CHEMICAL REVIEWS

Review

Silver-Mediated Synthesis of Heterocycles

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Silver-Mediated Synthesis of Heterocycles

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1. Introduction

Heterocyclic synthesis involving transition metal complexes has become of common use in the past decade because a transition-metal-catalyzed reaction can directly build complicated molecules from readily accessible starting materials under mild conditions. In comparison with other transition metals, silver(I) complexes have long been believed to have low catalytic efficiency, and most commonly, they are used as either cocatalysts or Lewis acids. Only recently have Ag-catalyzed reactions emerged as important synthetic methods for a variety of organic transformations. Ag(I) is known to interact with multiple bonds, such as alkenes, alkynes, and allenes. In addition, the use of silver(I) is economic relative to other expensive transition metals.

Efforts in studying homogeneous silver-catalyzed organic transformations have mostly focused on asymmetric catalysis. For instance, Yamamoto and others have developed the Yamamoto−Yanagisawa system [BINAP + silver(I) system] for the enantioselective allylation reactions,[1] and some applications of this methodology to the synthesis of heterocycles are beginning to appear.[2]

The purpose of this article is to summarize those heterocyclizations in which silver salts plays an important role: addition of nucleophiles to alkynes, allenes, and olefins; cycloaddition reactions, with special focus on enantioselective [3 + 2]-cycloaddition of azomethine ylides and nitrilimines, and [4 + 2]-cycloaddition of imines. Silver-catalyzed nitrene-transfer reactions have recently been reviewed[3] and will not be covered here.

2. Ag(I)-Mediated Addition of Nucleophiles to Alkynes

In this section, we have summarized those synthetic methodologies based on the coordination of silver salts with alkynes to form π-complexes. The activation of the alkyne is advantageously employed in cyclization reactions by intramolecular nucleophilic attack.

This synthetic strategy has been used to prepare a large number of *O*-heterocycles and *N*-heterocycles, and most of these rings are incorporated into a great number of physiologically active natural products. The chapter is organized in two sections, the first devoted to the reactions involving an oxygen nucleophile and the second to those with a nitrogen one.

2.1. Oxygen Nucleophiles

As early as 1958, Castañer and Pascual[4] showed that phenylpropargylidene malonic acid (**1**, R = Ph) could be converted to γ-benzylidene−α-carboxibutenolide (**2**, R = Ph) either by thermal isomerization or, more smoothly, in the presence of a silver salt at room temperature (Scheme 1). The reaction was applicable to other aromatic and aliphatic propargylidene malonic acids, and although those

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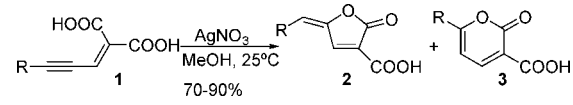
Míriam Álvarez-Corral was born in Granada, Spain, in 1972. She obtained her Ph.D. degree for work on the synthesis of natural products under the supervision of Prof. J. E. Oltra and Prof. A. F. Barrero (University of Granada, 2000). She performed a stay in The Ohio State University with Prof. Leo Paquette, and after a brief period at Instituto Biomar (Spain), she joined Dr. Rodríguez-García's group at the University of Almería, where she is now Profesor Contratado Doctor working on the development of synthetic methodologies for the preparation of biologically active compounds.

Manuel Muñoz-Dorado was born in La Carrasca (Jaén, Spain) in 1964. He studied Chemistry at the University of Granada and received his Ph.D. degree in 1991 under the supervision of Professor A. F. Barrero. During 1992 and 1993, he stayed as postdoctoral fellow in the Institut de Chimie de Substances Naturelles (Gif-sur-Yvette, France) where he worked in the total synthesis of taxol with Professor S. Arseniyadis. In 1994, he arrived at the University of Almería as Profesor Asociado and became Profesor Titular in 1997. His research is focused, at present, on the chemistry of siloxanes or carbenoids towards the synthesis of natural products.

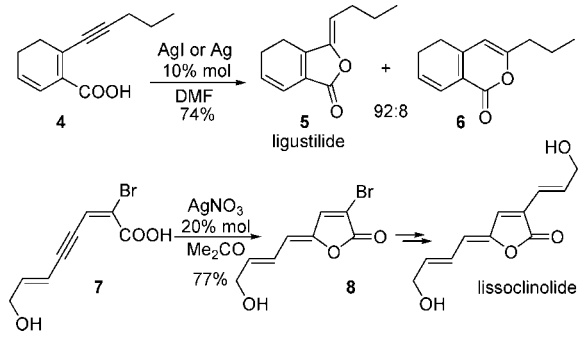
Ignacio Rodríguez-García was born in Granada (Spain) in 1964. He studied Chemistry at the University of Granada where he prepared his doctoral thesis on Chemistry of Natural Products under the supervision of Prof. A. F. Barrero and J. F. Sanchez, receiving the Ph.D. degree in 1991. Next he moved to the United Kingdom and joined S. V. Ley's research group for 1 year of postdoctoral studies on Natural Products Synthesis. He joined the University of Almería (Spain) and became Profesor Titular in 1994. He was a visiting scientist at Imperial College (London, U.K.) collaborating with Dr. S. P. Marsden (1997−1999) in the development of new synthetic methodologies. His present research interests include the utilization of transition metals in organic synthesis and the chemistry of bioactive molecules.

Scheme 1. First Results in the Synthesis of γ-Alkylidenebutenolides



R= Me, *n*-C_4H_9, Ph, *p*-Me-Ph, *p*-MeO-Ph, *p*-Cl-Ph, *p*-NO_2-Ph

Scheme 2. Synthesis of Natural γ-Alkylidene Butenolides



with an aromatic substituent always gave butenolides, their alkyl analogues afforded mixtures of butenolides and α-pyrones in a variable ratio (**3**, R = Me, *n*-C_4H_9).[5]

An increasing number of well stereodefined five-membered lactones have been isolated from natural sources, and many of them have been shown to display a wide number of biological activities. This is why their syntheses have attracted the attention of chemists, and several organometallic methods have been reported using silver and other metals[6,7] following the idea of Castañer and Pascual.

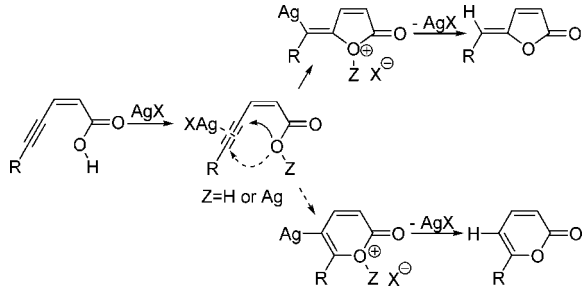
For example, the cyclization of alkynoic acid **4** (Scheme 2) was performed in the presence of catalytic amounts of AgI or Ag to afford the natural product ligustilide (**5**) in good yield and excellent regio- and stereoselectivities.[8] Lissoclinolide, an antibiotic butenolide, has also been synthesized in a stereoselective manner by a reaction sequence in which a key step is the Ag(I)-catalyzed lactonization of the alkyne **7**.[9] The same methodology has been applied to the preparation of ligustilide starting from a structurally close alkyne.[10]

In the former processes, the formation of the six-membered lactone via *endo*-type lactonization is not favored (Scheme 3). At this point, factors affecting the pyranone/furanone ratio are not yet very clear, although it is known that the ratio between the two products is strongly dependent on the substrate structures, the nature of Ag salts, and the solvents.[11]

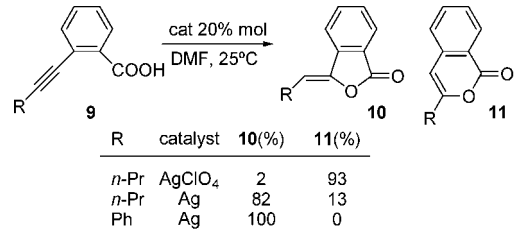
Depending on the substrate, the higher furanone/pyranone ratios can be obtained either with AgI, with Ag in DMF and high dilutions,[6,12] or with Ag_2CO_3 in DMF (Scheme 4).[11]

Besides all these examples in which α,β-unsaturated acids act as nucleophiles, acetylenic alcohols and acetylenic saturated acids have also been used in many cases. The cyclization process proved to be regiospecific as the exocyclic α-methylene heterocycles resulting from an *exo-dig* ring closure were always isolated as single regioisomers (Scheme

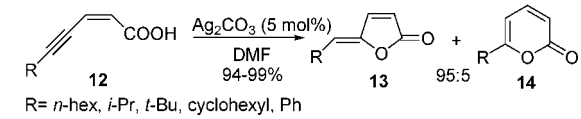
Scheme 3. Postulated Mechanism for the Silver-Catalyzed Cyclization of Alkynoic Acids



Scheme 4. Silver-Catalyzed Cyclization of Alkynoic Acids

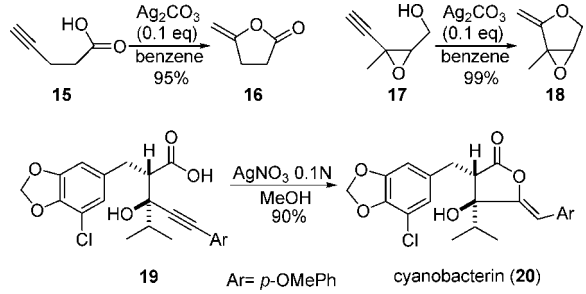


R	catalyst	10(%)	11(%)
n-Pr	$AgClO_4$	2	93
n-Pr	Ag	82	13
Ph	Ag	100	0

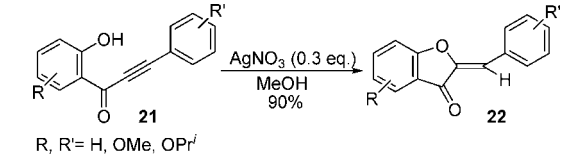


R= *n*-hex, *i*-Pr, *t*-Bu, cyclohexyl, Ph

Scheme 5. Selected Examples of Silver-Catalyzed Cyclizations of Acetylenic Alcohols and Acids



Scheme 6. Silver-Catalyzed Synthesis of Aurones



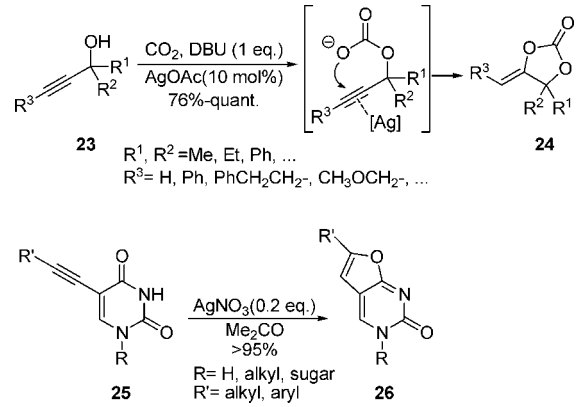
R, R'= H, OMe, OPr^i

5). Some authors reported that silver carbonate in aromatic solvents proved to be the best set of conditions,[13–15] but in other cases, $AgNO_3$ in MeOH was preferred, as in the total synthesis of cyanobacterin (**20**), a natural antibiotic.[16] Furthermore, the presence of an oxygen atom at the propargylic position of these kind of acetylenic alcohols and acids greatly favored their cyclizations.[17]

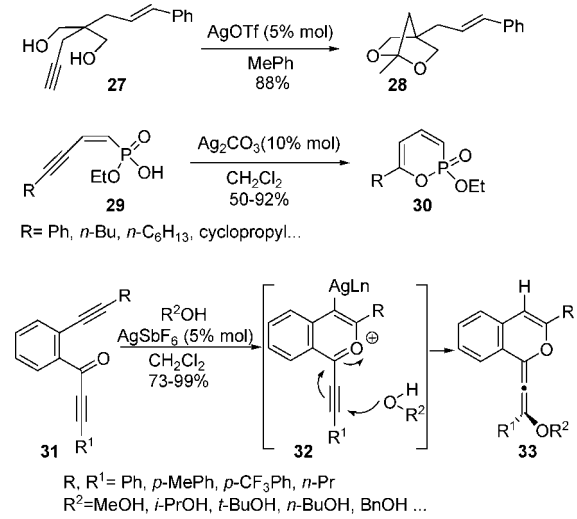
When the intramolecular nucleophile is a phenol, it is possible to prepare aurones (**22**) (Scheme 6) through an efficient and high yielding route, by cyclization of **21** in the presence of a catalytic amount of $AgNO_3$. Only traces of the isomeric flavones were detected.[18]

Cyclic carbonates have also been synthesized using this type of reaction (Scheme 7). The propargylic alcohol **23**, activated by DBU, reacts with carbon dioxide to generate a carbonate intermediate. Then, the intramolecular ring-closing

Scheme 7. Preparation of Cyclic Carbonates and Furanopyrimidine Nucleosides in the Presence of Silver Salts



Scheme 8. Silver-Catalyzed Synthesis of 6-Membered Heterocycles

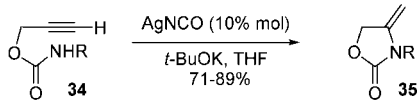


reaction proceeds on the alkyne, which is activated by complexation with the silver cation. Other metals such as rhodium, mercury, platinum, and palladium are inert for the catalysis of this reaction.[19] The versatile use of Ag(I) is also an efficient method for the synthesis of the furanopyrimidine nucleosides **26**.[20,21]

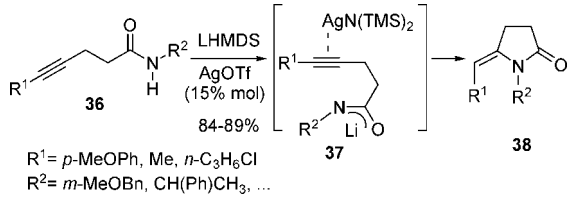
Although the formation of five-membered rings seems to be preferred in most of the silver-catalyzed cyclization of alkynols, conveniently chosen substrates can lead to six-membered heterocycles, as has been shown in recent years. Thus, silver triflate catalyzes the oxacyclization of structurally diverse homopropargylic diols (**27**) (Scheme 8), leading to bicyclic ketals bearing a functionalizable side chain (**28**).[22] Also, several representatives of a novel class of phosphorus heterocycles have been prepared through the intramolecular cyclization of P−OH to substituted alkynes, which leads to 2-ethoxy-2*H*-1,2-oxaphosphorin-2-oxides (**30**).[23]

The silver(I)-catalyzed reaction of alkynones with alcohols has been used as a tool for the synthesis of 1-allenyl isochromenes (**33**). The reaction most probably proceeds through a benzopyrylium cation (**32**), which would be formed by the nucleophilic attack of carbonyl oxygen to the silver-coordinated alkyne. The eventual addition of an alcohol molecule would lead to the formation of the allene system.[24]

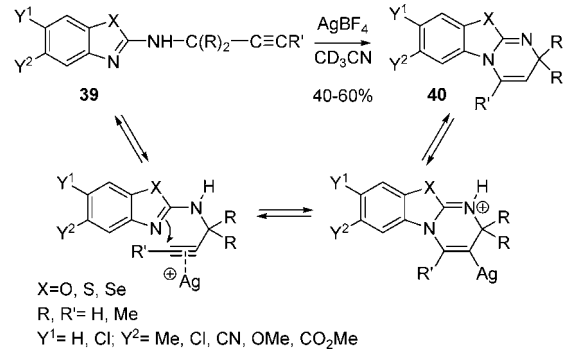
Scheme 9. Silver-Catalyzed Cyclization of *O*-Propargyl Carbamates



Scheme 10. Synthesis of γ-Alkylidene-γ-butyrolactams



Scheme 11. Silve-Catalyzed Rearrangement of 2-(Propargylamino)benzoxazoles, Benzothiazoles, and Benzoselenazoles into Dihydropyrimidines



2.2. Nitrogen Nucleophiles

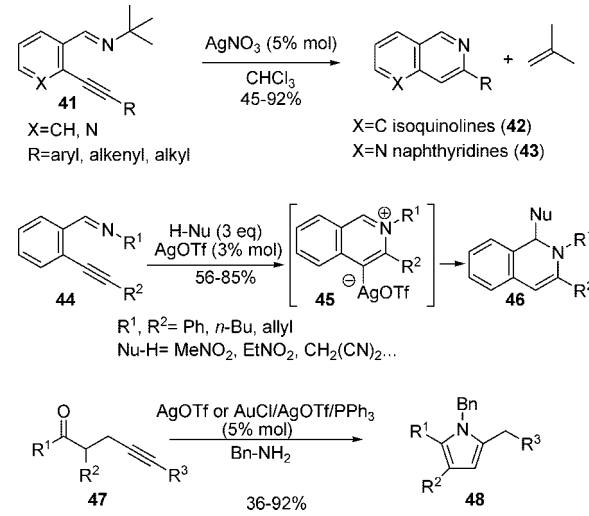
The intramolecular addition of nitrogen nucleophiles to acetylenic triple bonds, giving rise to a variety of *N*-heterocycles, has recently experienced a renaissance in the chemical literature. In contrast with oxygen heterocycles, there are no examples until 1990 when Kimura and co-workers reported that the nitrogen atom of the *O*-propargyl carbamates **34** (Scheme 9) acts as a nucleophile that allows the formation of the 4-methylene-2-oxazolidinones **35**. However, the reaction is highly dependent on the nature of the substituents and needs the catalysis of Cu(I) in some cases.[25]

On the other hand, β-alkynylpropanamides (**36**) can be used in intramolecular cyclizations to efficiently produce alkylidene−γ-butyrolactams (**38**) (Scheme 10). However, basic conditions are required to form the bis-metallated complex (**37**), which undergoes *trans*-aminometalation and protonolysis to eventually produce compound **38**.[26]

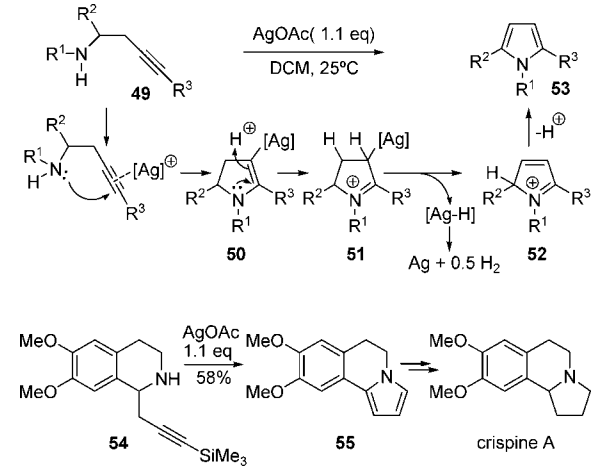
In addition to carbamates and amides, the imino group is another functional group frequently used in these kinds of cyclizations. For example, 2-(propargylamino)benzoxazoles, benzothiazoles, and benzoselenazoles (**39**) (Scheme 11) rearrange in the presence of a catalytic amount of silver salt to give dihydropyrimidines (**40**). An electron-donating group on the benzene ring accelerates ring closure, while an electron-withdrawing group retards it.[27]

The *tert*-butylimines of *o*-(1-alkynyl)benzaldehydes and analogous pyridine carbaldehydes like **41** (Scheme 12) have been cyclized under very mild reaction conditions in the presence of electrophiles such as I_2, ICl, PhSeCl, PhSCl, CuI, and $AgNO_3$. Although the reactions with I_2 and ICl to form

Scheme 12. Different Examples of the Use of Imines in the Syntheses of *N*-Heterocycles



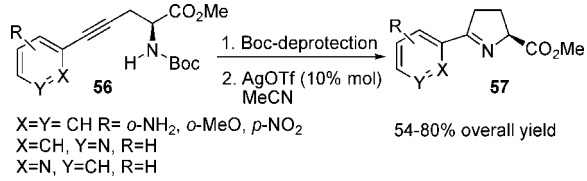
Scheme 13. Proposed Mechanism for Silver-Promoted Cyclization of Homopropargylamines and Synthesis of the Pyrrole Crispine A



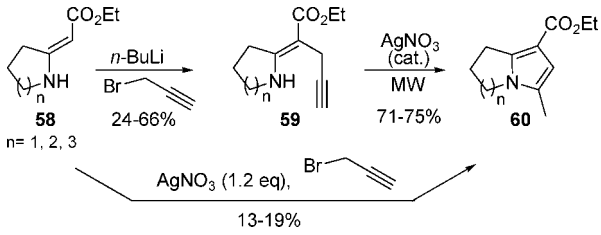
the six-membered ring isoquinolines (**42**) are the fastest, the yields are lower than those obtained when the reactions are catalyzed with $AgNO_3$ or CuI.[28] Also reported has been the synthesis of functionalized 1,2-dihydroisoquinoline derivatives (**46**) through AgOTf-catalyzed addition of carbon pronucleophiles to alkynylaryl aldimines **44**. After coordination of the silver atom to the triple bond, an isoquinolinium intermediate **45** is formed by means of the attack of the imino nitrogen atom to the electron-deficient triple bond. The addition of the nucleophile to **45** gives the desired product **46**.[29] As a last example, either silver or gold catalysts facilitate the intramolecular reaction between imines (formed in situ from **47**) and alkynes to yield functionalized pyrroles (**48**).[30]

Pyrrole annelation has also been achieved by silver-promoted oxidative cyclization of homopropargylamines (**49**). The proposed mechanism is represented in Scheme 13: the coordination of the alkyne to the silver cation initiates a nucleophilic attack of the amine to the alkyne, leading to intermediate **50**. Protonation of **50** affords the iminium ion **51**, which on subsequent β-hydride elimination generates the pyrrylium ion **52** and metallic silver. Finally, proton loss of **52** provides pyrrole **53**.[31] The same authors have applied this cyclization to the synthesis of the antitumor active alkaloid crispine A using alkyne **54**.[32]

Scheme 14. Synthesis of 2,5-Disubstituted Pyrrolines



Scheme 15. Preparation of *N*-Bridgehead Pyrroles



Enantiomerically pure 2,5-disubstituted pyrrolines (**57**) can be obtained from enantiopure arylsubstituted acetylene-containing amino acids (**56**) (Scheme 14).[33] The evaluation of several metal catalysts showed that AgOTf leads to a rapid 5-*endo-dig*-cyclization of the substrates. The yields are higher than when the process is catalyzed by other metals. The pyrrolines thus obtained can be easily converted into the corresponding 5-substituted proline analogues.

Functionalized pyrroles can be efficiently prepared using a two-step sequence: propargylation of secondary enaminones using *n*-BuLi and propargyl bromide and an intramolecular hydroamination catalyzed by silver nitrate (Scheme 15). The hydroamination can be carried out at room temperature (overnight) or in a domestic microwave oven (60 s).[34] The one-pot synthesis required equimolecular amounts of silver salts and did not generate high enough yields to be synthetically useful.[35,36] The methodology was extended to the preparation of *N*-bridgehead pyrroles (**60**).[37]

3. Ag(I)-Mediated Addition of Nucleophiles to Allenes

The utility of allenes in metal-catalyzed addition reactions has made these intermediates increasingly popular in organic synthesis.[38] Silver(I) is well-known to be an electrophilic trigger for allene cyclization with *O*- and *N*-nucleophiles. In this context, allenes parallel closely alkynes in their reactivity toward Ag(I)-mediated nucleophilic additions. However, unlike alkyne substrates, allenes offer the potential of axial chirality to allow enantio- and diastereoselective reactions. As in the previous section, references have been divided in two main groups: cyclizations with an *O*-nucleophile and those with an *N*-nucleophile.

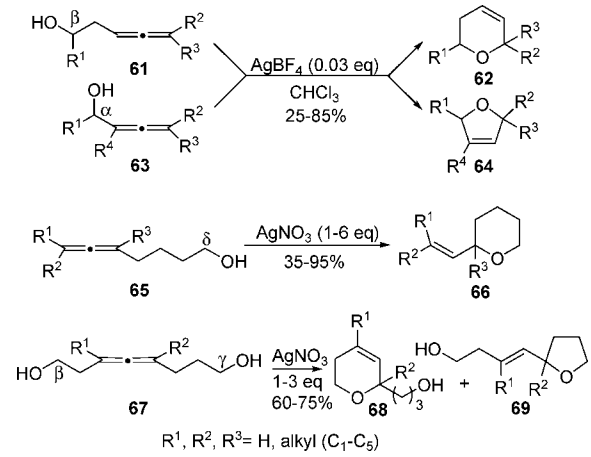
3.1. Oxygen Nucleophiles

Substituted tetrahydrofurans and dihydrofurans are useful synthetic intermediates and also important structural elements in natural products (like polyether antibiotics, polyene mycotoxins, macrolides, etc.). These facts stimulate a great interest for the development of general sterocontrolled routes to such compounds, and the use of alcohols, ketones, and acids, as nucleophiles, has extensively been described.

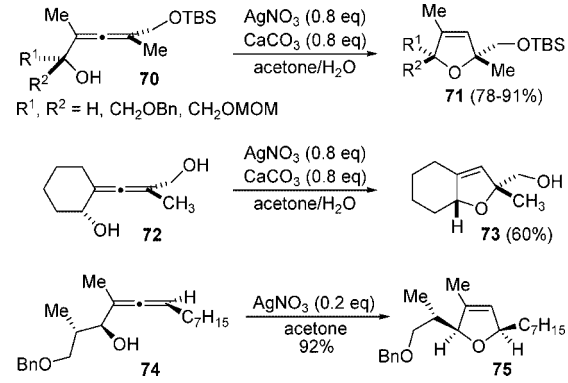
3.1.1. Allenic Alcohols

In 1979, Olsson and Claesson reported that 5,6-dihydropyran (**62**) and 2,5-dihydrofurans (**64**) were prepared by

Scheme 16. First Examples of Allene Cyclizations Using Alcohols as Nucleophiles



Scheme 17. Stereospecific Synthesis of Dihydrofurans



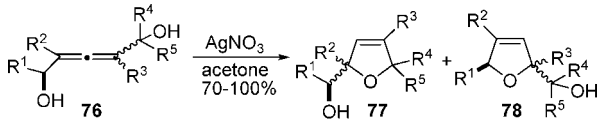
6-*endo-trig*-cyclization of β-allenic alcohols (**61**) and 5-*endo-trig*-cyclization of α-allenic alcohols (**63**), respectively (Scheme 16).[39] Some years later, an experiment was published where δ-allenic alcohols (**65**) suffer 6-*exo-trig*-cyclizations in the presence of silver nitrate to yield 2-alkenyl tetrahydropyranes (**66**).[40] On the other hand, β,γ'-allenic diols (**67**) were selectively converted into dihydropyrans (**68**) when R^1 was an alkyl group and into an equimolecular mixture of **68** and **69** when R^1 was hydrogen.[41]

Since these first results, a large number of examples of α-allenic alcohol stereospecific cyclizations have arisen, many of them published by Marshall and co-workers. Their earlier results are summarized in Scheme 17.[42] When a 1:1 mixture of diastereomers of the allenylcarbinols **70** is used, an identical ratio of dihydrofuran diastereomers **71** is formed, through a highly stereoselective and stereospecific process. With α,α′-allenic diols like **72**, cyclization of the secondary alcohol is favored, possibly because of the preferential complexation of Ag^+ at the less congested end of the allenyl π-system.[42]

Marshall and co-workers have also reported the enantioselective synthesis of the allenylcarbinols **74** (Scheme 17). These enantiopure compounds can be stereospecifically converted into the corresponding *cis*-2,5-dihydrofurans upon treatment with catalytic $AgNO_3$ in acetone.[43,44]

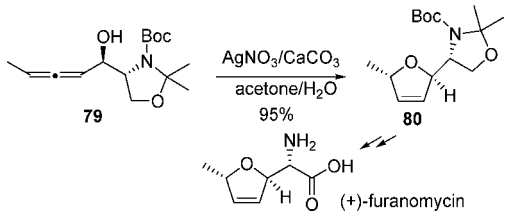
The silver(I)-promoted cyclization of the α,α′-allenic diols **76** (Scheme 18) containing different combinations of primary, secondary, and tertiary hydroxyl groups has been described. The reaction displays a preference for cyclization through the more hindered tertiary hydroxyl group to form **77**.[45] This is in agreement with the preference for the

Scheme 18. Silver (I)-Promoted Cyclization of α,α′-Allenic Diols



R^1	R^2	R^3	R^4	R^5	77/78
$(CH_2)_4$		H	$(CH_2)_5$		1/0
$(CH_2)_4$		H	Me or Et		1/0
$(CH_2)_4$		Me	$(CH_2)_5$		3.7/1
n-Hex	H	H	Et	Et	6.7/1

Scheme 19. Key Step in the Synthesis of (+)-Furanomycin



cyclization of secondary over primary hydroxyl groups previously described (**72** → **73**).[42] However, in this case, the authors suggest that the origin of this preference probably lies on the selective formation of the Ag(I)−allene complex, which best accommodates both the positive charge and the steric requirements of the allene terminus.[45]

Recently, this methodology has been used to prepare some natural products. For example, Ag^+-mediated cyclization of the allenic alcohol **79** is a key step in the synthesis of (+)-furanomycin, an isoleucine analog (Scheme 19).[46]

Metabolites belonging to the amphidinolide class, like amphidinolide X (**81**) and Y (**82**) (Figure 1), exhibit potent cytotoxic properties and, besides their activity profile, present a rather unique structure. The use of a chiral allene as latent progenitor of the tetrahydrofuran ring of these molecules is critical and is, therefore, addressed in an early stage of the synthesis. Once enantiopure allenes are obtained, they are treated with $AgNO_3/CaCO_3$ in aqueous acetone to afford the corresponding tetrahydrofurans with strict chirality transfer.[47,48]

Alcaide and co-workers have achieved $AgNO_3$-induced reaction of chiral α-allenols (**83**) to give spirocyclic dihydrofurans (**84**) in quantitative yields and with concomitant acetonide cleavage (Scheme 20). This spiranic *β*-lactam moiety is present in several marine natural products.[49]

3.1.2. Allenic Aldehydes and Ketones

In 1990, Marshall and co-workers published that, upon treatment with $AgNO_3$ or $AgBF_4$, allenals (**85**, R^1 = H) and allenones (**85**, R^1 = alkyl) afford furans (**86**) (Scheme 21).[50] This author has developed this methodology and published many applications, always trying to improve the experimental conditions. The best set of conditions can be $AgNO_3/CaCO_3$/acetone/water[51] or 10% $AgNO_3$ on silica gel and hexane.[52] The following reaction pathway has been proposed: the process is initiated by coordination of Ag(I) with the allenyl *π*-system. Attack by the carbonyl oxygen would lead to the oxo-cation **87**. Ensuing proton loss from cation **87** would result in the Ag(I)−furan intermediate **88**. This could undergo direct protonolysis with loss of Ag(I) to afford furan product **86**. Deuterium incorporation experiments support this mechanism.[53] It is important to point out that the choice of the transition-metal catalyst is crucial to form this kind of substituted furans, because, under similar conditions, allenic ketones delivered different products when catalyzed by Pd(II) or Hg(II).[54]

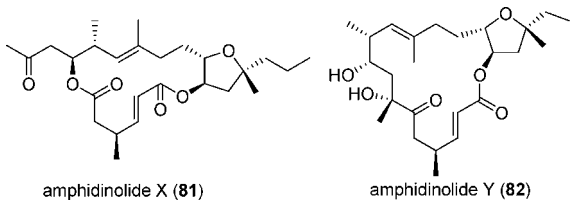
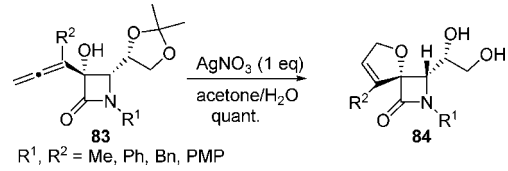
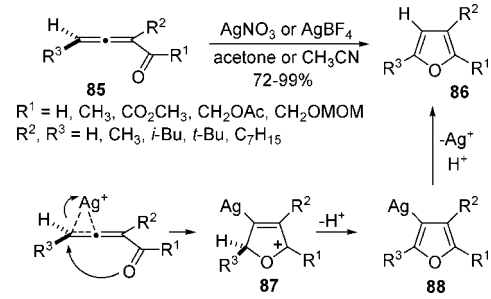


Figure 1. Natural compounds with a tetrahydrofuran segment prepared via allenes.

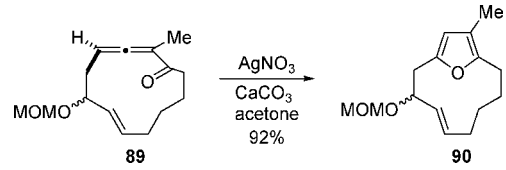
Scheme 20. Preparation of Enantiopure Spirocyclic Dihydrofurans



Scheme 21. Proposed Mechanism for Allenones Ag(I)-Catalyzed Cyclization



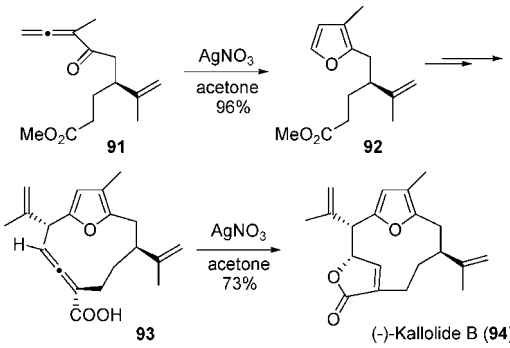
Scheme 22. Synthesis of 2,5-Bridged Furanomacrocyclic Compounds



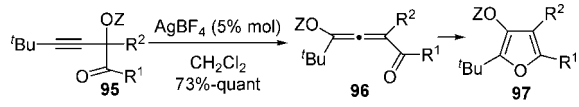
The successful preparation of furans like **86** suggested that this allenone cyclization could be applied to the synthesis of 2,5-bridged furanomacrocyclic compounds (**90**) (Scheme 22). Previous approaches to these compounds have experienced difficulties to achieve the ring closures, owing to the chemical reactivity and stereochemical constraints engendered by a preformed furan moiety. Marshall's approach defers introduction of the furan until macrocyclization has been effected.[55]

Kallolide B (**94**) is a furanocyclic pseudopterane diterpene, which structure presents a 2,5-bridged furane moiety similar to that in **90**, together with a bridged butenolide (Scheme 23). An elegant synthesis was developed that involved the use of allenones Ag(I)-catalyzed cyclization (**91** → **92**) (Scheme 23), together with an extension of the Ag^+-catalyzed synthesis of 2,5-dihydrofurans from allenylcarbinols (Scheme 17) to the bridged butenolide moiety from a chiral allenic acid (**93** → **94**).[56,57] Other furanocyclic metabolites of this rare pseudopterane family like (+)-kallolide A and (−)-deoxypukalide have been prepared using this synthetic sequence.[58,59]

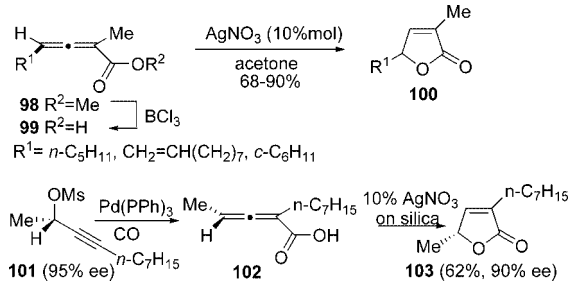
Scheme 23. Synthesis of (−)-Kallolide B



Scheme 24. Migrations on Allenyl Systems Leading to Furans



Scheme 25. Synthetic Routes to Butenolides



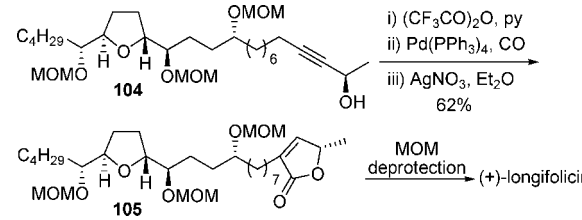
A novel 1,2-migration of the acyloxy, phosphatyloxy, and sulfonyloxy groups in the allenyl system has also been reported (Scheme 24). This unprecedented migration, included in the cycloisomerization reaction, is the key step in an efficient synthesis of valuable tri- and tetrasubstituted furans (**97**).[60]

3.1.3. Allenic Acids

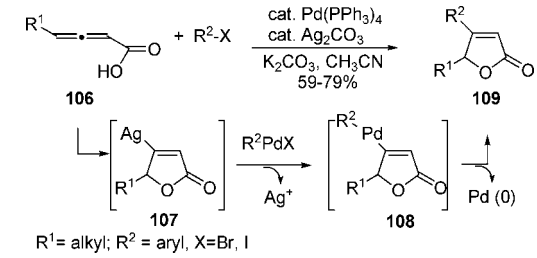
Recently, much attention has been paid to the synthesis of butenolide-containing natural products, which exhibit some interesting biological activities. Besides other strategies, allenic acids can be smoothly converted to butenolides, as previously described in the synthesis of kallolide B. In this way, racemic butenolides (**100**) (Scheme 25) were efficiently prepared from esters **98** trough treatment with BCl_3 and exposure of the derived acid **99** to catalytic $AgNO_3$. However, the application of this route using nonracemic allenic acids as precursors, to form enantioenriched butenolides, proved to be troublesome because of a significant decrease in enantiomeric excess. Therefore, an alternative two-step conversion was developed by sequential Pd-catalyzed hydrocarbonylation of a chiral homopropargylic mesylate (**101**) and Ag^+-catalyzed cyclization of the intermediate allenic acid (**102**).[61]

The total synthesis of the enantiomer of the marine furanocembrane rubifolide has been achieved by using this procedure.[62] In order to avoid the lability of the mesylate under the conditions of its formation and isolation, the entire sequence from alcohol to butenolide is best performed without isolation of any intermediate.[62] The synthesis of the

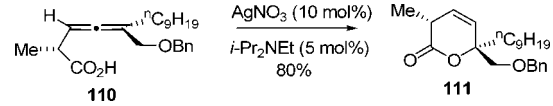
Scheme 26. Preparation of Butenolide Moiety of (+)-Longifolicin



Scheme 27. Pd(0)/Ag(I)-Cocatalyzed Synthesis of Butenolides



Scheme 28. Syntheis of δ-Lactone (111)



butenolide moiety present in (+)-longifolicin skeleton is also possible following the same procedure (**104** → **105**) (Scheme 26).[63]

Pd(0)/Ag(I) cocatalyze cyclizations of aryl halides with 1,2-allenic carboxylic acids (**106**). A plausible mechanism is shown in Scheme 27: Ag(I) forms a 3-silver-2-butenolide intermediate (**107**), which undergoes a transmetalation reaction with R^2PdX followed by reductive elimination to afford butenolide **109**.[64]

In addition to α-allenic acids, β-allenic acids (**110**) can also be used, and in this case δ-lactones (**111**) are obtained (Scheme 28). Electrophilic activation of the trisubstituted allene engaged the carboxilic acid in a 6-*endo-trig*-cyclization. This path is preferred to the competitive 5-*exo-dig* pathway, owing to the enhanced stabilization provided by the developing positive charge at the disubstituted allene terminus in the transition state, and eventually leading to the δ-lactone. This reaction belongs to an efficient asymmetric synthesis of the naturally occurring antibiotic (−)-malyngolide.[65]

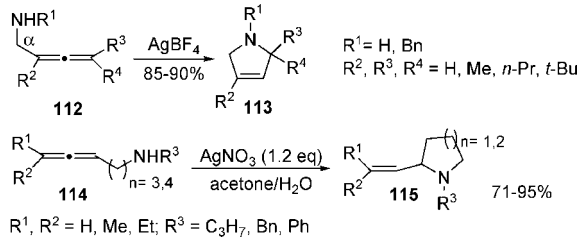
3.2. Nitrogen Nucleophiles

The C−N formation by addition of a nitrogen atom to allenic π-bonds has been extensively used. Introduction of an amino group in the proper position and with the desired stereochemistry is a challenge for the synthesis of natural products such as alkaloids or amino acids. Many transition metal salts have been examined in promoting this reaction, and Ag(I) has been successfully used with different *N*-functional groups.[66]

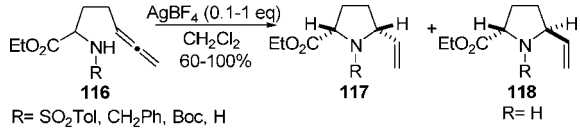
3.2.1. Allenic Amines

At the same time as was demonstrated the utility of Ag(I)-induced cyclization of allenic alcohols to synthesize *O*-heterocycles, the more reactive nitrogen analogs were also tested and successfully converted in Δ^3-pyrrolines (**113**)[67]

Scheme 29. First Examples of Allene Cyclizations Using Amines as Nucleophiles



Scheme 30. Stereoselectivity in the Synthesis of 2,5-Disubstituted Pyrrolidines



R	117:118	yield%
SO_2Tol	>50:1	100
CH_2Ph	>50:1	93
Boc	>50:1	70
H	1:1	60

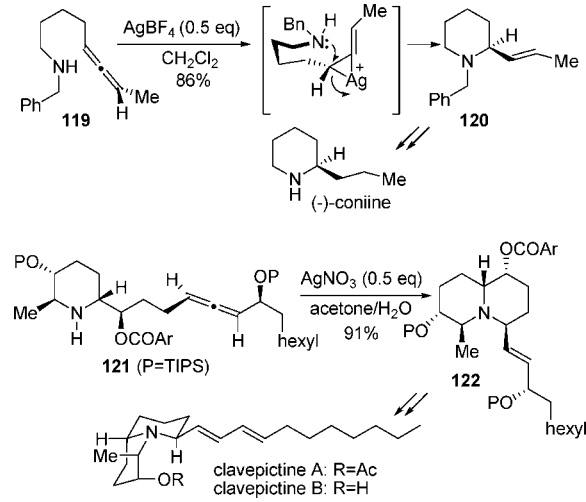
and 2-substituted pyrrolidines (**115**, $n = 1$) or piperidines (**115**, $n = 2$) (Scheme 29).[68,69] Compounds like **115** offer an alkenyl substituent in the heterocycle, which provides a high degree of functionality and the possibility to exploit this residue to manipulate the heterocycle at a later stage. These types of allenic amines smoothly cyclize under very mild reaction conditions and are free from the problems associated with equilibration by the ring-opening/ring-closure observed in the case of the alkene-based methods.

Considerable attention has been focused on the stereochemistry of this reaction leading to *cis*- and *trans*-2,5-disubstituted pyrrolidines (Scheme 30). High stereolectivity was observed for the cyclization of secondary amines, carbamates, and sulfonamides (**116**) (R ≠ H), which selectively affords substituted *cis*-pyrrolidines (**117**). However, the primary amine **116** (R = H) yielded equal amounts of the two isomers **117** and **118**.[70]

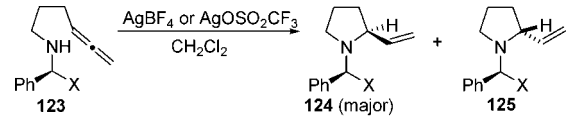
Gallagher and co-workers have extensively studied the use of an enantiopure allene residue in this strategy, specially for the asymmetric synthesis of alkaloids. They have demonstrated that the use of silver(I) as electrophilic reagent is compatible with the transfer of chirality during the cyclization step and proposed a disymmetric silver allene complex as an intermediate (Scheme 31).[71] Thus, chiral allene **119** can be used to prepare the alkaloid (−)-coniine through piperidine **120**.[71] The stereocontrolled total synthesis of (−)-clavepictine A and (+)-clavepictine B has been also developed. The pivotal step in the synthesis of these quinolizidine alkaloids is again a diastereoselective silver(I)-promoted cyclization of δ-amino allenes.[72]

Significant progress has also been made on the control of the orientation of the new stereocenter that is generated in the cyclization step, with respect to other substituents present on the newly formed heterocycle. In this way, a series of optically active allenic amines (**123**) have been prepared to be used in Ag(I)-mediated cyclizations, achieving good levels of asymmetric induction (Scheme 32).[73–75] This process has the advantage that the control element can, in principle, be removed from the reaction products **124** and **125**, to afford enantioselectively the corresponding pyrrolidines. The best results are obtained with sulfide and sulfoxide ligands (entries

Scheme 31. Asymmetric Syntheses via Allenes



Scheme 32. Asymmetric Synthesis of Functionalized Pyrrolidines



entry	X	mol%Ag	% d.e.	yield
1	Me	46	33	87
2	CH_2OH	15	60	90
3	CONHMe	50	81	90
4	CH_2NHMe	45	78	63
5	CH_2SPh	100*	96	90
6	$CH_2S(O)Ph$	98*	99	90

* Solvent $ClCH_2CH_2Cl$.

5 and 6, Scheme 32). However the observed diastereoselectivity is markedly influenced by changes in Ag(I) concentration and, to a lesser extent, changes in solvent.[75]

The interaction between Ag(I) and the allenic amine is likely to lead to a Ag(I)/π-complex through face-selective addition of metal cation to the π-bond of the allene that must reasonably involve interaction with the X-residue and the nitrogen atom destined to be incorporated into the heterocyclic ring. Cyclization must, however, involve back-side attack by the amine to the π-complex. Two chairlike conformations have been proposed (Figure 2): **126** (X = CH_2NHMe) resulting from the addition of Ag(I) to the *si*-face of the allene and **127** (X = CH_2NHMe) from addition of Ag(I) to the *re*-face of the allene. Cyclization via the pseudoequatorial conformer **126** should lead to the observed major stereoisomer **124**, rather than **125**.[74]

Several efficient syntheses of highly substituted Δ^3-pyrrolines have also been reported.[76,77] Starting from α-amino allenes, the pyrrolines **129** (Scheme 33) were formed in high levels of diastereomeric purity (ca. 95%). The *syn* configuration (R^3 = alkyl, R^4 = H) was assigned as the major one.[78]

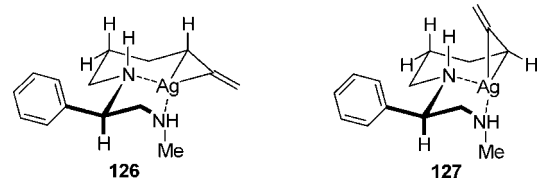
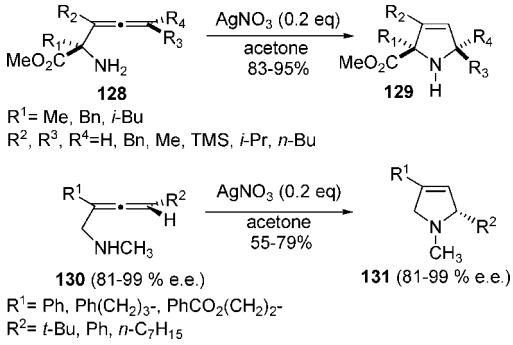
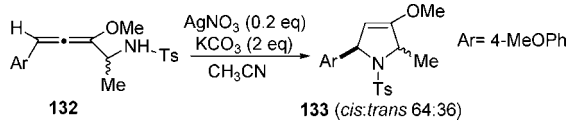


Figure 2. Proposed chairlike conformations intermediates.

Scheme 33. Stereoselective Synthesis of Substituted Δ^3-Pyrrolines



Scheme 34. Allenic Sulfonamides Cyclization



The synthetic sequence can also be used for the asymmetric synthesis of Δ^3-pyrrolines (**131**), with retention of the enantiopurity of the starting allenes (**130**).[79] This procedure can be applied to the synthesis of *N*-alkyl or *N*-aryl substituted Δ^3-pyrrolines. It is remarkable to point out the absence of formation of aziridines when the reaction is done in the presence of Ag(I). These three-membered heterocycles are exclusively formed when other metals are used, like Pd(0).[80]

3.2.2. Allenic Sulfonamides

We have previously mentioned that the allenic α-amino ester **116** (R = SO_2Tol) (Scheme 30) undergoes facile Ag(I)-catalyzed cyclization to give the *cis*-2,5-disubstituted pyrrolidine **117** as a single product in essentially quantitative yield.[70] This methodology has been applied to the synthesis of the natural product (±)-anatoxin-a (Figure 3), a low molecular weight exotoxin.[81] The pyrrolidine sulfonamide **133**, prepared as shown in Scheme 34, has been converted into the alkaloid (±)-codonopsinine (Figure 3).[82] In both cases, the yields with tosylamides are higher than with the corresponding amines. Other allenic sulfonamides have been used in this kind of transformation.[83,84]

3.2.3. Allenic Carbamates

Stereoselective preparation of 4-vinyl-2-oxazolidinones (**135**) can be achieved through silver -catalyzed amino cyclization of carbamates. The nature of the substituent on the nitrogen atom determines the yield of the cyclization step. Usually, electron-withdrawing groups facilitate the reaction. When the substituent is toluenesulfonyl, the cyclization takes place smoothly, in the presence of silver salt and triethylamine (10 mol % each). Preferential formation of *trans*-isomer can be rationalized considering that the transition state **A** (Scheme 35) is preferred over the transition state **B**, since the former is free from gauche repulsion between R^1 and C_3.[85] *O*-3,4-Pentadienyl carbamates **136** undergo aminocyclization similarly well and provide 4-vinyltetrahydro-1,3-oxazin-2-ones **137**. The *trans*-selectivity in the formation of **137** is preferred.[86]

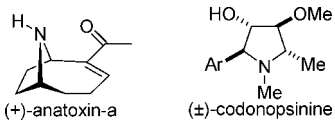
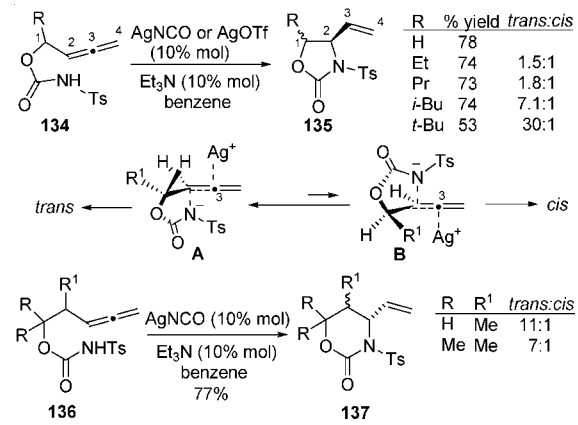
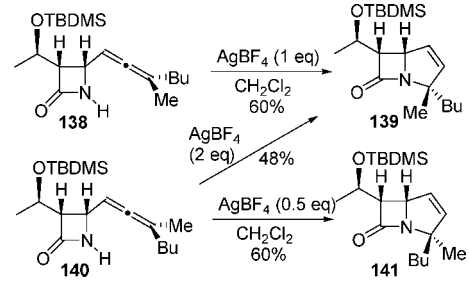


Figure 3. Alkaloids prepared through allenic sulphonamides.

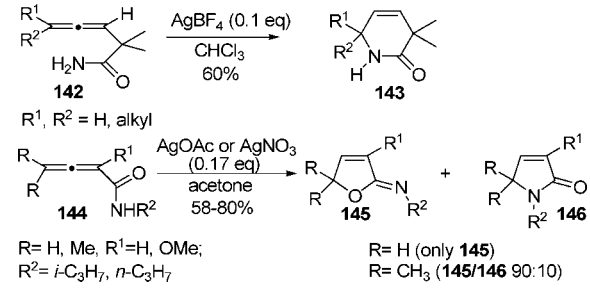
Scheme 35. Amino Cyclization of Allenic Carbamates



Scheme 36. Stereoselective Synthesis of Δ^3-Carbapenems



Scheme 37. Cyclization of α- and *β*-Allenic Amides

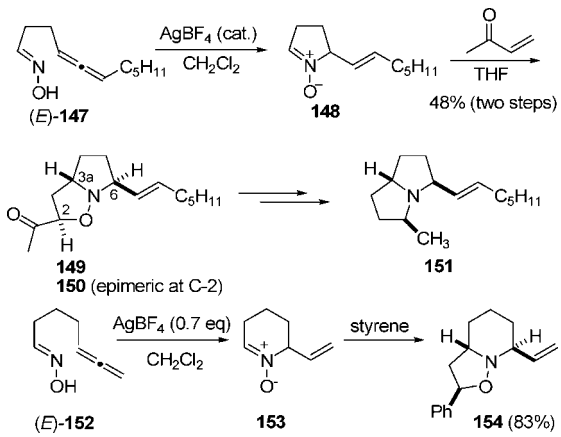


3.2.4. Allenic Amides

The use of single diastereomers of allenic amides such as **138** and **140** leads through ring closure to a stereodefined carbapenem (Scheme 36). Thus, treatment of **138** with 1 equiv of $AgBF_4$ gave only carbapenem **139**; interestingly, the diastereomeric allene **140** also gave **139** under an excess of Ag-salt. However, carbapenem **141** was selectively formed when only 0.5 equiv of $AgBF_4$ were used. Possibly, the diastereomer **139**, the less hindered product, is formed by equilibration of **141** in the presence of excess silver salt, via Ag-induced ionization of the allylic amide moiety to an allylic cation.[87]

Cyclization of *β*-allenic primary amides (**142**), in the presence of a catalytic amount of silver tetrafluoroborate, leads to 3,6-dihydro-2(1*H*)-pyridones (**143**) (Scheme 37), by exclusive attack of the nitrogen atom to the allene−silver complex.[88] However, it has also been reported that cyclization of *N*-monosubstituted allenic carboxamides (**144**) afford derivatives of dihydrofuran (**145**) or dihydropyrrole (**146**) by attack of oxygen or nitrogen, respectively, to the allenic

Scheme 38. Use of Allenic Oximes in Alkaloid Syntheses



system.[89,90] The cyclization of an amide via the oxygen onto the central carbon of the allene has also been published.[78]

3.2.5. Allenic Oximes

Oximes are also competent nucleophiles, and their cyclization generates nitrones (Scheme 38). In some cases, these may be sufficiently stable to be isolated, but usually nitrones are trapped in situ by alkenes (1,3-dipolarophile) such as styrene, ethyl acrylate, cyclopentene, cyclopentadiene, etc. Cyclization of γ-allenic oxime (*E*)-**147** with a catalytic amount of silver tetrafluoroborate gives the 5-substituted nitrone (**148**), which is trapped with methyl vinyl ketone to give a 1:1 mixture of isomeric isoxazolines (**149/150**). The formation of the *trans*-isomer would indicate that the dipolarophile approaches the nitrone in an *exo*-mode on the remote side from the vinyl substituent.[91] These isoxazolines are used in the synthesis of the pyrrolizidine alkaloid **151**.[92] When δ-allenic oximes (**152**) are subjected to silver-promoted cyclization, aldoxime derivatives (**153**) are formed,[93] and when trapped by 1,3-dipolarophiles, they provide access to *trans*-disubstituted piperidines (**154**). If a mixture of *E*- and *Z*-oximes is employed, yields are lower.[94] Electrophilic-mediated cyclization of ε-allenic oximes can be also applied to the synthesis of the hexahydroazepine skeleton.[95]

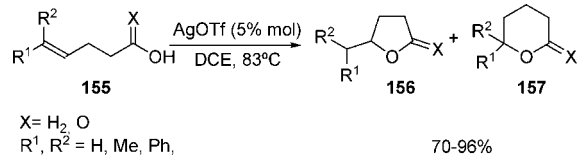
4. Ag(I)-Mediated Additions to Alkenes

The silver-mediated addition of nucleophiles to alkenes has been much less studied, as the reaction with inactivated alkenes has only been achieved with good yields in recent years. The addition of nucleophiles to alkenes activated with selenium compounds or iodine is also known, as is the silver-mediated addition of nucleophiles to alkenes with an allylic leaving group. In this section, other processes involving cyclization with oxidation or electrocyclic rearrangements will also be described. However, the formation of heterocycles from alkenes through 1,3-dipolar cycloadditions will be described in the next section.

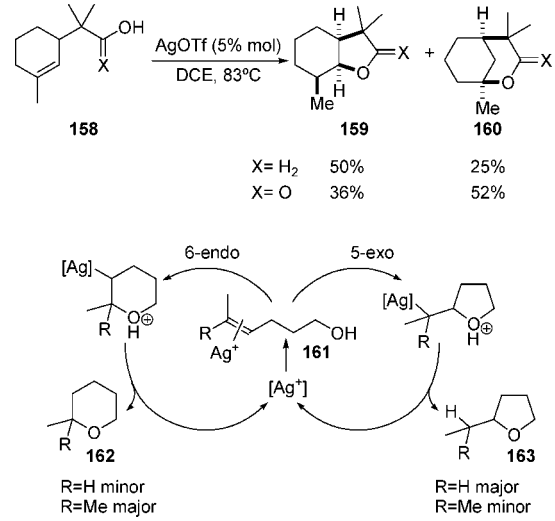
Intramolecular additions of hydroxyl or carboxyl groups to inert olefins catalyzed by silver(I) triflate in 1,2-dicholoethylene (DCE) is one of the simplest and newest methods to construct cyclic ethers or lactones (**156** or **157** in Scheme 39, **159** or **160** in Scheme 40) using silver-mediated chemistry.[96]

A study of the mechanism[96] showed that the silver(I) ion binds and activates the double bond to form the complex **161**, which is then attacked by the oxygen-nucleophile on

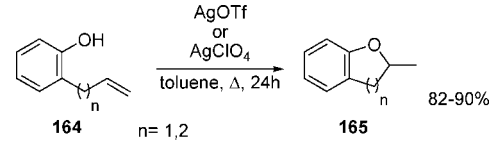
Scheme 39. Silver(I) Triflate-Catalyzed Intramolecular Additions of Alcohols or Carboxylic Acids to Olefins



Scheme 40. Investigation of Stereochemistry and Proposed Mechanism for Hydroalkoxylation



Scheme 41. Silver-Catalyzed Intramolecular Cyclization of Phenol Derivatives with a C=C Double Bond on a Side Chain



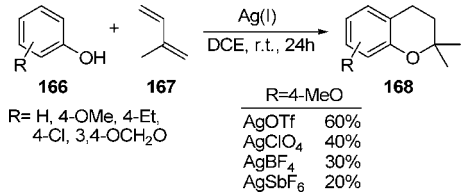
the opposite face (Scheme 40). This affords an intermediate with the newly formed carbon−oxygen bond positioned *trans* to the silver−carbon bond. Subsequent proton transfer results in the formation of the product (**162/163**) and the regeneration of the silver(I) catalyst.

Dihidrobenzofurans or dihidrobenzopyrans (**165**) can be obtained through intramolecular cyclization of phenol derivatives (**164**) with a C=C double bond on a side chain under the catalysis of silver salts (Scheme 41).[97] The catalytic activity depends on the nature of the silver−olefin complex and is affected by the coordination ability of the counteranion and the distance between it and the silver atom.[98] Thus, a silver cation, which has BF_4^- or PF_6^- as a counteranion, is strongly coordinated by oxygen atom and C=C double bond of substrate **164** and promotes no reaction. But the coordination ability of ClO_4^- and OTf^- weakens the coordination of Ag(I) by phenolic oxygen and promotes the reaction efficiently.

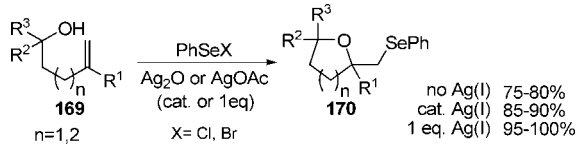
The sequential addition/cyclization of phenols to dienes in the presence of a catalytic amount of Ag(I) constitutes an intermolecular version of the method (Scheme 42).[99] Only AgOTf, $AgSbF_6$, $AgBF_4$, and $AgClO_4$ promoted the reaction, as other silver salts were not effective.

Besides the above-mentioned cyclizations through the addition of nucleophiles to inactivated alkenes, the silver-assisted seleno- or iodo-cyclizations are also excellent routes to oxygen heterocycles. Thus, tetrahydrofuran and tetrahy-

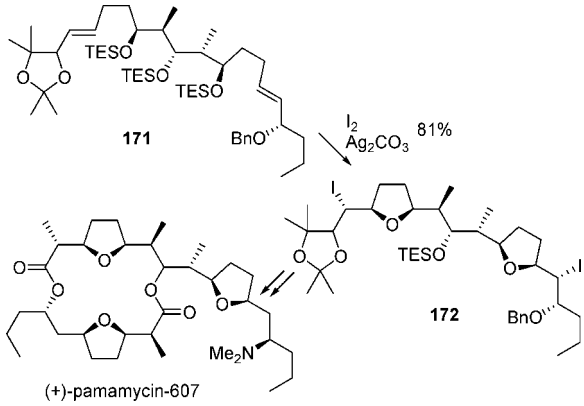
Scheme 42. Silver-Catalyzed Sequential C−C and C−O Bond Formation Between Phenols and Dienes



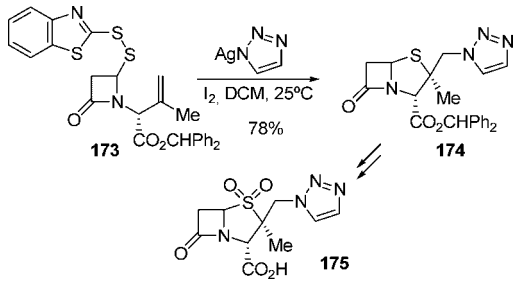
Scheme 43. Tetrahydrofurans and Tetrahydropyran Through Silver-Assisted Phenylselenoetherification



Scheme 44. (+)-Pamamycin−607 Tetrahydrofurans Synthesis Through Silver-Assisted Iodoetherification



Scheme 45. Silver-Mediated Synthesis of Thiazolidines

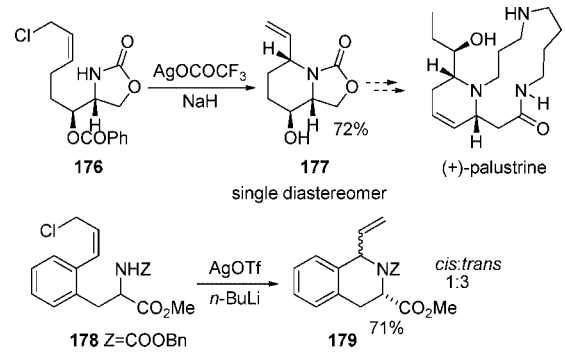


dropyran derivatives (**170**) can be prepared through phenylselenoetherification of alkenols (**169**) (Scheme 43). A catalytic amount of additive leads to higher yields, but with equimolar amounts, almost quantitative yields are achieved under extremely mild experimental conditions.[100–102] The procedure has been used in the total synthesis of the tetrahydrofuran-containing fragment of amphidinolide X (**81**) and Y (**82**).[103]

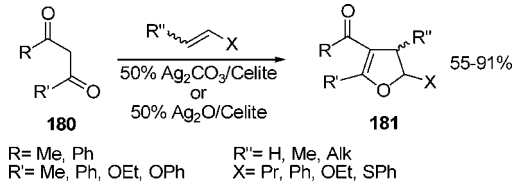
The generation of the tetrahydrofurans present in (+)-pamamycin−**607** through silver-assisted iodoetherification proved to be a key step for its highly enantioselective total synthesis (Scheme 44). Thus, exposure of the silylated hydroxalkene **171** to iodine in the presence of silver carbonate in diethyl ether promoted the cyclization toward the tetrahydrofurans rings present in **172** with complete *cis*-stereoselectivity through double iodoetherification.[104] (Scheme 45).

Alkenyldisulfides can cyclize in the presence of silver salts and iodine to afford the corresponding sulfur heterocyles. A

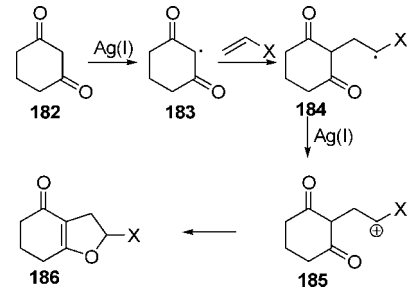
Scheme 46. Silver-Promoted Intramolecular N-Alkylation of Allyl Chlorides



Scheme 47. Silver(I)/Celite-Mediated Synthesis of 3-Acylfurans Through Cycloaddition of Dicarbonyl Compounds to Alkenes



Scheme 48. Silver(I)/Celite-Mediated Synthesis of 3-Acylfurans Through Cycloaddition of Dicarbonyl Compounds to Alkenes



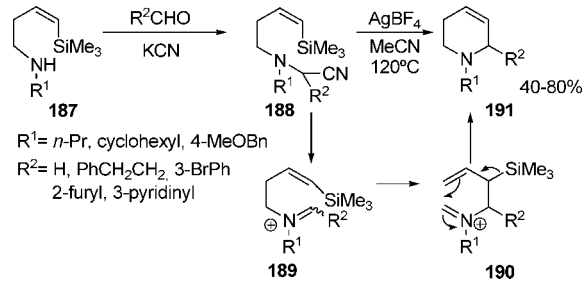
key step in the total synthesis of the β-lactamase inhibitor tazobactam (**175**) is the reaction of the azetidinone disulfide **173** with silver triazole to obtain the benzhydryl-2β-triazolylmethylpenicilinate **174**.[105]

Silver salts can also assist the formation of heterocyles through intramolecular addition of nucleophiles to activated alkenes, like allyl halides. Intramolecular cyclization of alkenylamines is one of the most important approaches for the stereoselective construction of nitrogen heteroalicycles, which are present in the skeletons of several biologically active natural products and related compounds. Hirai and co-workers developed a method for the diasteroselective synthesis of *cis*-1,3-disubstituted piperidines (**177**) based on the silver(I) salt-promoted cyclization of allyl chlorides (**176**) and showed its potential in the preparation of (+)-palustrine (Scheme 46).[106] The application of the method to the preparation of 1,3-disubstituted 1,2,3,4-tetrahydroisoquinolines (**179**) affords *cis*/*trans* mixtures.[107]

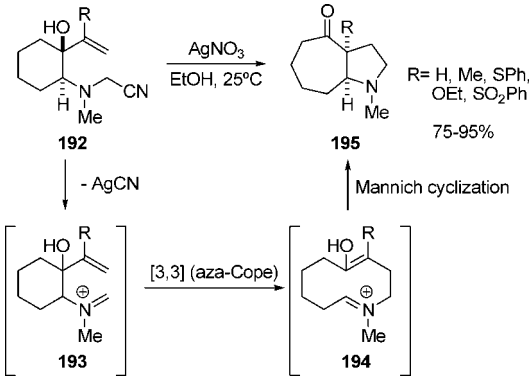
The silver(I)/celite-mediated oxidative addition of 1,3-dicarbonyl compounds (**180**) to terminal alkenes or internal enol ethers or thio ethers offers a facile and simple method for the synthesis of substituted dihydrofurans (**181**) (Scheme 47).[108]

Although the exact mechanism of the reaction is not clear, this result is best described as in Scheme 48. The 1,3-dicarbonyl compound **182** is first oxidized by silver(I) metal

Scheme 49. Synthesis of Tetrahydropyridines through Cyclization of Vinylsilanes and Iminium Ions Initiated by Silver Salts



Scheme 50. Silver(I) Pyrrolidine Synthesis



to generate the α-oxoalkyl radical **183**, which then attacks the olefin to give the radical **184**. This nucleophilic adduct **184** now undergoes fast oxidation by silver(I) to give a carbonium ion **185**, which cyclizes to the desired dihydrofuran **186**. The method has been applied to the total synthesis of the natural product α-clausenan.[109]

There are two examples of heterocycles formation mediated by silver that involve an aza-Cope rearrangement. Tetrahydropyridines (**191**) can be prepared through intramolecular electrophilic cyclization of α-cyanoamines incorporating a vinylsilane (**188**) in the presence of silver salts, possibly via a cationic aza-Cope rearrangement (from the intermediate **189** to **190**) (Scheme 49).[110]

Treatment of the α-cianoamines **192** with an equimolecular amount of $AgNO_3$ initiated the formation of an iminium cation that underwent a cationic aza-Cope rearrangement followed by a Mannich cyclization reaction, with the result of the formation of a new pyrrolidine ring (**195**) (Scheme 50).[111,112]

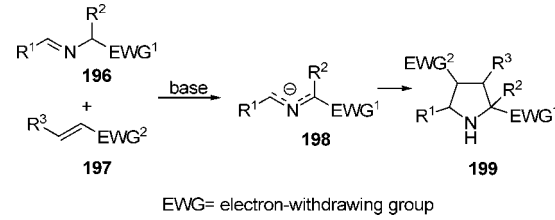
5. Ag(I)-Mediated Cycloaddition Reactions

Ag(I)-catalyzed *N*-heterocycloadditions allows the formation of two new bonds (C−C and/or C−N) in the synthesis of attractive *N*-heterocycles.[113] Among the described cycloadditions to obtain aza-heterocycles, the most outstanding is the 1,3-dipolar cycloaddition of azomethine ylides, a kind of reaction that can lead to polysubstituted pyrrolidines. In this section, this reaction will be analyzed together with the cycloadditions of nitrilimines and the aza-Diels−Alder.

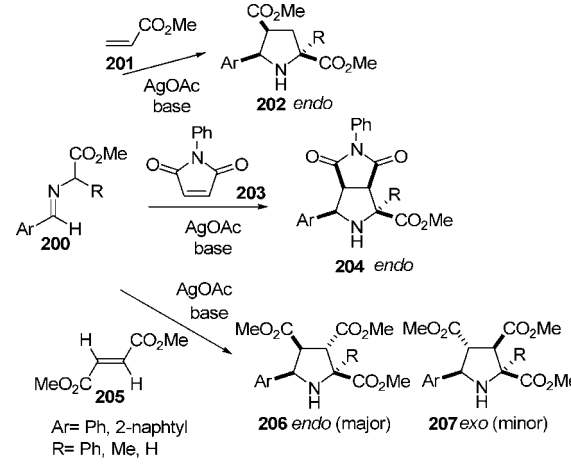
5.1. 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides

The reaction of azomethine ylides (**198**) with electrophilic alkenes (**197**) is an excellent method to synthesize pyrrolidine derivatives (**199**), through a 1,3-dipolar cycloaddition where

Scheme 51. 1,3-Dipolar Cycloaddition of Azomethine Ylides with Alkene Dipolarophiles



Scheme 52. [3 + 2]-Cycloaddition of Azomethine Derived from Imine Esters with Different Alkenes Using Stoichiometric Amounts of Ag Catalyst



two new C−C bonds and up to four chiral centers may be formed.[114–116] These ylides can be prepared *in situ* from properly substituted imines (**196**) in basic media (Scheme 51). The polysubstituted pyrrolidines are very important pharmaceuticals and natural alkaloids, and they are used as building blocks in organic synthesis or as organocatalysts.[117,118]

5.1.1. Achiral 1,3-Dipolar Cycloaddition of Azomethine Ylides with Alkenes

In 1982 Grigg published that Lewis acids accelerate these reactions with alkynes,[119] and since then, this group has developed the use of aromatic imines (**200**) with several silver salts (AgOAc, $AgNO_3$, AgOTs, etc.) in stoichiometric amounts.[120–122] In general, silver acetate and Et_3N give the best results with different alkene dipolarophiles, such as methyl acrylate (**201**), *N*-phenylmaleimide (NPM) (**203**), and dimethyl fumarate (**205**) (Scheme 52).

The heterocycles are formed in good yields (50−95%). THF or MeCN are preferred as solvents. Usually, the electron-withdrawing substituents are ester groups, as the metal coordinates to the N and O atoms, giving the more stable *E*,*E*(*syn*)-dipole (Figure 4), which produce *endo*-cycloadducts. This could explain the high regio- and stereoselectivity of the process, giving only the *endo*-isomers (**202**, **204**, and **206**) or minor amounts of the *exo*-product (**207**) from **205**. AgOAc is a more efficient and selective catalyst than LiBr.[122] This process has been extended to

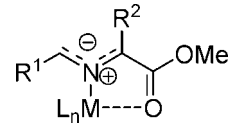
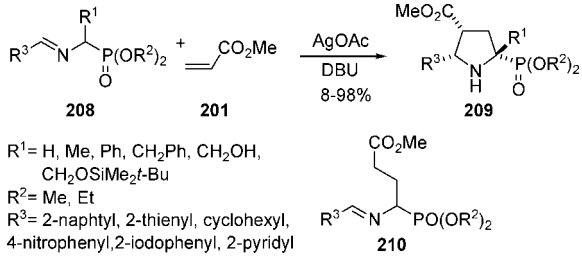
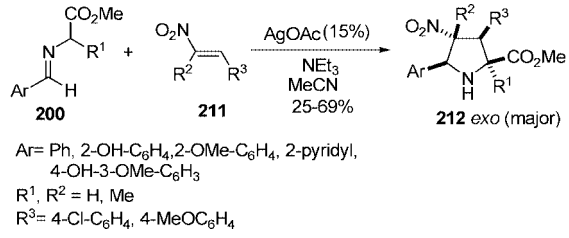


Figure 4. Metallo-azo-methine ylide involved in 1,3-dipolar cycloaddition.

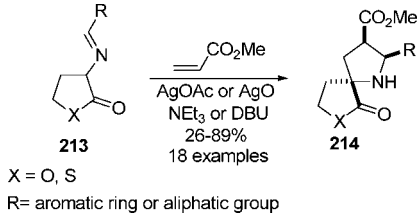
Scheme 53. 1,3-Dipolar Cycloaddition from Iminophosphonates



Scheme 54. [3 + 2]-Cycloaddition from Nitroalkenes



Scheme 55. Silver Salt/Base-Catalyzed Cycloaddition of Imines of 2-Amino-γ-lactone and Thiolactones

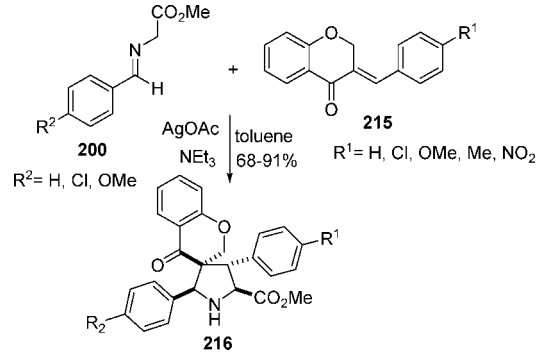


aliphatic imines.[123] The results are similar but the yields are lower, specially with methyl acrylate (45−55%).

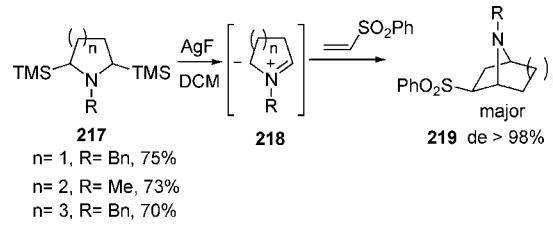
The method has been extended to the use of other imines not derived from aminoesters or other dipolarophiles without an ester group. Thus, iminophosphonates (**208**), with DBU and Ag(I), gave dialkyl pyrrolidine-2-phosphonates (**209**) along with the corresponding Michael adducts (**210**), in some cases. Reactions are slower than with iminoesters[124] (Scheme 53). The nitroalkenes **211** also react with azomethine ylides, using 15% of silver salt, to give preferential formation of the *exo*-cycloadducts (about 7:3 *exo*/*endo*) (**212**)[125] (Scheme 54). To explain this phenomenon, computational studies have been taken out and these suggest that the [3 + 2]-cycloaddition is actually a tandem Michael−Henry process.[125] On the other hand, the cycloaddition of imines of 2-amino-γ-lactones and thiolactones (**213**) with methyl acrylate (**201**) and AgOAc or Ag_2O affords spirolactones/thiolactones (**214**) regio- and stereoselectively as single cycloadducts in good yield via *syn*-dipoles and *endo* transition states (Scheme 55).[126] In the same way, the reaction of 3-aryliden-4-chromanones (**215**) with appropriate imines in toluene gives also complete selectivity in the formation of spiropyrrolidines (**216**) (Scheme 56).[127] This strategy has been applied to the synthesis of 4-(5^1-pyrrolidinyl)-β-lactams.[128]

Nájera and co-workers have employed phase-transfer catalysis (PTC) conditions in the reaction of the azomethine ylide **198** (R^1 = Ph, R^2 = Me, EWG^1 = $CO_2{}^i$Pr) with different dipolarophiles in the presence of substoichiometric silver acetate and inorganic bases.[129] They have analyzed the effects of solvent, phase-transfer agent, quantity of metal salt, and substituents on the 1,3-dipole. Sodium and potassium hydroxides provided the best *endo*-selectivity, while the use of other bases (K_2CO_3, LiOH, CsOH) resulted in

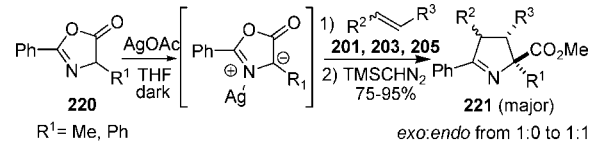
Scheme 56. Synthesis of Spiropyrrolidines from 3-Arylidene-4-chromanones



Scheme 57. Construction of *X*-aza-Bicyclo[*m*.2.1]alkanes by [3 + 2]-Cycloaddition Reaction



Scheme 58. Lewis Acid-Mediated Synthesis of Δ^1-Pyrrolines



significant quantities of Michael adducts. In general, PTC agents (as tetrabutylammonium chloride) enhanced the rates of the reaction in nonpolar solvents. In other research, the use of silver-exchanged zeolites and AgCl on titania were studied. The titania support retarded catalysis.[130]

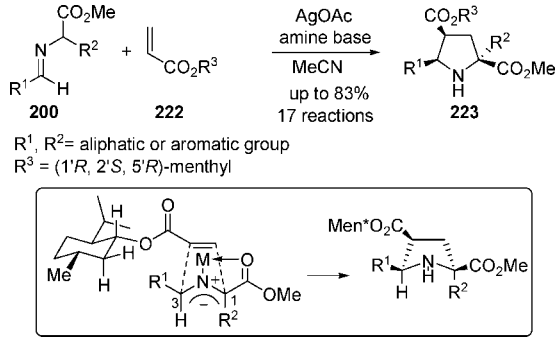
Cyclic azomethine ylides afford other types of heterocycles with *exo* preference. Pandey and co-workers employed nonstabilized cyclic azomethine ylides (**218**), from desilylation of bis(trimethylsilyl) cyclic amines (**217**), to construct *X*-aza-bicyclo[*m*.2.1]alkanes (**219**) (Scheme 57).[131] The structural rigidity of the *in situ* formed ylide induced a very good *exo*/*endo* selectivity. The asymmetric version was performed with camphor sultam as the auxiliary chiral group. On the other hand, Tepe and co-workers[132] described the synthesis of Δ^1-pyrrolines (**221**) from azalactones (**220**) and several dipolarophiles like methyl acrylate (**201**), NPM (**203**), and diethyl fumarate (**205**) (Scheme 58). The authors suggested that stabilizing electrostatic interactions in the transition state between the dipole and the dipolarophile explained the preference for the *exo*-cycloadduct (Scheme 58).

5.1.2. Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides with Alkenes Catalyzed by Ag(I)

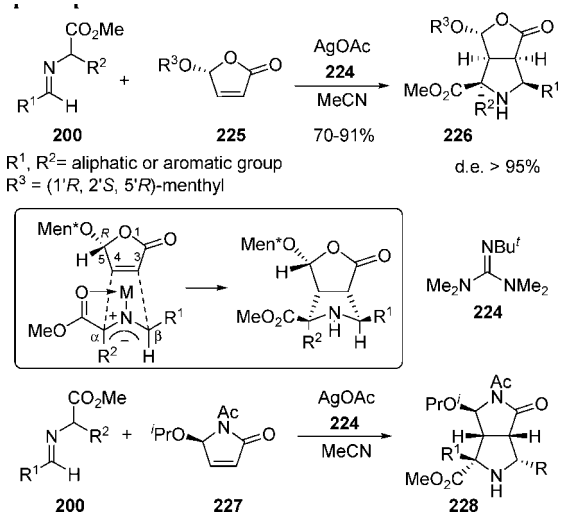
Asymmetric 1,3-dipolar cycloadditions of metalloazomethine ylides[133–136] can be achieved by three different strategies employing either chiral dipolarophiles, chiral azomethine ylides, or chiral catalysts. All of these have been used with Ag(I) as metal catalyst.

5.1.2.a. Chiral Dipolarophiles. The first asymmetric cycloaddition of an azomethine ylide with enantiopure menthyl acrylate (**222**), using Ag(I), was published by Grigg and

Scheme 59. Ag(I)-Catalyzed Asymmetric Cycloaddition of Imines and Menthyl Acrylate



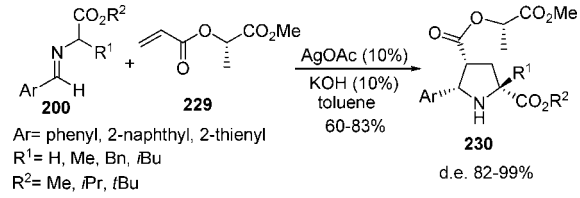
Scheme 60. [3 + 2]-Cycloaddition of Imines and Chiral Cyclic Dipolarophiles



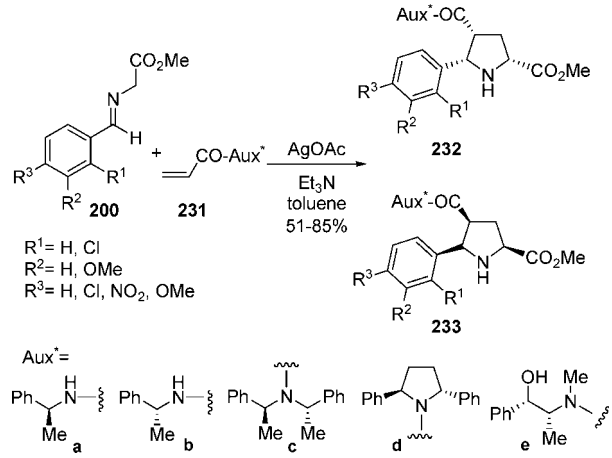
co-workers.[137,138] The reaction gave homochiral *endo*-pyrrolidines (**223**) in good yield. The stronger the base, the faster was the cycloaddition and the greater was the yield: 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (**224**) > DBU > NEt_3 (Scheme 59). To explain the stereochemistry, 1-*si*, 3-*re*-face of the dipole should add to the *re*-face of the *s-cis*-acrylate.[138] When the method is applied using chiral cyclic dipolarophiles as 5*R*-(1′*R*,2′*S*,5′*R*-menthyloxyl)-2(5*H*)-furanone (**225**), the corresponding *syn-endo* bicyclic cycloadducts (**226**) are obtained regio- and stereospecifically and in diastereomeric excesses (de's) higher than 95% (Scheme 60).[139] The different absolute configuration of the chiral carbons in the pyrrolidines **223** and **226** can be explained assuming a more stable *s-cis*-conformation for **222** but an enforced *s-trans* geometry for **225**. Thus, **226** derives from a transition state where the *E*,*E*-dipole (neglecting M) via its α-*re*/β-*si* face adds to the lactone 3-*si*/4-*re* face. However, when the reaction is carried out with the chiral 5*R*-lactam **227**, the cycloaddition occurs on the face of the dipolarophile that is *trans* to the bulky isopropoxy substituent and yields the opposite configuration in **228** than in **226**.

Recently, chiral acrylates derived from methyl (*S*)- and (*R*)-lactate (**229**) have been used.[140] Highly *endo*-diastereoselectivity is observed, and enantiopure compounds (**230**) are isolated. The results were interpreted on the basis of computational studies on model systems. One of these pyrrolidines was used for the asymmetric synthesis of a hepatitis C virus inhibitor (Scheme 61). Several chiral acrylamides (**231**) have been used to synthesize homochiral proline derivatives (**232** and **233**). The stereocontrol was

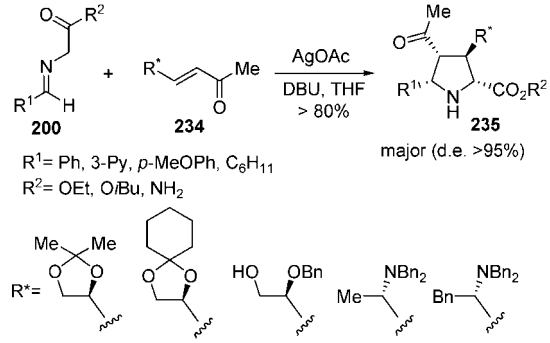
Scheme 61. Diastereoselective Synthesis of Pyrrolidines 230 from Chiral Acrylates



Scheme 62. Synthesis of Pyrrolidines from Chiral Acrylamides and Glycine Imines



Scheme 63. Synthesis of Enantiopure 4-Acetylprolines via 1,3-Dipolar Cycloaddition

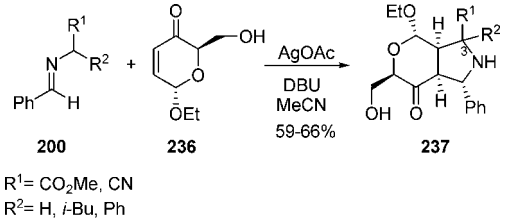


complete in the formation of **232** with the auxiliaries **d** and **e**[141,142] (Scheme 62).

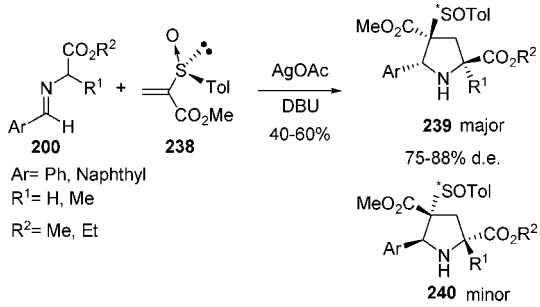
α,β-Unsaturated ketones (**234**) substituted by chiral alkoxy or amino groups (Scheme 63) were investigated as dipolarophiles. The DBU/AgOAc catalyst system gives the best results of selectivity. Compound **235** is always the major cycloadduct (de > 95%) and has excellent yield (Scheme 63).[143] The reaction does not work with *Z*-enones. When a chiral carbohydrate-derived enone (**236**) is used, single enantiomeric *endo*-pyranopyrrolidines (**237**) are achieved for methoxycarbonyl ylides, but mixtures are achieved for cyano ylides[144] (Scheme 64). The absolute configuration at C-3 in **237** depends on the steric hindrance of the R^2 groups. Finally, the optically pure vinyl sulfoxide methyl (*S*)-2-(*p*-tolylsulfinyl)acrylate (**238**) affords[145] complete regio- and *endo*-selectivities in the reaction with several metalloazomethine ylides, although as mixtures of the diastereomers **239** and **240** (75−88% de) (Scheme 65).

5.1.2.b. Chiral Azomethine Ylides. Not many works have been published using chiral azomethine ylides in 1,3-silver dipolar cycloadditions. Alcaide and co-workers described in 2001[146] the reaction of chiral 2-azetidinone tethered azome-

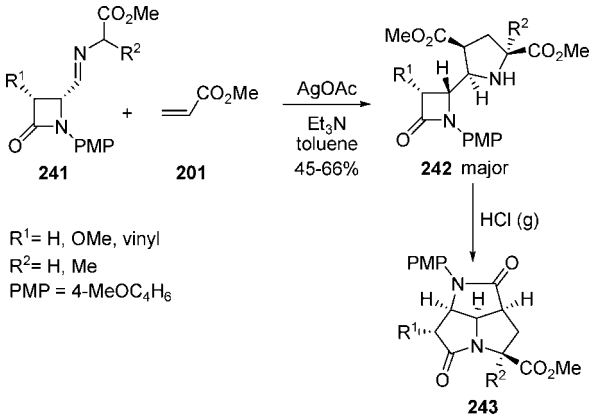
Scheme 64. Carbohydrate 236 as Chiral Dipolarophile in [3 + 2]-Cycloaddition



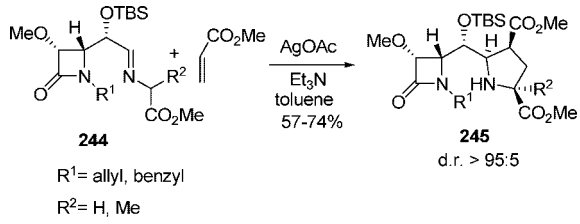
Scheme 65. Asymmetric 1,3-Dipolar Reaction of N-Metallated Azomethine Ylides with Chiral Vinyl Sulfoxide 238



Scheme 66. Synthesis of Enantiopure β-Lactam Pyrrolidines from Homochiral Azomethine Ylides

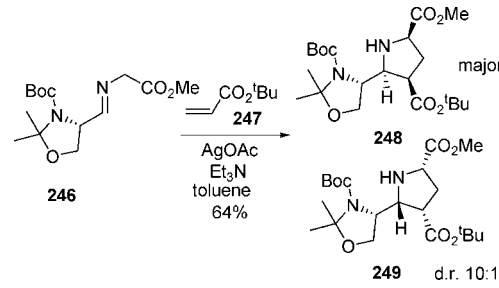


Scheme 67. Reaction of Chiral α-Alkoxy β-Lactamimines with Methyl Acrylate Mediated by Silver Acetate

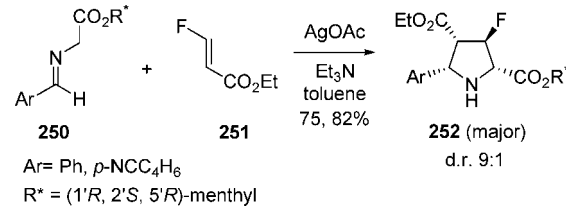


thine ylides (**241**) with different dipolarophiles (Scheme 66). Mixtures of homochiral diastereomer cycloadducts **242** are obtained and can be used in the synthesis of optically pure highly functionalized pyrrolizidine systems (**243**). With methyl acrylate (**201**) as dipolarophile, the diastereomeric ratio ranges from 65:35 to >95:5. Nevertheless, with α-alkoxy-β-lactam derivatives (**244**), the diastereoselectivity is much higher, as it produces the diastereomer **245** in a d.r. > 95:5 (Scheme 67).[147] In addition, Garner and Kaniskan, in 2005, reported the application of several chiral α-amino imines, as **246**, under the Grigg's conditions. Using the alkene **247**, a 10:1 mixture of cycloadducts **248** and **249** was obtained. These potentially labile α-aminoazomethine ylides

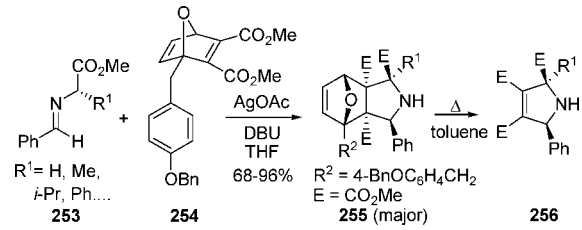
Scheme 68. 1,3-Dipolar Cycloaddition with *N-Boc*-Serinal Acetonide Imine



Scheme 69. Obtention of Enantiopure Fluorinated Prolines from [3 + 2]-Cycloaddition



Scheme 70. Synthesis of 3-Pyrrolines in a Two-Step Sequence Involving [3 + 2]-Cycloaddition and Retro-Diels−Alder Processes

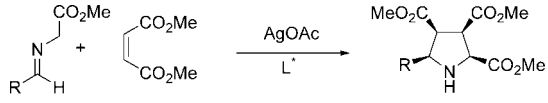


worked without significant α-racemization[148] (Scheme 68). By reaction between (*E*)-ethyl-3-fluoroacrylate (**251**) and the chiral menthyl imines **250**, enantiopure pharmacologically important fluorinated prolines (**252**)[149] were obtained with a 9:1 ratio of diastereomers (Scheme 69). On the other hand, the cycloaddition of the oxabicycloheptadiene dicarboxylate derivative **254** with silver−azomethine ylides derived from α-amino esters (**253**) gave mainly the corresponding *exo*-cycloadducts **255** (Scheme 70). In contrast, use of LiBr afforded the *endo*-cycloadduct isomers.[150] This methodology can be adapted to solid phase by using a polymer-supported dipolarophile. Retro-Diels−Alder of the cycloadducts in refluxing toluene produces 3-pyrrolines (**256**). This two-step sequence seems to be superior to the direct reaction of ylides with acetylene dicarboxylates.[150]

5.1.2.c. Chiral Ligands. Metalloazomethine ylides have been used in stereoselective synthesis of pyrrolidine derivatives with different ligands and metals, i.e., Co(II), Mn(II), Cu(II), Zn(II), and Ti(IV). However, Ag(I) salts are the most effective Lewis acids. The reaction times are generally short, and the products are normally isolated in very high yields.[135]

The first asymmetric 1,3-dipolar cycloaddition using AgOAc and a chiral ligand, both in substoichiometric amounts, was described by Zhang and co-workers in 2002.[151] They achieved poor enantioselectivity using several bisphosphine ligands, in the reaction with dimethyl maleate (**257**), but good results with a bisferrocenyl amide phosphine (FAP) (**258**) (Figure 5). Only the *endo*-products (**259**) were observed (Scheme 71). Similar or better results were obtained using *N,P*-ligands, as with ferrocenyloxazoline-derivative ligands like **260** (Figure 5) (up to 98% ee)[152] (Scheme 71). The

Scheme 71. Cycloaddition of Azomethine Ylides and Dimethyl Maleate with Different Ag(I)-Chiral Ligands Complexes



ligand	base	% yield	% *ee*	entries
258	$^{i}Pr_2NEt$	73-98	70-96	13
260	-	56-99	88-98	11
261	-	95-98	36-97	8
262	-	89-98	78-92[a]	8
263	-	86-96	84-89[a]	6

[a] With **262** and **263** as ligands, the products obtained were the enantiomers to the product with **261**

metal-bound azomethine ylide is formed by the deprotonation with acetate, and extra base is not necessary. In a recent paper,[153] the same research group has described the hydrogen-bonding directed reversal of enantioselectivity with ferrocene *N*,*P*-ligands (**261** and **262**) (Figure 5). This result shows that the reaction course is conditioned by the substitution degree of the amino group, primary (**261**) or tertiary (**262**) (Scheme 71). They have also used ferrocene-derived *P*,*S*-heterodonors ligands (**263** and **264**) (Figure 5).[154]

Atropisomeric *P*,*N*-ligands (**265**−**267**) (Figure 5) have been screened in reactions with different azomethine ylides and dipolarophiles. Using (*S*)-QUINAP (**265**), the best yields and enantioselectivities for pyrrolidines **269** are achieved in the reaction of the iminoesters derived from glycinate (**200**) and *tert*-butyl acrylate (**247**) (Scheme 72).[155] Carreira and co-workers reached similar results using PINAP (**266**) as ligand catalyst (Scheme 72).[156] Phosphinooxazoline complexes as **267** (Figure 5) give moderate selectivities in intermolecular cycloadditions with *N*-(2-naphthylidene)glycine methyl ester, but with the imine unsaturated esters **268**, the intramolecular reactions yielded the tricyclic derivative **270** with enantiomeric excesses (ee's)

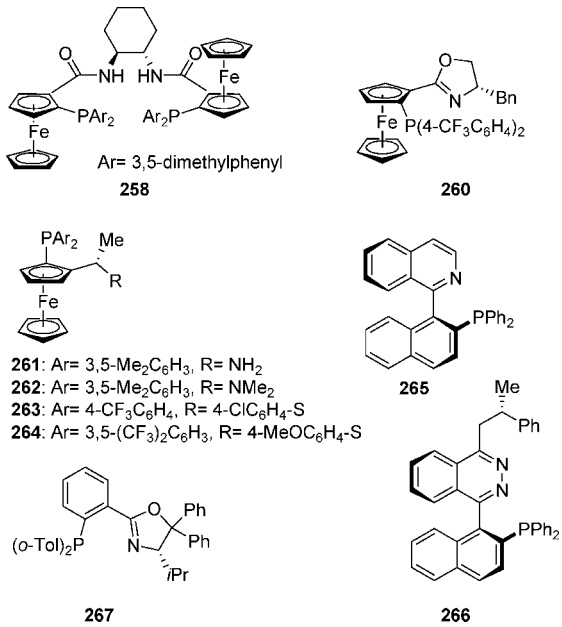
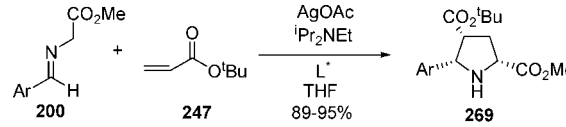


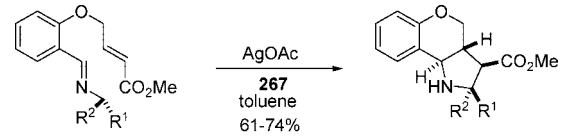
Figure 5. Chiral phosphine ligands screened for the azomethine ylide cycloadditions.

Scheme 72. Asymmetric Synthesis of Proline Derivatives Using Atropisomeric *P*,*N*-Ligands

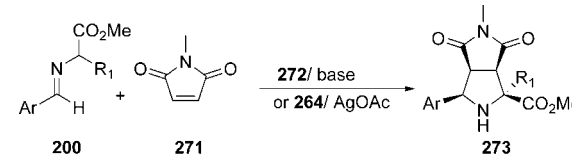


ligand	% yield	% *ee*	entries
265	89-95	89-95	5
266	88, 94	92, 95	2

Scheme 73. Asymmetric Ag(I)-Catalyzed Intramolecular [3 + 2]-Cycloaddition



Scheme 74. 1,3-Dipolar Cycloadditions of Azomethine Ylides with *N*-Methylmaleimide



ligand	base	% yield	% *ee*	entries
272	Et_3N	56-90	65-99	13
264	-	95-98	86-93[a]	5

[a] With **264** the products have the opposite configuration

up to 99% (Scheme 73). The absolute configuration of **270** remains unknown.[157]

Recently, the [(*S*)-BINAP]$AgClO_4$ complex (**272**) (Figure 6)[158] has been used in 1,3-dipolar cycloaddition of azomethine ylides with *N*-methylmaleimide (NMM) (**271**) (Scheme 74). This catalyst, which has a *P*,*P*-silver chelation, gives very good yields for the *endo*-cycloadducts **273**, in addition to high enantioselectivity levels. The complex is stable and recoverable by simple filtration. This reaction has been also reported using the ferrocene derived *P*,*S*-ligand **264** (Figure 5) with excellent results.[154] In addition, with cinchone alkaloids and AgF, chelation of the metal to the iminoester followed by deprotonation by the alkaloid, which acts as a chiral base, forms a metalloazomethine ylide−chiral base ion pair. This species reacts with acrylates in a chiral environment, affording the expected cycloadducts (**274**) stereoselectively (Scheme 75). The absolute configuration of compounds **274** was the opposite of the adducts **269**.[159]

Finally, a methodology with chiral nitroalkenes (**276**) and racemic or chiral imines (**275**) has been applied to the preparation of inhibitors of $\alpha_4\beta_1$-integrin-mediated hepatic melanoma metastasis (**277**) (Scheme 76).[160]

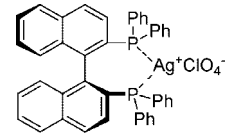
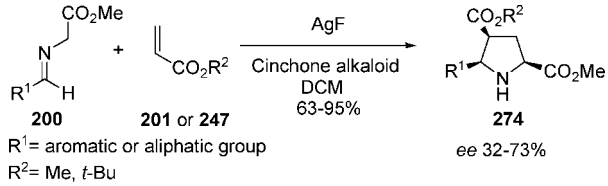
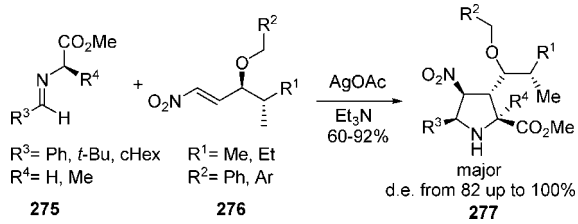


Figure 6. [(*S*)-BINAP]$AgClO_4$ complex.

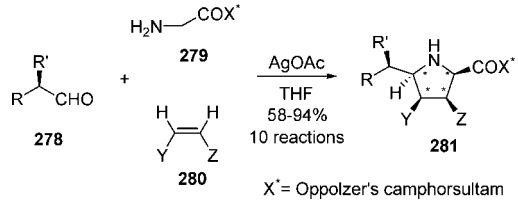
Scheme 75. Cycloaddition of Azomethine Ylides Activated by a Metal Salt and a Chiral Base



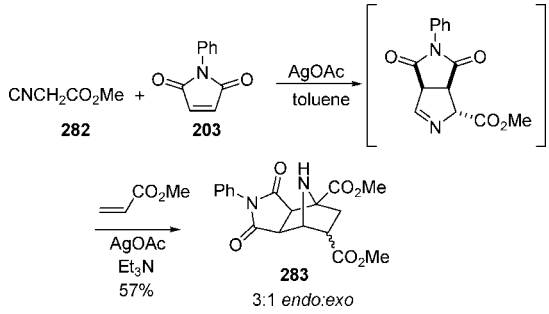
Scheme 76. Stereocontrolled [3 + 2]-Cycloaddition in the Preparation of Inhibitors of $\alpha_4\beta_1$-Integrin-Mediated Hepatic Melanoma Metastasis



Scheme 77. One-Pot Three-Component [3 + 2]-Cycloaddition



Scheme 78. Silver Acetate-Catalyzed Sequential Cycloadditions of Isocyanoacetates

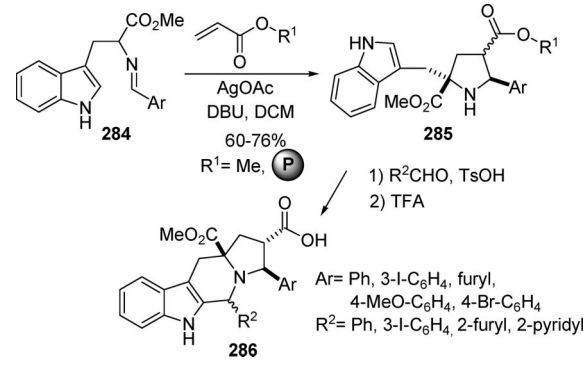


5.1.3. Sequential and Cascade Processes: Applications in Synthesis

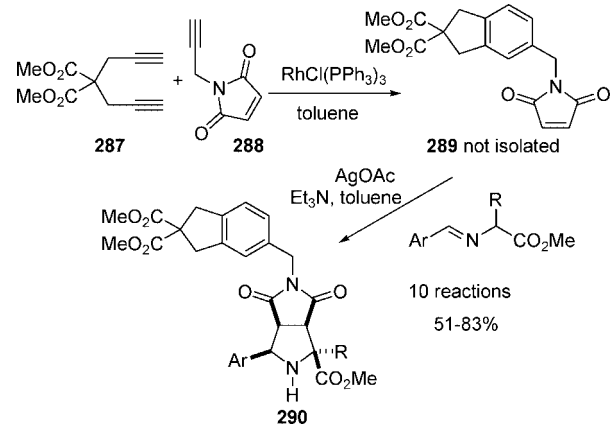
Garner and co-workers have proposed a three-component reaction where, in a single step, a selective Ag(I)-catalyzed asymmetric multicomponent [C + NC + CC] synthesis of a highly functionalized pyrrolidine (**281**) is achieved.[161,162] To generate the necessary imine, the Oppolzer's chiral glycyl sultam amine (**279**)[163] is used. The method was applied to aliphatic aldehydes (**278**) and different electrophillic alkenes (**280**) (Scheme 77). They obtained enantiomerically enriched products and mixtures ranging from 7:1 to 95:5 of the diastereoisomers **281**.

Grigg and co-workers have reported some sequential processes to afford complex heterocyclic systems where one step involves a [3 + 2]-cycloaddition of azomethine ylides. Cycloaddition of methyl isocyanoacetate (**282**) to Michael acceptors in combination with an azomethine ylide reaction in a one-pot cascade process afforded 7-azabicyclo-[2.2.1]heptane ring systems (**283**) (Scheme 78).[164] Sequential 1,3-dipolar cycloaddition−Pictet−Spengler reactions have been used in the synthesis of polyfunctional *N*-heterocycles (**286**)

Scheme 79. Sequential 1,3-Dipolar Cycloaddition−Pictet−Spengler Reactions



Scheme 80. Sequential One-Pot Rh(I)-Catalyzed [2 + 2 + 2]-Cyclotrimerization−Imine Cycloaddition Processes

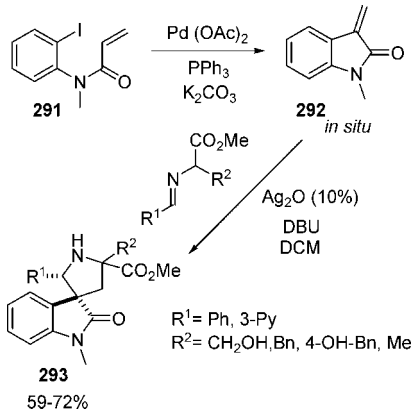


from salicylaldimine **284** and methyl acrylate (**201**) through the cycloadduct **285** (Scheme 79). The stereoselectivity in the cycloaddition was found to be only *endo*.[165] However, when the Wang resin acrylate was used, mixtures of *endo*/*exo* products were observed, due to the fact that the combined steric effects of the resin and the bulky 3-indolylmethyl group conspire to make the *endo*- and *exo*-transition states nearly equal in energy.[166]

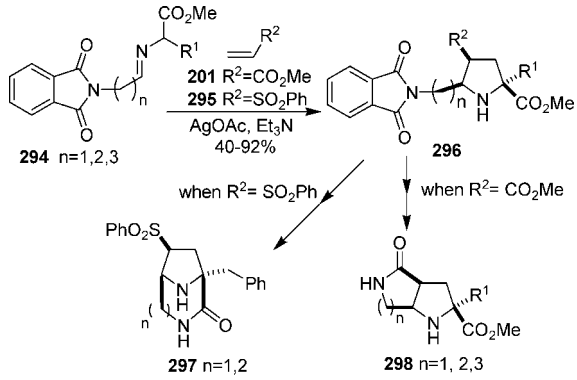
In a sequential one-pot Rh(I)-catalyzed [2 + 2 + 2]-alkyne cyclotrimerization−imine cycloaddition, diyne **287** and monoyne **288**, in the presence of the Wilkinson's catalyst, were first converted into the cycloadduct **289**, and later a fast reaction with an imine, AgOAc, and Et_3N gave access to the complex heterocyclic benzene derivative **290**. The intermediate **289**, a result of the cyclotriisomerization, was not isolated (Scheme 80). The processes were *endo*-specific.[167] The combination of an intramolecular Heck reaction with a subsequent Ag(I) cycloaddition cascade was described for the formation of spirooxindoles (**293**), using as reactants the Heck substrate **291** and several imines (Scheme 81). The 1,3-dipolar cycloaddition of the obtained indolinone (**292**) takes place with endoselectivity. The cycloadducts (**293**) are a ca. 4:1 to >9:1 mixture of two stereoisomers.[168]

Aldimines derived from aldehydes bearing an α-, *β*-, or *γ*-protected amino group (**294**) underwent cycloaddition with methyl acrylate (**201**) or phenyl vinyl sulfone (**295**) to give pyrrolidine endoisomers **296**. Subsequent unmasking of the amino group and lactamization, spontaneous in most cases, generated 5−7-membered bridged and fused bicyclic lactams (**297** and **298**) (Scheme 82).[169]

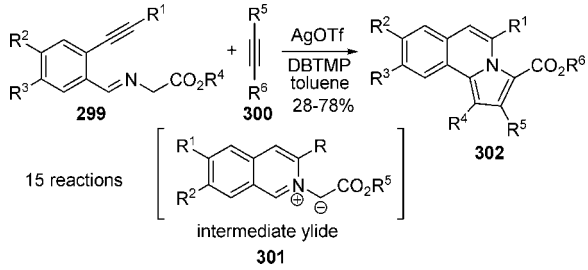
Scheme 81. Spirooxindoles from Intramolecular Heck−1,3-Dipolar Cycloaddition Cascade Reactions



Scheme 82. Obtainment of Fused and Bridged Bicyclic Lactams via Sequential Metalloazomethine Ylide Cycloaddition−Lactamization



Scheme 83. Synthesis of Pyrroloisoquinolines Using Silver-Catalyzed Cycloisomerization/Dipolar Cycloaddition

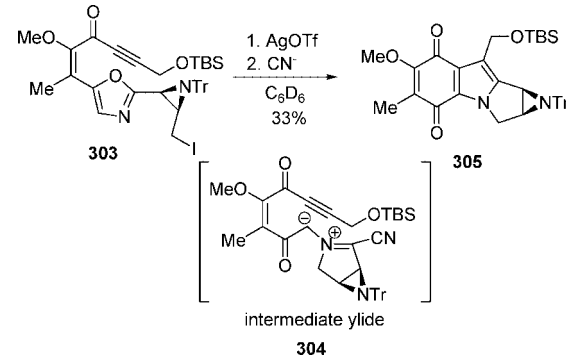


An interesting recent work about cycloisomerization−cycloadditions with alkynes as dipolarophiles has been published. Reaction of an alkynyl *N*-benzylidene glycinate (**299**) with an electrophilic alkyne (**300**) in the presence of AgOTf produced pyrroloisoquinolines (**302**). These are structurally close to the lamellarin family of natural products. The process involves domino cycloisomerization/dipolar-cycloaddition (Scheme 83). The intermediate ylide (**301**) suffered [3 + 2]-cycloaddition with the alkyne **300**.[170] In the same way, the oxazole **303**, in the presence of a crystallized benzene complex of AgOTf and $BnMe_3N^+CN^-$, yielded the quinone **305** through a cascade mechanism of *N*-alkylation, cyanide addition, electrocyclic ring opening, and intramolecular 1,3-dipolar cycloaddition of the ylide **304** (Scheme 84).[171]

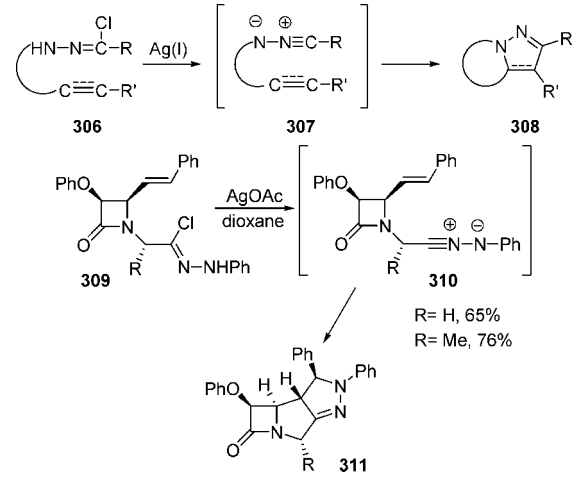
5.2. 1,3-Dipolar Cycloaddition Reactions of Nitrilimines

The group of Molteni has developed a methodology of intermolecular but mainly intramolecular 1,3-dipolar cycloadditions using nitrilimines (**307**) generated *in situ* from hydrazonoyl chlorides (**306**) with silver carbonate (Scheme 85). Alkenes or alkynes can be used as dipolarophiles. In this way, medium- and large-ring heterocyclic systems (**308**) have been formed. Stereoselective cycloadditions have also been carried out. A review has been recently published by the author.[172] One recent example is shown below (Scheme 85).[173] The β-lactamic hydrazonoyl chloride **309** gave the nitrilimine **310** under the influence of the silver ion. The intramolecular [3 + 2]-cycloaddition afforded the azetopyrrolopyrazole **311** with complete regio-, diastereo-, and enantioselectivity.

Scheme 84. Intramolecular 1,3-Cycloaddition of Azomethine Ylide and Alkynes



Scheme 85. Medium- and Large-Ring Pyrazole Synthesis via Intramolecular Nitrilimine Cycloaddition Catalyzed by Ag(I)

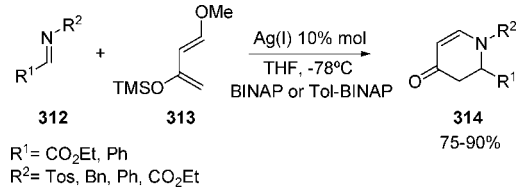


5.3. Ag-Catalyzed Aza-Diels−Alder Cycloadditions

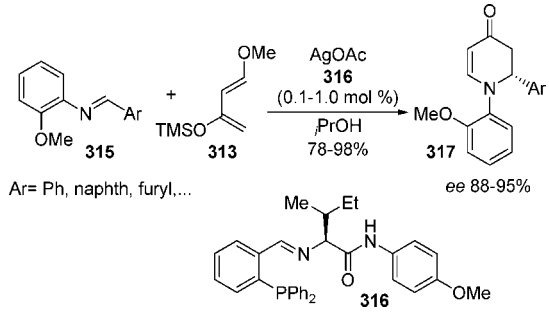
Asymmetric aza-Diels−Alder reactions provide a useful route to optically active nitrogen-containing heterocyclic compounds such as piperidines, tetrahydroquinolines, etc. Although successful examples of diastereoselective approaches using chiral auxiliaries have been reported, few examples of enantioselective reactions are known.[174] The role of the Ag(I) has already been described in the formerly discussed azomethine and nitrilimine 1,3-dipolar cycloadditions; in addition, other reactions such as aza-Diels−Alder may also be catalyzed by silver salts.

α-Imino carbonyl compounds (**312**) were investigated by Jorgensen and co-workers as substrates for aza-Diels−Alder reaction with Danishefsky's diene (**313**).[175] Different chiral *P*,*P*-ligands, such as BINAP and Tol-BINAP, were tested. Aza-Diels−Alder cycloadducts **314** were obtained under the

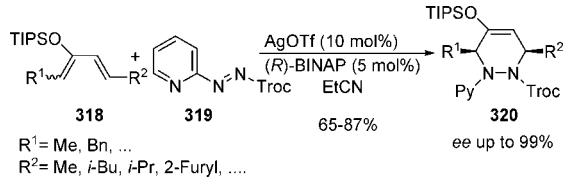
Scheme 86. Asymmetric Ag(I)-Catalyzed Aza-Diels−Alder Reactions from Imines and Danyshesky's Diene



Scheme 87. Ag-Catalyzed Cycloaddition between Arylimines and Danishefsky's Diene Using Chiral *P,N*-Ligands



Scheme 88. Asymmetric Azo-Hetero-Diels−Alder Reactions from a 2-Azopyridine Derivative

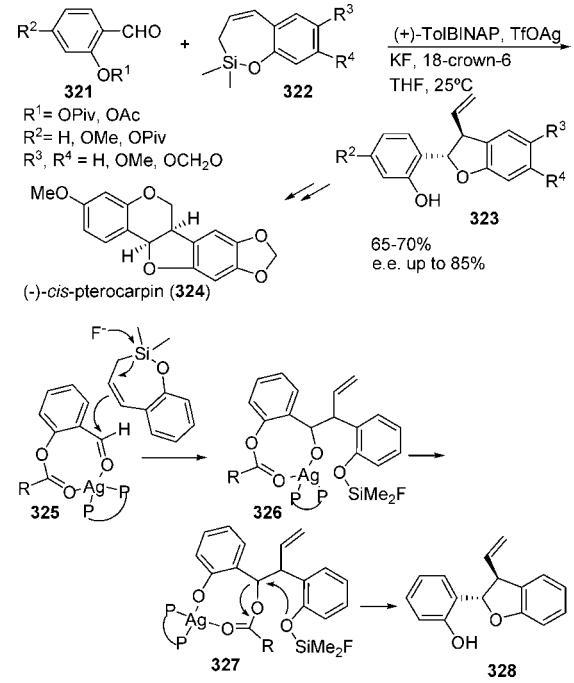


influence of several Lewis acids, like $AgSbF_6$, AgOTf, and $AgClO_4$ (Scheme 86). The yields were good, but poor enantioselectivity was achieved (30−34%). Also, when **313** reacted with *N*-benzylildeneaniline **312** ($R^1 = R^2 =$ Ph) in the presence of silver phosphane partnered with carborane monoanions, like $[Ag(PPh_3)(CB_{11}H_{12})]$,[176] **314** ($R^1 = R^2 =$ Ph) was obtained in good yield (up to 99%) with <0.1% of catalyst. Substoichiometric amounts of water accelerated the reaction, possibly by coordination of the water to the Ag^+ and the N of the imine. On the other hand, cycloaddition between diarylimines **312** and **313** took place smoothly in water in the presence of a catalytic amount of silver triflate and in high yields. (57−92%). The method was extended to a three-component reaction where the unstable imines could be generated *in situ*. Only a trace amount of the desired cycloadduct was observed when the diene was added in one portion, but under slow addition, the yield improved dramatically (51−90%). In some cases, yields were improved with the aid of the nonionic surfactant Triton X-100.[177]

Hoveyda and co-workers carried out an asymmetric Ag-catalyzed aza-Diels−Alder reaction using Danishefsky's diene (**313**). When the imines **315** reacted with **313** in the presence of <1% of AgOAc and the chiral imine ligand **316**, the cycloaddition afforded **317** with high yields (>90%) and enantioselectivity levels (>88% ee) (Scheme 87).[178] The reaction also worked well with other chiral imine ligands derived from **316**, including a supported ligand.

Yamamoto and Kawasaki have developed a highly regio-diastereo-, and enantioselective azo-hetero-Diels−Alder reaction using 2-azopyridine (**319**) and Ag(I)−BINAP 2:1 catalyst, from acyclic silyloxydiene (**318**) (Scheme 88).[179,180] The pyridazine derivatives (**320**) thus formed could be effectively transformed to 1,4-diamines, which are pharmaceutically important compounds.

Scheme 89. Silver-Catalyzed Asymmetric Synthesis of 2,3-Dihydrobenzofurans



6. Other Ag(I)-Mediated Heterocyclizations

In this section, we have included other silver-mediated reactions that do not fit among the main silver-mediated processes, but which are usually of high interest and synthetic potential.

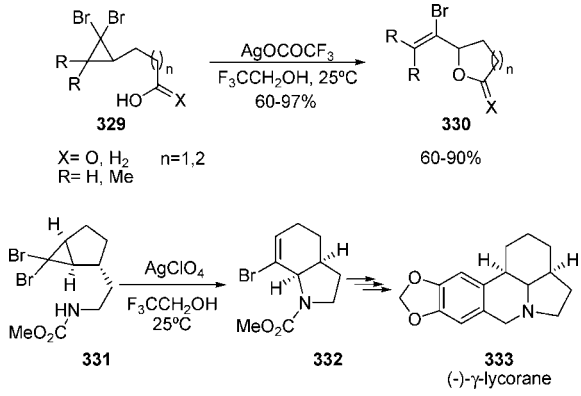
6.1. Silver-Catalyzed Sakurai Allylation of Aldehydes

2,3-Dihydrobenzofurans (**323**) can be diastereoselectively prepared by condensation of aromatic aldehydes (**321**) with 2,3-dihydrobenzoxasilepines (**322**) under the catalysis of Ag(I) complexes, and in the presence of a source of fluoride ion (Scheme 89).[2] Some mechanistic aspects of this reaction have been described.[181] The silver complex can coordinate both oxygen atoms of the aldehyde and the ester to form an eight-membered ring (**325**).[2] The addition of the allylsiloxane to this complex gives the intermediate **326** that, after silver-catalyzed transesterification, leads to the intermediate **327**. Eventually, cyclization takes place to form the 2,3-dihydrobenzofuran system (**328**). Using chiral catalysts, this strategy allowed us to develop a new enantioselective total synthesis of natural *cis*-pterocarpans and their *trans*-isomers. Through this method, the first enantioselective total synthesis of the antifungal agent (−)-pterocarpin (**324**) was achieved.

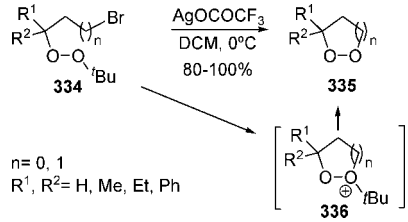
6.2. Silver-Promoted Cationic Cyclizations

The disrotatory electrocyclic cleavage of bromocyclopropane derivatives containing internal nucleophilic hydroxyl and carboxyl groups provides a useful method for the synthesis of lactones, tetrahydropyrans, and tetrahydrofurans[182] (Scheme 90). The silver salt initiates the ring opening of the *gem*-dibromocyclopropane (**329**), a process that leads to the formation of an incipient π-allyl cation, which is intramolecularly captured by the nucleophile to form

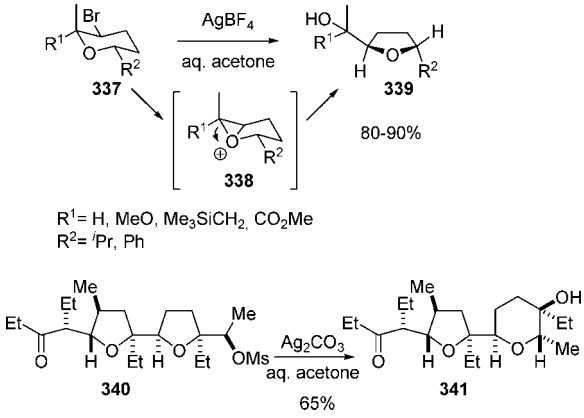
Scheme 90. Heterocyclizations Through Silver(I)-Promoted Ring Opening of *gem*-Dibromocyclopropanes



Scheme 91. Silver-Induced Synthesis of 1,2-Dioxetanes and 1,2-Dioxolanes



Scheme 92. Tetrahydrofurans and Tetrahydropyrans Through Ring Contraction or Enlargement Induced by Silver



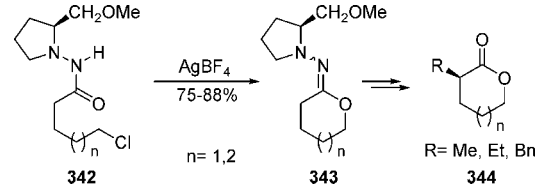
the desired heterocycle (**330**). The method has been extended to the synthesis of pyrrolidines (**332**) and applied to the total synthesis of (−)-γ-lycorane (**333**).[183]

1,2-Dioxetanes[184,185] and 1,2-dioxolanes[186] (**335**) can be prepared through silver salt-induced cyclizations of γ-bromoalkyl *t*-butyl peroxides (**334**) via cyclic trialkylperoxionium intermediates (**336**) (Scheme 91).

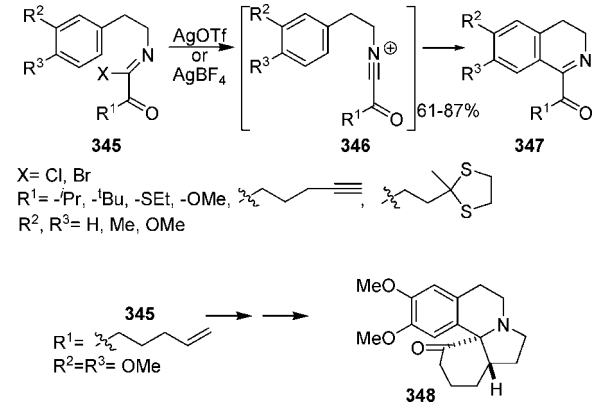
2,5-Disubstituted tetrahydrofurans (**339**) can be obtained with a high degree of stereocontrol by ring contraction of bromotetrahydropyrans (**337**) induced by silver tetrafluoroborate in acetone (Scheme 92).[187,188] The opposite transformation has also been described, as in the treatment of dihydrofuran **340** with Ag_2CO_3 to yield **341**.[189]

ω-Chloroalkanohydrazides cyclize when treated with $AgBF_4$ to yield *N,N*-disubstituted lactone hydrazones.[190] When this reaction is performed with enantiomerically pure (*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine hydrazides (**342**), it leads to the appropriate substrates for the synthesis, in high enantiomeric purities, of 2-alkyl-substituted six- and seven-membered lactones (**344**)[191] (Scheme 93).

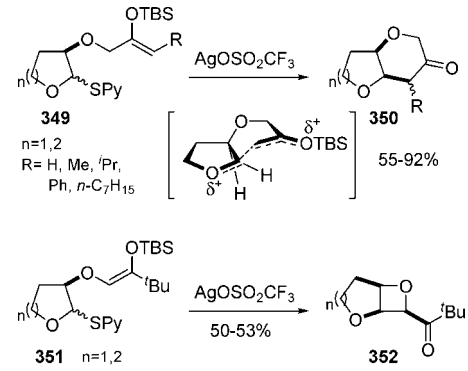
Scheme 93. Silver-Promoted Cyclization of ω-Chloroalkanohydrazides



Scheme 94. Silver-Mediated Synthesis of 1-Acyldihydroisoquinolines



Scheme 95. Silver-Mediated Intramolecular *C*-Glycosidation



1-Acyldihydroisoquinolines (**347**) can be prepared through cyclization of an appropriately substituted arene onto a highly reactive acylnitrilium cation (**346**) (Scheme 94). These intermediates are formed by treatment of (α-keto)imidoyl halides (**345**) with a silver salt. An efficient synthesis of the erythrinane skeletal system (**348**) (erythrina alkaloids), which relies upon the sequential utilization of this method followed by an azomethine ylide [3 + 2]-cycloaddition reaction, has been achieved.[192]

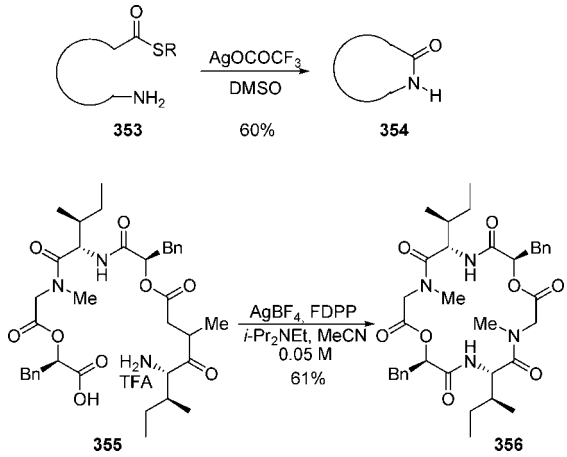
The treatment of *S*-glycosidic silyl enol ethers (**349**) with silver triflate can be used to prepare bicyclic *C*-glycosides (**350**)[193–195] as single, *cis*-fused diastereomers for both the five- and six-membered templates, and also for the synthesis of ketooxetanes (**352**) (Scheme 95).[196]

6.3. Silver-Induced Macrocyclizations

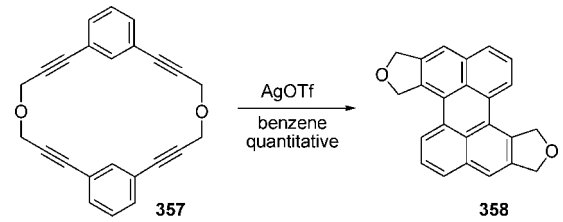
Cyclic peptides (**354**) can be prepared from unprotected peptide thioesters through silver ion coordination of the reactive ends to permit long-range acyl migration (Scheme 96).[197] An independent work achieved the synthesis of a stereoisomer of hirsutellide (**356**).[198]

Cyclyne **357** (consisting of 1,3-diethynylbenzene and ether units) undergoes Ag(I) ion-induced cyclization, leading to

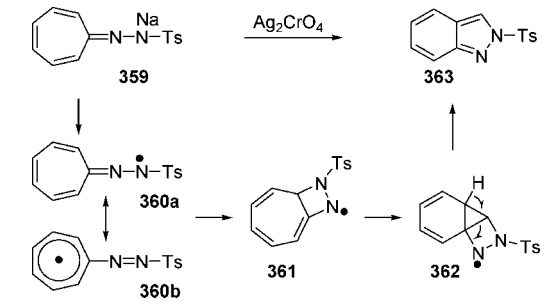
Scheme 96. Silver Ion-Mediated Macrocyclization of Peptides



Scheme 97. Ag^{+}-Induced Cyclization Leading to the Perylene Skeleton



Scheme 98. Reaction of Sodium Salts of Tosylhydrazone Compounds With Silver Chromate



the highly selective formation of the tetrahydrofuran ring-fused perylene **358**, which has intense blue fluorescence (Scheme 97).[199] The cyclization is considered to proceed by a double-zipper (concerted) reaction involving aromatization and successive protodemetalation. Sulfur analogues do not exhibit the same behavior.[200]

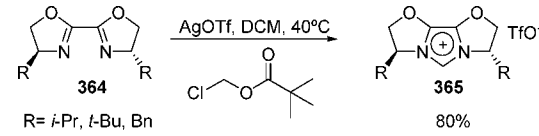
6.4. Other Types of Cyclization

Tropone tosylhydrazone sodium salt (**359**) reacts with silver chromate to give 2-tosyl-2*H*-indazole (**363**) (Scheme 98). The reaction is thought to proceed through the cyclization of the hydrazyl radical intermediate (**360**), which is stabilized by the canonical formula **360b**.[201]

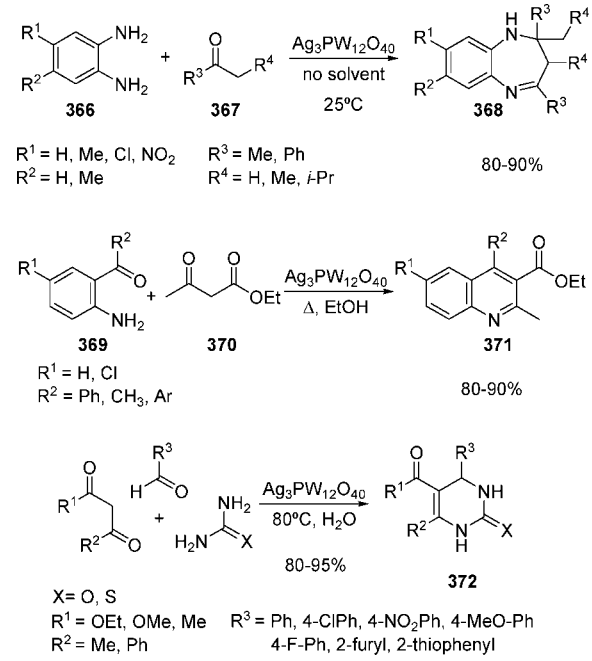
Silver triflate in combination with chloromethyl pivalate has been used to prepare the imidazolium triflate **365** from the bisoxazoline **364** (Scheme 99).[202]

$Ag_3PW_{12}O_{40}$ is a recyclable water-tolerant heteropolyacid that can be used for the preparation of 1,5-benzodiazepines (**368**),[203] quinolines (**371**)[204] (Friedländer annulation), or 3,4-dihydropyrimidinones (**372**)[205] (Biginelli condensation) (Scheme 100).

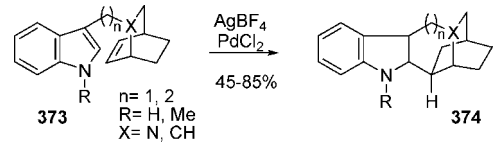
Scheme 99. Silver-Mediated Preparation of Imidazolium Triflates from Bisoxazolines



Scheme 100. $Ag_3PW_{12}O_{40}$ in the Synthesis of Heterocycles



Scheme 101. Silver Influence on the Stereoselection in Intramolecular Heck Reactions



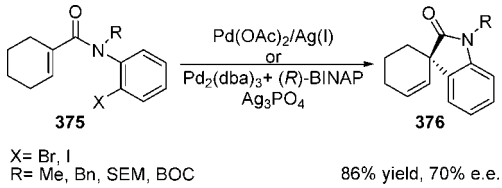
6.5. Silver as Cocatalyst with Pd, Au, Cu, Pt, Rh, and Ru

Silver salts are also known to be used as additives to other active transition metals. In this way, silver compounds generally react with transition metal halides to generate catalytically more active cationic species; often they are critical for successful organic transformations.[22] Many examples have been reported in different kinds of reactions, and we wanted to finish this review by showing some of these interesting applications.

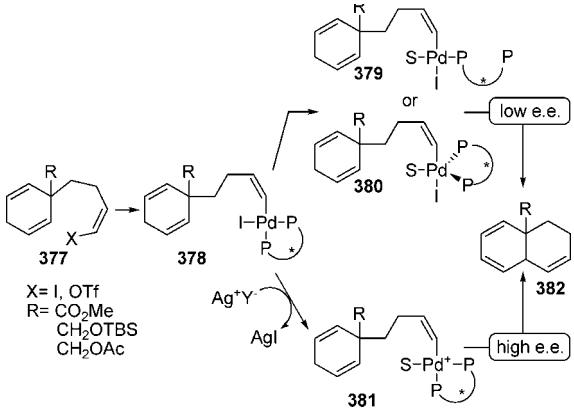
Many other syntheses of heterocycles in which silver salts are combined with other transition metal complexes have been described, mainly with Au,[206–218] Cu,[219,220] Pt,[221,222] Rh,[223] and Ru.[224] The role of silver in these processes has scarcely been described. However, for palladium-catalyzed reactions, the influence of silver salts seems to be clearer.

The benefits of using silver salts in combination with palladium catalysts for the synthesis of heterocycles through C−C bond formation was first reported by Trost and co-workers.[225] The mixed-metal system $PdCl_2$ and $AgBF_4$ can initiate the cyclization of an indole ring onto an olefin (**373**) to form six- and seven-membered rings (**374**) (Scheme 101). The role of the mixed-metal catalyst seems to involve enhancement of the electrophilicity of the palladium chloride in the presence of silver ion.[226]

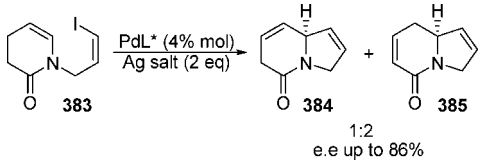
Scheme 102. Silver-Assisted Intramolecular Heck Synthesis of Spirooxindoles



Scheme 103. Silver Effect in the Catalytic Asymmetric Synthesis of Decalins



Scheme 104. Asymmetric Synthesis of Functionalized Indolizidine Derivatives



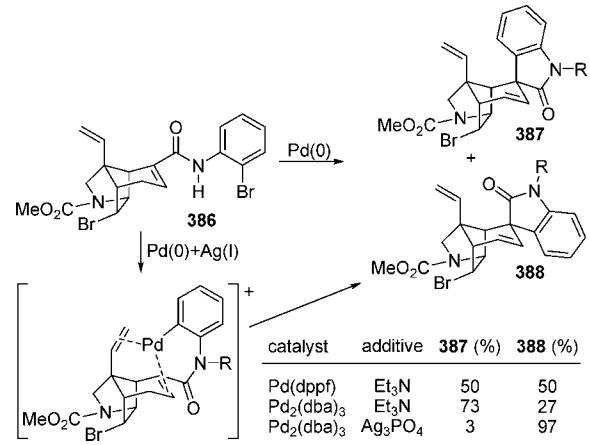
In the preparation of a variety of tricyclic ring systems by palladium-catalyzed cyclizations of unsaturated aryl halides (**375**) (Scheme 102), the addition of silver salts dramatically reduces double-bond isomerizations of the cyclization products (**376**).[227] Moreover, depending upon how HX is scavenged, either enantiomer of the Heck product can be formed with good selectivity using a single enantiomer of a chiral diphosphine ligand. A moderately strong Brönsted base must be present to obtain useful, good results. Silver salts having weakly basic counterions (e.g., OTf^-, NO_3^-, BF_4^-) do not effectively promote Heck cyclization.[228,229]

Shibasaki and co-workers have reported the catalytic asymmetric synthesis of the decalins **382** from the prochiral alkenyl iodides **377**.[230] They proposed that the Heck reaction proceeds via a 16-electron Pd^+ intermediate (**381**) in the presence of Ag(I), but via a neutral palladium intermediate (**379** and/or **380**) in the absence of Ag(I) (Scheme 103). In addition, the Ag(I) counteranion plays an important role in the reaction, as it largely influences the asymmetric induction. Counteranions that make tight ion pairs with Pd^+ interfere with the ideal square planar geometry in the intermediate and give products of low ee. Thus, the use of silver-exchanged zeolite leads to an "anion-free" square planar Pd^+ cation intermediate, which affords high asymmetric induction levels.[230]

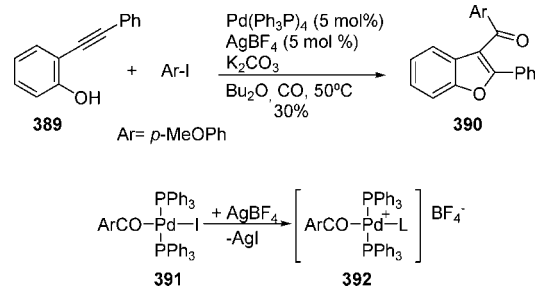
The same observations were made in the preparation of the functionalized indolizidine derivatives **384** and **385** from the iodoalkane **383** (Scheme 104).[230]

The stereoselectivity in the palladium-catalyzed intramolecular Heck cyclizations, which lead to congested quaternary carbon centers (**387**, **388**) (Scheme 105), can be inverted in the presence of a silver salt.[231] The high selectivity in this case is attributed to coordination of the angular vinyl group during the insertion step.

Scheme 105. Silver Influence on the Stereoselection in Intramolecular Heck Reactions



Scheme 106. Silver Effect on the Palladium-Catalyzed Carbonylative Annulation of *o*-Alkynylphenols



Yang and co-workers have found that cationic palladium complexes exhibit high reactivity toward coordination of alkenes or alkynes to bring about efficient carbonylation reactions. Such cationic complexes can be easily prepared in situ by reaction or silver salts of BF_4^-, ClO_4^-, and BAr_4^- with organopalladium halides in the presence or tertiary phosphine ligands or chelating diamine (diimine) ligands. When trying to convert **389** into **390** without Ag-salt, no 3-aroyl-benzo[*b*]furans (**390**) were detected; just the corresponding phenol ester was obtained (Scheme 106).[232] The authors have proposed a complex **392** as intermediate, generated from organopalladium iodide **391**. This complex **392** contains a cationic metal center with Lewis acid character and has a stronger tendency to coordinate the unsatured triple bond.

7. Concluding Comments

In the past several years, significant progress has been made in the exploration of the silver-based heterocyclizations. Silver complexes have been shown to efficiently catalyze the intramolecular addition of oxygen and nitrogen nucleophiles to alkynes, allenes, and olefins to generate oxygen and nitrogen heterocycles. Moreover, numerous natural and unnatural products have been prepared by synthetic routes that have a silver-mediated 1,3-dipolar cycloaddition of an azomethine ylide or a nitrilimine, as a crucial step for the construction of a nitrogen-containing, five-membered heterocycle. In addition, silver-catalyzed asymmetric aza-Diels−Alder reactions provide a useful route to optically

active nitrogen-heterocyclic compounds such as piperidines or pyridazines. Substituted dihydrobenzofurans can also be enantioselectively prepared through silver-promoted allylation of aldehydes. Other types of silver-mediated cyclizations can also be used in the synthesis of tetrahydrofurans, tetrahydropyrans, 1,2-dioxetanes, 1,2-dioxolanes, medium-sized lactones, dihydroisoquinolines, etc. Silver salts can also be used as cocatalysts with other transition metals. Unique activity was observed for these silver-based systems in several cases. Consequently, the use of silver can enrich several available heterocyclization methods, and further developments in the application of chiral silver complexes will hopefully appear in the near future.

8. Acknowledgments

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