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นางสาว วชิราภรณ์ สัตย์เจริญ

สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

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DIASTEREOSELECTIVE CYCLIZATION OF ALLENES USING ORGANOCOBALT REAGENTS

Miss. Wachiraporn Satcharoen

สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

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The cobalt mediated acylation-cyclization of γ-sulfonamidoallenes with a protected hydroxyl group in the α position has been developed.

The required disubstituted allenes were synthesized starting from acrolein and ethyl acetate. Treatment of the allenes with acetyl tetracarbonyl cobalt, under suitable condition, yielded the *trans*-substituted pyrrolidine as the major product. The stereochemistry was determined by analysis of the ^{1}H NMR spectra. Silyl protecting groups resulted in the highest yields and diastereoselectivity. The methyl thiomethyl protecting group resulted in the lowest diastereoselectivity.

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Department…….Chemistry..….....Student's signature.....

Field of study .....Chemistry....…….Advisor's signature.....…...

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br	Broad	m	Multiplet (NMR)
Cp*	η^5-Pentamethylcyclopenta-	m.p.	Melting point
	dienyl	MS	Mass spectrometry
d	Doublet (NMR)	MTM	Methylthiomethyl
DMAP	4-Dimethylaminopyridine	NBS	*N*-Bromosuccinimide
DMF	*N,N*-Dimethylformamide	NMR	Nuclear magnetic resonance
dppb	Bis(diphenylphosphino)	ppm	Part per million
	butane	PTC	Phase transfer catalysis
dppf	1,1'-Bis(diphenylphosphino)	q	Quartet (NMR)
	ferrocene	s	Singlet (NMR)
dt	Double triplet (NMR)	t	Triplet (NMR)
HRMS	High Resolution mass	TBS	*tert*-butyldimethylsilyl
	Spectrometry	THF	Tetrahydrofuran
IR	Infrared	TIPS	Triisopropylsilyl
LDA	Lithium diisopropylamide	TMS	Trimethylsilyl
Ln	Lanthanide metal	Ts	*p*-toluenesulfonyl

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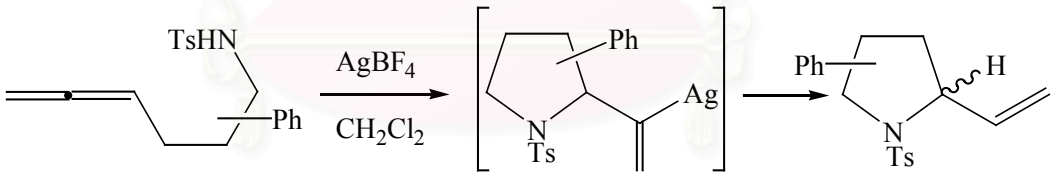
CHAPTER I

INTRODUCTION

Transition metal-mediated intramolecular cyclizations are important organometallic reactions which are used in organic synthesis. The transition metal can be used to induce cyclization and allow subsequent bond formation. Additionally, the products which are obtained from the cyclization of allenes also have an alkene moiety that can be useful for subsequent reactions.[1] Recently, this reaction with allenes has been used efficiently for the synthesis of various nitrogen- and oxygen-heterocycles and carbocycles.[2] An interesting aspect of the cyclization is the regioselectivity and the stereoselectivity that is involved due to substituents on the allene.

1) C-N bond formation

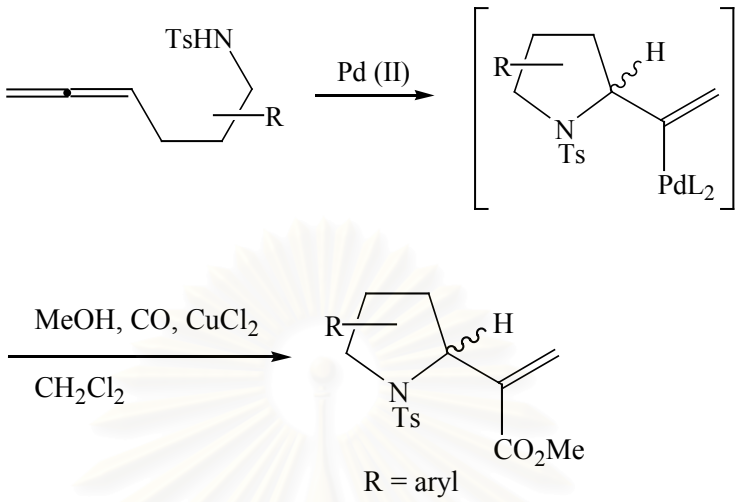
Gallagher has utilized both palladium(II) and silver(I) salts to induce cyclization. Gallagher showed that silver tetrafluoroborate acts as a catalyst to cyclize allenic sulfonamides (**scheme 1**).[3]



Scheme 1 Silver(I)-catalyzed cyclization of allenic sulfonamides

These reactions were highly stereoselective to generate the *cis*-2,5-disubstituted pyrrolidines whereas the 2,3-disubstituted pyrrolidines were obtained as the *trans*-isomers in high yield. However, the reaction was not stereoselective for the 2,4-disubstituted pyrrolidines which were obtained as a 1:1 mixture. Moreover, the carbon-silver bond in the intermediate underwent protonolysis *in situ* and could not be used for further chemistry.

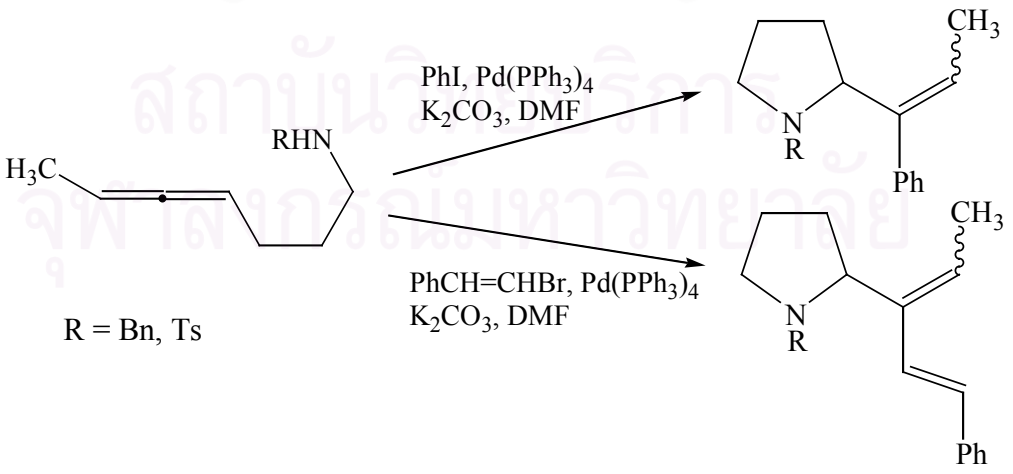
In a later report, palladium(II) catalyzed cyclization of a series of substituted allenic sulfonamides under carbonylation conditions was discussed (**scheme 2**).[4]



Scheme 2 Palladium(II)-catalyzed cyclization of allenic sulfonamides

It was found that only the α-substituted allene showed a high diastereoselectivity, leading to the *trans*-2,3-disubstituted pyrrolidine. Other allenes showed low diastereoselectivity, leading to mixtures of *cis*- and *trans*-pyrrolidines.

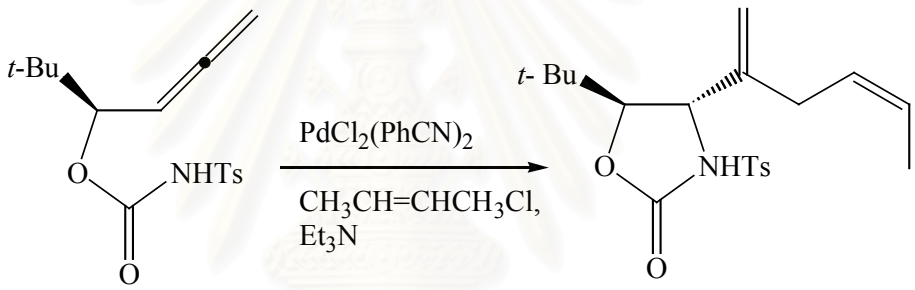
Moreover, they were also interested in the cyclization of the various N-substituted allenic amines with alkenyl and arylpalladium(II) complexes (**scheme 3**).[3] The required palladium(II) complexes were generated *in situ* by oxidative addition.



Scheme 3 Cyclization of substituted allenic amines

The arylation reaction yielded the pyrrolidine in good yield as 4:1 mixture of E/Z diastereoisomers whereas the alkenylation reaction gave a 1:1 mixture of E/Z isomers in good yield. This reaction was unsuccessful for electron-defficient aryl halides such as methyl 4-bromobenzoate, 2-bromopyridine and 3-iodopyridine. This can be attributed to an inefficient insertion step. It is known that the Heck reaction for electron poor aryl halide/electron rich alkene pairs is similarly inefficient.[5]

Subsequently, Tamaru and co-workers reported the regioselectivity and stereoselectivity of cyclizations of 2,3-butadienyl tosyl carbamates induced by π-allyl palladium complexes generated catalytically. These reactions gave 4-(1-allylvinyl)-2-oxazolidinones in high yield and mostly provided the *trans* isomers with excellent selectivity (**scheme 4**).[6,7] This reaction is similar to Gallagher's (**scheme 3**) and appears to involve allylpalladium(II) complexes which induce cyclization.



Scheme 4 Allyl palladium-induced cyclization of 2,3-butadienyl tosyl carbamates

Hiemstra has been shown that the palladium-catalyzed cyclization of lactam-allenes with organic halides or triflates under the Gallagher condition produces an unexpected major product in good yield (**scheme 5**).[8,9]

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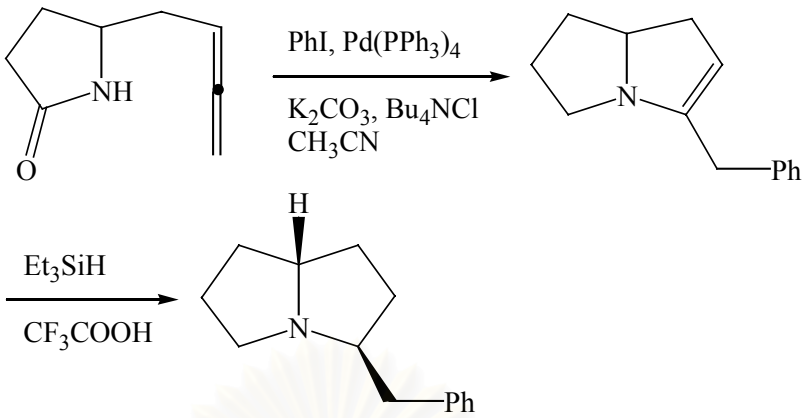
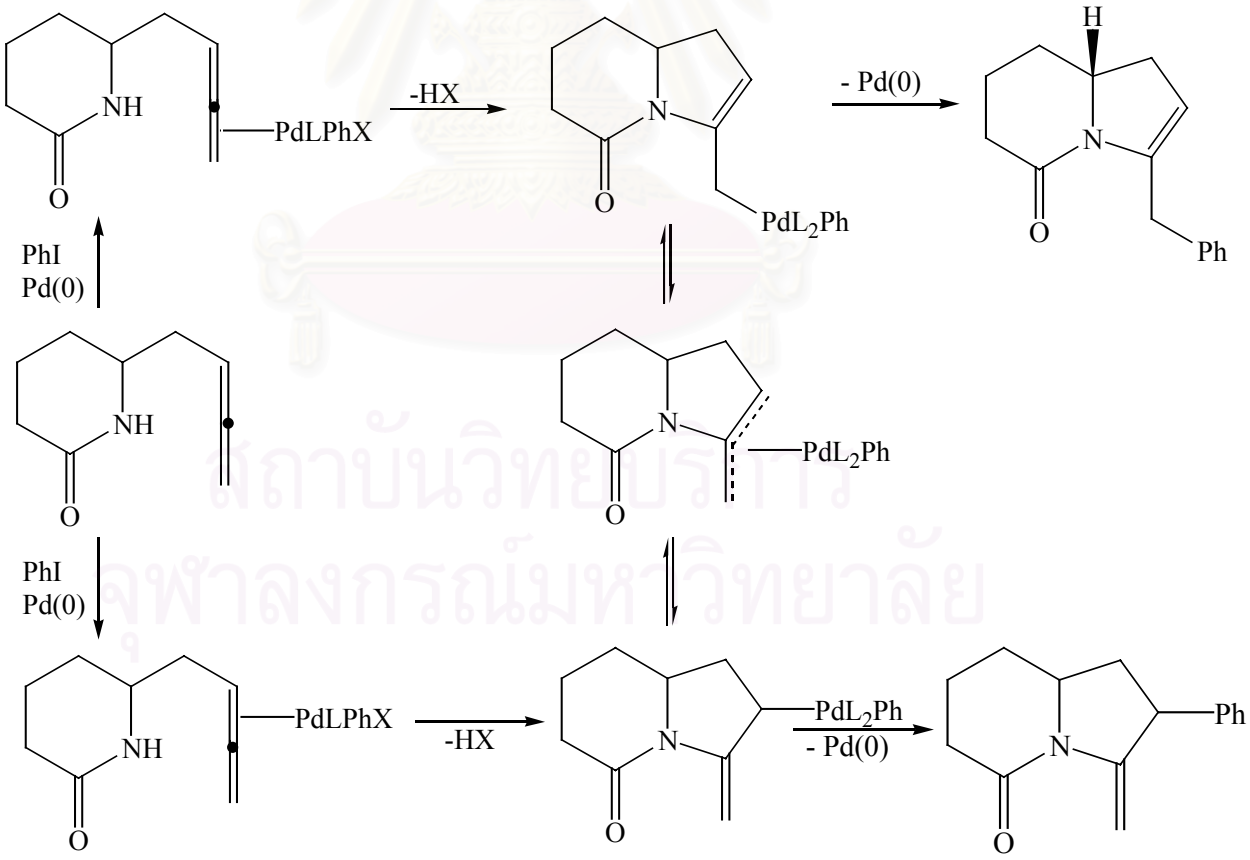


Scheme 5 Palladium–catalyzed cyclization of allenes under the Gallagher′s condition

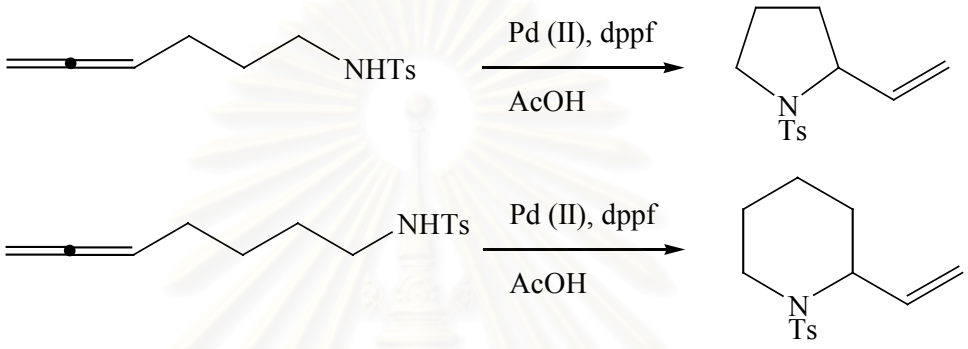
This involves apparent nucleophilic attack on the sp-hybridized carbon. The formation of these products can be explained by two different mechanisms (**scheme 6)** each involving cyclization of η^2-allylpalladium complexes, but not η^3-allylpalladium complexes.



Scheme 6 A mechanism of the palladium-catalyzed cyclization

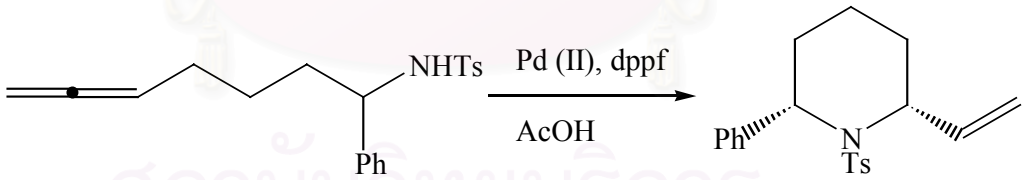
Nucleophilic attack on the internal carbon of η^3-allyl palladium complexes is known, but is generally observed when the metal has harder amino ligands. In addition the products are often stable metallocyclobutanes.[10]

Yamamoto has reported the intramolecular hydroamination reaction of allenes using palladium complex ($[\eta^3\text{-}C_3H_5)PdCl_2]$-dppf) and a catalytic amount of acetic acid giving the corresponding 2-vinylpyrrolidine and 2-vinylpiperidine (**scheme 7**).[11]



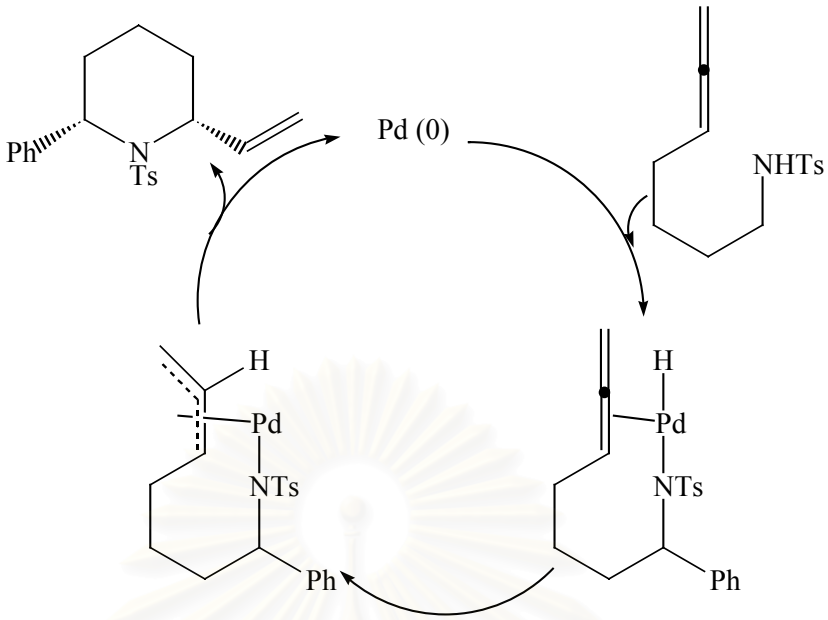
Scheme 7 Intramolecular hydroamination reaction

In addition, the cyclization of a γ-substituted allenylamine gave a 1:1 mixture of pyrrolidines. On the other hand, a γ-substituted allenylamine gave the *cis*-piperidine as the major isomer (**scheme 8**).



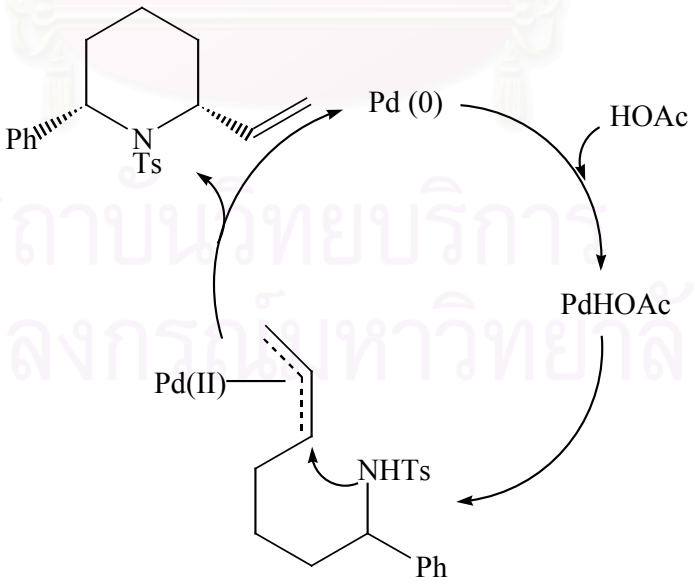
Scheme 8 The palladium-catalyzed cyclization of a γ-substituted allenylamine

A proposed mechanism involves the insertion of the allene into a Pd-H bond to form an η^3-allylpalladium complex. Reductive elimination then gives the cyclized product and regenerates the catalytic species (**scheme 9**).



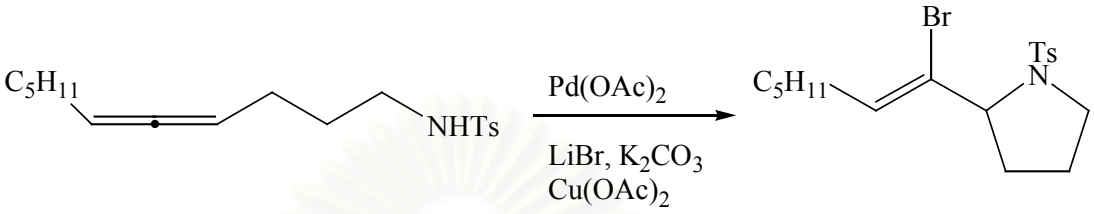
Scheme 9 A proposed catalytic cycle for the synthesis of *cis*-piperidines

Alternatively, a palladium(II) hydride might be generated by oxidative addition to acetic acid. Intermolecular insertion would then give an η^3-allyl palladium complex which could cyclize in a nucleophilic manner (**scheme 10**).



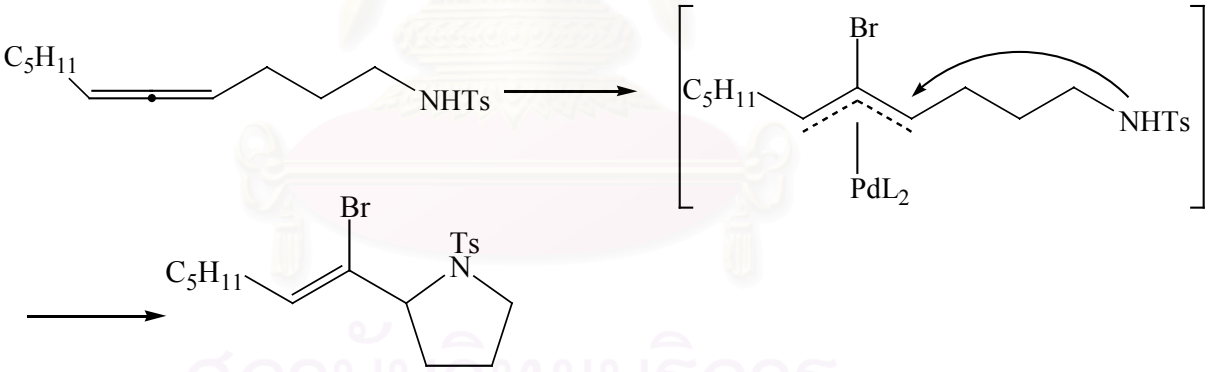
Scheme 10 The alternative catalytic cycle for the synthesis of *cis*-piperidines

Bäckvall has reported a mild palladium catalyzed cyclization of allenic sulfonamide (**scheme 11**).[12,13] Treatment of the allenic sulfonamide with LiBr, K_2CO_3 and $Cu(OAc)_2$ in the presence of a catalytic amount of $Pd(OAc)_2$ in acetonitrile under an oxygen atmosphere afforded the desired pyrrolidine in good yield.



Scheme 11 The palladium-catalyzed 1,2-oxidation of substituted allenic sulfonamides

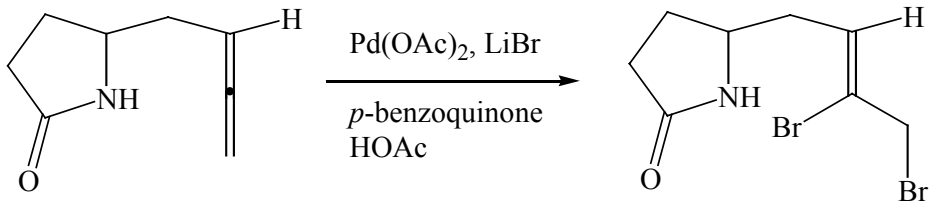
The mechanism is believed to involve formation of a π-allylpalladium complex (**scheme 12**). A related process with O-nucleophiles has also been reported (*vide infra*).



Scheme 12 The mechanism of the paladium-catalyzed intramolecular oxidation

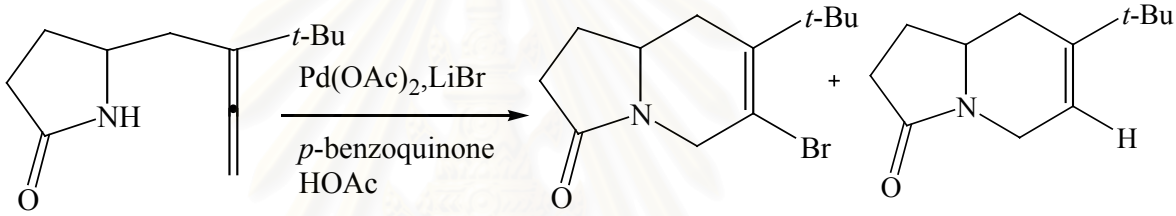
The oxygen and copper would serve to reoxidize palladium from (0) to (II) as in the Wacker reaction.[10]

Subsequently, Bäckvall has extended the cyclization to the allenic lactam (**scheme 13**) which is closely related to Hiemstra's allenes.[12,13] Treatment of the allenic lactam with LiBr, *p*-benzoquinone as the reoxidant and $Pd(OAc)_2$ yielded the 1,2-dibromo product as an 8:1 mixture of double bond isomers without cyclization.



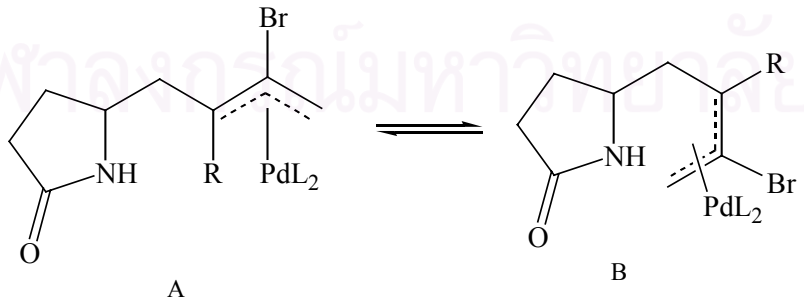
Scheme 13 Palladium-catalyzed cyclization of allenic lactam

On the other hand, the corresponding allenic lactams with a *t*-butyl group a substituent on the allene were cyclized under the same conditions giving a mixture of cyclic enamides (**scheme 14**).[12,13]



Scheme 14 Palladium-catalyzed cyclization of *t*-butyl substituted allenic lactam

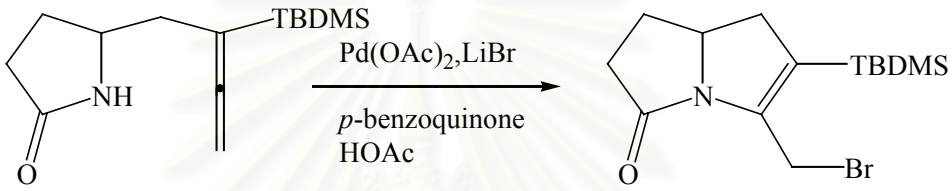
The formation of the products showed that nitrogen attacked the terminal sp^2- carbon, *via* an η^3-allylpalladium intermediate. The different result between the large substituent (R = *t*-Bu) in the C-3 position of the allene and the small substituent (R= H) could be explained by consideration of the equilibrium between isomeric π-allylpalladium intermediates (**scheme 15**).[12,13]



Scheme 15 The equilibrium between π-allylpalladium intermediates

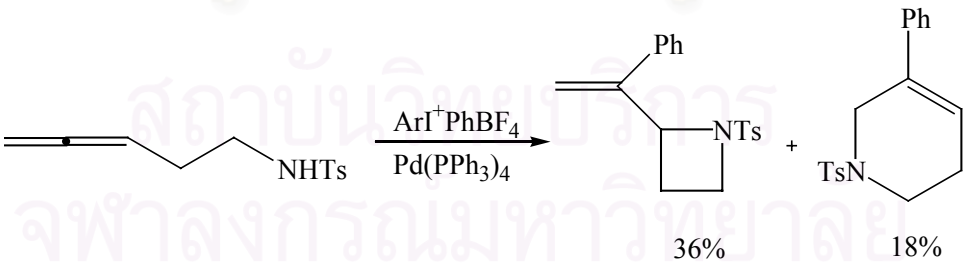
It was proposed that the allene bearing the large substituent (R = *t*-Bu) favoured η^3-allylpalladium intermediate B whereas with the small substituent (R = H) η^3-allylpalladium intermediate A was preferred.

Interestingly, the reaction of the TBDMS substituted allene under the same reaction conditions afforded a product in which the nitrogen attacked the central sp-carbon (**scheme 16**).[12] It is likely that the TBDMS group increases the electrophilicity of the sp-carbon via the silicon β-effect, causing ring closure before η^3-allylpalladium formation.



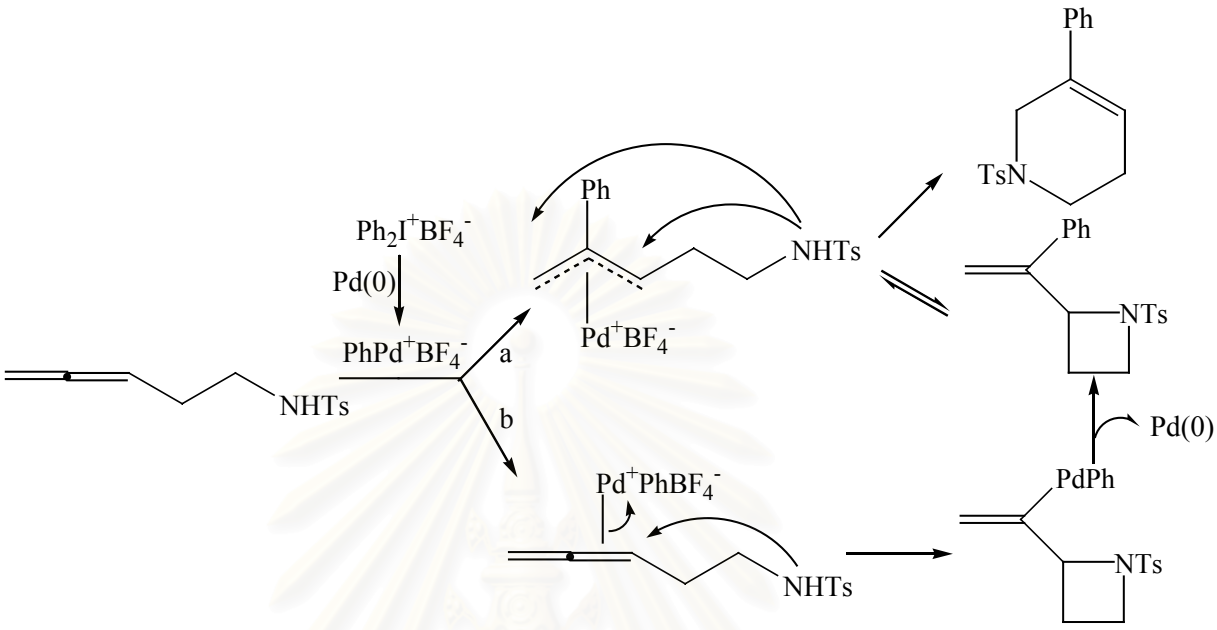
Scheme 16 Palladium-catalyzed cyclization of TBDMS substituted allenic lactam

The palladium-catalyzed cyclization of allene-substituted amines and amino acids afforded the four- and six-membered rings depending upon which sp^2-atom of the allene was attacked. Kang has reported one result of this type of cyclization (**scheme17**).[13]



Scheme 17 Palladium-catalyzed cyclization of allene with hypervalent iodonium salts

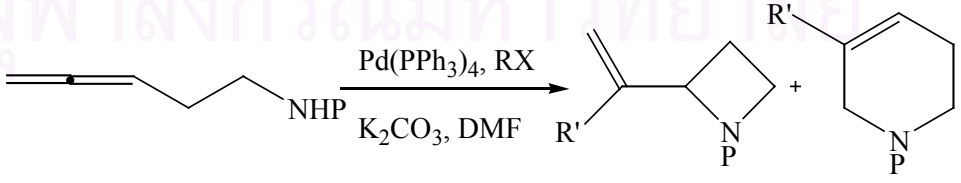
Plausible mechanisms for the formation of the four- and six-membered rings involving either η^2 or η^3-allylpalladium complexes can be put forward **(scheme18)**, although the experimental data cannot distinguish between them.



Scheme 18 Plausible mechanisms for the formation of the four- and six-membered rings

In path (a), the phenylpalladium(II) tetrafluoroborate can react with the allene forming a η^3-allylpalladium intermediate. Intramolecular cyclization then gives the product. Alternatively, path (b) involves an η^2-allylpalladium intermediate.

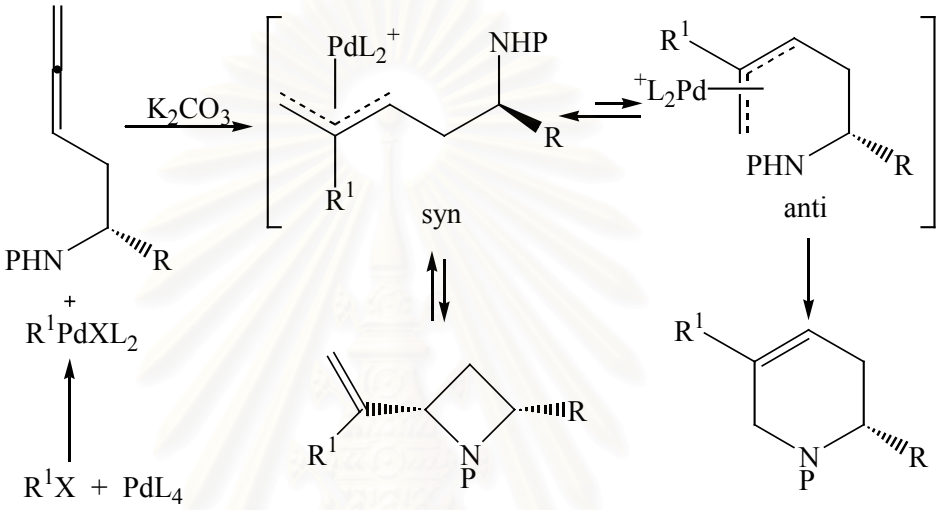
This idea has been extended by Hiemstra who demonstrated the highly selective formation of four- and six-membered rings (**scheme 19**).[14]



R' = aryl
P = Ts, Ns

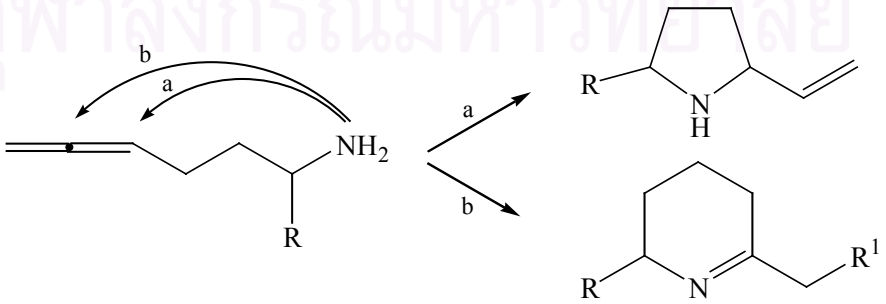
Scheme 19 Cyclization results for the unsubstituted aminoallenes

The contrasting results can be explained by two plausible intermediates: *syn*- and *anti*-π-allylpalladium complexes. The *syn*-isomer could cyclize to give the four-membered ring (kinetic product) which could, however, be isomerized to the thermodynamically more stable six-membered ring. Indeed, with extended reaction times, the tetrahydropyridines became the exclusive product.This isomerization depends on the substituents P and R^1. No pyrrolidines were isolated, indicating that the nucleophile attacks the sp^2-carbons of the allene, not the sp-carbon (**scheme 20**).[14]



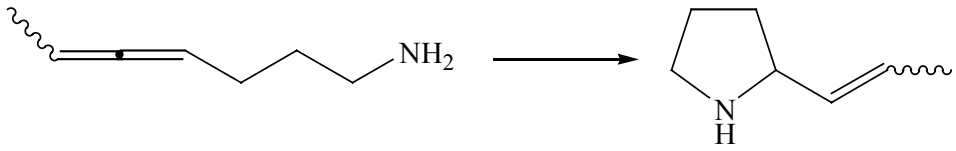
Scheme 20 A plausible intermediates of palladium-catalyzed cyclization

Marks and co-workers reported a different type of intramolecular cyclization of aminoallenes catalyzed by organolanthanide complexes. Treatment of monosubstituted aminoallenes with $Cp^*_2LnCH(TMS)_2$ afforded a mixture of tetrahydropyridines as the major product and 2-vinylpyrrolidines (**scheme 21**).[15]



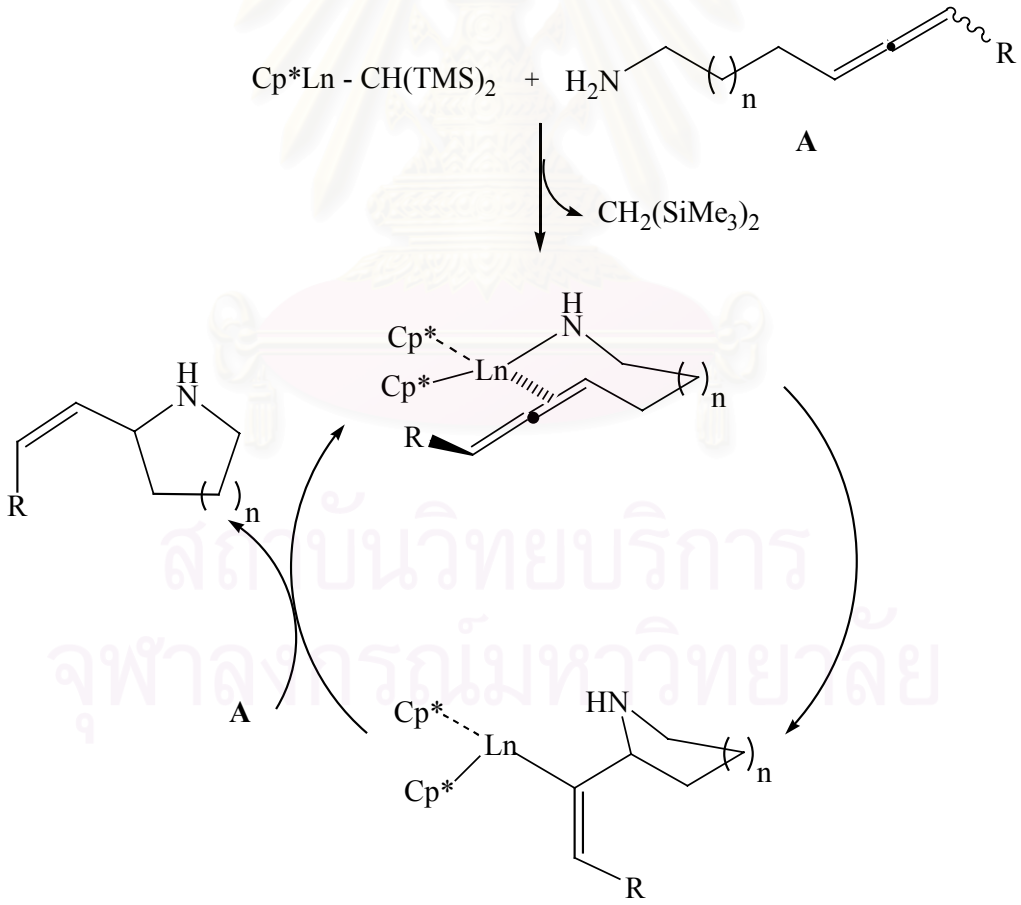
Scheme 21 The organolanthanide-mediated cyclization of aminoallenes

In addition, the reaction of 1,3-disubstituted aminoallenes afforded the desired product in which the nitrogen attacked the nearer sp^2-carbon of the allene to give the pyrrolidine in excellent yield and mostly Z selectivity (**scheme 22**).[15]



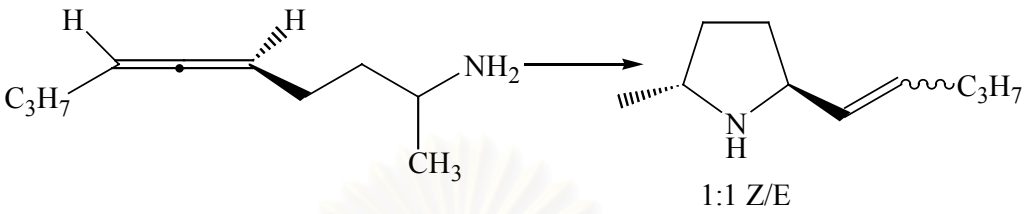
Scheme 22 The organolanthanide-mediated cyclization of 1,3-disubstituted aminoallenes

A catalytic cycle for this organolanthanide-mediated hydroamination/cyclization of aminoallenes has been proposed involving allene insertion into a lanthanide-nitrogen bond as a key step (**scheme 23)**.[15]



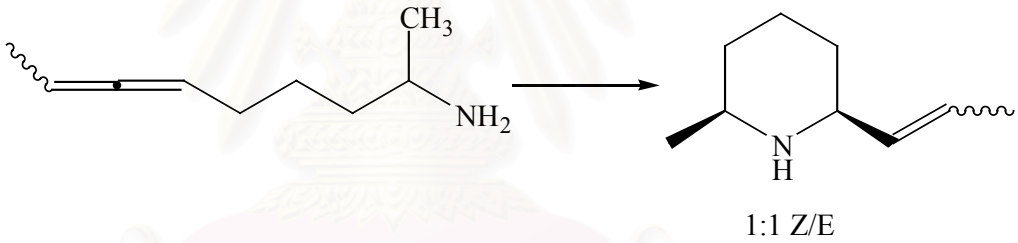
Scheme 23 A proposed catalytic cycle for organolanthanide-mediated hydroamination/cyclization of aminoallenes

The reaction of a 1,3-disubstituted aminoallene which had a substituent α to the amino group gave a *trans*-disubstituted pyrrolidine as a 1:1 mixture of Z/E isomers (**scheme 24**).[15]



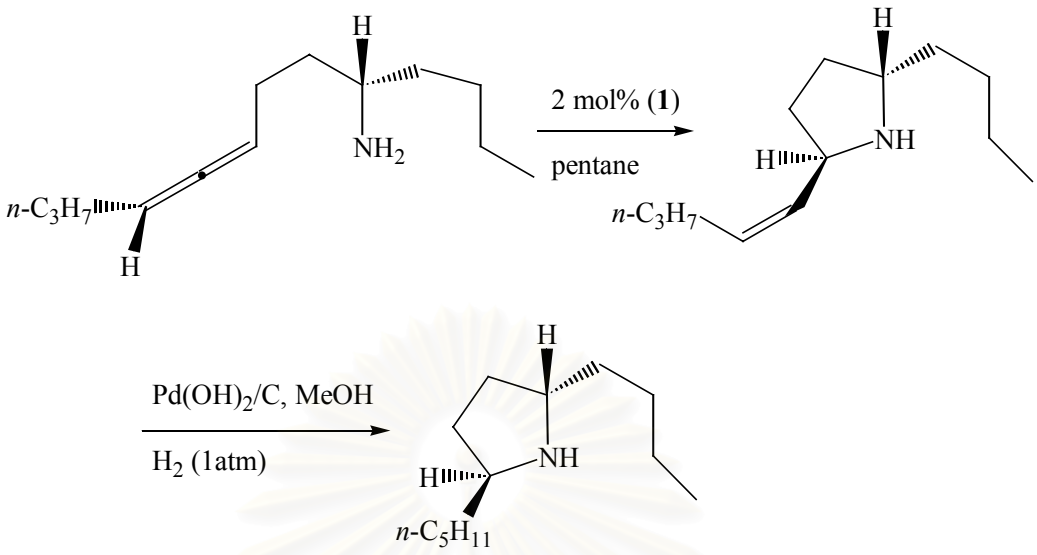
Scheme 24 The organolanthanide-catalyzed cyclization of 1,3-disubstituted aminoallenes

On the other hand, when an additional carbon was present in the tether, a piperidine was produced (**scheme 25**).[15]



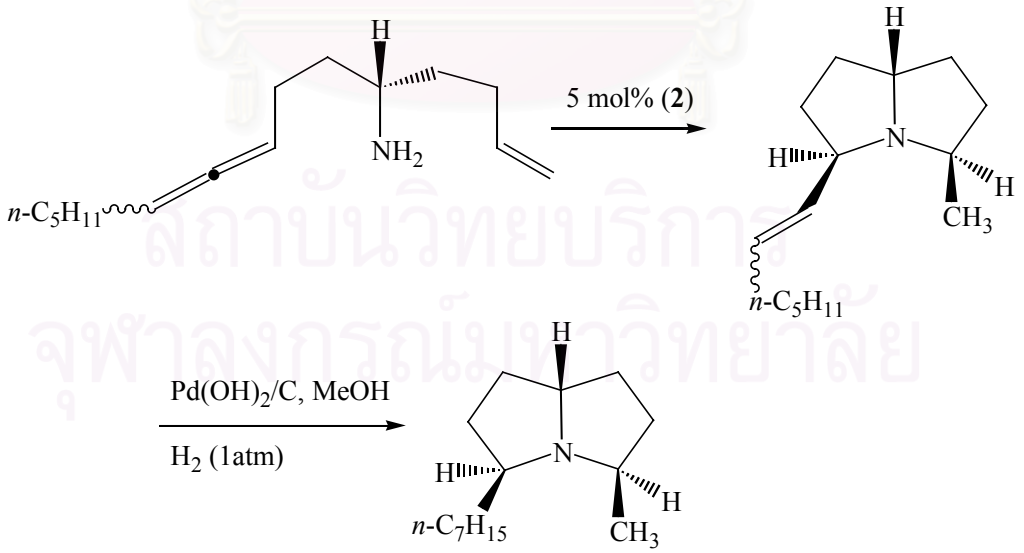
Scheme 25 The organolanthanide-catalyzed cyclization of the synthesis of *cis*-piperidine

Mark′s group reported the synthesis of the pyrrolidine alkaloid (+)-197B using this methodology. An organolanthanide complex, $Cp^*_2SmCH(TMS)_2$ (**1**), catalyzed the cyclization of (*5S*, *8S*)-5-amino-trideca-8,9-diene to afford the expected *trans* pyrrolidine with excellent Z selectivity (**scheme 26**). Reduction of the alkene then yielded the natural product.[16]



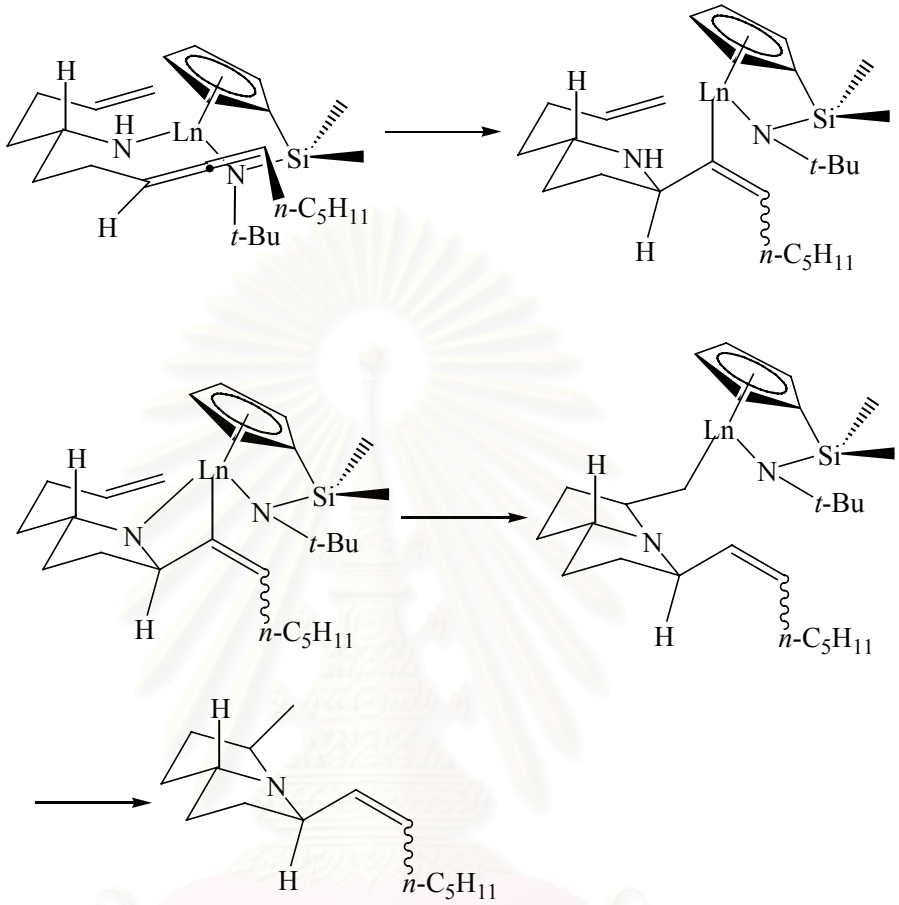
Scheme 26 The synthesis of (+)-Pyrrolidine 197B

In addition, the organolanthanide complex $Me_2Si(Me_4C_5)(tBuN)SmN(TMS)_2$ (**2**) catalyzed the bicyclization of (*5S*)-5-amino-pentadeca-1,8,9-triene to yield the bicyclic pyrrolizidine intermediate. Reduction of the double bond using $Pd(OH)_2/C$ and hydrogen afforded (+)-xenovenine (**scheme 27**).[16]



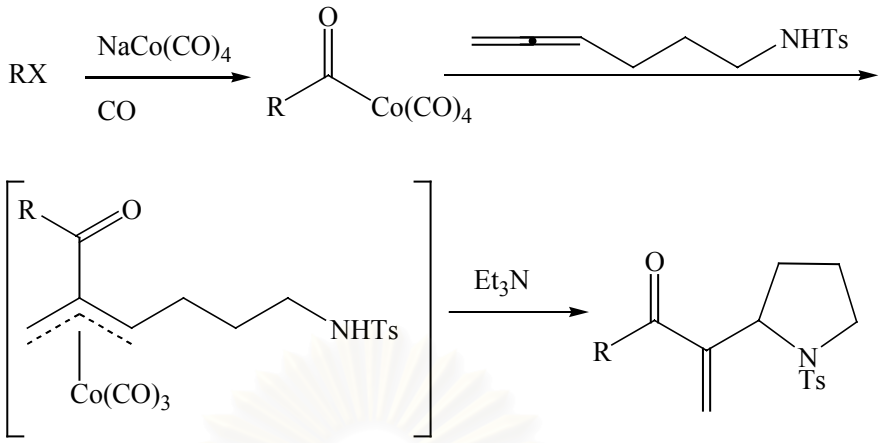
Scheme 27 The synthesis of (+)-xenovenine

A proposed mechanism of bicyclization reaction involves the protonolysis of Ln-N $(TMS)_2$ bond to generate the catalytically active lanthanide amido complex and the insertion of allene and alkene moiety (**scheme 28**).[16]



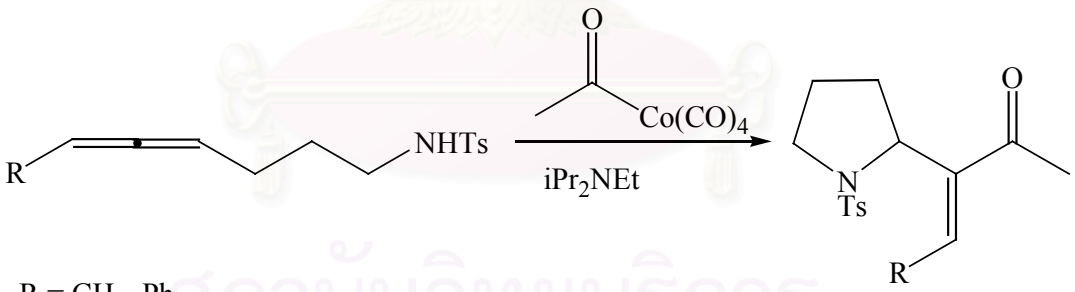
Scheme 28 Probable mechanism for the bicyclization of aminoallene-alkene (methyl group of Cp ring omited for clarily)

Recently, Bates has reported the acylation-cyclization of allenes bearing various tethered nucleophiles using cobalt complexes which were prepared by the alkylation of sodium tetracarbonylcobaltate with alkyl halides followed by insertion of carbon monoxide. In this case, treatment of monosubstituted allenes bearing sulfonamide nucleophiles with acetyltetracarbonyl cobalt in the presence of base afforded five-membered rings in good to excellent yield. The yield depended on the base and the reactivity of the halide (**scheme 29**).[17] Trialkylamines were found to be the best bases. Related intermolecular reactions had been studied by Heck and Hegedus, but were less efficient or general.



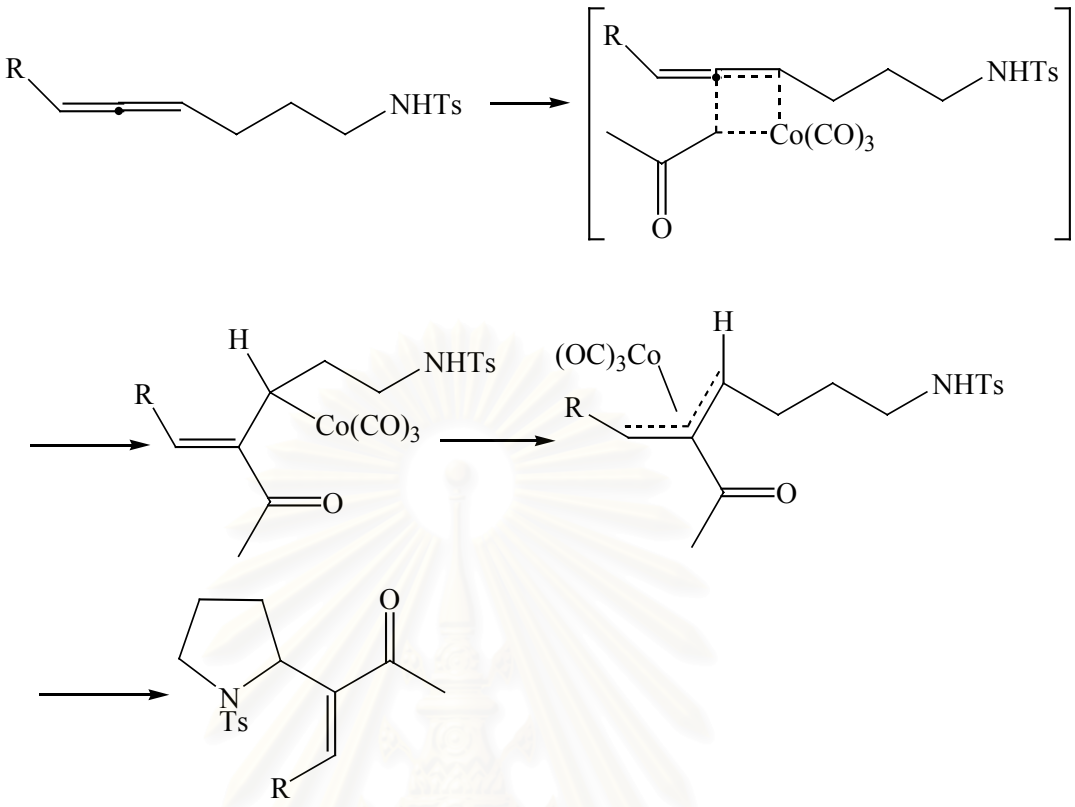
Scheme 29 Acylation-cyclization using cobalt complexes

Several classes of allenes have been used for this cobalt mediated acylation-cyclization. In addition to monosubstituted allenes, *gem*-disubstituted allenes and 1,3-disubstituted allenes were cyclized. Interestingly, the cyclization of 1,3-disubstituted allenes bearing the sulfonamide group gave the pyrrolidine with complete E selectivity (**scheme 30**).[17]



Scheme 30 The cobalt-mediated cyclization of 1,3-disubstituted allenes

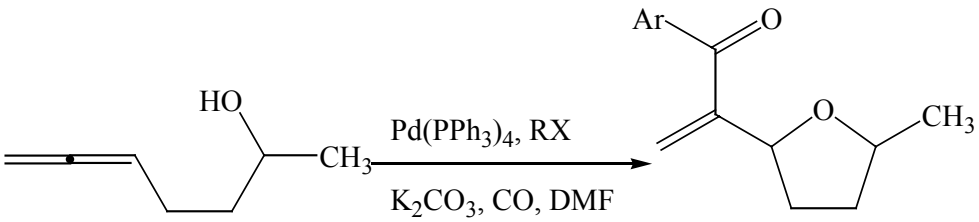
The reaction with trisubstituted allenes failed due to steric hindrance. The proposed mechanism involves the formation of an η^3-allylcobalt complex followed by nucleophilic addition (**scheme 31**).



Scheme 31 Proposed mechanism of the cobalt-mediated cyclization of 1,3-disubstituted allenes

1) C-O bond formation

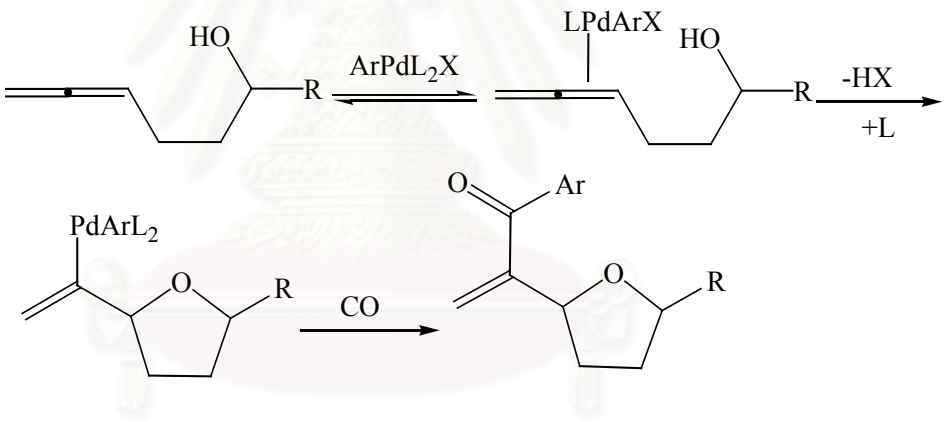
Walkup's group have shown that allenic alcohols can be regiospecifically cyclized using palladium(II) catalysts generated *in situ* from a pre-formed Pd(0) species and an aryl halide.[18] Thus treatment of 5,6-heptadiene-2-ol with $Pd(PPh_3)_4$, *p*-bromoacetophenone or *p*-bromonitrobenzene and potassium carbonate in *N,N*-dimethylformamide at 55-60°C under carbon monoxide afforded the tetrahydrofuran as the major product in moderate yield (**scheme 32**).



R = aryl

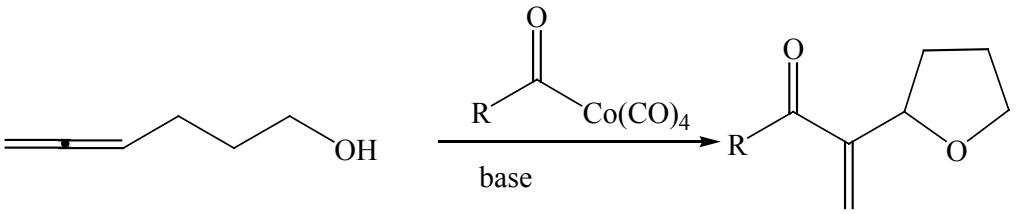
Scheme 32 The palladium-catalyzed cyclization of allenic alcohols

However, these reactions were not stereoselective, the *cis*/*trans* ratios for the isolated product being around 30:70 in favor of the *trans*-product. A possible mechanism involves a vinylpalladium intermediate which is formed *via* arylpalladium(II) halide activation of the allene followed by carbonyl insertion (**scheme 33**).[18] However, a mechanism involved an η^3-allyl intermediate cannot be ruled out.



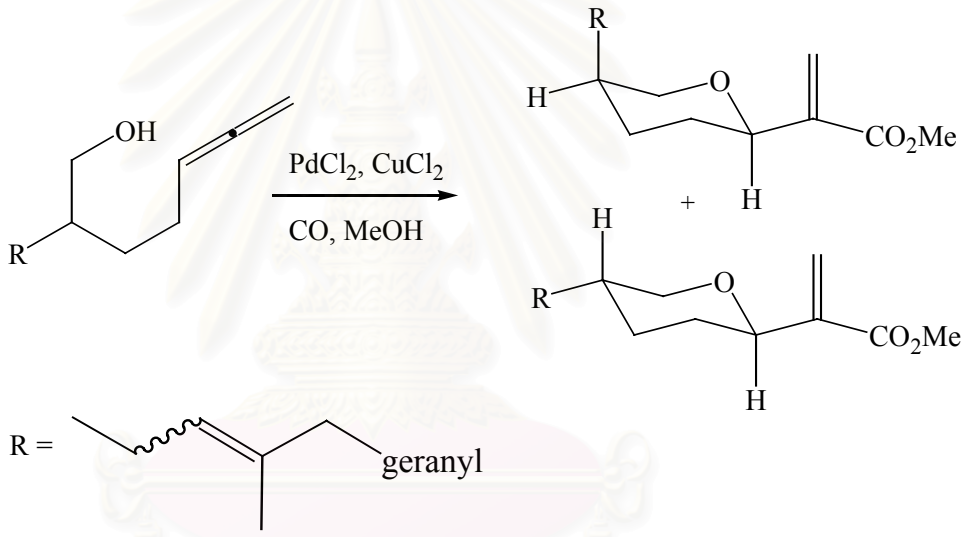
Scheme 33 A plausible mechanism for the synthesis of tetrahydrofuran

Bates has reported that the allenic alcohol can be cyclized using the acyl cobalt complexes.[17] Treatment of the monosubstituted allene with acetyltetracarbonyl cobalt and base result in cyclization to give the expected five-membered ring in moderate yield (**Scheme 34**).



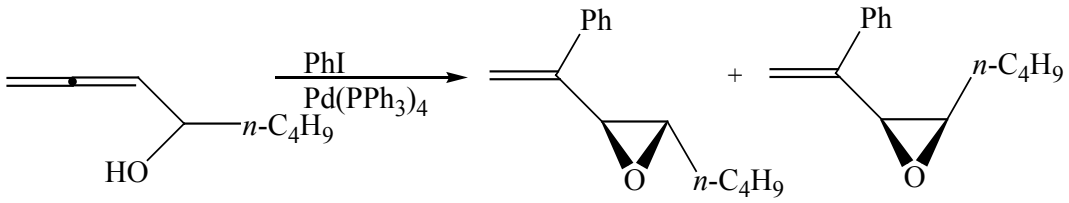
Scheme 34 The cobalt-mediated cyclization of allenic alcohols

Subsequently, Snider's group has achieved an efficient synthesis of Rhopaloate A using palladium(II) induced cyclization of an allenyl alcohol in the presence of $CuCl_2$, CO and MeOH to afford a 6:1 mixture of the desired *trans* diequatorial isomer and the *cis* isomer each as a 10:1 E/Z mixture (**scheme 35**).[19]



Scheme 35 The synthesis of Rhopaloate A

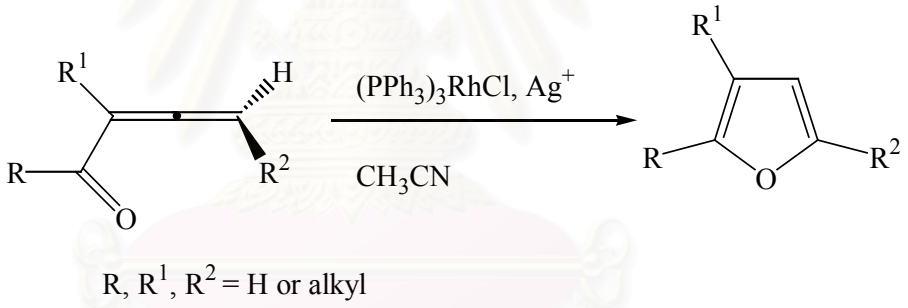
Surprisingly, Ma and Zhao have reported the highly diastereoselective synthesis of optically active *trans*-2,3-disubsituted vinylic oxiranes. Treatment of 1, 2-octadiene-4-ol with $Pd(PPh_3)_4$, PhI and K_2CO_3 in DMF as a solvent afforded a 30:1 of two diastereomers in good yield (**scheme 36**).[20]



Scheme 36 The synthesis of optically active *trans*-2,3-disubstituted vinylic oxiranes

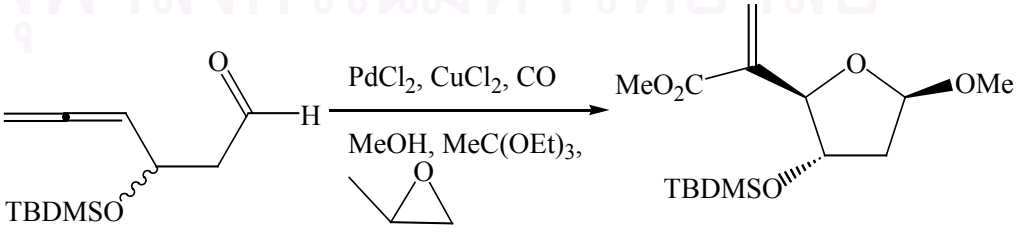
In principle, the palladium complexes can be react with the allyl epoxide product, but this is not observed here.[10]

The cyclization of allenals and allenones has also been reported by Walkup. Using catalytic amounts of Wilkinson's catalyst and a silver(I) salt in hot acetonitrile, furans were obtained in excellent yield (**scheme 37**).[21,22] The role of silver may be to generate an electrophilic Rh(I) cation.



Scheme 37 Cyclization using Wilkinson' s catalyst and a silver(I) salt

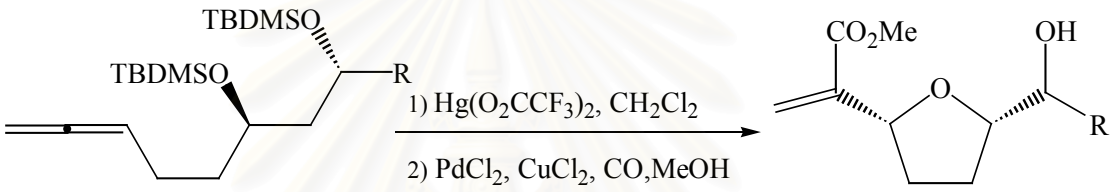
In addition, the allenals could be cyclized with a Pd(II)/Cu(II) system under carbon monoxide to produce the methyl furanosides in high yield (**scheme 38**).[18,23]



Scheme 38 Palladium-catalyzed cyclization of allenals

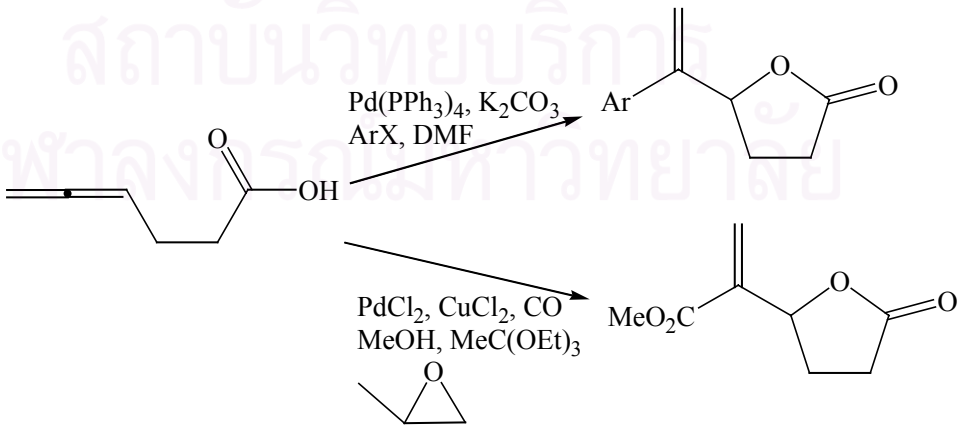
This reaction demonstrates the stereospecific cyclization-methoxycarbonylation in the presence of propylene oxide as an acid scarvenger. On the other hand, this reaction was unsuccesful for allenones, giving complex mixtures of products. The active nucleophile might be the hemiacetal which would be favoured in the ketone case.

Furthermore, Walkup has described the stereoselective cyclization of allenes bearing a silyl ether using a stepwise mercury(II)/palladium(II) protocol for the synthesis of the methyl ester moiety of the Pamamycins. These reactions involved the cyclization of silyl ethers with mercuric trifluoroacetate followed by transmetallation and methoxycarbonylation to afforded the *cis* cyclic alcohols as the major product in moderate yield (**scheme 39**).[24,25]



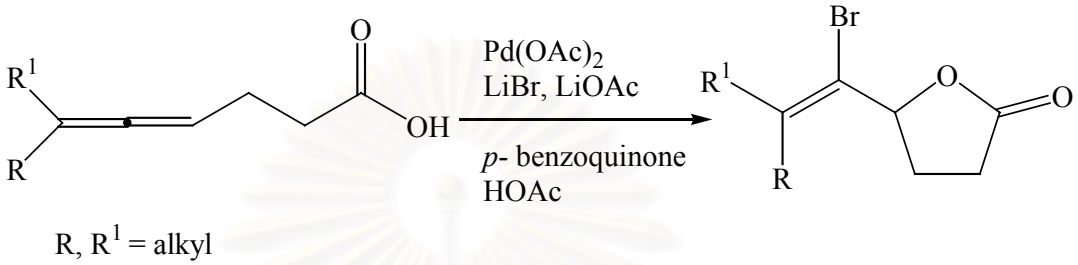
Scheme 39 Mercury(II)/palladium(II)-catalyzed cyclization

Walkup has extended the cyclization to allenic acids that could be cyclized to form the arylated lactones. Also, treatment of the allenic acid with a Pd(II)/Cu(II) mixture under carbon monoxide in methanol afforded the acrylyl substituted lactone (**scheme 40**).[23]



Scheme 40 Palladium-catalyzed cyclization of the allenic acid

Alternatively, Bäckvall showed that treatment of a γ-allenic acid with $Pd(PhCN)_2Cl_2$, acetic acid, *p*-benzoquinone as the oxidant gave no intramolecular cyclization . However, treatment of allenic acid with $Pd(OAc)_2$, *p*-benzoquinone, LiOAc and LiBr in acetic acid afforded γ-lactone product in high yield and gave the Z-stereoisomer as the major product (**scheme 41**).[26]



R, R^1 = alkyl

Scheme 41 Palladium-catalyzed 1,2-oxidation of allenic acid

A mechanism for this palladium-catalyzed intramolecular cyclization has been proposed (**scheme 42**). Palladium(II) coordinates to the allene giving an η^2-allenic palladium intermediate. This is followed bromide attack at the central allenic carbon to produce an η^3-allylpalladium intermediate. This may involve transfer of Br from palladium rather than direct nucleophilic attack on carbon. Intramolecular nucleophilic attack by the carboxylate then gives the product and a Pd(0) quinone complex which disproportionates to Pd(II) and hydroquinone. This reaction has also been applied to produce carbon-nitrogen bonds.

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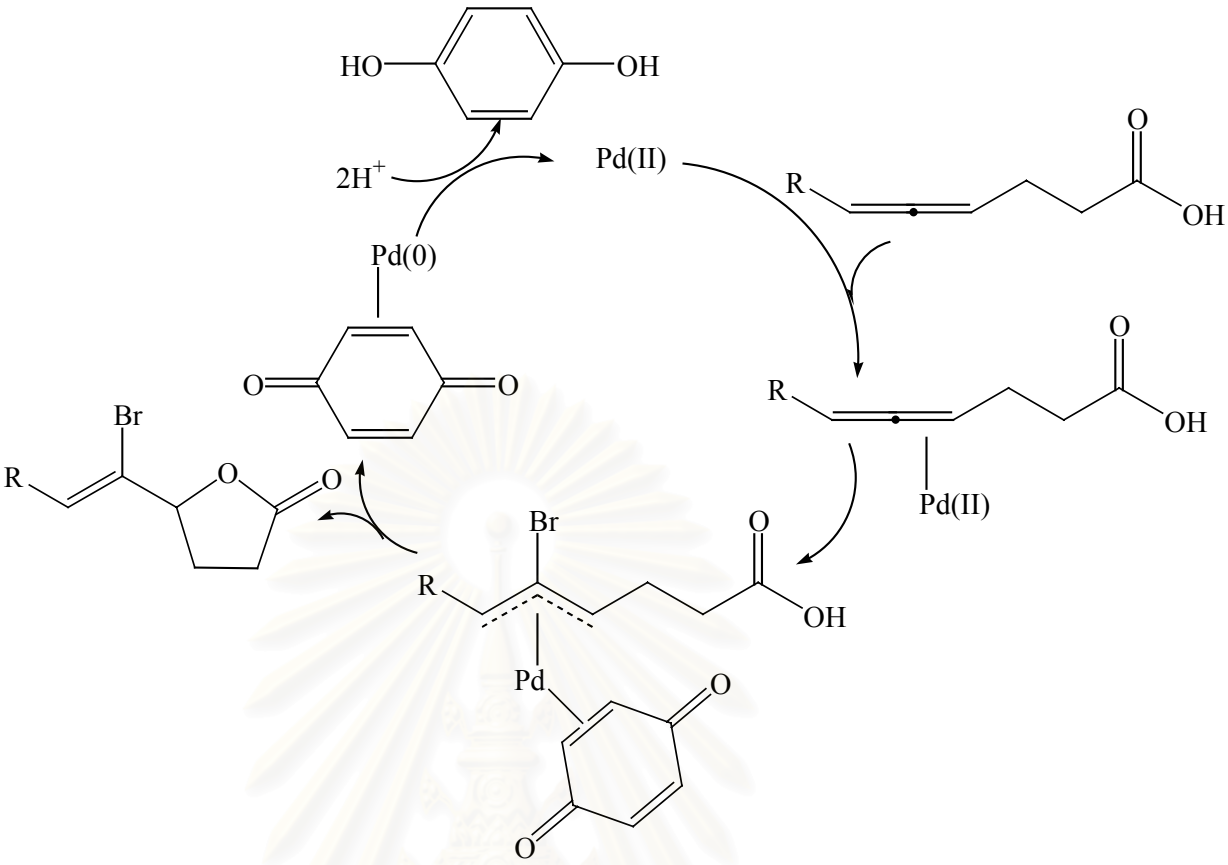
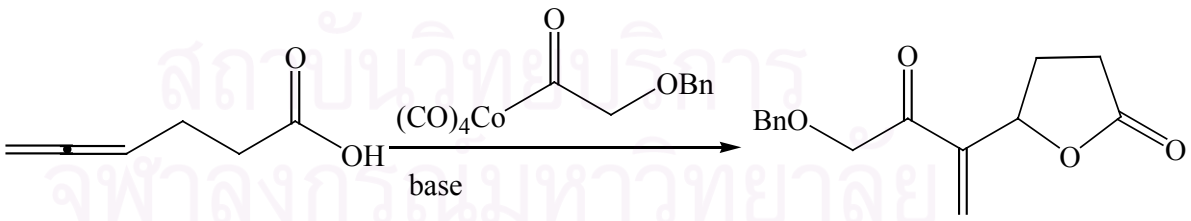


Scheme 42 A plausible mechanism for the palladium-catalyzed intramolecular oxidation

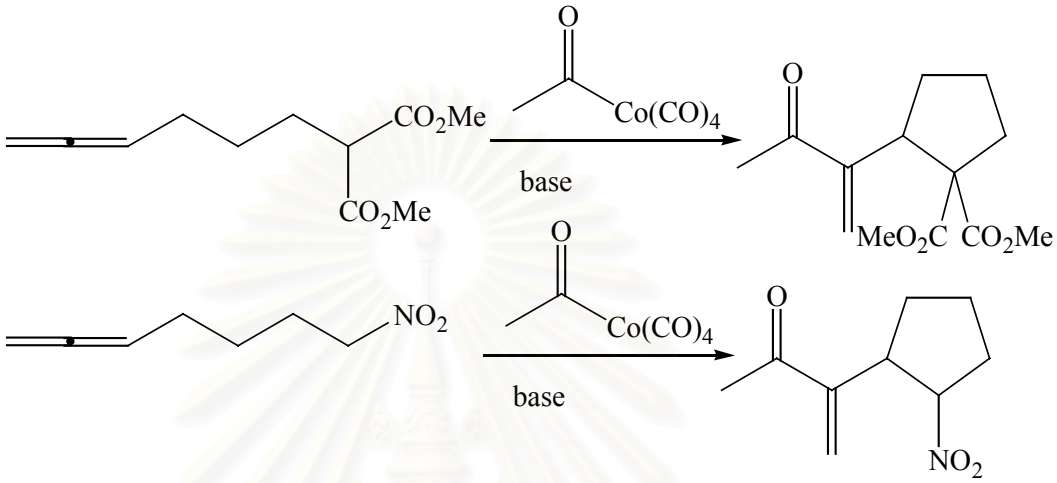
Moreover, Bates has reported the cyclization of an allenic acid using the acyl cobalt complexes to give a lactone in moderate yield (**scheme 43**).[17]



Scheme 43 Cobalt-mediated cyclization of allenic acid

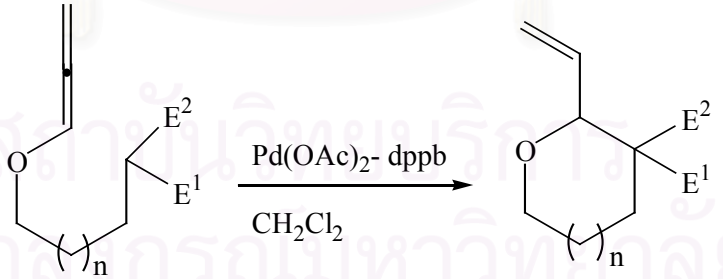
2) C- C bond formation

Interestingly, cobalt complexes mediated the cyclization of allene in which carbanions derived from malonates and a nitro compound act as the nucleophiles (**Scheme 44**). This reaction gave the expected five-membered ring in moderate to high yield depending on the base employed.[17]



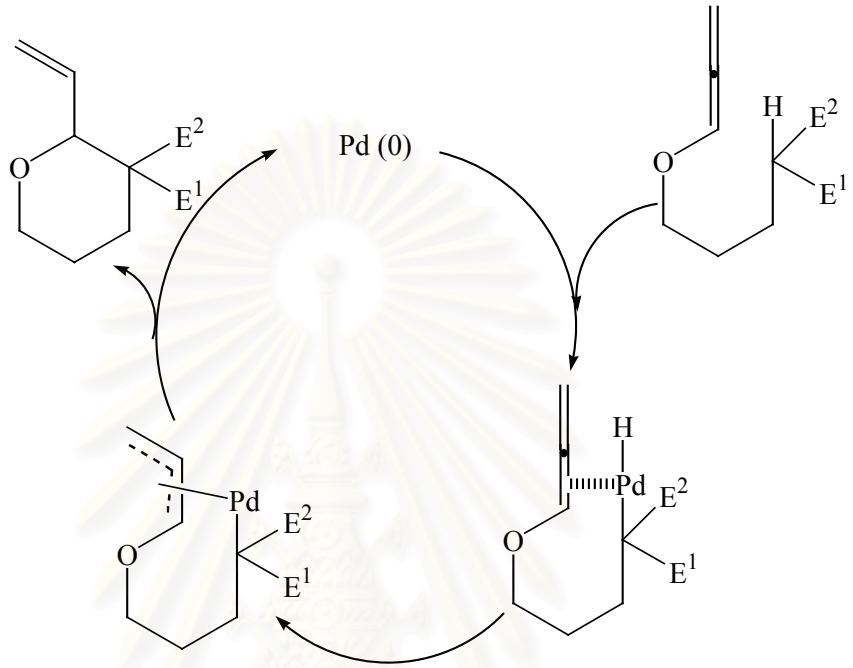
Scheme 44 Cobalt-mediated cyclization of malonates and nitro allenes

Yamamoto and co-workers have been reported the synthesis of cyclic ethers using palladium-catalyzed intramolecular hydrocarbonation of alkoxyallene. Treatment of the alkoxyallene with $Pd(OAc)_2$-dppb gave 5- to 7-membered cyclic ethers in good yield (**scheme 45**).[27]



Scheme 45 Palladium-catalyzed intramolecular hydrocarbonation of alkoxyallenes

A proposed mechanism involves the oxidative addition of palladium(0) to the C-H bond forming a hydridopalladium(II) intermediate. Insertion, forming an η^3-allylpalladium intermediate, followed by reductive elimination then gives the desired cyclic ether and regenerates the Pd(0) catalytic species (**scheme 46**).



Scheme 46 A proposed mechanism of the synthesis of cyclic ethers

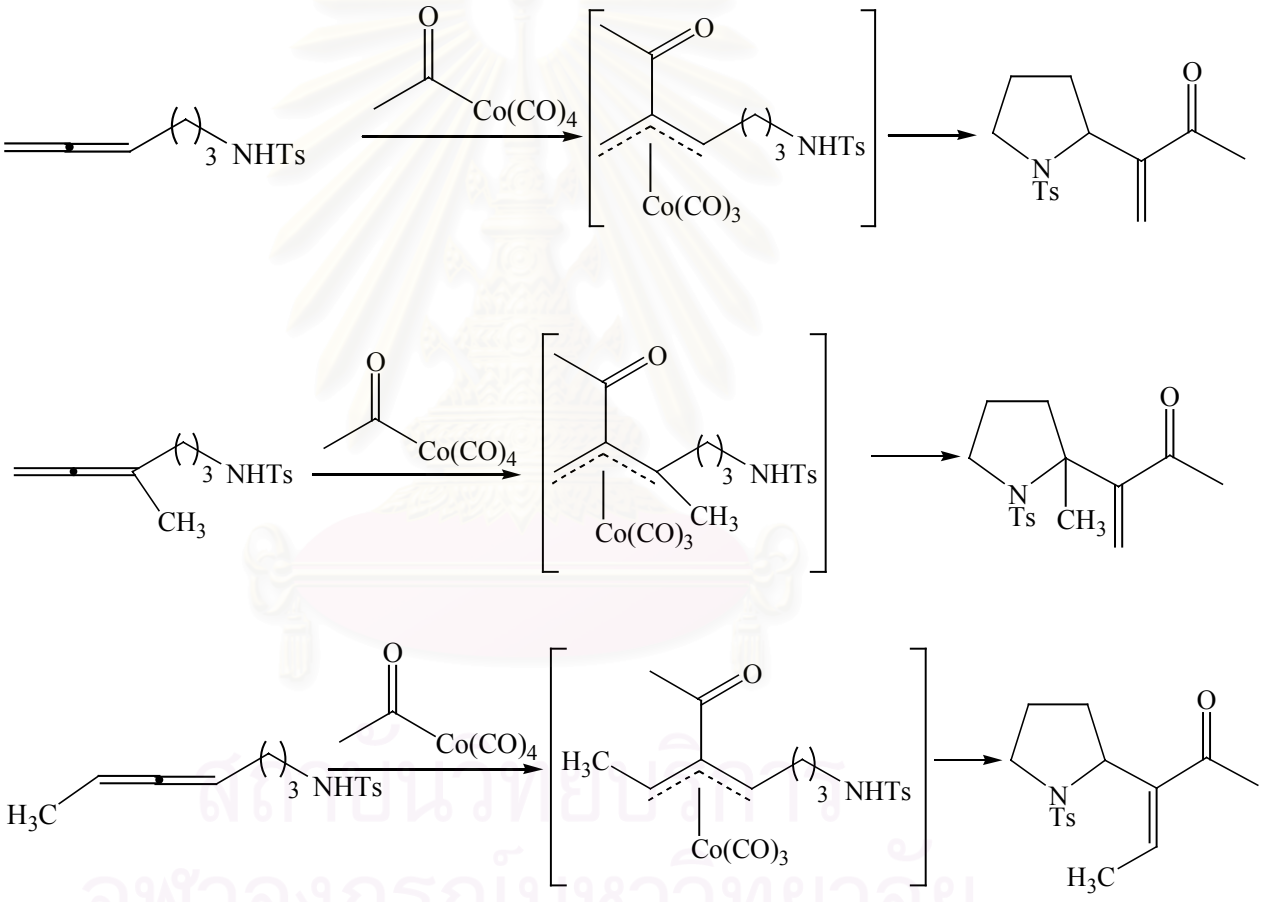
In conclusion, several transition metals have been used to induce intramolecular cyclization of several types of allenes to form both carbocycles and heterocycles. Palladium has, predictably, been most widely used. There is, however, considerable scope to employ other transition metals. An important aspect that needs further exploration is the diastereoselectivity of the reaction.

This chemistry has only been used for a few total syntheses, further applications can, however, be expected.

CHAPTER II

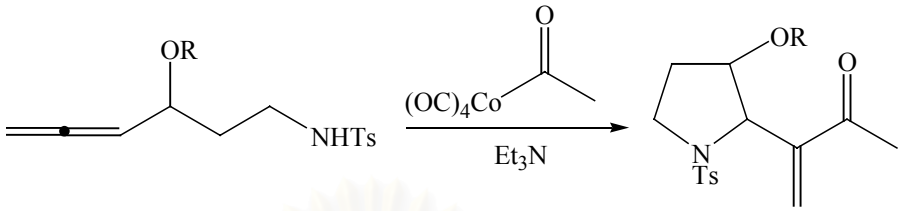
RESULTS AND DISCUSSION

The aim of this work was to develop a method for the preparation of 2,3-disubstituted pyrrolidines using the organocobalt methodology previously developed. Recently, the acylation-cyclization reaction of monosubstituted, *gem*-disubstituted and 1,3-disubstituted allenes using acyl cobalt reagents was reported to be an efficient route for the synthesis of pyrrolidines and other cyclic compounds (**scheme 47**).[17]



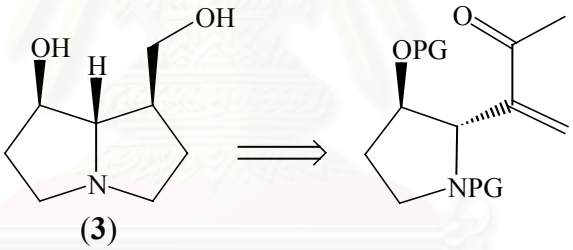
Scheme 47 Acylation-cyclization reaction of monosubstituted, *gem*-disubstituted and 1,3-disubstituted allenes

We were interested in examining the influence of a protected alcohol group α to the allene on the reaction and to determine the stereochemistry of the resulting pyrrolidines (**scheme 48**).



Scheme 48 The acylation-cyclization reaction of α substituted allene

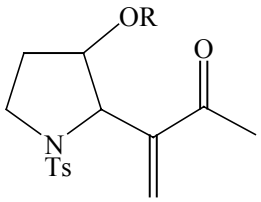
The products could be intermediates for the synthesis of hydroxylated pyrrolizidines such as hastanecine (**3**). In this case, the *trans* isomer of the pyrrolidine would be required to be the source of the hydroxy substituted pyrrolidine ring (**scheme 49**).



(**3**)

Scheme 49 Retrosynthesis of the hydroxylated pyrrolizidine

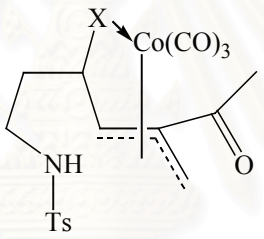
The acylation-cyclization reaction of α-substituted allenes using acyl cobalt reagents can give *trans*-pyrrolidines and *cis*-pyrrolidines. A hypothesis to predict the stereochemical results might involve two factors: firstly, the possibility of coordination between the substituent OR group and the cobalt atom, and secondly, the reactive conformation of the η^3-allylcobalt intermediates. We chose several common protecting groups for the O-substitutuent: *tert*-butyldimethylsilyl, triisopropylsilyl, benzoyl and benzyl. These represent the three major sets of alcohol protecting groups: silyl ethers, esters and alkyl ethers (**scheme 50**). Knowledge of the behavior of these groups would be important for synthetic planning in subsequent work.



R= *t*-$BuMe_2Si$, $(iPr)_3Si$, PhCO, Bn, CH_3SCH_2

Scheme 50 The hydroxy substituted pyrrolidine

In addition we chose the methylthiomethyl group. This would be most likely to exhibit coordination of cobalt because sulfur is a soft atom (**scheme 51**). The effect of a sulfur containing substituent on the course of the Pauson-Khand reaction has been noted. [28]

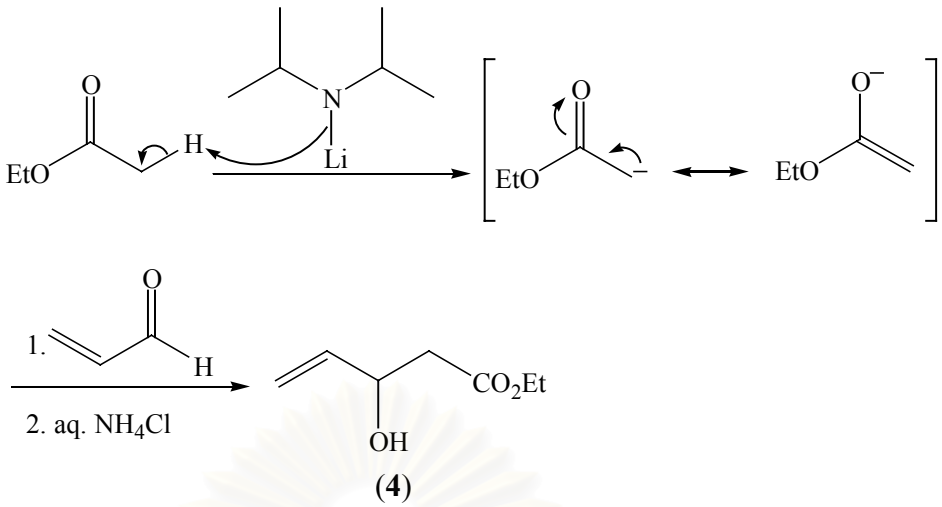


X= OCH_2SCH_3

Scheme 51 The chelation effect between sulfur and cobalt

II.1 The synthesis of the substituted allenes

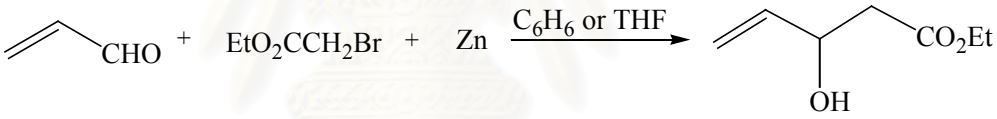
Enolate chemistry was used for the synthesis of ethyl-3-hydroxy-4-pentenoate (**4**) according to the reported procedure using acrolein, ethyl acetate and LDA (**scheme 52**).[29] The ^1H NMR spectrum of the crude product was clean and the product could be used without further purification. Only the 1,2-addition product was observed.



(**4**)

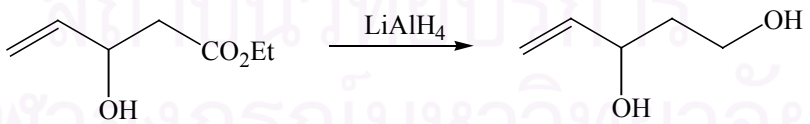
Scheme 52 The mechanism of the synthesis of the ester

The same compound can also be prepared by a Reformatsky reaction (**scheme 53**).[30] This method is, however, less reliable because an unpredictable induction period is observed. The reaction can also highly exothermic.



Scheme 53 Reformatsky reaction

Reduction of the ester function was achieved using lithium aluminium hydride to produce the diol (**5**) (**scheme 54**).[30]



(**5**)

Scheme 54 Reduction of the ester function

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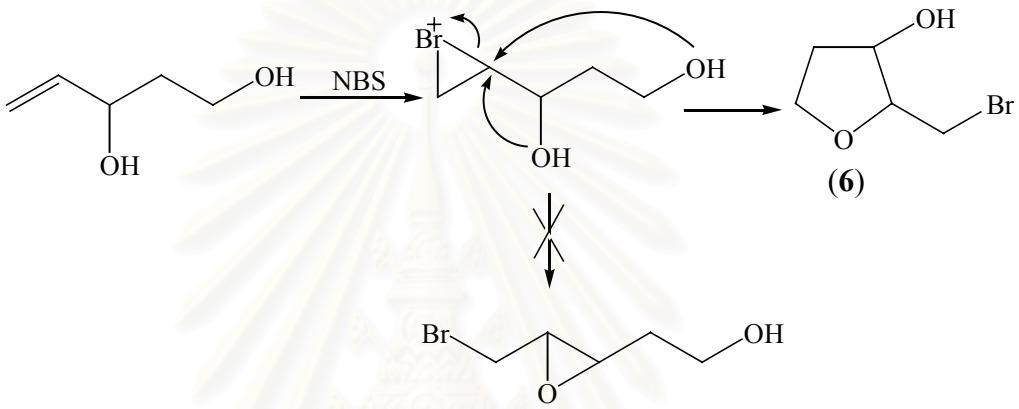
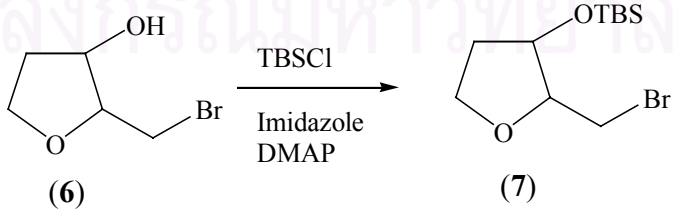
It was then necessary to oxidize the alkene to an alkyne, a reaction which can only be done indirectly. It was also necessary to differentiate the two alcohol groups, as one must be protected, and the other converted to a nitrogen nucleophile. Electrophile-induced cyclization on treatment of the diol with *N*-bromosuccinimide (NBS) yielded the tetrahydrofuran. In one step, it was thus possible to oxidize the alkene and differentiate the alcohols. This reaction *via* bromonium ion formation and trapping by one alcohol group, involves a favoured 5-*exo*-tet ring closure to produce the 5-membered ring (**6**) (**scheme 55**).[31]



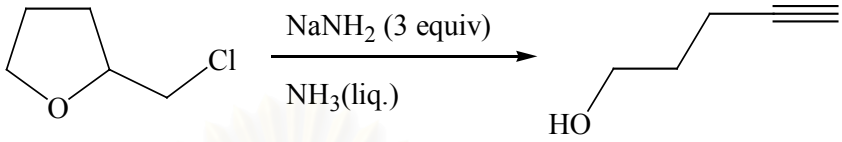
Scheme 55 Electrophile-induced cyclization reaction

The unprotected hydroxy substituted tetrahydrofuran (**6**) was unstable, therefore the remaining hydroxy group was protected as its *tert*-butyldimethylsilyl ether (**7**). This group is stable to the strong base required in a further reaction (**scheme 56**).[32] The product was mainly a single isomer. On the basis of Yoshida′s work,[33] this may be assigned *cis*-stereochemistry. This point was not, however, resolved as the stereochemistry is destroyed in subsequent steps.



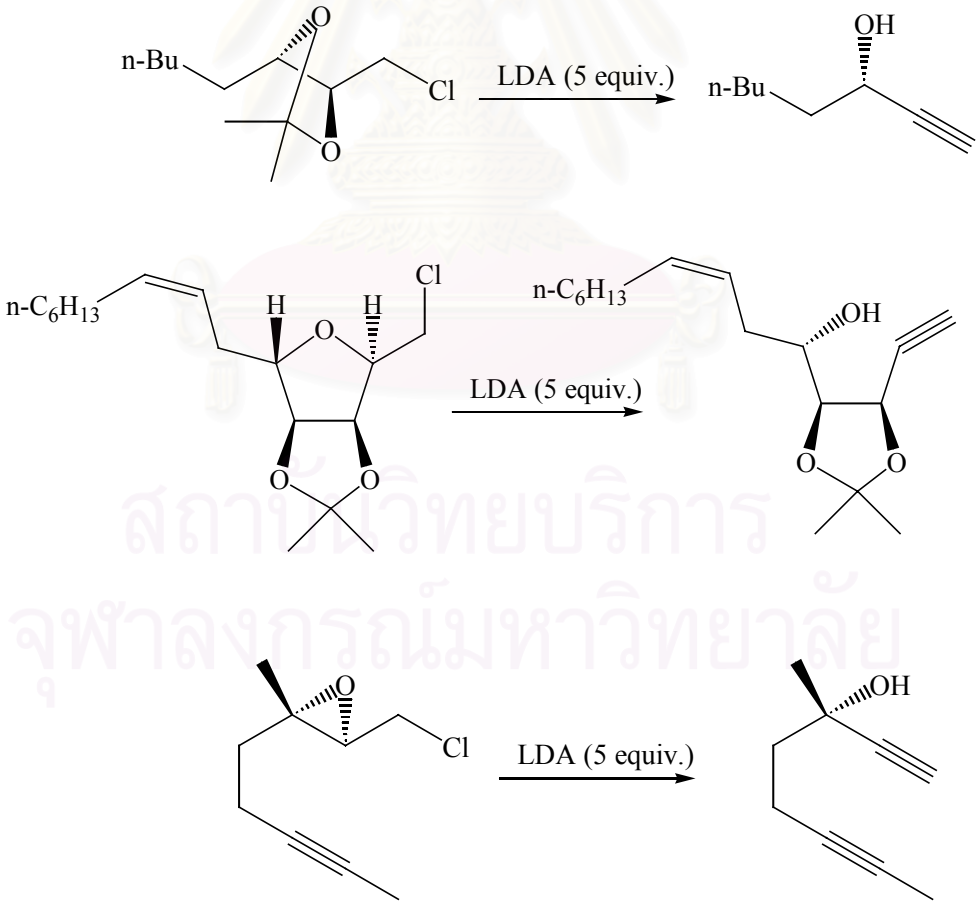
Scheme 56 Protection of the hydroxy group

Elimination with ring opening was achieved by treatment with an excess of LDA to give the alkynol. This reaction was originally reported by E.R.H.Jones using sodium amide for the preparation of 4-pentyn-1-ol from tetrahydrofurfuryl chloride (**scheme 57**).[34]



Scheme 57 Elimination reaction with sodium amide

Recently, it has been extended by Yadav, who has successfully used related eliminations for the preparation of optically active 3- and 5-hydroxyalkynes (**scheme 58**).[35,36,37]



Scheme 58 Elimination reactions with LDA

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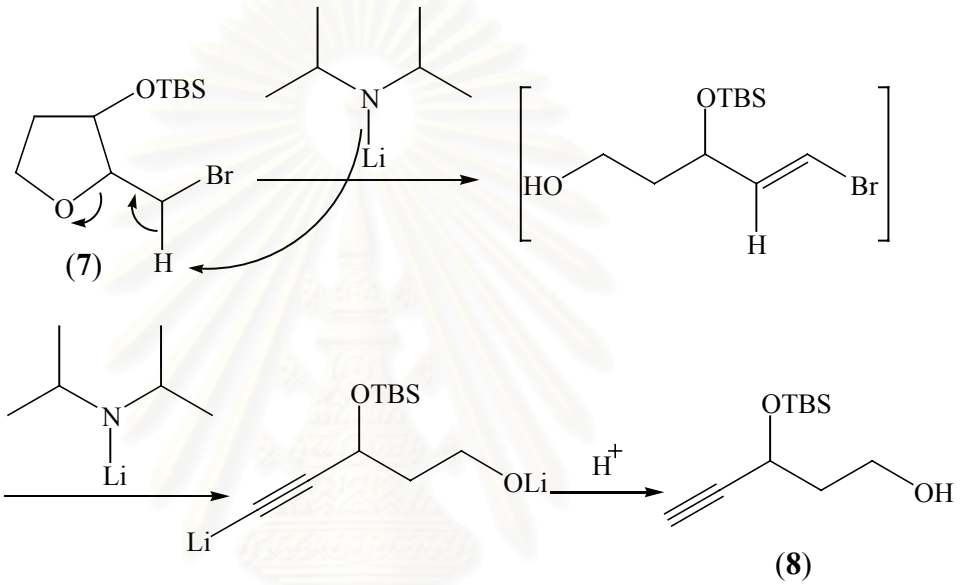
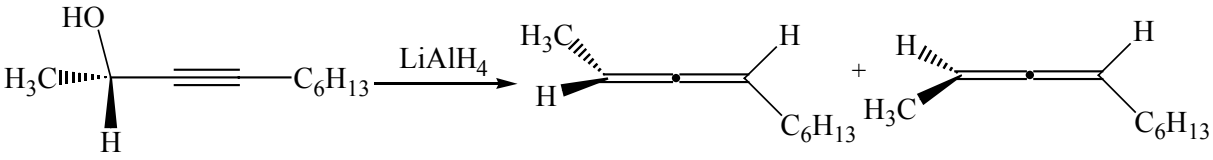
The product, a terminal alkyne (**8**), is deprotonated by the base employed, therefore, a large amount of LDA is required. The elimination proceeds *via* an initial deprotonation α to the halogen followed by elimination of the ether oxygen, affording an alkenyl halide intermediate. Yadav has reported that such vinyl halide intermediates can be isolated if the amount of the base is limited to one equivalent. Alkyne-forming involves a second equivalent of the base in a dehydrohalogenation reaction (**scheme 59**).



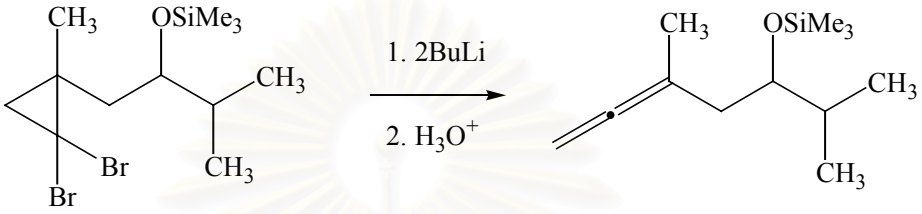
Scheme 59 The mechanism of the elimination reaction

The product was formed in moderate yield under the same conditions as reported by Yadav. Use of sodium amide, on the other hand, gave none of the desired product.

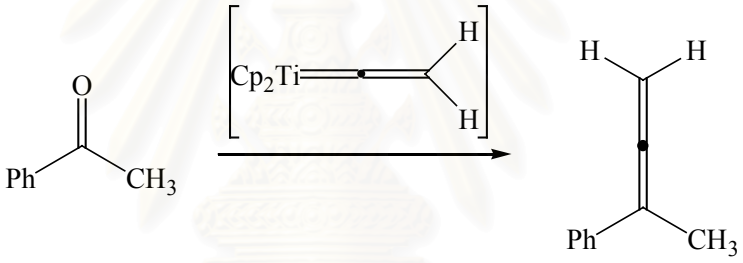
There are several methods to form allenes, including S_N2' substitution on propargyl derivatives (**scheme 60**),[38,39] rearrangement of cyclopropylidene carbenes (**scheme 61**),[40] allenation of carbonyl compounds with alkenyltitanocene derivatives (**scheme 62**)[41] and coupling of aldehydes with prop-2-ynyl bromides using an indium-mediated reaction in an aqueous medium (**scheme 63**).[42]



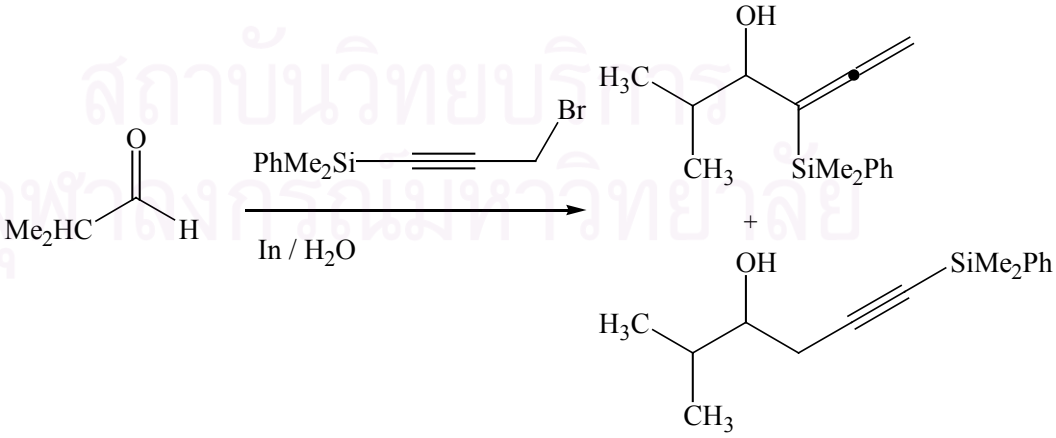
Scheme 60 S_N2' substitution on propargyl derivatives



Scheme 61 Rearrangement of cyclopropylidene carbenes (Skatterbϕl reaction)

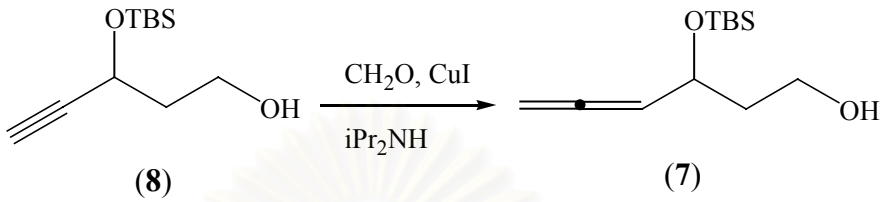


Scheme 62 Allenation of carbonyl compounds with alkenyltitanocene derivatives



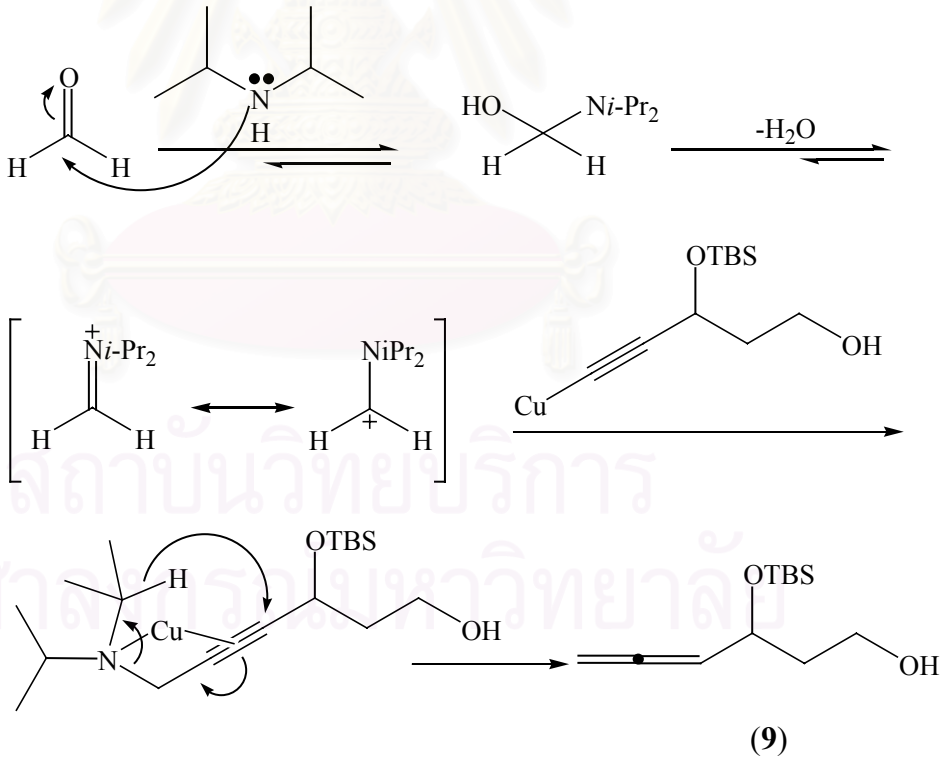
Scheme 63 Indium-mediated allenation

However, the Searles-Crabbé reaction is convenient and uses readily available reagents. Transformation of the alkyne function to the allene (**9**) was carried out according to the Searles-Crabbé procedure using paraformaldehyde, diisopropylamine and a catalytic amount of cuprous iodide in dioxane (**scheme 64**).[43]



Scheme 64 The Searles-Crabbé reaction

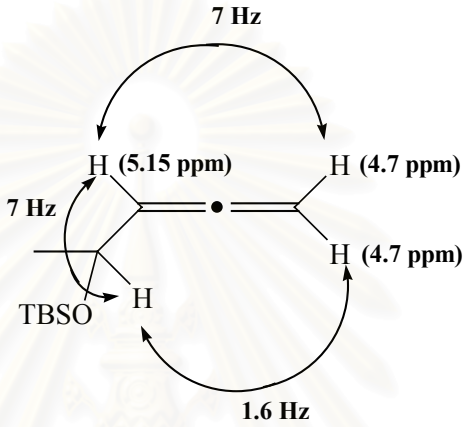
Based on labelling studies, Searles et al suggested a possible mechanism involving a Mannich reaction and a [1,5]-sigmatropic rearrangement of hydrogen which is encouraged by chelation of the cuprous ion by the triple bond and the nitrogen atom



(**scheme 65**).

Scheme 65 The mechanism of the synthesis of the allenes

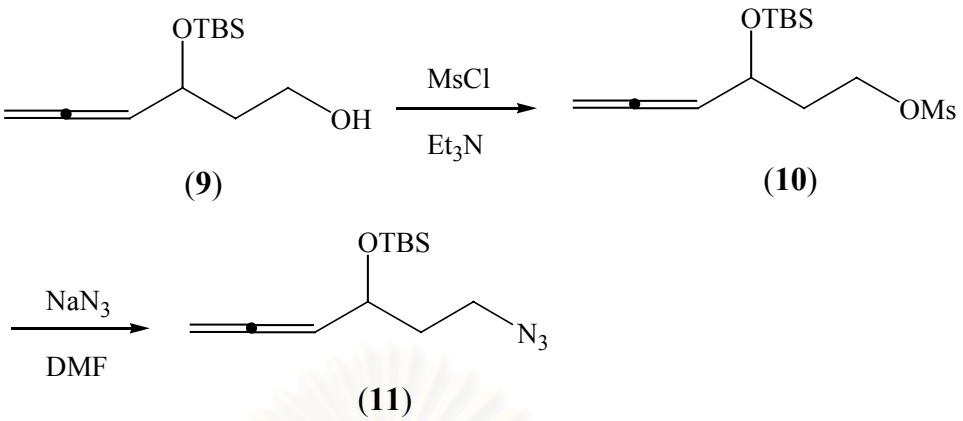
This procedure gave a higher yield of purified product compared with most examples reported by Searles *et al*. This high yield can be attributed to the inductive effect of the *tert*-butyldimethyl silyl ether moiety, possibly increasing the electrophilicity of the alkyne. The ^{1}H NMR spectrum clearly showed that the presence of the allene protons. They were found to be a double doublet (4.7 ppm) with coupling constants equal to 1.6 and 7 Hz and 5.15 ppm which was found to be a quartet with a coupling constant equal to 7 Hz (**scheme 66**).



Scheme 66 Coupling constant diagram for an allene

The highly characteristic carbons of the allene appeared in the ^{13}C spectrum at 76 ppm, 92 ppm and 208 ppm and the allene stretching frequency in the IR spectrum was found at 1956 cm^{-1}. All of there values are fully consistant with literature reports.[44]

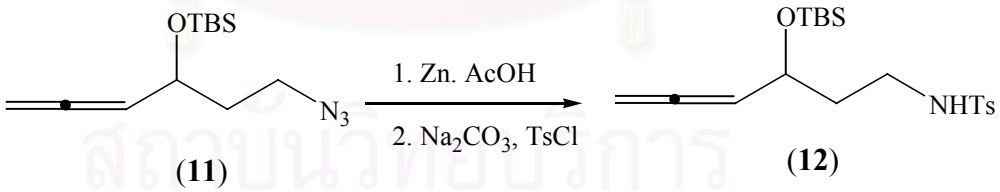
To introduce the sulfonamide moiety, the primary alcohol (**9**) was converted to a leaving group, the mesylate (**10**), then treated with sodium azide in DMF. The desired azide (**11**) was obtained but unsaturated azides are thermally labile materials.[45] It was, therefore, used immediately after synthesis (**scheme 67**). The presence of the azide moiety could be confirmed by the appearance of the azide stretching bond in the IR spectrum at 2100 cm^{-1}.



Scheme 67 Transformation of the hydroxy to azide moiety

Previously, direct substitution of mesylate by the sodium salt of *p*-toluene sulfonamide has been used to introduce nitrogen[17] but this requires high temperatures, and can result in di-N-alkylation by-products. In addition separation of the product from excess sulfonamide can be difficult. Therefore the azide route is now prefered, although it involves more steps.

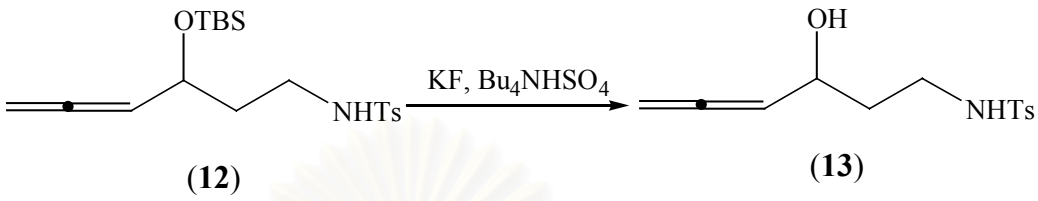
Reduction of the azide (**11**) was achieved using activated zinc under mildly acidic conditions,[46] then treatment with sodium carbonate and tosyl chloride produced the first allenic sulfonamide (**12**) required for the acylation-cyclization (**scheme 68**). Isolation of the intermediate amine was unnecessary.



Scheme 68 Transformation of the azide to the sulfonamide moiety

Azide can be reduced by a variety of low valent metals,[47] amongst which zinc is perhaps the most economical. Azides are not very reactive to hydride reagents, but are rapidly reduced by catalytic hydrogenation. We did not use this method due to the presence of the allene.

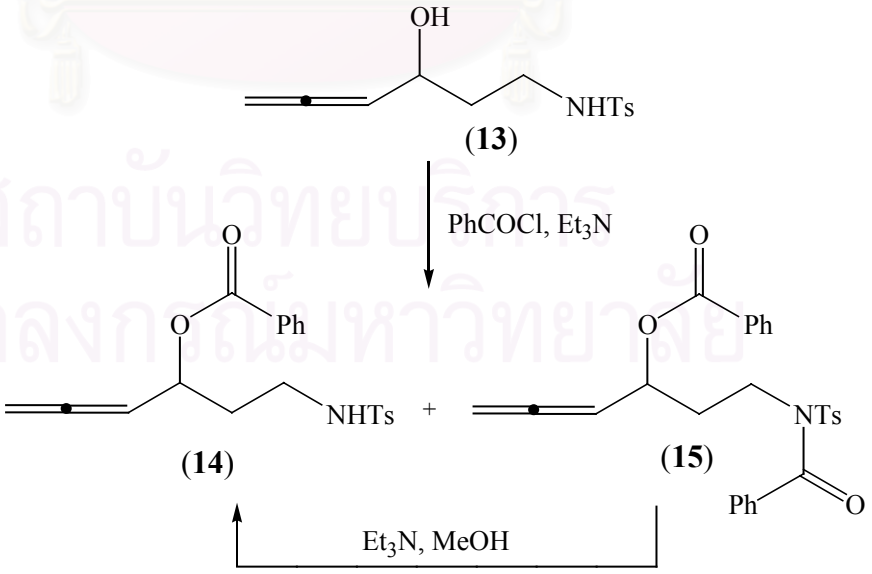
To obtain other derivatives, removal of the TBS group from the allenic sulfonamide (**12**) was carried out using potassium fluoride and tetrabutylammonium hydrogensulfate.[48] This mixture is cheaper than the normally used tetra-*n*-butylammonium fluoride (**scheme 69**).



(**12**) (**13**)

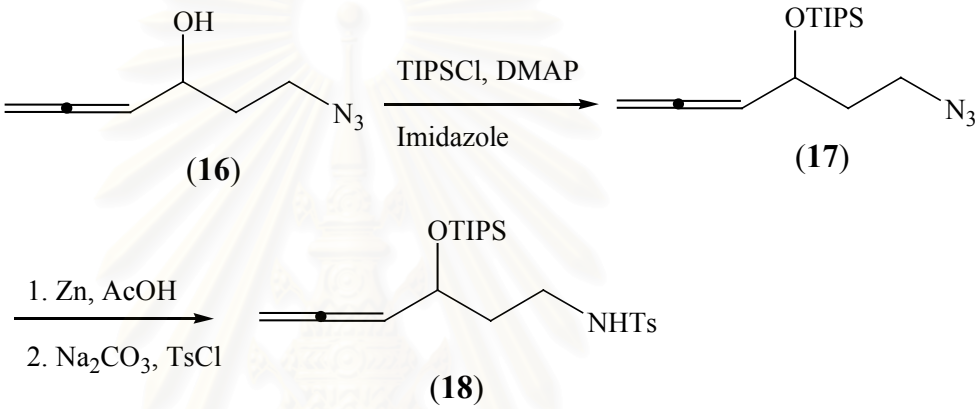
Scheme 69 Deprotection of the TBS group

On treatment with benzoyl chloride, we expected that only the O-acylated product would be obtained, not the N-alkylated product due to the low reactivity of the sulfonamide nitrogen. However, this reaction produced a mixture of the O-benzoylated (**14**) and O- and N-dibenzoylated compounds (**15**). This latter compound could be selectively N-debenzoylated on treatment with methanolic triethylamine (**scheme 70**). The selectivity may be attributed to the better leaving group ability of the sulfonamide compared to the alcohol.

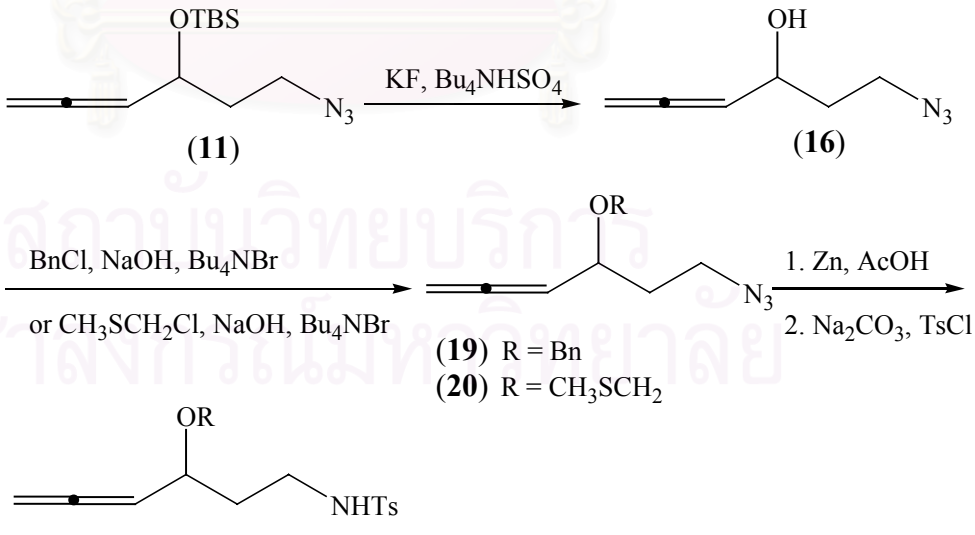


Scheme 70 Benzoylation and N-debenzoylation

Attempts to O-alkylate with selectivity were disappointing, therefore, for ether derivatives, we returned to the azide which was deprotected using potassium fluoride and tetrabutylammonium hydrogensulfate to give the azidoalcohol (**16**). O-alkylation using phase-transfer catalysis, tetra-*n*-butylammonium bromide and sodium hydroxide yielded the benzyl (**19**) and MTM ethers (**20**).[49] It has been reported that secondary MTM ethers are difficult to make by Williamson synthesis,[50] however, this method is efficient (**scheme 72**). Moreover, O-silylation using TIPSCl, DMAP and imidazole gave the triisopropylsilyl ether (**17**) (**scheme 71**).[51] All of these three ethers were converted to the sulfonamides using the method already described.



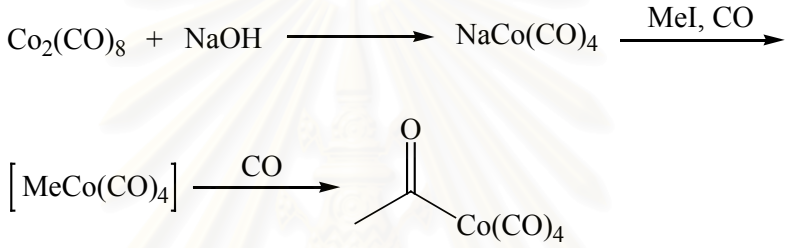
Scheme 71 The synthesis of the triisopropylsilyl ethers



Scheme 72 Synthesis of the benzyl and MTM ethers

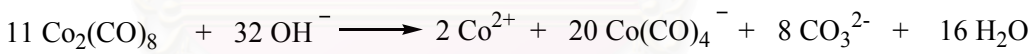
II.2 The acylation- cyclization reaction

Treatment of octacarbonyl dicobalt with powdered sodium hydroxide in THF yields sodium tetracarbonyl cobaltate. The THF solution of the salt can be separated from the excess NaOH and Co by-products by filtration under an inert atmosphere. This air sensitive salt is best stored as a THF solution under a carbon monoxide atmosphere. It is known that alkylation of sodium tetracarbonyl cobaltate with reactive alkyl halides, especially methyl iodide, followed by carbon monoxide insertion gives the corresponding acyl tetracarbonyl cobalt complexes (**scheme 73**) *via* the unstable alkyl complex intermediate.[17] All of these low valent cobalt reagents are highly sensitive to air. They are best handled under carbon monoxide.



Scheme 73 Generation of acyl tetracarbonyl cobalt complexes

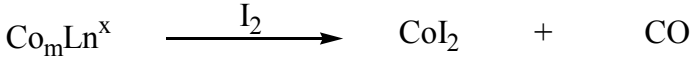
The stoichiometry of the reaction has been reported by Hieber (**scheme 74**).[52]



Scheme 74 The stoichiometry of the reaction

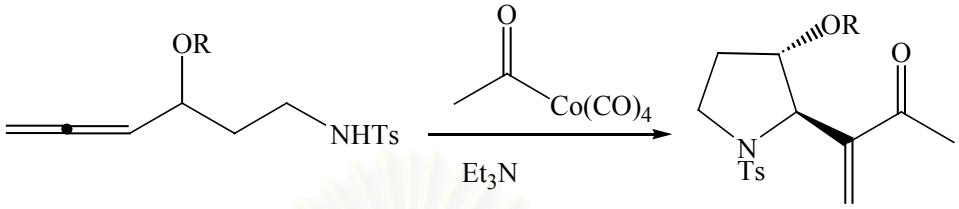
Although the cobaltate solution can be gasimetrically titrated,[53] this is not necessary because the solutions have concentrations close to the theoretical values.[53]

Treatment of the allenic sulfonamide with acetyltetracarbonyl cobalt and triethylamine result in smooth cyclization. Removal of the residual cobaltcarbonyl complexes was achieved by addition of iodine until the color of iodine became permanent and no further gas evolution was observed (**scheme 75**).



Scheme 75 Removal of the residual cobaltcarbonyl complexes

In most cases, two diastereomers of the pyrrolidine was obtained (**scheme 76**). The gross structure of the products could be determined by comparison of key spectroscopic features with those previously reported. Specifically, the three protons α to N and the geminal pair of vinyl protons are quite characteristic.



Scheme 76 The acylation-cyclization using cobalt complexes

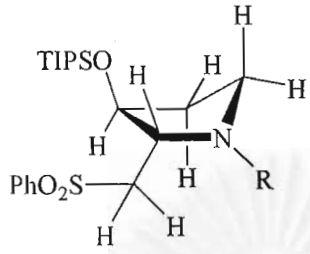
Table 1 The result of the cobalt mediated acylation cyclization

[a] after recovered starting material

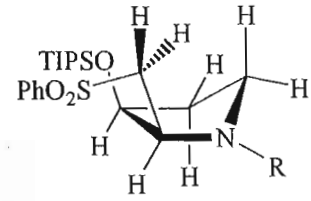
Compound	R	Trans (yield) (a)	Cis (yield) (b)	Ratio
23	TBS	74	2.8	26:1
24	COPh	28	-	-
25	CH_3SCH_2	24	6.7	3.6:1
26	Bn	36	1.4	26:1
27	TIPS	71[a]	-	-

In all cases, the *trans* isomer of the pyrrolidine was the major product. The diastereoselectivity was determined by observation of the H2-H3 coupling constant. The ^{1}H NMR spectra clearly showed that this coupling constant in the major isomer was always about 0 Hz. According to the Karpus relationship this corresponds to a dihedral angle of about 90°. Observation of molecular models of the *trans* pyrrolidine is consistant with this number. For the *cis* isomer, where isolated, the coupling constant was larger, about 4.5 Hz. Molecular models indicate an angle of about 30° (**Figure 1, 2**) and it was impossible to access a conformation with a greater angle. A similar stereochemical assignment was reported by Carretero for related compounds.[54] The value of the H2-H3 coupling constant of the *trans* pyrrolidine (**28**) was about 2.5 Hz, whereas the H2-H3 coupling constant of the *cis* pyrrolidine (**29**) was larger at 6.5 Hz. In addition, one of the H3-H4 coupling constants was also 0 Hz, indicating one

H3-H4 dihedral angle 90°. Gratifyingly, the conformation of the *trans* isomer with a H2-H3 angle of 90°, also suggested a 90° angle for H3-H4. This provides strong conformation of our stereochemical assignment.



(28)



(29)

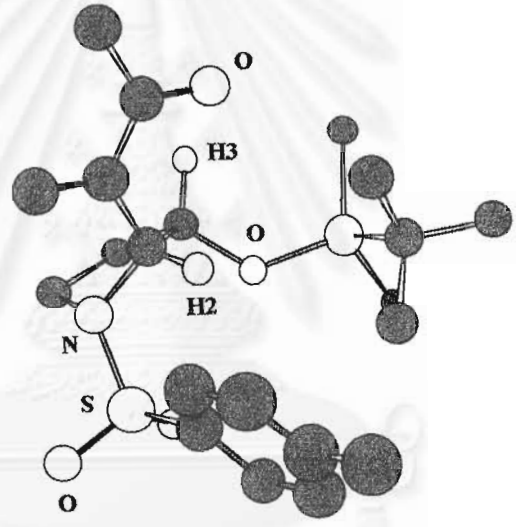


Figure 1 Chem 3D representation of the structure of *trans* pyrrolidine

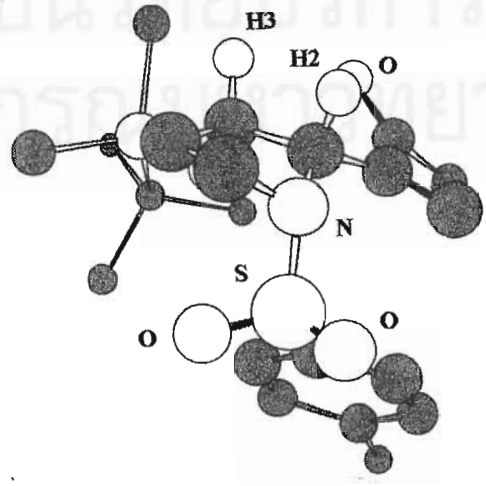
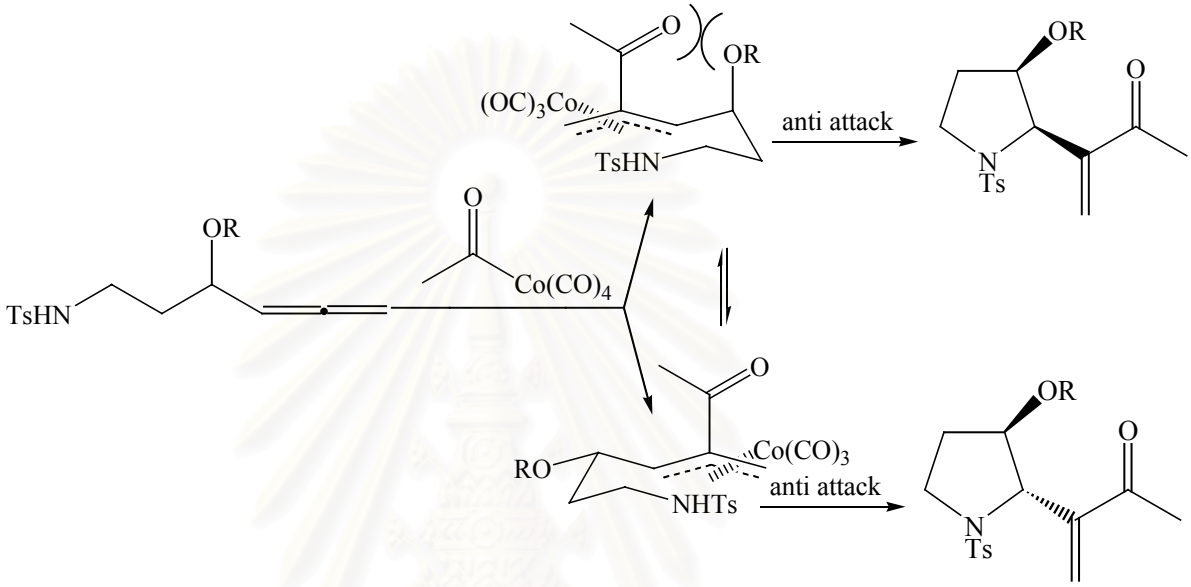


Figure 2 Chem 3D representation of the structure of *cis* pyrrolidine

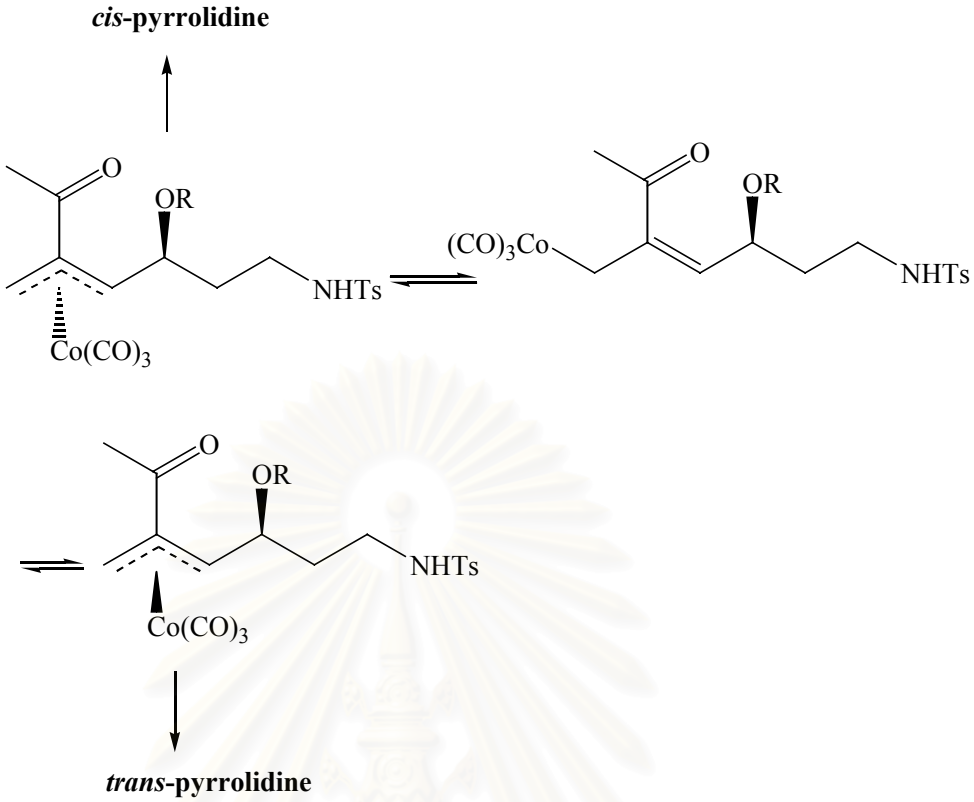
The stereochemical result could be due to a chair-like reactive conformation of the η^3-cobalt intermediate. The conformation that leads to the *trans* isomer places the oxygen substituent in a pseudo equatorial position. On the other hand, the conformation leading to the *cis* isomer places the substituent in a pseudo-axial position (**scheme 77**). In this position it would suffer a serious 1,3-interaction with the acyl substituent of the allyl complex.



Scheme 77 The conformation of the intermediates on the reaction

Interestingly, the cyclization of the allenes which have TBS and benzyl ethers gave similar high *trans*/*cis* ratios. This indicate that the conformation of the transition state can be the main factor influencing the ratio rather than O-Co coordination. With only oxygen as the donor atom, no chelation appears to operate. With hard metals such as Li, it is well known that TBS blocks chelation while benzyl allows it, leading to divergent stereochemical results.[55] In the present case, the ratios are very close indicating that neither allow chelation to the soft cobalt. The TIPS ether, which is bulkier than TBS gives no detectable *cis* isomer. This may be due to its greater size.

It is important to note that the two conformations are diastereomeric. It is known that many allyl complexes can interconvert via a π-σ-π mechanism (**scheme 78**) and we presume that such a process operates here.



Scheme 78 A π-σ-π rearrangement

In the case of the methyl thiomethyl ether, a lower ratio of the two diastereomers was obtained. This may be due to chelation between the sulfur and cobalt atoms. Chelation is geometrically possible for both reactive conformations but appears to favour slightly the conformation leading to the *cis* isomer, although not sufficiently to overcome the steric interaction between the alkoxy and acyl group in the conformation that leads to the *cis* isomer, thus reducing the ratio, but not reversing it.

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CHAPTER III

CONCLUSION

The results demonstrate the regio- and highly diastereoselective acylation-cyclization of α-O, γ-N disubstituted allenes using the organocobalt reagent. The stereochemical results can be attributed to a chair-like reactive conformation of the η^3-allylcobalt intermediate. In all cases, analysis of ^{1}H NMR coupling constant show the *tran*s pyrrolidine as the major product. Thus, development of this methodology will study the influence of a protected alcohol group β to the allene on the reaction and to determine the stereochemistry of the resulting 2,4-disubstituted pyrrolidine. It may be predicted that this will be *cis*, as the substituent will prefer a pseudo axial position. In addition, the preparation of optically active starting materials for the cyclization is important. A route is being developed using asymmetric sharpless epoxidation of an ene-yne-ol as the key step. The methodology can be applied to natural product synthesis. The α-substituted allenes should be useful starting materials for various pyrrolizidines, while the proposed β-substituted allenes could be precursor of amphorogynine alkaloids.

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CHAPTER IV

EXPERIMENTAL

General NMR spectra were obtained in $CDCl_3$ at 200 MHz (^1H) or 50 MHz (^{13}C) on a Bruker BZH 200 or a Varian Gemini Instrument. Chemical shift (δ) are in ppm and coupling constants (J) are in Hz. All reactions were followed by thin layer chromatography (TLC): glass or plastic sheets coated with silica gel F_{254} (Merck) and visualized using uv light (254 nm), iodine, molybdate or $KMnO_4$. Flash chromatography was carried out on silica gel: 230-400 Mesh. Tetrahydrofuran and dioxane were distilled from Na/benzophenone, dichloromethane and acetonitrile were distilled from CaH_2 and dimethylformamide was distilled from CaH_2 under reduced pressure. Other chemicals were obtained from Fluka or Merck and used as received. Carbon monoxide was obtained from Praxair. Evaporation refers to the rotary evaporation of solvent under aspirator pressure. Infrared spectra were acquired using a Nicolet Inpact 410 or a Perkin Elmer 1760X. Mass spectrometry and high resolution mass spectrometry were determined using a GCQ Mass Spectrometer from Finiganand a Mat 90 from Finigan. Elemental analysis were determined at the Instrument Centre of Chulalongkorn University.

3-hydroxy-2-(bromomethyl)-tetrahydrofuran (6) : A solution of diol **(5)** (0.69 g, 6.81 mmole) in CH_3CN (2.5 ml) was added to a solution of *N*-bromosuccinamide (1.21 g, 6.81 mmole) in CH_3CN (2.5 ml) at room temperature under N_2 with a water bath . The mixture was stirred for 3 hours. The organic solvent was evaporated. Water was added and the solution was extracted with methyl-*tert*-butyl ether. The organic layer was dried (Na_2SO_4) and evaporated to give tetrahydrofuran **(6)** as an oil (1.20 g, 97%).^1H NMR δ 1.4-2.3 (2H, m, CH_2), 2.72 (1H, s, OH), 3.50 (2H, m, CH_2Br), 3.8-4.15 (3H, m, H5, H3), 4.45 (1H, m, C<u>H</u>CH_2Br)

3-(*tert*-butyldimethylsilyloxy)-2-(bromomethyl)-tetrahydrofuran (7) : *tert*-butyldimethylchlorosilane (2.85 g, 18.9 mmole), *N, N*-dimethylaminopyridine (3.08 g, 2.52 mmole) and imidazole (1.89 g, 27.7 mmole) were added to a solution of 3-hydroxy-2-(bromomethyl)-tetrahydrofuran (**6**) (2.29 g, 12.6 mmole) in THF (15 ml) at room temperature under N_2 with a water bath. The mixture was stirred overnight, acidified with ammonium chloride and extracted with EtOAc. The organic layer was washed (brine), dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel (60 g) eluting with 10% and 20% EtOAc : hexane to give the tetrahydrofuran (**7**) as an oil (1.6 g, 70%). ^{1}H NMR δ 0.05 (6H, s, CH_3), 0.85 (9H, s, *t*-Bu), 1.95 (1H, m, H4′), 2.05 (1H, m, H4), 3.3-3.55 (2H, m, CH_2Br), 3.8-4.1 (3H, m, H5, H3), 4.39 (1H, m, H2); ^{13}C NMR δ 82.9, 71.9, 66.9, 35.9, 29.8, 25.6, 17.9, -4.6; IR (ν, cm^{-1}) 2954 (CH), 1256 (Si-CH_3), 1134 (Si-O), 1065 (C-O-C), 953 (C-O-C), 836 (Si-O); MS (m/z) 237/239 (26/27) (M^+-C_4H_8), 209 (75) (M^+-$C_4H_{10}O$), 139 (25) ($C_2H_6SiBr^+$+H), 83 (100) ($C_5H_7O^+$), 73 (64) ($C_4H_6O^+$).

3-(*tert*-butyldimethylsiloxy)-4-pentyn-1-ol (8) : *n*-Butyl lithium in hexane (42 ml of a 1.6 M solution, 16.94 mmole) was added dropwise to a solution of diisopropylamine (9.5 ml, 67.8 mmole) in THF (20 ml) at -35°C under N_2. The solution was stirred for 30 min. A solution of 3-(*tert*-butyldimethylsilyloxy)-2-(bromomethyl)-tetrahydrofuran **(7)** (5 g, 16.94 mmole) in THF (25 ml) was added at -78°C by cannula. The solution was stirred for 30 min, then allowed to warm to 0°C and stirring was continued for 30 min. Ammonium chloride and water were added to the mixture. It was extracted with EtOAc. The organic layer was washed (brine), dried (Na_2SO_4) and evaporated. The residue was applied to the top of a silica gel column (85 g) and it was eluted by flash chromatography with 10% and 15% EtOAc : hexane to give the alkyne (**8**) as an oil (1.86 g, 51%). ^{1}H NMR δ 0.15 (6H, s, CH_3), 0.89 (9H, s, *t*-Bu), 1.92 (2H, m, H2), 2.42 (1H, d, J = 2.2, ≡CH), 3.76 (1H, dt, J = 14.9, 5.5 Hz, C<u>H</u>OH), 3.89 (1H, m, C<u>H</u>OH), 4.62 (1H, dt, J = 5.6, 2.2 Hz, H3); ^{13}C NMR δ 84.2, 72.6, 61.1, 59.1, 39.8, 25.3, 18, -4.7; IR (ν, cm^{-1}) 3450 (OH), 3300 (≡CH), 2950- 2850 (CH), 2100 (C≡C); MS (m/z) 215 (45) (M^++H), 171 (13) (M^+-C_3H_7), 157 (12) (M^+-C_4H_9),

129 (100) (OTBS), 83 (13) (M^+-OTBS); HRMS calcd for $C_{11}H_{23}O_2Si$ (M^++H) [215.146733], found [215.146718].

3-(*tert*-butyldimethylsiloxy)-4,5-hexadien-1-ol (9) : paraformaldehyde (0.049 g, 1.65 mmole), anhydrous copper(I) iodide (0.063 g, 0.33 mmole) and diisopropylamine (185 µl, 1.32 mmole) were added to a solution of 3-(*tert*-butyldimethylsiloxy)-4-pentyn-1-ol (**8**) (0.14 g, 0.66 mmole) in anhydrous 1,4-dioxane (1.5 ml). The mixture was heated at reflux overnight under N_2, then cooled and filtered through celite, washing with methyl *tert*-butyl ether. The solution was evaporated forming a gum-like residue which was acidified with 2 M hydrochloric acid and extracted with methyl *tert*-butyl ether several times. The organic layer was washed with water and brine, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel (4 g) eluting with 4% EtOAc : hexane to give the allenol (9) as an oil (0.135 g, 89%). ^{1}H NMR δ 0.15 (6H, s, CH_3), 0.85 (9H, s, *t*-Bu), 1.75 (2H, m, H2), 2.40 (1H, br, OH), 3.75 (2H, m, H1), 4.45 (1H, m, H3), 4.78 (2H, dt, J = 7, 1.6 Hz, H_2C=C=), 5.15 (1H, q, J = 7 Hz, =CH); ^{13}C NMR δ 207.2, 94.2, 76.4, 70.6, 60.1, 39.9, 25.7, 20.1, 17.9, -4.7 ; IR (ν, cm^{-1}) 3388 (OH), 2858 (CH), 1957 (=C=); MS (m/z) 229 (13) (M^++H), 211 (6) (M^+-OH), 131 (100) (OTBS), 97 (27) (M^+-OTBS), 75 (97) (M^+-C_3H_3-TBS+H)

1-(mesyloxy)-3-(*tert*-butyldimethylsiloxy)-4,5-hexadiene (10) : Methanesulfonyl chloride (444 µl, 5.72 mmole) and triethylamine (870 µl, 6.24 mmole) were added to a solution of 3-(*tert*-butyldimethylsiloxy)-4,5-hexadienol (**9**) (1.19 g, 5.19 mmole) in CH_2Cl_2 (10 ml) at 0°C under N_2. The solution was stirred for 2 hours. Ammonium chloride and water were added and the solution was extracted with CH_2Cl_2 . The organic extract was washed (brine), dried (Na_2SO_4) and evaporated to give the mesylate (**10**) as an oil (1.56 g, 98%). ^{1}H NMR δ 0.15 (6H, s, CH_3), 0.35 (9H, s, *t*-Bu), 1.95 (2H, m, H2), 2.98 (3H, s, SO_2CH_3), 4.30 (2H, m, H2), 4.75 (2H, m, H_2C=C=), 5.05 (1H, m, =CH). It was used directly in the next reaction.

1-azido-3-(*tert*-butyldimethylsiloxy)-4,5-hexadiene (11) : Sodium azide (1.65 g, 25.39 mmole) was added to a solution of 1-(mesyloxy)-3-(*tert*-butyldimethylsiloxy)-4,5-hexadiene **(10)** (1.55 g, 5.08 mmole) in DMF (6 ml) at room temperature. The mixture was stirred overnight, then poured into water and extracted with EtOAc. The organic solvent was evaporated. Water was added and the solution was extracted with hexane. The organic layer was washed (brine), dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel (30 g) eluting with 5% EtOAc : hexane to give the unstable azide **(11)** as an oil (1.09 g, 84%); IR (ν, cm^{-1}) 2950 (CH), 2100 (N=N=N), 1956 (=C=).

3-(*tert*-butyldimethylsiloxy)-4,5-hexadienyl-*p*-toluenesulfonamide (12) : Glacial acetic acid (149 μl, 2.6 mmole) was added to a solution of 1-azido-3-(*tert*-butyldimethylsiloxy)-4,5-hexadiene **(11)** (0.17 g, 0.65 mmole) in THF (2 ml) at room temperature with a water bath. Activated zinc (0.21 g, 3.25 mmole) was added portionwise. The solution was stirred for an hour, then filtered through celite, washing with water (2 mL) and CH_2Cl_2 (2 mL). Anhydrous sodium carbonate (0.28 g, 2.6 mmole) and *p*-toluenesulfonyl chloride (0.15 g, 0.78 mmole) were added with a water bath and the solution was stirred for 2 hours then filtered through celite, washed with water and extracted with CH_2Cl_2. The organic layer was washed (brine), dried (Na_2SO_4) and evaporated.The residue was purified by flash chromatography on silica gel (5 g) eluting with 5% and 10% EtOAc : hexane to give the sulfonamide **(12)** as an oil (0.18 g, 73%).^{1}H NMR δ 0.05 (6H, s, CH_3), 0.85 (9H, s, *t*-Bu), 1.55-1.88 (2H, m, H2), 2.42 (3H, s, Ar$C\underline{H}_3$), 3.08 (2H, m, CH_2N), 4.15 (1H, m, H3), 4.68 (2H, dd, J = 5.5, 2.5 Hz, H_2C=C=), 4.98 (1H, q, J = 5.5 Hz, =CH), 5.05 (1H, t (br), NH), 7.25 (2H, d, J = 7.8 Hz, Ar), 7.75 (2H, d , J = 7.8 Hz, Ar); ^{13} C NMR 207.1, 143.0, 136.7, 129.4, 127.0, 93.6, 76.5, 64.6, 39.9, 36.7, 25.6, 21.3, 17.8, -4.2; IR (ν, cm^{-1}) 2929 (CH), 2857 (NH), 1957 (=C=), 1329 (SO_2N), 1163 (SO_2N); MS (m/z) 382 (4) (M^++H), 325 (24) (M^+-Ts-H), 324 (100) (M^+-C_4H_9), 155 (33) ($PhCH_3$).

1-azido-3-(hydroxy)-4,5-hexadiene (16) : Tetrabutylammonium hydrogen sulfate (0.09 g, 0.26 mmole) and potassium fluoride (0.60 g, 10.36 mmole) were added to a solution of 1-azido-3-(*tert*-butyldimethylsiloxy)-4,5-hexadiene **(11)** (0.99 g, 2.59 mmole) in CH_3CN (2 ml) at room temperature and the solution was stirred for 36 hours. Ammonium chloride and water were added and the solution was extracted with EtOAc. The organic layer was dried (Na_2SO_4) and evaporated.The residue was purified by flash chromatography on silica gel (30 g) eluting with 10% EtOAc : hexane to give the azidoalcohol **(16)** as an oil (0.26 g, 73%). IR (ν, cm^{-1}) 3350 (OH), 2100 (N=N=N), 1956 (=C=).

1-azido-3-(benzyloxy)-4,5-hexadiene (19) : Tetrabutylammonium bromide (0.067 g, 0.21 mmole), sodium hydroxide powder (0.17g, 4.27 mmole) and benzyl bromide (508 μl, 4.27 mmole) were added to the solution of 1-azido-3-(hydroxy)-4,5-hexadiene **(16)** (0.29 g, 2.13 mmole) in toluene (2.5 ml) at room temperature under N_2. The solution was stirred for 24 hours. Ammonium chloride was added and the solution was extracted with hexane. The organic layer was dried (Na_2SO_4) and evaporated.The residue was purified by flash chromatography eluting with 2% EtOAc : hexane to give the ether **(19)** as an oil (0.44 g, 90%).

3-(benzyloxy)-4,5-hexadienyl-*p*-toluenesulfonamide (21) : The same as for (**12**) but 1-azido-3-(benzyloxy)-4,5-hexadiene **(19)** was used instead of 1-azido-3-(*tert*-butyldimethylsiloxy)-4,5-hexadiene **(11)** to give the benzyl sulfonamide **(21)** as an oil (0.56 g, 60%). ^{1}H NMR δ 1.7-1.9 (2H, m, H2), 2.42 (3H, s, $ArCH_3$), 2.98 (1H, dt, J = 18.8,6.5 Hz, H1), 3.14 (1H, dt, J = 18.8, 6.5 Hz, H1′), 3.90 (1H, q (br), J = 4.4 Hz, H3), 4.32 (1H, d, J = 11.5 Hz, CHPh), 4.63 (1H, d, J = 11.5 Hz, CHPh), 4.74 (1H, td, J = 11.2, 6.2, 1.5 Hz, HC=C=), 4.82 (1H, td, J = 11.2, 6.2, 1.5 Hz, HC=C=), 4.9-5.0 (2H, m, =CH, NH), 7.25- 7.35 (5H, m, Ar), 7.25 (2H, d, J = 7.7 Hz, Ar), 7.65 (2H, d, J = 7.7 Hz, Ar); ^{13}C NMR 208.5, 143.1, 136.9, 129.8, 129.6, 127.0, 113.9, 90.6, 76.4, 69.8, 40.5, 34.8, 21.5; IR (ν,cm^{-1}) 3283 (NH), 2924 (CH_2), 2858 (CH_2), 1951 (=C=),

1321 (SO_2N), 1152 (SO_2N); MS (m/z) 358 (3) (M^+-H), 250 (2) (M^+-OBn), 184 (100) (CH_2NHTs), 155 (41) (Ts), 91 (88) ($PhCH_3$).

1-azido-3-(methyl thiomethoxy)-4,5-hexadiene (20) : The same as above but chloromethyl methyl sulfide was used instead of benzyl bromide to give the ether **(20)** as an oil (0.2 g, 77%) after purification by flash chromatography with 5% EtOAc:Hexane as an eluent.

3-(methyl thiomethoxy)-4,5-hexadienyl-*p*-toluenesulfonamide (22) : The same as for **(12)** but 1-azido-3-(methyl thiomethoxy)-4,5-hexadiene **(20)** was used instead of 1-azido-3- (*tert*-butyldimethylsiloxy)-4,5-hexadiene **(11)** to give the sulfonamide **(22)** as an oil (0.25 g, 76%). ^{1}H NMR δ 1.60-1.85 (2H, m, H2), 2.12 (3H, s, H_3CS), 2.43 (3H, s, $ArCH_3$), 3.0-3.2 (2H, m, CH_2N), 4.10-4.30 (1H, m, H3), 4.51 (1H, d, J = 11.6 Hz, HCS), 4.65 (1H, d, J = 11.6 Hz, HCS), 4.75 (2H, m, H_2C=C=), 4.89 (1H, m, =CH), 5.05 (1H, t (br), NH), 7.25 (2H, d, J = 9.8 Hz, Ar), 7.72 (2H, d, J = 9.8 Hz, Ar); ^{13}C NMR 208.5, 143.1, 136.8, 129.5, 126.8, 89.8, 76.3, 72.8, 72.5, 39.9, 34.7, 21.3, 14.2; IR (ν, cm^{-1}) 3280 (NH), 2922 (CH), 1955 (=C=), 1327 (SO_2N), 1160 (SO_2N); MS (m/z) 155 (87) (Ts), 184 (100) ($TsNHCH_2$), 250 (52) (M^+-OCH_2SCH_3), 280 (34) (M^+-SCH_3).

1-azido-3-(triisopropylsiloxy)-4,5-hexadiene (17) : triisopropylchlorosilane (209 μ l, 0.96 mmole), DMAP (0.02 g, 0.13 mmole) and imidazole (0.09 g, 1.43 mmole) were added to a solution of 1-azido-3-(hydroxy)-4,5-hexadiene **(16)** (0.09 g, 0.65 mmole) in CH_2Cl_2 (0.2 ml) at room temperature under N_2. The mixture was stirred overnight, acidified with ammonium chloride and extracted with EtOAc. The organic layer was washed (brine), dried (Na_2SO_4) and evaporated to give the ether **(17)** (0.13 g, 66%).

3-(triisopropylsiloxy)-4,5-hexadienyl-*p*-toluenesulfonamide (18) : The same as above but 1-azido-3-(triisopropylsiloxy)-4,5-hexadiene **(17)** was used instead of 1-azido-3-(*tert*-butyldimethylsiloxy)-4,5-hexadiene **(11)** to give the sulfonamide (0.07g, 40%) after purification by flash chromatographgy with 5% EtOAc : hexane as an eluent. ^{1}H NMR δ 1.02 (21H, m, $(iPr)_3$), 1.78 (2H, m, H2), 2.39 (3H, s, $ArCH_3$), 3.15 (2H, q, J= 6.3 Hz, CH_2N), 4.43 (1H, m, H3), 4.67 (2H, dd, J= 6.6, 1.8 Hz, $H_2C=C=C$), 5.01 (1H, q, J= 6.8 Hz, =CH), 5.12 (1H, t(br), NH), 7.29 (2H, d, J= 8.3 Hz, Ar), 7.78 (2H, d, J= 8.3 Hz, Ar); ^{13}C NMR 207.0, 143.2, 136.8, 129.6, 127.1, 93.6, 76.4, 70.2, 39.8, 36.7, 21.5, 18.0, 12.2; IR (ν, cm^{-1}) 2944 (CH), 2867 (NH), 1957 (=C=), 1331 (SO_2N), 1163 (SO_2N); MS m/z 422 (8) (M^+-H), 380 (54) (M^+-C_3H_7), 209 (100) (M^+-NHTs-C_3H_6), 155 (11) (Ts).

3-(hydroxy)-4,5-hexadienyl-*p*-toluenesulfonamide (13) : Tetra-*n*-butylammonium hydrogen sulfate (0.05 g, 0.16 mmole) and potassium fluoride (0.36 g, 6.26 mmole) were added to a solution of 3-(*tert*-butyldimethylsiloxy)-4,5-hexadienyl-*p*-toluenesulfonamide **(12)** (1.29 g, 3.13 mmole) in CH_3CN (5 ml) at room temperature. The solution was stirred for 48 hours. Ammonium chloride and water were added and the solution was extracted with EtOAc. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel (30 g) eluting with 10% and 25% EtOAc : hexane to give 3-(hydroxy)-4,5-hexadienyl-*p*-toluenesulfonamide **(13)** as an oil (0.8 g, 96%). ^{1}H NMR δ 1.60-1.85 (2H, m, CH), 2.05 (1H, br, OH), 2.43 (3H, s, $ArCH_3$), 2.92-3.30 (2H, m, CH_2N), 4.20-4.35 (1H, m, H3), 4.85 (2H, dd, J = 6.4, 2.4 Hz, $H_2C=C=$), 5.15 (1H, t (br), NH), 5.19 (1H, q, J = 6.4 Hz, =CH), 7.25 (2H, d, J = 9.5 Hz, Ar), 7.65 (2H, d, J = 9.5 Hz, Ar); ^{13}C NMR 206.7, 143.1, 136.6, 129.5, 126.8, 93.7, 76.4, 67.4, 39.9, 35.8, 21.2; IR (ν, cm^{-1}) 3504 (OH), 3282 (NH), 2928 (CH), 1957 (=C=), 1327 (SO_2N), 1159 (SO_2N); MS (m/z) 268 (5) (M^++H), 250 (15) (M^+-OH), 184 (92) (CH_2NHTs), 155 (81) (Ts), 91 (100) ($PhCH_3$),

Benzoylated sulfonamide (14, 15) : DMAP (0.009 g, 0.075 mmole), triethylamine (125.4 μl, 0.9 mmole) and benzoyl chloride (1.74 μl, 1.49 mmole) were added to a solution of 3-(hydroxy)-4,5-hexadienyl-*p*-toluenesulfonamide **(13)** (0.2 g, 0.75 mmole) in CH_2Cl_2 (2 ml) at room temperature under N_2. Ammonium chloride was added and the solution was extracted with CH_2Cl_2, washed (brine), dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel (6 g) eluting with 15% EtOAc : hexane to give N-benzoyl-3-(benzoyloxy)-4,5-hexadienyl-*p*-toluenesulfonamide **(15)** as an oil (0.16 g, 44%) and 20% EtOAc : hexane to give 3-(benzoyloxy)-4,5-hexadienyl-*p*-toluenesulfonamide **(14)** as an oil (0.089 g, 32%) ^{1}H NMR of O,N-dibenzoylated compound (15) δ 2.25 (2H, m, H2), 2.42 (3H, s, $ArCH_3$) 3.95 (2H, t, J = 10.6 Hz, CH_2N), 4.86 (2H, dt, J = 6.6, 2.2 Hz, H_2C=C=), 5.29 (1H, q, J = 6.6 Hz, =CH), 5.45 (1H, m, H3), 7.2-7.6 (10H, m, Ar), 7.73 (2H, d, J = 7.9 Hz, CHAr), 7.85 (2H, d, J = 7.9 Hz, CHAr); ^{13}C NMR 208.2, 171.3, 165.5, 144.8, 135.7, 134.9, 132.9, 131.5, 129.9, 129.5, 90.0, 78.1, 76.4, 69.4, 44.4, 33.9, 21.5; MS (m/z) 354 (2) (M^+-COPh), 320 (7) (M^+-Ts), 105 (100) (COPh), 77 (33) (M^+-Ts-$(OCOPh)_2$-H).

3-(benzoyloxy)-4,5-hexadienyl-*p*-toluenesulfonamide (14) : Triethylamine (53 μl, 0.38 mmole) was added to a solution of N-benzoyl-3-(benzoyloxy)-4,5-hexadienyl-*p*-toluenesulfonamide **(15)** (0.16 g, 0.34 mmole) in methanol (1.5 ml) at room temperature under N_2. The solution was stirred for 48 hours and evaported. The residue was purified by flash chromatography on silica gel (5 g) eluting with 10% EtOAc : hexane to give O-benzoylated compound **(14)** as an oil (0.05 g, 38%). ^{1}H NMR δ 1.9-2.1 (2H, m, H2), 2.39 (3H, s, $ArCH_3$), 3.09 (2H, m, CH_2N), 4.88 (2H, dt, J= 6.2, 1.8 Hz, H_2C=C=), 5.02 (1H, t (br), NH), 5.32 (1H, q, J = 6 Hz, =CH), 5.53 (1H, m, H3), 7.24 (2H, d, J = 8.5 Hz, Ar), 7.39-7.50 (2H, m, Ar), 7.50-7.65 (1H, m, Ar), 7.72 (2H, d, J = 8.5 Hz, Ar), 7.79 (2H, d, J = 8.5 Hz, Ar); ^{13}C NMR 208.2, 165.9, 143.3, 136.7, 133.1, 129.6, 128.3, 126.9, 90.2, 78.0, 69.4, 39.3, 34.1, 21.4; IR (ν, cm^{-1}) 3277 (NH), 2910 (CH), 1951 (=C=), 1710 (C=O), 1300 (SO_2N), 1170 (SO_2N); MS (m/z) 91 (33) ($PhCH_3$), 105 (84) (COPh), 155 (78) (SO_2PhCH_3), 250

(100) (M^+- COPh); Found C 64.62%, H 5.76%, N 3.82%, $C_{20}H_{21}NSO_4$ requires C 64.67%, H 5.69%, N 3.77%.

Pyrrolidine (23a,23b) : Methyl iodide (17.4 μl, 0.28 mmole) was added to a solution of sodium tetracarbonyl cobaltate (1.12 ml of 0.25 M solution, 0.28 mmole) in THF at 0°C under an atmosphere of carbon monoxide. The mixture was stirred for 30 min. A solution of 3-(*tert*-butyldimethylsiloxy)-4,5-hexadienyl-*p*-toluenesulfonamide **(12)** (100 mg, 0.26 mmole) in THF (1 ml) was added *via* cannula at room temperature under N_2. Stirring was continue for 10 min. Triethylamine (39.86 μl, 0.29 mmole) was added and the mixture was stirred overnight. Cobalt carbonyl complexes were decomposed by addition of iodine until the colour of iodine became permanent and gas evolution ceased. Sodium thiosulfate solution was added and the mixture was filtered through celite, washing with EtOAc. The mixture was washed with ammonium chloride and with brine, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel (3 g) eluting with 5% EtOAc : hexane to give the *cis*-pyrrolidine **(23b)** (0.0028 g, 2.6%) ^{1}H NMR δ -0.14 (3H, s, CH_3), -0.1 (3H, s, CH_3), 0.75 (6H, s, *t*-Bu), 1.25 (2H, m, H4), 2.34 (3H, s, $ArCH_3$), 2.42 (3H, s, $COCH_3$), 3.42-3.60 (2H, m, H5), 4.18 (1H, q, J = 4.5 Hz, H3), 4.64 (1H, d, J = 4.5 Hz, H2), 6.28 (1H, s, CH=), 6.31 (1H, s, CH=), 7.30 (2H, d, J = 8 Hz, Ar), 7.69 (2H, d, J = 8 Hz, Ar). And 10% EtOAc : hexane to give the *trans*-pyrrolidine **(23a)** as a solid (0.074 g, 68%). ^{1}H NMR δ -0.1 (3H, s, CH_3), 0 (3H, s, CH_3), 0.62 (9H, s, *t*-Bu), 1.70 (1H, m, H4),1.82 (1H, m, H4), 2.42 (3H, s, $ArCH_3$), 2.44 (3H, s, $COCH_3$), 3.29 (1H, dq, J = 5.2, 2.6 Hz, H5), 3.70 (1H, t, J = 3.5 Hz, H5′), 3.92 (1H, d, J = 1.7 Hz, H3), 4.36 (1H, s, H2), 6.34 (1H, s, =CH), 6.41 (1H, s, =CH), 7.25 (2H, d, J = 8 Hz, Ar), 7.75 (2H, d, J = 8 Hz, Ar); IR (ν, cm^{-1}) 2928 (CH), 1687 (C=O), 1599 (C=C), 1101 (Si-O), 834 (Si-O); ^{13}C NMR 199.4, 147.3, 143.3, 133.4, 129.6, 128.4, 127.8, 76.1, 68.3, 45.9, 31.7, 26.4, 25.7, 21.4, 17.5; MS (m/z) 366 (100) (M^+-C_4H_9), 291 (8) (M^+-OTBS-H), 210 (32) (M^+-Ts-C_4H_{10}). Found C 59.53 %, H 7.88%, N 3.32%, $C_{21}H_{33}NSO_4Si$ requires C 59.54%, H 7.85%, N 3.31%; mp 93-94 °C.

Pyrrolidine (24a) : The same as for **(23a, 23b)** but 3-(benzoyloxy)-4,5-hexadienyl-*p*-toluenesulfonamide **(14)** (137 mg, 0.37mmole) was used instead of 3-(*tert*-butyldimethylsiloxy)-4,5-hexadienyl-*p*-toluenesulfonamide **(12)** to give the *trans*-pyrrolidine **(24a)** as a solid (0.043 g, 30%) after purification by flash chromatography with 25% EtOAc : hexane as eluent. ^{1}H NMR δ 1.95-2.1 (2H, m, H4), 2.42 (3H, s, $ArCH_3$), 2.48 (3H, s, $COCH_3$), 3.30 (1H, m, H5), 4.82 (1H, m, H5′), 4.80 (1H, s, H2), 5.15 (1H, d, J = 7.5 Hz, H3), 6.41 (1H, s, HC=), 6.43 (1H, s, HC=), 7.30 (4H, m, Ar), 7.35 (2H, d, J = 9.2 Hz, Ar), 7.59 (1H, m, Ar), 7.82 (2H, d, J = 9.2 Hz, Ar); ^{13}C NMR 128.9, 178.8, 146.4, 143.4, 133.1, 129.8, 129.5, 128.8, 128.1, 76.4, 64.6, 46.9, 29.3, 26.4, 21.8; IR (ν, cm^{-1}) 2925 (CH), 1690 (C=O), 1590 (C=C); MS (m/Z) 291 (80) (M^+-$PhCO_2$+H), 258 (89) (M^+-Ts+H), 136 (100) (M^+-Ts-$PhCO_2$+H); mp 128-129 °C.

Pyrrolidine (26a) : The same as for **(23a, 23b)** but 3-(benzyloxy)-4,5-hexadienyl-*p*-toluenesulfonamide **(21)** was used instead of 3-(*tert*-butyldimethylsiloxy)-4,5-hexadienyl-*p*-toluenesulfonamide **(12)** to give the *trans*-pyrrolidine **(26a)** as a major product (0.04 g, 36%). after purification by flash chromatography with 10% EtOAc : hexane as an eluent. ^{1}H NMR δ 1.70-1.90 (2H, m, H4), 2.25 (3H, s, $COCH_3$), 2.39 (3H, s, $ArCH_3$), 3.32 (1H, q, J = 9 Hz, H5′), 3.68 (2H, m, H5, CHPh), 4.30 (1H, s, CHPh), 4.32 (1H, s, H3), 4.75 (1H, s, H2), 6.32 (1H, s, =CH), 6.40 (1H, s, =CH), 6.95 (2H, m, Ar), 7.20 (6H, m, Ar), 7.72 (2H, d, J = 7.2 Hz, Ar); ^{13}C NMR 198.9, 146.9, 143.5, 138.0, 133.5, 129.5, 128.7, 128.0, 127.7, 127.2, 127.1, 82.0, 69.9, 63.8, 47.4, 29.3, 26.4, 21.5; IR (ν, cm^{-1}) 3056 (CH), 2884 (CH), 1669 (C=), 1624 (C=C); MS (m/z) 291 (65) (M^+-OBn+H), 244 (9) (M^+-Ts), 136 (78) (M^+-Ts-OBn-H), 91 (100) (Bn); Found C 66.14%, H 6.28%, N 3.55%, $C_{22}H_{25}NSO_4$ requires C 66.14 %, H 6.31%, N 3.51%; mp 126-127 °C.

Pyrrolidine (25a) : The same as for **(23a, 23b)** but 3-(methyl thiomethoxy)-4,5-hexadienyl-*p*-toluenesulfonamide **(22)** was used instead of 3-(*tert*-butyldimethylsiloxy)-4,5-hexadienyl- *p*-toluenesulfonamide **(12)** to give the *trans*-pyrrolidine **(25a)** as a major product (0.04 g, 24 %) after purification by flash

chromatography with 20% EtOAc : hexane as an eluent. ^{1}H NMR δ 1.75 (2H, m, H4), 1.92 (3H, s, SCH_3), 2.34 (3H, s, $ArCH_3$),2.39 (3H, s, $COCH_3$), 3.26 (1H, m, H5), 3.66 (1H, dt, J = 6.9, 1.9 Hz, H5'), 3.95 (1H, d, J = 2.4 Hz, H3), 4.14 (1H, s, H2), 4.50 (2H, d, J = 11.2 Hz, CH_2S), 6.31 (1H, s, =CH), 6.33 (1H, s, =CH), 7.30 (2H, d, J = 8.5 Hz, Ar), 7.70 (2H, d, J = 8.5 Hz, Ar); ^{13}C NMR 198.7, 170.9, 146.3, 143.4, 133.3, 129.3, 128.5, 127.6, 78.7, 72.1, 63.6, 60.2, 47.4, 29.5, 28.9, 26.1, 21.4, 20.9, 14.3, 13.6; IR (ν, cm^{-1}) 2920 (CH), 1672 (C=O), 1598 (C=C), 1346 (SO_2N), 1162 (SO_2N); MS m/z 291 (26) (M^+-OCH_2SCH_3-H), 155 (18) (Ts), 136 (100) (M^+-OCH_2SCH_3-Ts-H), 91 (20) ($PhCH_3$); Found C 55.22%, H 6.31%, N 3.77%, $C_{17}H_{23}NS_2O_4$ requires C 55.26%, 6.27%, N 3.79%.

Pyrrolidine (27a) : The same as for **(23a, 23b)** but 3-(triisopropylsiloxy)-4,5-hexadienyl-*p*-toluenesulfonamide **(18)** was used instead of 3-(*tert*-butyldimethylsiloxy)-4,5-hexadienyl-*p*-toluenesulfonamide **(12)** to give the *trans*-pyrrolidine **(27a)** as a major product (0.08 g, 71 %). after purification by flash chromatography with 4 % EtOAc : hexane as an eluent. ^{1}H NMR δ 0.85 (21H, m, $(iPr)_3$), 1.68 (2H, m, H4), 2.33 (3H, s, $ArCH_3$), 2.42 (3H, s, $COCH_3$), 3.29 (1H, m, H5), 3.67 (1H, t, J= 7.6 Hz, H5′), 4.02 (1H, d, J= 2.5 Hz, H3), 4.42 (1H, s, H2), 6.26 (1H, s, =CH), 6.29 (1H, s, =CH), 7.25 (2H, d, J= 8.7 Hz, Ar), 7.70 (2H, d, J = 8.7, Ar); ^{13}C NMR 198.8, 147.5, 143.3, 133.8, 129.5, 128.5, 127.8, 68.4, 60.4, 46.8, 32.1, 26.4, 21.4, 17.9, 14.2, 11.9; IR (ν, cm^{-1}) 2942 (CH), 1673 (C=O), 1598 (C=C), 1340 (SO_2N), 1163 (SO_2N); MS (m/z) 422 (100) (M^+-C_3H_7), 267 (24) (M^+-Ts-C_3H_7), 266 (79) (M^+-Ts-C_3H_6); Found C 61.98%, H 8.48%, N 3.02%, $C_{24}H_{39}NSO_4Si$ requires C 61.89%, H 8.44%, N 3.01%; mp 121-124 °C.

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