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Abstract

A synthetic route to *N*-alkylated 2-vinylazetidines is presented, and highly regioselective methods for the palladium(0)-catalyzed insertion of heterocumulenes into these substrates have been established, employing a $Pd(OAc)_2/PPh_3$ catalyst system under very mild conditions. An assortment of tetrahydro-pyrimidin-2-ones, tetrahydro-pyrimidin-2-imines, and [1,3]thiazinan-2-imines have been acquired in reactions with isocyanates, diarylcarbodiimides, and arylisothiocyanates. Unoptimized results in reactions with ketenes and ketenimines indicate a variety of carbon electrophiles could be used for the insertion and suggest great potential for these methods in organic synthesis. The steric and electronic influence of substituents on either the azetidine or carbodiimide has established maximal characteristics of substrates suitable for the insertion. Two conformational isomers result from insertion of *o*-tolylisocyanate into a variety of 2-vinylazetidines, indicating that enhanced congestion about the heterocycle creates an energy barrier at room temperature and inhibits ring flexibility. Stereochemical and regiochemical evidence support a likely catalytic cycle that involves the formation of a π-allylpalladium intermediate as the active species for insertion and an equilibrium between a kinetic and thermodynamic product. An asymmetric procedure for the synthesis of optically active products could not be established, which suggests a more complex catalytic cycle.

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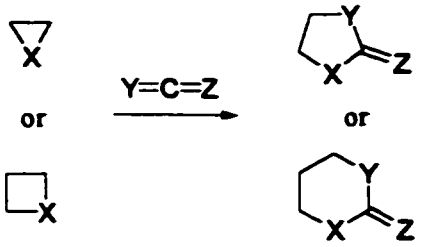
Chapter 1

1.1 Introduction

By examining the heterocyclic compounds present in nature, it becomes evident that the biological world could not exist without their contributions. Photosynthetic and molecular oxygen-transport mechanisms have evolved similar tetrapyrrolic macrocycles - chlorophyll and haem – as the cogs for these essential life processes. The purine and pyrimidine bases present in genetic material allow DNA and RNA molecules to be 'read' enabling the biochemical processes of protein synthesis and cell replication. Most of the biologically active compounds presently used in the pharmaceutical (e.g. anti-viral, anti-bacterial) and agricultural (e.g. insecticides, fungicides) arenas are heterocycles[1], and synthetic designs for these compounds are important.

In the field of diazine chemistry, the pyrimidine bases are the most important naturally occurring molecules present as constituents of nucleic acid[1a]. A variety of pyrimidine analogues have been developed with anti-viral and anti-tumor[1a, b] activity including AZT, a derivitive of thymine, which has been used in the treatment of AIDS. Anti-malarial and anti-bacterial compounds[1b] can be found in this family which also includes thiamin[1a], a vitamin requisite for enzyme function and synthesized as a food/feed additive.

Methods for the synthesis of pyrimidine rings have been known for over half of a century. Many of these involve the condensation of carbonyl species with amines and generally require high temperatures affording modest to good yields[1a, b]. Examples of very high yielding reactions[1a, b] are limiting due to the specificity or sensitivity of the starting materials. However, the last quarter of a century has seen the evolution of a family of cycloaddition reactions involving strained-ring heterocycles with activated cumulene systems (eq 1).



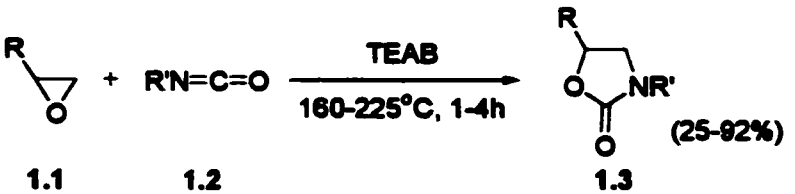
(eq 1)

From harsh, non-selective procedures, new methods for cycloaddition reactions have arisen that exploit metal catalysts, require mild conditions, and are capable of synthesizing heterocycles regio- and stereoselectively. Using this concept, the construction of the pyrimidine ring system could be obtained from the reaction of azetidines with *N*-containing heterocumulenes. However, very little research has involved azetidines as the substrates for these reactions. Even aziridines have received minor consideration compared to the oxygen analogues – oxirane and oxetane. Hence, the introductory focus will be on the cycloaddition reactions of these compounds with heterocumulenes.

1.2 Early cycloaddition reactions of oxiranes and oxetanes

1.2.1 Quaternary ammonium salts

Early reactions of heterocumulenes and epoxides employed nucleophilic catalysts, such as quaternary ammonium halides. It was known that basic substances catalyzed the oligomerization of isocyanates, and reported attempts to synthesize 2-oxazolidinones from isocyanates and oxiranes with such compounds resulted in dimers or trimers only[2]. Peppel *et al.* established the proficiency of ammonium salts in a series of cycloaddition reactions between oxiranes and isocyanates employing catalytic tetraethylammonium bromide[2] (eq 2).



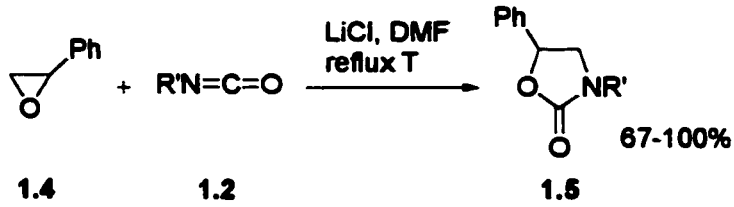
1.1 1.2 1.3

(eq 2)

The wide yield range for **1.3** exhibited the narrow scope of capability for these catalytic systems. Extremely low activity was observed for alkyl isocyanates (R′= C_2H_5, 25% yield), and varying results occurred by simply altering the oxirane substituent (R = H, 92%; R = CH_3, 64%; R = C_8H_{17}, 26%). In addition, severely high temperatures were required. Advances in catalytic systems would be necessary to expand these reactions to more sensitive substrates.

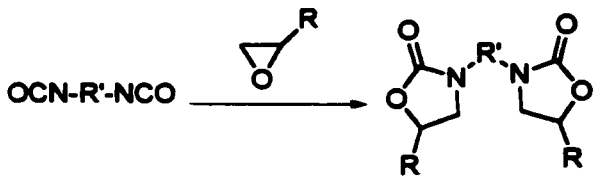
1.2.2 Lithium salts

Subsequent work by Herweh *et al.* explored methods for enhancing the cycloaddition using lithium salts[3]. Reactions of styrene oxide with isocyanates were chosen to test their catalysts. Preliminary results gave modest yields of oxazolidinones using catalytic lithium chloride in refluxing DMF whereby insertion occurred at the least sterically hindered C-O bond giving **1.5**[3a] (eq 3).

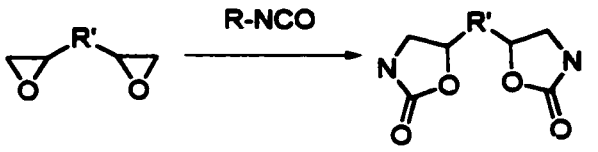


(eq 3)

Improving on the synthesis, more effective catalytic strategies were discovered. Lithium bromide/phosphine oxide complexes at reduced temperatures were capable systems providing better results[3b] (71-98%). Both aryl and alkyl isocyanates were suitable heterocumulenes for the reaction, but conditions were still harsh and more sensitive substrates could not be employed. In addition, nucleophilic catalysis again limited regioselectivity of the insertion since cleavage occurred only across the less hindered C-O bond[3]. Original methods would be required to obtain greater regio- and stereochemical control over the reaction. Herweh published some fascinating results, however, with the synthesis of bis-2-oxazolidinones from cycloaddition reactions of diisocyanates with epoxides (eq 4a) and bis-epoxides with monomeric isocyanates[3b] (eq 4b).



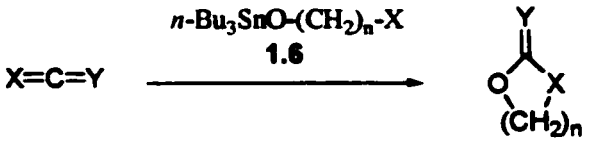
(eq 4a)



(eq 4b)

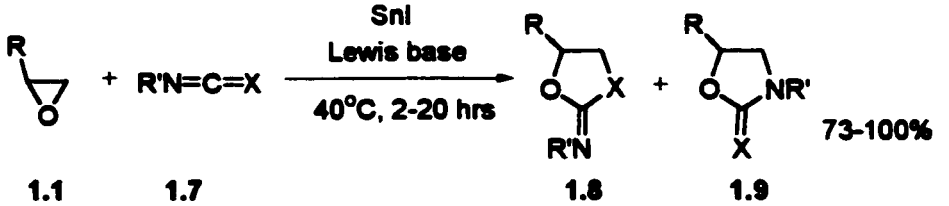
1.2.3 Organotin halides

An innovative procedure arose from a report in which stoichiometric amounts of tributyltin ω-haloalkoxides **1.6** reacted with heterocumulenes affording heterocycles[4a] (eq 5).



(eq 5)

From these results, a variety of heterocumulenes demonstrated facile insertion into the Sn-O bond. The metal alkoxide reagent could be considered an adduct of oxirane and trialkyltin halides which led to an investigation of the catalytic competence of organotin compounds[4, 5]. Matsuda *et al.* obtained excellent results with organotin iodide and Lewis base complexes for reactions of oxiranes with alkyl- and arylisocyanates, carbodiimides, and isothiocyanates[4a, b] (Scheme 2).



1.1 **1.7** **1.8** **1.9**

(eq 6)

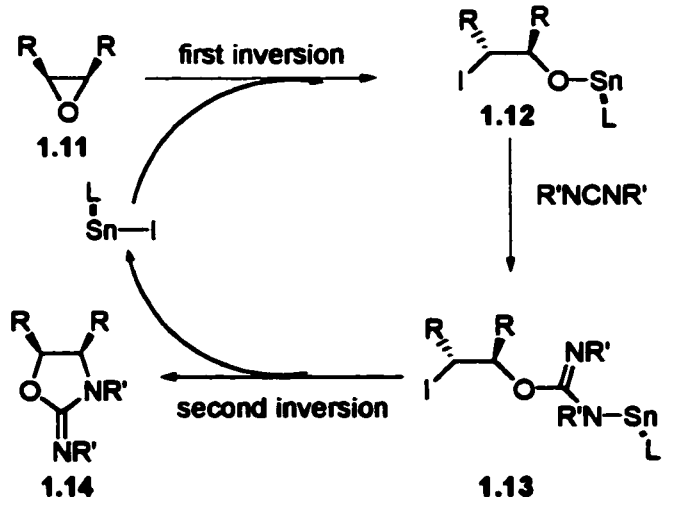
The cycloaddition reactions with isocyanates (X = O) gave mixtures of **1.8** and **1.9**, while isothiocyanates (X = S) were very selective resulting in **1.8** only. Using relatively mild conditions, cycloaddition with carbodiimides and oxiranes yielded 2-iminodioxazolidines **1.8**

(X = NR') whereas prior rigorous conditions promoted the isomerization to 2-oxazolidinones **1.10** (eq 7).

1.8 **1.10** (eq 7)

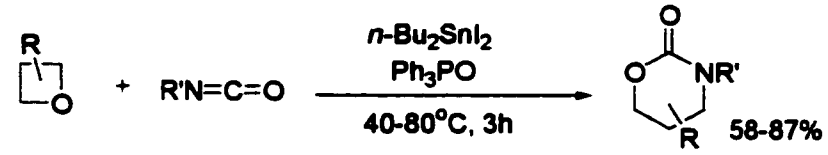
A further problem with previous methods was the inability to catalyze reactions of 2,3-disubstituted oxiranes with heterocumulenes. However, using this process, the 4,5-disubstituted products were afforded in good yields[4c] (56-100%). Additionally the reaction proceeded stereospecifically whereby *trans*-oxiranes **1.11** yielded *trans*-products **1.14**. From these results, a double inversion of configuration was presumed to be influencing this retention, and a mechanism was postulated (Scheme 1-1).

Scheme 1-1



Initial nucleophilic ring opening provides the tin-alkoxyhalide intermediate **1.12**. This complex was trapped with the addition of acetylchloride confirming its role in the mechanism. Insertion of the heterocumulene into the Sn-O bond sets up the internal cyclization reaction **1.13** giving **1.14** with simultaneous catalyst rejuvenation.

In the case of oxetane, previous reports of catalytic copolymerization with carbon dioxide by organotin-halide/base complexes indicated analogous synthetic procedures should be examined[5]. There are fewer examples of cycloaddition reactions for oxetanes than oxiranes perhaps due to their lower reactivity. Consequently, Matsuda *et al.* [5a] required stoichiometric amounts of the dialkyltin diiodide and base for the reaction of oxetanes and isocyanates to synthesize oxazinan-2-ones **1.16** (eq 8).



1.15 **1.2** **1.16** (eq 8)

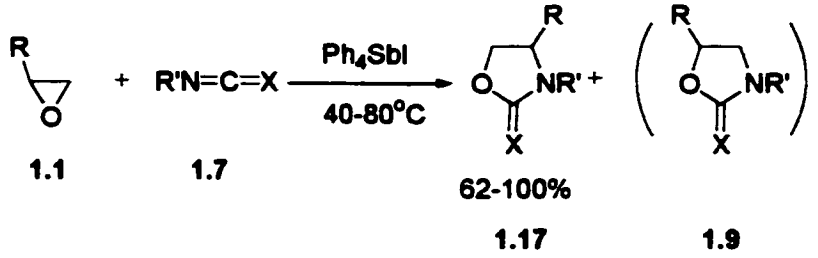
A similar mechanism was presumed to be operating for the cycloaddition with oxetane. However, instability of the tin complex, particularly at the higher temperatures required for the less reactive alkylisocyanates, disabled the catalytic property. Additional investigation with various organotin iodides and bases improved the catalytic nature of this reaction[5b], but with lower success than the oxirane procedure.

1.2.4 Organoantimony halides

Matsuda *et al.* [6] first explored organoantimony compounds for catalytic activity in cycloaddition reactions in 1980 using oxiranes and carbon dioxide. Dominated by high temperatures (80-120°C), many of these reactions yielded polymers as by-products[6a] and seemed to be abandoned in favor of organotin catalysts. However, interesting results were obtained upon returning to the pentavalent stibonium halides. Previously, exclusive synthesis of 3,5-disubstituted products **1.9** resulted from the cycloaddition of oxiranes and heterocumulenes[2, 3, 4] (eq 9).

1.1 **1.7** **1.9** **1.17** (eq 9)

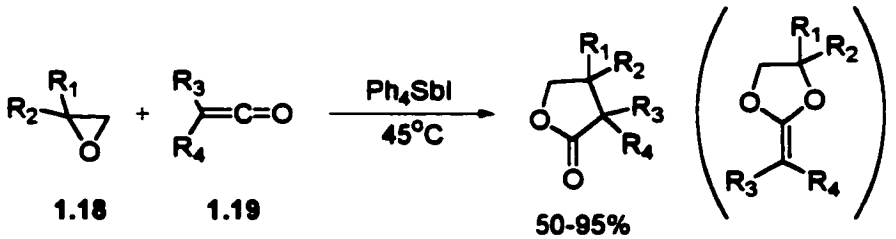
Styrene oxide (R = Ph) often gave mixtures of **1.9** and **1.17**[3], but this was the only exception. Tetraphenylstibonium iodide catalyzed the reaction of oxiranes and heterocumulenes demonstrating limited regiospecificity with isocyanates (mixtures of **1.9** and **1.17**), but producing 3,4-disubstituted products **1.17** exclusively with carbodiimides[6a, b] (eq 10).



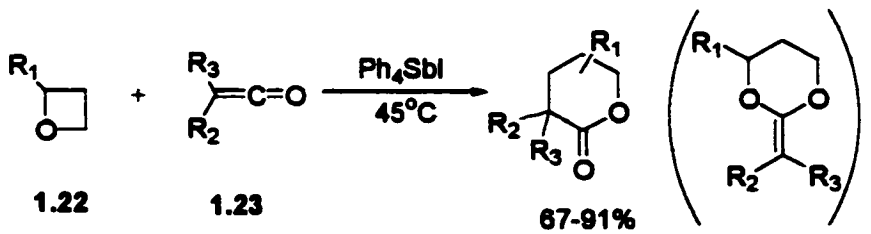
1.1 **1.7** **1.17** **1.9** (eq 10)

Interestingly, organotin-catalyzed reactions[4] afforded 3,5-disubstituted derivatives **1.9**, which introduces the opportunity for incredible regioselective control over the type of product obtained from these reactions.

A further application of these reactions was observed by the insertion of ketenes into both oxiranes and oxetanes[7] (eq 11 and eq 12).



1.18 **1.19** **1.20** **1.21** (eq 11)



1.22 **1.23** **1.24** **1.25** (eq 12)

Under optimized conditions, excellent selectivity could be obtained favoring the formation of lactones **1.20** and **1.24**. However, there were limitations to this method as 4- and 6-phenyl

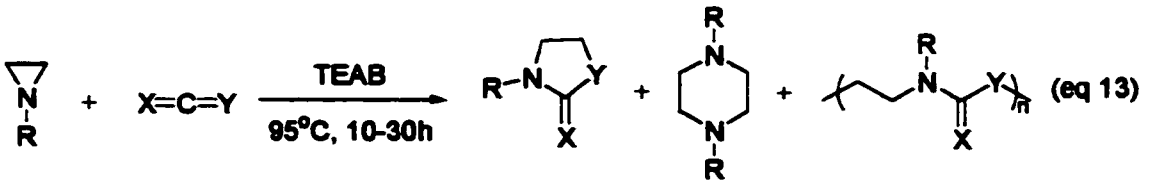
substituents **1.24** resulted from the reaction of 2-phenyloxetane **1.22** ($R_1 = C_6H_5$) and diphenylketene **1.23** ($R_2 = R_3 = C_6H_5$). The loss of regioselectivity was due to steric factors that arose in this particular instance. Little activity was found for **1.18** when both R_1 and R_2 were alkyl substituents and selectivity went in favor of the cyclic ketene acetal **1.21** due to steric interference. However, for the first time with organotin and organostibonium catalysts, this reaction[7] reported that stoichiometric amounts of substrates had been employed. Prior methods had required three to five times excess of the oxirane[4-6], so this improvement could be seen as great progress in these catalytic processes.

It would seem appropriate that many of the above systems could be used in similar chemistry with the nitrogen analogues of oxirane and oxetane. However, much less has been reported in the literature for cycloaddition reactions of aziridines and azetidines with heterocumulenes. In the next section, strategies for these compounds will be spotlighted.

1.3 Early cycloaddition reactions of aziridines and azetidines

1.3.1 Quaternary ammonium salts

Adaptation of useful catalytic systems for oxiranes onto aziridines should be a likely starting point for these reactions. Thus, approximately a decade after Peppel *et al.* reported their synthesis of 2-oxazolidinones using quaternary ammonium halides, a Russian report verified the capacity of these catalysts in the synthesis of other heterocyclic compounds[8]. An assortment of heterocumulenes was reacted with *N*-arylaziridines in the presence of tetraethylammonium bromide giving rise to various heterocyclic products and polymers (eq 13).

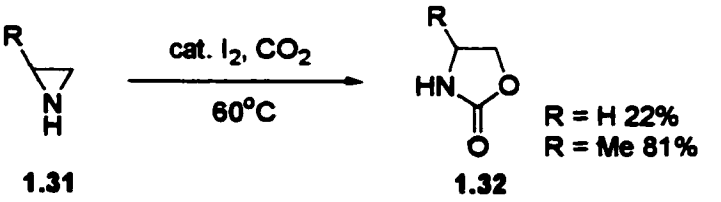


1.26 **1.27** **1.28** **1.29** **1.30**

In the reactions with phenylisothiocyanate, excellent yields were obtained for **1.28** (X = NPh, Y = S; 85-95%). However, when the heterocumulene was carbon dioxide, mixtures of **1.28** and **1.29** resulted, and yields of the desired product waned to only 50-80% leading to only piperazine **1.29** in some cases. Only polymeric material **1.30** was obtained when CS_2 and OCS were reacted with *N*-phenylaziridine. This could be pyrolyzed to monomeric **1.28**, but it was evident that better catalysts were required for these reactions.

1.3.2 Molecular iodine

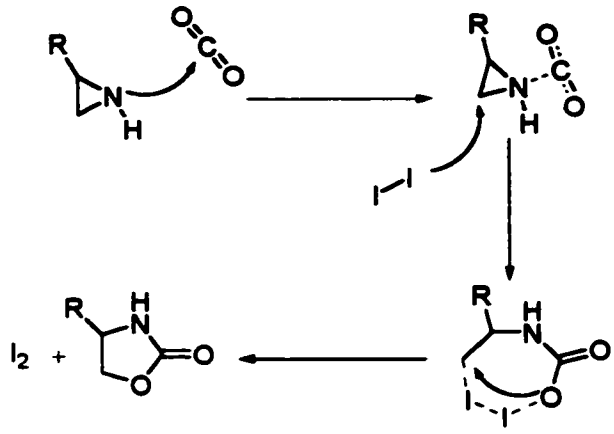
On the cusp of the organotin and organostibonium halide findings[4-7], some research explored a new synthetic route to 2-oxazolidinones using aziridines and carbon dioxide. Copolymerization of 2-methylaziridine and aziridine with carbon dioxide had previously been achieved in the absence of catalyst, but in the presence of iodine, monomeric material was obtained[9] (eq 14).



1.31 **1.32** (eq 14)

However, no further work was reported with this method. The reaction was not expanded to other substrates, and no mechanistic possibilities were considered. Potentially, complexation of aziridine with carbon dioxide facilitated a nucleophilic ring-opening reaction by the iodine. A quick intramolecular reaction yielded the 2-oxazolidinone **1.32** and is represented in Scheme 1-2.

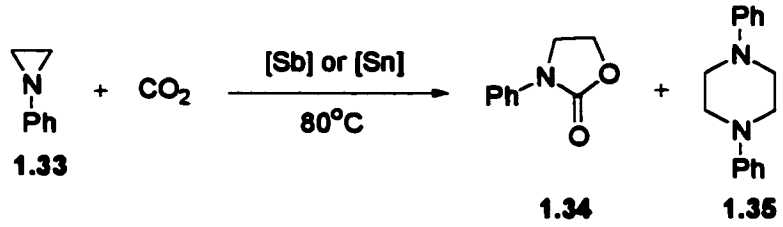
Scheme 1-2



Nevertheless, this report implicitly fueled more catalytic methods for cycloaddition reactions of aziridines with heterocumulenes.

1.3.3 Organoantimony halides

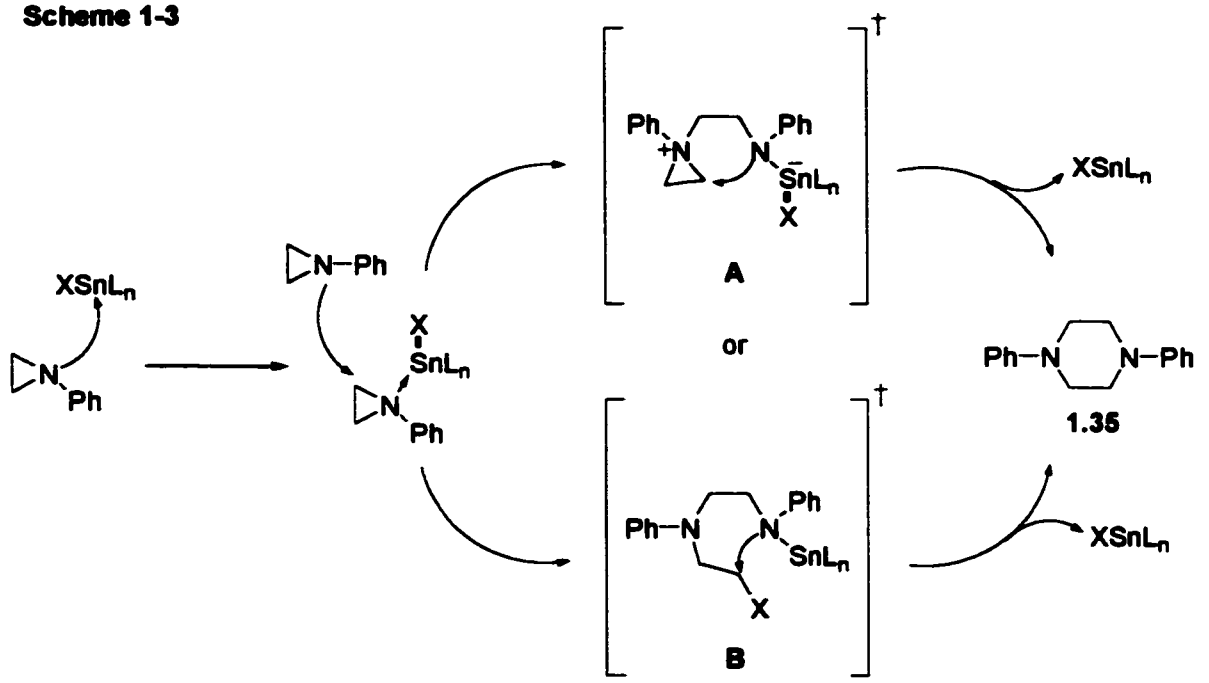
In the mid-1980s, Matsuda *et al.* applied their organoantimony and –tin catalysts to reactions of 1-phenylaziridine with carbon dioxide[10a] (eq 15).



1.33 **1.34** **1.35** (eq 15)

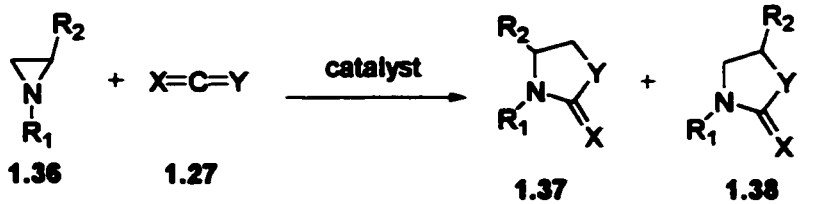
For organoantimony catalysts, such as Ph_4SbBr, the reactivity preference rendered oxazolidinone **1.34** in 86% yield. However the organotin catalysts had a higher propensity for dimerization, undesirably affording piperazine **1.35**. Many reports have indicated the heightened susceptibility of aziridine rings to activation and cleavage under acidic conditions[11]. Considering their greater Lewis acidity, tin catalysts will strongly activate the aziridine and promote dimerization over cycloaddition (Scheme 1-3).

Scheme 1-3



Subsequent to nucleophilic attack by one aziridine nitrogen, two possible mechanisms could be invisaged: (1) via intermediate **A**, where ring-opening of the tin-complexed aziridine produces a zwitterionic system followed by sequential attack on the now highly activated aziridine cation; or (2) intermediate **B**, in which nucleophilic attack causes both aziridine rings to open whereby an intermediate alkylhalide is displaced to produce the piperazine **1.35**. Of course, a combination of the two pathways is also feasible.

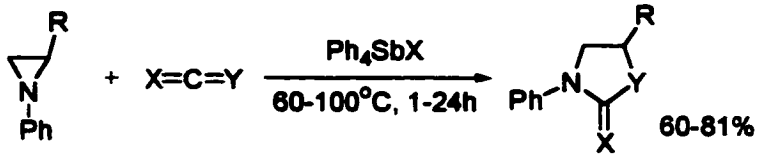
More importantly, however, organoantimony halides were suitable catalysts for this reaction. With lowered Lewis acidity, these compounds were unable to promote aziridine activation and consequently encouraged insertion of carbon dioxide. To further understand reactivity, additional studies were performed with these compounds, employing a variety of aziridine and heterocumulene substrates in subsequent reactions. For example, the direction of ring-opening in 2-substituted aziridines **1.36** invariably resulted in a mixture of two products arising from cleavage across both the N-CH_2 (β-cleavage affording **1.37**) and N-CHR (α-cleavage affording **1.38**) bonds[12] (eq 16).



(eq 16)

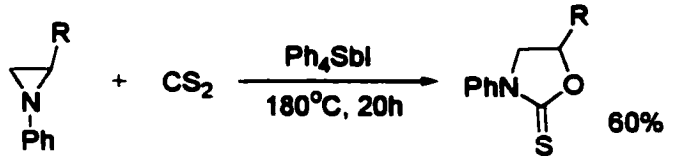
Greater regiochemical control would be necessary in a good catalyst.

Therefore, an assortment of 2-alkyl-1-phenylaziridines (R = H, Me, Et) was reacted with phenylisothiocyanate, carbon dioxide, and carbon disulfide using catalytic organostibonium halides[10b] (eq 17).



1.39 1.27 1.40 (eq 17)

Selectivity was excellent with the stibonium catalysts affording α-cleavage products **1.40** in moderate to good yield while classical ring-opening catalysts, such as ammonium salts, exhibited limited regioselectivity. Interestingly, organotin halides also favored α-cleavage, with lowered product yield due to dimerization, whereas with oxiranes they displayed the opposite preference to the antimony catalysts[4] (refer to eq 6, section 1.2.3). Reactions with phenylisothiocyanate (X = NAr, Y = S) and carbon dioxide predictably rendered **1.40** only. However, in the sole reaction with carbon disulfide (performed at 180°C due to low reactivity), the product was the oxazolidine-2-thione **1.41** (eq 18).



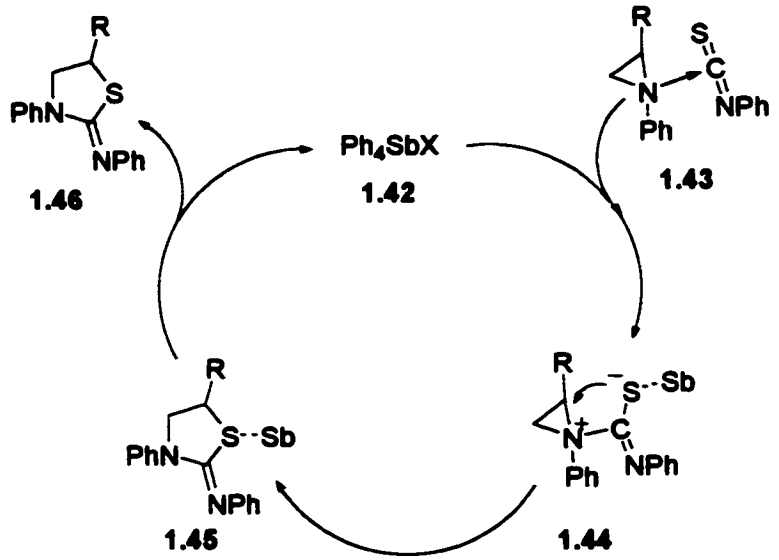
1.39 1.41 (eq 18)

No explanation was presented for the outcome of this reaction.

A general mechanism for the organostibonium-catalyzed cycloaddition reaction was postulated[10b] by examining the reaction of 1-phenylaziridine **1.39** and phenylisothiocyanate with ^{14}N and ^{13}C NMR spectroscopy. In particular, the $\delta^{14}NCS$ and $\delta N^{13}CS$ of phenylisothiocyanate appeared at higher fields when mixed with just the aziridine. This indicated electron donation to the NCS group by the aziridine (**1.43**). Moreover, addition of the organoantimony halide induced a shift to lower fields in the spectra, indicating interaction between the isocyanate and the catalyst (**1.44**). Following these events, it was

speculated that insertion into the metal-halide bond initiates the intramolecular reaction (Scheme 1-4).

Scheme 1-4



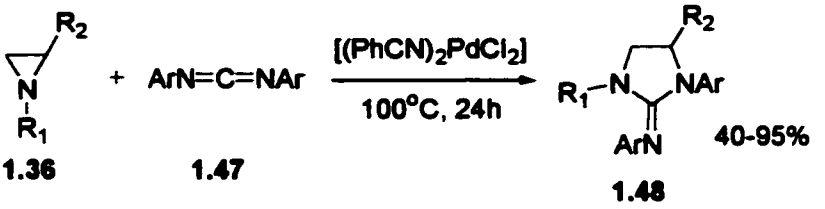
The selectivity of these catalysts can be rationalized from intermediate **1.44** where nucleophilic attack accomplished the cyclization. The methylene group exhibiting greater δ+ character (i.e. the better electrophilic center) will form the bond with sulfur. In the case of 2-alkylaziridines, the R group will stabilize the δ+ center better than CH_2 which promotes ring opening across the N-CHR bond (α-cleavage) resulting in the high selectivity for product **1.46** from this reaction.

Yet, it seemed necessary to develop other methods to optimize yields for these reactions. Some palladium (II) compounds were successful as catalysts for insertion reactions with highly strained ring systems at this time[13], suggesting the potential for new metal catalysts.

1.3.4 Palladium (II) catalysts

Besides the limited success encountered in the previous aziridine reactions, there was also restricted substrate inclusion. Baeg *et al.* experimented with catalytic methods that would extend the selectivity to a wider assortment of heterocumulenes and ring systems[14]. Initial results arose from reactions with 2-aryl-1-alkylaziridines **1.36** and

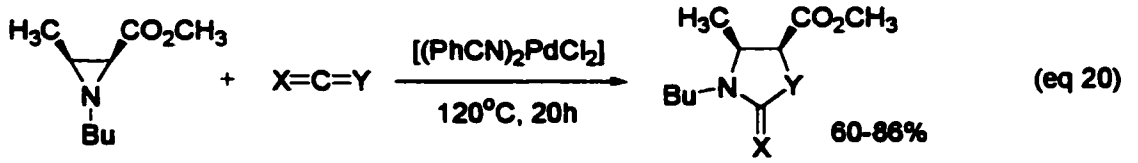
diarylcarbodiimides. At elevated temperatures, bis-(benzonitrile) palladium (II) dichloride proved to be an effective catalyst[14a] (eq 19).



1.36 **1.47** **1.48**

Modest to excellent yields were obtained producing imidazolidin-2-imines **1.48** regiospecifically with insertion across the more highly substituted bond. Supplementing this, ligand analyses offered more speculation on the reaction mechanism. Addition of triphenylphosphine prevented the cycloadditon whereas replacing the benzonitrile groups with acetonitrile retarded the reaction and afforded much lower product yields. In all likelihood, initial substrate complexation to the metal was required for the catalysis to proceed while more basic groups, such as triphenylphosphine and acetonitrile, displaced the substrate and hindered catalysis.

Baeg *et al.* subsequently introduced a modification to their approach by employing *cis*-2,3-disubstituted aziridines **1.49**[14b]. These compounds are highly sterically hindered and have proven quite unreactive for oxiranes as well as aziridines. In reactions with aryl-isocyanates, -carbodiimides, and –isothiocyanates, the reaction proceeded both regio- and stereospecifically (eq 20).



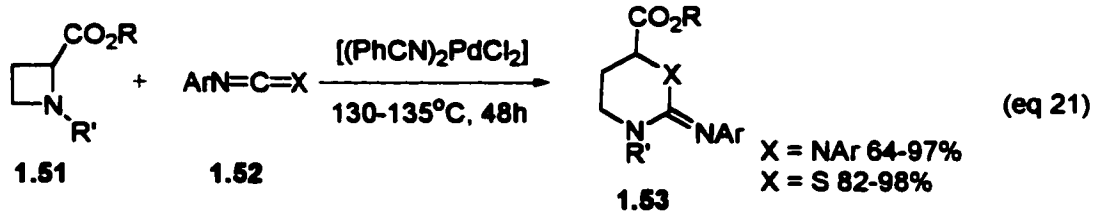
1.49 **1.27** **1.50**

Lower yields of *trans*-**1.50** were obtained for carbodiimide reactions (X = Y = NAr) that would largely be due to the steric congestion around the metal, but both isocyanates and isothiocyanates provided good yields. An indicator for retention of configuration was the coupling of the 4,5-protons characteristic of *cis*-vicinal proton coupling. However, to further verify the stereospecificity, both (S)-(+)- and (R)-(-)-1-alkyl-2-phenylaziridine were reacted

with a variety of heterocumulenes. In addition to obtaining high yields (80-90%), configuration was preserved, evident from resolution by ^{1}H NMR using a chiral shift reagent and X-ray crystallography.

The carboalkoxy group at the 2 position was required for reactivity of 1,2,3-trisubstituted aziridines such as **1.49**. Previous reactions using *N*-alkylated-3-methyl-2-phenylaziridine derivatives resulted in recovery of starting materials[14b]. The carboalkoxy group provided sufficient polarization of the N-C bond making it more labile to cycloaddition with the heterocumulene. This would be an important concept in establishing similar methods for the reactions of azetidines with heterocumulenes.

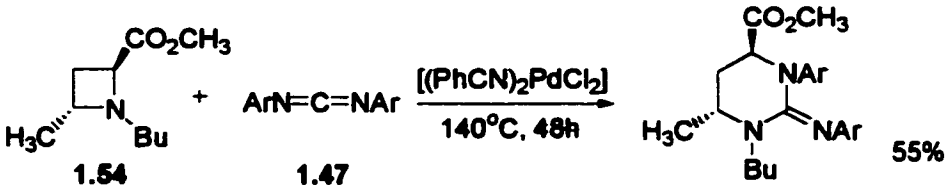
Azetidines are invariably less susceptible to ring opening than their three-membered counterparts. Reactivity is reduced since the angle strain is lessened with the larger ring size, and azetidines are capable of puckering which lessens torsional and eclipsing strain[1c]. Therefore a strategy must be adopted to activate the ring for cycloaddition reactions. 1-Alkyl-2-carboalkoxyazetidines **1.51** were synthesized and tested for reactivity with carbodiimides and isothiocyanates employing the same system[14d] (eq 21).



(eq 21)

Slightly higher temperatures were necessary, but the cycloaddition reaction of azetidines with heterocumulenes catalyzed by bis(benzonitrile)palladium(II) dichloride gave excellent results of **1.53** in general. It was again noted that more basic ligands, such as acetonitrile, reduced catalytic activity indicating an initial complexation with palladium. A common trend in both carbodiimide and isothiocyanate reactions involved the electronic character of the aryl-substituent. When electron-donating groups were present (Ar = tolyl), lower yields were reported due to a decrease in reactivity of the heterocumulene. Appropriately, better yields were obtained with electron-withdrawing substituents, such as a nitro- group. For these reactions, electrophilicity of the central carbon in the heterocumulene appeared greatly affected by minor alterations in the substrates.

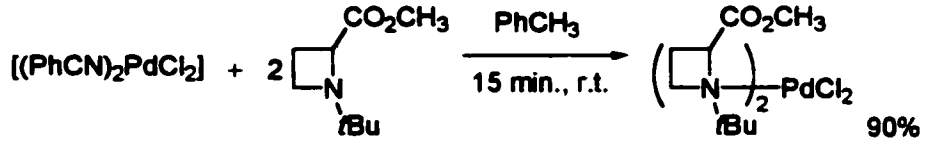
Analogous to the aziridine system, configuration was retained when *trans*-1-butyl-4-methyl-2-carbomethoxyazetidine **1.54** reacted with bis(*p*-chlorophenyl) carbodiimide yielding only the *trans*-isomer of **1.55**[14c] (eq 22).



1.54 **1.47** **1.55**

(Ar = p-ClC$_6$H$_4$) (eq 22)

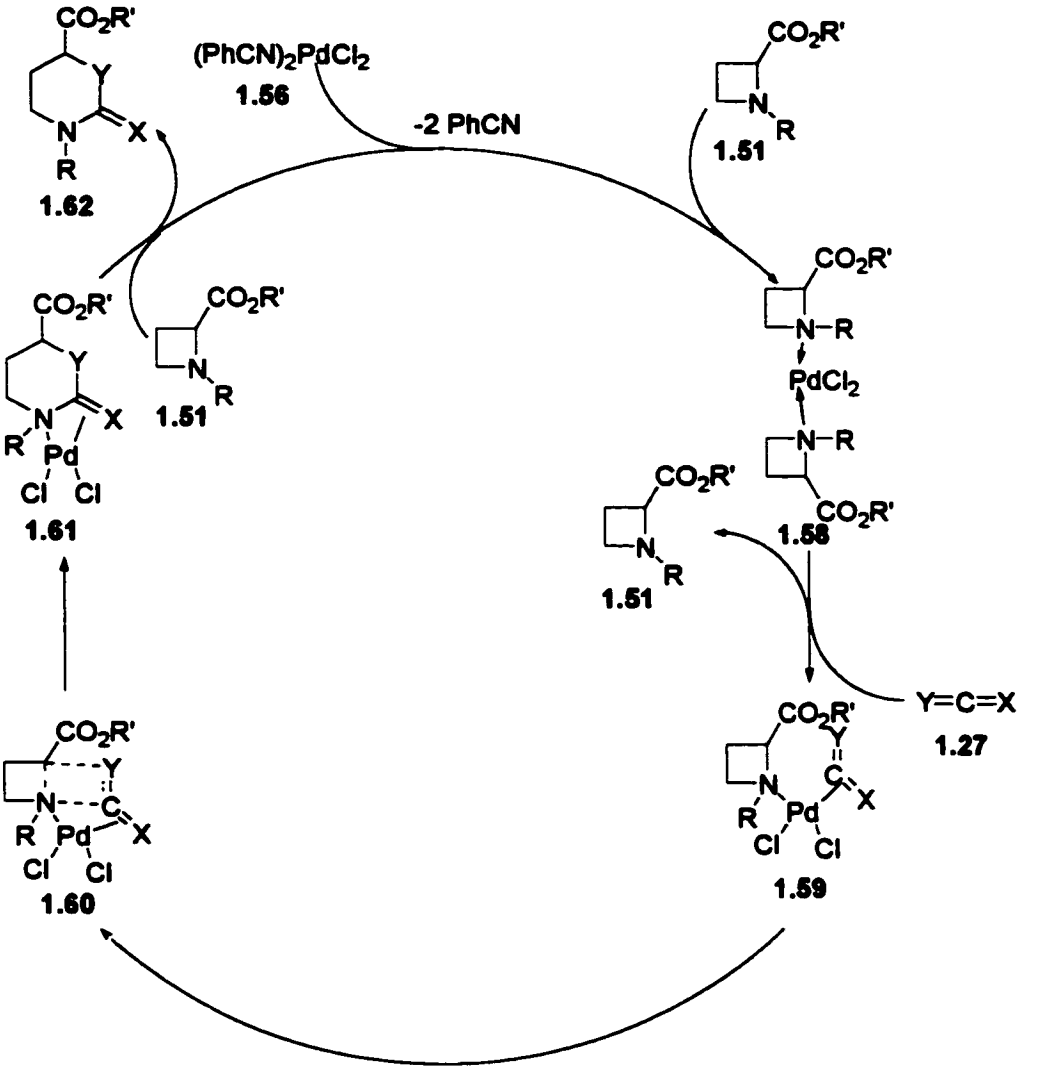
Another satisfying outcome arose from these investigations. A likely reaction intermediate **1.58** was isolated from the stoichiometric reaction of the palladium catalyst **1.56** with **1.57** at room temperature[14c] (eq 23).



1.56 **1.57** **1.58** (eq 23)

Complex **1.58** was equally capable of catalyzing the cycloaddition reaction as **1.56**, indicating that it has a role in the mechanism for the reactions of azetidines with heterocumulenes. Scheme 1-5 diagrams the postulated catalytic cycle[14] that was presumed to be analogous for aziridines.

Scheme 1-5

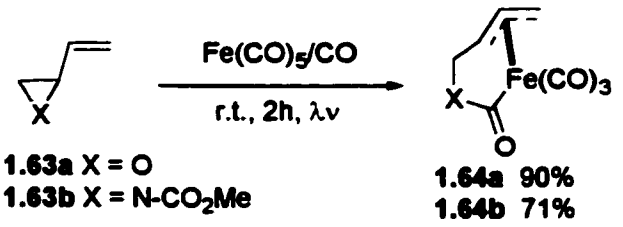


From intermediate **1.60**, the requirement of a polarized bond in the aziridine or azetidine ring and an electrophilic carbon on the heterocumulene are easily understood. The substrates first arrange themselves on the metal (**1.59**) with proper dipole alignment. Under thermal conditions (120-140°C), the cycloaddition reaction proceeds in a concerted manner leading to retention of configuration in products **1.62**. However, the introduction of stereoselectivity is not possible in this system. Elevated temperatures and long reaction times impart harsh conditions on the substrates, and sensitive groups could not be used. More active substrates would be required to allow for milder methods.

1.4 π-Allyl palladium reactions

1.4.1 Fundamental breakthrough

An attractive report of ring cleavage in three-membered heterocycles[15] introduced the concept that π-allyl metal complexes could be useful intermediates for insertion reactions. In a light induced reaction, $Fe(CO)_5$ carbonylated 2-vinyloxirane **1.63a** and 2-vinylaziridine **1.63b** affording high yields of **1.64a** and **1.64b** at room temperature (eq 24).



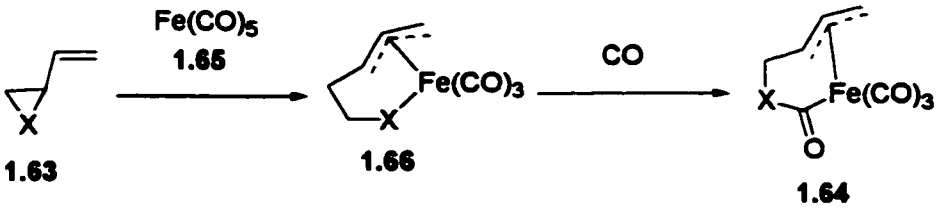
1.63a X = O
1.63b X = N-CO_2Me

1.64a 90%
1.64b 71%

(eq 24)

In these experiments, facile ring opening was speculated to occur due to formation of **1.65** (Scheme 1-6) in which the metal is coordinated to both the heteroatom and the π-allyl moiety. Carbonyl insertion afforded the metallolactone or –lactam.

Scheme 1-6

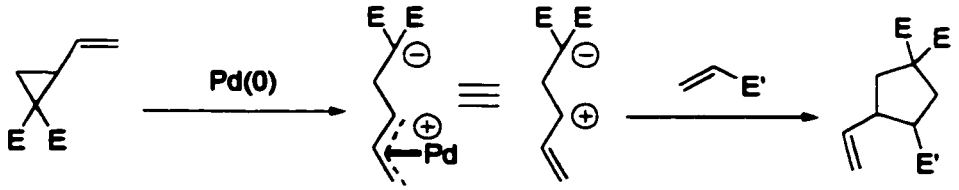


1.63 **1.66** **1.64**

Considering previous mechanisms, in which heterocumulene insertion into the metal-heteroatom bond readily occurred[4-7, 10], this catalytic design seemed a rather obvious opportunity for reactivity under milder reaction conditions for applications with strained heterocycles. No external energy source would be required. The driving force to intermediate **1.65** arises from release of ring strain and formation of the π-allyl palladium moiety. However, another decade passed before initial reports of Pd(0)-promoted reactions with vinyloxiranes would surface.

1.4.2 Vinyloxiranes and oxetanes

Surprisingly, the first account included no mention of heterocycles. In the preparation of 1,3-dipolar equivalents (**1.68'**), Tsuji *et al.* furnished zwitterionic π-allylpalladium complexes **1.68** using vinylcyclopropanes **1.67** containing two electron-withdrawing groups[16] that created polarization in the ring similar to a heteroatom (eq 25).



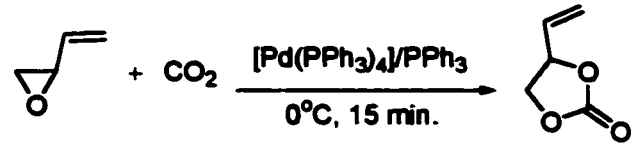
1.67 **1.68** **1.68'** **1.69**

(E = E' = CO_2Me)

(eq 25)

These intermediates reacted with activated olefins under mild conditions (30°C, 1-3h) affording the vinylcyclopentanes **1.69** in good yields.

Following closely on the heels of this report, an alternate synthesis for cyclic carbonates was proposed[17]. The previous method required high pressure and elevated temperatures for the catalytic cyclization of oxiranes and carbon dioxide. However, vinyloxirane **1.70** and carbon dioxide could be quite rapidly and quantitatively converted to vinylethylene carbonate **1.71** under a CO_2 atmosphere at 0°C or room temperature using zerovalent palladium (eq 26).



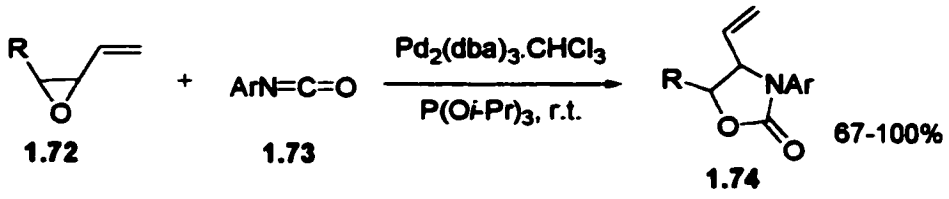
1.70 **1.71**

(eq 26)

Again, a π-allylpalladium intermediate was presumed responsible for the ease and proficiency of the reaction.

Isocyanates were first employed by Trost *et al.* in attempts to synthesize hydroxyamine intermediates in a diastereoselective fashion[18a]. Concerns arose over whether

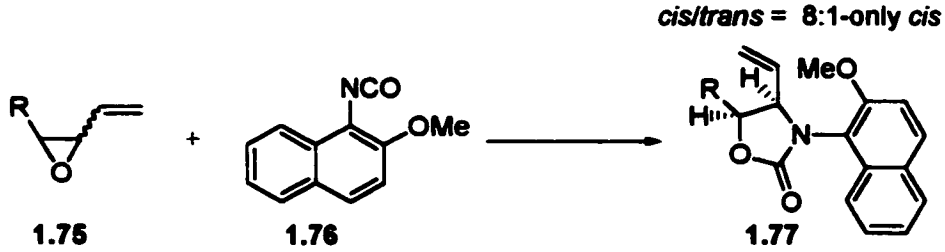
N- or *O*-alkylation would be favored – the latter being an unfavorable side-product for their purpose. However, only **1.74** arose from *N*-alkylation under their conditions (eq 27).



(eq 27)

Good to excellent yields were obtained in these reactions which proved to be both diastereo- and enantiospecific for *p*-toluenesulfonylisocyanate (Ar = Ts). The tosyl isocyanate was much more reactive and acted like a trap for the π-allylpalladium intermediate. They felt this might indicate some level of coordination between the isocyanate and oxirane beforehand facilitating ring cleavage. Application of this selective procedure accomplished the key conversion to the *N*-acetyl-*O*-methyl glucoside derivative of (-)-acosamine[18a].

Further exploration of the methodology with 2-vinyl-3-substituted oxiranes **1.75** by Trost *et al.* [18b] showed a remarkable preference with less activated arylisocyanates (eq 28). Whether the oxirane substrate was predominantly *cis* or *trans*, **1.77** displayed high ratios in favor of the *cis* configuration particularly with *o*-substituted arylisocyanates (**1.76**).

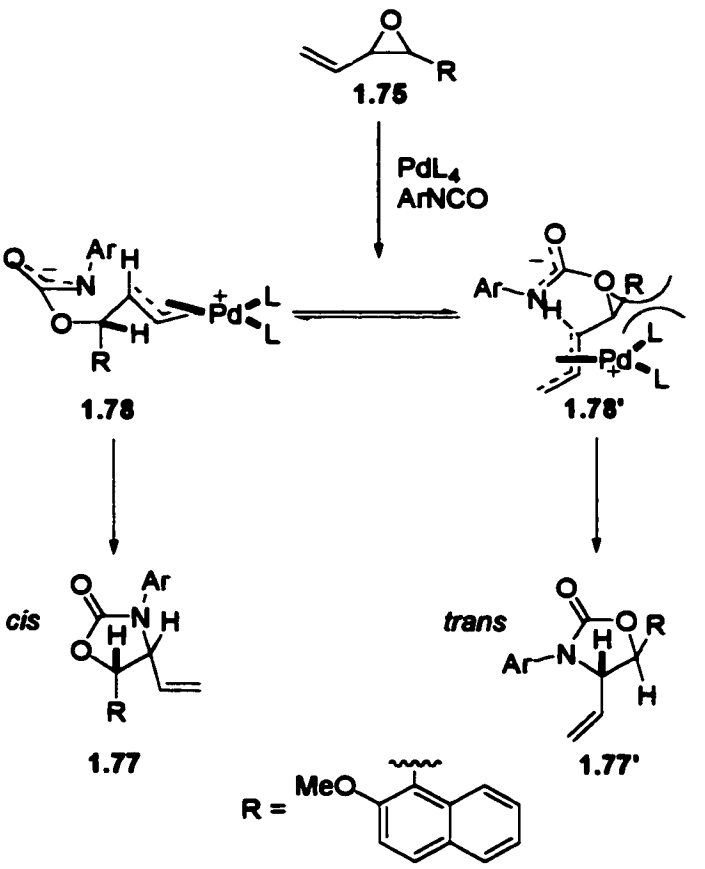


(eq 28)

R = $PhCH_2CH_2$, Cy, n-$C_{11}H_{23}$, $Cl(CH_2)_3$, $TBDMSOCH_2CH_2$, $CH{=}C(CH_2)_3$

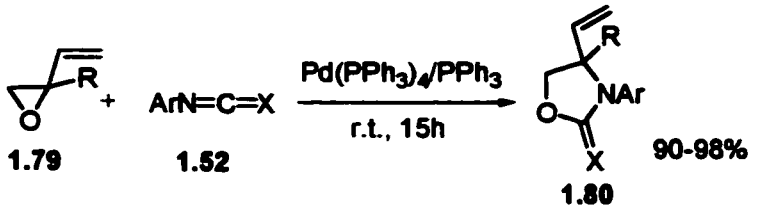
Since both *cis*-and *trans*-epoxides afforded these results, it was proposed that interconversion of the π-allylpalladium intermediate between diastereomeric complexes (**1.78** and **1.78′**) must occur preferentially to the cyclization with these isocyanates. A diagrammatic interpretation of the events was offered[18b] (Scheme 1-7).

Scheme 1-7



Ring cleavage by the catalyst and nucleophilic attack on the isocyanate produced a diastereomeric mixture of π-allylpalladium intermediates in equilibrium with one another. Two unfavorable situations arose within these systems: (1) in the formation of the *trans* product, **1.78'** created considerable interaction between the R group and the palladium complex; and (2) intermediate **1.78** leads to close contact for the R group and vinyl moeity. Since cyclization favors **1.77**, interaction with the palladium complex must far outweigh formation of the *cis* geometry in the equilibrium resulting in the high diastereomeric ratios for these reactions.

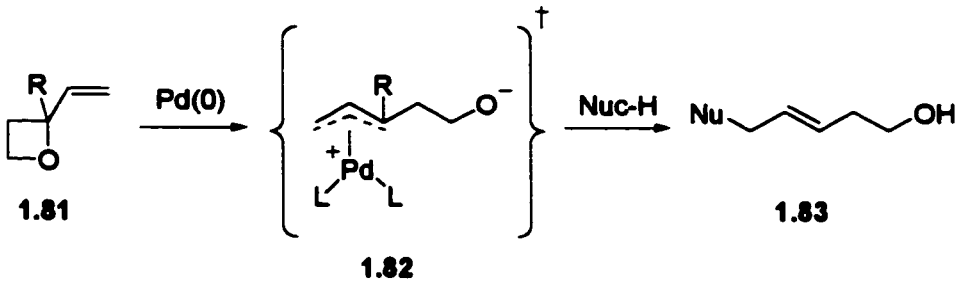
Recent work has fashioned more inclusive and selective cycloaddition reactions for extending the range of substrates and producing optically pure compounds[19, 21]. Larksarp *et al.* devised a general method for vinyloxiranes with carbodiimides and isocyanates[19a] (eq 29).



(eq 29)

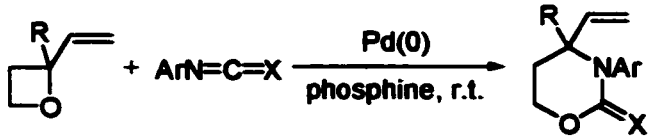
Excellent yields were obtained for **1.80** employing both heterocumulenes (X = O, X = NAr) under very mild conditions. Using chiral Pd(0)/TolBINAP systems, high enantioselectivity was accomplished maintaining excellent yields with e.e. values ranging from 69-94% for reactions with carbodiimides but only 43-49% for isocyanates[19a].

Once again, these mechanisms were presumed to proceed via π-allyl intermediates. Interestingly, Larock *et al.* similarly concluded that these zwitterionic species (**1.82**) existed in the synthesis of homoallylic alcohols from 2-vinyloxetanes[20] (eq 30).



(eq 30)

Therefore, a study undertaken by Larksarp *et al.* resulted in methodologies for the reactions of 2-vinyloxetanes with heterocumulenes[19b]. Due to the four-membered ring exhibiting less reactivity, greater difficulty would be expected. Many Pd/phosphine-based catalyst systems were examined; none of which were general for all reactions of 2-vinyloxetane with isocyanates and carbodiimides (eq 31).

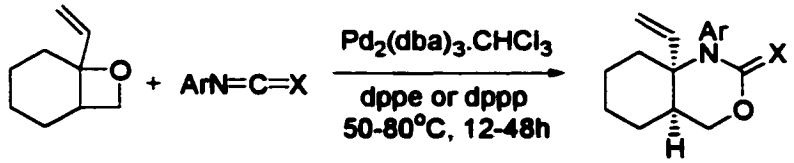


(eq 31)

1.84a X = O, R = H 34-83%
1.84b X = O, R = Me 25-45%
1.84c X = NAr, R = H 65-98%
1.84d X = NAr, R = Me 62-92%

Even though reaction times were relatively short (1-2h), yields for **1.84a-b** were somewhat reduced, possibly due to trimerization of the isocyanates preferentially over cycloaddition with the oxetane. Carbodiimides exhibited longer reaction times (12-48h) but afforded **1.84c-d** in better yields. Even with increased congestion about the π-allylpalladium intermediate (R = Me), good results were obtained with carbodiimides (**1.84d**).

Intriguing diastereoselectivity was demonstrated in the synthesis of bicyclic oxazines **1.86**[19b] (eq 32).

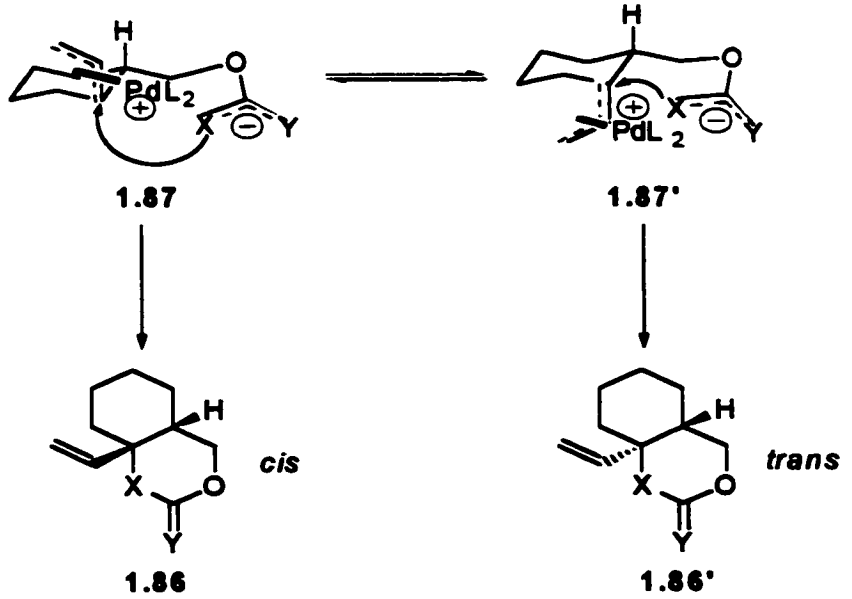


1.85 **1.52a** X = O, **1.52b** X = NAr → **1.86a** 43-55%, **1.86b** 66-98%

(eq 32)

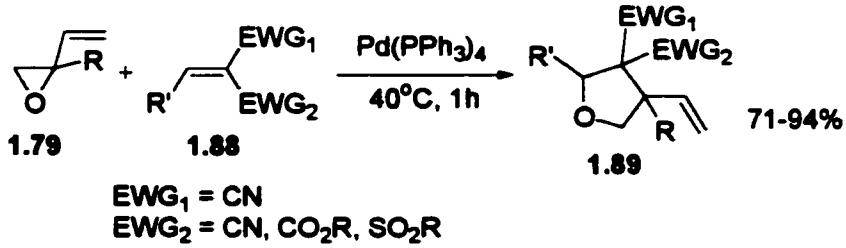
Because of steric bulk, the bicyclic substrates exhibited reduced reactivity, and the reactions required higher catalyst load and elevated temperatures. However, this bulkiness was presumed to have induced the selectivity, attributing *cis* geometry in the products. Similar to the findings of Trost *et al.*[18b], the preference arises via the π-allyl species in which both **1.87** and **1.87′** are two possible intermediates[19b] (Scheme 1-8).

Scheme 1-8



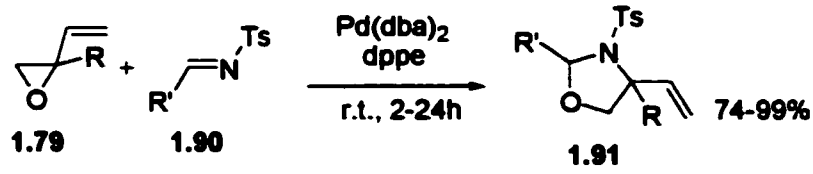
Interaction with the palladium catalyst prohibited ring closing in **1.87′** whereas intermediate **1.87** arranged a more favorable set up for intramolecular attack. In an equilibrium sense, preferable consumption of **1.87** tipped the balance toward formation of *cis*-bicyclic products **1.86** due to the lethargic reactivity of **1.87′** in producing the *trans*- configuration, **1.86′**.

Further expanding the utility of vinyloxirane reactions, activated olefins **1.88** were employed for insertion into π-allylpalladium intermediates by Shim and Yamamoto[21a] (eq 33).



(eq 33)

Tetrahydrofuran derivatives **1.89** were regioselectively obtained in good yields when sterically less bulky electron-withdrawing groups (EWG), such as nitriles, were used. No products resulted for olefins with two ester functions, but mixed nitrile/ester olefins were effective. Palladium tetrakis(triphenylphosphine) proved to be more suitable in this case, but substituting imines **1.90** for olefins[21b] necessitated a modification of the catalyst (eq 34).

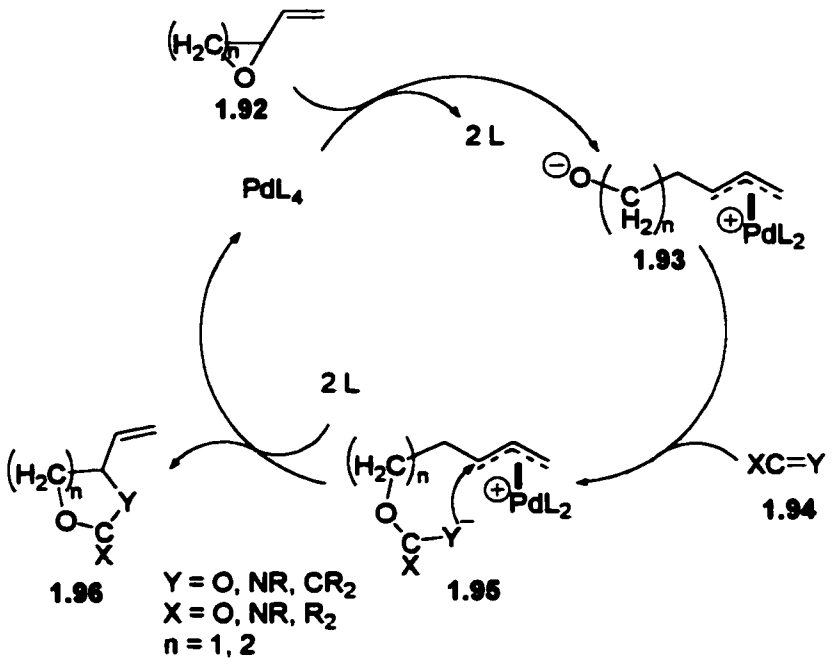


(eq 34)

A palladium bis(dibenzylideneacetone)/bis(diphenylphosphine)ethane system smoothly catalyzed the synthesis of oxazolidine products **1.91** under mild conditions. Other *N*-substituted imines, such as alkyl or aryl, did not react. As in reactions with activated olefins, (2,2)-disubstituted oxiranes (R = Me) required longer reaction times indicating congestion of the π-allyl palladium intermediates, likely hindering both incipient attack by the catalyst and subsequent intramolecular ring-closing.

A similar mechanism is proposed for the palladium-catalyzed reactions of polarized carbon electrophiles (**1.52, 1.88,** and **1.90**) with vinyloxiranes and –oxetanes that proceed via the π-allyl moiety in all instances[17-19, 21] (Scheme 1-9).

Scheme 1-9

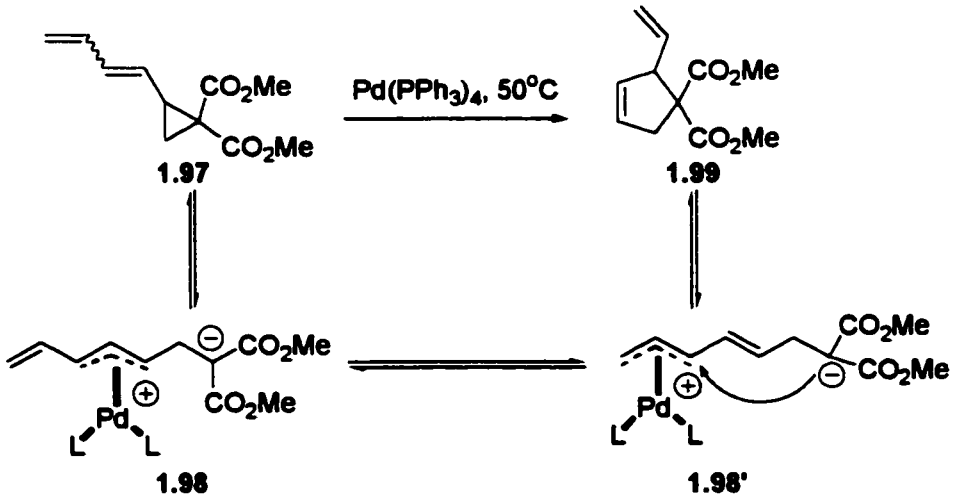


The vast array of applications that have originated from this methodology is of great importance to organic synthesis (Scheme 1-9). Both vinyloxirane and –oxetane have proven useful in these systems[17-19, 21], in addition to the bicyclic oxetane[19b]. The desired product can be secured by utilizing either a three- or four-membered ring **1.92**, modifying the substituents on the ring or heterocumulene, and by exchanging the carbon electrophile **1.94** for the insertion. Absolute regioselectivity can be achieved in all cases[16-19, 21], and the possibility for enantioselectivity has been demonstrated[19a]. Moreover, procedures for the deprotection of *N*-tosyl and some *N*-aryl groups are established[18] increasing the applicability of these cycloaddition reactions to organic synthesis. With many reported procedures for aziridines and azetidines[1c], an obvious route to nitrogen based heterocycles would be via the vinyl derivatives. However, whether the vinylaziridines and –azetidines will ring cleave and react similar to oxiranes and oxetanes should be examined.

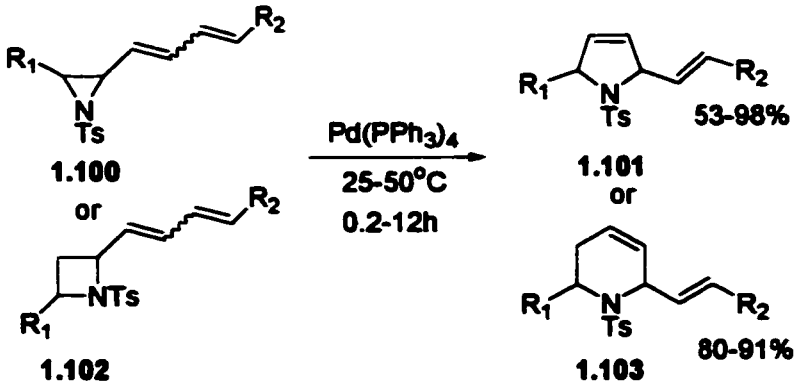
1.4.3 Vinylaziridines and –azetidines

Manipulations involving π-allyl species are less prevalent for the nitrogen analogues. After the carbonylation of vinylaziridines by $Fe(CO)_5$[15] (see eq 24, section 1.4.1), approximately a decade and a half passed with little or no research in this area. Oshima *et al.* elaborated on the synthesis of cyclopentane derivatives from vinylcyclopropanes and activated olefins (see eq 25, section 1.4.2) with rearrangement reactions (Scheme 1-10) that replaced the vinyl substituent with a dienyl group[22] (**1.97**).

Scheme 1-10



Under relatively mild conditions, **1.99** was obtained in excellent yield (87%). The dienyl system provided the means for this reaction. Intermediate **1.98** cannot undergo intramolecular attack to afford **1.99**, but required isomerization to **1.98'** for the cyclization to occur. Similarly, dihydro-pyrroles **1.101** and tetrahydro-pyridines **1.103** were synthesized from dienylaziridines **1.100** and -azetidines **1.102**[22] (eq 35).

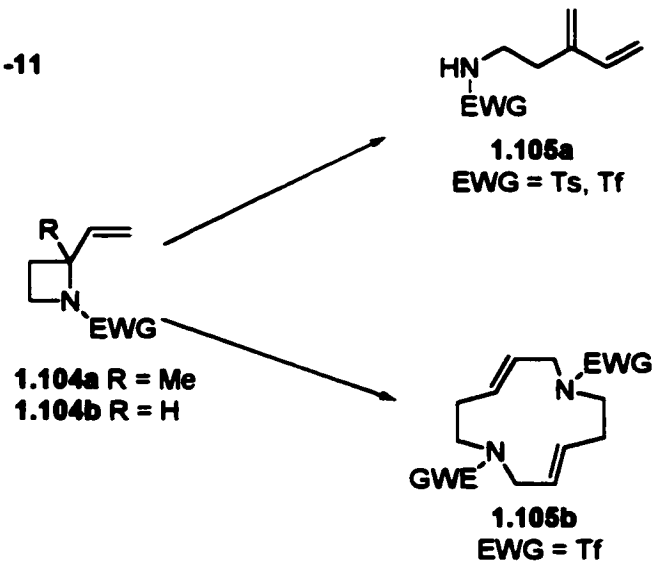


(eq 35)

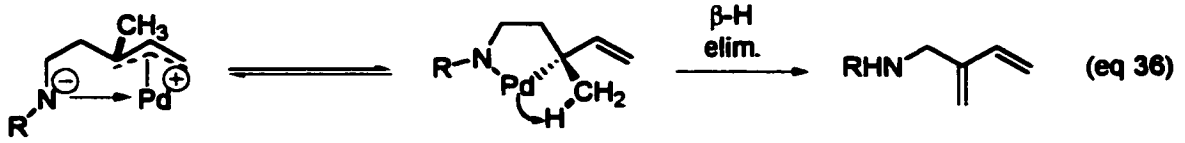
These Pd(0)-catalyzed events proved very facile and highly efficient synthetic procedures with both **1.100** and **1.102** indicating their susceptibility to ring cleavage via π-allyl intermediates.

Broadening the understanding of π-allyl induced rearrangements, Yamamoto *et al.* investigated the reactivity of 2-vinyl and 2-methyl-2-vinylazetidines **1.104** in the presence of zero-valent palladium[23] (Scheme 1-11).

Scheme 1-11



At ambient temperatures, radically different products were obtained with quite similar azetidine substrates. However, upon examination of the accepted transition state arrangements for these reactions, the results are quite easily explained. In the formation of **1.105a**, reorientation of the π-allyl moiety to **1.106′** set up a β-hydride elimination[23] (eq 36), supporting a case for a complex such as **1.106**.

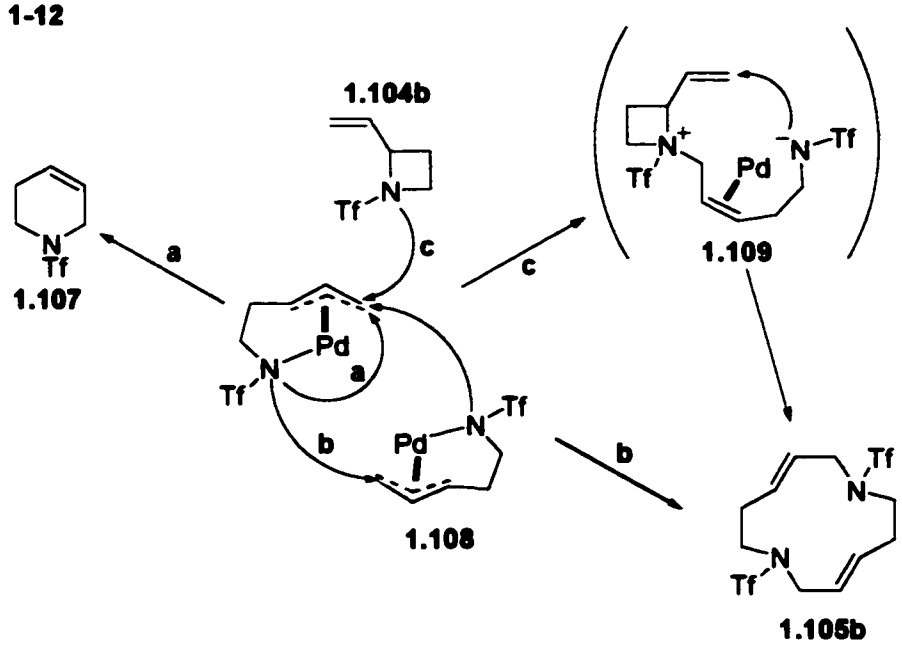


1.106 **1.106'** **1.105a**

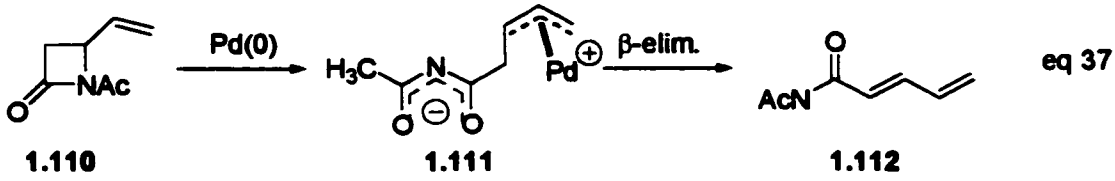
Without the 2-methyl group, the π-allyl complex may be quite stable. As mentioned previously, organization about the metal centre prevented intramolecular cyclization (route **a** of Scheme 1-12), and no hydrides are available for abstraction as in **1.105a**. Therefore, only intermolecular dimerization (route **b**) occurred (Fig. 23). Yamamoto *et al.* concluded that

two intermediate complexes interact affording **1.105b**, but it is conceivable that uncomplexed azetidine **1.104b** participated as the nucleophile (route c) affording the dimer via **1.109**.

Scheme 1-12



The authors speculate the azetidine nitrogen chelates to the palladium in the zwitterionic intermediate. Evidence for this arose from the rearrangement (eq 37) of a related vinylazetidinone, **1.110**.

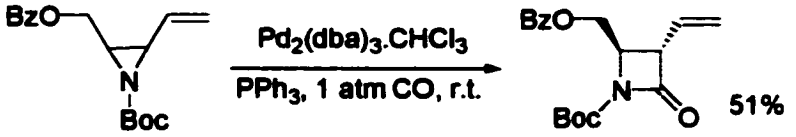


eq 37

The previous cases demonstrated no capacity for undergoing this β-hydride elimination. However, delocalization of the negative charge stabilized the zwitterionic character in **1.111** while the highly basic anionic amines of **1.106'** and **1.108** must bind to the metal. The latter two structures positioned the methylene hydrogens away from the palladium centre, but they are exposed in **1.111**, allowing for this elimination with the azetidinone example only.

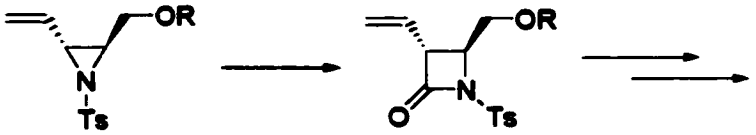
Findings of this sort advocate the validity of π-allylpalladium species resembling **1.108** in reaction mixtures of vinylaziridines and –azetidines with many zero-valent palladium species. However, the utility of these complexes for insertion-type procedures had been insufficiently established up to this point.

In independent reports[24], Tanner and Ohfune demonstrated that carbonylation of vinylaziridines could be a valuable application in the pharmaceutical arena. Ohfune *et al.* provided the initial account synthesizing only *trans*-3-substituted 4-vinylazetidin-2-one **1.114** under very mild conditions[24a] (eq 38).



1.113 **1.114** (eq 38)

This design displayed significance to the field of β-lactam antibiotics as Tanner and Somfai applied the Pd(0)-carbonylation method[24b] in a key synthetic step of (+)-PS-5, an intermediate in the total synthesis of carbapenem antibiotics (eq 39).

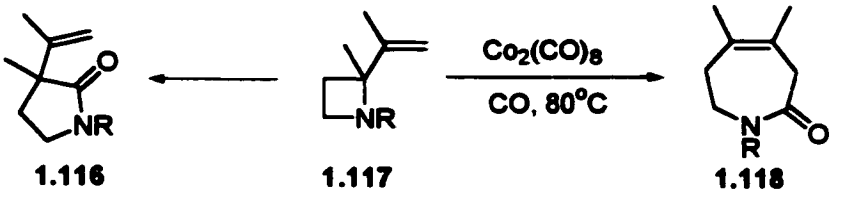


(eq 39)

In the latter case, retention of configuration was observed. Yet the initial method showed remarkable diastereoselectivity since a mixture of *cis*- and *trans*-aziridines were employed[24a]. Again, steric factors were determined to be responsible for inducing the selectivity. The π-allylpalladium moiety necessarily aligned itself away from the C_2 substituent **1.115'** to limit steric interaction whereby carbonyl insertion gave rise to only the *trans* isomer **1.114** (eq 40).

1.115 **1.115'** (eq 40)

In addition to this unusual diastereoselectivity, the carbonyl insertion was clearly regioselective in these reactions. However, Roberto and Alper[25] reported a noteworthy carbonylation of the vinylazetidine **1.118** (eq 41).



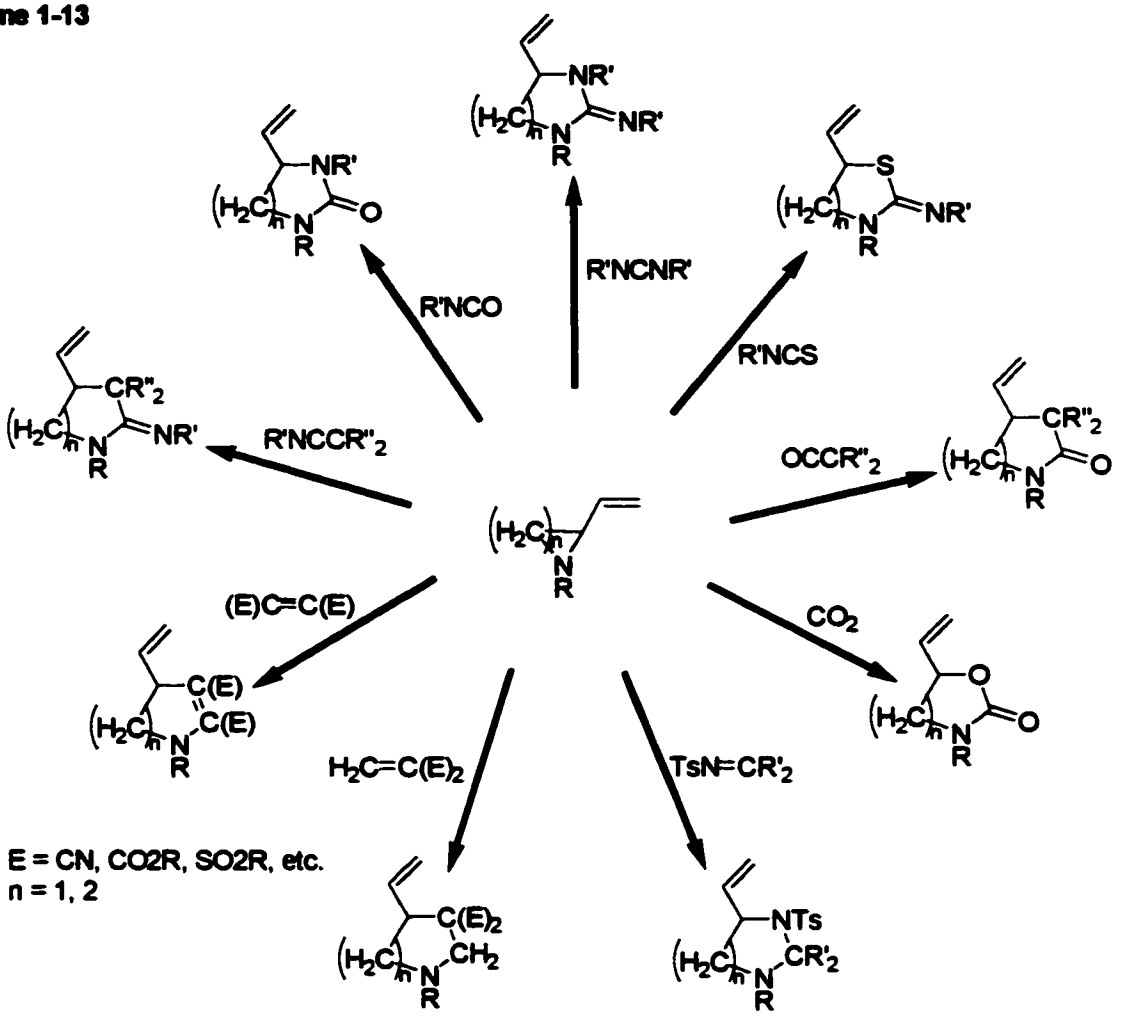
1.116 **1.117** **1.118**

R = H, $(CH_2)_2CO_2Me$, $(CH_2)_2CN$

Instead of yielding the expected five-membered lactam **1.116**, insertion occurred at the isopropenyl substituent producing the tetrahydroazepinone **1.118**. Perhaps due to the preference of cobalt versus palladium catalysts or simply due to the congestion already present at the anticipated carbonylation site, the regioselectivity of this reaction was quite unexpected. Nevertheless these model systems verified that vinylaziridines and –azetidines could be appropriate substrates for insertion reactions involving π-allyl complexes. In recent reports, related cases have found utility with such intermediates. For example, a variety of heterocycles have been prepared from decarboxylative-carbonylations of 5-vinyl cyclic-carbonates and –carbamates[26] and cyclizations of allene-substituted alcohols and amines[27]. All of these cases were considered to proceed via π-allyl complexes.

Applying what is already known of cycloaddition reactions from studies on the oxygen analogues[17-19, 21], many conceivable applications can be imagined for patterning a variety of new synthetic methods with vinylaziridines and –azetidines. Examples of the heterocyclic compounds that could potentially be prepared are in Scheme 1-13.

Scheme 1-13



Investigation of this methodology should lead to exciting new breakthroughs in heterocyclic chemistry.

1.5 Aims of research

Methods for the synthesis of *N*-alkyl-2-vinylazetidines via standard organic techniques were to be investigated and used to study the reactions of 2-vinylazetidines with heterocumulenes. From the study, a general and regioselective catalytic procedure was anticipated. It was hoped an array of six-membered heterocycles could be constructed through the reaction of *N*-alkyl-2-vinylazetidines with a variety of heterocumulenes using this procedure. Finally, applying chiral bidentate phosphine ligands to the method, it was expected that the reaction would proceed stereoselectively.

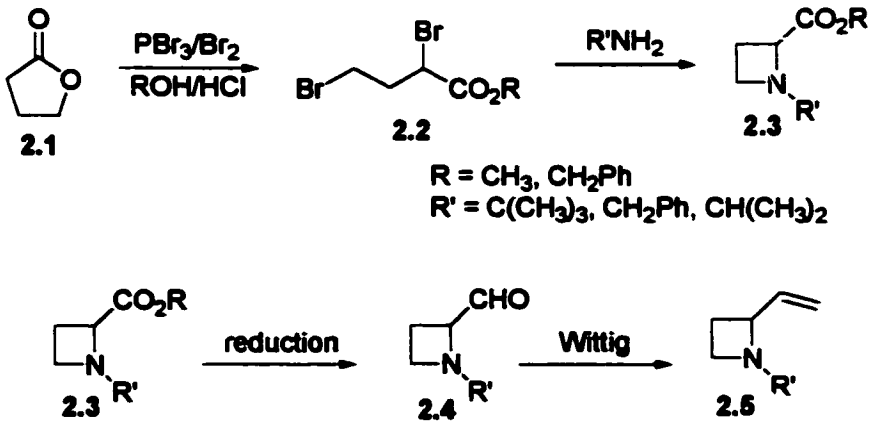
Chapter 2

2.1 Synthesis of starting materials

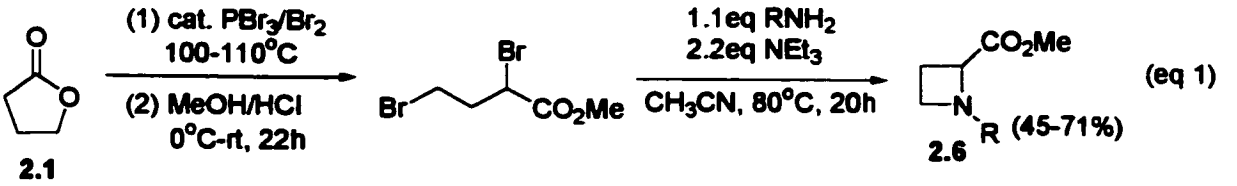
2.1.1 Azetidines

Prior examples of facile ring opening with azetidines and subsequent insertion reactions involved electron-withdrawing substituents on the ring nitrogen, such as tosyl and acyl groups. The increased polarization of the N-C bond by these groups made the ring more susceptible to cleavage. The carbonylations[22] and isomerizations[24, 25] of vinylaziridines and –azetidines proceeded with electron-withdrawing groups, advocating sufficient basicity of the nitrogen to perform the insertion and ring-closing steps required for this transformation. However, it would be important to establish these reactions with less activated systems to provide a more general method for all 2-vinylazetidine derivatives. Rodebaugh *et al.* published a two-step procedure for the synthesis of 2-carboalkoxyazetidines[28] **2.3** with *N*-alkyl substituents from γ-butyrolactone **2.1**, an available and relatively cheap compound. From this point, partial reduction of the ester and a Wittig reaction could be successively utilized in the synthetic design of *N*-alkylated 2-vinylazetidines **2.5** (Scheme 2-1).

Scheme 2-1



Employing the method by Rodebaugh *et al.*, three carbomethoxyazetidines **2.6** were synthesized (eq 1).

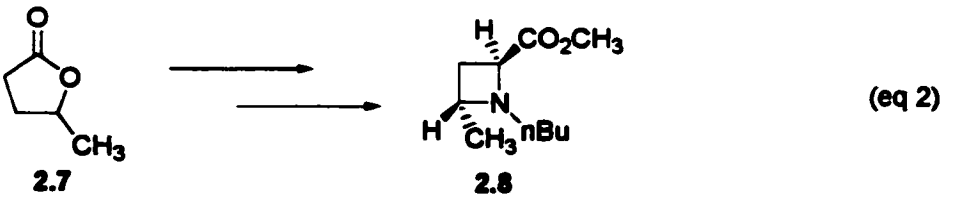


2.1 **2.6**

R = $CH_2(CH_2)_2CH_3$, C_6H_{11}, $C(CH_3)_3$

The initial bromination of **2.1** proceeded in almost quantitative fashion whereas the nucleophilic attack by the primary amine and ensuing intramolecular cyclization were much lower yielding. Forgoing a study of all possible alkyl substituents, only these sample derivatives were prepared - chains of a primary (*n*-butyl), secondary (cyclohexyl), and tertiary (*t*-butyl) alkyl group - as representatives of the larger series. This would assist in understanding the steric effect in the reaction and, possibly, to reveal any disparity in reactivity due to the minor electronic variations of these derivatives. Identification of the carbomethoxyazetidines could be ascertained by ^1H NMR spectra where a singlet at ~3.5 ppm and a triplet between 3.5-4.0 ppm correspond to the methoxy group and the α-proton on C_2, respectively.

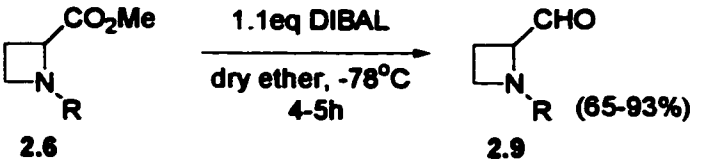
In addition, to study the stereochemistry of the cycloaddition reaction, the *trans* isomer of 1-butyl-2-carbomethoxy-4-methylazetidine **2.8** could be employed.



2.7 **2.8**

This compound had been prepared from **2.7**, γ-valerolactone, in similar fashion to eq 1 where distillation selectively yields **2.8**[29]. Only this diastereomer was present in the ^1H and ^{13}C NMR spectra, which was previously determined to have the *trans* configuration.

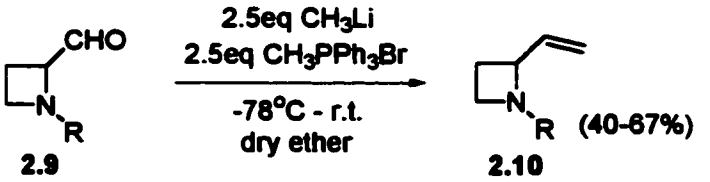
Partial reduction of **2.6** could be attained using excess DIBAL[22, 30]. A modification of this procedure (eq 3) optimized the yield of **2.9**, 1-alkylazetidine-2-carbaldehyde, which made this pathway a more desirable route to the vinyl derivative.



(eq 3)

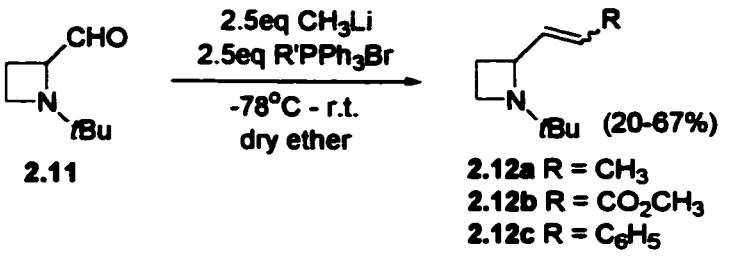
Identification was accomplished initially by GC-MS. Inseparable mixtures of the aldehyde and the alcohol predominated in early reactions as detected by mass spectra. When the amount of DIBAL employed was reduced to ~1-1.5 equivalents, the yield of the aldehyde was enhanced, but traces of the ester and alcohol were often carried over to the next step. Additionally, characteristic signals of the aldehyde group were present in the ^{1}H NMR spectra at 9.5-9.8 ppm and ^{13}C NMR spectra at 205-210 ppm respectively for **2.9**. In similar fashion, **2.8** could be reduced to the carbaldehyde in 85% yield, retaining the *trans* configuration in the product.

In the final step of the synthesis, a Wittig reaction (eq 4), based on a transformation reported by Fugami *et al.*[22], was employed where the reagent was prepared *in situ* prior to addition of **2.9**.



(eq 4)

Low yields of **2.10** were encountered and could be attributed to difficulties in purifying the low-boiling products as well as the potential for side reactions via the α-proton of **2.9** which is quite acidic. The reagent could instigate an aldol reaction. Applying the same procedure, additional vinylazetidine substrates could be prepared with different phosphine ylides yielding **2.12**, possessing substituents on the vinyl group (eq 5).

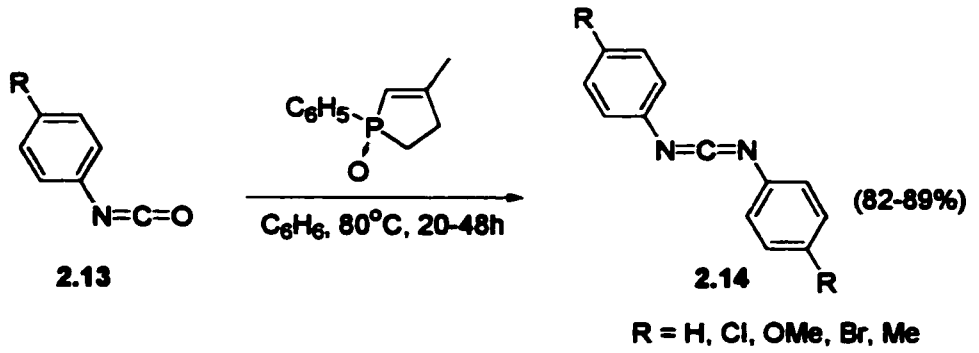


(eq 5)

Previous reports indicated a decline in reactivity with extra congestion present in the π-allyl moiety[18-19, 21]. However, groups positioned on the vinyl group should be tolerated for transformations of these kinds to have significance as synthetic procedures. The ^{1}H NMR spectra of **2.12** were quite simple with identifying peaks between 5 and 6 ppm characteristic of vinylic protons, and a broad multiplet at ~4 ppm arising from the ring proton adjacent to the vinyl group. For **2.12a**, a mixture of *cis/trans* (1:2) isomers resulted, but only traces of the *cis* isomer occurred in the other cases. Similarly, *N*-alkylated *trans*-4-methylazetidine-2-carbaldehyde could be transformed to its vinyl derivative with retention of configuration in 56% yield.

2.1.2 Heterocumulenes

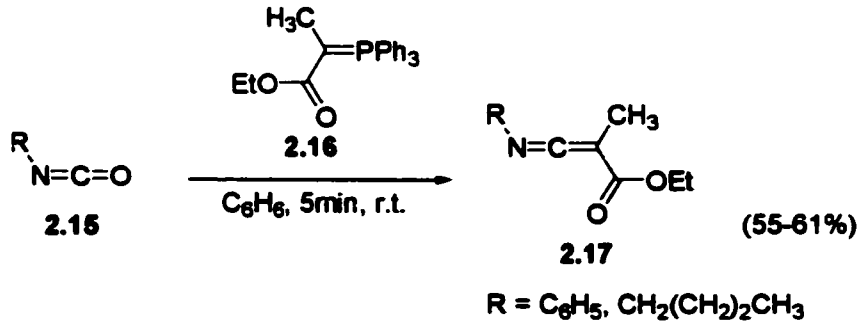
Isocyanate and isothiocyanate compounds are commercially available materials and both can provide the related carbodiimide. A literature procedure for the synthesis of **2.14** reported the use of **2.13** with a phospholene oxide catalyst[31] (eq 6), which afforded excellent yields.



(eq 6)

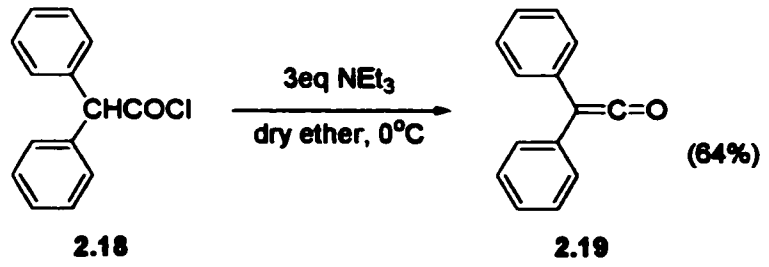
These reactions could be easily monitored by gas chromatography for conversion of isocyanate to carbodiimide where retention times for **2.14** were greater. IR analysis confirmed the identity of the products with stretches between 2140-2130 cm^{-1} characteristic of the NCN group.

Additionally, isocyanates can be used in the preparation of ketenimines[32]. The phosphine ylide, **2.16**, reacts with **2.15** in a Wittig-type reaction (eq 7).



(eq 7)

The products **2.17** could be purified by distillation and exhibited characteristic IR stretching frequencies of ketenimines (2040-2020 cm^{-1}). These heterocumulenes are quite stable and could be stored at reduced temperatures. However, diphenylketene was used directly upon preparation from **2.18** and triethylamine (eq 8), followed by distillation[33].



(eq 8)

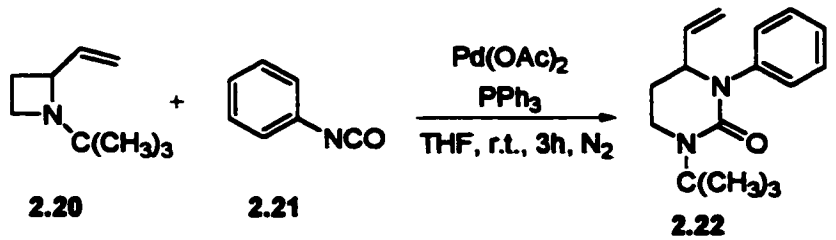
Identification of **2.19** could be performed using IR analysis as ketenes display a characteristic peak at ~2100 cm^{-1}. Further evidence in the identification of **2.19** was the dark orange color of the product which is indicative of this ketene.

2.2 Palladium(0) catalyzed insertion of isocyanates

2.2.1 Reactions of 2-vinylazetidines with phenylisocyanate

As previously mentioned, a variety of zero-valent palladium complexes displayed competency for ring-cleavage reactions of vinyloxiranes[17-19a, 21] and –oxetanes[19b] while a palladium (II) species had achieved cycloaddition of azetidines with heterocumulenes[14]. Therefore, many routes were initially available for testing. The method of Baeg *et al.*[14d-e] using $(PhCN)_2PdCl_2$ resulted in no conversion of the vinylazetidine likely due to the relatively unactivated N-C bonds in this case. Some success was found using $Pd_2(dba)_3.CHCl_3$ and $Pd(PPh_3)_4$, but problems were incurred. The former complex was mixed with four equivalents of triphenylphosphine, but gave reduced yields of the anticipated heterocycle with trimerized isocyanate as the major product. In catalytic procedures employing $Pd_2(dba)_3.CHCl_3$ and phosphine ligands, the metal is known to exhibit a reduction in reactivity relative to reactions using pre-catalysts that do not contain dibenzylideneacetone[34]. This group remains chelated to the metal in solutions of phosphines and hinders the formation of active catalyst complexes. In this case, the reduced reactivity resulted in competition between the cycloaddition reaction and polymerization of the heterocumulene.

Therefore it would be expected that $Pd(PPh_3)_4$ would be a more capable catalyst for the reaction. However, inconsistency in product yields was apparent when using this complex with a single equivalent of triphenylphosphine as the catalytic system. It was postulated that the sensitive nature of the compound resulted in impurities or degradation, both of which could be adversely affecting the reaction. Nevertheless, a similar catalyst can be prepared *in situ* by mixing $Pd(OAc)_2$ and triphenylphosphine where one equivalent of the phosphine will reduce the metal to palladium (0)[35]. Both of these materials are relatively cheap and easily handled.



2.20 **2.21** **2.22** (eq 9)

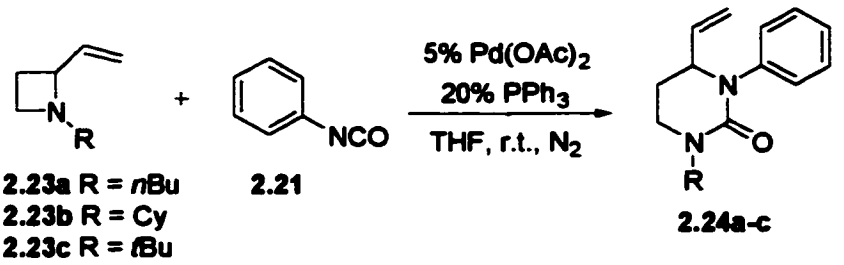
Since ring opening of 2-vinylazetidines occurs easily in the presence of zerovalent palladium[23], the insertion of heterocumulenes was tested at room temperature (eq 9). Highly polar solvents enhance these transformations[4]. Therefore, dry tetrahydrofuran was employed due to ease of removal. Phenylisocyanate (**2.21**) was chosen as the heterocumulene substrate because of its availability and proven reactivity in previous examples. Early experiments encouraged optimization of this system (Table 2.1).

Table 2.1 Reactions[a] of 1-(*tert*-Butyl)-2-vinylazetidine with Phenylisocyanate Catalyzed by [$Pd(OAc)_2/PPh_3$][b] at Room Temperature

Mol % $Pd(OAc)_2$	Mol % PPh_3	% conversion[c]	% yield
2.5	10	83	65
5	20	100	75
10	40	100	73

[a]PPh_3 and $Pd(OAc)_2$ were premixed for 30 min in 4.0 ml of dry, degassed solvent followed by addition of 1.0 mmol of **2.20** and **2.21** with 1.0 ml of dry solvent; [b]1:4 ratio of catalyst/ligand; [c]as calculated from the amount of **2.21** recovered.

Comparing the ^1H and ^{13}C NMR spectra with similar and well-characterized compounds[14d-e] indicated that the tetrahydro-pyrimidin-2-one, **2.22**, had been prepared, as expected from prior regioselectivity exhibited in these reactions[18, 19]. A C=O stretching frequency of 1645 cm^{-1} in the IR spectrum denoted a urea carbonyl, demonstrating a preference for *N*-alkylation over *O*-alkylation in the cyclization of **2.22**. At 5% catalyst load, the reaction had reached its optimum. The only prominent by-product was the isocyanurate, or trimerized isocyanate, indicating the catalyst still displayed some inadequacy at out-competing this side-reaction. The palladium species generated in solution was presumed to be quite sensitive to molecular oxygen, which would be capable of re-oxidizing the metal. In all likelihood, the catalyzed reaction would be retarded due to this disruption. Accordingly the solvent was degassed by bubbling dinitrogen into tetrahydrofuran before addition of any materials. Using this technique with 5 mol % catalyst, the system was applied to different vinylazetidines **2.23** in their reactions with **2.21** (eq 10).



(eq 10)

2.23a R = *n*Bu
2.23b R = Cy
2.23c R = *t*Bu

2.21

2.24a-c

The reactions were easily followed by gas chromatography, and the products were purified upon consumption of one or both of **2.21** and **2.23**. Excellent results (Table 2.2) were obtained under very mild conditions with high regioselectivity, implicating π-allylpalladium intermediates in the reaction mechanisms.

Table 2.2 The Effect of *N*-substituents on Pd(0) Catalyzed Reactions[a] of 2-Vinylazetidines with Phenylisocyanate at Room Temperature

Azetidine	Time[b] (h)	Product[c]	% Yield
2.23a	1	**2.24a**	97
2.23b	2	**2.24b**	89
2.23c	3.5	**2.24c**	89

[a]PPh_3 and $Pd(OAc)_2$ were premixed for 30 min in 4.0 ml of dry, degassed solvent followed by addition of 1.0 mmol of **2.23** and **2.21** with 1.0 ml of dry solvent; [b]reaction began with addition of substrates and was over when GC indicated consumption of one or both; [c]purified by column chromatography with appropriate ether/pentane solvent system.

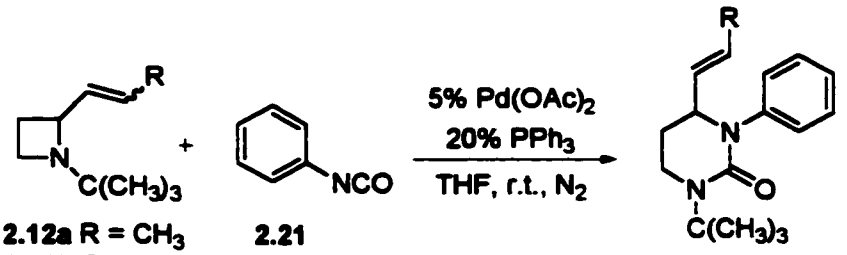
Quantitative conversion was observed in all cases by gas chromatography, and product loss might arise during the purification by column chromatogrphy or due to the purity of the starting materials. For example, the 2-vinylazetidines contained traces of solvent and, at times, unreacted 2-carbomethoxyazetidine (**2.6**) carried over from previous steps. Additionally, impurities in the isocyanate could arise through exposure to moisture or inherent oligomerization[36]. Nevertheless, the yields of **2.24** were very good and exhibited a relationship between the size of the substituent on the nitrogen and the reaction rate. The

bulkier azetidines, **2.23b** and **2.23c**, reacted slower than **2.23a**, which is probably due to steric hinderence in the nucleophilic attack on the heterocumulene.

Many defining characteristics were evident in the NMR spectra of **2.24**. The vinyl protons displayed signals at 5.1-5.3 ppm and 5.7-5.9 ppm, in addition to a broad multiplet at 4.2-4.3 ppm of the C_4 hydrogen. In the ^{13}C NMR spectra, a signal at 154 ppm was apparent for the carbonyl group in each case. The vinyl carbons also gave identical chemical shifts of 136 ppm and 116 ppm respectively. A very strong peak between 1645-1635 cm^{-1} was assigned to urea carbonyl stretching. Further evidence for the synthesis and purity of these compounds was obtained from EI-HRMS and accurate mass (see Experimental, section 3.3.2).

2.2.2 Reactions of 1-(*tert*-Butyl)-2-vinylazetidine derivatives with phenylisocyanate

With substituents on the vinyl group, as in **2.12**, informative results were obtained in reactions with phenylisocyanate (eq 11).



2.12a R = CH_3 **2.21**
2.12b R = CO_2CH_3
2.12c R = C_6H_5

2.25a-c

(eq 11)

In addition to demonstrating the capacity of this method to tolerate extra steric congestion, functionalization at this position enhances the possibility for further chemistry on these compounds. Furthermore, insight can be gained into the mechanism from the relative stereochemistries of **2.12** and **2.25**. All of the azetidine substrates in these reactions were a mixture of *cis* and *trans* isomers. However, the NMR spectra of **2.25** indicated only one isomer resulted, which was surmised to have the *trans* configuration. This observation provided good evidence for the presence of a π-allyl moeity since an intermediate of this kind would enable isomerization in the transformation. Additionally, good to excellent yields were obtained in reactions with **2.12** (Table 2.3).

Table 2.3 The Effect of Substituents on the Vinyl Group in Pd(0) Catalyzed Reactions[a] of 1-(*tert*-Butyl)-2-vinylazetidines with Phenylisocyanate

Azetidine	Time[b] (h)	Product[c]	% Yield
2.12a	5.5	**2.25a**	70
2.12b	2	**2.25b**	98
2.12c	6	**2.25c**	67

[a]PPh_3 and $Pd(OAc)_2$ were premixed for 30 min in 4.0 ml of dry, degassed solvent followed by addition of 1.0 mmol of **2.12** and **2.21** with 1.0 ml of dry solvent; [b]reaction began with addition of substrates and was over when GC indicated consumption of one or both; [c]purified by column chromatography with appropriate ether/pentane solvent system.

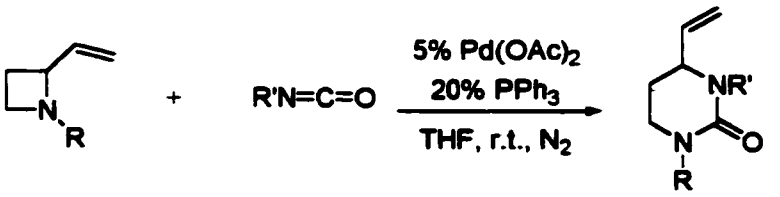
Simply exchanging the vinyl group for a propenyl group, as in **2.12a**, depressed reactivity through some steric congestion involved in the formation of the π-allylpalladium intermediate as well as by partially deactivating ring cleavage because of the inductive effect displayed by alkyl groups. The reaction became moderately slower, and trimerization of the isocyanate caused a reduction in the overall yield of **2.25a**. In addition to the vinylic (m, 5.3-5.6 ppm) and C_4 hydrogen (m, 3.9-4.1 ppm), an identifying doublet at 1.7 ppm in the ^1H NMR spectrum arose from the methyl group.

Electron withdrawing groups, as in **2.12b** and **2.12c**, should affect an activation of the 2-vinylazetidine ring through greater polarization of the C-N bond, enhancing the reaction with **2.21**. This was exemplified in the synthesis of **2.25b**. The reaction rate with the carbomethoxy group was greatly heightened and a better yield was obtained in comparison with **2.24c**. Similarly, the reaction with **2.12c** also exhibited this activating effect. The phenyl substituent will obviously impart much steric hindrance, more than a methyl group, throughout the reaction. However, with comparable yields obtained for **2.25a** and **2.25c**, it must be concluded that **2.12c** has greater reactivity towards ring cleavage than **2.12a**. From the ^1H NMR spectra of **2.25b** and **2.25c**, the electron withdrawing effect can be visualized. In both cases, the signals for the vinylic protons were shifted downfield by approximately 1 ppm (6.0/6.9 ppm for **2.25b** and 6.2/6.6 ppm for **2.25c**) while the C_4 hydrogen moved to 4.4-

4.5 ppm. Chemical shift increases in this region of the molecule indicated deshielding by the R groups due to removal of electron density.

2.2.3 Reactions of 2-vinylazetidines with various isocyanates

To further test the capability of this method, a variety of isocyanates were reacted with **2.23b-c** (eq 12).



(eq 12)

2.23b-c

2.26a R = *p*-C_6H_4Br
2.26b R = *p*-C_6H_4Cl
2.26c R = *p*-$C_6H_4NO_2$
2.26d R = *p*-C_6H_4OMe
2.26e R = *p*-C_6H_4Me
2.26f R = *m*-C_6H_4Me
2.26g R = C_6H_{11}

2.27a-i

The results from these cyclization reactions are listed in Table 2.4, which verify the utility of alkylisocyanates as substrates, as well as the tolerance for different functional groups.

Table 2.4 Palladium(0) Catalyzed Reactions[a] of 2-Vinylazetidines with Cyclohexylisocyanate and Mono-substituted Arylisocyanates

Azetidine	Isocyanate	Time[b] (h)	Product[c]	% Yield
2.23b	**2.26a**	2	**2.27a**	95
2.23b	**2.26b**	2.5	**2.27b**	90
2.23b	**2.26c**	2	**2.27c**	66
2.23b	**2.26d**	3	**2.27d**	89
2.23b	**2.26e**	3.5	**2.27e**	93
2.23b	**2.26f**	2	**2.27f**	97
2.23b	**2.26g**[d]	6	**2.27g**	73
2.23c	**2.26a**	2.5	**2.27h**	91
2.23c	**2.26d**	3	**2.27i**	87

[a]PPh_3 and $Pd(OAc)_2$ were premixed for 30 min in 4.0 ml of dry, degassed solvent followed by addition of 1.0 mmol of **2.23** and **2.26** with 1.0 ml of dry solvent; [b]reaction began with addition of substrates and was over when GC indicated consumption of one or both; [c]purified by column chromatography with appropriate ether/pentane solvent system; [d]purified by distillation prior to use.

No tangible trend could be identified from the yields of these reactions since affecting the electrophilicity of the central carbon would inevitably influence the heterocumulenes' capacity for trimerization. However, interesting results were obtained and demonstrated how the isocyanate substrate can be modified to optimize product formation. Highly electron-withdrawing substituents, such as the *p*-nitro group in **2.26c**, increased the reactivity of the isocyanate but caused greater trimerization. Thus, even though the rate of the reaction was quite rapid, a low yield of **2.27c** was acquired. Prior examples using aryl heterocumulenes possessing this group in palladium-catalyzed reactions with vinyloxiranes have been unsuccessful[19a], and this result can still be considered an accomplishment. Interestingly, **2.26b**, **2.26d**, and **2.26e** possessed similar reactivity to phenylisocyanate, whereas more subtle modifications, as in **2.26a** and **2.26f**, enhanced the insertion of the heterocumulene.

Presumably the *p*-bromo and *m*-methyl substituents electronically tailored the substrate for nucleophilic attack preferentially. Sufficient electrophilicity was present to optimize product synthesis, but not enough to activate the isocyanate for trimerization. Additionally, these results confirmed that alkylisocyanates are sufficiently reactive since **2.27g** was obtained in good yield, but arylisocyanates were the best substrates. Larksarp *et al.* reported comparable reaction kinetics for 2-vinyloxetanes and isocyanates[19b].

The usual defining characteristics were present in the ^{1}H and ^{13}C NMR spectra. Accompanying the broad peak at 4.2-4.3 ppm of the C_4 hydrogen, two multiplets substantiate the presence of the vinyl protons between 5-6 ppm. Signals at 153-154 ppm, attributable to the carbonyl group, and at approximately 136 ppm and 116 ppm for the vinyl carbons further verified that the structure of these compounds was **2.27**, analogous to the previously identified products. Confirmation of the structure/bond connectivity was accomplished by X-ray analysis of **2.27c** (R = C_6H_{11}, R′ = *p*-$C_6H_4NO_2$) and can be seen in Figure 2.1. As expected, shortened bond lengths between C_7-N_1 and C_7-N_2 indicated delocalization of the carbonyl group. Consequently, the heterocycle exhibits planarity in this region while the remainder of the ring appears to be flexible, directing the vinyl group away from the phenyl ring. Presumably, this portion of the ring could alternate between conformations in solution.

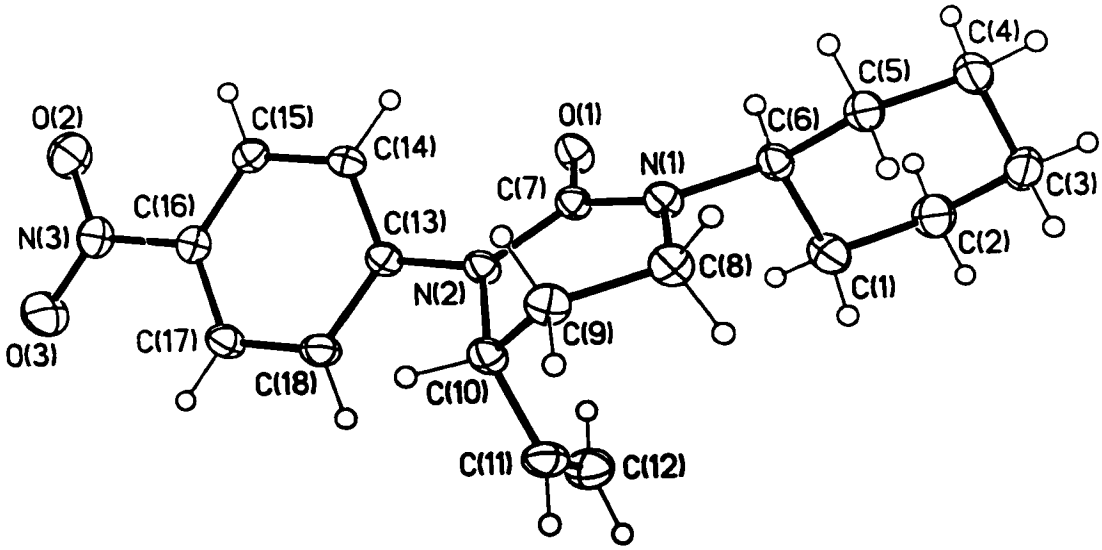
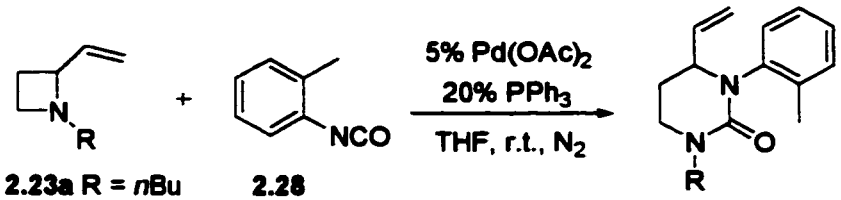


Figure 2.1. View of 2.27c (R = C_6H_{11}, R′ = *p*-$C_6H_4NO_2$), showing the atomic numbering scheme.

2.2.4 Reactions of 2-vinylazetidines with *o*-tolylisocyanate

Emerging from this structural information, an unusual development was noticed in the product from the reactions of **2.23** with *o*-tolylisocyanate (eq 13).



2.23a R = *n*Bu
2.23b R = Cy
2.23c R = *t*Bu

2.28

2.29a-c

(eq 13)

A slight decrease in the yields of **2.29** (see Table 2.5) could be attributed to lowered electrophilicity of the isocyanate carbon (similar to the *para* isomer) in combination with the steric demand conferred by the *o*-methyl group. From the reaction times, the steric influence of the *N*-alkyl group was also apparent.

Table 2.5 Palladium(0) Catalyzed Reactions[a] of 2-Vinylazetidines with *ortho*-Tolylisocyanate

Azetidine	Time[b] (h)	Product[c]	% Yield
2.23a	1.5	**2.29a**	89
2.23b	2.5	**2.29b**	70
2.23c	3.5	**2.29c**	75

[a]PPh_3 and $Pd(OAc)_2$ were premixed for 30 min in 4.0 ml of dry, degassed solvent followed by addition of 1.0 mmol of **2.23** and **2.28** with 1.0 ml of dry solvent; [b]reaction began with addition of substrates and was over when GC indicated consumption of one or both; [c]purified by column chromatography with appropriate ether/pentane solvent system.

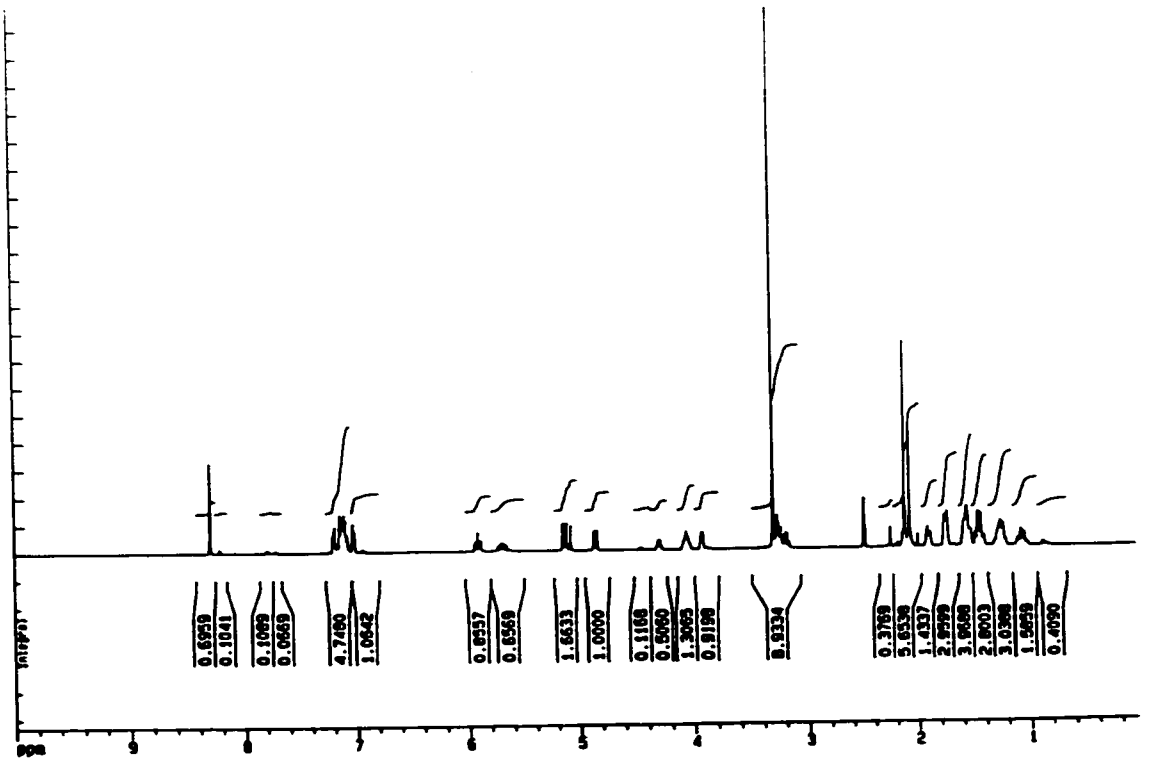
Two compounds could be identified in the ^1H and ^{13}C NMR spectra at room temperature. The characteristic vinyl and C_4 hydrogen multiplets were present but appeared to have doubled, where the related signals possessed slightly different chemical shifts (Fig. 2.2a).

Additionally, two methyl singlets occurred at 2.1-2.2 ppm and a highly complex phenyl region arose. EI-HRMS verified that **2.29** was the only product, exhibiting a single IR stretching frequency of ~1645-1640 cm^{-1} representative of urea carbonyl groups.

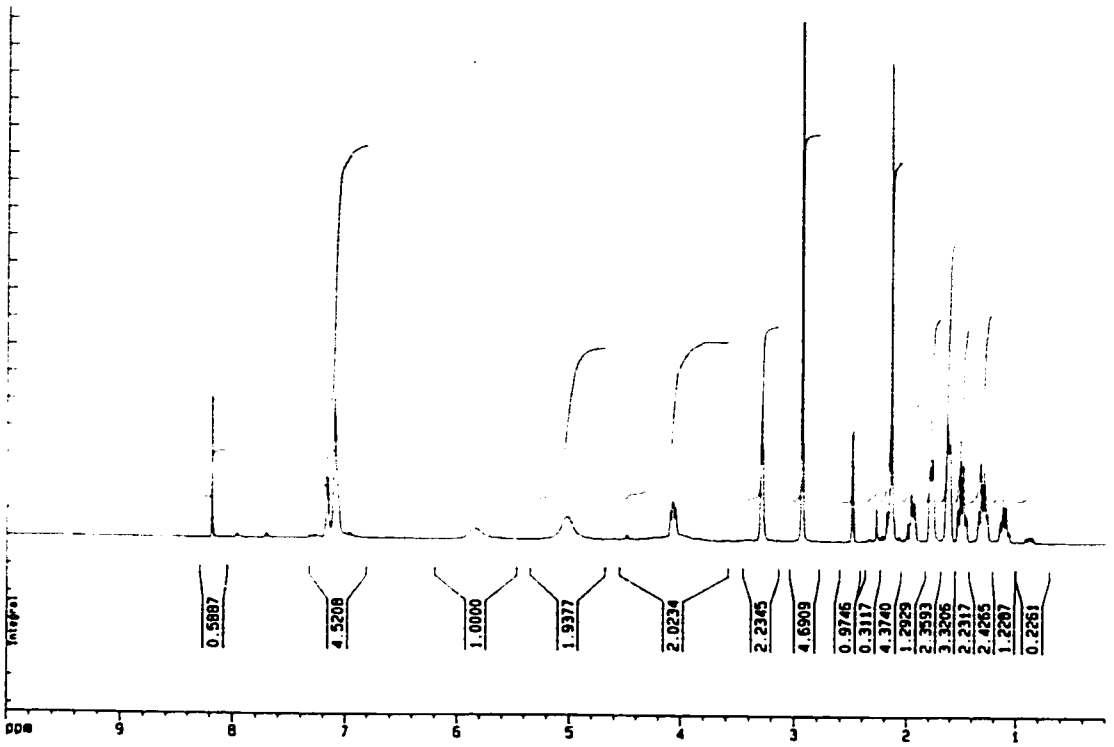
It was supposed that the congestion among the substituents on the heterocycle introduced an energy barrier between conformations, such that two structures were present in solution at room temperature. A variety of NMR experiments were performed on **2.29b** (R = C_6H_{11}) to determine the origin of this anomaly. At higher temperatures (100-120°C), the ^1H NMR spectra (Fig. 2.2b) coalesced, as anticipated, indicating that only one compound had been formed. The large singlet in the spectra at 3.3 ppm (Fig. 2.2a) and 3.0 ppm (Fig. 2.2b) arose from water in the deuterated solvent. Using the numbering from Scheme 2-2, the variable temperature NMR converged the related hydrogen signals of C_4 (4.1 ppm), C_6 (3.3 ppm), C_7 (5.9 ppm), C_8 (5.0 ppm), and C_9 (2.1 ppm) while the phenyl region was simplified.

Figure 2.2. (a) Room temperature ^1H NMR spectrum of 2.29b (R = C_6H_{11}) in d^6-DMSO (b) ^1H NMR spectrum of 2.29b (R = C_6H_{11}) at 100°C in d^6-DMSO.

(a)

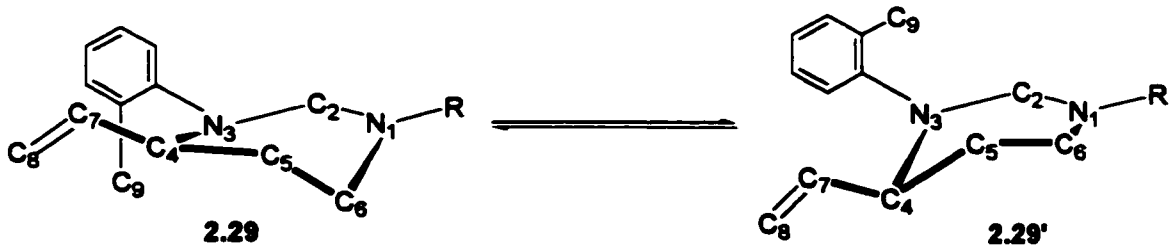


(b)



The different conformations appeared not to affect the alkyl substituents and the C_5 hydrogens upon comparison of the room temperature and high temperature ^1H NMR spectra. Using the X-ray structure shown in Figure 2.1 for **2.27c** (R = C_6H_{11}, R′ = p-$C_6H_4NO_2$) and the information obtained from the various spectral analyses, the distinct conformations exhibited by **2.29** are postulated in Scheme 2-2.

Scheme 2-2

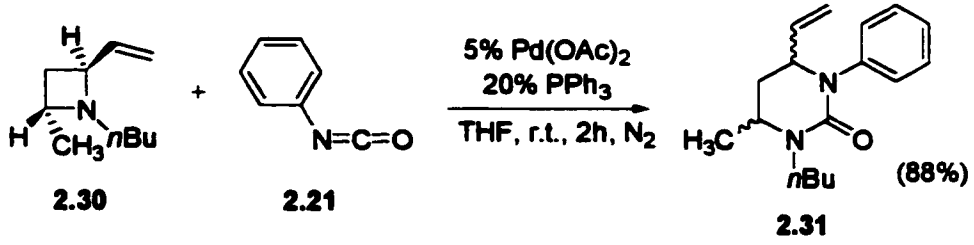


This fluctuating activity should occur for all such compounds, but the *o*-methyl group (C_9) created a barrier in **2.29** and **2.29′**, giving rise to distinct conformational isomers in solution. 2D NMR analysis supported this assumption. The COSY spectrum revealed two spin systems for the C_8, C_7, and C_4 hydrogens, indicating similarity in the structures but unequal chemical shifts for the related nuclei. Supplementing this, EXSY experiments displayed exchange between the C_4, C_7, and C_8 hydrogens as well as for the C_9 and phenyl protons,

which verified a slow equilibrium between **2.29** and **2.29'** in solution. For the related tetrahydro-pyrimidin-2-ones, which lack *ortho* substituents on the phenyl ring, an averaging of the chemical shifts of these conformations supported the occurrence of a fast equilibrium. Therefore, it can be hypothesized that the *o*-methyl group introduced the energy barrier. Subsequent NMR spectra obtained for **2.29a** and **2.29c** at 120°C similarly displayed coalescence of the conformational isomers.

2.2.5 Reaction of *trans*-1-butyl-4-methyl-2-vinylazetidine with phenylisocyanate

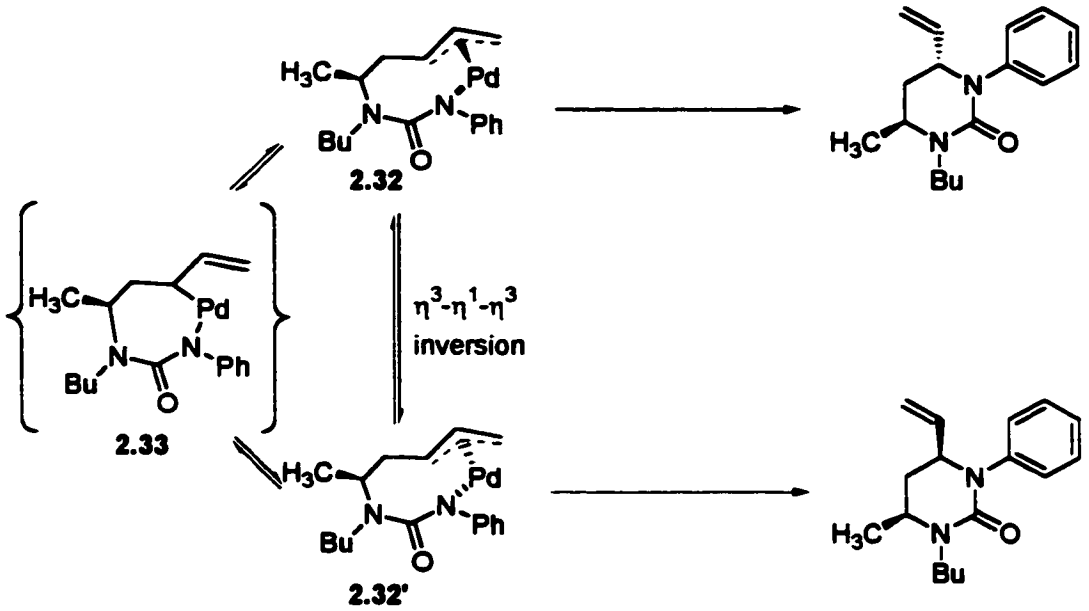
To conclude the study of reactions with isocyanates, the stereoselectivity of this method was tested. Baeg *et al.* demonstrated that the cycloaddition reaction of carboalkoxyaziridines and –azetidines with diarylcarbodiimides proceeded with retention of configuration[14b, 14d]. However, the palladium(0)-catalyzed reactions of vinyloxiranes with isocyanates, which require formation of π-allyl intermediates, resulted in scrambling of the stereochemistry[18a]. Therefore, an investigation was undertaken employing **2.30** as the azetidine substrate (eq 14).



2.30 **2.21** **2.31** (eq 14)

A comparable yield was obtained for **2.31**, which displayed the characteristic ^{1}H and ^{13}C NMR signals for such compounds and produced a peak at ~1645 cm^{-1} in the IR spectrum. However, the *trans* and *cis* isomers arose in a 2:1 ratio. Such scrambling of stereochemistry suggested the formation of π-allylpalladium intermediates in these reactions (Scheme 2-3).

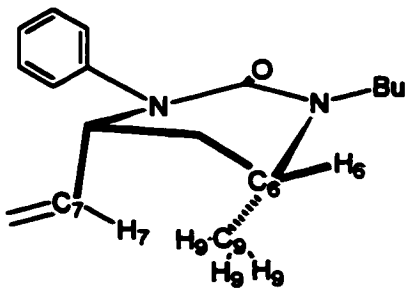
Scheme 2-3



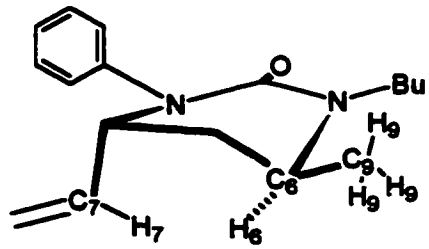
Ring cleavage of **2.30** followed by addition to **2.21** would form intermediate **2.32** in which there is η^3 binding between the vinyl group and palladium. This complex would be in equilibrium with the η^1 isomer, **2.33**, from which point both **2.32** and **2.32'** are accessible η^3 bound intermediates. Thus, the formation of the π-allyl moiety provides an explanation for the stereochemical scrambling, which in turn supports the claim for these transition states. Very recently, analogous results were observed for palladium-catalyzed reactions of *cis*-3-methyl-2-vinylaziridines with phenylisocyanate[37]. Attempts were made to control the stereochemistry in the aziridine case without success.

In these reactions, isomeric ratios indicated that there was preference for one configuration. Determining the preferred isomer could reveal some insight into the reaction. An examination of **2.31** using 2D NMR experiments featured crosspeaks between H_7 and H_9 for only one of the isomers (Scheme 2-4) in the NOESY spectrum.

Scheme 2-4



cis-**2.34**



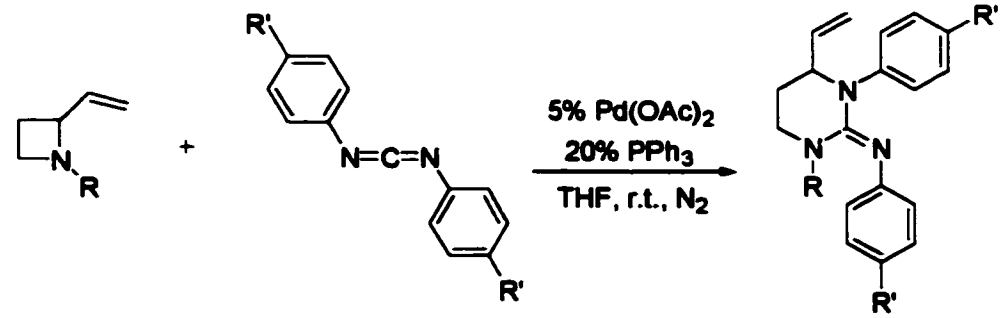
trans-**2.34**

Referring to Scheme 2-4, the origin of this interaction is evident, but no conclusions could be obtained from this information. Further nOE experiments were conducted with direct irradiation of the vinyl substituent. The minor product displayed coupling between H_7 and H_9, whereas the major product showed H_7 interacting with H_6. Therefore, *trans*-**2.34** was the preferred product from the reaction of **2.30** and **2.21**. The selectivity possibly arose due to the lower energy of this configuration. However, Trost *et al.* observed trapping of configuration in some instances[18a]. In the case of *cis*-3-methyl-2-vinylaziridine, the major product displayed the *cis*-configuration[37]. Thus, it can be suggested that the isomerization was insufficiently faster than the ring-closing, such that the stereochemistry was only partially scrambled.

2.3 Palladium(0) catalyzed insertion of other heterocumulenes

2.3.1 Reactions of 2-vinylazetidines with diarylcarbodiimides

In designing a procedure of this type, it was important for the reaction to be general for heterocumulenes as well as azetidines. Having established this for the latter, the method was next applied to diarylcarbodiimides in the synthesis of tetrahydro-pyrimidin-2-ylidenes **2.35** (eq 15).



(eq 15)

2.23a R = *n*Bu
2.23b R = Cy
2.23c R = *t*Bu

2.14a R = H
2.14b R = CH_3
2.14c R = Br
2.14d R = Cl
2.14e R = OCH_3

2.35a-g

Possessing similar electrophilicity as isocyanates at the central carbon[36], carbodiimides would be expected to afford excellent results. In cycloaddition reactions with

vinyloxiranes[19a] and –oxetanes[19b], even better yields had been reported with these heterocumulenes. However, the azetidine system will display a new steric interaction due to the substituent on the nitrogen.

Table 2.6 Palladium(0)-Catalyzed Reactions[a] of 2-Vinylazetidines with Mono-substituted Diarylcarbodiimides

Azetidine	Carbodiimide	Time[b] (h)	Product[c]	% Yield
2.23a	**2.14a**	10	**2.35a**	94
2.23b	**2.14a**	18	**2.35b**	86
2.23b	**2.14b**	18	**2.35c**	83
2.23b	**2.14c**	18	**2.35d**	92
2.23c	**2.14a**	20	**2.35e**	75
2.23c	**2.14d**	21	**2.35f**	70
2.23c	**2.14e**	20	**2.35g**	76

[a]PPh_3 and $Pd(OAc)_2$ were premixed for 30 min in 4.0 ml of dry, degassed solvent followed by addition of 1.0 mmol of **2.23** and **2.14** with 1.0 ml of dry solvent; [b]reaction began with addition of substrates and was over when GC indicated consumption of one or both; [c]purified by column chromatography with appropriate ether/pentane solvent system.

As expected, reaction rates decreased with subsequent reduction in the yields of **2.35**. As well, these products displayed a greater reluctance toward isolation and purification, which also contributed to the lowered yields. A clear trend was evident again in reference to the relationship between vinylazetidine reactivity and the nitrogen substituent. As for reactions with isocyanates, a pattern arose where **2.23a** exhibited faster kinetics and better yields versus **2.23b**, which in turn proved to be a superior substrate to **2.23c**. This effect was particularly amplified in reactions with **2.14** in view of the heightened bulkiness with two aryl groups. No other obvious tendencies were present. Therefore, it appeared that steric effects largely controlled these reactions, and not necessarily the electronic character of **2.23**.

Identification of **2.35** by ^{1}H and ^{13}C NMR was less challenging since full characterization of the tetrahydropyrimidin-2-ones had been previously completed. Analogous signals were present in the ^{1}H NMR spectra for the vinyl protons, with chemical shifts of 5.1-5.4 ppm and 5.9-6.3 ppm, and the hydrogen on C_4 at 3.9-4.1 ppm. Furthermore, the downfield region became more complicated with two similar, but chemically inequivalent, phenyl groups now present. A defining signal in the ^{13}C NMR spectra occurred at 151 ppm indicative of the imine carbon of the guanidine moiety, which contrasted with the chemical shift value of 154 ppm typical of the carbonyl group in the previous case. Similarly, the IR spectra of **2.35** displayed a strong C=N stretch around 1600-1580 cm^{-1}, further distinguishing the imine from the carbonyl group. In all cases, EI-HRMS was performed and accurate mass calculations carried out (see Experimental, section 3.3.3) to verify that **2.35** was the afforded product.

Additionally, an X-ray crystal structure of **2.35b** was obtained and supplemented all the spectra for these compounds. As seen in Figure 2.3, the heterocycle adopted an identical configuration to the tetrahydropyrimidin-2-ones. Short bond lengths for C_4-N_1 and C_4-N_3 supported a planar feature in this portion of the molecule while the remaining section again appeared capable of various conformations that would be constantly alternating in solution. An interesting property that arose from this crystal structure was the potential for π-stacking suggested by the arrangement of the aryl groups, which may restrict the flexibility in **2.35**.

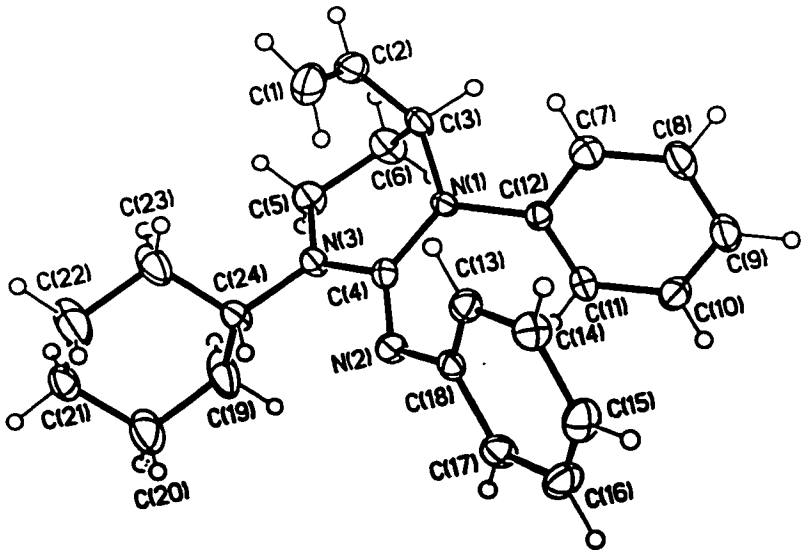
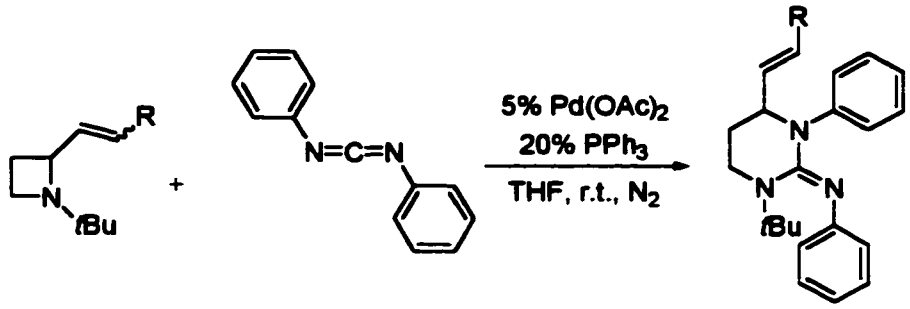


Figure 2.3. View of 2.35b (R = C_6H_{11}, R′ = H), showing the atomic numbering scheme.

Some additional reactions (eq 16) using **2.12a-b** as the azetidine substrates supplied further proof of the congestion created in these instances.



(eq 16)

2.12a R = CH_3
2.12b R = CO_2CH_3

2.14a

2.36a-b

It was assumed that **2.12a** would exhibit a much longer reaction time and afford a poorer yield of **2.36** relative to the unsubstituted substrate, **2.23c**. However, a swift rate of reaction was anticipated for **2.12b** suggested by its unique reactivity toward phenylisocyanate.

Table 2.7 The Effect of Substituents on the Vinyl Group in Pd(0) Catalyzed Reactions[a] of 1-(*tert*-Butyl)-2-vinylazetidines with Diphenylcarbodiimide

Azetidine	Time[b] (h)	Product[c]	% Yield
2.12a	48	**2.36a**	39[d]
2.12b	45	**2.36b**	92

[a]PPh_3 and $Pd(OAc)_2$ were premixed for 30 min in 4.0 ml of dry, degassed solvent followed by addition of 1.0 mmol of **2.12** and **2.14a** with 1.0 ml of dry solvent; [b]reaction began with addition of substrates and was over when GC indicated consumption of one or both; [c]purified by column chromatography with appropriate ether/pentane solvent system. [d]only 51% conversion calculated from recovery of **2.14a**.

Table 2.7 reveals the steric influence conveyed in these reactions. In both cases, long reaction times indicate very slow turnover rates, largely due to the bulkiness of the substrates. Nevertheless an excellent yield was obtained for **2.12b**, indicating that smaller groups at this position possessing electron-withdrawing character can enhance the insertion. As expected, mediocre results were obtained in the reaction with **2.12a**. The ^1H and ^{13}C

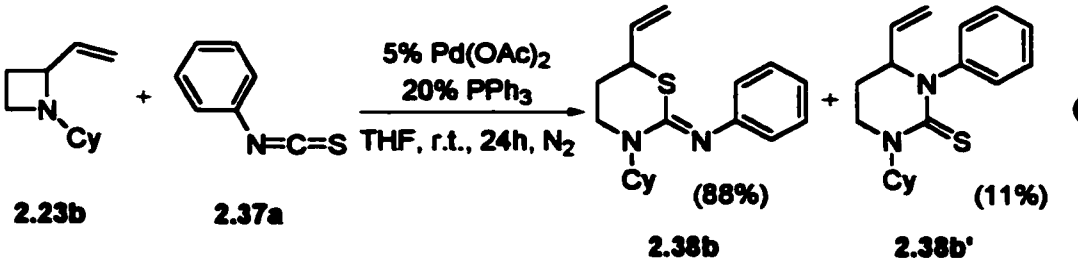
NMR spectra exhibited the anticipated features of these compounds. In addition to the vinyl protons, a doublet for the methyl group in **2.12a** arose at 1.8 ppm, and a peak at 151 ppm in the ^{13}C spectra was indicative of the imine carbon. The hydrogens on the vinyl group of **2.12b** revealed substantial deshielding with chemical shifts of 6.1-6.2 ppm and 7.2-7.3 ppm. In the ^{13}C NMR spectrum, a peak at 151 ppm corresponded to the imine carbon while the signal for the ester carbon occurred at 167 ppm. Again, these reactions afforded only the *trans* configuration even though *cis*- and *trans*-2-vinylazetidines had been employed.

The reaction was attempted with dicyclohexylcarbodiimide, but the conversion was negligible. Combined with reduced electrophilicity at the central carbon, typical of dialkylcarbodiimides[36], the steric hindrance of this group would have prevented the reaction. Previous cases[4a] reported the inability of the cyclohexyl and isopropyl derivatives to insert but were successful with less bulky substrates such as dibutylcarbodiimide. Due to particular restraints, this compound was not tested in these reactions.

2.3.2 Reactions of 2-vinylazetidines with arylisothiocyanates

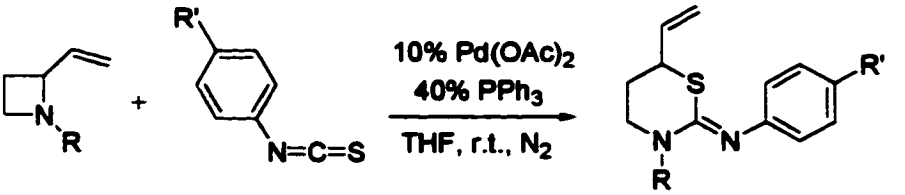
Continuing with the application of this method to various heterocumulenes, reactions of 2-vinylazetidines with arylisothiocyanates were attempted, in anticipation of [1,3]thiazinan-2-imines as products. Although arylisothiocyanates are known to undergo similar reactions as isocyanates, their reactivity is considerably less[36]. Additionally, where isocyanate reactions occur across the C=N bond, the isothiocyanates usually react across the C=S bond.

Other than the work by Baeg *et al.* in which palladium (II) promoted cylcoaddition reactions afforded similar compounds to **2.38**[14d], information on [1,3]thiazinane synthesis is scarce. Therefore, designing new synthetic approaches to this framework would be significant.



2.23b **2.37a** **2.38b** **2.38b'** (eq 17)

Unfortunately, early reactions demonstrated some complications with this method (eq 17). Phenylisothiocyanate and **2.23b** afforded the expected thiazinane, **2.38b**, in excellent yield, but the cyclic thiourea, **2.38b'**, occurred as a minor product and introduced problems for purification. Furthermore, when **2.23c** (R = *t*Bu) was employed as the substrate with **2.37a**, the conversion of the reaction dropped to only 18% after 24 hours. Increasing the temperature of the reactions reduced the yield of **2.38b** while a variety of different ligands could not influence the selectivity of the reaction nor affect the reaction between **2.23c** and phenylisothiocyanate. Middle ground was somewhat achieved by increasing the catalyst load (eq 18).



(eq 18)

2.23a R = *n*Bu
2.23b R = Cy
2.23c R = *t*Bu

2.37a R' = H
2.37b R' = Cl
2.37c R' = OMe

2.38a-e

The steric trend that had been noticed in reactions of **2.23** with isocyanates and carbodiimides became exaggerated in this case as **2.23a** reacted relatively quickly whereas **2.23c** was a very sluggish substrate (Table 2.8).

Table 2.8 Palladium(0) Catalyzed Reactions[a] of 2-Vinylazetidines with Arylisothiocyanates

Azetidine	Isothiocyanate	Time[b] (h)	Product[c]	% Yield
2.23a	**2.37a**	7	**2.38a**	92
2.23b	**2.37a**	20	**2.38b**	95
2.23b	**2.37b**	20	**2.38c**	90
2.23b	**2.37c**	20	**2.38d**	94
2.23c	**2.37a**	48	**2.38e**	47[d]

[a]PPh_3 and $Pd(OAc)_2$ were premixed for 30 min in 4.0 ml of dry, degassed solvent followed by addition of 1.0 mmol of **2.23** and **2.37** with 1.0 ml of dry solvent; [b]reaction began with addition of substrates and was over when GC indicated consumption of one or both; [c]purified by column chromatography with appropriate ether/pentane solvent system. [d]only 48% conversion calculated from recovery of **2.37a**.

Again, *para* substituents on the aryl group (**2.37b-c**) did not induce a significant effect. Admittedly, this study was not thorough, but when supplemented with the results of isocyanates and carbodiimides, adequate evidence was obtained to make this conclusion. Important to note was the reaction times in Table 2.8, in particular for **2.23b**, which were similar to the reaction employing only 5% $Pd(OAc)_2$. This indicates that the extra amount of catalyst primarily enabled isomerization of **2.38b'**, the thiourea, to **2.38b**. Presumably, the thiourea had also occurred as a kinetic product in this instance, but isomerization by the palladium catalyst (at 10% catalyst loading) concealed this fact and only **2.38a-e** were isolated as the thermodynamically-favored products.

The characteristic features of the ^1H NMR spectra seen in the previous products, signals of the C_4 and vinyl hydrogens, were evident for **2.38** with multiplets at 3.7-3.9 ppm, 5.0-5.2 ppm, and 5.6-5.8 ppm respectively. A peak between 150-153 ppm in the ^{13}C NMR spectra indicated the presence of an imine whereas thiocarbonyl carbons exhibit chemical shifts of ~180 ppm. Stretching frequencies at 1580-1575 cm^{-1} in the IR spectra were comparable to those seen for the products of carbodiimide reactions. Mass spectrometry and accurate mass analyses (see Experimental, section 3.3.5) confirmed that **2.38a-e** did result

from these reactions. Crystals of **2.38c** were obtained and a structure acquired by x-ray crystallography. Looking at Figure 2.4, the familiar framework observed for tetrahydro-pyrimidin-2-ones (Fig. 2.1) and –2-ylidenes (Fig. 2.3) was adopted by [1,3]thiazinan-2-ylidenes. Delocalization by the isothiourea group, indicated by shorter C_7-N_2 and C_7-S bonds, created rigidity in this portion of the ring while flexibility in the remaining section would allow for many configurations in solution.

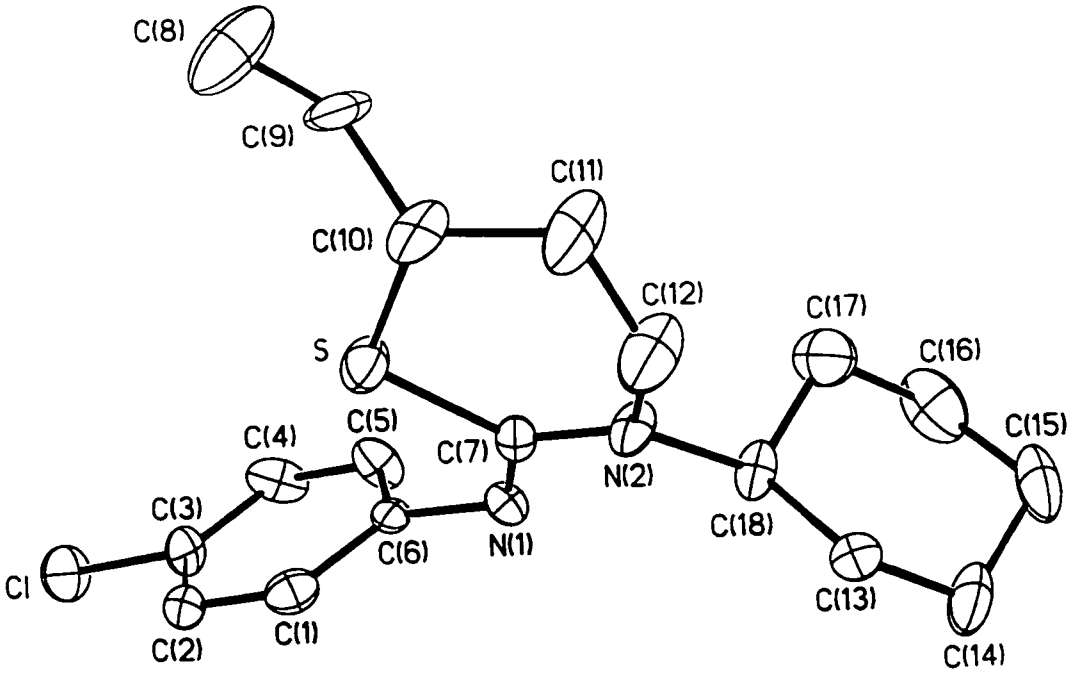
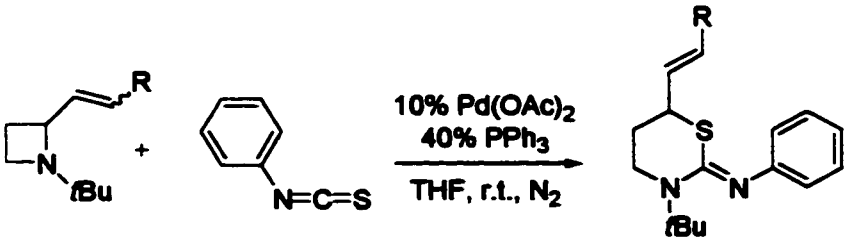


Figure 2.4. View of 2.38c ($R = C_6H_{11}$, $R' = Cl$), showing the atomic numbering scheme.

To reiterate the results encountered with 2-vinylazetidines that have substituents on the alkene moiety, reactions of **2.12a-b** with phenylisothiocyanate were performed (eq 19). Once more, **2.12b** was expected to be a more efficient substrate due to the electron-



(eq 19)

2.12a R = CH_3 **2.37a** **2.39a-b**
2.12b R = CO_2CH_3

withdrawing ability of the carbomethoxy group, while mediocrity was anticipated in the reaction of **2.12a** with **2.37a**.

Table 2.9 The Effect of Substitution on the Vinyl Group in Pd(0) Catalyzed Reactions[a] of 1-(*tert*-Butyl)-2-vinylazetidines with Phenylisothiocyanate

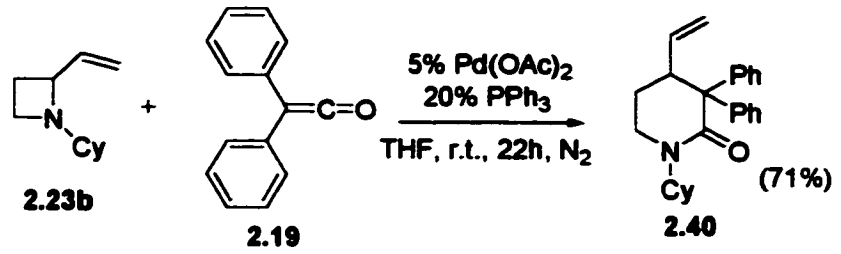
Azetidine	Time[b] (h)	Product[c]	% Yield
2.12a	48	**2.39a**	35[d]
2.12b	45	**2.39b**	89

[a]PPh_3 and $Pd(OAc)_2$ were premixed for 30 min in 4.0 ml of dry, degassed solvent followed by addition of 1.0 mmol of **2.12** and **2.37a** with 1.0 ml of dry solvent; [b]reaction began with addition of substrates and was over when GC indicated consumption of one or both; [c]purified by column chromatography with appropriate ether/pentane solvent system. [d]only 38% conversion calculated from recovery of **2.37a**.

The results in Table 2.9 validate these predictions, supporting the previous hypothesis that the methyl group not only added steric interference in **2.12a**, but likely deactivated the ring towards cleavage and subsequent product formation. In contrast, greater reactivity was observed with an electron-withdrawing substituent on the vinyl group even though there would be added steric hindrance. ^1H and ^{13}C NMR spectra again accomplished the identification of **2.39a-b** where trace amounts of the *cis* products could be detected. The crystal structure seen in Fig. 2.5 displayed much less congestion around the vinyl group in the [1,3]thiazinanes compared to the previous cases, explaining the discrepency. IR and EI-HRMS analysis supported the NMR spectra and can be found in the Experimental section 3.3.5.

2.3.3 Reactions of 1-cyclohexyl-2-vinylazetidine with ketenes and ketenimines

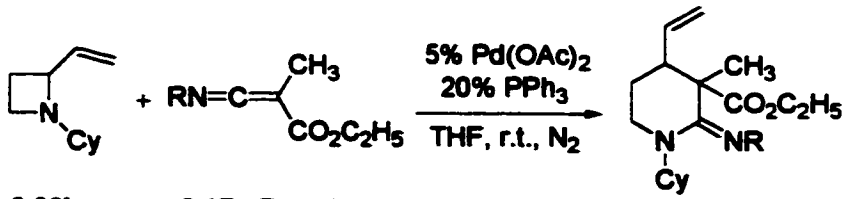
To introduce the prospect of using additional carbon electrophiles for insertion into π-allylpalladium complexes of 2-vinylazetidines, some exploratory reactions of **2.23b** with ketenes (eq 20) and ketenimines (eq 21) were conducted.



2.23b 2.19 2.40 (eq 20)

Ketenes are known to be more reactive species than isocyanates[36] due to better polarization of the cumulene as only one heteroatom is present. In the case of **2.19**, however, steric hindrance likely obstructed nucleophilic attack on the central carbon, which slowed the overall rate. This enabled some dimerization, a potential side reaction of these heterocumulenes[36], and caused a reduction in the yield of **2.40**. The ^{13}C NMR spectrum displayed a signal at 171 ppm, which is indicative of amide carbonyl carbons, verifying that this product did arise and not the alternative, where an exocyclic alkene would be present. The characteristic features of the ^{1}H NMR conclusively supported the structure of **2.40** with multiplets at 4.9-5.1 ppm and 5.7-5.9 ppm, representing the vinyl protons, and the broad multiplet at 3.5-3.7 ppm of the C_4 hydrogen. In addition, EI-HRMS and accurate mass analyses (see Experimental, section 3.3.3) were performed and supported the supposed structure.

Ketenimines were predicted to exhibit less reactivity than **2.19** as the polarization of the heterocumulene will be lessened, reducing the electrophilicity of the central carbon, and more steric hindrance would be present. To counter these problems, ketenimines (**2.17**) were prepared that possessed less sterically demanding groups while the carboethoxy group should enhance the electrophilic character (eq 21).



2.23b 2.17a R = *n*Bu 2.17b R = Ph 2.41a-b (eq 21)

From the lengthy reaction times and low isolated yields observed (Table 2.10), it was evident that these heterocumulenes exhibited much lower reactivity toward insertion under these

reaction conditions. No optimization was attempted. However, better yields may have been obtained by raising the reaction temperature or by increasing the catalyst load.

Table 2.10 Palladium(0) Catalyzed Reactions[a] of 1-Cyclohexyl-2-vinylazetidine with Ketenimines

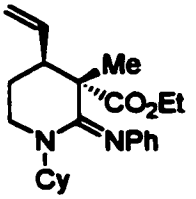
Ketenimine	Time[b] (h)	Product[c]	% Yield
2.17a	48	**2.40a**	57
2.17b	48	**2.40b**	61

[a]PPh_3 and $Pd(OAc)_2$ were premixed for 30 min in 4.0 ml of dry, degassed solvent followed by addition of 1.0 mmol of **2.23b** and **2.17** with 1.0 ml of dry solvent; [b]reaction began with addition of substrates and was over when GC indicated consumption of one or both; [c]purified by column chromatography with appropriate ether/pentane solvent system.

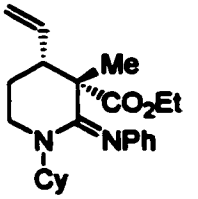
Hence these experiments indicated ketenimines are capable substrates that could potentially afford **2.41** in very high yields through reactions with 2-vinylazetidines under the proper conditions.

The ^1H and ^{13}C NMR spectra were quite complex indicating the presence of two related compounds. The lack of symmetry in **2.17** resulted in the formation of a diastereomeric mixture for **2.40** where the vinyl group has two possible configurations relative to the methyl or carboethoxy group (Scheme 2-5).

Scheme 2-5



(*E*)-**2.41**



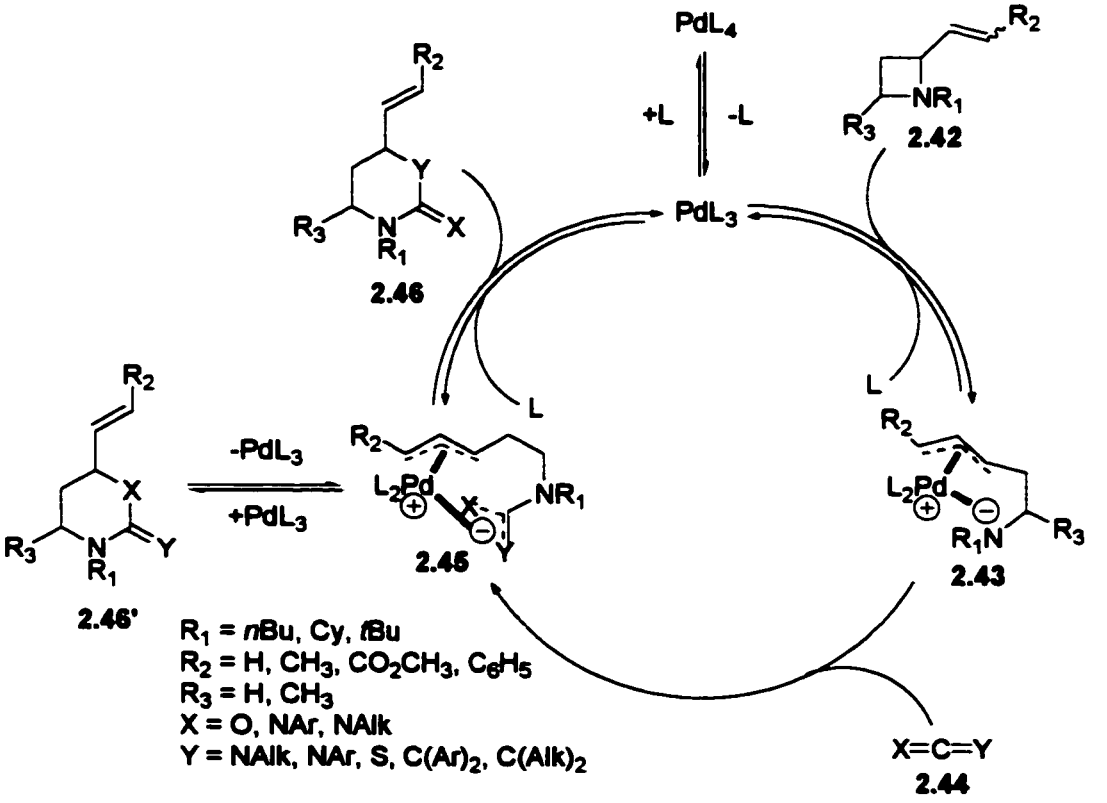
(*Z*)-**2.41**

Consequently, overlapping multiplets for the vinyl hydrogens are observed for **2.41a-b** at 4.9-5.1 ppm and 5.5-5.7 ppm while a broad, complicated signal between 3.8 and 4.2 ppm

denoted the C_4 hydrogen. In the ^{13}C NMR spectra, the ester and imine carbons appeared at 173 ppm and 151 ppm respectively. These groups also characterized the IR spectra with stretching frequencies of 1730 cm^{-1} (λ C=O) and 1615-1610 cm^{-1} (λ C=N). Again EI-HRMS was performed and accurate mass calculated, verifying the structure and purity of **2.41**.

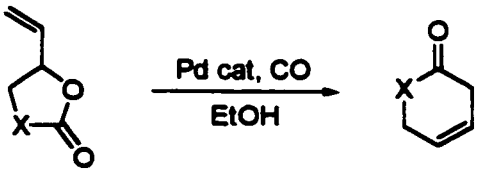
From past reports of heterocumulene insertion into palladium complexes of vinyloxiranes[17-19a, 21] and –oxetanes[19b], supplemented by the information provided by these reactions, a plausible mechanistic scheme can be proposed (Scheme 2-6).

Scheme 2-6



The rearrangements of 2-vinylazetidines reported by Yamamoto *et al.*[23] attest for the facile ring cleavage of **2.42**. The reversible formation of the π-allyl intermediate is an equilibrium that lies toward **2.43** when strongly electron-withdrawing groups are on the vinyl group enhancing the overall reaction. At this point, the R_2 group necessarily adopts a pseudo-*trans* configuration, because of the steric bulk around the metal centre, and is maintained throughout resulting in the observed configuration for **2.46**. An η^3-η^1-η^3 inversion can occur

in both **2.43** and **2.45**, causing the stereochemical scrambling of the 4-methyl derivative, **2.31**. Trost indicated that intramolecular cyclization in the reaction of vinyloxiranes with isocyanates could proceed giving *N*- or *O*-alkylated products[18a]. The latter was shown to isomerize with further exposure to a palladium catalyst yielding the thermodynamically favored, *N*-alkylated heterocycle. Reactions of 2-vinylazetidines with isothiocyanates also revealed the formation of a kinetic product. Therefore, **2.45** is predicted to cyclize to both **2.46** and **2.46'** with eventual thermodynamic equilibration to **2.46**. Recent accounts[26] verify ring opening of vinyl-substituted heterocycles, **2.47** (eq 22), and add credibility to the equilibrium speculated in Scheme 2-6.



2.47 **2.48**

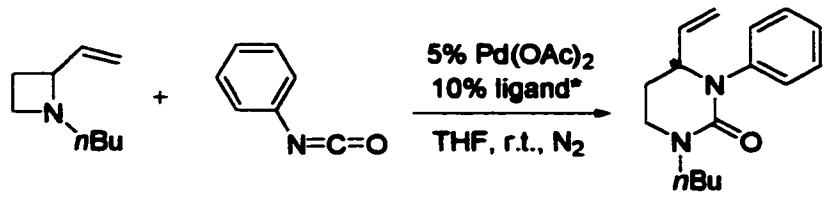
X = O, NH

(eq 22)

This catalytic cycle demonstrates the synthetic utility of π-allylpalladium complexes, such as **2.43**, in reactions with various heterocumulene systems. The 2-vinylazetidines exhibited comparable reactivity to 2-vinyloxetanes and with a similar mechanism as vinyloxiranes and –oxetanes, insertion of other carbon electrophiles is possible for the synthesis of many heterocycles. Even more appealing would be asymmetric processes that yield products with high optical purity.

2.4 Stereoselective reaction of 2-vinylazetidines and heterocumulenes

Examples of asymmetric synthesis with $Pd(OAc)_2$ and optically-active, bidentate phosphines have been reported[38]. Therefore, initial attempts simply replaced triphenylphosphine with a series of chiral ligands for the reaction of phenylisocyanate with **2.23a** (eq 23).



2.23a **2.21a** **2.24a** (eq 23)

It was expected that chiral induction would be a rudimentary process, having previously established efficient, non-asymmetric methodology for these reactions. However, little success was achieved.

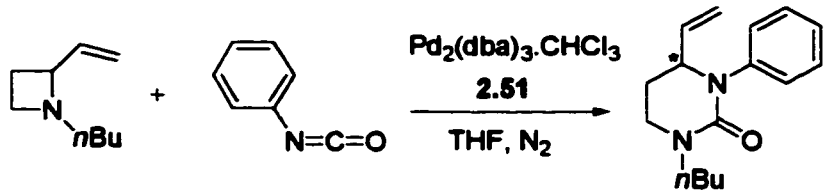
Table 2.11 Palladium(0) Catalyzed Reactions[a] of 1-Butyl-2-vinylazetidine with Phenylisocyanate using Chiral, Bidentate Phosphine Ligands

Ligand	Time[b] (h)	% Yield[c]	% e. e.[d]
(R, R)-DIOP	1.5	85	9
(R, R)-BDDP	1	91	3
(R, R)-NORPHOS	8	84	15
(R, R)-PROPHOS	21	40	2
(R)-(S)-JOSIPHOS	2	91	2

[a]$Pd(OAc)_2$ and ligand were premixed for 30 min in 4.0 ml of dry, degassed solvent followed by addition of 1.0 mmol of **2.23a** and **2.21a** with 1.0 ml of dry solvent; [b]reaction began with addition of substrates and was over when GC indicated consumption of one or both; [c]isolated by column chromatography with appropriate ether/pentane solvent system; [d]determined by chiral HPLC using Hex/iPrOH/MeOH (90:5:5) solvent system.

In general, the reactions proceeded quite well and afforded good yields of **2.24a**, which was verified by ^1H and ^{13}C NMR analysis. Yet no detectable optical rotations were observed for these products. Chiral HPLC confirmed that low to negligible enantiomeric excesses had been obtained with these ligands. (R)-BINAP and (S)-TolBINAP proved worse as they appeared to hinder the transformation, yielding no product. Larksarp *et al.* reported high asymmetric induction using either of these ligands for reactions of vinyloxirane with

heterocumulenes[19a], but a different palladium compound was applied in that example. Therefore, this procedure (eq 24) was explored since limited progress was being made with palladium (II) acetate.



2.23a 2.21a 2.24a (eq 24)

2.51a = BINAP
2.51b = TolBINAP

Previously, $Pd_2(dba)_3.CHCl_3$ demonstrated lower catalytic ability in non-asymmetric reactions of 2-vinylazetidines with isocyanates. However, such a palladium complex should be better suited to this case since it already possesses a zero valence, and no reduction will be required by the chiral bidentate ligand. As shown in Table 2.12, this catalytic system was optimized, and higher yields were obtained for **2.24a**.

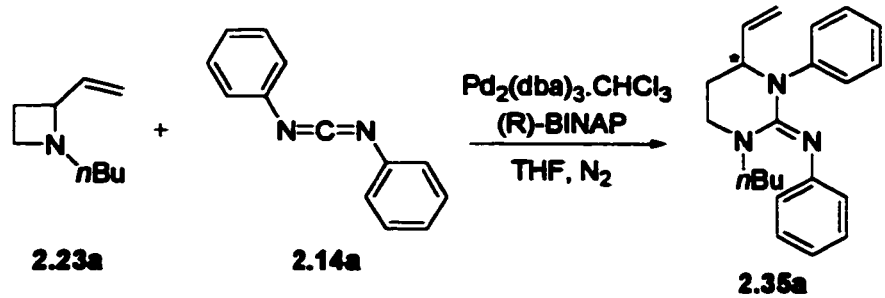
Table 2.12 Reactions[a] of 1-Butyl-2-vinylazetidine with Phenylisocyanate Catalyzed by $Pd_2(dba)_3.CHCl_3$ and 2.51[b]

Mol % Catalyst	Ligand	Mol % 2.51	Temp. (°C)	Time[c] (h)	% Yield[d]	% e. e.[e]
3	**2.51a**	6	20	24	55	14
5	**2.51a**	10	20	24	74	6
5	**2.51b**	10	20	24	60	6
7.5	**2.51a**	15	20	4	84	8
3	**2.51a**	6	60	4	85	11
3	**2.51a**	12	60	4	76	4

[a]$Pd_2(dba)_3.CHCl_3$ and **2.51** were premixed for 30 min in 4.0 ml of dry, degassed solvent followed by addition of 1.0 mmol of **2.23a** and **2.21a** with 1.0 ml of dry solvent; [b]both (R) and (S) isomers were used; [c]reaction began with addition of substrates and was over when GC indicated consumption of one or both; [d]isolated by column chromatography with appropriate ether/pentane solvent system; [e]determined by chiral HPLC using Hex/iPrOH/MeOH (90:5:5) solvent system.

Unfortunately, the enantioselectivity ratio could not be improved. Increasing the catalyst load or the reaction temperature rectified the low yields but was offset by lower selectivity. Changing the catalyst:ligand ratio further reduced the observed enantiomeric excess of **2.24a**.

In the work of Larksarp *et al.*, better selectivity had been observed with carbodiimides. Therefore, it was felt that exchanging the heterocumulene substrate could provide a new route in the reaction (eq 25).



2.23a **2.14a** **2.35a** (eq 25)

Even though much longer reaction times were required, the insertion of **2.14a** with this catalytic system proceeded more efficiently than phenylisocyanate insertion (Table 2.13).

Table 2.13 Reactions[a] of 1-Butyl-2-vinylazetidine with Diphenylcarbodiimide Catalyzed by $Pd_2(dba)_3.CHCl_3$ and (R)-BINAP

Mol % Catalyst	Mol % Ligand	Temp. (°C)	Time[b] (h)	% Yield[c]
3	6	20	88	81
3	6	60	18	80
7.5	15	20	86	84

[a] $Pd_2(dba)_3.CHCl_3$ and (R)-BINAP were premixed for 30 min in 4.0 ml of dry, degassed solvent followed by addition of 1.0 mmol of **2.23a** and **2.14a** with 1.0 ml of dry solvent; [b] reaction began with addition of substrates and was over when GC indicated consumption of one or both; [c] isolated by column chromatography with appropriate ether/pentane solvent system.

The enantiomers could not be accurately separated by chiral HPLC. Nevertheless, polarimetry readings denoted negligible optical rotation for **2.35a**. Reasons for the lack of chiral induction in this case are unclear. The speculated mechanism proposed by Larksarp *et al.* that induced asymmetry in the reaction of vinyloxiranes involved contact between the napthyl rings of the TolBINAP ligand with the aryl groups of the heterocumulene. After examining the differences in the two instances for explanations, it is possible the extra methylene group in the π-allylpalladium intermediate of the azetidine lessened the necessary interaction and disrupted the induction. Also, the more basic nitrogen, from the original azetidine ring, might remain bound to the palladium, which could also diminish the interaction with the BINAP ligand. Consequently, insignificant optical activity was detected in these products.

2.5 Conclusion

A synthesis of *N*-alkylated 2-vinylazetidine derivatives resulted by modification of literature procedures. Methods for the regioselective cycloaddition reactions of these 2-vinylazetidines with aryl- and alkylisocyanates, diarylcarbodiimides, and arylisothiocyanates were established with a $Pd(OAc)_2/PPh_3$ system. Greater reactivity was apparent for isocyanates in comparison with the corresponding sulfur derivatives, while good results for carbodiimides were negatively biased by the bulkiness of these substrates. An assortment of tetrahydropyrimidin-2-ones, tetrahydropyrimidin-2-imines, and [1,3]thiazinan-2-imines were synthesized in good to excellent yield using this design. In addition, these methods proved to be applicable to other heterocumulenes, ketenes and ketenimines, suggesting that different carbon electrophiles could be used.

Changes on the substrate affected the outcome of the reactions. Increasing the size of the *N*-alkyl group on the azetidine reduced product yields. The bulkier groups obstructed the reaction, favoring the formation of by-products such as dimerized heterocumulene, whereas much cleaner and higher yielding reactions were realized with the less hindering alkyl chain, *n*-butyl. Minor electronic effects were apparent with mono-substituted aryl groups on the heterocumulenes. With electron-withdrawing groups in the *para*-position, reaction rates increased indicating greater electrophilic character on the reactive carbon center. Additionally, electron-donating groups, such as *p*-tolylisocyanate, deactivated the substrate as compared to phenylisocyanate and *m*-tolylisocyante, which substantiates an electronic effect by these groups. Interesting findings arose from reactions with *o*-tolylisocyanate where steric congestion introduced a barrier between conformations that could not be overcome at room temperature. ^1H and ^{13}C NMR spectra indicated two conformations in the products, which coalesced at temperatures exceeding 100°C.

2-Vinylazetidines with substituents on the vinyl group demonstrated more electronic influences in these palladium-catalyzed insertion reactions. The ring cleavage step was activated by electron-withdrawing substituents on the vinyl group as faster reaction rates and improved yields resulted. The electron deficiency caused heightened polarization of the C-N bond and facilitated formation of η^3 binding by the vinyl. Similarly, exchanging for a propenyl group deactivated the azetidine ring towards cleavage. In addition to steric

hindrance, the inductive property of methyl groups hampered creation of the π-allyl intermediate. The optimal group would possess little steric bulk and remove electron density from the vinyl moeity.

As well, the formation of π-allylpalladium intermediates was substantiated by stereochemical evidence. These complexes were suggested as the active species in the insertion of heterocumulenes. The formation of a kinetic product was demonstrated, and an equilibrium between the two possible cyclization products was postulated in the catalytic cycle of 2-vinylazetidines and heterocumulenes. Lastly, asymmetric synthesis of these products proved difficult to accomplish. An established mechanism for chiral induction in the reaction of vinyloxiranes with heterocumulenes also failed to afford optically active products. Possibly, the extra methylene group of the azetidine or continued chelation by the basic nitrogen alleviated the required congestion, yielding compounds with discouraging enantiomeric excesses.

Chapter 3

3.1 General comments

trans-1-Butyl-4-methyl-2-carbomethoxyazetidine (**2.8**) had been previously prepared in our laboratory using the procedure reported by Rodebaugh and Cromwell[28] and was purified by distillation. All isocyanates and isothiocyanates were obtained from commercial sources. Only cyclohexylisocyanate was distilled before use. Tetrahydrofuran and diethyl ether were dried over Na/benzophenone and distilled prior to use. [$Pd(OAc)_2$] and all phosphines were obtained from Strem and were used as received. A literature procedure[34] provided [$Pd_2(dba)_3.CHCl_3$].

Most ^1H and ^{13}C NMR spectra were recorded on a Gemini 200 spectrometer while all variable temperature, 2D NMR, and specified ^1H and ^{13}C NMR spectra, were performed on a Bruker AMX 500 spectrometer. Generally, $CDCl_3$ was used as solvent and referenced to $CHCl_3$ (at 7.24 ppm) and $CDCl_3$ (at 77.0 ppm). Variable temperature experiments required d^6-DMSO as the solvent. Chemical shifts were reported in ppm.

A Bomem MB 100-C15 FT spectrometer provided all IR spectra where frequencies were reported in wavenumbers (cm^{-1}). GC analyses were performed with a Hewlett Packard 5890 Series II chromatograph. Mass spectra were obtained in EI^+ mode on a VG 7070E spectrometer. Melting points were determined on a Fisher-Johns apparatus. Optical rotation was measured on a Perkin-Elmer 241 polarimeter, and chiral HPLC was accomplished using a Varian 9012 solvent delivery system/Varian 9050 detector equipped with a Chiralcel OB column.

3.2 Synthesis of 1-alkyl-2-vinylazetidines and heterocumulenes

3.2.1 1-Alkyl-2-carbomethoxyazetidines (2.6)

The literature procedure of Rodebaugh and Cromwell[28] was used in the synthesis of 1-alkyl-2-carbomethoxyazetidines (Section 2.1.1) with a modification in the second step. They reported using an excess of the primary amine (3-3.5 equivalents) and requiring

multiple purification steps. Instead, only 1.1 equivalents of the primary amine was used in conjunction with 2.2 equivalents of triethylamine. After the reaction was completed, the solvent was removed and the crude material was taken up in ether. Filtration and concentration yielded a dark orange oil which was distilled to afford purified **2.6**.

1-Butyl-2-carbomethoxyazetidine (2.6, R = C_4H_9)

55-67% yield; bp 48-50°C/1-2 mmHg; IR (neat) ν (C=O) 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.7-0.9 (br, 3H, CH_3), 1.1-1.3 (br, 4H, CH_2CH_2), 2.1-2.4 (m, 3H, NCH_2CH_2 ring), 2.5 (m, 1H, NCH_2 ring), 2.7 (m, 1H, NCH_2), 3.3 (m, 1H, NCH_2), 3.5 (t, 1H, J = 8.3 Hz, $CHCO_2$), 3.6 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 173.27 (C=O), 65.05 (NCH_2), 58.77 ($CHCO_2$), 51.75 (OCH_3), 51.09 (NCH_2 ring), 29.26 (CH_2), 21.52 (CH_2 ring), 20.37 (CH_2), 13.84 (CH_3); MS (*m/e*) 171 $[M]^+$.

1-Cyclohexyl-2-carbomethoxyazetidine (2.6, R = C_6H_{11})

54-71% yield; bp 88-90°C/1-2 mmHg; IR (neat) ν (C=O) 1749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9-1.2 (br, 5H, cyclohexyl), 1.5-1.8 (br, 5H, cyclohexyl), 2.1 (m, 1H, NCH), 2.2 (m, 2H, CH_2 ring), 2.8 (m, 1H, NCH_2 ring), 3.4 (m, 1H, NCH_2 ring), 3.6 (t, 1H, J = 8.5 Hz, $CHCO_2$), 3.7 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 173.87 (C=O), 66.33 (NCH), 63.96 ($CHCO_2$), 51.90 (OCH_3), 49.41 (NCH_2 ring), 29.86 (cyclohexyl), 29.30 (cyclohexyl), 25.72 (cyclohexyl), 24.40 (cyclohexyl), 21.49 (CH_2 ring); MS (*m/e*) 197 $[M]^+$.

1-*tert*-Butyl-2-carbomethoxyazetidine (2.6, R = $C(CH_3)_3$)

45-57% yield; bp 51-52°C/1-2 mmHg; IR (neat) ν (C=O) 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (s, 9H, $C(CH_3)_3$), 2.0 (m, 1H, CH_2 ring), 2.1 (m, 1H, CH_2 ring), 3.1(m, 2H, NCH_2 ring), 3.6 (s, 3H, CO_2CH_3), 3.9 (t, 1H, J = 8.3 Hz, $CHCO_2$); ^{13}C NMR ($CDCl_3$) δ 174.11 (C=O), 58.02 ($CHCO_2$), 52.53 ($NC(Me)_3$), 51.77 (OCH_3), 43.34 (NCH_2 ring), 24.21 ($(CH_3)_3$), 20.26 (CH_2 ring); MS (*m/e*) 171 $[M]^+$.

***trans*-1-Butyl-2-carbomethoxy-4-methylazetidine (2.8)**

bp 55-59°C/1-2 mmHg; IR (neat) ν (C=O) 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8 (t, 3H, J = 7.0 Hz, CH_3), 1.1 (d, 3H, J = 6.0 Hz, CH_3), 1.2-1.3 (br, 4H, CH_2CH_2), 1.8 (m, 1H, CH_2 ring), 2.3

(m, 1H, CH_2 ring), 2.5 (m, 2H, NCH_2), 2.9 (m, 1H, NCHMe ring), 3.3 (t, 1H, J = 8.4 Hz, $CHCO_2$), 3.6 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 173.99 (C=O), 62.67 ($CHCO_2$), 59.41 (NCHMe ring), 58.92 (NCH_2), 52.25 (OCH_3), 30.09 (CH_2), 22.77(CH_2), 21.15 (CH_2 ring), 14.40 (CH_3); MS (*m/e*) 185 $[M]^+$.

3.2.2 1-Alkylazetidine-2-carbaldehydes (2.9)

To a stirred solution of **2.6** or **2.8** in dry diethyl ether (~0.10 g/ml) under a nitrogen atmosphere, 1.1 equivalents of diisobutylaluminum hydride (1.0M in hexanes) was slowly added, maintaining the temperature at –78°C. The reaction was monitored by thin layer chromatography for the disappearance of starting material. At this time, a small amount of dry methanol was added, and the reaction was warmed in an ice/water bath. A saturated $NaHCO_3$ solution was slowly added followed by a 10% NaOH solution. The mixture was stirred until it reached room temperature, and the layers could be separated. The aqueous layer was extracted three times with ether. The combined ethereal layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. Distillation of the crude yielded **2.9**, but often with traces of **2.6** or alcohol, both of which could be carried on to the next step.

1-Butylazetidine-2-carbaldehyde (2.9, R = C_4H_9)

71-86% yield; bp 41-42°C/1-2 mmHg; IR (neat) ν (C=O) 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8-1.0 (br, 3H, CH_3), 1.2-1.4 (br, 4H, CH_2CH_2), 1.9 (m, 1H, CH_2 ring), 2.1 (m, 1H, CH_2 ring), 2.5 (m, 1H, NCH_2), 2.8 (m, 1H, NCH_2), 3.3 (m, 2H, NCH_2 ring), 3.4 (m, 1H, NCH ring), 9.7 (d, 1H, J = 2.9 Hz, CHO); ^{13}C NMR ($CDCl_3$) δ 202.76 (C=O), 68.33 (NCH_2), 58.01 (NCH ring), 50.94 (NCH_2 ring), 29.62 (CH_2), 20.31 (CH_2), 18.52 (CH_2 ring), 13.93 (CH_3); MS (*m/e*) 141 $[M]^+$.

1-Cyclohexylazetidine-2-carbaldehyde (2.9, R = C_6H_{11})

65-85% yield; bp 67-69°C/1-2 mmHg; IR (neat) ν (C=O) 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.7-1.2 (br, 5H, cyclohexyl), 1.3-1.7 (br, 5H, cyclohexyl), 1.9-2.2 (m, 3H, NCH and CH_2 ring), 2.9 (m, 1H, NCH_2 ring), 3.3 (m, 1H, NCH_2 ring), 3.4 (dt, 1H, J = 3.3 and 8.5 Hz, NCH ring), 9.6 (d, 1H, J = 3.3 Hz, CHO); ^{13}C NMR ($CDCl_3$) δ 202.86 (C=O), 69.74 (NCH), 65.35

(NCH ring), 50.00 (NCH_2 ring), 29.91 (cyclohexyl), 29.23 (cyclohexyl), 25.54 (cyclohexyl), 24.20 (cyclohexyl), 23.97 (cyclohexyl), 23.93 (cyclohexyl), 18.36(CH_2 ring); MS (*m/e*) 167 $[M]^+$.

1-*tert*-Butyl-azetidine-2-carbaldehyde (2.9, R = $C(CH_3)_3$)

70-93% yield; bp 44-45°C/1-2 mmHg; IR (neat) ν (C=O) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (s, 9H, $C(CH_3)_3$), 2.1 (m, 2H, CH_2 ring), 3.2 (m, 2H, NCH_2 ring), 3.8 (dt, 1H, J = 3.5 and 8.3 Hz, NCH ring), 9.6 (d, 1H, J = 3.5 Hz, CHO); ^{13}C NMR ($CDCl_3$) δ 202.69 (C=O), 51.86 NCH ring, 50.94 ($NC(Me)_3$), 41.99 (NCH_2 ring), 23.75 ($(CH_3)_3$), 19.53 (CH_2 ring); MS (*m/e*) 141 $[M]^+$.

***trans*-1-Butyl-4-methylazetidine-2-carbaldehyde**

85% yield; bp 45-46°C/1-2 mmHg; IR (neat) ν (C=O) 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3H, J = 6.8 Hz, CH_3), 1.2 (d, 3H, J = 6.1 Hz, CH_3), 1.3-1.5 (br, 4H, CH_2CH_2), 2.1 (m, 2H, CH_2), 2.7 (m, 2H, NCH_2), 3.2 (m, 1H, NCHMe ring), 3.4 (m, 1H, NCH ring), 9.7 (d, 1H, J = 2.8 Hz, CHO); ^{13}C NMR ($CDCl_3$) δ 202.59 (C=O), 65.63 (NCH ring), 58.97 (NCHMe ring), 56.84 (NCH_2), 30.58 (CH_2), 22.59 (CH_3), 20.07 (CH_2 ring), 19.64 (CH_2 ring), 14.55 (CH_3); MS (*m/e*) 155 $[M]^+$.

3.2.3 1-Alkyl-2-vinylazetidines (2.10)

To a stirred solution of alkyltriphenylphosphonium bromide (2.5 eq.) in dry diethyl ether under a nitrogen atmosphere, 2.5 equivalents of methyllithium (1.4M in diethyl ether) was slowly added while maintaining the temperature at –78°C. The evolution of methane could be monitored with an oil bubbler as the solution slowly warmed to room temperature. When methane evolution was complete, the reaction was cooled to –78°C, and **2.9** (in dry diethyl ether) was slowly added to give a 0.05 g/ml reaction solution. The reaction was allowed to stir overnight at room temperature, at which point water was slowly added. The phases were separated, and the aqueous layer was extracted twice with ether. The combined ethereal layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation.

Flash chromatography with 1:20 ether/pentane afforded **2.10**, often with small amounts of solvent due to the low boiling points of these compounds.

1-Butyl-2-vinylazetidine (2.10, R = C_4H_9)

45-51% yield; bp 35-36°C/1-2 mmHg; ^{1}H NMR ($CDCl_3$) δ 0.6-0.8 (br, 3H, CH_3), 1.0-1.2 (br, 4H, CH_2CH_2), 1.8 (m, 2H, CH_2 ring), 2.1 (m, 1H, NCH_2), 2.3 (m, 1H, NCH_2), 2.5 (m, 1H, NCH_2 ring), 3.1 (m, 2H, NCH_2 ring and NCH ring), 4.8 (m, 2H, CH_2 vinyl), 5.7 (m, 1H, CH vinyl); ^{13}C NMR ($CDCl_3$) δ 140.29 (CH vinyl), 114.33 (CH_2 vinyl), 68.41 (NCH ring), 58.16 (NCH_2), 51.29 (NCH_2 ring), 29.36 (CH_2) 24.19 (CH_2 ring), 20.18 (CH_2), 13.52 (CH_3); MS (*m/e*) 139 $[M]^+$.

1-Cyclohexyl-2-vinylazetidine (2.10, R = C_6H_{11})

40-59% yield; bp 55-56°C/1-2 mmHg; ^{1}H NMR ($CDCl_3$) δ 0.6-1.0 (br, 5H, cyclohexyl), 1.2-1.6 (br, 5H, cyclohexyl), 1.6-1.8 (m, 3H, CH_2 ring and NCH), 2.4 (m, 1H, NCH_2 ring), 3.0 (m, 1H, NCH_2 ring), 3.2 (ABq, 1H, J = 7.8 Hz, NCH ring), 4.7 (m, 2H, CH_2 vinyl), 5.7 (m, 1H, CH vinyl); ^{13}C NMR ($CDCl_3$) δ 142.02 (CH vinyl), 113.52 (CH_2 vinyl), 67.13 (NCH ring), 66.74 (NCH), 48.97 (NCH_2 ring), 30.31 (cyclohexyl), 29.44 (cyclohexyl), 25.48 (cyclohexyl), 23.95 (CH_2 ring), 23.44 (cyclohexyl); MS (*m/e*) 165 $[M]^+$.

1-*tert*-Butyl-2-vinylazetidine (2.10, R = $C(CH_3)_3$)

47-67% yield; bp 33-34°C/1-2 mmHg; ^{1}H NMR ($CDCl_3$) δ 0.7 (s, 9H, $C(CH_3)_3$), 1.7 (m, 2H, CH_2 ring), 2.8 (m, 2H, NCH_2 ring), 3.6 (ABq, 1H, J = 7.9 Hz, NCH ring), 4.8 (m, 2H, CH_2 vinyl), 5.7 (m, 1H, CH vinyl); ^{13}C NMR ($CDCl_3$) δ 143.33 (CH vinyl), 113.73 (CH_2 vinyl), 61.08 (NCH ring), 52.49 ($C(Me)_3$), 42.96 (NCH_2 ring), 24.69 (($CH_3)_3$), 22.83 (CH_2 ring); MS (*m/e*) 139 $[M]^+$.

1-*tert*-Butyl-2-propenylazetidine (2.12a, R = CH_3)

55% yield; bp 37-39°C/1-2 mmHg; ^{1}H NMR ($CDCl_3$) δ (*trans*) 0.8 (s, 9H, $C(CH_3)_3$), 1.5 (d, 3H, J = 6.2 Hz, CH_3), 1.8 (m, 2H, CH_2 ring), 2.9 (m, 2H, NCH_2 ring), 3.7 (ABq, 1H, J = 7.7 Hz, NCH ring), 5.4 (m, 2H, vinyl); (*cis*) 0.8 (s, 9H, $C(CH_3)_3$), 1.6 (d, 3H, J = 6.3 Hz, CH_3),

1.8 (m, 2H, CH_2 ring), 2.9 (m, 2H, NCH_2 ring), 4.1 (ABq, 1H, J = 8.0 Hz, NCH ring), 5.3 (m, 2H, vinyl); ^{13}C NMR ($CDCl_3$) δ (*trans*) 136.41 (CH vinyl), 124.98 (CHMe vinyl), 60.39 (NCH ring), 54.44 ($C(Me)_3$), 42.85 (NCH_2 ring), 24.77 ($(CH_3)_3$), 23.11 (CH_2 ring), 17.31 (CH_3); (*cis*) 135.93 (CH vinyl), 122.83 (CHMe vinyl), 60.38 (NCH ring), 52.43 ($C(Me)_3$), 43.24 (NCH_2 ring), 24.57 ($(CH_3)_3$), 23.23 (CH_2 ring), 13.08 (CH_3); MS (*m/e*) 153 $[M]^+$.

Methyl-3-(1-*tert*-butylazetidin-2-yl)-acrylate (2.12b, R = CO_2CH_3)

67% yield; colorless oil; IR (neat) ν 1748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8 (s, 9H, $C(CH_3)_3$), 1.8 (m, 2H, CH_2 ring), 3.0 (m, 2H, NCH_2 ring), 3.6 (s, 3H, OCH_3), 3.8 (ABq, 1H, J = 7.9 Hz, NCH ring), 5.8 (dd, 1H, J = 1.0 and 15.7 Hz, $CHCO_2$ vinyl), 6.9 (dd, 1H, J = 7.1 and 14.8 Hz, CH vinyl); ^{13}C NMR ($CDCl_3$) δ 167.20 (C=O), 152.61 (CH vinyl), 119.70 (CH vinyl), 58.65 (NCH ring), 52.78 ($C(Me)_3$), 51.46 (OCH_3), 43.42 (NCH_2 ring), 24.90 ($(CH_3)_3$), 22.89 (CH_2 ring); MS (*m/e*) 197 $[M]^+$.

1-*tert*-Butyl-2-styrylazetidine (2.12c, R = C_6H_6)

20% yield; colorless oil; ^1H NMR ($CDCl_3$) δ 0.9 (s, 9H, $C(CH_3)_3$), 2.0 (m, 2H, CH_2 ring), 3.0 (t, 2H, J = 6.9Hz, NCH_2 ring), 3.9 (m, 1H, NCH ring), 6.3 (m, 2H, vinyl), 7.1-7.4 (m, 5H, phenyl); ^{13}C NMR ($CDCl_3$) δ 136.87 (phenyl), 134.95 (CHPh vinyl), 129.11 (CH vinyl), 128.24 (phenyl), 127.03 (phenyl), 126.07 (phenyl), 60.66 (NCH ring), 52.52 ($C(Me)_3$), 43.16 (NCH_2 ring), 24.89 ($(CH_3)_3$), 23.46 (CH_2 ring); MS (*m/e*) 215 $[M]^+$.

***trans*-1-Butyl-4-methyl-2-vinylazetidine (2.30)**

56% yield; bp 38-40°C/1-2 mmHg; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3H, J = 7.0 Hz, CH_3), 1.2 (d, 3H, J = 6.4 Hz, CH_3), 1.2-1.5 (br, 5H, CH_2CH_2 and CH_2 ring), 2.2 (m, 1H, CH_2 ring), 2.4 (m, 2H, NCH_2), 2.8 (m, 1H, NCH_2 ring), 3.2 (m, 1H, NCH_2 ring), 5.0 (m, 2H, CH_2 vinyl), 5.9 (m, 1H, CH vinyl); ^{13}C NMR ($CDCl_3$) δ 143.17 (CH vinyl), 114.53 (CH_2 vinyl), 64.19 (NCH ring), 58.44 (NCH_2), 51.60 (NCH_2 ring), 29.73 (CH_2), 24.17 (CH_3), 22.98(CH_2 ring), 21.58 (CH_2), 13.82 (CH_3); MS (*m/e*) 153 $[M]^+$.

3.2.4 Diarylcarbodimides (2.14)

Diarylcarbodiimides were prepared according to the literature procedure[31] replacing xylene with benzene as solvent and purifying by vacuum distillation or column chromatography. Characterization was primarily performed by IR spectral analyses.

Diphenylcarbodiimide (2.14a, R = H)

82% yield; bp 125-130°C/1-2 mmHg; IR (neat) ν (C=N=C) 2133 cm^{-1}; MS (*m/e*) 194 $[M]^+$.

Bis-(*p*-tolyl)carbodiimide (2.14b, R = CH_3)

88% yield; mp 57-58°C; IR ($CHCl_3$) ν (C=N=C) 2136 cm^{-1}; MS (*m/e*) 222 $[M]^+$.

Bis-(*p*-bromophenyl)-carbodiimide (2.14c, R = Br)

80% yield; mp 63-65°C; IR ($CHCl_3$) ν (C=N=C) 2130 cm^{-1}; MS (*m/e*) 349 $[M]^+$.

Bis-(*p*-chlorophenyl)-carbodiimide (2.14d, R = Cl)

89% yield; mp 56-57°C; IR ($CHCl_3$) ν (C=N=C) 2130 cm^{-1}; MS (*m/e*) 262 $[M]^+$.

Bis-(*p*-methoxyphenyl)-carbodiimide (2.14e, R = OCH_3)

81% yield; mp 52-53°C; IR ($CHCl_3$) ν (C=N=C) 2134 cm^{-1}; MS (*m/e*) 254 $[M]^+$.

3.2.5 Ketene and ketenimines

Diphenylketene was prepared from the literature preparation reported by Taylor *et al.*[33] IR analysis was used to identify the heterocumulene before using it as a substrate for the metal catalyzed reaction.

Diphenylketene (2.19)

64% yield; bright orange oil; IR (neat) ν (C=C=O) 2097 cm^{-1}; MS (*m/e*) 194 $[M]^+$.

The synthesis of ketenimines was accomplished from the literature procedure[32] reported by Froyen. These compounds were characterized by IR and mass spectral analyses.

1-Butyl-3-carboethoxy-3-methylketenimine (2.17a R = C_4H_9)

61% yield; bp 80-83°C/1-2 mmHg; IR (neat) ν (C=C=N) 2038 cm^{-1} MS (*m/e*) 183 $[M]^+$.

3-Carboethoxy-3-methyl-1-phenylketenimine (2.17b, R = C_6H_6)

55% yield; bp 110-115°C/1-2 mmHg; IR (neat) ν (C=C=N) 2027 cm^{-1}; MS (*m/e*) 203 $[M]^+$.

3.3 General procedures for the palladium(0) catalyzed reactions of 2-vinylazetidines with heterocumulenes

3.3.1 Synthesis of tetrahydro pyrimidin-2-ones

Palladium (II) acetate (0.050 mmol) and triphenylphosphine (0.20 mmol) were dissolved in 4.0 ml of dry, degassed tetrahydrofuran under a flow of dinitrogen, resulting in a bright yellow solution. Azetidine (1.0 mmol) and isocyanate (1.0 mmol) were added with 1.0 ml of dry thf, and the reaction was stirred until GC indicated the consumption of one or both of the substrates. The solvent was removed *in vacuo*, and the residue was taken up in chloroform for purification by column chromatography using the proper ether/pentane solvent system. The pooled fractions were decolorized with charcoal, filtered, and concentrated to yield **2.24**, **2.25**, **2.27**, **2.29**, and **2.31**.

1-Butyl-3-phenyl-4-vinyl-tetrahydropyrimidin-2-one (2.24a, R = C_4H_9)

97% yield; colorless oil; IR (neat) ν (C=O) 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3H, J = 7.2 Hz, CH_3), 1.3 (m, 2H, CH_2), 1.5 (m, 2H, CH_2), 1.8 (m, 1H, CH_2 ring), 2.2 (m, 1H, CH_2 ring), 3.1 (m, 2H, NCH_2), 3.4 (m, 2H, NCH_2 ring), 4.3 (br, 1H, NCH ring), 5.2 (m, 2H, CH_2 vinyl), 5.8 (m, 1H, CH vinyl), 7.0 (m, 1H, phenyl), 7.2 (dd, 4H, J = 3.6 and 4.6 Hz, phenyl); ^{13}C NMR ($CDCl_3$) δ 154.20 (C=O), 143.48 (phenyl), 136.75 (CH vinyl), 127.99 (phenyl), 125.76 (phenyl), 124.57 (phenyl), 116.52 (CH_2 vinyl), 59.82 (NCH ring), 47.72 (NCH_2), 42.19 (NCH_2 ring), 29.28 (CH_2), 26.75 (CH_2 ring), 19.75 (CH_2), 13.58 (CH_3); MS (*m/e*) 258 $[M]^+$; EIHRMS calcd for $C_{16}H_{22}N_2O$ 258.1732, found 258.1743.

1-Cyclohexyl-3-phenyl-4-vinyl-tetrahydropyrimidin-2-one (2.24b, R = C_6H_{11})

89% yield; colorless oil; IR (neat) ν (C=O) 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0-1.2 (br, 1H, cyclohexyl), 1.2-1.5 (br, 4H, cyclohexyl), 1.5-1.8 (m, 5H, cyclohexyl), 1.9 (m, 1H, CH_2 ring), 2.2 (m, 1H, CH_2 ring), 3.2 (dd, 2H, J = 4.1 and 8.7 Hz, NCH_2 ring), 4.3 (m, br, 2H, NCH ring), 5.2 (m, 2H, CH_2 vinyl), 5.8 (m, 1H, CH vinyl), 7.1 (m, 1H, phenyl), 7.3 (d, 4H, J = 4.2 Hz, phenyl); ^{13}C NMR ($CDCl_3$) δ 154.32 (C=O), 143.78 (phenyl), 137.00 (CH vinyl), 128.22 (phenyl), 126.35 (phenyl), 124.97 (phenyl), 116.71 (CH_2 vinyl), 59.55 (NCH ring), 53.61 (NCH), 36.41 (NCH_2 ring), 29.98 (cyclohexyl), 29.87 (cyclohexyl), 27.18 (CH_2 ring), 25.78 (cyclohexyl), 25.63 (cyclohexyl); MS (*m/e*) 284 $[M]^+$; EIHRMS calcd for $C_{18}H_{24}N_2O$ 284.1889, found 284.1892.

1-*tert*-Butyl-3-phenyl-4-vinyl-tetrahydropyrimidin-2-one (2.24c, R = $C(CH_3)_3$)

89% yield; colorless oil; IR (neat) ν (C=O) 1649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (s, 9H, $C(CH_3)_3$), 1.9 (m, 1H, CH_2 ring), 2.1 (m, 1H, CH_2 ring), 3.3 (m, 2H, NCH_2 ring), 4.2 (br, 1H, NCH ring), 5.2 (m, 2H, CH_2 vinyl), 5.8 (m, 1H, CH vinyl), 7.1 (m, 1H, phenyl), 7.2 (m, 4H, phenyl); ^{13}C NMR ($CDCl_3$) δ 155.20 (C=O), 144.09 (phenyl), 136.77 (CH vinyl), 128.16 (phenyl), 126.15 (phenyl), 124.64 (phenyl), 116.26 (CH_2 vinyl), 59.50 (NCH ring), 56.51 ($C(Me)_3$), 38.93 (NCH_2 ring), 28.61 ($(CH_3)_3$), 27.86 (CH_2 ring); MS (*m/e*) 258 $[M]^+$; EIHRMS calcd for $C_{16}H_{22}N_2O$ 258.1732, found 258.1760.

1-*tert*-Butyl-3-phenyl-4-propenyl-tetrahydropyrimidin-2-one (2.25a, R = CH_3)

70% yield; colorless oil; IR (neat) ν (C=O) 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (s, 9H, $C(CH_3)_3$), 1.7 (d, 3H, 6.0 Hz, CH_3), 1.9 (m, 1H, CH_2 ring), 2.1 (m, 1H, CH_2 ring), 3.4 (m, 2H, NCH_2 ring), 4.2 (br, 1H, NCH ring), 5.5 (m, 2H, vinyl), 7.1 (m, 1H, phenyl), 7.2 (m, 4H, phenyl); ^{13}C NMR ($CDCl_3$) δ 155.40 (C=O), 144.21 (phenyl), 129.79 (CH vinyl), 128.25 (phenyl), 127.25 (CH_2 vinyl), 126.42 (phenyl), 124.73 (phenyl), 59.06 (NCH ring), 56.60 ($C(Me)_3$), 39.14 (NCH_2 ring), 28.78 ($(CH_3)_3$), 28.72 (CH_2 ring), 17.45 (CH_3); MS (*m/e*) 272 $[M]^+$; EIHRMS calcd for $C_{17}H_{24}N_2O$ 272.1889, found 272.1905.

Methyl-3-(1-*tert*-butyl-2-oxo-3-phenyl-hexahydropyrimidin-2-yl)-acrylate (2.25b, R = CO_2CH_3)

98% yield; colorless oil; IR (neat) ν (C=O) 1724 and1644 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (s, 9H, $C(CH_3)_3$), 2.0 (m, 1H, CH_2 ring), 2.2 (m, 1H, CH_2 ring), 3.2 (dt, 1H, J = 4.8 and 11.8 Hz, NCH_2 ring), 3.4 (m, 1H, NCH_2 ring), 3.7 (s, 3H, OCH_3), 4.4 (br, 1H, NCH ring), 6.0 (dd, 1H, J = 1.5 and 15.6 Hz, $CHCO_2$ vinyl), 6.9 (dd, 1H, J = 5.0 and 15.6 Hz, CH vinyl), 7.2 (m, 5H, phenyl); ^{13}C NMR ($CDCl_3$) δ 166.00 (C=O ester), 154.48 (C=O ring), 146.40 (CH vinyl), 143.51 (phenyl), 128.37 (phenyl), 126.10, 125.07 (phenyl), 122.24 ($CHCO_2$ vinyl), 58.32 (NCH ring), 56.68 ($C(Me)_3$), 51.36 (OCH_3), 38.95 (NCH_2 ring), 28.47 ($(CH_3)_3$), 27.28 (CH_2 ring); MS (*m/e*) 316 $[M]^+$; EIHRMS calcd for $C_{18}H_{24}N_2O_3$ 316.1787, found 316.1782.

1-*tert*-Butyl-3-phenyl-4-styryl-tetrahydropyrimidin-2-one (2.25c, R = C_6H_6)

65% yield; colorless oil; IR (neat) ν (C=O) 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (s, 9H, $C(CH_3)_3$), 2.0 (m, 1H, CH_2 ring), 2.2 (m, 1H, CH_2 ring), 3.4 (m, 2H, NCH_2 ring), 4.4 (br, 1H, NCH ring), 6.2 (dd, 1H, J = 5.2 and 15.9 Hz, CH vinyl), 6.6 (dd, 1H, J = 1.4 and 15.9 Hz, CHPh vinyl), 7.1 (m, 1H, phenyl), 7.3 (m, 9H, phenyl); ^{13}C NMR ($CDCl_3$) δ 155.14 (C=O), 144.21 (phenyl), 136.29 (phenyl), 131.36 (phenyl), 128.44 (phenyl), 128.32 (phenyl), 127.58 (CHPh vinyl), 126.26 (phenyl), 126.14 (phenyl), 124.90 (CH vinyl), 118.42 (phenyl), 59.25 (NCH ring), 56.81 ($C(Me)_3$), 39.31 (NCH_2 ring), 28.79 ($(CH_3)_3$), 28.47 (CH_2 ring); MS (*m/e*) 334 $[M]^+$; EIHRMS calcd for $C_{22}H_{26}N_2O$ 334.2054, found 334.2034.

3-(4-Bromophenyl)-1-cyclohexyl-4-vinyl-tetrahydropyrimidin-2-one (2.27a, R = C_6H_{11}, R′ = *p*-C_6H_4Br)

95% yield; colorless oil; IR (neat) ν (C=O) 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9-1.1 (br, 1H, cyclohexyl), 1.2-1.5 (br, 4H, cyclohexyl), 1.5-1.8 (br, 5H, cyclohexyl), 1.9 (m, 1H, CH_2 ring), 2.1 (m, 1H, CH_2 ring), 3.2 (m, 2H, NCH_2 ring), 4.1-4.3 (m, br, 2H, NCH and NCH ring), 5.1 (m, 2H, CH_2 vinyl), 5.7 (m, 1H, CH vinyl), 7.1 (d, 2H, J = 8.5 Hz, phenyl), 7.3 (m, 2H, J = 8.4 Hz, phenyl); ^{13}C NMR ($CDCl_3$) δ 153.88 (C=O), 142.78 (phenyl), 136.58 (CH vinyl), 131.05 (phenyl), 127.69 (phenyl), 117.81 (CH_2 vinyl), 116.88 (phenyl), 59.34 (NCH ring), 53.63 (NCH), 36.36 (NCH_2 ring), 29.84 (cyclohexyl), 29.74 (cyclohexyl), 27.02 (CH_2 ring), 25.68 (cyclohexyl), 25.54 (cyclohexyl), 25.45 (cyclohexyl); MS (*m/e*) 362 $[M]^+$; EIHRMS calcd for $C_{18}H_{23}BrN_2O$ 362.1194, found 362.0977.

3-(4-Chlorophenyl)-1-cyclohexyl-4-vinyl-tetrahydropyrimidin-2-one (2.27b, R = C_6H_{11}, R′ = *p*-C_6H_4Cl)

90% yield; colorless oil; IR (neat) ν (C=O) 1633 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9-1.1 (br, 1H, cyclohexyl), 1.2-1.5 (br, 4H, cyclohexyl), 1.5-1.8 (m, 5H, cyclohexyl), 1.9 (m, 1H, CH_2 ring), 2.1 (m, 1H, CH_2 ring), 3.2 (dd, 2H, J = 4.1 and 8.8 Hz, NCH_2 ring), 4.2 (br, 2H, NCH and NCH ring), 5.1 (m, 2H, CH_2 vinyl), 5.7 (m, 1H, CH vinyl), 7.1 (s, 4H, phenyl); ^{13}C NMR ($CDCl_3$) δ 153.89 (C=O), 142.22 (phenyl), 136.57 (CH vinyl), 129.85 (phenyl), 128.02 (phenyl), 127.32 (phenyl), 116.77 (CH_2 vinyl), 59.35 (NCH ring), 53.58 (NCH), 36.31 (NCH_2 ring), 29.79 (cyclohexyl), 29.68 (cyclohexyl), 26.97 (CH_2 ring), 25.64 (cyclohexyl), 25.50 (cyclohexyl), 25.39 (cyclohexyl); MS (*m/e*) 318 $[M]^+$; EIHRMS calcd for $C_{18}H_{23}ClN_2O$ 318.1499, found 318.1503.

1-Cyclohexyl-3-(4-nitrophenyl)-4-vinyl-tetrahydropyrimidin-2-one (2.27c, R = C_6H_{11}, R′ = *p*-$C_6H_4NO_2$)

66% yield; yellow solid, mp 123-125°C; IR ($CHCl_3$) ν (C=O) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9-1.1 (br, 1H, cyclohexyl), 1.2-1.5 (br, 4H, cyclohexyl), 1.5-1.8 (m, 5H, cyclohexyl), 1.9 (m, 1H, CH_2 ring), 2.2 (m, 1H, CH_2 ring), 3.2 (m, 2H, NCH_2 ring), 4.2 (m, br, 1H, NCH), 4.4 (br, 1H, NCH ring), 5.2 (m, 2H, CH_2 vinyl), 5.8 (m, 1H, CH vinyl), 7.4 (d, 2H, J = 8.2 Hz, phenyl), 8.0 (d, 2H, J = 8.2, phenyl); ^{13}C NMR ($CDCl_3$) δ 153.20 (C=O), 149.82 (phenyl), 143.10 (phenyl), 135.56 (CH vinyl), 124.01 (phenyl), 123.60 (phenyl), 117.40 (CH_2 vinyl), 58.69 (NCH ring), 54.17 (NCH), 36.59 (NCH_2 ring), 29.73 (cylcohexyl), 29.66 (cylcohexyl), 26.64 (CH_2 ring), 25.66 (cylcohexyl), 25.56 (cylcohexyl), 25.40 (cylcohexyl); MS (*m/e*) 329 $[M]^+$; EIHRMS calcd for $C_{18}H_{23}N_3O_3$ 329.1739, found 329.1738.

1-Cyclohexyl-3-(4-methoxyphenyl)-4-vinyl-tetrahydropyrimidin-2-one (2.27d, R = C_6H_{11}, R′ = *p*-$C_6H_4OCH_3$)

89% yield; colorless oil; IR (neat) ν (C=O) 1633 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0-1.2 (br, 1H, cyclohexyl), 1.2-1.5 (br, 4H, cyclohexyl), 1.5-1.8 (m, 5H, cyclohexyl), 1.9 (m, 1H, CH_2 ring), 2.1 (m, 1H, CH_2 ring), 3.2 (dd, 2H, J = 4.0 and 8.3 Hz, NCH_2 ring), 3.7 (s, 3H, OCH_3), 4.1-4.4 (m, br, 2H, NCH and NCH ring), 5.1 (m, 2H, CH_2 vinyl), 5.7 (m, 1H, CH vinyl), 6.8 (d, 2H, J = 9.0 Hz, phenyl), 7.1 (d, 2H, J = 8.9 Hz, phenyl); ^{13}C NMR ($CDCl_3$) δ 156.98

(phenyl), 154.63 (C=O), 137.23 (CH vinyl), 136.70 (phenyl), 128.05 (phenyl), 116.54 (CH_2 vinyl), 113.51 (phenyl), 60.01 (NCH ring), 55.19 (NCH), 53.48 (OCH_3), 36.33 (NCH_2 ring), 30.01 (cylcohexyl), 29.82 (cylcohexyl), 27.35 (CH_2 ring), 25.75 (cylcohexyl), 25.59 (cylcohexyl), 25.54 (cylcohexyl); MS (*m/e*) 314 $[M]^+$; EIHRMS calcd for $C_{19}H_{26}N_2O_2$ 314.1994, found 314.2010.

1-Cyclohexyl-3-(*p*-tolyl)-4-vinyl-tetrahydropyrimidin-2-one (**2.27e**, R = C_6H_{11}, R′ = *p*-$C_6H_4CH_3$)

93% yield; colorless oil; IR (neat) ν (C=O) 1639 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9-1.2 (br, 1H, cyclohexyl), 1.2-1.5 (br, 4H, cyclohexyl), 1.5-1.8 (m, 5H, cyclohexyl), 1.9 (m, 1H, CH_2 ring), 2.1 (m, 1H, CH_2 ring), 2.2 (s, 3H, CH_3), 3.2 (dd, 2H, J = 3.8 and 8.3 Hz, NCH_2 ring), 4.2-4.4 (br, 2H, NCH and NCH ring), 5.2 (m, 2H, CH_2 vinyl), 5.8 (m, 1H, CH vinyl), 7.0 (m, 4H, phenyl); ^{13}C NMR ($CDCl_3$) δ 154.16 (C=O), 141.00 (phenyl), 136.93 (CH vinyl), 134.28 (phenyl), 128.59 (phenyl), 126.12 (phenyl), 116.30 (CH_2 vinyl), 59.43 (NCH ring), 53.27 (NCH), 36.14 (NCH_2 ring), 29.77 (cylcohexyl), 29.61 (cylcohexyl), 26.97 (CH_2 ring), 25.57 (cylcohexyl), 25.43 (cylcohexyl), 25.35 (cylcohexyl), 20.56 (CH_3); MS (*m/e*) 298 $[M]^+$; EIHRMS calcd for $C_{19}H_{26}N_2O$ 298.2045, found 298.2019.

1-Cyclohexyl-3-(*m*-tolyl)-4-vinyl-tetrahydropyrimidin-2-one (**2.27f**, R = C_6H_{11}, R′ = *m*-$C_6H_4CH_3$)

97% yield; colorless oil; IR (neat) ν (C=O) 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9-1.2 (br, 1H, cyclohexyl), 1.2-1.5 (br, 4H, cyclohexyl), 1.5-1.8 (m, 5H, cyclohexyl), 1.9 (m, 1H, CH_2 ring), 2.1 (m, 1H, CH_2 ring), 2.3 (s, 3H, CH_3), 3.2 (dd, 2H, J = 4.0 and 8.7 Hz, NCH_2 ring), 4.3 (m, br, 2H, NCH and NCH ring), 5.2 (m, 2H, CH_2 vinyl), 5.8 (m, 1H, CH vinyl), 7.0 (m, 4H, phenyl); ^{13}C NMR ($CDCl_3$) δ 154.33 (C=O), 143.74 (phenyl), 137.93 (phenyl), 137.08 (CH vinyl), 128.06 (phenyl), 127.29 (phenyl), 125.86 (phenyl), 123.26 (phenyl), 116.64 (CH_2 vinyl), 59.55 (NCH ring), 53.54 (NCH), 36.36 (NCH_2 ring), 29.99 (cylcohexyl), 29.86 (cylcohexyl), 27.20 (CH_2 ring), 25.80 (cylcohexyl), 25.63 (cylcohexyl), 21.25 (CH_3); MS (*m/e*) 298 $[M]^+$; EIHRMS calcd for $C_{19}H_{26}N_2O$ 298.2045, found 298.2054.

1,3-Dicyclohexyl-4-vinyl-tetrahydropyrimidin-2-one (**2.27g**, R = C_6H_{11}, R′ = C_6H_{11})

73% yield; colorless oil; IR (neat) ν (C=O) 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8-1.2 (br, 2H, cylcohexyl), 1.2-1.5 (br, 8H, cylcohexyl), 1.5-1.8 (m, 12H, cylcohexyl and CH_2 ring), 3.0 (m, 2H, NCH_2 ring), 3.9 (m, 1H, NCH ring), 4.2-4.4 (br, 2H, NCH and NCH), 5.1 (m, 2H, CH_2 vinyl), 5.7 (m, 1H, CH vinyl); ^{13}C NMR ($CDCl_3$) δ 154.87 (C=O), 138.68 (CH vinyl), 115.85 (CH_2 vinyl), 54.73 (NCH ring), 53.61 (NCH), 51.25 (NCH), 35.64 (NCH_2 ring), 35.51 (cyclohexyl), 31.43 (cyclohexyl), 30.42 (cyclohexyl), 30.15 (cyclohexyl), 29.83 (cyclohexyl), 27.27 (CH_2 ring), 26.11 (cyclohexyl), 25.93 (cyclohexyl), 25.85 (cyclohexyl), 25.67 (cyclohexyl), 25.61 (cyclohexyl); MS (*m/e*) 290 $[M]^+$; EIHRMS calcd for $C_{18}H_{30}N_2O$ 290.2358, found 290.2380.

3-(4-Bromophenyl)-1-*tert*-butyl-4-vinyl-tetrahydropyrimidin-2-one (2.27h, R = $C(CH_3)_3$, R' = *p*-C_6H_4Br)

91% yield; colorless oil; IR (neat) ν (C=O) 1641 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (s, 9H, $C(CH_3)_3$), 1.9 (m, 1H, CH_2 ring), 2.1 (m, 1H, CH_2 ring), 3.3 (m, 2H, NCH_2 ring), 4.2 (br, 1H, NCH ring), 5.2 (m, 2H, CH_2 vinyl), 5.8 (m, 1H, CH vinyl), 7.1 (d, 2H, J = 8.6 Hz, phenyl), 7.3 (d, 2H, J = 8.6 Hz, phenyl); ^{13}C NMR ($CDCl_3$) δ 154.85 (C=O), 143.15 (phenyl), 136.56 (CH vinyl), 131.18 (phenyl), 127.82 (phenyl), 117.76 (phenyl), 116.66 (CH_2 vinyl), 59.45 (NCH ring), 56.78 ($C(Me)_3$), 39.02 (NCH_2 ring), 28.64 (($CH_3)_3$), 27.91 (CH_2 ring); MS (*m/e*) 336 $[M]^+$; EIHRMS calcd for $C_{16}H_{21}BrN_2O$ 336.1037, found 336.0833.

1-*tert*-Butyl-3-(4-methoxyphenyl)-4-vinyl-tetrahydropyrimidin-2-one (2.27i, R = $C(CH_3)_3$, R' = *p*-$C_6H_4OCH_3$)

87% yield; colorless oil; IR (neat) ν (C=O) 1644 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (s, 9H, $C(CH_3)_3$), 1.9 (m, 1H, CH_2 ring), 2.1 (m, 1H, CH_2 ring), 3.3 (m, 2H, NCH_2 ring), 3.7 (s, 3H, OCH_3), 4.2 (br, 1H, NCH ring), 5.2 (m, 2H, CH_2 vinyl), 5.8 (m, 1H, CH vinyl), 7.3 (d, 2H, J = 8.9 Hz, phenyl), 7.1 (d, 2H, J = 8.9 Hz, phenyl); ^{13}C NMR ($CDCl_3$) δ 156.73 (phenyl), 155.31 (C=O), 137.01 (CH vinyl), 136.96 (phenyl), 127.86 (phenyl), 116.08 (CH_2 vinyl), 113.48 (phenyl), 59.89 (NCH ring), 56.37 ($C(Me)_3$), 55.03 (OCH_3), 38.84 (NCH_2 ring), 28.60 (($CH_3)_3$), 28.00 (CH_2 ring); MS (*m/e*) 288 $[M]^+$; EIHRMS calcd for $C_{17}H_{24}N_2O_2$ 288.1838, found 288.1817.

1-Butyl-3-(*o*-tolyl)-4-vinyl-tetrahydropyrimidin-2-one (2.29a, R = C_4H_9)

89% yield; colorless oil; IR (neat) ν (C=O) 1642 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ (major) 0.9 (t, 3H, J = 7.4 Hz, CH_3), 1.3 (m, 2H, CH_2), 1.5 (m, 2H, CH_2), 1.9 (m, 1H, CH_2 ring), 2.2 (s, 3H, CH_3), 2.2 (m, 1H, CH_2 ring), 3.3 (m, 2H, NCH_2 ring), 4.0 (br, 1H, NCH ring), 5.2 (m, 2H, CH_2 vinyl), 6.0 (m, 1H, CH vinyl), 7.1 (m, 5H, phenyl); (minor) 0.9 (t, 3H, J = 7.4 Hz, CH_3), 1.3 (m, 2H, CH_2), 1.5 (m, 2H, CH_2), 1.9 (m, 1H, CH_2 ring), 2.1 (s, 3H, CH_3), 2.2 (m, 1H, CH_2 ring), 3.3 (m, 2H, NCH_2 ring), 4.4 (m, br, 1H, NCH ring), 4.9 (m, 2H, CH_2 vinyl), 5.7 (m, 1H, CH vinyl), 7.1 (m, 5H, phenyl); ^{13}C NMR ($CDCl_3$, 500MHz) δ (major) 153.39 (C=O), 142.41 (phenyl), 138.20 (CH vinyl), 135.60 (phenyl), 130.20 (phenyl), 129.34 (phenyl), 126.25 (phenyl), 125.61 (phenyl), 115.92 (CH_2 vinyl), 59.65 (NCH ring), 46.79 (NCH_2), 41.82 (NCH_2 ring), 29.16 (CH_2), 27.06 (CH_2 ring), 19.36 (CH_2), 17.43 (CH_3), 13.61 (CH_3); (minor) 153.04 (C=O), 142.20 (phenyl), 137.56 (phenyl), 137.30 (CH vinyl), 129.65 (phenyl), 127.53 (phenyl), 126.04 (phenyl), 125.88 (phenyl), 116.17 (CH_2 vinyl), 61.39 (NCH ring), 46.70 (NCH_2), 42.45 (NCH_2 ring), 29.32 (CH_2), 28.42 (CH_2 ring), 19.32 (CH_2), 18.02 (CH_3), 13.61 (CH_3);MS (*m/e*) 272 $[M]^+$; EIHRMS calcd for $C_{17}H_{24}N_2O$ 272.1889, found 272.1871.

1-Cyclohexyl-3-(*o*-tolyl)-4-vinyl-tetrahydropyrimidin-2-one (2.29b, R = C_6H_{11})

70% yield; colorless oil; IR (neat) ν (C=O) 1633 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ (major) 0.9-1.2 (br, 1H, cyclohexyl), 1.2-1.5 (br, 4H, cyclohexyl), 1.5-1.8 (m, 5H, cyclohexyl), 1.9 (m, 1H, CH_2 ring), 2.1 (m, 1H, CH_2 ring), 2.2 (s, 3H, CH_3), 3.2 (m, 2H, NCH_2 ring), 3.9 (br, 1H, NCH), 4.1-4.2 (br, 1H, NCH ring), 5.1 (m, 2H, CH_2 vinyl), 5.9 (m, 1H, CH vinyl), 7.1 (m, 4H, phenyl); (minor) 0.9-1.2 (br, 1H, cyclohexyl), 1.2-1.5 (br, 4H, cyclohexyl), 1.5-1.8 (m, 5H, cyclohexyl), 1.9 (m, 1H, CH_2 ring), 2.1 (m, 1H, CH_2 ring), 2.2 (s, 3H, CH_3), 3.2 (m, 2H, NCH_2 ring), 4.1-4.2 (br, 1H, NCH ring), 4.3 (m, 1H, NCH), 4.9 (m, 2H, CH_2 vinyl), 5.7 (m, 1H, CH vinyl), 7.1 (m, 4H, phenyl); ^{13}C NMR ($CDCl_3$, 500MHz) δ (major) 153.19 (C=O), 142.61 (phenyl), 138.28 (CH vinyl), 137.64 (phenyl), 130.24 (phenyl), 129.44 (phenyl), 126.29 (phenyl), 125.63 (phenyl), 115.96 (CH_2 vinyl), 59.20 (NCH ring), 52.86 (NCH), 36.22 (NCH_2 ring), 29.45 (cyclohexyl), 29.40 (cyclohexyl), 27.31 (CH_2 ring), 25.54 (cyclohexyl), 25.23 (cyclohexyl), 25.10 (cyclohexyl), 18.07 (CH_3); (minor) 152.92 (C=O), 142.37 (phenyl), 137.31(phenyl), 135.63 (CH vinyl), 129.67 (phenyl), 127.50 (phenyl),

126.06 (phenyl), 125.87 (phenyl), 116.20 (CH_2 vinyl), 60.89 (NCH ring), 52.86 (NCH), 36.68 (NCH_2 ring), 29.75 (cyclohexyl), 29.33 (cyclohexyl), 28.73 (CH_2 ring), 25.49 (cyclohexyl), 25.39 (cyclohexyl), 25.12 (cyclohexyl), 17.43 (CH_3);MS (*m/e*) 298 $[M]^+$; EIHRMS calcd for $C_{19}H_{26}N_2O$ 298.2045, found 298.0234.

1-*tert*-Butyl-3-(*o*-tolyl)-4-vinyl-tetrahydropyrimidin-2-one (2.29c, R = $C(CH_3)_3$)

75% yield; colorless oil; IR (neat) ν (C=O) 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ (major) 1.4 (s, 9H, $C(CH_3)_3$), 1.9 (m, 1H, CH_2 ring), 2.1 (m, 1H, CH_2 ring), 2.2 (s, 3H, CH_3), 3.4 (m, 2H, NCH_2 ring), 3.9 (br, 1H, NCH ring), 5.1 (m, 2H, CH_2 vinyl), 5.9 (m, 1H, CH vinyl), 7.1 (m, 4H, phenyl); (major) 1.4 (s, 9H, $C(CH_3)_3$), 1.9 (m, 1H, CH_2 ring), 2.1 (m, 1H, CH_2 ring), 2.1 (s, 3H, CH_3), 3.4 (m, 2H, NCH_2 ring), 4.3 (br, 1H, NCH ring), 4.9 (m, 2H, CH_2 vinyl), 5.8 (m, 1H, CH vinyl), 7.1 (m, 4H, phenyl); ^{13}C NMR ($CDCl_3$, 500MHz) δ (major) 154.13 (C=O), 142.90 (phenyl), 138.41 (CH vinyl), 135.51 (phenyl), 130.16 (phenyl), 129.25 (phenyl), 126.09 (phenyl), 125.63 (phenyl), 115.74 (CH_2 vinyl), 59.13 (NCH ring), 55.74 $(C(Me)_3)$, 38.74 (NCH_2 ring), 28.46 ($(CH_3)_3$), 28.28 (CH_2 ring), 17.56 (CH_3); (minor) 153.84 (C=O), 142.82 (phenyl), 137.57 (phenyl), 137.21 (CH vinyl), 129.63 (phenyl), 127.38 (phenyl), 126.05 (phenyl), 125.72 (phenyl), 115.94 (CH_2 vinyl), 60.79 (NCH ring), 55.65 $(C(Me)_3)$, 38.74 (NCH_2 ring), 29.31 ($(CH_3)_3$), 28.53 (CH_2 ring), 18.06 (CH_3); MS (*m/e*) 272 $[M]^+$; EIHRMS calcd for $C_{17}H_{24}N_2O$ 272.1889, found 272.1883.

1-Butyl-6-methyl-3-phenyl-4-vinyl-tetrahydropyrimidin-2-one (2.31)

88% yield; colorless oil; IR (neat) ν (C=O) 1642 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ (*trans*) 0.9 (t, 3H, J = 6.4 Hz, CH_3), 1.3 (d, 3H, J = 6.6 Hz, CH_3), 1.3 (m, 2H, CH_2), 1.5 (m, 1H, CH_2), 1.6 (m, 1H, CH_2), 1.9 (m, 1H, CH_2 ring), 2.2 (m, 1H, CH_2 ring), 3.1 (m, 1H, NCHMe ring), 3.6 (m, 2H, NCH_2), 4.3 (m, 1H, NCH ring), 5.0 (m, 2H, CH_2 vinyl), 5.7 (m, 1H, CH vinyl), 7.2 (m, 5H, phenyl); (*cis*) 0.9 (t, 3H, J = 7.4 Hz, CH_3), 1.3 (d, 3H, J = 5.8 Hz, CH_3), 1.3 (m, 2H, CH_2), 1.5 (m, 1H, CH_2), 1.6 (m, 1H, CH_2), 2.0 (m, 2H, CH_2 ring), 3.0 (m, 1H, NCHMe ring), 3.6 (m, 1H, NCH_2), 3.7 (m, 1H, NCH_2), 4.3 (m, 1H, NCH ring), 5.1 (m, 2H, CH_2 vinyl), 5.8 (m, 1H, CH vinyl), 7.2 (m, 5H, phenyl); ^{13}C NMR ($CDCl_3$, 500MHz) δ (*trans*) 155.21 (C=O), 142.62 (phenyl), 139.20 (CH vinyl), 128.19 (phenyl), 127.57 (phenyl), 125.40 (phenyl), 116.09 (CH_2 vinyl), 59.52 (NCH ring), 49.37 (NCH_2), 44.91 (NCHMe

ring), 36.69 (CH_2 ring), 30.31 (CH_2), 21.12 (CH_3), 20.11 (CH_2), 13.77 (CH_3); (*cis*) 154.86 (C=O), 142.97 (phenyl), 137.82 (CH vinyl), 128.25 (phenyl), 126.46 (phenyl), 124.99 (phenyl), 116.51 (CH_2 vinyl), 58.07 (NCH ring), 47.54 (NCH_2), 44.70 (NCHMe ring), 36.00 (CH_2 ring), 30.08 (CH_2), 21.12 (CH_3), 20.11 (CH_2), 13.77 (CH_3); MS (*m/e*) 272 $[M]^+$; EIHRMS calcd for $C_{17}H_{24}N_2O$ 272.1889, found 272.1876.

3.3.2 X-ray analysis for 2.27c (R = C_6H_{11}, R′ = *p*-$C_6H_4NO_2$)

A crystal of **2.27c** (0.4 mm x 0.4 mm x 0.4 mm) was mounted on thin glass fibres 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, and no absorption corrections were required. A total of 13081 reflections were collected where the unique set contained 4002 reflections.

The structure was 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 3.1 Crystal data collection and refinement for 2.27c ($R = C_6H_{11}$, $R' = p\text{-}C_6H_4NO_2$)

Empirical formula	C18 H23 N3 O3
Formula weight	329.39
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 12.027(2) A alpha = 90 deg. b = 13.246(2) A beta = 118.481(2) deg. c = 12.177(2) A gamma = 90 deg.
Volume	1705.0(4) A^3
Z, Calculated density	4, 1.283 Mg/m^3
Absorption coefficient	0.089 mm^-1
F(000)	704
Crystal size	0.4 x 0.4 x 0.4 mm
Theta range for data collection	1.96 to 28.57 deg.
Limiting indices	-16<=h<=14, 0<=k<=17, 0<=l<=16
Reflections collected / unique	13081 / 4002 [R(int) = 0.0596]
Completeness to theta = 28.57	91.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.928073 and 0.713128
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4002 / 0 / 218
Goodness-of-fit on F^2	1.020
Final R indices [I>2sigma(I)]	R1 = 0.0489, wR2 = 0.1236
R indices (all data)	R1 = 0.0638, wR2 = 0.1270
Extinction coefficient	0.030(3)
Largest diff. peak and hole	0.276 and -0.213 e.A^-3

Table 3.2 Atomic parameters X, Y, Z, and U(eq) for 2.27c (R = C_6H_{11}, R′ = *p*-$C_6H_4NO_2$)

	x	y	z	U(eq)
N(1)	7235(1)	2190(1)	2298(1)	31(1)
N(2)	9139(1)	1682(1)	2347(1)	31(1)
N(3)	13534(1)	-695(1)	4129(1)	40(1)
O(1)	7993(1)	600(1)	2876(1)	37(1)
O(2)	13910(1)	-1141(1)	5115(1)	68(1)
O(3)	14099(1)	-703(1)	3518(1)	62(1)
[illegible]	5181(2)	1466(1)	769(2)	43(1)
[illegible]	3895(2)	1091(1)	550(2)	50(1)
C(3)	3203(2)	1912(1)	859(2)	49(1)
C(4)	3997(2)	2278(1)	2191(2)	45(1)
C(5)	5277(1)	2670(1)	2406(2)	39(1)
C(6)	5979(1)	1853(1)	2100(1)	33(1)
C(7)	8104(1)	1449(1)	2529(1)	29(1)
C(8)	7309(1)	3209(1)	1858(2)	36(1)
C(9)	8623(1)	3451(1)	2089(2)	37(1)
C(10)	9123(1)	2583(1)	1630(1)	33(1)
C(11)	8377(2)	2442(1)	243(1)	43(1)
C(12)	7737(2)	1637(1)	-337(2)	53(1)
C(13)	10182(1)	1021(1)	2763(1)	29(1)
C(14)	10634(1)	502(1)	3894(1)	30(1)
C(15)	11726(1)	-69(1)	4342(1)	32(1)
C(16)	12357(1)	-123(1)	3649(1)	33(1)
C(17)	11919(1)	363(1)	2516(1)	37(1)
C(18)	10831(1)	931(1)	2074(1)	38(1)

Table 3.3 Atomic bond lengths (in angstroms) and angles (in degrees) for 2.27c (R = C_6H_{11}, R′ = *p*-$C_6H_4NO_2$)

N(1)-C(7)	1.3611(17)
N(1)-C(8)	1.4692(17)
N(1)-C(6)	1.4804(18)
N(2)-C(7)	1.3987(18)
N(2)-C(13)	1.4109(16)
N(2)-C(10)	1.4732(16)
N(3)-O(2)	1.2154(18)
N(3)-O(3)	1.2245(18)
N(3)-C(16)	1.4594(17)
O(1)-C(7)	1.2308(16)
C(1)-C(2)	1.523(2)
C(1)-C(6)	1.525(2)
C(2)-C(3)	1.522(3)
C(3)-C(4)	1.516(2)
C(4)-C(5)	1.524(2)
C(5)-C(6)	1.525(2)
C(8)-C(9)	1.501(2)
C(9)-C(10)	1.522(2)
C(10)-C(11)	1.499(2)
C(11)-C(12)	1.307(2)
C(13)-C(14)	1.3968(18)
C(13)-C(18)	1.398(2)
C(14)-C(15)	1.3823(19)
C(15)-C(16)	1.379(2)
C(16)-C(17)	1.379(2)
C(17)-C(18)	1.377(2)
C(7)-N(1)-C(8)	124.28(12)
C(7)-N(1)-C(6)	116.00(11)
C(8)-N(1)-C(6)	116.91(11)
C(7)-N(2)-C(13)	120.81(11)
C(7)-N(2)-C(10)	120.78(11)
C(13)-N(2)-C(10)	118.23(11)
O(2)-N(3)-O(3)	122.91(13)
O(2)-N(3)-C(16)	118.73(14)
O(3)-N(3)-C(16)	118.36(13)
C(2)-C(1)-C(6)	111.59(14)
C(3)-C(2)-C(1)	110.67(14)
C(4)-C(3)-C(2)	110.69(13)
C(3)-C(4)-C(5)	111.23(14)
C(6)-C(5)-C(4)	110.35(13)
N(1)-C(6)-C(5)	112.76(12)
N(1)-C(6)-C(1)	110.52(12)
C(5)-C(6)-C(1)	110.87(12)
O(1)-C(7)-N(1)	122.17(13)
O(1)-C(7)-N(2)	120.37(12)
N(1)-C(7)-N(2)	117.46(11)
N(1)-C(8)-C(9)	111.68(11)
C(8)-C(9)-C(10)	109.54(12)
N(2)-C(10)-C(11)	113.51(12)
N(2)-C(10)-C(9)	106.81(12)
C(11)-C(10)-C(9)	112.28(12)
C(12)-C(11)-C(10)	126.29(15)
C(14)-C(13)-C(18)	118.88(12)
C(14)-C(13)-N(2)	121.43(12)
C(18)-C(13)-N(2)	119.56(12)

C(15)-C(14)-C(13)	120.57(13)
C(16)-C(15)-C(14)	118.89(13)
C(17)-C(16)-C(15)	121.93(13)
C(17)-C(16)-N(3)	118.52(14)
C(15)-C(16)-N(3)	119.54(13)
C(18)-C(17)-C(16)	118.97(14)
C(17)-C(18)-C(13)	120.72(14)

Symmetry transformations used to generate equivalent atoms:

3.3.3 Synthesis of tetrahydropyrimidin-2-ylidenes, piperidin-2-ones, and piperidin-2-ylidenes

Palladium (II) acetate (0.050 mmol) and triphenylphosphine (0.20 mmol) were dissolved in 4.0 ml of dry, degassed tetrahydrofuran under a flow of dinitrogen, resulting in a bright yellow solution. Azetidine (1.0 mmol) and the heterocumulene (1.0 mmol) were added with 1.0 ml of dry thf, and the reaction was stirred until GC indicated the consumption of one or both of the substrates. The solvent was removed *in vacuo*, and the residue was taken up in chloroform for purification by column chromatography using the proper ether/pentane solvent system. The pooled fractions were decolorized with charcoal, filtered, and concentrated to yield **2.35**, **2.36**, **2.40**, and **2.41**.

***N*-(1-Butyl-3-phenyl-4-vinyl-tetrahydropyrimidin-2-ylidene)-aniline (2.35a**, R = C_4H_9, R′ = H)

94% yield; colorless oil; IR (neat) ν (C=N) 1578 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3H, J = 7.2 Hz, CH_3), 1.4 (m, 2H, CH_2), 1.6 (m, 2H, CH_2), 1.9 (m, 1H, CH_2 ring), 2.2 (m, 1H, CH_2 ring), 3.2 (m, 1H, NCH_2), 3.4 (ABq, 2H, J = 4.9 Hz, NCH_2 ring), 3.9 (m, 1H, NCH_2), 4.0 (m, 1H, NCH ring), 5.4 (m, 2H, CH_2 vinyl), 6.1 (m, 1H, CH vinyl), 6.5 (m, 3H, phenyl), 6.9 (m, 7H, phenyl); ^{13}C NMR ($CDCl_3$) δ 151.05 (C=N), 150.58 (phenyl), 146.76 (phenyl), 137.77 (CH vinyl), 128.08 (phenyl), 127.64 (phenyl), 124.85 (phenyl), 123.50 (phenyl), 122.17 (phenyl), 118.54 (phenyl), 116.08 (CH_2 vinyl), 62.18 (NCH ring), 49.62 (NCH_2), 43.05 (NCH_2 ring), 29.29 (CH_2 ring), 27.38 (CH_2), 20.05 (CH_2), 13.86 (CH_3); MS (*m/e*) 333 $[M]^+$; EIHRMS calcd for $C_{22}H_{27}N_3$ 333.2205, found 333.2211.

***N*-(1-Cyclohexyl-3-phenyl-4-vinyl-tetrahydropyrimidin-2-ylidene)-aniline (2.35b**, R = C_6H_{11}, R′ = H)

86% yield; colorless solid, mp 110-112°C; IR ($CHCl_3$) ν (C=N) 1572 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0-1.3 (br, 1H, cyclohexyl), 1.3-1.6 (br, 4H, cyclohexyl), 1.6-1.9 (m, 5H, cyclohexyl), 1.9 (m, 1H, CH_2 ring), 2.3 (m, 1H, CH_2 ring), 3.3 (t, 2H, J = 6.8 Hz, NCH_2 ring), 4.1 (m, 1H, NCH ring), 4.5-4.7 (br, 1H, NCH), 5.3 (m, 2H, CH_2 vinyl), 6.1 (m, 1H, CH vinyl), 6.6 (m, 3H, phenyl), 6.9 (m, 7H, phenyl); ^{13}C NMR ($CDCl_3$) δ 151.36 (C=N), 151.08

(phenyl), 146.81 (phenyl), 138.48 (CH vinyl), 127.95(phenyl), 127.59 (phenyl), 124.28 (phenyl), 123.14 (phenyl), 122.21 (phenyl), 118.62 (phenyl), 115.80 (CH_2 vinyl), 61.61 (NCH ring), 55.16 (NCH), 36.97 (NCH_2 ring), 30.23 (cyclohexyl), 30.13 (cyclohexyl), 29.95 (cyclohexyl), 29.45 (CH_2 ring), 25.64 (cyclohexyl); MS (*m/e*) 359 $[M]^+$; EIHRMS calcd for $C_{24}H_{29}N_3$ 359.2361, found 359.2360.

***N*-(1-Cyclohexyl-3-(*p*-tolyl)-4-vinyl-tetrahydropyrimidin-2-ylidene)-(*p*-tolyl)-amine (2.35c, R = C_6H_{11}, R′ = CH_3)**

83% yield; colorless solid, mp 111-113°C; IR ($CHCl_3$) ν (C=N) 1584 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1-1.2 (br, 1H, cyclohexyl), 1.2-1.5 (br, 4H, cyclohexyl), 1.5-1.8 (br, 5H, cyclohexyl), 1.9 (m, 1H, CH_2 ring), 2.1 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 2.2 (m, 1H, CH_2 ring), 3.3 (m, 2H, NCH_2 ring), 4.0 (m, 1H, NCH ring), 4.5 (br, 1H, NCH), 5.3 (m, 2H, CH_2 vinyl), 6.0 (m, 1H, CH vinyl), 6.4 (d, 2H, J = 8.2 Hz, phenyl), 6.7 (d, 2H, J = 8.1 Hz, phenyl), 6.8 (s, 4H, phenyl); ^{13}C NMR ($CDCl_3$) δ 151.53 (C=N), 148.62 (phenyl), 144.58 (phenyl), 138.82 (CH vinyl), 132.58 (phenyl), 128.53 (phenyl), 128.19 (phenyl), 127.51 (phenyl), 124.20 (phenyl), 121.96 (phenyl), 115.65 (CH_2 vinyl), 61.79 (NCH ring), 55.18 (NCH), 37.08 (NCH_2 ring), 30.29 (cyclohexyl), 30.06 (cyclohexyl), 29.54 (CH_2 ring), 25.74 (cyclohexyl), 20.59 (CH_3), 20.47 (CH_3); MS (*m/e*) 387 $[M]^+$; EIHRMS calcd for $C_{26}H_{33}N_3$ 387.2674, found 387.2678.

***N*-(1-Cyclohexyl-3-(4-bromophenyl)-4-vinyl-tetrahydropyrimidin-2-ylidene)-4-bromoaniline (2.35d, R = C_6H_{11}, R′ = Br)**

92% yield; colorless solid, mp 98-100°C; IR ($CHCl_3$) ν (C=N) 1596 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0-1.2 (br, 1H, cyclohexyl), 1.2-1.5 (br, 4H, cyclohexyl), 1.5-1.8 (br, 5H, cyclohexyl), 1.9 (m, 1H, CH_2 ring), 2.2 (m, 1H, CH_2 ring), 3.3 (m, 2H, NCH_2 ring), 3.9-4.0 (br, 1H, NCH ring), 4.4-4.6 (br, 1H, NCH), 5.3 (m, 2H, CH_2 vinyl), 5.9 (m, 1H, CH vinyl), 6.4 (d, 2H, J = 8.6 Hz, phenyl), 6.7 (d, 2H, J = 8.6 Hz, phenyl), 6.9 (d, 2H, J = 8.6 Hz, phenyl), 7.1 (d, 2H, J = 8.6 Hz, phenyl); ^{13}C NMR ($CDCl_3$) δ 151.33 (C=N), 149.69 (phenyl), 145.50 (phenyl), 137.91 (CH vinyl), 131.21 (phenyl), 130.67 (phenyl), 125.95 (phenyl), 123.84 (phenyl), 116.51 (CH_2 vinyl), 111.51 (phenyl), 61.84 (NCH ring), 55.55 (NCH), 37.11 (NCH_2 ring), 30.27 (cyclohexyl), 29.97 (cyclohexyl), 29.60 (CH_2 ring), 25.64 (cyclohexyl), 25.59

(cyclohexyl); MS (*m/e*) 515 $[M]^+$; EIHRMS calcd for $C_{24}H_{27}Br_2N_3$ 515.0572, found 515.0629.

***N*-(1-*tert*-Butyl-3-phenyl-4-vinyl-tetrahydropyrimidin-2-ylidene)-aniline (2.35e, R = $C(CH_3)_3$, R′ = H)**

75% yield; colorless oil; IR (neat) ν (C=N) 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6 (s, 9H, $C(CH_3)_3$), 2.0 (m, 1H, CH_2 ring), 2.4 (m, 1H, CH_2 ring), 3.3 (m, 1H, NCH_2 ring), 3.6 (m, 1H, NCH_2 ring), 4.0-4.2 (br, 1H, NCH ring), 5.3 (dd, 2H, J = 7.0 and 10.0 Hz, CH_2 vinyl), 6.2 (m, 1H, CH vinyl), 6.6 (m, 3H, phenyl), 6.7-7.1 (br, m, 7H, phenyl); ^{13}C NMR ($CDCl_3$) δ 150.89 (C=N), 150.34 (phenyl), 147.04 (phenyl), 139.81 (CH vinyl), 128.05 (phenyl), 127.60 (phenyl), 123.90 (phenyl), 122.77 (phenyl), 121.72 (phenyl), 118.62(phenyl), 114.82 (CH_2 vinyl), 61.61 (NCH ring), 56.50 ($C(Me)_3$), 39.60 (NCH_2 ring), 32.63 (CH_2 ring), 28.91($(CH_3)_3$); MS (*m/e*) 333 $[M]^+$; EIHRMS calcd for $C_{22}H_{27}N_3$ 333.2205, found 333.2184.

***N*-(1-*tert*-Butyl-3-(4-chlorophenyl)-4-vinyl-tetrahydropyrimidin-2-ylidene)-4-chloroaniline (2.35f, R = $C(CH_3)_3$, R′ = Cl)**

70% yield; colorless solid, mp 88-89°C; IR ($CHCl_3$) ν (C=N) 1571 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (s, 9H, $C(CH_3)_3$), 2.0 (m, 1H, CH_2 ring), 2.3 (m, 1H, CH_2 ring), 3.2 (m, 1H, NCH_2 ring), 3.5 (m, 1H, NCH_2 ring), 3.9-4.0 (br, 1H, NCH ring), 5.3 (m, 2H, CH_2 vinyl), 6.1 (m, 1H, CH vinyl), 6.4 (d, 2H, J = 6.6 Hz, phenyl), 6.8 (m, 4H, phenyl), 6.9 (d, 2H, J = 9.0 Hz, phenyl); ^{13}C NMR ($CDCl_3$) δ 151.03 (C=N), 148.88 (phenyl), 145.48 (phenyl), 139.09 (CH vinyl), 128.28 (phenyl), 127.74 (phenyl), 125.11 (phenyl), 123.66 (phenyl), 122.71 (phenyl), 115.43 (CH_2 vinyl), 61.81 (NCH ring), 56.83 ($C(Me)_3$), 39.68 (NCH_2 ring), 32.39 (CH_2 ring), 28.84 ($(CH_3)_3$); MS (*m/e*) 401 $[M]^+$; EIHRMS calcd for $C_{22}H_{25}Cl_2N_3$ 401.1426, found 401.1430.

***N*-(1-*tert*-Butyl-3-(4-methoxyphenyl)-4-vinyl-tetrahydropyrimidin-2-ylidene)-4-methoxyaniline (2.35g, R = $C(CH_3)_3$, R′ = OCH_3)**

76% yield; colorless oil; IR ($CHCl_3$) ν (C=N) 1592 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (s, 9H, $C(CH_3)_3$), 2.0 (m, 1H, CH_2 ring), 2.3 (m, 1H, CH_2 ring), 3.3 (m, 1H, NCH_2 ring), 3.5 (m, 1H, NCH_2 ring), 3.6 (s, 3H, OCH_3), 3.6 (s, 3H, OCH_3), 3.9 (br, 1H, NCH ring), 5.2 (m, 2H, CH_2 vinyl), 6.1 (m, 1H, CH vinyl), 6.4 (d, 4H, J = 2.5 Hz, phenyl), 6.5 (d, 2H, J = 9.0 Hz,

phenyl), 6.7 (d, 2H, J = 9.0 Hz, phenyl); ^{13}C NMR ($CDCl_3$) δ 155.71 (phenyl), 152.86 (phenyl), 152.12 (C=N), 142.40 (phenyl), 140.15 (phenyl), 139.55 (CH vinyl), 125.91 (phenyl), 122.23 (phenyl), 114.83 (CH_2 vinyl), 113.43 (phenyl), 62.10 (NCH ring), 56.86 ($C(Me)_3$), 55.54 (OCH_3), 55.30 (OCH_3), 39.22 (NCH_2 ring), 31.40 (CH_2 ring), 28.63 (($CH_3)_3$); MS (*m/e*) 391 $[M]^+$; EIHRMS calcd for $C_{24}H_{31}N_3O_2$ 391.2416, found 391.2259.

***N*-(1-*tert*-Butyl-3-phenyl-4-propenyl-tetrahydropyrimidin-2-ylidene)-aniline (2.36a, R = CH_3)**

39% yield; colorless oil; IR (neat) ν (C=N) 1576 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 9H, $C(CH_3)_3$), 1.8 (dd, 3.0, J = 0.9 and 4.9 Hz, CH_3), 2.0 (m, 1H, CH_2 ring), 2.3 (m, 1H, CH_2 ring), 3.2 (m, 1H, NCH_2 ring), 3.5 (m, 1H, NCH_2 ring), 4.0 (m, 1H, NCH ring), 5.7-5.8 (m, 2H, vinyl), 6.5 (m, 3H, phenyl), 6.7 (m, 2H, phenyl), 6.9 (m, 5H, phenyl); ^{13}C NMR ($CDCl_3$) δ 151.30 (C=N), 150.10 (phenyl), 146.96 (phenyl), 132.69 (CH vinyl), 128.06 (phenyl), 127.63 (phenyl), 126.01 (phenyl), 123.81 (phenyl), 122.74 (CH_2 vinyl), 121.81 (phenyl), 118.84 (phenyl), 61.00 (NCH ring), 56.74 ($C(Me)_3$), 39.82 (NCH_2 ring), 33.33 (CH_2 ring), 29.17 (($CH_3)_3$), 17.70 (CH_3); MS (*m/e*) 347 $[M]^+$; EIHRMS calcd for $C_{23}H_{29}N_3$ 347.2361, found 347.2350.

Methyl-3-(1-*tert*-butyl-3-phenyl-2-phenylimino-hexahydropyrimidin-2-yl)-acrylate (2.36b, R = CO_2CH_3)

92% yield; colorless solid, mp 90-92°C; IR ($CHCl_3$) ν (C=N) 1580 cm^{-1}, ν (C=O) 1726; ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 9H, $C(CH_3)_3$), 2.1 (m, 1H, CH_2 ring), 2.4 (m, 1H, CH_2 ring), 3.3 (m, 1H, NCH_2 ring), 3.5 (m, 1H, NCH_2 ring), 3.8 (s, 3H, OCH_3), 4.1-4.2 (br, 1H, NCH ring), 6.1 (dd, 1H, J = 1.7 and 15.7 Hz, CH_2 vinyl), 6.5 (m, 3H, phenyl), 6.9 (m, 7H, phenyl), 7.2 (dd, 1H, J = 5.7 and 15.7 Hz, CH vinyl); ^{13}C NMR ($CDCl_3$) δ 166.56 (C=O), 150.15 (C=N), 149.76 (phenyl), 148.93 (CH vinyl), 146.39 (phenyl), 128.27 (phenyl), 127.70 (phenyl), 124.39 (phenyl), 123.52 (phenyl), 121.64 (phenyl), 120.64 (CH_2 vinyl), 119.01 (phenyl), 60.25 (NCH ring), 56.72 ($C(Me)_3$), 51.69 (OCH_3), 39.22 (NCH_2 ring), 31.40 (CH_2 ring), 28.63 (($CH_3)_3$); MS (*m/e*) 391 $[M]^+$; EIHRMS calcd for $C_{24}H_{29}N_3O_2$ 391.2260, found 391.2259.

1-Cyclohexyl-3,3-diphenyl-4-vinylpiperidin-2-one (2.40)

71% yield; pale yellow oil; IR (neat) ν (C=O) 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0-1.2 (br, 1H, cyclohexyl), 1.3-1.6 (br, 4H, cyclohexyl), 1.6-2.0 (br, m, 7H, cyclohexyl and CH_2 ring), 3.2 (ABq, 2H, J = 5.1 Hz, NCH_2 ring), 3.6 (m, 1H, CH ring), 4.5-4.7 (br, 1H, NCH), 5.0 (m, 2H, CH_2 vinyl), 5.8 (m, 1H, CH vinyl), 7.1-7.4 (m, 10H, phenyl); ^{13}C NMR ($CDCl_3$) δ 170.88 (C=O), 142.82 (phenyl), 141.27 (phenyl), 138.29 (CH vinyl), 130.50 (phenyl), 129.68 (phenyl), 127.25 (phenyl), 126.85 (phenyl), 126.43 (phenyl), 126.31 (phenyl), 115.77 (CH_2 vinyl), 61.04 (CPh_2 ring), 53.49 (NCH), 43.10 (NCH_2 ring), 40.33 (CH ring), 29.59 (CH_2 ring), 29.40 (cyclohexyl), 25.63 (cyclohexyl), 25.54 (cyclohexyl), 23.78 (cyclohexyl); MS (*m/e*) 359 $[M]^+$; EIHRMS calcd for $C_{25}H_{29}NO$ 359.2249, found 359.2236.

***N*-(3-Carboethoxy-1-cyclohexyl-3-methyl-4-vinylpiperidin-2-ylidene)-butylamine (2.41a, R = C_4H_9)**

57% yield; colorless oil; IR (neat) (C=N) 1613 cm^{-1}, ν (C=O) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (m, 3H, CH_3), 1.0-1.5 (br, m, 15H, cyclohexyl, CH_3 and CH_2CH_2), 1.5-1.9 (br, 7H, cyclohexyl, CH_3 and CH_2 ring), 2.7 (m, 1H, CH ring), 2.9-3.3 (br, m, 4H, NCH_2 and NCH_2 ring), 4.0-4.3 (br, m, 2H, OCH_2), 4.4-4.6 (br, 1H, NCH), 5.0 (m, 2H, CH_2 vinyl), 5.6 (m, 1H, CH vinyl); ^{13}C NMR ($CDCl_3$) δ 173.41 (C=O), 151.57 (C=N), 136.55 (CH vinyl), 116.50 (CH_2 vinyl), 61.14 (quarterny C), 60.85 (OCH_2), 53.75 (NCH), 46.84 (NCH_2), 46.38 (NCH_2 ring), 40.90 (CH ring), 30.29 (CH_2), 30.24 (cyclohexyl), 29.28 (CH_2 ring), 26.10 (CH_2), 25.67 (cyclohexyl), 25.57 (cyclohexyl), 24.29 (cyclohexyl), 20.46 (CH_3), 19.71 (CH_3), 14.08 (CH_3); MS (*m/e*) 348 $[M]^+$; EIHRMS calcd for $C_{21}H_{36}N_2O_2$ 348.2777, found 348.2777.

***N*-(3-Carboethoxy-1-cyclohexyl-3-methyl-4-vinylpiperidin-2-ylidene)-aniline (2.41b, R = C_6H_5)**

61% yield; colorless oil; IR (neat) (C=N) 1613 cm^{-1}, ν (C=O) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9-1.2 (br, 4H, cyclohexyl), 1.1 (t, 3H, J = 7.1 Hz, CH_3), 1.3 (s, 3H, CH_3), 1.3 (m, 2H, CH_2 ring), 1.5-1.9 (br, 6H, cyclohexyl), 2.9 (m, 1H, CH ring), 3.2 (m, 2H, NCH_2 ring), 3.9 (m, 2H, OCH_2), 4.0-4.2 (br, 1H, NCH), 5.0 (m, 2H, CH_2 vinyl), 5.6 (m, 1H, CH vinyl), 6.6 (m, 2H, phenyl), 6.8 (m, 1H, phenyl), 7.1 (m, 2H, phenyl); ^{13}C NMR ($CDCl_3$) δ 173.39 (C=O), 153.83 (C=N), 150.22 (phenyl), 136.84 (CH vinyl), 128.12 (phenyl), 121.19 (phenyl), 120.21

(phenyl), 116.60 (CH_2 vinyl), 60.61 (quarterny C), 60.05 (OCH_2), 54.95 (NCH), 45.36 (NCH_2 ring), 40.90 (CH ring), 29.32 (CH_2 ring), 28.93 (cyclohexyl), 25.73 (cyclohexyl), 25.55 (cyclohexyl), 24.39 (cyclohexyl), 19.15 (CH_3), 13.84 (CH_3); MS (*m/e*) 368 $[M]^+$; EIHRMS calcd for $C_{23}H_{32}N_2O_2$ 368.2464, found 368.2447.

3.3.4 X-ray analysis for 2.35b ($R = C_6H_{11}$, $R' = H$)

A crystal of **2.35b** (0.1 mm x 0.1 mm x 0.1 mm) was mounted on thin glass fibres 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, and no absorption corrections were required. A total of 11446 relectections was collected where the unique set contained 1947 collections.

The structure was 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 3.4 Crystal data collection and refinement for 2.35b ($R = C_6H_{11}$, $R' = H$)

Empirical formula	C24 H29 N3
Formula weight	359.50
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, Pbca
Unit cell dimensions	a = 13.687(5) A alpha = 90 deg. b = 12.791(3) A beta = 90 deg. c = 22.850(8) A gamma = 90 deg.
Volume	4000(2) A^3
Z, Calculated density	8, 1.194 Mg/m^3
Absorption coefficient	0.071 mm^-1
F(000)	1552
Crystal size	0.1 x 0.1 x 0.1 mm
Theta range for data collection	1.78 to 20.81 deg.
Limiting indices	0<=h<=13, 0<=k<=11, 0<=l<=22
Reflections collected / unique	11446 / 1947 [R(int) = 0.1579]
Completeness to theta = 20.81	92.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1947 / 0 / 244
Goodness-of-fit on F^2	1.057
Final R indices [I>2sigma(I)]	R1 = 0.0511, wR2 = 0.1129
R indices (all data)	R1 = 0.1030, wR2 = 0.1241
Largest diff. peak and hole	0.177 and -0.171 e.A^-3

Table 3.5 Atomic parameters X, Y, Z, and U(eq) for 2.35b ($R = C_6H_{11}$, $R' = H$)

	x	y	z	U(eq)
C(1)	3684(5)	4168(4)	7336(2)	60(2)
C(2)	2753(5)	3961(4)	7300(2)	50(2)
C(3)	2268(3)	3006(4)	7064(2)	38(1)
C(4)	3499(3)	1608(4)	7218(2)	30(1)
C(5)	2305(3)	2098(4)	8008(2)	43(1)
C(6)	1647(3)	2449(4)	7518(2)	49(2)
C(7)	2843(3)	2712(4)	5813(2)	40(1)
C(8)	2689(3)	2467(5)	5233(2)	47(2)
C(9)	2546(3)	1454(5)	5065(2)	48(2)
C(10)	2528(3)	681(4)	5484(2)	45(2)
C(11)	2669(3)	931(5)	6072(2)	36(1)
C(12)	2836(3)	1945(5)	6236(2)	28(1)
C(13)	5026(3)	1966(4)	6267(2)	35(1)
C(14)	5546(3)	1918(4)	5749(2)	40(1)
C(15)	5785(3)	970(5)	5507(2)	47(2)
C(16)	5522(3)	47(5)	5784(2)	50(2)
C(17)	5008(3)	93(4)	6302(2)	40(1)
C(18)	4732(3)	1055(4)	6550(2)	30(1)
C(19)	3693(4)	408(4)	8578(2)	89(2)
C(20)	4508(5)	79(4)	8993(2)	87(2)
C(21)	4772(4)	952(5)	9403(2)	48(2)
C(22)	5003(4)	1913(4)	9073(2)	89(2)
C(23)	4190(4)	2224(4)	8657(2)	81(2)
C(24)	3950(3)	1357(4)	8244(2)	38(1)
N(1)	2967(2)	2230(3)	6832(1)	30(1)
N(2)	4227(3)	1005(3)	7083(1)	34(1)
N(3)	3232(2)	1672(3)	7797(2)	32(1)

Table 3.6 Atomic bond lengths (in angstroms) and angles (in degrees) for 2.35b (R = C_6H_{11}, R′ = H)

C(1)-C(2)	1.305(6)
C(2)-C(3)	1.491(6)
C(3)-N(1)	1.477(5)
C(3)-C(6)	1.520(5)
C(4)-N(2)	1.297(5)
C(4)-N(3)	1.374(5)
C(4)-N(1)	1.394(5)
C(5)-N(3)	1.463(5)
C(5)-C(6)	1.505(5)
C(7)-C(8)	1.379(5)
C(7)-C(12)	1.376(5)
C(8)-C(9)	1.364(6)
C(9)-C(10)	1.375(6)
C(10)-C(11)	1.394(5)
C(11)-C(12)	1.368(5)
C(12)-N(1)	1.421(5)
C(13)-C(14)	1.382(5)
C(13)-C(18)	1.391(5)
C(14)-C(15)	1.372(6)
C(15)-C(16)	1.386(6)
C(16)-C(17)	1.378(6)
C(17)-C(18)	1.406(5)
C(18)-N(2)	1.401(5)
C(19)-C(24)	1.476(6)
C(19)-C(20)	1.524(6)
C(20)-C(21)	1.501(6)
C(21)-C(22)	1.476(6)
C(22)-C(23)	1.518(6)
C(23)-C(24)	1.492(6)
C(24)-N(3)	1.475(5)

C(1)-C(2)-C(3)	128.6(5)
N(1)-C(3)-C(2)	113.1(4)
N(1)-C(3)-C(6)	107.0(4)
C(2)-C(3)-C(6)	112.7(4)
N(2)-C(4)-N(3)	118.0(4)
N(2)-C(4)-N(1)	126.1(4)
N(3)-C(4)-N(1)	115.9(4)
N(3)-C(5)-C(6)	112.5(3)
C(5)-C(6)-C(3)	108.3(4)
C(8)-C(7)-C(12)	120.7(5)
C(9)-C(8)-C(7)	120.5(5)
C(8)-C(9)-C(10)	119.4(5)
C(9)-C(10)-C(11)	120.1(5)
C(12)-C(11)-C(10)	120.3(5)
C(11)-C(12)-C(7)	119.0(4)
C(11)-C(12)-N(1)	121.8(4)
C(7)-C(12)-N(1)	119.2(5)
C(14)-C(13)-C(18)	120.7(4)
C(15)-C(14)-C(13)	120.4(5)
C(14)-C(15)-C(16)	120.5(5)
C(17)-C(16)-C(15)	119.2(5)
C(16)-C(17)-C(18)	121.3(5)
C(13)-C(18)-N(2)	125.8(5)
C(13)-C(18)-C(17)	117.9(4)
N(2)-C(18)-C(17)	116.2(5)

C(24)-C(19)-C(20)	112.0(5)
C(21)-C(20)-C(19)	111.0(5)
C(22)-C(21)-C(20)	110.7(4)
C(21)-C(22)-C(23)	112.4(4)
C(24)-C(23)-C(22)	111.3(5)
N(3)-C(24)-C(19)	115.1(4)
N(3)-C(24)-C(23)	112.4(4)
C(19)-C(24)-C(23)	109.7(4)
C(4)-N(1)-C(12)	121.8(4)
C(4)-N(1)-C(3)	119.6(3)
C(12)-N(1)-C(3)	115.8(4)
C(4)-N(2)-C(18)	124.0(4)
C(4)-N(3)-C(5)	124.8(4)
[illegible]	[illegible]
[illegible]	[illegible]

Symmetry transformations used to generate equivalent atoms

3.3.5 Synthesis of [1,3]thiazinan-2-ylidenes

Palladium (II) acetate (0.10 mmol) and triphenylphosphine (0.40 mmol) were dissolved in 4.0 ml of dry, degassed tetrahydrofuran under a flow of dinitrogen, resulting in a cloudy yellow solution. Azetidine (1.0 mmol) and arylisothiocyanate (1.0 mmol) were added with 1.0 ml of dry thf, and the reaction was stirred, eventually turning a bright orange. When GC indicated the consumption of one or both of the substrates, the solvent was removed *in vacuo*. The residue was taken up in chloroform for purification by column chromatography using the proper ether/pentane solvent system. The pooled fractions were decolorized with charcoal, filtered, and concentrated to yield **2.38** and **2.39**.

***N*-(3-Butyl-6-vinyl-[1,3]thiazinan-2-ylidene)-aniline (2.38a**, R = C_4H_9, R′ = H)
92% yield; colorless oil; IR (neat) ν (C=N) 1579 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0 (t, 3H, J = 7.2 Hz, CH_3), 1.4 (m, 2H, CH_2), 1.7 (m, 2H, CH_2), 2.0 (m, 1H, CH_2 ring), 2.2 (m, 1H, CH_2 ring), 3.4 (dd, 2H, J = 4.5 and 6.7 Hz, NCH_2 ring), 3.6 (m, 2H, NCH_2), 3.8 (m, 1H, SCH ring), 5.1 (m, 2H, CH_2 vinyl), 5.7 (m, 1H, CH vinyl), 6.8 (dd, 2H, J = 1.2 and 8.3 Hz, phenyl), 7.0 (m, 1H, phenyl), 7.2 (m, 2H, phenyl); ^{13}C NMR ($CDCl_3$) δ 151.00 (C=N), 149.82 (phenyl), 136.86 (CH vinyl), 128.46 (phenyl), 122.58 (phenyl), 122.11 (phenyl), 117.02 (CH_2 vinyl), 50.97 (NCH_2), 47.18 (NCH_2 ring), 45.52 (SCH ring), 30.87 (CH_2 ring), 29.00 (CH_2), 20.08 (CH_2), 13.96 (CH_3); MS (*m/e*) 274 $[M]^+$; EIHRMS calcd for $C_{16}H_{22}N_2S$ 274.1504, found 274.1493.

***N*-(3-Cyclohexyl-6-vinyl-[1,3]thiazinan-2-ylidene)-aniline (2.38b**, R = C_6H_{11}, R′ = H)
95% yield; colorless oil; IR (neat) ν (C=N) 1574 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0-1.2 (br, 1H, cyclohexyl), 1.3-1.6 (br, 4H, cyclohexyl), 1.6-1.9 (m, 5H, cyclohexyl), 1.9 (m, 1H, CH_2 ring), 2.2 (m, 1H, CH_2 ring), 3.2 (m, 1H, NCH_2 ring), 3.4 (m, 1H, NCH_2 ring), 3.8 (m, 1H, SCH ring), 4.6-4.8 (br, 1H, NCH), 5.1 (m, 2H, CH_2 vinyl), 5.7 (m, 1H, CH vinyl), 6.8 (dd, 2H, J = 1.2 and 8.4 Hz, phenyl), 7.0 (m, 1H, phenyl), 7.2 (m, 2H, phenyl); ^{13}C NMR ($CDCl_3$) δ 150.48 (C=N), 149.99 (phenyl), 137.33 (CH vinyl), 128.51 (phenyl), 122.67 (phenyl), 122.10 (phenyl), 116.70 (CH_2 vinyl), 55.32 (NCH), 45.56 (SCH ring), 40.42 (NCH_2 ring),

31.50 (CH_2 ring), 29.68 (cyclohexyl), 25.77 (cyclohexyl), 25.69 (cyclohexyl); MS (*m/e*) 300 $[M]^+$; EIHRMS calcd for $C_{18}H_{24}N_2S$ 300.1660, found 300.1641.

4-Chloro-*N*-(3-cyclohexyl-6-vinyl-[1,3]thiazinan-2-ylidene)-aniline (**2.38c**, R = C_6H_{11}, R′ = Cl)

90% yield; colorless solid, mp 109-111°C; IR ($CHCl_3$) ν (C=N) 1576 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0-1.2 (br, 1H, cyclohexyl), 1.3-1.6 (br, 4H, cyclohexyl), 1.6-1.9 (br, 5H, cyclohexyl), 1.9 (m, 1H, CH_2 ring), 2.2 (m, 1H, CH_2 ring), 3.2 (m, 1H, NCH_2 ring), 3.4 (m, 1H, NCH_2 ring), 3.8 (m, 1H, SCH ring), 4.6-4.8 (br, 1H, NCH), 5.1 (m, 2H, CH_2 vinyl), 5.7 (m, 1H, CH vinyl), 6.8 (d, 2H, J = 8.8 Hz, phenyl), 7.2 (d, 2H, J = 8.8 Hz, phenyl); ^{13}C NMR ($CDCl_3$) δ 150.88 (C=N), 148.67 (phenyl), 137.09 (CH vinyl), 128.45 (phenyl), 127.00 (phenyl), 124.03 (phenyl), 116.88 (CH_2 vinyl), 55.37 (NCH), 45.55 (SCH ring), 40.41 (NCH_2 ring), 31.36 (CH_2 ring), 29.62 (cyclohexyl), 29.40 (cyclohexyl), 25.73 (cyclohexyl), 25.64 (cyclohexyl); MS (*m/e*) 334 $[M]^+$; EIHRMS calcd for $C_{18}H_{23}ClN_2S$ 334.1270, found 334.1270.

***N*-(3-Cyclohexyl-6-vinyl-[1,3]thiazinan-2-ylidene)-4-methoxyaniline** (**2.38d**, R = C_6H_{11}, R′ = OCH_3)

94% yield; colorless oil; IR (neat) ν (C=N) 1573 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0-1.2 (br, 1H, cyclohexyl), 1.2-1.5 (br, 4H, cyclohexyl), 1.6-1.9 (br, 7H, cyclohexyl and CH_2 ring), 2.2 (m, 1H, CH_2 ring), 3.1 (m, 1H, NCH_2 ring), 3.3 (m, 1H, NCH_2 ring), 3.7 (s, 3H, OCH_3), 3.7 (m, 1H, SCH ring), 4.6-4.8 (br, 1H, NCH), 5.0 (m, 2H, CH_2 vinyl), 5.7 (m, 1H, CH vinyl), 6.8 (d, 4H, J = 1.9 Hz, phenyl); ^{13}C NMR ($CDCl_3$) δ 154.86 (phenyl), 150.80 (C=N), 143.09 (phenyl), 137.24 (CH_2 vinyl), 123.20 (phenyl), 116.43 (CH_2 vinyl), 113.64 (phenyl), 55.30 (OCH_3), 55.07 (NCH), 45.36 (SCH), 40.24 (NCH_2), 31.30 (CH_2 ring), 29.48 (cyclohexyl), 29.29 (cyclohexyl), 25.55 (cyclohexyl); MS (*m/e*) 330 $[M]^+$; EIHRMS calcd for $C_{19}H_{26}N_2OS$ 330.1766, found 330.1756.

***N*-(3-*tert*-Butyl-6-vinyl-[1,3]thiazinan-2-ylidene)-aniline** (**2.38e**, R = $C(CH_3)_3$, R′ = H)

47% yield; colorless oil; IR (neat) ν (C=N) 1585 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 1.5 (s, 9H, $C(CH_3)_3$), 1.9 (m, 1H, CH_2 ring), 2.2 (m, 1H, CH_2 ring), 3.4 (m, 2H, NCH_2 ring), 3.8 (m,

1H, SCH), 5.1 (m, 2H, CH_2 vinyl), 5.8 (m, 1H, CH vinyl), 6.8 (m, 2H, phenyl), 7.0 (m, 1H, phenyl), 7.2 (m, 2H, phenyl); ^{13}C NMR ($CDCl_3$) δ 153.53 (C=N), 149.72 (phenyl), 137.15 (CH vinyl), 128.65 (phenyl), 122.28 (phenyl), 121.68 (phenyl), 116.41 (CH_2 vinyl), 58.49 ($C(Me)_3$), 45.15 (SCH), 42.87 (NCH_2 ring), 32.74 (CH_2 ring), 28.40 (($CH_3)_3$); MS (*m/e*) 274 $[M]^+$; EIHRMS calcd for $C_{16}H_{22}N_2S$ 274.1504, found 274.1512.

***N*-(3-*tert*-Butyl-6-propenyl-[1,3]thiazinan-2-ylidene)-aniline (2.39a**, R = CH_3)
35% yield; colorless oil; IR (neat) ν (C=N) 1584 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 1.5 (s, 9H, $C(CH_3)_3$), 1.6 (d, 3H, J = 1.2 Hz, CH_3), 1.8 (m, 1H, CH_2 ring), 2.2 (m, 1H, CH_2 ring), 3.4 (m, 2H, NCH_2 ring), 3.8 (m, 1H, SCH), 5.3 (m, 1H, CHMe vinyl), 5.5 (m, 1H, CH vinyl), 6.8 (d, 2H, J = 7.5 Hz, phenyl), 6.9 (m, 1H, phenyl), 7.2 (m, 2H, phenyl); ^{13}C NMR ($CDCl_3$) δ 153.86 (C=N), 149.81(phenyl), 129.85 (CH vinyl), 128.62 (phenyl), 127.97 (phenyl), 122.20 (CH_2 vinyl), 121.68 (phenyl), 58.42 ($C(Me)_3$), 44.83 (SCH), 43.14 (NCH_2 ring), 33.38 (CH_2 ring), 28.40 (($CH_3)_3$), 17.59 (CH_3); MS (*m/e*) 288 $[M]^+$; EIHRMS calcd for $C_{17}H_{24}N_2S$ 288.1660, found 288.1653.

Methyl-3-(3-*tert*-butyl-2-phenylimino-[1,3]thiazinan-6-yl)-acrylate (2.39b, R = CO_2CH_3)
89% yield; colorless oil; IR (neat) ν (C=N) 1586 cm^{-1}, ν (C=O) 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 1.5 (s, 9H, $C(CH_3)_3$), 1.9 (m, 1H, CH_2 ring), 2.2 (m, 1H, CH_2 ring), 3.4 (t, 2H, J = 6.3 Hz, NCH_2 ring), 3.7 (s, 3H, OCH_3), 3.9 (m, 1H, SCH), 5.8 (dd, 1H, J = 1.2 and 15.5 Hz, $CHCO_2$ vinyl), 6.7 (m, 1H, phenyl), 6.8 (dd, 1H, J = 8.1 and 15.5 Hz, CH vinyl), 7.0 (m, 1H, phenyl), 7.2 (m, 3H, phenyl); ^{13}C NMR ($CDCl_3$, 500MHz) δ 166.32 (C=O), 152.23 (C=N), 149.41 (phenyl), 146.35 (CH vinyl), 128.67 (phenyl), 122.53 (CH_2 vinyl), 121.66 (phenyl), 121.59 (phenyl), 58.68 ($C(Me)_3$), 51.61 (OCH_3), 42.94 (SCH), 42.57 (NCH_2 ring), 32.06 (CH_2 ring), 28.35 (($CH_3)_3$); MS (*m/e*) 332 $[M]^+$; EIHRMS calcd for $C_{18}H_{24}N_2O_2S$ 332.1558, found 332.1550.

3.3.6 X-ray anaylsis for 2.38c (R = C_6H_{11}, R′ = Cl)

A crystal of **2.38c** (0.1 mm x 0.1 mm x 0.03 mm) was mounted on thin glass fibres using viscous oil. Data were collected at room temperature 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, and no absorption corrections were required. A total of 5141 reflections was collected where the unique set contained 1486 reflections.

The structure was 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 collection and refinement for 2.38c ($R = C_6H_{11}$, $R' = Cl$)

Empirical formula	C18 H23 Cl N2 S
Formula weight	334.89
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 5.579(3) A alpha = 90 deg. b = 16.528(9) A beta = 90 deg. c = 18.905(7) A gamma = 90 deg.
Volume	1742.2 A^3
Z, Calculated density	4, 1.276 Mg/m^3
Absorption coefficient	0.337 mm^-1
F(000)	712
Crystal size	0.10 x 0.10 x 0.03 mm
Theta range for data collection	1.64 to 20.61 deg.
Limiting indices	-5<=h<=5, 0<=k<=11, 0<=l<=18
Reflections collected / unique	5141 / 1486 [R(int) = 0.1742]
Completeness to theta = 20.61	82.5 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1486 / 0 / 203
Goodness-of-fit on F^2	1.020
Final R indices [I>2sigma(I)]	R1 = 0.0415, wR2 = 0.0514
R indices (all data)	R1 = 0.1229, wR2 = 0.0638
Absolute structure parameter	-0.17(15)
Largest diff. peak and hole	0.144 and -0.154 e.A^-3

Table 3.8 Atomic parameters X, Y, Z, and U(eq) for 2.38c ($R = C_6H_{11}$, $R' = Cl$)

	x	y	z	U(eq)
Cl	-3431(5)	3365(1)	284(1)	63(1)
S	1659(4)	5766(1)	2526(1)	56(1)
N(1)	940(13)	4281(5)	3024(4)	41(2)
N(2)	2645(13)	5169(5)	3827(4)	44(3)
C(1)	-2225(16)	4422(5)	2148(4)	45(3)
C(2)	-3245(16)	4204(6)	1504(4)	43(3)
C(3)	-2092(19)	3669(7)	1091(4)	45(3)
C(4)	69(18)	3351(6)	1267(5)	50(3)
C(5)	1074(16)	3573(5)	1910(5)	49(3)
C(6)	-33(17)	4106(6)	2355(4)	36(3)
C(7)	1799(18)	4981(6)	3173(5)	40(3)
C(8)	4910(20)	7513(6)	1887(5)	97(5)
C(9)	5030(20)	6879(9)	2247(6)	74(7)
C(9')	2960(80)	7250(30)	2450(30)	74(7)
C(10)	3696(19)	6575(6)	2820(4)	56(3)
C(11)	4747(18)	6397(6)	3515(5)	97(5)
C(12)	3500(20)	5965(7)	4017(4)	90(4)
C(13)	2176(15)	4687(4)	5075(4)	51(3)
C(14)	2606(18)	3944(6)	5546(4)	70(4)
C(15)	5239(18)	3710(5)	5580(5)	77(4)
C(16)	6115(18)	3536(6)	4829(5)	84(4)
C(17)	5755(16)	4250(6)	4340(4)	69(4)
C(18)	3120(18)	4490(5)	4326(4)	38(3)

Table 3.9 Atomic bond lengths (in angstroms) and angles (in degrees) for 2.38c (R = C_6H_{11}, R′ = Cl)

Cl-C(3)	1.772(8)
S-C(7)	1.784(8)
S-C(10)	1.841(8)
N(1)-C(7)	1.284(9)
N(1)-C(6)	1.406(9)
N(2)-C(7)	1.360(9)
N(2)-C(12)	1.446(9)
N(2)-C(18)	1.490(8)
C(1)-C(6)	1.385(9)
C(1)-C(2)	1.392(9)
C(2)-C(3)	1.343(11)
C(3)-C(4)	1.356(10)
C(4)-C(5)	1.388(9)
C(5)-C(6)	1.367(9)
C(8)-C(9)	1.251(14)
C(8)-C(9')	1.58(5)
C(9)-C(10)	1.408(12)
C(9')-C(10)	1.39(5)
C(10)-C(11)	1.468(9)
C(11)-C(12)	1.376(10)
C(13)-C(14)	1.535(9)
C(13)-C(18)	1.545(8)
C(14)-C(15)	1.521(10)
C(15)-C(16)	1.530(10)
C(16)-C(17)	1.512(9)
C(17)-C(18)	1.522(10)

C(7)-S-C(10)	107.1(5)
C(7)-N(1)-C(6)	121.7(9)
C(7)-N(2)-C(12)	123.3(8)
C(7)-N(2)-C(18)	117.8(8)
C(12)-N(2)-C(18)	117.9(8)
C(6)-C(1)-C(2)	120.7(8)
C(3)-C(2)-C(1)	118.8(9)
C(2)-C(3)-C(4)	122.6(9)
C(2)-C(3)-Cl	119.0(9)
C(4)-C(3)-Cl	118.4(10)
C(3)-C(4)-C(5)	118.1(9)
C(6)-C(5)-C(4)	121.8(9)
C(5)-C(6)-C(1)	117.9(8)
C(5)-C(6)-N(1)	120.8(9)
C(1)-C(6)-N(1)	121.2(10)
N(1)-C(7)-N(2)	122.3(9)
N(1)-C(7)-S	119.3(7)
N(2)-C(7)-S	118.2(7)
C(9)-C(8)-C(9')	56(2)
C(8)-C(9)-C(10)	133.6(16)
C(10)-C(9')-C(8)	111(3)
C(9')-C(10)-C(9)	58.5(18)
C(9')-C(10)-C(11)	137(2)
C(9)-C(10)-C(11)	123.3(10)
C(9')-C(10)-S	104(2)
C(9)-C(10)-S	110.7(6)
C(11)-C(10)-S	111.8(6)
C(12)-C(11)-C(10)	121.3(9)
C(11)-C(12)-N(2)	117.9(9)

C(14)-C(13)-C(18)	108.0(7)
C(15)-C(14)-C(13)	112.3(8)
C(14)-C(15)-C(16)	108.4(8)
C(17)-C(16)-C(15)	112.3(9)
C(16)-C(17)-C(18)	110.0(8)
N(2)-C(18)-C(17)	112.2(8)
N(2)-C(18)-C(13)	111.1(7)
C(17)-C(18)-C(13)	111.6(7)

Symmetry transformations used to generate equivalent atoms:

Claims to Original Research

1. A novel synthetic route to *N*-alkyl-2-vinylazetidines was designed from the successive DIBAL reduction and Wittig reaction of the cognate 2-carbomethoxyazetidines.

2. Tetrahydropyrimidin-2-ones, tetrahydropyrimidin-2-imines, and [1,3]thiazinan-2-imines were prepared from the regiospecific reaction of *N*-alkylated 2-vinylazetidines with isocyanates, diarylcarbodiimides, and arylisothiocyanates under mild conditions, using a $Pd(OAc)_2/PPh_3$ catalyst system.

3. From stereo- and regiochemical evidence, a π-allylpalladium intermediate was suggested as the reactive species for the insertion of the heterocumulene, which initially cyclized to either the kinetic or thermodynamic product, ultimately affording the latter through a ring opening and closing equilibrium of the six-membered heterocycle.

4. A study of substitution on the vinyl group with chemically and sterically distinct substituents demonstrated an influence on reactivity whereby electron-withdrawing groups enhanced rates and yields, electron-donating groups reduced reactivity, and with increasing size, steric hindrance adversely affected the reaction.

5. Products from the reactions of various *N*-alkylated 2-vinylazetidines with *o*-tolylisocyanate displayed substantial congestion about the heterocycle, resulting in a barrier between two conformations that could be visualized and coelesced by ambient and high temperature NMR spectroscopy.

6. The palladium(0) catalyzed method for heterocumulene insertion into 2-vinylazetidines was successfully applied to ketenes and ketenimines, suggesting a variety of carbon electrophiles could serve as substrates.

7. **Preliminary experiments for asymmetric techniques in the palladium(0) catalyzed reaction of *N*-alkylated 2-vinylazetidines with heterocumulenes using optically active, bidentate phosphine ligands were unsuccessful.**

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