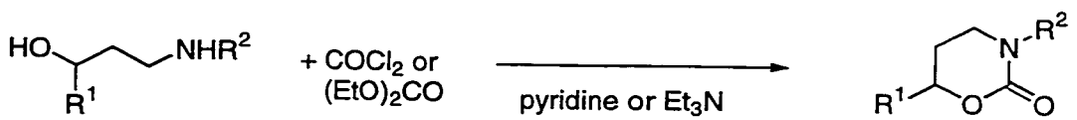


3.1 **3.2** (eq 1)



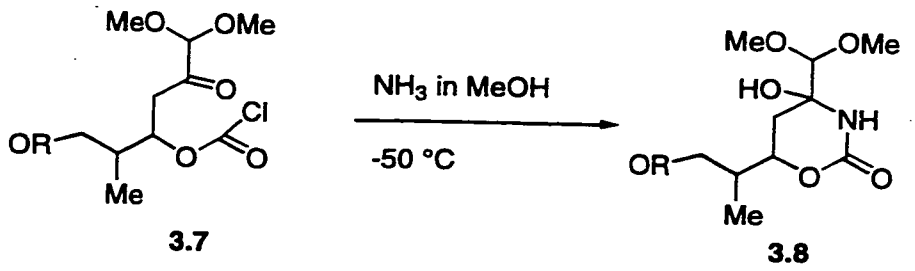
3.3 **3.4** (eq 2)

The reaction of 3-aminopropanol or it derivatives (**3.5**) with phosgene[22,23] or $(EtO)_2CO$[24-27] in the presence of pyridine or Et_3N, gave *N*-substituted-tetrahydro-1,3-oxazin-2-one derivatives (**3.6**) (eq 3). Unfortunately, very low product yields were obtained in some cases.



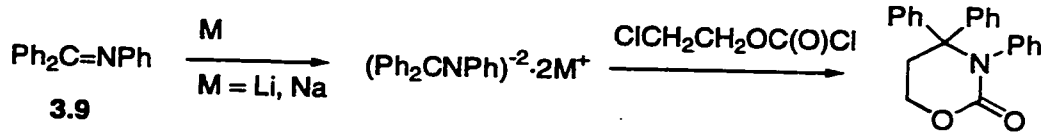
3.5 **3.6** (eq 3)

Meyers and Shaw[28] obtained **3.8**, a sub-structure of the antitumor agent, maytansine, from the reaction of the ketochloroformate, **3.7**, with ammonia (eq 4).



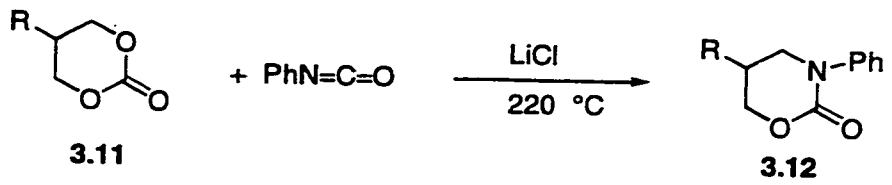
3.7 **3.8** (eq 4)

Smith et al.[29] reported the synthesis of tetrahydro-1,3-oxazin-2-one derivatives (**3.10**) by metalation of imines (**3.9**), followed by treatment with 2-chloroethyl chloroformate (eq 5).



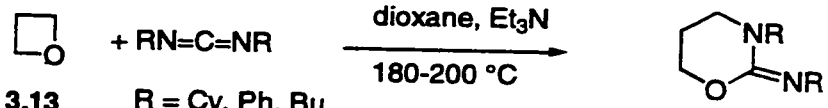
3.9 **3.10** M = Li, 88% Na, 67% (eq 5)

Heterocumulenes such as isocyanates and carbodiimides are often utilized in the preparation of tetrahydro-1,3-oxazine derivatives. Heating a 2-oxo-1,3-dioxane (**3.11**) with phenyl isocyanate in the presence of LiCl furnished 3-phenyltetrahydro-1,3-oxazin-2-one (**3.12**)[30] (eq 6).



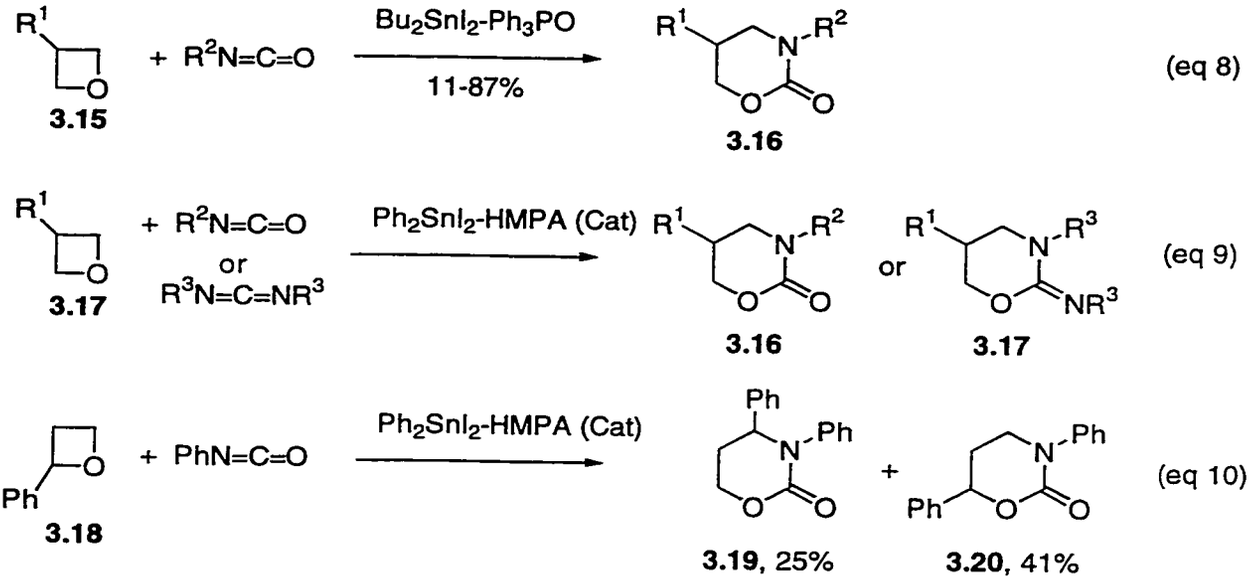
3.11 3.12 (eq 6)

Several methods have been described for the preparation of tetrahydro-1,3-oxazin-2-imines (**3.14**) by the cycloaddition of heterocumulenes with oxetanes. For instance, the reaction of oxetane (**3.13**) with carbodiimides in the presence of triethylamine has been described in US patent (eq 7).[31] Note that, relatively high reaction temperatures (180-200 °C) were needed in most cases.



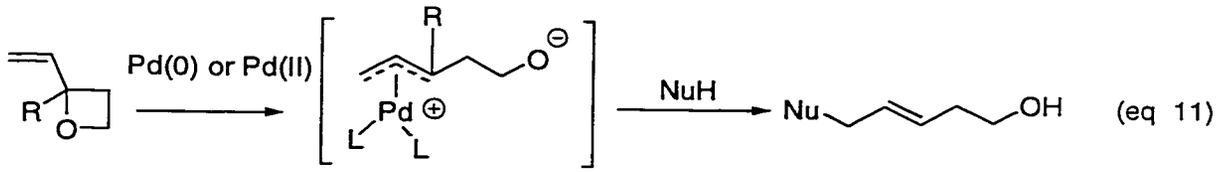
3.13 3.14 (eq 7)

Baba and co-workers reported the formation of tetrahydro-1,3-oxazin-2-ones (**3.16**) in 11–87% yields by the reaction of oxetanes (**3.15**) with isocyanates in the presence of an equimolar amount of a organotin-halide complex such as Bu_2SnI_2-Ph_3PO (eq 8).[32] The Ph_2SnI_2-HMPA complex can be used in catalytic quantities for the same reaction as well as for the reaction of **3.16** with carbodiimides to form tetrahydro-1,3-oxazin-2-imines (**3.17**) (eq 9).[33,34] However, the reaction is not regioselective in all cases, –e.g. two products (**3.19**) and (**3.20**) were obtained from the reaction of (**3.18**) with phenylisocyanate in 25 and 41% respectively (eq 10).



3.2 Aim of the research

Larock et al.[35-37] have observed the palladium (0)-catalyzed nucleophilic ring opening of 2-vinyloxetanes (**3.21**) in the synthesis of homoallyllic alcohols (eq 11).



3.21a, R =H
3.21b, R=CH_3

A π-allyl palladium complex is a proposed reaction intermediate, in analogy to the 2-vinyloxirane/heterocumulene process described in Chapter 2. Therefore, 2-

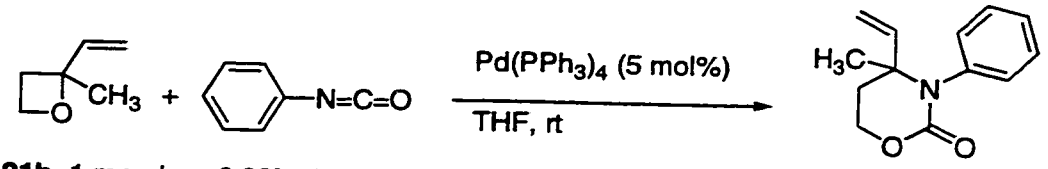
vinyloxetanes could, in principle, be used for cycloaddition with heterocumulenes to prepare 4-vinyltetrahydro-1,3-oxazine derivatives. In addition, to our knowledge, there are no examples for the preparation of tetrahydro-1,3-oxazine derivatives by palladium-catalyzed reactions.

This chapter presents the results obtained from the palladium-catalyzed cycloaddition reactions of monocyclic oxetanes with heterocumulenes affording 4-vinyltetrahydro-1,3-oxazines. Also included are results obtained by reactions of bicyclic oxetanes with heterocumulenes to form 3-aza-1-oxo-*cis*-bicylo[4.4.0]decanes.

3.3 Results and Discussion.

3.3.1 Cycloaddition reaction of monocyclic vinyloxetanes with heterocumulenes.

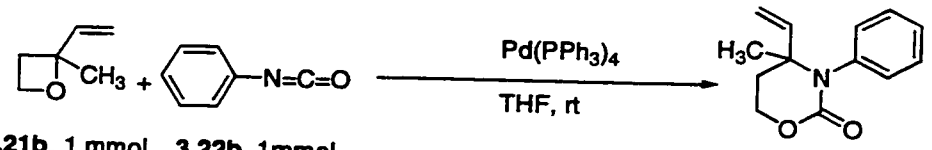
To determine the viability of the formation of tetrahydro-1,3-oxazine derivatives by the cycloaddition reaction of vinyloxetanes with heterocumulenes, we initially examined the reaction of 2-vinyloxetane (**3.21b**, R = CH_3) with phenylisocyanate (**3.22a**) in anhydrous THF (Table 3-1) with 5 mol% of $Pd(PPh_3)_4$ as the catalyst (eq 12). The latter was used in the nucleophilic ring opening reaction of 2-vinyloxetane with hard nucleophiles to form homoallylic alcohols as shown in eq 11.[35] The desired product, 4-vinyltetrahydro-1,3-oxazine-2-one (**3.23f**), was obtained in 47% yield (Table 3-1, entry 1).



3.21b, 1 mmol **3.22b**, 1mmol **3.23f**, 47% yield (eq 12)

Optimization of the amount of catalyst for this reaction was examined by reducing the quantity of the palladium catalyst, $Pd(PPh_3)_4$ (without addition of any phosphine ligands) from 5 mol% to 3 mol% (57% isolated yield of **3.23f**), 2 mol% (53% isolated yield of **3.23f**) and 1 mol% (38% isolated yield of **3.23f**). (See Table 3-1) Therefore, 2-3 mol % of palladium catalyst was used for the cycloaddition reactions.

Table 3-1 Determination of the Optimum Amount of Palladium Catalyst for the Cycloaddition Reaction of 2-Methyl-2-vinyloxetane (**3.21b**) with Phenylisocyanate (**3.22a**).[a]

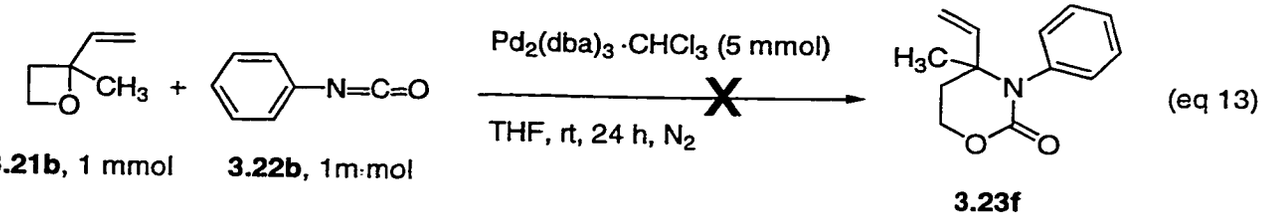


3.21b, 1 mmol **3.22b**, 1mmol **3.23f**

Entry	mol% of $Pd(PPh_3)_4$ to 1 mol of phenylisocyanate	Isolated yield of **3.23f** (%)[b]
1	5	47
2	3	57
3	2	53
4	1	38
5	0	0

[a] Reaction conditions: 2-methyl-2-vinyloxetane **3.21b** (1.0 mmol), phenylisocyanate **3.22a** (1.0 mmol), $Pd(PPh_3)_4$, 5 mL THF, room temperature, N_2 atmosphere.
[b] Purified by preparative TLC.

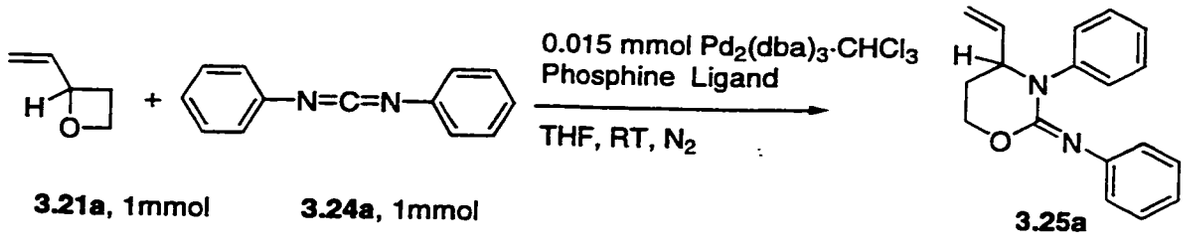
The presence of phosphine ligands was essential for the reaction catalyzed by $Pd_2(dba)_3 \cdot CHCl_3$, as no conversion of heterocumulenes occurred in the absence of a phosphine ligand (eq 13).



3.21b, 1 mmol **3.22b**, 1 mmol **3.23f** (eq 13)

To investigate the effect of the added phosphine ligands in the reaction, different types of phosphine ligands were employed when 2-vinyloxetane **3.21a** was treated with diphenylcarbodiimide **3.24a** to form *N*,3-di(phenyl)-4-vinyltetrahydro-1,3-oxazin-2-imine, **3.25a** (see Table 3-2). Modest changes in the product yields were observed with different phosphine ligands in the reaction. Triphenylphosphine and 1,5-bis(diphenylphosphino)pentane (dpppentane) were found to be less effective than 1,2-bis(diphenylphosphino)ethane (dppe), 1,3-bis(diphenylphosphino)propane (dppp), and 1,4-bis(diphenylphosphino)butane (dppb) for the palladium catalyzed reaction. Therefore, dppe and dppp are ligands of choice in the cycloaddition reactions.

Table 3-2 Effect of Added Phosphine Ligands in the Cycloaddition Reactions of 2-Vinyloxetane (**3.21a**) with Diphenylcarbodiimides (**3.24a**) using 1.5 mol% $Pd_2(dba)_3 \cdot CHCl_3$.[a]



3.21a, 1mmol **3.24a**, 1mmol **3.25a**

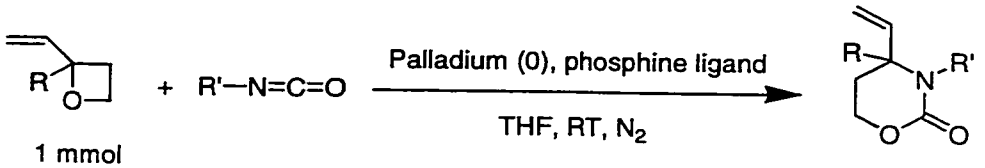
Entry	Ligand	Reaction time (h)[b]	Isolated yield of **3.25a** (%)[c]
1	0.06 mmol PPh_3	12	79
2	0.03 mmol dppe	12	**97**
3	0.03 mmol dppp	12	**98**
4	0.03 mmol dppb	12	94
5	0.03 mmol dpppentane	24	78

[a] Reaction conditions: 2-Vinyloxetane **3.21a** (1.0 mmol), diphenylcarbodiimide **3.24a** (1.0 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (0.015 mmol), 0.03 mmol of bidentate ligand or 0.06 mmol of PPh_3, room temperature, 5 mL THF, N_2 atmosphere. [b] Reaction times were based on the time necessary for the complete conversion of the carbodiimide. [c] Isolated yield by preparative TLC.

The cycloaddition reaction was successfully carried out by treatment of 2-vinyloxetane (**3.21a**, R = H, **3.21b**, R = CH_3) with heterocumulenes **3.22** or **3.24** in the presence of 2-3 mol % $Pd_2(dba)_3 \bullet CHCl_3$ and 2 equivalents of phosphine ligands in anhydrous THF at room temperature. The reaction times were 12 h when carbodiimides were utilized in the cycloaddition, whereas in the case of isocyanates the reaction times were always shorter (1 to 1.5 hr). Reaction times were based on the complete conversion of the heterocumulenes which was monitored by the shift of the IR absorption band of the carbodiimide C=N group at ~2100 cm^{-1} to the region of 1600 cm^{-1}; the absorption band for the isocyanate functionality (~ 2200 cm^{-1}) shifted to the 1700 cm^{-1} region.

All reactions were performed on a 1 mmol scale by using dppe and dppp and, in some reactions, PPh_3. 2-Vinyloxetanes, isocyanates and carbodiimides that are liquid were always freshly distilled before use. A mixture of $Pd_2(dba)_3 \bullet CHCl_3$ and a phosphine ligand was stirred in 3 mL THF under nitrogen atmosphere for 15 min before adding the 2-vinyloxetane and the heterocumulene, and then another 2 mL of anhydrous THF. The mixture was stirred under nitrogen until complete conversion of the heterocumulenes was detected. Products were purified by preparative silica gel TLC and Table 3-3 shows the result obtained from the reaction of 2-vinyloxetanes with isocyanates, while Table 3-4 illustrates the result from the reaction of 2-vinyloxetanes with carbodiimides.

Table 3-3 Cycloaddition Reactions of 2-Vinyloxetanes **3.21** with Isocyanates **3.22** in the Presence of a Palladium (0) Complex and a Phosphine Ligand.[a]



1 mmol
3.21a, R=H
3.21b, R=CH_3

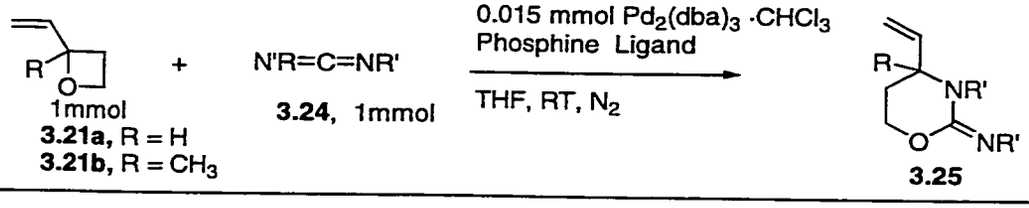
3.22, 1 mmol

3.23

Entry	**3.21**	R'N=C=O, **3.22**	Catalyst (mmol)	Ligand (mmol)	Reaction time (h)	product	Isolated yield (%)[b]
1	**3.21a**	O=C=NC_6H_5, **3.22a**	$Pd_2(dba)_3$·$CHCl_3$ (0.015)	dppp(0.03)	2	**3.23a**	83
2				PPh_3 (0.06)	2	**3.23a**	69
3				dppb(0.03)	2	**3.23a**	52
4	**3.21a**	O=C=NC_6H_4Cl-*p*, **3.22b**	$Pd(PPh_3)_4$ (0.02)	PPh_3 (0.04)	2	**3.23b**	62
5			$Pd_2(dba)_3$·$CHCl_3$ (0.01)	dppe(0.02)	2	**3.23b**	27
6				dppp(0.02)	2	**3.23b**	17
7	**3.21a**	O=C=NC_6H_4Br-*p*, **3.22c**	$Pd(PPh_3)_4$ (0.02)	PPh_3 (0.04)	2	**3.23c**	61
8	**3.21a**	O=C=N$C_6H_4OCH_3$-*p*, **3.22d**	$Pd_2(dba)_3$·$CHCl_3$ (0.015)	dppp(0.03)	2	**3.23d**	45
9	**3.21a**	O=C=N$C_6H_4CH_3$-*p*, **3.22e**	$Pd_2(dba)_3$·$CHCl_3$ (0.01)	dppp(0.02)	1	**3.23e**	34
10				dppe(0.02)	1	**3.23e**	34
11	**3.21b**	**3.22d**	$Pd_2(dba)_3$·$CHCl_3$ (0.01)	dppe(0.02)	1	**3.23f**	39
12				dppp(0.02)	1	**3.23f**	25
13	**3.21b**	**3.22e**	$Pd_2(dba)_3$·$CHCl_3$ (0.01)	dppp(0.02)	1	**3.23g**	45
14				dppe(0.02)	2	**3.23g**	37

[a] Refer to the Experimental Section for the general procedure. [b] purified by preparative TLC.

Table 3-4 Cycloadducts Obtained from the Reactions of 2-Vinyloxetanes **3.21** and Carbodiimides **3.24** in the Presence of 1.5 mol% $Pd_2(dba)_3 \cdot CHCl_3$ and a Phosphine Ligand.[a]



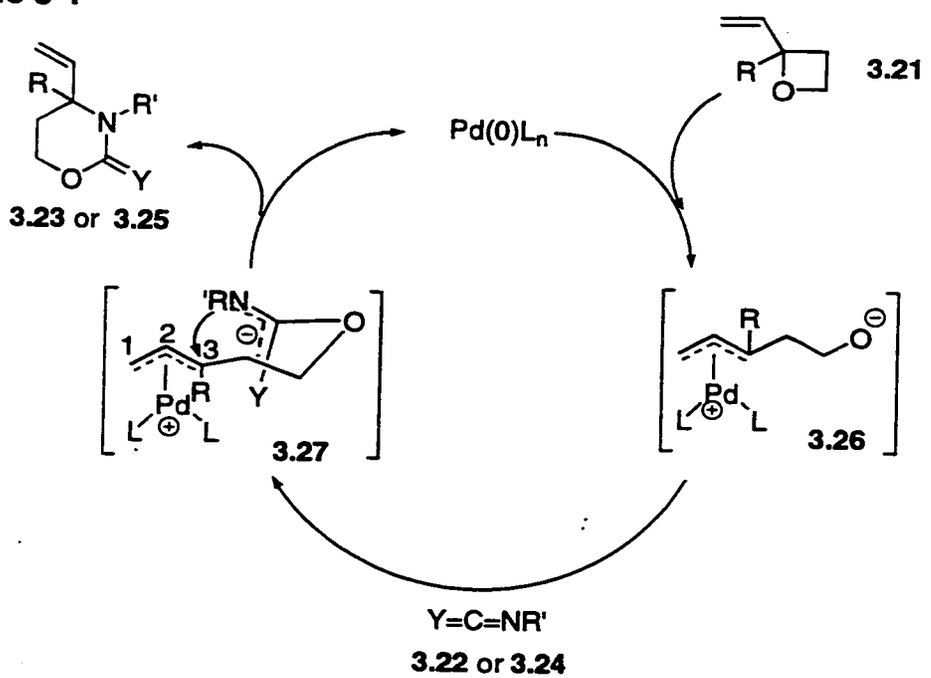
Entry	3.21	R'N=C=NR'	Ligand	Reaction time (h)	product	Isolated yield (%)[b]
1	**3.21a**	$C_6H_5N=C=NC_6H_5$, **3.24a**	dppp	12	**3.25a**	93
2			PPh_3	12	**3.25a**	88
3			dppe	12	**3.25a**	97
4			dppb	12	**3.25a**	94
5	**3.21a**	*p*-$ClC_6H_4N=C=NC_6H_4Cl$-*p*, **3.24b**	dppe	12	**3.25b**	86
6			dppp	12	**3.25b**	68
7	**3.21a**	*p*-$CH_3C_6H_4N=C=NC_6H_4CH_3$-*p*, **3.24c**	dppp	12	**3.25c**	94
8	**3.21a**	*p*-$CH_3OC_6H_4N=C=NC_6H_4OCH_3$-*p*, **3.24d**	dppp	12	**3.25d**	98
9	**3.21a**	*o*-$CH_3C_6H_4N=C=NC_6H_4CH_3$-*o*, **3.24e**	dppp	12	**3.25e**	98
10	**3.21a**	*p*-$BrC_6H_4N=C=NC_6H_4Br$-*p*, **3.24f**	dppe	12	**3.25f**	65
11			dppp	12	**3.25f**	45
12	**3.21b**	**3.24a**	dppp	48	**3.25g**	83
13	**3.21b**	**3.24b**	dppe	36	**3.25h**	62
14			dppp	36	**3.25h**	52
15	**3.21b**	**3.24c**	dppp	48	**3.25i**	92
16	**3.21b**	**3.24d**	dppp	15	**3.25j**	77
17	**3.21b**	**3.24e**	dppp	24	**3.25k**	78

[a] Refer to the Experimental Section for the gemeral procedure. [b] Yield of isolated product after silica gel TLC.

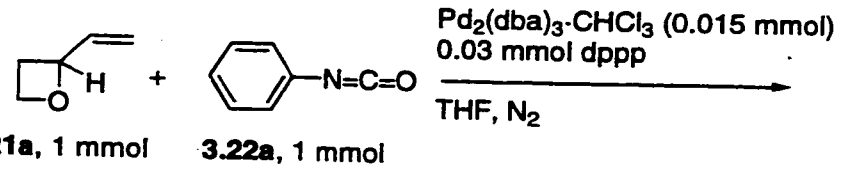
3.3.2 Proposed reaction mechanism for the cycloaddition reaction of monocyclic-2-vinyloxetanes with heterocumulenes.

A possible mechanism for the catalytic ring opening cycloaddition of 2-vinyloxetanes with heterocumulenes is illustrated in Scheme 3-1. The cycloaddition reaction involving vinyloxetanes may proceed in the same manner as for 2-vinyloxiranes (chapter 2), i.e. via a zwitterionic π-allyl palladium intermediate **3.26** generated by oxidative addition of vinyloxetane **3.21** to a palladium(0) complex. Intermediate **3.26** then reacts further with heterocumulenes to form **3.27**. Intramolecular attack of the nitrogen nucleophile at the C-3 carbon of **3.27** would afford the tetrahydro-1,3-oxazine derivatives.

Scheme 3-1



When using isocyanates for the reactions, product yields were considerably less than in the case of carbodiimides. The reaction conditions used might enhance the rate of dimerization and/or trimerization of isocyanates relative to the rate of cyclization. Attempt to reduce the reaction temperature to 0 °C (68% yield), – 20 °C (65% yield), and – 78 °C (40% yield) so as to reduce the rate of dimerization and/or trimerization proved to have no beneficial effect on the rate of cyclization (eq 14).



3.21a, 1 mmol **3.22a**, 1 mmol (eq 14)

Reaction temperature	% Isolated yield of **3.23a**
0 °C	68
-20 °C	65
-78 °C	40

Triphenylphosphine was the best ligand for reactions utilizing isocyanates containing a halogen at the *p*-position of the phenyl ring (entries 4 and 7, Table 3-3). In most other cases, the highest product yields were attained with dppp. However, in the reaction of *p*-methoxyphenylisocyanate **3.22d** with **3.21b**, dppe afforded a higher product yield (entry 8).

Good to excellent product yields were obtained for reactions of carbodiimides with 1.5 mol% of $Pd_2(dba)_3 \cdot CHCl_3$ and 3 mol% of dppp. In the reaction using carbodiimides having halogen at the *para*-position of the phenyl rings, dppe proved to be the best ligand for the reactions (entries 5, 9 and 12, Table 3-4). The reaction times were always longer for 2-vinyloxetanes containing a substituent at the carbon bearing the vinyl group (entries 11-15, Table 3-4).

3.3.3 Cycloaddition Reactions of Bicyclic Vinyloxetanes with Heterocumulenes.

Reactions of bicyclic vinyloxetanes with heterocumulenes offers a simple route to bicyclic tetrahydro-1,3-oxazines. We therefore investigated the formation of bicyclic tetrahydro-1,3-oxazines by the palladium-catalyzed reaction of appropiate vinyloxetanes with heterocumulenes.

We first performed the reaction using 1 mmol each of **3.28a** and diphenylcarbodiimide, **3.24a** (eq 15), with conditions identical to those used for monocyclic vinyloxetanes (**3.21a-b**) [1.5 mol% of $Pd_2(dba)_3 \cdot CHCl_3$, 3 mol% of dppp in 5 mL THF, at room temperature for 48 h (entry 1, Table 3-5)]; however no conversion of the carbodiimides was observed. Increasing the amount of the palladium catalyst to 2.5 mol% and the reaction temperature to 50 °C (entry 2) also gave recovered

heterocumulenes. However, complete conversion of **3.24a** occurred by using 4.5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$ and 9 mol% of dppp at 50 °C, with **3.29a** isolated in 52% yield (entry 4).

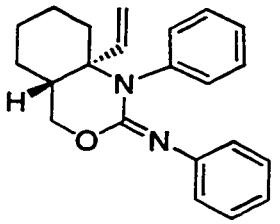
Furthermore, the yield increased to 70% when the reaction was carried out in a glass autoclave with 5 psi N_2 at 80 °C for 48 h (entry 5). Increasing the reaction temperature to 100 °C resulted in the formation of palladium black and **3.29a** was isolated in lower yield.

Table 3-5 Optimization of Reaction Conditions for the Cycloaddition of Bicyclic Vinyloxetane **3.28a** with Diphenylcarbodiimide **3.24a.**[a]

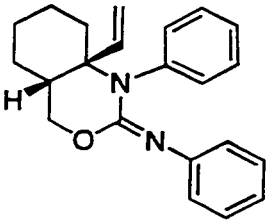
Entry	Conditions	Isolated yields [b]
1	0.015 mmol $Pd_2(dba)_3 \cdot CHCl_3$, 0.03 mmol dppp , RT, 48 h	0 %
2	0.025 mmol $Pd(PPh_3)_4$, 0.025 mmol PPh_3, 50 °C, 48 h	0%
3	0.045 mmol $Pd_2(dba)_3 \cdot CHCl_3$, 0.09 mmol dppp, RT, 48 h	0%
4	0.045 mmol $Pd_2(dba)_3 \cdot CHCl_3$, 0.09 mmol dppp, 50 °C, 48 h	52 %
5	0.045 mmol $Pd_2(dba)_3 \cdot CHCl_3$, 0.09 mmol dppp , 80 °C, 48 h [c]	70 %

[a] Reaction conditions: **3.28a** (1 mmol), **3.24a** (1 mmol), THF (10 mL), under a N_2 atmosphere. [b] Isolated yield of **3.29a** (by preparative TLC). [c] Reaction was stirred in a glass autoclave at 5 psi N_2.

Trans and *cis*-fused bicyclic oxazine-2-imines (**3.29a**) (Figure 3-2) are possible products of these reactions.



trans- **3.29a**



cis-**3.29a**

Figure 3-2 Two possible cycloaddition products, which could be obtained from the reaction of **3.28a** and **3.24a**.

Spectral data (^{1}H-NMR, ^{13}C-NMR) and a single crystal X-ray diffraction determination of **3.29a** (Figure 3-3) established the structure as *cis*-**3.29a**. Consequently, the cycloaddition proceeds with complete stereochemical control.

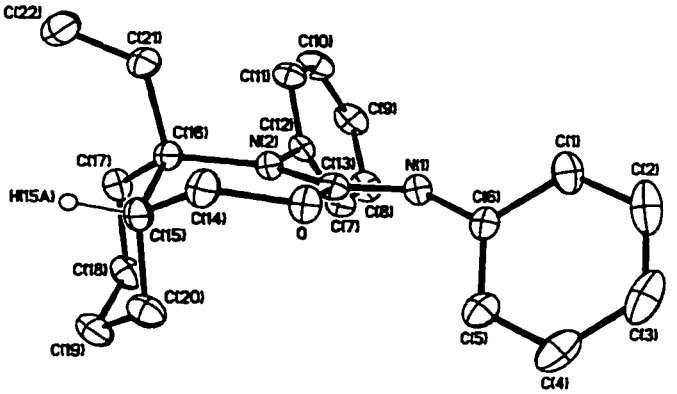
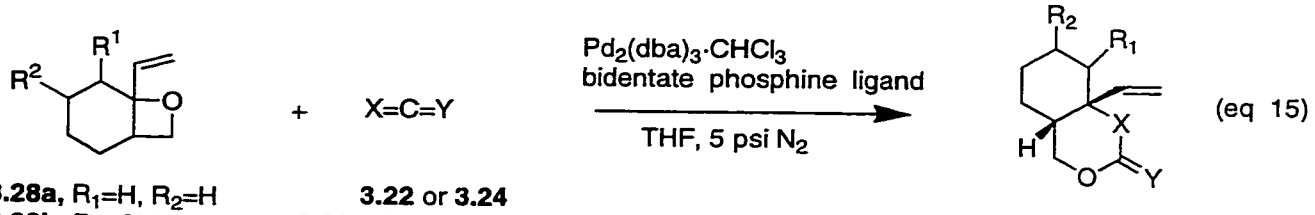


Figure 3-3 X-ray structure of **3.29a**

A series of heterocumulenes **3.22** and **3.24** were reacted with bicyclic vinyloxetanes **3.28a, 3.28b** and **3.28c** using $Pd_2(dba)_3$•$CHCl_3$ and a bidentate phosphine ligand as the catalytic system (eq 15), and the results are summarized in Table 3-6.



(eq 15)

3.28a, R_1=H, R_2=H
3.28b, R_1=CH_3, R_2=H
3.28c, R_1=H, R_2=CH_3

3.22 or **3.24**
3.22a: X = C_6H_5N, Y = O
3.22b: X = *p*-ClC_6H_4N, Y = O
3.22d: X = *p*-$CH_3OC_6H_4N$, Y = O
3.22e: X = *p*-$CH_3C_6H_4N$, Y = O
3.24a: X = Y = C_6H_5N
3.24b: X = Y = *p*-ClC_6H_4N
3.24c: X = Y = *p*-$CH_3C_6H_4N$
3.24d: X = Y = *p*-$CH_3OC_6H_4N$
3.24f: X = Y = *p*-BrC_6H_4N

3.29, X = Y = NR'
3.30, X =NR", Y =O

The reactions were carried out in a glass autoclave under 5 psi N_2 using 1 mmol of **3.28a, 3.28b** or **3.28c** with an equimolar amount of the heterocumulene (**3.22** or **3.24**) in the presence of 4-4.5 mol% of $Pd_2(dba)_3$•$CHCl_3$ and 8-9 mol% of a bidentate phosphine ligand (using carbodiimides), whereas a mixture of 3 mol% of $Pd_2(dba)_3$•$CHCl_3$ and 6 mol% of bidentate phosphine ligand was used for reactions involving isocyanates. The reaction mixture was stirred at 80 °C for carbodiimides and at 50 °C for isocyanates, until conversion of the heterocumulenes was complete (monitored by IR). The yields of the bicyclic *cis*-1,3-oxazine-2-imines (**3.29**) were significantly higher using dppe than dppp for the reaction of bicyclic oxetanes with carbodiimides (entries 2, 4, 6 and 8, Table 3-6). However, dppp was a superior ligand for the reaction of **3.28a** with isocyanates. Lower product yields were observed using isocyanates than carbodiimides in the cycloaddition reactions, analogous to results observed using monocyclic vinyloxetanes.

Table 3-6 Cycloaddition Reaction of Bicyclic 2-Vinyloxetanes **3.28a-c** with Heterocumulenes **3.22** or **3.24** Catalyzed by $Pd_2(dba)_3 \cdot CHCl_3$ and Bidentate Phosphine Ligands.[a]

Entry	3.28	X=C=Y	$Pd_2(dba)_3 \cdot CHCl_3$ (mmol)	Ligand (mmol)	Reaction time (h)	product	Isolated yield (%)[b]
1	**3.28a**	**3.24a**	0.045	dppp (0.09)	24	**3.29a**	70
2				dppe (0.09)	24		98
3	**3.28a**	**3.24b**	0.04	dppp (0.08)	48	**3.29b**	65
4				dppe (0.08)	48		85
5	**3.28a**	**3.24c**	0.04	dppp (0.08)	48	**3.29c**	20
6				dppe (0.08)	48		86
7	**3.28a**	**3.24d**	0.04	dppp (0.08)	48	**3.29d**	22
8				dppe (0.08)	48		66
9	**3.28a**	**3.24f**	0.045	dppe (0.09)	48	**3.29e**	86
10	**3.28a**	**3.22a**	0.03	dppp (0.06)	24	**3.30a**	51
11	**3.28a**	**3.22b**	0.03	dppp (0.06)	12	**3.30b**	46
12	**3.28a**	**3.22d**	0.03	dppp (0.06)	12	**3.30c**	55
13	**3.28a**	**3.22e**	0.03	dppp (0.06)	12	**3.30d**	43
14	**3.28b**	**3.24a**	0.045	dppe (0.09)	24	**3.29f**	80
15	**3.28b**	**3.24b**	0.045	dppe (0.09)	12	**3.29g**	77
16	**3.28b**	**3.24c**	0.045	dppe (0.09)	24	**3.29h**	70
17	**3.28c**	**3.24b**	0.045	dppe (0.09)	24	**3.29i**	98
18	**3.28c**	**3.24c**	0.045	dppe (0.09)	24	**3.29j**	82

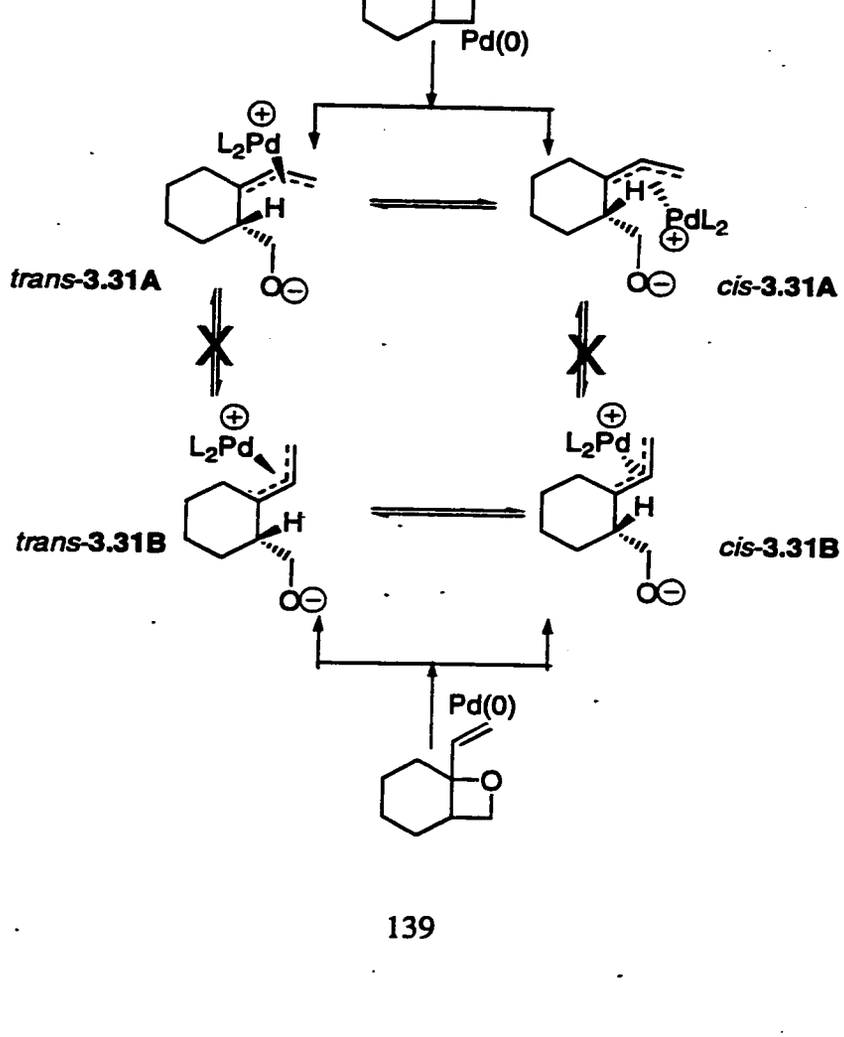
[a] See the Experimental Section for the general procedure for the cycloaddition reaction of bicyclic vinyloxetanes with heterocumulenes. [b] Purified by column chromatography using silica gel.

3.3.4 A postulated mechanism for the stereoselective formation of bicyclic-1,3-oxazines.

In the following section, the stereochemical course of the reaction will be discussed in an attempt to analyze the origin of the diasteroselectivity and to give a rationale for the possible mechanism.

Formation of a π-allylpalladium complex. Four stereoisomeric π-allyl palladium intermediates are possible after oxidative addition of bicyclic-2-vinyloxetanes to Pd(0) (Scheme 3-2).

Scheme 3-2



Two processes may account for the isomerization of π-allyl palladium complexes:[38]

-a bimolecular S_N2 displacement by Pd(0) (Figure 3-4) [39-42] consisting of a cis-trans isomerization [*trans*-**3.31A**↔*cis*-**3.31A** or *trans*-**3.31B**↔*cis*-**3.31B**], that cannot convert a type **A** to a type **B** complex.

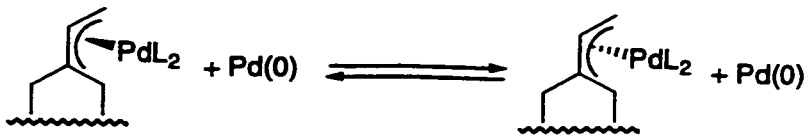


Figure 3-4 cis-trans isomerization by S_N2 displacement of an η^3-palladium complex by a Pd(0) complex.

-a monomolecular η^3-η^1-η^3 process consisting of cis-trans isomerization involving a palladium-primary carbon bond (Figure 3-5a) or an **A-B** isomerization which involved a palladium-tertiary carbon bond (Figure 3-5b).[43] The isomerizations of *trans*-**3.31A** to *cis*-**3.31A** and of *trans*-**3.31B** to *cis*-**3.31B** are possible via the former process. In contrast, **A-B** isomerization of **3.31** should be disfavored since this process involves the formation of a palladium-tertiary carbon bond.[44]

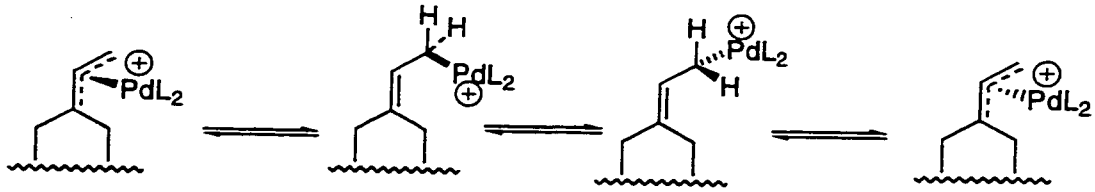


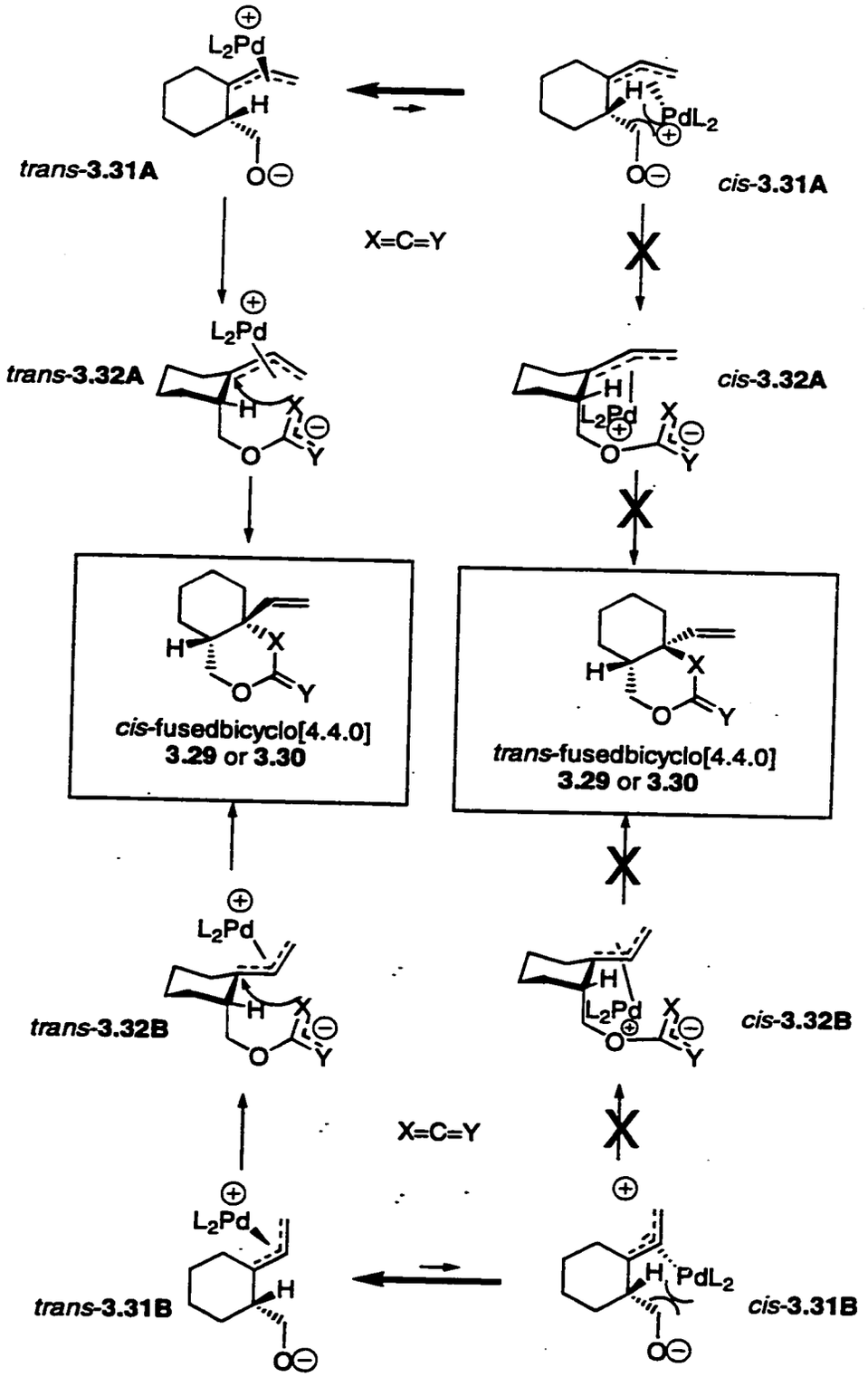
Figure 3-5a $\eta 3-\eta 1-\eta 3$–process involving a palladium-primary carbon bond.

Figure 3-5b $\eta 3-\eta 1-\eta 3$–process involving a palladium-tertiary carbon bond.

Figure 3-5 Isomerization via an η^3-η^1-η^3 process.

Nucleophilic attack. In our case the formation of *trans*-**3.31A** and *trans*-**3.31B** may be favored over that of *cis*-**3.31A** and *cis*-**3.31B**, the latter involving interaction of a π-allyl palladium moiety with a CH_2O^- (resulting from the ring-opening of the oxetane) on the adjacent carbon. Hence, the formation of *trans*-**3.32A** and *trans*-**3.32B** may be preferred rather than *cis*-**3.31A** and *cis*-**3.31B** following the reaction with heterocumulenes. Intramolecular nucleophilic addition of the nitrogen nucleophile in *trans*-**3.32A** and *trans*-**3.32B** may occur from the side opposite to the palladium moiety affording only the *cis*-product (Scheme 3-3).[45-48]

Scheme 3-3


L2Pd
H
PdL2
trans-3.31A
cis-3.31A
X=C=Y
trans-3.32A
cis-3.32A
cis-fusedbicyclo[4.4.0]
3.29 or 3.30
trans-fusedbicyclo[4.4.0]
3.29 or 3.30
trans-3.32B
cis-3.32B
X=C=Y
trans-3.31B
cis-3.31B

The cycloaddition of bicyclic vinyloxetanes **3.28b** and **3.28c** bearing a methyl substituent on the cyclohexyl ring was also stereoselective. An X-ray determination of the structure of **3.29f** revealed a *trans* relationship of the methyl and vinyl groups in the *cis*-bicyclic oxazine imine (Figure 3-6). Excellent yields resulted from the reactions of **3.28b** or **3.28c** with carbodiimides **3.24a-c** (entries 14-18, Table 3-6). These results demonstrate the ability to achieve complete regio- and stereoselective cycloaddition processes using non-chiral ligands.

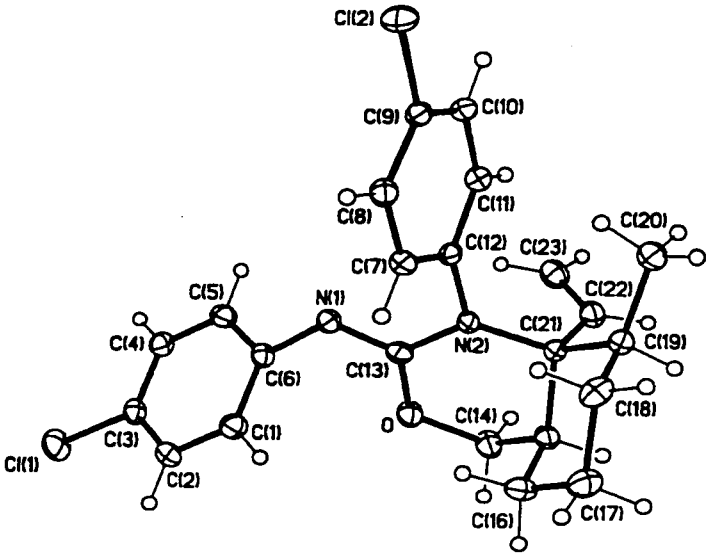


Figure 3-6 X-ray structure of **3.29f**

3.4 Conclusions

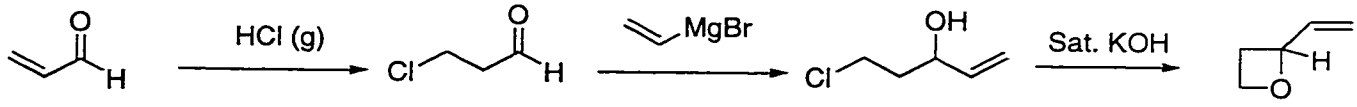
Mono and bicyclic oxazin-2-ones and oxazin-2-imines were isolated in fine yields by the cycloaddition reaction of 2-vinyloxetanes with heterocumulenes catalyzed by palladium complexes and phosphine ligands. This process is completely regio- and stereoselective. A particularly novel feature of the cycloaddition process is its use for the construction of bicyclic[4.4.0]systems by means of $Pd_2(dba)_3 \cdot CHCl_3$ and a achiral ligand such as dppe. The new reaction provides access to stereochemically-defined mono and bicyclic compounds some of which may prove to exhibit significant pharmaceutical activity.

3.5 Experimental Section

3.5.1 Preparation of monocyclic vinyloxetanes 3.21a and 3.21b.

3.5.1.1 The preparation of 2-vinyloxetane (3.21a)

Scheme 3-4



3.33 **3.34** **3.21a**

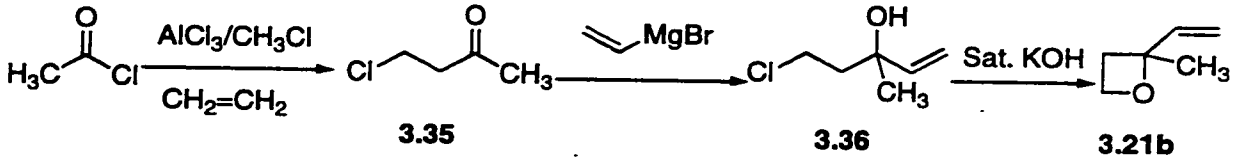
2-Vinyloxetane (**3.21a**) was prepared according to the procedures described in

literature (Scheme 3-4).[49,50]

2-Vinyloxetane (3.21a) R= H; 44% yield; Oily liquid; ^{1}H NMR [200 MHz, $CDCl_3$] δ 2.32-2.85 (m, 2H, C*H*$_2$-CH), 4.40-4.75 (m, 1H, CH_2-O), 5.21-5.40 (m, 3H, C*H*$_2$=CH and C*H*(CH_2=CH)), 6.15-6.21 (m, 1H, CH_2=C*H*). ^{13}C NMR [50 MHz, $CDCl_3$] δ 28.33 ((**C**H_2)CH), 68.08 (CH_2-O), 82.35 (**C**H-O), 115.56 (**C**H_2=CH), 139.39 (CH_2=**C**H).

3.5.1.2 The preparation of 2-methyl-2-vinyloxetane (3.21b)

Scheme 3-5



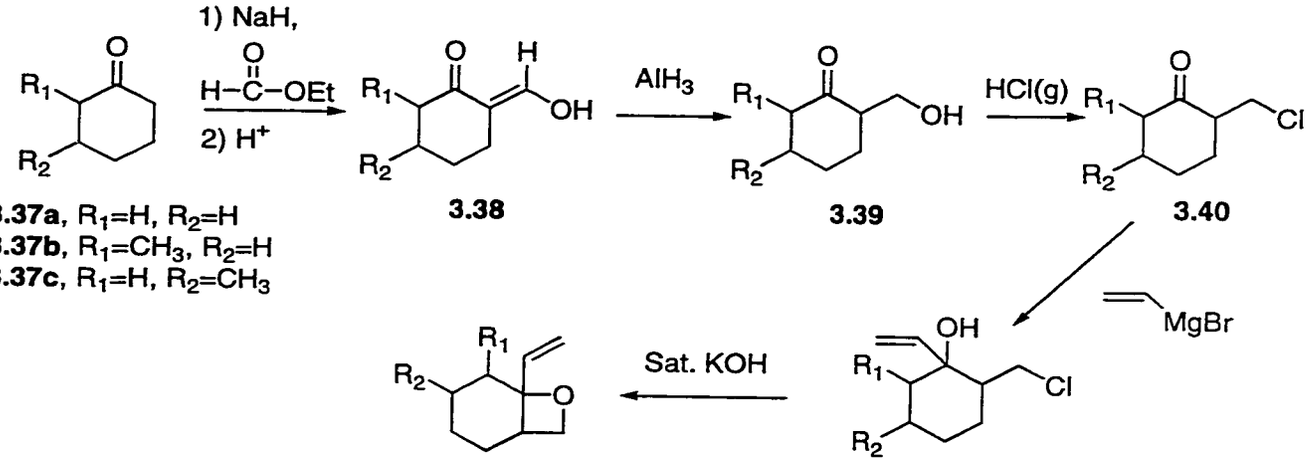
3.35 **3.36** **3.21b**

2-Methyl-2-vinyloxetane (**3.21b**) was synthesized from acetyl chloride by reported methods (Scheme 3-5).[50,51]

2-Methyl-2-vinyloxetane (3.21b) R= CH_3; 60% yield; Oily liquid; ^{1}H NMR [200 MHz, $CDCl_3$] δ 1.50 (s, 3H, CH_3), 2.42-2.52 (m, 2H, C*H*$_2$-CH), 4.41-4.48 (m, 1H, CH_2-O), 5.02-5.31 (m, 3H, C*H*$_2$=CH and C*H*(CH_2=CH)), 5.94-6.08 (m, 1H, CH_2=C*H*). ^{13}C NMR [50 MHz, $CDCl_3$] δ 22.73 ((CH_3)**C**(CH=CH_2), 30.51 ((CH_2)**C**(CH_3)), 67.07 (CH_2-O), 82.35 ((CH_3)**C**(CH=CH_2)), 112.42 (**C**H_2=CH), 144.39 (CH_2=**C**H).

3.5.2 The Preparation of Bicyclic Vinyloxetanes, 3.28a-c.

Scheme 3-6



3.37a, R_1=H, R_2=H
3.37b, R_1=CH_3, R_2=H
3.37c, R_1=H, R_2=CH_3

3.38 **3.39** **3.40** **3.41**

3.28a, R_1=H, R_2=H
3.28b, a_1=CH_3, R_2=H
3.28c, R_1=H, R_2=CH_3

2-Hydroxymethylenecyclohexanone (3.38a-c) was prepared from the corresponding cyloclohexanones using procedure described in the literature.[53] **3.38a**, **3.38b** and **3.38c** were obtained in 52, 57 and 79% yield respectively after distillation (lit 70-74% yield).

2-Hydroxymethyl cyclohexanone (3.39) were achieved by reduction of 2-hydroxymethylene cyclohexanone (**3.38**) by AlH_3 in THF. [54,55] The resulting product were used in next step without further purification due to their unstable.

2-Chloromethyl cyclohexanone (3.40)[52] was prepared by passing HCl gas to an ether solution of **3.41** at –10 °C to –15 °C. The organic layer was dried over anhydrous sodium sulfate and then immediately used for the Grignard reaction[52] resulted in **3.41a**, **3.41b** and **3.41c** in 70, 79 and 76% yields respectively.

3.28a-c were obtained by the reaction **3.41** to a hot solution of saturated KOH.[52]

1-Oxa-7-vinylbicyclo[4.2.0]octane (**3.28a**); 36% yield; Oily liquid ^{1}H NMR [200 MHz $CDCl_3$] δ 1.23-2.10 (m, 8H, CH_2-cyclohexane), 2.75 (m, 1H, (C*H*-CH_2-O), 4.22 (dd, 1H, *J* = 6.0 and 6.0 Hz, C*H*$_2$-O), 4.46 (dd, 1H, *J* = 7.9 and 5.8 Hz, C*H*$_2$-O), 5.06 (dd, 1H, *J* = 10.7 and 1.7 Hz, C*H*$_2$=CH), 5.29 (dd, 1H, *J* = 17.2 and 1.7 Hz, C*H*$_2$=CH), 5.96 (dd, 1H, *J* = 17.2 and 10.7 Hz, CH_2=C*H*). ^{13}C NMR [50 MHz $CDCl_3$] δ 18.84, 19.06, 24.28, 32.83 (CH_2-cyclohexane), 37.53 (**C**H-CH_2-O), 70.37 (**C**H_2-O), 85.92 ((CH_2=CH)**C**-O), 111.49 (**C**H_2=CH), 142.96 (CH_2=**C**H); m/e 138 $[M]^+$ HRMS Calcd for $C_9H_{14}O$ 138.1045 Found 138.1055.

2-Methyl-1-oxa-7-vinylbicyclo[4.2.0]octane (**3.30b**); 56% yield; Oily liquid ^{1}H NMR [200 MHz $CDCl_3$] δ 0.73 (d, 3H, *J* = 6.3 Hz, C*H*$_3$), 1.38-2.00 (m, 7H, CH_2-cyclohexane), 2.60 (m, 1H, C*H*-CH_2-O), 4.03-4.08 (m, 1H, C*H*$_2$-O), 4.55-4.61 (m, 1H, C*H*$_2$-O), 5.14 (dd, 1H, *J* =10.5 and 2.1 Hz, C*H*$_2$=CH), 5.40 (dd, 1H, *J* =17.1 and 2.1 Hz, C*H*$_2$=CH), 5.82 (dd, 1H, *J* = 17.1 and 10.5 Hz, CH_2=C*H*). ^{13}C NMR [50 MHz $CDCl_3$] δ 13.60 (**C**H_3), 19.65, 27.31, 35.34 (CH_2-cyclohexane), 24.99 (**C**H(CH_3)), 38.01 (**C**H-CH_2-O), 71.85 (**C**H_2-O), 88.27 ((CH_2=CH)**C**-O), 111.92 (**C**H_2=CH) 142.76 (CH_2=**C**H). m/e 152 $[M]^+$ HRMS calcd for $C_{10}H_{16}O$ 152.1201 Found 152.1223.

3-Methyl-1-oxa-7-vinylbicyclo[4.2.0]octane (**3.30c**); 59% yield; Oily liquid ^{1}H NMR [200 MHz $CDCl_3$] δ 0.92 (d, 3H, *J* = 6.4 Hz, C*H*$_3$), 1.50-2.20 (m, 7H, CH_2-cyclohexane), 2.49-2.65 (m, 1H, C*H*-CH_2-O), 4.01 (dd, 1H, *J* = 7.2 and 5.7 Hz, C*H*$_2$-O), 4.04 (dd, 1H, *J* = 5.7 and 4.4 Hz, C*H*$_2$-O), 5.08 (dd, 1H, *J* = 17.1 and 10.6 Hz, C*H*$_2$=CH), 5.34 (dd, 1H, *J* = 17.1 and 1.7 Hz, C*H*$_2$=CH), 5.95 (dd, 1H, *J* =16 and 1.7 Hz, CH_2=C*H*). ^{13}C NMR [50 MHz $CDCl_3$] δ 22.77 (**C**H_3), 25.37, 28.61, 36.18, (CH_2-cyclohexane), 25.64 (**C**H(CH_3)),

68.71 (CH-CH_2-O), 72.71 (CH_2-O), 86.87 ((CH_2=CH)C-O), 111.24 (CH_2=CH), 143.38 (CH_2=CH). m/e 152 $[M]^+$ HRMS calcd for $C_{10}H_{16}O$ 152.1201 Found 152.1209.

3.5.3 General Procedure for the Palladium-Catalyzed Cycloaddition Reaction of 2-Vinyloxetanes (3.21a-b) with Heterocumulenes.

A mixture of the palladium complex and a phosphine ligand [$Pd(PPh_3)_4$ (0.02 mmol) and PPh_3 (0.04 mmol), or $Pd_2(dba)_3$•$CHCl_3$ (0.01-0.015 mmol) and a bidentate phosphine ligand (0.02–0.03 mmol)] and THF (5 mL), was stirred in a three neck-round bottom flask under nitrogen at room temperature for 30 min. The vinyloxetane **3.21a** or **3.21b** (1.0 mmol) and heterocumulene (1.0 mmol) were added, and the mixture was then stirred under nitrogen at room temperature until the conversion of the heterocumulenes was complete [monitored by the disappearance of the N=C=N IR–absorption band in the free carbodiimide (~ 2100 cm^{-1}) and the appearance of the C=N band in the region of 1620-1630 cm^{-1}; the absorption of the isocyanate (~2200 cm^{-1}) is replaced by the carbonyl band at 1680-1690 cm^{-1}]. After the reaction was complete, the orange yellow solution was then concentrated by rotary evaporation, and the residue was purified by silica gel TLC using a mixture of pentane/ether as the developer. Melting points, IR, NMR, MS and analytical data for **3.23** and **3.25** are as follows.

***N*-Phenyl-4-vinyltetrahydro-1,3-oxazin-2-one (3.23a)** (R = H, R′ = C_6H_5): mp = 60-61°C; IR (C=O) 1695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.88-1.98 (m, 1H, CH_2-CH), 2.25-2.37 (m, 1H, CH_2-CH), 4.25-4.42 (m, 3H, O-CH_2 and C*H*-N), 5.04-5.14 (m, 2H,

CH_2=CH), 5.62-5.79 (m, 1H, CH_2=C*H*), 7.13-7.34 (m, 5H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.63 (**C**H_2-CH), 60.13 (CH_2-**C**H), 63.67 (O-**C**H_2), 117.99 (**C**H_2=CH), 126.67, 126.94, 128.72 (CH-aromatic carbons), 135.97 (CH_2=**C**H), 141.53 (quaternary aromatic carbons), 152.63 (**C**=O); MS (*m/e*) 203 $[M]^+$. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found C, 71.28; H, 6.44; N, 6.70.

***N*-(*p*-Chlorophenyl)-4-vinyltetrahydro-1,3-oxazin-2-one (3.23b)** (R = H, R′ = *p*-ClC_6H_4): mp = 68-69°C; IR (C=O) 1696 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.96-2.07 (m, 1H, C*H*$_2$-CH), 2.40 (m, 1H, C*H*$_2$-CH), 4.41 (m, 3H, O-C*H*$_2$ and C*H*-N), 5.17 (d, 1H, *J* = 15.9 Hz, C*H*$_2$=CH), 5.23 (d, 1H, *J* = 8.9 Hz, C*H*$_2$=CH), 5.79 (m, 1H, CH_2=C*H*), 7.20-7.37 (m, 4H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.82 (**C**H_2-CH), 60.38 (CH_2-**C**H), 63.89 (O-**C**H_2), 118.59 (**C**H_2=CH), 128.46, 129.04, 135.82 (CH-aromatic carbons), 131.84, 140.10 (quaternary aromatic carbons), 152.59 (**C**=O); MS (*m/e*) 237 $[M]^+$. Anal. Calcd for $C_{12}H_{12}ClNO_2$: C, 60.64; H, 5.09; N, 5.89. Found C, 60.54; H, 5.06; N, 6.04.

***N*-(*p*-Bromophenyl)-4-vinyltetrahydro-1,3-oxazin-2-one (3.23c)** (R = H, R′ = *p*-BrC_6H_4): mp = 87-88°C; IR (C=O) 1697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.98-2.02 (m, 1H, C*H*$_2$-CH), 2.28-2.32 (m, 1H, C*H*$_2$-CH), 4.32-4.40 (m, 3H, O-C*H*$_2$ and C*H*-N), 5.11 (d, 1H, *J* = 16.1 Hz, C*H*$_2$=CH), 5.18 (d, 1H, *J* = 9.34 Hz, C*H*$_2$=CH), 5.73 (m, 1H, CH_2=C*H*), 7.45 (s, 4H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.04 (**C**H_2-CH), 59.50 (CH_2-**C**H), 63.12 (O-**C**H_2), 117.83 (**C**H_2=CH), 119.61, 128.01, 131.24.(CH-aromatic carbons), 135.04, 139.88 (quaternary aromatic carbons), 151.73 (C=O); MS (*m/e*) 281 $[M-1]^+$, 283 $[M+1]^+$. HRMS. Calcd for $C_{12}H_{12}BrNO_2$: 283.0032, Found

283.0041.

***N*-(*p*-Methoxyphenyl)-4-vinyltetrahydro-1,3-oxazin-2-one (3.23d)** (R = H, R′ = *p*-$CH_3OC_6H_4$): mp = 72-73 °C; IR (C=O) 1696 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$); δ 1.98–2.08 (m, 1H, C*H*$_2$-CH), 2.38–2.48 (m, 1H, C*H*$_2$-CH), 3.78 (s, 3H, C_6H_4-OC*H*$_3$), 4.38 (m, 3H, O-C*H*$_2$ and C*H*-N), 5.13 (d, 1H, *J* = 11.72 Hz, C*H*$_2$=CH), 5.20 (d, 1H, *J* = 4.57 Hz, C*H*$_2$=CH), 5.69–5.88 (m, 1H, CH_2=C*H*), 6.85-6.89 (m, 2H, aromatic protons), 7.14–7.27 (m, 2H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.95 (**C**H_2-CH), 55.32 (C_6H_4-O**C**H_3), 60.72 (CH_2-**C**H), 63.74 (O-**C**H_2), 118.18 (**C**H_2=CH), 114.16, 128.42 (CH-aromatic carbons), 136.26 (CH_2=**C**H), 134.44, 153.15 (quaternary aromatic carbons), 158.16 (C=O); MS (*m/e*) 233 $[M]^+$. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found C, 66.92; H, 6.52; N, 6.26.

***N*-(*p*-Tolyl)-4-vinyltetrahydro-1,3-oxazin-2-one (3.23e)** (R = H, R′ = *p*-$CH_3C_6H_4$): mp = 68-69 °C; IR (C=O) 1698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 1.94–2.03 (m, 1H, C*H*$_2$-CH), 2.32 (s, 3H, C_6H_4-*p*-CH_3), 2.27–2.39 (m, 1H, C*H*$_2$-CH), 4.34–4.43 (m, 3H, O-C*H*$_2$ and C*H*-N), 5.10–5.21 (m, 2H, C*H*$_2$=CH), 5.11-5.19 (m, 1H, CH_2=C*H*), 7.14 (s, 4H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.90 (C_6H_4-*p*-**C**H_3), 27.85 (**C**H_2-CH), 60.35 (CH_2-**C**H), 63.70 (O-**C**H_2), 118.09 (**C**H_2=CH), 126.92, 129.53 (CH-aromatic carbons), 136.18 (CH_2=**C**H), 136.70, 138.99 (quaternary aromatic carbons), 152.95 (C=O); MS (*m/e*) 217 $[M]^+$. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found C, 71.75; H, 6.96; N, 6.83.

***N*-(*p*-Methoxyphenyl)-4-methyl-4-vinyltetrahydro-1,3-oxazin-2-one (3.23f)** (R = CH_3,

R′ = *p*-$CH_3OC_6H_4$): mp = 155-156 °C; IR (C=O) 1686 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$); δ 1.27 (s, 3H, (CH_3)C–N), 1.98–2.16 (m, 2H, CH_2-$C(CH_3)_3$), 3.78 (s, 3H, C_6H_4-*p*-OCH_3), 4.35–4.43 (m, 2H, O-CH_2), 5.18 (d, 1H, *J* = 17.8 Hz, CH_2=CH), 5.26 (d, 1H, *J* = 11.4 Hz, CH_2=CH), 6.00 (dd, 1H, 17.8 and 11.4 Hz, CH_2=C*H*), 6.83–7.12 (m, 4H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.89 ((CH_3)$_3$C–N), 35.43 (CH_2-$C(CH_3)_3$), 55.31 (C_6H_4-*p*-OCH_3), 60.23 ((CH_3)$_3$C–N), 62.81 (O-CH_2), 115.68 (CH_2=CH), 113.68, 130.78 (CH-aromatic carbons), 141.61 (CH_2=CH), 131.57, 153.68 (quaternary aromatic carbons), 158.68 (C=O); MS (*m/e*) 247 $[M]^+$. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found C, 67.70; H, 6.75; N, 5.25.

***N*-(*p*-Tolyl)-4-methyl-4-vinyltetrahydro-1,3-oxazin-2-one (3.23g)** (R = CH_3, R′ = *p*-$CH_3C_6H_4$): mp = 141-142 °C; IR (C=O) 1673 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 1.27 (s, 3H, (CH_3)C –N), 2..5–2.16 (m, 2H, CH_2-$C(CH_3)_3$), 2.33 (s, 3H, *p*-$CH_3C_6H_4$), 4.36–4.43 (m, 2H, O-CH_2), 5.20 (d, 1H, *J* = 17.4 Hz, CH_2=CH), 5.26 (d, 1H, *J*= 10.8 Hz, CH_2=CH), 6.01 (dd, 1H, *J* = 17.4 and 10.8 Hz, CH_2=C*H*), 7.04-7.17 (m, 4H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.20 (*p*-$CH_3C_6H_4$), 25.09 ((CH_3)C–N), 34.66 (CH_2-$C(CH_3)_3$), 59.31 ((CH_3)$_3$C–N), 61.99 (O-CH_2), 114.85 (CH_2=CH), 128.54, 128.70 (CH-aromatic carbons), 135.34, 136.67 (quaternary aromatic carbons), 140.92 (CH_2=CH), 152.65 (C=O); MS (*m/e*) 231 $[M]^+$. HRMS. Calcd for $C_{14}H_{17}NO_2$: 231.1259. Found 231.1226.

***N*, 3-Diphenyl-4-vinyltetrahydro-1,3-oxazin-2-imine (3.25a)** (R = H, R′ = C_6H_5): mp = 90-91°C; IR (C=N) 1636 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 1.96–2.05 (m, 1H, CH_2-CH), 2.35–2.42 (m, 1H, CH_2-CH), 4.19–4.32 (m, 2H, O-CH_2), 4.38–4.47 (m, 1H, C*H*-N), 5.15–5.24 (m, 2H, CH_2=CH), 5.77–5.95 (m, 1H, CH_2=C*H*), 6.86–6.92 (m, 2H, aromatic

protons), 7.13–7.29 (m, 4H, aromatic protons), 7.33–7.41 (m, 4H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.03 (CH_2-CH), 59.23 (CH-N), 63.29 (O–CH_2), 117.51 (CH_2=CH), 121.05, 123.32. 125.70, 127.03, 128.18, 128.73, (CH-aromatic carbons), 137.61 (CH_2=CH), 143.74, 148.12 (quaternary aromatic carbons), 148.97 (C=N); MS (*m/e*) 277 $[M-1]^+$, 278 $[M]^+$. Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found C, 77.40; H, 6.42; N, 10.02.

***N*, 3-Di(*p*-chlorophenyl)-4-vinyltetrahydro-1,3-oxazin-2-imine (3.25b)** (R = H, R′ = *p*-ClC_6H_4): mp = 99-100 °C; IR (C=N) 1630 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 1.99–2.10 (m, 1H, C*H*$_2$–CH), 2.39–2.43 (m, 1H, C*H*$_2$–CH), 4.22–4.42 (m, 3H, O–C*H*$_2$ and C*H*-N), 5.13–5.23 (m, 2H, C*H*$_2$=CH), 5.75–5.92 (m, 1H, CH_2=C*H*), 6.81–6.87 (m, 2H, aromatic protons), 7.11–7.19 (m, 2H, aromatic protons), 7.25–7.34 (m, 4H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.82 (CH_2–CH), 59.46 (CH–N), 63.47 (O–CH_2), 118.09 (CH_2=CH), 124.67, 128.17, 128.67, 128.96, (CH aromatic carbons), 137.02 (CH_2=CH), 126.59 , 129.21, 141.91, 146.43 (quaternary aromatic carbons), 149.04 (C=N); MS (*m/e*) 345 $[M-1]^+$, 346 $[M]^+$. Anal. Calcd for $C_{18}H_{16}Cl_2N_2O$: C, 62.26; H, 4.64; N, 8.07. Found C, 62.26; H, 4.68; N, 8.03.

***N*, 3-Di(*p*-tolyl)-4-vinyltetrahydro-1,3-oxazin-2-imine (3.25c)** (R = H, R′ = *p*-$CH_3C_6H_4$): mp = 104-105 °C; IR (C=N) 1638 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 1.95–2.06 (m, 1H, C*H*$_2$–CH), 2.27 (s, 3H, *p*-C*H*$_3$C$_6$H$_4$), 2.33 (s, 3H, *p*-C*H*$_3$C$_6$H$_4$), 2.35–2.43 (m, 1H, C*H*$_2$–CH), 4.23-4.43 (m, 3H, O-C*H*$_2$ and C*H*-N), 5.15–5.24 (m, 2H, C*H*$_2$=CH), 5.79–5.91 (m, 1H, CH_2=C*H*), 6.78–6.82 (d, 2H, *J* = 8.2 Hz, aromatic protons), 6.83–7.03 (d, 2H, *J* =8.1 Hz, aromatic protons), 7.13–7.17 (d, 2H, *J* =8.2 Hz, aromatic protons),

7.23–7.28 (d, 2H, J = 8.4 Hz, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.81 (*p*-$CH_3C_6H_4$), 20.03 (*p*-$CH_3C_6H_4$), 28.11 (CH_2–CH), 58.34 (CH-N), 62.21 (O-CH_2), 116.39 (CH_2=CH), 122.21, 126.03, 127.79, 128.43 (CH-aromatic carbons), 136.82 (CH_2=CH), 129.56, 134.38, 140.16, 144.06 (quaternary aromatic carbons), 148.17 (C=N); MS (*m/e*) 305 $[M-1]^+$, 306 $[M]^+$. Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found C, 78.39; H, 7.24; N, 9.00.

***N*, 3-Di(*p*-methoxyphenyl)-4-vinyltetrahydro-1,3-oxazin-2-imine (3.25d)** (R = H, R′ = *p*-$CH_3OC_6H_4$): mp = 86-87 °C; IR (C=N) 1628 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$), δ 1.98–2.01 (m, 1H, C*H*$_2$–CH), 2.38–2.45 (m, 1H, C*H*$_2$–CH), 3.73 (s, 3H, *p*-C*H*$_3$OC$_6$H$_4$), 3.77 (s, 3H, *p*-C*H*$_3$OC$_6$H$_4$), 4.21-4.36 (m, 3H, O-C*H*$_2$ and C*H*-N), 5.08–5.17 (m, 2H, C*H*$_2$=CH), 5.80–5.92 (m, 1H, CH$_2$=C*H*), 6.71–7.26 (m, 4H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.10 (CH_2–CH), 55.29 (*p*-$CH_3OC_6H_4$), 55.35 (*p*-$CH_3OC_6H_4$), 59.88 (CH-N), 63.26 (O-CH_2), 117.39 (CH_2=CH), 113.51, 114.03, 124.09, 128.75 (CH–aromatic carbons), 137.86 (CH_2=CH), 136.61, 141.52, 149.36, 154.36 (quaternary aromatic carbons), 157.37 (C=N); MS (*m/e*) 338 $[M]^+$. HRMS. Calcd for $C_{20}H_{22}N_2O_3$: 338.1630 Found 338.1622.

***N*, 3-Di(*o*-tolyl)-4-vinyltetrahydro-1,3-oxazin-2-imine (3.25e)** (R = H, R′ = *o*-$CH_3C_6H_4$): mp = 40-41 °C; IR (C=N) 1638 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$), δ 1.91–2.03 (m, 1H, C*H*$_2$–CH), 2.26 (s, 3H, *o*-C*H*$_3$C$_6$H$_4$), 2.33 (s, 3H, *o*-C*H*$_3$C$_6$H$_4$), 2.35–2.41 (m, 1H, C*H*$_2$–CH), 4.18-4.42 (m, 3H, O-C*H*$_2$ and C*H*-N), 5.14–5.25 (m, 2H, C*H*$_2$=CH), 5.86 (m, 1H, CH$_2$=C*H*), 6.69–6.73 (d, 2H, J =6.0 Hz, aromatic protons), 6.94–7.24 (m, 6H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.40 (*o*-$CH_3C_6H_4$), 21.49 (*o*-

$CH_3C_6H_4$), 29.07 (CH_2–CH), 59.19 (CH-N), 63.24 (O-CH_2), 117.39 (CH_2=CH), 120.28, 122.32, 124.05, 124.19, 126.58, 127.55, 127.95, 128.49 (CH-aromatic carbons), 137.75 (CH_2=CH), 138.44, 143.71, 148.12 (quaternary aromatic carbons), 148.97 (C=N); MS (*m/e*) 305 $[M-1]^+$, 306 $[M]^+$. HRMS Calcd for $C_{20}H_{22}N_2O$: 306.1732, Found 306.1739.

***N*, 3-Di(*p*-bromophenyl)-4-vinyltetrahydro-1,3-oxazin-2-imine (3.25f)** (R = H, R′ = *p*-BrC_6H_4): mp = 132-133 °C; IR (C=N) 1628 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 1.99–2.10 (m, 1H, CH_2–CH), 2.36–2.45 (m, 1H, CH_2–CH), 4.22–4.43 (m, 3H, O-CH_2 and C*H*-N), 5.14–5.26 (m, 2H, CH_2=CH), 5.75–5.92 (m, 1H, CH_2=C*H*), 6.74–6.79 (d, 2H, *J* = 8.7 Hz, aromatic protons), 7.19–7.37 (m, 4H, aromatic protons), 7.44–7.54 (d, 2H, *J* = 8.8 Hz, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.80 (CH_2–CH), 59.36 (CH-N), 63.48 (O-CH_2), 118.12 (CH_2=CH), 125.17, 128.99, 131.11, 131.91 (CH-aromatic carbons), 136.98 (CH_2=CH), 114.31, 119.43, 142.43 146.91 (quaternary aromatic carbons), 148.92 (C=N); MS (*m/e*) 434 $[M-1]^+$, 435 $[M]^+$. Anal. Calcd for $C_{18}H_{16}Br_2N_2O$: C, 49.57; H, 3.70; N, 6.42. Found C, 49.54; H, 3.73; N, 6.55.

***N*, 3-Diphenyl-4-methyl-4-vinyltetrahydro-1,3-oxazin-2-imine (3.25g)** (R = CH_3, R′ = C_6H_5): mp = 117-118 °C; IR (C=N) 1618 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 1.31 (s, 1H, (CH_3)C–N), 2.12–2.19 (m, 2H, CH_2–C(CH_3)), 4.27–4.34 (m, 2H, O-CH_2), 5.18 (d, 1H, *J* = 12.2 Hz, CH_2=CH), 5.26 (d, 1H, *J* = 5.6 Hz, CH_2=CH), 6.04–6.18 (dd, 1H, *J* = 17.3 and 0.7 Hz), 6.82–6.91 (m, 2H, aromatic protons), 7.13–7.39 (m, 8H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.12 ((CH_3)C–N), 36.58 (CH_2–C(CH_3)), 58.96 ((CH_3)C–N), 62.74 (O-CH_2), 115.02 (CH_2=CH), 121.29, 123.44, 126.94, 128.10, 128.43, 130.72 (CH-aromatic carbons), 142.97 (CH_2=CH), 140.82, 148.59 (quaternary aromatic

carbons), 149.65 (C=N); MS (*m/e*) 291 $[M-1]^+$, 292 $[M]^+$. Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found C, 77.91; H, 6.87; N, 9.56.

***N*, 3-Di(*p*-chlorophenyl)-4-methyl-4-vinyltetrahydro-1,3-oxazin-2-imine (3.25h)** (R = CH_3, R′ = *p*-ClC_6H_4): mp = 129-130 °C; IR (C=N) 1624 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ1.26 (s, 3H, (C*H*$_3$)C–N), 2.00–2.14 (m, 2H, C*H*$_2$–C(CH_3)), 4.23–4.29 (m, 2H, O-C*H*$_2$), 5.16 (d, 1H, *J* = 17.3 Hz, C*H*$_2$=CH), 5.24 (d, 1H, *J* = 10.7 Hz, C*H*$_2$=CH), 6.02 dd, 1H, *J* = 17.3 and 10. 7 Hz, CH_2=C*H*), 6.72–6.78 (m, 2H, aromatic protons), 7.07–7.32 (m, 6H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.92 ((CH$_3$)C–N), 36.24 (CH$_2$–C(CH_3)), 59.01 ((CH$_3$)C–N), 62.81 (O-CH$_2$), 115.51 (CH$_2$=CH), 124.71, 126.25, 128.04, 128.67, 131.93 (CH-aromatic carbons), 142.31 (CH$_2$=CH), 132.69, 139.07, 146.34 (quaternary aromatic carbons), 149.66 (C=N); MS (*m/e*) 359 $[M-1]^+$, 360 $[M]^+$. Anal. Calcd for $C_{19}H_{18}Cl_2N_2O$: C, 63.17; H, 5.02; N, 7.75. Found C, 63.10; H, 4.99; N, 7.84.

***N*, 3-Di(*p*-tolyl)-4-methyl-4-vinyltetrahydro-1,3-oxazin-2-imine (3.25i)** (R = CH_3, R′ = *p*-$CH_3C_6H_4$): mp = 132-133 °C; IR (C=N) 1629 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 1.28 (s, 3H, (C*H*$_3$)C–N), 2.06–2.13 (m, 2H, C*H*$_2$–C(CH_3)), 2.23 (s, 3H, *p*-C*H*$_3$C$_6$H$_4$), 2.32 (s, 3H, *p*-C*H*$_3$C$_6$H$_4$), 4.23–4.29 (m, 2H, O-C*H*$_2$), 5.14 (d, 1H, *J* = 12.3 Hz, C*H*$_2$=CH), 5.21 (d, 1H, *J* = 5.8 Hz, C*H*$_2$=CH), 6.01–6.15 (dd, 1H, *J* = 17.3 and 10.7 Hz, CH_2=C*H*), 6.70–6.73 (d, 2H, *J* = 8.1 Hz, aromatic protons), 6.93–6.97 (d, 2H, *J* = 8.1 Hz, aromatic protons), 7.13 (s, 4H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.78 (*p*-CH$_3$C$_6$H$_4$), 21.11 (*p*-CH$_3$C$_6$H$_4$), 26.27 ((CH$_3$)C–N), 36.55 (CH$_2$–C(CH_3)), 58.85 ((CH$_3$)C–N), 62.67 (O-CH$_2$), 114.81 (CH$_2$=CH), 123.19, 128.69, 128.97, 129.13, 130.32,

130.43, (CH-aromatic carbons), 143.08, (CH_2=CH), 130.66, 136.48, 138.09, 145.93 (quaternary aromatic carbons), 149.84 (C=N); MS (*m/e*) 319 $[M-1]^+$, 320 $[M]^+$. Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found C, 78.72; H, 7.52; N, 8.93.

***N*, 3-Di(*p*-methoxyphenyl)-4-methyl-4-vinyltetrahydro-1,3-oxazin-2-imine (3.25j)** (R = CH_3, R′ = *p*-$CH_3OC_6H_4$): mp = 95-96 °C; IR (C=N) 1624 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 1.28 (s, 3H, (C*H*$_3$)C–N), 2.09–2.11 (m, 2H, C*H*$_2$–C(CH_3)), 3.72 (s, 3H, *p*-C*H*$_3$OC_6H_4), 3.77, (s, 3H, *p*-C*H*$_3$OC_6H_4), 4.24–4.30 (m, 2H, O-C*H*$_2$), 5.09–5.22 (m, 2H, C*H*$_2$=CH), 6.00-6.14 (dd, 1H, *J* = 17.3 and 10.7 Hz, CH_2=C*H*), 6.73–6.86 (m, 6H, aromatic protons), 7.14–7.26 (m, 2H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.08 ((**C**H$_3$)C–N), 36.57 (**C**H$_2$–C(CH_3)), 55.26 (*p*-**C**H$_3$OC_6H_4), 55.38 (*p*-**C**H$_3$OC_6H_4), 58.95 ((CH$_3$)**C**–N), 62.65 (O-**C**H$_2$), 114.81 (**C**H$_2$=CH), 113.49, 113.65, 124.13, 131.71 (CH-aromatic carbons), 143.08 (**C**H$_2$=CH), 133.54, 141.92, 150.03, 154.29 (quaternary aromatic carbons), 158.07 (**C**=N); MS (*m/e*) 351 $[M-1]^+$, 352 $[M]^+$. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.52; H, 6.86; N, 7.95. Found C, 71.52; H, 6.87; N, 7.94.

***N*, 3-Di(*o*-tolyl)-4-methyl-4-vinyltetrahydro-1,3-oxazin-2-imine (3.27k)** (R = CH_3, R′ = *o*-$CH_3C_6H_4$): mp = 131-132 °C; IR (C=N) 1628 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 1.30 (s, 3H, (C*H*$_3$)C–N), 2.09–2.16 (m, 2H, C*H*$_2$–C(CH_3)), 2.26 (s, 3H, *o*-C*H*$_3$$C_6H_4$), 2.34, (s, 3H, *o*-C*H*$_3$$C_6H_4$), 4.26–4.32 (m, 2H, O-C*H*$_2$), 5.18 (d, 1H, *J* = 11.1 Hz, C*H*$_2$=CH), 5.25 (d, 1H, *J* = 4.2 Hz, C*H*$_2$=CH), 6.03-6.17 (dd, 1H, *J* = 17.3 and 10.8 Hz, CH_2=C*H*), 6.65–6.71 (m , 2H, aromatic protons), 7.02–7.27 (m, 6H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.39 (*o*-**C**H$_3$$C_6H_4$), 21.44 (*o*-**C**H$_3$$C_6H_4$), 26.17 ((**C**H$_3$)C–N), 36.61 (**C**H$_2$–C($CH_3$)), 58.90 (O-**C**H$_2$), 62.75 (O-**C**H$_2$), 114.88 (**C**H$_2$=CH), 120.38,

122.17, 124.17, 127.72, 127.79, 127.90, 128.16, 131.25 (CH-aromatic carbons), 143.09 (CH_2=CH), 137.68, 138.05, 140.66, 148.50 (quaternary aromatic carbons), 149.72 (C=N); MS (*m/e*) 319 $[M-1]^+$, 320 $[M]^+$. Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found C, 78.62; H, 7.63; N, 8.68.

3.5.4 General Procedure for the Cycloaddition Reaction of Bicyclic Vinyloxetanes (3.28a-c) with Heterocumulenes Catalyzed by $Pd_2(dba)_3$•$CHCl_3$ and a Bidentate phosphine ligand.

A mixture of $Pd_2(dba)_3$•$CHCl_3$ (0.03-0.045 mmol) and 2 equivalents of a bidentate phosphine ligand in THF (5 mL) was stirred in a glass autoclave under nitrogen at room temperature for 30 min. The bicyclic vinyloxetane **3.28a-c** (1.0 mmol), heterocumulene (1.0 mmol) and another 5 mL of THF were added, the glass autoclave was sealed, and then pressurized with N_2 to 5 psi. The reaction mixture was then stirred (see Table 3-6 for reaction times and temperatures in each case) until the conversion of the heterocumulene was complete (monitored by IR). The resulting solution was then concentrated by rotary evaporation, and the residue was purified by silica gel column chromatography using a mixture of pentane/ether as the eluant. Melting points, IR, NMR, MS and analytical data for **3.29** and **3.30** are as follows.

3-Aza-1-oxo-3, *N*-diphenyl-9-vinylbicyclo[4.4.0]decane-2-imine (3.29a) (R_1 = H, R_2 = H, X = Y = C_6H_5N): mp = 122-123 °C; IR (C=N) 1627 cm^{-1}; ^1H NMR (200 MHz,

$CDCl_3$), δ 1.30–2.25 (m, 9H, C*H*$_2$-cyclohexane and C*H*-CH_2-O), 4.05 (d, 1H, *J* = 10.6 Hz, C*H*$_2$–O), 4.55 (dd, 1H, *J* = 10.6 and 2.9 Hz, C*H*$_2$–O), 5.43 (d, 1H, *J* = 5.1 Hz, C*H*$_2$=CH), 5.50 (d, 1H, *J* = 1.45 Hz, C*H*$_2$=CH), 6.03 (dd, 1H, *J* = 17.5 and 10.5 Hz, CH_2=C*H*), 6.88–7.00 (m, 3H, aromatic protons), 7.15–7.50 (m, 7H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.90, 24.45, 25.67, 33.20 (CH_2-Cyclohexane), 38.25 (**C**H-CH_2-O), 61.76 (**C**($CH=CH_2$)), 68.44 (**C**H_2–O), 116.99 (CH=**C**H_2), 121.67, 123.66, 126.68, 128.16, 130.23 (CH-aromatic carbons), 139.93, 148.02 (quaternary aromatic carbons), 143.95 (**C**H=CH_2), 149.97 (C=N); MS (*m/e*) 331 $[M-1]^+$, 332 $[M]^+$. Anal. Calcd for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28; N, 8.43. Found C, 79.48; H, 7.17; N, 8.37.

3-Aza-1-oxo-3, *N*-di(*p*-chlorophenyl)-9-vinylbicyclo[4.4.0]decane-2-imine (3.29b) (R_1 = H, R_2 = H, X = Y = *p*-ClC_6H_4N): mp = 142-143 °C; IR (C=N) 1622 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$), δ 1.31-1.90 (m, 9H, C*H*$_2$-cyclohexane and C*H*-CH_2-O), 3.95 (dd, 1H, *J* = 10.8 and 1.4 Hz, C*H*$_2$–O), 4.48 (dd, 1H, *J* = 10.8 and 2.8 Hz, C*H*$_2$–O), 5.41 (d, 1H, *J* = 13.0 Hz, C*H*$_2$=CH), 5.46 (d, 1H, *J* = 6.6 Hz, C*H*$_2$=CH), 6.00 (dd, 1H, *J* = 17.2 and 10.8 Hz, CH_2=C*H*), 6.80 (d, 2H, *J* = 8.8 Hz, aromatic protons), 7.16 (d, 2H, *J* = 8.8 Hz, aromatic protons), 7.35 (m, 4H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.78, 24.43, 25.57, 33.14 (CH_2-Cyclohexane), 38.07 (**C**H-CH_2-O), 61.65 (**C**($CH=CH_2$)), 68.37 (**C**H_2–O), 117.00 (CH=**C**H_2), 124.73, 128.08, 128.22, 131.36 (CH-aromatic carbons), 126.20, 131.94, 138.80, 147.10 (quaternary aromatic carbons), 143.88 (**C**H=CH_2), 149.44. (**C**=N); MS (*m/e*) 400 $[M]^+$. Anal. Calcd for $C_{22}H_{22}Cl_2N_2O$: C, 65.84; H, 5.53; N, 6.98. Found C, 66.05; H, 5.60; N, 6.96.

3-Aza-1-oxo-3, *N*-di(*p*-tolyl)-9-vinylbicyclo[4.4.0]decane-2-imine (3.29c) (R_1 = H, R_2 =

H, X = Y = *p*-$CH_3C_6H_4N$): mp = 147-148 °C; IR (C=N) 1643 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 1.30-2.00 (m, 9H, C*H*$_2$-cyclohexane and C*H*-CH_2-O), 2.23 (s, 3H, *p*-$CH_3C_6H_4$), 2.31 (s, 3H, *p*-$CH_3C_6H_4$), 4.03 (dd, 1H, *J* = 10.8 and 1.6 Hz, C*H*$_2$–O), 4.47 (dd, 1H, *J* = 10.8 and 2.4 Hz), 5.36 (d, 1H, *J* = 10.4 Hz, C*H*$_2$=CH), 5.43 (d, 1H, *J* = 4.0 Hz, C*H*$_2$=CH), 5.93–6.07 (dd, 1H, *J* = 17.0 and 10.8 Hz, CH_2=C*H*), 6.82 (d, 2 H, *J* = 8.0 Hz, aromatic protons), 6.98 (d, 2H, *J* = 8.2 Hz, aromatic protons), 7.12 (d, 2H, *J* = 8.2 Hz, aromatic protons), 7.30 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.90 (*p*-$CH_3C_6H_4$), 21.00 (*p*-$CH_3C_6H_4$), 20.72, 24.08, 25.45, 32.79 (CH_2-cyclohexane), 37.92 (CH-CH_2-O), 61.88 (C(CH=CH_2)), 68.52 (CH_2-O), 117.01 (CH_2=CH), 128.72, 128.94, 129.81 (CH-aromatic carbons), 131.35, 136.37, 136.63 (quaternary aromatic carbons), 143.40 (CH_2=CH), 150.87 (C=N); MS (*m/e*) 359 $[M-1]^+$, 360 $[M]^+$. Anal. Calcd for $C_{24}H_{28}N_2O$: C, 79.96; H, 7.83; N, 7.77. Found C, 79.97; H, 7.70; N, 7.77.

3-Aza-1-oxo-3, *N*-di(*p*-metoxyphenyl)-9-vinylbicyclo[4.4.0]decane-2-imine (3.29d) (R_1 = H, R_2 = H, X = Y = *p*-$CH_3OC_6H_4N$): mp = 104-105 °C; IR (C=N) 1620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 1.25-1.90 (m, 9H, C*H*$_2$-cyclohexane and C*H*-CH_2-O), 3.70 (s, 3H, *p*-$CH_3OC_6H_4$), 3.71 (s, 3H, *p*-$CH_3OC_6H_4$), 3.97 (dd, 1H, *J* = 11.0 and 2.0 Hz, C*H*$_2$–O), 4.46 (dd, 1H, *J* = 10.8 and 2.6 Hz, C*H*$_2$–O), 5.34 (d, 1H, *J* = 11.3 Hz, C*H*$_2$=CH), 5.41 (d, 1H, *J* = 4.5 Hz, C*H*$_2$=CH), 5.99 (dd, 1H, *J* = 17.2 and 10.8 Hz, CH_2=C*H*), 6.69-6.73 (d, 2H, *J* = 8.7 Hz, aromatic protons), 6.80-6.86 (m, 4H, aromatic protons), 7.30 (d, 2H, *J* = 8.7 Hz, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.90, 24.15, 25.47, 32.85 (CH_2-cyclohexane), 37.99 (CH-CH_2-O), 55.16 (*p*-$CH_3OC_6H_4$), 55.26 (*p*-$CH_3OC_6H_4$), 61.73 (C(CH=CH_2)), 68.28 (CH_2-O), 113.35 (*p*-CH_3OC), 113.43 (*p*-

CH_3OC), 116.81 (CH_2=CH), 124.44, 131.03 (CH-aromatic carbons), 143.66 (CH=CH_2), 132.17, 140.10, 150.59, 154.62 (quaternary aromatic carbons), 157.80. (C=N); MS (*m/e*) 392 $[M]^+$. Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found C, 73.32; H, 7.15; N, 7.09.

3-Aza-1-oxo-3, *N*-di(*p*-bromophenyl)-9-vinylbicyclo[4.4.0]decane-2-imine (3.29e) (R_1 = H, R_2 = H, X = Y = *p*-BrC_6H_4N): mp = 144-145 °C; IR (C=N) 1620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 1.27-1.83 (m, 9H, C*H*$_2$-cyclohexane and C*H*-CH_2-O), 3.92 (d, 1H *J* = 10.9 Hz, C*H*$_2$–O), 4.45 (dd, 1H, *J* = 10.9 and 2.8 Hz, C*H*$_2$–O), 5.38 (d, 1H, *J* = 14.5 Hz, C*H*$_2$=CH), 5.45 (d, 1H, *J* = 7.9 Hz, C*H*$_2$=CH), 5.97 (dd, 1H, *J* = 17.2 and 10.7 Hz, CH_2=C*H*), 6.71 (d, 2H, *J* = 8.7 Hz, aromatic protons), 7.22-7.31 (m, 4H, aromatic protons), 7.40-7.44 (d, 2H, *J* = 8.8 Hz, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.74, 24.39, 25.53, 33.09 (CH_2-cyclohexane), 38.01 (CH-cyclohexane), 61.60 (C(CH=CH_2)), 68.36 (CH_2-O), 116.99 (CH_2=CH), 125.22, 130.97, 131.15, 131.71, (CH-aromatic carbons), 143.80 (CH_2=CH), 113.90, 120.08, 139.27, 147.50 (quaternary aromatic carbons), 149.32. (C=N); MS (*m/e*) 489 $[M]^+$. Anal. Calcd for $C_{22}H_{22}Br_2N_2O$: C, 53.90; H, 4.52; N, 5.71. Found C, 53.97; H, 4.50; N, 5.64.

3-Aza-1-oxo-3, *N*-di(*p*-chlorophenyl)-4-methyl-9-vinylbicyclo[4.4.0] decane-2-imine (3.29f) (R_1 = CH_3, R_2 = H, X = Y = *p*-ClC_6H_4N): mp = 174-175 °C; IR (C=N) 1619 cm^{-1}; H NMR (200 MHz, $CDCl_3$), δ 0.35 (d, 3H, *J* = 7.2 Hz, CH(C*H*$_3$)), 1.30-2.00 (m, 8H, C*H*$_2$ and C*H*-cyclohexane), 3.90 (dd, 1H, *J* = 10.9 and 2.2 Hz, C*H*$_2$–O), 4.47 (dd, 1H, *J* = 10.8 and 3.3 Hz, C*H*$_2$–O), 5.52 (d, 1H, *J* = 6.08 Hz, C*H*$_2$=CH), 5.59 (s, 1H, C*H*$_2$=CH), 5.89 (dd, 1H, *J* = 17.7 and 10.0 Hz, CH_2=C*H*), 6.70 (d, 2H, *J* =8.4 Hz, aromatic protons), 7.06

(d, 2H, J =8.4 Hz, aromatic protons), 7.24-7.36 (m, 4H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.41 (CH(CH_3)), 24.26, 25.59, 39.64 (CH_2-cyclohexane), 28.48 ($CH(CH_3)$), 41.88 (CH-CH_2-O), 65.91 (C($CH=CH_2$)), 68.87 (CH_2-O), 117.84 (CH_2=CH), 128.08, 128.61, 128.99, 129.51 (CH-aromatic carbons), 124.15, 126.19, 140.50, 147.10 (quaternary aromatic carbons), 143.96 (CH_2=CH), 150.13 (C=N); MS (*m/e*) 414 $[M]^+$. Anal. Calcd for $C_{23}H_{24}Cl_2N_2O$: C, 66.51; H, 5.82; N, 6.74. Found C, 66.44; H, 5.81; N, 6.69.

3-Aza-1-oxo-3, *N*-diphenyl-4-methyl-9-vinylbicyclo[4.4.0]decane-2-imine (3.29g) (R_1 = CH_3, R_2 = H, X = Y = C_6H_5N): mp = 142-143 °C; IR (C=N) 1625 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$), δ 0.34 (d, 3H, J = 6.9 Hz, CH(CH_3)), 1.00-2.10 (m, 8H, CH_2 and CH-cyclohexane), 3.93 (dd, 1H, J = 10.8 and 2.5 Hz, CH_2–O), 4.50 (dd, 1H, J = 10.8 and 3.6 Hz, CH_2–O), 5.57 (d, 1H, J = 9.7 Hz, CH_2=CH), 5.63 (d, 1H, J = 13.4 Hz, CH_2=CH), 5.90 (dd, 1H, J = 17.3 and 10.5 Hz, CH_2=CH), 6.85 (m, 3H, aromatic protons), 7.10-7.50 (m, 7H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.02 (CH(CH_3)), 24.16, 25.56, 39.59 (CH_2-cyclohexane), 28.33 ($CH(CH_3)$), 41.75 (CH-CH_2-O), 65.79 (C($CH=CH_2$)), 68.81 (CH_2-O), 117.64 (CH_2=CH), 121.38, 123.62, 127.29, 128.01, 128.04, 128.37, 131.45 (CH-aromatic carbons), 141.65, 148.02, (quaternary aromatic carbons) 144.01 (CH_2=CH), 150.35 (C=N); MS (*m/e*) 414 $[M]^+$. Anal. Calcd for $C_{23}H_{26}N_2O$: C, 79.73; H, 7.56; N, 8.09. Found C, 79.51; H, 7.41; N, 8.05.

3-Aza-1-oxo-3, *N*-di(*p*-tolyl)-4-methyl-9-vinylbicyclo[4.4.0]decane-2-imine (3.29h) (R_1 = CH_3, R_2 = H, X = Y = *p*-$CH_3C_6H_4N$): mp = 156-157 °C; IR (C=N) 1627 cm^{-1}; ^{1}H

NMR (200 MHz, $CDCl_3$), δ 0.39 (d, 3H, J = 7.1 Hz, CH(CH_3)), 1.24-2.00 (m, 8H, CH_2 and C*H*-cyclohexane), 2.22 (s, 3H, *p*-$CH_3C_6H_4$), 2.32 (s, 3H, *p*-$CH_3C_6H_4$), 3.99 (d, 1H, J = 1.5 Hz, CH_2–O), 4.51 (dd, 1H, J = 10.7 and 2.7 Hz, , CH_2–O), 5.51 (d, 1H, J = 1.7 Hz, CH_2=CH), 5.57 (d, 1H, J = 8.1 Hz, CH_2=CH), 5.88 (dd, 1H, J = 17.4 and 10.6 Hz, CH_2=C*H*), 6.80 (d, 1H, J = 8.1 Hz, aromatic protons), 6.97 (d, 2 H, J = 8.2 Hz, aromatic protons), 7.15 (d, 2H, J = 7.1 Hz, aromatic protons), 7.34 (d, 2H, J = 8.1 Hz, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.93 (CH(CH_3)), 20.76 (*p*-$CH_3C_6H_4$), 21.12 (*p*-$CH_3C_6H_4$), 23.60, 25.40, 39.09 (CH_2-cyclohexane), 28.29 (CH(CH_3)), 41.22 (CH-CH_2-O), 66.04 (C(CH=CH_2)), 69.32 (CH_2-O), 117.86 (CH_2=CH), 123.83, 128.77, 129.44, 130.80 (CH-aromatic carbons), 125.17, 131.66, 137.65, 142.90 (quaternary aromatic carbons), 143.38 (C*H*=CH_2), 151.61 (C=N); MS (*m/e*) 374 $[M]^+$. Anal. Calcd for $C_{25}H_{30}N_2O$: C, 80.17; H, 8.07; N, 7.48. Found C, 79.95; H, 7.99; N, 7.45.

3-Aza-1-oxo-3, *N*-di(*p*-chlorophenyl)-5-methyl-9-vinylbicyclo[4.4.0] decane-2-imine (3.29i) (R_1 = H, R_2 = CH_3, X = Y = *p*-ClC_6H_4N): mp = 132-133 °C; IR (C=N) 1625 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$), δ 0.64 (d, 3H, J =6.6 Hz, CH(CH_3)), 0.97-2.10 (m, 8H, CH_2 and C*H*-cyclohexane), 3.88 (d, 1H, J = 10.9 Hz, CH_2–O), 4.52 (dd, 1H, J = 10.9 and 3.3 Hz, CH_2–O), 5.40 (d, 1H, J = 10.3 Hz, CH_2=CH), 5.47 (d, 1H, J = 3.3 Hz, CH_2=CH), 6.03 (dd, 1H, J = 17.1 and 10.8 Hz, CH_2=C*H*), 6.74-6.78 (m, 2H, aromatic protons), 7.07-7.12 (m, 2H, aromatic protons), 7.23-7.37 (m, 4H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.78 (CH(CH_3)), 26.72 (CH(CH_3)), 25.96, 33.60, 37.88 (CH_2-cyclohexane), 41.78 (CH-CH_2-O), 62.27 (C(CH=CH_2), 68.18 (CH_2-O), 116.71 (CH_2=CH), 124.78, 128.13, 128.27, 131.13 (CH-aromatic carbons), 126.37, 132.02,

138.75, 146.88 (quaternary aromatic carbons), 144.19 (CH=CH_2), 149.44 (C=N); MS (*m/e*) 414 $[M]^+$. HRMS. Calcd for $C_{23}H_{24}Cl_2N_2O$: 414.1266. Found 414.1293.

3-Aza-1-oxo-3, *N*-di(*p*-tolyl)-5-methyl-9-vinylbicyclo[4.4.0]decane-2-imine (3.29j) (R_1 = CH_3, R_2 = H, X = Y = *p*-$CH_3C_6H_4N$): mp = 133-134 °C; IR (C=N) 1630 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 0.66 (d, 3H, *J* = 6.3 Hz, CH(C*H*$_3$)), 0.95-2.00 (m, 8H, C*H*$_2$ and C*H*-cyclohexane), 2.22 (s, 3H, *p*-C*H*$_3C_6H_4$), 2.31 (s, 3H, *p*-C*H*$_3C_6H_4$), 3.96 (d, 1H, *J* = 10.9 Hz, C*H*$_2$–O), 4.63 (m, 1H, C*H*$_2$–O), 5.36 (d, 1H, *J* = 10.9 Hz, C*H*$_2$=CH), 5.43 (d, 1H, *J* = 4.1 Hz, C*H*$_2$=CH), 6.15 (dd, 1H, *J* = 17.1 and 10.8 Hz, CH_2=C*H*), 6.85-6.88 (d, 2H, *J* = 8.1 Hz, aromatic protons), 6.96-7.01 (d, 2H, *J* =8.1 Hz, aromatic protons), 7.12-7.15 (d, 2H, *J* = 8.1 Hz, aromatic protons), 7.24-7.33 (d, 2H, *J* =8.1 Hz, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.81 (*p*-C*H*$_3C_6H_4$), 21.11 (*p*-C*H*$_3C_6H_4$), 21.66 (CH(**C**H_3)), 25.95, 33.41, 37.75 (**C**H_2-cyclohexane), 26.79 (**C**H(CH$_3$)), 41.38 (**C**H-CH_2-O), 62.73 (**C**(CH=CH_2)), 68.80 (**C**H_2-O), 116.66 (**C**H_2=CH), 123.94, 128.89, 129.33 (CH-aromatic carbons), 134.94, 135.49, 137.34, 141.61, (quaternary aromatic carbons), 143.56 (**C**H=CH_2), 151.74 (C=N); MS (*m/e*) 373 $[M-1]^+$, 374 $[M]^+$. HRMS. Calcd for $C_{25}H_{30}N_2O$: 374.2358. Found 374.2330.

3-Aza-1-oxo-*N*-(phenyl)-9-vinylbicyclo[4.4.0]decane-2-one (3.30a) (R_1 = H, R_2 = H, X = C_6H_5N, Y = O): mp = 162-163 °C; IR (C=O) 1683 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 1.54-2.30 (m, 9H, C*H*$_2$ and C*H*-cyclohexane), 4.41 (dd, 1H, *J* = 11.2 and 1.5 Hz, C*H*$_2$–O), 4.96 (dd, 1H, *J* = 10.8 and 2.2 Hz, C*H*$_2$–O), 5.72 (d, 1H, *J* = 17.3 Hz, C*H*$_2$=CH), 5.81 (d, 1H, *J* =10.7 Hz, C*H*$_2$=CH), 6.31 (dd, 1H, *J* = 17.3 and 10.7 Hz, CH_2=C*H*), 7.61-7.73 (m, 5H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.66, 24.22, 25.25, 32.75

(CH_2-Cyclohexane), 37.47 (CH-CH_2-O), 62.78 (C(CH=CH_2)), 68.22 (CH_2-O), 116.71 (CH_2=CH), 126.99, 128.11, 129.10 (CH-aromatic carbons), 138.53 (quaternary aromatic carbon), 143.30 (CH=CH_2), 153.36. (C=O); MS (*m/e*) 257 $[M]^+$. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found C, 74.65; H, 7.48; N, 5.45.

3-Aza-1-oxo-*N*-(*p*-chlorophenyl)-9-vinylbicyclo[4.4.0]decane-2-one (3.30b) (R_1 = H, R_2 = H, X = *p*-ClC_6H_4N, Y = O): mp = 167-168 °C; IR (C=O) 1676 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 1.52-2.21 (m, 9H, Cyclohexyl protons), 4.45 (d, 1H, *J* = 10.8 Hz, C*H*$_2$–O), 4.98 (dd, 1H, *J* = 10.8 and 2.2 Hz, C*H*$_2$–O), 5.74 (d, 1H, *J* = 17.3 Hz, C*H*$_2$=CH), 5.86 (d, 1H, *J* = 10.8 Hz, C*H*$_2$=CH), 6.35 (dd, 1H, *J* = 17.3 and 10.8 Hz, CH_2=C*H*), 7.70 (s, 4H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.71, 24.23, 25.26, 32.77 (CH_2-Cyclohexane), 37.49 (CH-CH_2-O), 62.95 (C(CH=CH_2)), 68.35 (CH_2–O), 117.14 (CH_2=CH), 130.85, 131.39 (CH-aromatic carbons), 120.83, 137.71 (quaternary aromatic carbons), 143.07 (CH=CH_2), 153.20. (C=O); MS (*m/e*) 291 $[M]^+$. Anal. Calcd for $C_{16}H_{18}ClNO_2$: C, 65.86; H, 6.22; N, 4.80. Found C, 66.03; H, 6.28; N, 4.78.

3-Aza-1-oxo-*N*-(*p*-methoxyphenyl)-9-vinylbicyclo[4.4.0]decane-2-one (3.30c) (R_1 = H, R_2 = H, X = *p*-$CH_3OC_6H_4N$, Y = O): mp = 121-122 °C; IR (C=O) 1683 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 1.31-1.75 (m, 9H, CH_2-cyclohexyl), 3.74 (s, 3H, *p*-C*H*$_3$OC$_6$H$_4$), 3.99 (d, 1H, *J* = 11.1 Hz, C*H*$_2$–O), 4.54 (d, 1H, *J* = 11.1 Hz, C*H*$_2$–O), 5.29 (d, 1H, *J* = 17.3 Hz, C*H*$_2$=CH), 5.39 (d, 1H, *J* = 10.7 Hz, C*H*$_2$=CH), 5.91 (dd, 1H, *J* = 17.7 and 10.7 Hz, CH_2=C*H*), 6.79 (d, 2H, aromatic protons), 7.22 (d, 2H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.86, 24.30, 25.37, 32.84 (CH_2-cyclohexane), 37.51 (CH-CH_2-O), 55.33 (*p*-$CH_3OC_6H_4$), 62.84 (C(CH=CH_2)), 68.21 (CH_2–O), 116.74 (CH_2=CH), 113.48,

130.19 (CH-aromatic carbons), 143.40 ($CH=CH_2$), 131.35, 153.80 (quaternary aromatic carbons), 158.21 (C=O); MS (*m/e*) 287 $[M]^+$. Anal Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87 Found C, 71.07; H, 7.37; N, 4.94.

3-Aza-1-oxo-*N*-(*p*-tolyl)-9-vinylbicyclo[4.4.0]decane-2-one (3.30d) (R_1 = H, R_2 = H, X = *p*-$CH_3C_6H_4N$, Y = O): mp = 156-157 °C; IR (C=O) 1680 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), δ 130-1.84 (m, 9H, Cyclohexyl protons), 2.30 (s, 3H, *p*-$CH_3C_6H_4$), 4.01 (dd, 1H, *J* =9.7 and 1.7 Hz, CH_2-O), 4.55 (dd, 1H, *J* = 10.5 and 2.1 Hz, CH_2-O), 5.33 (d, 1H, *J* =17.2 Hz, CH_2=CH), 5.41 (d, 1H, *J* =10.0 Hz, CH_2=CH), 5.94 (dd, 1H, *J* = 17.2 and 10.0 Hz, CH_2=CH), 7.07-7.24 (m, 4H, aromatic protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.99 (*p*-$CH_3C_6H_4$), 20.81, 24.33, 25.35, 32.85 (CH_2-cyclohaxane), 37.56 (CH-CH_2-O), 62.73 (C($CH=CH_2$)), 68.19 (CH_2–O), 116.71 (CH_2=CH), 128.90 (CH-aromatic carbons), 135.90, 136.85 (quaternary aromatic carbons), 143.41 (CH_2=CH), 153.57 (C=O); MS (*m/e*) 271 $[M]^+$. Anal. Calcd for$C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found C, 75.53; H, 7.79; N, 5.15.

3.5.5 Single-Crystal X-ray Diffraction Study of 3.29a and 3.29f

Suitable crystals were selected, mounted on thin glass fibers using viscous oil, and cooled to the data collection temperature. Data were collected on a Bruker AX SMART 1k CCD diffractometer using 0.3° ω-scans at 0, 90, and 180° in ϕ. Unit-cell parameters were determined from 60 data frames collected at different sections of the Ewald sphere. No absorption corrections were required.

No symmetry higher than triclinic was evident from the diffraction data. Solution in *P*-1 yielded chemically reasonable and computationally stable results of refinement. The structures were solved by direct methods, completed with difference Fourier syntheses and refined with full-matrix least-squares procedures based on F^2. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were treated as idealized contributions. All scattering factors and anomalous dispersion factors are contained in the SHEXTL 5.1 program library (Bruker AXS, 1997, Madison, WI).

Table 3-7 Crystal data and structure refinement for **3.29a.**

Empirical Formula	$C_{22}H_{24}N_2O$
Formula weight	332.43
Temperature	203 (2)K
Wavelength	0.71073
Crystal system, space group	Triclinic, P-1
Unit cell dimension	a = 8.946(8)Å α = 85.678(9)°
	b = 9.996(9)Å β = 69.315(9)°
	c = 10.825(9)Å γ = 85.678(9)°
Volume	902(1) Å^3
Z, Calculated density	2, 1.224 mg/m^3
Absorption coefficient	0.075 mm^{-1}
F(000)	356
Crystal size	0.4×0.4×0.4 mm
Theta range for data collection	2.01 to 27.93°
Limiting indices	-11≤h≤10, -13≤k≤10, -13≤l≤11
Reflections collected/unique	5225/3689 [R(int) = 0.0988]
Completeness to theta =27.93	85.3%
Absorption correction	none
Refinement method	Full-matrix least squares on F^2
Data/ Restraints/parameter	3689/0/227
Goodness of fit on F^2	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0490, wR2 = 0.1000
R indices (all data)	R1 = 0.0852, wR2 = 0.1051
Extinction coefficient	0.031 (3)
Largest diff. peak and hole	0.203 and –0.269 e Å^3

Table 3-8 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^4$) for **3.29a**.

	x	y	z	U(eq)
O	1175(1)	6378(1)	4411(1)	36(1)
N(1)	2226(2)	7778(1)	5394(1)	31(1)
N(2)	2021(2)	8489(1)	3382(1)	27(1)
C(1)	1354(2)	6943(2)	7680(2)	45(1)
C(2)	1378(3)	5944(3)	8630(2)	61(1)
C(3)	2225(3)	4753(3)	8310(2)	62(1)
C(4)	3072(2)	4532(2)	6997(2)	53(1)
C(5)	3051(2)	5511(2)	6042(2)	40(1)
C(6)	2189(2)	6722(2)	6351(2)	30(1)
C(7)	4192(2)	9777(2)	3477(2)	33(1)
C(8)	4814(2)	10990(2)	3536(2)	42(1)
C(9)	3919(2)	12171(2)	3543(2)	46(1)
C(10)	2411(3)	12144(2)	3536(2)	50(1)
C(11)	1758(2)	10930(2)	3504(2)	38(1)
C(12)	2668(2)	9749(2)	3466(1)	26(1)
C(13)	1828(2)	7554(2)	4425(2)	28(1)
C(14)	505(2)	6159(2)	3422(2)	38(1)
C(15)	1511(2)	6782(2)	2113(2)	34(1)
C(16)	1476(2)	8305(2)	2260(2)	29(1)
C(17)	2621(2)	8956(2)	973(2)	36(1)
C(18)	4292(2)	8299(2)	512(2)	44(1)
C(19)	4257(2)	6810(2)	352(2)	49(1)
C(20)	3188(2)	6124(2)	1625(2)	46(1)
C(21)	-224(2)	8896(2)	2552(2)	37(1)
C(22)	-977(3)	9080(2)	1727(2)	57(1)

Table 3-9 Bond lengths [Å] and bond angles [°] for **3.29a**.

O-C(13)	1.353(2)
O-C(14)	1.435(2)
N(1)-C(13)	1.261(2)
N(1)-C(6)	1.416(2)
N(2)-C(13)	1.380(2)
N(2)-C(12)	1.445(2)
N(2)-C(16)	1.487(2)
C(1)-C(2)	1.383(3)
C(1)-C(6)	1.393(3)
C(2)-C(3)	1.364(3)
C(3)-C(4)	1.380(3)
C(4)-C(5)	1.373(3)
C(5)-C(6)	1.385(3)
C(7)-C(12)	1.370(3)
C(7)-C(8)	1.385(3)
C(8)-C(9)	1.377(3)
C(9)-C(10)	1.355(3)
C(10)-C(11)	1.391(3)
C(11)-C(12)	1.380(3)
C(14)-C(15)	1.501(2)
C(15)-C(20)	1.521(3)
C(15)-C(16)	1.540(3)
C(16)-C(21)	1.525(3)
C(16)-C(17)	1.538(2)
C(17)-C(18)	1.517(3)
C(18)-C(19)	1.514(3)
C(19)-C(20)	1.519(3)
C(21)-C(22)	1.291(3)
C(13)-O-C(14)	121.05(13)
C(13)-N(1)-C(6)	118.90(15)
C(13)-N(2)-C(12)	116.94(14)
C(13)-N(2)-C(16)	123.41(14)
C(12)-N(2)-C(16)	119.43(12)
C(2)-C(1)-C(6)	119.4(2)
C(3)-C(2)-C(1)	122.0(2)
C(2)-C(3)-C(4)	119.04(19)
C(5)-C(4)-C(3)	119.6(2)
C(4)-C(5)-C(6)	122.00(19)
C(5)-C(6)-C(1)	117.94(17)
C(5)-C(6)-N(1)	123.03(16)
C(1)-C(6)-N(1)	118.81(17)
C(12)-C(7)-C(8)	119.90(17)
C(9)-C(8)-C(7)	120.06(19)
C(10)-C(9)-C(8)	120.00(18)
C(9)-C(10)-C(11)	120.60(19)
C(12)-C(11)-C(10)	119.39(19)
C(7)-C(12)-C(11)	120.03(16)
C(7)-C(12)-N(2)	120.18(15)
C(11)-C(12)-N(2)	119.78(16)
N(1)-C(13)-O	119.46(14)
N(1)-C(13)-N(2)	121.52(15)
O-C(13)-N(2)	119.02(15)
O-C(14)-C(15)	109.93(15)
C(14)-C(15)-C(20)	111.60(15)
C(14)-C(15)-C(16)	107.64(14)
C(20)-C(15)-C(16)	113.80(14)
N(2)-C(16)-C(21)	110.37(14)
N(2)-C(16)-C(17)	110.43(14)
C(21)-C(16)-C(17)	110.56(14)
N(2)-C(16)-C(15)	106.95(12)
C(21)-C(16)-C(15)	109.53(14)
C(17)-C(16)-C(15)	108.92(14)
C(18)-C(17)-C(16)	113.99(15)
C(19)-C(18)-C(17)	111.43(16)
C(18)-C(19)-C(20)	110.68(16)
C(19)-C(20)-C(15)	112.19(17)
C(22)-C(21)-C(16)	126.57(18)

Symmetry transformations used to generate equivalent atoms:

Table 3-10 Anisotropic displacement parameters [$Å^2 \times 10^3$] for **3.29a**.

	U11	U22	U33	U23	U13	U12
O	42(1)	31(1)	37(1)	5(1)	-18(1)	-18(1)
N(1)	32(1)	32(1)	29(1)	0(1)	-10(1)	-9(1)
N(2)	30(1)	24(1)	28(1)	-1(1)	-11(1)	-8(1)
C(1)	55(1)	49(1)	33(1)	0(1)	-17(1)	-19(1)
C(2)	79(2)	76(2)	34(1)	10(1)	-24(1)	-36(1)
C(3)	67(2)	68(2)	66(2)	34(1)	-44(1)	-31(1)
C(4)	43(1)	49(1)	73(2)	18(1)	-32(1)	-11(1)
C(5)	28(1)	46(1)	47(1)	7(1)	-14(1)	-8(1)
C(6)	26(1)	35(1)	32(1)	4(1)	-13(1)	-14(1)
C(7)	33(1)	29(1)	38(1)	-3(1)	-11(1)	-6(1)
C(8)	40(1)	41(1)	45(1)	-5(1)	-13(1)	-17(1)
C(9)	55(1)	30(1)	51(1)	-10(1)	-12(1)	-17(1)
C(10)	60(1)	24(1)	60(1)	-11(1)	-12(1)	1(1)
C(11)	33(1)	32(1)	44(1)	-7(1)	-7(1)	-2(1)
C(12)	28(1)	25(1)	22(1)	-3(1)	-4(1)	-8(1)
C(13)	22(1)	27(1)	32(1)	-1(1)	-5(1)	-6(1)
C(14)	42(1)	36(1)	42(1)	1(1)	-21(1)	-16(1)
C(15)	40(1)	30(1)	34(1)	-5(1)	-16(1)	-9(1)
C(16)	31(1)	29(1)	29(1)	0(1)	-12(1)	-6(1)
C(17)	39(1)	37(1)	30(1)	1(1)	-9(1)	-12(1)
C(18)	37(1)	52(1)	36(1)	-10(1)	-2(1)	-14(1)
C(19)	43(1)	53(1)	47(1)	-19(1)	-6(1)	0(1)
C(20)	51(1)	35(1)	50(1)	-14(1)	-14(1)	1(1)
C(21)	33(1)	40(1)	40(1)	0(1)	-13(1)	-6(1)
C(22)	45(1)	70(2)	59(1)	-2(1)	-23(1)	5(1)

Table 3-11 Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **3.29a**.

	x	y	z	U(eq)
H(1B)	780	7763	7928	53
H(2A)	794	6091	9523	73
H(3A)	2230	4092	8973	74
H(4A)	3662	3717	6759	63
H(5A)	3638	5354	5151	48
H(7A)	4815	8973	3445	40
H(8A)	5847	11008	3571	50
H(9A)	4356	12997	3553	55
H(10A)	1799	12951	3554	60
H(11A)	707	10915	3508	46
H(14A)	-588	6558	3679	45
H(14B)	458	5193	3350	45
H(15A)	999	6638	1461	40
H(17A)	2167	8918	275	43
H(17B)	2694	9905	1105	43
H(18A)	4932	8731	-336	52
H(18B)	4804	8428	1156	52
H(19A)	5345	6403	111	59
H(19B)	3859	6680	-364	59
H(20A)	3667	6156	2308	55
H(20B)	3121	5178	1478	55
H(21A)	-781	9152	3419	45
H(22C)	-472	8841	847	68
H(22A)	-2030	9454	2006	68

Table 3-12 Crystal data and structure refinement for **3.29f.**

Empirical Formula	$C_{23}H_{24}Cl_2N_2O$
Formula weight	415.34
Temperature	203 (2)K
Wavelength	0.71073
Crystal system, space group	Triclinic, P-1
Unit cell dimension	a = 7.974(2)Å α = 104.737(3)°
	b = 9.428(3)Å β = 90.368(4)°
	c = 14.058(4)Å γ = 102.628(4)°
Volume	995.2(5) $Å^3$
Z, Calculated density	2, 1.386 mg/m^3
Absorption coefficient	0.343 mm^{-1}
F(000)	436
Crystal size	0.3×0.1×0.05 mm
Theta range for data collection	1.50 to 28.60°
Limiting indices	$-10 \le h \le 10$, $-12 \le k \le 11$, $0 \le l \le 18$
Reflections collected/unique	7931/4463 [R(int) = 0.0385]
Completeness to theta =27.93	87.5%
Absorption correction	none
Refinement method	Full-matrix least squares on F^2
Data/ Restraints/parameter	4463/0/253
Goodness of fit on F^2	1.006
Final R indices [I>2sigma(I)]	R1 = 0.0443, wR2 = 0.1069
R indices (all data)	R1 = 0.0776, wR2 = 0.1122
Largest diff. peak and hole	0.271 and –0.305 e $Å^3$

Table 3-13 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^4$) for **3.29f**.

	x	y	z	U(eq)
Cl(1)	1923(1)	1401(1)	6360(1)	50(1)
Cl(2)	4403(1)	2302(1)	-1381(1)	41(1)
N(1)	6080(2)	1968(2)	2938(1)	28(1)
N(2)	8599(2)	2644(2)	2207(1)	27(1)
O	8606(2)	2594(2)	3870(1)	35(1)
C(1)	5273(3)	3047(3)	4601(2)	33(1)
C(2)	4287(3)	2916(3)	5393(2)	34(1)
C(3)	3200(3)	1561(3)	5370(2)	30(1)
C(4)	3080(3)	339(3)	4573(2)	33(1)
C(5)	4061(3)	488(3)	3780(2)	32(1)
C(6)	5190(3)	1841(2)	3782(2)	26(1)
C(7)	6630(3)	3598(3)	1342(2)	28(1)
C(8)	5633(3)	3525(3)	516(2)	29(1)
C(9)	5576(3)	2354(3)	-321(2)	29(1)
C(10)	6422(3)	1245(3)	-325(2)	31(1)
C(11)	7397(3)	1305(3)	511(2)	30(1)
C(12)	7526(3)	2499(2)	1345(1)	24(1)
C(13)	7718(3)	2392(2)	3010(2)	27(1)
C(14)	10463(3)	2871(3)	3936(2)	40(1)
C(15)	11227(3)	3804(3)	3259(2)	35(1)
C(16)	10898(4)	5400(3)	3559(2)	46(1)
C(17)	11637(4)	6348(3)	2877(2)	47(1)
C(18)	10979(3)	5560(3)	1822(2)	41(1)
C(19)	11307(3)	3969(3)	1515(2)	33(1)
C(20)	10991(3)	3326(3)	398(2)	43(1)
C(21)	10512(3)	2953(2)	2190(2)	28(1)
C(22)	11152(3)	1508(3)	1913(2)	35(1)
C(23)	10246(4)	136(3)	1831(2)	41(1)

Table 3-14 Bond lengths [Å] and bond angles [°] for **3.29f.**

Cl(1)-C(3)	1.747(2)
Cl(2)-C(9)	1.738(2)
N(1)-C(13)	1.274(3)
N(1)-C(6)	1.404(3)
N(2)-C(13)	1.377(3)
N(2)-C(12)	1.439(2)
N(2)-C(21)	1.490(3)
O-C(13)	1.346(2)
O-C(14)	1.444(3)
C(1)-C(2)	1.383(3)
C(1)-C(6)	1.387(3)
C(2)-C(3)	1.371(3)
C(3)-C(4)	1.373(3)
C(4)-C(5)	1.386(3)
C(5)-C(6)	1.390(3)
C(7)-C(8)	1.381(3)
C(7)-C(12)	1.382(3)
C(8)-C(9)	1.387(3)
C(9)-C(10)	1.362(3)
C(10)-C(11)	1.387(3)
C(11)-C(12)	1.388(3)
C(14)-C(15)	1.501(3)
C(15)-C(16)	1.537(3)
C(15)-C(21)	1.550(3)
C(16)-C(17)	1.510(4)
C(17)-C(18)	1.512(3)
C(18)-C(19)	1.533(3)
C(19)-C(20)	1.529(3)
C(19)-C(21)	1.557(3)
C(21)-C(22)	1.518(3)
C(22)-C(23)	1.313(3)
C(13)-N(1)-C(6)	119.67(18)
C(13)-N(2)-C(12)	114.83(17)
C(13)-N(2)-C(21)	123.78(17)
C(12)-N(2)-C(21)	121.29(17)
C(13)-O-C(14)	121.41(17)
C(2)-C(1)-C(6)	121.7(2)
C(3)-C(2)-C(1)	119.3(2)
C(2)-C(3)-C(4)	120.9(2)
C(2)-C(3)-Cl(1)	119.36(17)
C(4)-C(3)-Cl(1)	119.71(18)
C(3)-C(4)-C(5)	119.3(2)
C(4)-C(5)-C(6)	121.4(2)
C(1)-C(6)-C(5)	117.5(2)
C(1)-C(6)-N(1)	122.9(2)
C(5)-C(6)-N(1)	119.40(19)
C(8)-C(7)-C(12)	120.6(2)
C(7)-C(8)-C(9)	119.2(2)
C(10)-C(9)-C(8)	121.0(2)
C(10)-C(9)-Cl(2)	119.59(17)
C(8)-C(9)-Cl(2)	119.44(19)
C(9)-C(10)-C(11)	119.7(2)
C(10)-C(11)-C(12)	120.2(2)
C(7)-C(12)-C(11)	119.24(19)
C(7)-C(12)-N(2)	118.88(18)
C(11)-C(12)-N(2)	121.9(2)
N(1)-C(13)-O	120.4(2)
N(1)-C(13)-N(2)	120.36(18)
O-C(13)-N(2)	119.2(2)
O-C(14)-C(15)	110.92(19)
C(14)-C(15)-C(16)	112.4(2)
C(14)-C(15)-C(21)	108.52(19)
C(16)-C(15)-C(21)	111.97(19)
C(17)-C(16)-C(15)	113.1(2)
C(16)-C(17)-C(18)	110.7(2)
C(17)-C(18)-C(19)	111.3(2)
C(20)-C(19)-C(18)	110.2(2)
C(20)-C(19)-C(21)	118.22(19)
C(18)-C(19)-C(21)	113.78(19)
N(2)-C(21)-C(22)	111.72(18)
N(2)-C(21)-C(15)	106.14(17)
C(22)-C(21)-C(15)	107.57(18)
N(2)-C(21)-C(19)	115.40(18)
C(22)-C(21)-C(19)	108.70(19)
C(15)-C(21)-C(19)	106.88(17)
C(23)-C(22)-C(21)	126.9(2)

Symmetry transformations used to generate equivalent atoms:

Table 3-15 Anisotropic displacement parameters [$Å^2 \times 10^3$] for **3.29f**.

	U11	U22	U33	U23	U13	U12
Cl(1)	47(1)	73(1)	35(1)	22(1)	18(1)	14(1)
Cl(2)	40(1)	56(1)	27(1)	10(1)	-7(1)	8(1)
N(1)	28(1)	35(1)	22(1)	12(1)	5(1)	2(1)
N(2)	22(1)	37(1)	19(1)	6(1)	2(1)	6(1)
O	29(1)	57(1)	23(1)	15(1)	3(1)	12(1)
C(1)	34(1)	29(1)	34(1)	9(1)	4(1)	3(1)
C(2)	41(2)	37(2)	26(1)	6(1)	6(1)	11(1)
C(3)	27(1)	43(2)	26(1)	15(1)	5(1)	11(1)
C(4)	32(1)	35(1)	33(1)	14(1)	4(1)	1(1)
C(5)	34(1)	33(1)	27(1)	5(1)	3(1)	5(1)
C(6)	26(1)	34(1)	23(1)	12(1)	4(1)	9(1)
C(7)	28(1)	32(1)	22(1)	5(1)	3(1)	5(1)
C(8)	27(1)	36(1)	28(1)	12(1)	4(1)	10(1)
C(9)	22(1)	40(1)	22(1)	10(1)	1(1)	0(1)
C(10)	28(1)	31(1)	26(1)	1(1)	-1(1)	-2(1)
C(11)	28(1)	31(1)	29(1)	7(1)	2(1)	6(1)
C(12)	19(1)	31(1)	20(1)	8(1)	2(1)	0(1)
C(13)	31(1)	29(1)	19(1)	6(1)	1(1)	8(1)
C(14)	31(1)	68(2)	25(1)	12(1)	-1(1)	18(1)
C(15)	25(1)	56(2)	20(1)	4(1)	-1(1)	11(1)
C(16)	41(2)	53(2)	31(1)	-9(1)	-3(1)	8(1)
C(17)	41(2)	37(2)	52(2)	-2(1)	1(1)	1(1)
C(18)	34(2)	38(2)	47(2)	10(1)	-2(1)	0(1)
C(19)	27(1)	42(2)	28(1)	7(1)	2(1)	4(1)
C(20)	41(2)	55(2)	29(1)	12(1)	4(1)	0(1)
C(21)	22(1)	35(1)	23(1)	5(1)	1(1)	4(1)
C(22)	30(1)	44(2)	34(1)	9(1)	7(1)	11(1)
C(23)	46(2)	43(2)	39(1)	12(1)	7(1)	19(1)

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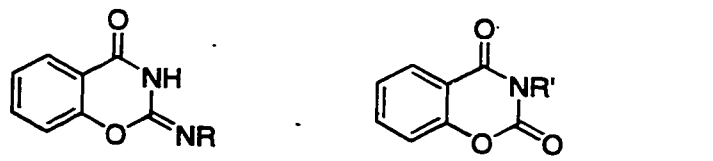
Chapter 4

Palladium-Catalyzed Cyclocarbonylation of *o*-Iodophenols and 2-Hydroxy-3-iodopyridine with Heterocumulenes; Regioselective Synthesis of Benzo[*e*]-1,3-oxazin-4-one and Pyrido[3,2-*e*]-1,3-oxazin-4-one Derivatives.

4.1 Introduction

4.1.1 Benzo[*e*]-1,3-oxazin-4-one derivatives.

Some benzo[*e*]-1,3-oxazin-4-one derivatives are known to possess pharmacological activity. For example, compounds of class **I** have potential analgesic properties [1,2] while **II** are effective against serine proteases [3-5] such as trypsin, thrombin, and plasmin (Fig. 4-1).



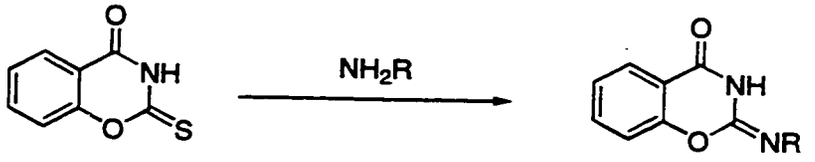
I
$R = CH_2C_6H_5$
$= C_6H_5$

II
$R' = CH_2C_6H_4R''$(*m* or *p*)

Figure 4-1 Structure of pharmaceutically active benzo[*e*]-1,3-oxazin-4-one derivatives.

To date a few reports have described the synthesis of these pharmaceutically interesting compounds containing the benzo[*e*]-1,3-oxazin-4-one nucleus.

Compounds of class I were prepared by treatment of 2*H*-1,3-benzoxazin-4-oxo-2-thione (**4.1**) with a primary amine (eq 1), however, no product yields was described in this report.[1]



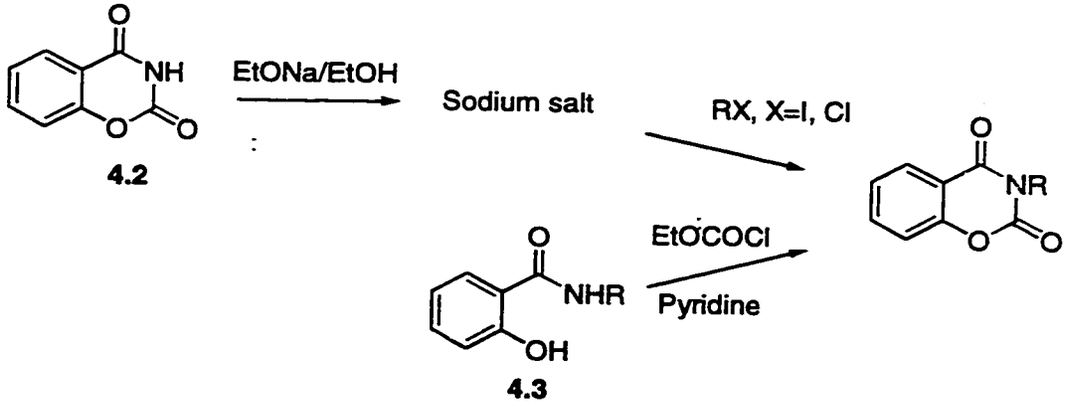
4.1

R = CH_2Ph, Ph, C_5H_{11}, $C_6H_4OCH_3$-*p*

(eq 1)

Two methods for the preparation of 3-substituted-2*H*-1,3-benzoxazin-2,4(3*H*)-diones were described by Crum and Franks (Scheme 4-1).[6] One method involves the reaction of **4.2** with ethanolic sodium ethoxide, followed by addition of an organic halide. Another procedure utilized the reaction of salicylamide (**4.3**) with ethylchloroformate in pyridine. The latter method was employed by the Warner-Lambert/Parke-Davis research group for the preparation of compounds of potential pharmaceutically interest.[7]

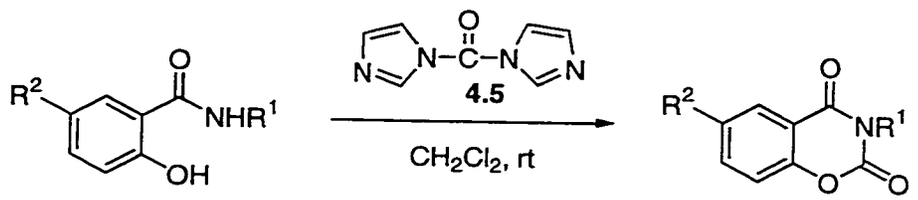
Scheme 4-1



4.2

4.3

The cyclization of salicylamides or salicylohydroxamic acids (**4.4**) with 1,1′-carbonyldiimidazole (**4.5**) leads to the formation of 2*H*-1,3-benzoxazin-2,4(3*H*)-diones (**4.6**) in good yields (eq 2).[8]



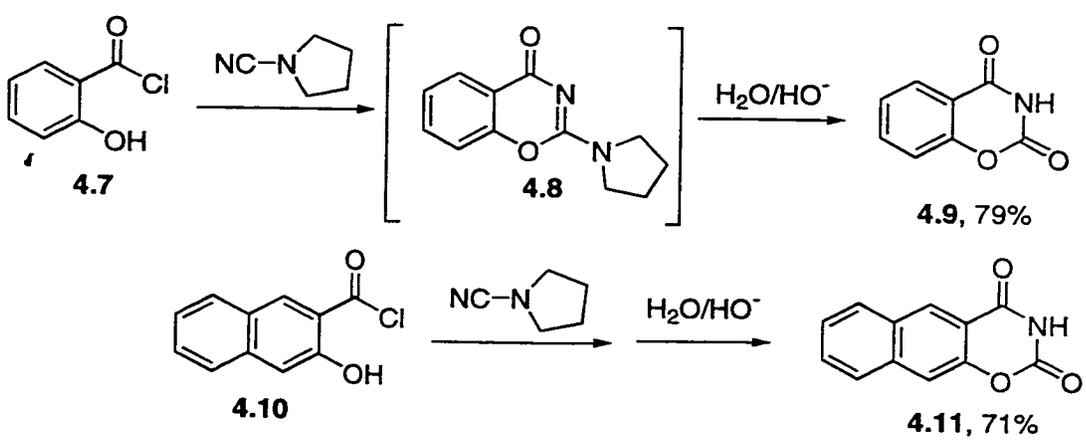
4.4
R^1 = H, Ph, OH
R^2 = H, Cl

4.6, 61-92%

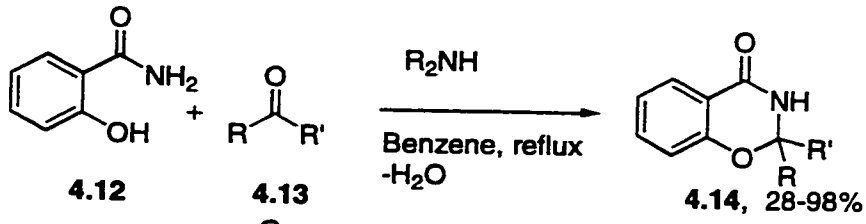
(eq 2)

2-Hydroxybenzoyl chloride (**4.7**) reacts with 1-cyanopyrrolidine to give **4.8** which was readily hydrolyzed to 1,3-benzoxazin-2,4-dione **4.9** in 79% yield. Applying the same procedure to 3-hydroxynaphthoyl chloride (**4.10**) led to **4.11** in 71% yield (Scheme 4-2).[9,10]

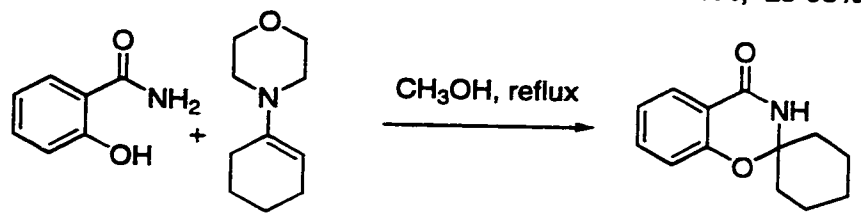
Scheme 4-2



Gammill described the amine-catalyzed condensation reaction of salicylamides (**4.12**) with aldehydes or ketones, which affords 2,3-dihydro-4*H*-1,3-benzoxazin-4-ones (**4.14**) (eq 3).[11] Enamines such as **4.15** can also be used as a substrate for this reaction, providing the corresponding products in high yield (eq 4).

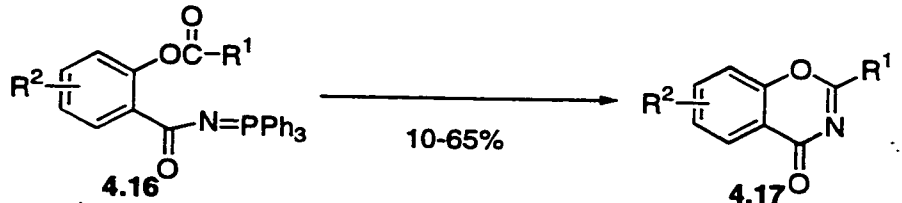


4.12 **4.13** **4.14**, 28-98% (eq 3)



4.12 **4.15** 94% (eq 4)

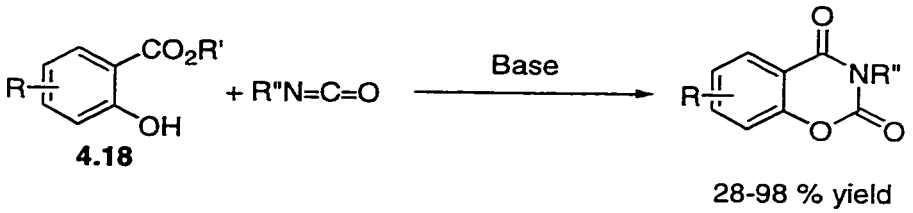
Iminophosphoranes **4.16** derived from a 2-acyloxycarboxamide undergo intramolecular condensation analogous to a Wittig reaction to give the corresponding 1,3-benzoxazin-4-one **4.17** in moderate yields (eq 5).[12]



4.16 **4.17** (eq 5)

R^1 = Me, Ph
R^2 = H, Me

Recently, another approach was described for the synthesis of benzoxazine-2,4-diones by reacting phenyl salicylate **4.18** with isocyanates in the presence of base such as Et_3N and/or DMAP (eq 6).[13]



4.18

28-98 % yield

(eq 6)

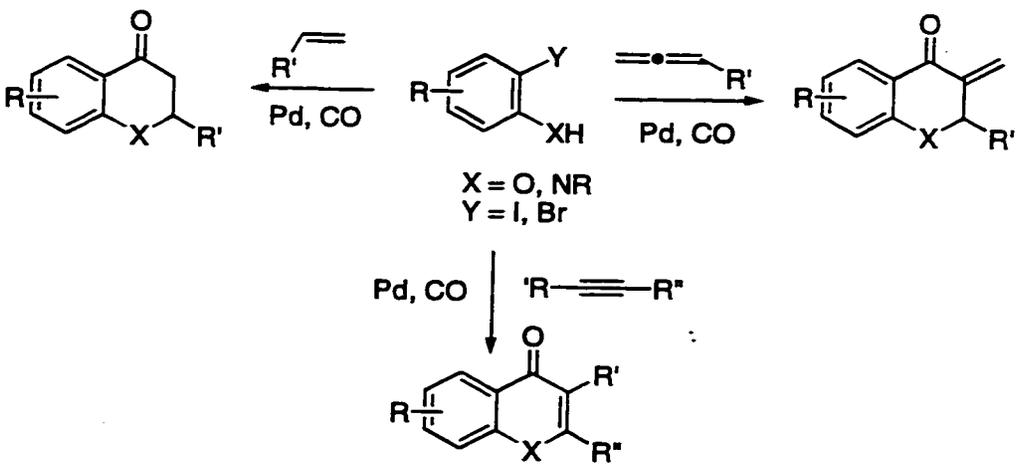
4.2 Aim of the research

Starting materials which are salicylic acid or its derivatives have always been employed for the preparation of 2*H*-1,3-benzoxazin-4-ones (see above), since they contain a carbonyl moiety which will consequently become the carbonyl unit at the 4-position of the product. Transition metal-catalyzed carbonylation is an alternative pathway to install the carbonyl moiety onto phenol derivatives to give the desired product.

The palladium-catalyzed carbonylation of aryl halides is an important, convenient and highly effective method for the synthesis of aromatic containing carbonyl compounds.[14-17] The reactions are well established to proceed by initial oxidative addition of palladium (0) to a carbon-halogen bond, followed by carbon monoxide

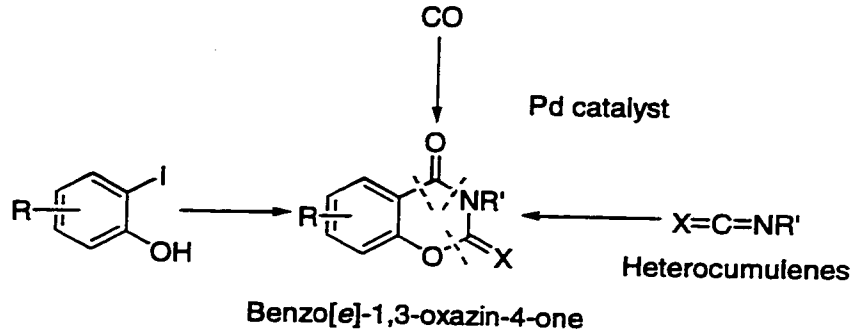
catalyzed cross coupling reactions of aromatic halides with a variety of unsaturated compounds [e.g. olefins,[18-28] alkynes,[29-39] and allenes[40-43] (Scheme 4-3, and see also chapter 1).

Scheme 4-3



Thus far no metal catalyzed carbonylative coupling reactions have been described of aromatic halides with cumulenes containing heteroatoms. Moreover, the preparative procedure for the target compounds by transition metal-catalyzed reactions has never been reported. We reasoned that *o*-iodophenols could undergo palladium catalyzed cyclocarbonylation with heterocumulenes to form benzo[*e*]-1,3-oxazin-4-ones and their derivatives (Scheme 4-4).

Scheme 4-4



Benzo[*e*]-1,3-oxazin-4-one

In this chapter, a simple and novel method for the synthesis of benzo[*e*]-1,3-oxazin-4-ones and benzo[*e*]-1,3-oxazin-2-imine-4-ones by palladium catalyzed cyclocarbonylation of *o*-iodophenols with heterocumulenes is described.

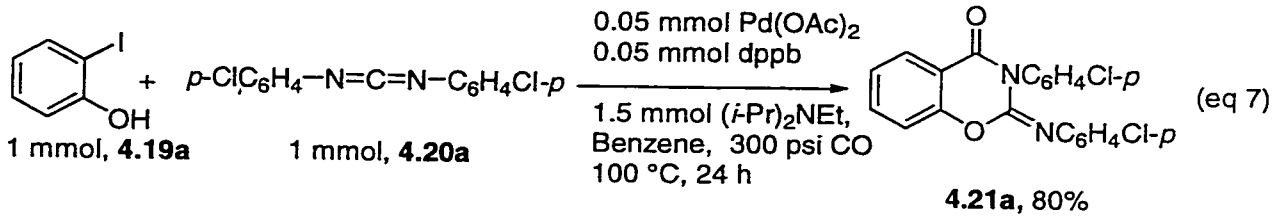
4.3 Results and Discussion

4.3.1 Optimization of the reaction conditions

We started our investigation by treatment of *o*-iodophenol (**4.19a**, R = H) with bis (*p*-chlorophenyl)carbodiimide (**4.20a**) using reaction conditions similar to those previously reported by Okuro and Alper[44] for the carbonylation of *o*-iodophenols with allenes (Scheme 1-15, Chapter 1).

The palladium (0)-1,4-bis(diphenylphosphino)butane (dppb) catalyst system was generated in situ by the reaction of 0.05 mmol $Pd(OAc)_2$ with 1 equivalent of dppb in

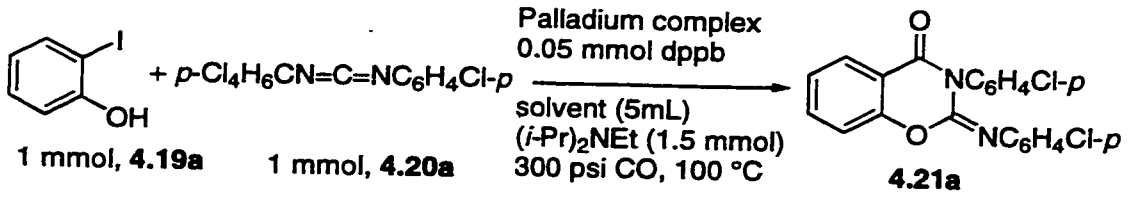
anhydrous benzene. After the mixture was stirred under N_2 at room temperature for 15 min, 1 mmol each of **4.19a** and **4.20a,** and 1.5 mmol of $(i\text{-Pr})_2$NEt were added, and the reaction mixture was stirred at 100 °C under 300 psi carbon monoxide for 24 h, resulting in the formation of *N*,3-di(*p*-chlorophenyl)benzo[*e*]-1,3-oxazin-2-imine-4-one (**4.21a**) in 80% isolated yield (eq 7).



1 mmol, **4.19a** 1 mmol, **4.20a** **4.21a,** 80% (eq 7)

The influence of the palladium complex, solvent, base and substrate/catalyst ratio was then extensively investigated. When $Pd_2(dba)_3 \cdot CHCl_3$ (0.025 mmol) was used instead of $Pd(OAc)_2$, 81% of **4.21a** was obtained; however, the complete conversion of the carbodiimide required 48 h. Benzene proved to be the best solvent for the reaction (Table 4-1) utilizing $Pd(OAc)_2$ (entry 1) whereas THF, benzene and DME gave similar results for $Pd_2(dba)_3 \cdot CHCl_3$ (entries 1-3). Poor product yields resulted when the reaction was performed in DMF.

Table 4-1 Effect of Solvent on the Cyclocarbonylation of *o*-Iodophenol (**4.19a**) with Bis(*p*-chlorophenyl)carbodiimide (**4.20a**) in the Presence of a Palladium Complex and dppb.[a]



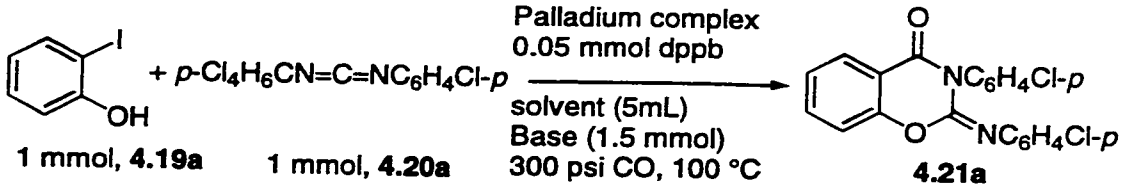
1 mmol, **4.19a** 1 mmol, **4.20a** **4.21a**

Entry	Solvent	Isolated yield of **4.21a** (%)[b]	
		0.05 mmol $Pd(OAc)_2$ and 0.05 mmol dppb[c]	0.05 mmol $Pd_2(dba)_3 \cdot CHCl_3$ and 0.05 mmol dppb[d]
1	Benzene	80	81
2	THF	69	82
3	DME	36	77
4	DMF	61	35

[a] Reaction conditions: **4.19a** (1 mmol), **4.20a** (1 mmol), (*i*-Pr)$_2$NEt (1.5 mmol), solvent (5 mL), CO (300 psi), 100 °C. [b] Isolated yield. [c] Reaction time was 24 h. [d] Reaction time was 48 h.

Table 4-2 shows the influence of different bases on the reactions. Using $Pd(OAc)_2$ as the catalyst, diisopropylethylamine was the best base (entry 1) while K_2CO_3 was superior when using $Pd_2(dba)_3 \cdot CHCl_3$ (entry 6). Cycloaddition of *o*-iodophenol (**4.19a**) with **4.20a** proceeds using other bases such as Et_3N, pyridine, proton sponge, and Na_2CO_3, but in lower product yields (entries 2-5).

Table 4-2 Effect of Base on the Cyclocarbonylation of *o*-Iodophenol (**4.19a**) with Bis(p-chlorophenyl) carbodiimide (**4.20a**) in the Presence of a Palladium Complex and dppb.[a]



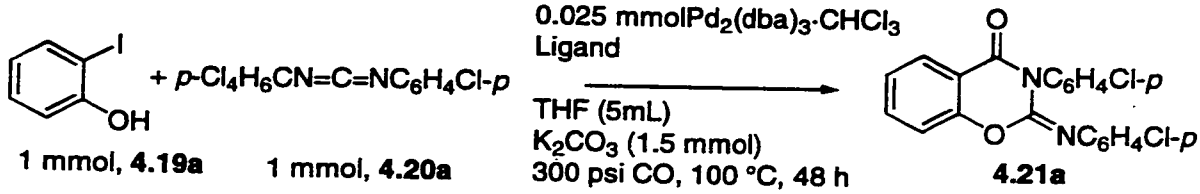
1 mmol, **4.19a** 1 mmol, **4.20a** **4.21a**

Entry	Base	Isolated yield of **4.21a** (%)[b]	
		0.05 mmol $Pd(OAc)_2$ and 0.05 mmol dppb in Benzene[c]	0.05 mmol $Pd_2(dba)_3 \cdot CHCl_3$ and 0.05 mmol dppb in THF[d]
1	$(i\text{-}Pr)_2NEt$	**80**	81
2	NEt_3	38	65
3	Pyridine	60	80
4	Proton Sponge	46	67
5	Na_2CO_3	47	92
6	K_2CO_3	34	**96**

[a] Reaction conditions: **4.19a** (1 mmol), **4.20a** (1 mmol), base (1.5 mmol), solvent (5 mL), CO (300 psi), 100 °C. [b] **4.21a** was purified by SiO_2 column Chromatography. [c] Reaction time was 24 h. [d] Reaction time was 48 h.

The nature of phosphine ligand has little influence on the product yields (Table 4-3). Slightly lower yields of **4.21a** were obtained in the reaction of **4.19a** with **4.20a** and K_2CO_3 under 300 psi CO in the presence of 2.5 mol% of $Pd_2(dba)_3 \bullet CHCl_3$ in THF using dppp (94%), dppe (91%), PPh_3 (95%) or PCy_3 (84%) compared with the same reaction employing dppb (96%) as the added ligand. Performing the reaction using only 2.5 mol% of $Pd_2(dba)_3 \bullet CHCl_3$ – i.e. no added phosphine ligand–afforded 62% of **4.21a.**

Table 4-3 Effect of The Added Phosphine Ligand on the Palladium-catalyzed Cyclocarbonylation of **4.19a** with **4.20a.**[a]



1 mmol, **4.19a** 1 mmol, **4.20a** **4.21a**

Entry	Ligand	Isolated yield of **4.21a** (%)[b]
1	dppp (0.025 mmol)	91
2	dppe (0.025 mmol)	95
3	PPh_3 (0.05 mmol)	84
4	PCy_3 (0.05 mmol)	96
5	-	62

[a] Reaction conditions: **4.19a** (1 mmol), **4.20a** (1 mmol), K_2CO_3 (1.5 mmol), THF (5 mL), CO (300 psi), 100 °C. [b] **4.21a** was purified by SiO_2 column chromatography using 1:1 pentane:ether as the eluant.

High product yields were achieved even in the presence of a very small amount of the palladium catalyst. The results in Table 4-4 show that **4.21a** was obtained in 70-76 % yield at a 500-1000:1 ratio of **4.19a** and **4.20a**: palladium catalyst (Table 4-4, entries 5 and 6). Isolated yields of at least 90% of **4.21a** using a 20-250/1 ratio of **4.19a**/$Pd_2(dba)_3 \cdot CHCl_3$ (entries 1-4). Somewhat lower yields were obtained with $Pd(OAc)_2$ as the catalyst. A ratio of 200/1 was used for subsequent experiments.

Table 4-4 Determination of the Optimum Amount of Palladium Catalyst Required for the Cyclocarbonylation of *o*-Iodophenol (**4.19a**) with Bis(*p*-chlorophenyl) carbodiimide (**4.20a**) in the Presence of 1:1 $Pd_2(dba)_3 \cdot CHCl_3$:dppb.[a]

Entry	Ratio of substrate : Palladium catalyst	% Isolated yield of **4.21a**[b]
1	20 : 1 (0.05 mmol Pd)	96 (80)[c]
2	100 : 1 (0.01 mmol Pd)	94 (87)[c]
3	172.5 : 1 (0.006 mmol Pd)	94
4	250 : 1 (0.004 mmol Pd)	90
5	500 : 1 (0.002 mmol Pd)	76
6	1000 : 1 (0.001 mmol Pd)	70

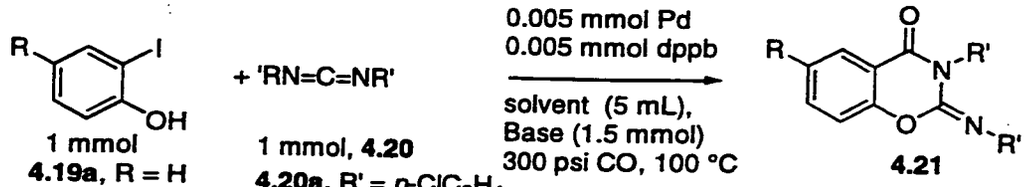
[a] Reaction conditions: **4.19a** (1 mmol), **4.20a** (1 mmol), base (1.5 mmol), solvent (5 mL), CO (300 psi), 100 °C, 48 h. [b] **4.21a** was purified by SiO_2 column chromatography. [c] Isolated yield of **4.21a** from the reaction using Pd $(OAc)_2$-dppb after 24 h.

As a consequence of the above results, two reaction systems will be employed for the cyclocarbonylation of *o*-iodophenols (**4.19**) with heterocumulenes.

1. When 0.005 mmol of $Pd(OAc)_2$ is used as the catalyst, 0.005 mmol dppb, 1.5 mmol $(i\text{-Pr})_2NEt$, and 1.0 mmol of *o*-iodophenol will be reacted in benzene under 300 psi of CO at 100 °C for 24 h.
2. When 0.0025 mmol of $Pd_2(dba)_3 \bullet CHCl_3$ is used as the catalyst, 0.005 mmol dppb, 1.5 mmol K_2CO_3, and 1.0 mmol of *o*-iodophenol will be reacted in THF under 300 psi of CO at 100 °C for 48 h.

4.3.2 The palladium-catalyzed cyclocarbonylation of *o*-iodophenols with carbodiimides.

A series of carbodiimides (**4.20**) were used for the Pd-catalyzed cyclocarbonylation reaction with *o*-iodophenols (**4.19**) for the formation of benzo[*e*]-1,3-oxazin-2-imine-4-one derivatives (**4.21**) (eq 8). The reactions were stirred at 100 °C under 300 psi CO, and after complete conversion of carbodiimide (monitored by IR), the reaction mixture was purified by silica gel column chromatography affording **4.21** in good to excellent yields (Table 4-5).



1 mmol
4.19a, R = H
4.19b, R = CH_3
4.19c, R = Cl

1 mmol, **4.20**
4.20a, R' = *p*-ClC_6H_4
4.20b, R' = *p*-$CH_3C_6H_4$
4.20c, R' = C_6H_5
4.20d, R' = *p*-BrC_6H_4
4.20e, R' = *p*-$CH_3OC_6H_4$
4.20f, R' = C_6H_{11}
4.20g, R' = $^iC_3H_7$

4.21

(eq 8)

o-Iodophenols bearing either electron donating (R = CH_3) or electron withdrawing (R = Cl) substituents on the aromatic ring were converted to **4.21** in good yields. 4-Methyl-2-iodophenol (**4.19b**) reacted with heterocumulenes in an analogous manner to **4.19a** giving rise to the anticipated heterocycles in high isolated yields (Table 4-5, entries 3, 7, 11, 17 and 19). When 4-chloro-2-iodophenol (**4.19c**) was used as the substrate, oxidative addition of palladium occurred selectively into the C-I bond (not C-Cl) to form **4.21** in high yield (entries 4, 8, 18 and 21).

When diarylcarbodiimides (**4.20a-e**) were utilized for the reaction, $Pd_2(dba)_3$•$CHCl_3$ afforded **4.21** in higher yields than $Pd(OAc)_2$. In contrast, $Pd(OAc)_2$ gives **4.21** in higher yields than does $Pd_2(dba)_3$•$CHCl_3$ for the reaction of dialkylcarbodiimides (**4.20f** and **4.20g**). Furthermore, for reactions using **4.20f** and **4.20g**, 2.5 mol% of palladium catalyst was needed since the reaction proceeded very slowly when 0.25 mol% of Pd was used, resulting in low product yields in the latter case. Good to excellent yields of **4.21k-o** were achieved from the reaction of **4.20f** and **4.20g** with **4.19a-c** in the presence of 2.5 mol% $Pd(OAc)_2$ and 5 mol% dppb in 5 mL benzene for 24 h at 100 °C and 300 psi CO (entries 15, 17, 18, 19 and 21).

Table 4-5 The Cyclocarbonylation of *o*-Iodophenols (**4.19**) with Carbodiimides (**4.20**) Catalyzed by a Palladium Complex and dppb.[a]

Entry	4.19	R′-N=C=N-R′, 4.20	Product	Catalyst[b] (mmol)	Isolated Yield of 4.21 (%)[f]
1	**4.19a**	**4.20a**	**4.21a**	$Pd_2(dba)_3 \bullet CHCl_3$(0.0025)	96
2	**4.19a**	**4.20a**	**4.21a**	$Pd(OAc)_2$ (0.005)	80
3	**4.19b**	**4.20a**	**4.21b**	$Pd_2(dba)_3 \bullet CHCl_3$(0.0025)	94
4	**4.19c**	**4.20a**	**4.21c**	$Pd_2(dba)_3 \bullet CHCl_3$(0.0025)	89
5	**4.19a**	**4.20b**	**4.21d**	$Pd_2(dba)_3 \bullet CHCl_3$(0.0025)	96
6	**4.19a**	**4.20b**	**4.21d**	$Pd(OAc)_2$ (0.005)	85
7	**4.19b**	**4.20b**	**4.21e**	$Pd_2(dba)_3 \bullet CHCl_3$(0.0025)	95
8	**4.19c**	**4.20b**	**4.21f**	$Pd_2(dba)_3 \bullet CHCl_3$(0.0025)	95
9	**4.19a**	**4.20c**	**4.21g**	$Pd_2(dba)_3 \bullet CHCl_3$(0.0025)	95
10	**4.19a**	**4.20c**	**4.21g**	$Pd(OAc)_2$ (0.005)	45
11	**4.19b**	**4.20c**	**4.21h**	$Pd_2(dba)_3 \bullet CHCl_3$(0.0025)	90
11	**4.19a**	**4.20d**	**4.21i**	$Pd_2(dba)_3 \bullet CHCl_3$(0.0025)	94
12	**4.19a**	**4.20d**	**4.21i**	$Pd(OAc)_2$ (0.005)	78
13	**4.19a**	**4.20e**	**4.21j**	$Pd_2(dba)_3 \bullet CHCl_3$(0.0025)	62
14	**4.19a**	**4.20e**	**4.21j**	$Pd(OAc)_2$ (0.005)	10
15	**4.19a**	**4.20f**	**4.21k**	$Pd(OAc)_2$ (0.025)[c]	93
16	**4.19a**	**4.20f**	**4.21k**	$Pd_2(dba)_3 \bullet CHCl_3$(0.0125)[d]	66
17	**4.19b**	**4.20f**	**4.21l**	$Pd(OAc)_2$ (0.025)[e]	93
18	**4.19c**	**4.20f**	**4.21m**	$Pd(OAc)_2$ (0.025)[e]	93
19	**4.19b**	**4.20g**	**4.21n**	$Pd(OAc)_2$ (0.025)[e]	94
20	**4.19b**	**4.20g**	**4.21n**	$Pd_2(dba)_3 \bullet CHCl_3$(0.0125)[d]	57
21	**4.19c**	**4.20g**	**4.21o**	$Pd(OAc)_2$(0.025)[e]	91

[a] Reaction conditions: refer to the Experimental Section for the general procedure for the cyclocarbonylation of *o*-iodophenols (**4.19**) with carbodiimides (**4.20**). [b] Reaction time was 48 h for $Pd_2(dba)_3 \bullet CHCl_3$ and 24 h for $Pd(OAc)_2$ respectively. [c] Reaction time was 36 h [d] Reaction time was 72 h [e] Reaction time was 48 h. [f] The products (**4.21**) were purified by silica gel column chromatography.

4.3.3 The palladium-catalyzed cyclocarbonylation of *o*-iodophenols with isocyanates.

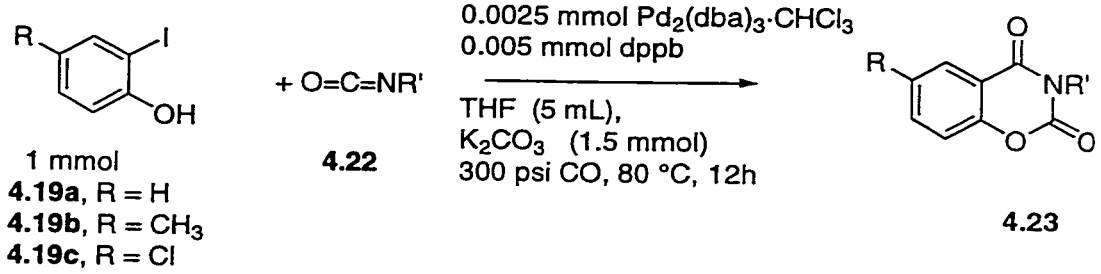
Benzo[*e*]-1,3-oxazin-2,4-diones (**4.23**) were obtained by the reaction of *o*-iodophenols (**4.19**) with isocyanates (**4.22**) and carbon monoxide catalyzed by $Pd_2(dba)_3 \cdot CHCl_3$ and dppb in THF, and the results are summarized in Table 4-6.

A mixture of $Pd_2(dba)_3 \cdot CHCl_3$ (0.0025 mmol) and dppb (0.005 mmol) was stirred under N_2 for 15 min and then 1 mmol each of **4.19b** and **4.22a** and 1.5 mmol of K_2CO_3 were added to the resulting solution. Note that complete conversion of isocyanate occurred after 12 h at lower reaction temperature (80 °C) than reactions with carbodiimides. After the mixture of **4.20b** and **4.22a** was stirred at 80 °C under 300 psi CO for 12 h, complete conversion of the isocyanate took place, with **4.23b** formed but in only 4% yield (entry 3, Table 4-6).

The amount of isocyanate used was found to be quite important for the reaction. Performing the reaction under the same conditions but at a 2:1 ratio of **4.22a/4.19b** gave **4.23b** in 84% yield (entry 2). No reaction occurred when using a 1:1 ratio of **4.22:4.19** in the case of **4.22b** (entry 6) and **4.22c** (entry 9); however, **4.23d** and **4.23f** were isolated in 52-58% yield by doubling the amount of the reactant isocyanates (entries 5 and 8). Those reactions that afford lower product yields may be a result of the presence of base in the reaction which induces dimer or trimer formation of the isocyanates. As Hoffman and Snape reported, dimerization and trimerization of isocyanates were observed in the presence of base for the reaction at elevated temperature.[45-47]

Good yields of benzo[*e*]-1,3-oxazin-2,4-diones (**4.23**) were attained by using **4.19**:**4.22**:K_2CO_3 in the ratio of 1:2:1.5 in the presence of 0.25 mol% of $Pd_2(dba)_3 \bullet CHCl_3$ and 0.5 mol% of dppb in THF under 300 psi CO at 80 °C for 12 h. An important application of this reaction is for the synthesis of 3-(benzyl)benzo[*e*]-1,3-oxazin-2,4-dione (**4.23h**, entry 11), which may be effective against serine proteases.[3] In this reaction, $Pd(OAc)_2$-dppb was used instead of $Pd_2(dba)_3 \bullet CHCl_3$-dppb in order to obtain **4.23h** in better yield. When the reaction of **4.19a** with **4.22e** was performed by using $Pd_2(dba)_3 \bullet CHCl_3$-dppb, **4.23h** was obtained in low yield, together with unidentified by-products.

Table 4-6 Cyclocarbonylation of *o*-Iodophenols (**4.19**) with Isocyanates (**4.22**) using $Pd_2(dba)_3$·$CHCl_3$-dppb.[a]



1 mmol
4.19a, R = H
4.19b, R = CH_3
4.19c, R = Cl

4.22

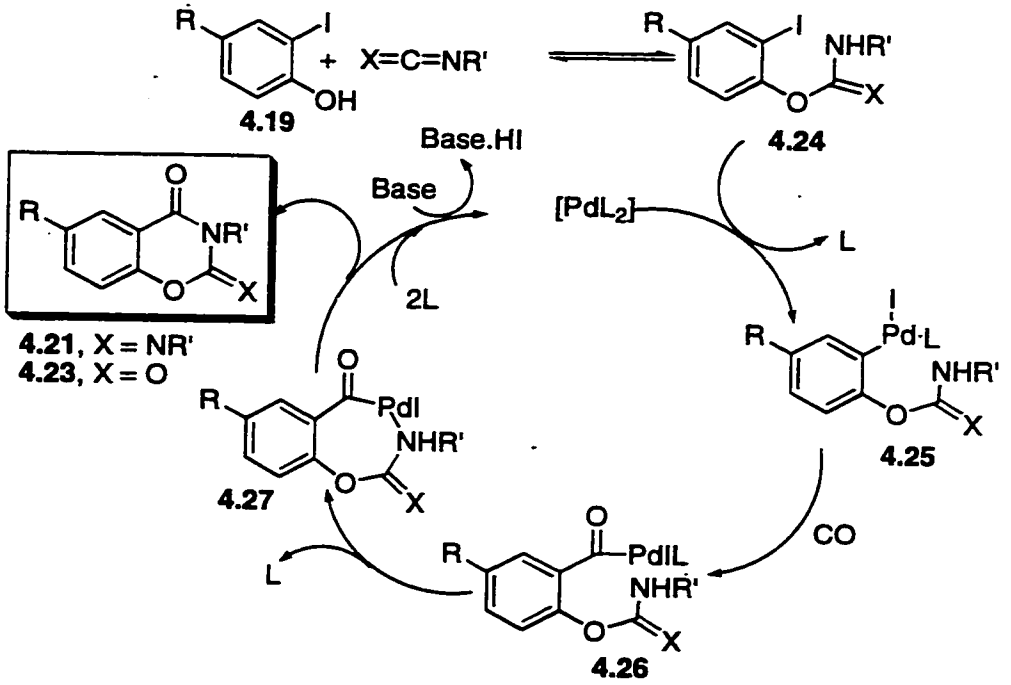
4.23

Entry	**4.19**	O=C=NR', **4.22**	Product	Ratio of **4.19**:**4.22**	Isolated yield of **4.23** (%)[b]
1	**4.19a**	O=C=NC_6H_4Cl-*p* **4.22a**	**4.23a**	1:2	79
2	**4.19b**	**4.22a**	**4.23b**	1:2	84
3	**4.19b**	**4.22a**	**4.23b**	1:1	4
4	**4.19b**	O=C=NC_6H_4Br-*p* **4. 22b**	**4.23c**	1:2	77
5	**4.19c**	**4.22b**	**4.23d**	1:2	58
6	**4.19c**	**4.22b**	**4.23d**	1:1	0
7	**4.19a**	O=C=N$C_6H_4CH_3$-*p* **4.22c**	**4.23e**	1:2	81
8	**4.19c**	**4.22c**	**4.23f**	1:2	52
9	**4.19c**	**4.22c**	**4.23f**	1:1	0
10	**4.19b**	O=C=N$C_6H_4OCH_3$-*p* **4.22d**	**4.23g**	1:2	82
11	**4.19a**	O=C=N$CH_2C_6H_5$ **4.22e**	**4.23h**	1:2	79[c]

[a] Reaction conditions: **4.19**:**4.22**:K_2CO_3:$Pd_2(dba)_3$•$CHCl_3$: dppb,1:2:1.5:0.0025:0.005 mmol in 5 mL THF, 80 °C, 300 psi Of CO, 12h. [b] Isolated yield by silica gel chromatography. [c] 0.005 mmol $Pd(OAc)_2$ was used instead of $Pd_2(dba)_3$•$CHCl_3$.

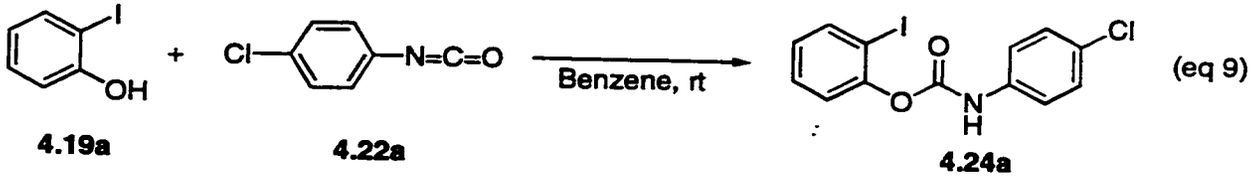
4.3.4 Reaction mechanism.

The mechanism of this reaction can be explained by the pathway outlined in Scheme 4-5. First the carbamate ester (**4.24**) may be formed in situ by reaction between *o*-iodophenols (**4.19**) with heterocumulenes. The latter undergo oxidative addition to $[Pd(0)L_2]$[48] and carbonyl insertion affording aroyl palladium intermediates (**4.26**). Hartwig et al. postulated that the inter– and intramolecular coordination of amine to palladium aryl halide complexes was enhanced by the nucleophilicity of the NH moiety.[49-51] Therefore, the amine moiety of the carbamate ester (**4.24**) may coordinate to the aroyl palladium halide to form intermediate **4.27.** Neutralization of HI by base [$(i\text{-Pr})_2$NEt or K_2CO_3] and reductive elimination would result in the formation of benzo[*e*]-1,3-oxazin-4-one derivatives.

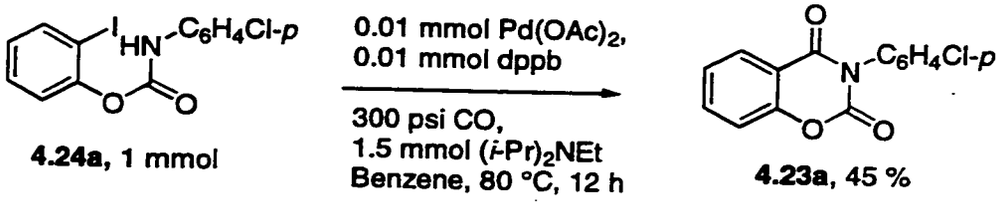


Scheme 4-5. Proposed mechanism for the cyclocarbonylation of *o*-iodophenols with heterocumulenes via an aroyl palladium intermediate.

To prove that the carbamate ester was formed first before entering the catalytic cycle, the carbamate ester, **4.24a,** was synthesized from the reaction of *o*-iodophenol (**4.19a**) with *p*-(chlorophenyl)isocyanate (**4.22a**) in benzene (eq 9). Compound **4.24a** was then subjected to carbonylation using 0.01 mmol $Pd(OAc)_2$, 0.01 mmol dppb and 1.5 mmol $(i\text{-Pr})_2NEt$ in benzene under 300 psi CO (eq 10). After 12 h at 80 °C, complete conversion of the carbamate ester was detected by TLC and 45% of **4.23a** was isolated.

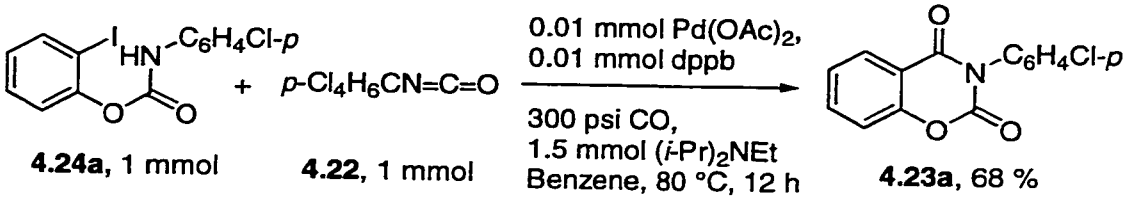


4.19a **4.22a** **4.24a** (eq 9)



4.24a, 1 mmol **4.23a**, 45 % (eq 10)

Performing the reaction in a similar manner but adding an extra 1 mmol of **4.22a** to the reaction mixture resulted in the formation of **4.23a** in 68% yield (eq 11). As previously noted, **4.23a** was obtained in 65% isolated yield when 1 mmol of **4.19a**, 2 mmol **4.22a**, 1.5 mmol $(i\text{-Pr})_2NEt$ was reacted in the presence of 1 mol% $Pd(OAc)_2$ and 1 mol% dppb under 300 psi CO in benzene at 80 °C for 12 h.



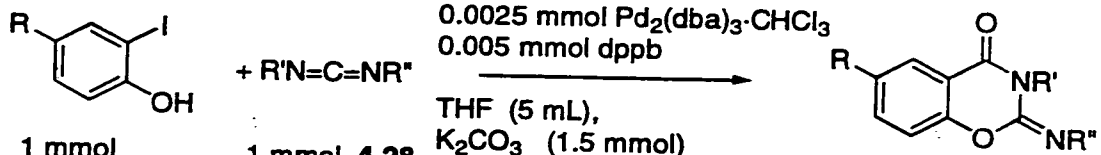
4.24a, 1 mmol **4.22**, 1 mmol **4.23a**, 68 % (eq 11)

This result also shows the importance of using excess isocyanate in palladium catalyzed cyclocarbonylation with *o*-iodophenols in which the equilibrium for the formation of the corresponding carbamate ester was driven in such a manner as to give more carbamate ester which enters the catalytic cycle.

4.3.5 The palladium-catalyzed cyclocarbonylation of *o*-iodophenols with unsymmetrical carbodiimides.

The cycloaddition reaction was also applied to unsymmetrical carbodiimides in order to determine the selectivity of this reaction and the results are listed in Table 4-7. We first used *N*-(n-butyl)-*N'*-phenylcarbodiimide (**4.28a,** 1 mmol) for the reaction with **4.19a** (1 mmol) in the presence of 0.0025 mmol $Pd_2(dba)_3$•$CHCl_3$, dppb (0.005 mmol), and 1.5 mmol K_2CO_3 in THF (5 mL). The reaction was stirred under 300 psi CO at 100 °C for 48 h. After purification of the solution, only one regioisomer was obtained in 94% yield (entry 1). Complete regioselectivity also resulted using either *o*-iodophenols or carbodiimides containing a substituent on the phenyl ring as reactants. For instance, only **4.29b** was formed using **4.19c** in reaction with **4.28a** (entry 2). Reaction of **4.19a-c** with **4.28b**, **4.28c** and **4.28d** gave only one isomer in high isolated yields (entries 3-7).

Table 4-7 The Cyclocarbonylation of *o*-Iodophenols (**4.19**) with Unsymmetrical Carbodiimides (**4.28**) Catalyzed by $Pd_2(dba)_3$·$CHCl_3$ and dppb in THF.[a]



1 mmol
4.19a, R = H
4.19b, R = CH_3
4.19c, R = Cl

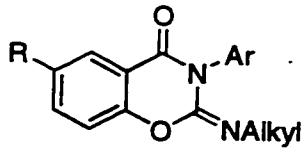
1 mmol, **4.28**

4.29

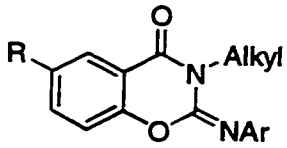
Entry	**4.19**	R'N=C=NR"	product	isolated yield of **4.29** (%)[b]
1	**4.19a**	C_6H_5N=C=NC_4H_9 **4. 28a**	**4.29a**	94
2	**4.19c**	**4.28a**	**4.29b**	77
3	**4.19b**	C_6H_5N=C=NC_6H_{11} **4.28b**	**4.29c**	94
4	**4.19c**	**4.28b**	**4.29d**	92
5	**4.19a**	*p*-FC_6H_4N=C=NC_6H_{11} **4. 28c**	**4.29e**	82
6	**4.19b**	**4.28c**	**4.29f**	82
7	**4.19a**	2,6$(CH_3)_2C_6H_3N$=C=NC_4H_9 **4.28d**	**4.29g**	93

[a] Reaction conditions: **4.19** (1 mmol), **4.28** (1 mmol), K_2CO_3 (1.5 mmol), THF (5 mL), CO (300 psi), 100 °C, 48 h. [b] Isolated yield by silica gel chromatography, using 1:1 n-pentane:ether as the eluant.

Two isomers are possible for products from reactions involving unsymmetrical carbodiimides, one with an aromatic substituent on the nitrogen of the oxazine ring (**4.29**) and the other with an alkyl group attached to the oxazine nitrogen (**4.29'**).



4.29



4.29'

To investigate the structure of the products, an X-ray determination of **4.29d** was performed. The ORTEP diagram shows that **4.29d** contains a phenyl group on the nitrogen of the oxazine ring (Figure 4-2) which contrasts with the major (not exclusive) isomer resulting from the reaction of the same carbodiimide with the vinyloxirane. (Chapter 2, section 2.2.1.3)

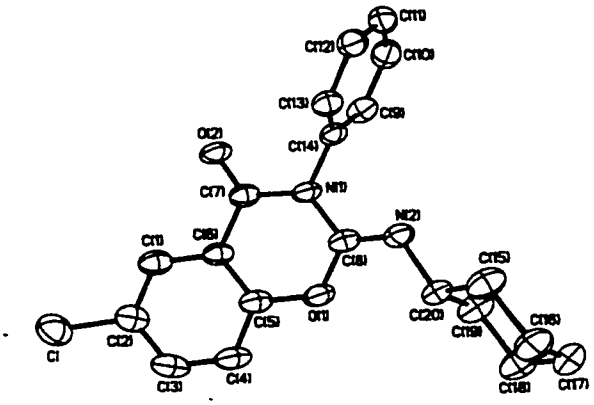
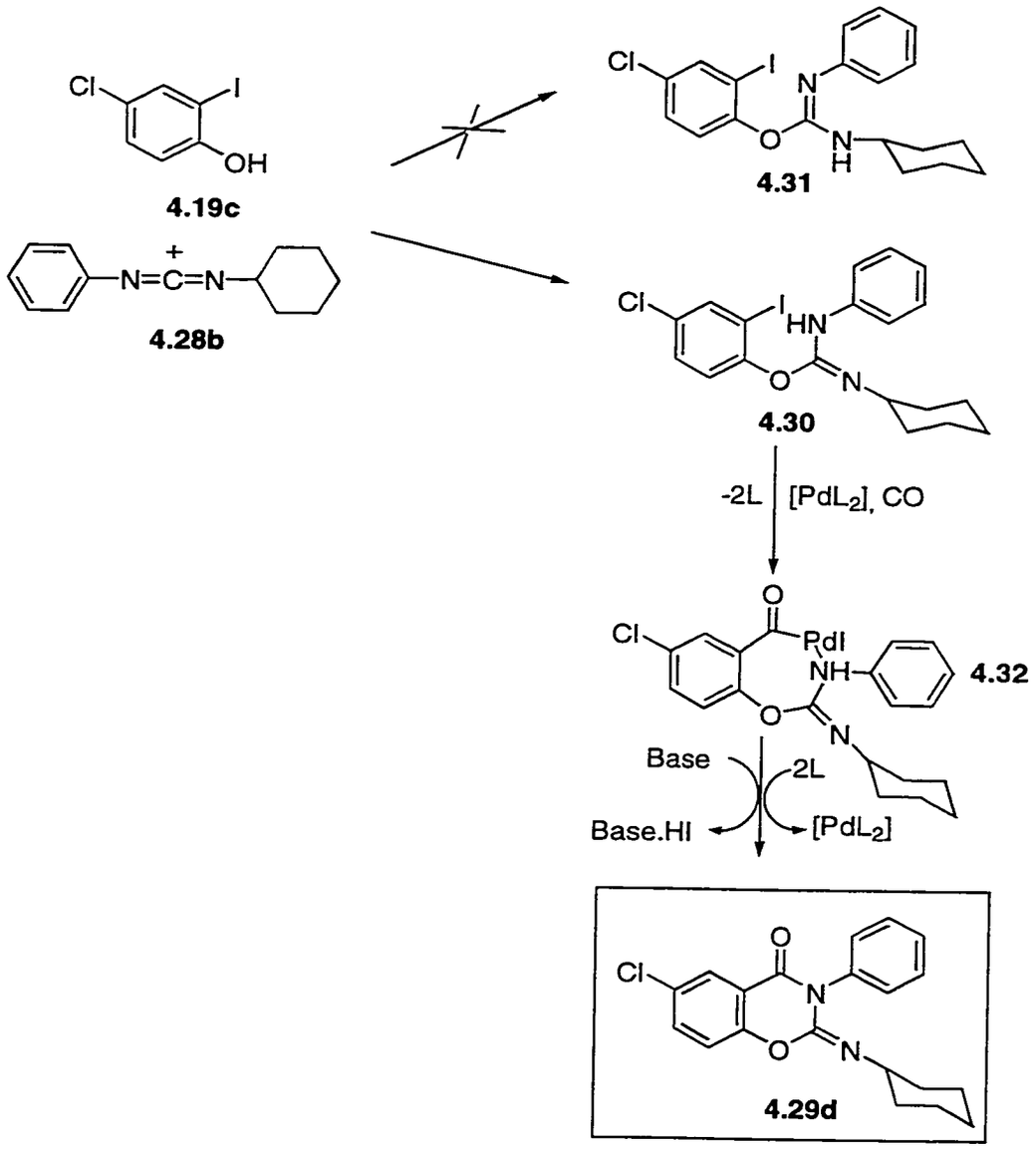


Figure 4-2 X-ray structure of **4.29d**.

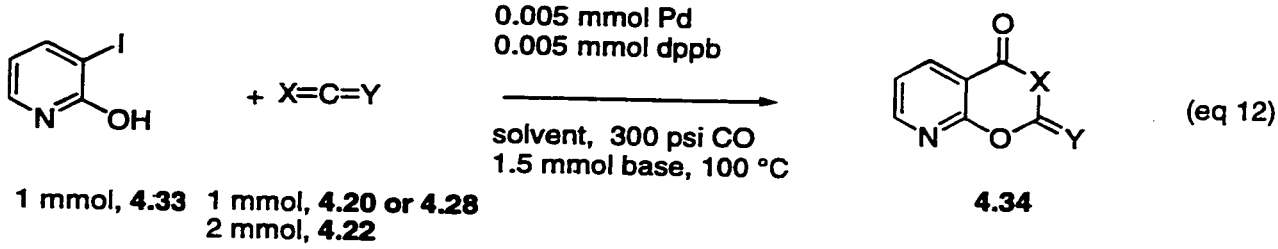
Only one isomer was obtained from the cyclocarbonylation of *o*-iodophenol (**4.19**) with unsymmetrical carbodiimides (**4.28a-d**). The selectivity may be due to the ease of formation of **4.30** compared to **4.31**. Reductive elimination of intermediate **4.32** and HI neutralization would afford **4.29d** (Scheme 4-6).



Scheme 4-6. Proposed mechanism for the regioselective formation of **4.29d**

4.3.6 The palladium-catalyzed cyclocarbonylation of 3-iodo-2-hydroxypyridine with heterocumulenes.

We then next investigated the cycloaddition reaction of 3-iodo-2-hydroxypyridine (**4.33**) with heterocumulenes utilizing the optimum reaction conditions which were used for the reaction of *o*-iodophenols (eq 12). The results showed that pyrido[3,2-*e*]-1,3-oxazin-2-imine-4-ones (**4.34**) were obtained in good yields from the reaction of **4.33** with carbodiimides in the presence of a catalytic amount of a palladium-dppb complex under 300 psi CO (see Table 4-8).



(eq 12)

$Pd(OAc)_2$ (entries 1 and 3) is superior to $Pd_2(dba)_3 \cdot CHCl_3$ (entries 2 and 4) for the reaction of 3-iodo-2-hydroxypyridine (**4.33**) with heterocumulenes to form **4.34**. A mixture of regioisomers of **4.34c**, in the ratio of 2:1, resulted from the reaction using unsymmetrical carbodiimides (**4.28e**) (entry 5). It is worth noting that no product was obtained in the reaction of **4.33** with *p*-chlorophenylisocyanate (**4.22a**), perhaps because the pyridine acts as a reagent for the dimerization of the isocyanate. [The dimerization of isocyanates catalyzed by pyridine and its derivatives was previously described by Wiley].[52]

Table 4-8 The Cyclocarbonylation of 3-Iodo-2-hydroxypyridine (**4.33**) with Heterocumulenes (**4.20a-b**, **4.22a**, 4.**28e**) Catalyzed by a Palladium Complex and dppb under 300 psi CO.[a]

Entry	X=C=Y	Product	Catalyst	Isolated yield (%)
1	*p*-ClC_6H_4N=C=NC_6H_4Cl-*p* **4.20a**	**4.34a**	$Pd(OAc)_2$	64[b]
2			$Pd_2(dba)_3$•$CHCl_3$	60[c]
3	*p*-$CH_3C_6H_4N$=C=$NC_6H_4CH_3$-*p* **4.20b**	**4.34b**	$Pd(OAc)_2$	50[b,c]
4			$Pd_2(dba)_3$•$CHCl_3$	30[c]
5	*p*-ClC_6H_4N=C=NC_4H_9 **4.28e**	**4.34c** and **4.34'c**	$Pd(OAc)_2$	65(2:1)[e]
6	*p*-ClC_6H_4N=C=O **4. 22a**	**nd**[f]	$Pd(OAc)_2$	0

[a] Reaction Conditions: **4.33** (1 mmol), **4.20** or **4.28** (1 mmol), 1.5 mmol base [K_2CO_3 for $Pd_2(dba)_3$·$CHCl_3$, (i-Pr)$_2$EtN for $Pd(OAc)_2$], 0.005 mmol Pd, 0.005 mmol dppb, 300 psi CO, in 5 mL solvent [THF for $Pd_2(dba)_3$·$CHCl_3$, benzene for $Pd(OAc)_2$] at 100 °C. [b] Reaction time was 24 h. [c] Reaction time was 48 h. [d] Isolated yield of **4.34b** after complete conversion of 15 after 24 h. [e] The ratio of **4.34c:4.34'c** was determined by GC. [f] The ratio of **4.33:4.22a** was 1:2 and complete conversion of the isocyanate occurred after 12h at 80 °C, however no desired product was isolated.

4.4 Conclusion

In conclusion, a novel method has been developed for the synthesis of benzo[*e*]-1,3-oxazin-4-ones and derivatives by the cyclocarbonylation of *o*-iodophenols with heterocumulenes using a palladium complex and a bidentate phosphine. The yields are good to excellent and the reaction proceeds with complete regioselectivity. Of particular note is the application of this reaction to the facile synthesis of a relative of a serine protease inhibitor.

4.5 Experimental Section

4.5.1 Preparation of 4-Methyl-2-iodophenol (4.19b), 4-chloro-2-iodophenol (4.19c)

4.19b and **4.19c** were prepared by using a method described for synthesis of *o*-iodophenol (**4.19a**).[53] 2-Amino-*p*-cresol (12.3 g, 0.1 mole) was dissolved in a mixture of 50 g of ice, 50 ml of water and 32 mL of concentrated sulfuric acid. To this solution (kept at 0 °C), was slowly added 36 g (0.1 mol) of sodium nitrite in 75 mL of water. The resulting mixture was stirred for another 20 min, followed by addition of 10 mL of concentrated sulfuric acid.

The reaction mixture was then poured into an ice-cold solution of 100 g (0.12 mol) of potassium iodide in 100 mL of water. After a few minutes 0.5 g of copper powder was added, the mixture was then warmed slowly to 75-80 °C, and kept at this temperature until the evolution of nitrogen ceased. The mixture was cooled to room temperature and extracted three times with 50 mL portions of CH_2Cl_2. The combined extracts were washed with dilute thiosulfate solution and brine, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography resulting in 8.5 g (34%) of pure 4-methyl-2-iodophenol (**4.19b**). 4-Chloro-2-iodophenol was prepared in the similar manner but 14.3 g of 2-amino-4-chlorophenol was used as the starting material. Product **4.19c** was obtained in 8.3 g (33%) after isolation by silica gel column chromatography.

4-Methyl-2-iodophenol (4.19b) IR (OH) 3280 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 2.24 (s, 3H, CH_3), 5.14 (s, 1H, OH), 6.86 (d, 1H, J = 8.24 Hz), 6.99-7.05 (m, 1H), 7.46 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 19.90 (CH_3), 85.40, 114.59, 130.75, 131.86, 138.19, 152.53; MS (*m/e*) 234 $[M]^+$.

4-Chloro-2-iodophenol (4.19c) IR (OH) 3282 cm^{-1}; ^1H ($CDCl_3$ δ 5.25 (s, 1H, OH), 6.90 (d, 1H, J = 8.70 Hz), 7.20 (dd, 1H, J = 2.5 and 8.7 Hz), 7.60 (d, 1H, J = 2.5 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 85.41, 115.62, 126.05, 130.09, 137.06, 153.68, MS (*m/e*) 254 $[M]^+$.

4.5.2 General Procedure for the Palladium-Catalyzed Cyclocarbonylation of *o*-Iodophenols (4.19) with Carbodiimides (4.20a-g, 4.28a-d).

An autoclave, its glass liner, and a magnetic stirring bar were dried in an oven and then cooled in a desiccator before use. The liner was charged with 0.5 mol% (unless otherwise noted in each case) of the palladium catalyst, an equivalent of a bidentate phosphine ligand (relative to palladium), and 3 mL of dried solvent (THF for $Pd_2(dba)_3 \cdot CHCl_3$ or benzene for $Pd(OAc)_2$). After the mixture was stirred under nitrogen for 15 min, *o*-iodophenol (**4.19**, 1 mmol), carbodiimide (**4.20** or **4.28**, 1 mmol), 1.5 mmol of base [K_2CO_3 for $Pd_2(dba)_3 \cdot CHCl_3$ or $(i\text{-Pr})_2NEt$ for $Pd(OAc)_2$] and another 2 mL of solvent were added to the mixture. The autoclave was then flushed three times with CO and pressurized to 300 psi. After stirring for 24 or 48 h [48 h for $Pd_2(dba)_3 \cdot CHCl_3$, 24 h for $Pd(OAc)_2$, unless otherwise stated] in an oil bath at 100 °C, the autoclave was removed from the oil bath and allowed to cool to room temperature. The excess gas was discharged and the system was disassembled. The reaction mixture was filtered and the filtrate was concentrated and purified by column chromatography on silica gel (1:1 ether: *n*-pentane).

Melting points, IR, NMR, MS and analytical data of **4.21** and **4.29** are as follows.

***N*, 3-Di(*p*-chlorophenyl)benzo[*e*]-1,3-oxazin-2-imine-4-one (4.21a)** (R = H, R′= *p*-ClC_6H_4): mp = 161-162 °C; IR (C=N) 1669 cm^{-1}, (C=O) 1710 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 6.90-7.55 (m, 11H), 8.10-8.15 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 114.57,

115.76, 124.02, 124.95, 128.32, 128.66, 128.86, 129.72, 129.91, 134.26, 134.65, 136.02, 142.23, 142.91, 152.78 (C=N), 159.50 (C=O); MS (*m/e*) 382 $[M]^+$; Anal. Calcd for $C_{20}H_{12}Cl_2N_2O_2$: C 62.68, H 3.16, N 7.31; found: C 62.82, H 3.29, N 7.26.

***N*, 3-Di(*p*-chlorophenyl)benzo[*e*]-6-methyl-1,3-oxazin-2-imine-4-one (4.21b)** (R = CH_3, R′= *p*-ClC_6H_4): mp = 164-165 °C; IR (C=N) 1671 cm^{-1}, (C=O) 1715 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 2.33 (s, 3H, $CH_3C_6H_3$), 6.82-7.00 (m, 4H), 7.10-7.30 (m, 4H), 7.30-7.50 (m, 2H), 7.80-7.85 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 20.66 ($CH_3C_6H_3$), 114.19, 115.52, 124.08, 127.94, 128.64, 128.81, 129.71, 129.95, 134.40, 134.62, 134.94, 136.90, 142.71, 143.03, 150.91 (C=N), 159.68 (C=O); MS (*m/e*) 396 $[M-1]^+$, 397 $[M]^+$; Anal. Calcd for. $C_{21}H_{14}Cl_2N_2O_2$: C 63.49, H 3.55, N 7.05; found C 63.28, H 3.45, N 6.95.

***N*, 3-Di(*p*-chlorophenyl)benzo[*e*]-6-chloro-1,3-oxazin-2-imine-4-one (4.21c)** (R = Cl, R′= *p*-ClC_6H_4): mp = 182-184 °C; IR (C=N) 1671 cm^{-1}, (C=O) 1710 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 6.86-6.93 (m, 2H), 7.03-7.09 (m, 1H), 7.20-7.32 (m, 4H), 7.45-7.61 (m, 3H), 8.02 (d, 1H, J = 2.61 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 115.81, 117.43, 123.93, 127.75, 128.72, 129.12, 129.81, 130.58, 133.99, 134.87, 135.98, 141.78, 142.57, 151.22 (C=N), 158.44 (C=O); MS (*m/e*) 416 $[M-1]^+$, 417 $[M]^+$, 418 $[M+1]^+$; Anal. Calcd for $C_{20}H_{11}Cl_3N_2O_2$: C 57.51, H 2.65, N 6.71, found: C 57.41, H 2.75, N 6.47.

***N*, 3-Di(*p*-tolyl)benzo[*e*]-1,3-oxazin-2-imine-4-one (4.21d)** (R = H, R′= *p*-$CH_3C_6H_4$): mp =164-165 °C; IR (C=N) 1669 cm^{-1}, (C=O) 1714 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 2.31 (s, 3H, *p*-$CH_3C_6H_4$), 2.41 (s, 3H, *p*-$CH_3C_6H_4$), 6.86-6.91 (m,1H), 7.06-7.27 (m, 3H), 7.30-7.49 (m, 5H), 7.59-7.70 (m, 1H), 8.06-8.10 (m, 1H); ^{13}C ($CDCl_3$, 50 MHz) δ 20.89 (*p*-$CH_3C_6H_4$), 21.32 (*p*-$CH_3C_6H_4$), 114.89, 115.72, 122.53, 124.50, 128.51, 128.26, 129.11, 130.13, 132.84, 133.41, 135.60, 138.41, 141.97, 142.12, 153.03 (C=N),

159.92 (C=O); MS (*m/e*) 342 $[M]^+$; Anal. Calcd for $C_{22}H_{18}N_2O_2$: C 77.17, H 5.30, N 8.18, found: C 77.29, H 5.44, N 8.12.

***N*, 3-Di(*p*-tolyl)benzo[*e*]-6-methyl-1,3-oxazin-2-imine-4-one (4.21e)** (R = CH_3, R′= *p*-$CH_3C_6H_4$): mp = 195-197 °C; IR (C=N) 1669 cm^{-1}, (C=O) 1714 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 2.30 (s, 3H, *p*-$CH_3C_6H_4$), 2.38 (s, 3H, $CH_3C_6H_3$), 2.40 (s, 3H, *p*-$CH_3C_6H_4$), 6.86-7.09 (m, 4H), 7.21-7.42 (m, 6H), 7.85-7.86 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 20.61 ($CH_3C_6H_3$), 20.86 (*p*-$CH_3C_6H_4$), 21.29 (*p*-$CH_3C_6H_4$), 114.47, 115.47, 122.57, 127.86, 128.17, 129.07, 130.09, 132.72, 133.52, 134.36, 136.44, 138.38, 142.08, 142.37, 151.11 (C=N), 160.06 (C=O); MS (*m/e*) 356 $[M]^+$; Anal. Calcd for $C_{23}H_{20}N_2O_2$: C 77.51, H 5.66, N 7.86, found: C 77.39, H 5.55, N 7.86.

***N*, 3-Di(*p*-tolyl)benzo[*e*]-6-chloro-1,3-oxazin-2-imine-4-one (4.21f)** (R = Cl, R′= *p*-$CH_3C_6H_4$): mp = 169-171 °C; IR (C=N) 1671 cm^{-1}, (C=O) 1714 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 2.21 (s, 3H, *p*-$CH_3C_6H_4$), 2.31 (s, 3H, *p*-$CH_3C_6H_4$), 6.75-6.79 (m, 2H), 6.90-7.01 (m, 3H), 7.10-7.25 (m, 4H), 7.38-7.46 (m, 1H), 7.92 (d, 1H, *J* = 2.58 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 20.83 (*p*-$CH_3C_6H_4$), 21.25 (*p*-$CH_3C_6H_4$), 116.05, 117.35, 122.40, 127.59, 128.01, 129.01, 129.98, 130.11, 133.00, 133.11, 135.41, 138.60, 141.37, 141.59, 151.39 (C=N), 158.75 (C=O); MS (*m/e*) 376 $[M]^+$; Anal. Calcd for $C_{22}H_{17}ClN_2O_2$: C 70.12, H 4.55, N 7.43, found: C 70.03, H 4.60, N 7.41.

***N*, 3-Diphenylbenzo[*e*]-1,3-oxazin-2-imine-4-one (4.21g)** (R = H, R′= C_6H_5): mp = 154-155 °C; IR (C=N) 1670 cm^{-1}, (C=O) 1713 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 6.92-7.20 (m, 4H), 7.21-7.75 (m, 9H), 8.15-8.20 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 114.82, 115.77, 122.63, 123.49, 124.63, 128.26, 128.50, 128.55, 128.67, 129.40, 135.71, 135.01,

142.12, 144.56, 149.85, 152.99 (C=N), 159.79 (C=O); MS (*m/e*) 313, $[M-1]^+$, 314 $[M]^+$; Anal. Calcd for $C_{20}H_{14}N_2O_2$: C 76.42, H 4.49, N 8.91, found: C 76.51, H 4.53, N 8.87.

***N*, 3-Diphenylbenzo[*e*]-6-methyl-1,3-oxazin-2-imine-4-one (4.21h)** (R = CH_3, R′= C_6H_5): mp = 175-176 °C; IR (C=N) 1670 cm^{-1}, (C=O) 1714 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 2.39 (s, 3H, $CH_3C_6H_3$), 6.95-7.10 (m, 4H), 7.23-7.52 (m, 8H), 7.85-7.86 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 20.63 ($CH_3C_6H_3$), 114.38, 115.51, 122.66, 123.39, 127.84, 128.50, 129.34, 134.50, 136.09, 136.55, 142.36, 144.63, 151.06 (C=N), 159.93 (C=O); MS (*m/e*) 328 $[M]^+$; Anal. Calcd for $C_{21}H_{16}N_2O_2$: C 76.81, H 4.91, N 8.53, found: C 76.60, H 4.73, N 8.49.

***N*, 3-Di(*p*-bromophenyl)benzo[*e*]-1,3-oxazin-2-imine-4-one (4.21i)** (R = H, R′= *p*-BrC_6H_5): mp =167-169 °C; IR (C=N) 1668 cm^{-1}, (C=O) 1713 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 6.88-6.94 (m, 2H), 7.13-7.17 (m, 1H), 7.25-7.50 (m, 5H), 7.62-7.78 (m, 3H), 8.11-8.15 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 114.61, 115.81, 116.67, 122.89, 124.49, 125.01, 128.39, 130.28, 131.66, 132.75, 134.83, 136.09, 142.40, 143.45, 152.84 (C=N), 159.48 (C=O); MS (*m/e*) 472 $[M]^+$; Anal. Calcd for $C_{20}H_{12}Br_2N_2O_2$: C 50.80, H 2.56, N 5.93, found: C 50.83, H 2.55, N 5.88.

***N*, 3-Di(*p*-methoxyphenyl)benzo[*e*]-1,3-oxazin-2-imine-4-one (4.21j)** (R = H, R′= *p*-$CH_3OC_6H_5$): mp = 178-180 °C; IR (C=N) 1667 cm^{-1}, (C=O) 1718 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 4.17 (s, 3H, *p*-$_3HCOC_6H_4$), 4.25 (s, 3H, *p*-$_3HCOC_6H_4$), 7.19-7.24 (m, 2H), 7.30-7.55 (m, 5H), 7.51-7.75 (m, 3H), 7.99-8.05 (m, 1H), 8.45-8.49 (m, 1H); ^{13}C ($CDCl_3$, 50 MHz) δ 55.37 [2(*p*-$_3HCOC_6H_4$)], 113.76, 114.67, 114.88, 115.68, 123.85, 124.51, 128.27, 128.62, 129.44, 135.60, 137.63, 142.15, 152.98, 155.89, 159.33 (C=N),

160.02 (C=N); MS (*m/e*) 374 $[M]^+$; Anal. Calcd for $C_{22}H_{18}N_2O_4$: C 70.58, H 4.85, N 7.48, found: C 70.28, H 4.83, N 7.48.

***N*, 3-Dicyclohexylbenzo[*e*]-1,3-oxazin-2-imine-4-one (4.21k)** (R = H, R′= C_6H_{11}): mp = 83-84 °C; IR (C=N) 1669 cm^{-1}, (C=O) 1703 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 1.14-1.90 (m, 18H, C*H*$_2$, Cyclohexane), 2.48-2.78 (m, 2H, C*H*$_2$, Cyclohexane), 3.70-3.85 (m, 1H, C*H*, Cyclohexane), 4.75-4.95 (m, 1H, C*H*, Cyclohexane), 6.99-7.24 (m, 2H), 7.41-7.53 (m, 1H), 7.93-7.97 (d, 1H, J = 7.8 and 1.6 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 24.23, 25.44, 25.95, 26.35, 28.16, 33.85 (**C**H$_2$, Cyclohexane), 53.11 (**C**H, Cyclohexane), 55.45 (**C**H, Cyclohexane), 114.71, 115.25, 123.38, 127.85, 134.42, 138.40, 153.08 (C=N), 160.18 (C=O); MS (*m/e*) 326 $[M]^+$; Anal. Calcd for $C_{20}H_{26}N_2O_2$: C 73.59, H 8.03, N 8.58, found: C 73.76, H 8.33, N 8.52.

***N*, 3-Dicyclohexylbenzo[*e*]-6-methyl-1,3-oxazin-2-imine-4-one (4.21l)** (R = CH_3, R′= C_6H_{11}): mp = 107-108 °C; IR (C=N) 1667 cm^{-1}, (C=O) 1705 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 1.14-1.82 (m, 18H, C*H*$_2$, Cyclohexane), 2.32 (s,3H, C*H*$_3$C$_6$H$_3$), 2.48-2.70 (m, 2H, C*H*$_2$, Cyclohexane), 3.70-3.82 (m, 1H, C*H*, Cyclohexane), 4.75-4.92 (m, 1H, C*H*, Cyclohexane), 6.92 (d, 1H, *J* = 8.3 Hz), 7.25 (d, 1H, *J* = 8.3 Hz), 7.73 (s, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 20.55 (C*H*$_3$C$_6$H$_3$), 24.33, 25.54, 26.03, 26.46, 28.25, 33.05, (**C**H$_2$, cyclohexane), 53.14, 55.47 (**C**H, cyclohexane), 114.54, 114.95, 127.64, 133.12, 135.31, 138.77, 151.24 (C=N), 160.41 (C=O); MS (*m/e*) 340 $[M]^+$; Anal. Calcd for $C_{21}H_{28}N_2O_2$: C 74.08, H 8.29, N 8.23, found: C 74.22, H 8.47, N 8.32.

***N*, 3-Dicyclohexylbenzo[*e*]-6-chloro-1,3-oxazin-2-imine-4-one (4.21m)** (R = Cl, R′= C_6H_{11}): mp = 127-129 °C; IR (C=N) 1671 cm^{-1}, (C=O) 1707 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 1.18-1.82 (m, 18H, C*H*$_2$, Cyclohexane), 2.42-2.70 (m, 2H, C*H*$_2$,

Cyclohexane), 3.69-3.82 (m, 1H, C*H*, Cyclohexane), 4.70-4.90 (m, 1H, C*H*, Cyclohexane), 6.98 (d, 1H, J = 8.7 Hz), 7.44 (dd, 1H, J = 8.7 and 2.6 Hz), 7.89 (d, 1H, J = 2.6 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 24.26, 25.46, 25.97, 26.39, 28.19, 33.87 (CH_2, Cyclohexane), 53.31, 55.89 (CH, Cyclohexane), 116.45, 116.55, 127.46, 128.94, 134.45, 137.85, 138.77, 151.60 (C=N), 159.13 (C=O); MS (*m/e*) 360 $[M]^+$; Anal. Calcd for $C_{20}H_{25}N_2O_2$: C 66.56, H 6.98, N 7.76, found: C 66.66, H 7.18, N 7.84.

***N*, 3-Diisopropylbenzo[*e*]-6-methyl-1,3-oxazin-2-imine-4-one (4.21n)** (R = CH_3, R′= C_6H_7); oily liquid; IR (C=N) 1668 cm^{-1}, (C=O) 1705 cm^{-1}; ^{1}H ($CDCl_3$, 200 MHz) δ 1.13 (d, 6H, J = 6.2 Hz, $CH(CH_3)_2$), 1.47 (d, 6H, J = 6.7 Hz, $CH(CH_3)_2$), 2.33 (s, 3H, $CH_3C_6H_3$), 4.04 (Sept, 1H, J= 6.2 Hz, $CH(CH_3)_2$), 5.23 (Sept, 1H, J = 6.7 Hz, $CH(CH_3)_2$), 6.92 (d, 1H, J = 8.4 Hz), 7.30 (dd, 1H, J = 2.2 and 2.2 Hz), 7.74 (d, 1H, J = 1.7 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 18.99 ($CH(CH_3)_2$), 20.57 ($CH_3C_6H_3$), 24.09 ($CH(CH_3)_2$), 45.88 ($CH(CH_3)_2$), 47.22 ($CH(CH_3)_2$), 114.58, 114.93, 127.57, 133.26, 135.40, 139.17, 151.20 (C=N), 160.29 (C=O); MS (*m/e*) 260 $[M]^+$; HRMS. Calcd for $C_{15}H_{20}N_2O_2$: 260.1525 Found 260.1522.

***N*, 3-Diisopropylbenzo[*e*]-6-chloro-1,3-oxazin-2-imine-4-one (4.21o)** (R = Cl, R′= C_6H_7): mp = 83-84 °C; IR (C=N) 1667 cm^{-1}, (C=O) 1702 cm^{-1}; ^{1}H ($CDCl_3$, 200 MHz) δ 1.12 (d, 6H J = 6.3 Hz, $CH(CH_3)_2$), 1.47 (d, 6H, J = 6.9 Hz, $CH(CH_3)_2$), 4.03 (Sept, 1H, J = 6.3 Hz, $CH(CH_3)_2$), 5.20 (Sept, 1H, J = 6.9 Hz, $CH(CH_3)_2$) 6.99 (d, 1H, J = 8.7 Hz), 7.43 (dd, 1H, J = 8.7 and 2.6 Hz), 7.88 (d, 1H, J = 2.6 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 18.90 ($CH(CH_3)_2$), 23.99 ($CH(CH_3)_2$), 46.02 ($CH(CH_3)_2$), 47.59 ($CH(CH_3)_2$), 116.44, 116.51, 127.37, 129.00, 134.48, 138.16, 151.52 (C=N), 158.92 (C=O); MS (*m/e*)

280 $[M]^+$; Anal. Calcd for $C_{14}H_{27}ClN_2O_2$: C 59.89, H 6.10, N 9.98, Found: C 59.98, H 6.24, N 9.99.

***N*-(*n*-Butyl)-3-phenylbenzo[*e*]-1,3-oxazin-2-imine-4-one (4.29a)** (R = H, R′= C_6H_5, R″= C_4H_9): mp = 107-108 °C; IR (C=N) 1652 cm^{-1}, (C=O) 1711 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 088 (t, 3H, *J* = 7.1 Hz, $CH_3(CH_2)_3$), 1.20-1.55 (m, 4H, $CH_3(CH_2)_2CH_2$), 3.38 (t, 2H, *J* = 6.9 Hz, $CH_3(CH_2)_2CH_2$), 7.16-7.62 (m, 8H), 8.05 (dd, 1H, *J* = 7.7 and 1.5 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.80 ($CH_3(CH_2)_3$), 20.36 ($CH_3CH_2(CH_2)_2$), 32.62 ($CH_3CH_2CH_2CH_2$), 45.36 ($CH_3CH_2CH_2CH_2$), 114.87, 115.26, 123.99, 128.26, 128.47, 129.11, 135.30, 136.32, 142.12, 153.22 (C=N), 159.78 (C=O); MS (*m/e*) 293 $[M-1]^+$, 294 $[M]^+$; Anal. Calcd for $C_{18}H_{18}N_2O_2$: C 73.45, H 6.16, N 9.52, Found: C 73.20, H 5.98, N 9.11.

***N*-(*n*-Butyl)-3-phenylbenzo[*e*]-6-chloro-1,3-oxazin-2-imine-4-one (4.29b)** (R = Cl, R′= C_6H_5, R″= C_4H_9): mp = 126-127 °C; IR (C=N) 1672 cm^{-1}, (C=O) 1714 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 0.86 (t, 3H, *J* = 6.9 Hz, $CH_3(CH_2)_3$), 1.18-1.62 (m, 4H, $CH_3(CH_2)_2CH_2$), 3.36. (t, 2H, *J* = 6.9 Hz, $CH_3(CH_2)_2CH_2$), 7.11-7.60 (m, 7H), 7.98-8.02 (d, 1H, *J* = 2.6 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.88 ($CH_3(CH_2)_3$), 20.44 $CH_3CH_2(CH_2)_2$), 32.64 ($CH_3CH_2CH_2CH_2$), 45.50 ($CH_3CH_2CH_2CH_2$), 116.16, 117.03, 127.79, 128.43, 128.51, 129.29, 129.60, 135.37, 136.13, 141.49, 151.75 (C=N), 159.84 (C=O); MS (*m/e*) 327 $[M-1]^+$, 328 $[M]^+$; Anal. Calcd for $C_{18}H_{17}ClN_2O_2$: C 65.75, H 5.21, N 8.52, found: C 65.74, H 5.04, N 8.50.

***N*-Cylohexyl-3-phenylbenzo[*e*]-6-methyl-1,3-oxazin-2-imine-4-one (4.29c)** (R = CH_3, R′= C_6H_5, R″= C_6H_{11}): mp = 138-139 °C; IR (C=N) 1654 cm^{-1}, (C=O) 1702 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 1.0-2.0 (m, 10H, CH_2, cyclohexane), 2.37 (s, 3H, $CH_3C_6H_3$),

3.61-3.80 (m, 1H, C*H*, cyclohexane), 7.04-7.08 (d, 1H, J = 8.2 Hz), 7.20-7.30 (m, 2H), 7.31-7.50 (m, 4H), 7.80-7.82 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 20.61 ($CH_3C_6H_3$), 24.41, 25.79, 33.68 (CH_2, cyclohexane), 53.57 (CH, cyclohexane), 114.59, 115.11, 127.95, 128.67, 128.87, 133.68, 136.12, 136.74, 151.50 (C=N), 160.15 (C=O); MS (*m/e*) 333 [M-1]$^+$, 334 [M]$^+$; Anal. Calcd for $C_{21}H_{22}N_2O_2$: C 75.42, H 6.63, N 8.38, found: C 75.33, H 6.53, N 8.20.

***N*-Cylohexyl-3-phenylbenzo[*e*]-6-chloro-1,3-oxazin-2-imine-4-one (4.29d)** (R = Cl, R′= C_6H_5, R″= C_6H_{11}): mp = 157-159 °C; IR (C=N) 1675 cm^{-1}, (C=O) 1712 cm^{-1}; ^{1}H ($CDCl_3$, 200 MHz) δ 1.06-1.80 (m, 10H, C*H*$_2$, cyclohexane), 3.71 (m, 1H, C*H*, cyclohexane), 7.08-7.57 (m, 7H), 8.00 (d, 1H, *J* = 2.2 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 24.30, 25.71, 33.60 (CH_2, cyclohexane), 53.65 (CH, cyclohexane), 116.23, 117.01, 127.71, 128.15, 128.50, 128.95, 129.36, 135.21, 136.36, 138.55, 151.85 (C=N), 158.89 (C=O); MS (*m/e*) 354 [M]$^+$; Anal. Calcd for $C_{20}H_{19}ClN_2O_2$: C 67.70, H 5.40, N 7.89, found: C 67.95, H 5.31, N 8.00.

***N*-Cylohexyl-3-(*p*-fluorophenyl)benzo[*e*]-1,3-oxazin-2-imine-4-one (4.29e)** (R = H, R′= *p*-FC_6H_4, R″= C_6H_{11}): mp = 103-104 °C; IR (C=N) 1676 cm^{-1}, (C=O) 1713 cm^{-1}; ^{1}H ($CDCl_3$, 200 MHz) δ 1.14-1.67 (m, 10H, C*H*$_2$, cyclohexane), 3.74 (m, 1H, C*H*, cyclohexane), 7.08-7.26 (m, 6H), 7.55-7.68 (m, 1H), 8.01-8.06 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 24.28, 25.70, 33.63 (CH_2, cyclohexane), 53.52 (CH, cyclohexane), 114.78, 115.32, 115.64, 115.95, 123.93, 128.21, 130.27, 130.38, 132.38, 135.35, 140.17, 153.30, 159.95 (C=N), 160.23 (C=O), 163.50 (C-F); MS (*m/e*) 337 [M-1]$^+$, 338 [M]$^+$; Anal. Calcd for $C_{20}H_{19}FN_2O_2$: C 70.99, H 5.66, N 8.28, found: C 70.96, H 5.58, N 8.30.

***N*-Cylohexyl-3-(*p*-fluorophenyl)benzo[*e*]-6-methyl-1,3-oxazin-2-imine-4-one (4.29f)** (R = CH_3, R′= *p*-FC_6H_4, R″= C_6H_{11}): mp = 126-128 °C; IR (C=N) 1675 cm^{-1}, (C=O) 1712 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 1.14–1.66 (m, 10H, C*H*$_2$, cyclohexane), 2.38 (s, 3H, C*H*$_3C_6H_3$), 3.71 (m, 1H, C*H*, cyclohexane), 7.04-7.25 (m, 5H), 7.35 (dd, 1H, *J* =8.4 and 2.2 Hz), 7.80-7.85 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 20.55 ($CH_3C_6H_3$), 24.33, 25.74, 33.68 (CH_2, cyclohexane), 53.51 (CH, cyclohexane), 114.39, 115.11, 115.65, 115.95, 127.87, 130.31, 130.42, 132.51, 133.73, 136.21, 140.47, 151.41, 160.15 (C=N), 160.22 (C=O), 163.49 (C-F); MS (*m/e*) 351 $[M-1]^+$, 352 $[M]^+$; Anal. Calcd for $C_{21}H_{21}FN_2O_2$: C 71.57, H 6.01, N 7.95, found: C 71.41, H 5.97, N 7.97.

***N*-(*n*-Butyl)-3-(2,6-dimethylphenyl)benzo[*e*]-1,3-oxazin-2-imine-4-one(4.29g)** (R = H, R′= 2, 6-$(CH_3)_2C_6H_3$, R″= C_4H_9): oily liquid; IR (C=N) 1676 cm^{-1}, (C=O) 1713 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 0.84 (t, 3H, C*H*$_3(CH_2)_3$), 1.18-1.50 (m, 4H, $CH_3(CH_2)_2CH_2$), 2.12 (s, 6H, (C*H*$_3)_2C_6H_3$), 3.37 (t, 2H, $CH_3(CH_2)_2CH_2$), 7.07-7.26 (m, 5H), 7.54–7.64 (m, 1H), 8.00-8.02 (m, 1H); ^{13}C ($CDCl_3$, 50 MHz) δ 13.88 ($CH_3(CH_2)_3$), 17.67 [$(CH_3)_2C_6H_3$], 20.43 [$CH_3CH_2(CH_2)_2$], 32.73 [$CH_3CH_2CH_2CH_2$], 45.40 [$CH_3CH_2CH_2CH_2$], 114.57, 115.37, 124.07, 126.42, 128.37, 128.54, 134.25, 135.18, 135.20, 140.20, 153.59 (C=N), 159.62 (C=O); MS (*m/e*) 322 $[M]^+$; HRMS Calcd for $C_{20}H_{22}N_2O_2$: 322.1681, found: 322.1661.

4.5.3 General Procedure for the Palladium-Catalyzed Cyclocarbonylation of *o*-Iodophenols (4.19) with Isocyanates (4.22a-e).

The cyclocarbonylation reactions of *o*-iodophenols with isocyanates were performed in a similar manner to that with carbodiimides but 2 equivalents of isocyanate were used in order to obtain higher product yields. The reaction mixtures were stirred in an oil bath at 80 °C for 12 h. After filtration and rotary evaporation of the filtrate, the residue was purified by silica gel column chromatography (using 1:1, ethyl acetate : *n*-pentane as the eluant).

Melting points, IR, NMR, MS and analytical data for **4.23** are as follows.

3-(*p*-Chlorophenyl)benzo[*e*]-1,3-oxazin-2,4-dione (4.23a) (R = H, R′= *p*-ClC_6H_4): mp =236-238 °C; IR (C=O) 1705, 1770 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 7.20-7.50 (m, 6H), 7.68-7.70 (m, 1H), 8.10-8.15 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 114.15, 116.66, 125.76, 128.48, 129.49, 129.87, 132.53, 136.68, 152.69 [O(C=O)N], 160.48 [(C=O)N]; MS (*m/e*) 273 $[M]^+$; Anal. Calcd for $C_{14}H_8ClNO_3$: C 76.81, H 4.91, N 8.53, found: C 76.60, H 4.73, N 8.49.

3-(*p*-Chlorophenyl)benzo[*e*]-6-methyl-1,3-oxazin-2,4-dione (4.23b) (R = CH_3, R′= *p*-ClC_6H_4): mp = 190-191 °C; IR (C=O) 1704, 1759 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 2.43 (s, 3H, $CH_3C_6H_3$), 7.19–7.28 (m, 3H), 7.45-7.55 (m, 3H), 7.86-7.88 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 20.71 ($CH_3C_6H_3$), 113.75, 116.39, 127.95, 129.51, 129.82, 132.67, 135.30, 135.83, 137.59, 147.86, 150.78 [O(C=O)N], 160.61 [(C=O)N]; MS (*m/e*) 287

$[M]^+$; Anal. Calcd for $C_{15}H_{10}ClNO_3$: C 62.62, H 3.50, N 4.87, found: C 62.45, H 3.40, N 4.80.

3-(*p*-Bromophenyl)benzo[*e*]-6-methyl-1,3-oxazin-2,4-dione (4.23c) (R = CH_3, R′= *p*-BrC_6H_4): mp = 198-200 °C; IR (C=O) 1700, 1765 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 2.43 (s, 3H, $CH_3C_6H_3$), 7.10-7.30 (m, 3H), 7.45-7.75 (m, 3H), 7.87-7.88 (m, 1H); ^{13}C ($CDCl_3$, 50 MHz) δ 20.74 ($CH_3C_6H_3$), 113.73, 116.39, 123.43, 127.95, 129.82, 132.80, 133.20, 135.28, 135.85, 137.61, 150.77 [O(C=O)N], 160.56 [(C=O)N]; MS (*m/e*) 332 $[M]^+$; Anal. Calcd for $C_{15}H_{10}BrNO_3$: C 54.24, H 3.03, N 4.22, found: C 54.40, H 3.08, N 4.09.

3-(*p*-Bromophenyl)benzo[*e*]-6-chloro-1,3-oxazin-2,4-dione (4.23d) (R = Cl, R′= *p*-BrC_6H_4): mp =229-230 °C; IR (C=O) 1700, 1759 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 7.14-7.28 (m, 3H), 7.32-7.72 (m,3H), 8.03-8.05 (m, 1H); ^{13}C ($CDCl_3$, 50 MHz) δ 115.34, 118.32, 123.69, 127.81, 129.68, 131.51, 132.77, 132.91, 136.70, 151.06 [O(C=O)N], 159.38 [(C=O)N]; MS (*m/e*) 352 $[M]^+$; Anal. Calcd for $C_{14}H_7BrClNO_3$: C 47.69, H 2.00, N 3.97, found: C 47.66, H 2.08, N 3.83.

3-(*p*-Tolyl)benzo[*e*]-1,3-oxazin-2,4-dione (4.23e) (R = H, R′= *p*-$CH_3C_6H_4$): mp = 217-218 °C; IR (C=O) 1692, 1763 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 2.41 (s, 3H, *p*-$CH_3C_6H_4$), 7.15-7.42 (m, 6H), 7.64-7.79 (m, 1H), 8.12 (dd, 1H, *J* =7.8 and 1.7 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 21.24 (*p*-$CH_3C_6H_4$), 114.35, 116.54, 125.52, 127.64, 128.40, 130.27, 131.47, 136.37, 139.40, 148.03, 152.72 [O(C=O)N], 160.69 [(C=O)N]; MS (*m/e*) 253 $[M]^+$; Anal. Calcd for $C_{15}H_{11}NO_3$: C 71.14, H 4.38, N 5.53, found: C 70.95, H 4.51, N 5.40.

3-(*p*-Tolyl)benzo[*e*]-6-chloro-1,3-oxazin-2,4-dione (4.23f) (R = Cl, R′= *p*-$CH_3C_6H_4$): mp =246-248 °C; IR (C=O) 1700, 1768 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 2.40 (s, 3H, *p*-$CH_3C_6H_4$), 7.14-7.35 (m, 5H), 7.62-7.72 (m ,1H), 8.06-8.10 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 21.29 (*p*-$CH_3C_6H_4$), 115.58, 118.25, 127.57, 127.82, 129.86, 130.38, 131.31, 136.45, 139.69, 151.14 [O(C=O)N], 159.70 [(C=O)N]; MS (*m/e*) 287 $[M]^+$; Anal. Calcd for $C_{15}H_{10}ClNO_3$: C 62.62, H 3.50, N 4.87, found: C 62.54, H 3.60, N 4.85.

3-(*p*-Methoxyphenyl)benzo[*e*]-6-methyl-1,3-oxazin-2,4-dione (4.23g) (R = CH_3, R′= *p*-$CH_3OC_6H_4$): mp = 175-176 °C; IR (C=O) 1700, 1765 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 2.42 (s, 3H, $CH_3C_6H_3$), 3.83 (s, 3H, *p*-$CH_3OC_6H_4$), 6.99–7.04 (m, 2H), 7.17-7.23 (m, 3H), 7.50 (dd, 1H, *J* = 8.4 and 2.2 Hz), 7.87 (d, 1H, *J* = 1.8).; ^{13}C ($CDCl_3$, 75 MHz) δ 20.69 ($CH_3C_6H_3$), 55.45 (*p*-$CH_3OC_6H_4$), 113.93, 114.82, 116.28, 126.73, 127.90, 129.02, 135.57, 137.30, 148.33, 150.77 [O(C=O)N], 159.90 [(C=O)N], 160.96 (C-OCH_3); MS (*m/e*) 283 $[M]^+$; Anal. Calcd for $C_{16}H_{13}NO_3$: C 67.84, H 4.63, N 4.94, found: C 62.85, H 4.65, N 4.80.

3-(Benzyl)benzo[*e*]-1,3-oxazin-2,4-dione (4.23h) (R = H, R′= $C_6H_5CH_2$-): mp = 119-120 °C; IR (C=O) 1691, 1756 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 5.18 (s, 2H, CH_2Ph), 7.22–7.72 (m, 8H), 8.07 (dd, 1H, *J* = 7.8 and 1.7 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 45.60 (CH_2Ph), 114.09, 116.31, 125.32, 128.02, 128.47, 129.46, 135.58, 136.05, 148.06, 152.45, 157.73 [O(C=O)N], 160.94 [(C=O)N]; MS (*m/e*) 253 $[M]^+$; HRMS. Calcd for $C_{15}H_{11}NO_3$: C 71.14, H 4.38, N 5.53, found: C 71.12, H 4.34, N 5.51.

4.5.4 General Procedure for the Palladium-Catalyzed Cyclocarbonylation of 3-Iodo-2-hydroxypyridine (4.33) with Heterocumulenes.

The cyclocarbonylation reactions of 3-iodo-2-hydroxypyridine with heterocumulenes (**4.20a-b**, **4.22a**, **4.28e**) were performed following the same procedure as that for the reaction of *o*-iodophenols with carbodiimides and isocyanates.

Melting points, IR, NMR, MS and analytical data of **4.34** after purification by silica gel column chromatography are shown below.

***N*, 3-Di(*p*-chlorophenyl)pyrido[3,2-*e*]-1,3-oxazin-2-imine-4-one (4.34a)** (X = Y = *p*-ClC_6H_4N): mp = 221-223 °C; IR (C=N) 1674 cm^{-1}, (C=O) 1728 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 6.86 (m, 2H), 7.19-7.33 (m, 4H), 7.43–7.61 (m, 4H), 8.64-8.66 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 123.81, 124.41, 128.73, 129.18, 129.64, 129.79, 131.98, 133.99, 134.85, 141.21, 142.40, 147.49, 150.63(C=N), 157.94 (C=O); MS (*m/e*) 383 $[M-1]^+$, 384 $[M]^+$; Anal. Calcd for $C_{19}H_{11}Cl_2N_3O_2$: C 59.39, H 2.89, N 10.94, found: C 59.04, H 2.88, N 10.88.

***N*, 3-Di(*p*-tolyl)pyrido[3,2-*e*]-1,3-oxazin-2-imine-4-one (4.34b)** (X = Y = *p*-$CH_3C_6H_4N$): mp =233-235 °C; IR (C=N) 1671 cm^{-1}, (C=O) 1713 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 2.29 (s, 3H, *p*-$CH_3C_6H_4$), 2.40 (s, 3H, *p*-$CH_3C_6H_4$), 6.83-6.87 (d, 2H, J = 8.2 Hz), 7.05-7.09 (d, 2H, J =8.2 Hz), 7.23-7.34 (m, 4H), 7.46-7.52 (m, 2H), 8.62-8.65 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 20.82 (*p*-$CH_3C_6H_4$), 21.25 (*p*-$CH_3C_6H_4$), 122.30, 124.29, 128.00, 129.14, 129.26, 130.15, 132.32, 133.14, 138.66, 140.83, 141.46, 147.08, 150.70

(C=N), 158.31 (C=O); MS (*m/e*) 342 $[M-1]^+$, 343 $[M]^+$; Anal. Calcd for $C_{21}H_{17}N_3O_2$: C 73.45, H 4.99, N 12.24, found: C 73.56, H 5.07, N 12.07.

***N*-(*n*-Butyl)-3-(*p*-chlorophenyl)pyrido[3,2-*e*]-1,3-oxazin-2-imine-4-one (4.34c)** (X = *p*-ClC_6H_4N, Y = C_4H_9N): mp = 157-159 °C; IR (C=N) 1681 cm^{-1}, (C=O) 1717 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 0.86 (t, 3H, *J* = 7.0 Hz, $CH_3CH_2CH_2CH_2$), 1.23-1.47 (m, 4H, $CH_3CH_2CH_2CH_2$), 3.37 (t, 2H, *J* =7.0 Hz, $CH_3CH_2CH_2CH_2$), 7.17-7.23 (m, 2H), 7.40-7.45 (m, 2H), 7.56-7.57 (m, 2H), 8.61-8.63 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 13.83 ($CH_3CH_2CH_2CH_2$), 20.41 ($CH_3CH_2CH_2CH_2$), 32.58 ($CH_3CH_2CH_2CH_2$), 45.54 ($CH_3CH_2CH_2CH_2$), 124.04, 129.31, 129.58, 129.87, 132.25, 134.38, 134.54, 140.62, 146.83, 150.89 (C=N), 158.25 (C=O); MS (*m/e*) 328 $[M-1]^+$, 329 $[M]^+$; Anal. Calcd for $C_{17}H_{16}ClN_3O_2$: C 61.91, H 4.89, N 12.74, found: C 62.04, H 5.07, N 12.48.

***N*-(*p*-Chlorophenyl)-3-(*n*-butyl)pyrido[3,2-*e*]-1,3-oxazin-2-imine-4-one (4.34c′)** (X = C_4H_9N, Y = *p*-ClC_6H_4N): mp = 118-120 °C; IR (C=N) 1665 cm^{-1}, (C=O) 1719 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 0.93 (t, 3H, *J* = 7.3 Hz, $CH_3CH_2CH_2CH_2$) 1.41 (m, 2H, $CH_3CH_2CH_2CH_2$), 1.75 (m, 2H, $CH_3CH_2CH_2CH_2$), 4.21 (t, 2H, *J* =7.4 Hz, $CH_3CH_2CH_2CH_2$), 6.96-7.00 (m, 2H), 7.24-7.31 (m, 2H), 7.41-7.50 (m, 2H), 8.62 (d, 1H, *J* = 4.3 and 0.5 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.83 ($CH_3CH_2CH_2CH_2$), 20.09 ($CH_3CH_2CH_2CH_2$), 28.98 ($CH_3CH_2CH_2CH_2$), 43.46 ($CH_3CH_2CH_2CH_2$), 123.99, 124.11, 128.87, 129.10, 132.06, 140.45, 146.02, 147.26, 150.26 (C=N), 157.94 (C=O) MS (*m/e*) 328 $[M-1]^+$, 329 $[M]^+$; HRMS Calcd for $C_{17}H_{16}ClN_3O_2$: 329.0931, found: 329.0907.

4.5.5 Preparation of carbamate ester 4.24a

In a 50-mL round bottom flask equipped with a stirring bar, *o*-iodophenol **4.19a** (1 g, 4.5 mmol) in benzene (5 mL) was added dropwise to a 10 mL solution of 0.7 g (4.5 mmol) of *p*-chlorophenylisocyanate **4.22a**. After the mixture was stirred at room temperature under N_2 overnight, the resulting solution was concentrated and purified by silica gel column chromatography. Carbamate ester **4.24a** was obtained in 1.22 g (71 %).

Carbamate ester (4.24a) mp = 123-125 °C; IR (C=O) 1727 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 6.97 (m, 1H, NH), 6.94-7.01 (m, 2H), 7.18-7.40 (m, 5H), 7.78-7.83 (dd, 1H, J = 7.9 and 1.4 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 90.68, 120.05, 123.28, 127.73, 129.13, 129.48, 135.73, 139.37, 150.47 [O(C=O)NH]; MS (*m/e*) 373 $[M]^+$; HRMS. Calcd for $C_{13}H_9ClINO_2$, 372.9367 found: 372:9353.

4.5.6 Palladium Catalyzed Cyclocarbonylation of Carbamate 4.24a.

To a 45-mL Parr autoclave fitted with a glass liner and a stirring bar was added $Pd(OAc)_2$ (0.01 mmol), dppb (0.01 mmol), **4.24a** (1 mmol), *N,N*-diisopropylethylamine (1.5 mmol), and dried benzene (5mL). The autoclave was fill-vented three times with CO and pressurized to 300 psi CO. The reaction mixture was stirred at 100 °C for 12 h. The excess CO was released, the resulting reaction mixture was separated by silica gel column chromatography (1:1, ethyl acetate : pentane) affording **4.23a** in 45% isolated

yield. Performing the same reaction but in the added presence of **4.22a** (1 mmol) afforded **4.23a** in 68% yield.

4.5.7 Single Crystal Diffraction Study of 4.29d.

Suitable crystals of **4.29d** were selected, mounted on thin glass fibers using epoxy cement. Data were collected on a Bruker AX SMART 1k CCD diffractometer using 0.3° ω-scans at 0, 90, and 180° in ϕ. Unit-cell parameters were determined from 60 data frames collected at different sections of the Ewald sphere. No absorption corrections were required ($\mu_{eff} = 2.24\ cm^{-1}$).

Systematic absences in the diffraction data and unit-cell parameters were uniquely consistent with the reported space group. The structure was solved by direct methods, completed with difference Fourier syntheses and refined with full-matrix least-squares procedures based on F^2. The Flack parameter refined to nil indicating that the true hand of the data has been determined correctly. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were treated as idealized contributions. All scattering factors and anomalous dispersion factors are contained in the SHEXTL 5.03 program library (Sheldrick, 1997, WI.).

Table 4-9 Crystal data and structure refinement for **4.29d.**

Empirical formula	$C_{20}H_{19}ClN_2O_2$
Formula weight	354.82
Temperature	298 K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2 (1)2 (1) 2 (1)
Unit cell dimensions	a = 5.5403 (7) Å, α = 90 °
	b = 15.365 (2) Å, β = 90 °
	c = 21.449 (3) Å, γ = 90 °
Volume	1825.9 (4) $Å^3$
Z, calculated density	4, 1.291 mg/m^3
Absorption coefficient	0.224 mm^{-1}
F (000)	744
Crystal size	0.4 x 0.1 x 0.1 mm
Theta range for data collection	1.63 to 28.67 °
Limiting indices	$-7 \leq h \leq 7, 0 \leq k \leq 20, 0 \leq 1 \leq 27$
Reflections collected/unique	14117/4349 [R (int) = 0.0602]
Completeness to theta = 28.67	94.4%
Absorption correction	none
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4349/0/226
Goodness of fit on F^2	1.053
Final R indices [I > 2 sigma (I)]	R1 = 0.0346, wR2 = 0.0651
R indices (all data)	R1 = 0.0754, wR2 = 0.0674
Absolute structure parameter	0.03 (6)
Largest diff. peak and hole	0.124 and –0.176 $Å^{-3}$

Table 4-10 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **4.29d.** U (eq) is defined as 1/3 of the trace of orthogonalized Uij tensor.

	x	y	z	U(eq)
Cl	15027(1)	8762(1)	1067(1)	101(1)
N(1)	7503(3)	8078(1)	3257(1)	54(1)
N(2)	5794(3)	9200(1)	3837(1)	64(1)
O(1)	7405(3)	9509(1)	2873(1)	68(1)
O(2)	9686(3)	7034(1)	2768(1)	67(1)
C(1)	11822(4)	8298(1)	1959(1)	65(1)
C(2)	12697(4)	8961(1)	1591(1)	71(1)
C(3)	11733(5)	9793(1)	1636(1)	80(1)
C(4)	9948(5)	9967(1)	2060(1)	74(1)
C(5)	9133(4)	9303(1)	2438(1)	60(1)
C(6)	10020(4)	8474(1)	2388(1)	54(1)
C(7)	9096(4)	7796(1)	2804(1)	55(1)
C(8)	6842(4)	8956(1)	3357(1)	58(1)
C(9)	4693(4)	6991(1)	3664(1)	65(1)
C(10)	4076(4)	6389(1)	4120(1)	75(1)
C(11)	5524(5)	6264(1)	4627(1)	71(1)
C(12)	7621(4)	6734(1)	4688(1)	64(1)
C(13)	8236(4)	7335(1)	4239(1)	58(1)
C(14)	6790(4)	7455(1)	3735(1)	52(1)
C(15)	5351(5)	10387(1)	4580(1)	75(1)
C(16)	4699(5)	11343(1)	4673(1)	85(1)
C(17)	2243(5)	11530(1)	4404(1)	89(1)
C(18)	2057(4)	11274(1)	3733(1)	93(1)
C(19)	2734(4)	10319(1)	3647(1)	80(1)
C(20)	5215(4)	10132(1)	3902(1)	61(1)

Table 4-11 Bond lengths [Å] and angle [°] for **4.29d**.

Cl-C(2)	1.738(2)
N(1)-C(7)	1.382(2)
N(1)-C(8)	1.415(2)
N(1)-C(14)	1.457(2)
N(2)-C(8)	1.240(2)
N(2)-C(20)	1.4748(19)
O(1)-C(8)	1.376(2)
O(1)-C(5)	1.375(2)
O(2)-C(7)	1.2182(17)
C(1)-C(2)	1.376(2)
C(1)-C(6)	1.384(3)
C(2)-C(3)	1.388(3)
C(3)-C(4)	1.370(3)
C(4)-C(5)	1.378(2)
C(5)-C(6)	1.370(2)
C(6)-C(7)	1.465(2)
C(9)-C(14)	1.372(3)
C(9)-C(10)	1.389(2)
C(10)-C(11)	1.364(3)
C(11)-C(12)	1.374(3)
C(12)-C(13)	1.378(2)
C(13)-C(14)	1.358(2)
C(15)-C(20)	1.507(2)
C(15)-C(16)	1.525(2)
C(16)-C(17)	1.506(3)
C(17)-C(18)	1.494(3)
C(18)-C(19)	1.525(2)
C(19)-C(20)	1.508(3)

C(7)-N(1)-C(8)	124.80(15)
C(7)-N(1)-C(14)	117.50(12)
C(8)-N(1)-C(14)	116.72(14)
C(8)-N(2)-C(20)	118.33(15)
C(8)-O(1)-C(5)	121.88(14)
C(2)-C(1)-C(6)	119.41(18)
C(1)-C(2)-C(3)	120.4(2)
C(1)-C(2)-Cl	120.16(17)
C(3)-C(2)-Cl	119.48(16)
C(4)-C(3)-C(2)	120.22(18)
C(3)-C(4)-C(5)	118.86(18)
O(1)-C(5)-C(6)	121.11(16)
O(1)-C(5)-C(4)	117.26(17)
C(6)-C(5)-C(4)	121.6(2)
C(5)-C(6)-C(1)	119.47(17)
C(5)-C(6)-C(7)	119.27(19)
C(1)-C(6)-C(7)	121.23(16)
O(2)-C(7)-N(1)	121.19(16)
O(2)-C(7)-C(6)	123.44(18)
N(1)-C(7)-C(6)	115.37(15)
N(2)-C(8)-O(1)	123.04(16)
N(2)-C(8)-N(1)	122.34(16)
O(1)-C(8)-N(1)	114.60(17)
C(14)-C(9)-C(10)	118.43(18)
C(11)-C(10)-C(9)	120.7(2)
C(10)-C(11)-C(12)	119.99(19)
C(11)-C(12)-C(13)	119.60(19)
C(14)-C(13)-C(12)	120.16(19)
C(13)-C(14)-C(9)	121.13(16)
C(13)-C(14)-N(1)	119.36(17)
C(9)-C(14)-N(1)	119.50(17)
C(20)-C(15)-C(16)	111.37(15)
C(17)-C(16)-C(15)	110.35(19)
C(18)-C(17)-C(16)	112.4(2)
C(17)-C(18)-C(19)	110.67(17)
C(20)-C(19)-C(18)	111.29(17)
N(2)-C(20)-C(15)	109.50(14)
N(2)-C(20)-C(19)	110.39(16)
C(15)-C(20)-C(19)	110.29(17)

Symmetry transformations used to generate equivalent atoms:

Table 4-12 Anisotropic displacement parameters [$Å^2$ x 10^3] for **4.29d.**

	U11	U22	U33	U23	U13	U12
Cl	122(1)	98(1)	82(1)	2(1)	24(1)	-10(1)
N(1)	75(1)	31(1)	57(1)	3(1)	-1(1)	4(1)
N(2)	84(1)	37(1)	72(1)	-2(1)	5(1)	3(1)
O(1)	102(1)	38(1)	64(1)	6(1)	4(1)	12(1)
O(2)	100(1)	34(1)	67(1)	-1(1)	6(1)	10(1)
C(1)	93(2)	48(1)	55(1)	-2(1)	-9(1)	-2(1)
C(2)	96(2)	64(1)	52(1)	-4(1)	0(1)	-11(1)
C(3)	121(2)	54(1)	65(1)	9(1)	-1(2)	-22(1)
C(4)	118(2)	39(1)	64(1)	2(1)	-4(2)	-2(1)
C(5)	93(2)	41(1)	47(1)	0(1)	-8(1)	-2(1)
C(6)	80(2)	38(1)	45(1)	-3(1)	-7(1)	-2(1)
C(7)	75(2)	41(1)	49(1)	-3(1)	-9(1)	-2(1)
C(8)	72(2)	36(1)	66(1)	0(1)	-8(1)	0(1)
C(9)	61(2)	53(1)	82(1)	-2(1)	-13(1)	4(1)
C(10)	65(2)	51(1)	109(2)	-4(1)	13(1)	-9(1)
C(11)	90(2)	48(1)	75(2)	4(1)	26(1)	3(1)
C(12)	76(2)	57(1)	59(1)	3(1)	1(1)	10(1)
C(13)	68(2)	43(1)	63(1)	-2(1)	-5(1)	-1(1)
C(14)	64(1)	32(1)	61(1)	-2(1)	0(1)	3(1)
C(15)	91(2)	51(1)	82(1)	-10(1)	-21(1)	3(1)
C(16)	107(2)	55(1)	94(2)	-22(1)	2(2)	-5(2)
C(17)	103(2)	61(1)	102(2)	-10(1)	23(2)	17(1)
C(18)	96(2)	69(1)	116(2)	5(1)	-11(2)	28(1)
C(19)	95(2)	59(1)	85(2)	-7(1)	-20(1)	13(1)
C(20)	75(2)	37(1)	73(1)	-2(1)	6(1)	7(1)

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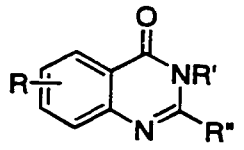
Chapter 5

Palladium-Catalyzed Cyclocarbonylation of *o*-Iodoanilines with Heterocumulenes; Regioselective Preparation of 4(3*H*)-Quinazolinone Derivatives.

5.1 Introduction

4(3*H*)-Quinazolinone derivatives (**5.1**) are of considerable interest because of their pharmacological properties,[1] –e.g. protein tyrosine kinase inhibitor,[2] cholecystokinin inhibitor,[3] antimicrobial,[4] anticonvulsant,[5] sedative and hypotensive,[6] antidepressant and antiinflammatory,[7] as well as antiallergy.[8] In addition, more than 40 alkaloids comprised of a 4(3*H*)-quinazolinone moiety were isolated from natural sources.[9] Some of these have interesting biological properties such as anti-malarial activity, biofungicide,[10] and diuretic properties.

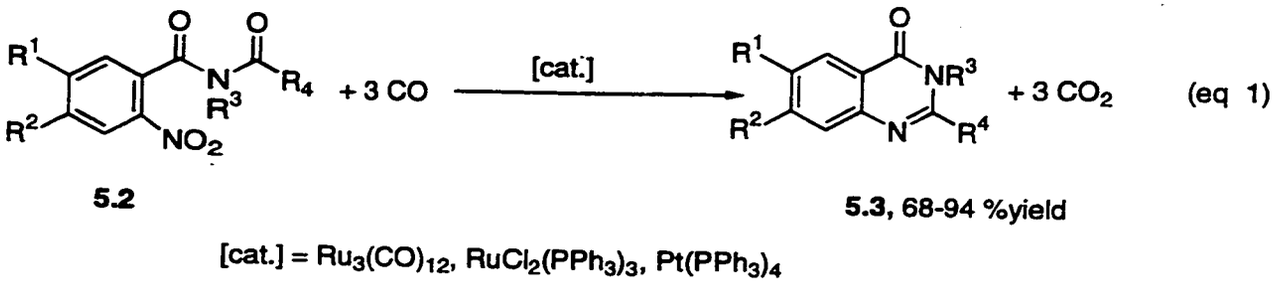


4(3*H*)-Quinazolinone, **5.1**

There are a number of methods described for the preparation of the noted compounds. The main synthetic routes to such compounds utilize 2-aminobenzoic acid or its

derivatives,[11] 2-aminobenzonitrile,[12] isatoic anhydride,[13] 2-carbomethoxyphenyl isocyanate,[14] *N*-arylnitrilium salts,[15] and 4*H*-3,1-benzoxazinones.[16] Recently, solid phase synthesis of 2,4-(1*H*, 3*H*)-quinazolinediones have been reported.[17] The direct ortho substitution of *N*-(*t*-butoxycarbonyl)aniline by lithium reagent was also described.[18]

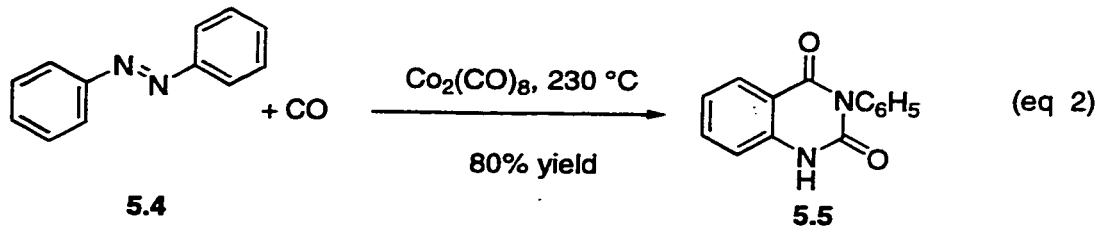
Transition metals were reported to be used in the preparation of 4(3*H*)-quinazolinones, e.g. Akazome et al[19] reported the use of ruthenium and platinum complexes for the catalytic reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)amides (**5.2**) under carbon monoxide pressure, resulting in the formation of 4(3*H*)-quinazolinone derivatives (**5.3**) in 68-94 % yield (eq 1).



5.2 **5.3**, 68-94 %yield

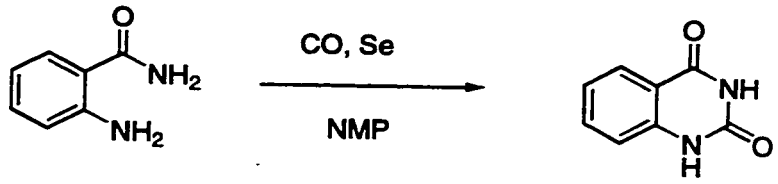
[cat.] = $Ru_3(CO)_{12}$, $RuCl_2(PPh_3)_3$, $Pt(PPh_3)_4$

A 2,4-(1*H*,3*H*)-quinazolinedione (**5.5**) was synthesized in 80% yield by the reaction of azobenzene (**5.4**) with a stoichiometric amount of dicobalt octacarbonyl under CO pressure at 230 °C (eq 2).[20]



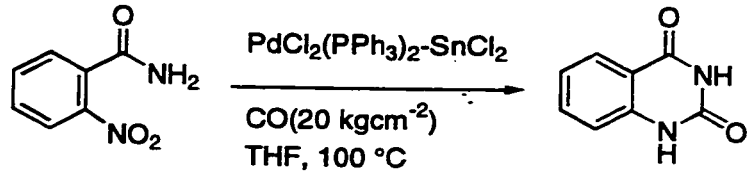
5.4 5.5 (eq 2)

The reaction of 2-carbamoylaniline (**5.6**) with carbon monoxide and a stoichiometric or excess amount of selenium in the presence of *N*-methylpyrrolidine afforded 2,4-(1*H*, 3*H*)-quinazolinediones (**5.7**) in fine yields (eq 3).[21]



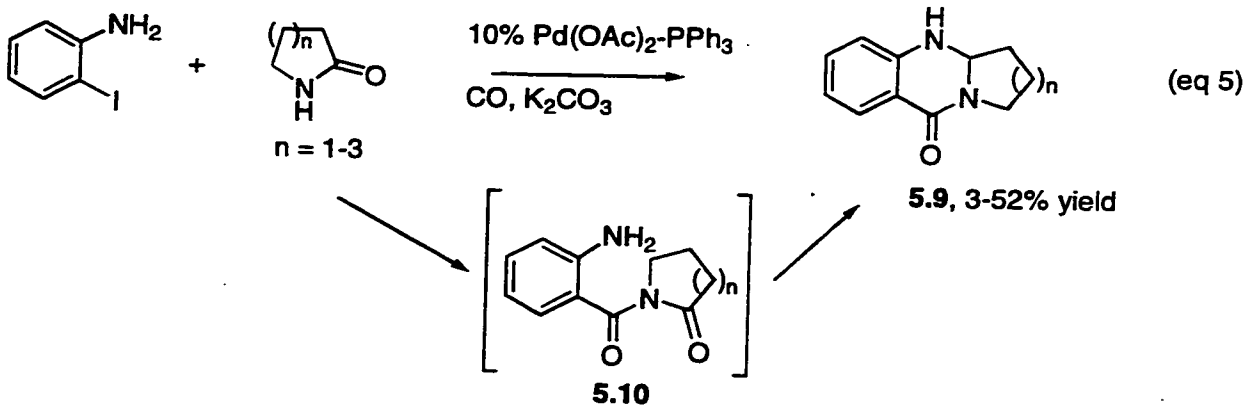
5.6 **5.7**, 21-23% yield (eq 3)

A combination of $PdCl_2(PPh_3)_2$ and $SnCl_2$ was reported for the reductive *N*-carbonylation of 2-nitrobenzamide (**5.8**) to give the corresponding quinazolinedione (**5.7**) in 28% yield.[22]



5.8 **5.7**, 28% yield (eq 4)

Mori et al.[23] described the synthesis of quinazoline-4-one derivatives in 3-52% yield (**5.9**) from the palladium-catalyzed carbonylation of a mixture of *o*-iodoaniline and lactams (eq 5). The reaction was proposed to process through intermediate **5.10**, which consequently forms a C=N bond by the reaction of carbonyl group of lactam and amino group of aniline.



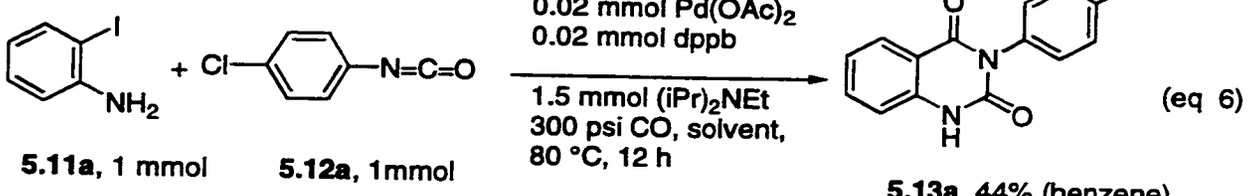
(eq 5)

Encouraged by the usefulness of 4(3*H*)-quinazolinone derivatives, it was therefore decided to explore the preparation of the title compounds by palladium catalyzed cyclocarbonylation reactions of *o*-iodoanilines with heterocumulenes.

5.2 Results and Discussion

5.2.1 The cyclocarbonylation reaction of *o*-iodoaniline with isocyanates.

Treatment of *o*-iodoaniline, **5.11a** (1 mmol) and *p*-chlorophenylisocyanate **5.12a** (2 mmol)[24] with 300 psi CO in benzene in the presence of 0.02 mmol $Pd(OAc)_2$, 0.02 mmol 1,4-bis(diphenylphosphino)butane (dppb) and $(i\text{-Pr})_2NEt$ for 12 h at 80 °C afforded 3-(*p*-chlorophenyl)-2,4-(1*H*,3*H*)-quinazolinedione (**5.13a**) in 44% isolated yield (eq 6). Performing the same reaction but using THF instead of benzene, resulted in the isolation of **5.13a** in 72% yield. Lower product yields were obtained when using DMF (56%) or DME (54%) as the solvent.



5.11a, 1 mmol **5.12a**, 1mmol

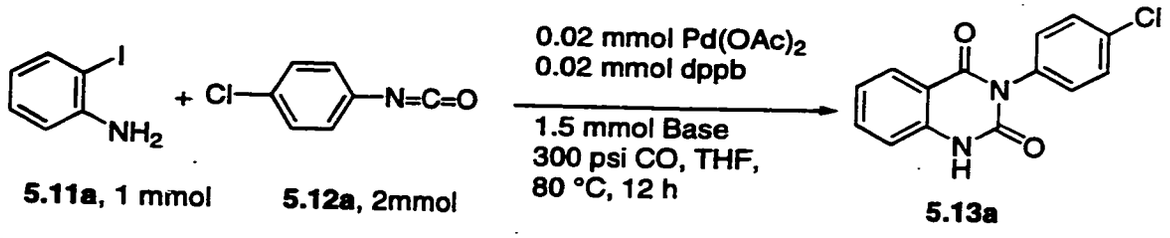
5.13a, 44% (benzene)
72% (THF)
56% (DMF)
54% (DME)

(eq 6)

Using the $Pd_2(dba)_3 \cdot CHCl_3$-dppb catalytic system under the same reaction conditions, in THF furnished **5.13a** in 72% isolated yield. The effect of base used in the

reaction was investigated in the reaction of **5.11a** 1 mmol) and **5.12a** (2 mmol) in the presence of 0.02 mmol each of $Pd(OAc)_2$ and dppb under 300 psi CO in THF and the results are summarized in Table 5-1. Potassium carbonate (entry 2) gave similar results to that obtained by using diisopropylethylamine (entries 1 and 3), while slightly lower yields of **5.13a** were obtained from the reaction using triethylamine and sodium carbonate as the base (entries 2 and 4).

Table 5-1 Determination of the Effect of Base on the Palladium-Catalyzed Cyclocarbonylation Reaction of **5.11a** with **5.12a**.[a]



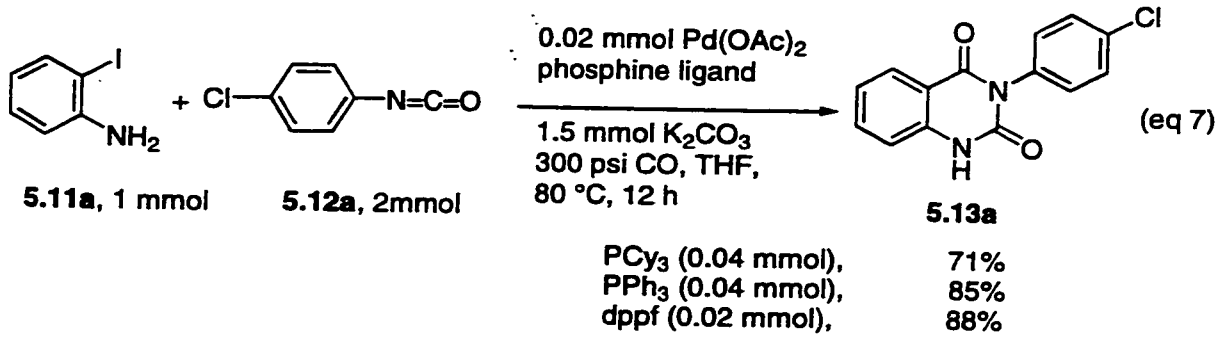
5.11a, 1 mmol **5.12a**, 2mmol **5.13a**

Entry	Base (1.5 mmol)	Isolated yield (%)[b]
1	$(i\text{-Pr})_2NEt$	72
2	Et_3N	63
3	K_2CO_3	75
4	Na_2CO_3	60

[a] **5.11a** (1mmol), **5.12a** (2 mmol), base (1.5 mmol), $Pd(OAc)_2$ (0.02 mmol), dppb (0.02 mmol), THF (5 mL), 300 psi CO, 80 °C, 12 h. [b] Isolated yield by silica gel column chromatography.

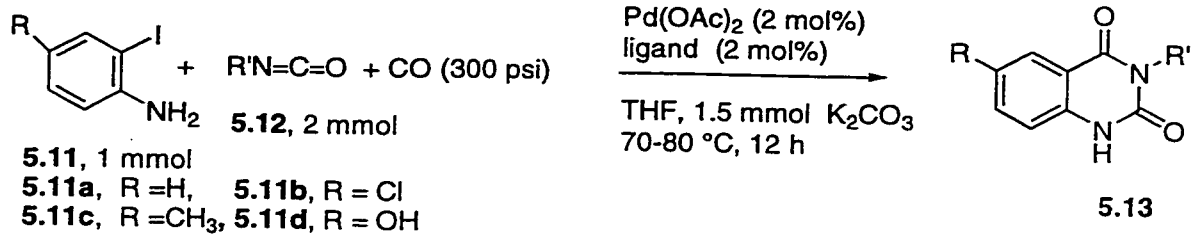
Similar yields of **5.13a** were observed in the reaction of **5.11a** with **5.12a** and K_2CO_3 under 300 psi CO in the presence of 2 mol% $Pd(OAc)_2$ in THF using PCy_3 (71%) compared to the same reaction employing dppb as the added ligand. Higher yields of

5.13a were obtained from the reaction employing PPh_3 (85%) or 1,1′-*bis*-(diphenylphosphino) ferrocene (dppf) (88%) (eq 7). It is worth noting that using dppb and dppf in some cases gave the same isolated product yield. Therefore, dppb and dppf were chosen to use in this study.



A variety of 3-substituted-2,4-(1*H*,3*H*)-quinazolinediones (**5.13**) can be prepared in moderate to good yields by the reaction of *o*-iodoanilines (**5.11**) with isocyanates (**5.12**) under carbon monoxide pressure in the presence of 2 mol% $Pd(OAc)_2$-bidentate phosphine (dppb or dppf) catalyst and 1.5 mol% K_2CO_3 in THF at 70-80 °C for 12 h (see Table 5-2). Two equivalents of isocyanates to *o*-iodoaniline were used since lower product yield may result if one equivalent is used.[25] Isocyanates containing either electron withdrawing or electron donating groups on the aromatic ring react with *o*-iodoaniline to yield 3-substituted-2,4-(1*H*, 3*H*)-quinazolinediones (**5.13**) in good yields. *o*-Iodoaniline (**5.11a**), *p*-chloro-*o*-iodoaniline (**5.11b**) and *p*-methyl-*o*-iodoaniline (**5.11c**) were converted to **5.13** in this reaction. However, none of the desired product was isolated, using *o*-iodoaniline with a hydroxyl group substituted at the C-4 of the phenyl ring (**5.11d**) with *p*-methoxyphenylisocyanate (**5.12c**) (entry 8), and this may be due to competitive reaction of the hydroxyl and amine groups with the isocyanate.

Table 5-2 Cyclocarbonylation Reactions of *o*-Iodoaniline (**5.11**) with Isocyanates (**5.12**) catalyzed by $Pd(OAc)_2$-bidentate Phosphine Complexes.[a]



5.11, 1 mmol
5.11a, R =H, **5.11b**, R = Cl
5.11c, R =CH_3, **5.11d**, R = OH

5.13

Entry	**5.11**	R'N=C=O, **5.12**, R' =	Product	Isolated yield(%)[b]
1	**5.11a**	*p*-ClC_6H_4, **5.12a**	**5.13a**	88[d]
2	**5.11b**	**5.12a**	**5.13b**	68[d]
3	**5.11c**	**5.12a**	**5.13c**	72[c]
4	**5.11a**	*p*-BrC_6H_4, **5.12b**	**5.13d**	68[d]
5	**5.11a**	*p*-$CH_3OC_6H_4$, **5.12c**	**5.13e**	80[d]
6	**5.11d**	**5.12c**	**5.13f**	90[c]
7	**5.11d**	**5.12c**	**5.13g**	0[d]
8	**5.11a**	C_6H_5, **5.12d**	**5.13h**	87[d]
9	**5.11c**	**5.12d**	**5.13i**	89[d]
10	**5.11a**	*p*-$CH_3C_6H_4$, **5.12e**	**5.13j**	83[c]
11	**5.11c**	**5.12e**	**5.13k**	77[c]

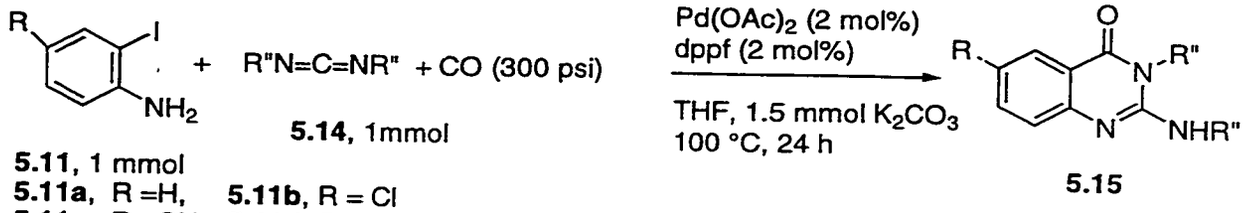
[a] Reaction conditions: **5.11**:**5.12**:K_2CO_3:$Pd(OAc)_2$:bidendate phosphine ligand, 1:2:1.5:0.02:0.02 mmol in 5 mL THF, 70-80 °C, 300 psi CO, 12 h [b] Isolated yield by silica gel column chromatography. [c] dppb was used in this reaction. [d] dppf was used in this reaction.

5.2.2 The cyclocarbonylation reaction of *o*-iodoaniline with carbodiimides.

2-Amino-4(3*H*)-quinazolinones (**5.15**) can be prepared in 55-90% yields by utilizing the developed method using *o*-iodoaniline (**5.11,** 1 mmol), carbodiimide (**5.14,** 1 mmol) and 300 psi carbon monoxide, catalyzed by 2 mol% $Pd(OAc)_2$ and dppf in the presence of 1.5 mmol K_2CO_3 in THF at 100 °C for 24 h (Table 5-3).

Using *o*-iodoanilines with electron withdrawing or electron donating groups substituted on phenyl ring does not have any effect on the selectivity of the reaction. The reaction tolerates nitrile (**5.11e**) as well as hydroxyl functional groups (**5.11d**) of *o*-iodoanilines (entries 4, 7 and 8). In contrast, using carbodiimides containing electron withdrawing substituted on nitrogen, such as **5.14d-f,** gave recovered starting material (entries 10-12).

Table 5-3 2-Amino-(3*H*)-quinazolin-4-ones (**5.15**) from the Palladium-Catalyzed Reaction of *o*-Iodoanilines (**5.11**) with Carbodiimides (**5.14**) and Carbon Monoxide.[a]



5.11, 1 mmol
5.11a, R =H, **5.11b**, R = Cl
5.11c, R =CH_3, **5.11d**, R = OH
5.11e, R =CN

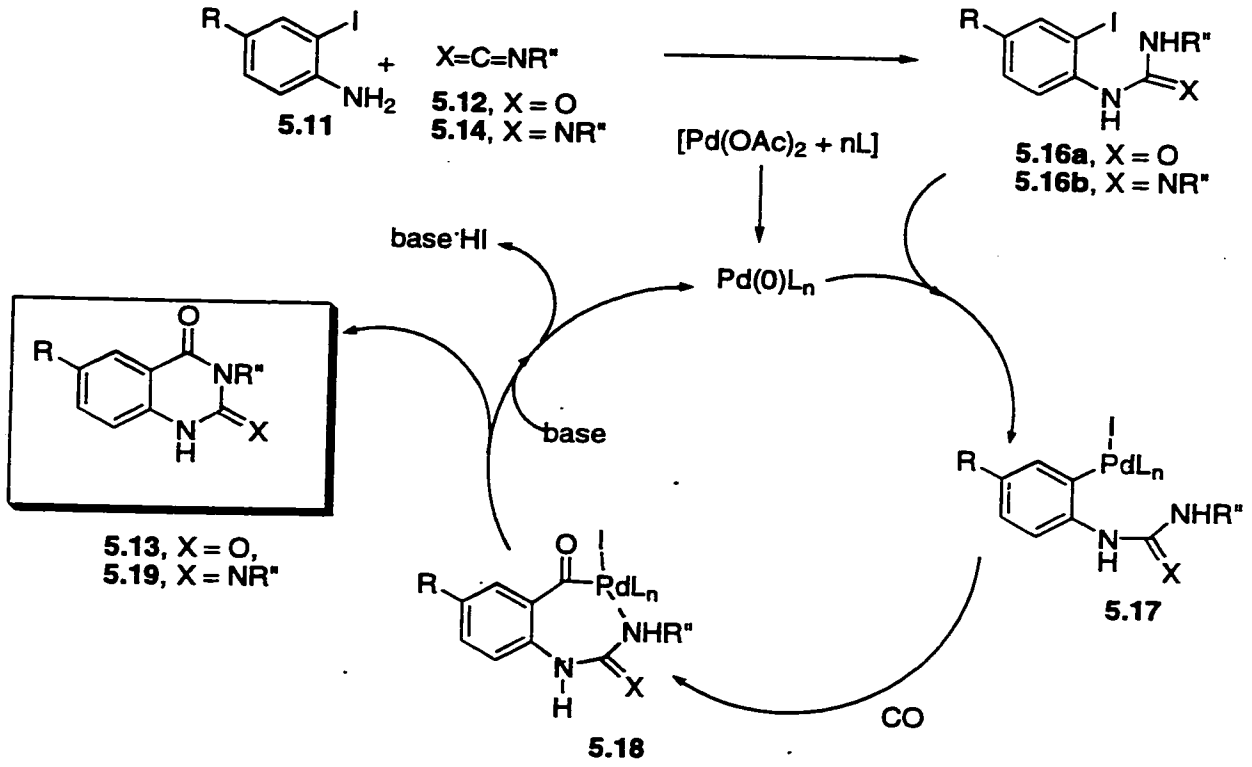
5.15

Entry	5.11	R"N=C=NR", 5.14, R" =	Product	Isolated yield(%)[b]
1	**5.11a**	*p*-ClC_6H_4, **5.14a**	**5.15a**	75
2	**5.11b**	**5.14a**	**5.15b**	67
3	**5.11c**	**5.14a**	**5.15c**	55
4	**5.11d**	**5.14a**	**5.15d**	90
5	**5.11a**	C_6H_5, **5.14b**	**5.15e**	64
6	**5.11b**	**5.14b**	**5.15f**	64
7	**5.11d**	**5.14b**	**5.15g**	78
8	**5.11e**	**5.14b**	**5.15h**	74
9	**5.11a**	*p*-BrC_6H_4, **5.14c**	**5.15i**	73(61)[c]
10	**5.11a**	*p*-$CH_3C_6H_4$, **5.14d**		0
11	**5.11a**	C_6H_{11}, **5.14e**		0
12	**5.11b**	*i*C_3H_7, **5.14f**		0

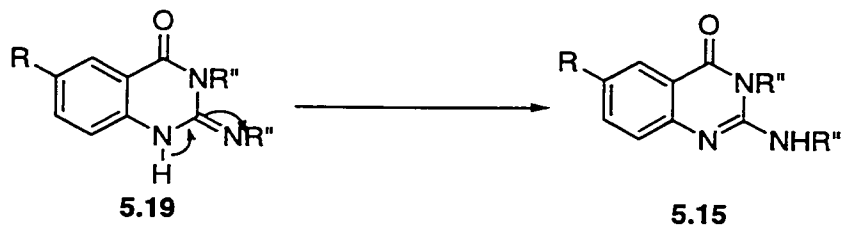
[a] Reaction conditions: refer to the Experimental Section for the General Procedure for the cyclocarbonylation of *o*-iodoanilines (**5.11**) with carbodiimides (**5.14**). [b] The products (**5.15**) were purified by silica gel column chromatography. [c] The yield in parenthesis was obtained from the reaction using dppb as the ligand.

A possible mechanism of the palladium-catalyzed cyclocarbonylation reaction of *o*-iodoanilines (**5.11**) with isocyanates (**5.12**) or carbodiimides (**5.14**) is outlined in Scheme 5-1. Initial reaction of *o*-iodoaniline with isocyanate or carbodiimide can give a urea (**5.16a**) or a guanidine (**5.16b**). Oxidative addition of palladium catalyst to C-I bond of **5.16a** or **5.16b** would afford **5.17**. Carbonyl insertion into the latter and possible coordination of the NHR″ moiety to the metal, would afford the aroyl palladium intermediate **5.18**. Reductive elimination would result in the formation of 3-substituted-4(3*H*)-quinazolinone derivatives.

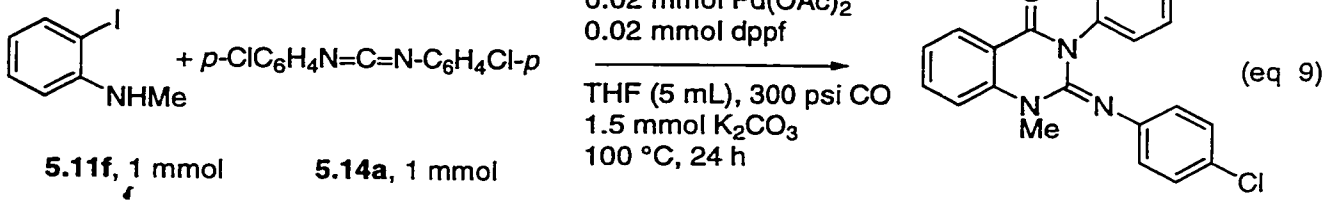
Scheme 5-1



When carbodiimides are used as reactants, 4(3*H*)-quinazolinone-2-imine intermediate (**5.19**) may be generated which, on rearrangement, would afford the more stable 2-amino-4(3*H*)-quinazolinone **5.15** (eq 8). Evidence for this process came from the reaction of *N*-methyl-*o*-iodoaniline (**5.11f**) with bis(*p*-chlorophenyl)carbodiimide (**5.14a**) under the same reaction condition afforded 1-methyl-3, *N*-di(*p*-chlorophenyl)-4(3*H*)-quinazolinone-2-imine (**5.19j**) in 61% isolated yield (eq 9). Rearrangement did not occur here, since such a process would require a methyl rather than a hydrogen transfer.



5.19 **5.15** (eq 8)



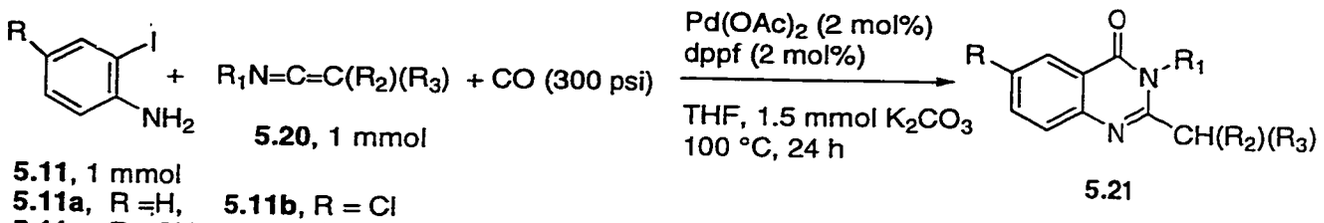
5.11f, 1 mmol **5.14a**, 1 mmol (eq 9)

5.19j, 61% isolated yield

5.2.2 The cyclocarbonylation reaction of *o*-iodoaniline with ketenimines.

2-Alkyl-4(3*H*)-quinazolinone derivatives can be synthesized by using ketenimines rather than carbodiimides in the reaction with *o*-iodoanilines and CO. Treatment of *o*-iodoaniline (**5.11**) with an equimolar amount of a ketenimine (**5.20**) at 300 psi CO, in the presence of 2 mol% each of $Pd(OAc)_2$ and dppf, gave 2-alkyl-4(3*H*)-quinazolinone (**5.21**) in good to excellent isolated yields (Table 5-4 for results). Ketenimine **5.20a-c** are quite stable and can be used in the reaction to obtain high product yields. However, ketenimine **5.20d** is not stable in air and should be kept under nitrogen at low temperature at all time. Therefore, freshly prepared **5.20d** gave better product yield than a sample which was kept for more than one month. For example **5.21k** was obtained in 94% isolated yield (entry 11) when freshly prepared **5.20d** was used, and in 60% yield using **5.20d** prepared one month earlier. Note that ketenimines, which are fully substituted with aromatic groups (**5.20e** and **5.20f**), do not react with *o*-iodoanilines (entries 12 and 13).

Table 5-1 Palladium-Catalyzed Cyclocarbonylation Reactions of *o*-Iodoaniline (**5.11**) with Ketenimines (**5.20**).[a]



5.11, 1 mmol
5.11a, R = H, **5.11b**, R = Cl
5.11c, R = CH_3, **5.11d**, R = OH
5.11e, R = CN

5.20, 1 mmol

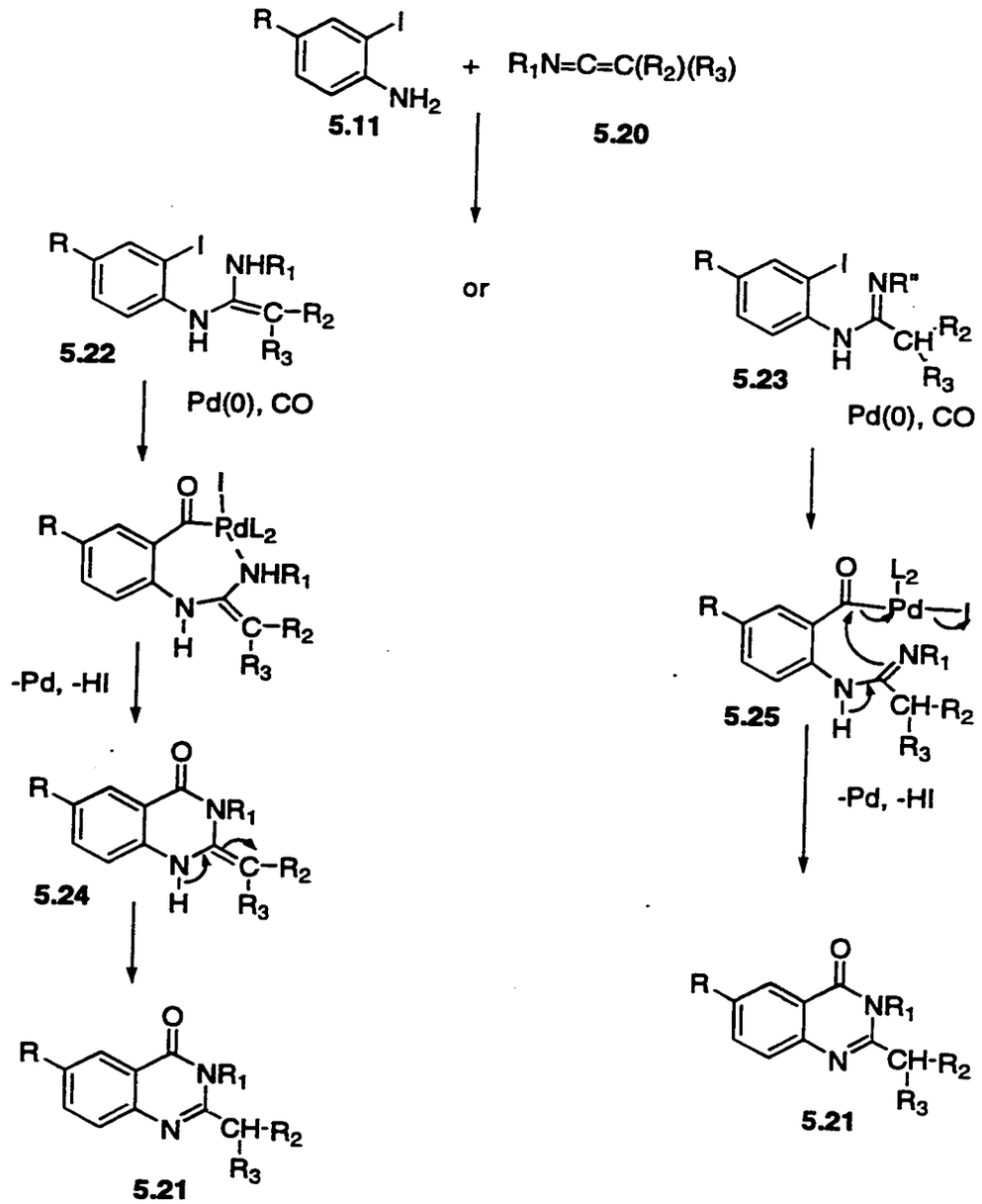
5.21

Entry	5.11	5.20	Product	Isolated yield(%)[b]
1	**5.11a**	PhN=C=C(CH_3)(COOEt) **5.20a**	**5.21a**	98
2	**5.11b**	**5.20a**	**5.21b**	87
3	**5.11c**	**5.20a**	**5.21c**	99
4	**5.11d**	**5.20a**	**5.21d**	45
5	**5.11e**	**5.20a**	**5.21e**	47
6	**5.11a**	^{n}BuN=C=C(CH_3)(COOEt) **5.20b**	**5.21f**	72
7	**5.11c**	**5.20b**	**5.21g**	74
8	**5.11a**	PhN=C=C(CH_3)(COPh) **5.20c**	**5.21h**	95
9	**5.11c**	**5.20c**	**5.21i**	95
10	**5.11a**	PhN=C=C(COOEt)$_2$ **5.20d**	**5.21j**	71
11	**5.11b**	**5.20d**	**5.21k**	94
12[c]	**5.11b**	PhN=C=C(Ph)$_2$ **5.20e**		0
13	**5.11b**	*p*-TolylN=C=C(Ph)$_2$ **5.20f**		0

[a] Reaction conditions: refer to the Experimental Section for the General Procedure for the cyclocarbonylation of *o*-iodoanilines (**5.11**) with Ketenimine (**5.20**). [b] The products (**5.21**) were purified by silica gel column chromatography.

The palladium-catalyzed cyclocarbonylation reaction of ketenimines with *o*-iodoanilines may proceed in the similar pathway to that of isocyanates and carbodiimides. There are two conceivable amidine intermediates which can be formed in situ from the reaction of an *o*-iodoaniline with a ketenimine, namely **5.22** and **5.23** (Scheme 5-2). If **5.22** is formed, oxidative addition and carbonyl insertion followed by coordination of the amine unit to palladium and subsequent reductive elimination would afford **5.24**. Rearrangement of **5.24** would form the more stable 2-alkyl-4(3*H*)-quinazolinone (**5.21**). An alternate pathway to **5.21** may involve oxidative addition and carbonyl insertion of **5.23** to give **5.25**. Base-catalyzed intramolecular cyclization of **5.25** would form **5.21**.

Scheme 5-2


R
I
NH2
5.11
+ R1N=C=C(R2)(R3)
5.20
or
NHR1
N
H
C–R2
R3
5.22
Pd(0), CO
O
I
PdL2
-Pd, -HI
NR1
5.24
CH-R2
5.21
NR"
CH
5.23
L2
Pd
5.25

5.3 Conclusion

A simple method for the synthesis of 2,4(1*H*,3*H*)-quinazolinediones (**5.13**), 2-amino-4(3*H*)-quinazolinones (**5.15**) and 2-alkyl-4(3*H*)-quinazolinone (**5.21**) derivative by palladium-catalyzed cyclocarbonylation reaction of *o*-iodoanilines with isocyanates, carbodiimides, and ketenimine respectively was described. The reaction proceeds in the regioselective manner resulting in the formation of the desired products in good to high yields.

5.4 Experimental Section

5.4.1 Preparation of *o*-iodoanilines (5.11)

5.4.1.1 Preparation of *p*-chloro-*o*-iodoaniline (5.11b), *p*-methyl-*o*-iodoaniline (5.11c).

p-Chloro-*o*-iodoaniline and *p*-methyl-*o*-iodoaniline were prepared by modified literature procedure.[25] *p*-Chloroaniline (6.3g, 0.05 mol), sodium bicarbonate (6.3 g, 0.075 mol) and 50 mL of water were placed in 200 mL beaker and cooled to 12-15 °C by adding a small amount of ice. Iodine (11.4 g, 0.045 mol) was added, in portion to the stirred mixture. The resulting mixture was then stirred for an additional 20-30 min. The product was separated from the reaction mixture by extraction with CH_2Cl_2 (3×50 mL) and purified by column chromatography using 1:1 mixture of ether:pentane as the eluant. *p*-Chloro-*o*-iodoaniline was obtained in 70% yield (8.8 g). *p*-Methyl-*o*-iodoaniline was obtained in 85% yield using the same procedure from *p*-toluidine.

***p*-Chloro-*o*-iodoaniline (5.11b)** IR 3367 cm^{-1}; ^{1}H-NMR ($CDCl_3$ 200 MHz) 4.02 (s, br, 2H, NH_2), 6.60 (d, 1H, J = 8.6 Hz), 7.08 (dd, 1H, J =8.6 and 2.2 Hz), 7.57 (d, 1H, J = 2.2 Hz); ^{13}C NMR ($CDCl_3$ 75 MHz) 83.44 (C-I), 114.92 (CH-C-NH_2), 123.00 (CH), 129.15 (CH-C-Cl), 137.65 (CH-C-I)., 145.45 (C-NH_2); m/e 253 $[M]^+$.

***p*-Methyl-*o*-iodoaniline (5.11c)** IR 3358 cm^{-1}; ^{1}H-NMR ($CDCl_3$ 200 MHz) 2.20 (s, 3H, CH_3), 3.85 (s, br, 2H, NH_2), 6.66 (d, 1H, J = 8.1 Hz), 6.90-6.95 (m, 1H), 7.45-7.46 (m, 1H); ^{13}C NMR ($CDCl_3$ 75 MHz) 19.83 (CH_3), 84.28 (C-I), 114.63 (CH-C-NH_2), 130.00 (CH-C-CH_3), 133.91 (C-CH_3), 138.98 (CH-C-I)., 144.25 (C-NH_2); m/e 233 $[M]^+$.

5.4.1.2 Preparation of *p*-hydroxy-*o*-iodoaniline (5.11d)[26]

m-Iodophenol (5.5 g) was dissolved in a small amount of water containing potassium hydroxide (1.4 g). To this solution was added a cold solution of diazotized sulfanilic acid, alkalinity being maintained. After mixture was allowed to stand half an hour, sodium hydrosulfite (12 g) was added and the mixture was warmed. The red dye quickly disappeared and after cooling the precipitate was filtered off and dried. The product was obtained in 2.85 g (58% yield) after purified by silica gel column chromatography using a mixture of ether and pentane (1:1) as the eluant.

***p*-Hydroxy-*o*-iodoaniline (5.11d)** IR 3346, 3281 cm^{-1}; ^{1}H-NMR (Acetone–d_6 200 MHz) 4.29 (s, br, 2H, NH_2), 6.63-6.69 (m, 2H, CH and OH), 7.13 (d, 1H, J = 2.3 Hz), 7.78 (s, 1H); ^{13}C NMR (Acetone–d_6 50 MHz) 83.87 (C-I), 116.05 (CH-C-OH), 117.81 (CH-C-NH_2), 125.39 (CH-C-I)., 143.04 (C-NH_2), 150.32 (C-OH); m/e 235 $[M]^+$.

5.4.1.3 Preparation of *p*-cyano-*o*-iodoaniline (5.11e)[27]

p-Aminobenzonirile (1.87 g, 0.015 mol) was suspended in aqueous methanol (50 mL) and calcium carbonate (1.75 g, 0.0175 mol) was added to the suspension. Iodine monochloride (2.85 g) was added dropwise, and the resulting mixture was stirred for another 30 min. The product was extracted with CH_2Cl_2 (3×75 mL) and purified by silica gel column chromatography using a mixture of ether and pentane (1:1) as the eluant resulting in *p*-cyano-*o*-iodoaniline in 2.8g (72%).

***p*-Cyano-*o*-iodoaniline (5.11e)** IR 3459, 3357, 2215 cm^{-1}; ^{1}H-NMR ($CDCl_3$ 200 MHz) 4.67 (s, br, 2H, NH_2), 6.66 (d, 1H, J = 8.4 Hz), 7.33 (dd, 1H, J =8.4 and 1.9 Hz), 7.85 (d, 1H, J = 1.9 Hz); ^{13}C NMR ($CDCl_3$ 50 MHz) 81.73 (C-I), 101.50 (C-CN), 113.44 (CH-C-NH_2), 118.31 (C≡N), 133.13 (CH), 142.65 (CH-C-I)., 150.59 (C-NH_2); m/e 244 $[M]^+$.

5.4.1.4 Preparation of *N*-methyl-*o*-iodoaniline (5.11f)[28]

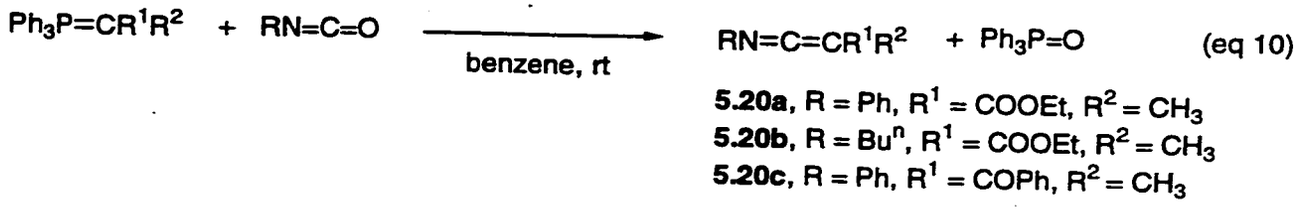
In a dried 100 mL round bottom flask, 2-iodoaniline (2.25g, 10.3 mmol) was dissolved in 30 mL of dry THF. The resulting solution was stirred at –78 °C under N_2. 1.6 M MeLi (6.25 mL, 10 mmol) was added dropwise, and the resulting solution was stirred at –78 °C for 30 min. To the solution was added Me_2SO_4 (1.90g, 15.1 mmol), and stirring was continued for 10 min at –78 °C. The solution was then warmed to rt and stirred for 2 h, followed by acidification with 10% HCl. The reaction mixture was

diluted with ether, and the aqueous layer was removed, and the organic phase was washed with water, dried with Na_2SO_4, and concentrated. Distillation at 101-105 °C (2.0 mmHg) yielded 2.0 g (89 %) of *N*-methyl-*o*-iodoaniline.

***N*-Methyl-*o*-iodoaniline (5.11f)** IR 3329 cm^{-1}; ^{1}H-NMR ($CDCl_3$ 200 MHz) 2.87 (s, 3H, CH_3), 4.20 (s, br, 1H, NH), 6.39-6.57 (m, 2H), 7.18-7.27 (m, 1H), 7.61-7.67 (m, 1H); ^{13}C NMR ($CDCl_3$ 75 MHz) 85.09 (C-I), 109.97 (CH-C-NH_2), 118.45 (CH), 129.44 (CH), 138.84 (CH-C-I), 148.13 (C-NH_2); m/e 233 $[M]^+$.

5.4.2 Preparation of ketenimines (5.20a-f)

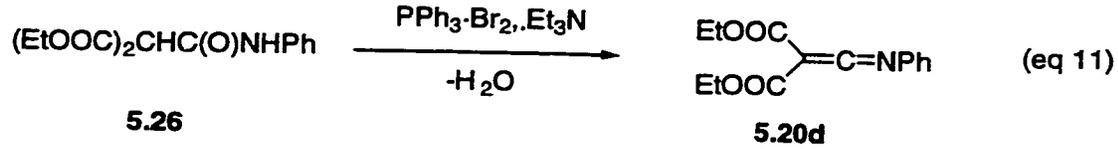
5.4.2.1 Preparation of ketenimine 5.20a-c.[29]



(eq 10)

In a dry 100 mL round bottom flask was placed 50 mL of dry benzene and the corresponding ylide. Thereafter a molar equivalent of isocyanate was slowly added. The reaction mixture was vigorously stirring during addition, and the stirring was continued at ambient temperature until complete conversion of isocyanate (determined by IR). Benzene was evaporated under reduced pressure and the ketenimine was purified by distillation. Ketenimines **5.20a**, **5.20b** and **5.20c** were obtained in 92, 78 and 30% yields respectively.

5.4.2.2 Preparation of ketenimnine 5.20d.[30]

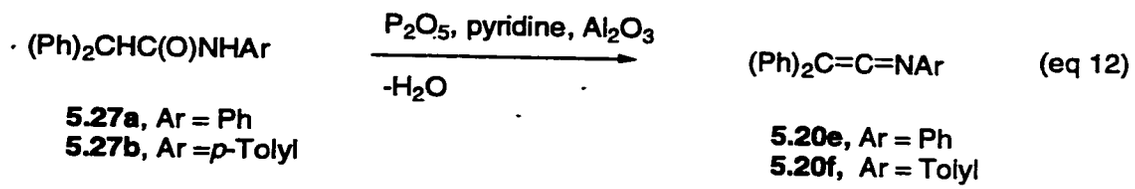


(eq 11)

5.26 **5.20d**

In a dry 100 mL round bottom flask, 5.24g (20 mmol) of triphenylphosphine was dissolved in 50 mL of CH_2Cl_2. The solution was cooled in an ice bath and 20 mmol of bromine was added dropwise to the stirred solution. The mixture was stirred for an additional 30 min and a mixture of 40 mmol of Et_3N and 5.52g of acetanilide (**5.26**) was added slowly at the ice bath temperature. The mixture was stirred for 30 min at room temperature and 10 min at 60 °C. After the reaction mixture was cooled to room temperature, the solid was isolated and the filtrate was concentrated. The pure product was obtained in 27% yield after florisil column chromatography and ether as the eluant.

5.4.2.3 Preparation of ketenimine 5.20e-f.[31]



(eq 12)

5.27a, Ar = Ph
5.27b, Ar = *p*-Tolyl

5.20e, Ar = Ph
5.20f, Ar = Tolyl

To a stirred solution of 10g of *N*-(phenyl)diphenylacetamide (**5.27a**) in 300 mL of dry pyridine was added 25g of phosphorus pentoxide, 50g of alumina, and 200 mL of

Pyridine. The mixture was refluxed for 7 h., then allowed to cool, and filtrated. The pyridine was evaporated under reduced pressure, and the crystalline mass was dissolved in ether, filtered and concentrated and allowed to crystallize. The ketenimine **5.19e** was obtained in 82% yield. Ketenimine **5.20f** was prepared using the same procedure start from *N*-(*p*-tolyl)diphenylacetamide (**5.27b**) in 80% yield.

5.4.3 General Procedure for the Palladium-Catalyzed Cyclocarbonylation of *o*-Iodoanilines (5.11) with Isocyanates (5.12a-e).

An autoclave, its glass liner, and a magnetic stirring bar were dried in an oven and then cooled in a desiccator before use. The liner was charged with the palladium catalyst (2 mol%), an equivalent of bidentate phosphine ligand relative to palladium used, and 3 mL of dried solvent. After the mixture was stirred under nitrogen for 15 min, *o*-iodoaniline (**5.11**, 1 mmol), isocyanate (**5.12**, 2 mmol), 1.5 mmol of base and another 2 mL of solvent were added to the mixture. The autoclave was then attached to a gauge block assembly, and was flushed three times with CO and pressurized to 300 psi. After 12 h in an oil bath at 70-80 °C, the autoclave was removed and allowed to cool to room temperature. The excess gas was discharged and the system disassembled. The reaction mixture was then filtered and the filtrate was concentrated and purified by column chromatography on silica gel using 1:1 mixture of ethyl acetate: pentane as the eluant.

3-(*p*-Chlorophenyl)-2,4-(1*H*,3*H*)-quinazolinediones (5.13a)[11j,13] (R = H, R′= *p*-ClC_6H_4); mp 296-297 °C (lit[11j] mp. 295-296 °C); IR 1725, 1649 cm^{-1}; ^1H ($CDCl_3$+DMSO–D_6, 200 MHz) δ 6.59-7.10 (m, 7H), 7.45 (d, 1H, *J* = 7.9 Hz), 10.99 (s, 1H, NH); ^{13}C ($CDCl_3$ +DMSO-d_6, 75 MHz) δ 113.12 [**C**-C(O)-N], 114.45, 118.73, 121.57, 126.70, 127.38, 127.98, 134.03 (**C**H-aromatic carbons), 129.21, 132.82 (quaternary aromatic carbons), 138.63 [**C**-NH-C(O)], 149.34 [N-**C**(O)-N], 161.35 [**C**(O)N]; MS (*m/e*) 272 $[M]^+$.

3-(*p*-Chlorophenyl)-6-chloro-2,4-(1*H*,3*H*)-quinazolinediones (5.13b) (R = Cl, R′= *p*-ClC_6H_4); mp >300 °C; IR 3280, 1739, 1640 cm^{-1}; ^1H ($CDCl_3$+DMSO–d_6, 200 MHz) δ 7.01-7.09 (m, 1H), 7.30-7.52 (m, 4H), 7.75-7.83 (m, 2H), 9.37 (s, br, 1H, NH); ^{13}C ($CDCl_3$ +DMSO–d_6, 75 MHz) δ 113.33 [**C**-C(O)-N], 119.24, 122.82, 124.45, 127.56, 137.60 (**C**H-aromatic carbons), 128.44, 133.17, 137.71(quaternary aromatic carbons), 147.31 [**C**-NH-C(O)], 149.94 [N-**C**(O)-N], 159.61 [**C**(O)N]; MS (*m/e*) 307 $[M+1]^+$, 308 $[M+2]^+$; HRMS cald for $C_{14}H_8Cl_2N_2O_2$; 305.9963, found 305.9933.

3-(*p*-Chlorophenyl)-6-methyl-2,4-(1*H*,3*H*)-quinazolinediones (5.13c) (R = CH_3, R′= *p*-ClC_6H_4); mp > 300 °C; IR 3293, 1732, 1643 cm^{-1}; ^1H ($CDCl_3$+DMSO–d_6, 200 MHz) δ 2.30 (s, 3H, CH_3-C_6H_3), 7.04-7.17 (m, 3H), 7.31-7.72 (m, 3H), 8.39 (s, 1H), 11.36 (s, 1H, NH); $^{13}C_t$($CDCl_3$ +DMSO–d_6, 75 MHz) 19.66 (CH_3-C_6H_3), 113.14 [**C**-C(O)-N], 114.45, 118.80, 127.58, 128.16, 129.31, 135.31 (CH-aromatic carbons), 131.31, 136.65, 137.26 (quaternary aromatic carbons), 149.34 [**C**-NH-C(O)], 151.69 [N-**C**(O)-N], 161.58 [**C**(O)N]; MS (*m/e*) 286 $[M]^+$; HRMS Cal. for $C_{15}H_{11}ClN_2O_2$ 286.0509 found 286.0507.

3-(*p*-Bromophenyl)-2,4-(1*H*,3*H*)-quinazolinediones (5.13d) (R = H, R″= *p*-BrC_6H_4); mp > 300 °C; IR 1722, 1668 cm^{-1}; ^1H ($CDCl_3$+DMSO–d_6, 200 MHz) δ 7.06-7.55 (m,

7H), 7.95 (d, 1H, J = 8.1 Hz), 11.48 (s, 1H, NH); ^{13}C ($CDCl_3$+DMSO–d_6, 75 MHz) δ 113.82 [**C**-C(O)-N], 115.10, 119.62, 122.28, 127.54, 127.94, 129.94, 131.04, 133.77 (CH-aromatic carbons) 121.82, 131.78 (quaternary aromatic carbons), 139.24 [**C**-NH-C(O)], 150.18 [N-**C**(O)-N], 162.07 [**C**(O)N]; MS (*m/e*) 316 $[M-1]^+$; 318 $[M+1]^+$ HRMS Cal. for $C_{14}H_9BrN_2O_2$ 315.9847 found 315.9848.

3-(*p*-Methoxyphenyl)-2,4-(1*H*,3*H*)-quinazolinediones (5.13e) (R = H, R′= *p*-$CH_3OC_6H_4$); mp 293-295 °C (lit[11j] mp = 297-299 °C); IR 1735, 1649 cm^{-1}; ^{1}H ($CDCl_3$+ DMSO–d_6, 200 MHz) δ 3.20 (s, 3H, *p*-C$H_3OC_6H_4$), 6.27-6.29 (m, 2H), 6.57-6.75 (m, 2H), 7.03-7.12 (m, 3H), 9.30 (s, br, 1H, NH); ^{13}C ($CDCl_3$ +$DMSOD_6$, 75 MHz) δ 54.05 (*p*-**C**$H_3OC_6H_4$), 112.44 [**C**-C(O)-N], 112.61, 120.48, 122.48, 123.37, 127.06, 135.27 (CH-aromatic carbons), 129.83 (quaternary aromatic carbon), 148.83 [**C**-NH-C(O)], 149.79 [N-**C**(O)-N], 154.34 (**C**-OCH_3), 158.34 [**C**(O)N]; MS (*m/e*) 268 $[M]^+$; Anal. Cal. for $C_{15}H_{12}N_2O_3$; C, 67.16, H, 4.51, N, 10.44, found; C, 67.02, H, 4.45, N, 10.45.

3-(*p*-Methoxyphenyl)-6-methyl-2,4-(1*H*,3*H*)-quinazolinediones (5.13f)[1] (R = CH_3, R′= *p*-$CH_3OC_6H_4$); mp >300 °C (lit[11j] mp = >300 °C); IR 3276, 1736, 1636 cm^{-1}; ^{1}H ($CDCl_3$+DMSO–d_6, 200 MHz) δ 2.30 (s, 3H, C$H_3C_6H_3$), 3.70 (s, 3H, CH_3O-C_6H_4), 6.78 (d, 2H, J = 9.0 Hz), 7.15 (d, 2H, J = 8.4 Hz), 7.36-7.37 (m, 1H), 7.55-7.68 (m, 3H), 9.58 (s, br, 1H, NH); ^{13}C ($CDCl_3$+DMSO–d_6, 75 MHz) δ 19.82 (**C**$H_3C_6H_3$), 54.42 (**C**H_3O-C_6H_4), 112.48 [**C**-C(O)-N-], 120.38, 123.60, 126.78, 136.90 (CH-aromatic carbons), 130.30 (**C**-CH_3), 132.54 (**C**-N), 146.97 [**C**-NH-C(O)], 149.76 [N-**C**(O)-N], 154.62 [**C**-OCH_3), 158.87 [**C**(O)N]; MS (*m/e*) 282 $[M]^+$.

3-Phenyl-2,4-(1*H*,3*H*)-quinazolinediones (5.13h)[11i, 11j, 13, 18, 20] (R = H, R′= C_6H_5); mp 279-280 °C (lit[11j] mp = 279-280 °C); IR 3283, 1740, 1644 cm^{-1}; ^{1}H ($CDCl_3$, 200 MHz) δ

7.00-7.98 (m, 9H), 11.57 (s, br, 1H, NH); ^{13}C ($CDCl_3$, 75 MHz) δ 114.08 [C-C(O)-N-], 119.84, 124.18, 124.77, 125.12, 128.79, 129.16 (CH-aromatic carbons), 136.53 (C-N), 136.84 (CH), 149.43 [C-NH-C(O)], 150.15 [N-C(O)-N], 159.52 [C(O)N]; MS (*m/e*) 238 $[M]^+$.

6-Methyl-3-phenyl-2,4-(1*H*,3*H*)-quinazolinediones (5.13i) (R = CH_3, R″= C_6H_5); mp >300 °C (lit[11j] mp = >300 °C); IR 3282, 1741, 1644 cm^{-1}; ^1H ($CDCl_3$, 200 MHz) δ 2.39 (s, 3H, $CH_3C_6H_3$), 7.07-7.87 (m, 8H), 11.57 (s, br, 1H, NH); ^{13}C ($CDCl_3$, 75 MHz) δ 20.91 [$CH_3C_6H_3$], 113.79 [C-C(O)-N-], 119.68, 124.02, 124.94, 128.25, 129.15, 134.79, 138.18 [CH-aromatic carbons], 136.98 (quaternary aromatic carbons), 147.16 [C-NH-C(O)], 149.68 [N-C(O)-N], 159.63 [C(O)N]; MS (*m/e*) 253 $[M]^+$.

3-(*p*-Tolyl)-2,4-(1*H*,3*H*)-quinazolinediones (5.13j) (R = H, R″= *p*-CH_3-C_6H_4); mp 264-266 °C (lit[11j] mp = 264-266 °C); IR 3175, 1723, 1675 cm^{-1}; ^1H ($CDCl_3$+DMSO–d_6, 200 MHz) δ 2.36 (s, 3H, *p*-CH_3-C_6H_4), 7.15-7.37 (m, 6H), 7.68-7.75 (m, 1H), 7.95-8.00 (m, 1H), 11.50 (s, br, 1H, NH); ^{13}C ($CDCl_3$+DMSO–d_6, 75 MHz) δ 19.52 (*p*-CH_3-C_6H_4), 113.08 [C-C(O)-N-], 114.83, 123.18, 126.27, 126.54, 128.19, 134.74 (CH-aromatic carbons), 130.67, 137.07 (quaternary aromatic carbons), 146.20 [C-NH-C(O)], 151.12 [N-C(O)-N], 159.06 [C(O)N]; MS (*m/e*) 253 $[M]^+$.

6-Methyl-3-(*p*-tolyl)-2,4-(1*H*,3*H*)-quinazolinediones (5.13k) (R = CH_3, R″= *p*-CH_3-C_6H_4); mp 286-288 °C (lit[11j] mp = 286-288 °C); IR 3200, 1732, 1647 cm^{-1}; ^1H ($CDCl_3$+DMSO–d_6, 200 MHz) δ 2.30 (s, 3H, $CH_3C_6H_3$), 2.36 (s, 3H, *p*-$CH_3C_6H_4$), 7.03-7.08 (m, 3H), 7.19-7.23 (m, 2H), 7.31-7.36 (m, 1H), 7.70 (s, 1H), 11.31 (s, br, 1H, NH); ^{13}C ($CDCl_3$+DMSO–d_6, 75 MHz) δ 19.29 [$CH_3C_6H_3$], 19.52 [*p*-$CH_3C_6H_4$], 112.91 [C-C(O)-N-], 114.08, 125.97, 127.11, 128.26, 130.63, 134.73 (CH-aromatic carbons),

131.59 (quaternary aromatic carbons), 136.52 [C-NH-C(O)], 149.38 [N-C(O)-N], 161.32 [C(O)N]; MS (*m/e*)266 $[M]^+$.

5.4.4 General Procedure for the Palladium-Catalyzed Cyclocarbonylation of *o*-Iodoanilines (5.11) with Carbodiimides (5.14a-f) or with ketenimines (5.20a-f).

The cyclocarbonylation reactions of *o*-iodoanilines with carbodiimides or ketenimines were performed in the same manner as that for isocyanates except for the use of one equivalent of a carbodiimide or ketenimine in THF. Two mol% of $Pd(OAc)_2$-ddpf catalyst system and K_2CO_3 were used for all reactions. The reaction mixtures were stirred in an oil bath at 100 °C for 24 h, cooled and filtered. The filtrate was concentrated and then purified by silica gel column chromatography using 1:1 mixture of ethyl acetate and pentane as the eluant.

2-(*p*-Chlorophenylamino)-3-(*p*-Chlorophenyl)-4(3*H*)-quinazolinone (5.15a). (R = H, R″= *p*-ClC_6H_4); mp 175-177 °C; IR 1684, 1607 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 5.89 (s, br 1H, N*H*), 7.22-7.66 (m, 11H, C*H*-aromatic), 8.15 (dd, 1H, *J* = 7.9, and 1.5 Hz, C*H*-aromatic); ^{13}C ($CDCl_3$ 75 MHz) δ 118.24 (C(C=O)N), 122.18, 124.05, 125.64, 127.18, 128.87, 130.45, 131.15, 134.96, (CH-aromatic), 129.18, 132.74, 136.20, 136.58 (quaternary aromatic carbons), 145.67 (C=N), 148.10 (C–N=C), 162.24 ((C=O)N); MS (*m/e*) 380 $[M-2]^+$, 382 $[M]^+$; Anal. Cal. for $C_{20}H_{13}Cl_2N_3O$; C, 62.84, H, 3.43; N, 10.99; Found C, 63.00, H, 3.45; N, 10.98.

2-(*p*-Chlorophenylamino)-3-(*p*-chlorophenyl)-6-chloro-4(3*H*)-quinazolinone (5.15b). (R = Cl, R″= *p*-ClC_6H_4); mp 181-182 °C; IR 1687, 1606 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 5.91 (s, br, 1H, N*H*), 7.23-7.59 (m, 10H, C*H*-aromatic), 8.01–8.02 (m, 1H, C*H*-aromatic); ^{13}C ($CDCl_3$ 75 MHz) δ 119.09 [C(C=O)N], 122.41, 126.33, 127.23, 128.87, 130.35, 131.20, 135.21 (CH-aromatic carbons), 129.42, 132.39, 135.96, 136.73 (quaternary aromatic carbons), 145.94 (C=N), 146.69 (C–N=C), 161.18 [(C=O)N]; MS (*m/e*) 416 $[M]^+$; Anal. Cal. for $C_{20}H_{12}Cl_3N_2O$; C, 57.65, H, 2.90, N, 10.08 found; C, 57.36, H, 2.99, N, 9.98.

2-(*p*-Chlorophenylamino)-3-(*p*-chlorophenyl)-6-methyl-4(3*H*)-quinazolinone (5.15c). (R = CH_3, R″= *p*-ClC_6H_4); mp 203-205 °C; IR 1680, 1608 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 2.40 (s, 3H, $CH_3C_6H_3$), 5.85 (s, br, 1H, N*H*), 7.22-7.58 (m, 10H), 7.88-7.89 (m, 1H); ^{13}C ($CDCl_3$ 75 MHz) δ 20.96 ($CH_3C_6H_3$), 117.84 (C(C=O)N), 121.96, 126.47, 128.82, 130.41, 130.97, 136.33 (CH-aromatic carbons), 125.36, 128.74, 132.84, 133.84 (quaternary aromatic carbons), 145.04 [C=N], 145.84 [C–N=C], 162.12 [(C=O)N]; MS (*m/e*) 394 $[M-2]^+$, 396 $[M]^+$; Anal. Cal. for $C_{21}H_{15}Cl_2N_2O$; C, 63.65, H, 3.82, N, 10.60 found C, 63.44, H, 3.82, N, 10.58.

2-(*p*-Chlorophenylamino)-3-(*p*-chlorophenyl)-6-hydroxy-4(3*H*)-quinazolinone (5.15d). (R = OH, R″= *p*-ClC_6H_4); mp 258-260 °C; IR 3306, 1674, 1608 cm^{-1}; ^1H ($CDCl_3$ +Acetone–d_6 200 MHz) δ 6.92–7.58 (m, 13H, CH-aromatic protons); ^{13}C ($CDCl_3$ +Acetone–d_6 75 MHz) δ 109.07 [C(OH)-CH-C], 117.98 [C(C=O)N], 121.12, 122.09, 123.16, 125.87, 127.13, 127.64, 129.32, 130.21 (CH-aromatic carbons), 124.21, 126.71, 132.84, 134.12, 136.89 (quaternary aromatic carbons), 140.90 [C=N], 143.08 [C–N=C],

152.74 [C-OH], 160.85 [(C=O)N]; MS (*m/e*) 397 $[M]^+$; Anal. Cal. for $C_{20}H_{13}Cl_2N_3O_2$: C, 60.32, H, 3.29, N, 10.55; found C, 60.22, H, 3.26, N, 10.55.

2-(Phenylamino)-3-(phenyl)-4(3*H*)-quinazolinone (5.15e). (R = H, R″= C_6H_5); mp 155-157 °C; IR 1683, 1609 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 5.96 (s, br, 1H, NH), 7.07-7.69 (m, 13H), 8.18 (dd, 1H, J = 7.9, and 1.6 Hz); ^{13}C ($CDCl_3$ 75 MHz) δ 118.38 [C(C=O)N], 120.78, 123.65, 123.98, 125.56, 127.14, 128.84, 128.99, 130.22, 130.79, 134.67 (CH-aromatic carbons), 134.50, 137.76 (quaternary aromatic carbons), 146.27 [C=N], 148.41 [C–N=C], 162.43 [(C=O)N]; MS (*m/e*) 312 $[M-1]^+$, 313 $[M]^+$; Anal. Cal. for $C_{20}H_{13}Cl_2N_3O$; C, 62.84, H, 3.43; N, 10.99; found C, 63.00, H, 3.45; N, 10.98.

6-Chloro-2-(phenylamino)-3-phenyl-4(3*H*)-quinazolinone (5.15f). (R = Cl, R″= C_6H_5); mp 184-185 °C; IR 1686, 1606 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 5.98 (s, br, 1H, NH), 7.08-7.67 (m, 12H), 8.10 (d, 1H, J = 2.4 Hz); ^{13}C ($CDCl_3$ 75 MHz) δ 110.08 [C(C=O)N], 121.00, 124.29, 126.36, 127.19, 128.89, 130.44, 130.92, 135.00 (CH-aromatic carbons), 128.99, 134.18, 137.47 (quaternary aromatic carbons), 146.55 [C=N], 147.02 [C–N=C], 161.42 [(C=O)N]; MS (*m/e*) 346 $[M-1]^+$, 347 $[M]^+$; Anal. Cal. for $C_{20}H_{14}ClN_3O$; C, 69.07, H, 4.06, N, 12.08; Found C, 68.75, H, 4.11, N, 12.02.

6-Hydroxy-2-(phenylamino)-3-phenyl-4(3*H*)-quinazolinone (5.15g). (R = OH, R″= C_6H_5); mp 290-292 °C; IR 3309, 1686, 1666 cm^{-1}; ^1H ($CDCl_3$+DMSO–d_6 200 MHz) δ 6.28 (s, br, 1H, NH), 6.87-7.73 (m, 13H), 9.25 (s, br 1H, OH); ^{13}C ($CDCl_3$+DMSO–d_6 75 MHz) δ 108.85 [C(OH)-CH-C], 117.59 [C(C=O)N], 119.82, 122.04, 123.17, 123.96, 125.49, 127.89, 128.55, 129.77 (CH-aromatic), 133.70, 137.30 (quaternary aromatic carbons), 140.33 [C=N], 143.50 [C–N=C], 152.64 [C-OH], 160.74 [(C=O)N]; MS (*m/e*) 328 $[M-1]^+$, 329 $[M]^+$; HRMS. Cal. for $C_{20}H_{15}N_3O_2$; 329.1164 found 329.1154.

6-Cyano-2-(phenylamino)-3-phenyl-4(3*H*)-quinazolinone (5.15h). (R = CN, R″= C_6H_5); mp 204-205 °C; IR 3337, 2224, 1686, 1661 cm^{-1}; ^1H ($CDCl_3$+DMSO–d_6 200 MHz) δ 6.79-8.29 (m, 14H); ^{13}C ($CDCl_3$+DMSO–d_6 75 MHz) δ 117.67 [**C**(C=O)N], 121.22, 121.99, 124.05 (**C**-CN), 125.79, 127.75, 127.91, 128.06, 129.51, 129.92, 131.49, 135.40, 138.76 (quaternary aromatic carbons), 148.37 [**C**=N], 151.11 [**C**–N=C], 152.18 [C≡N], 160.12 [(**C**=O)N]; MS (*m/e*) 337 $[M-1]^+$, 338 $[M]^+$; Anal. Cald. for $C_{21}H_{14}N_4O$: C, 74.54, H, 4.17, N, 16.55; found: C, 74.40, H, 4.23, N, 16.29.

2-(*p*-Bromophenylamino)-3-(*p*-bromohenyl)-4(3*H*)-quinazolinone (5.15i). (R = H, R″= *p*-BrC_6H_4); mp 141-142 °C; IR 1680, 1603 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 5.88 (s, br, 1H, NH), 7.21-7.75 (m, 11H), 8.08-8.13 (m, 1H); ^{13}C ($CDCl_3$ 75 MHz) δ 116.76 (**C**-Br), 118.99 [**C**(C=O)N], 122.59, 124.09 (CH-aromatic carbons), 124.66 (**C**-Br), 125.62 (N-**C**), 127.19, 130.75, 131.80, 133.28, 134.10, 135.00 (CH-aromatic carbons), 136.78 (N-**C**), 145.55 [**C**=N], 148.04 [**C**–N=C], 162.15 [(**C**=O)N]; MS (*m/e*) 470 $[M-1]^+$, 471 $[M]^+$; Anal. Cal. for $C_{20}H_{13}Br_2N_3O$; 468.9825 found 468.9842.

1-Methyl-*N*, 3-di(*p*-chlorophenyl)-4(3*H*)-quinazolinone-2-imine (5.15j). (R = H, R″= *p*-ClC_6H_4); mp 184-186 °C; IR 1692, 1628 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 3.50 (s, 3H, N-CH_3), 6.31-6.39 (m, 2H), 6.90-7.00 (m, 4H), 7.12-7.24 (m, 4H), 7.61-7.66 (m, 1H), 8,10-8.15 (m, 1H); ^{13}C ($CDCl_3$ 75 MHz) δ 34.84 [N-**C**H_3], 113.63 [**C**(C=O)N], 115.28, 122.00., 122.36, 128.30, 128.85, 129.09, 130.72, 135.52 (CH-aromatic carbons), 126.29, 129.78, 129.95, 133.91 (quaternary aromatic carbons), 142.82 (**C**=N), 145.74 [C-N(CH_3)], 161.94 [(**C**=O)N]; MS (*m/e*) 395 $[M-1]^+$, 396 $[M]^+$; Anal. Cal. for $C_{21}H_{15}Cl_2N_2O$; C, 63.65, H, 3.82, N, 10.60 found C, 63.38, H, 3.81, N, 10.63

2-(1-Ethoxycarbonylethyl)-3-phenyl-4(3*H*)-quinazolinone (5.21a). (R = H, R_1= C_6H_5, R_2= CH_3, R_3 = COOEt); mp 75-76 °C; IR 1735, 1686 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 1.15 (t, 3H, *J* = 7.1 Hz, CH_3CH_2), 1.50 (d, 3H, *J* = 7.1 Hz, $CH(CH_3)$), 3.58 (q, 1H, *J* = 14.1 and 7.1 Hz, $CH(CH_3)$), 4.08 (q, 2H, *J* = 14.4 and 7.1 Hz, CH_3CH_2), 7.20–7.80 (m, 8H), 8.23-8.28 (m, 1H); ^{13}C ($CDCl_3$ 75 MHz) δ 13.95 [CH_3CH_2], 15.70 [$CH(CH_3)$], 44.45 [$CH(CH_3)$], 61.31 [CH_3CH_2], 120.92 [C(C=O)N], 126.87, 126.95, 127.51, 128.17, 128.98, 129.42, 129.91, 134.41 (CH-aromatic carbons), 136.85 (quaternary aromatic carbons), 147.26 [N=C], 154.61 [C-N=C], 162.33 [C(=O)N], 171.05 [C(=O)O]; MS (*m/e*) 322 $[M]^+$; Anal. Cal. for $C_{19}H_{18}N_2O_3$; C, 70.79, H, 5.63, N, 8.69; Found C, 70.58, H, 5.68, N, 8.65.

6-Chloro-2-(1-ethoxycarbonylethyl)-3-phenyl-4(3*H*)-quinazolinone (5.21b). (R = Cl, R_1= C_6H_5, R_2= CH_3, R_3 = $COOCH_2CH_3$); mp 99-101 °C; IR 1737, 1689, 1605 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 1.14 (t, 3H, *J* = 7.1 Hz, CH_3CH_2), 1.50 (d, 3H, *J* = 7.0 Hz, $CH(CH_3)$), 3.55 (q, 1H, *J* = 14.1 and 7.0 Hz, $CH(CH_3)$), 4.05 (q, 2H, *J* = 14.4 and 7.1 Hz, CH_3CH_2), 7.19–7.32 (m, 3H), 7.44-7.70 (m, 4H), 8.18-8.22 (m, 1H); ^{13}C ($CDCl_3$ 75 MHz) δ 13.98 [CH_3CH_2], 15.70 [$CH(CH_3)$], 44.87 [$CH(CH_3)$], 61.44 [CH_3CH_2], 122.08 [C(C=O)N], 126.23, 128.13, 128.95, 129.27, 129.66, 129.97, 130.06, 136.62 (CH-aromatic carbons), 132.76, 134.86 (quaternary aromatic carbons), 145.84 [N=C], 155.03 [C-N=C], 161.36 [C(=O)N], 170.96 [C(=O)O]; MS (*m/e*) 356 $[M]^+$; Anal. Cal. for $C_{19}H_{17}ClN_2O_3$; C, 63.96, H, 4.80, N, 7.85 found C, 64.01, H, 4.71, N, 7.88.

2-(1-Ethoxycarbonylethyl)-6-methyl-3-phenyl-4(3*H*)-quinazolinone (5.21c). (R = CH_3, R_1= C_6H_5, R_2= CH_3, R_3 = $COOCH_2CH_3$); mp 104-105 °C; IR 1736, 1685 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 1.14 (t, 3H, *J* = 7.1 Hz, CH_3CH_2), 1.48 (d, 3H, *J* = 7.1 Hz,

$CH(CH_3)$), 2.46 (s, 3H, $CH_3C_6H_3$), 3.55 (q, 1H, J = 14.2 and 7.0 Hz, $CH(CH_3)$), 4.02 (q, 2H, J = 14.2 and 7.0 Hz, CH_3CH_2 and NH), 7.18–7.35 (m, 2H), 7.46-7.65 (m, 5H), 8.03-8.05(m, 1H); ^{13}C ($CDCl_3$ 75 MHz) δ 13.93 [CH_3CH_2], 15.69 [$CH(CH_3)$], 21.26 [$CH_3C_6H_3$], 44.70 [$CH(CH_3)$], 61.25 [CH_3CH_2], 120.70 [C(C=O)N], 126.23, 127.33, 128.22, 129.03, 129.34, 129.79, 129.87 (CH-aromatic carbons), 135.83, 137.10 (quaternary aromatic carbons), 145.27 [N=C], 153.69 [C-N=C], 162.34 [C(=O)N], 171.15 [C(=O)O]; MS (*m/e*) 336 $[M]^+$; Anal. Cal. for $C_{20}H_{20}N_2O_3$; C, 71.41, H, 5.99, N, 8.33 found C, 71.41, H, 5.97, N, 8.45

2-(1-Ethoxycarbonylethyl)-6-hydroxy-3-phenyl-4(3*H*)-quinazolinone (5.21d). (R = OH, R_1= C_6H_5, R_2= CH_3, R_3 = $COOCH_2CH_3$); mp 135-137 °C; IR 1731, 1659, 1605 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 1.13 (t, 3H, J = 7.1 Hz, CH_3CH_2), 1.18 (d, 3H, J = 7.1 Hz, $CH(CH_3)$), 3.55 (q, 1H, J = 14.2 and 7.1 Hz, $CH(CH_3)$), 4.06 (q, 2H, J = 14.2 and 7.1 Hz, CH_3CH_2), 7.19–7.33 (m, 3H), 7.49–7.60 (m, 4H), 7.72 (s, br, 1H, OH), 7.88 (d, 1H, J = 2.7 Hz); ^{13}C ($CDCl_3$ 75 MHz) δ 13.97 [CH_3CH_2], 15.79 [$CH(CH_3)$], 44.64 [$CH(CH_3)$], 61.45 [CH_3CH_2], 110.49 [C(OH)-CH-C-C(O)], 121.39 [C(C=O)N], 124.55, 128.14, 128.97, 128.21, 129.58, 129.93, 129.99 (CH-aromatic carbons), 136.82 (quaternary aromatic carbons), 141.25 [N=C], 151.54 [C-N=C], 156.07 [C(-OH)], 162.84 [C(=O)N], 171.45 [C(=O)O]; MS (*m/e*) 338 $[M]^+$; Anal. Cal. for $C_{19}H_{18}N_2O_4$; C, 67.44, H, 5.36, N, 8.28 found C, 67.44, H, 5.32, N, 8.23.

6-Cyano-2-(1-ethoxycarbonylethyl)-3-phenyl-4(3*H*)-quinazolinone (5.21e). (R = CN, R_1= C_6H_5, R_2= CH_3, R_3 = $COOCH_2CH_3$); mp 115-117 °C; IR 2986, 2230, 1732, 16931, 1605 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 1.15 (t, 3H, J = 7.1 Hz, CH_3CH_2), 1.50 (d, 3H, J = 7.1 Hz, $CH(CH_3)$), 3.59 (q, 1H, J = 14.0 and 7.1 Hz, $CH(CH_3)$), 4.05 (dd, 2H, J = 14.0 and

7.1 Hz, CH_3CH_2), 7.18-7.27 (m, 2H), 7.54-7.62 (m, 3H), 7.89-7.96 (m, 2H), 8.54-8.55 (m, 1H); ^{13}C ($CDCl_3$ 75 MHz) δ 13.94 [CH_3CH_2], 15.63 [$CH(CH_3)$], 45.09 [$CH(CH_3)$], 61.58 [CH_3CH_2], 110.39 [C(CN)-CH-C-C(O)], 117.96 [C(C=O)N], 121.49 [C-CN], 127.90, 128.73, 128.87, 129.92, 130.09, 130.17, 132.39, 136.34 (CH-aromatic carbons), 136.09 (quaternary aromatic carbons), 149.85 [C-N=C], 157.94 [C≡N], 160.85 [C(=O)N], 170.56 [C(=O)O]; MS (*m/e*) 347 $[M]^+$; Anal. Cal. for $C_{20}H_{17}N_3O_3$; C, 69.15, H, 4.93, N, 12.10 found C, 69.19, H, 4.92, N, 12.20.

2-(1-Ethoxycarbonylethyl)-3-n-butyl-4(*3H*)-quinazolinone (5.21f). (R = H, R_1= C_4H_9, R_2= CH_3, R_3 = $COOCH_2CH_3$); Oily liquid; IR 1744, 1681 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 0.96 (t, 3H, *J* = 7.2 Hz, $CH_3CH_2CH_2CH_2$), 1.19 (t, 3H, *J* = 7.1 Hz, CH_3CH_2O), 1.45 (q, 2H, *J* = 14.8 and 7.2 Hz, $CH_3CH_2CH_2CH_2$), 1.61-1.17 (m, 5H, $CH_3CH_2CH_2CH_2$ and $CH(CH_3)$), 3.95–4.23 (m, 5H, $CH_3CH_2CH_2CH_2$ and CH_3CH_2O and $CH(CH_3)$), 7.35-7.45 (m, 1H), 7.59-7.68 (m, 2H), 8.20-8.24 (m, 1H); ^{13}C ($CDCl_3$ 75 MHz) δ 11.69 [$CH_3CH_2CH_2CH_2$], 12.03 [CH_3CH_2O], 14.09 [$CH(CH_3)$], 18.20 [$CH_3CH_2CH_2CH_2$], 29.13 [$CH_3CH_2CH_2CH_2$], 41.76 [CH_2N], 42.24 [$CH(CH_3)$], 59.56 [CH_3CH_2O], 118.64 [C(C=O)N], 124.63, 124.66, 125.31, 131.99 [CH-aromatic carbons], 145.06 [C-N=C], 152.80 [C-N=C], 160.13 [C(=O)N], 168.94 [C(=O)O]; MS (*m/e*) 302 $[M]^+$; HRMS Cald for $C_{17}H_{22}N_2O_3$; 302.1630, found 302.1626.

2-(1-Ethoxycarbonylethyl)-3-n-butyl-6-methyl-4(*3H*)-quinazolinone (5.21g). (R = CH_3, R_1= C_4H_9, R_2= CH_3, R_3 = $COOCH_2CH_3$); mp 54-55 °C; IR 1744, 1681, 1592 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 0.95 (t, 3H, *J* = 7.2 Hz, $CH_3CH_2CH_2CH_2$), 1.17 (t, 3H, *J* = 7.1 Hz, CH_3CH_2O), 1.39-1.52 (m, 2H, $CH_3CH_2CH_2CH_2$), 1.59-1.70 (m, 5H, $CH_3CH_2CH_2CH_2$ and $CH(CH_3)$), 2.42 (s, 3H, $CH_3C_6H_3$), 3.92–4.21 (m, 5H,

$CH_3CH_2CH_2CH_2$ and CH_3CH_2O and $CH(CH_3)$), 7.48-7.50 (m, 2H), 8.00 (s, 1H); ^{13}C ($CDCl_3$ 75 MHz) δ 13.64 [$CH_3CH_2CH_2CH_2$], 13.96 [CH_3CH_2O], 16.02 [$CH(CH_3)$], 20.13 [$CH_3C_6H_3$], 21.23 [$CH_3CH_2CH_2CH_2$], 31.09 [$CH_3CH_2CH_2CH_2$], 43.63 [CH_2N], 44.11 [$CH(CH_3)$], 61.45 [CH_3CH_2O], 120.29 [C(C=O)N], 125.93, 127.07, 135.40 [CH-aromatic carbons], 136.73 [C-CH_3], 145.03 [C-N=C], 153.82 [C-N=C], 162.07 [C(=O)N], 170.99 [C(=O)O]; MS (*m/e*) 316 $[M]^+$; Anal. Cal. for $C_{18}H_{24}N_2O_3$; C, 68.33, H, 7.65, N, 8.85 found C, 68.47, H, 7.66, N, 8.97.

2-(1′-Benzoylethyl)-3-phenyl-4(*3H*)-quinazolinone (5.21h). (R = H, $R_1 = C_6H_5$, $R_2 = CH_3$, $R_3 = COC_6H_5$); mp 181-183 °C; IR 1681, 1606, 1592 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 1.58 (d, 3H, J = 7.0 Hz, $CH(CH_3)$), 4.55 (q, 1H, J = 14.1 and 7.0 Hz, $CH(CH_3)$), 7.06–7.60 (m, 11H), 7.75-7.80 (m, 2H), 8.23-8.25 (m, 1H); ^{13}C ($CDCl_3$ 75 MHz) δ 16.07 [$CH(CH_3)$], 47.33 [$CH(CH_3)$], 121.07 [C(C=O)N], 126.89, 127.03, 127.78, 127.82, 128.39, 128.42, 129.29, 129.83, 130.01, 133.06, 134.39 [CH-aromatic carbons], 135.56, 136.78 [quaternary aromatic carbons], 147.26 [C-N=C], 154.65 [C-N=C], 162.53 [C(=O)N], 198.06 [C(=O)Ph]; MS (*m/e*) 326 $[M-28]^+$, 354 $[M]^+$; Anal. Cal. for $C_{23}H_{18}N_2O_2$; C, 77.95, H, 5.12, N, 7.90 found C, 77.94, H, 4.96, N, 7.94.

2-(1′-Benzoylethyl)-6-methyl-3-phenyl-4(*3H*)-quinazolinone (5.21i). (R = CH_3, $R_1 = C_6H_5$, $R_2 = CH_3$, $R_3 = COC_6H_5$); mp 205-207 °C; IR 1681, 1606, 1590 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 1.55 (d, 3H, J = 7.1 Hz, $CH(CH_3)$), 2.46 (s, 3H, $CH_3C_6H_3$), 4.55 (q, 1H, J = 14.1 and 7.1 Hz, $CH(CH_3)$), 7.08–7.67 (m, 12H), 8.02-8.03 (m, 1H); ^{13}C ($CDCl_3$ 75 MHz) δ 16.03 [$CH(CH_3)$], 21.27 [$CH_3C_6H_3$], 47.21 [$CH(CH_3)$], 120.74 [C(C=O)N], 126.22, 127.55, 127.77, 128.36, 128.41, 129.17, 129.77, 129.79, 129.93, 132.97, 135.77 [CH-aromatic carbons], 135.56, 136.88, 137.15 [quaternary aromatic carbons], 145.25

[C-N=C], 153.74 [C-N=C], 162.49 [C(=O)N], 198.10 [C(=O)Ph]; MS (*m/e*) 366 $[M-2]^+$, 368 $[M]^+$; Anal. Cal. for $C_{24}H_{20}N_2O_2$; C, 78.24, H, 5.47, N, 7.60 found C, 78.21, H, 5.39, N, 7.54.

2-(Diethoxycarbonylmethyl)-3-phenyl-4(*3H*)-quinazolinone (5.21j). (R = H, R_1 = C_6H_5, $R_2 = R_3 = COOC_2H_5$); mp 93-95 °C; IR 1755, 1738, 1692, 1607 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 1.22 [t, 6H, *J* = 7.1 Hz, 2(CH_3CH_2O)], 4.13-4.53 [m, 4H, 2(CH_3CH_2O)], 4.53 (s, 1H, C*H*), 7.22-7.27 (m, 2H), 7.48-7.53 (m, 4H), 7.70-7.73 (m, 2H), 8.24-8.29 (m, 1H); ^{13}C ($CDCl_3$ 75 MHz) δ 14.20 [$COOCH_2CH_3$], 59.04 [CH], 62.65 [$COOCH_2CH_3$], 121.58 [C(C=O)N], 127.25, 127.86, 128.85, 129.05, 130.09, 130.35, 134.81 (CH-aromatic carbons), 136.57 [quaternary aromatic carbon], 147.22 [C-N=C], 149.28 [C-N=C], 162.34 [C(=O)N], 165.33 [C(O)OEt]; MS (*m/e*) 380 $[M]^+$; Anal. Cal. for $C_{21}H_{20}N_2O_5$; C, 66.31, H, 5.30, N, 7.36 found C, 66.53, H, 5.39, N, 7.36.

6-Chloro-2-(diethoxycarbonylmethyl)-3-phenyl-4(*3H*)-quinazolinone (5.20k). (R = Cl, $R_1 = C_6H_5$, $R_2 = R_3 = COOC_2H_5$); mp 112-113 °C; IR 1756, 1739, 1696, 1635 cm^{-1}; ^1H ($CDCl_3$ 200 MHz) δ 1.21 (t, 6H, *J* =7.1 Hz, 2(CH_3CH_2O), 4.13-4.24 (m, 4H, 2(CH_3CH_2O)), 4.51 (s, 1H, C*H*), 7.21-7.25 (m, 2H), 7.50-7.53 (m, 2H), 7.67-7.68 (m, 2H), 8.20-8.22 (m, 1H); ^{13}C ($CDCl_3$ 75 MHz) δ 13.86 [$COOCH_2CH_3$], 58.64 [CH], 62.41 [$COOCH_2CH_3$], 122.31 [C(C=O)N], 126.26, 128.56, 129.55, 129.44, 130.11, 134.91 [CH-aromatic carbons], 133.38, 135.88 [quaternary aromatic carbons], 145.34 [C-N=C], 149.35 [C-N=C], 160.96 [C(=O)N], 164.86 [C(O)OEt]; MS (*m/e*) 414 $[M]^+$; Anal. Cal. for $C_{21}H_{19}ClN_2O_5$; C, 60.80, H, 4.62, N, 6.75 found C, 60.77, H, 4.48, N, 6.71.

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24) As reported in Chapter 4, using 2 mole equivalents of isocyanate in the reaction with 1 mole of *o*-iodophenol gave a better product yield than performing the reaction using 1:1 ratio. Dimer or trimer formation of the isocyanate may occur in the presence of base. See (a) Hofmann, A. W. *Ber.* **1860**, *3*, 761. (b) Snape, H. L. *J. Chem. Soc.* **1886**, *49*, 254. (c) Hofmann, A. W. *Ber.* **1885**, *18*, 764.

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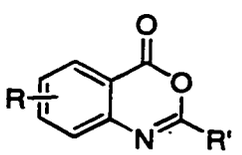
Chapter 6

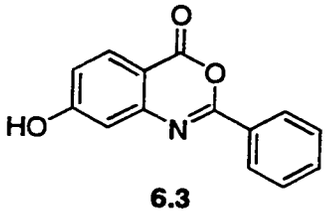
A Simple Synthesis of 2-Substituted-4*H*-3,1-benzoxazin–4-ones by Palladium-Catalyzed Cyclocarbonylation of *o*-Iodoanilines with Acid Chlorides.

6.1 Introduction

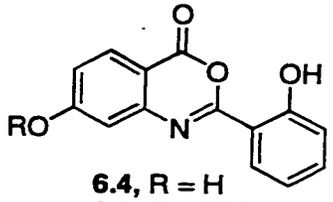
4*H*-3,1-Benzoxazin-4-ones (acylanthranils, **6.1**) are a class of fused heterocycles of considerable interest owing to their biological activity. Indeed some of these compounds act as chymotrypsin inactivators,[1] as well as inhibitors of human leukocyte elastase,[2,3] serine protease[4] while 2-aryl derivatives have the ability to lower the concentration of plasma cholesterol and triglycerides.[5] Compounds possessing this ring system are found in nature. For example, dianthalexin **6.2** and hydroxylated analogs **6.3** and **6.4** are isolated from infected carnations.[6,7] Moreover, 2-substituted-4*H*-3,1-benzoxazin-4-ones were reported to be used as precursors for the preparation of pharmaceutically active compounds such as antimicrobial agents (*N*-substituted-quinazolin-4-one derivatives)[8-11] and analgesics (4-hydroxy-3-quinoline-carboxamides).[12]



4*H*-3,1-Benzoxazin-4-ones, **6.1**



6.3

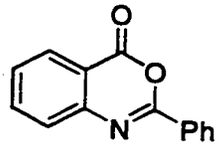


6.4, R = H
6.5, R = CH_3

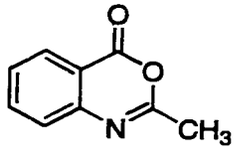
6.1.1 Synthesis of 4*H*-3,1-benzoxazin-4-ones.

6.1.1.1 Synthesis of 4H-3,1-benzoxazin-4-ones by conventional methods.

The first phenyl derivative **6.1a** was first synthesized in 1883[13] and the methyl analog **6.1b** seventeen years later.[14]



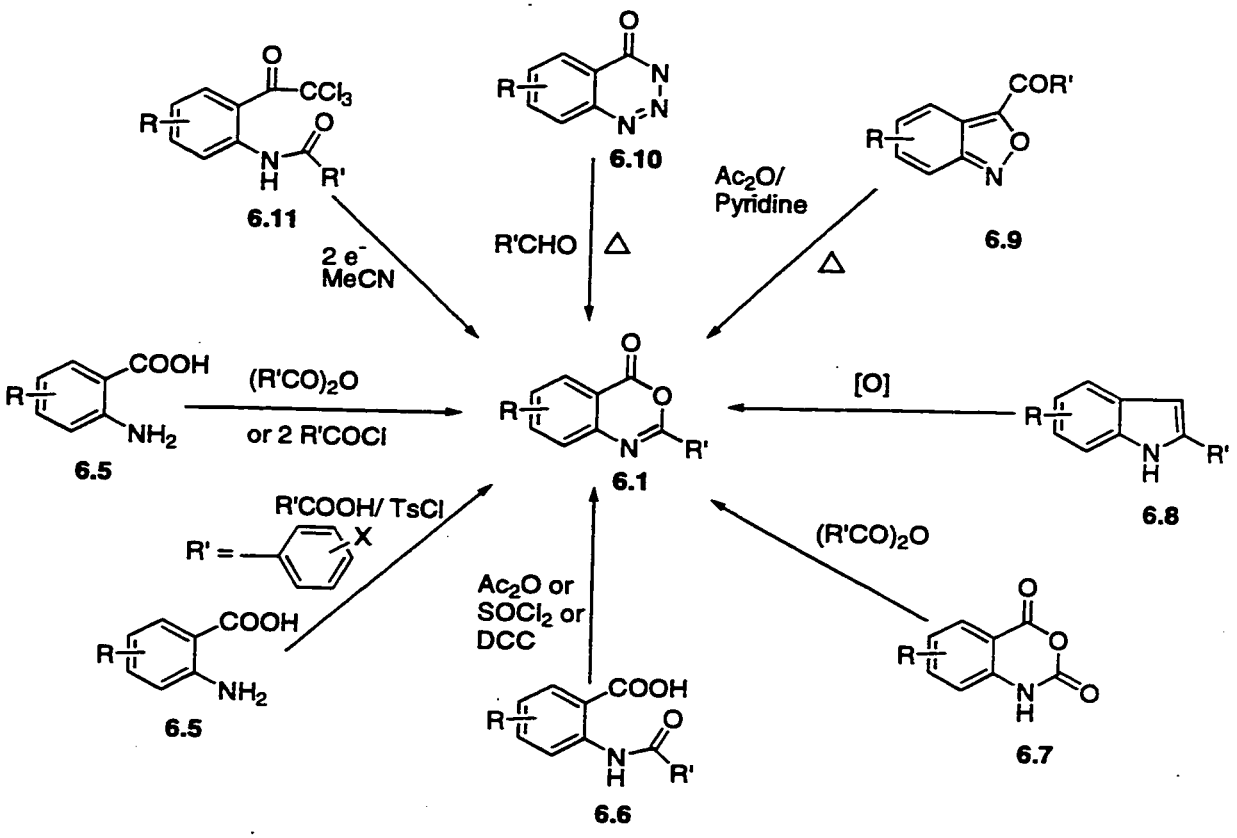
2-Phenyl-4*H*-3,1-benzoxazin-4-ones, **6.1a**



2-Methyl-4*H*-3,1-benzoxazin-4-ones, **6.1b**

An extensive study of the synthesis of 4*H*-3,1-benzoxazin-4-ones was conducted in the past decade. As a result several methods have been reported for the preparation of 2-substituted-*4H*-3,1-benzoxazin-4-ones (Scheme 6–1).[15] The most common pathways involve the use of anthranilic acid or its derivatives (**6.5**) as a starting material.[16-18] 2-

Substituted derivatives of **6.1** are prepared by heating **6.5** with an appropriate anhydride or 2 equivalents of an acid chloride. The reaction of **6.5** with *ortho* or *para*- substituted benzoic acid in the presence of tosyl chloride affords 2-aromatic substituted **6.1** in 33-62% yield.



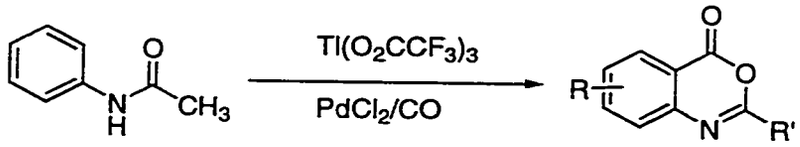
Scheme 6-1 Conventional methods for the preparation of 4*H*-3,1-Benzoxazin-4-ones.

The cyclodehydration reaction of *N*-acylanthranilic acids (**6.6**) with acetic anhydride gave **6.1** in good yield.[19-22] A wide range of analogs of **6.6** can be used for the reaction, where R′ can be hydrogen, alkyl, substituted phenyl or more complex functionalities such as chloroalkyl, trifluoromethyl, styryl, pyridyl and COOEt. When

isatoic anhydride (**6.7**) is refluxed in acetic anhydride or stirred with trifluoroacetic anhydride/pyridine at room temperature, the corresponding 4*H*-3,1-benzoxazin-4-ones were isolated in high yield.[23] Other synthetic methods such as the oxidation of indoles (**6.8**),[24-26] thermal rearrangement of **6.9** in acetic acid/pyridine, [4+2] cycloaddition of 1,2,3-benzotriazin-4-ones (**6.10**) with benzaldehydes,[27-29] electrochemical cyclization of *o*-trichloroacetylanilides (**6.11**),[30] and solid-phase syntheses[31] have been published in the literature.

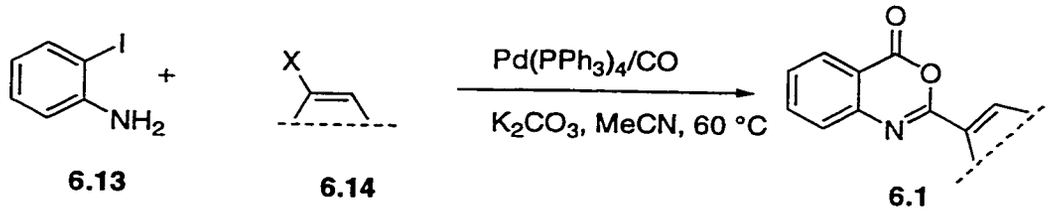
6.1.1.2 Synthesis of 2-substituted-4H-3,1-benzoxazin-4-ones by metal catalyzed carbonylation reactions.

For all syntheses of 4*H*-3,1-benzoxazin-4-ones in section 6.1.1.1, the usual strategy begins with starting materials which contain an amine and a carbonyl carbon which will consequently become the 1- and 4-position of the product. An alternate method is carbonylation, which will insert the carbonyl moiety into aniline derivatives to give the product. Two papers have reported the use of palladium-catalyzed carbonylation methodology for the preparation of 2-substituted-4*H*-3,1-benzoxazin-4-ones. Larock and Fellows[32] describe an example of thallation and subsequent palladium-catalyzed carbonylation of *N*-acetylaniline (**6.12**) which leads to **6.1b** in 40% yield (eq 1). A possible mechanism for this reaction was not described in this publication.



6.12 **6.1b**, 40% (eq 1)

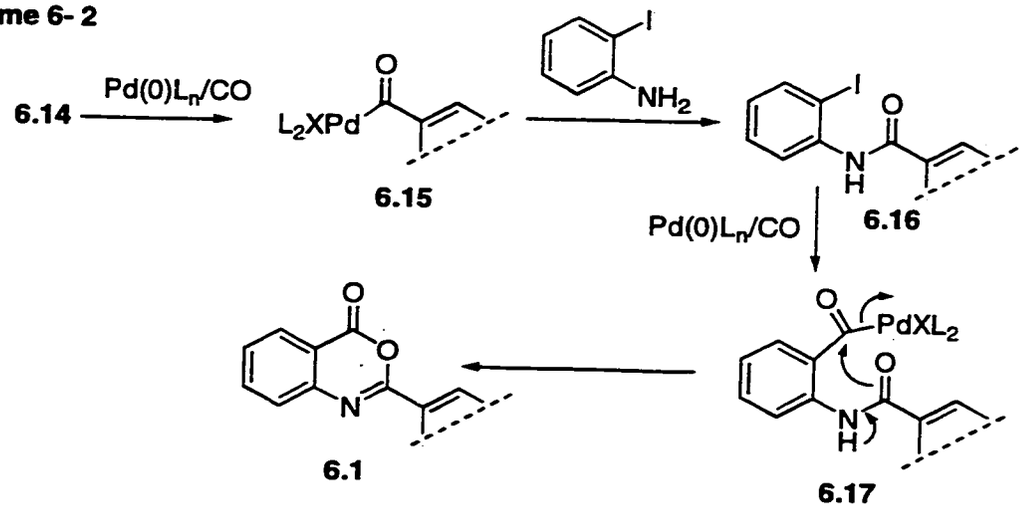
Cacchi et al. reported a three-component reaction using *o*-iodoanilines (**6.13**) with unsaturated or aryl halides or triflates (**6.14**), and carbon monoxide in the presence of a catalytic amount of Pd(0) for the synthesis of 2-substituted-4*H*-3,1-benzoxazin-4-ones (eq 2).[33]



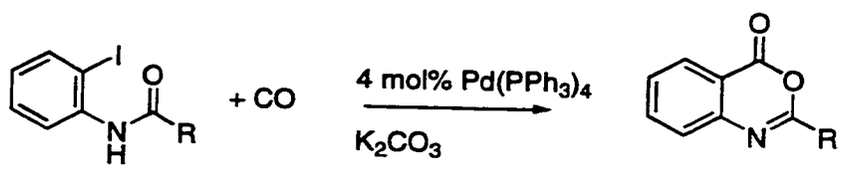
6.13 **6.14** X = Cl, Br, OTf **6.1** (eq 2)

The reaction was proposed to proceed via palladium-mediated carbon monoxide insertion into C-O (if X = OTf) or C-X of **6.14** to give the σ–acyl palladium complex, **6.15**. Trapping of **6.15** by *o*-iodoaniline affords the *o*-iodoanilide (**6.16**). Palladium-catalyzed carbonylation of **6.13** resulting in σ–acyl palladium complex **6.17**, followed by nucleophilic attack of the amide oxygen to an acyl palladium moiety, would afford **6.1** with regeneration of Pd(0) (Scheme 6–2).

Scheme 6- 2



In the latter publication, the authors observed that *o*-acylamidoiodobenzene (**6.18**) could undergo annulation to give 2-substituted-4*H*-3,1-benzoxazin-4-ones in the presence of K_2CO_3 and 4 mol% $Pd(PPh_3)_4$ under an atmosphere of carbon monoxide (eq 3). We envisioned that the formation of 2-substituted-4*H*-3,1-benzoxazin-4-ones (**6.1**) would be accessible directly by using *o*-iodoaniline and acid chlorides in the cyclocarbonylation reaction in the presence of base and palladium catalyst.



6.18

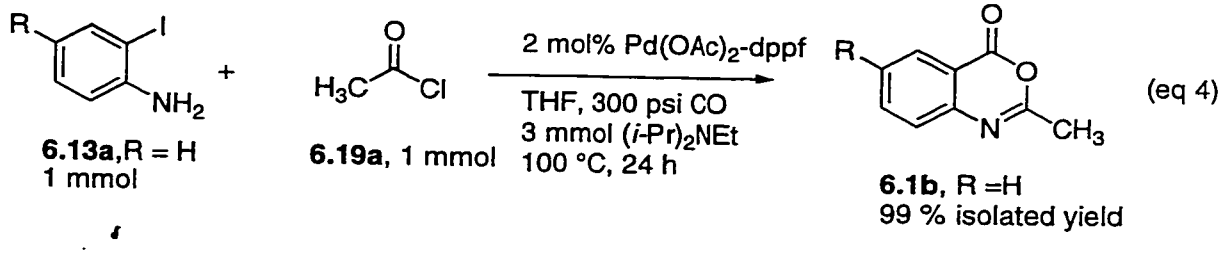
(eq 3)

R = Me, 60%
R = Et, 35%
R = Ph, 92%

6.2 Results and Discussion.

6.2.1 The cyclocarbonylation reaction of *o*-iodoaniline with acid chlorides.

We initiated our investigation by using a mixture of *o*-iodoaniline (**6.13a**, R = H), 1 equiv. of acetyl chloride (**6.19a**), 300 psi CO, 3 equiv. of (*i*-Pr)$_2$NEt and 2 mol% of Pd(OAc)$_2$-1,1′-*bis*-(diphenylphosphino)ferrocene (dppf) in THF, and after 24 h at 100 °C **6.1b** was isolated in 99% yield (eq 4). This encouraging result led us to further examine the one pot three-component reaction for the formation of the pharmaceutically interesting 2-substituted-4*H*-3,1-benzoxazin-4-ones (**6.1**) by palladium-catalyzed cyclocarbonylation reactions of *o*-iodoanilines (**6.13**) with a variety of acid chlorides (**6.19**). The results from this investigation are described below.



6.13a,R = H
1 mmol

6.19a, 1 mmol

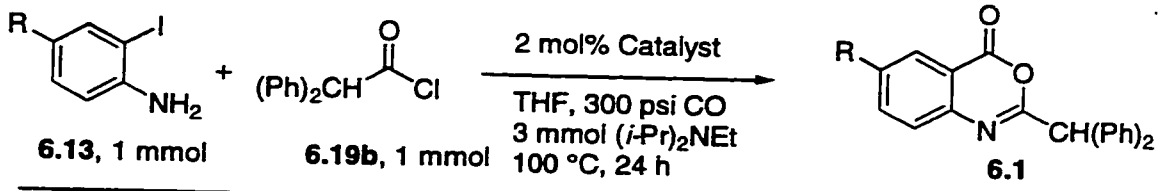
6.1b, R =H
99 % isolated yield

(eq 4)

A phosphine ligand is not necessary for this reaction e.g. reactions of 2-iodoanilines (**6.13a-c**) with diphenylacetyl chloride (**6.19b**) using 2 mol% Pd(OAc)$_2$ and dppf in THF at 100 °C under 300 psi CO for 24 h resulted in the formation of **6.1c**, **6.1d**

and **6.1e** in 88, 94 and 90% yield respectively. Without dppf, the yields were 90, 96 and 94% (Table 6-1).

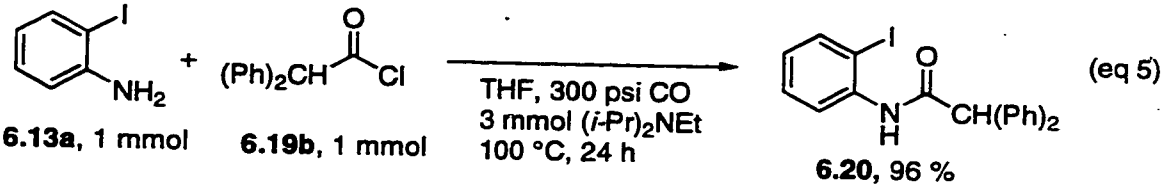
Table 6-1 The investigation of the requirement of phosphine ligand for the palladium-catalyzed cyclocarbonylation reaction of *o*-iodoanilines (**6.13a-c**) with diphenyl acetyl chlorides (**6.19b**).



6.13, 1 mmol **6.19b**, 1 mmol **6.1**

R	product	Isolated yield	
		2 mol% $Pd(OAc)_2$-dppf	2 mol% $Pd(OAc)_2$
R = H, **6.13a**	**6.1c**	88	90
R = Cl, **6.13b**	**6.1d**	94	96
R = CH_3, **6.13c**	**6.1e**	90	94

The palladium catalyst is needed in order to form the carbonylated product as the corresponding amide **6.20** was formed in 96% yield from the reaction of **6.13a** with **6.19b** in THF under 300 psi CO in the absence of $Pd(OAc)_2$ (eq 5).

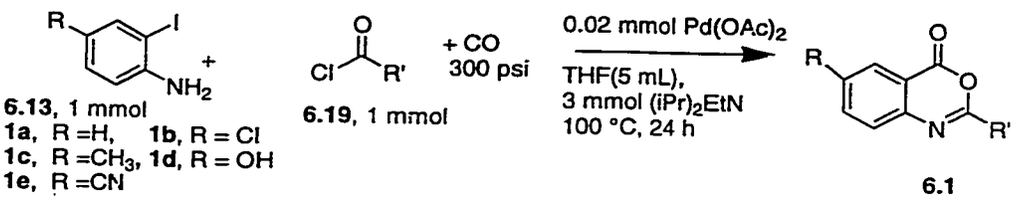


6.13a, 1 mmol **6.19b**, 1 mmol **6.20**, 96 % (eq 5)

Treatment of 2-iodoanilines (**6.13**) with carbon monoxide and a variety of acid chlorides (**6.19**) in the presence of 2 mol% $Pd(OAc)_2$ in THF at 100 °C, afforded 2-substituted-4*H*-3,1-benzoxazin-4-ones (**6.1**) in good to excellent yields (Table 6-2).

Both electron rich and electron poor 2-iodoanilines reacted with acid chlorides to form 2-substituted-4*H*-3,1-benzoxazin-4-ones in fine yields. This annulation process tolerates nitrile as well as hydroxyl substituents on the 2-iodoaniline (entries 5, 6, and 13). In general using α-di or tri-substituted acid chlorides affords better product yields (entries 2-6, 11-15, 18, 19 and 21) compared to the α-monosubstituted analogs (entries 7-10, 16-17). When cinnamoyl chloride (**6.19j**) was used for the palladium-catalyzed cyclocarbonylation reaction with **6.13a**, 2-styryl-4*H*-3,1-benzoxazin-4-one **6.1t** having the *E* configuration was isolated in excellent yield (entry 20).

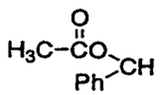
Table 6-2 The Cyclocarbonylation of *o*-Iodoanilines (**6.13**) with Acid Chlorides (**6.19**) Catalyzed by Palladium Acetate.[a]



6.13, 1 mmol
1a, R =H, **1b**, R = Cl
1c, R =CH_3, **1d**, R = OH
1e, R =CN

6.19, 1 mmol

6.1

entry	6.13	R'COCl, 6.19, R' =		Product	Isolated yield[b] (%)
1	**6.13a**	CH_3	**6.19a**	**6.1b**	99[c]
2	**6.13a**	$(Ph)_2CH$	**6.19b**	**6.1c**	90
3	**6.13b**		**6.19b**	**6.1d**	96
4	**6.13c**		**6.19b**	**6.1e**	94
5	**6.13d**		**6.19b**	**6.1f**	94
6	**6.13e**		**6.19b**	**6.1g**	80
7	**6.13a**	$PhCH_2$	**6.19c**	**6.1h**	63
8	**6.13c**		**6.19c**	**6.1i**	81
9	**6.13b**	*p*-$ClC_6H_4CH_2$	**6.19d**	**6.1j**	67
10	**6.13c**		**6.19d**	**6.1k**	71
11	**6.13a**	$Ph(CH_3CH_2)CH$	**6.19e**	**6.1l**	95
12	**6.13b**		**6.19e**	**6.1m**	94
13	**6.13e**		**6.19e**	**6.1n**	86
14	**6.13b**		**6.19f**	**6.1o**	95
15	**6.13c**		**6.19f**	**6.1p**	91
16	**6.13a**	$PhSCH_2$	**6.19g**	**6.1q**	80
17	**6.13c**		**6.19g**	**6.1r**	91
18	**6.13a**	Ph	**6.19h**	**6.1a**	98
19	**6.13c**	o-$CH_3OC_6H_4$	**6.19i**	**6.1s**	89
20	**6.13a**	PhCH=CH	**6.19j**	**6.1t**	98
21	**6.13a**	t-Bu	**6.19k**	**6.1u**	98

[a] All reactions were conducted in THF (5 mL) using **6.13** (1 mmol), **6.19** (1 mmol), $(i\text{-Pr})_2NEt$ (3 mmol), $Pd(OAc)_2$ (0.02 mmol), 300 psi CO, at 100 °C for 24h. [b] Isolated yield following silica gel column chromatography using 1:1 mixture of ether:pentane as the eluant. [c] 0.02 mmol dppf was used in this reaction.

These results demonstrate the superiority of this method in comparison to previously reported Pd-based syntheses of **6.1** –e.g. **6.1a** was formed in 99% yield while 40% and 60% yields of **6.1a** were obtained from the thallation-palladium-carbonylation of *N*-acetylaniline[32] and Pd(0)-catalyzed carbonylation of *N*-acetyl-*o*-iodoaniline,[33] respectively. In addition, **6.1s** was isolated in 89% yield while the yield of a similar compound, 2-(*o*-methoxyphenyl)-*4H*-3,1-benzoxazin-4-one was 29% by Pd(0)-catalyzed carbonylation of *o*-methoxyiodobenzene with *o*-iodoaniline; also **6.1t** was obtained in 98% yield following the reaction described herein while the yield was only 41 and 47% when β-bromostyrene and *o*-iodoaniline were subjected to carbonylation.[33] (See Table 6-3 for the comparison)

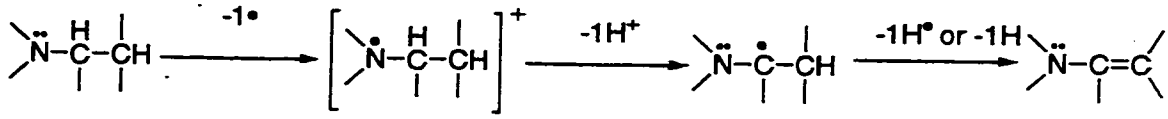
Table 6-3 Comparison of the yields of the same products obtained from different methods.

	% yield of **6.1**		
6.1	Cacchi's method	Larock's method	Our method
6.1a	60	40	99
6.1s	29		89
6.1t	41,47		98

6.2.2 Formation of Palladium (0) in situ in the absence of a phosphine ligand

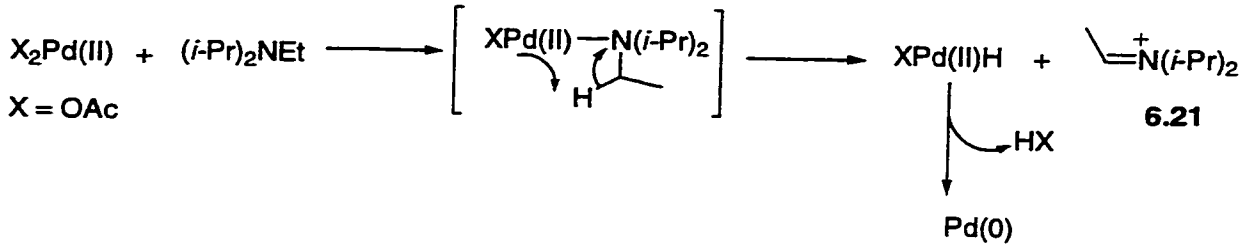
Since the reaction proceeds in the absence of a phosphine ligand, and knowing that a palladium (0) species is required for catalysis for the carbon monoxide insertion into the C-I bond of *o*-iodoanilines, in situ reduction must occur. McCrindle et al.[34] reported in 1984 that tertiary amines react quite rapidly with palladium (II) giving palladium (0) and enamines. Therefore, diisopropylethylamine is most likely to be reducing agent in this reaction. The pathway was proposed to proceed via one-electron oxidation to a planar aminium radical followed by deprotonation to yield an α-amino radical (Scheme 6–3).

Scheme 6-3



Another pathway was proposed by Collman et al. –coordination of $(i\text{–Pr})_2$NEt to Pd(II) followed by β-hydride elimination producing the iminium ion (**6.21**), acetic acid and Pd(0) (Scheme 6-4).[35]

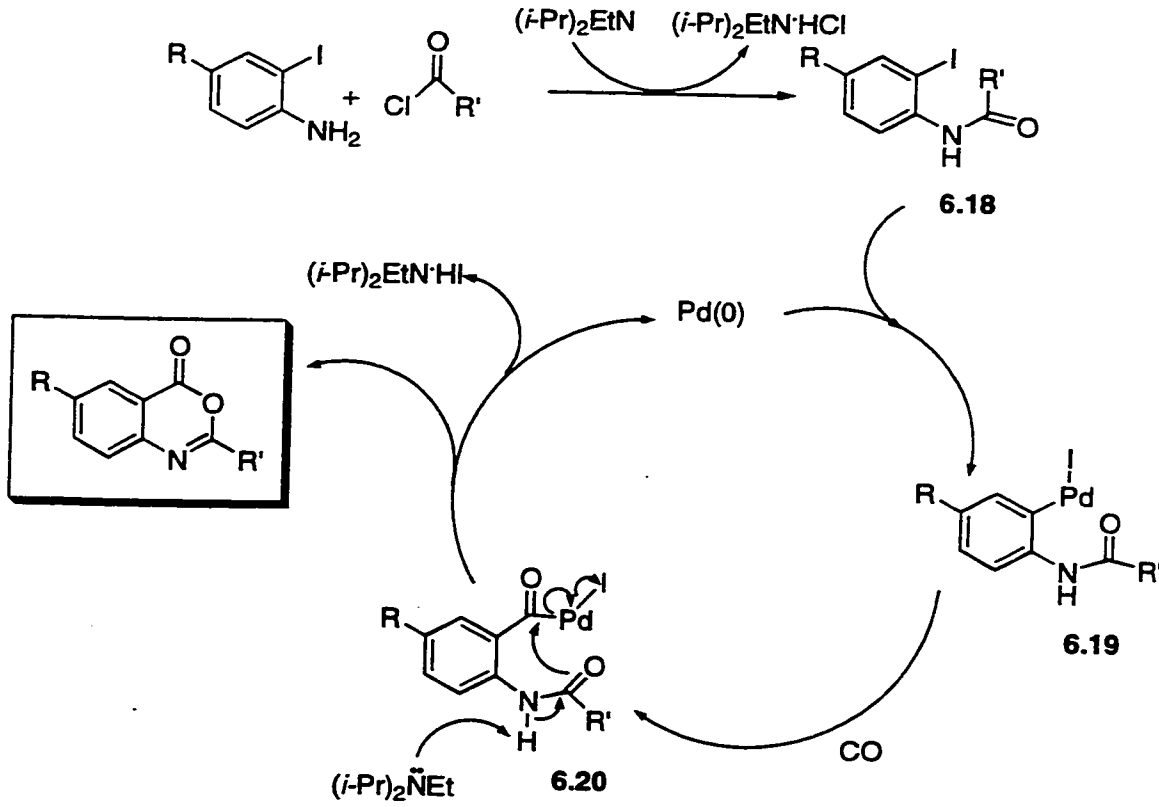
Scheme 6-4



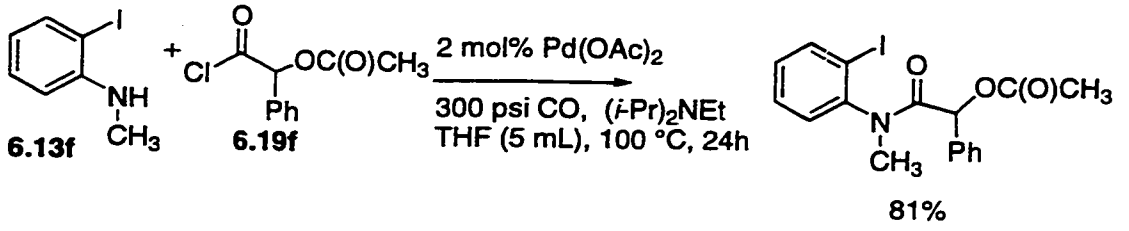
6.2.3 Mechanism for the cyclocarbonylation reaction

The cyclocarbonylation reaction appears to proceed via in situ formation of amides (**6.18**) from the reaction of *o*-iodoanilines with acid chlorides in the presence of base. Oxidative addition of the generated palladium (0) catalyst to **6.18** forms complex **6.19**. Carbonyl insertion into the aryl carbon-palladium bond of **6.19** would afford the aroylpalladium iodide complex **6.20**. Cyclization is presumably facilitated by deprotonation of the amide proton (or the proton of the enol tautomer of **6.20**) by diisopropylethylamine to give the desired product with regeneration of palladium (0) (Scheme 6–5).

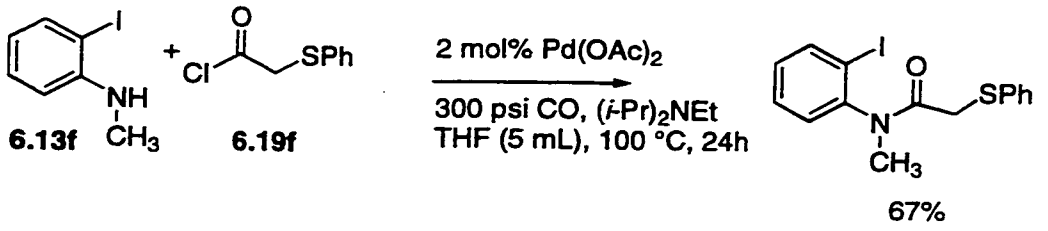
Scheme 6-5



The proposed mechanism accounts for the results for the corresponding amides in 81 and 65% yields, from the reaction of *N*-methyl-*o*-iodoaniline (**6.13f**) with acid chlorides **6.19f** (eq 6) and **6.19g** (eq 7) respectively. No cyclization occurs, since the enol-tautomer can not be formed in these cases.



(eq 6)



(eq 7)

6.3 Conclusion

In conclusion, we have demonstrated that 2-substituted-4*H*-3,1-benzoxazin-4-one derivatives can be easily synthesized by the reaction of 2-iodoanilines, acid chlorides and carbon monoxide in the presence of a palladium catalyst and diisopropylethylamine. The present methodology is a versatile synthetic approach for the one-pot three component reaction leading to 2-substituted-4*H*-3,1-benzoxazin-4-ones.

6.4 Experimental Section

6.4.1 Synthesis of acid chlorides 6.19d and 6.19g.

Acid chlorides **6.19d** and **6.19g** were prepared using the same procedure by refluxing *p*-chlorophenyl acetic acid or phenylthioacetic acid, respectively, in thionyl chloride for 3h. Excess thionyl chloride was removed by rotary evaporation and the resulting solution was distilled under reduced pressure to obtain pure products in quantitative yields.

6.4.2 The palladium-catalyzed cyclocarbonylation reaction of *o*-iodoanilines with acid chlorides.

The following general procedure was used: a mixture of **6.13** (1 mmol), **6.19** (1 mmol), $Pd(OAc)_2$ (0.02 mmol), $(i\text{-}Pr)_2NEt$ (3.0 mmol) and THF (5 mL) was reacted in an autoclave at 300 psi of carbon monoxide for 24 h at 100 °C. The reaction mixture was cooled to room temperature and excess carbon monoxide was released. The reaction mixture was filtered and the filtrate was concentrated by rotary evaporation. The residue was purified by silica gel column chromatography using ether-pentane (1:1) as the eluant.

2-Phenyl-4*H*-3,1-benzoxazin-4-one, 6.1a;[2,4,19] mp 121-123 °C (123-124 °C)[4]; IR 1622, 1764 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.42- 7.76 (m, 6H, aromatic protons), 8.22 (m, 3H, aromatic protons); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 116.93, 127.13, 128.13, 128.21,

128.47, 128.64, 130.14, 132.51, 136.43, 146.86, (aromatic carbons) 156.98, (C=N), 159.39 (C=O); MS m/e 223 $[M]^+$

2-Methyl-4*H*-3,1-benzoxazin-4-one, 6.1b;[4,19] mp 81-82 °C (80-81°C)[4]; IR 1646, 1758 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.42 (s, 3H, C*H*$_3$), 7.39-7.50 (m, 2H, aromatic protons), 7.68-7.80 (m, 1H, aromatic proton), 8.08-8.14 (m, 1H, aromatic proton); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.98 (CH_3), 116.85, 126.24, 128.05, 128.27, 136.30, 146.28, (aromatic protons), 159.50 (C=N), 160.06 (C=O); MS m/e 161 $[M]^+$

2-(Diphenylmethyl)-4*H*-3,1-benzoxazin-4-one, 6.1c; mp 120-122 °C; IR 1638, 1759 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.39 (s, 1H, C*H*), 7.24-7.77 (m, 13H, aromatic protons), 8.14-8.20 (m,, 1H, aromatic proton); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 56.92 (CH), 116.79, 127.05, 127.45, 128.34, 128.48, 128.63, 128.88, 136.41, 138.37, 146.21, (aromatic carbons), 159.45, (C=N), 162.17 (C=O); MS m/e 313 $[M]^+$ Anal Cald for $C_{21}H_{15}NO_2$; C 80.49, H 4.82, N 4.47; Found C 80.87, H 4.83, N 4.44.

6-Chloro 2-(diphenylmethyl)-4*H*-3,1-benzoxazin-4-one, 6.1d; mp 118-120 °C; IR 1634, 1766 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 5.36 (s, 1H, C*H*), 7.24–7.41 (m, 10H, aromatic protons), 7.55 (d, 1H, J = 8.6 Hz, aromatic proton), 7.70 (dd, 1H J = 8.6 and 2.4 Hz, aromatic proton), 8.10 (d, 1H, J = 2.4 Hz, aromatic proton); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 56.93 (CH), 118.00, 118.78, 127.61, 127.77, 128.74, 128.89, 134.22, 136.72, 138.19, 144.74, (aromatic carbons), 158.43, (C=N), 162.55, (C=O); MS m/e 347 $[M]^+$ Anal Cald for $C_{21}H_{14}ClNO_2$; C 72.52, H 4.06, N 4.03; Found C 72.11, H 4.08, N 4.01.

2-(Diphenylmethyl)-6-methyl-4*H*-3,1-benzoxazin-4-one, 6.1e; mp 122-123 °C; IR 1638, 1756 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.44, (s, 3H, C*H*$_3$), 5.36 (s, 1H, C*H*), 7.24–7.60 (m, 12H, aromatic protons), 7.95-7.97 (m, 1H, aromatic proton); ^{13}C-NMR

(75 MHz, $CDCl_3$) δ 21.22 (PhC*H*$_3$), 56.90 (C*H*), 116.53, 126.88, 127.43, 127.95, 128.63, 128.91, 137.62, 138.54, 138.94, 144.10, (aromatic carbons), 159.72, (C=N), 161.38 (C=O); MS m/e 327 $[M]^+$ Anal Cald for $C_{22}H_{17}NO_2$; C 80.71, H 5.23, N 4.28; Found C 80.54, H 5.32, N 4.26.

2-(Diphenylmethyl)-6-hydroxy-4*H*-3,1-benzoxazin-4-one, 6.1f; mp 189-191 °C; IR 1640, 1758 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$ and Acetone-d_6) δ 5.30 (s, 1H, C*H*), 7.11-7.50 (m, 13H, aromatic protons), 8.88 (br,s, 1H, O*H*); ^{13}C-NMR (75 MHz, $CDCl_3$ and Acetone-d_6) δ 56.43 (CH), 111.90, 117.51, 125.05, 127.08, 128.32, 128.38, 128.65, 138.58, 139.18, (aromatic carbons) 157.00 (C-OH), 159.11 (C=N), 159.44 (C=O); MS m/e 329 $[M]^+$ Anal Cald for $C_{21}H_{15}NO_3$; 329.1052; Found 329.1059.

2-(Diphenylmethyl)-6-cyano-4*H*-3,1-benzoxazin-4-one, 6.1g; mp 201-203 °C; IR 1638, 1774, 2231 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$ and DMSO-d6) δ 5.49 (s, 1H, C*H*), 7.23-7.37 (m, 10H, aromatic protons), 7.67-7.71 (m, 1H, aromatic proton), 8.04-8.16 (m, 1H, aromatic proton), 8.42-8.45 (m, 1H, aromatic proton); ^{13}C-NMR (75 MHz, $CDCl_3$ and DMSO-d6); δ 54.35 (CH), 109.28 (C-CN), 115.47 (C≡N), 116.12, 125.67, 126.54, 126.86, 127.18, 131.07, 136.67, 137.31, 146.92, 155.73 (C=N), 163.00 (C=O); MS m/e 338 $[M]^+$ Anal Cald for $C_{22}H_{14}N_2O_2$; C 78.09, H 4.17, N 8.28; Found C 78.16, H 4.10, N 8.23.

2-(Benzyl)-4*H*-3,1-benzoxazin-4-one, 6.1h;[2] mp 86-88 °C; IR 1642, 1758 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.96 (s, 2H, C*H*$_2$), 7.27-7.58 (m, 7H, aromatic protons), 7.71-7.76 (m, 1H, aromatic proton), 8.11-8.16 (m, 1H aromatic proton); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 41.55 (CH_2), 116.77, 126.74, 127.43, 128.29, 128.37, 128.75, 129.23, 134.15,

136.40, 146.36, (aromatic carbons), 159.52 (C=N), 161.10 (C=O); MS m/e 237 $[M]^+$ Anal Cald for $C_{15}H_{11}NO_2$; C 75.94, H 4.67, N 5.90; Found C 75.94, H 4.54, N 5.85.

2-(Benzyl)-6-methyl-4*H*-3,1-benzoxazin-4-one, 6.1i; mp 186-189 °C; IR 1642, 1756 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.42 (s, 3H, PhC*H*$_3$), 3.94 (s, 2H, C*H*$_2$), 7.24–7.58 (m, 7H, aromatic protons), 7.91-7.93 (m, 1H, aromatic proton); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.17 ($PhCH_3$), 41.47 (CH_2), 116.43, 126.48, 127.38, 127.95, 128.73, 129.22, 134.26, 137.61, 138.70, 144.16, (aromatic carbons) 159.72 (C=N), 160.35 (C=O); MS m/e 251 $[M]^+$ Anal Cald for $C_{16}H_{13}NO_2$; C 76.48, H 5.21, N 5.57; Found C 76.86, H 5.67, N 5.17.

2-[(*p*-Chlorophenyl)methyl]-6-chloro-4*H*-3,1-benzoxazin-4-one, 6.1j; mp 143-145 °C; IR 1640, 1765 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.91 (s, 2H, C*H*$_2$), 7.30 (s, 4H, aromatic protons), 7.51 (d, 1H, J = 8.6, aromatic proton), 7.72 (dd, 1H, J = 8.6 and 2.4 Hz, aromatic proton), 8.08 (d, 1H, J = 2.4 Hz, aromatic proton); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 40.76 (CH_2), 117.91, 127.79, 128.39, 128.98, 130.63, 132.27, 133.60, 134.14, 136.77, 144.72, (aromatic carbons), 158.28 (C=N), 160.85 (C=O); MS m/e 304 $[M-2]^+$, 306 $[M]^+$ Anal Cald for $C_{15}H_9Cl_2NO_2$; C 58.85, H 2.96, N 4.58; Found C 58.87, H 2.88, N 4.51.

2-[(*p*-Chlorophenyl)methyl]-6-methyl-4*H*-3,1-benzoxazin-4-one, 6.1k; mp 119-121 °C; IR 1644, 1759 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.42 (s, 3H, PhC*H*$_3$), 3.89 (s, 2H, C*H*$_2$), 7.24-7.57 (m, 6H, aromatic protons), 7.90-7.92 (m, 1H, aromatic proton); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.16 ($PhCH_3$), 40.72 (CH_2), 116.40, 126.51, 127.98, 128.85, 130.59, 132.68, 133.36, 137.65, 138.83, 144.05,(aromatic carbons) 159.55 (C=N),

159.73 (C=O); MS m/e 285 $[M]^+$ HRMS Cald for $C_{16}H_{12}ClNO_2$; 285.0557; Found 285.0536.

2-(1-Phenylpropyl)-4*H*-3,1-benzoxazin-4-one, 6.1l; mp 135-136 °C; IR 1638, 1759 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J* = 7.3 Hz, CH_2CH_3), 1.95-2.10 (m, 1H, CH_2CH_3), 2.22-2.41 (m, 1H, CH_2CH_3), 3.77 (t, 1H, *J* =7.8 Hz, C*H*), 7.24 – 7.79 (m, 8H, aromatic protons), 8.12-8.15 (m, 1H, aromatic proton); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 12.15 (CH_2CH_3), 26.44 (CH_2CH_3), 53.18 (CH), 116.91, 126.82, 127.46, 128.16, 128.25, 128.31, 128.67, 135.32, 139.07, 146.39, (aromatic carbons) 159.67 (C=N), 163.50 (C=O); MS m/e 265 $[M]^+$ Anal Cald for $C_{17}H_{15}NO_2$; C 76.96, H 5.70, N 5.28; Found C 77.20, H 5.91, N 4.92.

6-Chloro-2-(1-phenylpropyl)-4*H*-3,1-benzoxazin-4-one, 6.1m; mp 74-76 °C; IR 1635, 1765 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.95 (t, 3H, *J* = 7.3 Hz, CH_2CH_3), 1.98-2.09, (m, 1H, CH_2CH_3), 2.23-2.34 (m, 1H, CH_2CH_3), 3.75 (t, 1H, *J* = 7.7 Hz, C*H*), 7.24–8.10 (m, 8H, aromatic protons); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 12.12 (CH_2CH_3), 26.39 (CH_2CH_3), 53.14 (CH), 118.70, 127.58, 127.68, 128.12, 128.45, 128.75, 133.82, 135.60, 138.79, 144.88, (aromatic carbons) 158.59 (C=O), 163.85 (C=N); MS m/e 299 $[M]^+$ Anal Cald for $C_{17}H_{14}ClNO_2$; C 68.12, H 4.71, N 4.67; Found C 68.18, H 4.60, N 4.64.

6-Cyano-2-(1-phenylpropyl)-4*H*-3,1-benzoxazin-4-one, 6.1n; mp 90-91 °C; IR 1634, 1770, 2232 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.95 (t, 3H, *J* =7.3 Hz, CH_2CH_3), 1.97-2.38 (m, 2H, CH_2CH_3), 3.78 (t, 1H, *J* = 7.8 Hz, C*H*), 7.21-7.45 (m, 5H, aromatic protons), 7.52 (dd, 1H, *J* = 8.4 and 0.6 Hz, aromatic proton), 7.85 (dd, 1H, *J* = 8.4 and 2.0 Hz, aromatic proton), 8.41 (dd, 1H, *J* = 2.0 and 0.6 Hz, aromatic proton); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 12.05 (CH_2CH_3), 26.26 (CH_2CH_3), 53.26 (CH), 111.91 (C-CN), 117.02

(C≡N), 117.70, 127.75, 128.01, 128.12, 128.80, 133.07, 138.25, 138.56, (aromatic carbons) 149.16, 157.63 (C=N), 166.62 (C=O); MS m/e 290 $[M]^+$ Anal Cald for $C_{18}H_{14}N_2O_2$; C 74.47, H 4.86, N 9.65; Found C 74.14, H 4.95, N 9.47.

2-[(Acetoxy)(phenyl)methyl]-6-chloro-4*H*-3,1-benzoxazin-4-one, 6.1o; mp 123-125 °C; IR 1650, 1751, 1770 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.24 (s, 3H, C(O)C*H*$_3$), 6.34 (s, 1H, C*H*), 7.23-7.41 (m, 3H, aromatic protons), 7.53-7.73 (m, 4H, aromatic protons), 8.06-8.08 (m, 1H, aromatic proton); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.76 ($C(O)CH_3$), 74.16 (CH), 118.20, 127.62, 127.84, 128.71, 128.88, 129.49, 133.95, 134.42, 136.75, 144.27, (aromatic carbons), 157.47 (C=N), 158.82 (C=O), 169.93 ($OC(O)CH_3$); MS m/e 290 $[M]^+$ Anal Cald for $C_{17}H_{12}ClNO_4$; C 61.92, H 3.67, N 4.25; Found C 62.01, H 3.55, N 4.20.

2-[(Acetoxy)(phenyl)methyl]-6-methyl-4*H*-3,1-benzoxazin-4-one, 6.1p; mp 136-138 °C; IR 1651, 1754, 1769 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.23 (s, 3H, C(O)C*H*$_3$), 2.42 (s, 3H, PhC*H*$_3$), 6.37 (s, 1H, C*H*), 7.24 – 7.61 (m, 7H, aromatic protons), 7.85-7.92 (m, 1H, aromatic proton); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.89 ($C(O)CH_3$), 21.24 ($PhCH_3$), 74.28 (CH), 116.81, 126.99, 127.71, 128.15, 128.88, 129.41, 134.38, 137.75, 139.31, 143.66, (aromatic carbons), 157.75 (C=N), 158.87 (C=O), 170.02 ($OC(O)CH_3$); MS m/e 309 $[M]^+$ HRMS Cald for $C_{18}H_{15}NO_4$; 309.1001; Found 309.1014.

2-[(Phenylthio)methyl]-4*H*-3,1-benzoxazin-4-one, 6.1q; mp 156-158 °C; IR 1638, 1760 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.98 (s, 2H, C*H*$_2$SPh), 7.21-7.32 (m, 3H, aromatic protons), 7.44-7.54 (m, 4H, aromatic protons), 7.72-7.77 (m, 1H, aromatic proton), 8.13-8.18 (m, 1H, aromatic proton); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 37.78 (CH_2SPh), 116.79, 126.84, 127.43, 128.51, 128.63, 129.08, 129.76, 130.92, 134.22, 136.53, (aromatic

carbons), 146.04 (C=N), 159.11 (C=O); MS m/e 269 $[M]^+$ HRMS Cald for $C_{15}H_{11}NO_2S$; 269.0510; Found 269.0509.

6-Methyl-2-[(phenylthio)methyl]-4*H*-3,1-benzoxazin-4-one, 6.1r; mp 173-175 °C; IR 1638, 1760 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.42 (s, 3H, PhC*H*$_3$), 3.96 (s, 2H, C*H*$_2$SPh), 7.21-7.31 (m, 3H, aromatic protons), 7.38-7.58 (m, 4H, aromatic protons), 7.92-7.93 (m, 1H, aromatic protons); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.20 ($PhCH_3$), 37.68 (CH_2SPh), 116.45, 126.60, 127.32, 128.05, 129.03, 130.80, 134.32, 137.67, 139.06, 143.86, (aromatic carbons) 158.22 (C=N), 159.26 (C=O); MS m/e 283 $[M]^+$; HRMS Cald for $C_{16}H_{13}NO_2S$; 283.0667; Found 283.0672.

2-(*o*-Methoxyphenyl)-6-methyl-4*H*-3,1-benzoxazin-4-one, 6.1s; mp 132-134 °C; IR 1626, 1754 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.45, (s, 3H, PhC*H*$_3$), 3.89 (s, 3H, PhOC*H*$_3$), 6.96-7.06 (m, 2H, aromatic protons), 7.40-7.58 (m, 3H, aromatic protons), 7.79-7.84 (m, 1H, aromatic proton), 7.99-8.00 (m, 1H, aromatic proton); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.21 ($PhCH_3$), 56.03 ($PhOCH_3$), 112.08, 116.58, 120.48, 126.96, 127.88, 131.19, 132.93, 137.50, 138.67, 144.81, 156.87, (aromatic carbons), 158.50 (C=N), 159.93 (C=O); MS m/e 267 $[M]^+$; HRMS Cald for $C_{16}H_{13}NO_3$; C 71.90, H 4.90, N 5.24; Found C 71.86, H 4.81, N 5.34.

(*E*)-2-Styryl-4*H*-3,1-benzoxazin-4-one, 6.1t;[2,33] mp 144-146 °C; IR 1635, 1758 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 6.76 (d, 1H, CH=**CH**, *J* = 16.2 Hz), 7.36- 7.59 (m, 7H, aromatic protons), 7.77 (dd, 1H, *J* = 15.3 and 1.5 Hz, aromatic proton), 7.82 (d, 1H, **CH**=CH, *J* = 16.2 Hz), 8.18 (dd, 1H, *J* = 7.8 and 1.5 Hz, aromatic proton); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 116.90 (CH=CHPh), 118.81, 126.86, 127.95, 128.07, 128.55,

128.94, 130.24, 134.58, 136.45 (aromatic carbons), 141.90 (CH=**C**HPh), 147.07, 157.24 (**C**=N), 159.19 (**C**=O); MS m/e 248 $[M-1]^+$,249 $[M]^+$.

2-*t*-Butyl-4*H*-3,1-benzoxazin-4-one, 6.1u;[2] mp 117-118 °C; IR 1636, 1762 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.35 (s, 9H, C(CH_3)$_3$), 7.35- 7.51 (m, 2H, aromatic protons), 7.64-7.74 (m, 1H, aromatic proton), 8.04-8.10 (m, 1H, aromatic proton); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 27.53 (C(CH_3)$_3$), 37.75 (**C**(CH_3)$_3$), 116.61, 126.75, 127.82, 128.04, 136.07, 146.37 (aromatic carbons), 159.80 (**C**=N), 168.02 (**C**=O); MS m/e 203 $[M]^+$.

6.5 References

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CLAIMS TO ORIGINAL RESEARCH

1. Regioselective synthesis of 2-vinyloxazolidine derivatives by palladium-catalyzed cycloaddition reactions of 2-vinyloxiranes with heterocumulenes.
2. Asymmetric cycloaddition reactions of 2-vinyloxiranes with carbodiimides catalyzed by palladium complexes and chiral ligands.
3. Regio- and stereoselective formation of 1,3-oxazine derivatives by palladium catalyzed cycloaddition reactions of 2-vinyloxetanes with heterocumulenes.
4. Palladium catalyzed cyclocarbonylation of *o*-iodophenols with heterocumulenes for the formation of benzo[*e*]-1,3-oxazine-4-one compounds.
5. The selective formation of quinazoline-4-one derivatives by the reactions of *o*-iodoanilines with heterocumulenes in the presence of a catalytic amount of palladium complexes.
6. A simple synthesis of 2-substituted-4*H*-3,1-benzoxazin-4-ones by palladium catalyzed one-pot reactions of *o*-iodoanilines, acid chlorides and carbon monoxide.

LIST OF PUBLICATIONS

1. Larksarp, C.; Alper, H. Palladium(0)-Catalyzed Asymmetric Cycloaddition of Vinyloxiranes with Heterocumulenes Using Chiral Phosphine Ligands: An Effective Route to Highly Enantioselective Vinyloxazolidine Derivatives. *J. Am. Chem. Soc.* **1997**, *119*, 3709-3715.
2. Larksarp, C.; Alper, H. Highly Enantioselective Synthesis of 1,3-Oxazolidin-2-imine Derivatives by Asymmetric Cycloaddition Reactions of Vinyloxiranes with Unsymmetrical Carbodiimides Catalyzed by Palladium(0) Complexes. *J. Org. Chem.* **1998**, *63*, 6229-6223.
3. Larksarp, C.; Alper, H. Synthesis of 1,3-Oxazine Derivatives by Palladium-Catalyzed Cycloaddition of Vinyloxetanes with Heterocumulenes. Completely Stereoselective Synthesis of Bicyclic 1,3-Oxazines. *J. Org. Chem.* **1999**, *64*, 4152-4158.
4. Larksarp, C.; Alper, H. Palladium-Catalyzed Cyclocarbonylation of *o*-iodophenols and 2-Hydroxy-3-iodopyridine with Heterocumulenes: Regioselective Synthesis of Benzo[*e*]-1,3-oxazin-4-one and Pyrido[3,2-*e*]-1,3-oxazin-4-one Derivatives. *J. Org. Chem.* **1999**, *64*, 9194-9200.
5. Larksarp, C.; Alper, H. Palladium-Catalyzed Cyclocarbonylation of *o*-Iodoanilines with Heterocumulenes; Regioselective Preparation of 4(*3H*)-Quinazolinone Derivatives. *J. Org. Chem.* **2000**, in press.
6. Larksarp, C.; Alper, H. A Simple Synthesis of 2-Substituted-4*H*-3,1-benzoxazin-4-ones by Palladium-Catalyzed Cyclocarbonylation of *o*-Iodoanilines with Acid Chlorides. *Org. Lett.* **1999**, *1*, 1619-1622.