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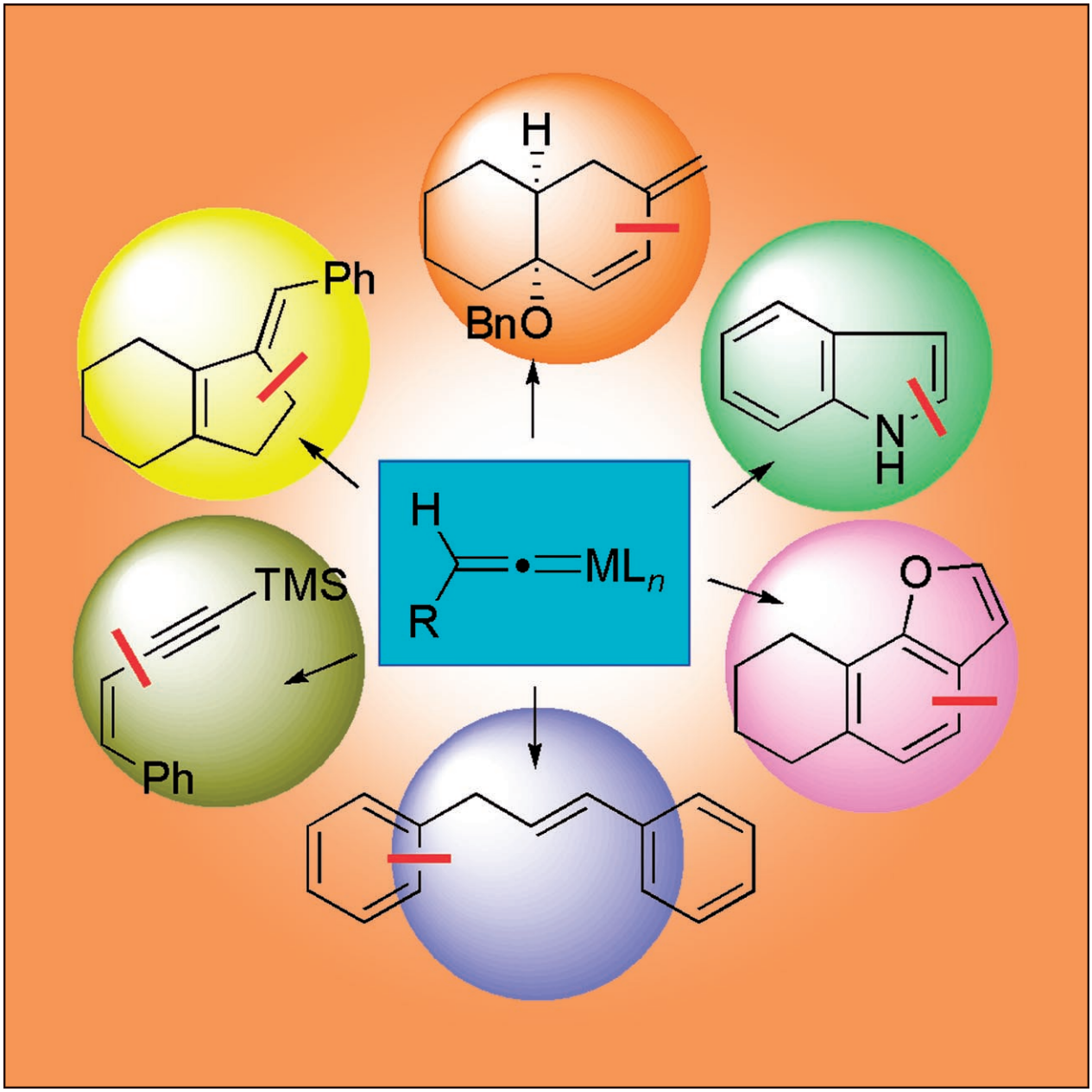
Metal Vinylidenes as Catalytic Species in Organic Reactions

Barry M. Trost* and Andrew McClory[a]

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

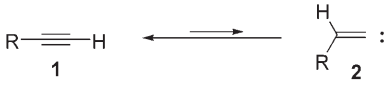


Abstract: Organic vinylidene species have found limited use in organic synthesis owing to their inaccessibility. In contrast, metal vinylidenes are much more stable and may be readily accessed through transition-metal activation of terminal alkynes. These electrophilic species may be trapped by a number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

Keywords: atom economy · catalysis · chemoselectivity · organic synthesis · vinylidene ligands

1. Introduction

Organic vinylidene species (**2**) are tautomers of the corresponding alkynes (**1**) but are thermodynamically much less stable (Scheme 1).[1] There is also a significant activation

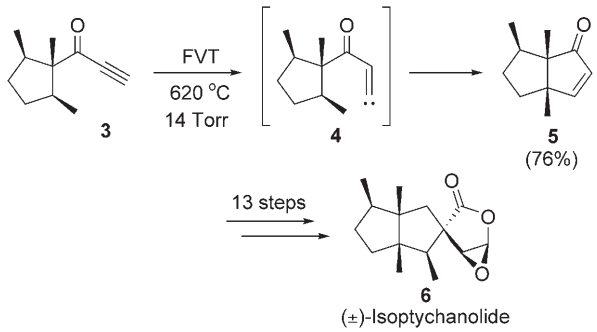


Scheme 1. Terminal alkynes and the corresponding vinylidenes.

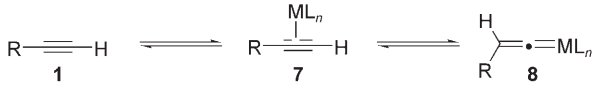
energy for the interconversion of the two species. As harsh conditions are required for the generation of organic vinylidenes, their application in organic synthesis has been severely limited.

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

A significant advance was the observation that metal vinylidenes are much more stable than organic (free) vinylidenes.[3] 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 electronic configuration of the



Scheme 2. Synthetic use of an organic vinylidene: the Dreiding synthesis of (±)-isoptychanolide. FVT = flash vacuum thermolysis.



Scheme 3. Formation of metal vinylidenes from terminal alkynes.

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 into metal vinylidenes. The first pathway involves oxidative addition of the metal to 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 the hydride over the alkyne (Scheme 4).

There has been experimental support for the first mechanism in some cases (i.e., observation or isolation of the alkynyl metal hydride intermediate **9**). This is the case for reactions that involve $[RhCl\{P(iPr)_3\}_2]$,[4] although even in this case it is not clear whether the [1,3] migration step is a unimolecular[5] or bimolecular[6] process. In the majority of reactions, however, it is not known which pathway is opera-

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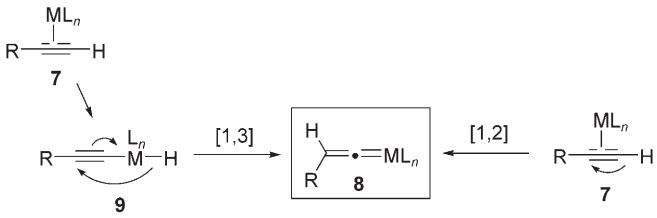

Scheme 4. Mechanisms of metal vinylidene formation.

tive, and both experimental and computational studies have been carried out to delineate the mechanism.[7]

Vinylidenes behave as electron-withdrawing ligands on the metal, and thus electron-donating ligands (L_n) would stabilize this species (**8**) relative to the metal-complexed alkyne (**7**; Scheme 3). However, a balance must be struck, as there is a danger of making the species so stable that it does not undergo further reactions. Traditionally, nucleophiles (such as alcohols) are added to metal vinylidenes in stoichiometric reactions to generate the corresponding Fischer carbene complexes (Scheme 5). This mode of reactivity reflects the inherent electrophilicity of the vinylidene α-carbon atom.

More recently, there has been a large number of publications that involve conversion of terminal alkynes into various products in which metal vinylidenes serve as catalytic species.[8] The three types of transformations most commonly investigated are: 1) nucleophilic addition to the α-carbon

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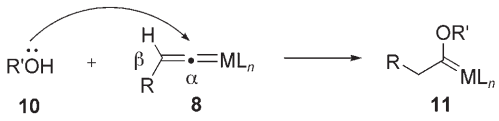
Andrew McClory *was born in Montreal in 1976. He received his BSc from Concordia University in 1999. He then carried out his graduate studies at Stanford University, where he worked on ruthenium- and rhodium-catalyzed atom-economical reactions under the guidance of Professor Barry M. Trost. He received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



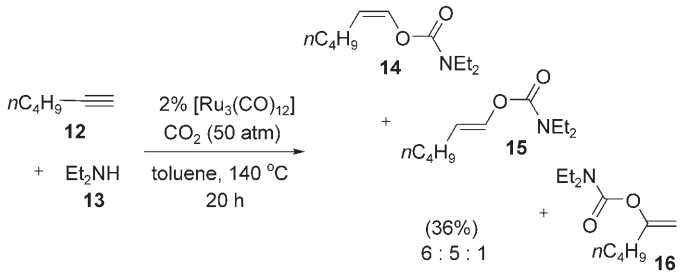
Scheme 5. Nucleophilic addition to metal vinylidenes: Fischer carbene formation.

atom, 2) [1,2] alkyl migration from the metal center to the α-carbon atom, and 3) pericyclic reactions.[9] In this Focus 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 to facilitate an understanding of the transformation at hand.

2. Heteroatom Nucleophile Reactions with Vinylidenes

2.1. Carbamate Nucleophiles

Sasaki and Dixneuf reported the first example of a metal vinylidene complex as a catalytic species in an organic reaction over 20 years ago.[10] 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



Scheme 6. Vinylcarbamates from terminal alkynes, secondary amines, and carbon dioxide.

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.[11]

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 be formed by nucleophilic attack on the more electrophilic (internal) carbon atom of the metal-coordinated alkyne **V**.

Although the selectivities and yields of the process were low, the results spurred further attempts at catalyst modifi-

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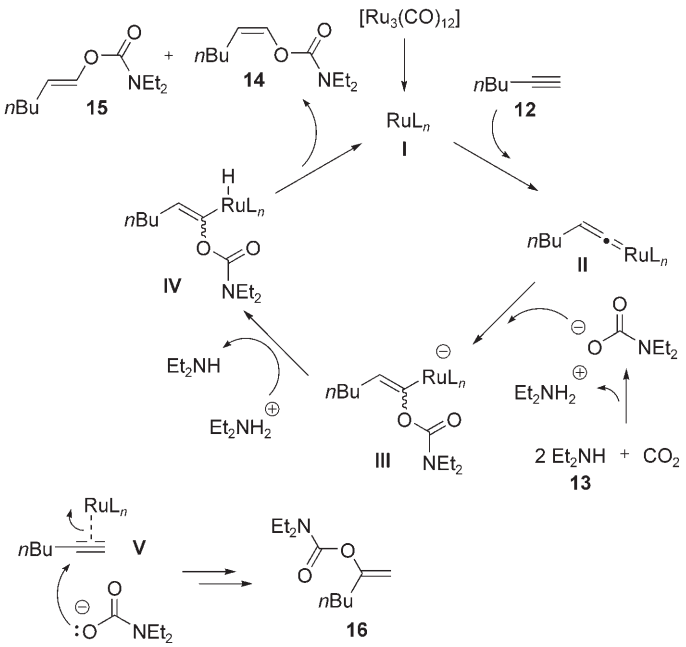
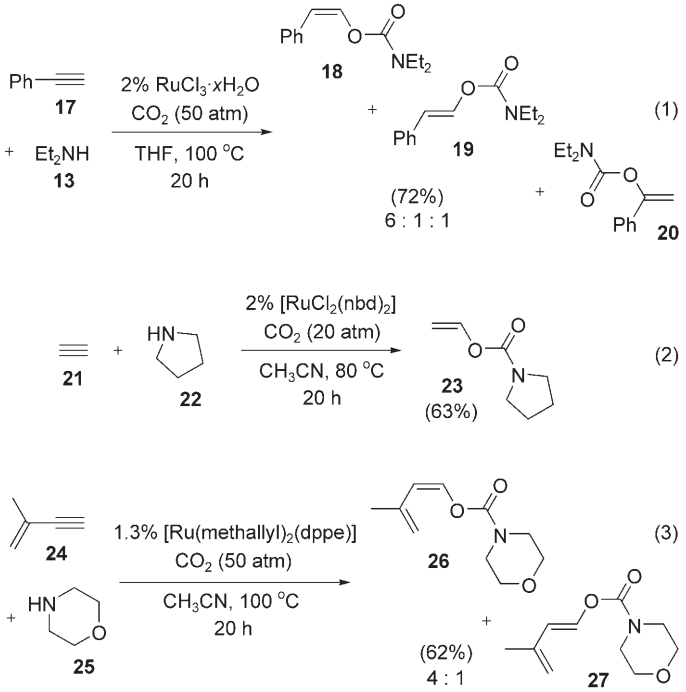


Scheme 7. Mechanism of vinylcarbamate formation.

cation to improve the transformation. Thus, by changing the catalyst and solvent, phenylacetylene (**17**) was treated with diethylamine to provide the corresponding vinylcarbamate in moderate yield and selectivity (Scheme 8, Equation (1)).[12] Acetylene (**21**) was also a viable coupling partner with pyrrolidine, although an excess of alkyne was required owing to competing polymerization of the alkyne (Scheme 8, Equation (2)).[13,14] Interestingly, 2-methyl-1-buten-3-yne (**24**) could be used as a substrate; it reacted with morpholine to give diene products that are activated Diels–Alder reaction partners (Scheme 8, Equation (3)).[15]

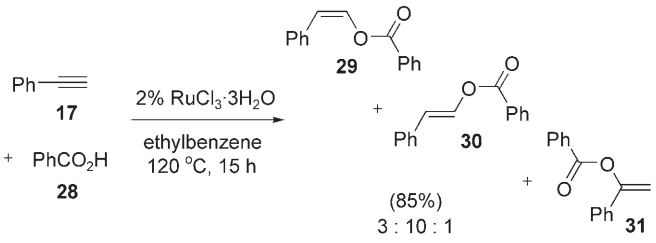


Scheme 8. Synthesis of vinylcarbamates: scope of alkynes and secondary amines. dppe = bis(diphenylphosphanyl)ethane, nbd = norbornadiene, THF = tetrahydrofuran.

2.2. Carboxylic Acid Nucleophiles

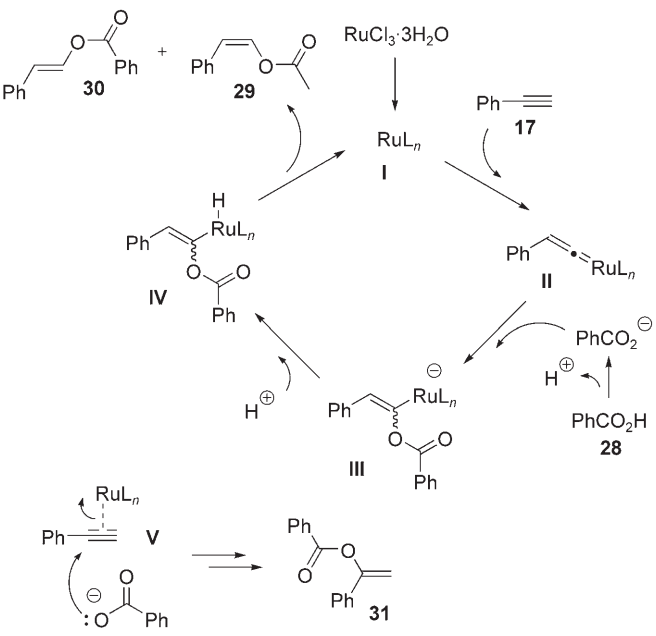
2.2.1. Intermolecular Reactions

Contemporaneous with their work on vinyl carbamate formation, Dixneuf and co-workers disclosed the use of carboxylic acid nucleophiles to capture metal vinylidenes in a catalytic synthesis of enol esters.[16,17] Thus, phenylacetylene (**17**) and benzoic acid (**28**) reacted, 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).



Scheme 9. Formation of enol esters from carboxylic acids and alkynes.

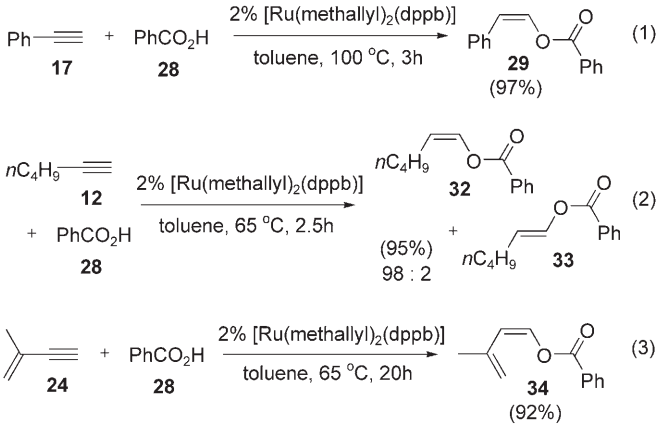
In a similar manner to the aforementioned formation of vinyl carbamates, the anti-Markovnikov enol ester products can be accounted for by invoking a vinylidene mechanism (Scheme 10). Thus, vinylidene formation between the ruthe-



Scheme 10. Mechanism of enol ester formation.

nium catalyst and the terminal alkyne **17**, followed by nucleophilic attack of the carboxylate, protonation of the metal, and reductive elimination, gives products **29** and **30**. The regioisomeric Markovnikov product **31** is probably formed by electrophilic activation of the alkyne followed by nucleophilic attack.

Subsequent studies showed that the complex [Ru(methallyl)$_2$dppb] is a better catalyst for a variety of alkynes and carboxylic acids (Scheme 11). For example, benzoic acid underwent addition in a regio- and stereoselective manner to phenylacetylene (Scheme 11, Equation (1)),[18] 1-hexyne (Scheme 11, Equation (2)),[19] and 2-methyl-1-buten-3-yne (Scheme 11, Equation (3))[20] to give the corresponding enol esters in excellent yields.

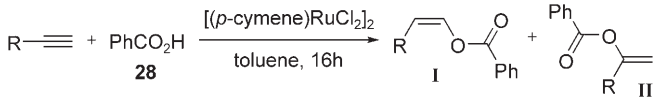


Scheme 11. Ruthenium-catalyzed formation of enol esters: scope of alkynes. dppb = bis(diphenylphosphanyl)butane.

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.[21,22] One of the most interesting reports showed that a change in the ligand and base, with the same ruthenium catalyst, allowed access to either the anti-Markovnikov or Markovnikov products in excellent yield (Table 1).[23]

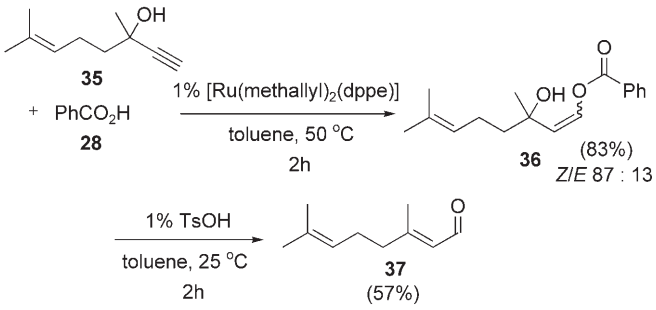
To highlight the utility of this type of reaction, Dixneuf and co-workers investigated a ruthenium-catalyzed isomerization process (Scheme 12). In this transformation, benzoic acid adds regioselectively to putative metal vinylidene complexes, and the resulting *Z* enol esters then fragment at higher temperatures to give enal products in good yields.[24] Alternatively, the intermediate enol esters may be treated with a catalytic amount of *p*-toluenesulfonic acid at room temperature to effect the elimination reaction.[25]

Table 1. Ligand control in the regioselectivity of the formation of enol esters.



R	Cat. [%]	Ligand ([%])	Base ([%])	*T* [°C]	Yield [%]	**I/II**
*n*Bu	1	P(4-Cl-C$_6$H$_4$)$_3$ (3)	DMAP (4)	60	89	50:1
*n*Bu	0.4	P(furyl)$_3$ (8)	Na$_2$CO$_3$ (1.6)	50	90	1:30
Ph	1	P(4-Cl-C$_6$H$_4$)$_3$ (3)	DMAP (4)	60	99	50:1
Ph	0.4	P(furyl)$_3$ (8)	Na$_2$CO$_3$ (1.6)	70	88	1:1.5
*t*Bu	1	P(4-Cl-C$_6$H$_4$)$_3$ (3)	DMAP (4)	80	68[a]	50:1
*t*Bu	0.4	P(furyl)$_3$ (8)	Na$_2$CO$_3$ (1.6)	50	80	1:10

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

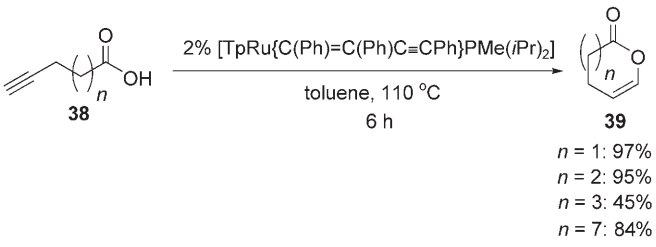


Scheme 12. The Dixneuf isomerization of propargyl alcohols to enals. Ts = *p*-toluenesulfonyl.

This process constitutes the synthetic equivalent of a Meyer–Schuster rearrangement,[26] 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 olefination of ketones.

2.2.2 Intramolecular Reactions

Valerga and co-workers found that carboxylic acids can add to terminal alkynes in an intramolecular fashion.[27] Thus, α,ω-alkynoic acids (**38**) may be converted into the corresponding enol lactones **39**, in one case even forming a macrocycle, in good to excellent yields by heating in the presence of a ruthenium catalyst (Scheme 13). The exclusive formation of the endocyclic enol lactone is consistent with vinylidene formation followed by intramolecular trapping by the tethered carboxylic acids. Verpoort and co-workers 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.[28]

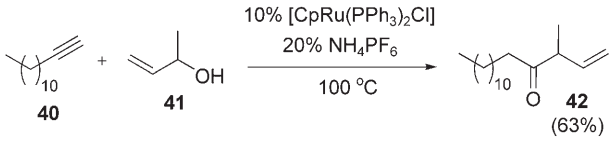


Scheme 13. The Valerga cyclization of α,ω-alkynoic acids. Tp = tris(pyrazolyl)borate.

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.[29] One notable exception, however, is the use of allylic alcohols. In what is termed the ruthenium-catalyzed reconstitutive condensation reaction, Trost et al. reported that treatment of alkyne **40** and an excess of allylic alcohol **41** with a ruthenium catalyst and ammonium hexafluorophosphate leads to β,γ-unsaturated ketone **42** (Scheme 14).[30] This result in fact represents the first use of vinylidenes to form C–C bonds in a catalytic reaction.

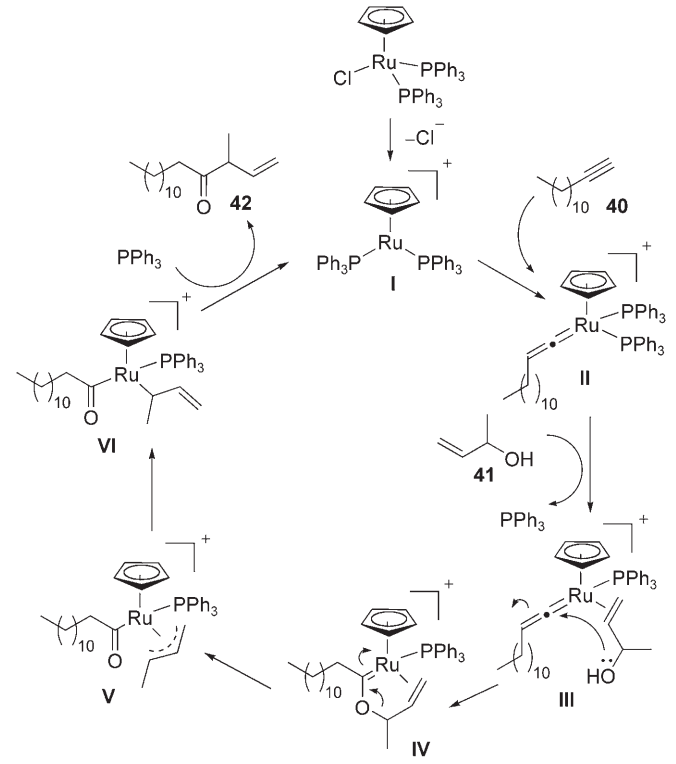


Scheme 14. Ruthenium-catalyzed reconstitutive condensation. Cp = η^5-cyclopentadienyl.

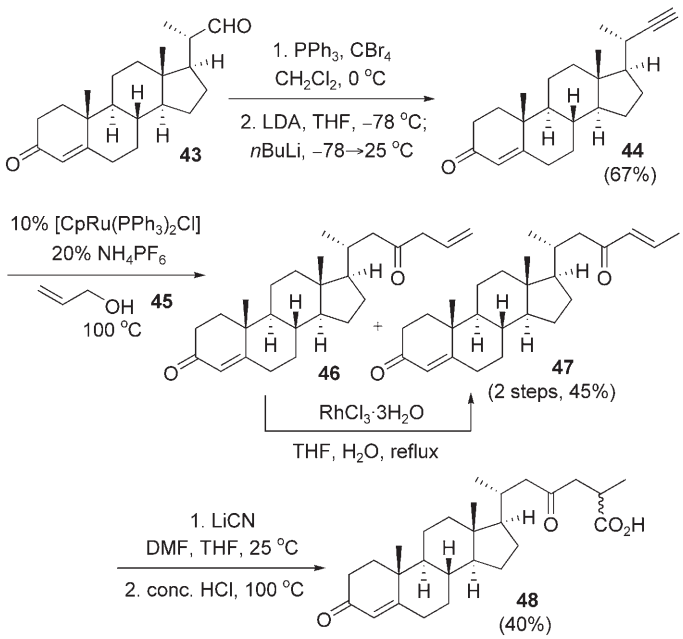
Evidence for vinylidene intermediates in this process was gathered through exploration of substrate scope and labeling studies; a mechanism consistent with the results was then proposed (Scheme 15).[31] Loss of chloride ion from the ruthenium complex is expected to lead to the active cationic catalyst **I**. Vinylidene formation with alkyne **40** leads to **II**. Coordination of olefin **41** with loss of phosphine results in **III**, and subsequent nucleophilic attack by the pendant alcohol gives **IV**. Ionization of the resulting allyl ether then provides acyl ruthenium species **V**, which can be represented as the coordinatively unsaturated 16-electron 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).[32] The terminal alkyne substrate **44** was prepared by Corey–Fuchs homologation[33] of the commercially available 3-oxopregn-4-ene-20β-carboxaldehyde (**43**). In this transformation, the enone present in the substrate was effectively protected from side reactions by conversion into the corresponding enolate prior to the reaction. The ruthenium-catalyzed reconstitutive condensation with allyl alcohol **45** then proceeded in good yield to give a mixture of **46** and **47**; treatment of this mixture with catalytic rhodium trichloride in aqueous tetrahydrofuran resulted in complete conversion into the α,β-unsaturated ketone **47**. Conjugate addition of cyanide followed by nitrile hydrolysis then gave **48**.

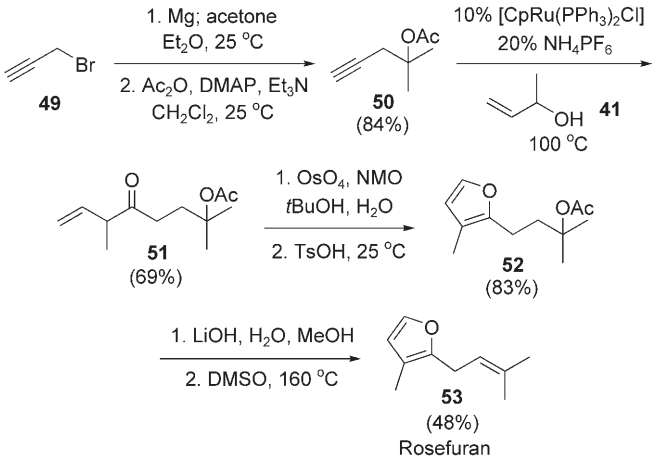
The utility of this transformation was further demonstrated in a short synthesis of the fragrance rosefuran (**53**; Scheme 17).[34] Thus, addition of propargylmagnesium bromide to acetone followed by acylation of the resulting tertiary alcohol gave alkyne **50** in good yield. Reconstitutive condensation with allylic alcohol **41** then gave **51**, a molecule that contains all of the carbon atoms present in the



Scheme 15. Proposed mechanism of ruthenium-catalyzed reconstitutive condensation.



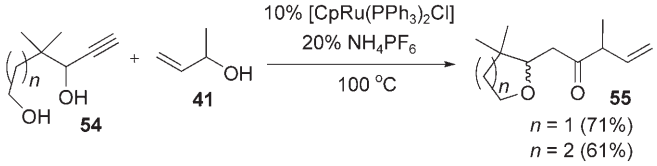
Scheme 16. The Trost synthesis of a functionalized steroid side chain. DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamide.



Scheme 17. The Trost synthesis of rosefuran. DMSO = dimethyl sulfoxide, NMO = *N*-methylmorpholine-*N*-oxide.

target molecule. A tandem dihydroxylation–cyclization provided furan **52**. Ester hydrolysis followed by thermal dehydration then gave rosefuran.

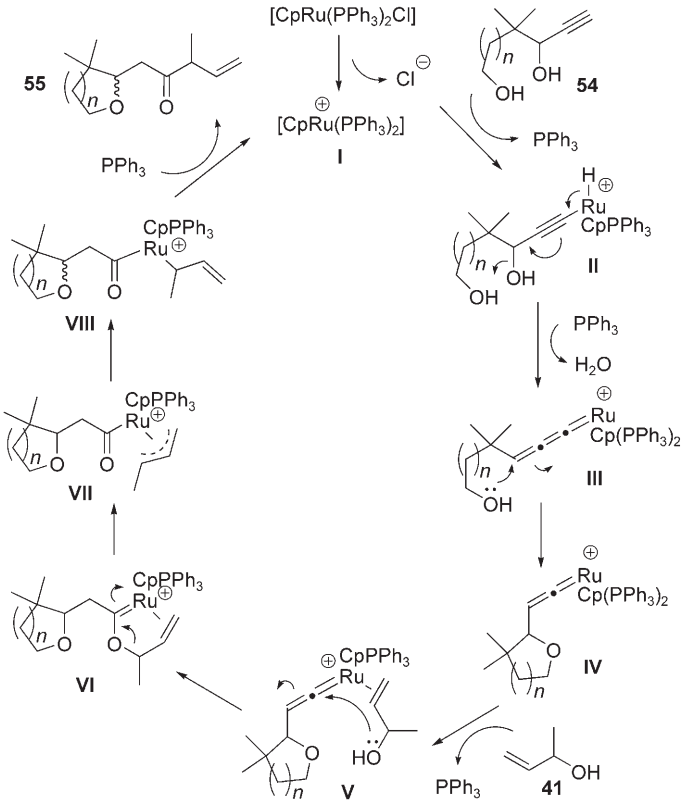
Terminal alkynes that bear propargyl alcohols have the ability to form allenylidene species. These complexes are electrophilic and thus offer opportunities for reactions with nucleophilic functional groups. In this context, Trost and Flygare reported the catalytic reaction of propargyl alcohol substrates that bear pendant alcohol groups to form tetrahydrofurans and tetrahydropyrans (Scheme 18).[35]



Scheme 18. The Trost tandem cyclization–reconstitutive condensation.

The mechanism of this tandem reaction is shown 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 was used in a synthesis of the spiroketal subunit of the phosphatase inhibitor (−)-calyculin A (Scheme 20).[36] The sequence begins 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 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



Scheme 19. Mechanism of the Trost tandem cyclization–reconstitutive condensation.

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.[37] This reaction was reported independently by Dotz and Sturm[38] as well as Parlier and Rudler[39] over 20 years ago, and later by McDonald et al. (Scheme 21).[40] 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

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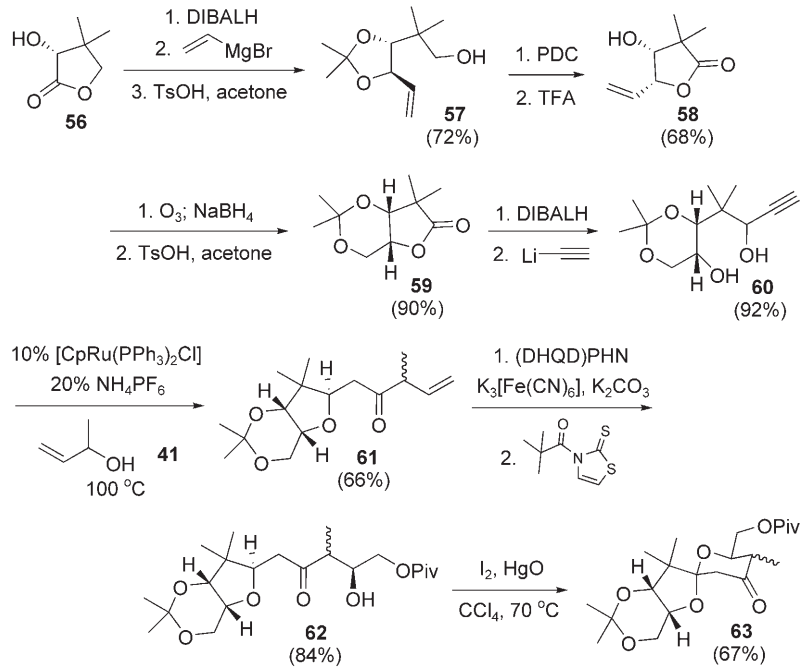
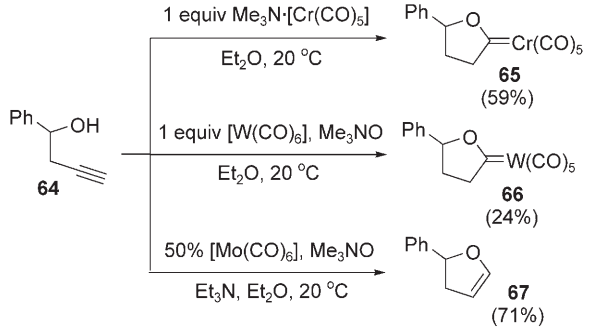
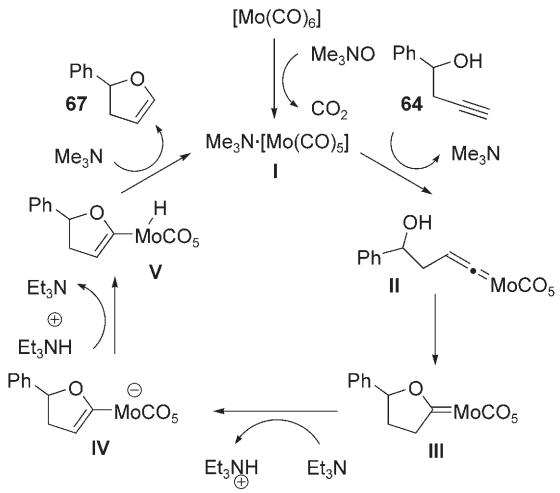


Scheme 20. The Trost synthesis of the spiroketal subunit of (−)-calyculin A. (DHQD)PHN = dihydroquinidine 9-*O*-(9′-phenanthryl) ether, DIBALH = diisobutylaluminum hydride, PDC = pyridinium dichromate, Piv = pivaloyl, TFA = trifluoroacetic acid.



Scheme 21. The McDonald seminal alkynol cycloisomerization reaction.

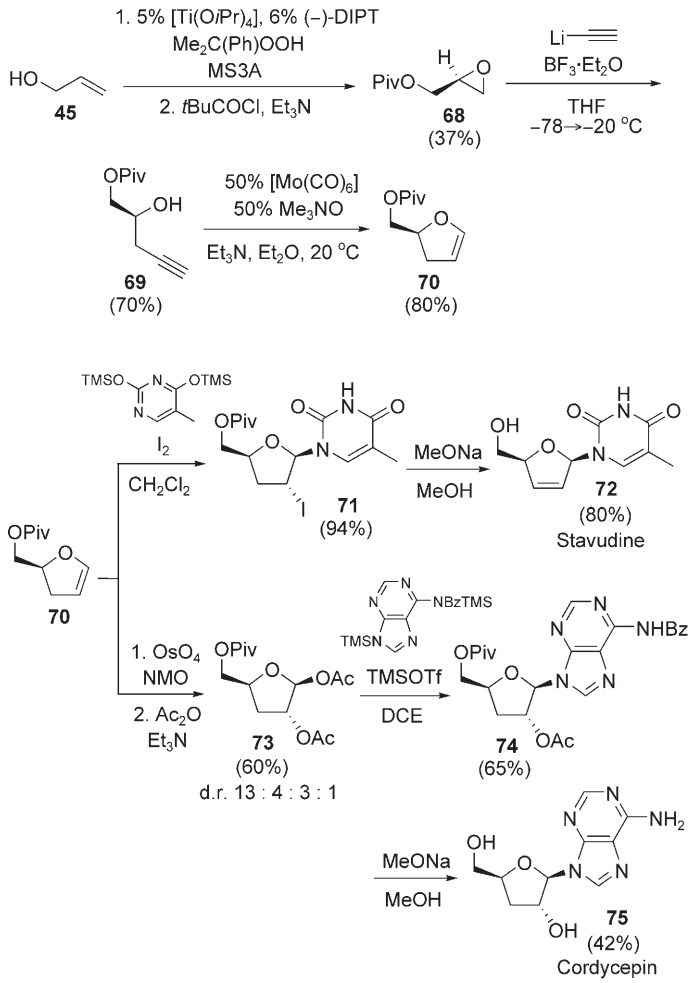


Scheme 22. Mechanism of molybdenum-catalyzed alkynol cycloisomerization.

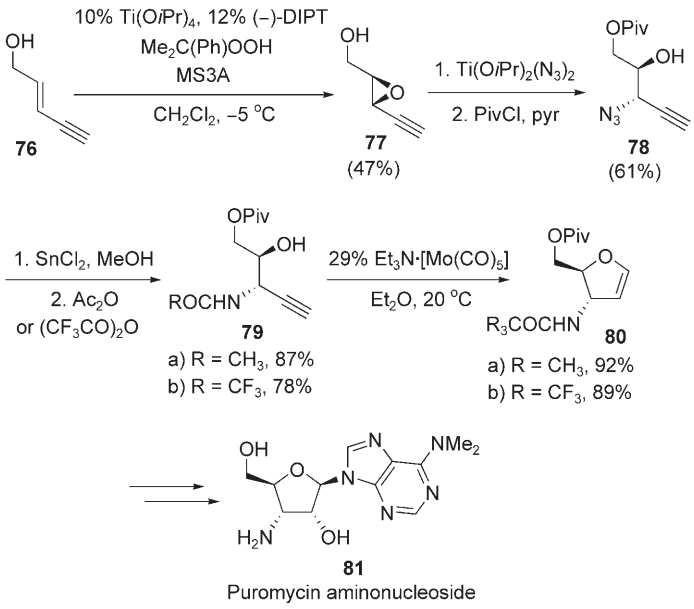
give Fischer carbene **III**. In the presence of triethylamine, deprotonation of this electrophilic oxacarbene gives anion **IV**. Protonation of the metal followed by reductive elimination gives **67** and releases the active catalyst. Although the catalyst loading was almost stoichiometric, this initial report paved the way for future investigations.

With the recognition of the utility of this transformation, synthetic applications followed soon after. McDonald and Gleason first used this reaction in concise enantioselective syntheses of the deoxynucleosides stavudine and cordycepin (Scheme 23).[41] 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; the key dihydrofuran intermediate **70** was provided in good yield. Iodine-mediated introduction of thymine onto this molecule provided iodonucleoside **71**. Pivaloate methanolysis and concomitant elimination of HI then gave stavudine (**72**), a substance with 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 with antibiotic activity.

This manner of deoxynucleotide synthesis was further extended to 3-aminofuranose glycals (Scheme 24).[42] 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 **79** for cycloisomerization. This 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 does 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**).

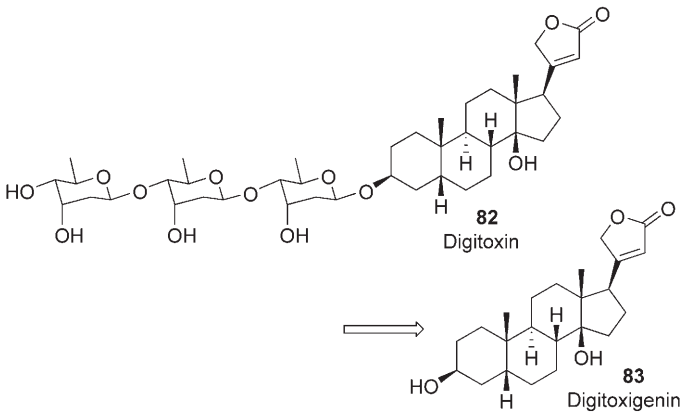


Scheme 23. The McDonald synthesis of stavudine and cordycepin. Bz = benzoyl, DCE = 1,2-dichloroethane, DIPT = diisopropyltartrate, MS3A = 3-Å molecular sieves, TMS = trimethylsilyl.



Scheme 24. The McDonald synthesis of 3-aminonucleosides.

McDonald and Reddy further demonstrated the utility of this transformation in a synthesis of digitoxin (**82**).[43] In this convergent approach, the trisaccharide moiety of the natural product was constructed by iterative cycloisomerizations[44] and then connected to digitoxigenin (**83**) by glycosidation (Scheme 25).

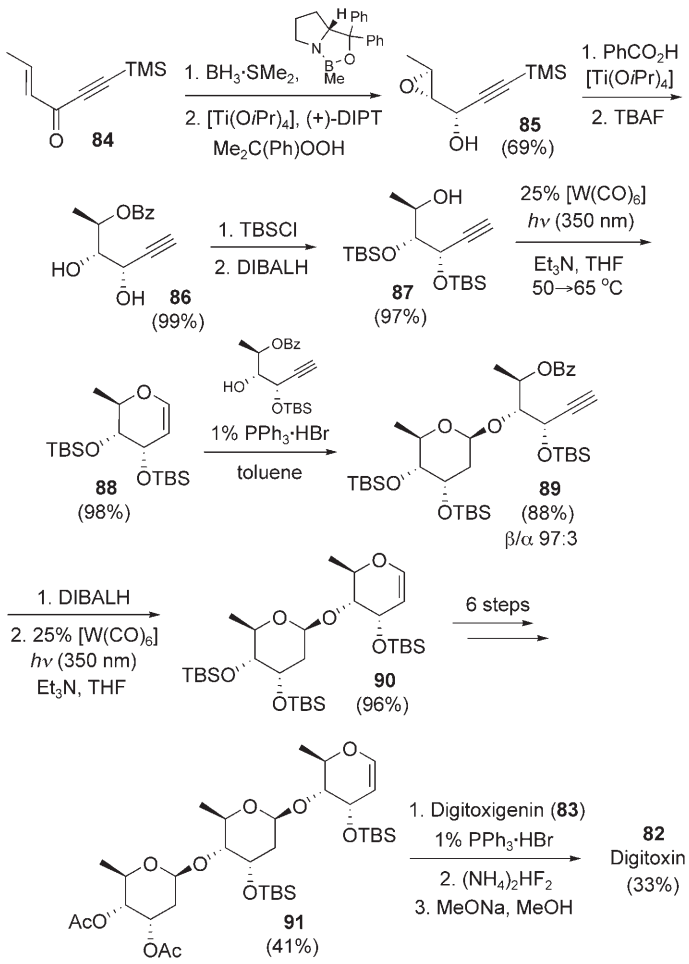


Scheme 25. The McDonald retrosynthetic analysis of digitoxin.

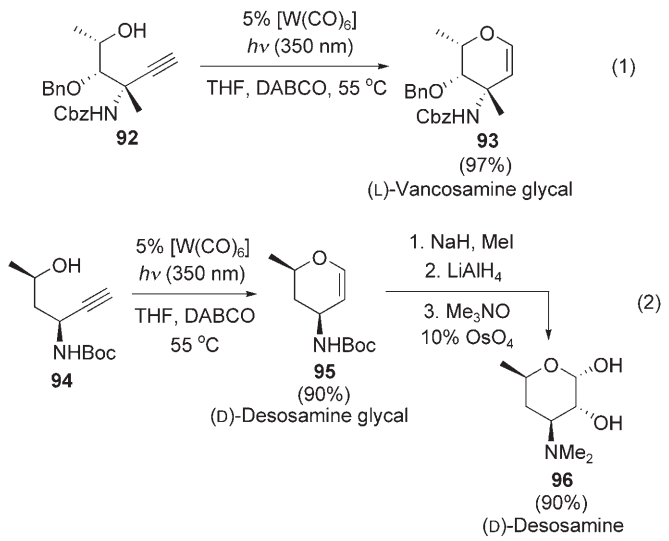
The chiral information of the nascent trisaccharide was installed by an enantioselective carbonyl reduction of enynone **84** and a diastereoselective epoxidation of the resultant allylic alcohol (Scheme 26). Regioselective epoxide opening with benzoic acid followed by protodesilylation afforded compound **86**. Diol protection followed by removal of the benzoate protecting group provided alkynol **87**, which underwent a smooth cycloisomerization to give 6-deoxy-D-riboglycal **88**.[45] 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 **91**. Finally, glycosidation with digitoxigenin followed by removal of the protecting groups gave digitoxin **82**.

More recently, McDonald reported that use of 1,4-diazabicyclo[2.2.2]octane (DABCO) as the base allows one to lower the catalyst loading for the formation of dihydropyrans significantly. This base may stabilize intermediates in the catalytic cycle more effectively than triethylamine. Wipf and Graham investigated these conditions with respect to the stereochemistry and nature of the substituents on the chain linking the alkyne and the alcohol in the substrate.[46] McDonald and co-workers successfully applied these new conditions in the syntheses of (L)-vancosamine (**93**)[47] and (D)-desosamine (**95**)[48] glycals (Scheme 27).

McDonald et al. 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** was converted into α-(tributylstannyl)-dihydrofuran **97** in reasonable yield with a catalytic amount of a molybdenum pentacarbonyl complex and tributyltin tri-

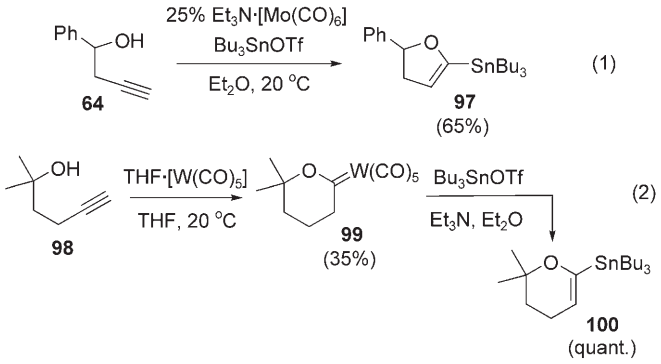


Scheme 26. The McDonald iterative cycloisomerization approach to digitoxin. TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl.



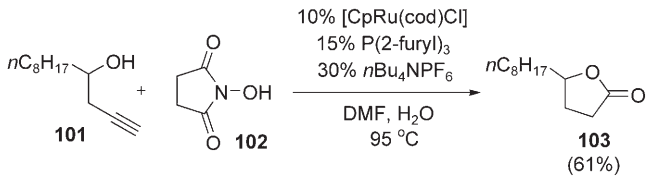
Scheme 27. The McDonald synthesis of (L)-vancosamine and (D)-desosamine glycals. Bn = benzyl, Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, DABCO = 1,4-diazabicyclo[2.2.2]octane.

flate (Scheme 28, Equation (1)).[49] The bis-homopropargyl alcohol **98**, on the other hand, was only converted into 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 (Scheme 28, Equation (2)).[50] 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.



Scheme 28. The McDonald formation of α-stannyl vinyl ethers from alkynols.

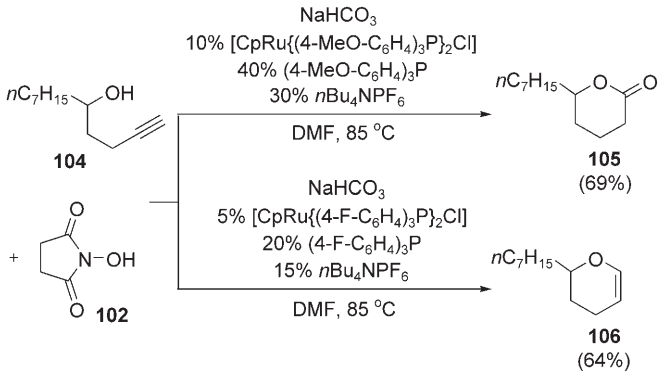
Trost and Rhee reported that the ruthenium-catalyzed cycloisomerization of homopropargyl alcohols such as **101** could be coupled to an oxidation reaction, thus providing γ-butyrolactones such as **103** (Scheme 29).[51]



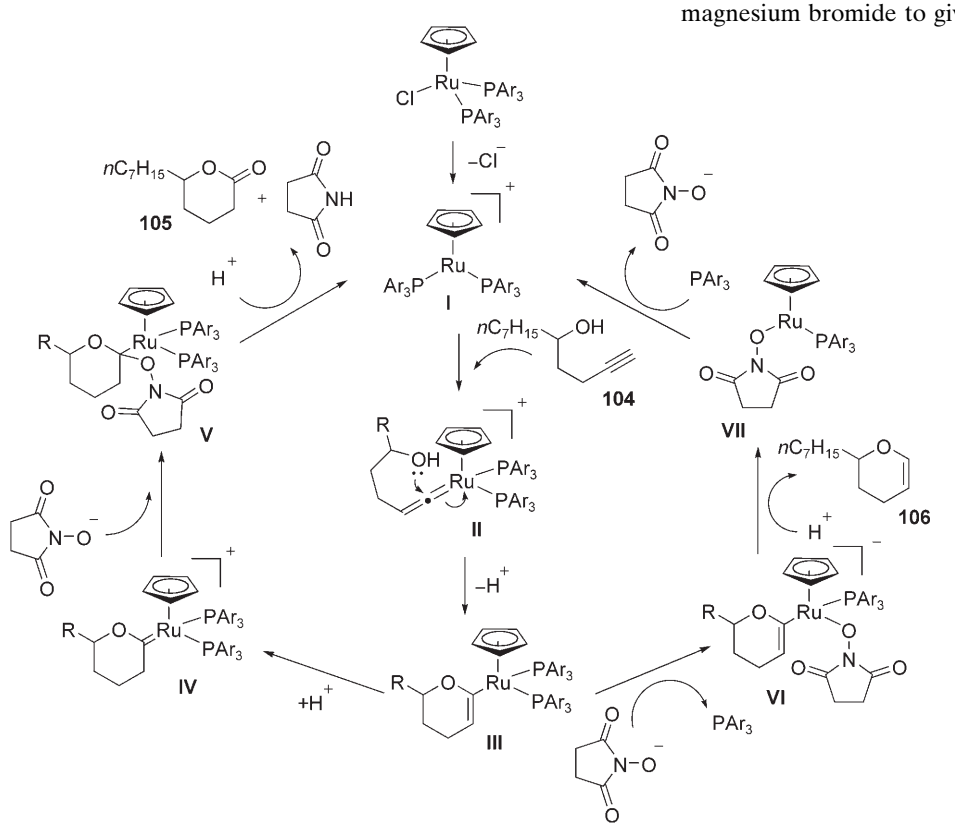
Scheme 29. Ruthenium-catalyzed oxidative cyclization of homopropargyl alcohols. cod = 1,5-cyclooctadiene.

Studies on the related reactions of bis-homopropargyl alcohols showed that use of 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.[52]

A mechanism that takes into account the ligand effects and explains the role of the base (*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 gives oxacarbene **IV**. Subsequent nucleophilic attack by the anion of *N*-hydroxysuccinimide followed by protonation and reductive elimination gives lac-



Scheme 30. Oxidative cyclization versus cycloisomerization of bis-homopropargyl alcohols.



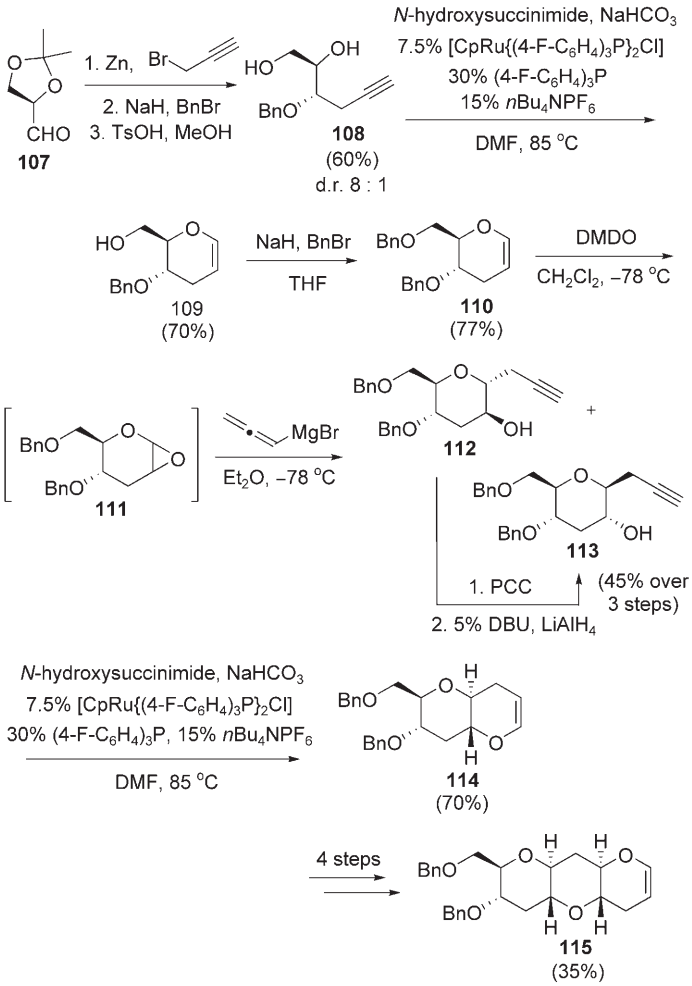
Scheme 31. Proposed mechanism of ruthenium-catalyzed oxidative cyclization and cycloisomerization.

tone product **105**. Alternatively, ligand displacement of complex **III** by the anion of *N*-hydroxysuccinimide gives **VI**. Protonation and reductive elimination then releases dihydropyran product **106** and structure **VII**, which undergoes 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.

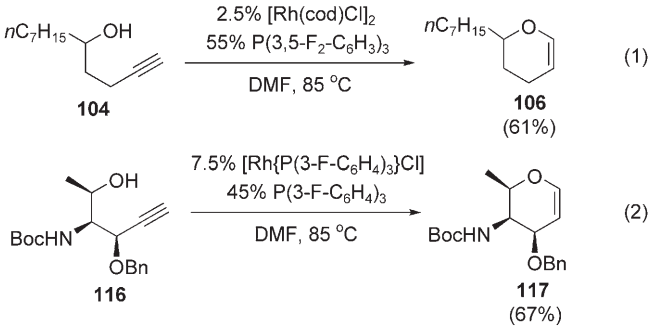
Trost and Rhee showed the utility of these reactions in a novel iterative cycloisomerization approach to the marine ladder toxins prymnesin and yessotoxin (Scheme 32).[53] The sequence of reactions begins with a diastereoselective addition of propargyl zinc to the acetonide of glyceraldehyde **107**. 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 be exclusively obtained by a simple epimerization sequence. Exposure of this compound to the aforementioned ruthenium conditions led to the cycloisomerization product **114** in good yield. A repeat of this sequence of events then gave the subunit of yessotoxin (**115**).

Trost and Rhee subsequently reported the cycloisomerization of homo- and bis-homopropargyl alcohols in the presence of rhodium complexes that bear electron-withdrawing phosphine ligands (Scheme 33).[54] Although relatively large amounts of ligand were still needed, the reaction required less additives and showed higher catalyst turnover numbers (lower catalyst loadings) than the ruthenium-based system. Importantly, propargyl ethers are resistant to elimination (Scheme 33, Equation (2)).

Barluenga et al. recently disclosed a tandem process that involves endo alkynol cyclization as the first step. Thus irradiation of substrates such as **118** in the presence of a catalytic amount of tungsten hexacarbonyl and triethylamine leads to tricyclic products such as **120**, presumably by cyclopropanation of the putative Fischer carbene intermediate **119** (Scheme 34).[55] These products were further observed to undergo a facile acid-promoted ring-cleavage reaction, thus giving access to eight-membered carbocycles such as **121**.



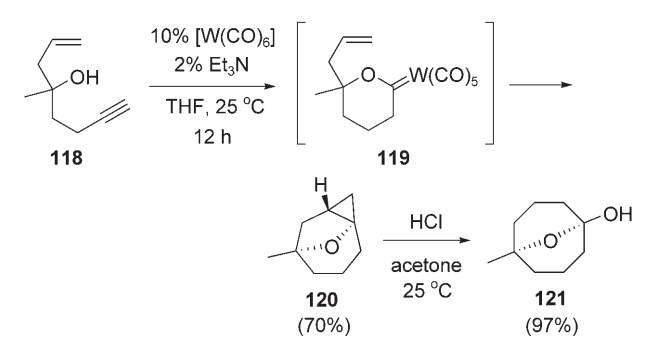
Scheme 32. The Trost iterative approach to *trans*-fused polycyclic ethers. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMDO = dimethyl dioxirane, PCC = pyridinium chlorochromate.



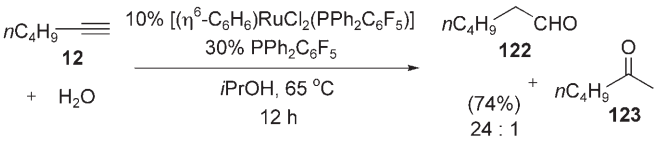
Scheme 33. Rhodium-catalyzed cycloisomerization of homo- and bis-homopropargyl alcohols.

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 gives an atom-economical conversion of terminal alkynes into aldehydes, a process that has 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. Tokunaga and Wakatsuki were the first to report this transformation; thus, treatment of *n*-hexyne (**12**) with aqueous isopropanol and a ruthenium catalyst led to the corresponding aldehyde (**122**) as the major product (Scheme 35).[56] However, hindered alkynes such as phenylacetylene and *tert*-butylacetylene failed to react.

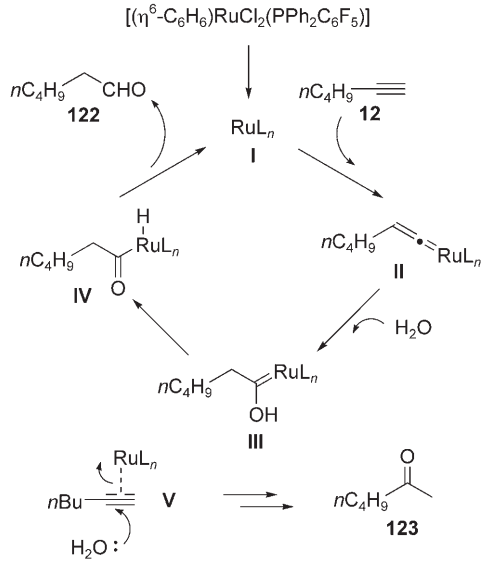


Scheme 34. The Barluenga tandem cycloisomerization–cyclopropanation reaction.



Scheme 35. The Wakatsuki anti-Markovnikov hydration of terminal acetylenes.

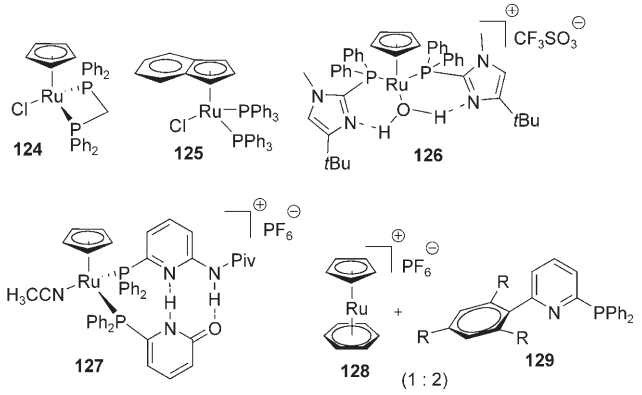
A mechanism consistent with the observed regioselectivity is shown in Scheme 36. The terminal alkyne and the metal species **I** form vinylidene species **II**, which is then trapped



Scheme 36. Mechanism of anti-Markovnikov alkyne hydration.

by water. Tautomerization and reductive elimination then lead to the aldehyde product. The ketone (Markovnikov) product is 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**).

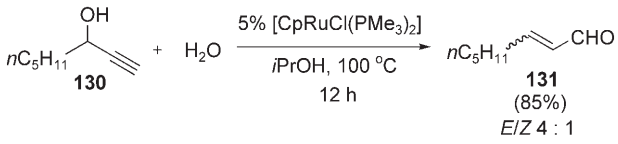
Wakatsuki and co-workers subsequently reported that a variety of alkynes, including hindered and functionalized alkynes, could be effectively hydrated to the corresponding aldehydes with lower amounts of ruthenium complex **124**.[57]



The bidentate nature of the bis(diphenylphosphanyl)methane (dppm) ligand was crucial to the success of this process. Other ruthenium complexes have also been used to catalyze this transformation. Bassetti and co-workers reported that ruthenium complex **125** can catalyze the anti-Markovnikov hydration of alkynes in water containing surfactants such as sodium dodecylsulfate.[58] Grotjahn et al. utilized ruthenium complex **126** to hydrate a variety of alkynes; this catalyst that may deliver water in an intramolecular fashion to the vinylidene intermediate.[59] Chevallier and Breit used ruthenium complex **127** to catalyze the transformation; this catalyst was generated in situ on the basis of the same principles of hydrogen bonding that guide the self-assembly of adenine and thymine in DNA.[60] More recently, Hintermann and co-workers reported the use of a catalyst generated from cationic ruthenium complex **128** and ligands such as **129**. The benefits of this catalyst system include modification of the ligand through a modular synthesis as well as exceptional catalytic activity.[61]

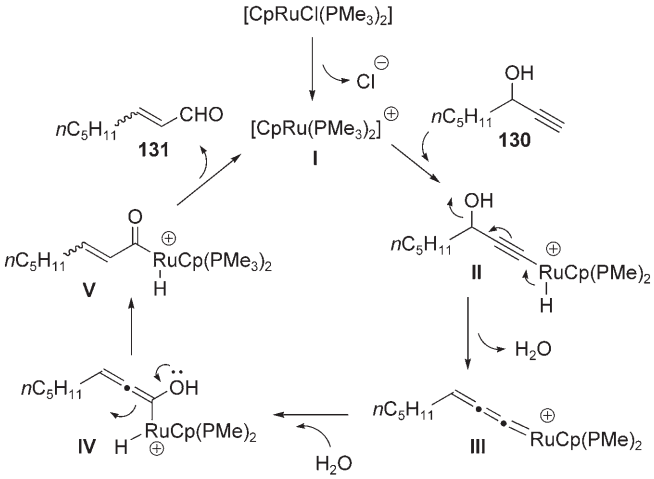
Wakatsuki and co-workers also investigated the regioselective ruthenium-catalyzed hydration of propargyl alcohols to give enals. This reaction is a transition-metal-catalyzed version of the Meyer–Schuster rearrangement and thus provides a complementary approach to the similar transformation involving benzoic acid developed by Dixneuf and co-workers (see above).[24,62] In an example of this reaction, propargyl alcohol **130** combined with water in the presence of a ruthenium catalyst to provide enal **131** in good yield and moderate *Z*/*E* stereoselectivity (Scheme 37).[63]

Labeling studies ($H_2{}^{18}O$) suggest that the mechanism does not involve transposition of the alcohol oxygen atom to the



Scheme 37. The Wakatsuki isomerization of propargyl alcohols.

carbonyl group. Although it is not clear at which stage dehydration occurs, a plausible mechanism is presented in Scheme 38. The active catalyst **I** inserts into the alkyne C–H

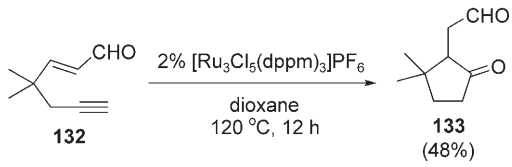


Scheme 38. Proposed mechanism of propargyl alcohol isomerization.

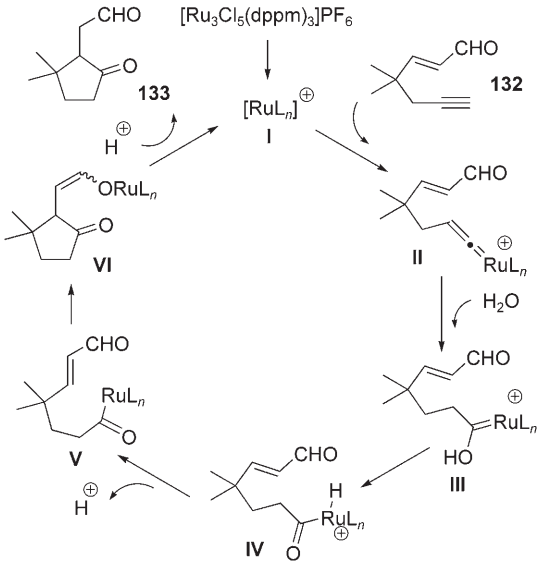
bond, and elimination of water then leads to allenylidene **III**. Addition of water to the electrophilic carbon atom then gives enol **IV**. Tautomerization followed by reductive elimination then gives enal **131** and regenerates the active catalyst.

A novel tandem reaction that involves water and a vinylidene intermediate was recently reported by Lee and co-workers. In a process termed hydrative cyclization, a ruthenium complex catalyzed the formation of cyclopentanones from 1,5-enynes. An example of this reaction is shown in Scheme 39.[64]

One mechanism that would explain this interesting domino reaction is depicted in Scheme 40. Thus, nucleophilic capture of vinylidene **II** by water followed by tautomerization gives **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 produces the cyclopentanone product **133**.



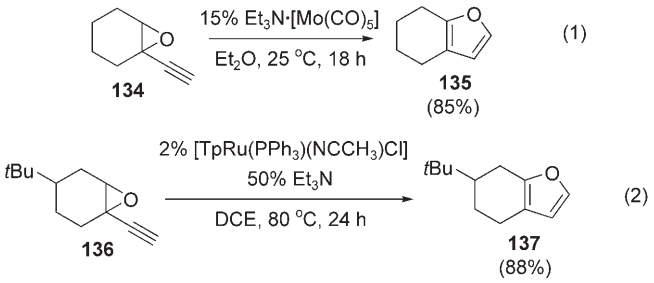
Scheme 39. The Lee hydrative cyclization of 1,5-enynes.



Scheme 40. Proposed mechanism for the Lee hydrative cyclization of 1,5-enynes.

2.5. Epoxide Nucleophiles

McDonald and Schultz were the first to report the cyclization of epoxyalkynes to furans through a vinylidene mechanism.[65] For example, treatment of **134** with a catalytic amount of a molybdenum pentacarbonyl catalyst led to **135** (Scheme 41, Equation (1)). Liu and co-workers subsequently

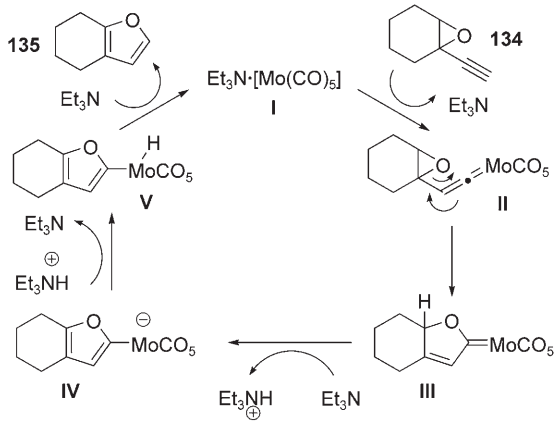


Scheme 41. Formation of furans from epoxyalkynes.

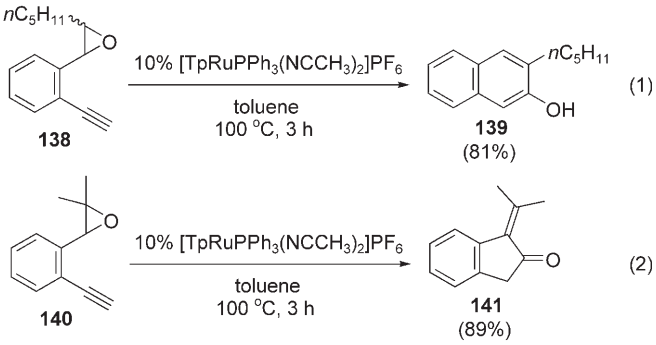
disclosed that the same type of transformation could be catalyzed by a lower loading of a ruthenium complex (Scheme 41, Equation (2)).[66]

The mechanism of this transformation is rationalized by considering vinylidene intermediate **II** (Scheme 42). Attack by the epoxide oxygen then leads 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.[67] Thus, (*o*-ethynyl)styrene epoxides such as **138**, when treated with a catalytic amount of $[TpRu(PPh_3)(NCCH_3)_2]PF_6$, lead to 2-naphthol products such as **139** (Scheme 43, Equation (1)). Higher-order substi-



Scheme 42. Mechanism of furan formation from epoxyalkynes.

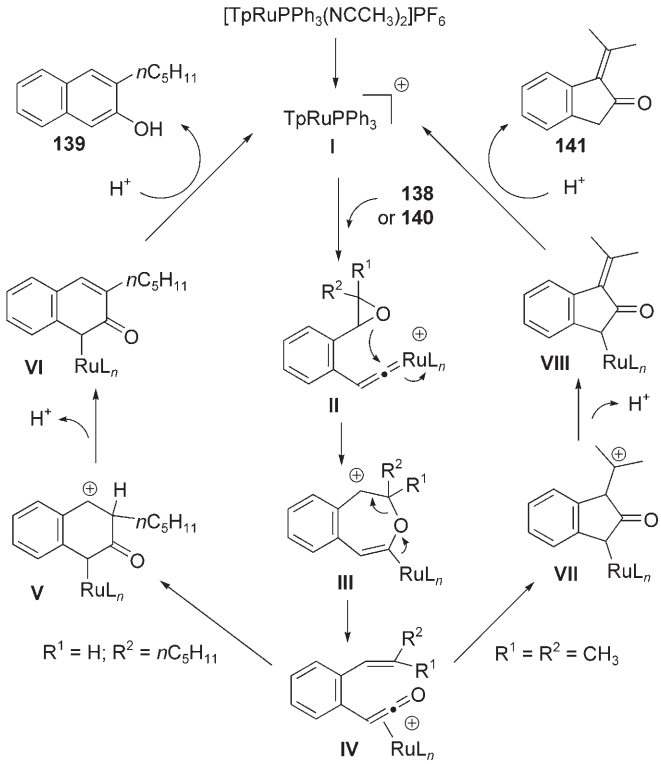


Scheme 43. The Liu synthesis of 2-naphthols and 1-alkylidene-2-indanones.

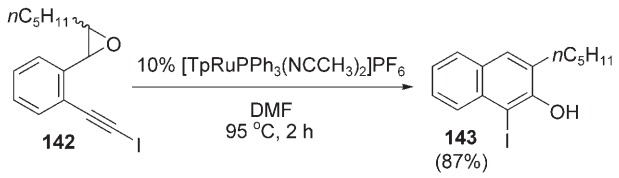
tuted epoxides (**140**), however, lead to 1-alkylidene-2-indanones **141** instead (Scheme 43, Equation (2)).

This dichotomy of products can be explained according to the mechanism depicted in Scheme 44. The loss of acetonitrile ligands opens up coordination spaces on the ruthenium complex to generate the active catalyst **I**. Vinylidene formation with either alkyne **138** or **140** then leads to **II**. Attack of the epoxide at the electrophilic carbon atom 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 ($R^1 = H$, $R^2 = nC_5H_{11}$), 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 **139** 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 **141**.

Recently, Liu and co-workers disclosed that iodoalkynes such as **142** can lead to 1-iodo-2-naphthol products such as **143** (Scheme 45).[68] This result adds to the synthetic utility of the method, as aryl iodides can be further elaborated through a variety of metal-catalyzed cross-coupling reactions. Furthermore, the position of the iodide in the product



Scheme 44. Mechanism for the formation of 2-naphthols and 1-alkylidene-2-indanones.



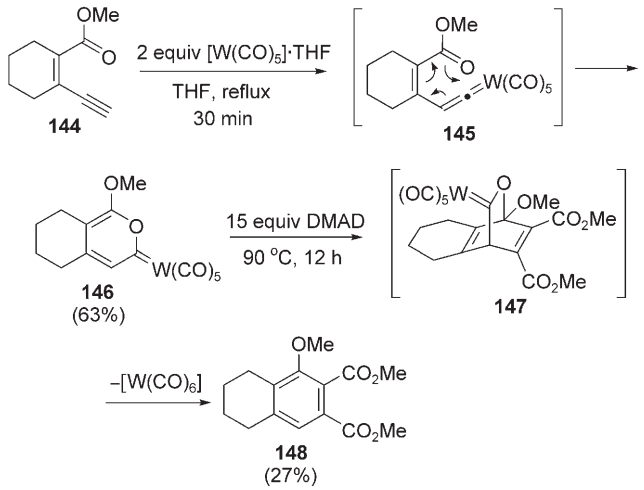
Scheme 45. The Liu formation of 1-iodo-2-naphthols.

lends credence to the proposed pathway of these reactions, as this group would migrate to the 1-position upon formation of the vinylidene intermediate (compare Scheme 43).

2.6. Carbonyl Nucleophiles

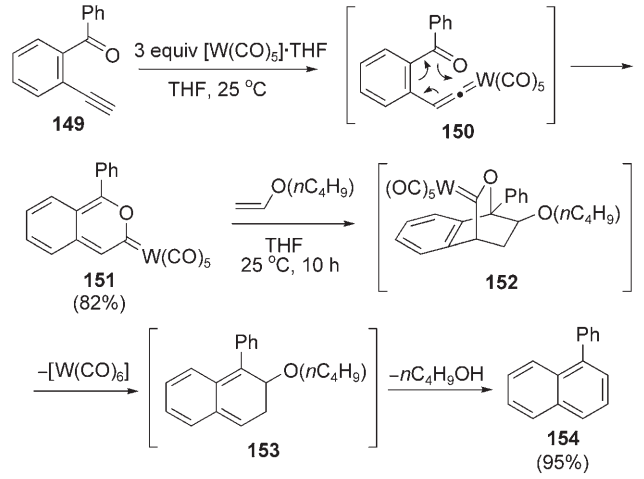
The interception of metal vinylidene intermediates by carbonyl groups has only been recently reported. In the first report, Uemura and co-workers disclosed that conjugated enyne ester **144** was transformed into pyranylidene metal complex **146**, presumably through formation of vinylidene **145** followed by [3,3] sigmatropic rearrangement (Scheme 46).[69,70] These Fischer carbene products are analogues of α-pyrones and were therefore anticipated to participate in Diels–Alder reactions with dienophiles. Thus, dimethyl acetylenedicarboxylate added to pyranylidene **146** to generate tetrahydronaphthalene **148** in low yield, presumably through retrocycloaddition of intermediate **147**.[69,70]

Iwasawa et al. contemporaneously reported a similar set of reactions. Thus, *o*-ethynyl aryl ketones such as **149** were



Scheme 46. The Uemura synthesis and Diels–Alder reaction of pyranylidenes. DMAD = dimethylacetylene dicarboxylate.

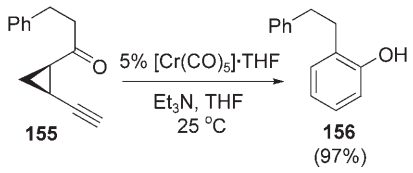
converted into benzopyranylidenes such as **151** by [3,3] sigmatropic rearrangement of vinylidene **150** (Scheme 47).[71] Diels–Alder reaction with *n*-butyl vinyl ether followed by retrocycloaddition provided **153**, whereby elimination of *n*-butanol provided naphthalene **154**.



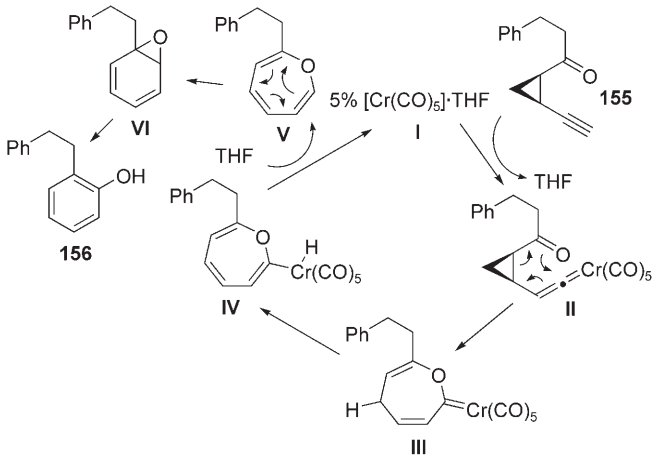
Scheme 47. The Iwasawa synthesis and Diels–Alder reaction of benzopyranylidenes.

Whereas these cases involved stoichiometric metal vinylidenes, Uemura and co-workers reported the first catalytic interception of metal vinylidene complexes by carbonyl groups. Treatment of *cis*-1-acyl-2-ethynylcyclopropanes such as **155** with catalytic amounts of either tungsten or chromium pentacarbonyl complexes led to 2-substituted phenols **156** in excellent yield (Scheme 48).[70,72]

The proposed catalytic cycle is shown in Scheme 49. Vinylidene formation between catalyst **I** and substrate **155** followed by [3,3] sigmatropic rearrangement affords **III**. A [1,5] hydrogen shift and reductive elimination then liberates



Scheme 48. The Uemura catalytic synthesis of phenols from *cis*-1-acyl-2-ethynylcyclopropanes.

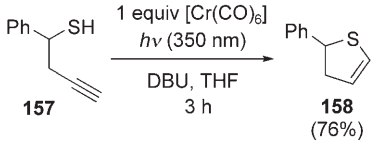


Scheme 49. Mechanism of phenol formation from *cis*-1-acyl-2-ethynylcyclopropanes.

the catalyst and arene oxide **V**. A second [3,3] sigmatropic rearrangement then gives **VI**, and subsequent rearrangement then yields product **156**.

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.[73] In this case, a stoichiometric amount of chromium hexacarbonyl was required to give the product in good yield (Scheme 50). The lack of catalytic processes is presumably due to the strong coordination of thiols to metals, thus leading to catalyst deactivation.

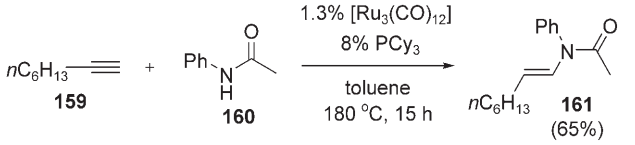


Scheme 50. Cycloisomerization of homopropargyl thiols.

2.8. Amine Nucleophiles

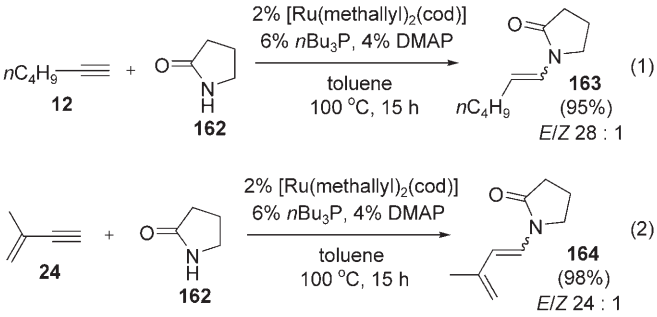
2.8.1. Intermolecular Reactions

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 co-workers reported the ruthenium-catalyzed addition of an amide (acetanilide, **160**) to 1-octyne (**159**) to give the enamide product **161** (Scheme 51).[74] There were only a limited number of examples reported for this hydroamination reaction, and the yields were moderate, but both the regio- and stereoselectivity of the process were excellent.



Scheme 51. The Watanabe synthesis of an enamide from acetanilide and 1-octyne. Cy = cyclohexyl.

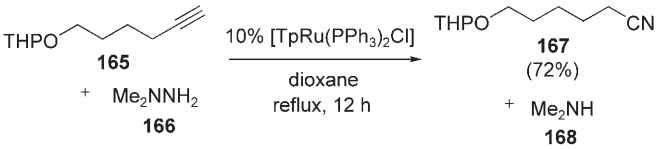
Several years later, Gooßen et al. reported that a number of amides could be added to terminal alkynes that bear a wide array of functional groups by using a different ruthenium catalyst (Scheme 52).[75] For example, 2-pyrrolidinone



Scheme 52. The Gooßen synthesis of enamides from amides and alkynes.

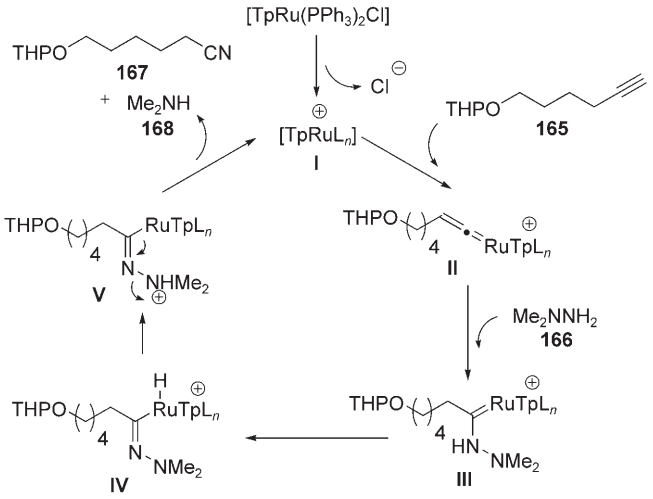
(**162**) reacted with *n*-hexyne (**12**) in excellent yield and with complete regioselectivity and good *E*/*Z* selectivity (Scheme 52, Equation (1)). Product **164** was prepared from enyne **24** and amide **162** (Scheme 52, Equation (2)), thus constituting an atom-economical synthesis of activated dienes for Diels–Alder reactions.

Fukumoto et al. recently reported the use of *N*,*N*-dialkylhydrazines as nucleophiles for vinylidene complexes.[76] A variety of aromatic and aliphatic alkynes were reported to combine with *N*,*N*-dimethylhydrazine to give nitrile products, an example of which is shown in Scheme 53.



Scheme 53. The Fukumoto nitrile synthesis from *N*,*N*-dimethylhydrazine and alkynes. THP = 2-tetrahydropyranyl.

The proposed mechanism of this process is outlined in Scheme 54, 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



Scheme 54. Proposed mechanism of the fukumoto nitrile synthesis.

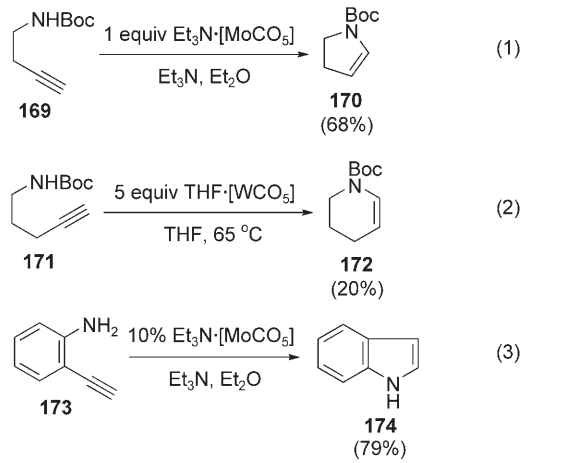
addition of *N*,*N*-dimethylhydrazine provides **III**, whereby tautomerization and proton transfer leads to **V**. Finally, fragmentation releases the product **167** and *N*,*N*-dimethylamine (**168**) and regenerates the active catalyst. Interestingly, the *N*,*N*-dimethylamine by-product does not 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

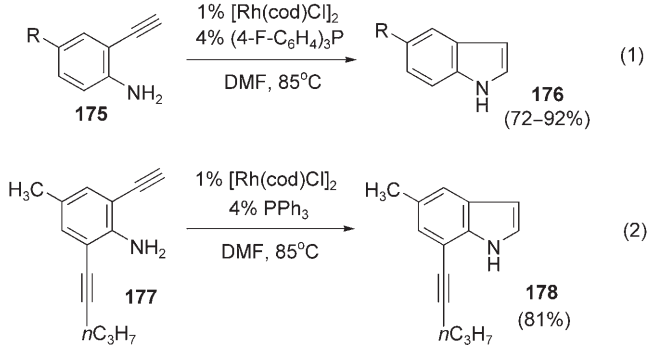
McDonald and Chatterjee were the first to report the cyclization of amines onto vinylidene intermediates. Thus *N*-Boc homopropargyl amines **169** and bis-homopropargyl amines (**171**) underwent *endo* cyclization in the presence of stoichiometric amounts of molybdenum and tungsten complexes, respectively (Scheme 55, Equations (1) and (2)).[77] The related amide and sulfonamide substrates were inert to the reaction conditions. Although the corresponding free amine substrates led to decomposition, *o*-ethynylaniline (**173**) was found to cyclize to indole (**174**) in the presence of a catalytic amount of the molybdenum complex (Scheme 55, Equation (3)).

More recently, Trost and McClory showed that a variety of *o*-ethynylanilines could cyclize to the corresponding indoles in the presence of a catalytic amount of a rhodium complex (Scheme 56, Equation (1)).[78] The exclusive participation of the terminal alkyne in Scheme 56, Equation (2) lends credence to the proposed vinylidene pathway. This process was further extended to tethered phenol and carboxylic acid nucleophiles.

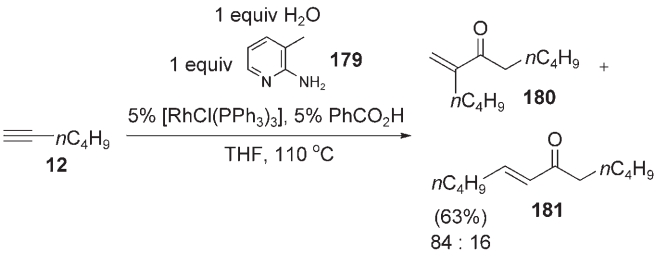
In an interesting transformation, Jun and co-workers recently reported that terminal alkynes dimerize in the presence of water, the Wilkinson catalyst, and 2-amino-3-picoline (**179**); the latter reagent acts as a cofactor for the reaction (Scheme 57).[79]



Scheme 55. The McDonald cycloisomerization of homo- and bis-homopropargyl amines.



Scheme 56. The Trost cycloisomerization of *o*-ethynylanilines to indoles.



Scheme 57. The Jun chelation-assisted hydrative dimerization of terminal alkynes.

The mechanism of this transformation is thought to involve formation of the metal vinylidene complex **II** followed by coordination of the 2-amino-3-picoline with the metal to give **III** (Scheme 58). This serves to template the amine group for an intramolecular addition to the vinylidene. Following attack and tautomerization, **IV**, a metallacycle into which a molecule of alkyne may be inserted, is obtained. Depending on the bulk of the alkyne, this insertion will favor either **V** or **VI**. The former case is favored for small

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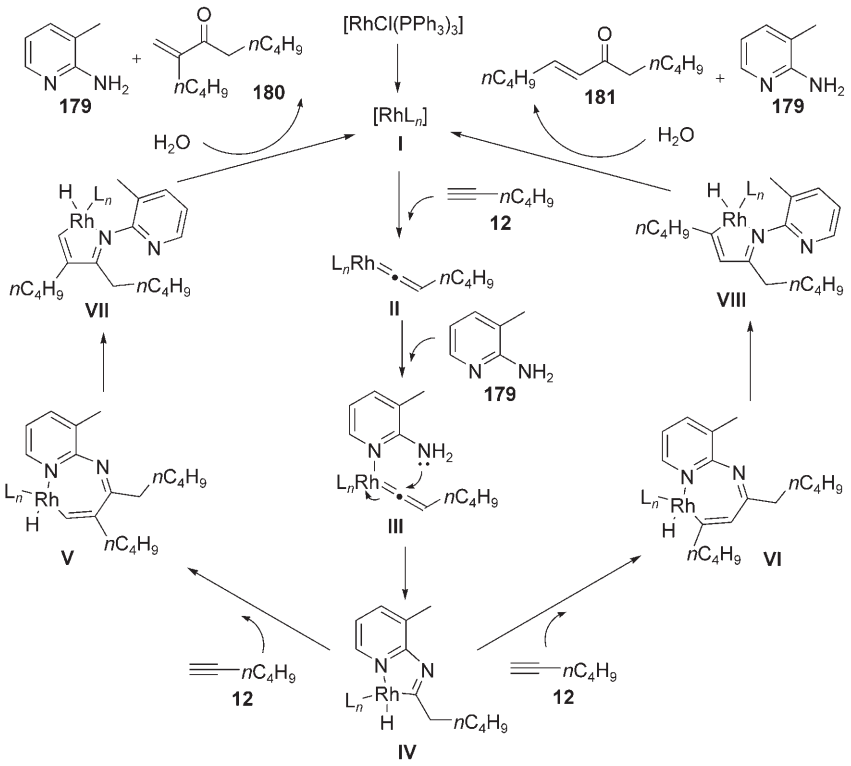
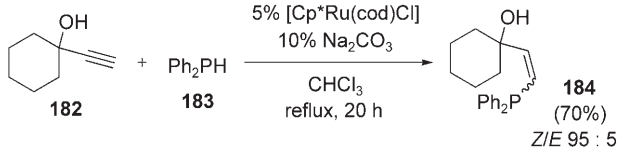


Scheme 58. Mechanism of the Jun chelation-assisted hydrative dimerization of terminal alkynes.

substituents (e.g., nC$_4$H$_9$), and after the subsequent ring contraction **VII** is obtained. Reductive elimination and hydrolysis then gives product **180** and the active catalyst. The minor product **181** 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 co-workers found that diphenylphosphine (**183**) adds to propargyl alcohols in good yield and with good Z/E selectivity (Scheme 59).[80]



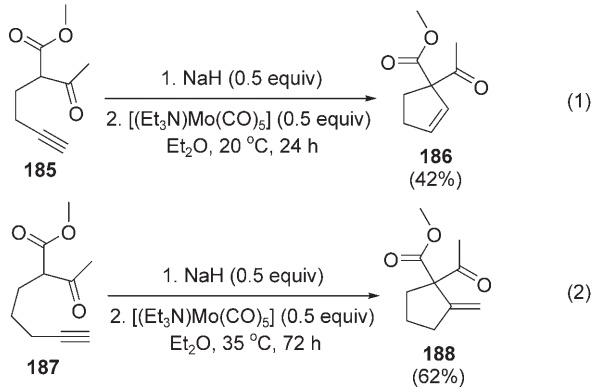
Scheme 59. Hydrophosphination of propargyl alcohols. Cp* = η^5-1,2,3,4,5-pentamethylcyclopentadienyl.

3. Carbon Nucleophile Reactions with Vinylidenes

McDonald and Olson reported the first trapping of vinylidene intermediates by pendant carbon nucleophiles. Homopropargyl malonates, β-ketoesters, and β-diketones (i.e., stabilized nucleophiles) underwent cyloisomerization (5-*endo* attack) in the presence of approximately stoichiometric amounts of a molybdenum pentacarbonyl complex (Scheme 60, Equation (1)).[81] The use of a bis-homopropargyl β-dicarbonyl substrate, however, resulted in only 5-*exo* attack (Scheme 60, Equation (2)).

A possible mechanism involves deprotonation of the β-dicarbonyl substrate followed by vinylidene formation to give **III** (Scheme 61). 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**.

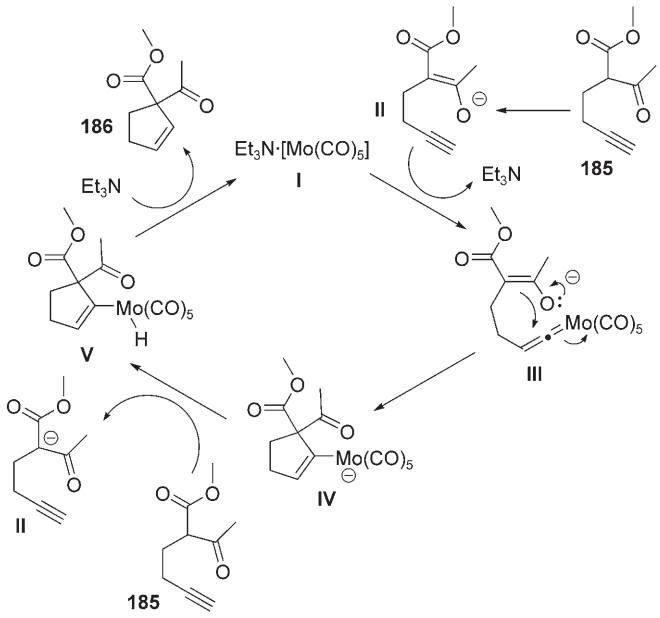
Maeyama and Iwasawa investigated this reaction further. Less stabilized nucleophiles (silyl enol ethers) were found



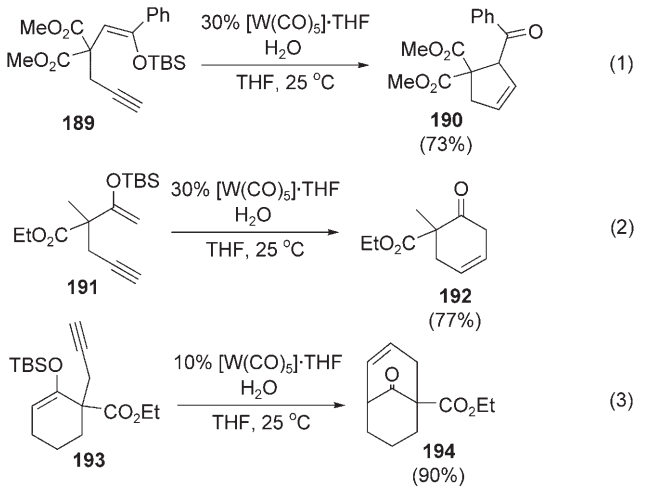
Scheme 60. Cyclization of homo- and bis-homopropargyl β-dicarbonyl compounds.

to function in the presence of lower loadings of a tungsten catalyst. Five-membered rings (Scheme 62, Equation (1)) as well as six-membered rings (Scheme 62, Equations (2) and (3)) were reported to form in good to excellent yield.[82]

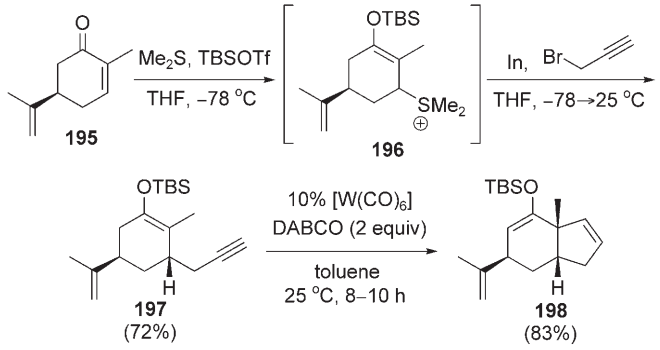
Iwasawa et al. subsequently extended this reaction into a general method for cyclopentene annulation (Scheme 63).[83,84] Indium-mediated propargylation of α,β-unsaturated ketones such as (*R*)-carvone (**195**) in the presence of dimethyl sulfide and *tert*-butyldimethylsilyl triflate provided the requisite substrates **197**. Cycloisomerization in the presence of catalytic amounts of a tungsten–carbonyl



Scheme 61. Mechanism of the McDonald cycloisomerization of homopropargyl β-dicarbonyl compounds.



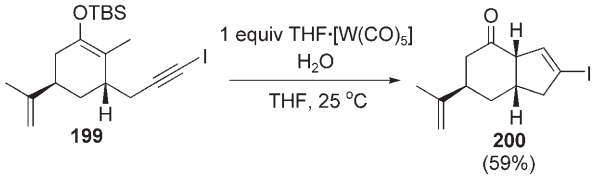
Scheme 62. The Iwasawa cycloisomerization of homo- and bis-homopropargyl silyl enol ethers.



Scheme 63. The Iwasawa method of cyclopentene annulation.

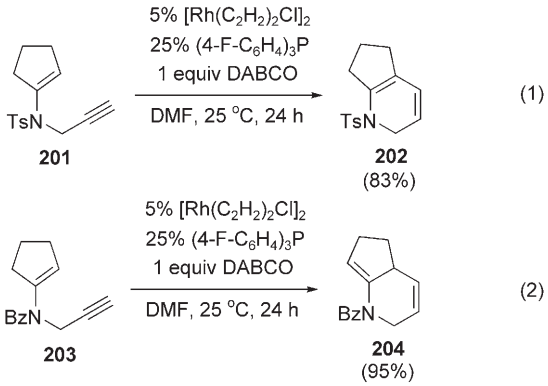
complex then gave the unsubstituted cyclopentene products such as **198**.

The use of iodoalkynes such as **199** led to the iodocyclopentene products such as **200** by migration of the iodine atom during vinylidene formation, thus extending the synthetic utility of the method (Scheme 64).



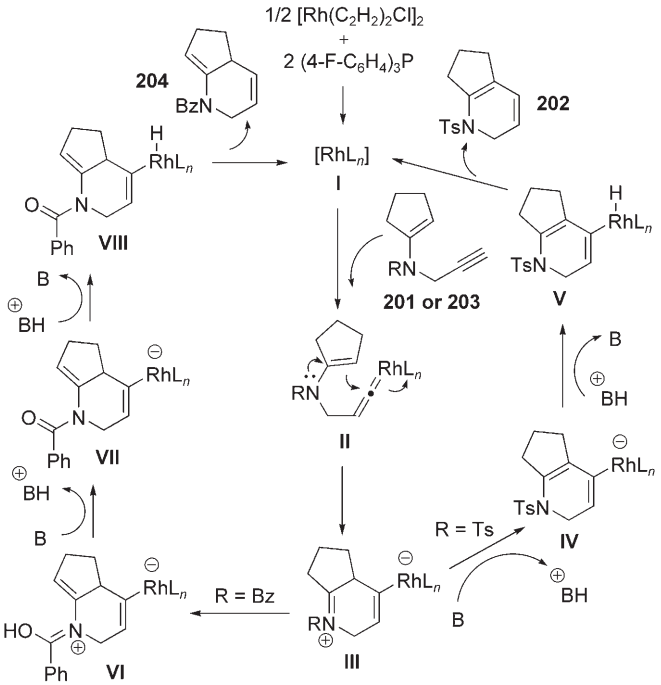
Scheme 64. The Iwasawa method of cyclopentene annulation: iodine migration.

More recently, Kim and Lee reported that *N*-propargyl enamines undergo cycloisomerization[85] in the presence of a rhodium catalyst developed by Trost and Rhee for the cycloisomerization of homo- and bis-homopropargyl alcohols (see above).[52] Thus, *N*-tosyl propargyl enamine **201** underwent cyclization to provide 1,3-diene product **202** (Scheme 65, Equation (1)), and *N*-benzoyl propargyl enamine **203** cyclized to form 1,4-diene **204** in excellent yield (Scheme 65, Equation (2));[85] both products contain the indolizidine skeleton.



Scheme 65. The Lee cycloisomerization of *N*-propargyl enamines.

The different products obtained may be rationalized according to Scheme 66. Terminal-alkyne substrates **201** or **203** 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 **202** and regenerates the active catalyst. On the other hand, when the protecting group is an amide, **III** undergoes a 1,5-H shift followed by deprotonation to yield **VII**. Protonation of the metal and reductive elimination then gives 1,4-diene product **204** and the active catalyst.

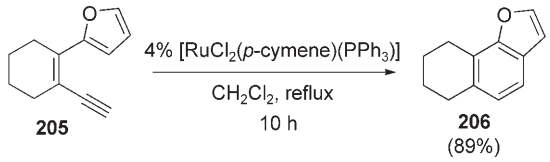


Scheme 66. Proposed mechanism for the cycloisomerization of *N*-propargyl enamines.

4. Pericyclic Reactions with Vinylidenes

4.1. Electrocyclization Reactions

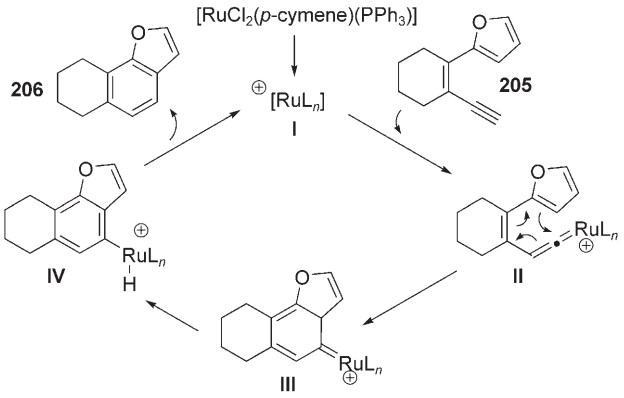
The oxa 6π electrocyclization of carbonyl groups onto vinylidene species was seen in stoichiometric reactions earlier in this Focus Review (see above). The first example of a reaction that involves an all-carbon 6π electrocyclization onto a catalytic vinylidene intermediate was reported by Merlic and Pauly. In this reaction, dienylalkynes such as **205** underwent conversion into benzene derivatives such as **206** (Scheme 67).[86]



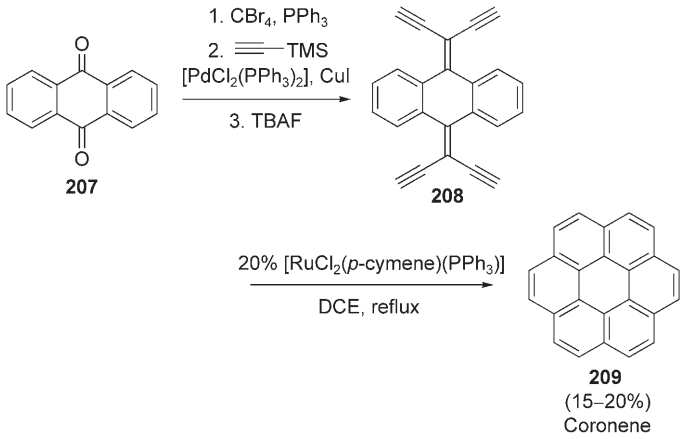
Scheme 67. The Merlic dienyne cycloisomerization.

The catalytic cycle for this transformation is depicted in Scheme 68. Following the formation of vinylidene **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**.

Donovan and Scott recently applied the Merlic conditions in a naphthoannulation procedure (Scheme 69).[87] For example, anthraquinone (**207**) was olefinated to the bis-*gem*-dibromide, and Sonogashira cross-coupling with trimethylsilylacetylene followed by protodesilylation provided substrate **208**. Exposure to the ruthenium catalyst then led to a fourfold dienyne cycloisomerization to provide coronene (**209**). Although the yield was modest, the convergence of the approach and the amount of complexity generated in the reaction is impressive.

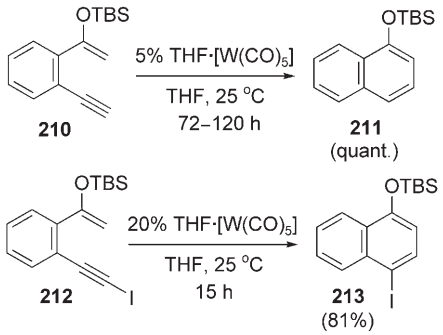


Scheme 68. Plausible mechanism for dienyne cycloisomerization.



Scheme 69. The Scott naphthonannulation procedure.

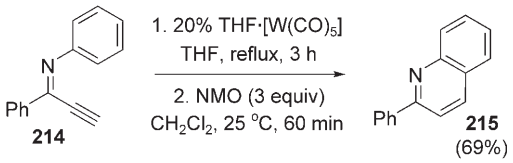
Maeyama and Iwasawa reported that a tungsten complex can also catalyze the 6π electrocyclization of dienynes (Scheme 70, Equation (1)).[88] The exclusive formation of 4-iodonaphthalene **213** from iodoalkyne **212** increases the syn-



Scheme 70. The Iwasawa dienyne cycloisomerizations.

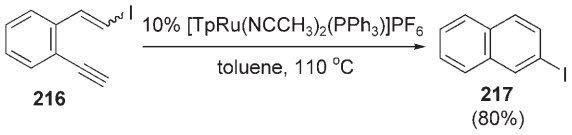
thetic utility of the reaction (Scheme 70, Equation (2)).[89] Contemporaneous with these publications, Dankwardt disclosed a related 4-silylnaphthalene synthesis with a rhodium catalyst.[90]

Akiyama and co-workers expanded the substrate scope to include alkynyl imines (Scheme 71).[91] The yields were improved by treating the crude reaction mixture with *N*-methylmorpholine-*N*-oxide, presumably to decomplex the product from the tungsten catalyst.



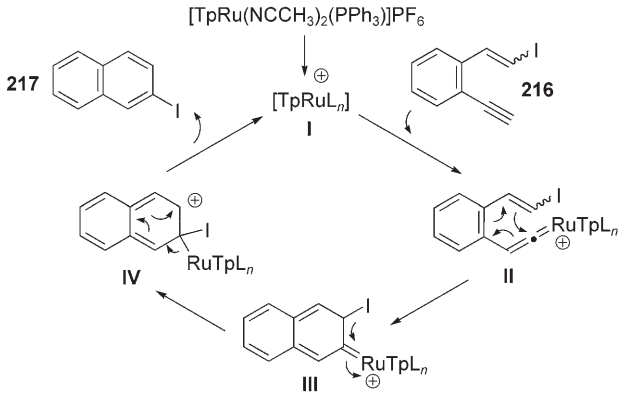
Scheme 71. The Akiyama cycloisomerization of alkynyl imines.

Liu and co-workers recently reported a number of ruthenium-catalyzed electrocyclizations of dienynes, followed by a variety of rearrangements that depend on the substitution pattern of the substrate. In one such process, iododienyne substrate **216** was converted into iodonaphthalene **217** in good yield (Scheme 72).[92]



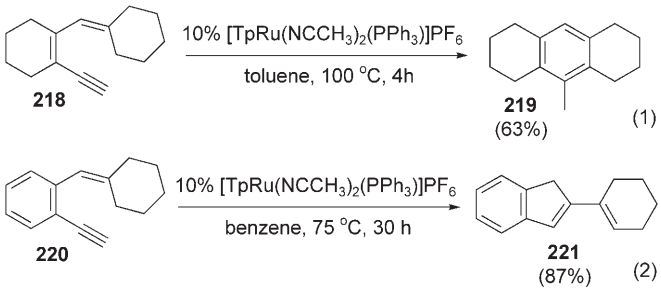
Scheme 72. The Liu electrocyclization and halide migration.

To account for this migration of the iodine atom, the mechanism shown in Scheme 73 was proposed, in which vinylidene **II** undergoes 6π electrocyclization. A 1,2-iodine migration leads to carbocation **IV**, which then rearranges to give the product.



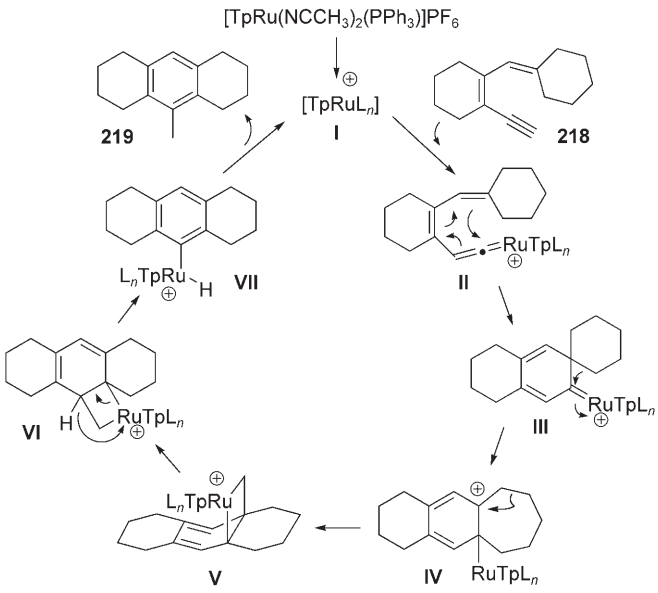
Scheme 73. Mechanism of the Liu electrocyclization and halide migration.

An interesting divergence in mechanism was observed in the reaction of dienyne substrates **218** and **220** (Scheme 74). In the former case, a highly substituted benzene was formed (**219**; Scheme 74, Equation (1)),[93] whereas in the latter case, a 1,3-diene product was formed (**221**; Scheme 74, Equation (2)).[94]



Scheme 74. The Liu formation of substituted benzenes and 2-vinyl 1*H*-indenes.

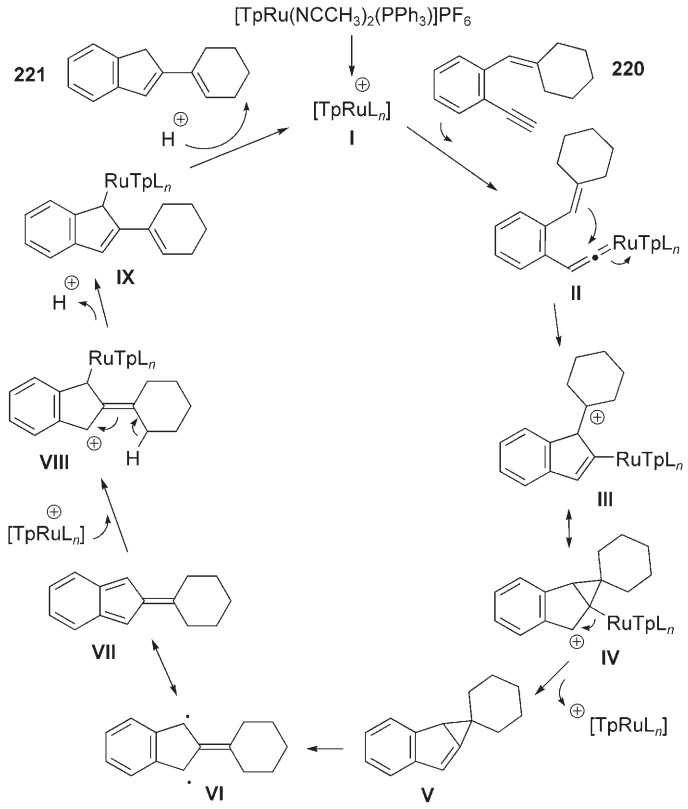
The formation of product **219** can be explained by the proposed mechanism in Scheme 75. Following its formation,



Scheme 75. Mechanism of the Liu synthesis of substituted benzenes.

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 **221**, the vinylidene species **II** is attacked by the pendant olefin to generate tertiary carbocation **III**, which may be represented by resonance structure **IV** (Scheme 76). Demetalation then gives methylene cyclopropane **V**, which is prone to the well-



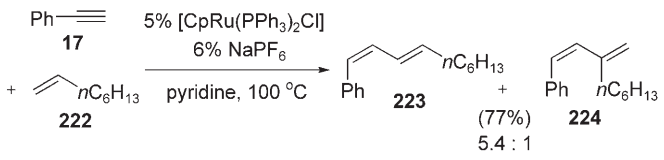
Scheme 76. Mechanism of the Liu synthesis of 2-vinyl 1*H*-indenes.

established ring opening to the diradical trimethylenemethane **VI**.[95] 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.

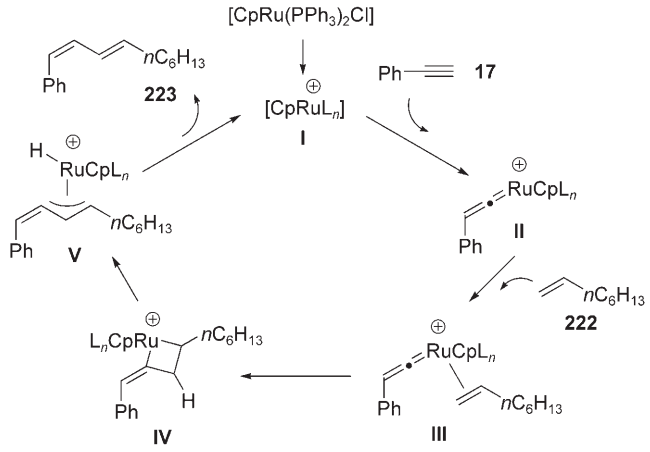
4.2. [2+2] Cycloaddition Reactions

The first example of a [2+2] cycloaddition reaction with a catalytic vinylidene complex involved the intermolecular coupling of alkynes with alkenes to generate 1,3-diene products (Scheme 77).[96]

A proposed mechanism for the enyne coupling reaction is shown in Scheme 78. The formation of vinylidene intermediate **II** followed by olefin coordination and oxidative coupling leads to metallacyclobutane **IV**. The π-allyl structure **V** is then formed by β-hydride elimination. Finally, reductive elimination releases the major product **223** and the catalyst. The minor isomeric 1,3-diene product **224** could arise from



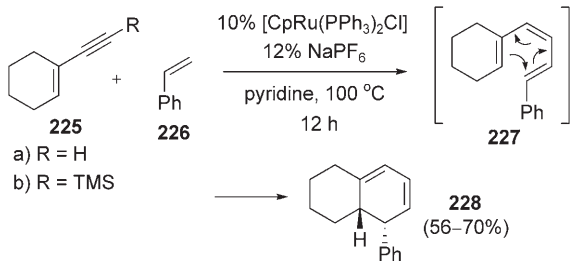
Scheme 77. The Murakami intermolecular alkene–alkyne coupling.



Scheme 78. Mechanism of intermolecular enyne coupling.

the alternative regiochemistry of metallacycle 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 metallacycle formation.

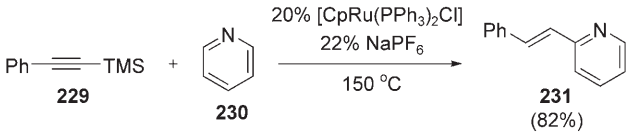
Murakami et al. subsequently used the enyne coupling reaction in an interesting tandem transformation (Scheme 79). Treatment of enyne **225a** with styrene in the presence of a



Scheme 79. The Murakami tandem enyne coupling–electrocyclization.

ruthenium catalyst provided cyclohexadiene **228** in moderate yield.[97] In this transformation, a 1,3-diene is produced in the enyne coupling step, with one of the olefins having a *Z* conformation. The presence of the third olefin (present in the substrate) set up the conjugated triene intermediate **227** for a facile thermal disrotatory 6π electrocyclization to give the product. The use of trimethylsilylalkyne **225b** 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 (see below). The silane presumably migrated during vinylidene formation and was removed by protodesilylation at some point in the reaction.

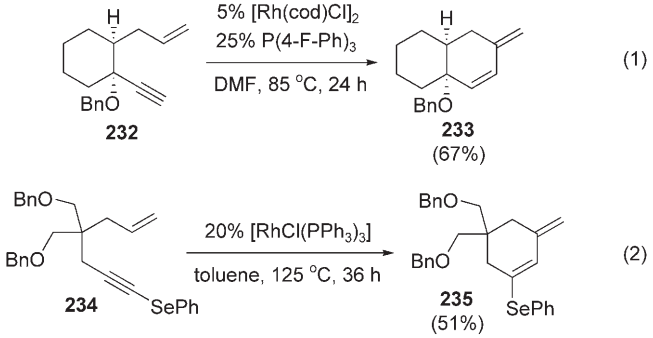
Murakami and Hori also discovered that pyridine is able to react with terminal alkynes through a vinylidene mechanism (Scheme 80).[98] Thus, trimethylsilyl phenylacetylene reacted with pyridine to give the 2-alkenyl pyridine derivative **231** in good yield and with complete selectivity for *E* olefin



Scheme 80. The Murakami alkenylation of pyridine.

geometry (presumably through thermal or base-catalyzed isomerization). Although the catalyst loading and temperature were elevated, this nonetheless constitutes an intriguing method for regioselective pyridine functionalization; the selectivity is a result of the two reacting substrates being brought together by coordination of the pyridine to the metal atom of the ruthenium vinylidene intermediate.

By tethering the two reacting partners, the regioselectivity of enyne coupling can be controlled. Grigg et al. reported some years ago that 1,6-enynes undergo cycloisomerization in the presence of catalytic Wilkinson catalyst to give the corresponding 1,3-dienes.[99] Recently, Lee and co-workers revisited this reaction and optimized the reaction conditions (Scheme 81).[100]

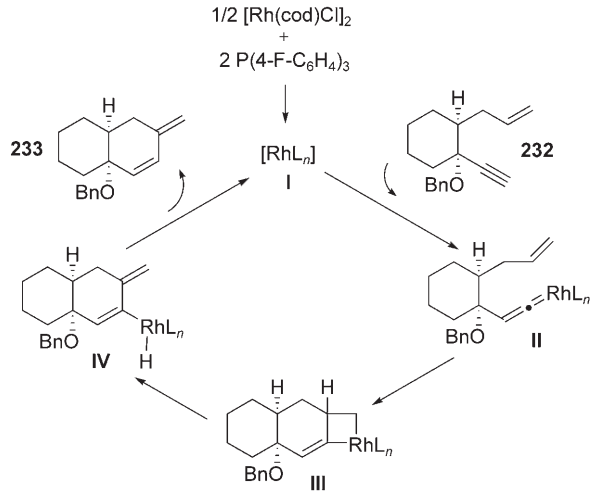


Scheme 81. Rhodium-catalyzed enyne cycloisomerization.

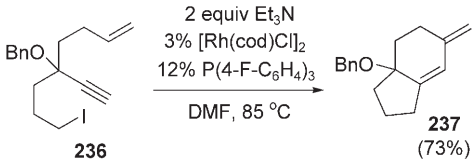
Lee proposed a mechanism for this reaction based on deuterium-labeling studies, as well as the selective migration of the selenyl group (Scheme 81, Equation (2)). The process thus involves formation of vinylidene **II**, [2+2] cycloaddition to give **III**, β-hydride elimination to yield **IV**, and reductive elimination (Scheme 82).

Lee and co-workers applied this transformation in a novel tandem process. Two rings were created when 1,6-enynes that bear appropriately tethered alkyl halides were treated with a catalytic rhodium species in the presence of triethylamine (Scheme 83).[101]

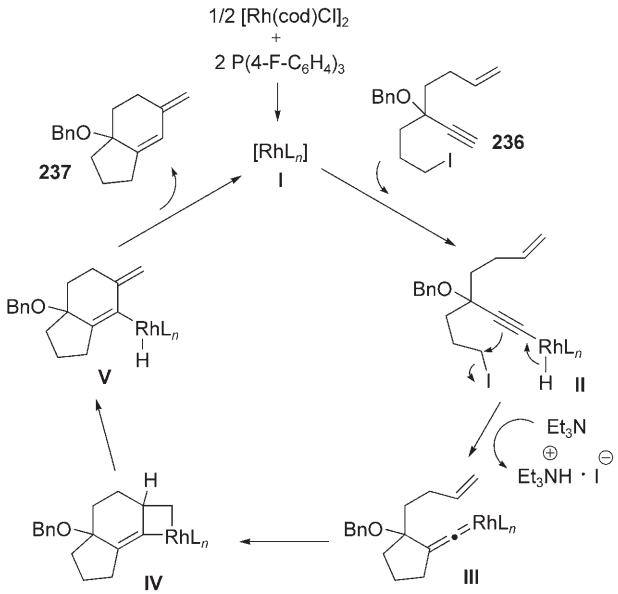
The proposed mechanism (Scheme 84) involves insertion of the metal into the alkyne C–H bond to give **II** (which is presumably in equilibrium with the corresponding vinylidene species). This alkynyl metal species may be deprotonated by triethylamine, which induces displacement of the pendant iodide, thus leading to the substituted vinylidene species **III**. A [2+2] cycloaddition then gives **IV**, and β-hydride elimination followed by reductive elimination leads to the product.



Scheme 82. Mechanism of rhodium-catalyzed enyne cycloisomerization.



Scheme 83. The Lee tandem cyclization of 1,6-enyne systems.

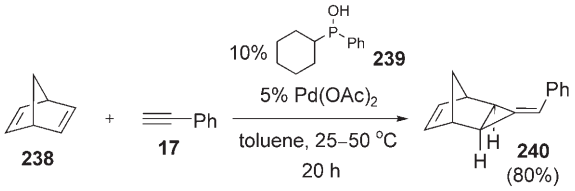


Scheme 84. Mechanism of the tandem 1,6-enyne cyclization.

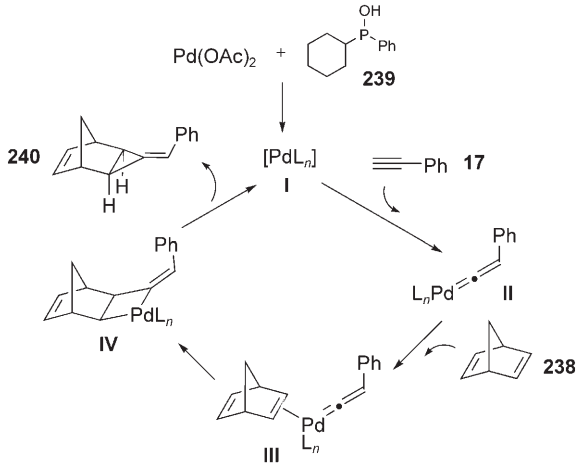
A recent paper from Buono and co-workers suggests that catalytic vinylidene reactions may not be the exclusive domain of ruthenium, rhodium, molybdenum, and tungsten. Palladium, when combined with the appropriate ligands, may also participate in vinylidene processes. Norbornadiene (or norbornene) and phenylacetylene have been reported to undergo a [2+1] cycloaddition reaction catalyzed by palla-

dium diacetate and phosphinous acid ligand **239** (Scheme 85).[102]

The proposed mechanism, outlined in Scheme 86, suggests the formation of vinylidene **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.



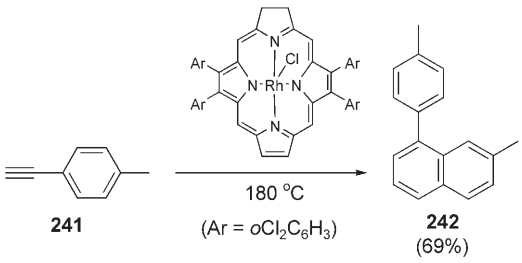
Scheme 85. The Buono palladium-catalyzed [2+1] cycloaddition.



Scheme 86. Mechanism of the Buono palladium-catalyzed [2+1] cycloaddition.

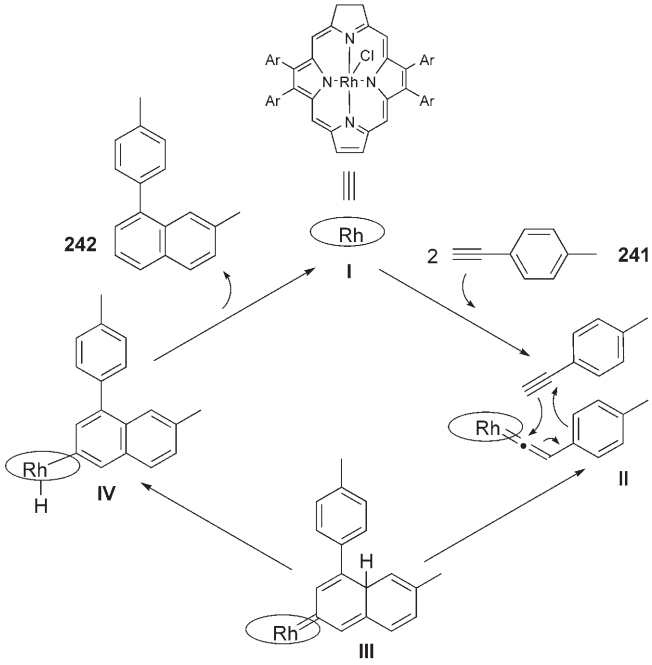
4.3. [4+2] Cycloaddition Reactions

Tagliatesta and co-workers reported the only example of a Diels–Alder reaction that involves a catalytic metal vinylidene complex.[103] In this transformation, rhodium– and ruthenium–porphyrin complexes were used to catalyze the conversion of aryl acetylenes into 1-aryl naphthalenes (Scheme 87).



Scheme 87. The Tagliatesta synthesis of 1-arylnaphthalenes.

The mechanism of the reaction can be rationalized according to Scheme 88. The rhodium–porphyrin complex, 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 by-products for most aryl acetylenes, it does suggest the viability of a Diels–Alder manifold for vinylidene intermediates.

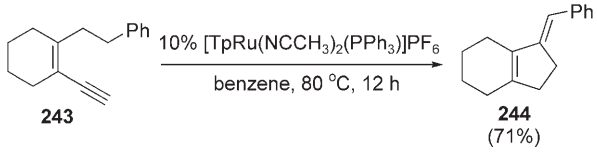


Scheme 88. Mechanism of 1-arylnaphthalene formation from aryl acetylenes.

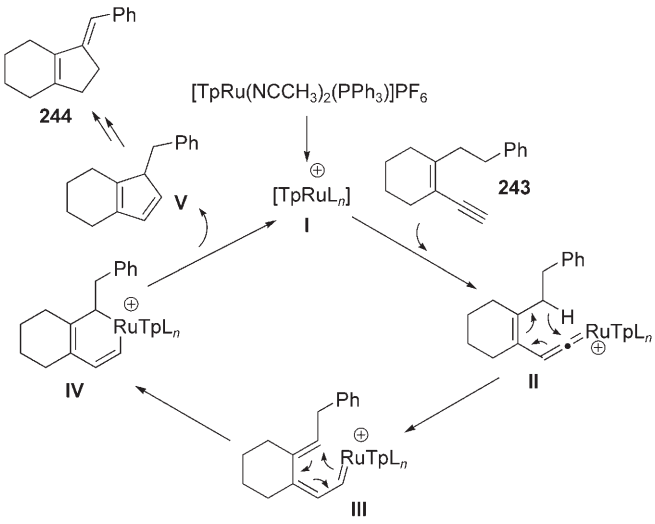
4.4. [1,5] Sigmatropic Rearrangement

Liu and co-workers 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.[104] In an example of this process, enyne **243** (or the corresponding propargyl alcohol) was converted into cyclopentadiene **244** in the presence of a ruthenium catalyst (Scheme 89).

The mechanism of this transformation, as outlined in Scheme 90, is thought to involve formation of vinylidene **II**



Scheme 89. The Liu cyclopentadiene synthesis.



Scheme 90. Mechanism of cyclopentadiene formation.

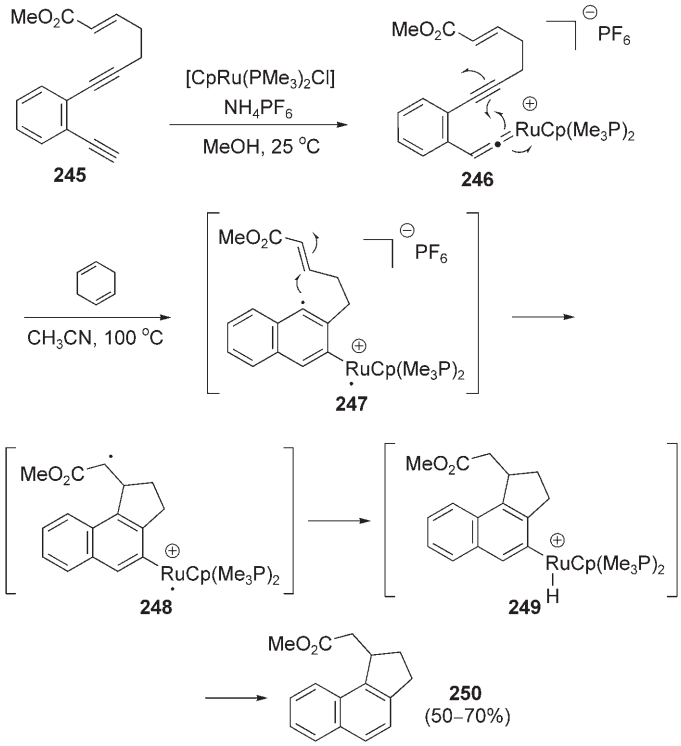
followed by a 1,5-hydrogen-atom migration onto the vinylidene moiety. This event is followed by a 6π electrocyclization that leads to **IV**; reductive elimination then gives the active catalyst **I** and compound **V**. This latter species may then undergo two successive 1,5-hydrogen migrations to give the observed product **244**.

5. Cycloaromatization

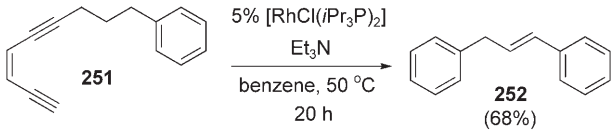
Wang and Finn were the first to report a metal vinylidene mediated cycloaromatization reaction (Scheme 91).[105] This process began with conversion of diyne **245** into the vinylidene complex **246** at room temperature. Subsequent treatment with cyclohexadiene in acetonitrile then induced a Myers–Saito rearrangement (i.e., cycloaromatization, at a lower temperature than required for the all-carbon version) to give diradical **247**. The carbon-centered radical then induced a 5-*exo*-dig cyclization to give diradical **248**. Hydrogen-atom abstraction followed by reductive elimination of the cationic metal fragment then provided **250**. The entire sequence (**245**→**250**) could conceivably be promoted by a catalytic amount of ruthenium, as 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 and co-workers were able to render the cycloaromatization process catalytic. Thus, treatment of enediyne **251** with a rhodium catalyst led to aromatic product **252** (Scheme 92).[106]

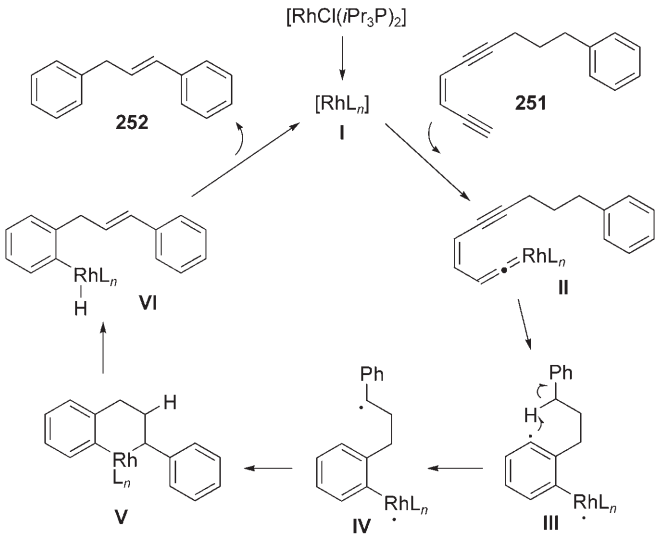
The proposed mechanism of this reaction involves vinylidene formation followed by cycloaromatization to give intermediate diradical **III** (Scheme 93). Intramolecular 1,5-hydrogen migration then gives **IV**, and radical–radical coupling leads to metallacycle **V**. β-Hydride elimination followed by reductive elimination then regenerates the catalyst and provides product **252**.



Scheme 91. The Finn stoichiometric metal-mediated cycloaromatization.



Scheme 92. The Uemura rhodium-catalyzed cycloaromatization: 1,5-hydrogen migration.



Scheme 93. Mechanism of Rhodium-catalyzed cycloaromatization: 1,5-hydrogen migration.

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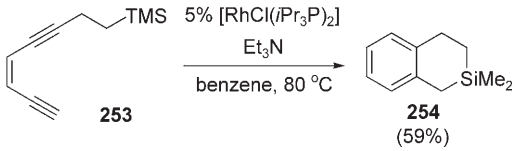
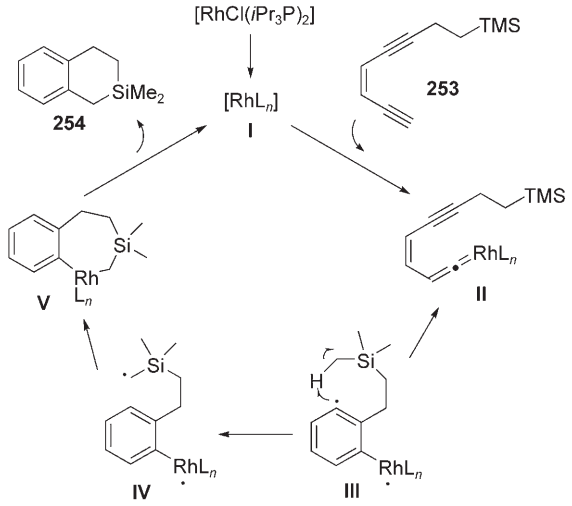
In the absence of an available hydrogen atom for the 1,5-shift, the reaction can follow a different course. This is seen in the example in Scheme 94, in which enediyne **253** was converted into silacycle **254** in moderate yield.[107]



Scheme 94. The Uemura rhodium-catalyzed cycloaromatization: 1,6-hydrogen migration.

The formation of this product can be rationalized by assuming vinylidene formation followed by cycloaromatization to give diradical **III** (Scheme 95). A 1,6-hydrogen-atom migration then leads to **IV**, and radical–radical coupling gives metallacycle **V**. Reductive elimination then provides the product.



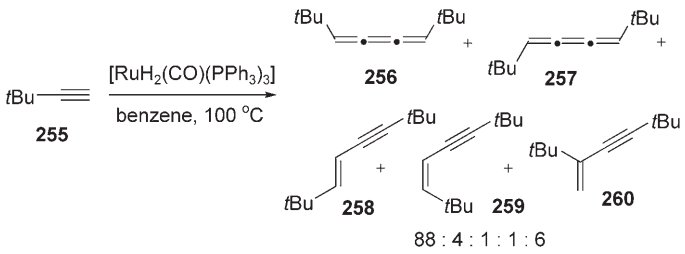
Scheme 95. Mechanism of rhodium-catalyzed cycloaromatization: 1,6-hydrogen migration.

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

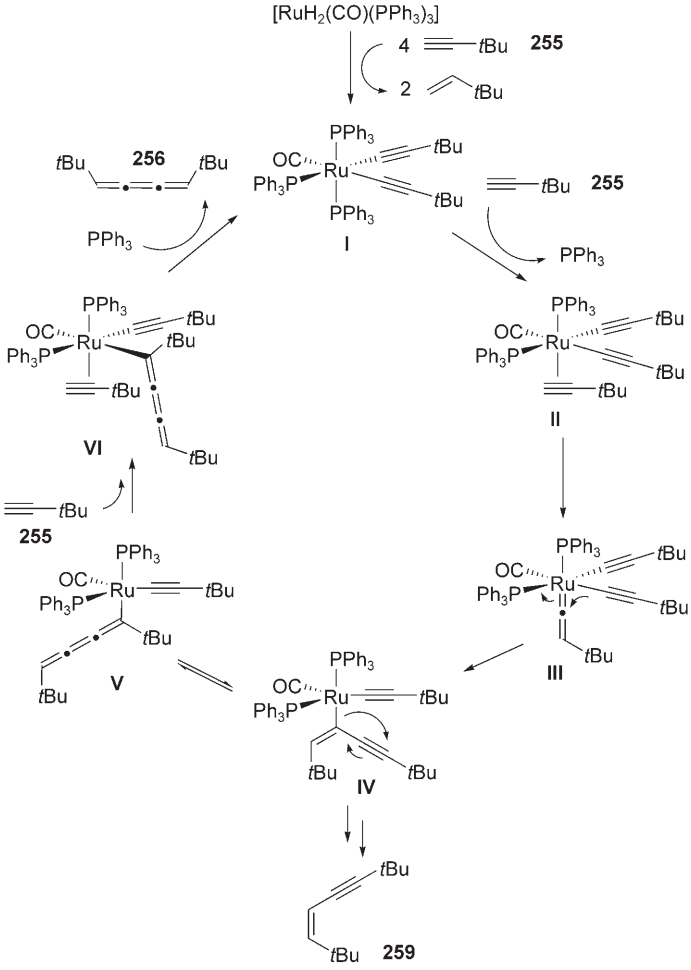
6.1. Alkyne Dimerization

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 *tert*-butylacetylene (**255**) was dimerized in the presence of a catalytic amount of a ruthenium complex to give a mixture of cumulenes **256** and **257**, head-to-head enynes **258** and **259**, and head-to-tail enyne **260** (Scheme 96).[108]

The preferential formation of **256** was later explained by Wakatsuki, Yamazaki, and co-workers (Scheme 97).[109] The formation of the active catalyst **I** was studied through iden-



Scheme 96. The Yamazaki dimerization of *tert*-butylacetylene.

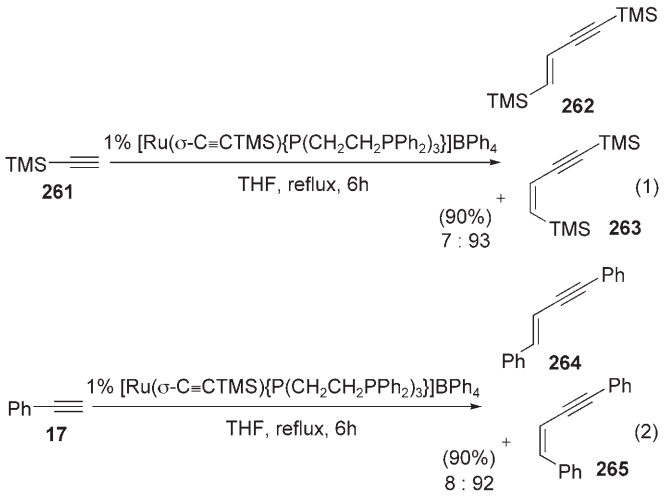


Scheme 97. Catalytic cycle for the Yamazaki dimerization of *tert*-butylacetylene.

tification of several intermediates leading to its formation. The catalytic cycle then commences with coordination of *tert*-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 *tert*-butyl group in close proximity with the ligand). This species leads to *Z*-enyne **259**, 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 *tert*-butylacetylene to **IV** is disfavored owing to steric effects; therefore, the reaction pref-

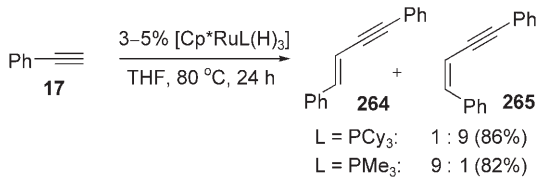
erentially continues on through **V**. Thus, coordination of the alkyne leads to **VI**, and oxidative addition of another alkyne followed by reductive elimination then gives the cumulene product **256** and regenerates the active catalyst.

Bianchini et al. 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 98).[110] This mechanism proceeds through a series of steps similar to those leading to **259** above.[111]



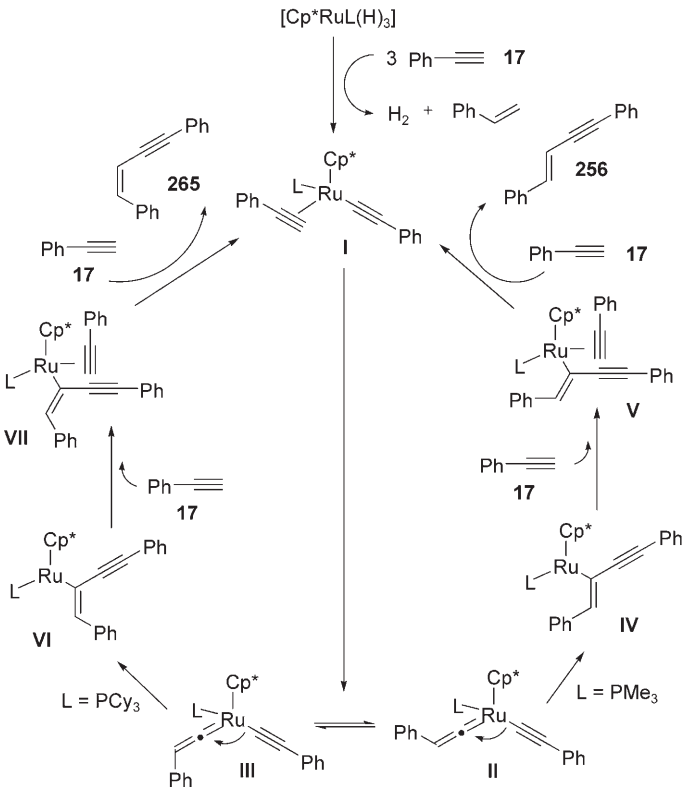
Scheme 98. The Bianchini dimerization of trimethylsilylacetylene and phenylacetylene.

Yi and Liu 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 99).[112]



Scheme 99. The Yi stereoselective dimerization of phenylacetylene: ligand effect.

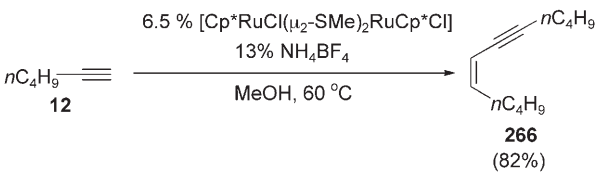
A mechanism that accounts for this ligand effect was proposed, the features of which are summarized in Scheme 100. A series of steps leads to active catalyst **I**, which can be converted into the equilibrating vinylidene complexes **II** and **III**. When the ligand is large ($L=PCy_3$), **III** is favored owing to repulsion between L and the phenyl group on the vinylidene in **II**; thus, reaction preferentially leads to *Z* enyne **265**. Conversely, when $L=PMe_3$, the steric interactions dictate that the reaction proceeds through **II** to give *E* enyne **264**.



Scheme 100. Alkyne dimerization: rationale for product formation.

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: $[TpRu(PPh_3)_2Cl]$,[113] $[TpRu(MeiPr_2P)C(Ph)=C(Ph)C\equiv CPh]$,[114] $[Ru(ma)_2(PPh_3)_2]$ (ma = maltolato, $C_6H_5O_3$),[115] $[(\eta^5\text{-}C_9H_7)Ru(PPh_3)_2C\equiv CPh]$,[116] and $[RuCl_2(PCy_3)_2{=}CHPh]$.[117] 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 co-workers reported that a dimeric ruthenium complex was able to catalyze the *Z*-selective dimerization of a variety of aliphatic terminal alkynes (Scheme 101).[118]

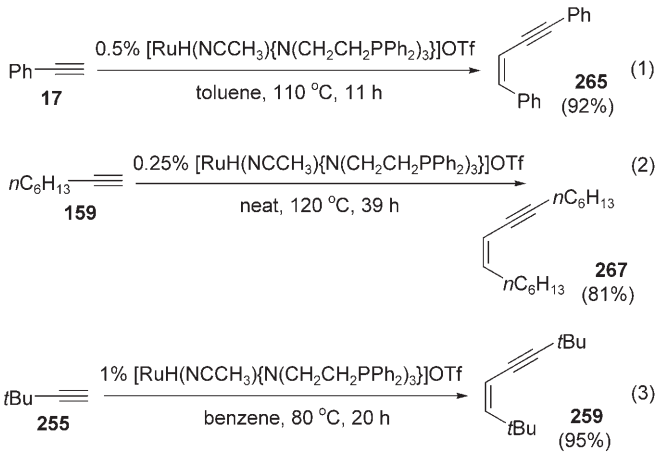
Bianchini and co-workers reported the most general catalyst to date, capable of head-to-head dimerization of both aromatic and aliphatic terminal alkynes with good *Z* selectivity. The catalyst loadings are quite low and the scope is



Scheme 101. The Hidai head-to-head dimerization of aliphatic terminal alkynes.

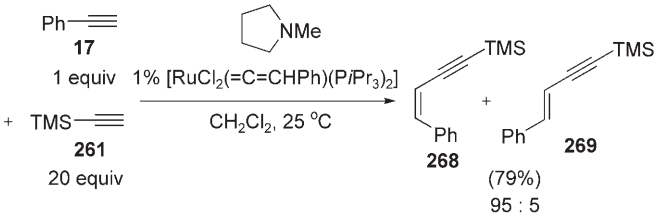
broad, with even *tert*-butylacetylene participating as a substrate (Scheme 102).[119]

The first *Z*-selective head-to-head cross-dimerization of aryl acetylenes with silyl acetylenes was recently reported,



Scheme 102. The Bianchini dimerization of aromatic and aliphatic terminal alkynes.

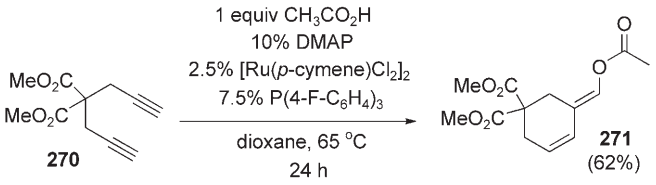
thus significantly enhancing the synthetic utility of this process (Scheme 103).[120] In this reaction, Katayama, Ozawa, and co-workers made use of the fact that aryl acetylenes preferentially form metal vinylidene intermediates; thus, by using an excess of trimethylsilylacetylene, they were able to capture these intermediates selectively.



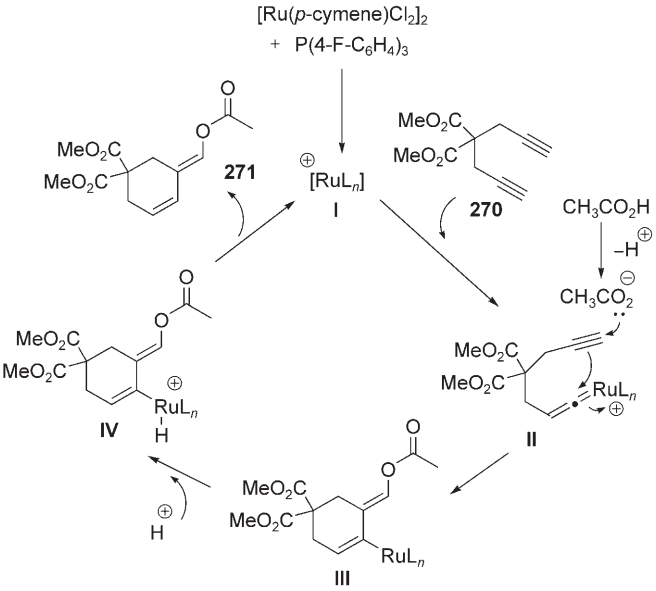
Scheme 103. The Katayama cross-dimerization of aryl acetylenes with silyl acetylenes.

Recent reports suggest that alkynes may add to metal vinylidenes in a manner different to 1,2-migration from the metal center. For example, when 1,6-diyne substrates were exposed to a ruthenium catalyst system and 1 equivalent of a carboxylic acid, cyclic enol esters were obtained in moderate to good yields (Scheme 104).[121]

The mechanism of this interesting process is shown in Scheme 105. 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.



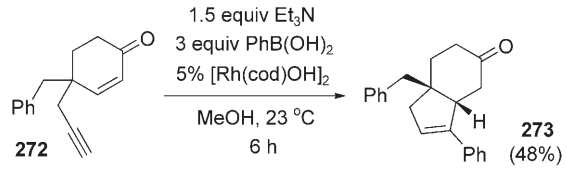
Scheme 104. The Lee carboxylative cyclization of 1,6-diynes.



Scheme 105. Mechanism of the carboxylative cyclization of 1,6-diynes.

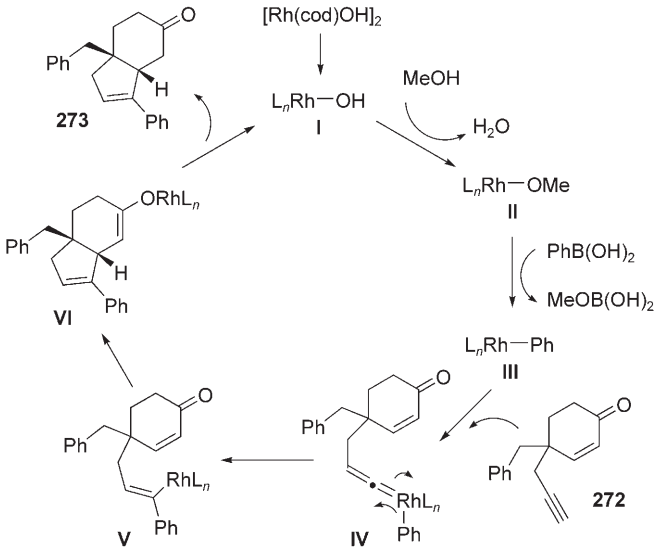
6.2. Arylative and Alkenylative Cyclization

Chen and Lee reported a new arylative (and alkenylative) cyclization reaction. Thus, 1,5-enynes, in which the alkene is conjugated to a carbonyl group, undergo a tandem carbometalation–cyclization reaction to give cyclopentene products. An example of this transformation is shown in Scheme 106.[122]



Scheme 106. The Lee arylative cyclization of 1,5-enynes.

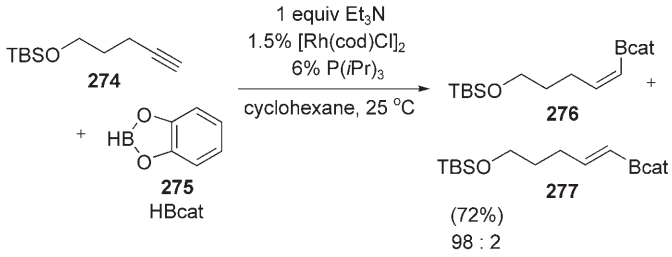
The product formation was rationalized according to Scheme 107. The active catalyst **I** undergoes ligand displacement with the solvent to give **II**. Transmetalation with the boronic acid then leads to **III**, which forms a vinylidene with the substrate. A 1,2-migration of the aryl group then leads to alkenyl rhodium species **V**, which coordinates the proximal enone and undergoes a 1,4-addition to give rhodium enolate **VI**. Finally, protonation and reductive elimination leads to product **273**.



Scheme 107. Mechanism of the arylative cyclization of 1,5-enynes.

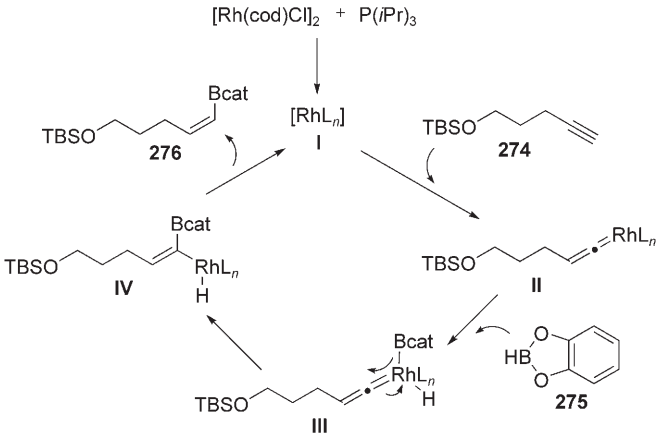
6.3. Hydroboration

Miyaura and co-workers reported the regio- and stereoselective hydroboration of terminal alkynes by using either a rhodium or an iridium catalyst with electron-rich phosphines.[123] An example of this transformation is shown in Scheme 108.



Scheme 108. The Miyaura *Z*-selective hydroboration of terminal alkynes.

This methodology has great synthetic promise as it offers *Z*-1-alkenylborane products, which can be valuable partners in Suzuki cross-coupling reactions. Traditionally, only direct access to *E*-1-alkenylboranes by rhodium-catalyzed hydroboration of terminal alkynes with the Wilkinson catalyst was possible.[124] To explain the regio- and stereoselectivity, Miyaura and co-workers proposed the mechanism shown in Scheme 109. The active catalyst **I** and the substrate form vinylidene intermediate **II**, a process that is consistent with deuterium-labeling studies. Oxidative addition of catecholborane (**275**) then leads to **III**, whereby a 1,2-migration followed by reductive elimination gives the product **276**. 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).



Scheme 109. *Z*-Selective hydroboration of terminal alkynes: mechanistic rationale.

7. Conclusion

The primary goal of organic synthesis should be to develop reactions that are efficient in terms of selectivity[125] and atom economy.[126] Selective addition and rearrangement reactions have the potential to fulfil these criteria perfectly. In this Focus 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 into metal vinylidenes. The variety of products formed 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.

Acknowledgements

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