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MINIREVIEW

Catalytic enantioselective carbon-carbon bond formation using cycloisomerization reactions

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This review describes important recent advancements in asymmetric cycloisomerization reactions. A wide variety of catalytic and asymmetric strategies have been applied to these reactions over the past twenty years. Cycloisomerization reactions have the ability to produce diverse polycyclic compounds in excellent yields and selectivity. They constitute a powerful and efficient strategy for asymmetric carbon-carbon bond formation in cyclic compounds. Enyne and related olefin cyclizations comprise the majority of reactions of this type and important advances have recently occurred in this area. However, significant changes have also occurred in the area of classical cyclization as well as intramolecular hydroacylation and C–H activation initiated cyclization and these will also be described.

1 Introduction

The synthesis of rings is central to the art of organic synthesis. Cyclic compounds abound in chemistry, from strained three membered rings to macrocyclic monsters. A common synthetic challenge is the creation of a ring within a certain target compound. In the simplest analysis, the chemist has two possible approaches, an annulation or a cyclization strategy. In an annulation two separate reactive entities combine to create a ring by the formation of two new bonds. A cyclization involves the formation of a ring by the reaction of two ends of a linear sequence, forming a single bond. Cycloisomerisation reactions comprise a particularly efficient subset of this class, as these reactions occur with quantitative atom economy.[1,2] Nothing is wasted in a cycloisomerization reaction; all the atoms in the starting materials are present in the products.

The last two decades have witnessed remarkable improvements in the methods and technologies available for use in asymmetric catalysis. Breakthroughs have often come through a deeper understanding of the mechanisms and processes of catalysis. These technological advances have meant that newly developed cycloisomerization protocols have impressive levels of chemo-, regio-, diastereo- and enantiocontrol. Due to their application, the past decade has seen impressive progress in the number and scope of published asymmetric cycloisomerization reactions. A wide variety of ligands, metals and catalyst systems have been applied to these cyclizations allowing many challenging and useful reactions to be rendered asymmetric.

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The purpose of this review is to describe important new advances in asymmetric cycloisomerization reactions. In particular, this review will focus on enantioselective carbon-carbon bond forming cycloisomerizations. Many aspects of cycloisomerization reactions have already been reviewed,[3] including mechanistic[4] and asymmetric aspects of the reaction.[5] This review will endeavor to summarize some of the most important and recent developments in this area.

2 Classic cycloisomerization reactions

Within the compendium of chemical reactions there exist a number of well known, historical cyclization reactions that are not usually classified as cycloisomerizations. Reactions such as the intramolecular Michael, Stetter and Diels–Alder reactions belong in this category. The fact that these named reactions are pre-labeled 'intramolecular' goes to the heart of why they are seldom spoken of in this context. These intramolecular examples are most often discussed with their pervasive intermolecular cousins. However, modern advancements in asymmetric catalysis have also been applied to 'classic' cyclization reactions and the results speak to the power of modern asymmetric catalysis.[6]

2.1 Intramolecular Michael addition

Conjugate addition of a carbanion onto an α,β-unsaturated carbonyl is a powerful and consequently ubiquitous reaction in organic synthesis. It is perhaps surprising that although there exist a plethora of asymmetric intermolecular approaches,[7] relatively few asymmetric intramolecular Michael protocols have been described. The application of enamine catalysis by List and coworkers showed that imidazolidinone catalyst **2** could be used to cyclize formyl enones (**1**) to ketoaldehyde products (**3**) in

excellent yields and enantioselectivities.[8,9] The reaction works well with both aromatic and aliphatic enones to give *trans*-disubstituted cyclopentanes. When an alkyl ketone is used as the Michael acceptor the products can be further cyclized to bicyclic products (**4**) by an intramolecular aldol reaction (Scheme 1).

Hayashi and coworkers have developed a desymmetrization strategy to provide the bicyclo[4.3.0]nonene skeleton contained in **4**, but in a single step. By using 4-substituted cyclohexadienes (**5**) with cysteine derived catalyst **6**, the *trans*-substituted bicyclic products (**7**) are produced in excellent enantioselectivity (Scheme 2).[10,11] When the authors applied catalyst **6** to the cyclization of formyl enones (**1**) they found that the products were predominantly the *cis*-isomer, which experiments showed was the kinetic product. This result is complementary to the production of the thermodynamic *trans*-isomer which occurs when using imidazolidinone catalyst **2** (Scheme 1).

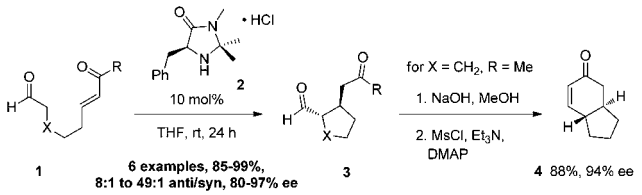
Cobb and coworkers approached the asymmetric Michael addition reaction of nitronates onto tethered conjugated esters by using bifunctional thiourea catalysts for the cyclization.[12] The method produces the six-membered cyclic products in excellent enantioselectivities (up to 99% ee) with reasonable diastereoselectivities (2 : 1 to 19 : 1 dr) and with up to three contiguous stereocenters. The authors propose that the thiourea catalysts activate the substrates by coordinating to both the nitronate and the ester groups.

If a pendant arene is used as the nucleophile in a conjugate addition a Friedel–Crafts type cyclization can occur.[13] Indeed, asymmetric indole cyclization has been achieved using a variety of catalyst systems including imidazolidinone catalyst **2** (Scheme 3)[14a–b] and chiral phosphoric acids,[14c] and has been used as a key transformation in the synthesis of a number of alkaloid natural products.[14d–e]

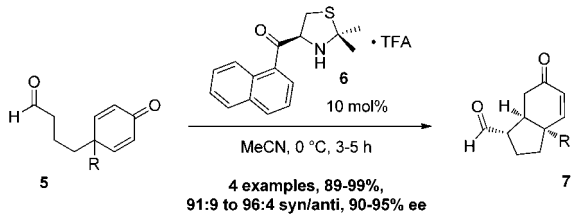
2.2 Intramolecular Morita–Baylis–Hillman and Rauhut–Currier reactions

The Morita–Baylis–Hillman (MBH) reaction involves the coupling of an activated alkene with an aldehyde. The reaction occurs through latent enolate formation by a nucleophilic catalyst to provide the zwitterion intermediate **11**. The enolate then undergoes an aldol reaction followed by proton rearrangement and regeneration of the nucleophilic catalyst (Scheme 4).

Although a low enantioselectivity had been observed in an early report,[15] the groups of Miller and Hong independently disclosed the first asymmetric intramolecular MBH reactions using similar co-catalyst systems.[16] Miller and coworkers used a co-catalyst system of pipecolinic acid and *N*-methylimidazole (NMI) with a protic solvent, which is interesting as this combination did not work well in intermolecular cases (Scheme 5).[16a]



Scheme 1



Scheme 2

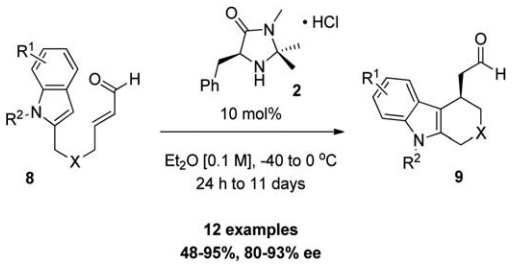
Hong and coworkers used proline and imidazole for the cyclization of hept-2-enedial in 74% yield and 98% ee.[16b] Other reported asymmetric catalysts include a chiral rhenium containing phosphine catalyst that cyclizes in up to 74% ee,[17] chiral phosphinothioureas[18] and chiral phosphine-squaramides[19] for the cyclization of formyl enones.

When the electrophilic aldehyde component of the MBH reaction is replaced with an activated alkene the reaction is called the Rauhut–Currier (RC) reaction. Miller and coworkers developed an asymmetric RC reaction using protected cysteines as the catalysts.[20] The *N*-acyl cysteine derivative **16** provided the highest enantioselectivities while optimization of the reaction conditions indicated the importance of added water and cooling (Scheme 6). Experiments indicated the significance of potassium ion chelation to both the chemo and enantioselectivity. Other reported asymmetric catalysts for this transformation include *ortho*-acidic aromatic thiols[21] and a phosphinothiourea catalyst.[22]

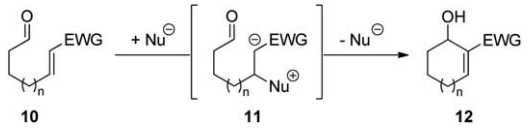
An approach that reversed the classical mechanistic manifold was employed by Christman and coworkers. Instead of using a nucleophilic catalyst, the authors applied iminium ion catalysis with a RC substrate. In this situation the aldehyde functionality is activated as the nucleophilic component which then cyclizes onto the Michael acceptor. In fact, when the authors used catalyst **19** with α,β-unsaturated aldehyde substrates (**18**) cyclopentene products (**20**) were achieved in high enantioselectivities (Scheme 7).[23]

2.3 Intramolecular benzoin condensation

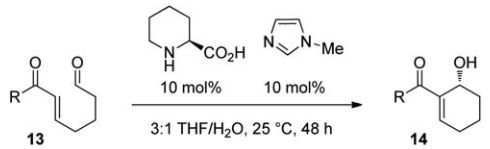
Benzoin condensation involves the nucleophilic reaction of an aldehyde onto another carbonyl group. The reaction, a nucleophilic acylation, occurs by catalytic generation of a nucleophilic centre on the aldehyde. Historically associated with cyanide as the nucleophilic catalyst, thiazolium salts are now generally used as catalysts for this reaction. Reaction of these catalysts with aldehydes generates an acyl anion equivalent (Breslow



Scheme 3

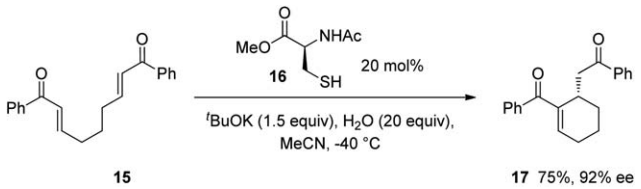


Scheme 4

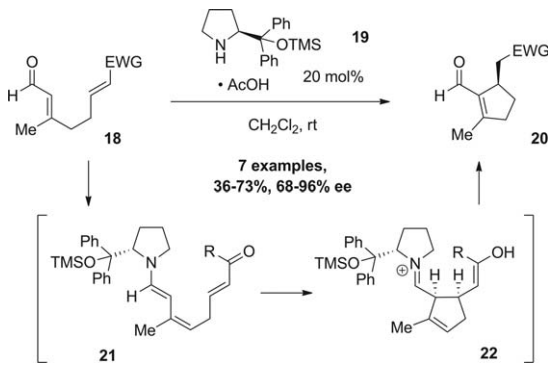


5 examples
82-92%, 51-84% ee

Scheme 5



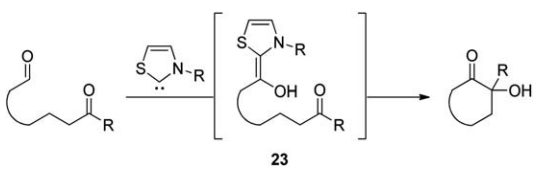
Scheme 6



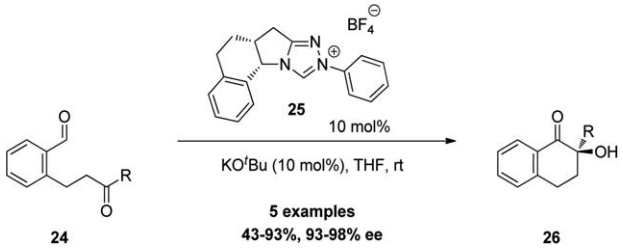
Scheme 7

intermediate **23**), reversing the polarity of the functional group which then reacts with the carbonyl electrophile *via* 1,2 addition (Scheme 8).

Enders and coworkers have developed an asymmetric intramolecular crossed benzoin reaction of ketoaldehydes. The authors found that the use of chiral tetracyclic triazolium salt **25** catalyzed the cyclization of a number of substrates in good enantioselectivities (Scheme 9).[24] These pre-catalysts are air and moisture stable crystalline solids. Treatment of the salt precursor



Scheme 8



5 examples
43-93%, 93-98% ee

Scheme 9

with base removes the triazolyl proton generating the carbene catalyst. In this reaction, catalytic amounts of base are required to prevent the competing aldol reaction.[25]

Suzuki and coworkers applied a chiral aminoindanol derived triazolium salt to this reaction and observed excellent enantioselectivities over an improved range of both five and six-membered cyclized products.[26] Further modification of the catalyst and reaction conditions allowed the application of the methodology toward the asymmetric synthesis of (+)-Sappanone B.[27] Sakai and coworkers applied this strategy to cyclic 1,3-diketones to generate desymmetrized products that contained two quaternary centres at bridgehead positions. Enantioselectivities ranged from poor to excellent depending on the substrate.[28]

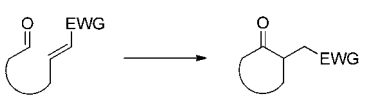
2.4 Intramolecular Stetter reaction

The Stetter reaction is the catalyzed nucleophilic addition of aldehydes to activated alkenes, providing 1,4-dicarbonyl products (Scheme 10). The reaction is similar to the benzoin reaction except the acyl anion equivalent attacks in a 1,4 manner.[29]

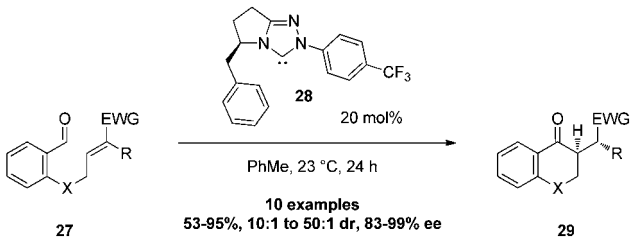
Rovis and coworkers have been very successful in using chiral triazolium salts to render the intramolecular Stetter reaction asymmetric.[30,31] The reaction works in the cyclization of five and six membered products, although only (*E*)-olefins react. The authors have had significant success in the application of this reaction to a range of challenging substrate cyclizations including the generation of quaternary centres,[30b] the desymmetrization of cyclohexadieones[30c] and the formation of multiple contiguous stereocentres.[30d] In this case, using catalyst **28**, the trisubstituted alkene substrates (**27**) are cyclized to the products in excellent diastereo and enantioselectivity (Scheme 11).

2.5 Intramolecular Diels–Alder

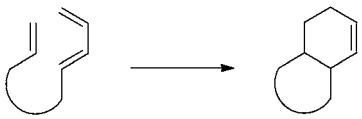
The Diels–Alder reaction is an annulation reaction, involving fusion of diene and dienophile components. When these are tethered together a bicyclic product results and this intramolecular Diels–Alder reaction (IMDA) is a cycloisomerization. The tether can be attached to the components in different ways leading to a number of IMDA types, with the most common



Scheme 10



Scheme 11

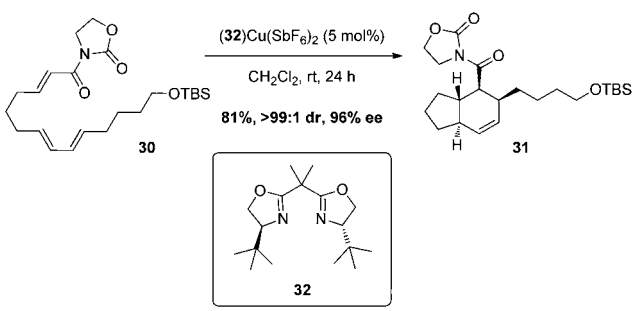


Scheme 12

being type I where both components are terminally substituted (Scheme 12).

The IMDA reaction has been extensively studied and has featured as a key step in large numbers of impressive total syntheses.[32] However, only recently have steps been taken towards the development of an asymmetric variant of the IMDA.[33] Initial attempts involved the application of chiral titanium tartrate catalysts with triene substrates containing oxazolidinone auxiliaries. These Lewis acid catalysts gave a limited number of products in good yields and enantioselectivities.[34,35] Evans and coworkers developed an enantioselective IMDA reaction using cationic copper(II)bis(oxazoline) catalysts.[36] These catalysts behaved similar to the previously developed intermolecular cases and provided both [4.3.0] and [4.4.0] bicyclic ring systems in excellent enantiomeric excess. The reaction is however, limited to substrates containing the oxazolidinone auxiliary. The authors applied this methodology to the synthesis of (-)-isopulo'upone, a marine natural product. The asymmetric IMDA reaction is at the heart of their synthetic scheme, producing the compound's four asymmetric centers in one step, in 96% ee (Scheme 13).

A number of other Lewis acidic catalysts have been described that do not require an auxiliary, but instead directly catalyze the cyclization of aldehyde trienes. Yamamoto and coworkers have developed a chiral Brønsted acid assisted Lewis acid (BLA), derived from a chiral triol and an aryl boronic acid for the asymmetric Diels–Alder reaction. The authors found this catalyst allowed cyclization of 2,7,9-decatrienal in 95% yield



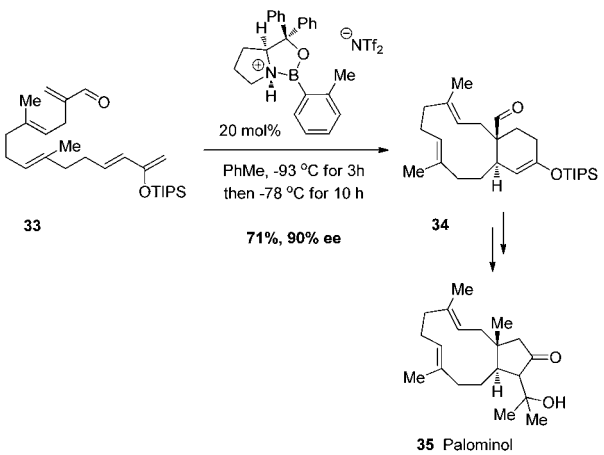
Scheme 13

and 80% ee.[37,38] Similarly, Corey and coworkers have applied their highly successful protonated oxazaborolidine catalysts to the asymmetric IMDA reaction.[33c,39] The reaction worked with both triene aldehydes and esters to give the cyclized products in excellent yields and enantioselectivities.[40a] The reaction was also applied in a macrobicyclization of triene aldehyde **33** to form **34** containing an 11-membered ring, a key intermediate in the asymmetric synthesis of Palominol (**35**, Scheme 14).[40b]

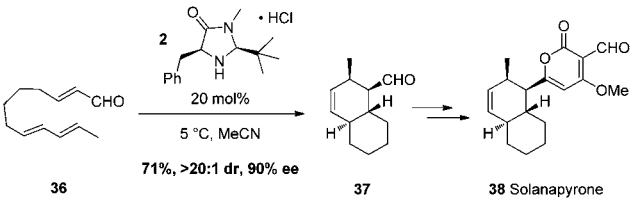
MacMillan and coworkers have developed a powerful catalytic enantioselective intramolecular Diels–Alder reaction.[41] Their LUMO-lowering iminium activation strategy was applied by using imidazolidinone catalyst **2**. A range of triene substrates work in this system, giving the cycloadduct products in excellent yields and enantioselectivities. The authors demonstrated the utility of their method by its use in the synthesis of marine metabolite Solanapyrone D (**38**, Scheme 15). Others have already applied this methodology to the synthesis of natural products such as Amaminol A and B,[42a,b] and the core of Eunicellin.[42c]

Jacobsen and coworkers have taken a unique approach by developing a transannular Diels–Alder reaction.[43] In this case the reacting groups are tethered together as part of a macrocycle and react across the ring, resulting in polycyclic products. The authors developed the first asymmetric approach to this type of reaction by applying Corey's chiral oxazaborolidine catalysts. Optimization led to the analogue containing the *ortho*-fluorophenyl substituent on boron. A number of triene macrocycles gave tricyclic products with good yields and enantioselectivities (Scheme 16). This included substrates with varying ring sizes of between five- and eight membered rings. By using a silicon linked macrocycle, the authors applied their reaction to the asymmetric total synthesis of 11,12-diacetoxydrimane, a sesquiterpene natural product.

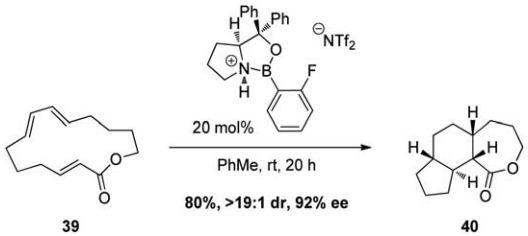
Unactivated trienes do not readily undergo thermal, or Lewis acid catalyzed Diels–Alder reactions. Gilbertson and coworkers have developed a system for the [4 + 2] cycloisomerization of unactivated trienes and dieneynes using cationic rhodium(I) catalysts. Excellent enantioselectivities were achieved for the cyclization of dieneynes (**41**), although for only a small number of substrates (Scheme 17). A single triene substrate was also cyclized in 98% ee using a cationic rhodium-BINAP catalyst.[44,45]



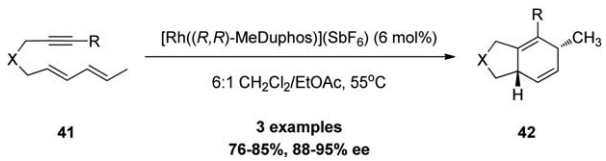
Scheme 14



Scheme 15

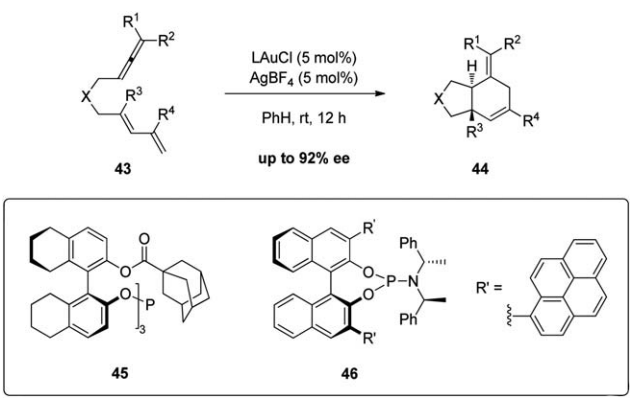


Scheme 16



Scheme 17

Allene-dienes can be selectively cyclized by gold catalysis in either a [4 + 2] or a [4 + 3] manner.[46] Toste and coworkers have reported a unique ligand system for the asymmetric gold catalyzed [4 + 2] cycloaddition reaction.[47] For most allene-diene substrates C_3-symmetric monodentate phosphite ligand **45** proved optimal providing the products (**44**) in very good yields and enantioselectivities (Scheme 18). The use of these ligand systems stands in contrast to the bidentate phosphines that are most commonly used in asymmetric gold catalysis (see sections 3.3 and 4). In the case of tethered amino substrates (**43** where X = NTs) leading to pyrrolidine products, the optimal ligand was found to be chiral phosphoramidite **46** (Scheme 18).



Scheme 18

2.6 Other [m + n] cycloadditions

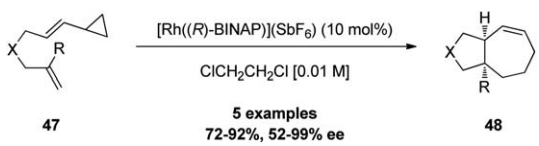
Cycloaddition reactions between vinylcyclopropanes (VCPs) and alkenes or alkynes may be efficiently catalyzed by several transition metals to form seven membered carbocyclic ring systems.[48] An asymmetric variant of the VCP alkene tethered cyclization was developed by Wender and coworkers using a cationic rhodium-BINAP catalyst system (Scheme 19).[49] These conditions were also applied to a small number of alkyne tethered VCP substrates, but enantioselectivities were low.[49] However, excellent enantioselectivities may be achieved through the use of phosphoramidite ligand **51** (Scheme 20).[50]

3 Enyne cycloisomerization

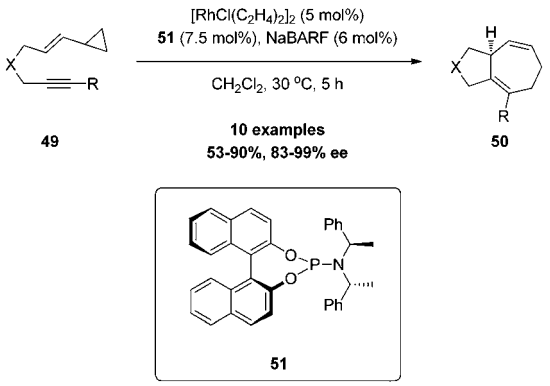
For many, the archetypal cycloisomerization reaction is the intramolecular Alder-ene reaction of 1,*n*-enynes. As the alkyne variant of the Ene reaction (Scheme 21), this reaction has been known for over 60 years in its uncatalyzed, thermal form.[51] The process involves the reaction of an olefin containing an allylic hydrogen (the ene) with an alkyne (the enophile). A six electron pericyclic rearrangement occurs causing the formation of two σ-bonds (Scheme 21). The thermal reaction, in the absence of a transition metal, has had few applications in organic synthesis. This limitation in its scope is presumably due to the high temperatures required.

In 1985, a palladium catalyzed variant of the Alder-ene reaction was discovered[52] and since then a multitude of other metals have been found to catalyze the cycloisomerization of 1,*n*-enynes (*n* = 5, 6, 7, 8, *etc.*), including Ti, Co, Fe, Rh, Ru, Ni–Cr, Pd, Pt and Au. The thermal variant of this transformation only provides 1,4-dienes. This is in contrast to the transition metal catalyzed version can provide either 1,3- or 1,4-dienes, often with high selectivity (Scheme 22). In fact, the catalyzed version of the reaction often gives different regiochemical or stereochemical outcomes to the thermal process, which sometimes fails to proceed. The reaction has developed into a powerful method for the rapid assembly of complex carbo- and heterocyclic frameworks in a highly chemo-, regio- and diastereoselective manner.

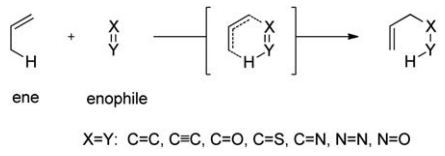
Different mechanistic pathways are possible for transition metal catalyzed cycloisomerization reactions, depending on reaction conditions and the choice of catalyst. The metal may complex to the alkene or alkyne, activating either or both. Intermediates that are thought to operate in the different mechanistic pathways for the cycloisomerization of enynes are highlighted in Scheme 23. In the first case, simultaneous activation of both the alkene and alkyne leads to a metallacycle intermediate **52**. Hydrometalation of the alkyne may instead lead to a vinyl metal species (**53**) that may then carbometalate the olefin. Alternatively, complexation of the alkyne by the metal



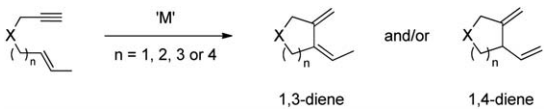
Scheme 19



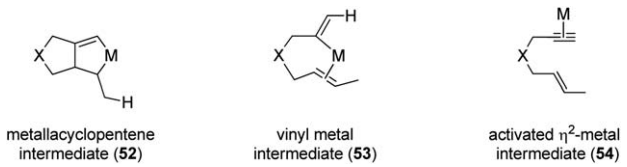
Scheme 20



Scheme 21



Scheme 22

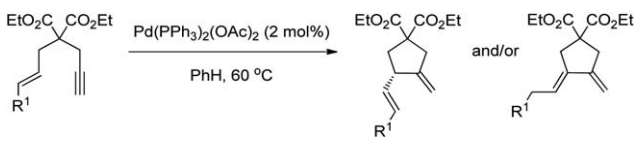


Scheme 23

catalyst (**54**) may activate it towards nucleophilic attack by the olefin generating carbocation intermediates.

3.1 Palladium

Trost and Lautens disclosed the discovery of the palladium-catalyzed cycloisomerization reaction in 1985.[52] With palladium(II) salts, they observed the cyclization of 1,6-enynes into 1,3- and 1,4-dienes (Scheme 24). Since its initial discovery, Trost has continued to provide significant contributions to the development and understanding of this reaction,[53] its mechanism[54] and application in synthesis.[55]



Scheme 24

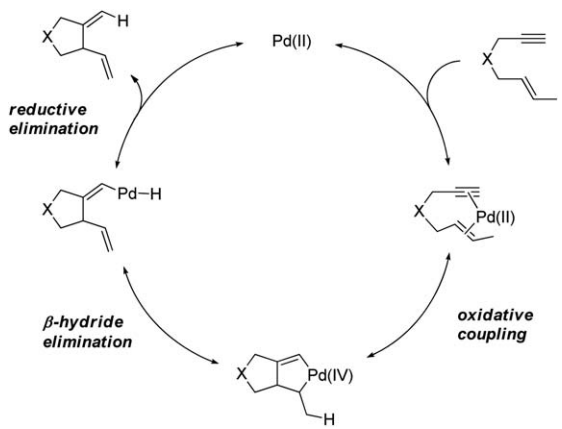
The reaction is thought to proceed through one of two possible catalytic cycles. Either a palladium(II)-palladium(IV) or a palladium(0)-palladium(II) cycle may occur, depending on the reaction conditions and the choice of pre-catalyst. In the absence of a reducing agent, the use of a palladium(II) salt such as $Pd(OAc)_2$ favors a palladium(II)-palladium(IV) cycle, which proceeds through a palladacyclopentene intermediate (Scheme 25).[54a] The proposed catalytic cycle initiates with coordination of the enyne to a coordinatively unsaturated palladium complex. Oxidative coupling produces the key palladium(IV) metallacyclopentene intermediate which undergoes fast β-hydride elimination followed by reductive elimination to afford the diene product (Scheme 25).

If a palladium(0) catalyst is used in the presence of an acid, a different mechanistic manifold operates (Scheme 26).[54b] Under these conditions, it is proposed that oxidative addition of palladium(0) into the acid H–A bond generates a palladium(II) hydride species. After complexation to the enyne, hydrometallation of the alkyne produces a vinyl palladium(II) species that undergoes 1,2-insertion of the pendant alkene. Finally, β-hydride elimination provides 1,3- or 1,4-diene products regenerating the palladium(II) hydride.

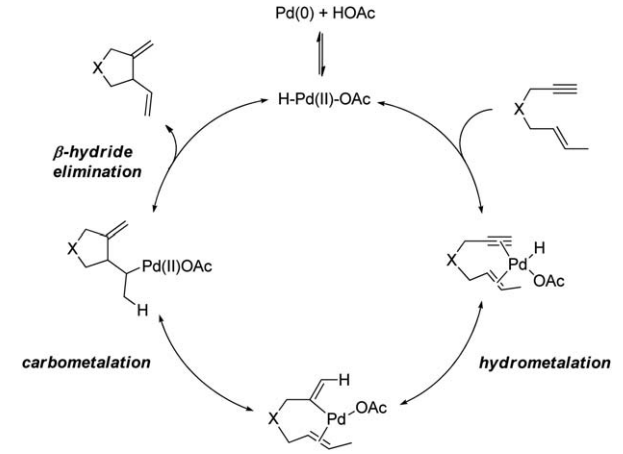
In the first example of an asymmetric cycloisomerization reaction, Trost and coworkers used a combination of palladium(0) and a chiral acid to catalyze the cycloisomerization of 1,6-enynes. Most of the chiral acids surveyed resulted in low enantioselectivities, although (*S*)-(-)-binaphthoic acid gave 1,4-diene **56** in 33% ee (Scheme 27).[56]

It is remarkable that this initial promising lead, without the aid of chiral phosphine ligands, was not pursued in the literature during subsequent decades. The modern development of chiral phosphoric acids derived from substituted BINOL ligands[57] has allowed a reexamination of this approach. Using palladium(0) and chiral acid (*S*)-TRIP, enyne **58** cyclizes to the 1,4-diene product **59** in 71% yield and 88% ee (Scheme 28).[58]

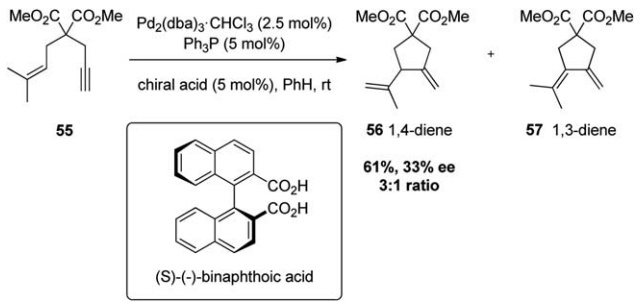
A number of more classical approaches to the asymmetric reaction, utilizing chiral bidentate ligands, have been developed. Ito and coworkers prepared pyrrolidine products by the asymmetric palladium catalyzed cycloisomerization of 1,6-enynes using *trans*-coordinating bisferrocenyldiphosphane bidentate ligand.[59] Other chiral phosphines such as chiraphos and DIOP gave poor results, while BINAP provided no



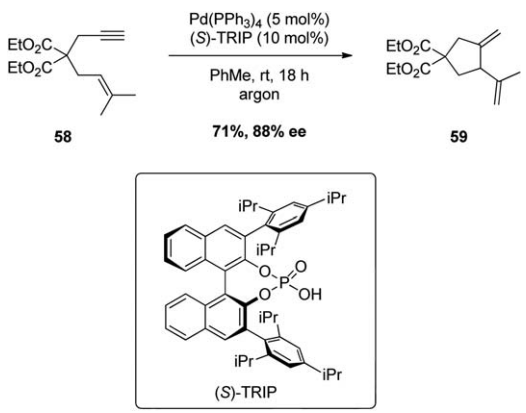
Scheme 25



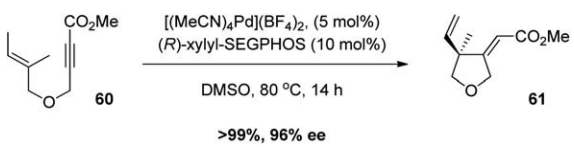
Scheme 26



Scheme 27



Scheme 28



Scheme 29

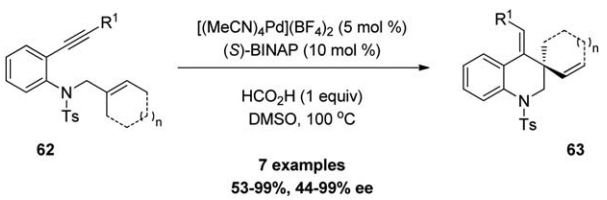
conversion even at 80 °C. Mikami and coworkers found that (*R*)-BINAP and structurally related ligands gave high enantioselectivity for the asymmetric palladium catalyzed cycloisomerization of 1,6-enyne **60** to furan **61**, containing a stereogenic quaternary center (Scheme 29). The use of typical palladium catalysts such as $Pd(OAc)_2$, $Pd_2(dba)_3 \cdot CHCl_3$/AcOH and $Pd_2(dba)_3 \cdot CHCl_3$/TFA gave poor yields of less than 25%. The authors found that switching to $Pd(TFA)_2$ caused a remarkable improvement in yield and enantioselectivity (99% yield, 93% ee) with (*R*)-BINAP. Further tuning led to the use of cationic palladium(II), with $[(MeCN)_4Pd](BF_4)_2$ as the catalyst precursor with (*R*)-xylyl-SEGPHOS as the ligand (Scheme 29). While an impressive yield and enantioselectivity was achieved, the method was only tested on a single substrate.[60]

Mikami and Hatano further extended this methodology by the application of their catalyst system to 1,7-enyne substrates (**62**).[61] Using $[Pd(MeCN)_4](BF_4)_2$ with (*S*)-BINAP as ligand in the presence of formic acid, 1,7-enynes formed six-membered quinoline derivatives (**63**) bearing stereogenic quaternary centers (Scheme 30). Unsubstituted or alkyl substituted alkyne substrates underwent the cycloisomerization reaction, while aryl- and silyl-substituted alkynes did not react.

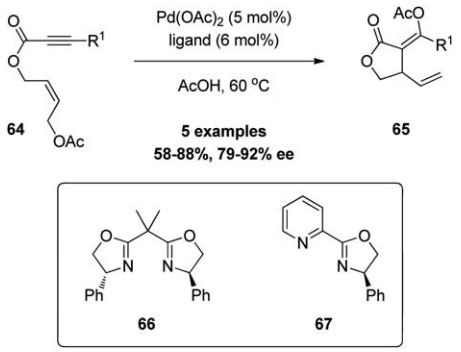
In both of the previously proposed palladium-catalyzed cycloisomerization mechanisms (Schemes 25 and 26), a hydride is added to the alkyne, by either reductive elimination, or hydropalladation. However, enynes can undergo a different tandem reaction in which a nucleophile is added across the alkyne followed by cyclization. In an example of such a transformation, Lu and coworkers have developed an asymmetric synthesis of γ-butyrolactones (**65**) by the acetoxypalladation initiated cycloisomerization of enyne esters (Scheme 31).[62] Various (*Z*)-4′-acetoxy-2′-butenyl-2-butynoates (**64**) underwent reaction in acetic acid at 60 °C in the presence of catalytic palladium(II) acetate and a bidentate diamine ligand. Optimal enantioselectivities were achieved using either bis-oxazoline ligand **65**, or pyridyl oxazoline ligand **67**. The reaction tolerated a number of different substitutions at the terminal position of the alkyne with good enantioselectivities (Scheme 31).

The mechanism of the reaction is thought to proceed by initial coordination of palladium(II) to the system followed by *trans*-acetoxypalladation of the triple bond. Cyclization onto the allyl acetate allows for a β-acetoxypalladation to yield the vinyl group and regenerate the catalytic species (Scheme 32).[62]

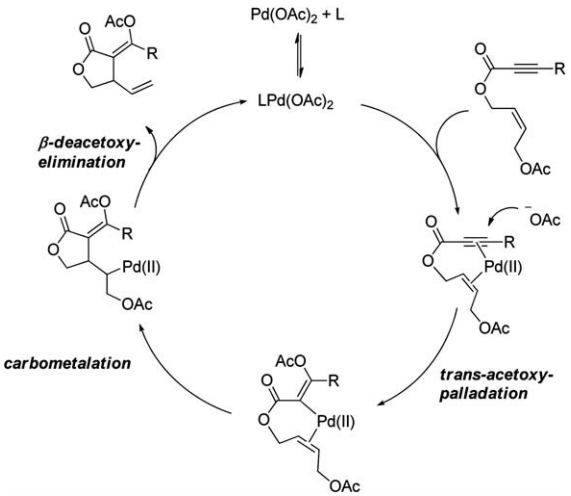
Tanaka and coworkers have used a palladium(II) catalyst with (*S*)-xylyl-SEGPHOS as ligand in the cycloisomerization of *N*-alkenyl arylethynylamides (**68**) for the enantioselective construction of axially chiral 4-aryl-2-pyridones (**69**) (Scheme 33).[63] The cycloisomerization reaction of a number of 1,5-enynes occurred in dichloroethane at room temperature. Unlike the previously discussed catalyst systems, the reaction is thought to proceed by π-complexation of the chiral palladium complex with the alkyne, facilitating cyclization by attack of the enamine functionality.



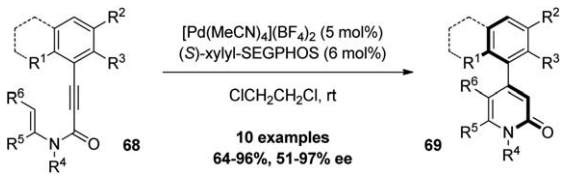
Scheme 30



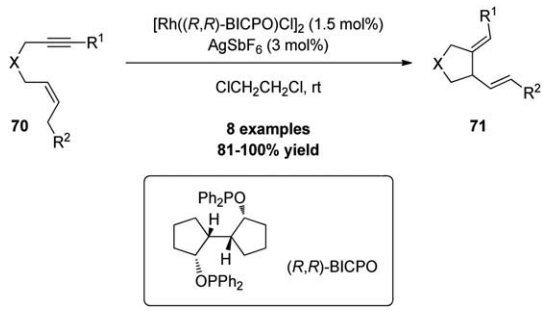
Scheme 31



Scheme 32



Scheme 33



Scheme 34

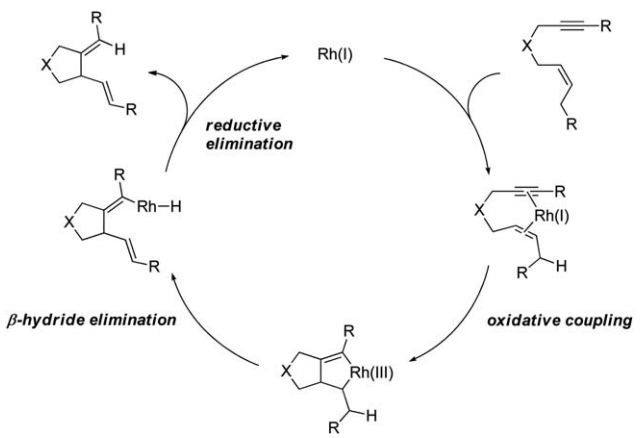
3.2 Rhodium and iridium

Some of the most reliable and wide ranging substrate scopes of all currently developed asymmetric cycloisomerization reactions have come from rhodium catalyst systems. The cyclic products are synthesized in excellent yields and enantioselectivities, often using BINAP as the chiral ligand. The first racemic rhodium-catalyzed cycloisomerization reaction was developed by Zhang and coworkers.[64] 1,6-Enyne substrates (**70**) containing *cis*-olefins were found to react with cationic rhodium(I) complexes in 1,2-dichloroethane (0.1 M) at room temperature, to give 1,4-diene products (**71**) in excellent yields (Scheme 34). Only *cis*-olefins underwent the cycloisomerization reaction efficiently; *trans*-olefins often do not react.

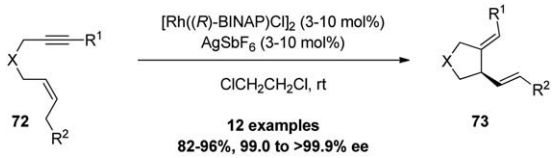
The mechanism of rhodium(I)-catalyzed cycloisomerization is proposed to consist of four steps. Initial bidentate coordination of the rhodium(I) species to the enyne is followed by oxidative cyclization to form a rhodium(III) metallacyclopentene. This intermediate then undergoes regiospecific β-hydride elimination to give the (*E*)-olefin geometry followed by reductive elimination to generate the 1,4-diene product (Scheme 35).

Working from their racemic reaction, Zhang and coworkers reported the first asymmetric rhodium-catalyzed cycloisomerization of 1,6-enynes (**72**) (Scheme 36).[65] A number of chiral bidentate phosphines and phosphones were screened, with MeDuphos, BICP and BICPO producing the highest enantioselectivities. The authors observed that the 1,4-diene product (**73**) isomerizes to the 1,3-diene in the presence of the rhodium(I) catalyst. In order to avoid this problem the reaction was carefully monitored and quenched as soon as the substrates were consumed. Although the bidentate phosphine BINAP initially gave no reactivity, the authors later discovered that *in situ* preparation of the rhodium catalyst led to significant improvements, giving uniformly high enantioselectivities and yields over a wide range of enyne substrates (Scheme 36).[66] A number of other substrates and ligands have been applied in this reaction providing similarly high enantioselectivities and yields for these substrates.[67]

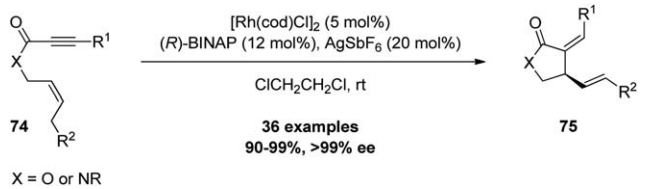
Zhang and coworkers next applied their methodology to the asymmetric synthesis of α-methylene-γ-butyrolactones (Scheme 37, X = O).[68] These reactions were carried out in the presence of $[Rh(cod)Cl]_2$, (*R*)-BINAP and $AgSbF_6$ in dichloroethane at room temperature to give the lactone products in minutes with uniformly high yield and enantioselectivity. The authors also



Scheme 35



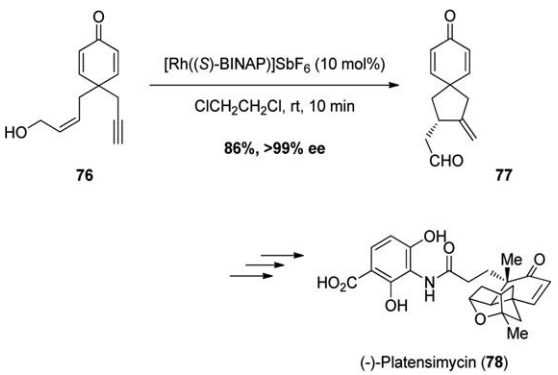
Scheme 36



Scheme 37

applied the same protocol to enyne amides to give functionalized lactam products in high yields and enantioselectivities (Scheme 37, X = NR).[69] Unprotected amides do not provide products, presumably because these amides exist predominately as the *trans*-isomer. The authors demonstrated the potential power of their rhodium-BINAP catalyzed cycloisomerization approach through a formal synthesis of (+)-pilocarpine.[68] Additionally, some 1,6-enyne substrates, with substituents in the allylic position, participated in a kinetic resolution to make substituted furan products in high enantioselectivities.[70]

Nicolaou and coworkers extended the rhodium(I)-catalyzed asymmetric enyne cyclization reaction to substrates with terminal alkynes (Scheme 38).[71] In these cases, the use of the preformed [Rh((*S*)-BINAP)]SbF_6 complex was found to be optimal over formation of the catalyst *in situ*. The reaction worked well with a variety of *cis*-allylic alcohols to give aldehyde products in excellent yields and enantioselectivities. The genesis for the authors' work in extending the reaction scope came from its use as a key step in the formal asymmetric synthesis of (-)-platensimycin (**78**). The key 1,6-enyne intermediate **76**, was reacted to afford spiro dienone aldehyde product **77** in 86% yield and greater than 99% ee. The product (**77**) intersects an intermediate from the authors' previous synthesis and therefore, constitutes a formal asymmetric total synthesis of (-)-platensimycin.



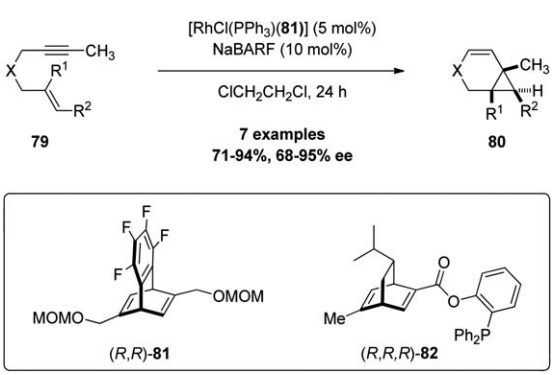
Scheme 38

Hayashi and coworkers have developed an asymmetric cycloisomerization reaction of heteroatom-bridged 1,6-enynes (**79**) to afford 3-aza and 3-oxabicyclo[4.1.0]heptene derivatives (**80**) in high enantioselectivity (Scheme 39).[72] The optimized catalyst complex was a rhodium-chiral diene complex bearing an achiral monophosphine as the second ligand. Chiral diene **81** was optimal and provided a less hindered, less electron-donating environment than a standard bis-phosphine ligand.[72a] In fact, the use of bidentate phosphines, such as dppe or BINAP, under these conditions did not afford any of the bicyclo[4.1.0]heptene products. Chiral diene/phosphine tridentate ligand **82** was also found to be applicable as a ligand, providing cyclopropane products in excellent enantioselectivities (Scheme 39).[72b] The tridentate nature of **82** was thought to address many of the drawbacks of a diene catalyst system including reducing enyne oligomerization and improving substrate scope.

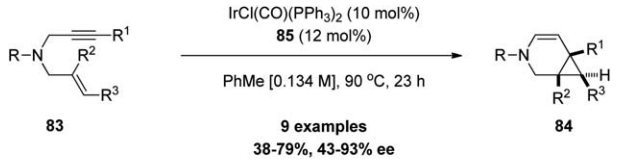
Iridium catalyst systems also catalyze this reaction although initially obtained enantioselectivities were modest.[73] The application of a chiral counterion strategy has enabled a successful asymmetric reaction to be developed. The use of the silver salt of TRIP (**85**) with Vaska's complex enables the cycloisomerization reactions to proceed with high enantioselectivity (Scheme 40).[74] Although the reaction works with oxygen tethered enynes the yields and enantioselectivities are generally low in these cases.

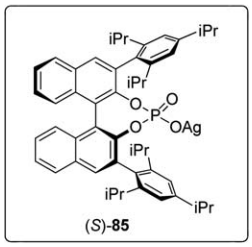
Widenhoefer and coworkers developed an asymmetric rhodium(I)-catalyzed cycloisomerization-hydrosilation protocol (Scheme 41).[75] Although rhodium-BINAP complexes were not effective catalysts for this transformation, it was found that the closely related BIPHEMP complexes were highly effective catalysts. Treatment of a number of functionalized 1,6-enynes with excess trialkylsilane and 5 mol% of the catalyst mixture in dichloroethane at 70 °C, gave functionalized silylated alkylidenecyclopentanes with high enantioselectivities (Scheme 41).

Krische and coworkers have developed hydrogen mediated reductive cyclization reaction of 1,6-enynes catalyzed by rhodium (Scheme 42).[76] The reaction is proposed to proceed by formation of a rhodium hydride followed by reaction with the 1,6-enyne to form a rhodium(III) metallocycle. Reductive elimination from this species generates the cyclic products. Chiral bidentate phosphine ligands such as (*R*)-BINAP or (*R*)-Cl-MeO-BIPHEP gave the cyclic products in excellent enantiomeric excess upon reaction with 1,6-enynes (Scheme 42, eqn. 1).[77] While the use of (*R*)-PHANEPHOS as a ligand usually afforded complex mixtures of conventional hydrogenated products, in the

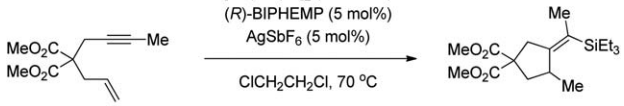


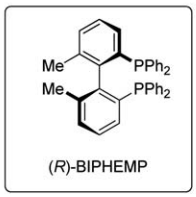
Scheme 39



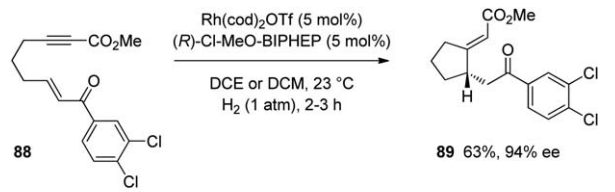


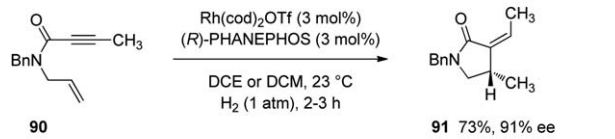
Scheme 40

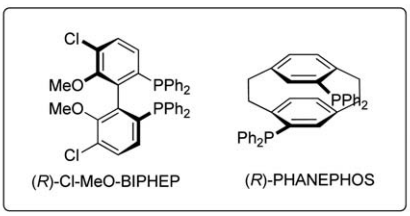




Scheme 41







Scheme 42

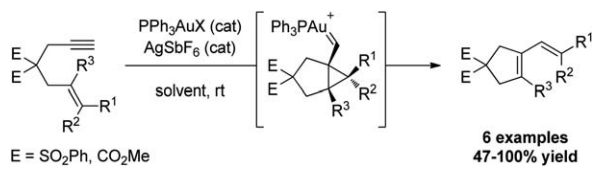
case of propargylic esters and amides the expected cyclic derivatives were formed in high yields and enantioselectivities (Scheme 42, eqn. 2).

3.3 Gold, platinum and copper

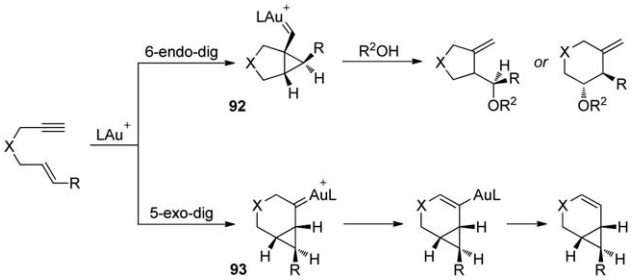
The air and moisture stability of phosphinegold(I) complexes makes them particularly appealing catalysts for synthesis. However, it is the propensity of gold(I) to activate alkynes, coupled with its ability to stabilize carbocation intermediates, that makes it an especially useful catalyst in cycloisomerization reactions.[78] Distinctive carbocyclic products are produced by the reaction of unsaturated substrates with these catalysts.[79] Unlike the Alder-ene type rearrangements observed with palladium and rhodium, in the presence of gold catalysts 1,6-enynes undergo a skeletal rearrangement to give 1,3-diene products in good yield (Scheme 43).

Cationic gold(I)-catalyzed cycloisomerization of 1,5-enynes to [3.1.0]bicyclic products was first reported in 2004,[80] followed by the reported cycloisomerization and methoxycyclization of 1,6-enynes to five-membered products.[81] By changing the reaction conditions, either the skeletally rearranged or methanol-trapped products can be isolated for these substrates. Six-membered products result from the reaction of allyl propargyl ether and amine substrates.[81] The mechanism for gold(I)-catalyzed cycloisomerization is thought to proceed by initial η^2-coordination of the metal to the alkyne followed by attack by the alkene (Scheme 44). The cyclization may occur in either a 5-*exo*-dig, or 6-*endo*-dig manner to generate, metal cyclopropyl carbene complexes **92** or **93** respectively. From intermediate **92**, skeletal rearrangement may form various conjugated dienes. Alternatively, attack of nucleophiles such as alcohols, onto intermediate **92** gives products of alkoxy- or hydroxycyclization (Scheme 44). Products derived from intermediate **93** have been found for substrates where X = O or NTs. In these cases, β-hydrogen elimination followed by protonation gives bicyclo[4.1.0]heptene derivatives. These pathways are distinct from the previously discussed mechanistic processes, where the simultaneous coordination of the metal to the alkyne and the alkene triggers cycloisomerization through metallacyclopentene intermediates.

Chiral bisphosphenegold(I) complexes, where the phosphine : gold stoichiometry is 1 : 1, have been employed in the asymmetric variants of a number of gold-catalyzed transformations. These complexes have a two-coordinate, linear geometry, making it remarkable that such high enantioselectivities are achieved in these processes.[82] An asymmetric variant of the methoxy cyclization of 1,6-enynes was developed by Echavarren and coworkers.[83] A variety of gold complexes were screened, with a (*S*)-Tol-BINAP gold(I) complex providing 94% ee for a single substrate and more modest enantioselectivities for other substrates under the same conditions. Genêt and coworkers developed a related platinum(II)-catalyzed asymmetric alkoxycyclization reaction.[84] Using catalytic $PtCl_2$ with (*R*)-Ph-BINEPINE as ligand in a mixture of dioxane and either



Scheme 43



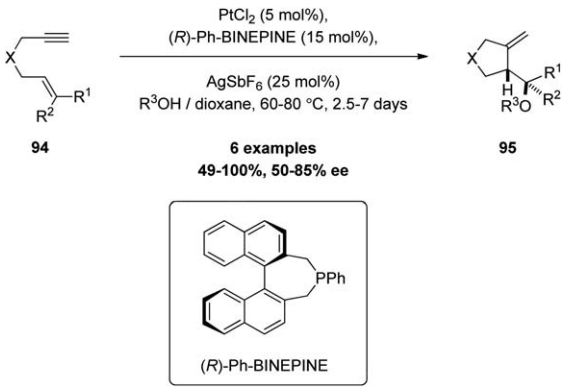
Scheme 44

water or methanol, the cycloisomerizations were performed in a screw-capped tube at 80 °C. Unlike the gold(I)-catalyzed rearrangements, these reactions proceeded over a number of days. Malonate-derived and *N*-tosylated enynes reacted smoothly under these conditions to give functionalized carba- and azacyclic adducts with good yields and moderate to good enantioselectivities (Scheme 45). On the other hand, allyl propargyl ethers lead to a complex mixture of products.

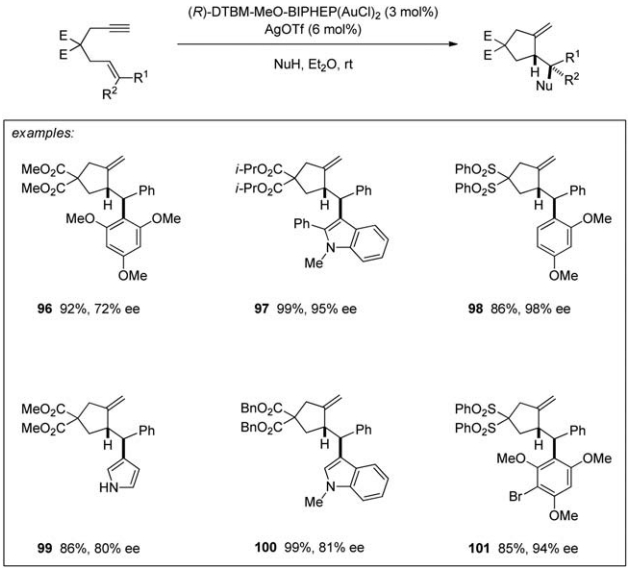
Other nucleophiles may be employed to trap the gold intermediate and Michelet and coworkers reported an asymmetric hydroarylation/cyclization reaction to afford functionalized cyclopentene products.[85] The optimal catalyst was found to be the bulky (*R*)-DTBM-MeO-BIPHEP(AuCl)$_2$ complex with AgOTf in diethyl ether at room temperature. A number of malonate type enynes and different electron-rich aromatic nucleophiles were tested under these conditions (Scheme 46).

Michelet and coworkers have also developed an asymmetric gold(I)-catalyzed intramolecular cyclopropanation reaction.[86] Again (*R*)-DTBM-MeO-BIPHEP(AuCl)$_2$ complex, with AgOTf, as catalyst in toluene at 0 °C provided bicyclo[4.1.0]heptene derivatives (**103**) in high enantioselectivities (Scheme 47). Although enantioselectivities were broadly high, yields were modest, with only one example above 60% yield.

The utility of this approach was shown by its application to the asymmetric synthesis of GSK1360707 (**106**). This antidepressant drug candidate was efficiently synthesized through intermediate **105**, using an asymmetric gold(I)-catalyzed reaction of enyne **104** as the key step. The reaction employed a chiral phosphoramidite ligand to prepare the product **105** in high yield and enantioselectivity (Scheme 48).[87] These ligands have also shown promise in other gold(I)-catalyzed cycloisomerization systems.[88]



Scheme 45

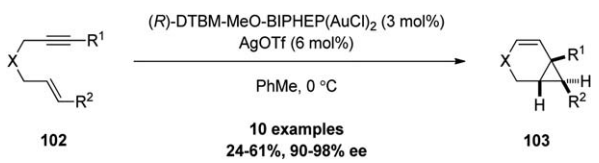


Scheme 46

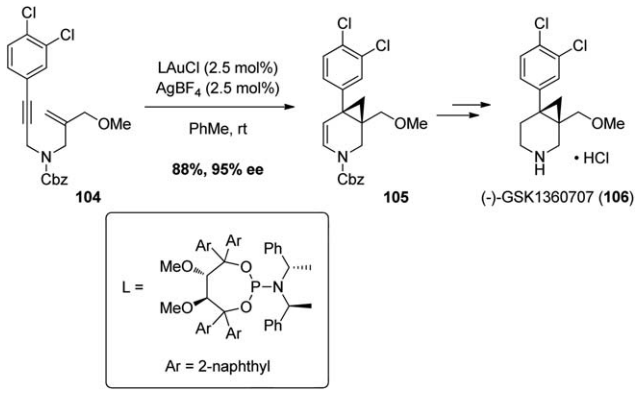
Marinetti and coworkers described an asymmetric intramolecular cyclopropanation reaction using well-defined chiral platinum(II) complexes.[89] These complexes (Scheme 49, **109**, **110**, **111**) contain a six-membered metallacycle made of both an *N*-heterocyclic carbene-platinum and a σ-aryl-platinum bond. Addition of the chiral monodentate phosphine (*S*)-Ph-BINEPINE afforded the cycloisomerization products in good yields and high enantioselectivity (Scheme 49).

Toste and coworkers found that for enynes substituted with an allyl alcohol (**112**) a rearrangement occurs to render tricyclic ring contracted products (**113**). The use of (*R*)-DTBM-MeO-BIPHEP(AuCl)$_2$ as catalyst rendered the reaction asymmetric providing a number of these products in excellent enantioselectivity. The mechanism is proposed to proceed by ring contraction of **114** to aziridinium intermediate **115**, which then rearranges and is quenched by the pendant alcohol (Scheme 50, eqn. 1). The gold carbenoid intermediate **114** can also be trapped by a pendant phenol in enyne **118** to produce **119** in 83% ee (Scheme 50, eqn. 2).[90]

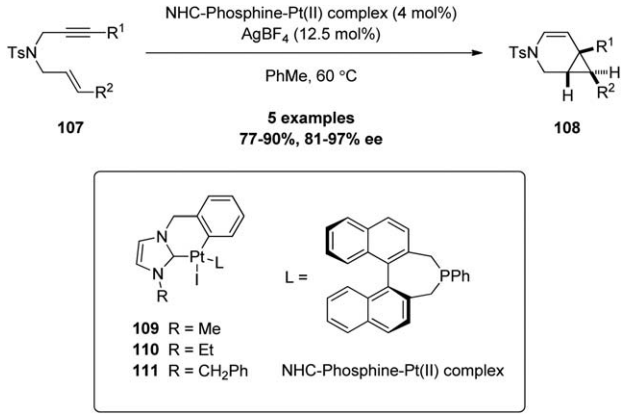
An asymmetric gold(I)-catalyzed synthesis of functionalized indenes was reported Sanz and coworkers.[91] Using *ortho*-alkynylstyrenes (**120**), the reaction proceeded with (*S*)-3,5-xylyl-MeO-BIPHEP(AuCl)$_2$ at −30 °C in dichloromethane. The substrates must be disubstituted at the alkene and an internal alkyne in order to form the desired indene by a 5-*endo*-dig cyclization. In addition to the alkene final products, the exocyclic carbocation that forms from **120** can be trapped by added water or alcohol nucleophiles. The reaction generally provided the



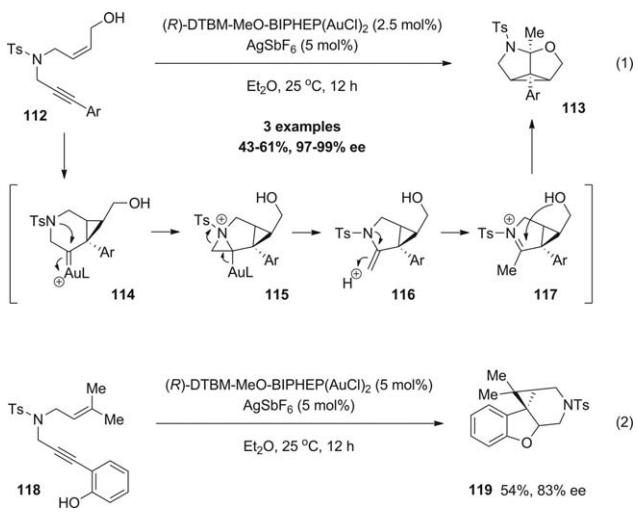
Scheme 47



Scheme 48



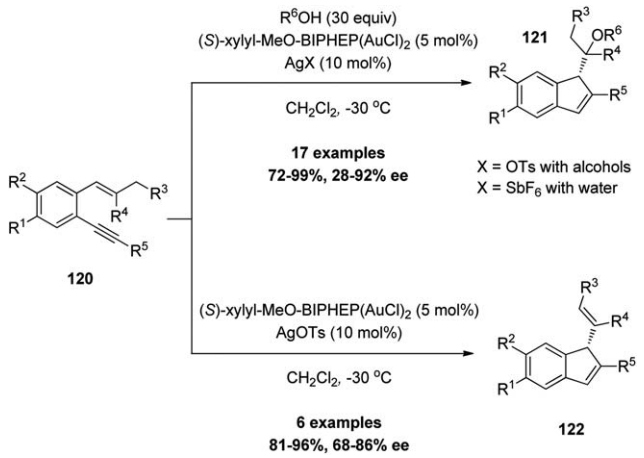
Scheme 49



Scheme 50

functionalized 1*H*-indene derivatives in high yields and enantioselectivities (Scheme 51).

Toste and coworkers have developed an efficient method for the asymmetric gold(I)-catalyzed preparation of medium sized rings.[92] The method provides seven- to nine-membered rings in excellent yield. High enantioselectivities were achieved for seven-



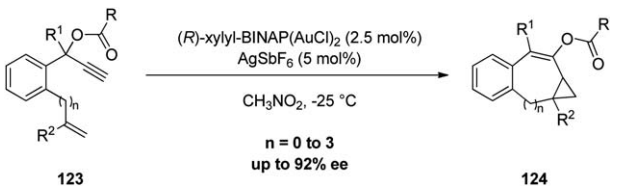
Scheme 51

and nine-membered ring products employing chiral gold(I) complexes (Scheme 52).

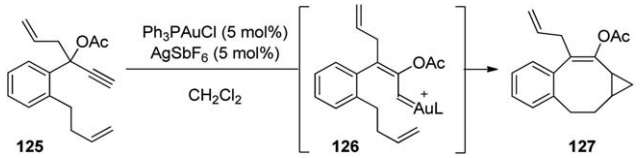
The proposed mechanism of the intramolecular cyclopropanation reaction (Scheme 53) involves coordination of cationic gold(I) to the alkyne followed by a 1,2-shift of the acetate to generate a gold-stabilized vinyl carbenoid (**126**). This intermediate is fluxional and the reaction may operate through either the (*E*)- or (*Z*)-olefin depending on the circumstances. Cyclopropanation of the pendant olefin generates the cyclic system. It is notable that the gold-catalyzed reaction of propargyl ester **125** containing two alkenes selectively afforded the larger eight-membered ring (**127**) over the five-membered ring, emphasizing the remarkable selectivity of the reaction for medium-sized rings.

When Toste and coworkers reacted propargyl esters (**128**) containing pendant allyl ethers, they observed benzopyrans (**129**) as products.[93] When the reaction was catalyzed by (*R*)-DTBM-MeO-BIPHEP(AuCl)$_2$ with AgSbF$_6$ in MeCN, benzopyran products were formed in moderate to good yields and excellent enantioselectivities (Scheme 54). Unlike substrates with all carbon linkers (Scheme 52), the products of intramolecular cyclopropanation were not observed with these systems. The mechanism is thought to proceed by a gold(I)-promoted 1,2-migration of the propargyl ester generating a gold-carbenoid intermediate, that subsequently undergoes nucleophilic attack by the allyl ether to generate oxonium intermediate **130**. The resultant allyl cation is trapped by the chiral allylgold(I) intermediate to generate the stereogenic quaternary center.[94]

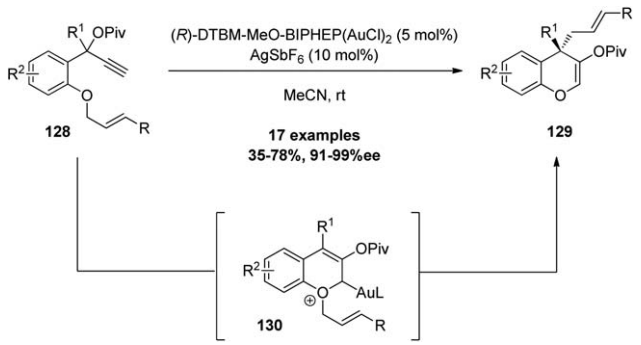
An asymmetric gold(I)-catalyzed polycyclization reaction of 1,5-enynes has been developed by Toste and coworkers.[95] Various nucleophiles were tested as terminating groups including acids, phenols, sulfonamide and aryl groups. In all these examples, excellent yields and enantioselectivities were achieved with



Scheme 52



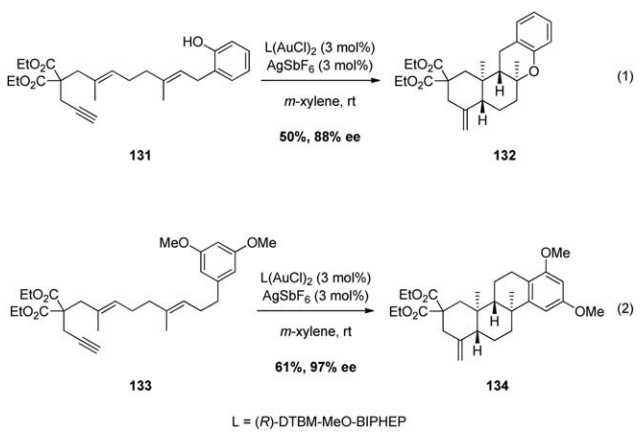
Scheme 53



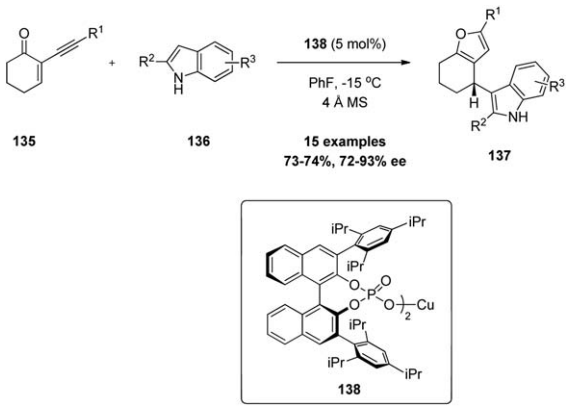
Scheme 54

the product as a single diastereomer. The success of these examples prompted the authors to examine tricyclization reactions. Both phenol **131** and diene **133** reacted smoothly at room temperature to afford tetracyclic products **132** and **134** in 88% and 97% ee, respectively (Scheme 55). These are strikingly successful examples of asymmetric cycloisomerization reactions providing complex cyclic products in remarkably high diastereo- and enantioselectivities.

Recently a unique copper-catalyzed cycloisomerization reaction was disclosed by Toste and coworkers using chiral copper(II) phosphonate catalyst **138**.[96] Heterocyclization of 2-(1-alkynyl)-2-alkene-1-ones (**135**) followed by attack with indole nucleophiles (**136**) generates products with high levels of enantioselectivity (Scheme 56). The reaction is thought to proceed by coordination of copper to the alkyne to initiate cycloisomerization and generate a cationic cuprated furan intermediate. The indole then traps the benzylic carbocation to generate the stereogenic center. Unlike the majority of examples in this review, in this transformation the catalyst is devoid of neutral chiral ligands.



Scheme 55



Scheme 56

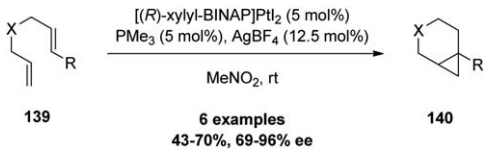
4 Diene cycloisomerizations

4.1 1,6- and 1,7-dienes

The transition metal-catalyzed cycloisomerization of 1,6-dienes is catalyzed by a number of different metals including palladium, nickel, rhodium, ruthenium and titanium. However, there have been relatively few successful enantioselective variants of the transformation. A palladium(II) system with (-)-sparteine and a *bis*-oxazole ligand has been developed, although the enantioselectivities were low (up to 60% ee).[97] A menthylphosphine-modified cationic nickel complex catalyzed the asymmetric cyclization of 1,6-heptadiene and diallylether, but again the enantioselectivity was low (up to 37% ee).[98] Leitner and coworkers have developed a nickel(II) system with an azaphospholene ligand, but only a single substrate was tested under these conditions.[99]

Gagné and coworkers reported platinum(II)-catalysts for diene cycloisomerization. Using (triphos)platinum(II) catalysts, 1,6- and 1,7-dienes reacted to form bicyclopropane products.[100] The key principle that guided the authors' choice of ligands for this reaction was the blocking of sites *cis* to the intermediate alkyl metal species, thereby inhibiting competing β-hydride elimination. In order to transfer the tridentate architecture of the triphos ligands into an asymmetric variant, the authors reasoned that it could be deconstructed into a combination of bi- and monodentate phosphine ligands. The catalyst was generated by adding monodentate phosphine PMe_3 to the chiral precursor, followed by activation with $AgBF_4$ in the presence of the diene substrate. Optimal enantioselectivities were achieved with (*R*)-xylyl-BINAP and in one case (*R*)-SEGPHOS (Scheme 57).

An ionic mechanism is proposed for the reaction, involving carbocation intermediates (Scheme 58). Electrophilic activation of the terminal olefin results in cyclization that forms a carbocation intermediate. The cyclization is known to be reversible



Scheme 57

and studies have shown that several cations are in equilibrium prior to proton transfer.[100b] Indeed, the initial cyclization may proceed by either a 6-*endo*, or 5-*exo* route with the resultant tertiary cation then undergoing a 1,2-hydride shift to generate a 1,3-relationship between the alkyl metal species and cation. Ring closing of this species results in the final cyclopropane product.

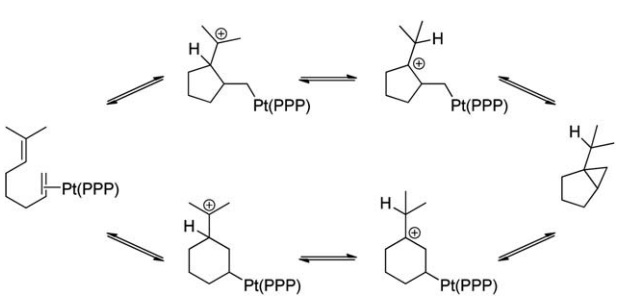
A platinum(II)-catalyzed intramolecular asymmetric hydroarylation has been described by Widenhoefer and coworkers. Indoles (**141**) with pendant alkenes were cyclized to furnish functionalized tricyclic indole derivatives (**142**) with moderate enantioselectivities (Scheme 59).[101] The bulky phosphine ligand (*S*)-DTBM-MeO-BIPHEP was found to be optimal for the transformation. Reactions were performed in MeOH at 60 °C without any special precautions to exclude air or moisture. Interestingly, a 1,7-diene successfully underwent cyclization using this protocol at room temperature to afford the tetrahydrocarbazole product in 74% ee.

Widenhoefer and coworkers developed a highly diastereoselective palladium(II)-catalyzed cycloisomerization-hydrosilylation protocol.[102a] Further development of this method led to an enantioselective variant for the reaction of functionalized dienes into cyclopentane products with excellent diastereo- and enantioselectivities.[102] The products could be isolated as alkyl silanes, or conveniently oxidized into the alkyl alcohols (Scheme 60). A number of palladium complexes containing chiral bidentate nitrogen ligands were screened in the reaction. A complex bearing a pyridine oxazoline ligand (**145**) was found to be an optimal and selective catalyst. The catalyst, activated by $NaBAr_4$ (Ar = 3,5-$C_6H_3(CF_3)_2$), was reacted with the diene in dichloromethane at −20 °C with 3 equivalents benzhydryldimethylsilane. The reaction tolerated both allylic and terminal olefinic substitution.

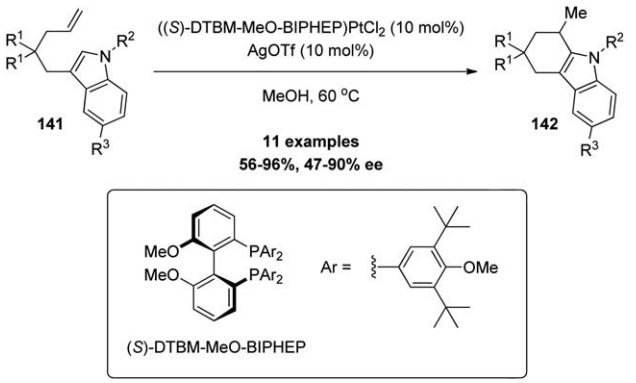
4.2 Ene-allene cycloisomerizations: 1,6- and 1,7-allenenes

The cycloisomerization of tethered ene-allene substrates has been catalyzed with Rh, Pd, Ru and Ni/Cr complexes. These reactions typically form five-membered ring products, although seven-membered rings have also been observed. In a logical progression from their work on diene cyclization reactions,[100] Gagné and coworkers developed a gold(I) catalyst for the cycloisomerization of 1,6-allenenes.[103] Interestingly, unlike the other catalyst systems, gold(I)-catalysts give six-membered vinyl cyclohexenes as products (Scheme 61).

Using chiral gold(I) phosphine complexes, the group found that (*R*)-xylyl-BINAP(AuCl)$_2$ with AgOTf was the optimal



Scheme 58



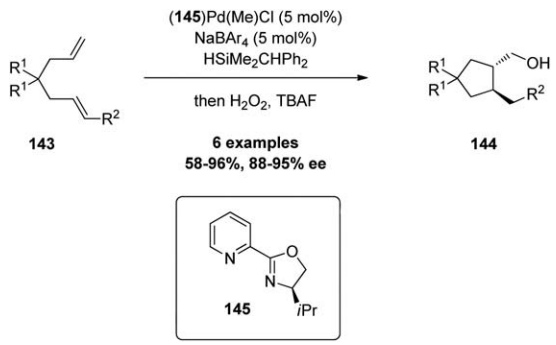
Scheme 59

catalyst for the enantioselective variant. Up to 77% ee could be achieved in this reaction, although isomeric product mixtures often occurred. Overall the enantioselectivities achieved were moderate (Scheme 61). Substrates bearing alkenes that are monosubstituted at the internal position were unreactive. Substitution at the internal position of the allene also led to lower yields and enantioselectivities. The reactions were generally run in $MeNO_2$ at room temperature over 16 h, although a slight improvement in enantioselectivity could be achieved at −12 °C.

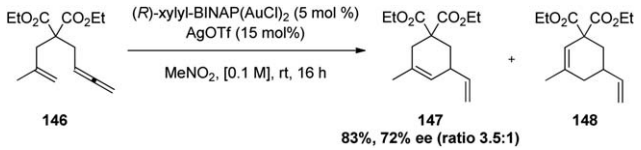
The reaction is thought to occur by electrophilic activation of the internal allene by a cationic gold(I) complex. Nucleophilic attack by the alkene generates a stabilized tertiary carbocation. Elimination and protodeauration completes the formation of the vinylcyclohexene products (Scheme 62).

Interestingly, Toste and coworkers independently developed a similar gold(I)-catalyzed cycloisomerization of 1,6-allenenes. However, these 1,6-allenenes were not internally substituted alkenes, but instead terminal styrene systems that cyclized to alkylidene cyclobutane products. Using the chiral biarylphosphinegold(I) complex (*R*)-DTBM-SEGPHOS(AuCl)$_2$ as catalyst allowed access to highly enantioenriched bicycle-[3.2.0] structures (Scheme 63).[104]

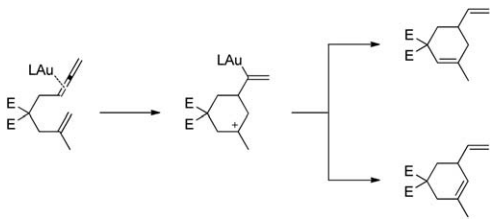
The reaction, a formal [2 + 2]-cycloaddition, is thought to proceed through a series of cationic intermediates in a stepwise process (Scheme 64). Activation of the allene by gold(I) (**151**) initiates cyclization of the system to generate the five-membered cyclopentane ring and a benzylic cation. This cyclization can occur to generate either *cis*- or *trans*-1,2-disubstituted cyclopentanes (**154** or **152**, respectively). Evidence for the reversibility



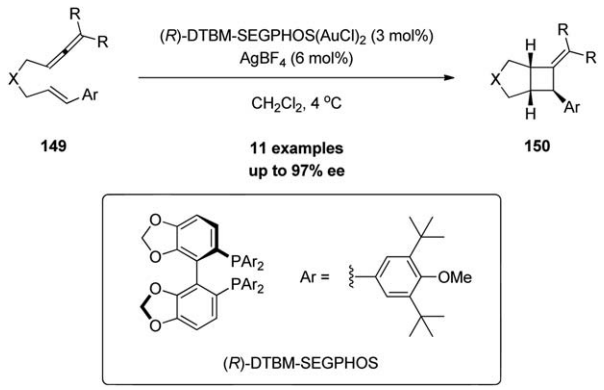
Scheme 60



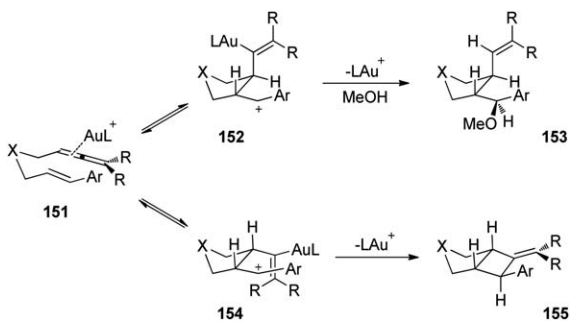
Scheme 61



Scheme 62



Scheme 63



Scheme 64

of the cyclization steps comes from experiments in the presence of MeOH, in which the presumed kinetic cation is trapped to give the *trans*-cyclopentene product (**153**). After cyclization, cyclobutane formation occurs from the reaction of the vinyl-gold species with the benzylic carbocation of the *cis*-species to generate **155**.

Widenhoefer and coworkers developed an intramolecular gold(I)-catalyzed hydroarylation of allenes with indoles for the preparation of tetrahydrocarbazoles (**157**).[105] Again chiral biarylphosphinegold(I) complexes were used for the asymmetric version of the reaction with the bulky (*S*)-DTBM-MeO-BIPHEP(AuCl)$_2$ complex used as the optimal catalyst. The reactions were performed in toluene at −10 °C and were complete in 18–24 h. This method allowed for the synthesis of functionalized tricyclic indole derivatives in good enantioselectivities (Scheme 65). The protocol is similar to another reported by the same authors involving hydroarylation of an alkene;[101] however in this case the product enantioselectivities are improved.

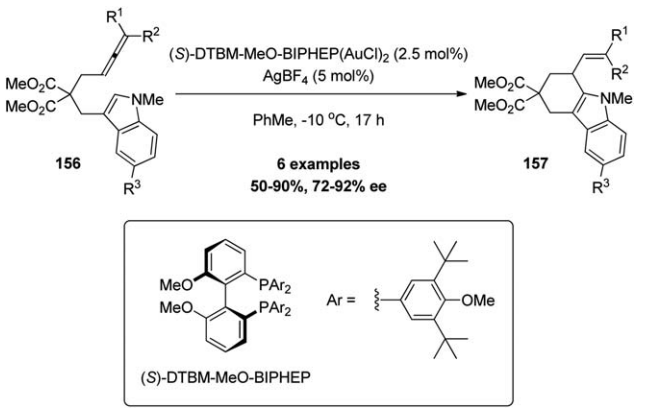
5 The carbonyl-ene reaction

The ene-reaction tolerates a wide number of variants in terms of the enophile used (see Scheme 21). When a carbonyl group is used as the enophile, the reaction is often called the carbonyl-ene reaction.[106] Large numbers of intermolecular diastereo- and enantioselective variants of the carbonyl-ene reaction have been developed. However, there have been relatively few asymmetric intramolecular versions of this reaction disclosed (Scheme 66).[107]

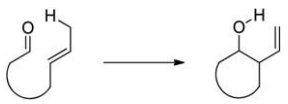
Early approaches used stoichiometric amounts of chiral Lewis acids. For example, 3-methylcitronellal cyclized in 90% ee using a zinc-BINAP reagent (3 equiv),[108] while a titanium catalyst with a tartrate-derived diol as ligand (1.1 equiv) promoted the cycloisomerization reaction of an oxazoline derivative of 2,8-dienoic acid in greater than 98% ee.[109] The use of chiral europium Lewis acid complexes gave low enantioselectivities (20 to 38% ee) for the carbonyl-ene cyclization of a key intermediate in the synthesis of anguidine, a trichothecene natural product.[110]

Mikami and coworkers developed a chiral titanium perchlorate-BINOL system for the cyclization of α-alkoxy aldehydes.[111] The reaction produced the *trans*-substituted six-membered ring preferentially in moderate enantioselectivities for the two substrates that were tested (**158** and **161**, Scheme 67, eqn. 1). When the olefin was substituted at the internal position (**164** and **166**) the sense of cyclization switches and a seven-membered ring alcohol is formed (**165** and **167**) in good enantioselectivity (Scheme 67, eqn. 2).[111]

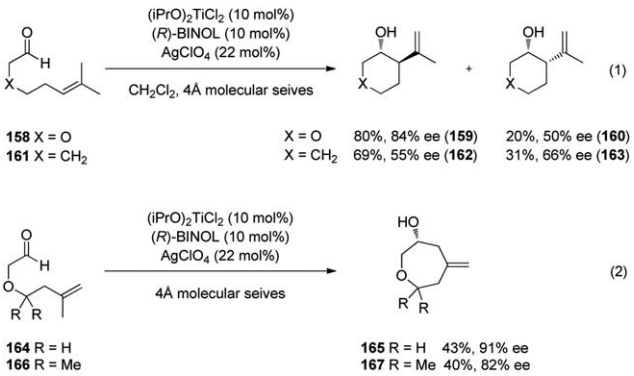
The Yang group reported a Lewis acid catalyzed cyclization of α-keto esters to cyclic alcohol products. In the absence of catalyst, these reactions proceeded at high temperature over several days. After examining different combinations of Lewis acid and chiral BOX-ligand, the authors found that copper(II)-Ph-BOX was an effective catalyst for the cyclization of a number of α-ketoesters.[112]



Scheme 65



Scheme 66



Scheme 67

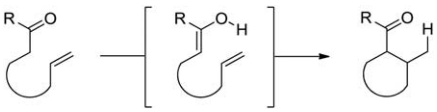
6 The Conia-ene reaction

The thermal cyclization of ketones onto a tethered alkene or alkyne is known as the Conia-ene reaction.[113] The reaction is a variant of the ene-reaction, and is thought to occur as a six-electron process, involving an enol hydrogen shift, followed by a concerted cyclization (Scheme 68). Catalysis with transition metals allows the reaction to operate at much lower temperatures.

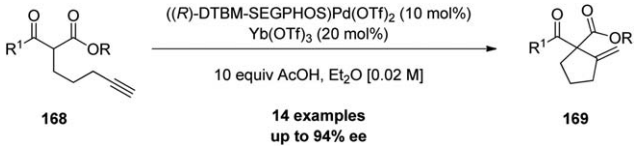
The reaction can be rendered asymmetric by use of a bis(triflate)-palladium(II) complex with (*R*)-DTBM-SEGPHOS although initially yields were low. Optimal conditions were found by the addition of both 10 equivalents of acetic acid and $Yb(OTf)_3$ (20 mol%). In this way, β-ketoesters can be cyclized onto alkynes to form α-vinylated ketone products (**169**) in both high yields and enantioselectivities (Scheme 69).[114] The reaction worked well on a range of β-dicarbonyl compounds and is thought to occur by the generation of a palladium enolate that undergoes Lewis acid promoted addition to the alkyne.[115]

A different approach was undertaken by Dixon and coworkers, who developed a cooperative catalyst system for the asymmetric Conia-ene reaction.[116] Reaction of β-ketoesters with a combination of copper(I) triflate and cinchona-derived urea catalysts provided the cyclized products in good to excellent enantioselectivities. Both components were required for catalytic activity; no background reaction was observed with either independently.

Toste and coworkers have also reported a series of methods for the enantioselective cyclization of silyloxy-1,6-enynes to functionalized methylene cyclopentane adducts. Two different, but



Scheme 68



Scheme 69

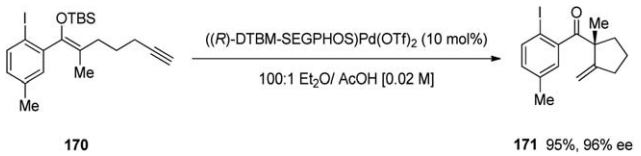
complementary catalyst systems were found with the choice depending on the substitution of the alkyne and the sense of cyclization. Initially the authors optimized chiral phosphine-palladium(II) bis(triflate) complexes for the 5-*exo*-dig cyclization of terminally unsubstituted alkyne substrates. The authors used the palladium-catalyzed cyclization as a key step in the asymmetric total synthesis of (-)-laurebiphenyl, a dimeric cyclolaurane-type sesquiterpene (Scheme 70).[117]

Later the authors found that gold(I) catalysts were preferable for the reaction of terminally substituted alkyne substrates for both 5-*exo* and 5-*endo*-dig cyclizations. Optimal conditions were found using (*R*)-DTBM-MeO-BIPHEP$(AuCl)_2$ and NaBARF as catalyst in dichloromethane or dichloroethane at low temperature to give the cyclopentene products. The use of silyloxy-1,3-dien-7-yne substrates (**172**) under the developed gold(I) conditions allows for an impressive asymmetric cycloisomerization reaction that produces bicyclo[3.3.0]octane ring systems. In this situation the vinyl gold intermediate (**175**) may perform an intramolecular conjugate addition to give gold carbenoid intermediate **176** which after 1,2-hydrogen migration produces the product (Scheme 71). This impressive dicyclization of a linear unsaturated substrate produces the bicyclic products with three contiguous stereocenters in good yield and enantioselectivity.[118]

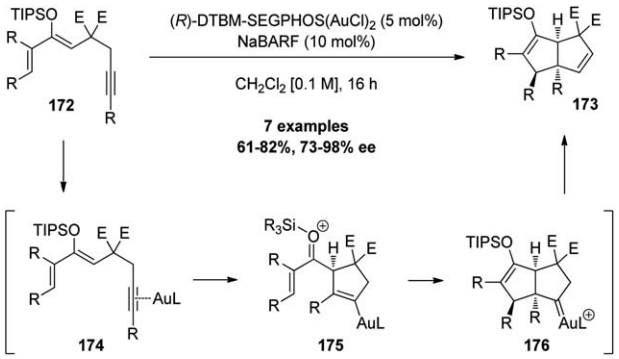
7 Intramolecular cyclization initiated by C–H activation

The addition of an acyl group and a hydrogen atom across an alkene, or an alkyne is a hydroacylation reaction. Early versions were stoichiometric in the transition metal catalyst,[119] but advances rendered a reaction operating with low catalyst loadings, mild conditions and excellent selectivity in both inter- and intramolecular cases.[120] The reaction is thought to initiate by the oxidative addition of rhodium(I) into the C–H bond of an aldehyde. The resultant acylrhodium(III) hydride then coordinates and hydrometalates the alkene. Reductive elimination renders the cyclization complete, forming the cyclic ketone product and regenerating the rhodium(I) catalyst (Scheme 72).

Early approaches toward the development of an asymmetric intramolecular hydroacylation reaction of γ,δ-unsaturated aldehydes gave moderate yields and enantioselectivities of the cyclopentanone products.[121] It was the application of cationic



Scheme 70

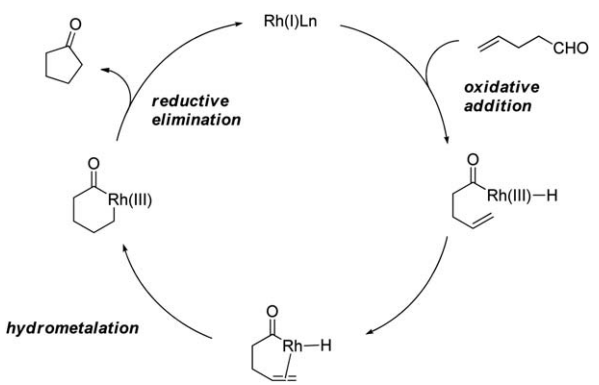


Scheme 71

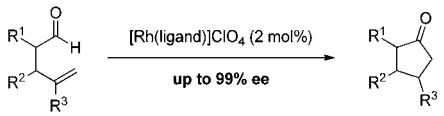
rhodium(I) complexes with chiral phosphine ligands, that allowed for high yields and enantioselectivities to be achieved in the cyclization of 4-pentenals (Scheme 73).[122] The use of (*S*)-BINAP as a ligand gave particularly high enantioselectivities for 4-substituted carbonyl, silyl and tertiary alkyl groups,[122b] while (*S*,*S*)-MeDuphos gave high enantioselectivities for 4-substituted alkyl substrates.[122c,123] Aryl substituted products afforded lower selectivities, from 70 to 75% ee, with (*S*,*S*)-Chiraphos as the optimal ligand.[122b,124] The reaction has also been applied to symmetrical dienes, allowing for enantioselective desymmetrization reactions and leading to the formation of cyclopentanone products with two stereocenters.[125] The cationic [Rh((*R*)-BINAP)]ClO_4 catalyst furnished *trans*-products in good yields and high enantioselectivities. Interestingly, when the neutral complex was used the diastereoselectivity of the process was reversed, and *cis*-products were selectively formed in low yields.

As an extension of this methodology, use of 2-vinylbenzaldehyde substrates in an asymmetric rhodium(I)-catalyzed hydroacylation produces chiral indanones in high yields and enantioselectivities.[126] Substitution was examined at the internal position of the olefin, with alkyl, aryl, and electron withdrawing groups being tolerated (Scheme 74).

Dong and coworkers developed an asymmetric hydroacylation approach for the preparation of medium sized seven- and eight-membered heterocycles.[127] Using *O*-alkylated salicaldehyde-derived substrates (**179**), they found that [Rh((*R*,*R*)-MeDuphos)]BF_4 catalyzed the hydroacylation to the seven-membered products (**180**) with high enantioselectivities and product selectivity



Scheme 72



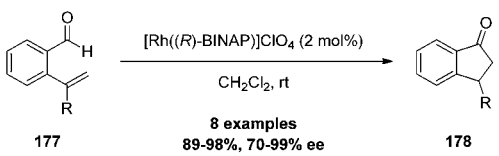
Scheme 73

over the eight-membered regioisomers (Scheme 75). Experiments showed that the efficiency of the reaction relied on coordination of the aryl ether linkage to rhodium to promote hydroacylation over competing nonproductive pathways such as olefin isomerization, aldehyde decarbonylation and catalyst decomposition.

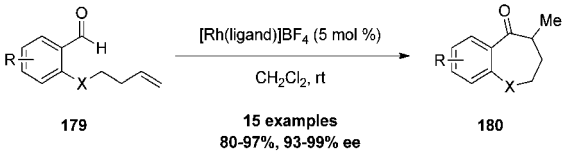
Fu and coworkers have developed a rhodium-catalyzed kinetic resolution of methoxy substituted 4-alkynals for the synthesis of enantioenriched cyclopentenones.[128] A number of terminally substituted 4-alkynals reacted with (*S*,*S*)-*i*Pr-DUPHOS as ligand to give the cyclopentenone product in excellent enantioselectivity, with selectivity factors ranging from 19 to 41 (Scheme 76, eqn. 1). Prochiral diynes also work in this system giving the desymmetrized products in excellent enantioselectivities. The fact that only methoxy substituted substrates give enantioenriched products is attributed to the ability of these substrates to coordinate the chiral rhodium catalysts. Interestingly, switching the ligand to (*S*)-Tol-BINAP results in a striking change in reactivity (Scheme 76, eqn. 1 *versus* 2). In these cases chiral cyclobutanones are also produced by a rare parallel kinetic resolution process.[129]

A cyclization may also be initiated by activation of an arene C–H bond. In this vein, Bergman, Ellman and coworkers have developed a rhodium catalyzed enantioselective cyclization reaction of aromatic ketimines.[130] This imine-directed C–H activation reaction forms a carbon bond between an aromatic ring and a pendant alkene, tethered at the *meta*-position. Substrates reacted to give the functionalized bicyclic products with high enantioselectivities and excellent yields using $[RhCl(coe)_2]_2$ and BINOL-derived phosphoramidite ligands. By fine tuning the *N*-benzyl group, it was found that the inclusion of the electron withdrawing bis(trifluoromethyl)benzyl imine allowed the reaction of aldamine **187** to successfully proceed to dihydropyrroloindole **188** (Scheme 77). This intermediate was then used to complete the asymmetric synthesis of a known protein kinase C inhibitor.[130b] A related asymmetric reaction had been reported earlier by Murai and coworkers,[131] although enantioselectivities were modest.[132]

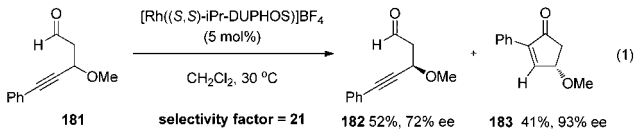
The asymmetric intramolecular hydrosilylation of alkenes is a powerful method for the synthesis of cyclic silanes.[133] These products can then be oxidized stereoselectively to give chiral diols using the Fleming–Tamao oxidation. Reactions are generally run in acetone, with less than 1% intermolecular hydrosilylation of the solvent observed. The silacyclohexyl substituent generally provided the best yields and enantioselectivity. Both the *trans*- or *cis*-cinnamyl substrates (**189** and **191** respectively) gave the same

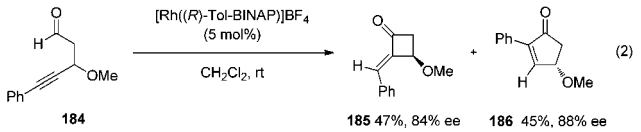


Scheme 74

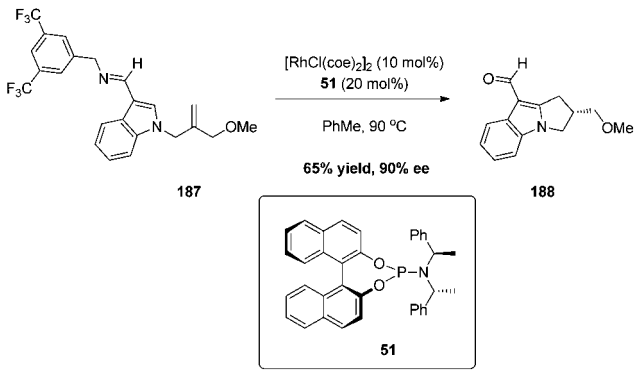


Scheme 75





Scheme 76

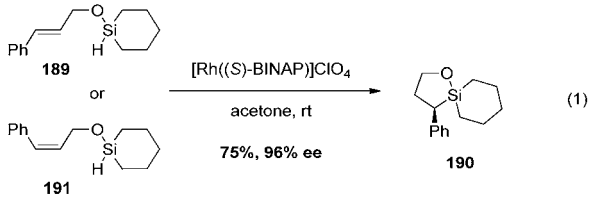


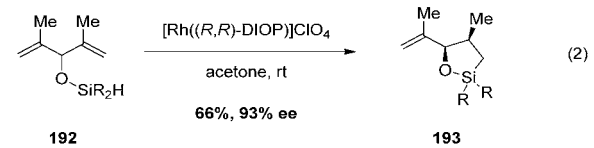
Scheme 77

product (**190**) in identical yield and enantioselectivity (Scheme 78, eqn. 1).[133c,133d] The reaction tended to give the product in good enantioselectivity when the alkene is terminally substituted with an aryl group, or internally substituted with a tertiary alkyl group. The desymmetrization reaction of *meso*-silyl ether **192** with DIOP as ligand proceeded with high enantio- and diastereoselectivity. In this case the sterically crowded 3,5-dimethylphenyl group gave the highest selectivity (Scheme 78, eqn. 2).[133b] Axially chiral spirosilane **194** could be prepared by double intramolecular hydrosilylation of bis(alkenyl)dihydrosilane **195**. Using the SILOP ligand, the C_2 symmetric spirosilane was obtained in excellent enantioselectivity and high diastereoselectivity (Scheme 78, eqn. 3).[133f]

8 Conclusions

The past 20 years have seen remarkable advances in the area of asymmetric cycloisomerization reactions. A breathtaking array of substrates can now be cyclized with excellent enantioselectivity. The power of the developed methodologies can be seen in their increasing use as critical steps in the asymmetric synthesis of complex synthetic targets. Chemists have applied all the tools





Scheme 78

of asymmetric catalysis to these cyclizations, from transition metals to organocatalysts, from chiral ligands to chiral cations, cycloisomerization reactions have served as a testing ground for cutting edge approaches in asymmetric catalysis. The rapid advancements in this area ensure that we will continue to see impressive innovations in the decade to come.

Notes and references

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2 Atom economy refers to the conversion efficiency of a chemical process in terms of the atoms involved. See: (*a*) B. M. Trost, *Acc. Chem. Res.*, 2002, **35**, 695–705; (*b*) B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259–281; (*c*) B. M. Trost, *Science*, 1991, **254**, 1471–1477.

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