# CHAPTER II

# RESULTS AND DISCUSSION

Several transition metals have been used as catalyst or reagents for cyclization of allenes, for example lanthanides[25], silver[26], palladium[27]. Recently, Bates has reported the acylation-cyclization of monosubstituted, gem-disubstituted and 1,3-disubstituted allenes bearing sulfonamides nucleophiles with organocobalt reagents in the presence of base. The five-membered rings were obtained in moderate to excellent yield (Scheme 11).[28]
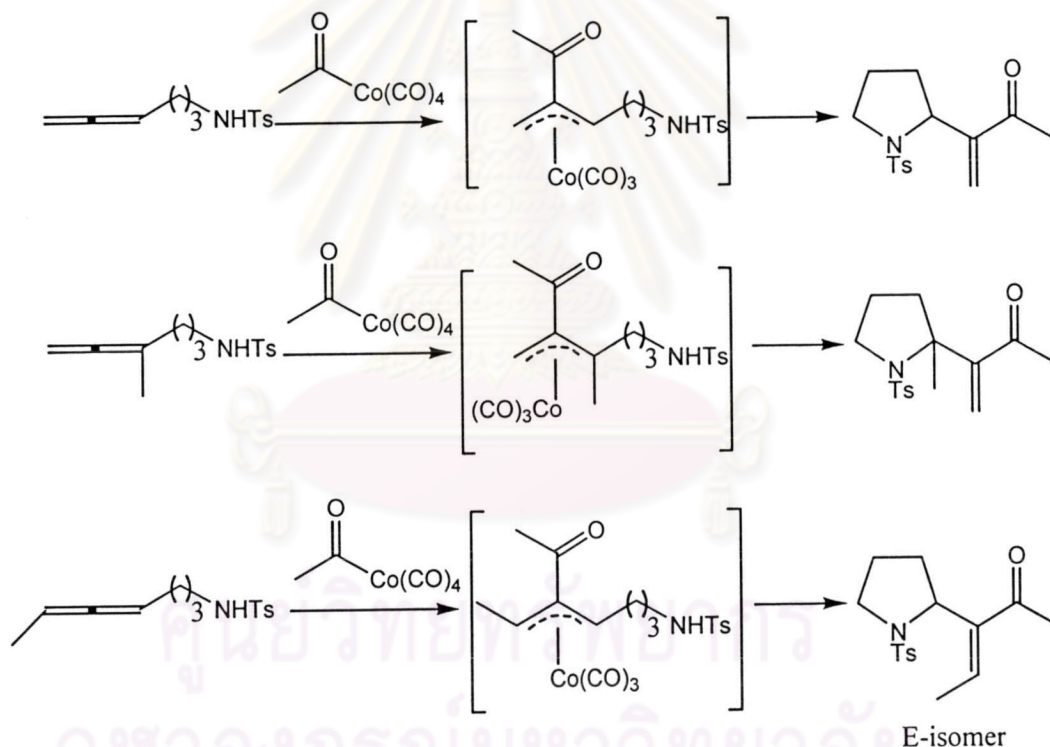


**Scheme 11** Acylation-cyclization of allenes

As interesting aspect is the stereoselectivity that is involved due to substitutents on the allene. It has been shown that α-substituted allenes undergo cyclization using organocobalt reagents to give the *trans* products. The stereochemical result could be attributed to a chair-like reactive conformation of the η³-cobalt intermediate (Scheme 12).[29] The conformation of the intermediate

leading to the *cis* isomer has a 1,3-interaction between the O-substitutent and the acyl substitutent of the allyl complex. On the other hand, the conformation leading to the *trans* isomer places the O-substitutent in a pseudo-equatorial position. In this case, the *trans* isomer was the major product.



*trans:cis* = 26:1
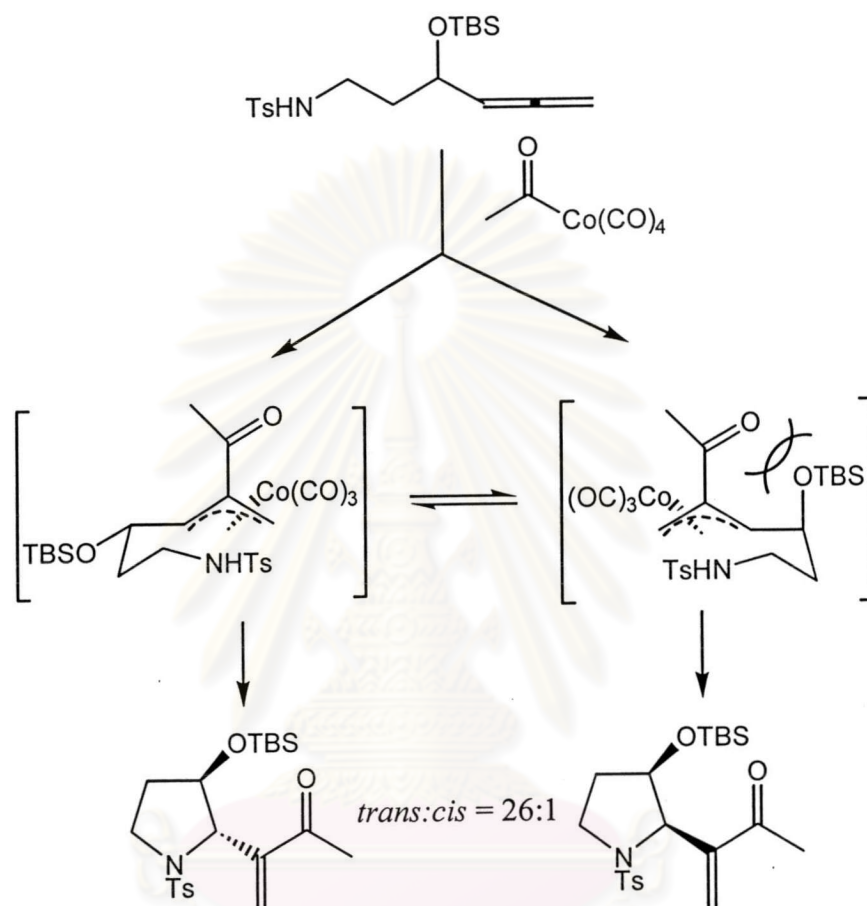
**Scheme 12** The comformation of the intermediates for AcCo(CO)₄-mediated cyclization of α-substituted allenes

If the allene substitutent was at the β-position, the stereochemical outcome would be expected to arise from an analogous intermediate. It can be predicted that the *cis* isomer will form, due to the preference for a pseudo-equatorial position (**Scheme 13**).
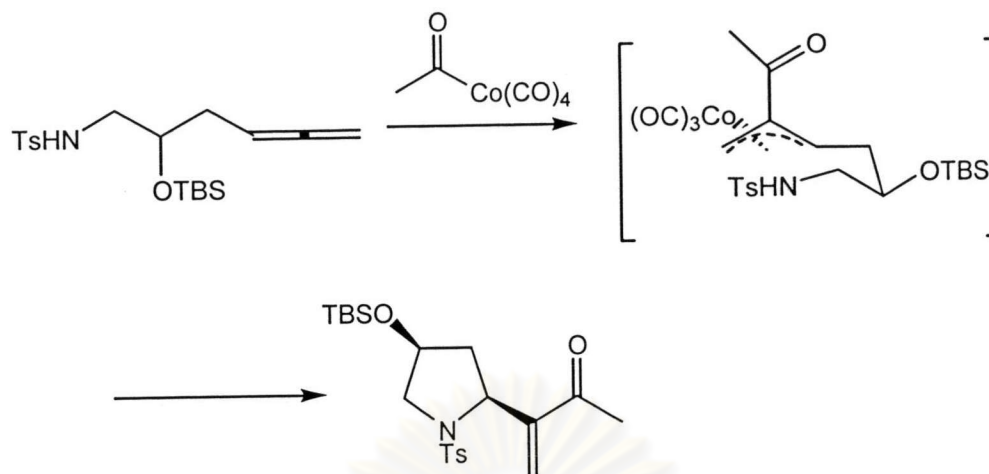
**Scheme 13**  The conformation of the intermediates for a β-substituted allene

The β-substituted allene might be derived from a protected cyclic sulfate or protected glycidol by ring opening with an acetylide nucleophile. The resulting terminal alkyne can be converted to a homologous allene easily using the Searles-Crabbé reaction **(Scheme 14)**.
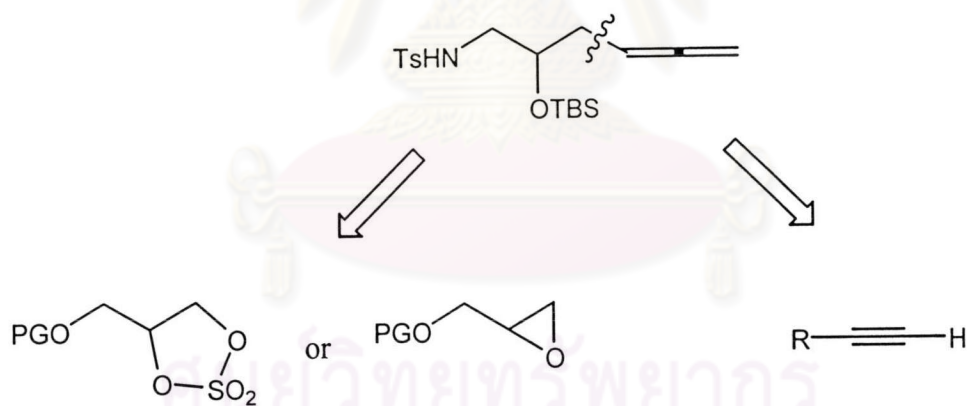


**Scheme 14**  Retrosynthetic strategy for a β-substituted allene

The cyclization product could be an intermediate for the synthesis of hydroxylated pyrrolizidines such as amphorogynine which was discussed in chapter I. In this case, either isomer of the pyrrolizidine could be used. In the case of the *cis* pyrrolidine, direct acylation would attach the side chain with retention of stereochemistry. In the case of the *trans* isomer, a Mitsunobu reaction would result in acylation with inversion.

Amphorogynine A (39) might be obtained from the unsaturated pyrrolizidine. The stereochemistry could be controlled by reduction of the alkene (52) from the convex face. The unsaturated pyrrolizidine (52) might be synthesized from the product of allene cyclization (54) (Scheme 15).
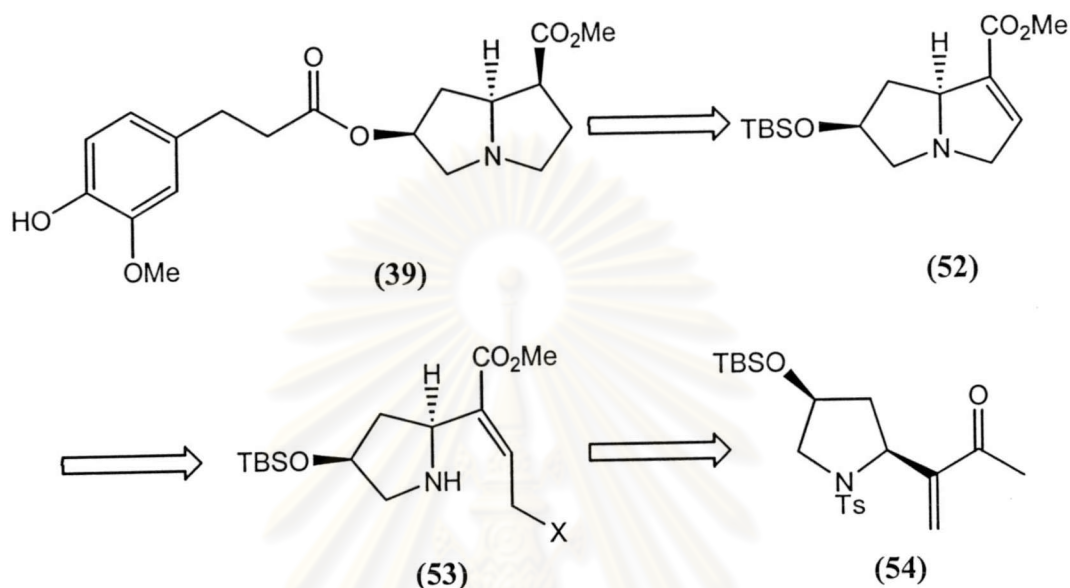


**Scheme 15** Retrosynthesis of Amphorogynine A

2.1 Synthesis of terminal alkyne intermediates.

2.1.1. Synthesis starting from cyclic sulfates.

It is known that cyclic sulfates are more reactive than epoxides in many reactions. Although cyclic sulfates have been known for a long time, a good preparative method was discovered only about ten years ago. A diol is treated with thionyl chloride (and Et$_3$N for acid sensitive substrates) in dichloromethane and almost quantitative formation of the corresponding mixture of diastereoisomeric cyclic sulfites is observed. In 1988, Sharpless reported that a catalytic amount of RuO$_4$, which is generated in situ by the reaction of ruthenium trichloride with sodium periodate, could oxidise the cyclic sulfites to cyclic sulfates cleanly and in high yield (Scheme 16).[30] Potassium permanganate has also been used for this oxidation[31], but is considered to be less convenient.
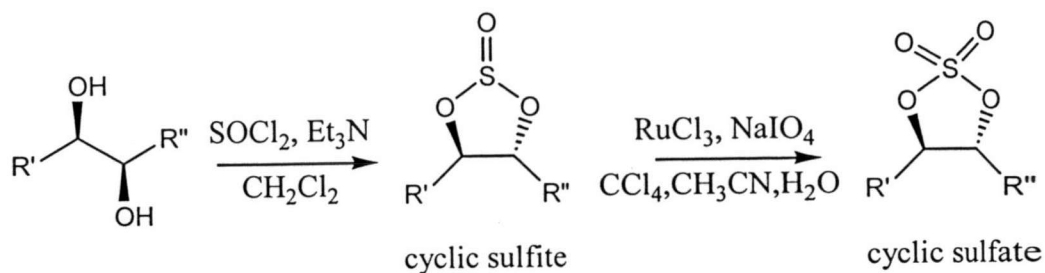
**Scheme 16** Transformation of a diol to a cyclic sulfate

Bittman has been compared the ring-opening reaction of glycidol with that of the corresponding cyclic sulfate using an acetylide nuclephile (**Scheme 17**).[32]
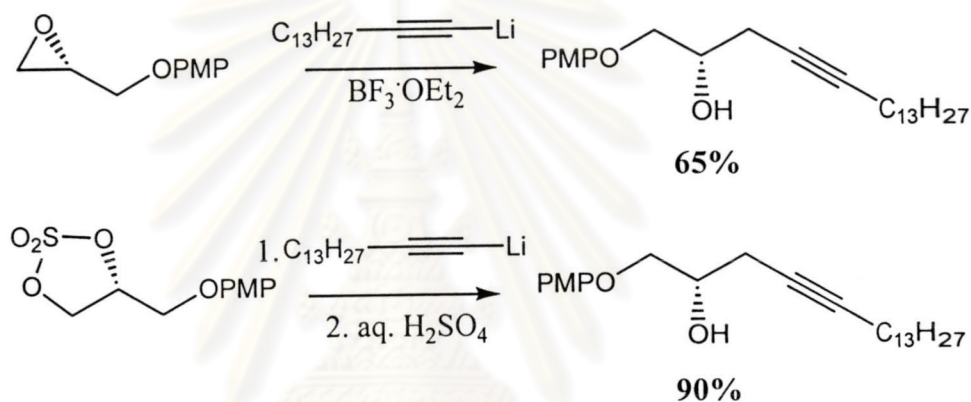


**Scheme 17** Comparative ring opening reactions

He found that the reaction of the cyclic sulfate gave a better yield than the reaction of glycidol and did not need Lewis acid. So, the cyclic sulfate was chosen as the starting material for the synthesis of the β-substituted allene.

Protected allyl alcohols were prepared from the reaction of selected hydroxy compounds with allyl bromide where the reaction conditions depended upon the acidity of the hydroxyls. The hydroxyl of the benzyl and *p*-methoxybenzyl alcohols are less acidic than *p*-methoxyphenol, so a strong base (NaOH) was used. In contrast, the phenolic proton of the *p*-methoxyphenol is more acidic, so a weak base ($K_2CO_3$) was used (**Scheme 18**).

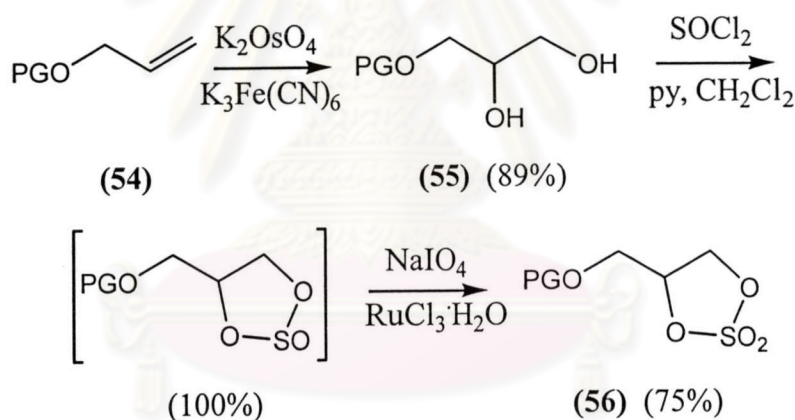ROH + (allyl bromide) $\xrightarrow{\text{(i) or (ii)}}$ RO (allyl)
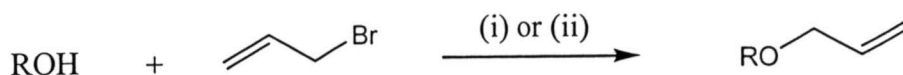
(i) : R= PMB, Bn ; NaOH(powder), Bu$_4$NBr, toluene

(ii) : R= PMP ; K$_2$CO$_3$, DMF

**Scheme 18** Protection of allyl alcohols

The allyl ethers was dihydroxylated using a catalytic amount of K$_2$OsO$_4$·2H$_2$O and K$_3$Fe(CN)$_6$ as the cooxidant.[33] The diols were treated with SOCl$_2$ in the presence of pyridine, followed by oxidation of the cyclic sulfite with NaIO$_4$ in the presence of a catalytic amount of RuCl$_3$·H$_2$O to give the cyclic sulfates **(56)** **(Scheme 19)**.[34]

PGO (allyl) $\xrightarrow[\text{K}_3\text{Fe(CN)}_6]{\text{K}_2\text{OsO}_4}$ PGO—CH$_2$—CH(OH)—CH$_2$OH $\xrightarrow[\text{py, CH}_2\text{Cl}_2]{\text{SOCl}_2}$

**(54)**      **(55)** (89%)

[PGO—CH$_2$—(cyclic sulfite, O—SO)] $\xrightarrow[\text{RuCl}_3\text{·H}_2\text{O}]{\text{NaIO}_4}$ PGO—CH$_2$—(cyclic sulfate, O—SO$_2$)

(100%)      **(56)** (75%)

**Scheme 19** Transformation of the protected allyl alcohol to cyclic sulfate

With the *p*-methoxybenzyl (PMB) protecting group, it was found that the cyclic sulfate was unstable. The cause of the instability may be traces of moisture opening the cyclic sulfate ring during storage. This generates strongly acidic species which can catalyse cleavage of the PMB-O bond.

With the acid-stable *p*-methoxyphenyl (PMP) group, the problem of instability of the cyclic sulfate was avoided, however, the oxidation of the cyclic sulfite to the corresponding cyclic sulfate never went to completion, although Bittman has synthesized the same cyclic sulfate and got complete oxidation

reaction using the same reagent.[32] It is likely that $RuO_4$ was reacting with the electron rich PMP group.

Another widely used protecting group is the benzyl (Bn) group. The corresponding cyclic sulfate is stable and can be made in high yield. Unfortunately, a problem arose in deprotection. The general method for the deprotection of benzyl groups is hydrogenation over Pd-C. This method will reduce the alkyne bond to the alkane. It is also known that the benzyl ether moiety can be readily cleaved by dissolving metals. Dissolving metals in liquid ammonia have been used in reductions for decades. The most notable system is the Birch reduction[35-36] with sodium in liquid ammonia and an alcohol. Calcium has been applied to the reduction of various functional groups.[37-44] However, both allenes and alkynes are also reduced under Birch conditions.

Enough of the PMP protected cyclic sulfate (56) was obtained for preliminary experiments. The cyclic sulfate (56) was opened by lithium trimethylsilylacetylide and the trimethylsilyl group was removed with a catalytic amount of the sodium methoxide in methanol[45] to give the terminal alkyne (58) (Scheme 20).
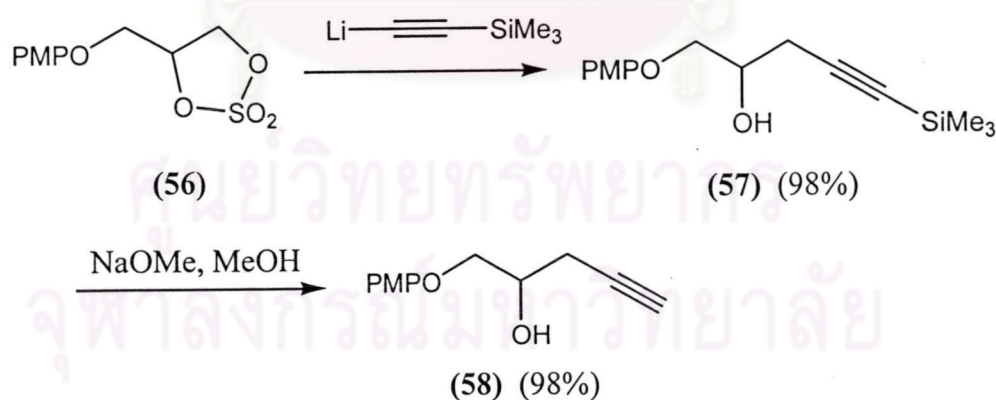


Scheme 20 Transformation of the cyclic sulfate to the terminal alkyne

Despite obtaining some of the desired alkyne, the inefficiency of cyclic sulfate synthesis made the route impractical for the total synthesis.

2.1.2 Synthesis starting from protected epoxide.

Given the problems with the cyclic sulfate route, the use of glycidol (59) was examined. Glycidol was protected with *p*-methoxybenzyl chloride. The epoxide ring (60) was opened with lithium trimethylsilylacetylide[46] in the presence of boron trifluoride-etherate to give the alcohol (61) quantitatively. The opening reaction of epoxide is more convenient than the reaction of the cyclic sulfate, because the number of steps for the synthesis of the electrophile is fewer. The alcohol (61) was treated with sodium methoxide to give the corresponding terminal alkyne (62) (Scheme 21).
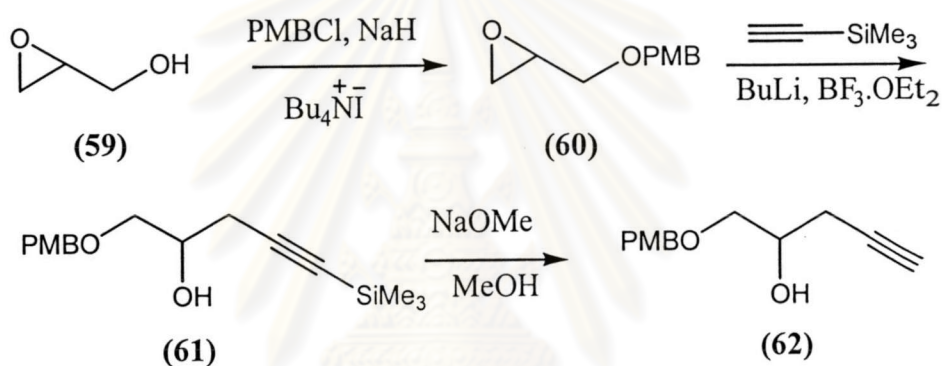


**Scheme 21** Synthesis of the terminal alkyne by ring opening of glycidol

Glycidol is available inexpensively as the racemate. For natural product synthesis, single enantiomers are highly desirable. Kinetic resolution is an attractive strategy for the production of optically active epoxides. Jacobsen *et al.* have used cobalt salen complexes (63) for the efficient asymmetric hydrolysis of terminal epoxides. This process can give both unreacted epoxide and 1,2-diol products in high enantiomeric excess and yield (Scheme 22).[47]
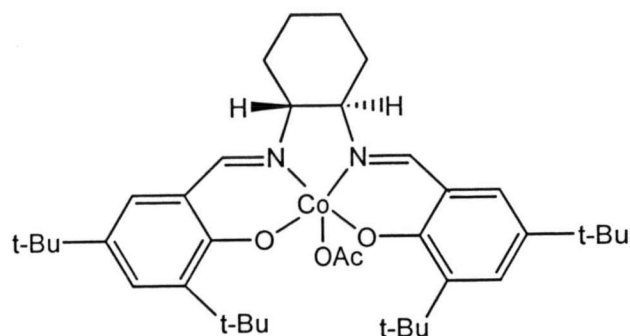
(*R*,*R*)-(salen)Co complex **(63)**
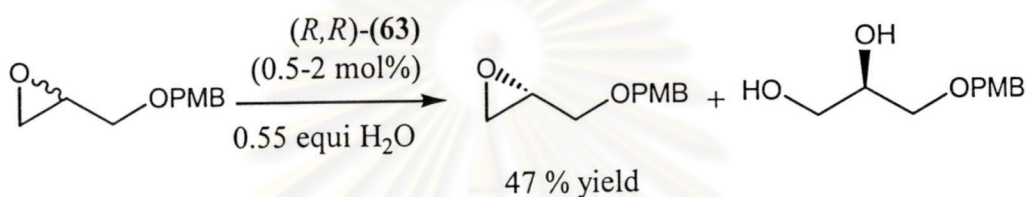


**Scheme 22** Hydrolytic kinetic resolution using (salen)Co complex

## 2.2 The synthesis of β-substituted allenes.

Since the *t*-butyldimethylsilyl group[48] promoted a high ratio of *trans*/*cis* isomers in the α–substituted allene cyclization[29], the same protecting group was selected in anticipation of a similarly highly diastereoselective acylation-cyclization (**Scheme 23**).
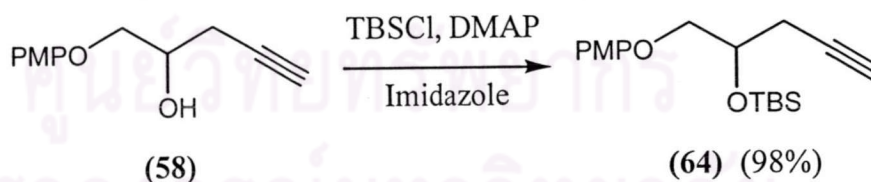


**Scheme 23** Protection of the hydroxyl group

There are several methods for the synthesis of allenes, because of their growing importance in organic synthesis. Myers and Zheng have reported a new and stereospecific method for the synthesis of allenes from propargylic alcohols that proceeds in a single operation and provides access to a wide range of substituted allenes[49]. The sulfonamide group of *o*-nitrobenzenesulfonylhydrazine

can function as the nucleophilic component in a Mitsunobu reaction (65→66). They showed that intermediate (66) fragments under mild condition in methanol *via* the spontaneous elimination of *p*-toluenesulfinic acid and dinitrogen to form the allene (67) (Scheme 24).[49]



Ar = $o$-$C_6H_4NO_2$

(65)          (66)          (67)
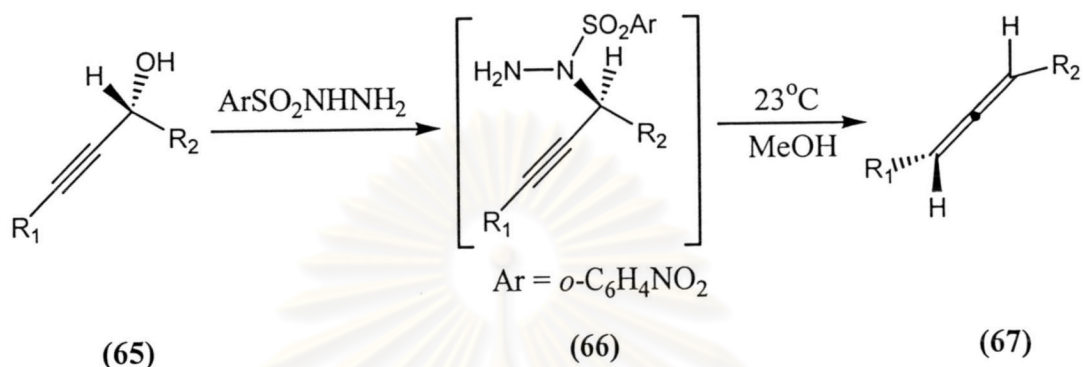
**Scheme 24** Stereospecific synthesis of an allene from a propagylic alcohol

Isaac and Chan have used the indium mediated coupling of aldehydes with prop-2-ynyl bromides in aqueous media.[50] They found that propargyl bromide (Y=H) reacted with aliphatic or aryl aldehydes to give mainly the homopropargyl alcohols. In contrast, when γ-substituted prop-2-ynyl bromides were used, the couping products were predominantly the allenic alcohols (**Scheme 25**).



| | Minor | Major |
|---|---|---|
| Y = H | Minor | Major |
| Y ≠ H | Major | Minor |
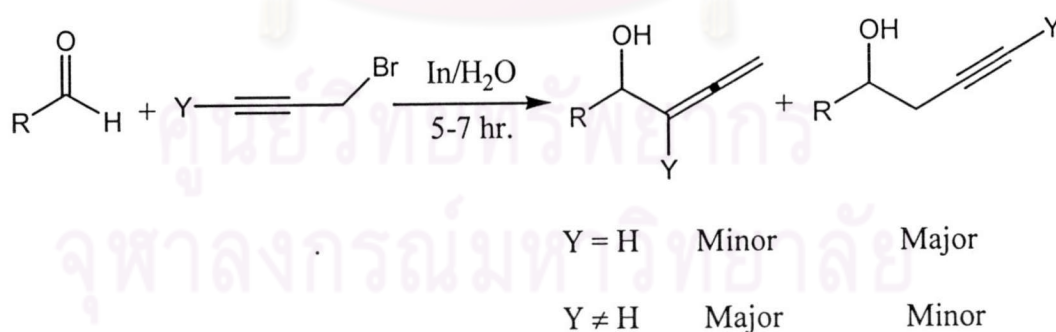
**Scheme 25** Indium mediated coupling of prop-2-ynyl systems

Takai's group has synthesized allenes by generating a geminal chromium dicarbenoid[51]. The chromium dicarbenoid species react with terminal alkenes (68) to give cyclopropylidene carbenoids (69), which readily decompose to allenes (70) (**Scheme 26**).[52] This reaction is similar to the Skatterbøl reaction in which

bromoform is used to generate dibromocarbene. *In situ* reaction with an alkene (71) yields a dibromocyclopropane (72). Rearrangement of the cyclopropylidine carbene generated by metallation in a second step gives an allene (73) (**Scheme 27**).[51]
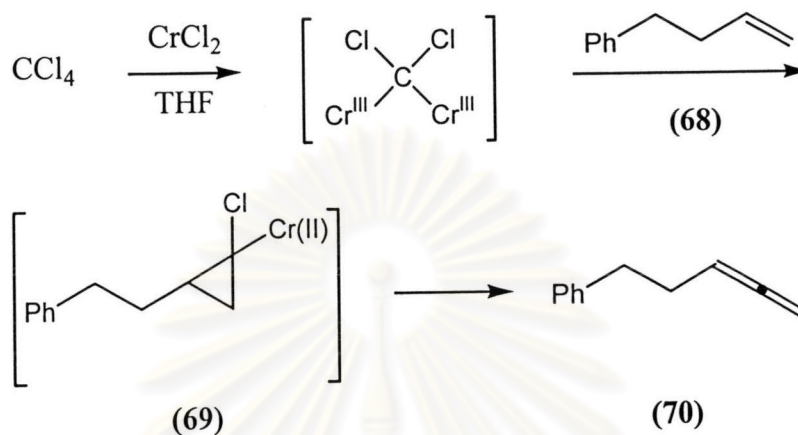


**Scheme 26**  Takai's allene synthesis
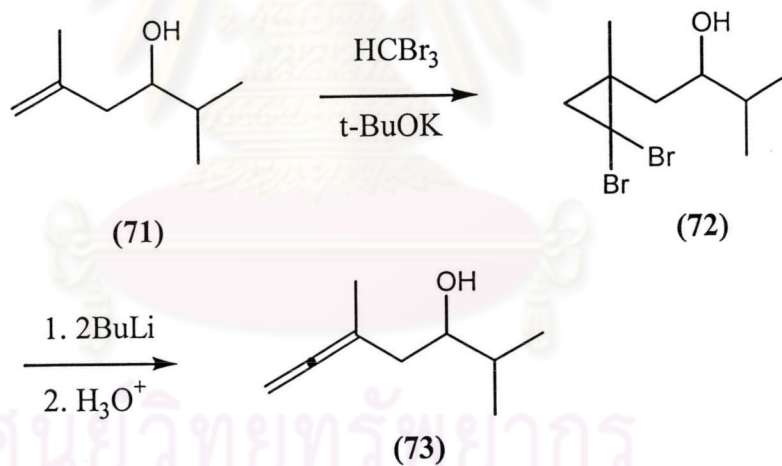


**Scheme 27**  The Skatterbøl reaction

For terminal allenes, the simplest synthetic procedure is the Searles-Crabbé reaction[53], because of its operational convenience and the ready availability of the reagents. It has been frequently used in these laboratories and elsewhere. Therefore, the terminal alkynes (62) and (64) were then homologated to the allenes (74) and (75) using paraformaldehyde, diisopropylamine and a catalytic amount of cuprous iodide in refluxing dioxane (**Scheme 28**).[53]

(62) : R = PMB   R' = H   (90%)

(64) : R = PMP   R' = TBS   (68%)

(74) : R = PMB   R' = H

(75) : R = PMP   R' = TBS
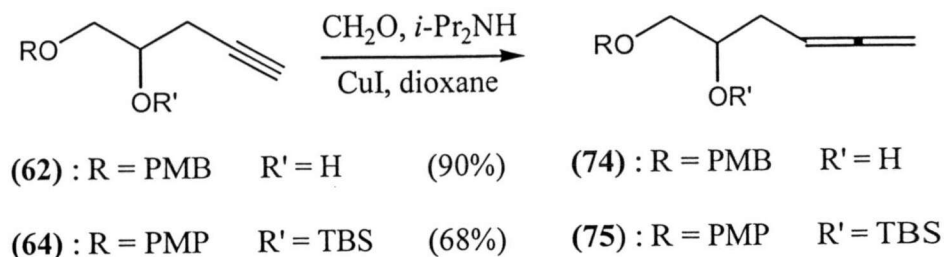
**Scheme 28** The Searles-Crabbé reaction

A modified work up was used to remove the Cu(I), which caused complications in subsequent extractions. Air was bubbled through the cooled reaction mixture in order to oxidize Cu(I) to Cu(II) which was then easily removed by filtration. After an extraction work up, the residue was purified by flash chromatography.

A two-step mechanism has been proposed for this homologation, the first step is a cuprous iodide-catalyzed Mannich reaction and the second is a 1,5-sigmatropic migration of hydrogen (**Scheme 29**).[54]
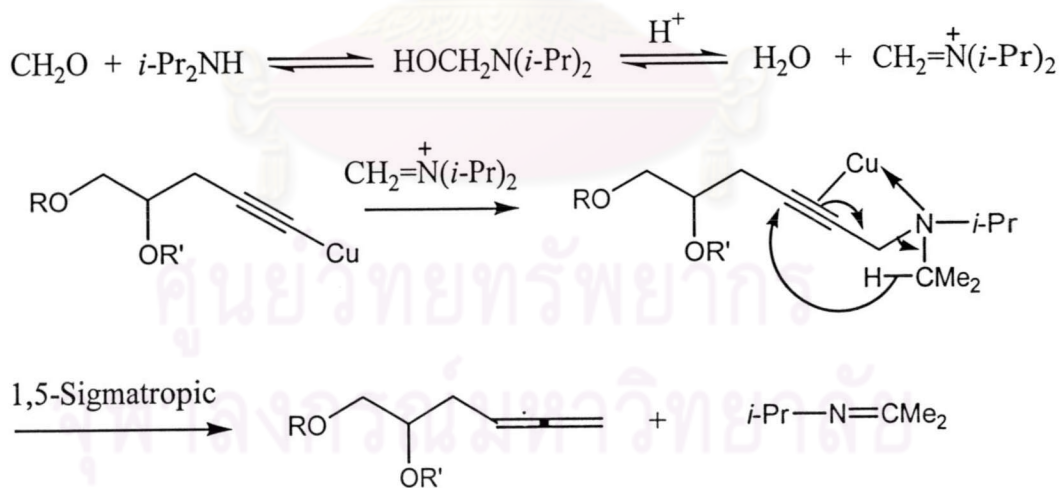


(74) R = PMB   R' = H

(75) R = PMP   R' = TBS

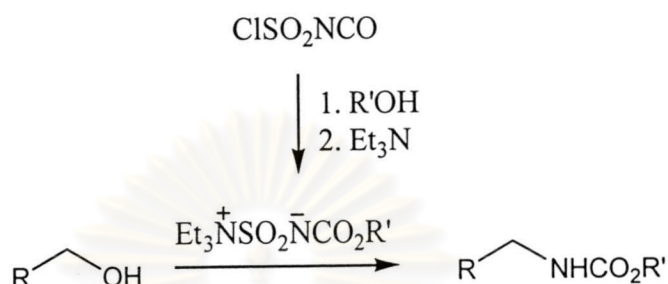**Scheme 29** The mechanism of the synthesis of the allene

Removal of the PMP group from the allene (**75**) was carried out using ceric ammonium nitrate (CAN)[55] to afford (**76**). The concurrent formation of benzoquinone was apparent by TLC, and it was difficult to separate this from the deprotected product (**76**). To introduce the sulfonamide moiety, the primary alcohol (**76**) was converted to a good leaving group. The mesylate group is frequently used, but subsequent treatment with sodium azide in DMF gave a poor yield of the azide product. The triflate group, which is better leaving group than mesylate, was then used and triflate (**77**) was treated with sodium azide in DMF. The desired azide (**78**) was obtained in moderate yield and confirmed by the appearance of the azide stretching bond in the IR spectrum at 2100 cm$^{-1}$. Reduction of the azide (**78**) was achieved using activated zinc under mildly acidic[56] conditions, then treatment with sodium carbonate and tosyl chloride produced the allenic sulfonamide (**79**) required for the acylation-cyclization (**Scheme 30**).
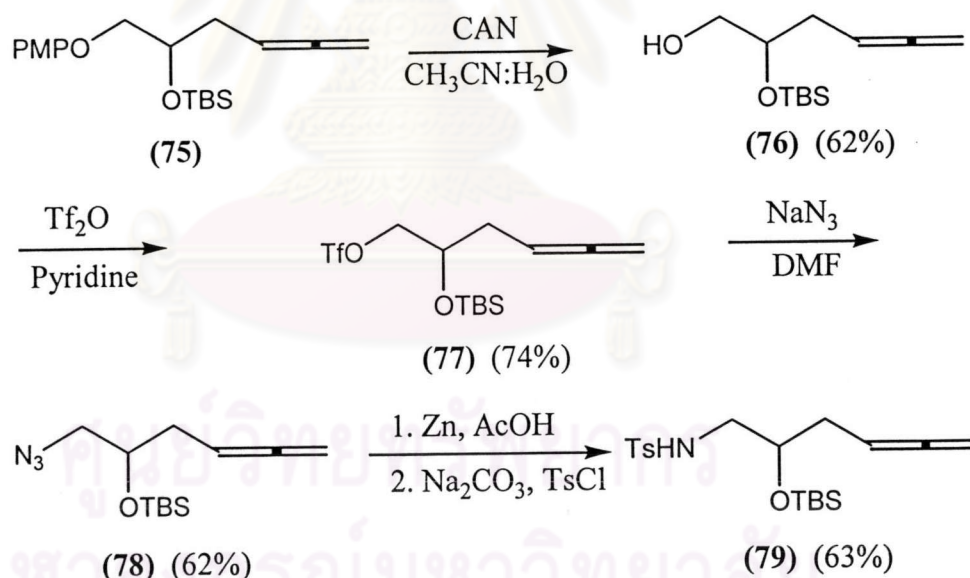
**Scheme 30** Sufonamide synthesis

Modifications to this synthesis were sought because the yield of azide was capricious and the deprotection of PMP group gave only a moderate yield. Firstly, it was decided to use the PMB group instead of the PMP group. Secondly, an alternative way to introduce nitrogen was employed. Burgess salt has been used to convert primary alcohols (but not secondary or tertiary alcohols) into methyl

carbamates in one step. The Burgess reagent[57] is easily prepared from methanol, chlorosulfonyl isocyanate and triethylamine in a two step procedure. It has recently been shown that alcohols other than methanol can also be used (**Scheme 31**).[58]

$$ClSO_2NCO$$

$$\downarrow \begin{array}{l} 1.\ R'OH \\ 2.\ Et_3N \end{array}$$

$$Et_3\overset{+}{N}SO_2\overset{-}{N}CO_2R'$$

$$R\diagup OH \xrightarrow{\hspace{3cm}} R\diagdown NHCO_2R'$$

**Scheme 31** Transformation of primary alcohols to carbamates

Recently, Nicolaou[59] has reported the regioselective and stereoselective synthesis of a variety of 1,2-amino alcohols form 1,2-diols using Burgess salt and its analogs.

A mechanism was proposed involving reaction of both hydroxy groups with Burgess'salt, followed by displacement of one by the nitrogen anion of the other. The amino alcohols could then be liberated by acidic hydrolysis of the cyclic sulfamidate intermediates (**Scheme 32**).
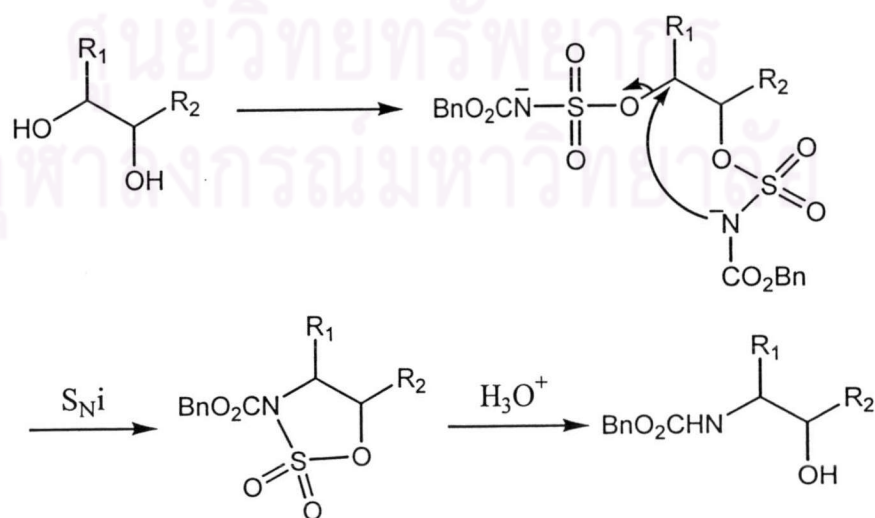
**Scheme 32** The mechanism proposed by Nicolaou

Removal of the PMB group from the allene (74) was carried out using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The product of deprotection was the allene diol (81) as the minor product and the ester (80) as the major product, which was hydrolyzed with LiOH gave the allene diol (81) (Scheme 33).
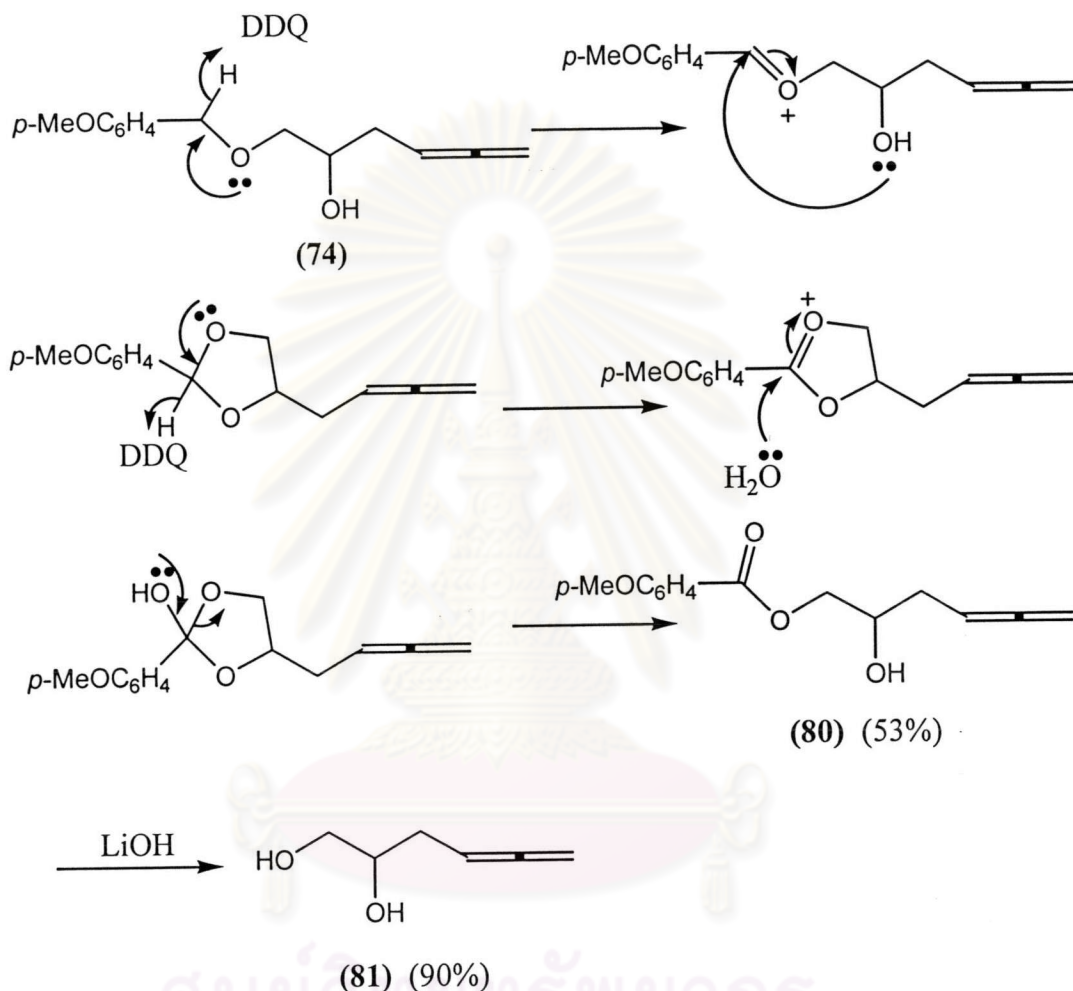


**Scheme 33** The mechanism of deprotection of the PMB group

Following Nicolaou's method, The allene diol (81) was easily converted to the cyclic sulfamidate (82). However hydrolysis with a 1:1 mixture of HCl (aq.) and dioxane gave only a low yield of the amino alcohol (83) accompanied by unreacted cyclic sulfamidate. Prolonged reaction times resulted in the beginning of decomposition (Scheme 34).
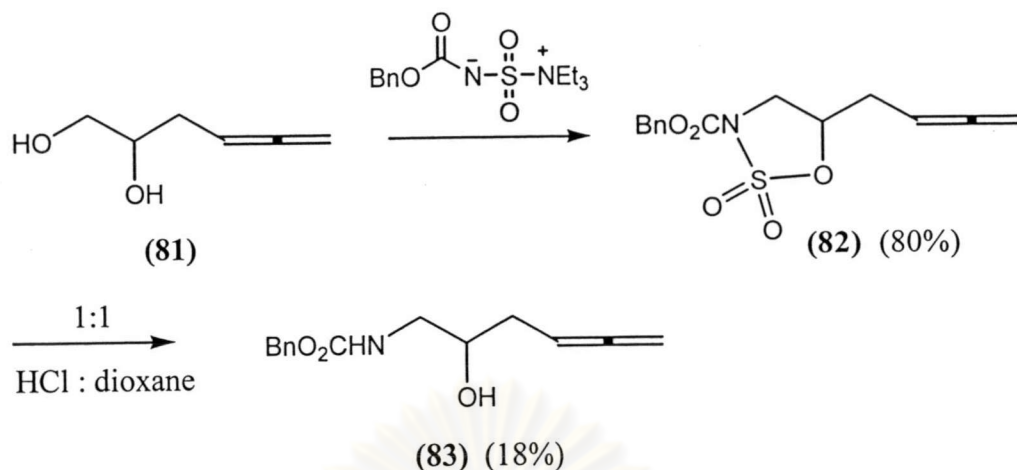
**Scheme 34** Tranformation of the allene diol to 1,2 –amino alcohol.

Due to the low yield from the Nicolaou procedure, another procedure was selected.

The Mitsunobu reaction is very useful in organic synthesis and has become a general method in organic synthesis, because a hydroxyl group can be replaced by many nucleophiles.[60-62] Many reports of intermolecular and intramolecular Mitsunobu reaction have been made. As the displacement of a leaving group with a β-electronegative substitutent is well known to be difficult, an intramolecular Mitsunobu reaction was selected. Treatment of the secondary alcohol with tosyl isocyanate, followed by deprotection of the PMB group using ceric ammonium nitrate (CAN) yielded the hydroxy carbamate **(85)**. The deprotection of the PMB group gave a better yield than the deprotection of the PMP group because purification was easier. Ring closing was achieved by activating the primary alcohol group *via* the Mitsunobu reaction.[63] During this work diethyl azodicarboxylate (DEAD) became commercially unavailable , and diisopropyl azodicarboxylate (DIAD) was also used. The cyclic oxazolidinone **(86)** was obtained in good yield with either reagent, but the by-product from DIAD was more difficult to separate from the cyclic oxazolidinone. The cyclic oxazolidinone **(86)** was hydrolyzed with LiOH in MeOH/$H_2O$ and gave the required allene **(87)**. An acidic work up of the reaction was unnecessary which is probably due to neutralization of the medium by the released $CO_2$ **(Scheme 35)**.
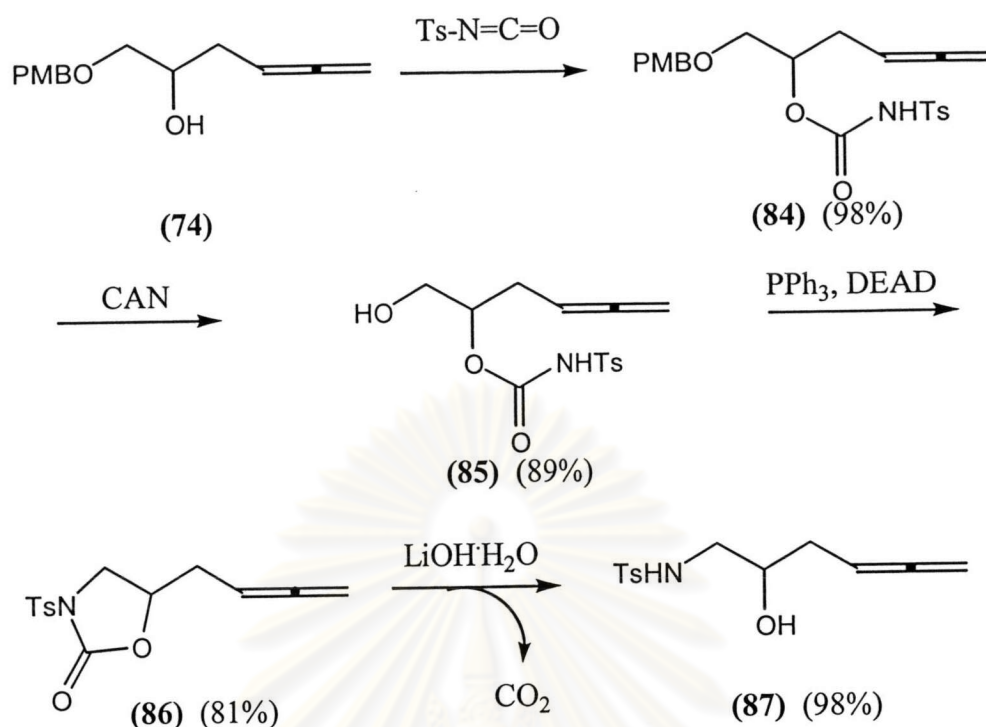
**Scheme 35** Transformation to sulfonamides *via* Mitsunobu reaction

### 3.1 Cyclization of β-substituted allene.

#### 3.1.1 The acylation-cyclization reaction using an organocobalt reagent.

Acetyltetracarbonyl cobalt **(89)** was prepared by treatment of octacarbonyl dicobalt with sodium hydroxide[64], and it was filtered under carbon monoxide. The sodium tetracarbonylcobaltate **(88)** was alkylated with methyl iodide followed by insertion of carbon monoxide to give the acetyltetracarbonyl cobalt **(89) (Scheme 36).**[28]
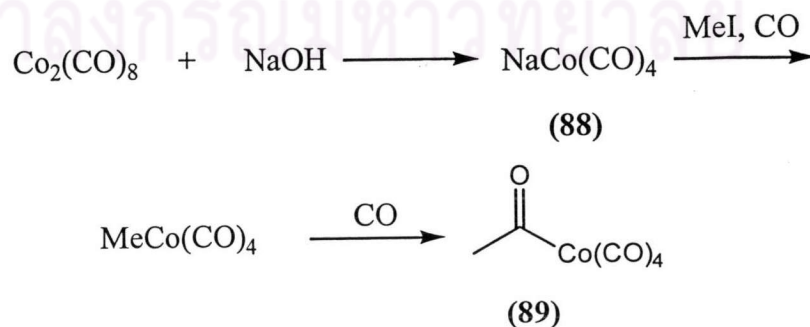


**Scheme 36** Generation of acyl tetracarbonyl cobalt complexes

Treatment of the allenic sulfonamide **(79)** with acetyltetracarbonyl cobalt and triethylamine yielded the pyrrolidine **(90)**. Unfortunately, the ratio of stereoisomeric cyclization products was 1:1 **(Scheme 37)**.
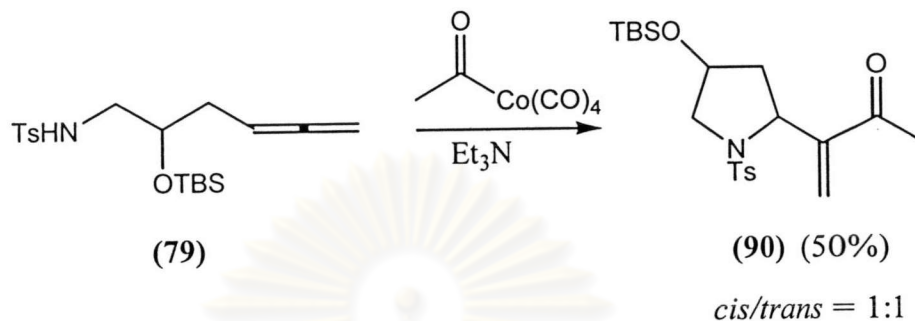


**Scheme 37**    The acylation cyclization using cobalt complexes

The two diastereoisomers were separated by flash chromatography. The stereochemistry was determined by NOE experiments. The *trans* isomer which was less polar was identified by irradiation of the H-3a which led to enhancement of H-2 but not enhancement of H-4. Irradiation of the H-3b led to no enchancement of H-2 but enchancement of H-4 **(Figure 11)**. On the other hand, for the *cis* isomer, irradiation of H-3a led to clear enhancement of both protons α to heteroatoms (H-2, H-4). Irradiation of H-3b led to no enhancement of either proton α to a heteroatom **(Figure 12)**.
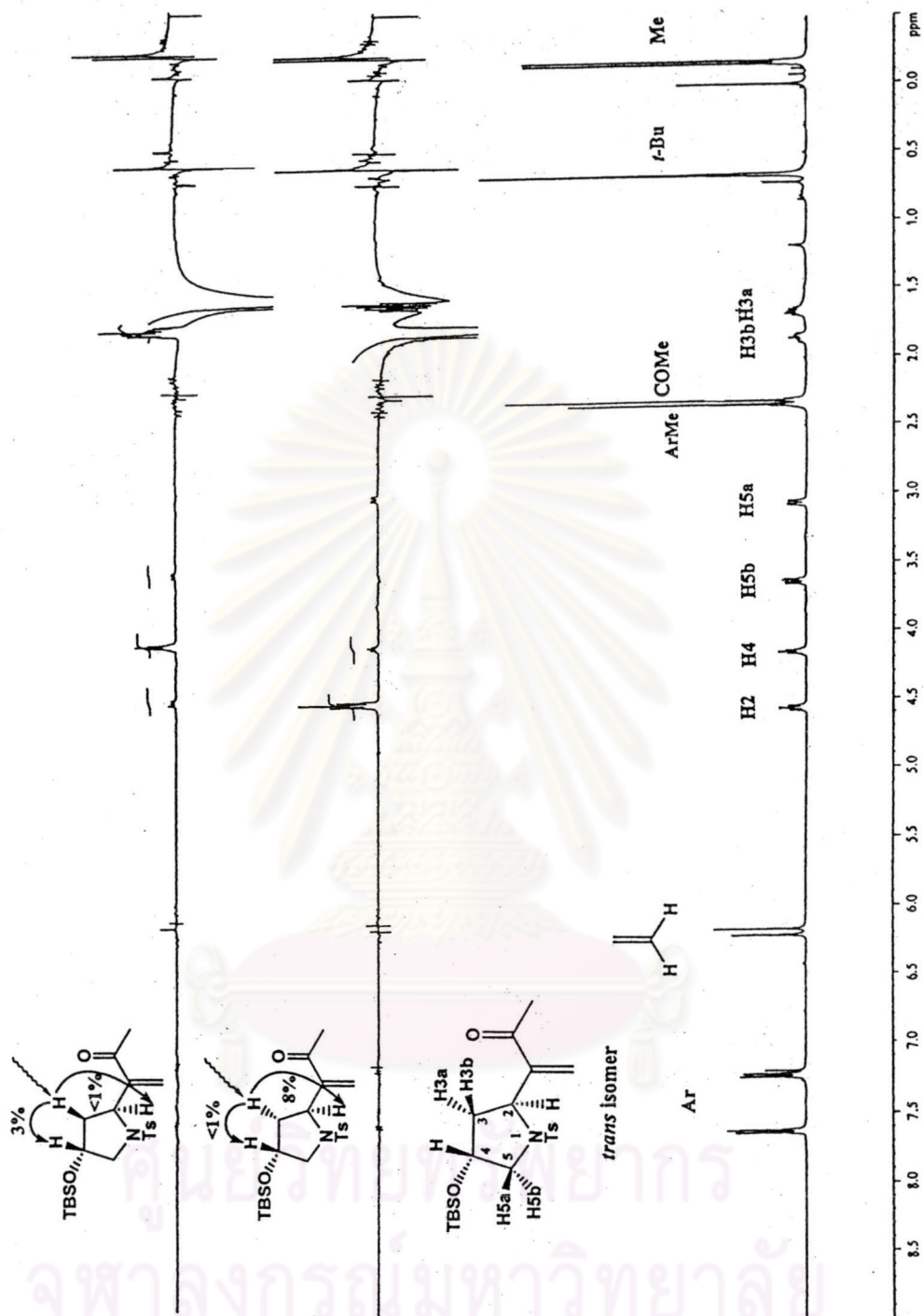
**Figure 11** NOE difference spectrum of *trans*-pyrrolidine with irradiation of H-3a and H-3b protons.
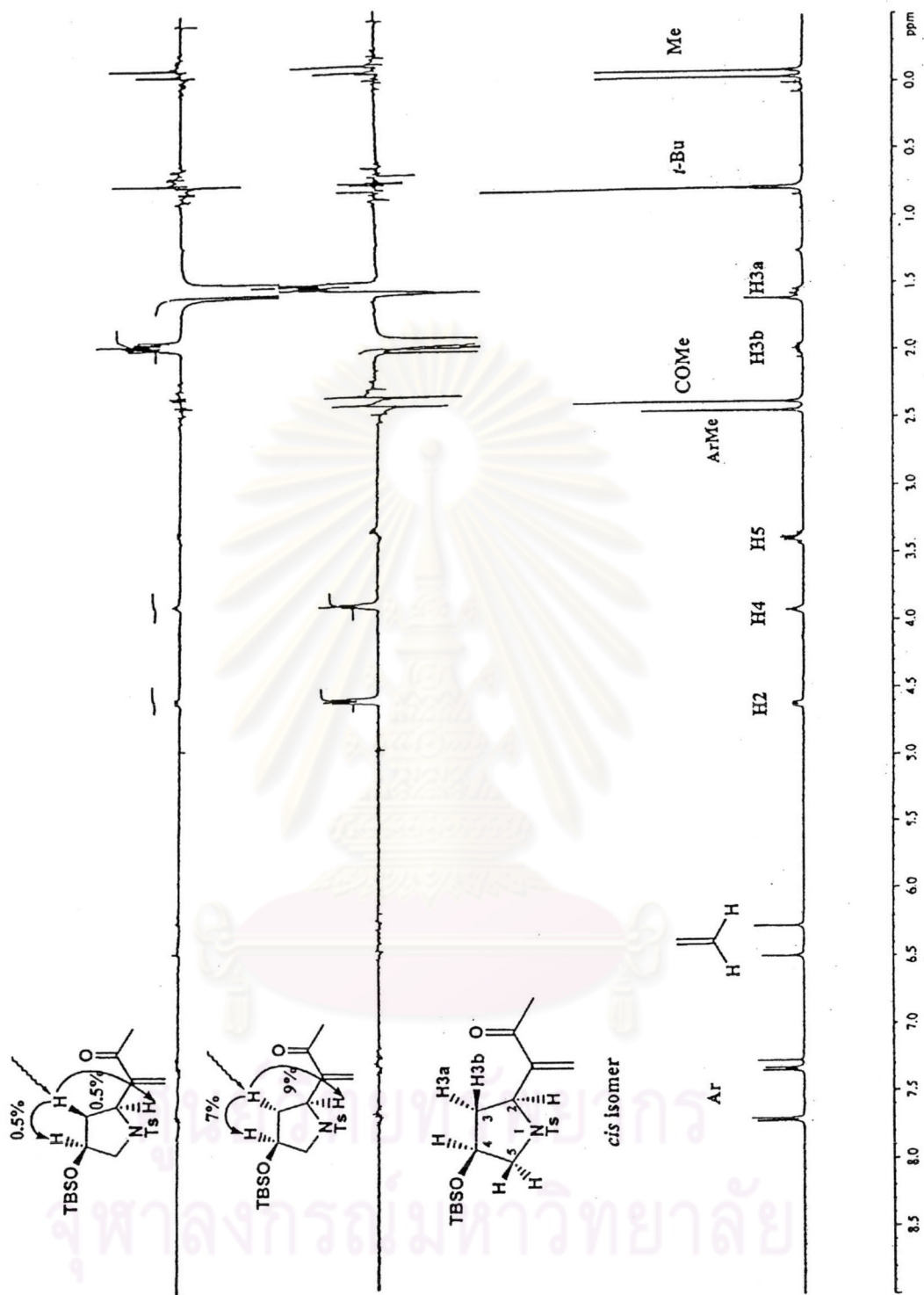
**Figure 12** NOE difference spectrum of *cis*-pyrrolidine with irradiation of H-3a and H-3b protons.

The interaction between substituents in the ring forming step was a key role in the *cis/trans* selectivity in cyclization. A cyclization leading to a 2,4-disubstituted pyrrolidine would, given the 1,3-interaction that between the C-4 residue and both N-substituent and the delveloped alkenyl function (as in **(91)**), be gave a mixture of *cis-* and *trans*-product **(Figure 13)**.



**(91)**
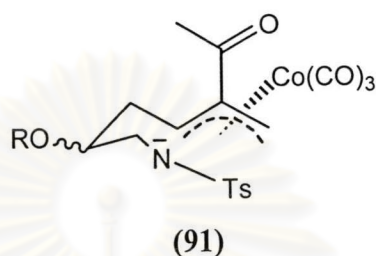
**Figure 13** The conformation of the π–allyl intermediate

### 3.1.2 The palladium catalyzed cyclization of allenes

The palladium-catalyzed reaction of heteroatom nucleophiles with allenes has been reported by several groups. In most examples the nucleophile attacks one of the $sp^2$ carbon atoms of the allene. Gallagher described the cyclization of a series of substituted allenic sulfonamides under carbonylation conditions in terms of the distribution of the *cis-* and *trans*-disubstituted pyrrolidine products that may be obtained **(Scheme 38)**.[27]
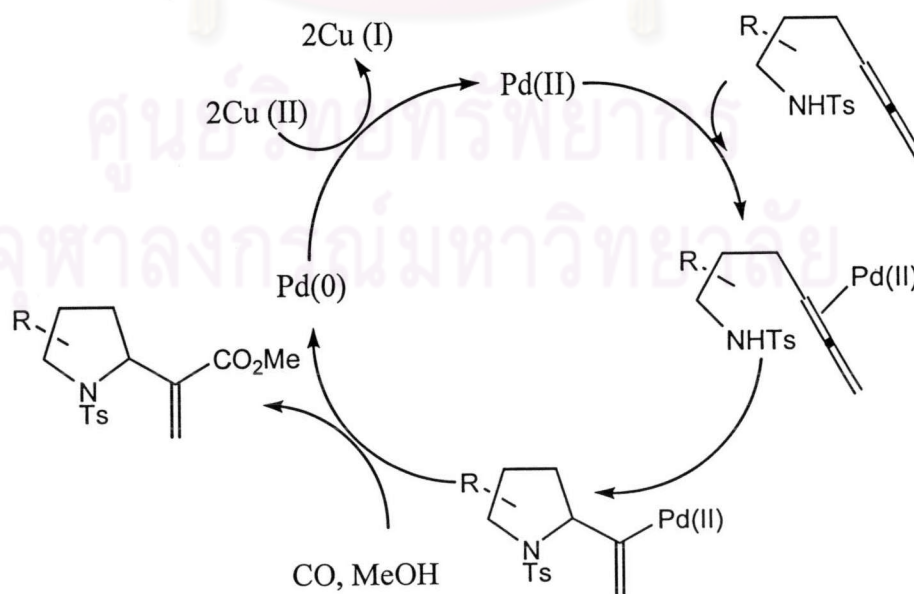


**Scheme 38** Pd(II)-catalyzed cyclization of allenic sulfonamides

These transformation were high yielding and also highly stereoselective for the 2,3-series (*trans* product obtained) and the 2,5-series (*cis* product obtained). However, the cyclization to give 2,4-disubstituted pyrrolidines was essentially nonselective. In one case, using a palladium catalyzed[65] cyclization, the stereoselectivity of the reaction allowed a formal synthesis of α-anatoxin (**Scheme 39**).



catalyst = Pd(II) : 3:1 (*cis:trans*)
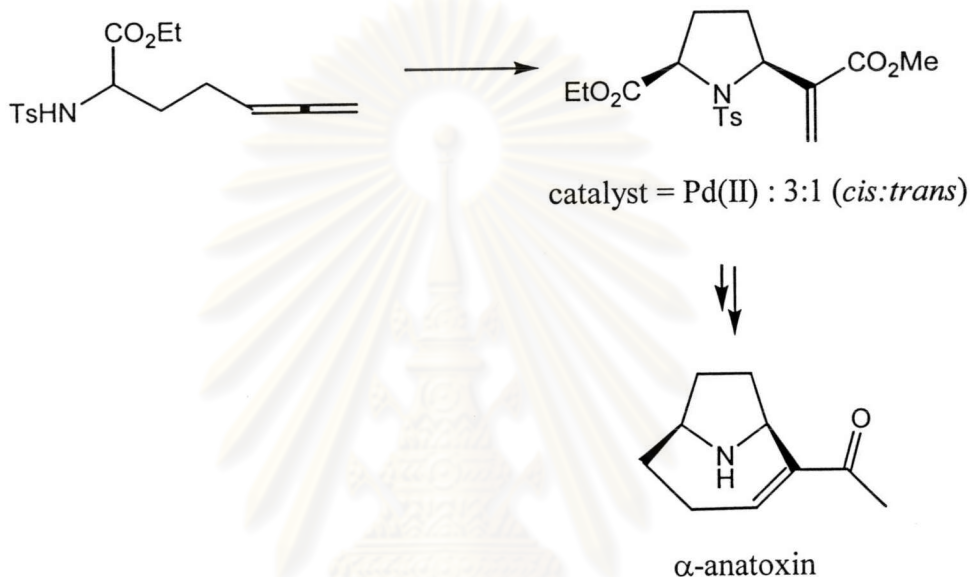
α-anatoxin

**Scheme 39**  Synthesis of α-anatoxin

Yoshida's group[66] has reported a very convenient and efficient synthesis of *cis*-3-hydroxytetrahydrofuran 2-acetic acid lactones, which could be achieved by a palladium catalyzed intramolecular oxycarbonylation of 4-penten-1,3-diols under very mild conditions (**Scheme 40**).



$PdCl_2$ (0.1 eq.)
$CuCl_2$ ( 3  eq.)
NaOAc ( 3  eq.)
CO        ( 1 atm)
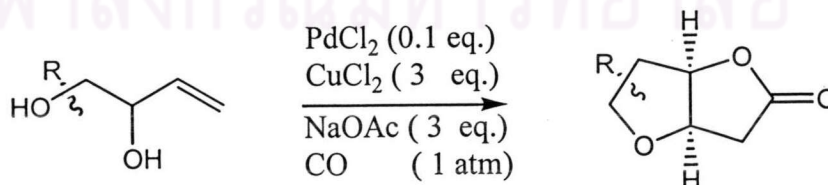
**Scheme 40**  Stereoselective cyclization using palladium catalysis

β-Substituted allene (**87**) was employed in this reaction in the expectation that good selectivity would be achieved by such an intramolecular acylation. This

reaction, however, resulted in the decomposition of starting materials, indicating that 6-membered ring formation is ineffective **(Scheme 41)**.
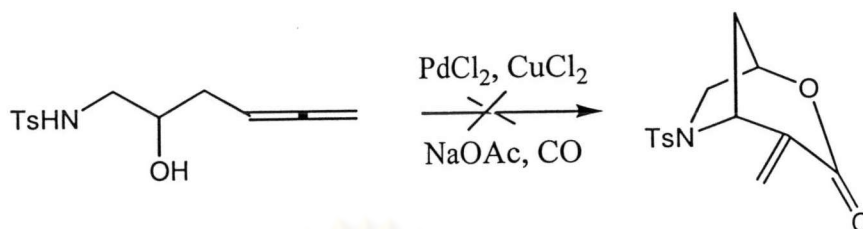


**Scheme 41** Intramolecular cyclization of β–substituted allene

As a test of the procedure β-substituted allene **(87)** was treated with palladium (II) chloride (cat.), and copper (II) chloride in MeOH under carbon monoxide. Cyclization occurred in 55 % yield and the product **(92)** was found to be a 2:1 mixture of stereoisomers by NMR spectroscopy **(Scheme 42)**.



**(87)**                                                    **(92)** (55%)
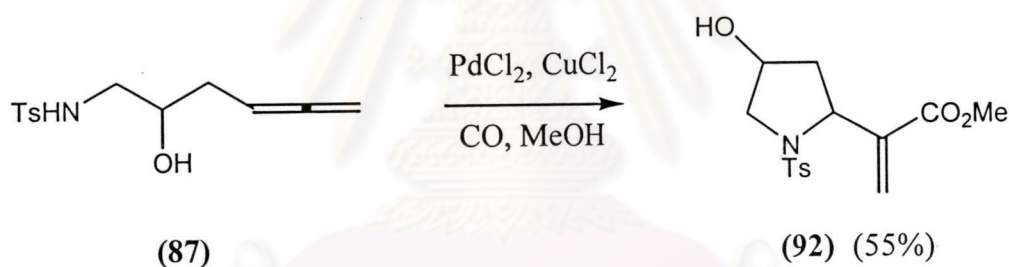
**Scheme 42** Pd(II) catalyst cyclization of β-substituted allene

The mixture of pyrrolidines **(92)** product could not be separated. In order to obtain crystals of one isomer suitable for X-Ray crystallography, the hydroxy substituted pyrrolidine was converted to its 3,5-dinitrobenzoyl ester. Numerous attempts to recrystallize the product failed to give single diastereoisomers. An alternative strategy is to convert the ester **(92)** group into a ketone **(90)** and correlate the products with those from the cobalt mediated cyclization. Petasis and co-workers have shown that when dimethyltitanocene is heated to 60-75 °C either in THF or toluene in the presence of a carbonyl compound, methylenation of the carbonyl compound results. Unlike the Wittig reaction, this chemistry also works for esters. The mixture of pyrrolidines was protected with the TBS group.

However, treatment with Petasis reagent resulted in decomposition of starting material (**Scheme 43**).
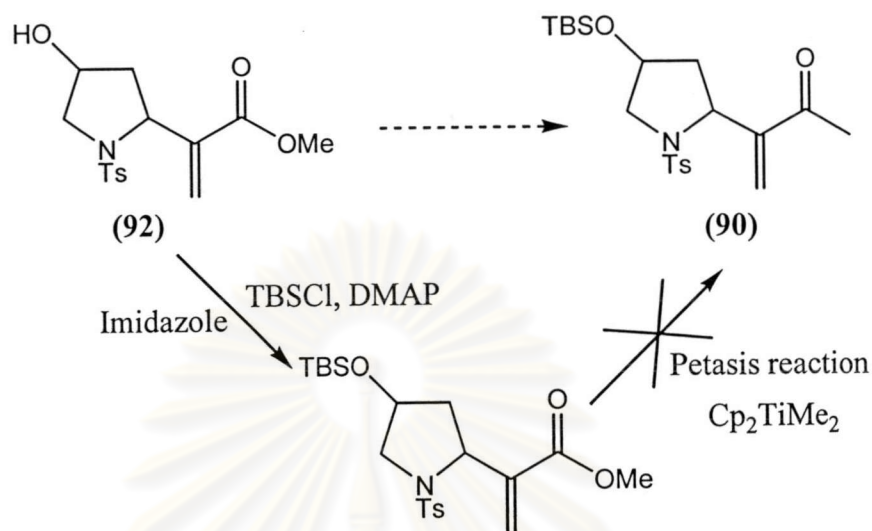


**Scheme 43** Transformation to ketone (**90**)

As the mixture of (**92**) was inseparable, it was carried through further steps towards a pyrrolizidine in the hope that separation could be achieved at a later stage. The hydroxy substituted pyrrolidine (**92**) was protected with the TBS group. Oxidation of the alkene (**92**) to a carbonyl using sodium periodate and a catalytic amount of osmium gave an α-ketoester. The α-ketoester (**94**) was treated with vinylmagnesium chloride solution, followed by acidification with amberlite IRC-86. This is a weakly acidic polymer, which can quench the intermediate alkoxide in the same manner as an ordinary aqueous acid quench, but can be easily removed by filtration, rather than extraction. The reaction of vinylmagnesium chloride with the mixture of pyrrolidines gave only a single pair of diastereomeric products (**95+96**) corresponding to the mixture of diastereoisomeric α-ketoesters. This may be due to chelation of the magnesium between the tosyl group and the carbonyl group of the α-ketoester resulting in preferred addition to one face. Sodium naphthalenide in DME at low temperature was used for deprotection of the tosyl group[67]. Although the tosyl group was removed, no identifiable product could be isolated (**Scheme 44**).
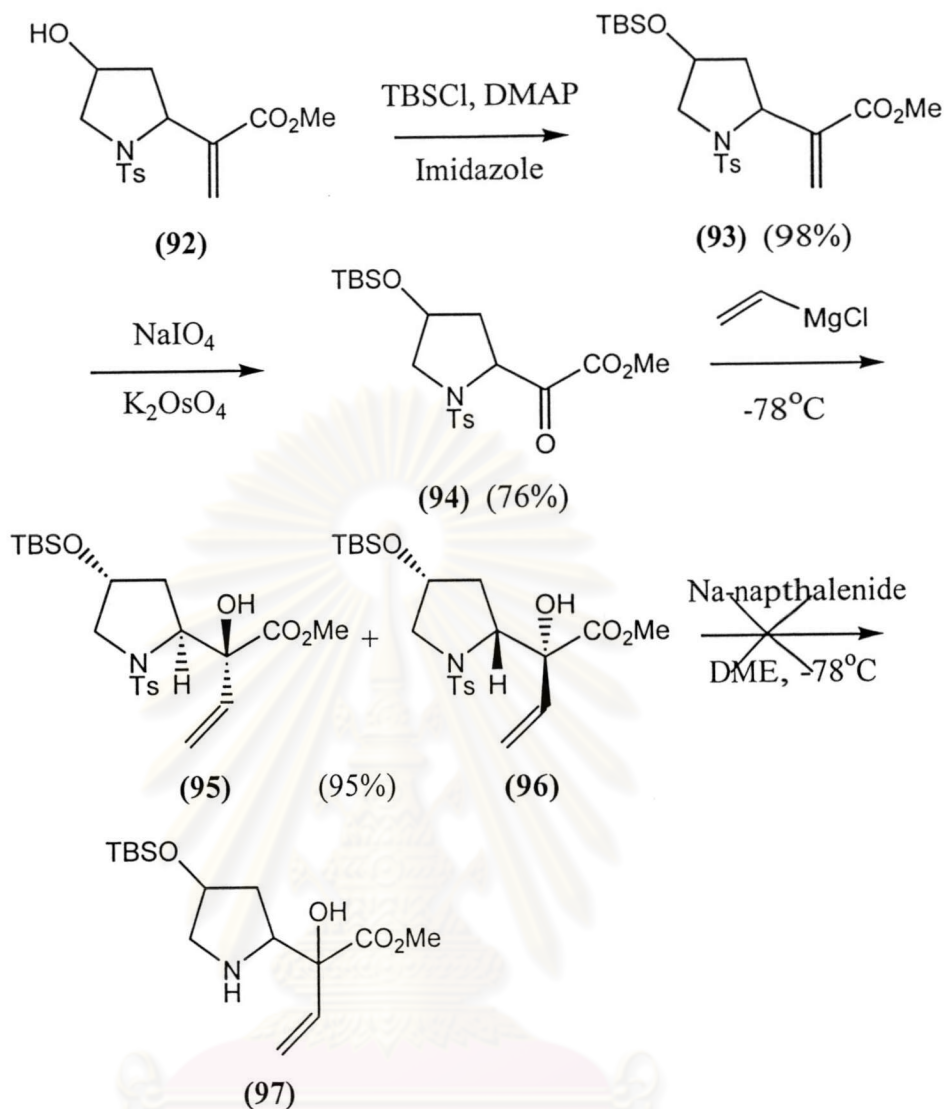
**Scheme 44**    Transformation to deprotected pyrrolidine **(97)**

In conclusion, diastereoselectivity in the allene cyclization could be achieved using palladium rather than cobalt chemistry. Further progress towards amphorogynine was made, but an alternative protecting group regime will be required.