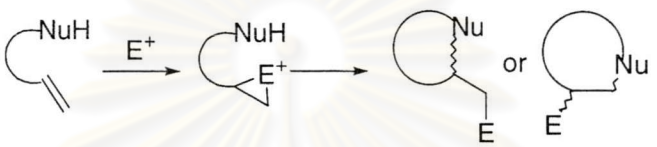
Chapter I

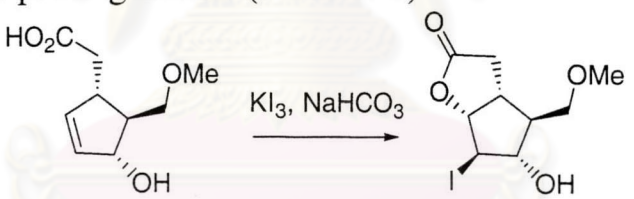
Introduction

Cyclofunctionalization is a type of cyclization reaction, initiated by electrophilic attack on an unsaturated bond and then cyclization to form a bond between an internal nucleophile and the unsaturated carbons. (**Scheme 1**)[1]



Scheme 1 Alkene cyclofunctionalization

Cyclofunctionalization has often been employed as a key step in many organic syntheses because of the resulting regio- and stereochemical control that results. An early example is in the Corey group's work on prostaglandin. (**Scheme 2**)[2]



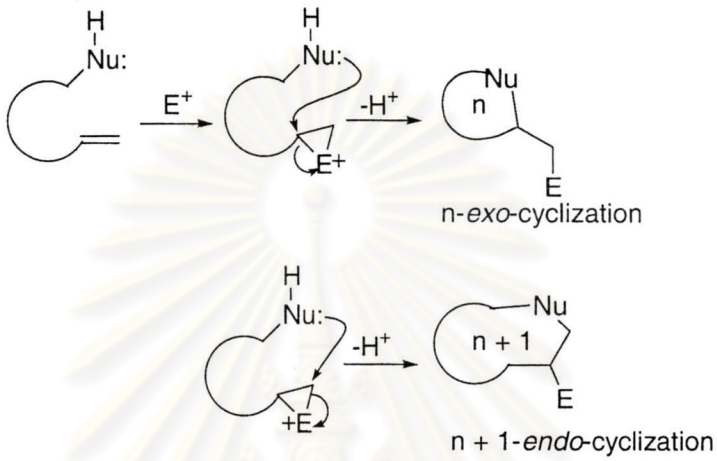
Scheme 2 Corey's cyclofunctionalization

Many types of electrophiles have been used, especially halogens, chalcogens and transition metals. Nitrogen, oxygen, sulfur nucleophiles have been frequently used in these cyclization reactions to give a wide range of heterocyclic compounds.

1. General mechanism

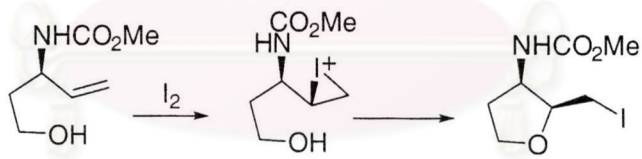
1.1 Regioselectivity

The regioselectivitiy of cyclofunctionalization has been extensively studied and can be generally described by the *exo*- and *endo*-cyclization modes. (**Scheme 3**)



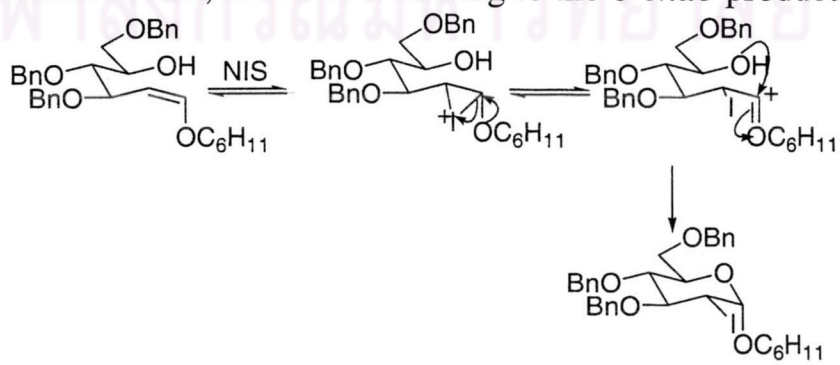
Scheme 3 Cyclofunctionalization modes

Scheme 4 shows an example of the regioselectivity of 5-*exo*-cyclofunctionalization, which has stereoelectronic control predominating. (**Scheme 4**)[3]



Scheme 4 5-*exo*-cyclofunctionalization

The reaction shown in **Scheme 5** demonstrates that the electron donating ability of the ether substituent can control the regioselectivity of cyclofunctionalization, in this case leading to the 6-*endo* product. [4]



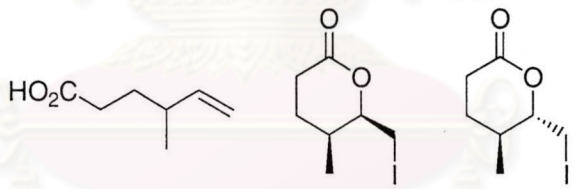
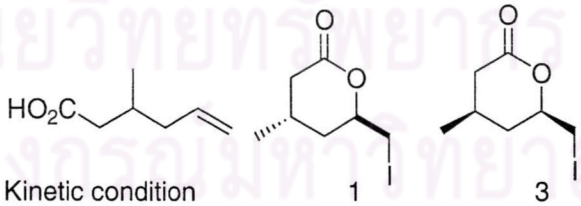
Scheme 5 6-*endo*-cyclofunctionalization

1.2 Stereoselectivity

The stereoselectivity of the cyclization reaction is a very important aspect of the reaction. When the internal nucleophile adds to the *anti* position relative to the induced electrophile, two diastereoisomeric cyclized products can be formed if the substrate contains a stereogenic center. The major product will be determined by the reaction conditions, in particular, either thermodynamic or kinetic condition is used.

It is not always, however, clear whether a given reaction is conducted under conditions of kinetic or thermodynamic control, which step is rate limiting, or which step controls the stereochemistry. The thermodynamic control products are the major products when the cyclization reactions are reversible because of the preferences for more stable structure. If the reactions are irreversible, the kinetic products will be generally formed.

Bartlett's group has reported the iodolactonization of unsaturated acids. (**Table 1**)[5] They showed that the use of thermodynamic or kinetic conditions could control the major product.

Entry	Substrates	Ratio of Products		yield
				
1	Kinetic condition	2.3	1	83%
2	Thermodynamic condition	1	15	77%
				
3	Kinetic condition	1	3	97%
4	Thermodynamic condition	1	6	81%

Kinetic condition: 3 eq. I_2, CH_3CN, $NaHCO_3$, 0 °C
Thermodynamic condition : 3 eq. I_2, CH_3CN, 0 °C

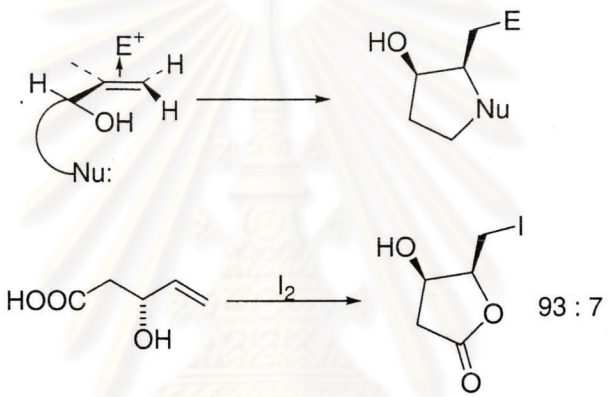
Table 1 Kinetic and thermodynamic cyclofunctionalization

Under conditions of kinetic control (iodine in acetonitrile in the presence of $NaHCO_3$ as an acid scavenger and a reaction accelerator), 4-methyl-5-hexenoic acid showed a modest preference for formation of the

cis-lactone. (Entry 1) Under thermodynamic conditions, without $NaHCO_3$, the *trans* product is major. (Entry 2)

For the formation of the disubstituted six-membered ring, it can be predicted that the thermodynamic product has both substituents equatorial.

The stereoselectivity can be determined by the diastereofacial discrimination of the attack of the electrophile on the π-system.[6] For the example in **Scheme 6**, the electrophile is reported to prefer to approach an OH-in-plane conformer of allyl-OH group. The *cis*-isomer of the cyclized product will be the major product if it has no substituent on the double bond.



Scheme 6 Allylic alcohol iodolactonization

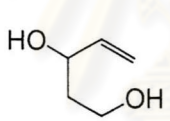
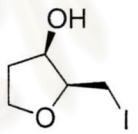
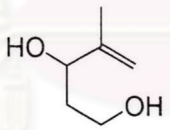
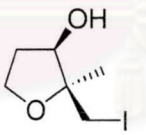
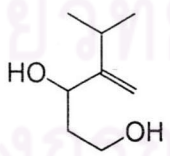
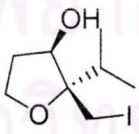
2. Electrophiles

2.1 Halocyclofunctionalization

Halogens (iodine and bromine) are very useful electrophiles for cyclofunctionalization reactions. Many types of starting materials can be cyclized by treatment with halogens to form cyclized products.

2.1.1 Iodocyclofunctionalization[7]

Stereocontrolled tetrahydrofuran synthesis with excellent 1,3 asymmetric induction on cyclization was demonstrated to give the *cis*-compounds. (**Table 2**) This is a notably effective way to construct a quaternary center.

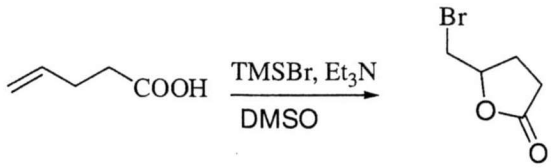
Entry	Substrates	Product	*cis* : *trans*	yield
1			95 : 5	87%
2			91 : 9	94%
3			100 : 0	73%

Conditions I_2 (1.5 eq.), $NaHCO_3$ (2 eq.), ether (5 mL) - H_2O (2 mL) to 1 mmol of substrate

Table 2 Iodocyclofunctionalization

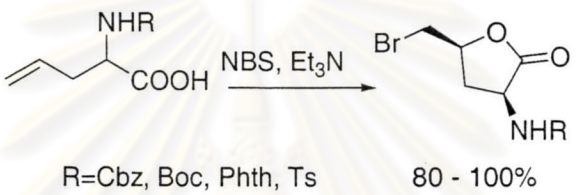
2.1.2 Bromocyclofunctionalization

Iwata has reported a route to synthesize bromolactones from the unsaturated acid. (**Scheme 7**)[8]



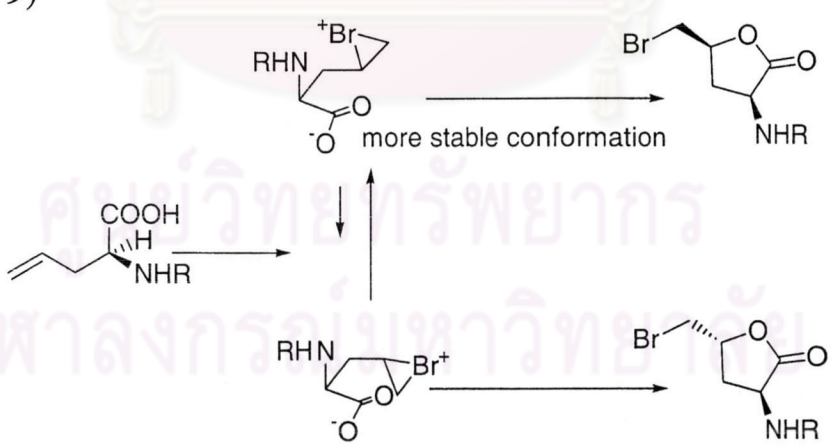
Scheme 7 Bromolactonization

Ohfune used NBS as the electrophile to induce cyclization of γ,δ-unsaturated-α-amino acid derivatives giving the *cis*-isomer as the major product. (**Scheme 8**)[9]



Scheme 8 Ohfune's cyclofunctionalization

The N-substituent has an effect on the *cis*-selectivity of the bromolactonization. It was assumed that the reaction proceeded *via* the more stable conformation of a cyclic intermediate in which the bromonium ion is stereoelectronically stabilized by the amino group. (**Scheme 9**)

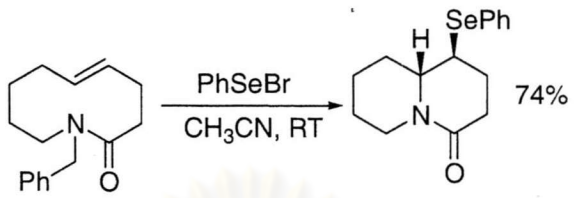


Scheme 9 Cyclic bromonium ion intermediates

2.1.3 Selenocyclofunctionalization

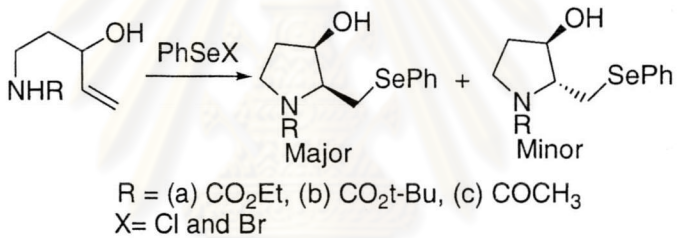
The ten membered ring lactams was cyclized to afford substituted quinolizidines. (**Scheme 10**)[10a] The reaction proceeded with the addition

of the electrophile (phenylselenogroup) and the nitrogen lone pair across the E-double bond of the substrate.



Scheme 10 Lactam cyclofunctionalization

Ward has reported the regio- and stereoselective cyclization of N-protected 3-hydroxy-4-phenylamine to give N-protected pyrrolidines in high yield.[10b] The *cis*-isomers were again the major products. (**Scheme 11**)



Scheme 11 Selenocyclofunctionalization of amino alcohols

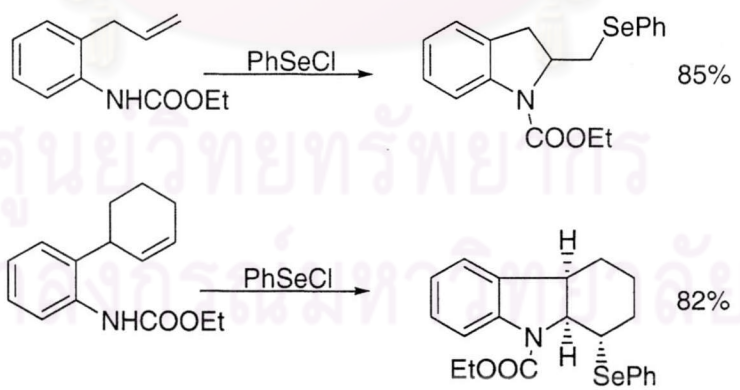
In all cases, cyclization proceeded regioselectively to give only the five membered ring adducts and with good diastereoselectivity. (**Table 3**) The reaction appears to be under kinetic control.

Substrates	PhSeX	Reaction conditions	Product ratio *cis : trans* (yield)
(a)	Cl	CH_2Cl_2, a, 4 h $CHCl_3$, b, 30 h dioxane, b, 40 min	75/25 (88) 85/15 (88) 76/24 (83)
	Br	CH_2Cl_2, a, 2 h $CHCl_3$, b, 20 min	76/24 (83) 87/13 (95)
(b)	Cl	CH_2Cl_2, a, 4 h	74/26 (56)
	Br	CH_2Cl_2, a, 2 h dioxane, b, 20 min	80/20 (60) 88/12 (70)
(c)	Cl	CH_2Cl_2, a, 24 h	90/10 (21)
	Br	CH_2Cl_2, a, 16 h $CHCl_3$, b, 1 h	>99/<1 (23) >99/<1 (40)

a = -78°C for 10 min then to RT, b = 0°C for 10 min then to RT

Table 3 The results of Ward's selenocyclofunctionalization

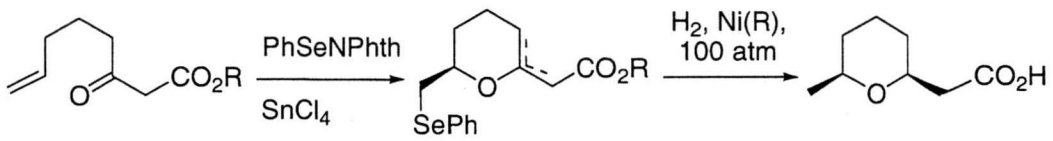
N-Arylcarbamates have also been cyclized with PhSeCl. (**Seheme 12**)[11] The reaction is efficient when it is carried out in the presence of silica gel, and the yields are generally above 80%. The stereochemical outcome of the reaction is noteworthy.



Scheme 12 The selenocyclofunctionalization of N-arylcarbamates

Ley has reported the use of N-phenylselenophthalimide as an electrophile and 0.01 equivalent of the Lewis acid ($SnCl_4$) to induce the cyclization of the alkenyl-β-ketoester to give a selenomethylpyran.[12]

Reduction under high pressure yielded the saturated tetrahydropyran, a civet cat gland component (**Scheme 13**).



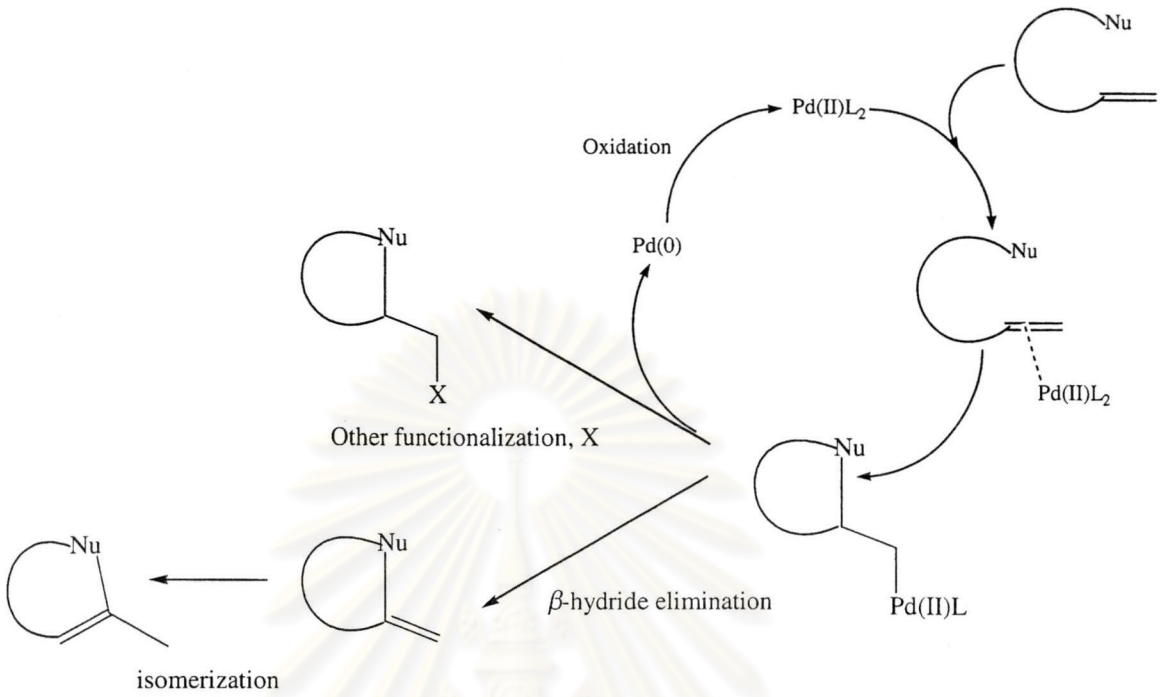
Scheme 13 Ley's tetrahydropyran synthesis

2.2 Transition metal cyclofunctionalization

Transition metal complexes can be used as the electrophiles to initiate cyclofunctionalization reactions, because transition metals in higher oxidation states can coordinate with the alkene and make it more electrophilic. In addition, the resulting carbon-transition metal-σ-bond can be functionalized directly in one reaction.[1, 13] There is often an intermediate CO insertion leading to carbonylated products. A number of transition metals have been studied in these cyclization reactions and palladium(II) is the most commonly used.

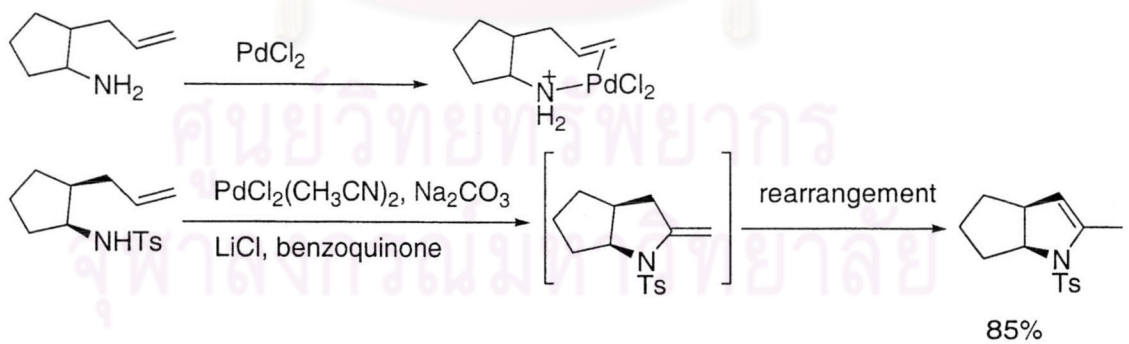
2.2.1 Palladium (II) complexes

The general mechanism of a Pd(II)-cyclization reaction is shown in **Scheme 14.** The first step is the coordination between palladium(II) and the alkene to give an η^2-palladium complex. Then the nucleophile approaches the electrophilic position to generate an η^1-complex with ring formation. The last step is functionalization. β-Hydride elimination can be the last step if the palladium complex has vicinal hydrogen. Palladium (0) can be reactivated by an oxidizing reagent to palladium(II) again and, hence, maintain the catalytic cycle. Frequently used oxidizing agents are Cu(II) salts and benzoquinone.



Scheme 14 The general mechanism of palladium catalyzed cyclofunctionalization

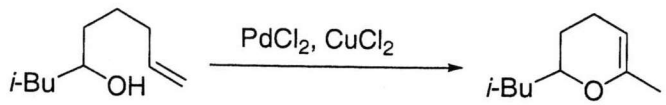
Cyclization of the amino olefin using Pd(II) complexes has been attempted. The reaction failed because the unsaturated amine acted as an efficient bidentate ligand for palladium to give inactive complexes. (**Scheme 15**)[14]



Scheme 15 Palladium cyclofunctionalization

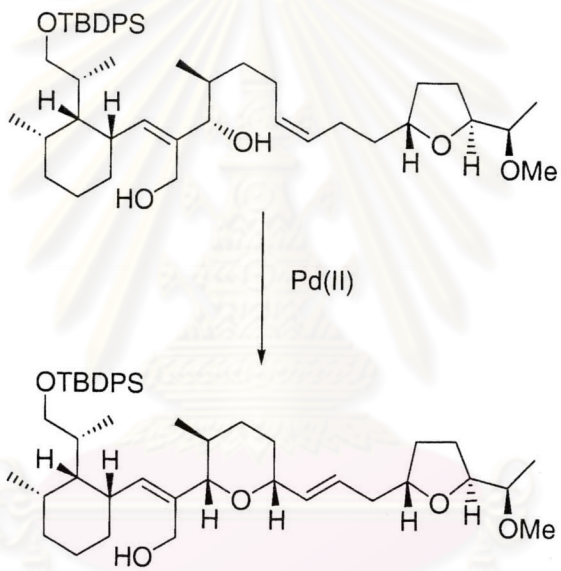
Olefinic sulfonamides can be employed to eliminate the problem because the nitrogen is much less basic. The last step is a β-hydride elimination to give an *exo*-cyclic alkene, however, rearrangement occurs to the *endo*-cyclic compound, which is more stable. It is unclear whether

or not the rearrangement is palladium catalyzed. (**Scheme 15**) Similar chemistry has been reported with oxygen nucleophiles. (**Scheme 16**)[15]



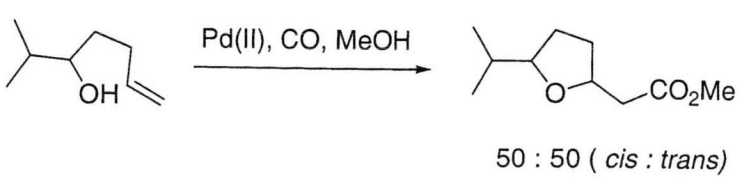
Scheme 16 Palladium catalyzed dihydropyran formation

The reaction was employed in a synthesis of tetronomycin by Semmelhack. (**Scheme 17**)[16, 17]

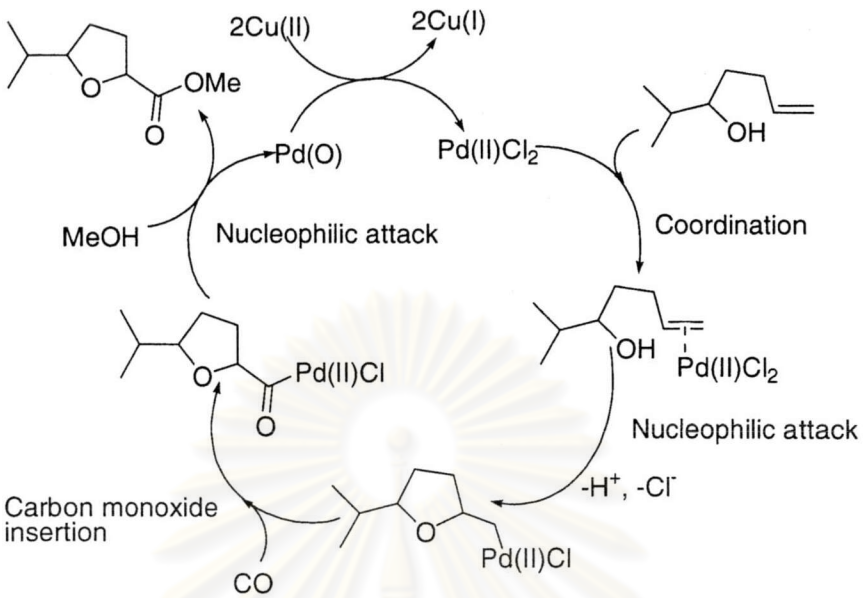


Scheme 17 Semmelhack's cyclization

The alkoxycarbonylation of bishomoallylic alcohols to tetrahydrofurans using Pd (II) has been reported by Semmelhack and by Liotta. (**Scheme 18**)[18, 19] The mechanism of the reaction is shown in **Scheme 19**.

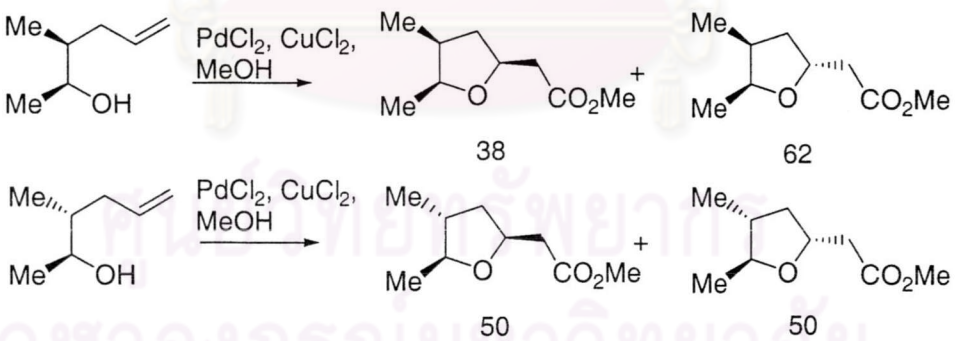


Scheme 18 The alkoxycarbonylation of bishomoallylic alcohols



Scheme 19 Palladium catalyzed cyclofunctionalization

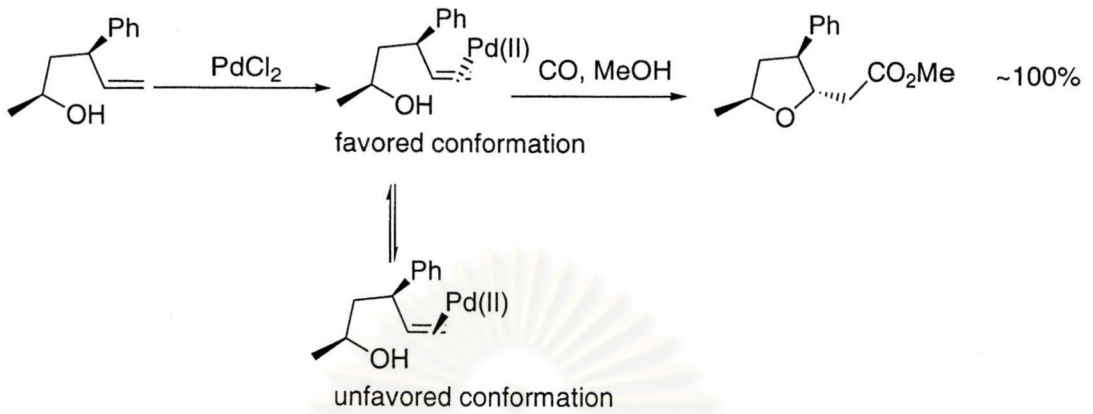
The β-hydride elimination is not observed because carbon monoxide can rapidly trap the intermediate Pd (II)-complex. **Scheme 20** shows that the reaction proceeds with poor stereoselectivity for 5-membered ring formation when there is a substituent α-to the nucleophile. A β-substituent is also poorly effective. (**Scheme 18**, **20**)



Scheme 20 Effect of α- and β-substituents on cyclocarbonylation

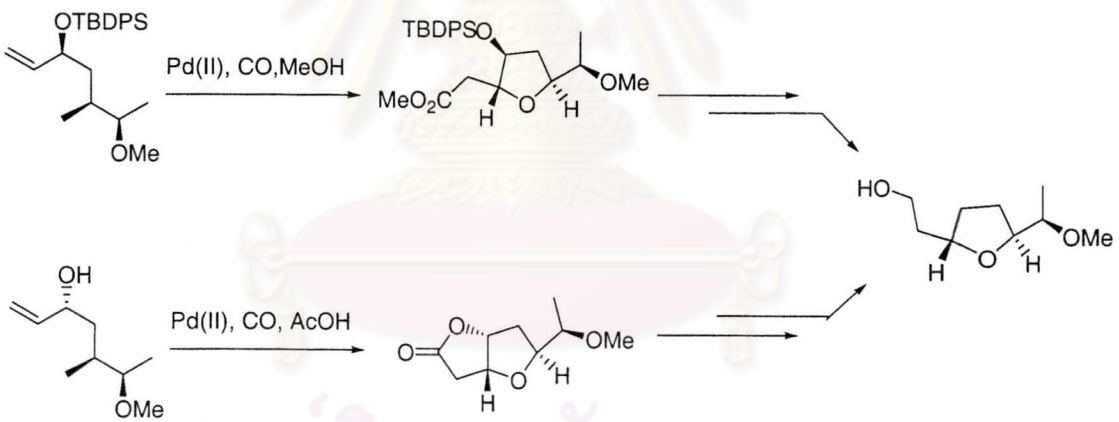
This implies that, with 5-membered rings, there is little or no energy difference between the conformation of the intermediates.

However, a substituent on the γ-position, relative to the nucleophile, exerts a strong stereochemical influence. Steric hindrance between the γ-substituent and the bulky palladium complex can make the difference between the favored and unfavored intermediate structures. (**Scheme 21**)



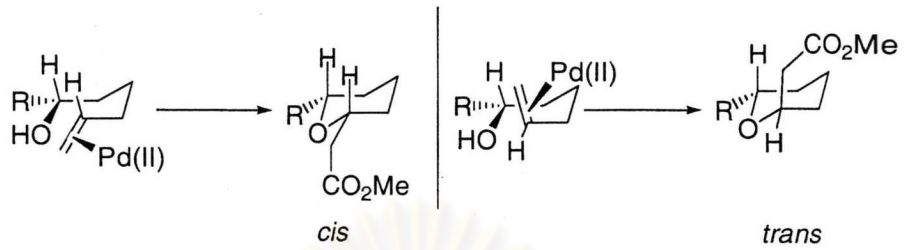
Scheme 21 γ-Substitutent effect

The effect is so significant that Semmelhack employed a temporary γ-substituent to control stereochemistry during formation of the tetrahydrofuran ring of tetranomycin. (**Scheme 22**)[16, 17]



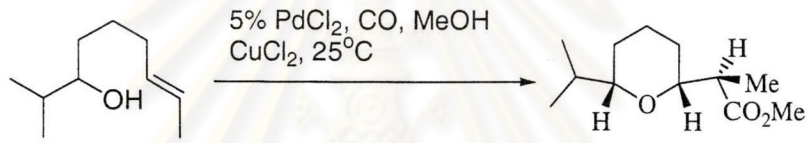
Scheme 22 Ring formation of tetrahydropyran of tetranomycin

For 6-membered ring formation, the pseudo chair conformation of an intermediate can be used to determine and explain which form is more favored. (**Scheme 23**)



Scheme 23 Intermediate conformations for 6-membered rings

Scheme 24 shows the result that follows from the pseudo chair conformation control.[18]



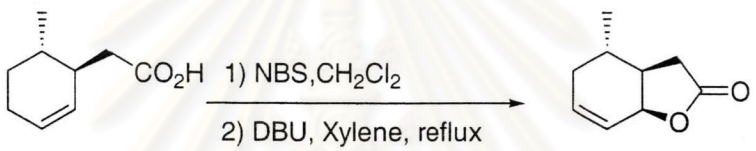
Scheme 24 Stereoselective THP formation

3. Nucleophile

There are several types of nucleophile have been used in cyclofunctionalization reactions. Oxygen and nitrogen are generally used to be the internal nucleophile to form heterocyclic rings.

3.1 Oxygen nucleophiles

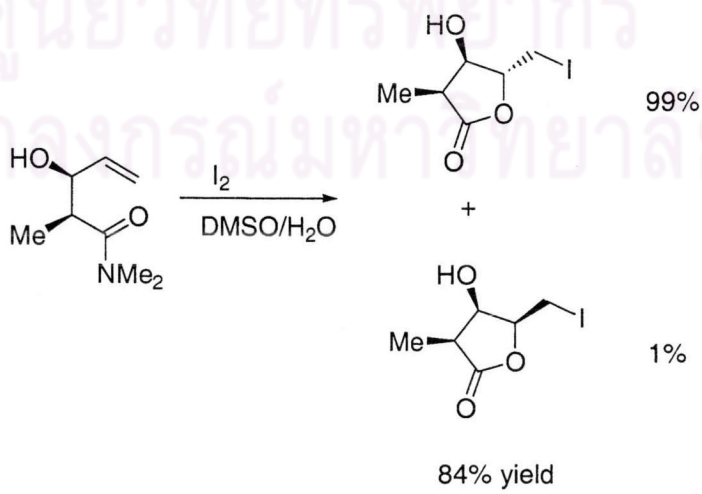
Halolactonization of unsaturated carboxylic acids is a very useful method for regio- and stereoselective cyclofunctionalization of double bonds and has been prominently applied in organic synthesis. (**Scheme 25**)[19]



Scheme 25 Halolactonization of an unsaturated carboxylic acid

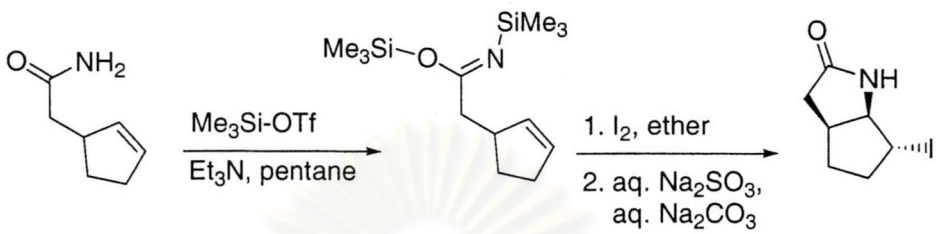
3.2 Nitrogen nucleophile

A problem arises with the halofunctionalization of unsaturated amides. These act as oxygen-nucleophiles. High stereoselectivity was observed when the N, N-dimethylpentenamide was cyclized with I_2 in $DMSO/H_2O$, but the products were the corresponding lactones, rather than the lactams. (**Scheme 26**)[20]



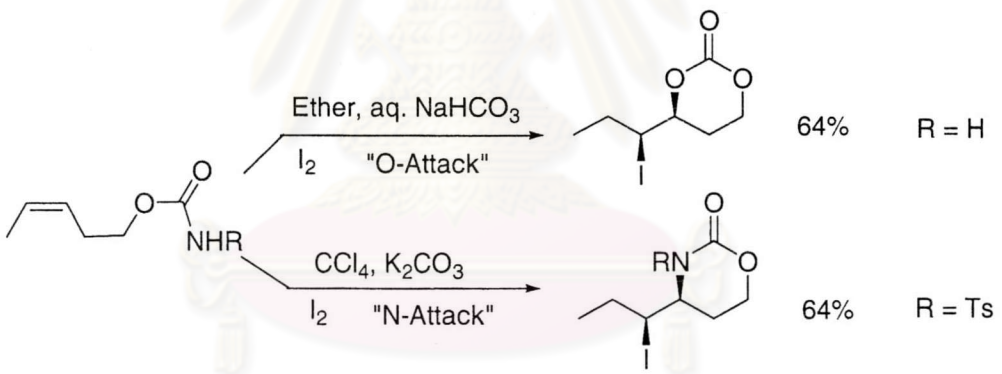
Scheme 26 Amide cyclization

One solution to this problem, introduced by Knapp, is to convert the amides to O-silyl amidates, which are nucleophilic on nitrogen. (**Scheme 27**)[21]



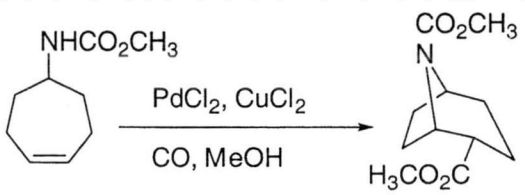
Scheme 27 O-Silyl amidate as a nitrogen nucleophile

Similar problems can also occur with carbamates. The neutral molecules often undergo cyclofunctionalization to yield cyclic carbonates, while the anions do act as nitrogen nucleophiles. (**Scheme 28**) [22]



Scheme 28 Carbamate tethered cyclization reaction

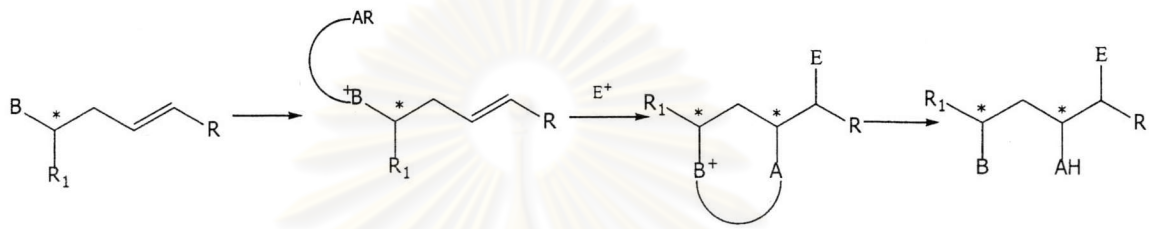
The cyclization of an unsaturated carbamate with $PdCl_2$ has been used as the key step in a synthesis of ferruginine. (**Scheme 29**)[23]



Scheme 29 The cyclization of a nitrogen nucleophile with $PdCl_2$

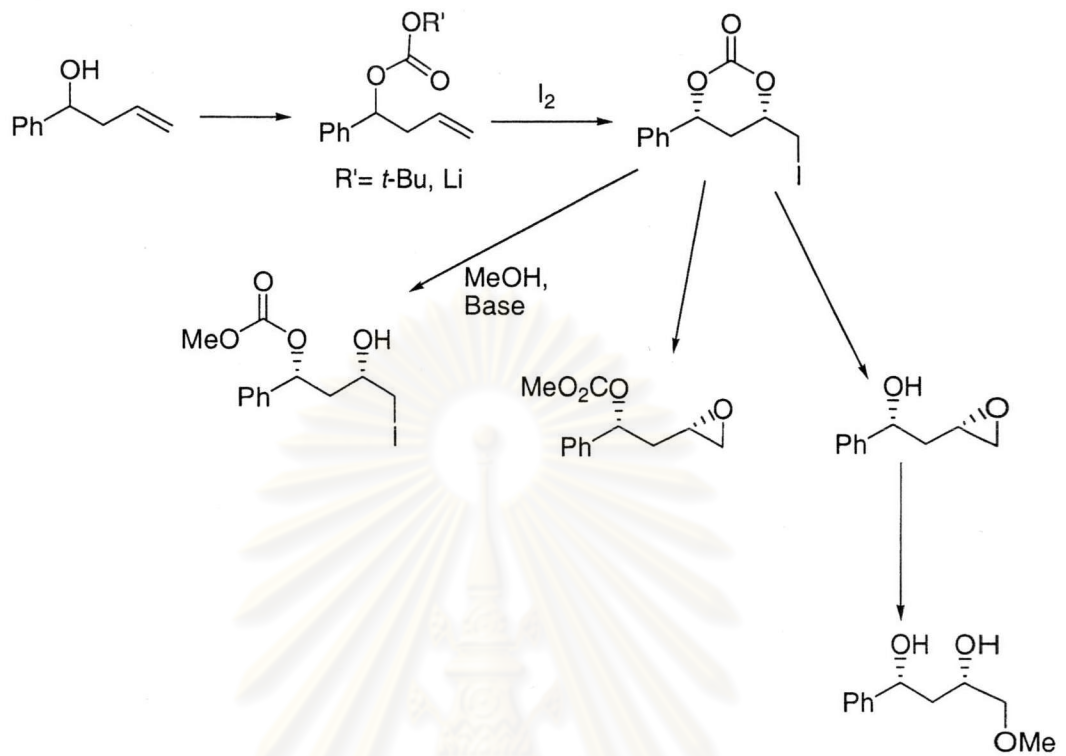
3.3 Tethers

A tether is a temporary group of atoms that connects the nucleophile to another functional group in the molecule (**Scheme 30**). The cyclofunctionalization then proceeds with the expected stereocontrol. Removable of the tether then leads to an acyclic molecule, often as a single stereoisomer. (**Scheme 30**)



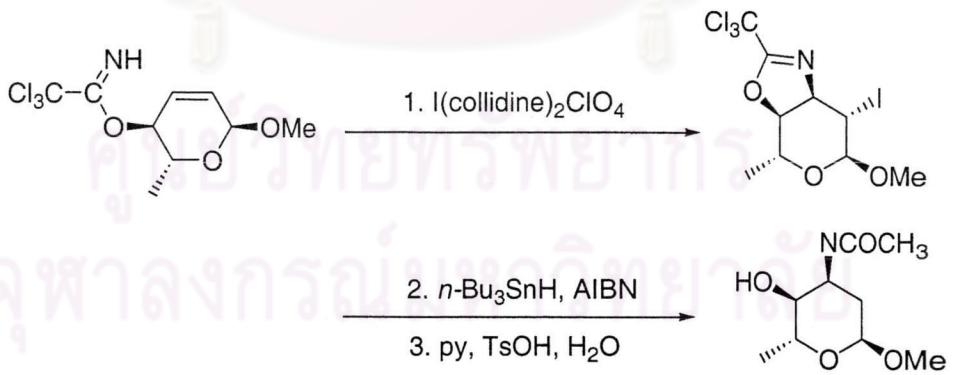
Scheme 30 Tethered cyclization strategy

One valuable application of this concept is in the formation of epoxides from homoallylic alcohols. Direct epoxidation gives mixtures of diastereomers[24] while the "carbonate extension" method developed by the groups of Bartlett and Cardillo gives very high diastereomeric ratios. Both groups convert the homoallylic alcohol to a carbonate derivative.[25] Iodination triggers cyclofunctionalization. Solvolytic removal of the carbonate tether can give various products according to the reaction conditions (**Scheme 31**).



Scheme 31 The carbonate extension method

The cyclofunctionalization of tethered nitrogen has been widely studied. Several groups have employed iodocyclofunctionalization of tethered nitrogen to synthesize amino-sugars.[26] The iodine is typically removed in a subsequent reductive step. (**Scheme 32**)



Scheme 32 Iodocyclofunctionalization of tethered nitrogen

In Fraser-Reid's synthesis of ristosamine, the trichloromethyl imidate ester was cyclized with iodonium dicollidine perchlorate to give the oxazoline, which was reduced by Bu_3SnH and then hydrolyzed. *N*–Acetylristosamine was obtained directly. (**Scheme 32**)

Surprisingly there is only one example of a tethered cyclofunctionalization reaction using palladium catalysis, to our knowledge. It was reported that *N*-toluenesulfonyl *O*-allyl and *O*-homoallyl carbamates underwent cyclization and carbonylation. (**Table 4**)[27]

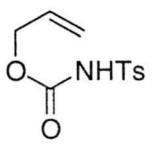
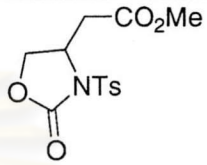
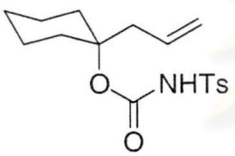
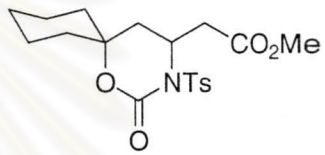
Substrate	Condition	Product	%yield
	$PdCl_2$, $CuCl_2$, NaOAc, CO MeOH-AcOH		71
	$PdCl_2$, $CuCl_2$, NaOAc, CO MeOH-AcOH		80

Table 4 Tamaru's carbonylation cyclofunctionalization