Ruthenium-Catalyzed Cycloadditions to Form 5-, 6- and 7-Membered Rings

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Abstract: Ruthenium-catalyzed cycloadditions to form 5-, 6-, and 7-membered rings are summarized, including applications in natural product total synthesis. Content is organized by ring size and reaction type. Coverage is limited to processes that involve formation of at least one C-C bond. Processes that are stoichiometric in ruthenium or exploit ruthenium as a Lewis acid (without intervention of organometallic intermediates), ring formations that occur through dehydrogenative condensation-reduction, σ-bond activation-initiated annulations that do not result in net reduction of bond multiplicity and photochemically promoted ruthenium-catalyzed cycloadditions are not covered.

1. Introduction and Scope of Review
2. Five-Membered Ring Formation
- **2.1 (2+2+1) Cycloadditions**
  - **2.1.1 Carbonylative (2+2+1) Cycloadditions**
  - **2.1.2 Non-Carbonylative (2+2+1) Cycloadditions**
- **2.2 (3+2) Cycloadditions**
  - **2.2.1 Dipolar (3+2) Cycloadditions**
  - **2.2.2 Carbene-Mediated (3+2) Cycloadditions**
  - **2.2.3 (3+2) Cycloadditions via Hydrogen Transfer**
  - **2.2.4 (3+2) Cycloadditions via C-C and C-N σ-Bond Activation**
- **2.3 (3+1+1) Cycloadditions**
- **2.4 (4+1) Cycloadditions**

3. Six-Membered Ring Formation
- **3.1 (2+2+1+1) Cycloadditions**
- **3.2 [2+2+2] Cycloadditions to Form Carbocycles**
  - **3.2.1 [2+2+2] Cycloadditions of COD and NBD as $2_{2\pi}$ Partners**
  - **3.2.2 [2+2+2] Cycloadditions of 3 Alkynes**
  - **3.2.3 [2+2+2] Cycloadditions of Alkynes + Alkenes**
- **3.3 [2+2+2] Cycloadditions to Form Heterocycles**
  - **3.3.1 [2+2+2] Cycloadditions of 2 Alkynes + Cumulenes**
  - **3.3.2 [2+2+2] Cycloadditions of 2 Alkynes + Nitriles**
  - **3.3.3 [2+2+2] Cycloadditions of 2 Alkynes/Alkenes + Carbonyl Compounds**
- **3.4 (3+2+1) Cycloadditions**
- **3.5 [4+2] Cycloadditions**
  - **3.5.1 Transfer Hydrogenative Cycloadditions**
  - **3.5.2 Formal Diels-Alder Type [4+2] Cycloadditions**
- **3.6 (5+1) Cycloadditions**

4. Seven-Membered Ring Formation
- **4.1 (3+2+2) Cycloadditions**
- **4.2 (5+2) Cycloadditions**

5. Conclusion and Outlook

1. Introduction and Scope of Review

Metal-catalyzed cycloadditions represent an expansive, atom-efficient class of transformations that have found wide-ranging utility in chemical synthesis.[1-11] The vast majority of metal-catalyzed cycloadditions exploit cobalt,[12-16] nickel[17-20] and rhodium;[21-25] however, in the past two to three decades, significant progress on ruthenium-catalyzed cycloadditions has been made,[26-34] including fundamentally new cycloaddition processes that are unknown for other metals.[34] While utilized less frequently as catalysts for cycloaddition, ruthenium offers several advantages. Ruthenium is significantly less expensive than other noble metals (Figure 1), yet ruthenium complexes are generally more tractable than their low-valent base-metal counterparts. Ruthenium can adopt a wide range of oxidation levels and engages in diverse modes of reactivity, including C-C bond activation, metallacycle formation via oxidative coupling, carbene/vinylidene/allenylidene formation, alcohol-mediated hydrogen transfer and much more. Although metal-catalyzed cycloadditions have been reviewed[1-11] and related ruthenium-catalyzed cycloadditions have appeared intermittently in more broadly focused monographs,[26-39] the topic of ruthenium-catalyzed cycloadditions has not been exhaustively cataloged. Here, we provide a summary of ruthenium-catalyzed cycloadditions to form 5-, 6-, and 7-membered rings (Figure 2). Reactions covered in this review adhere to the IUPAC definition of a cycloaddition as "*a reaction in which two or more unsaturated molecules (or parts of the same molecule) combine to form a cyclic adduct with a net reduction in bond multiplicity*."[40] Consequently, previously reviewed ruthenium-catalyzed annulations that proceed through C-H bond activation fall outside the purview of the present monograph,[41-43] as do certain C-C and C-N σ-bond activation-initiated annulations,[44-46] and cyclocarbonylations of unsaturated alcohols or amines.[47-51] Content is organized by ring size and reaction type. Coverage is limited to processes that involve formation of at least one C-C bond. Hence, the recently reviewed topic of ruthenium-catalyzed alkyne-azide "click" cycloadditions is not covered.[52-55] Reactions that are stoichiometric in ruthenium or exploit ruthenium as a Lewis acid (and do not proceed by way of intermediates that possess carbon-ruthenium bonds) are not covered. This includes dehydrogenative annulations that occur through successive condensation[56-58] and photochemically promoted ruthenium-catalyzed cycloadditions.[59-63] Ruthenium-catalyzed cyclopropanations[64-79] and (2+2) cycloadditions[80-86] have been exhaustively reviewed elsewhere and are not covered.

PRICE[a]	Pt	Pd	Rh	Ir	Ru
USD/Ounce	869	1,548	3,910	1,480	258
USD/Mole	5,449	5,297	12,937	9,146	839

[a]Data from (01/2019-01/2020) http://www.platinum.matthey.com

Figure 1. Cost of noble metals *vs* cost of ruthenium.

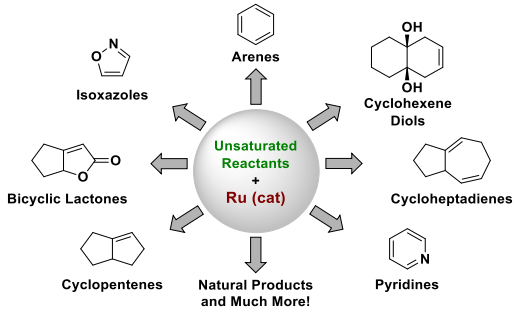


Figure 2. Diverse products delivered by ruthenium-catalyzed cycloadditions of unsaturated substrates.

2. Five-Membered Ring Formation

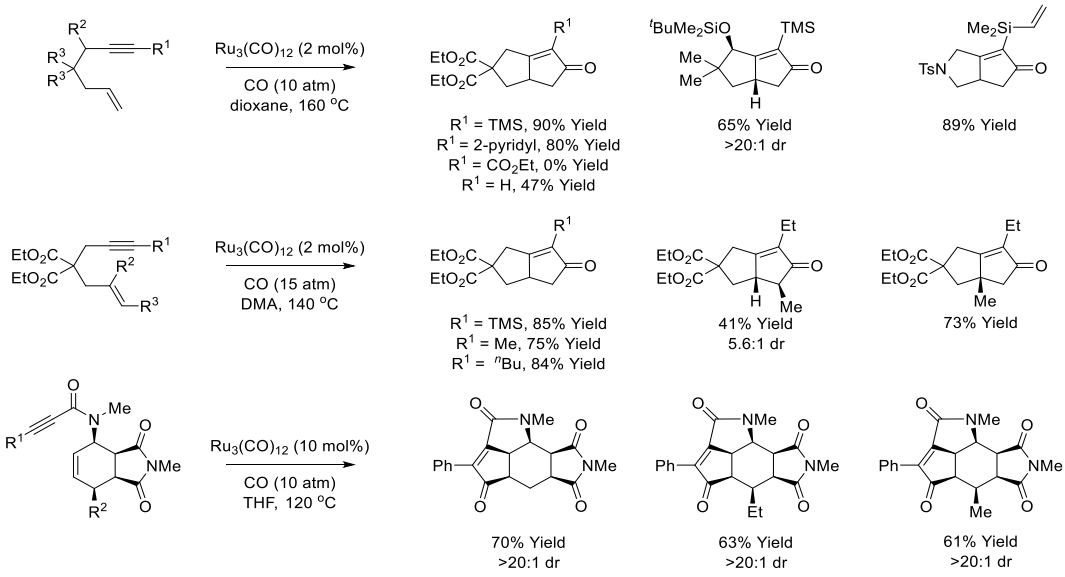
2.1 (2+2+1) Cycloadditions

2.1.1 Carbonylative (2+2+1) Cycloadditions

Pursuant to the discovery of the Pauson-Khand reaction (1973)[87] and its intramolecular variants,[88,89] catalytic carbonylative (2+2+1) cycloadditions of alkynes and alkenes based on cobalt[90-92] and

titanium[93-95] appeared in the 1990s. As described in the review literature, noble metal-catalyzed Pauson-Khand reactions, including enantioselective variants, soon followed.[96-99] In 1997, Murai and Mitsudo independently reported the first examples of ruthenium-catalyzed Pauson-Khand-type reactions (Scheme 1).[100,101] Upon exposure to substoichiometric quantities of $Ru_3(CO)_{12}$ under modest pressures of carbon monoxide (10−20 atm) at elevated temperatures (140−160 °C), 1,6-enynes are converted to the bicyclopentenones in high yields. Alkynoates notwithstanding, both terminal and internal alkynes participate in (2+2+1) cycloaddition, and 1,6-enynes bearing propargyl stereocenters deliver cycloadducts as single diastereomers. Whereas Murai's conditions,[100] which employ dioxane solvent, are intolerant of disubstituted alkenes, the use of DMA solvent under otherwise nearly identical conditions (as reported by Mitsudo)[101] overcomes this limitation. Beller and coworkers applied this method to the formation of cycloadducts that embody the fused tricyclic ring system of the dendrobine alkaloids.[102] Computational studies of the mechanism of the $Ru_3(CO)_{12}$-catalyzed Pauson-Khand reaction conducted by Wu in 2008 corroborate a reaction pathway in which a mononuclear alkyne-$Ru(CO)_4$ complex is converted to a ruthenacyclobutenone, which upon alkene insertion and C-C reductive elimination delivers the cyclopentenone (not shown).[103] This proposal deviates from the widely accepted mechanism for the parent Pauson-Khand reaction, which involves alkyne-alkene oxidative coupling to form a metallacyclopentene followed by CO-insertion.

Scheme 1. Intramolecular ruthenium-catalyzed Pauson-Khand reactions reported by Murai, Mitsudo and Beller.

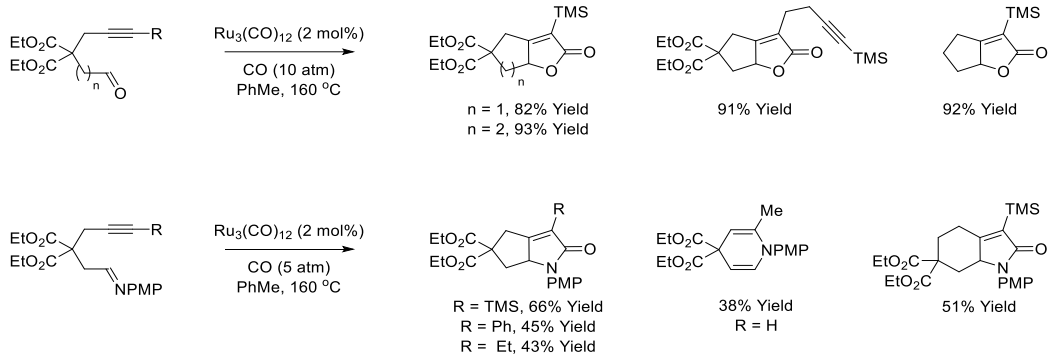


In 1998, Murai reported related $Ru_3(CO)_{12}$-catalyzed oxo-Pauson-Khand reactions of acetylenic aldehydes to form bicyclic α,β-unsaturated γ-lactones (Scheme 2).[104] The reaction is applicable to both 1,6- and 1,7-ynals. Thorpe-Ingold effects[105] induced by geminal substitution in the tether are not required for efficient cycloaddition. Under related cyclocarbonylation conditions, 1,6- and 1,7-acetylenic imines form bicyclic lactams in modest yield.[106] Internal alkynes are required as, in the absence of terminal substitution, hydroamination-alkene isomerization occurs by way of the enamine to form dihydropyridines.

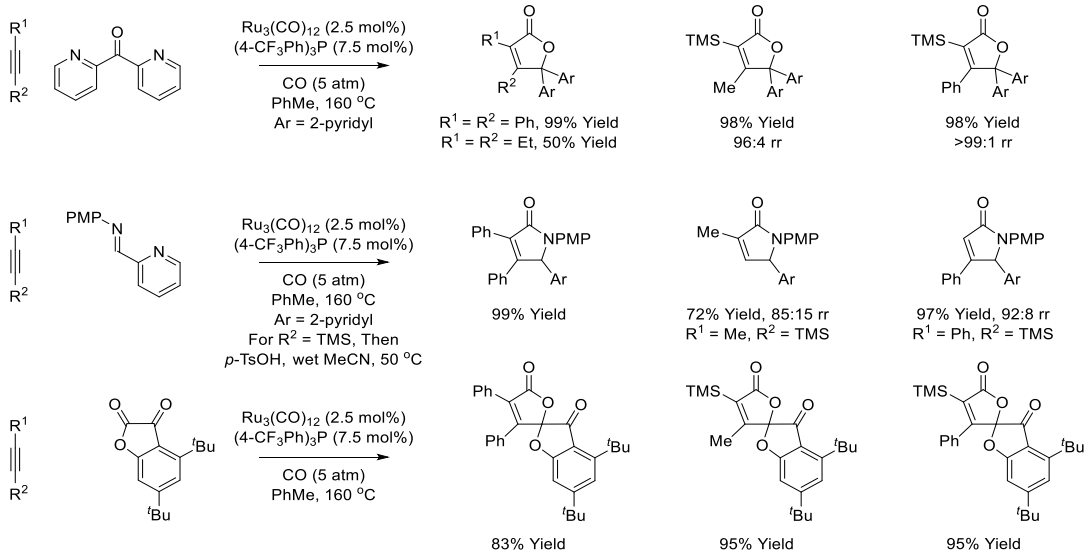
In 2000, Murai and co-workers developed the first intermolecular ruthenium-catalyzed oxo-Pauson-Khand-type cycloadditions of alkynes with a carbonyl compound (Scheme 3).[107] Unlike the intramolecular processes, the intermolecular reaction requires a carbonyl partner with vicinal dicarbonyl character. In their initial report, the indicated *bis*-(2-pyridyl) ketone was the only carbonyl partner described. Notwithstanding this limitation, cycloaddition occurs efficiently using the ruthenium catalyst

generated *in situ* from $Ru_3(CO)_{12}$ with $(4\text{-}CF_3Ph)_3P$. Murai and co-workers reported intermolecular ruthenium-catalyzed aza-Pauson-Khand-type cycloadditions of alkynes and imines the same year.[108] Under identical conditions using activated imines derived from 2-picolinaldehyde, cycloaddition delivers the α,β-unsaturated lactams in good yield. As alkynes bearing Me_3Si-substituents undergo partial desilylation, the crude reaction mixtures were subjected to hydrolysis to fully convert the cycloadducts to the desilylated cycloadducts. As illustrated in cycloadditions of Me_3Si-propyne vs Me_3Si-phenylacetylene, regioselectivity is alkyne-dependent. Later, in 2003, Chatani demonstrated these conditions also are effective in intermolecular oxo-Pauson-Khand-type cycloadditions of the indicated α-ketolactone and occur in a completely regio- and chemoselective fashion.[109]

Scheme 2. Intramolecular ruthenium-catalyzed hetero-Pauson-Khand reactions reported by Murai.



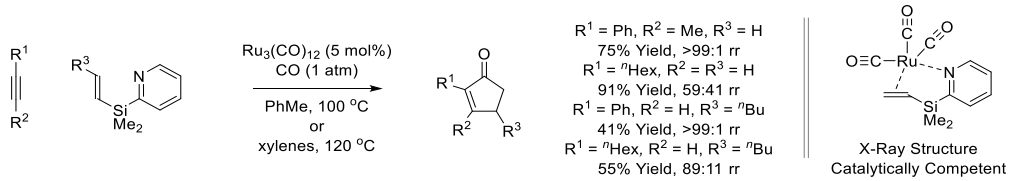
Scheme 3. Intermolecular ruthenium-catalyzed hetero-Pauson-Khand reactions reported by Murai.



Unlike intermolecular oxo- and aza-ruthenium-catalyzed Pauson-Khand-type cycloadditions, the intermolecular reaction of alkynes with alkene partners to form carbocycles remains limited in scope. As described by Itami and Yoshida in 2002, alkenes that incorporate a silyl-tethered pyridyl directing group are viable olefinic partners (Scheme 4).[110] As desilylation occurs spontaneously under the reaction conditions, the vinyl silane serves as a traceless directing group. However, the multi-step synthesis of such alkenyldimethyl(2-pyridyl)silanes,[111] which requires use of organolithium reagents under cryogenic conditions, makes them a poor substitute for ethylene or higher α-olefins, which are abundant feedstocks. In subsequent mechanistic work, a ruthenacyclopentene complex (not shown) and the indicated $Ru(vinylsilane)(CO)_3$ complex were isolated and characterized.[112] Both monometallic complexes are

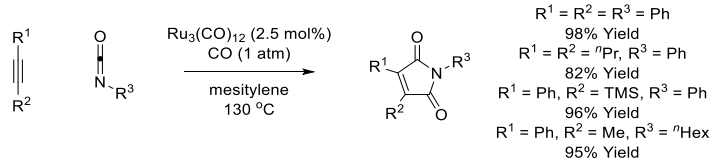
catalytically competent. At 50 °C, the ruthenacyclopentene complex is generated quantitatively, and at 100 °C, it was converted to the cyclopentenone. These data corroborate a catalytic mechanism involving rapid ruthenacyclopentene formation followed by slow CO migratory insertion, refuting prior computational investigations.[103]

Scheme 4. Intermolecular ruthenium-catalyzed Pauson-Khand reactions of alkenyldimethyl(2-pyridyl)silanes reported by Itami and Yoshida.



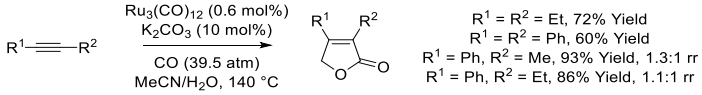
In 2006, Kondo reported intermolecular ruthenium-catalyzed hetero-Pauson-Khand reactions of alkynes with isocyanates (Scheme 5).[113] The reactions utilize substoichiometric quantities of $Ru_3(CO)_{12}$ in the absence of ligand under one atmosphere of CO. Aryl and alkyl substituents are tolerated in the alkyne and isocyanate partners. The reaction displays broad scope in both the alkyne and isocyanate, enabling direct generation of structurally diverse polysubstituted maleimides from abundant precursors.

Scheme 5. Intermolecular ruthenium-catalyzed hetero-Pauson-Khand reactions of alkynes with isocyanates reported by Kondo.



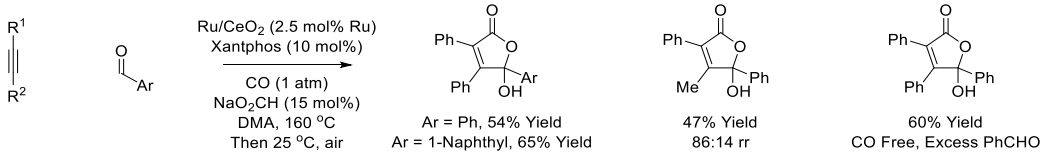
In 2007, Hua reported the $Ru_3(CO)_{12}$-catalyzed reductive cyclocarbonylation of internal alkynes in the presence of water to furnish 3,4-disubstituted furan-2(*5H*)-ones (Scheme 6).[114] A high pressure of CO (39.5 atm) was required to enforce conversion to the butenolide. Non-symmetric alkyl- and aryl-substituted alkynes provided good to excellent yields of cycloadduct; however, low levels of regioselectivity were observed.

Scheme 6. Intramolecular ruthenium-catalyzed cyclocarbonylation of internal alkynes reported by Hua.



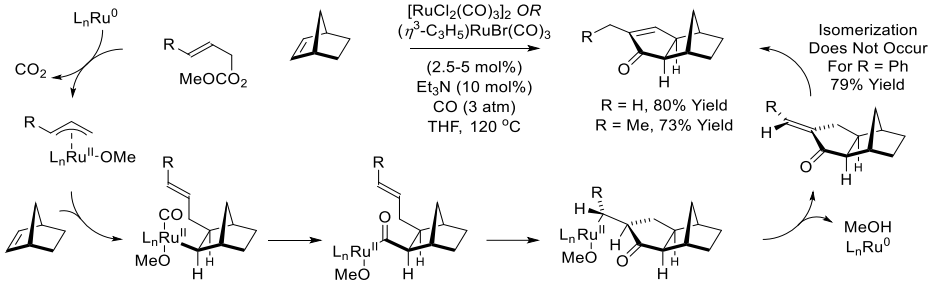
More recently, in 2016, Shishido reported oxidative intermolecular ruthenium-catalyzed oxa-Pauson-Khand reactions of alkynes with aryl aldehydes to form γ-hydroxybutenolides (Scheme 7).[115] This process exploits a CeO_2-supported ruthenium catalyst modified by Xantphos under one atmosphere of CO. Exposure of the reaction mixture to air to promotes oxidation of the initially formed cycloadducts. Unlike previously reported intermolecular ruthenium-catalyzed oxa-Pauson-Khand reactions catalyzed by $Ru_3(CO)_{12}$,[107] activated aldehydes are not required. Upon use of excess aldehyde, cycloaddition can occur in the absence of exogenous CO due to metal-catalyzed aldehyde decarbonylation.

Scheme 7. Intermolecular ruthenium-catalyzed oxidative oxo-Pauson-Khand reactions reported by Shishido.

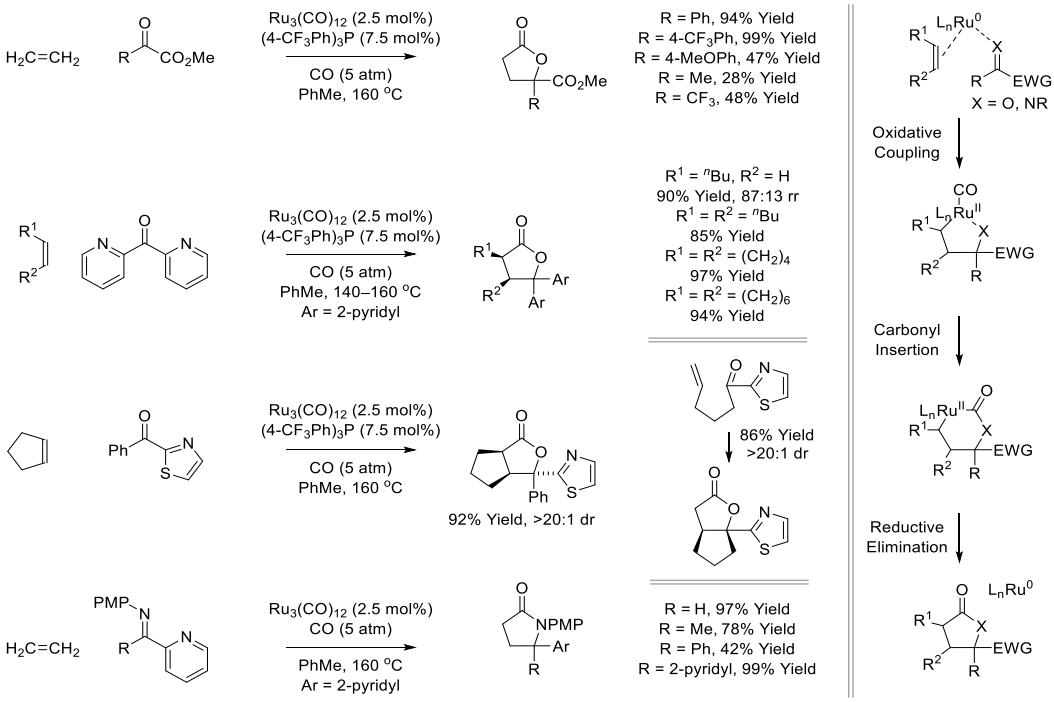


The preceding reactions exploit at least one alkyne as a 2π-component. Carbonylative (2+2+1) cycloadditions beyond alkynes were developed in parallel. In 2000, Kondo and Mitsudo described a carbonylative cycloaddition of allyl carbonates with norbornene to form cyclopentenones (Scheme 8).[116] Both $[RuCl_2(CO)_3]_2$/Et_3N and (η^3-allyl)$RuBr(CO)_3$/Et_3N were shown to be effective catalysts. The reaction is applicable to linear or branched alkyl-substituted allylic carbonates, and the cycloadducts form with complete *exo*-stereoselectivity. The proposed mechanism involves *cis*-carboruthenation of norbornene followed by carbonyl insertion to generate an acylruthenium intermediate, which upon olefin insertion-β-hydride elimination provides an exocyclic enone to close the catalytic cycle. Isomerization of the initially formed exocyclic enone to the endocyclic enone occurs under the reaction conditions for alkyl-substituted allylic acetates but not for aryl-substituted allylic acetates.

Scheme 8. Ruthenium-catalyzed carbonylative (2+2+1) cycloadditions of allylic carbonates with norbornene reported by Kondo and Mitsudo.

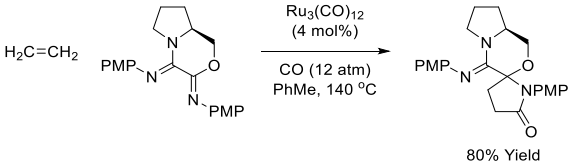


Scheme 9. Intermolecular carbonylative (2+2+1) cycloadditions of alkenes with activated carbonyl compounds and imines reported by Murai and Chatani.



Concurrent with their work on ruthenium-catalyzed oxa-Pauson-Khand reactions (Scheme 3), Murai and co-workers developed related carbonylative (2+2+1) cycloadditions of alkenes and activated carbonyl compounds and imines to provide saturated γ-lactones and γ-lactams (Scheme 9).[107-109,117] Using the ruthenium(0) catalyst derived from $Ru_3(CO)_{12}$ and $(4\text{-}CF_3Ph)_3P$, carbonylative cycloadditions of ethylene with α-ketoesters occurred in moderate to good yield.[107] Higher olefins, for example 1-hexene and 1,2-substituted alkenes, including 5-decene, cyclohexene and cyclooctene, undergo carbonylative cycloaddition with the indicated *bis*-(2-pyridyl) ketone to form the corresponding γ-lactones in high yield.[107] 1,1-Disubstituted, conjugated and electron-deficient olefins did not provide appreciable quantities of cycloadduct under these conditions. Beyond α-ketoesters and 2-pyridyl ketones, other activating groups that confer vicinal dicarbonyl character to the ketone partner can be used, as illustrated in inter- and intramolecular carbonylative cycloadditions of 2-thiazole ketones.[107] Benzofuran-2-pyridyl imines[108] and benzofuran-2,3-diones (not shown)[109] were subsequently explored. In the former case, γ-lactams were formed in high yield in the absence of phosphine ligand.[108] The proposed mechanism for carbonylative cycloaddition involves ruthenium(0)-mediated alkene-C=X (X = O, NR) oxidative coupling to furnish a ruthenacycle, which upon carbonyl insertion-C-C reductive elimination provides the lactone.

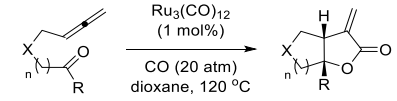
Scheme 10. Intermolecular carbonylative (2+2+1) cycloadditions of ethylene with activated imidates reported by Imhof.



In work closely related to that of Murai and Chatani,[107-109] Imhof developed a carbonylative (2+2+1) cycloaddition of activated imidates with ethylene to form spirocyclic lactams in 2001 (Scheme 10).[118] The reactants incorporate a preexisting stereocenter, yet in all cases the newly formed spirocyclic stereogenic center is formed with only low levels of substrate-directed diastereoselectivity. Internal alkenes, methyl acrylate and internal alkynes also were reported to engage in carbonylative cycloaddition with activated imidates to form the spirolactams, but in significantly lower yields (not shown).[119] In a follow-up report, similar selectivity was observed using 1,3,4-oxadiazines-based diazadienes (not shown),[120] and the reaction was limited to terminal olefins; no reaction took place with internal olefins or alkynes.

As demonstrated by Kang in 2002, allenyl aldehydes and ketones participate in intramolecular carbonylative (2+2+1) cycloaddition to form α-methylene-γ-butyrolactones and α-methylene-δ-butyrolactones (Scheme 11).[121] The reaction exploits Ru_3CO_{12} as a ruthenium(0) precatalyst in the absence of added ligand. Remarkably, even in the case of 6-membered ring formation, cycloadducts were generated as single diastereomers in good yield.

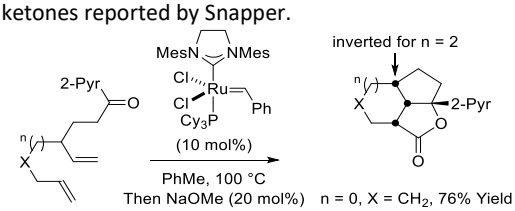
Scheme 11. Intramolecular carbonylative (2+2+1) cycloadditions of allenyl aldehydes and ketones reported by Kang.



n = 1, X = NBoc, R = H, 70% Yield, >20:1 dr
n = 2, X = NBoc, R = H, 72% Yield, >20:1 dr
n = 2, X = $C(CO_2Et)_2$, R = Me, 48% Yield, >20:1 dr

The ability of 2-pyridyl aldehydes and ketones to participate in carbonylative (2+2+1) cycloadditions with alkenes as initially described by Murai and Chatani[107] was elegantly exploited by Snapper in 2011, who reported a tandem ring-closing metathesis-carbonylative (2+2+1) cycloaddition (Scheme 12).[122] Here, ring-closing metathesis forms a cycloalkene, which is then exposed to CO and NaOMe to generate a Ru(0) catalyst that promotes cyclocarbonylation. In this way, diastereoselective formation of fused tricyclic ring systems is achieved from acyclic precursors. For reactions involving transient cycloheptenes, an inversion of diastereoselectivity is observed.

Scheme 12. Tandem ring-closing metathesis carbonylative (2+2+1) cycloadditions with activated ketones reported by Snapper.

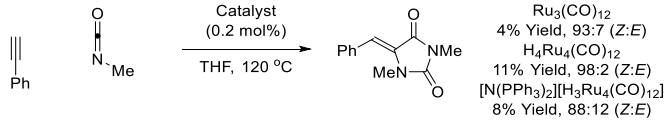


n = 0, X = CH_2, 76% Yield
n = 1, X = CH_2, 72% Yield
n = 2, X = CH_2, 71% Yield

2.1.2 Non-Carbonylative (2+2+1) Cycloadditions

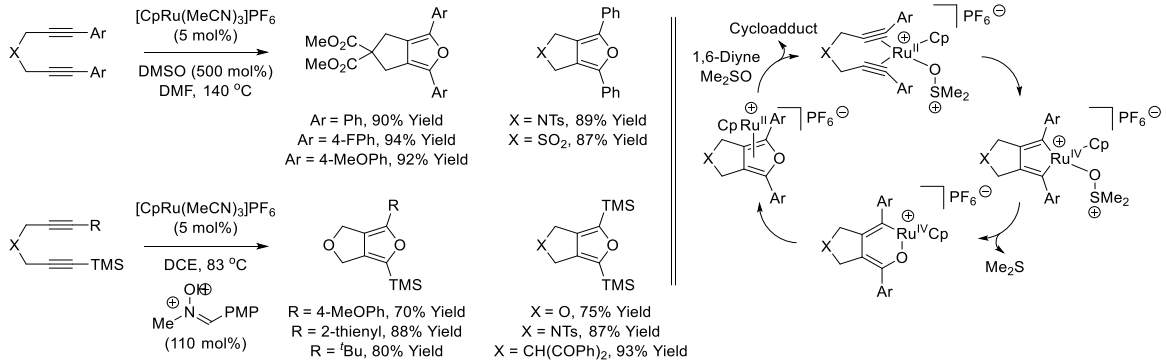
In 1987, Süss-Fink reported a ruthenium-catalyzed (2+2+1) cycloaddition that combines two isocyanates with phenylacetylene to form benzylidenehydantoins (Scheme 13).[123] Although the yields of cycloadduct are not in a preparatively useful range, this process represents the first ruthenium-catalyzed cycloaddition beyond 3- and 4-membered ring formation. A control experiment involving exposure of the cycloadduct to acid resulted in equilibration of the double bond geometry, corroborating the role of ruthenium as a catalyst in the reaction.

Scheme 13. Ruthenium-catalyzed (2+2+1) cycloaddition of alkynes with isocyanates reported by Süss-Fink.



In 2012, Yamamoto described the catalytic (2+2+1) cycloaddition of 1,6-diynes and DMSO to form bicyclic furans (Scheme 14).[124] Remarkably, in these processes, DMSO serves as an *O*-atom transfer agent. Although the initially reported process was restricted to aryl-substituted diynes, the authors later found that the reactions could be conducted at lower temperature using nitrones as *O*-atom donors which, in turn, enabled use of silyl-substituted alkynes.[125] Efforts to elucidate the reaction mechanism via experimental and computational studies corroborate a catalytic cycle involving rapid oxidative coupling of the 1,6-diyne to form ruthenacyclopentadiene followed by rate-determining oxygen atom transfer.[126]

Scheme 14. Ruthenium-catalyzed (2+2+1) cycloadditions with oxygen atom transfer reported by Yamamoto.

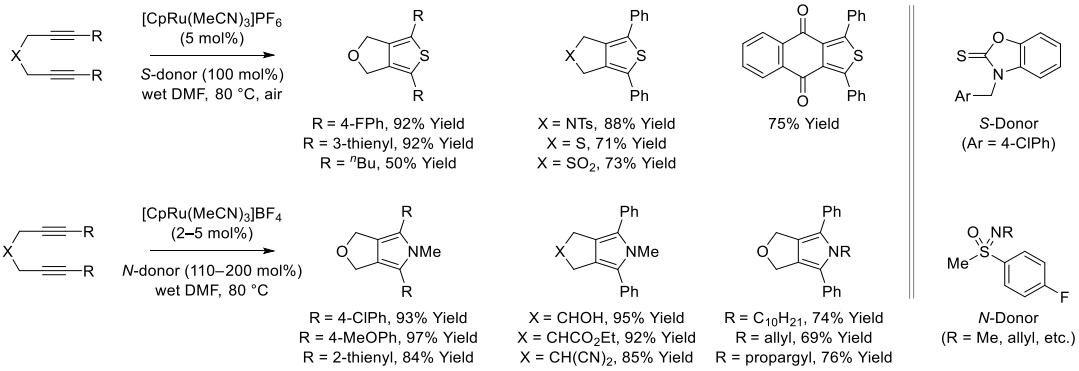


In 2016, Yamamoto developed related (2+2+1) cycloadditions of 1,6-diynes that occur with *S*-atom transfer, providing access to tetrasubstituted thiophenes (Scheme 15).[127] Thionocarbamates were identified as the optimal *S*-atom donors. Lawesson's reagent or elemental sulfur (S_8) failed to provide cycloadducts in useful yield. Isotopic-labeling experiments implicate water-promoted sulfur-atom transfer (not shown). More recently, in 2018, Yamamoto reported *N*-atom-transfer cycloadditions of 1,6-diynes based on the use of sulfoximines as nitrene equivalents.[128] This method delivers tetrasubstituted pyrroles that would be challenging to prepare by other means.

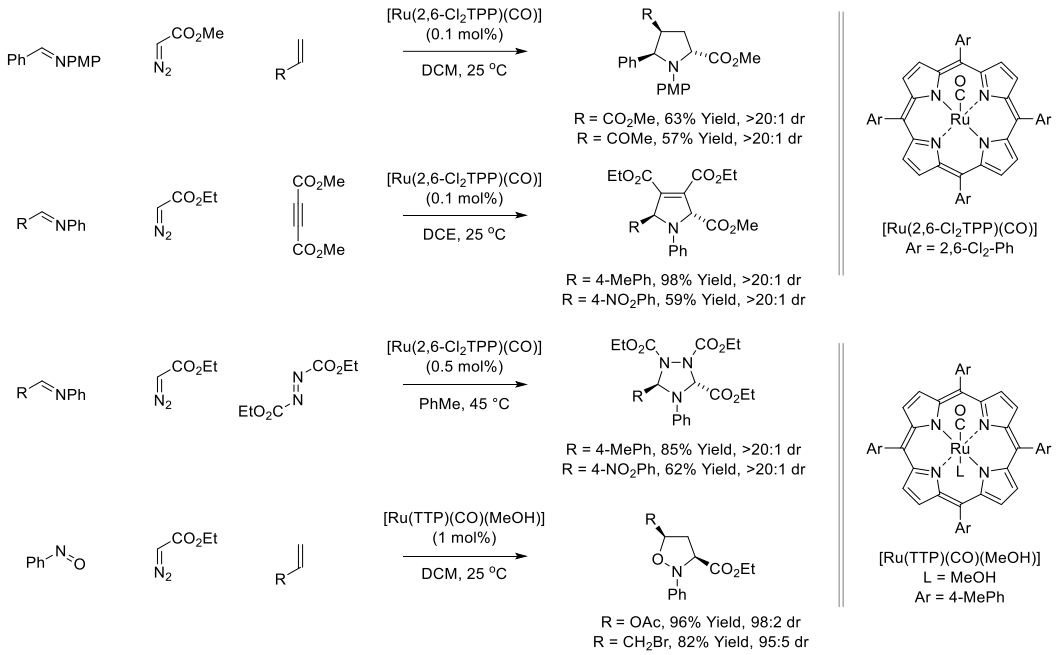
In 2003, Che reported a ruthenium porphyrin-catalyzed (2+2+1) cycloaddition of imines and α-diazoacetates with electron-deficient alkenes or alkynes to form functionalized pyrrolidines (Scheme 16).[129] In these processes, the ruthenium porphyrin reacts with the α-diazoacetate to provide a ruthenium carbenoid, which is transferred to the *N*-aryl aldimines to afford an azomethine ylide. Subsequent 1,3-dipolar cycloaddition with α,β-unsaturated carbonyl partners provides pyrrolidines and 3,4-dehydropyrrolidines as single diastereomers in high yield. Good levels of asymmetric induction were observed using (-)-8-phenylmenthol diazoesters; however, absolute stereochemistry was undetermined

(not shown).[130] It was subsequently shown that use of dialkyl azodicarboxylates and nitrosoarenes as 2π-components enables formation of 1,2,4-triazolidines and isoxazolidines, respectively.[131,132]

Scheme 15. Ruthenium-catalyzed (2+2+1) cycloadditions with sulfur and nitrogen atom transfer reported by Yamamoto.



Scheme 16. Ruthenium porphyrin-catalyzed (2+2+1) cycloadditions of imines and α-diazoacetates with olefins, azodicarboxylates or alkynes reported by Che.

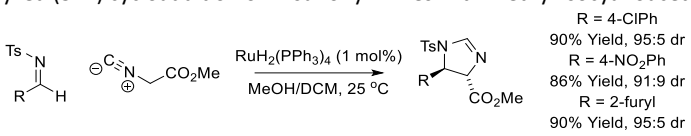


2.2 (3+2) Cycloadditions

2.2.1 Dipolar (3+2) Cycloadditions

In 1997, Lin described a $RuH_2(PPh_3)_4$-catalyzed stereoselective cycloaddition of *N*-sulfonylimines with methyl isocyanoacetate to provide *trans*-2-imidazolines (Scheme 17).[133] A mixed solvent system containing methanol was found to influence stereoselectivity and conversion more than the choice of ligand. As base-catalyzed *N*-sulfonylimine-isocyanoacetate cycloadditions have been described,[134] it is doubtful this process involves organoruthenium intermediates as suggested by the author. Rather, in the presence of methanol, the ruthenium hydride is expected to form a ruthenium alkoxide that simply serves as a Brønsted basic catalyst.

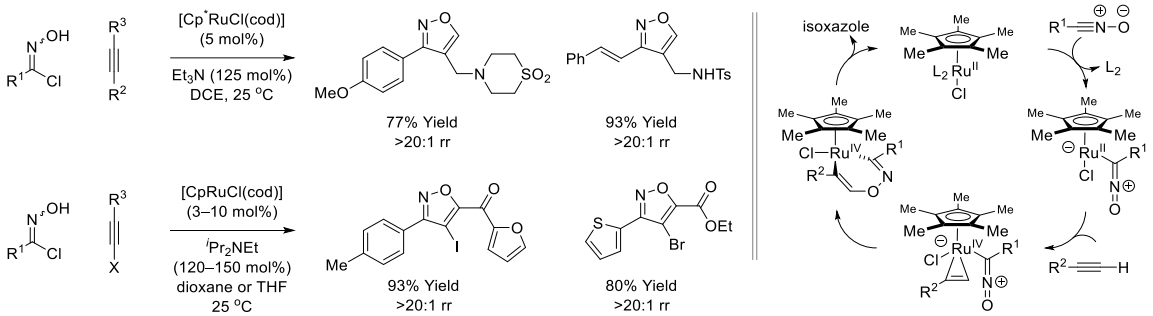
Scheme 17. Ruthenium-catalyzed (3+2) cycloaddition of *N*-sulfonylimines with methyl isocyanoacetate reported by Lin.



In 2008, Fokin reported ruthenium-catalyzed nitrile oxide-alkyne cycloadditions to form isoxazoles (Scheme 18).[135] Using [Cp*RuCl(cod)] as precatalyst, nitrile oxides (formed from hydroximoyl chlorides and Et_3N) react with terminal or internal alkynes to deliver 3,4-di- or 3,4,5-trisubstituted isoxazoles, respectively. The ruthenium-catalyzed reactions occur with an inversion of regioselectivity compared to the thermal and copper-catalyzed cycloadditions.[136,137] The authors propose a catalytic cycle in which nitrile oxide-alkyne oxidative coupling forms a ruthenacycle, which reductively eliminates to release the oxazole. In 2014, it was demonstrated that 1-haloalkynes participate in such cycloadditions, enabling access to 4-haloisoxazoles.[138] In 2018, Kniess applied the conditions reported by Fokin[135] to the synthesis of 3,4-diaryl isoxazole-containing derivatives of valdecoxib, a COX-2 inhibitor (not shown).[139]

Ruthenium-catalyzed alkyne-azide cycloadditions[52-55] and ruthenium-catalyzed dipolar cycloadditions in which the metal simply serves as a Lewis acid catalyst are beyond the scope of this monograph and the reader is referred to the review literature.[140-142]

Scheme 18. Ruthenium-catalyzed dipolar (3+2) cycloadditions of nitrile oxides and alkynes report by Fokin.



2.2.2 Carbene-Mediated (3+2) Cycloadditions

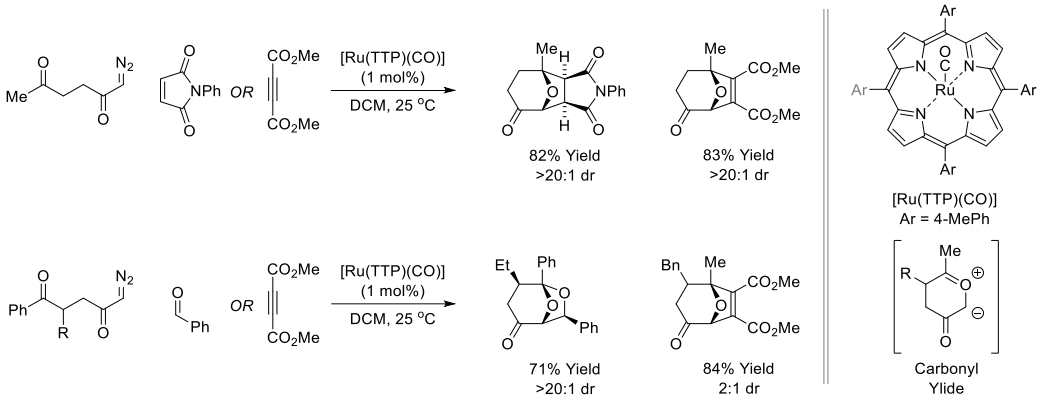
In 2002, Che reported ruthenium porphyrin-catalyzed 1,3-dipolar (3+2) cycloadditions wherein carbonyl ylides are formed from α-diazo ketones (Scheme 19).[143,144] In their initial studies,[143] unsubstituted α-diazo ketones were shown to engage in 1,3-dipolar (3+2) cycloadditions with a range of dipolarophiles, including maleimide and dimethyl acetylenedicarboxylate, to form oxa-[3.2.1]-bicycles in good yield with complete *exo*-diastereoselectivity. Notably, using a soluble poly(ethylene glycol)-supported ruthenium-porphyrin, cycloaddition could be performed at 0.1 mol% catalyst loading with no apparent loss of catalytic activity after 7 cycles (not shown). In subsequent work,[144] substituted α-diazo ketones were explored. However, diastereoselectivity was found to be highly substrate dependent.

In 2004, Chappellet and Müller reported enantioselective (3+2) cycloadditions of ethyl diazopyruvate with enol ethers using a PyBOX-modified ruthenium catalyst (Scheme 20).[145,146] Under optimal conditions, the (3+2) cycloaddition of 2,3-dihydrofuran occurred in good yield, albeit with moderate levels of enantiocontrol.[145] Absolute stereochemistry of the cycloadducts was not determined. In subsequent work, the authors developed ruthenium-catalyzed cycloadditions using phenyliodonium ylides as carbene precursors; however, low yields and negligible levels of enantioselectivity were observed (not shown).[146]

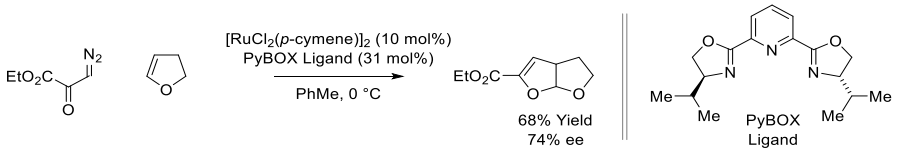
In 2013, Lee reported ruthenium-catalyzed (3+2) cycloadditions of α-diazo-1,3-dicarbonyl compounds with activated olefins (Scheme 21).[147] As illustrated in (3+2) cycloadditions of α-diazo-dimedone, exposure to substoichiometric quantities of $[Ru(PPh_3)_3Cl_2]$ in toluene solvent results in the

conversion of electronically diverse alkenes to the corresponding dihydrofurans. In each case, single regioisomers were observed. The authors used this method to generate a small library of dihydrofurans that displayed potent antibacterial activity (not shown).[148] In subsequent work, identical conditions were applied to the conversion of terminal alkynes to furans.[149] Exposure of cyclopropene byproducts to the reaction conditions resulted in furan formation, suggesting these transformations proceed through a mechanism involving tandem cyclopropanation-cycloisomerization. Later, in 2017, Gu demonstrated that the aforementioned transformations could be conducted using ruthenium catalysts immobilized on functionalized hypercrosslinked polymers (not shown).[150]

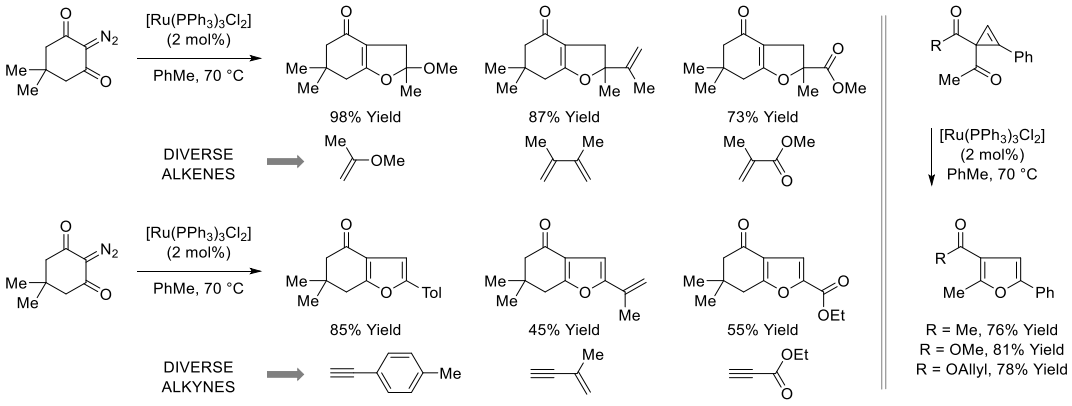
Scheme 19. Ruthenium porphyrin-catalyzed dipolar (3+2) cycloadditions of carbonyl ylides reported by Che.



Scheme 20. Ruthenium-catalyzed cycloaddition of ethyl diazopyruvate with 2,3-dihydrofuran reported by Chappellet and Müller.

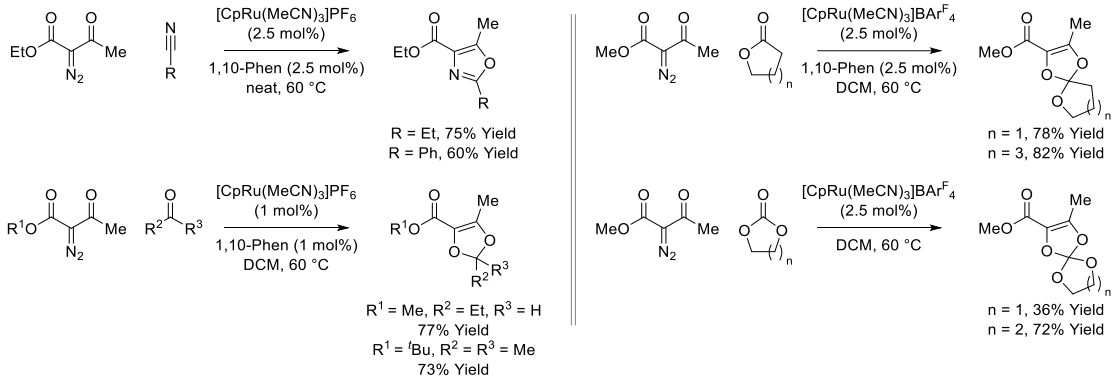


Scheme 21. Ruthenium-catalyzed dipolar (3+2) cycloadditions of α-diazo-dimedone with olefins or alkynes reported by Lee.



In 2011, Lacour reported ruthenium-catalyzed (3+2) cycloadditions of α-diazo-1,3-dicarbonyl compounds with nitriles and carbonyl compounds to form oxazoles and dioxoles, respectively (Scheme 22).[151] Enantioselective (3+2) cycloadditions using ruthenium catalysts modified by PyOX ligands were attempted but low levels of enantioselectivity were observed (not shown). Later, in 2016, Lacour reported related cycloadditions of α-diazo-1,3-dicarbonyl compounds with cyclic lactones and cyclic carbonates to form spirocyclic orthoesters and orthocarbonates, respectively (Scheme 22).[152] These reactions represent the first examples of intermolecular (3+2) cycloadditions of metal carbenes with esters and carbonates.

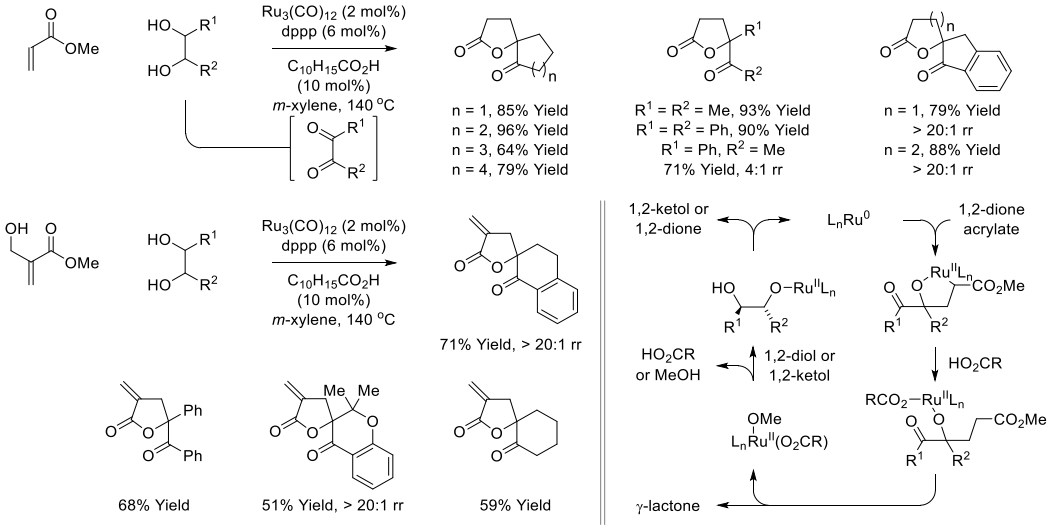
Scheme 22. Ruthenium-catalyzed dipolar (3+2) cycloadditions of α-diazo-1,3-dicarbonyl compounds with nitriles and carbonyl compounds reported by Lacour.



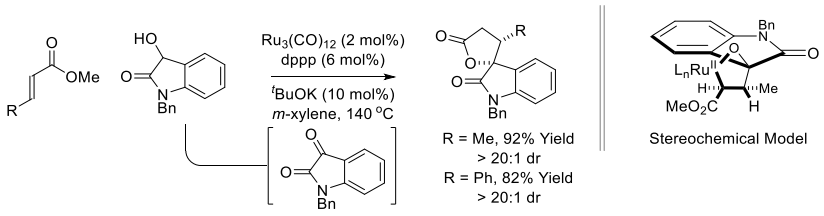
2.2.3 (3+2) Cycloadditions via Hydrogen Transfer

In 2013, Krische reported oxidative (3+2) cycloadditions of 1,2-diols with acrylic esters to form γ-lactones (Scheme 23).[153] The reaction mechanism involves ruthenium(0)-mediated oxidative coupling of the acrylate with a transient 1,2-dione to form an oxaruthenacycle. Protonolytic cleavage of the oxaruthenacycle by the carboxylic acid cocatalyst,[154,155] 1-adamantanecarboxylic acid, triggers lactonization. One equivalent of methyl acrylate is required as sacraficial hydrogen acceptor to mediate diol or ketol dehydrogenation. For acrylic esters bearing an α-hydroxymethyl-substituent, elimination of water occurs at the stage of the oxaruthenacycle, enabling formation of α-methylene-γ-butyrolactones. In the same study, redox-neutral cycloadditions of *N*-benzyl 3-hydroxy-2-oxindole with β-substituted acrylic esters were described (Scheme 24).[153] The spiro-γ-lactones are formed in excellent yields as single diastereomers. The observed diastereoselectivity was explained on the basis of the indicated model, in which the carbomethoxy group is oriented distal with respect to C4 of the oxindole ring.

Scheme 23. Ruthenium-catalyzed oxidative (3+2) cycloadditions of 1,2-diols with acrylic esters reported by Krische.

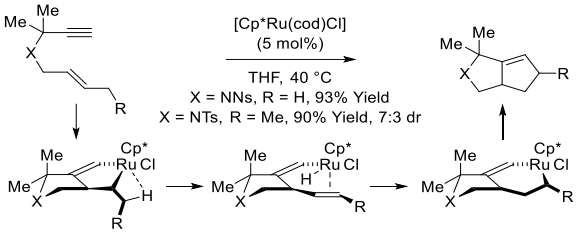


Scheme 24. Ruthenium-catalyzed redox-neutral (3+2) cycloadditions of *N*-benzyl 3-hydroxy-2-oxindole with β-substituted acrylic esters reported by Krische.



As demonstrated by Liu in 2019, ruthenium complex [Cp*Ru(cod)Cl] catalyzes intramolecular (3+2) cycloaddition of (*E*)-1,6-enynes to form [3.3.0] bicycles (Scheme 25).[156] Deuterium labeling and DFT calculations support a mechanism that involves initial alkyne-alkene oxidative coupling to deliver a ruthenacyclopentene, which undergoes internal hydrogen transfer via β-hydride elimination-hydroruthenation. This isomerization converts the ruthenacyclopentene to the ruthenacyclohexene, which can then undergo C-C reductive elimination to form the cycloadduct. Thorpe-Ingold effects[105] induced by geminal substitution in the alkyne tether were essential for efficient cycloaddition and to prevent formation of Alder-ene byproducts.

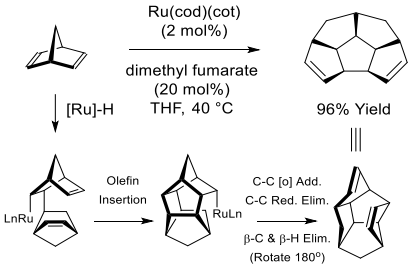
Scheme 25. Ruthenium-catalyzed intramolecular (3+2) cycloadditions of (*E*)-1,6-enynes by Liu.



2.2.4 (3+2) Cycloadditions via C-C and C-N σ-Bond Activation

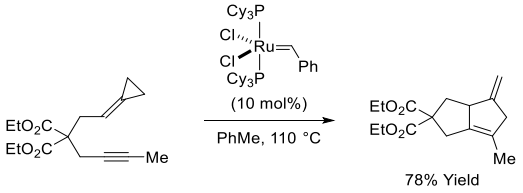
A remarkable dimerization of 2,5-norbornadiene to furnish pentaquinanes was reported in 1994 by Mitsudo and Watanabe (Scheme 26).[157] This process is catalyzed by the zero-valent ruthenium complex Ru(cod)(cot). Electron deficient olefinic additives, such as dimethyl fumarate (dmfm), are required.[158] In 1999, further exploration of the reaction revealed that the olefin additive underwent ligand exchange to form $Ru(cot)(dmfm)_2$, which serves as the active catalyst.[159]

Scheme 26. Ruthenium-catalyzed dimerization of 2,5-norbornadiene reported by Mitsudo and Watanabe.



In 2004, Mascareñas demonstrated that the first-generation Grubbs catalyst will promote intramolecular (3+2) cycloaddition of 1,6-enynes that incorporate alkynylidenecyclopropane moieties (Scheme 27).[160] The ruthenium complexes $Cp^*Ru(MeCN)_3PF_6/Et_4NCl$ or $Cl_2Ru(PPh_3)_3$ also are competent catalysts, providing the (3+2) cycloadduct in 11% and 35% yield, respectively (not shown). While the catalytic mechanism remains unclear, these data suggest non-carbene ruthenium species generated under the reaction conditions are responsible for the observed non-metathetic behavior.

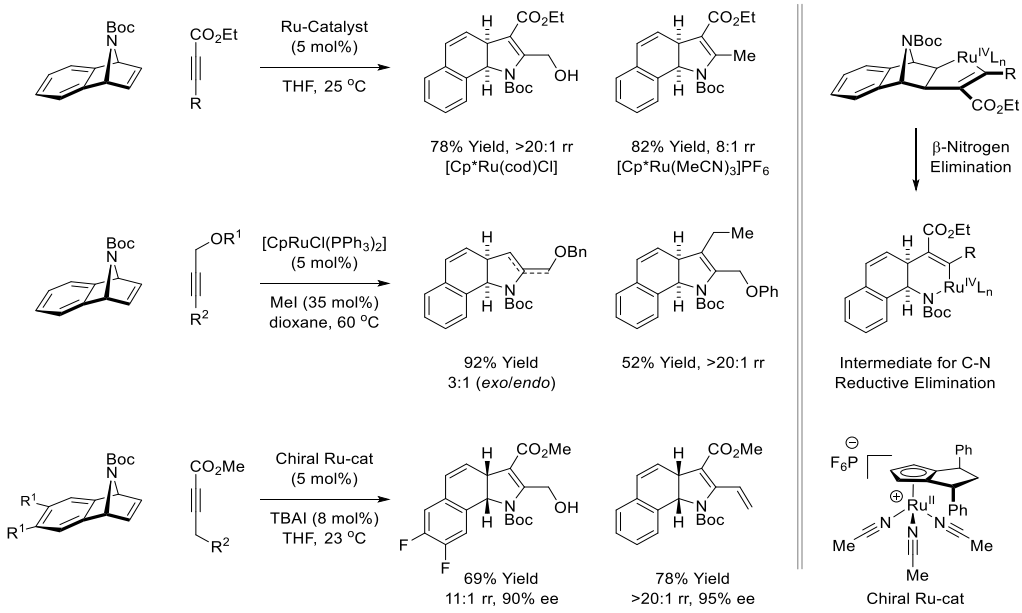
Scheme 27. Ruthenium-catalyzed intramolecular (3+2) cycloadditions of alkynylidenecyclopropanes reported by Mascareñas.



In 2007, Tam developed a ruthenium-catalyzed (3+2) cycloaddition of aza-benzonorbornadienes with conjugated alkynoates to form dihydrobenzoindoles (Scheme 28).[161] The neutral ruthenium complex [Cp*Ru(cod)Cl] was an effective catalyst for cycloadditions of γ-hydroxy alkynoates. For other acetylenic esters, the cationic ruthenium catalyst $[Cp^*Ru(MeCN)_3]PF_6$ was required. *N*-Carbamoyl protecting groups

were incorporated to suppress competing formation of [2+2] cycloadducts. In contemporaneous work, Tenaglia explored reported (3+2) cycloadditions of aza-benzonorbornadienes with alkynes using a cationic ruthenium catalyst generated *in situ* from [CpRuCl(PPh_3)$_2$] and iodomethane (Scheme 28).[162] Non-symmetric internal alkynes, including terminal alkynes, were converted to the cycloadducts with complete regiocontrol, favoring adducts in which the more polar functional group is placed proximal to the carbon atom vicinal to nitrogen. The reaction mechanism involves regioselective alkyne-alkene oxidative coupling to provide a ruthenacyclopentene, which upon β-nitrogen elimination forms a six-membered aza-ruthenacycle. Subsequent C-N reductive elimination delivers the cycloadduct. Competing C-C reductive elimination from the ruthenacyclopentene intermediate also can occur, producing cyclobutene side products (not shown). Computational studies by Chass implicate a different pathway involving isomerization of an initially formed cyclobutene [2+2] cycloadduct,[163] but this hypothesis is inconsistent with experimental data reported by Cramer (not shown).[164] In 2018, enantioselective variants of the ruthenium-catalyzed alkynoate-aza-benzonorbornadiene (3+2) cycloadditions were developed by Cramer using a novel class of C_2-symmetric cyclopentadienyl ligands (Scheme 28).[164] The addition of tetrabutylammonium iodide (TBAI) was required to enforce high levels of conversion to the cycloadduct. Diverse alkynoates and aza-benzonorbornadienes were tolerated, affording the dihydrobenzoindoles with uniformly high levels of regio- and enantioselectivity.

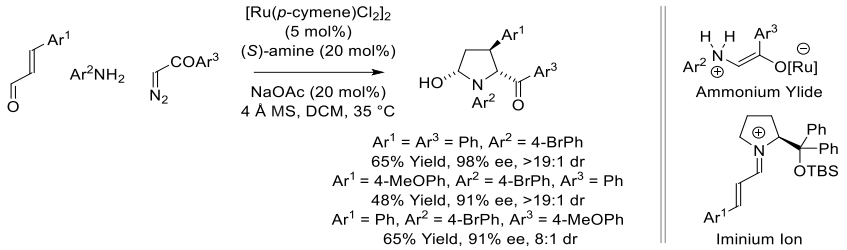
Scheme 28. Ruthenium-catalyzed (3+2) cycloadditions of aza-benzonorbornadienes with conjugated alkynoates reported by Tam, Tenaglia and Cramer.



2.3 (3+1+1) Cycloadditions

In 2017, Hu reported the enantioselective (3+1+1) cycloaddition reaction of enals, anilines and α-diazoacetophenones to form trisubstituted pyrrolidines (Scheme 29).[165] The authors exploit a dual catalytic system in which the aniline, the α-diazoacetophenones and ruthenium combine to form an ammonium ylide, which participates in an asymmetric conjugate addition to the iminium ion that arises upon condensation of the enal with the Hiyashi-Jørgensen secondary amine cocatalyst. Hydrolytic release of the organocatalyst followed by cyclization to form the *N*,*O*-acetal completes the catalytic cycle.

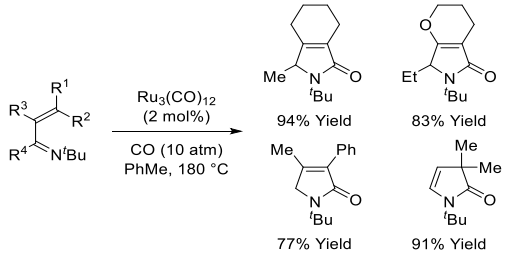
Scheme 29. Enantioselective ruthenium-catalyzed (3+1+1) cycloaddition of enals and α-diazoacetophenones reported by Hu.



2.4 (4+1) Cycloadditions

A ruthenium-promoted (4+1) cycloaddition of an α,β-unsaturated imine with CO was reported by Murai in 1999 (Scheme 30).[166] Upon exposure to $Ru_3(CO)_{12}$ under a CO atmosphere at elevated temperature, various conjugated imines or ketimines were converted to α,β-unsaturated γ-lactams. Aromatic imines failed to provide cyclocarbonylated products under these conditions. The authors proposed that the mononuclear ruthenium species $Ru(CO)_4$ undergoes cyclometalation with the unsaturated imines prior to migratory insertion of CO. Subsequent reductive elimination affords β,γ-unsaturated γ-lactams which isomerize to the thermodynamic product if an α-proton is present.

Scheme 30. Ruthenium-catalyzed (4+1) cycloadditions of α,β-unsaturated imines with CO reported by Murai.

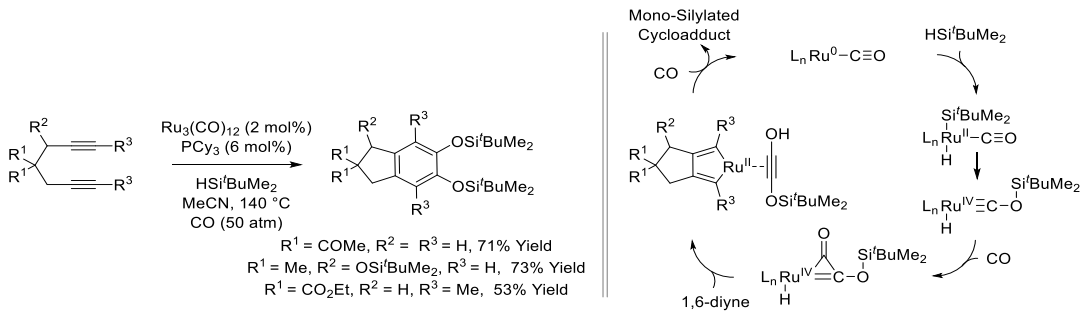


3. Six-Membered Ring Formation

3.1 (2+2+1+1) Cycloadditions

In 1993, Murai reported a ruthenium-catalyzed (2+2+1+1) cycloaddition of 1,6-diynes that involves successive incorporation of two molecules of carbon monoxide, resulting in formation of substituted catechol derivatives (Scheme 31).[167] This process is reductive and requires one equivalent of hydrosilane. The authors propose a mechanism in which oxidative addition of HSi^tBuMe_2 to Ru(0) triggers silyl migration to provide a siloxycarbyne complex. Incorporation of a second carbon monoxide followed by tautomerization and diyne oxidative coupling delivers a ruthenacyclopentadiene complex, which upon alkyne insertion and C-C reductive elimination forms the mono-silylated cycloadduct. Further silylation under the reaction conditions provides the observed product. In 2020, Crudden, Chatani and Murai

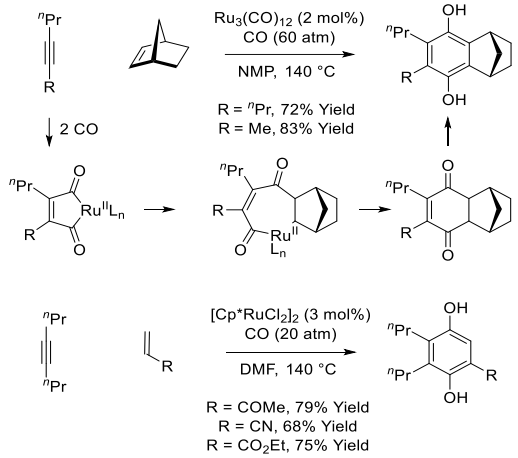
Scheme 31. Ruthenium-catalyzed carbonylative (2+2+1+1) cycloaddition of 1,6-diynes reported by Murai.



demonstrated that, in place of hydrosilane, water could be combined with carbon monoxide in a ruthenium-catalyzed water-gas shift (WGS) reaction to generate 1,2-hydroxyethyne, enabling analogous cycloadditions of 1,5-diynes to generate catechols (not shown).[168]

In 1998, Mitsudo reported the ruthenium-catalyzed (2+2+1+1) cycloaddition of alkynes with norbornene, which involves successive incorporation of two molecules of carbon monoxide, resulting in formation of hydroquinones (Scheme 32).[169] The proposed mechanism is initiated by double carbonylation of the alkyne to form a maleoylruthenium complex that inserts 2-norbornenes. C-C Reductive elimination followed by double tautomerization of the resulting 1,4-dione provides the hydroquinone. Later, in 2005, Ryu and Mitsudo identified reaction conditions that allowed for cycloaddition of symmetric alkynes with electron-deficient alkenes (Scheme 32).[170] An analogous catalytic cycle was proposed. In 2016, Sarpong applied this doubly carbonylative ruthenium-catalyzed (2+2+1+1) cycloaddition to the formal syntheses of the indole alkaloids herbindole B and *cis*-trikentrin A (not shown).[171]

Scheme 32. Ruthenium-catalyzed carbonylative (2+2+1+1) cycloaddition of alkynes with norbornenes or electron-deficient alkenes reported by Mitsudo.

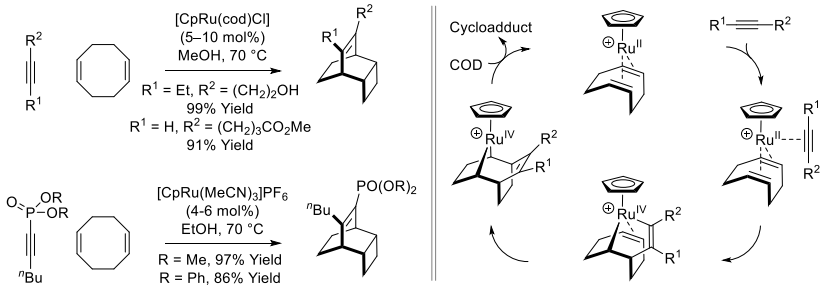


3.2 [2+2+2] Cycloadditions to Form Carbocycles

3.2.1 [2+2+2] Cycloadditions of COD and NBD as $2_{2\pi}$ Partners

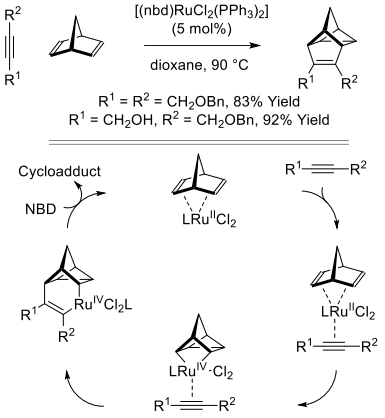
In 1993, Trost reported a remarkable transformation of 1,5-cyclooctadiene, a common spectator ligand, in a ruthenium-catalyzed bis-homo-Diels-Alder cycloaddition with alkynes to form [2.2.2] bicycles that are fused to a cyclobutane ring (Scheme 33).[172] Both terminal and internal alkynes are competent partners for cycloaddition. The authors posit that the catalytic cycle is initiated by methanol-assisted dissociation of chloride from ruthenium to form a cationic Cp-ruthenium(II) complex. Alkyne coordination followed by successive olefin insertion and C-C reductive elimination provides the cycloadduct. This interpretation of the reaction mechanism is supported by computational studies,[173] which suggest alkyne-alkene oxidative coupling to form the indicated ruthenacyclopentene is the rate-determining step. The catalytic competence of related cationic ruthenium complexes was subsequently demonstrated by

Scheme 33. Ruthenium-catalyzed bis-homo-Diels-Alder cycloadditions of 1,5-cyclooctadiene with alkynes reported by Trost and Tam.



Gimeno's use of the indenyl ruthenium(II) precatalyst [Ru(η^5-C_9H_7)Cl(cod)],[174] Hintermann's use of [CpRu(cod)(MeCN)]PF_6[175] and Tam's application of commercial Cp*RuCl(cod) (not shown).[176] In 2019, Tam further extended the scope of the reaction to include acetylenic phosphonates as 2π-components (Scheme 33).[177]

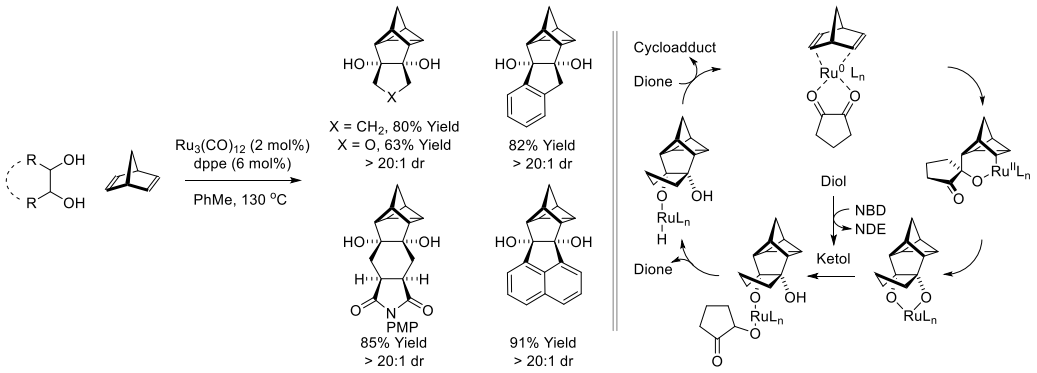
Scheme 34. Ruthenium-catalyzed homo-Diels-Alder cycloaddition of norbornadiene with alkynes reported by Tenaglia.



In 2004, Tenaglia reported a ruthenium-catalyzed homo-Diels-Alder reaction of internal alkynes with norbornadiene to form 8,9-disubstituted deltacyclenes (Scheme 34).[178] The ruthenium catalyst [(nbd)$RuCl_2(PPh_3)_2$] was found to provide optimal yields of cycloadduct. The reaction is initiated by dissociation of a phosphine ligand followed by alkyne coordination. Subsequent oxidative coupling of norbornadiene delivers a ruthenacyclobutane, which upon alkyne migratory insertion and C-C reductive elimination from the resulting ruthenacyclohexene delivers the cycloadduct. The same authors reported an intramolecular variant of this cycloaddition in 2007 (not shown).[179] Additionally, in 2011 Tam further extended the scope of the reaction to include acetylenic phosphonates as 2π-components (not shown).[180]

In 2017, Krische reported a ruthenium(0)-catalyzed transfer hydrogenative cycloaddition of norbornadiene with vicinal diols to form 8,9-cycloalkyl-substituted deltacyclene diols with complete *exo*-diastereoselectivity (Scheme 35).[181] Remarkably, the transformation is redox-independent and can be conducted with from the diol, ketol or 1,2-dione oxidation levels (not shown). The proposed mechanism, which was corroborated by computational studies performed by Li in 2019,[182] is initiated by 1,2-dione-norbornadiene oxidative coupling to form an oxaruthenacycle, which inserts the appendant ketone to form a dioxaruthenacycle. Ketol-mediated transfer hydrogenolysis of the dioxaruthenacycle delivers the *exo*-cycloadduct and regenerates the requisite ketone. As the overall process is oxidative, one equivalent of norbornadiene serves as hydrogen acceptor in the ruthenium-catalyzed dehydrogenation of the 1,2-diols to the 1,2-ketol.

Scheme 35. Ruthenium-catalyzed [2+2+2] cycloaddition of norbornadiene with 1,2-diols reported by Krische.



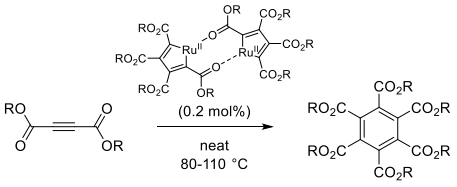
3.2.2 [2+2+2] Cycloadditions of 3 Alkynes

Metal-catalyzed alkyne trimerization via [2+2+2] cycloaddition to form aromatic compounds has been documented in the review literature.[183-188] Here, ruthenium-catalyzed alkyne [2+2+2] cycloadditions are catalogued on the basis of catalyst structure. Intermolecular alkyne [2+2+2] cycloadditions, as well as

reactions of tethered diynes with alkynes and completely intramolecular reactions of acyclic triynes are all described in this section.

The first intermolecular ruthenium-catalyzed alkyne trimerization via [2+2+2] cycloaddition was reported in 1989 by Lindner (Scheme 36).[189] The catalyst, which is a ruthenacyclopentadiene dimer formed from the reaction of $Ru_3(CO)_{12}$ with dimethyl or diethyl acetylenedicarboxylate, promotes efficient trimerization of acetylenedicarboxylates to form mellitic acid ester. As suggested by the structure of the catalyst, a mechanism involving ruthenium(0)-mediated oxidative coupling of the acetylenedicarboxylate to form ruthenacyclopentadiene followed by alkyne insertion and C-C reductive elimination was postulated.

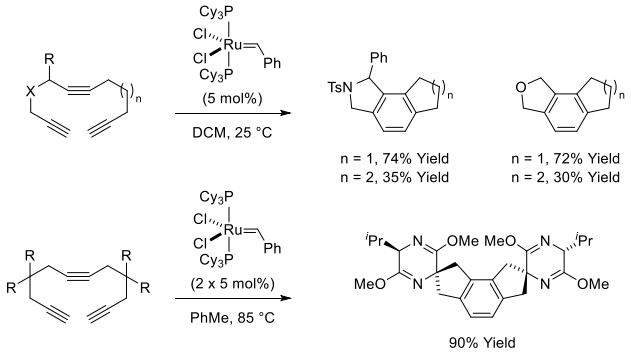
Scheme 36. Intermolecular ruthenium-catalyzed [2+2+2] cyclotrimerization of alkynes reported by Lindner.



R = Me, 98% Yield
R = Et, 97% Yield

As first reported by Blechert in 1997, the first-generation Grubbs catalyst is capable of promoting intramolecular [2+2+2] cycloadditions of acyclic triynes to furnish tricyclic cycloadducts that incorporate a central benzene ring (Scheme 37).[190] Acyclic tetraynes also form benzene-containing cycloadducts rather than products of [2+2+2+2] cycloaddition (not shown).[190] This process was most effective for the generation of benzene derivatives bearing fused 5-membered rings. The authors propose a mechanism involving a cascade of four metathesis reactions. Subsequent computational studies, however, refute this interpretation and corroborate a conventional non-metathetic pathway involving ruthenacyclopentadiene formation followed by alkyne insertion and C-C reductive elimination.[191] In 2002, Undheim applied this process to the construction of the indicated bis-(pyrazine spirocycle) and, therefrom, bis-(α-amino acid) derivatives (Scheme 37).[192,193] Additional examples of such alkyne [2+2+2] cycloadditions that are closely related to those initially described by Blechert were reported by Shi in 2013 (not shown).[194]

Scheme 37. Use of the first-generation Grubbs catalyst in intramolecular alkyne [2+2+2] cycloadditions of acyclic triynes reported by Blechert and Undheim.

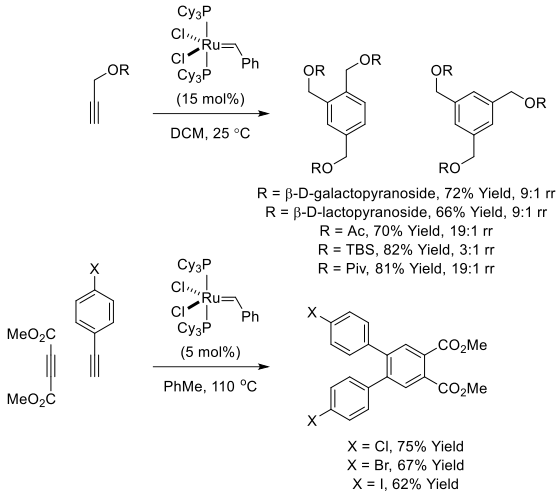


The first-generation Grubbs catalyst can also promote intermolecular alkyne [2+2+2] cycloadditions to furnish trisubstituted benzenes, as reported by Roy in 1999 (Scheme 38).[195] This reaction was applied to the cyclotrimerization of propargyl alcohol derivatives, including pyranosides, silyl ethers and esters. Mixtures of 1,2,4- and 1,3,5-trisubstituted benzenes were observed with a preference for the 1,2,4-trisubstituted regioisomers. In 2011, Kotha demonstrated crossed [2+2+2] cycloadditions of phenylacetylenes with dimethyl acetylenedicarboxylate (DMAD) to form 4,5-diarylphthalic acid esters using the first-generation Grubbs' catalyst (Scheme 38).[196] Other ruthenium alkylidene complexes were evaluated for their ability to promote alkyne [2+2+2] cyclotrimerization, including those reported by Karabulut[197,198] and phosphine-free ruthenium alkylidene complexes described by Czeluśniak (not shown).[199,200]

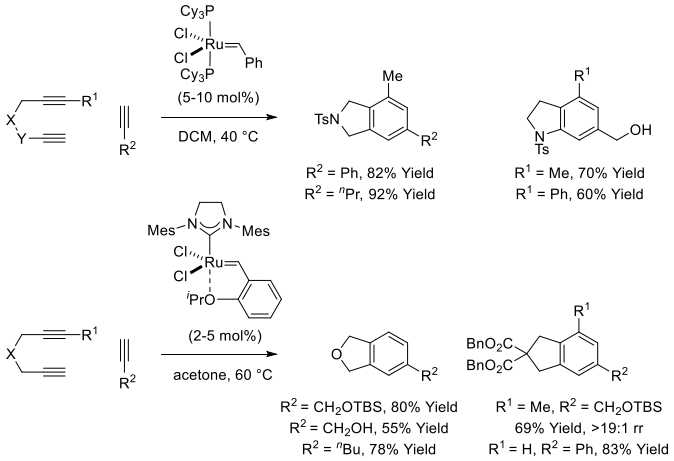
The first-generation Grubbs catalyst is also effective in promoting the chemo- and regioselective [2+2+2] cycloaddition of 1,6-diynes with alkynes to form 4,6-disubstituted isoindolines and indolines, as described by Witulski in 2000 (Scheme 39).[201] The authors demonstrated that use of Wilkinson's catalyst reversed regioselectivity to furnish the 4,5-disubstituted arenes, but was generally less tolerant of sterically demanding reactants (not shown). In work by Pérez-Castells in 2010, the second-generation

Hoveyda-Grubbs catalyst was used to promote the [2+2+2] cycloaddition of 1,6-diynes with alkynes to form related ring systems (Scheme 39).[202] The authors noted, however, that first-generation Grubbs catalyst delivered better results for the synthesis of more highly substituted arenes (not shown).

Scheme 38. Use of the first-generation Grubbs catalyst in intermolecular alkyne [2+2+2] cycloadditions reported by Roy and Kotha.

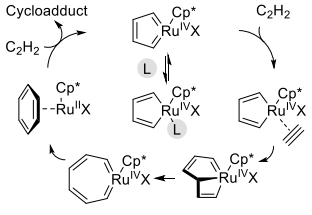


Scheme 39. Use of the first-generation Grubbs catalyst and second-generation Hoveyda-Grubbs catalyst in [2+2+2] cycloadditions of 1,6-diynes with alkynes reported by Witulski and Pérez-Castells, respectively.



Although η^5-cyclopentadienyl complexes are used widely to catalyze a variety of transformations, an initial attempt by Kirchner to exploit $[RuCp(MeCN)_3]PF_6$ as a catalyst for alkyne [2+2+2] cycloaddition led to relatively modest results due to formation of inactive $[CpRu(\eta^6\text{-arene})]^+$ complexes (not shown).[203] In special cases, the parent Cp-ligand can be effective (not shown);[204-206] however, corresponding ruthenium complexes bearing the η^5-pentamethylcyclopentadienyl or "Cp*" ligand are far more general catalysts for alkyne [2+2+2] cycloaddition. An abundance of data supports the indicated general catalytic mechanism for [2+2+2] cycloadditions catalyzed by [CpRuX] or [Cp*RuX] (Scheme 40).[188] Cycloaddition is initiated by alkyne-alkyne oxidative coupling to form a ruthenacyclopentadiene[207] or dicarbene ruthenacyclopentatriene species.[208,209] As corroborated by single crystal X-ray diffraction data,[209]

Scheme 40. Key intermediates and general mechanism of [CpRuX] and [Cp*RuX]-catalyzed [2+2+2] cycloaddition.

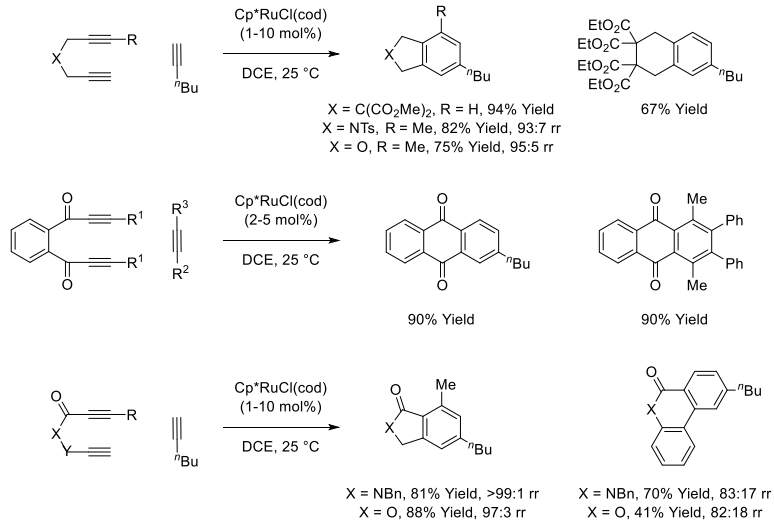


the degree of ligation at ruthenium partitions formation of these structurally distinct species.[188] Addition of a third alkyne to the coordinatively saturated ruthenacyclopentadiene is followed by migratory insertion to furnish a ruthenacycloheptatriene.[210] In 2003, computational studies on acetylene cyclotrimerization by Kirchner and Calhorda suggest this species converts to the more stable aromatic ruthenacycloheptatetraene.[210] Reductive elimination delivers $CpRuCl(\eta^2\text{-}C_6H_6)$, which releases the cycloadduct to close the catalytic cycle.

As demonstrated in pioneering work by Itoh and Yamamoto in 2000[211] and 2003,[212] exposure of non-symmetric 1,6- and 1,7- diynes to terminal alkynes in the presence of Cp*RuCl(cod) results in cycloaddition with excellent *meta*-selectivity, presumably due to steric influence of the Cp* ligand (Scheme 41). Reactions of homologous 1,7-diynes with 1-hexyne were inefficient, but the yield of cycloadduct could be improved by exploiting Thorpe-Ingold effects.[105] In 2003, Yamamoto extended the scope of the reaction to 1,2-bis(propiolyl)benzenes, which undergo [2+2+2] cycloaddition with alkynes to form substituted anthraquinones (Scheme 41).[213] Remarkably, in 2020, Tomás-Gamasa and Mascareñas performed ruthenium-catalyzed cyclotrimerizations to form anthraquinones inside live mammalian cells, demonstrating intracellular delivery of bioactive compounds that otherwise display poor cell permeability (not shown).[214]

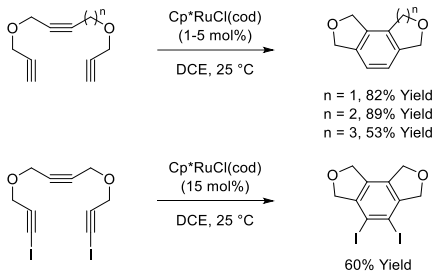
In 2004, Yamamoto reported the synthesis of benzo-fused lactams and lactones through the ruthenium-catalyzed [2+2+2] cycloaddition of 1,6- or 1,7-diynes bearing amide and ester tethers with terminal alkynes (Scheme 41).[215] The regioisomer in which the alkyne substituent resides *para* to the acyl moiety is favored due to the steric influence of the methyl group and the electron-withdrawing effect of the carbonyl.

Scheme 41. Ruthenium-catalyzed [2+2+2] cycloaddition of 1,6- and 1,7-diynes with alkynes reported by Yamamoto.



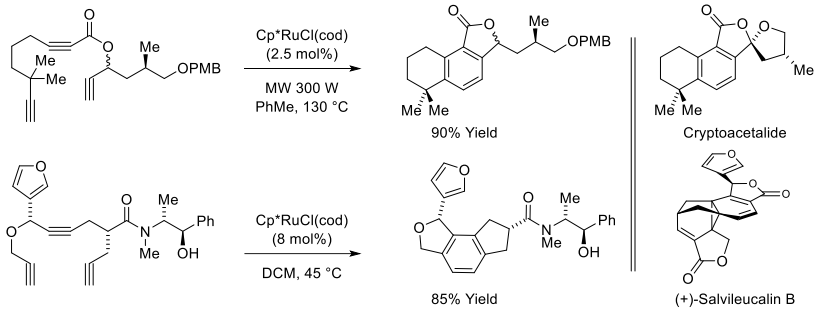
In his 2003 study, Yamamoto also reported highly efficient Cp*RuCl(cod)-catalyzed intramolecular [2+2+2] cycloadditions of acyclic triynes to form tricyclic cycloadducts containing fused 5-, 6-, and 7-membered rings (Scheme 42).[212] In 2006, the same authors applied these conditions to intramolecular [2+2+2] cycloadditions of acyclic diiodotriynes to form hexasubstituted diiodinated benzene derivatives (Scheme 42) and of diiodo-terminated 1,6-diynes and monoalkynes to form iodinated benzene derivatives bearing a wide range of functional groups (not shown).[216] This capability enabled synthesis of 2,5-dihydrofuran-fused quinones from ether-tethered diiododiynes and acetylene (not shown).[217] Interestingly, in a 2010 kinetic study, Yamamoto investigated the performance of a series of polymethylcyclopentadienyl ruthenium complexes in [2+2+2] cycloadditions[218] and found that for reactions of diiododiyne and acetylene, 1,2,4-Me_3CpRuCl(cod) and MeCpRuCl(cod) were the most efficient catalysts. Cycloaddition of the same diyne with phenylacetylene indicated steric interactions from the methyl groups on the Cp ring increase efficiency but decrease regioselectivity. A related study on the intramolecular [2+2+2] cycloadditions of diiodotriynes was reported by Aubert and Gandon in 2011 (not shown).[219]

Scheme 42. Ruthenium-catalyzed intramolecular alkyne [2+2+2] cycloadditions of acyclic triynes reported by Yamamoto.



Intramolecular Cp*RuCl(cod)-catalyzed alkyne [2+2+2] cycloadditions of acyclic triynes have been utilized to great effect in the total synthesis of natural products. In 2010, Deiters reported the first total synthesis of the terpenoid cryptoacetalide using a microwave-mediated alkyne [2+2+2] cyclotrimerization to construct the central benzene ring (Scheme 43).[220] Additionally, in 2011, Reisman completed the first enantioselective total synthesis of the norcaradiene-containing diterpenoid natural product (+)-salvileucalin B (Scheme 43).[221]

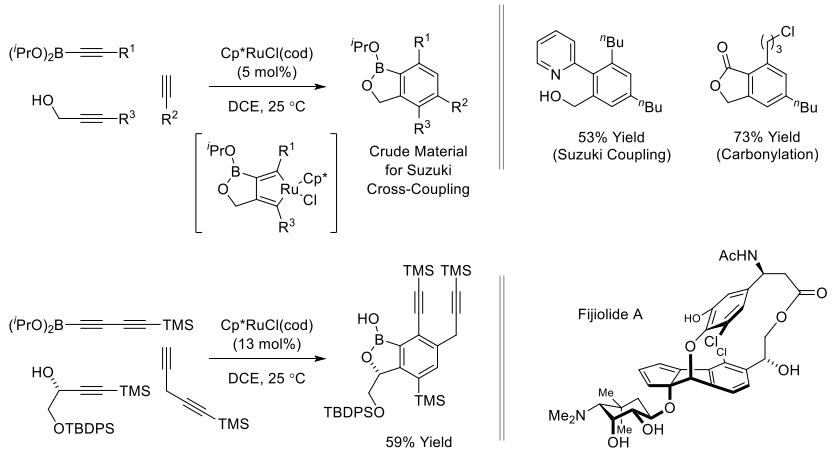
Scheme 43. Ruthenium-catalyzed intramolecular alkyne [2+2+2] cycloadditions of acyclic triynes for the total synthesis of cryptoacetalide and (+)-salvileucalin B reported by Deiters and Reisman, respectively.



In a remarkable advance, Yamamoto demonstrated in 2004 that Cp*RuCl(cod) could catalyze the chemo- and regioselective crossed [2+2+2] cycloaddition of three different non-symmetric alkynes (Scheme 44).[222-224] In this process, condensation of a propargyl alcohol with an alkynylboronate forms a 1,6-diyne-containing boronate ester, which upon oxidative coupling delivers a ruthenacyclopentadiene that inserts the terminal alkyne. The crude arylboronate underwent Suzuki-Miyaura cross-coupling with diverse aryl iodides to afford the corresponding biaryls[222,224] or, as described in subsequent work, could be subjected to carbonylation conditions to form phthalides (Scheme 44).[223] Independent computational studies by Kirchner[210,225] and Saá[226] on the mechanism of the parent Cp-ruthenium(II)-catalyzed alkyne [2+2+2] cyclotrimerization corroborate the proposed oxidative coupling-alkyne insertion pathway. Cp*RuCl(cod)-catalyzed crossed [2+2+2] cycloadditions of DMAD were studied further by Mitsudo,[227,228] Teplý[229] and Kotha,[230] but low isomer selectivities were observed (not shown). A stunning application of

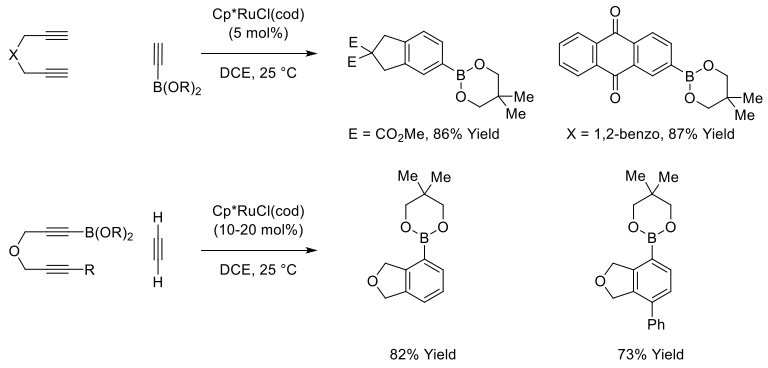
Yamamoto's crossed [2+2+2] cycloaddition of propargyl alcohols, alkynylboronate and terminal alkynes is found in Cramer's total synthesis of the highly complex glycosylated paracyclophane natural product fijiolide A, which was reported in 2015 (Scheme 44).[231] Here, steric interactions between the Cp* ligand and the TMS moiety of the propargyl alcohol at the stage of the ruthenacyclopentadiene guide the regioselectivity of terminal alkyne insertion, allowing the pentasubtituted benzene core of fijiolide A to form as a single constitutional isomer.

Scheme 44. Chemo- and regioselective crossed [2+2+2] cycloaddition of three different non-symmetric alkynes reported by Yamamoto and Cramer's total synthesis of fijiolide A.



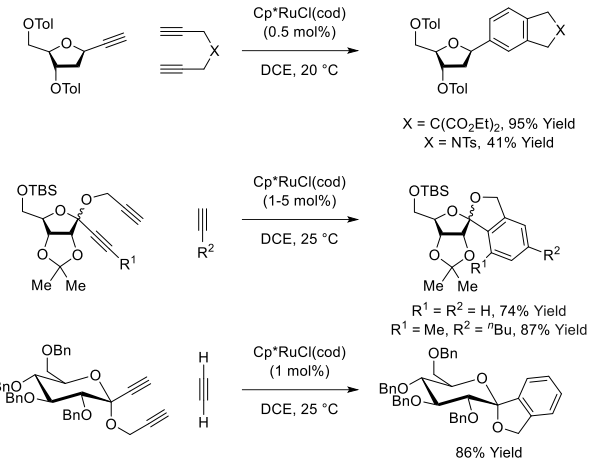
In 2005, Yamamoto demonstrated that the ethynylboronate of neopentyl glycol is a competent partner for [2+2+2] cycloadditions with 1,6- and 1,7-diynes to form arylboronates (Scheme 45).[232] The use of non-symmetric diynes in such cycloadditions resulted in the formation of regioisomeric mixtures (not shown). Yamamoto also showed that 1,6-diynes that incorporate the boronate moiety can react with acetylene to assemble bicyclic *ortho*-arylboronates (Scheme 45).[233] However, when terminal alkynes were used, only a slight preference for the *ortho*-regioisomer was observed (not shown). In 2008, Yamamoto also showed that ethynylboronates can participate in [2+2+2] cycloadditions with diiodo-terminated 1,6-diynes to form cycloadducts that were ultimately converted to oligo(*p*-phenylene ethynylenes) (not shown).[234]

Scheme 45. Use of alkynylboronates in ruthenium-catalyzed [2+2+2] cycloaddition of 1,6-diynes with alkynes reported by Yamamoto.



In 2006, Kotora and Hocek reported [2+2+2] cycloadditions of 1,6-diynes and 1-ethynyl-2-deoxyribose for the synthesis of *C*-aryldeoxyribosides (Scheme 46).[235] Various transition metal complexes beyond Cp*RuCl(cod) were evaluated, including those based on Rh, Ir, Co and Ni. The most general catalyst proved to be Wilkinson's complex, $RhCl(PPh_3)_3$. Later, Yamamoto reported the synthesis of spirocyclic *C*-ribosides (Scheme 46) and *C*-arylglycosides (Scheme 46).[236,237] Use of monoiodo-terminated 1,6-diynes delivered *C*-(*ortho*-iodoaryl)ribosides and *C*-(*ortho*-iodoaryl)glycosides, which were derivatized via palladium- or copper-catalyzed C-C or C-N couplings, respectively (not shown).

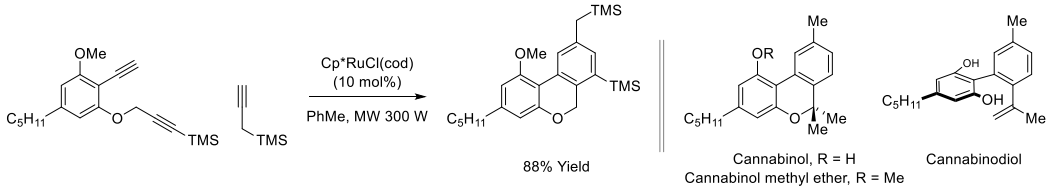
Scheme 46. Ruthenium-catalyzed [2+2+2] cycloaddition for the synthesis of *C*-aryldeoxyribosides, *C*-arylglycosides and *C*-ribosides reported by Kotora, Hocek, and Yamamoto.



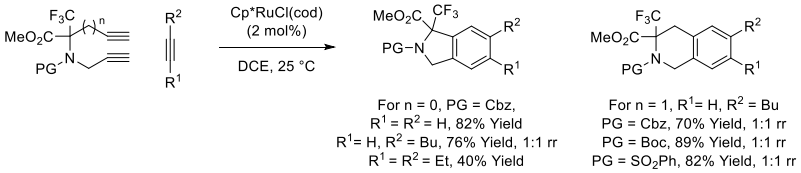
In 2006 and 2007, Deiters explored solid-supported Cp*Ru(cod)Cl-catalyzed [2+2+2] cycloadditions of diynes and monoalkynes, enabling the generation of phthalans,[238] indanones[239] and, in a microwave, a variety of carbo- and heterocycles (not shown).[240] In 2008, Deiters also reported regioselective microwave-mediated [2+2+2] cycloaddition of diynes and alkynes as the key step in syntheses of three cannabinoid natural products, cannabinol, cannabinol methyl ether and cannabinodiol (Scheme 47).[241]

The same year, Dixneuf utilized Cp*Ru(cod)Cl for [2+2+2] cycloaddition of CF_3-containing *N*-tethered 1,6- and 1,7-diynes with alkynes to access fluorinated bicyclic amino acid derivatives (Scheme 48).[242] The cyclized products were formed in good yields over short reaction times using acetylene or terminal alkynes, but internal alkynes gave lower yields of cycloadduct. The cycloaddition could also be promoted by the Grubbs first-generation catalyst, albeit with slightly lower yields (not shown).

Scheme 47. Application of ruthenium-catalyzed 1,6-diyne-alkyne [2+2+2] cycloaddition for the total synthesis of cannabinol, cannabinol methyl ether and cannabinodiol reported by Deiters.



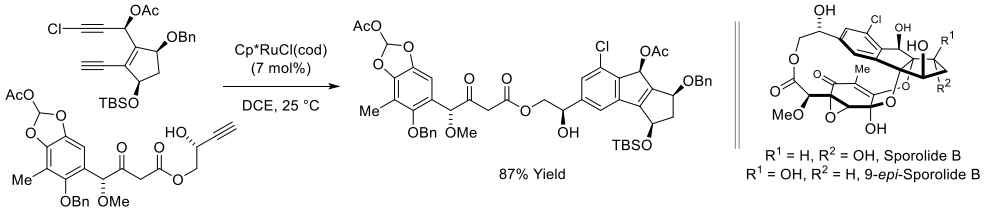
Scheme 48. Cp*Ru(cod)Cl-catalyzed [2+2+2] cycloaddition of 1,6- and 1,7-diynes with alkynes reported by Dixneuf.



In 2009, Nicolaou applied a 1,6-diyne-alkyne [2+2+2] cycloaddition to the synthesis of the marine natural product sporolide B,[243] and the following year, 9-*epi*-sporolide B (Scheme 49).[244] The chemoselectivity displayed in the [2+2+2] cycloaddition is truly remarkable, as both the 1,6-diyne and alkyne partners are highly complex and incorporate numerous sensitive functional groups, including a propargyl acetate, acetylenic chloride and unprotected hydroxyl. Using Cp*RuCl(cod) as precatalyst at

ambient temperature over a mere 30-minute time period, the cycloadduct in which the chloride and hydroxyalkyl side chains exist in a *meta*-relationship was obtained in 87% yield as a single regioisomer.

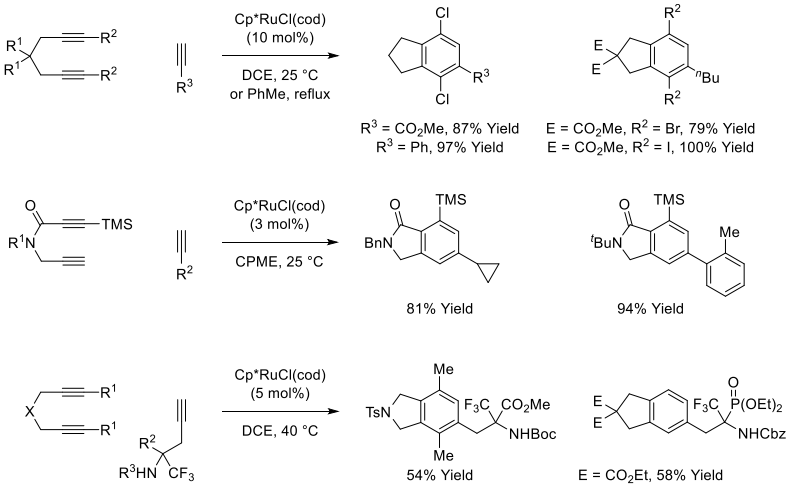
Scheme 49. Application of ruthenium-catalyzed 1,6-diyne-alkyne [2+2+2] cycloaddition to the total synthesis of sporolide B and 9-*epi*-sporolide B reported by Nicolaou.



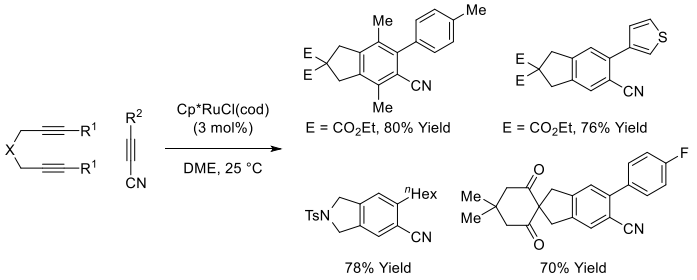
In their 2011 study,[219] Aubert and Gandon also described a ruthenium-catalyzed [2+2+2] cycloaddition of 1,6-diynyl dihalides and terminal alkynes (Scheme 50). Additional reports by Sheppard and Osipov described [2+2+2] cycloadditions of various 1,6-diynes with terminal alkynes to provide polysubstituted isoindolinones[245] (Scheme 50) or protected α-amino carboxylic or alkyl phosphonic acids derivatives (Scheme 50).[246] In 2016, Kotora described the reaction of cyclopropyl-terminated 1,6-diynes with alkynes to form cyclopropylarenes, but yields and regioselectivities were generally poor (not shown).[247]

In 2018, Goswami reported ruthenium-catalyzed cycloadditions of 1,6-diynes with acetylenic nitriles (Scheme 51).[248] The diyne, catalyzed by Cp*RuCl(cod), couples chemoselectively with the acetylene moiety in alkynylnitrile to deliver fused cyanoarenes as a single regioisomer. Interestingly, the chemoselectivity can be altered by adding a catalytic amount of AgOTf, resulting in the formation of 2-alkynylpyridines instead (*vida infra*, Scheme 62). The authors suggest that the electron-deficient cationic ruthenium complex formed by AgOTf and ruthenium chloride prefers to coordinate with the electron-rich nitrile, giving 2-alkynylpyridine as the sole cycloadduct.

Scheme 50. Ruthenium-catalyzed [2+2+2] cycloadditions of 1,6-diynes with alkynes reported by Aubert and Gandon, Sheppard and Osipov.

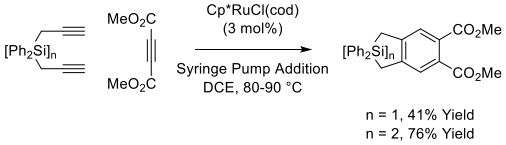


Scheme 51. Ruthenium-catalyzed [2+2+2] cycloadditions of 1,6-diynes with acetylenic nitriles reported by Goswami.



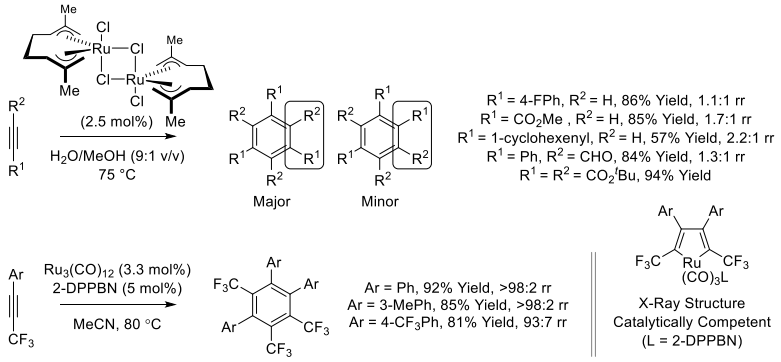
Reports of silacycle formation via ruthenium-catalyzed [2+2+2] cycloaddition are conspicuously absent from the literature. In 2020, in the course of experimentally and theoretically contrasting the mechanisms of cobalt and ruthenium cyclotrimerization, Kabe attempted to form silacycles from bispropargyl silanes and the homologous disilanes with alkynes (Scheme 52).[249] Among the alkynes surveyed, preparatively useful yields were only observed in reactions of dimethyl acetylenedicarboxylate. Thus, general methods for silacycle formation via ruthenium-catalyzed [2+2+2] cycloaddition remain an unmet challenge.

Scheme 52. Ruthenium-catalyzed [2+2+2] cycloadditions of silicon-containing 1,6- and 1,7-diynes with DMAD reported by Kabe.



Beyond the standard Cp*-ruthenium(II) complexes, other structurally distinct ruthenium complexes have proven to be effective catalysts for alkyne [2+2+2] cycloaddition. For example, in 2006, Cadierno and Gimeno demonstrated that the indicated bis(allyl)-ruthenium(IV) dimer could catalyze fully intermolecular alkyne [2+2+2] cycloadditions in aqueous media, albeit with poor levels of regioselectivity (Scheme 53).[250] The same authors utilized microwave irradiation in lieu of thermal heating, which allowed the reactions to reach completion in only 5 minutes (not shown).[251]

Scheme 53. Ruthenium(IV) and ruthenium(0) precatalysts for intermolecular alkyne [2+2+2] cycloadditions reported by Cadierno and Gimeno and Itoh and Kawatsura.



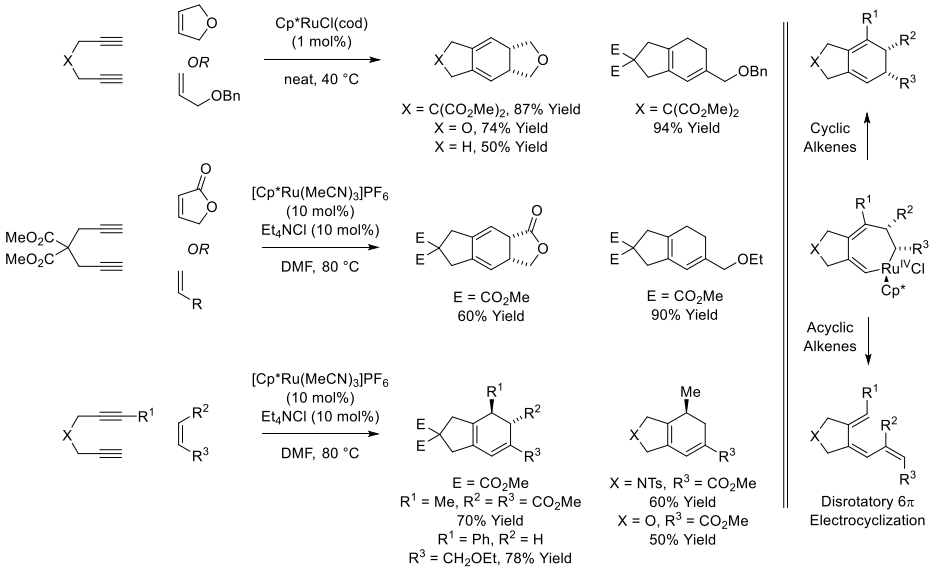
In 2007, Grigg introduced a cyclometallated *N*-phenylpyrazole ruthenium complex as a pre-catalyst for [2+2+2] cycloaddition of propargylic alcohols and symmetric 1,6-diynes (not shown).[252] In 2011, using a ruthenium(0) precatalyst in combination with *ortho*-(diphenylphosphino)benzonitrile (2-DPPBN), Itoh and Kawatsura reported highly regioselective intermolecular alkyne [2+2+2] cycloadditions of CF_3-substituted aryl alkynes (Scheme 53).[253] Isolation of a catalytically competent

ruthenacyclopentadiene, which was characterized by single crystal X-ray diffraction, corroborates a mechanism involving alkyne-alkyne oxidative coupling to form a ruthenacyclopentadiene followed by successive insertion-C-C reductive elimination of the third alkyne.[188] In contrast, in 2012 Holthausen and Ghosh explored the use of *arachno*-[(Cp*RuCO)$_2$B$_2$H$_6$] as a catalyst for intermolecular alkyne cyclotrimerization, and their computational studies implicated a mechanism in which the transient ruthenacyclopentadiene is converted to a benzene derivative through a Diels-Alder-type [4+2] cycloaddition with the third alkyne (not shown).[254] Finally, in 2015 and 2016, Ratovelomanana-Vidal and Michelet developed a cost-effective intermolecular [2+2+2] cycloaddition of α,ω-diynes with alkynes to construct benzene and fluorenone derivatives, catalyzed by $RuCl_3 \cdot nH_2O$ in the absence of ligand under solvent-free conditions (not shown).[255,256]

3.2.3 [2+2+2] Cycloadditions of Alkynes + Alkenes

Whereas the [2+2+2] cycloaddition of three alkynes provides substituted benzene derivatives, entry to cyclohexadienes and cyclohexenes is achieved via corresponding [2+2+2] cycloadditions of alkynes with alkenes. The first ruthenium-catalyzed cycloadditions of this type were described by Itoh and Yamamoto in 1998.[257,258] Their initial reports were on reactions of 1,6-diynes with norbornene using CpRu(cod)Cl and the indenyl complex, (η^5-C$_9$H$_7$)Ru(PPh$_3$)$_2$Cl; however, the resulting cyclohexadiene was susceptible to further [4+2] cycloaddition with norbornene, which led to low isolated yields (not shown).[257] Using Cp*Ru(cod)Cl as pre-catalyst, the authors later demonstrated that [2+2+2] cycloadditions of 1,6-diynes with cyclic and acyclic allylic ethers could be conducted in a highly efficient manner (Scheme 54).[258,259]

Scheme 54. Ruthenium-catalyzed [2+2+2] cycloadditions of 1,6-diynes with allylic ethers and other cyclic and acyclic alkenes reported by Itoh and Yamamoto and Saá.

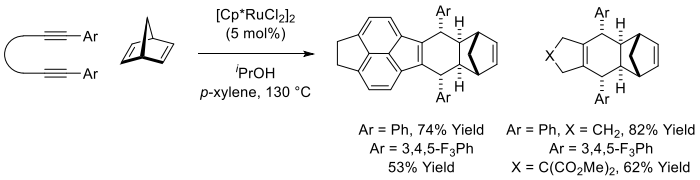


The authors posit that ether oxygen-assistance facilitates olefin insertion, and the steric demand of the Cp* ligand facilitates dissociation of the cycloadduct to increase turn-over number. Interestingly, cycloaddition of 1,6-heptadiyne with allyl benzyl ether resulted in formation of the regioisomeric cyclohexadiene, which the authors postulate arises from a 1,5-hydride shift of the initially formed cycloadduct. An alternate mechanism corroborated by experimental and computational studies was proposed by Saá, in which acyclic alkenes undergo β-hydride elimination followed by C-H reductive

elimination to a cyclohexatriene that forms the regioisomeric cyclohexadiene via disrotatory 6π-electrocyclization.[260] In 2006, Saá demonstrated that cationic ruthenium precatalyst, $[Cp^*Ru(MeCN)_3]PF_6$, promotes the [2+2+2] cycloaddition of 1,6-diynes with diverse alkenes (Scheme 54).[261] In 2008, Saá expanded the scope of the reaction to include non-symmetric diynes and disubstituted alkenes, which undergo [2+2+2] cycloaddition with high levels of regio- and *trans*-diastereoselectivity (Scheme 54).[262]

In 2000, Itoh and Yamamoto demonstrated for the first time the superior performance of the dinuclear ruthenium(III) complex $[Cp^*RuCl_2]_2$ as a catalyst for the [2+2+2] cycloaddition of 1,6-diynes with heterocyclic alkenes (not shown).[259] In 2010, Wu reported that $[Cp^*RuCl_2]_2$ was an effective catalyst for reductive [2+2+2] cycloadditions of 1,7-diaryl-1,6-heptadiynes with norbornadiene via 2-propanol-mediated transfer hydrogenation (Scheme 55).[263] The cyclohexene-containing cycloadducts are formed with complete levels of diastereoselectivity. Exposure of the cycloadducts to the first-generation Grubbs catalyst promotes ring-opening metathesis polymerization to form polynorbornenes (not shown).

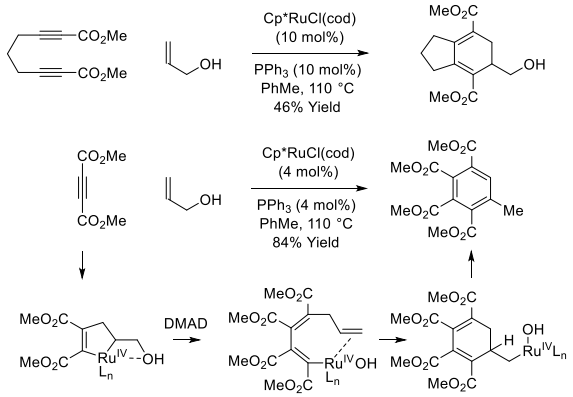
Scheme 55. Ruthenium-catalyzed reductive [2+2+2] cycloaddition of 1,6-heptadiynes with norbornadiene reported by Wu.



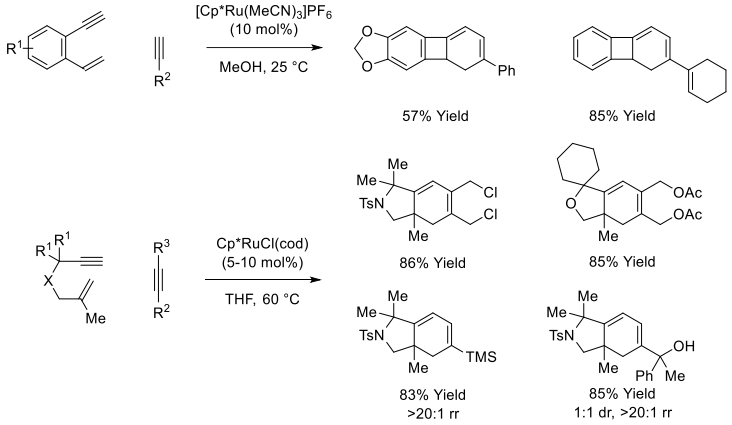
In 2002, Mitsudo reported the [2+2+2] cycloaddition of electron-deficient 1,6-diynes or dialkyl acetylenedicarboxylates with allyl alcohol using a ruthenium complex derived from Cp*RuCl(cod) and PPh_3 (Scheme 56).[264] Reactions of 1,6-diynes delivered the anticipated cyclohexadiene. However, under the same conditions, dimethyl acetylenedicarboxylates react with allyl alcohol to form benzene tetracarboxylates (Scheme 56). The authors propose a mechanism involving alkyne-allyl alcohol oxidative coupling to form a ruthenacyclopentene, which upon β-hydroxy elimination and insertion of a second equivalent of alkyne provides an acyclic vinylruthenium complex. Migratory insertion of the tethered alkene and subsequent aromatization via β-hydride elimination-alkene isomerization deliver the cycloadduct.

Beyond 1,6-diynes, 1,5- and 1,6-enynes are also competent partners for [2+2+2] cycloaddition. In 2014, Esteruelas and Saá reported [2+2+2] cycloadditions of 1,5-enynes (*ortho*-alkenylarylacetylenes) catalyzed by the cationic ruthenium complex $[Cp^*Ru(MeCN)_3]PF_6$ to form dihydrobiphenylenes (Scheme 57).[265] While in the absence of exogenous alkyne the 1,5-enyne undergoes dimerization (not shown), in the presence of terminal alkynes crossed [2+2+2] cycloaddition of the 1,5-enyne with the alkyne becomes the dominant reaction pathway. In 2017, Tenaglia reported a Cp*RuCl(cod)-catalyzed [2+2+2] cycloaddition of 1,6-enynes with both internal and terminal alkynes to provide bicyclohexa-1,3-dienes (Scheme 57).[266] This process displayed impressive chemoselectivity, as highlighted by compatibility with propargyl chloride and propargyl acetate functional groups. DFT calculations by Liu indicate that 1,6-enyne undergoes oxidative coupling to form a ruthenacyclopentene that undergoes regio-determining insertion of exogenous alkyne at the vinylic ruthenium-carbon bond.[267]

Scheme 56. Ruthenium-catalyzed [2+2+2] cycloaddition of electron-deficient 1,6-diynes or DMAD with allyl alcohol reported by Mitsudo.

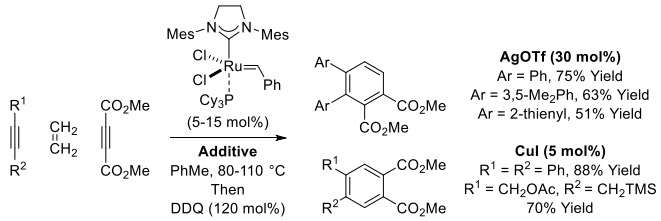


Scheme 57. Ruthenium-catalyzed [2+2+2] cycloaddition of 1,5- and 1,6-enynes with alkynes reported by Esteruelas and Saá and Tenaglia, respectively.



Fully intermolecular crossed [2+2+2] cycloadditions are highly uncommon. In 2012, Wang, Zhao and Shi reported crossed [2+2+2] cycloadditions of internal alkynes, dimethyl acetylene dicarboxylate and ethylene to form substituted *ortho*-phthalates using the second-generation Grubbs catalyst (Scheme 58).[268] In these processes, enyne metathesis of the internal alkyne with acetylene delivers a conjugated

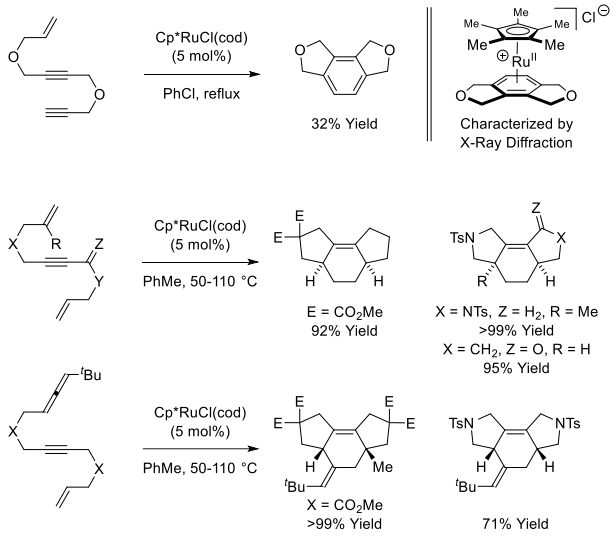
Scheme 58. Ruthenium-catalyzed intermolecular crossed [2+2+2] cycloaddition of internal alkynes, DMAD and ethylene reported by Wang, Zhao, and Shi.



diene, which is subsequently treated with dimethyl acetylene dicarboxylate and then DDQ to furnish a cyclohexadiene. Notably, using CuI or AgOTf as additives, regioisomeric *ortho*-phthalates were formed. In 2015, Pérez-Castells also explored the use of various Grubbs-type catalysts in [2+2+2] cycloadditions of 1,6-diynes with cyclic and acyclic alkenes; however, these reactions gave mixtures of cycloadducts in low yields (not shown).[269]

In contrast, several fully intramolecular [2+2+2] cycloadditions of alkynes with alkenes have been described. In the aforementioned 2003 study by Yamamoto, a [2+2+2] cycloaddition of a 1,6,11-enediyne was reported.[212] Rather than obtaining the expected cyclohexadiene, however, a dehydroaromatization product was observed in low yield (Scheme 59). High temperatures were necessary and side reactions from competing intermolecular [2+2+2] cycloadditions were not observed. The authors isolated a cationic ruthenium complex from the reaction mixture in which the cycloadduct is bound to ruthenium as an η^6-arene ligand, suggesting product inhibition may contribute to low conversion. In 2007, Sato and Mori reported a fully intramolecular [2+2+2] cycloaddition of 1,6,11-dienynes using Cp*RuCl(cod) (Scheme 59).[270] This reaction proceeds via enyne oxidative coupling to form a ruthenacyclopentene followed by insertion of the second olefin. C-C Reductive elimination from the resulting ruthenacycloheptene delivers the tricyclic product. Finally, in 2012, Saito and Sato reported fully intramolecular [2+2+2] cycloadditions of allene-yne-enes to form fused tricycles (Scheme 59).[271] Relative stereochemistry at the ring juncture and geometry of the (*Z*)-alkene were corroborated by single crystal X-ray diffraction analysis.

Scheme 59. Intramolecular ruthenium-catalyzed [2+2+2] cycloadditions of alkynes with alkenes and allenes reported by Itoh and Yamamoto, Sato, Mori and Saito.



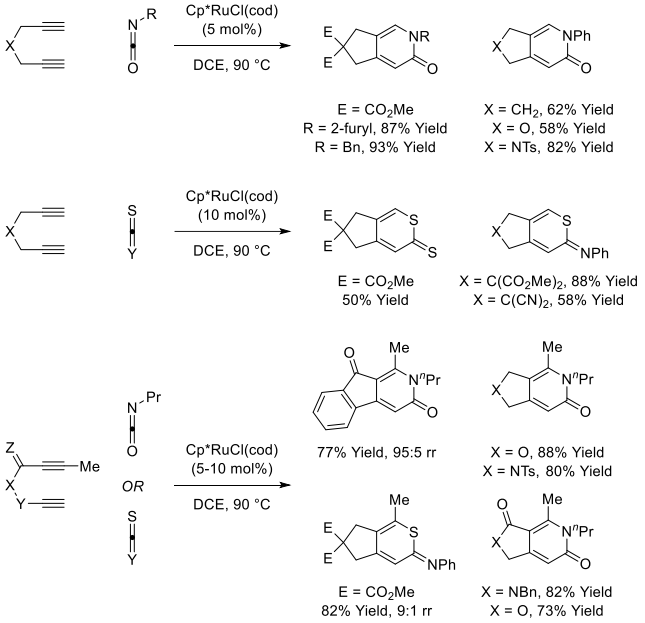
3.3 [2+2+2] Cycloadditions to Form Heterocycles

3.3.1 [2+2+2] Cycloadditions of 2 Alkynes + Cumulenes

In 2001, Itoh and Yamamoto reported Cp*RuCl(cod)-catalyzed [2+2+2] cycloaddition of 1,6-diynes with isocyanate to form diverse bicyclic pyridones (Scheme 60).[272] Expanding the scope of the reaction to include isothiocyanates and carbon disulfide, the authors demonstrated the ability to convergently access sulfur-containing heterocycles (Scheme 60).[273] As with related alkyne-mediated [2+2+2] cycloadditions, the Cp* ligand was uniquely effective for tranformations of this type, which proceed via oxidative coupling of the 1,6-diyne to form a ruthenacyclopentadiene followed by heterocumulene insertion and C-X reductive elimination (X = heteroatom).[274] A theoretical study of the origins of chemoselective heterocumulene insertion in cycloadditions of 1,6-diynes with isocyanates and thioisocyanates was performed by Kirchner in 2003.[275] Migratory insertion of the C=X π-bond (X = N, O, S) into the ruthanacycle is initiated by η^1 attack at ruthenium by the heteroatom X, which is incorporated into the cycle. For

isocyanates N attack is preferred over O, and for thioisocyanates S attack is irreversible. In 2005, Itoh and Yamamoto demonstrated that non-symmetric diynes participate in highly regioselective [2+2+2] cycloadditions with diverse cumulene partners (Scheme 60).[276] Reactions of this type also can be conducted using the second-generation Hoveyda-Grubbs catalyst, as reported in 2013 by Pérez-Castells (not shown).[277]

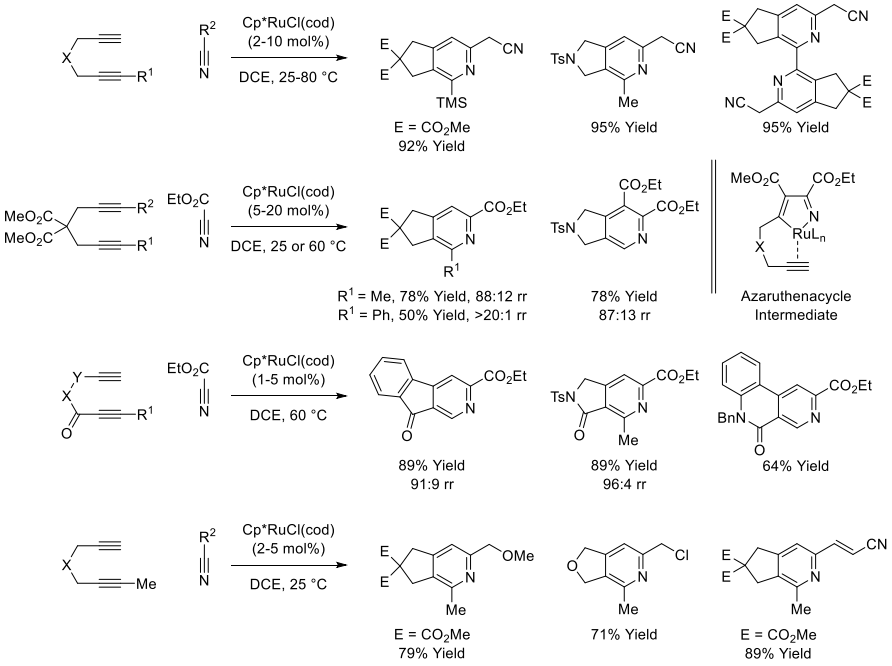
Scheme 60. Ruthenium-catalyzed cycloaddition of 1,6-diynes with heterocumulenes reported by Itoh and Yamamoto.



3.3.2 [2+2+2] Cycloadditions of 2 Alkynes + Nitriles

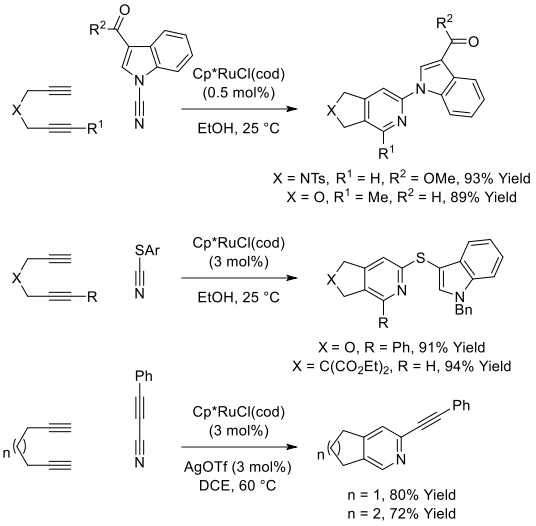
1,6-Diynes undergo chemoselective ruthenium-catalyzed [2+2+2] cycloaddition with nitriles to form substituted pyridines. The first ruthenium-catalyzed cycloaddition of this type was reported by Itoh and Yamamoto in 2001, who utilized Cp*RuCl(cod) to promote the [2+2+2] cycloaddition of 1,6-diynes with dicyanides to form pyridines bearing pendant nitriles (Scheme 61).[278] As illustrated in corresponding reactions of electron-deficient nitriles, an inversion of regioselectivity is observed upon use of 1,6-diynes that are terminally substituted by an electron-withdrawing group. The authors posit that for alkyl- and aryl-substituted 1,6-diynes, alkyne-nitrile oxidative coupling to form an azaruthenacyclopentadiene occurs at the monosubstituted alkyne, whereas electron-deficient alkynes preferentially participate in oxidative coupling (Scheme 61).[279] By introducing a carbonyl moiety at the 3-position of the 1,6-diyne, Yamamoto

Scheme 61. Ruthenium-catalyzed [2+2+2] cycloadditions of 1,6-diynes with nitriles reported by Itoh and Yamamoto.



and Itoh were able to control regioselectivity in [2+2+2] cycloadditions to form azafluorenones and related heterocycles (Scheme 61).[276] In later work, the authors demonstrated that nitriles bearing α-heteroatoms or other activating groups are essential for cycloaddition, as unactivated nitriles such as acetonitrile fail to participate (Scheme 61).[280,281] Taking advantage of these electronic effects, Itoh and Yamamoto conducted [2+2+2] cycloadditions 1,6-diynes with chloroacetonitriles for the synthesis of *C*-arylribosides,[236] and Kotora performed [2+2+2] cycloadditions of halogen-terminated 1,6-diynes with nitriles to form halopyridines (not shown).[282] Additional studies demonstrate that Cp*RuCl(cod)-catalyzed [2+2+2] cycloadditions of 1,6-diynes with nitriles can be conducted in air,[283] water[284] and even fetal bovine serum (not shown).[229]

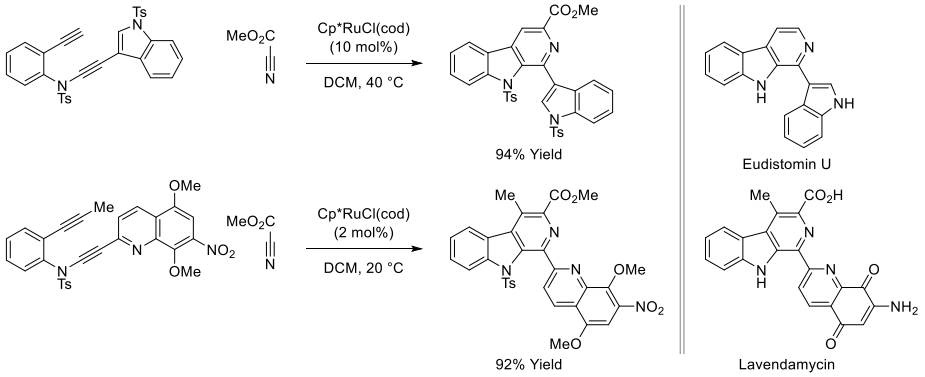
Scheme 62. Ruthenium-catalyzed [2+2+2] cycloadditions of 1,6- and 1,7-diynes with nitriles reported by Goswami.



In 2017, using Cp*RuCl(cod) as a precatalyst, Goswami reported [2+2+2] cycloadditions of 1,6-diynes with *N*-cyanoindoles to form *N*-(2-pyridyl)indoles (Scheme 62).[285] The same year, Goswami reported related [2+2+2] cycloadditions of 1,6-diynes with 3-thiocyanatoindoles to form 3-(2-thiopyridyl)indoles (Scheme 62).[286] Later in 2019, Goswami described analogous [2+2+2] cycloadditions of 1,6-diynes with selenocyanates or aryl cyanates to form selenopyridines[287,288] and 2-aryloxypyridines,[289] respectively (not shown). In 2018, in [2+2+2] cycloadditions of 1,6-diynes with acetylenic nitriles, Goswami found that neutral Cp*Ru catalysts provide benzonitriles (*vide supra*, Scheme 51), whereas cationic Cp*Ru catalysts (generated *in situ* from Cp*RuCl(cod) and AgOTf) provide 2-alkynylpyridines (Scheme 62).[248] In 2020, the same authors were able to perform sequential cationic ruthenium-catalyzed [2+2+2] cycloadditions of alkynylthiocyanates with 1,6-diynes, chemoselectively forming aryl thiocyanates and then 2-arylthiopyridines (not shown).[290]

Beautiful applications of the Cp*RuCl(cod)-catalyzed [2+2+2] cycloaddition of 1,6-diynes with electron-deficient nitriles in target-oriented synthesis have been accomplished. In 2011, Witulski completed the total synthesis of the β-carboline-containing natural product eudistomin U via [2+2+2] cycloaddition of the indicated 1,6-yne-ynamide with methylcyanoformate (Scheme 63).[291] In 2011, Nissen reported the formal synthesis of the antitumor antibiotic lavendamycin employing a similar [2+2+2] cycloaddition of a 1,6-yne-ynamide with methylcyanoformate (Scheme 63).[292] In 2012, Mori prepared

Scheme 63. Applications of ruthenium-catalyzed [2+2+2] cycloadditions of 1,6-diynes with nitriles in natural product synthesis reported by Witulski and Nissen.

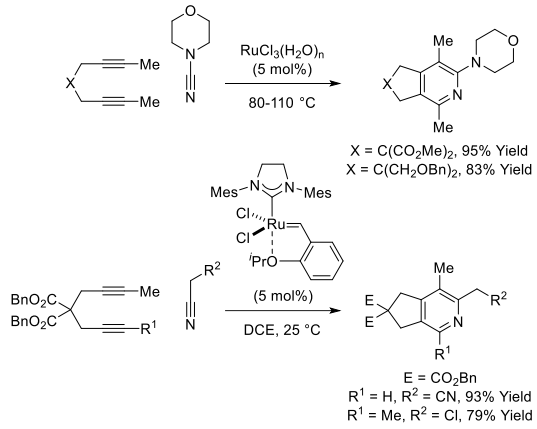


several *N,N,N′,N′*-tetrakis[(2-pyridylmethyl)ethylenediamine] (TPEN) ligands using the Cp*RuCl(cod)-catalyzed [2+2+2] cycloaddition of 1,6-diynes with bromoacetonitriles (not shown).[293]

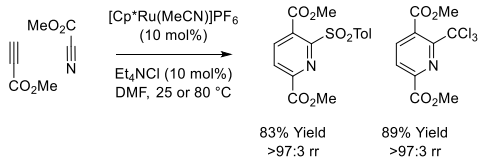
Beyond Cp*RuCl(cod), $RuCl_3 \cdot H_2O$ has been found to catalyze the [2+2+2] cycloaddition of 1,6-diynes with cyanamides to form 2-aminopyridines (Scheme 64).[294] The cationic ruthenium complex $Cp^*Ru(MeCN)_3PF_6$ also catalyzes the [2+2+2] cycloaddition of 1,6- and 1,7-diynes with cyanamides[295-298] or selenocyanates[299] to form 2-aminopyridines or 2-selenopyridines, respectively, as illustrated in a series of reports by Michelet and Ratovelomanana-Vidal (not shown). Finally, the second-generation Hoveyda-Grubbs catalyst has been shown to be an effective and chemoselective promotor of the [2+2+2] cycloaddition of 1,6-diynes with nitriles, even generating pyridines containing highly sensitive 2-chloromethyl substituents (Scheme 64).[300]

Fully intermolecular ruthenium-catalyzed [2+2+2] cycloadditions of alkynes with nitriles remain exceedingly uncommon, with only a single report from the laboratory of Saá appearing in the literature. Taking advantage of the superior reactivity displayed by electron-deficient alkynes and nitriles in related intramolecular processes, and using $Cp^*Ru(MeCN)_3PF_6$ as precatalyst, the 2,3,6-trisubstituted pyridines could be generated with high levels of regioselectivity (Scheme 65).[301]

Scheme 64. Ruthenium-catalyzed [2+2+2] cycloadditions of α,ω-diynes with nitriles reported by Pérez-Castells and Michelet and Ratovelomanana-Vidal, respectively.



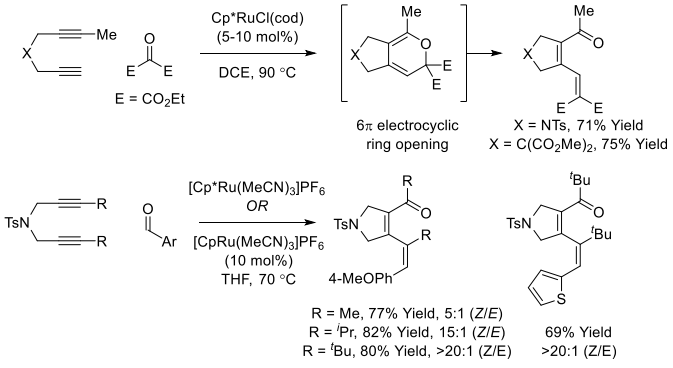
Scheme 65. Intermolecular ruthenium-catalyzed [2+2+2] cycloadditions of alkynes with nitriles reported by Saá.



3.3.3 [2+2+2] Cycloadditions of 2 Alkynes/Alkenes + Carbonyl Compounds

Due to the weaker coordinating ability of oxygen relative to nitrogen, [2+2+2] cycloadditions of alkynes with carbonyl partners are far less developed than analogous processes involving nitriles or isocyanates. However, some progress in this area has been made. In 2002, Yamamoto and Itoh reported ruthenium-catalyzed [2+2+2] cycloadditions of 1,6-diynes with diethyl ketomalonate (Scheme 66).[302] The initially formed pyran undergoes cycloreversion to form the indicated dienyl ketone. The authors proposed a mechanism involving alkyne-carbonyl oxidative coupling to form an oxaruthenacyclopentene that inserts the tethered alkyne. Subsequent computational studies by Rodríguez-Otero in 2009, however, implicate a mechanism involving oxidative cyclization of the 1,6-diyne to form a ruthenacyclopentadiene followed by carbonyl insertion and C-O reductive elimination to form the pyran.[303] In 2017, in a combined experimental and computational study, Yamamoto expanded the scope of the ruthenium-

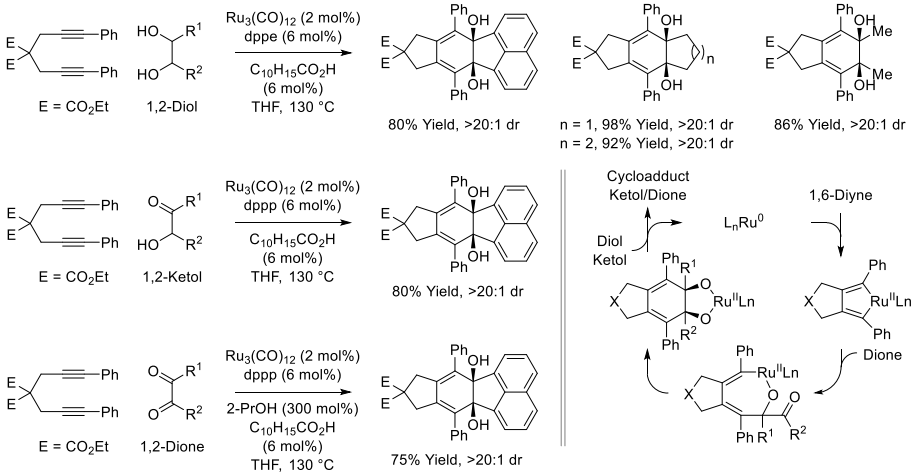
Scheme 66. Ruthenium-catalyzed [2+2+2] cycloaddition of 1,6-diynes and carbonyls reported by Yamamoto and Itoh.



catalyzed [2+2+2] cycloadditions of 1,6-diynes to aryl aldehydes (Scheme 66).[304] The resulting pyrans again suffered cycloreversion to provide dienyl ketones, and the computational studies corroborated the general features of the aforesaid catalytic mechanism calculated by Rodríguez-Otero.[303] Whereas aryl-substituted diynes delivered the dienyl ketones as mixtures of alkene geometrical isomers, alkyl-substituted diynes displayed increasing alkene (*Z*)-stereoselectivity with increasing size of the alkyl substituent (Scheme 66).[304] In contrast, the same reaction catalyzed by $[Rh(cod)_2]BF_4/H_8$-BINAP preferentially gives the (*E*)-isomer.[305]

In 2016, Krische reported the first use of 1,2-diones as $2_{2\pi}$ components in transition metal-catalyzed [2+2+2] cycloadditions, as illustrated in reactions of 1,6-diynes (Scheme 67).[306] A remarkable feature of these processes resides in the ability to conduct the cycloaddition using diols, ketols or diones as equivalent cycloaddition partners. Reactions of diols are oxidative processes in which one equivalent of diyne is sacrificed as a hydrogen acceptor. Reactions of α-ketols occur under identical conditions and are redox-neutral. Reactions conducted using diones are reductive processes and exploit 2-propanol as the source of hydrogen. The cycloaddition is initiated via oxidative cyclization of the 1,6-diyne to form a ruthenacyclopentadiene. Successive carbonyl insertions of the dione are followed by diol- or ketol- or 2-propanol-mediated transfer hydrogenonlysis of the resulting oxaruthenacycle to release product and return ruthenium to its zero-valent form. A carboxylic acid cocatalyst (adamantane carboxylic acid) was found to increase rate and conversion by catalyzing alcohol exchange and the transfer hydrogenolysis of transient oxaruthenacycles.[154,155] In 2020, this method was applied to the synthesis of diindenoperylenes (periflanthenes) (not shown).[307]

Scheme 67. Ruthenium-catalyzed [2+2+2] cycloaddition of 1,6-diynes with diones reported by Krische.

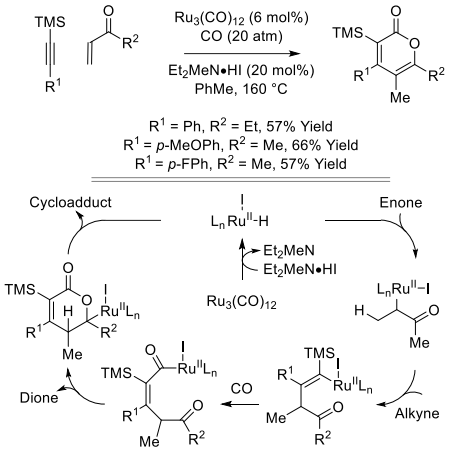


3.4 (3+2+1) Cycloadditions

Six-membered ring formation via ruthenium-catalyzed (3+2+1) cycloadditions is highly uncommon and, to our knowledge, only a single transformation of this type has been described. Following the development of carbonylative [2+2+1+1] cycloadditions by Ryu and Mitsudo that result in the generation of hydroquinones,[170] in 2007 Fukuyama and Ryu discovered that enones participate in

ruthenium(0)-catalyzed carbonylative (3+2+1) cycloadditions with silylacetylenes to furnish α-pyrones (Scheme 68).[308] The authors propose that the addition of substoichiometric quantities of ammonium salt plays a key role in promoting formation of a ruthenium hydride. Enone hydrometalation followed by alkyne carboruthenation delivers a vinylruthenium species, which upon insertion of carbon monoxide forms an acylruthenium complex. Cyclization onto the tethered ketone with subsequent β-hydride elimination delivers the α-pyrone and regenerates the ruthenium hydride to close the catalytic cycle.

Scheme 68. Ruthenium-catalyzed carbonylative (3+2+1) cycloaddition of silylacetylenes with enones reported by Fukuyama and Ryu.



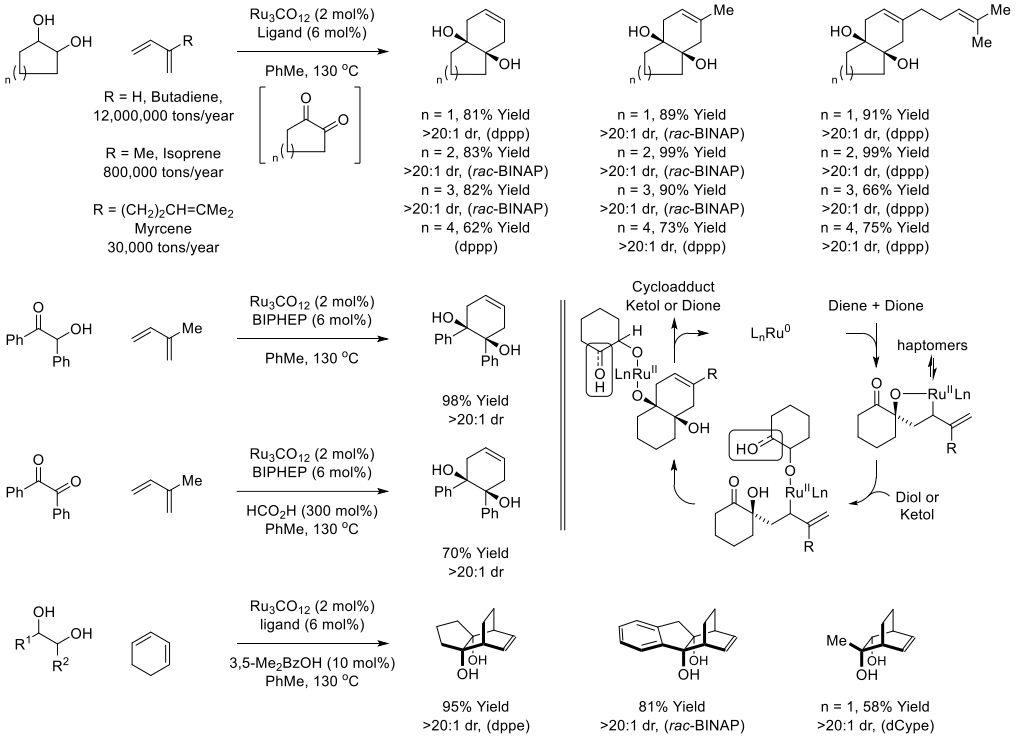
3.5 [4+2] Cycloadditions

3.5.1 Transfer Hydrogenative Cycloadditions

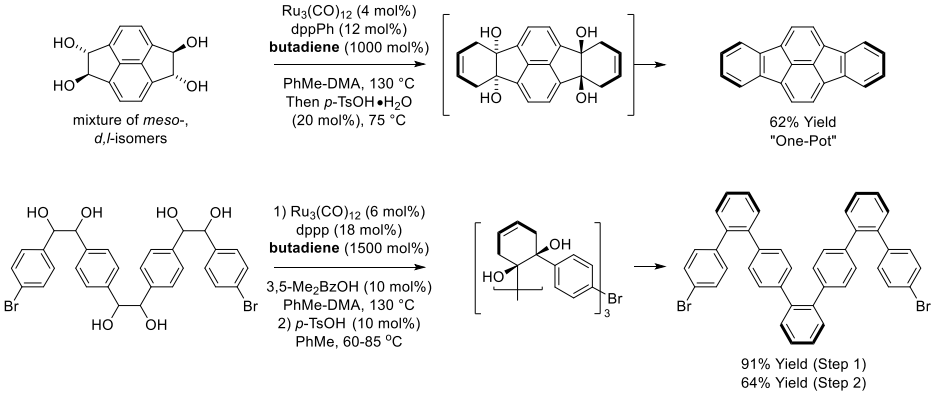
In connection with their exploration of carbonyl reductive couplings via metal-catalyzed hydrogenation, transfer hydrogenation and hydrogen auto-transfer,[309-315] the Krische group has developed a unique class of ruthenium(0)-catalyzed [4+2] cycloadditions in which 1,2-diones serve as $2_{2\pi}$ components.[32,34] In these transfer hydrogenative cycloadditions, 1,2-diones can be used directly in combination with a reductant, or they can be generated via dehydrogenation of 1,2-diols or 1,2-ketols, which represent oxidative and redox-neutral cycloadditions, respectively. Their initial 2013 report describes a phosphine-modified ruthenium(0) catalyst for the [4+2] cycloaddition of feedstock dienes with 1,2-diones from the alcohol, ketol or dione oxidation levels (Scheme 69).[316,317] Cyclic or acyclic *cis*- or *trans*-diols are all competent partners for cycloaddition, delivering the diol-containing cycloadducts as single diastereomers. The cycloaddition is initiated by diene-dione oxidative coupling to form an oxaruthenacycle. Protonolytic cleavage of the ruthenium-oxygen bond (mediated by diol or ketol) is followed by intramolecular carbonyl allylruthenation. The resulting ruthenium alkoxide undergoes β-hydride elimination and O-H reductive elimination to release the cycloadduct along with ketol or dione to be used in the next turnover of the catalytic cycle. In related mechanistic studies, the putative oxaruthenacycle was isolated and its reversible formation was demonstrated.[318] In subsequent work, the diol-containing cycloadducts were subjected to iodosobenzene diacetate mediated oxidative cleavage to form 9- to 12-membered 1,6-diketones (not shown).[317] Finally, a significant expansion in scope was realized through the use of carboxylic acid cocatalysts,[154,155] enabling [4+2] cycloadditions of cyclohexadiene to form bridged carbocycles with complete levels of exo-selectivity (Scheme 69).[181]

The ruthenium(0)-catalyzed transfer hydrogenative diene-dione [4+2] cycloaddition delivers diol-containing cycloadducts that are readily aromatized via acid-catalyzed dehydration (or deoxydehydration), thus opening new benzannulation strategies for the synthesis of polycyclic aromatic hydrocarbons (PAH). For example, bis-1,2-diols participate in two-directional [4+2] cycloaddition-dehydration to furnish acenes and, as shown, indeno[1,2,3-*cd*]-fluoranthenes (Scheme 70).[319] Similarly, oligo(*p*-phenylene ethylene glycols) are subject to triple [4+2] cycloaddition followed by exhaustive dehydration to furnish alternating oligo(o,p-phenylenes) (Scheme 70).[320] The Krische laboratory has applied benzannulation strategies of this type to the construction of nanographenes,[320] triple helical oligo(phenylene) cages,[321] as well as all-aryl caged *fac*-Ir(ppy)$_3$ analogs (not shown).[322]

Scheme 69. Ruthenium-catalyzed [4+2] cycloaddition of 1,3-dienes with 1,2-diols as dione precursors reported by Krische.

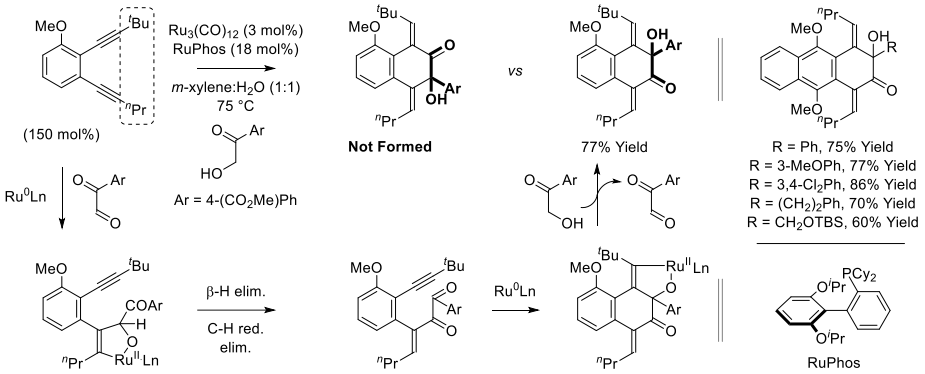


Scheme 70. Benzannulation via ruthenium-catalyzed [4+2] cycloaddition of 1,3-dienes with 1,2-diols as dione precursors reported by Krische.

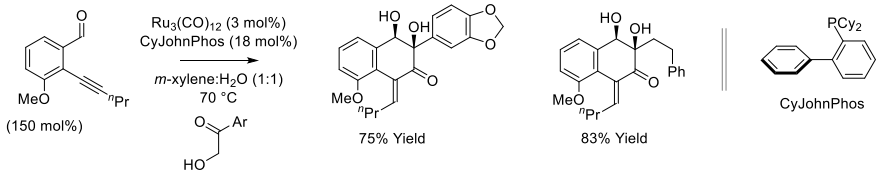


In 2015, Krische reported a related ruthenium(0)-catalyzed [4+2] cycloaddition of 3,4-benzannulated 1,5-diynes with 1,2-ketols (Scheme 71).[323] Use of diols as vicinal dicarbonyl precursors requires a sacrificial hydrogen acceptor, which led to competing transfer hydrogenation of the diyne reactant. Hence, the reaction was conducted using 1,2-ketols in a redox-neutral manner. Using a ruthenium catalyst derived from $Ru_3(CO)_{12}$ and RuPhos, cycloadducts bearing two trisubstituted alkenes were formed as single geometrical isomers through a mechanism involving consecutive alkyne-carbonyl oxidative coupling. To enforce head-to-tail regioselectivity, non-symmetric diynes terminally substituted by *n*-propyl and *t*-butyl groups were employed. Based on this pattern of reactivity, a mechanistically related ruthenium(0)-catalyzed [4+2] cycloaddition of *ortho*-acetylenic benzaldehydes was developed in which 1,2-ketols serve as latent α-ketoaldehydes (Scheme 72).[324]

Scheme 71. Ruthenium-catalyzed [4+2] cycloaddition of 3,4-benzannulated 1,5-diynes with 1,2-ketols as dione precursors reported by Krische.

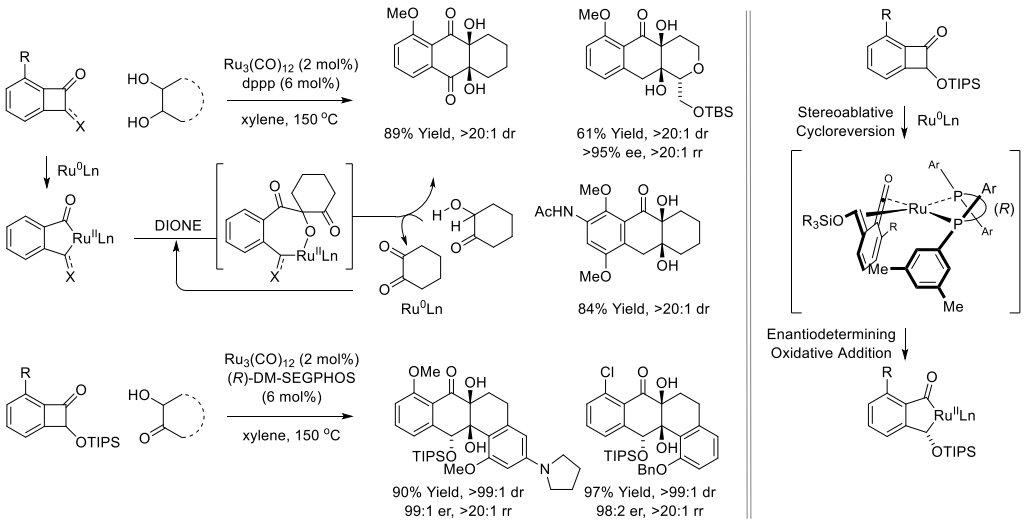


Scheme 72. Ruthenium-catalyzed [4+2] cycloaddition of *ortho*-acetylenic benzaldehydes with 1,2-ketols as α-ketoaldehyde precursors reported by Krische.



In 2017, Krische developed a ruthenium(0)-catalyzed [4+2] cycloaddition of benzocyclobutenones with 1,2-diols to deliver cycloadducts in which adjacent diol carbon atoms undergo formal insertion into the strained C-C bond (Scheme 73).[325] As in the preceding transfer hydrogenative [4+2] cycloadditions, the diol suffers dehydrogenation to form a transient dione. The benzocyclobutenone serves as a masked *ortho*-ketene methide that reacts with ruthenium(0) through a 1,4-oxidative addition to form a ruthenaindanone. Successive carbonyl addition to the dione is followed by transfer hydrogenolysis of the resulting oxaruthancycle to release the cycloadduct and return ruthenium to its zero-valent form. For cycloadditions that proceed through the intermediacy of non-symmetric diones, complete levels of head-to-tail regioselectivity are observed. Additionally, as illustrated in cycloadditions catalyzed by (*R*)-DM-

Scheme 73. Ruthenium-catalyzed [4+2] cycloaddition of benzocyclobutanones with 1,2-diols or 1,2-ketols as 1,2-dione precursors reported by Krische.

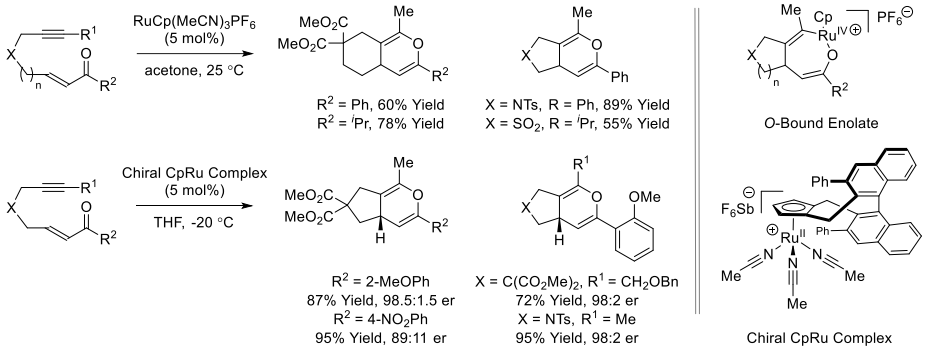


SEGPHOS-modified ruthenium(0) complexes, the stereoablative nature of the cycloreversion event allows chiral racemic benzocyclobutenones to be transformed to highly enantiomerically enriched cycloadducts via dynamic kinetic resolution (Scheme 73).[326]

3.5.2 Formal Diels-Alder Type [4+2] Cycloadditions

In 2000, Trost discovered an intramolecular ruthenium catalyzed [4+2] cycloaddition of an yne-enone to form a fused pyran ring (Scheme 74).[327] The authors propose that the reaction proceeds through a ruthenacycle intermediate, with interconversion between five-membered *C*-bound and seven-membered *O*-bound enolates. From the *O*-bound enolate, reductive elimination delivers the desired cycloadduct. In aqueous conditions, the corresponding 1,5-diketone is formed (not shown). In 2015, Cramer used a chiral ruthenium catalyst developed in his laboratory to accomplish the same transformation; enantioselective ruthenacycle formation selectively gave the pyran products (Scheme 74).[328] Interestingly, when a Weinreb amide was used in place of a ketone, an unstable cycloadduct formed under the reaction conditions and was directly converted into a dihydropyranone (not shown).

Scheme 74. Ruthenium-catalyzed intramolecular [4+2] cycloaddition of acetylenic enones reported by Trost and Cramer.

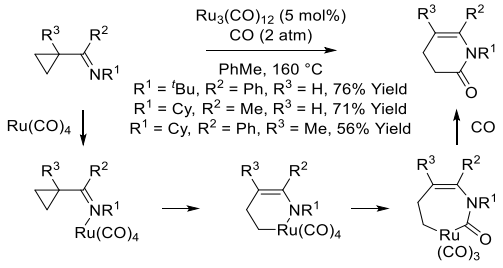


In 2004, Mitsudo reported a ruthenium-catalyzed [4+2] cycloaddition of cyclobutenones that results in the formation of α-pyrones (not shown).[329] The authors propose a mechanism involving cycloreversion of the cyclobutenone to form a transient vinyl ketene, which participates in a hetero-Diels-Alder type [4+2] cycloaddition to form the α-pyrone. The proposed mechanism of this process does not involve intervention of organometallic intermediates and, technically, falls outside the purview of this monograph.

3.6 (5+1) Cycloadditions

In 2000, Murai developed a ruthenium-catalyzed carbonylative (5+1) cycloaddition of cyclopropyl imines to form γ,δ-unsaturated lactams (Scheme 75).[330] $Ru_3(CO)_{12}$ was singularly effective, as other ruthenium complexes (e.g. Cp*Ru(cod)Cl, $Ru(CO)_2(PPh_3)_3$, $RuH_2(CO)(PPh_3)_3$) or metal carbonyl clusters such as $Co_2(CO)_8$ did not promote cyclocarbonylation. The cycloaddition was limited to *N*-cyclohexyl- or *N*-*tert*-butyl-substituted cyclopropyl imines. The requisite imines could be formed *in situ* from the corresponding cyclopropyl ketones and alkylamines, but diminished yields were obtained. The authors propose a mechanism in which

Scheme 75. Ruthenium-catalyzed carbonylative (5+1) cycloadditions of cyclopropyl imines by Murai.



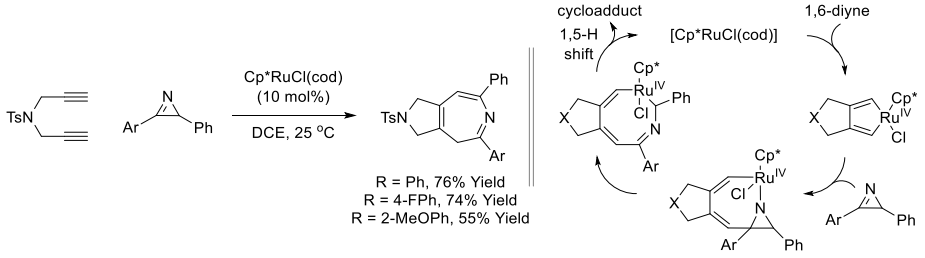
oxidative addition of the cyclopropyl imine to ruthenium(0) occurs prior to CO insertion and subsequent C-C reductive elimination to form the lactam. Moderate efficiencies were determined to arise from competing β-hydride elimination of the azaruthenacycle to form an inactive ruthenium-alkene complex (not shown).

4. Seven-Membered Ring Formation

4.1 (3+2+2) Cycloadditions

In 2016, Wang and Wan reported a Cp*RuCl(cod)-catalyzed (3+2+2) cycloaddition of 2*H*-azirines with 1,6-diynes for the construction of azepines (Scheme 76).[331] The authors propose a mechanism involving oxidative coupling of the 1,6-diyne to form a ruthenacyclopentadiene, which upon insertion of the imino moiety of 2*H*-azirine and subsequent β-carbon elimination forms an 8-membered ruthenacycle. Reductive elimination followed by a 1,5-hydride shift generates the azepine ring. Although diverse aryl-substituted 2*H*-azirine could be employed, substitution at the alkyne termini was not tolerated. In 2018, DFT calculations on this cycloaddition were conducted by Liu, who concluded that the rate-determining step is reductive elimination, in agreement with experimental results.[332]

Scheme 76. Ruthenium-catalyzed (3+2+2) cycloaddition of 1,6-diynes with 2*H*-azirines reported by Wang and Wan.

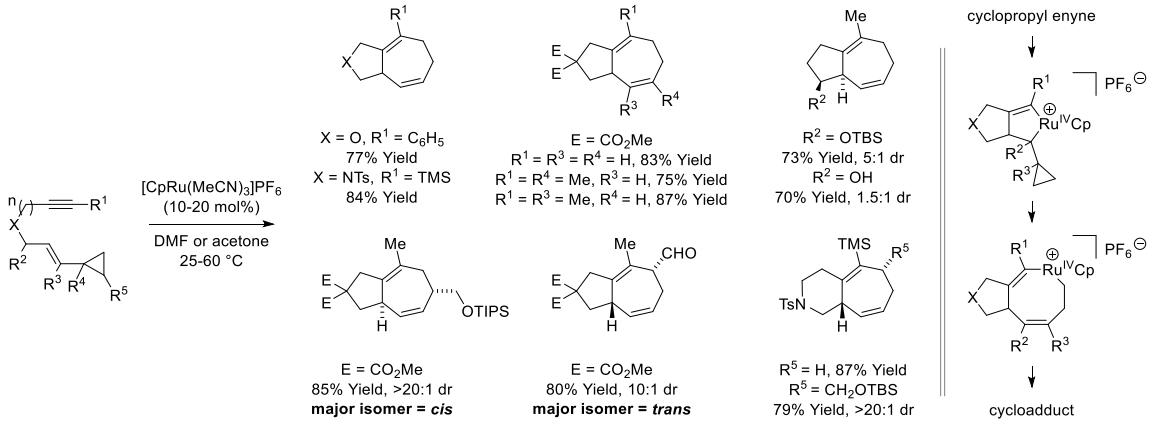


4.2 (5+2) Cycloadditions

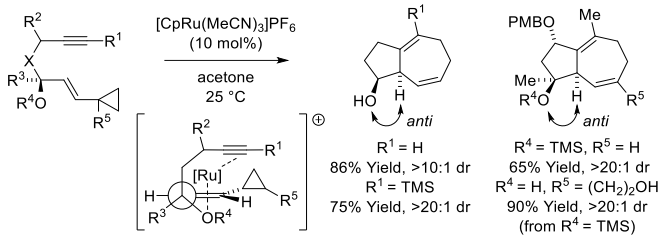
As summarized in the review literature,[39,333] the Trost laboratory discovered and developed intramolecular ruthenium-catalyzed (5+2) cycloadditions of alkynes with vinyl cyclopropanes to form fused seven-membered rings (Scheme 77).[334-337] In an initially proposed mechanism from their 2000 report,[334] which was later corroborated via DFT calculations by Houk,[335] coordination of cationic ruthenium to the 1,6-enyne triggers oxidative coupling to form a ruthenacyclopentene. β-Carbon elimination cleaves the cyclopropyl C-C bond delivering an eight-membered ruthenacycle, which upon C-C reductive elimination provides the cycloadduct. Substrate-directed regio- and diastereoselectivity was observed for reactants bearing substituents at the 2-position of the cyclopropane ring. Specifically, cyclopropanes that incorporate a silyloxymethyl group are transformed to the indicated *cis*-cycloadduct. In contrast, the corresponding aldehyde is transformed to the regioisomeric *trans*-cycloadduct (Scheme 77). Further investigations into the origins of regioselectivity of (5+2) cycloaddition[336] led the authors to conclude that for 1,2-*cis*-disubstituted cyclopropanes (notwithstanding aldehyde substituents), the less substituted C-C bond cleaves to form the eight-membered ruthenacycle, suggesting steric factors dominate regioselectivity. However, for 1,2-*trans*-disubstituted cyclopropanes, the more substituted C-C bond is cleaved, suggesting electronic effects dominate regioselectivity (not shown). In still deeper investigations, Trost examined the factors influencing diastereoselectivity in (5+2) cycloadditions of chiral cyclopropyl enynes to form hexahydroazulenes (Scheme 78).[337] A stereochemical model based on the Stork/Houk-Jäger "inside alkoxy" effect[338-340] was posited. The indicated reactive conformer avoids overlap between the C-O σ^* orbital and the alkene π orbital, which would diminish the coordinating ability

of the alkene. Oxidative coupling from this conformer ultimately leads to an *anti*-relationship between the homoallylic oxygen and the bridgehead hydrogen in the cycloadduct.

Scheme 77. Ruthenium-catalyzed intramolecular (5+2) cycloadditions of alkynes with vinyl cyclopropanes reported by Trost.

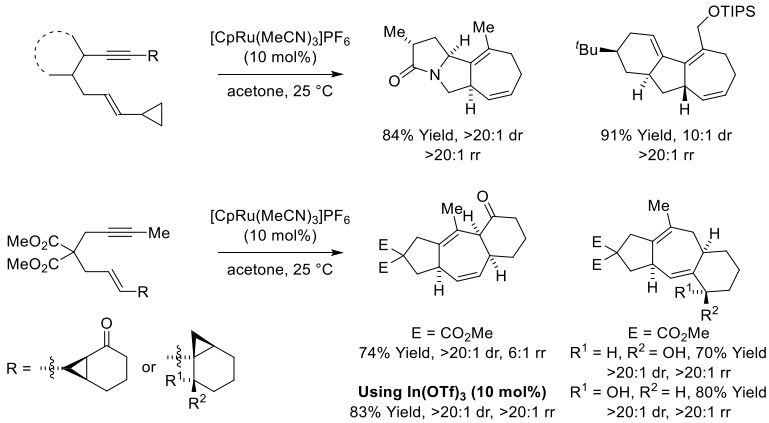


Scheme 78. Diastereoselectivity in ruthenium-catalyzed intramolecular (5+2) cycloadditions of alkynes with vinyl cyclopropanes reported by Trost.



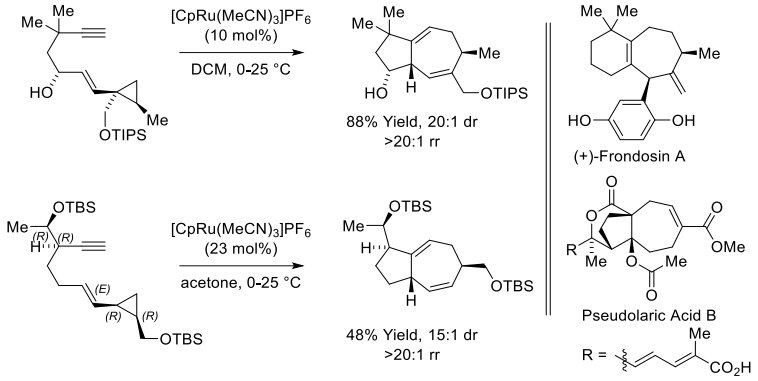
Trost subsequently examined the (5+2) cycloaddition of substrates that have rings in the tether connecting the 1,6-enyne or rings fused to the cyclopropane moiety (Scheme 79).[341,342] The tricyclic cycloadducts were formed in high yields, with excellent control of regio- and diastereoselectivity. For reactants that incorporate cyclopropropyl ketones, complexation by indium triflate was found to increase regioselectivity by rendering the C-C bond adjacent to the carbonyl more susceptible to cleavage. Notably, in a thorough survey of substrate scope, cyclization products that retain the cyclopropane ring were observed, demonstrating that oxidative coupling of the 1,6-enyne to form a ruthenacyclopentene is faster

Scheme 79. Ruthenium-catalyzed intramolecular (5+2) cycloadditions of cyclic cyclopropyl enynes reported by Trost.



than oxidative addition to the vinyl cyclopropane to form a ruthenacyclohexene (not shown).[342] The collective studies of Trost ultimately enabled total syntheses of the marine norsesquiterpenoid frondosin A (Scheme 80)[343] and pseudolaric acid B (Scheme 80),[344] which displays activity against multidrug resistant cancer cell lines; in the latter synthesis, however, an analogous rhodium-catalyzed cycloaddition[345] proved to be optimal for the (5+2) cycloaddition to form the core seven-membered ring. Synthetic studies toward the tricyclic core of rameswaralide also were disclosed (not shown).[346]

Scheme 80. Application of ruthenium-catalyzed intramolecular (5+2) cycloadditions of alkynes with vinyl cyclopropanes to the total synthesis of frondosin A and pseudolaric acid B reported by Trost.



5. Conclusion and Outlook

Despite enormous advances in the area of transition metal-catalyzed cycloadditions, the vast majority of ruthenium-catalyzed cycloadditions have only appeared within the last two decades. The first ruthenium-catalyzed cycloaddition (to form a 5-, 6- or 7-membered ring) was reported in 1987,[123] and in Lautens's authoritative 1996 review entitled "Metal-Mediated Cycloaddition Reactions,"[2] ruthenium-catalyzed cycloadditions to form 5-, 6-, and 7-membered rings were absent but for two reports.[167,172] While reasons for the delayed exploration of ruthenium in this context remain unclear, this relatively abundant metal has since evoked an incredibly diverse range of cycloadditions, including processes that are unknown for other metals.[34] Despite the diversity of cycloaddition processes, one can see that only a limited number of ruthenium complexes serve as efficient catalysts, allowing some generalizations regarding their use to be made. Zero-valent ruthenium complexes, in particular $Ru_3(CO)_{12}$, are most effective in cycloadditions that involve the insertion of carbon monoxide and those that proceed by way of oxaruthenacycles that arise via C=C/C=O oxidative coupling. In contrast, electron-rich [CpRuX], [Cp*RuX] and $[Cp^*Ru]^+$ catalysts are most frequently utilized in cycloadditions that involve oxidative coupling of all-carbon-containing π-unsaturated reactants (alkynes and alkenes). Additionally, ruthenium alkylidene complexes, which have famously found use in olefin metathesis, are also competent catalysts for [2+2+2] cycloaddition reactions of alkenes and alkynes. It is the authors' hope that the present catalog of ruthenium-catalyzed cycloadditions will expedite further progress in this burgeoning field of research.

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Notes

The authors declare no competing financial interest.

Biographies

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Tomáš Hodík received his MSc in Organic Chemistry from the University of Chemistry and Technology, Prague in 2015 where he conducted research with Professor Jiří Svoboda. In parallel, Tomáš earned an MSc in Physical Chemistry from the Charles University in Prague, and was trained in organometallic chemistry at the Academy of Sciences of the Czech Republic under the guidance of Dr. Jiří Pinkas. Tomáš completed his Ph.D. in the research group of Professor Christoph Schneider at Leipzig University, Germany, as a DAAD fellow. In 2019, Tomáš joined the research group of Professor Michael J. Krische as a Genentech postdoctoral research fellow. Tomáš is presently investigating the use of ruthenium complexes in site-selective protein modification.

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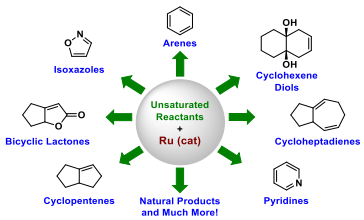
Arenes
Isoxazoles
Cyclohexene Diols
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