# Transition-Metal-Catalyzed Reactions in Heterocyclic Synthesis

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*Received August 12, 2003*

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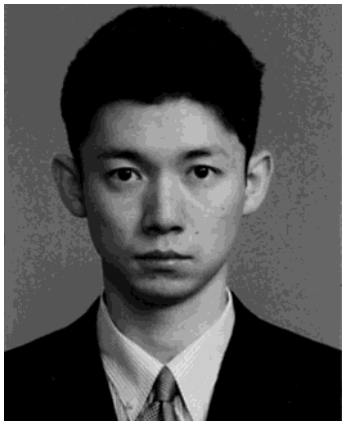
## *1. Introduction*

Heterocyclic compounds are worth our attention for many reasons; chief among them are their biological activities, and many drugs are heterocycles. Therefore, organic chemists have been making extensive

10.1021/cr020095i CCC: $48.50 
Published on Web 02/21/2004

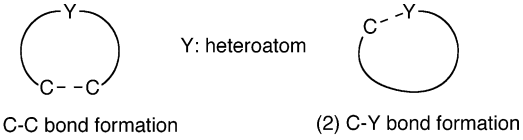


Itaru Nakamura was born in Sapporo, Japan, in 1973. He received his M.S. (1998) and Ph.D. (2001) degrees from Tohoku University working under the direction of Professor Y. Yamamoto. He was appointed as a Research Associate at Tohoku University in 2001. In 2003 he had a chance to stay in Georg-August-Universität Göttingen as a COE fellow under the supervision of Professor Armin de Meijere. His current research interest is focused on the development of new transition-metal-catalyzed reactions and their application to organic synthesis.

Yoshinori Yamamoto was born in Kobe, Japan, and received his M.S. and Ph.D. degrees from Osaka University. In 1970 he was appointed as an Instructor at Osaka University, after which he went to Professor H. C. Brown's research group at Purdue University, as a Postdoctoral Associate (1970–1972). In 1977 he was appointed as an Associate Professor at Kyoto University. In 1986 he moved to Tohoku University to take up his present position, Professor of Chemistry. He also holds a Professorship at IMRAM, Tohoku. He was awarded the Chemical Society of Japan Award for Young Chemists (1976), the Chemical Society of Japan Award (1996), and the Humboldt Research Award (2002). He is the Regional Editor of Tetrahedron Letters and Volume Editor of Science of Synthesis, and he was the President of the International Society of Heterocyclic Chemistry (2000–2001). He is the project leader of the 21 Century COE Program of MEXT "Giant Molecules and Complex Systems, Chemistry Group of Tohoku University" (2002–2006). He has a wide range of research interests in synthetic organic and organometallic chemistry. His recent work focused on the use of transition-metal complexes and Lewis acids as catalytic reagents in organic synthesis and synthesis of complex natural products.

efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations. Among a variety of new synthetic transformations, transition-metal-catalyzed reactions are some of the most attractive methodologies for synthesizing heterocyclic compounds, since a transition-metal-catalyzed reaction can directly construct complicated molecules from readily accessible starting materials under mild conditions. The catalytic construction of heterocyclic skeletons is classified into two major processes, as shown in Scheme 1: (1) C−C bond formation from the corresponding acyclic precursors and (2) C−Y bond formation from the corresponding acyclic precursors.

**Scheme 1. Two Major Processes of Heterocycle Synthesis**

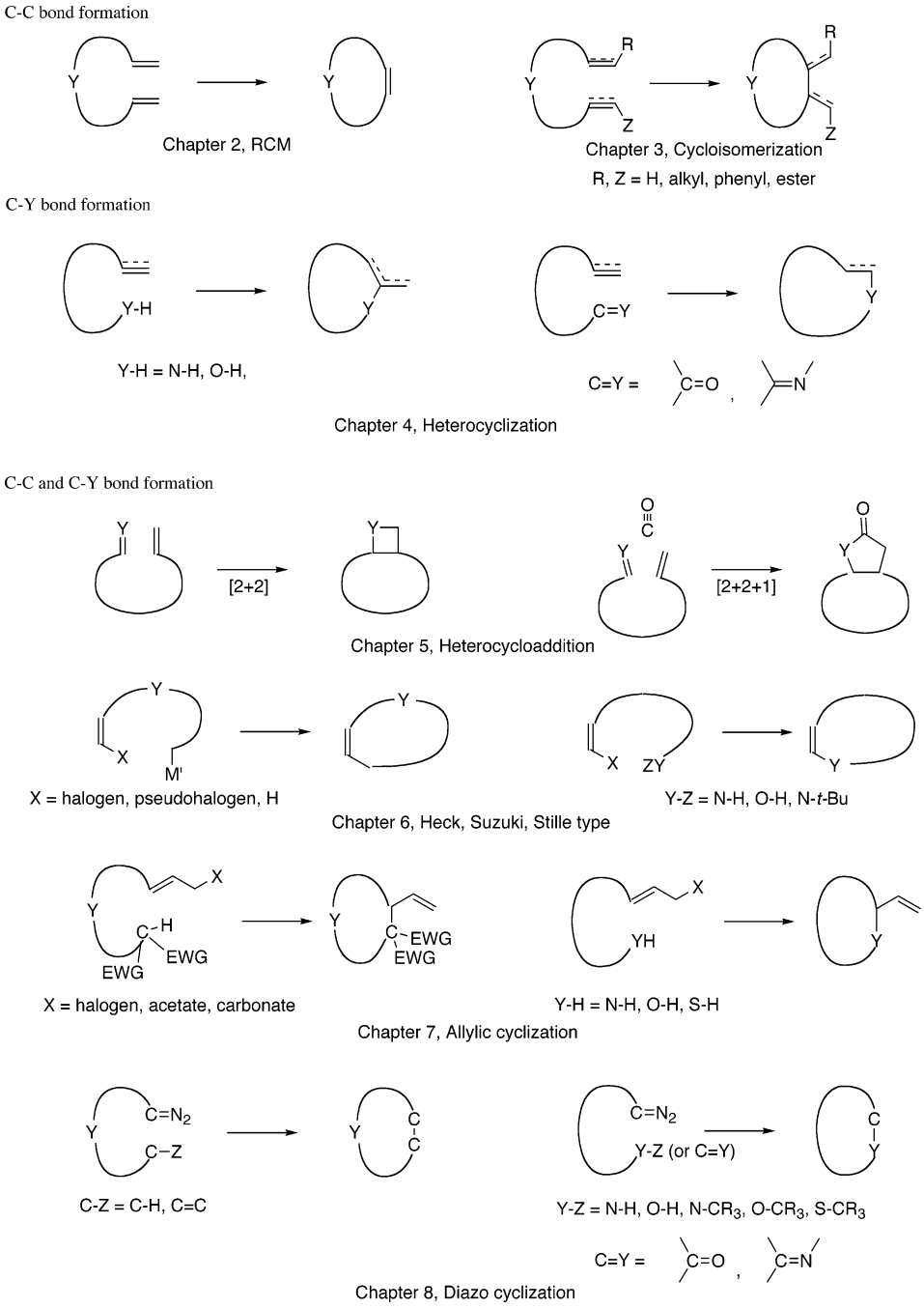



(1) C-C bond formation (2) C-Y bond formation

The synthesis of heterocycles via the olefin metathesis reaction (RCM, ring closing metathesis, section 2) and via the cycloisomerization of dienes, diynes, and enynes (section 3) belongs to category 1 (Scheme 2). The cyclization of alkenes, allenes, and alkynes bearing Y−Z at an appropriate position of the carbon chain (section 4) is classified under category 2. The two processes, C−C and C−Y bond formation, take place together in the intra- and intermolecular hetero-cycloaddition of alkenes and alkynes bearing a hetero-unsaturated bond at an appropriate position of the carbon chain (section 5); four-, five- or six-membered heterocycles can be synthesized, depending on the partner of the intra- and intermolecular reaction. The intramolecular reaction of aryl and vinyl halides via Heck-, Suzuki-, and Stille-type reactions proceeds through the C−C bond formation and that via the coupling with a heteroatom proceeds through the C−Y bond formation (section 6). The intramolecular reaction of allylic halides (section 7) proceeds through the two processes; if the reactive site is a carbon pronucleophile, the C−C bond formation takes place to lead to a heterocycle, whereas the C−Y bond formation occurs if the reactive site is a heteroatom pronucleophile. The intra- and intermolecular reaction of diazo and related compounds (section 8) contains the two processes similarly.

As can be seen from Scheme 2, the heterocycle synthesis with transition-metal catalysts is classified on the basis of both starting substrates and reaction patterns. It is noteworthy that all the starting materials possess C−C and/or C−heteroatom unsaturated bond(s) in (a) certain position(s) of their structural framework and those functional groups become a reactive site for making a new C−C and/or C−heteroatom bond (C−Y bond). This is a logical outcome, since the formation of a complex between a transition metal and C−C (or C−Y) unsaturated bond plays an important role in the transition-metal-catalyzed reaction and often triggers a key reaction for producing heterocycles. It should be also noted that, in most sections, the very popular and modern reactions in the field of transition-metal-catalyzed chemistry are utilized for the synthesis of heterocycles, for example, ring-closing metathesis (RCM), Pauson−Khand, Heck, Suzuki, Stille, and Tsuji−Trost reactions. Compared to the traditional organic

**Scheme 2. Classification of Heterocycle Synthesis, Based on Starting Substrates and Reaction Patterns**

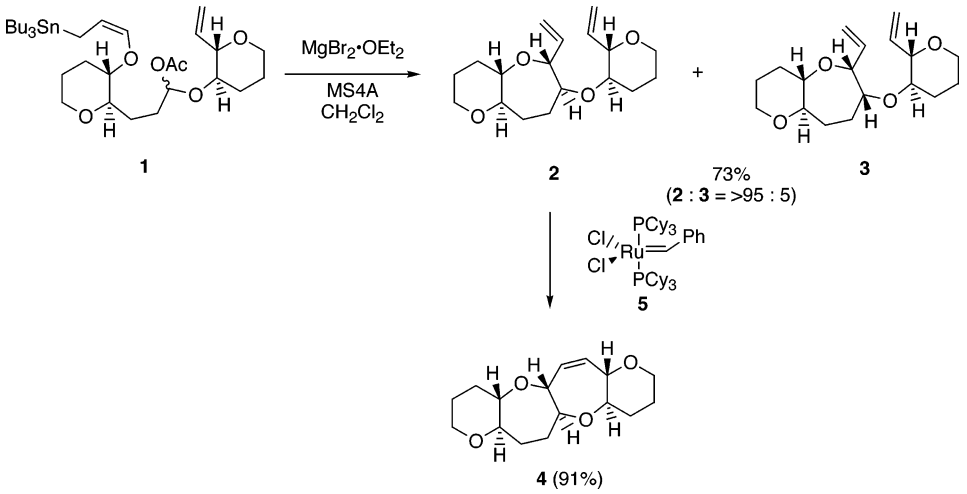



transformations leading to heterocycles, the transition-metal-catalyzed transformation seems to be not straightforward and not easily understandable in many cases. This is presumably due to the fact that sequential processes often are involved in the catalytic transformation, which makes it difficult to understand at a glance the conversion from a starting substrate to a final product. Accordingly, in this review, reaction processes of a complicated transformation are shown when the total conversion from a starting material to a product seems to be not easily understandable. An important feature in the modern heterocycle synthesis with transition-metal catalysts is that asymmetric catalytic synthesis is becoming very popular and attracting keen interest of a wide range of organic chemists. When possible, the structure of chiral transition-metal catalysts and the asymmetric transformations using those catalysts are shown in the text. The transition-metal-catalyzed synthesis of heterocyclic compounds has been summarized in several excellent reviews,[1] in which papers published before 2000 are extensively cited. Accordingly, in this review we summarize the recent contributions published after 2000.

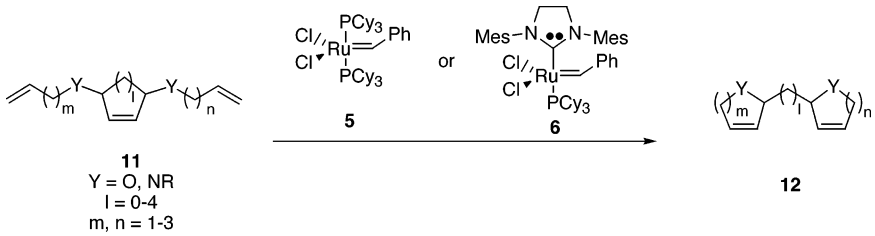
## 2. Intramolecular Reaction of 1,ω-Dienes and Enynes: Ring-Closing Metathesis (RCM)

Ring-closing olefin metathesis of 1,ω-dienes is one of the most important synthetic tools to construct carbo- and heterocycles and has frequently played the

**Scheme 3**




**Scheme 4**

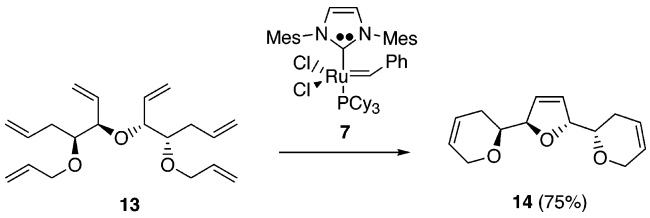



crucial role to complete the total synthesis of natural products.[2,3] A wide variety of heterocyclic compounds, which contain nitrogen,[4] oxygen,[5] boron,[6] silicon,[7] phosphorus,[8] and sulfur[9] atoms, have been synthesized by the olefin metathesis of 1,ω-dienes having one or more heteroatoms between two alkenes (Scheme 2). Development of metathesis catalysts[10] and improvement of reaction conditions[11] have enabled the synthesis of a wide variety of heterocyclic compounds in a highly efficient and environmentally friendly manner. It is characteristic that this methodology is highly useful for the synthesis of medium- and large-size heterocyclic compounds.[12] The chemistry of ring-closing metathesis is extensively summarized in several excellent reviews.[2,3]

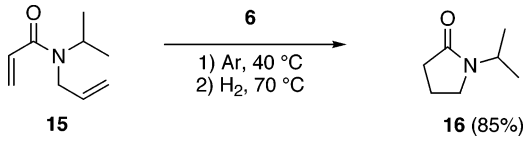
## 2.1. Ring-Closing Metathesis for Total Synthesis

In the past few years, RCM has been used explosively in the total synthesis of natural products, because it is reliable for synthesizing carbo- and heterocycles having complicated structures with many functional groups. For example, RCM is quite useful for the synthesis of polycyclic ethers: the intramolecular allylation of α-acetoxy ethers and subsequent ring-closing metathesis are highly efficient for the synthesis of polycyclic ethers.[13] The treatment of the γ-alkoxyallylstannane-α-acetoxy ether **1** with $MgBr_2$·$OEt_2$ gave the 1,8-diene **2** in 73% yield along with a trace amount of the epimer **3** (Scheme 3). Subsequent RCM of **2** using the catalyst **5** produced the polycyclic ether **4** in a high yield. This methodology was applied to the total synthesis of gambierol.[13c,d] Recent reports on the total synthesis of heterocyclic natural products using RCM are summarized in Table 1.[13c,d,14−84]

**Scheme 5**




**Scheme 6**

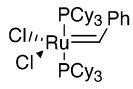



## 2.2. Tandem Olefin Metathesis

Tandem olefin metathesis reaction is an attractive methodology to produce complicated polycyclic compounds in one step. In the presence of a ruthenium carbene complex (**5** or **6**), the reaction of the triene derivatives **11** gives the bicyclic heterocycles **12** (Scheme 4; see also Table 1, entries 9, 13, and 23).[85] The tandem processes, ring-opening metathesis−ring-closing metathesis, are involved in this reaction. Heck et al. reported that the triple ring closing metathesis reaction of the hexaene compound **13** took place in the presence of the ruthenium-based imidazolinylidene complex **7** to give the tricyclic ether **14** (Scheme 5).[86]

It has been revealed that the ruthenium carbene complex **6** can promote not only the olefin metathesis but also hydrogenation and isomerization. Louie et al. reported that the one-pot tandem ring-closing

**Table 1. RCM in the Total Synthesis of Natural Products**

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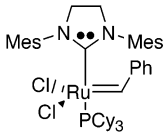
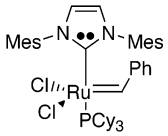



**6**

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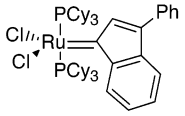


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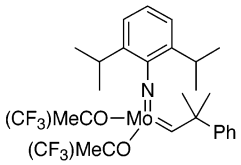


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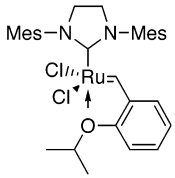



**10**

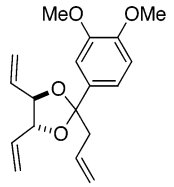
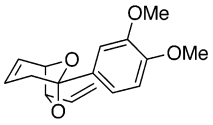
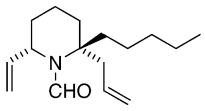
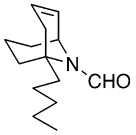
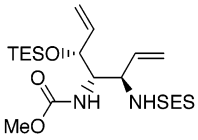
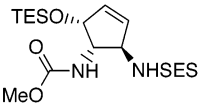
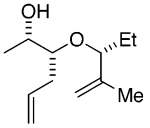
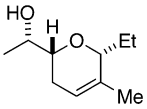
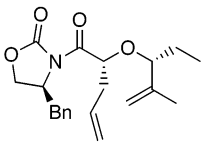
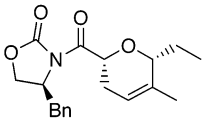
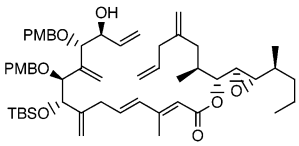
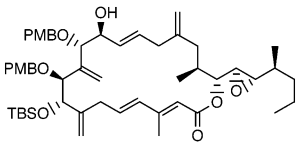
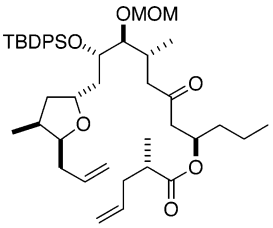
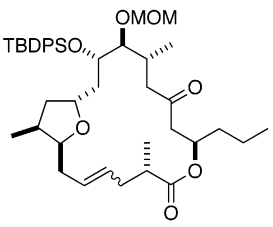
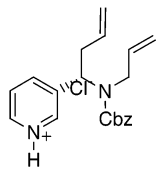
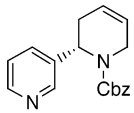
| entry | substrate | catalyst | product | yield | natural product | ref. |
|---|---|---|---|---|---|---|
| 1 |  | **5** |  | 93% | (–)-*N*-acetylneuraminic acid | 14 |
| 2 |  | **6** |  | 99% | (–)-adaline | 15 |
| 3 |  | **10** |  | 36%[a] | (–)-agelastatin A | 16 |
| 4 |  | **5** |  | 60%[a] | (+)-ambruticin S | 17 |
| 5 |  | **5** |  | 98% | (+)-ambruticin | 18 |
| 6 |  | **6** |  | 35% | amphidinolide A | 19 |
| 7 |  | 7 |  | 86% | amphidinolide T4 | 20 |
| 8 |  | **5** |  | 79%[a] | (*S*)-anabasine<br>(*S*)-anatabine | 21 |

**Table 1. (Continued)**

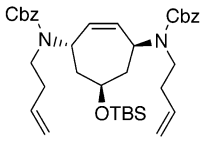
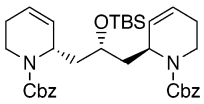
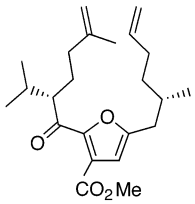
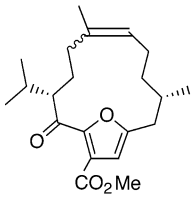
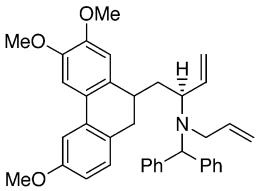
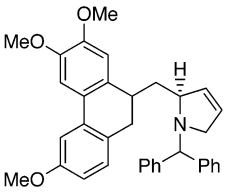
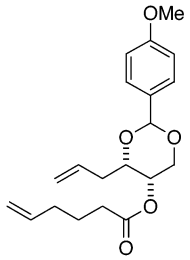
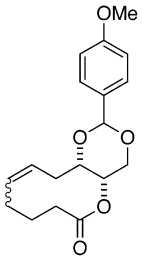
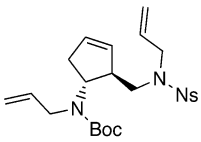
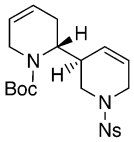
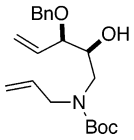
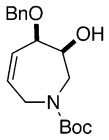
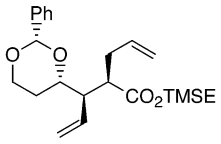
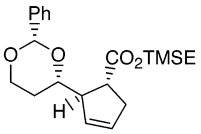
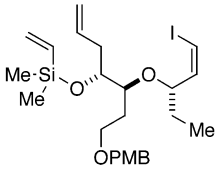
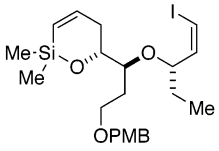
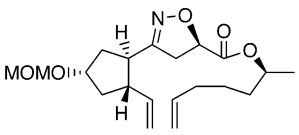
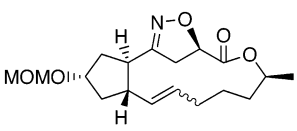
| entry | substrate | catalyst | product | yield | natural product | ref. |
|---|---|---|---|---|---|---|
| 9 |  | **5** |  | 87% | (–)-anaferine | 22 |
| 10 |  | **6** |  | 70%<br>*E*:*Z* = 26:44 | (+)-anhydrochatancin | 23 |
| 11 |  | **5** |  | 92% | (–)-antofine | 24 |
| 12 |  | **7** |  | 79%<br>*E*:*Z* = 1:2.8 | ascidiatrienolide A | 25 |
| 13 |  | **6** |  | 82% | (+)-astrophylline | 26 |
| 14 |  | **8** |  | 87% | (–)-balanol | 27 |
| 15 |  | **5** |  | 98% | (–)-borrelidin | 28 |
| 16 |  | **9** |  | 92% | (+)-brasilenyne | 29 |
| 17 |  | **5** |  | 42%<br>*E*:*Z* = 2.2:1 | (+)-brefeldin A | 30 |

**Table 1. (Continued)**

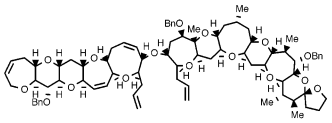
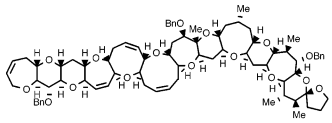
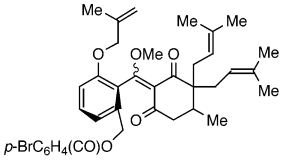
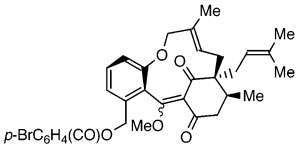
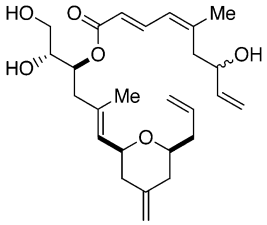
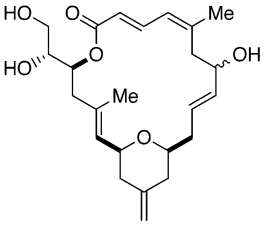
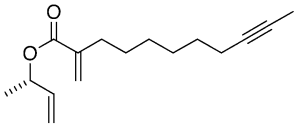
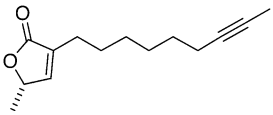
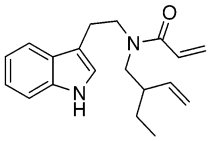
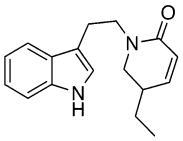
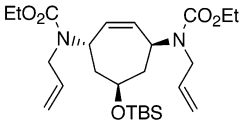
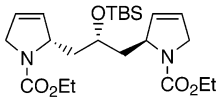
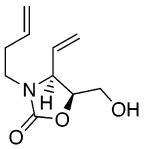
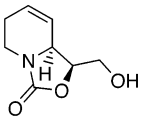
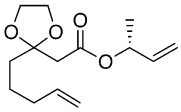
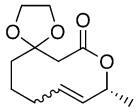
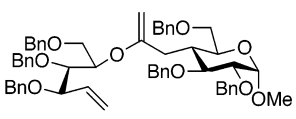
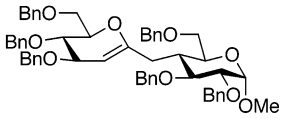
| entry | substrate | catalyst | product | yield | natural product | ref. |
|---|---|---|---|---|---|---|
| 18 |  | **5** |  | 60%[a] | ciguatoxin CTX3C | 31 |
| 19 |  | **6** |  | 86% | coleophomone B | 32 |
| 20 |  | **6** |  | 77%[a] | (–)-dactylolide | 33 |
| 21 |  | **5** |  | 70% | (*S,S*)-(+)-dehydrohomo-ancepsenolide | 34 |
| 22 |  | **5** |  | 91% | dihydrocorynantheol | 35 |
| 23 |  | **5** |  | 72%[a] | (+)-dihydrocuscohygrine cuscohygrine | 36 |
| 24 |  | **5** |  | 90% | (–)-4a,5-dihydrostreptazolin | 37 |
| 25 |  | **7** |  | 88%[a] | (+)-diplodialide A | 38 |
| 26 |  | **9** |  | 41% | β-*C*-disaccharide | 39 |

**Table 1. (Continued)**

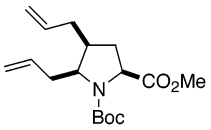
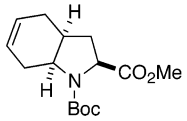
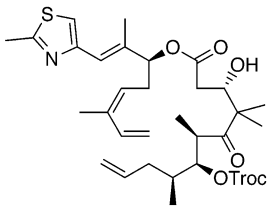
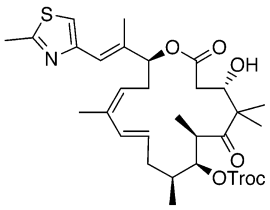
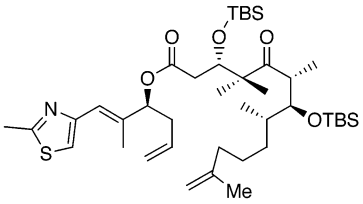
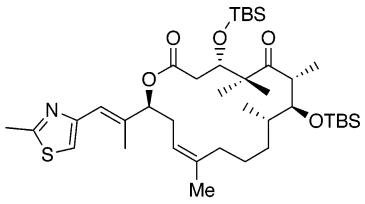
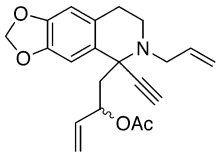
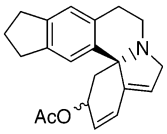
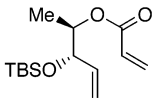
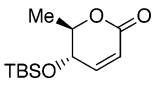
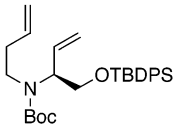
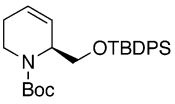
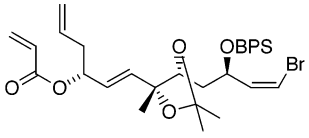
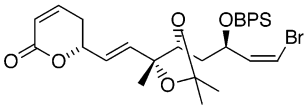
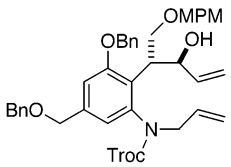
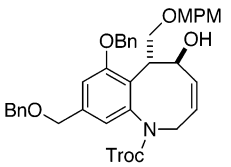
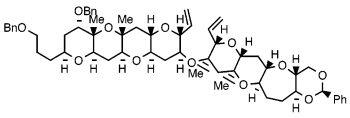
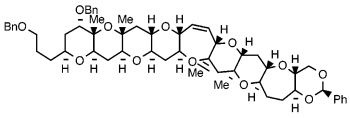
| entry | substrate | catalyst | product | yield | natural product | ref. |
|---|---|---|---|---|---|---|
| 27 |  | **5** |  | 99% | dysinosin A | 40 |
| 28 |  | **6** |  | 41% | epothilone 490 | 41 |
| 29 |  | **6** |  | 81%<br>*E:Z* = 1:1.1 | epothilone B | 42 |
| 30 |  | **5** |  | quant. | erythrocarine | 43 |
| 31 |  | **5** |  | 90% | everninomicin 13,384-1 | 44 |
| 32 |  | **5** |  | 97% | fagomine | 45 |
| 33 |  | **5** |  | 65%[a] | (+)-fostriecin | 46 |
| 34 |  | **5** |  | 78% | (+)-FR900482 | 47 |
| 35 |  | **6** |  | 88% | gambierol | 13c,d |

**Table 1. (Continued)**

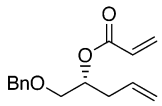
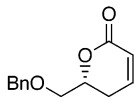
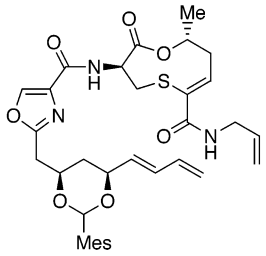
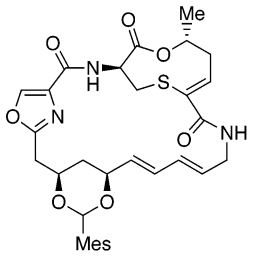
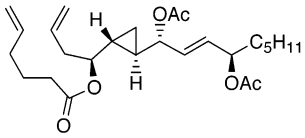
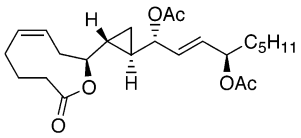
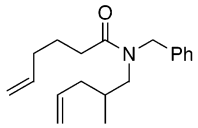
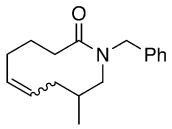
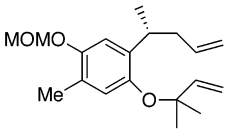
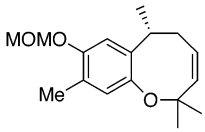
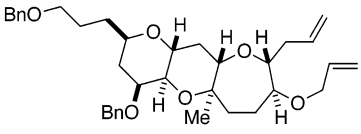
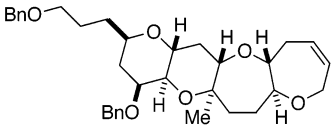
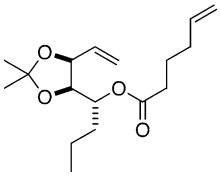
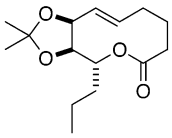
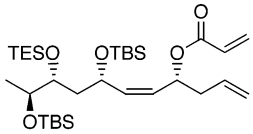
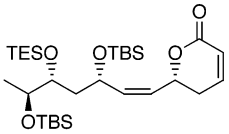
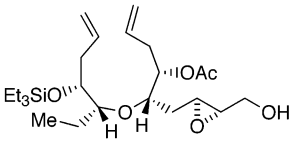
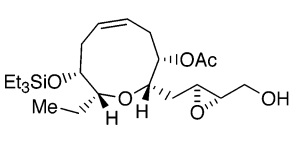
| entry | substrate | catalyst | product | yield | natural product | ref. |
|---|---|---|---|---|---|---|
| 36 |  | **5** |  | 91% | (+)-goniothalamin | 48 |
| 37 |  | **5** |  | 37-42% | (−)-griseoviridin | 49 |
| 38 |  | **5** |  | 72% | halicholatcone | 50 |
| 39 |  | **5** |  | 76%<br>*E*:*Z* = 3:1 | (±)-haliclorensin | 51 |
| 40 |  | **6** |  | 88% | (−)-heliannuol A | 52 |
| 41 |  | **5** |  | 88% | (±)-hemibrevetoxin B | 53 |
| 42 |  | **8** |  | 69% | herbarumin I | 54 |
| 43 |  | **5** |  | 82% | (+)-hyptolide | 55 |
| 44 |  | **5** |  | 94% | (−)-isolaurallene | 56 |

**Table 1. (Continued)**

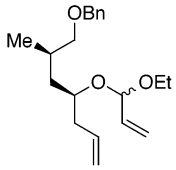
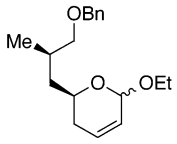
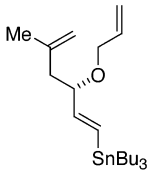
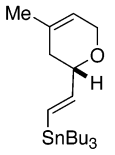
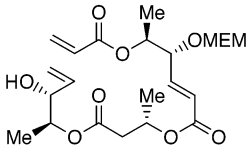
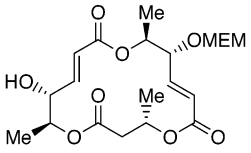
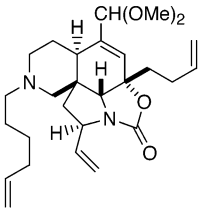
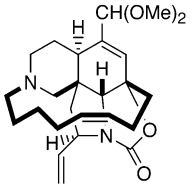
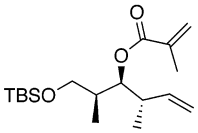
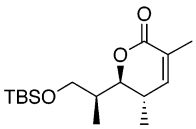
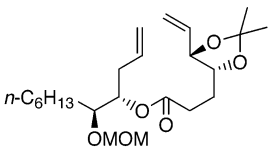
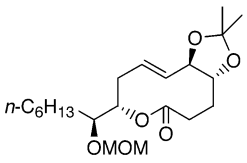
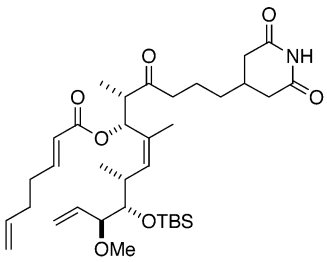
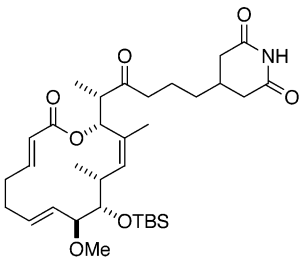
| entry | substrate | catalyst | product | yield | natural product | ref. |
|---|---|---|---|---|---|---|
| 45 |  | **5** |  | 97% | (–)-laulimalide | 57 |
| 46 |  | **9** |  | 81% | (–)-laulimalide | 58 |
| 47 |  | **6** |  | 77% | marcrosphelide A and B | 59 |
| 48 |  | **5** |  | 67% | manzamine A | 60 |
| 49 |  | **7** |  | 98% | (+)-methynolide | 61 |
| 50 |  | **5** |  | 67% | microcarpalide | 62 |
| 51 |  | **6** |  | 70% | (+)-migrastatin | 63 |

**Table 1. (Continued)**

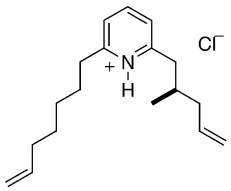
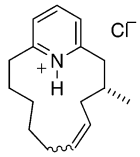
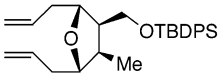
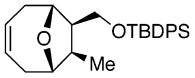
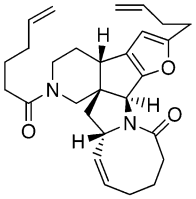
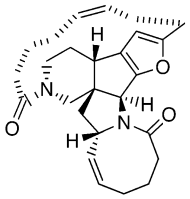
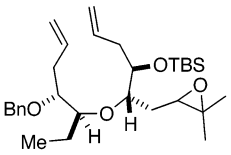
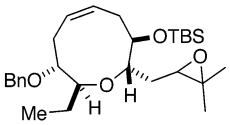
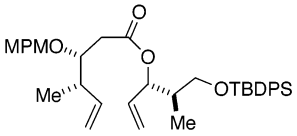
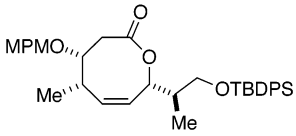
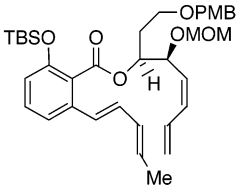
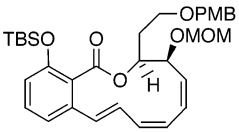
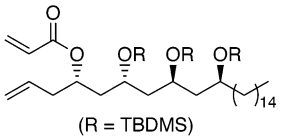
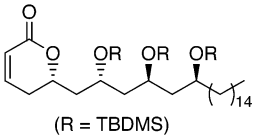
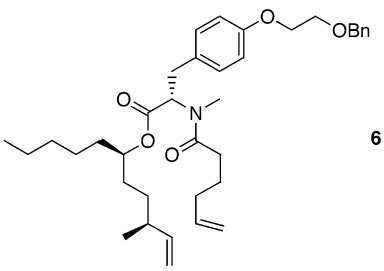
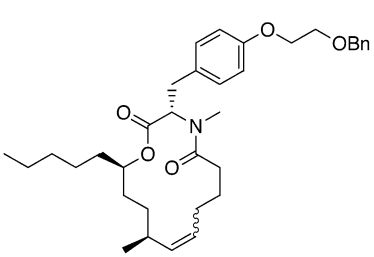
| entry | substrate | catalyst | product | yield | natural product | ref. |
|---|---|---|---|---|---|---|
| 52 |  | **8** |  | 57%[a] | (+)-muscopyridine | 64 |
| 53 |  | **5** |  | 83% | (±)-mycoepoxydiene | 65 |
| 54 |  | **5** |  | 26% | (+)-nakadomarin | 66 |
| 55 |  | **5** |  | 82% | (+)-obtusenyne | 67 |
| 56 |  | **5** |  | 86% | (–)-octalactin A | 68 |
| 57 |  | **6** |  | 48% | (–)-oximidine II | 69 |
| 58 |  (R = TBDMS) | **6** |  (R = TBDMS) | 87% | passifloricin A | 70 |
| 59 |  | **6** |  | 82% | (–)-PF1163B | 71 |

**Table 1. (Continued)**

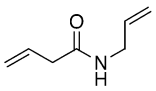
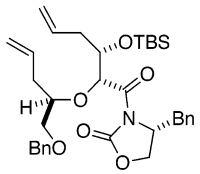
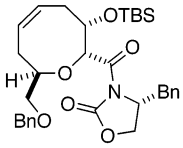
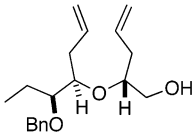
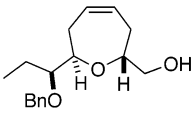
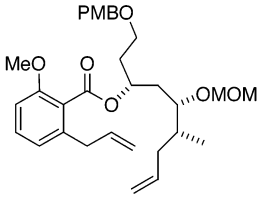
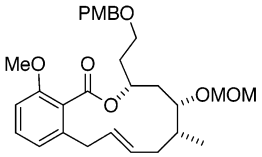
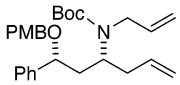
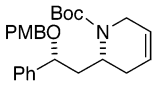
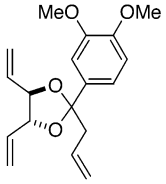
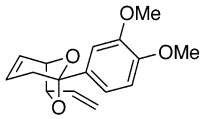
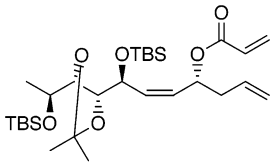
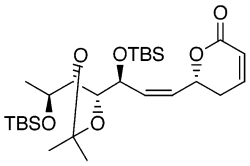
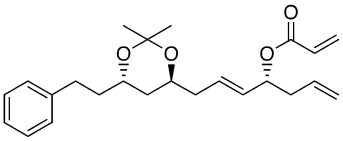
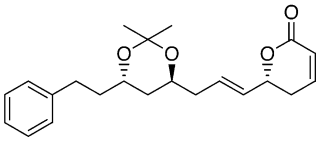
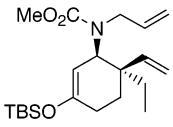
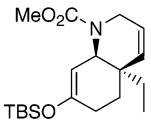
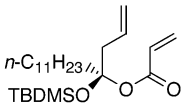
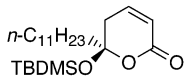
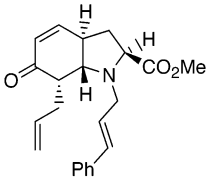
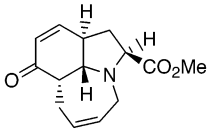
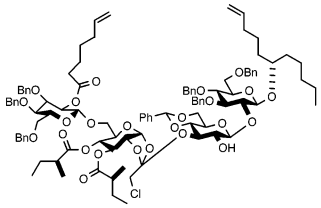
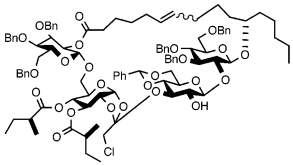
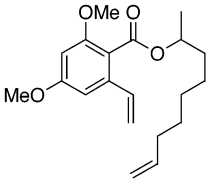
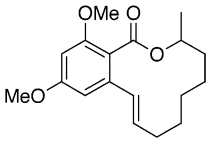
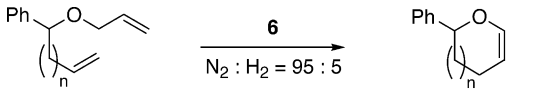
| entry | substrate | catalyst | product | yield | natural product | ref. |
|---|---|---|---|---|---|---|
| 60 |  | **5** |  | 80% | (*S*)- and (*R*)-pipermethystine | 72 |
| 61 |  | **5** |  | 95% | (+)-prelaureatin<br>(+)-laurallene | 73 |
| 62 |  | **5** |  | 96% | (+)-rogioloxepane A | 74 |
| 63 |  | **5** |  | 99%<br>*E*:*Z* = 10:1 | (–)-salicylihalamide A | 75 |
| 64 |  | **5** |  | 94% | (+)-sedamine | 76 |
| 65 |  | **5** |  | 93% | sialic acid | 77 |
| 66 |  | **5** |  | 86% | spicigerolide | 78 |
| 67 |  | **5** |  | 82% | (+)-Strictifolione | 79 |
| 68 |  | **9** |  | 88% | (±)-tabersonine | 80 |

**Table 1. (Continued)**

| entry | substrate | catalyst | product | yield | natural product | ref. |
|---|---|---|---|---|---|---|
| 69 |  | **10** |  | >99% | (+)-tanikolide | 81 |
| 70 |  | **6** |  | 92% | (–)-tuberostemonine | 82 |
| 71 |  | **8** |  | 94% | woodrosin I | 83 |
| 72 |  | **7** |  | 69% | (*S*)-(–)-zearalenone | 84 |

[a] The yield includes not only that of RCM but also that of other steps.

**Scheme 7**



**17**
**17a** (n = 0)
**17b** (n = 1)
**17c** (n = 2)

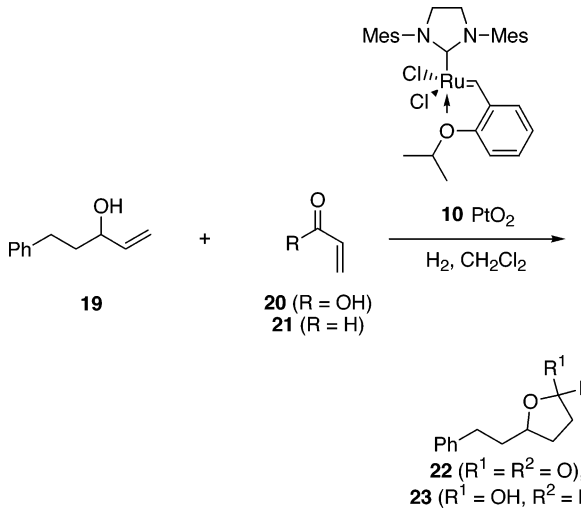
**6**
$N_2 : H_2 = 95 : 5$

**18**
**18a** (n = 0), 46%
**18b** (n = 1), 61%
**18c** (n = 2), 54%

metathesis−hydrogenation of **15** produced the saturated nitrogen heterocycle **16** in a rapid and convenient manner (Scheme 6).[87] Sutton et al. reported that the cyclic enol ethers **18** were obtained through the tandem ring-closing metathesis−olefin isomerization reaction of the 1,$\omega$-dienes **17** (Scheme 7).[88]

Cossy et al. demonstrated that, in the presence of the ruthenium catalyst **10** and $PtO_2$, the tandem cross-metathesis−hydrogenation−cyclization reactions of the alkenol **19** with acrylic acid **20** or acrolein **21** under $H_2$ atmosphere gave the lactone **22** or lactol **23**, respectively (Scheme 8).[89] The ruthenium catalyst **10** and $PtO_2$ are compatible under the reaction conditions.

**Scheme 8**



**19**

**20** (R = OH)
**21** (R = H)

**10** $PtO_2$
$H_2$, $CH_2Cl_2$

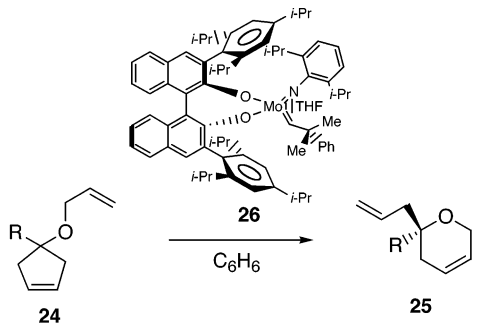
**22** ($R^1$ = $R^2$ = O), 70%
**23** ($R^1$ = OH, $R^2$ = H), 56%

## 2.3. Catalytic Enantioselective Olefin Metathesis

One of the most important advances in this field is the development of chiral olefin metathesis catalysts. Hoveyda et al. have reported the chiral molybdenum-catalyzed asymmetric olefin metathesis.[3h,90] For example, in the presence of the chiral molybdenum catalyst **26**, the enantioselective olefin metathesis of the allyl cycloalkenyl ethers **24** produced the unsaturated cyclic tertiary ethers **25** with very high ee values in high chemical yields (Scheme 9).[90c]

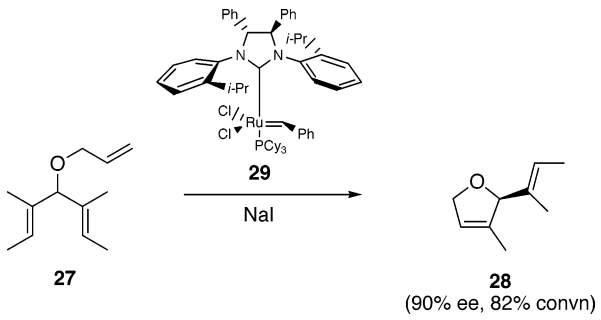
Seiders et al. reported that the enantioselective desymmetrization of the achiral triene **27** with the chiral ruthenium olefin metathesis catalyst **29** gave the dihydrofuran **28** with 90% ee (Scheme 10).[91]

**Scheme 9**

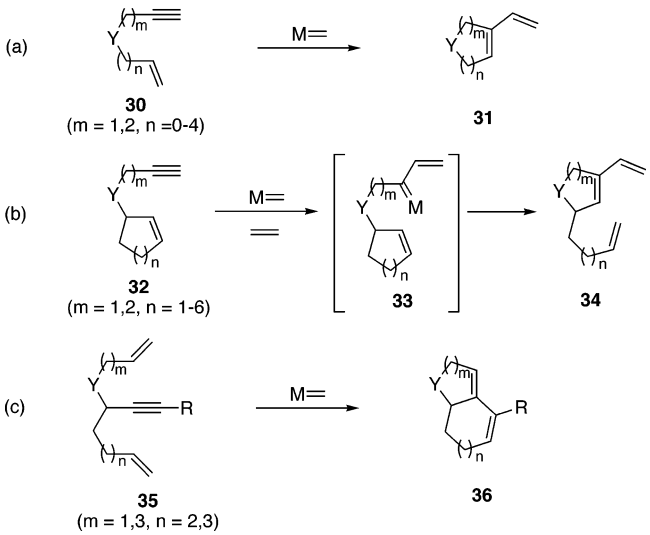


**24a** (R = *n*-Pent) **25a** (R = *n*-Pent) 87% yield, 96% ee
**24b** (R = Phenethyl) **25b** (R = Phenethyl) 95% yield, 91% ee
**24c** (R = *i*-Bu) **25c** (R = *i*-Bu) 93% yield, 93% ee

**Scheme 10**



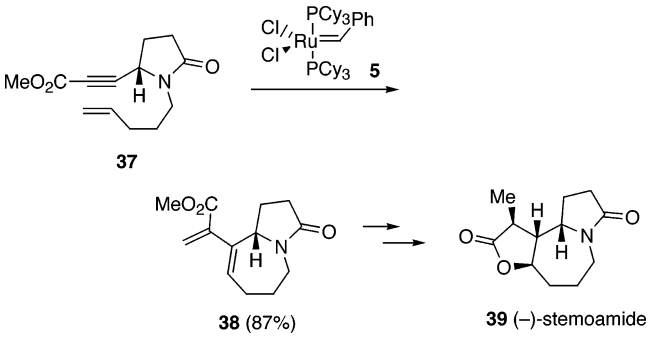
**Scheme 11. Three Categories of Enyne Metathesis**



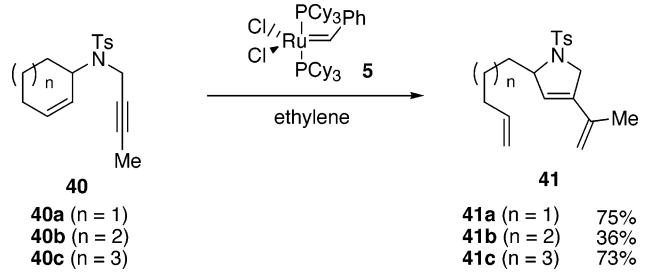
## 2.4. Enyne Metathesis

Intramolecular enyne metathesis has been developed as a useful synthetic method for cyclic dienes.[92] The enyne metathesis is categorized into the three reaction patterns as illustrated in Scheme 11. The metathesis of the 1,$\omega$-enynes **30**, which have a heteroatom between an alkyne and alkene moiety, gives the heterocycles **31** having *exo*- and *endo*-enes (type a).[93] The reaction of the alkynylcycloalkenes **32** with ethylene proceeds through the tandem ring-opening metathesis−ring-closing metathesis, in which most probably the intermediates **33** intervene, to give the ring-rearranged products **34** (type b).[94] The tandem metathesis of the dienynes **35** gives the

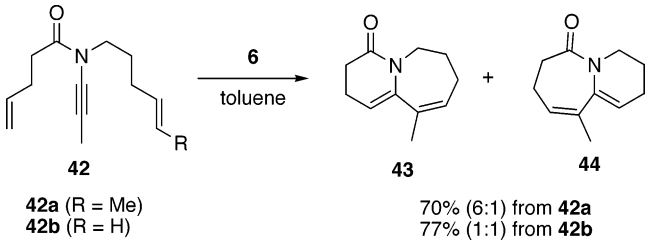
**Scheme 12**



**Scheme 13**



**Scheme 14**



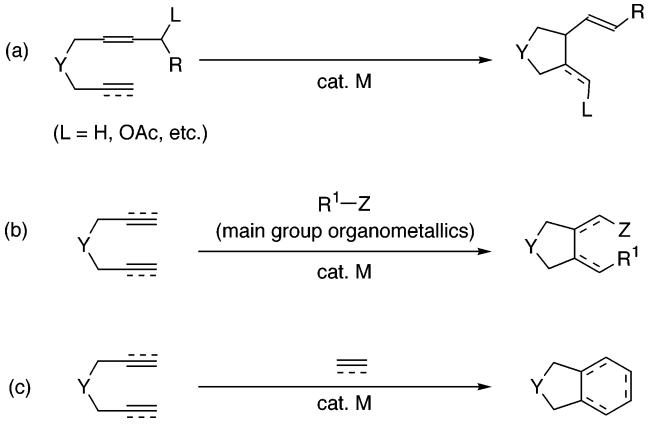
bicyclic heterocycles **36** (type c).[95] The enyne metathesis was applied to the synthesis of nitrogen-containing bicyclic natural products, such as (−)-stemoamide **39** (Scheme 12).[96] The transformation from **37** to **38** belongs to category a in the Scheme 11. The reaction of the 2-cycloalkenyl propargyl tosylamides **40** with ethylene gas in the presence of Grubbs' ruthenium carbene complex **5** gave the dihydropyrroles **41** in good yields (Scheme 13).[94a] The reaction is categorized into type b in the Scheme 11.

Hsung et al. reported the tandem metathesis of dienynamides gave the bicyclic heterocycles. The reaction of **42a**, which had two sterically differentiated olefinic tethers, gave the six-membered lactam **43** as the major product along with the seven-membered lactam **44**, while the reaction of **42b** having two monosubstituted olefin produced a 1:1 mixture of **43** and **44** (Scheme 14).[95d]

## *3. Intramolecular Reaction of 1,6-Dienes, -Enynes, and -Diynes: Cycloisomerization, Tandem Addition–Cyclization, and Cycloaddition*

A series of 1,*n*-dienes, -enynes, and -diynes has been widely utilized for the transition-metal-catalyzed cyclization reactions, since the cyclization of these compounds is a geometrically favored process.

**Scheme 15. Synthesis of Heterocycles from 1,6-Dienes, Enynes, and Diynes via (a) Cycloisomerization, (b) Tandem Addition−Cyclization, and (c) Cycloaddition**

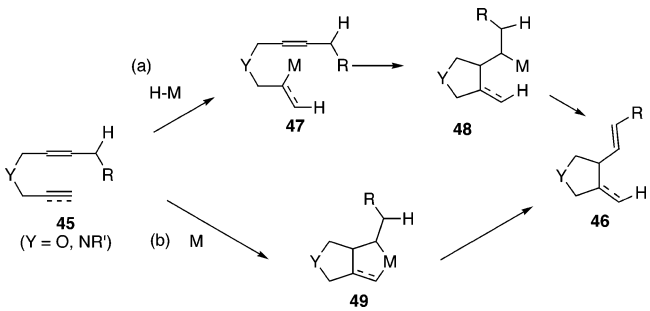



As 1,*n*-alkenes, 1,6-derivatives are used very frequently leading to five-membered heterocycles, while the use of 1,7-derivatives, which produce six-membered heterocycles, is very rare. The reactions of 1,6-dienes, -enynes, and -diynes are classified into three groups: (a) cycloisomerization, (b) tandem addition−cyclization, and (c) cycloaddition, such as the Pauson−Khand reaction, cyclotrimerization, and the Diels−Alder reaction (Scheme 15).[97] In these reactions five-membered heterocycles are constructed upon the carbon−carbon bond-forming processes.

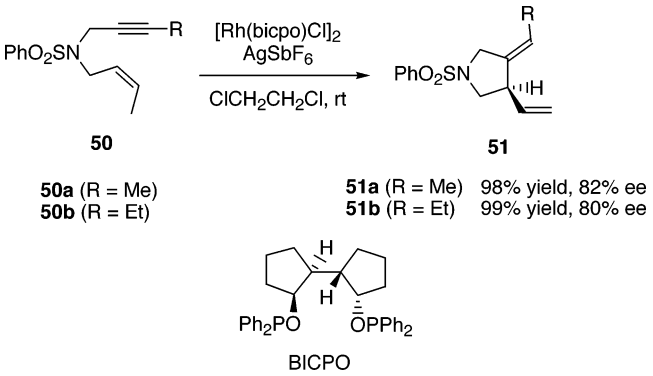
## 3.1. Cycloisomerization

In the reaction of 1,6-dienes and enynes **45**, which have a migration group such as a proton and acetate at an allylic position, the cycloisomerization occurs as shown in Scheme 16 to give the heterocycles **46** bearing an alkenyl group (Scheme 16, route a).[98] There are two possible pathways in the cycloisomerization; when a metal hydride species exists in the reaction of **45**, the hydrometalation of the terminal ene or yne group occurs to give **47** (route a). The intramolecular carbometalation of **47** leads to the cyclic intermediate **48** and the following $\beta$-elimination gives the heterocycles **46**. Meanwhile, the reaction of **45** with a transition-metal complex (M) starts from formation of the metallacycle **49** (route b). Subsequent $\beta$-elimination and reductive elimination affords the product **46**.

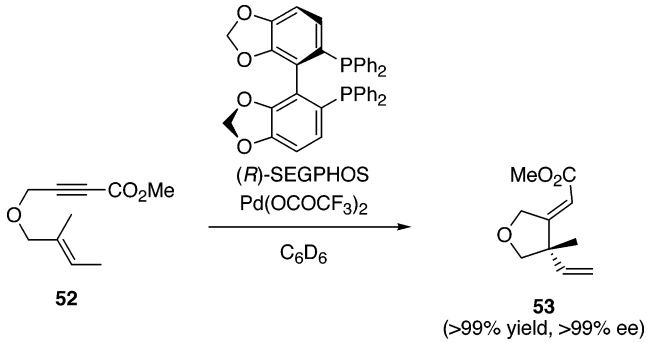
**Scheme 16. Catalytic Cycloisomerization of 1,6-Dienes and Enynes via (a) Hydrometalation or (b) Formation of the Metallacycle**




**Scheme 17**




**Scheme 18**




Recently, the transition-metal-catalyzed enantioselective enyne cycloisomerization has been reported.[99] Cao and Zhang reported that, in the presence of catalytic amounts of $[Rh(bicpo)Cl]_2$ and $AgSbF_6$, the enantioselective cycloisomerization of the 1,6-enynes **50** gave the functionalized lactams **51** in good yields with high ee values (Scheme 17).[99a] Hatano et al. reported that, in the presence of catalytic amounts of palladium(II) and (*R*)-SEGPHOS, the asymmetric cycloisomerization of the 1,6-enyne **52** gave the tetrahydrofuran derivative **53** in 99% yield with >99% ee (Scheme 18).[99b] It should be noted that the quaternary chiral center is constructed with extremely high ee in almost quantitative yield.

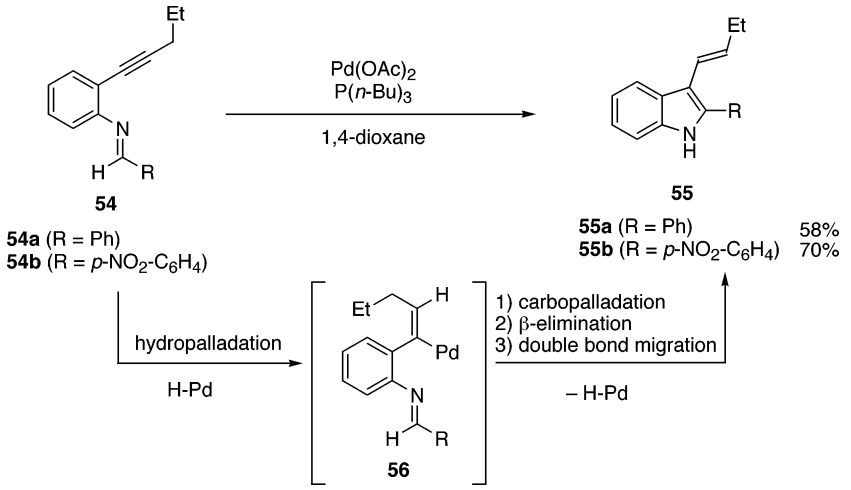
We reported that the palladium-catalyzed intramolecular cyclization of the *N*-(*o*-alkynylphenyl)-imines **54** gave the 3-alkenylindoles **55** in good to high yields (Scheme 19).[100] A hydridopalladium species, generated in situ through the reaction of $Pd(OAc)_2$, $P(n\text{-}Bu)_3$, and $H_2O$, reacts with alkynes to produce **56**, which undergoes the cycloisomerization via the carbopalladation−$\beta$-elimination−olefin isomerization.

The reaction type (a) (L = OAc) in Scheme 15 takes place in the palladium-catalyzed reaction of the alkyne-allyl acetates **57** with acetic acid; the *trans*-acetoxypalladation of alkyne leads to **59**, and subsequent carbopalladation of alkene followed by deacetoxypalladation gives the five-membered heterocycles 2-alkenylidenelactones **58** (Scheme 20).[101a]

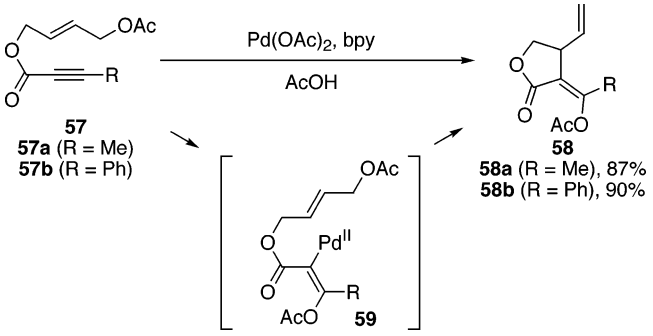
## 3.2. Tandem Addition−Cyclization

In the past decade, various kinds of transition-metal-catalyzed addition reactions of main group

**Scheme 19**



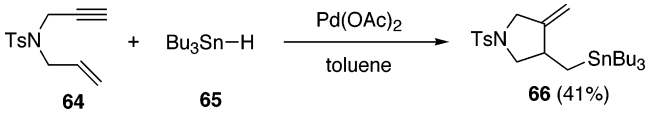

**Scheme 20**




organometallics to C−C unsaturated bonds have been developed (Scheme 21). This type of reaction was applied to the 1,6-dienes, -enynes, and -diynes **60**, instead of mono-enes and -ynes (Scheme 21). As the main group organometallics, $R^1$−Z, the reagents for hydrosilylation,[102] hydrostannation,[103] silylstannation,[104] distannation,[104a,d] silacarbonylation,[105] silaboration,[106] and stannaboration[107] were used. The insertion of a transition-metal catalyst M into $R^1$−Z, followed by the addition of the resulting $R^1$−MZ to one of the two C−C unsaturated bonds of **60** produces **61**. The cyclization through carbometalation gives the intermediate **62**, which affords the heterocycles **63** upon reductive elimination of M.

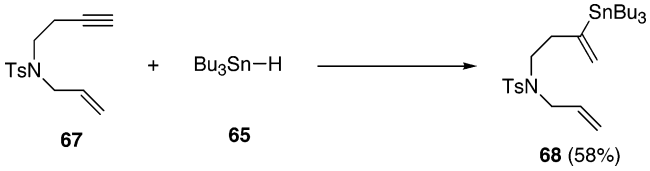
Lautens et al. reported that the palladium-catalyzed tandem hydrostannation−cyclization of the 1,6-enyne **64** with tributyltin hydride **65** gave the heterocycle **66** in 41% yield (Scheme 22).[103] On the

**Scheme 22**



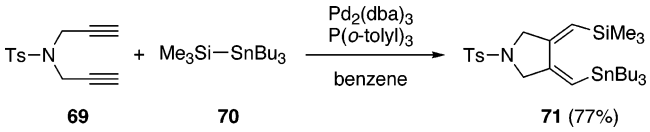

contrary, the reaction of the 1,7-enyne **67** with **65** produced the acyclic hydrostannation product **68** (Scheme 23).

**Scheme 23**



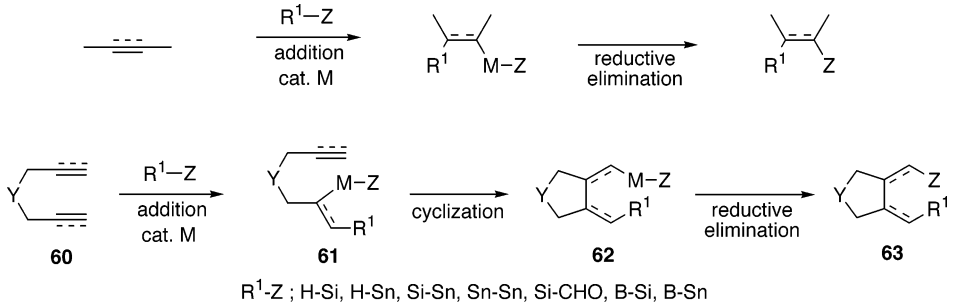

Shin and RajanBabu reported that the palladium(0)-catalyzed cyclization of the 1,6-diyne **69** with trimethylsilyltributyltin **70** gave the nitrogen heterocycle **71** with an uncommon (*Z*,*Z*)-geometry at the exo-double bonds in a good yield (Scheme 24).[104a]

**Scheme 24**



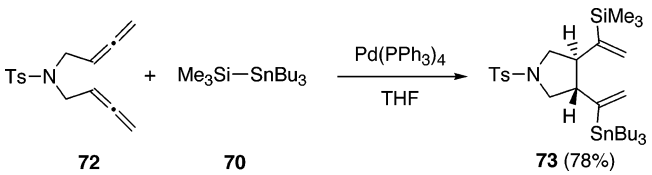

Kang et al. demonstrated that the palladium-catalyzed tandem cyclization−silastannation of the bis(allene) **72** with trimethylsilyltributyltin **70** produced the trans-fused heterocycle **73** (Scheme 25),

**Scheme 21. Addition−Cyclization Reaction of 1,6-Dienes, Diynes, and Enynes**



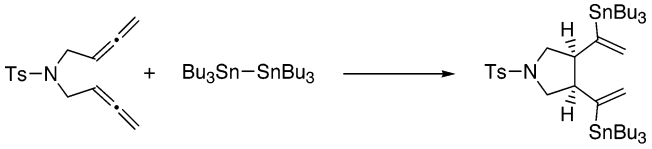

$R^1$-Z ; H-Si, H-Sn, Si-Sn, Sn-Sn, Si-CHO, B-Si, B-Sn

**Scheme 25**



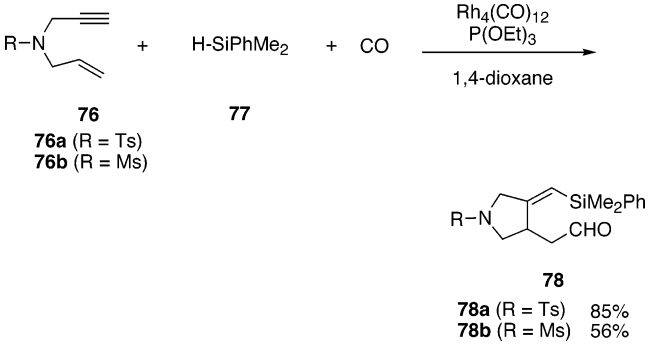

**72** **70** **73** (78%)

**Scheme 26**




**72** **74** **75** (73%)

**Scheme 27**

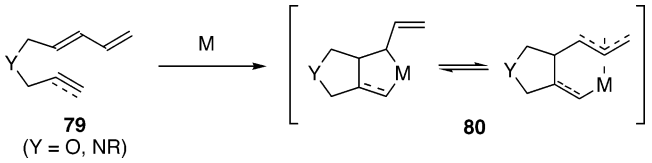



**76**
**76a** (R = Ts)
**76b** (R = Ms)

**77**

**78**
**78a** (R = Ts) 85%
**78b** (R = Ms) 56%

**Scheme 28. Cyclization of the Diene−ene and Diene−yne Derivatives**




**79**
(Y = O, NR)

**80**

while the tandem cyclization−distannation of **72** with hexabutylditin **74** gave the cis-fused heterocycle **75** (Scheme 26).[104b]

Ojima et al. reported the rhodium-catalyzed carbonylative silylcarbocyclization of the 1,6-enynes **76**.[105] In the presence of the rhodium catalyst the reaction of the 1,6-enynes **76** with the hydrosilane **77** under CO atmosphere gave the heterocycles **78**, which had both silylmethylene and formylmethyl groups, in good yields (Scheme 27).

The substrates **79** having a diene moiety, that is to say, an extended C−C unsaturated bond, have been focused in the catalytic addition−cyclization reactions, since the metallacyclic intermediates **80** possess an allylic metal functionality, which enables further manipulation (Scheme 28).

Takimoto and Mori reported that the nickel-catalyzed regio- and stereoselective ring-closing carboxylation of the bis-1,3-diene **81** with dialkylzincs **82** gave the 3-allyl-4-alkenylpyrrolidines **83** in high yields (Scheme 29).[108] The reaction proceeds through formation of the cyclic bis-$\pi$-allylnickel complex **84**, the insertion of $CO_2$ into a nickel−carbon bond of **84**, leading to **85**, and the addition of $R_2Zn$ to **85**.

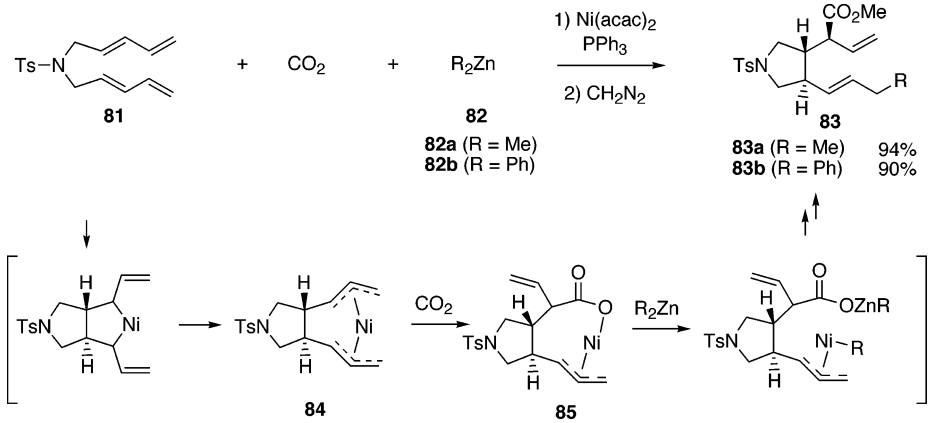
Kimura and Tamaru reported the nickel-catalyzed conjugated addition of $Me_2Zn$ **82a** and benzaldehyde **87** to the 1,3-dien-8-ynes **86** (Scheme 30).[109] The reaction produces the nitrogen and oxygen five-membered heterocycles **88** in good yields. Very likely, the first step is formation of the nickelacycle **89**, and the resulting allylic nickel reacts with benzaldehyde **87** to lead to the C−C bond forming intermediate **90**, which undergoes methylation with $Me_2Zn$, giving the product **88**.

## 3.3. Cycloaddition

### *3.3.1. [2 + 2 + 1]-Cycloaddition (Pauson–Khand Reaction)*

The catalytic [2 + 2 + 1]-cycloaddition reaction of two carbon−carbon multiple bonds with carbon monoxide has become a general synthetic method for five-membered cyclic carbonyl compounds. In particular, the Pauson−Khand reaction has been widely investigated and established as a powerful tool to synthesize cyclopentenone derivatives.[110] Various kinds of transition metals, such as cobalt, titanium, ruthenium, rhodium, and iridium, are used as a catalyst for the Pauson−Khand reaction. The intramolecular Pauson−Khand reaction of the allyl propargyl ether and amine **91** produces the bicyclic ketones **93**, which bear a heterocyclic ring as shown in Scheme 31. The reaction proceeds through formation of the bicyclic metallacyclopentene intermediate **92**, which subsequently undergoes insertion of CO to give **93**.

**Scheme 29**

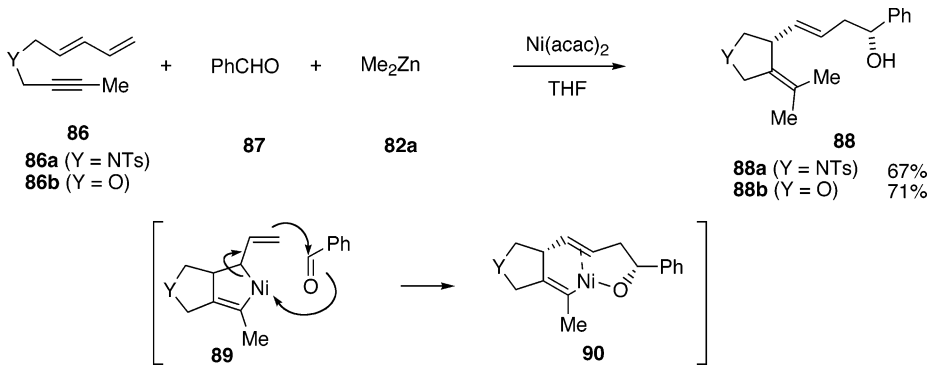



**81** **82** **83**

**82a** (R = Me) **83a** (R = Me) 94%
**82b** (R = Ph) **83b** (R = Ph) 90%

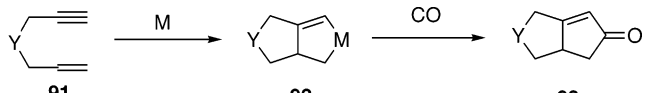
**84** **85**

**Scheme 30**



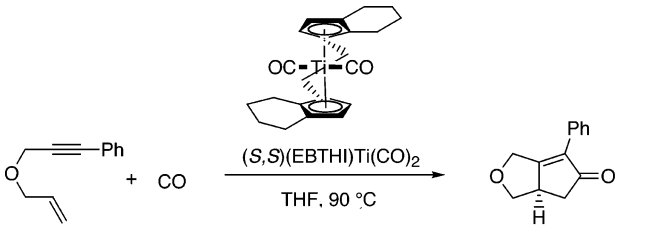

**86**
**86a** (Y = NTs)
**86b** (Y = O)
**87**
**82a**
**88**
**88a** (Y = NTs) 67%
**88b** (Y = O) 71%
**89**
**90**

**Scheme 31. Pauson−Khand Reaction**



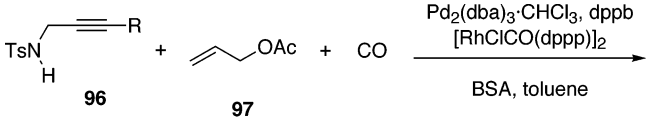

**91**
(Y = O, NR)
**92**
**93**

**Scheme 32**

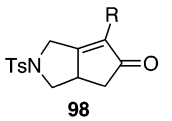



**94**
**95** (85% yield, 96% ee)

**Scheme 33**




**96**
**96a** (R = Ph)
**96b** (R = Me)
**96c** (R = H)
**97**

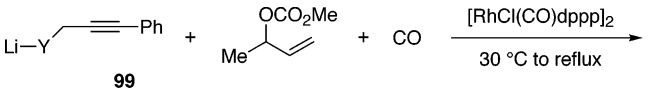



**98**
**98a** (R = Ph) 90%
**98b** (R = Me) 91%
**98c** (R = H) 92%

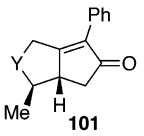
Recently, the enantioselective Pauson−Khand reaction has been developed using chiral ligands.[111] Hicks and Buchwald reported that, in the presence of (*S*,*S*)(EBTHI)Ti(CO)$_2$, the asymmetric Pauson−Khand reaction of the 1,6-enyne **94** gave the bicyclic heterocycle **95** in a high yield with good enantiomeric excess (Scheme 32).[111a,b]

Jeong et al. demonstrated that the tandem allylic alkylation/Pauson−Khand reaction of the propargylic amines **96** with allyl acetate **97** and CO took place in the presence of a mixture of palladium and rhodium catalysts to give the bicyclopentenones **98** in high yields (Scheme 33).[112] Most probably, the allylation of **96** with allyl acetate **97** occurs in the presence of palladium catalyst to give the corresponding enyne, which undergoes the Pauson−Khand reaction with CO in the presence of rhodium catalyst. Evans and Robinson reported that the regio- and diastereoselective tandem allylic alkylation/Pauson−Khand annulation reaction of the propargylic derivatives **99** with the allylic carbonate **100** and CO took place in the presence of a rhodium catalyst only (Scheme 34).[113]

**Scheme 34**

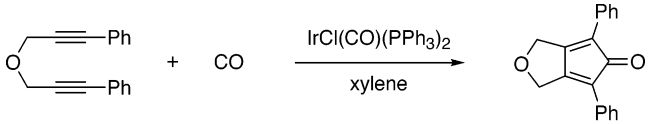



**99**
**99a** (Y = NTs)
**99b** (Y = O)
**100**




**101**
**101a** (Y = NTs) 81%
**101b** (Y = O) 81%

**Scheme 35**

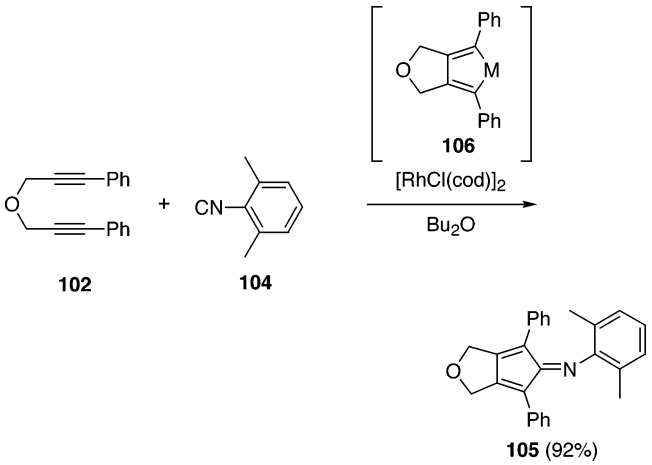



**102**
**103** (65%)

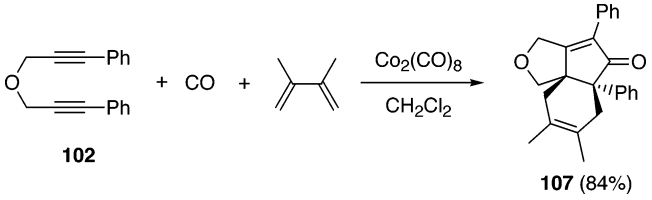
Shibata et al. reported that, in the presence of an iridium catalyst, the carbonylative alkyne−alkyne coupling reaction of the diyne **102** with carbon monoxide gave the tetrahydrofuran-fused cyclopentadienone **103** (Scheme 35).[114] The rhodium-catalyzed alkyne−alkyne coupling reaction of **102** with the isocyanide **104** produced the iminocyclopentadiene **105** (Scheme 36).[114b] These reactions proceed through formation of the metallacyclopentadiene intermediate **106**, which undergoes insertion either of CO or of the isocyanide **104**.

Son et al. reported that the cobalt-catalyzed [2 + 2 + 1]-cycloaddition of the diyne **102** with CO, followed by Diels−Alder reaction of the resulting product with 2,3-dimethyl-1,3-butadiene, gave the tricyclic heterocycle **107** in a good yield (Scheme 37).[115] The Pauson−Khand reaction of **69**, followed by the [2 + 2 + 2]-cycloaddition of the resulting bicyclopentadienone with the cobaltacyclopentadiene

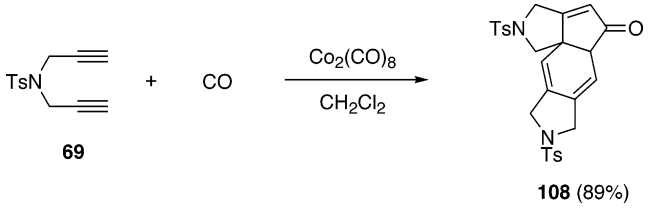
**Scheme 36**



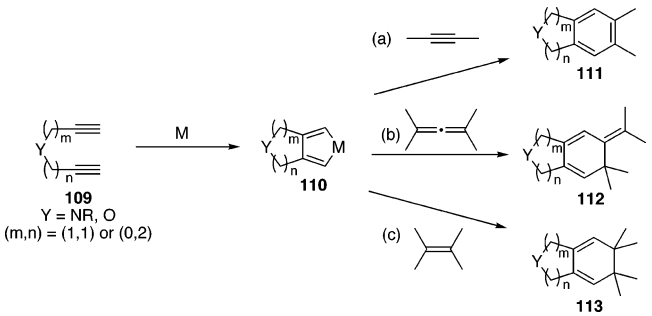

**Scheme 37**




**Scheme 38**




**Scheme 39. Catalytic [2 + 2 + 2]-Cycloaddition of Diynes with (a) Alkynes, (b) Allenes, and (c) Alkenes**

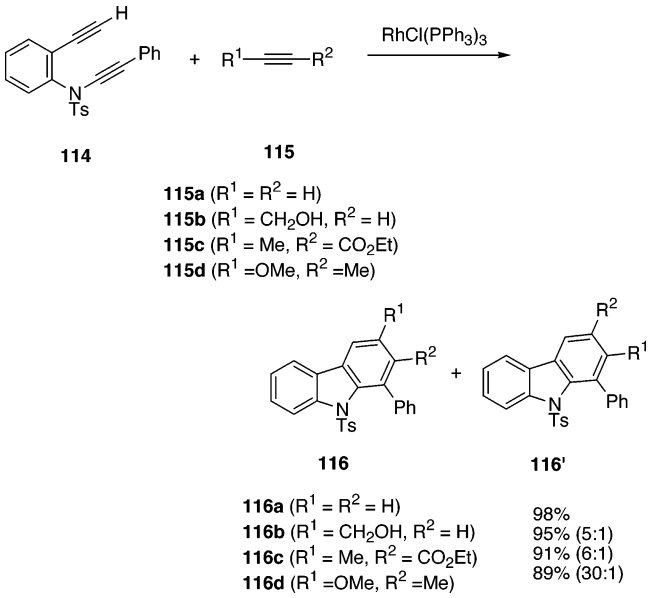



intermediate, gave the tetracyclic heterocycle **108** in a high yield (Scheme 38).[116]

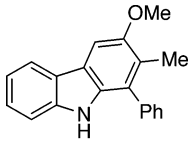
### *3.3.2. [2 + 2 + 2]-Cycloaddition*

Transition-metal-catalyzed [2 + 2 + 2]-cycloaddition of alkynes, so-called cyclotrimerization, has been widely investigated as a powerful tool to construct benzene rings.[117] Cyclotrimerization of the aminodialkynes and dialkynyl ethers **109** with alkynes provides various kinds of benzene-fused aza- and oxaheterocyclic compounds **111** (Scheme 39, route a).[118] The key intermediate for the [2 + 2 + 2]-cycloaddition is the metallacyclopentadienes **110**, as mentioned in Scheme 36 of section 3.3.1. The catalytic [2 + 2 + 2]-cycloaddition of the diyne **109** with allenes leads to the heterocyclic ring-fused methylenecyclohexadienes **112**, which often undergoes rapid olefin isomerization to give the corresponding benzene derivatives (route b).[119] Cycloaddition of **109** with alkenes affords the 1,3-cyclohexadiene derivatives **113**, which are used often as substrates for further manipulation (route c).[120] Various kinds of transition-metal complexes, such as ruthenium, palladium, rhodium, iridium, nickel, and cobalt, have been employed as a catalyst of the cyclotrimerization reaction. Noncatalytic cyclotrimerization of alkynes and/or nitriles using stoichiometric amount of zircona- and titanacyclopentadienes produces fused heterocycles, such as **111**, and/or heteroarenes,[121] but these heterocycle syntheses are beyond the scope of this review.

**Scheme 40**



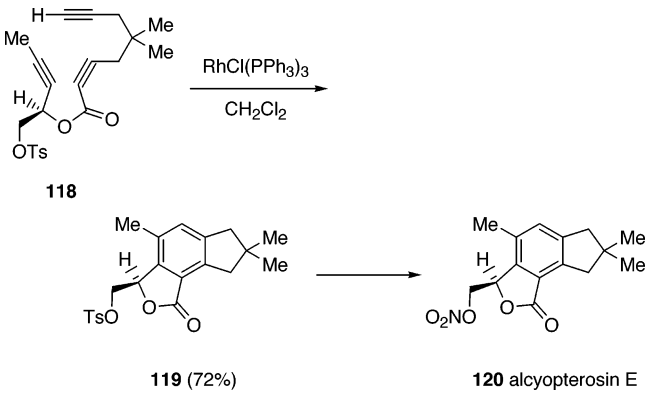

Witulski and Alayrac reported the highly efficient and flexible synthesis of substituted carbazoles by the rhodium-catalyzed cyclotrimerization. The reaction of 2,*N*-dialkynylaniline **114** with the alkynes **115** in the presence of $RhCl(PPh_3)_3$ gave the functionalized carbazoles **116** in high yields (Scheme 40).[118h] In the case of the reaction of **115b**−**d**, **116′** was produced as a minor regioisomer. The product **116d** was converted to hyellazole **117**, a marine carbazole



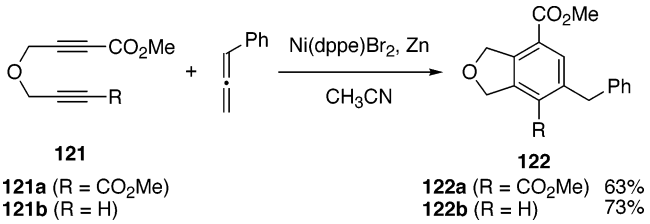

**117** Hyellazole

alkaloid. The synthesis of (*R*)-alcyopterosin E **120** was carried out by the rhodium-catalyzed intramolecular cyclotrimerization of the triyne ester **118** (Scheme 41).[118i]

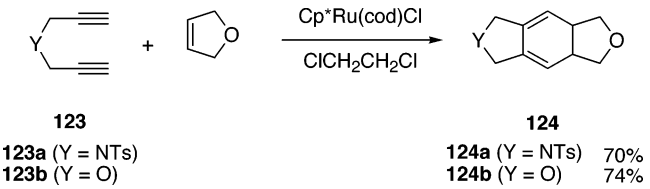
**Scheme 41**




**Scheme 42**



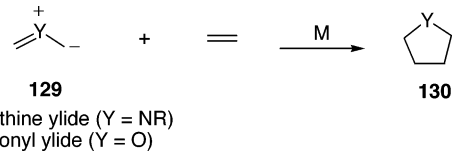

**Scheme 43**




Shanmugasundaram et al. reported that the nickel-catalyzed [2 + 2 + 2]-cycloaddition of the 1,6-diynes **121** with phenylallene gave the 1,3-dihydroisobenzofuran derivatives **122** in good yields (Scheme 42).[119a] The reaction of the unsymmetric diyne **121b** afforded only the meta-isomer **122b**.

Yamamoto et al. demonstrated that the [2 + 2 + 2]-cycloaddition of the 1,6-diynes **123** with 2,5-dihydrofuran in the presence of Cp*Ru(cod)Cl produced the polycyclic dienes **124** in good yields, while in the presence of a $\eta^5$-indenyl ruthenium catalyst ($\eta^5$-$C_7H_9$)Ru($PPh_3$)$_2$Cl, the reaction of the 1,6-diynes **123** with norbornene gave the cyclopropylcyclopentene derivatives **125** (Schemes 43 and 44).[120a,b] The reaction proceeds through the ruthenacyclopentadiene intermediate **126** and its resonance structure, ruthenacyclopentatriene **127**. Exo-selective cyclopropanation of **127** with norbornene leads to the ruthenium carbene complex **128** and subsequent second exo-cyclopropanation of **128** gives the product **125**.

**Scheme 45. [3 + 2]-Cycloaddition of Ylides with Olefins**



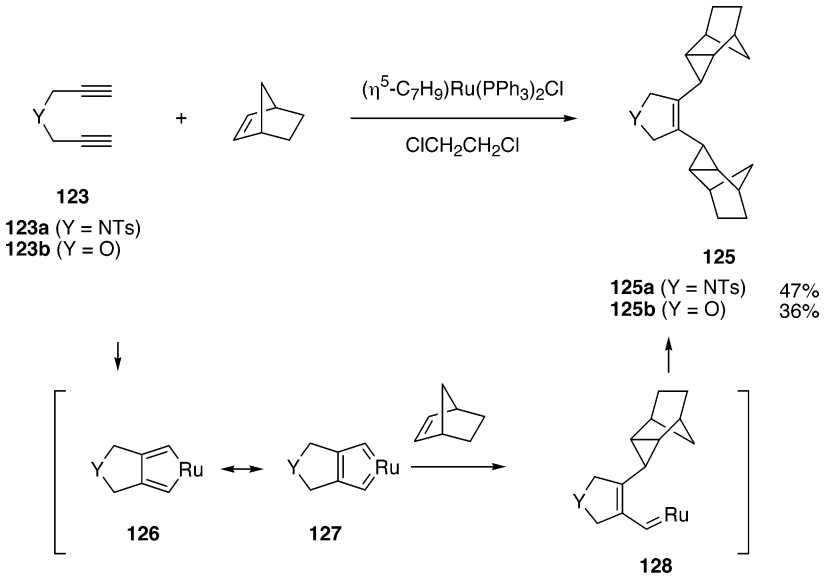

### 3.3.3. [3 + 2]-Cycloaddition

Catalytic [3 + 2]-cycloaddition of the carbonyl and azomethine ylides **129** with olefins gives the five-membered heterocycles **130** (Scheme 45). Longmire et al. reported that the catalytic asymmetric [3 + 2]-cycloaddition of the azomethine ylides **131** with dimethyl maleate in the presence of AgOAc and a bisferrocenyl amide ligand **133** gave the pyrrolidine triesters **132** in excellent yields with very high enantiomeric excesses (Scheme 46).[122] As described in section 8, the [3 + 2]-cycloaddition reaction of diazo compounds with olefins proceeds similarly through the formation of carbonyl ylides.

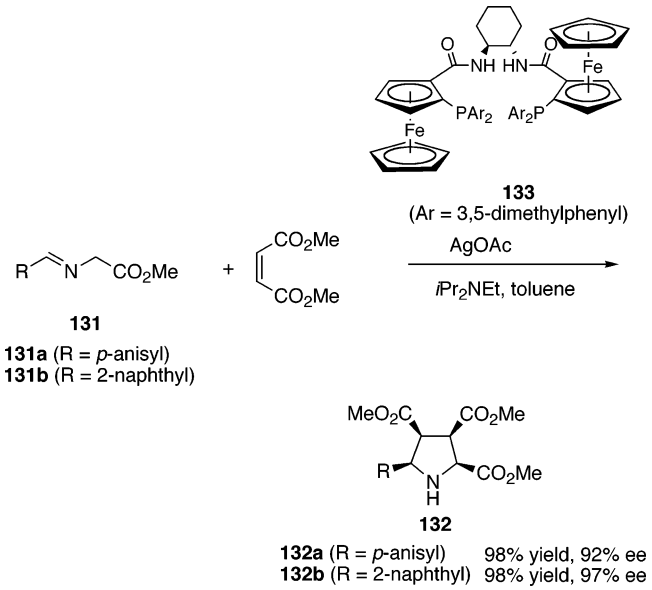
### 3.3.4. [4 + 2]-Cycloaddition

The Diels−Alder reaction is one of the most important methodologies for organic synthesis. Heterocycles **135** has been synthesized by the intramolecular Diels−Alder reaction using diene−ene or diene−yne compounds **134**, which have a heteroatom in a

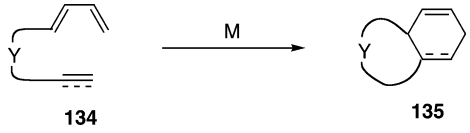
**Scheme 44**



**Scheme 46**




**Scheme 47. Synthesis of Heterocycles by Diels−Alder Reaction**



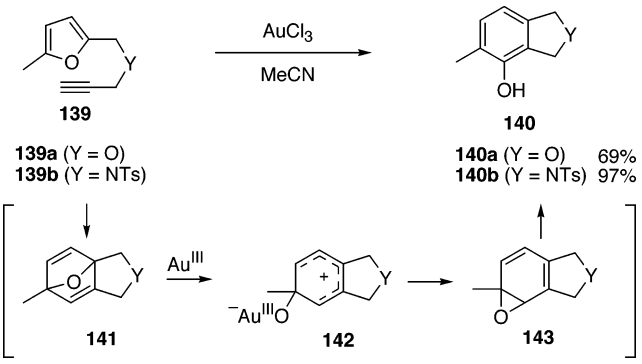

tether moiety (Scheme 47).[123] A wide variety of transition-metal complexes such as nickel, ruthenium, rhodium, and palladium, have been used as catalysts.

Mikami and Ohmura reported that the cycloaddition of isobenzofuran **138**, which was generated from the lactol methyl ether **136** upon treatment with palladium(0) catalyst, with dimethyl acethylenedicarboxylate gave the benzene-fused oxanorbornene **137** (Scheme 48).[124]

Hashmi reported that the gold-catalyzed [4 + 2]-cycloaddition reaction of furylmethyl propargyl ether **139a** and amine **139b** gave the arenes **140** in good to excellent yields (Scheme 49).[125] The intramolecular Diels−Alder reaction gives **141**, which undergoes Au(III)-promoted isomerization as shown in **142** and **143** and finally reaches **140** upon aromatization.

We reported that the phthalide **146** and 3,4-dihydroisocoumarin **147** were prepared using the palladium-catalyzed intramolecular benzannulation

**Scheme 49**




strategy (Scheme 50).[126] The reaction proceeds through formation of the palladacycle **148** followed by reductive elimination of palladium(0).

### *3.3.5. [4 + 2 + 2]-, [5 + 2]-, and [6 + 2]-Cycloaddition*

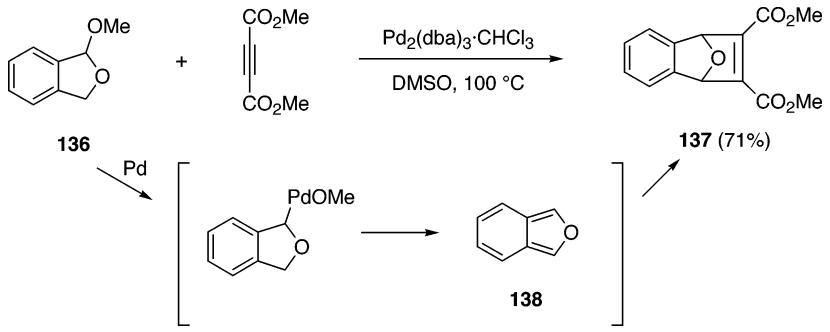
Gilbertson and DeBoef demonstrated that the [4 + 2 + 2]-cycloaddition of the yne−dienes **149** with the alkyne **150** took place in the presence of rhodium and silver catalysts to give the eight-membered trienes **151** in good yields (Scheme 51).[127]

Evans et al. reported that [4 + 2 + 2]-cycloaddition of 1,6-enynes **152** with 1,3-butadiene proceeded in the presence of catalytic amounts of $Rh(PPh_3)_3Cl$ and AgOTf and the corresponding 1,4-cyclooctadienes **153** were obtained in good to high yields (Scheme 52).[128]

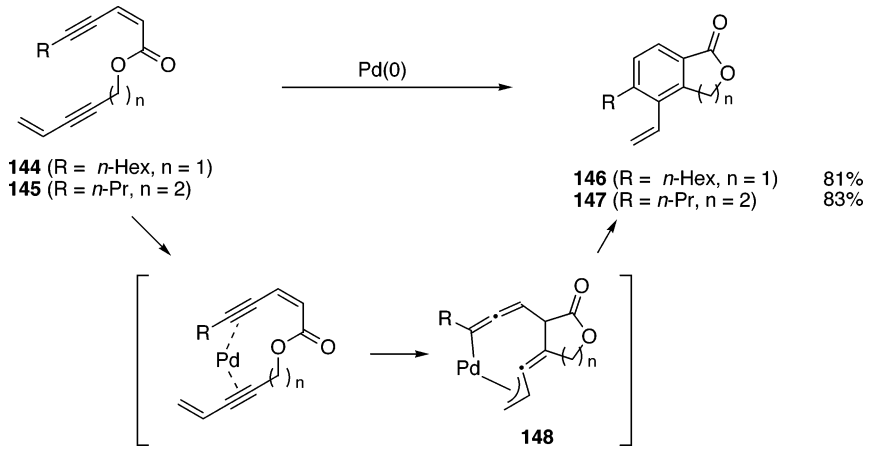
The transition-metal-catalyzed intramolecular [5 + 2]-cycloaddition of **154** bearing a heteroatom between an alkynyl and a cyclopropylalkenyl group provides the heterocycles **155** bearing a seven-membered carbocycle (Scheme 53).[129] Rhodium and ruthenium complexes have been used as catalysts of this [5 + 2]-cycloaddition. Trost and Shen extended this reaction for constructing the tricyclic heterocycle **157** from **156** (Scheme 54).[129i]

Wender et al. demonstrated the rhodium-catalyzed intramolecular [6 + 2]-cycloaddition of 2-(1,6-dienyl)-cyclobutanones **158** (Scheme 55).[130] The five-membered heterocycles **159** were synthesized using substrates **158**, which had a nitrogen or oxygen atom in a tether moiety. The reaction proceeds through formation of the five-membered metallacycle **160** and subsequent $\beta$-carbon elimination (de-carborhodation), leading to the nine-membered metallacycle **161**, which produces **159** upon reductive elimination of Rh.

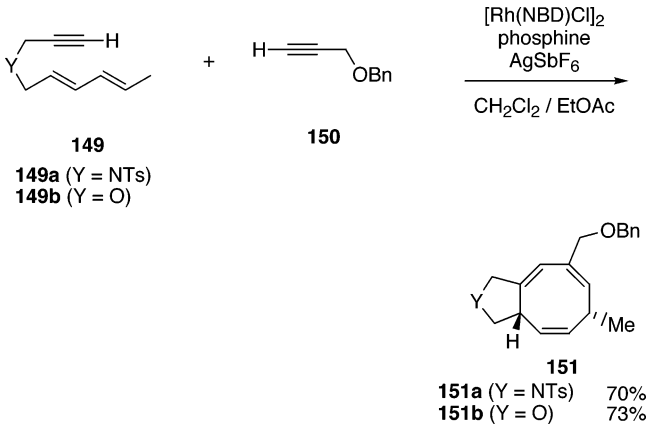
**Scheme 48**



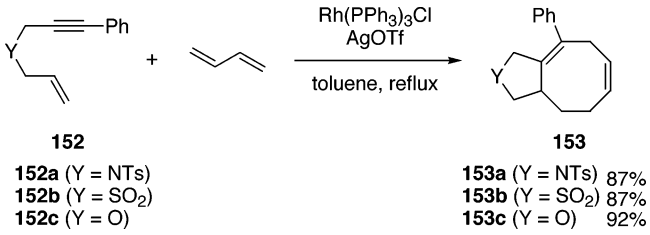
**Scheme 50**




**Scheme 51**

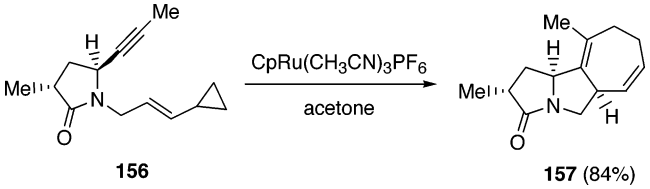



**Scheme 52**




**Scheme 53**

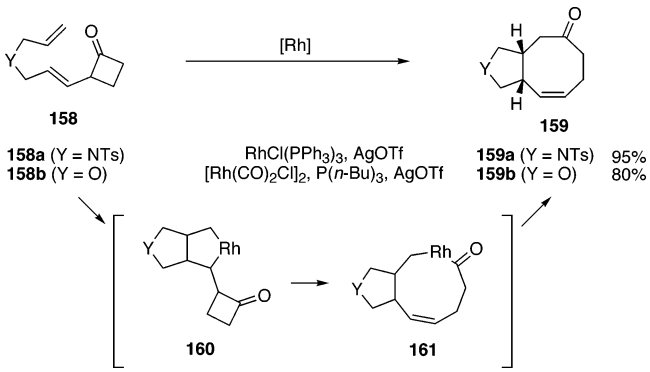

**Scheme 54**



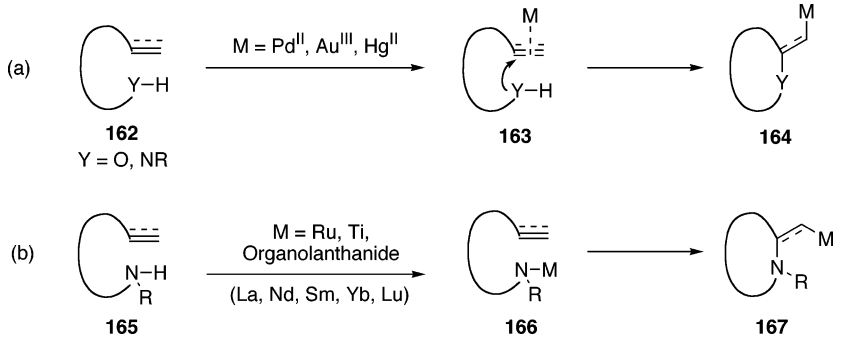

## *4. Intramolecular Reaction of Alkenes, Allenes, and Alkynes Bearing N–H, O–H, C═O, and C═N Groups: Heterocyclization*

Transition-metal-catalyzed intramolecular reactions of carbon−carbon unsaturated compounds tethered with N−H, O−H, C═O, and C═N groups have been extensively studied and have become a powerful tool for the synthesis of heterocycles. Alkenes, allenes, methylenecyclopanes, and alkynes have been utilized as a carbon−carbon unsaturated compound, and a wide variety of transition-metal complexes, such as palladium, platinum, gold, copper, titanium, tungsten, and organolanthanides, have been used as a catalyst. In these reactions the heterocyclic compounds are produced via carbon−heteroatom (C−Y) bond formation (see Scheme 2). The transition-metal-catalyzed intramolecular addition reaction of Y−H to the C−C unsaturated bonds is classified into two major groups, as illustrated in Scheme 56. In the presence of a higher valent transition-metal catalyst, such as $Pd^{II}$, $Au^{III}$, and $Hg^{II}$, the reaction of **162** having a Y−H group is initiated by the formation of the $\pi$-olefin complex **163** through the coordination of the carbon−carbon unsaturated bond to the transition metal. Subsequent intramolecular nucleophilic attack of the heteroatom to the electron-deficient unsaturated bond produces the new heterocyclic organometallics **164**. On the other hand, the ruthenium, titanium, and organolanthanide-catalyzed reaction of the amine derivatives **165** starts from the formation of the metal−amido complex **166**, and the following intramolecular aminometalation of the C−C unsaturated bond produces the new heterocyclic organometallics **167**. The organometallic compounds

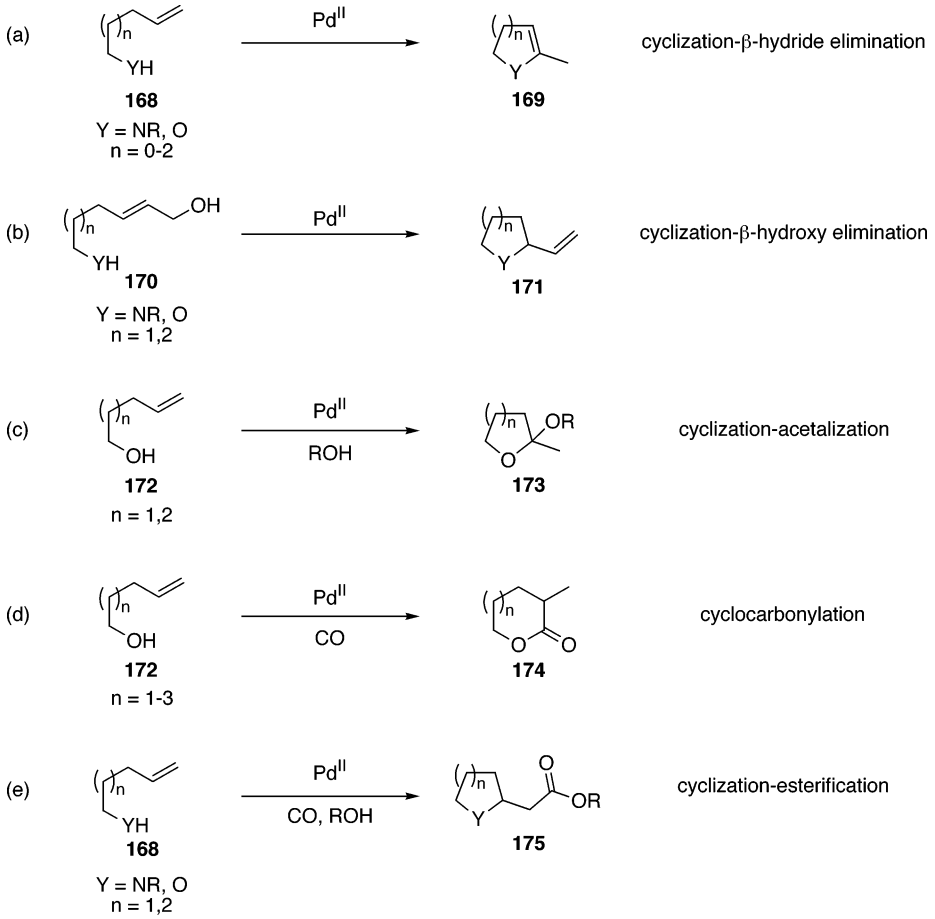
**Scheme 55**



**Scheme 56. Heterocyclization of C−C Unsaturated Compounds Having a Heteroatom−Hydrogen Bond**




**Scheme 57. Heterocyclization of Alkenylamines and Alcohols via (a) Cyclization−β-Hydride Elimination, (b) Cyclization−β-Hydroxy Elimination, (c) Cyclization−Acetalization, (d) Cyclocarbonylation, and (e) Cyclization−Carbonylative Esterification**

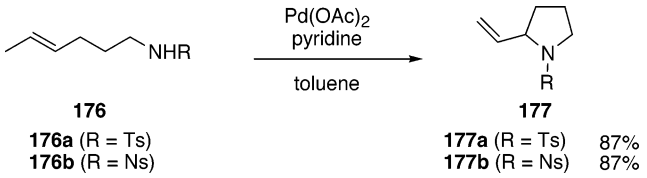



**164** and **167** undergo either β-elimination or the reaction with electrophiles to give the corresponding heterocyclic products.

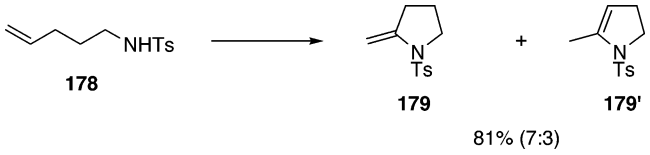
## 4.1. Alkenes

Higher valent palladium(II)-catalyzed reaction of alkenylamines and alkenyl alcohols have been widely investigated, and these reactions are categorized into the five different reaction patterns, as shown in Scheme 57. The cyclization of the alkenylamines or alcohols **168** followed by β-hydride elimination gives the cyclic enamines or enols **169** (type a).[131a,b,132] The reaction of the substrates **170** having an allyl alcohol moiety proceeds through the cyclization, and the subsequent β-hydroxy elimination gives the heterocycles **171** bearing a vinyl group (type b).[131b,133] The reaction of the alkenols **172** with an external alcohol produces the cyclic acetals **173** (type c).[131b,134] The cyclocarbonylation of **172** with carbon monoxide gives the lactones **174** (type d).[131c,135] The reaction of the alkenylamines or alkenyl alcohols **168** with carbon monoxide and an alcohol proceeds through the cyclization−esterification to give **175** (type e).[131d,136] In these reactions the carbon−carbon double bond of substrates coordinates to the Lewis acidic (that means higher valent) palladium(II) complex and intramolecular nucleophilic attack of a heteroatom takes place as shown in Scheme 56.

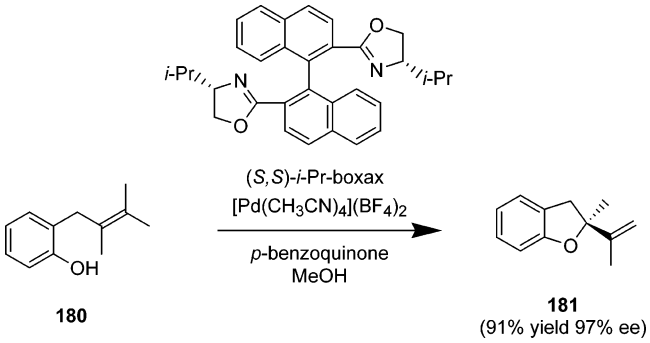
**Scheme 58**




**Scheme 59**




**Scheme 60**




Fix et al. reported the palladium-catalyzed oxidative cyclization of aminoalkenes.[132b] The reaction of the aminoalkenes **176** having a methyl group on the olefin moiety gave the 2-vinylpyrrolidines **177**, while the reaction of the aminoalkene **178** having a terminal olefin gave a mixture of the cyclic enamines **179** and **179′** (Schemes 58 and 59).

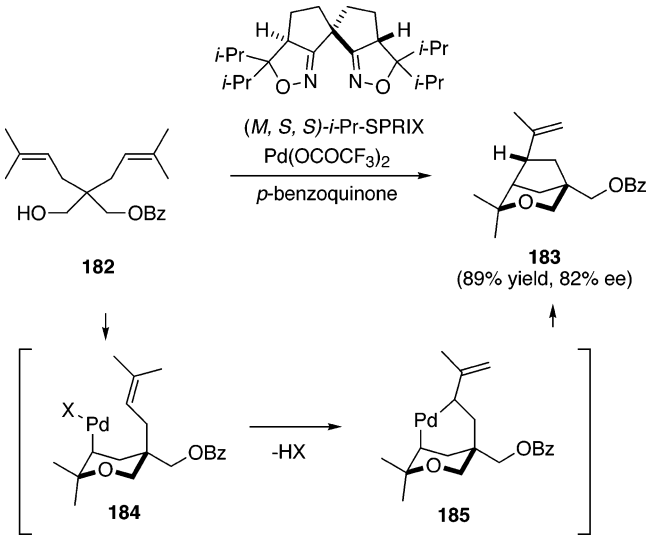
Uozumi et al. reported the palladium-catalyzed asymmetric heterocyclization. The reaction of the *o*-allylphenol **180** in the presence of $[Pd(CH_3CN)_4](BF_4)_2$ and (*S*,*S*)-*i*-Pr-boxax gave the dihydrobenzofuran **181** in 91% yield with 97% ee (Scheme 60).[132c]

Arai et al. reported that asymmetric tandem cyclization of the dialkenyl alcohol **182** in the presence of Pd(II)−spiro bis(isoxazoline) catalyst gave the bicyclic heterocycle **183** in 89% yield with 82% ee (Scheme 61).[132d] The reaction proceeds through Wacker-type oxypalladation, formation of the palladacycle **185** by carbopalladation of the resulting alkylpalladium intermediate **184**, elimination of HX, and subsequent reductive elimination of Pd(0) to give the product **183**.

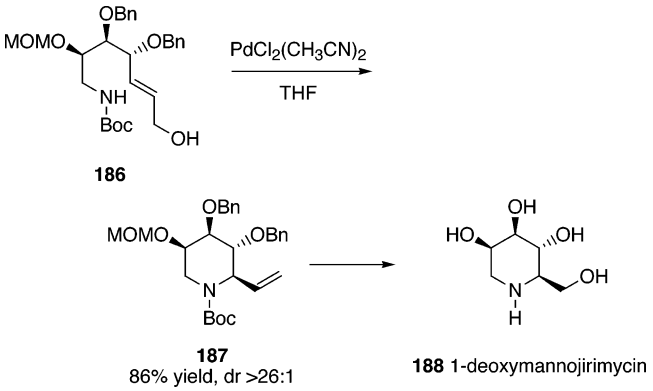
Yokoyama et al. reported that the palladium-catalyzed cyclization of the carbamate **186** gave the piperidine **187**, which was converted to 1-deoxymannojirimycin **188**, with excellent diastereoselectivity (Scheme 62).[133]

Kongkathip et al. reported the stereospecific synthesis of the amberketal homologue **190** by the palladium-catalyzed cyclization−acetalization.[134] The reaction of the alkenyldiol **189** in the presence of

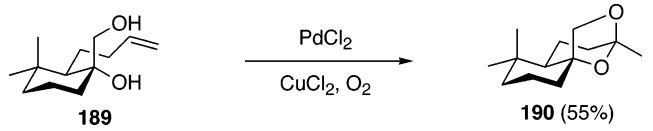
**Scheme 61**



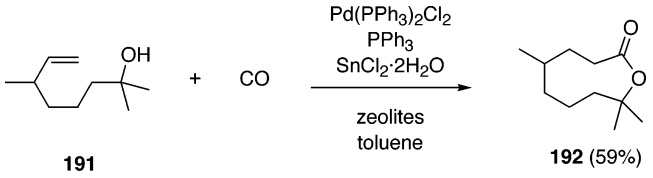

**Scheme 62**




**Scheme 63**




**Scheme 64**

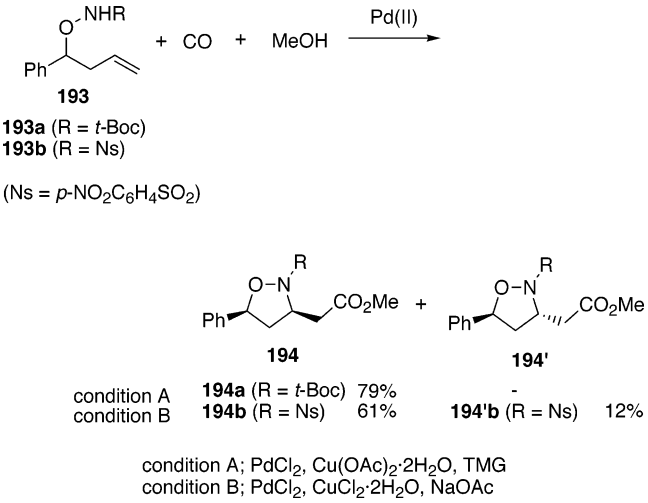



palladium chloride gave the polycyclic ketal **190** in 55% yield as a single isomer (Scheme 63).

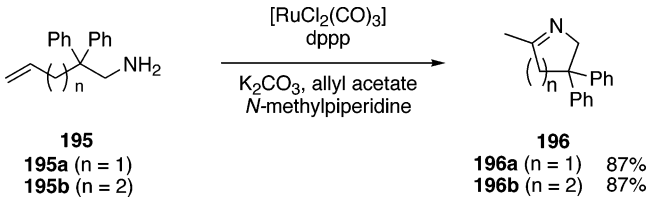
Lenoble et al. reported the cyclocarbonylation of the alkenyl alcohol **191** with carbon monoxide in the presence of palladium, phosphine, and tin catalysts gave the nine-membered lactone **192** selectively (Scheme 64).[135c]

Bates and Sa-Ei demonstrated that the reaction of *O*-homoallylhydroxyamines **193** with carbon monoxide and methanol in the presence of a palladium catalyst gave the isooxazolidine in good yields.[136a] The reaction of the carbamate **193a** gave only the cis-isomer **194a** diastereoselectively, while the reaction

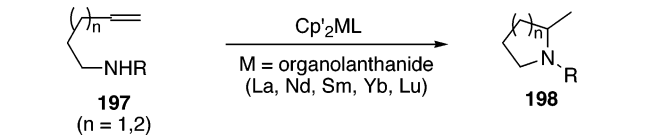
**Scheme 65**




**Scheme 66**




**Scheme 67**

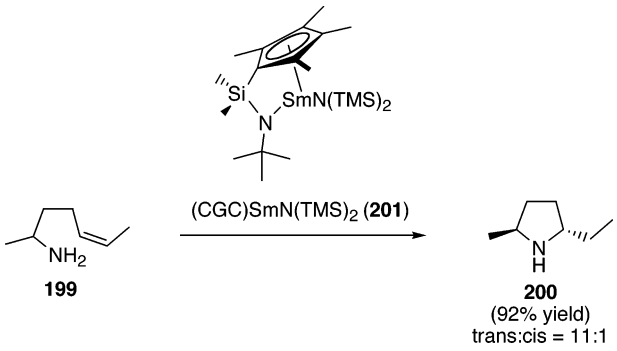



of the sulfonamide **193b** gave a 5:1 mixture of the cis−trans diastereomers (Scheme 65).

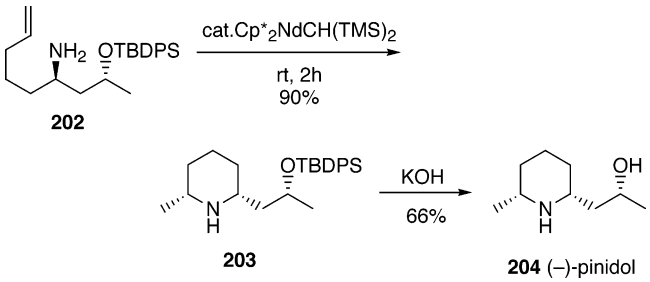
Mitsudo et al. reported that the ruthenium-catalyzed intramolecular oxidative amination of the aminoalkenes **195** gave the cyclic imines **196** in high yields (Scheme 66).[137] This reaction is categorized into type b in Scheme 56.

The organolanthanide-catalyzed intramolecular hydroamination of the aminoalkenes **197** is one of the most useful processes for constructing the nitrogen heterocycles **198**, whose skeletons are often found in naturally occurring alkaloids (Scheme 67).[138,139] Ryu et al. reported that, in the presence of (CGC)SmN(TMS)$_2$ (**201**), the reaction of the aminoalkene **199** having two methyl groups both at the olefin position and at the α-position of amino group gave the trans-2,5-disubstituted pyrrolidine **200** in a high yield with high diastereoselectivity (Scheme 68).[139h] Molander and Dowdy demonstrated that not only the synthesis of (−)-pinidiol **204** but also the synthesis of its (+)- and (±)-isomers was achieved using the diastereoselective intramolecular hydroamination of the aminoalkene **202** (Scheme 69).[139j]

**Scheme 68**



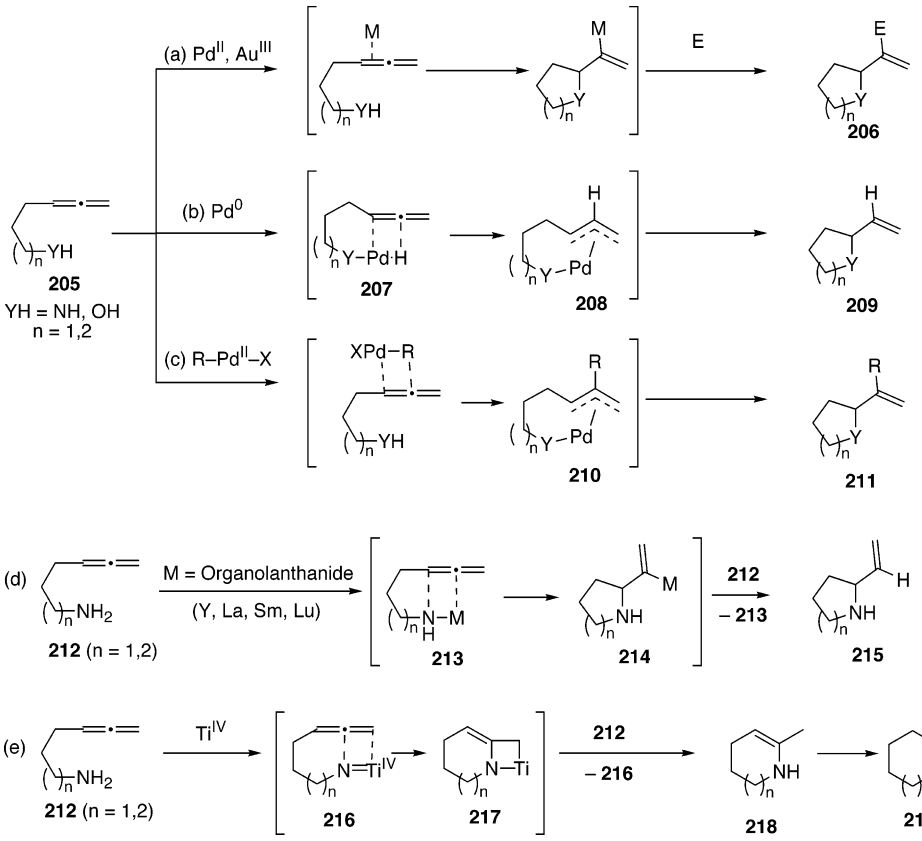

**Scheme 69**



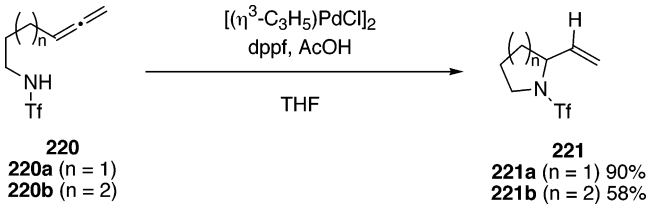

## 4.2. Allenes

Transition-metal-catalyzed cyclization reaction of allenes having N−H, O−H, C=O, and C=N groups is a useful method to construct heterocycles. In the presence of higher valent transition-metal catalysts, such as Pd$^{II}$ and Au$^{III}$, the reaction of the allenes **205** having a heteroatom−hydrogen (Y−H) bond proceeds through the nucleophilic attack of the Y−H bond to the electron-deficient allene coordinating to the transition-metal complex (Scheme 70, type a).[141] The resulting alkenylmetal intermediate reacts with a certain electrophile, such as a proton and α,β-unsaturated carbonyl, to give the heterocycles **206**. The palladium(0)-catalyzed intramolecular reaction of the allenes **205** is triggered by insertion of Pd(0) into a N−H bond to produce a hydridopalladium species, and subsequent intramolecular hydropalladation of **207** gives the π-allylpalladium intermediate **208** (type b).[142] Reductive elimination leads to the heterocycles **209** and regenerates Pd(0). The reaction of the allenes **205** with an organopalladium species (R−Pd−X), generated by oxidative addition of R−X to Pd(0), proceeds through carbopalladation of the allene moiety of **205** to give the π-allylpalladium intermediate **210** (type c).[141a,143] Subsequent reductive elimination produces the heterocycles **211**. Accordingly, the reaction sequence a−c starting from **205** are highly dependent on the oxidation state of the transition-metal catalysts. The organolanthanide-catalyzed hydroamination of the aminoallenes **212** starts from formation of the amido metal complex **213**, and the following aminometalation gives the alkenylmetal intermediate **214** (type d).[144] Subsequent protonolysis of **214** with the primary amine **212** affords the heterocycles **215**. The titanium(IV)-catalyzed hydroamination of the aminoallenes **212** proceeds through formation of the titanium imido complex **216** (type e).[145] Subsequent intramolecular

**Scheme 70. Heterocyclization of Allenes**




**Scheme 71**

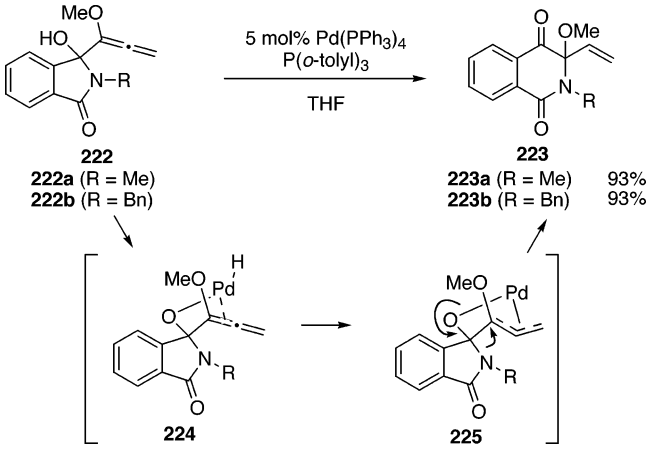



[2 + 2]-cycloaddition of the Ti═N bond with the external double bond of the allene group gives the titanacycle **217**. Protonolysis of **217** by the starting material **212** leads to the cyclic enamines **218**, which are rapidly isomerized to the stable cyclic imines **219**.

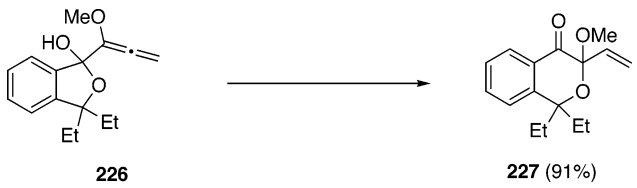
We found that the intramolecular hydroamination of the aminoallenes **220** took place in the presence of catalytic amounts of palladium, phosphine, and acetic acid to give the 2-alkenylpyrrolidine and -piperidine **221** in good to high yields (Scheme 71).[142] The reaction proceeds through formation of hydridopalladium species by the oxidative addition of an N−H bond to palladium(0) and subsequent hydropalladation of the allene moiety, as mentioned in Scheme 70, type b.

Nagao et al. reported that the ring expansion of the hydroxy methoxyallenylisoindolinones **222** occurred in the presence of a Pd(0) catalyst to give the isoquinolones **223** in high yields (Scheme 72).[146] Oxidative addition of an O−H bond of **222** to palladium(0) gives the hydridopalladium species **224**, and subsequent intramolecular hydropalladation of

**Scheme 72**

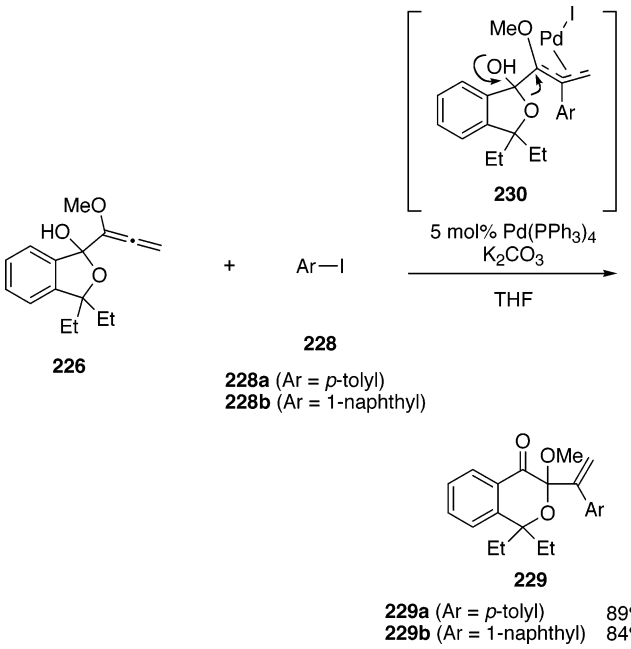



**Scheme 73**



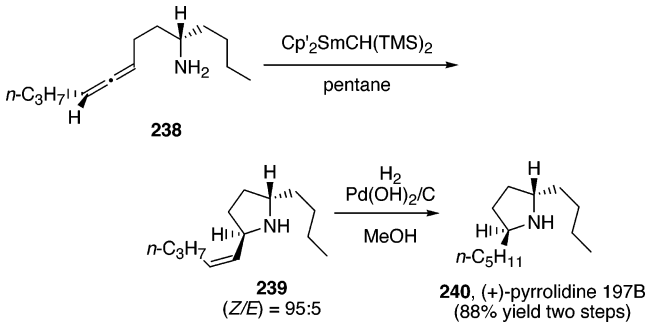

**224** leads to the π-allylpalladium intermediate **225**. The one-atom ring expansion occurs in the rearrangement of the methylamino group of **225** to the π-allylpalladium moiety to give **223**. The palladium-catalyzed ring-expansion reaction of the hydroxy methoxyallenylphthalan **226** produced the dialkylphthalide **227** in 91% yield (Scheme 73). The palladium-catalyzed reaction of **226** with aryl iodides

**Scheme 74**




**228** gave the ring expansion products **229** (Scheme 74).[147] Carbopalladation of the allenyl moiety of **226** with the aryl iodides **228** leads to the $\pi$-allylpalladium intermediate **230**, and subsequent ring expansion and elimination of H−Pd−I give the product **229**.

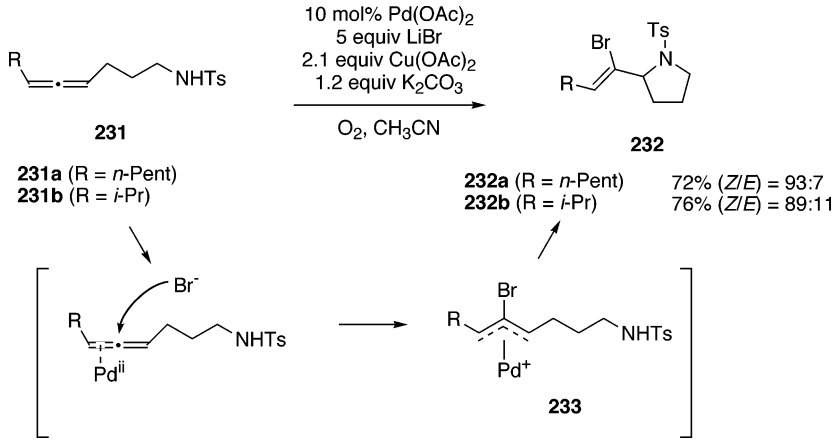
**Scheme 77**



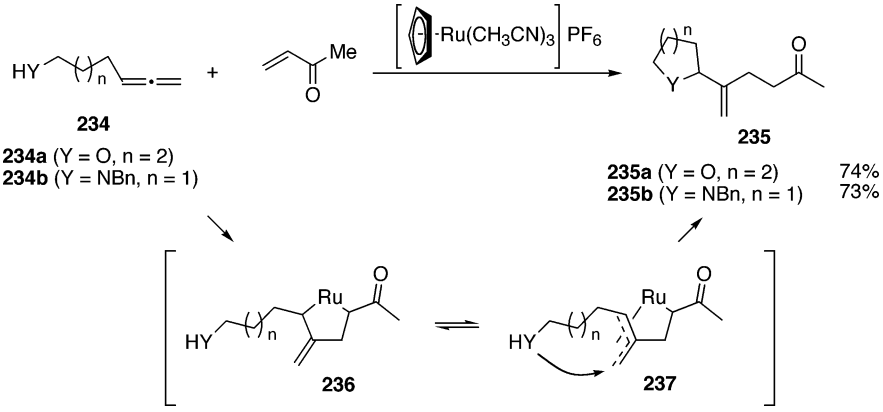

Bäckvall et al. reported that palladium-catalyzed 1,2-oxidation of the allenic tosylamides **231** with lithium bromide produced the 2-(1-bromoalkenyl)-*N*-tosylpyrrolidines **232** in good yields (Scheme 75).[148] This reaction proceeds through the coordination of palladium(II) to the allene moiety of **231**, followed by nucleophilic attack of bromine atom, formation of the $\pi$-allylpalladium intermediate **233**, and the intramolecular nucleophilic attack of NHTs to the $\pi$-allyl center carbon.

Trost et al. reported that the ruthenium-catalyzed reaction of the allenic alcohols and amines **234** with methyl vinyl ketone produced the 2-alkenyl heterocycles **235** in good to high yields (Scheme 76).[149] This reaction proceeds via formation of the ruthenacycle **236**, which could also exist as the $\pi$-allyl species **237**.

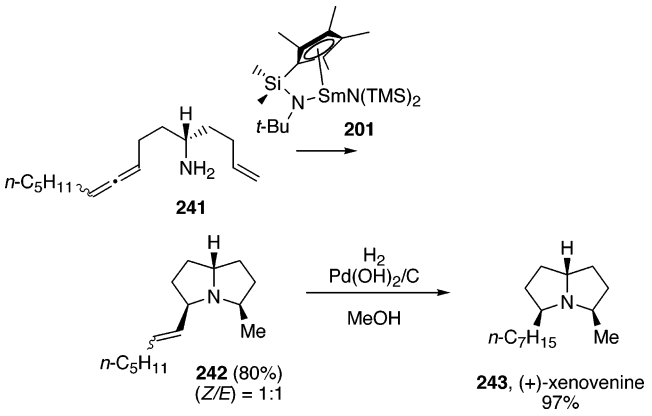
**Scheme 75**



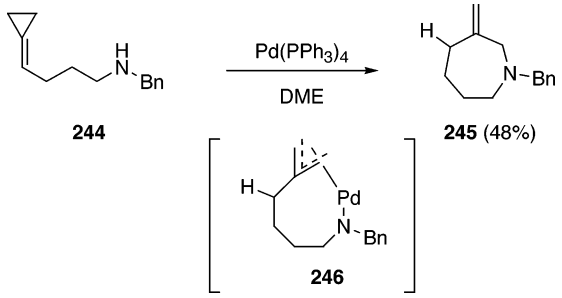

**Scheme 76**



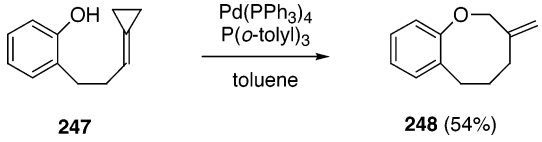
**Scheme 78**




**Scheme 79**




**Scheme 80**




Marks et al. reported the organolanthanide-catalyzed diastereoselective intramolecular hydroamination of aminoallenes.[140,150] In the presence of $Cp'_2SmCH(SiMe_3)_2$, the reaction of the aminoallene **238** gave the *trans*-2,5-disubstituted pyrrolidine **239** in high yield with excellent diastereo- and *Z*-selectivity (Scheme 77). The product **239** was converted to (+)-pyrrolidine-197B **240**. The tandem hydroamination/cyclization of the allenylalkenylamine **241** occurred in the presence of the samarium catalyst **201** to give the bicyclic pyrrolizidine **242** in a high yield (Scheme 78). Hydrogenation of **242** led to (+)-xenovenine **243**.

## 4.3. Methylenecyclopropanes

We reported that the intramolecular palladium-catalyzed hydroamination of the methylenecyclopropane **244** tethered to an amino group gave the azepane derivative **245** in 48% yield (Scheme 79).[151] The distal bond cleavage of the cyclopropane ring by the palladium catalyst leads to the $\pi$-allylpalladium intermediate **246**, which undergoes reductive elimination of Pd(0) to produce **245**. The intramolecular hydroalkoxylation of the methylenecyclopropanephenol **247** in the presence of a palladium catalyst produced the eight-membered cyclic ether **248** in good yield (Scheme 80).[152]

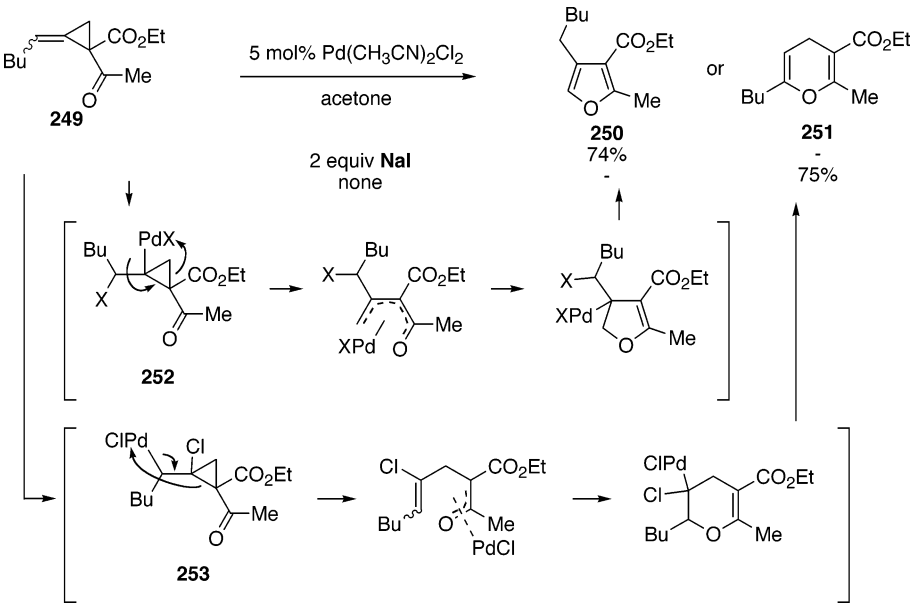
Ma and Zhang reported palladium-catalyzed isomerization of the alkylidenecyclopropyl ketone **249**.[153] In the presence of a catalytic amount of $Pd(CH_3CN)_2Cl_2$ and 2 equiv of NaI, the alkylidenecyclopropyl ketone isomerized to the corresponding 3-furyl ester **250** (Scheme 81). By contrast, in the absence of NaI, the 4*H*-pyran **251** was obtained selectively. The reaction of **249** with NaI proceeds through the cyclopropylpalladium intermediate **252**, while in the absence of NaI the formation of the cyclopropylcarbinylpalladium **253** takes place.

## 4.4. Alkynes

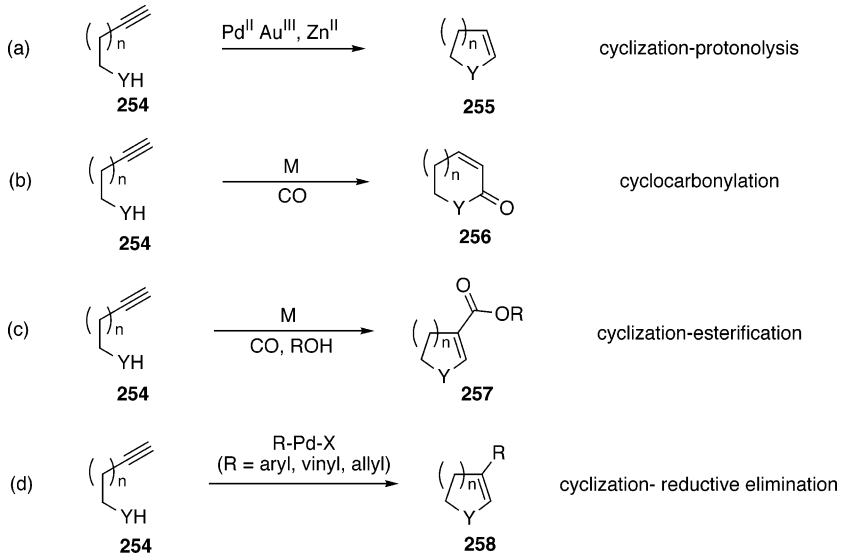
### *4.4.1. Intramolecular Reaction of Alkynes with N–H and O–H Functional Groups*

The Lewis acidic metal complexes, such as $Pd^{II}$, $Au^{III}$, $Zn^{II}$, and $W(CO)_6$, promote the intramolecular

**Scheme 81**

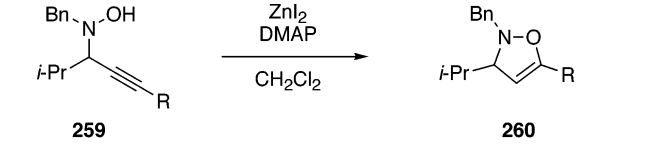


**Scheme 82. Heterocyclization of Alkynylamines, Amides, Alcohols, and Carboxylic Acids via (a) Cyclization-Protonolysis, (b) Cyclocarbonylation, (c) Cyclization−Esterification, and (d) Cyclization−Reductive Elimination**[a]




[a] YH; amine, amide, alcohol, carboxylic acid, $n = 1,2$.

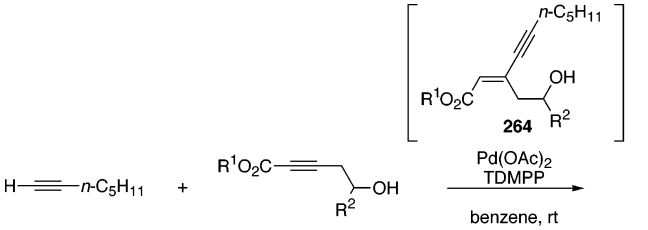
**Scheme 83**



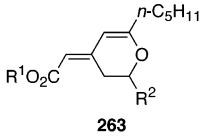

**259a** (R = $Ph(CH_2)_2$)
**259b** (R = $TBDMSOCH_2$)
**259c** (R = Ph)

**260a** (R = $Ph(CH_2)_2$) 95%
**260b** (R = $TBDMSOCH_2$) 94%
**260c** (R = Ph) 94%

**Scheme 84**




**262a** ($R^1$ = Me, $R^2$ = H)
**262b** ($R^1$ = Et, $R^2$ = Me)

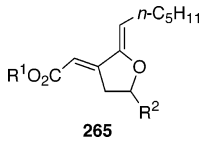



**263a** ($R^1$ = Me, $R^2$ = H) 61%
**263b** ($R^1$ = Et, $R^2$ = Me) 57%

reaction of an alkyne with an amine, amide, alcohol, and carboxylic acid. These reactions are classified into four types, as shown in Scheme 82. The cyclization of **254** and subsequent protonolysis gives the heterocycles **255** having a carbon−carbon double bond (type a).[131,138,154] The cyclocarbonylation of **254** occurs under carbon monoxide atmosphere to give the lactones and lactams **256** (type b).[131,155] The reaction of the alkynylamines or alkynyl alcohols **254** with carbon monoxide and an alcohol gives the heterocycles **257** having an α,β-unsaturated ester moiety (type c).[131,156] In the presence of organopalladium species R−Pd−X, the reaction of **254** proceeds through the cyclization promoted by the Lewis acidic R−Pd−X, and subsequent reductive elimination of Pd(0) from the resulting cycloalkenylpalladium(II)X complex gives **258** (type d).[157]

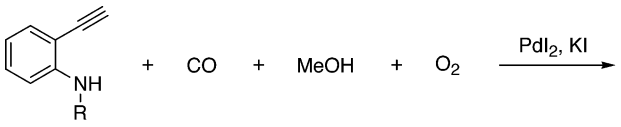
Aschwanden et al. reported that the reaction of the propargylic *N*-hydroxyamines **259** in the presence of zinc iodide and DMAP gave the 2,3-dihydroisoxazoles **260** in high yields (Scheme 83).[154e]

Trost and Frontier reported that the tandem palladium-catalyzed reaction of 1-heptyne **261** with the alkynols **262** produced the dihydropyrans **263** in good yields (Scheme 84).[154h] The reaction proceeds through the palladium-catalyzed coupling of 1-heptyne and the alkynols **262**, followed by subsequent palladium-catalyzed 6-endo-dig cyclization of the resulting enynols **264**. This reaction did not produce the regioisomeric adduct, tetrahydrofuran **265**, derived from 5-exo-dig cyclization.




Gabriele et al. reported that the palladium-catalyzed reaction of the *o*-ethynylanilines **266** with carbon monoxide, methanol, and oxygen gave the 1,3-dihydroinol-2-one derivatives **267** in good yields (Scheme 85).[155b] The reaction proceeds through the cyclocarbonylation−esterification (Scheme 82, routes

**Scheme 85**



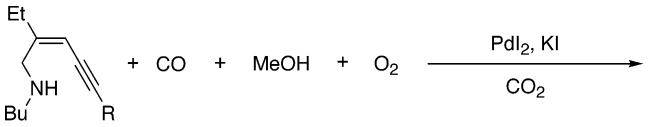

**266**

**266a** (R = H)
**266b** (R = Bn)
**266c** (R = Bu)


**267**

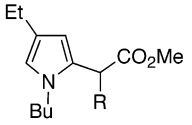
| | |
|---|---|
| **267a** (R = H) | 53% |
| **267b** (R = Bn) | 50% |
| **267c** (R = Bu) | 45% |

**Scheme 86**




**268**

**268a** (R = Bu)
**268b** (R = TMS)



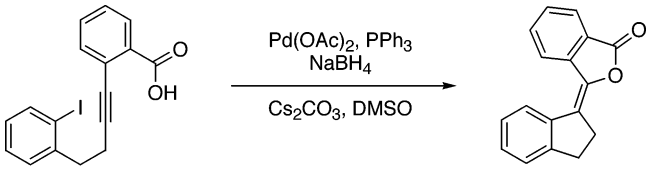

**269**

| | |
|---|---|
| **269a** (R = Bu) | 70% |
| **269b** (R = H) | 72% |

b and c). On the other hand, the reaction of the (*Z*)-(2-en-4-ynyl)amines **268** with carbon monoxide, methanol, and oxygen under $CO_2$ atmosphere gave the pyrroles **269**, derived from cyclization−esterification, in good yields (Scheme 86).[156e]

Arcadi et al. reported that the palladium-catalyzed cyclization of bis(*o*-trifluoroacetamidophenyl)acetylene **270** with aryl and vinyl halides **271** gave the indole[1,2-*c*]quinazolines **272** in high yields (Scheme 87).[157h] The reaction proceeds through aminopalladation−reductive elimination. The cyclization of the resulting 3-arylinodole derivatives **273** gives the tetracyclic heterocycle **272**. Bouyssi and Balme reported that the palladium-catalyzed bicyclization of the *o*-alkynylbenzoic acid **274** gave the indanylide phthalide **275**, which was a precursor of the core of fredericamycin A, in 64% yield (Scheme 88).[157f]

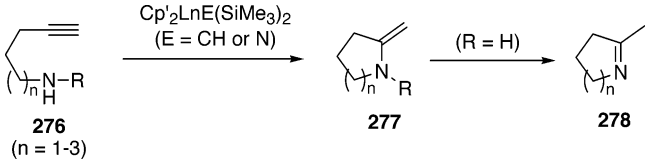
**Scheme 88**




**274** **275** (64%)

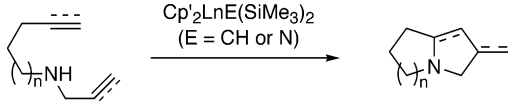
The organolanthanide-catalyzed hydroamination of the aminoalkynes **276** gives the nitrogen-containing heterocycles **277** or **278** (in the case of R = H).[158] The reaction of primary amines produces the cyclic imines **278**, while the reaction of secondary amines gives the cyclic enamines **277** (Scheme 89). The organolanthanide-catalyzed bicyclization of the aminodiynes, aminoenynes, and aminodienes **279** produces the pyrrolizidine and indolizidine derivatives **280** in a single reaction (Scheme 90).[159]

**Scheme 89**



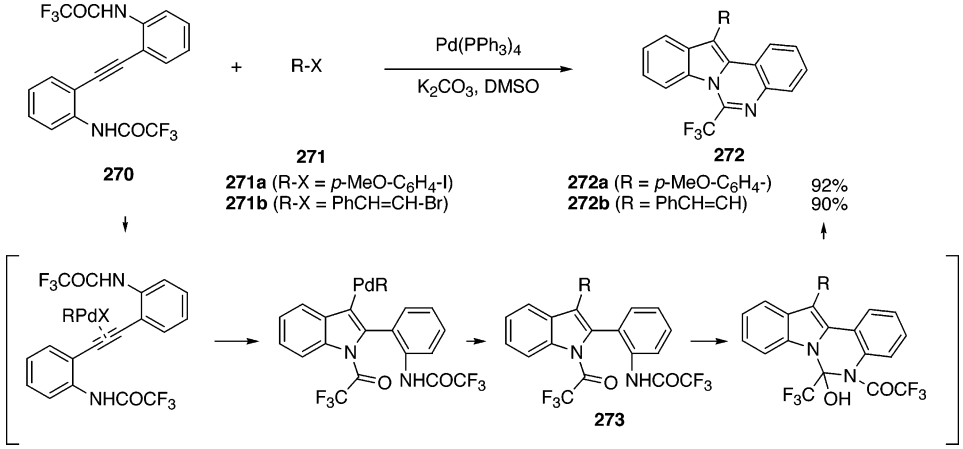

**276** (n = 1-3) **277** **278**

**Scheme 90**




**279** (n = 1,2) **280**

**Scheme 87**



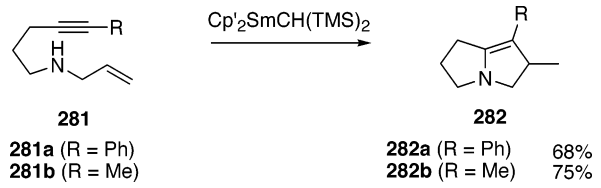

**270** **271** **272**

**271a** (R-X = *p*-MeO-$C_6H_4$-I)
**271b** (R-X = PhCH=CH-Br)

**272a** (R = *p*-MeO-$C_6H_4$-) 92%
**272b** (R = PhCH=CH) 90%

**273**

**Scheme 91**



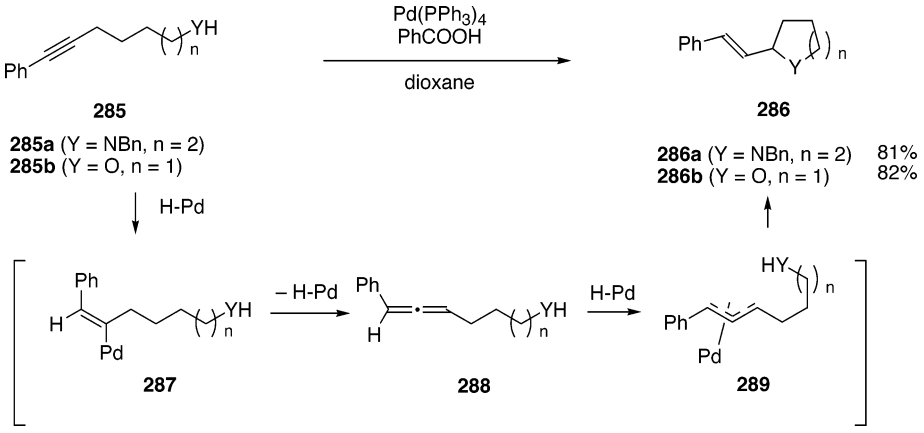

**Scheme 92**


Li and Marks reported that the reaction of the aminoenynes **281** in the presence of an organolanthanide catalyst gave the pyrrolizines **282** in good yields (Scheme 91).[159] The reaction of the aminodiyne **283** produced the pyrrolizine **284** bearing an *exo*-olefin in 95% yield (Scheme 92).

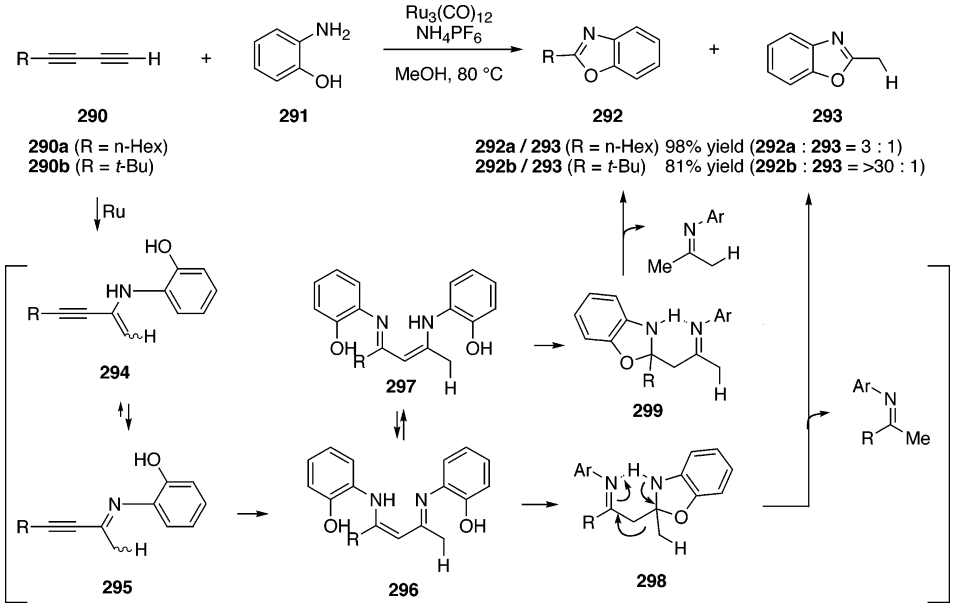
We reported that the intramolecular hydroamination and hydroalkoxylation of the alkynes **285** in the presence of palladium/benzoic acid catalysts produced the five- and six-membered heterocycles **286** in good to high yields (Scheme 93).[160,161] The reaction proceeds through palladium/protonic acid-promoted hydropalladation of an alkyne; the dehydropalladation of the resulting alkenylpalladium **287**; formation of the corresponding allene **288** and a hydridopalladaium, the second hydropalladation leading to a $\pi$-allylpalladium intermediate **289**; the intramolecular nucleophilic attack of YH to the $\pi$-allylpalladium complex **289**; and subsequent reductive elimination of Pd(0).

We demonstrated the synthesis of 2-substituted benzoxazoles by carbon−carbon cleavage of diynes **290** through the hydroamination with transition-metal catalysts (Scheme 94).[162] In the presence of 1 mol % of $Ru_3(CO)_{12}$ and 3 mol % of $NH_4PF_6$ the reaction of diynes **290** and 2-aminophenol **291** proceeded at 80 °C, and a mixture of 2-benzoxazoles **292** and **293** was obtained in good to excellent yields. The catalytic hydroamination of one of the alkyne groups of the diynes **290** gives the alkynylenamines **294**. Tautomerization of **294** gives the corresponding α,β-

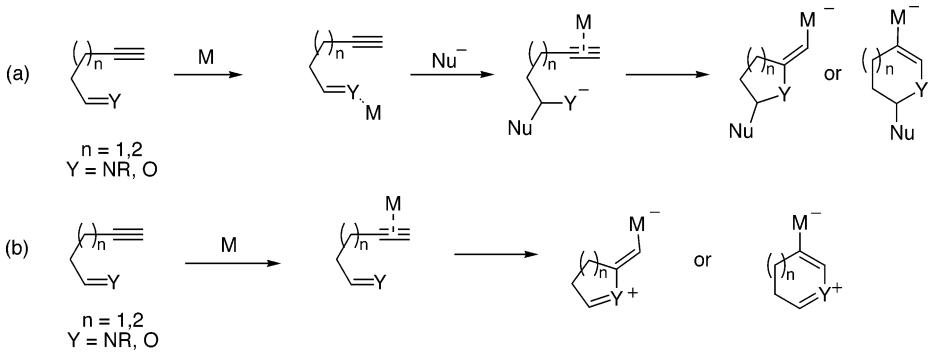
**Scheme 93**



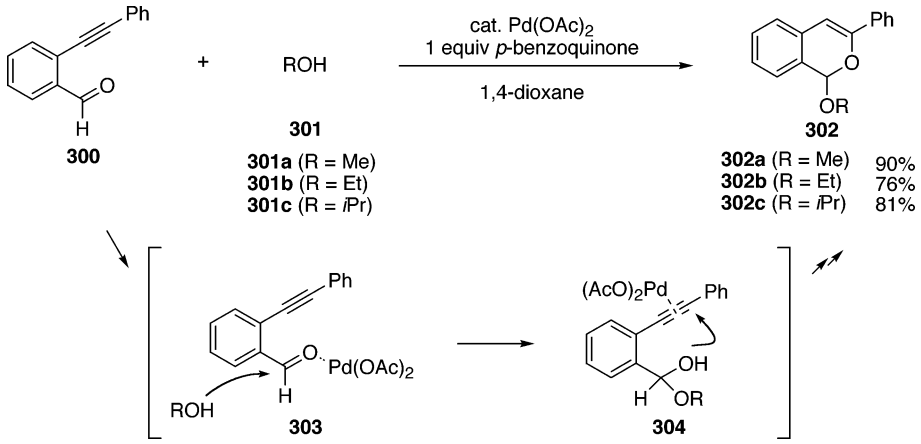

**Scheme 94**



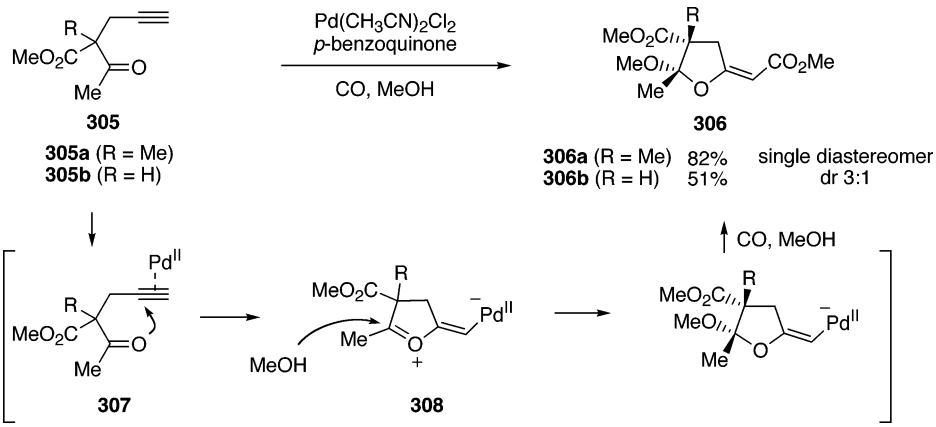
**Scheme 95. Heterocyclization of Alkynyl Aldehydes and Imines**




**Scheme 96**




**Scheme 97**



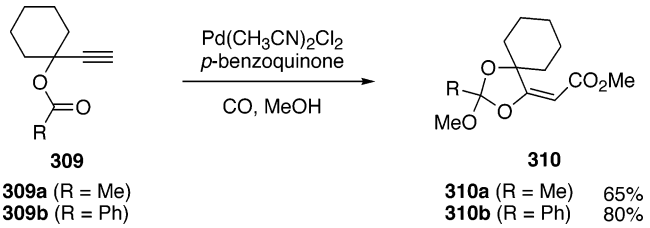

unsaturated imines **295**. The conjugate addition of 2-aminophenol **291** to **295** provides $\beta$-aminoimines **296** and their tautomers **297**. The intramolecular cyclization of the iminophenol groups of **296** and **297** gives the ketals **298** and **299**, respectively. The C−C bond cleavage through the retro-Mannich-type reaction produces the benzoxazoles **292** and **293**.

### *4.4.2. Intramolecular Reaction of Alkynes with C═O and C═N Functional Groups*

Heterocyclization of alkynyl aldehydes and imines proceeds through two different mechanistic pathways (Scheme 95, routes a and b). A Lewis acidic transition metal is coordinated by a heteroatom of C═Y, the nucleophilic addition of $Nu^-$ to the electron-deficient carbon of C═Y·M takes place first, and then the resulting $Y^-$ attacks an electron-deficient carbon of the alkyne coordinated to M (type a). It should be noted that the M acts simultaneously as a Lewis acid and as a typical transition-metal catalyst, that is to say, as a dual-role catalyst. Alternatively, the triple bond coordinates first to a transition-metal catalyst M, and then the nucleophilic attack of a heteroatom of C═Y takes place (type b).

We reported that the palladium-catalyzed reaction of *o*-alkynylbenzaldehyde **300** with the alcohols **301** gave the alkenyl ethers **302** in good to high yields (Scheme 96).[163] This reaction proceeds through formation of the hemiacetal **304** and subsequent nucleophilic attack of the OH group on the electron-

**Scheme 98**



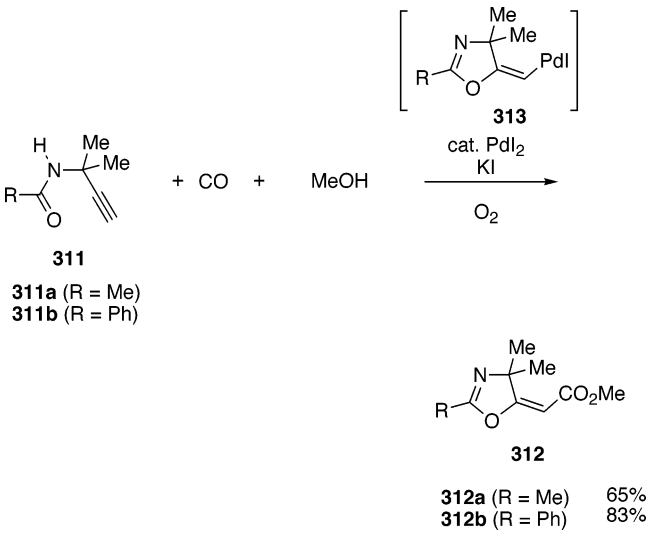

**309**

**309a** (R = Me)
**309b** (R = Ph)

**310**

**310a** (R = Me) 65%
**310b** (R = Ph) 80%

**Scheme 99**




**311a** (R = Me)
**311b** (R = Ph)

**312a** (R = Me) 65%
**312b** (R = Ph) 83%

deficient alkyne coordinated by palladium(II). In this reaction, $Pd(OAc)_2$ acted simultaneously as a Lewis acid and as a transition-metal catalyst; the carbonyl group is activated by a Lewis acidic Pd(II) (**303**) to make facile addition of ROH, and the alkynyl moiety is activated by Pd(II), having a typical transition-metal characteristic, as shown in **304**, to produce the cyclized alkenyl palladium(II) intermediate that undergoes protonation.

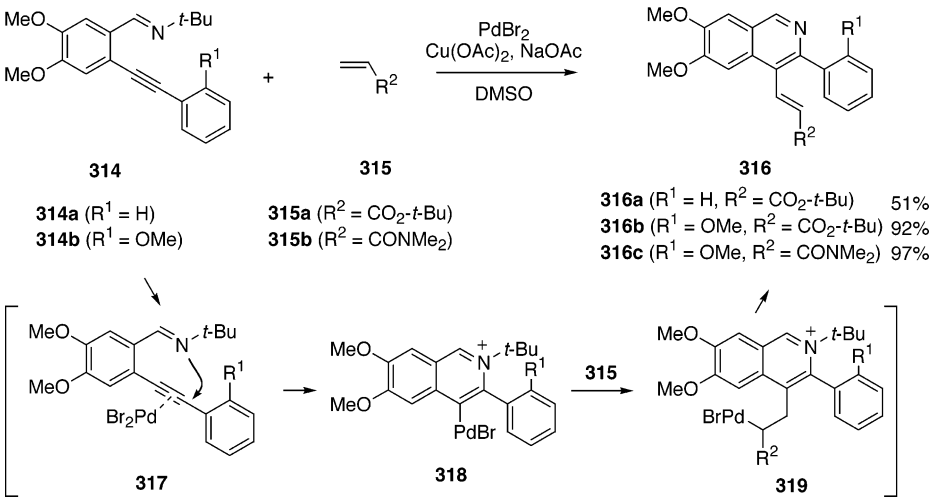
Kato et al. reported that palladium(II)-mediated cyclization−carbonylation of the 4-yn-1-ones **305** gave the cyclic acetals **306** (Scheme 97).[164] This reaction proceeds through nucleophilic attack of the carbonyl oxygen on the alkynyl moiety coordinated to palladium(II) (as shown in **307**), forming the five-membered oxacyclic intermediate **308**. Subsequent attack of MeOH on **308** produces **306**. They also demonstrated that the reaction of the propargylic acetates **309** under CO atmosphere in MeOH in the presence of Pd(II) catalyst and *p*-benzoquinone afforded the cyclic ortho esters **310** (Scheme 98).[165]

Bacchi et al. reported the efficient and general synthesis of the 5-(alkoxylcarbonyl)methylene-3-oxazolines **312** by the palladium-catalyzed oxidative carbonylation of the pro-2-ynylamides **311** (Scheme 99).[166] This reaction is initiated by nucleophilic attack of an oxygen atom of an amide group on an alkyne coordinated by palladium(II), forming the vinylpalladium intermediate **313**. The insertion of CO into the C−Pd bond of **313**, followed by methanolysis of the resulting acylpalladium complex, affords the esters **312** and Pd(0) catalyst. The Pd(0) is oxidized to Pd(II) by molecular oxygen, and thus the catalytic cycle operates well.

Huang and Larock reported that palladium-catalyzed cyclization/olefination reaction of the *o*-alkynylbenzaldimines **314** with the olefins **315** produced the isoquinolines **316** in good to high yields (Scheme 100).[167] The introduction of an *o*-methoxy group on the benzene ring of the alkynyl substituent increased the yields of the cyclization products. The reaction proceeds through the nucleophilic attack of the nitrogen atom on electron-deficient alkyne **317**, the formation of the alkenylpalladium intermediate **318**, the insertion of the alkenes **315** into the C−Pd bond **319**, and $\beta$-hydride elimination. They reported many examples of this type of reactions, but those are summarized in their own review in this issue of *Chemical Reviews*.[168]

Kel'in et al. reported that the copper-assisted cycloisomerization of the alkynyl imines **320** gave the pyrroles **321** in high yields (Scheme 101).[169] Mechanistic studies revealed that this reaction proceeded via the propargyl-allenyl isomerization of **320** to the

**Scheme 100**




**314**

**314a** ($R^1$ = H)
**314b** ($R^1$ = OMe)

**315**

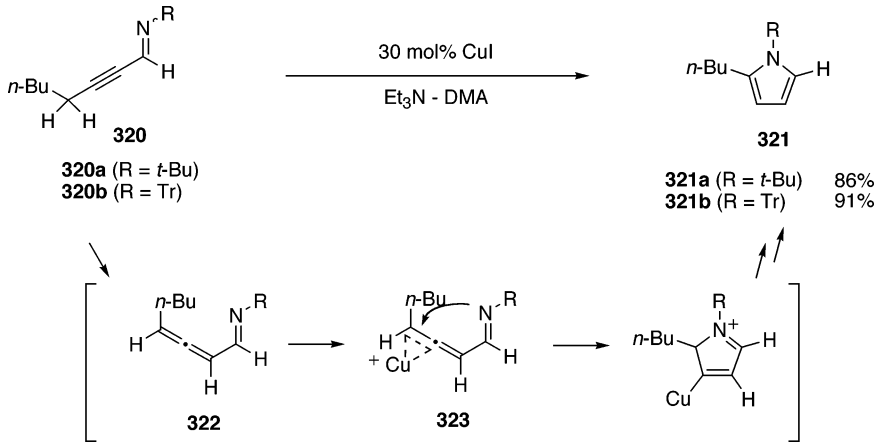
**315a** ($R^2$ = $CO_2$-*t*-Bu)
**315b** ($R^2$ = $CONMe_2$)

**316**

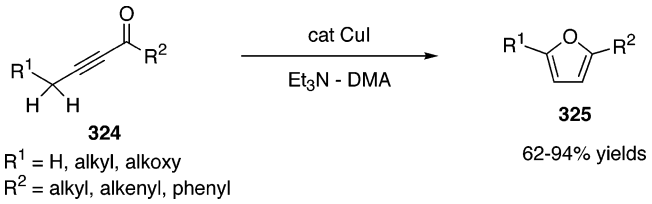
**316a** ($R^1$ = H, $R^2$ = $CO_2$-*t*-Bu) 51%
**316b** ($R^1$ = OMe, $R^2$ = $CO_2$-*t*-Bu) 92%
**316c** ($R^1$ = OMe, $R^2$ = $CONMe_2$) 97%

**317** **318** **319**

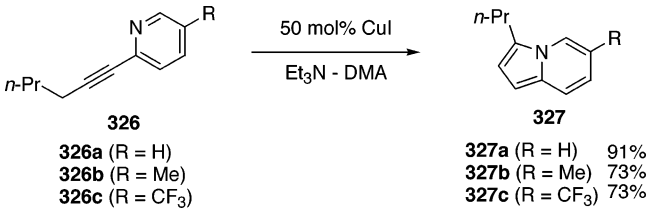
**Scheme 101**



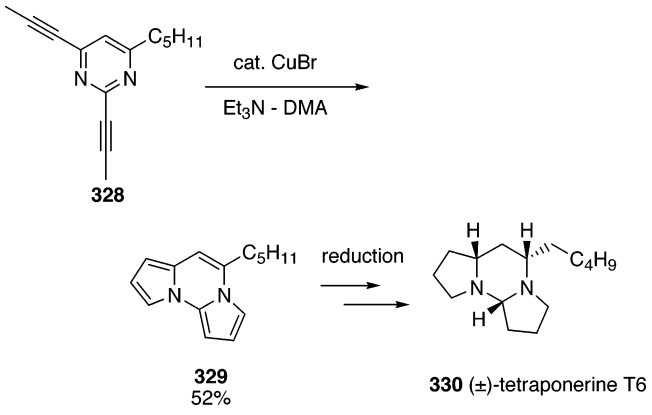

**Scheme 102**




**Scheme 103**

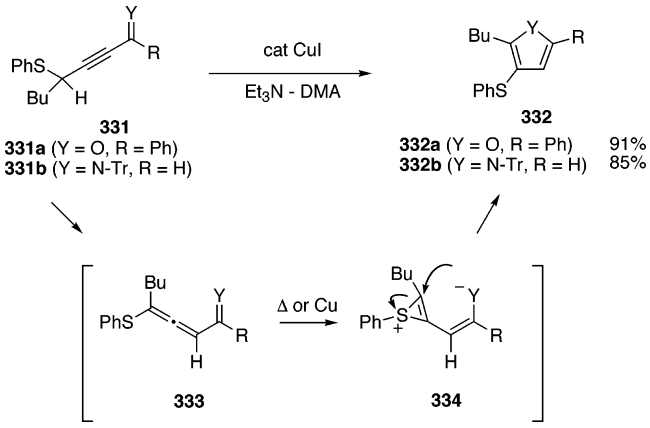



**Scheme 104**




allenyl imines **322** and through the nucleophilic attack of the nitrogen atom of imine on the electron-deficient carbon **323**. The cycloisomerization of alkynyl ketones **324** gave 2,5-disubstituted furans **325** (Scheme 102).[170] The copper-assisted reaction of the 2-alkynylpyridines **326** provided the indolizine derivatives **327** in good to high yields (Scheme 103).[169] The double cycloisomerization of the bis-alkynylpyrimidine **328** afforded the 5−6−5 tricyclic heteroaromatic product **329**, which was converted to (±)-tetraponerine T6 **330**. (Scheme 104).[171] The 3-thiofurans and pyrroles **332** were synthesized similarly

**Scheme 105**

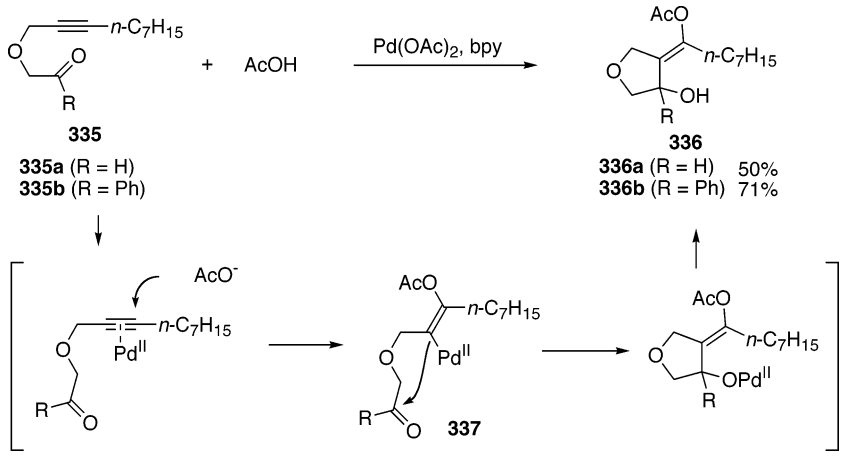



by the copper-catalyzed cycloisomerization of the keto- and iminopropargyl sulfides **331** (Scheme 105).[172] The reaction proceeds through the copper-catalyzed isomerization of alkyne to the corresponding allenes **333**, followed by the thermal or Cu-mediated 1,2-migration of the thio group **334**.

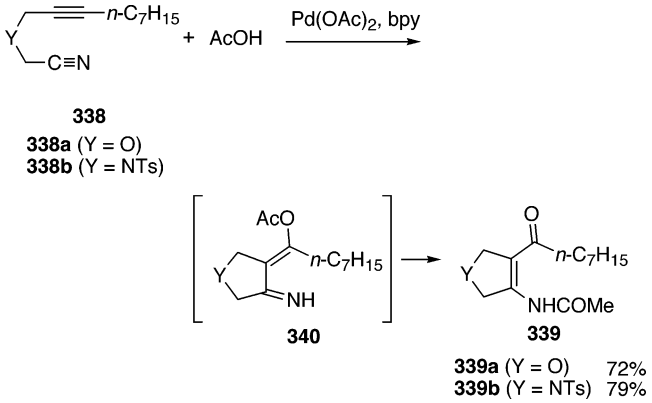
Zhao and Lu reported that the reaction of the alkynes **335**, containing a carbonyl group, with acetic acid in the presence of $Pd(OAc)_2$ and 2,2′-bipyridine (bpy) gave the cyclic ethers **336** in good yields (Scheme 106).[173] The reaction is initiated by acetoxypalladation of the alkyne moiety of **335**, forming the vinylpalladium intermediate **337**. The following cyclization and protonolysis give **336**. In the reaction of the alkynylnitriles **338**, migration of the acetyl group from the oxygen atom to nitrogen atom occurs in **340** to give the heterocycles **339** (Scheme 107).

Miki et al. reported that transition-metal-catalyzed cyclopropanation of the alkenes **342** with 1-benzoyl-*cis*-1-en-3-yne **341a** gave the corresponding (2-furyl)-cyclopropanes **343** (Scheme 108).[174a] Various kinds of transition-metal complexes, such as $Cr(CO)_5(THF)$, $Mo(CO)_5(THF)$, $W(CO)_5(THF)$, $[RuCl_2(CO)_3]_2$, $[RhCl(cod)]_2$, $PdCl_2$, and $PtCl_2$, showed the catalytic activity for this transformation. This reaction proceeds through formation of (2-furyl)carbene complex **344a**, which reacts with **342** to give the cyclopropanation products

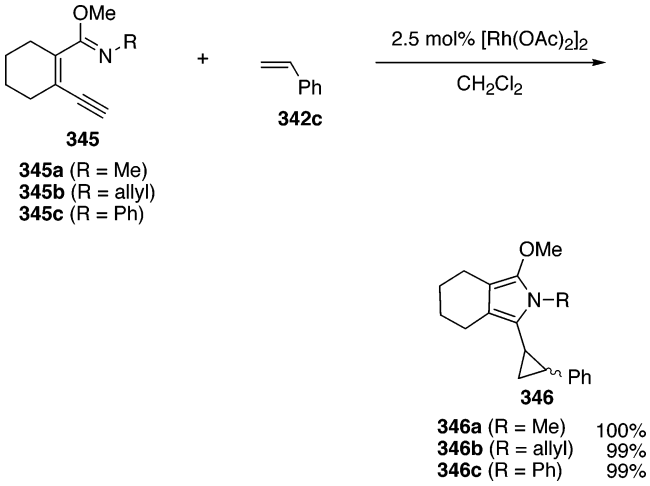
**Scheme 106**




**Scheme 107**



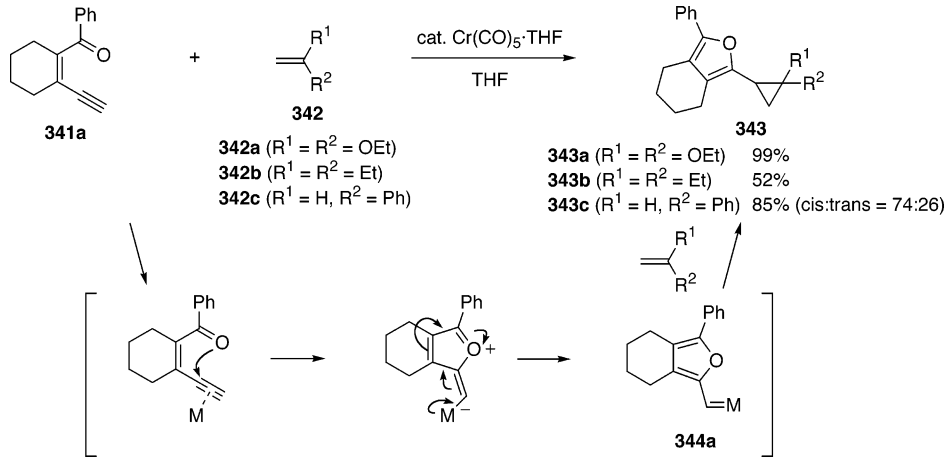

**Scheme 109**



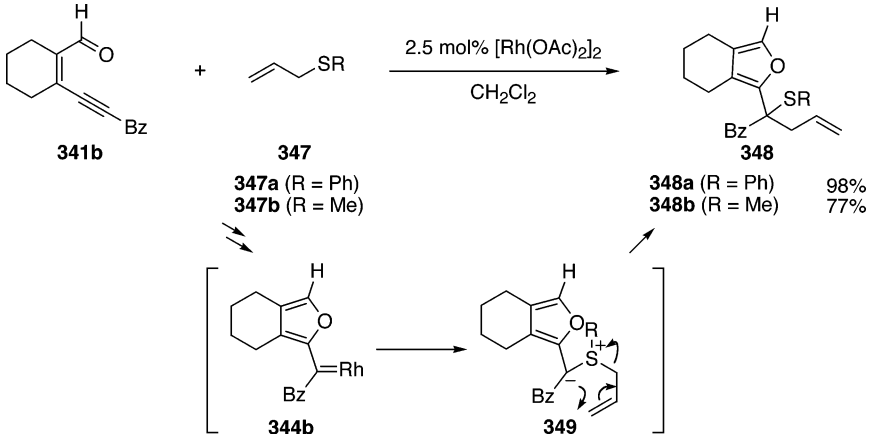

**343**. The reaction of conjugated ene−yne−imino ethers **345** with styrene **342c** produced (2-pyrrolyl)-cyclopropanes **346** in good yields (Scheme 109).[174b] The researchers demonstrated that the reaction of **341b** with allylic sulfides **347** proceeded in the presence of catalytic amounts of $[Rh(OAc)_2]_2$, and the corresponding furan-containing sulfides **348** were obtained in excellent yields (Scheme 110).[174c] The reaction proceeds through carbene transfer of **344b** with allylic sulfides **347** and subsequent [2,3]-sigmatropic rearrangement of the resulting sulfur ylide **349** to give **348**.

Iwasawa et al. reported that the tungsten-catalyzed reaction of *o*-ethynylbenzaldehyde **350** with the electron-rich olefins **351** gave the corresponding polycyclic ethers **352** in good yields (Scheme 111).[175] This reaction proceeds through generation of the carbonyl ylide **353** by the $\pi$-endo cyclization of the alkyne coordinating to tungsten complex. The [3 + 2]-cycloaddition of **353** with **351** proceeds via **354** to give

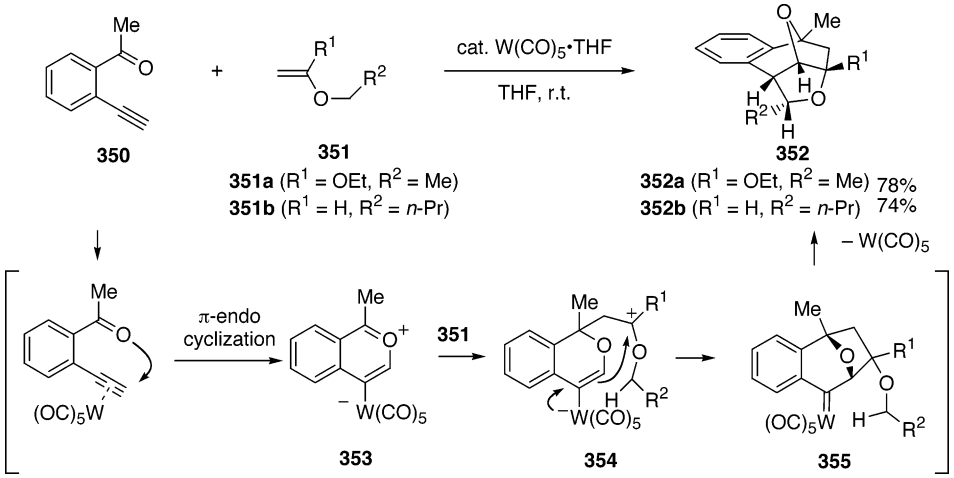
**Scheme 108**



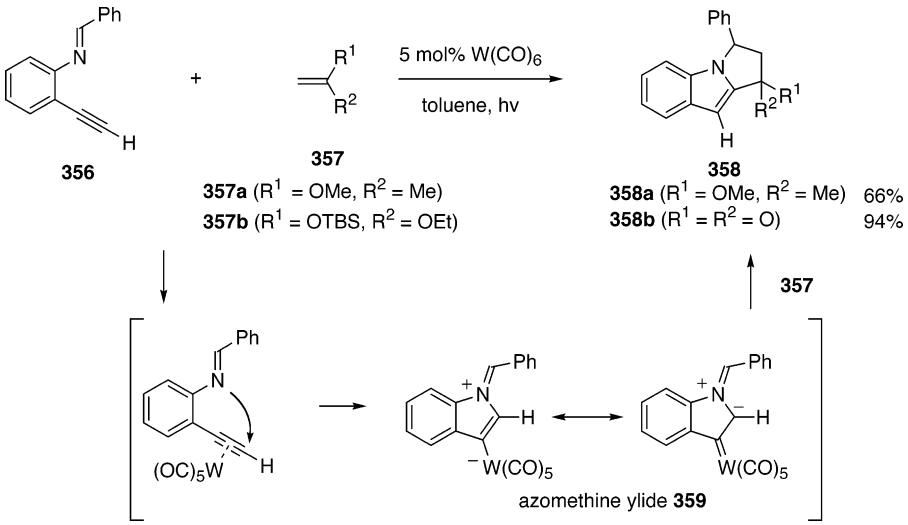
**Scheme 110**




**Scheme 111**

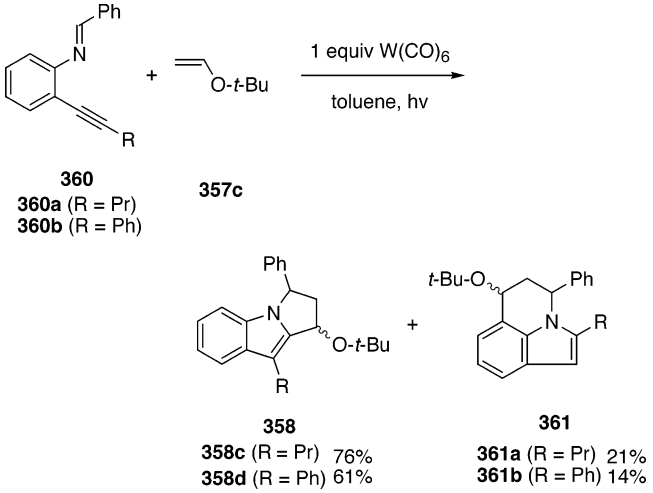



**Scheme 112**




the tungsten carbene complex **355**, in which the C−H insertion of the carbene−tungsten species takes place to give the polycyclic ethers **352**. The authors reported a facile method for the synthesis of the polycyclic indole derivatives **358** by the tungsten-catalyzed reaction of *N*-(*o*-ethynylphenyl)imine **356** with the electron-rich alkenes **357**.[176] This reaction proceeds through formation of the tungsten-containing azomethine ylide **359**, which undergoes the [3 + 2]-cycloaddition with **357** (Scheme 112). On the contrary, the reaction of the substrates **360**, bearing an internal triple bond, with **357c** proceeded in the presence of a stoichiometric amount of the tungsten complex to give the [1,2]-alkyl-migrated products **358** along with a small amount of the formal [4 + 2]-cycloadducts **361** (Scheme 113).

**Scheme 113**




**360** (**360a** (R = Pr), **360b** (R = Ph)) + **357c** → **358** + **361**

**358c** (R = Pr) 76%, **358d** (R = Ph) 61%

**361a** (R = Pr) 21%, **361b** (R = Ph) 14%

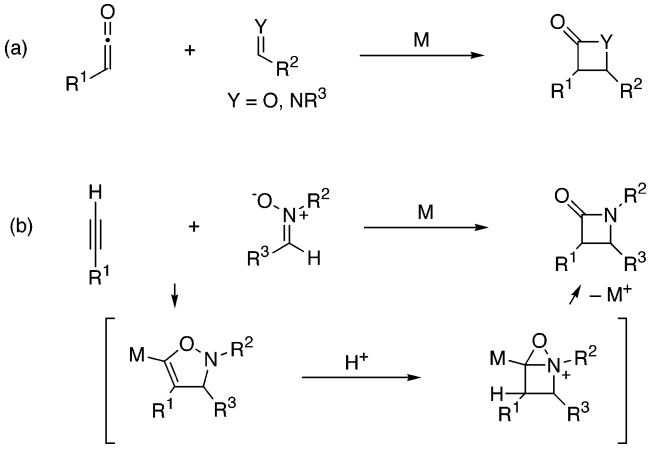
## *5. Intra- and Intermolecular Cycloaddition of Carbon–Carbon and Carbon–Heteroatom Unsaturated Compounds: Hetero-Cycloaddition*

The hetero-cycloaddition of C−C unsaturated bonds with C═O and C═N bonds constructs heterocycles through concerted formation of both a carbon−carbon and a carbon−heteroatom bond.[177] The hetero-Pauson−Khand reaction using CO, alkyne, carbonyl group is a typical hetero-[2 + 2 + 1]-cycloaddition, giving five-membered heterocycles. Hetero-Diels−Alder reaction, that is, hetero-[4 + 2]-addition, produces six-membered heterocycles.

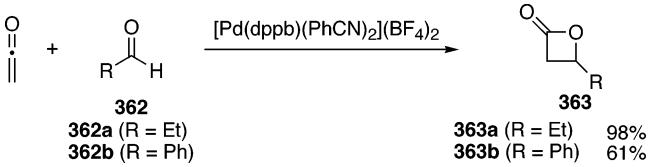
### 5.1. Hetero-[2 + 2]-Cycloaddition

Hetero-[2 + 2]-cycloaddition has been extensively investigated since this process provides a variety of *β*-lactones and *β*-lactams.[178] There are two types of hetero-[2 + 2]-cycloaddition reaction, as illustrated in Scheme 114; one is the reaction of ketenes with aldehydes or imines to give lactones and lactams (Scheme 114, route a) and the other is the reaction of alkynes with nitrones to give lactams (Scheme 114, route b).[179]

**Scheme 114. Hetero-[2 + 2]-Cycloaddition of (a) Ketenes with Aldehydes or Imines and (b) Alkynes with Nitrones**



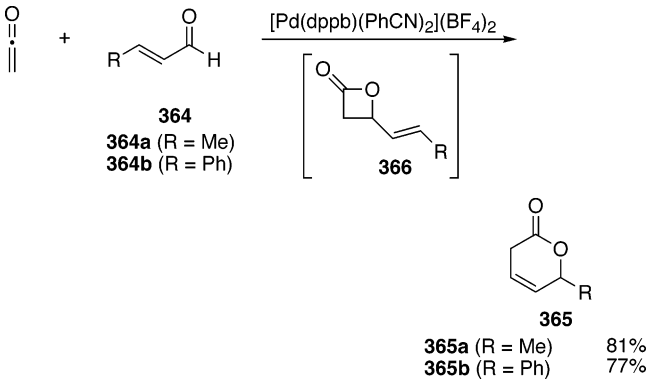

**Scheme 115**




**362** (**362a** (R = Et), **362b** (R = Ph)) → **363**

**363a** (R = Et) 98%, **363b** (R = Ph) 61%

**Scheme 116**




**364** (**364a** (R = Me), **364b** (R = Ph)) → **366** → **365**

**365a** (R = Me) 81%, **365b** (R = Ph) 77%

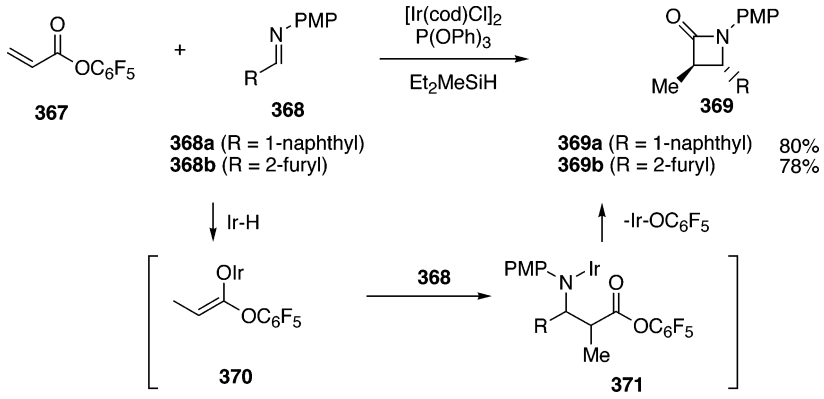
Hattori et al. reported the cationic palladium(II)-catalyzed hetero-[2 + 2]-cycloaddition of ketene with the aldehydes **362**.[180] The reaction of aliphatic and aryl aldehydes **362** gave the *β*-lactones **363** (Scheme 115), while the reaction of the α,*β*-unsaturated aldehydes **364** produced the 3,6-dihydro-*2H*-pyran-2-ones **365** in good yields (Scheme 116); the reaction proceeded via the hetero-[2 + 2]-cycloaddition to give **366** first, which underwent a rearrangement to lead to **365**.

Townes et al. synthesized the *trans*-*β*-lactams **369** through the reaction of the enoate **367**, the imines **368**, and diethylmethylsilane in the presence of an iridium catalyst (Scheme 117).[181] This reaction proceeds via the addition of iridium hydride to a double bond of the acrylate **367**, forming the iridium enolate **370**. The following aldol type reaction of **370** with the imines **368** gives **371**, and subsequent elimination of Ir−$OC_6F_5$ leads to the products **369**.

Akiyama et al. reported the Cu(I)-catalyzed enantioselective [2 + 2]-cycloaddition of 1-methoxyallenylsilane **372** with α-imino ester **373** (Scheme 118).[182] In the presence of catalytic amounts of [Cu(MeCN)$_4$]$BF_4$ and (*R*)-Tol-BINAP the reaction of 2 equiv of 1-methoxyallenylsilanes **372** with α-imino ester **373** afforded azetidine derivatives **374** in good to high yields with high enantioselectivities.

Lo and Fu reported Cu(I)/bis(azaferrocene)(**378**)-catalyzed enantioselective synthesis of the *β*-lactams **377** via the hetero-[2 + 2]-cycloaddition of the alkynes **375** with the nitrone **376** (Scheme 119).[183] The reaction of the arylacetylenes **375a** and **375b** gave the products **377a** and **377b** in good yields with high cis- and enantioselectivities, while the reaction of the alkyl-substituted alkyne **375c** produced **377c** with lower stereoselection.

**Scheme 117**



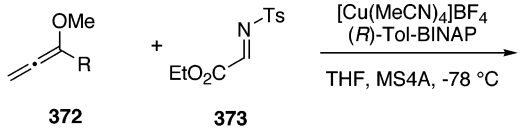

367 368 369

**368a** (R = 1-naphthyl)
**368b** (R = 2-furyl)

**369a** (R = 1-naphthyl) 80%
**369b** (R = 2-furyl) 78%

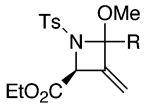
370 371

**Scheme 118**




372 373

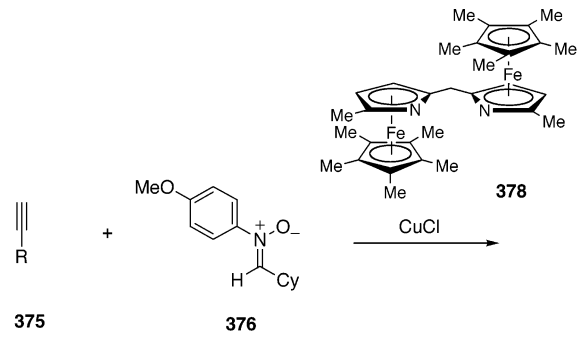
**372a** (R = $SiMe_3$)
**372b** (R = $SiMe_2Ph$)



374

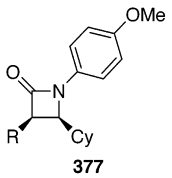
**374a** (R = $SiMe_3$) 90% yield 97% ee
**374b** (R = $SiMe_2Ph$) 89% yield 89% ee

**Scheme 119**




375 376

**375a** (R = Ph)
**375b** (R = *p*-$CF_3C_6H_4$)
**375c** (R = Bn)



377

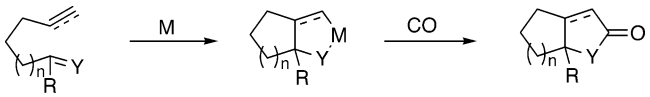
*cis*:*trans*

| | | |
|---|---|---|
| **377a** (R = Ph) | 65% yield, 92% ee | >95:5 |
| **377b** (R = *p*-$CF_3C_6H_4$) | 57% yield, 93% ee | >95:5 |
| **377c** (R = Bn) | 43% yield, 73% ee | 71:29 |

## 5.2. Hetero-[2 + 2 + 1]-Cycloaddition

Recently, catalytic hetero-[2 + 2 + 1]-cycloaddition of a carbon−carbon multiple bond, a carbon−heteroatom bond, and carbon monoxide, the so-called hetero-Pauson−Khand reaction, has been used frequently for the synthesis of functionalized γ-butyrolactones and γ-butyrolactams **381** (Scheme 120).

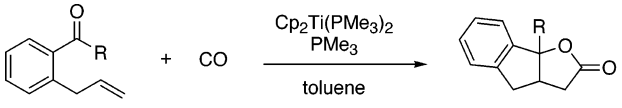
**Scheme 120. Hetero-Pauson−Khand Reaction**




**379**
Y = O, NR'
n = 1,2

380 381

**Scheme 121**

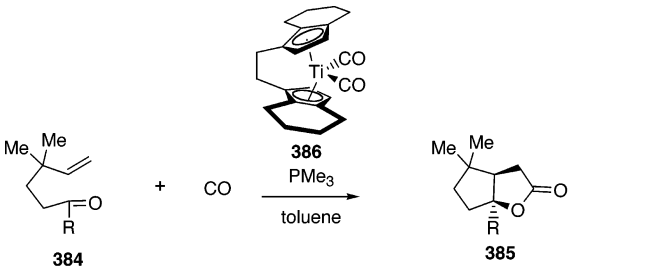



382 383

**382a** (R = Me)
**382b** (R = Ph)

**383a** (R = Me) 91%
**383b** (R = Ph) 97%

**Scheme 122**




384 385

**384a** (R = H)
**384b** (R = Me)

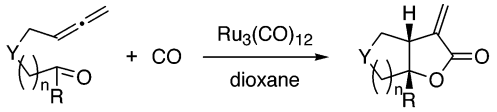
**385a** (R = H) 86% yield, 89% ee
**385b** (R = Me) 88% yield, 90% ee

The catalytic *intramolecular* hetero-Pauson−Khand reaction has been extensively studied by several groups.[184] Kablaoui et al. reported the titanocene-catalyzed hetero-Pauson−Khand reaction of the 2-allylphenyl ketones **382**.[184a,b] In the presence of $Cp_2Ti(PMe_3)_2$ and trimethylphosphine, the reaction of **382** with carbon monoxide gave the polycyclic lactones **383** in high yields (Scheme 121).

Mandal et al. recently demonstrated that the asymmetric *intramolecular* hetero-Pauson−Khand reaction of the enals and enones **384** in the presence of the chiral titanocene catalyst **386** gave the chiral γ-butyrolactones **385** with high ee values and in high chemical yields (Scheme 122).[185]

Kang et al. reported that the ruthenium-catalyzed intramolecular hetero-Pauson−Khand reaction of the allenyl aldehydes and ketones **387** gave the α-methylene-γ-butyrolactones **388** (Scheme 123).[186]

**Scheme 123**



**387**

**387a** (R = Me, Y = NTs, n = 1)
**387b** (R = H, Y = O, n = 2)

**388**

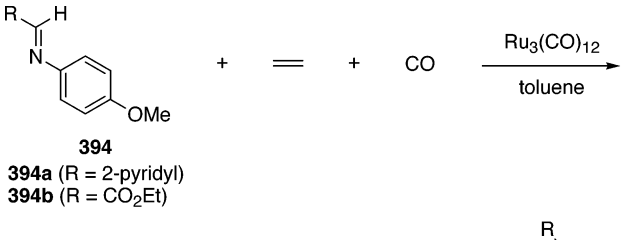
**388a** (R = Me, Y = NTs, n = 1) 82%
**388b** (R = H, Y = O, n = 2) 61%

Chatani et al. have reported the ruthenium-catalyzed *intermolecular* hetero-Pauson−Khand reaction. In the presence of $Ru_3(CO)_{12}$ and P(4-$CF_3C_6H_4)_3$, the reaction of the α-dicarbonyl compounds **389** with ethylene and carbon monoxide gave the corresponding lactones **390** in excellent yields (Scheme 124).[187] The reaction proceeds via the coordination of the dicarbonyl group to ruthenium, the oxidative cyclization of ethylene with **391** forming the ruthenacycle **392**, the insertion of CO, and the reductive elimination of Ru from **393**. They also reported that the reaction of the imines **394**, which contain a nitrogen heterocycle or an ester as the R group, with ethylene or diphenylacetylene and carbon monoxide in the presence of catalytic amounts of ruthenium carbonyl gave the γ-butyrolactams **395** or **396** in good yields (Schemes 125 and 126).[188]

## 5.3. Hetero-[2 + 2 + 2]-Cycloaddition

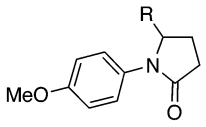
Transition-metal-catalyzed hetero-[2 + 2 + 2]-cycloaddition of alkynes with carbon−heteroatom multiple bonds, such as isocyanides, carbon dioxide, nitriles, aldehydes, and ketones, provides heteroarenes and unsaturated heterocycles. This reaction can be categorized into two groups: one is the reaction of 1,ω-diynes **397** with carbon−heteroatom multiple bonds, and the other is reaction of the alkynes **399**, having a carbon−heteroatom multiple bond with alkynes as illustrated in Scheme 127. The reaction of 1,ω-diynes **397** proceeds through formation of the metalacyclopentadiene intermediate **398** followed by insertion of a carbon−heteroatom multiple bond, such as heterocumulenes (route a),[189] nitriles (route b),[190] and carbonyls (route c).[191] On the other hand, the

**Scheme 125**



**394**

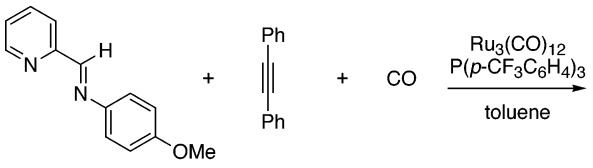
**394a** (R = 2-pyridyl)
**394b** (R = $CO_2Et$)



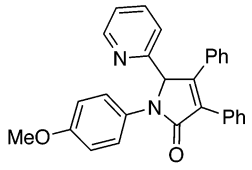
**395**

**395a** (R = 2-pyridyl) 97%
**395b** (R = $CO_2Et$) 68%

**Scheme 126**



**394a**



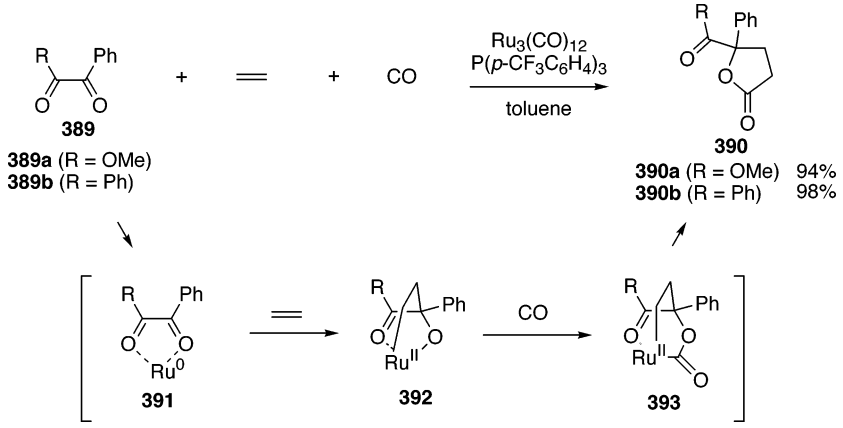
**396** (99%)

reaction of alkynes tethered with a carbon−heteroatom multiple bond (**399**) proceeds through formation of the heteroatom-containing metallacycle **400**,[192] followed by alkyne insertion (route d).

Louie et al. reported the nickel-catalyzed hetero-[2 + 2 + 2]-cycloaddition of $CO_2$ with diynes. The reaction of the diynes **401** with $CO_2$ under atmospheric pressures occurred in the presence of bis(1,5-cyclooctadiene)nickel and the *N*-heterocyclic carbene ligand (IPr, **403**) to give the corresponding pyrones **402** in high yields (Scheme 128).[189b]

Yamamoto et al. reported that the ruthenium-catalyzed cycloaddition of the 1,6-diyne **404** with the

**Scheme 124**



**389**

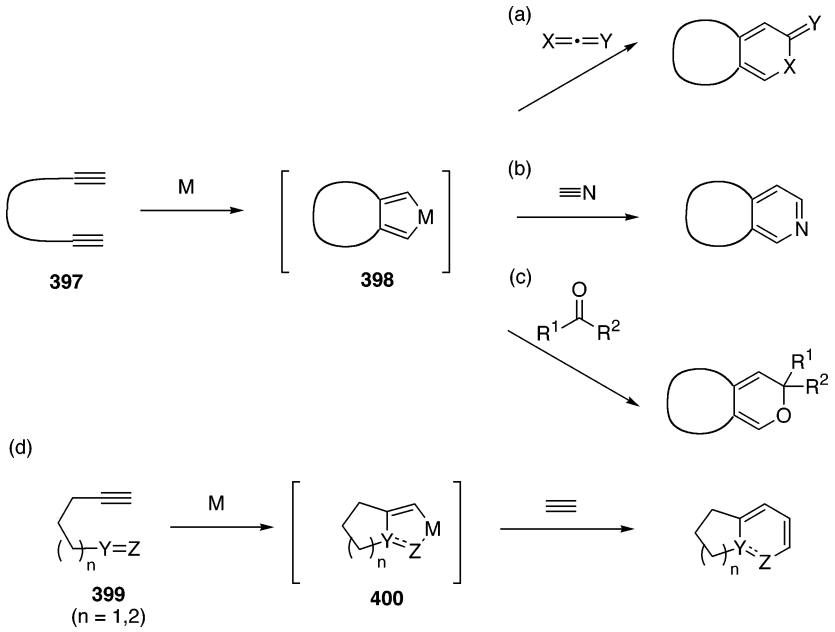
**389a** (R = OMe)
**389b** (R = Ph)

**390**

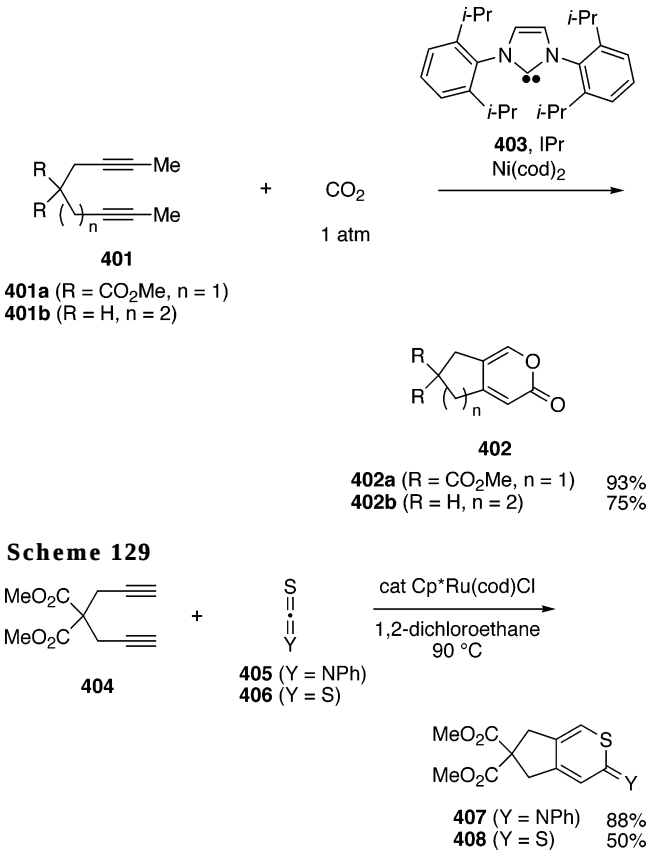
**390a** (R = OMe) 94%
**390b** (R = Ph) 98%

**391** **392** **393**

**Scheme 127. Hetero-[2 + 2 + 2]-Cycloaddition**




**Scheme 128**



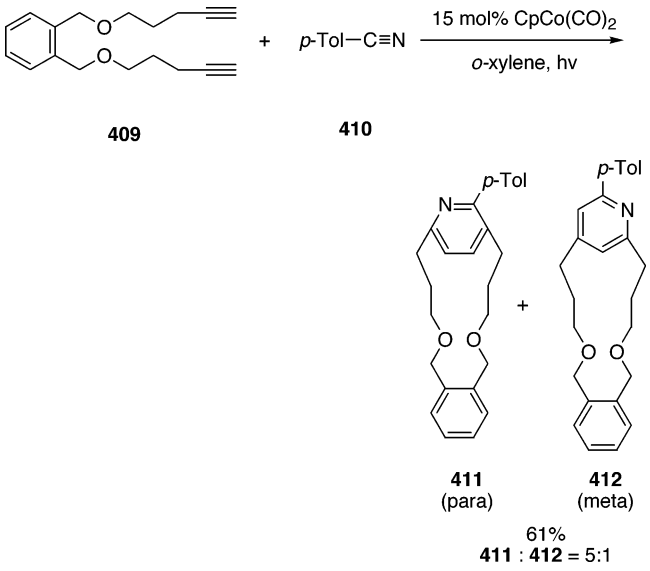

**Scheme 129**




isothiocyanate **405** or carbon disulfide **406** gave the thiopyranimine **407** or dithiopyrone **408**, respectively (Scheme 129).[193]

Moretto et al. reported the synthesis of the pyridine-containing macrocycles **411** and **412** by the cobalt-catalyzed hetero-[2 + 2 + 2]-cycloaddition of the diyne **409** with the nitrile **410** (Scheme 130).[190c] A high para-selectivity was obtained and **411** was produced as the major product.

**Scheme 130**



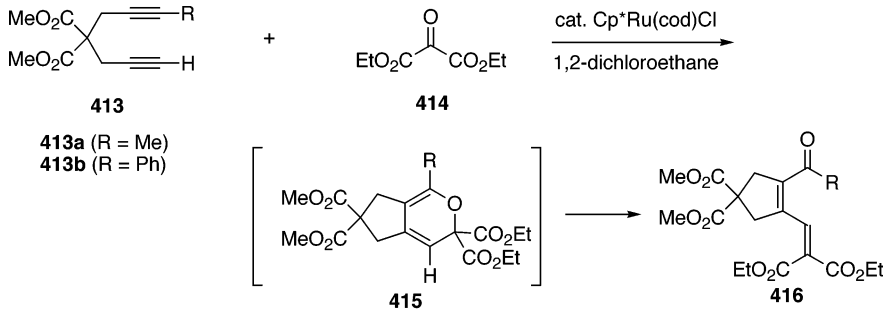

Yamamoto et al. reported the ruthenium-catalyzed hetero-[2 + 2 + 2]-cycloaddition of the 1,6-diynes **413** with the tricarbonyl compound **414** (Scheme 131).[191] The cycloadducts **415** were transformed in situ to the cyclic dienones **416** via electrocyclic ring opening.

## 5.4. Hetero-[3 + 2]-Cycloaddition

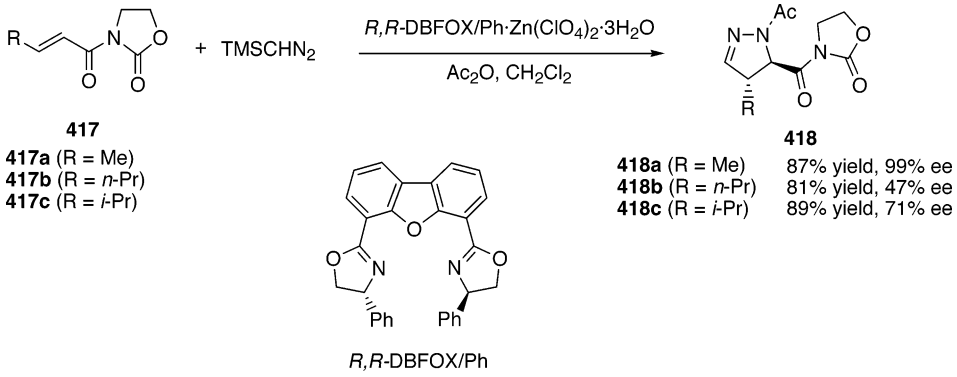
Kanemasa et al. reported that the enantioselective 1,3-dipolar cycloaddition of the 3-(alkenoyl)-2-oxazolidinones **417** and trimethylsilyldiazomethane in the presence of $Zn(ClO_4)_2$-*R*,*R*-DBFOX/Ph complex gave the 2-pyrazoline cycloadducts **418** in high yields with good to excellent ee values (Scheme 132).[194]

Shintani and Fu repored enantioselective coupling of terminal alkynes **420** with azomethine imines **419** by copper-catalyzed [3 + 2]-cycloaddition (Scheme 133).[195] In the presence of CuI and phosphafer-

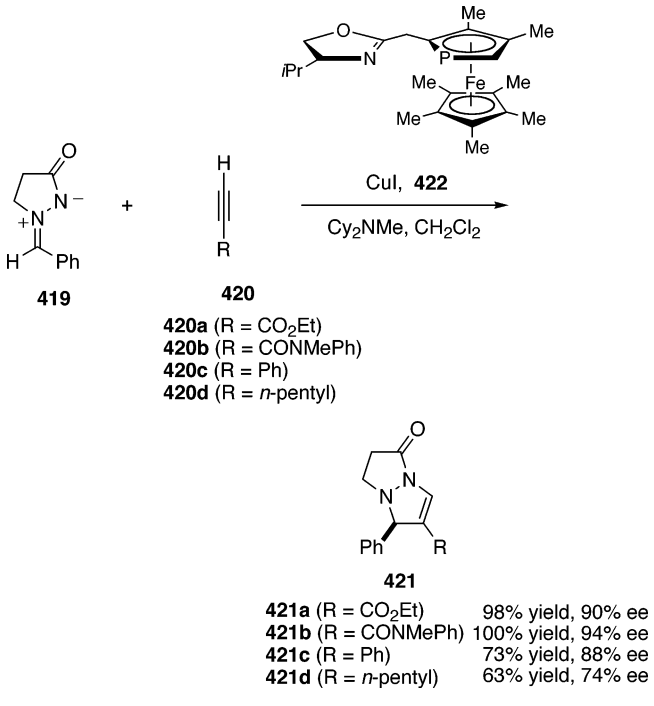
**Scheme 131**




**Scheme 132**




**Scheme 133**




rocene−oxazoline ligand **422**, the asymmetric [3 + 2]-cycloaddition of terminal alkynes **420** and azomethine imine **419** afforded the heterocycles **421** in excellent yields with high stereoselection. Not only electron-deficient alkynes (**420a** and **420b**) but also unactivated alkynes (**420c** and **420d**) were employed as substrates.

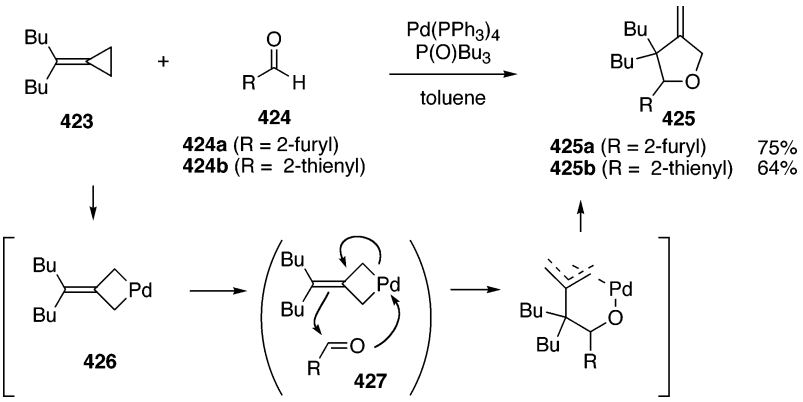
Alkylidenecyclopropanes have been used as a substrate for hetero-[3 + 2]-cycloaddition with heterocumulenes.[196] We reported that the palladium-catalyzed hetero-[3 + 2]-cycloaddition of the alkylidenecyclopropane **423** with the aldehydes **424** gave the 3-methylenetetrahydrofurans **425** in good yields (Scheme 134).[197a] This reaction proceeds through formation of the palladacyclobutane intermediate **426**, followed by pallada-ene type reaction, as shown in **427**. We also demonstrated that the palladium-catalyzed reaction of the alkylidenecyclopropane **423** with the imines **428** gave the 3-methylenepyrrolidines **429** in good to excellent yields (Scheme 135).[197b]

## 5.5. Hetero-[4 + 2]-Cycloaddition

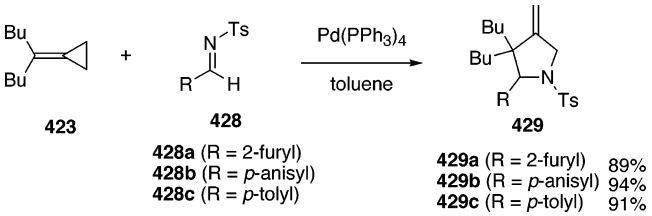
The catalytic hetero-Diels−Alder reaction is also of particular interest, since it allows a convenient access to prepare six-membered heterocycles. The hetero-Diels−Alder reaction is classified into two groups, as shown in Scheme 136: (a) [4 + 2]-cycloaddition of 1,3-dienes with a carbon-heteroatom or heteroatom−heteroatom double bond[198] and (b) [4 + 2]-cycloaddition of α,β-unsaturated carbonyl compounds with olefins.[199]

A wide variety of chiral catalysts, such as Ti, V, Mn, Cr, Co, Cu, Zn, Zr, Rh, Pd, La, Sm, Eu, and Yb, bearing a chiral ligand, has been developed for asymmetric hetero-Diels−Alder reaction. Yamashita et al. reported the asymmetric *trans*-selective hetero-Diels−Alder reaction using a chiral zirconium catalyst.[200] The reaction of the 1,3-diene **430a** with the aldehydes **431** proceeded smoothly in the presence

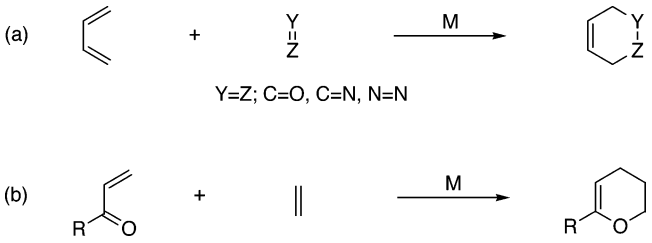
**Scheme 134**




**Scheme 135**

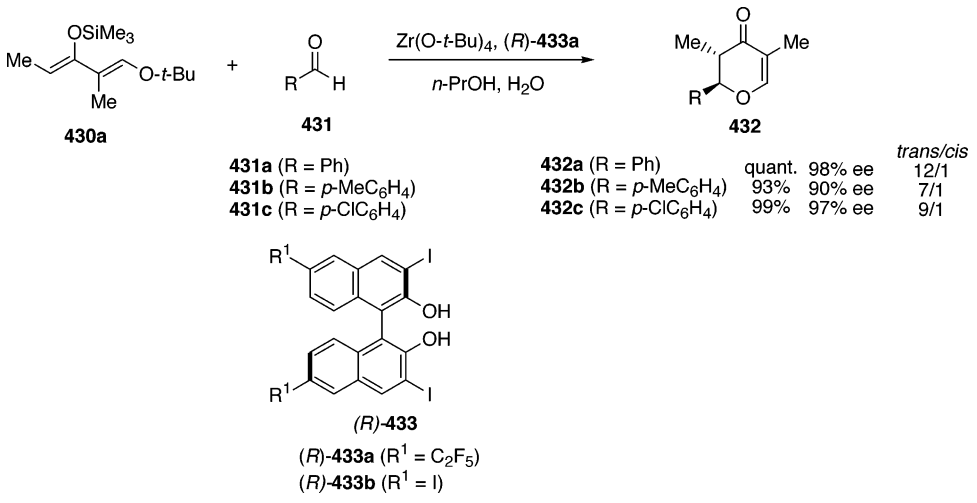



**Scheme 136. Hetero-Diels–Alder Reaction of (a) 1,3-Dienes with Carbon–Heteroatom and Heteroatom–Heteroatom Double Bonds and (b) α,β-Unsaturated Carbonyls with Olefins**

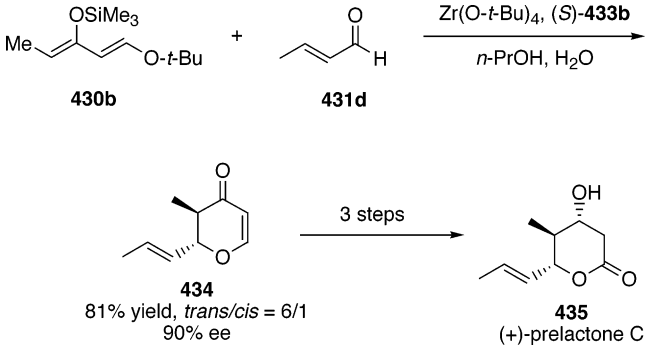



of the chiral zirconium complex, which was prepared from Zr(O-*t*-Bu)$_4$, the BINOL derivative (*R*)-**433a**, *n*-propanol, and water, and the corresponding pyranone derivatives **432** were obtained in high yields and with high *trans*-selectivities and enantioselectivities (Scheme 137). They performed the asymmetric synthesis of (+)-prelactone C **435** using (*S*)-**433b** as a chiral ligand (Scheme 138).

**Scheme 137**



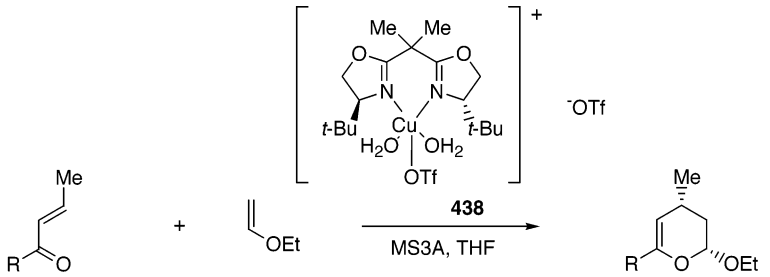

**Scheme 138**




Evans et al. reported that in the presence of $C_2$-symmetric bis(oxazoline)–Cu(II) complex **438** the inverse electron demand hetero-Diels–Alder reaction of the α,β-unsaturated carbonyl compounds **436** with ethyl vinyl ether gave the chiral dihydropyrans **437** in high diastereo- and enantioselectivities (Scheme 139).[199c]

Trost et al. reported the ruthenium-catalyzed hetero-[4 + 2]-cycloaddition and hydrative cyclization of yne–enone **439** (Scheme 140).[201] In the absence of water the reaction proceeds through the usual [4 + 2]-cycloaddition to give the bicyclic pyran **440**, while the hydrative cyclization occurs in the presence of water to afford the cyclic diketone **441**. The reaction is

**Scheme 139**



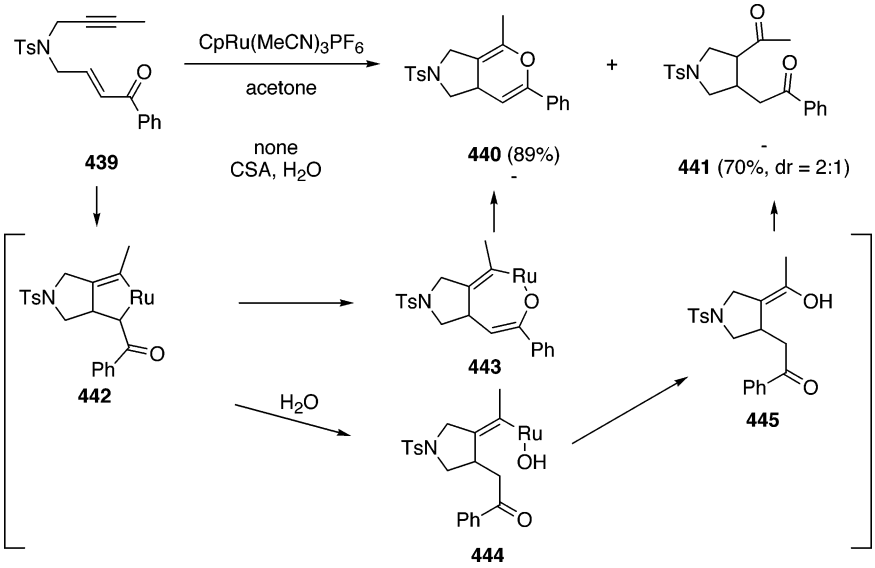

436

**436a** (R = $CO_2Et$)
**436b** (R = CONMeOMe)
**436c** (R = $PO(OMe)_2$)

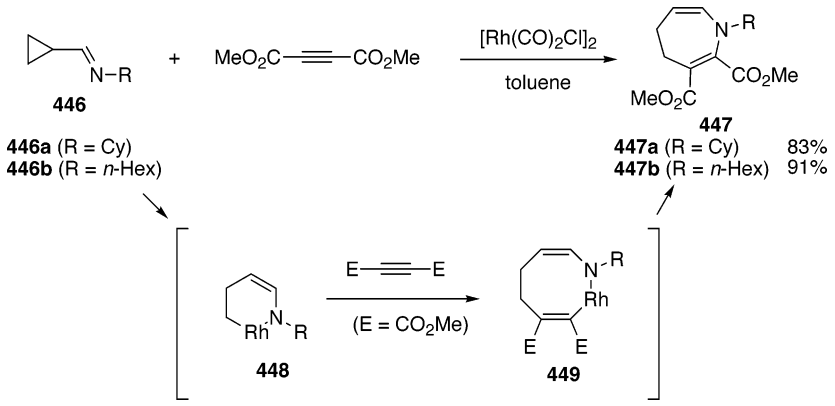
437

**437a** (R = $CO_2Et$) 87% yield, 97% ee
**437b** (R = CONMeOMe) 99% yield, 99% ee
**437c** (R = $PO(OMe)_2$) 84% yield, 93% ee

**Scheme 140**




**Scheme 141**




**446a** (R = Cy)
**446b** (R = *n*-Hex)

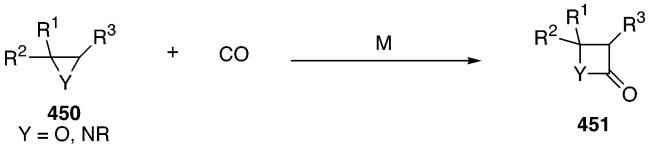
**447a** (R = Cy) 83%
**447b** (R = *n*-Hex) 91%

initiated by oxidative cyclization of **439** with ruthenium, forming the ruthenacycle **442**. In the absence of water, isomerization of the α-*C*-ruthenium ketone **442** to the *O*-enolate **443** occurs and subsequent reductive elimination gives the pyran **440**. Hydration of the ruthenacycle **442** takes place in the presence of water to form the alkenylruthenium hydroxide **444**. Reductive elimination of Ru and subsequent isomerization of the enol **445** take place to give the diketone **441**.

## 5.6. Hetero-[5 + 2]-Cycloaddition

Wender et al. reported that the rhodium-catalyzed hetero-[5 + 2]-cycloaddition of the cyclopropyl imines **446** and dimethyl acetylenedicarboxylate gave the dihydroazepines **447** in high yields (Scheme 141).[202] The rhodaheterocycle intermediate **448** is formed upon treatment of **446** with the rhodium catalyst, which undergoes insertion of the alkyne to give **449**, and finally the reductive elimination of Rh gives **447**.

**Scheme 142. Hetero-[3+1]-Cycloaddition: Synthesis of β-Lactones and β-Lactams by the Carbonylation of Three-Membered Heterocycles**




**450** Y = O, NR

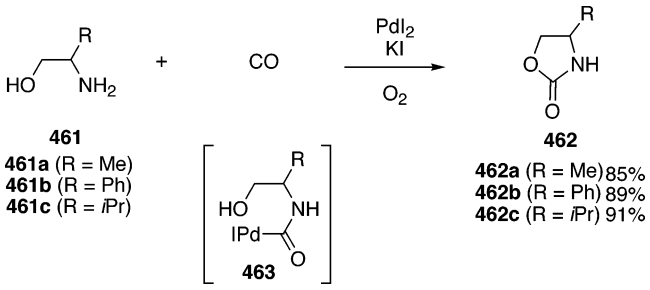
**451**

## 5.7. Carbonylation

The transition-metal-catalyzed carbonylation reaction has been extensively investigated, and especially the carbonylative ring expansion reaction of strained heterocycles has been shown to be a useful and efficient procedure to synthesize lactams, lactones, and thiolactones.[203] The carbonylation of epoxides and aziridines **450** is a powerful tool to construct the β-lactone and β-lactam skeletons **451** (Scheme 142).[204] This type of reactions can be regarded as a hetero-[3 + 1]-cycloaddition.

Kondo et al. reported that the ruthenium-catalyzed reconstructive carbonylation of the cyclopropenones **452** produced the pyranopyrandiones **453** (Scheme 143).[205] This reaction proceeds through C−C bond cleavage of the cyclopropene ring of **452** by oxidative insertion of the ruthenium catalyst to form the ruthenacyclobutene **454**. The insertion of CO and subsequent isomerization of the resulting maleoyl-ruthenium intermediate gives the ($\eta^4$-bisketene)-ruthenium **455**. The oxidative addition of the cyclopropene ring of **452** to the ruthenium of **455** and subsequent insertion of a ketene C═O bond to the acyl C−Ru bond leads to the ($\eta^2$-ketene)ruthenacycle **457**. Rapid tautomerization, insertion of a second CO to the Ru carbene complex **458**, insertion of the C═O bond of the ketene moiety of **459** to the acyl−ruthenium bond, and reductive elimination of Ru from the resulting ruthenacycle **460** give the heterocycle **453**.

**Scheme 144**




**461**
**461a** (R = Me)
**461b** (R = Ph)
**461c** (R = *i*Pr)

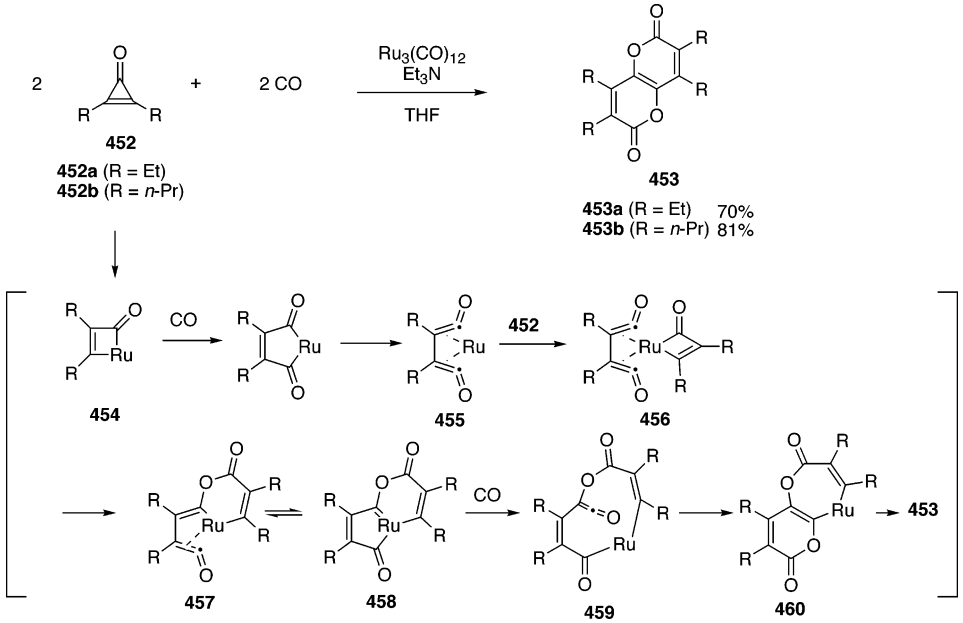
**463**

**462**
**462a** (R = Me) 85%
**462b** (R = Ph) 89%
**462c** (R = *i*Pr) 91%

Gabriele et al. reported that the 2-oxazolidinones **462** were synthesized by the palladium-catalyzed oxidative carbonylation of the 2-amino-1-alkanols **461** (Scheme 144).[206] The aminocarbonyl palladium complex **463** is formed as an intermediate, and subsequent ring closure gives **462**.

Van den Hoven et al. reported that the zwitterionic rhodium complex **467**-catalyzed chemo- and regioselective cyclohydrocarbonylation of the α-keto alkynes **464** afforded either the furanone **465** or **466**, depending on the substituent R (Scheme 145).[207] The reaction of **464a** with R = Ph gave the 2(*3H*)-furanone **465a** in 83% yield, while the reaction of **464b** with R = alkyl afforded 2(*5H*)-furanone **466b** in high yield. The reaction proceeds via hydrorhodation of the triple bond of ynones **464**. The insertion of CO into the C−Rh bond of **468**, rearrangement from **469** to the zwitterionic ketene **470**, and subsequent cyclization of **470** give **471**. Alternatively, the *E*−*Z* isomerization of **468** to **472**, CO insertion to the sp$^2$ C−Ru bond of

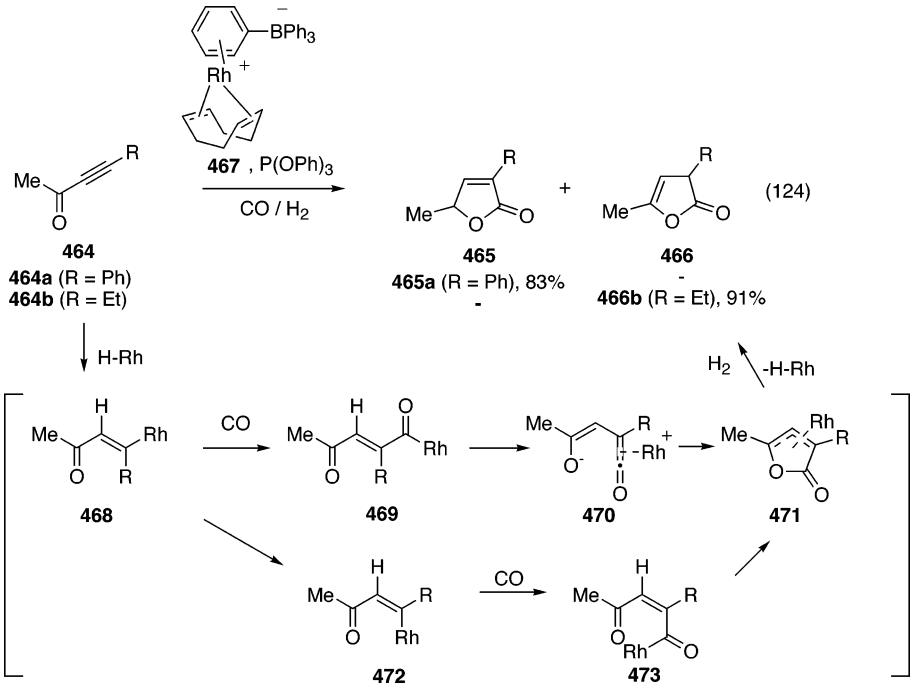
**Scheme 143**



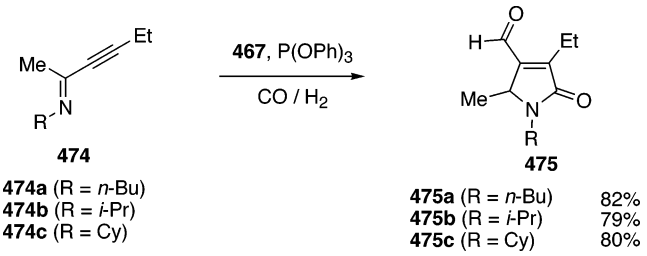

**452** **452a** (R = Et) **452b** (R = *n*-Pr)

**453** **453a** (R = Et) 70% **453b** (R = *n*-Pr) 81%

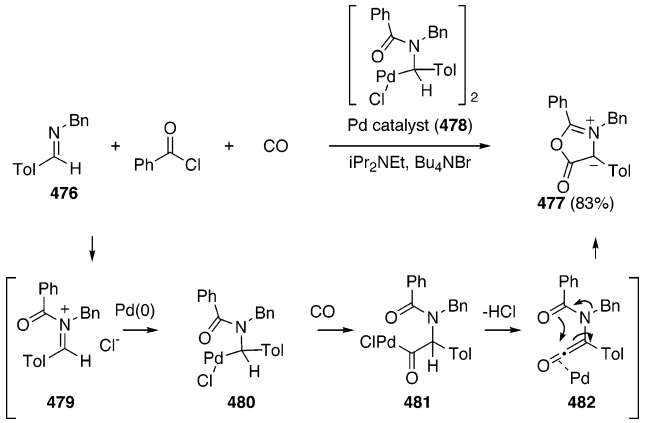
**Scheme 145**




**Scheme 146**




**Scheme 147**



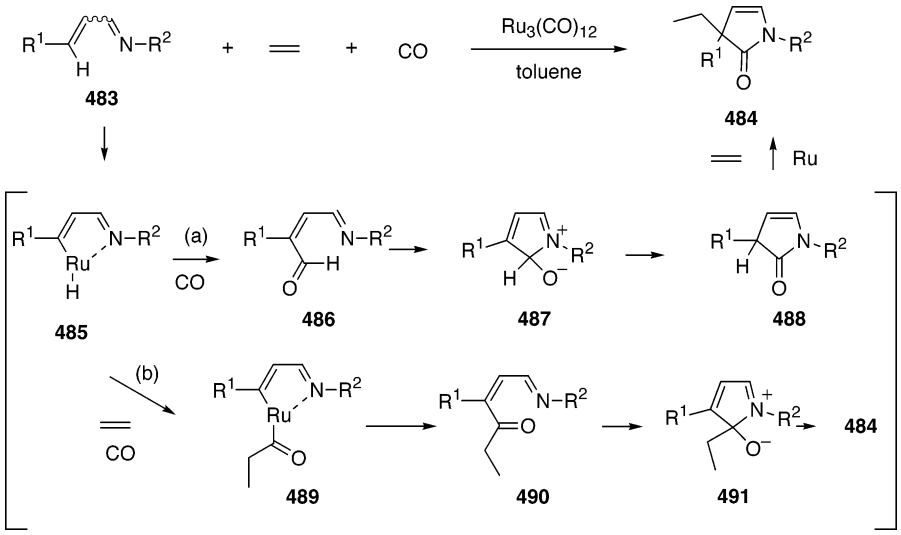

the alkenylruthenium **473**, and intramolecular acylrhodation of the carbonyl moiety of **473** give the same intermediate **471**. The reduction of the ruthenium complex **471** with $H_2$ gives **465** or **466**. Van den Hoven and Alper also demonstrated that the zwitterionic rhodium-catalyzed tandem cyclohydrocarbonylation/CO insertion of the α-imino alkynes **474** gave the 4-carbaldehydepyrrolin-2-ones **475** (Scheme 146).[208]

Dhawan et al. reported that the reaction of the imine **476** with benzoyl chloride and carbon monoxide in the presence of the palladium catalyst **478** gave münchnone **477** (Scheme 147).[209] This reaction proceeds through formation of the acyliminium salt **479**, the insertion of CO into the C−Pd bond of the intermediate **480**, dehydrochlorination from the resulting acylpalladium complex **481**, and cyclization by attack of the oxygen to the electron-deficient carbonyl coordinated to palladium (see **482**).

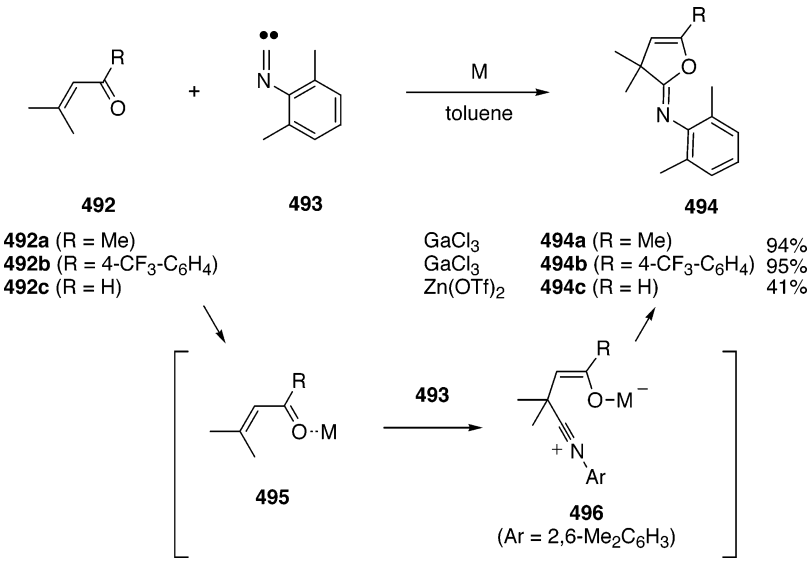
Imhof et al. and Chatani et al. independently reported that the ruthenium-catalyzed reaction of the α,β-unsaturated imines **483** with alkenes and carbon monoxide gave the β,γ-unsaturated γ-butyrolactams **484** (Scheme 148).[210] Imhof et al. proposed that the reaction proceeded through the aldehyde **486** formed by the ruthenium-catalyzed carbonylation of the C−H bond at the β-position of **483** (route a).[210a] Subsequent cyclization of **486**, 1,2-H shift of **487**, and the ruthenium-catalyzed insertion of ethylene into the C−H bond at the α-position of the ketone **488** give **484**. On the other hand, Chatani et al. proposed that the reaction was initiated by oxidative addition of the β-C−H bond of imine **483** to Ru, and subsequent insertion of CO and ethylene into the C−Ru bond of **485** gave the acylruthenium intermediate **489** (route b).[210b] Reductive elimination of Ru gives the α,β-unsaturated ketone **490**. The following cyclization of **490** and the subsequent 1,2-alkyl shift of **491** led to **484**.

Chatani et al. reported the catalytic [4 + 1]-cycloaddition of α,β-unsaturated carbonyl compounds

**Scheme 148**



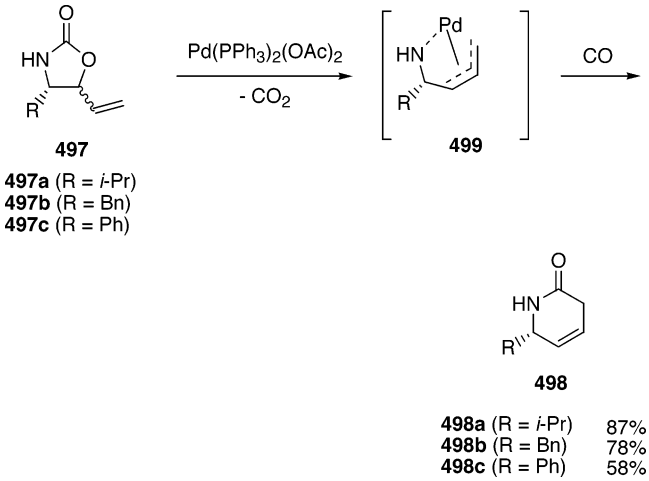

**Scheme 149**




**492** and isocyanides **493**, leading to unsaturated $\gamma$-lactone derivatives **494** (Scheme 149).[211] In the presence of a catalytic amount of $GaCl_3$, the reaction of $\alpha,\beta$-unsaturated ketones **492a** and **492b** with 2,6-dimethylphenyl isocyanide **493** proceeded in toluene, and the corresponding unsaturated iminolactones **494a** and **494b** were obtained in high yields. $Zn(OTf)_2$ was used as a catalyst in the reaction of $\alpha,\beta$-unsaturated aldehyde **492c**. The reaction proceeds through coordination of the catalyst to the oxygen atom of **492**, attack of the isocyanide on the $\beta$-carbon of **495**, and the intramolecular cyclization of **496**.

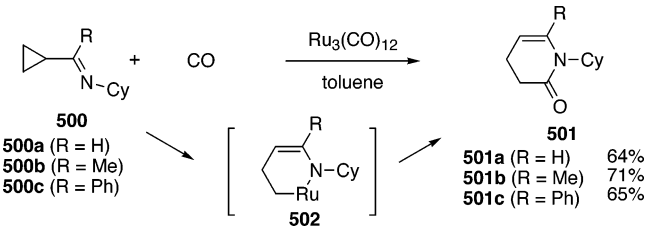
Knight et al. reported that the palladium-catalyzed decarboxylative carbonylation of amino acid-derived 5-vinyloxzolidin-2-ones **497** gave the corresponding $\delta$-lactams, 3,6-dihydro-1*H*-pyridin-2-ones **498**, in good to high yields (Scheme 150).[212] This reaction proceeds through release of carbon dioxide, forming the $\pi$-allylpalladium intermediate **499**, followed by insertion of CO.

**Scheme 150**

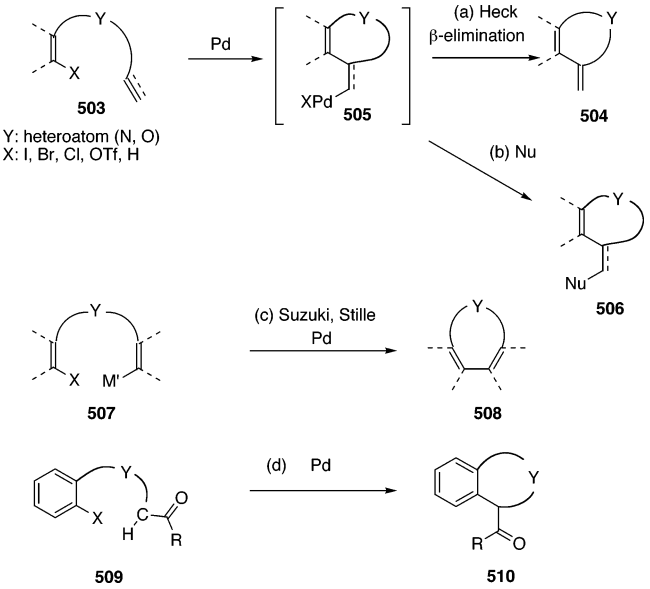



Kamatani et al. reported that $Ru_3(CO)_{12}$-catalyzed carbonylative [5 + 1]-cycloaddition of the cyclopropyl imines **500** gave the six-membered unsaturated lactams **501** (Scheme 151).[213] The reaction proceeds through the formation of ruthenacycle **502**.

**Scheme 151**




**Scheme 152. C−C Bond Formation by (a) Heck Reaction, (b) Tandem Cyclization−Coupling Reaction, (c) Cross-Coupling Reaction with Organometallics, and (d) α-Arylation of Ketones and Amides**

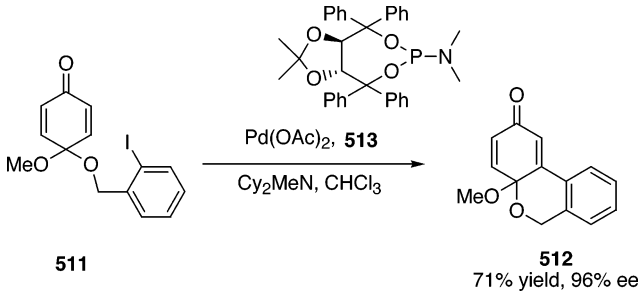



## 6. Intramolecular Reaction of Aryl and Vinyl Halides: Heck-, Suzuki-, and Stille-Type Reactions

### 6.1. Carbon–Carbon Bond Formation

Metal-catalyzed cross-coupling reactions of aryl and vinyl halides or their pseudohalide analogues have been widely investigated and become one of the most powerful and useful synthetic tools in organic chemistry.[214] Especially, catalytic carbon−carbon bond forming reactions of those derivatives with alkenes or with organometallics have been widely utilized in the synthesis of heterocyclic compounds. The intramolecular Heck reaction is very useful for constructing the heterocyclic rings **504** and **506** from the substrates **503**, which have both $sp^2$ carbon−halogen or −pseudohalogen and carbon−carbon unsaturated bonds; the insertion of Pd(0) into the C−X bond followed by carbopalladation of the unsaturated C−C bond gives the palladium intermediate **505**, and the $\beta$-elimination takes place, if **505** is an alkyl palladium and not an alkenyl palladium, leading to **504** (Scheme 152, route a).[215] In the presence of external nucleophilic reagents, such as organoboranes,[216] organostannanes,[217] amines,[218] hydride,[219] indium,[220] and aromatic rings,[221] trapping of the carbopalladium intermediate **505** with the nucleophiles leads to **506** (route b).[222] Even C−H activation takes place in certain ortho-heteroatom-substituted aryl substrates **503** (X = H) to give the heterocycles **504**,[223,224] although this type of reaction is not yet used widely in comparison with the reaction of aryl halides and pseudohalides. The intramolecular cross-coupling reactions of aryl and alkenyl halides with organometallics, the so-called Suzuki and Stille reactions, have been applied in the synthesis of natural and nonnatural heterocyclic compounds (route c).[225] Recently, the palladium-catalyzed intramolecular α-arylation of ketones, esters, and amides **509** has been utilized for the synthesis of heterocyclic compounds (route d).[226]

**Scheme 153**

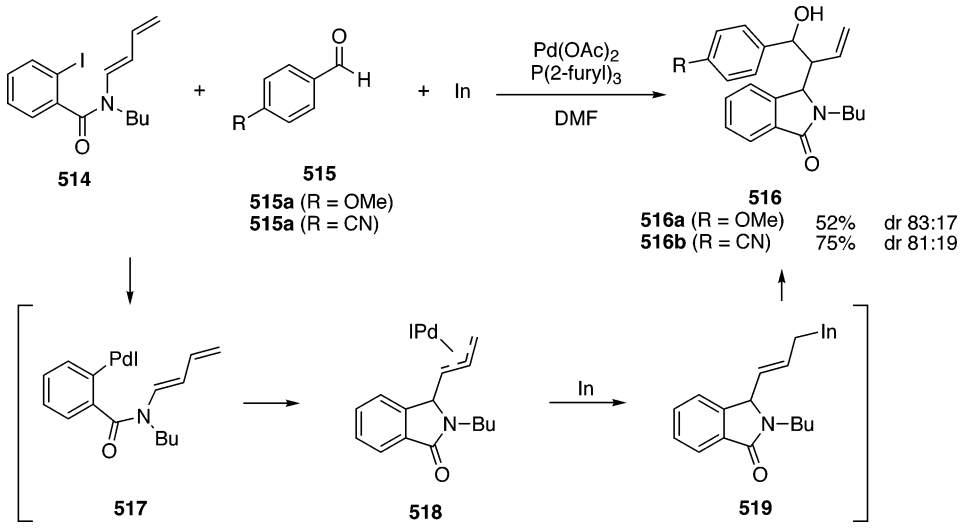



The intramolecular asymmetric Heck reaction has featured in the synthesis of complex heterocyclic compounds. Bidentate ligands, such as diphosphines (especially BINAP) and phosphine−oxazolines, have been used as a chiral ligand of the asymmetric Heck reaction. Imbos et al. demonstrated that the monodentate phosphoramidite **513** was an effective ligand for the asymmetric Heck reaction of the prochiral cyclohexadienone **511** (Scheme 153).[227] The reaction of **511** in the presence of catalytic amounts of $Pd(OAc)_2$ and the chiral phosphoramidite **513** gave the 4a-methoxy-4a*H*-benzo[*c*]chromen-2(6*H*)-one **512** in 71% yield with 96% ee. By contrast, the reaction of **511** using BINAP, instead of **513**, gave the product **512** in a poor yield with no enantioselectivity.

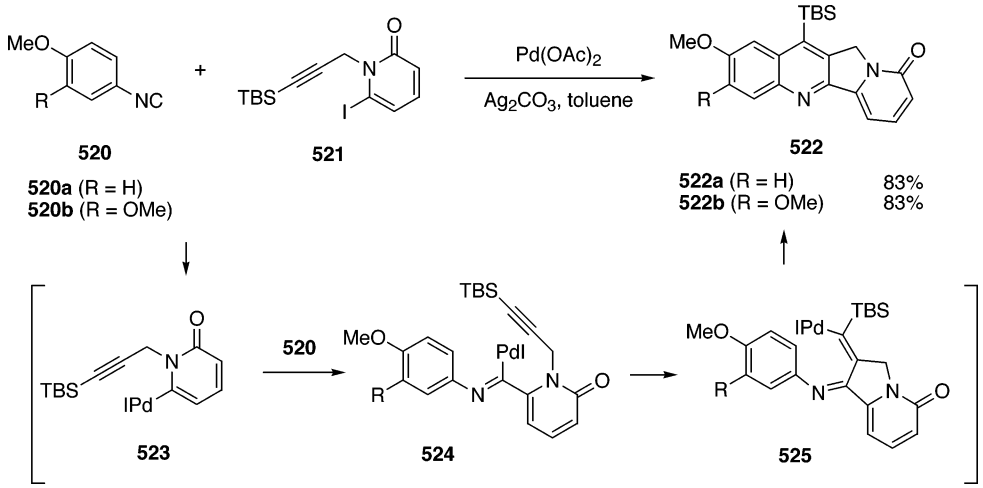
Cooper et al. reported that the cascade reaction of the palladium-catalyzed cyclization and the Barbier-type allylation of the 1,3-diene-aryl iodide **514**, the aldehydes **515**, and indium gave the heterocycles **516** in good yields (Scheme 154).[220b] The reaction proceeds through oxidative addition of a C−I bond of **514** to Pd(0) and subsequent insertion of a double bond of **517** to give the $\pi$-allylpalladium intermediate **518**. Transmetalation of the $\pi$-allylpalladium **518** with indium leads to the allylindium complex **519**, and the following reaction with the aldehydes **515** gives **516**.

Curran and Du reported that the cascade reaction of the isonitriles **520** with 6-iodo-*N*-propargylpyridone **521** in the presence of a palladium-catalyst gave the 11*H*-indolizino[1,2-*b*]quinolin-9-ones **522** in high

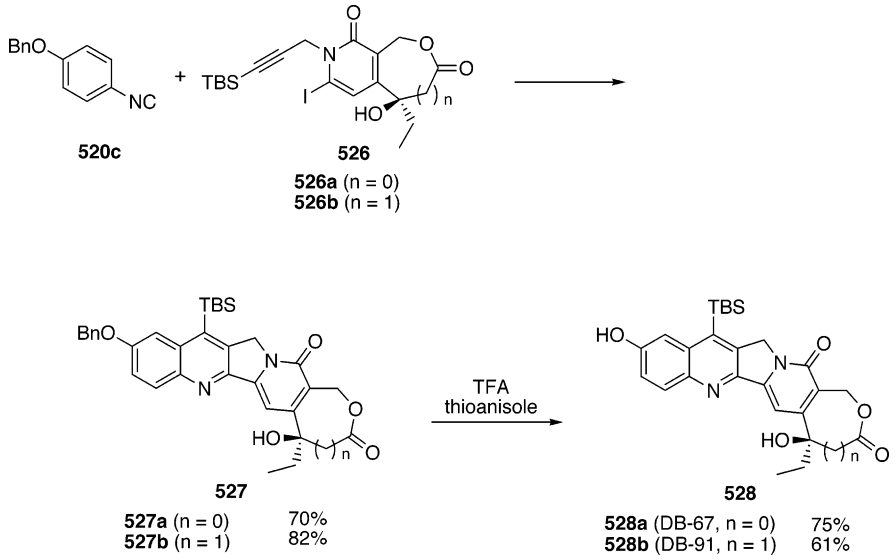
**Scheme 154**




**Scheme 155**

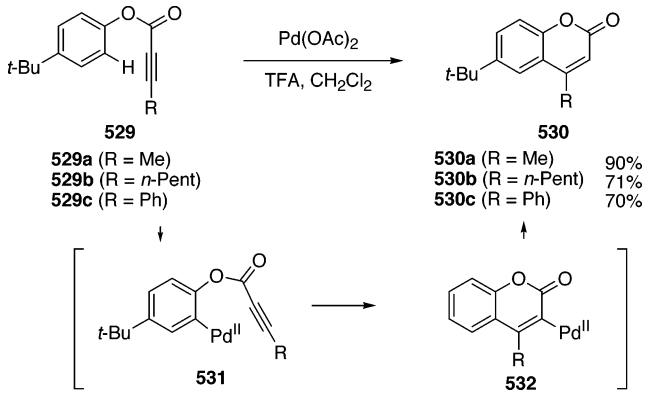



**Scheme 156**

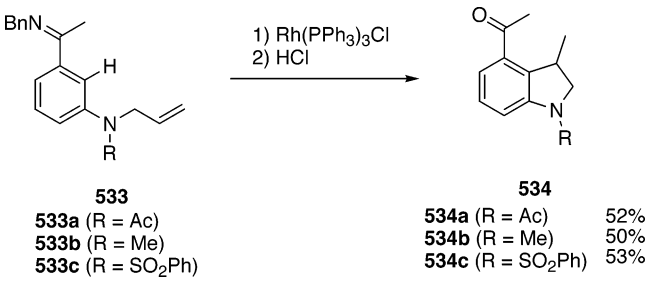



yields (Scheme 155).[221b] The reaction proceeds through oxidative addition of a C−I bond of **521**, insertion of the N═C carbon of **520** into the C−Pd bond of **523**, intramolecular insertion of the alkyne moiety of **524**, and trapping of the resulting alkenylpalladium **525** with an aromatic C−H bond to give **522**. They synthesized the silatecans DB-67 (**528a**) and DB-91 (**528b**) using the palladium-catalyzed reaction of the isonitrile **520c** and (*S*)-iodopyridones **526** (Scheme 156).

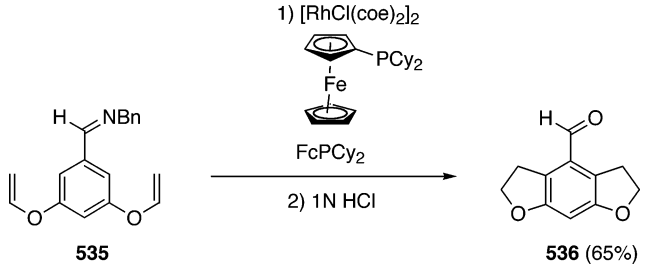
**Scheme 157**



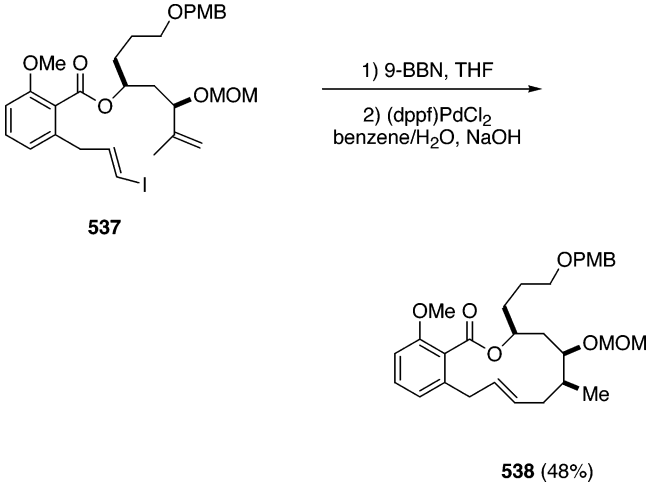

**Scheme 158**




**Scheme 159**

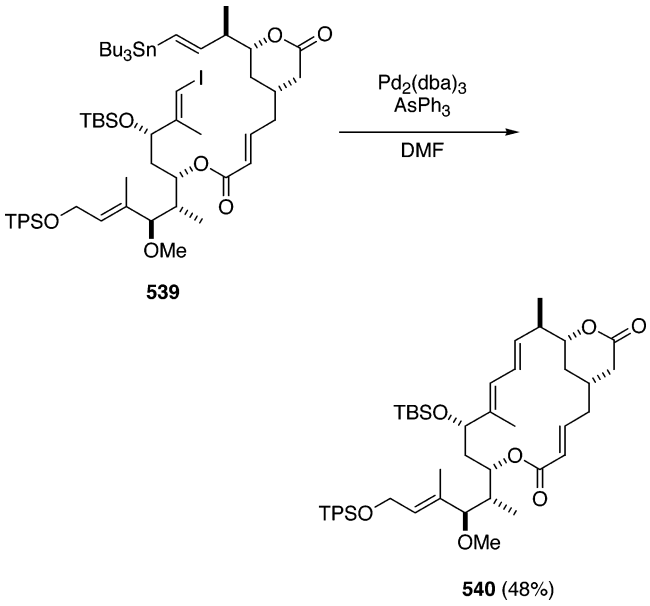



**Scheme 160**

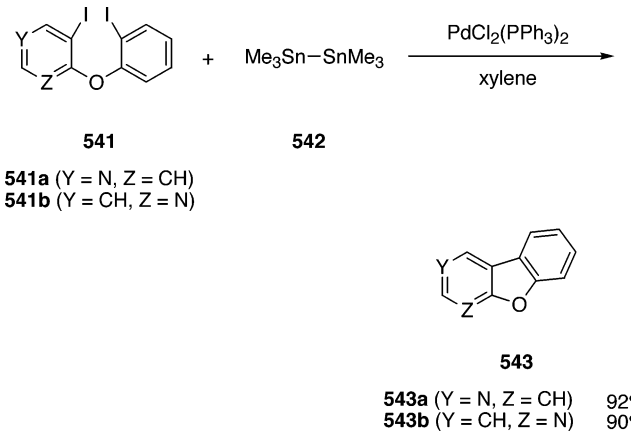



Recently, Heck-type reactions, which proceed through activation of aromatic C−H bonds, have been investigated. Jia et al. reported that the reaction of aryl alkynoates **529** in the presence of $Pd(OAc)_2$ in TFA gave the corresponding coumarins **530** in high yields (Scheme 157).[223] The reaction proceeds through electrophilic attack of Pd(II) to the aromatic C−H bond, trans-insertion of the C−C triple bond to the resulting aryl-Pd bond of **531**, and protonolysis of the vinyl−palladium bond of **532**.

**Scheme 161**




**Scheme 162**

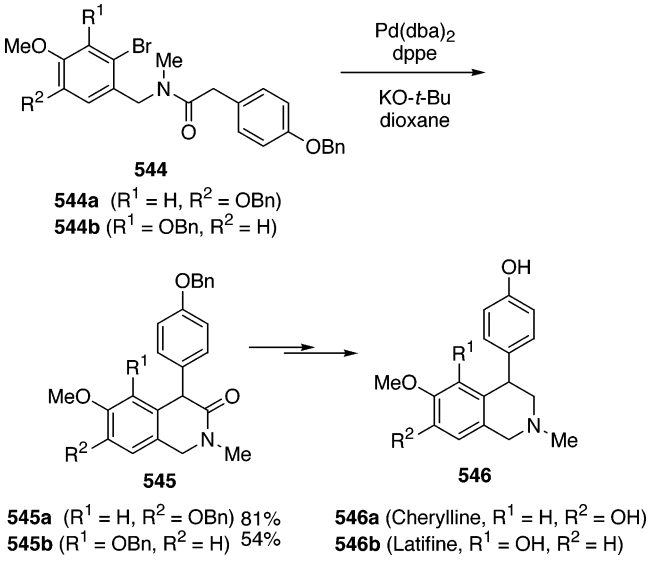



Bergman and Ellman and their co-workers reported the annulation of aromatic imines via direct C−H activation with Wilkinson's catalyst.[224] The reaction of *m*-(*N*-allylamino)phenyl methyl ketimines **533** in the presence of $Rh(PPh_3)_3Cl$ gave the dihydroindoles **534** in good yields (Scheme 158).[224b] The reaction of the benzyl imine **535** having two vinyl ethers at the 3- and 5-positions produced the tetrahydrobis(benzofuran) **536** in 65% yield (Scheme 159).[224d]

Bauer and Maier synthesized the benzolactone **538**, which has the core structure of salicylihalamide A, using intramolecular Suzuki reaction.[228] Hydroboration of the alkenyl iodide−alkene **537** with 9-BBN and subsequent Suzuki reaction in the presence of a palladium catalyst gave the macrolactone **538** in 48% yield (Scheme 160). The hydroboration proceeded with high diastereoselectivity.

Mitchell et al. utilized an intramolecular Stille reaction for the total synthesis of rhizoxin D.[229] The

**Scheme 163**

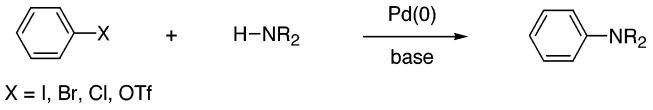



reaction of the alkenylstannane bearing the alkenyl iodide function (**539**) in the presence of palladium and arsenic catalysts gave the 16-membered macrocyclic lactone **540** in 48% yield (Scheme 161).

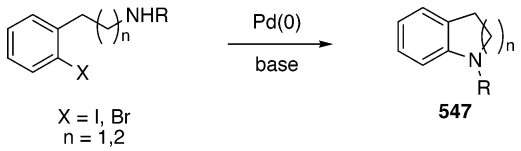
Yue and Li reported that the reaction of the diiodides **541** with hexamethylditin **542** in the presence of $PdCl_2(PPh_3)_2$ gave the benzo[4,5]furopyridines **543** in high yields (Scheme 162).[230]

The palladium-catalyzed intramolecular α-arylation of ketones, esters, and amides have been extensively investigated by Solé et al.,[226c,e,f,j,k] Gaertzen and Buchwald,[226h] and Hartwig et al.[226b,g] and has become

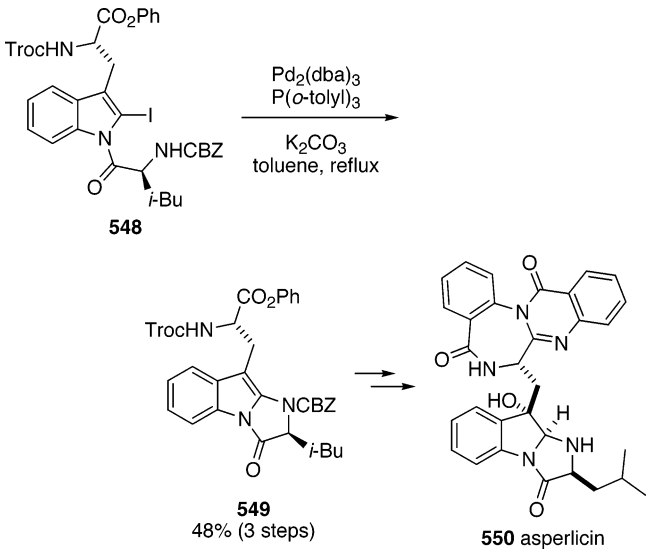
**Scheme 165**




**Scheme 166**

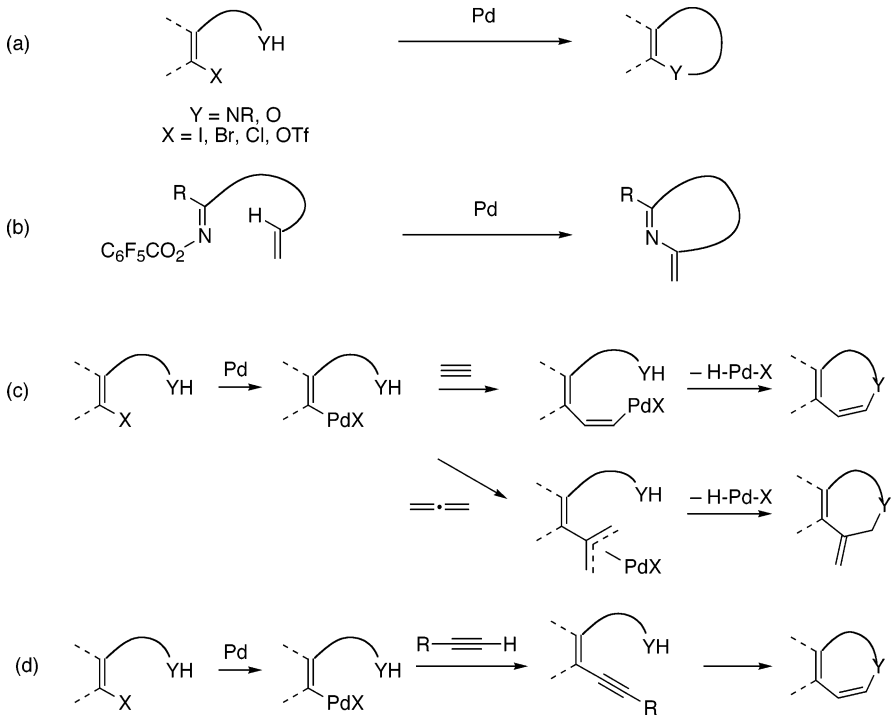



**Scheme 167**

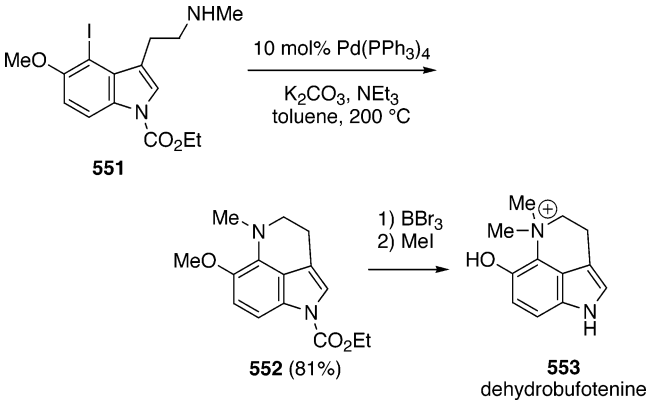



a useful synthetic tool for constructing heterocycles.[226a] Honda et al. demonstrated the synthesis of the

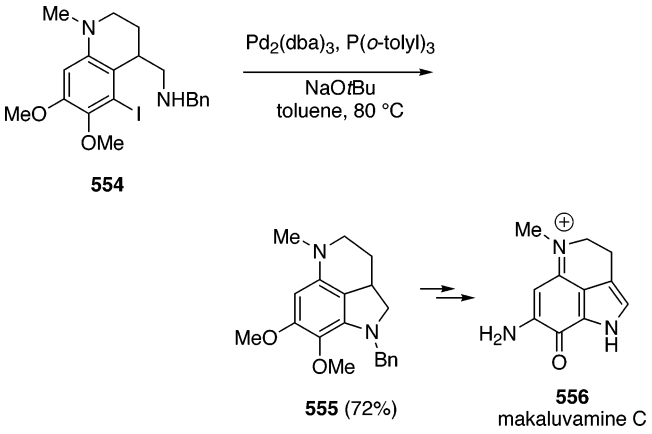
**Scheme 164. Carbon−Heteroatom Bond Formation by (a) Coupling with a Heteroatom, (b) Amino-Heck Reaction, (c) Insertion of C−C Unsaturated Bonds-Coupling with Heteroatoms, and (d) Sonogashira Coupling of Terminal Alkynes Followed by Cyclization**



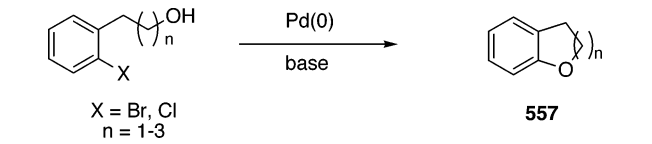
**Scheme 168**




**Scheme 169**




**Scheme 170**

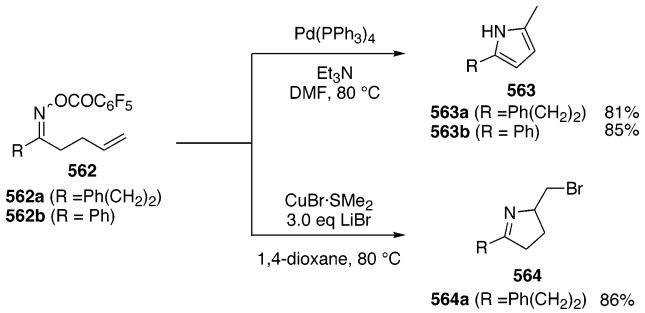



isoquinoline alkaloids cherylline (**546a**) and latifine (**546b**) by the intramolecular α-arylation of the amides **544** (Scheme 163).[226d]

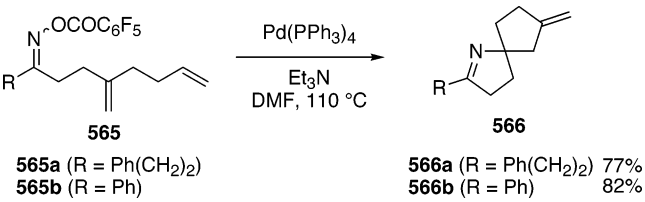
## 6.2. Carbon–Heteroatom Bond Formation

Catalytic synthesis of heterocyclic compounds via formation of carbon−heteroatom bond using aryl and vinyl halides can be classified into three groups, that is, (a) the coupling reaction with a heteroatom, (b) the amino-Heck reaction, (c) the insertion of alkenes and alkynes into aryl and vinyl halides and subsequent coupling with Y−H, and (d) Sonogashira coupling of the terminal alkynes followed by cyclization (Scheme 164).

**Scheme 172**



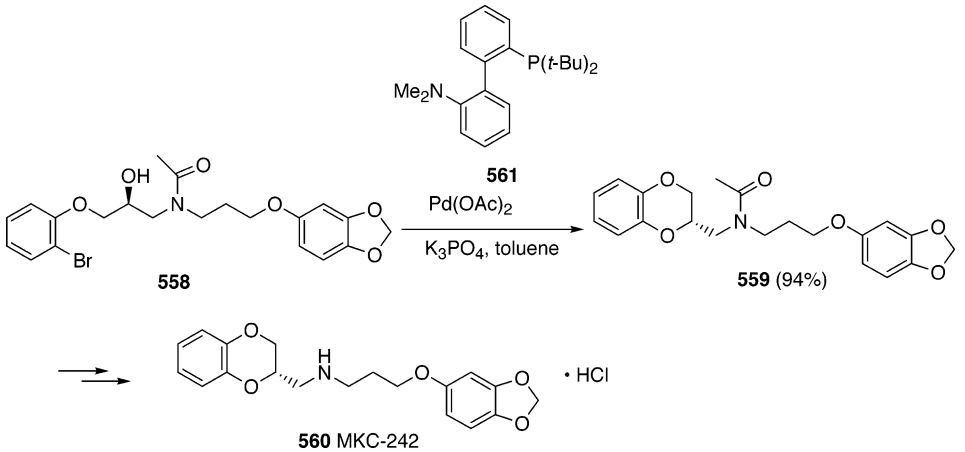

**Scheme 173**



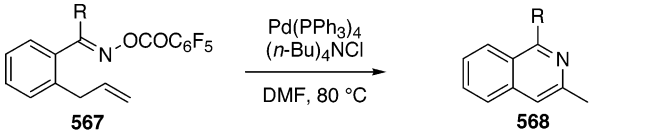

### *6.2.1. Intramolecular Coupling Reaction with a Heteroatom*

Recently, Buchwald and Hartwig have developed the palladium-catalyzed coupling reaction of aryl halides with amines (Scheme 165), and they have extended this reaction to the intramolecular version to give a variety of the aza-heterocyclic compounds **547** (Scheme 166).[231] This methodology has provided a wide variety of alkaloids, such as indoles,[232] indazoles,[233] benzimidazoles,[234] benazepines,[235] phenazines,[236] carbapenems,[237] the mitomycin ring system,[238] α-carbolines,[239] and polyheterocycles.[240] Pharmacologically active natural products, such as (−)-asperlicin (**550**) (Scheme 167),[241] dehydrobufotenine (**553**) (Scheme 168),[242] and makaluvamine C

**Scheme 171**



**Scheme 174**



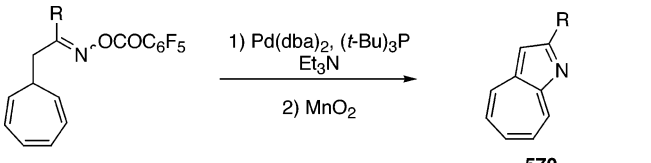

**567**

**567a** (R = Me)
**567b** (R = Et)
**567c** (R = Ph)

**568**

**568a** (R = Me) 77%
**568b** (R = Et) 63%
**568c** (R = Ph) 63%

**Scheme 175**



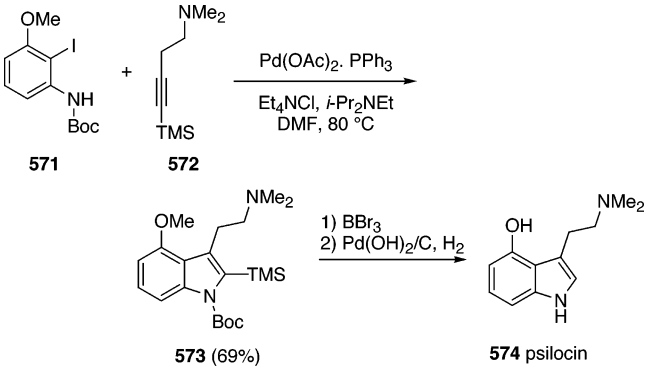

**569**

**569a** (R = Ph)
**569b** (R = *t*-Bu)
**569c** (R = *i*-Pr)

**570**

**570a** (R = Ph) 78%
**570b** (R = *t*-Bu) 84%
**570c** (R = *i*-Pr) 62%

**Scheme 176**

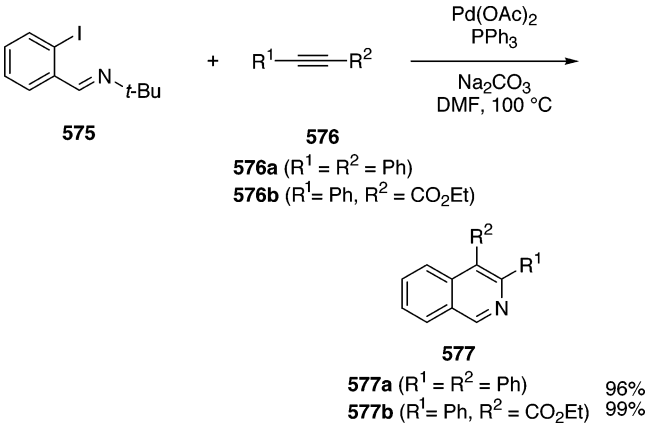



**571** **572**

**573** (69%)

**574** psilocin

**Scheme 177**




**575**

**576**

**576a** ($R^1 = R^2 = Ph$)
**576b** ($R^1$= Ph, $R^2 = CO_2Et$)

**577**

**577a** ($R^1 = R^2 = Ph$) 96%
**577b** ($R^1$= Ph, $R^2 = CO_2Et$) 99%

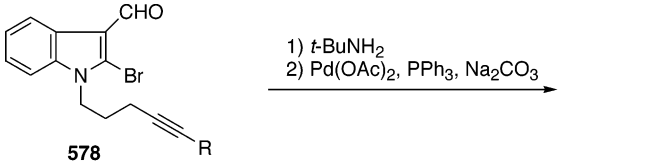
(**556**) (Scheme 169),[242] have been synthesized by the palladium-catalyzed aminocyclization of aryl and vinyl iodides.

Buchwald et al. demonstrated that the intramolecular palladium-catalyzed C−O bond formation was an attractive means to assemble the oxygen heterocycles **557** (Scheme 170).[243] They applied this methodology to the synthesis of MKC-242 (**560**), a benzodioxane antidepressant (Scheme 171).[243b]

### *6.2.2. Amino-Heck Reaction*

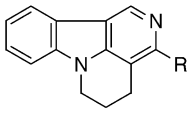
The amino-Heck reaction, which proceeded through N−O bond cleavage of oxime derivatives, has been

**Scheme 178**




**578**

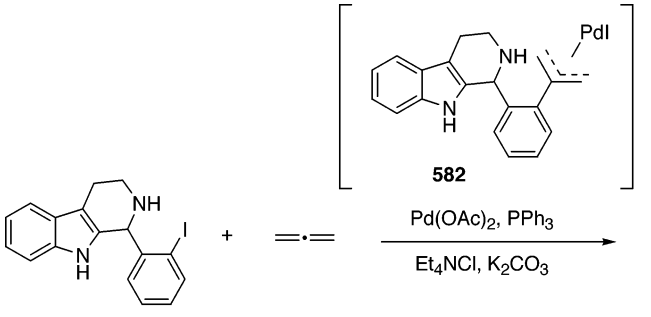
**578a** (R = Ph)
**578b** (R = *n*-Hex)




**579**

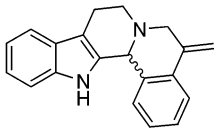
**579a** (R = Ph), 93%
**579b** (R = *n*-Hex), 95%

**Scheme 179**



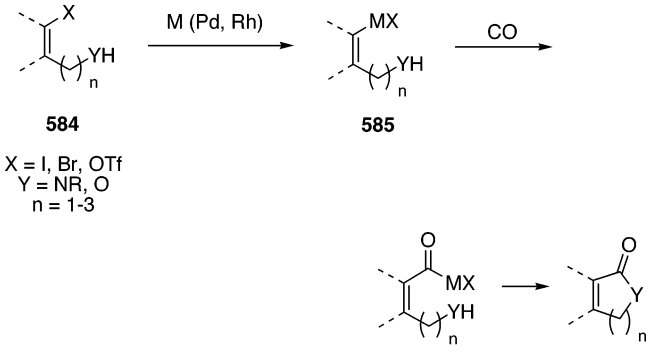

**582**

**580**




**581** (90%)

**Scheme 180**




**584**

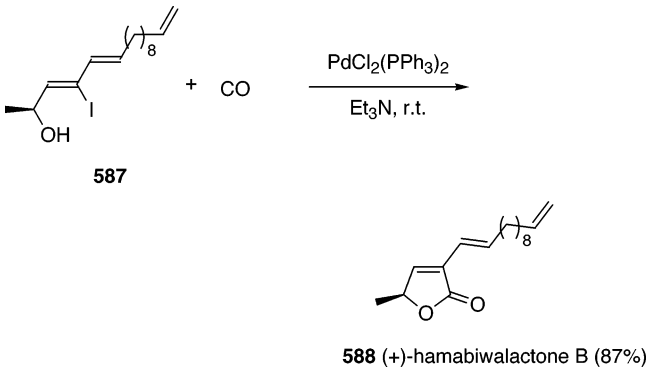
X = I, Br, OTf
Y = NR, O
n = 1-3

**585**

**586**

reported by Narasaka et al.[244−248] Various kinds of nitrogen heterocycles, such as pyrroles, pyridines, isoquinolines, spiroimines, and azaazulenes, were synthesized by this methodology. In the presence of $Pd(PPh_3)_4$ and $Et_3N$, the reaction of the $\gamma,\delta$-unsaturated ketone *O*-pentafluorobenzoyloximes **562** gave the corresponding pyrroles **563** in good to high yields (Scheme 172).[244] On the contrary, in the presence of catalytic amounts of CuBr, the reaction of **562a** with LiBr produced the dehydropyrrole **564a** (Scheme 172).[245] The reaction of the dienyl ketone oximes **565** proceeded through a cascade cyclization to give the spiro imines **566** (Scheme 173).[246] The palladium-

**Scheme 181**




catalyzed amino-Heck reaction of the *o*-allylphenyl ketone oximes **567** gave the isoquinoline derivatives **568** (Scheme 174).[247] The palladium-catalyzed amino-Heck reaction of the oximes **569** and successive treatment with $MnO_2$ afforded the 1-azaazulenes **570** in good yields (Scheme 175).[248]

### *6.2.3. Insertion of C–C Unsaturated Bonds—Coupling with Heteroatoms*

Alkynes and allenes are used as a carbon−carbon unsaturated compounds (see Scheme 164, route c).[249] Gathergood and Scammells applied this methodology to the synthesis of psilocin **574** (Scheme 176).[250]

Larock et al. reported that, in the presence of Pd-$(OAc)_2$ catalyst, the reaction of the *tert*-butyl imine of *o*-iodobenzaldehyde **575** with the alkynes **576** gave the isoquinolines **577** in good to high yields (Scheme 177).[251,252] This type of reaction was applied to the synthesis of the annulated $\gamma$-carbolines **579** (Scheme 178).[251e] This type of reaction is reviewed in a detailed way in this issue of *Chemical Reviews*.

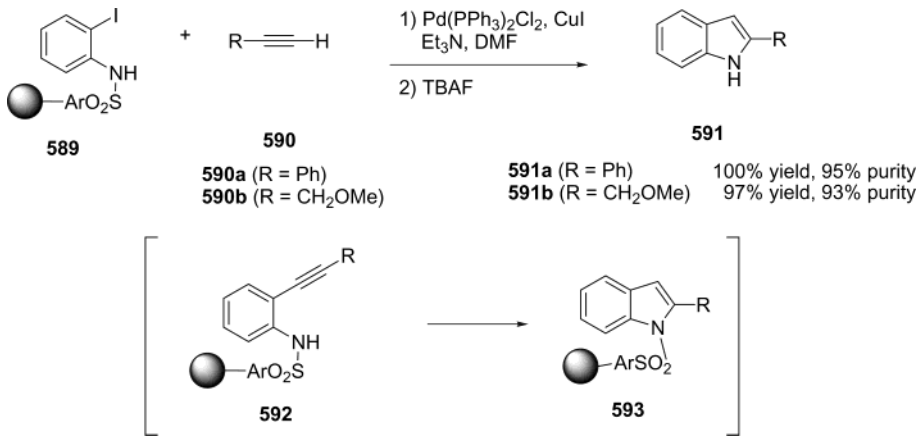
Grigg et al. reported that the palladium-catalyzed cyclization of **580** with allene gave the polycyclic heterocycle **581** in a high yield (Scheme 179).[253]

Carbon monoxide, instead of alkynes and allenes, also participates in the insertion into the C−M bond of **585**, leading to the framework of lactones and lactams **586** (Scheme 180).[254] Liao and Negishi synthesized (+)-hamabiwalactone B (**588**) from **587** (Scheme 181).[255]

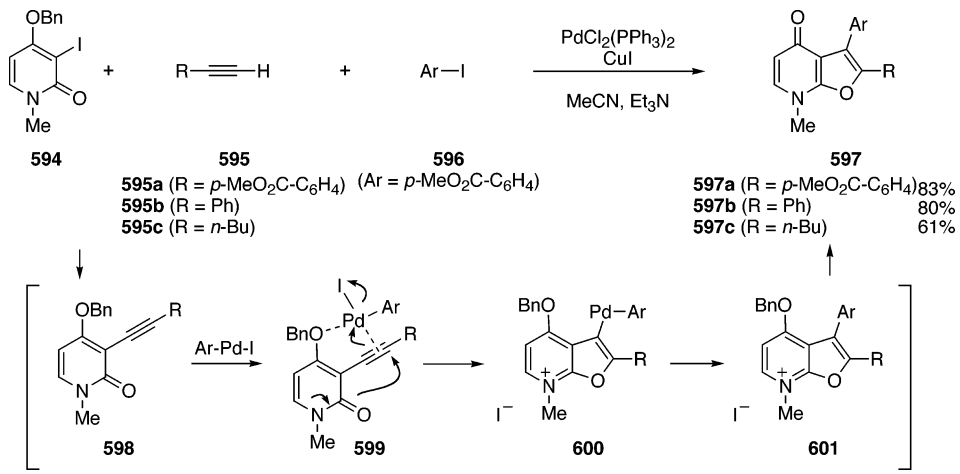
### *6.2.4. Sonogashira Coupling of Terminal Alkynes Followed by Cyclization*

Zhang et al. reported that the palladium-catalyzed coupling/indole cyclization of the terminal alkynes **590** with the resin-bound *o*-iodoaniline **589** and subsequent treatment with TBAF gave the indole derivatives **591** in high yields and with high purities (Scheme 182).[256a] The reaction proceeds through

**Scheme 182**




**Scheme 183**



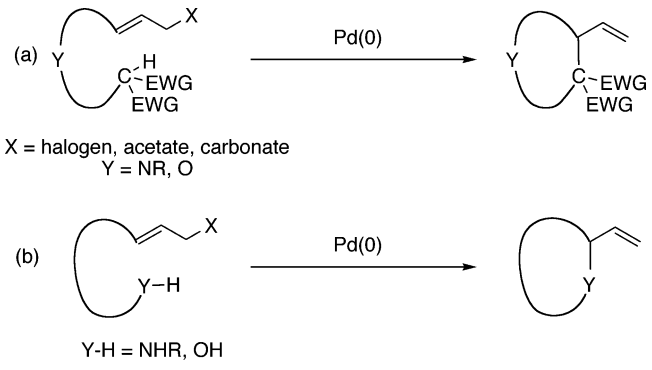
Sonogashira coupling and the subsequent cyclization of the resulting o-alkynylanline **592**, to give the indole **593**.

The one-pot assembly of 4-alkoxy-3-iodo-2-pyridones **594**, terminal alkynes **595**, and organic halides **596** afforded furo[2,3-*b*]pyridones **597** (Scheme 183).[257] For example, the reaction of 4-benzyloxy-3-iodo-2-pyridone **594** with terminal alkynes **595** and methyl *p*-iodobenzoate **596** in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI gave the corresponding furopyridines **597** in good to high yields. This reaction proceeds through Sonogashira coupling of **594** and **595**, coordination of Ar−Pd−X species to the resulting 3-alkynylpyridone **598**, heterocyclization of **599**, reductive elimination of Pd(0) from the furopyridinium intermediate **600**, and deprotection of the alkoxyl group of **601**.

## *7. Intramolecular Reaction of Allyl Halides: Tsuji–Trost-Type Reaction*

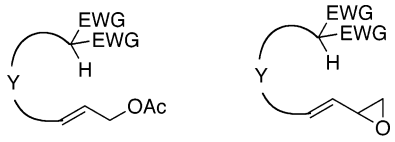
Allylation reaction using $\pi$-allylpalladium is one of the most powerful tools for constructing new chemical bonds in organic synthesis.[258] In general, $\pi$-allylpalladium species are generated by oxidative addition of allylic compounds, such as allylic halides, acetates, and carbonates, to palladium(0) catalysts. The palladium-catalyzed reaction of 1,3-dienes, allenes, methylenecyclopropanes, 1,3-enynes, and alkynes has been investigated for many years and it is revealed that the reaction of these unsaturated compounds proceeds often through formation of a $\pi$-allylpalladium intermediate, as mentioned in section 4. $\pi$-Allylpalladium complexes ($\pi$-allyl−Pd−X, X = halogen, OAc, OMe) react with nucleophiles, while bis-$\pi$-allylpalladium ($\pi$-allyl−Pd−$\pi$-allyl) reacts with electrophiles.[259] The intramolecular allylation reaction has been widely investigated and established as a useful methodology for the synthesis of carbo- and heterocyclic compounds.[260] There are two pathways to synthesize heterocycles via the palladium-catalyzed allylation: (a) intramolecular allylation of a carbon nucleophile that has one or more heteroatoms in a linkage moiety and (b) intramolecular allylation of nitrogen and oxygen nucleophiles (Scheme 184).

**Scheme 184. Intramolecular Allylation via (a) Carbon−Carbon Bond Formation, and (b) Carbon−Heteroatom Bond Formation**




### 7.1. Carbon–Carbon Bond Formation

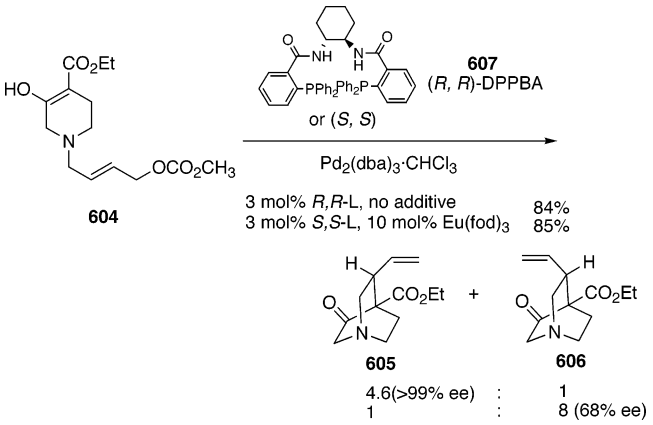
The substrates bearing both an active methyne or methylene group and an allylic moiety, such as allyl acetate **602** and alkenyl epoxide **603**, readily undergo




EWG; ketone, ester, nitrile, sulfonyl.

the palladium-catalyzed intramolecular C−C bond formation to give the corresponding heterocycles.[261] Trost et al. reported that the palladium-catalyzed intramolecular asymmetric allylic alkylation of the allylic carbonate **604** produced a diasteroisomeric mixture of bicyclo[2.2.2]quinucidin-2-ones (**605** and **606**) in high yields, which were potential precursors to quinine alkaloids (Scheme 185).[262] By the use of

**Scheme 185**



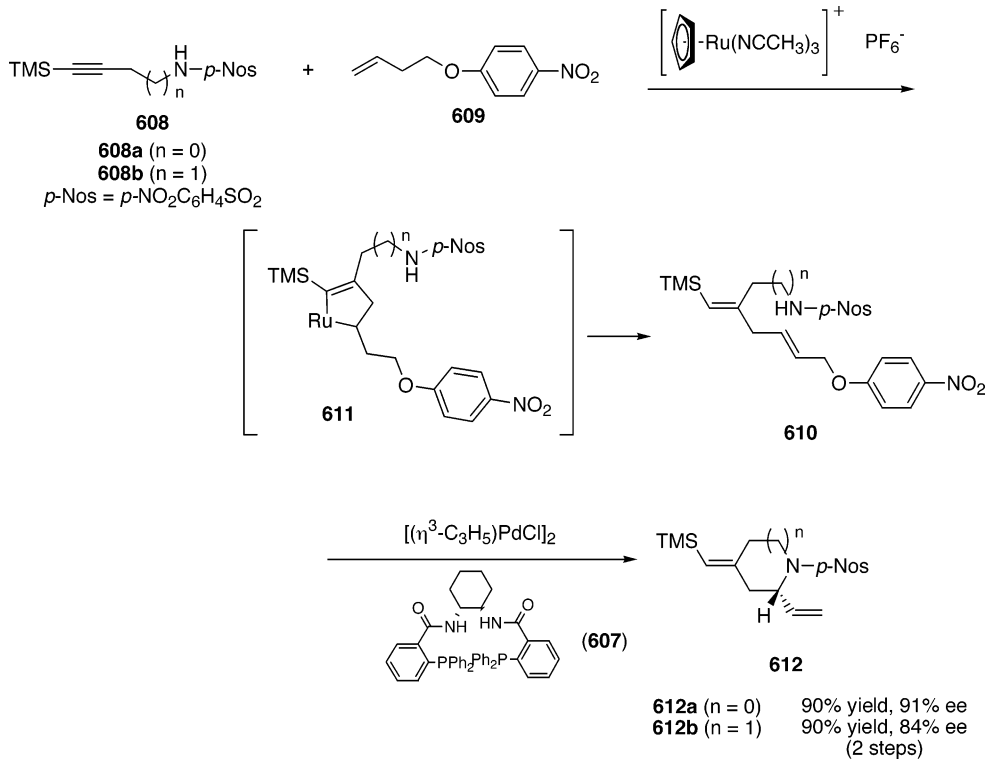

(*R*,*R*)-*N*-[2-(2′-diphenylphosphino)-benzaminocyclohexyl](2′-diphenylphosphino)benzamide (*R*,*R*-DPPBA, **607**) chiral ligand,[263] **605** was obtained as the major diastereomer with >99% ee, while **606** was produced as the major isomer with 68% ee by the combined use of *S*,*S*-DPPBA and 10 mol % of Eu(fod)$_3$.

### 7.2. Carbon–Heteroatom Bond Formation

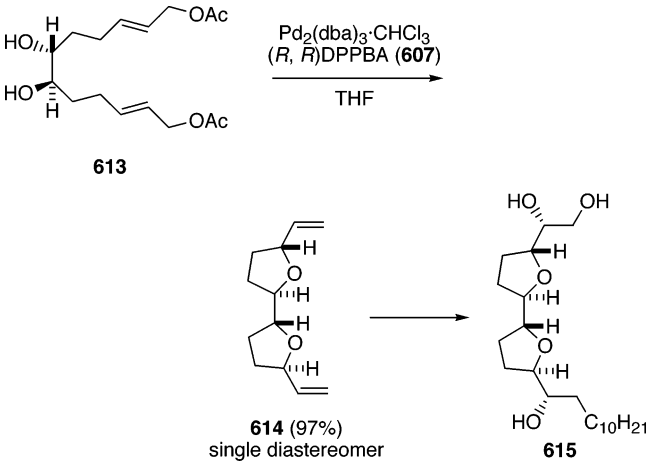
#### *7.2.1. Stereo- and Enantioselective Allylation*

The enantio- and diastereoselective synthesis of the nitrogen-containing heterocyclic compounds **612** was achieved by a one-pot reaction via the ruthenium-catalyzed enyne coupling of **608** with **609** followed by the palladium-catalyzed asymmetric C−N bond formation (Scheme 186).[264a] The enyne coupling reaction proceeds through formation of the ruthenacycle **611** followed by $\beta$-elimination−reductive elimination.

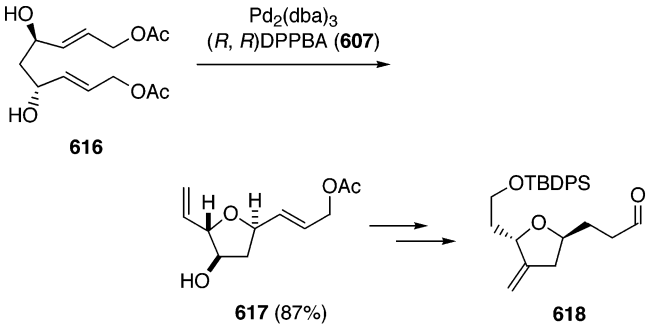
**Scheme 186**



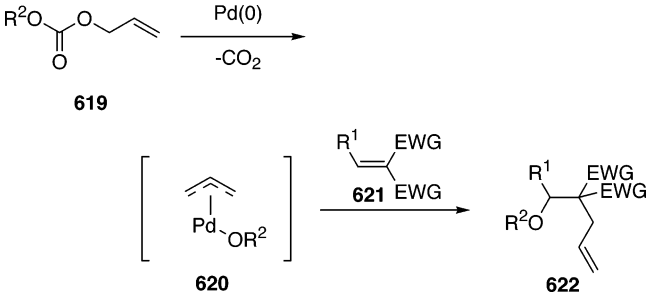

**Scheme 187**




**Scheme 188**




**Scheme 189**

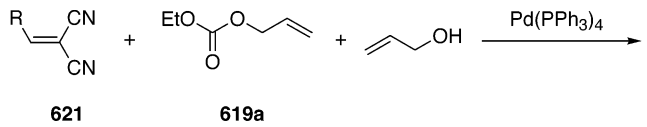



Burke and Jiang reported that the palladium-catalyzed diastereoselective double allylation of the diol bis(allylic acetate) **613** using (*R*,*R*)-DPPBA **607** afforded the bis-tetrahydrofuran core **614** in 97% yield (Scheme 187).[265] The resulting diene **614** was further transformed into a known intermediate **615** for the synthesis of uvaricin. They demonstrated that palladium(0)-catalyzed desymmetrization of the $C_2$ diol **616** with Trost's ligand **607** afforded the tetrahydrofuran **617** diastereoselectively (Scheme 188).[266] The product **617** was manipulated to the F ring of halichondrin B (**618**).

### *7.2.2. Intra- and Intermolecular Alkoxyallylation Reactions of Allyl Carbonates*

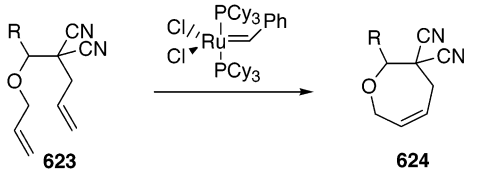
We found that the palladium-catalyzed alkoxyallylation reaction of allyl carbonates **619** with the activated olefins **621** led to $\gamma$-alkoxyalkenes **622**. This reaction proceeds through formation of alkoxy-$\pi$-allylpalladium species **620** (Scheme 189).[267] Xie and Hauske reported that highly functionalized seven-membered allyl ethers **624** were synthesized using palladium-catalyzed alkoxyallylation of activated olefins **621** with allyl ethyl carbonate **619a** and allyl alcohol and subsequent ring-closing olefin metathesis (Scheme 190).[268]

**Scheme 190**




**621** **619a**

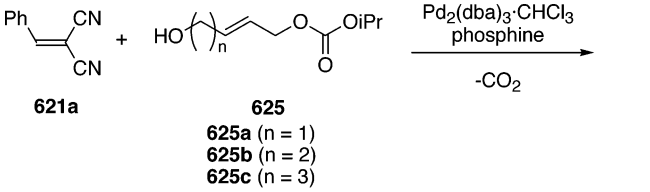
**621a** (R = Ph)
**621b** (R = *t*-Bu)




**623** **624**

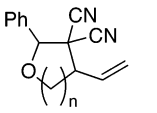
| | | | |
|---|---|---|---|
| **623a** (R = Ph) | 81% | **624a** (R = Ph) | 94% |
| **623b** (R = *t*-Bu) | 96% | **624b** (R = *t*-Bu) | 71% |

**Scheme 191**




**621a** **625**

**625a** (n = 1)
**625b** (n = 2)
**625c** (n = 3)




**626**

| | |
|---|---|
| **626a** (n = 1) | 92% |
| **626b** (n = 2) | 83% |
| **626c** (n = 3) | 31% |

The palladium-catalyzed cycloaddition of the activated olefin **621a** with allylic carbonates having a hydroxy group at the terminus of the carbon chain (**625**) gave the corresponding cyclic ethers **626** (Scheme 191).[269]

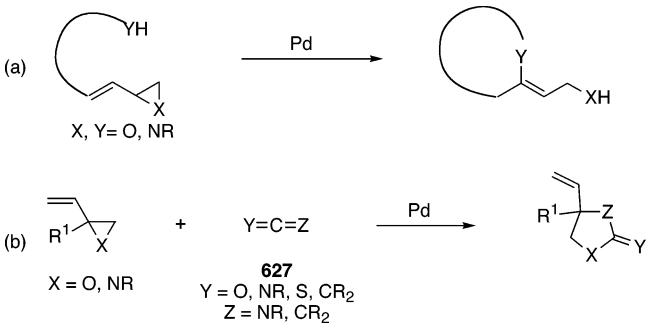
### *7.2.3. Intra- and Intermolecular Reactions of Alkenyl Epoxides, Aziridines, and Thiiranes*

The intra- and intermolecular carbon−heteroatom bond forming reactions using alkenyl epoxides and aziridines have been utilized for the synthesis of heterocyclic compounds.[261] There are two major processes for the preparation of heterocycles using these substrates, as illustrated in Scheme 192: (a) intramolecular allylation of alkenyl epoxides and aziridines with Y−H and (b) intermolecular cycloaddition of vinyl epoxides and aziridines with the heterocumulenes **627**, such as isocyanates, carbodiimides, and isothiocyanates.[270]

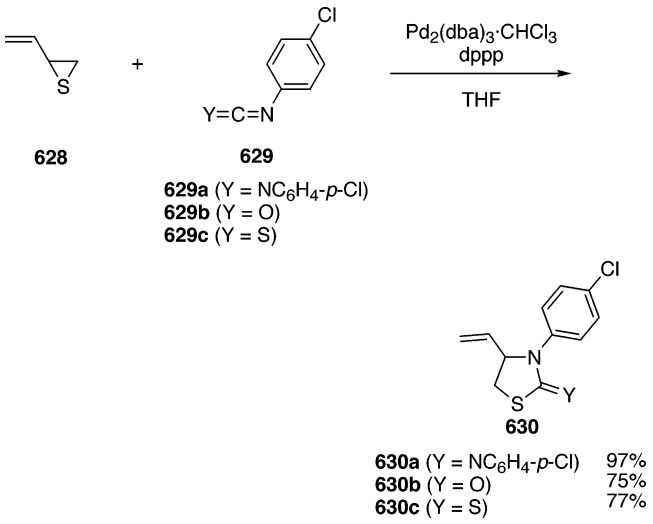
Larksarp et al. reported the regio- and enatioselective formation of the thiaolidine, oxathiolane, and dithiolane derivatives (**630**) by the palladium-catalyzed cyclization reaction of 2-vinylthiirane **628** with heterocumulenes **629** (Scheme 193).[271] The asymmetric reaction of 2-vinylthiirane **628** and carbodiimide **629a** was performed using (*S*)-tol-BINAP as a chiral phosphine ligand (Scheme 194).

We reported that the palladium-catalyzed [3 + 2]-cycloaddition of vinylic oxirane and aziridine **631** with the activated olefin **621a** produced the 2-vinyl tetrahydrofuran and pyrrolidine derivatives **632** in a regioselective manner (Scheme 195).[272] The palladium-catalyzed intermolecular reaction of imines **633** with vinyl oxirane **631a** gave the regioselective [3 + 2]-cycloaddition products 1,3-oxazolidine derivatives **634** in good to excellent yields (Scheme 196).[273]

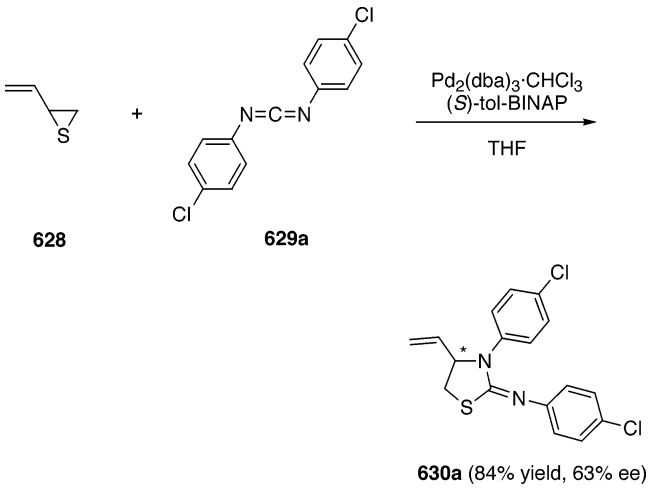
**Scheme 192. Reaction of Alkenyl Epoxides and Aziridines Producing Heterocycles via Carbon−Heteroatom Bond Formation by (a) Intramolecular Allylation of Oxygen and Nitrogen Nucleophiles and (b) Intermolecular [3 + 2]-Cycloaddition with Heterocumulenes**



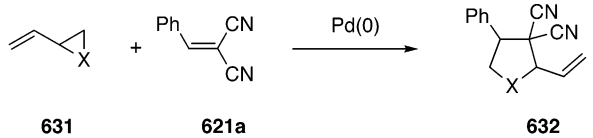

**Scheme 193**




**Scheme 194**



**Scheme 195**

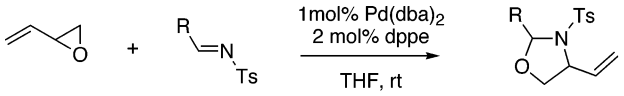


**631** **621a** **632**

**631a** (X = O)
**631b** (X = NTs)

**632a** (X = O) 90%
**632b** (X = NTs) >99%

**Scheme 196**

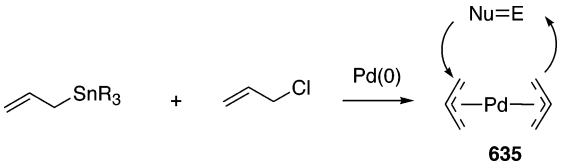


**631a** **633** **634**

**633a** (R = Ph)
**633b** (R = *t*-Bu)

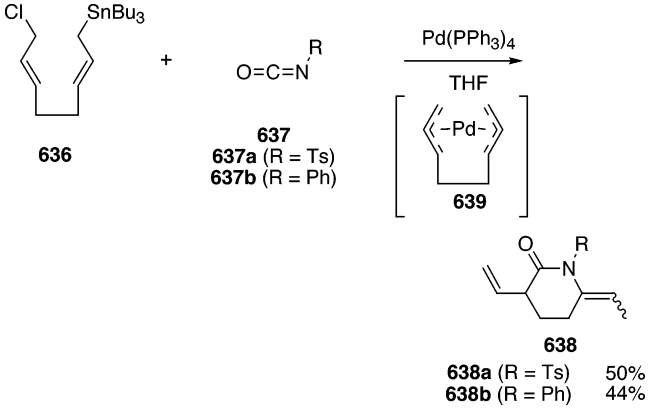
**634a** (R = Ph) 97%
**634b** (R = *t*-Bu) 82%

**Scheme 197**



**635**

**Scheme 198**

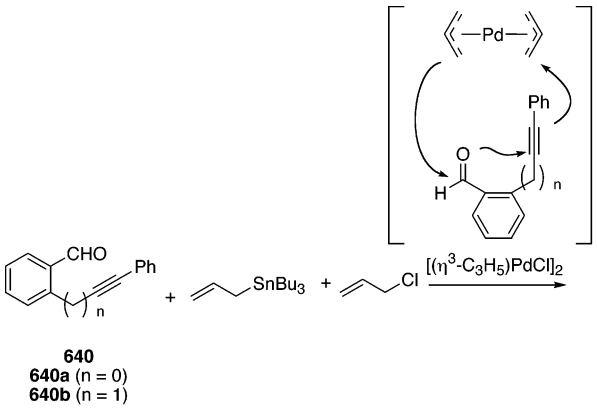


**636** **637** **639** **638**

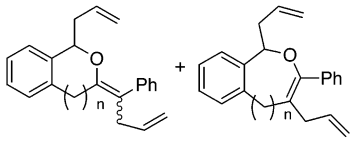
**637a** (R = Ts)
**637b** (R = Ph)

**638a** (R = Ts) 50%
**638b** (R = Ph) 44%

**Scheme 199**



**640**
**640a** (n = 0)
**640b** (n = 1)

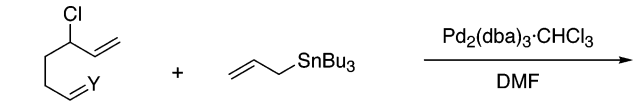


**641** (*exo*) **642** (*endo*)

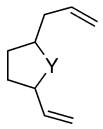
**641a** (n = 0) 86%
**641b** (n = 1) 90%

**642a** (n = 0) 10%

**Scheme 200**



**643**
**643a** (Y = O)
**643b** (Y= NBn)

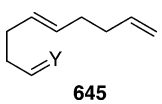


**644**

**644a** (Y = O) 64%
**644b** (Y =NBn) 67%

### *7.2.4. Amphiphilic Allylation via Bis-π-allylpalladium, and the Reaction through π-Allylpalladium Azide*

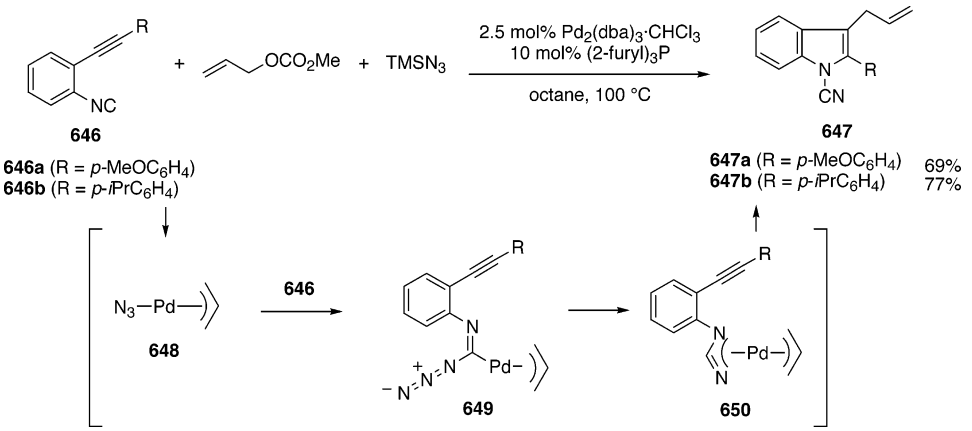
We found that bis-π-allylpalladium complex **635**, which was catalytically generated from allylic stannanes and allyl chloride with palladium(0), acted as an amphiphilic allylating agent and reacted with certain carbon−carbon and carbon−heteroatom multiple bonds in an amphiphilic manner, as shown in Scheme 197.[274] We applied the catalytic amphiphilic bis-allylation to the intramolecular reaction for synthesizing heterocyclic compounds. The reaction of the allyl stannane-allyl chloride **636** with the isocyanates **637** in the presence of a palladium catalyst produced the divinylpiperidones **638** (Scheme 198).[275] The reaction proceeds through the bis-π-allylpalladium intermediate **639**. The tandem nucleophilic allylation−alkoxyallylation of the alkynylaldehydes **640** with allyltributylstannane and allyl chloride provided the corresponding five- and six-membered cyclic ethers **641** and **642** (Scheme 199);[276] in the case of $n = 0$, a mixture of **641a** and **642a** was obtained, while only **641b** was produced in the case of $n = 1$. The reaction leading to **641** proceeds through the allylation of the aldehyde, the nucleophilic attack of an oxygen on the electron-deficient alkyne, and reductive elimination. The reaction of the allylic chlorides **643** having an aldehyde or an imine moiety in the molecule with allyltributylstannane proceeded in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ in DMF, giving the corresponding heterocycles **644** in good yields (Scheme 200).[277] In this reaction, the Stille coupling product **645** was not obtained.



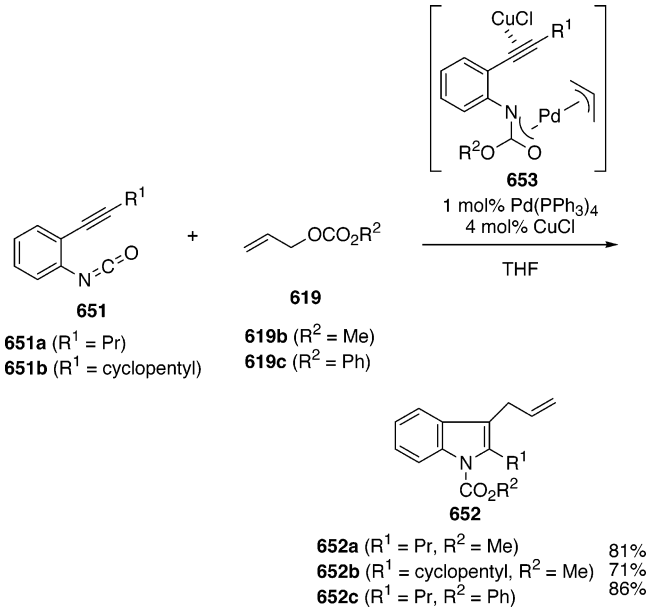
**645**

The bis-allylation reaction has been extended to the reaction of heteroatom-containing bis-π-allylpalladium analogues. We demonstrated that the palladium-catalyzed three-component coupling reaction of the 2-alkynylisocyanobenzenes **646**, allyl methyl carbonate, and trimethylsilyl azide gave the *N*-cyanoindoles **647** in good yields (Scheme 201).[278] This

**Scheme 201**

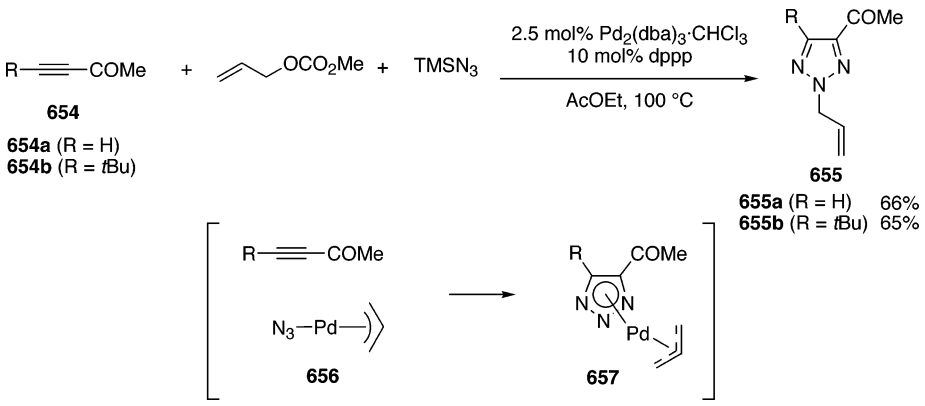



**Scheme 202**

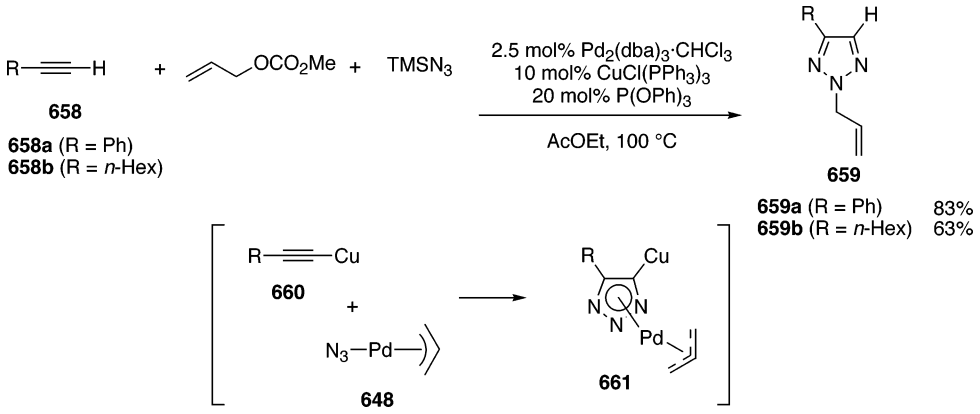



reaction proceeds through formation of $\pi$-allylpalladium azide **648**, and subsequent insertion of the divalent carbon of the isocyanide **646** into the N−Pd bond of **648** gives the $\pi$-allylpalladium intermediate **649**. Elimination of $N_2$ from **649** leads to the bis-$\pi$-allylpalladium analogue ($\eta^3$-allyl)($\eta^3$-cyanamido)palladium complex **650**. Insertion of the alkyne moiety into the N−Pd bond and subsequent reductive elimination give **647**. The coupling of (2-alkynyl)phenylisocyanides **651** with the allyl carbonates **619** proceeded in the presence of a palladium−copper bimetallic catalyst system to afford the 3-allylindoles **652** in good to high yields (Scheme 202).[279] The formation of the bis-$\pi$-allylpalladium analogue **653** and activation of the triple bond by coordination of Cu(I) are key to this reaction. The palladium-catalyzed three-component coupling reaction of alkynes **654**, allyl methyl carbonate, and trimethylsilyl azide gave the 2-allyl-1,2,3-tetrazoles **655** (Scheme 203).[280] The reaction proceeds via the [3 + 2]-cycloaddition of $\pi$-allylpalladium azide to the alkyne, followed by the formation of ($\eta^3$-allyl)($\eta^5$-triazoyl)palladium **657**. Synthesis of the triazoles **659** from the nonactivated terminal alkynes **658** was achieved by the three-component coupling reaction with allyl methyl carbonate and trimethylsilyl azide using a Pd(0)−Cu(I) bimetallic catalysts (Scheme 204).[281] In the absence of Cu(I), the desired product was not afforded at all. The reaction proceeds through [3 + 2]-cycloaddition between an alkyne of the copper acetylide **660**, in which copper acts as an activating group of the alkyne, and the azide palladium complex **648** to form the ($\eta^3$-allyl)($\eta^5$-triazoyl)palladium intermediate **661**. Subsequent reductive elimination of Pd(0) from **661** and protonolysis of the C−Cu bond give **659**. The selective synthesis of the 2-allyltetrazoles **663** by the three-component coupling reaction of the cyano com-

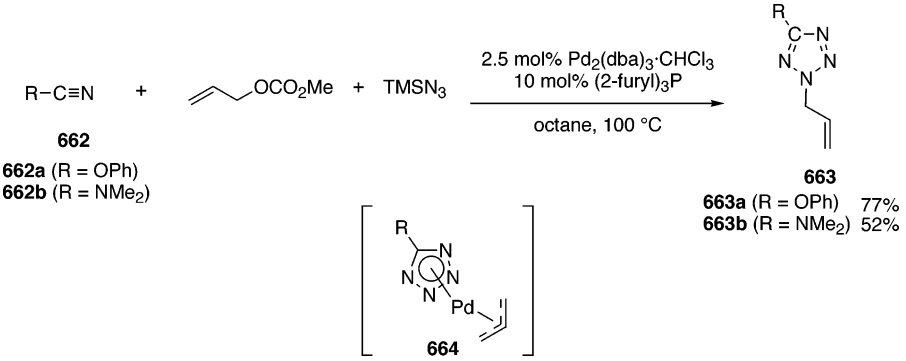
**Scheme 203**



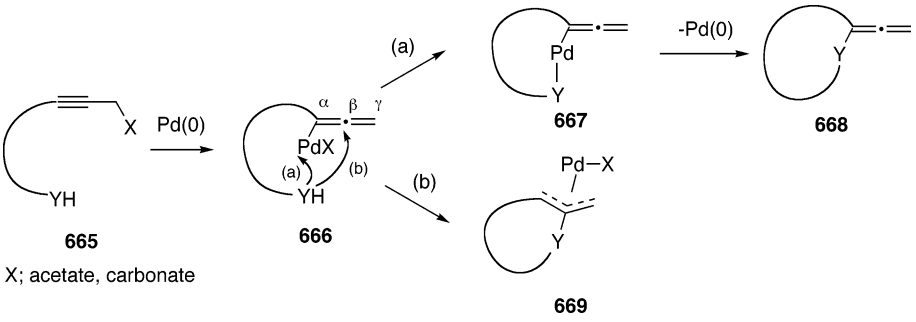
**Scheme 204**




**Scheme 205**




**Scheme 206. Intramolecular Reaction of Propargylic Derivatives via Carbon−Heteroatom Bond Formation at either (a) the α-Position or at (b) the *β*-Position**

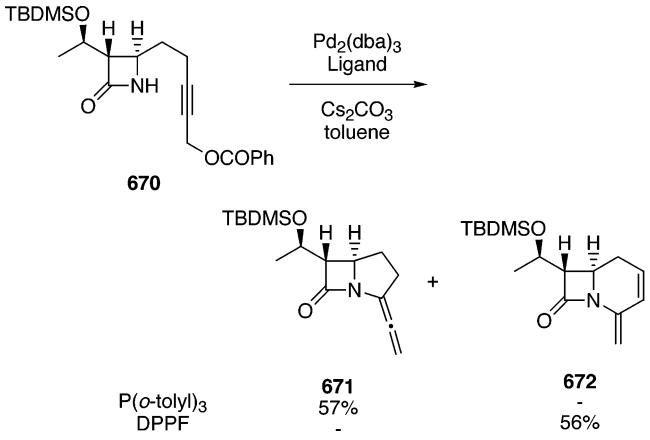



pounds **662**, allyl methyl carbonate, and trimethylsilyl azide was accomplished in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ and P(2-furyl)$_3$ (Scheme 205).[282] Similarly, the reaction proceeds through the [3 + 2]-dipolar cycloaddition of $\pi$-allylpalladium azide to the nitrile and the formation of ($\eta^3$-allyl)($\eta^5$-tetrazoyl)-palladium complex **664**.

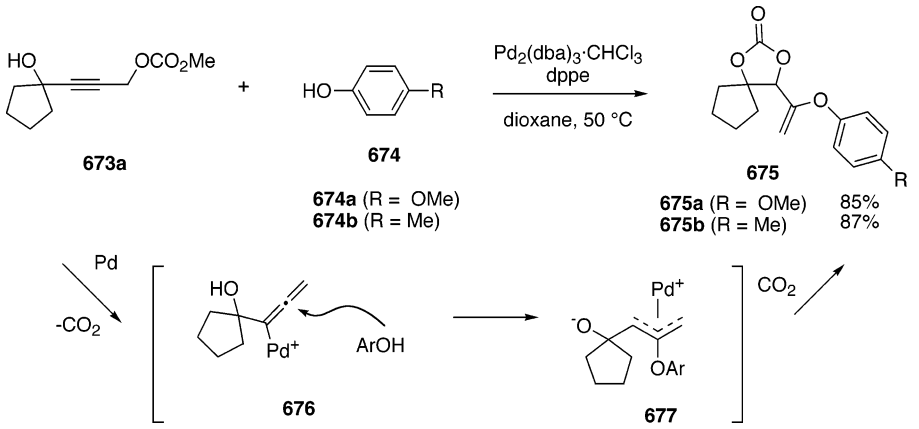
### *7.2.5. Intra- and Intermolecular Reaction of Propargyl Esters*

The reactivity of allenylpalladium species, derived from oxidative addition of propargyl alcohol derivatives to palladium(0), has attracted considerable attention in organic synthesis.[283] Recently, the intramolecular reaction of the propargylic derivatives **665** with an oxygen and nitrogen nucleophile has been widely utilized for the synthesis of heterocyclic compounds. The key step of formation of a heterocyclic ring is intramolecular nucleophilic attack of a heteroatom on allenylpalladium species, as shown in **666** (Scheme 206). When the heteroatom attacks the palladium atom (route a), carbon−heteroatom bond formation occurs at the α-position and the hetero-

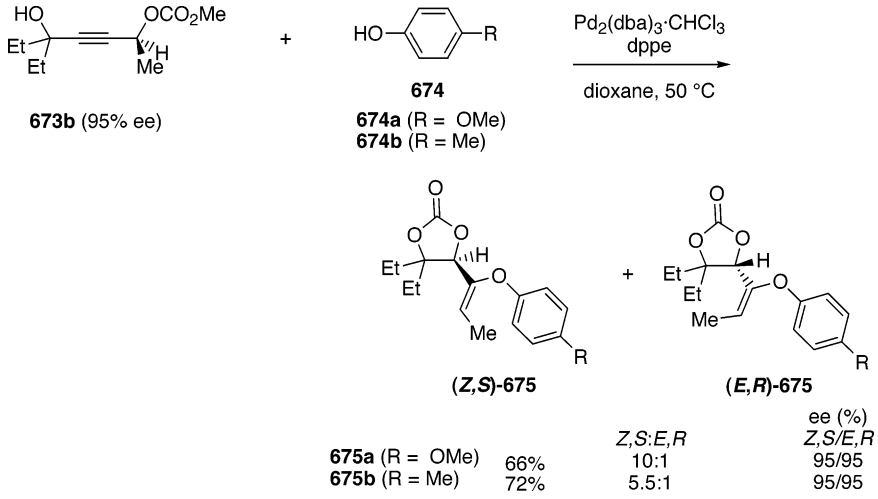
**Scheme 207**



**Scheme 208**




**Scheme 209**

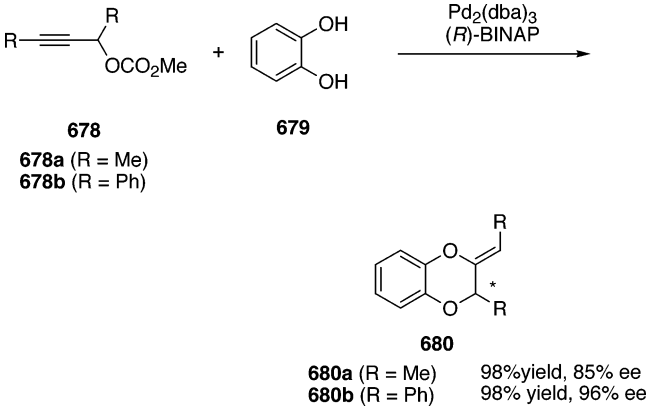



cycles **668** having a vinylidene moiety are obtained. On the other hand, when the heteroatom attacks the $\beta$-carbon of the allenyl moiety (route b), the allylpalladium species **669** are formed.

Kozawa and Mori reported the synthesis of different ring size heterocycles from the same propargyl ester **670** by a ligand effect on Pd(0) (Scheme 207).[284] When the reaction was carried out using P(o-tolyl)$_3$ as a ligand, the carbapenam **671** was obtained in 57% yield, while the reaction of **670** using DPPF gave the carbacepham **672** in 56% yield.

A novel synthetic method for the cyclic carbonates **675** was reported by Ihara et al. (Scheme 208).[285] The reaction of the 4-methoxycarbonyloxy-2-butyn-1-ol **673a** with phenols **674** in the presence of $Pd_2(dba)_3$·$CHCl_3$ and dppe gave **675** in good yields. The allenylpalladium **676** is attacked by ArOH **674** to produce the $\pi$-allylpalladium complex **677**, which undergoes insertion of $CO_2$ to give **675**. Accordingly, recyclable use of a $CO_2$ molecule is possible in this reaction. When the chiral starting material **673b** was used, a cascade chirality transfer occurred, and the chiral cyclic carbonates (*Z*,*S*)-**675** were obtained as a major product with high stereo- and enantioselectivity (Scheme 209).

**Scheme 210**

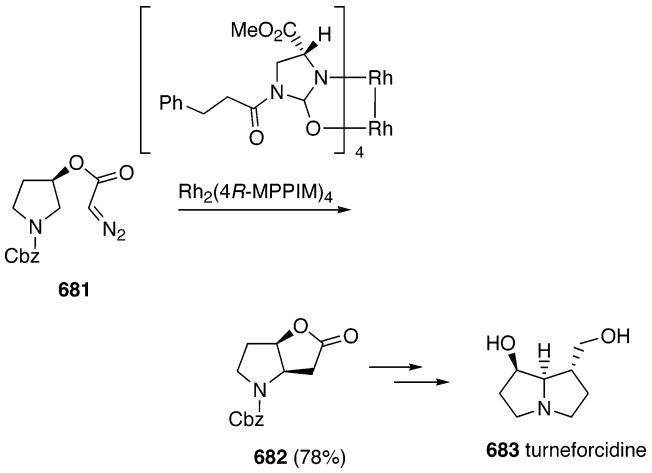



Sinou et al. reported that the palladium-catalyzed condensation of catechol **679** with various propargylic carbonates **678** gave the 2,3-dihydro-2-ylidene-1,4-benzodioxins **680**.[286] The reaction using (*R*)-BINAP as a chiral ligand gave the products **680** in high yields with high ee values (Scheme 210).

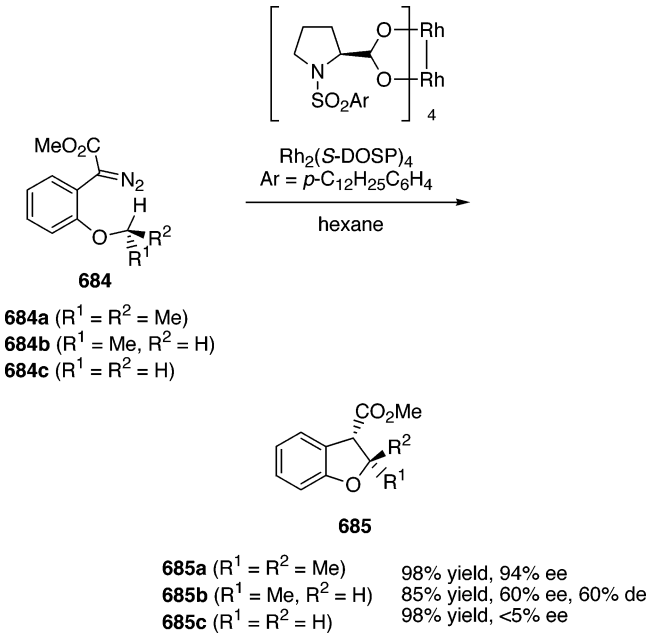
## *8. Intra- and Intermolecular Reaction of Diazo Compounds and Iminoiodinanes*

The development of catalytic metal carbene transformations for the construction of heterocycles has dramatically increased due to their synthetic advan-

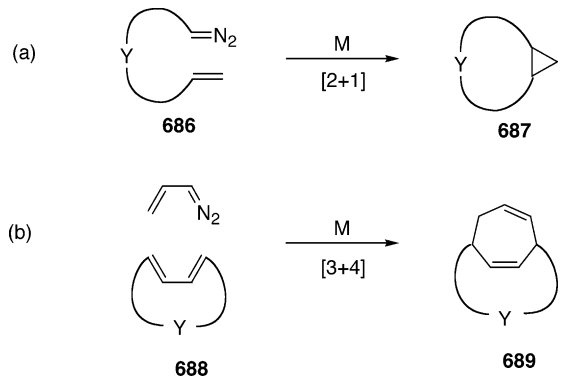
**Scheme 211**



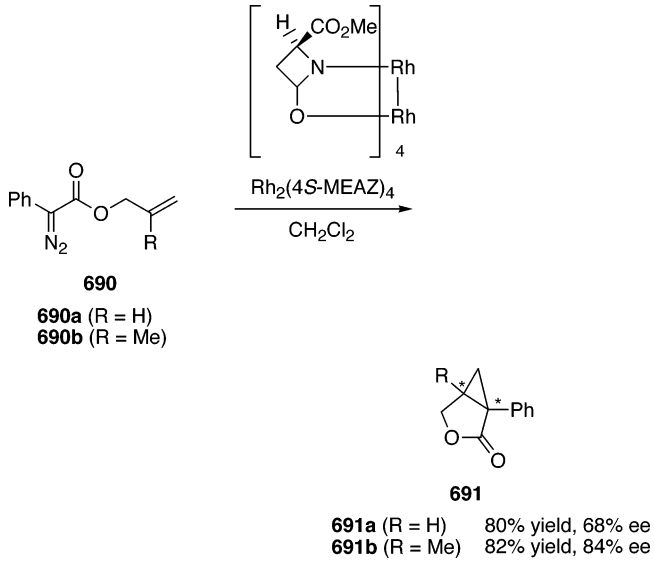

**Scheme 212**




**Scheme 213. Cycloaddition of Diazo Compounds with Carbon−Carbon Unsaturated Compounds via (a) [2 + 1]-Cycloaddition and (b) [3 + 4]-Cycloaddition**




**Scheme 214**




tages.[287] A typical example for this type of reactions is the RCM (ring-closing metathesis) of 1,$\omega$-dienes, as shown in section 2. Another important reaction through metal carbene complexes is mentioned in this section. A wide variety of transition-metal complexes, such as rhodium, palladium, copper, cobalt, platinum, ruthenium, osmium, rhenium, iron, tungsten, and chromium, are used as a catalyst of the reaction of diazo compounds.

## 8.1. Carbon–Carbon Bond Formation

### *8.1.1. Intramolecular Reaction of Diazo Compounds with a C–H Bond*

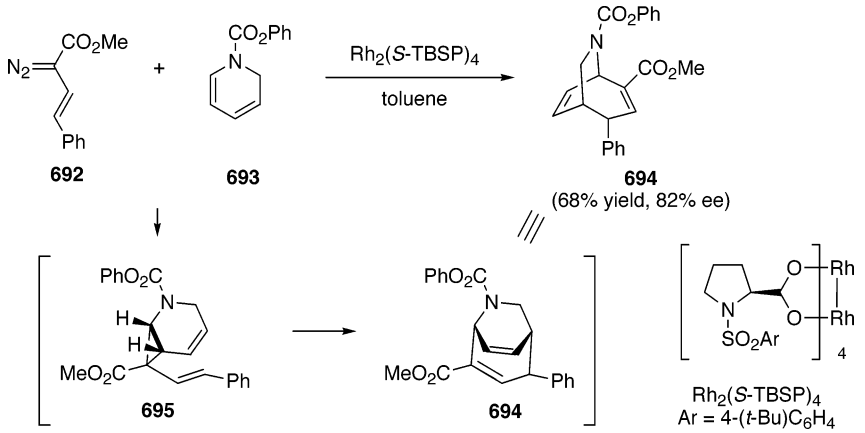
Transition-metal-catalyzed reaction of a diazo compound with a C−H bond, which is located at an appropriate position in the diazo molecule, gives a C−H insertion product. The intramolecular reaction of diazo compounds which have one or more heteroatoms between a diazo group and a reactive C−H bond produces a new C−C bond through C−H insertion, leading to heterocycles (Scheme 2).[288] The rhodium-catalyzed reaction of the diazo ester **681** in the presence of $Rh_2(4R\text{-MPPIM})_4$ complex gave the corresponding nitrogen heterocycle **682** in 78% yield with high *cis*-diastereoselectivity; **682** was converted to turneforcidine **683** through the conventional procedures (Scheme 211).[289]

Development of chiral transition-metal catalysts enables one to perform the catalytic C−H insertion to metal carbenoids, generated from diazo compounds, in an enantioselective manner. Davies et al. reported that the asymmetric intramolecular reaction of the aryldiazoacetates **684** in the presence of $Rh_2(S\text{-DOSP})_4$ gave the C−H insertion products **685** (Scheme 212).[288b] The enantioselectivity is strongly dependent on the site of the C−H activation; the highest enantioselectivity was obtained for insertion into the methyne C−H bond.

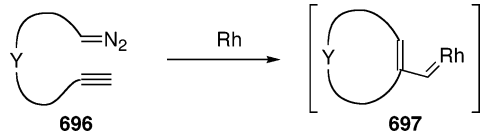
### *8.1.2. Intramolecular Reaction of Diazo Compounds with C–C Unsaturated Compounds*

The transition-metal-catalyzed reaction of diazo compounds with olefins gives the [2 + 1]-cycloaddi-

**Scheme 215**




**Scheme 216. Intramolecular Reaction of Diazo Compounds Bearing an Alkynyl Group**



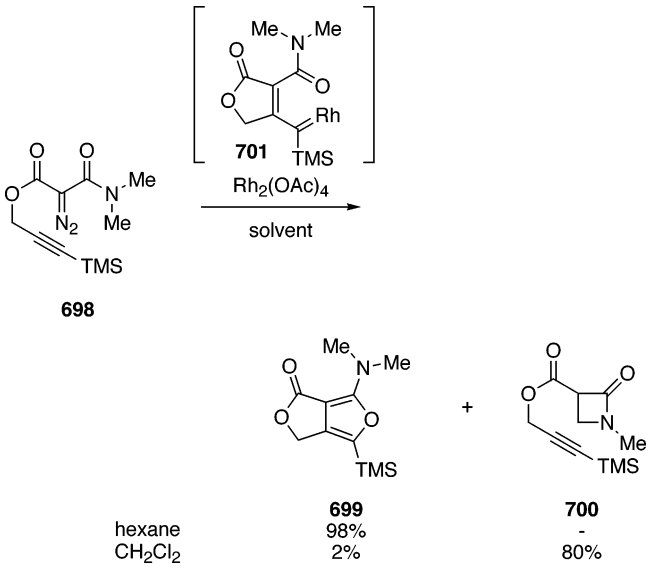

tion products, cyclopropanes. Cyclopropane-fused heterocyclic compounds **687** are obtained from the reaction of substrates **686** having a heteroatom between the diazo and alkenyl group (Scheme 213, route a).[290] The [3 + 4]-cycloaddition reaction of vinyl diazo compounds and 1,3-dienes **688** affords the bicyclic heterocycles **689** in good to high yields (Scheme 213, route b).[291]

Doyle et al. reported that the intramolecular cyclopropanation of the phenyldiazoacetate **690** in the presence of the chiral 2-oxaazetidine-4-carboxylate-ligated dirhodium(II) catalyst $Rh_2$(4*S*-MEAZ)$_4$ provided the bicyclic lactones **691** in high yields with high enantioselectivities (Scheme 214).[290d]

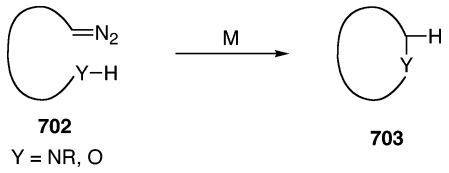
Davies et al. reported that the rhodium carboxylate-catalyzed [3 + 2]-cycloaddition of the vinyldiazoacetate **692** with the 1,2-dihydropyridine **693** gave the 6-azabicyclo[3.2.2] nonadiene **694** in good yield with high ee (Scheme 215).[291d] The reaction proceeds through cyclopropanation and subsequent Cope rearrangement from **695** to **694**.

The intramolecular reaction of diazo compounds **696** bearing an alkynyl group proceeds via the vinyl carbene intermediate **697**, which undergoes further transformations, such as C−H insertion, cyclopropanation, ylide formation, and [3 + 2]-cycloaddition (Scheme 216).[292] Padwa and Straub reported the rhodium-catalyzed reaction of the diazocarbonyl compound bearing an alkyne group **698**.[292e] The reaction of **698** in the presence of $Rh_2(OAc)_4$ in hexane gave the furan **699** in 98% yield, while the reaction of **698** using $CH_2Cl_2$ as a solvent produced the azetidinone **700** (Scheme 217). The reaction producing **699** proceeds through the rhodium vinyl carbenoid **701**, and subsequent 6-$\pi$ cyclization gives **699**. The azetidinone

**Scheme 217**




**Scheme 218. Intramolecular Reaction of Diazo Compounds Bearing a Heteroatom−Hydrogen Bond**



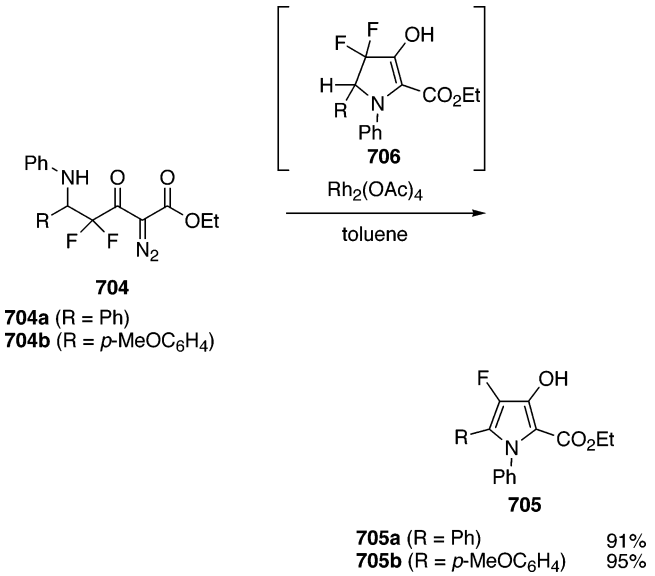

**700** is afforded by the C−H insertion into a methyl group of **698**.

## 8.2. Carbon–Heteroatom Bond Formation

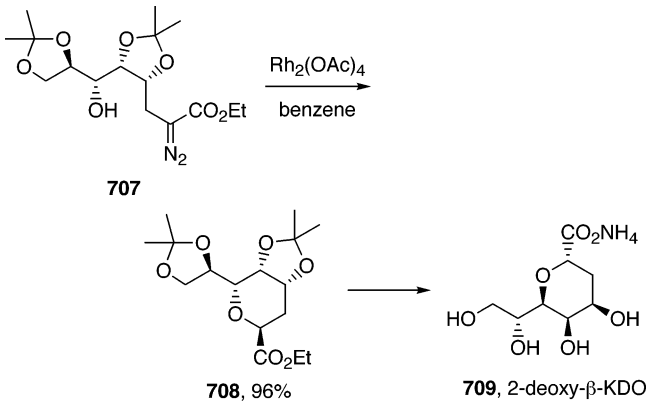
### *8.2.1. Intramolecular Reaction of Diazo Compounds with a N–H or O–H Bond*

The transition-metal-catalyzed reaction of diazo compounds **702**, which have a N−H or O−H bond at an appropriate position, gives nitrogen- and oxygen-containing heterocycles **703** (Scheme 218).[293] Wang and Zhu demonstrated a convenient synthesis of the polyfunctionalized $\beta$-fluoropyrroles by the rhodium-catalyzed intramolecular N−H insertion reaction.[293a] The reaction of $\delta$-amino-$\gamma$,$\gamma$-difluoro-$\alpha$-diazo-$\beta$-keto esters **704** in the presence of $Rh_2(OAc)_4$ gave the

**Scheme 219**




**Scheme 220**

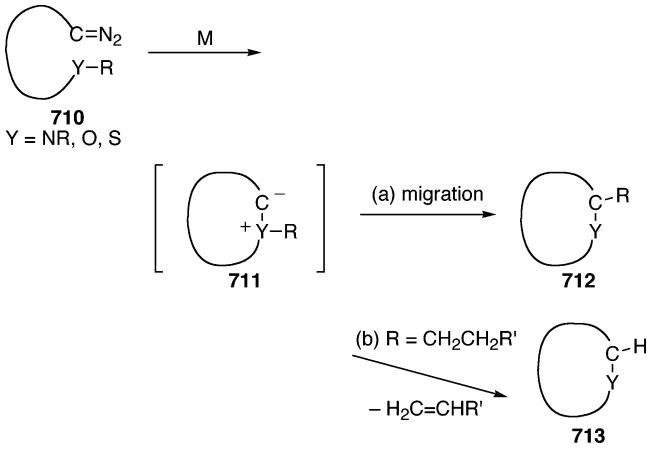



β-fluoropyrroles **705** in high yields (Scheme 219). The reaction proceeds via the dihydropyrrole **706**, which is formed by intramolecular N−H insertion, and subsequent elimination of H−F gives the pyrrole **705**. López-Herrera and Sarabia-García synthesized 2-deoxy-β-KDO **709**; the key step was the rhodium-catalyzed intramolecular O−H insertion of **707**, which gave **708** in 96% yield (Scheme 220).[293c]

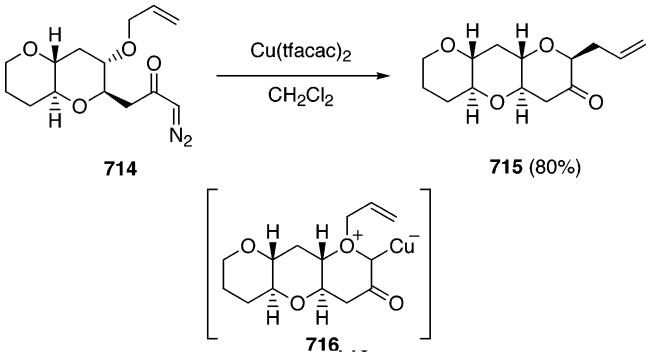
### *8.2.2. Intramolecular Reaction of Diazo Compounds with Tertiary Amines, Ethers, and Thioethers*

The intramolecular reaction of diazo compounds **710** having a tertiary amine, ether, or thioether proceeds through formation of ammonium,[294] oxonium,[295] or sulfonium ylide[296] **711**, as shown in Scheme 221. 1,2-Migration of the R group (route a) or elimination of an alkyl group on the heteroatom (route b) gives the heterocyclic compounds **712** or **713**, respectively. Marmsäter and West reported that the copper-catalyzed [2,3]-shift of oxonium ylides gave polycyclic ethers with high diastereoselectivity.[295b] The reaction of the diazocarbonyl compound **714** bearing an allyl ether in the presence of copper(II) trifluoroacetylacetate (Cu(tfacac)$_2$) produced the polycyclic ether **715** in 80% yield as a single diastereomer (Scheme 222). The reaction proceeds through the oxonium ylide **716**, and subsequent [2,3]-shift of an allyl group gives **715**.

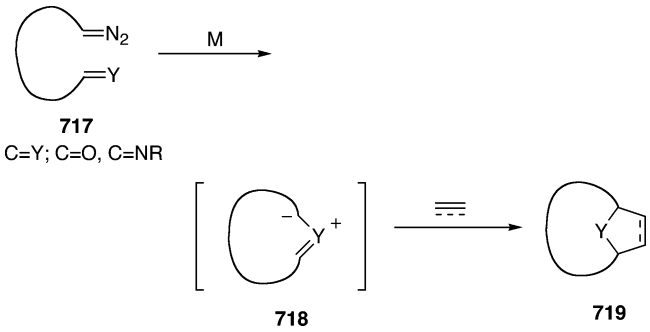
**Scheme 221. Ylide Formation from Diazo Compounds Bearing a Tertiary Amine, Ether, or Thioether**




**Scheme 222**



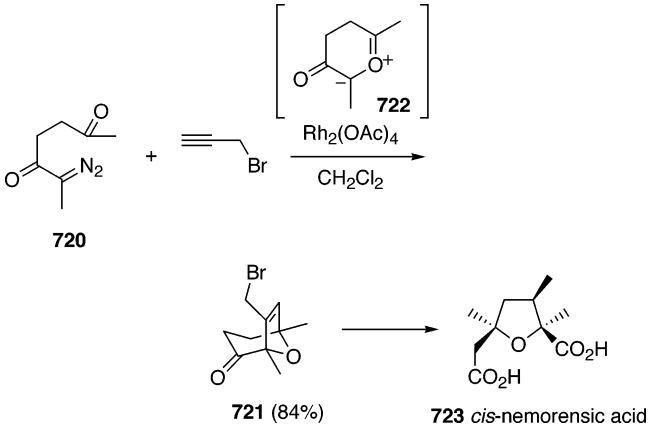

**Scheme 223. Ylide Formation from Diazo Compounds Bearing a Carbonyl or Imine Group**




### *8.2.3. Intra- and Intermolecular Reaction of Diazo Compounds with a C═O or C═N Bond*

The reaction of diazo compounds **717** with a C═O or C═N bond produces the carbonyl or azomethine ylides **718**, which undergo subsequent hetero-[3 + 2]-cycloaddition reaction, giving the five-membered heterocyclic compounds **719** (Scheme 223).[297,298] Hodgson et al. reported a concise, stereoselective synthesis of *cis*-nemorensic acid via the tandem carbonyl ylide formation-cycloaddition.[297l] The reaction of the diazodione **720** with propargyl bromide in the presence

**Scheme 224**



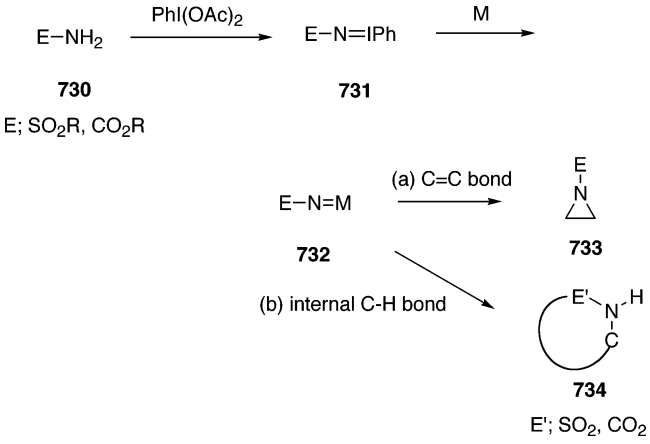

of $Rh_2(OAc)_4$ gave the heterocycle **721** in 84% yield (Scheme 224). The reaction proceeds through the carbonyl ylide **722**, and subsequent [3 + 2]-cycloaddition with propargyl bromide gives the bicyclic heterocycle **721**, which was converted to *cis*-nemorensic acid **723**.

Doyle et al. reported that the rhodium-catalyzed reaction of methyl styryldiazoacetate **724** with the imines of the cinnamaldehydes **725** produced the dihydropyrrole **726** and/or dihydroazepine **727**.[298a] The reaction of **725a** (R = Me) with **724** gave the azepine **727a** as the single product, while the reaction of **725b** (R = H) afforded a 1:2 mixture of **726b** and **727b** (Scheme 225). The reaction proceeds through the azomethine ylides **728** and **729**. When R = Me, the equilibrium is shifted toward **728**, leading to the selective yielding of **727**.

### *8.2.4. Intra- and Intermolecular Reaction of Iminoiodinanes*

Recently, transition-metal-catalyzed reaction of iminoiodinanes **731** has been focused as a method of nitrogen transferring (Scheme 226). The iminoiodinanes **731** are readily synthesized from sulforamides or carbamates **730** by treatment with $PhI(OAc)_2$. The reaction of **731** with a transition-metal catalyst M produces the metal nitrenoid **732**. The

**Scheme 226**




insertion of a C=C bond gives the aziridine compounds **733** (route a),[299] while the intramolecular C−H bond insertion gives the heterocycles **734** bearing N−S bond in the ring (route b).[300]

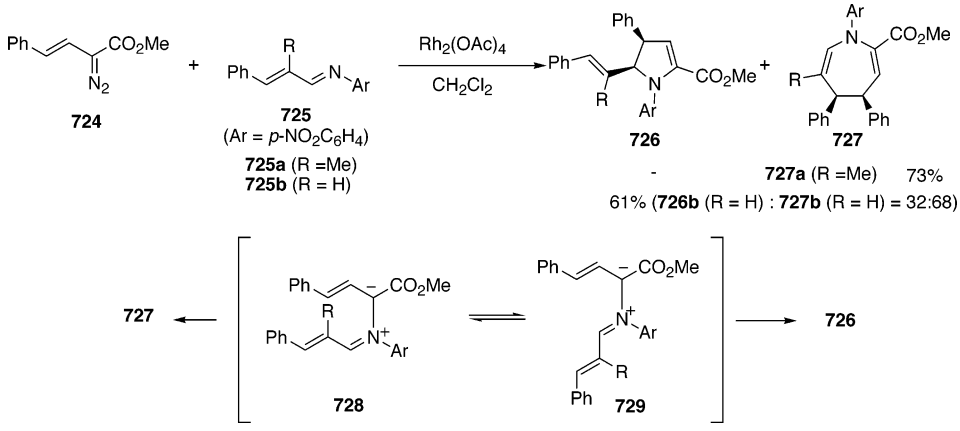
Levites-Agababa et al. reported that the reaction of the allyl 3-carbamate **735** with alcohols **736** and iodobenzene diacetate, in the presence of $Rh_2(OAc)_4$, gave the amidoglycosylation products **737** in good yields (Scheme 227).[299f] The reaction proceeds through the rhodium nitrenoid **738**, the aziridination of the double bond of **738**, and the nucleophilic attack of alcohol on the aziridine ring of the resulting **739**.

Espino et al. reported that the oxidative cyclization of the sulfamate esters **740** with $PhI(OAc)_2$, in the presence of $Rh_2(OAc)_4$, gave the heterocycles **741**, which had both S−O and S−N bonds in the ring, in high yields (Scheme 228).[300b] The oxidative cyclization of chiral **742** gave **743** in 91% yield with perfect stereocontrol, which was converted to (*R*)-*β*-isoleucine **744** (Scheme 229).

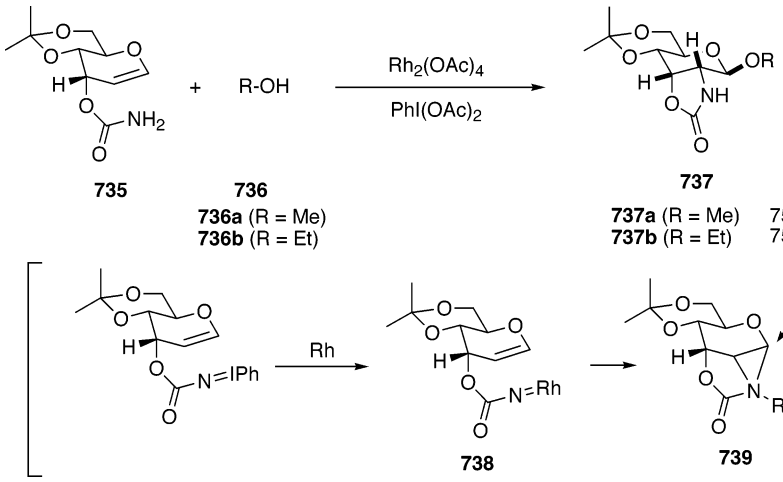
## *9. Conclusion*

When a new fundamental molecular transformation is discovered in organic chemistry, it is often concerning rather simple and small molecules mainly consisting of C, H, and O. It often happens that only

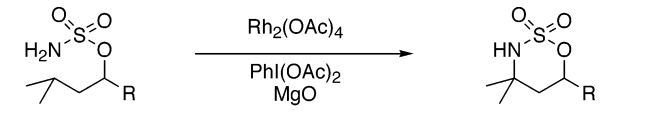
**Scheme 225. Heterocyclic Synthesis by the Reaction of Metal Nitrenoids Either with (a) a C=C Bond or with (b) an Internal C−H Bond**



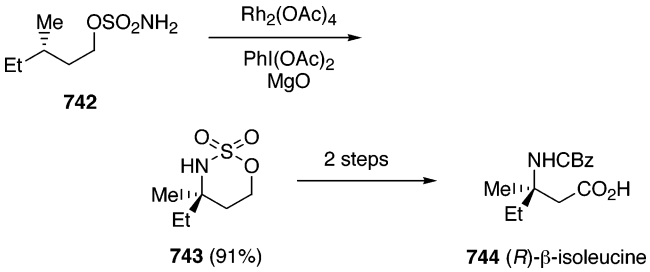
**Scheme 227**




**Scheme 228**




**Scheme 229**




academic people are interested in such a reaction at the beginning and it is not useful for industrial researchers. Then, the initially discovered reaction is improved and elaborated by many people through many years, and finally a robust and reliable process, which is applicable to more complicated and larger molecules having many functional groups consisting of C, H, O, N, X, S, etc., is developed. Such a reaction is used very often not only by many academic people but also by a wide range of industrial people. This is a history of the name reactions or equivalently useful unnamed reactions in organic chemistry. Some transition-metal-catalyzed reactions have taken a history similar to that mentioned above. For example, after a very long induction period, the olefin metathesis reaction including RCM has been very frequently used, especially in the past few years, for the synthesis of complicated natural products and heterocycles. Also, the Pauson−Khand reaction has seen a wide range of application and now has been extended to the hetero-Pauson−Khand protocol. Accordingly, transition-metal-catalyzed reactions are no more the possession of organometallic chemists but have become public property for organic, organometallic, heterocyclic, and natural product synthetic chemists. In fact, most of the important reactions quoted in this review, such as olefin metathesis and the Pauson−Khand, Heck, Suzuki, and Stille reactions, are mentioned in the standard textbook for graduate students, the March's 5th edition published in 2001.

Heterocycles are especially important in chemical and pharmaceutical industries. It seems that industrial people have been using mostly the traditional and conventional transformations for the synthesis of heterocycles, perhaps because those reactions are reliable and robust and proceed generally at low cost. However, it is also true that some of those reactions are accompanied with waste byproducts. In this sense, transition-metal-*catalyzed* reactions minimize such waste and are in general environmentally friendly. Heterocycles having a complicated structure with many labile functional groups can be synthesized often from rather simple starting materials through sequential catalytic processes. Especially, catalytic asymmetric synthesis of heterocycles, as shown in the several sections, deserves special attention, since it is realized only with transition-metal catalysts. We hope that this review will be useful not only for organic synthetic and organometallic chemists but also for heterocyclic and natural product synthetic chemists.

## 10. References

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CR020095I