Non-Metathesis Ruthenium-Catalyzed C–C Bond Formation

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I. Introduction

The efficient formation of carbon−carbon bonds forms the backbone of synthetic organic chemistry. In this area, transition metal catalyzed reactions have proven highly selective and atom economical. However, outside of ruthenium-catalyzed ring closing metathesis,[1] the application of ruthenium catalysis to the formation of carbon−carbon bonds is a relatively unexplored and new field.[2] The fact that 50% of the literature cited in this review was published in 1997 or later exemplifies this point. The vast amount of literature as well as previous reviews on ruthenium-catalyzed metathesis reactions precludes this class of reactions from being included in this review. The ability of ruthenium to assume a wide range of oxidation states (from −2 to +8) and coordination geometries provides unique opportunities for catalysis. As such, a wide range of mechanistically very different processes are catalyzed by ruthenium. These include reactions initiated by metallacycle formation, vinylidene formation, C−H activation, and activation of carbon−carbon mutiple bonds by coordination. The majority of the ruthenium complexes used herein are in the +2 to +4 oxidation state. These catalysts are generally the most versatile due to the facile redox chemistry between those oxidation states and therefore have the greatest ability to react in catalytic cycles. This review will focus on the ruthenium-catalyzed carbon−carbon bond formation from a mechanistic point of view. Understanding the mechanism by which these reactions proceed continues to provide the basis and impetus by which new reactions may be discovered and, indeed, invented.

II. Reactions Involving Ruthenacycle Intermediates

2.1. Ruthenacyclopentane

Ruthenacyclopentanes have been proposed as intermediates in the coupling of allenes and vinyl ketones to form 1,3-dienes (Scheme 1).[3] The reaction is proposed to proceed by coordination of the allene and enone by coordinatively unsaturated cyclopentadienylruthenium(+2) catalyst **1**, which leads to the formation of ruthenacycle **3**. β-Hydride elimination generates the 1,3-diene with concomitant formation of ruthenium hydride (**4**). Presumably, the steric interactions between the R-group and the *exo*-methylene group of the ruthenacycle (**3**) favor the depicted conformation, which leads to the formation of the *E*-isomer. Reductive elimination completes the catalytic cycle and regenerates the cationic ruthenium(+2) catalyst **1**.

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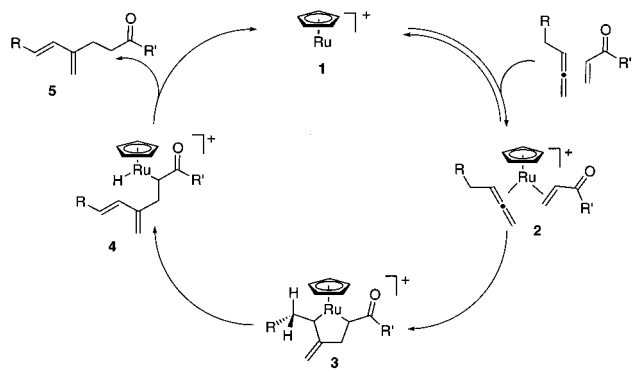
Barry M. Trost was born in Philadelphia, Pennsylvania in 1941 where he began his university training at the University of Pennsylvania (BA, 1962); he obtained a Ph.D. degree in Chemistry just three years later at the Massachusetts Institute of Technology (1965) and directly moved to the University of Wisconsin where he was promoted to Professor of Chemistry in 1969 and subsequently became the Vilas Research Professor in 1982. He joined the faculty at Stanford as Professor of Chemistry in 1987 and became Tamaki Professor of Humanities and Sciences in 1990 and currently serves as Chair. In 1994, he was presented with a *Docteur Honoris Causa* of the Université Claude-Bernard (Lyon I), France and, in 1997, with a *Doctor Scientiarium Honoris Causa* of the Technion, Haifa, Israel. His research interests revolve around the theme of selectivity, developing new reactions and reagents that are chemo-, regio-, diastereo-, and enantioselective and new synthetic strategies for the total synthesis of bioactive and novel molecules. In recognition of his many contributions, he has received a number of awards, including the ACS Award in Pure Chemistry (1977), the ACS Award for Creative Work in Synthetic Organic Chemistry (1981), the Baekeland Award (1981), Arthur C. Cope Scholar Award (1989), Guenther Award in the Chemistry of Essential Oils and Related Products (1990), the Dr. Paul Janssen Prize (1990), the ASSU Graduate Teaching Award (1991), Bing Teaching Award (1993), the ACS Roger Adams Award (1995), the Herbert C. Brown Award for Creative Research in Synthetic Methods, American Chemical Society (1999), the Belgian Organic Synthesis Symposium Elsevier Award (2000), the Nichols Medal (2000), and the Yamada Prize (2001). He was elected a Fellow of the American Academy of Sciences (1982) and a member of the National Academy of Sciences (1980). He coordinates the ACS course "Frontiers in Organic Chemistry." He edited a major compendium entitled Comprehensive Organic Synthesis consisting of nine volumes and serves as editor for ChemTracts/Organic Chemistry.

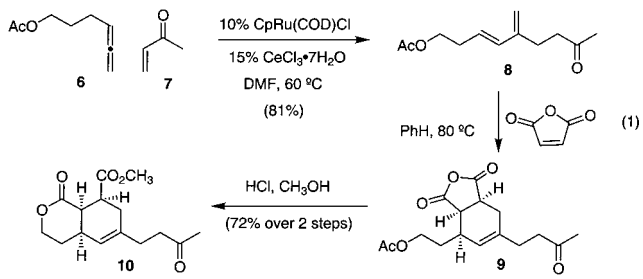
F. Dean Toste was born in Terceira, Azores, Portugal in 1971. He obtained his B.Sc. (1993) and M.Sc. (1995) from the University of Toronto (Canada) under the guidance of Prof. Ian W. J. Still. He then studied in the laboratories of Prof. Barry M. Trost and received his Ph.D. (2000) from Stanford University. His Ph.D. work focused on the development and applications of new palladium and ruthenium catalyzed methods for organic synthesis. He is currently conducting his postdoctoral studies in the laboratories of Prof. Robert H. Grubbs and the California Institute of Technology.

Tony Pinkerton is a native of Santa Fe, New Mexico. He obtained a B.S. in chemistry from the University of California, San Diego in 1995, where he worked in the laboratories of Professor Jay Siegel. He also spent five summers as a research assistant at Los Alamos National Laboratory. Upon graduation from UCSD, he continued his training at the ETH-Zürich, where he studied with Professor Dieter Seebach as a Fulbright Scholar. He then returned to California in the fall of 1996, where he began his graduate training with Professor Barry Trost at Stanford University. He completed his Ph.D. in 2001 and subsequently joined the medicinal chemistry department at Merck Research Laboratories in La Jolla, California.

The reaction is catalyzed by 10% CpRu(COD)Cl and 15% of cerium trichloride as a cocatalyst (eq 1). The role of the cocatalyst remains to be established in these reactions, but one possibility includes enone activation. Under these conditions, a variety of allenes are coupled to methyl vinyl ketone or phenyl vinyl ketone to provide 1,3-dienes in good yields (53−81%). The 1,3-dienes thus obtained serve as valuable intermediates. For example, by applying the ruthenium catalyzed coupling reaction in combination with the Diels−Alder reaction, bicyclic lactone **10** is produced with excellent chemo- and diastereoselectivity by additions (with only loss of methyl acetate) of allene **6**, methyl vinyl ketone (**7**), maleic anhydride, and methanol.

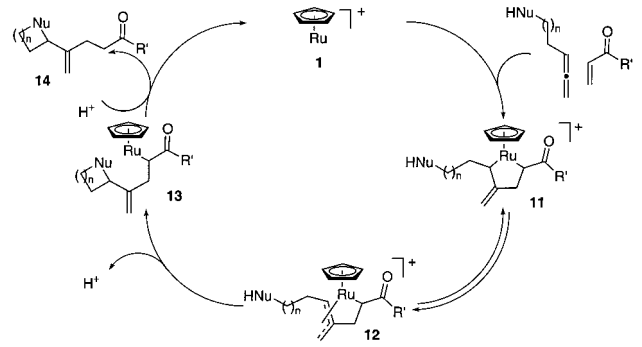
Scheme 1





The mechanism detailed in Scheme 1 postulates a σ-bound ruthenium-allyl complex (**3**) which undergoes a β-hydride elimination to form the 1,3-diene. This ruthenium-allyl can be trapped by an appropriately placed nucleophile, such as an alcohol[4] or an amine[5] (Scheme 2). It remains unclear whether

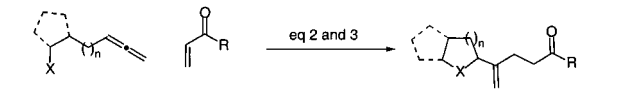
Scheme 2

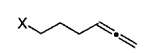
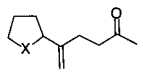
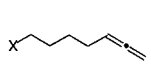
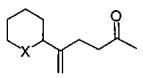
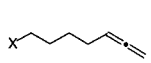
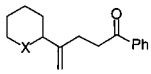
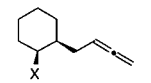
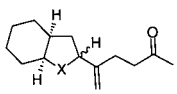
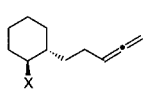
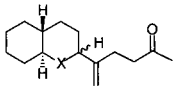


the nucleophilic addition is occurring onto a σ- (**11**) or π- (**12**) bound allylruthenium intermediate. In any case, nucleophilic addition to the allylruthenium complex generates ruthenium enolate **13**, which is protonated to produce cyclic ethers or amines (**14**) and regenerate the ruthenium(+2) catalyst (**1**).

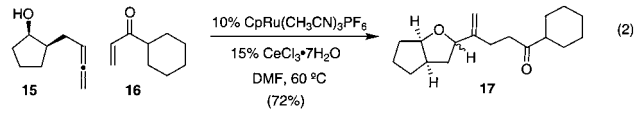
Ruthenium-catalyzed formation of cyclic ethers is catalyzed by 10% $CpRu(CH_3CN)_3PF_6$ and cocatalyzed by 15% cerium trichloride (eq 2). Under these conditions, a wide range of 5- and 6-membered ring ethers, including bicyclic ethers, are formed in good yields (Table 1). For example, reaction of cyclopentanol **15**

Table 1. Ruthenium-Catalyzed Alkylative Cycloetherification and Cycloamination

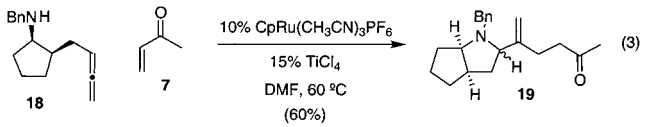


allene	R	Product	Yield
	-CH_3		X = O 82% X = NBn 73%
	-CH_3		X = O 74% X = NBn 67%
	-Ph		X = O 70% X = NBn 62%
	-CH_3		X = O 68% X = NPMB 90%
	-CH_3		X = O 67% X = NBn 71%

with cyclohexyl vinyl ketone **16** gave bicyclic tetrahydrofuran **17** in 72% yield.

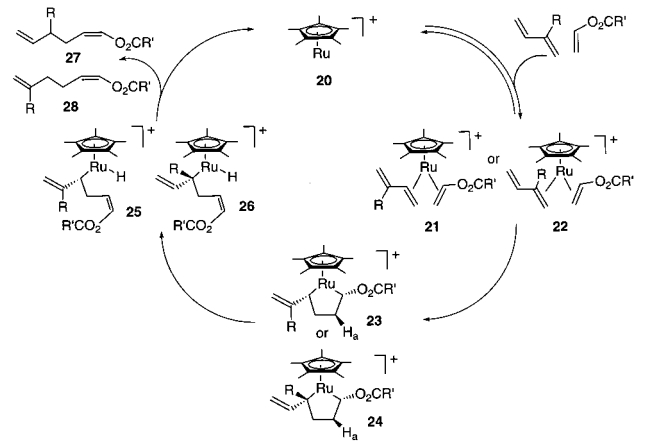


The formation of cyclic amines is also catalyzed by $CpRu(CH_3CN)_3PF_6$ but requires the use of 15% titanium tetrachloride or methylaluminum chloride as a cocatalyst (Table 1). Under these conditions, pyrrolidines and piperidines are formed in 47−90% yield. For example, reaction of amine **18** with methyl vinyl ketone (**7**) affords bicyclic pyrrolidine **19** in 60% yield (eq 3).



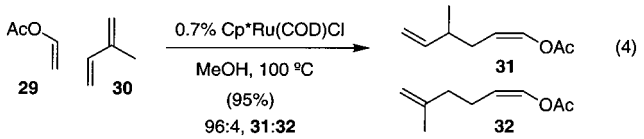
A ruthenacyclopentane has also been postulated as an intermediate in the coupling of dienes and enol esters (Scheme 3).[6] After coordination of the diene

Scheme 3



and enol ether (complexes **21** and **22**), cycloisomerization produces ruthenacyclopentanes **23** and **24**. The *cis*-geometry of the enol ester is generated by β-hydride elimination of H_a via a rather strained transition state due to the rigidity of the cyclopentane. This elimination produces allylruthenium hydrides **25** and **26** which undergo a reductive elimination to furnish 1,5-diene products **27**/**28** and regenerate the ruthenium(+2) catalyst **20**. Once again, it is unclear whether intermediates **25** and **26** are σ- or π-bound allylruthenium complexes. In any case, the factors determining the regioselectivity of the reductive elimination in the allylruthenium intermediates **25** and **26** also remain unresolved.

The reaction of vinyl acetate (**29**) and isoprene (**30**) is catalyzed by 0.7 mol % Cp*Ru(COD)Cl to afford a 96:4 mixture of 1,5-dienes **31** and **32** (eq 4). In general, the reaction produces 1,5-dienes with excellent control of olefin geometry and regioselectivity (≥94:6) and in good yields (41−95%). The major product is presumably generated via ruthenacycle **24**, which arises from coordination (complex **22**) of the ruthenium to the more substituted olefin of isoprene (Scheme 3). The reasons why ruthenacycle **24** is favored over **23** remain obscure, although the authors suggest electronic factors are important.

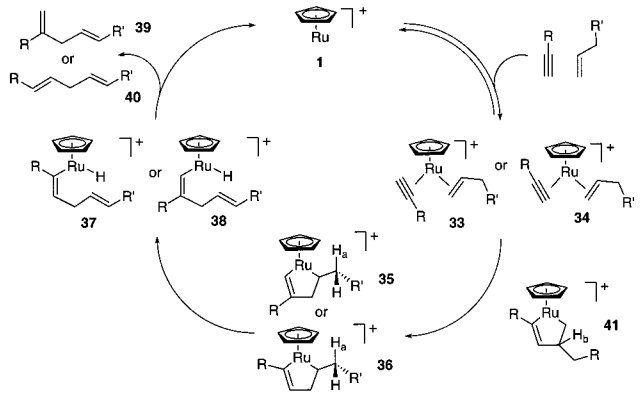


(4)

2.2. Ruthenacyclopentene

Cationic ruthenium(+2) complexes catalyze the coupling of alkynes and alkenes (an Alder-ene type reaction). A mechanism involving generation of a π-allylruthenium complex from activation of the alkene's allylic C−H was originally proposed; however, it is now generally believed that the reaction proceeds via a ruthenacyclopentene.[7] The proposed reaction mechanism is detailed in Scheme 4. After

Scheme 4

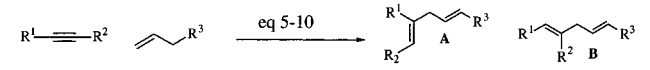


coordination of the alkyne and alkene by the coordinatively unsaturated ruthenium(+2) catalyst (**1**) to form complexes **33** and **34**, ruthenacyclopentenes **35** and **36** are formed by oxidative coupling of the two ligands. Two regioisomeric ruthenacycles are possible, depending on the orientation of the alkyne. Although, in principle, the alkene can also coordinate with the opposite orientation (to generate a ruthenacycle such as **41**), the difficulty in achieving the required geometry for *syn*-β-hydrogen elimination of H_b prevents this ruthenacycle from leading to product. Ruthenacycles **35** and **36** then undergo a *syn*-β-hydrogen elimination (of H_a) to generate vinylruthenium(+4) hydrides **37** and **38**. These complexes undergo a reductive elimination to form the 1,4-diene products (**39** and **40**) and regenerate the ruthenium-(+2) catalyst (**1**).

The Alder-ene reaction of alkene **42** and alkyne **43** is catalyzed by 10% CpRu(COD)Cl and 20% ammonium hexafluorophosphate to afford a 12.5:1 mixture of isomeric 1,4-dienes **44** and **45** (eq 5).[8] Diene **44** was taken on to a formal synthesis of alternaric acid. Thus, the reaction generally favors carbon−carbon bond formation at the more substituted carbon of the alkyne (the branched product) although several factors can reverse this trend (Table 2).

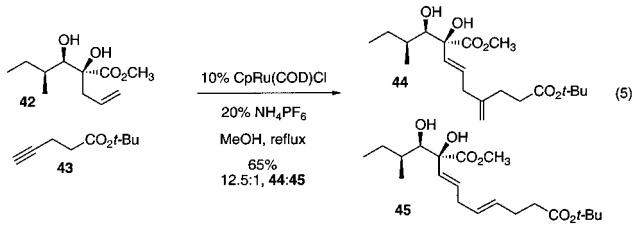
Steric factors, especially at the propargylic position, can control the regioselectivity of the carbon−carbon bond formation. In general, the ruthenium catalyzed reaction of alkynes bearing a quaternary propargylic carbon or silicon results in formation of the new carbon−carbon bond distal to this quaternary carbon or silicon. For example, the ruthenium catalyzed

Table 2. Ruthenium-Catalyzed Alder-ene Reaction[a]



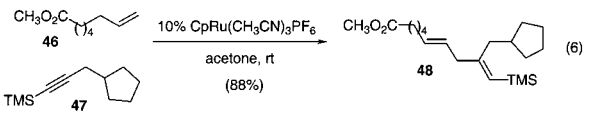
R^1	R^2	R^3	catalyst	Ratio A:B	Yield
$CH_3(CH_2)_2$-	H	-$(CH_2)_3CH_3$	**1**	5.2:1	56%
$CH_3(CH_2)_2$-	H	-$(CH_2)_2OH$	**1**	4:1	57%
$CH_3(CH_2)_2$-	H	-$COCH_3$	**1**	3.8:1	50%
$CH_3(CH_2)_2$-	H	-$(CH_2)_3CO_2CH_3$	**1**	3.8:1	71%
$CH_3(CH_2)_2$-	H	-$CH_2CH_2CH{=}CH_2$	**1**	6.4:1	52%
EtO_2C-	H	-$(CH_2)_3CH_3$	**1**	5.6:1	90%
TBDMSOCH$_2$-	H	-$(CH_2)_3CH_3$	**1**	5.0:1	86%
$CH_3(CH_2)_2$-	H	-$(CH_2)_6CH{=}CHCO_2Et$	**1**	5.3:1	46%
$CH_3(CH_2)_4CH(OBn)$-	H	-$(CH_2)_4CH_3$	**1**	1:2.0	53%
	H	-$(CH_2)_5CH_3$	**1**	1:9.9	65%
$HOCH_2$-	CH_3	-$(CH_2)_7CO_2CH_3$	**1**	1:2.6	38%
$MOMOCH_2$-	$CH_3(CH_2)_4$-	-$(CH_2)_7CO_2CH_3$	**1**	1:1.8	54%
$NC(CH_2)_3$-	H	-$(CH_2)_7CO_2CH_3$	**2**	8:1	65%
PhCH(NHBoc)$(CH_2)_2$-	H	-$(CH_2)_7CO_2CH_3$	**2**	>20:1	84%
$CH_3COCH_2CH_2$-	H	-$(CH_2)_7CO_2CH_3$	**2**	5:1	86%
	H	-$(CH_2)_7CO_2CH_3$	**2**	10:1	75%
$(CH_3)_2C(OH)$-	H	-$(CH_2)_7CO_2CH_3$	**2**	1:32	91%
$NC(CH_2)_3$-	$-CO_2CH_3$	-$(CH_2)_7CO_2CH_3$	**2**	3.3:1	73%
PhCH(NHBoc)$(CH_2)_2$-	$-CO_2Et$	-$(CH_2)_7CO_2CH_3$	**2**	1:5	62%
			1	1:3.5	61%
TsNHCH$_2$CH$_2$-	-TMS	-$(CH_2)_7CO_2CH_3$	**2**	>98:2	78%
$HOCH_2CH_2$-	-TMS	-$(CH_2)_4CH_3$	**2**	>98:2	79%
CH_3OCH_2-	-TMS	-CH_2COCH_3	**2**	>98:2	61%
			1	>98:2	31%
$CH_3(CH_2)_3$-	-TES	-$(CH_2)_2CH_2OAc$	**2**	>98:2	88%

[a] Catalyst: **1** = CpRu(COD)Cl, **2** = $CpRu(CH_3CN)_3PF_6$.



(5)

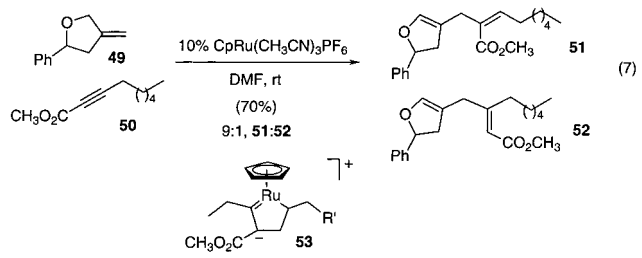
coupling of alkene **46** and trimethylsilyl alkyne **47** provides 1,4-diene **46** in 88% yield as a single regioisomer (eq 6).[9]



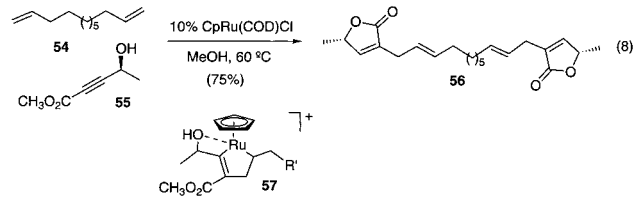
(6)

In the case of trimethylsilyl alkynes, the more reactive cationic ruthenium complex, $CpRu(CH_3CN)_3PF_6$, is used in place of the original catalyst CpRu(COD)Cl. The former catalyst also allows for the coupling of alkynes to 1,1- and 1,2-substituted alkenes,[10] both of which were unreactive when CpRu(COD)Cl was used as catalyst. For example, reaction of 4-methylenetetrahydrofuran **49** with alkynoate **50** affords a 70% yield of 1,4-dienes **51** and **52** with excellent control of regioselectivity (eq 7). Notably, excellent regioselectivity with respect to the alkene partner (**49**) is also obtained. This reaction also demonstrates the preference for formation of the new

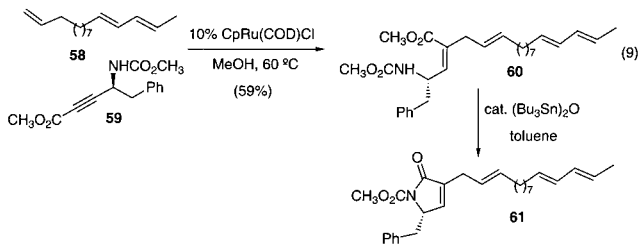
C−C bond at the α-carbon of the alkynoate. Polarization of the ruthenacycle, as shown in **53**, has been postulated as one of the factors which favors the placement of an electron withdrawing group at the *β*-carbon of the ruthenacycle.



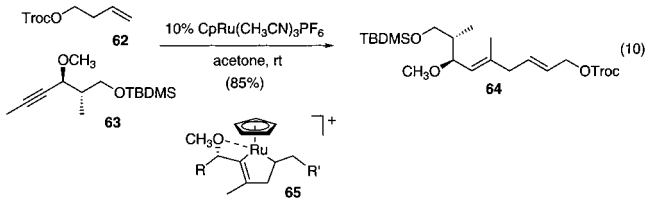
The ruthenium-catalyzed addition of alkenes to alkynoates is contra-electronic to the general preference of alkynoates to undergo addition to the *β*-carbon. This preference has been exploited for the preparation α-alkylated butenolides from 4-hydroxyalkynoates (eq 8).[11] In this case, the regiochemical preference for addition to the α-carbon of the alkynoate is further enforced by the coordination of the hydroxyl group, as in ruthenacycle **57**. The combination of these two factors produces the α-alkylated product with excellent control of regioselectivity. For example, reaction of 1,11-dodecadiene (**54**) with alkynoate **55** produces tetraene **56** in 75% yield. Chemoselective hydrogenation of the unconjugated olefins of **56** produced the naturally occurring acetogenin, (+)-ancepsenolide. A related approach was used to construct the butenolide portion in the total synthesis of more complex acetogenins, (+)-parviflorin, (+)-squamocin K, and (+)-5*S*-hydroxyparviflorin.[12]



A similar sequence has also been utilized to prepare pyrrolidinones (such as **61**) from the reaction of alkenes with 4-aminoalkynoates.[13] The exquisite chemoselectivity for the less hindered double bond is illustrated in eq 9. Reaction of alkynoate **59** with triene **58**, catalyzed by 10% CpRu(COD)Cl, affords **60** in 59% yield. This reaction also demonstrates the dominance of the ruthenium-catalyzed ene-type reaction over an alternative (and usually more facile) Diels−Alder type reaction.

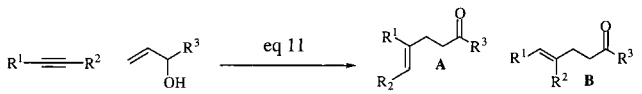


Other functional groups, besides the hydroxyl group, can coordinate to ruthenium and dramatically influence the regioselectivity of the coupling reaction. For example, $CpRu(CH_3CN)_3PF_6$ catalyzed reaction of propargylic methyl ether **63** with alkene **62** produces 1,4-diene **64** in 85% yield as a single regioisomer (eq 10).[14] Coordination of the propargylic methyl ether, as in ruthenacycle **65**, is postulated to be responsible for the excellent regioselectivity. The stability of the allyl ester in **64**, which could react to form a *π*-allylruthenium complex (see Section 5), is a testament to the mildness of the coupling reaction conditions.



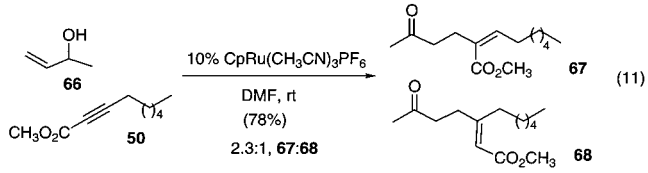
Ruthenacyclopentenes have also been proposed as intermediates in the coupling of alkynes and allylic alcohols to produce *γ*,*δ*-unsaturated ketones[15] and aldehydes (Table 3).[16] For example, the $CpRu(CH_3CN)_3PF_6$ catalyzed reaction of allyl alcohol **66** with alkynoate **50** furnishes a 78% yield of a 2.3:1 mixture of *γ*,*δ*-unsaturated ketones **67** and **68** (eq 11).[10]

Table 3. Ruthenium-Catalyzed Formation of *γ*,*δ*-Unsaturated Ketones and Aldehydes[a]



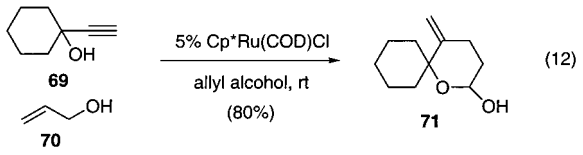
R^1	R^2	R^3	catalyst	ratio **A:B**	yield (%)
$CH_3(CH_2)_5$-	H	$-CH_3$	**1**	1:2.3	60
$CH_3(CH_2)_7$-	H	$-CH_3$	**2**	1:2.7	78
$CH_3(CH_2)_5$-	$-CO_2CH_3$	$-CH_3$	**1**	1:2.4	76
			2	1:2.3	82
$CH_3(CH_2)_4CH(OH)$-	H	$-CH_3$	**1**	1:4.4	60
Ph-	-Ph	$-CH_3$	**1**		50
Ph-	H	-H	**3**	3:1	85
$CH_3(CH_2)_5$-	H	-H	**3**	4:1	80
$HOCH_2CH_2$-	H	-H	**3**	1.4:1	70
t-C_4H_9-	H	-H	**3**	>98:2	60
TMS	H	-H	**3**	1:2.7	50
Ph-	$-CH_3$	-H	**3**	2.8:1	57

[a] Catalyst: **1** = CpRu(COD)Cl, **2** = $CpRu(CH_3CN)_3PF_6$, **3** = Cp*Ru(COD)Cl.

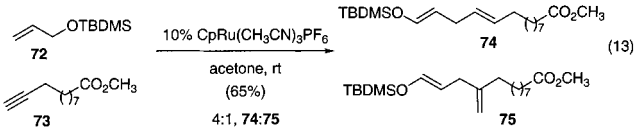


Similarly, the Cp*Ru(COD)Cl catalyzed reaction of allyl alcohol (**70**) and tertiary porpargyl alcohol **69** provides an aldehyde which, under the conditions of the reaction, cyclizes to afford hemiacetal **71** in 80% yield (eq 12).[17] In this case, allyl alcohol itself is utilized as solvent.

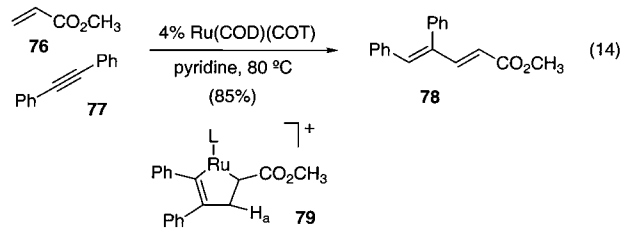
When an allyl silyl ether is used in place of the allyl alcohol, the $CpRu(CH_3CN)_3PF_6$ catalyzed reaction with an alkyne produces a silyl enol ether (eq 13).[18]



This reaction allows for the selective preparation of *E*-silyl enol ethers in the presence of functional groups that are incompatible for their preparation by traditional methods. For example, reaction of silyl ether **72** with alkyne **73** provides a 65% yield of a 4:1 mixture of enol ethers **74** and **75**.

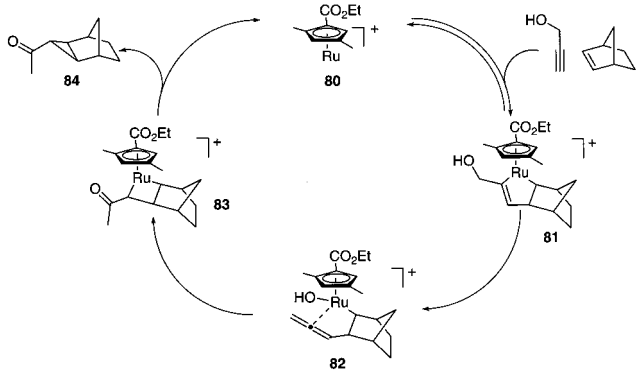


The ruthenium-catalyzed formation of 1,3-dienes, from the coupling of alkynes with acrylates, is also proposed to occur via a ruthenacyclopentene.[19] For example, reaction of methacrylate (**76**) with acetylene **77** affords 1,3-diene **78** in 85% yield (eq 14). Unlike the previous examples, the ruthenacycle formed from oxidative coupling of an acetylene and the acrylate must undergo β-hydrogen elimination of a proton located within the metallacycle (H_a in **79**). Notably, this type of β-hydrogen elimination is completely excluded when the alkene partner possesses allylic protons (see Scheme 4).



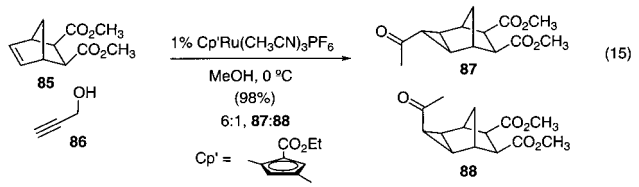
When β-hydrogen elimination is inhibited, the ruthenacyclopentene intermediate can undergo other processes. For example, the ruthenacyclopentene intermediate **81** generated from the oxidative coupling of norbornene and propargyl alcohol cannot achieve the geometry necessary to undergo β-hydrogen elimination (Scheme 5).[20] Furthermore, the β-hydrogen elimination of a norbornene bridgehead proton would generate a high energy *anti*-Bredt olefin.

Scheme 5

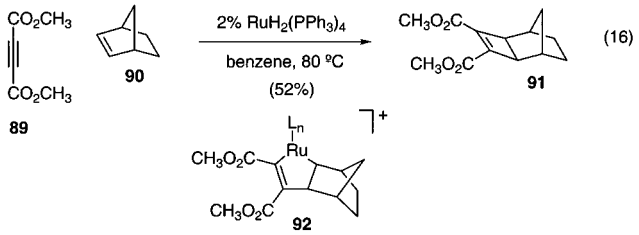


Therefore, ruthenacyclopentene **81** undergoes a β-hydroxy elimination to produce allene **82**. Addition of water to the central carbon of the allene produces ruthenium enolate **83** (a ruthenacyclobutane when C-bound) which undergoes a reductive elimination to furnish the cyclopropyl ketone (**84**) and regenerate the ruthenium(+2) catalyst **80**.

An example of this process is shown in eq 15. The reaction of 2-propyn-1-ol (**86**) with norbornene **85** is catalyzed by 1% Cp′$Ru(CH_3CN)_3PF_6$ to afford a 6:1 mixture of cyclopropyl ketones **87** and **88** in 98% yield.

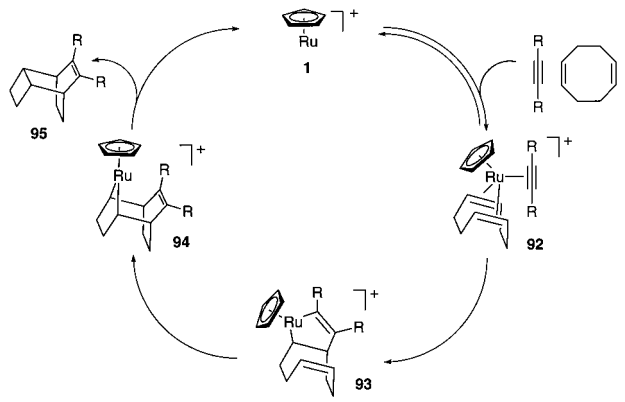


The ruthenium-catalyzed reaction of norbornene (**90**) with dimethylacetylene dicarboxylate (**89**) is proposed to proceed through a related ruthenacyclopentene **92** (eq 16).[21] Ruthenacycle **92** cannot undergo β-hydrogen elimination or β-hydroxy elimination (see Scheme 5); therefore, a reductive elimination takes place to produce a cyclobutene. For example, reaction of norbornene (**90**) with dimethyl acetylenedicarboxylate (**89**), catalyzed by 2% $RuH_2(PPh_3)_4$, afforded cyclobutene **91** in 52% yield.



Cyclobutanes are also available from the ruthenium-catalyzed homo-Diels−Alder reaction of cyclooctadiene and acetylenes (Scheme 6).[22,23] The reaction is

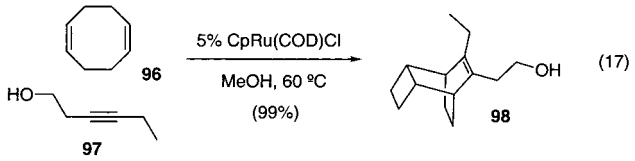
Scheme 6



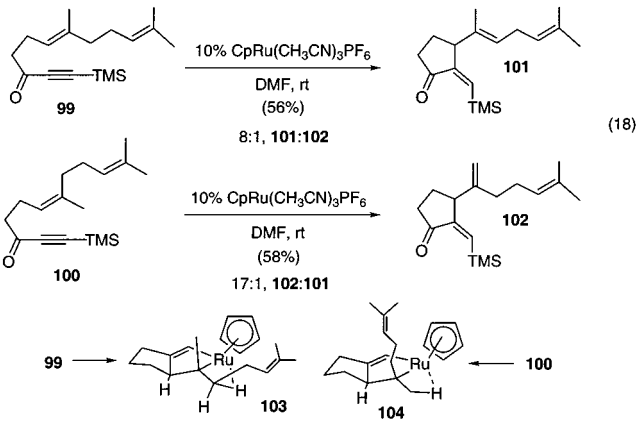
postulated to proceed through a ruthenacyclopentene (**93**) derived from the oxidative coupling of an acetylene to one of the olefins of cyclooctadiene. Instead of the normally observed β-hydrogen elimination (see Scheme 4), ruthenacycle **93** undergoes a 4-*exo*-car-

baruthenation to generate ruthenacycle **94**. As before, β-hydrogen elimination in ruthenacyclopentane **94** is inhibited; therefore, it undergoes a reductive elimination to form cyclobutane **95**.

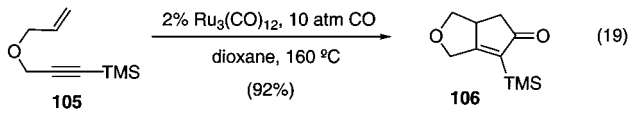
The reaction described in Scheme 6 is catalyzed by 5% CpRu(COD)Cl in methanol at 60 °C (eq 17). Under these conditions, a wide range of homo-Diels–Alder adducts are formed in good yields (78–100%). For example, 1,4-cyclooctadiene (**96**) reacts with alkyne **97** to provide tricyclo[4.2.2.0]dec-7-ene **98** in 99% yield.



Ruthenacyclopentenes have also been proposed as intermediates in the intramolecular coupling reaction of alkenes and alkynes (eq 18).[24] For example, $CpRu(CH_3CN)_3PF_6$ catalyzed cycloisomerization of geranyl based **99** selectively (8:1) affords the more substituted 1,4-diene **101**. Switching to the neryl based enyne **100** completely reverses the selectivity to afford **102** with a 17:1 selectivity. Examination of the proposed ruthenacycle intermediates, **103** and **104**, provides a possible explanation for this phenomenon. The substituent situated in a pseudoequatorial position places a hydrogen proximal to the metal center, in a position that allows for the necessary overlap for β-hydrogen elimination.

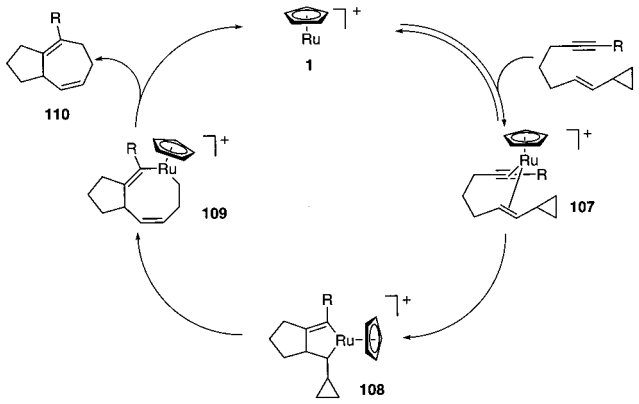


In the absence of a proton suitable for β-hydrogen elimination, the ruthenacyclopentene can undergo migratory insertion of a carbon monoxide prior to reductive elimination. This results in the formation of cyclopentenones from 1,6-enynes (eq 19).[25] For example, $Ru_3(CO)_{12}$ catalyzes the formation of bicyclic ketone **106** in 92% yield from 1,6-enyne **105**.

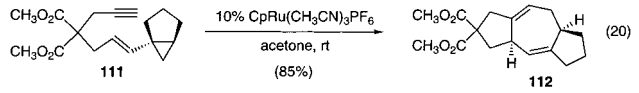


A ruthenacyclopentene (**108**) is also postulated as the intermediate formed in the intramolecular [5+2]-cycloaddition of an alkyne and vinylcyclopropane (Scheme 7).[26] This ruthenacycle (**108**) does not undergo β-hydrogen elimination (which would generate a methylenecyclopropane), but undergoes an insertion into the carbon–carbon bond of the cyclopropane to generate a ruthenacyclooctadiene **109**. Reductive elimination of **109** produces the cycloheptadiene product **110** and regenerates the ruthenium(+2) catalyst (**1**).

Scheme 7

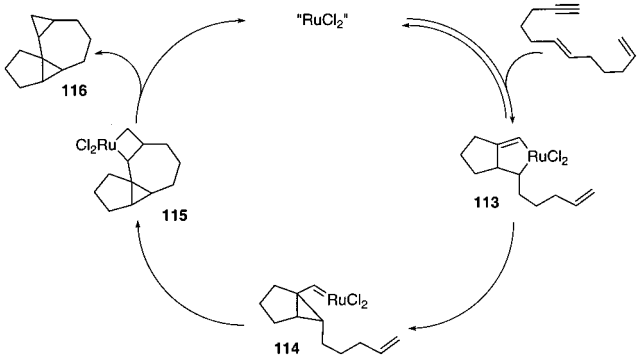


The [5+2]-cycloaddition reaction described in Scheme 7 is catalyzed by 10 mol % $CpRu(CH_3CN)_3PF_6$ in DMF or acetone at room temperature. Under these conditions, a wide range of bicyclic and tricyclic cycloheptadienes are formed in good yields (73–92%). For example, ruthenium-catalyzed reaction of vinyl cyclopropane **111** furnished tricycle **112** in 85% yield (eq 20).



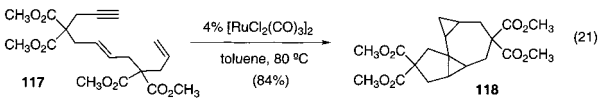
Cycloheptanes are also produced in the ruthenium-catalyzed cycloisomerization of 1,6-diene-11-ynes (Scheme 8).[27] The reaction is postulated to proceed through ruthenacyclopentene **113**, which, instead of a β-hydrogen elimination, undergoes a retro vinylcyclopropane-cyclopentene rearrangement to generate ruthenium carbene **114**. An intramolecular cyclopropanation, presumably via ruthenacyclobutane **115**, of the remaining olefin produces the cycloheptane product (**116**).

Scheme 8



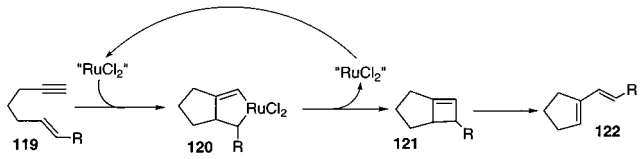
The reaction in Scheme 8 is catalyzed by 4% $[RuCl_2(CO)_3]_2$ and affords tetracyclic cycloheptanes in 62–84% yield (eq 21). For example, ruthenium-

catalyzed reaction of 1,6-diene-11-yne **117** gave biscyclopropyl adduct **118** in 84% yield.



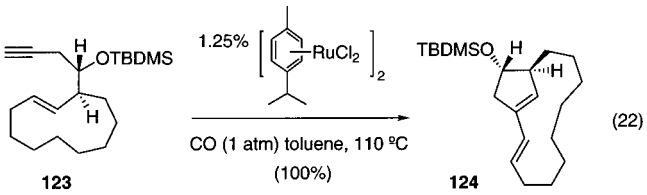
Ruthenacyclopentenes have also been postulated as intermediates in the ruthenium-catalyzed enyne metathesis to produce vinylcyclopentenes (Scheme 9).[28] Reaction of ruthenium(+2) with an enyne (**119**)

Scheme 9



generates ruthenacycle **120**. Ruthenacycle **120** undergoes a reductive elimination, in preference to β-hydrogen elimination, to produce cyclobutene **121** and regenerate the ruthenium catalyst. A conrotary cycloreversion of cyclobutene **121** furnishes the vinylcyclopentene product (**122**).

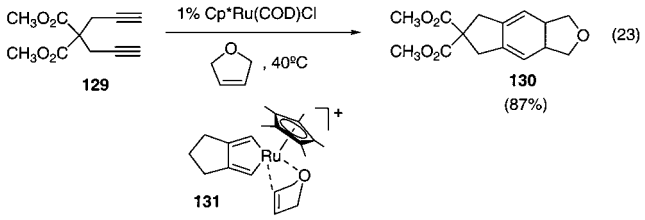
The reaction is catalyzed by ruthenium(+2) in the presence of a carbon monoxide atmosphere. For example, reaction of 1,6-enyne **123**, catalyzed by 1.25 mol % of cymeneruthenium chloride dimer, gave vinyl cyclopentene **124** in quantitative yield (eq 22).[29]



2.3. Ruthenacyclopentadiene

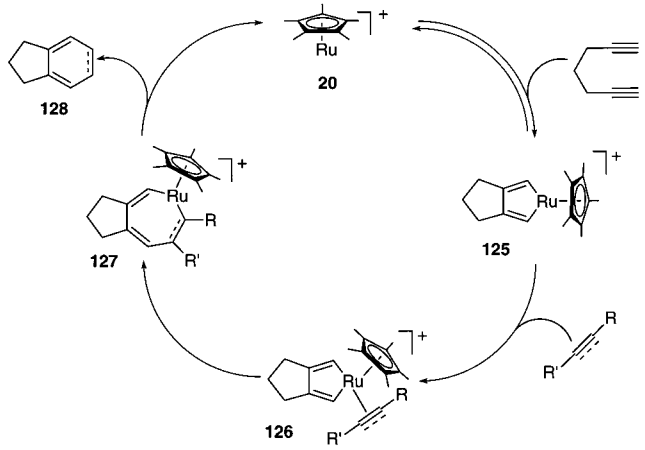
Ruthenacyclopentadienes have been postulated as intermediates in ruthenium-catalyzed reaction of 1,6-heptadiynes. The ruthenacycle (**125**) formed from the cycloisomerization of 1,6-diynes cannot undergo β-hydrogen elimination or reductive elimination. Therefore, in the presence of an alkene or an alkyne, ruthenacycle **125** can undergo an insertion of one of these ligands to produce a ruthenacycloheptatriene or diene (**127**). Reductive elimination produces the 1,3-diene or benzene adduct (**128**) and regenerates the ruthenium(+2) catalyst (**20**).

The [2+2+2] cycloaddition of 1,6-diyne **129** and 2,5-dihydrofuran is catalyzed by Cp*Ru(COD)Cl, using dihydrofuran as solvent (eq 23).[30] Under these conditions, tricyclic 1,3-cyclohexadienes, such as **130**, are produced in 50−90% yield. The reaction is limited to the coupling of 1,6-diyne and allylic ethers or norbornene,[31] although the reaction with norbornene is complicated by competing processes. The failure of other olefins, in particular cyclopentene, to participate in the reaction suggests that coordination of an ether oxygen is important for the insertion of the olefin into the ruthenacyclopentadiene. An intermediate **131** involving coordination of both the olefin and the ether oxygen of dihydrofuran to the cationic ruthenium has been postulated to initiate the insertion of the olefin.



The related [2+2+2] cycloaddition of 1,6-heptadiynes and alkynes is also catalyzed by Cp*Ru(COD)Cl (eq 24).[32,33] Notably, the benzene ring is produced with excellent control of regioselectivity. For example, reaction of diyne **132** with 1-hexyne (**133**) gave an 85% yield of a 93:7 mixture of cycloadducts **134** and **135**. Presumably, steric interaction between the R-group and the metal center, in ruthenacycloheptatriene **127**, forces the larger group to be situated in the R′-position (Scheme 10).

Scheme 10



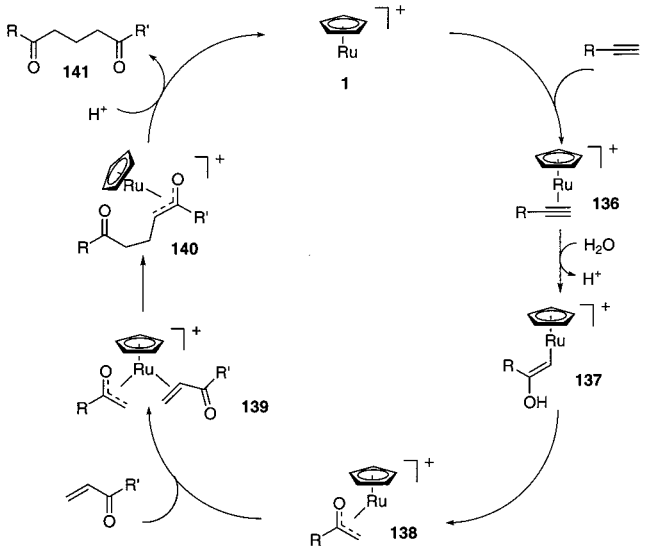
Ruthenacyclopentadienes have also been proposed as an intermediate in the coupling reaction of acetylene and acrylonitrile. In this case, two equivalents of acetylene react with Cp*Ru(PPh$_3$)$_2$Cl to form the ruthenacyclopentadiene species.[34]

III. Reactions Involving Heteroatom Additions to Alkynes

3.1. Additions of Water

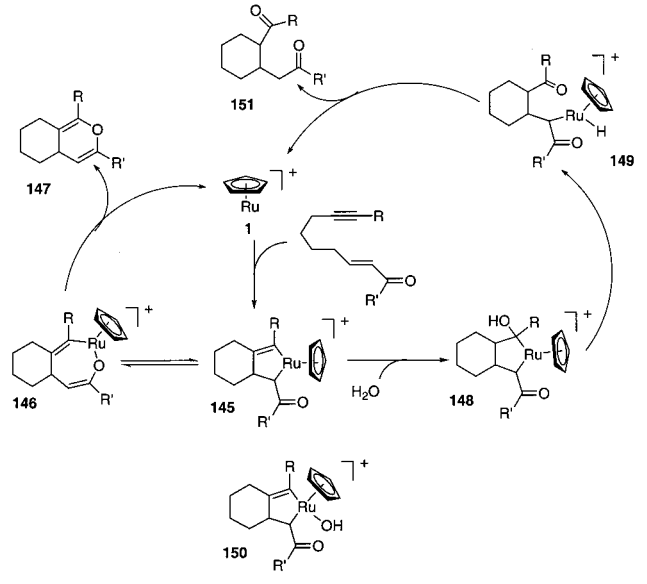
Ruthenium has been shown to catalyze the addition of water to alkynes followed by trapping with enones to generate 1,5-diketones (Scheme 11).[35] The reaction is proposed to proceed by the ruthenium-catalyzed addition of water to an alkyne to generate

Scheme 11

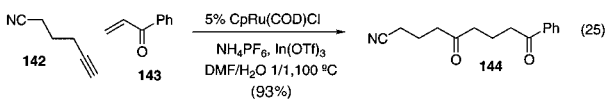


a ruthenium enolate **138**. This ruthenium enolate then inserts into the enone, via complex **139**, to generate another ruthenium enolate **140**. Protonation of this enolate releases the product 1,5-diketone (**141**) and regenerates the catalyst (**1**). As in the intramolecular version of this reaction, a mechanism involving an intermediate ruthenacyclopentene is also possible (see Scheme 12).

Scheme 12

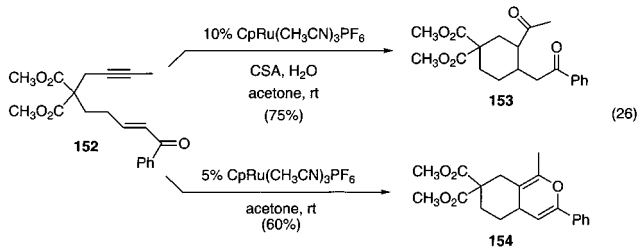


The optimal conditions for the reaction involve the use of 5% CpRu(COD)Cl and a mixture of ammonium hexafluorophosphate and indium triflate as cocatalysts in a DMF/water mixture. A variety of alkynes and enones are reactive under these conditions to give the 1,5-diketones in good yields (44−93%). For example, reaction of 5-cyanopentyne (**142**) with enone **143** affords 1,5-diketone **144** in 93% yield (eq 25).

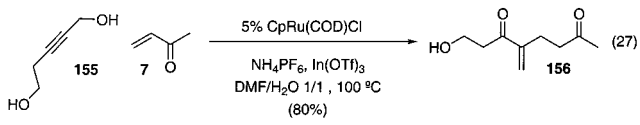


This reaction has also been extended to an intramolecular version wherein either cyclic 1,5-diketones or pyrans can be obtained, depending on the conditions. The mechanism shown in Scheme 11 cannot account for both products, so another mechanism, involving a ruthenacycle, is postulated (Scheme 12).[36] Coordination of the enone-yne leads to ruthenacycle **145**. This ruthenacycle can then either isomerize to O-bound ruthenium enolate **146** or add water to form hydroxy-ruthenium complex **148**. At this point, **146** can undergo a reductive elimination to give the pyran (**147**) and regenerate the coordinatively unsaturated ruthenium catalyst. Alternatively, complex **148** can undergo a β-hydrogen elimination to produce the hydridoruthenium complex **149**, which undergoes a reductive elimination to afford the 1,5-diketone (**151**). An alternative may be coordination of water to ruthenium to form **150** which may become a precursor to **149**. It is also possible that the 1,5-diketone simply arises from hydrolysis of the pyran after its initial formation.

The formation of cyclic 1,5-diketones is catalyzed by 10 mol % $CpRu(CH_3CN)_3PF_6$ in aqueous acetone with camphorsulfonic acid (CSA) as a cocatalyst. The corresponding formation of pyrans is catalyzed by 5 mol % $CpRu(CH_3CN)_3PF_6$ in anhydrous acetone. Under these conditions, a range of 1,5-diketones (45−86% yield) and pyrans (55−89% yield) can be accessed. For example, reaction of enone-yne **152** can selectively produce either 1,5-diketone **153** or pyran **154** (eq 26).



When propargylic alcohols are used in this reaction, enones are formed as shown in eq 27.[37] This reaction could either proceed through a mechanism as outlined in Scheme 11 or a metallacycle as outlined in Scheme 12. The reaction is catalyzed by 5 mol % CpRu(COD)Cl and a mixture of ammonium hexafluorophosphate and indium triflate or CSA as cocatalysts in a DMF-water mixture to produce α,β-unsaturated enones in good yields (55−80%). For example, propargyl alcohol **155** and methyl vinyl ketone (**7**) combine with water to form exclusively enone **156** in 80% yield (eq 27). This example appears more in accord with a metallacycle mechanism since none of the alternative type of dehydration product arises.

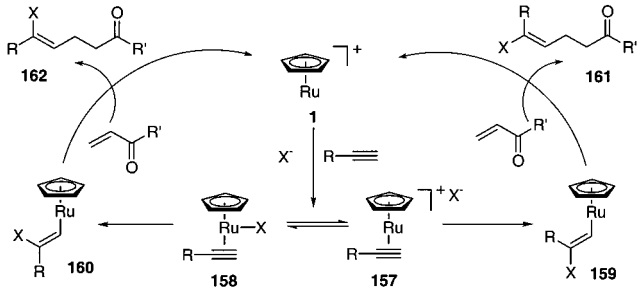


3.2. Additions of Halides

Ruthenium (+2) complexes also catalyze the addition of halides to alkynes and the subsequent trap-

ping with enones to form vinyl halides. Depending on the conditions, either *E* or *Z* vinyl halides can be obtained. The proposed mechanism is shown in Scheme 13. Coordination of the halide and the alkyne

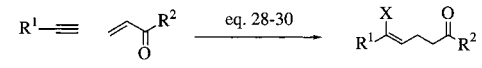
Scheme 13



leads to two species, **157** and **158**. Complex **157**, a more ionic species, leads to external attack and a trans halometalation to give vinyl ruthenium intermediate **159**. Upon trapping with an enone and protonation, **159** affords *E* vinyl halide **161** and regenerates the ruthenium catalyst (**1**). Conversely, complex **158**, a more covalent species results in internal attack and a cis halometalation. The resulting vinyl ruthenium species (**160**) eventually generates *Z* vinyl halide **162**. In general, chloride, being more nucleophilic, gives more **157** as compared to bromide. Also, the use of DMF as a solvent as compared to acetone favors **157**, leading to more of the *E* product.

For formation of *E* vinyl chlorides, use of 10 mol % CpRu(COD)Cl with stannic chloride as a cocatalyst in DMF is optimal.[38] A range of alkynes and enones are tolerated in yields ranging from 60 to 83% with *E:Z* ratios of 4−15:1 (Table 4). For example, alkyne

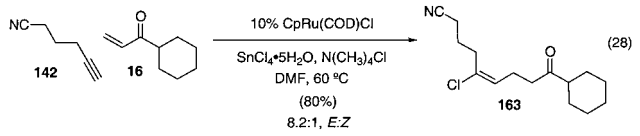
Table 4. Ruthenium-Catalyzed Formation of Vinyl Halides[a]



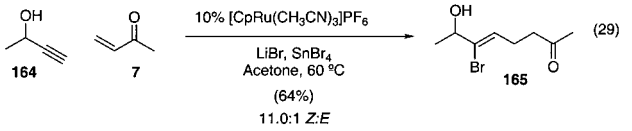
R^1	R^2	X	catalyst	Ratio *E:Z*	Yield
$CH_3(CH_2)_5$-	$-CH_3$	Cl	**1**	>15:1	72%
		Br	**2**	1:6.6	88%
$NC(CH_2)_3$-	$-CH_3$	Cl	**1**	12:1	80%
		Br	**2**	1:3.3	90%
$CH_3CH(OH)$-	$-CH_3$	Cl	**1**	5.3:1	78%
		Br	**2**	1:11	64%
$CH_3CH(OH)CH_2$-	$-CH_3$	Cl	**1**	8.5:1	80%
		Br	**2**	1:6.0	82%
$NC(CH_2)_3$-		Cl	**1**	8.2:1	80%
		Br	**2**	1:4.7	77%
TMS	$-CH_3$	Br	**2**	*Z*-only	50%
Ph-	$-CH_3$	Br	**2**	*Z*-only	72%
Ph-	-Ph	Br	**2**	*Z*-only	72%
	$-CH_3$	Br	**2**	*Z*-only	55%

[a] Catalyst: **1** = CpRu(COD)Cl, **2** = $CpRu(CH_3CN)_3PF_6$.

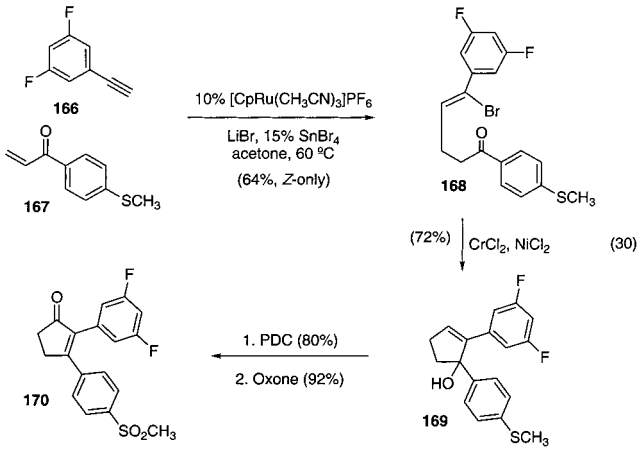
142 and cyclohexyl vinyl ketone (**16**) combine to form *E* vinyl chloride **163** in 80% yield (eq 28).



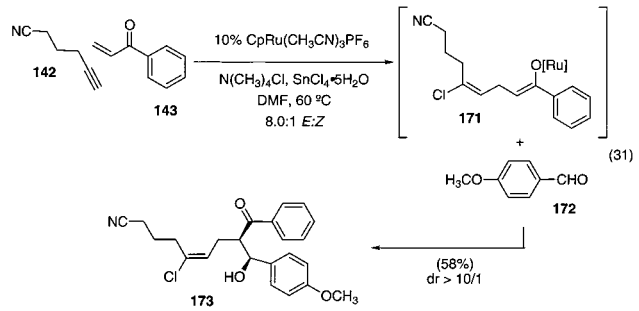
Z Vinyl bromides are formed by the use of 10 mol % $CpRu(CH_3CN)_3PF_6$ with stannic bromide as a cocatalyst in acetone.[39] For example, 3-butyn-2-ol (**164**) reacts with methyl vinyl ketone (**7**) to form vinyl bromide **165** in 64% yield (eq 29). A similar wide range of substrates is tolerated, with yields ranging from 64 to 92% and *Z:E* ratios of 3−11:1 (Table 4).



Notably, when aryl alkynes or acetylenes with a quaternary propargylic carbon are used as substrates, exclusive *Z*-selectivity in bromoalkylation of alkynes with vinyl ketones is observed (eq 30).[40] For example, ruthenium-catalyzed coupling of aryl alkyne **166** with enone **167** affords vinyl bromide **168** in 64% yield as a single olefin isomer. The vinyl bromides thus obtained can be employed in a highly efficient cyclopentenone synthesis.[41] For example, Kishi-Nozaki reaction of vinylbromide **168** gave cyclopentenol **169**, which was subjected to sequential oxidative rearrangement and oxidation of the sulfide to the sulfone to produce the potent COX-2 inihibitor **170**.



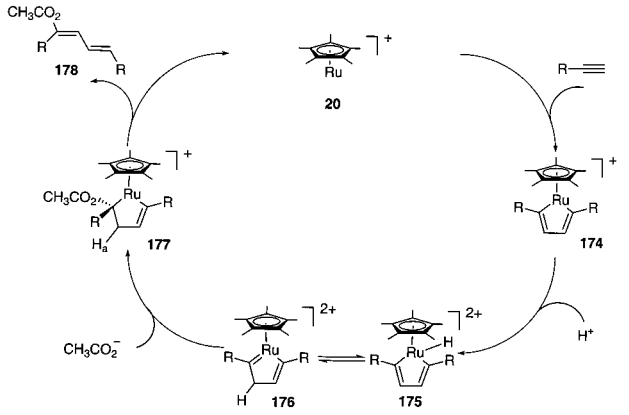
When an aldehyde is added to the reaction mixture in either the vinyl chloride or vinyl bromide forming reaction, the proposed ruthenium enolate can be trapped in an aldol reaction to give four component coupling products.[42] For example, combination of alkyne **142**, phenyl vinyl ketone (**143**), tetramethylammonium chloride, and *p*-anisaldehyde (**172**) furnishes four component coupling product **173** in 58% yield, with a *Z:E* ratio of 8:1 (eq 31). Interestingly, the aldol reaction proceeds with excellent syn diastereoslectivity, indicating that *Z*-ruthenium enolate (**171**) was formed with good geometrical selectivity.

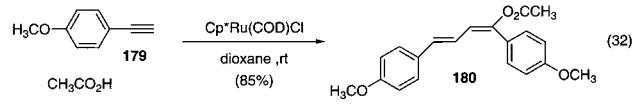


3.3. Additions of Carboxylic Acids

There has also been a large amount of work on the additions of carboxylic acids to alkynes to form enol esters.[43] Carboxylic acids can also be added to alkynes with subsequent trapping with an alkyne (Scheme 14).[44] This reaction is proposed to proceed via metallacyclopentadiene intermediate **174**. Protonation of ruthenium complex **174** followed by addition of the carboxylate produces ruthenacyclopentene **177**. A β-hydrogen elimination of H_a followed by a reductive elimination releases the 1,3-diene product (**178**) and regenerates the active ruthenium catalyst (**20**). For example, aryl alkyne **179** and acetic acid combine to form 1,3-dienyl ester **180** in 85% yield (eq 32). Another potential mechanism for this reaction involves the trans addition of a carboxylic acid catalyzed by the ruthenium to generate a vinyl ruthenium which then does a cis carbometalation of another alkyne. This reaction therefore can be considered mechanistically similar to the reactions in sections 3.1 and 3.2.

Scheme 14



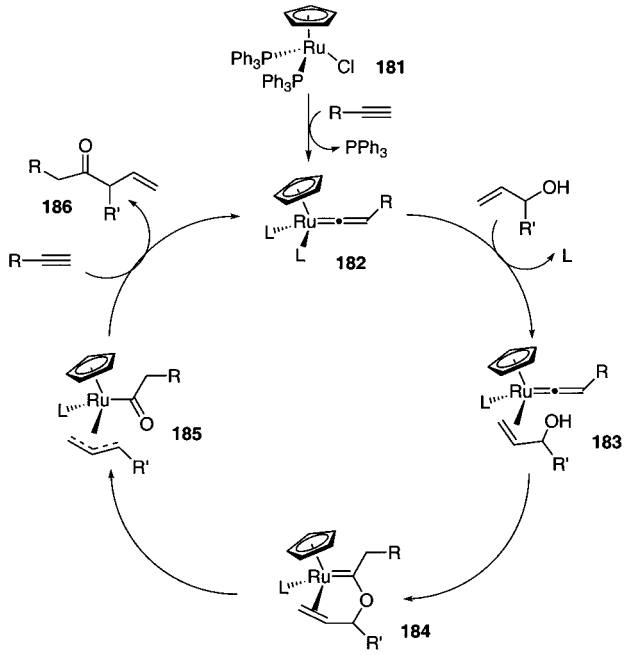


IV. Reactions Involving Additions to Ruthenium Vinylidene Species

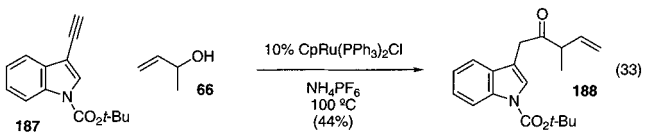
4.1. Oxygen Nucleophiles

Ruthenium(+2) complexes catalyze the reconstitutive addition of alkynes and allyl alcohols to give β,γ-unsaturated ketones.[45] A mechanism involving the coordination of the terminal alkyne to the ruthenium followed by vinylidene (**182**) formation is postulated. Coordination of the allyl alcohol followed by addition of the alcohol to the ruthenium vinylidene leads to ruthenium carbene **184**. Ionization, by a metalla-Claisen process, produces acyl-allylruthenium complex **185**. This intermediate undergoes a reductive elimination to give product **186** and regenerate the catalytically active ruthenium species (Scheme 15). The regioselectivity of the carbon–carbon bond formation to the allyl is independent of the site of the initial ionization but derives from the intrinsic selectivity of the reductive elimination. That is, when either 1-methylallyl alcohol or crotyl alcohol is used as substrate, bond formation occurs on the more substituted terminus of the π-allylruthenium complex (**185**).[46]

Scheme 15

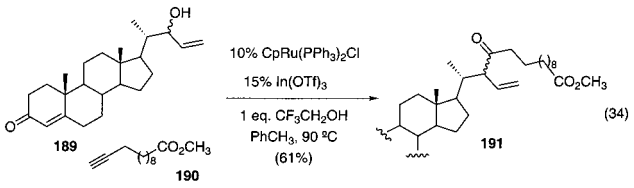


For example, the reconsitutive addition of ethynyl indole **187** and 1-methylallyl alcohol (**66**) is catalyzed by 10 mol % $CpRu(PPh_3)_2Cl$ with the addition of ammonium hexafluorophosphate, using 1-methylallyl alcohol as the solvent, to provide β,γ-unsaturated ketone **188** in 44% yield (eq 33). In general, the yields range from 44 to 72%, which is remarkable considering the many steps and the formation of multiple bonds in this reaction.

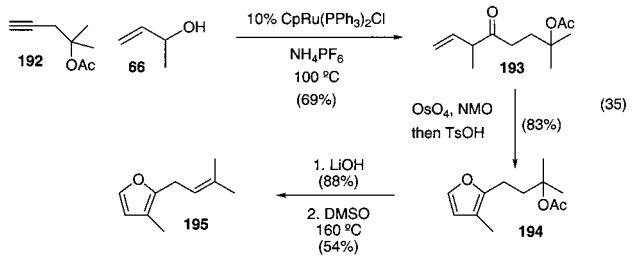


The use of excess allyl alcohol derives, in part, from its competitive redox isomerization to saturated ketone with these ruthenium catalysts. Addition of 1 equivalent of trifluoroethanol and 15 mol % of indium triflate can minimize the isomerization process. This modification allows more nearly stoichiometric amounts of allyl alcohol and alkyne to be used. As shown in eq 34, use of as little as 1.5 equivalents

of the allyl alcohol **189** produces the reconstitutive addition product (**191**) in 61% yield.[47]

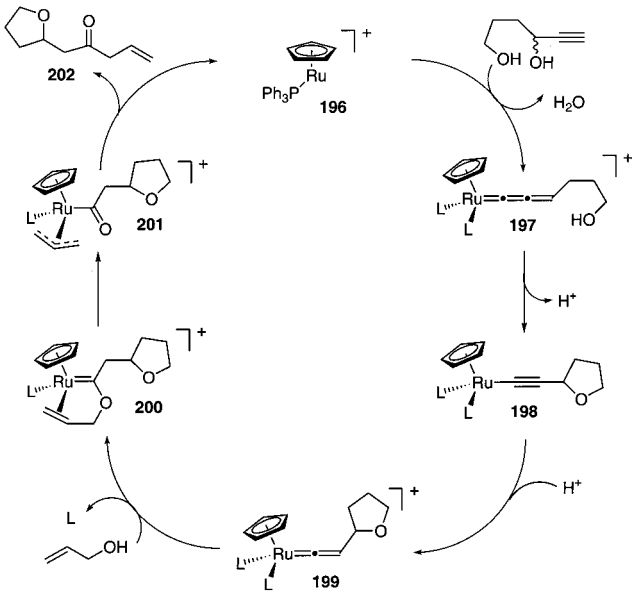


The products from the reconstitutive addition can be used in a general furan synthesis, as illustrated by a synthesis of rosefuran (eq 35).[48] Ruthenium-catalyzed condensation of alkyne **192** and methylallyl alcohol (**66**) gives ketone **193** in 69% yield. Dihydoxylation of the resulting olefin followed by acid-catalyzed cyclization then leads to furan **194**. Rosefuran (**195**) is then accessed by hydrolysis of the acetate and elimination. The reconstitutive addition has also been used as a method to form functionalized steroid side chains from ethisterone.[49] There has also been modest success rendering this reaction enantioselective using chiral cyclopentadienyl ruthenium catalysts.[50]



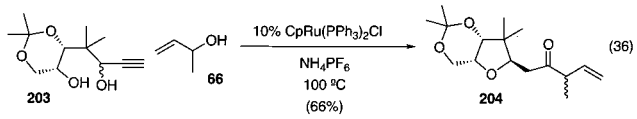
The generation of allenylidene species followed by attack is also possible using ruthenium catalysts (Scheme 16). For example, using a propargylic alcohol

Scheme 16



with another pendant alcohol, initial vinylidene formation followed by elimination of water forms the allenylidene **197**. Attack of the alcohol leads to alkynyl ruthenium species **198**. This intermediate subsequently forms ruthenium vinylidene **199**, which reacts with the allyl alcohol as described in Scheme 15.[51]

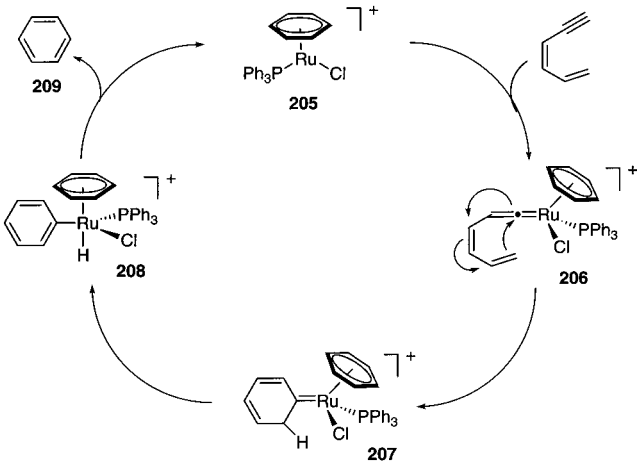
This remarkable reaction is catalyzed by 10 mol % $CpRu(PPh_3)_2Cl$, and the yields range from 59 to 72% (eq 36). For example, the reaction of propargyl alcohol **203** with methallyl alcohol (**66**) gives tetrahydrofuran **204** in 66% yield. This product is eventually converted to the spiroketal unit of (−)-calyculin A.[52]



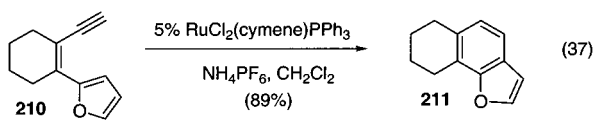
4.2. Carbon Nucleophiles

Ruthenium(2+) species can also catalyze the formation of vinylidene species which are trapped by carbon nucleophiles. Ruthenium vinylidene **206** is attacked by the olefin to afford the ruthenium carbene **207**. A 1,3-hydrogen shift provides **208**, which subsequently undergoes reductive elimination to release the arene product (**209**) and regenerate the active catalyst **205** (Scheme 17).[53]

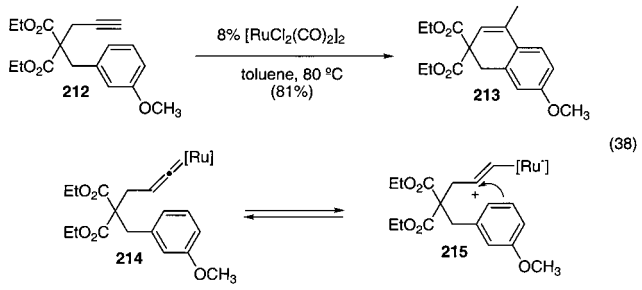
Scheme 17



The cyclization of dienyl alkyne **210** is catalyzed by 5 mol % $RuCl_2$(*p*-cymene)PPh_3 and ammonium hexafluorophosphate to give an 89% yield of arene **211** (eq 37). In general, the yields for this reaction are good (57−89%), but enol ethers, enones, and allylic alcohols are poorly tolerated as the alkene portion.

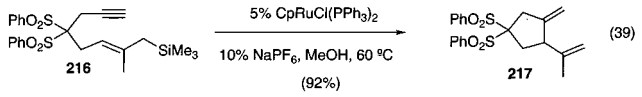


Alkynyl arene **212** can also undergo a similar cyclization, in this case catalyzed by 8 mol % $[RuCl_2(CO)_2]_2$, to afford bicyclic arene **213** in 81% yield (eq 38).[54] A significant contribution from cationic resonance structure **215** is consistent with the reactivity of the ruthenium vinylidine (**214**) toward the aromatic ring.[55]



(38)

Ruthenium catalyzes the cyclization of 1,6-alkyne-allyl silanes and stannanes to produce 1,4-dienes by a similar mechanism.[56] For example, reaction of allyl silane **216**, catalyzed by 5 mol % $CpRuCl(PPh_3)_2$, gave diene **217** in 92% yield (eq 39).

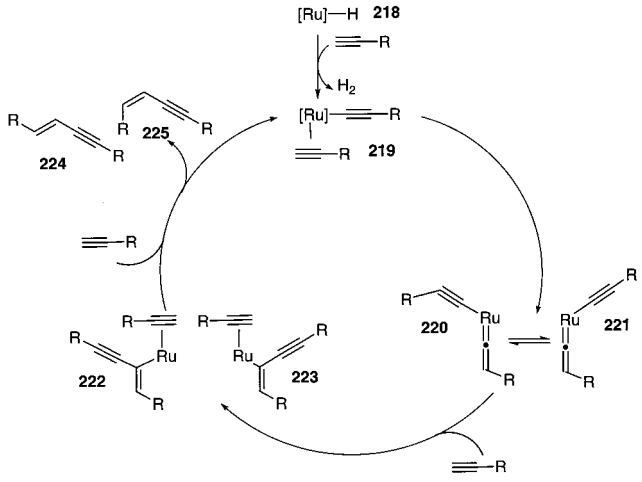


(39)

4.3. Reactions Involving Carbametalations from Ruthenium Vinylidene Species

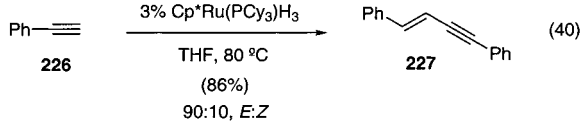
Ruthenium vinylidene complexes can also undergo carbametalation reactions.[57] As shown in Scheme 18,

Scheme 18



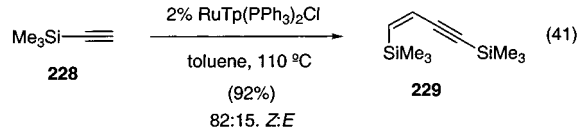
dimerization of alkynes to form enynes can proceed via this mechanism. Coordination of two equivalents of the alkyne to a ruthenium hydride leads initially to alkynyl ruthenium **219**. Two possible vinylidenes are then formed, **220** and **221**.[58] For steric reasons, **220** is generally preferred due to interactions with ligands on the metal. However, as shown below, the ratio can be changed with the use of different catalysts. Insertion into the alkyne gives vinyl ruthenium complexes **222** and **223**. These are displaced by another equivalent of alkyne to release the product (**224**/**225**) and regenerate the active catalyst.[59]

Phenylacetylene (**226**) can be dimerized to give enyne **227** in 86% yield (eq 40).[60] This reaction is catalyzed by 3 mol % $Cp^*Ru(PCy_3)H_3$ to give a good yield of predominantly the *E* isomer (**227**) as shown. Methyl propiolate can be dimerized in a similar manner.[61]



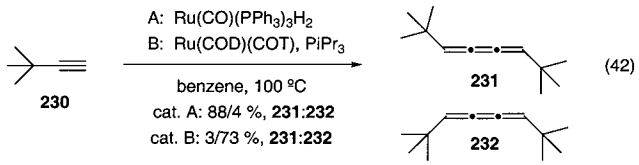
(40)

The relative propensity to form either the *E*- or *Z*-enyne is dependent on the nature of the substrate as well. When trimethylsilyl acetylene (**228**) is reacted with 2 mol % $RuTp(PPh_3)_2Cl$, a mixture of predominantly *Z* enyne **229** is obtained in 92% yield (eq 41).[62] Presumably, this selectivity arises due to steric interactions of the trimethylsilyl group with the catalyst.



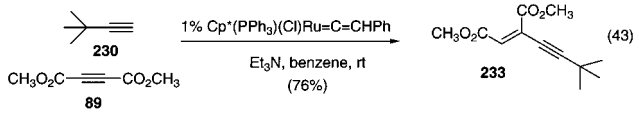
(41)

When *tert*-butylacetylene (**230**) is dimerized, initial formation of the enyne leads to cumulene formation via isomerization. Depending on the choice of catalyst, either the *E*- or *Z*-isomer of cumulene can be formed. Using $Ru(CO)(PPh_3)_3H_2$, predominantly the *E*-isomer (**231**) is formed, whereas with Ru(COD)(COT) and tributylphosphine predominantly the *Z*-isomer (**232**) is formed (eq 42).[63]



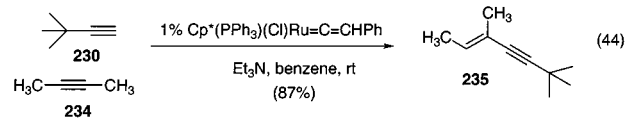
(42)

Similar ruthenium vinylidene complexes can also undergo insertion into internal alkynes to generate more substituted enynes. For example, 1 mol % of a ruthenium vinylidene species catalyzes the addition of *tert*-butylacetylene (**230**) to dimethyl acetylenedicarboxylate (**89**) to generate substituted enyne **233** in 76% yield (eq 43). A range of terminal and internal alkynes can be coupled with generally good yields (44−90%).[64]



(43)

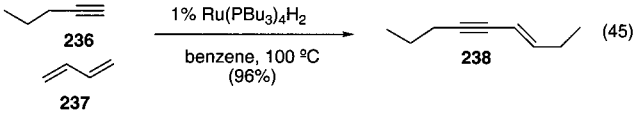
Notably, the reaction is not limited to alkynes bearing electron-withdrawing groups. For example, ruthenium-catalyzed reaction of 2-butyne (**234**) and *tert*-butylacetylene (**230**) gave enyne **235** in 87% yield (eq 44).



(44)

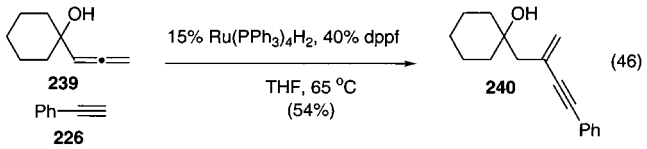
Extending the use of coupling partners, 1 mol % $Ru(PBu_3)_4H_2$ can catalyze the addition of terminal alkynes to a range of 1,3-dienes. Yields range from 31% to quantitative. For example, 1-pentyne (**236**) is added to butadiene (**237**) to generate enyne **238**

in 96% yield (eq 45).[65] The mechanism for this reaction is similar to the one outlined in Scheme 18, with initial alkyne insertion onto the 1,3-diene leading to the nonconjugated enyne. Under the reaction conditions, the olefin moves into conjugation with the alkyne.



(45)

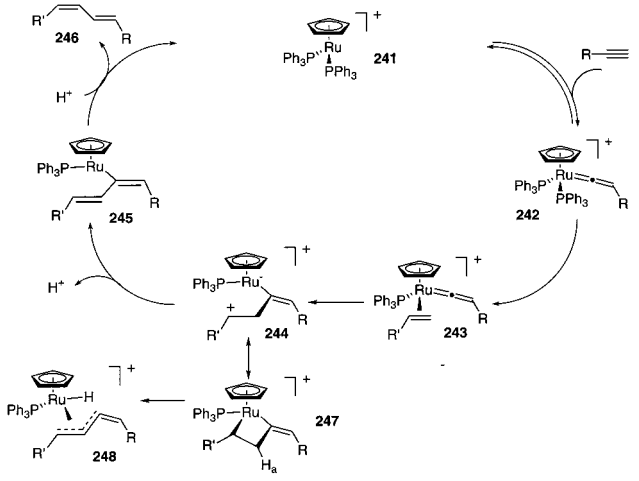
Allenes can also participate as coupling partners. Under similar reaction conditions, allenes and terminal alkynes can react, via a ruthenium vinylidene intermediate, to give enynes. For example, 15% Ru(PPh$_3$)$_4$H$_2$, with dppf as an added ligand, catalyzes the addition of phenylacetylene (**226**) to allene **239** to give enyne **240** in 54% yield (eq 46).[66]



(46)

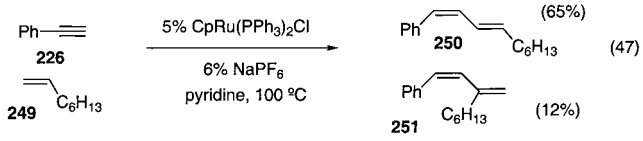
Finally, ruthenium vinylidene complexes have also been postulated as reactive intermediates in the coupling of olefins with alkynes to generate 1,3-dienes. As shown in Scheme 19, coordination of the

Scheme 19



alkyne to the coordinatively unsaturated ruthenium(+2) complex **241** leads to ruthenium vinylidene **242**. Coordination of the olefin followed by addition to the vinylidene generates complex **244**. Deprotonation of **244** produces vinylruthenium complex **245**, which undergoes protonolysis of the vinylruthenium bond to afford diene **246** and regenerate the active catalyst (**241**). An alternative mechanism, involving a ruthenacyclobutane (**247**) has also been proposed.[67] Subsequently, β-hydrogen elimination of H$_a$ generates π-allylruthenium complex **248**, which undergoes a reductive elimination to release the 1,3-diene product (**246**) and regenerate the active catalyst (**241**). However, it is difficult to envision how the ruthenium can achieve the geometry necessary for interaction with H$_a$ which is required for the β-hydrogen elimination.

An example of this process is shown in eq 47. Phenylacetylene (**226**) and 1-octene (**249**) are dimerized using 5% CpRu(PPh$_3$)$_2$Cl and pyridine to give 65% of the desired product (**250**) as well as 12% of the regioisomeric product (**251**) resulting from insertion into the other terminus of the olefin.



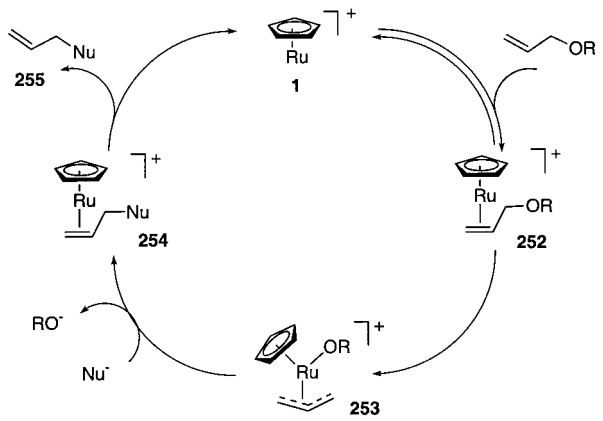
(47)

V. Reactions Involving Allyl-ruthenium Intermediates

5.1. Nucleophilic Addition to π-Allylruthenium Complexes

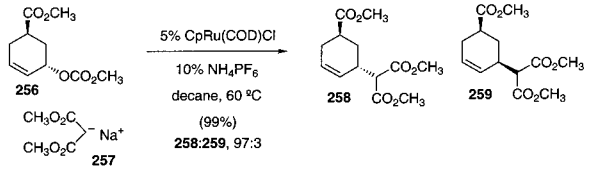
The ruthenium-catalyzed addition of carbon nucleophiles to allylic carbonates is postulated to proceed through the formation of π-allylruthenium complex **253** (Scheme 20). The catalytic cycle involves

Scheme 20



initial coordination of the cationic ruthenium(+2) catalyst to the allylic carbonate to form complex **252**. Subsequent, ionization of the allylic carbonate generates the π-allylruthenium(+4) complex **253**. Nucleophilic addition to complex **253**, followed by decomplexation of the resulting olefin, produces the allylated product **255**.

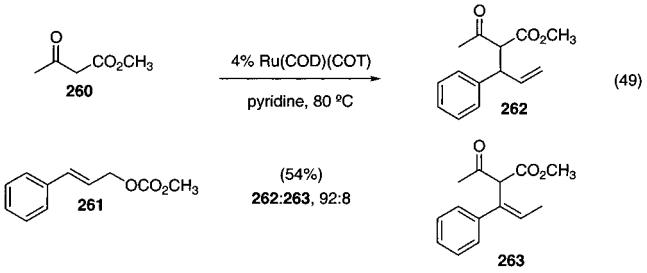
The addition of malonate **257** to allylic carbonate **256** is catalyzed by 5 mol % CpRu(COD)Cl and 10 mol % ammonium hexafluorophosphate to afford a 99% yield of a 97:3 mixture of adducts **258** and **259** (eq 48).[68] Notably, the addition of malonate occurs with retention of the stereochemistry of the original carbonate. This implies a mechanism, similar to that for palladium catalyzed allylic alkylation,[69] involving double inversion of configuration.[70]



(48)

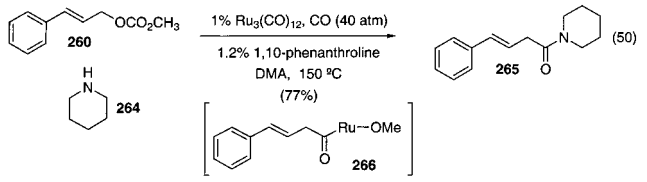
The addition of β-ketoesters to allylic carbonates is catalyzed by RuH$_2$(PPh$_3$)$_2$[71] or Ru(COD)(COT).[72]

The latter catalyzes the addition of nucleophiles to cinnamyl carbonate **261** with a bias for the addition to the more substituted terminus of the ruthenium π-allyl. For example, the Ru(COD)(COT) catalyzed addition of methyl acetoacetate (**260**) to cinnamyl carbonate **261** affords a 54% yield of a 92:8 mixture of adducts **262** and **263** (eq 49).



(49)

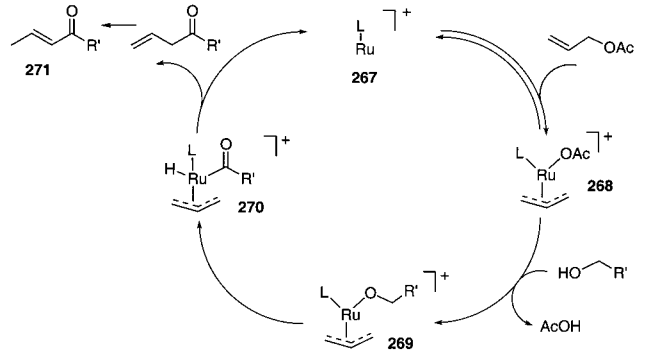
In the presence of carbon monoxide, π-allylruthenium complexes can be carbonylated to produce acylruthenium species such as **266** (eq 50).[73,74] Nucleophilic addition of amines to **266** results in the formation of an amide. For example, the Ru_3CO_{12} catalyzed reaction of cinnamyl carbonate **260** with piperidine (**264**), under 40 atm of CO, gave β,γ-unsaturated amide **265** in 77% yield.



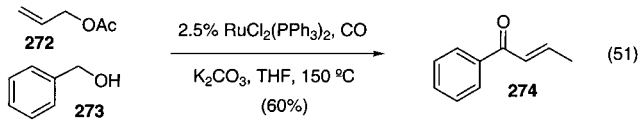
(50)

Alcohols react with π-allylruthenium complexes (**268**) by a different mechanism (Scheme 21).[75] Nucleophilic addition of alcohols occurs on the ruthenium, rather than on the allyl ligand, to generate π-allylruthenium complex **269**. Complex **269** undergoes a β-hydrogen elimination to produce acylruthenium complex **270**. Reductive elimination of **270** forms a β,γ-unsaturated ketone, which subsequently, isomerizes to the α,β-unsaturated ketone (**271**).

Scheme 21



The reaction in Scheme 21 is catalyzed by 2.5 mol % $RuCl_2(PPh_3)_3$ in THF under carbon monoxide. For example, the ruthenium-catalyzed reaction of 5 equivalents of allyl acetate (**272**) with benzyl alcohol (**273**) furnished α,β-unsaturated ketone **274** in 60% yield (eq 51).

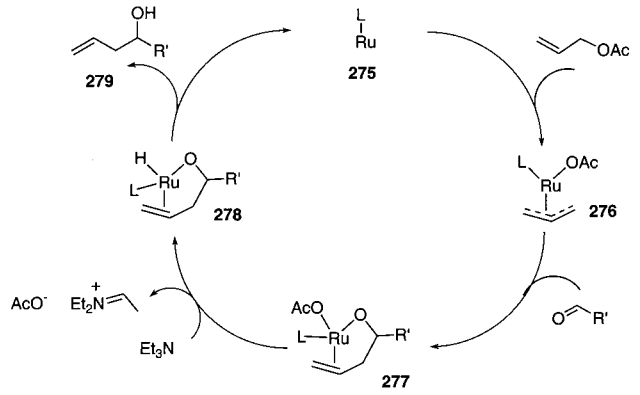


(51)

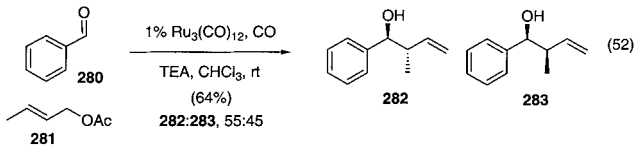
5.2. Electrophilic Addition to π-Allylruthenium Complexes

Unlike most other π-allylmetal complexes, the wide range of oxidation states energetically accessible to ruthenium allows π-allylruthenium complexes to demonstrate nucleophilic, as well as electrophilic, behavior. The ruthenium-catalyzed addition of allylic acetates to aldehydes is postulated to occur via a π-allylruthenium complex **276** which shows nucleophilic character (Scheme 22).[76,77] Addition of an aldehyde to complex **276** is postulated to occur by direct insertion into the π-allyl complex to provide **277** rather than by addition (via allyl inversion) of the σ-allyl complex to the aldehyde. Coordination of the tertiary amine to complex **277** and subsequent β-hydrogen elimination generates hydridoruthenium complex **278.** Reductive elimination of **278** releases the homoallyl alcohol product (**279**) and regenerates the ruthenium catalyst (**275**).

Scheme 22



The allylation of aldehydes with allylic acetates is catalyzed by Ru_3CO_{12} in the presence of 3 equiv of triethylamine and under an atmosphere of carbon monoxide. For example, the addition of crotyl acetate (**281**) to benzaldehyde (**280**) affords a 64% yield of a 55:45 mixture of homoallyl alcohols **282** and **283** (eq 52). The poor diastereoselectivity of the reaction is consistent with the suggestion that the nucleophilic addition does not proceed through an σ-allyl inversion, which would require a six-membered ring transition state. Notably, carbon−carbon bond formation occurs exclusively at the more substituted carbon of the π-allylruthenium complex.

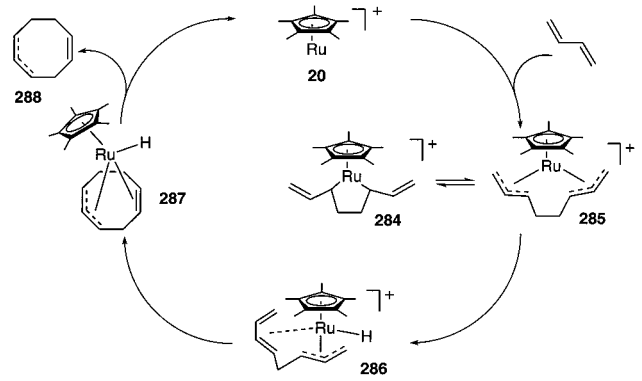


(52)

5.3. Carbometalation by Allyl-Ruthenium Complexes

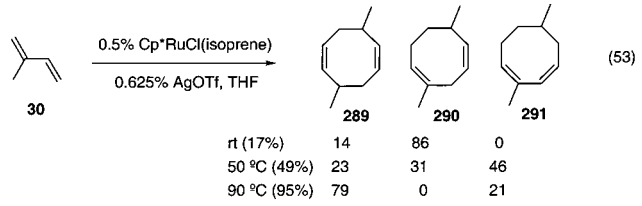
The homo-coupling of dienes is postulated to proceed through π-allylruthenium complexes **285** and **286** (Scheme 23).[78] Oxidative coupling of two dienes

Scheme 23

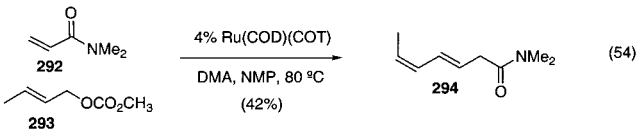


produces bis-π-allylruthenium complex **285**, which undergoes a β-hydrogen elimination to generate π-allylcomplex **286**. An 8-*endo*-trig carboruthenation produces (η^5-cyclooctadienyl) ruthenium hydride **287**. Subsequent reductive elimination gives the 1,4- and 1,5-cyclooctadiene products (**288**) and regenerates the ruthenium catalyst (**20**).

The dimerization of isoprene (**30**) is catalyzed by 0.5 mol % Cp*RuCl(isoprene) and cocatalyzed by 0.625 mol % silver triflate (eq 53).[78] The ratio of dienes derived from this reaction is temperature dependent. When the reaction is carried out at room temperature, the expected mixture (see Scheme 21) of 1,4- (**289**) and 1.5-dienes (**290**) is observed. As the temperature is increased to 90 °C, a greater amount of the 1,5-cyclooctadiene (**289**) is obtained.

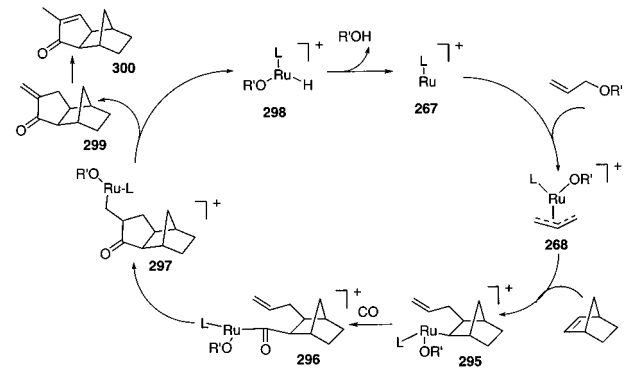


The ruthenium-catalyzed coupling of allyl carbonates and α,β-unsaturated esters and amides is also postulated to occur via a π-allylruthenium complex (eq 54).[79] The mechanism is proposed to involve intermolecular carbaruthenation of the $\alpha-\beta$-unsaturated esters or amides, followed by β-hydrogen elimination of the resulting ruthenium enolate. The initial 1,4-diene adduct is proposed to undergo isomerization to the 1,3-diene product. Interestingly, it is also suggested that the formation of a *cis*-olefin derives from the increased reactivity of the *anti*-π-allylruthenium complex in the carbametalation step. For example, Ru(COD)(COT) catalyzed reaction of crotyl carbonate (**293**) and acrylamide (**292**) gave diene **294** in 42% yield. Notably, in contrast to the addition of aldehydes (eq 52), addition of acrylamide occurs selectively to the less substituted terminus of the π-allylruthenium intermediate.



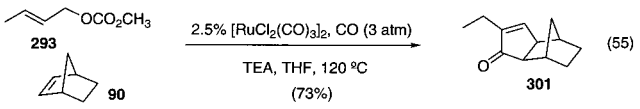
Ruthenium π-allyl complexes can also carbametalate unactivated olefins (Scheme 24).[80] Norbornene

Scheme 24



undergoes *syn*-carbametalation by π-allylruthenium complex **268** to generate intermediate **295**. Unlike the above example, complex **295** cannot undergo *syn*-β-hydrogen elimination. A migratory insertion of carbon monoxide gives acylruthenium complex **296**, which undergoes a 5-*exo*-trig carbaruthenation to provide **297**.[81] A β-hydride elimination gives α,β-unsaturated cyclopentanone **299** which further isomerizes to **300**. The alkoxyruthenium hydride (**298**), generated from β-hydrogen elimination, undergoes a reductive elimination to regenerate the catalyst (**267**) along with an equivalent of alcohol.

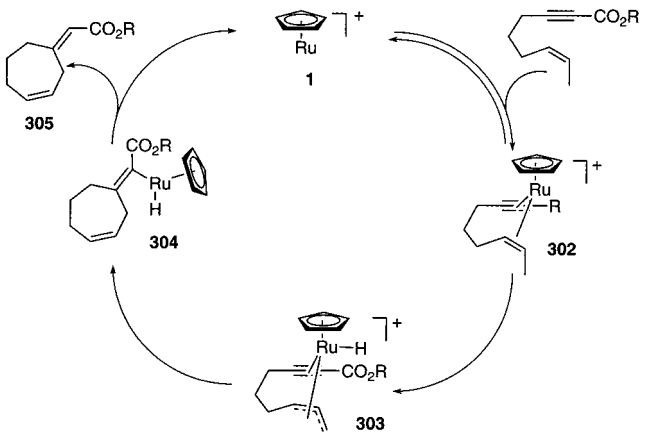
The reaction detailed in Scheme 24 is catalyzed by 2.5 mol % $[RuCl_2(CO)_3]_2$ under 3 atm of carbon monoxide (eq 55). Under these conditions, a number of norbornene-cyclopentenones are obtained in 65−95% yield with complete *exo* selectivity. For example, the ruthenium-catalyzed reaction of methylcrotyl carbonate (**293**) with norbornene (**90**) gave cyclopentenone **301** in 73% yield. As in eq 44, addition of norbornene occurs selectively to the unsubstituted terminal carbon of the π-crotylruthenium intermediate



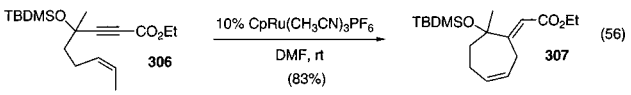
The ruthenium-catalyzed intramolecular coupling of alkenes and alkynoates to form seven-membered rings is also postulated to occur via a π-allylruthenium intermediate (Scheme 25).[82] The reaction is initiated by activation of the allylic C−H to form π-allylruthenium complex **303.** A 7-*exo*-dig carboruthenation of the alkynoate produces (hydrido)-ruthenium enolate **304**. Equilibration of **304** followed by β-hydrogen elimination furnishes cycloheptene **305** and regenerates the cationic ruthenium(+2) catalyst (**1**).

Ruthenium-catalyzed formation of cycloheptenes from the cycloisomerization of alkenes and alkynoates

Scheme 25



is catalyzed by 10 mol % $CpRu(CH_3CN)_3PF_6$ in DMF at room temperature (eq 56). Under these conditions, seven-membered rings are formed in 53−83% yield. For example, the ruthenium-catalyzed reaction of 1,6-enyne **306** gave cycloheptene **307** in 83% yield.

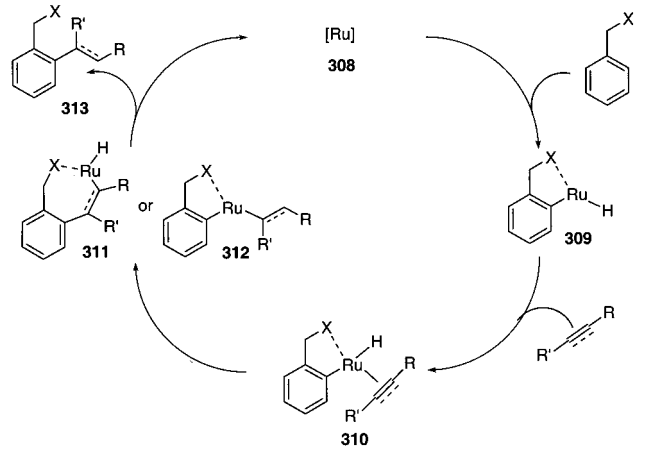


VI. Reactions Involving C–H Activation

6.1. Activation of Aromatic C–H

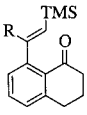
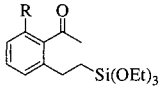
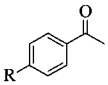
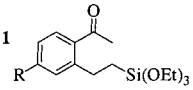
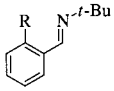
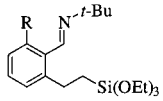
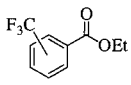
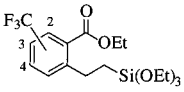
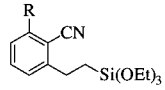
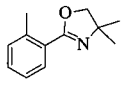
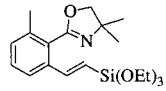
Regio- and chemoselective addition of alkenes and alkynes to aromatic compounds can be accomplished by ruthenium-catalyzed aromatic C−H bond activation (Scheme 26).[83] The oxidative addition of coordinatively unsaturated ruthenium into the sp^2 C−H occurs with the aid of chelation from an *ortho*-coordinating functional group. The resulting arylruthenium hydride (**309**) can add to an alkene or an alkyne by one of two pathways. Carbaruthenation of the alkene or alkyne gives hydridoruthenium intermediate **311** which undergoes a reductive elimination to give the coupling product **313**. Alternatively, hydroruthenation gives the arylruthenium species **312**, which can also undergo reductive elimination to give adduct **313** and regenerate the ruthenium catalyst (**308**).

Scheme 26



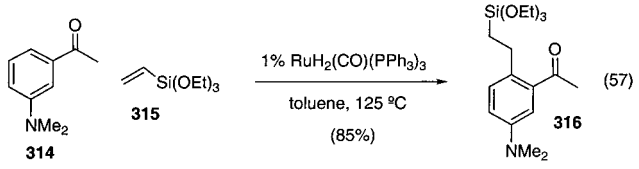
A variety of functional groups can serve to direct the *ortho*-C−H activation by ruthenium (Table 5).

Table 5. Ruthenium-Catalyzed Coupling of Aromatic C-H Bonds[a]

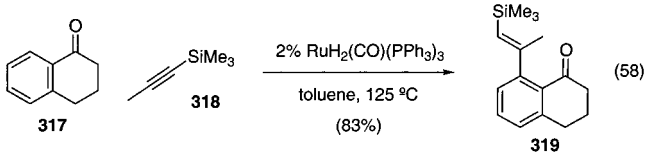
Ar-H	olefin/alkyne	catalyst	Product(s) (yield)
		1	 R = Me (83%) R = C_6H_{13} (100%) 11:1 *E*:*Z* R = Ph (76%) 2:1 *E*:*Z*
		1	 R = H (80%) R = CF_3 (92%) R = OMe (11%) R = CH_3 (100%)
		1	 R = NMe_2 -- R = CF_3 (63%) R = CN (88%) R = CH_3 (69%)
		2	 R = H (78%) R = CF_3 (75%) R = F (79%) R = CH_3 (81%)
		1	 2-CF_3 (97%) 3-CF_3 (95%) 4-CF_3 (48%)
		1	 R = CH_3 (97%) R = CF_3 (95%) R = Ph (95%) R = *i*-Pr (100%)
		2	 (97%)

[a] Catalyst: **1** = $Ru(H)_2(CO)(PPh_3)_3$, **2** = $Ru_3(CO)_{12}$.

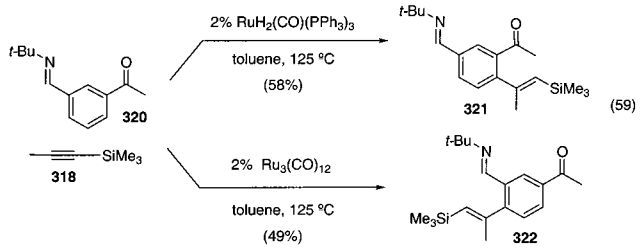
The most common functional group is an *ortho* ketone. For example, the reaction of ketone **314** with vinyl silane **315**, catalyzed by $RuH_2(CO)(PPh_3)_3$, affords *ortho*-alkylated ketone **316** in 85% yield (eq 57).[84] Notably, the reaction generally shows excellent control of regioselectivity for activation of the aromatic C−H at the less hindered *ortho*-position.



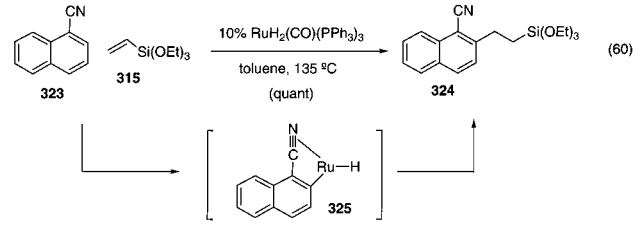
The *ortho*-vinylation of ketones is also possible by replacing the vinyl silane with an alkyne.[85] For example, the $RuH_2(CO)(PPh_3)_3$ catalyzed reaction of α-tetralone (**317**) with acetylene **318** gave vinylsilane **319** in 83% yield and with complete control of olefin geometry (eq 58). In some cases, the vinylsilane products react further with the ketone to produce cyclopentenols.[86]



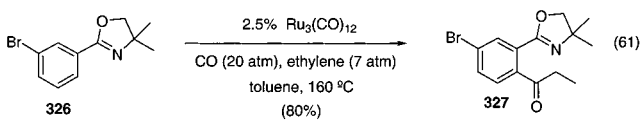
The imines can also serve as directing groups for the ruthenium-catalyzed *ortho*-alkylation of arenes. In the case of imines, $Ru_3(CO)_{12}$ is the preferred catalyst.[87] This allows for the differentation of aromatic C−H bonds *ortho* to ketones or imines by simply changing the catalyst.[88] For example, the $RuH_2(CO)(PPh_3)_3$ catalyzed reaction of **320** with acetylene **318** gave vinylsilane **321** in 58% yield (eq 59). Changing the catalyst to $Ru_3(CO)_{12}$ results in the regioselective formation of vinyl silane **322** in 49% yield. It appears that in the $RuH_2(CO)(PPh_3)_3$ catalyzed reaction polar factors dominate, whereas in the $Ru_3(CO)_{12}$ catalyzed reaction coordination becomes more important.



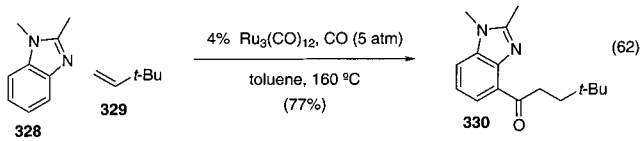
Other functional groups, such as esters,[89] nitriles,[90] cyclic imidates,[91] and secondary amines,[92] can also serve as directing groups for the ruthenium-catalyzed *ortho*-vinylation and alkylation. For example, reaction of 1-cyanonaphthalene (**323**) and vinylsilane **315**, catalyzed by 10 mol % $RuH_2(CO)(PPh_3)_3$, afforded **324** in quantitative yield as single regioisomer (eq 60). The directing ability of the nitrile group is particularly interesting since it implies edge coordination of the cyano group, as in complex **325**, to the ruthenium.



In the presence of carbon monoxide, insertion of carbon monoxide into the arylruthenium hydride (**309**) occurs prior to the addition of the olefin.[93] For example, the $Ru_3(CO)_{12}$ catalyzed reaction of phenyloxazoline **326** with carbon monoxide (20 atm) and ethylene (7 atm) produces ethyl ketone **327** in 80% yield (eq 61).



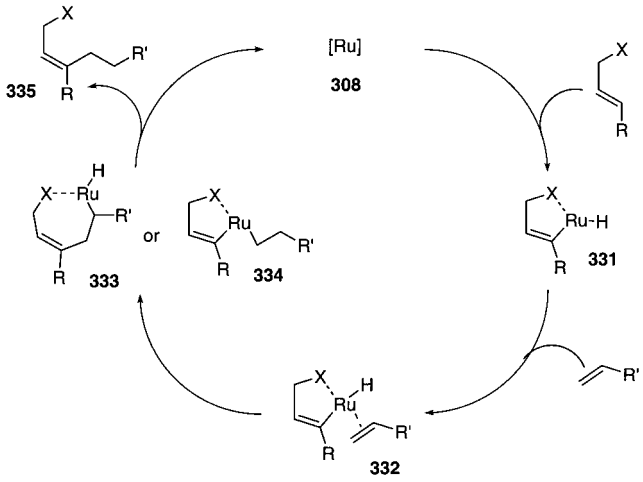
Heterocyclic compounds also serve as substrates for the ruthenium-catalyzed sp^2-C−H activation.[94] For example, the $Ru_3(CO)_{12}$ catalyzed reaction of benzimidazole **328** with alkene **329** under carbon monoxide (5 atm) affords ketone **330** in 77% yield (eq 62).



6.2. Activation of Vinylic C–H

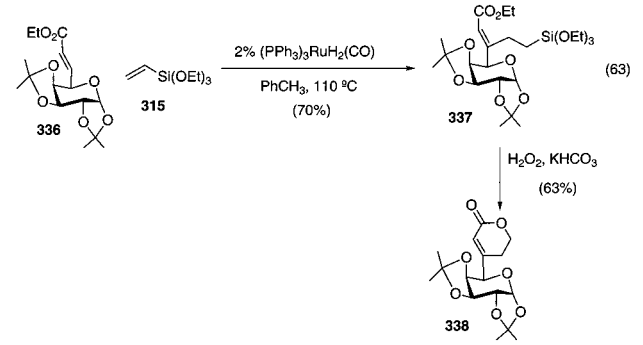
Ruthenium-catalyzed activation of vinylic C−H bonds proceeds through a mechanism similar to that described for the activation of aromatic C−H bonds (Scheme 27). Insertion of coordinatively unsaturated

Scheme 27



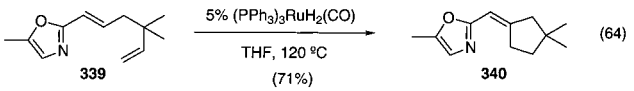
ruthenium into the sp^2-C−H, aided by coordination to a vinylic activating group, provides vinylruthenium hydride **331**. Coordination of the olefin to **331** is followed by either carbaruthenation or hydroruthenation to provide **333** or **334**, respectively. A reductive elimination of either **333** or **334** affords the alkylated olefin **335** and regenerates the ruthenium catalyst (**308**).

The mechansim detailed in Scheme 27 is proposed to be operative in the ruthenium-catalyzed heterocoupling of α,β-unsaturated esters and ketones to alkenes (eq 63).[95] For example, $RuH_2(CO)(PPh_3)_3$ catalyzes the addition of ethyl ester **336** to vinyl silane **315** to afford **337** in 70% yield. Oxidative cleavage of silane **337** afforded lactone **338**.

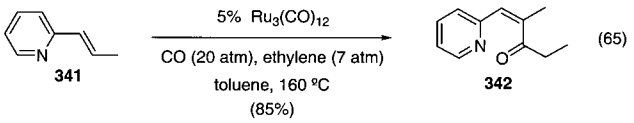


Vinyl pyridines, imidazoles, and oxazoles also undergo selective activation of the vinylic C−H (eq 64).[96] For example, $RuH_2(CO)(PPh_3)_3$ catalyzed reaction of 1,5-diene **339** affords methylenecyclopentane **340** in 71% yield. The reaction presumably proceeds by activation of the vinylic C−H of the olefin attached

to the oxazole ring, followed by intramolecular hydroruthenation of the terminal alkene.



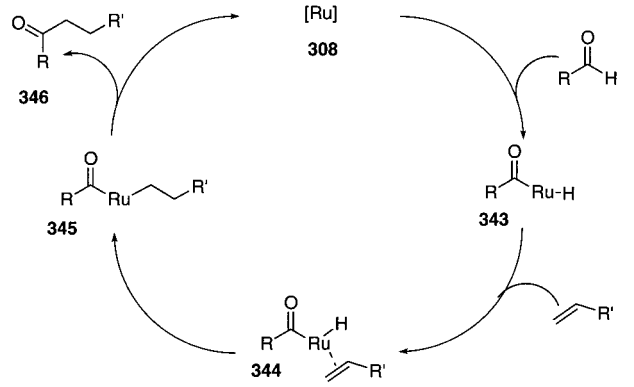
When the ruthenium-catalyzed reaction of vinylpryidines and alkenes is performed under an atmosphere of carbon monoxide, α,β-unsaturated ketones are produced (eq 65).[97] For example, $Ru_3(CO)_{12}$ catalyzed reaction of vinylpyridine **341** with carbon monoxide (20 atm) and ethylene (7 atm) furnishes ethyl ketone **342** in 85% yield.



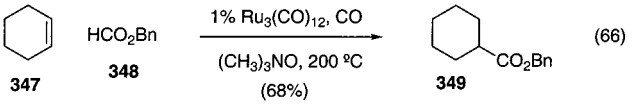
6.3. Activation of Aldehydic C–H

Coordinatively unsaturated ruthenium complexes can also insert into aldehydic sp^2-C−H bonds to generate an acylruthenium hydride (**343**) (Scheme 28). After coordination of the alkene, a hydroruthenation produces acylruthenium complex **345**. A reductive elimination of **345** furnishes the product **346** and regenerates the coordinatively unsaturated ruthenium catalyst (**308**).

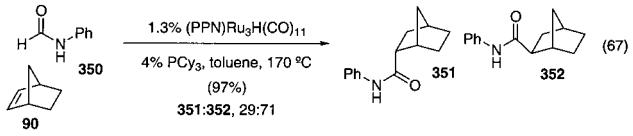
Scheme 28



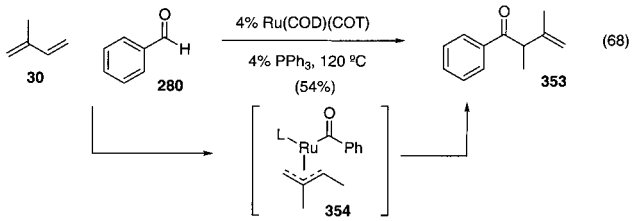
A variety of ruthenium complexes have been described that catalyze the addition of formates to olefins. These include $RuCl_2(PPh_3)_3$,[98] $RuCl_3$-Et_4NI,[99] $Ru_3(CO)_{12}$,[100] $Ru_3(CO)_{12}$-$(PPh_3)_4NCl$,[101] $Ru_3(CO)_{12}$-$(CH_3)_3NO$,[102] $Ru_3(CO)_{12}$-$(n\text{-}C_4H_9)_3P$,[103] and RuH_2-$(PPh_3)_4$.[104] For example, the $Ru_3(CO)_{12}$-$(CH_3)_3NO$ catalyzed reaction of cyclohexene (**347**) and benzylformate (**348**) produced ester **349** in 68% yield (eq 66).



Formamides are also substrates for the ruthenium-catalyzed aldehydic-like C−H activation.[105] For example, $[Ru_3H(CO)_{11}]^-[PPN]^+$ [PPN = bis(triphenylphosphine) iminium)] catalyzed reaction of *N*-formylaniline (**350**) with norbornene (**90**) gave a 97% yield of a 29:71 mixture of *endo*:*exo* amides (eq 67). Notably, utilizing these conditions, the reaction does not have to be carried out under carbon monoxide pressure.



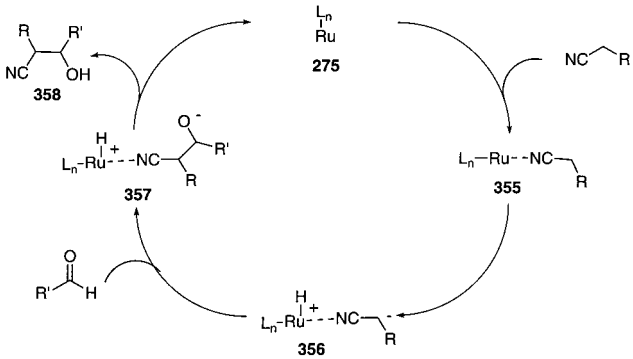
Ruthenium-catalyzed addition of aldehydes to olefins[106] and dienes[107] also proceeds through activation of the aldehydic C−H. For example, Ru(COD)(COT) catalyzed addition of benzaldehyde (**280**) to isoprene (**30**) affords β,γ-unsaturated ketone **353** in 54% yield (eq 68). Notably, formation of the new C−C bond occurs regioselectively to only one of the four carbons of isoprene. This requires chemoselective hydroruthenation of the less substituted olefin to produce π-allylruthenium complex **354** and regioselective reductive elimination to form the C−C bond at the more substituted terminus of the π-allyl.



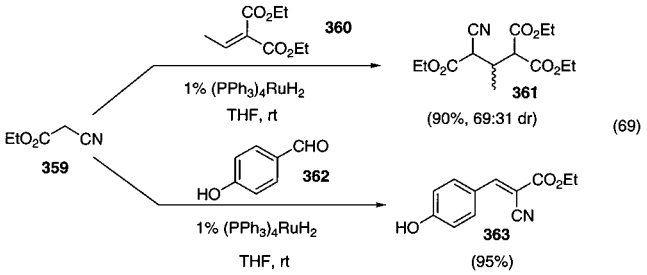
6.4. Reactions Involving sp^3-CH Activation

Ruthenium complexes can also activate the C−H bond of sp^3-carbons adjacent to an activating group. The most common activating group is a nitrile (Scheme 29).[108] The reaction is initiated by coordination of a coordinatively unsaturated ruthenium complex **275** with the nitrile to produce **355**. Oxidative addition of the ruthenium into the α-C−H bond of the nitrile generates hydrido ruthenium complex **356**. Addition of the enolate ligand to an aldehyde (or a Michael acceptor) produces hydrido ruthenium complex **357**, which undergoes a reductive elimination to afford the alcohol product (**358**) and regenerate the coordinatively unsaturated ruthenium catalyst (**275**).

Scheme 29

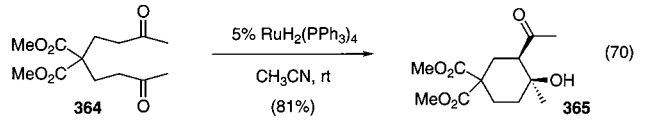


The addition of nitriles to aldehydes or Michael acceptors is catalyzed by either $RuH_2(PPh_3)_4$[109] or $CpRuCl(PPh_3)_2$.[110] For example, $RuH_2(PPh_3)_4$ catalyzed addition of cyanoester **359** to acrylate **360** gave Michael adduct **361** in 90% yield and modest diastereoselectivity (69:31) (eq 69). The addition of cyanoester **359** to aldehyde **362** is also catalyzed by 1 mol % $RuH_2(PPh_3)_4$ to afford acrylate **363** in 95% yield.



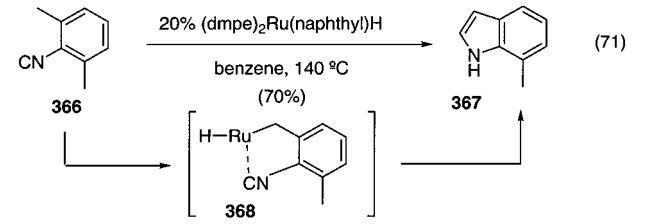
(69)

Ruthenium complexes also catalyze the aldol and Michael addition of ketones and esters (eq 70).[111] For example, $RuH_2(PPh_3)_4$ catalyzed reaction of 1,7-diketone **364** produces a single diastereomer of α-hydroxyketone **365** in 81% yield.



(70)

The synthesis of indoles from *ortho*-tolylisocyanide is catalyzed by 20 mol % $(dmpe)_2Ru(naphthyl)H$.[112] For example, the ruthenium-catalyzed reaction of isocyanide **366** gave indole **367** in 70% yield (eq 71). The reaction is postulated to proceed through activation of the benzylic C−H to provide hydridoruthenium complex **368**.



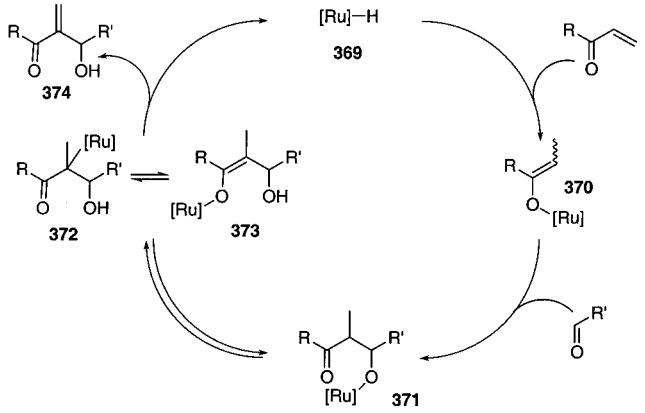
(71)

Ruthenium complexes have also been shown to C−H activate benzylic[113] and allylic[114] amines followed by insertion into olefins.

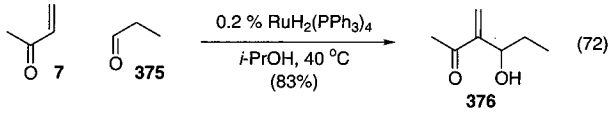
VII. Reactions Initiated by Hydrometalations

Ruthenium hydride catalysts can also initiate a variety of catalytic cycles that lead to C−C bond formation. For example, a ruthenium(+2) hydride catalyst can undergo a hydrometalation of an enone to generate ruthenium enolate **370**. This enolate can then be trapped by an aldehyde in an aldol reaction to give ruthenium alkoxide **371**. Isomerization and β-hydrogen elimination releases the product, a Baylis−Hillman adduct (**374**), and regenerates the active ruthenium catalyst (**369**) (Scheme 30).[115]

Scheme 30



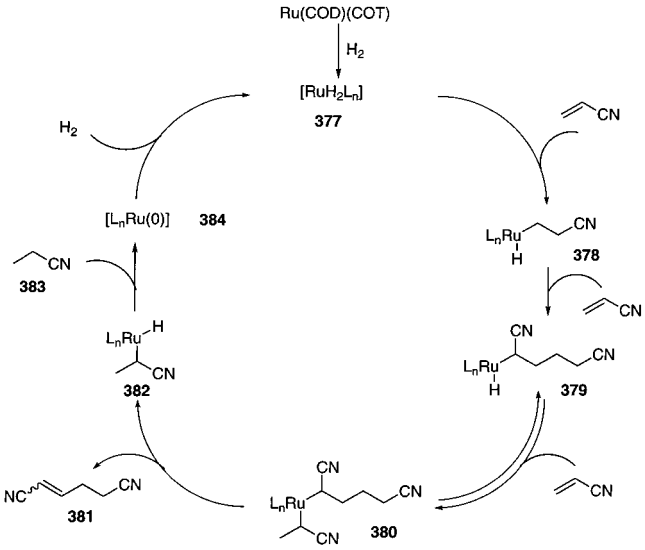
For example, 0.2 mol % $RuH_2(PPh_3)_4$ catalyzes the hydrometalation of methyl vinyl ketone (**7**), which then undergoes an aldol reaction with propanal (**375**) to give the adduct **376** in 83% yield (eq 72).



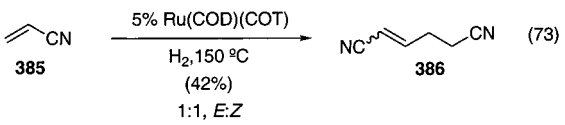
(72)

Ruthenium-catalyzed hydrometalation can also lead to other catalytic pathways, such as the dimerization of acrylonitrile (Scheme 31).[116] The catalytically active ruthenium hydride species (**377**) is generated by addition of hydrogen to a catalyst precursor. Hydrometalation of acrylonitrile generates alkylruthenium hydride **378**. This complex inserts another equivalent of the olefin to generate **379**. A further hydroruthenation generates species **380**, which then undergoes a β-hydride elimination and a reductive elimination to give the dimerized product **381** and an equivalent of propionitrile (**383**).[117]

Scheme 31

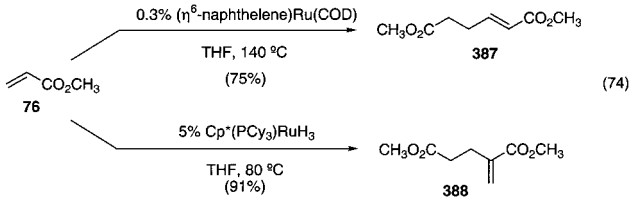


An example of this process is shown in eq 73, where 5 mol % Ru(COD)(COT) is used as the catayst precursor which is activated by addition of hydrogen. A 1:1 mixture of *E*:*Z* olefin isomers (**386**) is obtained, due to lack of selectivity in the β-hydrogen elimination step from **380** (Scheme 31).



(73)

A similar mechanism may be operative in the preparation of tail-to-tail dimerization of acrylates[118] or acrolein.[119] For example, the ruthenium-catalyzed dimerization of methyl acrylate (**76**) produces diester **387** in 75% yield (eq 74). Interestingly, when 5 mol % of Cp*(PCy_3)RuH_3 is employed as catalyst the head-to-tail dimer (**388**) of methyl acrylate is obtained in 91% yield.[120] The difference in regioselectivity may be a result of the reaction proceeding by different mechanism. Aside from the hydrometalation mechanism (Scheme 31), a mechanism involving a metallacyclopentane intermediate (Scheme 3) or vinyl C−H activation (Scheme 27) can be envisioned.

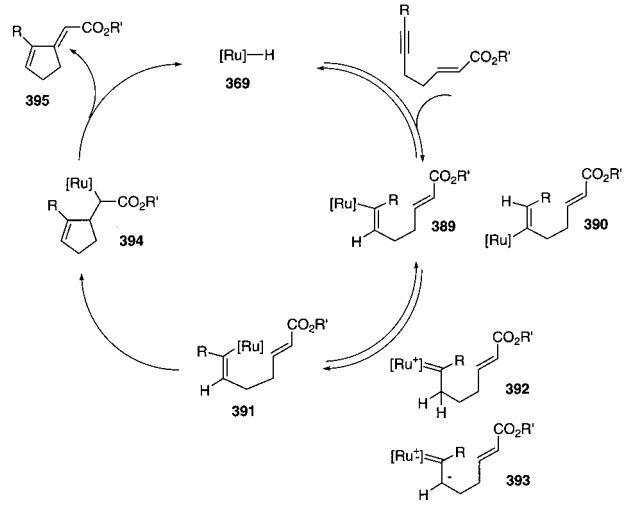


(74)

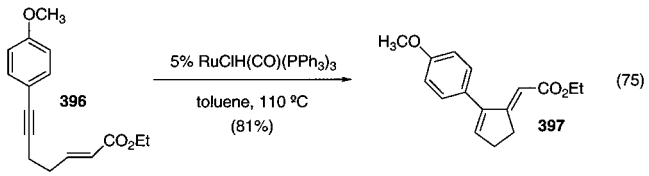
Ruthenium hydride species have also been postulated as catalysts in a number of cycloisomerization reactions, including those involving enynes as well as dienes. For example, ruthenium hydride catalyzes the hydrometalation of 1,5-enyne to initially generate vinyl ruthenium complex **389**. Presumably, the regioisomeric vinyl ruthenium complex **390** is also formed. However, since the hydrometalation is reversible and **390** cannot undergo a facile carbometalation of the pendant acrylate, products derived from **390** are not observed. The vinyl ruthenium complex also cannot readily undergo an intramolecular carbometalation, however, it can interconvert to isomeric vinyl ruthenium complex **391**. The isomerization may proceed by a process involving protonation−deprotonation (via **392**). Alternatively, the importance of resonance form **393** may be responsible for the low energy barrier for the isomerization of **389** to **391**. Vinylruthenium complex **391** undergoes a 5 exo-*trig* carbometalation to generate ruthenium enolate **394**. A β-hydrogen elimination releases the 1,3-diene **395** product and regenerates the active ruthenium catalyst (**369**) (Scheme 32).

An example of this process is shown in eq 75. Cyclization of 1,5-enyne **396** with 5 mol % RuClH(CO)(PPh_3)$_3$ leads to cyclopentene **397** in 81% yield.[121] Notably, an α,β-unsaturated ester, not a simple

Scheme 32



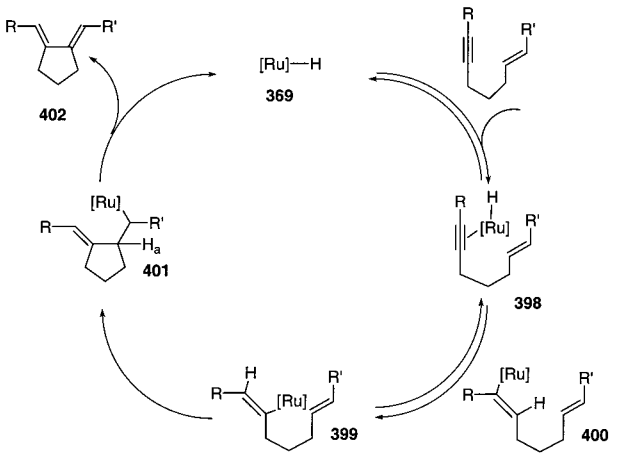
alkene, appears to be required for this reaction to proceed.



(75)

The ruthenum-catalyzed cycloisomerization of 1,6-enynes proceeds by an analogous mechanism (Scheme 33). Hydroruthenation of the alkyne provides vinyl-

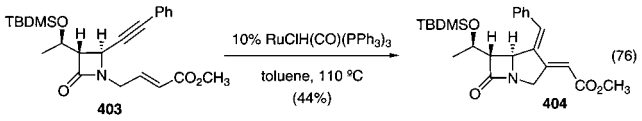
Scheme 33



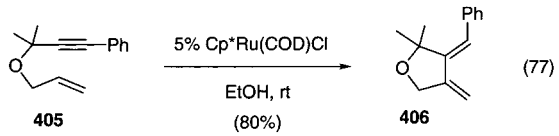
ruthenium complex **399**, which undergoes a 5-*exo*-trig cyclization to produce alkylruthenium intermediate **401**. The hydroruthenation reaction can produce regioisomeric vinylruthenium complexes **399** and **400**. Presumably, this hydrometalation reaction is reversible and only vinylruthenium complex **399** leads to a productive cyclization. A β-hydrogen elimination of H_a in complex **401** produces the 1,3-diene product (**402**) and regenerates the ruthenium hydride catalyst (**369**).

The process in Scheme 33 can be catalyzed by 10 mol % RuClH(CO)(PPh_3)$_3$ in refluxing toluene (eq 76).

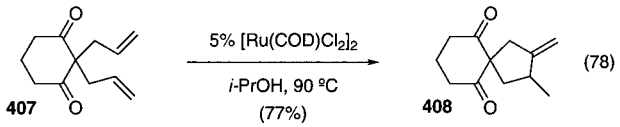
For example, ruthenium-catalyzed cycloisomerization of 1,6-enyne **403** provides the carbapenam skeleton **404** in 44% yield.[122]



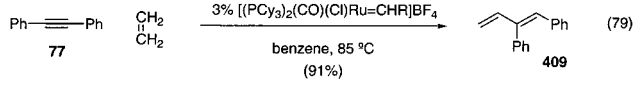
The combination of ruthenium(+2) and an alcohol or carboxylic acid can also generate the ruthenium hydride (**369**) necessary for the cycloisomerization of 1,6-enynes. For example, reaction of aryl propargyl ether **405** with 5 mol % Cp*Ru(COD)Cl in ethanol gave 3,4-dimethylenetetrahydrofuran **406** in 80% yield (eq 77).[123]



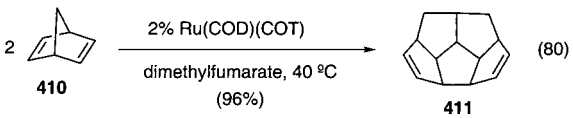
A related catalyst system has been applied to the cycloisomerization of 1,6-dienes to generate *exo*-methylenecyclopentanes in 77−86% yield. For example, 5 mol % $[Ru(COD)Cl_2]_2$, which along with the added 2-propanol generates a ruthenium hydride species, catalyzes the cyclization of diene **407** to give the bicyclic system **408** in 77% yield (eq 78).[124]



Intermolecular reactions between alkynes and alkenes are also possible. Diphenylacetylene (**77**) and ethylene react with a ruthenium hydride catalyst to give the 1,3-diene **409** in 91% yield (eq 79).[125] The postulated mechanism for this reaction is similar to the mechanisms outlined in Schemes 32 and 33. Hydrometalation of the alkyne leads to a vinyl ruthenium complex, which can insert into the olefin. Subsequently, β-hydrogen elimination gives the product and regenerates the active catalyst.

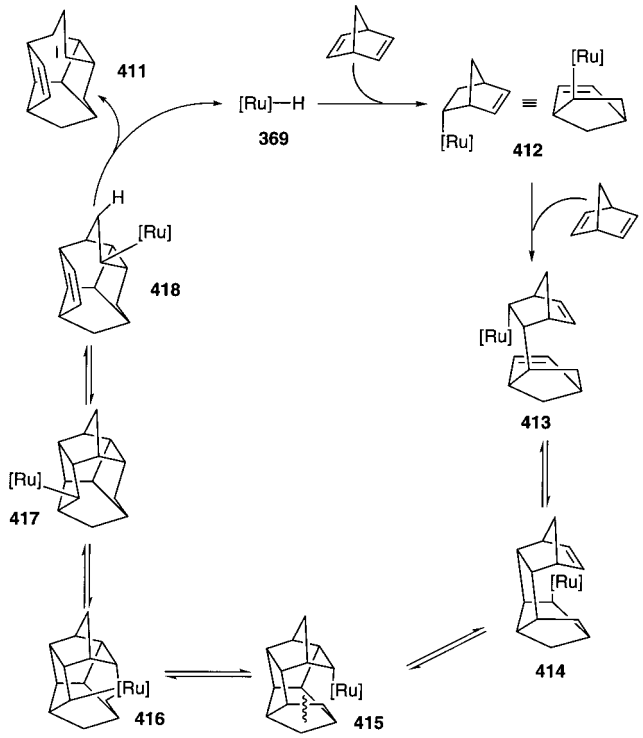


Finally, a ruthenium hydride species is implicated in the remarkable reaction involving the dimerization of norbornadiene (**410**) to generate pentacyclotetradeca-4,11-diene **411** (eq 80).[126] As shown, an exceptional yield (96%) is obtained, utilizing 2 mol % Ru(COD)(COT) as the ruthenium hydride catalyst precursor.



The proposed mechanism for this reaction is outlined in Scheme 34. Initial hydrometalation of norbornadiene gives alkyl ruthenium complex **412**.

Scheme 34

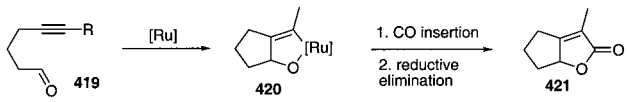


Insertion of **412** into the olefin of another equivalent of norbornadiene gives **413**, which undergoes intramolecular carbametalation of the other norbornadiene olefin to produce pentacyclic system **414**. Alkyl ruthenium intermediate **414** undergoes a second 5-*exo*-trig carboruthenation to generate **415**. At this point, ruthenium inserts in the C−C bond indicated to generate trialkyl ruthenium complex **416**. Reductive elimination forms a new C−C bond to give **417**. A β-carbon elimination generates **418**, which contains the first olefin found in the product. Finally, a β-hydrogen elimination gives the product (**411**) and regenerates the active ruthenium hydride catalyst (**369**).

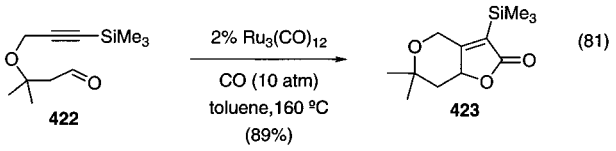
VIII. Reactions Involving Carbonylations

Ruthenium carbonyl complexes have been shown to catalyze a number of carbonylation reactions. In general, these reactions proceed via CO insertion pathways. For example, ruthenium can catalyze the cyclization of yne-als (**419**) to give oxometallacycles (**420**), which can insert carbon monoxide and generate γ-butyrolactones (**421**) (Scheme 35).[127]

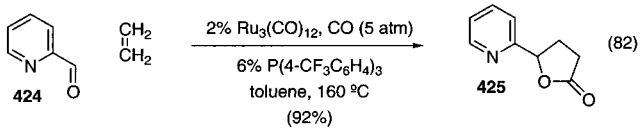
Scheme 35



This reaction is catalyzed by 2 mol % $Ru_3(CO)_{12}$ under carbon monoxide pressure at elevated temperatures. The yields are generally high (62−93%), although the reaction appears to be limited to disubstituted alkynes. For example, ruthenium catalyzed carbonylation of yne-al **422** gave butenolide **423** in 89% yield (eq 81).

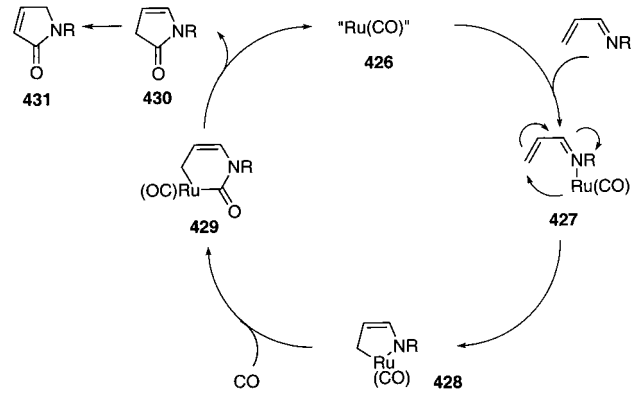


This reaction can also be carried out intermolecularly, with ethylene instead of an alkyne as the unsaturated partner. Under similar conditions, a range of lactones can be formed. For example, reaction of 2-pyridinecaboxyaldehyde (**424**) with ethylene, under 5 atm of carbon monoxide, affords lactone **425** in 92% yield (eq 82).[128] One limitation is that a coordinating group adjacent to the aldehyde or ketone partners (for example a pyridine, as below, or ester, ketone, and oxazole) is necessary, presumably to make the coordination of the ruthenium to the aldehyde more favorable.



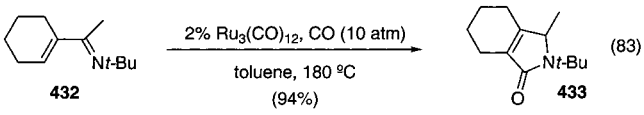
Ruthenium carbonyl complexes can also catalyze the carbonylative [4+1] cyclization of unsaturated imines (Scheme 36). Coordination of the ruthenium

Scheme 36

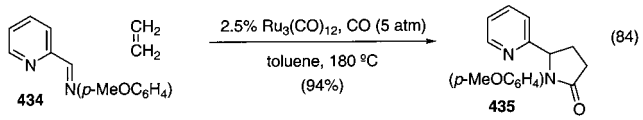


to the imine leads to cyclization giving ruthenacycle **428**. Insertion of carbon monoxide provides **429**, which undergoes reductive elimination to give γ-lactam **430**. Isomerization of **430**, under the reaction conditions, yields α,β-unsaturated lactam **431**.

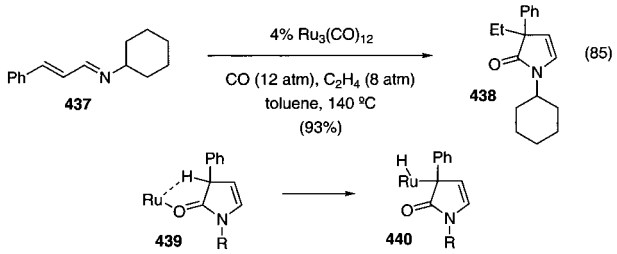
$Ru_3(CO)_{12}$ catalyzes the formation of the lactams, in yields ranging from 56 to 96%. For example, imine **432** reacts with carbon monoxide under ruthenium catalysis to generate the bicyclic lactam **433** in 94% yield (eq 83).



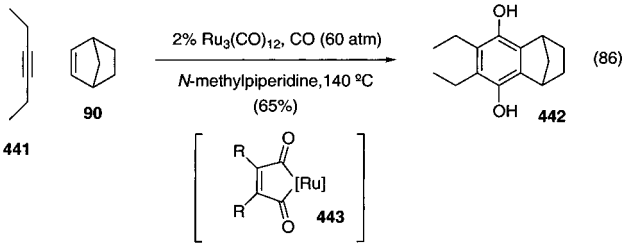
When the similar intermolecular reaction with imines and ethylene is performed, the reaction proceeds via the mechanism outlined in Scheme 36 to form saturated lactams. For example, the ruthenium carbonyl complex reacts with pyridyl imine **434** under carbon monoxide and ethylene pressure to form lactam **435** in 94% yield (eq 84).[129] As in the reaction depicted in eq 82, coordinating groups attached to the imine appear to be necessary for the reaction to proceed.



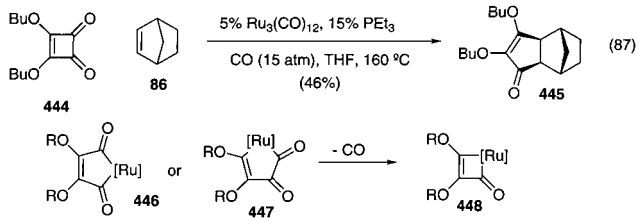
Ruthenium carbonyl complexes can also undergo C−H insertion reactions after carbonylations. Using a similar intramolecular case as in eq 83, except with ethylene in the reaction mixture, the ruthenium complex can insert in the C−H bond α to the carbonyl to generate hydridoruthenium enolate **440**. This intermediate then inserts ethylene to generate the product.[130] For example, unsaturated imine **437** is reacted with carbon monoxide and ethylene under ruthenium catalysis to form lactam **438** in 93% yield (eq 85).



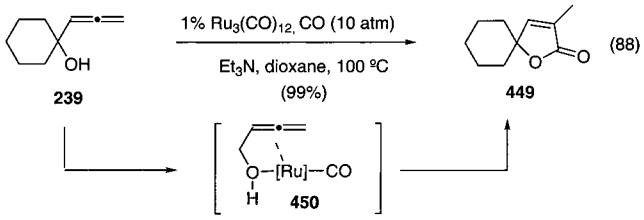
Bis-insertion of carbon monoxide can also be achieved with the use of alkynes and norbornenes as the coupling partner. The reaction is proposed to proceed by $Ru_3(CO)_{12}$ catalyzed addition of two equivalents of CO to the alkyne to generate ruthenium maleoyl **443**. This intermediate then inserts into the olefin to generate the quinone product. For example, 3-hexyne (**441**) reacts with norbornene (**90**) and carbon monoxide, catalyzed by 2 mol % $Ru_3(CO)_{12}$, to form hydroquinone **442** in 65% yield (eq 86).[131]



Ruthenium has also been proposed to promote the decarbonylation of squaric acid derivatives. As depicted in eq 87, reaction of cyclobutenedione **444** with norbornene (**86**) generates cyclopentenone **445** in 46% yield.[132] It is proposed that the ruthenium carbonyl catalyst inserts into the carbon−carbon bond to form metallacycle **446** or **447**. This intermediate subsequently undergoes a decarbonylation to generate the metallacyclobutene **448**, which inserts into the olefin to produce the cyclopentenone.



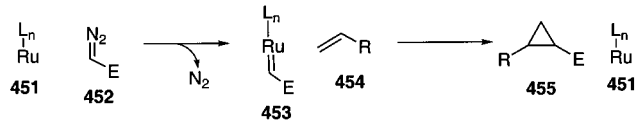
Finally, ruthenium carbonyl complexes have been shown to catalyze the carbonylative cyclization of allenic alcohols. An example is shown in eq 88: 1 mol % $Ru_3(CO)_{12}$ catalyzes the formation of γ-butyrolactone **449** from allenol **239** in 99% yield.[133] The reaction is proposed to be initiated by ruthenium coordination to the alcohol and allene to produce intermediate **450**. This complexation promotes the insertion of carbon monoxide on the central carbon of the allene.



IX. Reactions Involving Additions of Diazo Compounds

Two mechanisms have been proposed for the ruthenium-catalyzed cyclopropanation of olefins, a carbenoid mechanism and a coordination mechanism. The first involves the formation of a ruthenium carbenoid **453** from the diazo compound (**452**) (Scheme 37).[134] Reaction of the metal carbenoid with an olefin

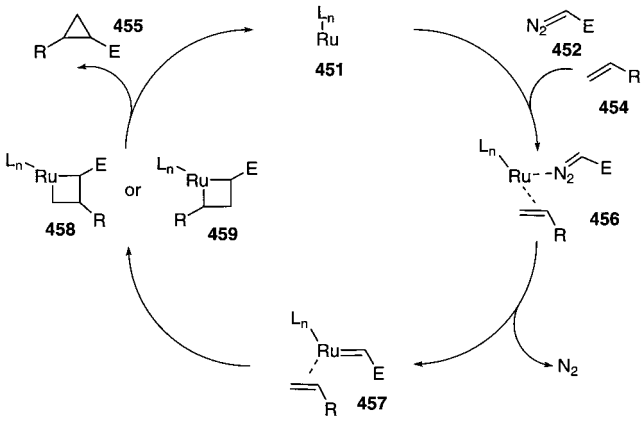
Scheme 37



(**454**) generates the cyclopropane (**455**) and returns the ruthenium catalyst (**451**).

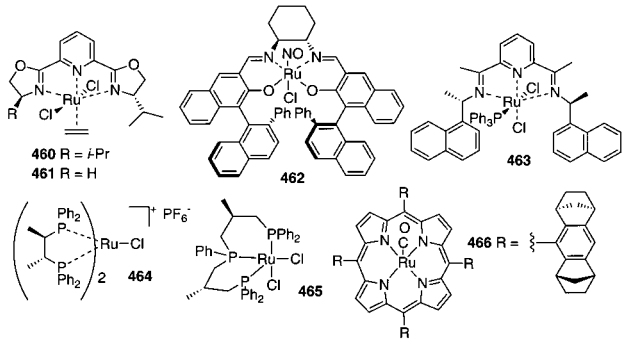
The second mechanism involves coordination of the diazo comound and the olefin prior to formation of the carbenoid (**457**) (Scheme 38).[135] Intramolecular

Scheme 38



reaction of the ruthenium carbene and the olefin produces ruthenacyclobutanes **458** and **459**, which undergo a reductive elimination to give the cyclopropane (**455**) and regenerate the ruthenium catalyst (**451**). This mechanism is consistent with the formation of alkene metathesis adducts as byproducts in the cyclopropanation.

A variety of ruthenium catalysts have been developed that catalyze the reaction of diazo compounds with olefins to produce cyclopropanes. These include ruthenium porphyrins,[136] ruthenium-bis(oxazolinyl)-pyridine (Pybox) complexes,[137] ruthenium(II) phosphine complexes,[138] CpRu(II),[139] Cp*Ru(II), and Cp*Ru(IV) catalysts,[140] arene ruthenium complexes,[141] ruthenium-bis(imino)pyridine complexes,[142] and ruthenium-salen complexes.[143]

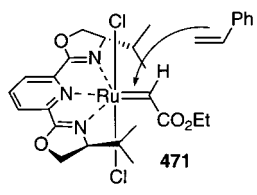


Various chiral ruthenium catalysts have been employed in the asymmetric cyclopropanation of olefins (Table 6). Perhaps the most successful are

Table 6. Ruthenium-Catalyzed Assymmetric Cyclopropanation of Styrene

entry	catalyst	yield (%)	**469** (%ee):**470** (%ee)	ref
1	5% **460**	73	91 (89):8 (78)	132c
2	5% **461**	93	89 (90):11 (66)	132a
3	5% **462**	45	7 (15):93 (97)	138a
4	5% **463**	65	86 (--):14 (76)	137
5	1% **464**	29	58 (25):42 (14)	133a
6	2% **465**	84	59 (17):41 (40)	133b
7	0.15% **466**	100	95 (91):5 (27)	133d

Nishiyama's Pybox complexes (entries 1 and 2). Ruthenium(Pybox) **460** catalyzed the reaction of styrene (**467**) and ethyl diazoacetate (**468**) to afford cyclopropane **469** with excellent diastereo- (91:8) and enantioselectivity (89% ee). The reaction is postulated to proceed via addition of styrene to carbenoid ruthenium complex **471** by the mechanism detailed in Scheme 37.

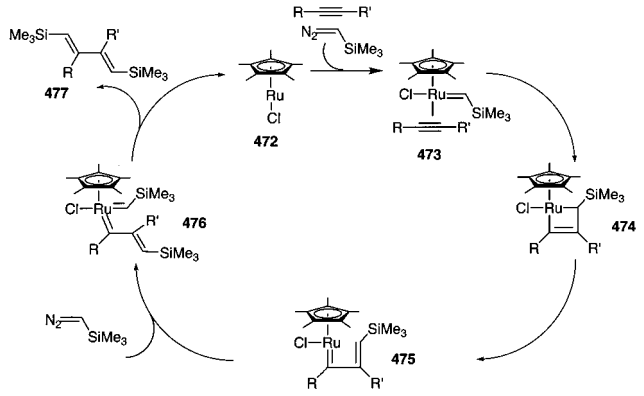


Ruthenium-porphyrin catalyst **466** provides the trans cyclopropane **469** with similar diastereo- (91:8) and enantioselectivity (89% ee) but with improved

turnover numbers (entry 7). Notably, Katsuki's Salen-ruthenium catalyst **462** offers the complentary cis cyclopropane **470** with excellent diastereo- (93:7) and enantioselectivity (97% ee) (entry 3). On the other hand, the ruthenium phosphine catalyst **464** and **465** produce the cyclopropane with poor control of diastereoselectivity and only moderate enantioselectivity (entries 5 and 6).

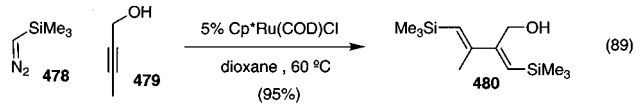
The ruthenium-catalyzed addition of diazo compounds to acetylenes produces 1,3-dienes by the mechanism shown in Scheme 39.[134] Reaction of

Scheme 39



coordinatively unsaturated ruthenium with an acetylene and a diazo compound produces ruthenium carbenoid **473**. Coupling of the carbene and the acetylene provides ruthenacyclobutene **474**, which undergoes a retro-[2+2] ring opening to generate ruthenium vinyl carbene **475**. Reaction of **475** with a second equivalent of the diazo compound generates the bis-carbene **476**. Subsequent coupling of the two carbenes produces the 1,3-diene product (**477**) and regenerated the coordinatively unsaturated ruthenium catalyst (**472**).

The reaction of diazo compounds and acetylenes is catalyzed by 5 mol % Cp*Ru(COD)Cl in dioxane at 60 °C (eq 89). Under these conditions, a variety of 1,3-dienes are prepared, with only nitrogen as a byproduct, in 30−95% yield. For example, Cp*Ru(COD)Cl catalyzed reaction of trimethylsilyl diazomethane (**478**) and propargyl alcohol **479** gave 1,3-diene **480** in 95% yield.

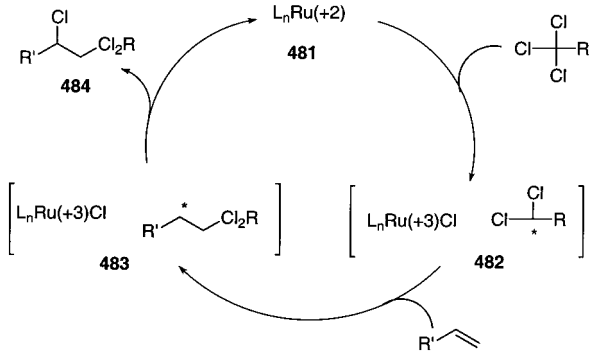


(89)

X. Radical Reactions

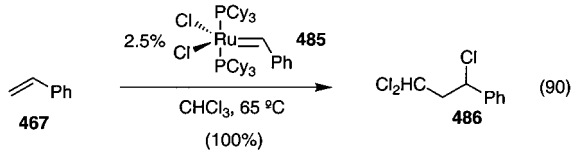
The ability of low-valent ruthenium complexes to participate in electron transfer has led to the development of a variety of ruthenium-catalyzed radical reaction of organic halides. Ruthenium complexes catalyze the radical reaction of α-chloro amides or esters, sulfonyl chlorides and polyhaloalkyl chlorides by the general mechanism detailed in Scheme 40. Reaction of ruthenium(+2) complexes with an organic halide results in electron transfer to generate the

Scheme 40



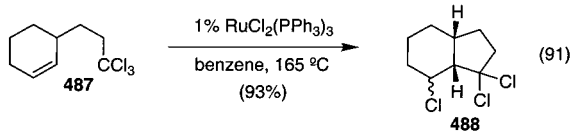
ruthenium(+3) caged radical intermediate **482**.[145] Reaction of **482** with an olefin results in radical addition to generate ruthenium(+3)-alkyl radical complex **483**. Transfer of a chlorine to the alkyl radical produces the alkyl chloride **484** and regenerates the ruthenium(+2) catalyst (**481**).

Ruthenium(+2) catalyzes the radical addition of carbon tetrachloride or chloroform to olefins (Kharasch addition reaction). The first report of this reaction employed $(Ph_3P)_2RuCl_2$ as the catalyst,[146] but subsequently Grubbs ruthenium catalyst,[147] Cp*Ru$(Ph_3P)_2Cl$[148] and ruthenium-carborane phosphine complexes have been utilized.[149] For example, Grubbs' catalyst (**485**) catalyzes the addition of chloroform to styrene (**467**) to afford chloride **486** in quantitative yield (eq 90).



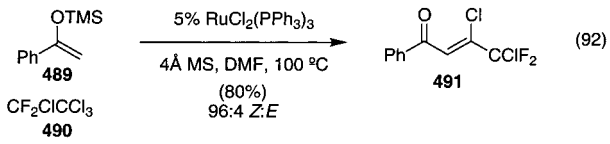
(90)

The ruthenium-catalyzed intramolecular radical reactions have also been described (eq 91).[150] For example, $(Ph_3P)_2RuCl_2$ catalyses the cyclization of trichloromethyl(alkene) **487** to afford only the *cis*-fused [6,5]-product **488** in 93% yield.



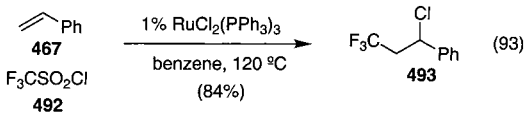
(91)

Ruthenium phosphine complex, $(Ph_3P)_2RuCl_2$, also catalyzes the regioselective radical addition to silyl enol ethers.[151] In this case, the resulting ketone undergoes β-elimination of a chloride to produce an α,β-unsaturated ketone. For example, $(Ph_3P)_2RuCl_2$ catalyzed reaction of trichloride **490** to trimethylsilyl enol ether **489** produces α,β-unsaturated ketone **491** in 90% yield (eq 92).

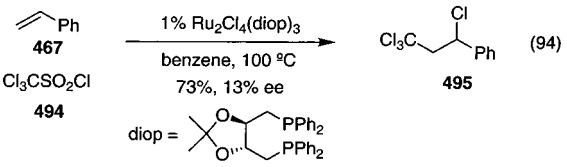


(92)

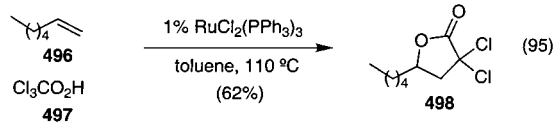
The reaction of ruthenium(+2) with trihalomethylsulfonyl chlorides generates the sulfonyl radical, which subsequently extrudes sulfur dioxide to generate the alkyl radical.[152,153] The $(Ph_3P)_3RuCl_2$ catalyzed reaction of trifluoromethylsulfonyl chloride with a variety of olefins produces trifluoromethyl adducts in 46−84% yield (eq 93). For example, the reaction trifluoromethylsulfonyl chloride (**492**) with styrene (**467**) afforded **493** in 84% yield.



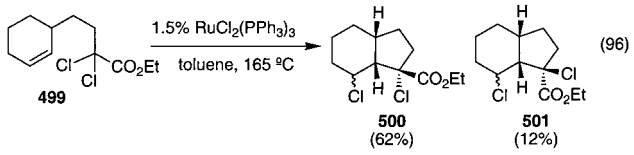
The asymmetric version of this reaction has been attempted utilizing $Ru_2Cl_4(diop)_3$ as catalyst (eq 91).[154] Unfortunately, the ruthenium-catalyzed reaction of trichloromethylsulfonyl chloride (**494**) with styrene (**467**) produced tetrachloride **495** with only 13% ee.



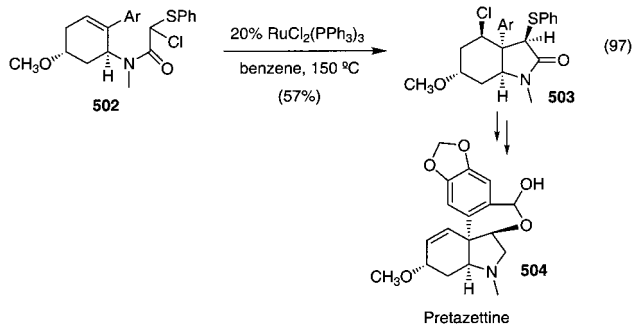
The intermolecular addition of trichloroacetic acid,[155] ester,[156] and acid chloride[157] to olefins is also catalyzed by $(Ph_3P)_3RuCl_2$. When trichloroacetic acid is employed, the resulting acid reacts further to produce a lactone. For example, $(Ph_3P)_3RuCl_2$ catalyzed reaction of trichloroacetic acid (**497**) with 1-heptene (**496**) gave lactone **498** in 62% yield (eq 95).



The ruthenium-catalyzed intramolecular reaction of α,α-dichloro esters, acids, and nitriles has also been described.[158] For example, $(PPh_3)_3RuCl_2$ catalyzed reaction of ester **499** produced a 74% yield of a 6:1 mixture of diastereomeric *cis*-fused [6,5]-carbocycles **500** and **501** (eq 96).

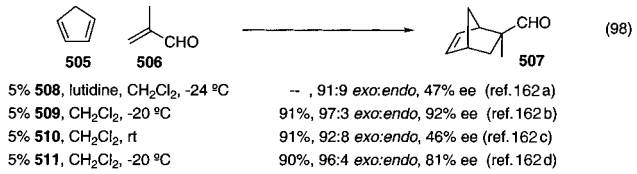


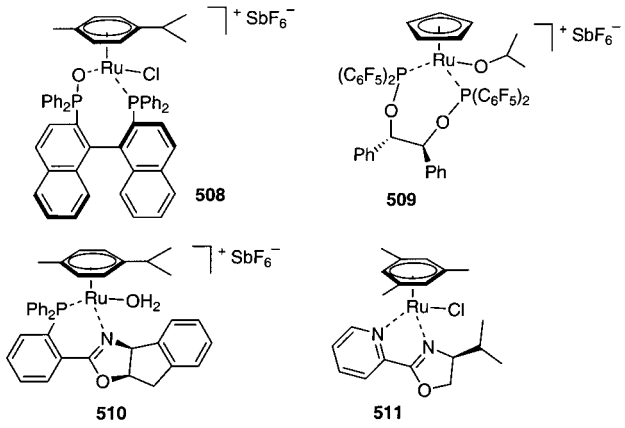
Trichloroacetamides[159] and α-chloro-*N*-tosylamides[160] and α-chloro-α-thioacetamides[161] also participate in the ruthenium-catalyzed intramolecular addition to olefins. For example, α-chloroamide **502** reacts with 20 mol % $(Ph_3P)_3RuCl_2$ to generate bicyclic amide **503** in 57% yield (eq 94). Using amide **503**, formal syntheses of alkaloids (±)-pretazettine (**504**) and (±)-haemanthidine were completed.



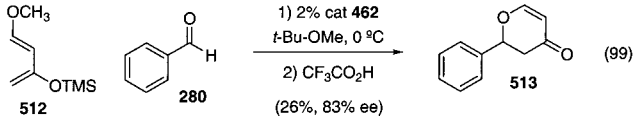
XI. Lewis Acid Catalyzed Reactions

Various ruthenium complexes have been reported that catalyze the Diels−Alder reaction of dienes and methacrolein.[162] The ruthenium-catalyzed enantioselective Diels−Alder reaction of methacrolein (**506**) and cyclopentadiene (**505**) produces norbornene adduct **507** with excellent control of *endo*:*exo* selectivity and moderate to excellent enantioselectivities (eq 98). To date the best results are obtained with Kündig's cationic cyclopentadienyl ruthenium catalyst **509**, which affords the *exo*-norbornene adduct **507** in 92% ee.



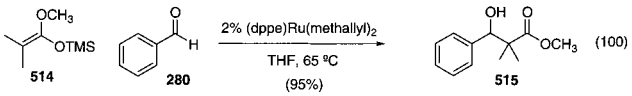


Ruthenum catalysts have also been reported to catalyze the hetero-Diels−Alder reaction of aldehyde and dienes.[163] For example, chiral salen(ruthenium) complex **462** catalyzes the reaction of Danishefsky's diene **512** and benzaldehyde (**280**) to afford pyrone **513** in 26% yield and 83% enantiomeric excess (eq 99).

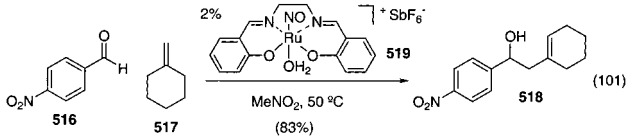


Similarly, the addition of silyl ketene acetal **514** to benzaldehyde (**280**), catalyzed by 2 mol % of a ruthenium(+2) complex, affords ester **515** in 95% yield (eq 100).[164] Ruthenium-salen complexes also

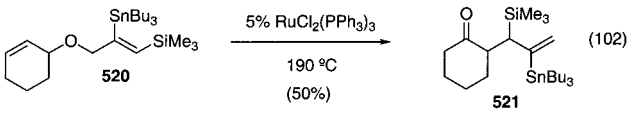
catalyze the Mukaiyama aldol reaction of silyl enol ethers and aldehydes.[165]



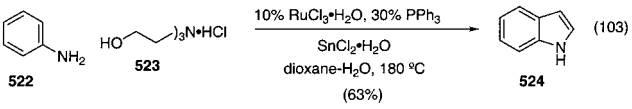
The oxa-ene reaction of electron-deficient aldehydes and alkenes is catalyzed by cationic ruthenium-salen complex **519** in nitromethane at 50 °C (eq 101).[166] Under these conditions, homoallylic alcohols are obtained in 35−88%. For example, ruthenium catalyzed reaction of *p*-nitrobenzaldehyde (**516**) with methylenecyclohexane **517** affords homoallylic alcohol **518** in 83% yield.



Ruthenium(+2) also catalyzes the Claisen rearrangement of allyl vinyl ethers and diallyl ethers.[167] For example, 5 mol % $(PPh_3)_2RuCl_2$ catalyzes the tandem isomerization-Claisen rearrangement of diallyl ether **520** to afford ketone **521** in 50% yield (eq 102).



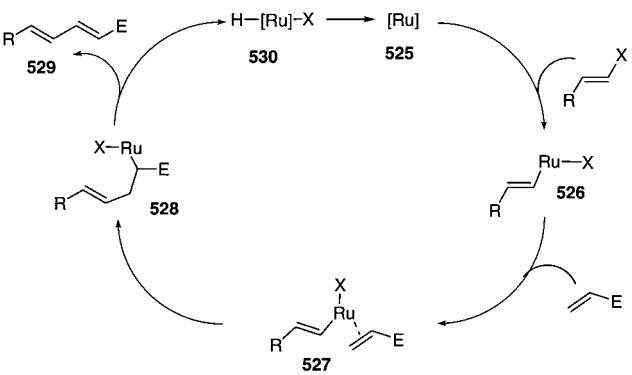
Electron-rich olefins and aromatic compounds undergo a ruthenium-catalyzed Friedel−Crafts alkylation with alcohols and formates.[168,169] For example, ruthenium-catalyzed reaction of aniline (**522**) with triol **523** afforded indole (**524**) in 63% yield (eq 103).



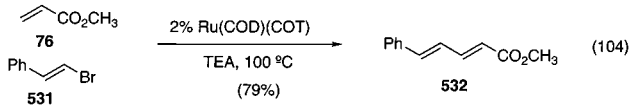
XII. Reactions of Vinyl Halides

The cross-coupling of vinyl halides with olefins[170] and alkyl Grignard reagents[171] is also catalyzed by ruthenium complexes. The reaction is postulated to proceed by the oxidative addition of ruthenium into the vinyl halide bond to provide vinyl ruthenium halide **526** (Scheme 41). Carboruthenation of an acceptor olefin produces ruthenium complex **528** which undergoes β-hydrogen elimination to afford the diene product **529** along with hydrido ruthenium complex **530**. Base promoted loss of HX regenerates the active ruthenium catalyst (**525**).

Scheme 41



An example of the ruthenium-catalyzed cross coupling reaction is shown in eq 104. The coupling is β-bromostyrene (**531**) with methyl acrylate (**76**) is catalyzed by 2 mol % Ru(COD)(COT) to afford diene **532** in 79% yield.



XIII. Conclusion

Ruthenium-catalyzed C−C bond forming reactions have been largely unknown. The development of the ruthenium-catalyzed metathesis reaction has significantly changed the landscape and dramatically brought to the fore the prospects that ruthenium catalysis was useful for something more than redox chemistry. The incredible array of feasible oxidation states for ruthenium provides an almost unprecedented potential for developing reactions far beyond metathesis chemistry. The extraordinary number of new C−C bond forming reactions discovered within the last several years already attests to the wealth of opportunity. Using mechanistic reasoning, semirational invention becomes possible. Thus, numerous reactions involving intermediates such as ruthenacycles or allenylideneruthenium complexes have emerged. Using coordinatively unsaturated ruthenium, processes initiated by C−H insertion have led to atom economic alkylation protocols via addition reactions. Electron transfer also serves to initiate C−C bond forming processes. In other cases, common transition metal catalyzed reactions such as cyclopropanations, cycloadditions such as the Diels−Alder reaction, additions such as Alder-ene reactions and allylic alkylations can also be found to be catalyzed by the appropriate ruthenium complexes. The fact that so many new reactions have been discovered means that these processes will need to be developed and improved. More importantly, the prospects are clearly bright for many more reactions to be discovered. It is amazing that so much has been done with only a handful of ruthenium complexes as the actual catalysts. Given the obvious scope of possibilities for catalyst design strongly reinforces the notion that immense opportunity abounds.

XIV. Acknowledgment

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