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Metal Vinylidenes as Catalytic Species in Organic Reactions

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Abstract

Organic vinylidene species have found limited use in organic synthesis due to their inaccessibility. In contrast, metal vinylidenes are much more stable, and may be readily accessed through transition metal activation of terminal alkynes. These electrophilic species may be trapped by a number of nucleophiles. Additionally, metal vinylidenes can participate in pericyclic reactions and processes involving migration of a metal ligand to the vinylidene species. This review addresses the reactions and applications of metal vinylidenes in organic synthesis.

Keywords

atom economy; catalysis; chemoselectivity; organic synthesis; vinylidene

1. Introduction

Organic vinylidene species (**2**) are tautomers of the corresponding alkynes (**1**), but they are thermodynamically much less stable (Scheme 1). There is also a significant activation energy for the interconversion of the two species. Since harsh conditions are required for the generation of organic vinylidenes their application in organic synthesis has been severely limited.

A rare example of an organic vinylidene used in a synthetic context is displayed in Scheme 2. In a synthesis of (+/−)-isoptychanolide, Dreiding and coworkers reported that flash vacuum thermolysis of ynone **3** leads to cyclopentenone **5**, presumably *via* generation of the transient vinylidene species **4** and its insertion into the proximal C-H bond.[1]

A significant advance was the observation that metal vinylidenes are much more stable than organic (free) vinylidenes.[2] The most straightforward route to metal vinylidenes is by the transition metal activation of terminal alkynes (Scheme 3). This process is reversible, and the relative stabilities of the metal-coordinated alkyne (**7**) and the metal vinylidene (**8**) depend on the electron configuration of the metal (M), the nature of the ligands (L_n), and the alkyne substituents.

There are two proposed mechanisms for the conversion of metal-coordinated terminal alkynes to metal vinylidenes. The first pathway involves oxidative addition of the metal into the alkyne C-H bond, followed by a concerted [1,3]-shift of the hydride. The second mechanism consists of a direct [1,2]-migration of a hydride over the alkyne (Scheme 4).

There has been experimental support for the first mechanism in some cases (*ie*. observation or isolation of the alkynyl metal hydride intermediate **9**). This is the case for reactions involving $RhCl(iPr_3)_2$,[3] although even in this case it is not clear whether the [1,3]-migration step is a unimolecular[4] or a bimolecular[5] process. In the majority of reactions, however, it is not

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known which pathway is operative, and both experimental and computational studies have been carried out in order to delineate the mechanism.[6]

Vinylidenes behave as electron-withdrawing ligands on the metal, and thus electron-donating ligands (L_n) will stabilize this species (**8**) relative to the metal-complexed alkyne (**7**, Scheme 3). However, there must be a balance, as there is a danger of making the species too stable such that it does not undergo further reactions. Traditionally, nucleophiles (such as alcohols) have been added to metal vinylidenes in stoichiometric reactions to generate the corresponding Fischer carbene complexes. This mode of reactivity reflects the inherent electrophilicity of the vinylidene α carbon.

More recently, there has been a large number of publications involving conversion of terminal alkynes to various products in which metal vinylidenes serve as *catalytic* species.[7] The three types of transformations most commonly investigated are: (a) nucleophilic addition to the α carbon, (b) [1,2]-alkyl migration from the metal center to the α carbon, and (c) pericyclic reactions.[8] In this review, the various reactions involving catalytic metal vinylidene species are analyzed, with an emphasis on those that synthetic chemists may find useful. In most cases, a proposed mechanism (catalytic cycle) is presented in order to facilitate an understanding of the transformation at hand.

2. Heteroatom Nucleophile Reactions with Vinylidenes

2.1. Carbamate Nucleophiles

Dixneuf reported the first report of a metal vinylidene complex as a catalytic species in an organic reaction over 20 years ago.[9] In an interesting three component coupling reaction, $Ru_3(CO)_{12}$ catalyzed the addition of *N*,*N*-diethylcarbamate to *n*-hexyne to generate both the anti-Markovnikov (**14** and **15**) and Markovnikov (**16**) vinyl carbamates in low yield (Scheme 6). Such a transformation is noteworthy from the standpoint of atom economy, as well as the fact that it involves carbon dioxide, a highly stable molecule that is not easily activated in organic synthesis.[10]

The proposed mechanism for the formation of the anti-Markovnikov product involves vinylidene formation between the ruthenium catalyst (**I**) and the terminal alkyne, followed by nucleophilic attack of the carbamate (generated *in situ*) to give **III** (Scheme 7). Protonation of the metal, followed by reductive elimination, then releases both the anti-Markovnikov products **14** and **15** and regenerates the active catalyst. The Markovnikov product **16**, however, is believed to form by nucleophilic attack on the more electrophilic (internal) carbon of the metal-coordinated alkyne (**V**).

Although the selectivities and yields of the process were low, the results spurred further generations of catalyst modification to improve the transformation. Thus by changing the catalyst and solvent phenylacetylene (**17**) was reacted with diethylamine to provide the corresponding vinylcarbamate in moderate yield and selectivity (equation 1, Scheme 8).[11] Acetylene (**21**) was also a viable coupling partner with pyrrolidine, although an excess of alkyne was required due to competing polymerization of the alkyne (equation 2).[12,13] Interestingly, 2-methyl-1-buten-3-yne (**24**) could be used as a substrate, reacting with morpholine to give diene products that are activated Diels-Alder reaction partners (equation 3).[14]

2.2. Carboxylic Acid Nucleophiles

2.2.1 Intermolecular Reactions—Contemporaneous with his work on vinylcarbamate formation, Dixneuf disclosed the use of carboxylic acid nucleophiles to capture metal vinylidenes in a catalytic synthesis of enol esters.[15,16] Thus phenylacetylene (**17**) and benzoic

acid (**28**) react, in the presence of a catalytic amount of ruthenium trichloride trihydrate, to give a mixture of anti-Markovnikov (**29** and **30**) and Markovnikov (**31**) addition products (Scheme 9).

Similar to the aforementioned formation of vinylcarbamates, the anti-Markovnikov enol ester products can be accounted for by invoking a vinylidene mechanism (Scheme 10). Thus vinylidene formation between the ruthenium catalyst and the terminal alkyne **17**, followed by nucleophilic attack of the carboxylate, protonation of the metal, and reductive elimination can give products **29** and **30**. The regioisomeric Markovnikov product **31** likely forms by electrophilic activation of the alkyne followed by nucleophilic attack.

Subsequent studies showed that the complex Ru(methallyl)$_2$dppb was a better catalyst for a variety of alkynes and carboxylic acids. For example, benzoic acid added in a regio- and stereoselective manner to phenylacetylene (equation 1),[17] *n*-hexyne (equation 2),[18] and 2-methyl-1-buten-3-yne (equation 3)[19] to give the corresponding enol esters in excellent yields (Scheme 11).

A number of ruthenium catalysts have since been found to catalyze the regioselective, anti-Markovnikov formation of enol esters from various alkynes and carboxylic acids.[20,21] One of the most interesting reports showed that changing the ligand and base, with the same ruthenium catalyst, allowed access to either the anti-Markovnikov or Markovnikov products in excellent yield (Table 1).[22]

To highlight the utility of this type of reaction, Dixneuf and coworkers have investigated a ruthenium-catalyzed isomerization process (Scheme 12). In this transformation, benzoic acid adds regioselectively to putative metal vinylidene complexes, and the resulting *Z*-enol esters then fragment at higher temperatures to give enal products in good yields.[23] Alternatively, the intermediate enol esters may be treated with a catalytic amount of *p*-toluenesulfonic acid at room temperature to effect the elimination reaction.[24]

This process constitutes the synthetic equivalent of a Meyer-Schuster rearrangement,[25] but has the advantage of taking place under much milder reaction conditions. Although this reaction has not yet been used in target-oriented synthesis, one can imagine that it might find use as an alternative to the Horner-Wadsworth-Emmons or Wittig olefinations of ketones.

2.2.2 Intramolecular Reactions—Valerga and coworkers have found that carboxylic acids can add to terminal alkynes in an intramolecular fashion.[26] Thus α,ω-alkynoic acids (**38**) may be converted to the corresponding enol lactones **39**, in one case even forming a macrocycle, in good to excellent yield by heating in the presence of a ruthenium catalyst (Scheme 13). The exclusive formation of the endocyclic enol lactones is consistent with vinylidene formation, followed by intramolecular trapping by the tethered carboxylic acids. Verpoort and colleagues later reported that ruthenium complexes of the form RuCl$_x$(*p*-cymene)(triazol-5-ylidene) were able to catalyze the cyclization of 4-pentynoic acid in excellent yield and regioselectivity.[27]

2.3. Alcohol Nucleophiles

2.3.1 Intermolecular Reactions—Despite the success of carboxylic acids, the use of alcohols to intercept metal vinylidene intermediates in intermolecular catalytic reactions has been problematic. For the most part, such reactions occur only stoichiometrically to provide the corresponding Fischer carbenes.[28] One notable exception, however, has been the use of allylic alcohols. In what is termed the ruthenium-catalyzed reconstitutive condensation reaction, Trost has reported that treatment of alkynes **40** and excess allylic alcohol **41** with a ruthenium catalyst and ammonium hexafluorophosphate leads to β,γ-unsaturated ketone **43**

(Scheme 14).[29] This in fact represents the first use of vinylidenes to form C-C bonds in a catalytic reaction.

Evidence for vinylidene intermediates in this process was gathered through exploration of substrate scope and labeling studies; a mechanism consistent with the results was then proposed (Scheme 15).[30] Loss of chloride ion from the ruthenium complex is expected to lead to the active cationic catalyst **I**. Vinylidene formation with alkyne **40** leads to **II**. Coordination of olefin **41**, with loss of phosphine, can lead to **III**, and subsequent nucleophilic attack by the pendant alcohol can give **IV**. Ionization of the resulting allyl enol ether then provides acyl ruthenium species **V**, which can be represented as σ complex **VI**. Finally, reductive elimination releases the product (**42**) and regenerates the active catalyst.

The power of this reaction was demonstrated in a concise synthesis of the fully functionalized side chain of the steroid ganoderic acid (**48**, Scheme 16).[31] The terminal alkyne substrate **44** was prepared by Corey-Fuchs homologation of the commercially available 3-oxopregn-4-ene-20β-carboxaldehyde (**43**).[32] In this transformation, the enone present in the substrate was effectively protected from side reactions by conversion to the corresponding enolate prior to the reaction. The ruthenium-catalyzed reconstitutive condensation with allyl alcohol (**46**) then proceeded in good yield to give a mixture of **46** and **47**; treatment of this mixture with catalytic rhodium trichloride in aqueous tetrahydrofuran accomplished complete conversion to the α,β-unsaturated ketone **47**. Conjugate addition of cyanide, followed by nitrile hydrolysis, then gave **48**.

The utility of this transformation was further demonstrated in a short synthesis of the fragrance rosefuran (**53**, Scheme 17).[33] Thus addition of propargylmagnesium bromide to acetone, followed by acylation of the resulting tertiary alcohol, gave alkyne **50** in good yield. Reconstitutive condensation with allylic alcohol **41** then gave **51**, a molecule containing all of the carbon atoms present in the target molecule. A tandem dihydroxylation-cyclization provided furan **52**. Ester hydrolysis, followed by thermal dehydration, then gave rosefuran.

Terminal alkynes bearing propargyl alcohols have the ability to form allenylidene species. These complexes are electrophilic, and thus offer opportunities for reactions with nucleophilic functional groups. In this context, Trost has reported the catalytic reaction of propargyl alcohol substrates bearing pendant alcohol groups to form tetrahydrofurans and tetrahydropyrans (Scheme 18).[34]

The mechanism of this tandem reaction is depicted in Scheme 19. The active catalyst is generated by loss of chloride ion to give **I**. Insertion of the metal into the alkyne C-H bond then forms **II**, whereby loss of water leads to allenylidene **III**. The pendant alcohol then attacks this electrophilic species to give vinylidene **IV**. The mechanism then follows the same sequence of events as shown in Scheme 15 to give the β,γ-unsaturated ketone products.

This reaction has been used in a synthesis of the spiroketal subunit of the phosphatase inhibitor (−)-calyculin A (Scheme 20).[35] The sequence began with reduction of (R)-pantolactone (**56**) to the corresponding lactol. Addition of vinylmagnesium bromide, followed by acetonide formation, then afforded **57**. Oxidation and subsequent acetonide cleavage-lactonization then led to **58**. Ozonolysis of this intermediate with reductive workup then gave a diol that was ketalized with acetone to give **59**. Reduction of the lactone to the lactol, followed by addition of lithium acetylide, then provided a mixture of epimeric propargyl alcohols. Ultimately, the stereochemistry was inconsequential, as the ruthenium-catalyzed tandem cyclization-reconstitutive condensation gave **61** as a single diastereomer with respect to the tetrahydrofuran ring. Asymmetric dihydroxylation, followed by selective protection of the primary alcohol, led to **62**. Finally, oxidative cyclization gave the spirocyclic core of (−)-calyculin A (**63**).

2.3.2 Intramolecular Reactions—Contrary to the intermolecular reaction of alcohols with terminal alkynes through vinylidene intermediates, the endo cyclization of alkynols has found success.[36] The first report of such a transformation dates back almost 15 years (Scheme 21).[37] Although the yields were modest, chromium, tungsten, and molybdenum carbonyl complexes were found to promote the stoichiometric cyclization of homopropargyl alcohol **64** to the corresponding Fischer carbene complexes. In the latter case triethylamine was able to effect *in situ* demetalation to the corresponding dihydrofuran **67**.

The products formed can be explained by considering the putative mechanism (Scheme 22). Molybdenum hexacarbonyl reacts with trimethylamine oxide to give the active catalyst **I**. Vinylidene formation with alkyne **64** gives **II**, which undergoes nucleophilic capture by the pendant alcohol to give Fischer carbene **III**. In the presence of triethylamine, deprotonation of this electrophilic oxacarbene can give anion **IV**. Protonation of the metal, followed by reductive elimination, gives **67** and releases the active catalyst. Although the catalyst loading was almost stoichiometric, this initial report paved the way for future investigations.

Recognizing the utility of this transformation, synthetic applications followed soon after. McDonald first used this reaction in concise enantioselective syntheses of the deoxynucleosides stavudine and cordycepin (Scheme 23).[38] The starting point was a Katsuki-Sharpless epoxidation of allyl alcohol (**45**), followed by *in situ* protection of the alcohol, to provide (S)-glycidyl pivaloate **68**. Regioselective epoxide opening with lithium acetylide then gave **69**, which proved to be a capable substrate for the molybdenum-catalyzed cycloisomerization reaction, providing the key dihydrofuran intermediate **70** in good yield. Iodine-mediated introduction of thymine on to this molecule provided iodonucleoside **71**. Pivaloate methanolysis and concomittant elimination of HI then gave stavudine (**72**), a substance possessing anti-HIV activity. Alternatively, dihydroxylation of **70** and acylation of the crude diol provided a mixture of four diastereomeric diacetates, the major product being **73**. Lewis acid-catalyzed addition of a protected adenine derivative then gave **74**, whereby methanolysis of the pivaloate, acetate, and benzoate protecting groups gave cordycepin (**75**), a substance possessing antibiotic activity.

This manner of deoxynucleotide synthesis was further extended to 3-aminofuranose glycals (Scheme 24).[39] Once again, asymmetric epoxidation provided the enantioenriched starting material. Regioselective opening of epoxide **77**, followed by protection of the primary alcohol, gave **78** in moderate yield. Azide reduction, and protection of the resulting amine as either the acetamide or the trifluoroacetamide, gave substrates for cycloisomerization (**79**). In the event, the key molybdenum-promoted cycloisomerization provided the desired dihydrofurans (**80**) in excellent yield. Importantly, it was demonstrated that the presence of the amide in the propargylic position did not affect the reaction, unlike alcohol and azide functionalities (which are prone to elimination). Subsequent transformations finally allowed access to a variety of 3-aminofuranose glycals, including puromycin aminonucleoside (**81**).

McDonald further demonstrated the utility of this transformation in a synthesis of digitoxin (**82**).[40] In this convergent approach, the trisaccharide moiety of the natural product was constructed by iterative cycloisomerizations,[41] and then connected to digitoxigenin (**83**) by glycosidation (Scheme 25).

The chiral information of the nascent trisaccharide was installed by an enantioselective carbonyl reduction of enynone **84** and a diastereoselective epoxidation of the resultant allylic alcohol (Scheme 26). Regioselective epoxide opening with benzoic acid, followed by protodesilylation, then afforded compound **86**. Diol protection followed by removal of the benzoate protecting group provided alkynol **87**, which underwent a smooth cycloisomerization to give 6-deoxy-D-ribo glycal **88**.[42] Glycosidation with a chiral alcohol proceeded in good

yield and facial selectivity. Benzoate removal followed by cycloisomerization afforded disaccharide **90** in excellent yield. A series of transformations, including another cycloisomerization, provided **82**. Finally, glycosidation with digitoxin, followed by protecting group removal, gave digitoxin.

More recently, McDonald has reported that use of DABCO as the base allows one to significantly lower the catalyst loading for the formation of dihydropyrans. This base may stabilize intermediates in the catalytic cycle more effectively than does triethylamine. Wipf has investigated these conditions with respect to the stereochemistry and nature of substituents on the chain linking the alkyne and the alcohol in the substrate.[43] McDonald has successfully applied these new conditions in syntheses of (L)-vancosamine (**93**)[44] and (D)-desosamine (**95**)[45] glycals (Scheme 27).

McDonald and colleagues have also reported that α-stannyl vinyl ethers could be prepared from alkynols by either trapping the intermediate Fischer carbene anions with a tin electrophile *in situ* or through a stepwise process. For example, homopropargyl alcohol **64** could be converted to α-(tributylstannyl)dihydrofuran **97** in reasonable yield with a catalytic amount of a molybdenum pentacarbonyl complex and tributyltin triflate (equation 1, Scheme 28).[46] The bis-homopropargyl alcohol **98**, on the other hand, could only be converted to a Fischer carbene by treatment with a tungsten pentacarbonyl complex. Upon treatment with the tin reagent, α-(tributylstannyl)dihydrofuran **100** was then obtained in quantitative yield (equation 2).[47] The vinyl tin moiety can undergo a variety of metal-catalyzed cross coupling reactions with alkyl halides, thus making these products useful building blocks for organic synthesis.

Trost has reported that the ruthenium-catalyzed cycloisomerization of homopropargyl alcohols, such as **101**, could be coupled to an oxidation reaction, thus providing γ-butyrolactones, such as **103** (Scheme 29).[48]

Studies on the related reactions of bis-homopropargyl alcohols showed that employing the electron-donating ligand tris(4-methoxphenyl)phosphine gave δ-valerolactone products (Scheme 30). Interestingly, the electronics of the ligand could be tuned to give a different product. Thus use of the electron-withdrawing ligand tris(4-fluorophenyl) phosphine gave dihydropyrans.[49]

A mechanism that takes into account the ligand effects and explains the role of N-hydroxysuccinimide (**102**) is shown in Scheme 31. Vinylidene formation of active catalyst **I** with alkyne **104** gives **II**, and nucleophilic attack by the pendant alcohol then provides **III**. From this key intermediate C-protonation can give oxacarbene **IV**. Subsequent nucleophilic attack by the anion of N-hydroxysuccinimide, followed by protonation and reductive elimination, gives lactone product **105**. Alternatively, ligand displacement of complex **III** by the anion of N-hydroxysuccinimide may give **VI**. Protonation and reductive elimination then can release dihydropyran product **106** and structure **VII**, which can undergo ligand displacement to regenerate the active catalyst. Electron-donating phosphines may promote protonation of intermediate **III**, thus leading to the preferential formation of lactone products. On the other hand, electron-withdrawing phosphines may enhance the electrophilicity of intermediate **III**, thus promoting nucleophilic attack by the anion of N-hydroxysuccinimide at ruthenium and leading to the formation of dihydropyrans. The large amount of phosphine ligands in *both* processes may serve to saturate the metal center. This would attenuate the electrophilicity of the metal, thus inhibiting competing processes while promoting vinylidene formation.

Trost has shown the utility of these reactions in a novel iterative cycloisomerization approach to the marine ladder toxins prymnesin and yessotoxin (Scheme 32).[50] The sequence of reactions begins with a diastereoselective addition of propargyl zinc to the acetonide of

glyceraldehyde (**107**). Protection of the resulting alcohol, followed by cleavage of the ketal, then gave diol **108**. The ruthenium-catalyzed cycloisomerization reaction then gave dihydropyran **109** in good yield. Following protection of the alcohol, the enol ether was treated with dimethyl dioxirane, and the intermediate epoxide was regioselectively opened with allenylmagnesium bromide to give a mixture of diastereomeric bis-homopropargyl alcohols **112** and **113** (4: 1 ratio). The fact that a mixture was obtained is inconsequential though, as the desired isomer **113** could exclusively be obtained by a simple epimerization sequence. Exposure of this compound to the aforementioned ruthenium conditions led to the cycloisomerization product **114** in good yield. Repeating this sequence of events then gave the subunit of yessotoxin (**115**).

Trost subsequently reported the cycloisomerization of homo- and bis-homopropargyl alcohols in the presence of rhodium complexes bearing electron-withdrawing phosphine ligands (Scheme 33).[51] Although relatively large amounts of ligand were still required, the reaction required less additives and showed higher catalyst turnover numbers (lower catalyst loadings) than the ruthenium-based system. Importantly, propargyl ethers were resistant to elimination (equation 2).

2.4 Water as a Nucleophile

Whereas alcohols have failed to act as nucleophiles in catalytic intermolecular reactions with metal vinylidenes, water has been successful. This process accomplishes an atom economical conversion of terminal alkynes to aldehydes, a process that has been traditionally involved stoichiometric regioselective hydroboration and subsequent oxidation. This transformation thus holds considerable promise for organic synthesis, although it has not yet been utilized in target-oriented synthesis. Wakatsuki was the first to report this transformation; thus treatment of *n*-hexyne (**12**) with aqueous isopropanol and a ruthenium catalyst led to the corresponding aldehyde (**118**) as the major product (Scheme 34).[52] However, hindered alkynes such as phenylacetylene and *t*-butylacetylene failed to react.

A mechanism consistent with the observed regioselectivity is shown in Scheme 35. The terminal alkyne and the metal species **I** may form vinylidene species **II**, which is then trapped by water. Tautomerization and reductive elimination then can lead to the aldehyde product. The ketone (Markovnikov) product may be formed by electrophilic activation of the alkyne (**V**) and regioselective attack of water at the more electrophilic site. The excess phosphine ligand is thought to promote vinylidene formation (**II**) over simple alkyne activation (**V**).

Wakatsuki subsequently reported that a variety of alkynes, including hindered and functionalized alkynes, could be effectively hydrated to the corresponding aldehydes with lower amounts of ruthenium complex **120** (Figure 1).[53] The bidentate nature of the dppm ligand was crucial to the success of this process. Other ruthenium complexes have also been used to catalyze this transformation. Bassetti and coworkers have reported that ruthenium complex **121** can catalyze the anti-Markovnikov hydration of alkynes in water containing surfactants such as sodium dodecylsulfate.[54] Grotjahn and colleagues utilized ruthenium complex **122** to hydrate a variety of alkynes, a catalyst that may deliver water in an intramolecular fashion to the vinylidene intermediate.[55] Breit has used ruthenium complex **123** to catalyze the transformation, a catalyst generated *in situ* based on the same principles of hydrogen bonding that guide the self-assembly of adenine and thymine in DNA.[56] More recently, Hintermann and colleagues reported the use of a catalyst generated from cationic ruthenium complex **124** and ligands such as **125**. The benefits of this catalyst system include modification of the ligand through a modular synthesis as well as exceptional catalytic activity.[57]

Wakatsuki has also investigated the regioselective ruthenium-catalyzed hydration of propargyl alcohols to give enals. This reaction is a transition metal-catalyzed version of the Meyer-Schuster rearrangement, and thus provides a complimentary approach to the similar transformation involving benzoic acid developed by Dixneuf and coworkers (*vide supra*).[23,58] In an example of this reaction, propargyl alcohol **126** combines with water in the presence of a ruthenium catalyst to provide enal **127** in good yield and moderate *Z*/*E* stereoselectivity (Scheme 36).[59]

Labeling studies ($H_2{}^{18}O$) suggest that the mechanism does not involve transposition of the alcohol oxygen to the carbonyl group. While it is not clear at which stage dehydration occurs, a plausible mechanism is presented in Scheme 37. The active catalyst **I** may insert into the alkyne C-H bond, and elimination of water then leads to allenylidene **III**. Addition of water to the electrophilic carbon then gives enol **IV**. Tautomerization, followed by reductive elimination, then gives enal **127** and regenerates the active catalyst.

A novel tandem reaction involving water and a vinylidene intermediate has been recently reported by Lee and coworkers. In a process termed hydrative cyclization, a ruthenium complex catalyzes the formation of cyclopentanones from 1,5-enynes. An example of this reaction is depicted in Scheme 38.[60]

One mechanism that would explain this interesting domino reaction is depicted in Scheme 39. Thus nucleophilic capture of vinylidene **II** by water, followed by tautomerization, can give **IV**. Deprotonation of the metal and Michael addition of the acyl ruthenium species **V** leads to **VI**. Finally, protonation and reductive elimination regenerates the active catalyst and the cyclopentanone product **129**.

2.5 Epoxide Nucleophiles

McDonald was the first to report the cyclization of epoxyalkynes to furans through a vinylidene mechanism.[61] For example, treatment of **130** with a catalytic amount of a molybdenum pentacarbonyl catalyst led to **131** (equation 1, Scheme 40). Liu and coworkers subsequently disclosed that the same type of transformation could be catalyzed by a lower loading of a ruthenium complex (equation 2).[62]

The mechanism of this transformation is rationalized by considering vinylidene intermediate **II** (Scheme 41). Attack by the epoxide oxygen can then lead to the rearranged Fischer carbene **III**. Vinylogous deprotonation, followed by protonation on the metal center, yields intermediate **V**, and reductive elimination then gives the product and regenerates the catalyst **I**.

An interesting variation of the substrate structure can lead to different products.[63] Thus (*o*-ethynyl)styrene epoxides such as **134**, when treated with catalytic amount of $[TpRu(PPh_3)(NCCH_3)_2]PF_6$, lead to 2-naphthol products such as **135** (equation 1, Scheme 42). Higher substituted epoxides (**136**), however, lead to 1-alkylidene-2-indanones **137** instead (equation 2).

This dichotomy of products can be explained according to the mechanism depicted in Scheme 43. The loss of acetonitrile ligands opens up coordination spaces on the ruthenium complex to generate the active catalyst **I**. Vinylidene formation with either alkyne **134** or **136** then leads to **II**. Attack of the epoxide at the electrophilic carbon of the vinylidene species then leads to **III**, whereby cleavage gives the key ruthenium π-ketene intermediate **IV**. In the case of 1,2-disubstituted olefins (R_1 = H, R_2 = $n C_5H_{11}$), 6-endo-dig electrocyclization leads to benzylic carbocation **V**. Subsequent elimination provides **VI**, whereby protonation of the metal, followed by reductive elimination, gives 2-naphthol product **135** and liberates the active

catalyst. Alternatively, in the case of trisubstituted olefins, **IV** undergoes 5-endo-dig cyclization to give the relatively stable tertiary carbocation **VII**. Elimination then gives **VIII**, and protonation at the metal, followed by reductive elimination, gives 1-alkylidene-2-indanone **137**.

Recently, Liu and colleagues have disclosed that iodoalkynes, such as **138**, can lead to 1-iodo-2-naphthol products, such as **139** (Scheme 44).[64] This result adds to the synthetic utility of the method, since aryl iodides can be further elaborated through a variety of metal-catalyzed cross-coupling reactions. Furthermore, the position of the iodide in the product lends credence to the proposed pathway of these reactions, as this group would migrate to the 1-position upon formation of the vinylidene intermediate (*cf.* Scheme 43).

2.6 Carbonyl Nucleophiles

The interception of metal vinylidene intermediates by carbonyl groups has only been recently reported. In the first report, Uemura and coworkers disclosed that conjugated enyne esters (**140**) were transformed into pyranylidene metal complexes (**142**), presumably from vinylidene formation (**141**) followed by [3,3]-sigmatropic rearrangement (Scheme 45). These Fischer carbene products are analogs of α-pyrones, and thus were anticipated to participate in Diels-Alder reactions with dienophiles. In the event, dimethyl acetylenedicarboxylate added to pyranylidene **142** to generate tetrahydronaphthalene **144** in low yield, presumably *via* retrocycloaddition of intermediate **143**.[65,66]

Iwasawa and colleagues contemporaneously reported a similar set of reactions. Thus *o*-ethynyl arylketones, such as **145**, are converted into benzopyranylidenes, such as **147**, *via* [3,3]-sigmatropic rearrangement of vinylidene **146** (Scheme 46).[66] Diels-Alder reaction with *n*-butyl vinyl ether, followed by retrocycloaddition, provides **149**, whereby elimination of *n*-butanol provides naphthalene **150**.

Whereas these cases involved stoichiometric metal vinylidenes, Uemura and coworkers reported the first catalytic interception of metal vinylidene complexes by carbonyl groups. Treatment of *cis*-1-acyl-2-ethynylcyclopropanes, such as **151**, with catalytic amounts of either tungsten or chromium pentacarbonyl complexes led to 2-substituted phenols (**152**) in excellent yield (Scheme 47).[66,68]

The proposed catalytic cycle is depicted in Scheme 48. Vinylidene formation between catalyst **I** and substrate **151**, followed by [3,3]-sigmatropic rearrangement, affords **III**. A [1,5]-hydrogen shift, and reductive elimination, then liberates the catalyst and arene oxide **V**. A second [3,3]-sigmatropic rearrangement then gives **VI**, and subsequent rearrangement then yields product **152**.

2.7 Thiol Nucleophiles

Despite the success of homopropargyl alcohol cycloisomerization, there has only been one report of homopropargyl thiols undergoing cyclization to the corresponding dihydrothiophenes.[69] In this case, a stoichiometric amount of chromium hexacarbonyl was required to give the product in good yield (Scheme 49). The lack of catalytic processes is presumably due to the strong coordination of thiols to metals, thus leading to catalyst deactivation.

2.8 Amine Nucleophiles

2.8.1 Intermolecular Reactions—There have been no reports of simple primary or secondary amines adding to metal vinylidene intermediates in a catalytic reaction, again possibly due to catalyst deactivation by the amine substrates. However, Watanabe and

coworkers have reported the ruthenium-catalyzed addition of an amide (acetanilide, **156**) to 1-octyne (**155**) to give the enamide product **157** (Scheme 50).[70] There were only a limited number of examples reported, and the yields were moderate, but the regio- and stereoselectivity of the process were excellent.

Several years later, Gooβen and colleagues reported that a number of amides could be added to terminal alkynes bearing a wide array of functional groups using a different ruthenium catalyst (Scheme 51).[71] For example, 2-pyrrolidinone (**158**) reacts with *n*-hexyne (**12**) in excellent yield, with complete regioselectivity and good *E*/*Z* selectivity (equation 1). Product **160** can be prepared from enyne **24** and amide **58** (equation 2), thus constituting an atom economical synthesis of activated dienes for Diels-Alder reactions.

Fukumoto and coworkers recently reported the use of *N*,*N*-dialkylhydrazines as nucleophiles for vinylidene complexes.[72] A variety of aromatic and aliphatic alkynes were reported to combine with *N*,*N*-dimethylhydrazine to give nitrile products, an example of which is depicted in Scheme 52.

The proposed mechanism of this process is outlined in Scheme 53, starting with loss of chloride ion from the ruthenium complex to generate cationic species **I**. Vinylidene formation with the alkyne substrate then gives **II**. Nucleophilic addition of *N*,*N*-dimethylhydrazine provides **III**, whereby tautomerization and proton transfer leads to **V**. Finally, fragmentation releases the product **163**, *N*,*N*-dimethylamine (**164**), and regenerates the active catalyst. It is interesting that the *N*,*N*-dimethylamine byproduct does not shut the reaction down by coordination with the catalyst, a fact that bodes well for future examinations of catalytic amine additions to vinylidenes.

2.8.2 Intramolecular Reactions—McDonald was the first to report the cyclization of amines on to vinylidene intermediates. Thus *N*-Boc homopropargylamines (**165**) and bis-homopropargyl amines (**167**) undergo endo cyclization in the presence of stoichiometric amounts of molybdenum and tungsten complexes, respectively (equations 1 and 2, Scheme 54).[73] The related amide and sulfonamide substrates were inert to the reaction conditions. Although the corresponding free amine substrates led to decomposition, *o*-ethynylaniline (**169**) was found to cyclize to indole (**170**) in the presence of a catalytic amount of the molybdenum complex (equation 3).

More recently, Trost has shown that a variety of *o*-ethynylanilines could cyclize to the corresponding indoles in the presence of a catalytic amount of a rhodium complex (equation 1, Scheme 55).[74] The exclusive participation of the terminal alkyne in equation 2 lends credence to the proposed vinylidene pathway. This process was further extended to tethered phenol and carboxylic acid nucleophiles.

In an interesting transformation, Jun and coworkers have recently reported that terminal alkynes may be dimerized in the presence of water, Wilkinson's catalyst, and 2-aminopicoline (**171**), the latter reagent acting as a cofactor for the reaction (Scheme 56).[75]

The mechanism of this transformation is thought to involve vinylidene formation (**I**), followed by coordination of the 2-amino-3-picoline with the metal (**II**, Scheme 57). This serves to template the amino group for an intramolecular addition to the vinylidene. Following attack and tautomerization, one obtains **IV**, a metalacycle that may insert a molecule of alkyne. Depending on the bulk of the alkyne, this insertion will favor either **V** or **VI**. The former case is favored for small substituents (Ex. $n C_4H_9$), and after the subsequent ring contraction one obtains **VII**. Reductive elimination and hydrolysis then gives product **172** and the active catalyst. The minor product **173** is obtained from **VI** in a series of similar steps.

2.9 Phosphine Nucleophiles

There has only been one example of anti-Markovnikov hydrophosphination of alkynes, although the utility of such products has not been demonstrated. Dixneuf and coworkers have found that diphenylphosphine (**175**) adds to propargyl alcohols in good yield and *Z*/*E* selectivity (Scheme 58).[76]

3. Carbon Nucleophile Reactions with Vinylidenes

McDonald and coworkers reported the first trapping of vinylidene intermediates by pendant carbon nucleophiles. Homopropargyl malonates, β-ketoesters, and β-diketones (*i.e*. stabilized nucleophiles) undergo cyloisomerization (5-endo attack) in the presence of approximately stoichiometric amounts of a molybdenum pentacarbonyl complex (equation 1, Scheme 59).[77] The use of a bis-homopropargyl β-dicarbonyl substrate, however, only resulted in 5-exo attack (equation 2).

A possible mechanism involves deprotonation of the β-dicarbonyl substrate, followed by vinylidene formation, to give **III** (Scheme 60). Nucleophilic trapping then leads to **IV**, whereby protonation at the metal by the substrate, followed by reductive elimination, gives the product and the metal complex **I**.

Iwasawa and coworkers have further investigated this reaction. Less stabilized nucleophiles (silyl enol ethers) were found to function in the presence of lower loadings of a tungsten catalyst. Five-membered rings (equation 1) as well as six-membered rings (equations 2 and 3) have been reported to form in good to excellent yield (Scheme 61).[78]

Iwasawa subsequently extended this reaction into a general method for cyclopentene annulation (Scheme 62).[79,80] Indium-mediated propargylation of α,β-unsaturated ketones (ex. (R)-carvone, **187**), in the presence of dimethyl sulfide and *t*-butyldimethylsilyl triflate, provides the requisite substrates (**189**). Cycloisomerization in the presence of catalytic amounts of a tungsten carbonyl complex then give the unsubstituted cyclopentene products, such as **190**.

The use of iodoalkynes, such as **191**, led to the iodocyclopentene products such as **192** *via* migration of the iodine atom during vinylidene formation, thus extending the synthetic utility of the method (Scheme 63).

More recently, Lee and colleagues have reported that *N*-propargyl enamines undergo cycloisomerization in the presence of a rhodium catalyst developed by Trost for the cycloisomerization of homo- and bis-homopropargyl alcohols (*vide supra*).[51] Thus *N*-tosyl propargyl enamine **193** underwent cyclization to provide 1,3-diene product **194** (equation 1), while *N*-benzoyl propargyl enamine **195** cyclized to form 1,4-diene **196** in excellent yield (equation 2), both products containing the indolizidine skeleton (Scheme 64).[81]

The different products obtained may be rationalized according to Scheme 65. Terminal alkyne substrates **193** or **195** form vinylidene intermediate **II**, which undergoes intramolecular attack by the pendant enamine to give zwitterionic iminium species **III**. In the case of the sulfonamide protecting group, the base (DABCO) deprotonates the iminium species to give **IV**. Protonation at the metal, followed by reductive elimination, then gives 1,3-diene product **194** and regenerates the active catalyst. On the other hand, when the protecting group is an amide, **III** may suffer a 1,5-H shift, followed by deprotonation to yield **VII**. Protonation of the metal and reductive elimination then gives 1,4-diene product **196** and the active catalyst.

4. Pericyclic Reactions with Vinylidenes

4.1 Electrocyclization Reactions

The oxa 6π electrocyclization of carbonyl groups onto vinylidene species was seen in stoichiometric reactions earlier in this review (*vide supra*). The first example of a reaction involving an all-carbon 6π electrocyclization onto a catalytic vinylidene intermediate was reported by Merlic. In this reaction, dienylalkynes, such as **197**, underwent conversion to benzene derivatives, such as **198** (Scheme 66).[82]

The catalytic cycle for this transformation is depicted in Scheme 67. Following vinylidene formation (**II**), the key 6π electrocyclic ring closure leads to **III**. The latter step may be either concerted or stepwise. Tautomerization, followed by reductive elimination, then gives the product and regenerates the active catalyst **I**.

Scott has recently applied Merlic's conditions in a naphthoannulation procedure (Scheme 68).[83] For example, anthraquinone (**199**) was olefinated to the bis-gem dibromide, and Sonogashira cross-coupling with trimethylsilylacetylene, followed by protodesilylation, provided substrate **200**. Exposure to the ruthenium catalyst then led to a four-fold dienyne cycloisomerization, providing coronene (**201**). Although the yield was modest, the convergency of the approach and the amount of complexity generated in the reaction is impressive.

Iwasawa has reported that a tungsten complex can also catalyze the 6π electrocyclization of dienynes (equation 1, Scheme 69).[84] Exclusive formation of iodonaphthalene **205** from iodoalkyne **204** increases the synthetic utility of the reaction (equation 2).[85]

Akiyama and coworkers have expanded the substrate scope to include alkynyl imines (Scheme 70).[86] The yields were improved by treating the crude reaction mixture with *N*-methylmorpholine-*N*-oxide, presumably to decomplex the product from the tungsten catalyst.

Liu and coworkers have recently reported a number of ruthenium-catalyzed electrocyclizations of dienynes, followed by a variety of rearrangements depending on the substitution pattern of the substrate. In one such process, iododienyne substrate **208** was converted to iodonaphthalene **209** in good yield (Scheme 71).[87]

To account for this migration of the iodine atom, the mechanism shown in Scheme 72 was proposed in which vinylidene **II** is proposed to undergo 6π electrocyclization. A 1,2-iodine migration leads to carbocation **IV**, which then rearranges to give the product.

An interesting divergence in mechanism is observed in the reaction of dienyne substrates **210** and **212** (Scheme 73). In the former case, a highly substituted benzene is formed (**211**, equation 1),[88] whereas in the latter case a 1,3-diene product is formed (**213**, equation 2).[89]

The formation of product **211** can be explained by the proposed mechanism in Scheme 74. Following its formation, vinylidene **II** undergoes 6π electrocyclization to give **III**, whereby a 1,2-alkyl shift gives tertiary carbocation **IV**. A second 1,2-alkyl shift then gives cyclobutyl ruthenium species **V**. A 1,5-alkyl shift, followed by β-hydride elimination, leads to **VII**, and reductive elimination then yields the product and regenerates the active catalyst.

To explain the formation of 1,3-diene product **213**, the vinylidene species **II** is attacked by the pendant olefin to generate tertiary carbocation **III**, which may be represented by resonance structure **IV** (Scheme 75). Demetalation then gives methylene cyclopropane **V**, which is prone to the well-established ring opening to the diradical trimethylenemethane **VI**.[90] This structure can be represented as fulvene **VII**, and electrophilic attack by the ruthenium catalyst on this

species gives carbocation **VIII**. E1 elimination then leads to 1,3-diene species **IX**, and protonation of the metal, followed by reductive elimination, completes the catalytic cycle.

4.2 [2+2] Cycloaddition Reactions

The first example of a [2+2] reaction on a catalytic vinylidene complex involved the intermolecular coupling of alkynes with alkenes to generate 1,3-diene products, as shown in Scheme 76.[91]

A proposed mechanism for the enyne coupling reaction is shown in Scheme 77. The formation of vinylidene intermediate **II**, followed by olefin coordination and oxidative coupling, leads to metalacyclobutane **IV**. The π-allyl structure **V** can then be formed by β-hydride elimination. Finally, reductive elimination releases the major product **215** and the catalyst. The minor isomeric 1,3-diene product **216** could arise from the alternative regiochemistry of metalacycle formation. Steric factors may then govern the product distribution, as the system would prefer to place the bulky olefin substituent closest to the developing (longer) carbon-ruthenium bond during metalacycle formation.

Murakami subsequently used the enyne coupling reaction in an interesting tandem transformation (Scheme 78). Treatment of enyne **217a** with styrene, in the presence of a ruthenium catalyst, provided cyclohexadiene **220** in moderate yield.[92] In this transformation, Murakami takes advantage of the fact that a 1,3-diene is produced in the enyne coupling step, one of the olefins being *Z*. The presence of the third olefin (present in the substrate) sets up the conjugated triene intermediate **219** for a facile thermal disrotatory 6π electrocyclization to give the product. The use of the trimethylsilylalkyne (**217b**) provided the same product, but the yield was higher. This was explained as being due to the suppression of alkyne dimerization, a well-known reaction pathway for vinylidenes (*vide infra*). The silane presumably migrated during vinylidene formation, and was removed by protodesilylation at some point in the reaction.

Murakami also discovered that pyridine is able to react with terminal alkynes through a vinylidene mechanism (Scheme 79).[93] Thus trimethylsilyl phenylacetylene reacts with pyridine to give the 2-alkenyl pyridine derivative **223** in good yield and with complete selectivity for the *E* olefin geometry (presumably through thermal or base-catalyzed isomerization). Although the catalyst loading and temperature are elevated, this nonetheless constitutes an intriguing method for regioselective pyridine functionalization; the selectivity results from templating the two reacting substrates by coordination of the pyridine to the metal of the ruthenium vinylidene intermediate.

Tethering the two reacting partners can control the regioselectivity of enyne coupling. Grigg and colleagues reported some years ago that 1,6-enynes undergo cycloisomerization in the presence of catalytic Wilkinson's catalyst to give the corresponding 1,3-dienes.[94] Recently, Lee and coworkers revisited this reaction and optimized the reaction conditions (equations 1 and 2, Scheme 80).

Lee proposed a mechanism for this reaction based on deuterium labeling studies, as well as the selective migration of the selenyl group in equation 2 above.[95] The process thus involves vinylidene formation (**II**), [2+2] cycloaddition to give **III**, β-hydride elimination to yield **IV**, and reductive elimination (Scheme 81).

Lee has applied this transformation in a novel tandem process. Two rings are created when 1,6-enynes, bearing appropriately tethered alkyl halides, are treated with a catalytic rhodium species in the presence of triethylamine (Scheme 82).[96]

The proposed mechanism, depicted in Scheme 83, does not involve a metal vinylidene, but rather a metal alkenylidene (**III**). The first step involves insertion of the metal into the alkyne C-H bond to give **II** (which is presumably in equilibrium with the corresponding vinylidene species). This alkynyl metal species may be deprotonated by triethylamine, which induces displacement of the pendant iodide, leading to the alkenylidene species **III**. A [2+2] cycloaddition then gives **IV**, and β-hydride elimination, followed by reductive elimination, leads to product.

A recent paper from Buono and coworkers suggests that catalytic vinylidene reactions may not be the exclusive domain of ruthenium, rhodium, molybdenum, and tungsten. Palladium, when combined with the appropriate ligands, may in fact participate in vinylidene processes. Norbornadiene (or norbornene) and phenylacetylene has been reported to undergo a [2+1] cycloaddition reaction, catalyzed by palladium diacetate and phosphinous acid ligand **231** (Scheme 84).[97]

The proposed mechanism, outlined in Scheme 85, suggests vinylidene formation (**II**, supported by labeling experiments), followed by coordination of norbornadiene to give **III**. A [2+2] cycloaddition, followed by reductive elimination, then gives the product and regenerates the catalyst.

4.3 [4+2] Cycloaddition Reactions

Tagliatesta and colleagues reported the only example of a Diels-Alder reaction involving a catalytic metal vinylidene complex.[98] In this transformation, rhodium and ruthenium porphyrin complexes were used to catalyze the conversion of arylacetylenes to 1-arylnaphthalenes (Scheme 86).

The mechanism of the reaction can be rationalized according to Scheme 87. The rhodium porphyrin, represented by **I**, combines with the alkyne to form vinylidene **II**. An intermolecular Diels-Alder reaction then leads to **III**, and tautomerization, followed by reductive elimination, gives the product and releases the porphyrin catalyst. Although this reaction produced significant amounts of cyclotrimerization byproducts for most arylacetylenes, it does suggest the viability of a Diels-Alder manifold for vinylidene intermediates.

4.4 [1,5]-Sigmatropic Rearrangement

Liu and coworkers recently reported another reaction pathway for metal vinylidenes. In a novel cyclopentadiene synthesis, the researchers made use of a [1,5]-hydrogen atom migration onto a vinylidene intermediate as a key step in the catalytic cycle.[99] In an example of this process, enyne **235** (or the corresponding propargyl alcohol) is converted to cyclopentadiene **236** in the presence of a ruthenium catalyst (Scheme 88).

The mechanism of this transformation, as outlined in Scheme 89, is thought to involve vinylidene formation (**II**), followed by a [1,5]-hydrogen atom migration onto the vinylidene moiety. This event is followed by a 6π electrocyclization, leading to **IV**, and then reductive elimination to give the active catalyst **I** and compound **V**. This species may then undergo two successive [1,5]-hydrogen migrations to give the observed product **236**.

5. Cycloaromatization

Finn was the first to report a metal vinylidene mediated cycloaromatization reaction (Scheme 90).[100] This process begins with conversion of diyne **237** to the vinylidene complex **238** at room temperature. Subsequent treatment with cyclohexadiene in acetonitrile then induced Myers-Saito rearrangement (*i.e.* cycloaromatization, at a lower temperature than required for the all-carbon version) to give diradical **239**. The carbon centered radical then induced a 5-

exo-dig cyclization to give diradical **240**. Hydrogen atom abstraction, followed by reductive elimination of the cationic metal fragment, then provided **242**. The entire sequence (**237** → **242**) could conceivably be promoted by a catalytic amount of ruthenium, since the metal complex is released in the final step of the mechanism, but in practice a stoichiometric amount of metal was required.

In switching to a rhodium catalyst, Uemura was able to render the cycloaromatization process catalytic. Thus treatment of enediyne **243** with a rhodium catalyst led to aromatic product **244** (Scheme 91).[101]

The proposed mechanism of this reaction involves vinylidene formation, followed by cycloaromatization, to give intermediate diradical **III** (Scheme 92). Intramolecular 1,5-hydrogen migration then gives **IV**, and radical-radical coupling leads to metalacycle **V**. β-Hydride elimination, followed by reductive elimination, then regenerates the catalyst and provides product **244**.

In the absence of an available hydrogen atom for the [1,5] shift, the reaction can follow a different course. This is seen in the following example, in which enediyne **245** was converted to silacycle **246** in moderate yield (Scheme 93).[102]

The formation of this product can be rationalized by assuming vinylidene formation, followed by cycloaromatization, to give diradical **III** (Scheme 94). A 1,6-hydrogen atom migration then leads to **IV**, and radical-radical coupling gives metalacycle **V**. Reductive elimination then provides the product.

6. 1,2-Migration of Metal Ligands to Vinylidenes

6.1 Alkyne Dimerization

In principle, the metal-catalyzed head-to-head dimerization of terminal alkynes constitutes a direct method for the selective formation of conjugated enynes. In practice, there has been difficulty in controlling the selectivity of such processes. This is seen in the early work of Yamazaki, in which *t*-butylacetylene (**247**) was dimerized in the presence of a catalytic amount of a ruthenium complex to give a mixture of cumulenes **248** and **249**, head-to-head enynes **250** and **251**, and head-to-tail enyne **252** (Scheme 95).[103]

The preferential formation of **248** was later explained by Yamazaki and Wakatsuki (Scheme 96).[104] The formation of the active catalyst **I** was studied through identification of several intermediates leading to its formation. The catalytic cycle then commences with coordination of *t*-butylacetylene to give **II**. Vinylidene formation then leads to **III**, and intramolecular migration of an alkynyl ligand to the vinylidene leads to the *Z* σ-enynyl complex **IV** (the *E* σ-enynyl species would place a *t*-butyl group in close proximity with the ligand). This species leads to *Z*-enyne **251**, but it is also in equilibrium with cumulene species **V** through a 1,3-shift. Although **IV** is more stable than **V**, coordination of the bulky *t*-butylacetylene to **IV** is disfavored due to steric effects, and thus the reaction preferentially continues on through **V**. Thus coordination of the alkyne leads to **VI**, and oxidative addition of another alkyne, followed by reductive elimination, then gives the cumulene product **248** and regenerates the active catalyst.

Bianchini subsequently reported that a σ-alkynyl ruthenium complex catalyzes the head-to-head dimerization of trimethylsilylacetylene and phenylacetylene in good yield and *Z*-selectivity (Scheme 97).[105] This mechanism proceeds through a series of steps similar to those leading to **232** above.[106]

Yi later reported an interesting ligand effect for the ruthenium-catalyzed dimerization of phenylacetylene. When Cp*Ru(L)H_3 (L = PCy_3) was used as the catalyst, phenylacetylene was dimerized in good yield to the *Z*-isomer, whereas with L = PMe_3 the *E*-isomer was obtained as the major product (Scheme 98).[107]

A mechanism that accounts for this ligand effect was proposed, the features of which are summarized in Scheme 99. A series of steps leads to active catalyst **I**, which can be converted to the equilibrating vinylidene complexes **II** and **III**. When the ligand is large (L = PCy_3), **III** is favored due to repulsion between L and the phenyl group on the vinylidene in **II**, thus reaction preferentially leads to *Z*-enyne **257**. Conversely, when L = PMe_3, the steric interactions dictate that reaction proceeds through **II** to give *E*-enyne **256**.

There have since been numerous reports of ruthenium-catalyzed head-to-head dimerization of phenylacetylene through a vinylidene mechanism, with various levels of *Z*/*E* selectivity. Some of the catalysts that have been employed include: TpRu(PPh_3)$_2$Cl,[108] TpRu(Me*i*Pr_2P)C(Ph)=C(Ph)C≡CPh,[109] Ru(ma)$_2$(PPh_3)$_2$,[110] (η^5-C_9H_7)Ru(PPh_3)$_2$C≡CPh,[111] and $RuCl_2(PCy_3)_2$=CHPh.[112] The selective head-to-head dimerization of aliphatic alkynes through a vinylidene mechanism, however, was not successfully addressed for some time. Towards this goal, Hidai and coworkers reported that a dimeric ruthenium complex was able to catalyze the *Z*-selective dimerization of a variety of aliphatic terminal alkynes (Scheme 100).[113]

Bianchini has reported the most general catalyst to date, capable of head-to-head dimerization of both aromatic and aliphatic terminal alkynes with good Z-selectivity. The catalyst loadings are quite low and the scope is broad, with even *t*-butylacetylene participating as a substrate (equations 1 → 3, Scheme 101).[114]

The first *Z*-selective head-to-head cross-dimerization of arylacetylenes with silylacetylenes was recently reported, thus significantly enhancing the synthetic utility of this process (Scheme 102).[115] In this reaction, Katayama and Ozawa make use of the fact that arylacetylenes preferentially form metal vinylidene intermediates, and so by using an excess of trimethylsilylacetylene they were able to selectively capture these intermediates.

Recent reports suggest that alkynes may add to metal vinylidenes in a different manner than 1,2-migration from the metal center. For example, when 1,6-diyne substrates are exposed to a ruthenium catalyst system and one equivalent of a carboxylic acid, cyclic enol esters are obtained in moderate to good yields (Scheme 103).[116]

The mechanism of this interesting process is depicted in Scheme 104. The key step of the catalytic cycle is thought to involve carboxylate anion-induced cyclization of an alkyne onto the electrophilic vinylidene intermediate (**II** → **III**), a process that would be consistent with the observed geometry of the enol ester. Finally, protonation and reductive elimination releases the product and the active catalyst.

6.2 Arylative and Alkenylative Cyclization

Lee and coworkers have reported a new arylative (and alkenylative) cyclization reaction. Thus 1,5-enynes, where the alkene is conjugated to a carbonyl group, can undergo a tandem carbometalation-cyclization reaction to give cyclopentene products. An example of this transformation is depicted in Scheme 105.[117]

The product formation was rationalized according to Scheme 106. The active catalyst (**I**) may undergo ligand displacement with the solvent to give **II**. Transmetalation with the boronic acid then leads to **III**, which can form a vinylidene with the substrate. A 1,2-migration of the aryl

group then leads to alkenyl rhodium species **V**, which can coordinate the proximal enone and undergo a 1,4-addition to give rhodium enolate **VI**. Finally, protonation and reductive elimination leads to product **265**.

6.3 Hydroboration

Miyaura has reported the regio- and stereoselective hydroboration of terminal alkynes using either a rhodium or an iridium catalyst with electron-rich phosphines.[118] An example of this transformation is shown in Scheme 107.

This methodology has great synthetic promise as it offers *Z*-1-alkenylborane products, which can be valuable partners in Suzuki cross-coupling reactions. Traditionally one has only had direct access to *E*-1-alkenylboranes by rhodium-catalyzed hydroboration of terminal alkynes using Wilkinson's catalyst[119] In order to explain the regio- and stereoselectivity, Miyaura proposed the mechanism shown in Scheme 108. The active catalyst (**I**) and the substrate form a vinylidene intermediate (**II**), a process that is consistent with deuterium labeling studies. Oxidative addition of catecholborane (**267**) then leads to **III**, whereby a 1,2-migration, followed by reductive elimination, gives the product **268**. It was reasoned that the thermodynamic stability of the alkene geometry (*E*) of **IV** is reflected in the product distribution (*Z* product **268** preferentially formed).

7. Conclusion

The prime goal of organic synthesis should be to develop reactions that are efficient in terms of selectivity[120] and atom economy.[121] Selective addition and rearrangement reactions have the potential to fulfill these criteria perfectly. In this review it is evident that transition metals can catalyze these two types of reactions simply by taking advantage of the facile conversion of terminal alkynes to metal vinylidenes. The variety of products made in such reactions is impressive, and the list of such transformations will no doubt continue to grow, particularly as chemists apply these useful reactions in tandem bond-forming processes. Although most reactions involve ruthenium, rhodium, molybdenum, or tungsten complexes, other metals and ligands could potentially catalyze the same (or even new) reactions. The application of such reactions in target oriented synthesis remains limited, but this will change as chemists become aware of the advantages associated with converting readily available terminal alkynes into a wide variety of functionalized products.

Biographies

Barry M. Trost was born in Philadelphia, PA in 1941 and studied at the University of Pennsylvania (BA, 1962). He obtained his Ph.D. in 1965 at MIT. He moved to the University of Wisconsin where he was made Professor in 1969 and subsequently Vilas Research Professor in 1982. He moved to Stanford University in 1987 and became Tamaki Professor of Humanities and Sciences in 1990. In addition to holding Visiting Professorships at several universities worldwide, he has been awarded numerous prizes. His interests span the entire field of organic synthesis, particularly in the development of novel methodology.

Andrew McClory was born in Montreal in 1976. He received his B.Sc. from Concordia University in 1999. He then carried out his graduate studies at Stanford University, where he worked on ruthenium and rhodium-catalyzed atom economical reactions under the guidance of Professor Barry M. Trost. He received his Ph.D. in 2007. He is currently a postdoctoral researcher in the laboratory of Professor Brian M. Stoltz at the California Institute of Technology.

References

1. (a) Huguet J, Karpf M, Dreiding AS. Tetrahedron Lett 1983;24:4177–4180. (b) Solaja B, Huguet J, Karpf M, Dreiding AS. Tetrahedron 1987;43:4875–4886.
2. (a) Bruce MI, Swincer AG. Adv Organomet Chem 1983;22:59. (b) Werner H. Angew Chem Int Ed Engl 1990;29:1077–1089. (c) Bruce MI. Chem Rev 1991;91:197–257. (d) Bruce MI. Chem Rev 1998;98:2797–2858. [PubMed: 11848978]
3. Wolf J, Werner H, Serhadli O, Ziegler ML. Angew Chem Int Ed Engl 1983;22:414–416.
4. Unimolecular pathway supported experimentally by double crossover studies: Grotjahn DB, Zeng X, Cooksy AL. J Am Chem Soc 2006;128:2798–2799. [PubMed: 16506748]
5. Bimolecular pathway supported by computational studies: Wakatsuki Y, Koga N, Werner H, Morokuma K. J Am Chem Soc 1997;119:360–366.
6. Review: Wakatsuki Y. J Organomet Chem 2004;689:4092–4109.
7. Reviews: (a) Bruneau C, Dixneuf PH. Acc Chem Res 1999;32:311–323. (b) Bruneau C, Dixneuf PH. Angew Chem Int Ed Engl 2006;45:2176–2203. [PubMed: 16521143]
8. Review: Varela JA, Saa C. Chem Eur J 2006;12:6450–6456.
9. Sasaki Y, Dixneuf PH. J Chem Soc Chem Commun 1986;790–791
10. Bruneau C, Dixneuf PH. J Mol Cat 1992;74:97–107.
11. Mahe R, Dixneuf PH, Lecolier S. Tetrahedron Lett 1986;27:6333–6336.
12. (a) Sasaki Y, Dixneuf PH. J Org Chem 1987;52:314–315. (b) Mahe R, Sasaki Y, Bruneau C, Dixneuf PH. J Org Chem 1989;54:1518–1523.
13. A comparison of ruthenium catalysts for this transformation: Bruneau C, Dixneuf PH, Lecolier S. J Mol Cat 1988;44:175–178.
14. Hofer J, Doucet H, Bruneau C, Dixneuf PH. Tetrahedron Lett 1991;32:7409–7410.
15. Ruppin C, Dixneuf PH. Tetrahedron Lett 1986;27:6323–6324.
16. Review: Bruneau C, Dixneuf PH. Chem Commun 1997:507–512.
17. Doucet H, Martin-Vaca B, Bruneau C, Dixneuf PH. J Org Chem 1995;60:7247–7255.

18. Doucet H, Hofer J, Bruneau C, Dixneuf PH. J Chem Soc Chem Commun 1993:850–851.
19. Doucet H, Hofer J, Derrien N, Bruneau C, Dixneuf PH. Bull Soc Chim Fr 1996;133:939–944.
20. Ru(HB(pz)$_3$)(COD)Cl: (a) Gemel C, Trimmel G, Slugovc C, Kremel S, Mereiter K, Schmid R, Kirchner K. Organometallics 1996;15:3998–4004. Ru(methallyl)$_2$dppe: (b) Doucet H, Derrien N, Kabouche Z, Bruneau C, Dixneuf PH. J Organomet Chem 1997;551:151–157. RuCl$_x$(p-cymene)(triazol-5-ylidene): (c) Melis K, Samulkiewicz P, Rynkowski J, Verpoort F. Tetrahedron Lett 2002;43:2713–2716.
21. Review: Bruneau C, Dixneuf PH. Chem Commun 1997:507–512.
22. Gooβen LJ, Paetzold J, Koley D. Chem Commun 2003:706–707.
23. Picquet M, Bruneau C, Dixneuf PH. Chem Commun 1997:1201–1202.
24. Picquet M, Fernandez A, Bruneau C, Dixneuf PH. Eur J Org Chem 2000:2361–2366.
25. Swaminathan S, Narayanan KV. Chem Rev 1971;71:429–438.
26. Jimenez-Tenorio M, Puerta MC, Valerga P, Moreno-Dorado FJ, Guerra FM, Massanet GM. Chem Commun 2001:2324–2325.
27. Melis K, Samulkiewicz P, Rynkowski J, Verpoort F. Tetrahedron Lett 2002;43:2713–2716.
28. Fischer EO. Adv Organomet Chem 1976;14:1–32.
29. Trost BM, Dyker G, Kulawiec RJ. J Am Chem Soc 1990;112:7809–7811.
30. Trost BM, Kulawiec RJ. J Am Chem Soc 1992;114:5579–5584.
31. Trost BM, Kulawiec RJ, Hammes A. Tetrahedron Lett 1993;34:587–590.
32. Corey EJ, Fuchs PL. Tetrahedron Lett 1972;13:3769–3772.
33. Trost BM, Flygare JA. J Org Chem 1994;59:1078–1082.
34. Trost BM, Flygare JA. J Am Chem Soc 1992;114:5476–5477.
35. Trost BM, Flygare JA. Tetrahedron Lett 1994;35:4059–4062.
36. Reviews: (a) Weyershausen B, Dotz KH. Eur J Inorg Chem 1999:1057–1066. (b) McDonald FE. Chem Eur J 1999;5:3103–3106. (c) McDonald FE, Reddy KS. J Organomet Chem 2001;617–618:444–452.
37. McDonald FE, Connolly CB, Gleason MM, Towne TB, Treiber KD. J Org Chem 1993;58:6952–6953.
38. McDonald FE, Gleason MM. Angew Chem Int Ed Engl 1995;34:350–352.
39. McDonald FE, Gleason MM. J Am Chem Soc 1996;118:6648–6659.
40. McDonald FE, Reddy KS. Angew Chem Int Ed Engl 2001;40:3653–3655. [PubMed: 11592211]
41. McDonald FE, Zhu HYH. J Am Chem Soc 1998;120:4246–4247.
42. McDonald FE, Reddy KS, Diaz Y. J Am Chem Soc 2000;122:4304–4309.
43. Wipf P, Graham TH. J Org Chem 2003;68:8798–8807. [PubMed: 14604347]
44. Cutchins WW, McDonald FE. Org Lett 2002;4:749–752. [PubMed: 11869118]
45. Davidson MH, McDonald FE. Org Lett 2004;6:1601–1603. [PubMed: 15128246]
46. McDonald FE, Schultz CC, Chatterjee AK. Organometallics 1995;14:3628–3629.
47. McDonald FE, Bowman JL. Tetrahedron Lett 1996;37:4675–4678.
48. Trost BM, Rhee YH. J Am Chem Soc 1999;121:11680–11683.
49. Trost BM, Rhee YH. J Am Chem Soc 2002;124:2528–2533. [PubMed: 11890802]
50. Trost BM, Rhee YH. Org Lett 2004;6:4311–4313. [PubMed: 15524471]
51. Trost BM, Rhee YH. J Am Chem Soc 2003;125:7482–7483. [PubMed: 12812465]
52. Tokunaga M, Wakatsuki Y. Angew Chem Int Ed Engl 1998;37:2867–2869.
53. Suzuki T, Tokunaga M, Wakatsuki Y. Org Lett 2001;3:735–737. [PubMed: 11259049]
54. Alvarez P, Bassetti M, Gimeno J, Mancini G. Tetrahedron Lett 2001;42:8467–8470.
55. (a) Grotjahn DB, Incarvito CD, Rheingold AL. Angew Chem Int Ed Engl 2001;40:3884–3887. [PubMed: 11668563] (b) Grotjahn DB, Lev DA. J Am Chem Soc 2004;126:12232–12233. [PubMed: 15453733] (c) Grotjahn DB. Chem Eur J 2005:7146–7153.
56. Chevallier F, Breit B. Angew Chem Int Ed Engl 2006;45:1599–1602. [PubMed: 16447296]
57. Labonne A, Kribber T, Hintermann L. Org Lett 2006;8:5853–5856. [PubMed: 17134289]

58. Picquet M, Fernandez A, Bruneau C, Dixneuf PH. Eur J Org Chem 2000:2361–2366.
59. Suzuki T, Tokunaga M, Wakatsuki Y. Tetrahedron Lett 2002;43:7531–7533.
60. Chen Y, Ho DM, Lee C. J Am Chem Soc 2005;127:12184–12185. [PubMed: 16131171]
61. McDonald FE, Schultz CC. J Am Chem Soc 1994;116:9363–9364.
62. Lo CY, Guo H, Lian JJ, Shen FM, Liu RS. J Org Chem 2002;67:3930–3932. [PubMed: 12027718]
63. Madhushaw RJ, Lin MY, Md S, Sohel A, Liu RS. J Am Chem Soc 2004;126:6895–6899. [PubMed: 15174858]
64. Lin MY, Maddirala SJ, Liu RS. Org Lett 2005;7:1745–1748. [PubMed: 15844896]
65. Ohe K, Miki K, Yokoi T, Nishino F, Uemura S. Organometallics 2000;19:5525–5528.
66. Review: Miki K, Uemura S, Ohe K. Chem Lett 2005;34:1068–1073.
67. Iwasawa N, Shido M, Maeyama K, Kusama H. J Am Chem Soc 2000;122:10226–10227.
68. Ohe K, Yokoi T, Miki K, Nishino F, Uemura S. J Am Chem Soc 2002;124:526–527. [PubMed: 11804476]
69. McDonald FE, Burova SA, Huffman JG Jr. Synthesis 2000:970–974.
70. Kondo T, Tanaka A, Kotachi S, Watanabe Y. J Chem Soc Chem Commun 1995:413–414.
71. Gooβen LJ, Rauhaus JE, Deng G. Angew Chem Int Ed Engl 2005;44:4042–4045. [PubMed: 15924283]
72. Fukumoto Y, Dohi T, Masaoka H, Chatani N, Murai S. Organometallics 2002;21:3845–3847.
73. McDonald FE, Chatterjee AK. Tetrahedron Lett 1997;38:7687–7690.
74. Trost BM, McClory A. Angew Chem Int Ed Engl 2007;46:2074–2077. [PubMed: 17285670]
75. Park YJ, Kwon BI, Ahn JA, Lee H, Jun CH. J Am Chem Soc 2004;126:13892–13893. [PubMed: 15506728]
76. Jerome F, Monnier F, Lawicka H, Derien S, Dixneuf PH. Chem Commun 2003:696–697.
77. McDonald FE, Olson TC. Tetrahedron Lett 1997;38:7691–7692.
78. Maeyama K, Iwasawa N. J Am Chem Soc 1998;120:1928–1929.
79. Iwasawa N, Miura T, Kiyota K, Kusama H, Lee K, Lee PH. Org Lett 2002;4:4463–4466. [PubMed: 12465913]
80. For another method of cyclopentene annulation, see: Danheiser RL, Fink DM, Tsai Y-M. Org Synth 1988;66:8–13.
81. Kim H, Lee C. J Am Chem Soc 2006;128:6336–6337. [PubMed: 16683796]
82. Merlic CA, Pauly ME. J Am Chem Soc 1996;118:11319–11320.
83. Donovan PM, Scott LT. J Am Chem Soc 2004;126:3108–3112. [PubMed: 15012140]
84. Maeyama K, Iwasawa N. J Org Chem 1999;64:1344–1346.
85. Miura T, Iwasawa N. J Am Chem Soc 2002;124:518–519. [PubMed: 11804472]
86. Sangu K, Fuchibe K, Akiyama T. Org Lett 2004;6:353–355. [PubMed: 14748591]
87. Shen HC, Pal S, Lian JJ, Liu RS. J Am Chem Soc 2003;125:15762–15763. [PubMed: 14677964]
88. Lian JJ, Odedra A, Wu CJ, Liu RS. J Am Chem Soc 2005;127:4186–4187. [PubMed: 15783197]
89. Madhushaw RJ, Lo CY, Hwang CW, Su MD, Shen HC, Pal S, Shaikh IR, Liu RS. J Am Chem Soc 2004;126:15560–15565. [PubMed: 15563185]
90. (a) Rule M, Salinaro RF, Pratt DR, Berson JA. J Am Chem Soc 1982;104:2223–2228. (b) Salinaro RF, Berson JA. J Am Chem Soc 1982;104:2228–2232.
91. Murakami M, Ubukata M, Ito Y. Tetrahedron Lett 1998;39:7361–7364.
92. Murakami M, Ubukata M, Ito Y. Chem Lett 2002:294–295.
93. Murakami M, Hori S. J Am Chem Soc 2003;125:4720–4721. [PubMed: 12696885]
94. Grigg R, Stevenson P, Worakun T. Tetrahedron 1988;44:4967–4972.
95. Kim H, Lee C. J Am Chem Soc 2005;127:10180–10181. [PubMed: 16028924]
96. Joo JM, Yuan Y, Lee C. J Am Chem Soc 2006;128:14818–14819. [PubMed: 17105287]
97. Bigeault J, Giordano L, Buono G. Angew Chem Int Ed Engl 2005;44:4753–4757. [PubMed: 15981291]
98. Elakkari E, Floris B, Galloni P, Tagliatesta P. Eur J Org Chem 2005:889–894.

99. Datta S, Odedra A, Liu RS. J Am Chem Soc 2005;127:11606–11607. [PubMed: 16104729]
100. Wang Y, Finn MG. J Am Chem Soc 1995;117:8045–8046.
101. Ohe K, Kojima M, Yonehara K, Uemura S. Angew Chem Int Ed Engl 1996;35:1823–1825.
102. Manabe T, Yanagi S, Ohe K, Uemura S. Organometallics 1998;17:2942–2944.
103. Yamazaki H. J Chem Soc Chem Commun 1976:841–842.
104. Wakatsuki Y, Yamazaki H, Kumegawa N, Satoh T, Satoh JY. J Am Chem Soc 1991;113:9604–9610.
105. Bianchini C, Peruzzini M, Zanobini F, Frediani P, Albinati A. J Am Chem Soc 1991;113:5453–5454.
106. Bianchini C, Frediani P, Masi D, Peruzzini M, Zanobini F. Organometallics 1994;13:4616–4632.
107. (a) Yi CS, Liu N. Organometallics 1996;15:3968–3971. (b) Yi CS, Liu N. Synlett 1999:281–287.
108. (a) Slugovc C, Mereiter K, Zobetz E, Schmid R, Kirchner K. Organometallics 1996;15:5275–5277. (b) Slugovc C, Doberer D, Gemel C, Schmid R, Kirchner K, Winkler B, Stelzer F. Mon fur Chem 1998;129:221–233. (c) Pavlik S, Gemel C, Slugovc C, Mereiter K, Schmid R, Kirchner K. J Organomet Chem 2001;617–618:301–310.
109. Tenorio MAJ, Tenorio MJ, Puerta MC, Valerga P. Organometallics 2000;19:1333–1342.
110. Fryzuk MD, Jonker MJ, Rettig SJ. Chem Commun 1997:377–378.
111. Bassetti M, Marini S, Tortorella F, Cadierno V, Diez J, Gamasa MP, Gimeno J. J Organomet Chem 2000;593–594:292–298.
112. Melis K, De Vos D, Jacobs P, Verpoort F. J Organomet Chem 2002;659:159–164.
113. Qu JP, Masui D, Ishii Y, Hidai M. Chem Lett 1998:1003–1004.
114. Chen X, Xue P, Sung HHY, Williams ID, Peruzzini M, Bianchini C, Jia G. Organometallics 2005;24:4330–4332.
115. Katayama H, Yari H, Tanaka M, Ozawa F. Chem Commun 2005:4336–4338.
116. Kim H, Goble SD, Lee C. J Am Chem Soc 2007;129:1030–1031. [PubMed: 17263374]
117. Chen Y, Lee C. J Am Chem Soc 2006;128:15598–15599. [PubMed: 17147363]
118. Ohmura T, Yamamoto Y, Miyaura N. J Am Chem Soc 2000;122:4990–4991.
119. Manning D, Noth H. Angew Chem Int Ed Engl 1985;24:878–879.
120. Trost BM. Science 1983;219:245–250. [PubMed: 17798254]
121. (a) Trost BM. Science 1991;254:1471–1477. [PubMed: 1962206] (b) Trost BM. Angew Chem Int Ed Engl 1995;34:259–281.

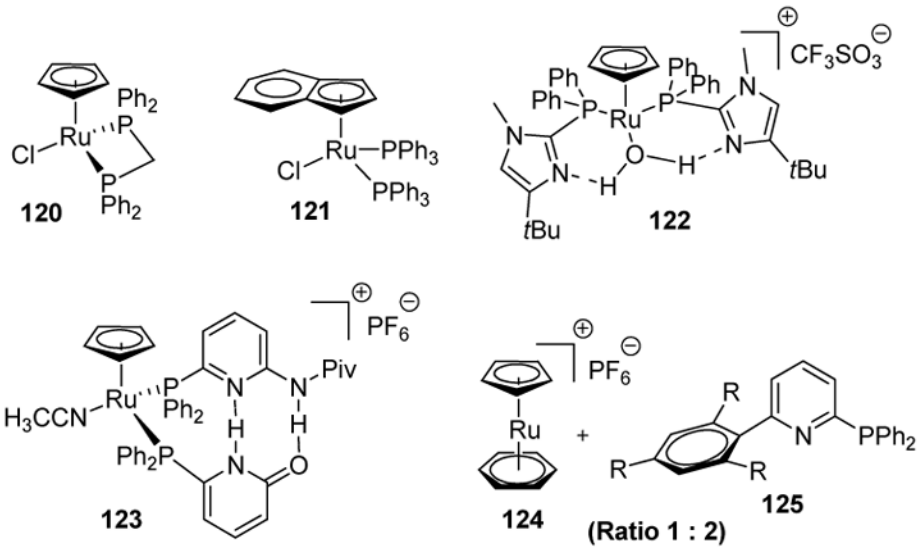
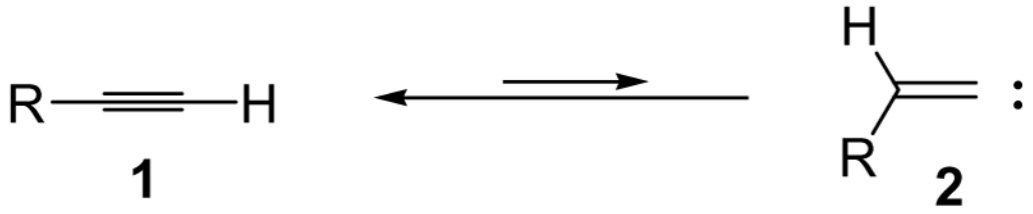
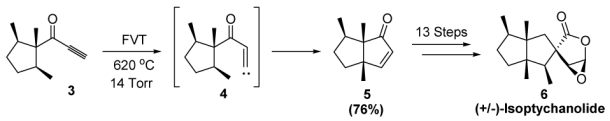


Figure 1.
Ruthenium Catalysts for Anti-Markovnikov Alkyne Hydration.

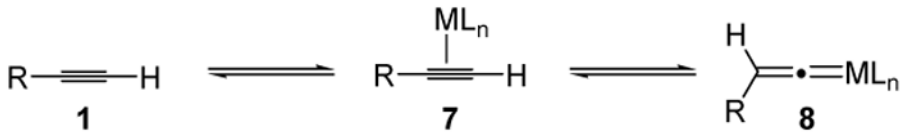


Scheme 1.
Terminal Alkyne and the Corresponding Vinylidene

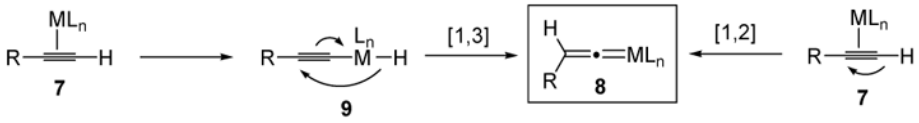


Scheme 2.

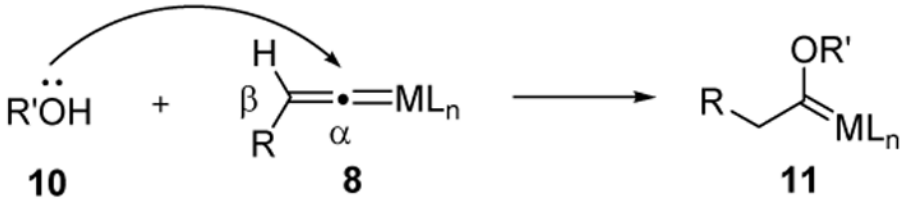
Synthetic Use of an Organic Vinylidene: Dreiding's Synthesis of (+/−)-Isoptychanolide. FVT=flash vacuum thermolysis.



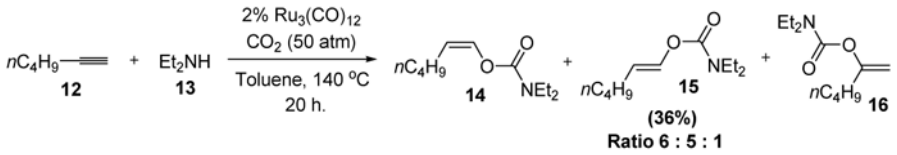
Scheme 3.
Formation of Metal Vinylidenes from Terminal Alkynes



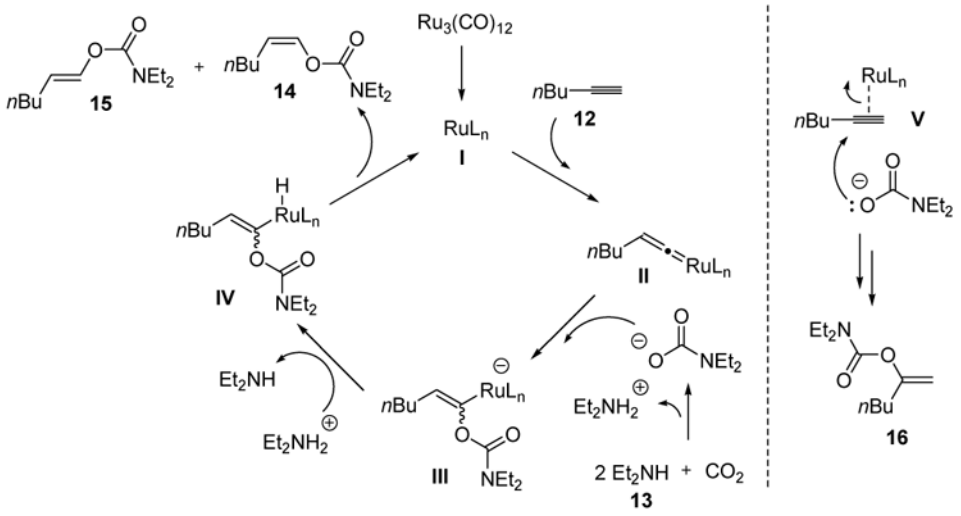
Scheme 4.
Mechanisms of Metal Vinylidene Formation



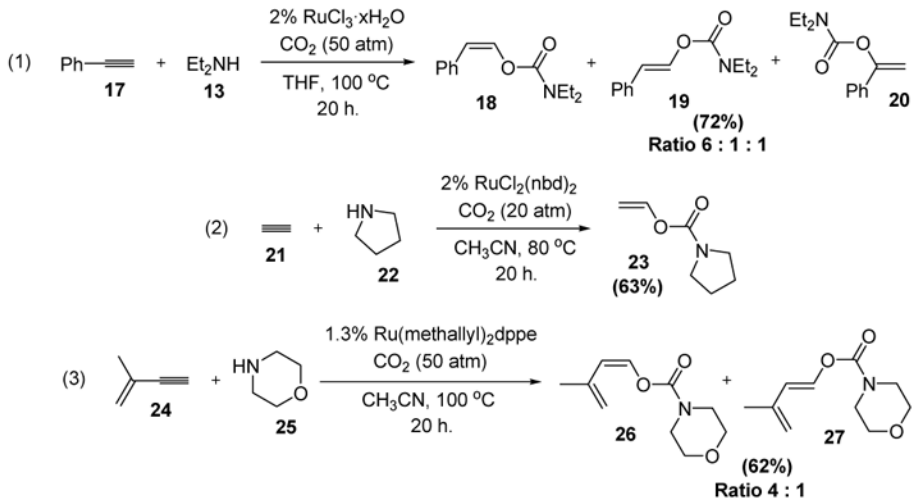
Scheme 5.
Nucleophilic Addition to Metal Vinylidenes: Fischer Carbene Formation



Scheme 6.
Vinylcarbamates from Terminal Alkynes, Secondary Amines, and Carbon Dioxide

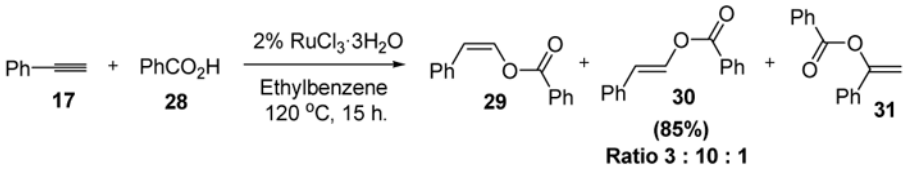


Scheme 7.
Mechanism of Vinylcarbamate Formation

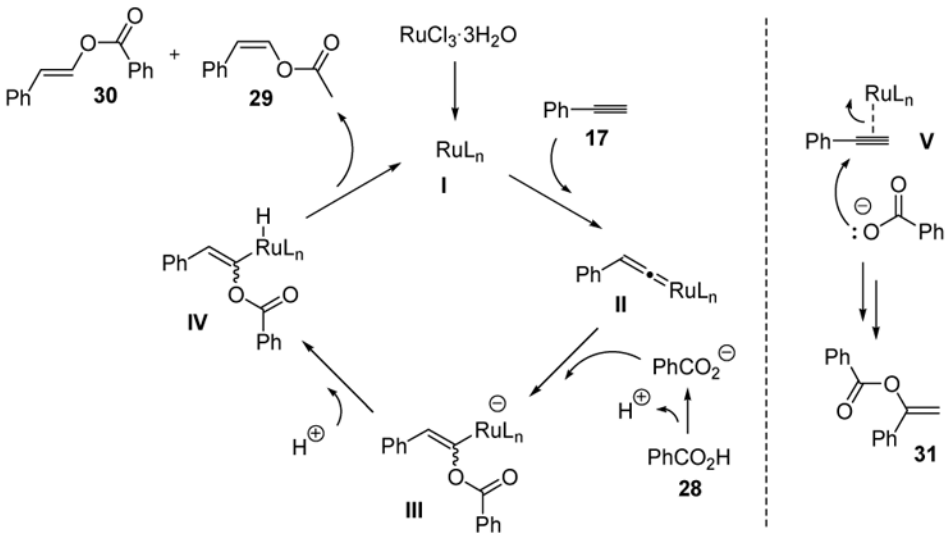


Scheme 8.

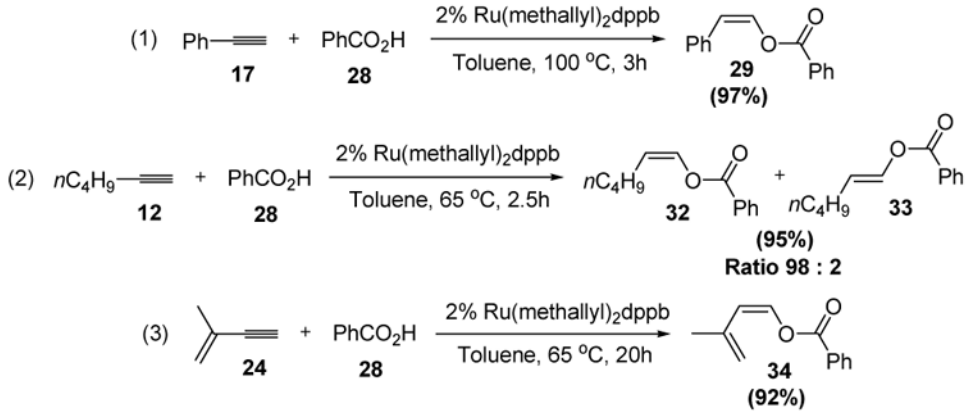
Synthesis of Vinylcarbamates: Scope of Alkynes and Secondary Amines. dppe=bis (diphenylphosphino)ethane, nbd=norbornadiene, THF=tetrahydrofuran.



Scheme 9.
Formation of Enol Esters from Carboxylic Acids and Alkynes

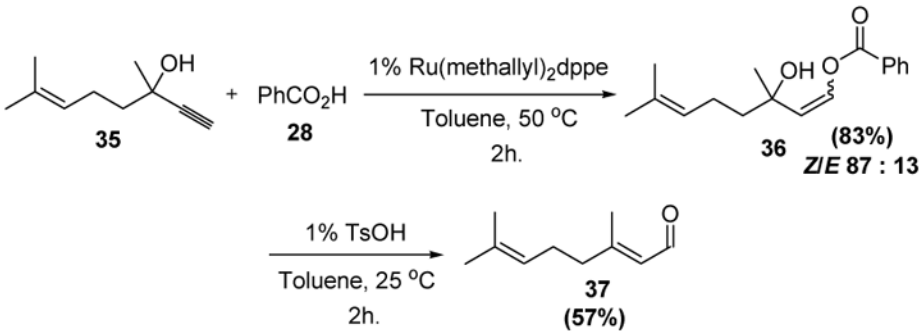


Scheme 10.
Mechanism of Enol Ester Formation



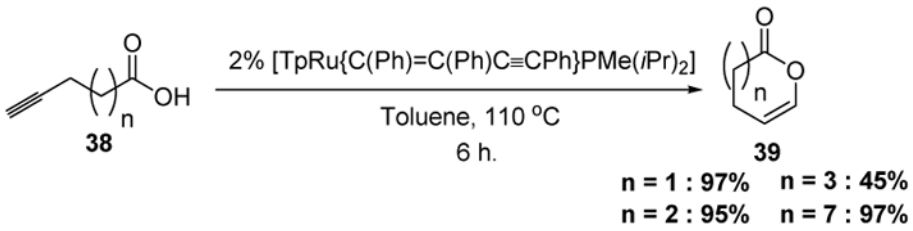
Scheme 11.

Ruthenium-Catalyzed Formation of Enol Esters: Scope of Alkynes. dppb=bis (diphenylphosphino)butane.

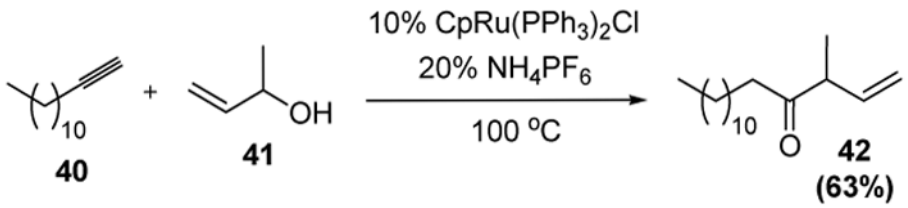


Scheme 12.

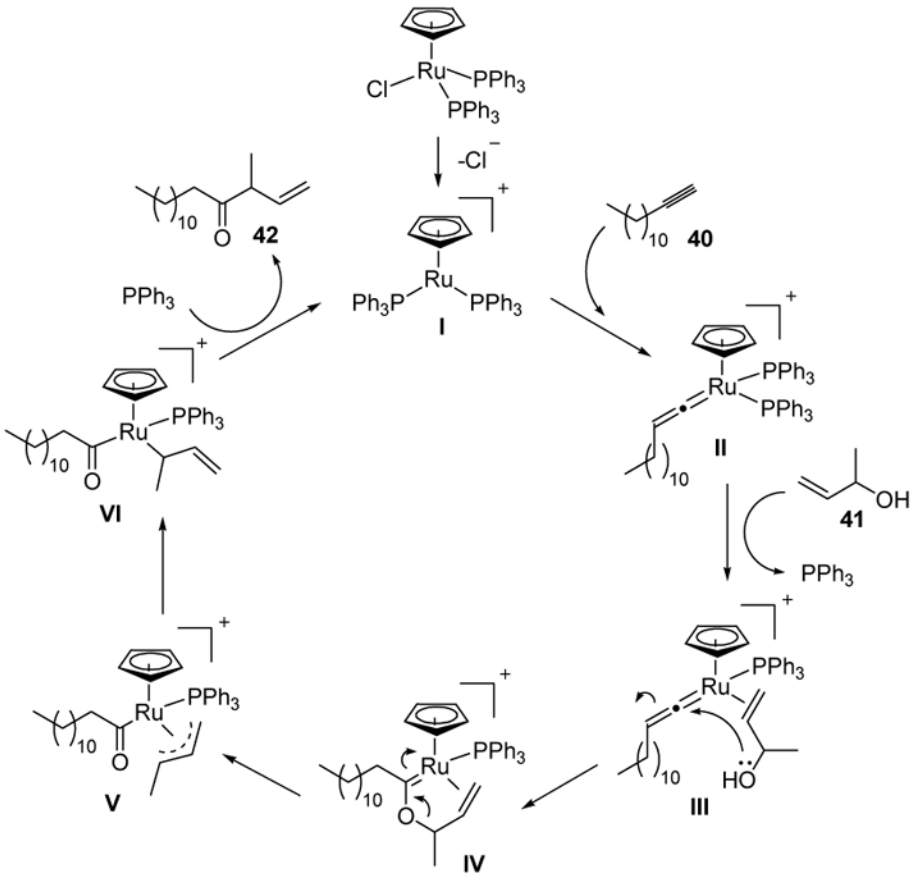
Dixneuf's Isomerization of Propargyl Alcohols to Enals. dppe=bis(diphenylphosphino)ethane, TsOH=*p*-toluenesulfonic acid.



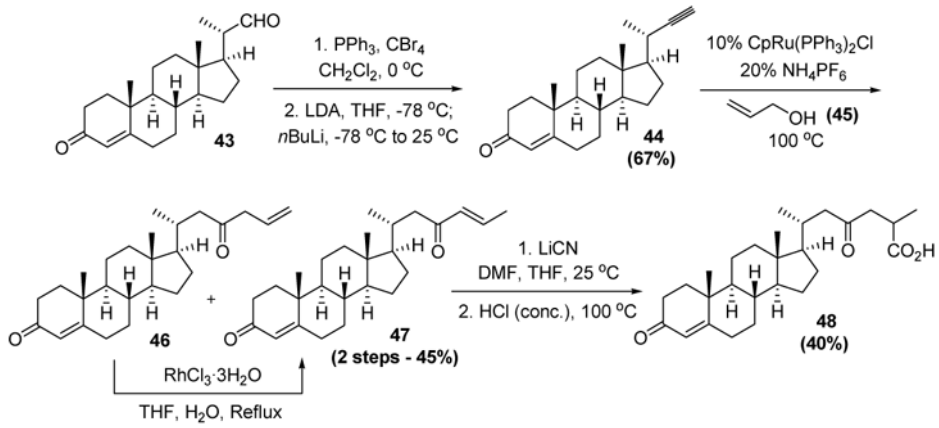
Scheme 13.
Valerga's Cyclization of α,ω-Alkynoic Acids



Scheme 14.
Ruthenium-Catalyzed Reconstitutive Condensation. Cp=η^5-cyclopentadienyl.

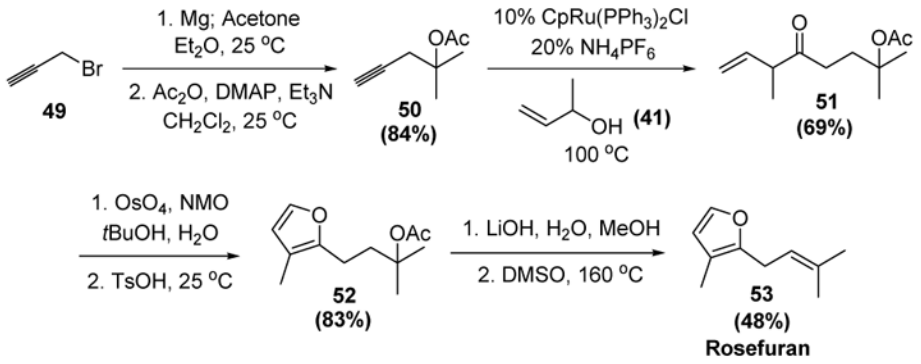


Scheme 15.
Proposed Mechanism of Ruthenium-Catalyzed Reconstitutive Condensation



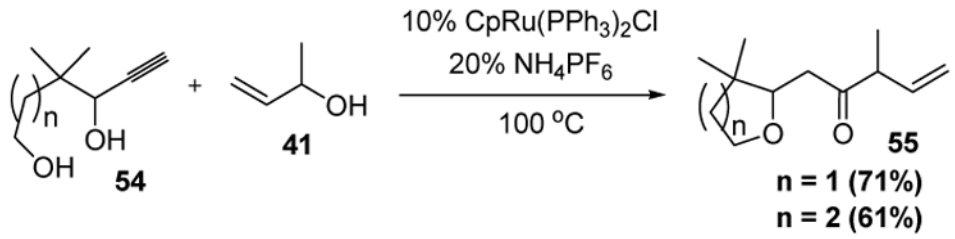
Scheme 16.

Trost's Synthesis of a Functionalized Steroid Side Chain. Cp=η^5-cyclopentadienyl., DMF=*N*,*N*-dimethylformamide, LDA=lithium diisopropylamide, THF=tetrahydrofuran.

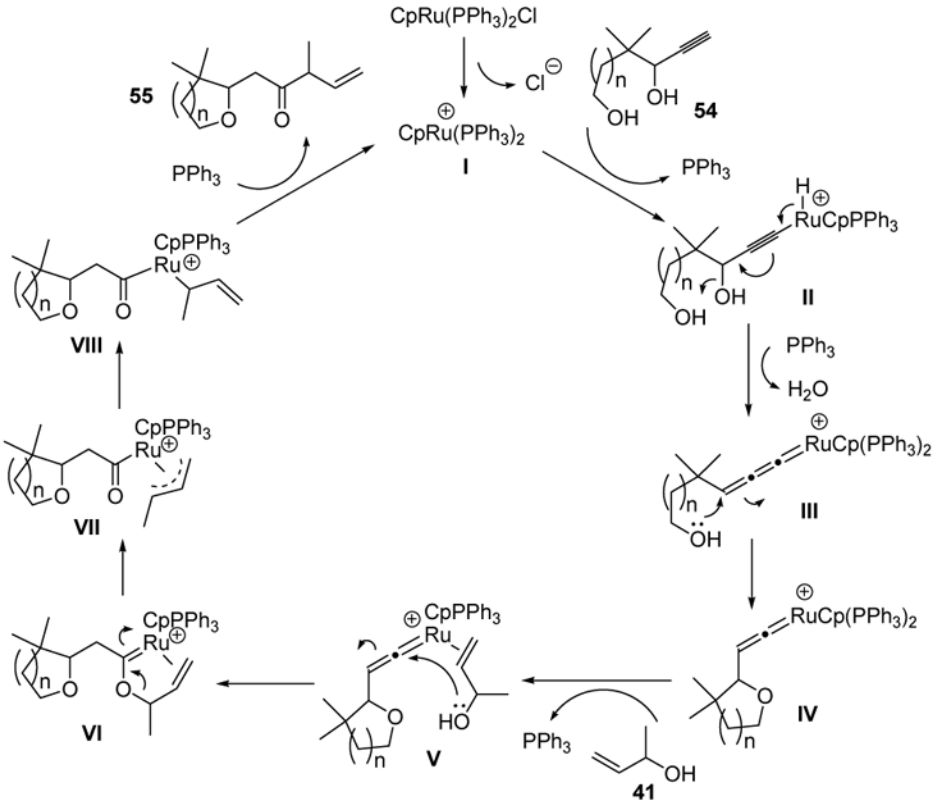


Scheme 17.

Trost's Synthesis of Rosefuran. Cp=η^5-cyclopentadienyl., DMSO=dimethyl sulfoxide, NMO=*N*-methylmorpholine-*N*-oxide, TsOH=*p*-toluenesulfonic acid.

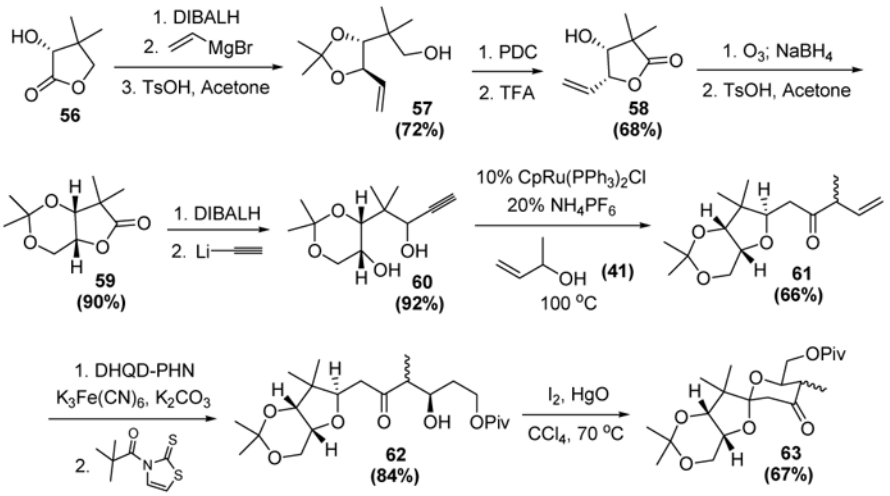


Scheme 18.
Trost's Tandem Cyclization-Reconstitutive Condensation. Cp=η^5-cyclopentadienyl.



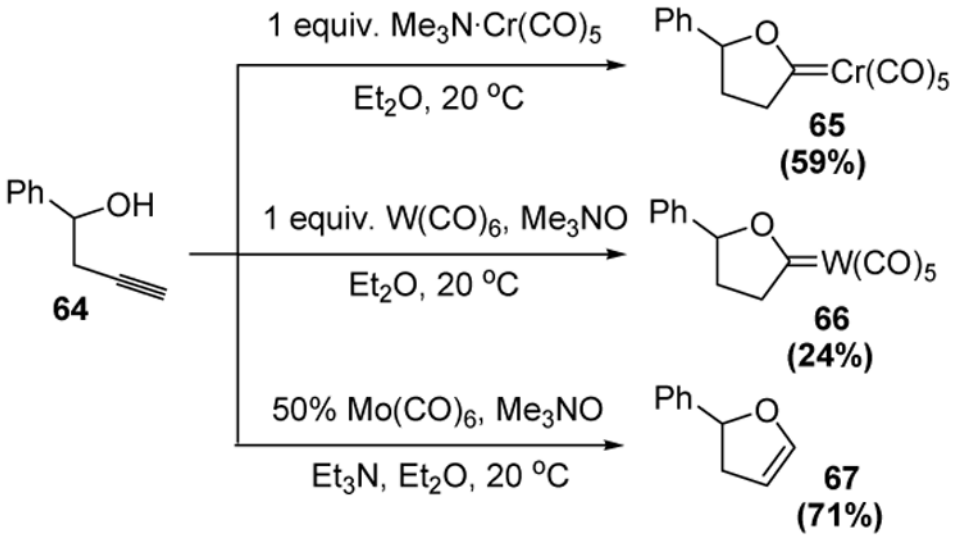
Scheme 19.

Mechanism of Trost's Tandem Cyclization-Reconstitutive Condensation. Cp=η^5-cyclopentadienyl.

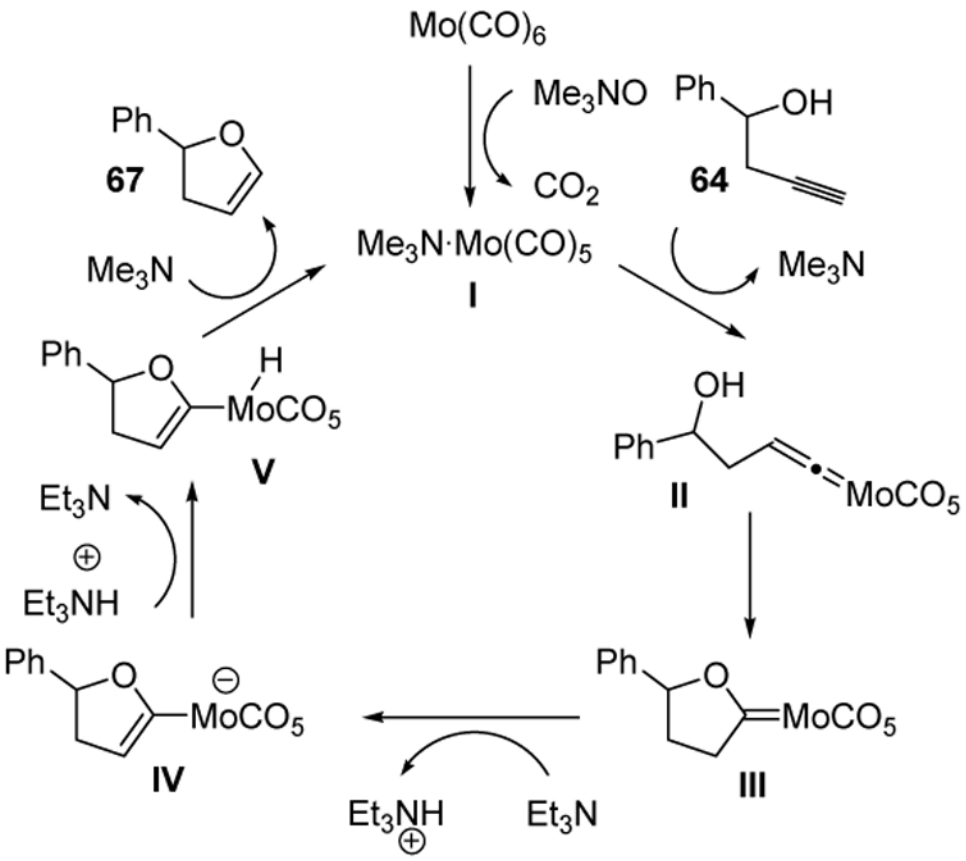


Scheme 20.

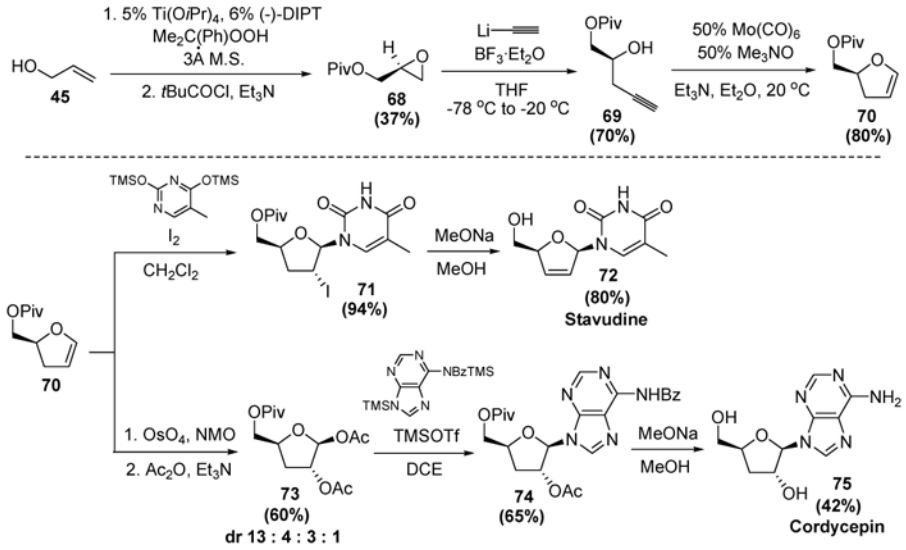
Trost's Synthesis of The Spiroketal Subunit of (−)-Calyculin A. Cp=η^5-cyclopentadienyl, (DHQD)PHN=dihydroquinidine 9-*O*-(9′-phenanthryl) ether, DIBALH=diisobutylaluminum hydride, PDC=pyridinium dichromate, TFA=trifluoroacetic acid, TsOH=*p*-toluenesulfonic acid.



Scheme 21.
McDonald's Seminal Alkynol Cycloisomerization Reaction

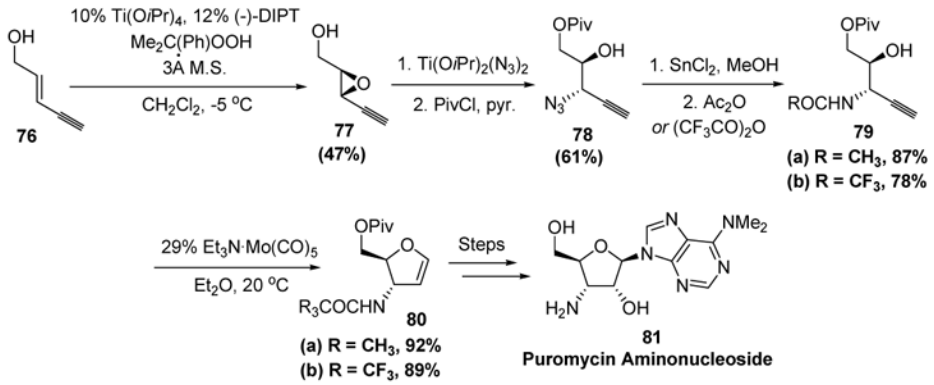


Scheme 22.
Mechanism of Molybdenum-Catalyzed Alkynol Cycloisomerization

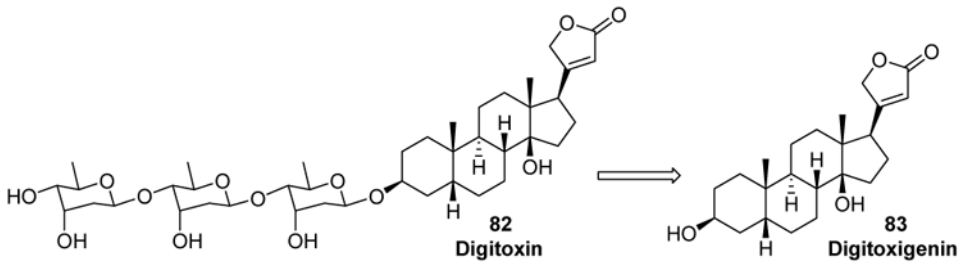


Scheme 23.

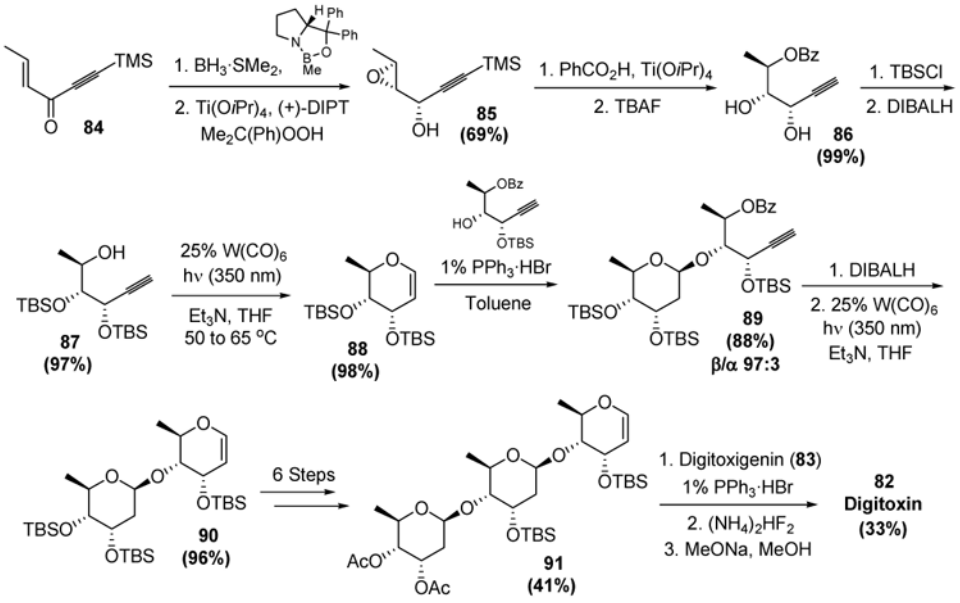
McDonald's Syntheses of Stavudine and Cordycepin. DCE=1,2-dichloroethane, DIPT=diisopropyltartrate, M. S.=molecular sieves, NMO=*N*-methylmorpholine-*N*-oxide, THF=tetrahydrofuran, TMSOTf=trimethylsilyl trifluoromethanesulfonate.



Scheme 24.
McDonald's Syntheses of 3-Aminonucleosides

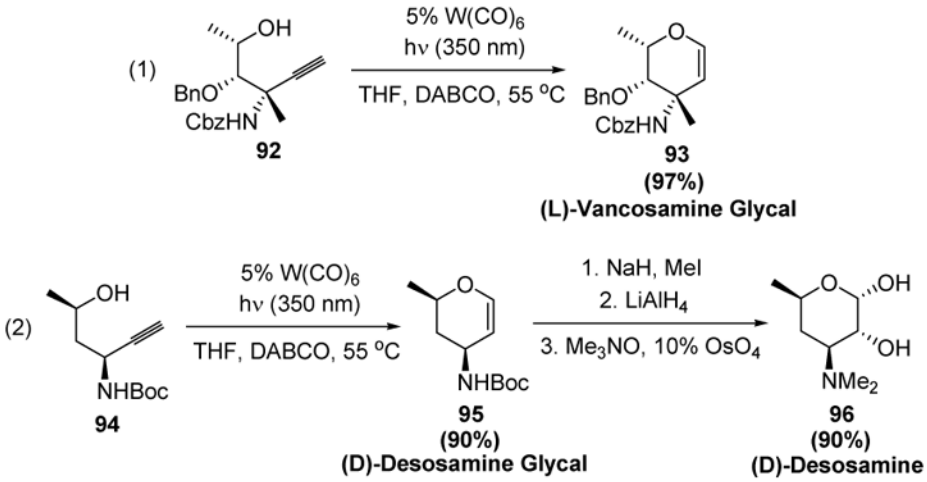


Scheme 25.
McDonald's Retrosynthetic Analysis of Digitoxin



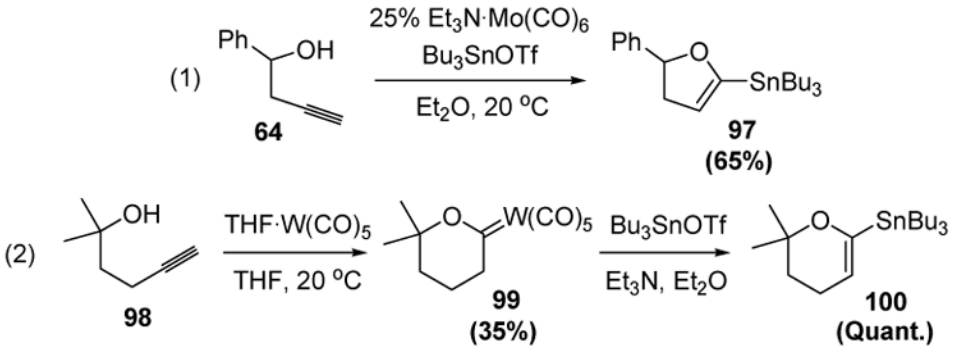
Scheme 26.

McDonald's Iterative Cycloisomerization Approach to Digitoxin. DIBALH=diisobutylaluminum hydride, DIPT=diisopropyltartrate, TBAF=tetrabutylammonium fluoride, TBSCl=*tert*-butyldimethylsilyl chloride, THF=tetrahydrofuran.

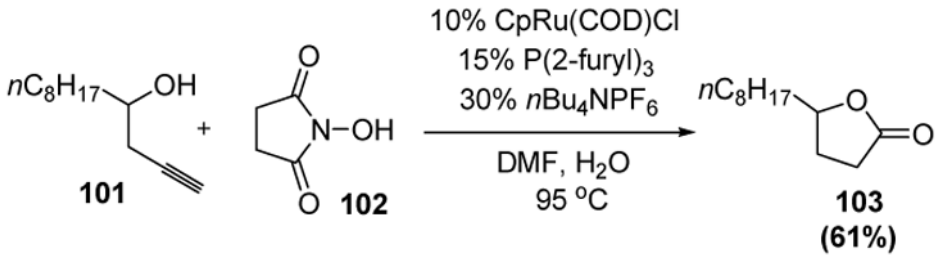


Scheme 27.

McDonald's Syntheses of (L)-Vancosamine and (D)-Desosamine Glycals. DABCO=1,4-diazabicyclo[2.2.2]octane, THF=tetrahydrofuran.

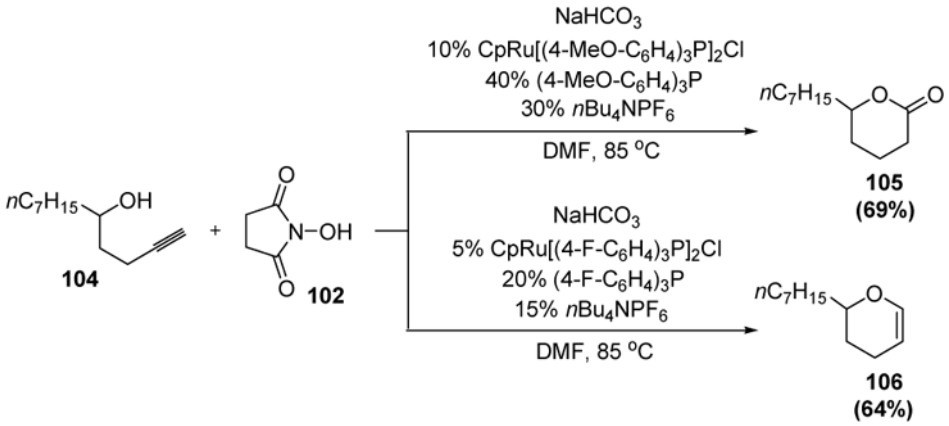


Scheme 28.
McDonald's Formation of α-Stannyl Vinyl Ethers from Alkynols. THF=tetrahydrofuran.



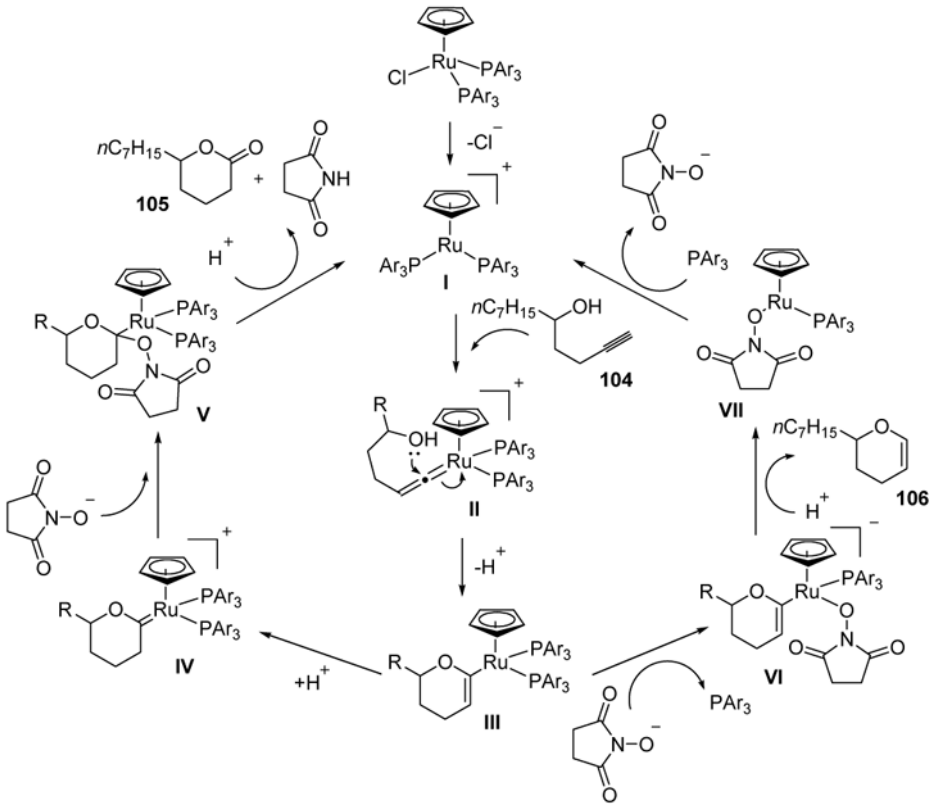
Scheme 29.

Ruthenium-Catalyzed Oxidative Cyclization of Homopropargyl Alcohols. COD=1,5-cyclooctadiene, Cp=η^5-cyclopentadienyl, DMF=*N*,*N*-dimethylformamide.

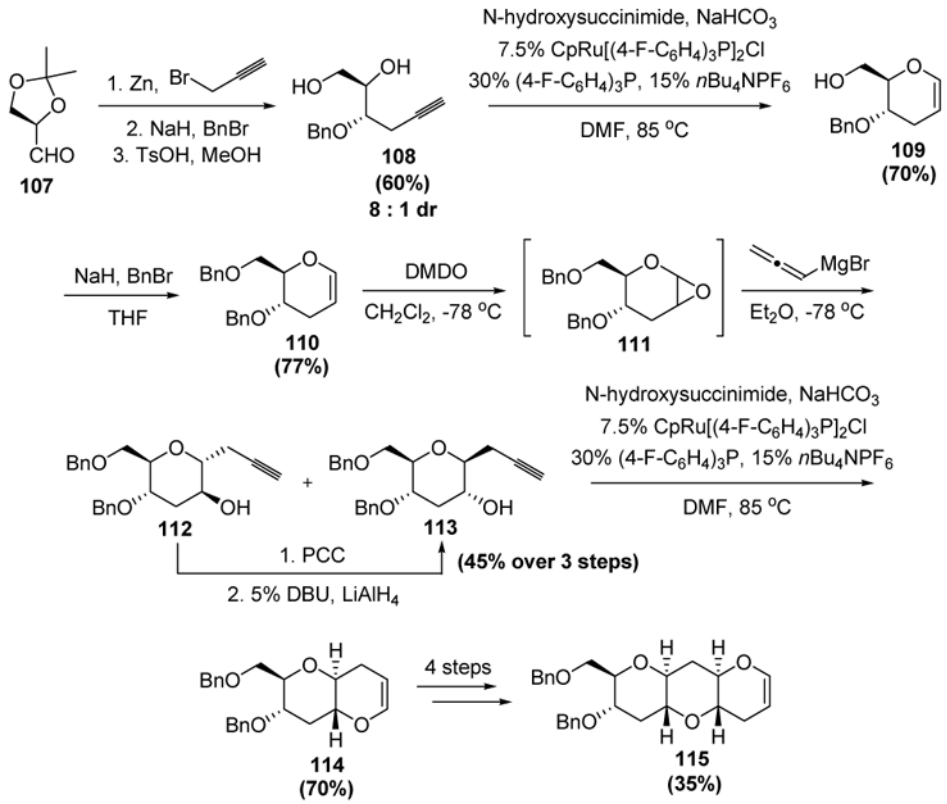


Scheme 30.

Oxidative Cyclization *vs*. Cycloisomerization of Bis-homopropargyl Alcohols. Cp=η^5-cyclopentadienyl, DMF=*N*,*N*-dimethylformamide.

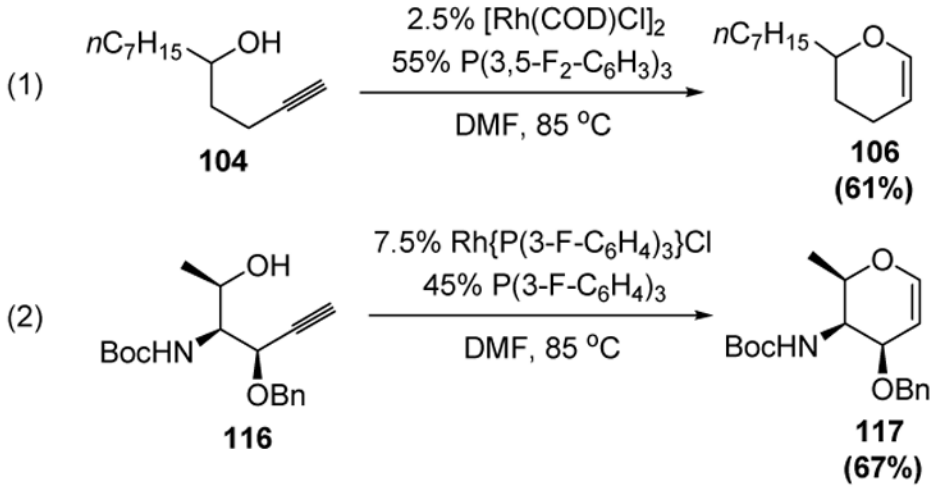


Scheme 31.
Proposed Mechanism of Ruthenium-Catalyzed Oxidative Cyclization and Cycloisomerization

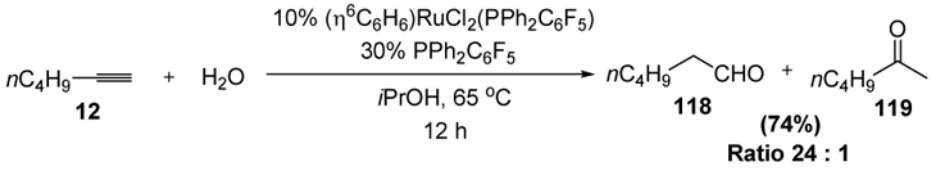


Scheme 32.

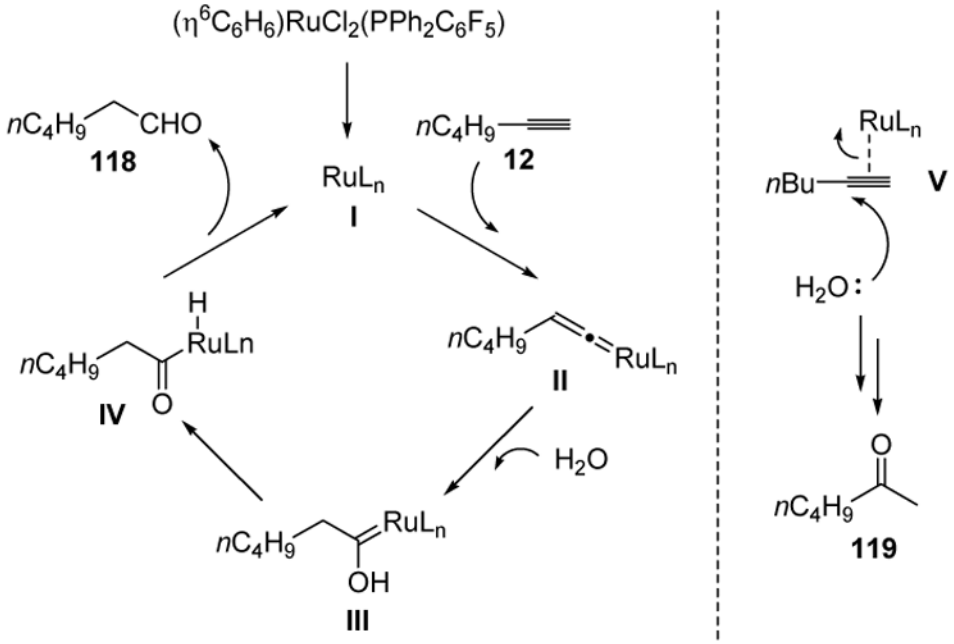
Trost's Iterative Approach to Trans-Fused Polycyclic Ethers. BnBr=benzyl bromide, Cp=η^5-cyclopentadienyl, DBU=1,8-diazabicyclo[5.4.0]undec-7-ene, DMDO=dimethyl dioxirane, DMF=*N*,*N*-dimethylformamide, PCC=pyridinium chlorochromate, THF=tetrahydrofuran, TsOH=*p*-toluenesulfonic acid.



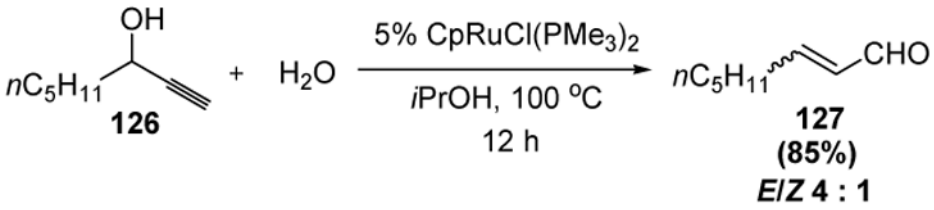
Scheme 33.
Rhodium-Catalyzed Cycloisomerization of Homo- and Bis-homopropargyl Alcohols. COD=1,5-cyclooctadiene, DMF=*N*,*N*-dimethylformamide.



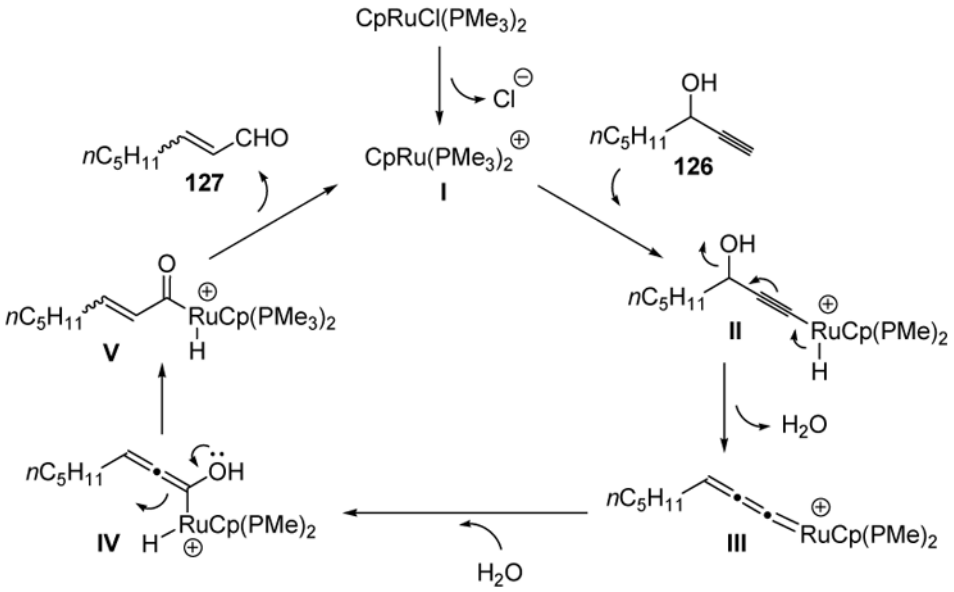
Scheme 34.
Wakatsuki's Anti-Markovnikov Hydration of Terminal Acetylenes



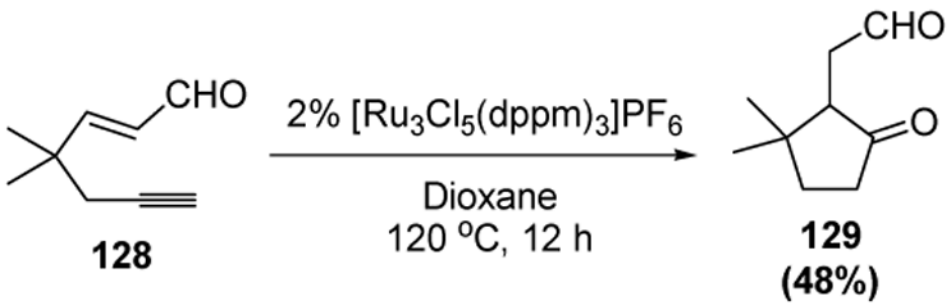
Scheme 35.
Mechanism of Anti-Markovnikov Alkyne Hydration



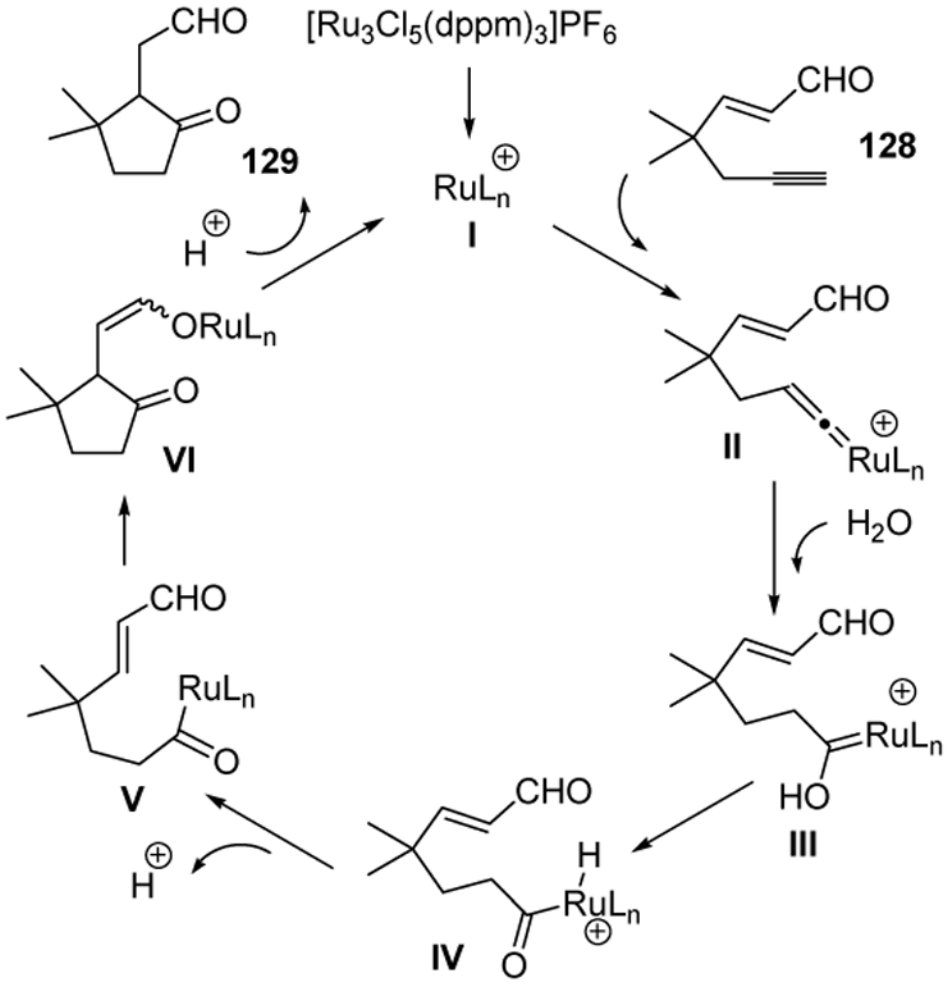
Scheme 36.
Wakatsuki's Isomerization of Propargyl Alcohols. Cp=η^5-cyclopentadienyl.



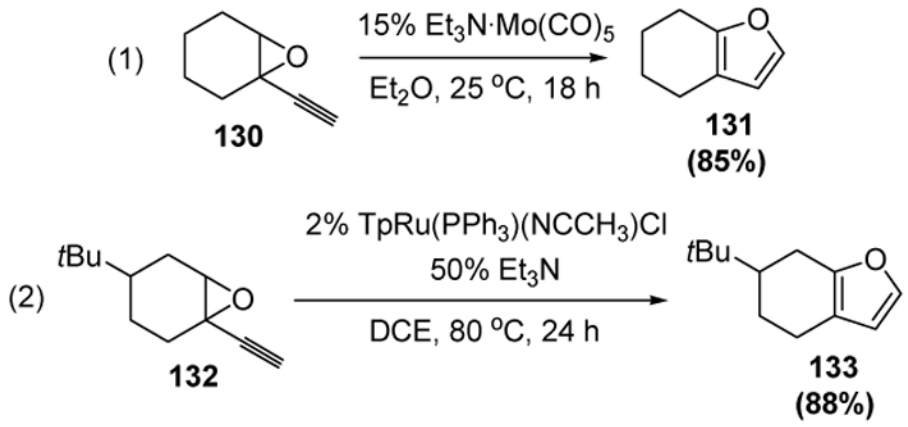
Scheme 37.
Proposed Mechanism of Propargyl Alcohol Isomerization. Cp=η^5-cyclopentadienyl.



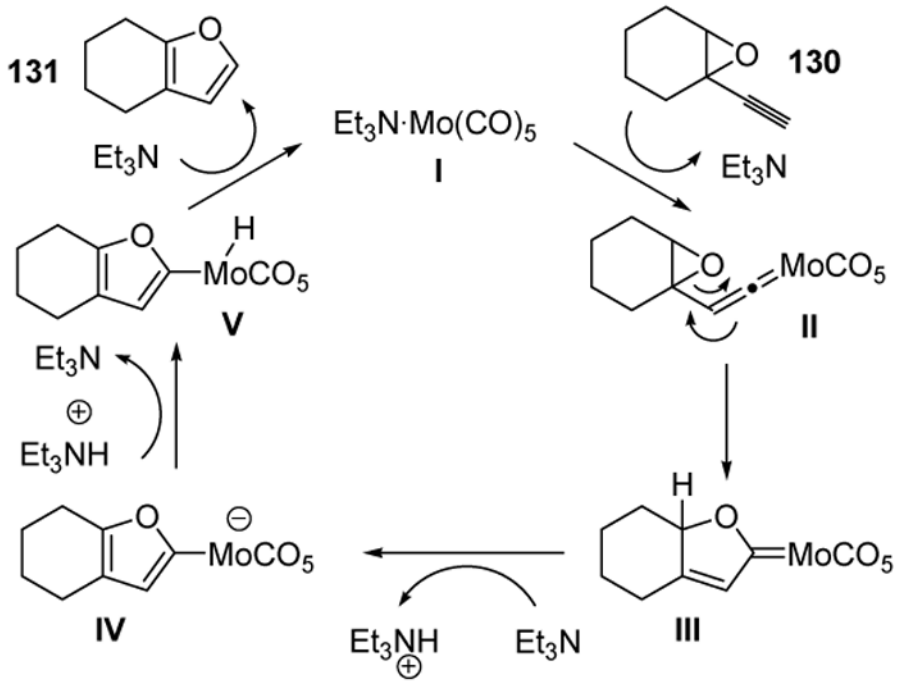
Scheme 38.
Lee's Hydrative Cyclization of 1,5-Enynes. dppm=bis(diphenylphosphino)methane.



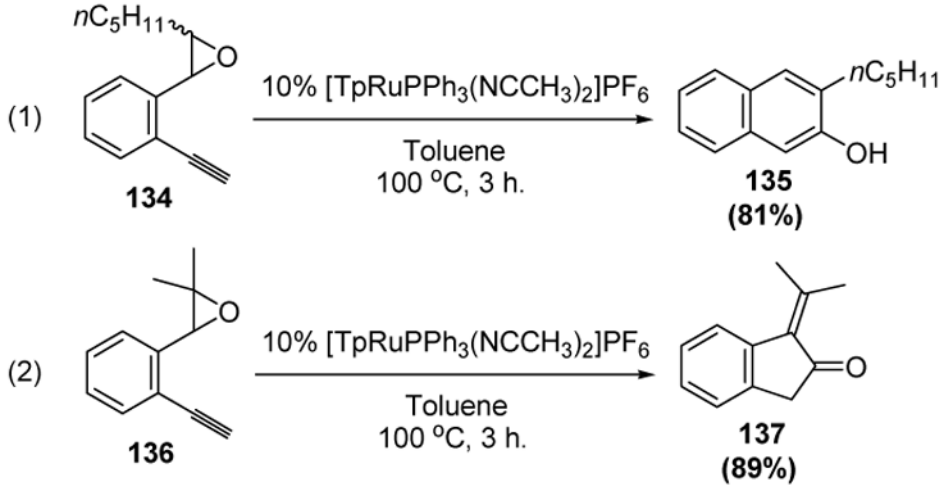
Scheme 39.
Proposed Mechanism for Lee's Hydrative Cyclization of 1,5-Enynes. dppm=bis (diphenylphosphino)methane.



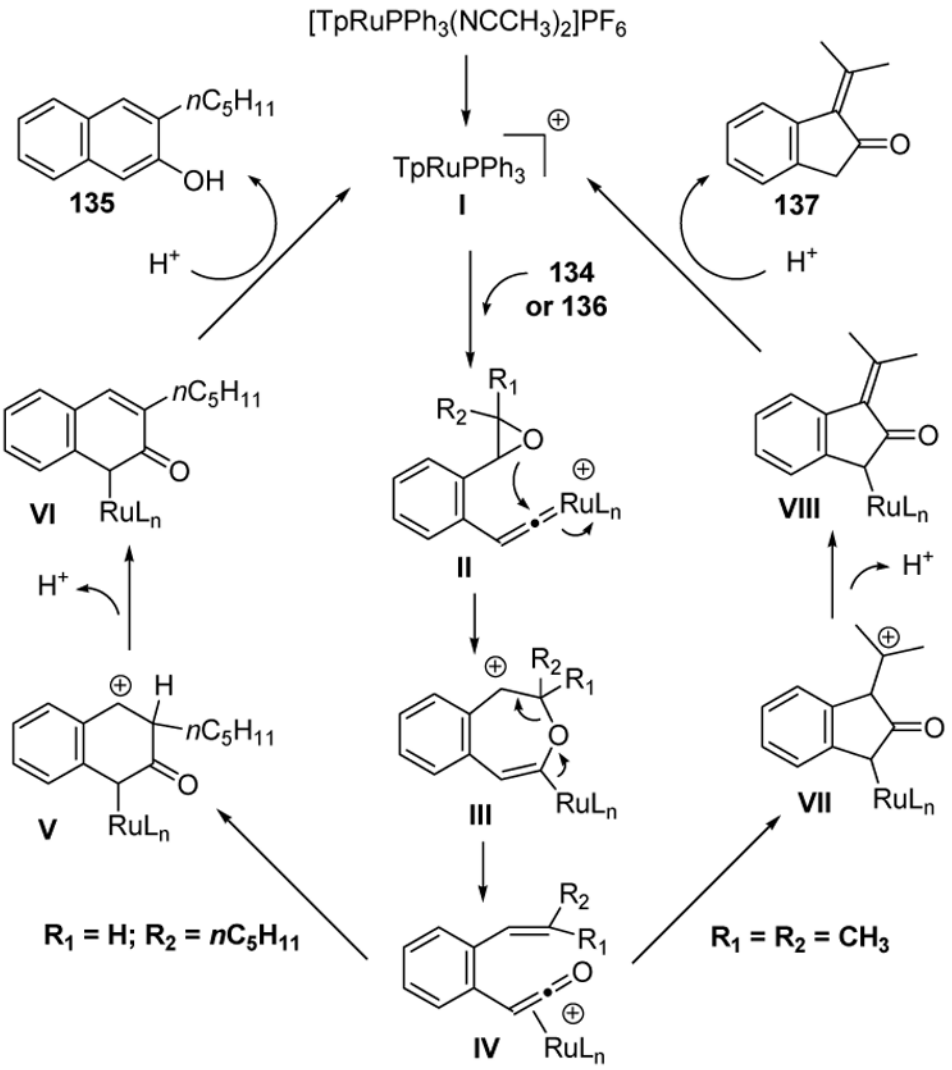
Scheme 40.
Formation of Furans from Epoxyalkynes. DCE=1,2-dichloroethane, Tp=tris(pyrazolyl)borate.



Scheme 41.
Mechanism of Furan Formation from Epoxyalkynes.

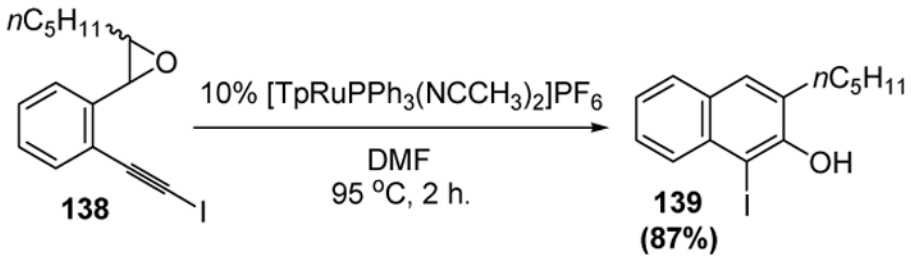


Scheme 42.
Liu's Syntheses of 2-Naphthols and 1-Alkylidene-2-Indanones. Tp=tris(pyrazolyl)borate.

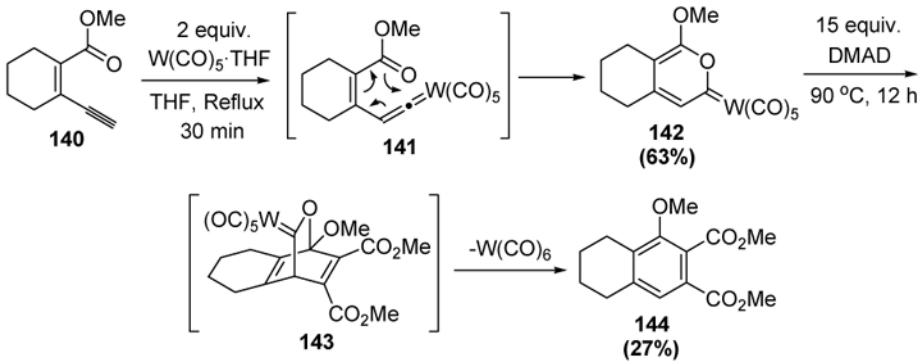


Scheme 43.

Mechanism of 2-Naphthol and 1-Alkylidene-2-Indanone Formation. Tp=tris(pyrazolyl)borate.

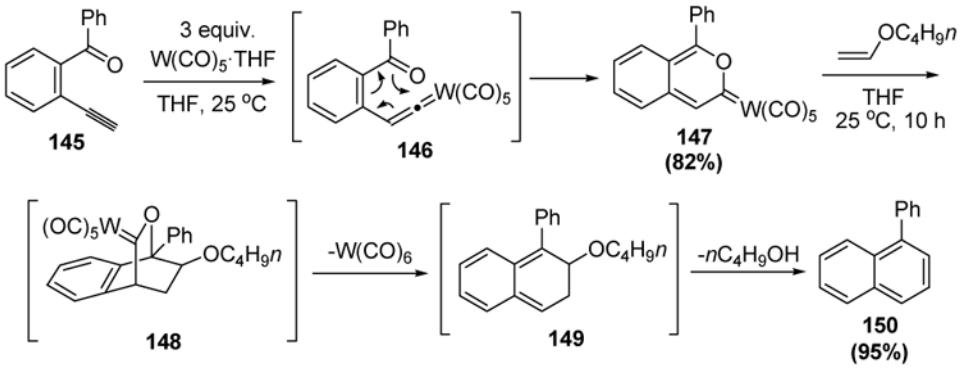


Scheme 44.
Liu's Formation of 1-Iodo-2-Naphthols. Tp=tris(pyrazolyl)borate.

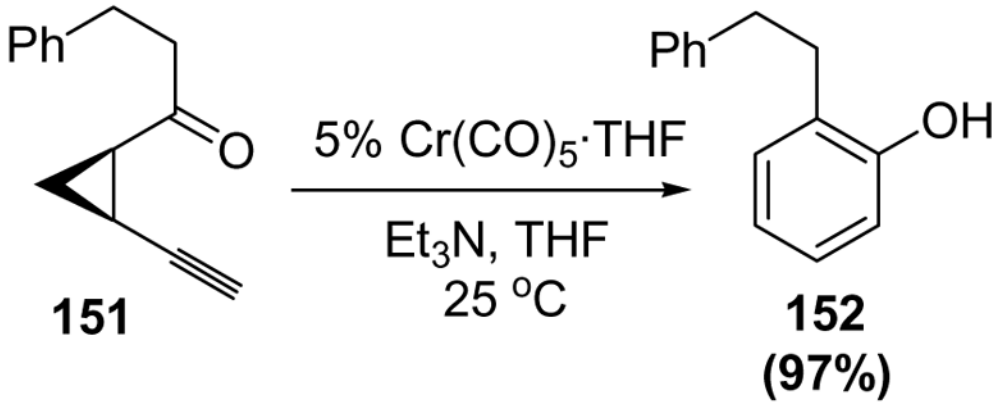


Scheme 45.

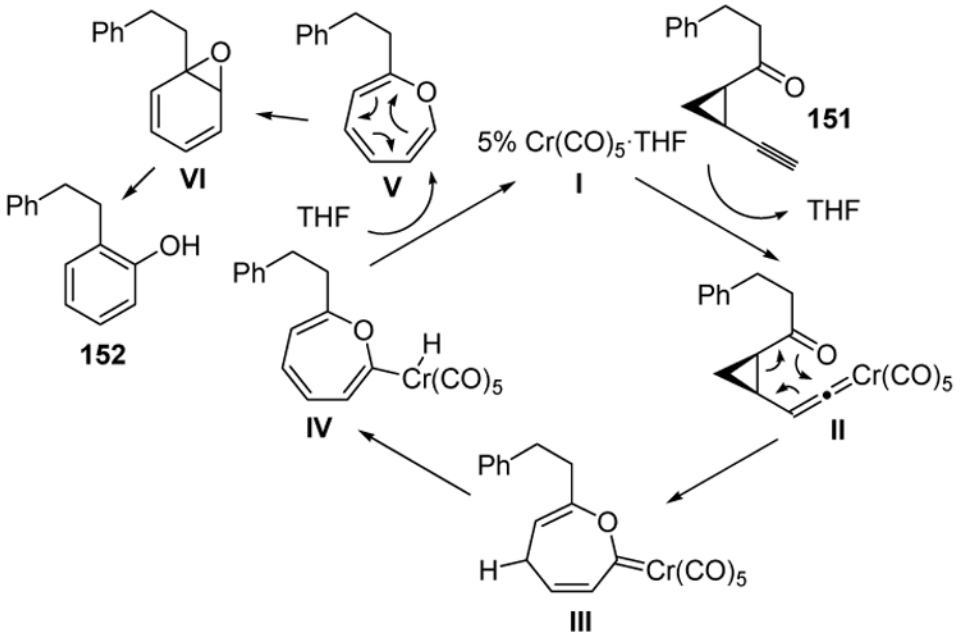
Uemura's Synthesis and Diels-Alder Reaction of Pyranylidenes. DMAD= dimethylacetylene dicarboxylate, THF=tetrahydrofuran.



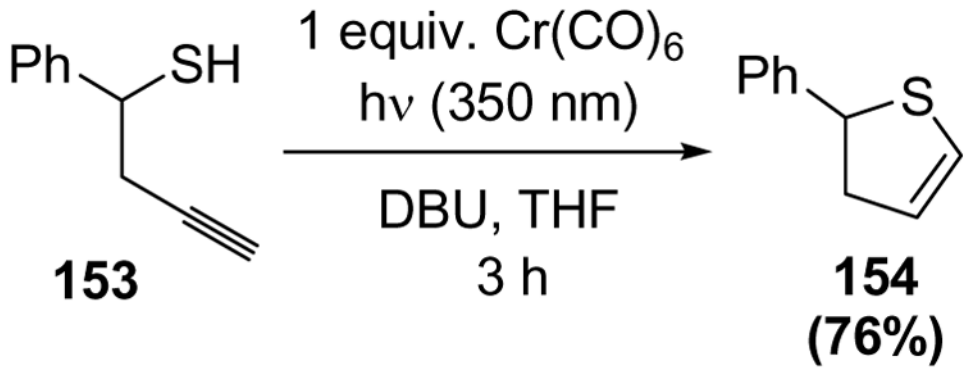
Scheme 46.
Iwasawa's Synthesis and Diels-Alder Reaction of Benzopyranylidenes. THF=tetrahydrofuran.



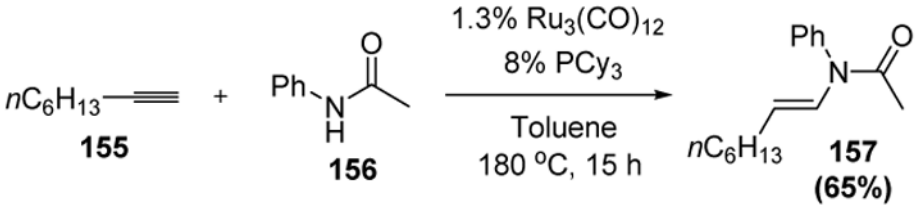
Scheme 47.
Uemura's Catalytic Synthesis of Phenols from *cis*-1-Acyl-2-ethynylcyclopropanes. THF=tetrahydrofuran.



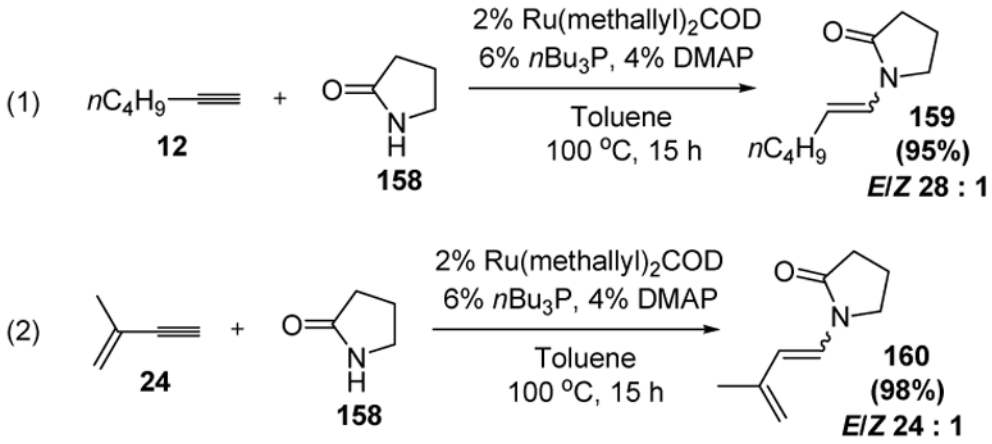
Scheme 48.
Mechanism of Phenol Formation from *cis*-1-Acyl-2-ethynylcyclopropanes. THF=tetrahydrofuran.



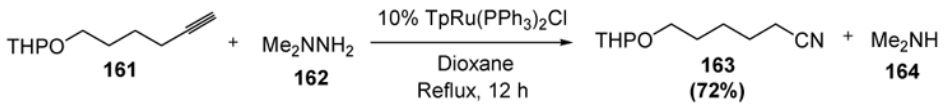
Scheme 49.
Cycloisomerization of Homopropargyl Thiols. DBU=1,8-diazabicyclo[5.4.0]undec-7-ene, THF=tetrahydrofuran.



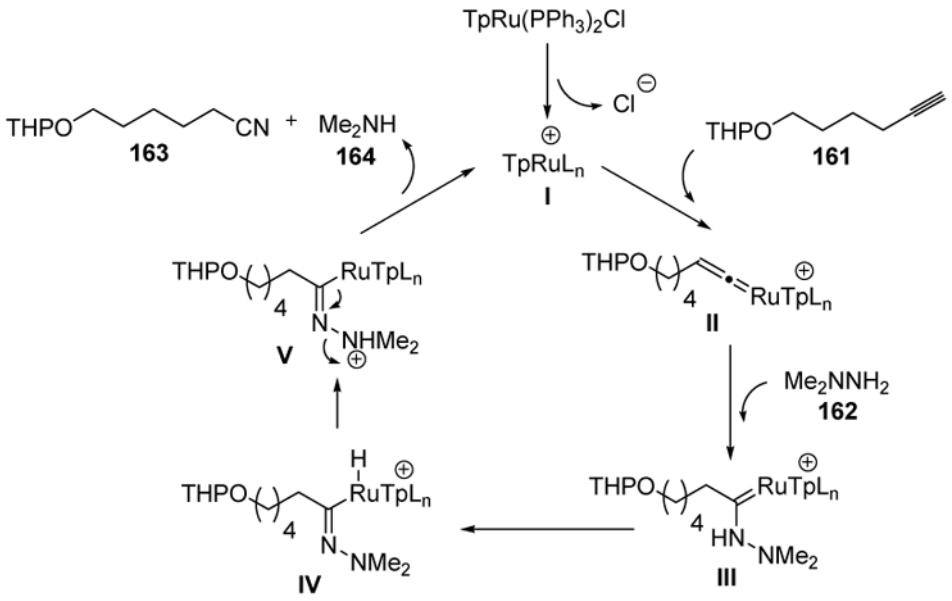
Scheme 50.
Watanabe's Synthesis of an Enamide from Acetanilide and 1-Octyne



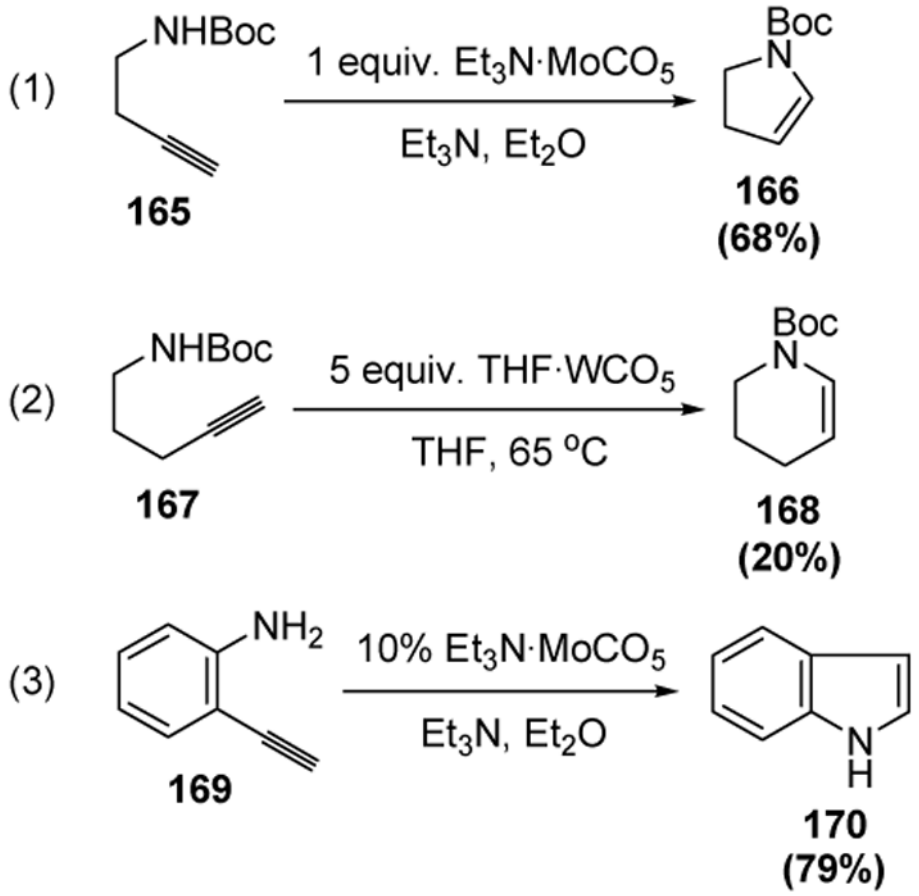
Scheme 51.
Gooβen's Synthesis of Enamides from Amides and Alkynes. COD=1,5-cyclooctadiene, DMAP=4-dimethylaminopyridine.



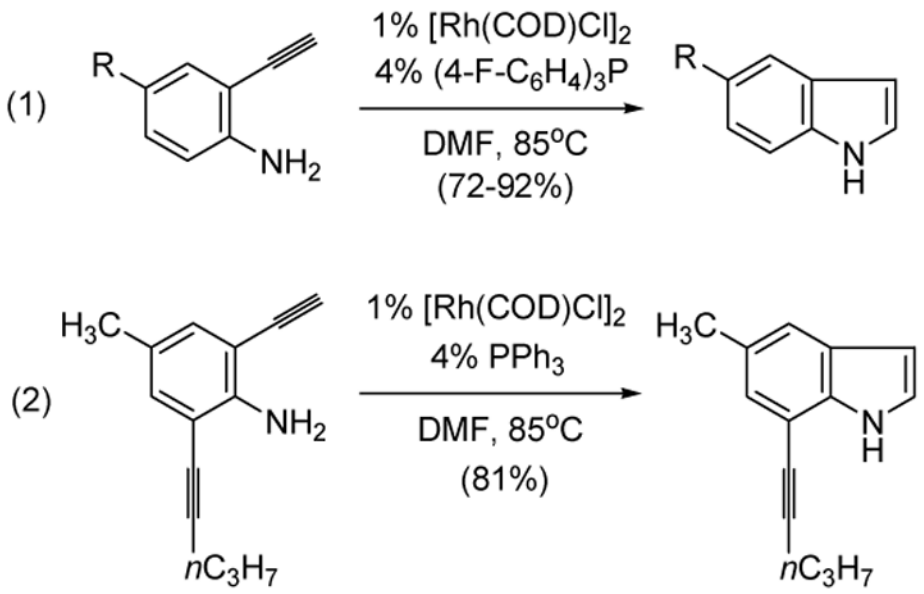
Scheme 52.
Fukumoto's Nitrile Synthesis from *N*,*N*-Dimethylhydrazine and Alkynes. Tp=tris(pyrazolyl) borate.



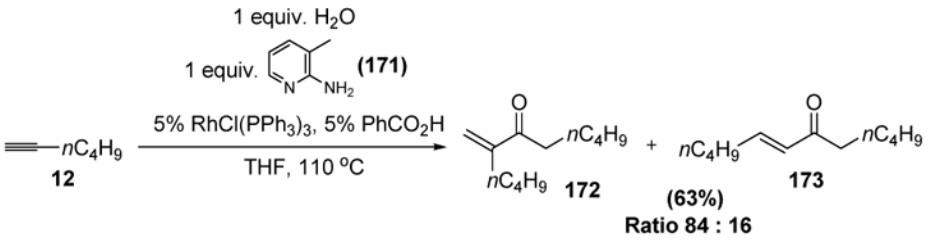
Scheme 53.
Proposed Mechanism of Fukumoto's Nitrile Synthesis. Tp=tris(pyrazolyl)borate.



Scheme 54.
McDonald's Cycloisomerization of Homo- and Bis-homopropargyl Amines. THF=tetrahydrofuran.

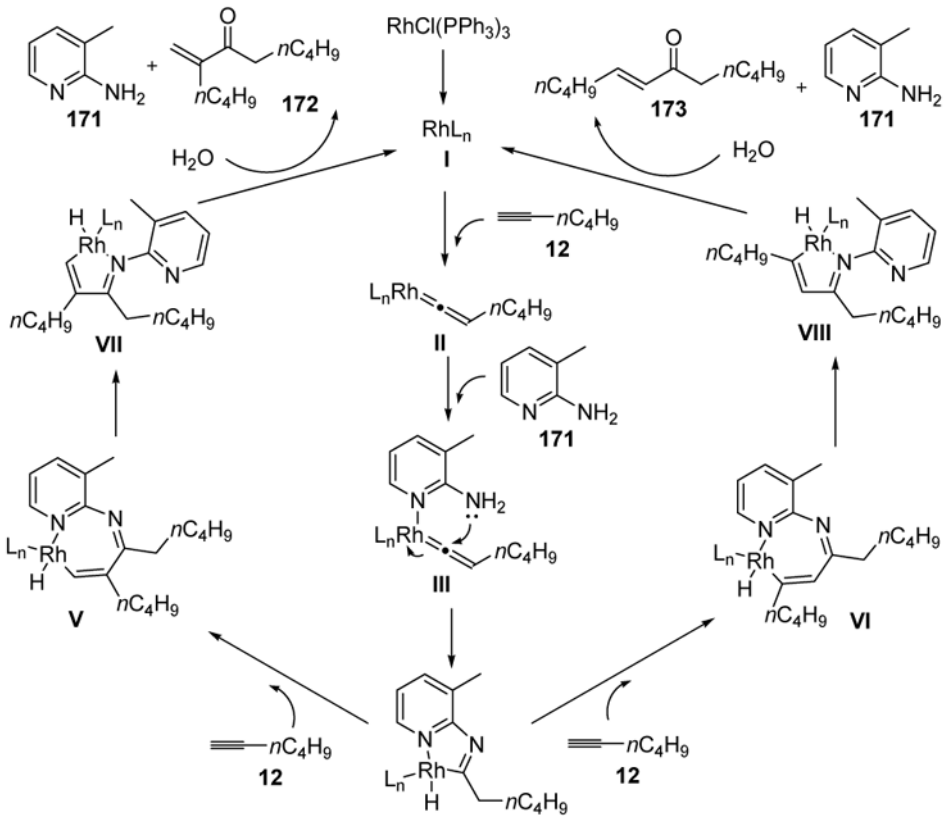


Scheme 55.
Trost's Cycloisomerization of *o*-Ethynylanilines to Indoles

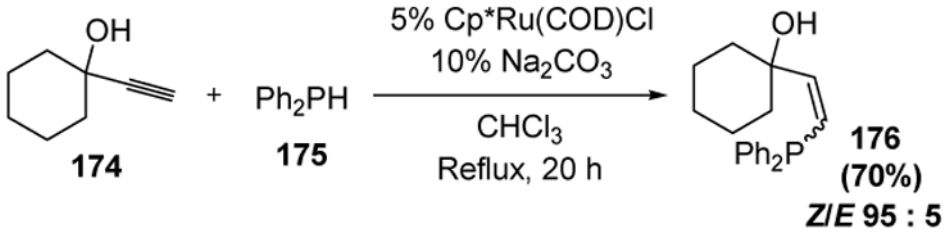


Scheme 56.

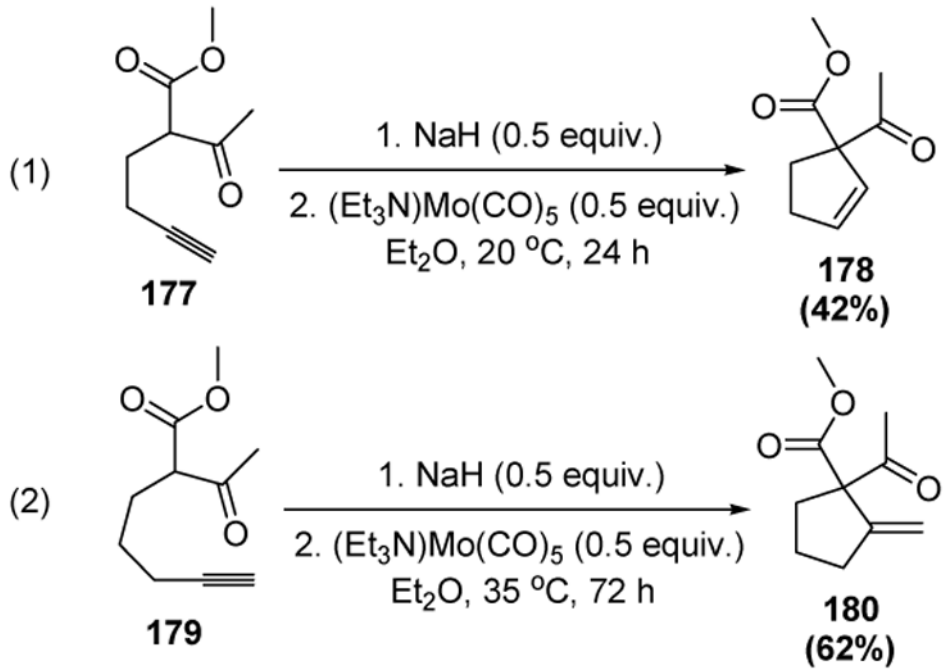
Jun's Chelation-Assisted Hydrative Dimerization of Terminal Alkynes. THF=tetrahydrofuran.



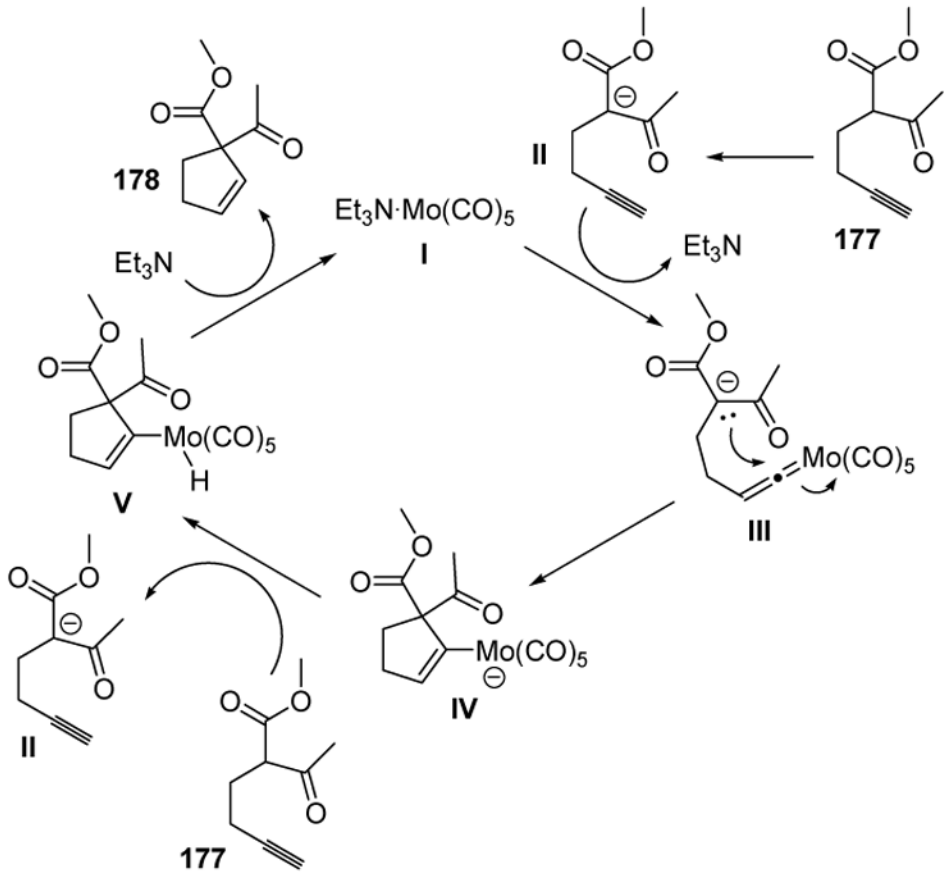
Scheme 57.
Mechanism of Jun's Chelation-Assisted Hydrative Dimerization of Terminal Alkynes



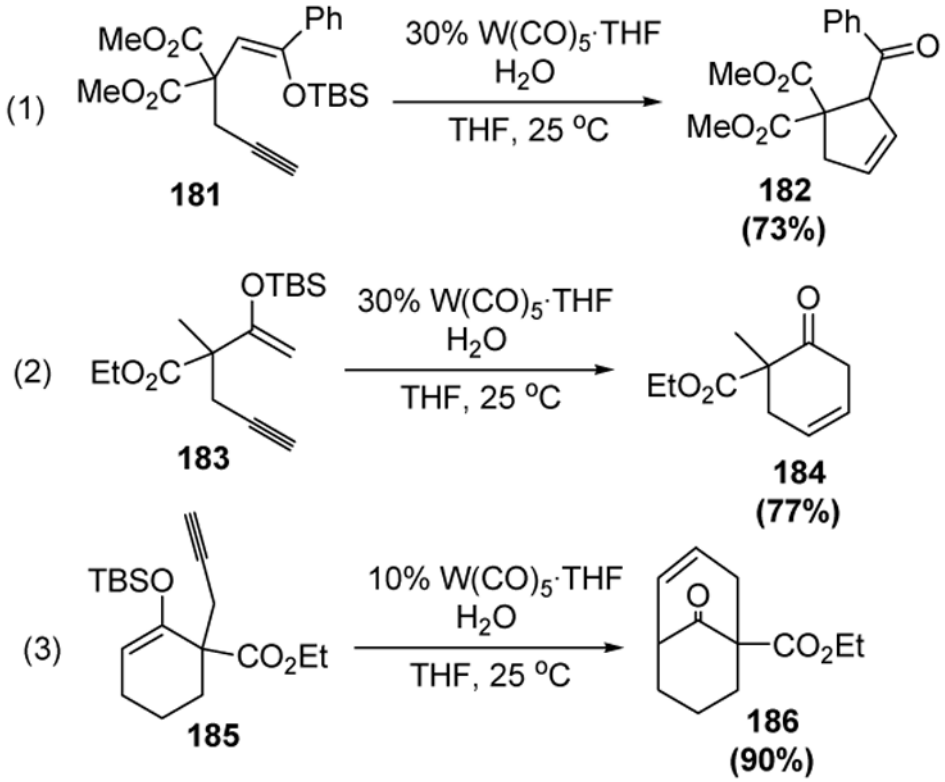
Scheme 58.
Hydrophosphination of Propargyl Alcohols. COD=1,5-cyclooctadiene, Cp=η^5-cyclopentadienyl.



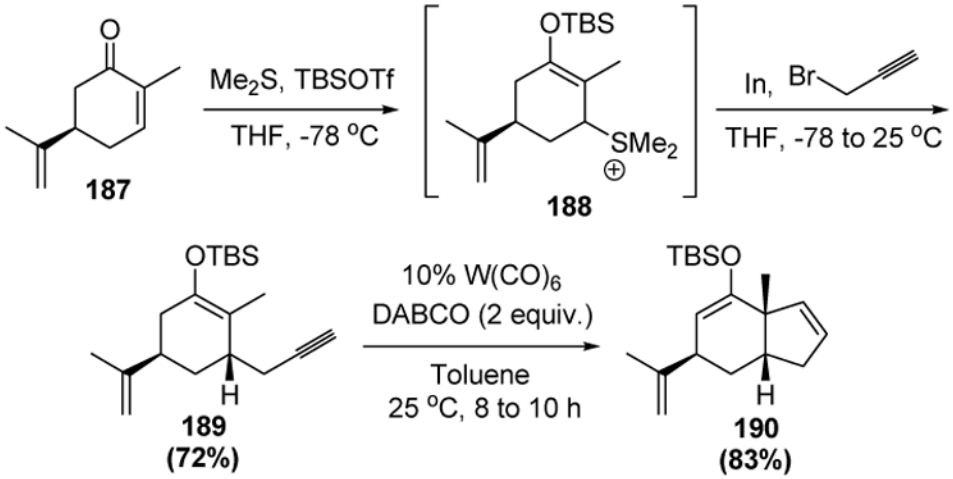
Scheme 59.
Cyclization of Homo- and Bis-homopropargyl β-Dicarbonyl Compounds



Scheme 60.
Mechanism of McDonald's Homopropargyl β-Dicarbonyl Cycloisomerization

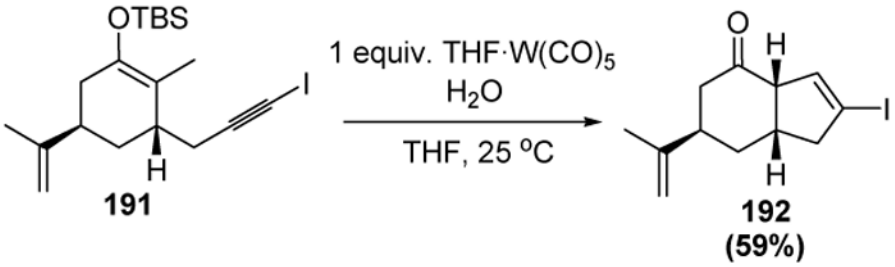


Scheme 61.
Iwasawa's Cycloisomerization of Homo- and Bis-homopropargyl Silyl Enol Ethers. THF=tetrahydrofuran.

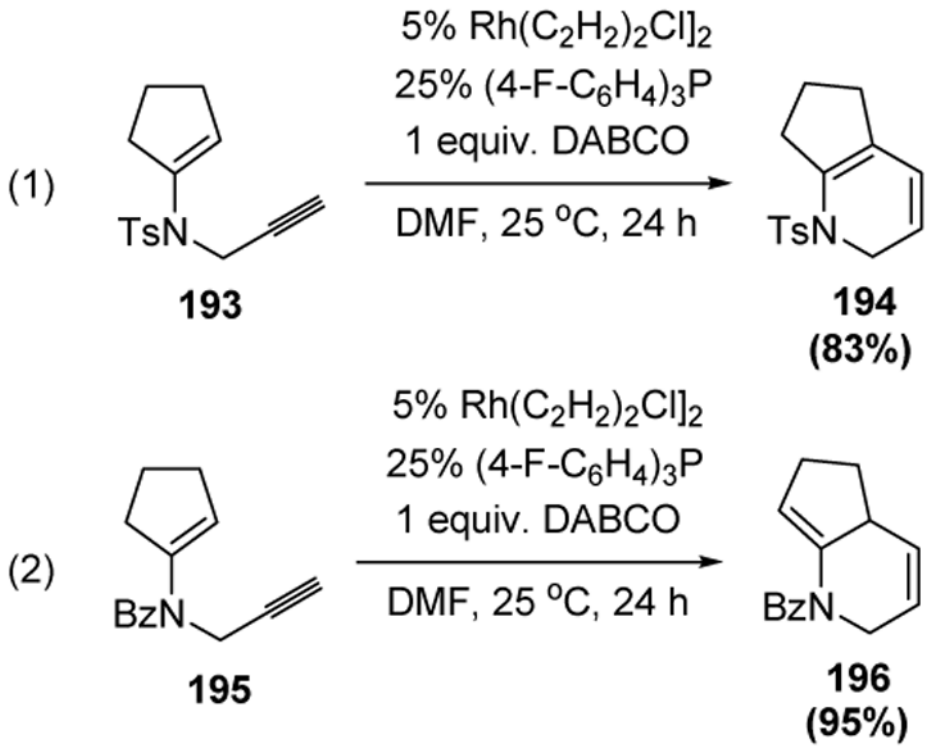


Scheme 62.

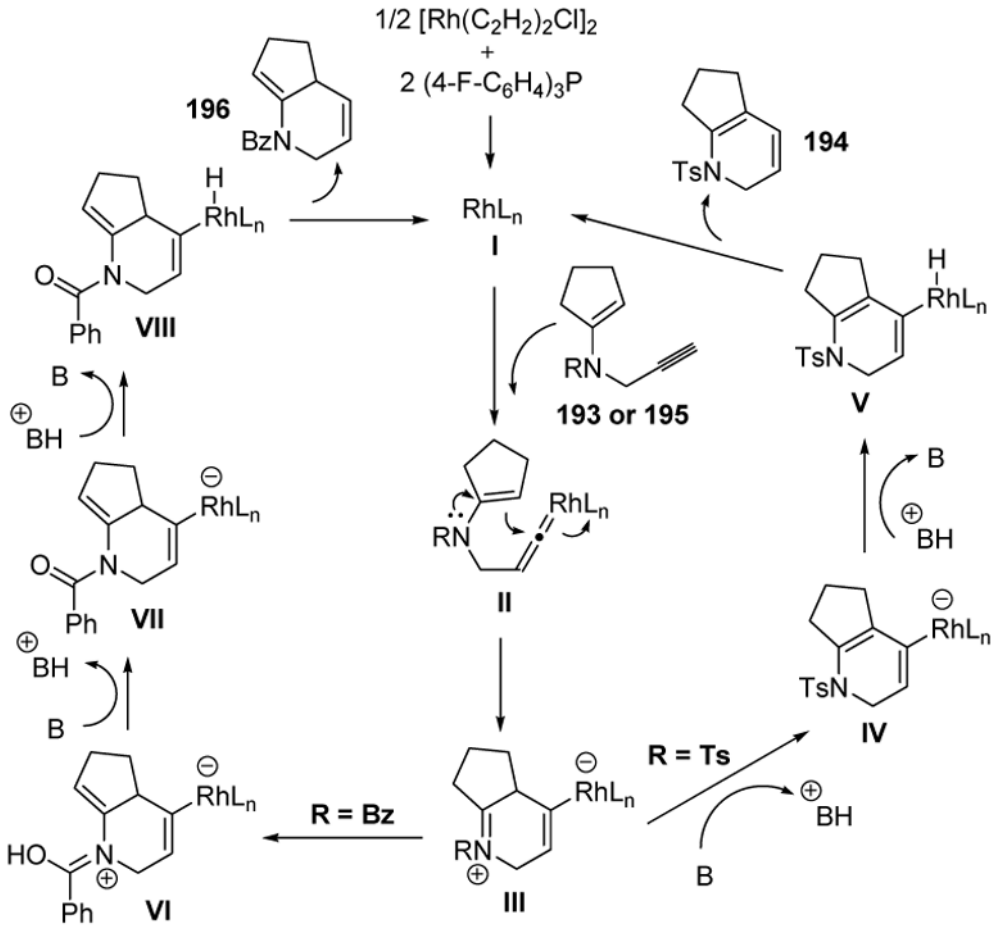
Iwasawa's Cyclopentene Annulation Method. DABCO=1,4-diazabicyclo[2.2.2]octane, TBSOTf= *tert*-butyldimethylsilyl trifluoromethanesulfonate, THF=tetrahydrofuran.



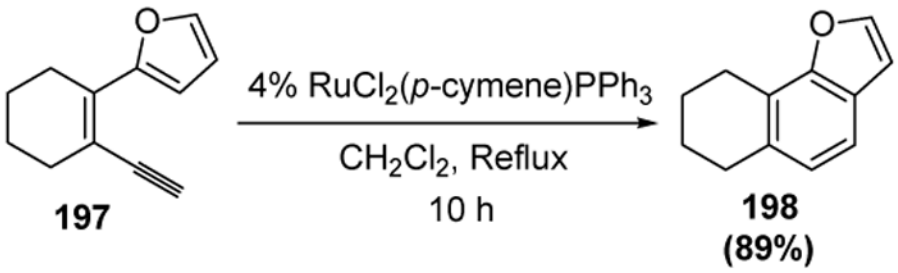
Scheme 63.
Iwasawa's Cyclopentene Annulation Method: Iodine Migration. THF=tetrahydrofuran.



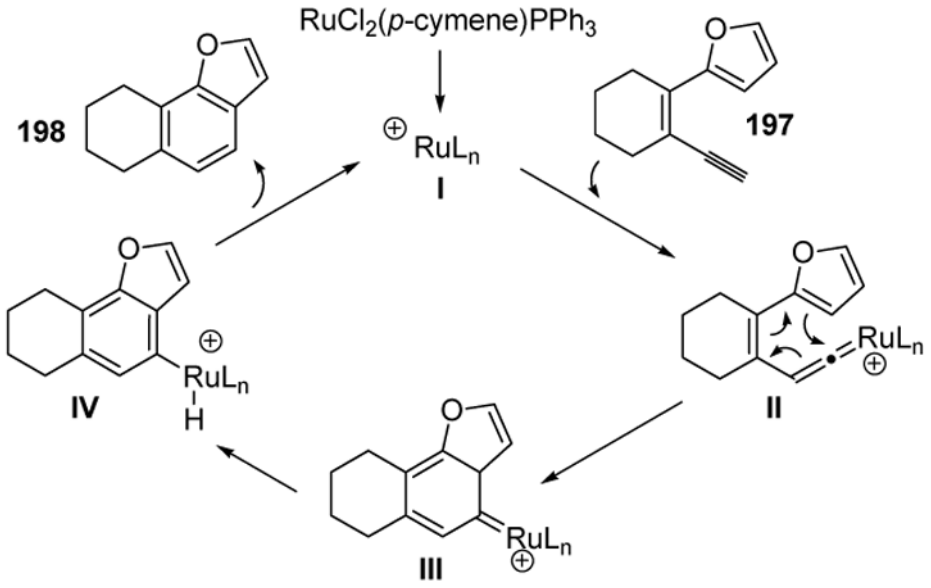
Scheme 64.
Lee's *N*-Propargyl Enamine Cycloisomerization. DABCO=1,4-diazabicyclo[2.2.2]octane, DMF= *N*,*N*-dimethylformamide.



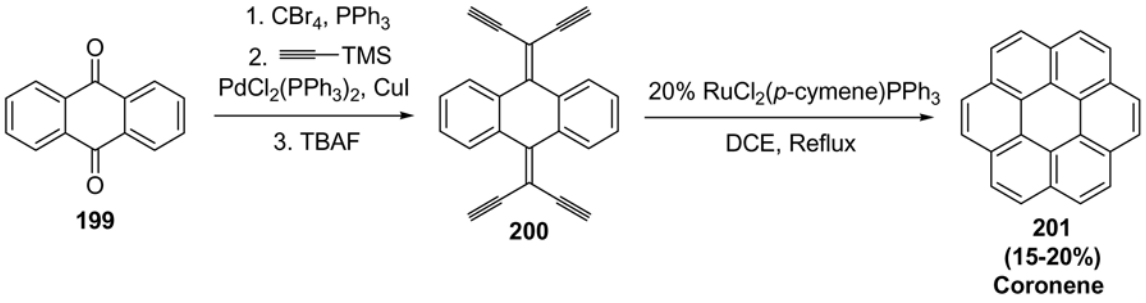
Scheme 65.
Proposed Mechanism of *N*-Propargyl Enamine Cycloisomerization



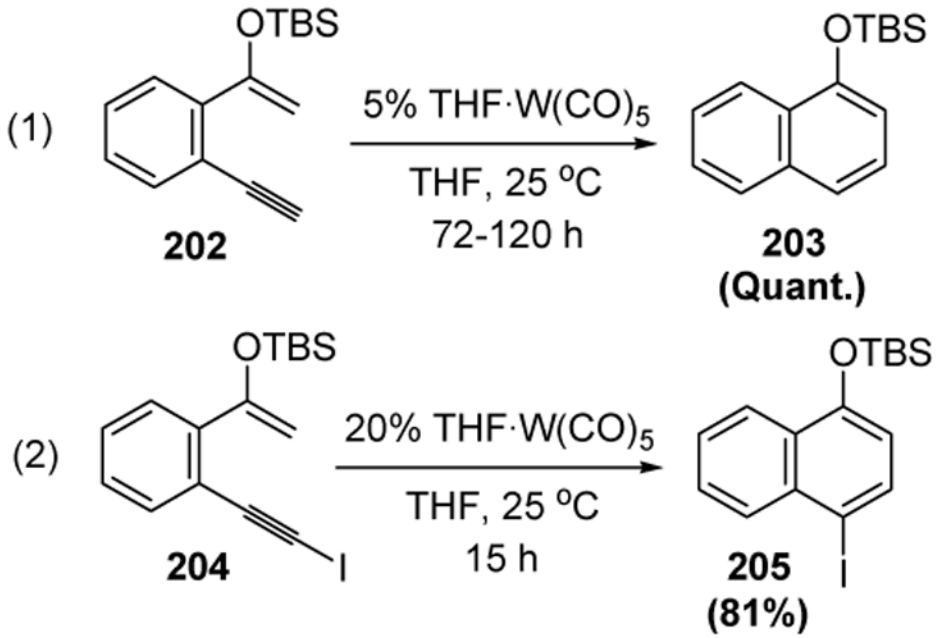
Scheme 66.
Merlic's Dienyne Cycloisomerization



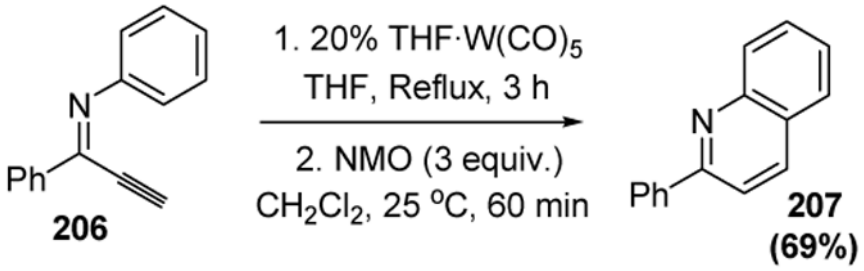
Scheme 67.
Plausible Mechanism for Dienyne Cycloisomerization



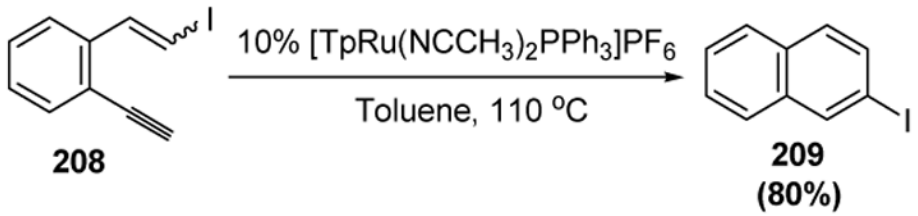
Scheme 68.
Scott's Naphthonannulation Procedure. DCE=1,2-dichloroethane, TBAF=tetrabutylammonium fluoride.



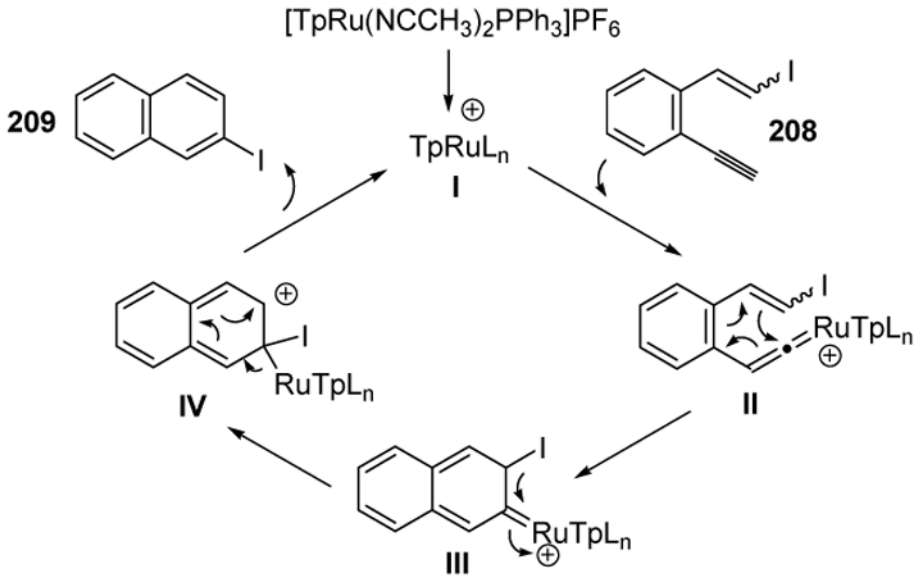
Scheme 69.
Iwasawa's Dienyne Cycloisomerization. THF=tetrahydrofuran.



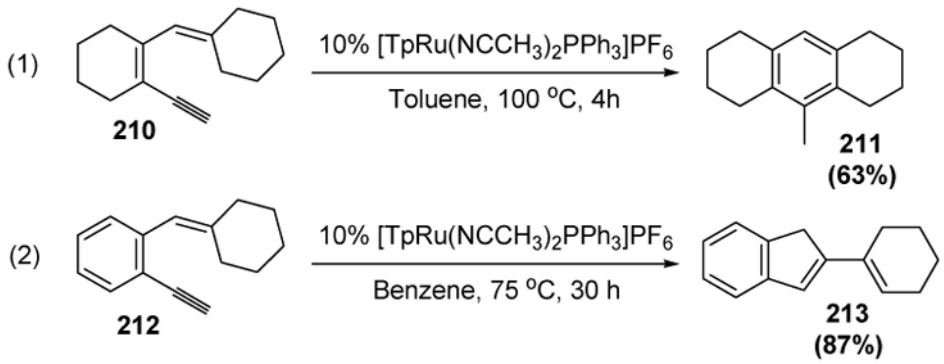
Scheme 70.
Akiyama's Cycloisomerization of Alkynyl Imines. NMO= *N*-methylmorpholine *N*-oxide, THF=tetrahydrofuran.



Scheme 71.
Liu's Electrocyclization and Halide Migration. Tp=tris(pyrazolyl)borate.

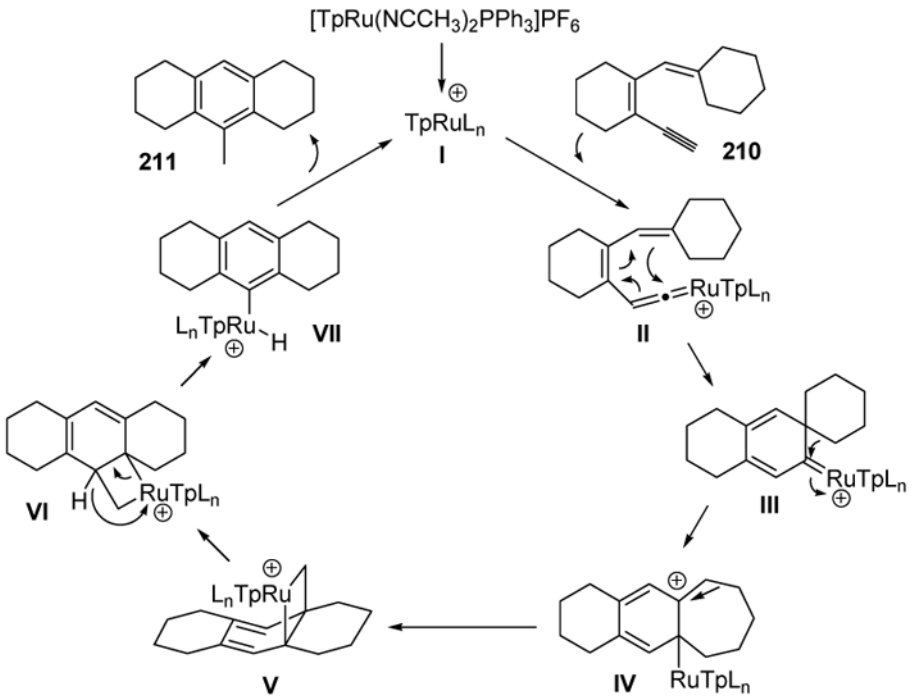


Scheme 72.
Mechanism of Liu's Electrocyclization and Halide Migration. Tp=tris(pyrazolyl)borate.

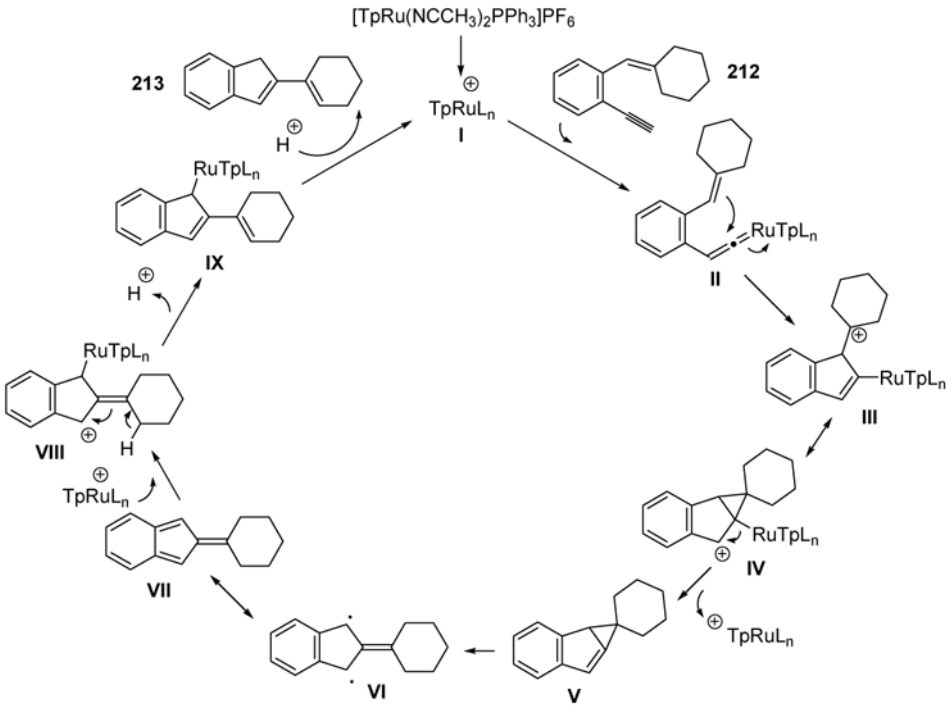


Scheme 73.

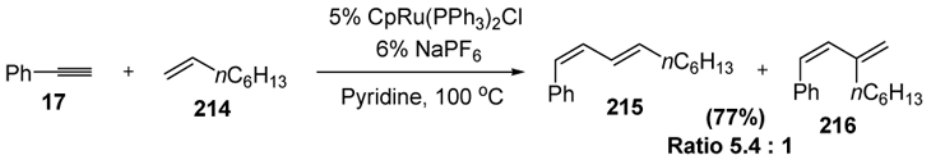
Liu's Formation of Substituted Benzenes and 2-Vinyl 1*H*-Indenes. Tp=tris(pyrazolyl)borate.



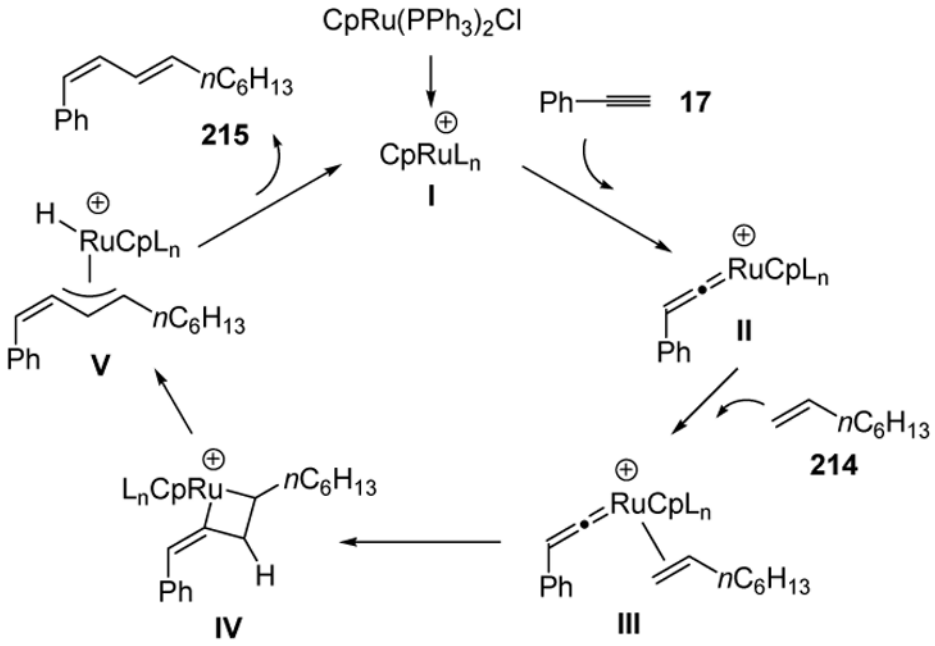
Scheme 74.
Mechanism of Liu's Substituted Benzene Synthesis. Tp=tris(pyrazolyl)borate.



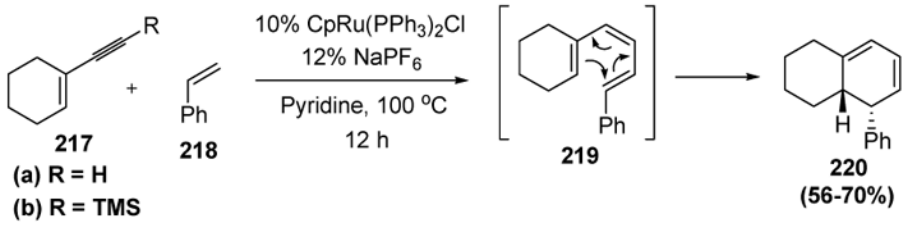
Scheme 75.
Mechanism of Liu's 2-Vinyl 1*H*-Indene Synthesis. Tp=tris(pyrazolyl)borate.



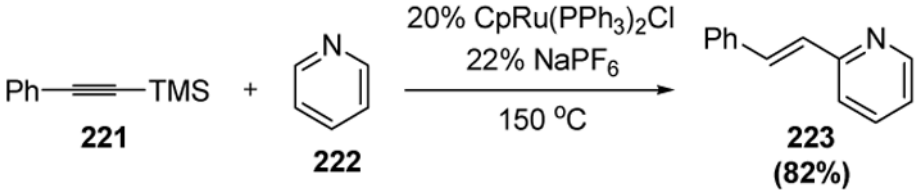
Scheme 76.
Murakami's Intermolecular Alkene-Alkyne Coupling. Cp=η^5-Cyclopentadienyl.



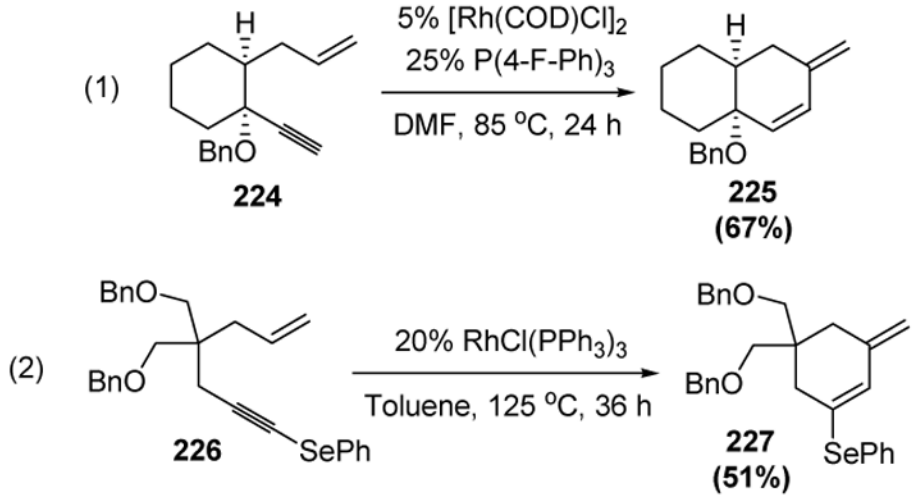
Scheme 77.
Mechanism of Intermolecular Enyne Coupling. Cp=η^5-Cyclopentadienyl.



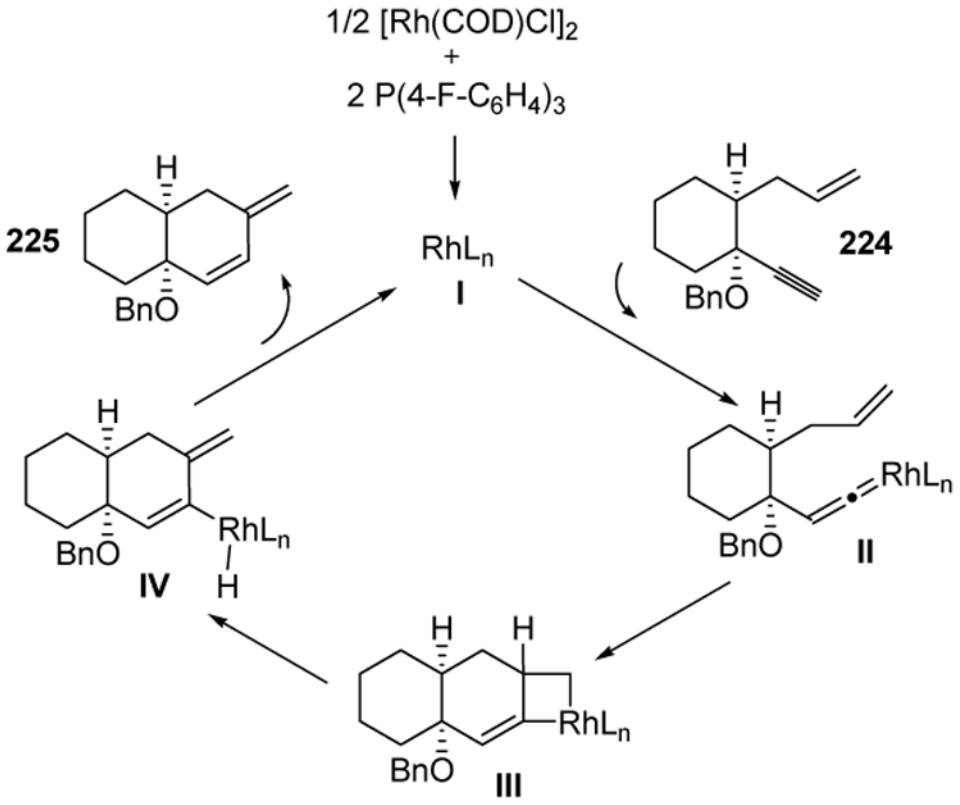
Scheme 78.
Murakami's Tandem Enyne Coupling-Electrocyclization. Cp=η^5-Cyclopentadienyl.



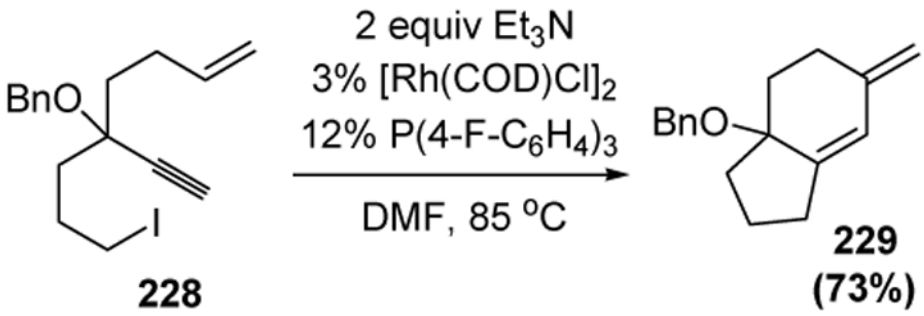
Scheme 79.
Murakami's Alkenylation of Pyridine. Cp=η^5-Cyclopentadienyl.



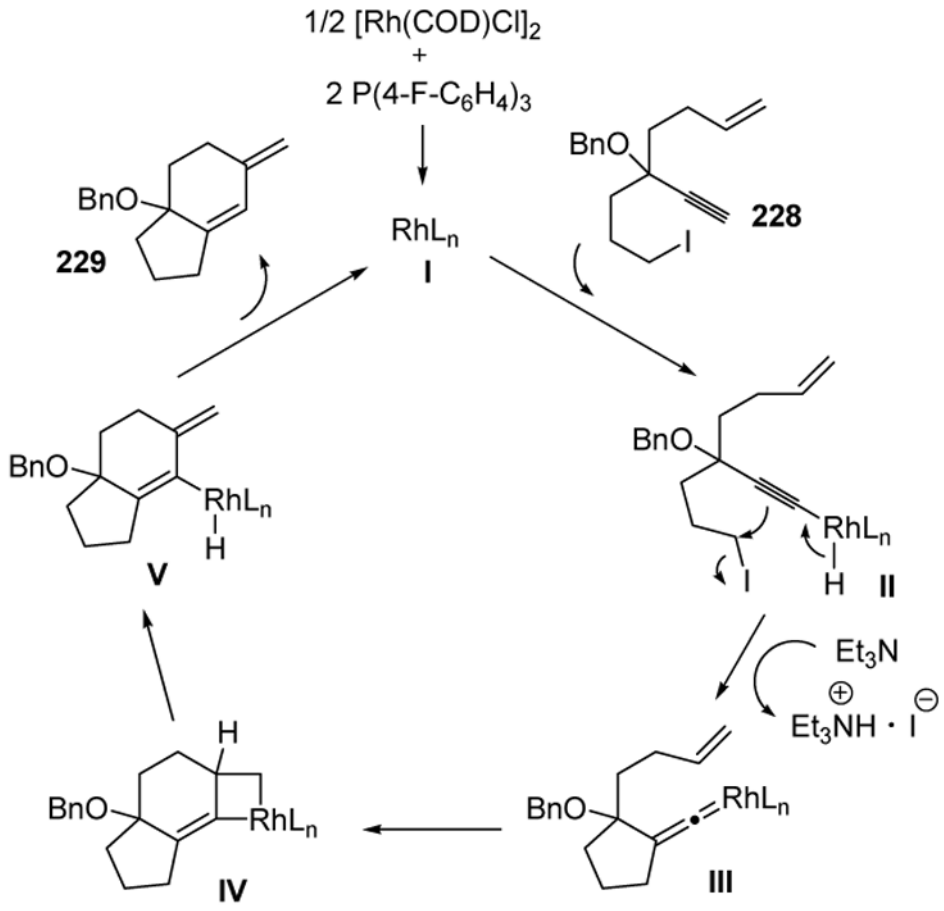
Scheme 80.
Rhodium-Catalyzed Enyne Cycloisomerization. COD=1,5-cyclooctadiene, DMF= *N*,*N*-dimethylformamide.



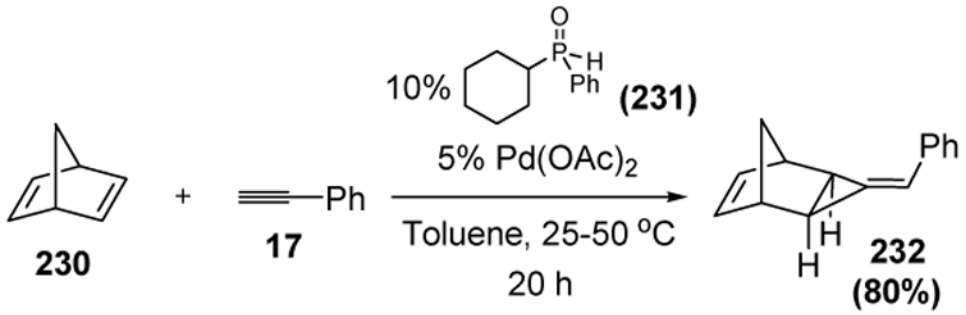
Scheme 81.
Mechanism of Rhodium-Catalyzed Enyne Cycloisomerization. COD=1,5-cyclooctadiene.



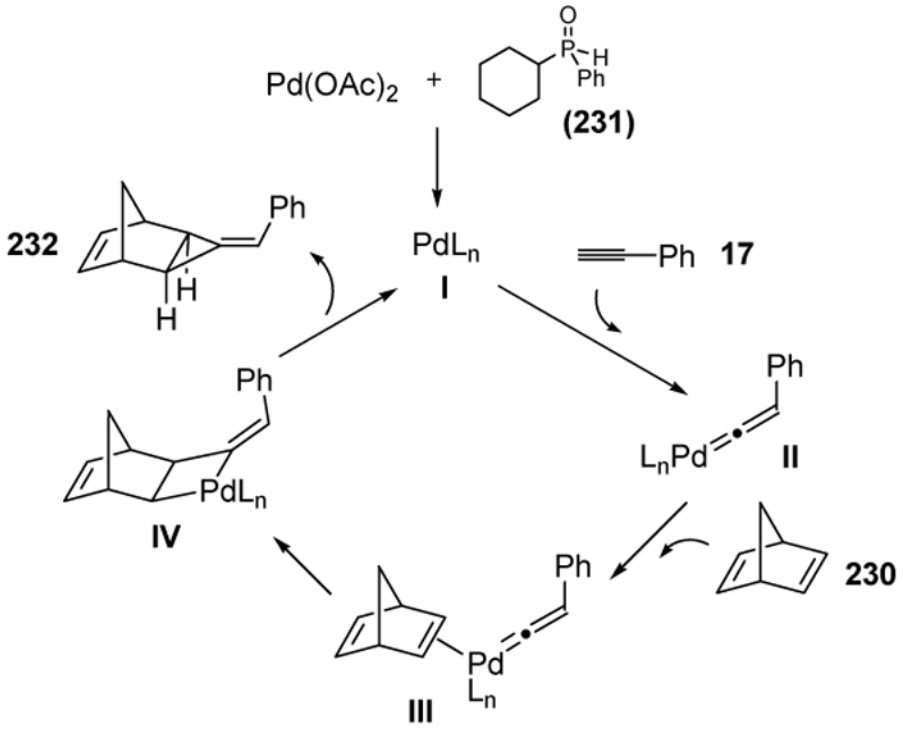
Scheme 82.
Lee's Tandem Cyclization of 1,6-Enyne Systems. COD=1,5-cyclooctadiene, DMF= *N*,*N*-Dimethylformamide.



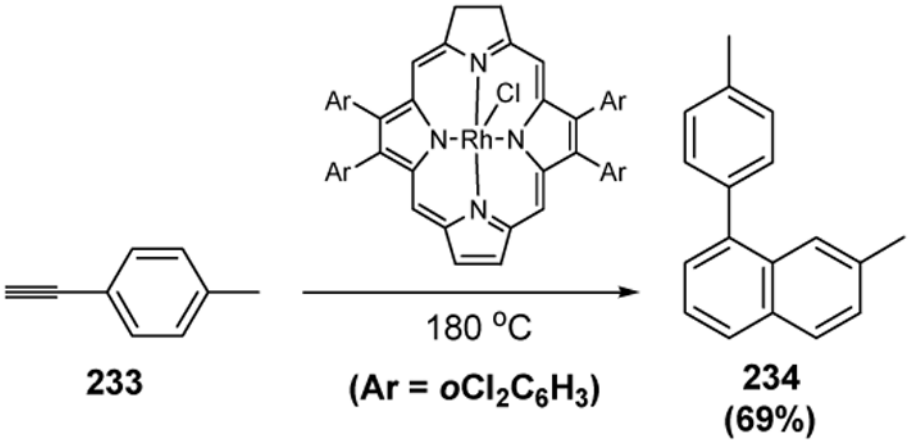
Scheme 83.
Mechanism of the Tandem 1,6-Enyne Cyclization. COD=1,5-cyclooctadiene.



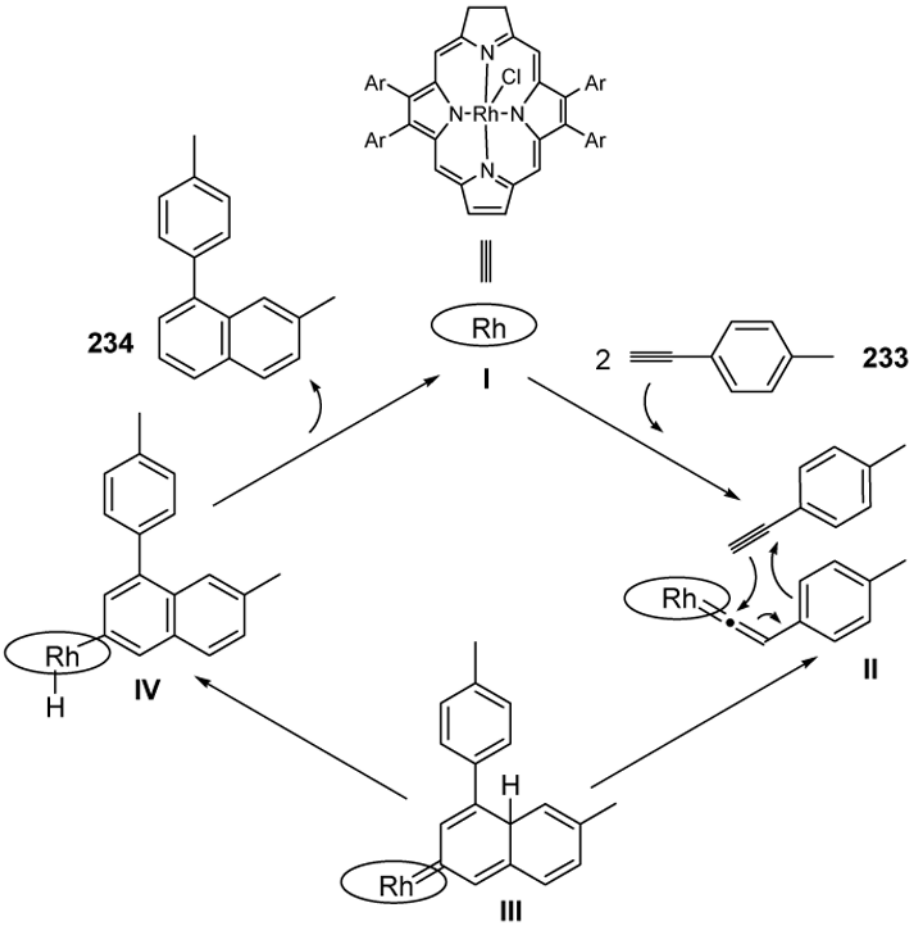
Scheme 84.
Buono's Palladium-Catalyzed [2+1] Cycloaddition



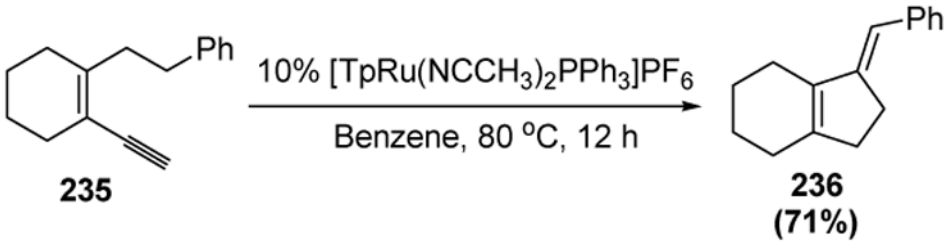
Scheme 85.
Mechanism of Buono's Palladium-Catalyzed [2+1] Cycloaddition



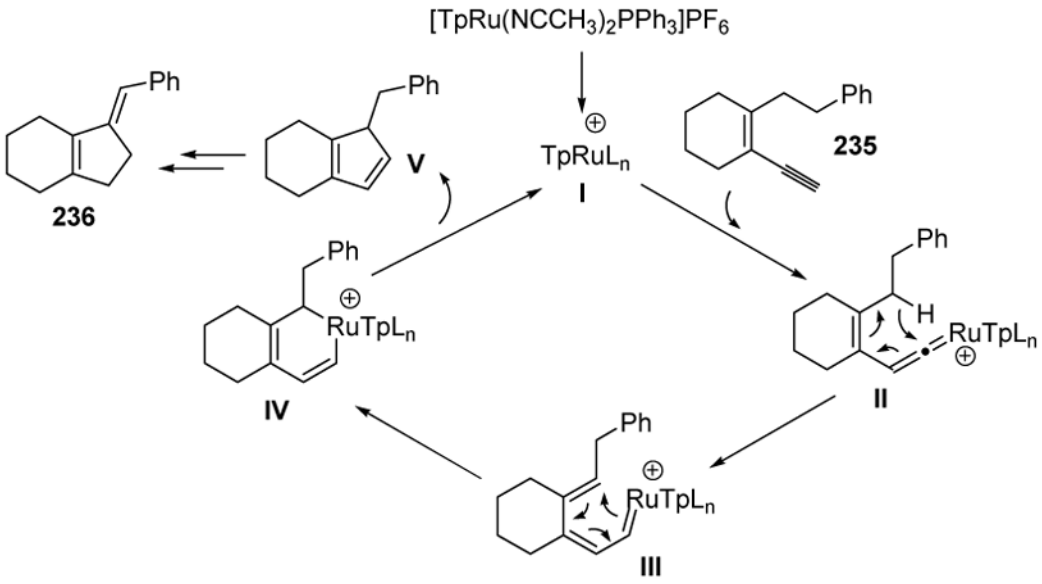
Scheme 86.
Tagliatesta's Synthesis of 1-Arylnaphthalenes



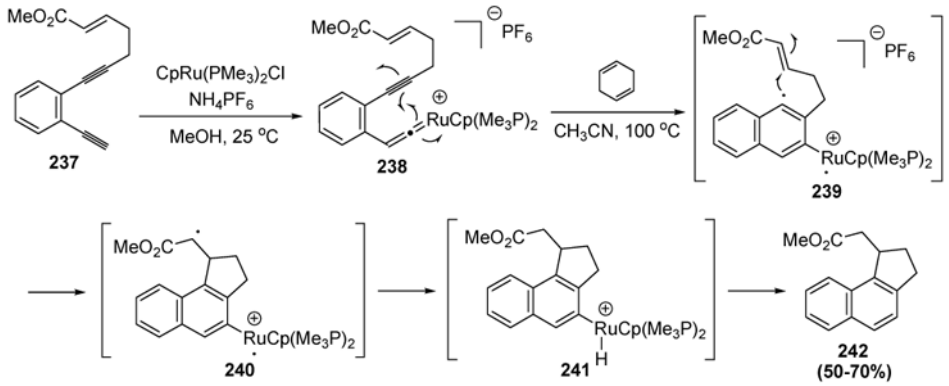
Scheme 87.
Mechanism of 1-Arylnaphthalene Formation from Arylacetylenes



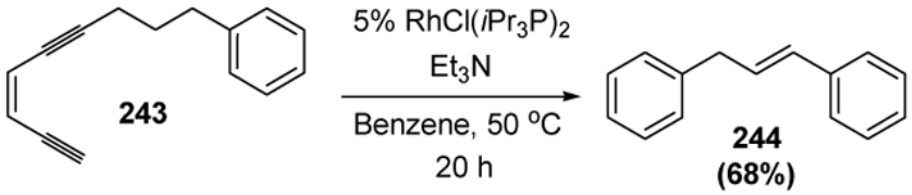
Scheme 88.
Liu's Cyclopentadiene Synthesis. Tp= tris(pyrazolyl)borate.



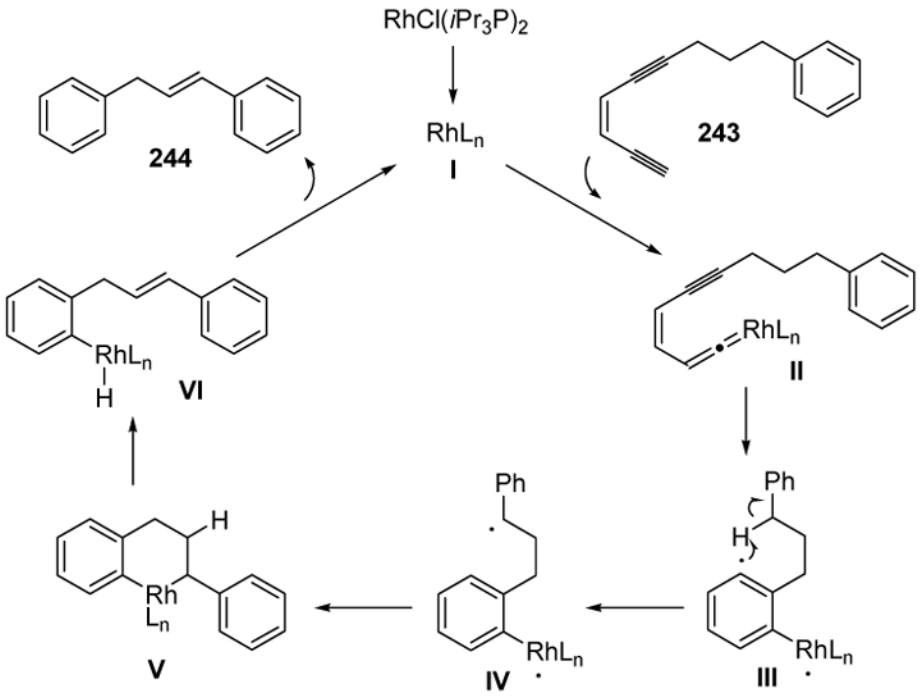
Scheme 89.
Mechanism of Cyclopentadiene Formation. Tp= tris(pyrazolyl)borate.



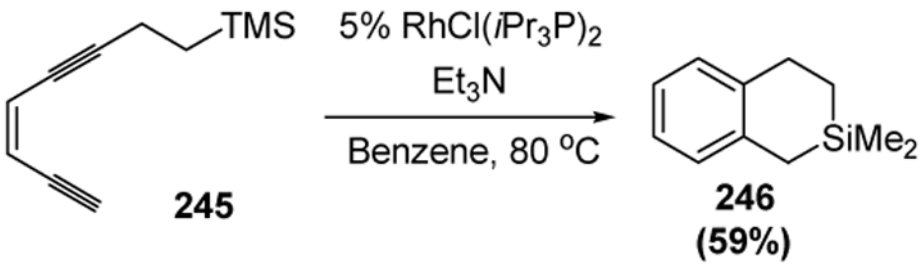
Scheme 90.
Finn's Stoichiometric Metal-Mediated Cycloaromatization. Cp=η^5-Cyclopentadienyl.



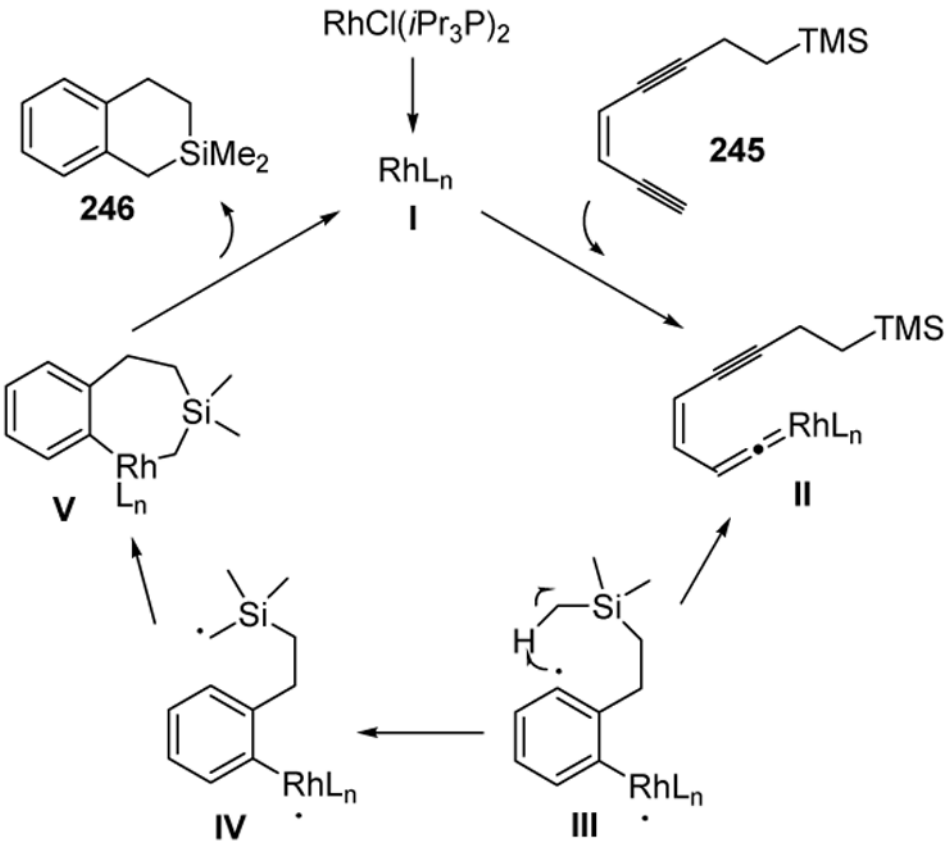
Scheme 91.
Uemura's Rhodium-Catalyzed Cycloaromatization: 1,5-Hydrogen Migration



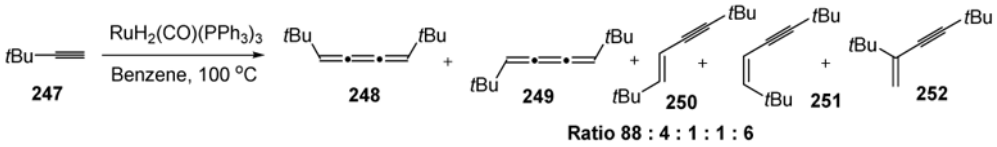
Scheme 92.
Mechanism of Rhodium-Catalyzed Cycloaromatization: 1,5-Hydrogen Migration



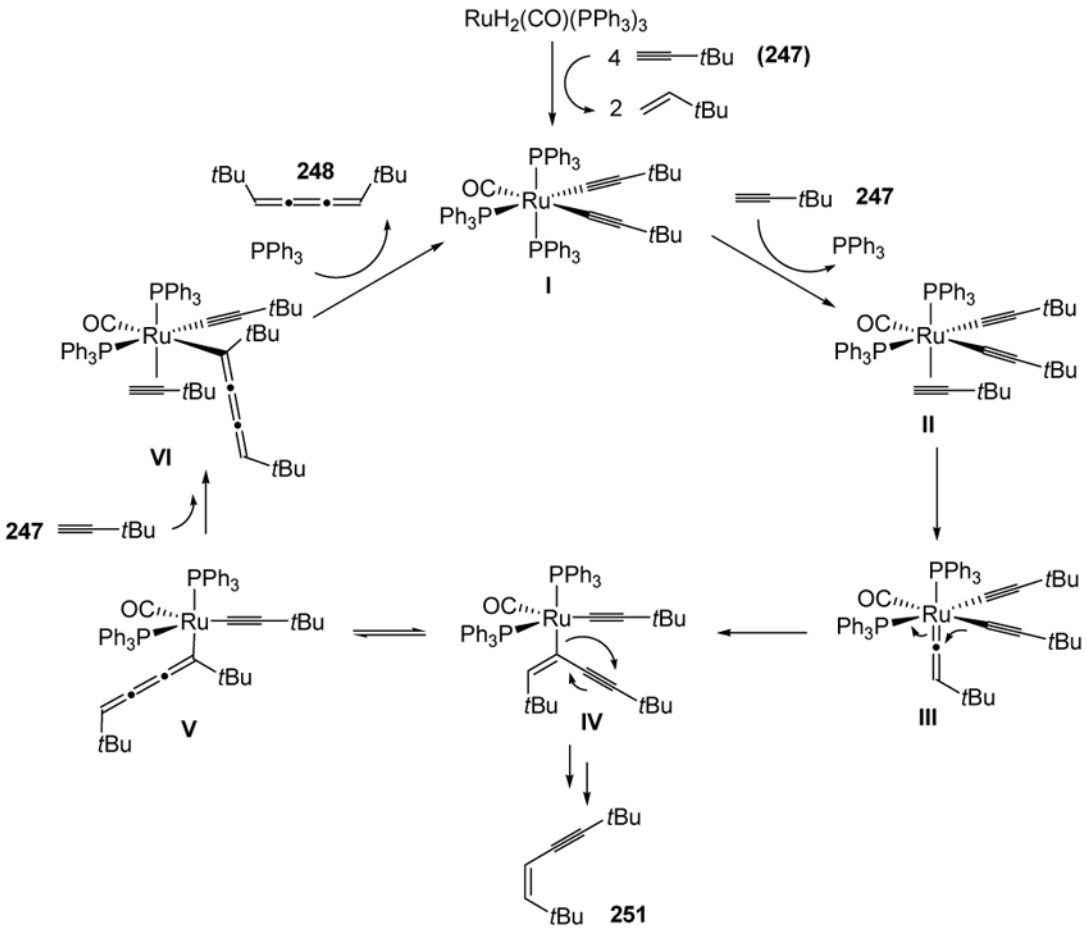
Scheme 93.
Uemura's Rhodium-Catalyzed Cycloaromatization: 1,6-Hydrogen Migration



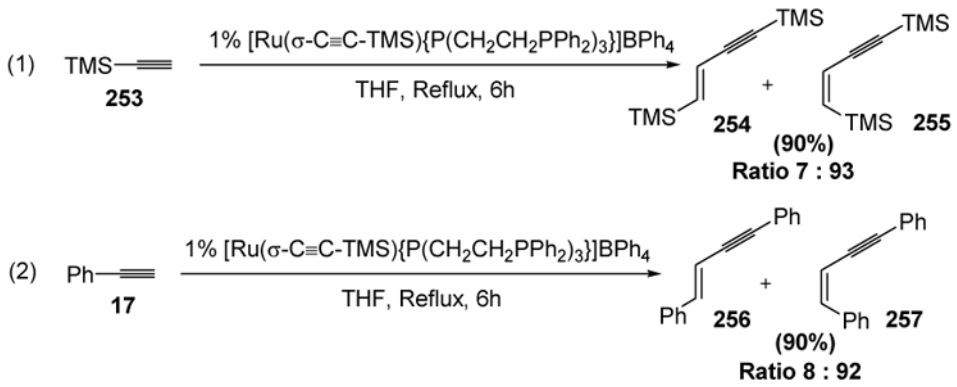
Scheme 94.
Mechanism of Rhodium-Catalyzed Cycloaromatization: 1,6-Hydrogen Migration



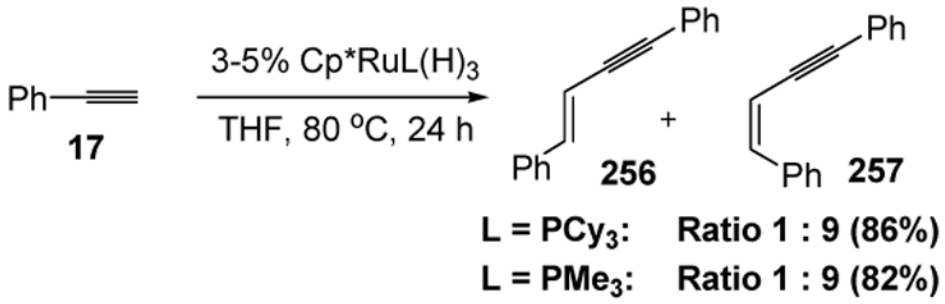
Scheme 95.
Yamazaki's Dimerization of t-Butylacetylene



Scheme 96.
Catalytic Cycle for Yamazaki's Dimerization of *t*-Butylacetylene

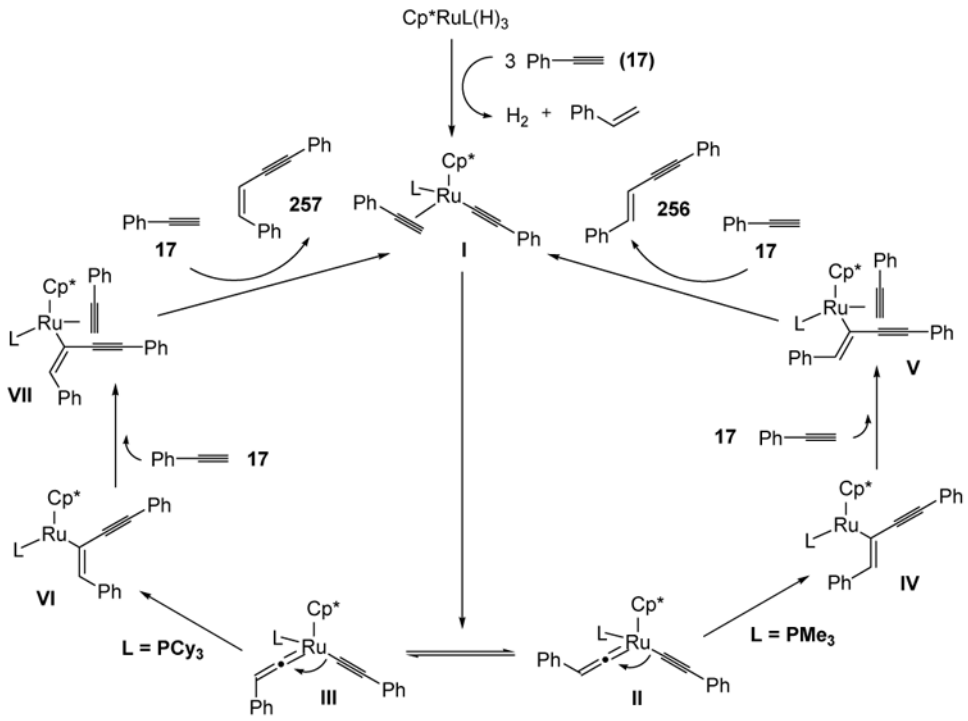


Scheme 97.
Bianchini's Dimerization of Trimethylsilylacetylene and Phenylacetylene. THF=tetrahydrofuran.



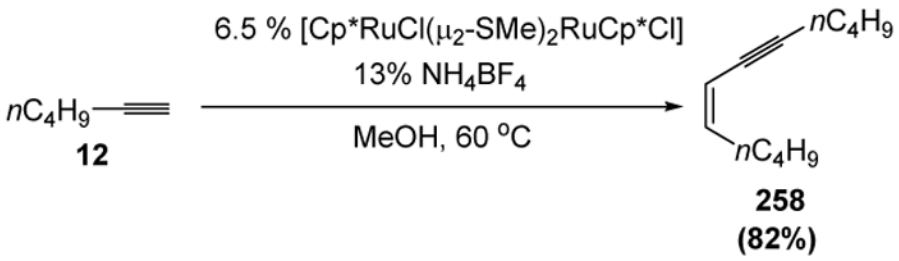
Scheme 98.

Yi's Stereoselective Dimerization of Phenylacetylene: Ligand Effect. Cp*=1,2,3,4,5-η^5-pentamethylcyclopentadienyl, THF=tetrahydrofuran.

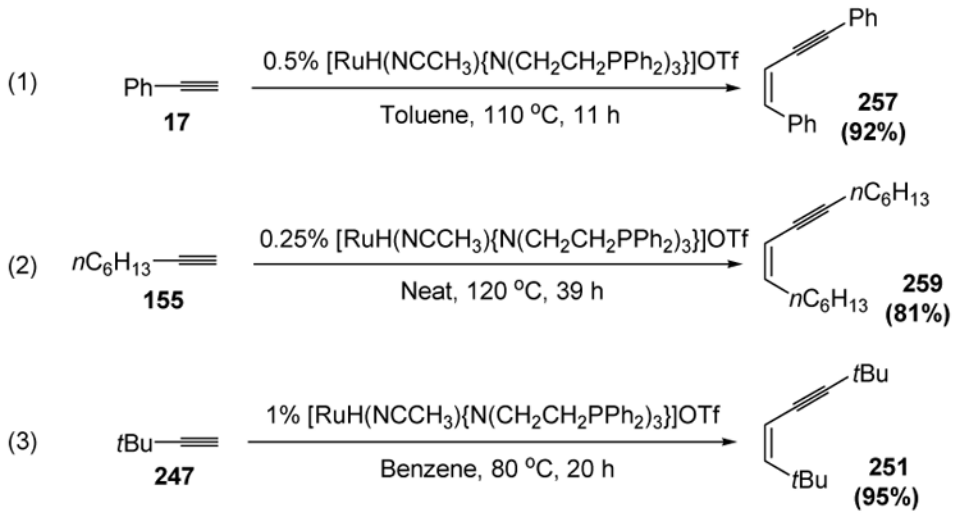


Scheme 99.

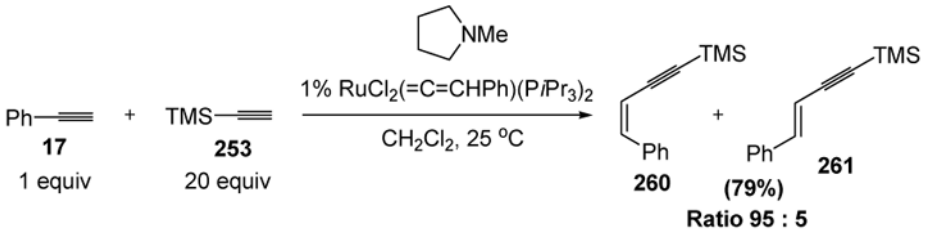
Alkyne Dimerization: Rationale for Product Formation. Cp*=1,2,3,4,5-η^5-pentamethylcyclopentadienyl.



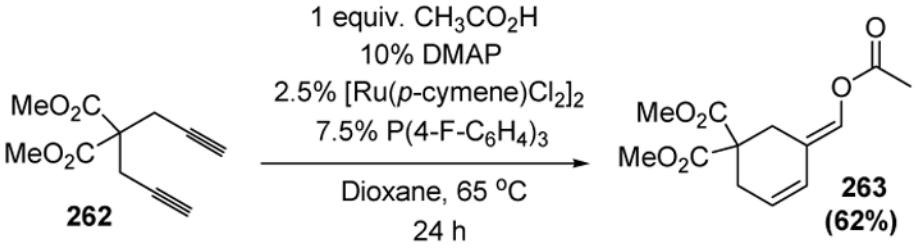
Scheme 100.
Hidai's Head-to-Head Dimerization of Aliphatic Terminal Alkynes. Cp*=1,2,3,4,5-η^5-pentamethylcyclopentadienyl.



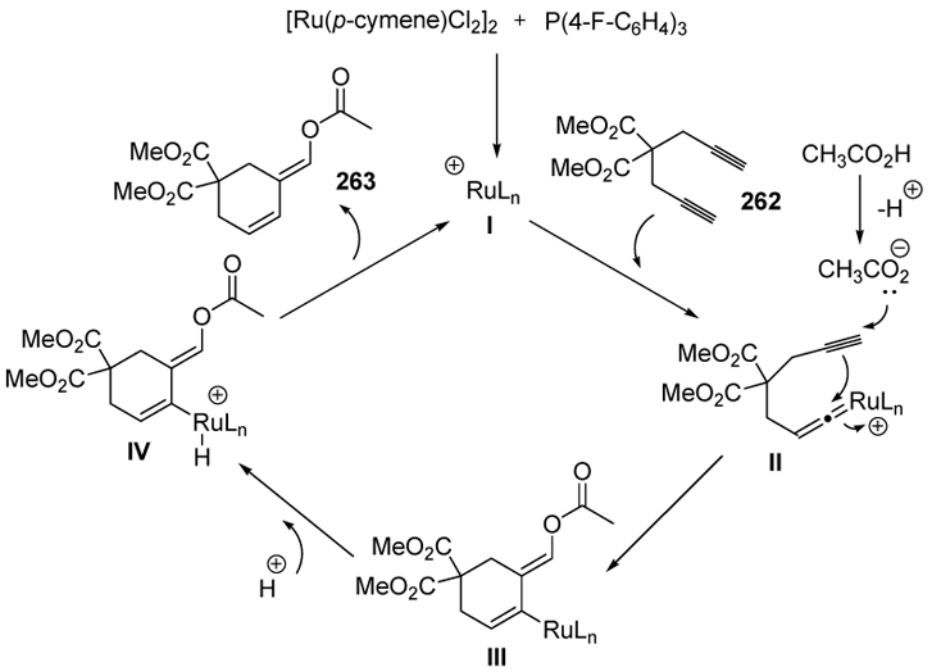
Scheme 101.
Bianchini's Dimerization of Aromatic and Aliphatic Terminal Alkynes



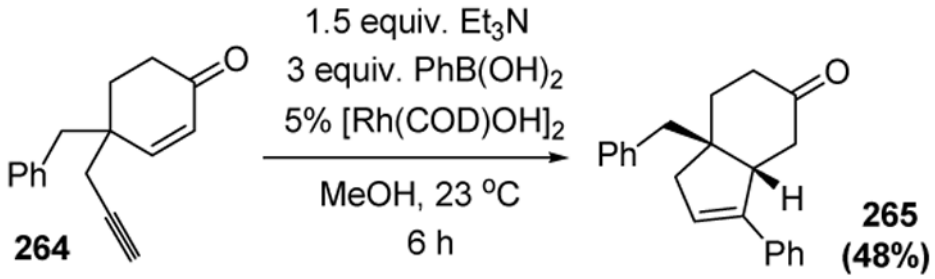
Scheme 102.
Katayama's Cross-Dimerization of Arylacetylenes with Silylacetylenes



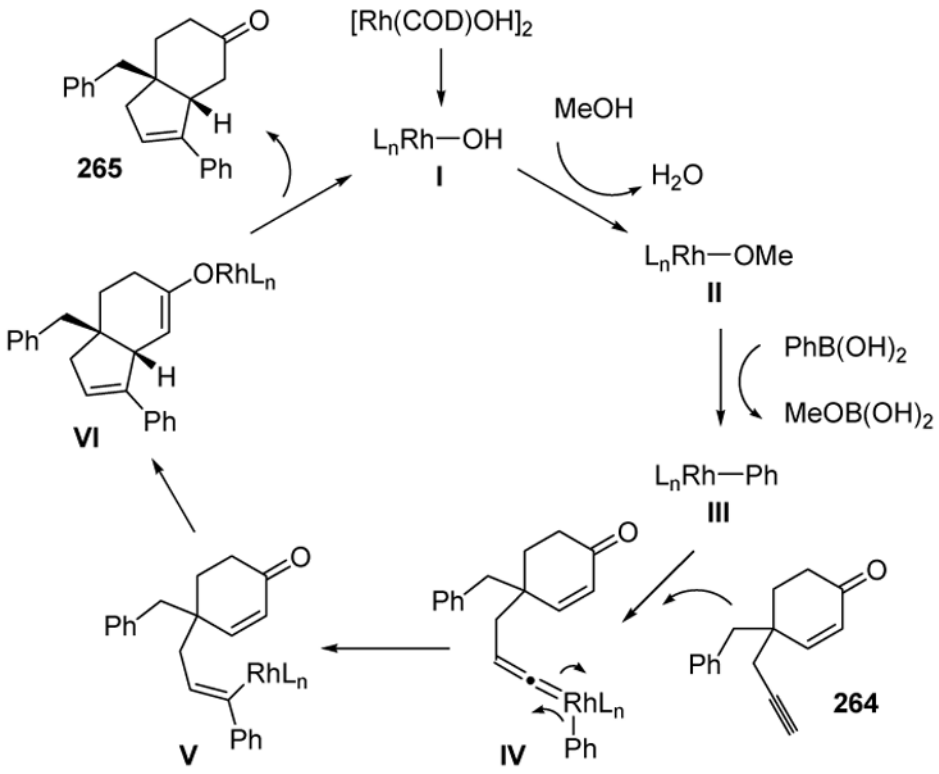
Scheme 103.
Lee's Carboxylative Cyclization of 1,6-Diynes



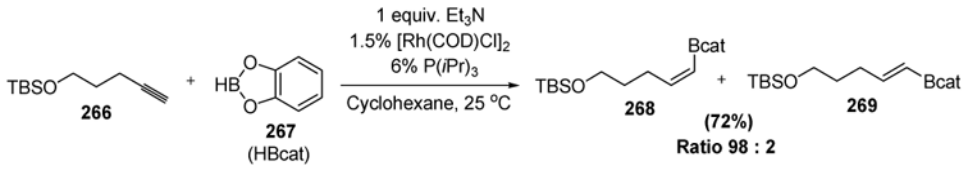
Scheme 104.
Mechanism of the 1,6-Diyne Carboxylative Cyclization



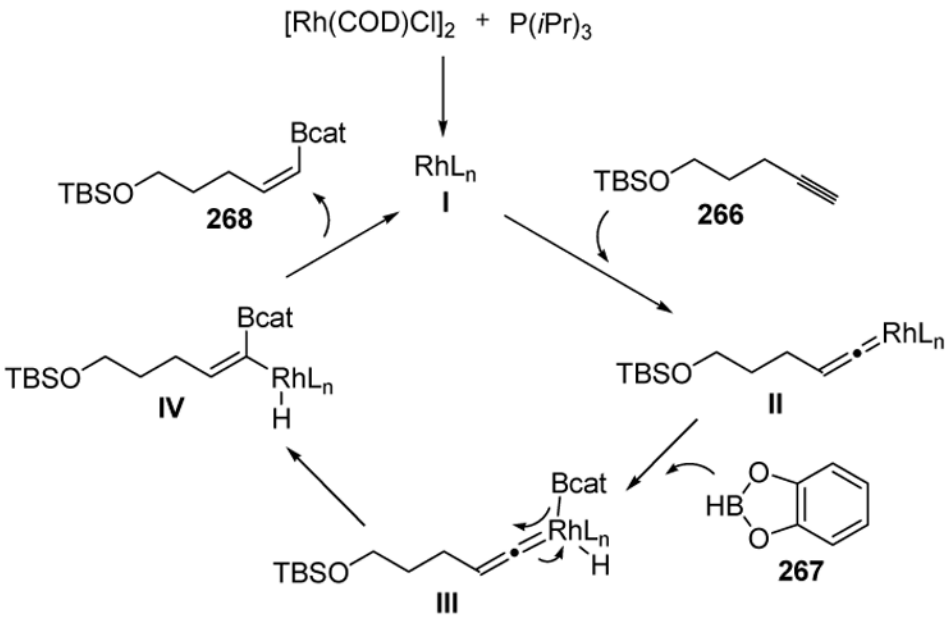
Scheme 105.
Lee's Arylative Cyclization of 1,5-Enynes. COD=1,5-cyclooctadiene.



Scheme 106.
Mechanism of 1,5-Enyne Arylative Cyclization. COD=1,5-cyclooctadiene.



Scheme 107.
Miyaura's *Z*-Selective Hydroboration of Terminal Alkynes. COD=1,5-cyclooctadiene.

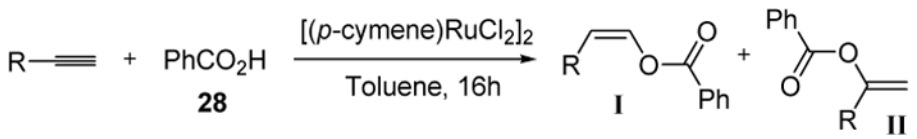


Scheme 108.

Z-Selective Hydroboration of Terminal Alkynes: Mechanistic Rationale. COD=1,5-cyclooctadiene.

Table 1

Ligand Control in Regioselectivity of Enol Ester Formation



Alkyne (R)	% Catalyst	Ligand	Base	Temp (°C)	Yield (%)	Ratio (I/II)
*n*Bu	1	3% P(4-Cl-C_6H_4)$_3$	4% DMAP	60	89	50:1
*n*Bu	0.4	0.8% P(furyl)$_3$	1.6% Na_2CO_3	50	90	1:30
Ph	1	3% P(4-Cl-C_6H_4)$_3$	4% DMAP	60	99	50:1
Ph	0.4	0.8% P(furyl)$_3$	1.6% Na_2CO_3	70	88	1:1.5
*t*Bu	1	3% P(4-Cl-C_6H_4)$_3$	4% DMAP	80	68[a]	50:1
*t*Bu	0.4	0.8% P(furyl)$_3$	1.6% Na_2CO_3	50	80	1:10

[a] Solvent: 1,2-dichloroethane. DMAP=4-dimethylaminopyridine.