Review

Coinage Metal-Assisted Synthesis of Heterocycles

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Coinage Metal-Assisted Synthesis of Heterocycles

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Contents

1. Introduction

Substituted heterocycles are a structural component of a vast number of biologically active natural and non-natural compounds. Synthesis of various heterocycles has been a research objective for over a century, and a variety of well-established methods are available in the literature. Development of new approaches for their syntheses, employing efficient and atom-economical routes, is currently a popular research area. Among the many new synthetic transformations, transition metal-catalyzed reactions are the most attractive methodologies, since those reactions can directly construct complicated molecules from readily accessible starting materials under mild conditions. The formation of heterocycles by using various transition metals such as Pd, Ni, Ru, and Rh has been extensively investigated and documented in the literature.

Recently, we published a paper in *Chemical Reviews* about transition metal-catalyzed heterocycle synthesis.[1] Several other researchers have reviewed this subject as well;[2] however, all those reviews are very general. Since this thematic issue of *Chemical Reviews* is focused on coinage metals (Cu, Ag, Au), we would like to review their uses in the synthesis of heterocycles.[3] Recently, catalysis by coinage metals has emerged as a powerful tool for various C−C and C−X bond formation reactions, often with interesting mechanistic pathways. We tried to include a discussion of the mechanism of the reactions, whenever possible, to give an idea about the activation of substrates and possible reaction pathways.

Coinage metal catalysts are used not only as sole catalysts but also as cocatalysts. We formerly referred to such a catalyst as a bimetallic catalyst because it consists of a combination of two metals.[4] Examples of bimetallic systems include Pd−Cu, Pd−Ag, Rh−Ag, Pt−Ag, Au−Ag, and Mn−Cu. Since the subject of multimetallic catalysis was thoroughly reviewed previously,[4] in this review we will discuss the use of coinage metals as a sole catalyst for the synthesis of heterocycles. There are a large number of reports on the use of Cu, Ag, and Au catalysts to generate heterocycles. We have tried to include many recent examples in this review. Although a discussion of all reports is desirable, it is not possible to explain all papers in the text. Therefore, we discuss only the most essential reactions here; however, we cite additional relevant reviews and reports in the References section. This review covers studies up to November 2007, and any omissions on this wide topic are unintentional. It should be noted that only reactions in which a heterocyclic ring is essentially generated are described. Other reactions, in which a heterocyclic ring already exists in the molecule and a coinage metal catalyzes the further structural manipulations, are not described here. For example, as shown in Scheme 1, a heterocyclic ring is generated by the catalysis of coinage metals; on the other hand, in Scheme 2, coinage metals catalyze the side ring closure of heterocycles.

2. Cyclization of Unsaturated C−C Bonds with Tethered Nucleophiles

2.1. Cyclization of Allenyl/Alkynyl/Cyclopropenyl Carbonyls, Imines, Epoxides, Sulfoxides, Dithioacetals, and Azides

Cyclization of allenyl/alkynyl carbonyls, imines, and epoxides represents a very convenient method for the

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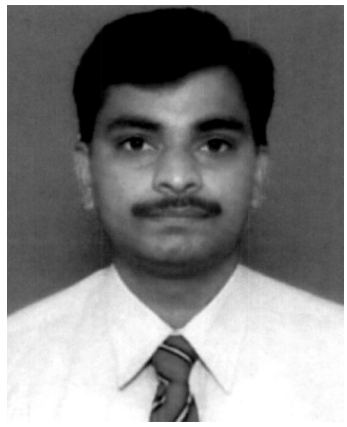
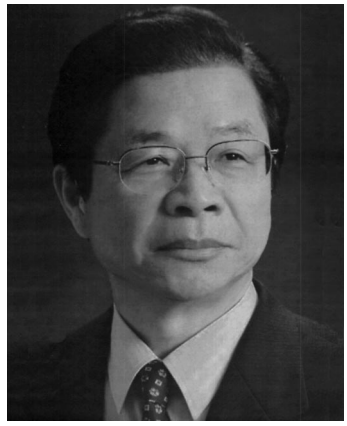
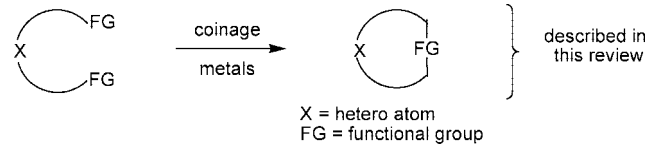


Nitin Patil was born in Jalgaon (Maharashtra), India, in 1975. After completing his master studies in 1997 at North Maharashtra University, he joined Dr. Dilip Dhavale's research group at University of Pune for Ph.D. work. He completed his doctoral study in 2002 on the synthesis of polyhydroxylated piperidine and indolizidine alkaloids. After working for about a year as a postdoctoral fellow at University of Goettingen with Prof. Christoph Schneider on enantioselective opening of epoxides, he moved to Tohoku University, Japan, as a JSPS fellow to work with Prof. Yoshinori Yamamoto. Later, in April 2005, he was appointed as Assistant Professor of Organic Chemistry in the same laboratory. In June 2006, he joined Prof. K. C. Nicolaou's laboratory at Singapore, and in January 2008, he moved to Nicolaou's other laboratory at Scripps Research Institute. His research interests include transition metal- and Lewis acid-mediated development of new synthetic methods, asymmetric catalysis, and synthesis of biologically important natural and unnatural compounds. He has authored 30 research publications in international peer-reviewed journals as well as book chapters and reviews.

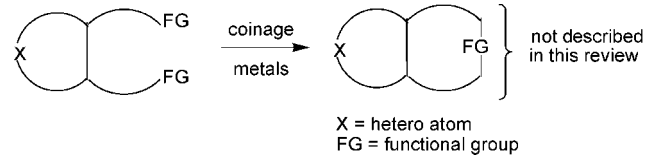


Yoshinori Yamamoto was born in Kobe, Japan, and received his M.S. and Ph.D. degrees from Osaka University. In 1970, he was appointed as an Instructor at Osaka University, after which he went to Prof. H. C. Brown's research group at Purdue University as a Postdoctoral Associate (1970−1972). In 1977, he was appointed as an Associate Professor at Kyoto University. In 1986, he moved to Tohoku University to take up his present position, Professor of Chemistry. He was awarded the Chemical Society of Japan Award for Young Chemists (1976), the Chemical Society of Japan Award (1996), the Humboldt Research Award (2002), Purple Ribbon Medal from The Cabinet (2006), and A. C. Cope Scholar Award from ACS (2007). He is the Regional Editor of *Tetrahedron Letters* and Volume Editor of *Science of Synthesis*, and he was the President of the International Society of Heterocyclic Chemistry (2000−2001). He was the project leader of the 21st Century COE Program of MEXT "Giant Molecules and Complex Systems, Chemistry Group of Tohoku University" (2002−2006). Further, he was a vice-president of Tohoku University (2006−2007) and a vice-president of the Chemical Society of Japan (2006−2007). Since 2006, he is the director of WPI-Advanced Institute for Materials Research in Tohoku University. He has a wide range of research interests in synthetic organic and organometallic chemistry. His recent work focused on the use of transition metal complexes and Lewis acids as catalytic reagents in organic synthesis and synthesis of complex natural products.

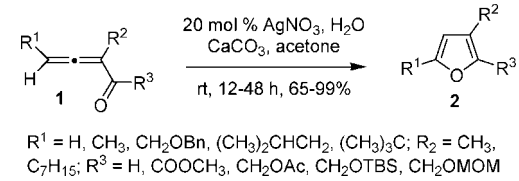
Scheme 1



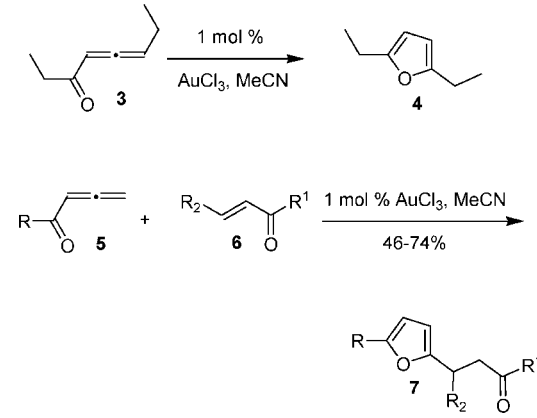
Scheme 2



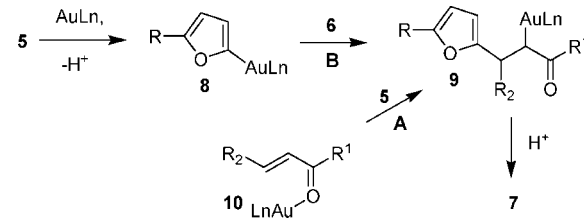
Scheme 3



Scheme 4



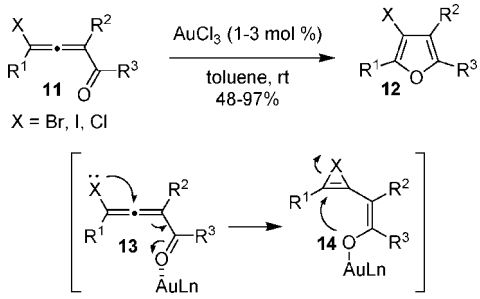
Scheme 5



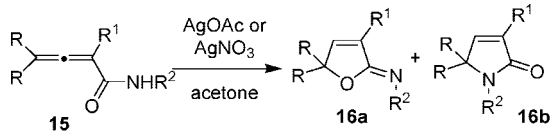
preparation of multiply substituted furans and pyrroles. Marshall et al. reported a route for the syntheses of furans **2** involving Ag(I)-catalyzed cyclization of allenyl ketones/aldehydes **1** (Scheme 3).[5] This group was the first to show that this type of cyclization is very useful for the synthesis of multiply substituted furans.

It is reported that cyclization of allenyl ketone **3** provided furan **4** in the presence of catalytic amounts of $AuCl_3$. The reaction was extended to one-pot cyclization/dimerization of **5** with α,β-unsaturated ketones **6** to give C-2-substituted furans **7** (Scheme 4).[6] The mechanism of the reaction is shown in Scheme 5. The authors believed the intermediacy of **9** and proposed two possibilities for its formation: Either the $AuCl_3$ activates the enones **6** to form **10**, which then create the new C−C bonds by an electrophilic aromatic substitution at the 5-position of the furan to provide **9** (path

Scheme 6

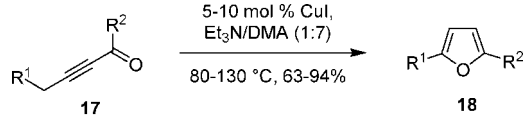


Scheme 7



R = H, R^1 = OMe, R^2 = alkyl: only **16a**
R = Me, R^1 = H, R^2 = alkyl: **16a** + **16b** mixture

Scheme 8



R^1 = H, C_5H_{11}, C_3H_7, OMe, $THPOCH_2$, OTHP, $Ph(CH_2)_2$;
R^2 = Ph, C_6H_{13}, Me, $CH{=}CMe_2$, $(CH_2)_2COOMe$, C_6H_{13}, $(CH_2)_3OH$, ^{t}Bu, CH_2OTHP

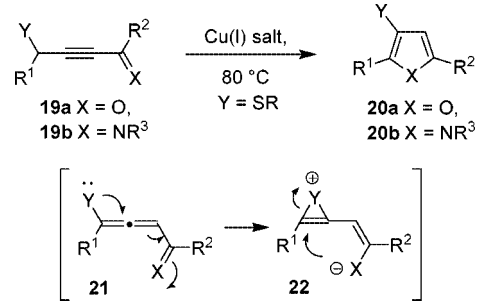
A), or a cyclization of **5** under gold catalysis forms a furylgold species **8**, which subsequently undergoes a 1,4-addition to the Michael acceptor (path B). The intermediate **9** then undergoes proto-demetalation to form **7** along with regeneration of the gold catalyst. Recently, gold(III)−porphyrin complexes have been utilized for the cyclization of allenones.[7]

Gevorgyan et al. have shown that 1,2-iodine, -bromine, and -chlorine migration in haloallenyl ketones **11** takes place in the presence of $AuCl_3$.[8] For this reaction, iodo and bromo allenyl ketones gave better results, compared to their chloro analogues. This chemistry is interesting not only as a novel cascade transformation but also as a mild, selective, and efficient approach to different types of 3-halofurans **12**. It was reported that the reaction proceeded through halirenium intermediate **14**, formed by intramolecular Michael addition of X to the enone moiety as shown in **13**, which via subsequent addition−elimination furnishes 3-halofurans **12** (Scheme 6). It is interesting to note that simply switching the solvent from toluene to THF caused a dramatic change in selectivity, affording 2-halofurans as the major product.

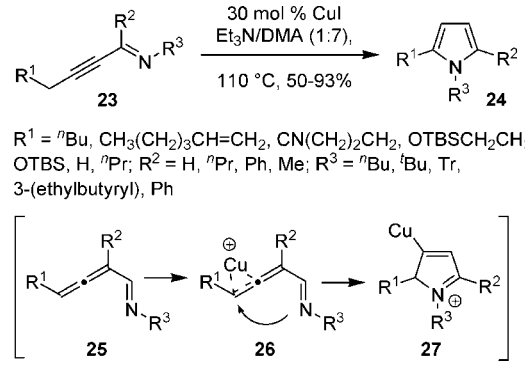
Cyclization of *N*-monosubstituted allenic carboxamides **15** in the presence of AgOAc or $AgNO_3$ was reported by Brandsma and co-workers (Scheme 7).[9] The product **16a** or a mixture of **16a** and **16b** was obtained, depending on the substitution pattern. Other reagents, such as KO^{t}Bu in DMSO, copper(II) bromide, and palladium catalysts, did not work for the reaction.

Gevorgyan and co-workers have shown that alkynes can also be used instead of allenes for furan synthesis. They developed a method for the synthesis of 2-monosubstituted and 2,5-disubstituted furans **18** via the CuI-catalyzed cyclization of alkynyl ketones **17** (Scheme 8).[10] It was demonstrated that furans containing both acid and base labile

Scheme 9

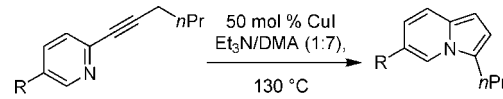


Scheme 10



R^1 = ^{n}Bu, $CH_3(CH_2)_3CH{=}CH_2$, $CN(CH_2)_2CH_2$, $OTBSCH_2CH_3$, OTBS, H, ^{n}Pr; R^2 = H, ^{n}Pr, Ph, Me; R^3 = ^{n}Bu, ^{t}Bu, Tr, 3-(ethylbutyryl), Ph

Scheme 11



28a R = H
28b R = Me
28c R = CF_3

29a R = H, 91%
29b R = Me, 73%
29c R = CF_3, 73%

groups could be easily synthesized using this methodology. Pioneering work from the same group revealed that 3-thio-substituted furans **20a** and pyrroles **20b** could be obtained from propargyl ketones **19a** and propargyl imines **19b**, respectively, by heating in *N*,*N*-dimethylacetamide in the presence of CuI (Scheme 9).[11] The key in the mechanism was the 1,2-migration of the Y group from the sp^2 carbon atom in the allenyl species, as shown in intermediates **21** and **22**.

The same researchers also reported a new route for the synthesis of pyrroles **24** via copper(I)-catalyzed cyclization of alkynyl imines **23** (Scheme 10).[12] Mechanistic studies revealed that this reaction proceeded via the propargyl−allenyl isomerization of **23** to the allenyl imines **25** and through the nucleophilic attack of the nitrogen atom of imine on the electron-deficient carbon, as shown in intermediate **26**, which forms the copper-containing pyrrole ring skeleton **27**. Isomerization in **27**, protonation, and regeneration of the catalyst affords pyrroles **24**. This methodology was also applied for the synthesis of indolizidines. The copper-assisted reaction of 2-alkynylpyridines **28** provided the indolizidine derivatives **29** in good yields (Scheme 11).[13] The copper-assisted double-cyclization of bis-alkynylpyrimidine **30** afforded the 5-6-5 tricyclic heteroaromatic skeleton **31** (Scheme 12).[13] This transformation was used as a key step in the diastereoselective total synthesis of (±)-tetraponerine T6. Liu and Yan reported gold-catalyzed multicomponent reactions of aldehydes, amines, and alkynes for the synthesis of aminoindolizines.[14] The same research group later reported

Scheme 12

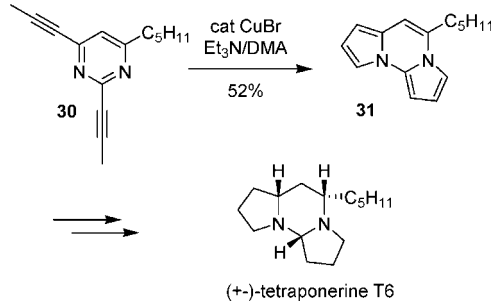
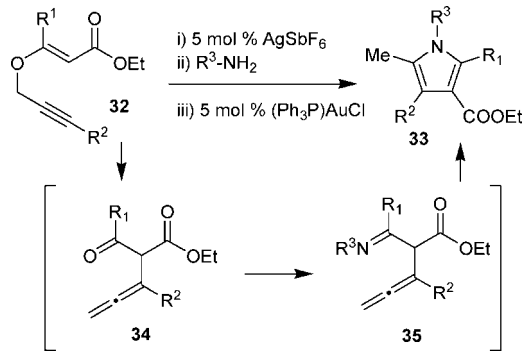


Table 1



entry	R^1	R^2	R^3	yield (%)[a,b]
1	Me	Ph	Ph	75
2	Me	Ph	*p*-MeO-C_6H_4	75
3	Me	o-MeO-C_6H_4	Ph	83
4	*n*-Pent	Me	Ph	68
5	Ph	Ph	Ph	65
6	Ph	3-thienyl	Ph	74
7	Ph	CH_{20}-C_6H_{12}	Ph	90
8	Ph	CH_{20}-C_6H_{12}	1-naphthyl	79
9	Ph	$(CH_2)_3$OTEP	Ph	70
10	Ph	H	Ph	52
11	Ph	TBS	Ph	77

[a] Conditions: (1) 0.2 mmol of **1**, 5 mol % $AgSbF_6$, 23 °C, CH_2Cl_2 (0.4 M), 30 min; (2) R^3-NH_2 (1.5 equiv), 23 °C; (3) 5 mol % $(PPh_3)AuCl$, 38 °C, 30−240 min. [b] Yield of pure product after column chromatography.

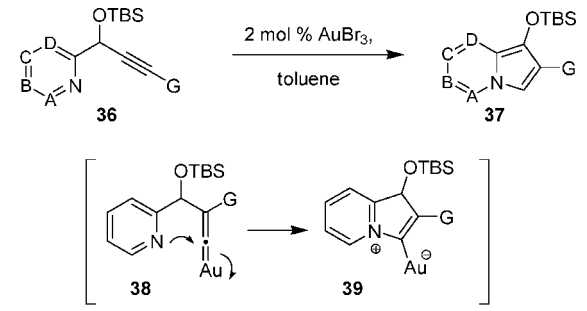
the synthesis of indolizines and indolizinones from 2-pyridyl-substituted propargylic alcohols.[15]

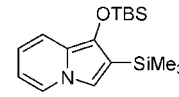
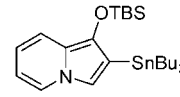
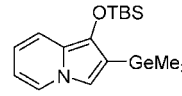
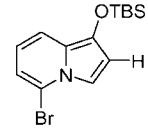
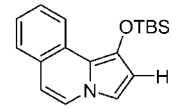
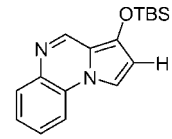
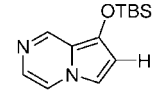
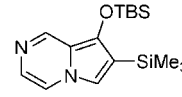
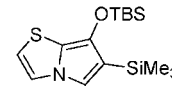
Kirsch et al. reported a one-pot process for the synthesis of pyrroles **33** from easily accessible propargyl vinyl ethers **32** and aromatic amines (Table 1).[16] The cascade reaction proceeds through a silver(I)-catalyzed propargyl Claisen rearrangement (cf. **34**), an amine condensation (cf. **35**), and a gold(I)-catalyzed 5-*exo-dig* heterocyclization.

A new gold-catalyzed cascade cycloisomerization of propargylic derivatives **36** into pyrrole-containing heterocycles **37** has been reported (Table 2).[17] This cascade transformation involves 1,2-migration of silyl, stannyl, and germyl groups and allows an efficient synthesis of various C-2-substituted fused pyrrole-containing heterocycles. Mechanistically, first isomerization of alkyne **36** results in the formation of vinylidene species **38**, followed by nucleophilic attack of the nitrogen lone pair at the vinylidene carbon resulting in formation of zwitterions **39**, which undergo a series of 1,2-hydride shifts to furnish **37**.

Dake and co-workers reported a domino process for the synthesis of pyrroles **41** starting from ketoalkynes **40** and

Table 2

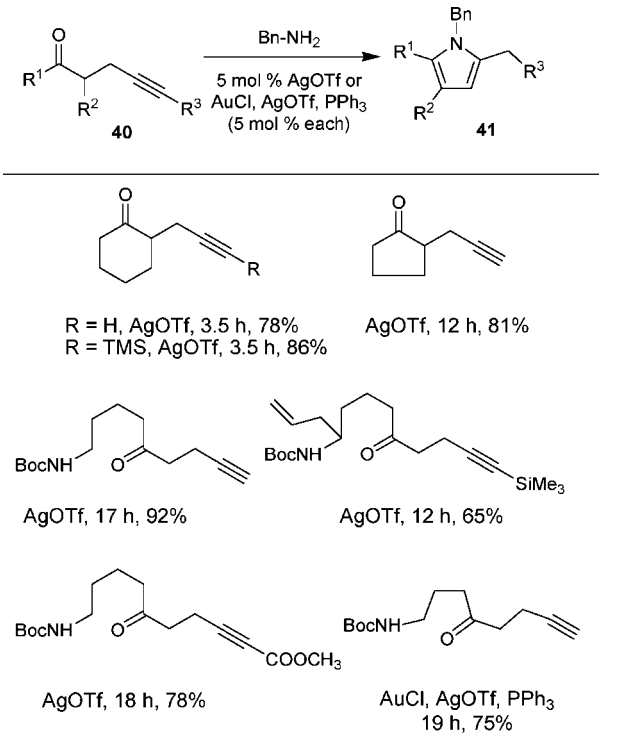


entry	G	T(°C)	time	product	yield (%)[a]
1	$SiMe_3$	50	1.5		63[b]
2	$SnBu_3$	50	0.5		64[d]
3	$GeMe_3$	25	0.5		92[b]
4	H	50	1.5		62
5	H	25	0.5		81
6	H	50	2.0		94
7	H	60	4.5		72
8	$SiMe_3$	25	0.5		87[e]
9	$SiMe_3$	50	3.5		56

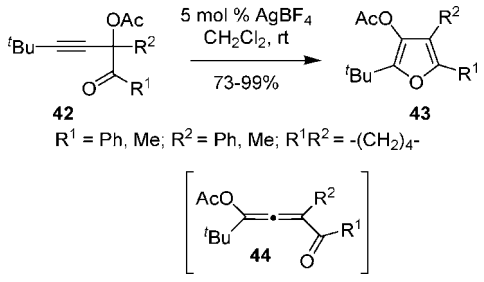
[a] Isolated yield and reactions performed on 0.5 mmol scale. [b] Yield over two steps. [c] Reaction was performed on 5.0 mmol scale in the presence of AuCl catalyst (0.5 mol %). [d] NMR yield. [e] AuCl was used as catalyst.

amines. Either silver trifluoromethanesulfonate or a mixture of gold(I) chloride, silver trifluoromethanesulfonate, and triphenylphosphine catalyzed the formation of pyrroles from substituted β-alkynyl ketones and amines (Table 3).[18] The reactions proceeded by using 5 mol % of catalyst, with yields of isolated pyrroles ranging from 13% to 92%.

Table 3



Scheme 13

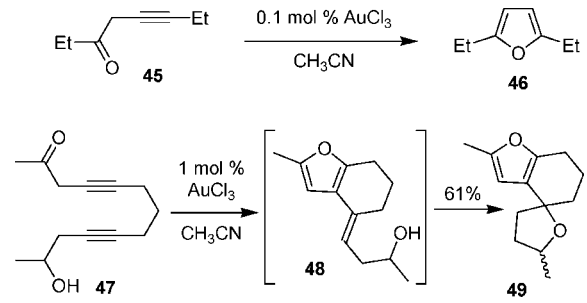


Recently, Gevorgyan et al. reported the syntheses of furans **43** from alkynyl ketones **42** via 1,2-migration of acetate groups (Scheme 13).[19] The reactions were conducted in the presence of 5 mol % $AgBF_4$ at room temperature. Not only acetate but also $-OP(O)(OEt)_2$ and $-OTs$ groups migrated; however, a somewhat high temperature (60 °C) was needed in order to complete the reaction. The reaction involves the intermediacy of allene **44**. This is the first example of 1,2-migration of acyloxy, phosphatyloxy, and sulfonyloxy groups from sp^2 carbon.

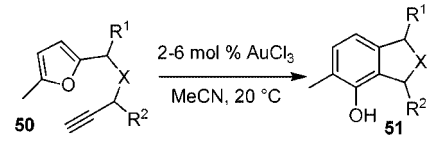
The reaction of a propargyl ketone such as **45** in the presence of 0.1 mol % $AuCl_3$ at 20 °C gave the furan **46** in quantitative yield (Scheme 14).[6] On the other hand, with palladium as catalyst, heating at 100 °C was needed in order for the reaction to proceed. A novel cascade cyclization of the propargyl ketone **47** to form **49** in the presence of $AuCl_3$ was reported in the same paper. The authors proposed the intermediacy of **48** for that cascade cyclization.

Hashmi et al. described an interesting cascade cyclization of **50**, in which alkynes are tethered with furans, for the synthesis of five- or six-membered heterocycles **51** (Scheme 15).[20] This method proved applicable only to terminal alkynes; disubstituted alkynes did not give the desired products under similar conditions. These researchers also extended this approach for the one-pot synthesis of

Scheme 14

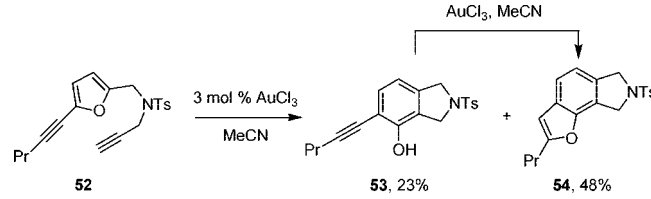


Scheme 15

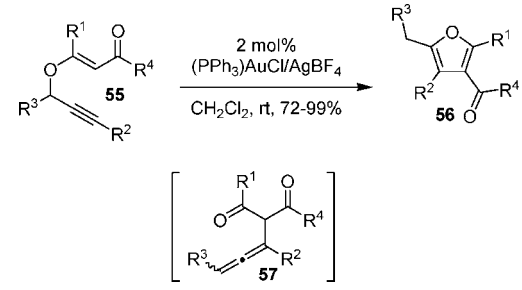


a X = O, R^1=R^2= H, 69%
b X = NTs, R^1=R^2= H, 97%
c X = NTs, R^1= Me, R^2= H, 94%
d X = NTs, R^1=H, R^2= Me, 93%
e X = NNs, R^1=H, R^2= Me, 96%
f X = C(COOMe)$_2$, R^1=R^2= H, 88%
g X = N(Ts)CH$_2$, R^1=H, R^2= H, 81%

Scheme 16



Scheme 17

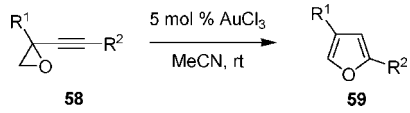


benzofuran **51** from **52**, albeit in low yield (Scheme 16).[21] Alkynylphenol **53**, obtained as a minor product in 23% yield, could be cyclized to **54** under gold catalysis conditions.

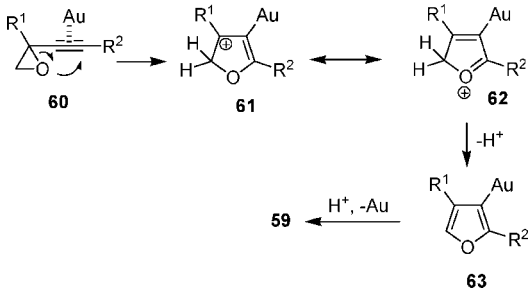
Kirsch and co-workers recently described the synthesis of highly substituted furans **56** from **55** under gold(I) catalysis (Scheme 17).[22] The reaction is accomplished at room temperature, using just 2 mol % catalyst loading. A mechanism for the cascade cyclization involves the formation of β-allenic ketone **57**, which then undergoes gold(I)-catalyzed 5-*exo-dig* cyclization, affording furans **56**.

The conversion of alkynyl epoxides **58** into furans **59** in the presence of gold(III) chloride took place at room temperature (Scheme 18).[23] Coordination of the triple bond of **58** to $AuCl_3$ enhances the electrophilicity of the alkyne (cf. **60**), and subsequent nucleophilic attack on the epoxide oxygen at the distal position of alkyne forms the species **61**, which on isomerization−deprotonation−protodemetalation (cf. **62** and **63**) give furans **59** (Scheme 19).

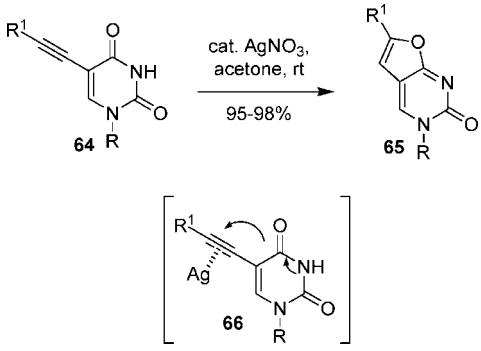
Scheme 18



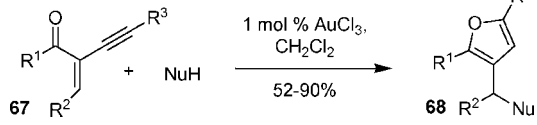
Scheme 19



Scheme 20



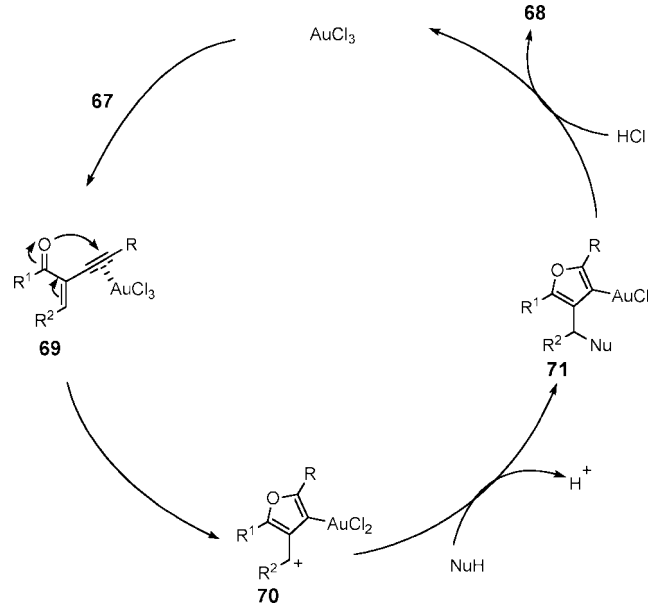
Scheme 21



An efficient method for the synthesis of substituted furanopyrimidines **65** was described by Agrofoglio and co-workers (Scheme 20).[24] Upon treatment of amidoalkynes **64** with catalytic amounts of $AgNO_3$ in acetone at room temperature, the cyclized products **65** were obtained in almost quantitative yields. Activation of alkyne by silver catalyst, as shown in intermediate **66**, was proposed.

Recently, Larock et al. reported an entirely new approach for the cyclization of 2-(1-alkynyl)-2-alken-1-ones **67** with nucleophiles in the presence of catalytic amounts of $AuCl_3$, which led to the formation of highly substituted furans **68** (Scheme 21).[25] Examples of nucleophiles include alcohols, activated methylenes, and electron-rich arenes such as *N*,*N*-dimethylaniline and *N*-methylindole. The mechanism of the reaction is depicted in Scheme 22. Coordination of the triple bond of **67** to $AuCl_3$ enhances the electrophilicity of the triple bond (cf. **69**), and subsequent nucleophilic attack of the carbonyl oxygen on the electron-deficient triple bond generates carbocation **70**. Intermolecular nucleophilic attack of nucleophiles on the carbocation gives furyl gold species **71**, which after protonation of the carbon−gold bond affords furans **68** and regenerates the catalyst $AuCl_3$. The authors ruled out the possibility of an alternative mechanism wherein $AuCl_3$ first acts as a Lewis acid, forming a complex with the carbonyl oxygen and thereby facilitating Michael addition. We later showed that inexpensive and air -stable Cu(I) catalyst in DMF could also be used for this reaction (Table 4).[26]

Scheme 22



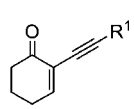
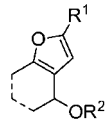
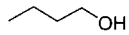
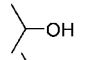
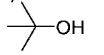
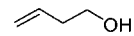
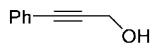
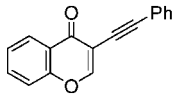
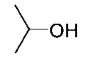
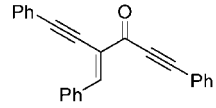
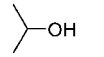
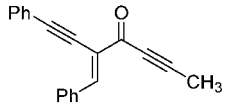
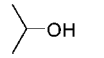
Gold-catalyzed cyclization reactions of 2-oxo-3-butynoic ester **72a** or disubstituted 1,2-dione **72b** with a variety of nucleophiles are reported by Liu and co-workers (Scheme 23).[27] The method provided an efficient and general route to multiply substituted 3(2*H*)-furanones **73a**−**i**.

Recently, Schmalz and Zhang reported the gold-catalyzed cascade cyclization of substrates of type **74** (Table 5).[28] The process provided efficient access to highly substituted furans **75** under mild conditions. A variety of nucleophiles, such as alcohols (including *tert*-butanol), phenols, or acetic acid, can be used for the reaction. Two different intermediates, **76** and **77**, were proposed for this reaction.

Kirsch and co-workers reported the gold-catalyzed synthesis of 3(2*H*)-furanones **79** from alkynyl carbonyl compound **78** bearing a hydroxy group at the propargylic position (Scheme 24).[29] They mentioned that this reaction is catalyzed by either $AuCl_3$ or $PtCl_2$, and the yield depends on the type of substrate used. For instance, when R was an aryl group, the reaction worked well with gold catalyst; however, when R was an alkyl group $PtCl_2$ proved superior. The mechanism typically involves the activation of alkyne by metal catalyst (cf. **80**), which results in the formation of oxonium ion **81**. The intermediate oxonium ion **81** underwent 1,2-shifts analogous to a formal α-ketol rearrangement to afford **79a**−**c**. In the case of silyl-protected alcohols, the iododemetalation of **81** in the presence of external NIS and alcohol as a proton source is possible.[30]

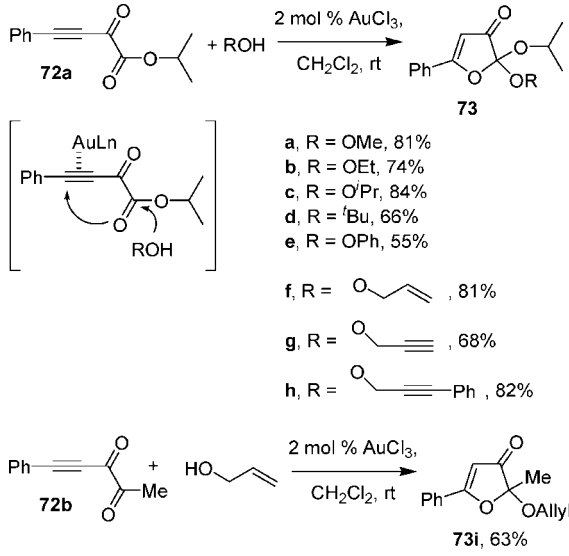
Zhang reported gold-catalyzed synthesis of highly functionalized 2,3-indoline-fused cyclobutanes **83** from propargylic esters **82** (Scheme 25).[31] The proposed mechanism for the formation of the cyclobutanes **83** is shown in Scheme 26. Activation of the C−C triple bond in propargylic esters **82** by $[Au(PPh_3)]^+$ promotes a 3,3-rearrangement of the indole-3-acetoxy group, which leads to the formation of allenylic esters **86** via the intermediates **84** and **85**. The allene moiety of **86** is further activated by the cationic Au(I) complex as shown in **87**, resulting in the formation of oxonium ion **88**. The cyclobutanes **83** are produced via C−C

Table 4

entry	substrate	R^2OH	yield (%)[a]
		R^2OH	
1	R^1 = Ph		66
2	R^1 = Ph		62
3	R^1 = Ph		0[b]
4	R^1 = Ph		66
5	R^1 = Ph		43
6	$R^1 = C_6H_4$-*p*-CF_3	MeOH	73
7	$R^1 = C_6H_4$-*p*-CH_3	MeOH	76
8	R^1 = 	MeOH	72
9		MeOH	71
10	---		78
11		MeOH	89
12	---		79
13		MeOH	74
14	---		66

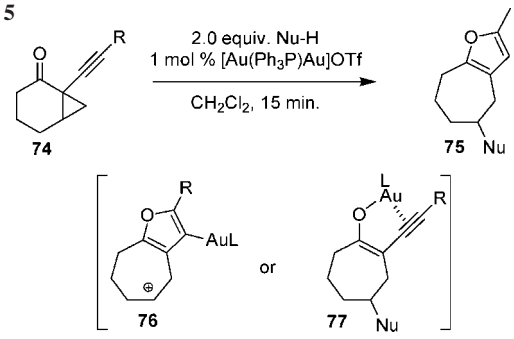
[a] Substrates (0.2 mmol), alcohols (0.3 mmol), CuBr (10 mol %) 80 °C, DMF. [b] A complex mixture was obtained.

Scheme 23



bond formation between the oxonium carbon of **88** and the C-3 carbon of the indole ring, followed by intramolecular trapping of the iminium with the alkenylgold(I) (cf. **89**). The

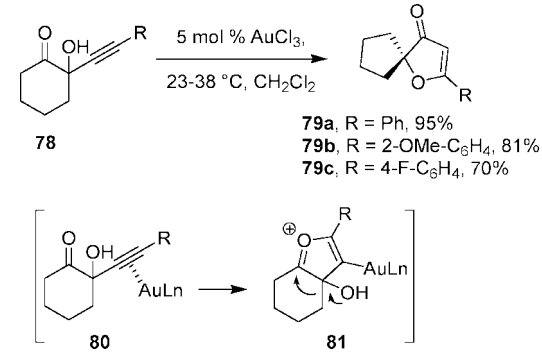
Table 5



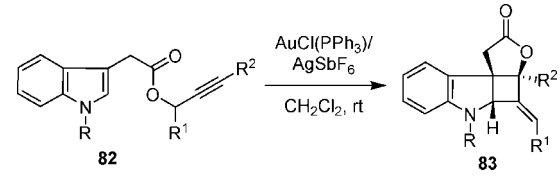
entry	R	Na−H	yield (%)[a]
1	Ph	MeOH	91 (85)
2	Ph	*i*-PrOH	90 (85)
3	Ph	^{t}BuOH	85 (77)
4	Ph	$PhCCCH_2OH$	77 (88)
5	Ph	*p*-MeO-C_3H_4-OH	84
6	Ph	AcOH	84 (61)
7	Ph	indole	73 (31)[b]
8	1-cyclohexenyl	MeOH	80
9	cyclopropyl	MeOH	82
10	cyclopropyl	2-pyrididone	68 (59)
11	*n*-butyl	MeOH	86
12	H	MeOH	76
13	TMS	MeOH	35

[a] Yields given in parentheses refer to reactions performed with AgOTf (5 mol %, 1 h). [b] Indole (1.5 equiv).

Scheme 24



Scheme 25

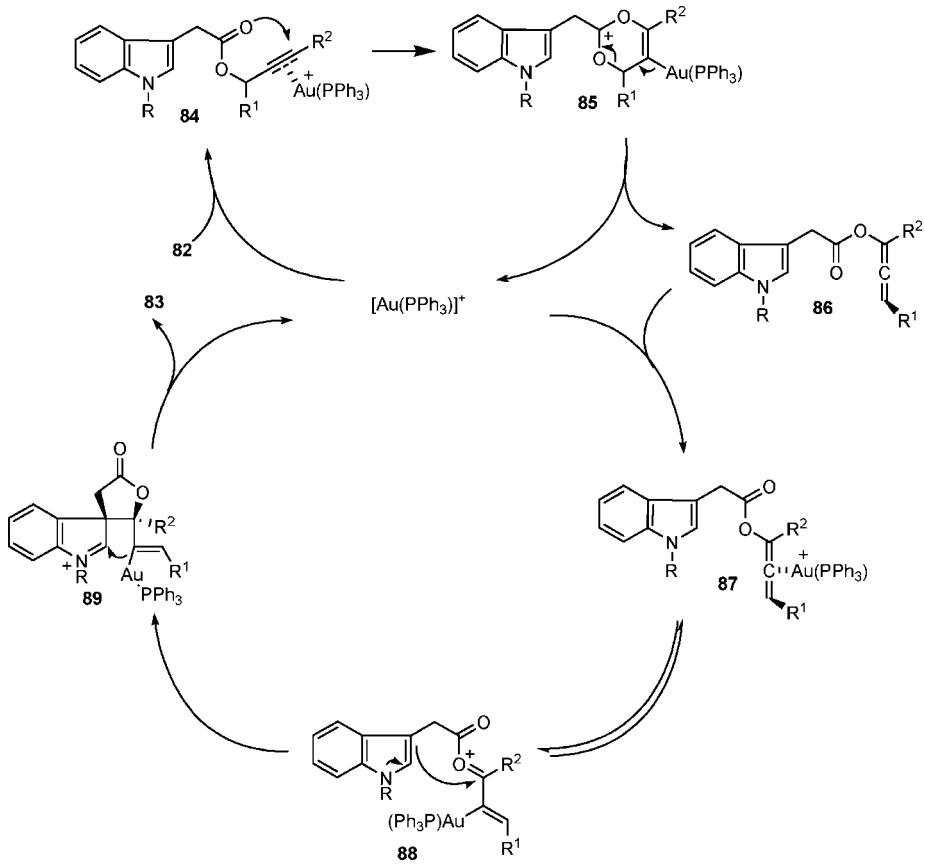


gold-catalyzed [3,3] sigmatropic rearrangement was applied for the synthesis of complex α-pyrone by Schreiber and Luo.[32]

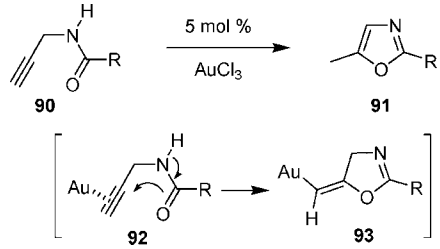
Recently, Hashmi and co-workers reported gold-catalyzed synthesis of 2,5-disubstituted oxazoles **91** from the corresponding propargylcarboxamides **90** (Scheme 27).[33] The 5-*exo-dig* cyclization of gold-coordinated alkyne, as shown in **92**, forms the vinyl gold species **93**, which gave products **91** on protonation and regeneration of catalyst.

Ma and Zhang developed copper(I)-catalyzed conversion of cyclopropenyl ketones **94** into 2,3,4-trisubstituted furans **95** (Scheme 28).[34] Regioselective iodocupration of the C=C bond of **94** produces **96**, which on subsequent β-decarbocupration gives delocalized intermediate **97**. Intramolecular endo-mode insertion of the C=C bond into the oxygen−copper

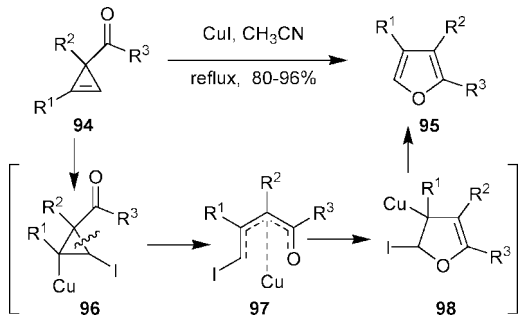
Scheme 26



Scheme 27



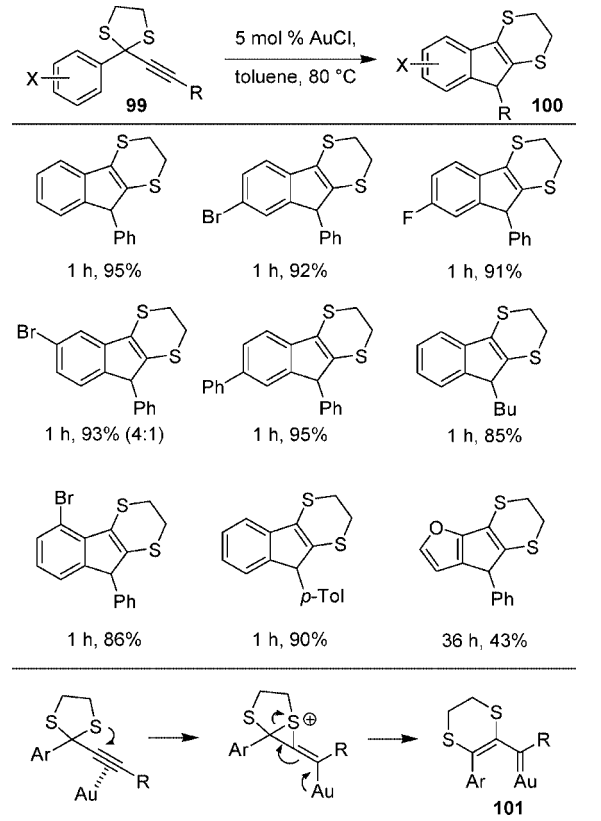
Scheme 28



bond of intermediate **97**, and subsequent β-halide elimination of intermediate **98**, affords **95** with the regeneration of CuI. An analogous reaction using iminocyclopropenes as substrate led to the formation *N*-fused pyrroles.[35]

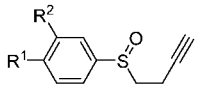
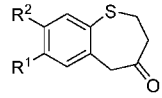
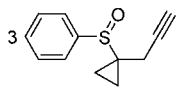
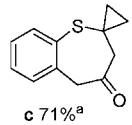
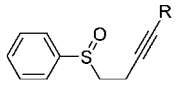
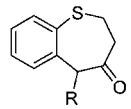
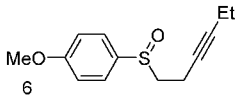
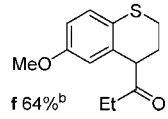
Gold-catalyzed reaction of propargylic dithioacetals **99** gave indene derivatives **100** through pentannulation of the aromatic rings (Table 6).[36] The five-membered dithioacetal ring is expanded to a six-membered ring through the intermediacy of vinylcarbenoids **101**.

Table 6

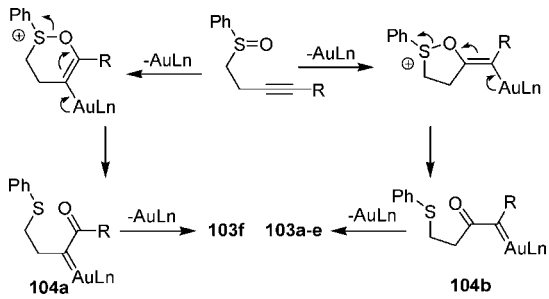


Rearrangement of alkynyl sulfoxide **102**, catalyzed by gold(I) complexes, was reported by Toste and co-workers (Table 7).[37] Various benzo-fused sulfur-containing hetero-

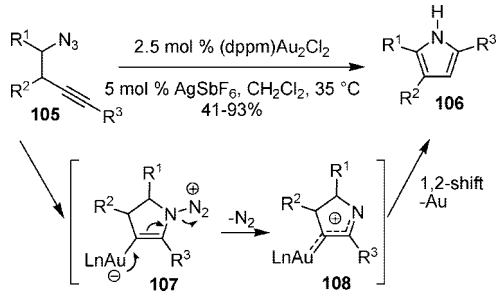
Table 7

substrate (**102**)	product (**103**)
 1 2	 **a** $R^1 = NO_2$, $R^2 = H$, 71%[a] **b** $R^1 = R^2 = OMe$, 87%[a]
 3	 **c** 71%[a]
 4 5	 **d** R = 4-NO_2-C_6H_4, 63%[b] **e** R = COOEt, 91%[a]
 6	 **f** 64%[b]

[a] Reaction conditions: 5 mol % IMesAuCl, 5 mol % $AgSbF_6$, rt. [b] Reaction conditions: 5 mol % Ph_3PAuCl, 5 mol % $AgSbF_6$, rt.



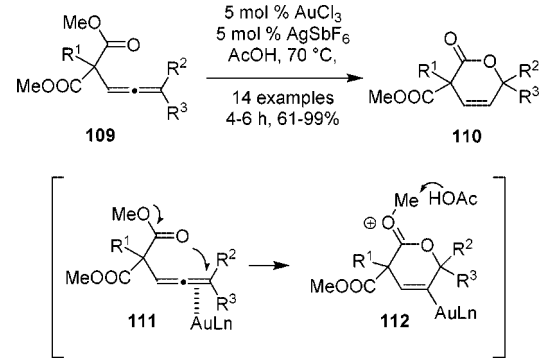
Scheme 29



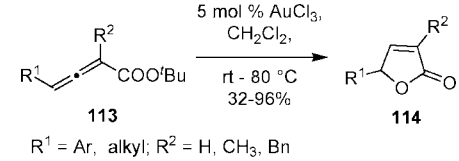
cycles **103** were synthesized in good yields by this method. It is interesting to note that the substrate containing an alkyne substituted with hydrogen and an electron-withdrawing group gave benzothiepinones (entries 1−5), in contrast to the alkyl-substituted alkyne, which afforded benzothiopine (entry 6). Formation of carbenoids **104a** and **104b** was proposed, which undergo intramolecular Friedel−Crafts alkylation to give the products **103f** and **103a−e**, respectively.

Toste and co-workers developed a gold(I)-catalyzed intramolecular acetylenic Schmidt reaction of homopropargyl azides **105** for the synthesis of multiply substituted pyrroles **106** (Scheme 29).[38] The reactions were performed under extremely mild conditions, and preparation of the catalyst was very easy. Mechanistically, gold(I) serves both to activate the alkyne to form **107** and also to donate electron density back into an electron-deficient π-system, as shown in **108**.

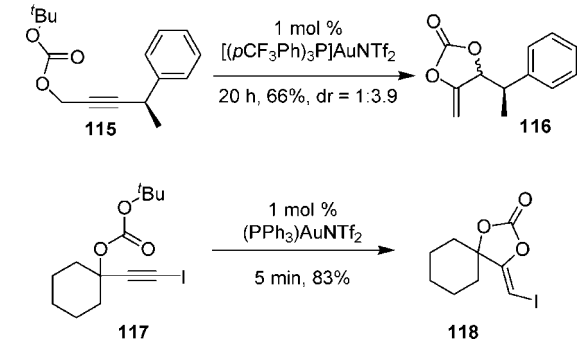
Scheme 30



Scheme 31



Scheme 32



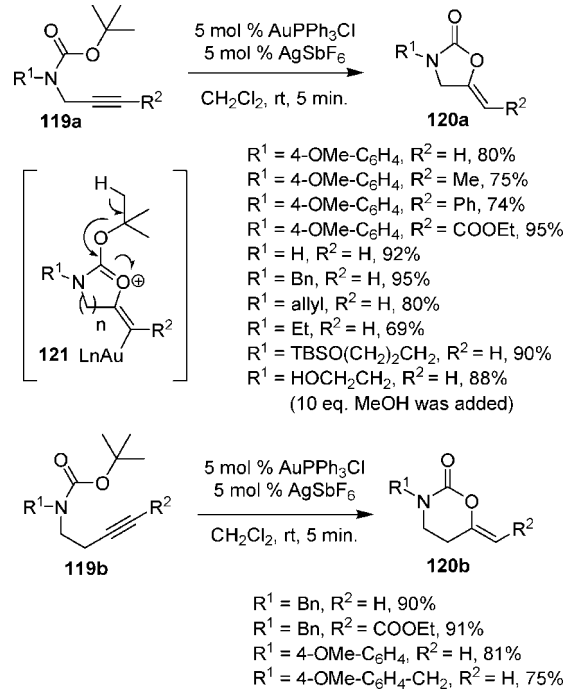
An efficient method for the preparation of β,γ-unsaturated δ-lactones **110** has been reported recently (Scheme 30).[39] The starting materials for the synthesis of these compounds are allene-substituted malonates **109**, which undergo gold-catalyzed cyclization by means of nucleophilic attack of the ester moieties on the allenes (cf. **111** and **112**).

$AuCl_3$ efficiently catalyzes cyclization of *tert*-butyl allenoates **113** into γ-butenolides **114** (Scheme 31).[40] The authors of that work believed that, mechanistically, formation of allenic acid took place first, and subsequent cyclization then afforded furan **114**.

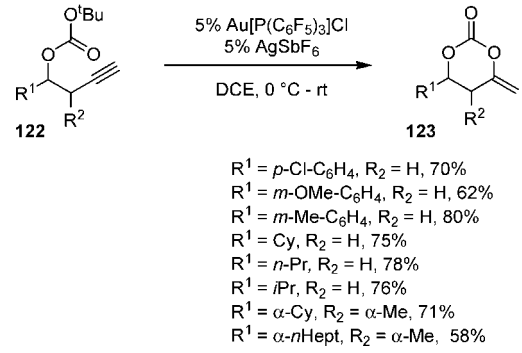
Gold-catalyzed rearrangement of propargylic *tert*-butyl carbonates **115** and **117** into 4-alkylidene-1,3-dioxolan-2-ones **116** and **118** was described by Gagosz and Buzas (Scheme 32).[41] A variety of cyclic carbonates were synthesized under these milder conditions.

A new method for the synthesis of 2-oxazolidinones **120a** and 2-oxazinones **120b** from the corresponding *N*-Boc-protected alkynylamines **199a** and **199b** was reported recently (Scheme 33).[42] The reaction is very general in its scope and can be carried out at extremely neutral conditions in a short time. Since the *N*-methyl carbamate of propargyl amine failed to react under standard conditions, fragmentation of the ^{t}Bu group (cf. **121**), releasing isobutene, was proposed as the key aspect of this process. Li and co-workers have shown that a methyl group (instead of a ^{t}Bu group) can also

Scheme 33



Scheme 34

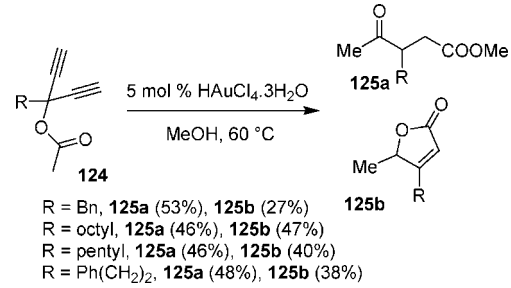


be used for similar cyclization processes.[43] Asao and co-workers have shown that *o*-alkynylbenzoic acid alkyl ester can be used as an alkylating agent for alcohols or arenes.[44] Hashmi and co-workers reported cyclization of *N*-alkynyl carbamates bearing a Boc group on nitrogen.[45]

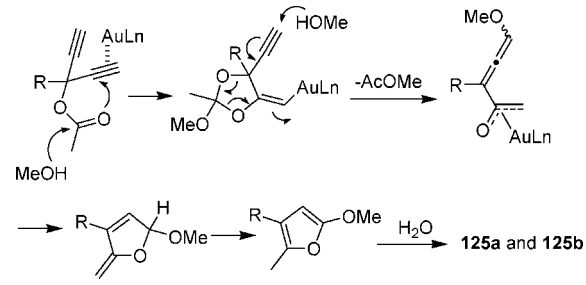
Shin and Kang reported gold-catalyzed cyclization of *tert*-butyl carbonates **122**, derived from homopropargylic alcohols, which led to formation of cyclic enol carbonates **123** (Scheme 34).[46] It is reported that internal alkynes were not viable substrates for this cyclization. The same research group reported gold-catalyzed synthesis of 2-oxazolidinones from *N*-Boc-protected alkynylamines under low catalyst loading.[47] They[48] and Hashmi et al.[49] reported gold(I)-catalyzed intramolecular hydroamination of trichloroacetimidates derived from propargyl and homopropargyl alcohols. Shen et al. reported gold(I)-catalyzed cyclizations of silyl ketene amides and carbamates with tethered alkynes.[50]

Gold-catalyzed double-Wacker-type reaction of 1,1-diethynyl acetates **124** for the synthesis of lactones **125b** was reported (Scheme 35).[51] The mechanism of the reaction is interesting (Scheme 36); however, the lactones were obtained in low yields due to the formation of γ-keto esters **125a** as a side product.

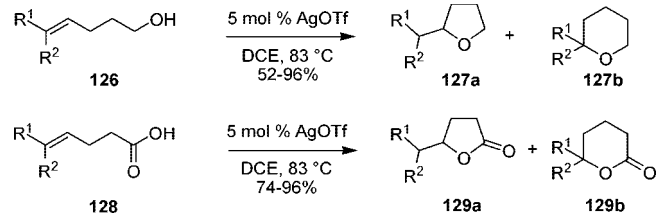
Scheme 35



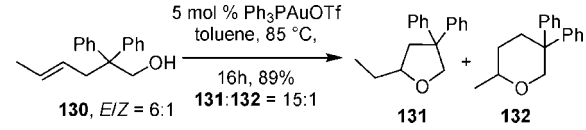
Scheme 36



Scheme 37



Scheme 38



2.2. Cyclization of Alkenes, Allenes, Dienes, and Alkynes with Nucleophiles (H-Nu)

2.2.1. Cyclization of Alkenes

Silver(I) triflate-mediated intramolecular addition of hydroxyl or carboxyl group to inert olefins, to form cyclic ethers **127** and lactones **129**, was described by He and co-workers (Scheme 37).[52] Good to excellent yields were obtained over a wide range of substrates **126** and **128** under experimentally simple reaction conditions. The role of the silver(I) catalyst is mainly to activate the olefin, which is then attacked by the tethered oxygen nucleophiles.

The gold-catalyzed intramolecular cyclization of alkenol was reported by Yang and He (Scheme 38).[53] They observed that the formation of cyclic ethers **131/132** from **130** using 5 mol % $Ph_3PAuOTf$ in toluene at 85 °C took place smoothly. This is the first example of intramolecular hydroalkoxylation of alkenes in the case of gold catalysis.

He and co-workers reported the Au(I)-catalyzed synthesis of dihydrobenzofurans **134** from aryl allyl ethers **133** (Table 8).[54] They probed the mechanism of the reaction and found that the reaction proceeded by a Claisen rearrangement, followed by an intramolecular addition of the resulting phenol to the allyl group. Ohno and co-workers reported gold-

Table 8

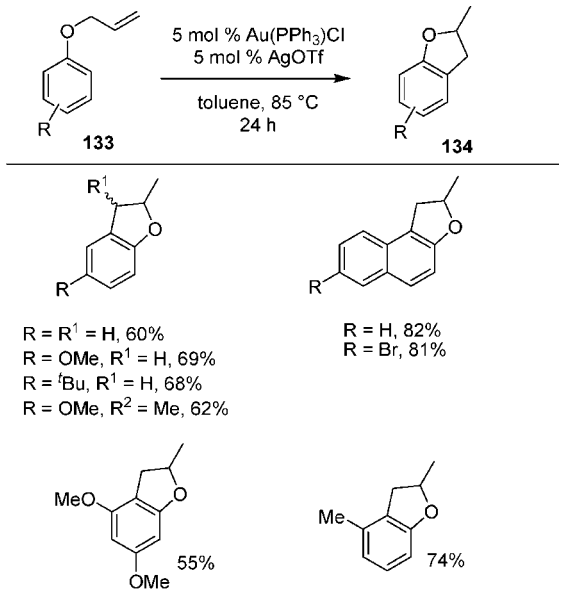
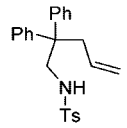
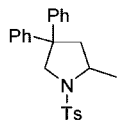
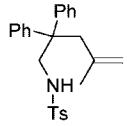
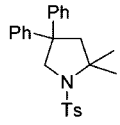
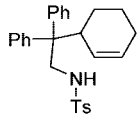
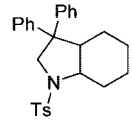
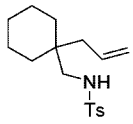
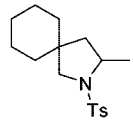
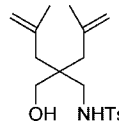
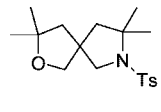


Table 9[a]

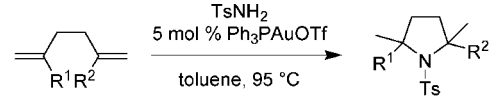
entry	substrate	time (h)	product	yield(%)
1		17		96
2		15		91
3		15		95
4		15		99
5		10		97

[a] Reaction conditions: 5 mol % Ph_3 PAuOTf, 85 °C.

catalyzed intramolecular hydroarylation of allenes for the synthesis of dihydroquinoline and chromene derivatives.[55]

Recently, He and co-workers reported gold(I)-catalyzed intramolecular hydroamination of unactivated olefins which led to a variety of nitrogen heterocycles (Table 9).[56] They further examined hydroamination of 1,5-dienes **135** with $TsNH_2$(Scheme 39). First intermolecular hydroamination of a 1,5-diene by $TsNH_2$, followed by intramolecular hydroamination, produces pyrrolidines **136** in one pot. Just after the publication of the above paper, a similar report on intramolecular hydroamination appeared in the literature.[57] Che and co-worker reported gold(I)-catalyzed hydroamination of

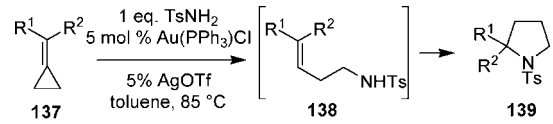
Scheme 39



135a R^1 = H, R^2 = H
135b R^1 = H, R^2 = Me
135c R^1 = Me, R^2 = Me

136a R^1 = H, R^2 = H, 64% (*cis*/*trans*:37/63)
136b R^1 = H, R^2 = Me, 90%
136c R^1 = Me, R^2 = Me, 80%

Table 10



entry	R^1, R^2	time (h)	yield (%)
1	*o*-C_6H_4, H	8	68
2	*m*-Me-C_6H_4, H	8	76
3	*p*-Me-C_6H_4, H	8	70
4	*o*-OMe-C_5H_4, H	4	34
5	1-naphthyl, H	12	54
6	C_6H_5, Me	12	68
7	*p*-Me-C_6H_4, Me	8	72
8	*o*-OEt-C_6H_4, Me	8	71
9	*p*-Cl-C_6H_4, Me	24	43
10	*p*-Br-C_6H_4, Me	24	47
11	^{n}Bu, ^{n}Bu	8	70
12	*n*-$C_{17}H_{15}$, Me	8	64
13	cyclohexylene	8	63
14	4-phenylcyclohexylene	8	75

alkenes under thermal and microwave-assisted conditions.[58] Widenhoefer and Bender reported intramolecular hydroamination of aminoalkynes catalyzed by a gold(I)/*N*-heterocyclic carbene complex at relatively low temperature.[59]

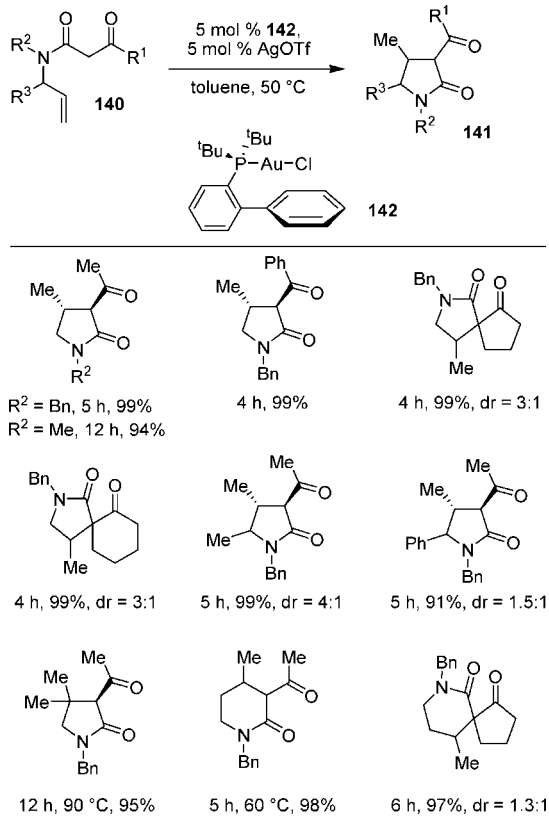
Shi et al. reported gold-catalyzed domino ring-opening/ring-closing hydroamination of methylenecyclopropanes **137** with sulfonamides for the synthesis of pyrrolidines **139** (Table 10).[60] Opening of **137** by $TsNH_2$ took place to form aminoalkenes **138**, which on intramolecular hydroamination gave pyrrolidines **139**.

Che and Zhou reported highly efficient Au(I)-catalyzed intramolecular addition of β-ketoamide to unactivated alkenes (Table 11).[61] The substrates **140** underwent cyclization in the presence of Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl (**142**, 5 mol %) and AgOTf (5 mol %) under mild conditions with excellent regioselectivities and yields. The process provided an efficient method to prepare highly substituted lactams **141**.

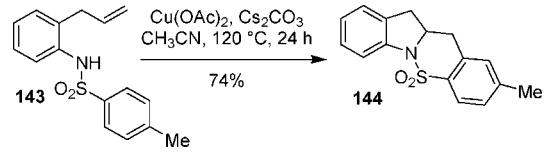
Oxidative cyclization of tosyl-*o*-allylaniline **143** to produce tetracycle **144** was reported by Chemler and co-workers (Scheme 40).[62] The oxidative cyclization of **143** occurred upon treatment with 3 equiv of $Cu(OAc)_2$ and 1 equiv of Cs_2CO_3 in CH_3CN or DMF at 120 °C. The mechanism of this reaction is different and involves the activation of nucleophiles. One plausible mechanism is depicted in Scheme 41. Presumably, formation of a nitrogen−copper(II) bond takes place (cf. **145**) at the beginning of the reaction, followed by intramolecular migratory insertion to form indole nucleus **146**. Intramolecular cyclization in **146** via a radical pathway affords **147**, which on loss of a hydrogen radical gives **144**.

Chemler and co-workers also reported the intramolecular 1,2-diamination of unactivated olefin **148** in the presence of $Cu(OAc)_2$, which gave nitrogen-containing heterocycle **149**

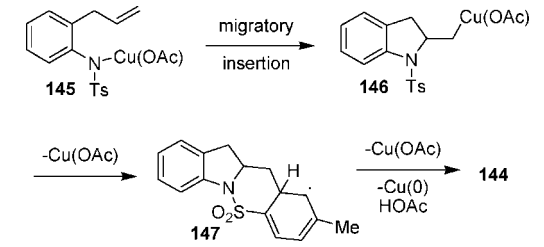
Table 11



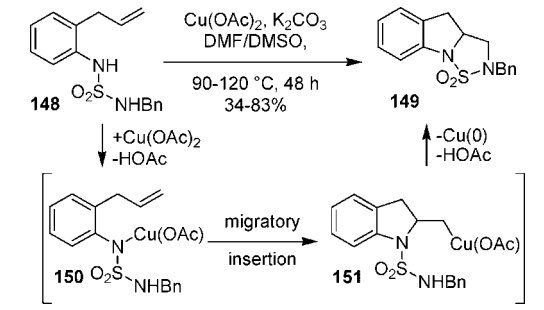
Scheme 40



Scheme 41

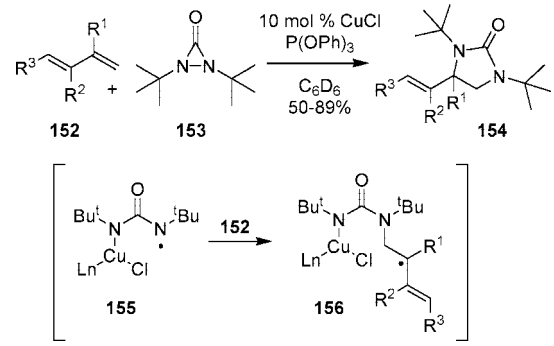


Scheme 42

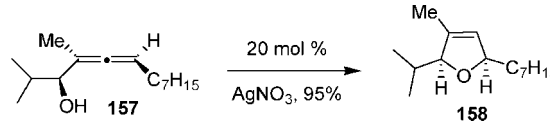


(Scheme 42).[63] The in situ-generated **150**, on migratory insertion, gives organocopper species **151**, which on ligand exchange with a nitrogen followed by reductive elimination affords product **149**.

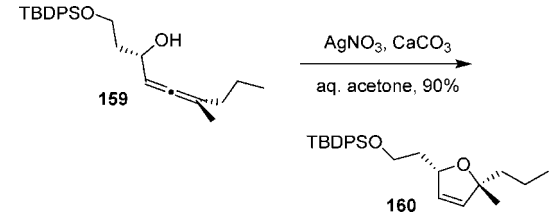
Scheme 43



Scheme 44



Scheme 45



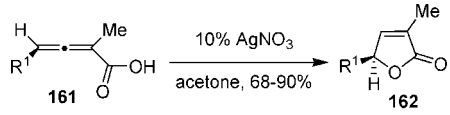
Shi et al. reported copper-catalyzed intermolecular diamination process for the synthesis of *N*-heterocycles **154** from diene **152** and di-*tert*-butyldiaziridinone **153** (Scheme 43).[64] It is interesting to note that only the terminal double bond is diaminated in this process. The CuCl first reductively cleaves the N−N bond of diaziridinone **153** to form radical species **155**. Addition of **155** to diene **152** forms radical intermediate **156**, which on homolytic cleavage of the Cu−N bond and formation of the C−N bond gave **154** with regeneration of catalyst.

2.2.2. Cyclization of Allenes

The activation of allenes can be achieved by using transition metal catalysts[65] enabling the synthesis of heterocycles. Like those transition metals, coinage metals coordinate to allenes, allowing the attack of tethered nucleophiles, leading to the formation of various heterocycles. Marshall and co-workers reported the activation of allenes by silver catalysts. As shown in Scheme 44, the use of optically pure allenylcarbinol **157** gave *cis*-2,5-dihydrofuran **158** in high yield.[66] Furstner et al. also reported that allenyl alcohol **159** cyclized in the presence of $AgNO_3$ to afford dihydrofuran **160** with complete chirality transfer; however, a stoichiometric amount of the silver salt was needed in this case (Scheme 45).[67] Marshall et al. later reported the cyclization of allenic acids **161** in the presence of catalytic amounts of $AgNO_3$ to give butenolides **162** (Scheme 46).[68] High yields were generally obtained in all cases.

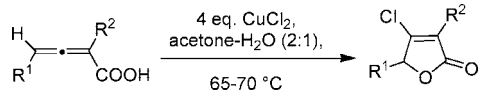
Ma et al. reported an efficient method for the synthesis of β-chlorobutenolides **164** from allenic acids **163** in the presence of excess amounts of $CuCl_2$ (Scheme 47).[69] β-Bromobutenolides could also be obtained by replacing $CuCl_2$ for $CuBr_2$. The reaction proceeds through the stereoselective halocupration of **163** to form the Cu-containing intermediate (*E*)-**165**. Intramolecular attack of the carboxylic

Scheme 46

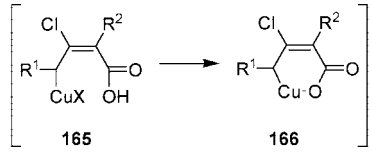


R^1 = *n*-C_5H_{11}, CH_2=CH$(CH_2)_7$, *c*-C_6H_{11}

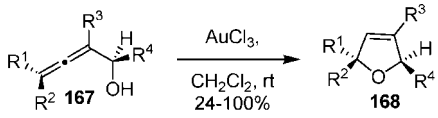
Scheme 47



164a R^1 = Ph, R^2 = CH_3, 93%
164b R^1 = *c*-C_6H_{11}, R^2 = H, 92%
164c R^1 = Ph, R^2 = $^nC_3H_7$, 100%



Scheme 48



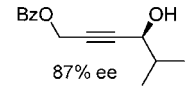
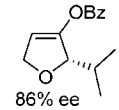
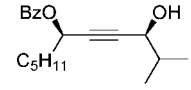
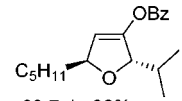
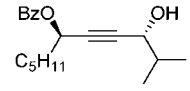
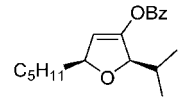
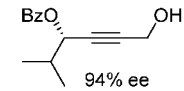
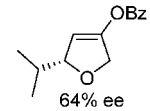
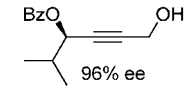
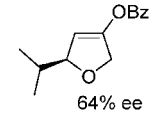
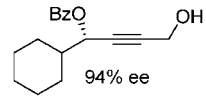
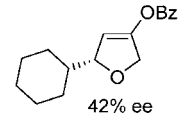
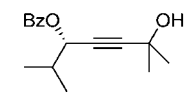
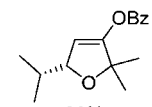
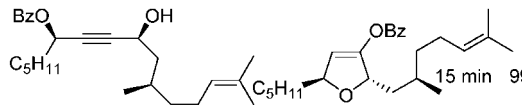
R^1 = *t*-Bu, H, H_2C=CH$(CH_2)_2$; R_2 = Me, *n*-Bu, *n*-Hex, H;
R^3 = H, Me; R^4 = COOEt, COOMe, CH_2OH, CH_2OTBS, CH_2OMe

group on copper forms the six-membered intermediate **166**, which provides the products **164** after reductive elimination.

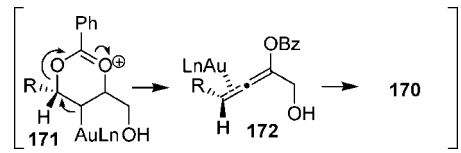
Functionalized α-hydroxyallenes **167** were smoothly converted into the corresponding 2,5-dihydrofurans **168** by using 5−10 mol % of gold(III) chloride as catalyst. This cyclization method was applied to alkyl- and alkenyl-substituted allenes, which furnished tri- and tetrasubstituted dihydrofurans in good to excellent chemical yields and with complete axis-to-center chirality transfer (Scheme 48).[70] Evidence for the in situ reduction of gold(III) during the cyclization of allenyl carbinols was reported recently.[71] The methodology also proved applicable for the cyclization of *β*-hydroxyallenes into dihydropyrans.[72] An application of this strategy for the synthesis of *β*-carboline alkaloids (−)-isochrysotricine and (−)-isocyclocapitelline was reported.[73] A similar reaction was reported in the synthesis of (±)-annularin H by Brasholz and Reissig.[74] Chiral allenamides bearing an alcohol functional group are also known to undergo cyclization to form highly substituted dihydrofurans.[75]

Gagosz et al. reported the gold(I)-catalyzed rearrangement of butynediol monobenzoates **169** into functionalized 2,5-dihydrofurans **170**. The reaction proved quite general, and various substituted butynediol monobenzoates reacted using 2 mol % $(Ph_3P)AuNTf_2$ as the catalyst.[76] As can be judged from Table 12, in most cases excellent chirality transfer occurred from substrates to products. Activation of alkyne by gold catalyst promotes the nucleophilic attack of the benzoate moiety, to form the stabilized cationic species **171**. Fragmentation of the C−O bond in **171** led to the 1,3-shift of the benzoate group to form allene **172** stereoselectively. The intramolecular hydroalkoxylation of allene in the presence of gold catalyst afforded products **170**. Shin and co-workers reported a similar cyclization process for the synthesis of spirocyclic furans (Scheme 49).[77]

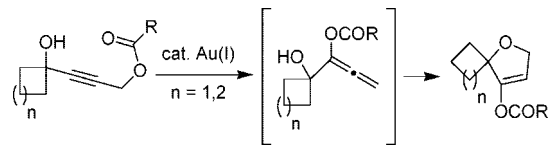
Table 12

entry	substrate (**169**)	product (**170**)	time	yield (%)[a]
1	 87% ee	 86% ee	3 h	83%
2	 93:7 dr, 98% ee	 93:7 dr, 98% ee	40 min	97%
3	 94:6 dr, 98% ee	 92:8 dr, 98% ee	35 min	99%
4	 94% ee	 64% ee	10 min	99%
5	 96% ee	 64% ee	15 min	99%
6	 94% ee	 42% ee	10 min	89%
7	 81% ee	 80% ee	50 min	95%
8	 9:1dr, 98% ee	9:1dr, 98% ee	15 min	99%

[a] Reaction conditions: 2 mol % $(Ph_3P)AuNTf_2$, CH_2Cl_2, rt.



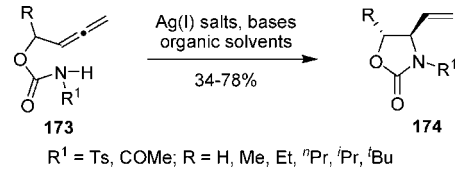
Scheme 49



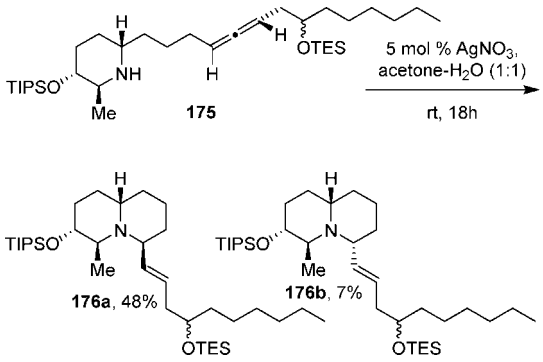
Silver salts effectively catalyze the cyclization of *O*-(2,3-butadienyl)-*N*-tosyl-carbamates **173** to provide the *trans*-oxazolidinones **174** predominantly or exclusively (Scheme 50).[78] It was observed that the ease of cyclization depends on the kind of substituents on the nitrogen atom. Generally, electron-withdrawing groups facilitate the reaction.

Cha and co-workers reported the stereocontrolled synthesis of (−)-clavepictine A and (−)-clavepictine B using silver(I)-mediated cyclization of *δ*-aminoallene as a key step (Scheme 51).[79] Silver(I) nitrate-catalyzed annulation of diastereomerically pure aminoallene **175** produced a 7:1 mixture of the

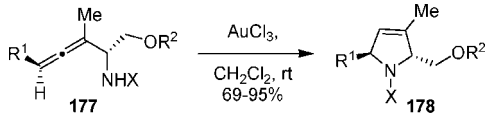
Scheme 50



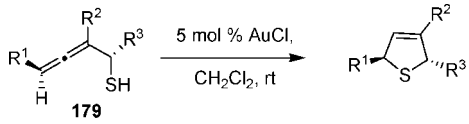
Scheme 51



Scheme 52



Scheme 53



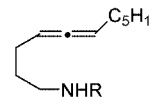
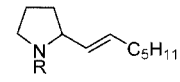
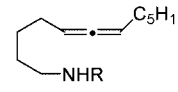
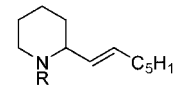
desired *cis*-quinolizidines **176a** and **176b** in 54% yield. Further structural manipulation from **176a** gave (−)-clavepictine A and (−)-clavepictine B.

Gold(III) chloride-catalyzed cyclization of various α-aminoallenes **177** gave the corresponding 3-pyrrolines **178** in good yields (Scheme 52).[80] It was reported that the reactivity depends on the nature of protecting groups. For example, when X = H, 5 days (room temperature) was needed to get a 74% yield of the product. On the other hand, when X = Ts, the reaction afforded the corresponding product in 95% yield within 1 h at 0 °C. The same research group reported the cyclization of α-thioallenes **179** into 2,5-dihydrothiophenes **180** (Scheme 53).[81] This was the first example of C−S bond formation in the case of gold catalysis. Dieter et al. has shown that silver salts can also be used as a catalyst for the synthesis of 3-pyrrolines from α-aminoallenes.[82]

We have reported gold-catalyzed intramolecular hydroamination of allenes **181** which gave access to five- and six-membered ring heterocycles **182** (Table 13).[83] It was found that the chirality is transferred from the starting aminoallenes into the products under this reaction conditions. A few months later, Widenhoefer et al. also reported the synthesis of heterocycles via gold-catalyzed activation of allenes with much broader scope.[84]

Widenhoefer and Zhang reported gold(I)-catalyzed intramolecular enantioselective hydroalkoxylation of allenes

Table 13

entry	aminoallene (**181**)		product (**182**)		time (h)	yield(%)[a]
						
1	R = Ts	$AuBr_3$	R = Ts		3	99
2	R = Ts	$AuCl_3$	R = Ts		3	98
3	R = Ts	AuCl	R = Ts		3	99
4	R = COOEt	AuCl	R = COOEt		3	97
5	R = Cbz	AuCl	R = Cbz		3	99
6	R = Bn	AuCl	R = Bn		24	76
						
7	R = Ts	AuCl	R = Ts		24	53[b]
8	R = Cbz	AuCl	R = Cbz		24	80[b]

[a] The reactions of **181** in the presence of 1 mol % gold salts were carried out at rt in THF unless otherwise noted. [b] 5 mol % of catalyst was used.

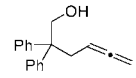
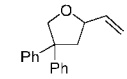
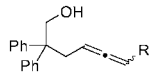
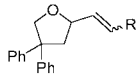
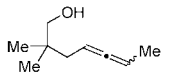
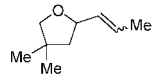
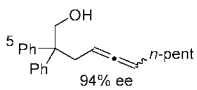
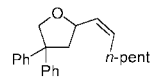
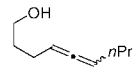
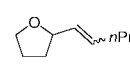
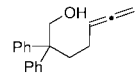
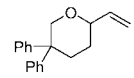
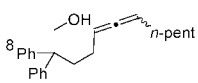
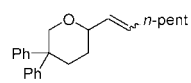
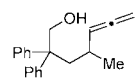
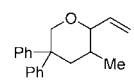
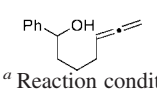
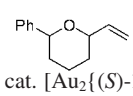
183 for the synthesis of optically active five- and six-membered cyclic ethers **184** (Table 14).[85] This is the first example of catalytic enantioselective hydroalkoxylation of allenes catalyzed by transition metals.

Gold-catalyzed enantioselective intramolecular hydroamination of allenes **186** and **188**, for the synthesis of pyrrolidines **187** and piperidines **189**, respectively, was reported by Toste and co-workers (Scheme 54).[86] This is the first example of catalytic enantioselective hydroamination of allenes catalyzed by transition metals. This process was restricted to *N*-allenyl sulfonamides that possessed a terminally disubstituted allenyl moiety. The authors also noted that *N*-allenyl carbamates failed to undergo hydroamination under these conditions. Later, Widenhoefer et al. reported gold(I)-catalyzed enantioselective hydroamination of *N*-allenyl carbamates with a wide range of allenes.[87] More recently, the research group of Toste reported a chiral counterion strategy for asymmetric transition metal catalysis, and they performed asymmetric hydroalkoxylation, hydroamination, and hydrocarboxylation reactions.[88]

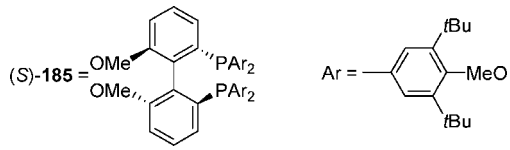
2.2.3. Cyclization of Dienes

Li and co-workers reported efficient annulation of phenols and naphthols with cyclohexadiene to form the benzofurans **190** by using a combination $AuCl_3$/AgOTf catalyst (Scheme 55).[89] It was reported that the use of gold(I) (5 mol % AuCl/5% mol AgOTf) as a catalyst led to very low conversions of the starting materials, whereas a cationic gold(I) triphenylphosphine complex [5 mol % $AuCl(PPh_3)$/15 mol % AgOTf] did not lead to any desired product at all. The presence of electron-donating groups on the aromatic ring seems to promote the reaction. A Friedel−Crafts-type reaction (cf. **191**) and intramolecular hydroalkoxylation (cf. **192**) are the key features of the mechanism. Quite recently, Youn and Eom reported the silver-catalyzed annulation of

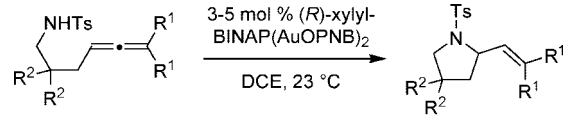
Table 14

entry	substrate **183**	product **184**[a]	ratio[b]	yield	ee(%)
1			-	67	93
					
2	R = *n*-pentyl		1:1	94	95/95
3	R = Me		1:1	96	97/99
4			1:1	95	93/95
5	 94% ee		20:1	88	95
6			1.5:1	94	28/39
7			-	96	88
8			1.5:1	92	67/93
9			1.3:1	99	81/82
10			1:3.3	95	88/45

[a] Reaction conditions: cat. $[Au_2\{(S)\text{-}\mathbf{185}\}Cl_2]$ and AgOTs, toluene, −20 °C, 18 h. [b] Ratio of isomers refers to *trans*/*cis* or *E*/*Z*.

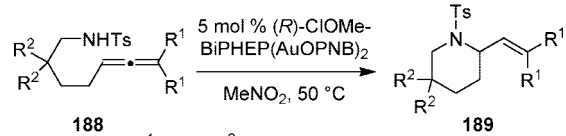


Scheme 54



186 **187**

R^1 = Me, R^2 = H, 15h, 98%, 99%ee
R^1 = Et, R^2 = H, 17h, 90%, 99%ee
R^1 = $-CH_2(CH_2)_2CH_2-$, R^2 = H, 15h, 75%, 83%ee
R^1 = $-CH_2(CH_2)_3CH_2-$, R^2 = H, 17h, 88%, 98%ee



188 **189**

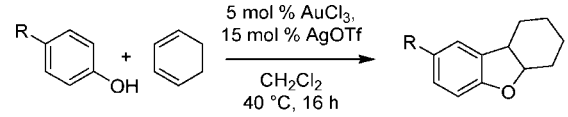
R^1 = Me, R^2 = H, 15h, 88%, 81%ee
R^1 = Et, R^2 = H, 24h, 41%, 74%ee
R^1 = Me, R^2 = Me, 24h, 70%, 98%ee
R^1 = Me, R^2 = Ph, 24h, 70%, 88%ee
R^1 = Me, R^2 = $-CH_2(CH_2)_3CH_2-$, 17h, 66%, 97%ee

phenols and naphthols with cyclic as well as acyclic dienes to form dihydrobenzopyran and dihydrobenzofuran.[90]

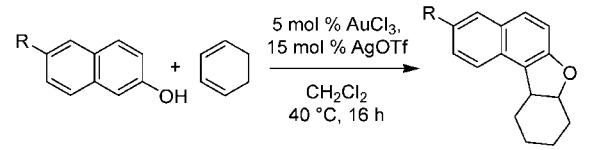
2.2.4. Cyclization of Alkynes

Deng and co-workers reported the reactions of propargylic alcohols **193** with CO_2 in a $[BMIm][PhSO_3]$/CuCl catalyst

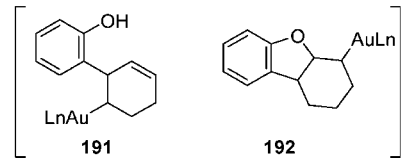
Scheme 55



190a R = H, 71%, (syn:anti = 3:1)
190b R = Me, 74%, (syn:anti = 4:1)
190c R = Br, 53%, (syn:anti = 3:1)

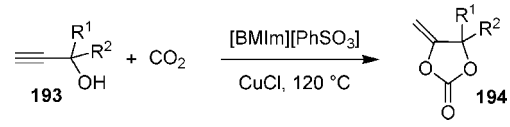


190d R = OMe, 71%, (syn:anti = 11:1)
190e R = Br, 58%, (syn:anti = 3:1)



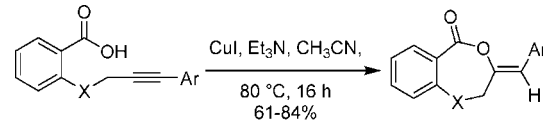
191 **192**

Scheme 56



193 **194**

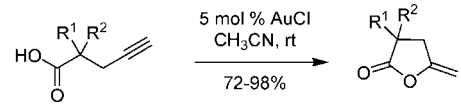
Scheme 57



195a X = O
195b X = NBn

196a X = O
196b X = NBn

Scheme 58



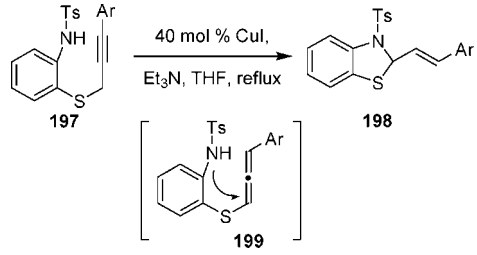
R^1 = COOMe, COOEt, CH_2OBn, Ph; R^2 = cyclohex-2-enyl, but-2-enyl, allyl, but-3-enyl, 4-hydroxybut-2-enyl, C_4H_6OTIPS, propargyl, Cl, ^{n}Bu, Bn, cinnamyl

system to produce the corresponding α-methylene cyclic carbonates **194** in high yields (Scheme 56).[91] It was reported that copper catalysts immobilized in ionic liquids could be reused three times without losing their activity. A silver-catalyzed process was also reported recently by Yamada and co-workers.[92]

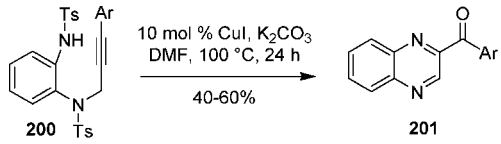
The synthesis of benzodioxepinone **196a** and benzoxazepinone **196b** via cyclization of alkynoic acid **195a** and **195b**, respectively, in the presence of 5 mol % cuprous iodide and 1 equiv of triethyl amine in acetonitrile at 80 °C, was reported by Chaudhuri and Kundu (Scheme 57).[93] Quite recently, the cyclization of alkynoic acids under extremely mild conditions in the presence of AuCl catalysts and without additives was reported (Scheme 58).[94] A gold-catalyzed *N*-acyl iminium ion cyclization cascade, triggered by the intramolecular addition of carboxylic acid to tethered alkynes, was reported by Dixon and co-workers.[95]

Nandi and Kundu reported copper-catalyzed cyclization of **197** into (*E*)-2-substituted benzothiazolines **198** (Scheme

Scheme 59

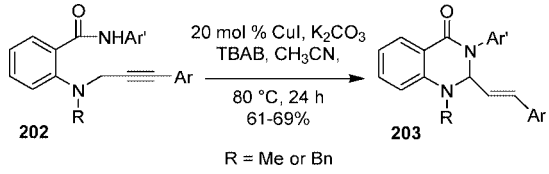


Scheme 60



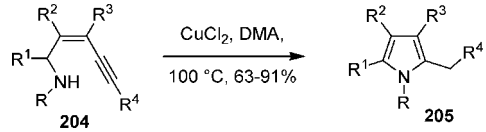
Ar = Ph, 1-Np, *m*-Cl-C_6H_4, *p*-Cl-C_6H_4, *o*-Cl-C_6H_4, *p*-OMe-C_6H_4, *o*-OMe-C_6H_4, 2-thienyl

Scheme 61



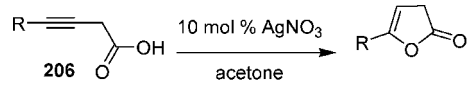
R = Me or Bn

Scheme 62



R = Bn, Bu, ^{t}Bu, H, R^2 = H, Et; R^3 = Me, ^{n}Bu, Ph; R^4 = Bu, CH=CMe_2

Scheme 63



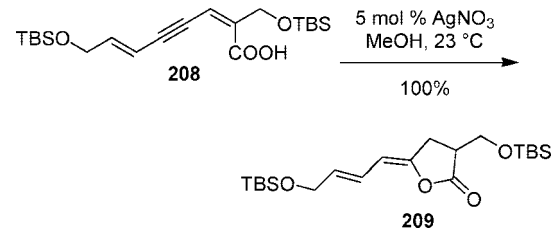
207a R = n-C_5H_{11} (95%)
207b R = CH_2=$CH(CH_2)_7$ (95%)

59).[96] Isomerization of **197** to the allenic intermediates **199** was proposed as a key step. Interestingly, they found that, when substrates of type **200** were subjected to CuI catalysis in the presence of K_2CO_3 in DMF at 100 °C, 2-aroylquinoxalines **201** were obtained (Scheme 60).[97] They also extended their approach for the synthesis of (*E*)-2-(2-arylvinyl)quinazolinones **203** from **202** (Scheme 61).[98]

The cyclization of (*Z*)-(2-en-4-ynyl)amines **204** into pyrroles **205** was reported by Gabriele and co-workers (Scheme 62).[99] $CuCl_2$ was found to be an excellent catalyst for the cyclization of the substrates substituted at C-3, while PdX_2 in conjuction with KX (X = Cl, I) turned out to be a superior catalyst for the reaction of enynamines unsubstituted at C-3.

Dalla and Pale reported the cyclization of alkynylacetic acids **206**, which efficiently gave lactones **207** (Scheme 63).[100] Negishi and Xu showed that Ag catalyzed lactonization of alkynoic acid **208** for the synthesis of (*Z*)-γ-alkylidenebutenolide **209**, a precursor for the synthesis of lissoclinolide (Scheme 64).[101] It is interesting to note that *exo-dig*/*endo-dig* cyclization depends on the nature of catalysts.[102] Rossi and co-workers also reported the cyclization of bromoalkynylacetic acids **210** into the (*Z*)-3-bromo-5-ylidene-5*H*-furan-2-ones **211** (Scheme 65).[103]

Scheme 64



Scheme 65

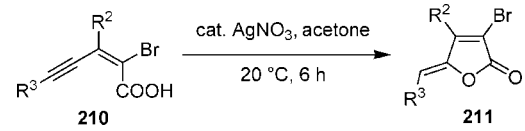
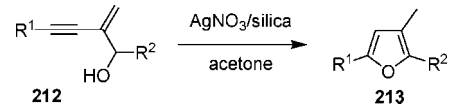
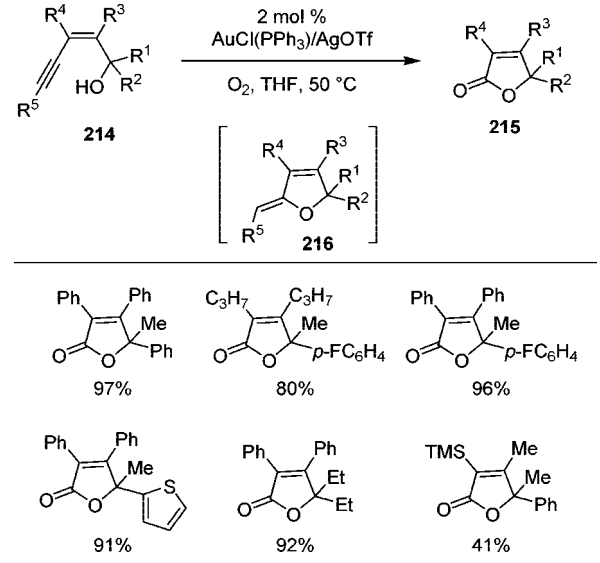


Table 15



R^1	R^2	time (h)	equiv of $AgNO_3$	yield (%)
C_2H_{15}	C_5H_{11}	1	0.1	96
MOMO$(CH_2)_4$	Et	0.25	0.2	99
MOMO$(CH_2)_4$	H	0.25	0.2	89

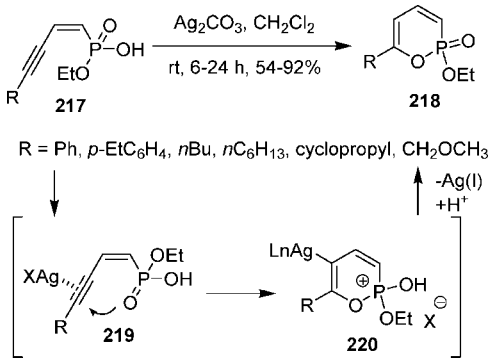
Table 16



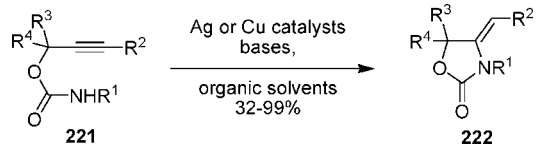
Marshall et al. reported the synthesis of furans **213** from β-alkynyl allylic alcohols **212** in high yields under $AgNO_3$ catalysis (Table 15).[44] They examined the activity of other silver salts such as AgOTf, $AgBF_4$, and AgOTFA, all of which gave comparable yields of the products.

The use of a cationic gold complex is reported for the conversion of (*Z*)-enynols **214** into butenolides **215** (Table 16).[104] The cleavage of carbon−carbon triple bonds in (*Z*)-enynols under mild conditions is an important feature of this reaction. It was proposed that the intermediate **216** was produced via gold-catalyzed intramolecular hydroalkoxylation and was further converted to butenolide by reaction with dioxygen.

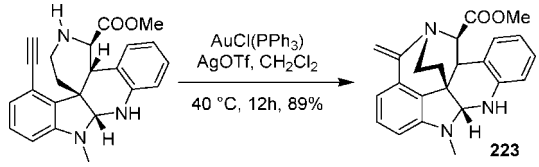
Scheme 66



Scheme 67



Scheme 68

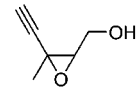
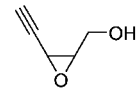
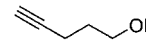
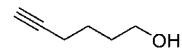
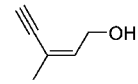
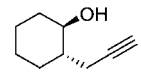
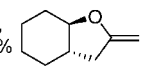


Ding and Peng developed a novel and effective Ag_2CO_3-catalyzed cyclization of (*Z*)-2-alken-4-ynylphosphonic monoesters **217** to 2-ethoxy-2*H*-1,2-oxaphosphorin 2-oxides **218** in CH_2Cl_2 at room temperature (Scheme 66).[105] This is the first example of the cyclization of P(O)−OH to substituted alkynes and might be of synthetic interest. Coordination of the alkynyl moiety of **217** with Ag(I) activates the triple bond (cf. **219**). Regioselective nucleophilic attack of the triple bond by the phosphonyl oxygen in the *endo* fashion gave the vinyl silver species **220**, which subsequently underwent proton transfer with regeneration of the silver catalyst to produce **218**.

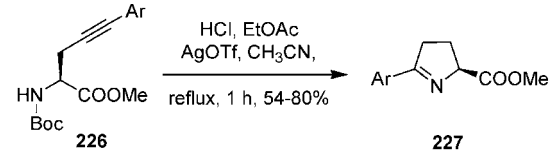
The cyclization of *O*-propargyl carbamates **221** afforded 4-methylene-2-oxazolidinones **222** via intramolecular nucleophilic addition of a nitrogen atom to alkynes (Scheme 67).[106] The reaction is highly dependent on the kind of substituent (R^1) on nitrogen. Later, Murai[107] and Schmalz[108] independently reported similar processes. Shin et al. reported the synthesis of 2,5-dihydroisoxazoles via gold-catalyzed intramolecular hydroamination of *O*-propargyl-*N*-Boc-hydroxylamines.[109] The gold-catalyzed intramolecular hydroamination of alkyne methodology has been successfully applied for the construction of a hexacyclic substructure of communesin B **223** (Scheme 68).[110]

Pale and Chuche reported silver-catalyzed cyclization of acetylenic alcohols **224** which led to 2-methylene-oxolanes **225** in high yields.[111] As can be judged from Table 17, the cyclization of the acetylenic alcohols, in which the two reacting parts of the molecule are relatively close together in space, required only catalytic amounts of Ag_2CO_3, while other reactions needed a stoichiometric quantity. Later, a gold-catalyzed intramolecular process was developed by the same research group.[112] Jung and Floreancig reported gold-catalyzed synthesis of oxygen- and nitrogen-containing heterocycles, homopropargylic ethers containing pendent oxygen or nitrogen nucleophiles.[113]

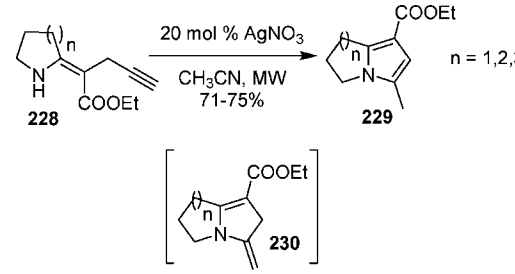
Table 17

entry	alkynol (**224**)	condition and yield	product (**225**)
1		10 mol % Ag_2CO_3, benzene, 80 °C, 1 h, 99%	
2		10 mol % Ag_2CO_3, benzene, 80 °C, 1 h, 90%	
3		100 mol % Ag_2CO_3, C_6D_6, 80 °C, 6 h, 90%	
4		100 mol % Ag_2CO_3, C_6D_6, 80 °C, 6 h, 90%	
5		100 mol % Ag_2CO_3, C_6D_6, 20 °C, 2 h, 95%	
6		100 mol % Ag_2CO_3, C_6D_6, 80 °C, 6 h, 95%	

Scheme 69



Scheme 70



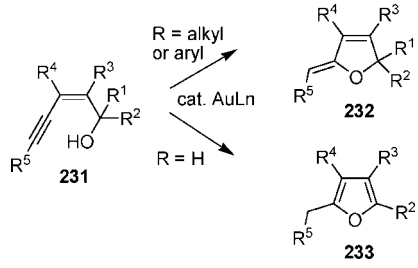
A novel synthetic approach to the synthesis of enantiomerically pure 2,5-disubstituted pyrrolines **227** was described by Rutjes et al. (Scheme 69).[114] The methodology involves a Ag-catalyzed 5-*endo-dig* cyclization of amino alkynes obtained from **226** after removal of *N*-Boc functionality.

The concept of silver-catalyzed intramolecular hydroamination was extended by Dovey and co-workers for the synthesis of *N*-bridgehead pyrroles **229** from amino alkynes **228** using microwave irradiation. The reaction was believed to proceed via intermediate **230** which, on proton migration, affords products (Scheme 70).[115]

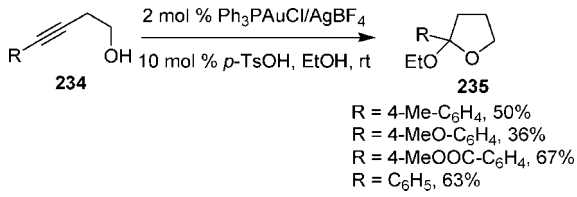
The gold-catalyzed cyclization of (*Z*)-enynols **231** gave (*Z*)-5-ylidene-2,5-dihydrofurans **232** and fully substituted furans **233**, depending on the nature of the R^1 group (Scheme 71).[116] For instance, when R^5 = alkyl or aryl, **232** was formed. On the other hand, when R^5 = H, **233** was obtained. Two reaction conditions were employed: (i) $AuCl_3$ in CH_2Cl_2 and (ii) $(PPh_3)AuCl/AgOTf$. Both of them generally gave product in high yields.

Krause and Belting reported the tandem cyclization−hydroalkoxylation of homopropargylic alcohols **234** in the presence of an alcohol and a dual catalyst system co-

Scheme 71



Scheme 72



nsisting of a gold catalyst and a Brønsted acid (Scheme 72).[117] The process offers an attractive and efficient route for the synthesis of tetrahydrofuranyl ethers **235** in moderate to good yields. Not only alcohols but also electron-rich arenes can also be used as nucleophile for this reaction.[118] This concept of a dual catalyst system consisting of a gold catalyst and a Brønsted acid has been applied for the synthesis of A−D rings of azaspiracid **238** from suitably functionalized alkyne substrate **236** (Scheme 73).[119]

A highly atom-economical procedure for the cyclization of bis-homopropargylic diols **239** was described by Genet and co-workers (Scheme 74).[120] The process provided access to the strained bicyclic ketals **240** under extremely mild conditions. Lewis acid-type activation of alkynes was reported in order to effect the two intramolecular cyclizations, as shown in intermediate **241**. Brabander and Liu reported gold-catalyzed synthesis of spiroketals from unactivated internal alkynols.[121]

Barluenga et al. reported tandem 6-*exo-dig* cyclization/Prins-type cyclization of allyl-substituted 5-hexyn-1-ol derivatives **242** catalyzed by $AuCl_3$ (Scheme 75).[122] The bicyclic heterocycles **243** were obtained in excellent yields. Optimization studies revealed that $AuCl_3$ catalyst is efficient compared to AuCl. The reaction was initiated by coordination of gold to the triple bond, giving intermediate **244**, which on subsquent Prins-type cyclization (cf. **245**) afforded **243**.

The gold-catalyzed intramolecular addition of amines to alkynes for the synthesis of piperidines was reported by Utimoto and Fukuda (Scheme 76).[123] 5-Alkynylamines **246**, on reaction with catalytic amounts of $NaAuCl_4$, afforded 2,3,4,5-tetrahydropyridines **247** in high yields.

The gold(III)-catalyzed sequential amination/annulation reaction of 2-propynyl-1,3-dicarbonyl compounds **248** with primary amines produces 1,2,3,5-substituted pyrroles **249** in moderate to high yields (Scheme 77).[124] Reaction of **248** with primary amines under the reaction conditions generates enaminone intermediate **250**. Cyclization of **250** through a 5-*exo-dig* pathway, followed by protonolysis of the resulting C−Au bond and subsequent isomerization reaction, affords the pyrroles **249**.

2.3. Cyclization of *Ortho*-Substituted Ethynylbenzene Derivatives

The transition metal-catalyzed synthesis of various heterocycles via cyclization of alkynes with nucleophiles tethered through aromatic rings is one of the most important processes in organic synthesis. The use of coinage metals to activate the alkynes is very common for this purpose. The synthesis of benzofurans is one of the simplest examples of this reaction (Scheme 78). If one of the carbon atoms in a benzene ring is replaced by a heteroatom, the methodology provides an efficient access to furans fused with heteroaromatics. For example, reaction of **251** under Cu catalysis produced the furopyridine **252** in 86% yield (Scheme 79).[125] The TMS group did not survive under the reaction conditions.

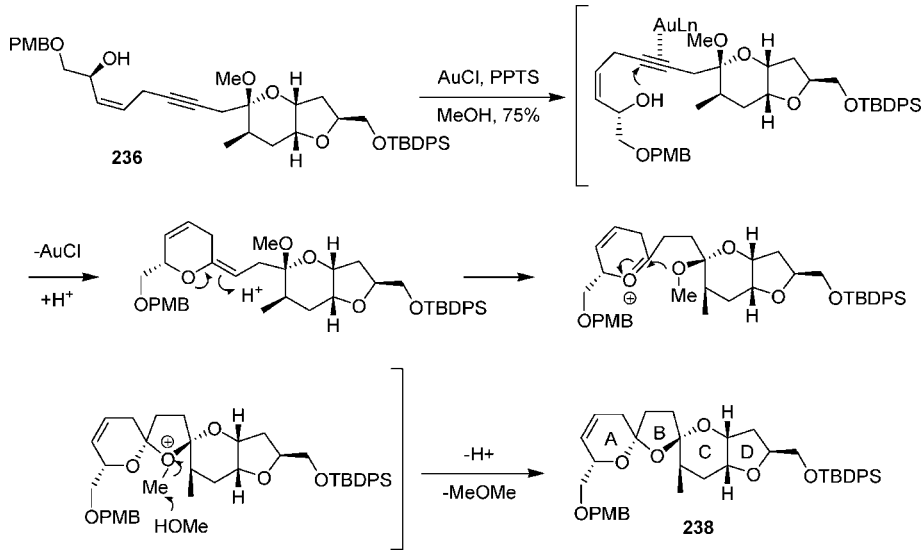
Ding and Peng reported the Cu(I) iodide-catalyzed cyclization of *o*-ethynylphenylphosphonic acid monoethyl esters **253**, which led to the formation of phosphaisocoumarins **254** (Scheme 80).[126] In all cases, only six-membered products were obtained via 6-*endo-dig* cyclization. The activation of alkyne by copper catalyst and enhancement of the nucleophilicity of the PO−H bond by the use of DMF are the key features of this reaction. The simplest example of this type was reported by Hashmi et al.[127] Ding's group later developed a novel procedure for the incorporation of an allyl group in the phosphaisocoumarins, as shown in Scheme 81.[128] Pal and co-workers reported a similar type of cyclization for the synthesis of benzothiazines from *o*-(1-alkynyl)benzenesulfonamides.[129]

A new method for the synthesis of cyclic alkenyl ethers **256** via the Cu(I)-catalyzed intramolecular cyclization of *o*-alkynylbenzaldehydes **255** with alcohols has been developed by us (Table 18).[130] The reaction most likely proceeds through the formation of benzopyrilium cation **257**, which undergo trapping by alcohols. A survey of metal catalysts and solvents revealed that the combination of copper(I) iodide and DMF was the catalytic system of choice. The superiority of this catalyst system is evident by the fact that even terminal alkynes gave the desired products, in comparison with the previous catalyst system, $[Pd(OAc)_2]$, which gave the products in very low yields along with unidentified byproducts.[131] Shi et al. reported an interesting reactivity pattern when they treated alkynyl epoxide and alcohol/water with gold catalysts.[132]

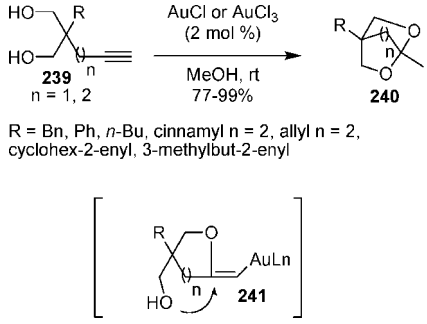
We have also reported a novel procedure for the incorporation of an allene moiety into the isochromenes. The silver(I)-catalyzed cascade cyclization reaction of alkynones **258** with alcohols represents a general and versatile approach to the 1-allenyl chromenes **259** (Table 19).[133] The reaction was tolerated over a wide range of substrates, except for the terminal alkynes and TMS-protected alkynes. The reaction most probably proceeds through the benzopyrylium cation **260**.

A tandem alkynylation−cyclization of terminal alkynes with *o*-alkynylaryl aldehydes leading to 1-alkynyl-1*H*-isochromenes **261** by using a gold−phosphine complex as catalyst in water was developed by Li and Yao (Scheme 82).[134] Mechanistically, the reaction of terminal alkynes with Me_3AuCl in the presence of a weak base generates the gold acetylide, which then forms the chelating intermediate **262**, followed by attack to the triple bond to give the vinylgold intermediate **263**. The intermediate **263** then affords the final product by protonolysis, followed by regeneration of the catalyst.

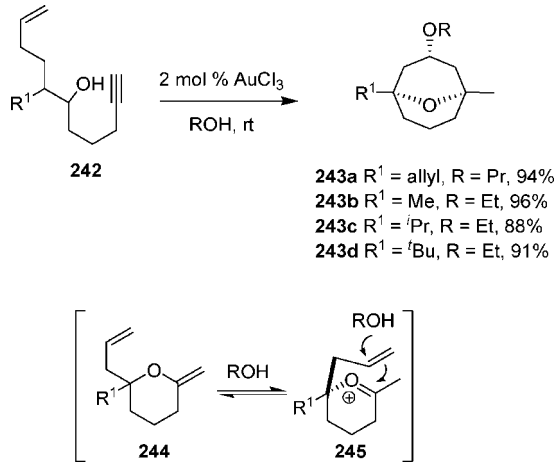
Scheme 73



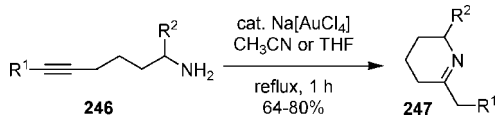
Scheme 74



Scheme 75

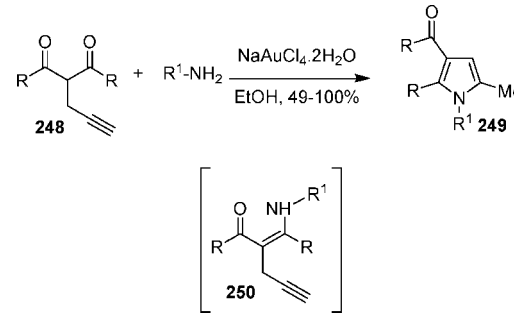


Scheme 76

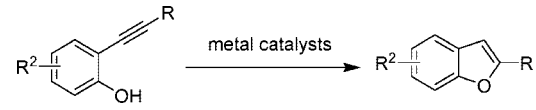


This chemistry has also been applied for the synthesis of various azaphilones, which are known to be a component of many natural products. Gold-catalyzed cyclization of *o*-alkynylbenzaldehydes **264** into 2-benzopyrylium salts and subsequent oxidation using IBX in conjuction with a phase-transfer catalyst provided products **265** in high yields (Scheme 83).[135] A copper-mediated enantioselective version

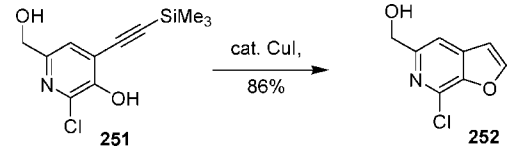
Scheme 77



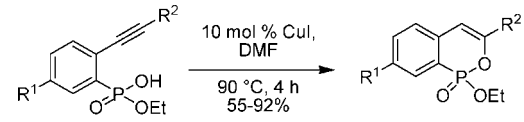
Scheme 78



Scheme 79



Scheme 80



R1 = H, Cl, OMe, NO2; Ph, *n*-Bu, *p*-CH3CH2C6H4, *p*-NO2C6H4, CH2OH, CH2OCH3, H, cyclopropyl

of the above process to give enantiomerically pure azaphilones **267** has been reported by the same research group (Scheme 84).[136] The intermediacy of **268** was proposed for this novel cyclization.

The indole nucleus is a prominent structural motif found in numerous natural products and synthetic compounds with important biological activities. Similar to the cyclization of *o*-alkynylphenols, *o*-alkynylamines undergo cyclization under

Scheme 81

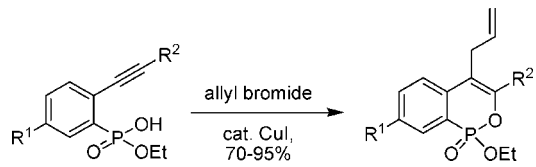
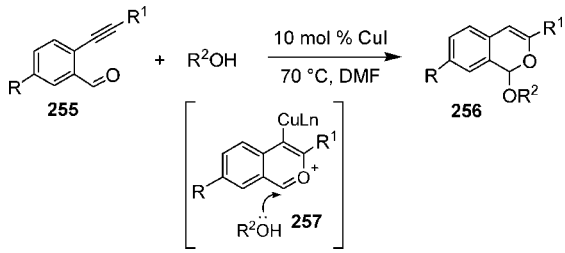
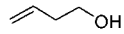


Table 18



entry	R	R^1	R^2OH	yield (%)
1	H	*n*-Pr	^{n}BuOH	97
2	H	*n*-Pr		82
3	H	*n*-Pr	*i*PrOH	98
4[a]	H	*n*-Pr	BnOH	53
5	H	H	MeOH	99
6	H	H	*i*PrOH	98
7	CF_3	*n*-Pr	MeOH	93
8	CF_3	*n*-Pr	*i*PrOH	85
9	H	*n*-Bu	MeOH	87
10	H	TMS	MeOH	91
11	H	Ph	MeOH	93
12	H	Ph	*i*PrOH	91
13	H	CH_2OMe	MeOH	88
14	H	CH_2OMe	*i*PrOH	92

[a] The reaction was heated at 100 °C for 12 h.

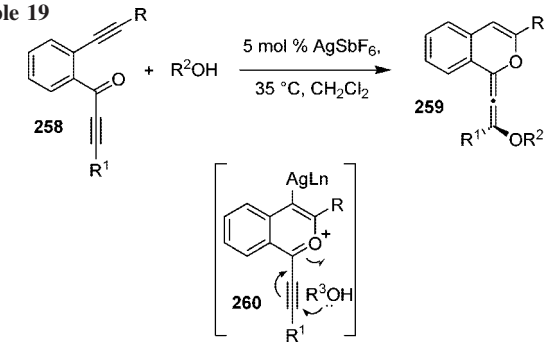
copper catalysis, giving indoles in a highly atom-economical manner (Scheme 85).[137]

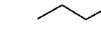
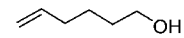
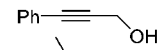
Hiroya et al. studied the cyclization of **269** in the presence of Cu(II) salts and found that copper acetate was the best catalyst for the synthesis of various 1-*p*-tolylsulfonyl- or 1-methylsulfonylindoles **270** (Scheme 86).[138] The methodology is quite general and tolerates both electron-donating and electron-withdrawing substituents on the aromatic ring. It should be noted that $Cu(OTf)_2$ showed good activities for the primary aniline derivatives, while $Cu(OAc)_2$ was a good catalyst for the cyclization of the secondary anilines. Hiroya's group also developed the sequential cyclization of 2-ethynylaniline derivatives **271**, which have a leaving group at the end of the carbon chain (Scheme 87). As can be judged from the yields of the products, the ratio of **272a/272b** was dependent on the ring size of the products; larger ring formation does not take place.

Copper(I) salts in DMF is also a well-known catalyst system for the cyclization of *o*-alkynyl amines **273** (Scheme 88).[139] Indoles **274** were obtained in excellent yields; however, the TMS group did not survive. A similar observation of deprotection of the TMS group was also made by others.[140]

The CuI-mediated synthesis of 5-azaindole **276** from acetylenic aminopyridine **275** was reported by Xu et al.

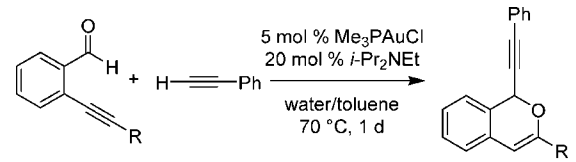
Table 19



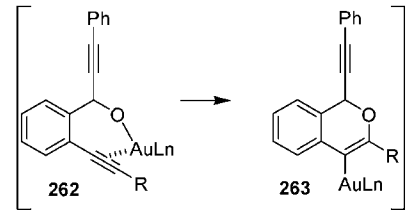
entry	substrate	R-OH	yield (%)
1	R = Ph, R^1 = *n*-Pr		93
2	R = Ph, R^1 = *n*-Pr		95
3	R = Ph, R^1 = *n*-Pr		78
4	R = Ph, R^1 = *n*-Pr		92
5	R = Ph, R^1 = *n*-Pr		0[a]
6	R = Ph, R^1 = *n*-Pr	BnOH	73
7	R = C_6H_4-*p*-CH_3, R^1 = *n*-Pr	MeOH	80
8	R = C_6H_4-*p*-CH_3, R^1 = *n*-Pr		70
9	R = C_6H_4-*p*-CF_3, R^1 = *n*-Pr	MeOH	99
10	R = C_6H_4-*p*-CF_3, R^1 = *n*-Pr		94
11	R = R^1 = *n*-Pr	MeOH	65
12	R = R^1 = Ph	MeOH	93

[a] A mixture of unidentified products was obtained.

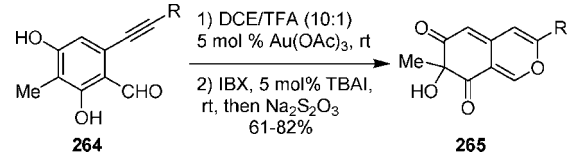
Scheme 82



261a, R = Ph, 81%
261b, R = *p*-CH_3-C_6H_4, 78%
261c, R = *p*-Br-C_6H_4, 74%



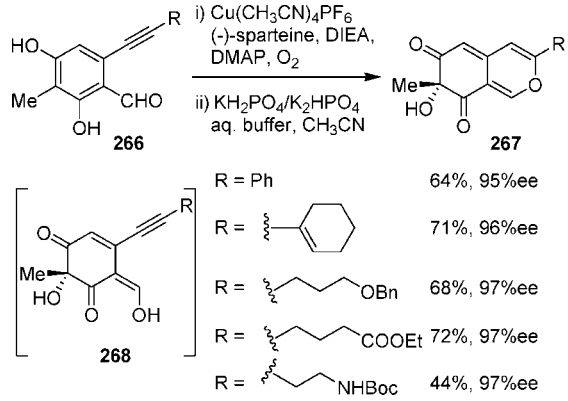
Scheme 83



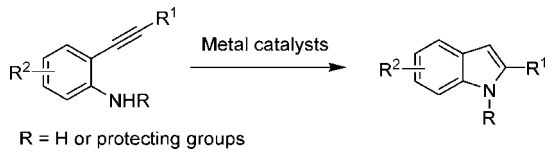
(Scheme 89).[141] Reaction at a temperature higher than 80 °C resulted in deprotection of the Boc group of the product. At 80 °C, **276** was obtained in 84% yield.

Larock et al. reported the cyclization of 2-(1-alkynyl)benzaldimines **277** into a variety of 3-arylisoquinolines **278** in the presence of 10 mol % CuI at 100 °C in DMF (Scheme

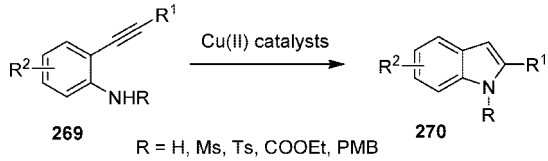
Scheme 84



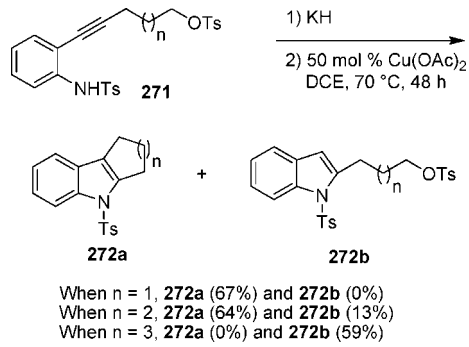
Scheme 85



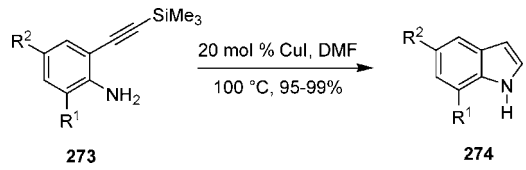
Scheme 86



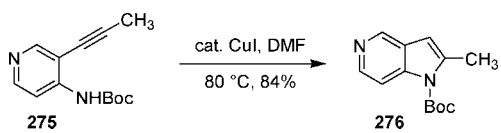
Scheme 87



Scheme 88



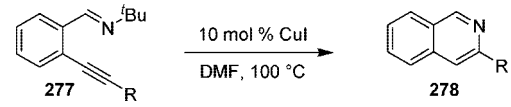
Scheme 89



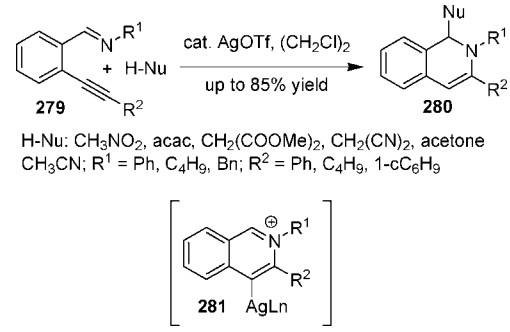
90).[142] The methodology was also extended for the synthesis of β- and γ-carbolines.[143]

We have recently reported the reaction of *o*-alkynylaryl aldimines **279** with various nucleophiles, which gave 1,2-dihydroisoquinolines **280** (Scheme 91).[144] Examples of pronucleophiles include nitromethane, acetyl acetone, dimethyl malonate, malononitrile, acetone, and acetonitrile. The

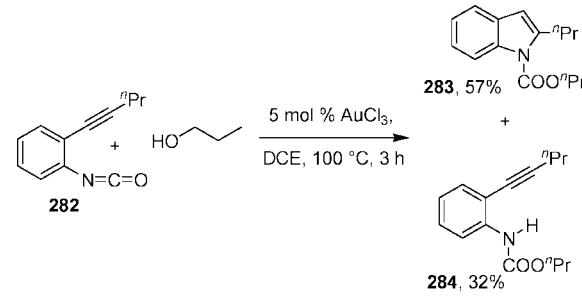
Scheme 90



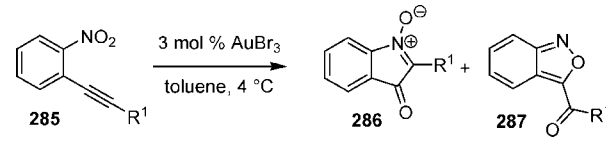
Scheme 91



Scheme 92



Scheme 93

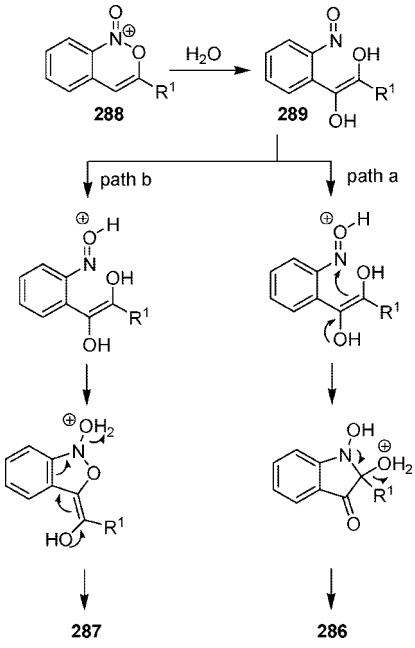


reaction was carried out in the presence of 3 mol % AgOTf in dichloroethane solvent at 60−80 °C. Not only simple carbon nucleophiles but also terminal alkynes could be used as a pronucleophile for the present reaction. It was proposed that the generation of isoquinolinium salts **281** was the key step for the reaction to proceed. The research group of Takemoto has shown that this reaction can also be catalyzed by gold complexes.[145] Ding and Wu reported tandem AgOTf and proline catalysis for the synthesis of 1,2-dihydroisoquinolines from 2-alkynylbenzaldehydes, amines, and ketones.[146] The use of diethylphosphite as a nucleophile is also known for this reaction.[147]

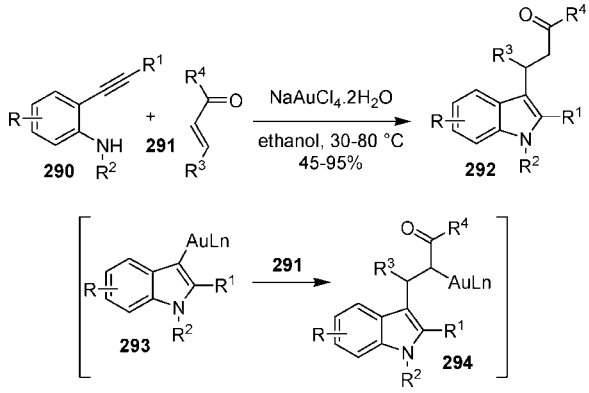
We have reported a new method for the synthesis of *N*-(alkoxycarbonyl)-indoles **283** via $AuCl_3$-catalyzed cyclization of 2-(alkynyl)phenylisocyanates **282** in the presence of alcohols (Scheme 92).[148] The product was obtained in 57% yield, along with side product **284** in 32% yield. Other gold catalysts, such as $NaAuCl_4 \cdot 2H_2O$, gave **283** and **284** in 41 and 40% yields, respectively.

Recently, we have reported $AuBr_3$-catalyzed cyclization of *o*-alkynylnitrobenzenes **285** (Scheme 93).[149] This reaction afforded isatogens **286** or anthranils **287**, depending on the nature of R^1. For instance, when R^1 = Ar or cyclohexenyl, the corresponding isatogens **286** were formed in a major amount, together with small amounts of anthranils **287**. However, when R^1 = Pr or ^{t}Bu, the corresponding anthranils

Scheme 94



Scheme 95

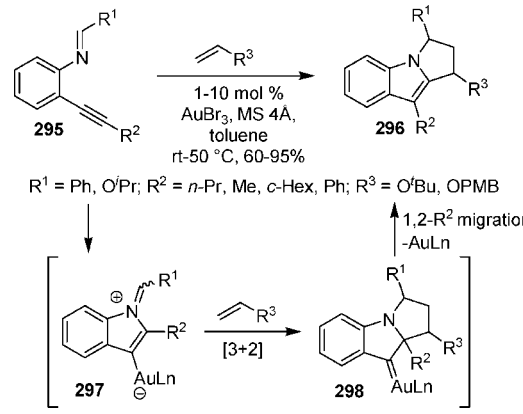


287 were obtained as a sole product. The mechanism of the reaction is interesting and is depicted in Scheme 94. As common intermediates, **288** and **289** are most probably involved in the formation of both types of products.

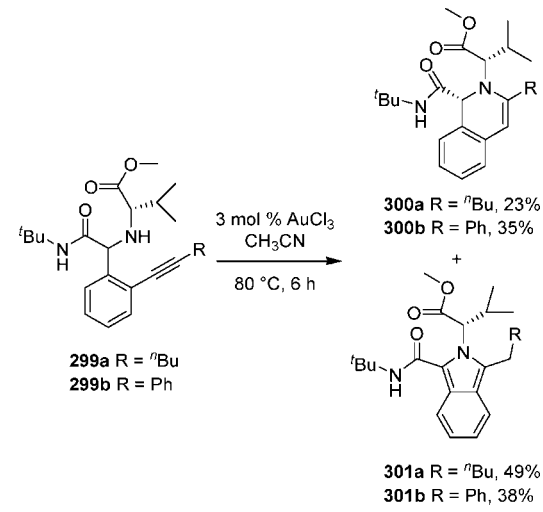
The gold-catalyzed reaction of 2-alkynyl-phenylamines **290** with α,β-enones **291** in the presence of catalytic amounts of $NaAuCl_4 \cdot 2H_2O$ was reported (Scheme 95).[150] These sequential cyclization/alkylation reactions provided access to C-3-substituted indoles **292** in good yields. It was reported that Au(III) salts exhibited higher activity compared to Pd(II) and Cu(II) catalysts. Indoles and furans, on reaction with enones in the presence of the Au catalyst, afforded C-3-substituted products[151] and C-2-substituted products,[152] respectively, indicating that **293** might be the true intermediate for the reaction. It was thought that the intermediate **293**, on reaction with **291**, would give **294** which, on protonolysis/regeneration of catalyst, would afford C-3-substituted indoles **292**.

A highly efficient method for the preparation of tricyclic indole derivatives **296**, having a substituent at the 3-position of the indole nucleus, from *N*-(*o*-alkynylphenyl)imines **295** was established by Iwasawa and co-workers (Scheme 96).[153] The reaction of ylides **297**, derived from **295**, with olefins afforded **298**. Subsequent 1,2 migration of the R^2 group, followed by demetalation, gave **296**. The products were

Scheme 96



Scheme 97



obtained in high yields, although they generally consisted of a diastereomeric mixture. Terminal alkynes were not tolerated under this condition.

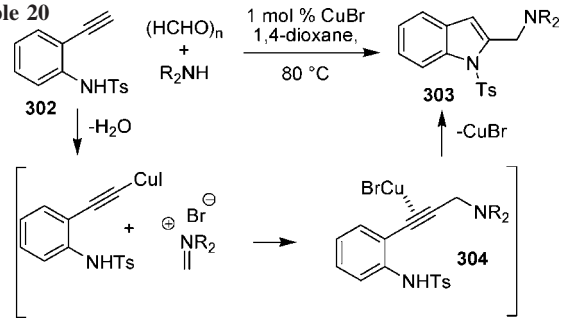
Dyker and co-workers reported $AuCl_3$-catalyzed intramolecular hydroamination of optically pure **299**, which gave chiral dihydroisoquinolines **300** and isoindoles **301** (Scheme 97).[154] The former was obtained via 6-*endo*-dig cyclization, whereas the latter was obtained from the 5-*exo*-dig cyclization/isomerization cascade. An achiral example of this type of reaction catalyzed by silver has been reported recently.[155] Gabriele et al. developed a route for the synthesis of substituted quinolines by regioselective copper-catalyzed dehydrative cyclization of anilino-alkynes.[156]

Recently, synthesis of 2-(aminomethyl)indoles **303** from aminoalkynes **302**, through a copper(I)-catalyzed three-component coupling reaction, has been reported (Table 20).[157] The reaction proceeded through a Mannich-type reaction, followed by the formation of indoles from the intermediate **304**. It should be noted that no formation of [2-(*N*-tosylamino)phenyl]allene was obtained in this case, although such allene formation is known in the literature.[158]

A new approach to *N*-vinylindoles **305** was reported by Li and co-workers, starting from *o*-alkynylanilines (Scheme 98).[159] Since the reaction of 2-phenyl-1*H*-indole and phenyl acetylene did not proceed under standard conditions, they proposed a double-hydroamination mechanism (cf. **306** and **307**).

The gold-catalyzed intramolecular carbothiolation of alkynes for the synthesis of 2,3-disubstituted ben-

Table 20



amine	time (h)	R	yield (%)
$^{i}Pr_2NH$	0.25	^{i}Pr	81
piperidine	0.25	$-(CH_2)_4-$	87
pyrrolidine	0.25	$-(CH_2)_4-$	69
Et_2NH	0.25	Et	89
Bn_2NH	2	Bn	78

Scheme 98

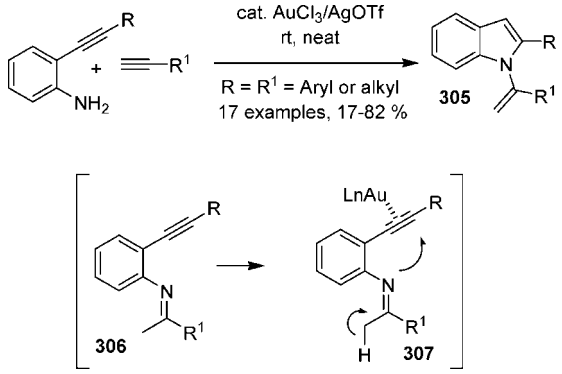
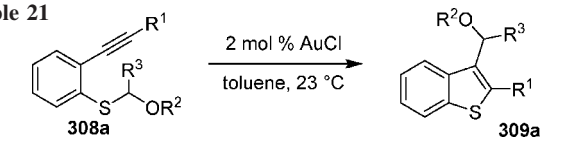
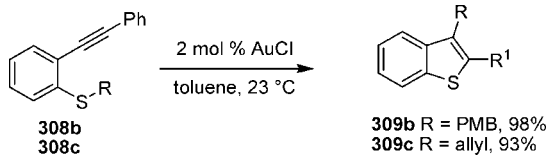


Table 21



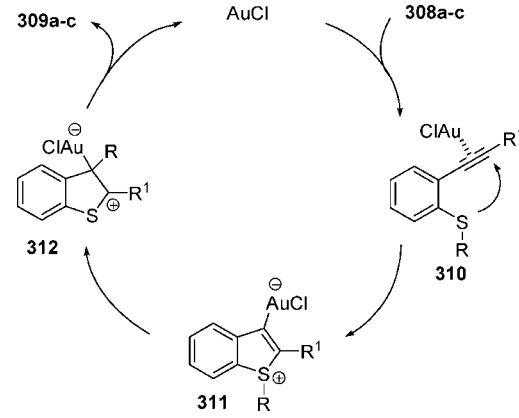
entry	R^1	R^2	R^3	yield (%)
1	^{n}Pr	Me	H	93
2[a]	cyclohexyl	Me	H	92
3[a]	^{t}Bu	Me	H	96
4	Ph	Me	H	99
5	p-CF_3-C_6H_4	Me	H	quant.
6	p-MeO-C_5H_4	Me	H	96
7	COOEt	Me	H	85
8	Ph	TBS	H	99
9	Ph	MPM	H	95
10	Ph	TMSE	H	92
11	^{n}Pr	Et	Me	92
12	Ph	Et	Me	98
13	^{n}Pr	$-(CH_2)_4-$		98
14	Ph	$-(CH_2)_4-$		93

[a] 10 mol % of AuCl was used.



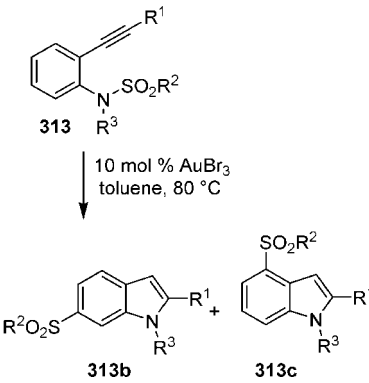
zothiophenes has been reported by us (Table 21).[160] The reaction involves the migration of groups such as α-alkoxy alkyl, PMB, and allyl from the sulfur atom to the alkyne. Various thiophene derivatives **309a−c** were obtained from readily available **308a−c**, respectively. A plausible mechanism is illustrated in Scheme 99. Nucleophilic attack of the sulfur atom of **310** to gold-coordinated alkyne gave the cyclized intermediate **311**. Migration of the R groups of **311** to the carbon atom bonded to the gold atom produces the intermediate **312** which, on elimination of gold catalyst, gave the products. Recently, we have shown that a SiR_3 group is also capable of such 1,3 migration.[161]

Scheme 99



We have also reported gold-catalyzed intramolecular amino-sulfonylation (formal addition of a N−S bond to a triple bond) for the synthesis of 3-sulfonylindoles **314** (Table 22).[162] The method involved the treatment of *o*-alkynyl-*N*-sulfonylanilines **313** with cat. $AuBr_3$ in toluene at 80 °C for 1 h. The mechanism is similar to that reported for benzothiophene synthesis (see Scheme 99). Gagosz and Istrate reported a similar type of reaction for pyrrole synthesis, and they proposed an aza-Claisen-type mechanism.[163]

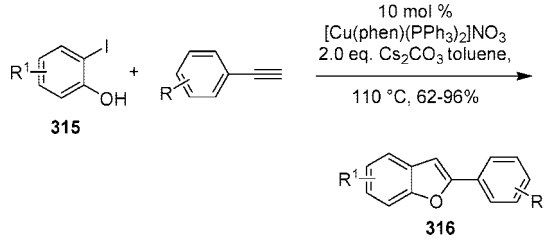
Table 22



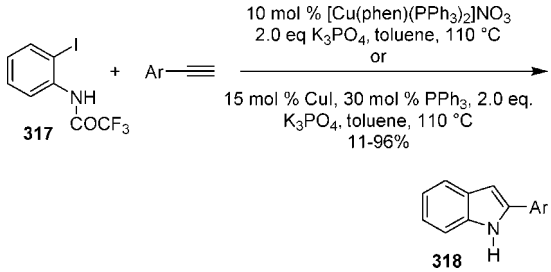
				yield (%)	
entry	R^1	R^2	R^3	**a**	**b** and **c**[a]
1	^{n}Pr	Me	Me	95	
2	cyclohexyl	Me	Me	62	25
3	^{t}Bu	Me	Me	38	10
4	Ph	Me	Me	92	2
5	p-tolyl	Me	Me	87	
6	p-anisyl	Me	Me	81	5
7	p-F_3C-C_6H_4	Me	Me	51	20
8	H	Me	Me	71	
9	COOEt	Me	Me	decomposition	
10	^{n}Pr	Me	Bn	44	
11	^{n}Pr	Me	^{i}Pr	60	
12	^{n}Pr	Me	Me	52	22
13	nPr	p-anisyl	Me	85	7
14	^{n}Pr	p-Ac-C_6H_4	Me	80	5

[a] Yield of an inseparable mixture of **313b/313c** determined by GC.

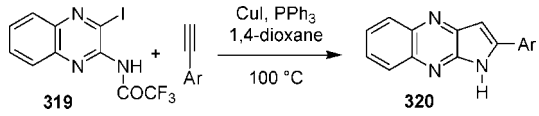
Scheme 100



Scheme 101



Scheme 102



2.4. Tandem sp−sp^2 Coupling/Cyclization

A copper(I)-catalyzed procedure for the synthesis of 2-arylbenzo[*b*]furans **316** from *o*-iodophenols **315** and terminal arylalkynes was described by Venkataraman and co-workers (Scheme 100).[164] This method could tolerate a variety of functional groups, and it is noteworthy that the reaction did not require the use of palladium.

A new method for the synthesis of 2-aryl- and 2-heteroarylindoles **318** from *o*-iodoanilines **317** and terminal arylalkynes through a domino copper-catalyzed process was reported by Cacchi and co-workers (Scheme 101).[165] The best results were obtained with $[Cu(phen)(PPh_3)_2]NO_3$ in the presence of K_3PO_4 in toluene or 1,4-dioxane at 110 °C. An alternative catalyst derived from CuI and PPh_3 can be used with equal ease. The same group also extended this approach for the synthesis of quinoxalines **320** from 2-bromo-3-trifluoroacetamidoquinoxaline **319**, adopting the same methodology (Scheme 102).[166] Ma and co-workers reported a similar cyclization process using CuI/L-proline as catalyst.[167]

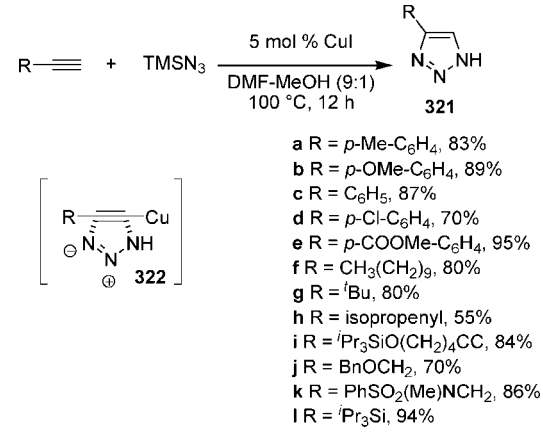
3. Cycloaddition Reactions

The transition metal-catalyzed cycloaddition reaction is one of the most efficient methods for the synthesis of a variety of heterocyclic compounds. Research in this area has been extensively reviewed.[168] Like other transition metals, coinage metals could also be used as a catalyst.

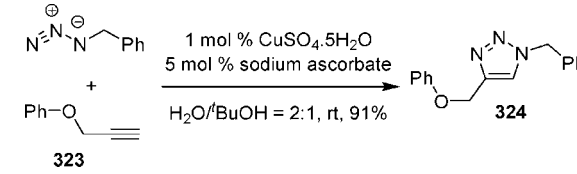
3.1. [3+2] Cycloaddition

The [3+2] cycloaddition reaction provides an efficient tool for the formation of five-membered heterocycles.[169] For example, triazoles, tetrazoles, isoxazoles, substituted pyrrolidines, isoxazolidines, and related heterocycles can be obtained efficiently. The copper-catalyzed [3+2] cycloaddition between alkyne and azide species (click chemistry) is also thoroughly reviewed and is not covered in this review. Only selected examples are described here.

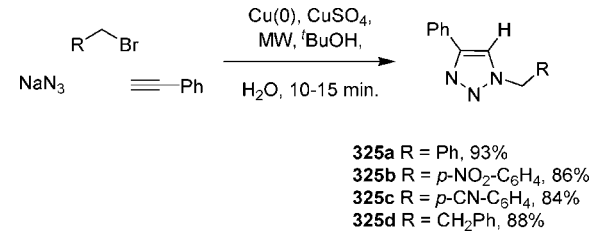
Scheme 103



Scheme 104



Scheme 105



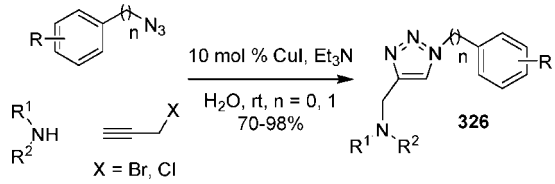
3.1.1. Triazole/Isoxazole-Forming Reactions

Recently, we have reported the copper-catalyzed synthesis of triazoles. The [3+2] cycloddition of nonactivated terminal alkynes and trimethylsilyl azide proceeded smoothly in the presence of CuI catalyst in DMF−MeOH (9:1) to give *N*-unsubstituted 1,2,3-triazoles **321** in good yields (Scheme 103).[170] The reaction proceeds through the in situ formation of a copper acetylide species and hydrazoic acid, followed by a [3+2] cycloaddition reaction (cf. **322**). This reaction avoids the use of harmful hydrazoic acid (HN_3), which was used in the previous synthesis.

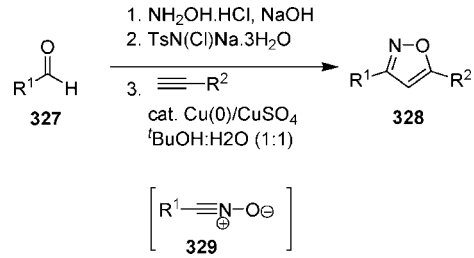
Sharpless and co-workers reported that copper-catalyzed regiospecific reaction between terminal alkynes and organic azides gave 1,4-disubstituted 1,2,3-triazoles. For example, the reaction between phenyl propargyl ether **323** and benzylazide in the presence of 5 mol % of sodium ascorbate and 1 mol % of copper sulfate in a 2:1 mixture of water and *tert*-butyl alcohol furnished the 1,4-disubstituted triazole product **324** in 91% yield after stirring for 8 h at room temperature (Scheme 104).[171]

A microwave-assisted and copper-catalyzed three-component reaction between alkyl halides, sodium azide, and alkynes for the synthesis of triazoles **310** was reported by Eycken and co-workers (Scheme 105).[172] Yields and regioselectivity were reported to be very high in all cases. Most importantly, these copper-catalyzed reactions do not require

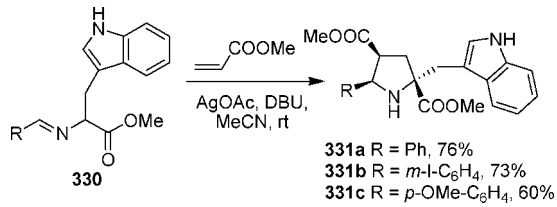
Scheme 106



Scheme 107



Scheme 108



the handling of organic azides, as they are generated in situ. Another copper-catalyzed three-component coupling involves the treatment of amines, propargyl halides, and organic azides in water (Scheme 106).[173] The triazoles **326** were obtained in good to excellent yields.

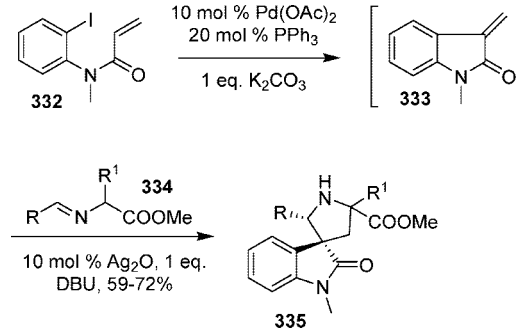
Recently, Fokin et al. reported the synthesis of 3,5-disubstituted isoxazoles **328** by a one-pot, three-step procedure utilizing a regioselective copper(I)-catalyzed cycloaddition reaction between nitrile oxides **329**, generated in situ from aldehydes **327**, and terminal alkynes (Scheme 107).[174]

3.1.2. Reactions of Azomethine Ylides

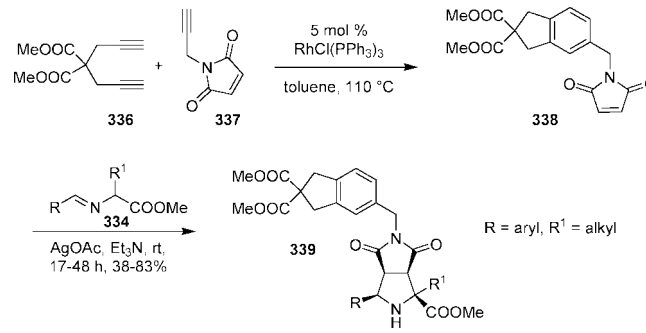
Reaction of azomethine ylides with alkene/alkynes offers an attractive strategy for the synthesis of pyrrolidine rings.[175] Only representative examples are described here. Grigg and co-workers studied the Ag(I)-promoted cycloaddition between methyl acrylate and the azomethine ylides derived from indole-based imines **330** (Scheme 108).[176] Imines **330** were treated with methyl acrylate (1.2 equiv), AgOAc (1.2 equiv), and DBU in MeCN to afford cycloadducts **331**. In all cases, the *endo* cycloadduct was obtained regio- and stereospecifically in good yields.

Grigg and co-workers reported the synthesis of spiro-oxindoles **335** by intramolecular Heck reaction followed by 1,3-dipolar cycloaddition using palladium and silver catalysts (Scheme 109).[177] The palladium catalyst promotes the intramolecular Heck reaction of **332**, to afford a relatively unstable 3-methyleneoxindole intermediate **333**. Introduction of the Ag salt together with the imines **334** and DBU provides the spiro-oxindoles **335** regiospecifically. The same group also developed a one-pot procedure involving cyclotrimerization and imine cycloaddtion.[178] The Rh(I)-catalyzed [2+2+2] cyclotrimerization of 1,6-diyne **336** with monoyne **337** led to the formation of **338** which, on subsequent silver-catalyzed cycloaddition with imines **334**, gave the complex heterocyclic benzene derivatives **339** (Scheme 110).

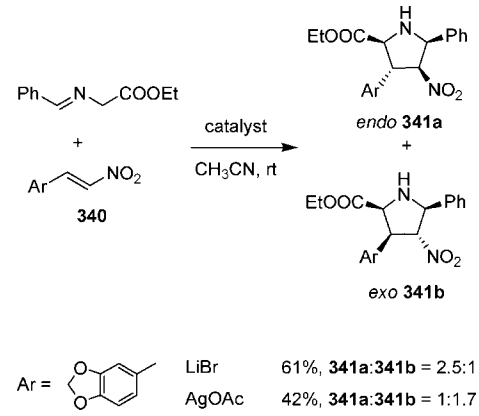
Scheme 109



Scheme 110



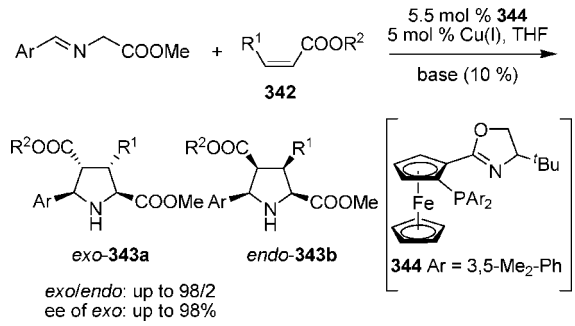
Scheme 111



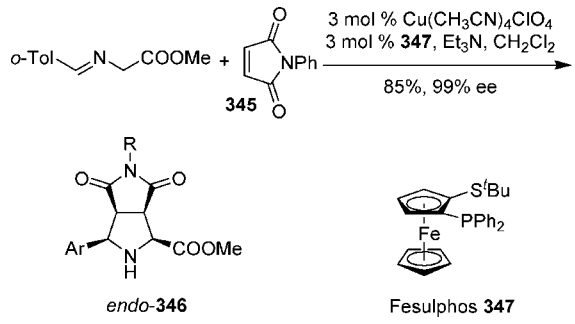
An interesting observation regarding the reversal of the stereochemistry of the product controlled by the catalyst was reported by Toke and co-workers (Scheme 111).[179] The [1,3] dipolar cycloaddition between an ester-stabilized azomethine ylide and aryl-nitro olefins **340**, catalyzed by Li(I) salts, gave a mixture of diasteromeric products **341**, in which the different stereochemistry arose from processes catalyzed by Ag(I).

Recent research revealed that these reactions can be carried out in a catalytic asymmetric manner by the use of chiral ligands. A stereocontrolled constrution of substituted pyrrolidines **343** via Cu(I)-catalyzed asymmetric 1,3-dipolar cycloadditon of azomethine ylides with acrylates **342** was reported by Zhang and co-workers (Scheme 112).[180] The ferrocenyl-based ligand **344** was effective for this reaction. The *exo* adduct was obtained as the major product in all cases, with high enantioselectivity. Interestingly, the reaction of an α-imino ester with *N*-phenylmaleimide **345** in the presence of copper(I) catalyst and Fesulphos ligand **347** gave *endo* product **346** selectively (Scheme 113).[181] A Cu(II)−BINAP catalyst system is also reported to catalyze the asymmetric 1,3-dipolar cycloaddition reaction; however, yields and ee's

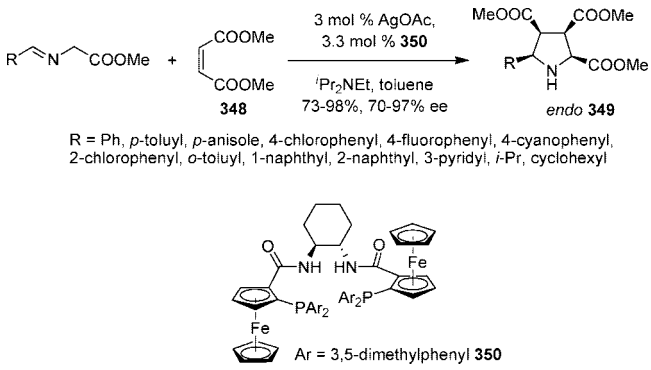
Scheme 112



Scheme 113



Scheme 114



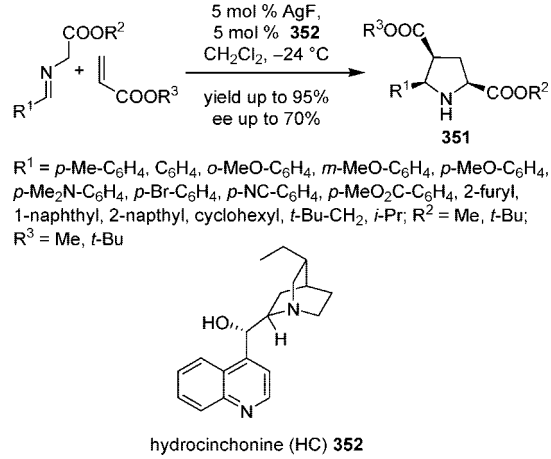
are reported to be lower.[182] Carretero and co-workers reported Cu(I)-catalyzed enantioselective [3+2] cycloaddition of azomethine ylides with vinyl sulfones.[183]

Zhang and co-workers reported silver-catalyzed asymmetric [3+2] cycloaddition of azomethine ylides (Scheme 114).[184] Using a ferrocene-based chiral phosphine ligand **350**, the cycloaddition of imino ester with dimethyl maleate **348** proceeded smoothly to give the pyrrolidines **349** in high yields with high ee's. Following that report, Carreira,[185] Hou,[186] and Schreiber[187] independently described the asymmetric version of this process. An interesting observation of hydrogen-bonding-directed reversal of enantioselectivity was reported recently.[188] Najera et al. developed recyclable chiral (*R*)- or (*S*)-binap-$AgClO_4$ complexes for this purpose.[189]

The enantioselective 1,3-dipolar cycloaddition of azomethine ylides, generated in situ from imino esters and alkenes for the synthesis of pyrrolidines **351**, was described by Jorgensen et al. (Scheme 115).[190] The chincona alkaloid **352** was used as a chiral base. This process does not need special precautions such as drying, degasifying, or the use of an inert atmosphere.

Pandey et al. described sequential double desilylation of **353** by Ag(I)F for the generation of a nonstabilized azomethine ylide and its application for the synthesis of 1-azabicyclo

Scheme 115



Scheme 116

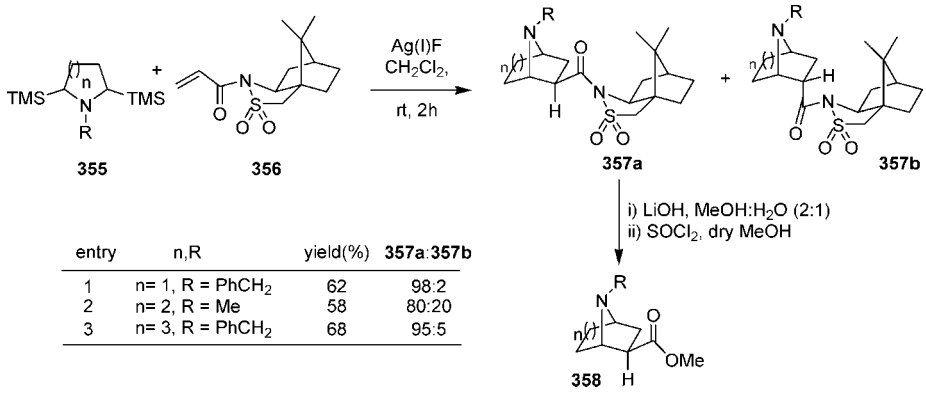
[3.3.0]alkane **354** (Scheme 116).[191] They also achieved the asymmetric synthesis of azabicyclo compounds **358** by [3+2] cycloaddition reactions of cyclic azomethine ylides **355** with Oppolzer's acryloyl camphor sultam **356**, followed by removal of the chiral auxiliary from the cycloadducts **357a** (Scheme 117).[192] Pioneering work from the same group revealed that the intermolecular reaction could be extended to an intramolecular version for the synthesis of **360** from **359** (Scheme 118).[193] Successful application of these methodologies for the syntheses of (±)-pancracine,[194] epiboxidine,[195] and epibatidine and analogues[196] has been reported.

A silver-catalyzed [3+2] cycloaddition reaction between azalactones **361** and *N*-phenylmaleimide was reported by Tepe et al. (Table 23).[197] The reaction proceeded in the presence of 10 mol % AgOAc in THF at room temperature to provide highly substituted *exo*-pyrrolines **362**. An asymmetric version of this process was reported by Toste et al., using chiral gold complexes.[198] Grigg and co-workers reported a silver-catalyzed cycloaddition reaction between methyl isocyanoacetate and alkenes to form pyrrolines **363** in good yields (Scheme 119).[199]

Alkynes can also be used as dipolarophiles instead of alkenes. Fu and Shintani reported asymmetric 1,3-dipolar cycloadditions of azomethine imines **349** with alkynes, catalyzed by Cu(I) complexes. By employing a phosphaferrocene oxazoline **366** as a chiral bidentate ligand, heterocycles **365** were obtained in high yields and enantioselectivities (Scheme 120).[200] It was assumed that the formation of copper acetylide took place at the beginning, which enhanced the reactivity of the dipolarophiles.

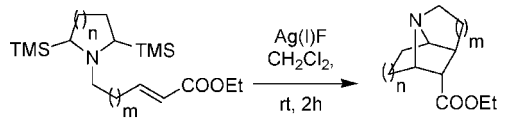
The copper-catalyzed reaction of isocyanides **367** with electron-deficient alkynes **368** gave substituted pyrroles **369** (Scheme 121).[201] Among the catalysts tested, the combination of Cu_2O and 1,10-phenanthroline showed the highest catalytic activity. A proposed mechanism is illustrated in Scheme 122. 1,4-Addition of the nucleophilic intermediate **370a** or **370b**, generated from **367** with the extrusion of H_2O,

Scheme 117



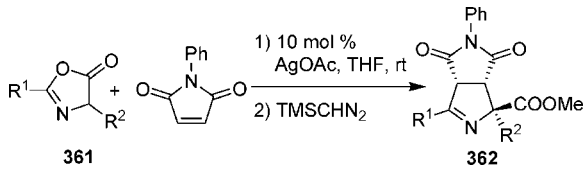
entry	n,R	yield(%)	**357a**:**357b**
1	n= 1, R = $PhCH_2$	62	98:2
2	n= 2, R = Me	58	80:20
3	n= 3, R = $PhCH_2$	68	95:5

Scheme 118



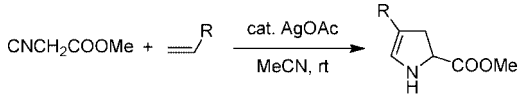
360a n = 1, m = 2, 61%
360b n = 1, m = 3, 41%
360c n = 2, m = 2, 69%
360d n =2, m = 3, 64%

Table 23



entry	R^1	R^2	yield (%)
1	Ph	Bn	67
2	Ph	3-indolylmethyl	70
3	Me	Me	59
4	Bn	Me	75

Scheme 119

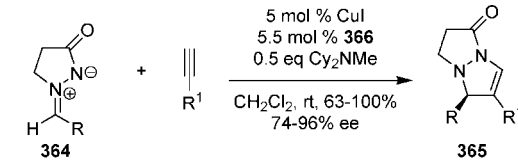


363a R = COOMe, 67%
363b R = CN, 72%
363cR = $COCH_3$, 82%
363d R = CHO, 73%

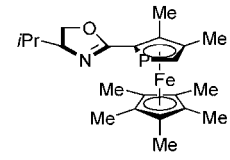
to the alkynes **368** takes place first. The newly generated copper enolate would intramolecularly attack the isonitrile carbon to generate the cyclized intermediate **371**. This process can be termed a formal [3+2] cycloaddition process. The C−Cu bond in the intermediate **371** is protonated by isocyanides, and the intermediate **372** is produced with regeneration of the copper intermediate **370**. 1,5-Hydrogen shift in **372** forms the pyrroles **369**.

Hayashi et al. reported a silver(I)-catalyzed asymmetric aldol reaction of methyl isocyanoacetate with aldehydes in the presence of chiral ferrocinyl-based ligand **374** (Scheme 123).[202] The chiral oxazolines **373** were obtained by this method, and their ee's ranged from 37 to 88%. Not only aldehydes but also ketones, although fluoroalkyl ketones, could be employed for this reaction (Scheme 124).[203] High diastereoselectivity (**375a**:**375b**) was achieved in the case

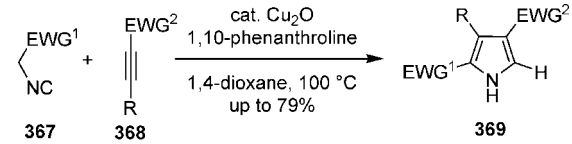
Scheme 120



R = Ph, *o*-FC_6H_4, *m*-BrC_6H_4, *p*-$CF_3C_6H_4$, 1-cyclohexenyl, *n*-pentyl, cy; R^1 = CO_2Et, CO_2Me, CONMePh, *p*-$EtO_2CC_6H_4$, *p*-$CF_3C_6H_4$, 2-pyridyl, Ph, *n*-pentyl



Scheme 121



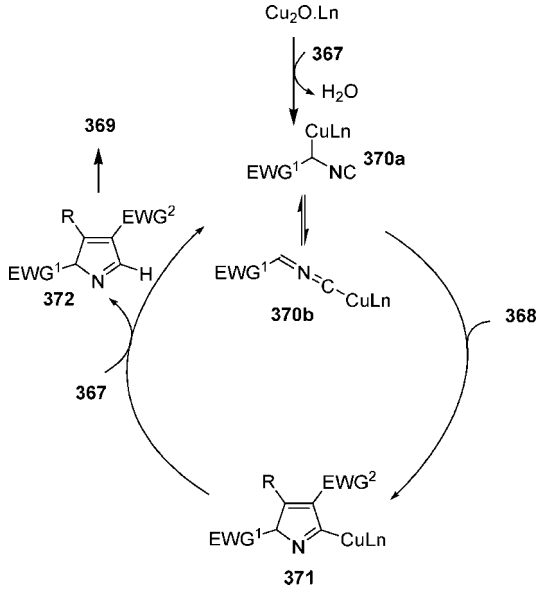
EWG^1 = CO_2Me, $CO_2{}^tBu$, $CONEt_2$, $P(O)(OEt)_2$, Ph; EWG^2 = COOEt, COMe, $CONEt_2$, CN, SO_2Ph; R = Me, $HO(CH_2)_4$, ^tBu, Ph, H, COOEt

of the fluorinated ketones, but a very poor diastereoselectivity was obtained in the similar reaction of the non-fluorinated ketones. Gold(I) complexes are also capable of this transformation.[204]

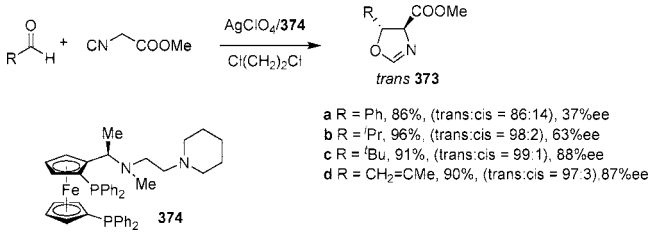
Recently, Porco and Su reported an efficient synthesis of pyrroloisoquinolines **377** related to the lamellarin natural products involving domino cyclization/[3+2] dipolar cycloaddition of alkynyl *N*-benzylidene glycinates **376** (Table 24).[205] It was reported that the intramolecular cyclization in **376** gave isoquinolinium species which, on subsequent proton transfer and regeneration of Ag(I), afforded azomethine ylides **378** which, on [3+2] dipolar cycloaddition followed by isomerization and oxidation, gave pyrroloisoquinolines **377**.

A highly diastereoselective copper-catalyzed three-component coupling reaction between imine, diazo compound, and olefins for the synthesis of spiropyrrolidinyloxindoles was reported by Scheidt and co-workers. For example, the treatment of **379** with imine and ethyl diazoacetate in the presence of catalytic amounts of $(C_6H_5)\cdot[(Cu(OTf)]_2$ in refluxing dichloromethane gave spiropyrrolidinyloxindoles **380** in high yield and diastereoselectivity (Scheme 125).[206]

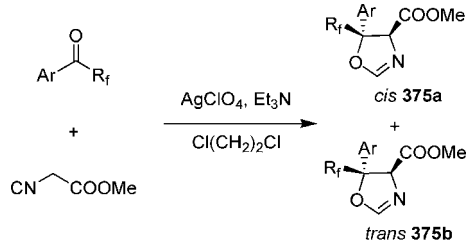
Scheme 122



Scheme 123



Scheme 124



Ar = C_6F_5, R_f = CF_3, 92% (**375a**:**375b** = 94:6)

Mechanistically, an azomethine ylide **381a** is generated, which after isomerization to **381b** underwent [3+2] cycloaddition with **379** to form the product **380**.

3.1.3. Cycloaddition of Nitrones

A copper-catalyzed diastereo- and enantioselective 1,3-dipolar cycloaddition reaction between nitrones and alkenes has been reported by JorgensEn et al. For example, in the presence of $Cu(OTf)_2$−bisoxazoline **384** as a catalyst, the nitrone **382** reacted smoothly with ethyl vinyl ether at room temperature to give isoxazolidines **383a** and **383b** (Scheme 126).[207]

The reaction between nitrones and copper acetylide, leading to the formation of β-lactams, was described by Kinugasa in 1972.[208] However the asymmetric variant has been reported only recently. Fu and Lo reported the use of C_2-symmetric planar chiral bis(azaferrocene) ligand **386** for the copper-catalyzed enantioselective Kinugasa reaction between terminal alkynes and nitrones. β-Lactams **385** were obtained with good enantiomeric excesses favoring *cis* diastereoselectivity (Scheme 127).[209] This catalyst system is an advance compared to Miura's catalyst system, wherein a maximum ee of 57% was reported.[210] The mechanism of this reaction reported by Kinugasa in the original publication is shown in Scheme 128. Zhao and Li reported three-component reactions of *N*-substituted hydroxylamines, aldehydes, and phenylacetylene catalyzed by CuCl/bipy in the presence of NaOAc under neat conditions to give the corresponding β-lactams.[211]

3.1.4. Other [3+2] Reaction

Akiyama and co-workers reported copper-catalyzed enantioselective [3+2] cycloaddition reactions of 1-alkyl-substituted allenylsilanes **387** with α-imino ester **388** using $[Cu(MeCN)_4]BF_4$ as a copper source and (*R*)-DM-SEGPHOS **390** as a chiral ligand (Scheme 129).[212] Silyl-substituted dehydroproline derivatives **389** were obtained in high yields and enantioselectivities. The presence of the COOEt group on the imine carbon was essential for the reaction to proceed.

Kende and Journet observed an interesting intramolecular [1,3] dipolar cycloaddition reaction of **391** in the presence of a silver catalyst, when they had intended to perform an Arndt−Eistert homologation. Novel polycyclic pyrazole derivatives **377** were obtained by this method (Table 25).[213] However, the reaction is very limited in terms of substrate scope. For example, geminal dimethyl substituents α to carbonyl (Thorpe−Ingold effect) were essential for the reaction to occur.

Broggini et al. reported a stereoselective intramolecular nitrile imine cycloaddition reaction of **395**, generated in situ from **393**, which gave novel heterocycles **394a** and **394b** (Scheme 130).[214] Since the chiral auxiliary is present in the starting material, chirality is transferred to the products.

3.2. [4+2] Heterocycloaddition

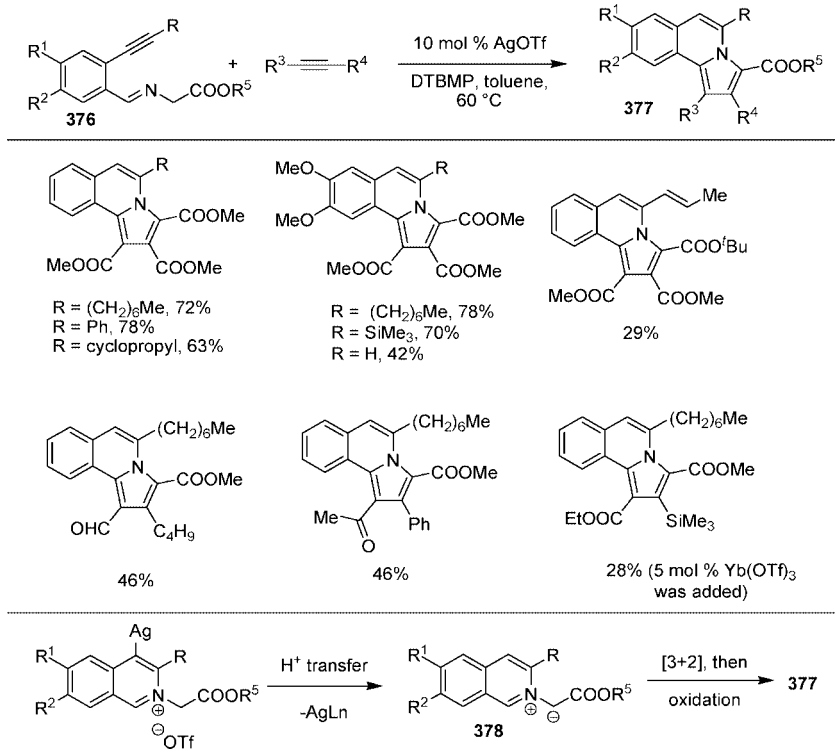
The [4+2] hetero-Diels−Alder reaction catalyzed by copper complexes has becoming very routine chemistry. The subject has been reviewed thoroughly.[215] Herein we show only a few examples which will give a general idea about this chemistry. An asymmetric hetero-Diels−Alder reaction between 1,3-cyclohexadiene and ethyl glyoxalate **396**, catalyzed by a chiral copper complex, gave cycloaddition product **397** with excellent selectivity (*endo*:*exo* = 99:1) (Scheme 131).[216] The chiral copper complex was generated by mixing an equimolar amount of $Cu(OTf)_2$ and (*S*,*S*)-bis(sulfoximine) **398** in dichloromethane at room temperature.

The C_2-symmetric bis(oxazoline)−Cu(II) complexes **401a** and **401b** catalyzed the inverse electron-demand hetero-Diels−Alder reactions of heterodienes **399** with ethyl vinyl ether with high diastereo- and enantioselectivities (Table 26).[217] This represents an efficient method for the synthesis of optically pure dihydropyrans **400**.

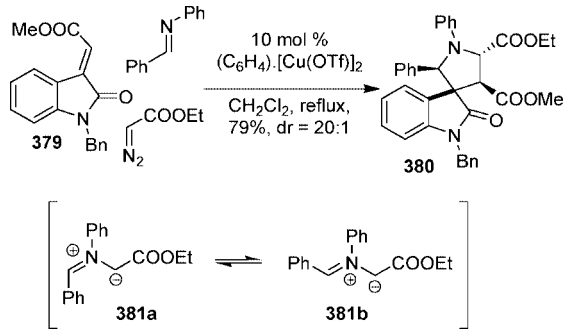
Jnoff and Ghosez reported asymmetric Diels−Alder reactions of 2-azadienes **402** with olefinic dienophiles, catalyzed by chiral copper(II) complex **404** (Scheme 132).[218] The method provides multiply substituted piperidones **403** with high enantiomeric purities. The intramolecular version led to the formation of oxazinopiperidines (Scheme 133).[219] In a similar manner, dihydrothiopyrans were synthesized via $Cu(OTf)_2$-catalyzed enantioselective thia-Diels−Alder reactions (Scheme 134).[220]

Kobayashi et al. reported aza-Diels−Alder reactions of imines **405** with Danishefsky's diene **406** in water (Scheme

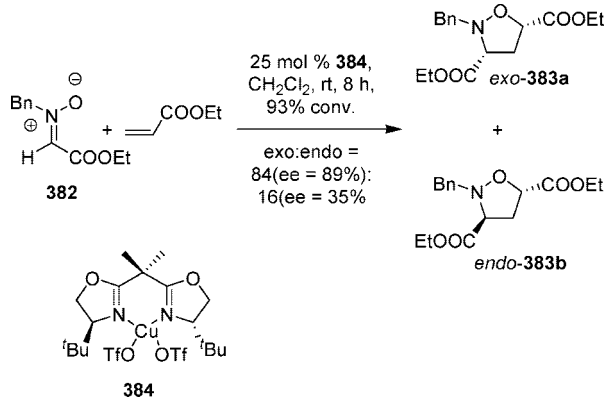
Table 24



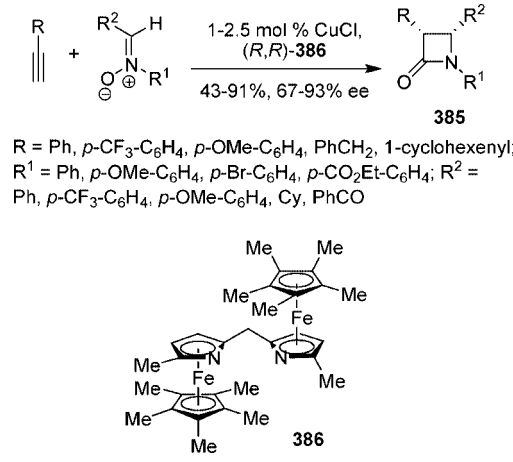
Scheme 125



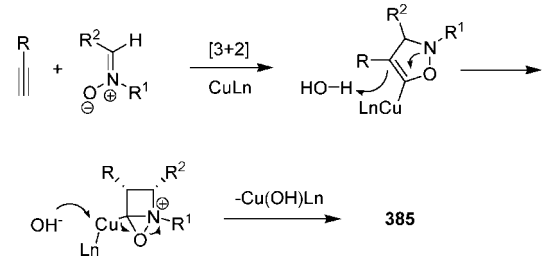
Scheme 126



Scheme 127

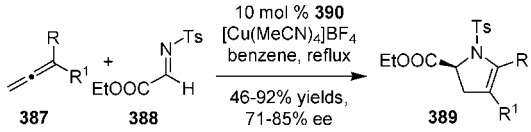


Scheme 128



135).[221] The reaction took place smoothly in the presence of a catalytic amount of silver triflate to afford dihydro-4-pyridones **407** in high yields. The silver triflate-catalyzed three-component reaction starting from aldehydes, amines, and Danishefsky's diene was also discribed in the same report (Scheme 136). In a recent report, Carretero and co-workers[222] have further investigated the use of chiral copper complexes of phosphino sulfenyl ferrocenes as efficient catalysts for enantioselective aza-Diels−Alder reactions. Hoveyda[223] and Jorgensen[224] independently reported aza-Diels−Alder reactions between imines and dienes. Weller and Frost[225] also reported silver(I) complexes partnered with carborane anions, which could be used as a catalyst for asymmetric aza-Diels−Alder reactions at comparatively lower catalyst loading.

Scheme 129



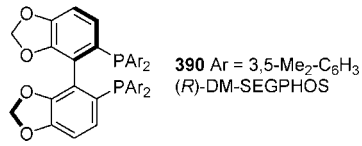
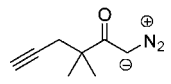
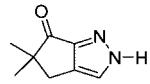
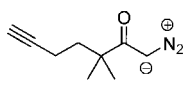
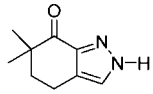
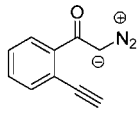
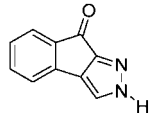
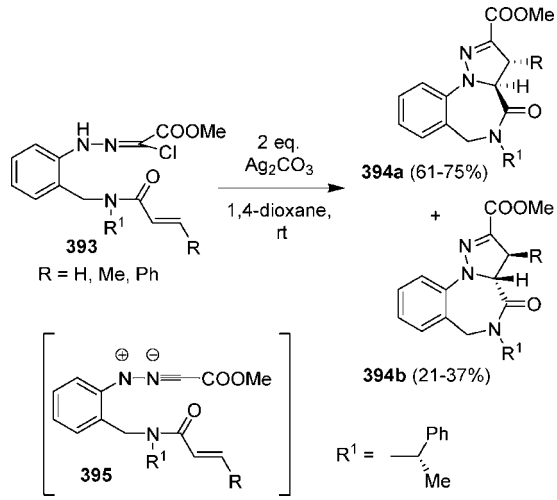


Table 25[a]

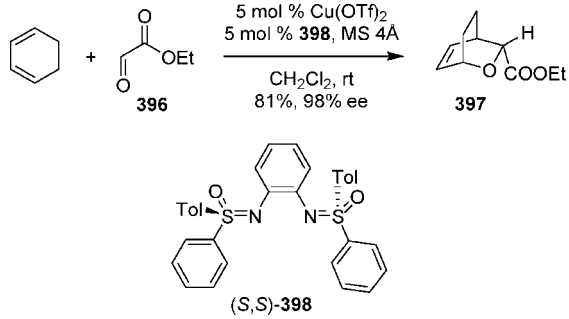
entry	α-diazoketone (**391**)	cycloadduct (**392**)	yield (%)
1			47
2			55
3			69

[a] Reaction conditions: 20 mol % Ag_2CO_3/Celite as catalyst, THF, reflux, 3 h.

Scheme 130

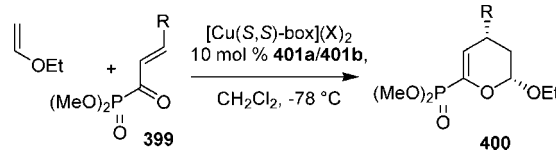


Scheme 131



Yamamoto and Kawasaki reported a copper-catalyzed asymmetric azo-hetero-Diels−Alder reaction for the synthesis of cyclic azo compounds **412** (Table 27).[226] 2-Azopyridine **411** and silyloxy dienes **410** were used as coupling partners.

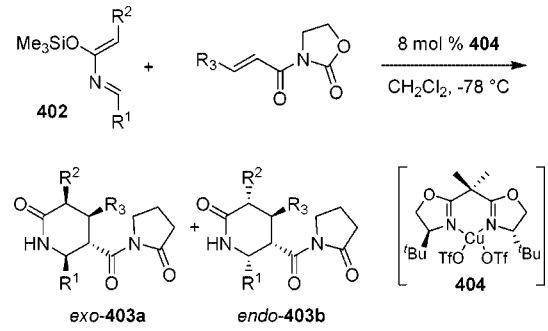
Table 26



product	catalyst[a]	yield (%)	*endo*:*exo*	ee (%)
400a	**401a**	88	32:1	94
ent-**400a**	**401b**	98	99:1	98
400b	**401a**	78	32:1	93
ent-**400b**	**401b**	99	99:1	96
400c	**401a**	96	99:1	93
ent-**400c**	**401b**	49	99:1	77

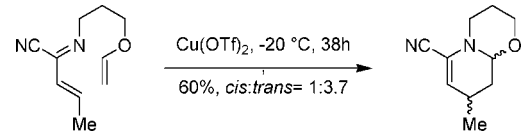
[a] **401a**, [Cu(*S*,*S*)-^{t}Bu-box)](SbF$_6$)$_2$; **401b**, [Cu(*S*,*S*)-Ph-box)](SbF$_6$)$_2$.

Scheme 132

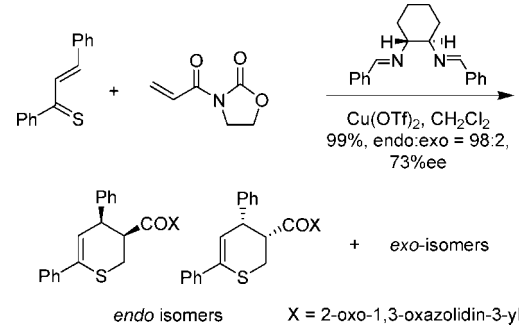


R^1 = Ph; R^2 = R^3 = Me; 80%, *exo*:*endo* = 99:1; 95%ee
R^1 = Ph; R^2 = R^3 = H; 83%, *exo*:*endo* = 6.1:1; 98%ee
R^1 = Ph; R^2 = Me, R^3 = H; 96%, *exo*:*endo* = 99:1; 98%ee

Scheme 133



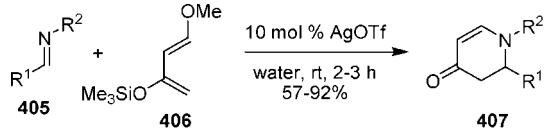
Scheme 134



3.3. [2+2] Cycloaddition

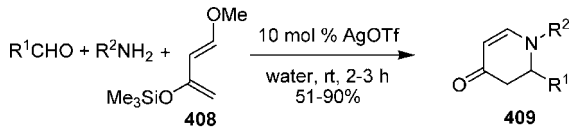
Akiyama and co-workers reported enantioselective [2+2] cycloaddition reaction of 1-methoxyallenylsilanes **413** with α-imino ester **414** in the presence of the [Cu(MeCN)$_4$]BF$_4$/(*R*)-Tol-BINAP catalyst system (Scheme 137).[227] The reac-

Scheme 135



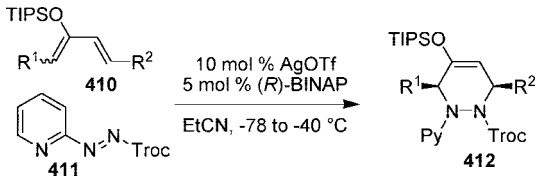
R^1 = Ph, *p*-OMe-C_6H_4, *p*-Br-C_6H_4, *p*-NO_2-C_6H_4, PhCH=$CHCH_3$ (*E*);
R^2 = Ph, *p*-Br-C_6H_4

Scheme 136



R^1 = Ph, *c*-C_6H_{11}, $Ph(CH_2)_2$, $(CH_3)_2CHCH_2$
R^2 = Ph, *p*-Br-C_6H_4, *o*-$OMeC_6H_4$

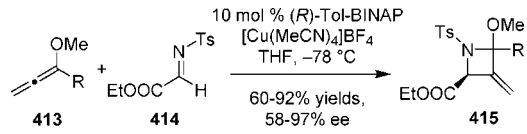
Table 27



R^1	R^2	yield (%)	ee (%)
Me	Me	87	99
Me	*n*-C_5H_{11}	84	95
Me	^{i}Pr	65	84
Me	$(CH_2)_3COOMe$	74	98
Bn	Me	74	92
4-MomO-Bn	Me	85	90
$(CH_2)_3OTBS$	^{t}Bu	82	95
$(CH_2)_3OTBS$	CH_2OBn	84	98
$(CH_2)_3NNsBoc$	^{t}Bu	77	98
Me	2-furyl	78	92
Me	Ph	70[a]	55

[a] 20 mol % of AgOTf and 10 mol % of (*R*)-BINAP were used.

Scheme 137



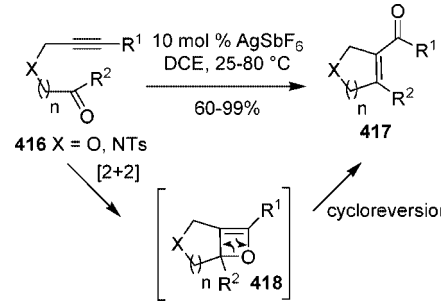
R = $SiMe_3$, $SiMe_2Ph$, $Si(^tBu)Me_2$, $Si(^iPr)_3$

tion afforded azetidines **415** in good yields with excellent enantiomeric excesses.

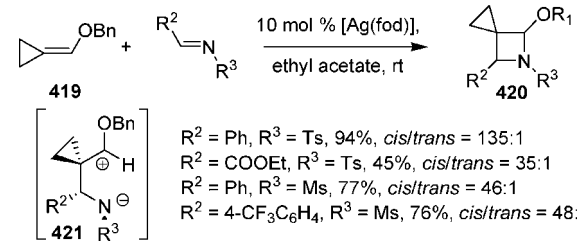
Krische and Rhee developed a novel process for the synthesis of heterocycles **417** via intramolecular [2+2] cycloaddition of keto alkynes **416** promoted by $AgSbF_6$ (Scheme 138).[228] Five- and six-membered heterocycles **417** were easily synthesized by this procedure. A comparison to other catalysts, such as $BF_3 \cdot OEt_2$ and HBF_4, revealed that the $AgSbF_6$-catalyzed process is more efficient in certain cases. The authors proposed the intermediacy of oxete intermediate **418** which, on cycloreversion, afforded products.

Recently, we reported the silver-catalyzed [2+2] cycloaddition of imines with (benzyloxymethylene)cyclopropane **419** (Scheme 139).[229] Azetidines **420** were obtained in good yields, predominantly as *cis* diastereomers. This cycloaddition reaction can also be performed without any catalysts; however, higher temperature (80 °C) is necessary. It is important to mention that the stabilization of the zwitterionic

Scheme 138

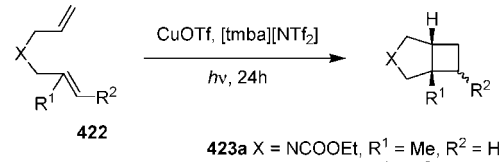


Scheme 139



R^2 = Ph, R^3 = Ts, 94%, *cis*/*trans* = 135:1
R^2 = COOEt, R^3 = Ts, 45%, *cis*/*trans* = 35:1
R^2 = Ph, R^3 = Ms, 77%, *cis*/*trans* = 46:1
R^2 = 4-$CF_3C_6H_4$, R^3 = Ms, 76%, *cis*/*trans* = 48:1

Scheme 140



423a X = NCOOEt, R^1 = Me, R^2 = H, 75%
423b X = NCOOEt, R^1 = R^2 = H, 65%
423c X = NCOOEt, R^1 = H, R^2 = Me, 57%
423d X = O, R^1 = H, R^2 = Ph, 79% (based on recovered starting material)

intermediate **421** by the cyclopropyl group adjacent to the cationic center is essential, as the enol ether that does not contain a cyclopropane ring did not react with the imines under the standard reaction conditions.

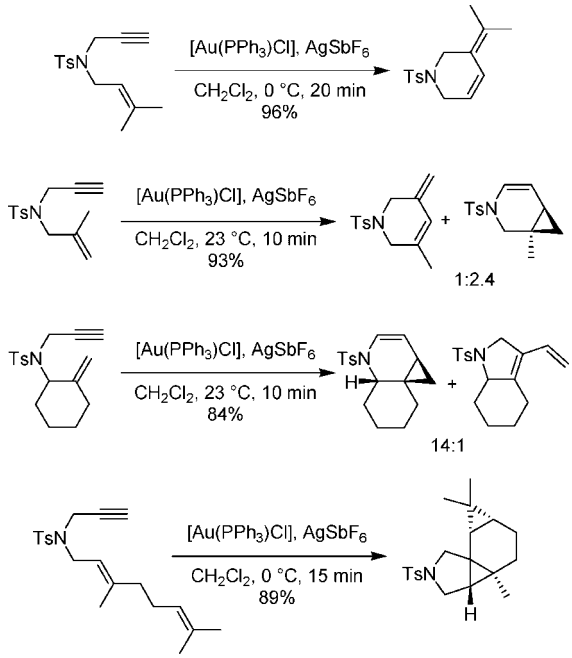
Ghosh and co-workers reported copper-catalyzed [2+2] photocycloaddition of alkenes **422** in ionic liquid such as [tmba][NTf_2] at room temperature. The process gave access to azabicyclo[3.2.0]heptanes **423a**−**c** and oxabicyclo[3.2.0] heptanes **423d** (Scheme 140).[230] Recently, Toste et al. reported gold-catalyzed [2+2] cycloaddition of allenenes for the synthesis of enantioenriched bicyclo[3.2.0] heterocycles using chiral biarylphosphinegold(I) complexes as catalysts.[231]

4. Cycloisomerization of Enynes/Diynes

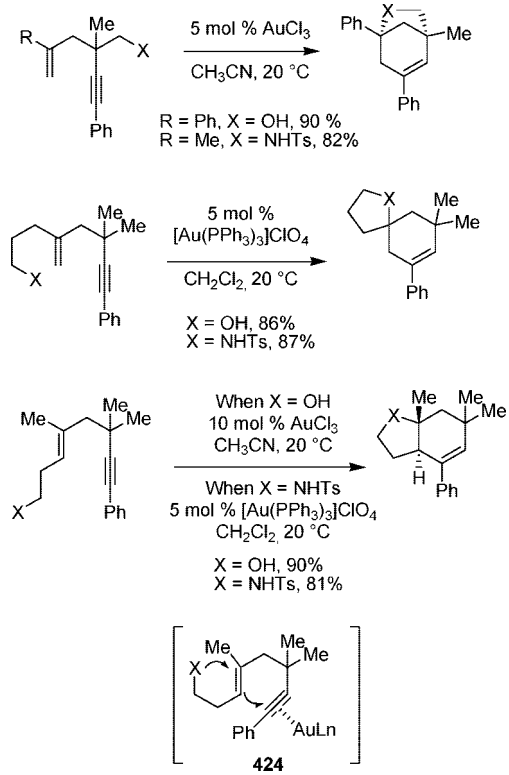
Transition metal-catalyzed carbocyclization of alkenes and alkynes is one of the most important methods for the synthesis of heterocycles.[232] Enynes are extremely reactive substrates and undergo a variety of reactions in the presence of transition metals.[233] The gold-catalyzed cyclization of enynes offers an attractive route for the synthesis of a variety of heterocycles (Scheme 141).[234] The yields and diastereoselectivities obtained are excellent in many cases.

Recently, Kozmin and co-workers reported the gold-catalyzed cycloisomerization of 1,5-enynes, tethered with oxygen or nitrogen nucleophiles.[235] This process provided diastereoselective access to oxa- and azabicyclic compounds containing bridged, fused, and spirocyclic architectures. Representative examples are shown in Scheme 142. The authors proposed a concerted mechanism for the process, and **424** was proposed as an intermediate.

Scheme 141

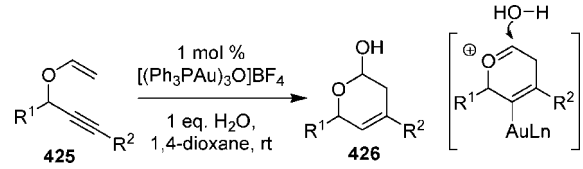


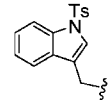
Scheme 142



Toste et al. reported gold-catalyzed synthesis of dihydropyrans **426** from propargyl vinyl ether **425** (Table 28).[236] The propargylic position was tolerant of substitutions, including linear and branched substituents. Moreover, substrates derived from electron-rich alkene (entry 9) and *N*-tosylindole (entry 10) showed high selectivity for the desired pyran formation. It has also been reported that the present cycloisomerization proceeds with excellent chirality transfer from starting propargyl vinyl ethers to dihydropyrans. The silver-catalyzed annulations of propargyl vinyl ethers **427** for the synthesis of 2*H*-pyrans **428** was reported by Kirsch and Menz (Table 29).[237]

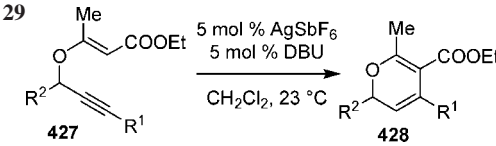
Table 28



entry	R^1	R^2	yield (%)[a]
1	$Ph(CH_2)_2$-	$(CH_2)_4OTs$	89
2	$Ph(CH_2)_2$-	$(CH_2)_4CN$	88
3	$Ph(CH_2)_2$-	*c*-C_3H_5	92
4	$Ph(CH_2)_2$-	*c*-C_6H_{11}	80
5	$Ph(CH_2)_2$-	*t*-Bu	60
6	*i*-Pr	$(CH_2)_3Ph$	90
7	Bn	*n*-Bu	95
8	$TBSOCH_2$	*n*-Bu	77
9	$(Me)_2CCH(CH_2)_2$	*n*-Bu	92
10		*n*-Bu	83

[a] A mixture of 1−1.3:1 of anomers after purification by column chromatography.

Table 29

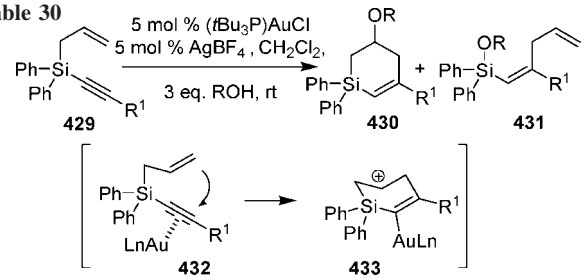


entry	R^1	R^2	yield (%)
1	Ph	Et	76
2	*p*-^{t}Bu-C_6H_4	Et	77
3	*p*-OPh-C_6H_4	Et	63
4	3-thienyl	Et	90
5	$(CH_2)_2OTBS$	Et	82
6	CH_2(*c*-C_6H_{11})	Et	75
7	Ph	Et	72
8	Ph	^{i}Pr	60
9	Ph	CH_2Ph	50
10	Ph	H	61
11	*o*-OMe-C_6H_4	H	59
12	3-thienyl	H	53

A cationic gold complex-catalyzed acetylenic sila-Cope rearrangement of **429** has been developed by Toste and co-workers (Table 30).[238] The process gave efficient access to silacycles **430** and vinyl silane **431**, depending on the type of nucleophiles used. For example, when methanol was used, silacycles were obtained (entries 1, 3, and 5), and when less nucleophilic phenol was used, vinyl silanes were obtained (entires 2, 4 and 6). The vinyl silanes are obtained through β-silyl fragmentation of **433**, which could be obtained via the attack of the double bond to gold-coordinated alkynes, as shown in **432**.

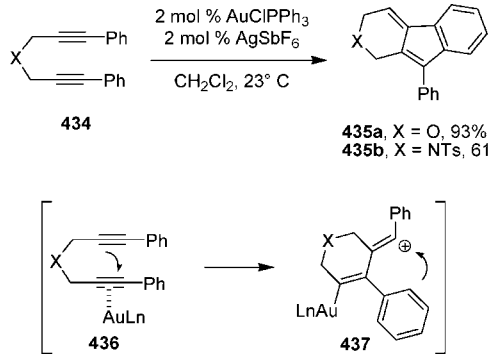
Gold-catalyzed intramolecular [3+2] cycloaddition of arenyne-yne functionalities for the synthesis of novel oxygen- and nitrogen-containing heterocycles **435** from **434** has been reported by Liu and co-workers (Scheme 143).[239] The mechanism most probably involves the activation of one of the alkynes by gold catalyst (cf. **436**) to form the vinylic carbocations **437** which, after Friedel−Crafts-type reactions followed by aromatization, afforded products.

Table 30



entry	R^1	ROH	yield (%) 430	431
1	H	MeOH	78	5
2	H	PhOH	0	99
3	*n*-Bu	MeOH	82	16
4	*n*-Bu	PhOH	0	50
5	CH_2OBBn	MeOH	74	5
6	CH_2OBn	PhOH	9	72

Scheme 143

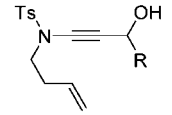
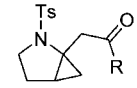
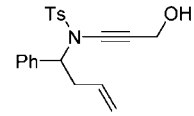
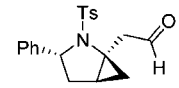
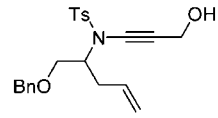
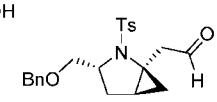
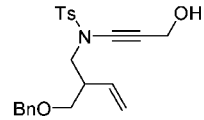
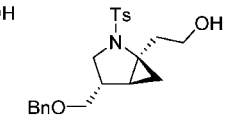


Cossy and co-workers reported the gold-catalyzed highly diastereoselective cyclization of ene-ynamides (Table 31).[240] For instance, the ynamides **438**, bearing a propargylic alcohol moiety, were reacted with AuCl (5 mol %) in CH_2Cl_2 to give heterocycles **439**. The primary alcohols were smoothly converted into the aldehyde, whereas the secondary alcohols led to the ketones. The pinocol-type rearrangement in carbenoid intermediate **440** was proposed as a key feature of the mechanism.

A diastereoselective cycloisomerization of enyne **441** involving Friedel−Crafts-type addition of electron-rich aromatic and heteroaromatic derivatives to unactivated alkenes was reported (Table 32).[241] A variety of oxygen- and nitrogen-containing heterocycles **442** could be synthesized by this method. Not only electron-rich arenes but also water and alcohols work well as nucleophiles for the reaction.[242] Echavarren et al. reported gold(I)-catalyzed addition of electron-rich arenes and heteroarenes to 1,6-enynes.[243]

The other example where bicyclic heterocycle **444** could be obtained from enyne **443** involved the Prins cyclization of alkenylgold intermediates (Scheme 144).[244] The mechanism of this reaction is shown in Scheme 145. The first step is the formation of cyclopropyl metal carbene **445**, which undergoes ring expansion to form **446**. The alkenylgold complex **446** reacts with the oxonium cation to form **447**, which upon demetalation forms tricycles **444a**. The nonconcerted reaction occurs via cyclopropyl-stabilized cation **445**, which undergoes a nonstereospecific ring expansion to give mixtures of **448** and **446**. The intermediate **449**, on demetalation, forms **444b**. An interesting extension has recently been outlined in which the putative gold carbenoid

Table 31

substrate (**438**)	product (**439**)	yields (dr)[a]
		R = H, 40% R = Me, 60% R = *i*Pr, 42%
		61% (dr = 95:5)
		51% (dr = 95:5)
		60% (dr = 90:10)[b]

[a] A solution of compound in CH_2Cl_2 was treated with 5 mol % AuCl at rt. [b] After treatment with $NaBH_4$ in methanol.

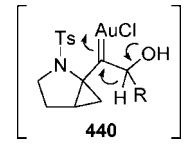
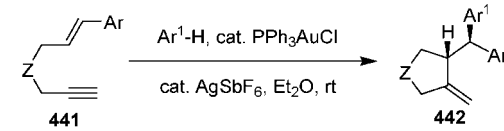
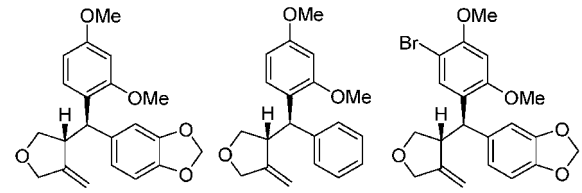
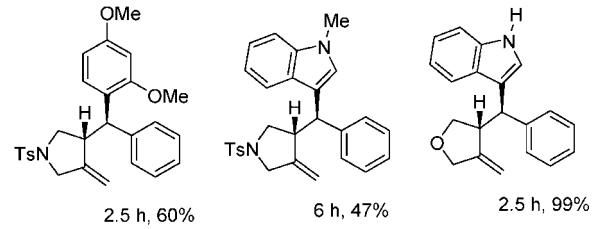


Table 32



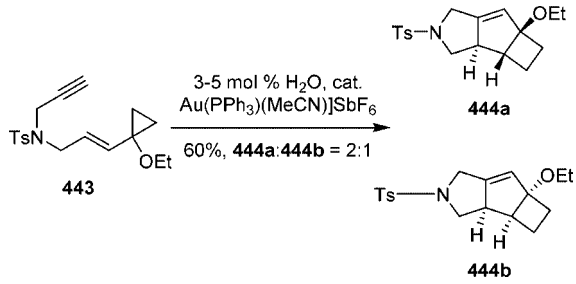




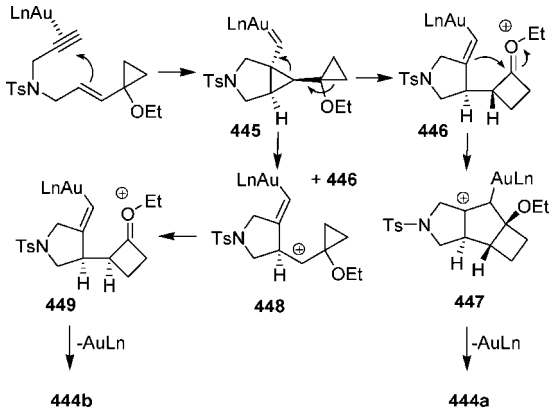
is trapped by the olefins (Scheme 146).[245] The same group also reported cycloisomerization of 1,7-enynes.[246] The cycloisomerization of 1,6-enynes involving Prins-type reaction was reported by Helmchen et al.[247]

Gold(I)-catalyzed cyclization of enynes **450** containing an olefinic cycle, for the synthesis of highly fused bicyclic heterocycles **451**, has been described by Chung and coworkers (Scheme 147).[248] The introduction of an olefinic ring instead of a terminal alkene in enynes dramatically increased the yield of the reaction. It should be noted that

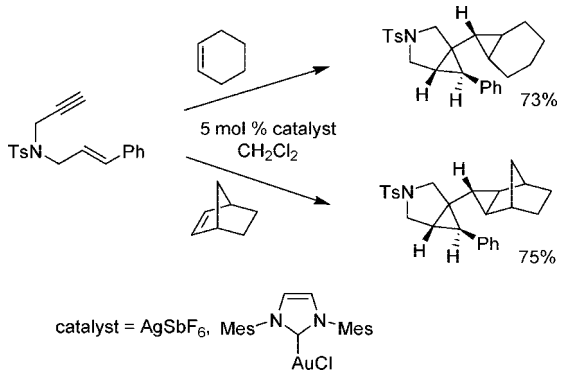
Scheme 144



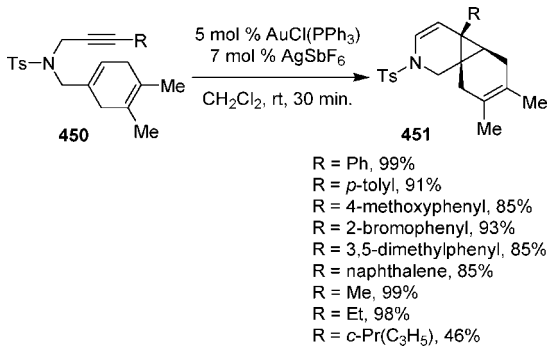
Scheme 145



Scheme 146



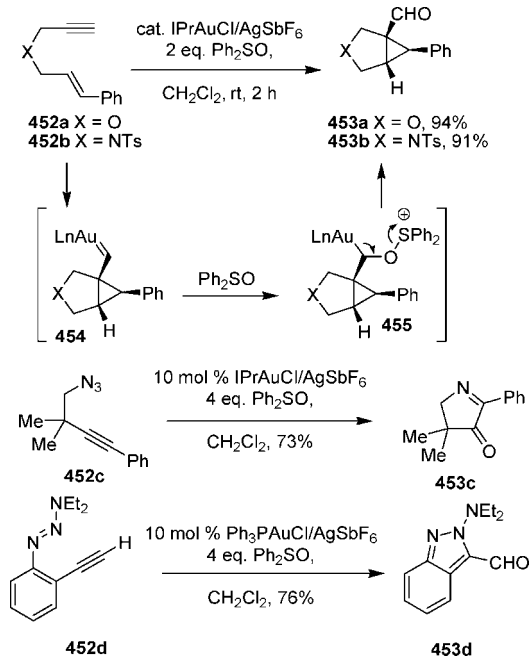
Scheme 147



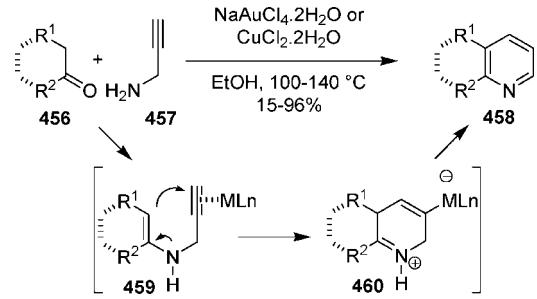
the reaction proceeds at room temperature, in contrast to the reactions catalyzed by Pt(II), which require heating at 80 °C.

Toste and co-workers reported gold(I)-catalyzed oxidative rearrangement reactions of **452a**−**d** using sulfoxides as stoichiometric oxidants (Scheme 148).[249] The heterocycles **453a**−**c** were obtained in good yields. The reactions are postulated to proceed through intermolecular oxygen atom transfer from the sulfoxide to gold(I)−carbenoid intermediates such as **454** and **455**.

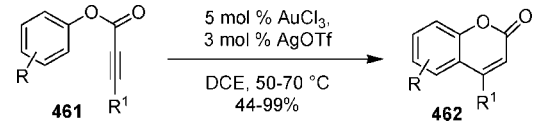
Scheme 148



Scheme 149



Scheme 150

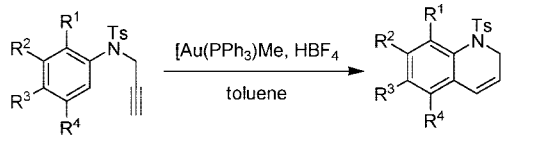


Abbiati et al. reported a general and one-pot synthesis of pyridines **458** from the reaction of acyclic/cyclic carbonyl compounds **456** with propargylamine (Scheme 149).[250] Gold and copper salts are found to be efficient catalysts. The mechanism involves the formation of enyne **459** via metal salt-catalyzed condensation between **456** and propargylamine, followed by imine−enamine isomerization. Cycloisomerization of enyne **459** produces organometallic intermediate **460** which, on protonolysis and subsquent dehydrogenation, gives pyridine derivatives **458**.

5. Intramolecular Friedel−Crafts-Type Reactions

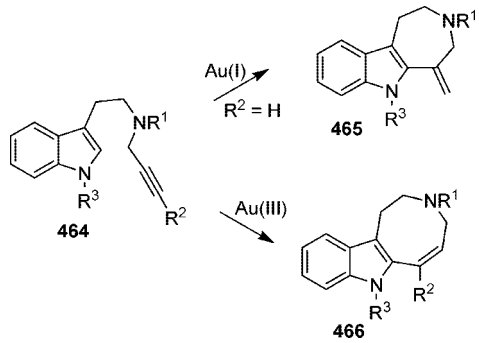
Shi and He described an efficient method for the preparation of coumarins from aryl alkynoates (Scheme 150).[251] The substrates **461**, on treatment with gold catalyst ($AuCl_3$/AgOTf) in dichloroethane at an appropriate temperature, gave the corresponding isocoumarins **462** in excellent to fair yields. The silver salt was proposed to have a role in the generation of more electrophilic gold species from $AuCl_3$. The authors proposed that metalation of arene is the key step,

Scheme 151

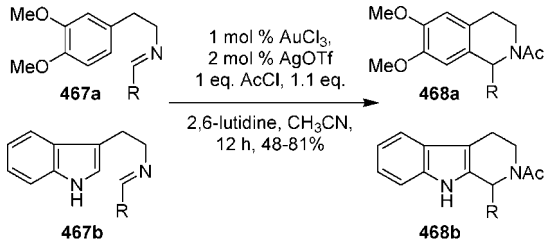


463a $R^1 = R^4 = OMe$, $R^2 = R^3 = H$ **464a** (23 °C, 4h, 71%)
463b $R^1 = R^4 = H$, $R^2 = R^3 = OMe$ **464b** (50 °C, 4h, 89%)
463c $R^1 = H$, $R^2 = R^3 = R^4 = OMe$ **464c** (50 °C, 17h, 92%)

Scheme 152



Scheme 153



R = COOEt, Ph, *p*-NO_2-C_6H_4, *p*-OMe-C_6H_4, 2-(5-methylfuran-2-yl), 2-(6-methylpyridin-2-yl), cinnamyl, ^{n}pent

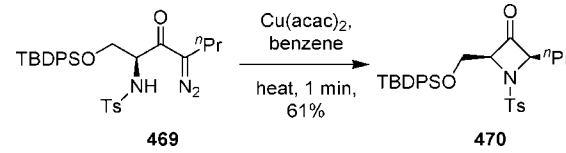
which leads to attacks on the electron-deficient alkynes, giving the products.

The cyclization of *N*-propargyl *N*-tosylanilines **463** is also catalyzed by the cationic complex produced from [Au(PPh_3)Me] and HBF_4 (Scheme 151).[252] This intramolecular reaction gave 1,2-dihydroquinolines **464** and proceeded under milder conditions and with better yields than the cyclization catalyzed by Pt(II).

Echavarren recently reported a novel gold-catalyzed cyclization of the substrates of type **464** (Scheme 152).[253] When gold(I) was used as a catalyst, azepino[4,5-*b*]indole derivatives **465** were obtained, whereas the use of Au(III) catalysts led to indoloazocines **466** by an 8-*endo-dig* process. This type of regiochemical control by the oxidation state of the metal catalyst is noteworthy.

Gold complexes have also been used as a catalyst for the Pictet−Spengler reaction. A variety of tetrahydroisoquinolines **468a** and tetrahydro-β-carbolines **468b** were obtained in good yields from imines **467a** and **467b** under the catalysis of a $AuCl_3$−AgOTf combined catalyst system (Scheme 153).[254] To enhance the reactivity of imines, an acylating agent AcCl was used; the absence of acylating agent resulted in a low yield of the products. It was proposed that the reaction followed an electrophilic pathway involving imine activation by coordinating gold(III) complex.

Scheme 154



6. Reactions of α-Diazocarbonyl Compounds

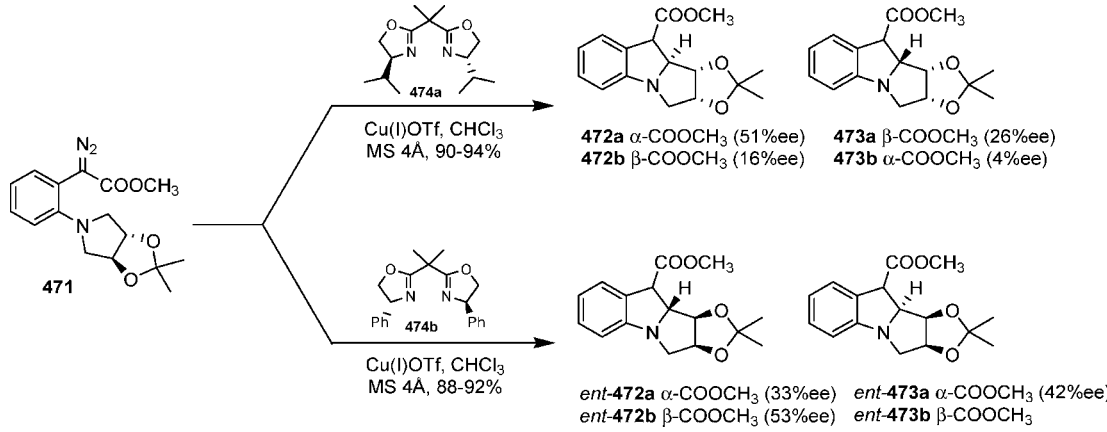
Correia and Burtoloso reported the synthesis of *cis*-substituted azetidines **470** by copper carbenoid insertion of α,α′-dialkyl-α-diazoketones **469** (Scheme 154).[255] The catalytic asymmetric C−H insertion using chiral ligands was reported by Sulikowski (Scheme 155).[256] The catalyst was generated in situ by mixing bis(oxazoline) ligand and copper(I) triflate in chloroform. Addition of a chloroform solution of diazo ester **471** to a mixture of Cu(I)−**474a** afforded **472** and **473** in a 3:1 ratio, with a combined yield of 90−94%. The *anti* isomers **472** were produced as a 1.7:1 mixture, while the corresponding *syn* diastereomers **473** were generated as a 1.3:1 mixture. In a similar fashion, the antipodal set of isomers (*ent*-**472** and *ent*-**473**) were generated from reaction using Cu(I) and **474b** catalyst system. In this instance, a 3:1 ratio of *ent*-**472** and *ent*-**473** was produced as a 1:3 (*ent*-**472a** and *ent*-**472b**) and 10:1 (*ent*-**473a** and *ent*-**473b**) mixture of epimeric esters, respectively.

The generation and rearrangement of cyclic ylides from diazocarbonyl precursors has evoled as an important strategy for the synthesis of heterocycles. Copper-based catalysts are often used because of their relatively low cost, permitting their use in larger quantities, if necessary. West and co-workers reported the cyclization of amino diazoketone **475** to piperidine **476** in the presence of $Cu(acac)_2$ in refluxing toluene (Scheme 156).[257] Optically active morpholin-2-ones **478** could also be synthesized from **477** by a similar process (Scheme 157).[258] They also used this approach for the synthesis of polycyclic ether **480** from the corresponding α-diazoketone **479** in the presence of copper(II) trifluoroacetylacetone in refluxing dichloromethane (Scheme 158).[259]

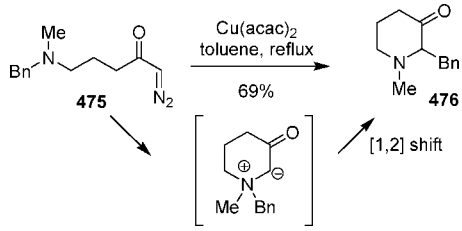
Clark and Hodgson reported enantioselective synthesis of the CE ring system of the alkaloids Manzamine A, E, and F and Ircinal A, using copper carbenoid chemistry as a key step. The key step in the synthesis of these natural products is the treatment of **481** with $Cu(acac)_2$ in benzene at reflux, to afford the fused bicyclic product **482**. The reaction was assumed to proceed via [2,3]-sigmatropic rearrangement of the spiro-fused bicyclic ammonium ylide intermediate **483**, resulting in three-carbon ring expansion of the pyrrolidine (Scheme 159).[260] McMills and co-workers used a similar approach to azacyclooctene and azacyclononene via the intermediacy of a spirocyclic ammonium ylide (Scheme 160). Copper-catalyzed decomposition of **484**, in which an α-diazoester moiety is tethered to the nitrogen atom of 2-vinylpyrrolidine, gave azacyclooctene **485**, along with a minor amount of product **486**.[261] The transition states are shown in Scheme 161.

Chiral copper complexes have also been employed as catalysts for carbenoid generation in order to prepare substituted heterocycles enantioselectively from achiral α-diazo ketones. For example, Clark et al. studied the copper complexes having a wide variety of diimine ligands for the

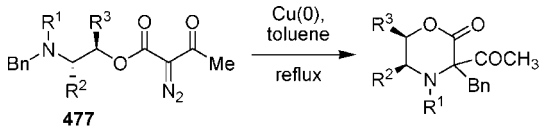
Scheme 155



Scheme 156

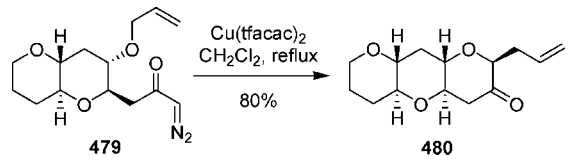


Scheme 157

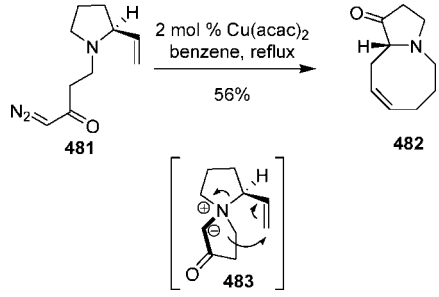


478a $R^1 = R^2 = CH_3$, R^3 = H; 71% (1:1 dr)
478b R^1 = CH3, R^2 = Bn, R^3 = H; 70% (1.5:1 dr)
478c R^1 = CH_3, $R^2 = CH_3$, R^3 = Ph; 70% (3:1 dr)

Scheme 158



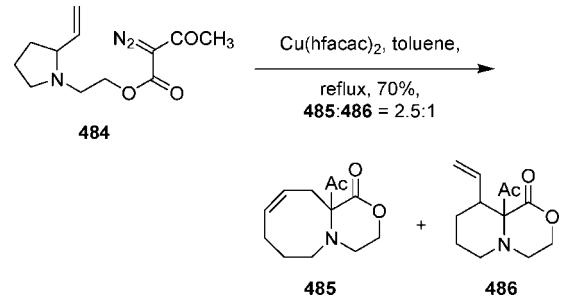
Scheme 159



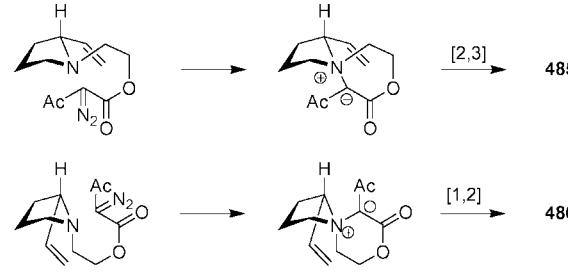
synthesis of cyclic ethers **488** from **487** (Scheme 162).[262] The copper complex obtained by the in situ reaction of ligand **489** with $Cu(MeCN)_4PF_6$ gave good results.

Intramolecular carbenoid reaction of diazoacetates in which an alkynyl function is tethered to the diazo group by a Si−O link was reported Mass and co-workers. The reaction of **490** with CuOTf provided oxa-silaheterocycles **491** in moderate yields (Scheme 163).[263]

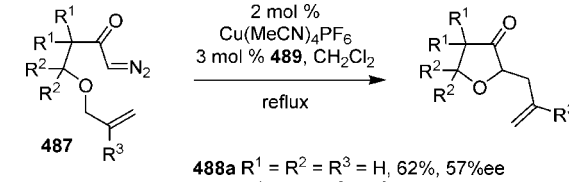
Scheme 160



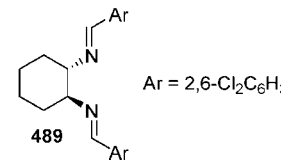
Scheme 161



Scheme 162

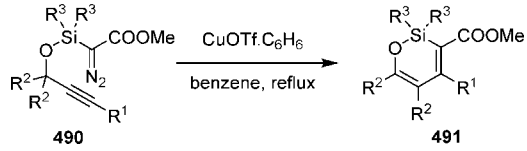


488a $R^1 = R^2 = R^3$ = H, 62%, 57%ee
488b R^1 = Me; $R^2 = R^3$ = H, 57%, 56%ee
488c R^1 = Me; R^2 = H; R^3 = Me, 92%, 42%ee

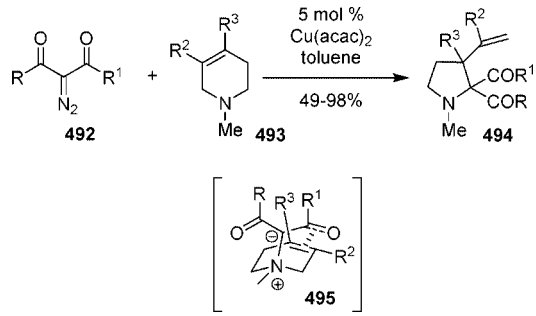


A ring-contracting and highly diastereoselective [2,3]-sigmatropic rearrangement was reported by Sweeney and co-workers (Scheme 164).[264] The reaction between diazoesters **492** and tetrahydropyridines **493** under copper catalysis gave substituted prolines **494** via intermediates **495**. The nature of the α-substituent in the diazo compound exerts a dramatic

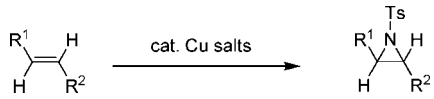
Scheme 163



Scheme 164



Scheme 165



effect upon the yields of the reaction. In general, electron-withdrawing substituents enhance the rate of reaction.

7. Aziridination of Olefins

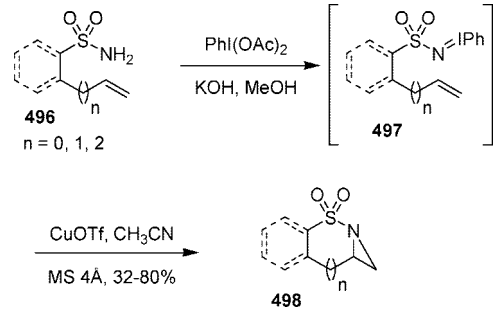
Aziridines are useful substrates in organic chemistry due to their versatility as intermediates for the preparation of a number of nitrogen-containing products. The discovery of hypervalent iodinane reagents for nitrene transfer to alkenes by means of transition metal complexes has led to the development of efficient catalytic processes, including asymmetric versions. Copper-catalyzed aziridination of olefins is one of the best ways to prepare aziridines (Scheme 165). Several reports on their synthesis using copper-catalyzed processes have appeared in the literature,[265] and recent research revealed that these small ring compounds could be prepared in good to excellent enantioselectivities.[266] The use of disilver(I) compound for olefin aziridination has been realized only recently.[267] In general, PhI=N−SO_2R and RSO_2NH_2 are used as nitrogen-transferring agents. However, there are few reports on the identical transformation involving epoxidation of olefins which led to epoxides in the presence of oxygen-transferring agents.[268]

Dodd and co-workers reported the intramolecular aziridination of olefins.[269] Olefinic primary sulfonamides **496** were treated first with iodobenzene diacetate and potassium hydroxide in methanol to give intermediate iminoiodinanes **497**. The copper(I) salt then allows intramolecular nitrene delivery, leading to aziridines **498** (Scheme 166). Fleming et al.[270] and Lebel et al.,[271] in their independent papers, reported copper-catalyzed intramolecular nitrene addition to alkenes. Enantioselective intramolecular copper-catalyzed aziridination of sulfamates is also known.[272] Gold complexes can also be used as catalysts for this purpose.[273]

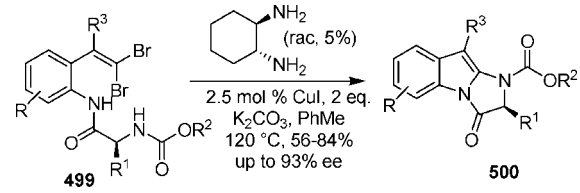
8. N/O-Vinylation/Arylation

The copper-mediated *N*-vinylation/arylation reaction is an important transformation and has been used for the synthesis of a variety of heterocycles.[274] Lautens and co-workers

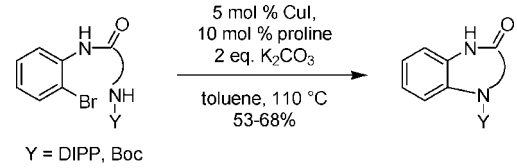
Scheme 166



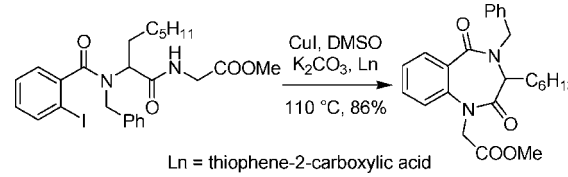
Scheme 167



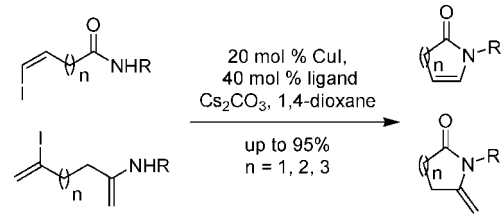
Scheme 168



Scheme 169

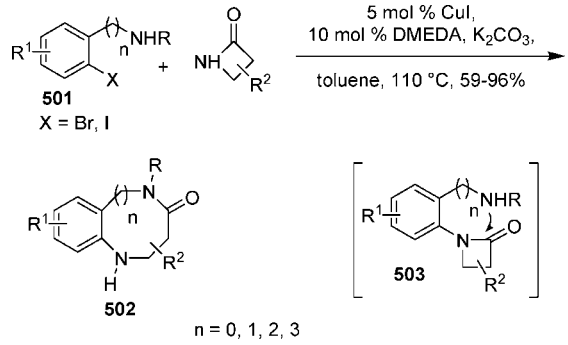


Scheme 170

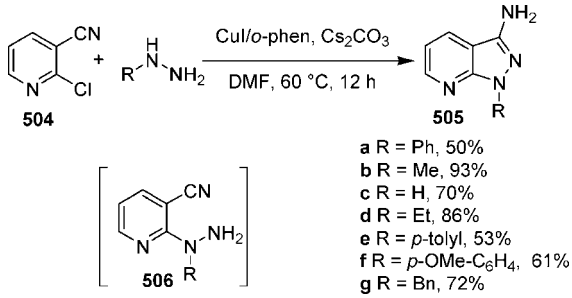


described the application of copper-catalyzed intramolecular amidation for the synthesis of imidazoindolones (Scheme 167).[275] The *gem*-dibromovinyl compounds **499**, on treatment with CuI−diamine catalyst in the presence of K_2CO_3 in refluxing toluene, afforded imidazoindolones **500** in good yields. In most cases, significant amounts of chirality transferred from the starting materials to the products. In another report, Fu and co-workers reported the preparation of medium and large nitrogen heterocycles via copper-catalyzed intramolecular *N*-arylation of phosphoramidates and carbamates (Scheme 168).[276] Using a similar approach, Cuny et al. reported the synthesis of 1,4-benzodiazepine-2,5-diones (Scheme 169).[277] An intramolecular copper-catalyzed vinylation of iodoenamides was reported by Li and Hu (Scheme 170).[278] With CuI as the catalyst and *N*,*N*′-dimethylethylenediamine as the ligand, several five- to seven-membered lactams were obtained in good yields.

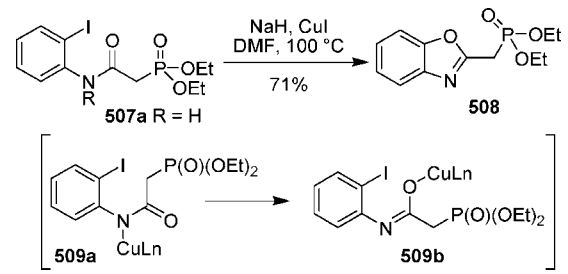
Scheme 171



Scheme 172



Scheme 173

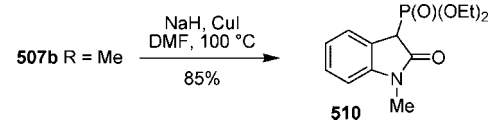


A simple method for the preparation of medium-ring heterocycles **502** has been developed by Buchwald and co-workers (Scheme 171).[279] The process involves a copper-catalyzed coupling of β-lactams with aryl halides **501**, followed by intramolecular attack of a tethered amino group, as shown in intermediate **503**.

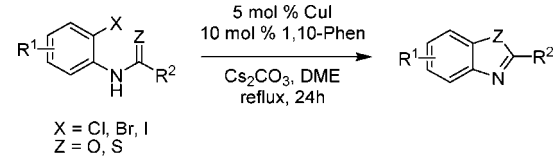
Reactions of 2-chloro-3-cyanopyridine **504** with excess hydrazines in the presence of 5−10 mol % CuI/*o*-phenanthroline and cesium carbonate in DMF afforded 1-substituted-3-aminopyrazolo[3,4-*b*]pyridines **505** in moderate yields (Scheme 172).[280] The reaction proceeded via intermediate **506**.

Copper-mediated intramolecular *O*-arylation and *C*-arylation gave access to benzo-fused heterocycles. Reaction of **507a** with sodium hydride in DMF at 100 °C in the presence of copper(I) iodide gave **508** (Scheme 173).[281] The formation of **508** can be explained by the intramolecular *O*-arylation of the copper metalated amide intermediates **509a**,**b**. However, in case of **507b**, which does not contain a NH proton, the reaction under similar conditions led to oxindole **510** (Scheme 174). A similar approach was used by Batey and co-workers for the synthesis of benzoxazoles and benzothiazoles (Scheme 175).[282] A domino copper-catalyzed C−N and C−O cross-coupling process for the synthesis of oxazoles was reported by Schuh and Glorius.[283] Thasana et al. reported intramolecular copper-mediated and microwave-assisted carboxylic acid arylation for the synthesis of benzopyranones and isolamellarin alkaloids.[284]

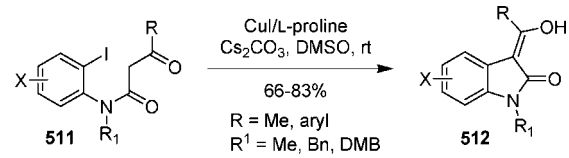
Scheme 174



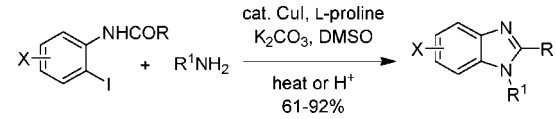
Scheme 175



Scheme 176



Scheme 177

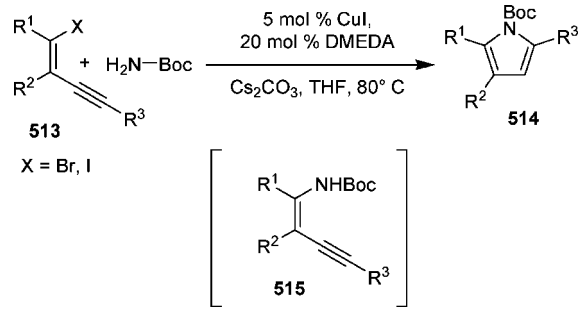


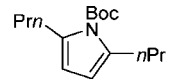
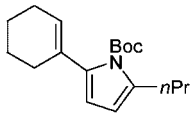
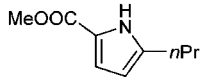
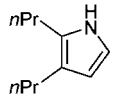
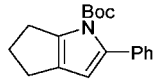
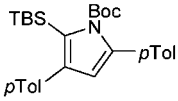
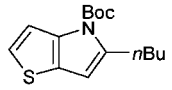
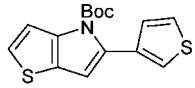
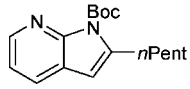
Recently, Ma and Lu reported a new approach to 3-acyloxyindoles **512** via CuI/L-proline-catalyzed intramolecular arylation of β-keto esters **511** (Scheme 176).[285] It should be noted that electronic effects on the aromatic ring have little influence on the efficiency of this reaction, and generally good yields were obtained in all cases. They reported the copper-catalyzed synthesis of benzimidazoles via a tandem aryl amination/condensation sequence (Scheme 177).[286] At the same time, a similar process was reported by Buchwald and co-workers.[287] Ma's research group developed a new route for the synthesis of benzofurans from 1-bromo-2-iodobenzenes with β-keto esters.[288] The synthesis of benzofurans under Cu-TMEDA catalysis using water as solvent was reported.[289] The copper-catalyzed synthesis of 2,3-disubstituted indoles from 2-iodoaniline and various β-keto esters was described by Tanimori et al.[290] Such a copper-catalyzed cross-coupling tool was applied for the synthesis of benzoselenazoles and benzotellurazoles.[291]

A domino process involving copper-catalyzed C−N coupling and intramolecular hydroamidation for the synthesis of pyrroles **514** from haloenynes **513** (via intermediate **515**) was described by Buchwald and co-workers (Table 33).[292] The reaction of a substrate bearing a terminal alkyne did not give the product; however, this transformation can be accomplished by the use of a TMS group, which masks the terminal acetylene and is deprotected in situ. They also reported synthesis of pyrazoles **517** from iodoenynes **576** through the intermediacy of **518** (Table 34). Lu and co-workers reported synthesis of pyrroles via copper-catalyzed coupling of amines with bromoenones.[293]

Li et al. reported the copper-catalyzed intramolecular coupling of aryl bromides with 1,3-dicarbonyls (Table 35).[294] With CuI (10 mol %) as the catalyst, *N*,*N*-dimethylethylenediamine as the ligand, and Cs_2CO_3 as the base, the reactions of α-(2-bromobenzyl)-β-keto esters **519** in THF at refluxing temperature afforded the corresponding substituted 4*H*-1-benzopyrans **520** in high yields via *O*-arylation.

Table 33



entry	product	X	yield (%)[a,b]
1[a]		I	74
2		I	84
3[a]		Br	82
4[b]		I	68
5		I	52
6		I	95
7[a]		Br	83
8[a]		Br	74
9		I	71

[a] Reaction conditions: K_2CO_3 (2.0 equiv) and toluene (0.5 M) at 110 °C. [b] R_3 = TMS.

The copper-catalyzed synthesis of 2-alkylideneazetidines **522** from *N*-tosyl-3-halo-3-butenylamines **521** was also reported by the same research group (Table 36).[295] They extended this methodology for the synthesis of 2-alkylideneoxetanes.[296]

9. Radical Cyclization of Haloalkenes and Haloalkynes

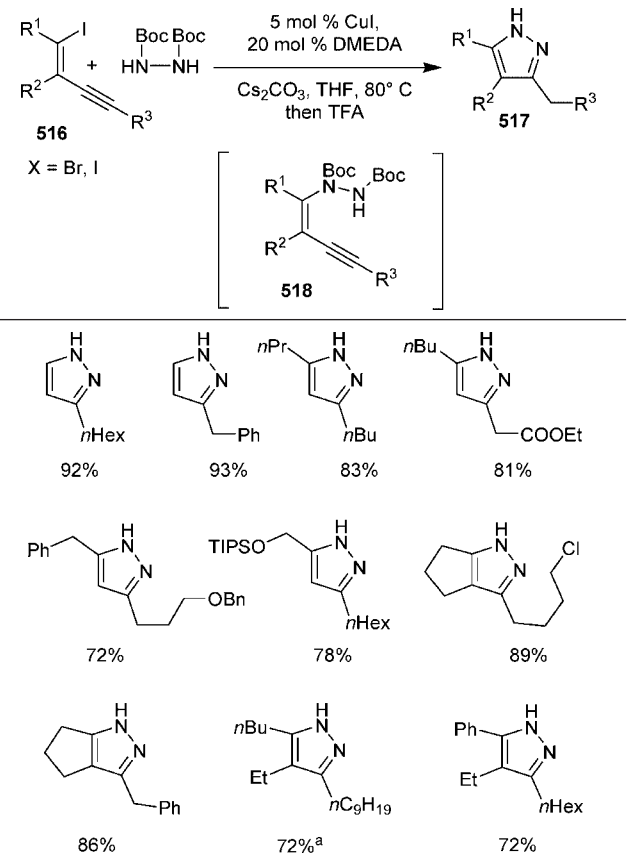
Formation of heterocycles using a radical cyclization reaction has attracted significant attention from synthetic chemists for many years.[297] Tributyltin hydride was often used for this purpose. Owing to the high toxicity of Bu_3SnH, an alternate method which involves the use of copper(I) complexes is becoming popular. These reactions are commonly referred as atom-transfer radical cyclization (ATRC). In these processes, abstraction of a halogen atom by, for example, CuCl is followed by radical cyclization (Scheme 178). The resulting cyclic carbon-centered radical can then abstract a halogen atom from the $CuCl_2$ to form the cyclic organohalide and CuCl, which continues the chain reaction. Numerous reports have appeared on the application of this chemistry for the synthesis of heterocycles. Only a few examples are described herein.

The ATRC reaction represents a powerful tool for the synthesis of halogenated lactams.[298] For example, the cyclization of *N*-allylhalodifluoroacetamides **523** afforded α,α-difluoro-γ-lactams **524** under copper catalysis (Scheme 179).[299] The actual catalyst is CuX(bipy), which is generated in situ by mixing equimolar amounts of CuX and bipyridine.

The copper-catalyzed cyclization of trichloroacetamides tethered with alkenes also gave lactams by the ATRC reaction.[300] The cyclization of trichloroacetamides **525** into the corresponding octahydroindol-2-ones **526** was achieved using a CuCl−bipyridine catalyst system (Scheme 180).[301] The presence of alkoxycarbonyl groups such as Cbz and COOMe was essential for the reaction to proceed. It was reported that not only five-membered rings but also larger rings can be obtained through this strategy in the presence of multidentate amine **527** (Scheme 181).[302]

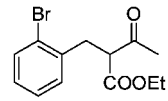
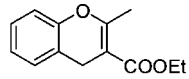
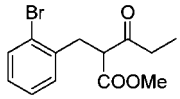
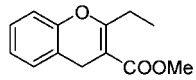
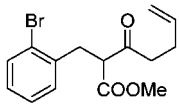
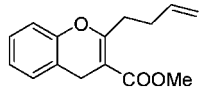
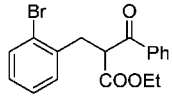
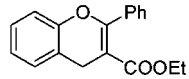
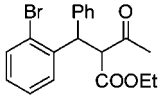
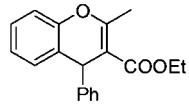
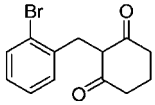
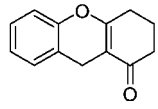
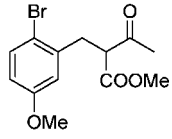
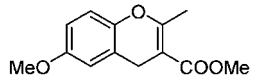
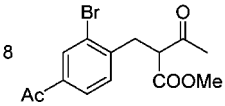
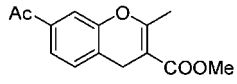
There are very few reports on the application of this strategy for the cyclization of alkynes. This is probably due

Table 34



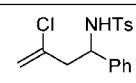
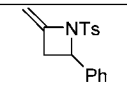
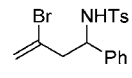
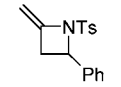
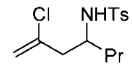
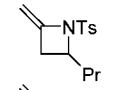
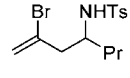
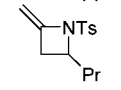
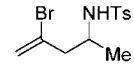
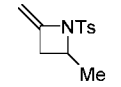
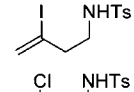
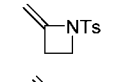
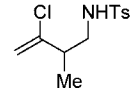
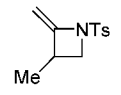
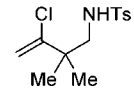
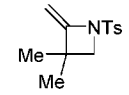
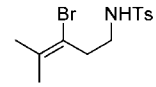
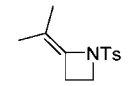
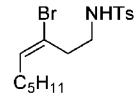
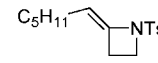
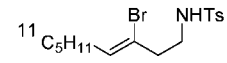
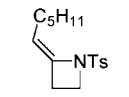
[a] Ligand *trans*-1,2-cyclohexanediamine (20 mol %) was used.

Table 35

entry	substrate (**519**)	time (h)	product (**520**)	yield (%)[a]
1		1		99
2		3		99
3		2		92
4		21		80[b]
5		5		80
6		2		89
7		16		90
8		21		90[b]

[a] Reaction conditions: 10 mol % CuI, 20 mol % DMEDA, Cs_2CO_3, THF, reflux. [b] The reaction was run in 1,4-dioxane at refluxing temperature.

Table 36

entry	substrate (**521**)	CuI (mol %)	temp/time (°C/h)[a,b]	product (**522**)	yield (%)
1		20	100/2		99
2		10	68/1		99
3		20	100/2		99
4		10	68/1		99
5		10	68/1		99
6		10	40/2		94
7		20	100/5		99
8		20	100/3		99
9		20	68/6		99
10		20	68/3		86
11		20	68/12		89

[a] Reaction conditions: substrate, CuI, DMEDA, Cs_2CO_3 solvent, reflux. [b] 100 and 68 °C refer to the refuxing temperatures of 1,4-dioxane and THF, respectively.

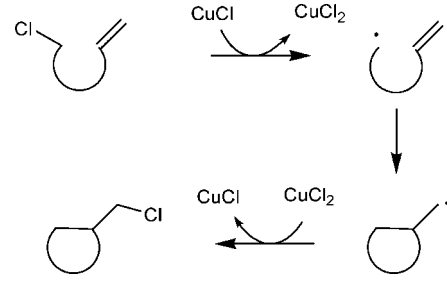
to the fact that terminal alkynes undergo facile oxidative dimerization and intermolecular coupling reaction at the terminal carbon when subjected to copper halide/pyridine complexes. Clark et al. reported that the amine **530**-derived copper(I) halide mediated the ATRC reaction of 1-halo-*N*-propargylacetamides **528**, giving the cyclic lactams **529** in moderate yields (Scheme 182).[303]

10. Miscellaneous Reactions

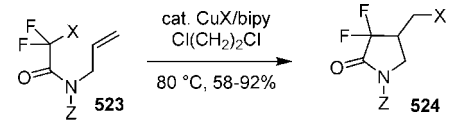
Copper bisphosphine complexes catalyzed the intramolecular reductive aldol reaction of **531**, in which α,β-unsaturated esters and ketones are in the same molecule, affording five- and six-membered β-hydroxylactones **532** with high stereoselectivity (Scheme 183).[304] The asymmetric version of the reaction was reported in the same paper, and ee up to 83% was achieved.

Doring et al. reported a new route to 1,2,4-triazoles **534** by oxidative intramolecular cyclization of heterocyclic hydrazones **523**, mediated by $CuCl_2$ (Scheme 184).[305] By using this simple transformation, 1,2,4-triazolo[4,3-*a*]pyridines, -pyrimidines, -pyradazines, -phthalazines, and -quinoxalines were synthesized. The cyclization of α-aminohydrazone **535** into imidazole **536** was reported by Arcadi and co-workers (Scheme 185).[306]

Scheme 178



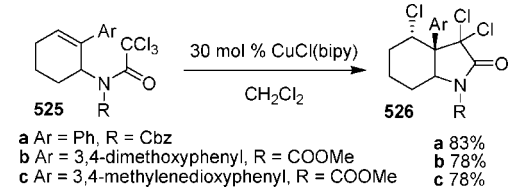
Scheme 179



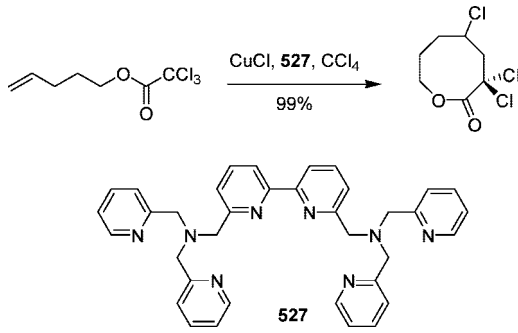
X = Br, I; Z = allyl, benzyl, tosyl

Wang and co-workers developed a new protocol for synthesis of aminobenzimidazoles. *N*-(2-Aminoaryl)thioureas **537** underwent a CuCl-promoted intramolecular cyclization to give the corresponding 2-(*N*-substituted amino)benzimi-

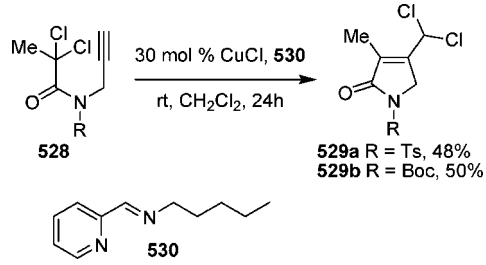
Scheme 180



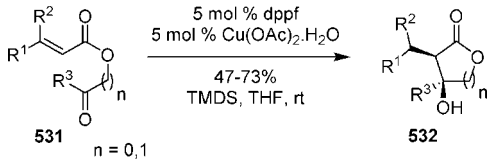
Scheme 181



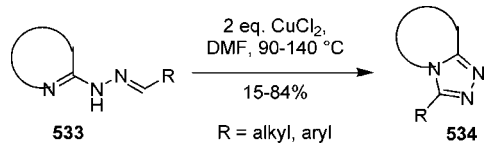
Scheme 182



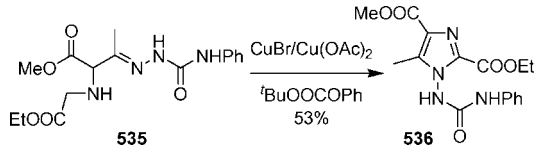
Scheme 183



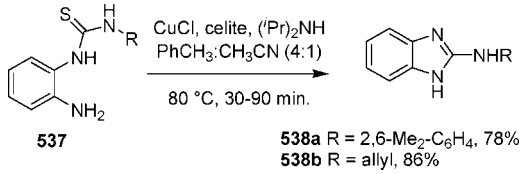
Scheme 184



Scheme 185

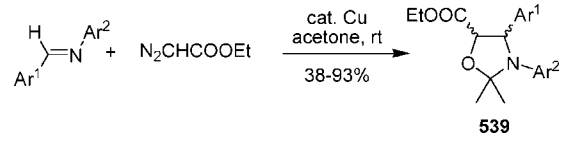


Scheme 186

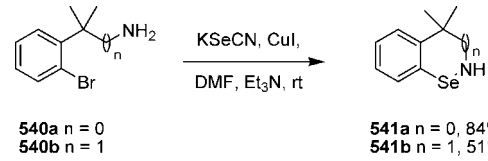


dazoles **538** in good yields (Scheme 186).[307] This reaction is a key step in the synthesis of LFA-1 inhibitors.[308] Terada and co-workers synthesized chiral guanidines for asymmetric transformation using a similar methodology.[309]

Scheme 187



Scheme 188



Lee et al. reported the synthesis of 1,3-oxazolidines **539** by copper-catalyzed addition of acetone and ethyl diazoacetate to imines (Scheme 187).[310] $Cu(OTf)_2$ or copper(I) tetrafluoroborate, generated in situ from $CuI/AgBF_4$, was used as catalyst.

Erdelmeier et al. reported the synthesis of hitherto unknown selenium-containing heterocycles by copper(I)-assisted incorporation of selenium. Benzisoselenazoline **541a** and benzisoselenazine **541b** were synthesized from bromoamines **540a** and **540b** (Scheme 188).[311] An equimolar quantity of CuI and the presence of Et_3N as a base are necessary.

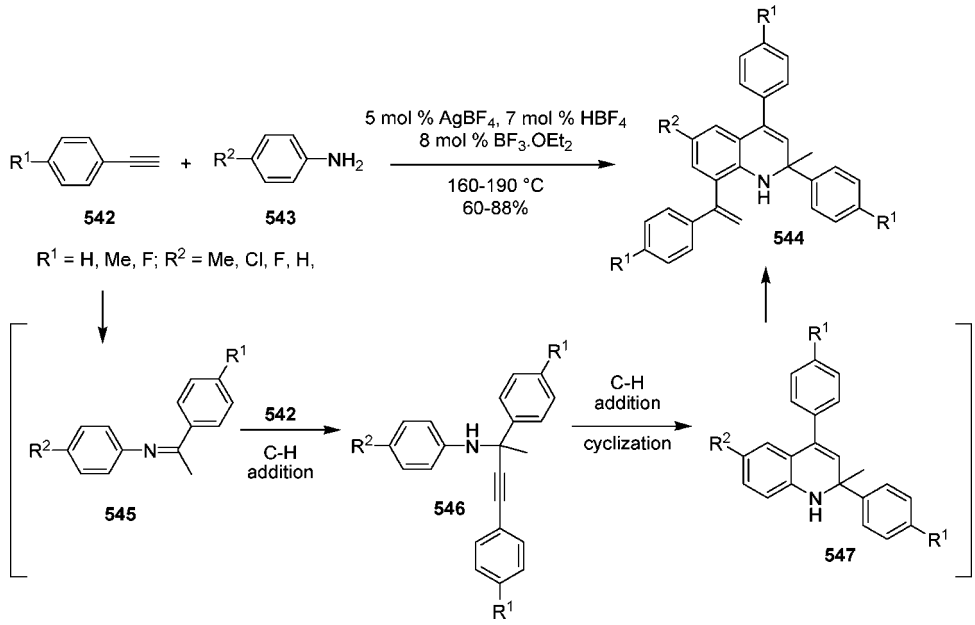
A silver-catalyzed reaction of alkynes **542** and anilines **543** gave 1,2-dihydroquinolines **544** under solvent-free conditions (Scheme 189).[312] An attractive feature of the process is that a series of reactions, such as hydroamination (cf. **545**), alkyne addition (cf. **546**), intramolecular hydroarylation, and hydroarylation of a third molecule of alkynes (cf. **547**), could be accomplished in one pot. Recently, Che and co-workers reported the synthesis of 1,2-dihydroquinolines and quinolines from aromatic amines and terminal alkynes by gold-catalyzed tandem hydroamination−hydroarylation under microwave conditions.[313]

Silver-catalyzed silylene transfer from **549** to alkynes **548** for the formation of substituted silacyclopropenes **550** was described by Woerpel and Clark (Scheme 190).[314] Terminal alkynes which are normally difficult substrates for silylene transfer provided high yields under this condition. The same authors then developed one-pot silacyclopropenation/carbonyl insertions of terminal and internal alkynes. For instance, the reaction of phenylacetylene with benzaldehyde gave oxasilacyclopentene **551** in the presence of bimetallic catalyst 10 mol % Ag_3PO_4 and 15 mol % $CuBr_2$ (Scheme 191). Pioneering work from Woerpel's laboratory revealed that siver-catalyzed silylene transfer to imines for the formation of silaaziridines is possible.[315]

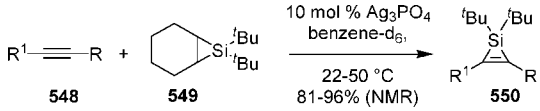
The synthesis of 1,2,4-triazoles **553** via Ag_2CO_3-mediated cyclization of triazenes **552** was described by Paulvannan et al. (Scheme 192).[316] They proposed that the oxidizing property of Ag_2CO_3 proved important for the reaction as it proceeded through azoimine formation, tautomerization, cyclization, and oxidation. This approach is flexible and compatible with a wide range of functional groups.

The reaction of *O*,*S*-acetal **554** in the presence of 2 equiv of AgOTf gave the ring-closing product in 76% yield with a 1.7:1 ratio of **555a** and **555b** (Scheme 193).[317] On the other hand, another diastereomer, **556**, on reaction under the same conditions, gave an 8.5:1 ratio of **555a** and **555b**. The

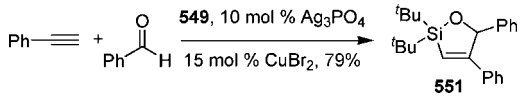
Scheme 189



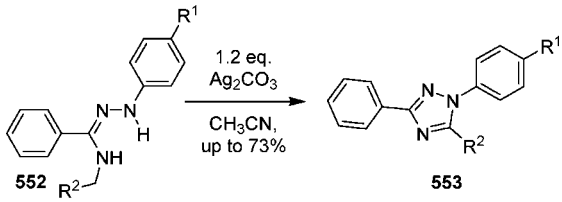
Scheme 190



Scheme 191

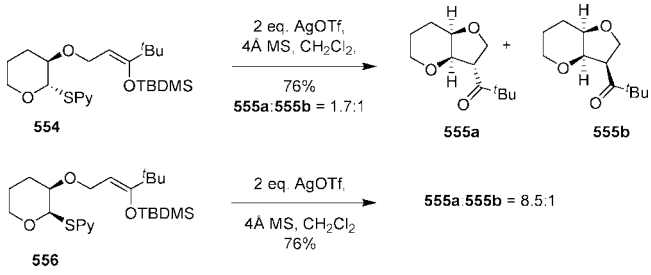


Scheme 192



R1 = H, OMe, NO2; R2 = Ph, Bn, Ph2CH, Me2CH, CH2=CH, 3-Pyr, 1-Mor-CH2, MeO2C(CH2)2

Scheme 193



observed dependence of cyclization stereochemistry on the configuration of the anomeric substituent suggests that **554** and **556** undergo ring closure via different mechanisms.

Six- and seven-membered cyclic ethers were stereoselectively synthesized on the basis of the rearrangement of cyclic ethers with simultaneous ring expansion (Scheme 194).[318] For example, treatment of five- and six-membered cyclic ethers **557a** and **557b** with AgOAc/AcOH−H_2O under reflux

Scheme 194

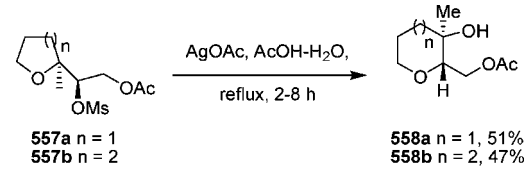
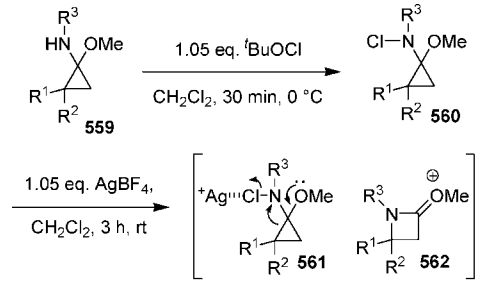


Table 37

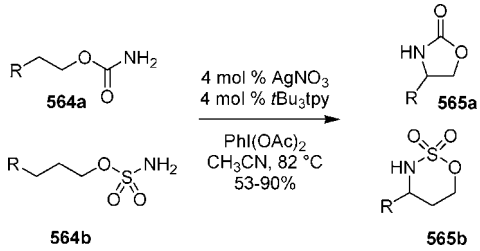


563	R^1	R^2	R^3	yield (%)
a	Me	Me	^{i}Pr	86
b	Me	Me	^{t}Bu	75
c	Me	Et	^{t}Bu	40
d	Et	Et	^{t}Bu	87
e	Me	Bn	^{i}Pr	41
f	Me	Bn	^{t}Bu	95

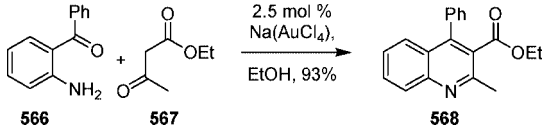
conditions gave six- and seven-membered cyclic ethers **558a** and **558b**, respectively. This type of ring expansion from pyrrolidine to piperidine is also known.[319]

Kimpe and co-workers found that 1-methoxycyclopropylamines underwent ring enlargement in a regiospecific way via *N*-chlorination and subsequent rearrangement in the presence of halophilic silver salt (Table 37).[320] 2,2-Disubstituted 1-methoxycyclopropylamines **559** reacted with *tert*-butyl hypochlorite in dichloromethane at 0 °C to give the corresponding *N*-chlorocyclopropylamines **560** in situ, which underwent ring expansion into β-lactams **563** (cf. **561** and **562**) by reaction with silver tetrafluoroborate in CH_2Cl_2 at ambient temperature in 3 h. All β-lactams **563** were obtained

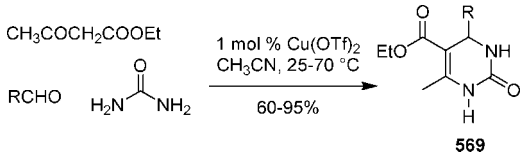
Scheme 195



Scheme 196



Scheme 197



in good to excellent yields, except in the case of **563c** and **563e**. The mechanism of this reaction was later investigated theoretically by means of the B3LYP method and the PCM solvation model.[321] The results indicated that these reactions proceed via facile two-step processes involving a nitrenium intermediate having a short life. A few interesting cascade cyclizations for the synthesis of natural products employing the halophilicity of silver salts are reported in the literature.[322]

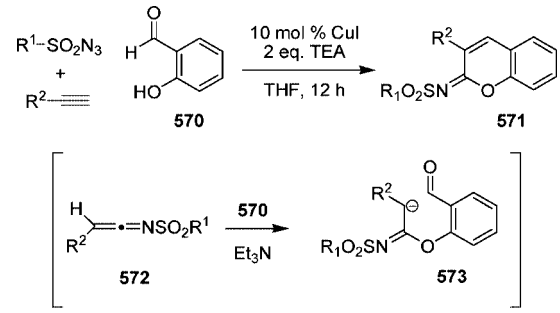
Cui and He reported an efficient amidation reaction of saturated C−H bonds catalyzed by a silver(I) complex. The reactions of acyclic carbamates **564a** and sulfamates **564b** were conducted in acetonitrile, in the presence of $AgNO_3$, $^tBu_3tpy$, and $PhI(OAc)_2$ at 82 °C, to afford cyclic carbamates **565a** and sulfamates **565b** in good yields (Scheme 195).[323] The active catalyst is $[Ag_2(^tBu_3tpy)_2(NO_3)](NO_3)$, which is generated in situ. Different types of ligands were tested, and the products were obtained in high yields only when $^tBu_3tpy$ was used.

Arcadi and co-workers reported a new approach to Friedlander synthesis of quinolines using Au catalyst (Scheme 196).[324] Polysubstituted quinoline **568** was readily prepared by this sequential condensation/annulation reaction from *o*-benzyloxyaniline **566** and *β*-keto ester **567** in the presence of $NaAuCl_4$. The same group also reported the synthesis of pyrrole derivatives via gold-catalyzed amination/annulation reactions of 2-propynyl-1,3-dicarbonyl compounds.[325]

Sudalai et al. reported $Cu(OTf)_2$-catalyzed Biginelli's three-component cyclocondensation between aldehydes, ethyl acetoacetate, and urea. The reaction produces 3,4-dihydropyrimidin-2(1*H*)-ones **569** in good yields (Scheme 197).[326] They reported that the catalyst can be reused with negligible loss of activity.

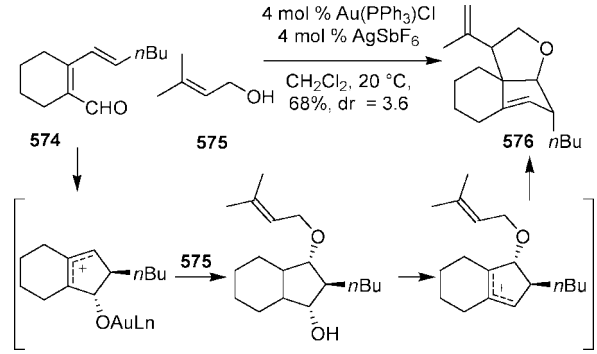
Wang and co-workers have developed a versatile synthesis of substituted iminocoumarin derivatives **571** via a copper-catalyzed multicomponent reaction of sulfonyl azides, terminal alkynes, and salicylaldehyde **570** (Table 38).[327] In the presence of TEA and CuI, sulfonyl azide reacts with alkyne to form the highly reactive ketenimine **572**, which is trapped by **570** to generate the anionic intermediate **573**. An intramolecular Aldol-type reaction of **573** gave iminocoumarins **571**. Later, the synthesis of a novel class of heterocycles via reaction of sulfonyl azides with alkynes and aziridines was described.[328] Fu and co-workers reported the synthesis of medium and large heterocycles by a similar process.[329] The use of this chemistry for the synthesis of substituted azitidine derivatives was reported by Xu and co-workers.[330]

Table 38



entry	R^1	R^2	Yield
1	4-Me-C_6H_4	Ph	77
2	C_6H_5	Ph	80
3	Me	Ph	75
4	4-Cl-C_6H_4	4-Et-C_6H_4	81
5	4-Me-C_6H_4	*n*-Bu	65
6	C_6H_5	$THPOCH_2$	68

Scheme 198



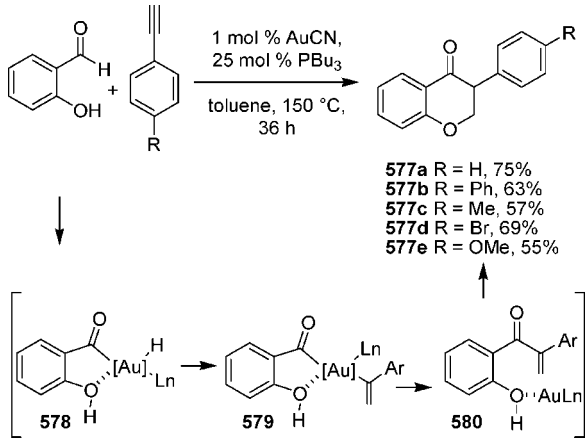
Gold-catalyzed one-pot synthesis of highly functionalized polycyclic frameworks was reported by Liu and co-workers (Scheme 198).[331] For example, the reaction of 2,4-dien-1-al **574** with 3-methyl-2-buten-1-ol **575** in the presence of gold catalyst gave the oxacycle **576** in 68% yield.

Li and Skouta reported gold-catalyzed annulation of salicylaldehydes and aryl acetylenes for the synthesis of isoflavanones **577** (Scheme 199).[332] The mechanism involves the C−H activation of the aldehyde (cf. **578**), followed by hydroauration of alkyne to form intermediate **579**. Subsequent conjugation of the hydroxyl group to the α,*β*-unsaturated ketone in **579** leads to the formation of isoflavanones **577** through intermediate **580**. This approach was extended for the synthesis of azaisoflavanone starting from 2-tosylaminobenzaldehydes and alkynes.[333]

11. Conclusion

This review has shown that the application of coinage metals as catalysts for the synthesis of heterocycles is an active area of research. It is also emphasized that, in addition

Scheme 199



to the conventional copper and silver catalysts, gold complexes are also becoming a powerful tool for the synthesis of heterocycles. The most important aspect of gold catalysis lies in its efficiency, since the reaction can be performed often at lower catalyst loading and at ambient temperature. Moreover, the reaction proceeds under relatively mild conditions and tolerates a wide variety of functional groups. This review has described a salient feature of the development of coinage metal catalysis in heterocyclic synthesis. We think that, with this continued investigation, many more new approaches for heterocyclic synthesis will be discovered.

12. Abbreviations

aq.	aqueous
bipy	2,2′-bipyridine
^{n}Bu	*n*-butyl
^{t}Bu	*tert*-butyl
^{t}Bu$_3$tpy	4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine
Bn	benzyl
cat.	catalytic
DCE	1,2-dichloroethane
DIEA	diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMB	2,4-dimethoxybenzyl
DME	1,2-dimethoxyethane
DMEDA	*N*,*N*′-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
equiv	equivalent
IMes	1,3-dimesitylimidazol-2-ylidene
Me	methyl
min	minute
MPM	(*p*-methoxyphenyl)methyl
MS	molecular sieves
MW	microwave
Np	naphthyl
Ph	phenyl
Phen	phenanthroline
rt	room temperature
TBAC	tetra-*n*-butylammonium chloride
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetate
TFP	tri-2-furylphosphine
THF	tetrahydrofuran
TMDS	1,1,3,3-tetramethylhydrosiloxane
TMSE	2-(trimethylsilyl)ethyl

13. References

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