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METAL-CATALYZED HETEROCYCLIZATION: FORMATION OF FIVE- AND SIX-MEMBERED OXYGEN HETEROCYCLES THROUGH CARBON-OXYGEN BOND FORMING REACTIONS

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Abstract-This review describes the synthesis of five- and six-membered oxygen heterocycles through carbon-oxygen bond formation by metal catalyzed heterocyclization published during 2005 to 2008.

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1. INTRODUCTION

Various heterocyclic backbones appear in different natural products and are very much important for their therapeutic properties. They have wide applications in pharmaceutical field.[1] Heterocyclic compounds are also versatile building blocks in organic synthesis by virtue of their multiple reactivity profiles. Thus from the drug discovery perspective the synthesis of these heterocycles have attracted organic chemists for active research directed towards the development of novel and effective synthetic strategies. Many of these strategies involve the formation of either carbon-carbon or carbon-heteroatom bond from the corresponding acyclic precursors. Most of the classical methods employ comparatively harsh conditions and suffer disadvantages such as the use of expensive catalyst, elevated temperature, longer reaction time, poor yield of the final product, tedious work-up etc. So these methodologies have obvious limitations. These drawbacks and limitations necessitate the search for new methods for the construction of organic molecules from simple starting materials which is an ongoing challenge for the organic chemists. The search may be for the modification or expansion of the existing one, the development of complementary methods, scale up etc. The protocol should be simple, mild, direct method to be compatible with the previous one, for the rapid access to heterocycles and should have further application in future for rapidly constructing other useful heterocycles.

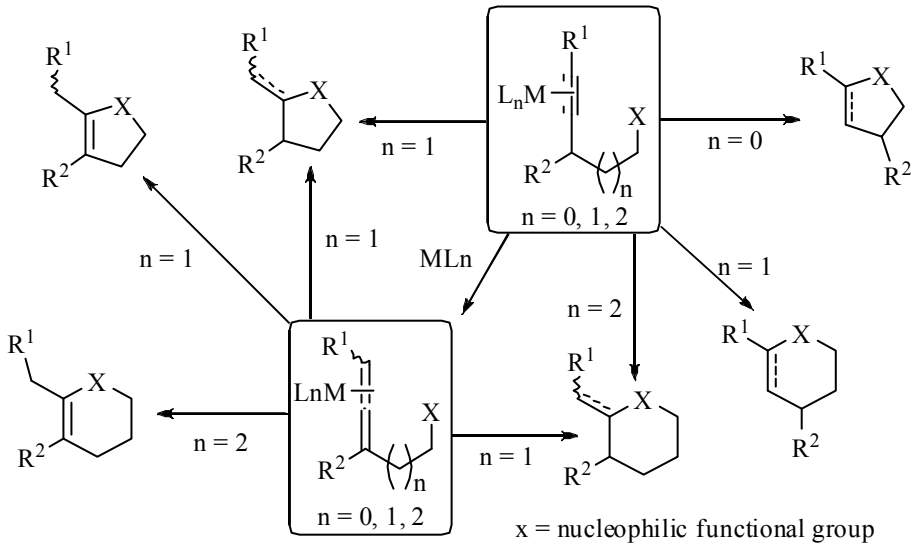
Among several newly developed methodologies, the employment of transition metal catalysis in the synthesis of heterocycles have proven its efficiency and importance to the level where this is now routinely considered in strategy level planning of complex targets. The wide utility of metals in organic synthesis is evident from the huge number of name reactions where the deep influences of this versatile transition metal enable it in the formation of C-C, C-O, C-N and even C-S bond under relatively mild conditions. The catalytic requirement and excellent tolerance of functional groups avoiding the protection-deprotection chemistry has made possible the use of transition metal in the synthesis of small to large ring heterocyclic compounds. Moreover, the development of asymmetric transformation using chiral ligand is a major progress in the metal-catalyzed synthesis of heterocycles.[2] In addition, the metal-catalyzed domino multiple transformation, in recent years, have been the general need both from economical and ecological ground. Recently, several reviews have appeared describing the metal

catalyzed various type of reactions.[3-12] However, there is no such review describing the synthesis of five- and six-membered oxygen heterocycles via the selective formation of C-O bond. In this brief review we provide an updated summary of transition metal-catalyzed approaches for the preparation of heterocycles through the formation C-O bond directly.

2. CATALYST AND GENERAL ASPECT OF THE CATALYSIS

Heteroannulation processes involving the activation of alkenes, alkynes, and allenes bearing a tethered nucleophilic substituent are among the most versatile and efficient synthetic way for constructing a wide array of heterocycles. For this purpose various transition metals[3-12] such as Cu, Pd, Pt, Ru, Rh, Au, W, Mo, Ir etc have been extensively used. Only late transition metal complexes behave as soft Lewis acid. Such a property allows the metal to activate the unsaturated carbon-carbon bonds, to create carbon-carbon and carbon-heteroatom bonds under extremely mild conditions. Choice of catalyst and ligand variation is the most powerful tool in metal catalysis and key features of transition metal catalysts such as activities, selectivity and stability are dictated by the steric and electronic properties of ligands that are co-ordinated to the metal.

Generally, the reactions are initiated via the formation of a π-complex between the metal catalyst and unsaturated bond followed by the nucleophilic attack onto activated unsaturated bonds of alkynes or alkenes or allenes (Scheme 1).



Scheme 1. General representation of metal-mediated heterocyclization

Protodemetalation provides various types of five- and six-membered heterocycles. The nucleophile (X) may be the oxygen atom of alcohols, carbonyls, carboxylic acids, carbonates, carbamates and amides etc. Important heterocycles such as furans, pyrans, benzofurans, benzopyrans, furanones and pyranones have been accessed using this protocol.

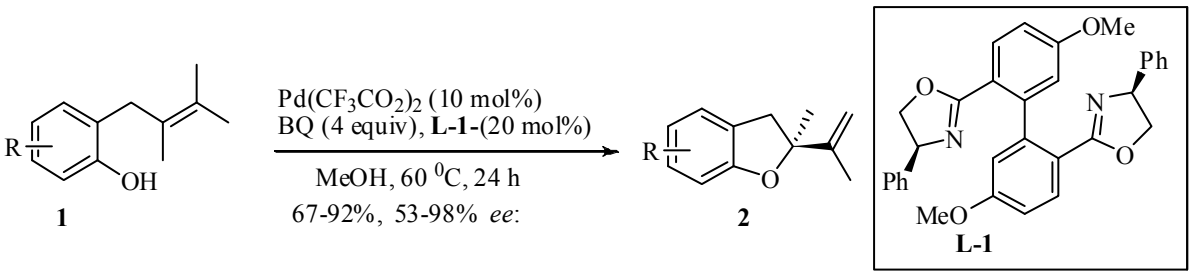
3. SYNTHESIS OF FIVE-MEMBERED OXYGEN HETEROCYCLES

The furan or dihydrofuran ring widely occurs as key structure subunits in numerous natural products,[13] which find a variety of application as pharmaceuticals, flavor and fragrance compounds.[14] Thus, there are continuous demand for increasingly clean and efficient chemical synthesis of furans from both economic and environmental points of view. The development of synthetic tools to connect highly functionalized fragments still remains an exciting challenge for organic chemists.

Transition metal mediated synthesis is increasingly employed for the formation of biologically important molecules in a regio- and chemoselective manner.[15] Transition metal-mediated addition of oxygen nucleophiles across a carbon-carbon double and/or triple bond is one of the most interesting and important reactions to the synthesis of oxygenated heterocycles.[16] The intramolecular version of this reaction falls under the broad category of cycloisomerization. Cycloisomerization reactions are characterized by their complete atom economy and have been recognized as an attractive tool for the preparation of complex molecules.[17]

3. 1 SYNTHESIS FROM ALKENES

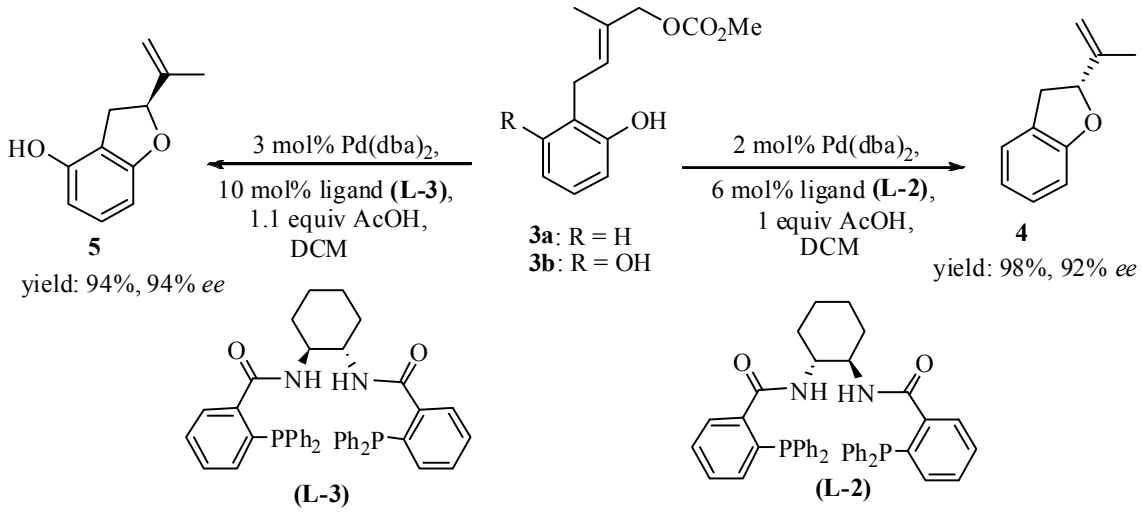
Pd-catalyzed synthesis of a number of five- and six-membered oxygen heterocycles has been reported *via* oxidative cyclization of a variety of nucleophiles such as phenol, alcohol, and carboxylic acid, onto unactivated alkene.[5a,18] The use of chiral bisoxazoline ligands based on binaphthyl[19] and biphenyl backbones[20] in the Pd(II)-catalyzed enantioselective Wacker-type cyclization of *o*-ally phenols have been well documented. In a related study, C_2-asymmetric bisoxazoline ligand bearing an axis-unfixed biphenyl backbone-**(L-1)** was utilized in highly enantioselective Pd(II) catalyzed Wacker-type cyclization of 2-allylphenols **1**. The reactions were catalysed by Pd(II)-(**L-1)** complexes generated *in situ* by mixing $Pd(CF_3COO)_2$ with bisoxazolines-(**L-1**) (Pd/ligand 1:2) in the presence of 4 equiv of *p*-benzoquinone (BQ) in methanol (MeOH) to afford the corresponding chiral 2,3-dihydrobenzofurans **2** with good to excellent enantioselectivity (Scheme 2).[21]



Scheme 2. Pd-Catalyzed enantioselective synthesis of benzofurans

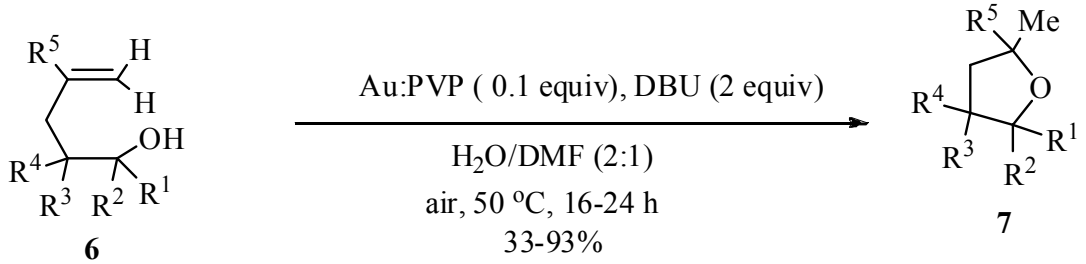
Yamaguchi *et al*. reported[22] that asymmetric cyclization of 2-(3-methylbut-2-enyl)phenol with a chiral ligand and catalytic palladium afforded both the desired product 2-isopropenyl-2,3-dihydrobenzofuran

and the unwanted pyran derivative. The reaction suffered from poor conversion and poor enantioselectivity. Koning *et al.* showed that Trost condition for the synthesis of chiral 2-substituted-2-vinyl chromans using chiral ligand (**L-2**)[23] and catalytic $Pd(dba)_2$ furnished the required volatile 2-isopropenyl-2,3-dihydrobenzofuran **4** from the alcohol **3a**.[24] They also synthesized the opposite enantiomer, **5** by similar treatment of **3b** with $Pd(dba)_2$ in the presence of acetic acid (AcOH) and enantiomeric Trost-ligand, (**L-3**) (Scheme 3).



Scheme 3. Pd-Catalyzed asymmetric synthesis of benzofurans

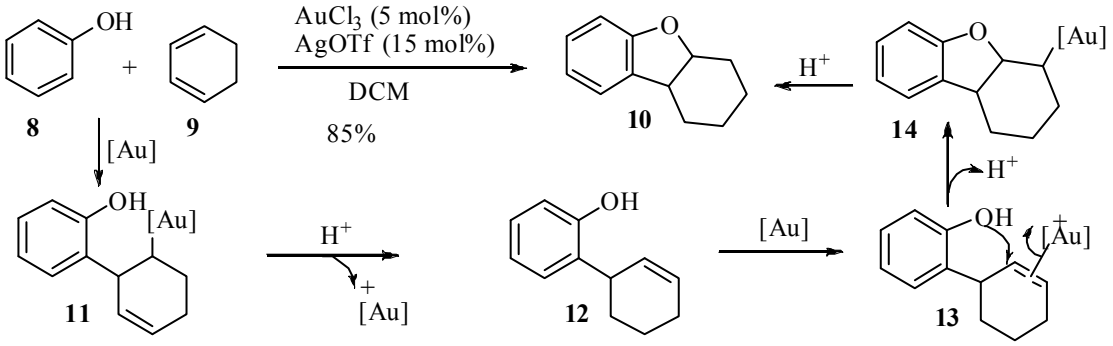
Sakurai *et al*. recently carried out the cycloisomerization of a variety of γ-hydroxy alkenes **6**, under the air atmosphere, using a gold nanocluster, Au/PVP, as the catalyst in H_2O/DMF mixture containing DBU (Scheme 4).[25]



Scheme 4. Au-Catalyzed synthesis of tetrahydronfurans

A highly efficient gold-catalyzed annulation of phenol **8** with diene **9** to construct tricyclic furan derivative **10** was reported by Li and co-workers.[26] The use of an excess of diene in the presence of $AuCl_3$ (5 mol%)/AgOTf (15 mol%) led to a high yield of the desired product. However, the use of $AuCl_3$ or AgOTf alone, or AuCl/AgOTf as the catalyst gave only a trace or no product. On the other hand, acyclic diene did not give the product under similar reaction conditions. Mechanistically, the reaction involves

two gold-catalyzed processes including a Friedel-Crafts reaction to form intermediate **11** and a subsequent hydrophenoxylation of intermediate **12** giving the product **10** (Scheme 5).



Scheme 5. Au-Catalyzed synthesis of tricyclic furans.

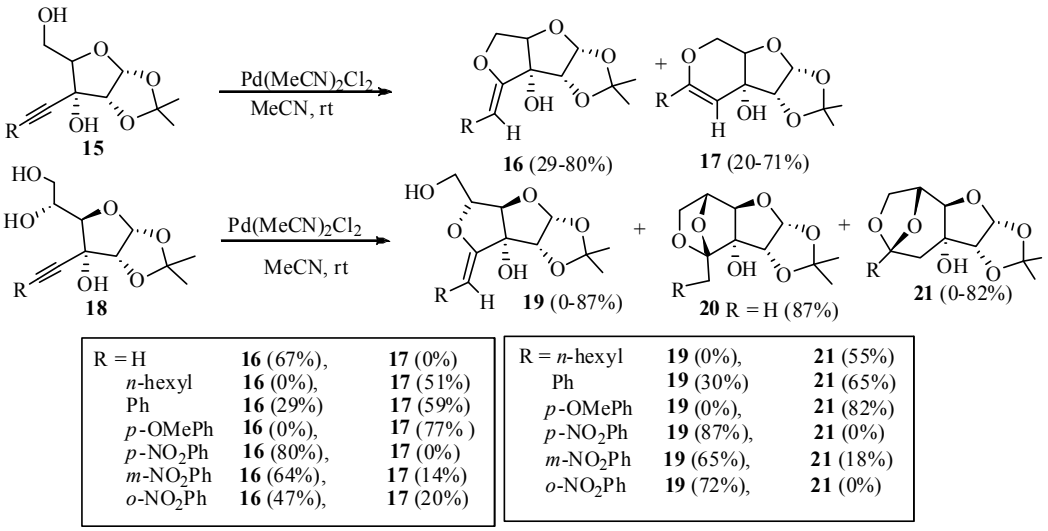
3. 2 SYNTHESIS FROM ALKYNES

Similar to alkenes, the metal complexes catalyzed intramolecular cycloisomerization of precursors containing alkynes and various oxygenated nucleophiles was also exploited for the construction of a range of oxygen containing heterocycles.[27]

3. 2. 1 INTRAMOLECULAR CYCLIZATION OF ALCOHOLIC-, PHENOLIC-, CARBONYL-, ETHER- AND EPOXY-OXYGEN TO ALKYNE

Cycloisomerization of alkynols[11,28] has been utilized as a tool to synthesize oxygen-containing heterocycles encompassing functionalized furan, pyran, benzopyran, and spiroketal skeletons. Ru[29]- and Pd[30]-catalyzed cycloisomerization of a variety of *Z*-enynols have also been reported.

Substituted 2,3-dihydrofurans were synthesized by the palladium-catalyzed reaction of propargylic carbonate containing a homopropargylic hydroxyl group with different phenols in moderate to excellent yields.[30] The reaction was best carried out using $Pd_2(dba)_3.CHCl_3$-dppf catalytic system in dioxane. The key issue is the mode of cyclization i.e., *exo*-dig versus *endo*-dig.[31] Ramana *et al*. very recently reported[32] the electronic control over the 5-*exo*-dig versus 6-*endo*-dig modes of Pd-catalyzed cycloisomerization of 3-C-alkynylfuranosyl derivatives using a set of two different alkynol substrates **15** and **18** (Scheme 6). It is interesting to note that electron-donating group attached to the aromatic ring favored 6-*endo*-dig while electron attracting group favored 5-*exo*-dig modes of cyclization.



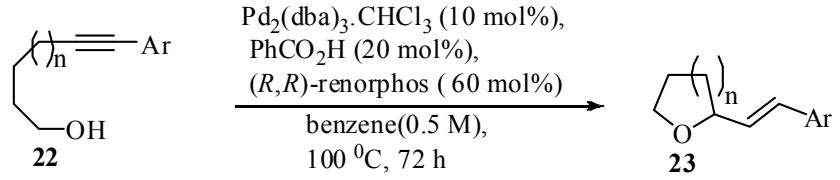
R = H	**16** (67%),	**17** (0%)
n-hexyl	**16** (0%),	**17** (51%)
Ph	**16** (29%)	**17** (59%)
p-OMePh	**16** (0%),	**17** (77%)
p-NO_2Ph	**16** (80%),	**17** (0%)
m-NO_2Ph	**16** (64%),	**17** (14%)
o-NO_2Ph	**16** (47%),	**17** (20%)

R = *n*-hexyl	**19** (0%),	**21** (55%)
Ph	**19** (30%)	**21** (65%)
p-OMePh	**19** (0%),	**21** (82%)
p-NO_2Ph	**19** (87%),	**21** (0%)
m-NO_2Ph	**19** (65%),	**21** (18%)
o-NO_2Ph	**19** (72%),	**21** (0%)

Scheme 6. Pd-Catalyzed 5-*exo vs* 6-*endo*-dig cyclization

The intramolecular asymmetric hydroxylation of alkynols for the synthesis of five- and six-membered cyclic ethers was examined by Yamamoto *et al*.[33] Better result was observed in the presence of $Pd_2(dba)_3.CHCl_3$ (10 mol%) $PhCO_2H$ (20 mol%) and (*R,R*)-renorphos (60 mol%) in benzene and a variety of five- and six-membered cyclic ethers were obtained with moderate to good enantioselectivities (Scheme 7). The reaction is also successful with benzo substitutent at 2,3-position of the alcohol **22**.

The tandem cycloisomerization-hydroalkoxylation of various homopropargylic alcohols **24** in the presence of the dual catalyst system $Ph_3PAuCl/AgBF_4$ and a Brønsted acid *p*-TsOH in alcohol at room temperature gave tetrahydrofuranyl ethers **25** (Scheme 8).[34] The hydroalkoxylation step occurs with various primary and secondary alcohols. Both gold(I) and gold(III) precatalysts were found active for the



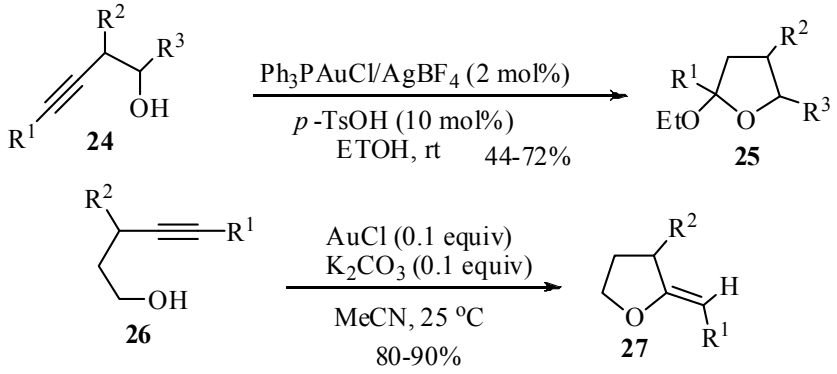
Ar : C_6H_5, C_6H_4-*p*-OMe, C_6H_4-*p*-CF_3

n = 1; Yield : 48-60%; *ee*: 40-82%
n = 2; Yield : 61-67%; *ee*: 74-78%

Scheme 7. Pd-Catalyzed hydroxylation of propargyl alcohols

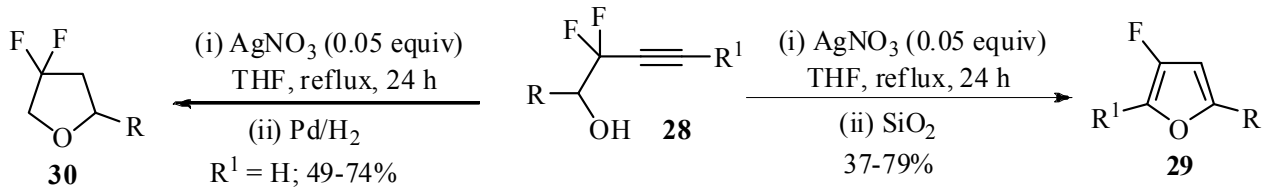
cyclization and afforded the cyclic acetal. However, Ph_3PAuCl alone was inactive towards the cyclization. But, gave the desired product rapidly along with the silver salts as additive, may be due to the formation of cationic gold species. Other gold catalyst such as AuCl, $Au(OH)_3$, $Au(OAc)_3$, $AuCl_3$, $HAuCl_4$ were also found to be active for the cyclization but gave lower yields of the products. Subsequently, Pale *et al*. synthesized[35] functionalized tetrahedrofurans and pyrans **27**, regio- and stereoselectively, *via* oxycyclization of primary 4(or 5)-yn-1-ols **26** catalyzed by a 1:1 mixture of AuCl and K_2CO_3 (Scheme 8).

They proposed that stereoselectivity of the cycloisomerization is due to the *trans*-addition of the alcohol to the Au-coordinated C≡C bond.



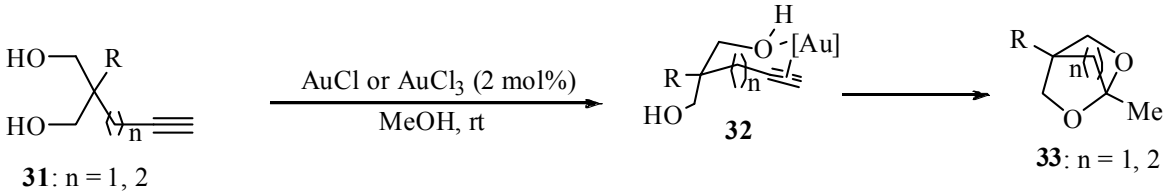
Scheme 8. Au-Catalyzed hydroxylation of propargylalcohols to furan derivatives

Recently, Hammond *et al*. reported the Ag-catalyzed direct activation of electron deficient triple bonds by using the combined electron withdrawing effects of the fluorine atoms to modulate the electronic density of the triple bond. Substituted 3,3-difluro-4,5-dihydrofurans (unstable) was synthesized in excellent yields from *gem*-difluorohomopropargyl alcohols **28** by activation of the triple bond using $AgNO_3$[36] (10 mol%) as Lewis acid, which on treatment with SiO_2 or Pd/H_2 yielded the corresponding 3-fluorinated furans **29** and 3,3-difluorotetrahydrofurans **30**, respectively (Scheme 9). However, the cyclization of *gem*-difluorohomopropargyl alcohols **28** mediated by catalytic amounts of $AuBr_3$ or CuI afforded 3-fluoro-furans **29** directly in poor yield.[37]



Scheme 9. Ag-Catalyzed cycloisomerization of homopropargyl alcohols to furans

Genet and co-workers described[38] the cycloisomerization of various homopropargylic diols, catalyzed by AuCl or $AuCl_3$ leading to the strained dioxabicyclo[2.2.1], -[2.2.2], or -[3.2.1] ketals. The cyclization was attempted with bis-homopropargylic diols **31** in the presence of 2 mol% of AuCl or $AuCl_3$ in MeOH at room temperature to afford the corresponding bicyclic ketals **33** regioselectively (Scheme 10). In these reactions the styrene-like olefin in the other side chain, which is equidistant from the hydroxyl groups, does not compete with the alkyne. The reaction may be initiated by the formation of the π-alkynyl complex **32**, followed by two intramolecular additions of alcohols leading to the bicyclic ketals **33**.



31: n = 1, 2

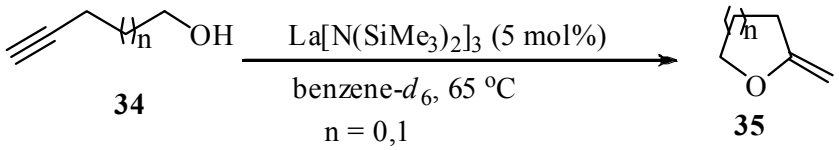
32

33: n = 1, 2

n = 1, AuCl: R = Bn (99%), Ph (99%), *n*-Bu (80%)
n = 1, $AuCl_3$: R = Bn (99%), Ph (99%), allyl (74%), cinnamyl (82%)
n = 2, AuCl: R = allyl (91%), cinnamyl (82%)

Scheme 10. Au-Catalyzed synthesis of bicyclic ketals

The addition of AgOTf to the Au catalyst in 1,2-dichloroethane, led to the participitation of the tethered C=C bond and traces of water to afford a triol.[39] Similarly, Liu *et al*. have carried[40] out the cyclization of 4-nonyne-1,9-diol and its monoprotected form by the Au-catalyzed cyclization conditions. Mixture of [5,5]- and [4,6]-spiroketal resulting from the 6-*exo*-dig and 7-*endo*-dig cyclizations, respectively, were obtained. The yield of the products and the ratio of the two isomers depend upon the nature of the catalyst. Intramolecular hydroxylation/cyclization of alkynyl and allenyl alcohols mediated by homogeneous lanthanide catalyst to give cyclic ethers **35** was reported[41] (Scheme 11). It was observed that homoleptic lanthanide amides, $La[N(SiMe_3)_2]_3$ (5 mol%) is an effective precatalyst for the hydroxylation/cyclization of alkynyl and allenyl alcohols than the other lanthanide amide complexes, Ln = Nd, Sm, Y, and Lu.



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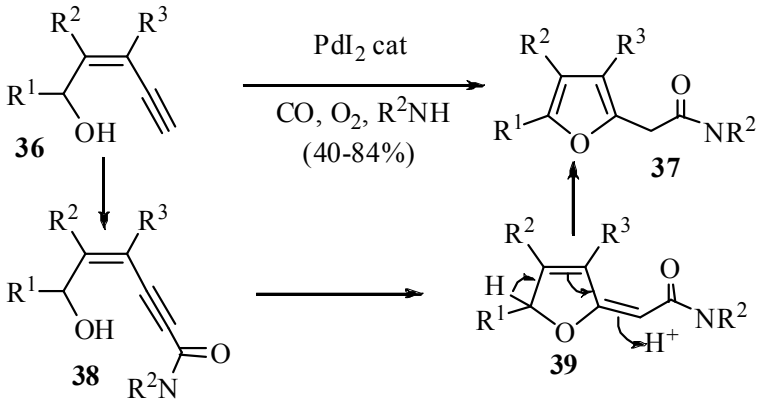
Scheme 11. La-Catalyzed hydroxylation of propargyl alcohols to furans

PdI_2-catalyzed oxidative aminocarbonylation of the triple bond of (*Z*)-2-en-4-yn-1-ols **36** may initially give the corresponding 2-ynamide intermediates **38**, which then undergo intramolecular conjugate addition to give 2-(5*H*-furan-ylidene)acetamide derivatives **39**.[42] The intermediates **39** may finally undergo aromatization to afford the furanacetamide derivatives **37** (Scheme 12).



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38

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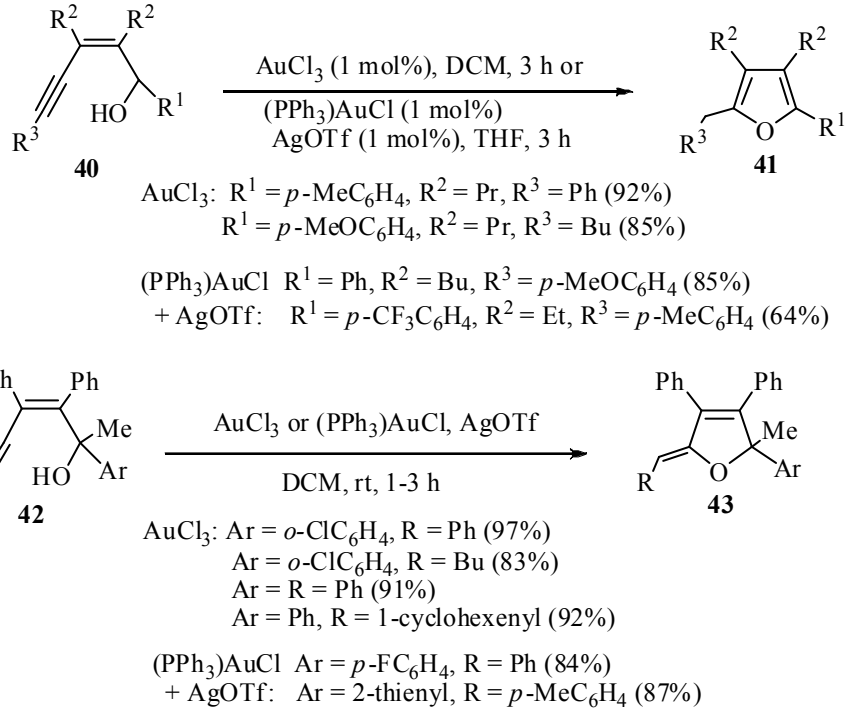
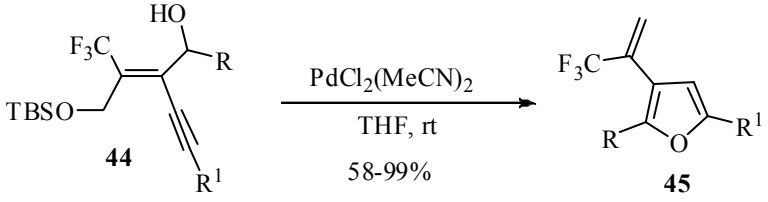
Scheme 12. Pd-Catalyzed oxidative aminocarbonylation of the triple bond to furans

Hashmi *et al*. reported[43] that gold-catalyst is more effective in the cyclization of 2-methylpent-2-en-4-yn-1-ol to furans. Liu *et al*. synthesized[44a] a variety of highly substituted furans and 5-ylidene-2,5-dihydrofurans from (*Z*)-enynols containing a secondary and tertiary alcoholic group, respectively, based on gold-catalyzed cyclization. Treatment of (*Z*)-enynols **40** having a secondary alcoholic group with 1 mol% of $AuCl_3$ in DCM or with cationic gold(I) complex, $(PPh_3)AuCl/AgOTf$ in THF for 3 h, afforded cycloisomerized products furans **41** in high yields (Scheme 13). However, when the same cyclization of the tertiary alcohols **42** was carried out at room temperature, stereoisomerically pure compounds (*Z*)-5-ylidene-2,5-dihydrofurans **43** were obtained (Scheme 13).[44b]



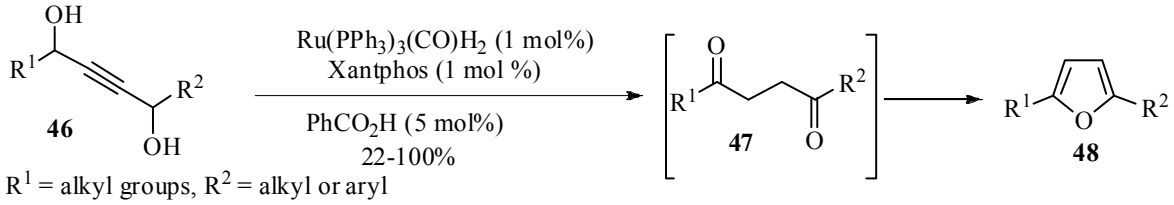
Scheme 13. Au-Catalyzed cycloisomerization of *sec*- and *tert*-alcohols to tetrasubstituted furans

The 3,3,3-trifluoroprop-1-en-2-yl substituted furans **45** were efficiently synthesized by $PdCl_2(CH_3CN)_2$ catalyzed cyclization-isomerization of 1,1,1-trifluoro-2-[*tert*-butyldimethylsilyloxy)methyl]-3-alkynylbut-2-en-1-ols **44** (Scheme 14).[45] The catalysts like $Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$ and $PdCl_2(PPh_3)_2$ were found to be inactive under the reaction conditions. The furan ring is assumed to form *via* a 5-*endo*-*dig* ring closure of the hydroxyl group to activated alkyne.



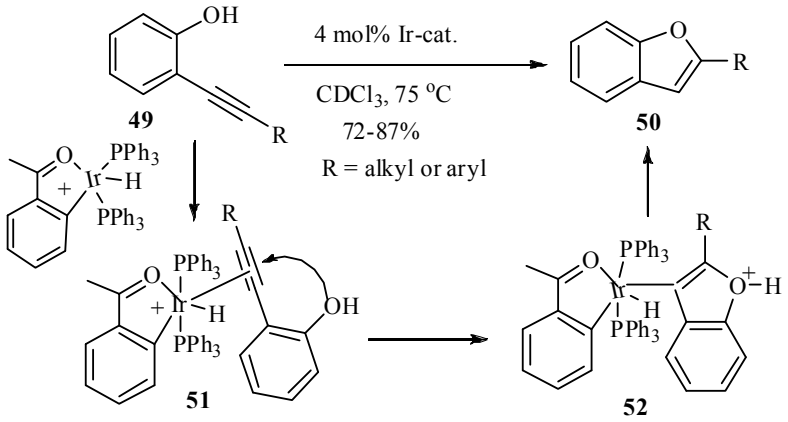
Scheme 14. Pd-Catalyzed cycloisomerization of propargyl alcohols

Different approachs, such as palladium-catalyzed isomerization of 1,4-alkyne diols to respective 1,4-dicarbonyl compounds was reported by Lu *et al.* In the presence of an acid resin, in situ ring closure of the diketones gave the corresponding furan derivatives.[46] Williams *et al.* synthesized[47] a range of 2,5-disubstituted furans **48** from 1,4-alkynediols **46** based on ruthenium catalyzed isomerization to diketones **47**, followed by in situ conversion into the corresponding furans **48** by acid-catalyzed dehydration (Scheme 15). Alkyl/alkyl disubstituted alkynediols and aryl/alkyl disubstituted alkyne diols were converted into the required furan derivatives along with a small amount of unreacted diketones **47**.



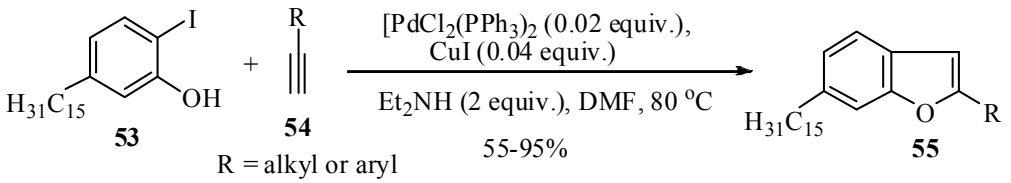
Scheme 15. Ru-Catalyzed isomerization of alkynediols to furans

o-Alkynylphenols **49** underwent regioselective 5-*endo* cyclization with 4 mol% of Ir(III)-catalyst to give the corresponding benzofurans **50**.[48] The mechanism involves electrophilic activation of the alkyne towards the nucleophilic attack by binding to the Ir(III) center, followed by direct selective protonolysis of the Ir-C bond to give the desired product (Scheme 16).



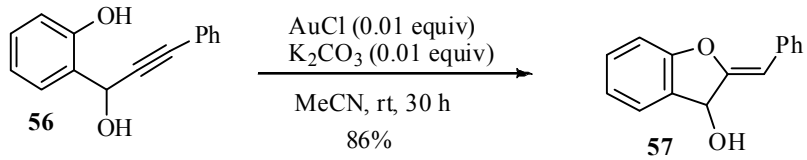
Scheme 16. Ir-Catalyzed cyclization of alkynylphenols to benzofurans

Similarly, Li *et al.*[49] and Liao *et al.*[50] independantly carried out the palladium-catalyzed oxycyclization of 2-alkylphenols to 2-substituted benzo(*b*)furans and benzo(*b*)furans-3-carboxylic acids, respectively. Liang *et al.* reported[51] a novel route to disubstituted benzodifurans in moderate to good yields by $Pd(OAc)_2$-catalyzed double cyclization of the dihydroxy-*bis*(alkyl-substituted 1-alkynyl)benzenes. Cacchi *et al.* extended the alkyne cyclization chemistry to the preparation of a variety of lipophilic 2-substituted and 2,3-disubstitutedbenzo[*b*]furans **55** from cardanol **53** by palladium-catalyzed Sonogashira cross coupling/cyclization (Scheme 17).[52]



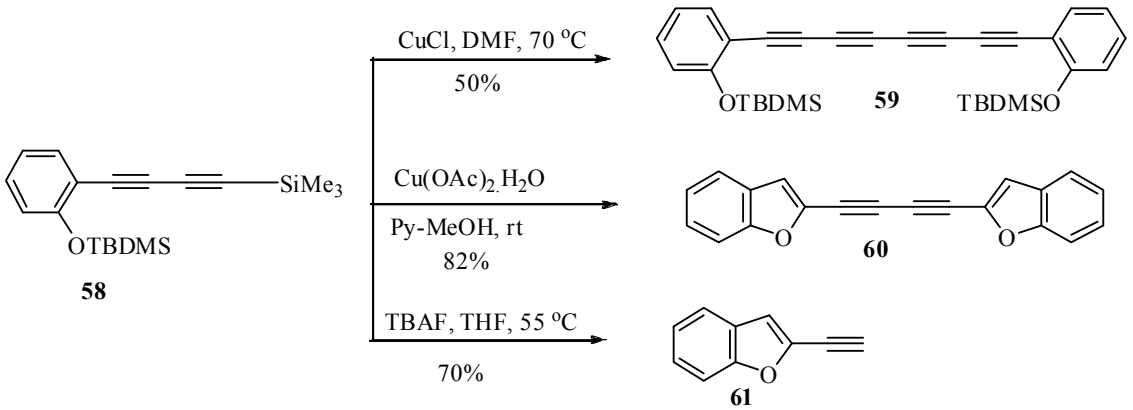
Scheme 17. Pd-Catalyzed synthesis of substituted benzofurans

Venkataraman showed[53] that 2-iodophenols coupled with phenylacetylenes underwent cyclization to give 2-phenylbenzo[*b*]furans in excellent yields in the presence of $[Cu(phen)(PPh_3)_2]NO_3$ as catalyst, Cs_2CO_3 as base in refluxing toluene. Subsequently, Zhang *et al*. reported[54] that $NaAuCl_4$ catalyzed cyclization of (*E*)-3-benzylidene-1,1,1-trifluoro-5-phenylpent-4-yn-2-ol gave an inseparable mixture of products. However, Pale *et al*. reported[55] the synthesis of 3-hydroxybenzofuran **57** by the AuCl catalyzed cyclization of 2-(1-hydroxy-3-phenylprop-2-ynyl) phenol **56** (Scheme 18).



Scheme 18. Au-Catalyzed synthesis of 3-hydroxybenzofuran

A novel methodology for the synthesis of benzofurans and indole derivatives starting from *ortho*-substituted aryl diynes has been reported.[56] The product of the reaction depends upon the Cu-catalyst used in the reaction. For example, treatment of compound **58** by employing copper salt, $Cu(OAc)_2.H_2O$ in pyridine/MeOH at room temperature gave bis-(1*H*)-benzofuran **60**, with the two benzofuran rings linked

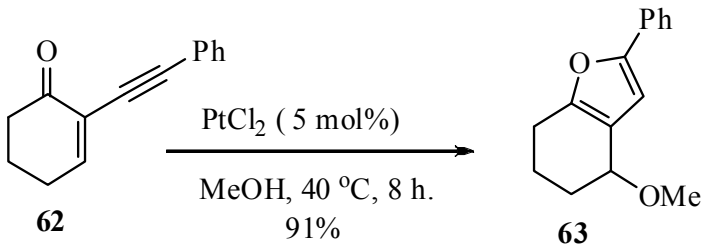


Scheme 19. Cu-Catalyzed cyclization to bis-(1*H*)-benzofuran

to the positions 2,2'-by two triple bonds. However, when the reaction was performed with CuCl in DMF at 70 °C led to the tetrayne derivative **59** and with TBAF in THF at 50 °C, gave 2-ethylnylbenzofuran **61** (Scheme 19). However, a different selectivity of the copper salts was observed in a similar reaction for

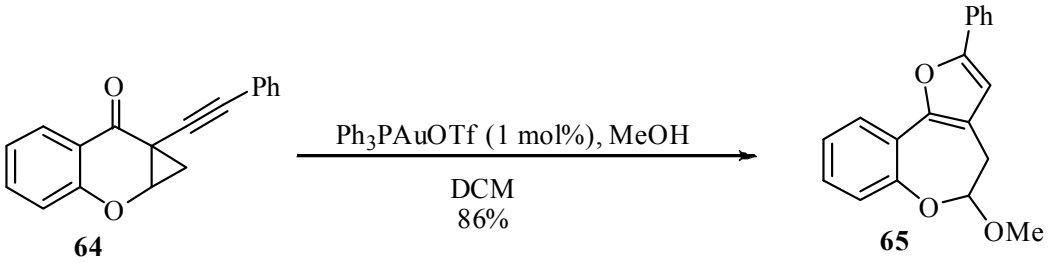
the synthesis of indole derivatives. Activation of alkynes by coordination of electrophilic transition-metal complexes has led to the development of a variety of catalytic cyclizations involving a carbon-carbon or carbon-heteroatom bond formation.[57] Recently, Echevarren and co-workers[58] investigated the late-transition metal-based Lewis acid catalyzed reaction for hydroxy- or alkoxy cyclization of enynes. Larock *et al*.[59] used $AuCl_3$ and Yamamoto *et al.*[60] used CuBr as catalyst, respectively to the synthesis of substituted furans by sequential nucleophilic domino attacks onto a metal-complexed alkyne. Liang *et al*. used $Bu_4N[AuCl_4]$ as catalyst for the same cyclization in ionic liquid, namely $[bmim]BF_4$.[61]

In a related reactions, Oh *et al*.[62] observed that Pt complexes were also highly effective catalysts for the hydroxy- or alkoxy cyclization of 2-(1-alkynyl)-2-alkene-1-ones. The Pt(0) complexes like $Pt(PPh_3)_4$ and $Pt(C_2H_4)(PPh_3)_2$ were ineffective for the transformation. However, treatment of compound **62** with 5 mol% of Pt(II) catalyst in MeOH afforded the corresponding methoxy-incorporated furan derivative **63** in high yield (Scheme 20).



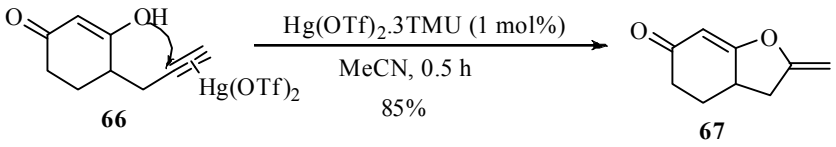
Scheme 20. Pt-catalyzed cyclization to furans

Subsequently, Schmalz and Zhang have reported[63] the synthesis of a furan derivative **65** from cyclopropyl alkynyl ketone **64**, by $Ph_3PAuOTf$-catalyzed ring-opening of the cyclopropane ring by nucleophilic attack of MeOH (Scheme 21).



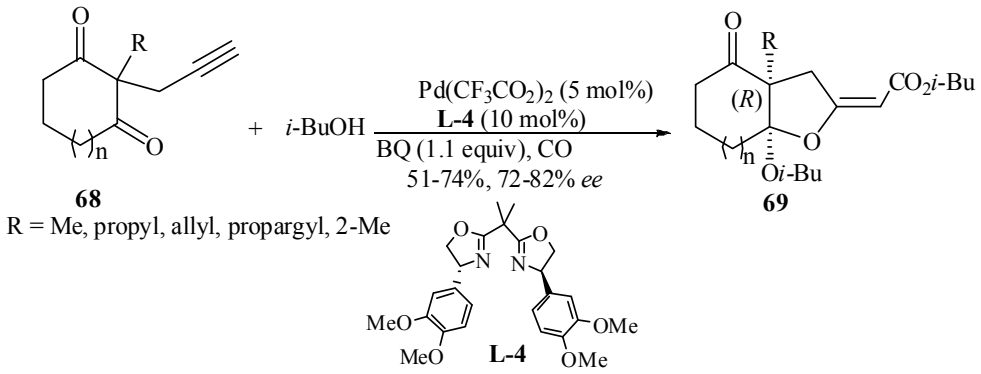
Scheme 21. Au-catalyzed synthesis of tricyclic furans

Similarly, Liu *et al*. have prepared[64] cyclic acetals through a two-step reaction: an Au-catalyzed cycloisomerization followed by acidic treatment of the resulting product with $MeOH/HC(OMe)_3$. Nishizawa *et al*.[65] utilized $Hg(OTf)_2$ as catalyst for the cycloisomerization of alkynyl-1,3-cyclohexanedione and cyclopentanedione to the corresponding oxygen heterocycle (Scheme 22). Gosselin *et al*. also carried out similar cyclization of terminal propargylic ketones to furan derivatives in the presence of $Hg(OTf)_2$.TMU complex.[66]



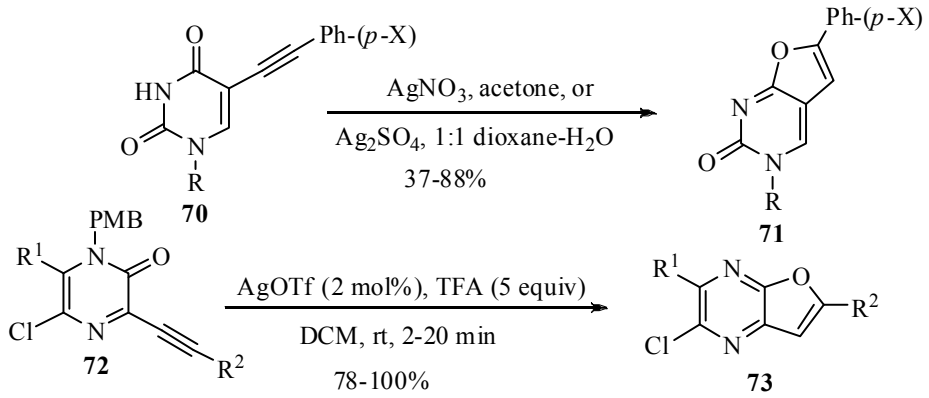
Scheme 22. Hg-Catalyzed synthesis of exocyclic furan derivatives

Oxidative cyclization-carbonylation of 2-alkyl-2-propargylcyclohexane-1,3-diones **68** mediated by $Pd(CF_3CO_2)_2$ in the presence of ligand 2,2'-isopropylidenebis[(4*R*)-4-(3,4-dimethoxyphenyl)-2-oxazoline], **L-4** afforded *cis*-fused bicyclic-β-alkoxyacrylates, hydrindanes **69** (Scheme 23).[67]



Scheme 23. Pd-Catalyzed synthesis of *cis*-fused bicyclic furans

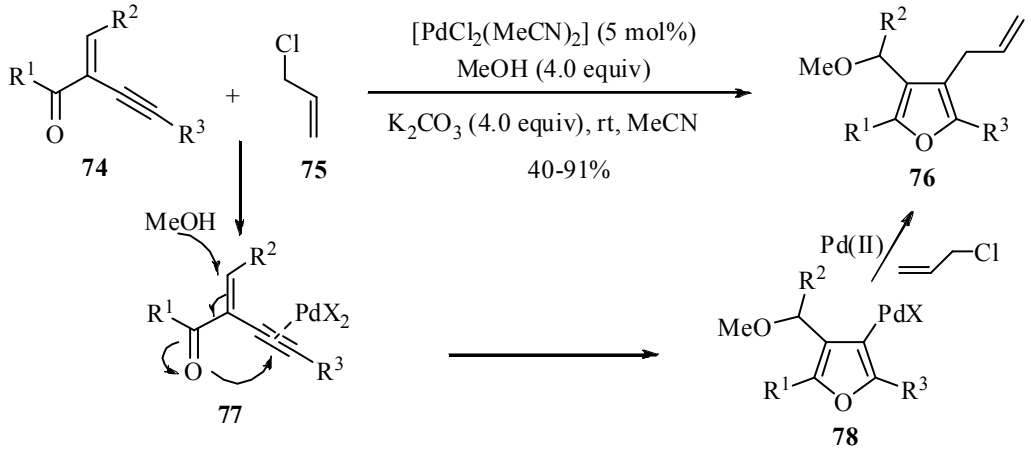
A number of cyclic 6-(phenyl)furo[2,3-d]pyridin-2(3*H*)-ones **71** were synthesized by $AgNO_3$-catalyzed oxycyclization of 5-alkynyluracil **70** (Scheme 24). Electron-rich alkynes were cyclized more rapidly than electron-deficient alkynes.[68] By applying similar methodology Eycken *et al*. reported[69] the preparation of trisubstituted furo[2,3-*b*]pyrazines **73**.



Scheme 24. Ag-Catalyzed synthesis of furopyridinones and furopyrazines

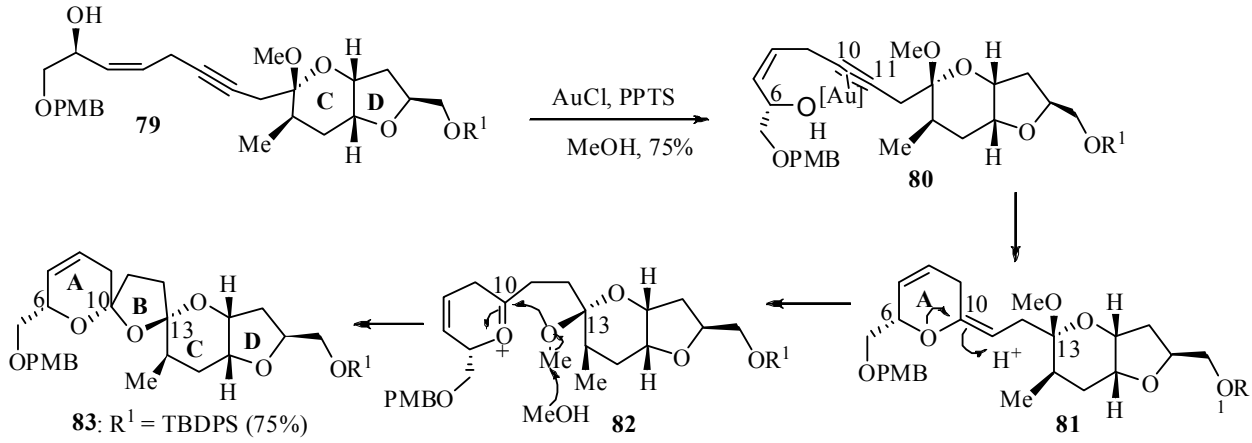
Zhang *et al*. developed[70] a $[PdCl_2(MeCN)_2]$-catalyzed three-component Michael addition/cyclization/cross-coupling reaction of 2-(1-alkynyl)-2-alken-1-ones **74** with various nucleophiles and allyl chloride, to provide an efficient route to functionalized tetrasubstituted furans **76** (Scheme 25). For substituted allyl chloride, coupling occurs exclusively at the less substituted terminus of the allyl chloride. The catalyst $[PdCl_2(MeCN)_2]$ acts as a Lewis acid and transition metal (dual character) in this

transformation for the activation of the carbonyl and alkyne, respectively of **74**. The alkynes bearing aryl groups afforded relatively higher yields than those bearing alkyl groups.



Scheme 25. Pd-Catalyzed synthesis of tetrasubstituted furans

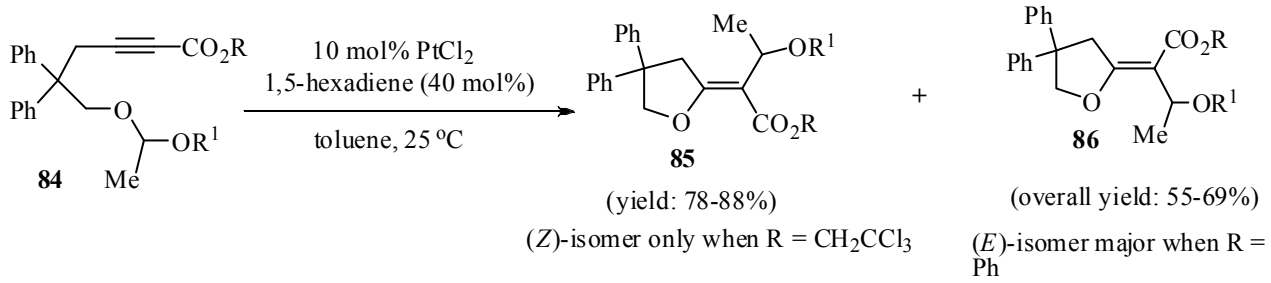
Forsyth *et al*. reported[71] gold(I)-catalyzed *bis*-spiroketalization towards the synthesis of trioxadispiroketal containing A-D rings of azaspiroacid, in which one of the key steps was AuCl catalyzed oxycyclization. The enyne **79** was converted into the desired *bis*-spiroketal **83** using AuCl and PPTS. This process may proceed through an initial *syn* addition of the C-6 hydroxy group and π-coordinated alkynes-Au(I) complex across the alkynes to generate A-ring enol ether **81**, followed by protodeauration in the presence of an acid, and cyclization of the resultant enol ether at C-11 would attract the C-13 methoxy oxygen atom to add to C-10 and close the B ring. Methyl group of the solvent molecule would quench the B-ring oxonium species and gave the desired azaspiroacid **83** (Scheme 26).



Scheme 26. Au-Catalyzed synthesis of A-D rings of azaspiroacid

This method provided thermodynamically favoured establishment of both the newly formed spiroketal centers. The cyclization of 6-(1-alkoxyethyl)hex-2-ynoates **84** in the presence of platinum-olefin catalyst system gave the corresponding multisubstituted 2-(dihydrofuran-2(3*H*)-ylidene)acetates **85** and **86** as a mixture of two isomers (Scheme 27).[72] The stereoselectivity can be controlled by switching the electronic property of the ester group. For example, the reaction of 2,2,2-trichloroethyl ester (R = CH_2CCl_3) in the

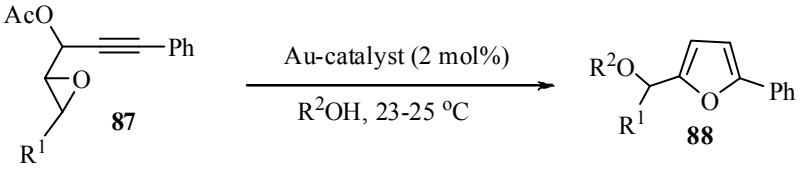
presence of $PtCl_2$ (10 mol%) and 1,5-hexadiene in toluene at 35 °C gave exclusively (*Z*)-**85** in 84% yield,



Scheme 27. Pt-Catalyzed stereoselective synthesis of dihydrofuran derivatives

derived from *trans*-addition of the acetal C-O bond to the alkynyl moiety, while substrates having a relatively electron-rich ester, particularly phenyl ester (R = Ph) gave *E* isomers, from *cis* addition of the acetal C-O bond.

Metal-catalyzed cycloalkoxylation of epoxy alkynes is an important route for the synthesis of substituted furans. Hashmi *et al*. synthesized[73]a number of furan derivatives from α-epoxy alkynes in the presence of $AuCl_3$ catalyst. Recently, Liang *et al*. reported[74] the cycloisomerization/alkoxylation of alkynyloxiranes **87**, using a Au(I) or Au(III) catalysts and alcohols (Scheme 28).

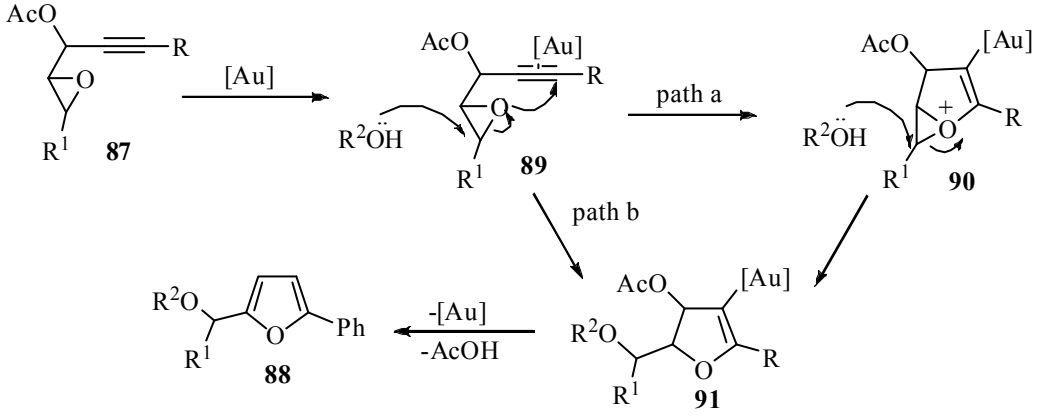


R^1 = Ph, R^2 = Me; AuCl (74%); $Ph_3PAuCl/AgSbF_6$ (57%),
$HAuCl_4.4H_2O$ (74%), $Bu_4NAuCl4$ (74%), $AuCl_3$ (93%)

$AuCl_3$, R^1 = Ph; R^2 = Me (78%), Et (70%), *i*-Pr (62%),
t-Bu (60%), allyl (60%), Bn (61%)

Scheme 28. Au-Catalyzed cycloisomerization of alkynyloxiranes to furans

The cyclization may proceed by the addition of alcohol to the intermediate **89** (path a) or by simultaneous addition of alcohol and cyclization (path b), to give the gold intermediate **91**. The protodeauration followed by elimination of AcOH gave the 2,5-disubstituted furan **88** (Scheme 29).

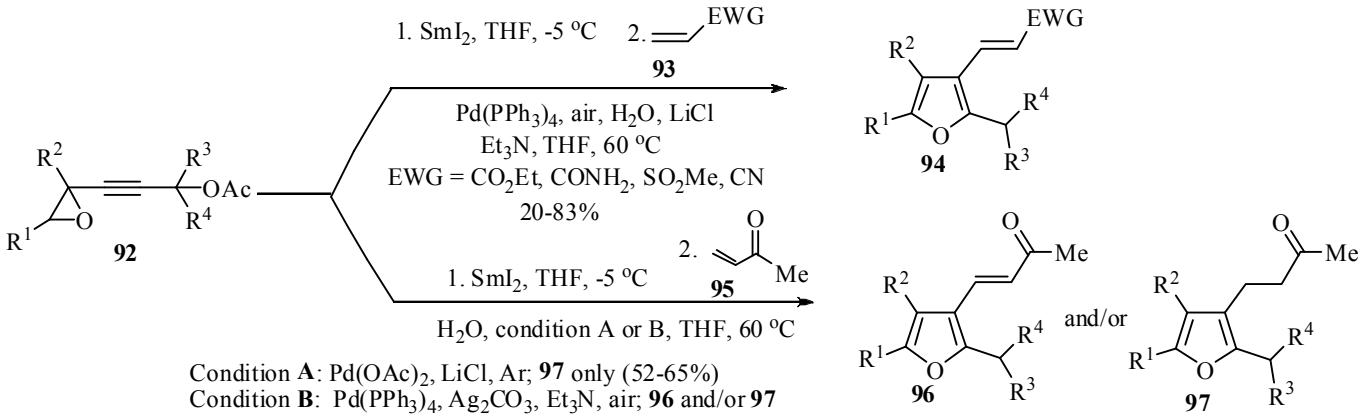


Scheme 29. Mechanism of cycloisomerization /alkoxylation of alkynyloxiranes

SmI_2- catalyzed reduction of alkynyloxiranes into cumullenes followed by Pd-catalyzed cyclization is an expeditious entry into the functionalized furans. Recently, an efficient Pd(II)-catalyzed heterocyclization-coupling reaction to the synthesis of polysubstituted furans having an vinylic group at C-3 position starting from buta-1,2,3-trienyl carbinols **92** and electron-deficient alkenes **93** has been reported (Scheme 30).[75] The formation of either Heck- or conjugated-addition type products is in part dependent upon the choice of electron-withdrawing group on the alkene. Activating groups such as ester, amide, nitrile, and sulfone cause the reaction to follow exclusively the Heck pathway, whereas the coupling with methyl vinyl ketone **95** affords selectively either Heck- or hydroarylation-type products depending on the reaction conditions (Scheme 30).

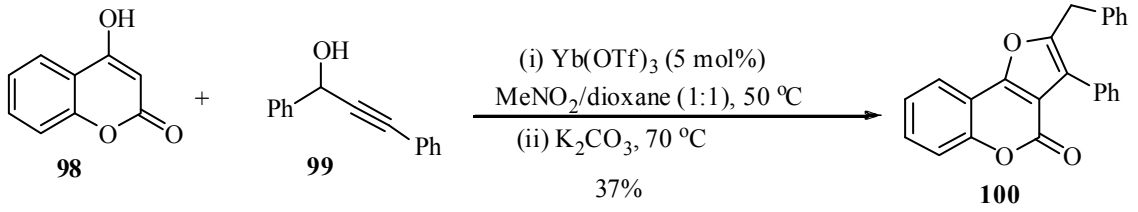
3. 2. 2 INTERMOLECULAR CYCLIZATION OF ALKYNE

Zhou *et al*. reported[76] $Yb(OTf)_3$-catalyzed coupling reaction of 1,3-dicarbonyl compounds with propargylic alcohols. Selective propargylation or allenylation products were obtained depending on the nature of the propargylic alcohols. By applying this reaction as the key step, multi-substituted furocoumarin **100** was synthesized by the treatment of 4-hydroxycoumarin **98** with propargylic alcohol **99**



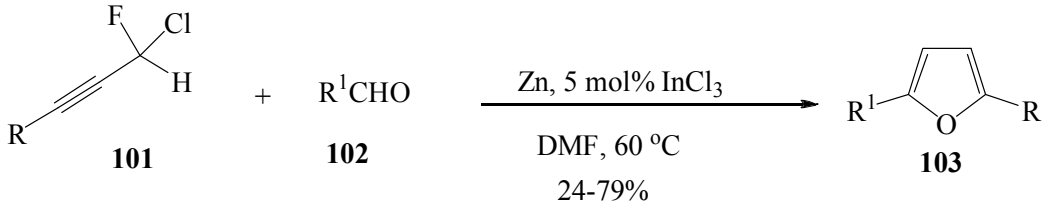
Scheme 30. Pd-Catalyzed synthesis of polysubstituted furans having an vinylic group at C-3

in the presence of 5 mol% $Yb(OTf)_3$ (Scheme 31).



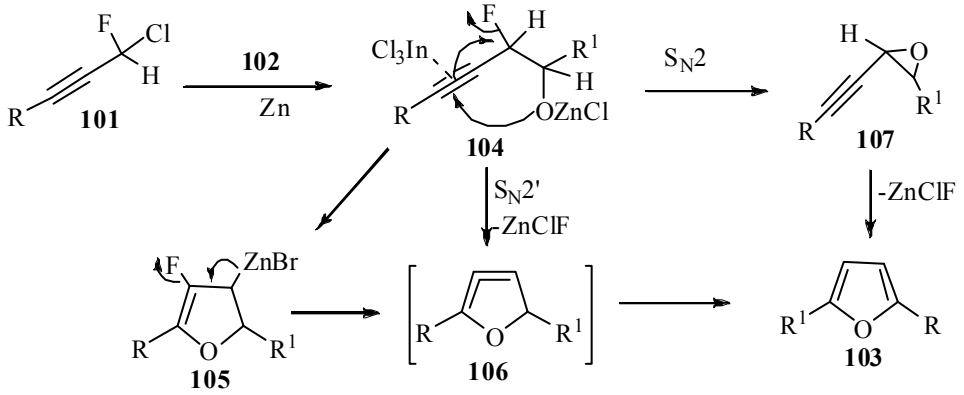
Scheme 31. Yb-Catalyzed synthesis of furocoumarin

Fluoropropargyl chloride reacted with carbonyl compounds to give propargylic fluorohydrins at room temperature, but when higher temperature and longer reaction time was employed, the same starting materials gave 2,5-disubstituted furans **103** (Scheme 32).[77]



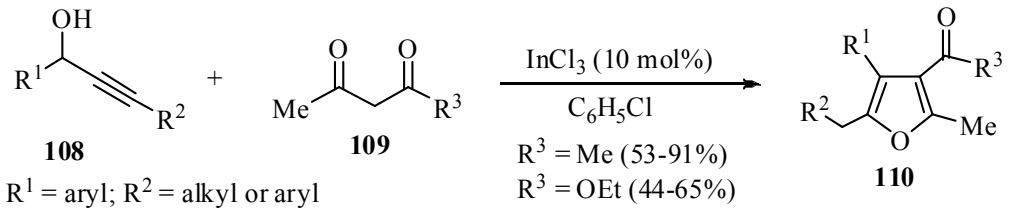
Scheme 32. $InCl_3$-Catalyzed synthesis of 2,5-disubstituted furans from fluoropropargyl chloride

A plausible mechanism for the above conversion suggests that fluoropropargyl chloride **101** initially reacts with zinc and aldehydes **102** to give intermediates **104**, which undergo a stepwise addition-elimination or a concerted S_N2' displacement, to give the corresponding furan **103**, through an allene intermediate **106**. An alternative mechanism, in which a vicinal S_N2 attack by intermediate **104** yield a propargyl epoxides **107**, which then isomerize to the corresponding furan derivatives(Scheme 33).



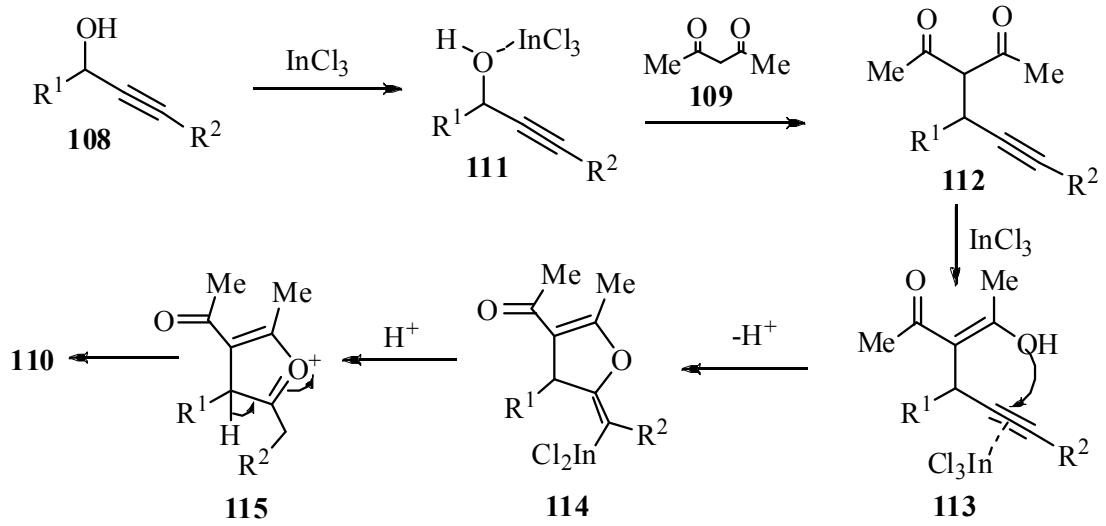
Scheme 33. Mechanism for the synthesis of 2,5-disubstituted furans

Synthesis of tetrasubstituted furans via $InCl_3$ catalyzed propargylation of 1,3-dicarbonyl compounds was developed by Xiang *et al*.[78] The reaction of propargyl alcohols **108** with three equivalent of 1,3-diketone or ethyl acetoacetate (**109**) catalyzed by 10 mol% of $InCl_3$ gave tetrasubstituted furan derivatives **110** in high yields (Scheme 34). The yields of furans are lower with ethyl acetoacetate than that with acetylacetone.



Scheme 34. In-Mediated synthesis of tetrasubstituted furans

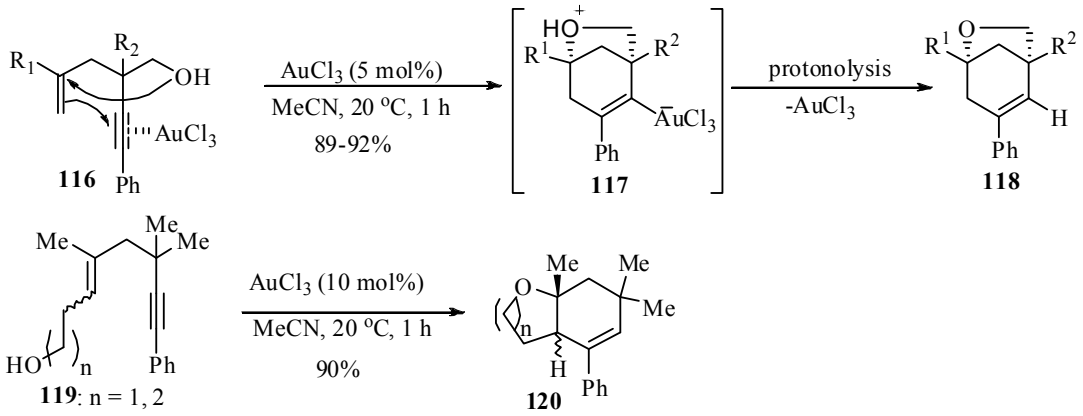
A tentative mechanism for the reaction is outlined in Scheme 35. Initially, $InCl_3$ coordinates with the oxygen atom of the propargyl alcohol to generate a carbocation, which is subsequently trapped by the dicarbonyl compounds to form the substituted product **112**. $InCl_3$ may again coordinate with the triple bond of **112**, followed by the nucleophilic attack at the activated triple bond by the lone-pair electron of the carbonyl group to generate **114**. The carbon-indium bond was broken down and the desired furan product was obtained through a series of proton addition/elimination, double bond isomerization processes.



Scheme 35. Mechanism for the synthesis of tetrasubstituted furans

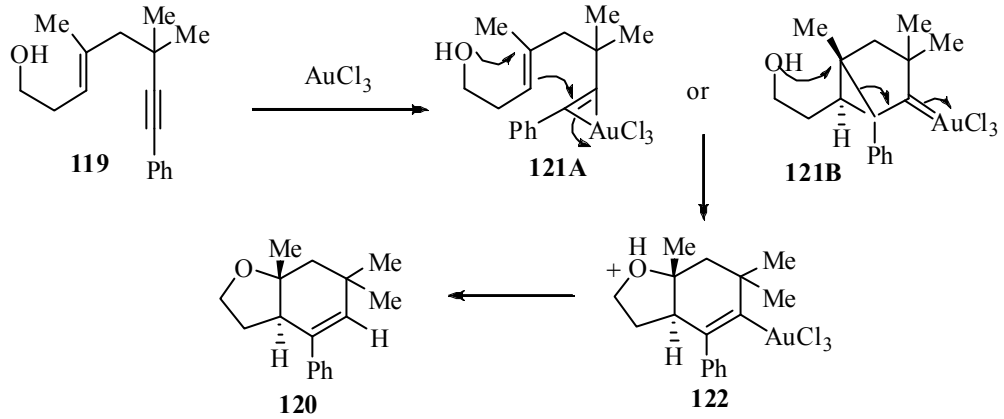
3. 2. 3 TANDEM CYCLIZATION OF ALCOHOLIC OXYGEN TO ENYNES

The catalytic metal-mediated intramolecular cyclization of precursors containing enyne and different oxygenated nucleophiles can be exploited for the construction of a wide variety of oxygen-containing heterocycles. Zhang *et al*. observed[79] that the treatment of a 1,5-enyne **116** armed with a primary alcohol, in the presence of a catalytic amount of $AuCl_3$ triggered the double cyclization to produce intermediate **117**, which underwent subsequent protonolysis to afford the oxabicyclic products **118** (Scheme 36). According to them the reaction involved a 6-*endo*-dig cyclization of the enyne with a concomitant intramolecular formation of the C-O bond. However, the structure of the product depended upon both the geometry of the alkene moiety and the length of the hydroxylated tether. Enynes **119** (*E*-alkenes) afforded the *trans*-oxabicyclic products **120**, whereas enynes **119** (*Z*-alkenes) produced the *cis*-oxabicyclic products **120** (Scheme 36). The tosyl amine moiety behaved similarly in the presence of the $[Au(PPh_3)]ClO_4$ catalyst.



Scheme 36. Au-Catalyzed double cyclization of 1,5-enynes to oxabicyclic products

The proposed mechanism of the $AuCl_3$-catalyzed double cyclization of (*E*)-4,6,6-trimethyl-8-phenyloct-3-en-7-yn-1-ol (**119**, n = 1) involves a concerted process from **121A** or the ring opening of cyclopropyl gold carbene **121B** (Scheme 37).



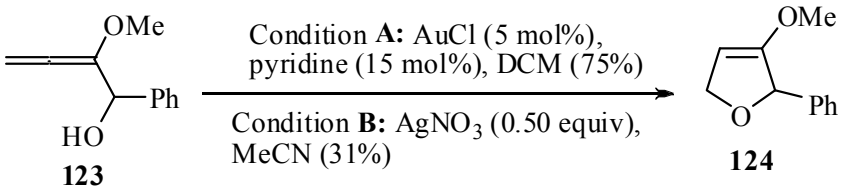
Scheme 37. Mechanism for Au-Catalyzed double cyclization reaction of 1,5-enynes

Similarly, the double cyclization of 1,6-enynes armed with secondary alcohol has been reported to undergo Ph_3PAuCl and $AgSbF_6$ catalyzed formal 5-*exo*-trig addition of the alcohol to the double bond followed by a 5-*exo*-dig addition to the triple bond.[80] In a related study Cossy *et al*. reported[81] a diastereoselective Au(I)-catalyzed cycloisomerization of ene-ynamides bearing a propargylic alcohol moiety, leading to 2-azabicyclo[3.1.0]hexane framework and Toste *et al*. reported[82] a stereoselective synthesis of substituted 5,6- and 6,6-spiroketal from 1,5-enynes bearing a hydroxyalkyl chain, catalyzed by Au-complex.

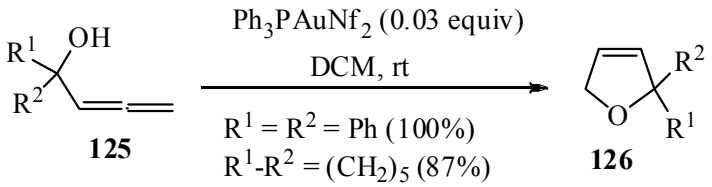
3. 3 SYNTHESIS FROM ALLENES

The transition metal-catalyzed cyclization reaction of functionalized allenes has attracted the attention of many synthetic chemists due to their unique reactivity and stereoselectivity.[83] Metal catalyzed addition of heteroatom nucleophiles to allenes followed by trapping of the intermediate alkenyl metal intermediate by

proton or any electrophilic species have found extensive applications in the synthesis of heterocycles.[84] Electrophile-induced 5-*endo*-trig cyclization of α-allenyl alcohols constitute a well-known and elegant route to synthetically useful 2,5-dihydrofurans. Gold- salts have been found to be very efficient catalyst for this purpose.[85] Reissig *et al*. synthesized 3-alkoxy-2,5-dihydrofuran **124** (Scheme 38) by AuCl catalyzed 5-*endo* oxycyclization of α-hydroxy allene (*sec*-alcohol).[86] Hashmi *et al.* reported[87] the formation of various side products, when α-hydroxy allenes were reacted with $AuCl_3$ catalyst in MeCN. However, substrates **125** afforded 2,5-dihydrofurans **126** in high yields with $Ph_3PAuNTf_2$ in DCM (Scheme 39). On the other hand, Huang and Zhang obtained[88] a substituted bicycle[4.3.0]nonene as the main product instead of dihydrofuran, from the Au(III)-catalyzed cycloisomerization of 1-cyclohexenyl-2-(methoxymethoxy)buta-2,3-dien-1-ol.

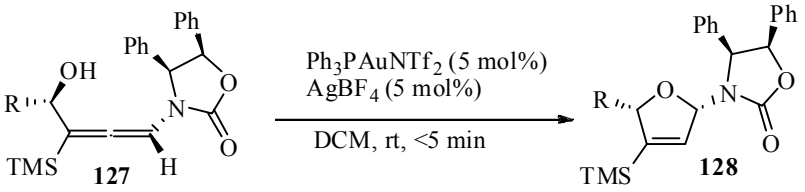


Scheme 38. Au-Catalyzed cyclization of α-hydroxy allene having a *sec*-OH



Scheme 39. Au-Catalyzed cyclization of α-hydroxy allenes having a *tert*-OH

Gold(I) or gold(III)-catalyzed cycloisomerization of α-and β-hydroxyallenes bearing alkyl substituents at

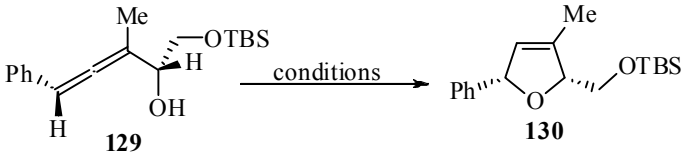


R = Ph (80%), *i*-Pr (87%), $TBSOCH_2$ (81%)
MeCH(OBn) (78%), CH_2=$CH(CH_2)_2$ (86%)

Scheme 40. Au-Catalyzed cycloisomerization of a-hydroxyallene with chirality transfer

the allene takes place with complete transfer of chirality from the axis to the newly formed stereogenic center in the product.[89] For example, the synthesis of furan derivatives **128** with complete chirality transfer was observed with the catalytic system $Ph_3PAuNTf_2$ and $AgBF_4$ in DCM at room temperature (Scheme 40).[90]

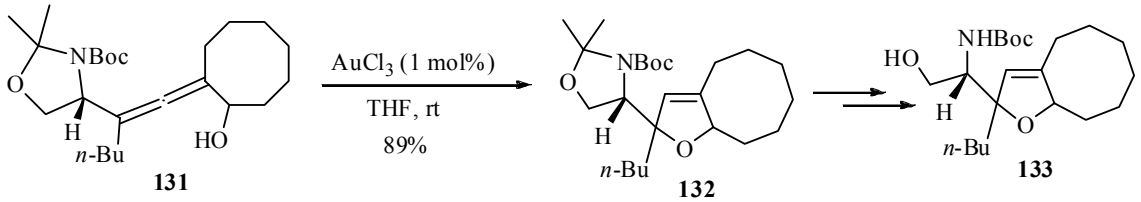
Krause *et al*. observed[91] that gold(I) and gold(III) salts are able to epimerize aryl-substituted hydroxyallenes, thereby causing a diminished stereochemical purity of the product. However, this problem was overcome by the addition of a sigma-donar ligand such as 2,2'-bipyridine as an additive or by using a moderately coordinating solvent such as THF, which reduces the Lewis acidity of the gold catalyst (Scheme 41).



$AuCl_3$ (2.0 mol%), THF, 2 h, 78%, *cis*:*trans* = 97:3
$AuCl_3$ (0.1 mol%), 2,2'-bipyridine (0.2 mol%) THF, 12 h, 92%, *cis:trans* = 85:15
AuCl (0.1 mol%), 2,2'-bipyridine (3.8 mol%) DCM, 10 h, 96%, *cis:trans* = 95:5

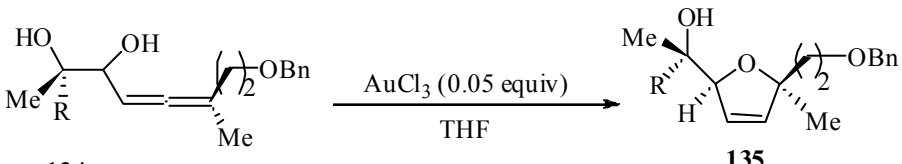
Scheme 41. Au-Catalyzed cycloisomerization of α-hydroxy allene to furan derivative

Recently, the same group also reported the synthesis of bicyclic furanomycin derivative **133** as a mixture of two diastereomers using $AuCl_3$ catalyzed cycloisomerization of α-hydroxyallenes as the key step.[92] The cycloisomerization of **131** in the presence of 1 mol% of $AuCl_3$ in THF proceeded smoothly and gave 89% yield of the bicyclic dihydrofuran **132**, from which after several steps the bicyclic furanomycin derivative **133** was obtained as a mixture of diastereomers (Scheme 42).



Scheme 42. Au-Catalyzed synthesis of bicyclic furanomycin derivative

Subsequently, an excellent stereoselectivity without loss of optical purity and the participation of a second hydroxyl group in the β-position have also been reported by Krause *et al*. (Scheme 43)[93]

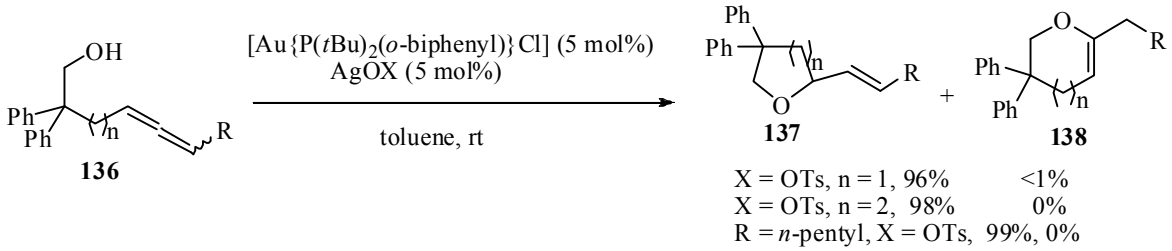


R = H; 96% yield, 96% de, >98% *ee*
R = Me; 97% yield, 96% de, >98% *ee*

Scheme 43. $AuCl_3$ Catalyzed enantioselective synthesis of furan derivatives

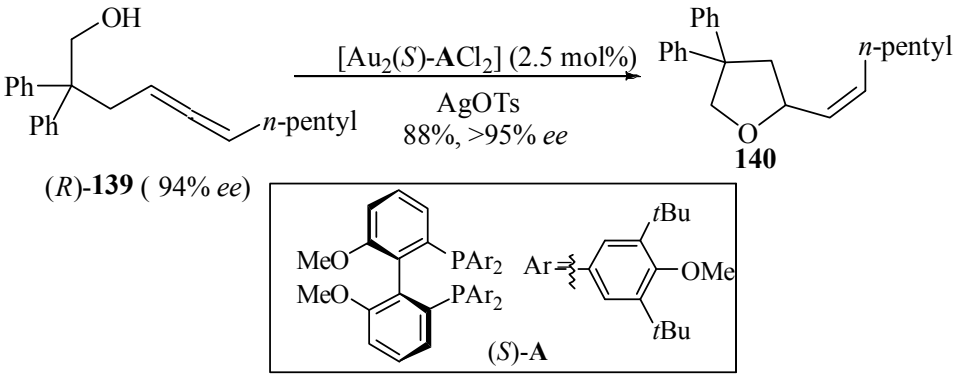
Widenhoefer *et al.* obtained a 1.3:1 mixture of tetrahydrofuran and dihydropyran derivatives from toluene solution of 2,2-diphenyl-4,5-hexadien-1-ol **136** containing a catalytic 1:1 mixture of [Au{P(*t*Bu)$_2$(*o*-

biphenyl)}Cl] and AgOTf. Switching from AgOTf to AgOTs, to form the highly active cationic Au(I) catalyst, gave almost *exo*-hydroalkoxylation products, 2-vinyltetrahydrofurans **137** in excellent yields *via* the transfer of chirality from the allenyl moiety to the newly formed stereogenic tetrahedral C-atom. (Scheme 44)[94]

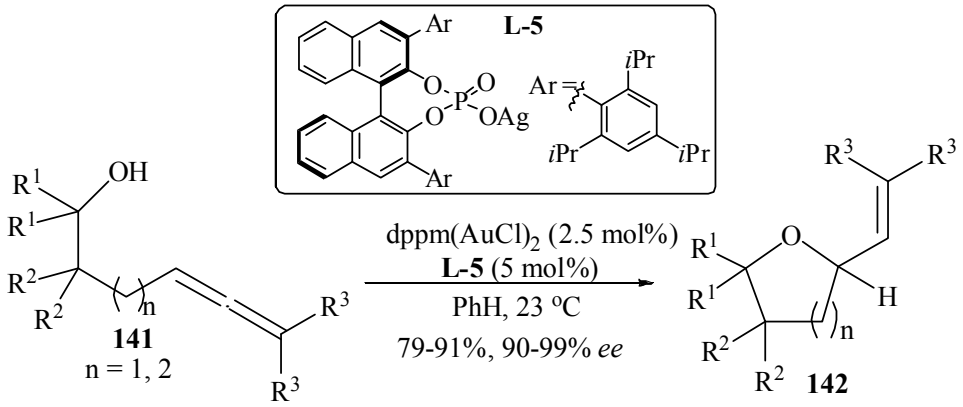


Scheme 44. Au(I)-Catalyzed synthesis of 2-vinyltetrahydrofurans

Recently, Zhang *et al.*[95] demonstrated that *exo*-hydroalkoxylation of γ- and δ-hydroxyallenes occurred with high enantioselectivity when a cationic gold(I) catalyst generated from 1:2 mixture of [Au_2(*S*)-**A**Cl_2] (2.5 mol%) and AgOTs. Enantioselective hydroalkoxylation of (*R*)-**139** (94% *ee*) led to the isolation of (*Z*)-**140** in 88% yield with greater than 95% *ee* and greater than 20:1 diastereoselectivity (Scheme 45). Subsequently, Toste *et al.*[96] carried out the enantioselective hydroxylation of terminal disubstituted allenes in high yields and up to 99% *ee*, by using a mixture of Au(I) complex [AuCl)$_2$dppm] and the chiral silver phosphate ligand **L-5** (Scheme 46).

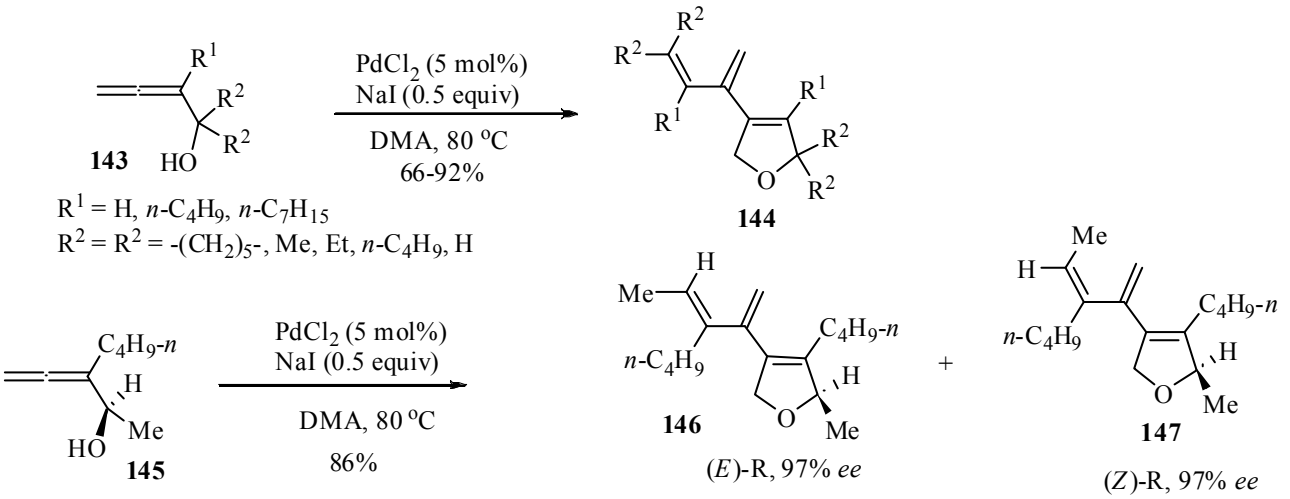


Scheme 45. Au(I)-Catalyzed enantioselective hydroalkoxylation of γ-hydroxyallenes to furans



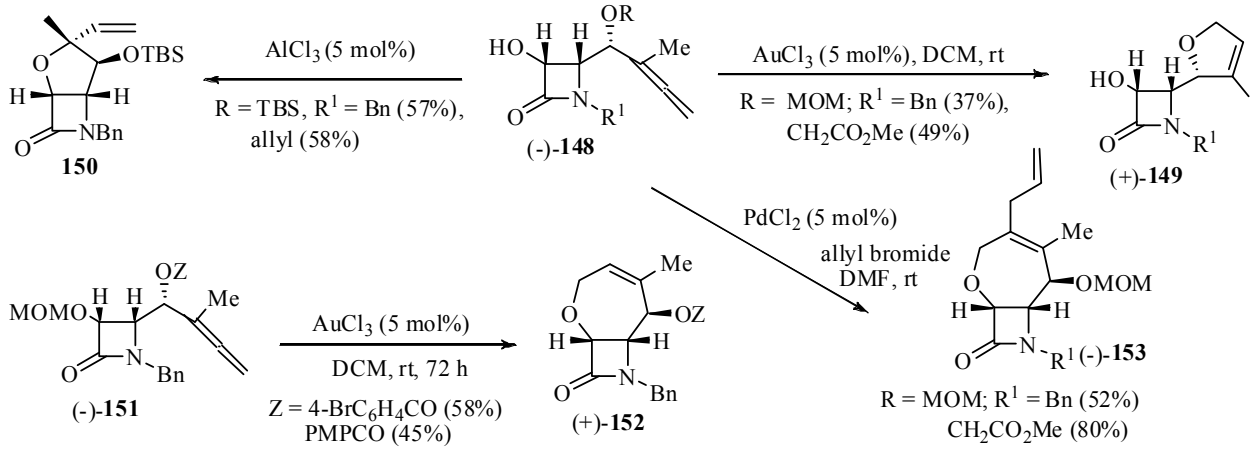
Scheme 46. Au(I)-Catalyzed enantioselective hydroxylation of terminal disubstituted allenes

The transition metal-catalyzed cyclizative dimerization of allenes is attractive to the organic chemists for the enantioselective synthesis of furan derivatives with chirality transfer.[97] The Pd-catalyzed first homodimerization reaction of 1,2-allenyl ketones has been reported by Hashmi *et al*. for the synthesis of 3-(3'-oxo-1'-alkenyl)substituted furan derivatives.[98] The $AuCl_3$-catalyzed reaction of 1,2-allenyl ketones and 2,3-allenols also provide substituted furan derivatives.[99] Recently, a $PdCl_2$/NaI catalyzed homodimeric coupling-cyclization of 2,3-allenols **143** has been reported by Ma *et al*.[100] to provided an efficient route to the stereoselective synthesis of 4-(1',3'-dien-2'-yl)-2,5-dihydrofuran derivatives **144**. Optically active 2,3-allenols **145** afforded optically active furans **146** and **147** as a mixture of isomers in good yields (Scheme 47). An efficient metal-controlled regiodivergent preparation of tetrahydrofurans and tetrahydrooxepines[101] was recently reported from the enantiopure γ-allenols substituted in the α-position by a protected hydroxyl moiety. The TBS protecting group was inert under experimental conditions, whereas MOM group underwent cleavage, and controls the regioselectivity of the reaction.



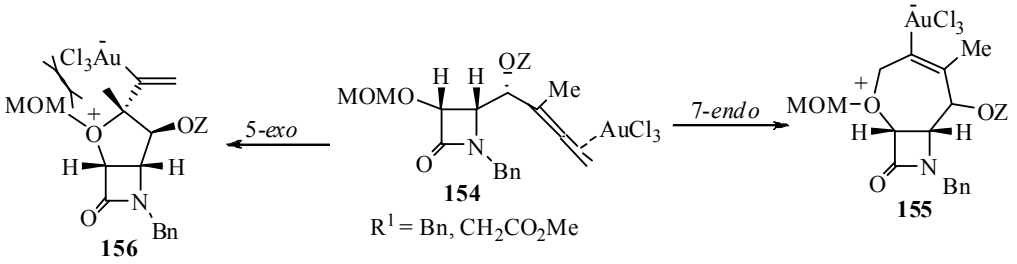
Scheme 47. Pd-Catalyzed cyclizative dimerization reaction of allenes to substituted furans

Reactivity of $AuCl_3$ catalyst depends upon the presence of the MOM protecting group at the γ-allenol oxygen atom. The free γ-allenols **148** having a MOM-protected OH group at the α-position, gave 5-*endo* hydroalkoxylation products **149**, whereas γ-allenols **148** having a TBS protected OH group at the α-position gave 5-*exo*-product **150** and MOM-protected γ-allenols **151** exclusively underwent a 7-*endo* oxycyclization. However, cyclizative coupling reaction of γ-allenols **148** with allyl halide in the presence of $PdCl_2$ gave the seven-membered adducts **153**, exclusively, via 7-*endo* oxycyclization (Scheme 48). Thus, it seems that a (mothoxymethyl)oxy protecting group not only masks the hydroxyl functionality, but also exerts directing influence as a controlling unit in regioselectivity reversal.

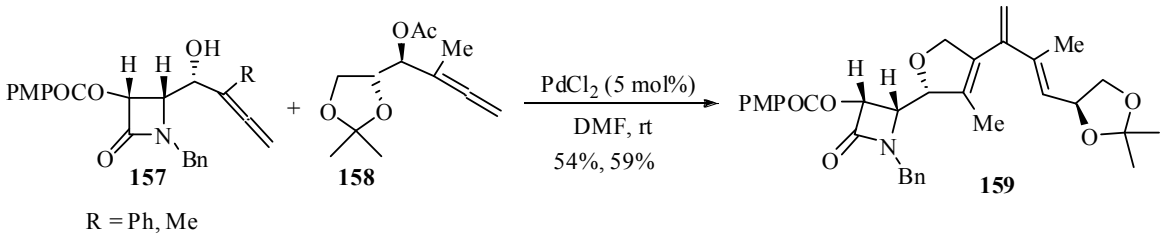


Scheme 48. Regiodivergent preparation of tetrahydrofurans and tetrahydrooxepines

Mechanistically, it is assumed that the initially formed allene-gold complex **154** undergoes an intramolecular attack by the (methoxymethyl)oxy group via a 7-*endo* mode to give intermediate **155**. Protonolysis of the carbon-gold bond followed by elimination of methoxymethanol may give the bicyclic compounds **150**. The 5-*exo* oxycyclization via **156** is restricted by the steric hinderance between the (methoxymethyl)oxy group and the substituent at the quaternary stereocenter (Scheme 49). Similarly, $PdCl_2$-catalyzed heterocyclization/cross-coupling reaction of two different α-allenols gave 2,3,4-trifunctionalized 2,5-dihydrofurans, regioselectively. The α-allenols **157** reacted smoothly with the protected α-allenols **158** to give the desired optically active dihydrofuran derivatives **159** (Scheme 50).[102]



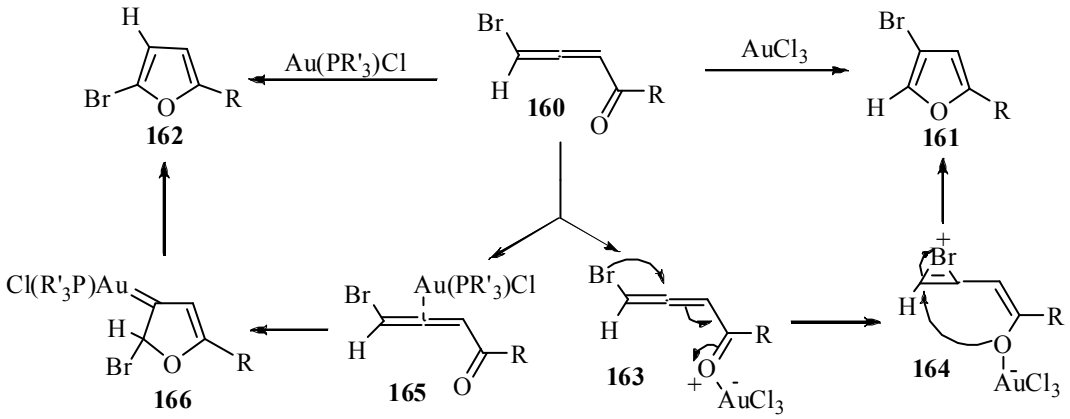
Scheme 49. Mode of regioselectivity cyclization



Scheme 50. Pd-Catalyzed heterocyclization/cross-coupling reaction of two different α-allenols to furans

Gevorgyan group, recently, reported the gold-catalyzed regiodivergent cycloisomerization of bromoallenyl ketones **160** into isomeric bromofurans **161** and **162** via 1,2-migration.[103] Initially, it was thought that more oxophilic Au(III) catalyst coordinates to the carbonyl oxygen **163**, which, via the halirenium intermediate **164** produces the 1,2-Br migration product, 3-bromofuran **161**. Alternatively, the

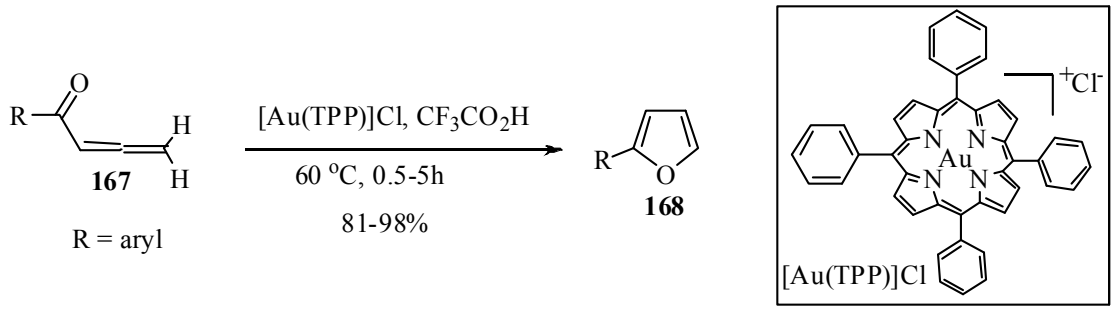
more π-philic Au(I)(PR'_3)Cl- (R' = H, Me)-catalyst may coordinate to the distal double bond of the allene



Scheme 51. Au-Catalyzed regiodivergent cycloisomerization of bromoallenyl ketones into isomeric bromofurans

to form **165**, from which the gold carbenoid intermediate **166** may be formed. Subsequent 1,2-hydride shift may give 2-bromofurans **162** (Scheme 51). Recently, the mechanism of Au-catalyzed cycloisomerization of bromoallenyl ketones was studied by DFT calculations.[104] Both Au(I) and Au(III) catalysts activate the distal double bond of the allene to produce cyclic zwitterionic intermediates, which undergo a kinetically favoured 1,2-migration. However, in the cases of Au(PR'_3)L (L = Cl, OTf) catalysts, the counterion-assisted H-shift is the major process, indicating that the regioselectivity of the Au-catalyzed 1,2-H *vs* 1,2- Br migration is ligand dependent.

Che *et al*. used gold(III) porphyrin complex, [Au(TPP)]Cl as a resonable catalyst for the cycloisomerization of allenones **167** into the corresponding furans **168** in good to excellent yields (Scheme 52).[105] Mechanistically, the gold catalyst $[Au(TPP)]^+$ reversibly binds to the C=C=C moiety which facilitates the nucleophilic attack of the carbonyl oxygen at the terminal of the allene carbon. The furyl-gold intermediate undergoes acid-catalyzed demetalation to give the furan products.

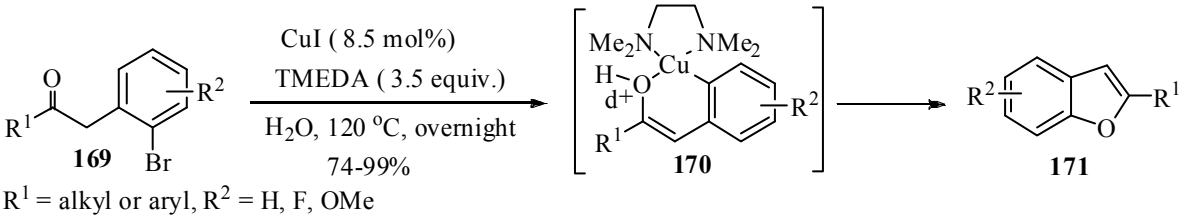


Scheme 52. Au(TPP)]Cl-Catalyzed cycloisomerization of allenones to furans

3. 4 INTRAMOLECULAR CYCLIZATION OF HALOAROMATIC COMPOUNDS

A more sustainable protocol to give 2-alkyl- or 2-aryl substituted benzo[*b*]furans was reported involving a copper-TMEDA complex which catalyzed the transformation of readily available ketone derivatives **169**

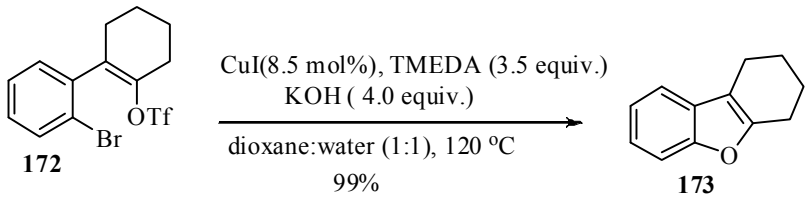
into the corresponding benzofurans **171** (Scheme 53).[106] The reaction is proceeded smoothly in water without any organic co-solvents. The TMEDA act as a ligand and it may also coordinate with the copper to facilitate the formation of enol-type intermediate through coordination to the oxygen as shown in Scheme 53. Similar reaction was also applied by Chen *et al*. to synthesize a variety of benzo[*b*]furans via CuI-catalyzed ring closure[107] of 2-haloaromatic ketones. The methodology is tolerant to various functional groups, affording benzo[*b*]furans in 72-99% yields. However, Pd(II)-catalyst in similar reactions yielded products in lower yields.[108]



Scheme 53. CuI-Catalyzed cyclization of 2-haloaromatic ketones to substituted benzo[*b*]furans

Recently, an efficient methodology for the indirect anti-Markovnikov hydration of unsymmetrically substituted terminal and internal alkynes to 2-haloaromatic ketones was developed based on $TiCl_4$-catalyzed hydroamination reaction. It's application to *ortho*-alkynylhaloarenes, followed by a copper iodide catalyzed O-arylation, provides flexible access to substituted benzo[*b*]furans.[109]

Willis *et al*. demonstrated[110] the effectiveness of the combination of KOH and CuI/TMEDA for the synthesis of benzofurans **215** from aryl bromide-alkenyl triflates **214** (Scheme 54). The yield of the products was reduced on decreasing the amount of TMEDA, or lowering the reaction temperature. The reaction may proceed via the hydrolysis of the alkenyl triflates to generate enolates, which may then get converted to the benzofurans under the action of Cu(I).



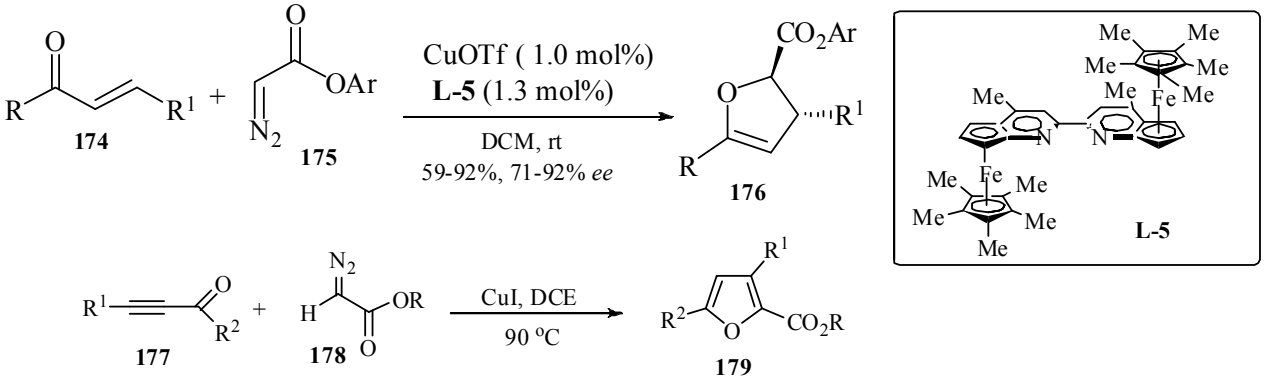
Scheme 54. Synthesis of benzofurans from aryl bromide-alkenyl triflates

3. 5 SYNTHESIS FROM DIAZO COMPOUNDS

Metal carbenes are easily obtained from diazo compounds in the presence of copper and rhodium complexes.[111] Stabilized diazo compounds, particularly α-diazo ketones or esters, are suitable precursors for the metal carbenes that exhibit electrophilic properties at the carbon center, which allow them to undergo attack of the nucleophiles with eventual release of the metal. Lee *et al*. applied this strategy[112] to

synthesize a number of dihydrofurans with *exo*-olefin and furans from diazocarbonyl compounds and allyl halides catalyzed by $Rh_2(OAc)_4$ (1 mol%).

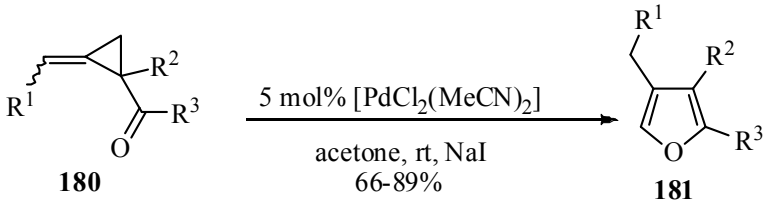
Fu *et al.* reported the stereoselective synthesis of 2,3-dihydrofurans by copper-catalyzed [4+1] cycloaddition reaction of enones and diazo compounds. Treatment of α,β-unsaturated ketones **174**, and 2,6-diisopropylphenyl diazoacetate **175** in the presence of 1.0 mol% CuOTf and 1.3 mol% planar-chiral 2,2'-bipyridine (-bpy) ligand (**L-5**) in DCM gave the 2,3-dihydrofuran derivatives **176** (Scheme 55).[113] The enantiomeric excess (*ee*) is highest (92%) when the enone substitutents (R and R^1) are unsaturated. Similarly, Liang *et al*. synthesized[114] highly substituted furans **179** by CuI catalyzed [4+1] cycloaddition reaction of α,β-acetylenic ketones **177** with α-diazo esters **178** in dry DCE at 90 °C (Scheme 55).



Scheme 55. Cu-Catalyzed stereoselective synthesis of 2,3-dihydrofurans from enones and diazo compounds

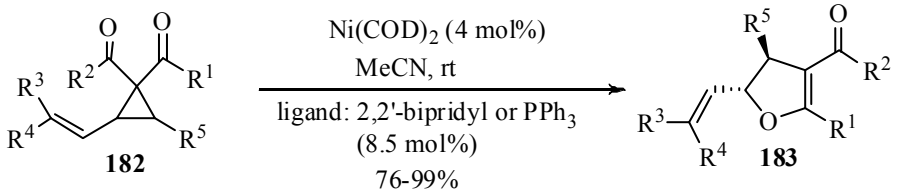
3. 6 SYNTHESIS VIA CYCLOPROPANE RING OPENING

2-Methylenecyclopropanyl ketones **180** owing to the presence of the *exo*-cyclic C=C bond and the strained cyclopropane ring, underwent highly selective ring-opening cycloisomerization with $PdCl_2(CH_3CN)_2$ catalyst in the presence of NaI to afford substituted furan derivatives **181** (Scheme 56).[115] Interestingly, the reaction of the cyclopropyl ketones in the absence of NaI afforded substituted pyrans in good yields. The formation of pyrans or furans presumably proceed through a highly regioselective cleavage of a carbon-carbon single bond in the cyclopropane ring, triggered by regioselective halometalation of the C=C bond and *β*-decarbopalladation, halogen anion attack on the unsubstituted carbon atom of the cyclopropane ring, or the direct oxidative addition of the distal C-C single bond of the cyclopropane ring with Pd(0).



Scheme 56. Pd-Catalyzed cycloisomerization of 2-methylene cyclopropanyl ketones to substituted furans.

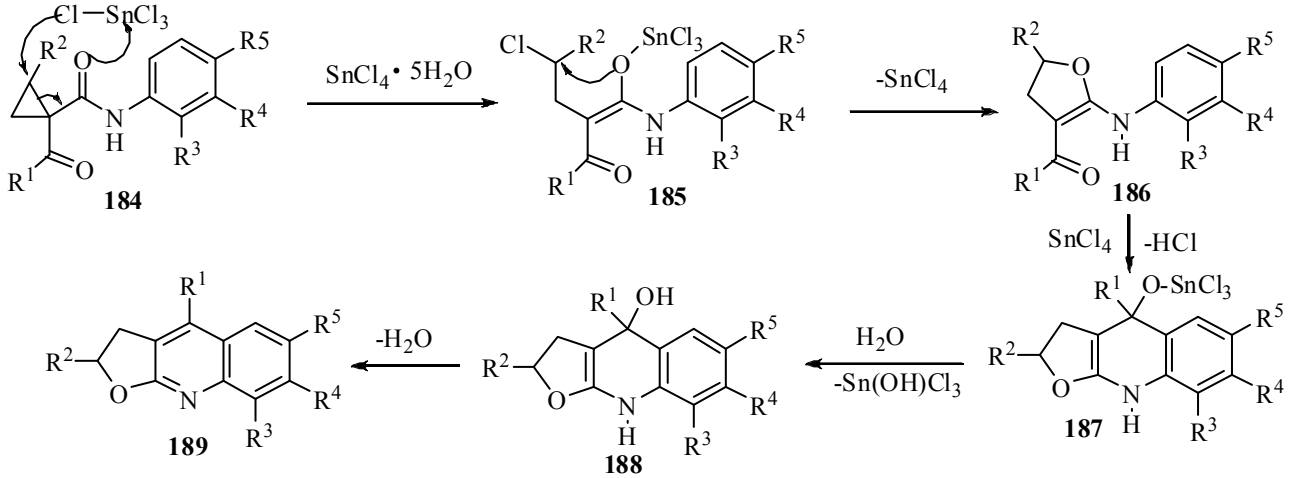
Subsequently, Johnson *et al*. demonstrated Ni(0)-catalyzed rearrangement of 1-acyl-2-vinylcyclopropanes **182** to dihydrofurans **183** in high yields.[116] The vinyl cyclopropyl ketones **182**, having geminal electron-withdrawing substitution, on treatment with $Ni(COD)_2$ (2 mol%) and 2,2'-bipyridyl as ligand (2.2 mol%) in CH_3CN gave dihydrofurans **183** (Scheme 57). Use of triphenylphosphine as ligand, reduced the catalyst loading to 1 mol% and use of $(PPh_3)Ni(COD)$ gave incomplete conversion of the starting materials. Lewis acid $Cu(OTf)_2$ also facilitated the complete conversion of the cyclopropane at room temperature with catalyst loading 10 mol%. The overall reaction proceeds with the retention of configuration at the vinyl bearing stereogenic center.



$R^1 = R^2 = Ph$, $R^3 = R^4 = H$, $R^5 = Me$ (94% yield, 88% *ee*)

Scheme 57. Ni-Catalyzed rearrangements of 1-acyl-2-vinylcyclopropanes to dihydrofurans

A new strategy for the synthesis of furo[2,3-*b*]quinoline derivatives **189** through $SnCl_4$ mediated tandem ring-opening/recyclization reaction of the doubly activated cyclopropanes of readily available 1-acyl *N*-aryl cyclopropylcarboxamides **184** was reported by Liu *et al*.[117] The overall transformation may involve the $SnCl_4.5H_2O$ initiated opening of the cyclopropane ring of **184** followed by oxycyclization to form the dihydrofuran intermediate **186**. Furoquinolines **189** may then be generated through Combes-type annulation reactions (Scheme 58).[11]

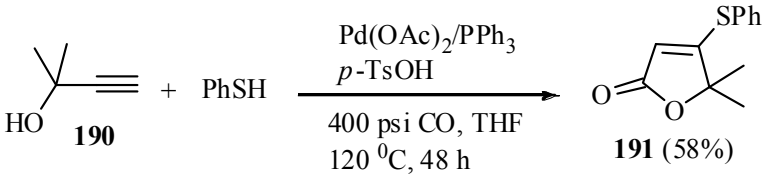


Scheme 58

3. 7 SYNTHESIS OF FURANONES

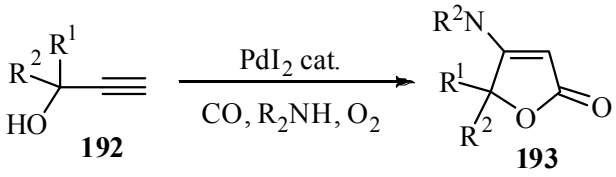
Transition metal-catalyzed 5-*endo* heterocyclization of alkynyl alcohol through the activation of triple bond is an important method for the synthesis of 3-(2*H*)-furanones.[119,120] Recently, Liu *et al*. demonstrated[44b] the oxidative cleavage of triple bonds in (*Z*)-enynols by $AuCl(PPh_3)/AgOTf$ (2 mol%) in

the presence of oxygen to butenolides. Initially the intermediate of (*Z*)-5-ylidene-2,5-dihydrofurans is formed via 5-*exo*-dig oxycyclization, which is oxidized by gold-catalyst in the presence of oxygen into the corresponding butenolides in 70-97% yields. Xiao *et al*. carried out the reaction between 2-methylbut-3-yn-2-ol **190** and thiophenol in the presence of $Pd(OAc)_2$ (3 mol%) to give thiolactonization product **191** as major one along with mono- and dithiocarboxylation product (Scheme 59).[121]



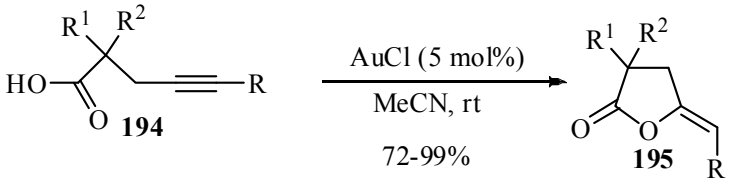
Scheme 59. Pd-Catalyzed synthesis of 4-thiophenylfuranones

PdI_2-catalyzed oxidative aminocarbonylation of the terminal alkynes is a facile route for the synthesis of five-membered oxygen and nitrogen heterocycles.[122] Propargyl alcohol **192** when subjected to PdI_2, carbon monoxide and oxygen in the presence of a secondary amine afforded 4-dialkylamino-5*H*-furan-2-ones **193** (Scheme 60) by a sequential oxidative aminocarbonylation-intramolecular conjugate addition-cyclization route.



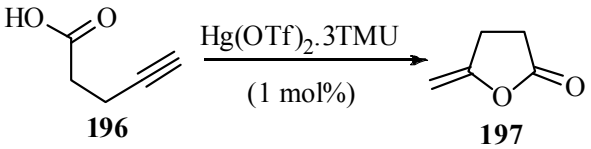
Scheme 60. PdI_2-Catalyzed oxidative aminocarbonylation-cyclization

The intramolecular addition of carboxylic acids to alkynes gives lactones. Perfect regioselectivity for the Au-catalyzed cyclization step in favor of the 5-*exo* isomer was observed for terminal alkynes, whereas a mixture of 5-*exo* and 6-*endo* products resulted from the cyclization of internal alkynes. For example, terminal acetylenic acids **194** (R = H) undergo selective *exo*-cyclization in the presence of gold(I)-catalyst, AuCl to give a number of functionalized γ-lactones **195** (R = H).[123] However, the reaction of internal alkynes **194** afforded selectively (*Z*)-γ-lactones **195** (Scheme 61), which indicate an intramolecular addition of the carboxylic acid to the Au-alkyne intermediate, resulting from an initial activation of the triple bond by Au(I)-catalyst. Even in the presence of a styrene chain, no competition of the activated alkene with the alkyne was observed. More recently, Michelet *et al*. also observed[124] 5-*exo* mode of cyclization with *Z*-stereoselectivity resulting from anti aeration using Au_2O_3 catalyst.



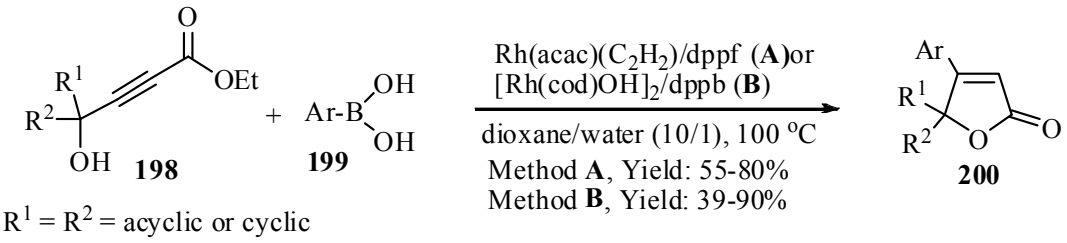
Scheme 61. Au(I)-Catalyzed cyclizationof acetylenic acids to γ-lactones

$Hg(OTf)_2$ tetramethylurea (TMU)-catalyzed cyclization of alkynoic acid **196** to ene-γ-lactone **197** has been reported (Scheme 62). The alkynoic acid residue has been used as the leaving group for $Hg(OTf)_2$-catalyzed glycosylation via S_N1 reaction mechanism.



Scheme 62. Hg-Catalyzed cyclization of alkylnoic acid to γ-methyl-γ-lactone

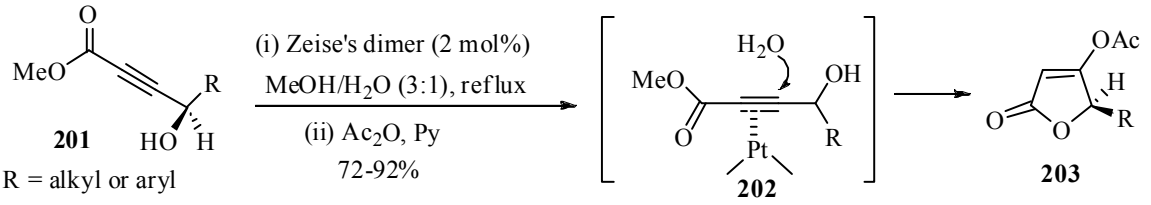
Access to 2-(5*H*)-furanone skeleton could also be accomplished through palladium-mediated cyclization-carbonylation[125] or coupling-cyclization[126] reaction of propargyl esters. Palladium–catalyzed reaction of unsaturated triflates and halides with methyl-4-hydroxy-2-butenoate and tetrahydropyranyl derivatives, afforded 4-aryl- and 4-vinyl-2-(5*H*)-furanones through *in situ* vinylic substitution/anulation sequence.[127] Recently, 4-substituted-2(5*H*)-furanones were synthesized by Arcadi *et al*. through a sequential regioselective rhodium-catalyzed addition/lactonization reaction of organoboron derivatives to γ-hydroxy-α,β-acetylenic esters.[128] The reaction was carried out with $Rh(acac)(C_2H_2)$/dppf or $[Rh(cod)OH]_2$/dppb



Scheme 63. Rh-Catalyzed lactonization of γ-hydroxy-α,β-acetylenic esters to furanones

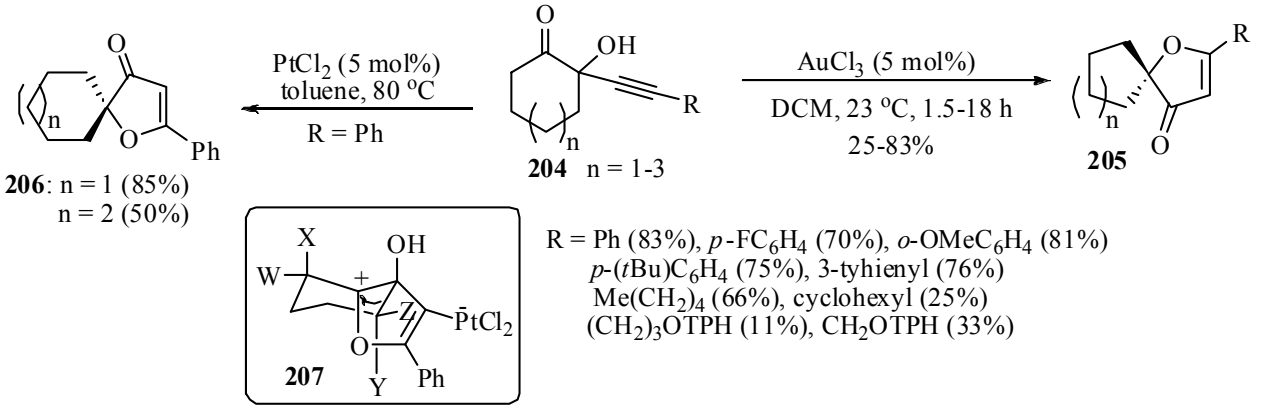
as catalytic system in dioxane/H_2O (10/1) at 100 °C using following molar ratios **198**:**199**:[$Rh(acac)(C_2H_2)$]:dppf (**A**) = 1:5:0.03:0.066 or $[Rh(cod)OH]_2$:dppb (**B**) = 1:2.0:0.03:0.06 (Scheme 63). Rh-catalyzed reaction of alkyl 4-hydroxy-2-alkynoates bearing a tertiary propargyl alcohol group resulted in reversal of the regioselectivity compared to that of palladium-catalyzed process. However, the regioselectivity of the secondary propargylic alcohol is not affected by the bulkiness of groups close to the C-C triple bond.

The optically active γ-hydroxy-α,β-acetylenic esters **201** undergo regiospecific hydration in the presence of Zeise's dimer, $[PtCl_2(C_2H_2)]_2$, to produce the optically active tetronic acid derivatives **203**.[129] The observed regiospecific hydration is explained by considering intermediate **202** (Scheme 64). Electron withdrawing effect of the ester group, Lewis acidity of Pt(II) center and the chelating effect of the acetylenic ester to Pt induce attack of water at β-position.



Scheme 64. Pt(II)-Catalyzed hydration of γ-hydroxy-α,β -acetylenic esters to tetronic acid derivatives

Furanones can also be obtained from alkynones having a hydroxyl group at the α-position.[130] This tandem reaction consisting of heterocyclization and 1,2-migration is believed to proceed via a acyclic oxonium ion intermediate **207**. For example, treatment of the alkynes **204,** with the catalyst, $AuCl_3$ or $PtCl_2$ underwent a domino heterocyclization and subsequent 1,2-alkyl shift to give spirocyclic compounds, 3-(2*H*)-furanone derivatives **205** or **206**, respectively (Scheme 65).[131] When 5 mol% of $AuCl_3$ was used as the catalyst, spirocyclic compounds **205** were obtained in high yields, but R was restricted to aryl substituent only. The use of Au(I) catalysts such as Ph_3PAuBF_4 and Ph_3PAuCl mainly caused decomposition. However, $PtCl_2$-catalyzed reaction proceeded soomthly with contraction of the ring size.

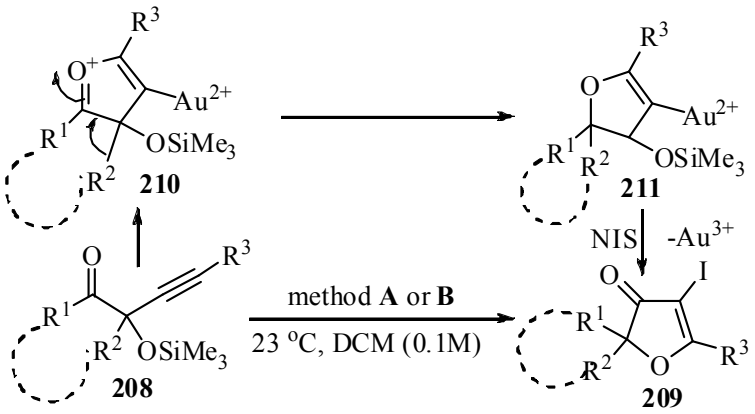


Scheme 65. Cycloisomerization of alkynones having a hydroxyl group at the α-position to furanones

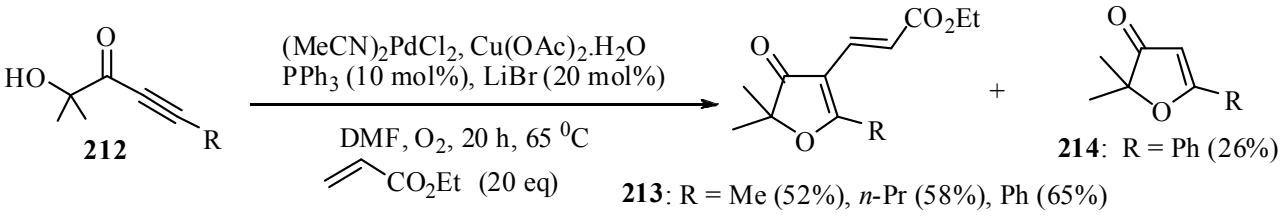
Recently, there has been a report[132] of a novel electrophile-induced tandem cyclization/1,2-migration reaction of 2-alkynyl-2-siloxy carbonyl compounds **208** to fully substituted 3(2*H*)-furanones **209** in excellent yields containing an iodo-substituent at C-4 position, catalyzed by $AuCl_3$ (5 mol%) in DCM at room temperature (Scheme 66). However, without $AuCl_3$, a variety of trimethylsilyl ethers were also effectively converted into the corresponding spiro 4-iodo-3-furanones but took longer time for cyclization. The reaction of substrates with $R^1 = R^2 =$ Et, failed to give furanones by method **A,** but by method **B** these cyclized giving low yields (27% and 43% only).

Gouverneur *et al*. devised a palladium(II)-catalyzed Wacker-Heck reaction involving the union of structurally diverse hydroxyynone and ethyl acrylate to the synthesis of 4(2*H*)-pyranones.[133] In addition, the same author also applied the domino cyclization reaction to α-hydroxyenones. Tetrasubstituted

furanones **213** were prepared under the optimized reaction condition in isolated yields ranging from 52-65% (Scheme 67). Additionally, Liu *et al.* have succeeded[134] in achieving a number of substituted 3(2*H*)-furanones **216** from 2-oxo-3-butynoic esters or disubstituted-1,2-diones **215** via gold-catalyzed cyclization and nucleophilic addition sequence.

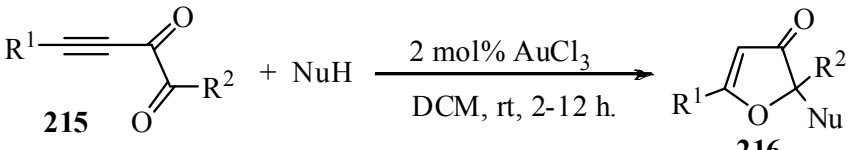


Scheme 66. Tandem cyclization/1,2-migration of 2-alkynyl-2-siloxy carbonyls to 3(2*H*)-furanones



Scheme 67. Domino cyclization reaction of α-hydroxyynones to tetrasubstituted furanones

The reaction proceeded smoothly with 2 mol% $AuCl_3$ catalyst in DCM at room temperature in the presence of nucleophiles to give the cyclized products in moderate to excellent yields (Scheme 68).

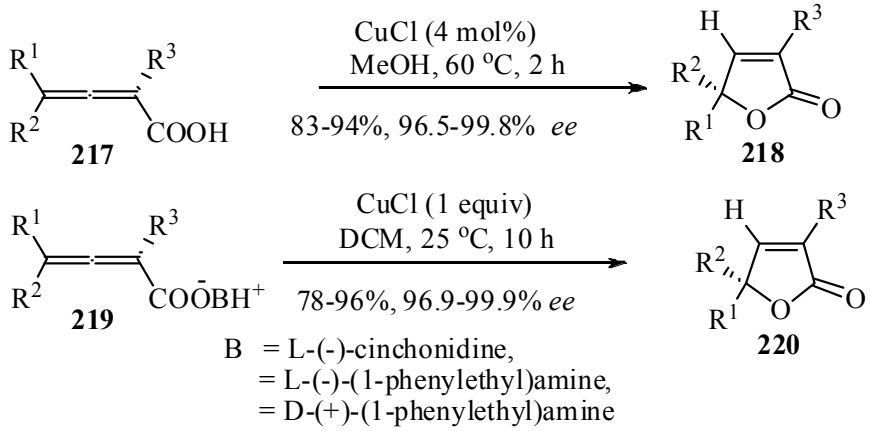


Scheme 68. Au-Catalyzed synthesis of substituted 3(2*H*)-furanones

Ma *et al.* reported CuCl-catalyzed oxycyclization of optically active 2,3-allenoic acids or 1:1 salts of optically active 2,3-allenoic acids with chiral amine to the corresponding 2(5*H*)-furanones (Scheme

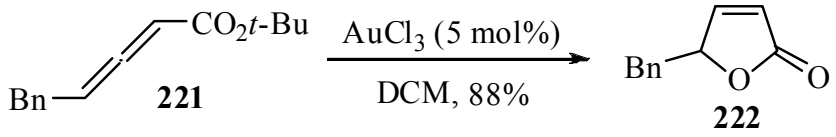
69).[135] It was observed that the reaction of optically active 2,3-allenoic acids **217** in methanol required only catalytic amount of CuCl, whereas the reaction of the 1:1 salts of optically active 2,3-allenoic acids with chiral amine required one equiv. of CuCl and DCM as solvent to ensure high efficiency of the chirality transfer. Shin *et al*. utilized *trans*-2,3-allenoic esters for the synthesis of 2-furanones, catalyzed by $AuCl_3$ (Scheme 70).[136]

The reaction between two same or differently functionalised allenes, i.e, homodimerization reaction of functionalised allenes is of considerable interest. Hashmi *et al*. first reported the homodimerization reaction of allenyl ketone.[137] The intermolecular dimerization of 2,3-allenoic acids using $PdCl_2$ as catalyst afforded bicyclic butenolides.[138] Moreover, in the heterodimerization the reactions between 2,3-allenoic acids or 2,3-allenamides and 1,2-allenyl ketones, both allenes were cyclized to form products with two different rings.[139] An interesting *β*-hydroxy elimination to dienyl unit was observed during the palladium



217 **218** **219** **220**

Scheme 69. Cu-Catalyzed cyclization of 2,3-allenoic acids to 2(5*H*)-furanones

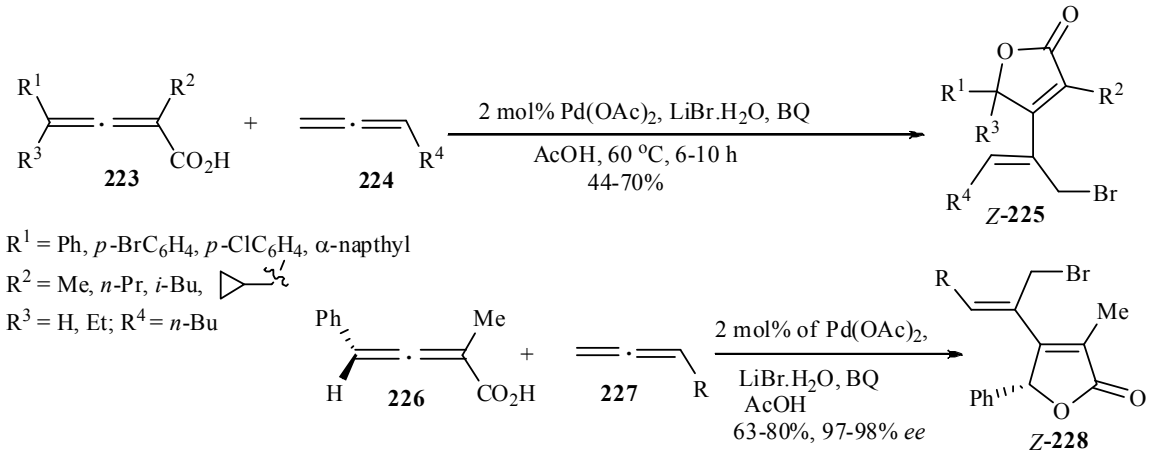


221 **222**

Scheme 70. $AuCl_3$-Catalyzed cyclization of 2,3-allenoic esters to 2-furanones

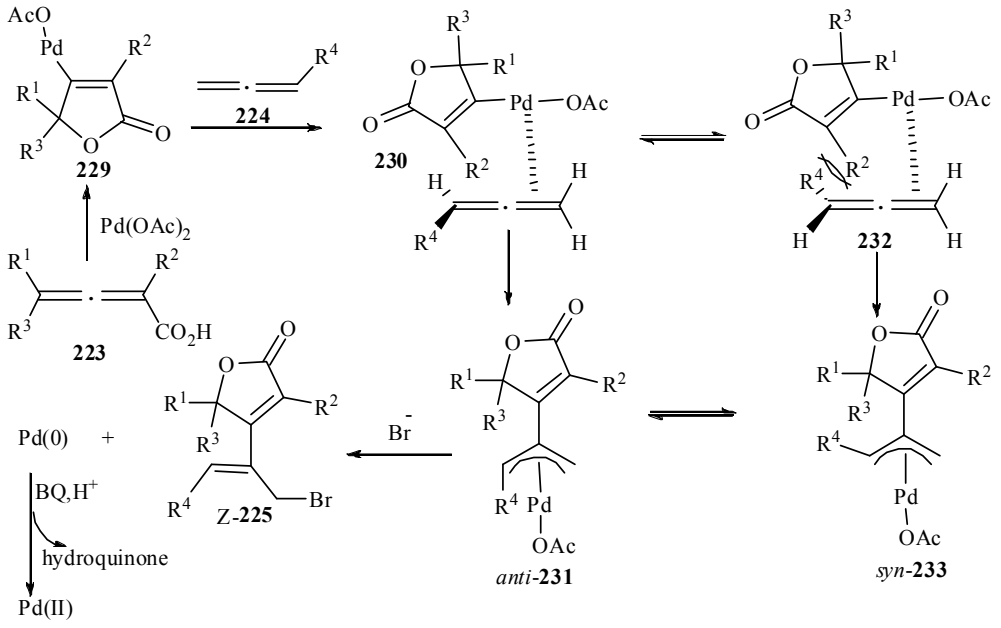
catalyzed cyclization of 2,3-allenoic acids in the presence of 2,3-allenols.[140] Alcaide and co-workers also reported similar cross-coupling cyclization reactions of (*R*)-allenols in the presence of 2,3-allenyl carboxylates.[141]

Recent investigation of Ma *et al*. also demonstrated the intermolecular cross coupling reaction between 2,3-allenoic acids **223** and simple allenes **224** in the presenece of $Pd(OAc)_2$, $LiBr.H_2O$, and benzoquinone (BQ) in AcOH to give highly substituted furan-2(5*H*)-ones, *Z*-**225**.[142] The reaction of optically active 2,3-allenoic acid **226** in the presence of allene afforded the product *Z*-**228** in high enantiopurity (Scheme 71).



Scheme 71. Pd-Catalyzed cross coupling reaction of 2,3-allenoic acids to substituted furan-2(5*H*)-ones

The catalytic cycle leading to furan-2(5*H*)-one is assumed to proceed via initial cyclic oxypalladation of 2,3-allenoic acid with Pd(II) to generate furanonyl palladium intermediate **229** which is trapped by the allene to generate a π-allylic intermediate *anti*-**231**. This is presumably nucleophilically attacked by Br^- in *anti*-**231** to yield 4-(1'-bromoalk-2'(*Z*)-en-2'-yl)furan-2(5*H*)-one derivatives, *Z*-**225** with the regeneration of Pd(0) by the oxidant BQ (Scheme 72). The exclusive formation of the *Z*-isomer may be explained by face-selective coordination of the allene **224** with the palladium atom in intermediate **230** to avoid steric congestion.



Scheme 72. Mechanism for the cross-coupling reactions

4. SYNTHESIS OF SIX-MEMBERED OXYGEN HETEROCYCLES

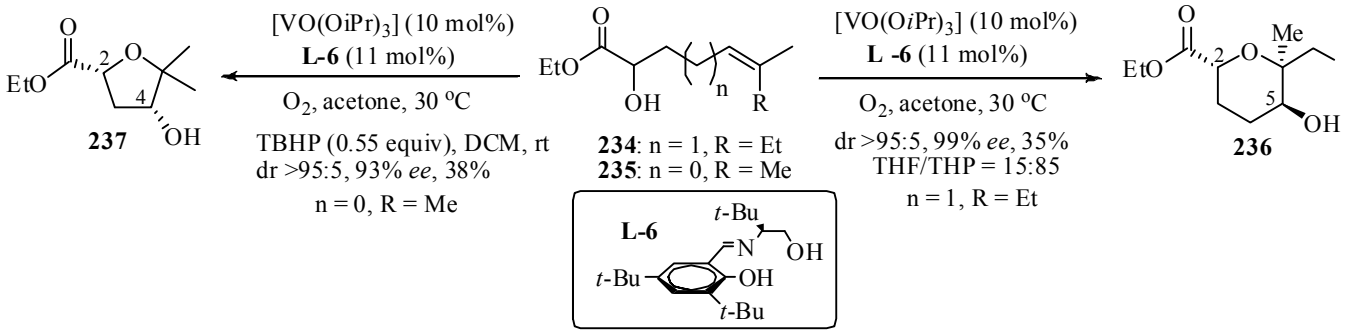
Six-membered oxygenated heterocycles i.e. pyran ring system can be synthesized by intramolecular cyclization, cycloaddition or five-membered ring expansion. In addition to these processes, there is a set

of important methodologies based on the cyclization of oxygenated precursors catalyzed by different transition metals that afford pyran rings in a highly efficient and straightforward manner.[143]

4. 1 SYNTHESIS FROM ALKENES: CYCLIZATION OF ALCOHOLIC- AND PHENOLIC-OXYGEN TO ALKENES

The cyclization of δ-hydroxy-*cis*-alkenes promoted by Hg(II) salts[144] and chiral bisoxazolines as ligands affords 2-substituted tetrahydropyrans in excellent *ee*.[155] The intramolecular oxymercuriation has been applied to the synthesis of the C22-C26 tetrahydropyran of phorboxazole B. The mercury(II)-mediated electrophilic ring opening reaction of hydroxy cyclopropylcarbinol strategy[146] has been applied to the construction of the C3-C7 tetrahydropyran ring of zincophorin.[147]

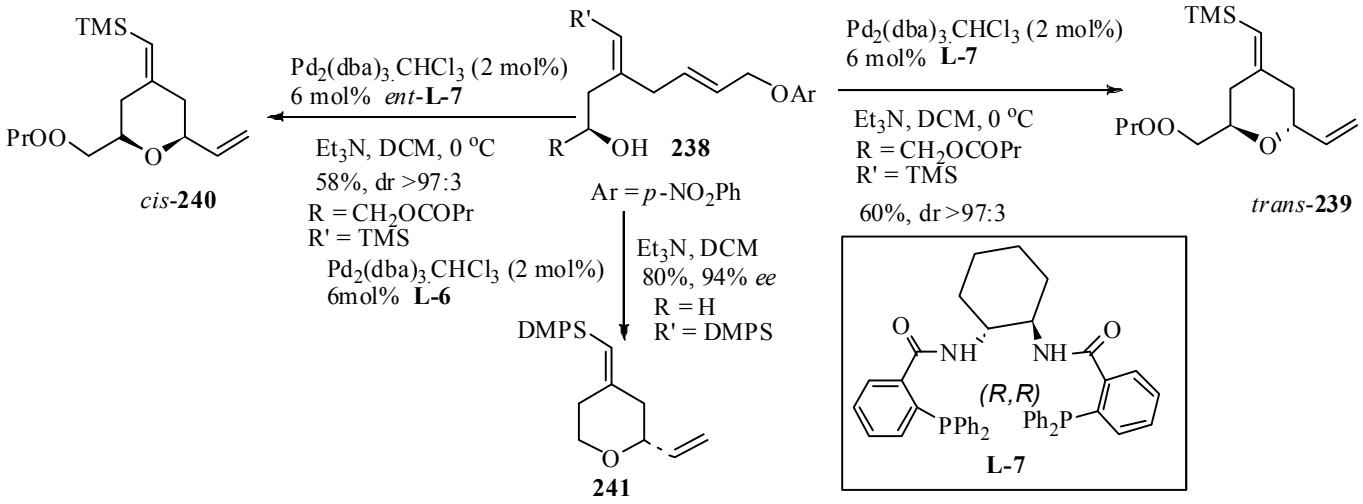
Toste *et al*. reported vanadium(v)-oxo complex catalyzed highly diastereo- and enantioselective synthesis of 2,5-*trans*-tetrahydropyran **236** and 2,4-*cis*-tetrahydrofuran **237** using sequential resolution/oxidative cyclization of racemic *bis*- and homoallylic α-hydroxyesters (Scheme 73).[148] Both steps in the reaction sequence are catalyzed by vanadium(v)-oxo complex with a readily available tridentate Schiffs base ligand **L-6**. The reverse selectivity has been explained by assuming the chelation of the ester carbonyl group to the vanadium catalyst during the epoxidation and formation of a transition state in which the sterically more demanding substituent occupies in a position to minimize the steric interaction. This synthetic protocol also provides an enantioselective synthesis of (-)-pantofuranoid E.



Scheme 73. V-Catalyzed enantioselective synthesis of 2,5-*trans*-tetrahydropyran and 2,4-*cis*-tetrahydrofuran

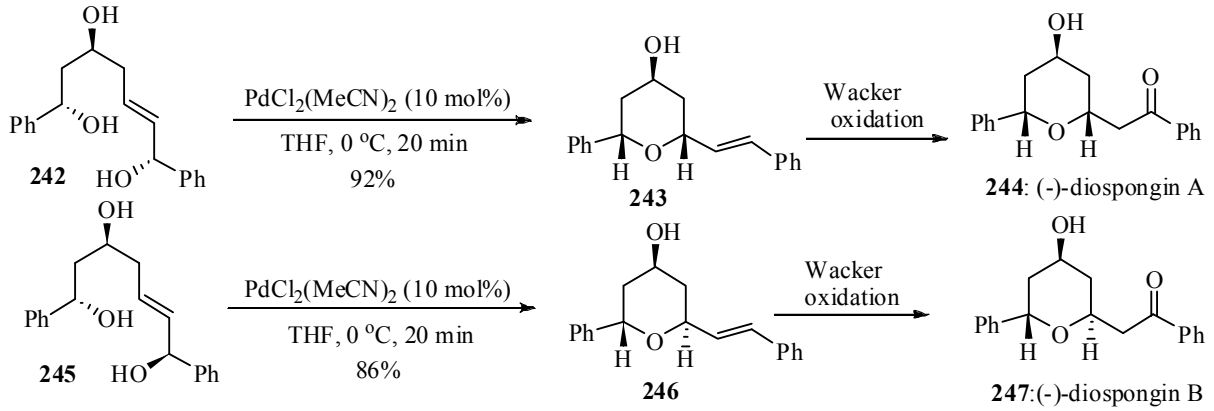
Pd-complexes catalyze the cyclization of δ-hydroxy alkenes having an allylic leaving group such as OH, OAc, CO_2R, $OPO(OR)_2$, OAr, Cl, Br etc, leading to the pyrans[149] via the π-allylpalladium cations followed by intramolecular attack of the hydroxy oxygen. From a stereochemical point of view, substrate-controlled cyclization usually proceeds with the retention of configuration of the reacting centre. Coordination of the palladium to the carbon-carbon double bond occurs on the less hindered side and opposite to the leaving group. In this context, Trost *et al*. demonstrated that intramolecular asymmetric allylic alkylation of hydroxy alkenes can be highly enantioselective, with the nucleophilic addition of the

alcohol to the π-allylic cation being the enantio-determining step of the process. Indeed, treatment of the hydroxy alkene **238** (R = H) with $Pd_2(dba)_3.CHCl_3$, chiral diphosphine ligand **L-7**, and Et_3N provided the tetrahedropyran **241**. Moreover, the chiral starting material **238** (R = CH_2OCOPr) with **L-7** gave the tetrahydropyran *trans*-**239** or isomer *cis*-**240**, exclusively, by switching the configuration of **L-7 (**Scheme 74).[150] High stereochemical control has also been observed in δ-hydroxy alkenes containing other allylic leaving groups.[151]



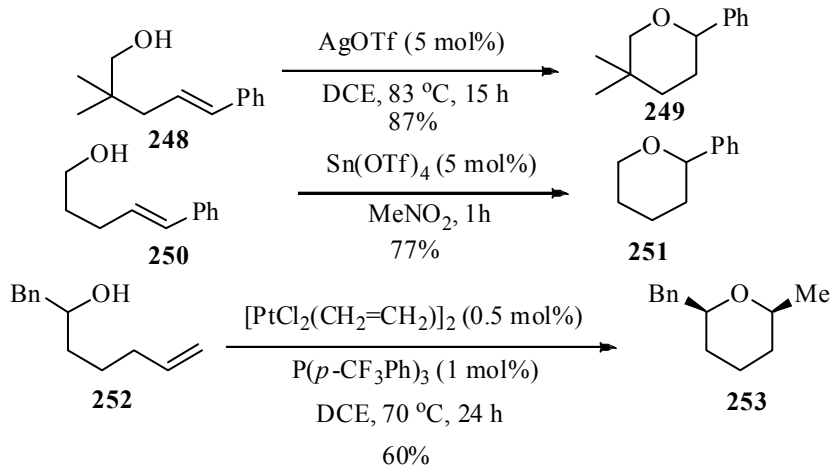
Scheme 74. Pd(0)-Catalyzed asymmetric alkylation of hydroxy alkenes to pyrans

Similar to Pd(0)-complexes, Pd(II) complexes also catalyze the intramolecular cyclization of hydroxy alkenes.[152] By applying this strategy, Antiosteoporotic diarylheptanoids (-)-diospongins A and B were synthesized stereoselectively. The key steps in the synthesis is the stereospecific $PdCl_2$ catalyzed oxycyclization of chiral 1,5,7-trihydroxy-2-heptenes, **242** and **245**, to form *cis* and *trans* tetrahydropyran rings **243** and **246,** respectively, depending upon the the configuration of the allylic stereocentre (Scheme 75). The regioselective Wacker oxidation of **243** and **246** gave (-)-diospongins A and B, respectively.[153] This strategy has also been applied to the constraction of various pyran ring system,[154] present in many natural products.



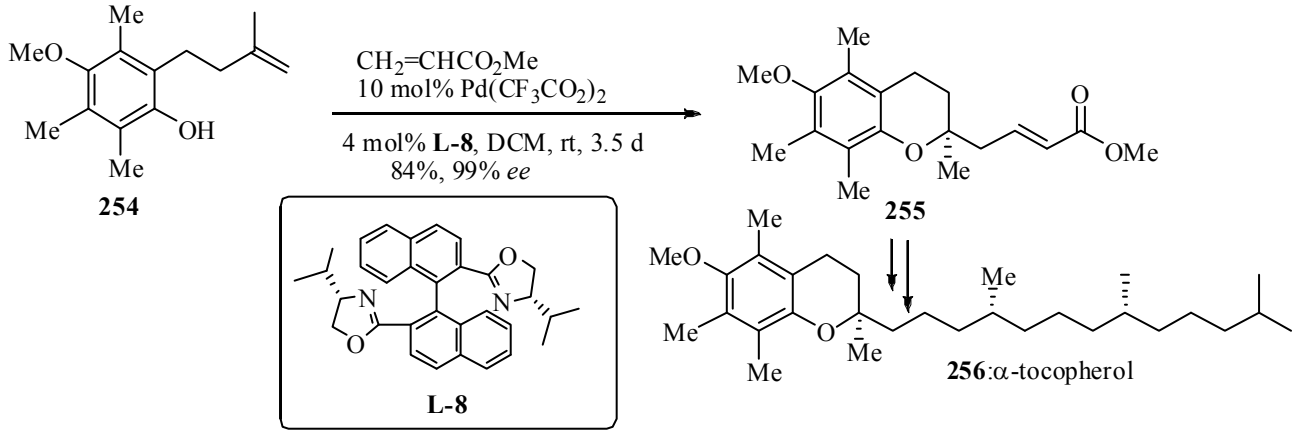
Scheme 75. Regioselective synthesis of (-)-diospongins A and B

Besides palladium, other metal complexes such as platinum,[155] tin,[156] cerium,[157] silver[158] have been successfully used for the cyclization of δ- and γ-hydroxy alkenes, based on the activation of the olefin, followed by a 6-*endo* cyclization (Scheme 76).



Scheme 76. Ag, Sn and Pt-Catalyzed cyclization of δ - and γ-hydroxy alkenes to pyrans

It has been observed that the intermediate, σ-alkylpalladium(II) can be trapped by CO and the resulting acylpalladium species is easily converted into the corresponding methylester. This methodology has been successfully applied to the synthesis of leucascandrolide **A** and phorboxazole.[159] The σ-alkylpalladium

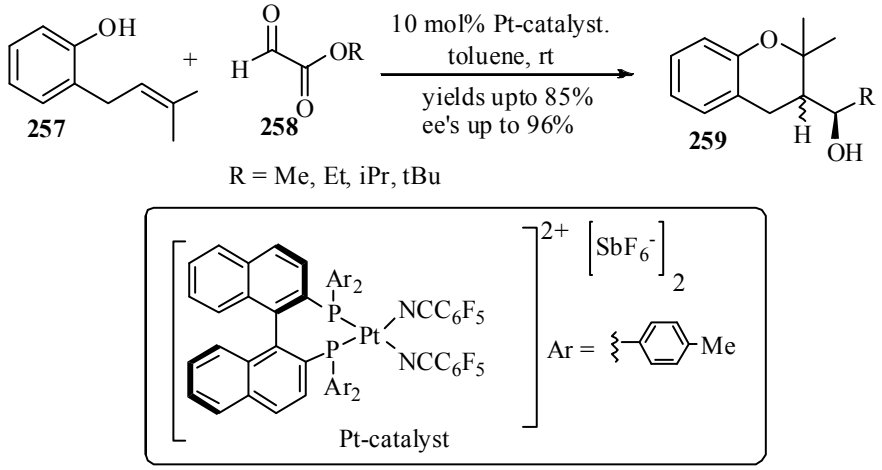


Scheme 77. Pd-Catalyzed sequencial synthesis of α-tocopherol

intermediate can also be trapped through a Heck reaction.[160] This possibility is illustrated by a palladium-catalyzed sequence synthesis of α-tocopherol. The reaction of phenol **254** with methyl acrylate in the presence of catalytic amounts of $Pd(OCOCF_3)_2$, the chiral ligand **L-8**, and BQ afforded chroman **255** (Scheme 77).

Recently, Gagne *et al*. disclosed[161] a Pt-based catalyst, which catalyzed the highly enantioselective Prins reaction between 2-allylphenol **257** and glyoxylate esters **258** to provide the Prins product **259** (Scheme

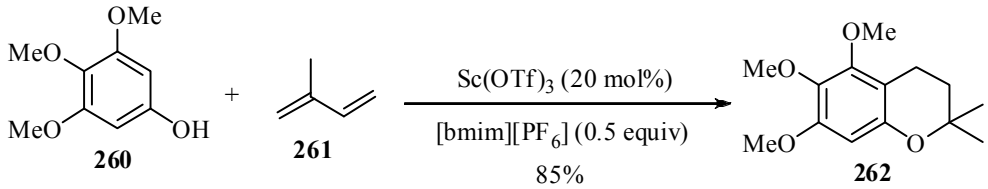
78). Enantiomeric excess (*ee*) of the product depends upon the R group of the ester. However, treatment with Lewis acid gave only Prins reaction product, homoallylic alcohols.



Scheme 78. Pt-Catalyzed enantioselective Prins reaction between 2-allylphenol and glyoxylate esters.

Perumal *et al*. observed[162] that indium trichloride and triphenyl phosphonium perchlorate (TPP) are very effective catalyst for the cyclization of *o*-hydroxyaldimines with 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran, and afforded *cis*-pyrano and furobenzopyran ring system, respectively. In a related reaction Yadav *et al.* observed that use of $Sc(OTf)_2$ as a Lewis acid gave *trans*-fused pyranobenzopyrans, stereoselectively.[163]

Atom economical sequential C-C/C-O bond formations between phenols and dienes using the reusable catalyst $Sc(OTf)_3$ and an ionic liquid $[bmim][PF_6]$ have been developed by Youn for the synthesis of a variety of dihydrobenzopyran and dihydrobenzofuran ring systems in good yields (Scheme 79).[164] In this reaction ionic liquid plays an important role as not only an efficient additive but also an immobilizing agent for facilitating the catalysis.



Scheme 79. Sc-Catalyzed synthesis of dihydrobenzopyran

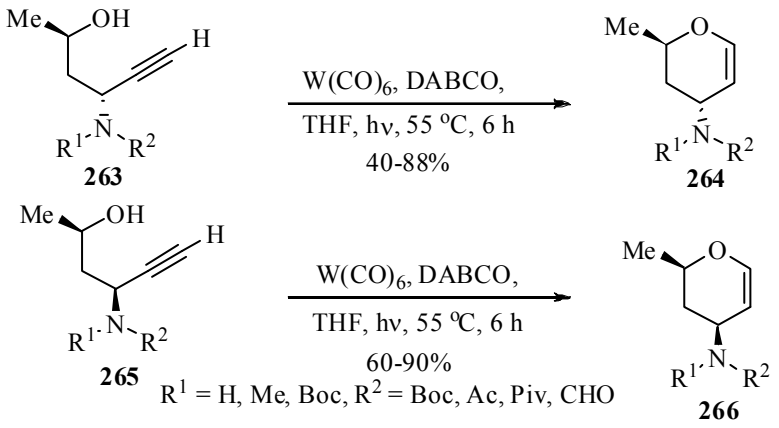
Tanaka *et al*. recently reported the $[Rh(cod)_2]BF_4$/(*R*)-H_8-binap complex catalyzed [2+2+2] cycloaddition of 1,6-enynes with electron-deficient ketones to give fused dihydropyrans containing two quaternary carbon centers with excellent regio-, diastereo-, and enantioselectivity.[165] However, the reaction of electron-rich aryl ketones with 1,6-enynes in the presence of the same catalyst gave *ortho*-functionalized aryl ketones with excellent regio-and enantioselectivity.

4. 2 SYNTHESIS FROM ALKYNES: CYCLIZATION OF ALCOHOLIC-, BENZYLIC-, CARBONYL- AND EPOXY-OXYGEN TO ALKYNES

The transition metal catalyzed isomerization of 4-hydroxy terminal alkynes represent a highly valuable route to 3,4-dihydro-2*H*-pyrans.[166] The reaction proceeds through the vinylidene intermediate that undergoes intramolecular attack by alcohol oxygen.

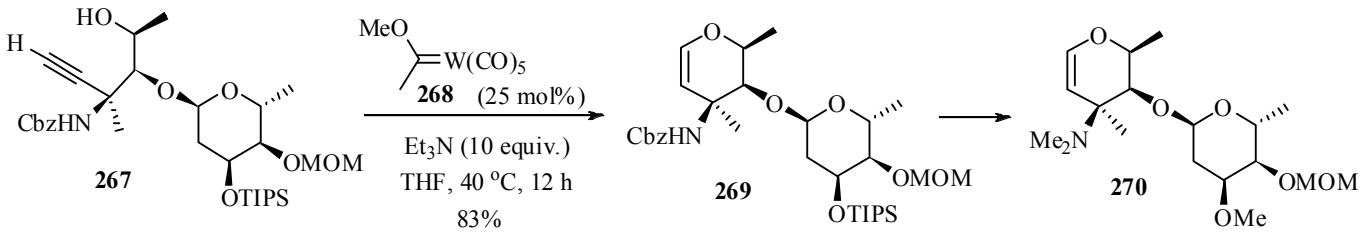
Tungsten has also attracted much attention. The most common tungsten complex used for the cycloisomerization of 4-alkynols is $W(CO)_6$ which is photochemically activated in situ to generate the true catalytic species, presumably $W(CO)_5$.[167] The methodology has been successfully applied to the construction of the trisaccharide component of digitoxin.[168]

Stereoselective synthesis of D-desosamine diacetate ester was achieved from the glycal which is obtained by tungsten carbonyl catalyzed exclusive 6-*endo*-cycloisomerisation of the corresponding N-protected amino alkynol. The cyclization reaction proceeds smoothly with both diastereoisomers of the alkynol substrates **263** and **265** in the presence of 5-15 mol% of catalyst to afford the glycal cycloisomerization products **264** and **266**, respectively (Scheme 80). [169]



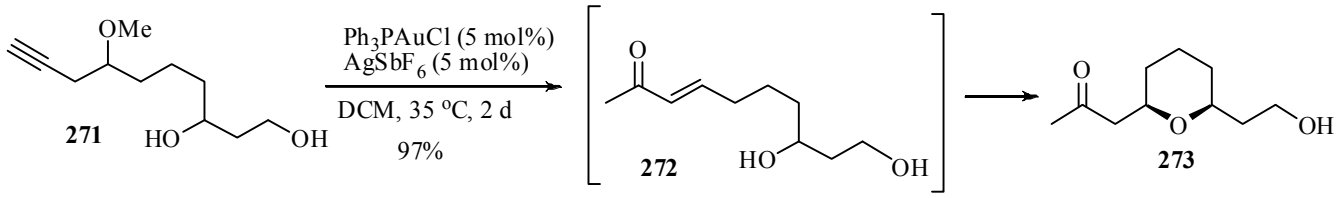
Scheme 80. W-Catalyzed cycloisomerisation of the N-protected amino alkynols

Recently, McDonald *et al*. reported[170] a new catalyst system **268** that does not require photochemical activation. The optimal results are obtained with 25 mol% of oxacarbene **268** in the presence of Et_3N (10 equiv.) by simple warming at 40 °C in THF (Scheme 81). The methodology has been successfully applied to the synthesis of altromycin disaccharide **270**.



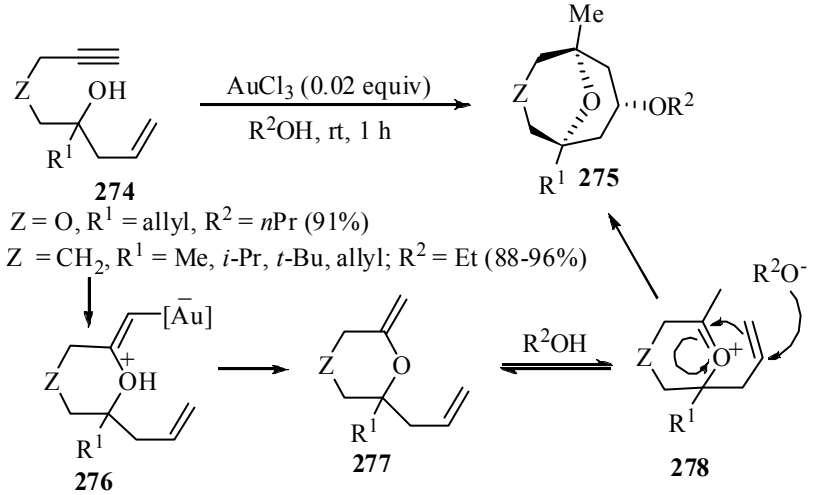
Scheme 81. W-Catalyzed synthesis of altromycin disaccharide

Treatment of homopropargylic ether **271** with Ph_3PAuCl (5 mol%) and $AgSbF_6$ (5 mol%) in wet DCM generated the enone intermediate which underwent cyclization to 2,6-*cis*-tetrahydropyran **273** in excellent yield (Scheme 82).[171]



Scheme 82. Au-Catalyzed synthesis of 2,6-*cis*-tetrahydropyrans

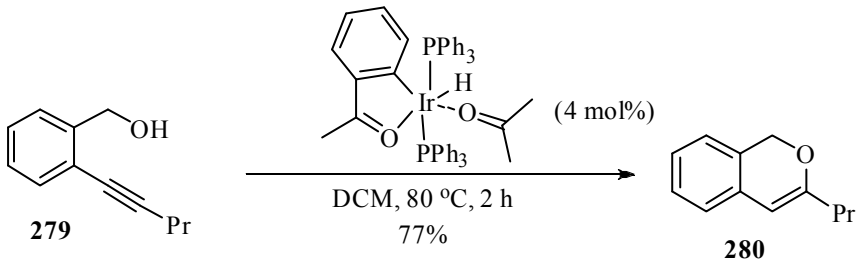
5-Alkynols with a terminal triple bond undergo complete regioselective 6-*exo*-dig ring closure to exocyclic enol ethers in the presence of palladium, iridium,[11] platinum[172] or gold.[173] For example, Barluenga *et al*. examined[173] the metal-catalyzed cycloisomerization of 1-en-8-yn-4-ols **274** using alcohol as the solvent (Scheme 83). The use of $AuCl_3$ or $PtCl_2$ catalyst smoothly catalyzes the domino reaction, leading to the bicyclic compounds **275** with incorporation of one molecule of solvent. The transformation has a low efficiency with AuCl, and was not observed with Ph_3PAuCl. Experiments carried out with deuteriated substrates and deuteriated alcohols supported the 6-*exo*-dig cyclization leading to an exocyclic enol **277**, which is in equilibrium with the oxocarbenium **278** under the reaction conditions. Finally a Prins-type cyclization occurred by the addition of the counterion to the C=C.



Scheme 83. Au-Catalyzed cycloisomerization of 1-en-8-yn-4-ols to bicyclic compounds

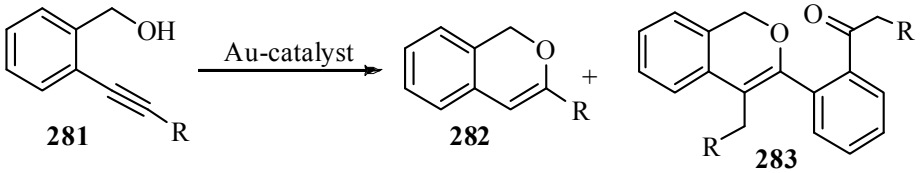
The homoallylic alcohols, carbonyl compounds and nitriles underwent a tandem Prins-Ritter type cyclization in the presence of $CeCl_3.7H_2O$/AcCl at ambient temperature to produce 4-amidotetrahydropyrans in high yields with *cis*-selectivity. Cyclic ketones gave spirocyclic 4-amidotetrahydropyrans.[174]

Intramolecular cyclization of benzylic oxygen to activated C≡C of 2-(1-alkynyl)-benzyl alcohol gave isochromenes. Recent reports on the cyclization of 4- and 5-alkynol have established the synthetic potentiality of such an approach. Palladium[175] and iridium[48] complexes catalyzed the 6-*endo*-dig ring closure of 2-alkynylbenzyl alcohol with internal triple bond to yield the corresponding isochromenes in good yield (Scheme 84).



Scheme 84. Ir-Catalyzed cyclization of 2-alkynylbenzyl alcohol to isochromenes

Recently, Hashmi *et al*. described related gold-catalyzed ring closure by C-H activation at the benzylic position of 2-(1-alkyknyl)-benzyl alcohol.[176] The substrates **281** underwent expected 6-*endo*-dig cyclization to give the isochromene derivatives **282**. When $AuCl_3$ was used as catalyst, the initially formed **282** underwent significant decomposition and conversion was low. However, Au(I)-catalyst, $[(Mes_3PAu)_2Cl]BF_4$ affords good conversion and good yields when the substituent R is sterically shielded. When the alkynyl moiety contains an additional nucleophilic group such as ester or amide function, the reaction leads to unexpected dimer products **283** along with the monomeric products **282,** with both the gold(I) and gold(III) catalysts. (Scheme 85)[176]



$AuCl_3$ (5 mol%): **282** (16-37%) and **283** (29-78%)
$[(Mes_3PAu)_2Cl]BF_4$ (2.5 mol%): **282** (36-48%) and **283** (33-37%)

Scheme 85. Au-Catalyzed cyclization of 2-alkynylbenzyl alcohol to isochromenes

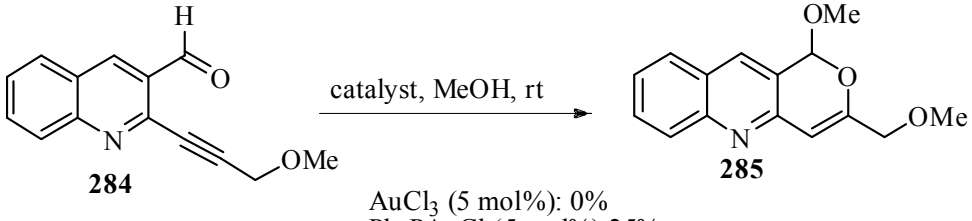
Electrophilic activation of unsaturated C-C bond of 2-alkynylbenzaldehydes and related systems, followed by the nucleophilic attack of the carbonyl oxygen on the activated alkene or alkynes yielded the benzopyran derivatives.[177, 178]

In this context, Yamamoto *et al*. reported the reaction of alkenyl aldehydes with methanol in the presence of Pd(II) catalyst to give a mixture of five- and six-membered alkenyl ethers.[179] However with alkynyl benzaldehyde, the cyclization in the presence of 5 mol% of $Pd(OAc)_2$, 1 equiv. of benzoquinone (BQ) and 2 equiv. of MeOH in 1,4-dioxane gave exclusively six-membered product in moderate yield.[180] It is to

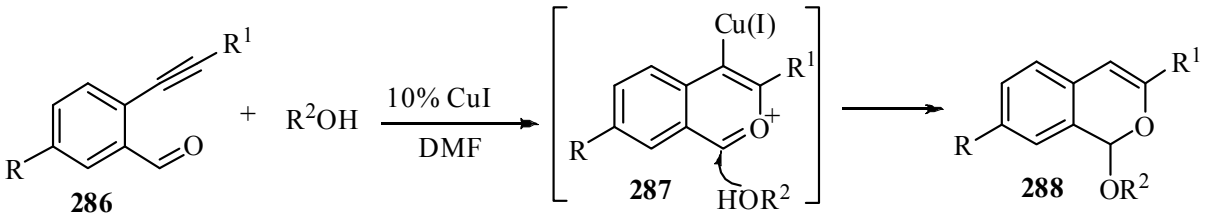
note that in this transformation $Pd(OAc)_2$ played dual role both as a Lewis acid for enhancing the electrophilicity of aldehyde as well as a transition metal catalyst for enhancing the electrophilicity of the alkyne bond, for constructing the (*R*)-methoxycyclic alkenyl ether from the *o*-alkynylaryl aldehyde.

Belmont *et al*. have recently disclosed the synthesis of pyranoquinolines **285** from the Au-catalyzed reaction between 1-alkynyl-2-carbonyl-quinolines **284** and methanol (Scheme 86).[181] No reaction or low yields were obtained using $AuCl_3$ or Ph_3PAuCl as the catalyst. The acetalization/cycloisomerization process was efficiently promoted with a 1:1 mixture of Ph_3PAuCl and $AgSbF_6$. Similar result was also obtained by using silver salt.

Subsequently, Yamamoto *et al* utilized CuI in DMF for similar cyclization of alkenyl ethers from acetylenic aldehydes.[182] It is proposed that the resonance-stabilized oxonium ion **287** formed by the nucleophilic attack of the aldehydic oxygen to the copper coordinated alkynes, is being trapped by alcohols to give the desired products (Scheme 87). Recently, Yao and Li[183] developed a highly efficient gold-catalyzed Grignard-type alkynylation of *ortho*-alkynylaryl aldehydes with terminal alkynes in water. In this reaction, terminal alkynes **290** reacted with *ortho*-alkynylaryl aldehydes **289** by the application of

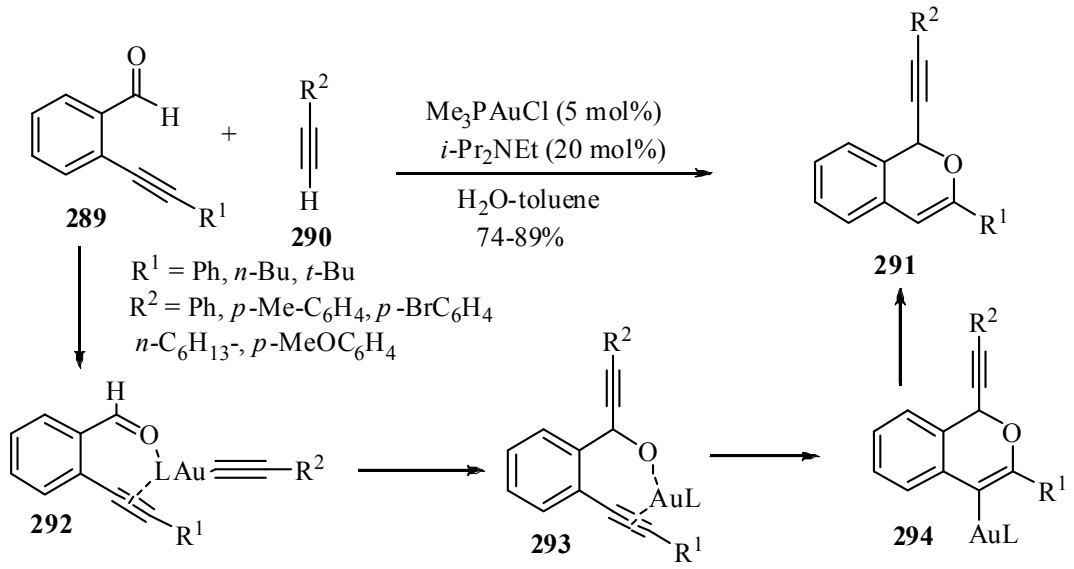


Scheme 86. Au-Catalyzed reaction of 1-alkynyl-2-carbonyl-quinolines to pyranoquinolines



Scheme 87. Cu-Catalyzed reaction of 2-acetylenic benzaldehydes to isochromene derivatives

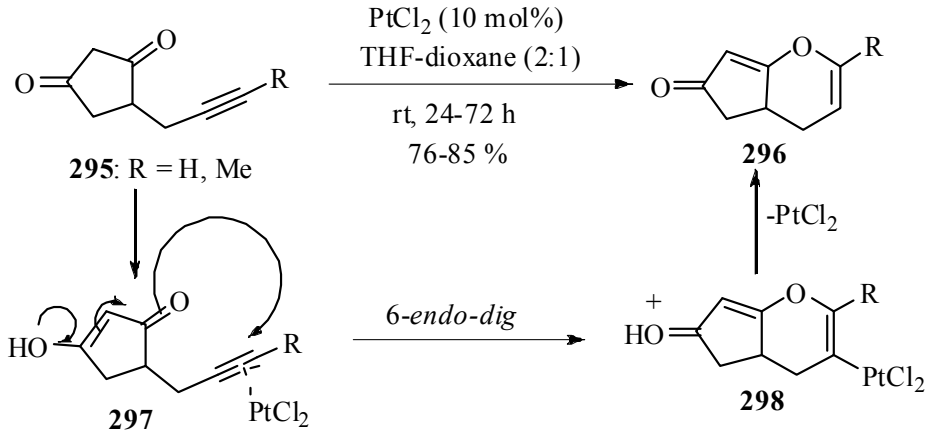
5 mol% of Me_3PAuCl and 20 mol% of *i*-Pr_2NEt as base in toluene and H_2O mixture to afford 1-alkynyl-1*H*-isochromene derivatives **291** (Scheme 88).



Scheme 88. Au(I)-Catalyzed synthesis of 1-alkynyl-1*H*-isochromene derivatives

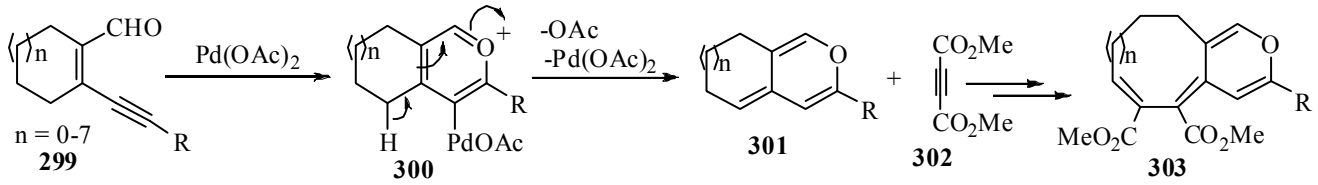
The reaction was found to be dually promoted by an electron-donating phosphine ligand and the presence of the *ortho*-alkynes. Presumably, alkynyl gold intermediate which is formed in the presence of base, may add to the aldehyde **289** to form intermediate **292**. The resulting secondary alcohol **293** may then undergo an intramolecular *trans*-oxyauration, and protodeauration to give the isochromene **291** (Scheme 88).

It has also been observed that 4-propargyl-1,3-cyclopentanediones **295** gave exclusively bicycles **296** upon treatment with 10 mol% $PtCl_2$ at room temperature (Scheme 89). These 6-*endo*-dig cyclizations are supposed to proceed under kinetic control by coordination of the catalyst to the triple bond.[65a] Palladium acetate catalyzed reaction of enynals **299** with dimethyl acetylenedicarboxylate **302** produces the pyran derivatives **303**, fused with medium and large rings (n = 0-7). The key step of this reaction is the intramolecular oxycyclization of **299** by $Pd(OAc)_2$, to give an electron rich olefin **300**, which undergoes cycloaddition reaction with **302** in the presence of an additive and subsequent ring expansion may give



Scheme 89. $PtCl_2$-Catalyzed cycloisomerization of 4-propargyl-1,3-cyclopentanediones to bicyclicpyrans

the product **303** (Scheme 90).[184] However, in the absence of an additive cycloaddition product is obtained in poor yield.

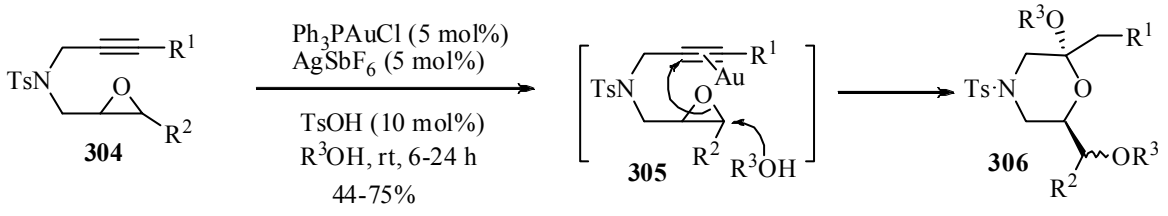


R = Ph; n = 1, 56 % (additive COD) and 69 % (additive norbornadiene)

Scheme 90. $Pd(OAc)_2$-Catalyzed synthesis of pyran derivatives fused with medium to large rings

A new palladium-catalyzed chemoselective cycloisomerization of *cis*-2,4-diene-1-als to 4-alkylidene-3,4-dihydro-2*H*-pyrans was reported by Liu *et al*.[185] The reaction is carried out in the presence of $PdCl_2(C_6H_5CN)_2$ in toluene and is found to be very much efficient for the construction of 2*H*-pyranderivatives.

Shi *et al*. disclosed gold catalyzed ring-opening of epoxides **304**, which can undergo highly regio- and diastereoselective cascade double intermolecular addition of alcohol to alkyne to give 2,6-*trans*-substituted morpholines **306** (Scheme 91).[186] A possible mechanism involves alcohol addition to the complex **305** formed by the coordination of both the triple bond and the oxirane, followed by protodeauration, and re-coordination to promote the addition of a second molecule of alcohol.

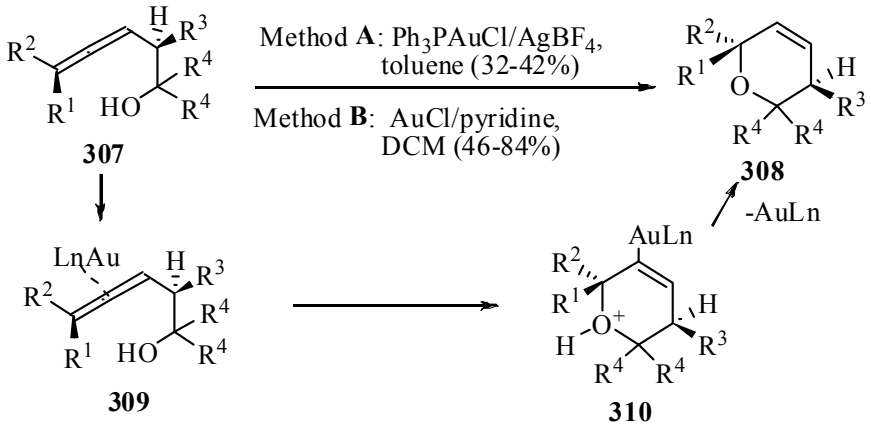


R^1 = H, Me; R^2 = H, Ph; R^3 = Me, Et, *i*Pr, allyl

Scheme 91. Au(I)-Catalyzed ring-opening of epoxides to 2,6-*trans*-substituted morpholine

4. 3 SYNTHESIS FROM ALLENES

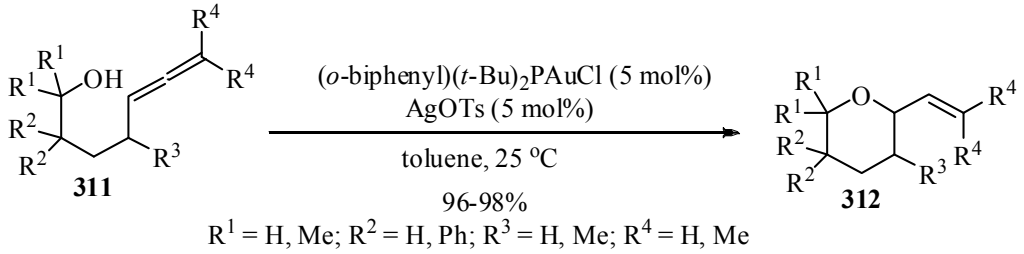
Allenes containing a nucleophile can undergo intramolecular cyclizations on treatment with transition metal catalysts. In particular, gold-catalyzed cycloisomerization of β-hydroxy or γ-hydroxyallenes give access to six-membered oxygenated heterocycles. Krause and co-workers showed[89b] that β-hydroxyallenes and β-aminoalllene can readily be converted to the corresponding chiral dihydropyrans and tetrahydropyridine in good yields via stereoselective gold(I)-catalyzed or gold(III)-catalyst 6-*endo* cycloisomerizations. The increase in products by the addition of 3-hydroxypropionitrile or $AgBF_4$, may be due to the formation of cationic gold species.



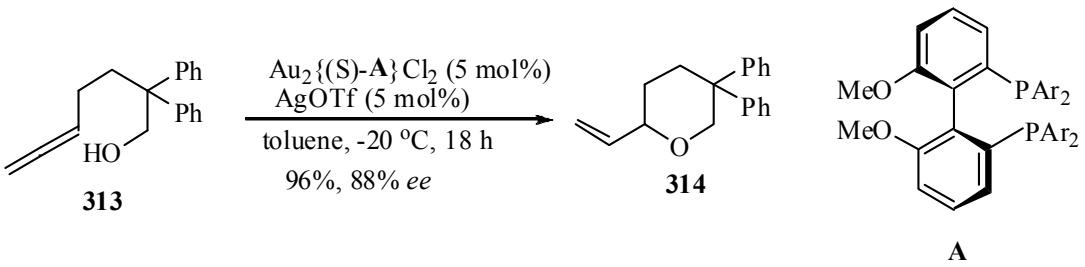
Scheme 92. Au-Catalyzed cycloisomerization of β-hydroxyallenes to pyran derivatives

But in the case of gold(I) chloride, the addition of pyridine or 2,2′-bipyridine induced a remarkable increase of the reactivity. The chiral transfer observed for the β-hydroxyallenes **307** to the dihydropyrans **308** could be explained by the coordination of the gold catalyst to the terminal double bond of the allene **307** resulting in the formation of **309** which upon nucleophilic attack of the oxygen, is conducted into the δ-gold complex **310**. Protodemetalation of the latter provides the heterocyclic product **308** and releases the gold catalyst into the catalytic cycle (Scheme 92).

A number of 2-alkenyl tetrahydropyrans **312** was prepared from 5,6-heptadien-1-ols **311** under achiral experimental conditions, catalyzed by cationic gold complex, (*o*-biphenyl)(*t*-Bu)$_2$PAuCl (Scheme 93).[94] Remarkably, gold-mediated hydroalkoxylation of **313** in the presence of the chiral diphosphine Au$_2${(*S*)-**A**)}Cl$_2$ (5 mol%) afforded **314** (Scheme 94).[95]



Scheme 93. Au-Catalyzed synthesis of pyrans under achiral conditions

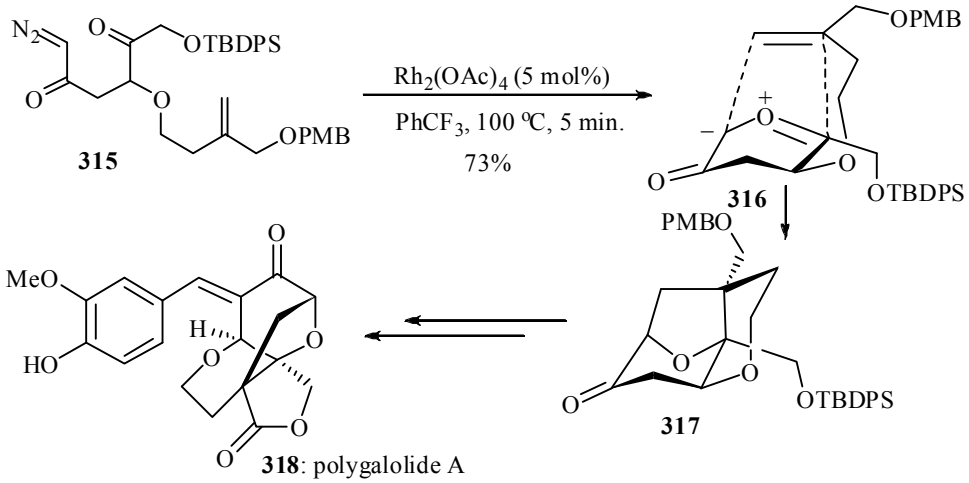


Scheme 94. Au-Catalyzed synthesis of to pyrans under chiral conditions

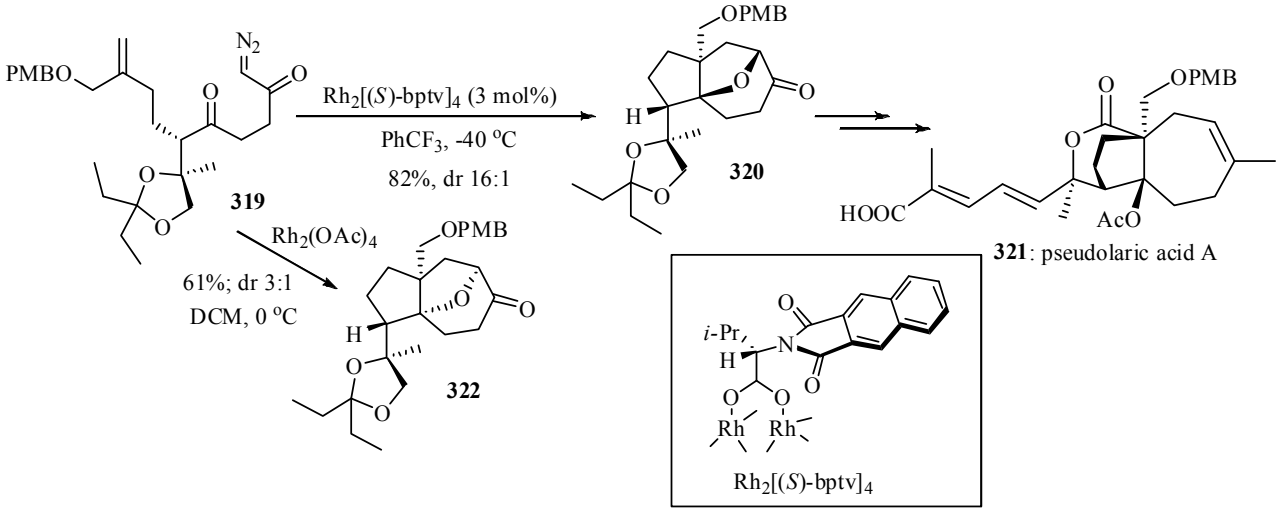
4. 4 SYNTHESIS FROM DIAZO COMPOUNDS

Catalytic conversion of the diazo groups into the corresponding metal carbenes followed by intramolecular reaction with alcohol, ether, or carbonyl compounds afford a wide variety of oxygenated heterocycles.[187]

The use of carbonyl as oxygenated nucleophiles produces carbonyl ylide from the attack of the oxygen atom of C=O bond on the metal carbene. This carbonyl ylide undergoes 1,3-dipolar cycloaddition to give oxygenated heterocycles. By applying this methodology structurally complex natural products such as zaragozic acid C[188] and polygalolide A[189] have been synthesized. The intramolecular trapping of the carbonyl ylide, obtained from α-diazo ester **315** by treatment with $Rh_2(OAc)_4$ (5 mol%), by internal alkene gave the cycloadduct **317** as a single diastereoisomer, from which polygalolide A (**318**) was obtained after several steps (Scheme 95). Similarly, Geng *et al*. achieved[190] the enantioselective synthesis of diastereoisomer **320** as the major product from the α-diazo ketone **319** by treatment with a chiral Rh-catalyst, Rh_2[(*S*)-bptv]$_4$, whereas in the presence of achiral rhodium catalyst the oxatricyclic compound **322** was obtained as the major product (Scheme 96).



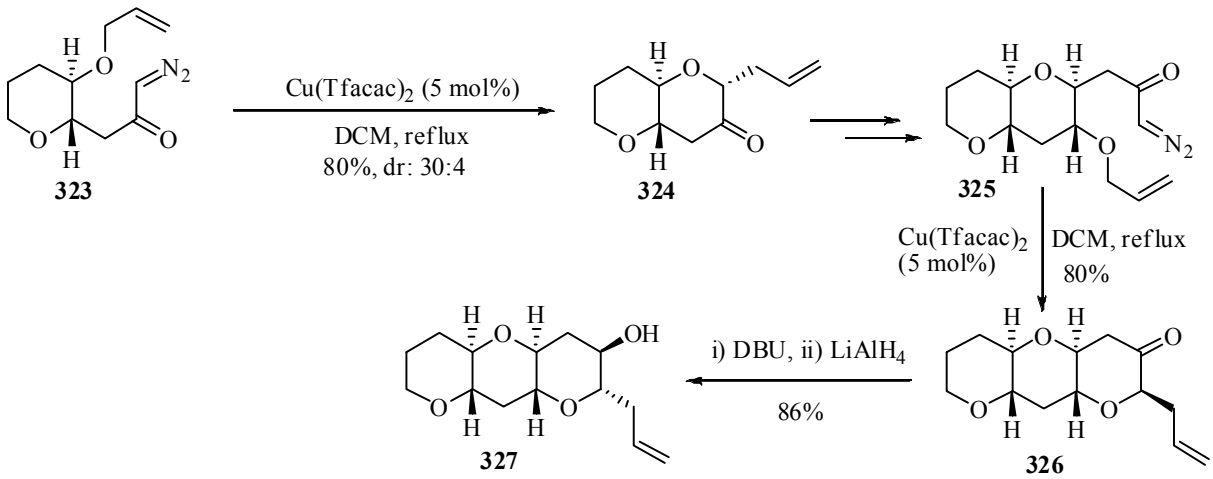
Scheme 95. Rh-Catalyzed diastereoselective synthesis of polygalolide A from α-diazo ketone



Scheme 96. Rh-Catalyst enantioselective synthesis of pseudolaric acid A from the α-diazo ketone

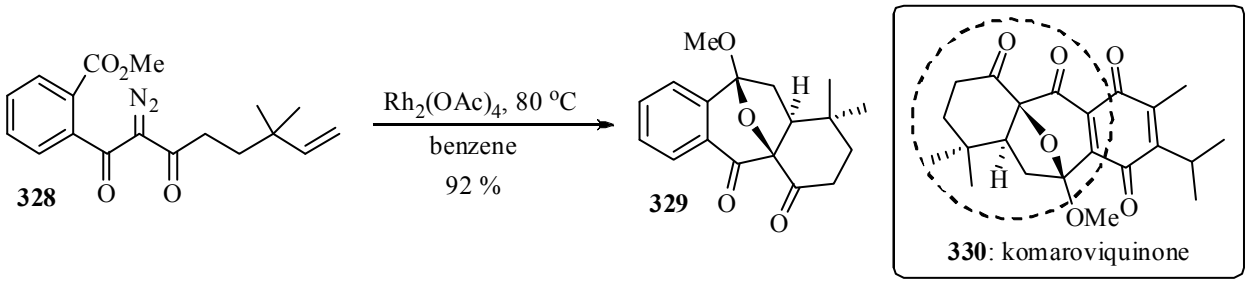
The ether nucleophile also reacts with metal carbenes via an oxonium ylde intermediate to give six-membered oxygenated heterocycles.[191] For example; copper-catalyzed cyclization of diazo ketones containing allyl ether has been applied to the synthesis of natural products. Treatment of O-allyldiazo ketone **323** with $Cu(tfacac)_2$ provides the bicyclic compound **324** in excellent diastereomeric ratio. Epimerization to more stable isomer followed by reduction and further functional group manipulations afford the diazo ketone **325**. This diazo compound after a second cyclization-epimerization-reduction sequence gave polyether **327** via **326** (Scheme 97).[192]

In a similar approach, Padwa *et al*. utilized ester carbonyl as a nucleophile towards the synthesis of icetexane core of komaroviquinone **330** using a rhodium(II)-catalyzed cyclization/cycloaddition sequence as the key step.[193] The ylide generated by the cyclization of rhodium carbenoid intermediate onto the



Scheme 97. Cu-Catalyzed cyclization of α-diazo ketones to polyether

proximal ester group, followed by intramolecular dipolar-cycloaddition of the carbonyl ylide dipole across the tethered π-bond afforded cycloadduct **329** (Scheme 98).

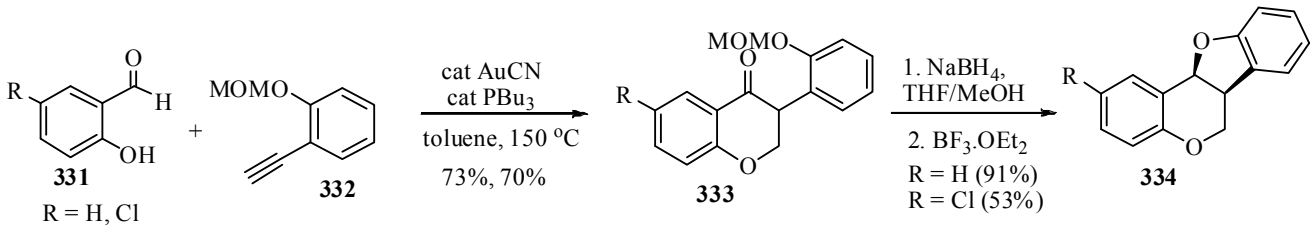


Scheme 98. Rh(II)-Catalyzed synthesis of icetexane core of komaroviquinone

4. 5 SYNTHESIS OF PYRANONES

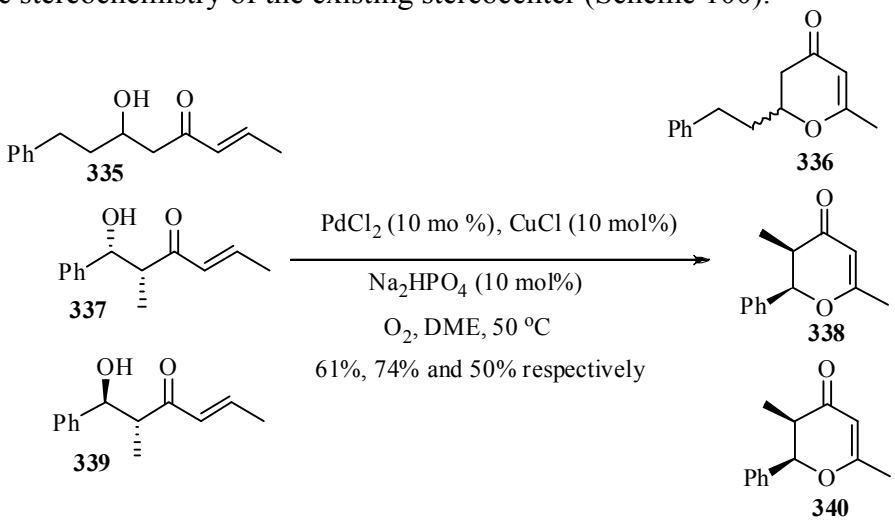
A novel annulation of simple *o*-hydroxyaldehydes with alkynes catalyzed by gold (I) catalyst gives isoflavanones. The best yield for this annulation was obtained by using 1 mol% of AuCN and 25 mol% of

PBu_3.[194] The annulation efficiently generates isoflavanone-type structures with many possible applications in the synthesis of isoflavanone natural products. By applying this strategy, recently, Li *et al*. reported[195] an efficient two steps procedure for the synthesis of (±)-pterocarpan and isoflavone[196] natural products. To synthesize (±)-pterocarpans **334**, salicylaldehydes **331** and 2-(methoxymethoxy)-1-ethynylbenzene **332** were treated with AuCN in the presence of PBu_3 in toluene at 150 °C, to give the desired isoflavanone **333**, followed by reduction with $NaBH_4$ and addition of excess $BF_3.OEt_2$ afforded (±)-pterocarpans **334** (Scheme 99). The tentative mechanism for the novel annulation is similar to the previous mechanism discussed in Scheme 88.



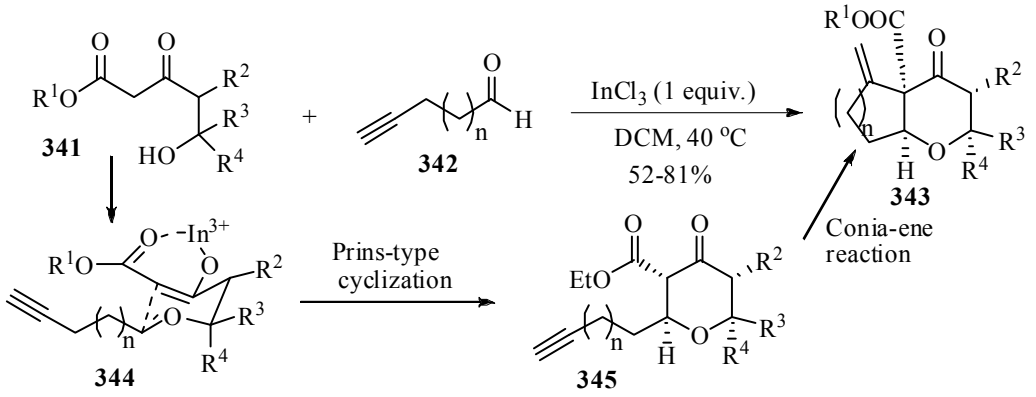
Scheme 99. Au(I)-Catalyzed synthesis of (±)-pterocarpans

The oxidative cyclization of β-hydroxy enones with $PdCl_2$ gave 2,3-dihydro-4*H*-pyranones.[197] This methodology represents a new approach to the enantioselective synthesis of pyranones based on the 6-*endo* ring closure of Pd(II)-complex followed by complete regioselective β-hydride elimination, without disturbing the stereochemistry of the existing stereocenter (Scheme 100).



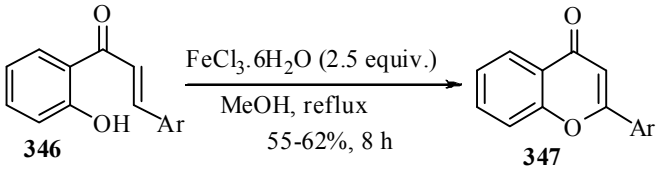
Sccheme 100. Enantioselective synthesis of pyranones by Pd(II)-catalyzed reactions

A one pot, two components $InCl_3$-mediated cascade reaction between β-keto esters **341** and alkynals **342** gave highly functionalized 1-oxadecalins **343** in good yields and excellent diastereoselectivity.[198] The high diastereoselectivity could be rationalized by the six-membered chair-like transition state **344**, which on Prins-type cyclization gave tetrahydropyran. The subsequent Conia-ene reaction leads to *cis*-oxadecalin ring junction selectively (Scheme 101).



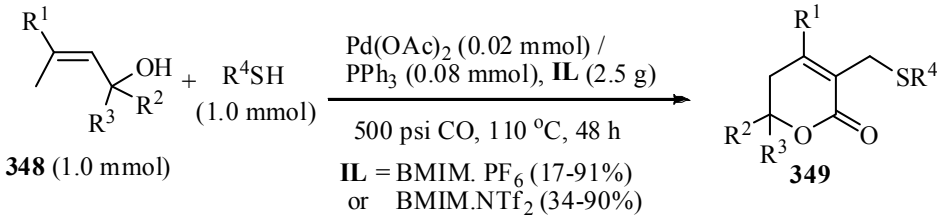
Scheme 101. In(III)-Mediated synthesis of highly functionalized 1-oxadecalins

When 2'-hydroxychalcones **346** was treated with 2.5 equivalent of $FeCl_3.6H_2O$ in refluxing MeOH for 8 h, the O-heterocyclization occurred to give the corresponding flavones **347** (Scheme 102).[199]



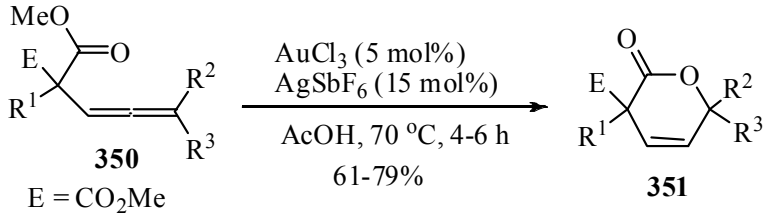
Scheme 102. Fe(III)-Catalyzed synthesis of flavones from 2'-hydroxychalcone

A novel palladium-catalyzed cyclocarbonylation and thiocarbonylation reaction of allylic alcohols with thiols afford double carbonylated products, thioester-cotaining 6-membered-ring lactones using THF as solvent.[200] The effect of ionic liquids on this palladium-catalyzed carbonylation of enols with thiols was also studied.[201] The reaction of allylic alcohols with a variety of thiols under 500 psi of carbon monoxide in the presence of a catalytic amount of $Pd(OAc)_2$ (2 mol%) and PPh_3 (8 mol%) in ionic liquid, BMIM.PF_6 or BMIM.NTf_2 gave chemoselectivly monocarbonylated products **349** in variable yields (Scheme 103).[201]



Scheme 103. Effects of ionic liquids on Pd-catalyzed carbonylation of enynols with thiols

Backvall *et al.* reported[202] the cyclization of allene-substituted malonates leading to β,γ-unsaturated δ-lactones by $AuCl_3$ catalyzed intramolecular nucleophilic attack of the carboxy oxygen onto the allene. Indeed, the allenes **350**, on treatment with $AuCl_3$ (5 mol%) in the presence of silver salts $AgSbF_6$ (15 mol%) as additive in AcOH furnished β,γ-unsaturated δ-lactones **351** (Scheme 104). The other gold catalysts such as AuCl and $Au(PPh_3)_3Cl$ also furnished lactones in lower yields than $AuCl_3$.

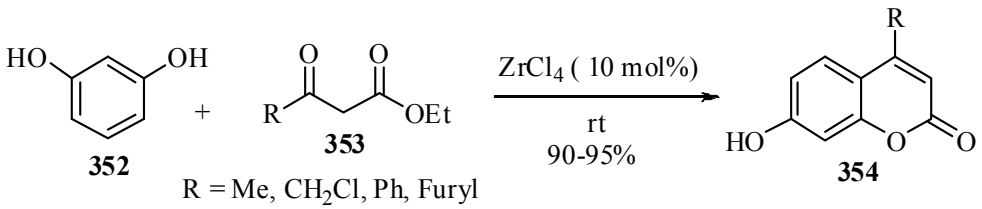


Scheme 104. Au(III)-catalyzed cyclization of allene-substituted malonates to β,γ-unsaturated d-lactones

4. 6 SYNTHESIS OF COUMARIN DERIVATIVES

Bahekar *et al*. reported the Pechmann condensation using Sm(III) as the catalyst under solvent free conditions. $Sm(NO_3)_3.6H_2O$ (10 mol%) effectively catalyzed the reaction of ethyl acetoacetate and resorcinol at 80 °C to give 7-hydroxy-4-methylcoumarin in 98% yield.[203]

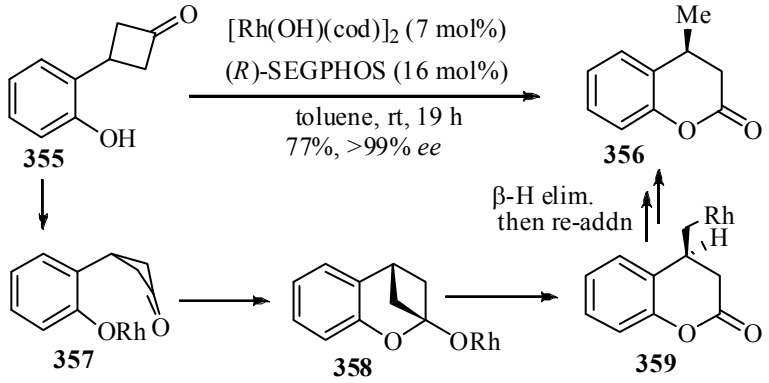
Sharma *et al*. observed[204] that an equimolecular mixture of resorcinol and β-ketoesters such as ethyl-4-chloroacetoacetate, ethyl benzoylacetate and ethyl furoacetate gave 4-substituted coumarins **354** in 90-95% yields on treatment with 10 mol% $ZrCl_4$ at room temperature under solvent free condition via Pechmann reaction (Scheme 105). Similarly, Kirsch *et al*. also synthesized coumarin derivatives by using zirconyl octahydrate (1 mol%) as a Pechmann catalyst.[205] $BiCl_3$ has also been found to be an efficient catalyst in the Pechmann condensation reaction of phenols with β-keto esters leading to the formation of coumarin derivatives under solvent free conditions.[206]



Scheme 105. Zr-Mediated synthesis of coumarins

Interestingly, Murakami *et al.* reported Rh(I)-catalyzed enantioselective synthesis of 3,4-dihydrocoumarin.[207] When 3-(2-hydroxyphenyl)cyclobutanone **355** was treated with a catalytic amount of a rhodium(I) catalyst, obtained in situ from $[Rh(OH)(cod)]_2$ (7 mol%) and (*R*)-SEGPHOS (16 mol%), in toluene at room temperature, 4-methyl-3,4-dihydrocoumarin **356** was obtained. BINAP and *Tol*- BINAP were also effective as the chiral ligand and gave 96% *ee* (Scheme 106).

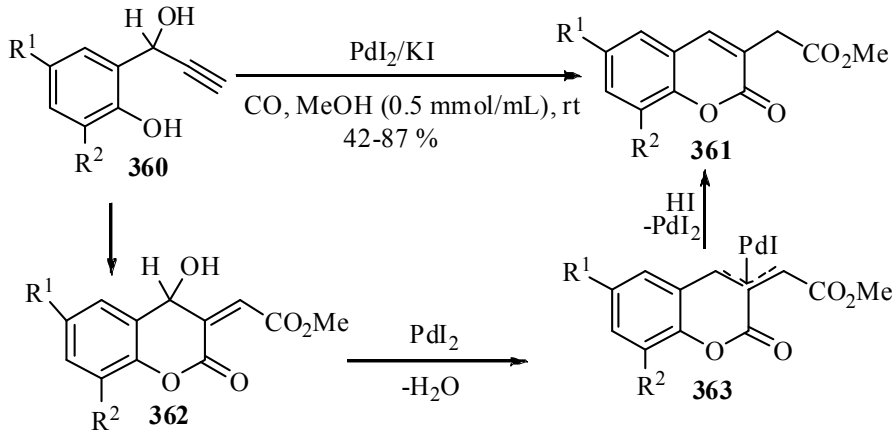
The proposed mechanism for the transformation involoves of the generation of rhodium aryloxide **357** followed by its addition to the carbonyl group to give the rhodium cyclobutanoate intermediate **358**. The ring opening of the cyclobutane skeleton may give intermediate coumarin derivative **359**, followed by a series of β-hydride elimination and re-addition afforded coumarin **356** (Scheme 106).



Scheme 106. Rh-Catalyzed synthesis of dihydrocoumarin

Larock *et al*. reported[208] that the palladium-catalyzed annulation of internal alkynes by *o*-iodophenol in the presence of CO employing 5 mol% $Pd(OAc)_2$, 2 equiv. of pyridine, and 1 equiv. of *n*-Bu_4NCl in DMF at 120 °C, afforded coumarin derivatives in moderate yields. The methodology was found to be very much effective for the simultaneous double annulation of 2,5-diiodo-1,4-hydroquinone.

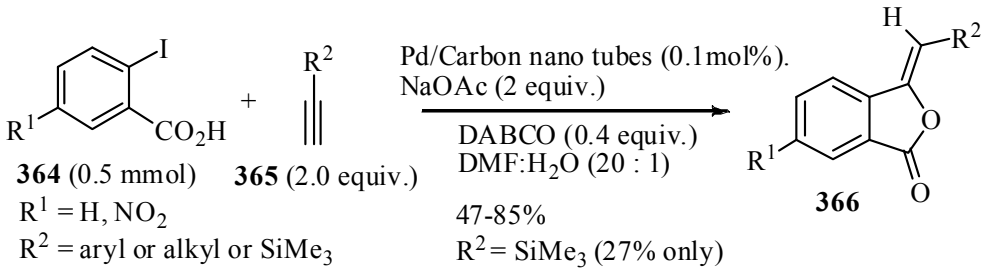
2-Allyloxyaryl-2yn-1-ols undergo deallylation to the corresponding 2-propargylphenols, catalyzed by Pd(0). The resulting 2-propargylphenols undergo Pd(II)-catalyzed heterocyclization-alkoxycarbonylation reactions with CO and MeOH, to give 2-benzofuran-2-ylacetic esters.[209] 2-(1-Hydroxyprop-2-ynyl)phenols **360** bearing a terminal alkyne selectively underwent a dicarbonylation reaction with the formation of 3-[(methoxycarbonyl)methyl]coumarins **361**.[210] The reaction was carried out in the presence of PdI_2 in conjugation with KI in MeOH at room temperature. However, a benzofuran derivative was obtained instead of coumarin in the case of propargyl phenol having an internal alkyne. The reaction may proceed through the formation of intermediate **362**, followed by elimination of water and protonolysis of allylpalladium complex by HI, leading to the coumarin derivatives **361** (Scheme 107).



Scheme 107. PdI_2-catalyzed synthesis of 3-[(methoxycarbonyl)methyl]coumarins

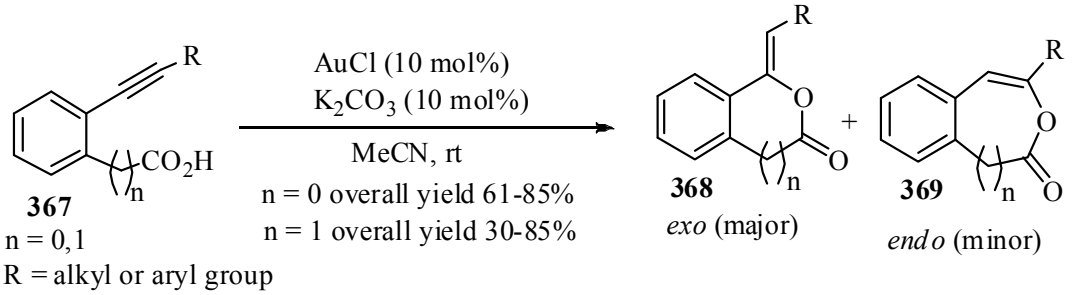
2-Ethynyl benzoic acid underwent metal-catalyzed cyclization to give a mixture of phthalides and isocoumarins.[211] Pal *et al*. reported that isocoumarins could be obtained as major products when *o*-

iodobenzoic acid was reacted with terminal alkynes in the presence of Pd/C-Et_3N-CuI catalytic system.[212] Jiang *et al*. described[213] a phosphine and copper free protocol for the synthesis of phthalides (major) and isocoumarins (minor), via Pd/carbon nanotubes-catalyzed tandem coupling-cyclization between *ortho*-iodobenzoic acids **364** and terminal alkynes **365**. Interestingly, when 5 mol% of H_2O was added to DMF as the solvents, phthalides **366** were isolated as the sole product (Scheme 108).



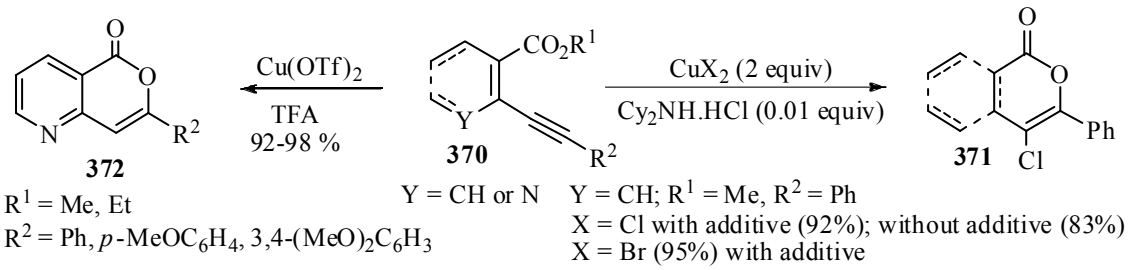
Scheme 108. Pd/carbon Nanotubes-Catalyzed synthesis of phthalides

Gold(I)-catalyzed intramolecular cyclization of γ-and δ-alkynes acids **367** gave various alkylidene lactones in high yields.[214] A slight electronic effect of the R group was observed on the regioselectivity of the cyclization. Bulky substituent on the R group bearing the alkyne strongly modifies the reactivity. The *exo*-dig mode of cyclization predominated. The lactones **368** were obtained as major product and as a single stereoisomer *Z*. The electron-rich group on the aromatic ring of R decreases the *exo* selectivity (Scheme 109). The cycloisomerization of methyl *o*-alkynylbenzoate with $AuCl_3$ in aqueous medium also furnished the isocoumarins exclusively, via 6-*endo* cyclization intermediate.[214]



Scheme 109. Au(I)-Catalyzed intramolecular cyclization of γ-and δ-alkynes acids to alkylidene lactones

Similarly, Li *et al*. utilized CuX_2 (X = Cl, Br) as catalyst to cyclize a variety of *o*-(alk-1-ynyl)benzoates and (*Z*)-alk-2-en-4-ynoate to the corresponding 4-haloisocoumarins and 5-halo-2-pyrone, respectively, in moderate to excellent yields.[215] It was observed that $Cy_2NH.HX$ could improve the rate of the reaction and the selectivity of the product.[216a] For example, in the presence of $CuCl_2$ (2 equiv.), cyclization of methyl 2-(2-phenylethynyl)benzoate **370** afforded the corresponding isocoumarin **371** in 83% yield, whereas the yield was enhanced to 92% when 0.1 equiv. of $Cy_2NH.HCl$ was added to the reaction mixture (Scheme 110).



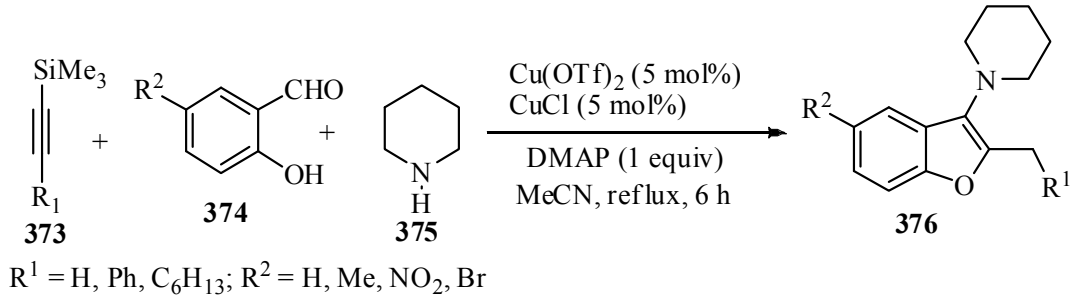
Scheme 110. Cu(II)-Catalyzed cyclization of *o*-(alk-1-ynyl)benzoates and (*Z*)-alk-2-en-4-ynoate

In a similar approach regiocontrolled cyclization of 2-(2-arylethynyl)heteroaryl esters **370** (Y = N) to isocoumarins in high yields was carried out through a 6-*endo*-dig cyclization.[216] The reaction was performed in the presence of a catalytic amount of Lewis acids such as $Cu(OTf)_2$, $AuCl_3$ or $(CF_3CO_2)Ag$ in combination with Brønsted acid, TFA under microwave irradiation. For example, the microwave irradiation of methyl nicotinate **370** (Y = N, R^1 = Me) in TFA in the presence of either $Cu(OTf)_2$ (5 mol%) or $AuCl_3$ (5 mol%) or CF_3CO_2Ag (5 mol%) gave the lactone **372** in 92%, 83%, 72% yield, respectively (Scheme 110). A range of *N*-heterocyclic esters underwent similar cyclization to the corresponding lactones in high yields by this protocol.

5. MISCELLANEOUS REACTIONS

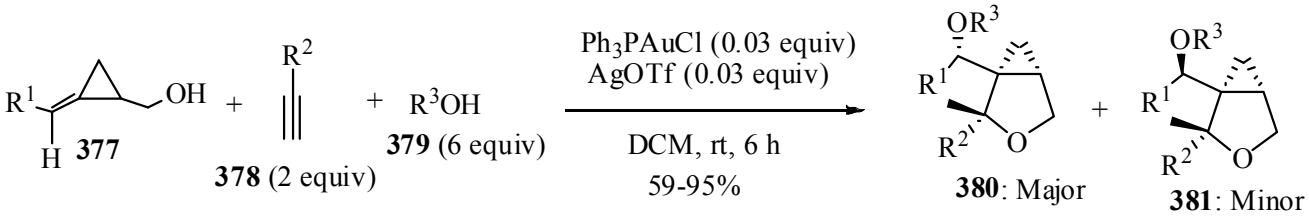
A novel three-component reaction gave access to new dihydrobenzofuran derivatives.[217] Indeed, the domino reaction of 2-iodophenol, methyl bromomethylacrylate and phenylboronic acid in the presence of $Pd(OAc)_2$, K_2CO_3 and *n*-Bu_4NCl in DMF at 80 °C provided 3,3-disubstituted 2,3-dihydro benzofuran in moderate yield. In a similar approach, a three-component coupling reaction of aliphatic or aromatic aldehydes, homoallylic alcohols and ammonium thiocyanate by $In(OTf)_3$ (10 mol%) gave 4-thiocyanotetrahydropyrans through heterocyclization in excellent yields with all *cis*-selectivity.[218]

The combination of 5 mol% $Cu(OTf)_2$ and CuCl in the presence of DMAP effectively catalyzed the coupling reaction involving an alkynylsilane **373**, an *o*-hydroxybenzaldehyde derivatives **374**, and a secondary amine **375**.[219] The reaction proceeded via intramolecular 5-*exo*-dig cyclization, resulting in the direct synthesis of the corresponding benzofuran derivatives **376** in moderate to excellent yields (Scheme 111). Recently, Shi *et al.* reported gold(I)-catalyzed condensation of (*E*)- and (*Z*)-2-(arylmethylene)cyclopropylcarbinols **377** with terminal alkynes **378** and alcohols **379** to afford 3-oxabicyclo[3.1.0]hexane (Scheme 112).[220] The mechanism of the addition reaction was confirmed by deuterium labeling and trapping of the intermediates. This reaction may proceed *via* intramolecular tandem hydroalkoxylation/Prins-type reaction pathway.



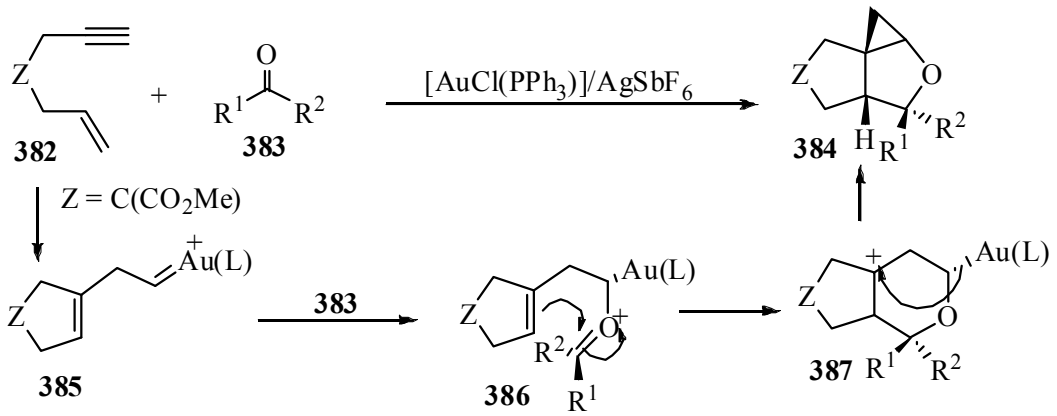
R^1 = H, Ph, C_6H_{13}; R^2 = H, Me, NO_2, Br

Scheme 111. Cu-Catalyzed three-component reaction for dihydrobenzofuran derivatives



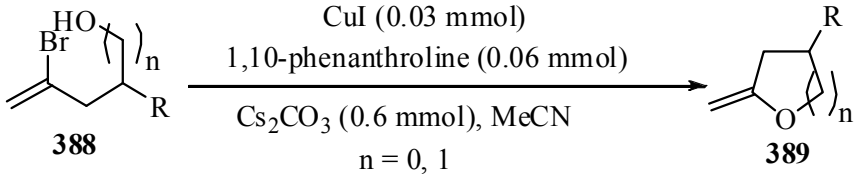
Scheme 112. Au(I)-Catalyze condensation reaction for 3-oxabicyclo[3.1.0]hexane

Helmchen *et al*. reported the first intermolecular gold-catalyzed addition of aldehydes and ketones to 1,6-enynes. The reaction proceeds smoothly with $[AuCl(PPh_3)]/AgSbF_6$ (5 mol%) to give the tricyclic oxygenated compounds **384** in high diastereoselectivity (Scheme 113).[221]



Scheme 113. Au-Catalyzed synthesis of tricyclic oxygenated heterocycles from 1,6-enynes

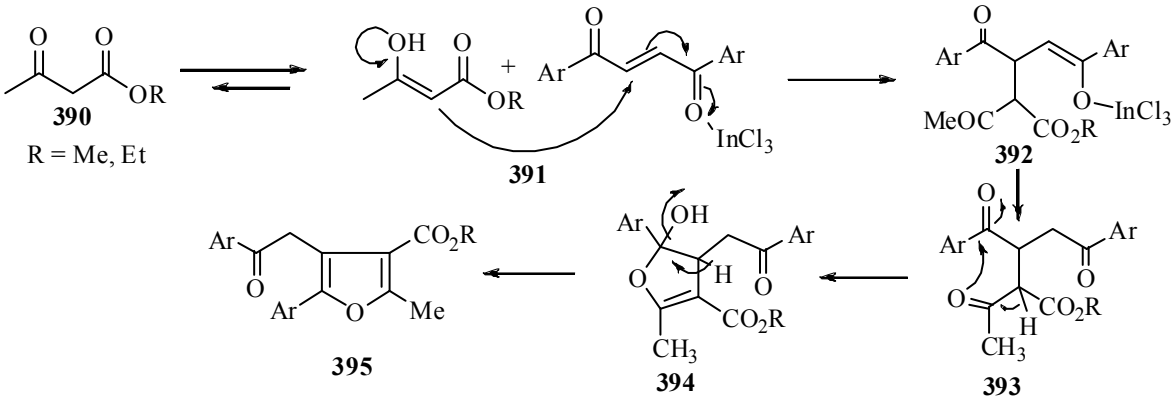
Li *et al.* reported[222] the synthesis of 2-methyleneoxetanes **389** by O-vinylation of γ-bromohomoallylic alcohols **388** with CuI as catalyst in the presence of 1,10-phenanthroline as ligand and Cs_2CO_3 as base in CH_3CN (intramolecular Ullmann Coupling, Scheme 114). The selectivity between 4-*exo* and 5-*exo* cyclization is completely reversed by changing the catalyst from Cu to Pd.



n = 0; R = -$(CH_2)_2$OBn (6 h, 82%); R = -$(CH_2)_3$OBn (3 h, 86%)
n = 1; R = *p*-Cl (11 h, 85%), X = *p*-OMe (11 h, 86%)

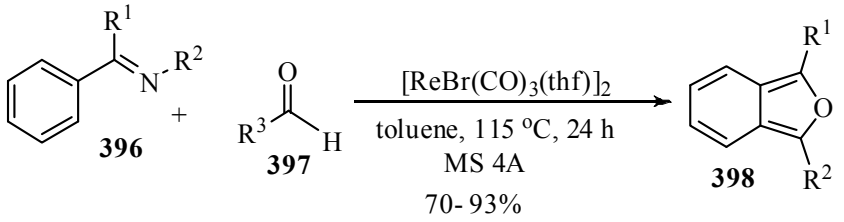
Scheme 114. CuI-Catalyzed synthesis of 2-methyleneoxetanes

Jaisankar *et al*. synthesized tetrasubstituted furan derivatives **395** by $InCl_3$-catalyzed reaction between but-2-ene-1,4-diones **390** and acetoacetate esters **391** using *i*-PrOH as solvent.[223] In this reaction but-2-ene-1,4-diones act as Michael acceptors and acetoacetate esters as the nucleophiles resulting in Michael adduct **392** which under the influence of $InCl_3$, formed the hemiacetal **393** followed by spontaneous dehydration afforded furans **395** in 78-90% yields (Scheme 115).



Scheme 115. $InCl_3$-Catalyzed synthesis of tetrasubstituted furans

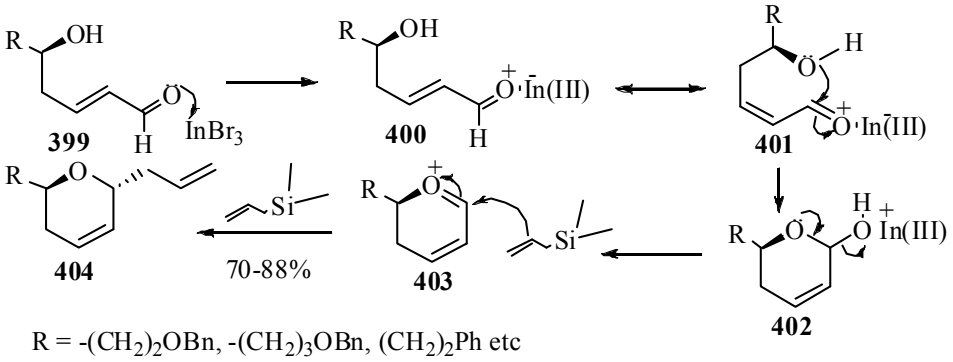
The insertion of aldehydes into a C-H bond of aromatic ketimines activated by rhenium complex, $[ReBr(CO)_3(thf)]_2$ (2.5 mol%), provided the isobenzofuran derivatives **398** (Scheme 116).[224]



Scheme 116. Re-Catalyzed synthesis of isobenzofuran derivatives from aromatic ketimines

Stereoselective synthesis of *trans*-2,6-disubstituted 3,6-dihydro-2*H*-pyrans **404** from δ-hydroxy-α,β-unsaturated aldehydes **399** and allyltrimethylsilane/TMSCN based on $InBr_3$ (5 mol%)-catalyzed

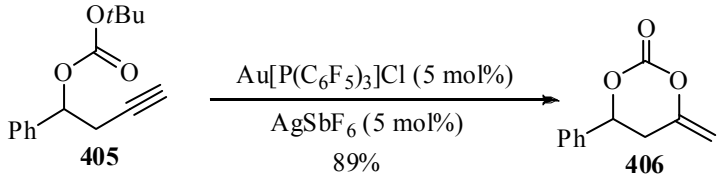
heterocyclization was also reported (Scheme 117).[225] The Lewis acid induced tandem allylation or cyanation of δ-hydroxy-α,β-unsaturated aldehydes to produce dihydropyrans in good yields and with *trans*-selectivity at room temperature. Mechanistically, the reaction proceeds with activation of aldehyde



Scheme 117. $InBr_3$-Catalyzed stereoselective synthesis of *trans*-2,6-disubstituted 3,6-dihydro-2*H*-pyrans

by In(III) bromide and subsequent nucleophilic attack by oxygen of OH group to give an oxonium intermediate **403** in which stereoelectronic and/or steric factors dictate the direction of the incoming new nucleophile and gave the *trans* products selectively.

Ihara *et al*. observed that the reaction of chiral propargylic carbonates proceeded in a highly enantiospecific manner to give chiral cyclic carbonates via an overall cascade chirality transfer process.[226] The catalyst $Au(PAr_3)Cl$ (5 mol%, Ar = C_6F_5) in combination with $AgSbF_6$ (5 mol%) gave the better results than corresponding PPh_3 complex.[227]



Scheme 118. Au-Catalyzed synthesis of cyclic carbonates

6. CONCLUSION

Due to immense importance of heterocyclic compounds various classical methods were developed for their synthesis. Many of those methods are endowed with inherent limitations. The challenge to synthetic chemists is to overcome these problems and make the synthesis clean, straightforward and environment friendly. One of the several efforts is to search for suitable transition metal based catalysts. The development of catalysts has simplified the earlier harsh, tedious and time consuming reactions. Moreover, some of the unsuccessful reactions have been made successful with the use of catalysts. Use of

catalysts has broaden the scope of the reaction. Moreover, the use of co-catalysts and additives in combination with the catalyst sometimes make the reaction selective and more useful. Thus the process becomes more effective and economic and the target compounds can be easily accessed. The foregoing discussion clearly demonstrates that a wide variety of transition metal based catalysts have already been developed. Though a vast number of catalysts and their useful applications have appeared in the literature, the complete listing is not possible due to lack of space. Only those recent catalysts which are typical for the synthesis of oxygen heterocycles are included in this report. The development and scope of transition metal catalysts is tremendous and the last decades have seen enormous growth and the growth is ever increasing. It seems like the transition metal catalysts hold the future of organic synthesis. Therefore, there is still much scope for development of new catalysts and application to challenging selective and target oriented synthesis. We believe this report will be useful to heterocyclic and medical chemists in particular and synthetic chemists in general.

7 ACKNOWLEDGEMENTS

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