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Transition Metal-Mediated Cycloaddition Reactions

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1. Introduction

The discovery and development of new chemical reactions is a major focus of research activity in organic chemistry. The chemical synthesis of molecules provided by Nature has traditionally been the arena in which the utility of new reactions are critically evaluated. A vast array of new methods and creative strategies has arisen from this activity.[1] The development of new strategies and reactions is also stimulated by efforts to rationally design syntheses of nonnatural compounds with interesting molecular architectures. Concepts of bonding, binding, reactivity, and inter- and intramolecular interactions can then be examined.

The reactions and classes of reactions which have found the broadest applicability in organic chemistry are those that address the issues of stereo- and enantiocontrol and are compatible with a variety of functional groups. Reactions which form multiple bonds, rings, and/or stereocenters are particularly important tools for the efficient assembly of complex molecular structures.[2] Of the many families of reactions discovered over the past 75 years, cycloaddition reactions hold a prominent place in the arsenal of synthetic methods currently available to organic chemists and research activity in this field shows no signs of abatement.[3]

Cycloadditions have been promoted by heat, light, Lewis acids, high pressure, or sonication. Many of these reaction conditions require the presence of polarized functional groups in the substrate to facilitate the transformation. In general, the reaction of unactivated olefins, dienes, and acetylenes is notoriously poor and extreme conditions or special methods are necessary to achieve good yields of the cycloadducts. Particular difficulty is encountered in the cycloaddition of two unactivated species since homodimerization can be a competitive and dominant reaction pathway.

Metal catalysts provide new opportunities for highly selective cycloaddition reactions since complexation of the metal to an olefin, diene, or acetylene significantly modifies the reactivity of this moiety, opening the way for improved reactivity and novel chemistry. One of the most important consequences

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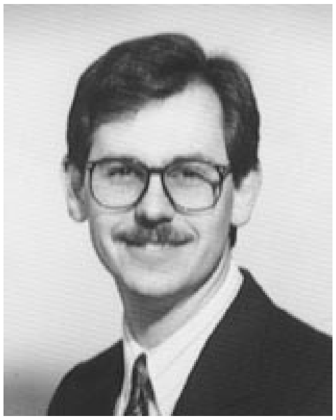


Mark Lautens was born in Hamilton, Ontario, in 1959. He received his B.Sc. at the University of Guelph in 1981 and his Ph.D. from the University of Wisconsin—Madison in 1985 with Barry M. Trost where he discovered molybdenum catalysts for allylic alkylations and the palladium(II) enyne cyclization. He was an NSERC Postdoctoral Fellow with David A. Evans at Harvard University from 1985 to 1987 prior to taking a position at the University of Toronto where he is now Professor of Chemistry. He was awarded an Alfred P. Sloan Fellowship, Eli Lilly Granteeship, Rutherford Memorial Medal from the Royal Society of Canada, and an E.W.R. Steacie Fellowship from NSERC. His research interests include the development of new reactions using metal catalysts, asymmetric synthesis and ring-forming and ring-cleaving reactions.

Wolfgang Klute was born in Balve, Germany, in 1966 and studied chemistry at the Philipps-University at Marburg, Germany. He completed his Diplomarbeit in 1991 and his Ph.D. thesis in 1994, both under the supervision of Prof. Dr. R. W. Hoffmann. His research in Marburg focused on enantioselective synthesis with chiral organolithium compounds. He studied transition metal-catalyzed hydrostannylations as a Deutsche Forschunggemeinschaft postdoctoral fellow in the group of Mark Lautens and is currently employed at Dr. Karl Thomae GmbH.

William Tam was born in Hong Kong on January 19, 1968. He received his B.Sc. degree from the University of Hong Kong in 1990. He then joined Professor Mark Lautens' group at the University of Toronto for his doctoral studies where he held a Simcoe Fellowship (1990–1995). His research focused on the studies of the transition metal-catalyzed cycloaddition reactions and the synthesis of polycyclic compounds. He will join Professor Anthony G. M. Barrett's group at Imperial College, University of London, in 1996 as a postdoctoral research associate.

of complexation is to temporarily polarize and activate an otherwise unreactive species. In addition to the rate enhancements observed in the presence of the metal catalyst, the opportunity to achieve enantioselective transformations by adding chiral ligands is one of the most attractive features of this strategy.

A discussion of established and interesting new cycloaddition reactions promoted by metal species is presented in this review. *Reactions were selected which proceed via complexation of the metal to the unsaturated carbon-containing species rather than activation by Lewis acid complexation to a carbonyl group or heteroatom which is remote from the reacting atoms.* Whenever possible, the state-of-the-art in Lewis acid-catalyzed or nonmetal-catalyzed processes is presented to allow a comparison of the relative merits of the different strategies. Processes which are catalytic in the metal were favored over stoichiometric reactions unless there were compelling reasons to include them. Synthetically important reactions which have no catalytic process currently available were included in many cases. Some exceptions to this selection process were included in order to make appropriate comparisons and provide a more comprehensive overview of the field. The review is organized by the size of the ring being formed rather than the number of electrons involved in the process.

Finally it should be emphasized that while the products of the reactions presented in this article are clearly cycloadducts, most if not all reactions proceed in a stepwise fashion and probably involve a cyclization reaction as a key event.

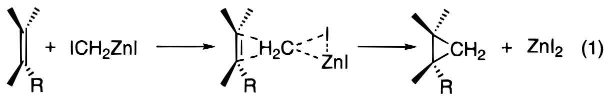
2. Three-Membered Ring Formation

This section provides an overview of useful or novel cyclopropanation and aziridination reactions. In general these reactions involve cycloaddition between a double bond and a metal carbene or nitrene. While the primary focus is on the different methods of generating the reactive species, recent synthetic advances in Simmons−Smith-type reactions are also presented due to the importance of this reaction in organic synthesis. Cyclopropanation employing *stoichiometric* amounts of transition metal carbenes ($M = Cr, W$, etc.) is not discussed.[4]

2.1. [2 + 1] Cycloadditions Using Stoichiometric Amounts of Zinc Carbenoids (Simmons–Smith Type)

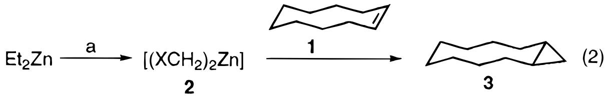
The cyclopropanation of simple alkyl-substituted olefins or electron-rich enol ethers with diiodomethane and Zn/Cu (Simmons−Smith[5]) has been known for many years, and its synthetic utility is well documented.[6] The mechanism of the reaction is proposed to proceed via a concerted, stereospecific transfer of a methylene unit from (iodomethyl)zinc iodide to an alkene and it therefore qualifies as a [2 + 1] cycloaddition (eq 1).[7] Prior complexation of the alkene to the zinc is not considered to be a dominant interaction.

In 1966, Furukawa generated an active zinc species (bis(iodomethyl)zinc) from diethylzinc and 2 equiv of



R = alkyl, O-alkyl, $OSi(CH_3)_3$

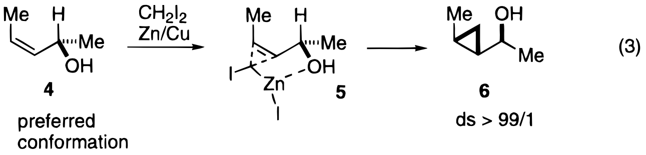
diiodomethane and utilized it to cyclopropanate alkenes and enol ethers.[8] More recently, Denmark obtained important structural information on the zinc carbenoids by X-ray crystallography and showed that bis(chloromethyl)zinc was more reactive than bis(iodomethyl)zinc. This trend was particularly evident in the reaction with cyclodecene **1** (eq 2).[9]

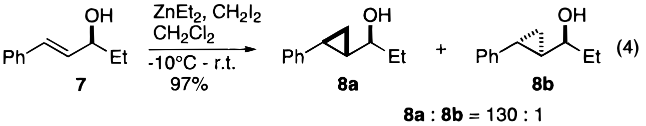


a: 2 equiv. XCH_2I, dichloroethane 0 °C, 15 min

X = Cl: 94 %
X = I: 12 %

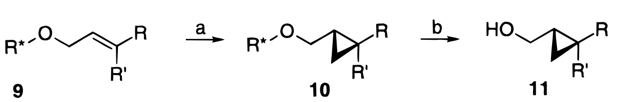
Early studies revealed that the reactivity of the reagent can be amplified by coordination of a heteroatom such as oxygen to the metal, resulting in a rate enhancement in the cyclopropanation of allylic alcohols.[10] Highly diastereoselective [2 + 1] cycloadditions could be achieved in the reaction with chiral allylic alcohols. Due to allylic 1,3-strain, the (*Z*)-alkene preferentially adopts conformation **4** leading to a front-side attack of the zinc carbenoid (eq 3). Subjecting conformationally flexible (*E*)-olefins such as **7** to the classical Simmons–Smith conditions usually results in low diastereoselectivity.[11] Very recently Charette showed that a zinc species tentatively formulated as "$EtZnCH_2I$" (from treatment of 1 equiv of diethylzinc with 1 equiv of diiodomethane) is more diastereoselective than the bis(halomethyl)zinc reagents.[9b] Under the optimized conditions the syn isomer **8a** is favored (eq 4).





A focus of recent attention is the development of methods for the preparation of enantiomerically pure cyclopropanes. This has been examined from the perspective of chiral auxiliary-based diastereoselective methods or enantioselective cyclopropanations using chiral catalysts. Building on the pioneering studies of Mash,[12] Yamamoto,[13] Imai,[14] and Tai,[15] Charette found an effective, covalently attached carbohydrate auxiliary for the cyclopropanation of prochiral *cis*- and *trans*- allylic alcohols.[16] Utilizing the directing effect of the hydroxy groups of various 2-hydroxyglucopyranosides **9** on the metal carbenoid, cyclopropanes **10** were produced in nearly quantitative yields and very high diastereoselectivities by reaction with 10 equiv diethylzinc/diiodomethane (Table 1). Reducing the amount of the reagent to less than 2 equiv led to a significant decrease of diastereoselectivity, which suggests that more than 1 equiv of the zinc reagent is involved in the reactive complex. This methodology is attractive since the auxiliary could be efficiently removed under mild conditions.

Table 1



entry	R	R'	ds (**10**)	entry	R	R'	ds (**10**)
1	Ph	H	130 / 1	3	H	Pr	114 / 1
2	Pr	H	124 / 1	4	Me	Me	111 / 1

a: 10 equiv. Et_2Zn, 10 equiv. CH_2I_2, toluene, -35°C - 0°C (>97%).
b: 1. Tf_2O, pyr (95%); 2. DMF, pyr, H_2O, 160°C; 3. $NaBH_4$ (90%) (entry 1)

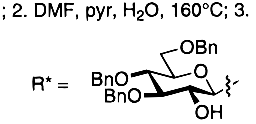
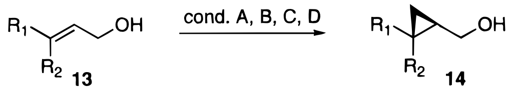


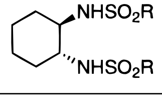
Table 2. Enantioselective Cyclopropanations with Chiral Amine 12



entry	R_1	R_2	cond.	yield (%)	ee (%)	ref.
1	Ph	H	A	82	76	17a
2	Ph	H	B	quant.	80	19a
3	Ph	H	C	quant.	86	19a
4	Ph	H	D	quant.	76	17b
5	$TrtOCH_2$	H	A	86	80	17a
6	H	$TrtOCH_2$	A	79	66	17a
7	H	Bu_3Sn	A	75	66	17c
8	H	Me_2PhSi	A	67	59	17c
9	Bu_3SnH	H	A	94	86	17c
10	Me_2PhSi	H	A	83	81	17c

A: 0.12 eq **12a**, 2.0 eq Et_2Zn, 3.0 eq CH_2I_2, CH_2Cl_2-10%hexanes, -23°C, 5h. B: 1.0 eq Et_2Zn, 0.1 eq **12b**, 1.0 eq $Zn(CH_2I)_2$, CH_2Cl_2, -23°C.
C: 1.0 eq ZnI_2 added to B. D: 0.1 eq **12c**, 0.08 eq *i*-Bu_2AlH, 2.0 eq Et_2Zn, 3.0 eq CH_2I_2, CH_2Cl_2-10%hexanes, -20°C, 14h.

12 =

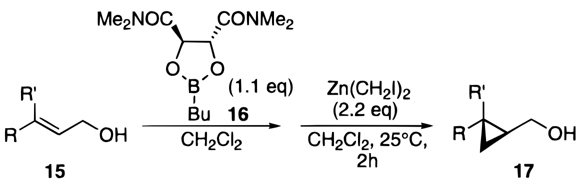


12a: R = p-NO_2-C_6H_4
12b: R = CH_3
12c: R = C_6H_5

The first useful enantioselective cyclopropanation reactions using a catalytic amount of a chiral ligand **12** were disclosed by Kobayashi (Table 2).[17,18] Mechanistic studies carried out by Denmark suggested that prior formation of the zinc alkoxide was crucial for the success of this method.[19] Furthermore, the rate of product formation increases significantly after an induction period, which was ascribed to an autocatalytic effect of the zinc iodide. Support for this proposal comes from the increase in rate and selectivity upon addition of zinc iodide (entry 3). This information should be useful in designing catalysts with improved enantioselectivity.

Cyclopropanation with a chiral metal complex was also recently developed by Charette, who employed the dioxaborolane of tetramethyltartaric acid diamide (**16**) as a chiral ligand in the presence of zinc carbenoids.[20] High ee's are observed in the cyclopropanation of *cis*-, *trans*-, and 3,3-disubstituted allylic alcohols (Table 3). Charette attributed the success of the chiral auxiliary **16** to the formation of a conformationally restricted bidentate chelate be-

Table 3. Enantioselective Cyclopropanations with Chiral Boralane 16



entry	R	R'	yield	ee (**17**)
1[a]	Ph	H	>98 %	93 %
2	Prop	H	80 %	93 %
3[a]	H	$TBSOCH_2$	80 %	91 %
4	H	Et	90 %	93 %
5[a]	Me	Me	85 %	94 %

a: The absolute stereochemistry corresponds to the one displayed in the equation above and was established by comparing the signs of the optical rotation with literature data.

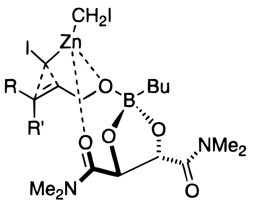
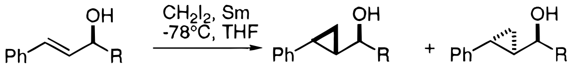


Figure 1.

tween the reagent and the substrate. The allylic oxygen and one of the carbonyl oxygen's of the amide groups were proposed to coordinate to the metal (Figure 1). Although the reaction currently requires stoichiometric quantities of the chiral metal complex, there has been rapid acceptance of this methodology by the chemical community.[21]

2.2. [2 + 1] Cycloadditions with Stoichiometric Amounts of Samarium Carbenoids

Molander reported that Sm carbenoids are easily formed, reactive species and are useful alternatives to Zn reagents. The cyclopropanation of the (*E*)-allylic alcohol **18a** led to the preferred formation of the *anti*-cyclopropane **19a** and reaction could be performed at −78 °C (eq 5).[22] The diastereoselectivity in this case was modest; however, the opposite diastereomer was formed to that obtained by Charette using "$EtZnCH_2I$" (cf. eq 4). Increased stereoselectivity in favor of the syn-diastereomer **20b** could be attained in the cyclopropanation of (*E*)-allylic alcohols bearing α-branched substituents such as in **18b**. $ClCH_2I$ was shown to exhibit similar selectivities and yields to CH_2I_2.

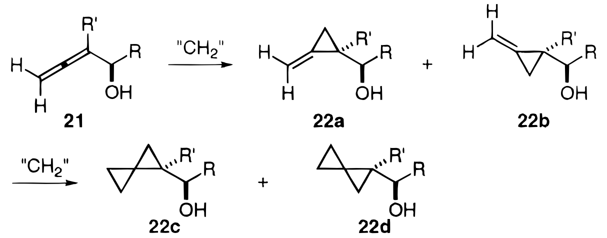


(5)

18a: R = Me
18b: R = *i*-Pr

R = Me: **19a**/**20a** = 1/6 (98%)
R = *i*-Pr: **19b**/**20b** = 200/1 (88%)

Table 4. Cyclopropanation of α-Allenic Alcohols



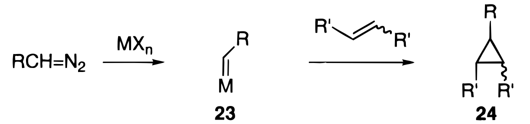
entry	R	R'	22a : 22b : 22c : 22d	yield
1[a]	*c*-hexyl	H	4 : 1 : 3.5 : 1.5	73 %
2[b]	*c*-hexyl	H	9.5 : 1 : 0 : 0	64 %
3[b]	*t*-Bu	H	50 : 1 : 0 : 0	57 %
4[b]	*n*-heptyl	H	1 : 2.1 : 0 : 0	73 %
5[b]	*c*-hexyl	Me	7.9 : 1 : 0 : 0	66 %
6[b]	*c*-hexyl	MeO	50 : 1 : 0 : 0	47 %

a: 2.1 eq Zn(Cu), 2 eq CH_2I_2, Et_2O, reflux.
b: 5-10 eq Sm(Hg), 10 eq CH_2I_2, THF, -78°C to r.t.

Lautens and Delanghe reported that samarium carbenoids show remarkable levels of regioselectivity in the cyclopropanation of α-allenic alcohols (Table 4).[23] Four products were observed when the reaction was carried out under the classical Simmons−Smith conditions (entry 1). With samarium the formation of the spirocycles **22c** and **22d** was not observed (entries 2−6). Furthermore, excellent diastereoselectivities favoring **22a** were obtained when R was sterically demanding (entries 2−4). The level of diastereoselectivity also was influenced by the substituent R′ with R′ = MeO giving the best selectivity for a given R group (entries 2 and 5 vs 6).

2.3. [2 + 1] Cycloadditions with Transition Metal-Stabilized Alkyl Carbenes of Cu, Pd, Ni, Co, and Rh

Diazoalkanes efficiently form transition metal carbene complexes of general structure **23** in the presence of Cu , Pd , Ni, or Rh catalysts. As earlier reviews have pointed out, the reactivity of the carbenoid carbon is significantly affected by the metal, which alters the chemoselectivity of the complex toward different classes of olefins (eq 6).[24]

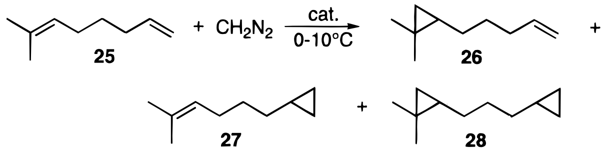


(6)

R = alkyl, H
M = Cu, Pd, Ni, Co, Rh

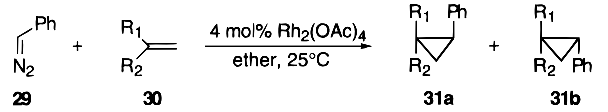
Cu(I) and Cu(II) salts were among the first catalysts shown to promote the cyclopropanation of nonpolarized olefins by diazo compounds. Some Cu(II) salts including $Cu(OTf)_2$ and $CuCl_2$ are reduced by diazoalkanes to Cu(I), which alters the regioselectivity of the cyclopropanation. By varying the counterion on the Cu(II) salt, either the mono- or trisubstituted double bond of **25** was preferentially reacted. The propensity of Cu^IOTf to form olefin complexes was used to account for the preference to react with terminal double bonds, whereas catalysts unable to coordinate to double bonds promote carbene addition to the more substituted, more electron-rich olefin (Table 5).[25] Reactions with CuOTf have been proposed to involve coordination of the double bond to the metal prior to carbene transfer in order to account for the observed selectivities in favor of strongly coordinating olefins;[24b] however, a detailed mechanism has not been put forward.

Table 5. Effect of the Counterion on Cu(II)-Catalyzed Cyclopropanation



cat.	26	:	27	:	28	conversion (%)
$Cu(acac)_2$	1	:	0.1	:	0.6	90
$Cu(OTf)_2$	1	:	2.5	:	0.4	50

Table 6. Rh-Catalyzed Cyclopropanations

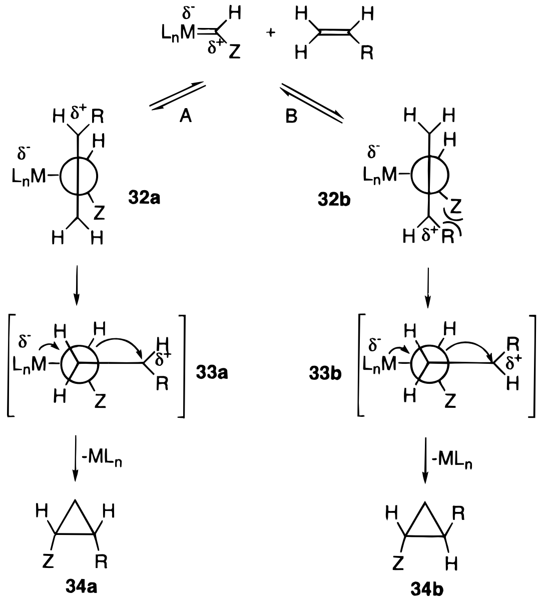


entry	R_1	R_2	yield 29 (%)	31a/31b
1	OMe	Ph	98	0.67
2	OMe	Me	82	1.2
3	OMe	*t*-Bu	92	0.15
4	*n*-BuO	H	92	2.5
5	Ph	H	38	3.3

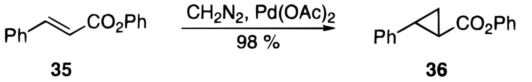
Rhodium carbenes derived from phenyldiazomethanes and $Rh_2(OAc)_4$ exhibited different reactivity, as they not only added to nonconjugated olefins, but also to electron-rich double bonds such as enol ethers.[26] The reaction products were usually obtained as *E*/*Z*-mixtures although in some cases (*Z*)-cyclopropanes were strongly favored (entries 3, 5) (Table 6).

On the basis of an earlier model by Casey,[27] Doyle suggested a pathway which accounted for the inability of $Rh_2(OAc)_4$ to form olefin complexes.[24b] He invoked the formation of an initial π-complex between the terminal alkene carbon and the electrophilic carbene carbon (**32a**) rather than the formation of a metallacyclobutane intermediate (Scheme 1). Following rotation around the newly established σ-bond, the cyclopropane ring is formed via a backside displacement of the metal by the developing carbenium ion (**33a**). This model explains the preference for the formation of (*Z*)-cyclopropanes (**34a**) by path A (R = OR, Z = Ph) due to the minimization of steric interactions between R and Z in **32a** compared to **32b**. The chemoselectivity toward electron-rich olefins can be rationalized by a stabilization of the developing positive charge in **32a** and **33a** by the electron-donating substituent R.

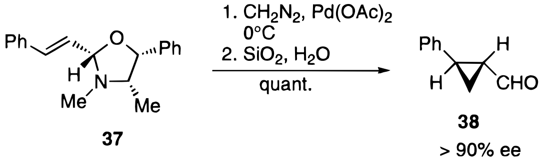
Scheme 1



Palladium complexes including $Pd(OAc)_2$[28] and $Pd(PPh_3)_4$[29] catalyze the reaction of diazomethane with electron-deficient olefins including α,β-unsaturated ketones and esters (eq 7), strained aryl- and alkyl-substituted alkenes. For example, the chiral allylic acetal **37** underwent diastereoselective cyclopropanation and after removal of the chiral auxiliary, **38** was isolated in high ee (eq 8).[30] Despite these promising initial results, little additional work has been reported.

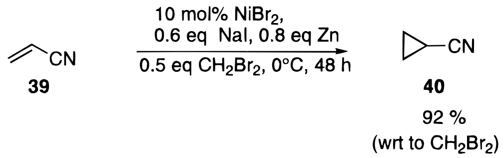


(7)



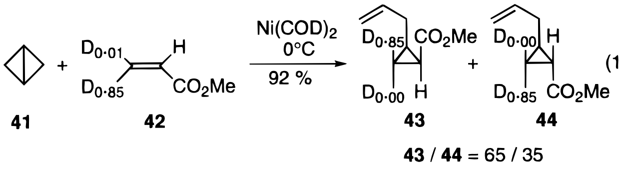
(8)

Kanai showed that Ni carbenes generated from a Ni(0) species such as $Ni(PPh_3)_4$ in the presence of diazomethane, show an even higher tendency to add to electron-deficient olefins.[31] The carbenes are also generated by reaction of dibromomethane with NaI, Zn, and $NiBr_2$. In the presence of **39**, cyclopropane **40** was formed in high yield (eq 9).[31] Similar results were obtained using $CoBr_2$.



(9)

Noyori developed an alternative method for the generation of allyl Ni carbenes from highly strained hydrocarbons.[32] When bicyclo[1.1.0]butane **41** was treated with catalytic amounts of bis(cyclooctadiene)-nickel(0) ($Ni(COD)_2$) in the presence of the deuterated methyl acrylate **42**, two diastereomeric allylcyclopropanes **43** and **44** were isolated in which the stereochemistry of the double bond was retained (eq 10).



(10)

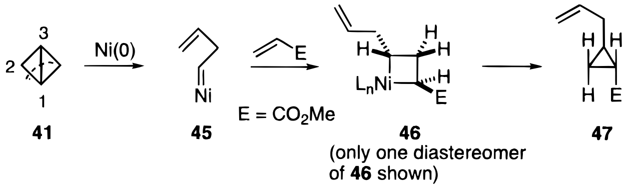
On the basis of these observations, Noyori suggested a mechanism in which a nickel-induced cleavage of the geminal C_1-C_3 and C_1-C_2 bond generated the allylcarbene–nickel complex **45**. A stereospecific [2+2] cycloaddition ensues yielding the nickelacy-

Table 7. General Reactivity Trends with Various Catalysts

entry	catalyst	reactive olefins
1	$Rh_2(OAc)_4$	styrene, enol ethers
2	$Cu(acac)_2$, $CuCl{\cdot}P(OMe)_3$	enamines, alkyl substituted olefins
3	$Cu(OTf)_2$, Cu(OTf), $Cu(BF_4)_2$	terminal olefins
4	$Pd(OAc)_2$, $PdCl_2$, $Pd(PPh_3)_4$	styrene, strained, conjugated terminal olefins, α,β-unsatured carbonyl compounds
5	$Ni(COD)_2$, $Ni(PPh_3)_4$, NaI/Zn and $NiBr_2$ or $CoBr_2$	α,β-unsatured carbonyl compounds, acrylonitrile

clobutane **46** which undergoes a reductive elimination to the cyclopropane **47** (Scheme 2).

Scheme 2



(only one diastereomer of **46** shown)

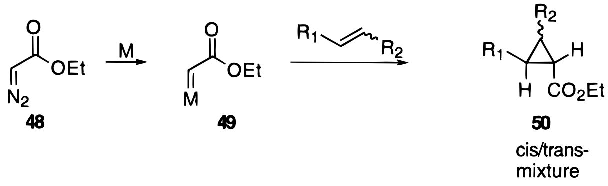
A similar mechanism involving a metallacyclobutane was also discussed by Kanai for cyclopropanations using Ni carbenes.[31d] Jennings isolated a stable platinacyclobutane generated from a Pt−olefin complex and diazafluorene, which provides further support for the intermediacy of a metallacyclobutane.[33] This species was converted to a cyclopropane under thermal conditions.

In summary, Rh and Cu carbenes react with electron-rich olefins although they show different behavior with enol ethers. Ni catalysts provide carbenes which are more nucleophilic. Clearly a wide range of olefins undergo cyclopropanation with nonstabilized carbenes. A survey of olefins and metal catalysts which give cyclopropanes is presented in Table 7.

2.4. Cyclopropanations with Metal Carbenes Derived from α-Diazocarbonyl Compounds

Metal carbenes bearing a carbonyl group in the β-position are an important class of cyclopropanating agents which are generated by the reaction of diazo ketones or diazo esters with Pd(II), Cu(II), Cu(I), or Rh(II) salts. This subject has been extensively reviewed and will only be briefly discussed.[34] In terms of reactivity, basically the same trends were observed for α-keto carbenes as for alkyl carbenes. Due to the electron-withdrawing effect of the carbonyl group, all metal carbenes are electrophilic and reacted preferentially with electron-rich double bonds. Carbenes generated from a metal with only one free coordination site (e.g. $Rh_2(OAc)_4$, $Cu(acac)_2$) add to a variety of olefins including those bearing alkyl to alkoxy substituents. Metals with more than one available coordination site such as $Pd(OAc)_2$ or Cu(OTf) add preferentially to conjugated (Table 8, entry 4) and strained olefins (entry 3). Poorer yields are obtained with terminal, disubstituted olefins or enol ethers implying that precoordination of the olefin to the Pd or Cu occurs. Addition to electron-deficient olefins has not been efficiently achieved to date (entry 6). In the case of unsymmetrical olefins the products are usually obtained as mixtures with the *trans* diastereomer favored over the *cis*.[25b]

Table 8. Cyclopropanations with Metal Carbenes Derived from α-Diazocarbonyl Compounds



entry	olefin	yield (%) with[a]		
		$Pd(OAc)_2$	$Cu(OTf)_2$	$Rh_2(OAc)_4$
1	1-hexene[b]	30	36	86
2	*cis*-2-octene	36	40	65
3	norbornene	87	95	95
4	styrene	98	80	90
5	dihydropyran	20	55	71
6	dimethyl maleate	traces	traces	traces

[a] The *E*/*Z* ratios were not reported. [b] The methyl ester of diazoacetic acid was used instead of the ethyl ester.

Since Nozaki and Noyori's[35h] pioneering studies, significant effort has been focused on the development of an enantioselective cyclopropanation by decomposition of a diazo ester in the presence of a chiral ligand and a Cu(I) or Cu(II) salt (Table 9). With some ligands a chiral ester led to higher de values (entries 3, 6, 9), whereas bulky esters gave improved *trans/cis* ratios in other cases (entries 1, 2 vs 5). The best results were obtained with the chiral bis(oxazolidine) **54**, entry 5.[35] Recently good ee's have also been obtained in intramolecular cyclopropanations.[36]

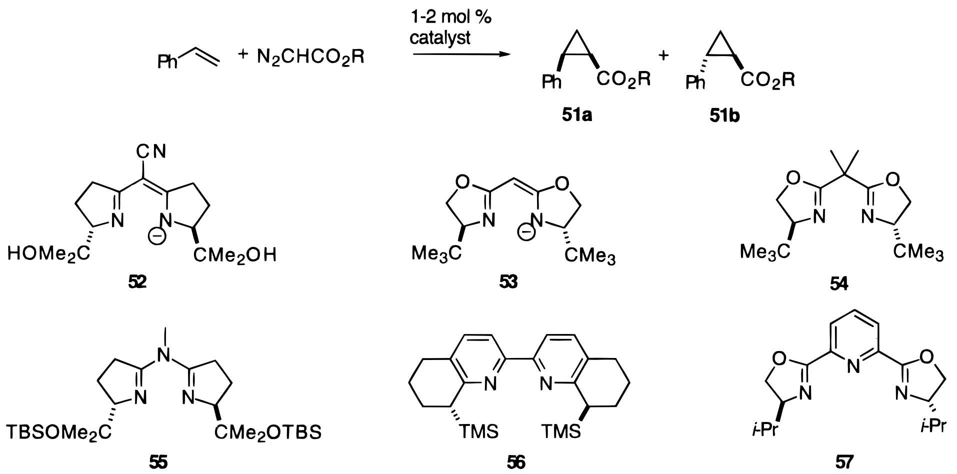
The mechanism of cyclopropanations using carbonyl substituted Rh carbenes was also rationalized by Doyle using the same model as for the phenyl substituted analogues (Scheme 1). However, in this case path B dominates (Z = CO_2R, R = alkyl) due to a stabilizing interaction between the carbonyl oxygen and the developing positive charge of the double bond. Following studies correlating *cis/trans* stereoselectivities of Pd, Cu, and Rh carbenes in the reaction with various olefins, Doyle concluded that this model might also applied to Pd- and Cu-catalyzed cyclopropanations. However, the model does not account for the differences in reactivities between the different catalysts.

2.5. [2 + 1] Cycloadditions with Vinylcarbenes

The reactivity of transition metal-stabilized vinyl carbenes often resembles that observed with simple metal carbenes. Since vinylcarbenes can also equilibrate to metallacyclobutenes, new reaction pathways are observed. In addition, rearrangements have been observed to occur after the cycloaddition which further complicates any mechanistic interpretation.

The first reports of cycloadditions with vinylcarbenes were disclosed by Salomon, who treated diazopropene with copper hexafluoroacetylacetonate

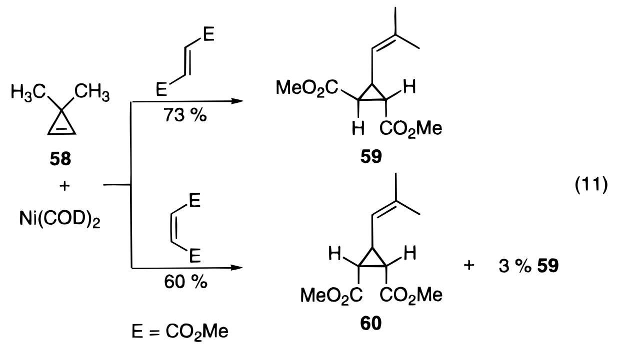
Table 9. Cu-Catalyzed Enantioselective Cyclopropanations with Diazoesters



entry	catalysis	R	ee (**51a**), %	ee (**51b**), %	**51a**/**51b**	yield **51**	ref
1	(**52**)$_2$Cu	Et	68	85	22/78	65	35a,b
2	(**52**)$_2$Cu	*t*-Bu	92	93	16/84	60	35a,b
3	(**52**)$_2$Cu	*d*-menthyl	95	97	18/82	60–70	35a,b
4	(**53**)$_2$Cu, PhNHNH$_2$	*l*-menthyl	96	98	14/86	72	35c
5	**54**·CuOTf	BHT[a]		99	6/94	85	35d
6	**55**·CuOTf	*d*-menthyl	98	99	16/84	75	35e
7	**56**·CuOTf	*t*-Bu	98	92	14/86	75	35f
8	[Ru(**57**)Cl$_2$(C$_2$H$_4$)]	*t*-Bu	87	94	3/97	65	35g
9	[Ru(**57**)Cl$_2$(C$_2$H$_4$)]	*l*-menthyl	84	96	2/98	84	35g

[a] BHT = 2,6-di-*tert*-butyl-4-methylphenol.

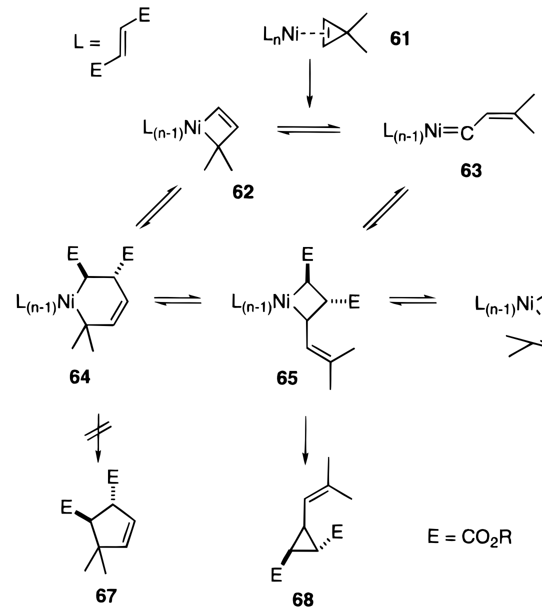
(Cu(hfacac)$_2$) in the presence of various alkyl-substituted olefins, but the yields obtained in the reaction with *trans*- or *cis*-butene were poor.[37] Access to vinyl carbenoids was also developed by Binger, who obtained a cyclopropane when 3,3-dimethylcyclopropene (**58**) was treated with catalytic amounts of Ni(COD)$_2$ in the presence of electron-deficient olefins including dimethyl fumarate or dimethyl maleate (eq 11).[38] The reaction was stereospecific and cyclopropanes **59** and **60** were isolated in high yield. The formation of a small amount of **59** during the reaction with dimethyl maleate was attributed to a Ni-catalyzed bond isomerization of the starting olefin followed by a stereospecific cyclopropanation.



(11)

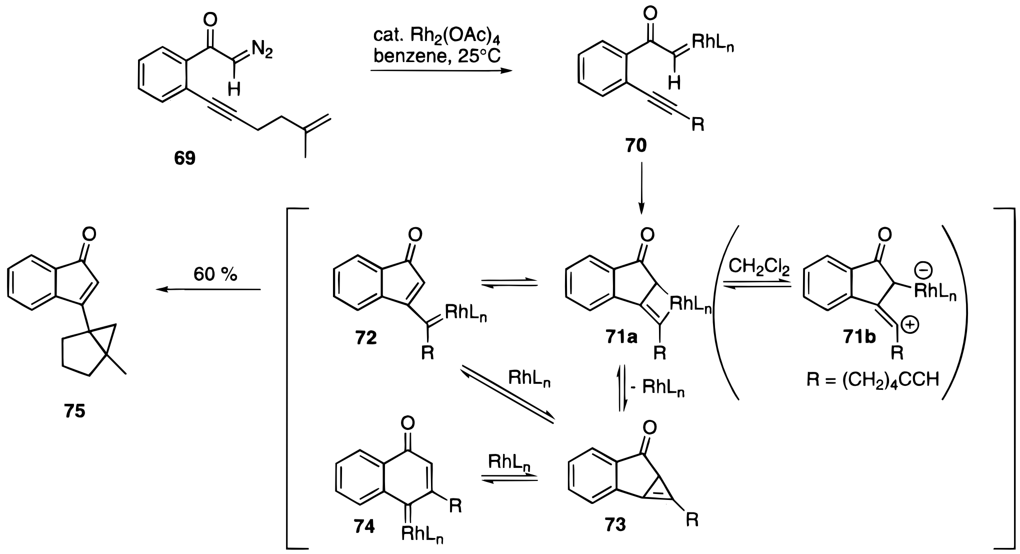
Binger proposed that a complex between the nickel, the cyclopropene, and the electron-deficient olefin (**61**) was formed, which underwent insertion into the three-membered ring to provide either a nickelacyclobutene **62** or a vinyl nickelcarbene **63** (Scheme 3). Carbometalation onto the olefin would give rise to nickelacyclohexane **64**, which could exist as a nickelacyclobutane **65** or Ni–π-allyl complex **66**. Irrespective of which species predominates, the reductive elimination occurred exclusively to yield the vinyl cyclopropene **68**; the formation of cyclopentene **67** was not observed.

Scheme 3



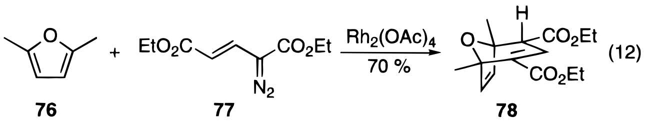
Recently, Padwa showed that the intramolecular reaction of the α-keto rhodium carbene **70** and a triple bond generated the rhodium vinyl carbene **72**, which added intramolecularly to a double bond forming the cyclopropane **75** (Scheme 4). Initially he suggested that **72** was formed by a carbenoid–alkyne metathesis reaction via the metallacyclobutene **71a**. However, in substrates bearing a hydroxy group (e.g. R = (CH$_2$)$_4$OH) he observed products that were derived from a cyclopropene intermediate analogous

Scheme 4



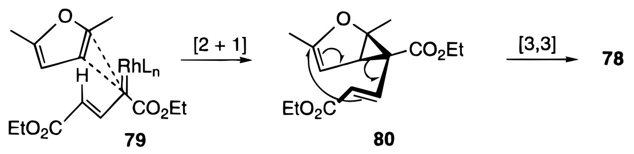
to **73**. Therefore an alternative sequence of steps was suggested, in which an extrusion of Rh, yielding the highly strained cyclopropene **73**, is followed by a regioselective reinsertion of the metal affording **72**. Insertion into the other cyclopropene bond yielding the Rh carbene **74** appeared to be less likely since products derived from this species were not observed. It is also conceivable that all species are rapidly equilibrating with **72** as the intermediate which leads to the product. In dichloromethane a dipolar structure **71b** was proposed to predominate, which did not lead to cyclization products.[39]

Davies investigated the reactivity of the unsaturated diazo ester **77** and dimethylfuran **76** in the presence of catalytic amounts of $Rh_2(OAc)_4$. Exclusive formation of the *endo*-oxabicyclo[3.2.1]octene **78** was observed (eq 12).[40]



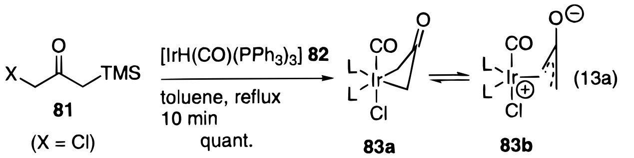
Although this reaction can be described as a [4 + 3] cycloaddition, the authors proposed a mechanism in which cyclopropanation with the vinyl carbenoid **79** is followed by a Cope rearrangement (Scheme 5).

Scheme 5

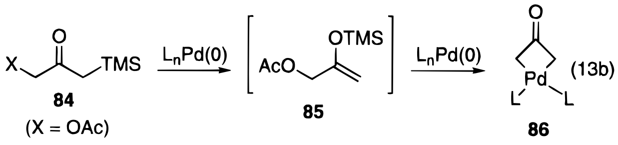


2.6. [2 + 1] Cycloadditions with Palladium Complexes of Oxatrimethylenemethane

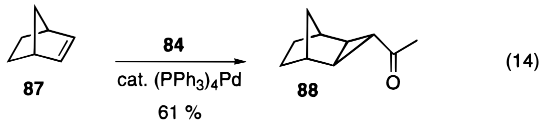
Transition metal complexes of oxatrimethylenemethane were first reported by Kemmitt, who prepared the stable iridacyclobutanone **83** from the iridium complex **82** and trimethylchloropropenone **81** (eq 13a). The structure of **83**, which was elucidated by X-ray crystallography and NMR spectroscopy, could also be described as an oxatrimethylenemethane complex. Similar complexes were obtained using Pt and Os.[41]



Trost then investigated the scope and reactivity of the corresponding Pd complexes, which were available from the reaction of Pd(0) with 1-acetoxy-3-(trimethylsilyl)propanone **84**.[42] Pd(0) was suggested to induce **84** to undergo a Brook rearrangement to form the silyl enol ether **85**. Subsequent palladium-catalyzed oxidative addition into the allyl acetate and acetate-induced desilylation would form metallacyclobutanone **86** (eq 13b).

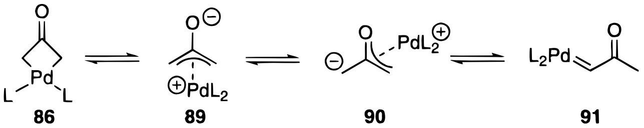


Reaction of **84** and norbornene (**87**) in the presence of a palladium catalyst gave the cyclopropane **88** as a single stereoisomer (eq 14).



The isomeric oxatrimethylenemethane complexes **89** and **90** and the acylcarbene complex **91** are alternative representations of **86** which need to be considered in order to explain the observed reactivity (Scheme 6). Zwitterion **89**, the oxa analogue of the

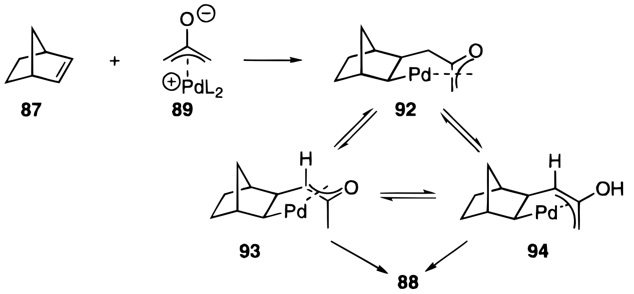
Scheme 6



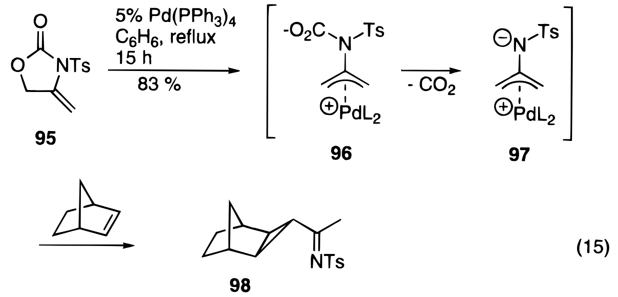
TMM–Pd complex was proposed by Trost to be the reactive form. However, a [3 + 2] cycloaddition between **84** and dimethyl dibenzylidenmalonate (which is highly reactive in TMM reactions, cf. section 4) was not observed. The α-keto carbene **91** is unlikely to be the reactive complex since Pd(II)-catalyzed additions of carbenes derived from ethyl diazoacetate to norbornene-type molecules gave mixtures of *exo* and *endo* isomers.[43]

The following mechanism was proposed for the cycloaddition. Carbometalation of the strained alkene by **89** leads to the oxyallyl–Pd complex **92.** Equilibration to the tautomeric oxyallyl complex **93** and/or the π-allyl complex **94** then occurs which undergoes a reductive cyclization to form the product **88** (Scheme 7).

Scheme 7



Similar observations were made by Murai, who developed an approach to the azatrimethylenemethane analogue of **86**.[44] Treatment of methylene oxazolidine **95** with Pd(0) presumably generates a Pd–π-allyl complex **96** which suffers decarboxylation. In analogy to **86** and in a similar fashion as outlined in Scheme 7 this species provides the cyclopropyl imine **98** (eq 15).

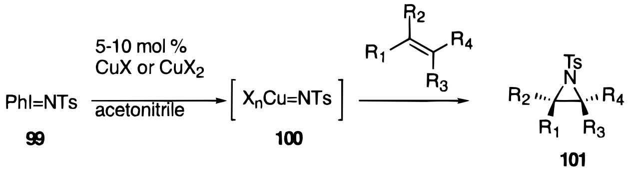


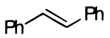
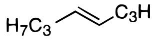
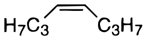
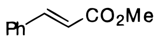
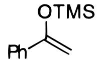
2.7. Transition Metal-Catalyzed Aziridinations

Aziridines are valuable intermediates in organic synthesis and new routes to their preparation have been the focus of recent investigations with an emphasis on metal-catalyzed processes.[45] Copper salts including CuOTf and $Cu(OTf)_2$ were shown by Evans to be effective at catalyzing the aziridination reaction between (*N*-(*p*-tolylsulfonyl)imino)phenyliodinane **99** and a range of electron-rich and electron-poor olefins.[46] Cu nitrenes of general structure **100** were proposed as intermediates (Table 10).

The aziridination process is stereospecific with *alkyl*-substituted olefins. However, while addition to *trans*-stilbene generated the (*E*)-aziridine, addition to *cis*-stilbene was accompanied by partial loss of the olefin geometry. Jacobsen has proposed that these observations are best explained by invoking two different mechanisms in which alkyl-substituted olefins react via a concerted mechanism, whereas alkenes bearing aryl substituents undergo a stepwise process. A radical intermediate was proposed for substituents such as an aryl group which are capable of stabilizing the radical.[47] Rotation around the C–N bond prior to the formation of the second bond accounts for the formation of a *trans*-aziridine from a (*Z*)-olefin (Scheme 8).

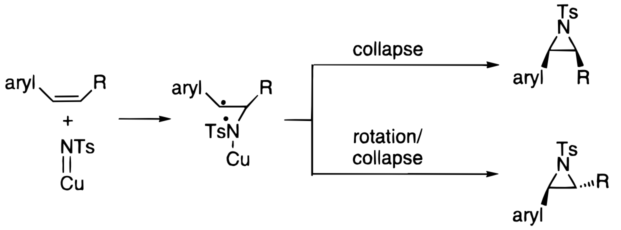
Table 10. Cu-Catalyzed Aziridinations



entry	olefin	catalyst	aziridine **101** *trans : cis*	yield (%)
1		$CuClO_4$	>95 : 5	56
		$Cu(acac)_2$	> 95 : 5	50
2		$CuClO_4$	17 : 83	73
		$Cu(acac)_2$	60 : 40	54
		$Cu(OTf)_2$	10 : 90	67
3		$CuClO_4$	>95 : 5	64
4		$CuClO_4$	<5 : 95	78
5		$CuClO_4$	-	69
		$Cu(OTf)_2$	-	75
6		$CuClO_4$	-	75[a]

a: The product was isolated as a α-tosylamino ketone

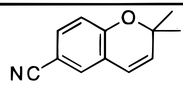
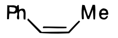
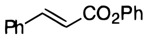
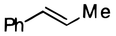
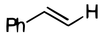
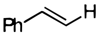
Scheme 8



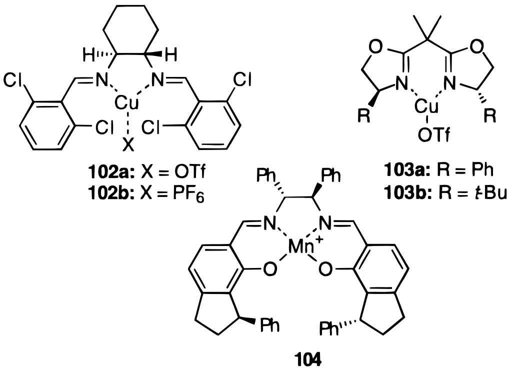
Significant progress has been made in the development of an enantioselective aziridination reaction. Jacobsen employed chiral bis(benzylidenediamino)-cyclohexane complexes **102** and Cu(OTf) with considerable success.[48] High enantiomeric excesses were obtained with *cis*-olefins, although the reaction was not stereoselective. Evans reported that copper complexes of chiral methyleneoxazolines **103** were also very efficient.[49] Manganese(III) bis(benzylidenediamino)ethane complexes **104** were less effective (Table 11).[50]

Several features of the reaction mechanism have been elucidated. Evidence to support the existence of a discrete (diamine)Cu=NTs species as the catalyst was put forward by Jacobsen. A copper nitrene solution generated under photochemical conditions from tosyl azide in the presence of **102b** gave the same ee with styrene as the reaction of **99** with **102b**.[51] Furthermore, similar levels of enantioselectivity were observed in $CuPF_6$-catalyzed aziridination

Table 11. Cu-Catalyzed Aziridinations

entry	substrate	catalyst	yield (%)	ee (%)	ref.
1		**102**	75	>98	48
2		**102**	79^a	67 (cis) 81 (trans)	48
3		**103a**	64	97	49
4		**103b**	62	70	49
5		**103b**	89	63	49
6		**104**	34	28	50

a: cis : trans = 3 : 1



104

and cyclopropanations with ethyl diazoacetate when the same ligands were employed.

Several observations support the intermediacy of a copper in the +2 oxidation state. Evans observed similar enantioselectivities with $Cu(OTf)_2$ or Cu(OTf). In addition, the iodine(III) reagent was shown to be an oxidant for Cu(I). The UV spectrum taken of a solution of the ligand and Cu(OTf) after treatment with the iodine reagent was "indistinguishable" from a spectrum of a solution of $Cu(OTf)_2$.

The importance of three-membered-ring-containing compounds as target molecules and useful building blocks has stimulated significant activity and led to creative solutions for their synthesis. Further advances are anticipated in the areas of selectivity and efficiency.

3. Four-Membered Ring Formation

The [2 + 2] cycloaddition of alkenes and/or alkynes represents an important strategy for the synthesis of cyclobutane derivatives.[52] A thermally forbidden process by the Woodward–Hoffmann rules,[53] this cycloaddition has been achieved photochemically,[54] by thermal reactions via biradical intermediates,[55] by the use of Lewis acid catalysts,[56] and by the use of transition metal catalysts.[57–65] To date, the range of substrates which undergo [2 + 2] reactions with transition metals is rather limited. Reactions of strained alkenes have received the most attention and further studies to expand the scope of this reaction are needed. The reactions of Fischer carbenes and olefin metathesis are not covered.[66,67]

3.1. [2_{π} + 2_{π}] Cycloadditions of Strained Alkenes with Electron-Deficient Olefins

The transition metal-catalyzed dimerization of norbornadiene (NBD) **105** was first reported in 1957.[57a] Since then various dimerization reactions of NBD have been observed with Ni, Co, and Fe catalysts providing **106a–f** (Figure 2).[57]

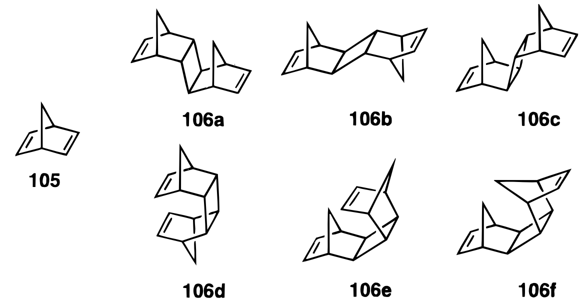
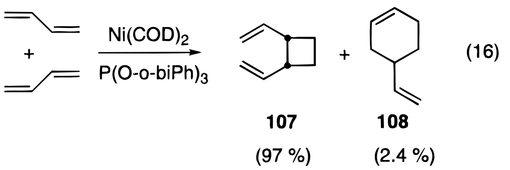
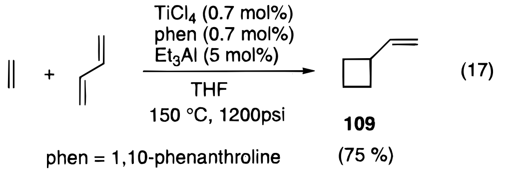


Figure 2. NBD and various [2 + 2] NBD dimers.

1,3-Butadiene is known to dimerize in the presence of metal catalysis.[58] In an early example, *cis*-1,2-divinylcyclobutane (**107**) was formed via a nickel-catalyzed [2 + 2] dimerization of 1,3-butadiene (eq 16).[59a] In 1972, the titanium-catalyzed cross coupling of 1,3-butadiene with ethylene was reported (eq 17).[64]

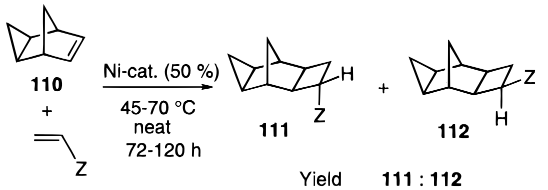


(16)



(17)

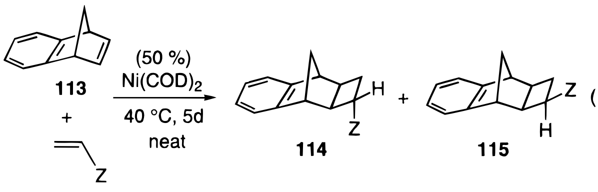
Strained alkenes such as *exo* cyclopropyl norbornene **110**, the benzo derivatives **113** and **116** have been reported to undergo nickel-catalyzed [2 + 2] cycloadditions with electron-deficient olefins (eqs 18–20).[59e,140g] These cycloadditions are highly *exo* selec-



(18)

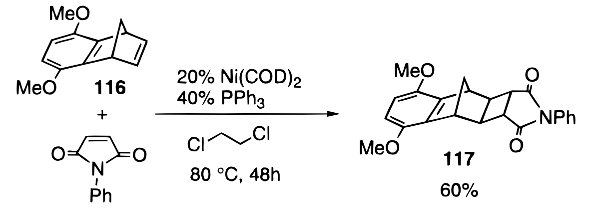
	Yield	**111 : 112**
Z = CN	55%	63 : 37
Z = COOMe	72%	78 : 22

Ni-cat. = $Ni(COD)_2$ or $Ni(AN)_2$ where AN = acrylonitrile



(19)

	Yield	**114 : 115**
Z = COOMe	34%	87 : 13



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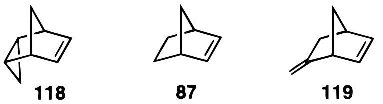
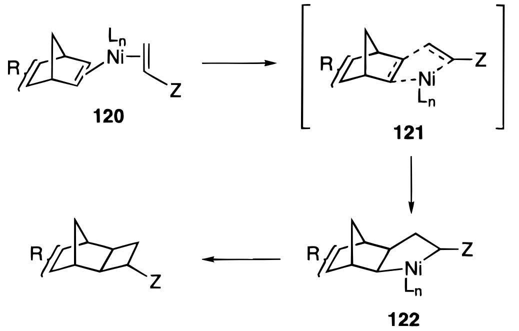


Figure 3.

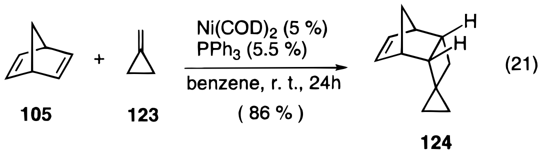
tive (little if any of the *endo* cycloadduct was observed) and can exhibit high stereoselectivity with respect to the substituent on the enophile (Z). With a very reactive olefin such as *N*-phenylmaleimide (NPM), a single *exo-(cis-anti-cis)* cycloadduct was formed (eq 20).[140g] In contrast, the *endo* cyclopropane isomer **118**, the parent norbornene **87**, and 5-methylenenorbornene **119** failed to react, illustrating that the reactivity of a given norbornene is highly sensitive to the structural changes at a site remote from the reacting double bond (Figure 3).[59e]

Noyori suggested that homoconjugation between the double bond and the cyclopropane or the benzene ring lowers the energy of the transition state **121** which gives rise to metallacyclopentane intermediate **122** (Scheme 9).[59e] MO considerations are consistent with this proposal; homoconjugation in the norbornene system reduces the bond order of the C=C bond which facilitates a bonding interaction between the alkene, norbornene, and nickel.

Scheme 9



Electron-deficient olefins react with norbornadiene **105** in the presence of a Ni(0) catalyst to give [2 + 2 + 2] homo-Diels–Alder adducts (*inter alia*). However, Noyori showed that certain strained olefins such as methylenecyclopropane **123** give an *endo* [2 + 2] cycloadduct **124** as the major product (eq 21).[59b] The *endo* stereochemistry is considered to originate from the mixed-ligand complex **125**, in which norbornadiene coordinates to the Ni as an *endo* bidentate ligand (Figure 4). Enantioselective cycloaddition between **105** and **123** using a chiral phosphine ligand has been investigated but no ee was reported.[59b] However, if a Pd(0) catalyst was used instead of Ni(0), a [3 + 2] cycloaddition was observed.[94]



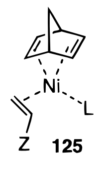
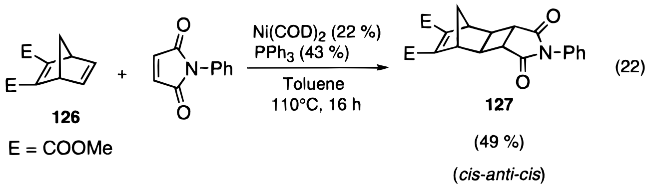
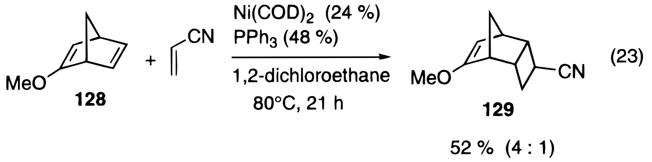


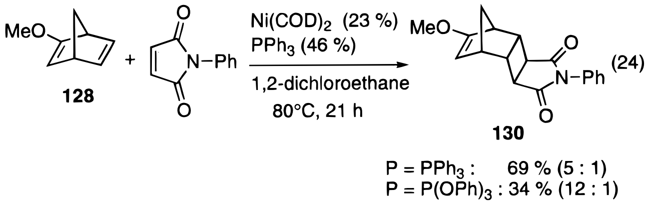
Figure 4.

Substituted norbornadienes usually undergo [2 + 2 + 2] homo-Diels–Alder reactions with electron-deficient olefins (*inter alia*), but in some cases [2 + 2] cycloaddition can occur exclusively with high chemo- and regioselectivity and moderate levels of stereoselectivity.[140g] Highly reactive enophiles appear to be most prone to the [2 + 2] reaction mode.

With an electron-deficient 2,3-disubstituted norbornadiene (NBD) such as **126**, cycloaddition with *N*-phenylmaleimide afforded exclusively *exo*-cyclobutane **127** (eq 22). Cycloaddition between an electron-rich 2-substituted NBD **128**, and acrylonitrile or *N*-phenylmaleimide led to exclusive formation of *endo* [2 + 2] adducts **129** and **130** (eqs 23 and 24). The *endo* stereoselectivity improved to 12:1 using $P(OPh)_3$ as the ligand (eq 24).

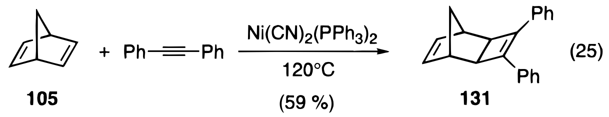






3.2. $[2_{2\pi} + 2_{2\pi}]$ Cycloadditions of Strained Alkenes with Acetylenes

Although the nickel-catalyzed [2 + 2] cycloaddition of norbornadiene with diphenylacetylene was first reported in 1964 (eq 25), very few acetylenes have been found to undergo [2 + 2] cycloadditions. Instead, most activated acetylenes undergo an alternative [2 + 2 + 2] homo-Diels–Alder reaction with norbornadiene.[57m,59g] Cobalt and iron catalysts were shown to promote [2 + 2] cycloadditions but the yields were generally low.[61,62] In the presence of low-valent cobalt complexes, unactivated acetylenes usually react with norbornadienes to give [2 + 2 + 2] homo-Diels–Alder adducts instead of [2 + 2] products (*inter alia*). However, 2,3-disilyl-substituted norbornadiene and a benznorbornene were shown to give exclusive formation of the *exo* [2 + 2] adducts **133** (eq 26).[68]



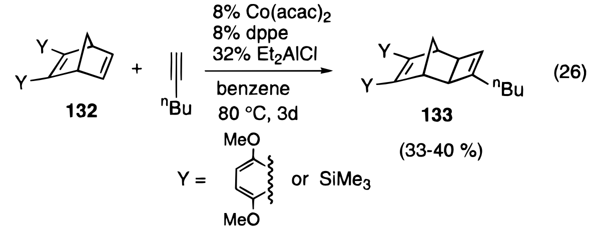
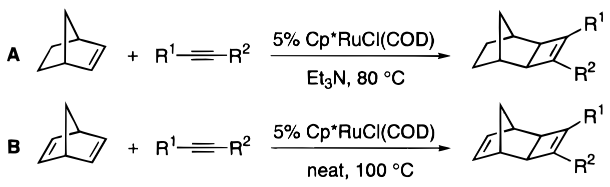


Table 12. Ru-Catalyzed [2 + 2] Cycloadditions



Reaction	R^1	R^2	t (h)	Yield (%)
A	Ph	Ph	15	91
A	Ph	Me	15	87
A	n-pentyl	n-pentyl	20	40
A	Me	COOMe	15	79
B	COOMe	COOMe	24	37
B	Me	COOMe	24	87
B	Ph	Ph	120	23

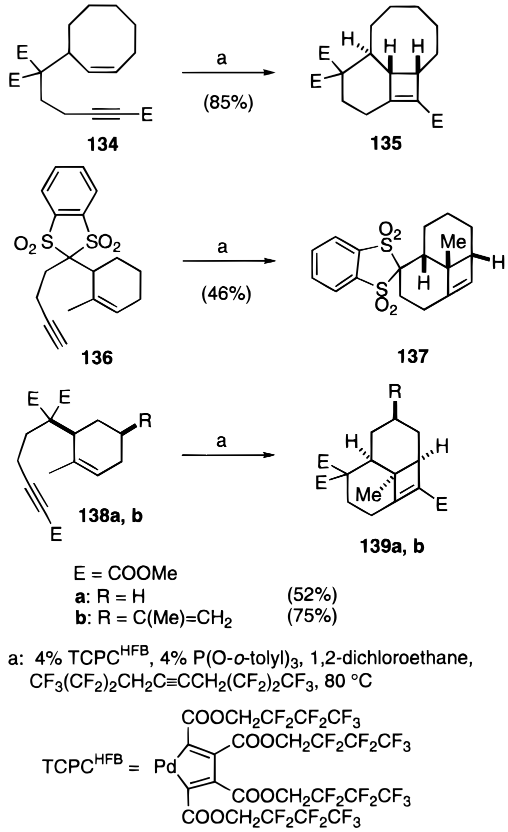
Low-valent ruthenium complexes have been used to catalyze [2 + 2] cycloadditions between norbornenes and norbornadiene with various acetylenes. $RuH_2(CO)(PPh_3)_3$ and $Ru(COD)(COT)/PR_3$ catalysts gave [2 + 2] adducts when strained alkenes were reacted with acetylene dicarboxylates.[60a−c] Less activated acetylenes were inert with these catalysts but Mitsudo recently showed that a catalytic amount of Cp*RuCl(COD) induced various acetylenes (both activated or unactivated) to undergo [2 + 2] cycloadditions with norbornene and norbornadiene (Table 12).[60d]

It is striking that transition metal-catalyzed [2 + 2] cycloadditions of norbornenes and norbornadienes give the *exo* cycloadducts with acetylenes, whereas olefins yield the *endo* adducts.

3.3. Intramolecular $[2_{2\pi} + 2_{2\pi}]$ Cycloadditions

Trost and co-workers have recently reported that in the presence of a low-valent palladium catalyst, enyne **134** underwent an intramolecular [2 + 2] cycloaddition to yield a highly strained, tricyclic compound **135** which contained a cyclobutene ring as well as a *trans*-fused 8/6 ring system (Scheme 10).[63b] Enynes **136** and **138a,b**, which contain cyclohexene rings, gave a *cis*−*cis* ring fusion. These results parallel the observations with the intramolecular Pd-catalyzed [3 + 2] cycloadditions of TMM to cyclooctenyl vs cyclohexenyl acceptors, *inter alia*.[89]

Scheme 10



a: 4% $TCPC^{HFB}$, 4% P(O-*o*-tolyl)$_3$, 1,2-dichloroethane, $CF_3(CF_2)_2CH_2C{\equiv}CCH_2(CF_2)_2CF_3$, 80 °C

Additional studies are required before metal-catalyzed [2 + 2] cycloadditions become widely used in organic synthesis. Limitations in the range of reaction partners remains a problem and better catalysts are needed. The possibility of developing enantioselective processes is an area for future investigation.

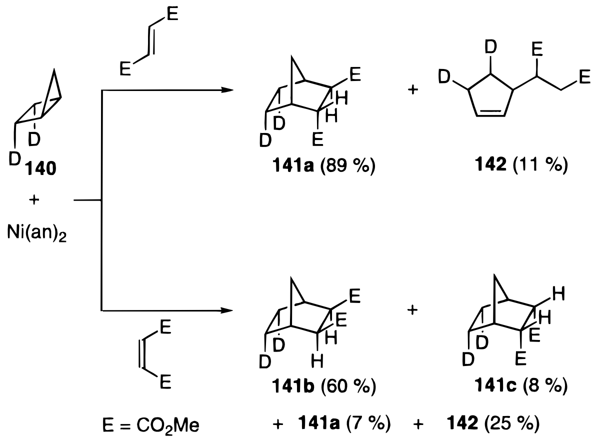
4. Five-Membered Ring Formation

Five-membered rings can be formed by cycloadditions involving either four π-electrons ($[3_{2\sigma} + 2_{2\pi}]$, $[3_{2\pi} + 2_{2\pi}]$) or six π-electrons ($[3_{4\pi} + 2_{2\pi}]$), $[4_{4\pi} + 1_{2\pi}]$, $[2_{2\pi} + 2_{2\pi} + 1_{2\pi}]$). The latter type in many cases employs Co catalysts (Pauson−Khand reaction) and requires *stoichiometric* amounts of the metal. This subject has been thoroughly reviewed and will not be discussed.[69a−e] Recently effective catalytic[69f−h] and enantioselective[69i−k] versions of this reactions have emerged. Alternatively, these reactions can also be catalyzed by Ti, Zr, or Ir complexes.[69l−o]

4.1. $[3_{2\sigma} + 2_{2\pi}]$ Cycloadditions with Metallacyclobutanes

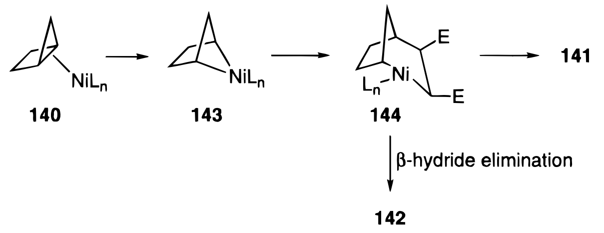
Various transition metals (Rh(I), Ag(I), Ni(II), Pd(II)) are known to insert into the strained bonds of cyclopropanes giving rise to metallacyclobutanes, which can be intercepted by an olefin.[70] These reactions were studied in detail by Noyori.[71] When bicyclo[2.1.0]pentane **140** was treated with bis(acetonitrile)nickel ($Ni(an)_2$) in the presence of dimethyl fumarate or maleate, the stereospecific formation of bicyclo[2.2.1]heptanes **141** occurred (Scheme 11).

Scheme 11

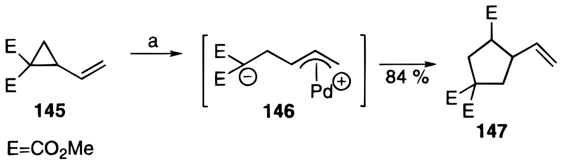


Noyori proposed a mechanism in which an oxidative addition of the nickel into the strained inner bond of **140** produces the metallacyclobutane **143**. Following complexation and carbometalation on the olefin, metallabicycle **144** is formed. This species either undergoes reductive elimination to give the bicyclic adduct **141** or gives cyclopentene **142** via a β-hydride elimination (Scheme 12).

Scheme 12



In a related process Tsuji showed that insertion of palladium into vinylcyclopropane **145** formed the stabilized zwitterion **146** which reacted with methyl acrylate to yield the vinyl cyclopentane **147** (eq 27).[72]



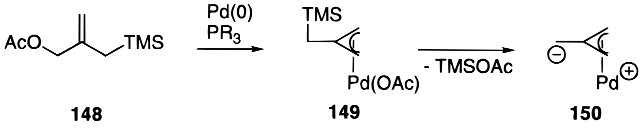
(27)

a: methyl acrylate, $Pd_2dba_3 \cdot CHCl_3$, dppe, DMSO, 80°C, 2 h

4.2. $[3_{2\sigma} + 2_{2\pi}]$ Cycloadditions with Pd–Trimethylenemethane Complexes

TMM complexes of various transition metals including Fe and Mo are known, but most of these complexes do not react with olefins.[73] Trost showed that Pd–TMM complexes, which are accessible by treatment of an allyl acetate **148** with a Pd(0) catalyst, react with olefins to give methylenecyclopentanes. An intermediate π-allyl complex **149** is formed, which readily undergoes loss of trimethylsilyl acetate to generate the TMM complex **150** (Scheme 13).[74]

Scheme 13

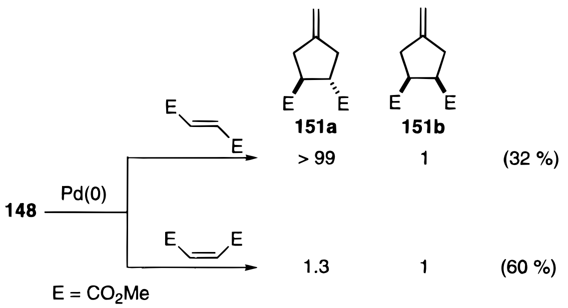


Reactions of Pd–TMM complexes and complexes generated from methylenecyclopropanes were recently reviewed and only a brief description of the basic reaction pathways will be given followed by a detailed discussion of recent developments with a focus on intramolecular cycloadditions.[75]

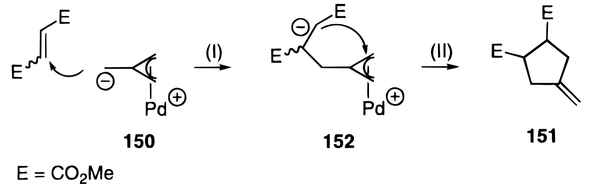
The Pd complex **150** generated *in situ* from **148** reacts with a variety of electron-deficient olefins. The reaction with dimethyl fumarate was stereoselective, whereas reaction with dimethyl maleate produced *cis/trans* mixtures of methylenecyclopentanes **151** (Scheme 14).[76]

The lack of stereospecificity in the reaction with *cis*-alkenes suggests a stepwise, nonconcerted mechanism. Michael addition of the negatively charged atom of the TMM complex with the double bond (step I) would generate an enolate tethered to a π-allyl–palladium complex (**152**). The second bond is formed by an intramolecular nucleophilic addition (step II) of the enolate to the Pd complex (Scheme 15).

Scheme 14

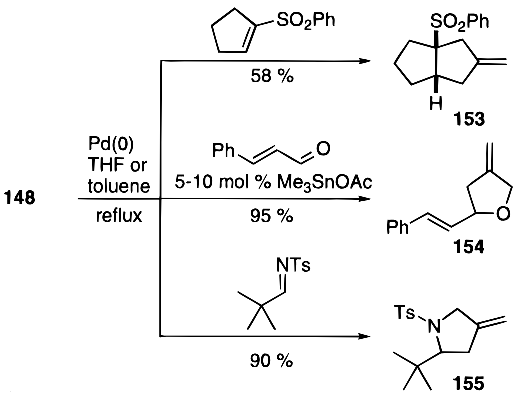


Scheme 15



Electron-deficient alkenes including α,β-unsaturated esters, ketones, and sulfones participate in the cycloaddition. Several natural products have been prepared using this strategy.[77] More recently, this method has been extended to additions to carbonyl groups (e.g. aldehydes,[78] ynones,[79] certain kinds of reactive ketones,[80] and even *N*-tosylimines[81]). With enals and aldehydes, a silyl ether is formed after step I, which does not undergo the cyclization step (II). However, cyclization occurred upon addition of catalytic amounts of trimethyltin acetate due to the *in situ* formation of a more reactive tin alkoxide (Scheme 16).

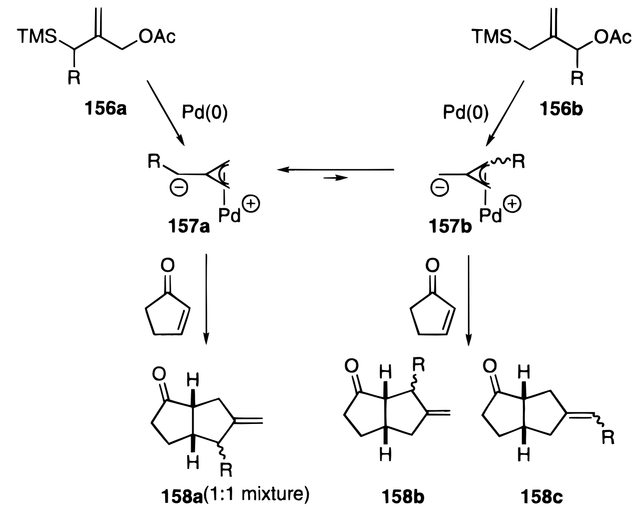
Scheme 16



Cycloadditions of substituted Pd–TMM complexes revealed the dynamic behavior of these complexes.[82] Depending on the position of the substituent R in **156a** or **156b**, two regioisomeric complexes, **157a** or **157b**, could be formed which would then lead to cycloadducts **158a–c** (Scheme 17). However, irrespective of the substitution pattern of the precursor, the reaction with an electrophile such as cyclopentenone always gave the same ratio of products favoring **158a**. This indicates that equilibration between complexes **157a** and **157b** occurs faster than the trapping reaction. Calculations imply that **157a** is also thermodynamically more stable.[83] Stabilization of the negative charge of the TMM complex was also accentuated by electron-withdrawing and electron-donating substituents (R = CN, OAc).[75c]

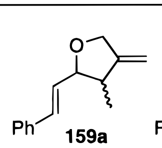
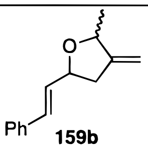
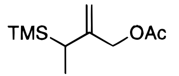
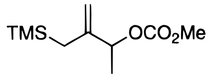
However, trapping reactions with aldehydes are faster than equilibration of **157a** or **157b** and either

Scheme 17



precursor (R=Me)	158a	158b	158c
156a	43 %	0 %	2 %
156b	49 %	0 %	3 %

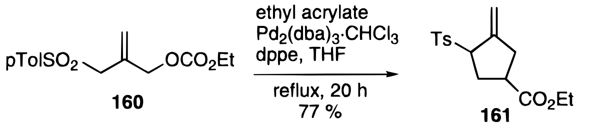
Table 13. Effect of the Leaving Group on the Furan Substitution Pattern

TMM precursor	 159a	 159b	combined yield
 156a	200	1	94
 156b	1	11.8	86

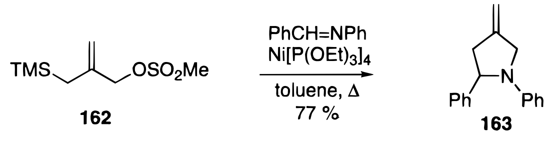
Reaction conditions: PhCH=CHCHO, $Pd(OAc)_2$, PPh_3, Me_3SnOAc, benzene, reflux

of the regioisomeric tetrahydrofurans **159** could be obtained. The formation of the π-allyl–Pd complex on the way to TMM complex **157** is particularly efficient starting from a carbonate (Table 13).[84]

Two other approaches were developed for the generation of novel substituted TMM–Pd complexes. Tsuji showed that the tosyl-substituted allyl acetate **160** reacts with ethyl acrylate to give the methylenecyclopentane **161** without loss of the tosyl group (eq 28).[85] The mesyl-substituted allyl silane **162** reacts with an imine in the presence of a Ni(0) catalyst to form methylenepyrrolidine **163** (eq 29).[86]



(28)

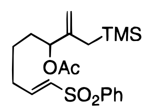
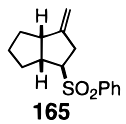
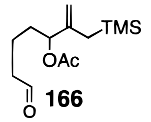
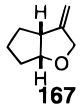
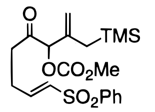
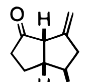
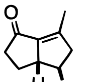
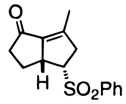
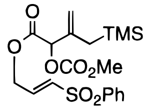
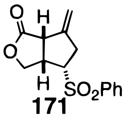
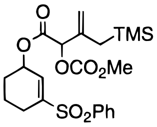
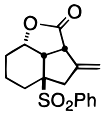
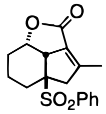
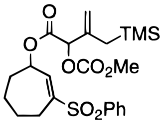
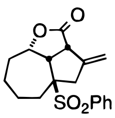
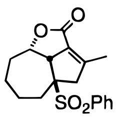
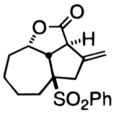


(29)

4.3. Intramolecular $[3_{2\sigma} + 2_{2\pi}]$ Cycloadditions with Pd–TMM Complexes

Intramolecular palladium-catalyzed [3 + 2] reactions have also been investigated. When the 1,7-diene **164** was subjected to the usual reaction conditions, the *cis*-fused bicyclo[3.3.0]octane **165** was isolated as a single isomer (Table 14, entry 1).[87] High selectivity in the formation of *cis*-fused rings was also observed in the formation of the oxabicyclo[3.3.0]octane **167** from the 1,7-unsaturated aldehyde **166**, entry 2,[88] as well as in the cyclization of carbonyl substituted TMM complexes, entries 3–6.[89] However, in the latter case substantial amounts of products containing endocyclic double bonds were obtained, entries 3, 5, and 6. Remarkably, the cyclization of **174** led to small amounts of compound **175c** with the energetically unfavorable *trans*-fused five-membered rings.

Table 14. Intramolecular TMM Cycloadditions

Entry	Precursor	Product(s)	Yield (ratio)
1[a]	 164	 165	65 %
2[b]	 166	 167	31 %
3[c]	 168	 169a  169b  169c	47 % (5.4:2:1)
4[d]	 170	 171	16 %
5[d]	 172	 173a  173b	62 % (1.7:1)
6[d]	 174	 175a  175b  175c	63 % (25:7:1)

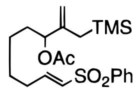
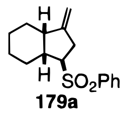
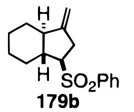
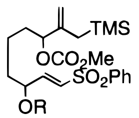
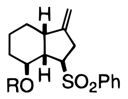
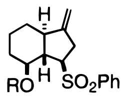
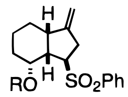
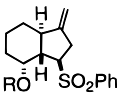
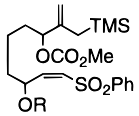
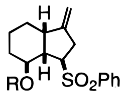
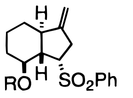
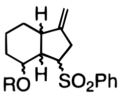
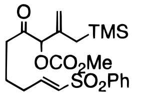
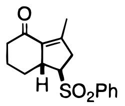
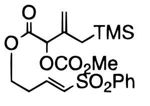
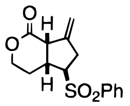
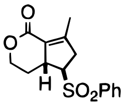
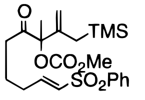
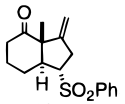
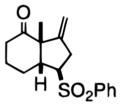
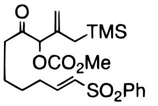
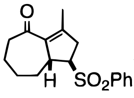
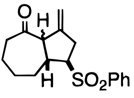
a: 9 mol% $Pd(PPh_3)_4$, 4-6 mol% dppe, DME, reflux.

b: $Pd_2dba_3.CHCl_3$, $(^iPrO)_3P$, Bu_3SnOAc, BSA, THF, reflux.

c: $Pd(OAc)_2$, $(^iPrO)_3P$, dioxane, 100°C.

d: 5 mol% $Pd(OAc)_2$, 30 mol% $(i\text{-}PrO)_3P$, dioxane, reflux.

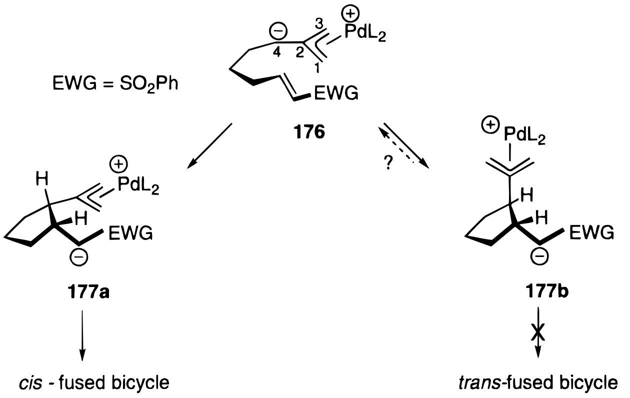
Table 15. Effect of Allylic Substituents on the Reaction

Entry	Precursor	Product(s)	Yield (ratio)
1[a]	 **178**	 **179a**  **179b**	70 % (2:1)
2[b,e]	 **180**	 **181a**  **181b**  **181c**  **181d**	76-82 % (9.4:1: 3.5:1.6)
3[b,e]	 **182**	 **181a**  **181e**  **181f**[f]	67 % (5.2:4.5:1)
4[c]	 **183**	 **184**	81 %
5[d]	 **185**	 **186a**  **186b**	72 % (1:7.2)
6[d]	 **187**	 **188a**  **188b**	66 % (2.4:1)
7[d]	 **189**	 **190a**  **190b**	51 % (8.2:1)

a: 9 mol% $Pd(PPh_3)_4$, 9 mol% PPh_3, DME, reflux.
b: 5 mol% $Pd(OAc)_2$, 30 mol% $(^iPrO)_3P$, BSA, THF, reflux.
c: 5 mol% $Pd(OAc)_2$, 30 mol% $(^iPrO)_3P$, THF, r.t..
d: 5 mol% $Pd(OAc)_2$, 30 mol% $(^iPrO)_3P$, dioxane, 100°C.
e: R = TBDPS; f: relative stereochemistry was not assigned.

The regioselectivity of the first ring closure to form a cyclopentane rather than a cycloheptane was attributed to the increased stabilization of the negative charge of the TMM complex **176** at the more substituted internal carbon (C-4) in analogy to the intermolecular cycloaddition results (Scheme 18). Selective formation of a *cis*-fused bicyclo[3.3.0] **175a** can be explained by a preference for the formation of **177a** or by invoking the existence of an equilibrium between **177b** and **176**, although it has not been possible to confirm the existence of **177b**. In analogy to intermolecular reactions, the *trans* stereochemistry of the vinyl sulfone was preserved during the reaction.

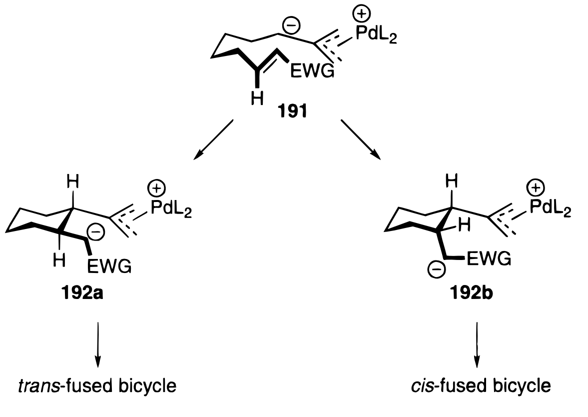
Scheme 18



Intramolecular cycloadditions to form bicyclo[4.3.0]nonanes were less stereoselective with respect to the ring junction. The 1,8-divinyl sulfone **178** yielded a 2:1-product mixture of *cis*- and *trans*-fused products **179** (Table 15, entry 1). However, the stereochemistry of the *trans*-vinyl sulfone was retained in the two cycloadducts. Cycloaddition of **180** provided an opportunity to study the effect of allylic substitution on the diastereoselectivity. Four different reaction products were obtained and in which the stereochemistry of the vinyl sulfone was retained, entry 2. The *cis*/*trans* selectivity of the ring fusion (**181a** + **181c**)/(**181b** + **181d**) was only 5:1 which indicates that the influence of the substituent on the stereoselectivity was modest. When the corresponding *cis*-vinyl sulfone **182** was subjected to the same conditions, a mixture of two major and one minor cycloadducts were obtained. In analogy to the intermolecular cycloadditions with (*Z*)-alkenes, this reaction was not stereospecific with respect to the olefin stereochemistry and the major product was identical to that obtained from the (*E*)-vinyl sulfone **180**, entry 2. In spite of the modest stereoselectivities obtained in these reactions, when the substrate contained a carbonyl group as a part of the tether (e.g. **183** or **185**), the initially formed exocyclic double bond was readily isomerized into conjugation which afforded one major reaction product **184** or **186b**, entries 4 and 5. This cyclization–isomerization procedure was also applied to the preparation of bicyclo[5.3.0]decanes, entry 7.

The low degree of *cis*/*trans* selectivity with respect to the ring junction was attributed to a low *cis*/*trans* selectivity in the formation of the first ring and a high propensity for each monocycle **192a** and **192b**, to undergo the second cyclization step (Scheme 19).

Scheme 19

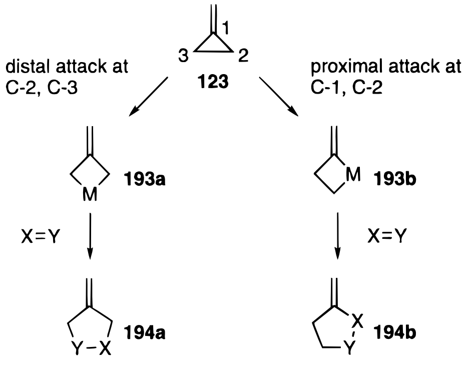


4.4. [$3_{2\sigma}$ + $2_{2\pi}$] Cycloadditions with Methylenecyclopropane

Transition metal-catalyzed cycloadditions between methylenecyclopropanes and olefinic double bonds provide an efficient entry into methylenecyclopentane skeletons and therefore appear to resemble cycloadditions with Pd−TMM complexes. However, studies by Noyori and Binger revealed significant differences with respect to chemo- and stereoselectivity. This topic has been reviewed.[90] More that 25 years after the discovery of this reaction many questions remain unanswered and as yet there is no unifying mechanism to explain all the experimental observations. Intramolecular cycloadditions have recently been examined from the synthetic perspective with an eye on answering some of the mechanistic issues. A brief introduction to the basic principles of the reaction and the available mechanistic information is presented, followed by a discussion of recent advances in intramolecular cycloadditions.

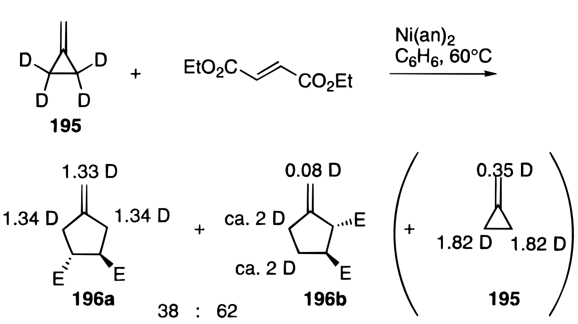
Metal-catalyzed cycloaddition between methylenecyclopropane (**123**) and a double bond can proceed via two different reaction pathways leading to regioisomeric products. An oxidative addition into the distal bond between C-2 and C-3 would lead to metallacyclobutane **193a**. Subsequent carbometalation onto the double bond and reductive elimination leads to the formation of a cyclopentane **194a** with the newly introduced C_2 unit in a distal position to the exocyclic double bond. Alternatively, proximal bond cleavage between C-1 and C-3 leads to the isomeric metallacyclobutane **193b**, and subsequently cyclopentane **194b** (Scheme 20).[91]

Scheme 20



Noyori showed that the cycloaddition between the deuterated methylenecyclopropane **195** and dimethyl fumarate in the presence of catalytic amounts of bis(acetonitrile)nickel (Ni(an)$_2$) yielded a mixture of cycloadducts derived from both distal (**196a**) and proximal (**196b**) ring opening. Upon distal ring opening, complete scrambling of the carbons bearing deuterium occurred, whereas in the proximal ring opening almost no scrambling was observed. The recovered starting material **195** also showed partial scrambling (eq 30).[92]

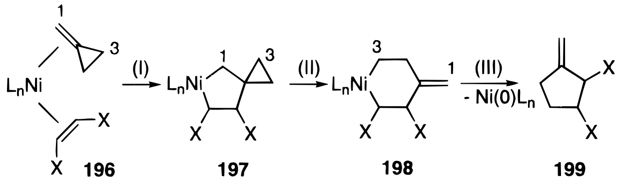
From the examples collected over the years, it has been established that cycloadditions catalyzed by "naked" nickel catalysts Ni(COD)$_2$ favor the proximal ring opening, whereas in the presence of phosphine or phosphite ligands a preference for a cleavage of the distal bond is observed. No clear reason for this trend has emerged.[90]



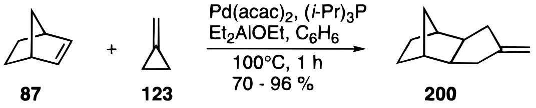
(30)

On the basis of the ^{1}H NMR spectroscopic characterization of stable nickelacyclopentane (**197**) and nickelacyclohexane (**198**) intermediates, a mechanism for the reaction via a proximal ring opening was put forward by Binger which also accounted for the lack of deuterium scrambling.[93] Following precoordination of both olefins to the metal **196**, a π−σ-rearrangement (I), a cyclopropylmethyl-3-butenyl rearrangement (II), and a reductive elimination (III) occurs (Scheme 21).

Scheme 21



Palladium(0) catalysts also promote the cycloaddition of methylenecyclopropane (**123**) and electron-rich olefins. In contrast, reactions between TMM precursor **148** and electron-rich olefins failed in the presence of Pd catalysis, providing further evidence that the two reactions are proceeding via different intermediates. Reaction occurs exclusively at the distal bond of **123** with palladium catalysts whereas nickel catalysts are less selective (eq 31).[94]

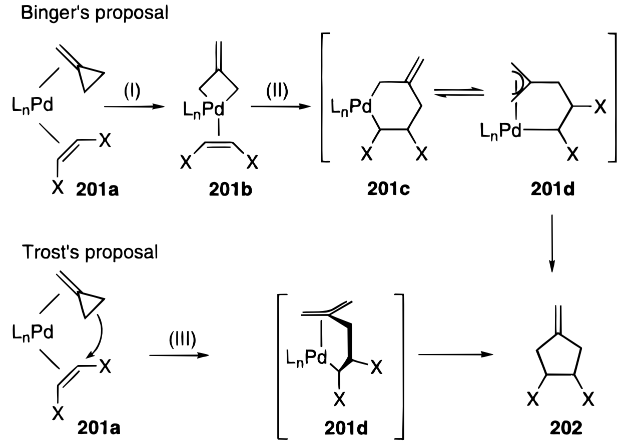


(31)

Some electron-deficient olefins also participate in the cycloaddition, but acrylonitrile or maleic anhydride appear to form inactive olefin−metal complexes. On the basis of this observation, a distal ring opening might be initiated by a precoordination of both reaction partners to the metal, followed by an oxidative addition of the palladium into the distal cyclopropyl σ-bond (I to II) (Scheme 22). It is not clear if **201c** or **201d** better represents the intermediate on the way to product, but the deuterium scrambling observed by Noyori using nickel (eq 30) supports the presence of a σ-allyl complex in rapid equilibrium with the isomeric σ-allyl species or a π-allyl complex.[94a,c] Trost has proposed that the distal bond of the methylenecyclopropane directly attacks the double bond of the acceptor following complexation of the two partners (i.e. III) to generate π-allyl complex **201d**.[75a]

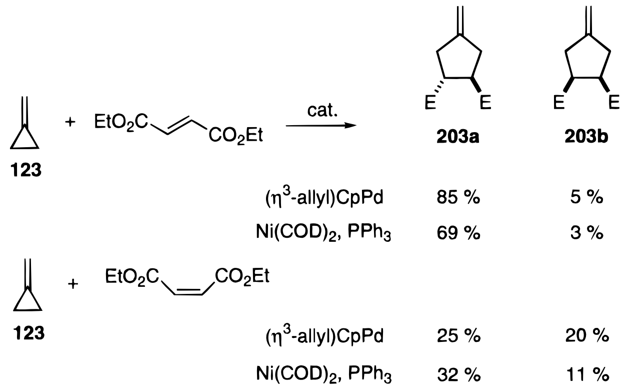
When methylenecyclopropane (**123**) was reacted with diethyl fumarate and diethyl maleate using a palladium catalyst or a nickel/triphenylphosphine catalyst, both reactions occurred selectively at the

Scheme 22

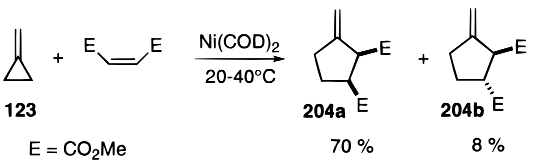


distal position. The addition to an (*E*)-olefin was highly stereoselective, whereas addition to the (*Z*)-olefin was accompanied by a metal-catalyzed (*Z*) to (*E*) isomerization of the starting olefin leading to mixtures of stereoisomers (Scheme 23).[94c,95]

Scheme 23



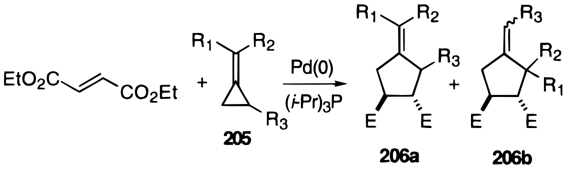
The cycloaddition between methylenecyclopropane (**123**) and dimethyl maleate using $Ni(COD)_2$ in the absence of phosphine proceeds exclusively via proximal ring opening and with higher stereoselectivity (eq 32).[90]



(32)

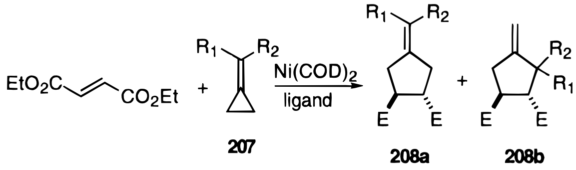
When substituted methylenecyclopropanes **205** were reacted with diethyl fumarate using Pd(0) catalysis, ring opening occurred exclusively at the distal bond in all reactions (Table 16). Reactions of monosubstituted methylenecyclopropanes gave cycloadducts with nearly identical product distributions irrespective of the starting location of the substituent, entries 1 and 2. These results indicate that rapid scrambling of the intermediate σ- or π-allyl Pd complex is occurring (**201c** or **201d** in Scheme 22). However, methylenecyclopropanes bearing two substituents on the methylene group give **206b** exclusively implying there is a preferred reactive intermediate, entries 3 and 4. These results further illustrate the difference between the palladium-catalyzed reactions of methylenecyclopropanes and the TMM precursor **148** (compare Tables 16 and 17).[90,96]

Table 16. Pd-Catalyzed Methylenecyclopropane Cycloadditions



entry	R_1	R_2	R_3	**206a/206b**	yield
1	C_5H_{11}	H	H	53/47	58 %
2	H	H	CH_3	60/40	67 %
3	Me	Me	H	100/0	83 %
4	Ph	Ph	H	100/0	100 %

Table 17. Ni-Catalyzed [3 + 2] Cycloadditions

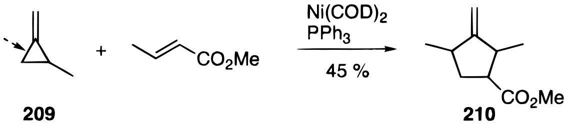


entry	R_1	R_2	**208a/208b**	yield **208**
1[a]	n-C_5H_{11}	H	57/43	87 %
2[a]	Ph	H	91/9	82 %
3[b]	Me	Me	37/63	83 %
4[c]	Ph	Ph	100/0	98 %

a: ligand = PPh_3. b: ligand = tris(*o*-phenylphenyl). c: no ligand was used.

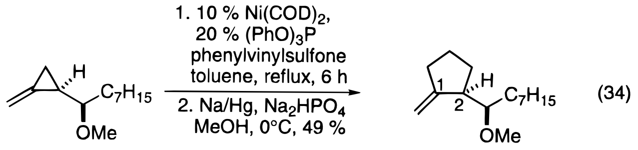
Nickel-catalyzed cycloadditions of methylenecyclopropanes **207** bearing a phenyl substituent on the methylene group give products similar to those with palladium (Table 17, entries 2 and 4), whereas mixtures were obtained with alkyl substituents products, entries 1 and 3.[96b,97]

However, when the substituent is on the cyclopropyl ring (e.g. **209**), opening at the less substituted proximal bond dominates and **210** is formed (eq 33).[90,93b,97b,c] The relative stereochemistry was not determined in this case.



(33)

If insertion occurred at the distal bond, the stereochemical integrity at the stereocenter would have been an issue. Lautens and Delanghe subjected the diastereomerically pure, ring-substituted, methylenecyclopropane **211** to cycloaddition conditions with phenyl vinyl sulfone and Ni(0) catalysis to learn about the fate of this stereocenter.[98] The resulting inseparable mixture of diastereomers was desulfonylated to provide methylenecyclopentane **212** as a 10:1 mixture of diastereomers (eq 34). A single diastereomer would be expected if proximal ring opening was the exclusive pathway. This result suggests that distal opening did occur with this



211
diastereomerically pure

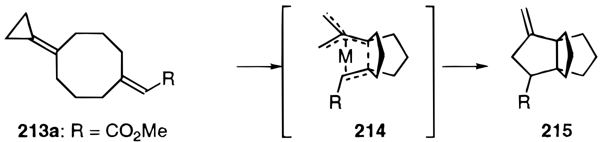
212
10 / 1 mixture at C-2

substrate and the intermediate underwent epimerization.

4.5. Intramolecular $[3_{2\sigma} + 2_{2\pi}]$ Cycloadditions with Methylenecyclopropanes

The earliest examples of intramolecular methylenecyclopropane cycloaddition were reported independently by Motherwell and Nakamura in 1988.[99,100] Nakamura reported an example of an intramolecular [3 + 2] cycloaddition when methylenecyclooctane **213** was treated with nickel or palladium catalysts.[99] The tricyclic system **215** was obtained in high yield, which served as a precursor for the synthesis of modhephane. The mechanism of the cyclization was rationalized by a distal bond cleavage followed by an equilibration to a metal–TMM complex **214**. The regiochemistry of the subsequent cyclization was dictated by geometric constraints; the new bond was formed at the more substituted atom of the palladium complex. However, in contrast to the Pd–TMM complex studied by Trost, cycloaddition was feasible on both an electron-deficient (**213a**) and an electron-rich olefin (**213b**) (Table 18).

Table 18. Intramolecular Cycloadditions

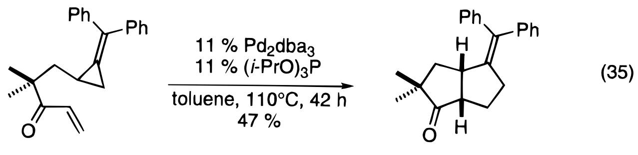


213a: R = CO_2Me
213b: R = H
214
215

diene	catalyst (20 mol %)[a]	temperature	yield of **215**
213a	$Ni(COD)_2$, PPh_3	110°C	74 %
213a	$(PPh_3)_2PdCl_2$, DIBAL	130°C	98 %
213b	$(PPh_3)_2PdCl_2$, DIBAL	90°C	74 %

a: reaction procedure: the catalyst in degassed toluene was treated with DIBAL and **213** at -78°C, then heated at the indicated temperature

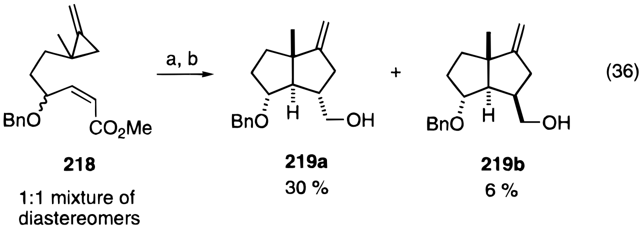
Motherwell investigated the scope of intramolecular cycloadditions of methylenecyclopropanes linked by a three-carbon tether as a route to bicyclo[3.3.0]octanes.[100] When **216** was exposed to a Pd(0) catalyst, a kinetically favored 5-exo-trig cyclization provided the *cis*-fused adduct **217** (eq 35).



216

217

The palladium-catalyzed cycloaddition of a 1:1 diastereomeric mixture of the *cis*-ester **218** resulted in the formation of an inseparable mixture of two bicyclic compounds. Reduction of the ester moiety provided the alcohols **219a** and **219b** which each possessed a thermodynamically disfavored *trans*-fused ring junction. Furthermore, the relative stereochemistry between the bridgehead hydrogen and the hydroxymethyl group indicates that the ester epimerized prior to the final bond closing step (eq 36).[101] Under identical reaction conditions, the precursor devoid of the benzyloxy group as well as the *trans* isomer failed to undergo cycloaddition. Motherwell proposed that an intramolecular complexation between the palladium and the ether oxygen minimized the steric interactions between the allyl complex and the carbomethoxy group which favored formation of the *trans*-fused monocycles **220**. The first cyclization generated **221** in which the ether adopts a pseudoaxial orientation enabling it to stabilize the cationic π-allyl–Pd complex. Rotation around bond "a" and subsequent nucleophilic addition yielded **219** (Scheme 24).



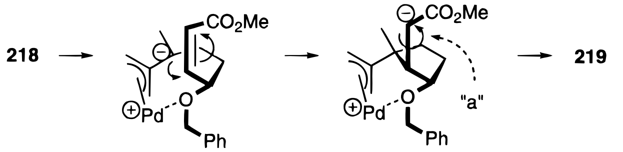
218
1:1 mixture of diastereomers

219a
30 %

219b
6 %

a: Pd_2dba_3, (i-PrO)$_3$P, toluene, 110°C; b: DIBAL, -78°C, toluene

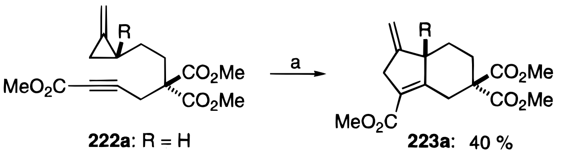
Scheme 24



220
221

Motherwell also investigated the intramolecular cycloaddition of a methylenecyclopropane leading to bicyclo[4.3.0]nonenes. When **222a** and **222b** were subjected to a palladium catalyst, **223a** and **223b** were obtained in moderate yield. Both the insertion and the addition to the triple bond occurred exclusively at the distal bond of the cyclopropane (eq 37). However, if the carbomethoxy group in **222b** was replaced by a TMS group, no cycloaddition occurred.[102] When the cyclization of **222a** or **222b** was initiated by a Ni(0) catalyst, the less substituted proximal bond reacted yielding the anti-Bredt bicyclo[4.2.1]octene **224** (eq 38).

The methylenecyclopropanes studied by Motherwell were chiral but not enantiomerically pure, and thus, the issue of the configurational stability of the cyclopropane stereocenter could not be addressed. Following the development of methodology for the diastereoselective synthesis of methylenecyclopropanes, Lautens and Ren examined this question. When **225a** was exposed to a palladium catalyst, **226a** was obtained in good yield as a single isomer (eq 39). The reaction of diastereomer **225b** gave exclusively the diastereomeric adduct **226b**, establishing that the cycloaddition was stereospecific (eq 40). X-ray crystallography confirmed that the cycloaddition proceeds with overall retention of stereo-



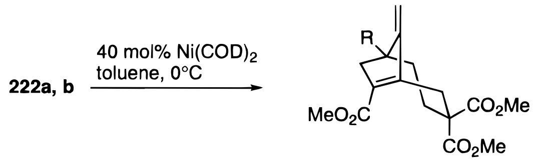
(37)

222a: R = H
222b: R = Me

223a: 40 %
223b: 59 %

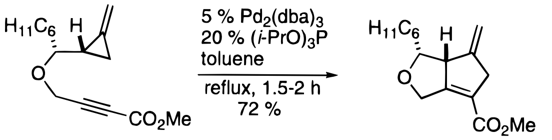
a: 10 mol% $Pd_2(dba)_3$, 40 mol% $(i\text{-PrO})_3P$, toluene, 110°C, 42 h

222a, b



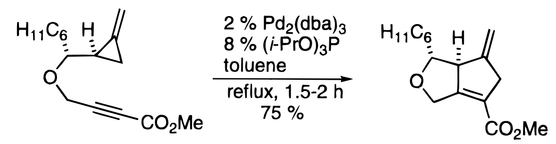
(38)

224a: 20 %
224b: 50 %



(39)

225a **226a**

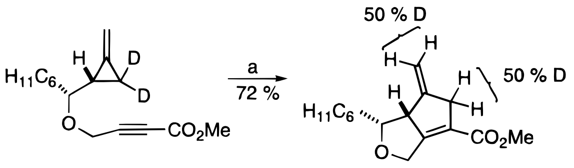


(40)

225b **226b**

chemistry.[98] Therefore the mechanism must either involve a stereospecific double inversion or a double retention. Previous studies have established that metal insertions into cyclopropanes occur with retention, suggesting that a double retention mechanism is operating.[103]

To gain insight into the dynamic behavior of the intermediate palladium complex, the dideuterated methylenecyclopropane **227** was reacted with Pd(0). The resulting cycloadduct showed a random distribution of the deuterium atoms at the vinylic and allylic position which indicated that a rapid equilibration between the intermediate π-allyl complex **201d** and the σ-bonded complex **201c** had taken place (Scheme 22). When the reaction was run to 18% conversion, the recovered starting material showed no scrambling of the label between C-3 and C-4. Therefore the initial step (I or III, Scheme 22) must be irreversible (eq 41).[98]



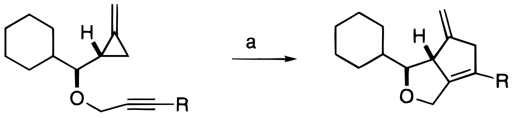
(41)

227 **228**

a: 5 % $Pd_2(dba)_3$, 20 % $(i\text{-PrO})_3P$, toluene, reflux, 7 h.

The scope of this reaction was demonstrated by employing substrates with various substitution patterns on the olefin, cyclopropane, alkyne, and carbinol carbon. Changing the carbomethoxy substituent to a less electron-withdrawing hydroxymethyl or siloxymethyl group did not significantly affect the reaction and **230a** and **230b** were obtained in excellent yield. However, in analogy to Motherwell's work, silyl substituents directly attached to the alkyne were detrimental to the cycloaddition; a TMS group significantly attenuated the reactivity and the TBDMS group prevented any cycloaddition (eq 42).

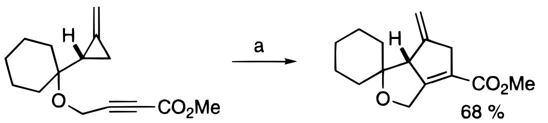
Recently, molecular sieves were shown to be beneficial in Pd-catalyzed methylenecyclopropane cycloadditions. Under these conditions both **230d** and **e** reacted although a higher percentage of palladium catalyst was required. Substrate **231** containing a tertiary alcohol in the β-position of the cyclopropyl group also underwent cycloaddition (eq 43). Replacing the terminal hydrogens on the methylene group with alkyl substituents has little effect on the efficiency of the reaction and no scrambling of the alkyl groups was observed (eq 44).[104]



(42)

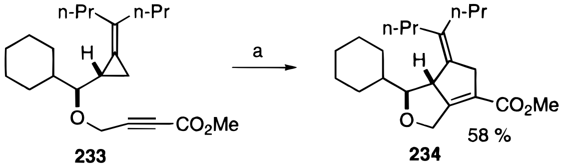
229a: R = CH_2OH
229b: R = $CH_2OTBDMS$
229c: R = CH_3
229d: R = TMS[b]
229e: R = TBDMS

230a: 85 %
230b: 100 %
230c: 5 %
230d: 57 %
230e: 0 % (40%)[b,c]



(43)

231 **232**

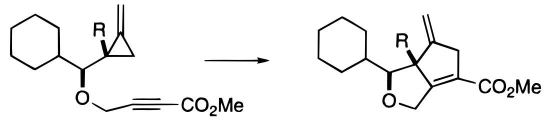


(44)

233 **234**

a: 5-7 mol % Pd_2dba_3, 4 equiv. $(i\text{-OPr})_3P$, toluene, reflux, 1.5-2 h.
b: 40-50 mol% of the catalyst was required, prolonged reaction time.
c: 4 A° molecular sieves were added to the reaction.

An additional substituent on the cyclopropyl carbon C-2 also affected the reactivity. Whereas a substrate bearing a methyl group led to decomposition of the starting material, **235b** bearing a methoxy substituent underwent the cycloaddition in moderate yield (eq 45). Motherwell reported that methyl-substituted compounds related to **235a** gave a mixture of dienes rather than cycloadducts. Lautens and Ren recently showed that **236a** was formed in 43% yield in the presence of $Pd(Ph_3P)_4$, demonstrating the subtle effect of ligand and ligand/catalyst ratios.[104]



(45)

235a: R = Me
235b: R = OMe

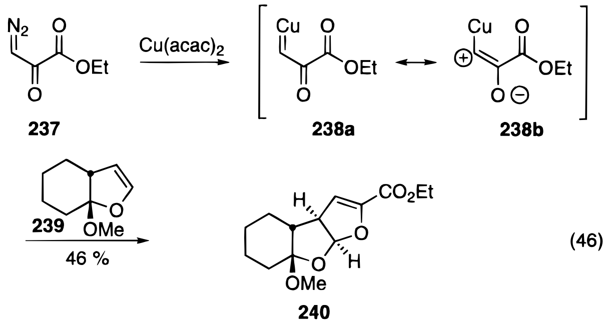
236a: 0 %
236b: 58 %

These results demonstrate that intermolecular [3 + 2] cycloadditions with methylenecyclopropanes proceed with full control of stereochemistry at the cyclopropyl ring carbons and provide an expeditious route to highly substituted bicyclic compounds.

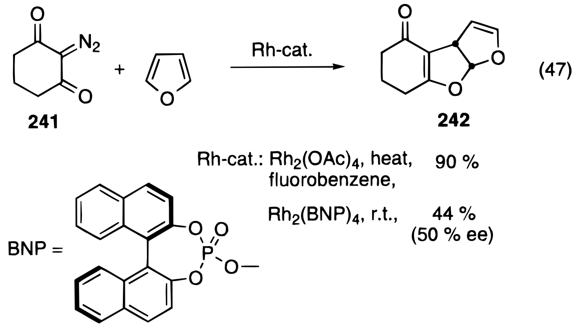
4.6. [$3_{4\pi}$ + $2_{2\pi}$] Cycloadditions with Metal Carbenoids

The [3 + 2] cycloadditions described above are 4π-electrons processes and are therefore thermally forbidden according to the Woodward–Hoffmann rules. Transition metal catalysts overcome this problem since the reactions are stepwise rather than concerted. In contrast, [3 + 2] cycloadditions of classical 1,3-dipoles involve 6π-electrons and are therefore thermally allowed. However, the generation of some 1,3-dipoles is accomplished by a metal catalyst which has an influence on the reaction pathway. α-Ketocarbenes react with electron-rich olefins leading to five-membered rings and can be therefore considered as [3 + 2] cycloadditions.[105]

Ethyl diazopyruvate **237** reacts in the presence of a Cu(II) salt to form a copper carbenoid, which adds to many types of olefins to form a cyclopropane[25] (see section 2). However, Alonso and Wenkert showed that the intermediate metal carbenoid can also serve as a 1,3-dipole (**238b**) and add stereoselectively to a dihydrofuran like **239** with formation of the tricyclic adduct **240** (eq 46).[106]



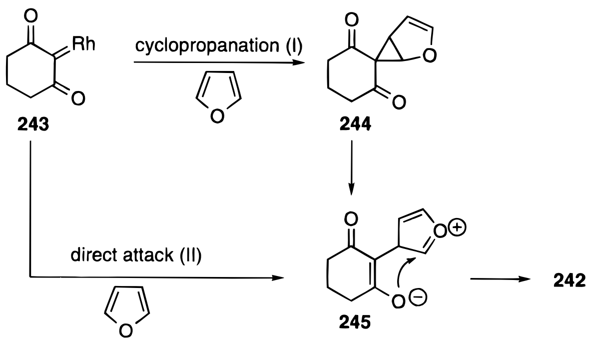
Pirrung showed that the reaction of diazodimedone **241** with furan in the presence of $Rh_2(OAc)_4$ led to the formation of the tricycle **242** via a [3 + 2] cycloaddition (eq 47).[107] No cyclopropanation adduct was observed (cf. section 2.4). Recently a modest enantiomeric excess was obtained using a chiral ligand.[108]



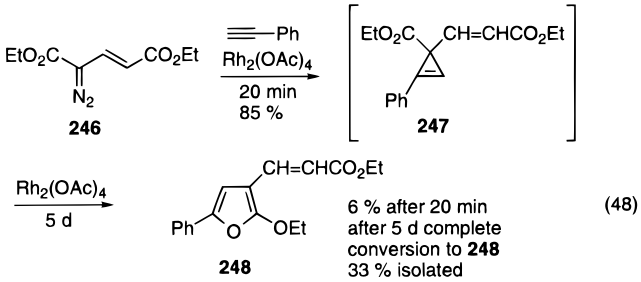
Two mechanisms have been proposed for this reaction. Pathway I illustrates a sequence that is initiated by a cyclopropanation of the double bond followed by a fragmentation to the zwitterion **245** which is stabilized by the additional carbonyl group. O-Alkylation of the enolate by the oxonium ion would give **242**. Pathway II bypasses the formation of the cyclopropane and leads directly to **245** (Scheme 25).

Support for the second mechanism includes the failure to observe the intermediate cyclopropane in many cases and the failure to convert the cyclopropane to the furan in those cases where it was isolated.[109] However, Pirrung recently pointed out that the established reactivity patterns of substituted furans with other metal carbenes is consistent with a cyclopropanation–rearrangement pathway via the cyclopropane **244**.[107b]

Scheme 25

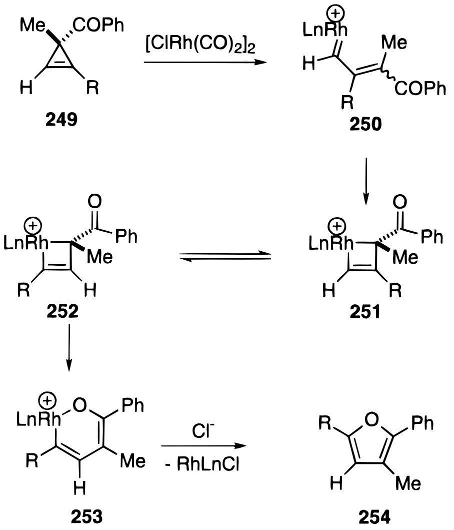


The addition of Rh carbenes such as **243** to alkoxy-substituted acetylenes also led to the formation [3 + 2] cycloadducts without any intermediate being detected. However, when **246** was treated with $Rh_2(OAc)_4$, the starting material was completely converted to the isolable cyclopropene **247** within 20 min. Rearrangement to the furan **248** occurred in the absence of catalyst but the rate of conversion increased upon addition of $Rh_2(OAc)_4$ (eq 48).[110]



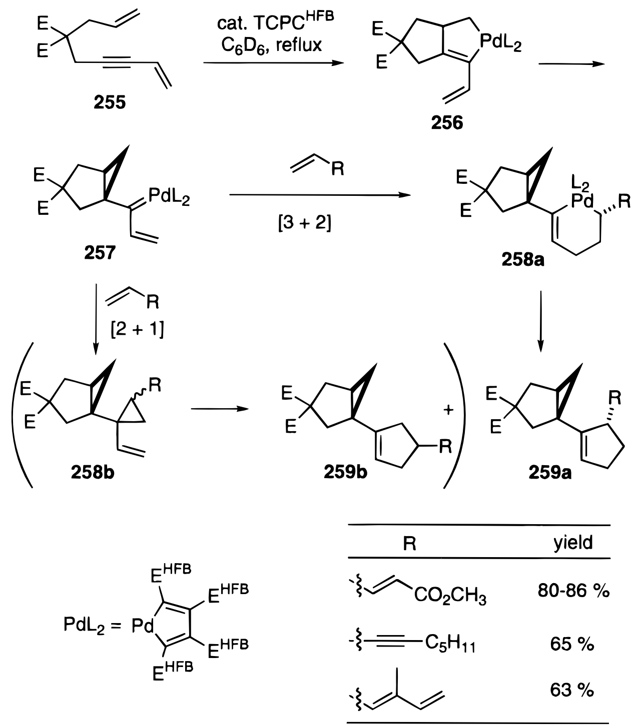
The transition metal-catalyzed rearrangement of structurally related 1-ketocyclopropenes to furans was investigated by Liebeskind and Padwa[111] who suggested that vinylcarbene **250** and metallacyclobutenes **251** and **252** are in equilibrium (Scheme 26).

Scheme 26



A [3 + 2] cycloaddition was observed by Trost when dienyne **255** was treated with a variety of conjugated olefins in the presence of the heptafluorobutyl (HFB) ester of tetrakis(hydroxycarbonyl)palladacyclopentadiene (TCPC^{HFB}).[112] Cyclopentenes **259a** were formed exclusively and a multistep sequence initiated by a Pd-catalyzed enyne cyclization followed by a retro cyclopentene–vinylcyclopropane rearrangement was proposed. Palladadiene **257** was suggested to be trapped with an olefin via a [3 + 2] cycloaddition leading to the palladacyclohexene **258a**, which extrudes Pd(0) to form the cyclopentene moiety **259a** (Scheme 27).

Scheme 27



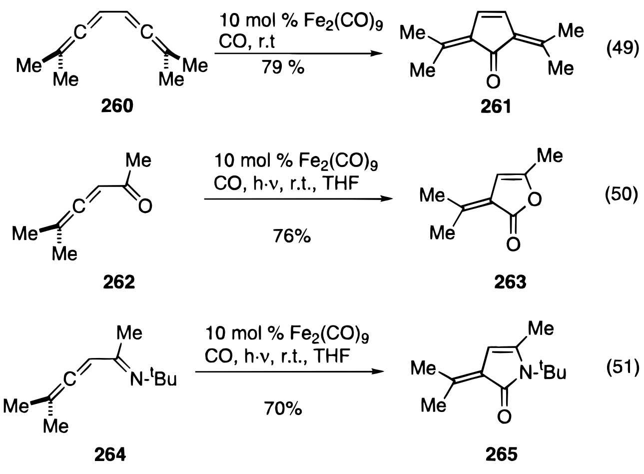
An alternative mechanism for the [3 + 2] cycloaddition would be a [2 + 1] cycloaddition leading to the vinylcyclopropane **258b** followed by a vinylcyclopropane–cyclopentene rearrangement. However, this rearrangement might lead to two products with a preference for **259b**. This pathway was considered less likely since only **259a** was observed.

4.7. $[4_{4\pi} + 1_{2\pi}]$ Cycloadditions

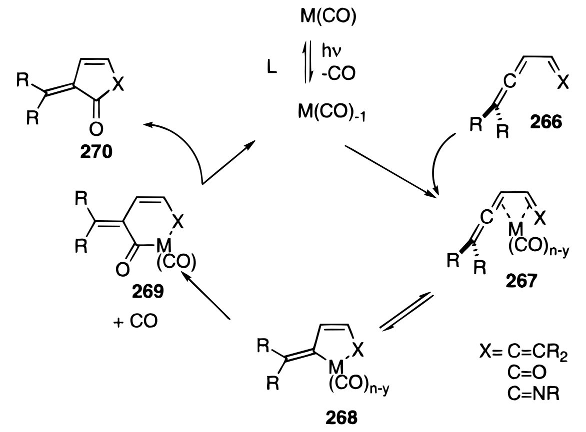
There are very few reports of metal-catalyzed [4 + 1] cycloadditions. The first example was disclosed by Eaton, who reacted the conjugated bis-allene **260** with carbon monoxide in the presence of substoichiometric amounts of iron pentacarbonyl.[113–115] He obtained the 3-cyclopentenone **261** at ambient temperature within minutes (eq 49). Replacing one of the allenes with a carbonyl group or an imine provided a route to lactones or lactams (eqs 50 and 51).[114] These latter reactions were promoted by the use of fluorescent light.

Kinetic experiments showed that the rate is unaffected by CO pressure and is first order in $Fe(CO)_5$. In polar solvents (e.g. CD_3CN) significant attenuation of the rate was observed. On the basis of these observations a mechanism was proposed which begins with a photochemical generation of $Fe(CO)_4$ and is followed by complexation to give an η^2- or η^4-complex **267**. CO insertion ensues to give **269** which undergoes reductive elimination to regenerate $Fe(CO)_4$ and furnish the product **270** (Scheme 28).

These recent discoveries indicate that further studies of [4 + 1] cycloadditions will lead to other interesting transformations.



Scheme 28



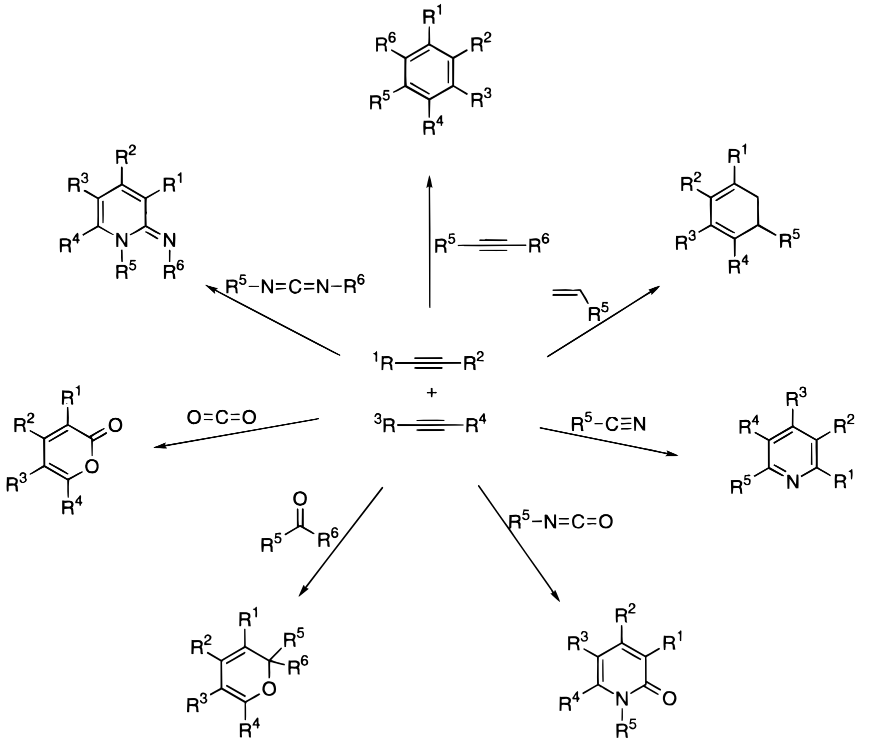
5. Six-Membered Ring Formation

The [4 + 2] Diels–Alder cycloaddition is the most widely used method to prepare six-membered rings and is the standard by which all other cycloadditions are judged. Other classes of cycloaddition reactions that lead to the formation of a six-membered ring include: [2 + 2 + 2], [3 + 2 + 1] (Dötz-type cycloaddition), and [3 + 3] cycloadditions. The Dötz cycloaddition of a metal carbene requires a *stoichiometric* amount of reagent and will not be described in this article.[66]

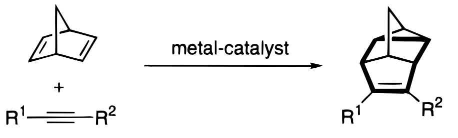
5.1. $[2_{2\pi} + 2_{2\pi} + 2_{2\pi}]$ Cycloadditions

Although in principle thermal [2 + 2 + 2] cycloadditions are symmetry allowed,[53] entropic barriers associated with bringing three reaction partners together and enthalpic activation energy contributions[116] mitigate against such process, and literature examples of purely thermal [2 + 2 + 2] cycloaddition are rare. However, the use of a transition metal catalyst enables the entropic constraints to be circumvented by coordination of the reaction partners to the metal complex in a stepwise process. Thus metal-catalyzed cyclotrimerization of acetylenes to benzene derivatives is well known and can be achieved with many transition metals including Ni, Co, Pd, Cr, Rh, Fe, and Ta.[117–124] This cyclotrimerization has been modified to incorporate olefins,[121c,d,124b,125–128] nitriles,[130–132] isocyanates[133,134] aldehydes and ketones,[135,136] carbon dioxide,[137] imines,[138] and diimides[139] (Scheme 29). This topic has been extensively reviewed.[117a]

Scheme 29



The homo-Diels–Alder (HDA) cycloaddition has begun to attract increasing attention following its discovery many years ago.[140−143] Three new carbon–carbon bonds and a complex, highly strained polycycle are created in one step (eq 52).

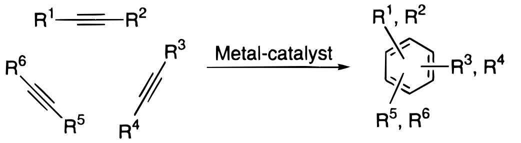


(52)

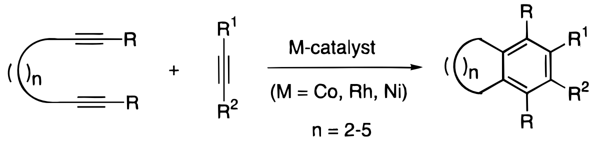
These two classes of reactions will be discussed in detail in this section.

5.2. Acetylene $[2_{2\pi} + 2_{2\pi} + 2_{2\pi}]$ Cyclotrimerization Reactions

Although various transition metals (e.g. Ni, Co, Pd, Cr, Fe, Ru, and Ta)[117−124,171c,d] as well as the Ziegler-type catalyst,[144] are known to promote acetylene cyclotrimerization, many difficulties are encountered in intermolecular cyclotrimerization reactions (eq 53). Chemo- and regioselectivity problems lead to complex mixtures of products which severely limits the utility of this reaction. In contrast, a *partially intramolecular* cyclotrimerization of a α,ω-diyne **271** with a monoalkyne which generates an annelated benzene **273** has become a very useful synthetic procedure (eq 54). Among various metal catalysts, cobalt[117a] and rhodium[119] complexes are the most effective catalysts to promote the partially intramolecular [2 + 2 + 2] acetylene cyclotrimerization.



(53)



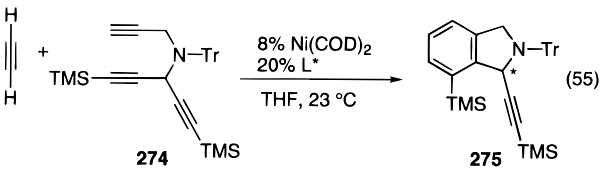
271 **272** **273**

(54)

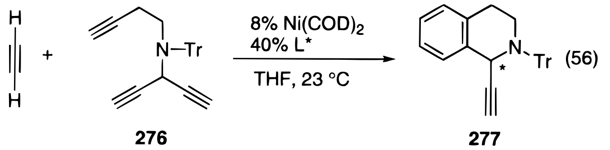
CpCo(CO)$_2$ is an excellent catalyst for the [2 + 2 + 2] cycloaddition of diynes **271** (when n = 3 and 4) bearing a wide variety of substituents (e.g. H, alkyl, aryl, vinyl, COOR, CH$_2$OH, CH$_2$OR, COR, C=NOR, NR$_2$, SR, and SiR$_3$). Alkynes **272** bearing bulky silyl groups (R$_1$, R$_2$ = SiMe$_3$) have become widely used in this reaction since they fail to trimerize but do participate in cycloadditions with less hindered alkynes. Diminished yields are encountered when diynes bearing trimethylsilyl substituents are used in the cycloaddition. Benzocycloheptenes **273** (n = 5) are formed in low yield but benzocyclobutanes (n = 2) are readily accessed using this methodology. Some functional groups including NO$_2$, alkyl halides, and reactive vinyl and aryl halides react with the catalyst and cannot be present in the substrates.[145]

In contrast to cobalt complexes, rhodium complexes generally react with acetylenes to give linear dimers.[146] There were few reports[120] of successful cyclotrimerizations of acetylenes using rhodium complexes until the recent developments by Grigg and Stevenson.[119] The cycloaddition between hepta-1,6-diynes (when n = 3) and *unhindered terminal* monoalkyne occurs smoothly in the presence of 0.5–2 mol % of Wilkinson's catalyst (RhCl(PPh$_3$)$_3$) in ^{t}BuOH, THF, EtOH, or EtOH–CHCl$_3$. The rhodium catalyst appears to offer improved selectivity compared to existing cobalt catalysts since it does not induce any dimerization of the diyne and very little homotrimerization of the monoalkyne. However, this catalyst appears to be limited to reactions of diynes with a three-atom tether and unhindered terminal monoalkynes.

Recently an asymmetric version of this cyclotrimerization has been developed (eqs 55 and 56).[118h]

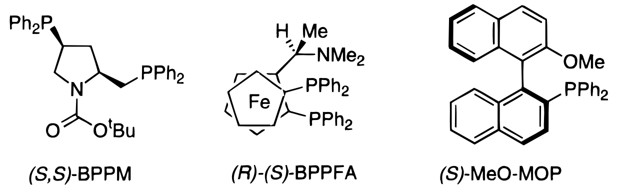


L*	Yield	ee
(S,S)- BPPM	92%	60%
(R)-(S)- BPPFA	52%	73%



L*	Yield	ee
(S,S)- BPPM	42%	6%
(S)- MeO-MOP	62%	54%

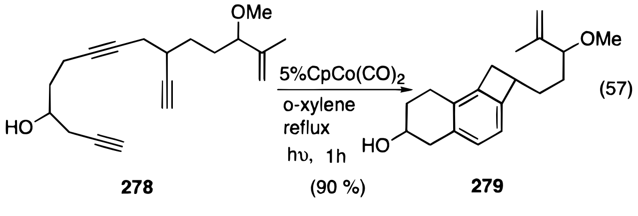
Although the level of asymmetric induction was modest, the possibility of further improvements is exciting. It is interesting to note that the cycloaddition of **274** (forming a five-membered heterocycle) gave similar ee's with a chiral monodentate or bidentate ligands, whereas **276** (forming a six-membered heterocycle) gives poor ee's with a chiral bidentate ligand (Figure 5).

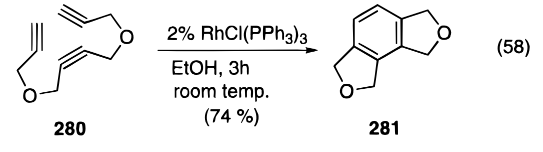


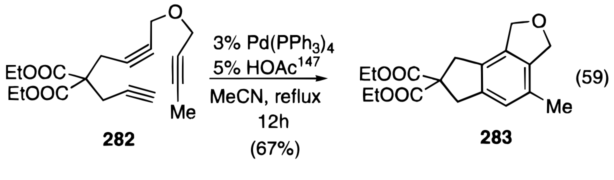
(S,S)-BPPM (R)-(S)-BPPFA (S)-MeO-MOP

Figure 5.

Cycloaddition has also been achieved when all three alkynes were incorporated into the substrates as shown in eqs 57–59. Low-valent cobalt,[117b] rhodium,[119a] and palladium[121b] catalysts have been shown to be very effective for promoting this process. The fully intramolecular cycloaddition represents one of the most efficient entries into polycyclic compounds.

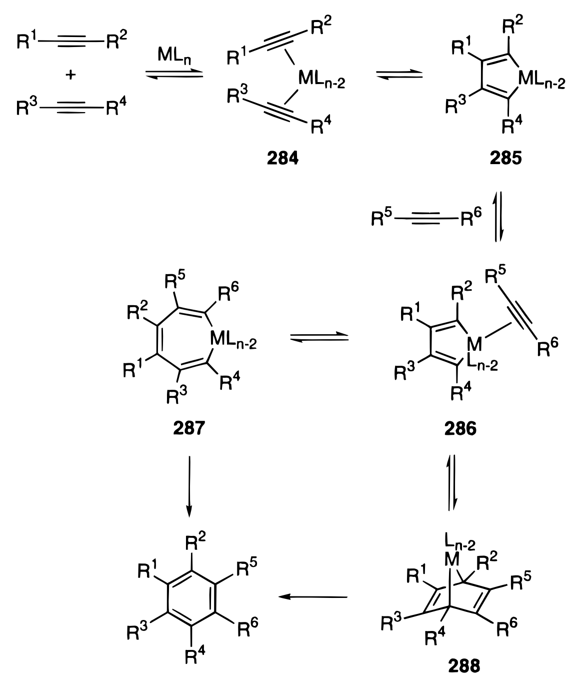






The generally accepted mechanism of metal-catalyzed acetylene cyclotrimerization is illustrated in Scheme 30.[117a,119b,145] Initially, two alkyne moieties displace two ligands on the metal to form dialkyne complex **284**. Oxidative coupling to give the coordinatively unsaturated metallacyclopentadiene **285** is supported by the isolation and characterization of this species with a variety of metals. Following complexation of a third molecule of the alkyne to give **286**, an alkyne insertion to form the metallacycloheptatriene **287** or a Diels–Alder-type cycloaddition to give **288** occurs followed by reductive elimination of these complexes to furnish the aromatic product.

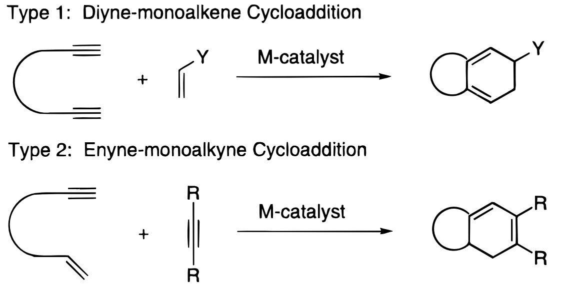
Scheme 30



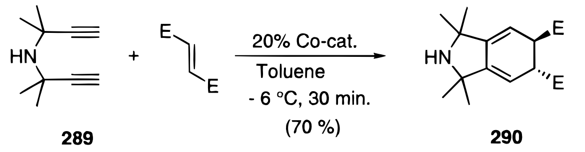
5.3. Acetylene–Olefin [$2_{2\pi} + 2_{2\pi} + 2_{2\pi}$] Cyclotrimerizations

Two classes of cyclotrimerization reactions of substrates containing alkynes and alkenes have been developed. These can be categorized as diyne-alkene cycloadditions (type 1) and enyne-alkyne cycloadditions (type 2) (Scheme 31).

Scheme 31



Cobalt and rhodium are effective in catalyzing type 1 processes, but they are inert in type 2 cycloadditions.[125,128] However, the most commonly used catalyst, $CpCo(CO)_2$, requires *stoichiometric* amounts of the metal since the product complexes tightly to the cobalt.[117a,125c] Recently, Chiusoli and co-workers showed that a catalytic amount of bis(acetonitrile)-bis(diethyl fumarate)cobalt promotes the cycloaddition but the generality of this process has not yet been established (eqs 60 and 61).[125a,b]



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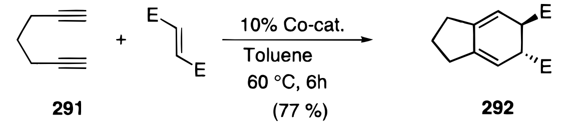
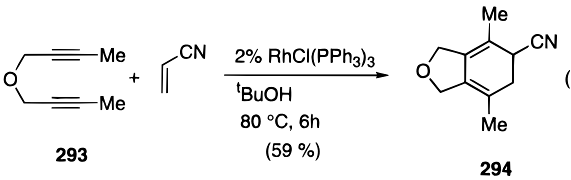


(61)

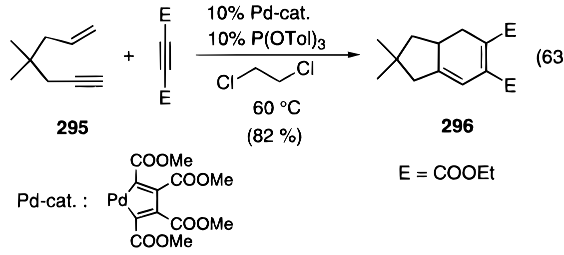
Co-cat.: $Co(CH_3CN)_2$(*trans*-ECH=CHE)$_2$;
E: COOEt

Wilkinson's catalyst was also found to promote type 1 reactions but it was limited to substrates containing three-atom tethers with unhindered, disubstituted diynes (eq 62).[128b] With terminal and substituted diynes bearing bulky substituents, complicated mixtures were obtained.



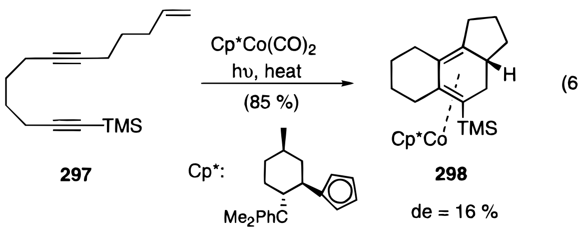
(62)

Trost has reported that cycloaddition of an enyne with an electron-deficient alkyne (type 2) is catalyzed by the Pd (II) complex tetracarbomethoxypalladacyclopentadiene (TCPC) (eq 63).[121c]



(63)

The intramolecular ene-diyne [2 + 2 + 2] cycloaddition using stoichiometric $CpCo(CO)_2$ has been used as a key step in many natural products syntheses including the preparation of steroids.[117a,b] Thus far cycloadditions using a chiral cobalt complex have given adducts of low de (eq 64).[117c]

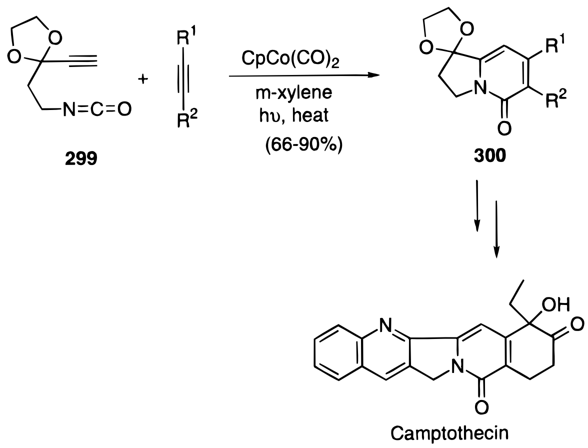


(64)

5.4. Hetero [$2_{2\pi}$ + $2_{2\pi}$ + $2_{2\pi}$] Cyclotrimerizations

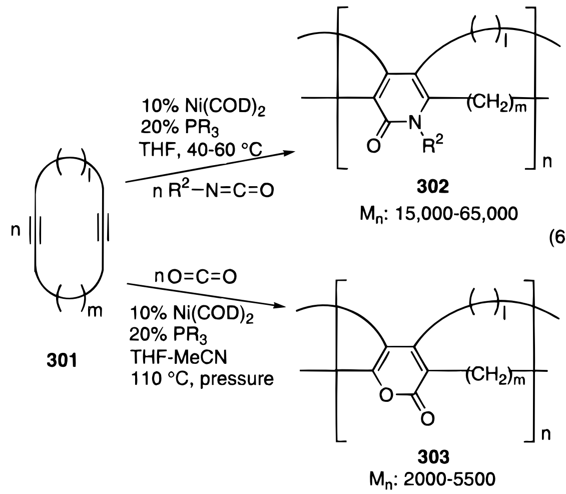
Rhodium and cobalt complexes were reported to catalyze hetereotrimerization of acetylenes with nitriles,[130−132] whereas nickel and cobalt complexes catalyze the corresponding cyclotrimerization with isocyanates.[133,134] Vollhardt has utilized the cobalt version of this reaction in the synthesis of vitamin B_6,[130f] lysergene,[130h] and camptothecin (eq 65).[133d]

Aldehydes, ketones, and carbon dioxide also undergo [2 + 2 + 2] cycloadditions with α,ω-diynes in



(65)

the presence of $Ni(COD)_2$.[135−137] Recently Tsuda and co-workers extended these studies to the synthesis of new polymeric materials. Copolymerization of cyclic diynes with isocyanates or carbon dioxide gives soluble ladder polymers of general structures **302** and **303** which may have novel electronic and optical properties (eq 66).[148]



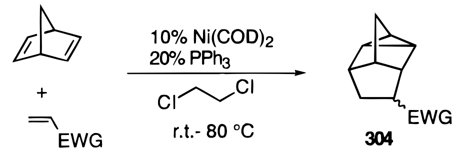
(66)

5.5. Homo-Diels−Alder [$2_{2\pi}$ + $2_{2\pi}$ + $2_{2\pi}$] Cycloadditions

The homo-Diels−Alder (HDA) reaction is a six-electron [2π + 2π + 2π] process which occurs under thermal and metal-catalyzed conditions and generates novel, strained polycyclic compounds. The HDA reaction was discovered in the late 1950s and was examined sporadically during the 1970s and 1980s. The thermal HDA process was moderately efficient with activated alkenes, whereas transition metal catalysts were investigated and found to broaden its scope.[140−143,149] For example, low-valent nickel complexes were shown to catalyze the HDA reaction of norbornadiene with electron-deficient olefins to give cycloadducts of low to excellent stereoselectivity (Table 19).

Unlike thermal HDA reactions in which *endo* adducts predominate[149h] (presumably due to the more favorable "endo transition state" in accord with a typical Diels−Alder reaction), nickel-catalyzed HDA reactions of acyclic electron deficient dienophiles give *exo* isomers as the major cycloadducts (Table 19). However the situation is complicated since *exo*/*endo* selectivities are highly dependent on the nature of

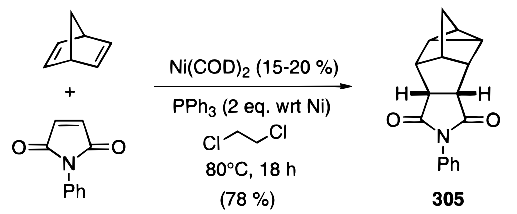
Table 19. Ni-Catalyzed HDA Reaction[140g]



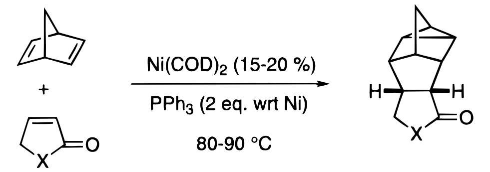
Entry	EWG	Temp.	Yield of **304**	*exo* : *endo*
1	COMe	80 °C	99%	**>20 : 1**
2	CHO	r.t.	58%	3 : 1
3	CN	80 °C	82%	4 : 1
4	SO_2Ph	r.t.	75%	1 : 1
5	SOPh	r.t.	73%	**>19 : 1**[a]

a: $P(OPh)_3$ was used instead of PPh_3.

the dienophile, the phosphine ligands, and the reaction temperature.[140] In contrast to the reactions with *acyclic* dienophiles, *cyclic* enones, lactones, and maleimides favor the formation of *endo* cycloadduct (eqs 67 and 68).[140g]



305 (67)



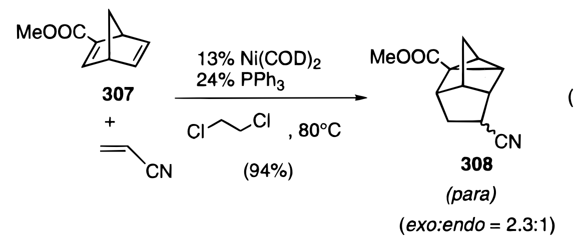
(68)

306a: X = O 58 %
306b: X = CH_2 56 %
306c: X = CH_2CH_2 23 %

Recently the regio- and stereoselectivity of cycloadditions with unsymmetrical NBD's and alkenes has been reported. Nickel-catalyzed HDA reactions of 2-substituted norbornadienes and electron-deficient olefins indicated that an electron-withdrawing substituent on the NBD favored the *para* cycloadduct, an electron-donating substituent favored the *ortho* regioisomer, and a silyl group favored the *meta′* regioisomer.[140g] Moderate to high regio- and stereoselectivity was observed and representative examples are shown in eqs 69−71. The diene and dienophile substituents as well as the ligands were found to exert a dramatic effect on the selectivities.

Reactions with 7-substituted NBD's were often highly regioselective.[140f] In general, high *exo* selectivity was observed irrespective of the nature of the 7-substituent, whereas the *anti* to *syn* selectivity increased as the group electronegativity of the 7-substituent increased (Table 20). Changing the reaction temperature or the phosphine (from PPh_3 to $P(OR)_3$) had very little effect on the selectivity of these cycloadditions.

The selectivity was explained by examining the results of *ab initio* calculations of various 7-substituted norbornadienes using the STO-3G basis set which indicated a shift of electron density from the



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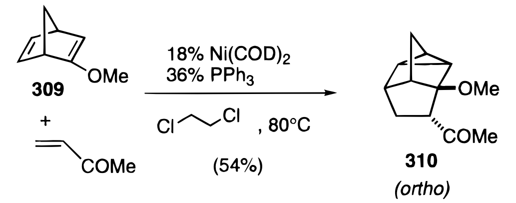

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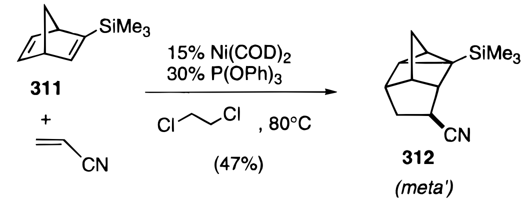
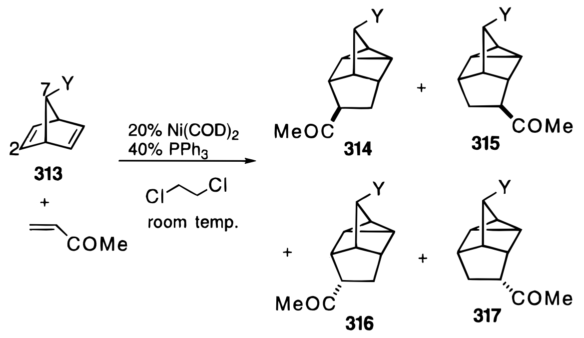


(71)

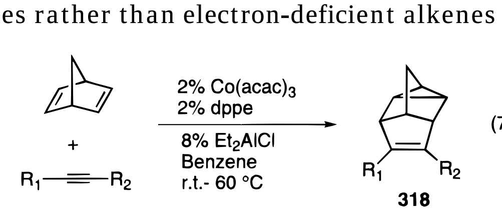
Table 20. Effect of the 7-Substituent on Ni-Catalyzed HDA Reaction



Entry	Y	Yield	**314:315:316:317**	*anti* : *syn*	*exo* : *endo*
1	^{n}hexyl	83%	40 : 58 : 1.6 : 0.4	42 : 58	98 : 2
2	Ph	84%	54 : 45 : 0.8 : 0.2	55 : 45	99 : 1
3	Cl	60%	71 : 28 : 0.8 : 0.2	72: 28	99 : 1
4	OCOPh	97%	80 : 20 : 0 : 0	80 : 20	100 : 0
5	OTIPS	90%	90 : 9 : 1 : 0	91 : 9	99 : 1
6	OMEM	89%	88 : 9 : 3 : 0	91 : 9	97 : 3
7	O^{t}Bu	95%	95 : 5 : 0 : 0	95 : 5	100 : 0

anti-π olefin to the *syn-π* olefin as the substituent group electronegativity increases.[150−152]

In addition to nickel, cobalt catalysts gave HDA adducts but unactivated acetylenes were the dienophiles rather than electron-deficient alkenes (eq 72).

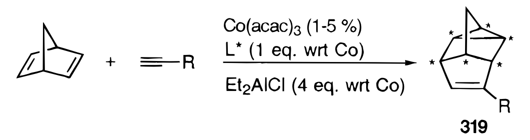


318 (72)

R_1, R_2 = H, Ar, alkyl, $(CH_2)_nOR$ 50-100 %

The scope of this reaction was recently expanded to include alkyl substituted alkynes.[141c−f] Under the standard conditions, a cobalt complex in the presence of a bidentate phosphine ligand was reduced using Et_2AlCl.

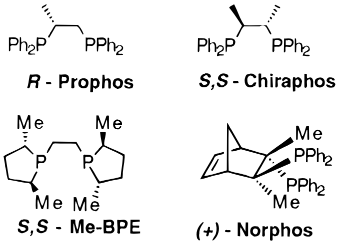
Table 21. Cobalt-Catalyzed Enantioselective HDA Reaction



319

Entry	R	L*	Yield (%)	ee (%)
1[a]	Ph	*(+)*- Norphos	99	99
2[b]		*(S,S)*- Me-BPE	70	82
3[a]	^{n}Bu	*(+)*- Norphos	99	98
4[c]		*(S,S)*- Chiraphos	83	91
5[c]	^{i}Pr	*(S,S)*- Chiraphos	75	36
6[c]		*(R)*- Prophos	33	55
7[c]	$(CH_2)_4OAc$	*(S,S)*- Chiraphos	85	85
8[c]	$(CH_2)_4OTBS$	*(S,S)*- Chiraphos	60	80

a: reference 142c; b: reference 141f; c: reference 142a



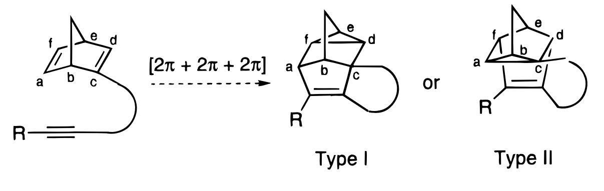
The first examples of the enantioselective HDA reaction were reported independently by Lautens and Brunner in 1990.[142] Moderate to excellent enantiomeric excess was observed with the use of various chiral phosphines and representative examples are shown in Table 21.

The absolute stereochemistry of the product obtained can be rationalized by examining steric interactions between the substituent on the alkyne and the aryl groups on the phosphine.[141f,151]

The regioselectivity of the cobalt-catalyzed HDA reaction of 2- and 7-substituted norbornadienes with unactivated acetylenes has also been investigated, but low to moderate selectivities were observed.[141f] The lack of selectivity may be due to the similarity in electron density of the two acetylenic carbons.

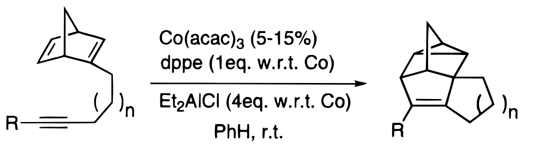
An intramolecular version of this metal-catalyzed HDA reaction has also been reported.[141d] While intramolecular reactions are entropically favored compared to the intermolecular reaction, substituted norbornadienes where the substituent is directly attached to the alkene are significantly less reactive in the HDA process.[140e,g] Although two possible modes of cycloaddition can be considered, all the intramolecular HDA adducts carried out to date gave type I adducts (Scheme 32).[141d]

Scheme 32



Dienynes with a 3-carbon tether **320** (*n* = 1) gave higher yields than the homologous series with a 4-carbon tether **321** (*n* = 2) (Table 22). Cycloadditions on dienynes with a 2-carbon or 5-carbon tether failed to give the desired adducts. Reduction of $Co(acac)_2$ or $Co(acac)_3$ gave effective catalysts but the latter gave slightly better yields.

Table 22. Co-Catalyzed Intramolecular HDA Reactions

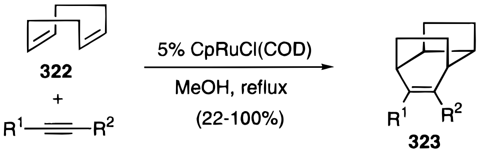


320 **321**

	Yield (%)	
R	n = 1	n = 2
H	78	64
Me	69	43
TMS	63	48
Ph	70	–

5.6. Bis-Homo-Diels–Alder [$2_{2\pi}$ + $2_{2\pi}$ + $2_{2\pi}$] Cycloadditions

1,5-Cyclooctadiene (COD) **322** is generally considered to coordinate weakly to transition metals and undergo ligand exchange as the first step in many catalytic cycles. However in the presence of a low-valent ruthenium complex, COD undergoes a [2 + 2 + 2] cycloaddition with a variety of acetylenes to yield a novel class of tricyclo[4.2.2.0^{2,5}]dec-7-enes (eq 73).[129a] It is too early to determine the generality of this process but further studies to identify related transformations appear warranted.



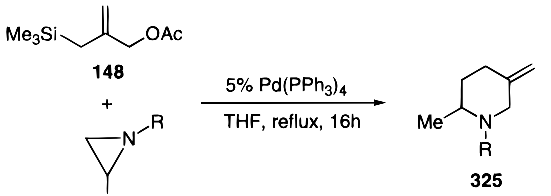
322 **323** (73)

R^1 = H, Me, Et, CH_2OR
R^2 = CH_2OR, COOMe, CH_2CH_2OH, C_3H_7COOMe

5.7. [$3_{2\pi}$ + $3_{2\sigma}$] Cycloadditions

The are very few reports of metal-catalyzed [3 + 3] cycloadditions for the preparation of six-membered rings.[153-157] A few specific examples are illustrated below.

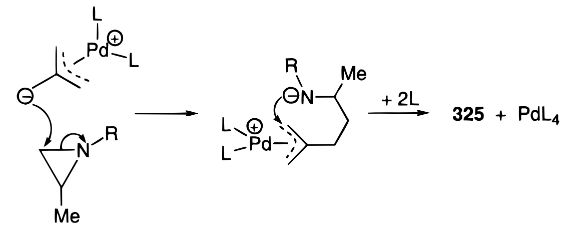
In the presence of a Pd(0) catalyst, activated aziridines undergo formal [3 + 3] cycloadditions with **148** to give the corresponding piperidines **325** in high yields (eq 74).[153] The reaction may take place by addition of a zwitterionic palladium complex to the aziridine, followed by an intramolecular ring closure (Scheme 33). Excellent regioselectivity, with reaction at the less hindered carbon atom, is observed in this process.[154] Reactions with activated cyclopropanes rather than aziridines did not give methylenecyclohexenes.



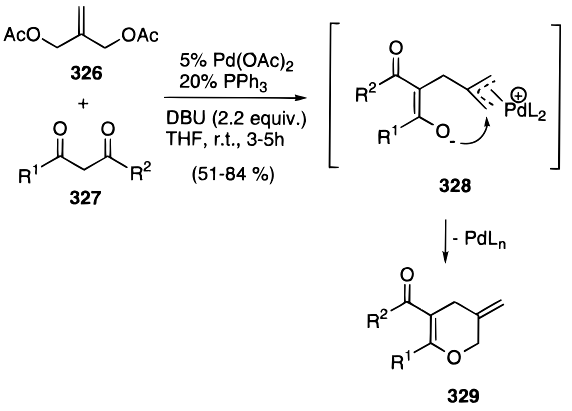
148 **324** **325** (74)

R = $SO_2C_6H_4Me$-*p* 75 %
= $COC_6H_4NO_2$-*p* 71 %

Scheme 33



The bifunctional allylic acetate **326** was also shown to undergo a formal [3 + 3] cycloaddition with a β-diketone or β-keto ester (**327**) in the presence a palladium catalyst (eq 75).[155a] The ambident nucleophile (β-diketone or β-keto ester) reacts with **326** first at carbon and then at oxygen to form pyran derivatives in a one-pot reaction. The carbanion formed reacts with the π-allyl complex derived from **326** to form **328**, and then palladium-mediated intramolecular O-alkylation takes place to give **329**. The bifunctional allylic acetate **326** can also react with other 1,3-bis-nucleophiles such as **330** to generate the bicyclo[3.3.1]nonane **331** (eq 76).[155b] Kozikowski has utilized this methodology in the synthesis of the AChE-inhibitor huperzine A.[156]



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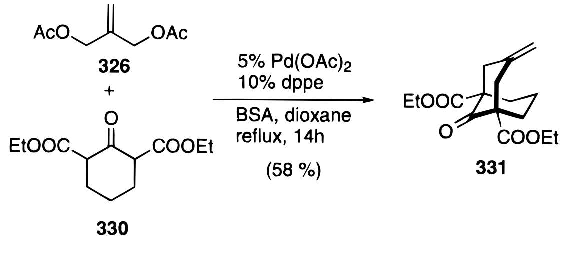


(76)

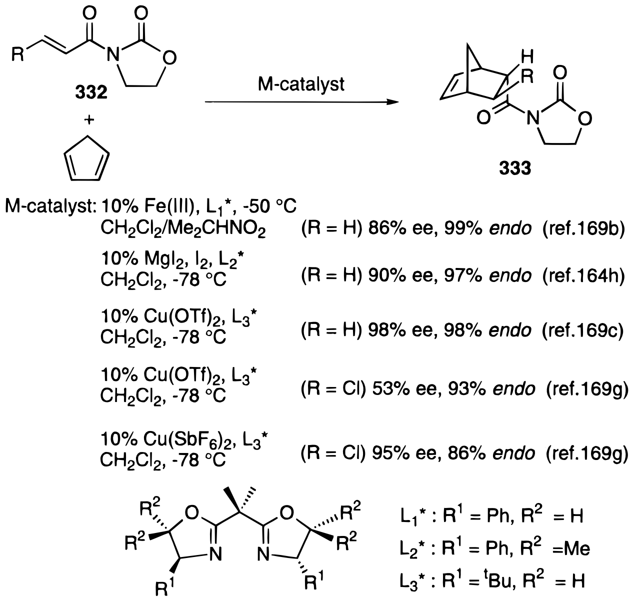
5.8. [$4_{4\pi}$ + $2_{2\pi}$] Cycloadditions

The remarkable versatility of the Diels–Alder reaction for the stereospecific construction of six-membered rings has made this reaction one of the most widely studied methods in organic chemistry.[158–160] The severity of the reaction conditions required for a purely thermal [4 + 2] cycloaddition depends on the substituents on the diene and dienophile. Various modifications have been developed to enhance the rate of the cycloaddition and to the improve selectivities including: the use of high pressure,[161] ultrasound,[162] Brönsted acids,[163] traditional Lewis acids,[158c,159,164] special solvent effects,[165] molecular sieves,[166] adsorption on chromatography adsorbents,[167] *in situ* radical formation,[168] and the use of transition metals.[169–175] The past 10 years has seen a tremendous increase in the development of useful transition metal catalysts which promote the reaction. This interest stems from the mild reaction conditions and the ability to modify the chemo- and regioselectivities as the metal and ligand are varied.

Two main classes of metal-catalyzed Diels–Alder reactions can be identified. The metal either serves as a Lewis acid and complexes to a carbonyl or other polarized group[169,170] or the metal complexes to the π-bonds of alkene or alkyne and the diene.[171–175] A brief review of recent results using Lewis acids will be presented in order to compare the state of the art with emerging olefin complexing reactions.

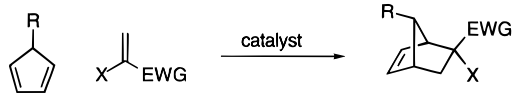
The vast majority of synthetically useful [4 + 2] cycloaddition reactions reported contain an *electronically dissimilar* diene and dienophile. Lewis acid catalysts were the first to be investigated and are now the most widely used. When the metal acts as a Lewis acid, complexation with a functional group in the substrate generates a highly polarized η^1-complex. The enhancement in reactivity and regio- and stereoselectivity has been attributed to a change in the coefficients in the LUMO of the dienophile upon complexation.[158c,d,159] Recently, impressive advances in the development of new chiral ligands which induce high levels of enantioselectivity have been reported. Excellent ee's have been achieved although the range of dienes explored is still somewhat limited (Scheme 34 and Table 23).[158,159,164,169]

Scheme 34



In contrast, dienes and dienophiles which are *electronically similar* undergo cycloaddition under more extreme reaction conditions which has severely limited their use in organic synthesis until the relatively recent discovery of metal catalysts which accelerate these reactions. Activation occurs by a combination of proximity and complexation induced polarization effects. Interaction of the π-bonds of the diene and the dienophile leads to the formation of the π-complex **341** (Scheme 35). Oxidative coupling could occur via pathway A to generate an η^1,η^3-complex **342**.[172b, 173b] A reasonable alternative would involve the formation of the metallacyclopentene **343** via pathway B. Both **342** and **343** could lead to the formation of the metallacycle **344** which could un-

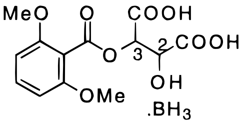
Table 23. Lewis Acid-Catalyzed Asymmetric Diels–Alder Reactions



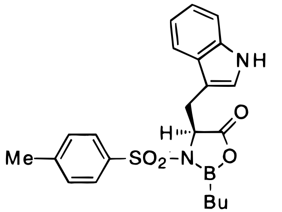
334 **335** **336**

Entry	R	EWG	X	Catalyst	Yield(%)	ee (%)	*exo : endo*
1[a]	H	COOH	H	**337a**	93	78	4 : 96
2[b]	H	CHO	H	**337a**	90	84	12 : 88
3[b]	H	CHO	Me	**337b**	85	96	90 : 10
4[c]	H	CHO	Me	**340**	79	82	95 : 5
5[d]	H	CHO	Br	**338**	95	>99	96 : 4
6[d]	CH_2OBn	CHO	Br	**338**	81	92	95 : 5
7[e]	H	CHO	Br	**339**	>99	>99	>99 : 1
8[e]	H	CHO	Me	**339**	>99	>99	>99 : 1
9[e]	H	CHO	Et	**339**	>99	92	97 : 3
10[e]	CH_2OBn	CHO	Br	**339**	>99	94	>99 : 1

a: ref. 164d; b: ref. 164e; c: ref. 164g; d: ref. 164f



330a: (2R, 3R)
330b: (2S, 3S)



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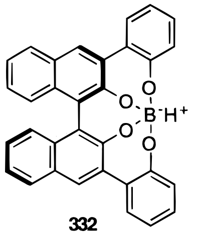

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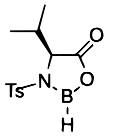
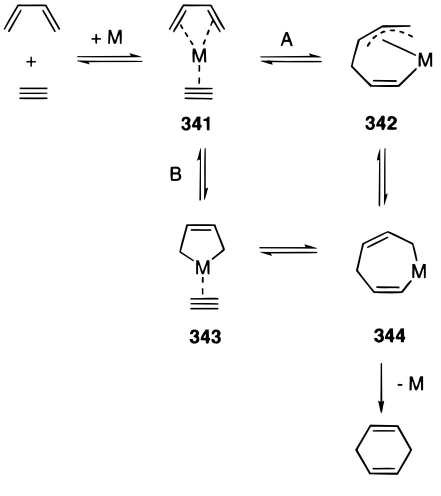


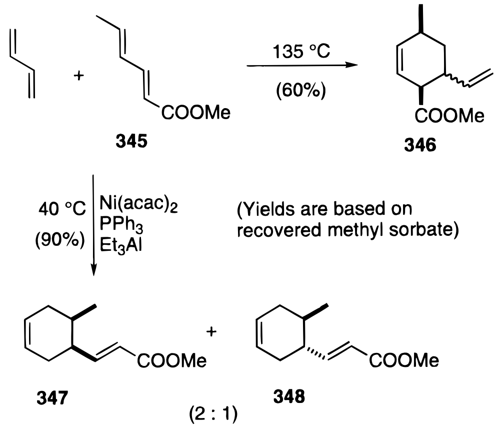
333

Scheme 35



dergo reductive elimination of the metal to give the carbocycle and regenerate the active catalyst. To date, Rh, Ni, Ti, Fe, and Pd have been reported to catalyze the [4 + 2] cycloaddition.[171–175] These are discussed in detail below.

Scheme 36

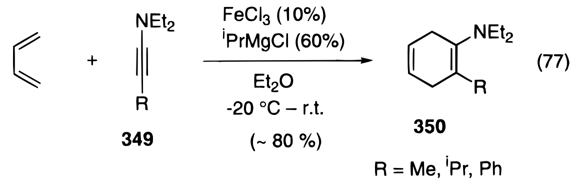


In 1974 Garratt showed that low-valent nickel complexes influenced the selectivity of Diels–Alder reactions between 1,3-butadiene and methyl sorbate (Scheme 36).[172a] Under purely thermal conditions the methyl sorbate was the "diene" component and the 1,3-butadiene was the "dienophile". In contrast, a low-valent nickel complex (generated by reduction of $Ni(acac)_2$ with Et_3Al) reversed the reactivity such that 1,3-butadiene was the "diene" component, and the remote double bond in **345** was the "dienophile" component. Recently Mortreux and co-workers have studied the chemo- and enantioselectivity of this reaction in the presence of chiral aminophosphine–phosphinite and diphosphine ligands.[172e] Unfortunately the yield and the chemoselectivity were only moderate, and the enantioselectivity was rather low (<5%).

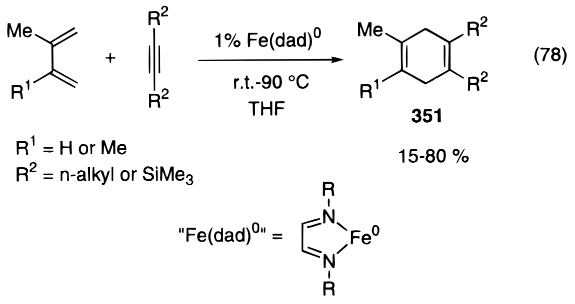
The low reactivity of unactivated alkynes as dienophiles has significantly limited their use in the Diels–Alder reaction.[176] The recent developments using transition metals to catalyze the reaction has therefore stimulated significant interest. Early findings by Ficini,[171b] tom Dieck,[171c,d] and Matsuda[173a] on the use of low-valent iron and low-valent rhodium complexes to catalyze intermolecular [4 + 2] cycloadditions between 1,3-butadienes and unactivated alkynes were important breakthroughs in this area. Low-valent iron (generated by the reduction of $FeCl_3$ with PrMgCl) catalyzes the [4 + 2] cycloaddition between butadiene and ynamines **349** to afford 1,4-cyclohexadienes **350** in good yields (eq 77).[171b] In the presence of "$Fe(dad)^0$" (generated *in situ* by reduction of Fe^{2+} or Fe^{3+} salts with Et_3Al or EtMgBr in the presence of diazadiene (dad)), *internal* alkynes react with 1,3-butadienes to afford [4 + 2] cycloadducts in moderate yield (eq 78).[171c,d] Terminal alkynes do not undergo [4 + 2] cycloadditions under these conditions; instead trimerization of the alkyne was observed.

In contrast to iron-based catalysts, the cationic rhodium(I) complex, $[Rh(COD)(dppb)]^+$, catalyzed the [4 + 2] cycloaddition of *terminal* but not *internal* alkynes with dienes (Table 24).[173a] Use of a rhodium catalyst with 2-substituted 1,3-butadienes and unactivated terminal acetylenes generated the *para* regioisomer (R^1 and R^2 are 1,4-oriented on the cyclohexadiene). When R^1 = Me, conjugated 1,3-cyclohexadienes **352** were formed preferentially indicating that isomerization to the thermodynamically favored isomer occurred under the reaction conditions.

Recently, Wender studied the intramolecular variant of the dienyne Diels–Alder reaction and reported that nickel catalysts gave high yields of cycloadducts under mild conditions (eqs 79 and 80). In contrast,

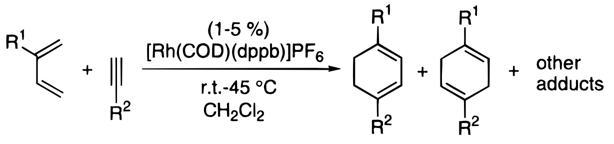


(77)



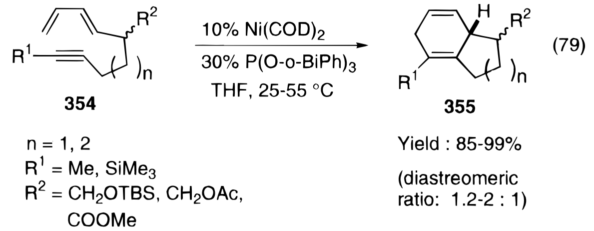
(78)

Table 24. Rh-Catalyzed Diels–Alder Reactions

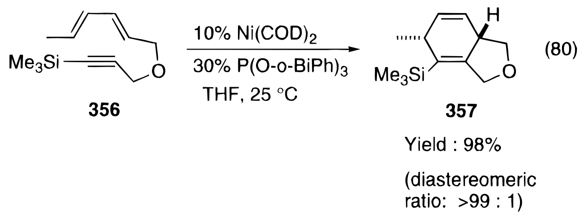


R^1	R^2	Yield	Selectivity (%) 352	353	other
Me	Ph	85%	93	3	4
Me	n-pentyl	74%	88	4	8
H	Ph	69%	40	42	18
H	n-pentyl	58%	8	78	14

thermal cycloadditions required prolonged heating at 80–200 °C. The diastereoselectivities reported range from modest to excellent (1.2–2:1 to >99:1).[172b]

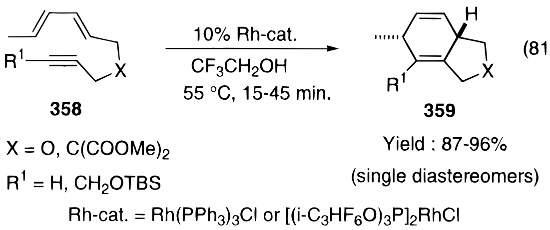


(79)

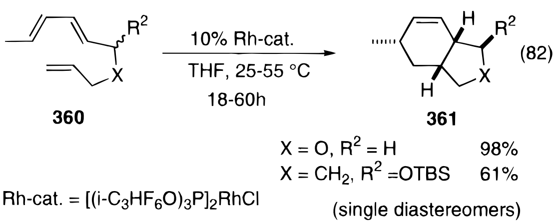


(80)

Livinghouse recently reported the advantages of rhodium catalysts in the intramolecular Diels–Alder reaction.[173b] These cycloadditions are not confined to substrates bearing nonterminal alkynes as [4 + 2] addends. Terminal alkynes and more importantly, *unactivated* alkenes readily participate in the cycloadditions to provide the corresponding bicyclic products in good to excellent yields (eqs 81 and 82). In addition, Rh(I)-catalyzed cycloadditions were highly diastereoselective giving a single cycloadduct in each case.

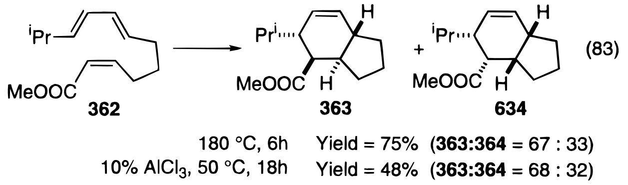


(81)

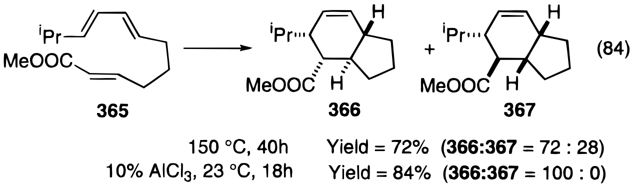


(82)

By way of comparison, noncatalyzed intramolecular [4 + 2] cycloadditions of activated alkenes proceed at a much higher temperature to afford the cycloadducts in moderate yield with low selectivity (eqs 83 and 84).[177] Lewis acid catalysts can only be used



(83)

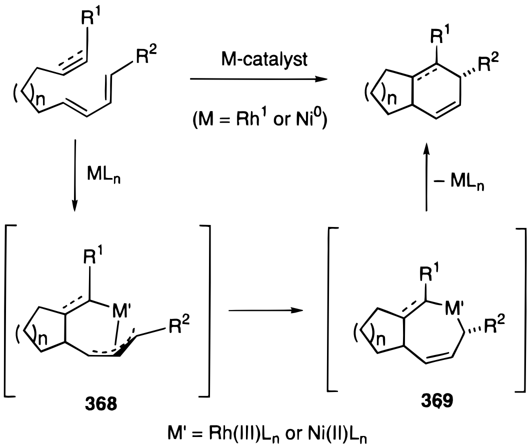


(84)

when an activating group is present in which case the yields and the selectivities are highly dependent on the geometry of the alkene.[177]

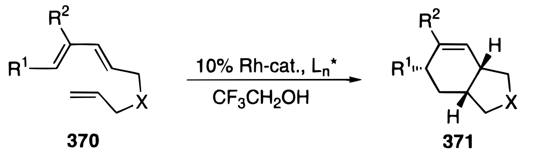
The mechanism of the intramolecular Rh(I)- and Ni(0)-catalyzed cycloadditions are presumed to follow a similar pathway (Scheme 37), which is related to

Scheme 37



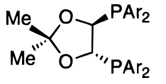
the intermolecular process outlined in Scheme 35.[172b,173b] Carbocyclization with concomitant oxidative addition would form an η^1,η^3-complex **368** [Rh(I) to Rh(III) and Ni(0) to Ni(II)], which would be followed by the formation of metallacycle **369**. Re-

Table 25. Enantioselective Rh-Catalyzed Intramolecular Diels−Alder Reactions



	Yield (%)	ee (%)
R^1 = H, R^2 = Me, X = O (L_1*)	79	62
R^1 = H, R^2 = Me, X = $C(CH_2OMe)_2$ (L_2*)	69	67
R^1 = Me, R^2 = H, X = O (L_3*)	84	73

Rh-cat. = $Rh(PPh_3)_3Cl$ or $[(i\text{-}C_3HF_6O)_3P]_2RhCl$

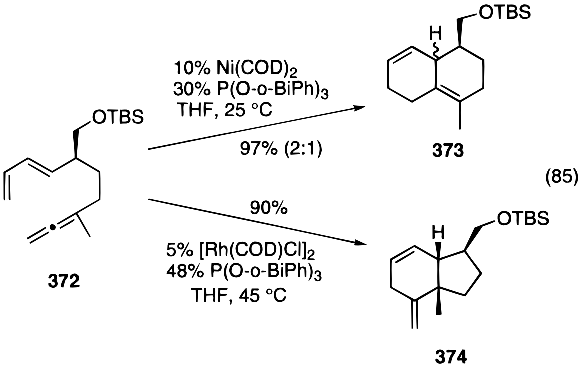


L_1*: Ar = 2-$(CF_3)C_6H_4$
L_2*: Ar = 2-$(CH_3)C_6H_4$
L_3*: Ar = Ph

ductive elimination yields the corresponding cycloadduct with regeneration of the active catalyst.

An enantioselective variant of this cycloaddition was reported by Livinghouse (Table 25).[173c] The degree of asymmetric induction was only moderate (as compared to the ee that could be achieved by using chiral Lewis acid catalysts with *activated* alkenes).[178] However, Lewis acids would be ineffective for this class of substrates and further fine-tuning of the chiral ligands should lead to improved ee's.

Nickel-catalyzed intramolecular [4 + 2] cycloadditions between a diene and an unactivated allene have also been reported (eq 85).[173d] Treatment of allene



372 with a low-valent nickel catalyst resulted in the chemoselective addition of the diene to the terminal π-system of the allene moiety, affording cycloadducts **373** as a 2:1 mixture of stereoisomers in 97% yield. Remarkably, when the same starting material was treated with a low-valent rhodium catalyst, the cycloaddition occurred exclusively on the internal position, providing **374** as a single stereoisomer in 90% yield. By varying the length of the tether between the diene and allene, construction of 6,5-, 6,6-, and 6,7-fused ring systems was achieved.

In summary, transition metal-catalyzed [4 + 2] cycloadditions are emerging as synthetically useful processes. Improvements in the enantioselectivity will further enhance the utility of this reaction.

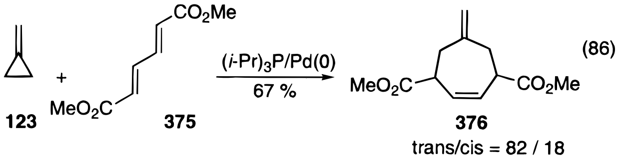
6. Seven-Membered Ring Formation

This section will describe the formation of seven-membered rings by metal-catalyzed [4 + 3] and [5 + 2] cycloadditions. Cobalt-catalyzed [3 + 2 + 2] cycloadditions which utilize *stoichiometric* amount of metal will not be discussed.[179]

6.1. $[4_{4\pi} + 3_{2\sigma}]$ Cycloadditions

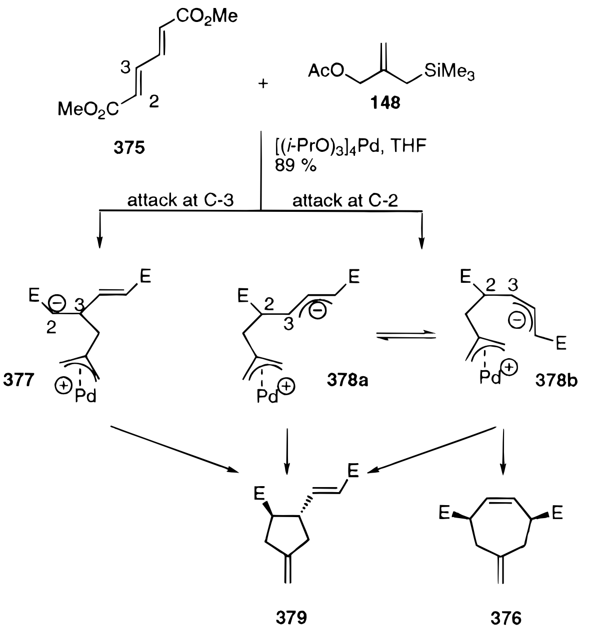
Cycloadditions between dienes and oxyallyl cations using $Fe_2(CO)_9$[180] or Zn[181] are well-established methods but utilize stoichiometric amounts of the metal. There are very few examples where catalytic amounts of the transition metal generate a zwitterionic C_3-unit which will add to a diene.

For example, Pd-catalyzed [4 + 3] cycloaddition between methylenecyclopropane (**123**) and dimethyl muconate (**375**) was reported by Binger. He obtained the 5-methylenecycloheptene **376** as a mixture of stereoisomers (eq 86).[90]



Cycloaddition between **148** and dimethyl muconate (**375**) in the presence of palladium gave a mixture of five- and seven-membered carbocycles **379** and **376** in nearly equal amounts.[182] Two different reaction pathways were proposed. Attack of the Pd−TMM complex at C-3 leads to intermediate **377**, which undergoes ring closure to methylenecyclopentane **379** ([3 + 2] cycloaddition). However, attack at C-2 would lead to a conjugated enolate, with a transoid (**378a**) or a *cis*oid (**378b**) extended enolate. Geometric constraints lead **378a** to cyclize to a five-membered ring ([3 + 2]), whereas **378b** generates **379** ([3 + 2]) or the methylenecycloheptane **376** ([4 + 3]) (Scheme 38).

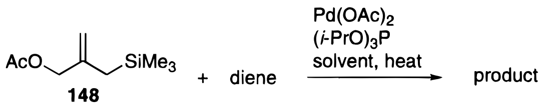
Scheme 38

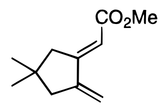
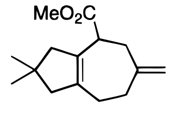
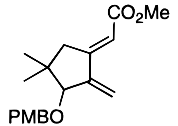
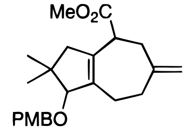
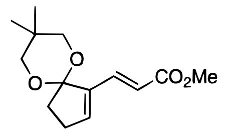
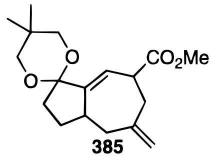
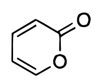
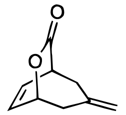
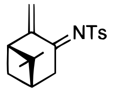
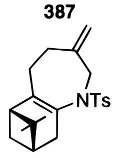


379/**376** = 1.1/1

In cyclic systems containing two exocyclic double bonds which are forced to adopt an *s-cis* geometry, attack of the Pd−TMM complex at the less substituted exocyclic carbon is favored and leads to an

Table 26. Pd-Catalyzed [4 + 3] Cycloadditions with s-*cis*-1,3-Dienes



entry	diene	product	yield	ref.
1	 380	 381	88 %	183
2	 382	 383 1.5/1 mixture	80 %	183
3[a]	 384	 385 1 diast.	48 %	184
4	 386	 387	70 %	185
5	 388	 389	75 %	81

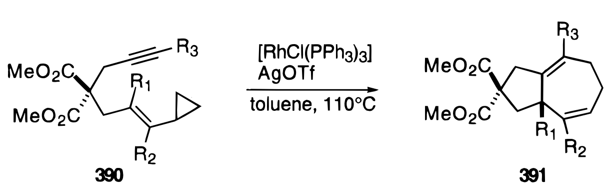
a: *tert*-butylcarbonate was used instead of the acetate as a TMM-precursor

enolate with a *cis*-oid conformation. Cyclization forms the methylenecycloheptenes in good to excellent yield (Table 26).

6.2. [$5_{2\pi+2\sigma} + 2_{2\pi}$] Cycloadditions

Wender recently disclosed the first example of a metal-catalyzed [5 +2] cycloaddition.[186] When vinylcyclopropane **390** was treated with Wilkinson's catalyst, the bicyclo[5.3.0]decanes **391** were isolated in high yield. Addition of silver triflate increased the rate of the reaction which was relatively insensitive to the nature of the substituents on the double bond or triple bond (Table 27).

Table 27. [5 +2] Cycloadditions with Vinyl Cyclopropanes



entry	react. cond.	R_1	R_2	R_3	yield (%)
1	A, 20 min	H	H	Me	83
2	B, 2 d	H	H	Me	84
3	B, 2 d	H	Me	H	82
4	B, 16 h	H	Me	CO_2Me	81
5	B, 7 d	H	Me	TMS	71
6	C, 30 min	Me	H	Me	82

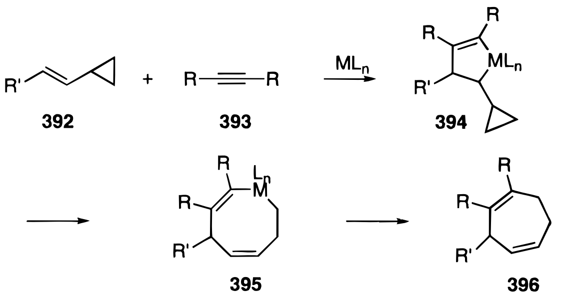
A: 0.5 mol % $[RhCl(PPh_3)_3]$, 0.5 mol % AgOTf;

B: 10 mol % $[RhCl(PPh_3)_3]$;

C: 10 mol % $[RhCl(PPh_3)_3]$, 10 mol % AgOTf.

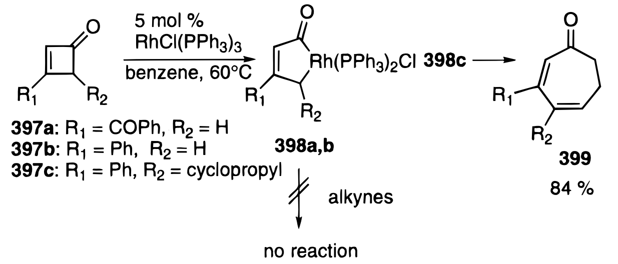
Wender proposed that initial formation of a metallacyclopentene **394** is followed by a cyclopropylcarbinyl rearrangement to the metallaoctadiene **395**. Subsequent reductive elimination provided the 1,4-cycloheptadiene **396** (Scheme 39). The rearrangement reaction bears some resemblance to one suggested by Binger in the [3 + 2] cycloaddition reaction of methylenecyclopropanes (Scheme 21).[93]

Scheme 39



Support for the rearrangement of cyclopropylmetallacyclopentane **394** to metallacyclooctadiene **395** was provided by the work of Liebeskind.[187] He observed that treatment of various cyclobutenones including **397a,b** with Rh(I) catalysts led to the formation of stable η^4-metallacyclopentenes **398**, which failed to react with alkynes. Their structure has been confirmed in one case (**397a**) by X-ray crystallography and in the other (**397b**) by NMR and IR spectroscopy. In the case of the cyclopropyl-substituted precursor **397c**, the Rh complex could not be isolated but, under the reaction conditions, it spontaneously rearranged into the cycloheptadienone **399** (Scheme 40). Another mechanistic pathway might also be considered, in which an initial insertion of the metal into the strained allylic cyclopropyl bond leads to a vinyl-substituted metallacyclobutane.[70,72]

Scheme 40



397a: R_1 = COPh, R_2 = H
397b: R_1 = Ph, R_2 = H
397c: R_1 = Ph, R_2 = cyclopropyl

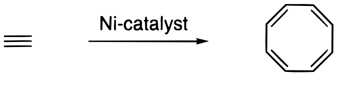
This reaction provides an interesting new approach to the synthesis of seven-membered ring systems and further advances are anticipated.

7. Eight-Membered Ring Formation

Various types of metal-catalyzed cycloadditions leading to the formation of eight-membered rings will be discussed in this section. These cycloadditions include: [2 + 2 + 2 + 2], [4 + 2 + 2], [4 + 4], and [6 + 2] cycloadditions. Reactions in which three of four components must come together are entropically disfavored and are also forbidden by the Woodward–Hoffmann rules. Thus metal complexes play a unique role in promoting these reactions.

7.1. $[2_{2\pi} + 2_{2\pi} + 2_{2\pi} + 2_{2\pi}]$ Cycloadditions

The first [2 + 2 + 2 + 2] cycloaddition was discovered 50 years ago by Reppe, who reacted ethyne in the presence of $NiBr_2/CaC_2$ and obtained cyclooctatetraene (COT) **400** (eq 87). This reaction is also catalyzed by $Ni(acac)_2$ or $Ni(COT)_2$ and has been used for the production of COT on an industrial scale.[188]



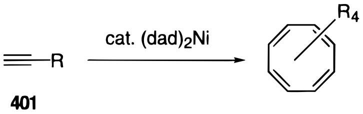
(87)

400

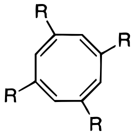
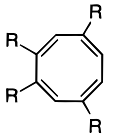
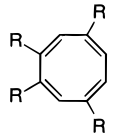
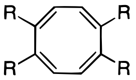
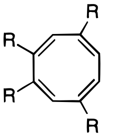
Ni-catalyst = $NiCl_2/CaC_2$ or $Ni(acac)_2$ or $Ni(COT)_2$

When the cycloaddition is performed with substituted alkynes, a number of cycloadducts with different substitution patterns are possible. tom Dieck developed the first method for regioselective cycloadditions with monosubstituted alkynes by employing sterically hindered 1,2-diaza diene nickel complexes, $(dad)_2Ni$, as catalysts (Table 28). He showed that a propargylic alcohol[189] is converted preferentially into the 1,3,5,7-substituted COT (Table 8, entry 1) and a propargylic ether[190] into the 1,4,5,8-substituted COT (entry 3). A secondary propargylic alcohol (entry 2) and propargylic esters[191] (entry 4) furnished 1,3,6,8-substituted COT's.

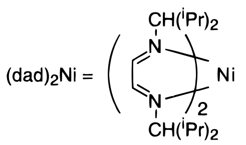
Table 28. Synthesis of Substituted COT's



401 **402**

entry	R	major product	minor product	turnover no.
1[a]	CH_2OH			ca. 500
2[a]	$CH(CH_3)OH$		not identified	ca. 500
3[b]	CH_2OTol		-	not reported
4[b]	CH_2CO_2Me		-	1000

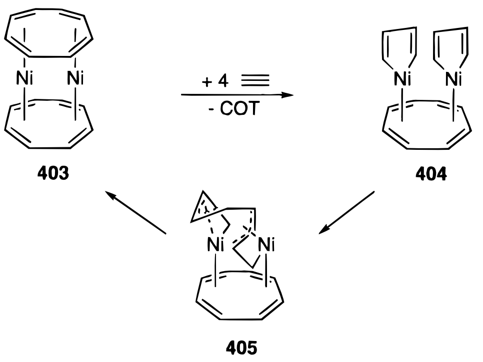
a: C_6H_6 as solvent. b: C_6H_{12} as solvent.



Reactions in neat propargylic alcohol gave turnover numbers up to 10^6 irrespective of the catalyst.[192] However, 2:1 mixtures of 1,3,5,7- and 1,3,6,8-regioisomers were obtained.

Wilke has proposed that the binuclear $(COT)_2Ni_2$ complex **403** reacts with four acetylene molecules to form the bis(cyclopentadienylnickel) complex **404** (Scheme 41).[193] C–C bond formation generates a C_8-chain containing two nickel atoms, **405**, which undergoes reductive coupling to regenerate complex **403**.

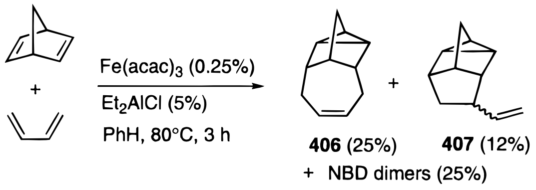
Scheme 41



Several observations support this proposal. The structure of **403** was determined by X-ray crystallography and this complex was shown to be an active catalyst.[194] Furthermore, when $(COT)_2Ni_2$ was used as the catalyst there was no induction period which was observed with all other catalysts.[195] Vollhardt and Carpenter have carried out labeling and kinetic studies which also support this proposal.[196,197]

7.2. $[4_{4\pi} + 2_{2\pi} + 2_{2\pi}]$ Cycloadditions

Transition metal-catalyzed [4 + 2 + 2] cycloaddition between norbornadiene (NBD) and 1,3-butadiene was first reported in 1970 by Carbonaro and coworkers using an iron catalyst (eq 88).[198a] The cycloadduct **406** was formed in 25% yield accompanied by a [2 + 2 + 2] adduct **407** (12%) and several NBD dimers (25%). A catalytic system based on cobalt ($CoCl_2$/dppe/Et_2AlCl, in toluene at 75 °C for 5 h) gave **406** in 68% yield and avoided the formation of the [2 + 2 + 2] adduct **407**.[198c]



(88)

Lyons reported that $Co(acac)_3$/dppe/Et_2AlCl in benzene induced the coupling between NBD and butadiene or substituted butadienes **408** to provide **409** (eq 89).[198d]

Recently the enantioselective [4 + 2 + 2] cycloaddition was reported by Lautens, Tam, and Sood (Table 29).[198e,f] $Co(acac)_2$ or $Co(acac)_3$ in the presence of a chiral phosphine and a reducing agent (Et_2AlCl) were both effective as precatalysts and gave similar levels of asymmetric induction. Of the various chiral phosphines tested, *(R)*-Prophos gave the highest ee's which were typically in excess of 70%.

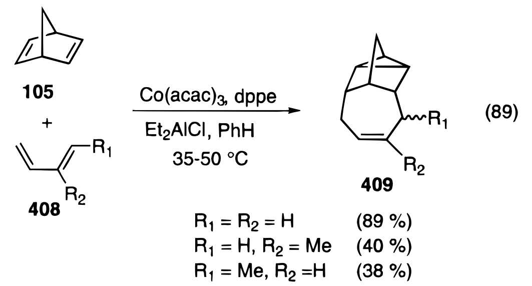
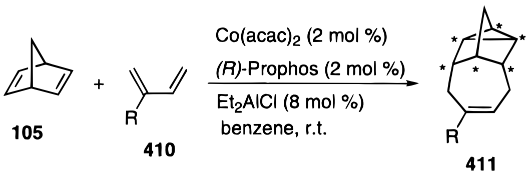
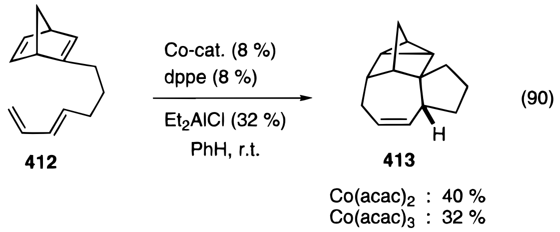


Table 29. Co-Catalyzed Enantioselective [4 + 2 + 2] Cycloadditions



R	Yield (%)	ee (%)
CH_3	66	72
$(CH_2)_8CH_3$	40	74
$CH_2CH_2CH{=}CMe_2$	49	79
$(CH_2)_3OTBS$	40	73
$(CH_2)_3OAc$	52	73
CH_2SiMe_3	49	71

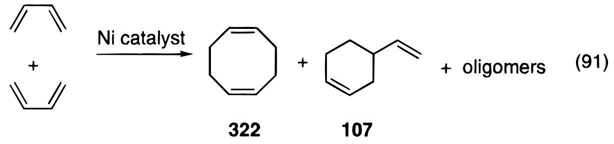
The first example of an intramolecular [4 + 2 + 2] cycloaddition was reported recently but the yield was modest (eq 90).[198f]



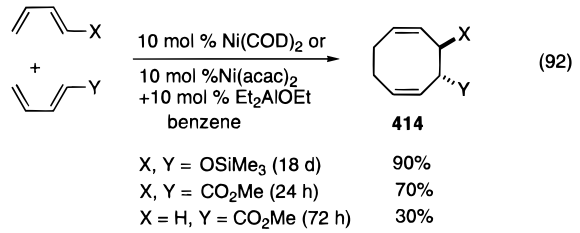
The existing catalysts for [4 + 2 + 2] reactions have a number of shortcomings including low yields and a lack of selectivity for the desired cycloaddition over dimerization of NBD or polymerization of the dienes. New catalysts are required to enhance the utility and generality of this methodology.

7.3. [$4_{4\pi}$ + $4_{4\pi}$] Cycloadditions

The cyclodimerization of butadiene has been known since the pioneering work of Ziegler and Reed in the 1950s (eq 91).[199] Under optimized conditions, Wilke and Heimbach showed that cyclooctadiene could be isolated in 95% yield using nickel catalysts in the presence of a phosphine ligand.[200] Depending on the ligand and the ligand/metal ratio, cyclooctadiene (COD) **322** was formed in preference to vinylcyclohexene (VCH) **107**, divinylcylobutane and cyclic trimers of butadiene. A bis(π-allyl)nickel complex has been isolated and shown to lead to both cyclooctadiene and vinylcyclohexene. From these seminal studies has evolved elegant work on the stereo-, regio-, and enantioselectivity of diene cycloadditions.[118a,188b]



Waegell and co-workers were the first to investigate the regio- and stereoselectivity in the intermolecular homodimerization of substituted butadienes using nickel complexes.[201] They showed that dienes bearing siloxy and carbomethoxy groups undergo smooth reaction to form adducts **414** in preference to the three other regio- or stereoisomers (eq 92).



Dienyl esters were found to be significantly more reactive than siloxydienes. Unfortunately other dienes including methyl sorbate, 1-acetoxybutadiene, and 2-siloxybutadiene failed to react, while dienes lacking a polar functionality directly on the olefin gave mixtures of regioisomers. Attempted heterodimerization between butadiene and methyl pentadienoate gave the desired product in 30% yield accompanied by [4 + 2] adducts.

tom Dieck showed that iron diazadiene (dad) complexes are also efficient at inducing intermolecular [4 + 4] cycloaddition reactions (Figure 6).[202] The substituent on the diazadiene ligand exerted significant control over the formation of COD vs VCH. R-groups such as 2,6-$Me_2C_6H_3$ favored the formation of COD by up to 49:1 with complete exclusion of linear dimers. When R is extremely bulky the ligand complex disproportionates to an inactive $Fe(dad)_2$ complex and a "ligand-free Fe species" which catalyzes formation of linear oligomers.[203] With small R groups no dimerization of butadiene was observed. VCH was the dominant cycloadduct with pyridyl-derived dad ligands. Diazadiene ligands bearing chiral R groups such a menthol gave the VCH **107** in up to 62% ee.[203]

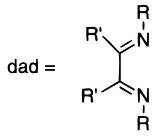
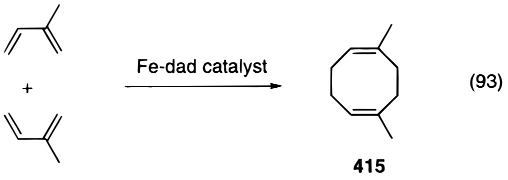
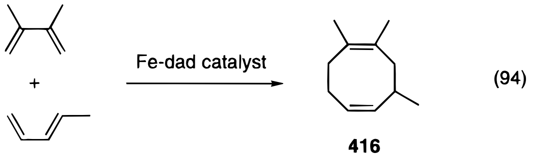


Figure 6.

The substituents on the dad ligand also influence the binding between the iron and the number and type of diene ligand(s). For example, the dimerization of butadiene is fast when R = i-Pr_2CH, R′ = H, whereas isoprene homodimerizes slowly using this catalyst + ligand. However, the homodimer **415** can be preferentially formed with Fe–dad catalysts when R = i-Pr, R′ = H,or R=Ph, R′ = Me (eq 93).[204]

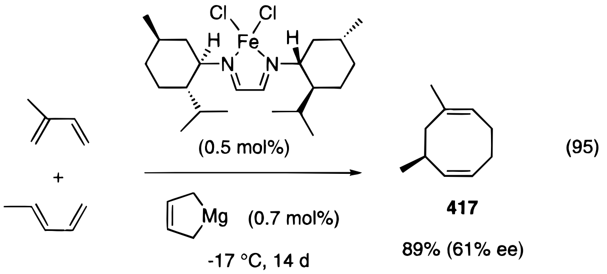


The reduced activity of the catalyst with R = *i*-Pr_2-CH, R′ = H toward homodimerization made it possible to carry out a 1:1 heterodimerization reaction. 2,3-Dimethylbutadiene and *trans*-piperylene undergo cycloaddition to give **416** (eq 94).



416

Isoprene and *trans*-piperylene give adduct **417** in 88% isolated yield accompanied by 3.3% of isoprene dimers and 9.5% of 2-methyl-4-*trans*-propenylcyclohexane for R = CH-*i*-Pr_2, R′ = H. Recently this latter process has been made enantioselective by the use of a menthyl-derived dad ligand (eq 95). The adduct

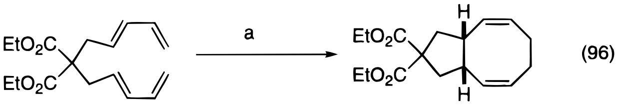


417

89% (61% ee)

417 is obtained in 89% yield and 61% ee.[205] The very high turnovers associated with this reaction are particularly noteworthy and examination of other chiral ligands may lead to further improvements.

Intramolecular nickel-catalyzed [4 + 4] cycloaddition reactions were first reported by Wender in 1986 (eq 96).[206a] When **418** was treated with $Ni(COD)_2$ and triphenylphosphine, **419** was isolated in 70% yield (19:1 mixture of *cis* and *trans* isomers). In addition, a vinylcyclohexene and *β*-elimination product were obtained in 2.6% and 12% yields, respectively.



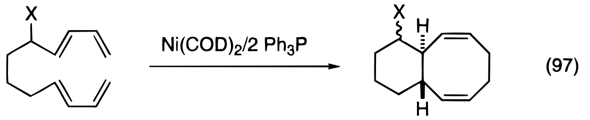
418

419

70% (19:1 cis:trans)

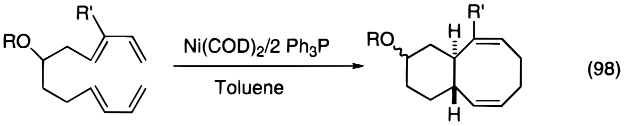
a: 11 mol% $Ni(COD)_2$, 33 mol% Ph_3P, toluene 60 °C

In contrast to these results, bis-dienes with four-atom tethers preferentially furnish the *trans*-fused adducts **421** and **423** by reaction through an *exo* cycloaddition mode (eqs 97 and 98). A study to determine the effect of the substituent on the level of induction led to the conclusion that steric effects play a predominant, but not an exclusive role.[206c] High stereoinduction from the preexisting stereocenter was not observed when the substituent was more remote from the diene. Increasing the substitution on one of the dienes gave adducts in similar yields and selectivities.



420

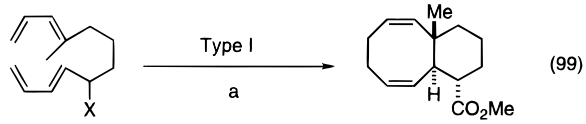
X = CN **421**α:β =1.5:1
= CH_3 20:1
= CH_2OAc 21:1
= CO_2CH_3 >70:1



422

423

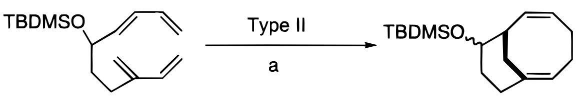
R=Ac, R'=Me, α:β=1:2.2, 82%
R=TBDMS, R'=H, α:β=1:1.7, 92%



424

425

a: 10 mol%$Ni(COD)_2$, 20 mol% Ph_3P 92%



426

427

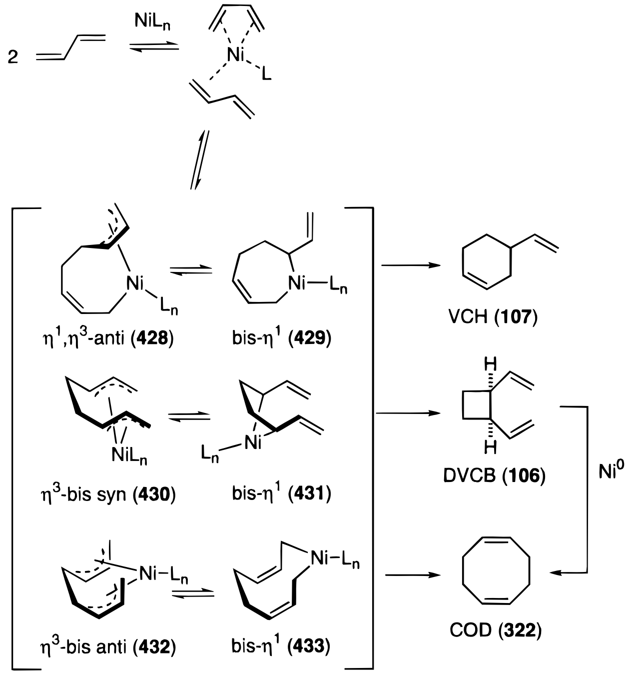
a: 20 mol%$Ni(COD)_2$, 40 mol% Ph_3P, toluene, 110 °C 52%

(100)

Two different cycloaddition modes have been identified (eqs 99 and 100). The reaction described in eq 100 provides access to the carbon skeleton of the taxane family of natural products.[206b] The effect of ligand and ligand to metal ratio has been explored in some detail for type II reactions. Ligands with a cone angle of 150° and χ value of 29 gave the best results as did a 3:1 ratio of phosphine to nickel.[207]

The mechanism of the cyclodimerization has been considered in some detail (Scheme 42).[118a,195] Complexation of the two dienes to the metal and subsequent carbon–carbon bond formation is proposed to generate the key intermediates. Bis-allyl (**430**, **432**), allyl-*σ* (**428**) and bis-*σ* (**429**, **431**, **433**) complexes

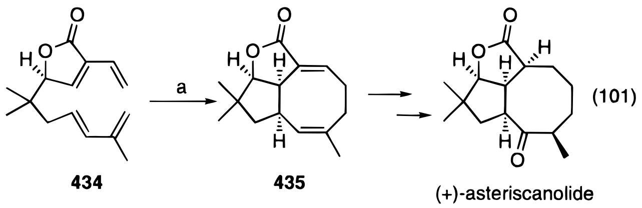
Scheme 42



appear to be in dynamic equilibrium and lead to three different cycloadducts. At temperatures as low as 24 °C, divinylcyclobutane DVCB **106** has been shown to undergo a nickel-catalyzed Cope rearrangement to COD **322** and under more typical reaction conditions (80 °C) both thermal and metal-catalyzed rearrangements occur.[208] It is possible to isolate up to 36% yield of DVCB **106** (at low conversion and using tris-(2-biphenyl) phosphite as a ligand).

Gugelchuk and Houk have investigated the energetics of nickel-catalyzed [4 + 4] cycloaddition reactions using Allinger's MM2 force field with additional parameters for nickel−carbon bond strengths.[209] They successfully reproduced a number of Wender's stereochemical results by using anti-η^1,η^3 nickel phosphine complex **428**.

The first example of a total synthesis using this reaction has appeared. In the key step of the preparation of the naturally occurring sesquiterpene asteriscanolide, **434** is reacted with $Ni(COD)_2/2Ph_3P$ at 90 °C in toluene to furnish **435** in 67% yield as a single isomer (eq 101).[210]

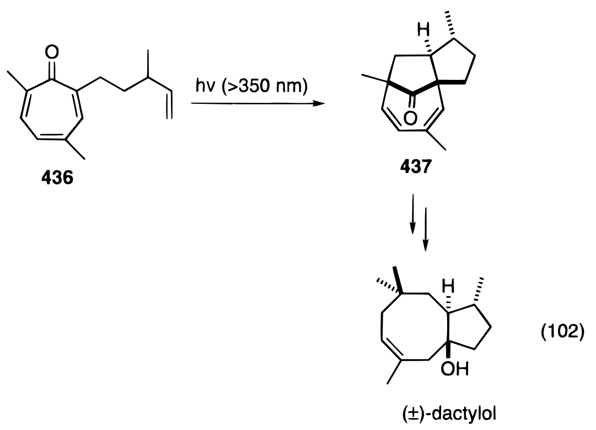


434 **435** (+)-asteriscanolide

a: $Ni(COD)_2/ 2Ph_3P$, toluene, 90 °C, 67%

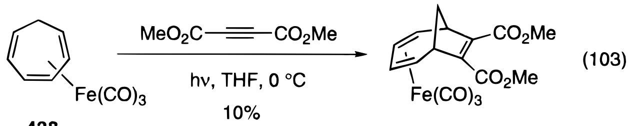
7.4. [$6_{6\pi}$ + $2_{2\pi}$] Cycloadditions

[6 + 2] suprafacial cycloadditions are thermally forbidden processes according to the Woodward−Hoffmann rules, whereas photochemical reactions are allowed. The viability and synthetic utility of the photochemical processes have been explored in some detail by Feldman who showed that tropone derivatives undergo intramolecular cycloaddition onto an unactivated alkene when photolyzed.[211] The addition of an acid often has a marked effect on the reactivity and selectivity of the photocycloaddition. Efficient access to the bicyclo[4.2.1]nonane skeleton and, subsequently, eight membered rings has been achieved (eq 102).



436 **437** (±)-dactylol

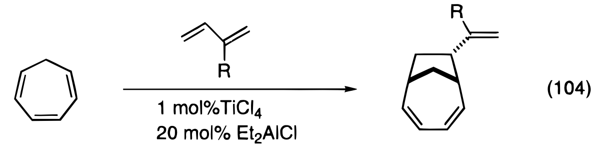
Metal-catalyzed processes have also attracted considerable attention since Pettit's seminal studies in 1974.[212] A [6 + 2] cycloaddition between a cycloheptatriene−iron tricarbonyl complex **438** and an electron-deficient acetylene was reported using photolytic conditions (eq 103).



438 **439**

Irradiation of the iron complex at low temperature followed by addition of the alkyne gave the same product which showed that the cycloaddition step was a "dark" reaction and that during photolysis, activation of the metal by loss of a carbon monoxide ligand was occurring. Thus the metal played an important role in the thermal [6 + 2] cycloaddition reaction. The structure of the resulting iron−diene complex **439** was unambiguously determined by X-ray analysis which indicated that prior complexation of the alkyne to the metal preceded the carbon−carbon bond-forming steps. In some examples the free organic ligand was isolated rather than the metal complex. While this reaction was not catalytic in iron, it did demonstrate the importance of the metal as a template for a formally forbidden eight electron thermal cycloaddition. Others made similar observations on related complexes but the field remained in its infancy for a decade.

In 1983 Mach and co-workers examined the cycloaddition between cycloheptatriene (CHT) **440** and butadiene in the presence of 1 mol % of a titanium catalyst formed from treatment of $TiCl_4$ with Et_2AlCl (eq 104).[213] Under the optimized conditions, adduct **441a** (R = H) was obtained in 78% yield accompanied by other cycloadducts in 1−8% yield. These adducts included [6 + 4] heterodimers and two homodimers. When butadiene was replaced by isoprene, cycloaddition occurred exclusively on the less substituted olefin providing **441b** (R = Me) in 61% yield. Reaction with 2,3-dimethylbutadiene led to a [6 + 4] adduct; the [6 + 2] product was isolated in only 8% yield. Thus far, this methodology has not been exploited in the synthesis of any natural products.

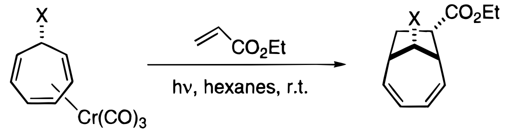


CHT (**440**)

441a: R=H, 78%
441b: R=Me, 61%

Kreiter investigated the reactivity of $(CHT)Cr(CO)_3$ complexes which were irradiated in the presence of dienes and found that [6 + 2] and/or [6 + 4] cycloadditions can occur depending on the structure of the diene.[214,215] These studies provided important mechanistic information but did not address questions of selectivity and synthetic utility which were investigated in detail by Rigby.[216,217] These contributions have been thoroughly reviewed and only a few highlights will be presented here.[218] The principal features of this reaction are the high yields and selectivity arising from cycloadditions between cycloheptatriene complexes and electron-poor olefins under photolytic or thermal conditions. Photolysis is usually carried out in an inert solvent such as hexane, whereas thermal reactions give much better results with rigorously degassed *n*-Bu_2O. Rigby has proposed that *n*-Bu_2O acts as a ligand toward chromium and assists in the decomplexation of the metal from the product. It may also stabilize the coordinatively unsaturated chromium species following decomplexation.

High diastereoselectivity was observed in the reaction of **442a** (X = H) with ethyl acrylate which gave **443a** in 92% yield as a single diastereomer (eq 105).



442a: X=H
442b: X=OMe

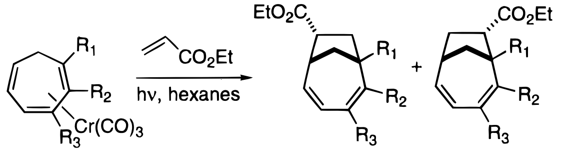
443a: X=H, 92%
443b: X=OMe, 68%

(105)

In analogy to the results of Petit, the primary function of the light was to generate a reactive metal complex rather than induce a photochemical [6 + 2] reaction. Reaction of a stereochemically homogeneous chromium complex **442b** revealed that complexation of the alkene to the metal occurred prior to carbon−carbon bond formation in accord with Petit's results with iron complexes (eq 105).

The regioselectivity of the cycloaddition depended on the position and nature of the substituent (Table 30). Single regioisomers were obtained with 1-substituted cycloheptatrienes; only the "ortho" isomer was observed. In contrast, virtually no selectivity was observed in reactions with 2-substituted CHT's for electron-rich and electron-poor substituents. The level of selectivity with 3-substituted CHT's was excellent with an electron-poor CHT and modest with an electron-rich CHT. No clear understanding of these trends has emerged and further studies are necessary.

Table 30. Regioselectivity in [6 + 2] Cycloadditions

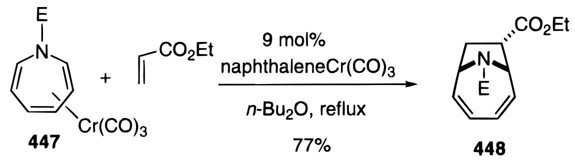


444 **445** **446**

R_1	R_2	R_3	445	446	yield
OMe	H	H	0	1	81%
Me	H	H	0	1	87%
H	OMe	H	1	1	64%
H	CO_2Et	H	1	1	67%
H	H	OMe	1	4	82%
H	H	CO_2Et	0	1	92%

Azepines participate as triene partners and, most importantly, a reaction was disclosed in which a catalytic amount or a naphthalenechromium tricarbonyl complex promoted the cycloaddition of an azepine with at least eight turnovers (eq 106).[217a]

Recently, other two-electron partners including an isocyanate, ketene, and in more modest yield, a chromium carbene complex and isothiocyanate were shown to cycloadd to CHT and/or azepine complexes using photolysis.[217b] Since the yields are typically 18−55%, further work in this area is needed.

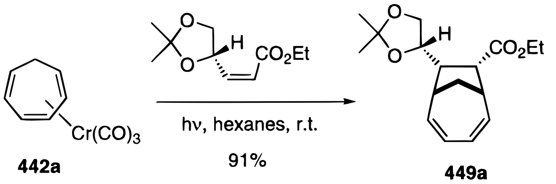


447 **448**

E = CO_2Me

(106)

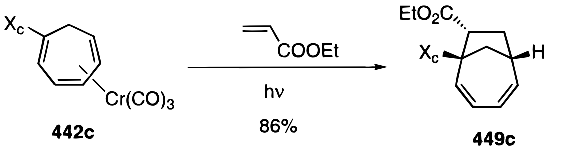
Studies to control of the absolute stereochemistry have been reported. Use of a chiral sultam gives the adduct in 55% de, whereas **449a** was obtained in 91% de when a *cis* γ-substituted chiral acrylate was reacted with **442a** (eq 107a).[218] Very recently Rigby has shown that enantiomerically enriched cycloadducts can be obtained from cycloadditions of alkenes and tricarbonyl(cycloheptatriene)chromium complexes bearing the chiral auxiliary.[217d] Cycloaddition of **442c** with ethyl acrylate afforded **449c** in 86% yield with de >98% (eq 107b).



442a

449a
91% de

(107a)

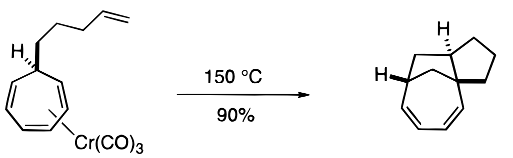


442c
X_c = isopinocampheol

449c
>98% de

(107b)

Rigby has also reported that the intramolecular cycloaddition of **450** occurs with a simple unactivated olefin under thermal conditions. Isomerization of the complex to the 1-substituted CHT−chromium complex precedes the cycloaddition process (eq 108).

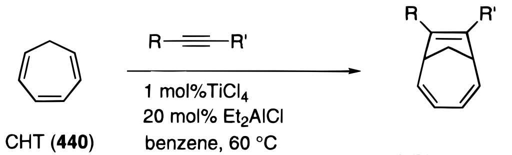


450 **451**

(108)

A catalytic amount of a molybdenum oxadiene complex (3−5 mol %) was recently shown by Schmidt to induce a stereoselective cycloaddition between pinocarvone and cycloheptatriene (50 °C in THF) furnishing a [6 + 2] adduct in 94% isolated yield.[219] A molybdenum complex was reported by Green to catalyze a [6 + 2] cycloaddition between CHT or COT and a disubstituted acetylene.[220]

Mach reported that a titanium complex induces cycloaddition with an unactivated acetylene such as bis(trimethylsilyl)acetylene to provide **452a** in 78% isolated yield, whereas diphenylacetylene gave **452b** in only 21% yield (eq 109).[213] The major product in the latter reaction was hexaphenylbenzene (57%) which arises from a [2 + 2 + 2] cycloaddition. 2-Butyne gave only hexamethylbenzene using titanium catalysts and an allyl complex in the presence



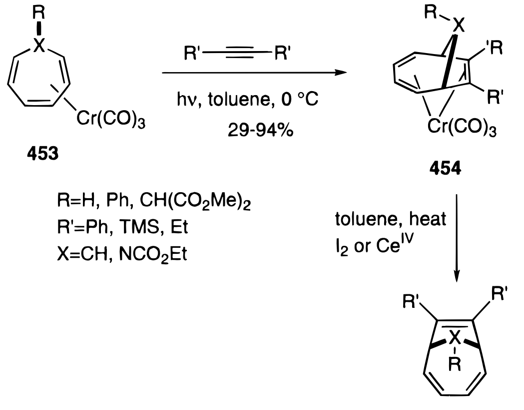
CHT (**440**)

(109)

452a: R,R'=TMS, 78%
452b: R,R'=Ph, 21%

of molybdenum. The intramolecular titanium-catalyzed cycloaddition of a trienyne does not appear to have been explored.

Sheridan has extended these studies to include chromium complexes and found that (CHT)Cr(CO)$_3$ **453** and electron-poor alkynes such as dimethyl acetylenedicarboxylate react under photolytic conditions in toluene or hexane to give a metal complex of the cycloadduct.[221] The reaction is significantly more general than reactions with titanium since a variety of disubstituted acetylenes react to give bicyclic adducts of general structure **454** in 29−94% yield with little competing acetylene trimerization (eq 110).



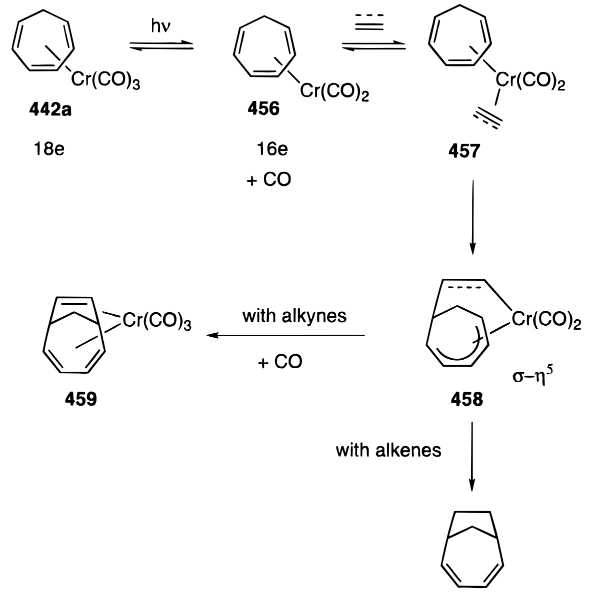
453 **454** **455**

(110)

Demetalation can be achieved by transfer of the Cr(CO)$_3$ unit to toluene or under oxidative conditions. Catalytic reactions between CHT and various electron-rich alkynes has been achieved using 10 mol % Cr(CO)$_6$ or Fe$_2$(CO)$_9$ in *n*-Bu$_2$O at reflux for 2−3 days. It is particularly impressive that 2-butyne gives an 81% yield of the final adduct since unhindered alkynes are prone to undergo the trimerization reaction described above.

The detailed mechanism of the [6 + 2] cycloaddition is not known but a reasonable proposal can be put forward in analogy with data on the related [6 + 4] cycloadditions presented by Kreiter and Rigby and examined in detail by Stufkens (Scheme 43).[218,222] Photolysis of the metal complex would generate a coordinatively unsaturated 16-electron species (**456**) via ejection of a CO ligand or by a hapticity slippage of the CHT from η^6 to η^4. Following complexation of the alkene (or alkyne) to the metal (**457**), the first carbon−carbon bond is formed. The resulting oxidized metal species (**458**) with a σ-metal−carbon bond and an η^5 bond undergoes reductive elimination to form the cycloadduct as its metal complex. Decomposition of the metal then occurs to liberate the free organic species for alkene cycloadditions. If an alkyne is used as the two-electron component, the CO ligand must be recaptured in order to generate the known cycloadduct−Cr(CO)$_3$ complexes (**459**) which are isolated.

Scheme 43

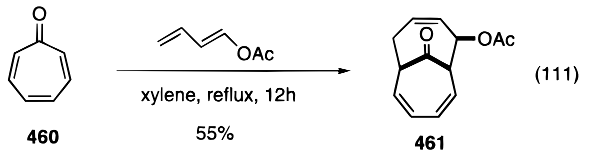


442a **456** **457** **459** **458**

In summary, the field of [6 + 2] cycloadditions has expanded rapidly in the past 10 years. The development of better catalysts, improvements in the enantioselective process, and additional applications of the methodology to natural and unnatural product synthesis lie ahead.

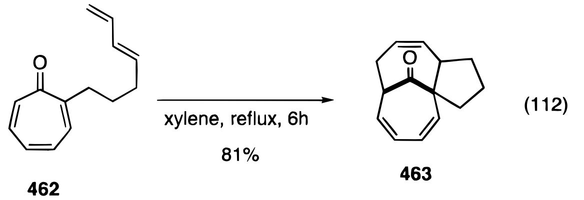
8. Ten-Membered Ring Formation

[6 + 4] cycloadditions are thermally allowed processes according to the Woodward−Hoffmann rules. In spite of this situation, cycloheptatriene itself is notoriously poor as a six-electron partner and typically yields a complex mixture of cycloadducts. In contrast, tropone **460** is reasonably well behaved and typically reacts via an exo transition state leading to bicyclo[4.4.1]undecanones in modest to excellent yield (eq 111).[223] The intramolecular cycloaddition has also been reported (eq 112).



460 **461**

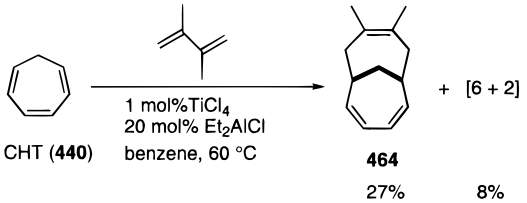
(111)



462 **463**

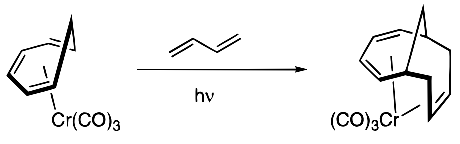
(112)

Transition metals promote the cycloaddition of cycloheptatriene (CHT) **440** and various substituted cycloheptatrienes and therefore offer an advantage over thermal reactions. During a study of titanium-catalyzed cycloadditions between CHT and dienes, Mach observed that a [6 + 4] adduct predominated when 2,3-dimethylbutadiene was used.[213] However, the yield of **464** was only 27% and all other dienes gave predominantly the [6 + 2] adduct (eq 104 vs eq 113).



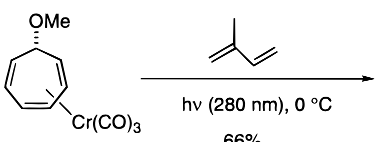
CHT (**440**) **464** (113)

Kreiter observed that photolysis of the chromium cycloheptatriene complex **442a** in the presence of a diene leads to a [6 + 4] cycloadduct (**465**) (eq 114).[214,215] This utility of metal complexes in promoting this process has been expanding rapidly in the past five years.

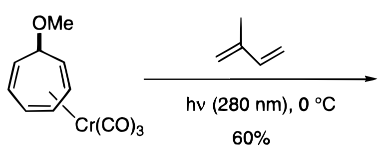


442a **465** (114)

Rigby found that treatment of adducts of general structure **465** with trimethyl phosphite demetalated the organic moiety in good overall yield and showed that improved yields of adducts bearing electron-rich dienes were obtained if the photolysis reactions were carried out under a blanket of carbon monoxide. Reaction of the stereoisomeric complexes **466** and **468** with isoprene demonstrated that the reaction was stereospecific and occurs through the metal (eqs 115 and 116).[224]

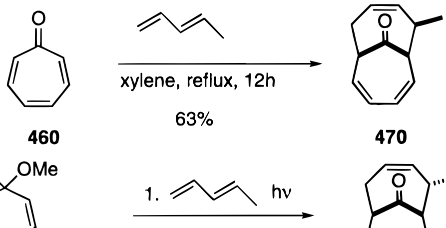


466 **467** (115)

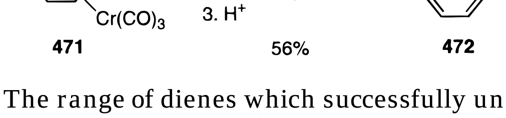


468 **469** (116)

The metal-catalyzed process gives adducts of complementary stereochemistry to those formed in the thermal reaction as demonstrated in the reactions of **460** and **471** (eqs 117 and 118).

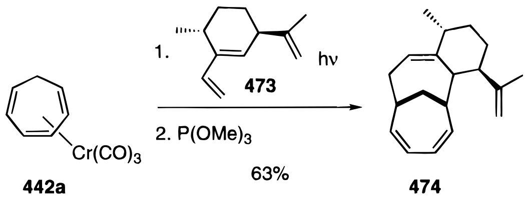


460 **470** (117)



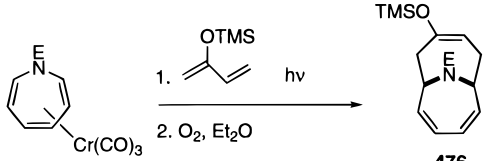
471 **472** (118)

The range of dienes which successfully undergo the cycloaddition is significantly broader than those reported in the thermal process. Electron-rich and electron-poor dienes react in yields of 80–96% under the conditions optimized by Rigby. Furthermore, hindered dienes such as **473** undergo highly diastereoselective cycloaddition with **442a** to provide the ring system of the sesterterpene cerorubenol **474** (eq 119). Unidentified products were formed when tropone was heated with the diene demonstrating the importance of the metal.

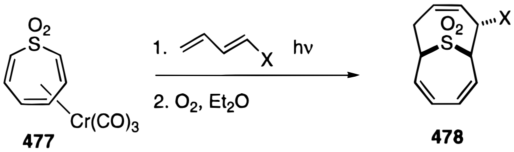


442a **474** (119)

Azepine and thiapene 1,1-dioxide complexes (**475** and **476**) also participated as triene partners in the [6 + 4] cycloaddition and typically provided the adducts in >65% yield (eqs 120 and 121). The only exception was the reaction of thiapene 1,1-dioxides with electron-poor alkenes which generally gave 21–38% yields.



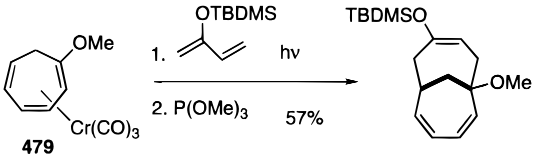
475 **476** (120)



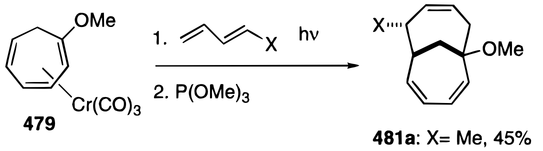
477 **478** (121)

X=OTMS, 65%
X=OAc, 78%
X=CO_2Me, 38%

The regioselectivity in cycloadditions between substituted CHT's and butadienes has also been investigated. Both 2- and 3-substituted CHT's bearing a carbomethoxy or methoxy group react with electron-rich and electron-poor dienes with little or no selectivity although the yields are typically >75%. However, **479** does react with a 2-siloxybutadiene with good selectivity in analogy with the results obtained in the [6 + 2] cycloaddition reactions (eq 122). Isoprene reacts with **479** to give the same major product but with only 3:1 selectivity. When a 1-substituted butadiene undergoes cycloaddition, the product obtained can be rationalized on the basis of "steric approach control" (eq 123).



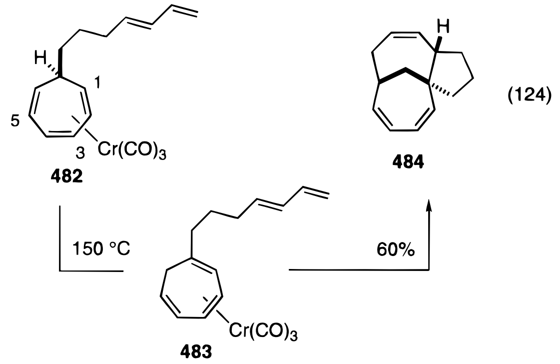
479 **480** (122)



479 (123)

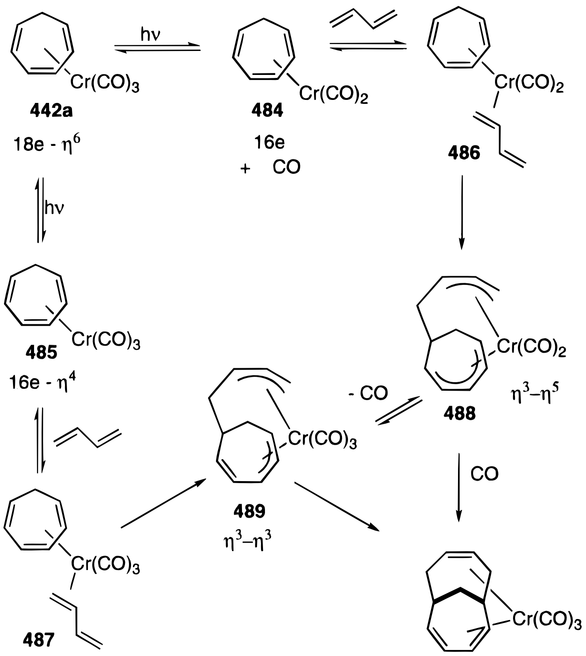
481a: X= Me, 45%
481b: X=OTMS, 38%

Intramolecular cycloadditions have also been reported. For example, complex **483** undergoes cycloaddition to **484** in 90% yield when photolyzed. Thermolysis of **482** also gives **484** but isomerization to **483** proceeds the cycloaddition (eq 124).



There has been significant interest in the mechanism of the [6 + 4] cycloaddition with important contributions from Kreiter, Rigby, and Stufkens.[214,222,225] The reaction pathway may be very similar to the one followed in the [6 + 2] reaction. It is not yet clear if the mechanism is identical for all classes of dienes and trienes but certain steps appear to be common to the various reactions. Two proposals have been put forward and both follow a stepwise pathway rather than a concerted reaction (Scheme 44). Photolysis generates an coordinatively unsaturated species either by loss of CO (**484**) or by a hapticity slippage (**485**). Complexation to the diene (**486** or **487**), oxidative coupling, and reductive elimination provides the cycloadduct–chromium complex. Ejection of CO in the first step with eventual formation of **488** requires CO be present to recomplex and form **489** which continues toward the isolated product. Hapticity slippage via **485** does not require this series of events. Rigby observed that added CO leads to improved yields with electron-rich dienes. In one case the cycloadduct was not formed until excess CO was added and the unstable intermediate showed only two CO stretches in the IR spectrum. Stufkens' low-temperature experiments support this pathway.

Scheme 44



A limitation of the current methodology is that catalytic reactions have not yet been developed which would significantly enhance the utility of the this reaction. Nevertheless the ability to promote an otherwise difficult reaction and modulate the stereochemistry by the presence of the metal warrants further study in this area.

9. Conclusion and Remarks

The use of metal catalysts to promote cycloaddition reactions is growing at an exponential rate. Some metal catalysts induce otherwise impossible reactions to occur while others simply accelerate the rate of known reactions. The ability to alter the regio-, chemo-, and stereoselectivity of reactions compared to thermal or Lewis acid-catalyzed processes is an important feature associated with metal complexes. Enantioselective transformations have been achieved but further advances in this area can be expected as more active catalysts are discovered and new classes of ligands are designed. Since most cycloaddition reactions appear to have no equivalent biotransformation, organic chemistry will play the key role in advancing this field.[226]

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