Addition of Metal Enolate Derivatives to Unactivated Carbon−Carbon Multiple Bonds

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1. Introduction

Because of the presence of their π-system, electron-rich alkenes and alkynes are prone to react as nucleophiles with various electrophiles. The complexation of an alkene or alkyne moiety with a metal salt can reverse this reactivity, and nucleophiles can then add onto the unsaturated system.[1] The efficiency of the activation (particularly with transition metal species) can be so important that stabilized nucleophiles such as enolates and related species can undergo a carbometalation reaction onto unactivated unsaturated systems. This reaction mode is highly interesting, both for its synthetic utility and its mechanistic features: indeed these addition reactions of enolate-type nucleophiles onto unsaturated systems can be considered endothermic since the resulting organometallic species is less stabilized than the starting one (Scheme 1).

This review covers the literature up until 2009 and is focused on the carbometalation of alkenes, alkynes, arenes, and related unsaturated systems involving stabilized anions such as enolates, malonates, and related stabilized nucleophiles. Related reactions, for example, additions of enamines or enols, as in the Conia-ene reaction,[2] will not be considered in detail. However, as it is sometimes difficult to distinguish between "true" carbometalation processes and other related mechanisms, these alternative processes will be mentioned when necessary or relevant. We will focus this review only on the substrates where the unsaturation partner is not activated by an electron-withdrawing group. However, the activation of the unsaturated system by heteroatom or aromatic (heteroaromatic) substituents will be included in the scope of this review.

Nucleophilic addition onto unactivated C−C multiple bonds requires the activation via complexation with a metal salt. This activation can be achieved either in an intramolecular or intermolecular manner. In a number of cases it is difficult to know whether the activation of the unsaturated partner is achieved by the metal enolate (intramolecular pathway, Scheme 2) or by an extra metal species (intermolecular pathway). Depending upon the metal and the nucleophile used for this transformation, the stereochemistry of the addition can be either *anti* or *syn*. For clarity reasons, the classification of the carbometalation processes within this review will be made by taking into account the nature of the metal species employed to activate the unsaturation, no matter what the nature of the metal enolate.

The review is organized with respect to the nature of the unsaturated partner: alkenes, dienes (1,2-dienes and 1,3-dienes), alkynes, and arenes. As we will see, not only transition metals but also simple alkali metals can mediate this transformation. The reaction can be conducted either in an intramolecular or intermolecular manner yielding interesting building blocks, often with high regio- and/or diastereoselectivity. The recent advances in this field are reviewed here.

Some of these carbometalation processes have already been reviewed elsewhere. For example, previous reviews focused only on the addition of zinc enolates (and related stabilized anions) onto unactivated alkenes have appeared,[3,4] as well as more general reviews dealing with carbometalations of alkenes and alkynes using zinc,[3] palladium,[5,6] and gallium.[7] More general reviews dealing with carbometalation reactions,[8] heteroatom-directed carbometalation reactions,[9] and enantioselective carbometalations of unactivated olefins[10] have also appeared. However, no comprehensive review presenting specifically the *reactivity of enolates and related stabilized organometallic nucleophiles toward electron-rich π-systems* has been published thus far.

Dr. Fabrice Dénès was born in Paris, France, in 1975. After undergraduate study at the University Pierre et Marie Curie (Paris VI), he received his Ph.D. in 2002 under the supervision of Prof. J.-F. Normant and Prof. F. Chemla. From Sept. 2002 to Feb. 2005, he was a postdoctoral associate of Prof. P. Renaud at the University of Bern (Switzerland). In 2005, he moved to the University of Nantes (France), where he was appointed assistant professor in the group of Prof. J. Lebreton and Dr. A. Guingant. His research interests include the development of synthetic methods based on organometallic or radical reactions, as well as the synthesis of natural products and/or analogues possessing a biological activity.

Dr Alejandro Pérez-Luna was born in London in 1977. He obtained an engineer diploma from the Ecole Nationale Supérieure de Chimie de Paris in 2000. After his Ph.D. in Professor Husson's laboratory (Université Paris 5) under the guidance of Dr Micouin in 2003, he joined Professor Kündig's group in Geneva (Switzerland) for a postdoctoral stay as a Lavoisier Fellow. He took up a permanent position in CNRS in 2004 as Chargé de Recherche in Professor Chemla's group (UPMC, Paris 6). His scientific interests include the fields of metal-mediated synthesis, organozinc chemistry, and asymmetric synthesis.

2. Addition of Stabilized Carbanions onto Alkenes

2.1. Group 1, Alkali Metals: Lithium, Sodium, and Potassium

Alkali enolates were recognized to react with alkenes at a quite early stage. In the mid-1950s, Magnus and Levine reported that the carbanions obtained by treatment of several nitriles with sodium could undergo addition onto vinylpyridines.[11] Following this early report, several bases have been shown to catalyze the addition of nitriles onto aryl-conjugated substrates. NaH- and lithium diisopropylamide (LDA)-catalyzed additions of isobutyronitrile onto styrenes and

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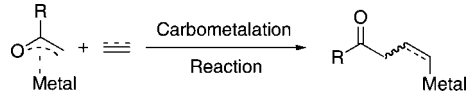
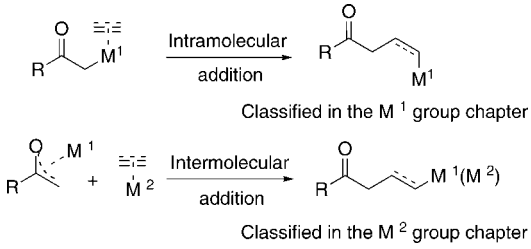
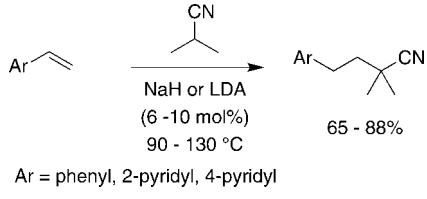
Scheme 1



Scheme 2



Scheme 3

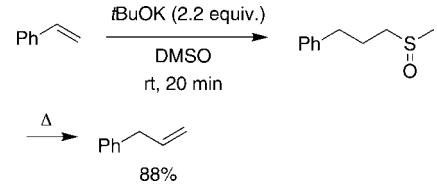


vinylpyridines have been used to prepare interesting adducts for perfumery applications (Scheme 3).[12]

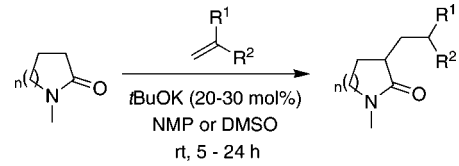
In the 1960s, Walling and Bollyky reported the base-catalyzed addition of dimethyl sulfoxide onto aryl-conjugated olefins, styrene, and 1,1-diphenylethylene. The reaction occurred rapidly at room temperature and gave the corresponding methyl 3-arylpropylsulfoxides in high yields.[13] Pyrolysis of the resulting sulfoxides gave the corresponding 3-arylpropenes in high yields with no double-bond isomerization (Scheme 4). The reaction failed with simple aliphatic olefins.

Pines and co-workers reported that enolates of *N*-methyl-2-pyrrolidinone and *N*-methyl-2-piperidone add onto aryl-conjugated olefins and vinylsilanes in the presence of a catalytic amount of *t*BuOK (Scheme 5).[14] The presence of

Scheme 4



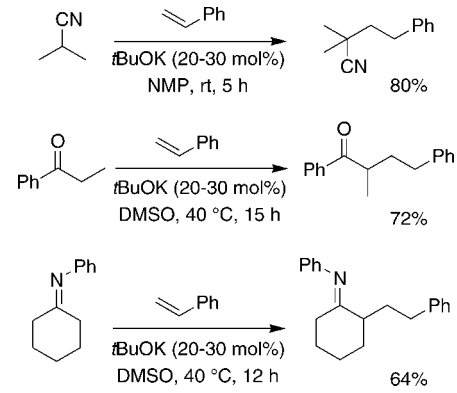
Scheme 5



n = 1, 2	R^1 = Ph	R^2 = H	99%
	Ph	Me	99%
	TMS	H	99% *

* mono-adduct/bis-adduct = 67:33

Scheme 6

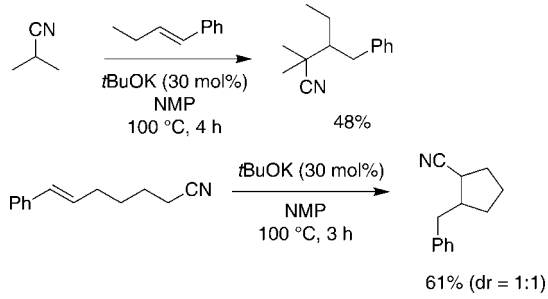


dimethylsulfoxide (DMSO) facilitated the addition onto α-methylstyrene and was crucial to achieve the addition onto vinylsilanes. In some cases, compounds resulting from a double addition process were observed as byproducts in the reaction mixture.

Recently, Knochel and co-workers have extended this methodology to include the addition of potassium anions derived from nitriles, ketones, and imines onto styrene derivatives (Scheme 6). The monoaddition products were obtained in good to high yields by using a catalytic amount of *t*BuOK in DMSO or *N*-methylpyrrolidone (NMP). Control of the temperature (38−41 °C) was found to be crucial in order to limit the formation of products resulting from a double addition. However, in some cases, the bisalkylated products could be isolated in 6−11% yields.[15]

Anions derived from nitriles exhibited the highest reactivity. Regioselective addition onto styrenes having a terminal carbon−carbon double bond could be achieved at room temperature in NMP using *t*BuOK as a catalyst and furnished the adducts in 74−91% yields. The presence of electron-withdrawing substituents such as fluorine or bromine considerably shortened the reaction times. By contrast, the presence of an additional substituent onto the double bond of the styrene moiety slowed down the reaction, which required then higher temperatures, even in intramolecular additions (Scheme 7). Interestingly, no influence was noted when radical traps were added. This, coupled to the reactivity of 2-substituted styrenes, seems to indicate that the reactive species is not a radical.

Scheme 7



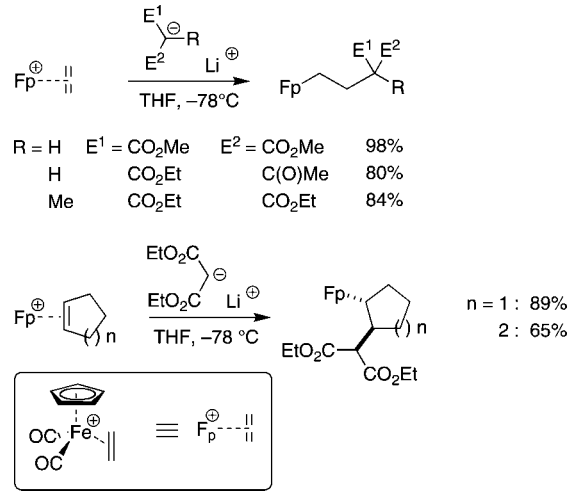
Very recently, *t*BuOK was found to promote the cyclization of 2-allyl-phenoxy-1-aroylethanone derivatives (Scheme 8).[16] While the use of only 1 equiv of *t*BuOK at 0 °C in tetrahydrofuran (THF) resulted in the migration of the carbon−carbon double bond into the benzylic position, 6-*endo*-cyclization took place in the presence of a 2-fold excess of *t*BuOK in refluxing THF. The proposed mechanism involves the addition of the potassium enolate onto the alkene moiety, followed by isomerization of the resulting carbanion into the more stable potassium enolate. The latter leads to the observed mixture of diastereoisomers via a protonation−deprotonation sequence with *t*BuOH/*t*BuOK.

2.2. Group 8: Iron-Mediated Additions

Complexation with iron efficiently activates alkenes toward the addition of metal enolates. Accordingly, strategies involving the use of preformed cationic (η^2-alkene)Fe(I) and neutral (η^2-alkene)Fe(0) complexes have been disclosed.

Cationic (η^2-alkene)Fe complexes can be prepared by reaction of (η^5-C_5H_5)Fe(CO)$_2$(Br) with olefins in the presence of Lewis acids,[17,18] by protonation of (η^1-allyl)(η^5-C_5H_5)Fe(CO)$_2$ complexes,[19] or by hydride abstraction from alkyl−(η^5-C_5H_5)Fe(CO)$_2$ complexes.[20] They are also readily accessible either by ligand exchange[21] or nucleophilic ring-opening of epoxides.[22] In the early 1970s, Rosenblum and co-workers reported the intermolecular addition of a variety of enolate anions onto cationic (η^2-alkene)(η^5-C_5H_5)Fe(CO)$_2$ (Fp(alkene)) complexes leading to the corresponding neutral complexes in moderate to good yields (Scheme 9).[23,24] The addition of lithium dialkyl malonates and ethyl acetoacetate onto the ethylene complex could be achieved at −78 °C in THF and led to the formation of the corresponding adducts in acceptable to excellent yields. With substituted alkenes,

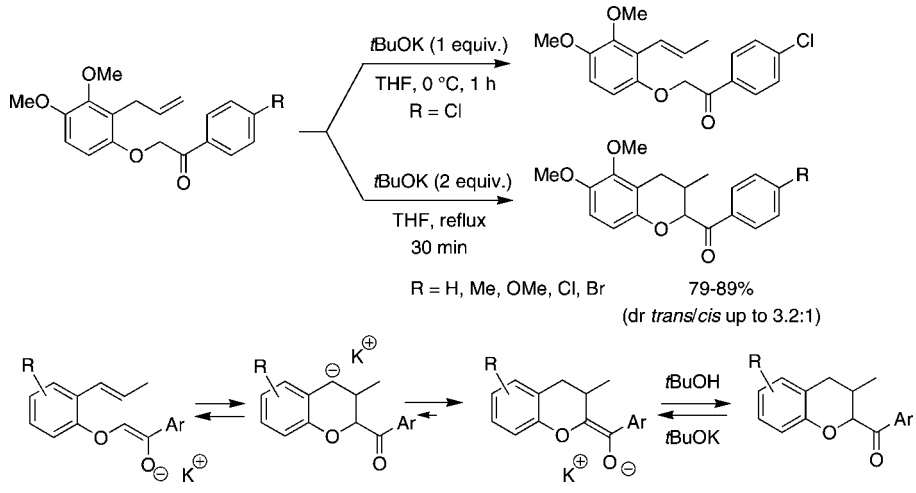
Scheme 9



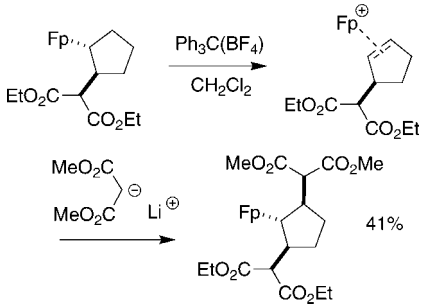
even if yields were also high, the regioselectivity was variable. For instance, the addition of lithium dialkyl malonates and ethyl acetoacetate onto the propene complex were poorly regioselective (2:1 and 3:1, respectively),[24,25] while the reaction with the styrene complex furnished a single regioisomer with each nucleophile, with the attack taking place exclusively at the internal carbon atom of the coordinated olefin. Related nucleophiles such as enamines also reacted efficiently with cationic Fp(olefin) complexes, providing a general and simple route to ketone- or aldehyde-functionalized (alkyl)Fp complexes.

Contrary to the addition of heteroatomic nucleophiles, the addition of enolate anions onto cationic Fp(olefin) complexes is not a reversible process. The addition of nucleophiles onto cationic Fp(olefin) complexes was found to proceed in a stereospecific manner with acenaphthalene complexes[26] and was expected to be general for all addition onto cationic Fp(olefin) complexes. Other possible reaction pathways, including nucleophilic addition onto the cyclopentadienyl ring or onto a carbonyl ligand, allylic deprotonation, displacement of the olefinic ligand, and formation of complex dimer−olefin ($C_5H_5Fe(CO)_2)_2$, have generally not been observed with simple olefin complexes. The corresponding cyclopentene and cyclohexene complexes were also found to be excellent substrates, affording the adducts in high yields upon reaction with a number of enolate derivatives (Scheme 9). As with acyclic olefin complexes, deprotonation of these

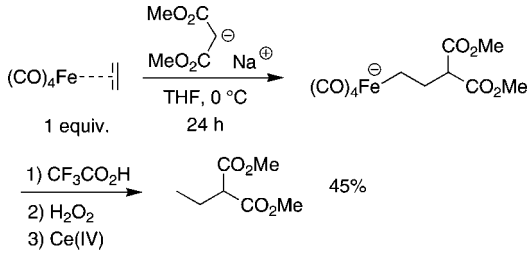
Scheme 8



Scheme 10



Scheme 11

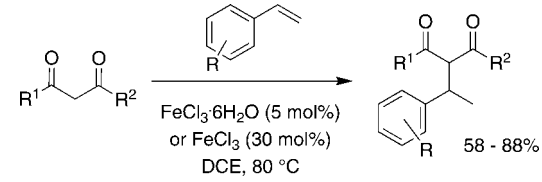


cations did not compete with nucleophilic addition onto the activated olefin. However, a displacement process became the dominant reaction mode with cationic Fp(cyclooctene) and *exo*-Fp(norbornene) complexes where steric effects block *trans*-addition onto the coordinated olefin, or in the addition of more hindered nucleophiles such as diethyl methylmalonate or diethyl phenylmalonate anions onto the cationic Fp(cyclohexene) complexes.

Although nucleophilic addition of stabilized anions onto cationic Fp(olefin) complexes could be very easily achieved, the resulting carbon−iron bond was found to be relatively unreactive. Upon treatment with HBF_4 in Et_2O or with HCl in CH_2Cl_2, the adducts led to reversion into the unsubstituted cationic Fp(olefin) complexes, with the exception of the Fp(cyclopentene) complex. In this case, double addition of malonate could be achieved through a sequence involving a β-hydride abstraction (upon treatment with $Ph_3C(BF_4)$ or HBF_4) followed by nucleophilic addition of a second malonate anion. The product of β-hydride abstraction was obtained in high yield, and the addition of methylmalonate anion gave the product resulting from a double addition in 41% yield as a single isomer (Scheme 10). From a more general point of view, removal of iron moiety from the organic substrate following addition has been achieved upon oxidative cleavage with ceric ammonium nitrate (CAN) in MeOH saturated in carbon monoxide.

Because of their low stability, neutral (η^2-ethylene)$Fe(CO)_4$ complexes have been seldom used, and very few examples of their reaction with stabilized nucleophiles have been reported. Reaction of (η^2-ethylene)$Fe(CO)_4$ with sodium dimethyl malonate at 0 °C in THF, followed by addition of trifluoroacetic acid and oxidation of the iron species, furnished dimethyl ethylmalonate in 45% yield (Scheme 11).[27] It is assumed that the steric accessibility and the formation of an alkyltetracarbonylferrate anion might provide a driving force for the preferential attack of a nucleophile onto the coordinated olefin rather than onto a CO ligand. The proposed mechanism consists of the addition of the malonate anion onto the (η^2-alkene)Fe complex. Upon treatment with trifluoroacetic acid (TFA), the resulting anionic alkyltetracarbonylferrate intermediate leads to the formation of a hydridoalkyl−$Fe(CO)_4$ complex, which undergoes reductive elimination to give the observed product.

Scheme 12



R^1 = Me, Ph; R^2 = Me, Ph, OMe; R = H, Me, Cl, Br

As opposed to the above-mentioned reaction of stabilized nucleophiles onto (η^2-alkene)Fe complexes, the related iron-catalyzed hydroalkylation reactions are scarce. Only lately Wu, Duan, and co-workers[28] and Beller and co-workers[29] have shown independently that the addition of 1,3-dicarbonyl compounds onto aromatic alkenes could be achieved in the presence of $FeCl_3$ and $FeCl_3 \cdot 6H_2O$, respectively. In both cases, the optimized conditions involved the reaction of an excess of the dicarbonyl compound at 80 °C in 1,2-dichloroethane with catalyst loadings of, respectively, 30 mol % and 5 mol %. Aliphatic and aromatic 1,3-diketones and β-ketoesters were found to react regioselectively with a range of styrenes, furnishing the corresponding adducts in moderate to good yields (58−88%) from regioselective addition at the internal carbon. Interestingly, the reaction could be carried out under an air atmosphere, and addition of a small amount of water did not dramatically lower the yields (Scheme 12).

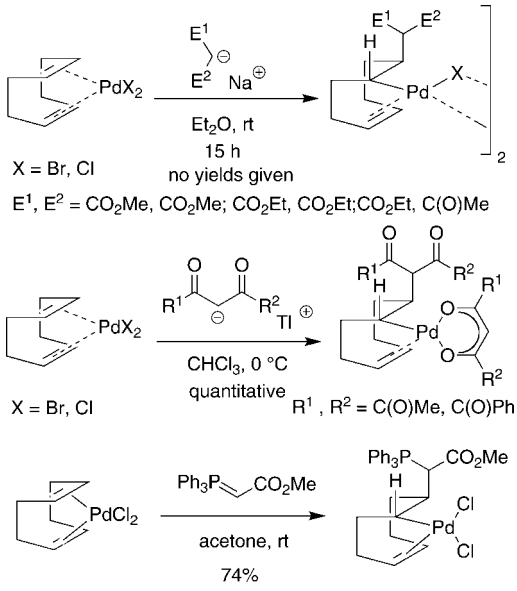
2.3. Group 10: Palladium and Platinum

2.3.1. Palladium(II)-Mediated Additions

Complexation with palladium(II) salts activates alkenes very efficiently toward additions of nucleophiles, including stabilized metal enolates and silyl enol ethers. Carbopalladation leads to σ-alkylpalladium species, which have a marked tendency to undergo β-hydride elimination. As a consequence, many of the established synthetic methods lead to unsaturated products. However, strategies to prevent or override the β-elimination have also been successfully developed, thus allowing either the reduction of the C−Pd bond to produce saturated compounds or its subsequent reaction in new C−C bond-formation processes. Early examples involved the use of stoichiometric amounts of the activating metal and offered the possibility to gain in-depth knowledge of the carbopalladation reaction. Later, as a consequence of the high cost and troublesome removal of palladium salts in the case of large-scale reactions, significant efforts have been made to develop catalytic approaches.

2.3.1.1. Enolates as Nucleophiles. *2.3.1.1.1. Intermolecular Additions.* In the mid 1960s, the first examples of nucleophilic addition of the enolate of β-dicarbonyl compounds onto (η^4-1,5-cyclooctadiene)PdX_2 (X = Cl, Br) complexes ((cod)PdX_2 complexes) were reported by Tsuji and Takahashi.[30,31] The addition of an excess of the sodium anion of dialkyl malonates (R = Me, Et), ethyl acetoacetate, and 1,3-diketones onto (cod)PdX_2 complexes was achieved at room temperature in Et_2O and led to the formation of bridged binuclear complexes, which were stabilized by intramolecular complexation with the pendant π-system (Scheme 13).[31,32] Addition of the related thallium anion of 1,3-diketones onto (cod)PdX_2 complexes led to β-diketonate derivatives.[33−36] More recently, Vicente and co-workers have reported the addition of stabilized phosphorus ylides onto

Scheme 13

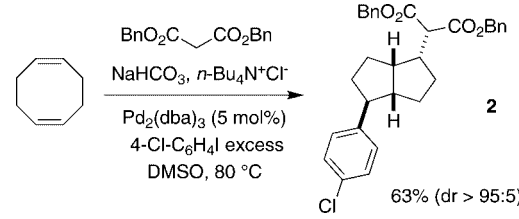


(cod)$PdCl_2$ complexes in acetone.[37] Mechanistically, an *anti*-addition process was proposed in the initial reports 19 and has been supported more recently by X-ray and NMR studies. This *anti*-addition process is consistent with the mechanism of addition of other soft nucleophiles onto (η^2-alkene)Pd.[32]

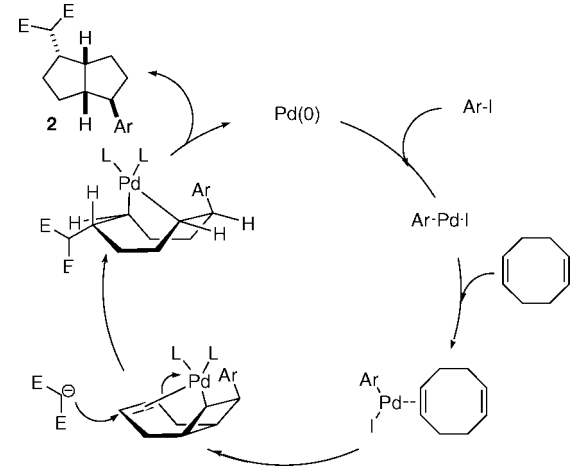
Being unusually stable toward β-hydride elimination, the resulting σ-alkyl−Pd adducts such as **1** offered the possibility for several subsequent functionalizations (Scheme 14).[31] Alternatively, upon treatment with $Ph_3C(BF_4)$ or HF, the β-diketonate derivatives led to the formation of cationic Pd−diene complexes via removal of the β-dicarbonyl compound from the diene ligand.[35,36]

In 2004, Hulin and co-workers reported a catalytic version of the Pd(II)-mediated addition of malonates onto 1,5-cyclooctadiene involving the use of only 5 mol % of palladium.[38] In a first approach, the reaction was carried out in DMSO in the presence of O_2 (1 atm) to reoxidize the Pd(0) formed by reductive elimination. Alternatively, generation of the Pd(II) species required for the activation of the alkene could also be achieved by insertion of Pd(0) into the C−X bond (X = I, OTf) of an aryl iodide or triflate (for related reactions, see section 2.3.1.1.2.a). For instance, intermolecular addition of the sodium dibenzyl malonate anion onto 1,5-cyclooctadiene led to bicyclic compound **2** in 63% yield and excellent diastereoselectivity (dr > 95:5) in the presence of a catalytic amount of tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$) and an excess of 4-Cl−C_6H_4I (Scheme 15).

Scheme 15



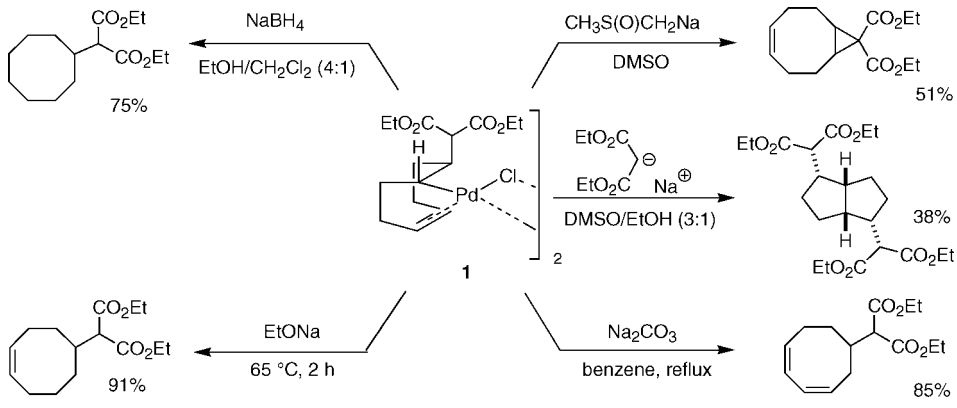
Scheme 16



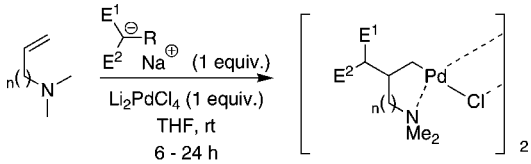
The stereochemical outcome of the process was explained on the basis of a mechanistic picture involving a sequential Heck reaction (*syn*-addition process), followed by the *anti*-addition of the malonate anion onto the resulting σ-alkyl−Pd(alkene) complex intermediate. The observed product **2** is obtained from the newly formed σ-alkyl−Pd complex following reductive elimination (Scheme 16). An alternative mechanism involving *anti*-addition of the malonate anion onto a Pd(II)−alkene complex prior to Heck reaction has also been proposed.

Holton and co-workers developed an efficient Pd(II)-promoted addition of 1,3-diketones, malonate and β-ketoester derivatives, onto allylic[39] and homoallylic[40] amines (Scheme 17) and sulfides. In the presence of a stoichiometric amount of Li_2PdCl_4, various 1,3-dicarbonyl compounds were found to add efficiently onto allylamines and allyl sulfides at room temperature in THF. In all cases, a complete regioselectivity was observed, with the addition taking place exclusively at the internal position of the alkene. As for the 1,5-cyclooc-

Scheme 14

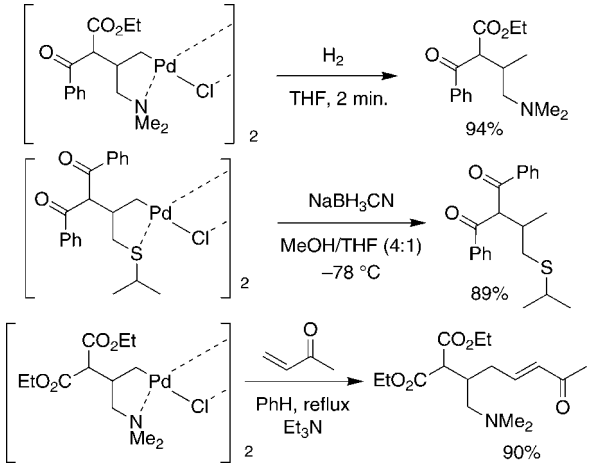


Scheme 17



n = 1	R = H	E^1 = CO_2Et	E^2 = CO_2Et	91%
1	H	CO_2Et	C(O)Me	93%
1	H	C(O)Ph	C(O)Ph	89%
1	Et	CO_2Et	CO_2Et	81%
2	H	CO_2Et	CO_2Et	86%

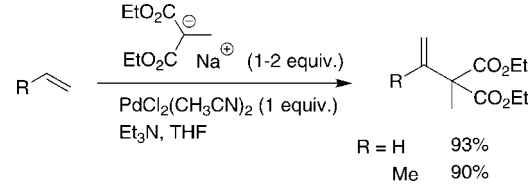
Scheme 18



tadiene case, stabilization by intramolecular complexation rendered the resulting dimeric σ-alkylpalladium complexes non-air- nor moisture-sensitive, thus allowing their isolation in high yields (81−95%). Rather surprisingly, allyl alcohols and allyl ethers did not react under these conditions. Likewise, less stabilized anions such as ketone or ester enolates did not give any addition product.

Several synthetic transformations could be performed on the complexes resulting from the carbopalladation. Reduction under different conditions ($NaBH_4$, $NaBH_3CN$, or by bubbling H_2 in the solution) could be achieved either in situ or after isolation and gave the corresponding saturated adducts in 89−96% yields (Scheme 18). Alternatively, the σ-alkyl−Pd complexes could also engage in a new C−C bond formation. For instance, the complex obtained by reaction of the diethyl malonate anion with *N*,*N*-dimethylallylamine reacted with methyl vinyl ketone in refluxing benzene and in the presence of Et_3N to give the Heck coupling product in 90% yield.[41] Worthy of note, the addition of sodium diethyl malonate to 3-(*N*,*N*-dimethylamino)cyclopent-1-ene was nicely exploited for the formal synthesis of racemic prostaglandins.[42]

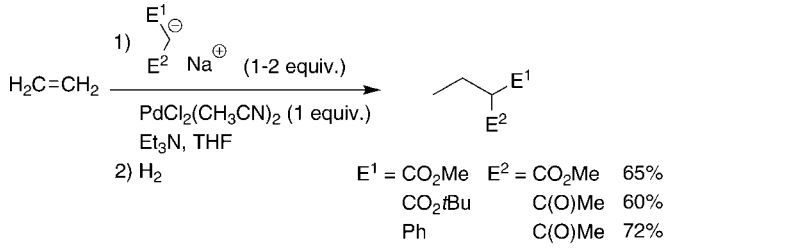
Scheme 20



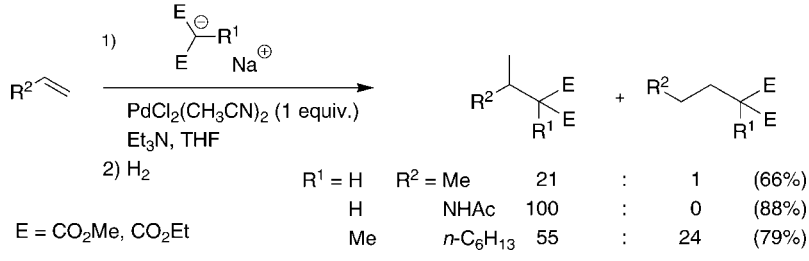
While Li_2PdCl_4 was found to be ineffective in promoting the intermolecular addition of malonate derivatives onto simple olefins, other Pd(II) complexes gave better results.[43] In the late 1970s, Hegedus and co-workers reported that the addition of the sodium or lithium anion of dialkyl malonates, phenyl ketones, and β-ketoesters onto ethylene and terminal alkenes could be achieved in high yields at low temperature in THF by using a stoichiometric amount of $PdCl_2(CH_3CN)_2$ and 2 equiv of Et_3N. The introduction of the latter prior to the anion was found to be crucial for the success of the reaction. Following in situ reduction with H_2, the saturated adducts could be obtained in good to high yields (65−95%) (Scheme 19). The regioselectivity was found to be variable and dependent upon the alkene, the nucleophile, and the reaction conditions. As a general trend, less stabilized anions tended to react at the terminal position of the alkene, whereas attack at the internal position was observed with the more stabilized anions. Internal alkenes such as cyclohexene or (*E*)-but-2-ene did not react under these reaction conditions.

The intermediate σ-alkyl−Pd complexes resulting from carbopalladation were prone to undergo β-hydride elimination, and accordingly, the corresponding unsaturated adducts were obtained in moderate to high yields (53−95%) upon warming (Scheme 20). The use of sodium diethyl malonate usually gave lower yields than substituted sodium diethyl methylmalonate, as a result of the rearrangement of the products into the corresponding alkylidene malonates, which could react further as Michael acceptors.[43,44] Addition of less

Scheme 19



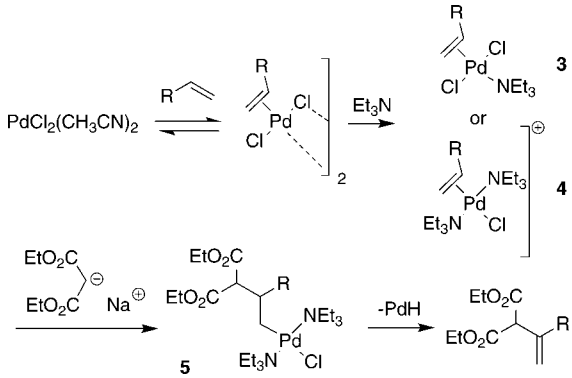
E^1 = CO_2Me	E^2 = CO_2Me	65%
CO_2tBu	C(O)Me	60%
Ph	C(O)Me	72%



R^1 = H	R^2 = Me	21	:	1	(66%)
H	NHAc	100	:	0	(88%)
Me	n-C_6H_{13}	55	:	24	(79%)

E = CO_2Me, CO_2Et

Scheme 21



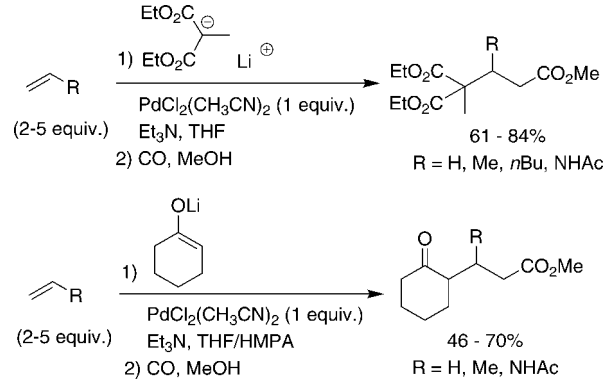
stabilized anions such as ketone- or ester enolates, oxazoline, and cyanohydrin anions were found to be less efficient and required the presence of hexamethylphosphoramide (HMPA) as an additive. Interestingly, besides increasing the reactivity of the anion, HMPA also increased the regioselectivity of the nucleophilic attack.[43,45]

From a mechanistic standpoint, the following picture was put forward (Scheme 21). The initial step involves the formation of a binuclear (η^2-olefin)Pd complex. The addition of Et_3N onto the (η^2-olefin)Pd complex at −60 °C leads to the cleavage of the chlorine bridge and gives either the neutral **3** or cationic **4** reactive Pd species. Low temperature is required for the addition of Et_3N since decomplexation of the alkene ligands with Et_3N becomes a competitive pathway at temperatures higher than −20 °C. The cationic bisamino−Pd complex **4** is expected to be more reactive than the neutral monoamino−Pd species **3**, but the exact nature of the reactive species is only postulated. The *anti*-addition of the stabilized anion onto the (η^2-olefin)Pd complex leads to an unstable σ-alkyl−Pd species **5**, which undergoes β-hydride elimination upon warming to give the unsaturated adducts.

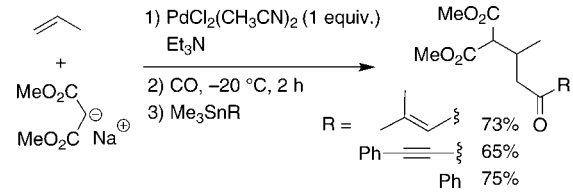
The authors proposed that the difference in the regioselectivity observed depending on the nature of the nucleophile results from a dichotomy in the addition step: while the more stabilized anions react following the described *anti*-addition process at the internal position of the alkene ligand in the (η^2-alkene)Pd complex, less stabilized anions add directly onto the palladium, leading to a σ-alkyl−Pd intermediate that undergoes olefin insertion (*syn*-addition process).

In spite of its rather low thermal stability, the intermediate σ-alkyl−Pd could undergo subsequent transformations other than reduction or β-elimination. For instance, CO insertion could be achieved at low temperature and, following trapping of the resulting σ-acyl−Pd complexes by MeOH, the corresponding methyl ester could be obtained in moderate to good yields (Scheme 22).[46−48] The process called for a two-step sequence because the nucleophilic addition onto the (η^2-olefin)Pd complex had to be complete prior to the introduction of CO in order to avoid displacement of the alkene. The control of the regioselectivity of the addition proved of major importance since secondary σ-alkylpalladium complexes were less prone to undergo CO insertion than the corresponding primary σ-alkylpalladium ones.[49] Indeed, when the nucleophilic addition led to the formation of a primary σ-alkylpalladium intermediate, the process gave the acylated products in good yields (61−84% for the addition of lithium diethyl methylmalonate to terminal alkenes), while complex mixtures resulting from many rearrangements were observed when a secondary σ-alkyl−Pd

Scheme 22



Scheme 23



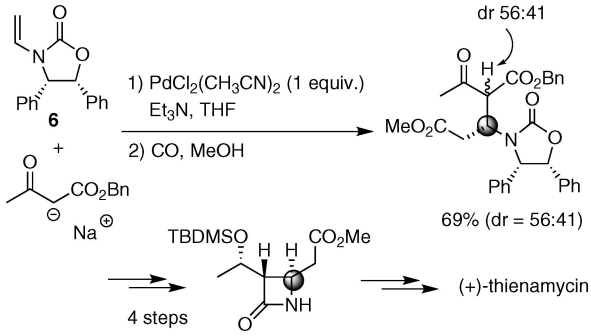
intermediate possessing a β-hydrogen atom was formed. In some cases (e.g., R = n-C_6H_{11}), HMPA was used as a cosolvent in order to increase the regioselectivity of the nucleophilic addition and render the overall sequence more efficient.

The σ-acylpalladium species resulting from CO insertion could also engage in a new C−C bond formation with vinyl-, aryl-, heteroaryl-, and alkynylstannane reagents.[50−52] After addition of a stannyl derivative to the reaction mixture, the corresponding adducts were obtained in good to high yields (59−95%) even from simple terminal alkenes such as propene (Scheme 23).[50,51]

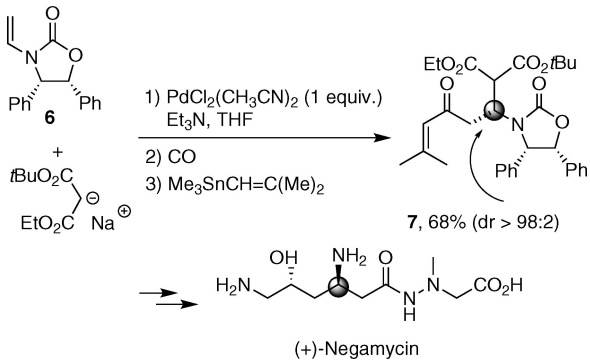
The carbopalladation/functionalization process was very effective when applied to ene−carbamates as, first, the carbometalation was highly regioselective (the addition of the stabilized nucleophile occurring exclusively at the internal position of the C−C double bond) and, second, the resulting σ-alkylpalladium intermediate was again stabilized by internal complexation. Furthermore, enantiomerically pure ene−carbamates could be used, thus providing an entry to asymmetric synthesis. For example, the addition of sodium dimethyl malonate to *syn*-4,5-diphenyl-3-vinyl-2-oxazolidinone **6** followed by CO insertion was carried out under the aforementioned conditions and gave the corresponding adduct in 82% yield as a single diastereoisomer, indicating complete control of the new chiral center. The addition of benzyl acetoacetate gave a mixture of two diastereoisomers (dr = 56:41), out of the four possible isomers. This methodology has been applied to the synthesis of both racemic[47] and optically pure[48] lactam thienamycin (Scheme 24).

Similarly, the palladium-mediated alkylation/carbonylative coupling involving trimethylstannanes and enantiomerically pure ene−carbamates such as **6** or (*S*)- or (*R*)-3-ethenyl-4-phenyl-2-oxazolidinone was achieved in good yields, and again, a high asymmetric induction was observed.[50] In particular, the addition of sodium ethyl *tert*-butyl malonate onto **6** followed by carbonylative Stille-type cross-coupling afforded in 68% yield **7**, a key intermediate for the synthesis of (+)-negamycin and (−)-5-*epi*-negamycin (Scheme 25).[51]

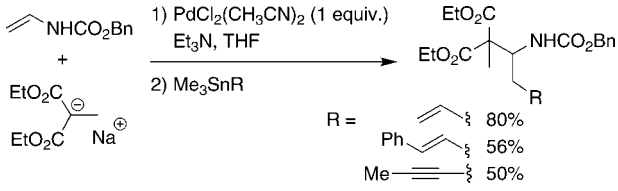
Scheme 24



Scheme 25



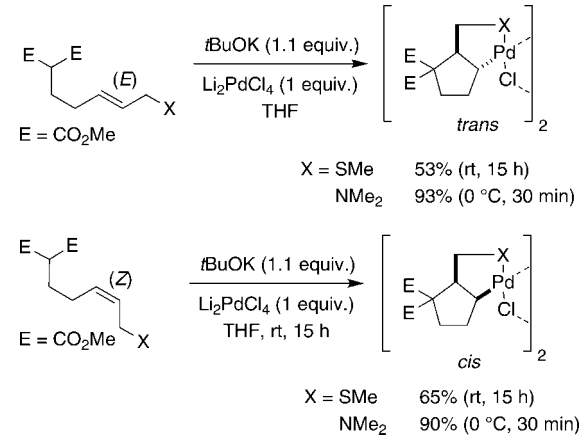
Scheme 26



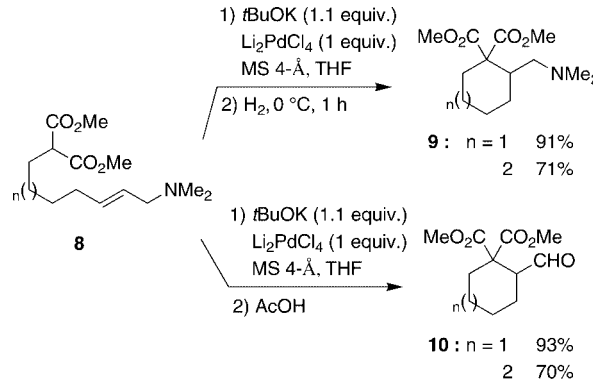
Direct coupling of the σ-alkyl−Pd intermediate resulting from the addition of malonates onto ene−carbamates with vinyl- or alkynylstannanes without previous carbonylation has also been studied.[50] For instance, the intermediate formed by addition of the sodium anion of diethyl methylmalonate onto *O*-benzyl-*N*-vinylcarbamate reacted with trimethylalkenyl- or trimethylalkynylstannanes to give the corresponding adducts in moderate to high yields (50−80%) (Scheme 26). Surprisingly, other unsaturated stannyl derivatives such as the related tri-*n*-butylstannane derivatives gave only low yields under the same conditions. The nucleophilic addition needed to be complete prior to the introduction of the organostannane derivative; otherwise, byproducts formed by homocoupling of the tin reagent were observed. Unlike the carbonylative sequence, this reaction was limited to ene−carbamates, which afforded more stable σ-alkylpalladium species.

2.3.1.1.2. Intramolecular Additions. ***2.3.1.1.2.a. Alkali Enolates As Nucleophiles.*** Ring construction using Pd(II)-promoted intramolecular additions of alkali enolates onto unactivated alkenes has attracted a great deal of attention. Building on their previously developed conditions for intermolecular carbopalladations, Holton and co-workers were able to prepare 5-, 6-, and 7-membered rings by treating malonates bearing pendant allylamines or allyl sulfides with a stoichiometric amount of Li_2PdCl_4 and *t*BuOK.[53] In the case of 5-membered ring formation, the palladacyclic intermediates resulting from the cyclization were isolated in good to high yields (53−93%) either as the *trans*- or *cis*-isomers, depending on the configuration of the starting alkene (*E* vs *Z*) (Scheme 27).

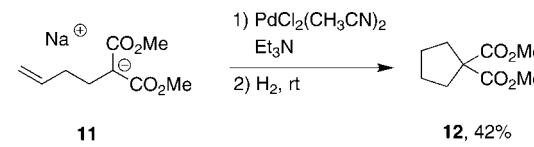
Scheme 27



Scheme 28



Scheme 29

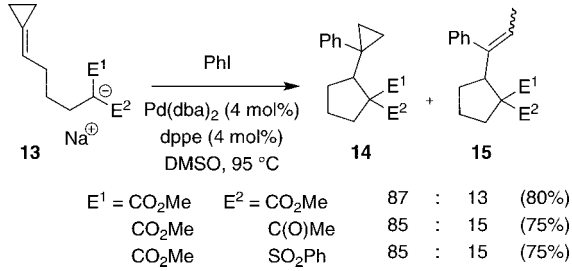


On the contrary, the cyclization of **8** leading to 6- and 7-membered rings resulted in the formation of less stable σ-alkylpalladium complexes. The latter were either reduced in situ with H_2 into the saturated dimethylamino compounds **9** or hydrolyzed in the presence of AcOH to give the corresponding aldehydes **10** (Scheme 28). The authors proposed that, in this case, the unstable palladacyclic intermediate undergoes a base-catalyzed elimination of Pd leading to an iminium ion, which was then either reduced or hydrolyzed depending upon the reaction conditions. Worthy of note, the cyclization onto allyl sulfides appeared less facile, probably due to the stronger electron-donating character of these ligands, which reduces the Lewis acidity of the Pd atom, and thus the activation of the alkene.

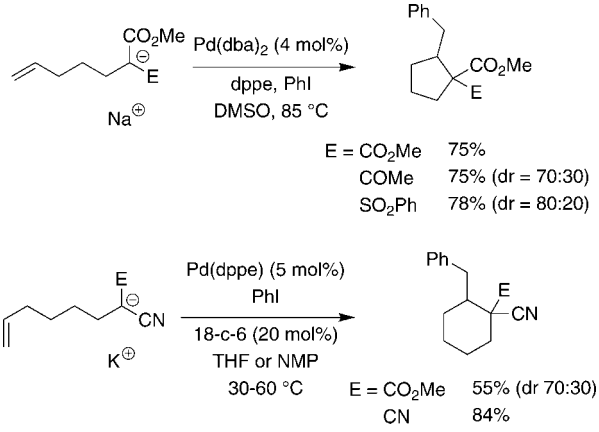
In an early example, Hegedus and co-workers reported the cyclization of the anion of methyl 2-methoxycarbonyl hex-5-enoate **11** in the presence of $PdCl_2(CH_3CN)_2$ and Et_3N via an uncommon 5-*endo* process. Following hydrogenolysis of the resulting σ-alkyl−Pd complex, cyclopentane **12** was obtained in 42% yield (Scheme 29).[43]

During the course of their studies on the Pd-mediated addition of malonate anion derivatives onto methylenecyclopropanes, Goré and co-workers reported that the cyclization of compounds **13** in the presence of a slight excess of

Scheme 30



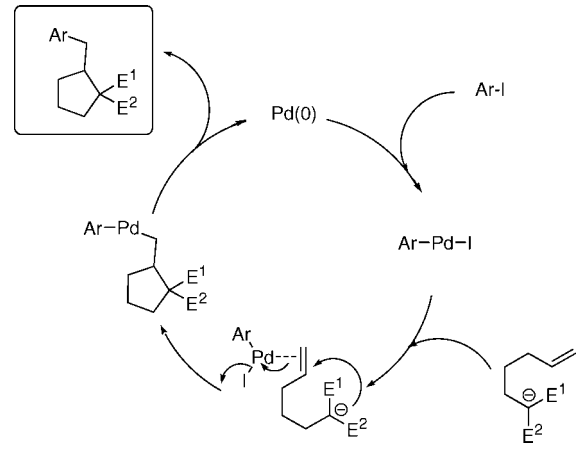
Scheme 31



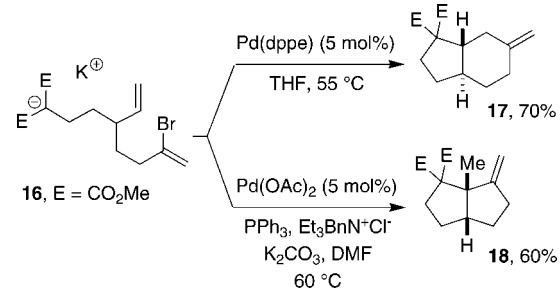
an aryl halide and a catalytic amount of Pd(0) and 1,2-bis(diphenylphosphino)ethane (dppe) led to the formation of **14** bearing a cyclopropyl group in good yields (64−70%). Under these conditions, only minor amounts (10−15%) of the expected cyclopentanes **15** resulting from cyclization onto the (π-allyl)Pd intermediate formed by ring-opening of the methylenecyclopropane were obtained (Scheme 30).[54] This first example of Pd-promoted nucleophilic attack of a malonate derivative onto an alkene proceeding with a catalytic amount of Pd(0) paved the way to various subsequent studies based upon this approach.

Balme and co-workers developed a Pd-catalyzed cyclization reaction of active methyne compounds possessing a terminal alkenyl side chain. The reaction was carried out at 85 °C in DMSO with a slight excess of a vinyl- or aryl halide (X = Br, I) and in the presence of only 4 mol % of $Pd(dba)_2$ and dppe (Scheme 31). Under these conditions, the sodium anion of β-ketoesters, β-sulfonylesters, and malonate derivatives led to the corresponding cyclized product in good to high yields (57−80%). A slight improvement was noted when the more nucleophilic potassium anion was used in the presence of 18-6 crown ether. Comparable results were obtained in toluene and in more polar solvents such as THF or NMP by using 5 mol % of Pd(dppe) or $Pd(OAc)_2$. Under these conditions, the reaction was complete within 1−3 h at room temperature.[55] While cyclization leading to the formation of five-membered rings was faster than the competitive Heck reaction, this was not the case for the 3-membered ring formation, which was unsuccessful.[56,57] For 6-membered ring formation, the nature of the nucleophile was found to play a crucial role. 6-*exo*-Cyclization products were obtained from cyanomalonate and cyanoester derivatives, but not from malonate, β-ketoester, and β-sulfonylester derivatives. The best results were obtained from potassium enolates in THF or NMP (30−60 °C) in the presence of 18-6 crown ether (20 mol %) by using 5 mol % of Pd(dppe) and a slight excess of an aryl iodide. Under these conditions, the cyclohexane

Scheme 32



Scheme 33



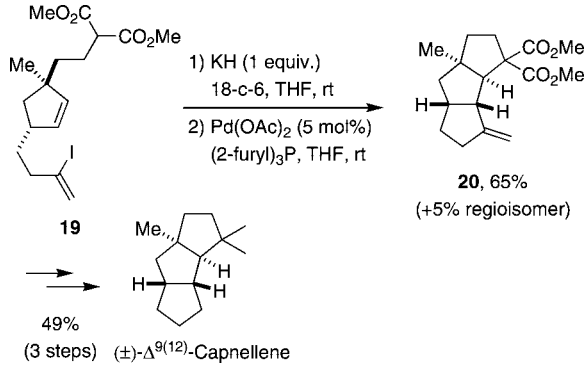
derivatives were obtained in moderate to high yields (55−84%) (Scheme 31). Aryl- and vinyl bromides led to the formation of the cyclized product in lower yields (26−47%).[58]

The proposed mechanism involves the formation of a Pd(II) species by oxidative addition into the C−X bond of the aryl- or vinyl halide, followed by the *anti*-addition of the nucleophile onto the (η^2-alkene)Pd(II) complex (Scheme 32).[59] The resulting σ-alkyl−Pd complex undergoes reductive elimination to give the cyclized product and regenerate the Pd(0) species.[55,60,61] The stereochemical outcome has been demonstrated for cyclizations leading to bicyclo[3.3.0]octane derivatives.[55,60,61]

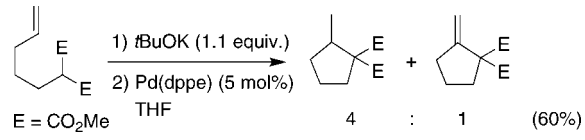
This sequence was extended to include active methyne compounds bearing both a pendant alkene and vinyl- or arylhalide moieties. In this case, following oxidative addition, Pd(II) activation took place intramolecularly and the transformation resulted in the formation of two new cycles in a single step. For instance, cyclization of precursor **16** led to the formation of *trans*-hydrindane **17** in 70% upon treatment with 5 mol % Pd(dppe) (Scheme 33). However, depending on the experimental conditions, the intramolecular Heck reaction was found to be a competitive reaction pathway. Accordingly, when treated with $Pd(OAc)_2/PPh_3$ in dimethylformamide (DMF) and in the presence of Et_3BnNCl, **16** furnished **18** in 60% yield after a Heck reaction/palladium migration/Tsuji−Trost allylation sequence.[62] Significantly, a closely related approach involving a substrate bearing an arylbromide moiety proved successful to access the skeleton of *trans*-hexahydro-1*H*-benz[*f*]indenes via the "carbocyclization" path.[63]

Furthermore, the strategy also proved applicable for 1,4-disubstituted cyclopentenes and was used in a concise total synthesis of (±)-$\Delta^{9(12)}$capnellene (Scheme 34).[64] Deprotonation of substrate **19** with KH in THF in the presence of

Scheme 34



Scheme 35

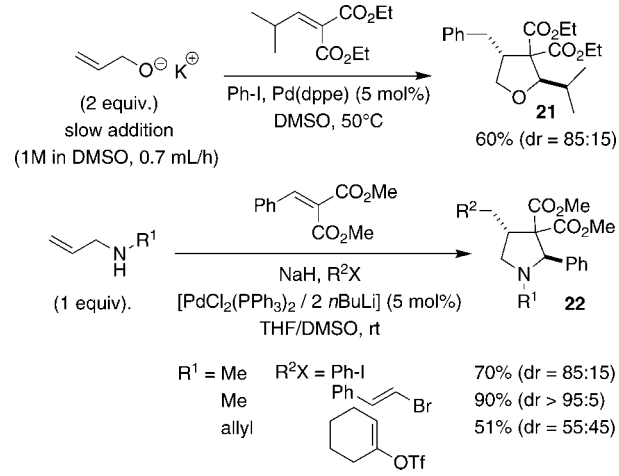


18-6 crown ether, followed by addition of the Pd(0) catalyst precursors, gave the tricyclic skeleton in 70% yield as a 93:7 mixture of regioisomers (the minor isomer arising from the migration of the C−C double bond). Major isomer **20** was advanced to (±)-$\Delta^{9(12)}$capnellene in 49% overall yield over three steps. Generalization of this approach to other bicyclo[3.3.0]octane skeletons was possible but called for modifications of the initial conditions.[60,61] Indeed, the angular methyl substituent in **19** proved essential in order to favor the carbocyclization reaction over the competitive intramolecular Heck reaction. With substrates devoid of this angular methyl group, the carbocyclization path could be favored either by using less reactive vinyl bromides, in order to disfavor the insertion process for the Heck reaction, or by using more nucleophilic anions, such as the potassium anion of cyanoesters in the presence of 18-6 crown ether, in order to increase the rate of addition onto the (η^2-alkene)Pd complex.

The cyclization of hexenyl-substituted malonate derivatives could also be achieved in the absence of aryl- or vinyl halides by using *t*BuOK (1.1 equiv) as a base (Scheme 35). In the optimized conditions (5 mol % of Pd(dppe), THF, rt), the cyclization led to a mixture of saturated cyclopentane and methylene cyclopentane derivatives in a 4:1 ratio (60% yield). In this instance, the alkene activating species was proposed to be a Pd(II)−hydride species formed by reaction of Pd(0) with *t*BuOH. Nucleophilic *anti*-addition of the malonate anion onto the (alkene)Pd−hydride complex then leads to a σ-alkyl−Pd−hydride species, which undergoes either reductive elimination, affording the saturated product (major pathway), or β-hydride elimination, to give the methylene cyclopentane derivative.[65,66]

More recently, heterocycles such as tetrahydrofurans[67] and pyrrolidines[68] have also been prepared by Pd-catalyzed cyclization of active methyne compounds bearing alkenyl side chains. In these approaches, the enolate was formed via conjugate addition of an allyl alkoxide or -amide onto benzylidene- or alkylidenemalonates (Scheme 36). The optimum conditions for the preparation of tetrahydrofurans involved addition of the potassium alkoxide (2 equiv, solution in DMSO) to a solution of benzylidene- or alkylidenemalonate (1 equiv), aryl iodide (1.5 equiv), and a catalytic amount of Pd(dppe) in DMSO at 50 °C. Slow addition of

Scheme 36

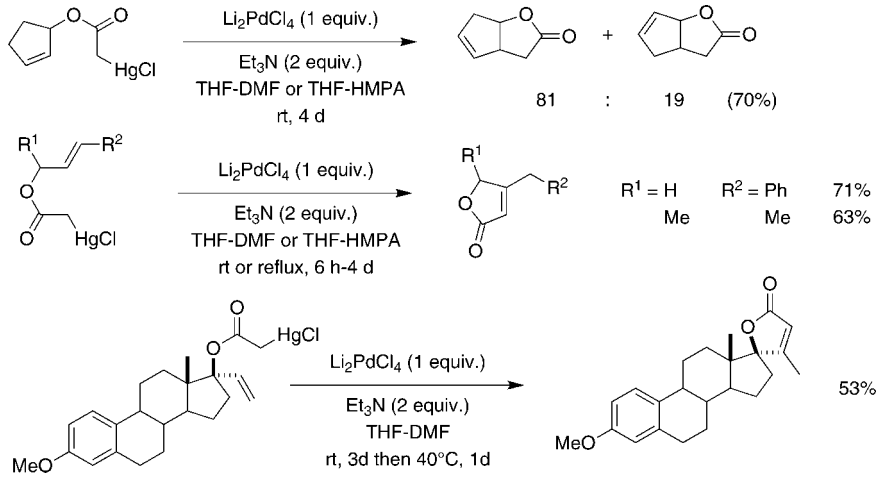


the alkoxide proved necessary in order to avoid side reactions such as Heck reaction or reaction of the alkoxide with the Pd(II) complex.[67] Using simple allyl alcohol, tetrahydrofurans such as **21** were obtained in good yields (60−70%) and with moderate levels of diastereoselectivity (dr *trans*/*cis* = 85:15). More hindered nucleophiles such as 2-methyl-3-buten-2-ol gave the tetrahydrofurans in only low yields even though the use of the Li−alkoxide proved to be slightly more efficient. Pyrrolidine formation using allylamines was achieved at room temperature in THF−DMSO with 5 mol % of [$PdCl_2(PPh_3)_2$/2 BuLi], in the presence of an aryl iodide and NaH (1.1 equiv). Interestingly, this time all the reagents could be mixed at the start without the need of a syringe pump. Pyrrolidine derivatives such as **22** were obtained in moderate to high yields (40−90%) and with low to excellent levels of diastereoselectivity in favor of the *trans* isomer (dr = 55:45 to >95:5) from secondary allylamines (R^1 = Me, allyl) and benzylidenemalonate (Scheme 36). This sequence proved quite general since other acceptors such as α-sulfonyl ester derivatives as well as other halides, including vinyl bromides and vinyl triflates, participated efficiently in the reaction. The stereochemical outcome of the cyclization leading both to *trans*-tetrahydrofurans and *trans*-pyrrolidines could be accounted for by a pseudo-chair transition state in which the substituent α to the heteroatom (X = O, NR) adopts a pseudo-equatorial position.

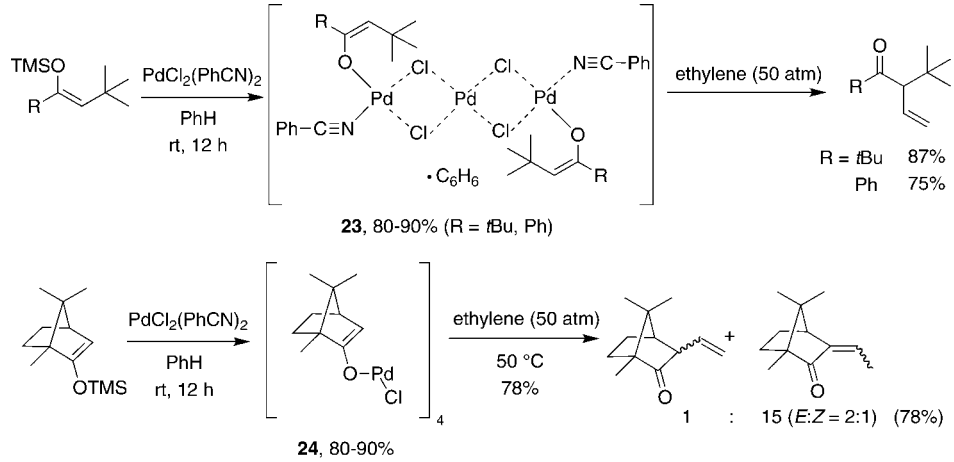
2.3.1.1.2.b. Mercury Enolates as Nucleophiles. In addition to alkali enolates, Pd(II)-mediated addition onto alkenes has also been reported with mercury enolates. Larock and coworkers developed the cyclization of allyl α-chloromercurioacetate esters readily prepared either from allyl alcohols by esterification with α-chloromercurioacetic acid in the presence of *N*,*N*-dicyclohexylcarbodiimide (DCC), or by mercuration of the acetate ester enolates. The reactions were carried out at room temperature in THF in the presence of 1 molar equiv of Li_2PdCl_4 (prepared in situ from $PdCl_2$ and LiCl) and 2 equiv of Et_3N using DMF or HMPA as a cosolvent (Scheme 37). While acyclic precursors gave the corresponding butenolide derivatives in moderate to high yields (53−95%),[69] the cyclization of cyclic precursors was more problematic. α-Chloromercurioacetate esters for which the steric hindrance at the carbon−carbon double bond was low led to the formation of [3.3.0]-, [4.3.0]-, and [5.3.0]-bicyclic skeletons in moderate to high yields (47−90%) as a mixture of regioisomers.[70]

The proposed mechanism involves initial transmetalation of the α-mercurioacetate ester into the corresponding

Scheme 37



Scheme 38



Pd−enolate species, which then undergoes insertion of the alkene ligand (*syn*-addition process) and β-hydride elimination. Migration of the carbon−carbon double bond was explained by a process involving Pd−hydride addition/elimination. Worthy of mention, similar Pd−enolate intermediates were proposed by Mori and co-workers for the Pd(0)-promoted cyclization of related α-iodoesters.[71−75] However, in this case, as the authors themselves had also considered,[76] the cyclization was later proved to follow a radical pathway,[77] thus ruling out the implication of a Pd−enolate.

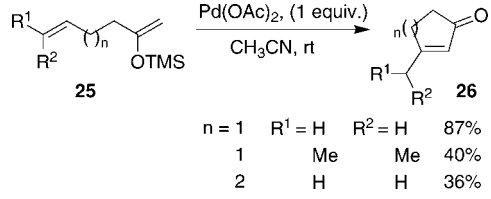
2.3.1.2. Silyl Enol Ethers As Nucleophiles. Saegusa and co-workers reported in the late 1970s the first examples of intermolecular addition of palladium enolates onto an olefin, in a behavior that contrasts with all of the above-mentioned reactions where the palladium complexes the alkene and activates it toward nucleophilic addition of a preformed metal enolate. Stable Pd−enolates whose structure prevented β-hydride elimination were prepared in high yields (80−90%) from silyl enol ethers of camphor, pinacolone, and *t*-butyl neopentyl ketones.[78] Addition of these enolates onto ethylene (50 atm, 50 °C) (Scheme 38) and butadiene led to the corresponding unsaturated adducts in high yields (75−87%) following β-elimination of the intermediate σ-alkyl−Pd species. Depending upon the substrate and presumably as a result of differences in steric hindrance, double-bond migration could be observed and, thus, a mixture of isomers obtained from the reaction. For instance, in the case of reaction of **23** (dimeric structure) with ethylene, no migration of the C−C double bond was observed, while Pd−enolate **24** (tetrameric structure) led to a mixture of isomers.

The use of Pd−enolates derived from silylenol ethers to create C−C bonds intermolecularly by nucleophilic addition onto alkenes has not been further developed, most probably due to the limitation concerning the structures that prevent β-hydride elimination. Conversely, the intramolecular version of this approach has been extensively studied and has been successfully applied to the preparation of complex cyclic skeletons.

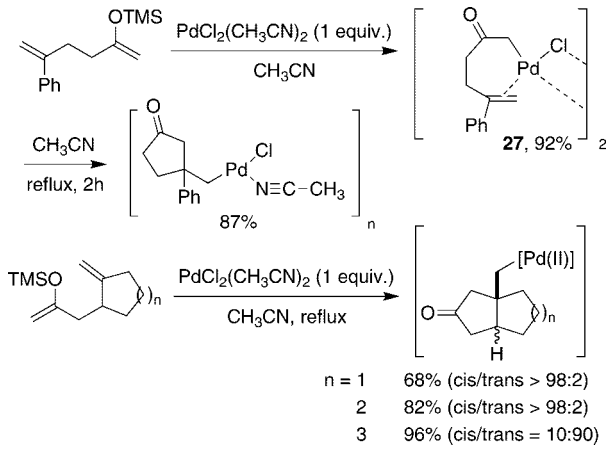
Saegusa and co-workers reported initial examples of Pd-mediated cyclization of silyl enol ethers of methyl ketones and ketones involving the formation of Pd−enolates from which β-hydride elimination was structurally impossible.[79] Following intramolecular addition and β-hydride elimination from the resulting σ-alkyl−Pd intermediate, unsaturated cyclized products were obtained. In some cases, migration of the C−C double bond was observed. For example, α,β-cyclopentenones of type **26** were obtained by reaction of silyl enol ethers **25** at room temperature in CH_3CN in the presence of a stoichiometric amount of $Pd(OAc)_2$ (Scheme 39). Five-membered ring formation from substrates possessing a terminal alkene moiety was achieved in high yields (83−99%). On the contrary, 6- or 7-membered ring formation and cyclization onto mono- or disubstituted alkenes were less efficient.

Silyl enol ethers bearing a pendant 2,2-disubstituted terminal alkene moiety were found to react with $PdCl_2(CH_3CN)_2$ in CH_3CN to furnish air-stable Pd−enolates

Scheme 39



Scheme 40



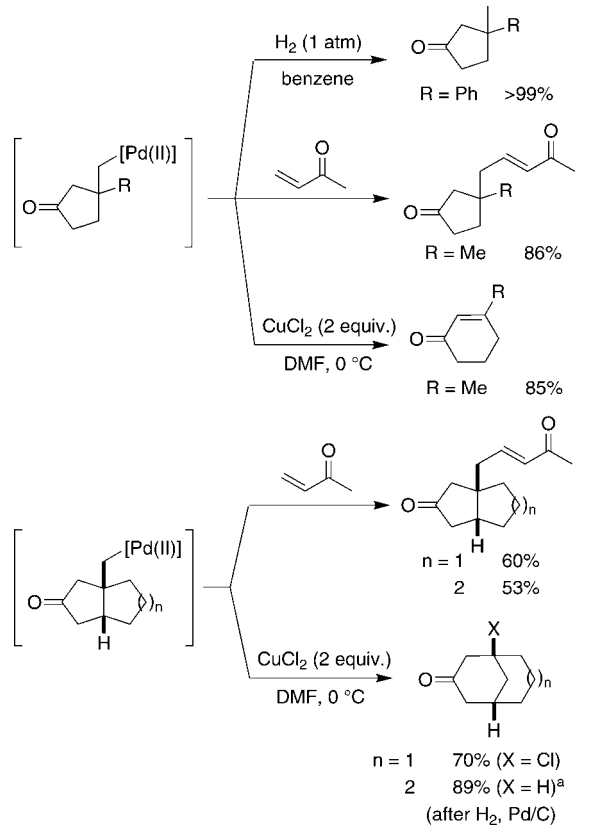
in high yields (92% for **27**, Scheme 40). The structure of the complexes was assigned as a bridged-dimer where the alkene moiety acts as a ligand for the Pd atom. Upon heating at reflux in CH_3CN, intramolecular carbopalladation occurred, leading to the σ-alkyl−Pd complexes that could also be isolated in good to high yields (68−96%) (Scheme 40).

Moreover, these σ-alkyl−Pd complexes could be reduced in good yields under a H_2 atmosphere (1 atm, 1 h in benzene) or engage in a new C−C bond formation with olefins such as methyl vinyl ketone to give the corresponding Heck-type products. Oxidative ring expansions could also be achieved upon treatment with $CuCl_2$ in DMF at 0 °C (Scheme 41).[80]

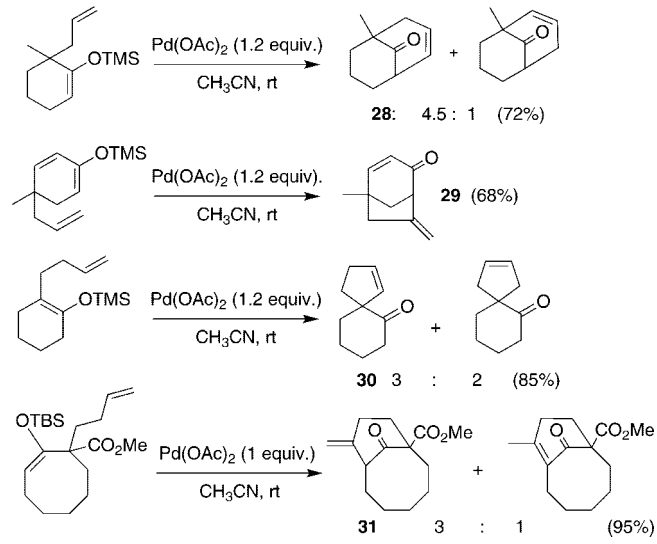
During the synthesis of a precursor to ajugarin, Kende and co-workers observed that the Pd-promoted cyclization of silyl enol ethers onto alkenes could occur, overriding the dehydrosilylation reaction, even in the case of silyl enol ethers leading to Pd−enolates where β-hydride elimination was structurally possible.[81,82] $Pd(OAc)_2$-mediated cyclization of trimethylsilyl enol ethers was found to proceed following a variety of cyclization modes and was used to obtain a range of bicyclic cores (Scheme 42). Bridged-bicyclic [3.3.1]- and [3.2.1]-skeletons such as **28** and **29** were prepared via, respectively, a 6-*endo*- and a 5-*exo* process in good to high yields (47−80%), provided that the corresponding precursors had a quaternary center to increase the rate of the cyclization. Cyclizations following a 5-*endo* mode led readily to bridged-[4.3.1] systems but were less efficient for the preparation of bicyclo[5.3.1]- and [9.3.1]-skeletons. Spirocyclic skeletons such as **30** could also be prepared in high yields (85−98%) via 5-*exo*- or 5-*endo*-cyclizations.[81,82] As in the case of **31**, rings such as bicyclo[4.3.1]-, [5.3.1]-, and [9.3.1]-skeletons were also prepared from *t*-butyldimethylsilyl enol ethers in moderate to high yields (35−95%) via 6-*exo* or 6-*endo* cyclization processes.[83]

More recently, transannular Pd(II)-mediated cyclization of silyl enol ethers has been reported (Scheme 43).[84] Cyclization of *t*-butyldimethylsilyl enol ethers of 9- and 10-membered cyclic ketones in the presence of a stoichiometric amount

Scheme 41



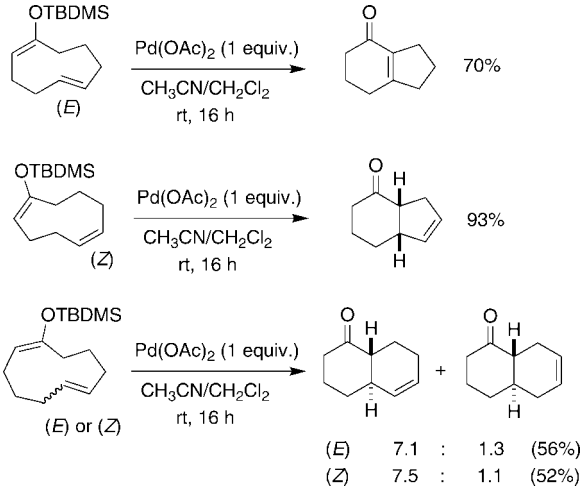
Scheme 42



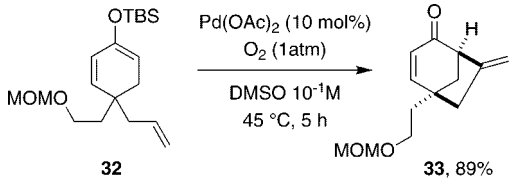
of $Pd(OAc)_2$ gave, respectively, [4.3.0]- and [4.4.0]-bicyclic products in good to high yields (70−93% from 9-membered ketones, 52−56% from 10-membered ketones). Interestingly, the position of the C−C double bond in the final products depended upon the configuration of the starting alkene. Remarkably, cyclization of ketene acetals of 10-membered lactones, while unsuccessful with $Pd(OAc)_2$, was achieved in moderate yield (45%) with the more electrophilic $Pd(O_2CCF_3)_2$ complex. Under these same conditions, the ketene acetal of the 9-membered ring precursor led only to the uncyclized α,β-unsaturated lactone.

Even though Saegusa and co-workers pointed out at an early stage that the Pd(II)-assisted carbocyclization of silyl enol ethers could be carried out using a substoichiometric

Scheme 43



Scheme 44



amount of palladium in the presence of a co-oxidant to regenerate the Pd(II) species,[79] no efficient catalytic approach was disclosed until much more recently. This issue was addressed by Ihara and Toyota, who developed a cycloalkenylation process using only 3−10 mol % of $Pd(OAc)_2$. The best results were obtained using bulky *t*-butyldimethylsilyl enol ethers under an O_2 atmosphere (1 atm) at 45 °C in DMSO.[85] For instance, under these conditions, silyl enol ether **32** gave the [3.2.1]-bicyclic compound **33** in 89% yield (Scheme 44). The use of *t*-butyldimethylsilyl enol ethers was necessary since, with the related trimethylsilyl- and triethylsilyl enol ethers, competitive dehydrosilylation was observed. Interestingly, these cyclizations could also be achieved in fair yields at room temperature in H_2O/DMSO (9:1).[86,87] Construction of fused-bicyclic [3.3.0]- and [4.3.0]-skeletons from trimethylsilyl enol ethers of substituted cyclopentanones and cyclohexanones following the catalytic procedure, though still possible, was significantly hampered by competitive dehydrosilylation and only proved moderately efficient with particular substrates whose structure made the rate of the cyclization step very fast.[88]

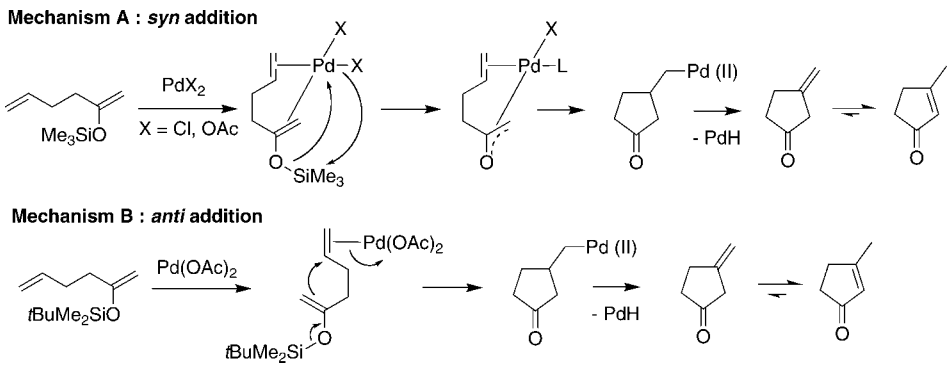
There has been some debate concerning the mechanism of the aforementioned alkenylation reactions. Two different pathways have been proposed to explain the formation of the adducts. The first one (mechanism A in Scheme 45)[80,89,90] consists of the formation of a Pd−enolate (σ-bonded or oxo-π-allyl−Pd(II) species) by reaction of the silyl enol ether with the Pd(II) salt, followed by insertion of the alkene, which leads to a σ-alkyl−Pd species. The latter can be isolated in the absence of a hydrogen atom at the β-position or can undergo a fast β-hydride elimination if a β-hydrogen atom is present. This proposal is based on the isolation of some stable Pd−enolate complexes [vide supra]. Furthermore, Larock's stereoselective synthesis of carbacyclins provides good evidence of a *syn*-addition process,[89] expected if a Pd−enolate is the reactive species. Alternatively, a second mechanism (mechanism B in Scheme 45) involving *anti*-addition of the silyl enol ether onto a (η^2-alkene)Pd complex has also been postulated.[82,90] In fact, the first mechanism seems to be predominant in the case of trimethylsilyl enol ethers, while the work of Ihara and Toyota supports the second proposal in the case of more *tert*-butyldimethylsilyl (TBDMS)−enol ethers.[90]

Stoichiometric and catalytic Pd-promoted cycloalkenylations of silyl enol ethers onto unactivated alkenes have found numerous applications in synthesis. Synthetic approaches to products of interest include the total or formal syntheses of quadrone,[82] $\Delta^{9(12)}$-capnellene-8β,10α-diol and $\Delta^{9(12)}$-capnellene-3α,8β,10α-triol,[91] carbacyclins,[89] hirsutene,[92] gibberellins,[93−95] kaurane-, atisirane-, and trachylobane diterpenes,[86,96] aphidicolin,[97] and platencin,[98,99] as well as the construction of the skeletons of stemodin[100,101] and gymnomitrene.[87,102] The subject has been recently reviewed by Toyota and coworkers and will not be discussed here in further detail.[90]

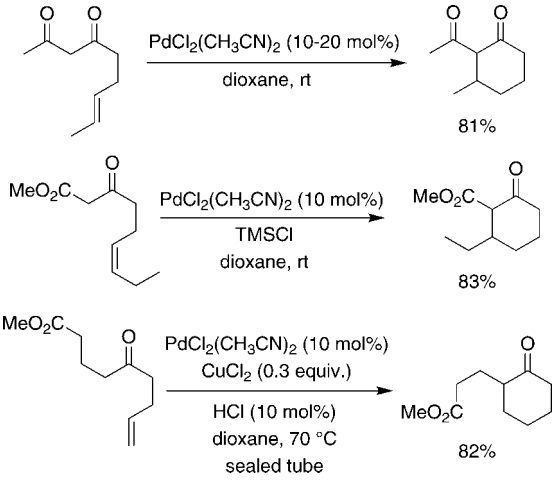
2.3.1.3. Palladium-Mediated Hydroalkylations. Intra-[103] and intermolecular[104] hydroalkylation of ε-alkenyl-1,3-diketones, arylketones, β-ketoesters, and β-ketoamides can be achieved under mild conditions using a catalytic amount of a Pd(II) source. While being related to the aforementioned addition of silyl enol ethers onto alkenes, these hydroalkylation reactions involve the addition of a β-dicarbonyl moiety reacting in its enol form[105−107] and, thus, not as an enolate. As a consequence, these reactions lie beyond the scope of this review and will only be briefly commented upon.

The cyclization of 1,3-diketones was achieved at room temperature in THF or dioxane in the presence of 10−20 mol % of $PdCl_2(CH_3CN)_2$ and, in contrast with the silyl enol ether cycloalkenylations, led to formation of saturated cycloalkanone derivatives (Scheme 46). In this case, following carbopalladation, palladium migration and protonolysis of the resulting Pd−enolate occurred. Worthy of note, the carbocycles obtained were formed with a high *endo*-selectivity. Terminal-, 1,2-disubstituted-, and trisubstituted

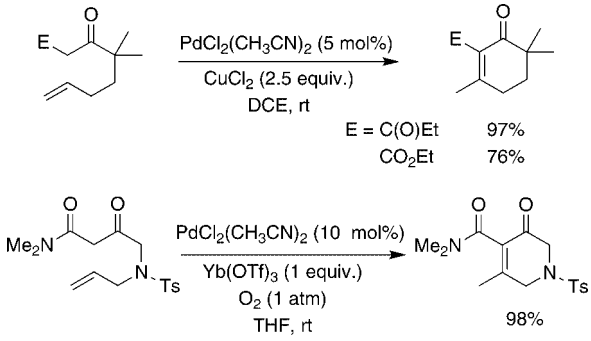
Scheme 45



Scheme 46



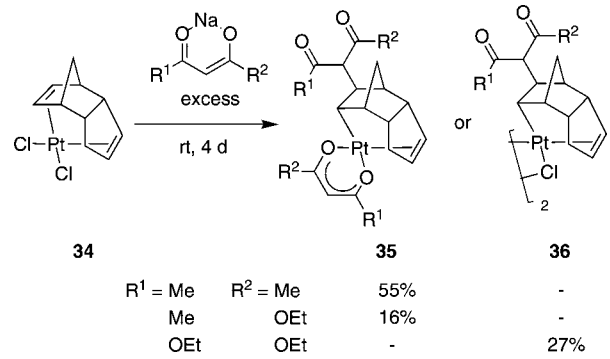
Scheme 47



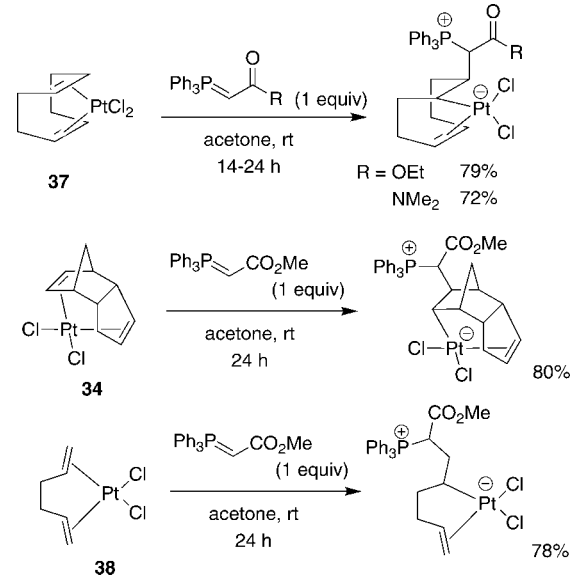
alkenes were suitable reaction partners, though yields were found to be strongly dependent upon the substitution pattern, with trisubstituted olefins leading only to the cyclized products in moderate yields.[103,107] The cyclization of the related β-ketoesters and β-ketoamides was less efficient under these conditions[103] but could be achieved in high yields either in the presence of additives such as Brønsted (HCl, trimethylsilylchloride (TMSCl)/H_2O)[108,109] or Lewis acids ($Yb(OTf)_3$, $La(OTf)_3$, and $Sm(OTf)_3$)[110,111] or under neutral conditions by performing the reaction at 55 °C (sealed tube) in poly(ethylene glycol-400) in the presence of 10 mol % of $PdCl_2(CH_3CN)_2$ and 1 equiv of $CuCl_2$.[112] The addition of $CuCl_2$ as an oxidant was commonly employed in order to avoid decomposition of the active Pd(II) catalyst. The cyclizations carried out in the presence of TMSCl or TMSCl/$CuCl_2$ might have involved intramolecular attack of an in situ-generated silyl enol ether onto a (η^2-alkene)Pd complex. However, Brønsted acid-catalyzed formation of the enol by traces of HCl (formed by partial hydrolysis of TMSCl with traces of water) seemed more likely.[109]

Interestingly, the cyclization of the related ξ-alkenyl-1,3-diketones,[105,113] β-ketoesters,[105] and β-ketoamides[114] led this time to the conjugated enone derivatives (Scheme 47). So far, no rationale has been proposed to explain the difference observed with the previous hydroalkylations.[105] Similar reaction conditions have also been applied to the addition of active methylene compounds onto ethylene and propylene.[104] Depending upon the nature of the nucleophile, either α-vinyl-β-diketones or α-ethylidene-β-diketones were formed selectively.

Scheme 48



Scheme 49



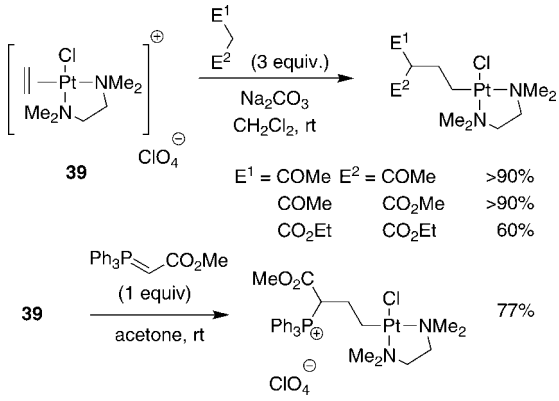
2.3.2. Platinum(II)-Mediated Additions

The use of Pt(II) salts to activate alkenes toward the addition of stabilized carbanions is far less developed than the corresponding Pd(II) complexes.[115] In early studies, it was shown that the addition onto (cod)Pt(II), first of sodium malonates and ethyl acetoacetate enolate[31] and next of thallous β-diketone enolates,[33,34] was directly comparable to the addition of the same nucleophiles onto the (cod)Pd(II) complex (see section 2.3.1.1.1). Other diene ligands such as dicyclopentadiene were also found to be suitable substrates for the nucleophilic addition of 1,3-diketones, β-ketoesters, and malonate derivatives, with the addition taking place exclusively at the more reactive carbon−carbon double bond of **34** (Scheme 48). The resulting complexes were obtained in low to moderate yields (16−55%) as mononuclear complexes **35** or as chloro-bridged dimers **36** depending on the nature of the nucleophile.[116]

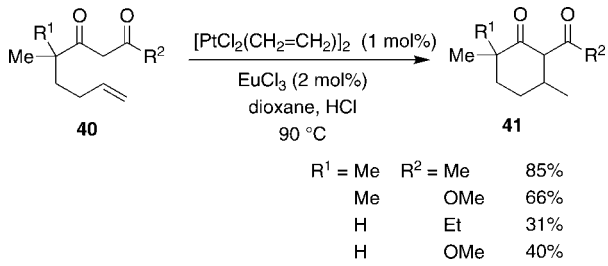
More recently, Vicente and co-workers described the addition of stabilized phosphorus ylides onto (η^4-diene)Pt(II) complexes bearing diene ligands such as 1,5-cyclooctadiene (**37**),[37] 1,5-hexadiene (**38**), or dicyclopentadiene (**34**).[117] The reaction was carried out at room temperature in acetone with 1 equiv of phosphorus ylide, and the resulting mononuclear complexes were obtained in good to high yields (66−80%) by simple precipitation from Et_2O (Scheme 49).

The Pt-promoted addition of stabilized carbanions onto simple alkenes is less common because the major reaction pathway has been found to be the displacement of the alkene

Scheme 50



Scheme 51

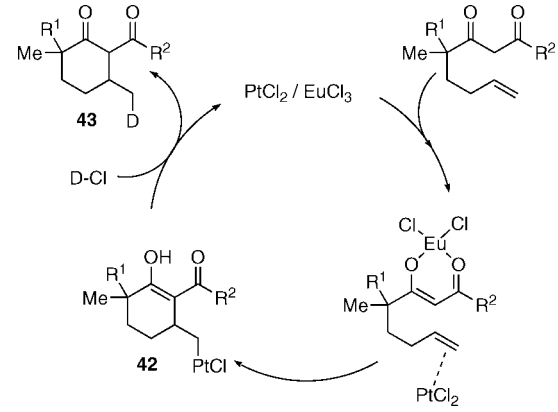


ligand instead of the nucleophilic addition. Nevertheless, the desired reaction starting with acetylacetone, ethyl acetoacetate, dimethyl malonate,[118] and stabilized phosphorus ylide[117] could be achieved by using highly electrophilic cationic (η^2-alkene)platinum complexes. For instance, the addition of acetylacetone, ethyl acetoacetate, and dimethyl malonate onto [Pt(η^2-ethylene)Cl(TMEDA)]ClO_4 **39** was observed at room temperature in CH_2Cl_2 in the presence of a 3-fold excess of the nucleophile and using Na_2CO_3 as a base (Scheme 50). The best results were obtained with the more acidic 1,3-diketones and β-ketoesters, and the resulting complexes were isolated in good to high yields (60−90%). Similar results were obtained with the related [(η^2-ethylene)Pt(NO_2)(TMEDA)]ClO_4 complex. Interestingly, no β-hydride elimination was observed under these mild reaction conditions.[119] The C−Pt bond of the σ-alkyl−Pt adducts could be cleaved under acidic conditions (gaseous or aqueous HCl, $HClO_4$), and the starting platinum complexes could be reformed by treating the acidic solution with ethylene (4−5 atm).[118]

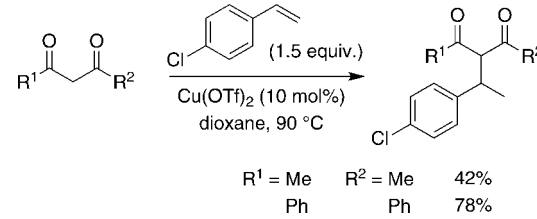
A Pt-catalyzed hydroalkylation reaction of 4-pentenyl β-dicarbonyl compounds **40** has been developed by Widenhoefer and co-workers.[120] The cyclization was carried out at 90 °C in dioxane containing HCl in the presence of 1 mol % of [$PtCl_2(CH_2{=}CH_2)]_2$ and 2 mol % of $EuCl_3$, furnishing the cyclic products **41** in moderate to high yields (31−93%). The highest yields were obtained with substrates bearing a *gem*-dialkyl substituent (Scheme 51).

The reaction process was very similar to the Pd(II)-catalyzed hydroalkylation reaction (see section 2.3.1.3, Scheme 47) and differed only by the exclusive formation of saturated cycloalkanone derivatives. Contrary to the Pd(II)-catalyzed reaction, the σ-alkyl−Pt(II) complex **42** arising from the cyclization (Scheme 52) did not undergo β-hydride elimination, and thus, isomerization to the corresponding Pt(II)−enolate was not possible. Instead, cleavage of the C−Pt bond was observed in the presence of HCl. The formation of the deuterated compound **43** when the reaction

Scheme 52



Scheme 53



was carried out in the presence of DCl confirmed the formation of the σ-alkyl−Pt(II) complex.

2.4. Group 11: Copper, Silver, and Gold

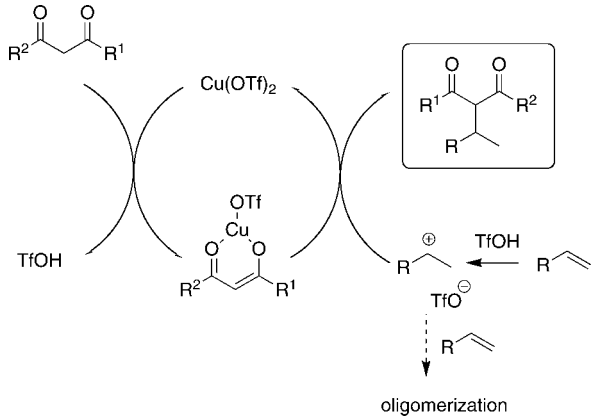
Copper(II)-, silver(I)-, and gold(I) salts have attracted a great deal of attention over the past few years as catalysts for the hydroalkylation of alkenes with active methylene compounds. While being synthetically related, these addition reactions contrast with the majority of the palladium-mediated systems described above since they are conducted under neutral conditions. It has been often accepted that, even under these conditions, the metal salt reacts with the active methylene compound (if it is acidic enough) to form a Cu−, Ag−, or Au−enolate, which then adds onto the alkene. However, this view is not definitive and other mechanistic proposals involving addition of the nucleophiles in their enol form have also been put forward and will be discussed herein.

2.4.1. Copper(II)-Mediated Additions

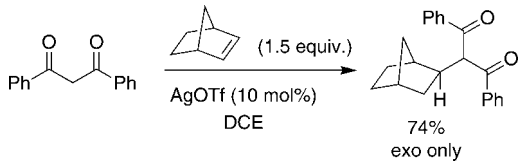
$Cu(OTf)_2$ has been shown very recently to catalyze efficiently the addition of diketones onto styrene derivatives (Scheme 53), norbornene, cyclopentadienes, and cyclic enol ethers. In the optimized conditions involving the use of 10 mol % of the catalyst at 90 °C in dioxane, the corresponding adducts were obtained in moderate to high yields (27−99%). Interestingly, the reaction could also be carried out under neat conditions, as well as in the ionic liquid [bmin]PF_6.[121,122] On the contrary, no reaction was observed with the less acidic dimethyl malonate,[121] and other Cu(II) salts, such as $CuBr_2$ and $CuCl_2 \cdot 2H_2O$, or Cu(I) salts proved ineffective.

Mechanistically, it has been proposed that the catalyst reacts with the enol form of the diketone to produce a Cu(II)−enolate and TfOH, which then protonates the alkene and generates a carbocation (Scheme 54). Addition of the Cu(II)−enolate onto the carbocation gives the observed adduct and regenerates the Cu(II) catalyst. Alternatively, the carbocation can react with another molecule of alkene, leading to oligomers.

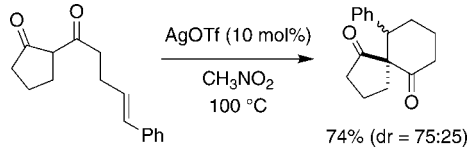
Scheme 54



Scheme 55



Scheme 56



2.4.2. Silver(I)-Mediated Additions

A highly efficient silver-catalyzed inter- and intramolecular addition of 1,3-diketones and β-ketoesters onto alkenes was reported by Li and co-workers (Scheme 55).[123] Silver triflate showed the highest catalytic activity, and other silver salts including AgI, $AgNO_3$, AgCN, Ag_2SO_4, $AgSbF_6$, $AgCO_2CF_3$, and $AgBF_4$ proved ineffective at promoting the reaction. Interestingly, the reaction was found to be reversible, with the Ag-promoted cleavage of a carbon−carbon bond occurring at elevated temperature. However, the exact cause of the reversibility remains unclear.

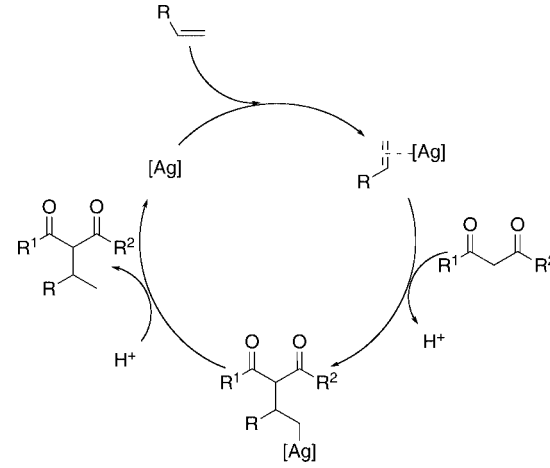
Both 1,3-diketones and β-ketoesters were found to undergo 6-*endo* cyclization onto conjugated alkenes. Spirocyclic skeletons could also be formed in good yields (Scheme 56). Interestingly, the favored diastereoisomer was reversed relative to the gold-catalyzed addition (75:25 vs 39:61, respectively). It was proposed that, in this case, the thermodynamic isomer was favored due to the reversible nature of the silver-catalyzed reaction, whereas the kinetic product was favored in the gold-catalyzed reaction. With nonconjugated alkenes, only *O*-alkylated products were obtained, albeit in low yields.

The proposed mechanism[123] involves the addition of the 1,3-diketone onto a (η^2-alkene)Ag(I) complex leading to the formation of a σ-alkyl−Ag intermediate. Protonolysis of the C−silver bond generates the final product (Scheme 57).

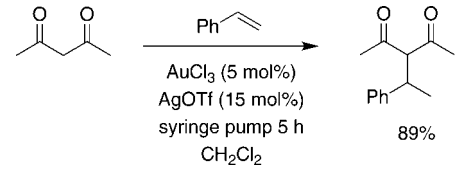
2.4.3. Gold(I)-Mediated Additions

Since the gold-catalyzed addition reaction of carbon nucleophiles onto alkenes and alkynes has been reviewed recently,[124] only the main features of this reaction will be developed herein.

Scheme 57



Scheme 58

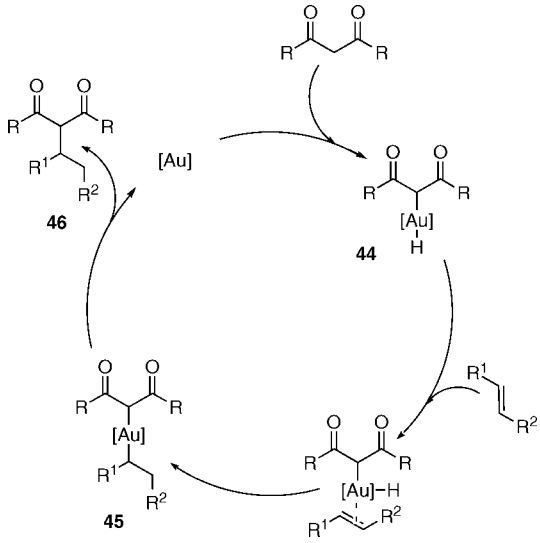


Intermolecular addition of 1,3-diketones onto alkenes was reported recently. Li and co-workers showed that 1,3-diketones add efficiently onto styrene derivatives at room temperature in CH_2Cl_2 in the presence of catalytic amounts of a Au(I) salt (generated in situ from the reduction of $AuCl_3$ by the activated methylene) and AgOTf (Scheme 58).[125] $(PPh_3)AuCl$ proved less efficient, in constrast to intramolecular additions onto alkynes where the presence of a phosphine ligand was often crucial (see section 4.7.2). Dialkyl malonates and β-ketoesters on their side did not give the corresponding adducts. While simple terminal alkenes failed to react, cyclic enol ethers, cyclic dienes, and trienes (see section 3.2.5) proved to be suitable partners.[126]

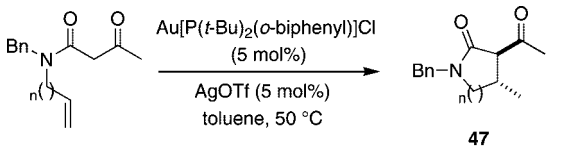
The mechanism proposed by the authors for the addition onto styrenes involves the activation of the C−H bond of the 1,3-diketone by a Au(I) species, followed by addition of the resulting Au(III)−hydride intermediate **44** onto the styrene to give intermediate **45** (Scheme 59). Reductive elimination leads to the observed adduct **46** and regenerates the Au(I) catalyst. Alternatively, a Au−enolate addition onto the alkene was also considered as a possible path. Interestingly, in the case of the addition onto enol ethers, a tentative mechanism involving the addition of the 1,3-diketone to a (alkene)Au(III) complex was proposed.[126]

The cyclization of β-ketoamides was achieved in excellent yields (90−99%) at 50−90 °C in toluene in the presence of 5 mol % of Au[P(*t*-Bu)$_2$(*o*-biphenyl)Cl] and AgOTf (Scheme 60).[127] The more widely used $(PPh_3)AuCl$/AgOTf system was also very efficient but gave slightly lower yields (e.g., 87% instead of 99% for compound **47**). Contrary to the intermolecular version developed by Li for the addition of 1,3-diketones, no reaction was observed with $AuCl_3$/AgOTf. β-Diamides and related esters failed to react under these reaction conditions. In the presence of Au[P(*t*-Bu)$_2$(*o*-biphenyl)Cl]/AgOTf, monocyclic, as well as spirocyclic 5- and 6-membered rings, were obtained in excellent yields, in all cases via an *exo*-cyclization process. The presence of a

Scheme 59

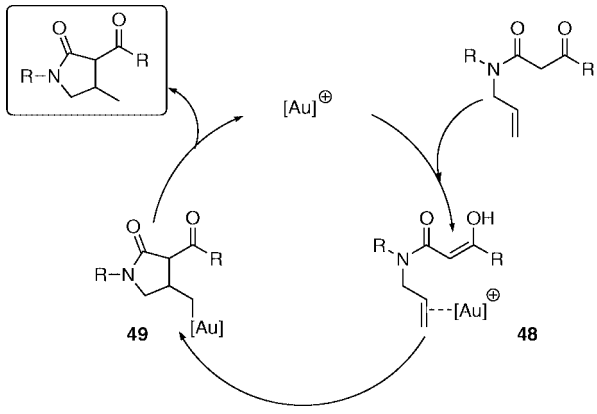


Scheme 60



n = 1 : 99% (dr > 95:5) (90% on 5 g scale)
2 : 98% (relative configuration unknown)

Scheme 61



substituent at the internal position of the alkene moiety slowed down the rate of the reaction, but the cyclized products were still obtained in high yields. Remarkably, the presence of a substituent at the terminal position led to a different skeletal rearrangement, probably via a tandem Claisen rearrangement/hydroamination reaction.

The proposed mechanism is related to the one proposed for the $AuCl_3$/AgOTf-catalyzed intermolecular addition of 1,3-diketones onto enol ethers, with the difference that activation of the alkene is achieved by complexation with Au(I) and not Au(III). The authors proposed a picture involving the intramolecular nucleophilic attack of the enol form of the 1,3-ketoamide onto (η^2-alkene)Au(I) complex **48**. The resulting alkyl−Au species **49** furnishes the final product after protonation. The existence of alkyl−metal species **49** was supported by deuterium labeling experiments (Scheme 61).

2.5. Group 12: Zinc(II)-Mediated Additions

Zinc-stabilized nucleophiles are reagents of choice to perform carbometalations of unactivated olefins.[3,4] In addition, in most cases, the resulting organometallic species can be used for various subsequent synthetic transformations. The first examples of addition of a Zn−enolate onto an unfunctionalized or nonstrained double bond were only disclosed a decade ago.[128−130] From then on, a steady input has enriched this field following two main directions. On the one hand, inter- and intramolecular carbozincations involving Zn−azaenolates derived mainly from hydrazones and imines have been disclosed. This process leads, after hydrolysis, to α-alkylated ketones in an overall process that can be regarded as an "olefinic aldol reaction". On the other hand, inter- and intramolecular carbometalations of unactivated double bonds with Zn−enolates of esters and amides have been developed, especially in the case of α- and *β*-amino esters, in an overall process that can be regarded as a "carbo-Reformatsky reaction".

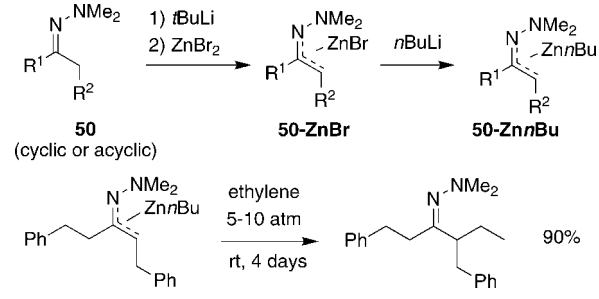
2.5.1. Carbozincation with Azaenolates

2.5.1.1. Carbometalation with Zincated Hydrazones. Zinc azaenolates derived from cyclic and acyclic *N,N*-dimethylhydrazones were reported to give the corresponding carbometalation adducts in moderate to high yields (30−90%) after stirring at 20−35 °C for several days in the presence of an excess of olefin (Scheme 62).[128] The Zn−azaenolates were prepared by metalation of hydrazones with *t*BuLi in Et_2O (in the case of nonsymmetric substrates at the less hindered side) followed by transmetalation with $ZnBr_2$ and ligand exchange with *n*BuLi. The use of butylated species **50**−Zn*n*Bu was found to be essential for an efficient addition since other species such as **50**−ZnBr, **50**−ZnMe, or **50**−Zn*t*Bu were far less reactive. High yields (83−90%) were obtained in the case of the addition onto ethylene. On the contrary, monosubstituted alkenes (R = Ar, alkyl) were far less reactive, and the reaction, though regioselective since mainly the "branched" adducts were obtained (branched/linear >88:12), gave only moderate to good yields (33−69%). Moreover, a complete lack of diastereoselectivity was observed for the branched product.

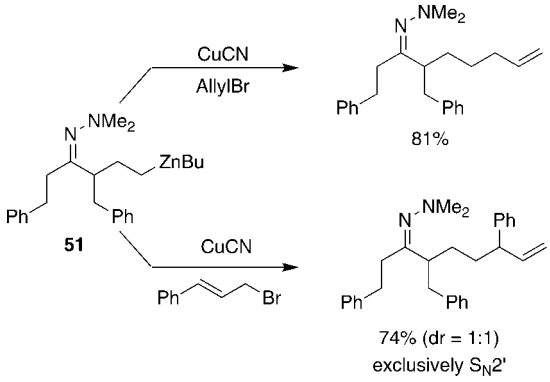
The resulting organozinc hydrazones **51** were stable in the reaction media and gave, upon hydrolysis, hydrazones (that could be further converted in high yields into the corresponding ketones with $CuCl_2$ catalysis). The organozinc species **51** could also react with carbon electrophiles after transmetalation with copper salts (45−81%), thus providing a one-pot, three-component coupling reaction (Scheme 63).

The constrained cyclopropenone acetal **52** was found to be a suitable substrate for the addition of zincated hydrazones (Scheme 64), as well as the less reactive zinc amide- and

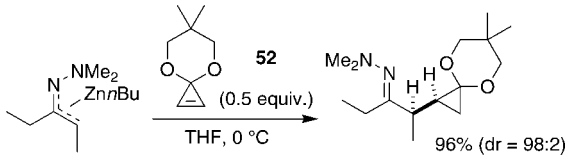
Scheme 62



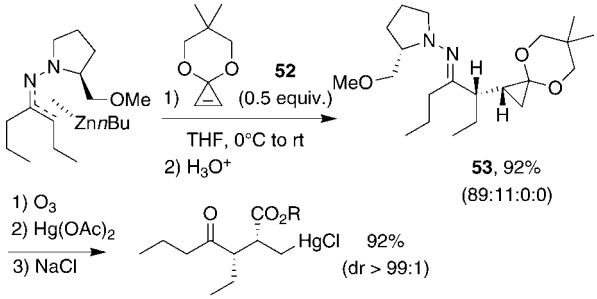
Scheme 63



Scheme 64



Scheme 65

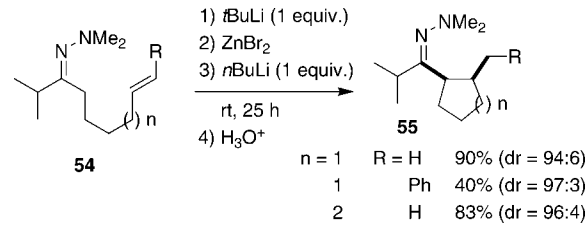


zinc ester enolates. A high level of 1,2-diastereoselectivity was usually observed for the newly formed C−C bond. As evidenced in the addition of zincated δ-lactam **80** to the constrained cyclopropenone−acetal **52** (see section 2.5.2, scheme 81), carbometalation of alkenes with zincated anions was found to take place in a *cis* addition manner.[131]

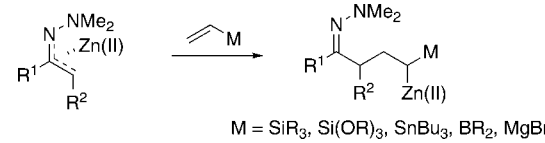
A high level of diastereocontrol (dr = 89:11) and a complete 1,2-selectivity were obtained in the addition of the zincated hydrazone derived from (*S*)-(−)-amino-2-(methoxymethyl)pyrrolidine (SAMP) and heptan-4-one onto cyclopropenone acetal **52**. A slightly higher chiral induction, but a lower yield, was obtained by using $ClZn^+$ as a countercation. The hydrazone moiety could be cleaved by ozonolysis and the cyclopropane could be ring-opened in the presence of Hg(II) salts without loss of the diastereoselectivity (Scheme 65), and the resulting C−Hg(I) bond could be cleaved under reductive conditions. The reaction of zincated SAMP hydrazones was considered in an initial approach to an asymmetric version of the "olefinic aldol reaction", but it proved to be limited in scope. While addition onto cyclopropenal acetal **52** led to the formation of β-cyclopropylhydrazone **53** in very good yields (79−92%) and with synthetically useful selectivities (78−98% selectivity for the major isomer),[131] addition onto ethylene resulted in lower diastereoselectivity (dr = 82:18) and moderate yield (42%).[128]

Zincated hydrazones were also found to add onto alkenes in an intramolecular manner (Scheme 66).[132] 5-*exo*- and 6-*exo*-Cyclizations of terminal alkenes were observed following zincation of compounds **54**. After hydrolysis, the

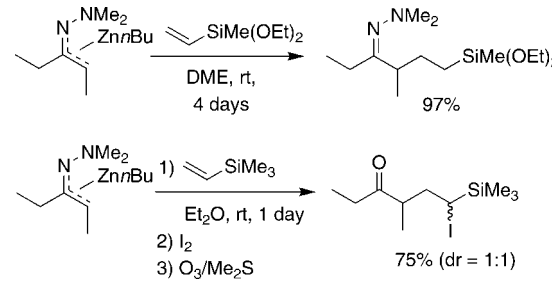
Scheme 66



Scheme 67



Scheme 68



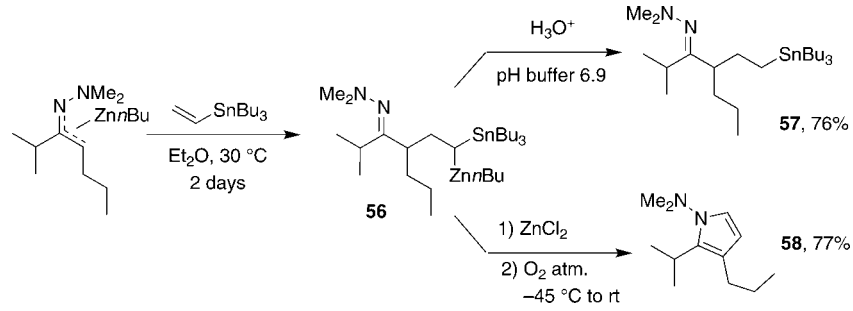
corresponding carbocycles **55** could be obtained in high yields (83−90%) from hydrazones of isopropyl ketones. On the contrary, the carbocyclization process was slower with a disubstituted double bond (R = Ph) or with hydrazones derived from bulkier *tert*-butyl ketones. Good diastereoselectivities (dr > 94:6) in favor of the *cis* isomers were observed in all cases.

Vinyl metals proved to be excellent electrophiles toward azaenolates, leading to original bimetallic intermediates (Scheme 67).[133] Initially it was shown that unsubstituted vinylsilanes[134] and vinylstannanes[135] react with zincated hydrazones to afford, respectively, *gem*-Zn/Si and *gem*-Zn/Sn adducts. Again, the use of $Zn nBu^+$ countercation was found to be crucial. The regiochemical integrity of the bimetallic species obtained was dependent upon both the nature of the metal and the hydrazone's structure. When stable, the reagents could be further elaborated by subsequent reactions with electrophiles or by oxidation.

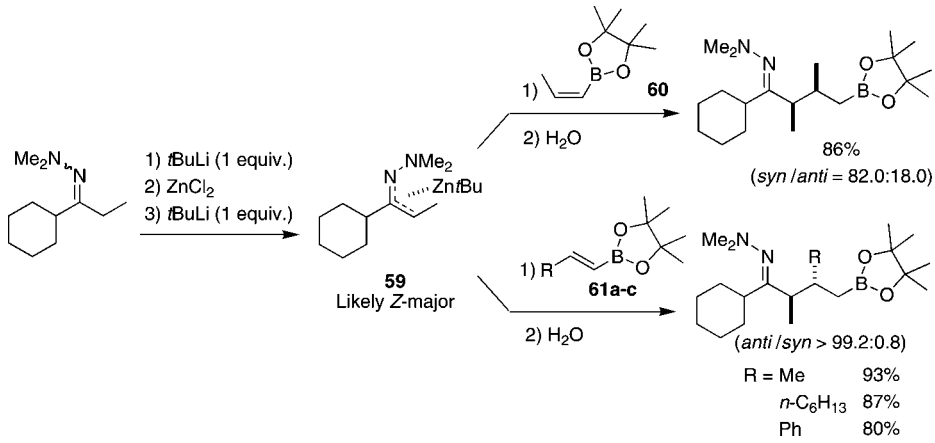
The intermolecular addition of zincated hydrazones onto vinylsilanes was highly regioselective, with the addition taking place exclusively at the terminal position of the alkene (Scheme 68).[134] Here again, the success of the reaction required the use of a dummy ligand on the zinc atom. The best results were obtained with $nBuZn^+$ as countercation, whereas $MeZn^+$ and $tBuZn^+$ proved less efficient. The solvent was found to play an important role in terms of both reaction rate and product yields. The reaction was faster in the less coordinating Et_2O than in 1,2-dimethoxyethane (DME) or THF. Trialkylvinylsilanes and triphenylvinylsilane were found to be less reactive than the corresponding alkoxyvinylsilanes. The reaction was limited to unsubstituted vinylsilanes.

The carbozincation of vinylstannanes using zincated hydrazones was found to be much faster than the addition onto the related vinylsilanes. This methodology was employed to access pyrrole derivatives via aerobic oxidation of the

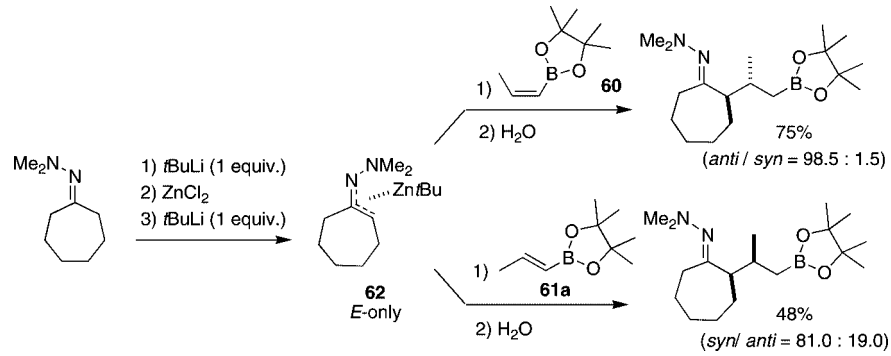
Scheme 69



Scheme 70



Scheme 71



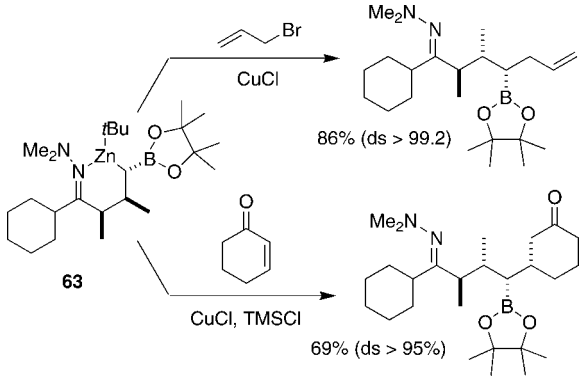
resulting bimetallic species **56** (Scheme 69).[135] The addition was highly regioselective and furnished *gem*-bimetallic species that were stable even at room temperature for a few days. Upon hydrolysis, the corresponding γ-stannylhydrazones **57** were obtained in moderate to good yields (45−82%). Oxidation of the Sn/Zn-bimetallic species under an O_2 atmosphere (after removal of the butyl group by the use of $ZnCl_2$) could also be achieved and led to the formation of 1-(dimethylamino)-1*H*-pyrroles **58** in moderate to good yields (29−77%). Cleavage of the N−N bond could be achieved in good yields under Birch's conditions.

More recently, alkenylboronates have been shown to undergo diastereoselective addition with zincated hydrazones.[136] Zn−azaenolate **59** (likely in its *Z*-diastereomeric form) reacted with *Z*-alkenylboronate **60** (respectively, *E*-alkenylboronate **61a**−**c**) to give upon hydrolysis *syn*- (respectively, *anti*-) γ-borylhydrazones with selectivities up to 82.0:18.0 (respectively, 99.6:0.4) (Scheme 70). On the contrary, Zn−azaenolate **62** derived from a cyclic hydrazone (locked in its *E*-diastereomeric form) led to the formation of *anti*- (respectively, *syn*-) γ-borylhydrazones following addition onto *Z*-alkenylboronate **60** (respectively, *E*-alkenylboronate **61a**) and hydrolysis (Scheme 71). Using theoretical calculations,[137] these stereochemical outcomes have been rationalized by a six-centered boatlike transition state involving a *syn*-carbometalation.

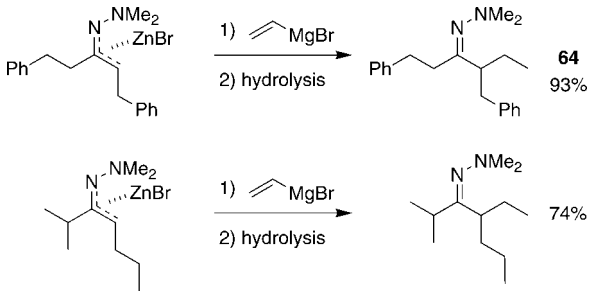
Regarding C−Zn stereochemistry, *gem*-Zn/B bimetallic intermediates were found to epimerize into their thermodynamically more stable *gem*-Zn/B bimetallic **63**, which involves intramolecular complexation between zinc and nitrogen. Electrophilic trapping with carbon electrophiles in the presence of CuCl occurred with overall retention of configuration, thus offering the opportunity to create one or two additional stereogenic centers with excellent overall levels of diastereoselectivity (Scheme 72). Interestingly, the similar sequence with SAMP hydrazones occurred with high levels of asymmetric induction for the addition step and without loss of diastereomeric control in the addition/trapping sequence, thus affording diastereo- and enantiomerically pure compounds.

Vinylmagnesium halides proved to be excellent electrophiles toward zincated hydrazones and underwent rapid

Scheme 72



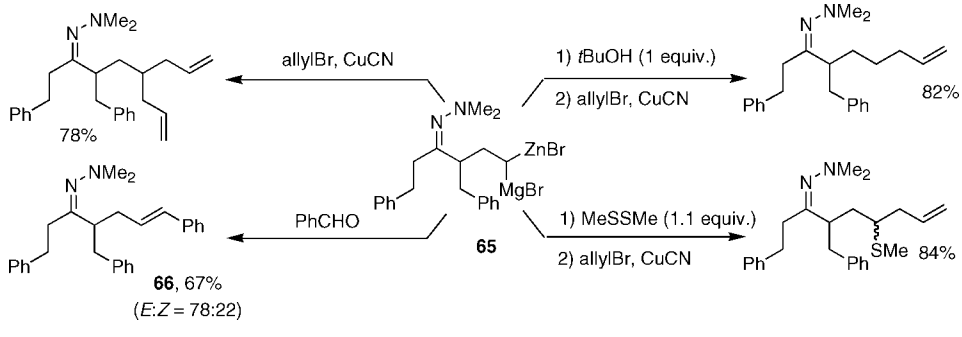
Scheme 73



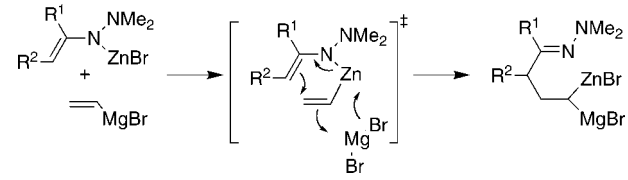
addition to furnish *gem*-Zn/Mg bimetalated hydrazones (Scheme 73).[138] In this case, the use of a dummy ligand (R = *n*Bu, or *t*Bu) was not necessary in order to obtain high yields. Addition of zincated hydrazones onto simple vinyl Grignard reagent was usually complete within 1 h at 0 °C and generated a bimetalated hydrazone intermediate in a nearly quantitative yield. Cyclic and acyclic Zn−azaenolates of hydrazones participated equally well in the reaction and gave the corresponding adducts in good to high yields (67−93%). For instance, metalation of the *N*,*N*-dimethylhydrazone of 1,5-diphenylpentan-3-one with *t*BuLi in Et_2O, followed by transmetalation with $ZnBr_2$ and addition to a solution of vinylmagnesium bromide, gave the corresponding ethylated hydrazone **64** in 93% yield upon hydrolysis (Scheme 73). Deprotonation of unsymmetrical ketone hydrazones took place at the less hindered side, and subsequent reaction with the vinyl Grignard reagent occurred with retention of this regiochemistry. Here again, the hydrazone anion bearing a lithium countercation was found to be unreactive toward vinylmagnesium bromide, as well as the Zn-anions of ketones, esters, and amides. Substituted vinyl Grignard reagents reacted very sluggishly with zincated hydrazones.

As exemplified in the case of bimetallic hydrazone **65**, the nucleophilic behavior of these adducts was shown to be

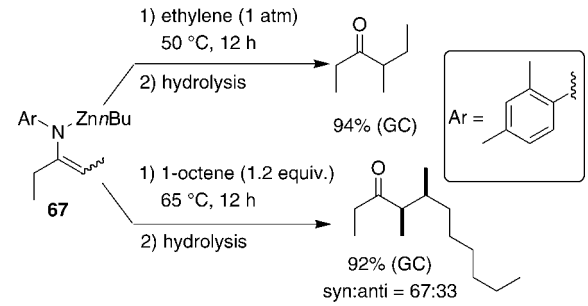
Scheme 74



Scheme 75



Scheme 76

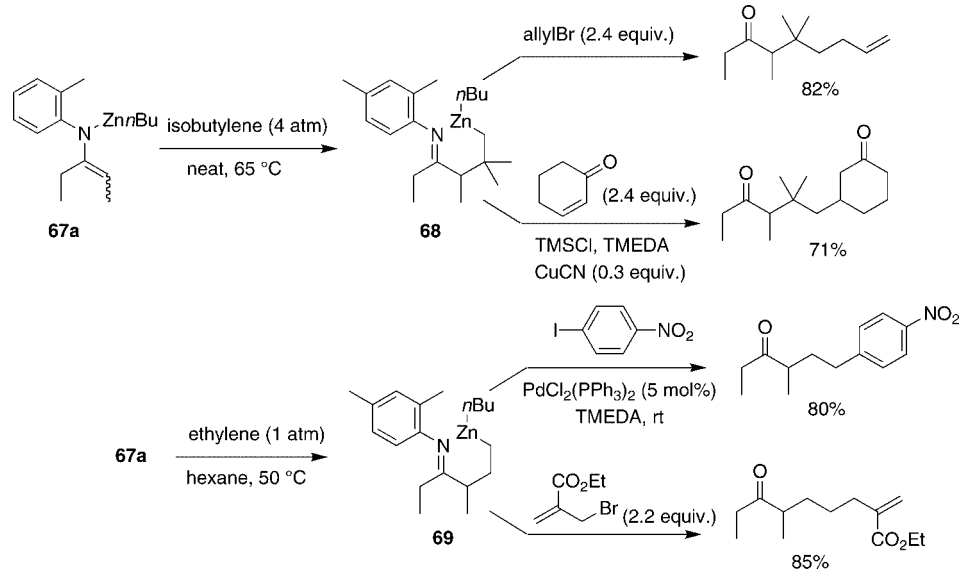


rich.[138] Electrophilic trapping could occur for both C−M bonds either with the same electrophile or sequentially with two different electrophiles. Interestingly, reaction with benzaldehyde gave **66** following addition of the C−Mg bond and subsequent β-elimination of BrMgOZnBr (Scheme 74).

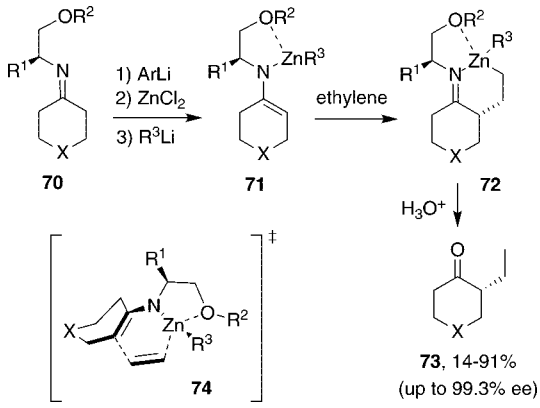
Though synthetically related to the examples described above (M = SiR_3, $SnBu_3$, BR_2), the mechanism of the reaction with vinyl Grignard reagent (M = MgX) is completely different since it involves most likely a metalla-aza-Claisen rearrangement rather than a direct carbozincation (Scheme 75).

2.5.1.2. Carbometalation with Zinc Enamides. While addition of zincated hydrazones proceeded conveniently onto ethylene or vinylmetals, additions onto substituted alkenes were found to be generally too slow to be synthetically useful. The use of zinc enamides obtained by deprotonation of the parent imines with *t*BuLi or LDA (at the less hindered side for nonsymmetric ones) followed by transmetalation with a suitable zinc salt was investigated.[139] Optimum reactivity was obtained with *N*-(2,4-dimethylphenyl)-substituted enamides (Scheme 76). In this case, provided Zn*n*Bu$^+$ was used as a countercation, the carbozincation reaction could be achieved under synthetically exploitable conditions with a range of enamides such as **67**, affording substituted ketones in high yields upon hydrolysis. Not only ethylene, but also simple monosubstituted alkenes, styrene, and 1,1-disubstituted alkenes were found to participate effectively in the reaction. In the addition onto 1,1-disubstituted alkenes, Zn−enamides derived from acyclic ketones showed a higher reactivity than cyclic ones. In general, total regioselectivity in favor of the branched regioisomer (>99:1) was observed.

Scheme 77



Scheme 78



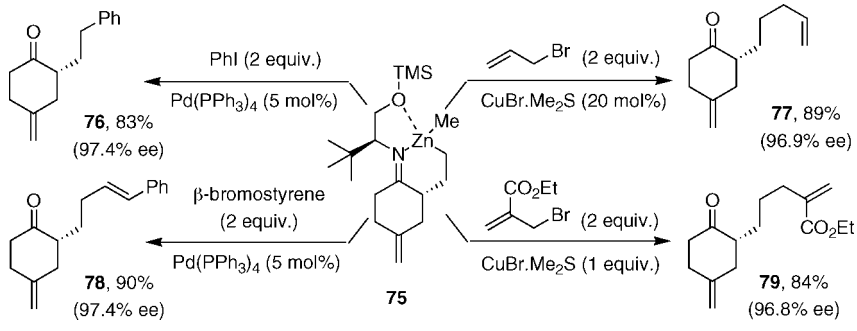
Nevertheless, the case of styrene was somewhat specific since variable mixtures of branched/linear adducts were obtained depending upon the starting enamine. In particular, unlike zincated hydrazones, the addition of zincated cyclic enamines onto styrene led exclusively to the formation of linear products. When two stereogenic centers were created, a low level of diastereoselectivity was observed.

As exemplified with organozinc compounds **68** and **69**, the carbometalation adducts proved stable under these conditions and could thus undergo subsequent functionalization upon electrophilic trapping with or without Pd catalysis or copper salt addition (Scheme 77).

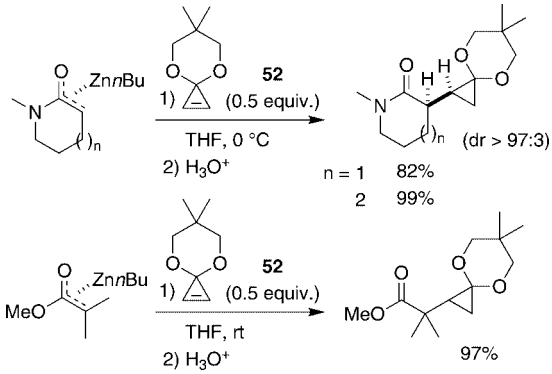
Zn−enamides prepared from imines **70** derived from (*S*)-valinol or (*S*)-*tert*-leucinol were reported to add onto ethylene in a diastereoselective manner (Scheme 78).[140] In the optimized conditions (R^1 = *t*Bu, R^2 = TMS, R^3 = Me), Zn−enamides **71** were prepared by deprotonation of the imine with mesityllithium at 0 °C in Et_2O, followed by successive addition of $ZnCl_2$ and MeLi. The polar solvent was then replaced with hexane, and ethylene (20−30 atm) was introduced. Under these conditions, very high levels of stereoinduction could be obtained for a range of cyclic enamides. Upon hydrolysis, organometallic intermediates **72** afforded the corresponding α-alkylated ketones with enantiomeric excesses higher than 90% in what was regarded as an enantioselective version of the "olefin aldol reaction". The enantiomeric purity of the final ketones **73** did not reflect the selectivity of the carbometalation reaction since racemization of the chiral center resulting from epimerization of an imine intermediate during hydrolysis was evidenced. In fact, enantiomeric excesses as high as 99.3% could be obtained after only several minutes of hydrolysis, albeit at the expense of a dramatic drop in the overall yield. The sense of stereoinduction was rationalized by six-centered transition state **74** that involves a Zn−O interaction, resulting in the shielding of one of the faces of the imine by the bulky *tert*-butyl group (R^1 = *t*Bu in Scheme 78).

γ-Zincioimine intermediates such as **75** were also trapped with an electrophile (under Pd- or Cu-catalysis) without significant erosion of enantioselectivity. For example, ketones **76**−**79** resulting from the three-component sequence were obtained in high yields and with high levels of enantioselectivity (Scheme 79).

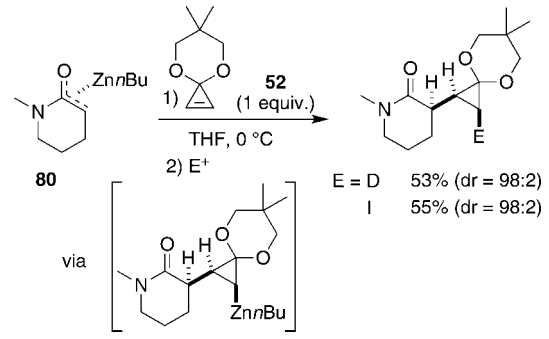
Scheme 79



Scheme 80



Scheme 81



Generalization of this method to alkenes other than ethylene resulted in lower yields and/or diastereoselectivities and was thus found to be nonpractical. Moreover, acyclic imine precursors led to the formation of the corresponding ketones in only low to moderate enantiomeric excesses.

2.5.2. Carbozincation with Ester and Amide Enolates

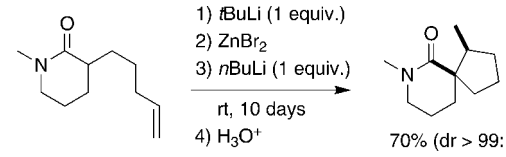
Because of the lower reactivity of Zn−enolates of esters and amides, only few examples of intermolecular addition onto unactivated alkenes have been reported. The constrained cyclopropenone acetal **52** was found to be a suitable substrate for the intermolecular addition of zincated amides and lactams. Using nBuZn$^+$ as a countercation, the corresponding adducts could be obtained in good to high yields (64−99%) and with a high level of diastereoselectivity (dr up to 99:1). Ester enolates were not reactive enough, except when α,α-disubstituted esters were employed (Scheme 80).[131]

As evidenced by subsequent functionalization of the zinc derivative resulting from the addition of zincated δ-lactam **80** onto the constrained cyclopropenone acetal **52**, the carbozincation process occurs in a *cis* manner (Scheme 81).[131] Remarkably, for this addition, a high level of 1,2-diastereoselectivity (dr > 98:2) for the newly formed C−C bond was obtained.

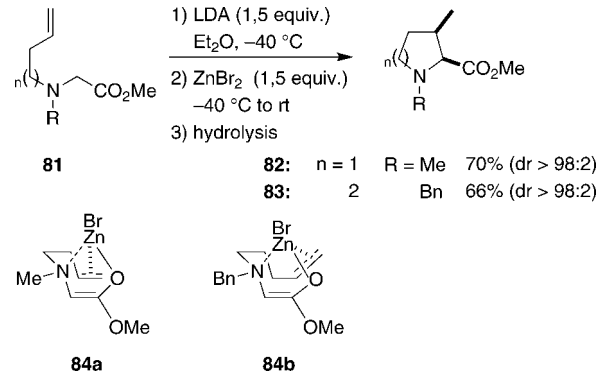
A single example of intramolecular addition of zincated lactam onto a terminal alkene has been reported. The approach gave access to a spirocyclic skeleton in good yield and with virtually complete stereoselectivity. However, the reaction time (10 days at room temperature) is too long for this method to be synthetically useful (Scheme 82).[132]

2.5.2.1. Enolates Derived From α-(*N*-Homoallyl- and α-(*N*-4-Pentenylamino)esters. Building on their work concerning the Zinca−ene−allene reaction, Normant and coworkers reported,[130,141] simultaneously with others,[129] the carbometalation reaction of α-(N-butenylamino)esters (Scheme 83). Initially it was shown that the Reformatsky-type reagent, obtained by deprotonation of α-amino esters **81** followed by transmetalation with $ZnBr_2$, underwent (unlike its parent lithium enolate) intramolecular addition leading to pyrrolidine **82** upon hydrolysis. Remarkably, a similar behavior was observed with α-(N-pentenylamino)esters, leading this time to polysubstituted piperidines **83**.[142] In both cases, the carbocyclization was completely diastereoselective, affording exclusively the *cis* diastereoisomer. Zn−enolate intermediates **84a** and **84b**, where the O-centered enolate eclipses the terminal reacting double bond, were proposed to explain this selectivity.

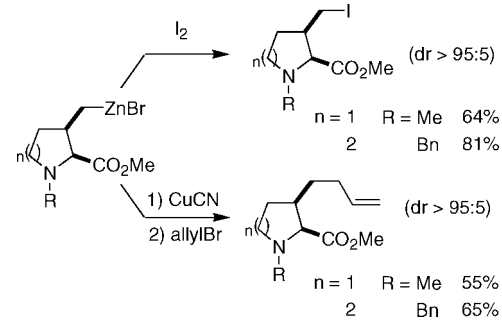
Scheme 82



Scheme 83



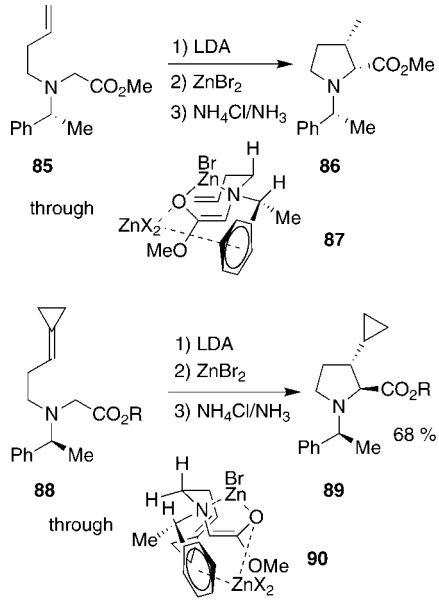
Scheme 84



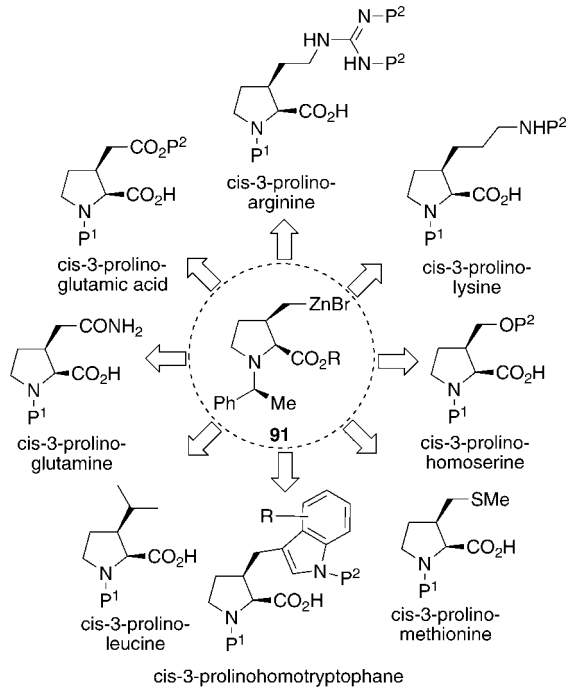
The resulting alkyl−Zn species were reacted further with different electrophiles to afford diversely substituted pyrrolidines or piperidines (Scheme 84).

An enantioselective version of the carbocyclization of α-(N-homoallylamino) Zn−enolates using the 1-phenylethylamino group as a stereoinductor was developed (Scheme 85). Thus, carbocyclization of the Zn−enolate derived from **85** led to pyrrolidine **86** as a single diastereoisomer, presumably via chair like zinc−enolate−ene-type transition state **87** where excess of zinc salt is chelated by the aromatic ring (zinc(II)−Ar interaction) and the amino−zinc−enolate. Interestingly, this asymmetric version was also reported with substrate **88** bearing a cyclopropylidene moiety (Scheme 85).[143] Intramolecular carbozincation led to **89** and was once again totally diastereoselective. However, while the same relative configuration was observed between the chiral inductor and C2, a *trans* relationship was obtained between

Scheme 85



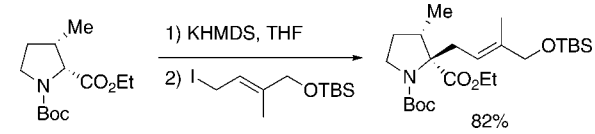
Scheme 86



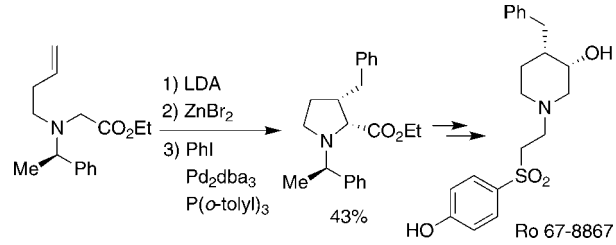
the newly created centers. It was proposed that, in this case, the bulkier cyclopropyl group disfavored the chairlike zinc−enolate−ene-type transition state similar to **87** and the carbometalation rather took place through boatlike transition state **90**.

The synthetic usefulness of the α-amino−zinc−enolate carbocyclization reaction has been very nicely exploited by Karoyan and co-workers to prepare proline chimeras of proteinogenic amino acids valuable for structure−activity relationship studies of biologically active peptides.[144−147] By functionalization of the enantiopure *cis*-3-zincioprolines **91** with a variety of electrophiles, *cis*-3-prolinomethionines, -glutamic acids, -arginines, -homoserines, -lysines, -glutamines, -leucines, and -homotryptophanes suitable for peptide synthesis have been prepared (Scheme 86). The electrophiles that have been used to trap the resulting organozinc species

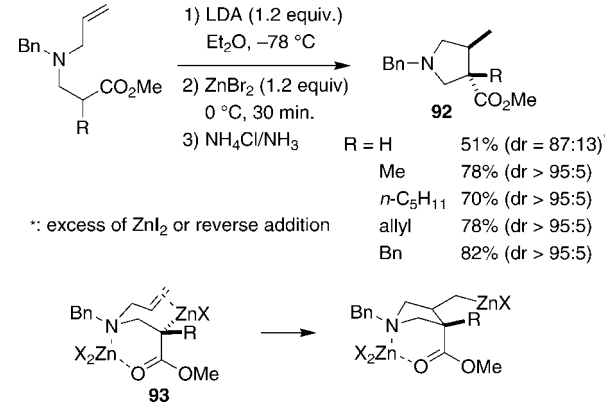
Scheme 87



Scheme 88



Scheme 89



include nitroalkenes, molecular O_2, molecular iodide, tosyl cyanide, aryl iodide, $RSSO_2R$, and allyl bromide. Furthermore, intramolecular carbozincation of α-amino enolates has been carried out on solid phase, thus allowing the preparation of libraries of 3-substituted prolines.[148]

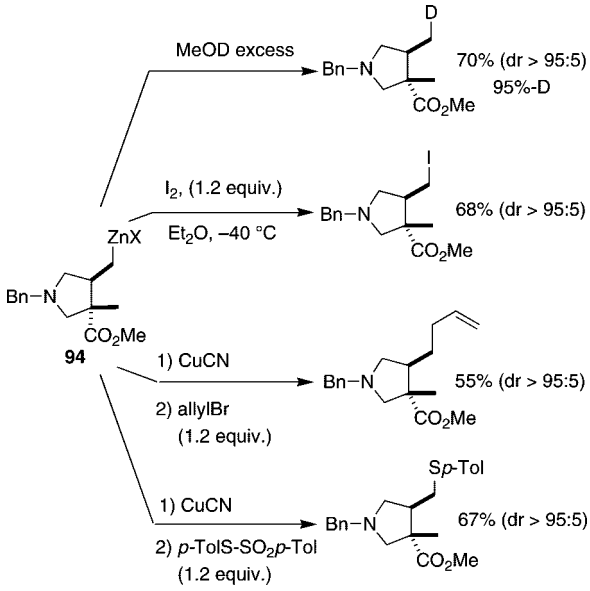
This methodology has also been recently applied in an approach to paraherquamides E and F, as well as asperparaline A. A potential common intermediate has been prepared by diastereoselective alkylation of the *β*-methylproline derivative (Scheme 87).[149]

A one-pot sequence involving carbocyclization and subsequent trapping of the organozinc adduct with aryl iodide under palladium catalysis has been developed[150] and applied[151] to the asymmetric synthesis of Ro 67-8867, a NMDA 2B receptor antagonist (Scheme 88).

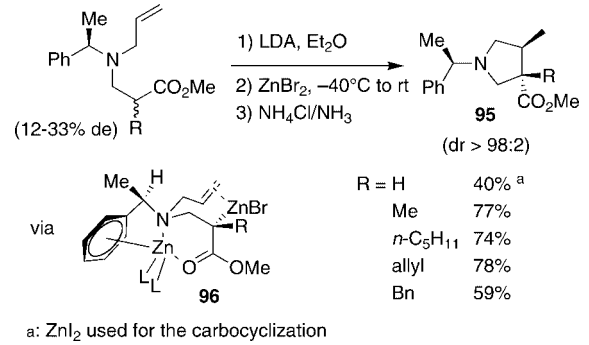
It is worthy of note that the analogous enantiopure *trans*-3-substituted prolines have been obtained using the carbocyclization method followed by epimerization of C2 stereogenic center either under basic[144] or thermal[145] conditions.

2.5.2.2. Enolates Derived from *β*-(*N*-Allylamino)esters. Carbocyclization of Zn−enolates derived from *β*-aminoesters has also been developed. Smooth intramolecular carbozincation leading to *β*-proline analogues was observed with Zn−enolates prepared from *β*-(*N*-allylamino)esters by deprotonation with LDA followed by transmetalation with a zinc salt (Scheme 89).[152] With substituted *β*-(*N*-allylamino)esters, the corresponding pyrrolidines **92** were obtained in good yields upon hydrolysis (70−82%) and, contrary to the α-aminoester case, as single *trans* isomers. With the less reactive unsubstituted substrate, however, a slight drop in yield and selectivity was noted. Furthermore, the use of ZnI_2 and/or reverse addition (addition of the Li−enolate onto a

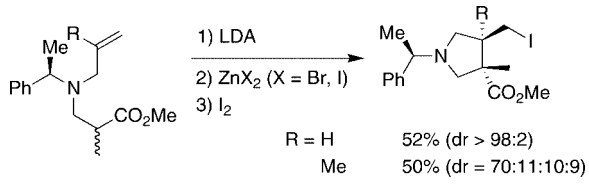
Scheme 90



Scheme 91



Scheme 92

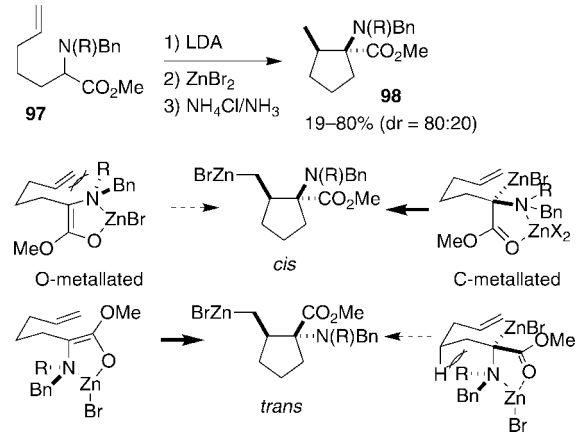


zinc bromide solution) was here necessary to prevent competitive β-elimination. A C-centered zinc−enolate-carbometalation-type reactive intermediate **93** accounts for the observed *trans* selectivity.[153] Here again, the functionalization of Zn−pyrrolidine **94** could be achieved with several electrophiles (Scheme 90).[152]

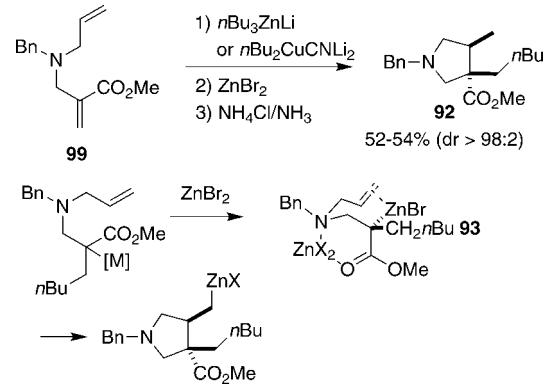
An enantioselective version using the 1-phenylethylamino as a stereodirecting group was also developed (Scheme 91).[154] *trans*-Pyrrolidines **95** were obtained in diastereo- and enantiomerically pure form (even in the case of the unsubstituted amino ester, i.e., when R = H). Cyclization via C-metalated reactive intermediate **96** involving a zinc chelation between the methoxy group and the nitrogen was proposed to account for the observed selectivities. The chirality transfer would result from an interaction between the chelated zinc salt and the aryl moiety.

Again, the organometallic species resulting from carbozincation was reacted further with electrophiles leading to diversely substituted β-prolines (Scheme 92). Interestingly, intramolecular addition also took place on a methallyl moiety,

Scheme 93



Scheme 94



offering the opportunity to generate stereoselectively two contiguous quaternary carbon centers, though the levels of stereoselectivity remained moderate.[154]

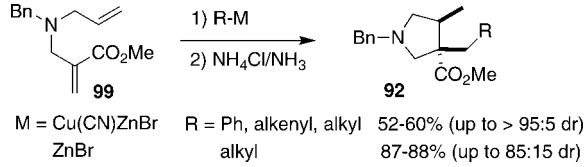
2.5.2.3. Enolates Derived from α-Pentenyl-α-aminoesters. The carbocyclization of Zn−enolates of α-pentenyl-α-aminoesters **97** furnished the corresponding *cis*-1-amino-1-methoxycarbonyl-2-methyl cyclopentanes **98** in low to good yields and with moderate levels of stereoselectivity (Scheme 93).[153] From a mechanistic standpoint, the formation of the major *cis* compounds indicates that, in this case, even though an α-amino ester is involved, carbozincation presumably proceeds through a C-metalated reactive intermediate, as an O-metalated intermediate would have afforded the *trans*-cyclopentanes.

2.5.3. Domino 1,4-Addition/Carbocyclization Reactions

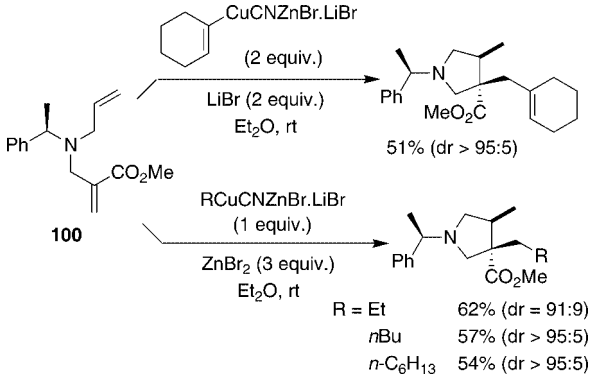
The possibility to generate β-aminozinc enolates by 1,4-addition of organometallic reagents onto an appropriate Michael acceptor was also studied. Following Michael addition of triorganozincates or higher-order cyanocuprates onto (*N*-allylamino)enoate **99**,[155] transmetalation with $ZnBr_2$ led to a Zn−enolate intermediate that underwent carbocyclization (Scheme 94). The cyclization was totally diastereoselective and afforded the same *trans*-isomer **92** (R = n-C_5H_{11}) that had been obtained previously from β-(*N*-allylamino)esters (see section 2.5.2.2), presumably via intermediate **93**, which tended to prove that the intermediate Zn−enolate behaved similarly regardless of its preparation method (deprotonation/transmetalation or 1,4-addition/transmetalation).

Species that had been previously described to undergo 1,4-addition processes only under Lewis acid-activation or in

Scheme 95



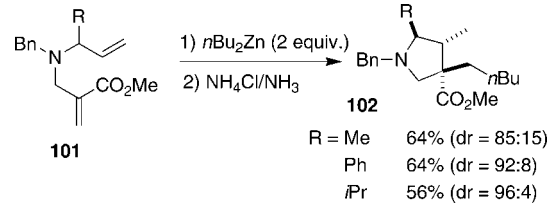
Scheme 96



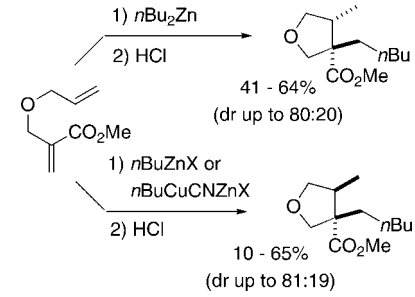
the presence of TMSCl also underwent clean 1,4-addition/carbocyclization domino reaction without any additives. Alkyl−, vinyl−, and arylcopper−zinc reagents RCu(CN)-ZnBr were reacted with enoate **99** and gave the desired *trans*-2,3 disubstituted pyrrolidines **92** in good yields and with good to excellent levels of diastereoselectivity. In a similar manner, less reactive organozinc halides also underwent the domino process and furnished the corresponding *trans* cyclized derivatives in good yields but slightly lower diastereoselectivities (Scheme 95).[156] The diastereoselectivity of the carbocyclizations involving alkylcopper−zinc and alkylzinc halides as nucleophiles was found to be dramatically influenced by both the amount and the nature of salts (LiX, ZnX_2, CuX) present in the reaction mixture.

Reaction of copper−zinc mixed reagents with enantiopure enoate **100** resulted in a smooth domino process with an excellent chirality transfer, leading to the corresponding β-prolines in basically enantio- and diastereomerically pure form (Scheme 96).[154] Here again, the amount of salts (LiX, ZnX_2) was found to strongly influence the selectivity. While aryl− and alkenylcopper−zinc reagents gave excellent levels of diastereoselectivity (51−58% yield, dr > 95:5) in the standard conditions (2 equiv of RCuCNZnX·LiX, prepared from RLi·LiX), additional zinc salts (typically 3 equiv) were

Scheme 98



Scheme 99



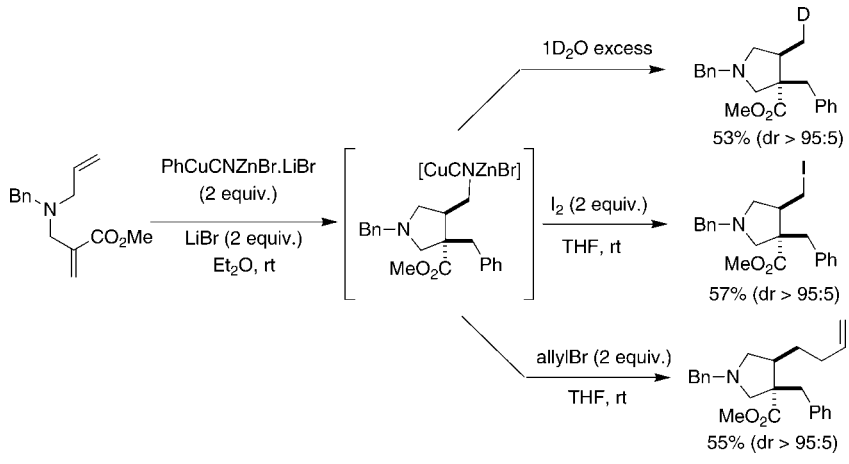
crucial to ensure a high chirality transfer (54−62% yield, dr up to >95:5) with alkylcopper−zinc reagents (RCuCNZnBr·LiX, prepared from the "salt-free" RLi).

As illustrated with the particular cases of PhCu(CN)ZnBr (Scheme 97) and Bu_2Zn,[156,157] the intermediacy of metalloprolines in the domino processes with both copper−zinc and dialkylzinc reagents has been evidenced by their reaction with several electrophiles.

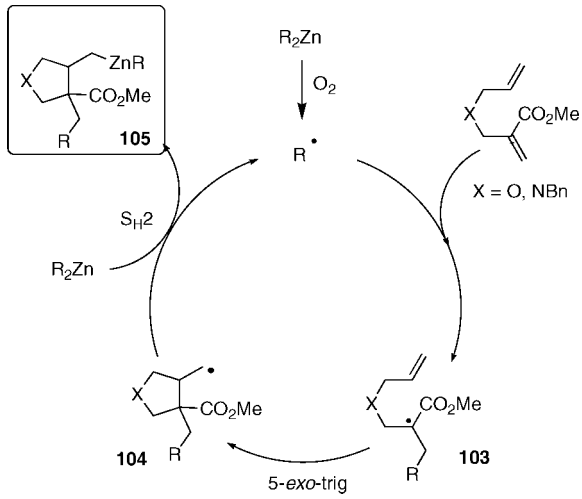
Enoates **99** and **101** reacted with dialkylzinc reagents to give the corresponding pyrrolidines **102** with moderate to high levels of diastereoselectivity (49−88% yields, dr = 75:25 up to 96:4), but this time in favor of the *cis*-isomers (Scheme 98).[157] Reaction of di-*n*-butylzinc with enantiopure enoate **100** showed no chirality transfer, and thus, a mixture of all possible diastereoisomers was obtained.[154]

The 1,4 addition/carbocyclization process could also be carried out with β-allyloxy enoates, thus providing polysubstituted tetrahydrofurans (Scheme 99).[158] The same general features as for amino enoates were observed: the use of dialkylzinc reagents led to the formation of 2,3-*cis* tetrahydrofurans, while the use of organozinc and copper−zinc mixed reagents (though the latter in much lower yields) furnished 2,3-*trans* tetrahydrofurans. Competitive 1,4-addition/fragmentation sometimes hampered the efficiency of the reaction, especially in the presence of Lewis acids. In

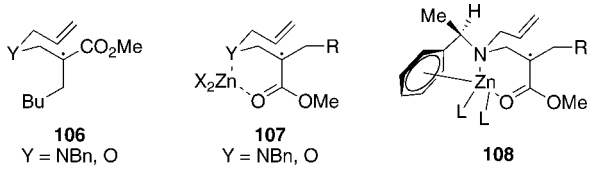
Scheme 97



Scheme 100



Scheme 101

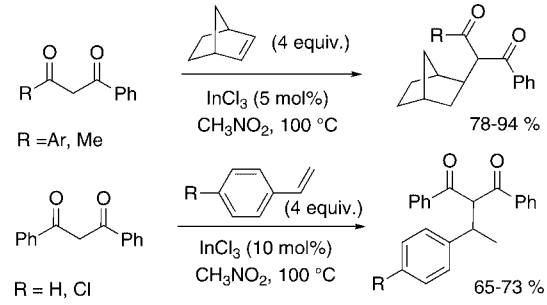


particular, it precluded the use of copper−zinc mixed reagents. Moreover, lower levels of selectivity were generally observed for reactions leading to the *trans* diastereomers.

Mechanistic investigations led to the proposal of a radical-polar crossover mechanistic picture described as following (Scheme 100). Oxygen initiation produces a radical from the organometallic species. This nucleophilic radical adds onto the enoate to give electrophilic enol radical **103**, which undergoes a 5-*exo*-trig cyclization to form radical **104**. Reduction by the organometallic species gives organozinc **105** and a radical that propagates the radical chain. This remarkable reduction seems to be unfavorable, and the driving force of the reaction could be the chelation of the resulting organozinc species by the methoxycarbonyl moiety.

The diastereoselectivity of the radical-polar domino process involving R_2Zn, RZnX, and RCuCNZnX (R = alkyl) was proposed to result from the diastereoselectivity of the 5-*exo*-trig radical cyclization (Scheme 101). In the case of nBu$_2$Zn, the carbocyclization leading to *cis*-pyrrolidines or furans occurs via an intermediate **106** where the methoxycarbonyl moiety adopts a more favorable pseudoequatorial position. In the presence of stronger Lewis acids, however, chelation of the metal salt [Zn(II) or Cu(I)] by the nitrogen (or oxygen) atom and the oxygen atom of the carbonyl group makes the cyclization occur via **107**, leading to *trans*-pyrrolidines (or *trans*-furans). Finally, the high levels of diastereoselectivity observed for reactions of copper−zinc mixed reagents with enoate **100** having the stereodirecting α-methylbenzyl group can be explained on the basis of an Ar−metal interaction. Radical intermediate **108**, similar to organometallic intermediate **96** in Scheme 91, accounts for the observed selectivity. Remarkably, the bases of stereoselectivity were found to be the same in both polar and radical/polar mechanisms, although different intermediates were involved (organometallic or radical species).

Scheme 102



2.6. Group 13: Indium

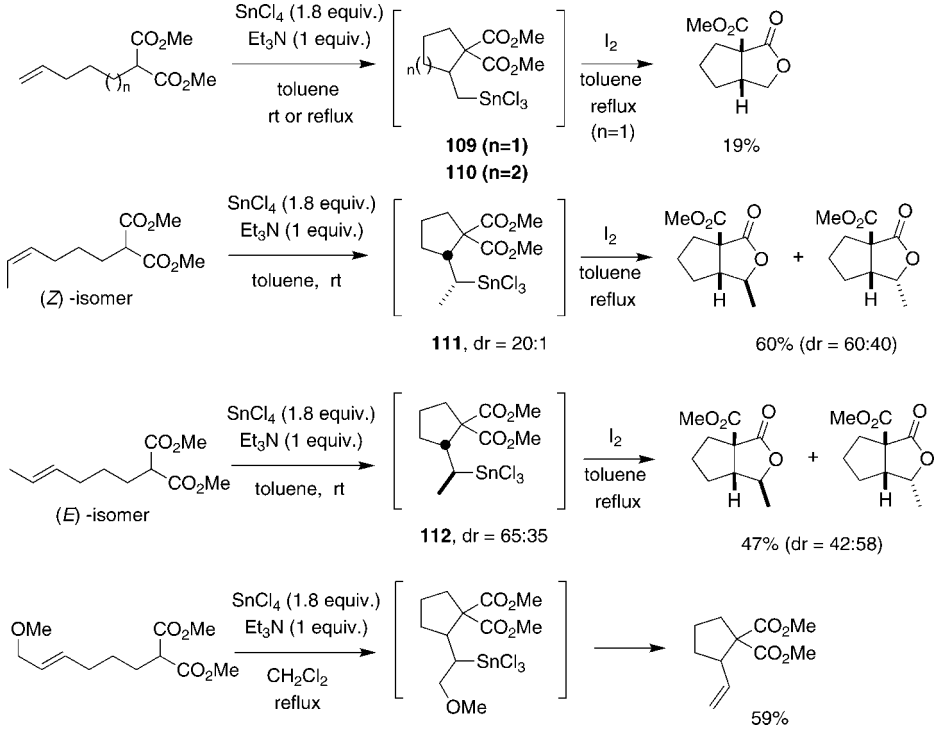
Yuan and Shi reported recently the addition of 1,3-dicarbonyl compounds onto alkenes.[159] For the reaction between dibenzoylmethane and norbornene, among the several Lewis acidic catalysts screened, only indium and gallium salts emerged as efficient promoters. In the optimized conditions using $InCl_3$ (5 mol %) at 100 °C in nitromethane, the product resulting from *exo*-addition onto the reactive bicyclic alkene was obtained in 78% yield (Scheme 102). Other dibenzoylmethane and 1-benzoylacetone compounds were also found to react with norbornene from its *exo*-face and gave the corresponding adducts in good yields. For nonsymmetrically substituted nucleophiles however, a mixture of diastereoisomers was obtained with low levels of diastereoselectivity. For their part, acetylacetone and 1,3-cyclohexadione gave the adducts in moderate yields. Concerning the scope of alkene substrates, it was found that dibenzoylmethane reacts with styrenes regioselectively at the benzylic carbon, albeit with a higher $InCl_3$ catalyst loading (10 mol %). Dihydropyran proved to be highly reactive toward the addition that was best achieved in this case at 50 °C in CH_2Cl_2.

2.7. Group 14: Tin(IV)-Mediated Additions

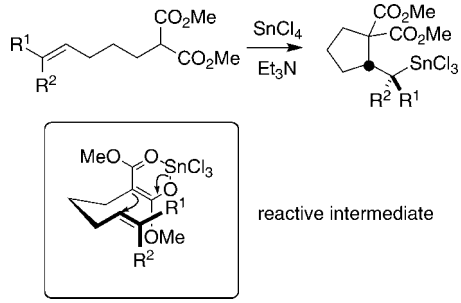
$SnCl_4$ was recognized as a good catalyst for the Conia-ene reaction at an early stage. For instance, the cyclization of β-ketoesters bearing appended alkenes was used in the late 1970s for the total syntheses of mokupalide[160] and Δ-$^{8(14)}$-podocarpen-13-one.[161]

Taguchi and co-workers reported more recently the Sn(IV)-promoted cyclization of malonate derivatives onto terminal- and 1,2-disubstituted alkene moieties.[162] The cyclization took place in the presence of an excess of $SnCl_4$ (1.8 equiv) and a stoichiometric amount of Et_3N. The reaction was carried out in toluene, at room temperature or reflux, depending on the length of the alkenyl side chain. The carbometalation process led to the formation of cyclic alkyl−Sn intermediates, which could be characterized by ^{1}H and ^{13}C NMR (Scheme 103). Although the alkyl−Sn intermediates were formed in high yields (NMR analysis), they showed a low reactivity toward electrophiles, probably due to intramolecular complexation of the tin atom with one of the two carbonyl groups, as observed in the solid state by X-ray analysis. Synthetically useful transformations of these adducts thus remained difficult and highly dependent upon the substitution at the alkene moiety (terminal vs disubstituted). In the case of primary alkyl−Sn bonds, only treatment with iodine in refluxing toluene led to the functionalization of the C−Sn. Stannane intermediate **109** afforded the corresponding bicyclic lactone in low yield (19%) via an iodination/lactonization sequence. However, under the same

Scheme 103



Scheme 104



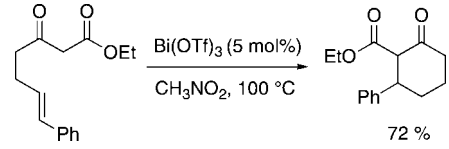
conditions, the related stannane **110** led to degradation. Iodination of secondary alkyl−Sn intermediates proved to be more efficient. Cyclization of (*Z*)-4-hexenylmalonate (respectively, (*E*)-4-hexenylmalonate) afforded alkyl−Sn intermediate **111** (respectively, **112**) with a 20:1 diastereoisomeric ratio (respectively, 65:35 dr). Iodination led to a mixture of bicyclic lactones in only 60% yield (respectively, 47%) and poor stereoselectivity (dr = 60:40 (respectively, dr = 42:58)). Interestingly, the presence of a leaving-group on the alkenyl side chain allowed the facile removal of the Sn moiety via β-elimination.

The proposed mechanism for the carbostannation involves a *syn*-addition of a Sn−enolate (generated in situ from the malonate derivative in the presence of $SnCl_4/Et_3N$) onto the alkenyl side chain as depicted in Scheme 104.

2.8. Group 15: Bismuth(III)-Mediated Additions

The direct hydroalkylation of alkenes with 1,3-dicarbonyl compounds was also shown to be catalyzed by bismuth salts.[163] The use of 5 mol % $Bi(OTf)_3$ at 100 °C in the highly polar solvent CH_3NO_2 was optimum. Aliphatic and aromatic 1,3-diketones reacted intermolecularly with a variety of styrenes bearing electron-withdrawing or electron-donating substituents to give the corresponding adducts in moderate to good yields (41−89%) from reaction at the internal carbon.

Scheme 105



Indene, norbornene, and cyclohexadiene were also suitable partners for this hydroalkylation reaction. Even though the catalytic system was not efficient to achieve intermolecular hydroalkylation with β-ketoesters, intramolecular addition in a 6-*endo*-mode was possible (Scheme 105).

3. Addition of Stabilized Carbanions onto Dienes

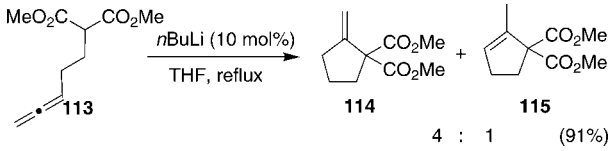
1,2-Dienes (allenes) and 1,3-dienes have been considered as olefinic partners for carbometalation reactions. While true carbometalation reactions of allenes are scarce, far more reports have concerned the addition onto 1,3-dienes. Moreover, the mechanism of the carbometalation of allenes (particularly in Pd(II)-mediated additions) has been discussed for a long time. By contrast, activation of 1,3-dienes with organometallic species is well-established, and a number of metal−dienes complexes have been isolated and characterized.

3.1. Additions onto 1,2-Dienes (Allenes)

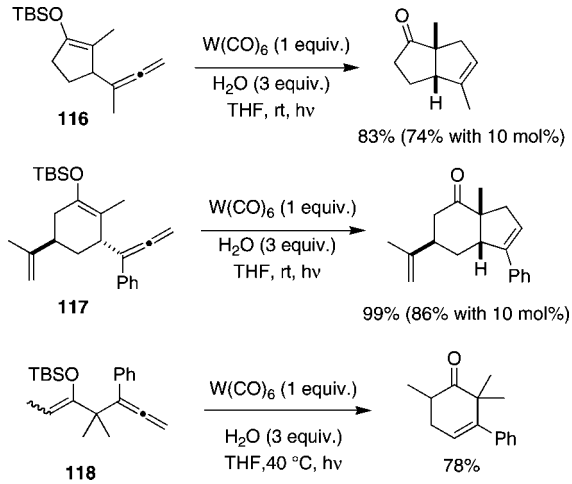
3.1.1. Group 1: Lithium(I)-Mediated Additions

The reaction of allenyl derivative **113** in the presence of a catalytic amount of *n*BuLi gave the corresponding cyclized products **114** and **115** in 91% combined yield (Scheme 106). In this case, *exo*-methylene derivative **114** and cyclopentene **115** were obtained in a 4:1 ratio following protonation of the allyllithium intermediate that results from the carbocyclization.[164]

Scheme 106



Scheme 107



3.1.2. Group 6: Tungsten(0)-Mediated Additions

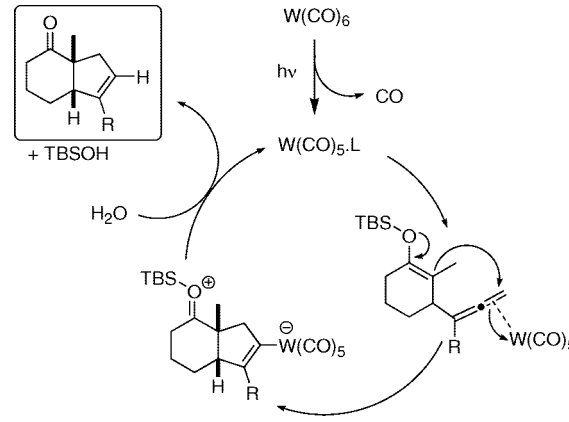
Iwasawa and co-workers reported a very efficient W(0)-promoted intramolecular addition of silyl enol ethers onto 1,2-dienes.[165] The cyclization of 6-silyloxy-1,2,5-trienes was carried out at room temperature in THF in the presence of a stoichiometric amount of a W(0) complex (either $W(CO)_5$(THF) prepared separately or $W(CO)_6$ used under irradiation). The irradiation enhanced the rate of ligand exchange and, thus, shortened the reaction time (4 h instead of 3 days), allowing the reaction to be carried out with a catalytic amount of the catalyst (typically 10 mol %). The reaction was carried out in the presence of 3 equiv of H_2O in order to hydrolyze the anionic vinyl−W(0) intermediate (see Scheme 108) and regenerate the catalyst. The formation of the vinyl−W intermediate was proved by conducting the reaction in the presence of D_2O. 6-Silyloxy-1,2,5-trienes such as **116** or **117**, as well as 5-silyloxy-1,2,5-trienes **118**, gave the cyclopentenyl and cyclohexenyl adducts in a highly regioselective 5- or 6-*endo* manner, respectively (Scheme 107). Worthy of note, this approach complements nicely the related cyclization onto alkynes (see section 4.3.2, cyclization of **171** in Scheme 162), which leads to the other regioisomer.

The proposed mechanism consists of the nucleophilic addition of the silyl enol ether moiety onto a (η^2-allene)W(0) complex. The resulting anionic vinyl−W(0) species is protonated by H_2O, thus leading to the cyclized product and regenerating the catalyst (Scheme 108).

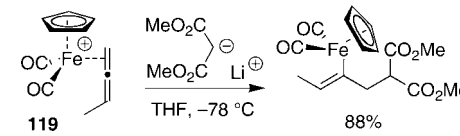
3.1.3. Group 8: Iron(II)-Mediated Additions

Addition of lithium dimethyl malonate onto cationic (*syn*-3-methylallene)(η^5-C_5H_5)$Fe(CO)_2$ complex **119** was reported to give the corresponding σ-vinyl−Fe complex in 88% yield via a highly regioselective attack at the C1 position (Scheme 109).[24]

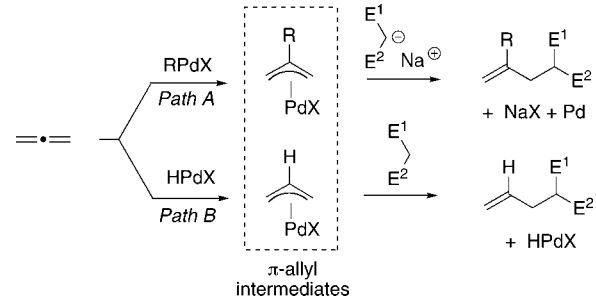
Scheme 108



Scheme 109



Scheme 110



3.1.4. Group 10: Palladium(II)-Mediated Additions

The palladium-mediated addition of stabilized carbanions onto allenes has been achieved under basic or neutral conditions. Although the mechanism of the reaction has been debated for a long time, it is now widely admitted that this reaction involves the formation of a π-allyl−Pd intermediate (Scheme 110) either through a carbopalladation reaction (involving a RPdX species, path A)[166−176] or a hydropalladation reaction (involving a HPdX species, path B).[177−185] The resulting π-allyl−Pd is attacked by the enolate or enol nucleophile (mainly as an enolate species in path A, whereas an enol or enolate form can be envisioned in path B, depending on the reaction conditions). While the overall process results in the formation of an addition product, these reactions do not involve true carbometalation of unactivated dienes with stabilized carbanions and, thus, will not be discussed in this review.

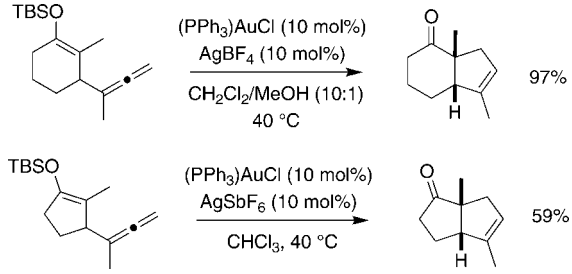
3.1.5. Group 11: Gold(I)-Mediated Additions

Gold-catalyzed addition of enolates onto allenes are still scarce. In the only example to our knowledge, Toste and co-workers reported the cyclization of silyl enol ethers bearing a pendant allenyl side chain in the presence of a catalytic amount of Au(I) salts (Scheme 111).[186]

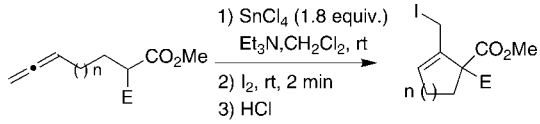
3.1.6. Group 14: Tin(IV)-Mediated Additions

Taguchi and co-workers reported examples of highly regioselective Sn(IV)-mediated cyclization of malonate

Scheme 111

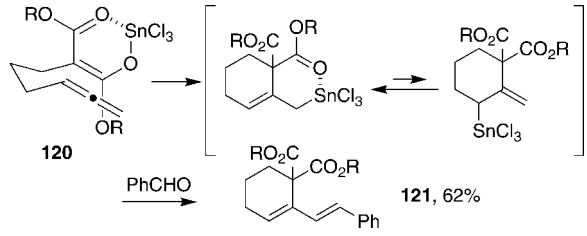


Scheme 112



n = 1	E = CN	62%
1	C(O)Me	79%
2	CN	39%
2	C(O)Me	61%
3	CO_2Me	10%

Scheme 113



derivatives onto 1,2-dienes.[187] The reaction was carried out at room temperature in CH_2Cl_2 in the presence of $SnCl_4$ (1.8 equiv) and Et_3N (1 equiv). Malonate, acetoacetate, and cyanoacetate derivatives could be cyclized efficiently in a regioselective 5-*exo*- or 6-*exo*-mode, leading to the corresponding allyl−Sn species via the exclusive addition of Sn−enolate at the central atom of the allene. Upon regioselective trapping of the resulting allyl−Sn species with I_2, the corresponding allyl iodides were obtained in moderate to high yields, while 7-membered rings were obtained in only low yields (Scheme 112). Other Lewis acids such as $Ti(OiPr)_4$ or $Sn(OTf)_2$ did not promote the reaction, and the use of $TiCl_4$ led directly to the cyclized allyl chloride following halogen exchange.[162,187]

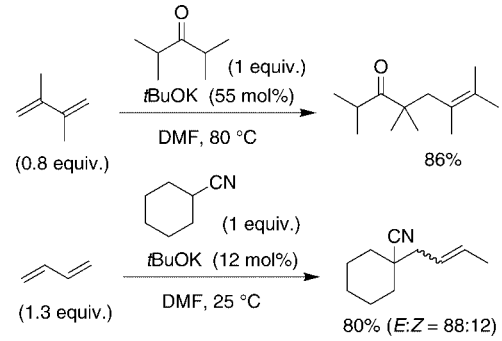
The resulting allyl−Sn species could also engage in reaction with aldehydes. For example, the cyclization of Sn−enolate **120**, followed by treatment with benzaldehyde, gave diene **121** in 62% yield after addition onto the aldehyde and subsequent dehydration (Scheme 113). Since allyl−Sn are known to react with aldehydes via allylic rearrangement,[188] this suggested that two different allyl−Sn species were in equilibrium via a metallotropic rearrangement.

Worthy of note, the regioselectivity observed in this cyclization was in sharp contrast with the regioselectivity of the related Pd(0)-catalyzed carbocyclization of malonate derivatives onto allenes, which proceeds via the formation of a π-allyl−Pd(II) complex intermediate.

3.2. Addition onto 1,3-Dienes

The 1,3-diene unit is known to form stable complexes with a variety of transition metals, thus resulting in activation of the diene ligand toward nucleophilic addition. A range of 1,3-diene metal salts have been reported to undergo carbometalation reactions with metal enolates, including mainly molybdenum, iron, and palladium complexes.

Scheme 114



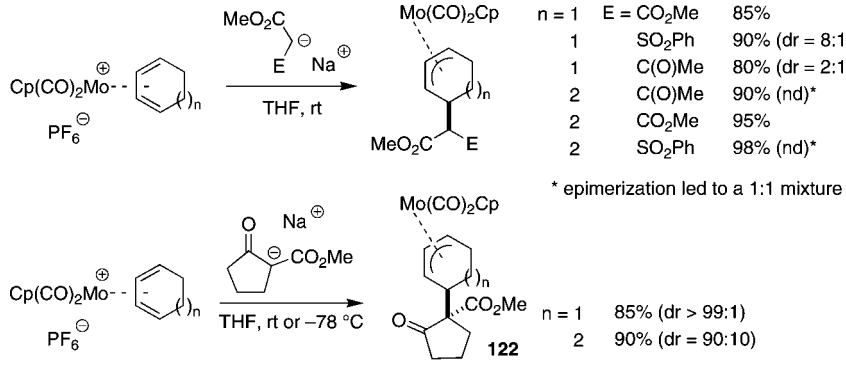
3.2.1. Group 1: Potassium(I)-Mediated Additions

Direct nontransition metal-promoted additions of enolates onto 1,3-dienes are, on the contrary, very rare. A significant difficulty lies in the fact that the addition products can also undergo a second addition, thus leading to mixtures of products. The first report of a system allowing one to efficiently achieve such a transformation was reported in 2008.[189] A slight excess of 2,4-dimethyl-3-pentanone was found to react with 2,3-dimethyl-1,3-butadiene in the presence of a catalytic amount of *t*BuOK to afford the linear monoaddition compound in 86% yield (Scheme 114). The reaction took place at 60 °C or higher temperatures in polar aprotic solvents such as DMF, DMSO, or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU). NMP could not be used because the addition of the 1-methyl-2-pyrrolidinone anion onto the 1,3-diene was also observed. On the contrary, DMSO did not interfere with the expected reaction outcome despite the fact that the addition of the corresponding dimsyl anion onto 1,3-dienes has also been reported.[190] Under the optimized conditions (*t*BuOK, DMF), various other ketones and nitriles also underwent addition onto 2,3-dimethyl-1,3-butadiene and gave the monoadducts in moderate to high yields (45−86%). In the case of nitriles, which reacted more cleanly and more rapidly than ketones, a slight excess of diene was used to avoid a subsequent addition of the product onto the diene. The procedure was also quite general with respect to the 1,3-diene partner. For instance, 1,3-butadiene showed a much higher reactivity and addition could be observed at room temperature and even below. The products were obtained in good to high yields (60−80%) as a mixture of *E*/*Z* isomers (*E*/*Z* ratio from 1:1 up to 88:12). For unsymmetrical or cyclic 1,3 dienes, though yields were good, the levels of regio- and stereoselectivity were often low and, as a result, product distribution was complicated.

3.2.2. Group 6: Molybdenum(I)−Diene Complexes

Cationic η^4-diene complexes of molybdenum are readily prepared from the corresponding (η^3-allyl)$CpMo(CO)_2$ complexes by β-hydride abstraction with strong cations such as $Ph_3C(PF_6)$ or HBF_4.[191] Complexation with the cationic $CpMo^+(CO)_2$ complex activates the 1,3-diene moiety toward nucleophilic addition and, in particular, toward addition of stabilized carbanion. The reaction is highly stereoselective as it takes place exclusively from the face opposite to the

Scheme 115

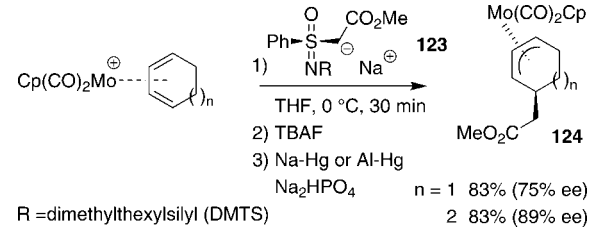


metal. In terms of regioselectivity, the addition occurs exclusively at the terminal position of the diene, in marked contrast with the behavior observed with (η^4-diene)Fe complexes (see section 3.2.3). The neutral (π-allyl)CpMo(CO)$_2$ complexes resulting from the addition are highly stable and can be easily isolated.[191,192] However, their low nucleophilicity precludes reaction with carbon electrophiles or protonation. Demetalation leading to the corresponding alkene thus requires activation of the molybdenum moiety (typically upon treatment with NO(PF$_6$)) followed by reduction with NaBH$_4$ and decomplexation.[191]

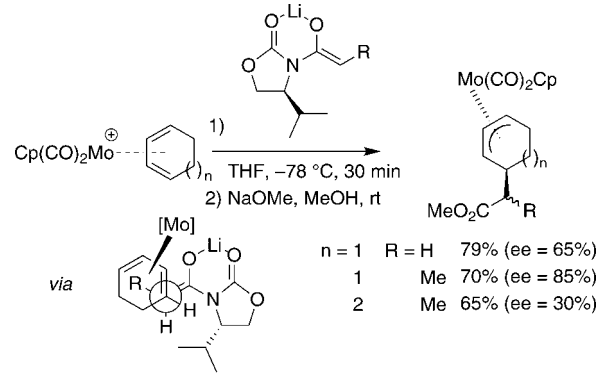
More specifically, Pearson and co-workers reported a series of studies on the intermolecular addition of the sodium anion of different active methylene and methyne compounds onto cationic [(η^4-diene)CpMo(CO)$_2$] complexes derived from substituted- and unsubstituted-1,3-cyclohexadienes[193−195] and 1,3-cycloheptadienes (Scheme 115).[196] The addition of β-ketoesters, α-sulfonylesters, and malonate derivatives was carried out at room temperature in THF and gave the corresponding neutral [(η^3-allyl)CpMo(CO)$_2$] complexes in high yields (80−98%). In some cases, prochiral nucleophiles led to the adducts with a very high level of diastereoselectivity, which was not rationalized by the authors.[194,195] For example, the addition of the sodium anion of methyl phenylsulfonylacetate onto the cationic complex [(η^4-1,3-cyclohexadiene)CpMo(CO)$_2$] gave the corresponding adduct in 90% yield as a 8:1 mixture of diastereoisomers (Scheme 115). Addition onto cycloheptadiene ligands afforded π-allyl complexes that epimerized readily. Interestingly, the reaction of the sodium salt of methyl 2-cyclopentanonecarboxylate with the cationic complex [(η^4-1,3-cyclohexadiene)CpMo(CO)$_2$] gave the corresponding nonepimerizable [(η^3-allyl)CpMo(CO)$_2$] complex **122** in high yield and excellent stereoselectivity (85% yield, dr > 99:1), whereas a somewhat lower selectivity was obtained in the addition onto the related [(η^4-1,3-cycloheptadiene)CpMo(CO)$_2$] complex (90% yield, dr = 90:10).[195]

Asymmetric versions of the addition onto (η^4-diene)Mo complexes using chiral nonracemic nucleophiles have been disclosed. Pearson and co-workers obtained good results by using optically pure sulfoximines[197,198] and *N*-acyloxazolidinones.[199] Addition of α-sulfoximine ester anions onto cyclic (η^4-diene)Mo complexes occurred readily at 0 °C in THF (Scheme 116). A very high level of chiral induction was observed in the addition of the sodium anion of bulky *N*-dimethylthexylsilyl (DMTS) sulfoximine **123** onto the cationic [(η^4-cycloheptadiene)CpMo(CO)$_2$] complex. The corresponding adduct **124** was obtained in high yield and high optical purity (83% yield after removal of the chiral auxiliary by desulfonylation, 89% ee). Similar levels of

Scheme 116



Scheme 117

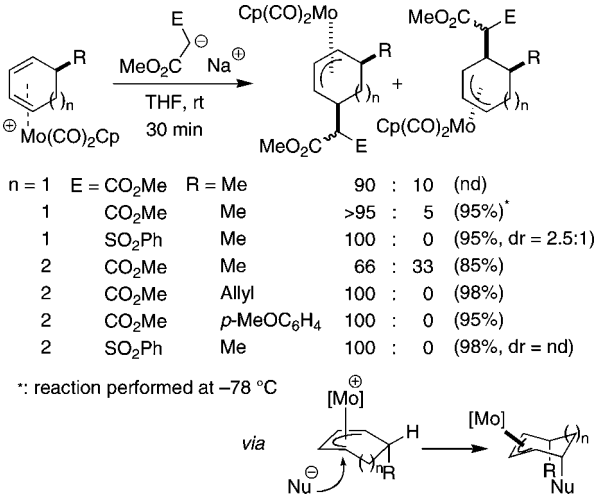


selectivity were obtained with the corresponding Na-anion of *N*-TBDMS sulfoximine and with the K-anion of these sulfoximines, but not with less sterically demanding (e.g., *N*-Me) or electron-withdrawing (e.g., *N*-Ts) substituent at the nitrogen atom, or with the Li-anions. Furthermore, the addition of *N*-DMTS sulfoximine ester onto the cationic [(η^4-cyclohexadiene)CpMo(CO)$_2$] complex furnished the adduct in high yield but with a lower level of enantioselectivity (80% yield after desulfonylation, 75% ee with the Na-anion or 80% ee with the K-anion).

The use of chiral stabilized nucleophiles derived from optically pure *N*-acyloxazolidinones gave slightly higher levels of chiral induction in the addition onto the cationic [(η^4-cyclohexadiene)CpMo(CO)$_2$] complex (up to 85% ee). The stereoselectivity observed was explained by an open transition state with a synclinal arrangement of the Li−enolate and the (η^4-diene)Mo complex (Scheme 117). Interestingly, following this approach, the chiral auxiliary could be recovered after saponification, unlike in the case of sulfoximines, where removal led to its destruction. Surprisingly, the selectivity of the addition onto the related (η^4-cycloheptadiene)Mo complex was very low (ee < 32%).[199]

The regio- and stereoselectivity of the addition onto cationic [(η^4-diene)CpMo(CO)$_2$] complexes of substituted 1,3-cyclohexadiene and 1,3-cycloheptadiene was also studied.

Scheme 118

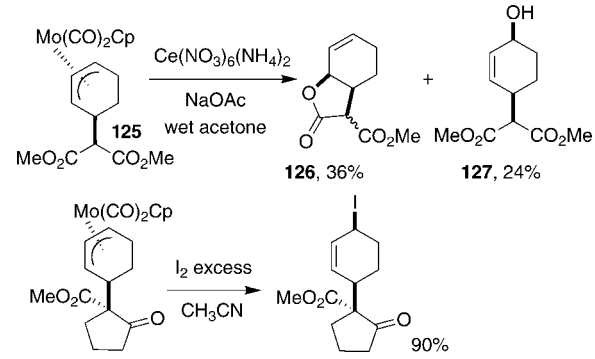


Again, a different behavior was observed between 6- and 7-membered rings for most cases.[196,200] By analogy with the related (η^4-cyclohexadiene)$Fe(CO)_2L$ complexes for which the structure had been determined by X-ray analysis,[201−203] the shape of the cyclohexadiene ligand in cationic [(η^4-diene)$CpMo(CO)_2$] complexes was proposed to resemble a boat cyclohexene. In this conformation, the substituent occupies a pseudo-axial disposition and directs the addition of the nucleophile at the remote position of the cyclohexadiene ligand, leading to the highly regioselective formation of [(η^3-allyl)$CpMo(CO)_2$] complexes (Scheme 118). For example, the addition of the Na-anion of dimethyl malonate onto the cationic [(η^4-cyclohexadiene)$CpMo(CO)_2$] complex at room temperature gave the adduct resulting from the regioselective addition at the less hindered position of the diene ligand and only a small amount (<10%) of the second regioisomer. A slightly higher selectivity was obtained at lower temperature. On the contrary, the addition of the Na-anion of dimethyl malonate onto related cycloheptadiene ligands resulted in a poor regioselectivity (2:1 in favor of the addition at the less hindered position). However, in the addition of more sterically demanding nucleophiles such as α-phenylsulfonylesters, or with bulkier substituents at the diene ligand (R = allyl, aryl), complete regioselectivity was observed in all cases, even at room temperature.

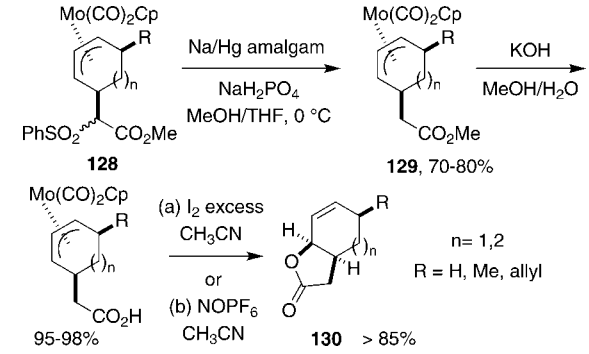
Though direct protonation or reaction with carbon electrophiles could not be achieved (contrary to the related complexes obtained by nucleophilic addition onto neutral $Fe(CO)_3$(diene) complexes, see section 3.2.3), further transformations of the resulting molybdenum π-allyl complexes were nevertheless possible. As reported for (dienyl)$Mn(CO)_3$ complexes,[192,204] upon treatment with $Ce(NO_3)_6(NH_3)_2$ (CAN) in buffered wet acetone, smooth decomplexation accompanied by introduction of an OH group (*trans* to the metal moiety) was observed. With unsymmetrical allyl ligands, this process resulted in the formation of regioisomers, as illustrated by the oxidation of **125** that led to a mixture of **126** and **127** (Scheme 119).[194] Alternatively, the neutral (η^3-allyl)$CpMo(CO)_2$ complexes could be trapped with iodine, leading to the regioselective formation of the corresponding allyl iodide derivatives.[195]

This methodology was used for the preparation of diastereomerically pure cyclohexene derivatives. Following saponification of the methoxycarbonyl substituent of complexes **129** (resulting from the desulfurization of **128**) and

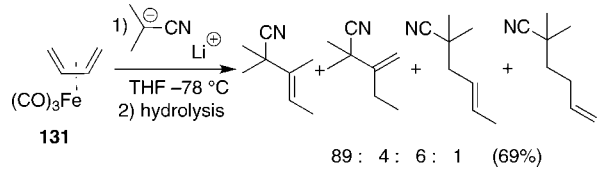
Scheme 119



Scheme 120



Scheme 121



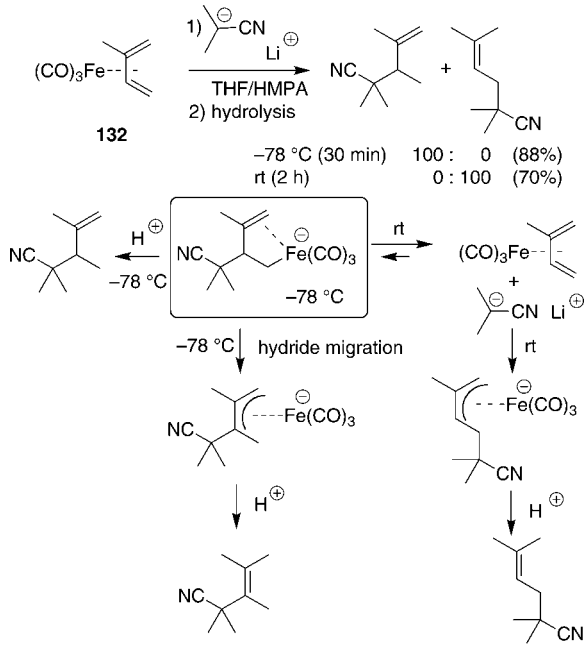
oxidative treatment with I_2, the corresponding lactones **130** were obtained in high yields (Scheme 120). The approach proved useful in the synthesis of the east-part of magnamycin B, a macrolide antibiotic.[195]

3.2.3. Group 8: Iron(0)−Diene Complexes

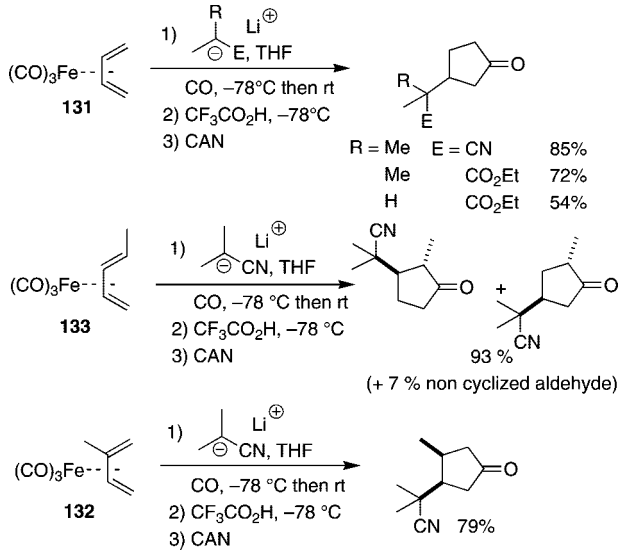
While the relative unstability of iron tetracarbonyl complexes of simple alkenes represents a limitation for their practical application in synthesis (see section 2.2), the greater stability of neutral (η^4-1,3-diene)$Fe(CO)_3$ complexes has attracted far more attention of synthetic chemists. Inter- and intramolecular additions of stabilized nucleophiles onto (η^4-1,3-diene)iron complexes of acyclic- and cyclic dienes have been disclosed. In this case, addition of the nucleophile resulted in the formation of an allylmetal or, alternatively, a chelated homoallyl complex, which can then react following different pathways.

3.2.3.1. Intermolecular Additions. Semmelhack and coworkers have extensively investigated the addition of stabilized nucleophiles onto the (η^4-butadiene)- and (η^4-cyclohexadiene)$Fe(CO)_3$ complexes **131** and **137**.[8,205−211] Kinetically controlled addition at −78 °C was strongly favored at an unsubstituted internal position of the diene ligand. The resulting anionic (η^3-homoallyl)$Fe(CO)_3$ complexes led to the corresponding alkene after protonation (Scheme 121). This observation was supported by ab initio calculations indicating a lower electronic density at the internal position of the diene ligand in the complex.[205,206]

Scheme 122



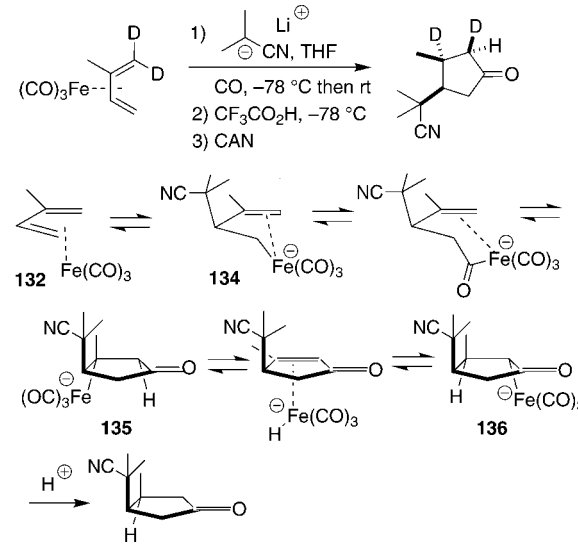
Scheme 123



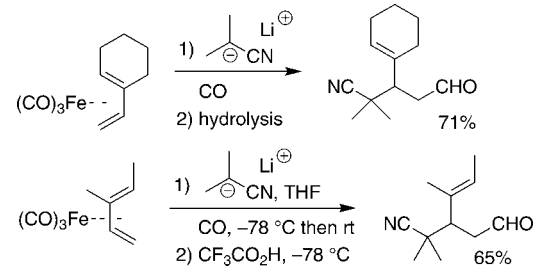
However, the addition was found to be reversible at higher temperature; therefore, equilibration of the initially formed chelated homoallyl complexes into the more stable (η^3-allyl)Fe complexes was observed via nucleophilic addition at a terminal position (substituted preferred over unsubstituted) and, in special cases, via hydride migration.[210] In the case of complex **132**, the addition of $LiC(CH_3)_2CN$ was complete within a few minutes at −78 °C and strongly favored at C3. The rearrangement into the corresponding allyl complex occurred during warming to 0 °C and was complete after 2 h at 25 °C (Scheme 122).

When the reaction was carried out under a CO atmosphere (1.5 atm), the anionic (η^3-homoallyl)$Fe(CO)_3$ complexes intermediate could be efficiently converted into the corresponding anionic (acyl)Fe complexes via CO insertion. With most open-chain monosubstituted 1,3-diene ligands, further cyclization occurred, producing cyclopentanone derivatives (Scheme 123).[208] For instance, the addition of a variety of stabilized nucleophiles onto (η^4-butadiene)$Fe(CO)_3$ complex **131** at −78 °C under a CO atmosphere gave the cyclopentanone derivatives in good to high yields (54−85%). Reaction of 2-lithio-2-methylpropionitrile with (η^4-(*E*)-piperylene)-$Fe(CO)_3$ complex **133** led to a mixture of cyclopentanones (approximately in a 1:1 ratio) resulting from nonregioselective addition of the nucleophile at both internal positions of the diene ligand. Interestingly, cyclopentanone derivatives were formed with a high level of diastereoselectivity from 2-substituted 1,3-dienes. For example, nucleophilic addition of 2-lithio-2-methylpropionitrile onto (η^4-isoprene)$Fe(CO)_3$ complex **132** at −78 °C under a CO atmosphere gave exclusively *cis*-3,4-disubstituted cyclopentanone in 79% yield.

Scheme 124



Scheme 125

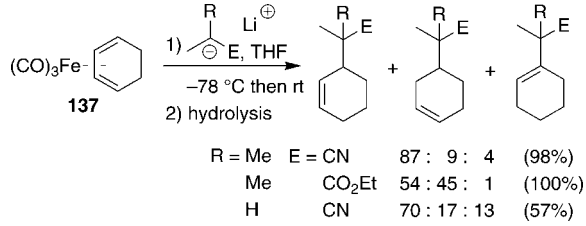


The formation of the less stable *cis*-isomer is consistent with a regioselective addition at the internal position of the diene ligand, leading to the formation of anionic (η^3-homoallyl)$Fe(CO)_3$ complexe **134**, followed by rapid migration onto a carbonyl ligand and intramolecular alkene insertion (Scheme 124). A β-hydride elimination/addition sequence was proposed to explain the stereospecific rearrangement of the initial cyclopentanone intermediate **135** into the corresponding Fe−enolate derivative **136** and was supported by deuterium labeling experiments. It is noteworthy that the anionic (η^3-allyl)$Fe(CO)_3$ complexes formed at higher temperature did not readily incorporate CO.

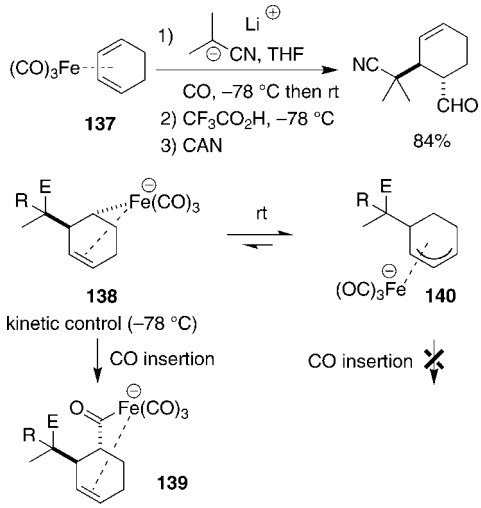
With substituents at both C1 and C2 of the diene ligand, ring closure to form cyclopentanones was not observed and only aldehydes were obtained following CO insertion and protonation (Scheme 125).[208]

The same preference for regioselective addition of stabilized anion at the internal position of the diene ligand was observed with cyclic ligands such as in (η^4-cyclohexadiene)-$Fe(CO)_3$ **137** (Scheme 126), in contrast with the behavior of

Scheme 126



Scheme 127

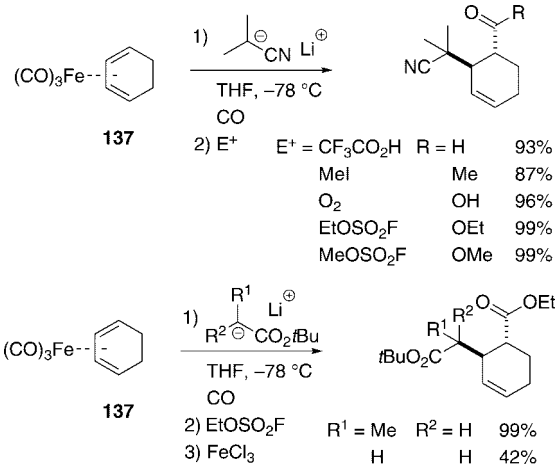


cationic (η^4-diene)Mo complexes (see section 3.2.2). Cyano-stabilized anions and ester enolates added efficiently onto **137** to give a mixture of cyclohexene derivatives in good to high yields (57−100%). Less reactive nucleophiles including ketone enolates and diethyl malonate anions did not react under the same reaction conditions.[207]

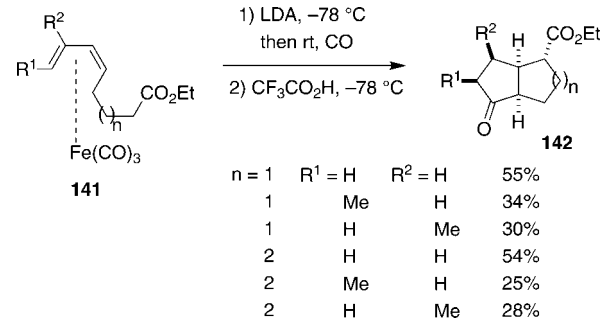
Conversely, under a CO atmosphere, aldehydes were obtained in high yields as single regio- and stereoisomers. For example, nucleophilic addition of 2-lithio-2-methylpropionitrile onto (η^4-cyclohexadiene)Fe(CO)$_3$ **137** at −78 °C in THF/HMPA (4:1) under a CO atmosphere led to the formation of the corresponding aldehyde in 84% yield (Scheme 127). This result provided good evidence that kinetically controlled nucleophilic addition onto (η^4-1,3-cyclohexadiene)Fe(CO)$_3$ complexes occurs preferentially at the internal positions of the diene ligand, leading to the formation of anionic (η^3-homoallyl)Fe(CO)$_3$ intermediate **138**, which is stable only at low temperature. Under a CO atmosphere, this anionic (η^3-homoallyl)Fe(CO)$_3$ complex intermediate readily undergoes CO insertion to give the corresponding acylferrate complex **139**, which leads to the aldehyde upon hydrolysis.[209] Upon warming, intermediate **138** rearranges into the more stable anionic (η^3-allyl)Fe(CO)$_3$ complex **140**, which does not incorporate CO. Indeed, when the reaction was carried out at low temperature under an argon atmosphere and the CO atmosphere introduced only after warm-up to room temperature, no aldehyde was formed and the only products isolated were the simple addition products onto the diene ligand.

The acylferrate complex intermediate **139** could also react with electrophiles (Scheme 128). Upon treatment with an excess of MeI, the corresponding methyl ketone was obtained in 87% yield. Similarly, oxidation by molecular oxygen gave the carboxylic acid in 96% yield. The corresponding ethyl and methyl esters were obtained quantitatively by reaction

Scheme 128



Scheme 129



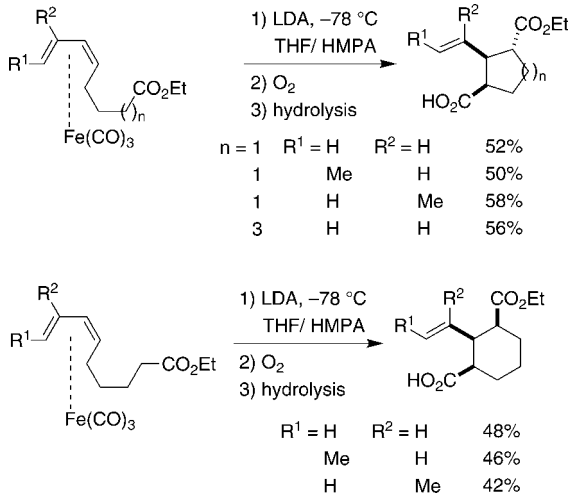
with the appropriate alkyl fluorosulfonate followed by ferric chloride oxidation.[208b]

3.2.3.2. Intramolecular Additions. (η^4-Diene)Fe(CO)$_3$ complexes of dienes bearing pendant metal enolates were reported to undergo intramolecular addition, thus leading to the formation of carbocyclic derivatives. Yeh and co-workers described an access to fused bicyclo[3.3.0]octanone and bicyclo[4.3.0]nonanone derivatives in which, following deprotonation with LDA, (η^4-diene)Fe(CO)$_3$ complexes **141** reacted in the presence of CO to furnish bicyclic ketones **142** in moderate yields (25−55%) as single diastereoisomers (Scheme 129).[212]

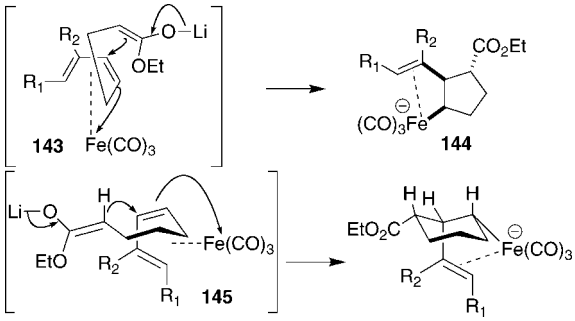
Following addition and CO insertion at −78 °C, in situ oxidation with molecular oxygen could be carried out. Under these conditions, alkene insertion could be prevented and, following acidic quenching with trifluoroacetic acid, cycloalkane carboxylic acid derivatives were obtained (Scheme 130). With this procedure, trisubstituted cyclopentane-, cyclohexane-, and cycloheptanecarboxylic acid derivatives could be obtained in moderate yields (42−58%) as single diastereoisomers.[213]

The high level of stereocontrol observed in the aforementioned cyclizations leading to cyclopentanes and bicyclooctanones is consistent with an *anti*-, *Si*-face addition at the internal C3 position of the diene ligand (**143** in the Scheme 131) to give anionic (η^3-homoallyl)Fe(CO)$_3$ intermediate **144**, which rearranges into the corresponding anionic (acyl)Fe complex. Oxidation by molecular oxygen at low temperature, or otherwise alkene insertion, affords the corresponding products upon hydrolysis. For 6-membered ring formation, *anti*-, *Si*-face addition of the enolate would result in a boatlike transition state due to the longer side chain. The alternative chairlike transition state **145** derived from *anti*-addition of

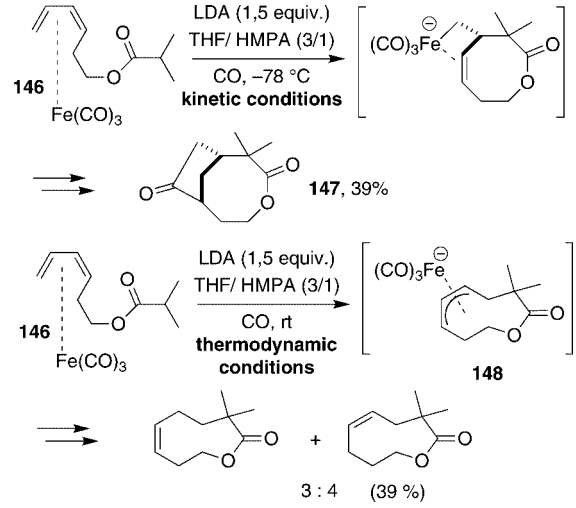
Scheme 130



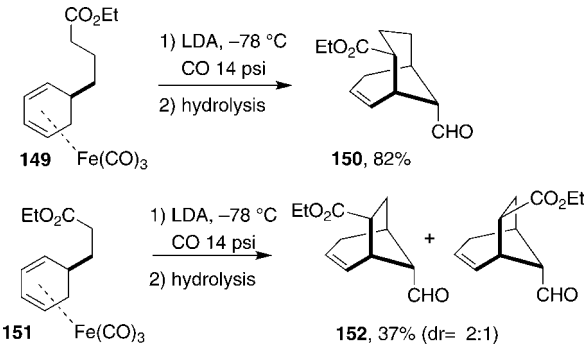
Scheme 131



Scheme 132



Scheme 133



the *Re*-face of the enolate may be favorable and could explain the *cis*−*cis* stereochemistry observed in the cyclohexanecarboxylic acid derivatives. Quite intriguingly however, a *cis*−*trans* relative stereochemistry was reported for the formation of bicyclononanones, perhaps as a consequence of the epimerization of the carbon α to the ester. Finally, the relative configurations in the 7-membered ring have been assigned as 1,2-*cis*, 2,3-*trans* on the basis of $^1H-^1H$ decoupling experiments.

Medium-sized lactones and cyclic ethers were also prepared by cyclization of enolates onto (η^4-diene)iron complexes.[214] Under kinetic conditions (−78 °C), cyclization of complex **146** occurred at the C2 internal position of the diene ligand. Following CO and alkene insertion, bicyclic lactone **147** was obtained in 39% yield (Scheme 132). By contrast, under thermodynamic conditions (25 °C), cyclization at the terminal position of the diene ligand generated anionic (η^3-allyl)$Fe(CO)_3$ complex **148**, which did not incorporate CO and led to a mixture of nine-membered ring lactones in a 3:4 ratio in 39% yield.

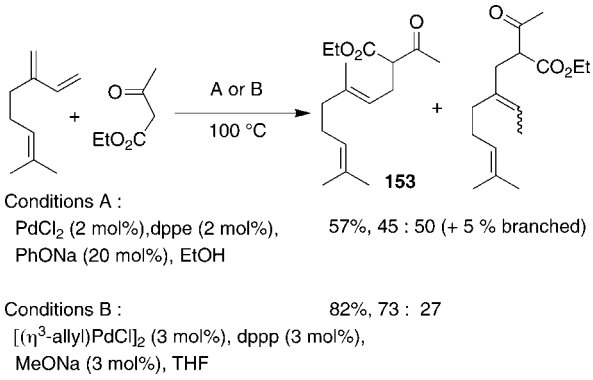
Intramolecular additions involving (η^4-cyclohexadiene)-$Fe(CO)_3$ complexes of dienes bearing a side chain with an ester moiety at the terminal position were also utilized to prepare bridged systems (Scheme 133).[212] For instance, deprotonation of **149** and **151** with LDA at −78 °C followed by cyclization onto the cyclohexadiene ligand under a CO atmosphere produced bicyclic derivatives **150** and **152** (82% and 37% yield, respectively). The diastereoselectivity observed for this type of cyclization was dependent upon both the length of the side chain and the nature of the electron-withdrawing group (substrates with a cyano group gave poor selectivities). It is noteworthy that the acylferrate intermediate could also be trapped with alkyl halides such as MeI or BnBr to give the corresponding ketones.

3.2.4. Group 10: Palladium(II)-Mediated Additions

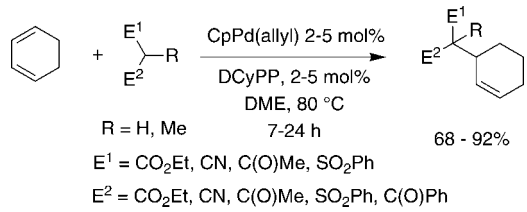
The palladium-catalyzed telomerization of 1,3-dienes with nucleophiles (in particular active methylene compounds) to give octadiene derivatives is well-documented.[215−218] Detailed mechanistic studies[216,219−221] have shown that it does not proceed via a carbometalation reaction, and thus, the topic will not be covered in this review. The telomerization can be suppressed by using catalysts with bidentate phosphine ligands instead of monodentate ligands[218] and by varying the reaction temperature.[222] Thus, in the presence of a catalytic amount of a Pd(0) source, in association with bidentate ligands, various active methylene compounds were found to add efficiently onto a range of 1,3-dienes, leading to the corresponding 1:1 adducts in high yields.[222,223] Intramolecular versions of this reaction have also been reported.[224]

The addition of ethyl acetoacetate onto myrcene leading to the formation of 3-methoxycarbonyl-6,10-dimethyl-*E*,*E*-5,9-undecadien-2-one **153** (Scheme 134), an intermediate for the synthesis of Vitamins A and E, is representative. Baker and Popplestone,[225] and later Trost and Zhi,[222] reported that the addition could be achieved in good to high yields (57−86%) in the presence of a catalytic amount of $PdCl_2$ and dppe,[225] or [(η^3-allyl)PdCl]$_2$ and 1,3-bis(diphenylphosphino)propane (dppp).[222] In both cases, the major adducts arose from the addition of the nucleophile at the terminal positions of the diene, and only traces of the corresponding branched isomer were observed. The regioselectivity was,

Scheme 134



Scheme 135



however, strongly dependent upon the catalyst and the nucleophile used.[225]

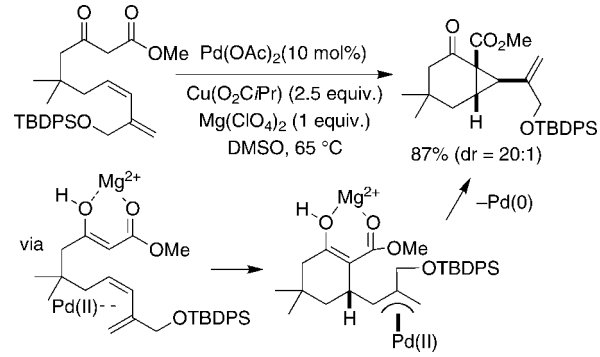
Remarkably, Hartwig and co-workers reported recently a very efficient catalyst that operates in the absence of a base (Scheme 135).[226] The optimized reaction conditions involved the use of 1−5 mol % of (η^3-allyl)CpPd complex and bidentate phosphine ligands (1,3-bis(dicyclohexylphosphino)propane (DCyPP) or 1,3-bis(diisopropylphosphino)-propane). Under these conditions, the addition of a wide range of active methylene and methyne compounds, including activated ketones, nitriles, esters, lactones, and oxindole derivatives, onto 1,3-cyclohexadiene and 2,3-dimethylbutadiene led to the corresponding 1:1 adducts in good to high yields (52−97%). Enantioselective versions using a chiral diphosphine ligand (Josiphos) were also disclosed, and ee's up to 81% were obtained in the addition onto 1,3-cyclohexadiene.[223,226]

The proposed mechanism consists of the formation of a (π-allyl)Pd intermediate by insertion of the diene into a Pd−hydride species that is generated either by deprotonation of the acidic active methylene compound by the electron-rich metal center or alternatively by insertion of Pd(0) into the activated C−H bond.[226] Thus, no carbometalation seems to be involved.

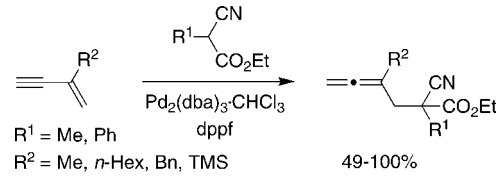
Very recently, Coscia and Lambert reported a Pd-catalyzed formal [4 + 1]-annulation based upon the intramolecular addition of the Mg(II)-stabilized enol of β-ketoesters onto a (η^4-diene)Pd(II) complex (Scheme 136).[227,228] The cyclization onto the diene moiety was carried out at 65 °C in DMSO in the presence of a catalytic amount of $Pd(OAc)_2$, 1 equiv of $Mg(ClO_4)_2$, and an excess of a Cu(II) salt as a co-oxidant. The best results were obtained with 2.5 equiv of $Cu(O_2CiPr)_2$, since the use of $Cu(OAc)_2$ led to the competitive formation of an allyl ester as a byproduct. The vinylcyclopropanes resulting from the cyclization reaction underwent a vinylcyclopropane−cyclopentene rearrangement in the presence of MgI_2 in CH_3CN at 40 °C.

Finally, the related palladium-mediated addition of active methylene compounds onto enynes was reported. The reaction carried out in the presence of $Pd_2(dba)_3 \cdot CHCl_3$/dppf

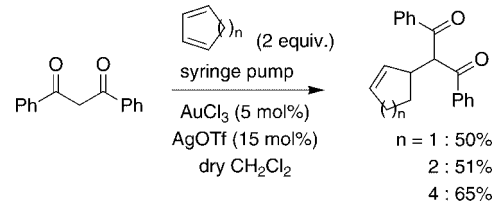
Scheme 136



Scheme 137



Scheme 138



gave allenes in moderate to excellent yields (Scheme 137). When an excess of reactive pronucleophile was used, further addition onto the allenyl double bond took place and the 1,4-bisadducts were isolated.[229]

3.2.5. Group 11: Gold(I)-Mediated Additions

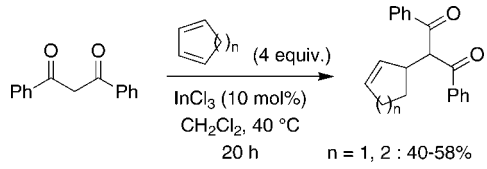
The intermolecular addition of 1,3-diketones onto cyclic dienes and trienes was achieved at room temperature in CH_2Cl_2 or CH_3NO_2 in the presence of a gold catalyst. Moderate to good yields were obtained with the Au(I) salt prepared in situ by reaction of a Au(I) species with AgOTf (the Au(I) species is presumably generated from the reduction of $AuCl_3$ by the activated methylene). The reaction was highly regioselective, with the addition taking place at the internal position of the diene (Scheme 138). Other catalytic systems such as $(PPh_3)AuOTf$ gave only traces of the addition product. The use of more coordinating solvents such as dioxane led to a dramatic decrease of the reactivity.[126]

3.2.6. Group 13: Gallium and Indium

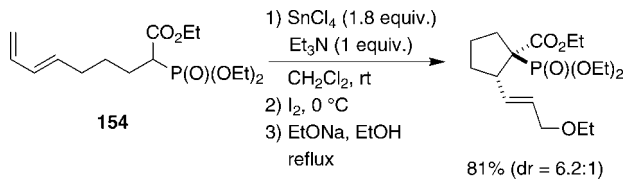
Cyclic 1,3-dienes were reported to react with dibenzoylmethane at 20 °C in CH_2Cl_2 in the presence of $InCl_3$ (10 mol %). Under these conditions, moderate yields (40−58%) of the corresponding cyclic alkenes were obtained (Scheme 139).[159]

The gallium-catalyzed hydroalkylation of dienes with β-ketoesters was also reported.[230] In the presence of $Ga(OTf)_3$ (15 mol %), TfOH (5 mol %), and H_2O (2 equiv), benzoyl β-ketoesters reacted at room temperature in CH_2Cl_2 with cyclic dienes, affording diastereomerically pure fused-bicyclolactones. However, this transformation involves ac-

Scheme 139



Scheme 140



tivation of the diene by the Brønsted acid, and thus, a true carbometalation reaction is not involved.

3.2.7. Group 14: Tin(IV)-Mediated Additions

Taguchi and co-workers reported the Sn(IV)-mediated cyclization of malonate derivatives onto 1,3-dienes.[162] The reaction was carried out at room temperature in CH_2Cl_2 in the presence of $SnCl_4$ (1.8 equiv) and a stoichiometric amount of Et_3N. The reaction proceeded efficiently with (*E*)-4,6-heptadienylmalonate, as well as with the related phosphonoacetate **154**, cyanoacetate, and acetoacetate derivatives (Scheme 140). The process was highly regioselective, and only the allyl−Sn species resulting from a 5-*exo*-cyclization process was observed. Upon treatment with I_2, the allyl−Sn species resulting from the cyclization of malonate- and phosphonoacetate derivatives could be converted into the corresponding allyl iodides in a regioselective manner. The highly unstable allyl iodides were converted into the corresponding methyl (respectively, ethyl) ether upon treatment with MeONa (respectively, EtONa) in MeOH (respectively, EtOH) without further purification. On the contrary, iodination of the allyl−Sn species resulting from the cyclization of the related cyanoacetate and acetoacetate derivatives led to degradation.

4. Addition of Stabilized Carbanions onto Alkynes

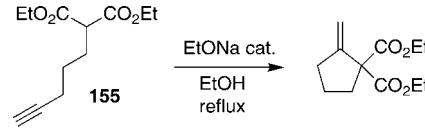
Alkynes have been largely used as unsaturated partners in the metal-mediated addition reactions of enolate derivatives. The organometallic species produced by carbometalation differs in nature from the case of addition onto alkenes, since it is a more stable vinylic species (particularly toward β-hydride elimination). Furthermore, vinylic metal species, because of their stability, are known to undergo a wider variety of transformations than alkylmetals.

4.1. Group 1, Alkali Metals: Lithium, Sodium, Potassium, and Cesium

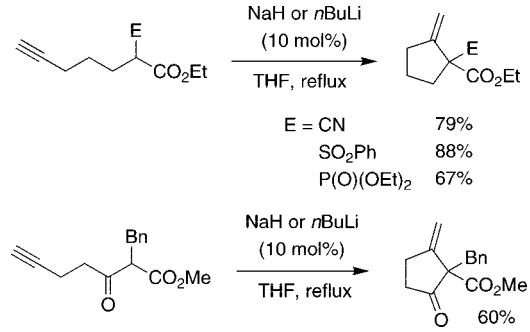
4.1.1. Intramolecular Additions

In 1953, during their work on the preparation of carboxylic acid derivatives bearing an alkynyl side chain, Eglinton and Whiting reported an unexpected reaction between sodium diethyl malonate and pent-4-ynyl-*p*-toluenesulfonate. Once the nucleophilic displacement of the sulfonate moiety was achieved, cyclization onto the carbon−carbon triple bond was observed.[231] Optimization of the reaction conditions

Scheme 141



Scheme 142



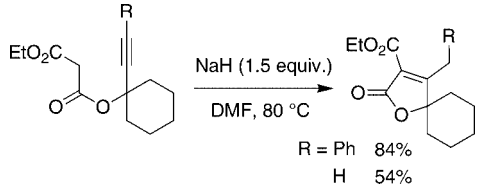
allowed the preparation of methylene cyclopentanes in acceptable yields starting from 4-iodopentyne and a slight excess of sodium diethyl malonate, or alternatively, from malonate **155** and a catalytic amount of EtONa in refluxing EtOH (Scheme 141). The success of this nucleophilic addition relies on the intramolecular environment, and no intermolecular addition was observed with 1-hexyne and diethyl malonate, even at higher temperature. This cyclization reaction was limited to malonate derivatives (no cyclization was observed with 4-pentynyl acetoacetate or the corresponding ester) and was applicable only to the formation of five-membered rings.

More recently, Taguchi and co-workers reinvestigated this reaction and extended this methodology to include a variety of active methyne compounds bearing a 4-pentynyl- (Scheme 142) or 3,4-pentadienyl side chain.[164] The reaction proceeded in good yields in refluxing THF in the presence of a catalytic amount of NaH or *n*BuLi. Under these reaction conditions, β-ketoesters, cyanoacetates, malonate, sulfonylacetate, and phosphonoacetate derivatives possessing a 4-pentynyl side chain gave the methylenecyclopentanes in good to high yields (60−99%). On the other hand, the use of a stoichiometric amount of base gave only low yields (<20%). The reaction could be applied neither to substituted alkynyl derivatives such as 4-hexynyl- or 5-pentynylmalonate nor to 6-membered ring formation.

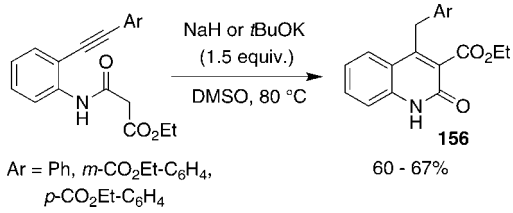
The proposed mechanism involves *trans*-addition of the Li- or Na-anion onto the terminal alkyne. The cyclization of active methyne derived anion is a thermodynamically unfavored process, but irreversible protonation of the highly reactive vinylmetal intermediate can displace the equilibrium. Therefore, upon using a catalytic amount of *n*BuLi or NaH, the reaction may proceed efficiently through a proton transfer mechanism, whereas the cyclization reaction hardly proceeds in the presence of a stoichiometric amount of a base.

Under basic conditions, substituted propargyl ethyl malonates also underwent regioselective 5-*exo*-dig cyclization to give substituted butenolides (Scheme 143).[232] The best results were obtained with disubstituted propargyl ethyl malonates, while unsubstituted propargyl ethyl malonates gave only low to moderate yields. An aryl substituent on the alkyne moiety rendered the cyclization process easier, but its presence was not essential. In the case of unsubstituted alkynes, however, disubstituted propargyl ethyl malonate was required. The cyclization process leads to the formation of

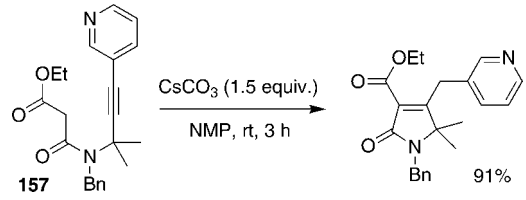
Scheme 143



Scheme 144



Scheme 145



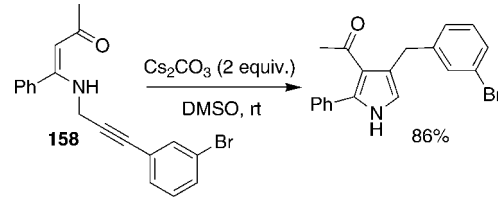
a highly reactive vinylic anion intermediate, which probably isomerizes into the more stable malonate anion.

This methodology allowed the formation of 6-membered rings and was applied to the synthesis of 3,4-disubstituted-2(1*H*)-quinolones **156** (Scheme 144).[233] In this case, the presence of an aromatic ring having an electron-withdrawing substituent on the alkyne moiety was required in order to observe the cyclization process. This methodology could be extended to an in situ coupling/carbocyclization procedure involving (*o*-trimethylsilylethynyl)malonanilide derivatives and an aryl iodide.[233] However, this protocol gave satisfactory results only with *p*-iodoacetophenone.

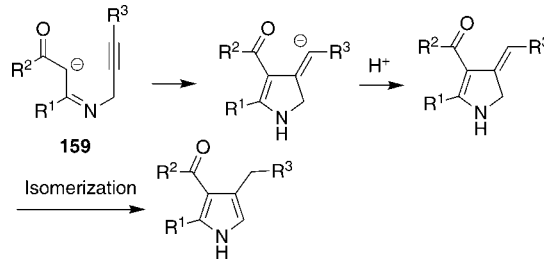
A related base-mediated cyclization of *o*-alkynylacetophenone and *o*-alkynylpropiophenone leading to 3-alkylnaphthols was reported by Makra and co-workers.[234] In this case, the authors proposed a 6π-electrocyclization mechanism involving the formation of an allene intermediate prior to cyclization. The success of the reaction with *t*-butylacetylene derivatives, however, indicates that direct addition of a potassium enolate to the alkyne can also take place.

Smooth base-promoted 5-*exo*-dig cyclization onto phenylacetylenes was also observed with *N*-propargylmalonamides **157**.[235] Again, following double-bond migration, highly substituted 3-pyrrolin-2-ones were obtained (Scheme 145). NaH could mediate the reaction, but at temperatures higher than 80 °C. More conveniently, using Cs_2CO_3, *t*BuOK, K_2CO_3, or $NaHCO_3$ as a base, the cyclized products could be obtained at room temperature. The best yields (60−91%) were obtained by using Cs_2CO_3 in NMP or DMSO. The procedure tolerated a variety of substituents on the aryl moiety, provided they were electron-withdrawing. On the contrary, substitution at the propargyl carbon and at the nitrogen atom were found to play a crucial role. For instance, cyclization of free amides was only reported for substrates having a tertiary spirocyclic propargyl carbon and required higher temperatures (80 °C), and attempts to cyclize *N*-benzyl protected substrates having a secondary propargyl carbon remained unsuccessful.

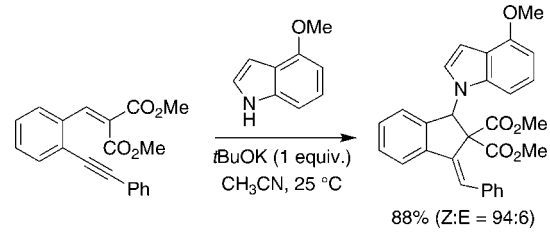
Scheme 146



Scheme 147



Scheme 148

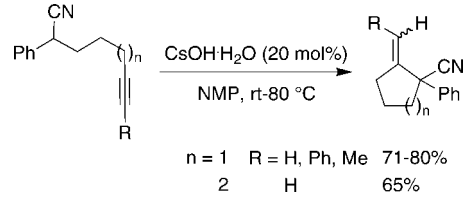


The base-promoted carbocyclization of *N*-propargylic β-enaminones **158** leading to the formation of pyrroles was also reported (Scheme 146).[236] The optimized conditions involved the use of Cs_2CO_3 (2 equiv) at room temperature in DMSO. β-Enaminones bearing aryl-substituted or -unsubstituted *N*-propargylic moieties furnished the corresponding pyrroles in moderate to excellent yields (42−96%).

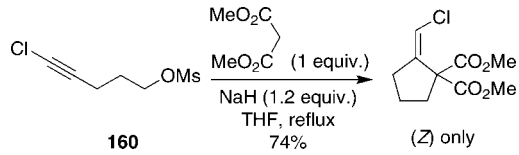
The authors proposed that the reaction proceeds via a 5-*exo*-dig cyclization process involving intramolecular addition of the enaminone enolate **159** onto the alkyne. The regioselectivity of the addition was explained by a planar approach mode, which provides good interaction of the nucleophile with the proximal orbital of the alkyne. The pyrroles are obtained following protonation of the resulting metalated *exo*-methylene pyrrolidine in the reaction medium and double-bond migration (Scheme 147).

Very recently, Wu and co-workers reported the base-catalyzed addition of pyrrole and indoles onto a variety of 2-(2-(alkynyl)benzylidene)malonate derivatives (Scheme 148).[237] Deprotonation of pyrrole and indole with *t*BuOK (1 equiv) in CH_3CN, followed by Michael addition of the resulting anion onto benzylidenemalonates produced a malonate anion that cyclized onto the alkyne moiety. The cyclic derivatives were obtained in high yields and with a high level of stereoselectivity (*Z*/*E* ratio from 91:1 up to >99:1). While alkyl substituents at the terminal position prevented the cyclization of the malonate anion, precursors having a phenyl or TMS substituent led to the formation of the cyclized products in high yields. In the case of the TMS substituent, however, further desilylation occurred under these reaction conditions. The nature of the solvent was found to be crucial: CH_3CN and DMF appeared to be the best solvents to achieve the cyclization (97% and 70% yield, respectively, for the addition of indole). On the contrary, no products were formed in 1,2-dichloroethane, THF, or toluene, and protic solvents

Scheme 149



Scheme 150



such as *t*BuOH gave only low yields. The presence of Lewis acids such as CuI, $FeCl_3$, and $Mg(ClO_4)_2$ were found to reduce the reaction times (from 24 to 7 h).

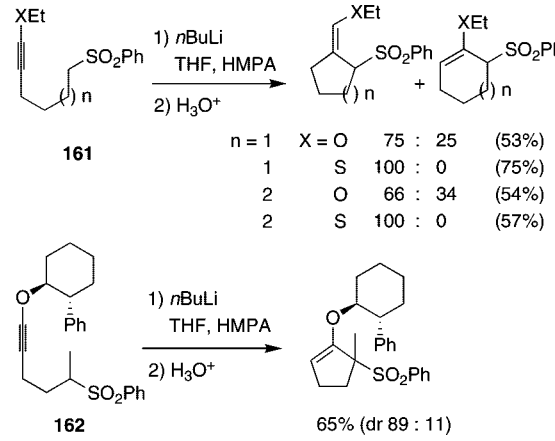
Cesium hydroxide was shown to catalyze the intramolecular addition of benzyl cyanides onto a range of terminal and internal alkynes.[238] 5-*exo*-dig Cyclizations onto terminal alkynes, phenylacetylenes, and trimethylsilylacetylenes (in this case, desilylation of the adduct was observed) were achieved at room temperature in NMP, while a higher temperature (80 °C) was required for less reactive methyl-substituted alkynes (Scheme 149). For internal alkynes, the corresponding *exo*-vinylidene carbocycles were obtained as a *E*/*Z* mixture of diastereoisomers with moderate levels of stereoselectivity. Interestingly, one example of a 6-*exo* cyclization onto a terminal alkyne was also reported at 60 °C.

Under reaction conditions close to those reported earlier by Eglington and Whiting,[231] Taguchi and co-workers showed that the cyclization of a malonate derivative onto a chloroalkynyl side chain could also be achieved in good yield in refluxing THF through the substitution of the mesyl group in **160** by the sodium anion of dimethyl malonate followed by subsequent carbocyclization. Under these reaction conditions, the NaH-catalyzed cyclization proceeded in a complete *trans*-addition manner to give the chloromethylenecyclopentane derivative in good yield as a single diastereoisomer (Scheme 150).[164]

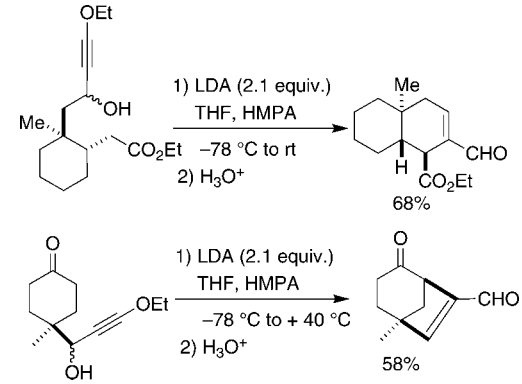
Similarly, alkoxy- and alkylthioacetylenes were also found to participate smoothly in cyclization reactions with a variety of stabilized lithio carbanions to provide functionalized *exo*- and/or *endo*-cyclic enol (thioenol) ethers.[239] The reaction was usually carried out in the presence of HMPA (2 equiv). The regioselectivity of the cyclization process (*exo* vs *endo*) was found to be dependent upon the length of the side chain. For sulfones **161** bearing a ynol ether moiety, as well as for the analogous alkylthioacetylenes, cyclization occurred preferentially in an *exo*-manner, thus delivering the more stable α-alkoxy (α-alkylthio) vinyl anion (Scheme 151). In the case of alkylthioacetylenes, the cyclization reaction was totally regio- and stereoselective (*Z*-isomer exclusively). As previously, the observed stereoselectivity could either result from a *trans*-carbometalation process, or alternatively, a *cis*-carbometalation followed by equilibration of the resulting anion. Attempts to quench the resulting vinyl anion remained unsuccessful. In some cases, the electrophile was introduced at the phenyl substituent. These results clearly indicate that deprotonation of the solvent and/or *ortho*-metalation of the phenylsulfonyl moiety represent the driving force of this reaction.

Useful levels of asymmetric induction were obtained with the enantiomerically pure *trans*-2-phenylcyclohexyloxyacetylene derivative **162**, which underwent 5-*endo*-dig cyclization, furnishing a 89:11 mixture of diastereomers in 65% yield (Scheme 151).

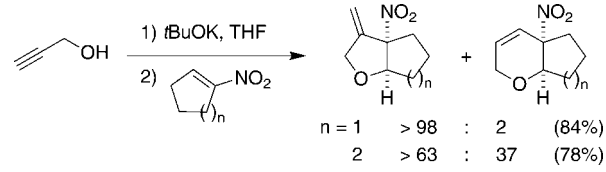
Scheme 151



Scheme 152



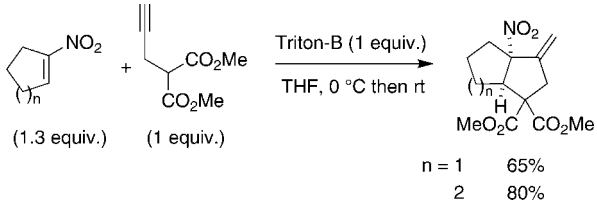
Scheme 153



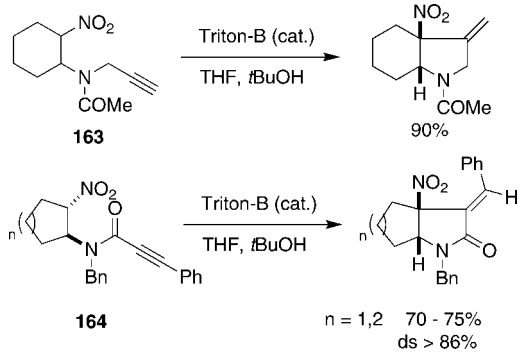
Not only sulfones but also phosphorus ylides, cyano-stabilized anions, ester- and ketone Li−enolates were found to participate effectively in the cyclization reaction with ynol ethers. In the case of ketone Li−enolates, the regioselectivity of the cyclization was sensitive to the degree of substitution. This methodology could be applied to the preparation of fused, bridged, and spiro bicyclic compounds (Scheme 152). Analogous malonate Li-anions did not cyclize under these reaction conditions.

Dulcère and co-workers reported the preparation of heterocycles via a cascade Michael addition/cyclization of potassium propargyl alkoxides onto substituted nitroalkenes (Scheme 153). The best results were obtained by using a slow addition of nitroalkenes to a solution of propargyl K−alkoxides in THF. Under these reaction conditions, the Michael addition of simple propargyl alcohol onto a variety of α,β-disubstituted nitroalkenes led to a mixture of methylenetetrahydrofurans and dihydropyrans in moderate to high yields (57−84%). The nature of the substitution on the nitroalkene derivative was found to be crucial for the regioselectivity of the cyclization (5-*exo*-dig vs 6-*endo*-dig

Scheme 154



Scheme 155



from >98:2 to 1.7:1). Secondary propargyl alcohols also participated in the reaction and gave the cyclized products in low to high yields (20−80%) and with low levels of diastereoselectivity (dr from 1:0.7 to 1:0.9). Tertiary propargyl alcohols also led to the cyclized products (25−78% yield). The authors mentioned that methylenepyrrolidines were also successfully prepared from *N*-methylpropargylamine, although no yields were given.[240]

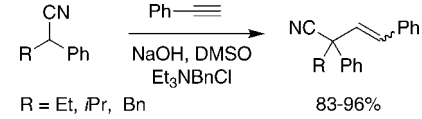
Although being clearly out of the scope of this review, as the reaction occurs without any organometallic species, it should be mentioned that the same authors disclosed more recently a related one-pot diastereoselective synthesis of nitromethylenecyclopentanes by [3 + 2]-annulation of dimethyl propargylmalonate and nitroalkenes in the presence of Triton-B (benzyltrimethylammonium hydroxide).[241] Again, the process involves the formation of a nitronate anion that undergoes carbocyclization. Both cyclic and acyclic nitroalkenes led to the formation of the corresponding bicyclic or monocyclic products in moderate to good yields (47−80%) and with excellent levels of stereoselectivity in favor of the *cis* diastereoisomers (Scheme 154). Interestingly, other bases, including *t*BuOK, K_2CO_3, Na_2CO_3, KH, and NaH, proved to be unsuccessful or afforded only poor yields and/or stereoselectivities.

Also related to the above-mentioned results is the Triton-B-promoted cyclization of 1-nitro-2-propargylamino cyclohexane **163** (Scheme 155) that led to the formation of the fused bicyclic product in excellent yield.[242] The procedure was extended to include the preparation of α-methylene-γ-lactams by cyclization onto acetylenic amides. For example, the cyclization of phenyl-substituted alkynes **164** gave the corresponding α-methylene-γ-lactams in good yields. Interestingly, a high stereocontrol was observed in the formation of the carbon−carbon double bond, presumably as the result of a more favorable protonation from the less hindered side of the vinyl carbanion intermediate.

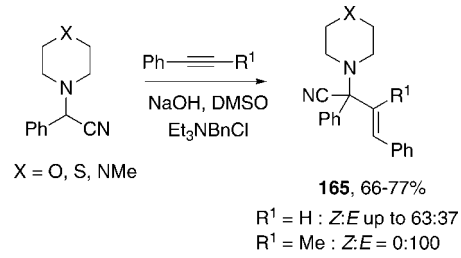
4.1.2. Intermolecular Additions

Quite a few examples of intermolecular addition of stabilized carbanions onto alkynes proceeding without the assistance of a transition metal have been reported. Makosza disclosed in the 1960s the addition of α-arylalkanenitriles derived anions onto

Scheme 156



Scheme 157

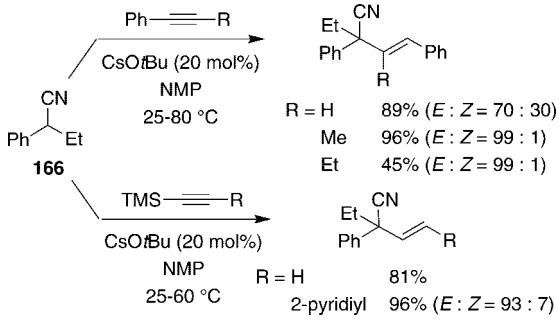


alkynes under mild conditions. For instance, the addition of the 2-phenylbutyronitrile onto acetylene could be achieved in DMSO in the presence of NaOH or KOH and triethylbenzylammonium chloride and gave 2-vinyl-2-phenylbutyronitrile in 80% yield.[243] Other phenylalkanenitrile derivatives behaved similarly. The addition onto phenylacetylene proceeded still easier and in a highly regioselective manner, with the addition occurring exclusively at the terminal carbon atom to give the corresponding alkene as a *E*/*Z* mixture of diastereomers (Scheme 156).[244]

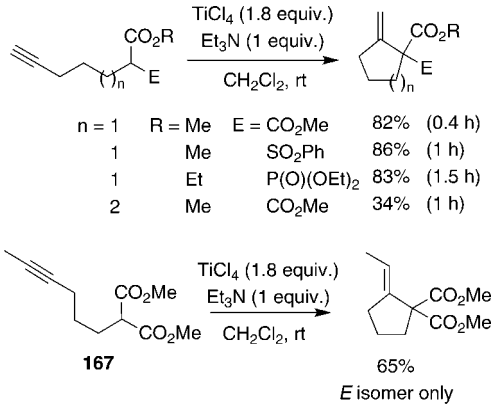
Similar reaction conditions also enabled the preparation of vinylaminonitriles by addition of 2-(dialkylamino)arylacetonitriles onto acetylene,[245] phenylacetylene[246] and 1-phenylpropyne (Scheme 157).[247] For phenyl-substituted alkynes, the reaction occurred regioselectively at the carbon opposite to the phenyl group (no reaction took place with diphenylacetylene). While the addition onto phenylacetylene led to **165** as a *Z*/*E* mixture (*Z* being the major isomer), the addition onto 1-phenylpropyne furnished a single *E* isomer. The aminonitrile adducts having a morpholine, thiomorpholine, or *N*-methylpiperazine amino moiety could be isolated and gave α,β-unsaturated ketones upon acidic workup. On the contrary, adducts bearing more basic amine moieties (i.e., piperidine, pyrrolidine, or dimethylamine groups) were not stable under the reaction conditions and led to the formation of an iminium ion intermediate that underwent a second nucleophilic addition. The sequence was also studied with *N*-(benzylidene)glycinonitriles, but only moderate yields were observed for the additions onto acetylene or phenylacetylene.[248]

Vinylation of phenylacetonitrile derivatives could also be achieved under mild conditions by using CsOH as a base. As for the intramolecular case,[238] intermolecular addition of benzyl nitriles onto acetylene and phenylacetylene occurred in the presence of a catalytic amount of $CsOH \cdot H_2O$ (20 mol %) in NMP and furnished the addition products in high yields (80−83%).[238,249] Additions carried out with the more soluble base Cs*O*t*B*u proved broader in scope. Under these conditions, 2-phenylbutanenitrile **166** added regioselectively not only onto phenylacetylene but also onto disubstituted phenylacetylenes such as 1-phenylpropyne and 1-phenylbutyne, despite a rate decrease related to the increase of steric hindrance (Scheme 158). For the latter, however, double-bond isomerization in the adduct resulted in lower yields of isolated product. Other nitriles like 2-phenylbut-3-enenitrile, isobutyronitrile, or benzyl cyanide also underwent the addition onto substituted phenylacetylenes. Interestingly, the reaction with silylated acetylenes also proceeded well but furnished the corresponding desilylated alkenes.

Scheme 158



Scheme 159

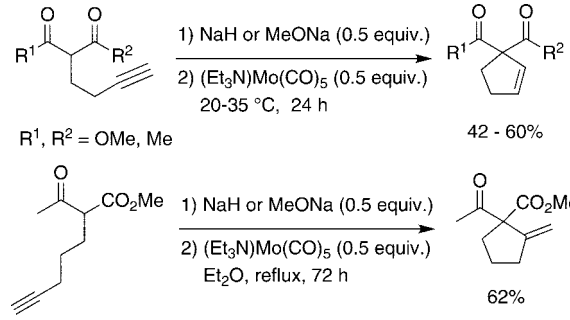


4.2. Group 4: Titanium(IV)-Mediated Additions

During the course of their work on the Ti(IV)-promoted iodocyclization of 4-alkenylmalonates,[250−256] Taguchi and co-workers reported that the cyclization of related alkynyl derivatives could be achieved in the presence of Ti(IV) and a tertiary amine.[257,258] The best results were obtained at room temperature in CH_2Cl_2 in the presence of 1.8 equiv of $TiCl_4$ and 1 equiv of Et_3N. The nature of the Ti(IV) species was found to be crucial: while Ti(O*i*-Pr)$_4$ did not give any cyclization reaction, the more Lewis acidic Ti(O*i*-Pr)$_2$Cl$_2$ and $TiCl_4$ led to the methylenecyclopentane derivatives in low to high yields (21% and 82%, respectively). Five-membered rings could be obtained in good to high yields (65−86%) from malonate precursors having a terminal- or a disubstituted alkynyl side chain such as **167** (Scheme 159). The preparation of a 6-membered ring was less efficient.

An iodocyclization process was observed when Ti(O*i*-Pr)$_4$ was combined with the use of iodine. In this case, the corresponding vinyl iodides were obtained with a very high level of *E*-selectivity (*E*/*Z* = 28:1) via *anti*-addition of a Ti(IV)−enolate onto the alkyne, activated as the iodonium ion. Interestingly, the same cyclization carried out in the presence of $TiCl_4$ led to the opposite selectivity (*E*/*Z* = 1:30).

Scheme 161



This time, the selectivity observed can be explained by the formation of vinyl−Ti intermediate **169**, which arose from malonate **168** via a *syn*-carbometalation process (Scheme 160). This observation suggests that hydrolysis of the vinyl−Ti intermediate by the ammonium salt $Et_3N{\cdot}HCl$ present is not a fast process, thus allowing the functionalization by trapping with other electrophiles.

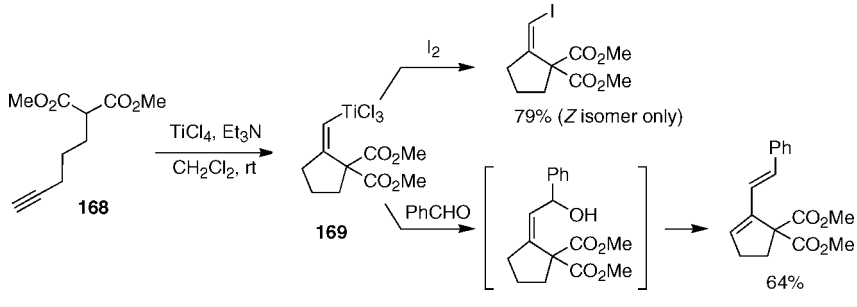
Albeit slower (14 h vs 0.5−1.5 h), this cyclization proceeded also efficiently in the absence of a base (80% yield from **168**). However, in this case, with the protonation of the resulting vinyl−Ti intermediate by HCl being a fast process, no functionalization could be achieved.

4.3. Group 6: Molybdenum and Tungsten

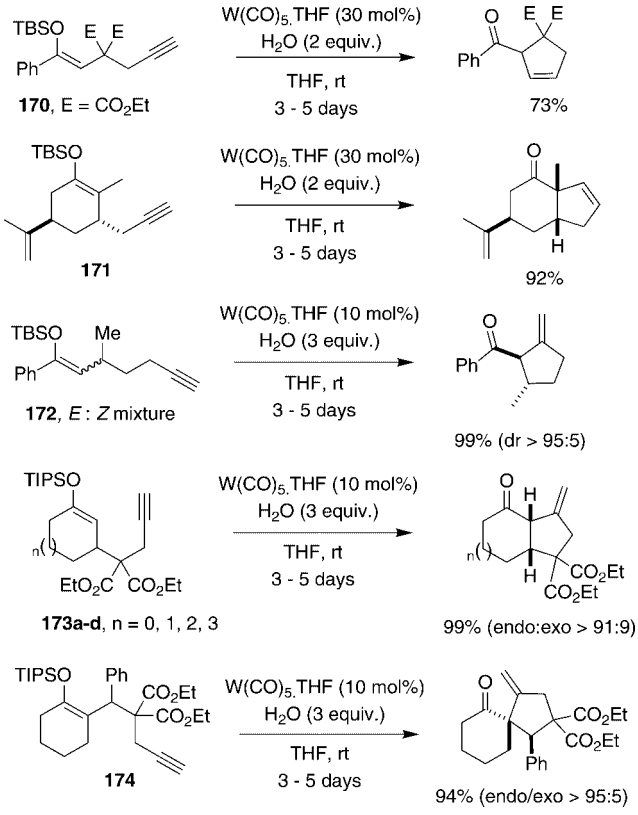
4.3.1. Molybdenum(0)-Mediated Additions

In 1997, McDonald and Olson reported the Mo(0)-promoted cyclization of 1,3-diketones, β-ketoesters, and malonate derivatives onto pendant terminal alkynes.[259] The precursors were deprotonated by NaH in Et_2O, and the resulting anions were added to a solution of freshly prepared $Mo(CO)_5{\cdot}(Et_3N)$. The best results were obtained by using 0.5 equiv of the base and the catalyst, at room temperature or reflux in Et_2O. Under these reaction conditions, the cyclized products were obtained in moderate yields (42−62%) via a 5-*endo*- or 5-*exo*-dig cyclization, depending upon the length of the alkynyl side chain. No reaction was observed in the absence of a base (Scheme 161). The authors mentioned that the $Cr(CO)_6$/Et_3N-*N*-oxide and $W(CO)_5{\cdot}$(THF)-catalyzed reactions were far less effective (vide infra). Even though no mechanistic rationale was proposed for these reactions, previous work by the same authors on the intramolecular addition of nucleophiles onto vinylidene carbene species tends to relate this system to W(0)-catalyzed cyclizations, for which mechanistic studies have been disclosed by Iwasawa and co-workers (see section 4.3.2).

Scheme 160



Scheme 162



4.3.2. Tungsten(0)-Mediated Additions

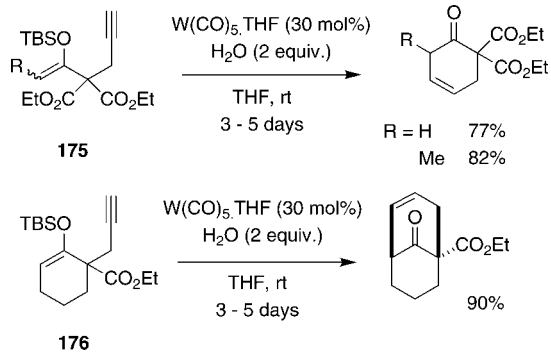
Silyl enol ethers were found to cyclize onto terminal- and disubstituted alkynes in the presence of a W(0)-catalyst. Iwasawa and co-workers reported the cyclization of a wide range of silyl enol ethers in the presence of $W(CO)_5$•(THF), a catalyst prepared before use by irradiation of a $W(CO)_6$ slurry in dry THF with a high-pressure Hg lamp. The best results were obtained in the presence of a stoichiometric amount of a proton source such as MeOH or H_2O. Reducing the catalyst loading from 1.5 equiv to 10 mol % had almost no influence on the chemical yields, but the reaction was much slower (7 days vs 1−2 days).[260]

Substrates such as **170** or **171** (where the enolate moiety was *outside* the newly formed ring) cyclized in a selective *endo* mode, leading to cyclopentene derivatives, as well as fused- and spirobicyclic skeletons in good to high yields (64−97%) without isomerization of the double bond (Scheme 162).[260,261] Substrates for which the length of the alkynyl side chain resulted in potential competition between the 5-*exo* and 6-*endo* modes (such as **172**, **173a**−**d**, and **174**) cyclized exclusively in a 5-*exo* mode.[262]

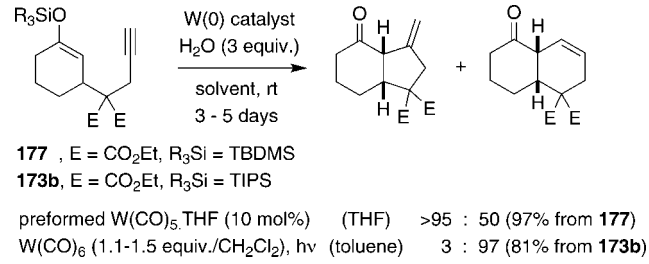
Cyclization of substrates such as **175** and **176** (where the enolate moiety was *inside* the newly formed ring) were also highly *endo* selective, thus leading to the formation of monocyclic, as well as bridged-bicyclic, 6-membered rings in high yields (83−90%) in the presence of a catalytic amount of $W(CO)_5$•(THF) and 2 equiv of H_2O (Scheme 163).

Interestingly, this W(0)-catalyzed cyclization reaction was found to be highly solvent-dependent. Indeed, the regioselectivity could be reversed by replacing THF with a less-donating solvent such as CH_2Cl_2, Et_2O, or toluene. For this purpose, the $W(CO)_5$ complex was prepared in situ by irradiation of the reaction mixture in CH_2Cl_2. While the cyclization of **177** in THF led to the regioselective formation

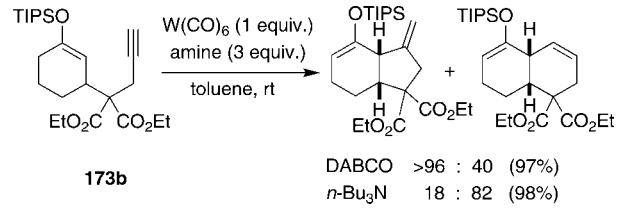
Scheme 163



Scheme 164



Scheme 165



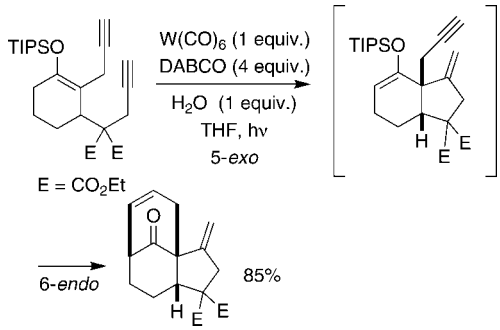
of the 5-membered ring via a 5-*exo* mode, the preparation of the 6-membered ring from **173b** via a regioselective 6-*endo* cyclization process could be achieved by carrying out the reaction in toluene (Scheme 164).[260,262]

Tertiary amines could also be used as additives in order to control the regioselectivity of the cyclization process for the reaction carried out in toluene under irradiation. The nature of the amine influenced dramatically the regioselective outcome of this W(0)-mediated cyclization: indeed, 5-*exo* cyclizations were favored in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) (4 equiv), whereas the competitive 6-*endo* mode became the major reaction pathway in the presence of bulky tertiary amines such as n-Bu_3N (Scheme 165). Moreover, the presence of a base in the reaction medium allowed the isolation of a new silyl enol ether. Under these reaction conditions, the presence of a protic source was not necessary.[263] When THF was used as a solvent, the nature of the base had only a minor influence on the regioselectivity, with the *exo*-cyclization always being favored.

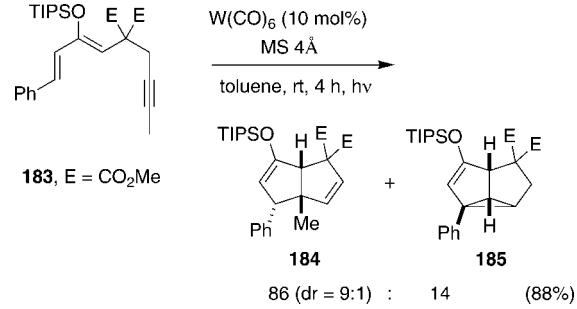
This strategy was applied to the construction of tricyclic skeletons via a sequential 5-*exo*/6-*endo* cyclization cascade. In this case, additional H_2O had to be introduced in order to achieve the last cyclization prior to the hydrolysis of the intermediate (Scheme 166).[263]

From a mechanistic standpoint, the authors proposed as the first step the formation of an (η^2-alkyne)W complex **178** onto which the nucleophilic addition of the silyl enol ether occurs, leading to vinyl−tungstate species **179** that gives cyclopentene **180** upon hydrolysis (Scheme 167).[260] On the

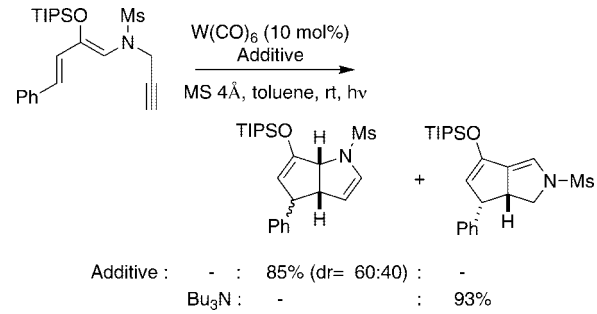
Scheme 166



Scheme 168



Scheme 169



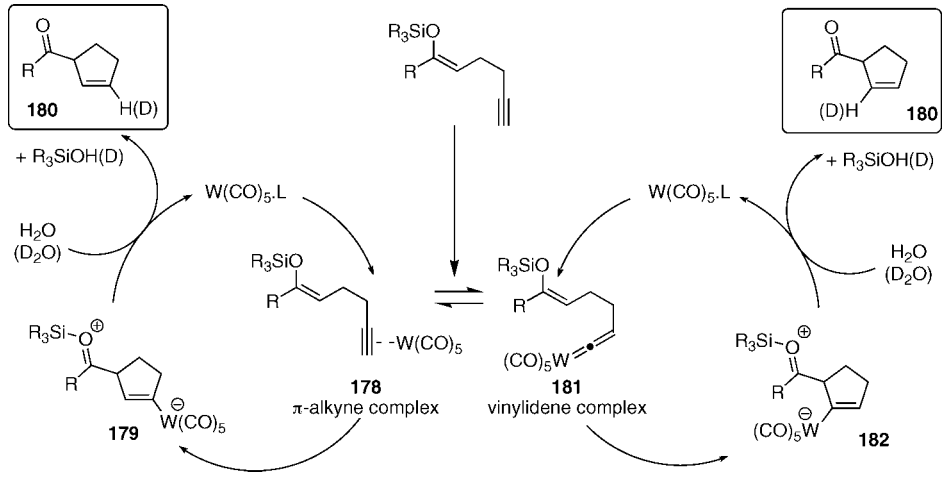
other hand, the formation of vinylidene complex **181** represents an alternative pathway since it is known that both complexes can be formed with low-valent transition metals including, among others, Cr, Mo, and W. In this case, intramolecular addition of the silyl enol ether onto vinylidene complex **181** furnishes another possible vinyl−tungstate species **182** which gives the same cyclopentene **180** upon hydrolysis. On the basis of deuterium labeling experiments (reaction conducted in the presence of 2 equiv of D_2O), the authors concluded that the two possible reaction pathways are actually followed. On the basis of deuterium incorporation, it is possible to estimate the ratio of the two intermediates (η^2-alkyne vs vinylidene complex), which appears to be substrate-dependent.

Substrates having a disubstituted alkynyl side chain can only react via the formation of a (η^2-alkyne)W(0) complex, thus leading to the formation of a single vinyl metal intermediate. The cyclization of disubstituted ω-acetylenic dienol ether **183** could be achieved at room temperature in toluene and under irradiation in the presence of 5−20 mol % of $W(CO)_6$ and molecular sieves.[264] The first cyclization was followed by the nucleophilic attack of the vinyl−tungstate species onto the α,β-unsaturated silyloxonium intermediate, which led to the formation of a bicyclic W−carbene intermediate. The latter rearranged via a 1,2-shift to form unsaturated *cis*-bicyclic product **184** (major pathway, 67−87% yield) and a small amount of tricyclic compound **185** (Scheme 168) arising from insertion of the carbene into the neighboring C−H bond.

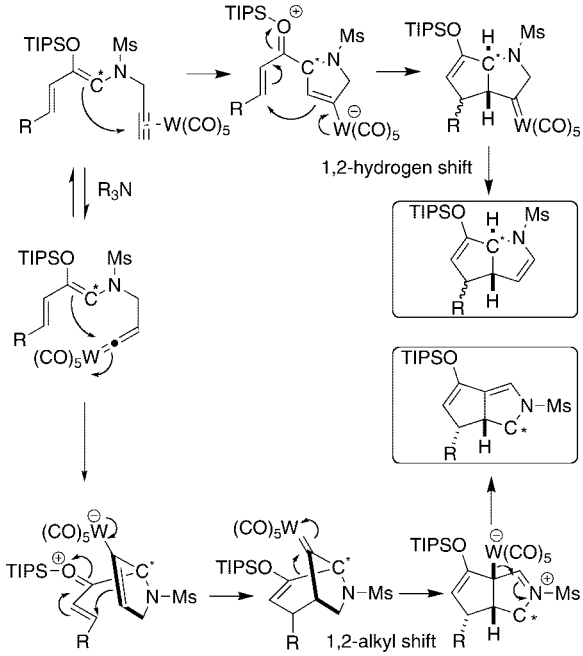
As previously discussed, the presence of tertiary amines was reported to dramatically influence the outcome of the reaction carried out in toluene by favoring the formation of one of the two possible intermediates (η^2-alkyne vs vinylidene complex). In the presence of 10 mol % of $W(CO)_6$ and under irradiation, the cyclization of ω-acetylenic dienol ethers led to varying skeletal rearrangements depending on the presence or absence of a stoichiometric amount of tertiary amine (Scheme 169).[265]

On the basis of ^{2}D- and ^{13}C-labeling experiments, the formation of the cyclized products in the absence of a base was rationalized by the nucleophilic addition of the silyl enol ether moiety onto the (η^2-alkyne)W(0) complex, followed by nucleophilic addition of the resulting vinyl−W species onto the α,β-unsaturated silyloxonium intermediate. The resulting W−carbene undergoes a 1,2-hydrogen shift to give the expected bicyclic compound (Scheme 170). Alternatively, in the presence of a tertiary amine, the vinylidene complex is preferentially formed. Nucleophilic addition of the silyl enol ether moiety gives another vinyl−W intermediate that cyclizes onto the α,β-unsaturated silyloxonium intermediate. The resulting bridged-W−carbene rearranges via a 1,2-alkyl shift and elimination of the metal species, furnishing the rearranged bicyclic product.

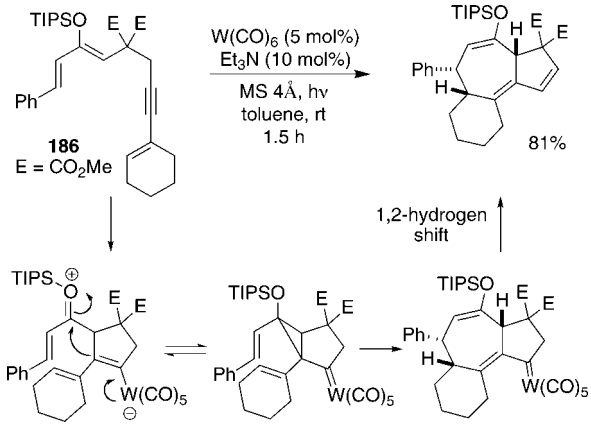
Scheme 167



Scheme 170



Scheme 171



In some cases, such as the ω-acetylenic dienol silyl ether **186** bearing a 1,3-enyne substituent, the reaction led to the formation of a fused-bicyclic [5.3.0] skeleton via the Cope rearrangement of a divinylcyclopropyl carbene intermediate (Scheme 171).[266]

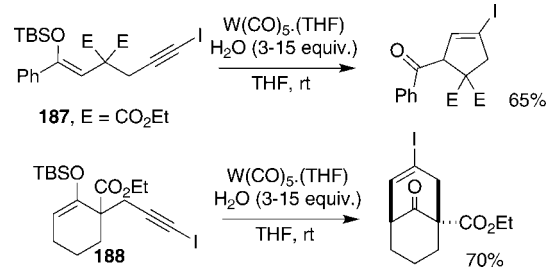
The *endo*-cyclization of substrates possessing a 1-iodoalkynyl side chain was also reported to proceed efficiently. In the presence of a stoichiometric amount of $W(CO)_5$·(THF) and 3 equiv of H_2O, 1-iodo-6-siloxy-5-en-1-yne and 1-iodo-5-siloxy-5-en-1-yne precursors **187** and **188** could undergo cyclization at room temperature to furnish the corresponding iodo-substituted cycloalkenes (Scheme 172).[261,267,268] Oxidation by air provided diketones in high yields (76−82%). This process, which occurred simply in an open air vessel, was complete after several days at room temperature and was proposed to proceed via the formation of an α,β-unsaturated γ-peroxy ketone.[267]

4.4. Group 7: Manganese and Rhenium

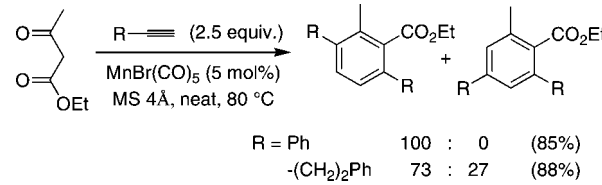
4.4.1. Manganese(I)-Mediated Additions

Very recently, formal [2 + 2 + 2]-coupling of 1,3-dicarbonyl compounds and terminal alkynes have been reported independently

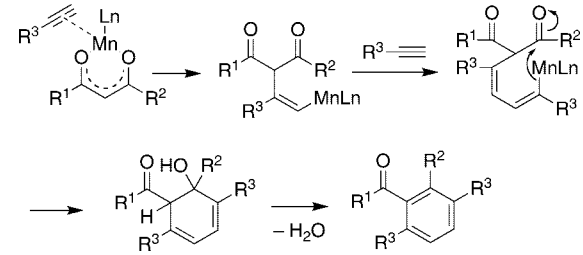
Scheme 172



Scheme 173



Scheme 174



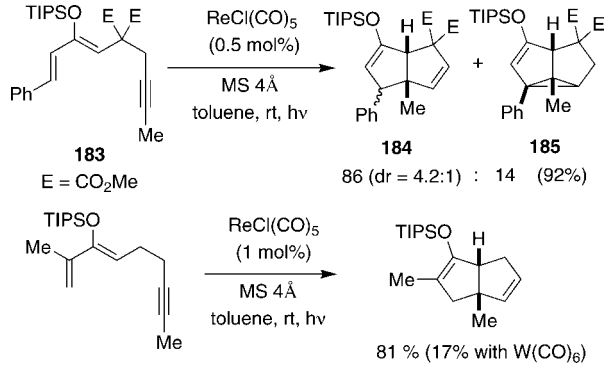
by Kuninobu, Takai, and co-workers[269] and Tsuji, Nakamura, and co-workers.[270,271] In the presence of a catalytic amount of $MnBr(CO)_5$, alkyl- and aryl-substituted terminal alkynes were found to react with a range of β-ketoesters and 1,3-diketones to furnish tetrasubstituted benzenes in good to high yields. The reaction could be carried out at 80 °C under neat conditions and in the presence of 4 Å molecular sieves,[269] or in toluene at 65 °C using $MgSO_4$ as an additive.[270] While high levels of regioselectivity were generally observed in the case of aryl-substituted alkynes, alkyl-substituted alkynes led to a mixture of regioisomers (Scheme 173). Internal alkynes did not react under these reaction conditions.

Initially, a mechanism related to the classical alkyne trimerization was proposed by the authors and involved the formation of either a manganacyclopentadiene intermediate (formed by cycloisomerization with two molecules of alkyne), or alternatively a manganacyclopentene (obtained by cycloisomerization between a 1,3-dicarbonyl compound and an alkyne).[269] A second possibility involves the addition of a Mn−enolate onto an alkyne in the initial step, an alternative mechanism that was discussed more recently by Nakamura and co-workers (Scheme 174). In this case, the vinyl−Mn species resulting from the addition of the Mn−enolate onto the alkyne adds onto a second alkyne to furnish a dienyl manganese intermediate, which cyclizes onto the carbonyl group. The substituted benzenes are obtained following dehydration of the resulting cyclohexadiene derivatives. This mechanism was supported by experimental data and density functional theory (DFT) calculations.[271]

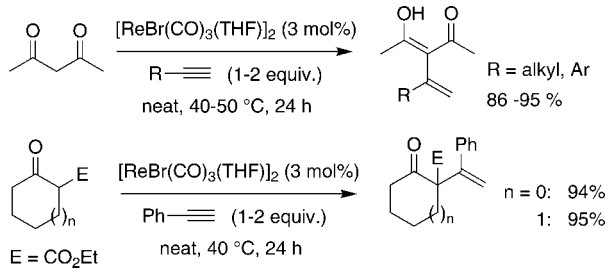
4.4.2. Rhenium(I)-Mediated Additions

Building on their work using W(0) complexes, Iwasawa and co-workers reported quite recently that rhenium could also efficiently activate terminal and disubstituted alkynes

Scheme 175



Scheme 176



toward the intramolecular addition of silyl enol ethers (Scheme 175). Upon treatment of a solution of ω-acetylenic dienol silyl ethers in toluene with a catalytic amount (0.5−1 mol %) of $ReCl(CO)_5$ and under irradiation, *cis*-bicyclic derivatives such as **184** were obtained in moderate to high yields (51−98%). These Re(I)-catalyzed cyclizations are likely to proceed according to the above-mentioned mechanism for the related W(0)-catalyzed reactions (see section 4.3.2).[264] Interestingly, the $[ReCl(CO)_5]$-catalyzed reaction gave generally superior results relative to $W(CO)_5(L)$ catalysis, especially in the case of substrates bearing an unsubstituted terminal dienol silyl ether.

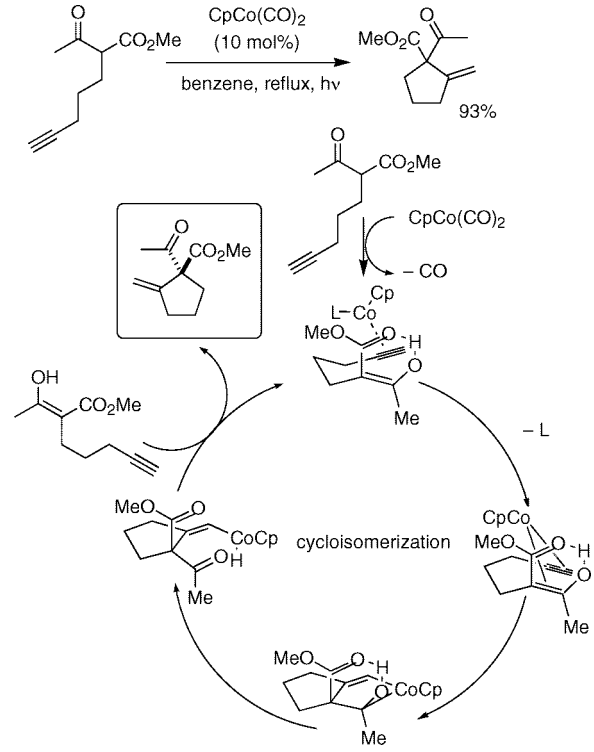
Kuninobu and Takai showed that Re(I) complexes could also promote the inter- and intramolecular addition of 1,3-diketones and β-ketoesters onto terminal alkynes (Scheme 176).[272] The reaction could be carried out under solvent-free conditions in the presence of 3 mol % of $[ReBr(CO)_3(THF)]_2$ with a slight excess of alkyne (1−2 equiv). The use of a catalytic amount of $Dy(OTf)_3$ as a cocatalyst was found to increase the yields of cyclization for some substrates, but its presence was usually not essential. Two different mechanisms based on analogous Co(I)- (section 4.5.1, Scheme 177) and Ni(II)-catalyzed (section 4.6.1, Scheme 180) cyclizations were proposed by the authors, and both involve the initial formation of an enol−yne−Re(I) complex. This transformation is thus thought to be related to Conia-ene type cyclizations and does not involve the addition of a metal enolate. Interestingly, in the presence of a catalytic amount of an isocyanide[273] or by using TBAF/4 Å-MS[274] as an additive, the reaction of cyclohexanone-2-carboxylic acid ethyl ester with alkyl- and aryl-substituted terminal alkynes led to totally different skeletal rearrangements involving ring-expansion reactions.

4.5. Group 9: Cobalt and Iridium

4.5.1. Cobalt(I)-Mediated Additions

Cobalt(I) complexes have attracted a great deal of attention as catalysts for Conia-ene type reactions. Malacria, Aubert and co-workers have extensively studied the cyclization of β-ketoesters bearing appended terminal alkynes for the construction of a wide array of 5-membered rings.[275−278] The reaction was found to take place in a refluxing apolar solvent in the absence of a base and under irradiation and is likely to proceed via a cycloisomerization mechanism involving the enol form of the β-ketoester as the reactive intermediate (Scheme 177).[279] Again, since no metal enolate is involved in the addition step, this chemistry lies beyond the scope of this review and will not be discussed in detail herein. Noteworthy, examples of this methodology include the synthesis of polycyclic molecules possessing the carbon skeleton of kauranes[280] and phyllocladanes.[281]

Scheme 177

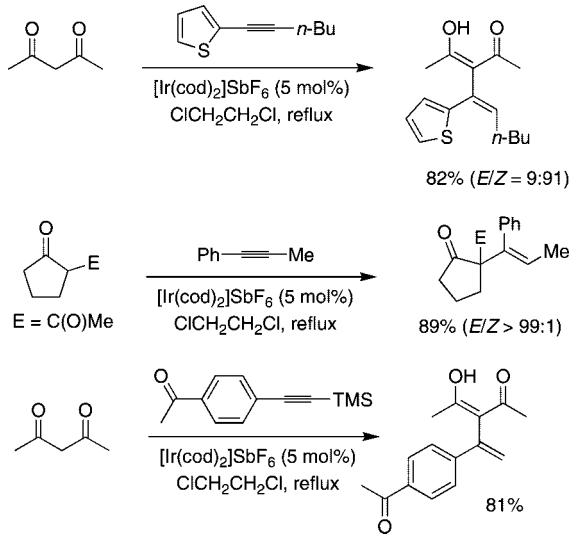


4.5.2. Iridium(I)-Mediated Additions

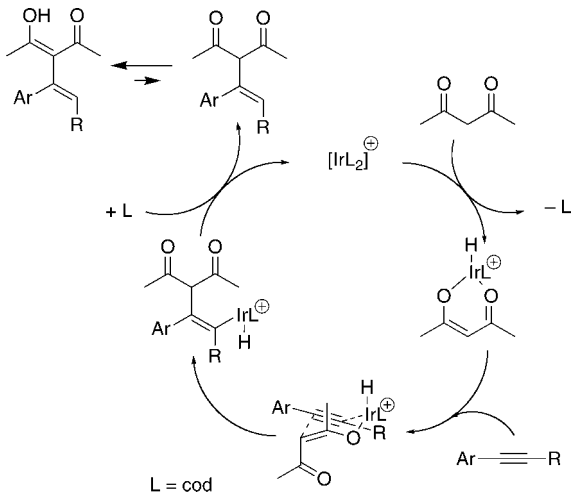
Very recently, Takeuchi and co-workers reported that the addition of 1,3-diketones onto internal alkynes could be carried out in refluxing 1,2-dichloroethane in the presence of a catalytic amount of an iridium(I) complex.[282] The best results were obtained with the cationic $[Ir(cod)_2]X$ complex ($X = SbF_6$), but other cationic iridium complexes ($X = BF_4$, PF_6, OTf) were also found to promote the reaction. On the contrary, neutral $[Ir(cod)Cl]_2$ was found to be ineffective. The addition of a range of 1,3-diketones onto aryl- and alkenyl-substituted internal alkynes was found to be highly regioselective, with the addition taking place almost exclusively at the carbon substituted with the aryl or alkenyl group (49−93% yields, regioselectivity > 91/9). Although terminal alkynes did not give satisfactory yields, similar adducts could be obtained from TMS−alkynes since removal of the silyl group was observed under these reaction conditions (Scheme 178).

The proposed mechanism involves the formation of a cationic Ir(III)−enolate by reaction between the 1,3-diketone and the cationic Ir(I) complex (Scheme 179). The Ir−enolate adds onto the alkyne at the more electrophilic carbon atom (substituted with the aryl group) in a *syn*-addition manner,

Scheme 178



Scheme 179



resulting in the regio- and stereoselective formation of a vinyl−Ir intermediate that undergoes reductive elimination to give the product. The formation of the vinyl−Ir intermediate was supported by deuterium labeling experiments.

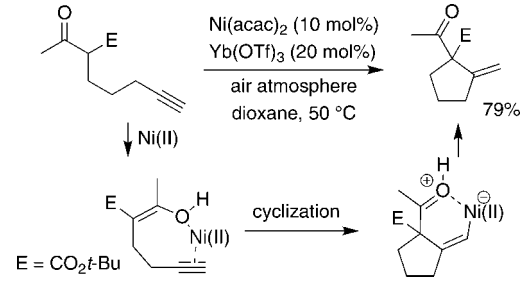
To the best of our knowledge, this Ir(I)-catalyzed reaction represents the most effective approach to date to achieve intermolecular addition of stabilized carbanions onto internal alkynes (for some examples of efficient intermolecular addition of more reactive α-arylalkanenitriles onto internal alkynes proceeding with a complete reverse regioselectivity, see section 4.1.2)

4.6. Group 10: Nickel, Palladium, and Platinum

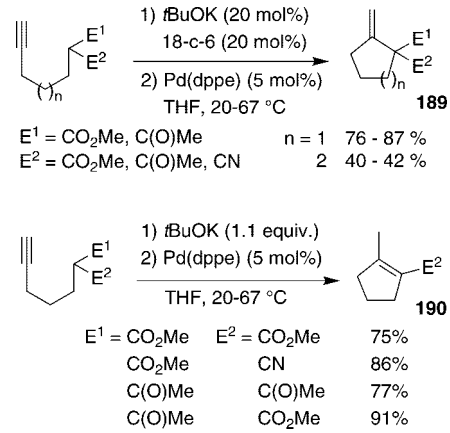
4.6.1. Nickel(II)-Mediated Additions

A Ni(II)-catalyzed Conia-ene reaction of 1,3-dicarbonyl compounds with alkynes was reported recently by Yang and co-workers. In the presence of a catalytic amount of $Ni(acac)_2$ and using $Yb(OTf)_3$ as a cocatalyst, 1,3-diketones, β-ketoesters, and β-ketoamides could be cyclized in high yields into the corresponding methylenecyclopentane derivatives (Scheme 180).[283] As for the previous Re(I)- or Co(I)-catalyzed Conia-ene reactions (see sections 4.4.2 and 4.5.1), deuterium labeling experiments supported a mechanism involving the cyclization of an enol−yne−Ni(II) complex. In this case, the authors proposed a mechanism involving

Scheme 180



Scheme 181



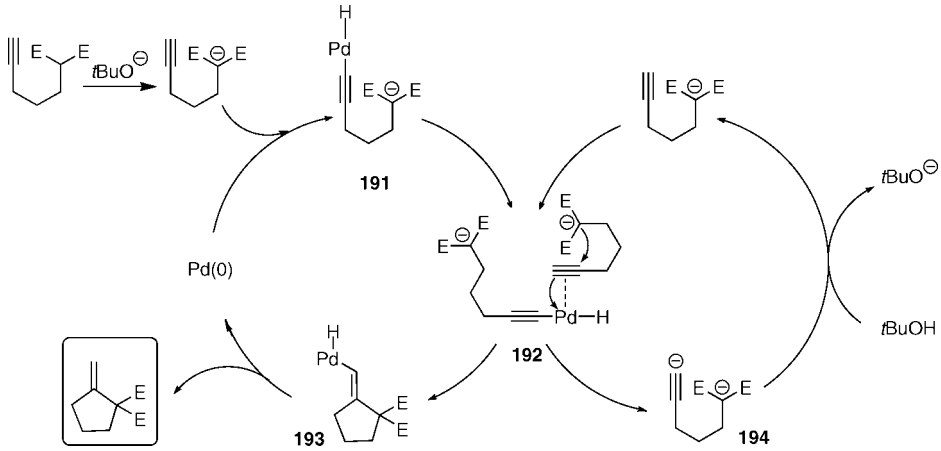
generation of a vinyl−Ni(II) species by insertion of the Ni−enolate rather than by cycloisomerization/β-elimination as in the case of cobalt (Scheme 177).

4.6.2. Palladium(II)-Mediated Additions

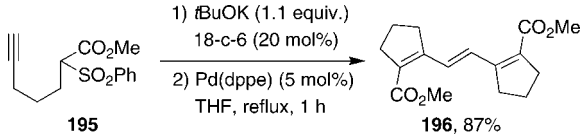
Palladium(II) salts have been shown to very efficiently activate alkynes toward the intramolecular addition of enolate-type nucleophiles. Significant developments have been reported in this field; in particular, synthetic applications for the construction of carbo- and heterocycles are numerous. The subject has been reviewed recently and, therefore, will not be discussed in full detail herein.[6]

4.6.2.1. Synthesis of Carbocycles. In early studies on the Pd-catalyzed cyclization of malonate derivatives, Balme, Goré, and co-workers reported that, upon treatment with a stoichiometric amount of *t*BuOK and 5 mol % of Pd(dppe) at room temperature in THF, pentynyl- and hexynylmalonate derivatives underwent cyclization, leading to a mixture of methylenecyclopentane **189** and decarboxylated cyclopentene **190** isolated in 80% combined yield (Scheme 181).[65,66] Because the decarboxylation reaction was found to be promoted by the base, an appropriate choice of the reaction conditions made it possible to drive the reaction exclusively toward the formation of either **189** or **190**. The latter was obtained in 75% yield using 1.1 equiv of *t*BuOK in refluxing THF, whereas the former was obtained in 76% yield using 20 mol % of *t*BuOK and 18-6 crown ether at room temperature in THF. The presence of a crown ether to increase the nucleophilicity of the malonate anion proved to be crucial in order to obtain good results with a catalytic amount of base. The two sets of optimized conditions were quite general in scope regarding the nucleophilic moiety as β-keto- and α-cyano esters could also be converted selectively into the corresponding methylenecyclopentanes or 2-methylcyclopentenes in good yields (76−87%, and 75−91%, respectively; Scheme 181). The related cyclization leading

Scheme 182



Scheme 183



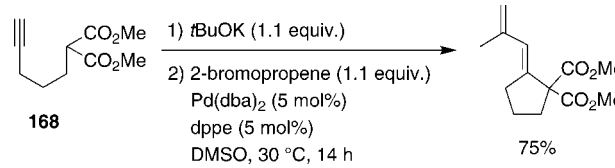
to a 6-membered ring was, however, less effective due to a competing intermolecular coupling (40−42% yield).

The authors proposed that the activation of the alkyne was promoted by complexation with Pd(II)−hydride species **191** arising from the oxidative addition of Pd(0) into the terminal C−H bond of the alkyne (Scheme 182).[66] The nucleophilic *anti*-addition of the malonate anion onto σ-alkynyl−Pd(II)−hydride complex **192** led to the formation of vinyl−Pd(II)−hydride intermediate **193** and acetylide **194**, which was subsequently protonated either by *t*BuOH (for the stoichiometric reaction) or the acidic proton of another malonate molecule (for the catalytic reaction). Reductive elimination from the vinyl−Pd(II)−hydride complex gave the cyclized product and regenerated the Pd(0) catalyst. The formation of σ-alkynyl−Pd(II)−hydride complex **192** was supported by the formation of enynes as byproduct in some cases[284] and the absence of reactivity of disubstituted alkynes under these conditions.

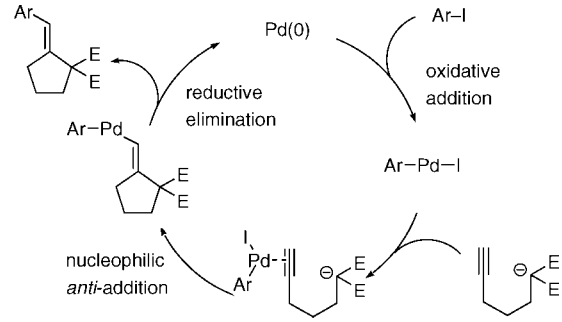
Interestingly, the cyclization of α-sulfonyl ester derivative **195** (Scheme 183) led to the formation of dimer **196** in 87% yield, possibly by dimerization of a Pd−carbene intermediate (for an efficient cyclization of α-sulfonyl ester derivatives, see section 4.7). The existence of such a species was supported by the formation of cyclopropanes, when the reaction was carried out in the presence of norbornadiene, and furans, when α-sulfonyl arylketones were used as substrates (see section 4.6.2.2, Scheme 198).[285,286]

In a connected approach, Balme and co-workers also reported the preparation of substituted methylenecyclopentane derivatives via a Pd(II)-catalyzed cyclization of malonate anion derivatives (E = CO_2Me, C(O)Me, SO_2Ph) onto alkynes. The preformed K−enolate added efficiently onto the terminal alkyne moiety at 30 °C in DMSO in the presence of an aryl- or vinyl halide (1.1 equiv) and a catalytic amount of $Pd(dba)_2$ (5 mol %) and dppe (5 mol %). Under these reaction conditions, the methylenecyclopentane derivatives were obtained in good to high yields (57−88%) as single (*E*)-isomers (Scheme 184).[287−289] Interestingly, an example of 5-*exo*-dig cyclization onto a disubstituted alkyne bearing a pendant aryl bromide moiety leading to a tetrasubstituted alkene following biscyclization was also disclosed.[290]

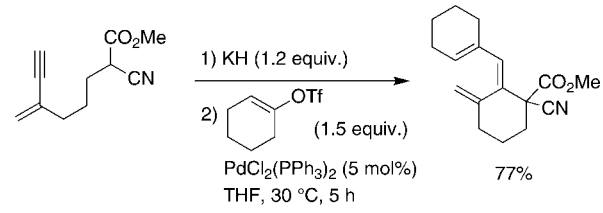
Scheme 184



Scheme 185



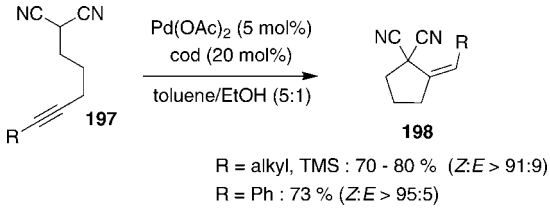
Scheme 186



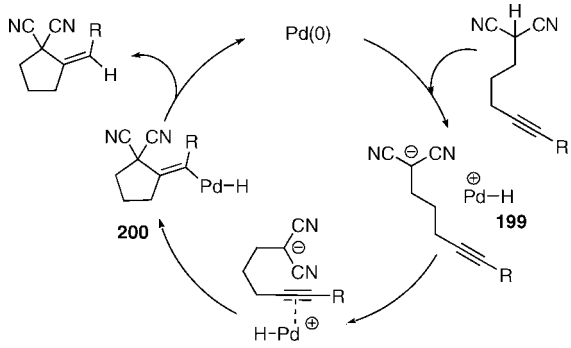
Here again, the proposed mechanism involves the addition of the malonate anion onto a (η^2-alkyne)Pd(II) complex. However, in this case, the Pd(II) species that activates the alkyne moiety is formed by oxidative addition of Pd(0) into the C−X bond of an aryl- or vinyl halide (X = Br, I). The addition of the malonate anion leads to the formation of a σ-alkenyl−Pd(II) species, which undergoes reductive elimination. The exclusive formation of the (*E*)-isomer supports the mechanism involving the *anti*-addition of the nucleophile onto the (η^2-alkyne)Pd(II) complex (Scheme 185).

The intramolecular addition could also be achieved with conjugated enynes, thus furnishing 1,3-bis-exocyclic dienes (Scheme 186). Cyclizations leading to 5-membered rings were less efficient than in the case of simple alkynes. On the contrary, 6-membered ring formation was achieved in better yields than in the case of alkynes where competitive intermolecular Sonogashira cross-coupling reaction hampered

Scheme 187



Scheme 188



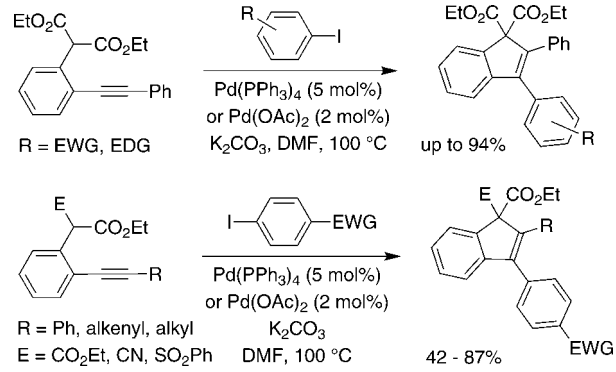
the procedure.[288,291] Bismethylene-*exo*cyclohexanes are valuable synthetic intermediates that have been further elaborated into polycyclic compounds via 6π-electrocyclization,[288,291] Diels−Alder cycloaddition under high pressure,[291,292] or Friedel−Crafts intramolecular cyclization.[293]

Pd(II)-catalyzed 5-*exo*-dig cyclizations of malonate derivatives and cyanoesters onto substituted alkynes have generally proved ineffective or very sluggish. On the contrary, Yamamoto and co-workers reported that the cyclization of malononitriles onto internal alkynes could be achieved at room temperature in toluene/EtOH (5:1) or THF/EtOH (5:1) in the presence of a catalytic amount of $Pd(OAc)_2$ and 1,5-cyclooctadiene (cod).[294] No base was needed but the presence of EtOH was found to be crucial for the success of this cyclization, although its exact role remains unclear. Under these conditions, substrates **197** gave the cyclized products **198** in high yields (70−88%) and with high levels of regio- and stereoselectivity, with the 5-membered ring being formed exclusively in all cases (except R = Ph) with a *Z*-trisubstituted exocyclic double bond (Scheme 187). Interestingly, terminal alkynes gave lower yields, presumably due to side reactions initiated by the insertion of Pd(0) into the alkyne C−H bond.

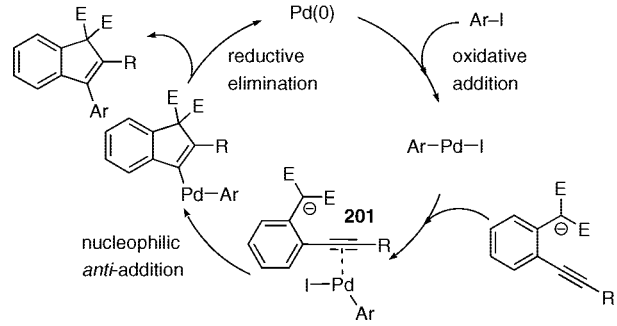
The authors proposed that abstraction of the active methyne proton from the malononitrile by Pd(0) leads to the formation of cationic Pd−hydride species **199** and a carbanion. Intramolecular nucleophilic addition of the latter onto the alkyne activated by the cationic Pd(hydride) complex leads to the formation of vinyl−Pd−hydride intermediate **200**, which gives the final product after reductive elimination (Scheme 188).

Cyclization onto substituted alkynes following a 5-*endo*-dig mode was also reported. Quite recently, the groups of Liang and Larock reported independently a Pd-catalyzed cyclization approach to substituted indenes.[295,296] Cyclization of diethyl 2-(2-(2-alkynyl)phenyl)malonate derivatives was achieved at 100 °C in DMF in the presence of an aryl iodide, K_2CO_3, and a catalytic amount of $Pd(PPh_3)_4$ or $Pd(OAc)_2$. The highest yields of the corresponding arylated indenes were obtained with electron-deficient aryl iodides such as *p*-, *m*-, *o*-iodobenzoates and *p*-, *m*-, (nitro)- or (trifluoromethyl)iodobenzenes. Electron-rich and some *o*-substituted aryl iodides provided lower yields (Scheme 189). Arylation with bromobenzene was also effective, but the reaction with chlorobenzene or phenyl triflate remained unsuccessful. Vinylated indenes could be obtained by reaction in the presence of bromostyrene, whereas vinyl- and alkynyl iodides were ineffective. The protocol was also effective, especially with electron-deficient aryl iodides, for the reaction of malonate-containing arylalkynes bearing an alkyl or a 1,3-cyclohexenyl substituent at the acetylene terminus. Reaction of α-cyano or α-sulfonylesters as pronucleophiles resulted in moderate yields.

Scheme 189



Scheme 190

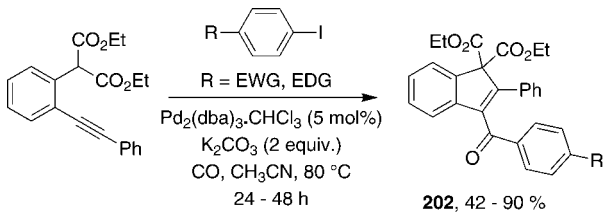


Two different mechanisms have been proposed to account for this reaction. Liang et al. initially proposed a route involving initial *trans*-carbopalladation for the insertion of the alkyne into the aryl−Pd(II) bond, followed by nucleophilic attack of the malonate anion onto the Pd(II) atom. The resulting 6-membered palladacyclic intermediate leads to the products following reductive elimination. This mechanism was later challenged by Larock and co-workers who, by analogy with Balme and co-workers' reports on related 5-*exo*-dig cyclizations, have put forward a rationale involving a more likely 5-*endo*-dig intramolecular *anti*-addition of the stabilized carbanion onto the (η^2-alkyne)Pd(II) complex **201** in which the Pd(II) species results from oxidative addition of the aryl iodide to the Pd(0) catalyst. Reductive elimination from the resulting vinyl−Pd intermediate gives the substituted indene (Scheme 190).

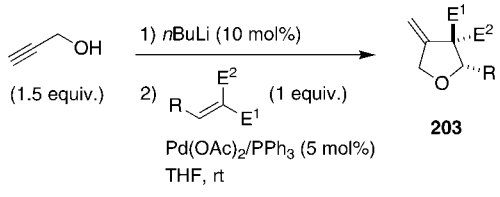
Interestingly, when performed under a CO atmosphere, the reaction led to the corresponding aroylindene derivatives via a Pd-catalyzed carbonylative cyclization (Scheme 191).[297] A mixture of products (aroylindene and indene) was obtained when the reaction was carried out in DMF with $Pd(PPh_3)_4$ as the catalyst. On the contrary, the aroylindene derivatives **202** were obtained as the sole products in moderate to high yields (51−90%) at 80 °C in CH_3CN by using 5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$.

4.6.2.2. Synthesis of Heterocycles. Pd(II)-catalyzed intramolecular additions of enolate anions have also been used for the preparation of oxygen- and nitrogen-containing heterocycles. Because of the tendency of anions bearing

Scheme 191

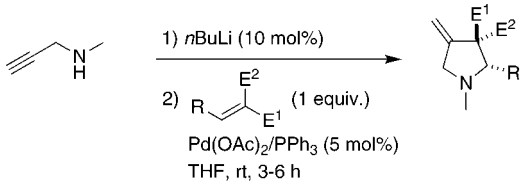


Scheme 192



E^1	E^2	R	
CO_2Et	CO_2Et	Ph	94%
CO_2Et	CO_2Et	Me	66%
CO_2Et	CO_2Et	*i*-Pr	52%
CN	CN	Ph	51%
CO_2Et	CN	Ph	47% (dr > 98:2)
CO_2Et	C(O)Me	Ph	86% (dr > 98:2)

Scheme 193



E_1	E_2	R	
CO_2Et	CO_2Et	Ph	79%
CO_2Et	CN	Ph	75% (dr = 85:15)
CN	CN	Ph	-
CO_2Et	CO_2Et	Me	16%
CO_2Et	CO_2Et	*c*-hexyl	-

heteroatoms in the β-position to undergo β-elimination, the required malonate anions cannot be easily prepared by simple deprotonation. This problem has been solved very elegantly by Balme and co-workers via an overall process involving a cascade Michael addition/carbocyclization process.[298]

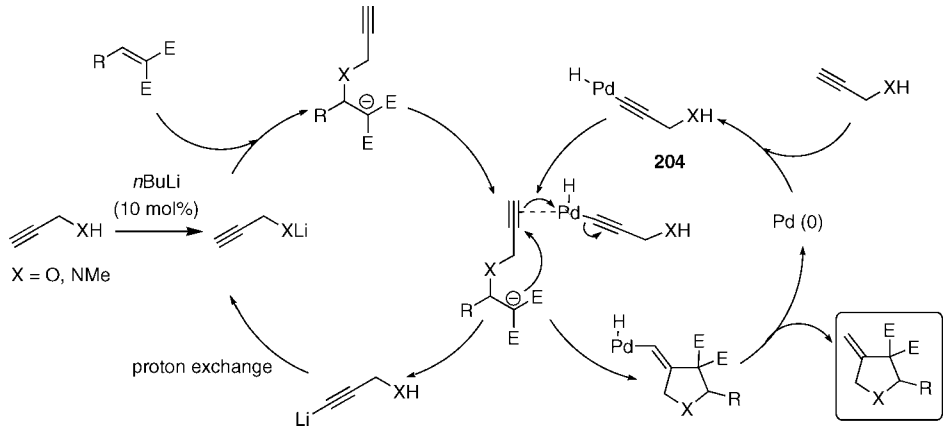
3-Methylidenetetrahydrofurans **203** were obtained in moderate to high yields by the reaction of primary, secondary, or tertiary propargyl alcohols with arylidene- and alkylidenemalonate derivatives (EWG = CO_2Et, CN, C(O)R) in the presence of a catalytic amount of a Pd(0) complex and a base (Scheme 192).[299] The best results were obtained using $Pd(OAc)_2/PPh_3$ (5 mol %) and *n*BuLi (10 mol %) at room temperature in THF. Interestingly, a complete diastereoselectivity was observed in the reaction of propargyl alcohol with dissymmetric Michael acceptors. On the contrary, moderate levels of stereoselectivity were observed with secondary propargyl alcohols.

The same procedure could also be used for the preparation of methylenepyrrolidines but proved less general.[300] While *N*-methylpropargylamine added efficiently onto benzylidenemalonate derivatives and gave the corresponding pyrrolidines in high yields (75−79%, 2 examples), the reaction with alkylidene malonates proved ineffective (Scheme 193). *N*-Tosyl, *N*-Boc, *N*-Bn, and simple propargylamine did not give any cyclized product. However, the cyclization could be achieved efficiently in the presence of Cu(I) salts (see section 4.7.1).

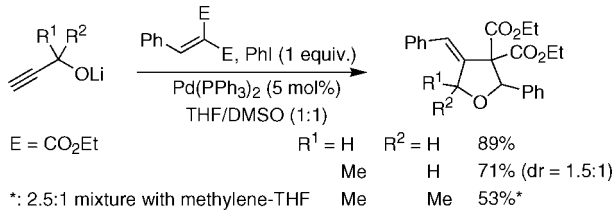
As previously for the carbocycles synthesis, the proposed mechanism involves the activation of the alkyne moiety by complexation with σ-alkynyl−Pd(II)−hydride species **204** formed by oxidative insertion into the C−H bond of the terminal alkyne (Scheme 194).[300] The Li−alkoxide (or Li−amide) that initiates the reaction is regenerated by proton exchange from the Li−acetylide liberated during the nucleophilic *anti*-addition of the malonate anion onto the (η^2-alkyne)Pd(II) complex (where the Pd(II) species is σ-alkynyl−Pd(II)−hydride **204**).

Analogous cascades where the Pd(II) salt was generated by oxidative addition of Pd(0) into a C−X bond (X = I, Br, OTf) offered a multicomponent approach for the preparation of substituted *exo*-arylidenetetrahydrofurans and -pyrrolidines. For instance, under the optimized conditions involving the use of $Pd(PPh_3)_2$ (5 mol %) prepared in situ by reduction of $PdCl_2(PPh_3)_2$ with *n*BuLi in a DMSO/THF (1:1) solvent mixture (in order to inhibit the formation of byproduct arising from the Pd−hydride species), propargyl Li−alkoxide added at room temperature onto diethyl benzylidenemalonate in the presence of iodobenzene to give the corresponding benzylidenetetrahydrofuran in 89% yield in less than 15 min (Scheme 195).[301] The reaction was rather general in scope. Alkylidenemalonates, vinyl bromides, and vinyl triflates were also found to participate effectively in the cascade reaction. Secondary and tertiary propargyl alcohols required higher temperature (30−50 °C) but still gave the cyclic products in moderate to good yields. No selectivity was observed during the Michael addition with secondary propargyl alcohols, and thus, following cyclization,

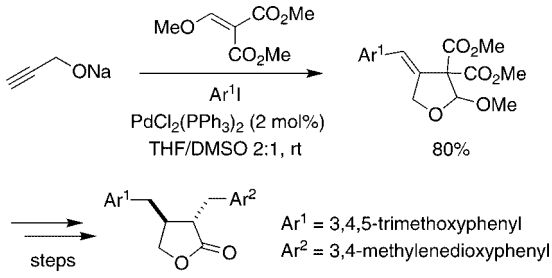
Scheme 194



Scheme 195



Scheme 196



a mixture of diastereomers was obtained. When 1-substituted propargyl alcohols were used, a mixture of tetrahydrofuran and dihydropyran was obtained as a result for a competitive 6-*endo*-dig cyclization.

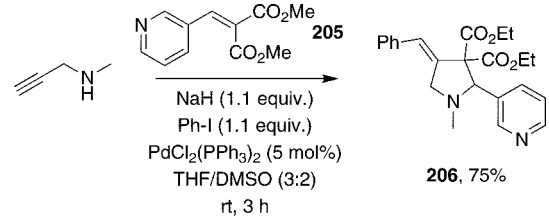
Various lactol ethers could be prepared in good to high yields (58−82%) from propargyl alcohols and commercially available diethyl ethoxymethylenemalonate.[302] The best results were obtained at room temperature in THF/DMSO (2:1) with aryl iodides or vinyl triflates in the presence of $Pd(PPh_3)_2$ prepared in situ. The resulting lactol ethers could be easily converted into the corresponding furans via a *t*BuOK-promoted decarboxylative elimination. In some cases, the lactol ether could not be isolated and the furan was obtained as the sole product of the cascade Michael addition/carbocyclization. The furan derivatives could be obtained in a one-pot procedure in similar yields.

This reaction was recently applied to a short racemic synthesis of dibenzyl butyrolactone lignans (Scheme 196). For this purpose, the cascade Michael addition/carbocyclization was achieved in 80% yield on multigram scale from sodium propargyl alkoxide, dimethyl methoxymethylenemalonate, and 3,4,5-trimethylphenyl iodide in the presence of 2 mol % $PdCl_2(PPh_3)_2$.[302,303]

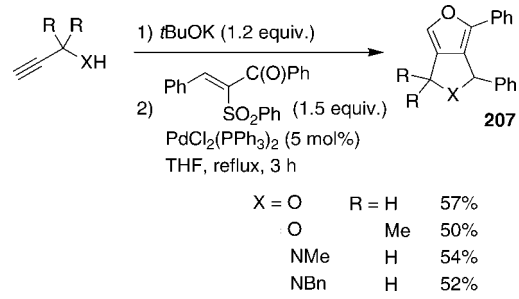
Again, pyrrolidines could also be prepared from *N*-alkylpropargylamines and alkylidene- or benzylidenemalonate derivatives according to the same strategy.[304] The kinetics of the reaction was strongly influenced by the nature of the base, and in this case, the best results were obtained with NaH. The cascade Michael addition/cyclization was carried out at room temperature in THF/DMSO (3:2) in the presence of 5 mol % of $Pd(PPh_3)_2$ prepared in situ. For instance, under these optimized conditions, *N*-methylpropargylamine reacted with the pyridyl-substituted vinylidenemalonate **205** in the presence of iodobenzene to furnish the corresponding benzylidenepyrrolidine **206** in 75% yield (Scheme 197). *N*-Tosyl, *N*-Boc, and *N*-benzyl protected propargylamines did not participate in the reaction or gave the cyclized product in low yield.

Interestingly, the addition of propargyl alcohols and propargylamines onto α-sulfonyl-α,β-unsaturated ketones in refluxing THF in the presence of a stoichiometric amount of *t*BuOK led to the formation of bicyclic furo[3,4-*c*] heterocyclic derivatives **207** in moderate yields (42−60%). Primary and tertiary propargyl alcohols as well as *N*-methyl- and *N*-benzylpropargylamines were found to participate in the reaction (Scheme 198).[298]

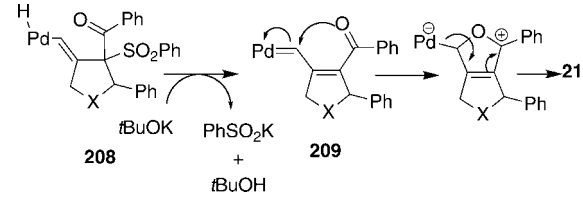
Scheme 197



Scheme 198



Scheme 199

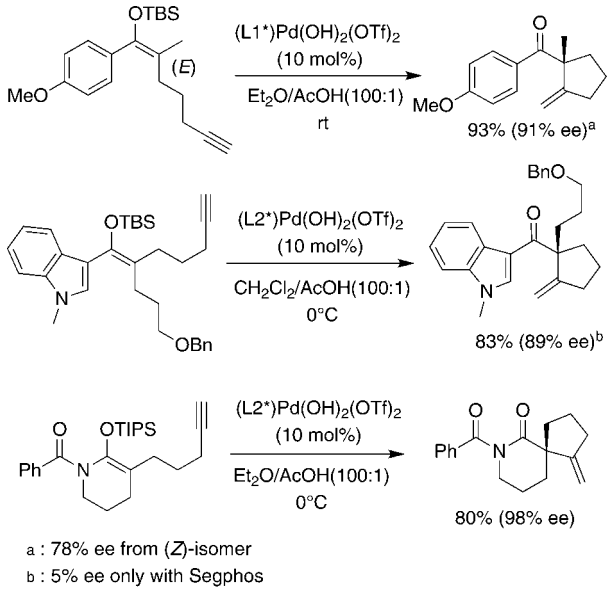


The authors proposed a mechanism involving the formation of an electrophilic Pd−carbene species (Scheme 199).[305] Deprotonation of vinyl−Pd−hydride **208** resulting from the cyclization onto the (η^2-alkyne)Pd complex with *t*BuOK, followed by elimination of the allylic sulfonyl group affords the electrophilic Pd−carbene **209**, which is attacked by the neighboring carbonyl group, thus leading to furan **210** after rearrangement of the zwitterionic intermediate.[306] A similar approach to dihydrofurans and pyrroline derivatives based upon a copper-catalyzed cyclization followed by an intramolecular Pd-catalyzed allylic substitution was disclosed shortly after by the same authors (see section 4.7.1).[307,308]

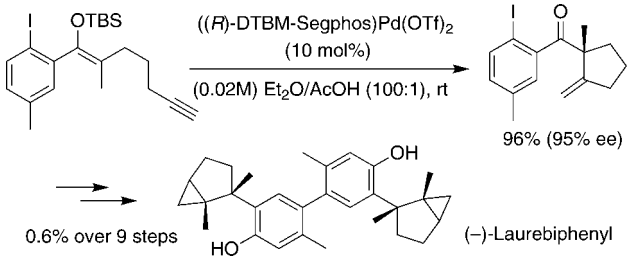
Silyl enol ethers and silyl ketene aminals have been recently shown to undergo Pd(II)-catalyzed intramolecular addition onto alkynes.[309] In particular, the enantioselective cyclization of silyl enol ethers of aryl ketones was achieved at 0 °C or room temperature in the presence of 10 mol % of ((*R*)-DTBM-segphos)$Pd(OTf)_2$ in Et_2O/AcOH (100:1). The resulting methylenecyclopentanes were obtained in high yields (70−93%) and high enantiomeric excesses (73−91% ee). The proposed mechanism involves the nucleophilic *anti*-addition of the silyl enol ether moiety onto an (alkyne)Pd(II) complex. The level of chiral induction was found to depend upon both the nature of the silyl group and the configuration of the double bond of the silyl enol ether moiety. The best results were obtained with the bulky TBS−enol ether in the (*E*)-configuration (Scheme 200). The cyclization of nonaryl-substituted silyl enol ethers and silyl ketene aminals gave better results with ((*R*)-Binaphane)$-Pd(OH)_2(OTf)_2$.

This methodology has been applied to the total synthesis of (−)-laurebiphenyl, a dimeric sesquiterpene isolated from *Laurencia nidifica,* for which the absolute configuration of

Scheme 200



Scheme 201



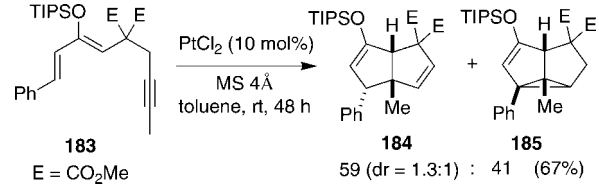
the first quaternary center was controlled by a Pd(II)-catalyzed enantioselective cyclization (Scheme 201).[309]

Interestingly, the same chiral Pd(II)-catalysts also proved highly efficient for the enantioselective Conia-ene reaction of malonates bearing pendant terminal alkynes.[310] While cationic Au(I)-catalysts did not lead to any enantioselectivity, the combination of (DTBM-Segphos)Pd(OTf)$_2$ with a protic source and/or Yb(OTf)$_3$ in CH_2Cl_2 or Et_2O gave methylenecyclopentane derivatives in high yields and with high levels of chiral induction (up to 94% ee). However, contrary to the Pd(II)-catalyzed reactions described previously in this paragraph, this transformation does not seem to involve the intramolecular addition of an enolate because the presence of a base such as Et_3N inhibits the cyclization process.

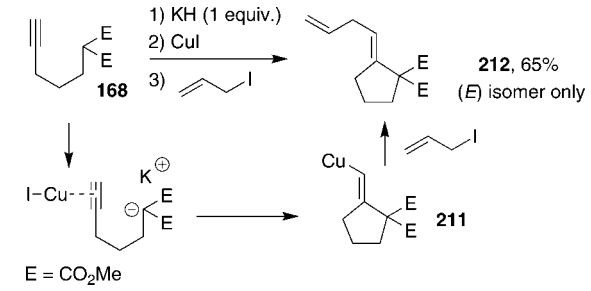
4.6.3. Platinum(II)-Mediated Additions

Platinum(II) complexes have been rarely used to promote the cyclization of stabilized carbanions onto alkynes. One could note, for example, Iwasawa and co-workers' report on $PtCl_2$-catalyzed cyclization of dienol silyl ethers onto alkynes in a behavior analogous to W(0) and Re(I) complexes

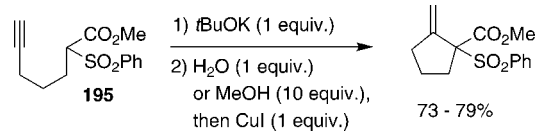
Scheme 202



Scheme 203



Scheme 204



(see section 4.3.2 and 4.4.2, respectively, for mechanistic considerations). For example, compound **183** was cyclized at 70 °C in toluene in the presence of 10 mol % of $PtCl_2$, leading to the formation of a mixture of bicyclic compound **184** and tricyclic compound **185** (6:4 ratio) in 67% yield (Scheme 202).[264] However, W(0)- as well as Re(I)-catalysts were more efficient and gave not only higher yields but also a higher diastereomeric ratio for the bicyclic product.

4.7. Group 11: Copper and Gold

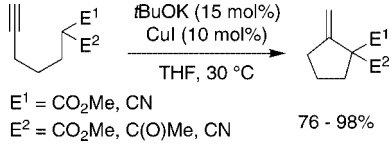
4.7.1. Copper(I)-Mediated Additions

4.7.1.1. Preparation of Carbocycles. Copper(I) salts have been shown to activate alkynes toward the addition of enolates very efficiently. More specifically, in connection with their studies on palladium(II)-catalyzed cyclizations, Balme, Goré, and co-workers showed that following addition of CuI, the potassium enolate of **168** furnished the carbocupration product **211**, which could be trapped subsequently with allyl iodide to give alkylidene cyclopentane **212** in 65% yield as a single isomer (Scheme 203).[311] The observed (*E*)-configuration was consistent with a mechanism involving the *anti*-addition of the K−malonate anion onto the (η^2-alkyne)-Cu(I) complex, as the formation of a Cu−enolate would have led to the opposite selectivity through a *cis*-addition process.

The association of the Cu(I) salt with a protic source allowed the cyclization to be carried out in the absence of any halogenating agent (Scheme 204). For instance, deprotonation of sulfonyl ester **195** with *t*BuOK in THF, followed by sequential addition of a protic source (H_2O or MeOH) and CuI, gave the corresponding methylene cyclopentane derivatives in high yield (79% and 73%, respectively).[285]

By using catalytic amounts of *t*BuOK and Cu(I), the reaction could be carried out at 30 °C in THF without need of any other protic source than *t*BuOH formed during the deprotonation step. This protocol gave methylenecyclopentane derivatives in high yields (76−98%) under very mild

Scheme 205



reaction conditions (Scheme 205)[312] and could be applied on a gram scale without any significant erosion of the yield.[313]

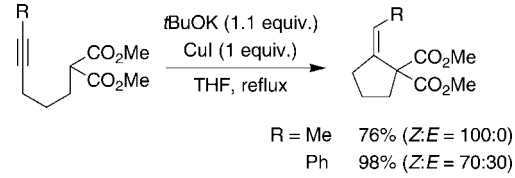
A double catalytic cycle was proposed to account for the reaction outcome (Scheme 206). In a first cycle, cyclization of the malonate anion (formed by deprotonation with *t*BuOK) onto (η^2-alkyne)*t*BuOCu(I) complex **213** gives a vinyl−Cu(I) species and regenerates *t*BuOK, which can react in a second cycle to form the enolate. Protonolysis of the vinyl−Cu with *t*BuOH gives the observed product and *t*BuO−Cu(I), which activates the alkyne moiety.

Copper-mediated 5-*exo*-dig cyclization onto disubstituted alkynes is generally a sluggish process. However, in the presence of stoichiometric amounts of *t*BuOK and CuI, the cyclization onto internal alkynes could be achieved in refluxing THF. In this case, moderate to high levels of (*Z*)-selectivity were observed, which is consistent with an *anti*-addition process (Scheme 207).

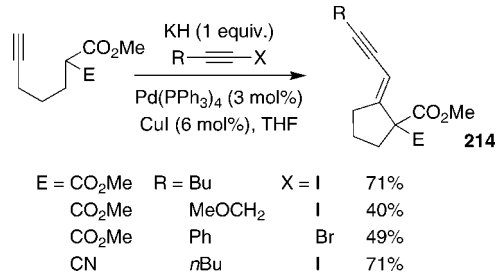
Interestingly, in a similar bicatalytic process, the vinyl−Cu(I) intermediate reacted with an alkynyl iodide or bromide in the presence of a Pd(0) catalyst to give the corresponding stereodefined enynes **214** in moderate to good yields (Scheme 208). The presence of a Cu(I) salt in this reaction was found to be crucial in order to avoid the polymerization side reactions which were observed if only Pd was used.[311]

In connection with the above-mentioned systems disclosed by Balme and co-workers, Larock and co-workers reported the Cu(I)-catalyzed 5-*endo* carbocyclization of malonate anions onto arylalkynes.[296] The cyclization of malonate derivatives could be achieved at 55 °C in THF in the presence of *t*BuOK (5 mol %) and CuI (2 mol %). Under these reaction conditions, the resulting indenes were obtained in good to excellent yields (61−96%), as illustrated by the cyclization of **215** into **216** (Scheme 209). The arylalkynes that gave satisfying yields include terminal alkynes, alkyl- and aryl-substituted alkynes, and enynes. The cyclization reaction also tolerated alkyne substituents bearing functional groups such as methoxy, hydroxy, methyl ester, diethoxyacetal, or cyano. Sterically hindered alkynes were considerably less reactive and, as a consequence, secondary and tertiary alkyl substituted substrates required longer reaction times. Moreover, diethyl [2-(trimethylsilylethynyl)phenyl]-

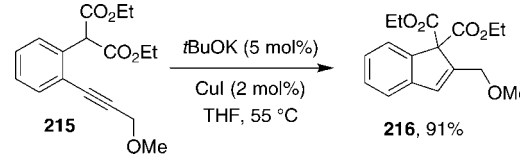
Scheme 207



Scheme 208



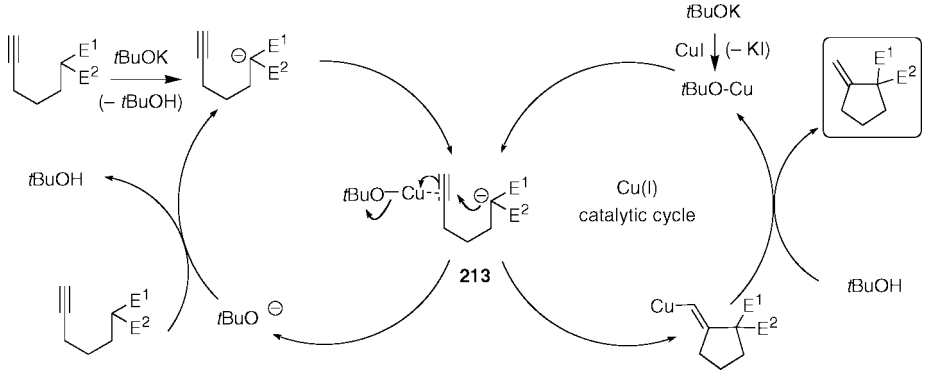
Scheme 209



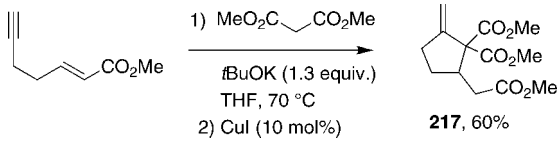
malonate failed to cyclize even in the presence of a stoichiometric amount of *t*BuOK and CuI. A mechanistic rationale involving an 5-*endo*-dig *anti*-carbocupration analogous to the one presented for the Cu-mediated 5-*exo-dig* cyclizations (see Scheme 206) was proposed by the authors.

Functionalized methylenecyclopentanes could also be accessed efficiently by a two-component reaction involving a malonate derivative and an α,β-unsaturated ester having an alkynyl side chain. Addition of the malonate anion onto the Michael acceptor followed by proton transfer gave a new malonate anion that cyclized in the presence of a Cu(I) salt. For example, this sequence carried out with *t*BuOK as a base and a catalytic amount of CuI (10 mol %) led to the formation of **217** in 60% yield (Scheme 210).[312] Both 1,2- and 1,1-disubstituted α,β-unsaturated esters could participate in the cascade reaction, as well as various active methylene pronucleophiles. Depending upon their nature, different bases (*t*BuOK, NaH, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or *N*,*N*-diisopropylethylamine (DIPEA)) and solvents (THF or CH_3CN) could be used to achieve the Michael addition. Because of the solubility problems, the best results were

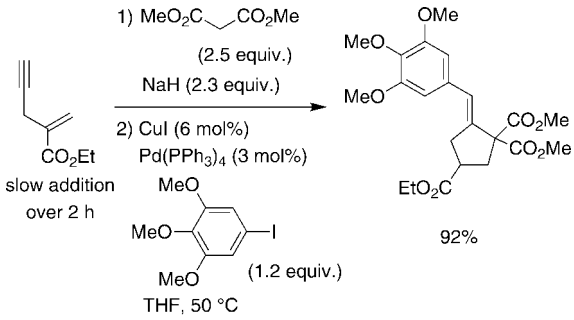
Scheme 206



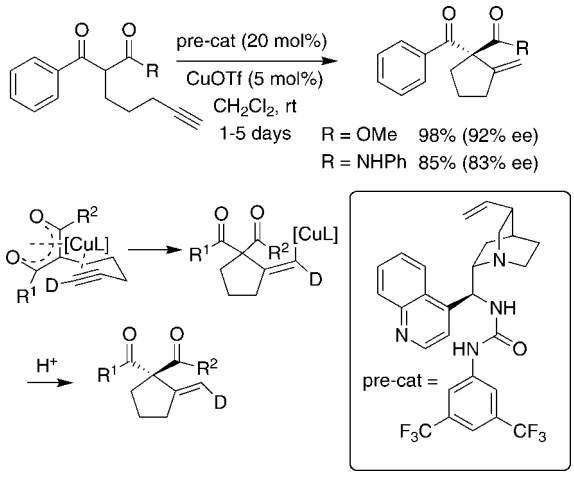
Scheme 210



Scheme 211



Scheme 212

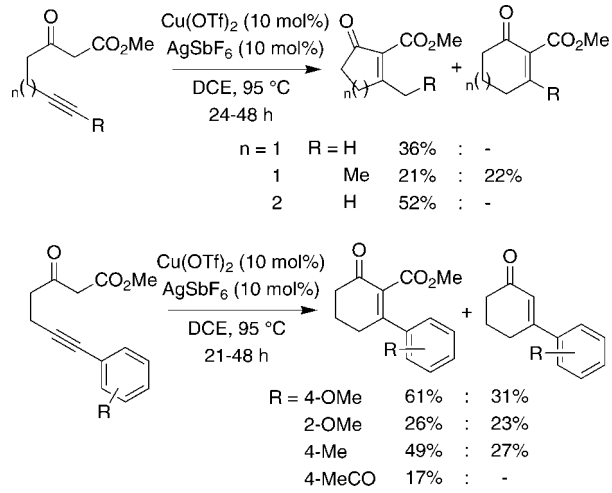


obtained in some cases in the presence of a catalytic or stoichiometric amount of triethylbenzylammonium chloride.[289]

Here again, when the reaction was carried out in the presence of both Cu(I) and Pd(0), the vinyl−Cu species resulting from the Cu-mediated cyclization process could react in a Pd-catalyzed cross-coupling reaction with an aryl- or benzyl halide (Scheme 211). The best results were obtained in the presence of 6 mol % of CuI and 3 mol % of $Pd(PPh_3)_4$ by using slow addition of an excess of the Michael acceptor. Under these optimized conditions, this one-pot sequence led to the formation of functionalized methylenecyclopentane derivatives in moderate to high yields (50−92%).[289]

Very recently, Dixon and co-workers reported an enantioselective Cu(I)-catalyzed Conia-ene reaction. The cyclization reaction was carried out at room temperature in CH_2Cl_2 in the presence of a catalytic amount of CuOTf and an urea derived from a 9-amino-9-deoxyepicinchonidine scaffold as a precatalyst (Scheme 212).[314] Under the optimized reaction conditions, a range of pentynyl β-ketoester and β-ketoamide derivatives were cyclized in good to high yields (67−99%, 18 examples) and with a high level of enantioselectivity (up to 93% ee). The presence of both the precatalyst and CuOTf was found to be crucial because no conversion was observed with either independently. Other metal salts such as $Zn(OTf)_2$ and $NiCl_2$(dppe) showed a moderate catalytic activity, albeit only low levels of enantioselectivity were observed (ee < 30%). The proposed mechanism was supported by deuterium labeling experiments and involves the formation of a ligated Cu−enolate that undergoes enantioselective *syn*-carbocupration of the alkyne. The chiral precatalyst is supposed to be involved in the deprotonation of the β-ketoester and acts as an effective ligand for the Cu−enolate.

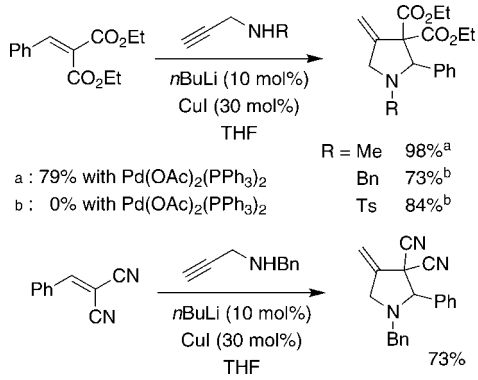
Scheme 213



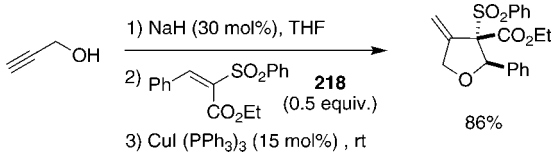
Recently, copper(II) salts have also proved to efficiently catalyze Conia-ene type reactions. Li and co-workers reported the Cu(II)/Ag(I)-catalyzed cyclization of linear β-alkynyl β-ketoesters to yield cyclopentenones and cyclohexenones.[315] The combination of both metal salts was found to be optimal as barely no reaction was observed in the absence of AgOTf or $Cu(OTf)_2$. Cyclization in a 5-*exo*- or a 6-*endo*-mode was observed depending upon the substitution of the alkyne moiety. Whereas terminal alkynes gave exclusively the cyclic products arising from a 5-*exo*-dig cyclization process, alkynes substituted with an aryl group reacted following a 6-*endo*-dig mode (Scheme 213). Alkyl substituents on the alkynes led to a nonregioselective cyclization process. Under the developed reaction conditions, isomerization of the carbon−carbon double bond following cyclization was observed for both the *endo*- and *exo*-cyclic products. Furthermore, products resulting from decarboxylation were also observed in the case of β-ketoesters (Scheme 213). Mechanistically, this system is fundamentally different from the previously described cyclizations as CuI afforded only traces of the cycloadducts. The authors proposed that this Cu(II)/Ag(I)-catalyzed Conia-ene reaction occurs via the *syn*-addition of a M−enolate (M = Ag, or Cu) onto a (η^2-alkyne)M complex (M = Ag or Cu). The 5-*exo* versus 6-*endo* regioselectivity was explained on the basis of the bulkiness of the substituent of the alkyne moiety.

4.7.1.2. Preparation of Heterocycles. Tandem Michael addition/cyclization cascades were utilized to prepare pyrrolidines and tetrahydrofurans. One should note that analogous reactions were developed with Pd(0) (see section 4.6.2). However, the Cu(I)-promoted versions were often more efficient and general. For instance, base-catalyzed addition of a range of propargylamines onto benzylidenemalonate and benzylidenemalononitrile derivatives, followed by cyclization of the resulting anion in the presence of a catalytic amount of CuI, led to the formation of the corresponding *exo*-methylene pyrrolidines in good to high yields (73−98%).[300] The addition to the related alkylidenemalonates was less

Scheme 214



Scheme 215



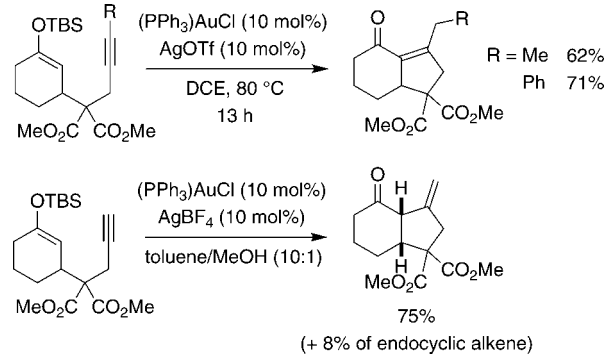
effective due to the competing deprotonation of the substrate with the propargylamide (Scheme 214).

Similarly, propargyl alcohol added onto ethyl 2-phenylsulfonylcinnamate **218** in the presence of catalytic amounts of NaH and a Cu(I) salt to give methylene tetrahydrofurans in good to high yields (Scheme 215).[307] The reaction could be carried out with CuI or with $CuI(PPh_3)_n$ ($n = 1-3$) complexes, which are more soluble in organic solvents. The procedure was extended to solution-phase parallel synthesis of tetrahydrofurans. A variety of propargyl alcohols (simple propargyl alcohol, as well as secondary- and tertiary propargyl alcohols) were condensed efficiently with benzylidene- and alkylidenemalonates. The polysubstituted tetrahydrofurans were obtained in moderate to high yields (44−99%) and high purity (>95%). The best results were obtained with mono- or disubstituted propargyl alcohols.[316]

The proposed mechanism of these transformations involves the cyclization onto (η^2-alkyne)Cu(I) complex **219** of the anionic intermediate **220** obtained by Michael addition of the alkoxyde (respectively, amide) onto the benzylidenemalonate. The resulting vinyl−Cu(I) species **221** is quenched by propargyl alcohol (respectively, propargylamine), thus regenerating the Cu(I)−alkoxyde (respectively, amide) species (Scheme 216).

Methylenepyrrolidines and methylenetetrahydrofurans possessing an allyl sulfone moiety were versatile intermediates

Scheme 217

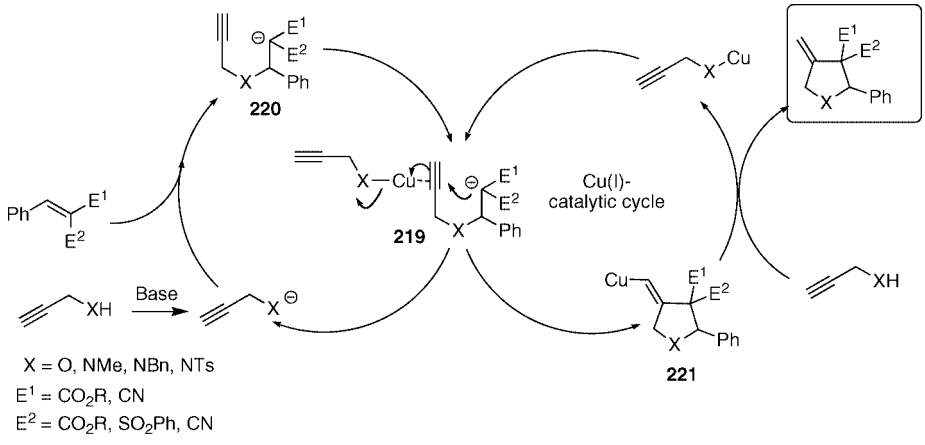


that could react further in a Pd(0)-catalyzed nucleophilic displacement. Interestingly, this transformation could be achieved in situ in a multicomponent domino reaction.[307,308,317] The same strategy applied to nitroalkene as Michael acceptors[318] led to the formation of the corresponding pyrrolidine derivatives in moderate to good yields (46−68%, 3 examples).[308]

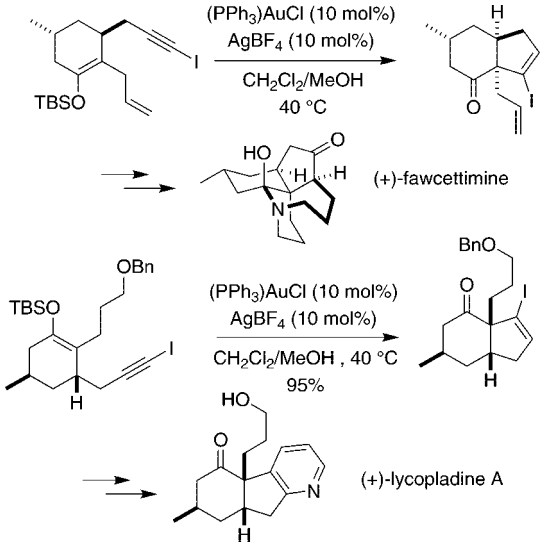
4.7.2. Gold(I)-Mediated Additions

Complexation with gold(I) has emerged over the last few years as a method of choice to activate alkynes toward nucleophilic addition, including intramolecular addition of enolates.[319] More specifically, Toste and co-workers, as well as Lee and co-workers, reported the Au(I)-catalyzed carbocyclization of silyl enol ethers of cyclic ketones bearing pendant alkynes.[186,320−322] The reaction was carried out in CH_2Cl_2, toluene, or 1,2-dichloroethane with the cationic Au(I) catalyst prepared from $(PPh_3)AuCl$ and $AgBF_4$ or AgOTf. The product distribution was found to be dependent upon the reaction conditions. In the absence of a protic source, following the addition step, migration of the newly formed exocyclic carbon−carbon double bond to give the more stable α,β-unsaturated ketone was observed (Scheme 217).[321] On the contrary, in the presence of a protic source (H_2O or MeOH), bond migration could be prevented and the *exo*-methylene adducts were obtained (Scheme 217). The scope of the reaction was found to be broad, allowing the preparation of a range of fused and spirobicyclic structures. Changing the length of the alkynyl side chain led to different modes of cyclization (5-*exo* and 5-*endo*), resulting in a different location of the newly formed carbon−carbon double bond. The reaction was not limited to terminal alkynes because substrates bearing a phenyl, heteroaryl, or iodine

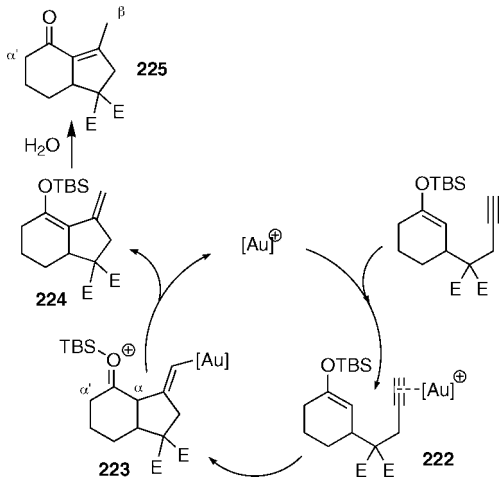
Scheme 216



Scheme 218



Scheme 219

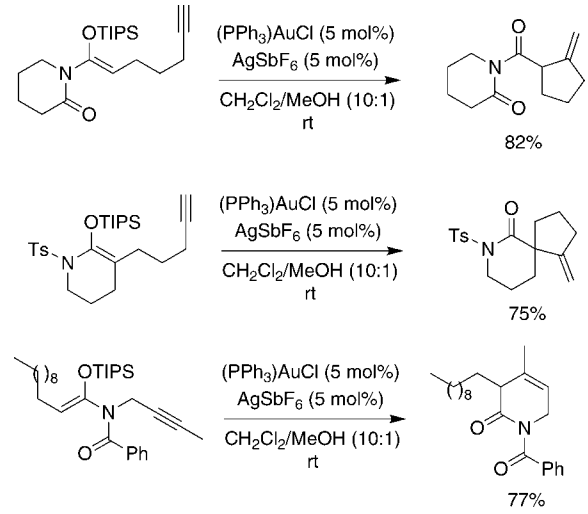


atom in the terminal position of the alkyne also gave the corresponding cyclic products in high yields.

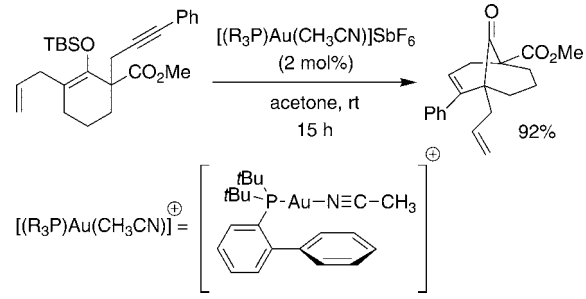
The gold-catalyzed carbocyclization of silyl−enol ethers bearing substituted appended iodoalkynes was applied to the synthesis of (+)-fawcettimine[320] and (+)-lycopladine A,[186] which both present a polycyclic skeleton and a quaternary carbon center that was installed in a diastereoselective manner during the Au(I)-catalyzed carbocyclization (Scheme 218). Attempts to control the absolute configuration of the quaternary center of simple methylenecyclopentane derivatives using chiral Au(I)-catalyst have been so far unsuccessful. For this purpose, Pd(II)-catalysts have proved to be much more efficient (see section 4.6.2).[310]

It was proposed that the cyclization reaction occurs via *anti*-addition of the silyl enol moiety onto cationic (η^2-alkyne)Au(I) complex **222** (Scheme 219).[321] In the absence of a proton source, the resulting vinyl−Au intermediate **223** presumably abstracts a proton at the α- and/or α′-position leading to compound **224**, which isomerizes further into the final product **225** upon hydrolysis. This picture was proposed to account for the observed deuterium incorporation at the α′-position of **225** (instead of at the β-position) when D_2O was added after the cyclization reaction. In the presence of a protic source (MeOH or H_2O), direct protodemetalation of vinyl−Au **223** leads to the *exo*-methylene adducts without double-bond migration.

Scheme 220



Scheme 221

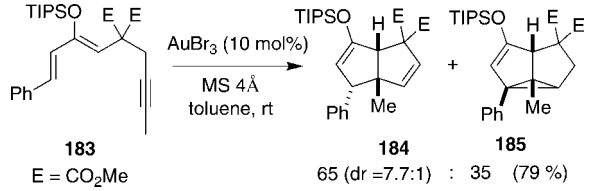


Cyclization of silyl ketene amides and carbamates was also reported. The best results were obtained at room temperature in a CH_2Cl_2/MeOH (10:1) using 5 mol % of $(Ph_3P)AuCl$ and $AgSbF_6$ as a cocatalyst. Depending on the position of the nitrogen atom, exclusive formation of 5-membered or 6-membered rings was observed. Presumably due to steric requirements, terminal amides or carbamates bearing appended alkynes were cyclized following a 5-*exo*-dig mode, whereas a 6-*endo*-dig cyclization process was observed for substrates containing a C−N linker (Scheme 220).[322] Interestingly, the reaction carried out with the silyl ketene acetal of a chiral oxazolidinone resulted in the formation of the corresponding methylene cyclopentane with a very high level of stereoinduction (dr > 20:1), albeit in low yield (30%).

Other examples of Au(I)-promoted 6-*endo*-dig cyclizations have been recently reported by Barriault and co-workers. The nature of the phosphine ligand in the cationic phosphinogold(I) complex was found to be crucial for the formation of bicyclo[3.2.1]-, bicyclo[3.3.1]-, and bicyclo[5.3.1]alkenones possessing a bridgehead ketone (Scheme 221).[323] The best results were obtained by carrying out the reaction at room temperature in the presence of a catalytic amount (2 mol %) of the air-stable Echavarren catalyst.[324] Various solvents could be used, including acetone, acetonitrile, and chloroform. Under the optimized reaction conditions, the bicyclo[m.3.1]alkenones were obtained in high yields (78−93%, 14 examples). Not only terminal alkynes but also internal-, 1-iodo-, and 1-bromoalkynes were found to participate effectively in the reaction.

In another example of gold-catalyzed addition of silyl enol ethers onto alkynes, Iwasawa and co-workers reported that Au(III) catalysts could also promote the cyclization of dienol silyl ethers. For example, compound **183** was cyclized at

Scheme 222



room temperature in toluene in the presence of 10 mol % of $AuBr_3$ and gave a mixture of bicyclic and tricyclic products **184** and **185** (65:35 ratio) isolated in 79% yield (Scheme 222).[264] As for the analogous W(0)-, Re(I)-, and Pt(II)-catalyzed reactions (see sections 4.3.2, 4.4.2, and 4.6.3), the formation of a tricyclic intermediate by the insertion of a Au−carbene intermediate in the neighboring benzylic C−H bond was observed.

As for the cyclization of silyl enol ethers, gold(I) salts proved to be excellent catalysts for Conia-ene type cyclizations. For instance, Toste and co-workers reported the cyclization of β-ketoesters onto alkynes in the presence of cationic $(PPh_3)Au(I)$ salt.[325] The reaction proceeded smoothly under neutral conditions with a range of enolizable β-ketoesters that were converted into monocyclic, as well as fused- and bridged-bicyclic, compounds in high yields. From then on, multiple inputs and catalyst optimizations enhanced the scope of the transformation, regarding among others: the nature of the pronucleophile (malonates and β-ketoamides),[326] the catalyst loading,[327] the nature of the alkyne (internal or terminal),[328,329] and the cyclization modes (5-*endo-dig,*[328] 6-*endo-dig*,[329] 6-*exo-dig*, and 7-*exo-dig*[330]). Mechanistically, deuterium labeling experiments ruled out a potential path involving the formation of a Au−enolate and a subsequent *syn*-carboauration. The levels of selectivity observed were on the contrary consistent with a route involving the intramolecular addition of an enol onto a (η^2-alkyne)Au(I) complex.

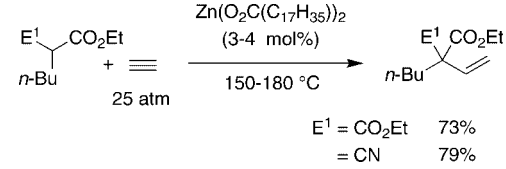
In a related transformation, organocatalysis and gold catalysis were recently combined to mediate the 5-*exo-dig* cyclization of formyl alkynes, thus affording an interesting alternative for the direct functionalization of aldehydes with unactivated alkynes.[331,332] Though beyond the scope of our review, enamines were found to be good nucleophiles for the Au(I)-catalyzed addition onto alkynes.[333] Accordingly, for this cascade reaction, the intramolecular attack of an enamine formed in situ onto a gold-complexed alkyne was invoked. It should be nevertheless noted that no unequivocal proof was obtained to rule out an alternative mechanism involving the amine-catalyzed formation of a gold enolate.[334]

4.8. Group 12: Zinc and Mercury

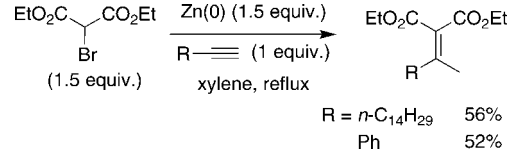
4.8.1. Zinc(II)-Mediated Additions

4.8.1.1. Intermolecular Additions. Intermolecular addition of Zn−enolates derivatives onto alkynes has been so far restricted to anions derived from β-dicarbonyl compounds and α-cyanoesters. In 1962, Seefelder reported the vinylation of various active methyne compounds by reaction with acetylene in the presence of a catalytic amount (3−4 mol %) of zinc stearate at high temperature (150−180 °C) and under pressure (25 atm) (Scheme 223). Substituted malonate derivatives, β-ketoesters, and α-cyanoesters were found to react under these reaction conditions.[335] Though no mechanistic rationale was proposed, subsequent results (vide infra) suggest that carbozincation of acetylene (or metalated

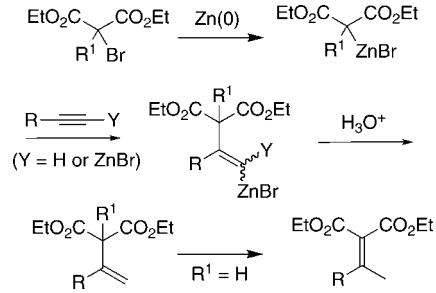
Scheme 223



Scheme 224



Scheme 225



acetylene) by a Zn−enolate of the active methyne was involved. However, under these reaction conditions, a second mechanism involving a Zn-catalyzed Conia-ene reaction cannot be ruled out.

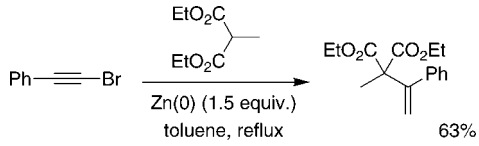
Zn−enolates of malonate derivatives and β-cyano esters have also been reported to add onto terminal alkynes. In a first report by Schulte and co-workers,[336] diethyl bromomalonate was shown to react with alkyl- and aryl-substituted terminal alkynes in the presence of zinc metal to give alkylidene- and benzylidenemalonate derivatives in low to moderate yields (Scheme 224).

The process was described as involving the initial in situ formation of the Reformatsky reagent by zinc insertion into the C−Br bond, followed by regioselective carbozincation of the alkyne (Y = H, Scheme 225), with the addition taking place exclusively at the internal position of the alkyne. Following protonation of the resulting vinyl−Zn species and, eventually (R^1 = H), isomerization of the carbon−carbon double bond, the products were obtained in low to moderate yields (Scheme 225). Following more recent studies, however (vide infra),[337] the carbometalation process could also have taken place onto a metalated alkyne (Y = ZnBr), therefore proceeding with the excellent observed regioselectivity. When the diethyl malonate was replaced by diethyl methylmalonate, migration of the newly formed carbon−carbon double bond was not possible anymore and the reaction furnished the terminal alkenes.

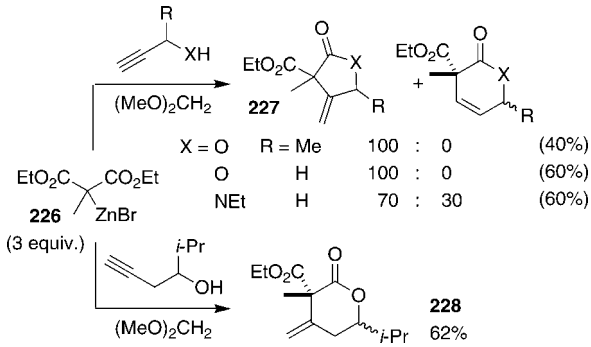
Interestingly, a similar reaction was observed between diethyl malonates and 1-halo-2-phenylacetylenes (Scheme 226).[336,338] In this case, the alkynyl−Zn reagent formed by zinc insertion into the carbon−halogen bond deprotonates the malonate which then adds onto the alkyne, with the addition taking place at the internal position of the alkyne, as observed above.

Gaudemar's report of the high-yielding synthesis of the Reformatsky reagent **226** (Scheme 227) derived from α-bromodiethyl methylmalonate[339] opened the way to studies on

Scheme 226



Scheme 227

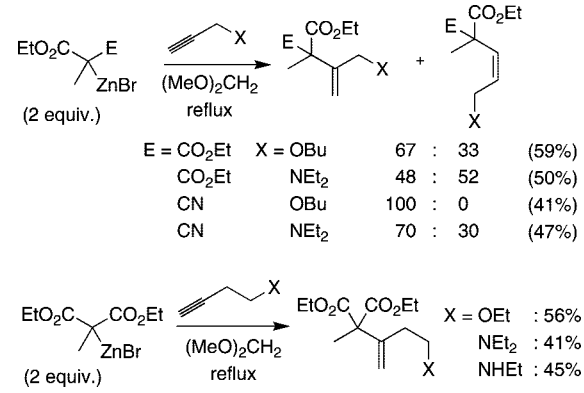


its use as nucleophile for the addition onto alkynes. Miginiac and co-workers reported that, unlike for the previous "Barbier-type" procedures, carbozincations onto a range of terminal alkynes could be observed at lower temperatures (refluxing dimethoxymethane, 42 °C).[340,341] The addition of the Reformatsky reagent was considered to occur onto the alkynyl−Zn compound, resulting from initial deprotonation of the terminal alkyne (see Scheme 217, Y = ZnBr). It was reported that addition of **226** onto propargyl or homopropargyl alcohols furnished the corresponding 5- or 6-membered lactones following regioselective addition at the internal position and subsequent lactonization (Scheme 227). Under these conditions, lactones such as **227** and **228** were obtained in moderate to high yields (40−60% and 38−79% yield from propargyl- and homopropargyl alcohols, respectively). In the case of secondary propargylamines, however, a lower level of regioselectivity was observed, and as a result, a mixture of 5-membered and 6-membered lactams was obtained (Scheme 227). On the other hand, the addition of the Reformatsky reagent onto secondary homopropargylamines was highly regioselective. However, in this case, lactamization proved less efficient than the formation of the corresponding lactones. The addition of the Zn−enolate obtained from α-bromo methylcyanoacetate onto terminal propargyl alcohols was also investigated, but proved less efficient.[342] Besides low yields (<40%), the regioselectivity was found to be variable and strongly dependent upon the nature of the substituent at the propargylic position. Moreover, for free alcohols (or amines), possible lactonization (or lactamization) on either the ester or the nitrile group led to mixtures of products.

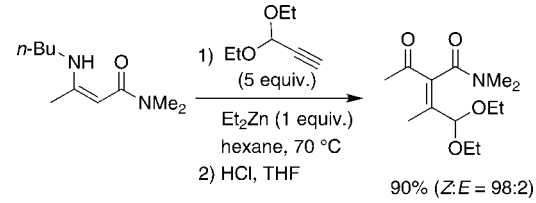
According to the authors, the significant drop in the regioselectivity observed in the case of tertiary propargylamines and propargyl ethers could be a consequence of the steric bulk. Interestingly, reaction at the terminal position furnished exclusively the *Z*-isomer, which led the authors to postulate an *anti*-addition. With homopropargyl ethers, as well as secondary and tertiary homopropargylamines, high levels of regioselectivity in favor of the addition at the internal position were observed (Scheme 228).

After more than 30 years of inactivity in the field, the addition reaction of Zn−enolates derived from β-dicarbonyl derivatives was revisited by Nakamura and co-workers. They showed that the addition of β-aminocrotonamides onto

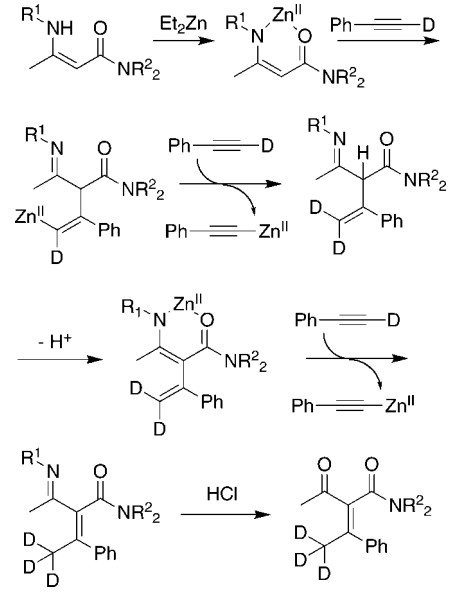
Scheme 228



Scheme 229



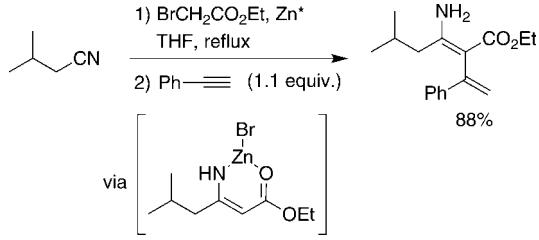
Scheme 230



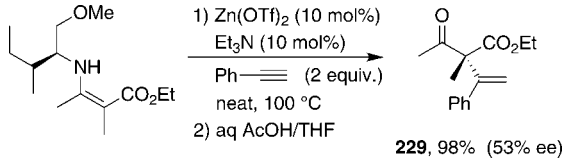
terminal alkynes could be effectively achieved in the presence of a stoichiometric amount of diethylzinc.[343] Upon hydrolysis and following migration of the newly formed carbon−carbon double bond, α-alkylidene β-dicarbonyl compounds were obtained in high yields (82−99%, 17 examples) and excellent levels of diastereoselectivity (*Z*/*E* ratio up to >99:1). Under these conditions, aryl-substituted terminal alkynes, as well as alkenyl- and alkyl-substituted terminal alkynes, were found to participate effectively in the reaction (Scheme 229).

When the reaction was carried out with deuterium-labeled phenylacetylene, incorporation of three deuterium atoms at the methyl group of the final product was observed (Scheme 230). To account for this result, the following mechanistic rationale was put forward. A Zn−enolate intermediate formed by deprotonation of the β-aminocrotonamide with diethylzinc adds onto the alkyne at the internal position to generate an alkenyl−Zn intermediate, which is then protonated by the excess of alkyne. Isomerization into the β-imino-

Scheme 231



Scheme 232



α-alkylidene amides that leads to the products upon hydrolysis takes place via a sequential deprotonation/reprotonation with the excess of alkyne at the γ-carbon of the Zn−enamide intermediate. Interestingly, these results show that, at least in this case, carbometalation occurred at 70 °C onto the nonmetalated phenylacetylene.

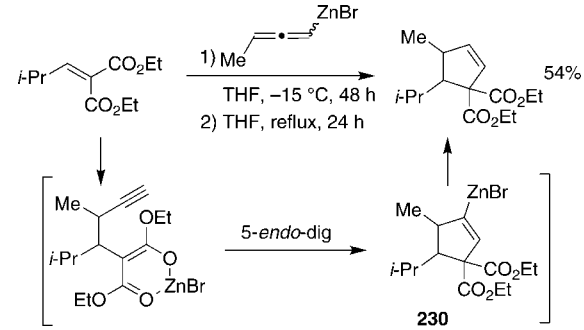
Conditions involving the use of a catalytic amount of diethylzinc were also tested.[343] However, while reaction with aromatic alkynes proceeded in good yields in the presence of only 5 mol % of Et_2Zn, reaction with the less acidic aliphatic alkynes proved ineffective.

Very recently, Lee, Shin, and co-workers reported a related one-pot synthesis of α-vinylated β-enaminoesters from aromatic-, heteroaromatic-, and aliphatic nitriles using a tandem reaction based upon the formation of a Blaise reaction intermediate (BrZn-intermediate).[344] The latter was prepared in situ in refluxing THF by addition of ethyl bromoacetate to a solution of nitrile and preactivated zinc powder, or alternatively, in dioxane at 80 °C. The addition of the BrZn-intermediate onto terminal alkynes was carried out in refluxing THF (or in dioxane at 80 °C) and furnished the α-vinylated β-enaminoesters in good to high yields (62−95%) upon hydrolysis (Scheme 231). While the addition onto methyl phenyl acetylene gave the corresponding trisubstituted alkene in 63% yields, other internal alkynes proved unreactive under the same reaction conditions. The alkenylations carried out with related *n*BuZn-intermediates were far less efficient, indicating that the Lewis acidity of the zinc species plays a crucial role in the activation of the alkyne. A mechanism closely related to the one depicted in Scheme 230 was proposed by the authors.

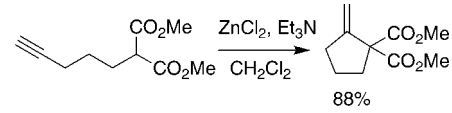
Nakamura and co-workers reported the addition of enaminoesters derived from α-amino acids onto phenylacetylene.[345] This approach gave access to β-ketoesters possessing a chiral quaternary center. The best results were obtained with β-enaminoesters derived from L-isoleucine (Scheme 232). High yields (96−98%) were obtained at 70−100 °C with 10 mol % of Et_2Zn or $Zn(OTf)_2/Et_3N$ under neat conditions. However, following acidic workup, the chiral β-ketoester **229** was isolated in only moderate enantiomeric excess (ee < 53%). Far better results were obtained using indium salts (see section 4.9.3.1).

Generalization of this approach to acetylacetone and β-ketoesters was also evaluated. Additions onto phenylacetylene catalyzed by Et_2Zn were sluggish, and despite the fact that $Zn(acac)_2$ and $Zn(OTf)_2/Et_3N$ gave somewhat better results, zinc was abandoned to the benefit of indium, which has proved much more efficient for this transformation (see section 4.9.3.1).

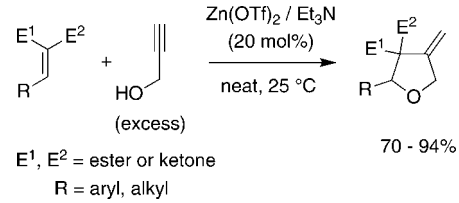
Scheme 233



Scheme 234



Scheme 235

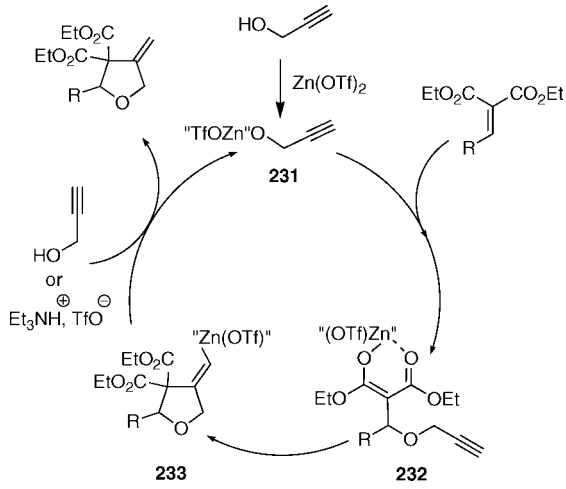


4.8.1.2. Intramolecular Additions. At the end of the 1970s, Gaudemar and co-workers reported the preparation of cyclopentenes by reaction of allenylzinc reagents with alkylidenemalonates (Scheme 233).[346] The process was proposed to involve initial 1,4-addition of the allenyl−Zn species onto the Michael acceptor, followed by cyclization of the resulting Zn−malonate species onto the terminal alkyne in a highly uncommon 5-*endo*-dig mode. However, no evidence was given to support this mechanism, and in particular, the formation of vinylzinc species **230** was not proved. Moreover, only moderate yields of cyclopentanes were generally obtained.

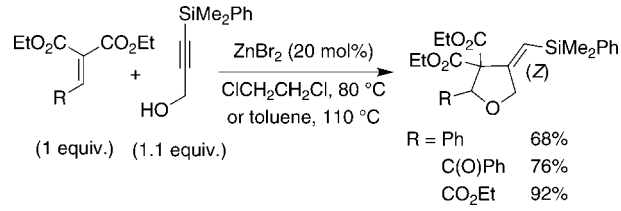
On their side, intramolecular additions of Zn−malonates onto alkynes in a 5-*exo*-dig mode are much more frequent. As a complement to their studies on intramolecular carbotitanation (see section 4.2), Taguchi and co-workers showed that a smooth cyclization took place when 4-pentynyl malonate was treated with $ZnCl_2$ and Et_3N in CH_2Cl_2, affording the corresponding methylenecyclopentane derivative in high yield (Scheme 234).[347] However, in this case, the vinyl−Zn species resulting from the cyclization process is protonated by $Et_3N{\cdot}HCl$, and its trapping with an electrophile cannot be envisaged.

A Zn-catalyzed tandem 1,4-addition/cyclization between propargyl alcohol and 2-alkylidene-1,3-dicarbonyl compounds was developed by Nakamura and co-workers (Scheme 235). The reaction could be achieved at room temperature under neat conditions (or at 70 °C in THF) in the presence of catalytic amounts of $Zn(OTf)_2$ and Et_3N. Various 3- or 4-methylenetetrahydrofurans could be obtained in high yields (70−94%) under these conditions.[348] Other ZnX_2 salts (X = Cl, Br, I) did not promote the reaction at 70 °C in THF. On the other hand, Et_3N could be replaced by other bases, including DABCO, DBU, and proton sponge, without

Scheme 236



Scheme 237

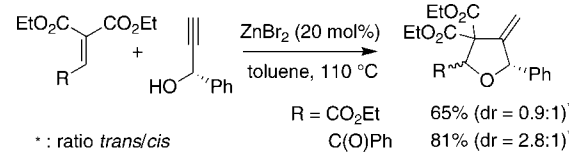


significant changes in the yields. The procedure was rather general as both electron-rich and electron-poor benzylidene- and alkylidenemalonate derivatives bearing a primary or secondary side chain gave similar results. However, a large excess (2−5 equiv) of propargyl alcohol was required.

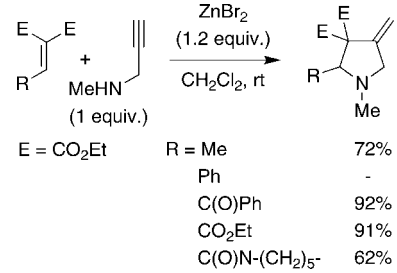
The mechanistic rationale proposed by the authors for the catalytic sequence involves the initial formation of Zn−alkoxide **231** by the reaction of propargyl alcohol with Et_3N in the presence of $Zn(OTf)_2$. Subsequent 1,4-addition onto the Michael acceptor leads to the formation of Zn−enolate **232**, which undergoes intramolecular carbozincation to give alkenylzinc intermediate **233**. Protonation leads to the corresponding tetrahydrofuran and regenerates the Zn−alkoxide. Interestingly, no 1,4-adduct was detected, indicating that 1,4-addition was reversible and that the Zn−enolate was reactive enough to undergo rapid cyclization and displace the equilibrium, which is in favor of the starting material (Scheme 236).

In a related approach, Yamazaki and co-workers studied the Lewis acid-promoted reactions of propargyl alcohols with ethenetricarboxylates and benzylidenemalonate derivatives.[349,350] The cyclization with simple propargyl alcohol could be achieved in good to high yields (60−78%) at room temperature in CH_2Cl_2 but required the use of 1.2 equiv of $ZnBr_2$. At higher temperature (110 °C in toluene), primary, secondary, and tertiary propargyl alcohols were found to participate in the reaction in the presence of only 20 mol % of $ZnBr_2$, leading to the formation of the corresponding methylenetetrahydrofurans in low to good yields depending on the substitution. In the presence of a catalytic amount of $ZnBr_2$ and upon heating, silyl-substituted propargyl alcohols led to methylenetetrahydrofurans in good to high yields (53−92% from silyl-substituted propargyl alcohol) as diastereomerically pure (*Z*)-vinyl silanes (Scheme 237). On the contrary, no cyclization was observed from alkyl- and aryl-substituted propargyl alcohols.

Scheme 238



Scheme 239



An asymmetric version of this procedure based upon the use of enantiomerically pure secondary propargyl alcohols was envisioned (Scheme 238). The reaction was carried out at 110 °C in toluene in the presence of 20 mol % of $ZnBr_2$, and even though the overall sequence remained efficient, only moderate levels of diastereoselectivity were observed (up to 48% de, in favor of the 2,5-*trans*-disubstituted tetrahydrofurans).

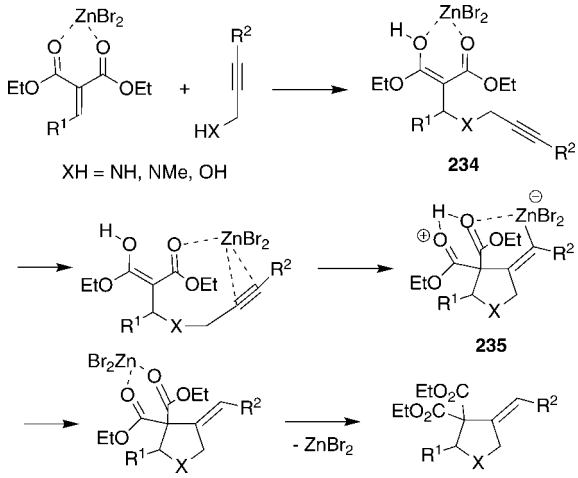
Propargylamine and *N*-methyl propargylamine also proved to be good coupling partners in the 1,4-addition/cyclization sequence with ethenetricarboxylates and methylene- and alkylidenemalonate derivatives, though a stoichiometric amount of $ZnBr_2$ was required to attain high yields (Scheme 239).[349] Examination of a variety of Lewis acids showed that only zinc and indium salts (see section 4.9.3.2) were effective for the formation of methylenepyrrolidines. With other Lewis acids, or in the absence of a Lewis acid, only the 1,4-adduct was observed. Moreover, treatment of the 1,4-adducts with $ZnBr_2$ (or $InBr_3$) resulted in a smooth carbocyclization even at room temperature, stressing the distinctive reactivity of Zn−malonates (or In−malonates) for the carbometalation of alkynes.

The addition of 2-(trimethylsilylethynyl)anilines onto ethenetricarboxylate was recently reported. The reaction was carried out in the presence of a catalytic amount of $Zn(OTf)_2$ and furnished bridged quinoline derivatives in moderate to high yields.[351]

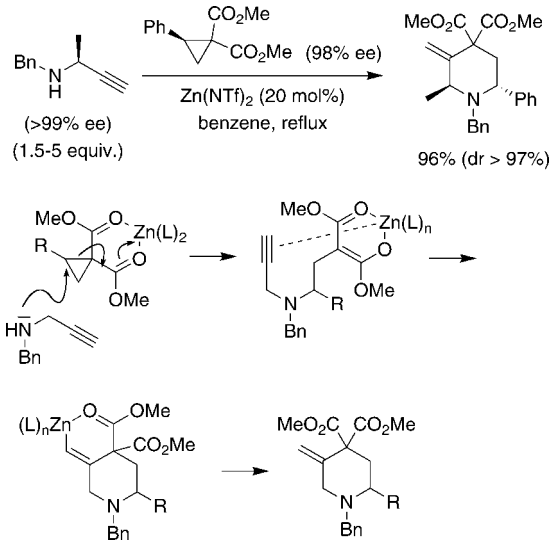
A mechanistic picture, supported by B3LYP/6-31G* calculations, was proposed for the tandem 1,4-addition/cyclization with ethenetricarboxylates (Scheme 240).[352] Initial conjugated addition of the propargylamine (or alcohol) onto the Zn-coordinated diester leads to the formation of coordinated 1,4-adduct **234** following proton transfer. Zinc coordination with the alkyne moiety triggers the stereoselective intramolecular *syn*-carbozincation and leads to the formation of vinyl−Zn species **235**, which retains its configuration. The ease of cyclization was thus attributed to a dual activation ability of the carbonyl and alkyne moieties. The end of the process involves protonation of the sp^2 carbon by the generated proton, which is accompanied by coordination of the zinc salt to the diester moiety of the cyclized products. Zinc decomplexation furnishes the methylene heterocycles and releases the catalyst.

Though mechanistically related, this procedure differs from Nakamura's approach described above in the sense that the high reactivity of the Michael acceptor toward the nucleo-

Scheme 240



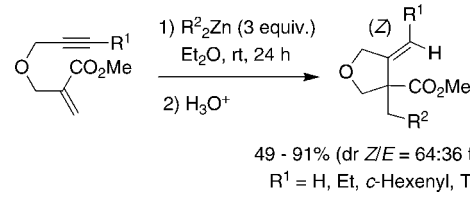
Scheme 241



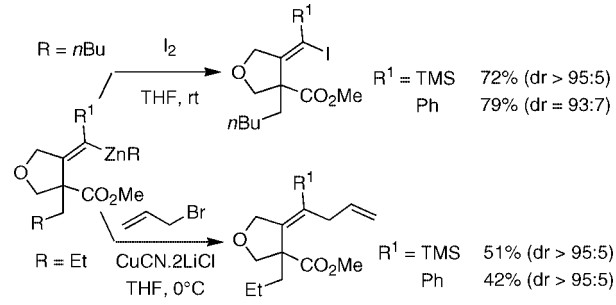
phile, along with a less favorable reverse 1,4-addition, makes it such that no base is needed and only a stoichiometric amount of propargyl alcohol is sufficient. It is also worth noting that, in both cases, the vinyl−Zn derivative obtained following cyclization is not exploitable for a subsequent reaction.

Very recently, Kerr and co-workers reported an elegant approach to functionalized piperidines based upon a tandem cyclopropane ring-opening/Conia-ene cyclization.[353] *N*-Benzyl-propargylamines were found to react with 1,1-cyclopropane diesters in refluxing benzene in the presence of a catalytic amount of $Zn(OTf)_2$ or $Zn(NTf)_2$ to give piperidines in good to high yields (59−98%, 16 examples). The best results were obtained with *N*-benzyl derivatives, whereas no reaction was observed with the corresponding *N*-Tosyl-, *N*-Boc-, and primary amines. Substituted 1,1-cyclopropane diesters reacted under these reaction conditions in a very regioselective manner. Interestingly, when homochiral cyclopropanes were employed, the corresponding piperidines were obtained in high enantiomeric excesses (up to >99% ee). Moreover, the use of optically active propargylamines led to the selective formation of *cis*- or *trans*-2,6-disubstituted piperidines with a high diastereomeric purity (Scheme 241). The proposed mechanism consists of the nucleophilic ring-opening of the 1,1-cyclopropane diester by the amine. The coordination of the diester moiety with the Lewis acid

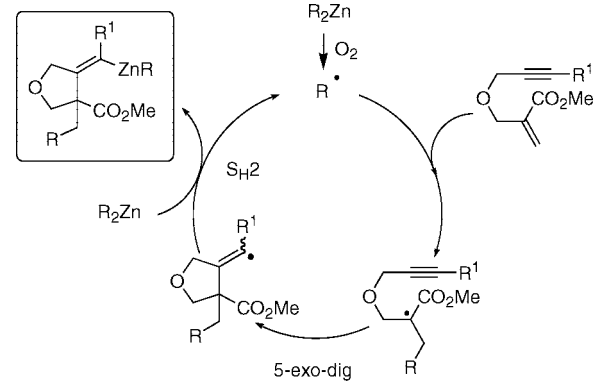
Scheme 242



Scheme 243



Scheme 244

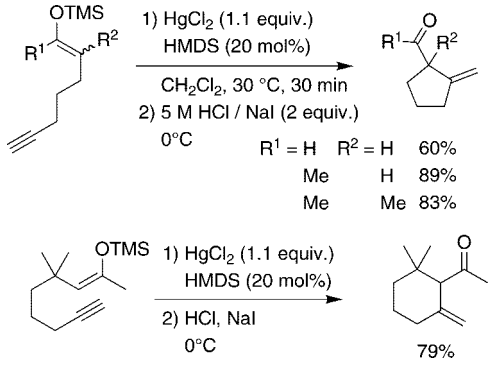


facilitates the cleavage of the C−C bond and results in the formation of a Zn−malonate anion that undergoes a 6-*exo*-cyclization onto the alkyne. The piperidines are obtained following protonation of the vinyl−Zn species resulting from the carbometalation (Scheme 241).

Recently, Chemla and co-workers showed that β-(propargyloxy)enoates lead to polysubstituted alkylidenetetrahydrofurans in moderate to high yields (49−91%) by the reaction with dialkylzinc reagents (R = Et, *n*Bu, *i*Pr) following a tandem 1,4-addition/carbocyclization sequence (Scheme 242).[354] The system was efficient both for terminal- and internal alkynes, including silyl-, aryl-, and alkyl-substituted internal alkyne moieties. For silyl- and aryl-substituted alkynes, excellent levels of stereoselectivity were observed in favor of products bearing the substituent *anti* to the ester group. In the case of alkyl-substituted alkynes, diastereoselectivities were only moderate. Functionalization of the vinyl−Zn species resulting from the cyclization was possible (for example by iodolysis or Cu-mediated cross-coupling reactions), thus offering an opportunity to carry out stereoselective multibond-forming events (Scheme 243).

It was proposed that, as for the related (*N*-allylamino)enoates and β-(allyloxy)enoates (see section 2.5.3), the overall intramolecular carbozincation proceeds through a radical-polar crossover mechanism involving a zinc atom radical transfer (Scheme 244). 1,4-Addition of an alkyl radical generated by oxidation of the dialkylzinc reagent,

Scheme 245



followed by 5-*exo*-dig cyclization and subsequent stereoselective reduction by S_H2 onto R_2Zn, affords the vinyl−Zn product.

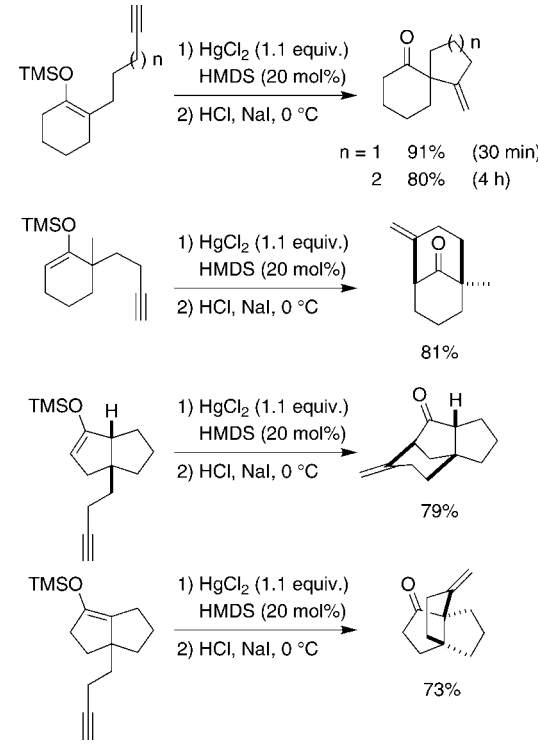
4.8.2. Mercury(II)-Mediated Additions

Conia and co-workers reported in the early 1970s their pioneering work on the Hg(II)-catalyzed cyclization of carbonyl compounds possessing an alkynyl side chain. Initial examples that paved the way to many other metal-catalyzed versions of the so-called Conia-ene reaction[2] involved the conversion of β-diketones and β-ketoesters bearing an alkynyl side chain into the corresponding methylenecyclopentane derivatives upon treatment with a catalytic amount of aqueous HCl and $HgCl_2$ (typically 10 mol %). The reactivity increase with respect to the analogous thermal reaction was attributed both to a higher enolization of the substrate in the presence of a strong acid and to an activation of the alkyne by formation of a (η^2-alkyne)Hg(II) complex.[355]

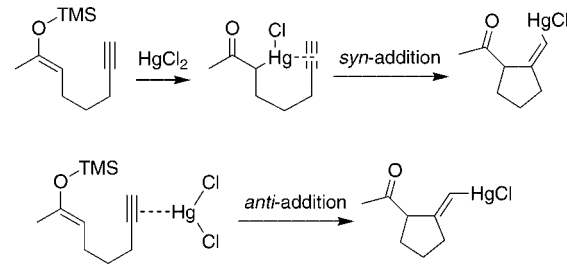
In a related manner, cyclization of silyl enol ethers leading to *exo*-methylene carbocycles was achieved under mild conditions in the presence of a Hg(II) salt.[356−359] The reaction was carried out at 30 °C in CH_2Cl_2 in the presence of a stoichiometric amount of $HgCl_2$ and 20 mol % of hexamethyldisilazane (HMDS) in order to prevent partial hydrolysis of the silyl enol moiety.[356] The reaction scope was quite broad and allowed the formation of 5- and 6-membered rings (Scheme 245). Fused-, bridged-, and spiranic-bicyclic skeletons (Scheme 246) could also be prepared in high yields (73−91%).[357,359] Hydrolysis of the resulting vinyl−Hg species was somewhat tricky, being either very slow in 2 M aqueous HCl (24 h) or leading to isomerization of the double bond in a 8 M HCl solution. The combination of a 5 M aqueous HCl solution with 2 equiv of NaI gave excellent results, with the products being isolated in high yields and without isomerization of the carbon−carbon double bond. Alternatively, the vinyl−Hg species could be further functionalized upon treatment with various electrophiles and with retention of configuration at the carbon center.[356] Together with the Al-promoted version, this Hg(II)-promoted cyclization represents the only opportunity to functionalize the carbon−carbon bond formed in a Conia-ene reaction.

Two different mechanisms were considered for this Hg(II)-promoted cyclization (Scheme 247). On the basis of deuterium labeling experiments and ^{1}H NMR analysis, Conia and co-workers initially proposed a mechanism involving the formation of a Hg(II)−enolate by reaction between the silyl enol ether and the Hg(II) salt, followed by a subsequent *syn*-carbomercuration.[356,358] The opposite stereochemistry was observed later by Forsyth and co-workers in the case of

Scheme 246



Scheme 247



structurally and sterically more constrained systems.[360−362] Accordingly, and in agreement with the mechanism proposed for other metal-catalyzed cyclizations of silyl enol ethers, an alternative rationale involving the *anti*-addition of the silyl enol ether moiety onto the (η^2-alkyne)Hg(II) complex was proposed.

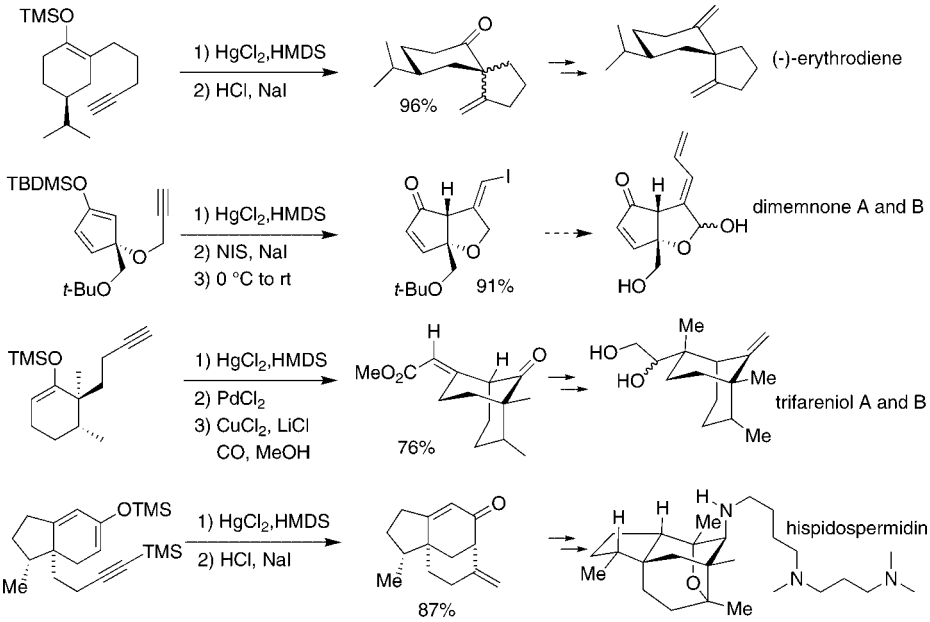
Thanks to the functionalization opportunities that it offers, the mercury-promoted cyclization of silyl enol ether onto alkynes has found applications in total synthesis (Scheme 248). In the 1990s, Forsyth and co-workers used it to construct the fused-bicyclic skeleton of dimemnones A and B,[360,363] as well as the 6,5-spiro-bicyclic system of (−)-erythrodiene[361,364] and (+)-Spirojatamol[361] and the [3.3.1]bridged-bicyclic skeleton of trifareniol A and B.[362] More recently, Danishefsky and co-workers have also used it to construct the *cis*-fused tricyclic core of hispidospermidin.[365,366]

4.9. Group 13: Aluminum, Gallium, and Indium

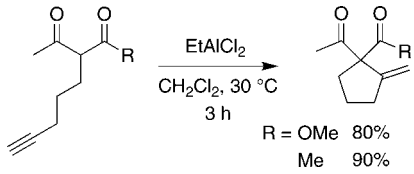
4.9.1. Aluminum(III)-Mediated Additions

As part of their early work on the metal-catalyzed Conia-ene reaction, Conia and co-workers reported the cyclization of 1,3-diketones and β-ketoesters in the presence of a stoichiometric amount of $EtAlCl_2$.[355] The Al-mediated reaction proceeded efficiently at 30 °C in CH_2Cl_2 and, unlike the case of mercury, in the absence of

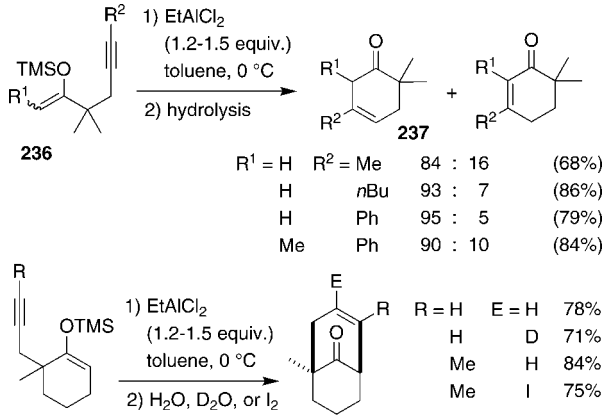
Scheme 248



Scheme 249



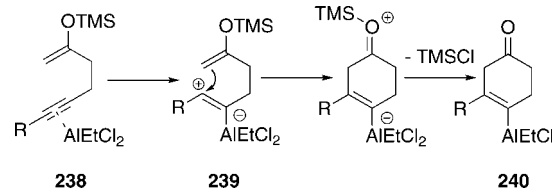
Scheme 250



acid. Nevertheless, under these reaction conditions, the postulated vinyl−Al intermediate was hydrolyzed in situ, and therefore, no functionalization could be achieved (Scheme 249).

More recently, Yamamoto and co-workers reported the use of $EtAlCl_2$ (1.2−1.5 equiv) to promote the cyclization of silyl enol ethers.[367,368] Interestingly, under these reaction conditions, the cyclization of substrates **236** (Scheme 250) possessing a disubstituted alkynyl side chain could be achieved. The addition process was highly regioselective as only 6-*endo*-dig cyclization was observed, leading to the corresponding β,γ-unsaturated cyclohexanones **237** in good to high yields (57−80%), accompanied with only 4−11% of the corresponding α,β-unsaturated regioisomers. The existence of the vinyl−Al intermediate was supported by deuteration and reaction with iodine. This methodology also allowed the preparation of bridged-bicyclic compounds.

Scheme 251

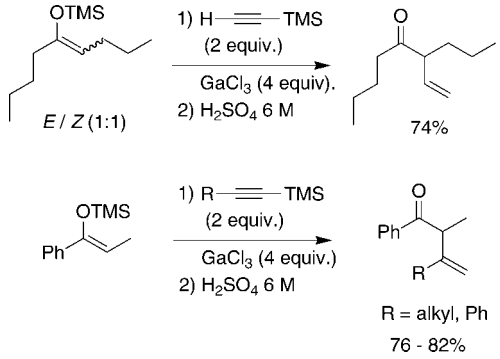


The proposed mechanism involves the nucleophilic addition of the silyl enol ether onto zwitterionic intermediate **239** formed from the (alkyne)Al(III) complex **238**, followed by departure of TMSCl to give vinyl−Al intermediate **240** (Scheme 251).

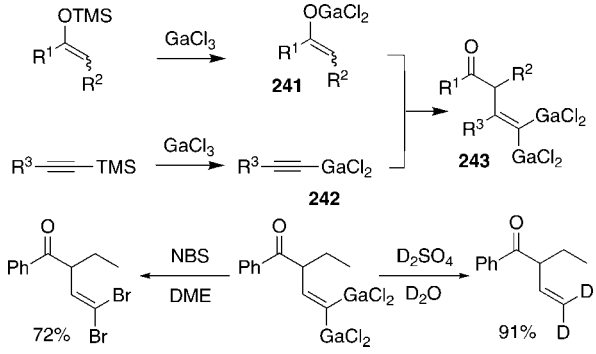
4.9.2. Gallium(III)-Mediated Additions

Yamaguchi and co-workers reported that Ga(III) salts[369] promote the intermolecular addition of silyl enol ethers onto TMS−alkynes.[370] The reaction was achieved within a few minutes at room temperature in methylcyclohexane or toluene with a 2-fold excess of TMS−alkyne and in the presence of a 4-fold excess of $GaCl_3$. The α-alkenylated carbonyl compounds were recovered upon acidic workup. The hydrolysis conditions were found to be crucial for the success of the procedure, with the best conditions involving the use of 6 M aqueous H_2SO_4. A wide range of silyl enol ethers were found to react efficiently with TMS−alkynes, affording the corresponding adducts in moderate to high yields (56−82%) and with high levels of regioselectivity in favor of addition at the internal carbon, regardless of the *E*/*Z*-geometry of the silyl enol ethers (Scheme 252). In most cases, open-chain silyl enol ethers gave the product without isomerization of the carbon−carbon double bond.[370,371] Unsubstituted cyclic silyl enol ethers with a small ring gave mixtures of α- and β-enones. Substituted cyclic cyclohexanones led to β-enones in moderate to high yields (36−90%) with the alkene moiety introduced mostly in the equatorial position.[372] This is in contrast with the normal axial attack observed in most alkali metal−enolate alkylations and points toward a C-metalated Ga−enolate as the reactive species.

Scheme 252



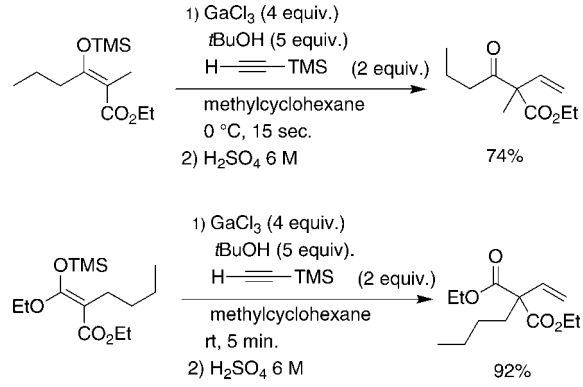
Scheme 253



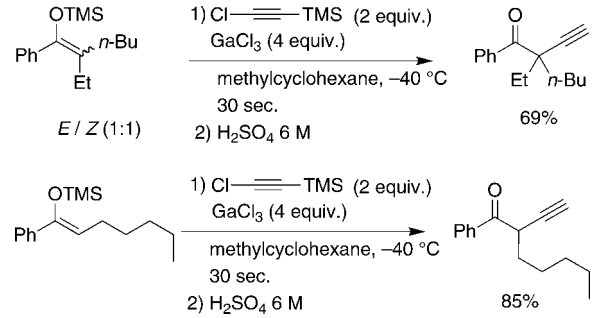
The proposed mechanism of this Ga(III)-promoted transformation involves the addition of Ga−enolate **241** (formed in situ by reaction of the silyl enol ether with $GaCl_3$) onto σ-alkynyl−Ga species **242**, which is formed by Si−Ga exchange from the TMS−alkyne (Scheme 253). The formation of the Ga−enolate was proved by spectroscopy (^{13}C NMR and IR) by reacting $GaCl_3$ and 1-trimethylsilyloxy-3-butylcyclohexene in cyclohexane-d_{12}. The authors contemplated the possibility of an equilibrium between an O-centered- and a C-centered Ga−enolate.[372] Whatever the reactive species involved, the carbogallation process results in the formation of organo-*gem*-bimetallic **243**. The latter is generally insoluble in nonpolar solvents (methylcyclohexane, toluene), and this low solubility often avoids side reactions.[373] Addition of THF leads to a homogeneous solution of this organo-*gem*-bimetallic species, which can either be hydrolyzed (efficiently only with 6 M aqueous H_2SO_4) to give to β-enone or trapped with N-bromosuccinimide (NBS) to furnish the corresponding *gem*-dibromoalkene. The formation of the vinyl−bimetallic species **243** was also evidenced by deuterium labeling experiments.

Silyl enol ethers of β-ketoesters and alkylmalonates also reacted efficiently with TMS−acetylene in the presence of $GaCl_3$ (Scheme 254).[374] The reaction was best carried out at 0 °C in methylcyclohexane with a 2-fold excess of TMS−alkyne, 4 equiv of $GaCl_3$, and in the presence of *t*BuOH (5 equiv). The transformation was extremely fast with cyclic and acyclic silyl enol ethers of β-ketoesters in the (*E*)-configuration and led to the formation of the ethenylated products in moderate to high yields (55−92%). On the contrary, (*Z*)-silyl enol ethers were found to be less reactive. Silyl enol ethers of substituted alkylmalonates reacted within 5 min at room temperature and gave the ethenylated products in high yields (85−92%). On their side, silyl enol ethers of unsubstituted malonates gave the corresponding β-enones in moderate yields after careful quenching of the reaction at

Scheme 254



Scheme 255

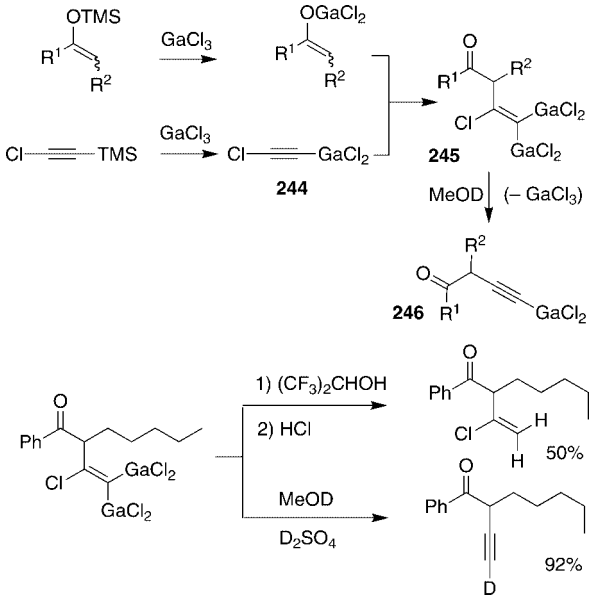


−20 °C and purification by flash chromatography at −78 °C in order to suppress the isomerization into the α-enone. Finally, silyl enol ethers of *S*-alkyl- and *S*-aryl thioesters were also found to react in this Ga-mediated alkenylation reaction, and ethenylation of α-mono- and α,α-disubstituted thioesters could be achieved in good to high yields (61−94%) without isomerization of the double bond.[375]

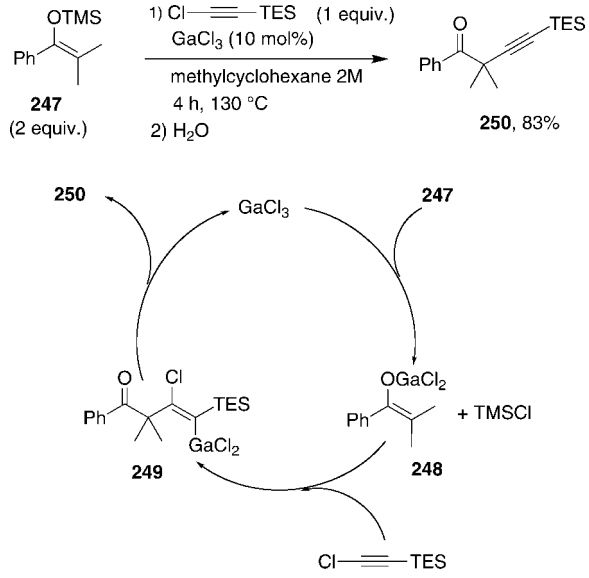
Silyl enol ethers of ketones were also shown to react in the presence of $GaCl_3$ (4 equiv) with chloro−TMS−acetylene (2 equiv). This time, the reaction led to the formation of the corresponding α-ethynylated carbonyl compounds, in what represents a highly valuable extension of the above-described method.[373] The reaction was found to be extremely fast and was complete within less than 1 min at −40 °C in methylcyclohexane, providing the α-ethynyl ketones upon treatment with MeOH and hydrolysis with 6 M H_2SO_4 at low temperature (Scheme 255). Under these conditions, the adducts possessing α-quaternary centers were obtained in moderate to excellent yields (58−95%). On the other hand, the adducts with an α-tertiary center were easily isomerized into the corresponding α-allenyl ketones. However, in the case of silyl enol ethers of arylketones, this isomerization could be prevented if the product was purified by flash chromatography on neutral silica gel at −78 °C. Other aliphatic Ga−enolates did not react efficiently with chloro−TMS−acetylene. An interesting solvent effect was observed for this reaction. Indeed, when the reaction was carried out at −40 °C in CH_2Cl_2/methylcyclohexane (1:1) and quenched after 5 min, chloroenynes arising from a second carbogallation were isolated in moderate to good yields (45−74%), together with small amounts of enediynes.[376]

The formation of the α-ethynyl ketones was assumed to involve the addition of a gallium enolate onto chloroalkynyl−$GaCl_2$ species **244** (Scheme 256). Interestingly, the resulting organo-*gem*-bimetallic **245** could be quenched with 1,1,1,3,3,3-hexafluoro-2-propanol to give the corresponding

Scheme 256



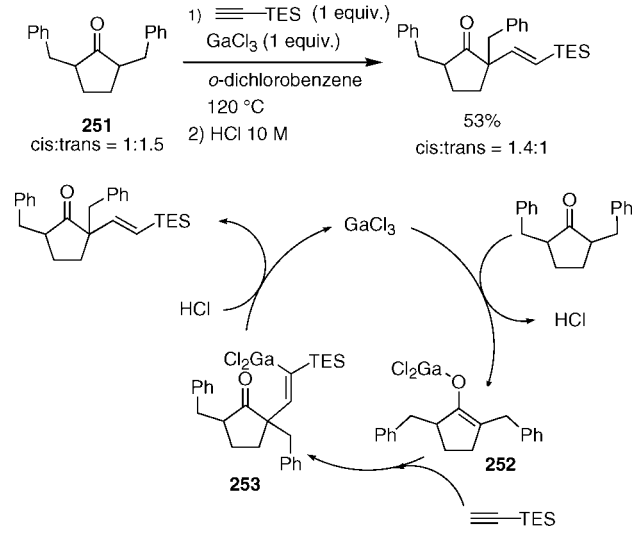
Scheme 257



β-chloro-β-enone. Although the yields remained moderate (47−50%), this observation proves that β-elimination is a slow process at −40 °C that occurs not following the carbometalation step but instead during the addition of the polar solvent (MeOH). Following addition of the polar solvent, elimination of the chlorine atom leads to alkynyl−Ga **246**, which is hydrolyzed upon treatment with 6 M H_2SO_4. The formation of the alkynyl−Ga species was supported by deuterium labeling experiments.

A catalytic version of the ethynylation of silyl enol ethers such as **247** with chloro−ethynyltriethylsilane was also developed (Scheme 257). The operating protocol to achieve such a process involved the use of 10 mol % of $GaCl_3$ in methylcyclohexane at 130 °C. Under these conditions, α-silylethynylated alkyl- and arylketones possessing an α-quaternary center were obtained in moderate to high yields (36−98%) with a 2-fold excess of silyl enol ether.[376] Interestingly, no desilylation was observed under these reaction conditions. This time, the addition of Ga−enolate **248** occurs onto the Et_3Si−alkyne (and not onto a $GaCl_2$−alkyne) and leads to the formation of the corresponding 1-gallio-1-silyl-2-chloroalkene **249**, which undergoes fast β-elimination to give TES−ethynylated products **250** and regenerate $GaCl_3$.

Scheme 258

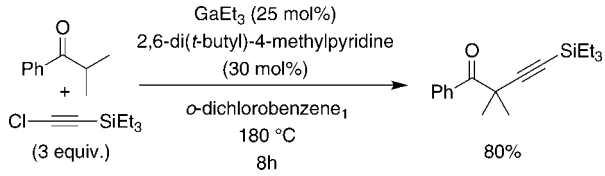


The catalytic reaction failed with silyl enol ethers that were not disubstituted at the α-carbon. Nevertheless, the addition of monosubstituted silyl enol ethers onto chloro−TES−acetylene in the presence of 1 equiv of $GaCl_3$ and a base such as 2,6-di(*t*-Bu)-4-methylpyridine led to α,α-diethynylated ketones in low to moderate yields (23−48%) after 5−12 h at 150 °C in chlorobenzene. The same type of behavior was observed in the preparation of α,α-diethenylated ketones by reaction of α-monosubstituted silyl enol ethers with TMS−acetylene.[377]

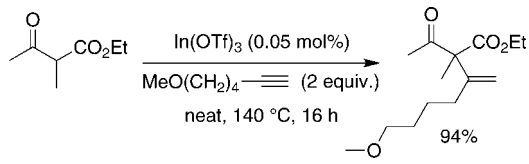
Ketones were found to react with TES−alkynes at high temperature in *o*-dichlorobenzene in the presence of a stoichiometric amount of $GaCl_3$.[378] For instance, 2,5-dibenzylcyclopentanone **251** (Scheme 258) reacted with ethynyltriethylsilane (1.5 equiv) at 120 °C in the presence of $GaCl_3$ (1 equiv) to afford a mixture of 2,5-dibenzyl-2-(2-triethylsilylethenyl)cyclopentanones (*cis*/*trans* = 1.4:1) in 53% yield upon acidic workup with 10 M HCl. Under these conditions, gallium enolate **252** is formed simply by the reaction of the ketone with $GaCl_3$ (above 80 °C), and subsequent carbogallation of the silylated alkyne occurs prior to the formation of an alkynyl−Ga species and leads to 1-gallio-1-silylalkene **253**, which is protodegallated upon treatment with HCl. While $GaCl_3$ itself could promote the reaction, the addition of a base such as 2,6-di-*tert*-butyl-4-methylpyridine (1 equiv) afforded higher yields (up to 62%) both by enabling in situ protodegallation and by preventing decomposition of the resulting vinylsilanes. Furthermore, following this procedure, no acidic hydrolysis was necessary. A catalytic procedure allowing the alkenylation of cyclic α,α′-disubstituted ketones was also reported. Under these conditions, acyclic ketones reacted only in low yields.[378]

Direct α-ethynylation of ketones with chloro−silylacetylenes could also be achieved under catalytic conditions provided trialkylgalliums were used (Scheme 259). In the presence of catalytic amounts of 2,6-di-*tert*-butyl-4-methylpyridine and GaR_3 (R = Me, Et), cyclic and acyclic ketones were ethynylated in moderate to good yields (43−80%).[379] For cyclic α,α′-disubstituted ketones, mono- or diethynylation could be achieved by modifying the reaction conditions and the chloro−silylalkyne used. The addition of a catalytic amount of butyllithium was found to increase the yields.

Scheme 259



Scheme 260



4.9.3. Indium(III)-Mediated Additions

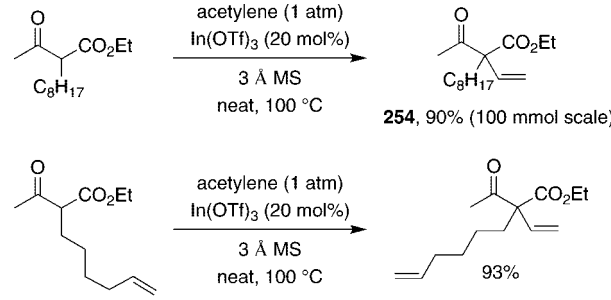
Indium(III) salts have emerged over the last five years as powerful catalysts for the addition of β-dicarbonyl derivatives onto alkynes. Inter- and intramolecular alkenylation reactions have been reported.

4.9.3.1. Intermolecular Additions. Searching for promoters to catalyze the addition of β-ketoester derivatives onto terminal alkynes, Nakamura and co-workers screened a large number of metallic salts among which only zinc, gallium, mercury, and indium triflates showed a catalytic activity.[380] While the three first salts required the presence of an organic base such as Et_3N or DBU, $In(OTf)_3$ was found to be a countercation powerful enough to catalyze the alkenylation reaction without any additives.[381] However, the use of a catalytic amount of a base was sometimes found to be beneficial, especially in the case of acid-sensitive substrates and/or products.

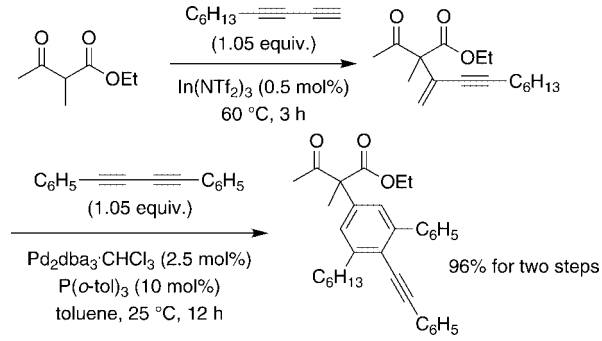
The system has been studied in some detail.[382] The addition of 2-substituted β-ketoesters onto aryl- and alkyl-substituted alkynes was best carried out under neat conditions at 60−160 °C in a sealed tube and in the presence of 1−3 equiv of alkyne and 0.05−20 mol % of $In(OTf)_3$ (Scheme 260). Under these conditions, the alkenylated adducts were usually obtained in good to excellent yields. The reaction tolerated structural variations of the nucleophile, including cyclic β-ketoesters. Furthermore, unsubstituted β-ketoesters, such as 3-oxobutanoate, were also found to participate in the addition but furnished the corresponding alkylidene derivatives following isomerization of the double bond. The presence of a solvent such as toluene lowered the rate of the reaction and was only used in specific cases to avoid decomposition or side reactions. Terminal alkynes also took part in the reaction, including aryl-, vinyl-, alkynyl-, silyl-, and alkyl-substituted alkynes. The regioselectivity was excellent, with the addition occurring exclusively at the internal position of the alkyne, except in the case of silylacetylene derivatives, for which the addition occurred at the terminal position. Alkyl-substituted alkynes were in general less reactive than aryl-substituted ones. However, the rate of addition onto aryl-substituted derivatives was strongly dependent upon the nature of the substituent on the aromatic ring. For instance, electron-deficient substituted derivatives reacted more slowly and the presence of a dimethylamino group on the aromatic ring inhibited the reaction. Disubstituted alkynes (except 1-iodoalkynes) did not react under these conditions.

Addition onto acetylene (even commercially available cheap welding grade) was possible provided 3 Å molecular sieves were added in order to prevent side reactions (Scheme 261). The reaction took place at 100 °C under neat conditions (or in toluene) with a 1 atm acetylene atmosphere and in the presence of 20 mol % of $In(OTf)_3$. The corresponding vinylated β-ketoesters were obtained in high to excellent yields (74−100%, 90% yield in compound **254** for the reaction carried out on 100 mmol scale).[383]

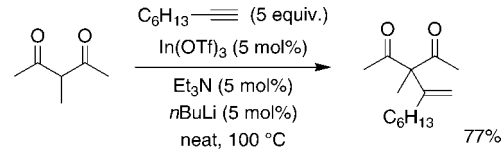
Scheme 261



Scheme 262



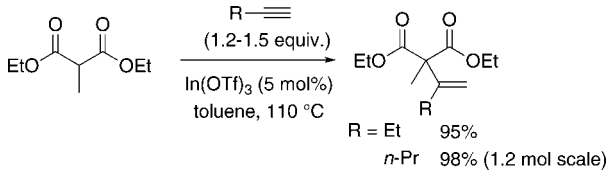
Scheme 263



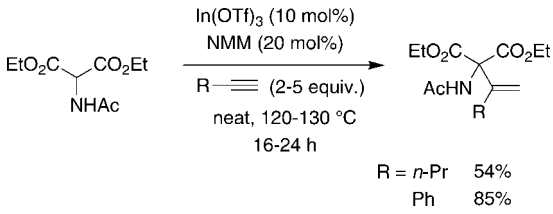
$In(NTf_2)_3$ was found to be even more reactive than $In(OTf)_3$, and although its cost made it less attractive, it was used when $In(OTf)_3$ proved ineffective. This is for example the case for additions of β-ketoesters onto 1,3-diynes.[384] This reaction is of significant synthetic interest since, combined in situ with Yamamoto's palladium-catalyzed [4 + 2]-benzannulation, it offers a modular approach to α-arylated carbonyl compounds (Scheme 262).

Unlike other nucleophiles screened such as β-nitroketones, cyanoketones, cyanoesters, phosphonylesters, and sulfonylesters that were not reactive under these reaction conditions, 1,3-diketones were also found to be good partners for the $In(OTf)_3$-catalyzed alkenylation reaction but called for slight variations of the operating conditions. In this case, the addition was carried out at 100 °C in a sealed tube with an excess of terminal alkynes (2.5−5 equiv) and required the use of Et_3N and *n*BuLi in order to reduce the formation of byproduct. Under the optimized reaction conditions, good to excellent yields (77−99%) of the adducts were obtained (Scheme 263). Following intermolecular addition onto the alkyne and isomerization of the newly formed carbon−carbon double bond, unsubstituted 1,3-diketones gave the addition products as a mixture of the enol form and the α,β-unsaturated diketones.[382]

Scheme 264



Scheme 265

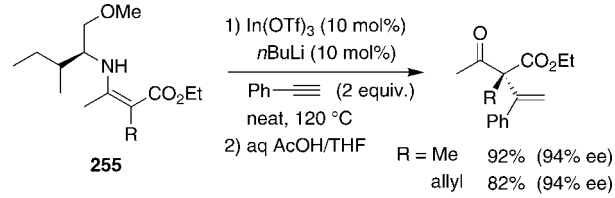


Zhang and co-workers extended the approach to include malonate derivatives and developed additional operating conditions for low boiling point terminal alkynes.[385] They reported that the addition of diethyl methylmalonate onto 1-pentyne and 1-hexyne resulted in low yields under neat conditions. Moreover, under these conditions, the reaction became self-heating and the temperature became difficult to control. As a consequence, the authors recommended to carry out the reaction at 110−135 °C in a high boiling point solvent such as toluene, or better *o*-xylene, in the presence of 5 mol % of $In(OTf)_3$. Under these modified reaction conditions, furthermore compatible with large-scale experiments, the addition of diethyl methylmalonate onto 1-pentyne gave the alkenylated adduct in 98% yield for the reaction carried out on a 1.2 mol scale (Scheme 264). Interestingly, the authors established that, at high temperature (130−140 °C), $InCl_3$ and $InBr_3$ (but not InF_3) could also be used to promote the reaction, even at low catalyst loadings (0.5−5 mol %). This finding seems rather general for additions of malonates and β-ketoesters onto alkyl- and aryl-substituted alkynes and contrasts with Nakamura and co-worker's report that no addition occurred at 40 °C under neat conditions in the presence of $InCl_3$ (5 mol %), except if the catalyst was used in combination with AgOTf (15 mol %). The addition of unsubstituted malonates furnished arylidene- and alkylidenemalonates in good to high yields (71−82%) after carbon−carbon double-bond migration.

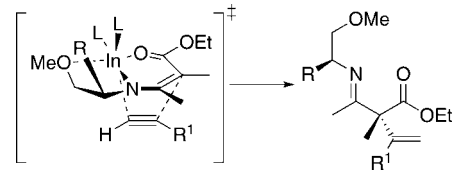
The addition of diethyl acetamidomalonate onto terminal alkynes (2−5 equiv) could be achieved at 120−130 °C under neat conditions in the presence of catalytic amounts of $In(OTf)_3$ and *N*-methylmorpholine (NMM). The reaction proceeded in good to high yields with a range of aryl-substituted terminal alkynes (59−85%), while alkyl-substituted terminal alkynes were less reactive and disubstituted alkynes did not participate in the reaction (Scheme 265). The presence of a base in order to promote the formation of the In−enolate was found to be crucial. The best results were obtained with NMM, but other bases, including *t*BuOM (M = Li, Na, K) and LiOTf, were also effective (62−85% yields). In all cases, the amount of base could not exceed 20 mol %; otherwise, only poor results were obtained. Following hydrogenation using Pd/C and subsequent *N*-deacylation/ester hydrolysis/decarboxylation upon treatment with 6 M HCl, β-branched α-aminoacids were obtained as a mixture of diastereomers (dr *anti*/*syn* < 60:40).[386]

An asymmetric version of the intermolecular addition of β-ketoesters onto terminal alkynes was also reported.[345] This approach relied on the formation of β-enaminoesters derived from chiral β-aminoalcohols and allowed the preparation of optically enriched β-ketoesters possessing a chiral quaternary center at the α-position (up to 97% ee). Enamines **255** (mostly *Z*-isomer) were easily prepared in high yields (80−90%) from the corresponding β-ketoesters (Scheme 266). The reaction was usually carried out under neat conditions (eventually in toluene) in the presence of 10 mol % of $In(OTf)_3$ and with a 2-fold excess of alkyne. The presence of *n*BuLi (10 mol %) or LiOTf (10 mol %) was found to have a beneficial effect on both the rate of the reaction and the selectivity. The use of L-isoleucine as a chiral auxiliary gave the best results. It was found that the temperature has a dramatic effect on the enantiomeric excesses: the best results were obtained at 120 °C and the selectivity decreased at lower or higher temperatures. The reaction was applicable to alkyl- and aryl-substituted terminal alkynes and gave the corresponding alkenylated adducts in high yields (78−93%) and high optical purity (88−97% ee) upon acidic workup. On the other hand, the vinylation with the less hindered acetylene gave the adducts in high yields but with lower levels of enantioselectivity (72−84% yield, 28−86% ee).

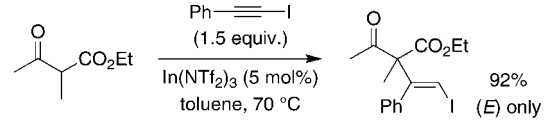
Scheme 266



Scheme 267



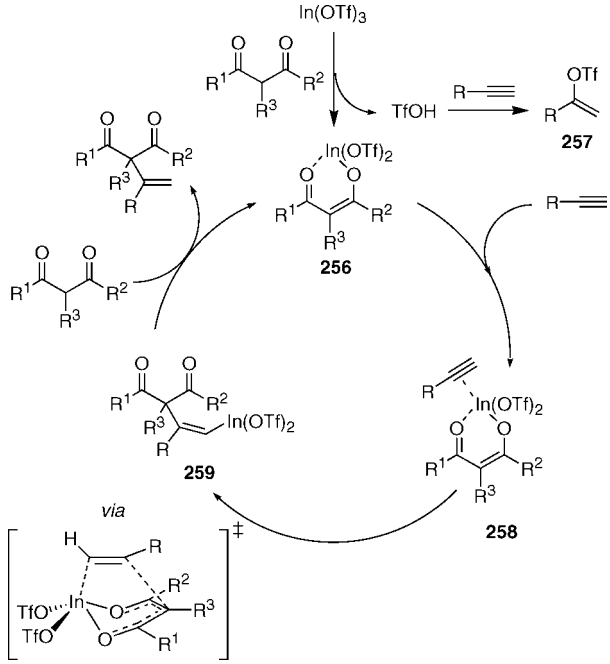
Scheme 268



A rationale for the observed stereoselectivity was proposed on the basis of a transition state that involves a concerted *syn*-addition of the In−enolate onto the alkyne (see below for mechanistic considerations). In such a case, the methoxy group forms a bicyclic system with the In(III) atom that forces the alkyne to approach on the face opposite to the R group (Scheme 267).

The scope of the reaction was then extended to include 1-iodoalkynes. The addition of β-ketoesters, malonate derivatives, and 1,3-diketones onto alkyl- and aryl-substituted 1-haloalkynes could be achieved at 50−70 °C in toluene in the presence of 5 mol % of $In(NTf_2)_3$ (Scheme 268).[387] The best results were obtained with 1-iodoalkynes, which appeared to be much more reactive than the corresponding bromo- and chloro-derivatives. Alkyl-substituted 1-iodoalkynes were less reactive than the aryl-substituted 1-iodoalkynes. The reaction was so far limited to 2-substituted

Scheme 269

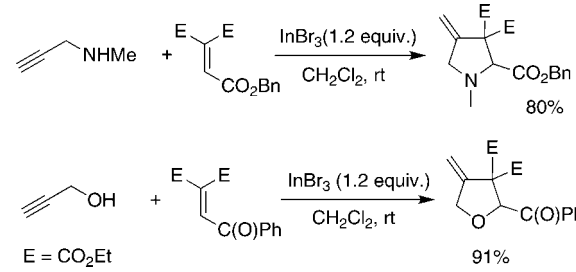


β-ketoesters and β-diketones since unsubstituted 1,3-dicarbonyl compounds, such as ethyl acetoacetates, led only to a complex mixture of products. The reaction was highly regio- and stereoselective, with the addition taking place exclusively at the C2 position and the trisubstituted iodoalkenes being obtained as the (*E*)-isomer only. The resulting iodoalkenes were engaged in Pd-catalyzed cross-coupling reactions that could be carried out in a single pot.[387]

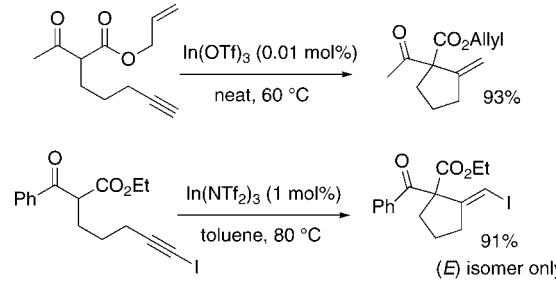
Upon the basis of experimental observations[382] and density functional calculations, the proposed mechanism (Scheme 269) involves the initial formation of In(OTf)$_2$−enolate **256** by reaction between the dicarbonyl compound and In(OTf)$_3$. This process generates 1 equiv of TfOH (with respect to the indium catalyst) that adds onto the alkyne and produces vinyl triflate **257**, which is hydrolyzed into the corresponding ketone during the workup of the reaction. This hypothesis is supported by the isolation of acetophenone in 17% yield (85% yield based on the catalyst) in the addition reaction onto phenylacetylene. After initiation, the addition of the In−enolate onto the alkyne takes place via a concerted mechanism involving In−alkyne complex **258**. Calculations showed that the formation of the C−In bond is more advanced than the C−C bond between the In−enolate carbon and the internal carbon atom of the alkyne, thus suggesting the importance of the interaction between the alkyne and the metal prior to the addition. Finally, protonation of the resulting vinyl−In species **259** by the β-dicarbonyl compound leads to the alkenylated adduct and regenerates the In(OTf)$_2$−enolate **256**.

4.9.3.2. Intramolecular Additions. Indium-catalyzed addition of active methyne derivatives onto unactivated alkynes can also take place in an intramolecular manner. A first example was disclosed by Yamazaki and co-workers who reported the preparation of methylenetetrahydrofurans and methylenepyrrolidines via a cascade reaction involving a conjugate addition/5-*exo*-dig cyclization sequence (Scheme 270).[349] The addition of primary and secondary propargylamines onto alkylidene- and arylidenemalonates, as well as onto ethenetricarboxylates, was achieved at room temperature in CH_2Cl_2 using equimolar amounts of both reagents and a

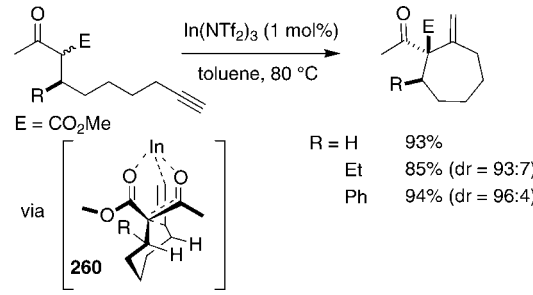
Scheme 270



Scheme 271



Scheme 272



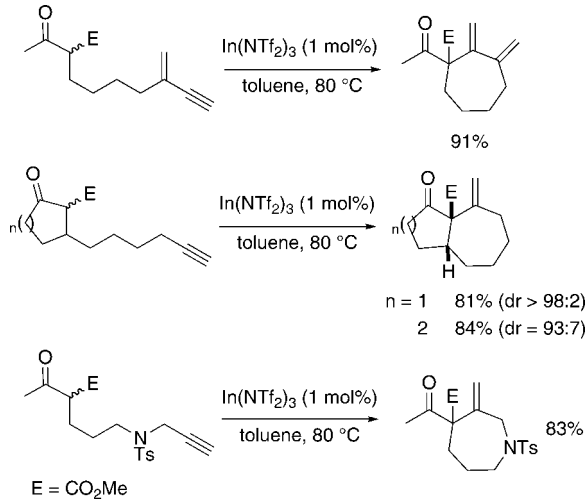
stoichiometric amount of $InBr_3$. Under these conditions, methylenepyrrolidines were obtained in low to high yields (22−100%). Propargyl alcohol was also found to react with ethenetricarboxylate derivatives and furnished the corresponding methylenetetrahydrofurans in good to high yields (63−91%). Both reactions also proceeded in the presence of a catalytic amount of $InBr_3$ (20 mol %), albeit generally in lower yields and at higher temperature (80 °C in $ClCH_2CH_2Cl$). Worthy of note, the use of a stoichiometric amount of ZnX_2 salts (X = Cl, Br, I, OTf) also gave good results for these reactions (see section 4.8.1.2).

The cyclization of α-(ω'-alkynyl)-β-ketoesters was achieved in the presence of 0.01−1 mol % of In(OTf)$_3$, or better In(NTf$_2$)$_3$, under neat conditions (or in toluene), and led to the formation of *exo*-methylene five- or six-membered-ring carbocycles in high yields, following, respectively, 5-*exo* or 6-*exo* cyclization modes (Scheme 271).[388,389]

The more challenging formation of seven-membered rings via a 7-*exo* cyclization was accomplished in good to excellent yields by using In(NTf$_2$)$_3$ at 80 °C. Interestingly, with substrates bearing a substituent at the β-position (Scheme 272), a high level of stereoselectivity was observed. The selectivity was rationalized according to transition state **260** in which the steric repulsion between the R substituent and the methyl ketone is minimized, assuming that the two hydrogen atoms indicated in the scheme occupy two diaxial positions.

Under these reaction conditions, the 7-*exo* cyclization process also proved effective with substrates having a

Scheme 273

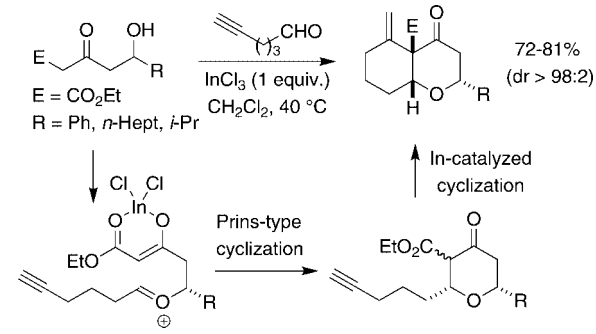


terminal enyne side chain, as well as for the formation of *cis*-fused bicyclic products and nitrogen-containing heterocycles (Scheme 273).[389]

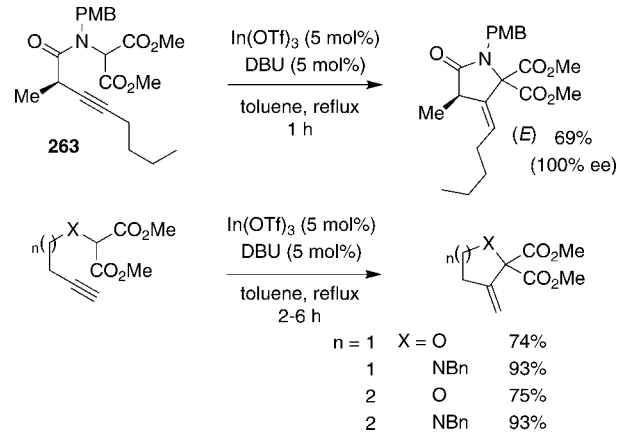
Preparation of the larger eight-membered rings from α-(ω′-alkynyl)-β-ketoesters failed, presumably because of unfavorable transannular steric interactions in the cyclization transition state. By contrast, in addition to 6- and 7-membered rings, larger ring systems could be obtained from ω-alkynyl-β-ketoesters at 100−150 °C in toluene in the presence of a catalytic amount of $In(NTf_2)_3$.[388,389] This time, the cyclization led to the corresponding cycloadducts isolated as the *endo* olefinic enone and/or the keto/enol forms. With simple substrates having a linear carbon chain linker, good to high yields were obtained (51−98%) for the 6-, 7-, and 8-membered ring formation, but not for the 9- and 10-membered ring formation (Scheme 274). Nevertheless, with several specific substrates that induced reduced transannular steric interactions in the cyclization transition state, high yields of 8-, 9-, and 10-membered carbocyclic products could be obtained. Remarkably, the cyclization of **261** with 2 mol % of $In(NTf_2)_3$ led to the formation of the 15-membered ring **262** in 27% yield after 18 h at 150 °C. The latter was converted into (±)-muscone in 58% over two steps (Scheme 274).[388]

Lee and co-workers reported recently the preparation of 1-oxadecalins via a cascade reaction involving either a Lewis acid-catalyzed Maitland−Japp-type reaction or Prins-type cyclization, followed by intramolecular cyclization of the

Scheme 275



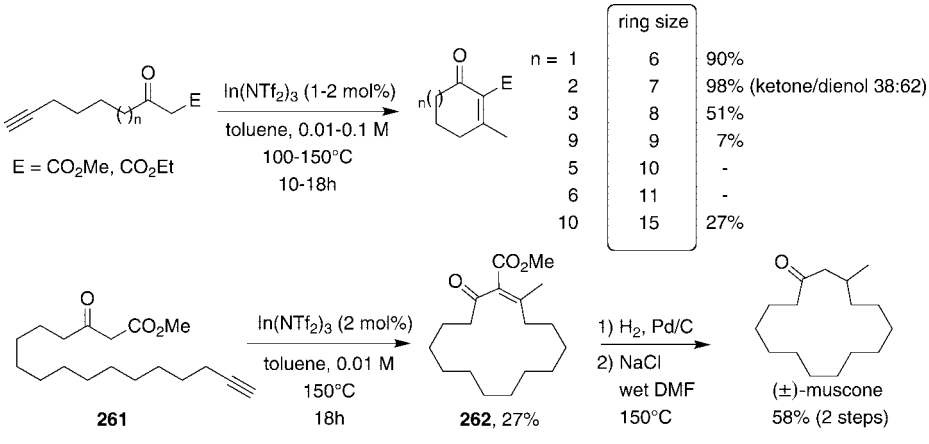
Scheme 276



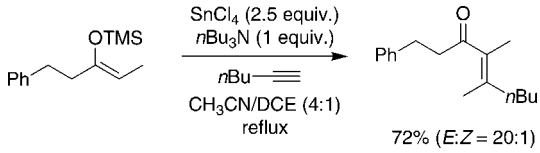
resulting β-ketoester onto the alkyne moiety (Scheme 275). The best results were obtained at 40 °C in CH_2Cl_2 or $CHCl_3$ in the presence of a stoichiometric amount of $InCl_3$, which promoted both reactions efficiently (72−81%). The reaction also proceeded in CH_3CN or toluene at 70 °C, albeit in lower yields.[390]

An intramolecular version of the alkenylation of acetoamido- and alkoxymalonates was developed by Hatakeyama and co-workers. This approach gave access to 5-, 6-, and 7-membered ring nitrogen- or oxygen-containing heterocycles.[391] The reaction was carried out in refluxing toluene in the presence of 5−15 mol % of $In(OTf)_3$ and DBU. Interestingly, the reaction proceeded without racemization, as demonstrated by the efficient cyclization of compound **263** (Scheme 276). Moreover, disubstituted alkynes were found to participate effectively in this intramolecular version, leading to trisubstituted alkenes in a highly stereoselective

Scheme 274



Scheme 277



manner (*E*-isomer only). Substrates possessing a basic amine (e.g., *N*-Bn) underwent the cyclization as well and gave pyrrolidine and piperidine derivatives in good to high yields (71−93%). The method was applied to the asymmetric synthesis of (−)-salinosporamide A.[391]

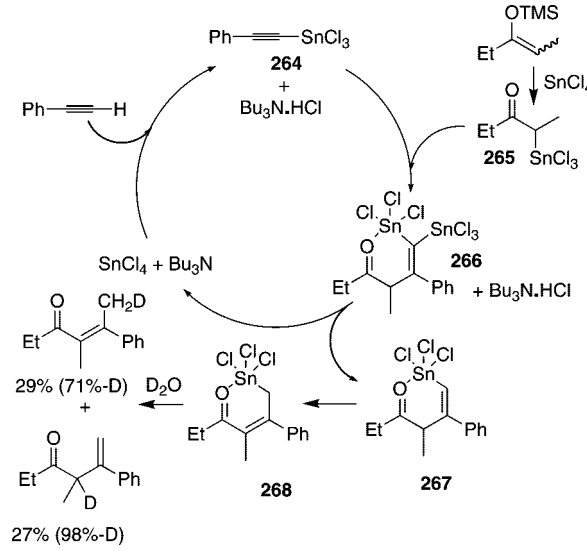
4.10. Group 14: Tin(IV)-Mediated Additions

4.10.1. Intermolecular Additions

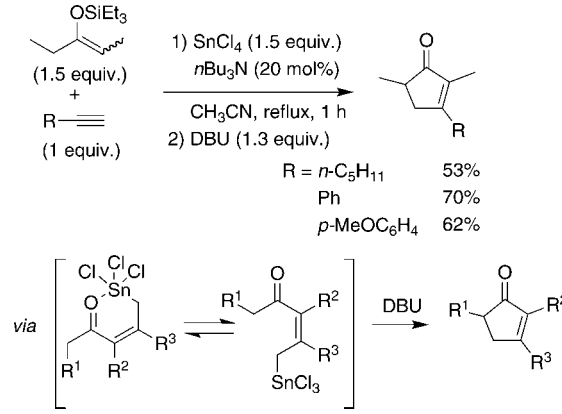
Yamaguchi and co-workers reported the first examples of intermolecular carbostannylation of alkynes with Sn−enolates in the early 1990s.[392] α,β-Unsaturated enones could be obtained by the addition of α-trichlorostannyl ketones onto alkynyl−$SnCl_3$[393] derivatives. The α-trichlorostannyl ketones were prepared at room temperature by stirring a solution of a silyl enol ether and $SnCl_4$ in 1,2-dichloroethane. The alkynyl−$SnCl_3$ derivatives were obtained upon treatment of a terminal alkyne with stoichiometric amounts of nBu_3N and $SnCl_4$ in CH_3CN. Under these conditions, the addition of silyl enol ethers of simple linear ketones and cycloalkanones onto alkyl- and aryl-substituted terminal alkynes gave the corresponding α,β-unsaturated ketones in good to high yields (58−85%) upon hydrolysis. In all cases, the addition was highly regioselective and occurred exclusively at the internal position of the alkyne. Moreover, the migration of the carbon−carbon double bond into the α,β-position led to the diastereoselective formation of *E*-isomers (typically *E*/*Z* = 20:1), irrespective of the configuration of the starting silyl enol ethers. No silyl transposition was observed with silyl enol ethers of unsymmetrical ketones (Scheme 277). Disubstituted alkynes, such as 1-phenyl-1-hexyne or TMS−phenylacetylene, were not reactive under these conditions.

The proposed mechanism involves the *syn*-carbometalation of alkynyl−Sn species **264** with the in situ-generated α-Sn−enolate **265** leading to the formation of organo-*gem*-bimetallic adduct **266** (Scheme 278). Protonation of the latter with $nBu_3N\cdot HCl$ gives vinyl−Sn intermediate **267**, which, as supported by deuterium incorporation upon deuterolysis with D_2O, rearranges into the more stable allyl−Sn species **268** that gives the final addition products upon aqueous workup. *gem*-Bimetallic stannane **266** was isolated following addition of the silyl enol ether onto nBu_3Sn−phenylacetylide and studied by ^{119}Sn NMR and X-ray analysis. Structural features of this intermediate included the presence of tetra- and pentacoordinated Sn atoms in CD_2Cl_2 solution, the complexation of the *syn* tin atom with the oxygen atom of the carbonyl group, the bond lengths (C−Sn and C=C), and the planar geometry of the C=C bond being consistent with a vinyl−Sn structure. Interestingly, the X-ray structure indicated two $SnCl_3$ groups, suggesting that an exchange between alkynyl−$SnBu_3$ and $SnCl_4$ had occurred. Notably, in the proposed mechanism, catalytic activation of the alkyne was involved. In accordance with this observation, the reaction could also be carried out in the presence of only 20 mol % of tertiary amine without a significant drop in the yields.

Scheme 278



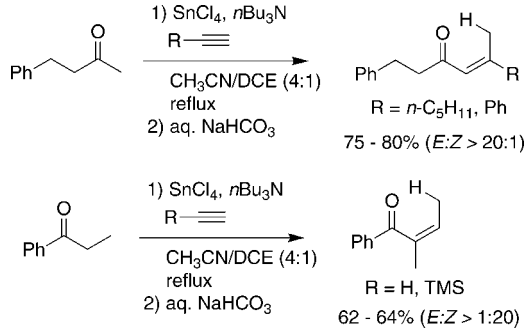
Scheme 279



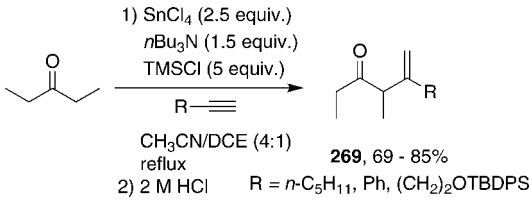
Remarkably, the $SnCl_3$ moiety of the allylstannane resulting from the overall process could also react as a leaving group.[394] Thus, an access to cyclopent-2-enones based upon the intermolecular addition of silyl enol ethers of ketones onto terminal alkynes, followed by a base-mediated intramolecular nucleophilic displacement of the $SnCl_3$ group, was developed (Scheme 279).[395] For instance, following carbometalation of a range of alkynes with the α-Sn−enolate, addition of a base led to the formation of cyclopentenones in moderate to good yields (39−74%). The nature of the amine was found to be crucial for the cyclization process, and the best results were obtained with hindered and non-nucleophilic amines such as DBU.

As an alternative to the use of silyl enol ethers, the direct formation of Sn−enolates from ketones in the presence of $SnCl_4$ and Et_3N was also studied.[396] Even though the enolate/ketone equilibrium lies in favor of the ketone, intermolecular carbometalation was shown to occur at reflux in CH_3CN/DCE (4:1) in the presence of a terminal alkyne (R = H, alkyl, aryl, TMS). Under these conditions, the corresponding α,β-unsaturated ketones were obtained (Scheme 280) in moderate to high yields (52−88%) and with very high levels of stereoselectivity (*E*/*Z* up to 20:1 for R = alkyl, aryl; *Z*/*E* up to 20:1 for R = TMS, H). The selectivity observed could be explained by the regioselective protonation of the allyl−Sn intermediate at the γ-position. Unsymmetrical ketones reacted exclusively at the less substituted α-position. Desilylation occurred when trimethylsilylacetylene was used.

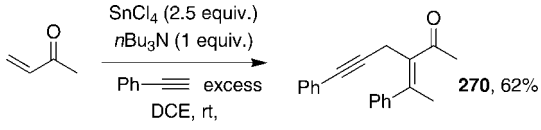
Scheme 280



Scheme 281



Scheme 282



An interesting difference in the regioselectivity was observed when the reaction was treated with TMSCl prior to acidic quench. Under these conditions, the corresponding β,γ-unsaturated ketones could be obtained. For instance, reaction of ketones with a range of alkynes (R = H, alkyl, aryl, TMS) in refluxing CH_3CN/DCE (4:1) in the presence of $SnCl_4$, nBu_3N, and TMSCl yielded β-alkenylated ketones **269** upon hydrolysis with HCl (Scheme 281). Athough the exact role of TMSCl remains unclear (its addition at the beginning of the reaction gave actually similar results), the origin of the selectivity observed is very likely related to the hydrolysis of the allylstannane intermediate resulting from the carbometalation. The selectivity was, however, highly substrate-dependent and, for example, a methyl ketone afforded the corresponding α-enone predominantly.

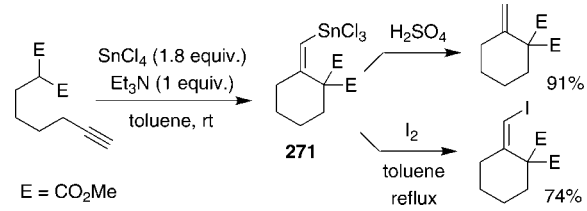
Finally, α-Sn−enolates could also be prepared by 1,4-addition of an alkynyl−Sn species onto α,β-unsaturated ketones.[393] For instance, methyl vinyl ketone reacted with an excess of phenylacetylene in the presence of $nBu_3N/SnCl_4$ to give compound **270** in good yield following a tandem 1,4-addition/carbometalation process (Scheme 282).

4.10.2. Intramolecular Additions

$SnCl_4$-mediated carbocyclizations of carbonyl derivatives bearing pendant terminal alkynes have been known for a long time. Early examples of this version of the catalytic Conia-ene reaction include cyclizations of substrates such as monoketones[355] or β-ketoesters leading to cyclopentenes or *cis*-decalins.[397]

More recently, Taguchi and co-workers reported an example of intramolecular carbostannation of 5-dimethyl hexynylmalonate (Scheme 283). The cyclization was carried out at room temperature in toluene in the presence of $SnCl_4$ and Et_3N and led to the formation of the corresponding methylenecyclohexane in high yield (91%) upon hydrolysis

Scheme 283



with 11 M H_2SO_4. The vinyl−Sn intermediate **271** was formed exclusively in the *Z*-configuration, as proved by the electrophilic trapping with I_2 in refluxing toluene, which gave the corresponding *Z*-vinyl iodide derivative in 74%. These results supported a mechanism involving a *syn*-addition of a Sn−enolate onto the alkyne.[162]

5. Addition onto Arenes

It is well-known that temporary complexation of the π-system of arenes with an electrophilic transition metal activates them toward nucleophilic addition and enables disruption of the aromaticity (dearomatization).[398,399] Such transformations are of significant synthetic importance since they offer the possibility to use widely available, low-cost arenes as the starting material for the synthesis of complex alicyclic molecules containing new carbon−carbon bonds and stereogenic centers.[400,401] Specifically, addition of enolate-type carbanions has been achieved onto arene metal complexes, predominantly of $Cr(CO)_3$ and $Mn^+(CO)_3$ and to a lesser extent of Fe^+Cp and Ru^+Cp. In every case, the addition reaction requires preformation of the (η^6-arene)complexes. Preparation procedures are generally well-established and often high yielding[399] but will not be discussed here.

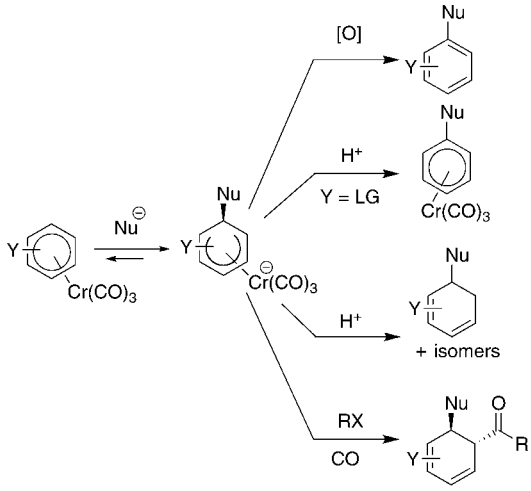
5.1. Group 6: Chromium(0)−Arene Complexes

5.1.1. General Trends

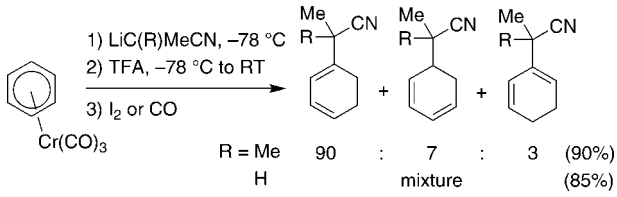
Stabilized carbanions add readily onto neutral (arene)-$Cr(CO)_3$ complexes to afford anionic cyclohexadienyl complexes. Addition onto substituted arenes can occur *ipso*, *ortho, meta*, or *para* to the pre-existing substituent group, and prediction is often difficult since many factors such as the nature and the relative positions of the substituents, the conformation of the $Cr(CO)_3$ tripod, or the nucleophile are to be considered. As a (very) general trend, arenes bearing electron-donor or -acceptor substituents are usually attacked at the *meta*-position, while bulky groups direct *para* and groups that can coordinate the incoming nucleophile direct *ortho*.

After the nucleophilic attack, several paths are possible (Scheme 284). Oxidation of the intermediate complex (I_2, O_2, Ce(IV)) leads to a new arene, and treatment with acids in the case where a leaving group is present leads to a new (arene)$Cr(CO)_3$ complex following a protonation−elimination sequence. From a synthetic point of view, no overall addition is effected for these two pathways (formal C−H and C−X substitution, respectively),[402,403] and thus, they lie beyond the scope of this review. Alternatively, cyclohexadienes can result from reaction of the intermediate cyclohexadienyl anion with electrophiles. The *trans*-stereochemistry observed in Cr-mediated dearomatizations results from the reaction of the electrophile first at the Cr-center in anionic (η^5-cyclohexadienyl)Cr complexes. For ester- and nitrile-stabilized carbanions, a difficulty arises from the fact that,

Scheme 284



Scheme 285



unlike in the case of nonstabilized and sulfur-stabilized carbanions, the initial addition is reversible. As a consequence, in order to perform a dearomatization sequence, electrophilic trapping must be faster than anion dissociation.

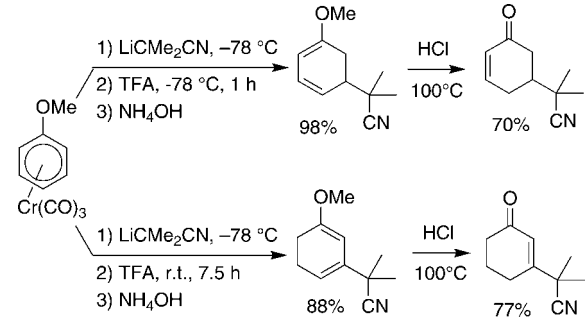
5.1.2. Nucleophilic Addition−Protonation

The first example of such a reaction involved addition of 2-lithio-2-methylpropionitrile onto (η^6-benzene)$Cr(CO)_3$ followed by protonation at low temperature of the intermediate cyclohexadienyl $Cr(CO)_3$ anion with trifluoroacetic acid (Scheme 285).[404] A mixture of cyclohexadienes was obtained whose distribution varied accordingly with the reaction conditions and tended to converge to the more stable diene. It was later demonstrated that double-bond isomerization resulted from interconversion of isomeric (diene)$Cr(CO)_3$ complexes via 1,5-hydride migrations and 1,2-hydride exchange processes and could only be avoided at very low temperatures.[405] 2-Lithiopropionitrile was also used successfully for the dearomatization of benzene. Interestingly, protonation under a CO atmosphere allows recovery of $Cr(CO)_6$.[406]

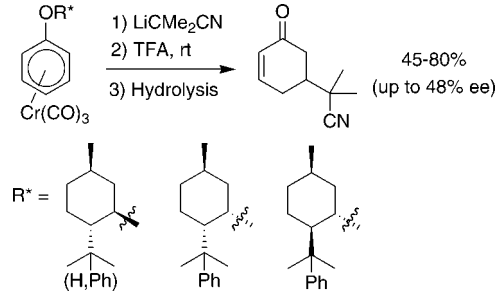
Anisole could also be dearomatized by addition of 2-lithio-2-methylpropionitrile onto (η^6-anisole)$Cr(CO)_3$ followed by protonation. Regiocontrol regarding the resulting dienes could be achieved by carefully controlling the temperature and reaction time (Scheme 286).[407,408] Low temperatures and short reaction times provided the 5-substituted methoxycyclohexa-1,3-diene, whereas higher temperatures and longer reaction times afforded only the 3-substituted regioisomer. Acidic hydrolysis of the dienol ethers led to the corresponding substituted cyclohexenones.

Owing to the synthetic value of this route to cyclohexenones, diastereoselective approaches were envisioned. In a seminal work, Semmelhack and co-workers showed that dearomatization of complexes bearing menthol-derived chiral auxiliaries led to nonracemic cyclohexenones in good yields

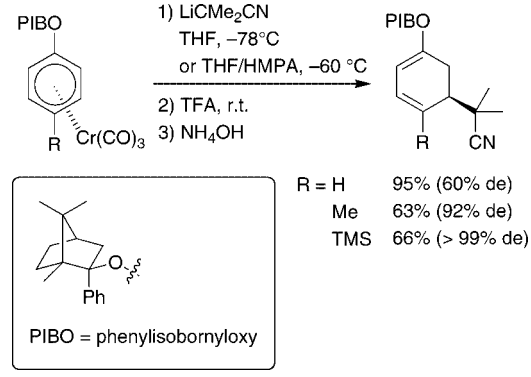
Scheme 286



Scheme 287



Scheme 288

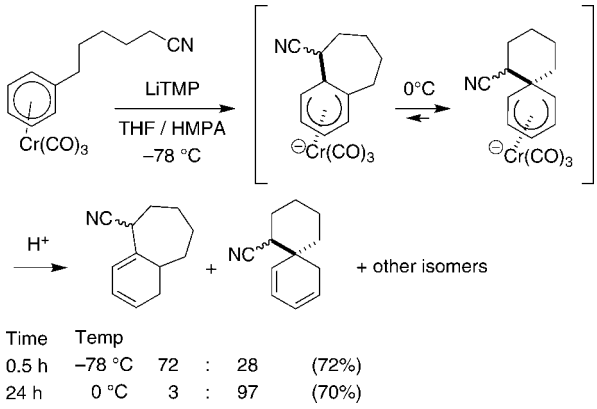


(45−80%) but only moderate enantioselectivities (<48% ee) (Scheme 287).[409]

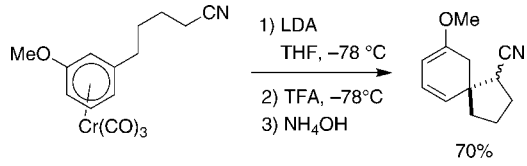
Building on these results, Pearson and co-workers achieved higher product diastereoselectivities (up to 76% de) using terpenoid derived chiral auxiliaries (Scheme 288).[410−412] A *para*-Me or TMS group in the starting complex significantly enhanced the diastereoselectivity. For instance, the addition of 2-lithio-2-methylpropionitrile onto (η^6-arene)$Cr(CO)_3$ complex derivatives bearing a phenylisobornyloxy chiral auxiliary could be achieved in good to high yields and with almost complete chiral induction for the TMS-substituted substrate (Scheme 288).

Intramolecular nucleophilic addition/protonation was reported with nitrile-stabilized carbanions. Fused bicyclic ring systems (mixtures of diene isomers) and spirocyclic systems could be obtained depending on the length of the carbon chain and the reaction conditions. For example, in the case of a hexyl chain, the (η^5-cyclohexadienyl)-$Cr(CO)_3$ anion resulting from an *ortho*-addition at low temperature equilibrated upon warming at 0 °C with the (η^5-cyclohexadienyl)$Cr(CO)_3$ anion resulting from an *ipso* addition.[413] As a consequence, kinetic conditions favored the fused bicyclic product, while thermodynamic conditions favored the formation of the spirocyclic compound (Scheme 289).

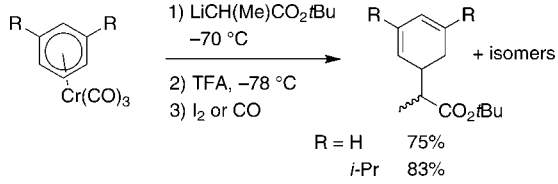
Scheme 289



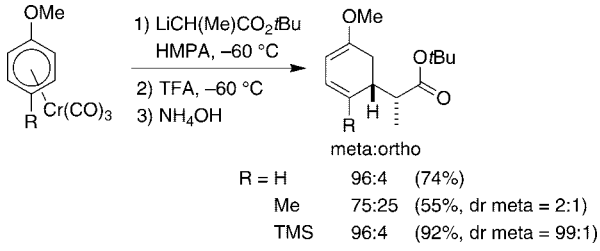
Scheme 290



Scheme 291



Scheme 292

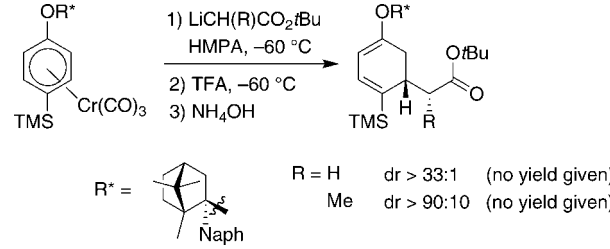


In a similar approach, intramolecular addition/protonation starting from *meta*-methoxy-substituted complexes afforded in good yields the corresponding spirocyclic dienol ethers, which upon hydrolysis led to 5-spiro cyclohexenones (Scheme 290).[407] This synthetic strategy was successfully applied to the synthesis of acorenone and acorenone B.[414]

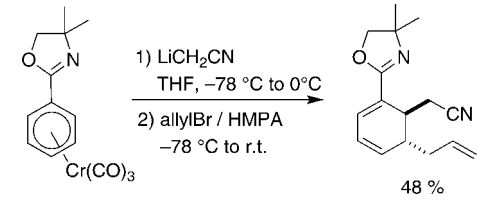
Nucleophilic addition/protonation sequences were also reported with ester enolates. In an early example,[406] the Li−enolate derived from *t*-butyl propionate was shown to react with (η^6-benzene)$Cr(CO)_3$ and (η^6-*meta*-diisopropylbenzene)$Cr(CO)_3$ to afford mixtures of isomeric cyclohexadienes after protonation at low temperature (Scheme 291).

More recently, addition/protonation sequences of anisole derived (η^6-arene)$Cr(CO)_3$ complexes with ester enolates leading to dienol ethers were studied (Scheme 292).[415] In the presence of HMPA to enhance the reactivity of the ester enolate, addition occurred with good levels of *meta* regioselectivity (with respect to the methoxy group), and good yields were generally observed for the overall sequence. The use of a prochiral nucleophile, *tert*-butyl lithiopropionate, resulted in the formation of two new adjacent stereocenters. While for the unsubstituted and the *para* Me-substituted

Scheme 293



Scheme 294



anisole complexes a mixture of stereoisomers was observed for the final products, excellent vicinal stereocontrol (>99:1) was observed starting from (4-TMS−anisole)$Cr(CO)_3$. In this case, the resulting dienol ether was used as an intermediate for the synthesis of (±)-juvabione.

In order to develop an asymmetric version of this reaction, addition of ester enolates onto anisole complexes bearing isobornyl derived chiral auxiliaries was investigated.[412,415] Starting from a 4-TMS−anisole derived $Cr(CO)_3$ complex, excellent levels of diastereoselectivity (1,5-asymmetric induction) were observed in the addition/protonation sequence with the enolate of *t*-butyl acetate (Scheme 293). When prochiral *tert*-butyl lithiopropionate was used, good overall diastereoselectivity was observed (>80% de) resulting from the combination of 1,2-vicinal stereoselection and 1,5-asymmetric induction.

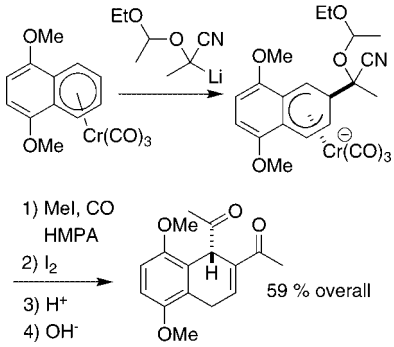
5.1.3. Double Addition of a C-Nucleophile and C-Electrophile

Double addition of an enolate and a carbon electrophile across the double bond of an (η^6-arene)$Cr(CO)_3$ complex affords polysubstituted cyclohexadienes. However, owing to the reversibility of the nucleophilic addition, successful examples are still scarce. In all cases, addition of HMPA to enhance the reactivity of the anionic (η^5-cyclohexadienyl)-$Cr(CO)_3$ complex is crucial in order to reduce anion dissociation and obtain the desired electrophilic quench. Reaction of the carbon electrophile takes place by coordination to the metal center and subsequent *endo* migration onto the ring. Thus, the resulting stereochemical relationship in the cyclohexadiene is *trans*.

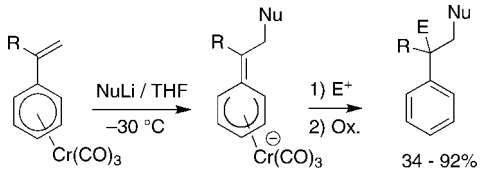
In a first example, double addition of lithio−acetonitrile and allyl bromide was obtained across the double bond of an (oxazoline)$Cr(CO)_3$ complex (Scheme 294).[416]

Addition of a Li−enolate derived from a protected acetaldehyde cyanohydrin onto (1,4-dimethoxynaphthalene)$Cr(CO)_3$ also led to a cyclohexadienyl anion reactive enough to be alkylated and, thus, provided dearomatization products. Using MeI as the electrophile under a CO atmosphere, migratory CO insertion preceded the reductive elimination and led to formation of a methyl ketone (Scheme 295).[417]

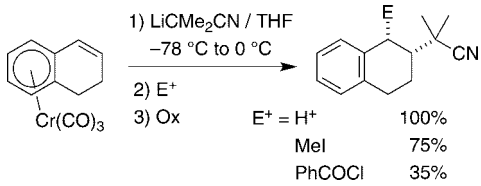
Scheme 295



Scheme 296



Scheme 297



5.1.4. Addition to Styrene-Type Ligands

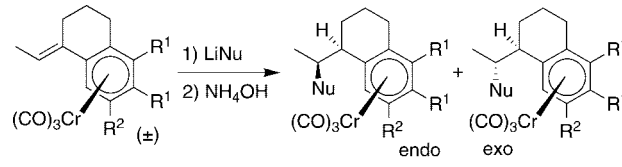
As for arenes, complexation of styrenes with $Cr(CO)_3$ was found to activate them toward nucleophilic addition. As a consequence, a variety of nucleophiles, including certain enolates of esters and nitrile anions, were reported to add at the β-position of the η^6-styrene ligand (Scheme 296). Electrophilic trapping of the resulting *exo*-alkylidene cyclohexadienyl anion occurred at the benzylic position providing a new (η^6-arene)$Cr(CO)_3$ complex and ultimately a new arene after decomplexation. Even though the addition step remained reversible, the quenching reaction was more favorable than for simple cyclohexadienyl anions, and thus, a wider range of electrophiles including alkyl halides, acyl chlorides, and disulfides could be employed.[418]

Similarly, (dihydronaphthalene)$Cr(CO)_3$ complexes underwent nucleophilic addition to afford cyclohexadienyl anions that could be reacted further at the benzylic position with several electrophiles such as strong acids, MeI, and, to a lesser extent, acyl chlorides (Scheme 297).[418,419] Interestingly, unlike the cyclohexadienes resulting from dearomatization of arenes, a *cis* stereochemistry was observed for the tetralins obtained following decomplexation after double addition (vide infra).

The addition/protonation sequence of lithiated nitriles onto (1-ethylidene−tetralin)$Cr(CO)_3$ derivatives has been investigated in some detail (Scheme 298).[420] Addition took place at the *exo*cyclic double bond, and following protonation, new (tetralin)$Cr(CO)_3$ complexes were obtained where two new stereogenic centers have been created.

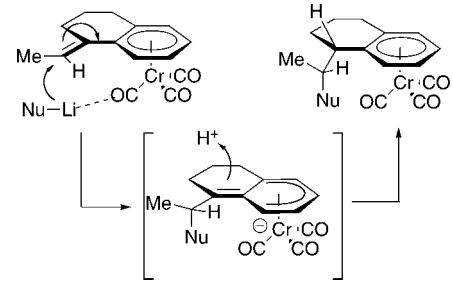
The stereochemical outcome of the reaction was remarkable. While bulkier 2-lithio-2-methylpropionate added onto

Scheme 298

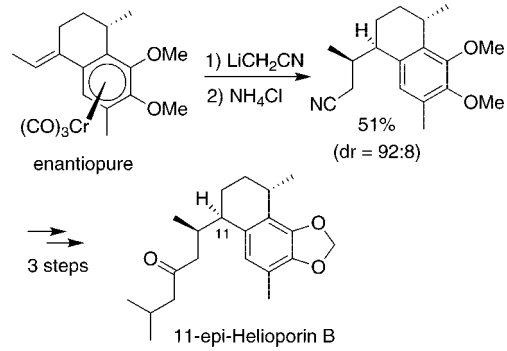


R^1 = H	R^2 = H	Nu = CH_2CN	> 98	2	(72%)
H	H	CH(TMS)CN	> 98	2	(75%)
H	H	CMe_2CN	> 15	85	(86%)
OMe	Me	CH_2CN	> 92	8	(39%)
OMe	Me	CH(TMS)CN	> 78	22	(68%)
OMe	Me	CMe_2CN	> 35	65	(82%)

Scheme 299



Scheme 300



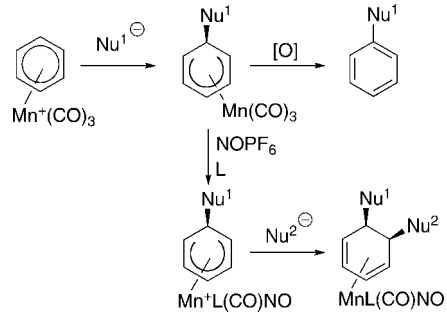
the π-ligand mainly in a classical *exo* mode (i.e., from the face opposite to the $Cr(CO)_3$ moiety), lithio−acetonitrile and lithio−1-TMS−acetonitrile added in a much rarer *endo* mode (Scheme 299), presumably as a result of coordination of the lithium atom to a carbonyl ligand. Whatever the addition mode, protonation of the intermediate occurred in an *exo* mode.

Starting from a nonracemic chiral chromium tricarbonyl complex, and following removal of the $Cr(CO)_3$ moiety, enantiopure tetralin intermediates were obtained. This efficient strategy was applied to the synthesis of marine diterpenoid 11-epi-Helioporin B and other serrulatane diterpenes (Scheme 300).[420,421]

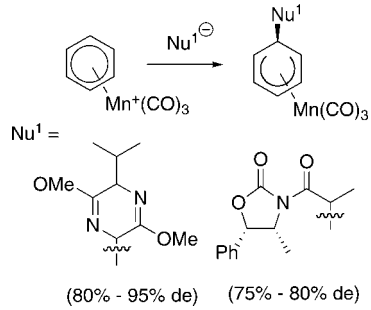
5.2. Group 7: Additions to Manganese(I)−Arene Complexes

Cationic arene tricarbonyl manganese complexes show an enhanced electrophilic character when compared with their $Cr(CO)_3$ analogues.[422,423] As a consequence, a broader range of stabilized carbon nucleophiles to be added is accessible,[398,399,403,424,425] including among others ketone enolates[426] and malonates.[427] The reactivity of the resulting (η^5-cyclohexadienyl)$Mn(CO)_3$ differs significantly from the chromium counterpart (Scheme 301). Their stability often allows for simplified isolation and manipulation. However, the low

Scheme 301



Scheme 302

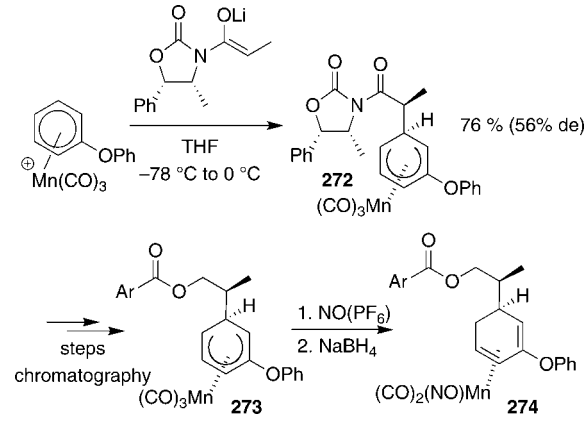


nucleophilicity of the neutral (η^5-cyclohexadienyl)$Mn(CO)_3$ complexes precludes reaction with carbon electrophiles, and protonation generally leads to rearomatization following oxidative removal of manganese. Routes to dearomatized cyclohexadienes are, therefore, significantly more limited than for chromium, and those involving stabilized nucleophiles are quite unusual. These routes are based on "reactivation" of the cyclohexadienyl complex by substitution of a CO ligand by NO^+ in order to increase the electrophilic character and, thus, enable a second nucleophilic addition.[428] Interestingly, the second nucleophile attacks the complex *exo* to the manganese moiety, ultimately leading to *cis*-disubstituted cyclohexadienes, which makes dearomatization procedures using chromium and manganese complementary from a synthetic perspective (Scheme 301).

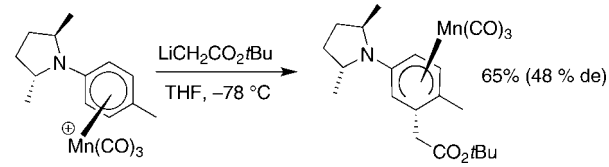
The use of prochiral nucleophiles was envisioned in order to access nonracemic products. Addition of Schöllkopf's chiral glycine enolate equivalent was used to prepare aryl glycine derivatives, including diaryl ethers.[429,430] The most selective reaction involved the addition onto (η^6-benzene)$Mn^+(CO)_3$ to afford the corresponding cyclohexadienyl intermediate in 80% yield and an excellent 95% diastereomeric excess (Scheme 302).

Addition of a Li−enolate derived from Evan's *N*-acyloxazolidinones was also reported,[431] though somewhat lower levels of diastereoselectivity were obtained (80% de, for the (η^6-benzene)$Mn^+(CO)_3$ complex). In the case of (η^6-phenoxyphenyl)$Mn^+(CO)_3$, though addition occurred with excellent *meta*-selectivity, only moderate levels of 1,2-stereoinduction were observed (Scheme 303). This reaction nevertheless found an interesting application in synthesis. Functional group transformations to remove the chiral inductor from the resulting cyclohexadienyl complex **272** led to a new cyclohexadienyl complex **273** in diastereo- and enantiomerically pure form that could be reduced by $NaBH_4$ to the corresponding complexed dienol ether **274** after activation. Decomplexation and hydrolysis afforded a cyclohexenone that was advanced to (+)-juvabione.[432]

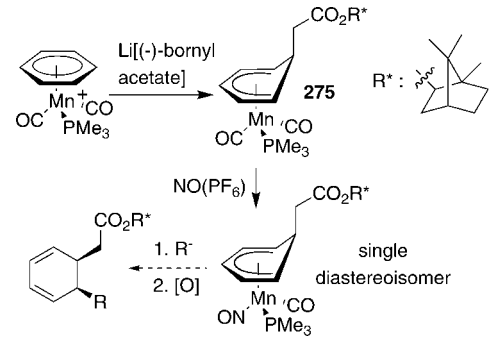
Scheme 303



Scheme 304



Scheme 305

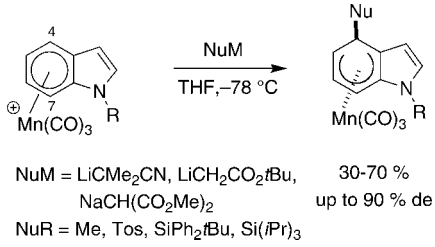


Very recently, this methodology has been successfully applied to the resolution of *ortho*- and *meta*-disubstituted planar chiral racemic (η^6-arene)Mn complexes. The best results were obtained with the Li−enolate of D-(+)-camphor that led to the formation of four diasteroisomers. The new C9 stereogenic center formed on the camphyl group could be easily epimerized upon treatment with K_2CO_3 in MeOH, therefore leading to the more thermodynamically stable complexes. Following separation of the diastereoisomers and recrystallization, the chiral auxiliary was removed upon treatment with $AgBF_4$/TMSCl and the optically enriched (η^6-arene)Mn complexes were obtained in high enantiomeric purity (>98% ee).[433]

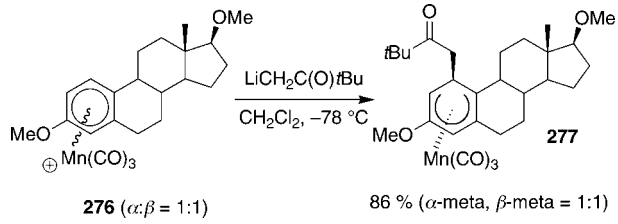
A second approach to access nonracemic products investigated the use of complexes bearing a C_2-symmetric chiral pyrrolidine auxiliary (Scheme 304).[434] Addition of the Li−enolate of *tert*-butyl acetate occurred with high *meta*-selectivity but only moderate diastereoselectivity (48% de). Manipulation to the dearomatized products, however, proved impossible with this system.

A third potential approach to nonracemic products relied upon the use of a chiral manganese tripod (Scheme 305).[424] Replacement of a CO ligand by NO by reaction with $NOPF_6$ of the adduct **275** of the Li−enolate of (−)-bornyl acetate and (η^6-benzene)$Mn^+(CO)_3$ was stereospecific and, thus, made possible a chirality transfer to the manganese atom. Since it had been shown that reduction by metal hydrides

Scheme 306



Scheme 307



was diastereoselective with respect to a chiral manganese moiety,[435] one diastereoisomer of the initial bornyl adduct was expected to lead in principle to an enantiomerically pure diene after NO^+ exchange, reduction, and decomplexation.

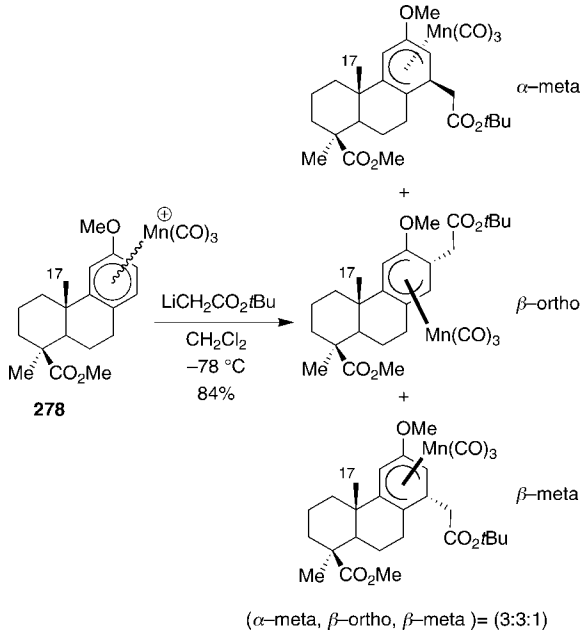
Another application of electrophilic activation of arenes by manganese cations concerned the functionalization of indoles.[436] Coordination of indoles to $Mn^+(CO)_3$ occurred through the carbocyclic ring, and attack by a range of stabilized nucleophiles took place at carbons C4 or C7 to afford the corresponding cyclohexadienyl complexes in good yields (Scheme 306). The C4/C7 ratio depended mainly on steric bulk, as increase in the size of either the nucleophile or the substituent on the pyrrole nitrogen enhanced the preference toward attack at C4.

Functionalization of aromatic steroids and related natural products by addition of stabilized nucleophiles mediated by manganese complexation was also studied. The Li−enolate of pinacolone added onto a (1:1) mixture of (α- and β-estradiol-3,17-dimethyl ether)$Mn^+(CO)_3$ complexes **276** in high yield to afford the corresponding α- and β-(cyclohexadienyl)$Mn^+(CO)_3$ adducts **277** (Scheme 307). Full regioselectivity (attack occurred *meta* to the methoxy substituent of the arene moiety) and diastereoselectivity (*exo* to the metal) was observed. Fractional crystallization enabled the separation of α- and β-isomers.[437]

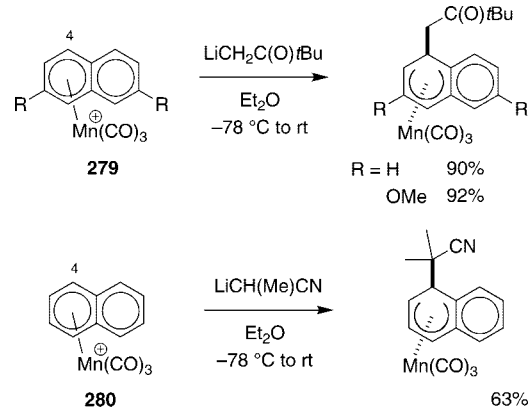
In a similar approach, addition of $LiCH_2CO_2tBu$ to a (1:1) mixture of α- and β-$Mn^+(CO)_3$ complexes **278** of a dimethylated derivative of podocarpic acid was also found to give a mixture of three isomeric products (Scheme 308).[438] Interestingly, while for the α isomer *meta* addition to the −OMe substituent was observed, predominant *ortho* addition was observed for the β isomer. This difference in behavior was attributed to a steric interaction between the Me-17 and a carbonyl ligand that induced a specific orientation of the $Mn^+(CO)_3$ tripod that activated the rings toward *ortho* attack.

In an approach to polyarene functionalization, addition of enolates on (η^6-polyarene)$Mn^+(CO)_3$ **279** and **280** was reported by Sweigart and co-workers. Provided that the reaction was carried out in Et_2O (and not THF) in order to prevent ligand displacement, $LiCH_2C(O)t$-Bu and $LiCMe_2CN$ added onto complexes containing naphthalene type ligands regioselectively at C-4 to give good yields of the corresponding cyclohexadienyl complexes (Scheme 309).[439]

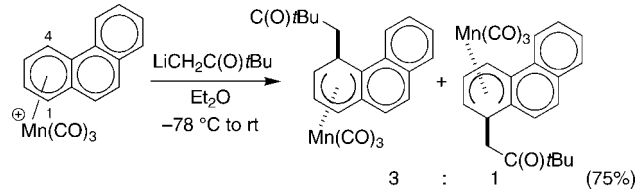
Scheme 308



Scheme 309



Scheme 310



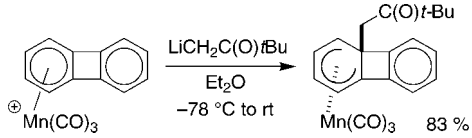
With phenantrene, however, a (3:1) mixture of isomers resulting from C4/C1 addition was obtained (Scheme 310).

The Li−enolate of pinacolone also reacted smoothly with biphenylene complexed by $Mn^+(CO)_3$. Addition was unusual in the sense that it occurred at a substituted (bridgehead) carbon. The reasons for this selectivity appeared to be related to a higher relaxation upon addition of steric and electronic constraints inherent in the "cyclobutadiene" ring (Scheme 311).[440]

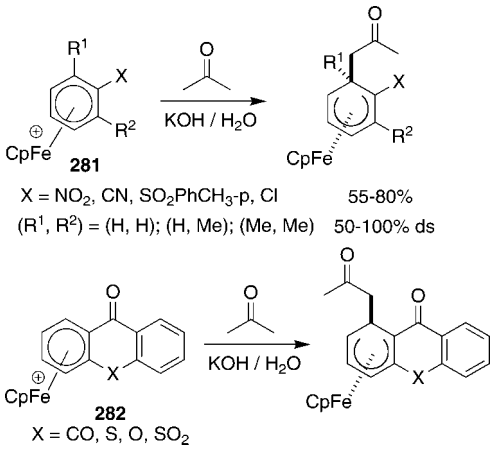
5.3. Group 8: Iron and Ruthenium

Electrophilic activation of arenes to facilitate addition of stabilized nucleophiles can also be obtained by complexation to cyclopentadienyl iron and cyclopentadienyl ruthenium cations. The level of activation obtained is similar for both families of complexes and lies in between the levels observed

Scheme 311



Scheme 312



for complexation with $Cr(CO)_3$ and $Mn^+(CO)_3$.[422,423,441] In a behavior related to that of (η^6-arene)$Mn^+(CO)_3$ derivatives, addition onto cationic (η^6-arene)Fe^+Cp and (η^6-arene)Ru^+Cp complexes leads to the formation of neutral (η^5-cyclohexadienyl)FeCp and (η^5-cyclohexadienyl)RuCp complexes.

5.3.1. Additions to Iron(II)−Arene Complexes

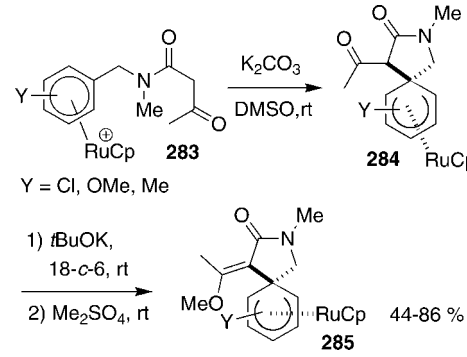
Stabilized carbanions that have been added onto (η^6-arene)Fe^+Cp complexes include ketone enolates and nitrile stabilized anions.[441] More than 20 years ago, Sutherland and co-workers reported the addition of the acetonyl anion by reaction of complexes **281** of arenes bearing electron-withdrawing substituents with acetone in the presence of aqueous KOH.[442−444] Interestingly, high *ortho* selectivity (with respect to the electron-withdrawing group) was observed even in the case of highly hindered 2,6-dimethyl substituted compounds (Scheme 312). In a related approach, the acetonyl anion was also reported to react with heterocyclic complexes **282**.[445,446] Selective addition was observed for the metal complexed ring; addition was again *ortho* to the carbonyl group.

In most cases, following addition, the resulting (η^5-cyclohexadienyl)FeCp could be isolated in good yields. However, synthetic exploitation of these intermediates has proved rather limited so far. The lack of reactivity has certainly hampered the development of this methodology. To date, only rearomatization by oxidative demetalation using CAN or 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) has been reported.[446]

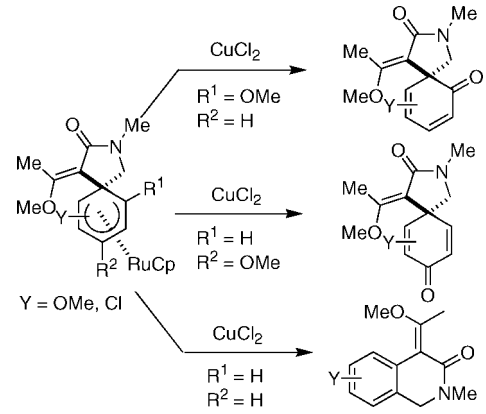
5.3.2. Addition to Ruthenium(II)−Arene Complexes

Addition of stabilized nucleophiles onto arenes via complexation to an electrophilic Ru^+Cp moiety is a much more recent reaction. Still in its infancy, only a limited number of examples have been reported. The group of Pigge has studied the intramolecular addition of enolates obtained on treatment of (η^6-*N*-benzyl acetoacetamide)Ru^+Cp complexes **283** with K_2CO_3.[447,448] Presumably, as a result of conformational constraints, whatever the substituent (OMe-, Cl-, or Me-) and its position (*ortho*-, *meta*-, or *para*-), cyclization took place regio- and stereoselectively onto the *ipso* carbon from the opposite face to the Ru^+Cp moiety. Isolation of the resulting spirocyclic (η^5-cyclohexadienyl)RuCp complex **284** was carried out following a second deprotonation that formed a new enolate and subsequent *O*-methylation (Me_2SO_4) that furnished the enol ether **285**. Several alternative *O*-alkylating agents such as allyl tosylate, triflic anhydride, or TBDMSCl could also be used in the trapping sequence, and for all cases, the *E*-ether was formed exclusively (Scheme 313).

Scheme 313



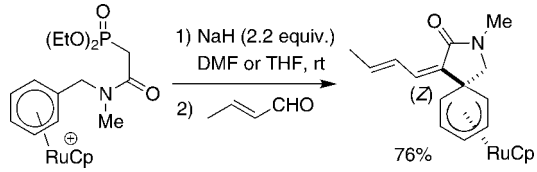
Scheme 314



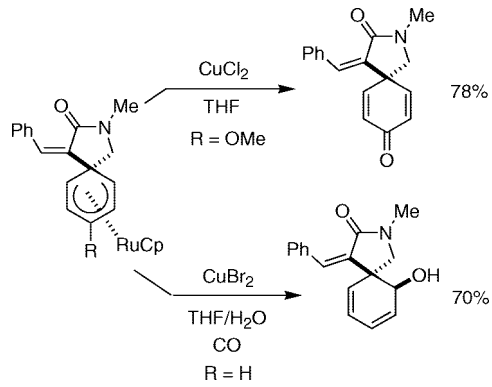
These spirocyclic (η^5-cyclohexadienyl)RuCp complexes proved to be remarkably stable and could be manipulated and stored in the open air at room temperature. Attempts at demetalation of the intermediate cyclohexadienyl complexes under protic conditions to afford the corresponding diene were unsuccessful and led to the formation of complex mixtures. Demetalation was, however, achieved by oxidative treatment with CuX_2 (X = Br, Cl).[449−451] The resulting compound depended on the nature and the position of the ring substituents. Spirodienones were formed from cyclohexadienyl complexes substituted with a methoxy group at the 2- or 4-position, while tetrahydroisoquinolines were obtained from 3-OMe and Cl-substituted complexes (Scheme 314).

More recently, the reaction was extended to include complexes derived from *N*-benzyl-β-amido phosphonates.[452] In this case, following addition of the phosphonate anion, the second deprotonation led to a Horner–Wadsworth–Emmons olefination in the presence of an aldehyde RCHO (R = H, alkyl, alkenyl, aryl). With both the addition and olefination steps being stereoselective, the corresponding cyclohexadienyl complexes bearing olefins of *Z*-configuration were obtained in good to high yields (55−81%) as single diastereoisomers (Scheme 315).

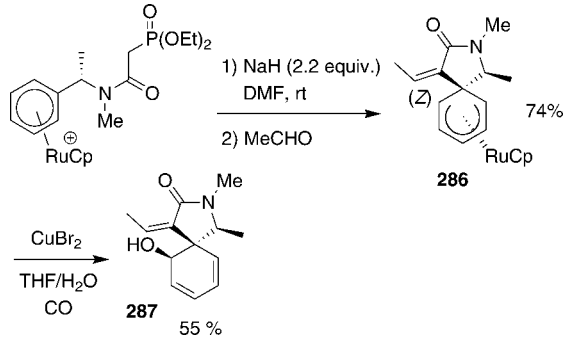
Scheme 315



Scheme 316



Scheme 317



Here again, oxidative demetalation of 4-OMe substituted complexes provided the corresponding dienones. More significantly, treatment of the unsubstituted cylohexadienyl complexes with $CuBr_2$ under a CO atmosphere in the presence of a nucleophile (MeOH or H_2O) provided the corresponding dearomatized 1,2 disubstituted dienes (Scheme 316).

A remarkable induction was observed when a chiral nonracemic α-Me substituted benzylamine ligand was used, as the corresponding cyclohexadienyl complex **286** was obtained as a single isomer. Moreover, oxidative demetalation in the presence of water was also totally diastereoselective and provided the corresponding dienol **287** in enantiomerically pure form (Scheme 317).

6. Conclusion

Since the earliest reports on the transition metal-catalyzed addition of stabilized anions to unactivated olefins, this field of research has gained significant interest. Various metals have been shown to promote the addition of enolate- or malonate-type nucleophiles onto alkenes, alkynes, 1,3-dienes, allenes, or arenes under mild reaction conditions. Inter- and intramolecular additions involving enolate-type nucleophiles often afford a new organometallic species that can be further functionalized. For most systems, the nature of the electrophile is highly dependent on the nature of the metal used to achieve this transformation. Highly diastereoselective and regioselective transformations have been reported. More recently, efficient atom-economical processes for the addition of stabilized nucleophiles onto alkenes and alkynes that do not require a stoichiometric amount of transition metal and/or the use of a base have been developed. These advances make such transformations more and more attractive for their applications in natural product synthesis. However, in a number of examples, an in-depth knowledge of the mechanism of these transformations is still lacking, in particular the mode of activation of the carbon−carbon multiple bond to be reacted. Undoubtedly this research topic will be developed in the near future in order to enhance the mechanistic understanding and broaden the synthetic scope of these fascinating endothermic processes.

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8. References

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