5-*Endo-dig* cyclizations in organic syntheses

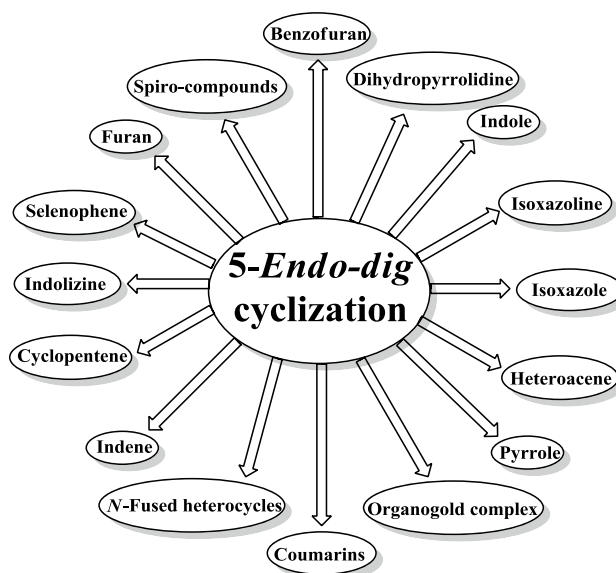Muhammad Aamir Sajid[1] · Zulfiqar Ali Khan[1] · Sohail Anjum Shahzad[2] · Syed Ali Raza Naqvi[1] · Muhammad Usman[1]

Abstract

The favorability of ring closure reactions as per Baldwin rules has gained immense importance recently. This is evident from the current literature such as research articles, reviews, and books that have been published in this area. This review covers the recent applications of 5-*endo-dig* cyclization in organic synthesis focusing in the last two decades. A variety of 5-membered heterocycles as well as carbocycles could be synthesized via 5-*endo-dig* cyclization reactions. The important applications of 5-*endo-dig* cyclization in organic synthesis covering different aspects have been summarized in this review.

Graphical abstract

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Introduction

The article published in "Chemical Communication" more than 40 years ago summarized the Baldwin rules [1], that eventually became the most cited article of the journal. This article described a series of guidelines outlining the relative favorability of ring closure reactions. The favorability of ring closure reactions as per Baldwin's guidelines gained valuable insight into the role of stereo-electronic factors. A cyclization reaction is designated by using three prefixes, the first of which gives the number of atoms forming a ring that can undertake any value ≥ 3. The second one prefix, *exo-* versus *endo-*, describes the placement of the bond that needs to be damaged in the cyclization relative to the forming ring. The prefix "*exo*" indicates that the bond being broken is outside of the new ring, while prefix "*endo*" indicates that the bond being broken is in the new ring (Fig. 1). The third prefix, *tet*, *trig*, and *dig*, refers back to the hybridization at the ring closure factor, *tet* (tetrahedral) for sp^3, *trig* (trigonal) for sp^2, and *dig* (digonal) for an sp-hybridized atom [2, 3].

Radical cyclizations are generally used in the preparation of hetero- and carbocyclic compounds. In *dig* cyclizations the geometric restrictions are of minor importance, because the reacting orbitals may attack the in-plane π-system of acetylene functionality. This approach with less geometric strain and along with relatively low energy requirement for bending of the alkyne moiety provides many digonal cyclization ways [4, 5].

The alkynes are versatile functional groups that can undergo an array of reactions such as reductions, oxidations, additions, polymerizations, hydrations, metal-catalyzed carbon–carbon bond forming reactions. Carbocyclization of alkynes and alkenes is a highly useful reaction for the preparation of array of heterocyclic and carbocyclic compounds. Carbocyclization of alkynes is of special interest because it permits one to obtain hetero- and carbocycles with higher degree of unsaturation [6].
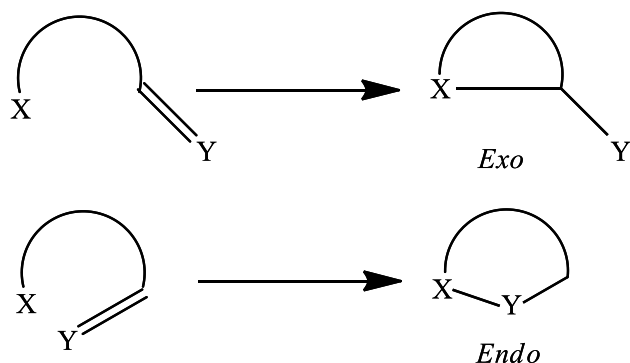
The scope of 5-*endo-dig* cyclization is constantly and speedily developing. Among the diversity of compounds, the 5-*endo-dig* cyclization is utilized for the synthesis of different classes of compounds such as indoles, cuomarins, cyclopentenes, benzofurans, furans. This review deals with fundamental applications of 5-*endo-dig* cyclization in organic synthesis.

Aims and scope of review

Given the marvelous impact of 5-*endo-dig* cyclization in the last few years, many publications in the last years covered different aspects. These tremendous applications of 5-*endo-dig* cyclization encouraged us to summarize the important applications in the field of synthetic organic chemistry.
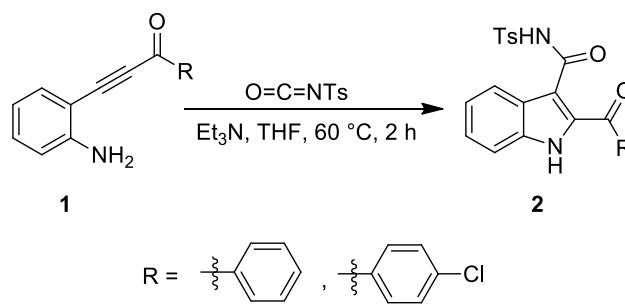
Indole derivatives

Rode et al. [7] reported a metal-free approach for the synthesis of 2-aroyl-*N*-tosyl-1*H*-indole-3 carboxamides **2** with 91–94% yields, through *5-endo-dig* carboxamidation reaction of β-(2-aminophenyl)-α,β-ynones **1** with a small excess of the tosyl-isocyanate and catalytic amount of Et$_3$N in THF as solvent (Scheme 1).

Rodriguez et al. reported the potassium or cesium-base-mediated synthesis of 2-substituted indoles **5** with 72–76% yields by the reaction of **4** with KO*t*Bu or CsO*t*Bu in *N*-methylpyrrolidinone (NMP) [8]. The precursors **4** were prepared by Sonogashira coupling of the corresponding (2-iodo or 2-bromoanilines) **3** with terminal alkynes in good yields (Scheme 2) [9].

Andreev et al. [10] reported an un-catalyzed thermally induced 5-*endo-dig* cyclization of amino propargylic alcohols **6** by heating at 160–170 °C for 1–3 h to give 4,5,6,7-tetrahydroindoles **7** with 73–90% yields. Further Dess–Martin periodinane oxidation gives 5,6-dihydro-1*H*-indol-2(4*H*)ones **8** (Scheme 3).

Naoe et al. reported the gold-catalyzed tandem cyclization of aniline derivatives having conjugated diyne functionality **9** into the indole merged with a seven-membered

Fig. 1 The format of bond broken during ring closure

Scheme 1 Synthesis of 2-aroyl-*N*-tosyl-1*H*-indole-3 carboxamides **2**

ring **10** with 86% yield and small amount of six-membered ring **11** (Scheme 4) [11].

Jalal et al. [12] reported the 1,5-enyne cycloisomerization of (3-methylene)indoline-tethered alkyne derivatives **12** catalyzed by Fe(OTf)$_3$-catalyzed to give highly substituted 3-(1-indenyl)indole derivatives **13** with 80–89% yields (Scheme 5).

In a mechanistic explanation, iron coordinates with triple bond to form **A** which is followed by 5-*endo-dig* cyclization via intramolecular nucleophilic attack of the exo-cyclic double bond forming an intermediate **B**. Subsequently, isomerization of **B** leads to **C**, which on protonolysis affords the desired product **13** (Scheme 5).

Sharma et al. described the metal-/oxidant-free microwave-assisted synthesis of 3-sulfenylindoles **16** by cascade electrophilic sulfenylation/5-*endo-dig* cyclization reaction of 2-alkynylaniline **14** with sulfonyl hydrazide **15** in the presence of iodine and *p*-TsOH at 110 °C in 1,4-dioxane as solvent (Scheme 6) [13].

Palimkar et al. [14] described one-pot preparation of 2-substituted indoles **19** in 71–90% yields by palladium-acetate-catalyzed domino Sonogashira coupling/5-*endo-dig* cyclization of 2-iodo-4-substituted-*N*-tosylbenzenamine **17** and terminal alkynes **18** with ultrasonic irradiation at room temperature (Scheme 7).

Palimkar et al. described the synthesis of KDR kinase inhibitor generating the indole moiety via domino Sonogashira coupling/5-*endo-dig* cyclization reaction of *o*-iodoanilide derivative **20** with terminal alkyne **21** in the presence of Pd(OAc)$_2$ and Bu$_4$NOAc as the base to give indole-chloroquinoline **22** in 80% yield [15]. Hydrolysis of indole-chloroquinoline **22** by acetic acid/water mixture (1:1) as reported in the previous literature [16] gives KDR kinase inhibitor **23** in 93% yield (Scheme 8).
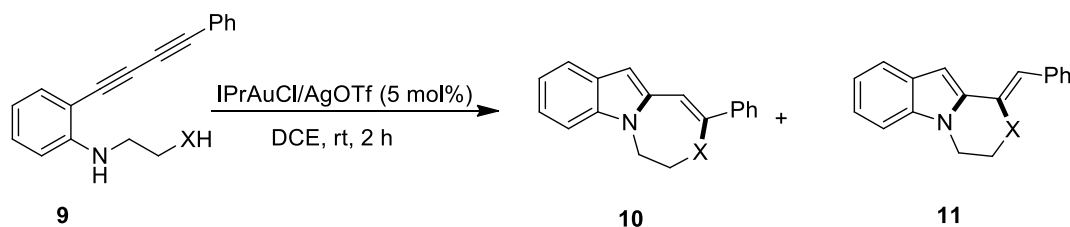
Cai et al. described the gold-catalyzed synthesis of fused tetracyclic indoles **25** with 78–89% yield. The diaryl alkyne **24** undergoes 5-*endo-dig* cyclization to form the α-imino
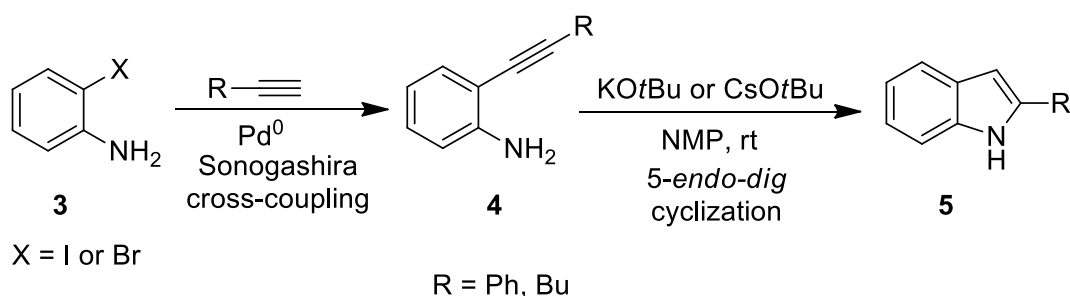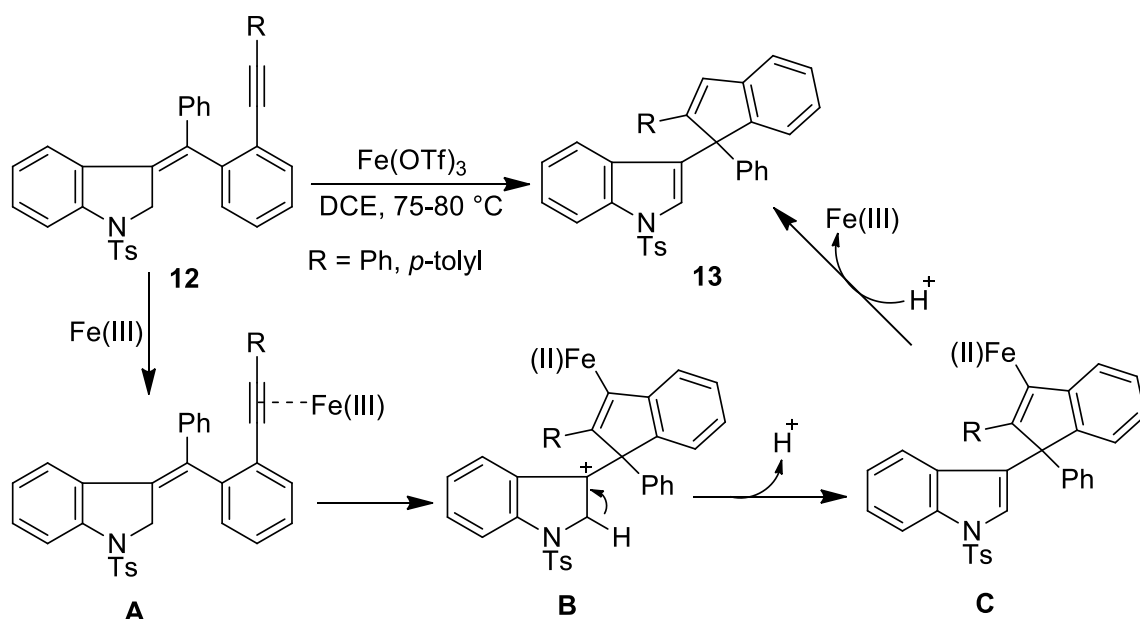

Scheme 2 Synthesis of 2-substituted indoles **5**
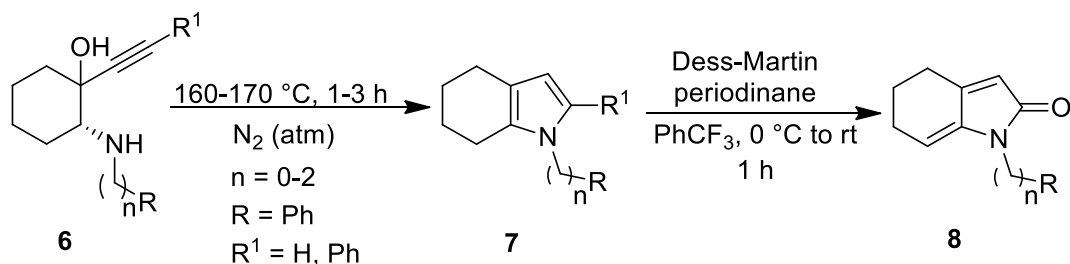
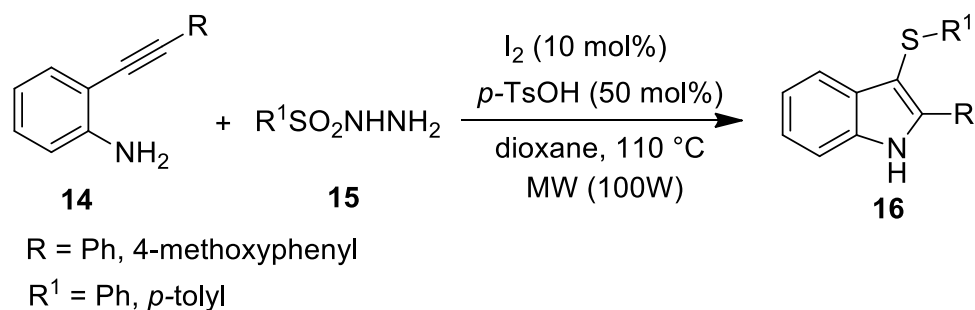**Scheme 3** Synthesis of 5,6-dihydro-1*H*-indol-2(4*H*)ones **8**

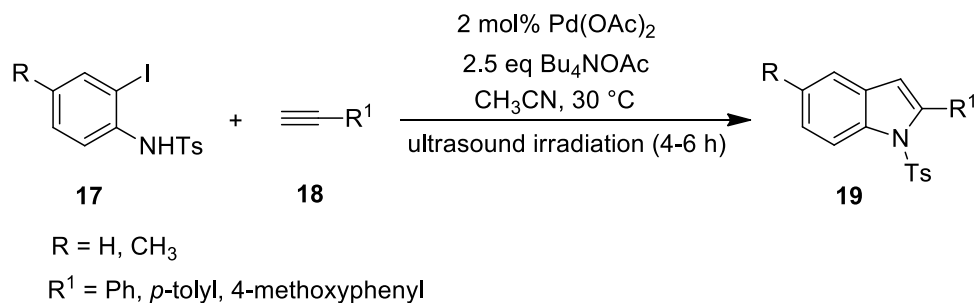**Scheme 4** Synthesis of indole fused with seven- and six-membered rings

Scheme 5 Synthesis of 3-(1-indenyl)indole derivatives **13**

Scheme 6 Synthesis of 3-sulfe-nylindoles **16**

R = Ph, 4-methoxyphenyl

R^1 = Ph, p-tolyl

Scheme 7 Synthesis of 2-substituted indoles **19**

R = H, CH$_3$

R^1 = Ph, p-tolyl, 4-methoxyphenyl

carbenoid and followed by O–H/N–H insertion to give the desired product (Scheme 9) [17].

Benzofuran derivatives

The synthesis of highly substituted benzo[b]furan **27** in 74% yield from ynamide **26** via gold(I)-catalyzed 5-*endo-dig* cyclization and subsequent alkylic oxonium intermediate

rearrangement (Scheme 10) was described by Jaimes et al. [18].

In a mechanistic explanation, the ynamide **26** was activated by gold species to give **E**. The alkyl-oxonium intermediate **F** formed through the nucleophilic attack of the oxygen atom and followed by the generation of stabilized alkyl carbocation and vinylgold(I) derivative **G**. The carbocation transfers to the most nucleophilic position on

benzofuran ring to give more substituted benzo[b]furan **27** and gold species was regenerated (Scheme 10).

Saha et al. [19] reported a one-pot method for the preparation of 2-substituted benzo[b]furans **30** by the reaction of 2-iodophenol **28** with arylacetylenes **29** in the presence of Na_2PdCl_4 and sodium dodecyl sulfate (SDS) in water at 100 °C.

The Sonogashira coupling occurs through the oxidative addition of 2-iodophenol to Pd^0 to afford **H**. Subsequently, transmetalation with phenylacetylene **29** gives **I** and then reductive elimination leads to **J**. Then **J** undergoes 5-*endo-dig* cyclization to furnish product **30** (Scheme 11).

Mantovani et al. described the mechanochemical cyclization reaction of 2-(arylethynyl)anisoles **31** to give 3-iodo-benzofurans **32** in 78–83% yields by solvent-less milling
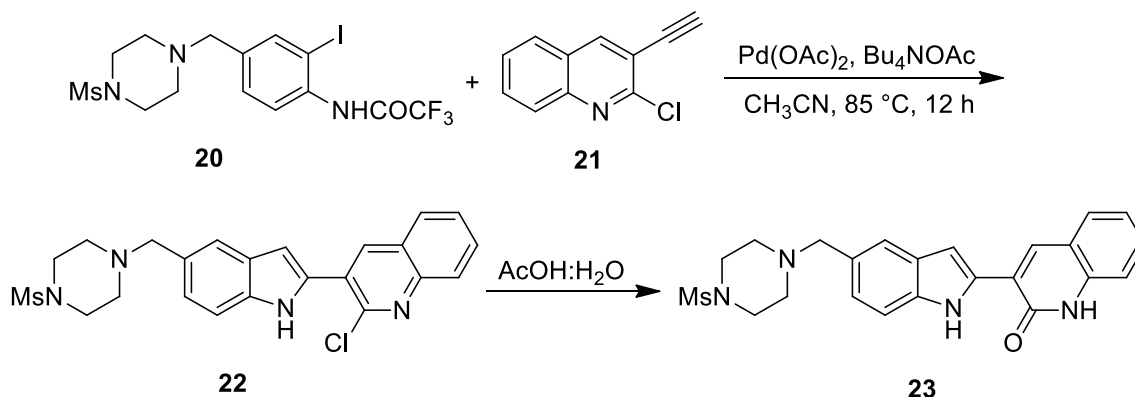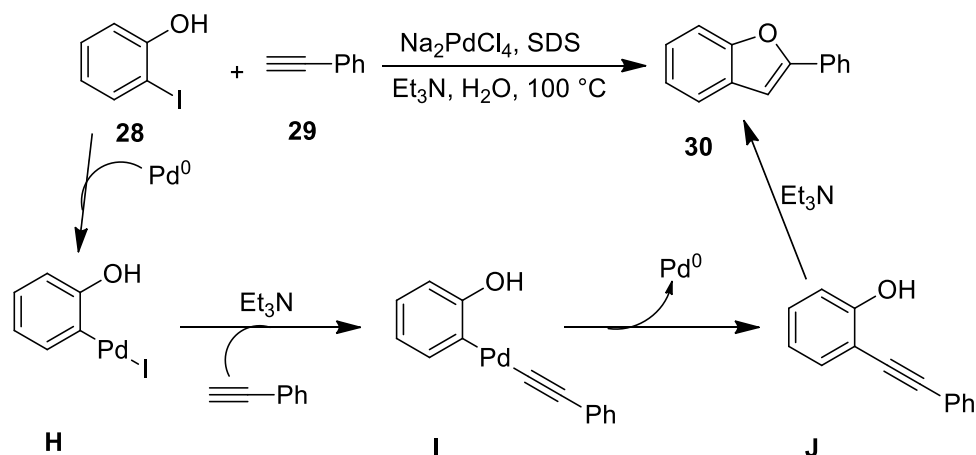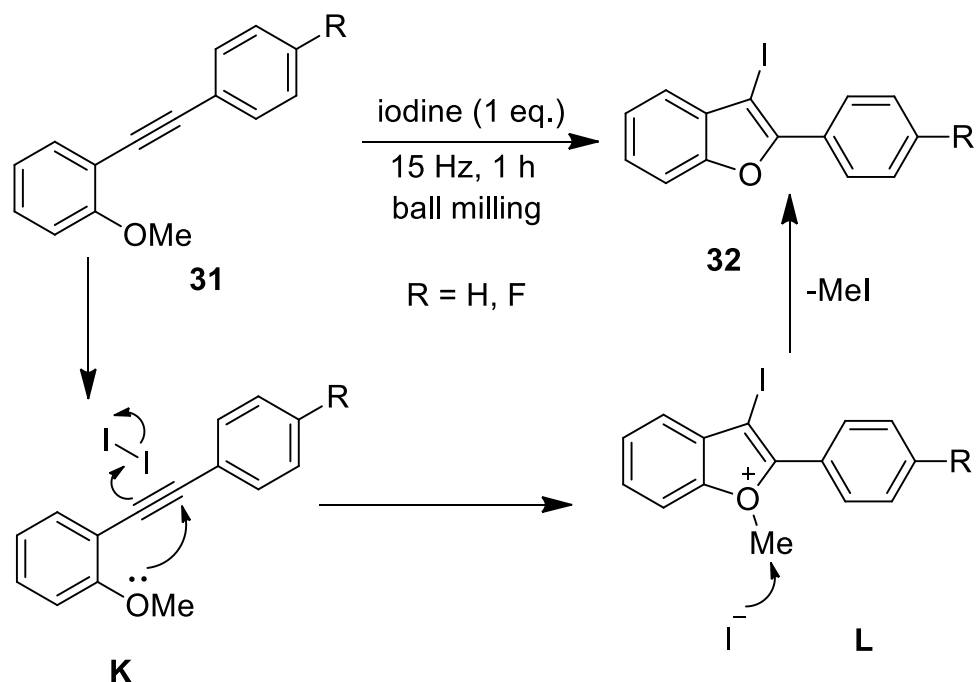

Scheme 8 Synthesis of KDR kinase inhibitor **23**

Scheme 9 Synthesis of fused tetracyclic indoles **25**
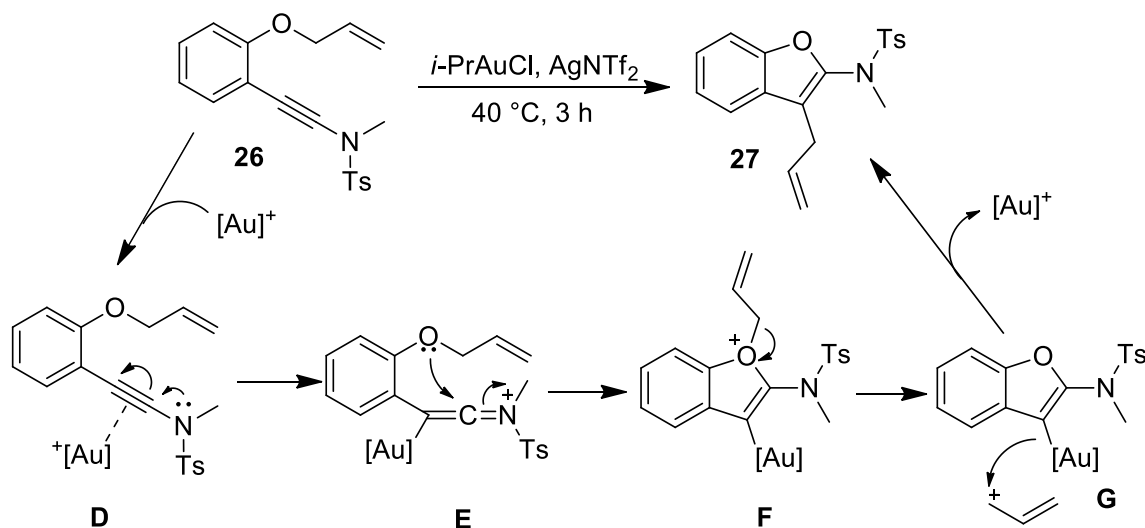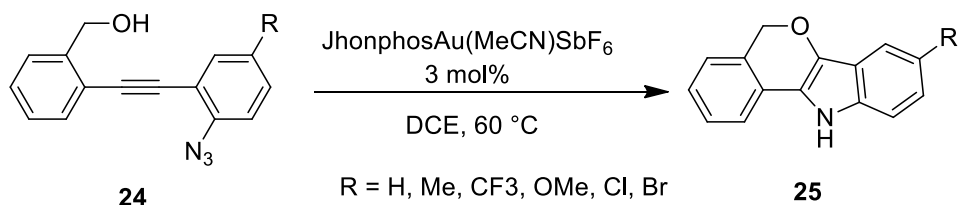
Scheme 10 Synthesis of benzo[b]furan **27**

Scheme 11 Synthesis of 2-substituted benzo[b]furans **30**

Scheme 12 Synthesis of 3-iodobenzofurans **32**

of **31** with equimolar amount of iodine at 15 Hz for 1 h (Scheme 12) [20]. The molecular iodine alkyne interaction leads to intermediate **L**, which on simultaneous demethylation gives 3-iodobenzofurans **32**. In solvent-less mechanochemical conditions, charge stabilizing effects are fewer, while, in solution conditions, charge-separated species as well as iodide would experience considerable interaction by solution molecules.

Kim et al. [21] synthesized the 2-substituted 5-hydroxybenzofurans **34** by Pt-catalyzed cascade dienone-phenol rearrangement/5-*endo-dig* cyclization reaction of quinols **33** having alkyne moiety in dimethoxyethane/methanol (20:1) at 40 °C. The alkyne moiety in **M** shifts to adjacent carbon atom to give alkynone **N**. Subsequent 5-*endo-dig*

cyclization furnishes 2-substituted 5-hydroxy benzofuran **34** (Scheme 13).

Palimkar et al. [22] synthesized benzofuran derivatives **37** via Sonogashira cross-coupling/5-*endo-dig* cyclization reaction of **35** with phenylacetylene **36** under ultrasonic irradiation using Bu$_4$NOAc and Pd(OAc)$_2$ in CH$_3$CN at room temperature (Scheme 14).

Coumarin derivatives

Majumdar et al. synthesized 3-iodopyrrolocoumarin **40** by Sonogashira coupling [23] of 5-bromo-6-aminocoumarin **38** with different alkynes to afford **39**, followed by iodine-induced 5-*endo-dig* cyclization reaction of **39** in acetonitrile at room temperature (Scheme 15) [24].
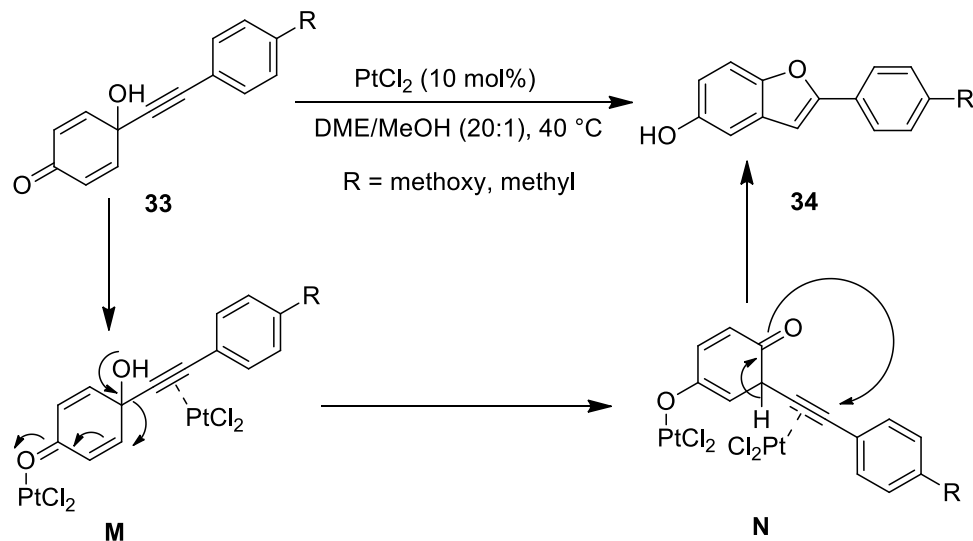
Cyclopentene derivatives

Staben et al. developed a gold(I)-catalyzed 5-*endo-dig* carbocyclization reaction of dicarbonyl compound **41** onto internal alkyne to give cyclopentene derivative **42** under open-flask conditions in dichloromethane at room temperature (Scheme 16) [25].
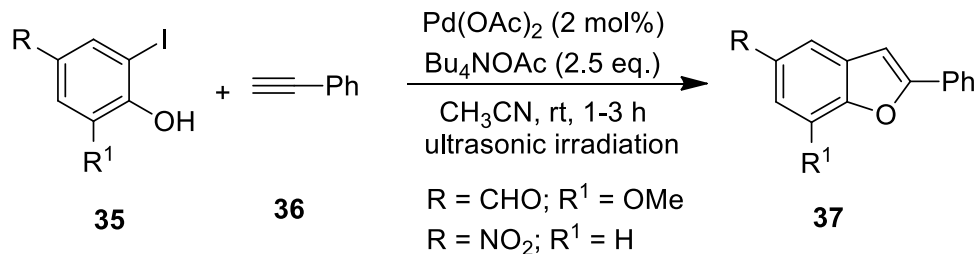
Suzuki et al. [26] reported the 5-*endo-dig* carbocyclization of β-ketoesters **43** onto internal alkyne to afford cyclopentene derivatives **44** by using (S,S)-Box-Ph/Zn(II)/HFIP/
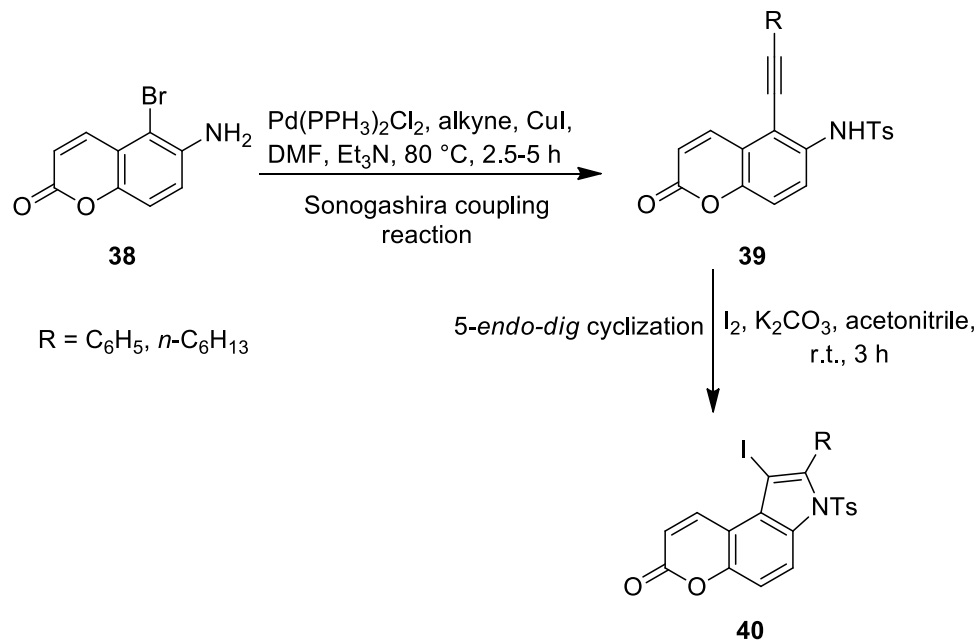

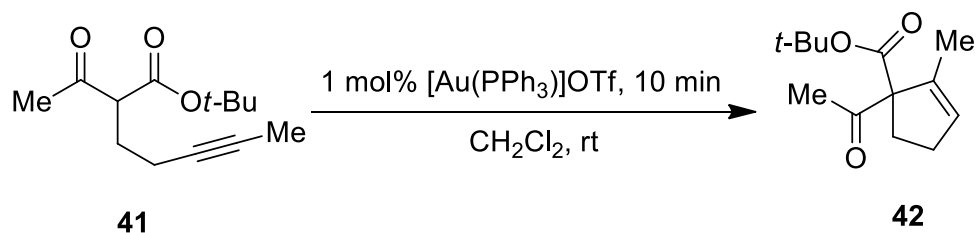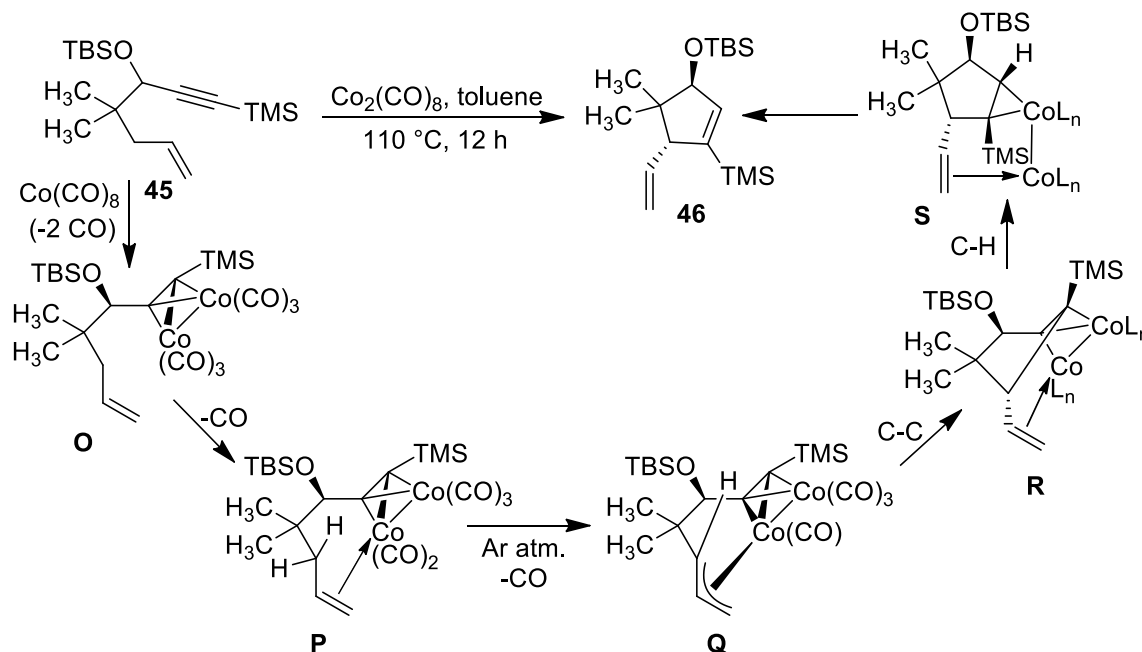**Scheme 13** Synthesis of 2-aryl-5-hydroxybenzofurans **34**

Scheme 14 Synthesis of benzofuran derivatives **37**

Scheme 15 Synthesis of 3-iodopyrrolocoumarin derivatives **40**

Scheme 16 Synthesis of cyclo-pentene derivative **42**

Scheme 17 Synthesis of cyclo-pentene derivative **44**

Ar = Ph, 2-BrC$_6$H$_4$

(S,S)-Box-Ph
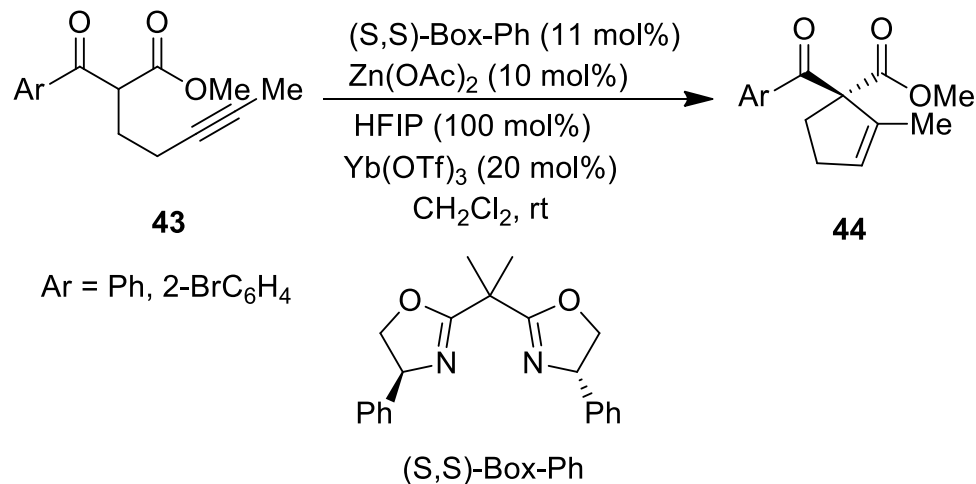
Scheme 18 Synthesis of 5-vinylcyclopentene **46**

Yb-(OTf)$_3$, a four-component system in dichloromethane at ambient temperature (Scheme 17).

Dolaine and Gleason reported the dicobalt octacarbonyl [Co$_2$(CO)$_8$]-mediated synthesis of 5-vinylcyclopentene **46** in good yield from 1,6-enynes **45** under argon atmosphere (Scheme 18).

Mechanistically, the cobalt complex **O** formed from substrate **45** at room temperature. One CO ligand is lost on heating and alkene coordinates in place of that ligand to

form complex **P**. An allylic C–H oxidative addition generates η^3-allylcobalt hydride **Q** and on reductive elimination a C–C bond between C1 and C5 was generated (complex **R**). It is followed by reductive elimination to generate a C–H bond to get complex **S**, then after decomplexation gives cyclopentene **46** [27].

Iwasawa et al. described the annulations of cyclopentene onto α,β-unsaturated ketones. 1,4-Propargylation onto α,β-unsaturated ketone **47** was carried out by reacting *t*-butyldimethylsilyl triflate and dimethyl sulfide with **47** and in situ generated organoindium reagent (previously reported literature) [28] at room temperature in THF to afford **48** with 76% yield. Followed by 5-*endo-dig* cyclization reaction of **48** catalyzed by W(CO)$_5$(thf) to afford the cyclopentene derivative **49** in 72% yield (Scheme 19) [29].

Fujino et al. [30] synthesized 1,2-disubstituted cyclopentenes **52** via 5-en*do-dig* cyclization of homopropargyl-substituted dicarbonyl compounds **50** with organic halides **51** catalyzed by Pd(dba)$_3$ in the presence of XPhos and NaHMDS in DMF at 60 °C.

In mechanistic explanation oxidative addition of 'Pd' to aryl halide gives arylpalladium intermediate **T**, which activates the alkyne functionality of complex **U** via π-coordination. The complex **U** undergoes 5-*endo-dig* cyclization to give vinylpalladium complex **V**. Followed by reductive elimination to afford phenyl-substituted cyclopentene **52** and palladium complex was regenerated (Scheme 20).
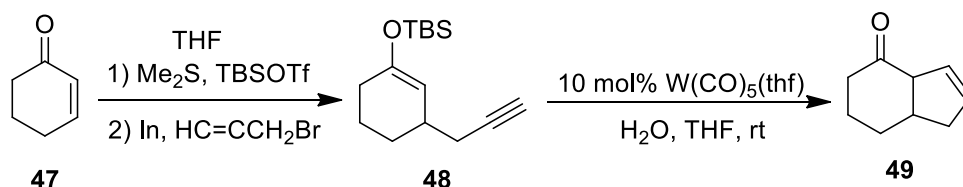
Dehydropyrrolidine derivatives

French and Diver reported the effective synthetic route to dehydropyrrolidine **54** under gold(I) catalysis. The unsubstituted propargylic acetate **53** undergoes direct 5-*endo-dig* cyclization under gold(I) catalysis to give **54** (Scheme 21). Mechanistically gold(I) coordinate with alkyne moiety (complex **W**) and in the absence of substitution on the acetyl group leads to direct 5-*endo-dig* cyclization to give **X** which subsequently gives dehydropyrrolidine **54** [31].
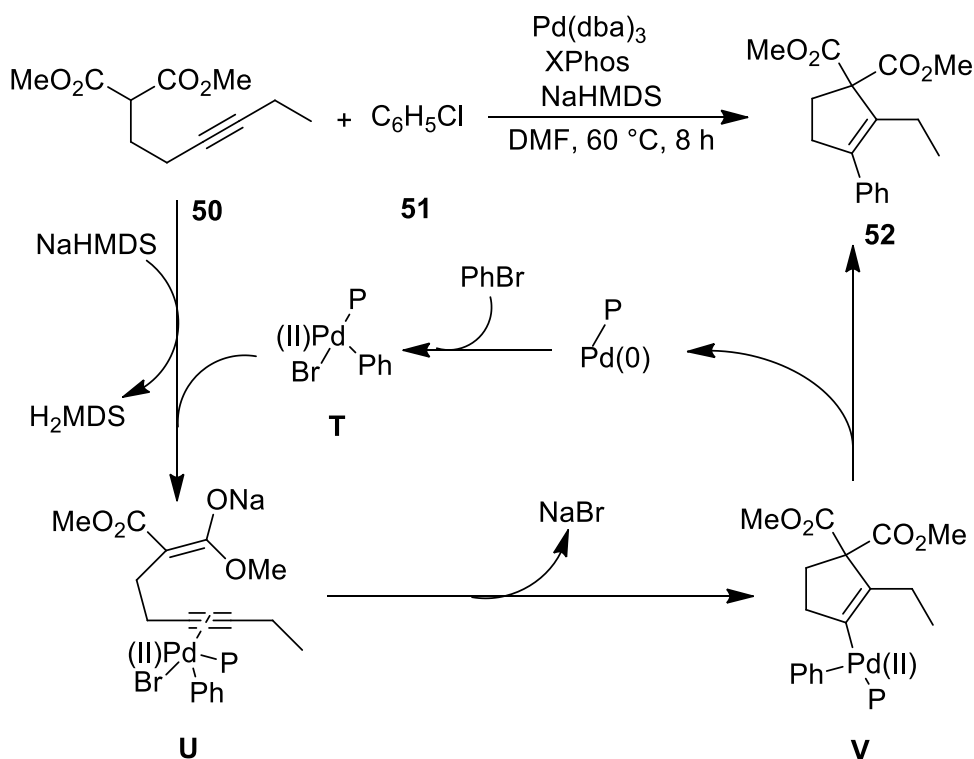
Furan derivatives
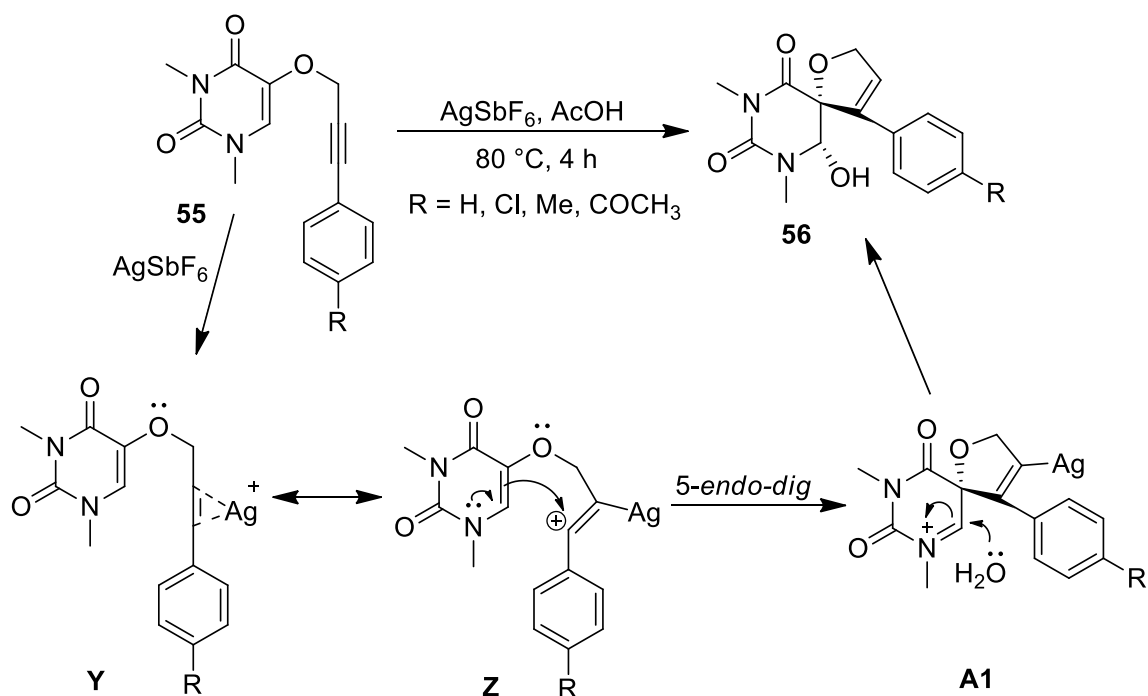
Majumdar et al. [32] reported the synthesis of pyrimidine-annulated spiro-dihydrofurans **56** with 69–87% yields by

Scheme 19 Synthesis of cyclopentene derivative **49**

Scheme 20 Synthesis of 1,2-disubstituted cyclopentene **52**

Scheme 21 Synthesis of dehydropyrrolidine derivative **54**
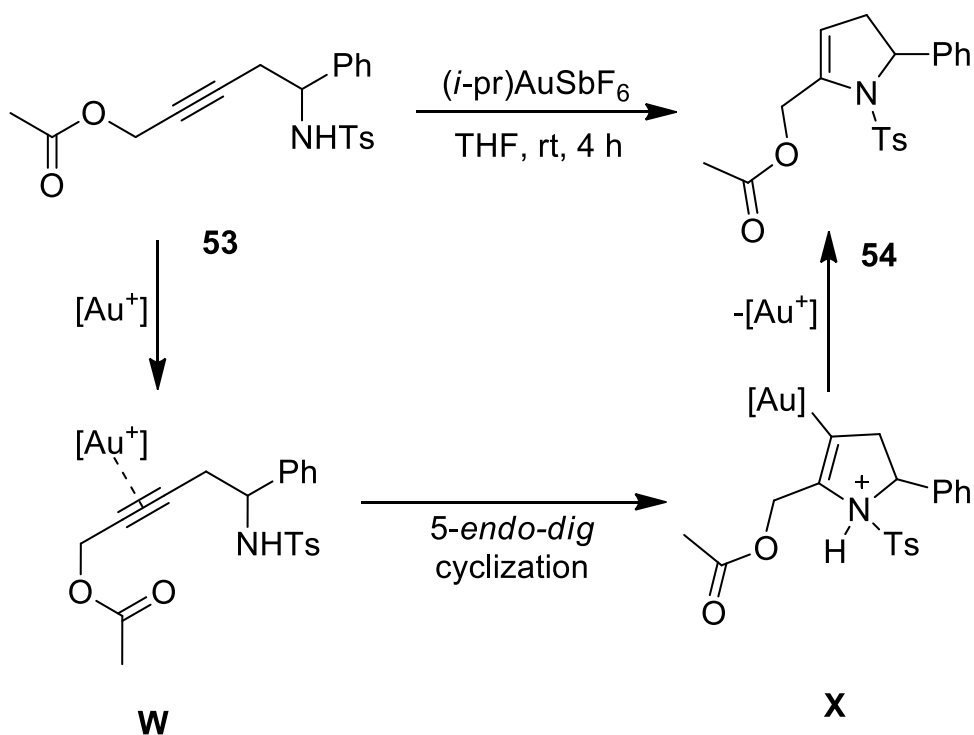
Scheme 22 Synthesis of pyrimidine-annulated spiro-dihydrofurans **56**

silver-catalyzed 5-*endo-dig* cyclization of various *O*-propargylated uracil derivatives **55** in AcOH as solvent at 80 °C.

In a mechanistic explanation initially a π-complex **Y** is suggested to be formed which rearranges to carbocation **Z**.

The *N*-atom of pyrimidine ring undergoes 5-*endo-dig* cyclization by the formation of Mannich species **A1**. Then water attacks the imino bond to afford the spiro-dihydrofuran **56** (Scheme 22).

Sniady et al. described the synthesis of 2,5-disubstituted 3-halofurans **58** and **59** in 84–89% yields through the electrophilic 5-*endo-dig* cyclization of 1,4-aryl-butynone **57** with *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) in acetone as solvent (Scheme 23) [33].

Sniady et al. [34] described zinc chloride-catalyzed cycloisomerization of 1,4-disubstituted-butynones **60** in the presence of a catalytic amount of zinc chloride in dichloromethane at room temperature to afford 2,5-disubstituted furans **61** in good yields (Scheme 24).

El-Taeb et al. reported the iodine-mediated 5-*endo-dig* cyclization of 3-alkyne-1,2-diols **62** prepared by previously reported method [35]. The reaction of **62** with 3 equivalents of I_2 and $NaHCO_3$ in dichloromethane as solvent at ambient temperature provides β-iodofurans **63** with high yields (Scheme 25) [36].

Shi et al. described the synthesis of 2,5-dihydrofurans **66** with 69–78% yield through the Pd(II)-catalyzed [4 + 1]

cycloaddition of aryl diazoacetates **64** and aryl propargyl alcohols **65** in dichloromethane at room temperature (Scheme 26) [37].

Heteroacene derivatives

Oechsle et al. [38] synthesized sulfur-containing heteroacenes via palladium-catalyzed C–S cross-coupling/5-*endo-dig* cyclization of bis-alkynes. The Sonogashira coupling of **67** with 4-diphenylaminophenylacetylene **68** furnished monoalkyne **69** and bis-alkyne **70** in 70 and 76% yield, respectively. Consequent reaction of **70** with potassium thioacetate (KSAc) in the presence of DPPF and Pd(OAc)$_2$ gives heteroacene **71** in 73% yield. Monoalkyne **69** was further used to get the zinc reagent by magnetization using *i*PrMgCl and transmetalation using zinc chloride. Negishi coupling of this reagent with one equivalent of **69** or 0.5 equivalents of **67** furnishes the
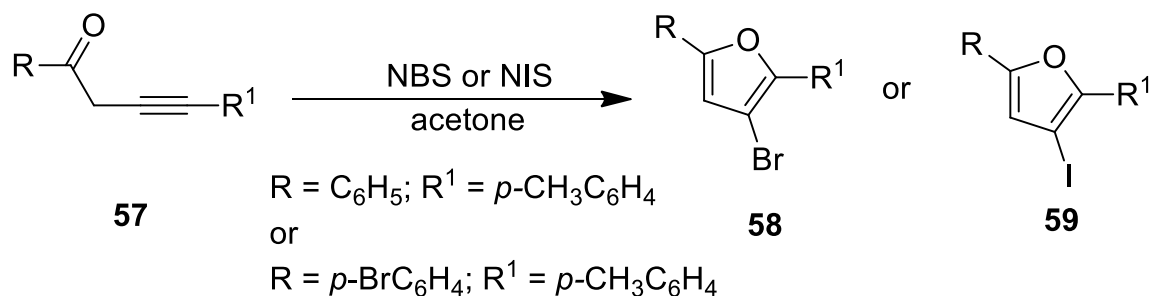
Scheme 23 Preparation of 2,5-disubstituted-3-halofurans **58** and **59**

Scheme 24 Preparation of 2,5-disubstituted furans **61**
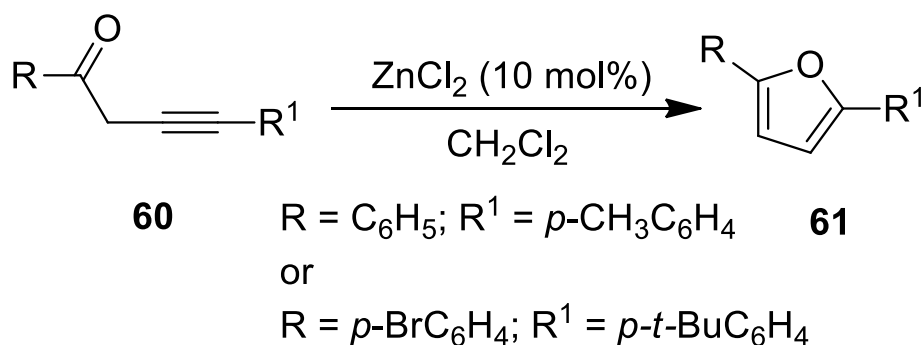
Scheme 25 Synthesis of β-iodofurans **63**
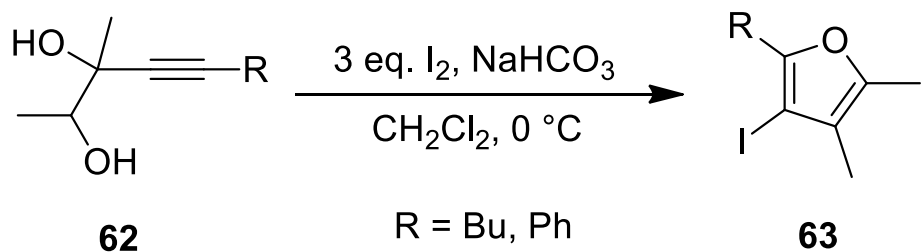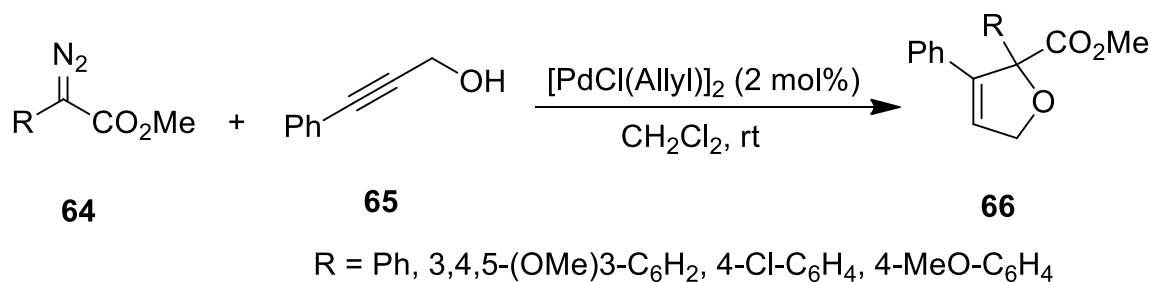
Scheme 26 Synthesis of 2,5-dihydrofurans **66**

biphenyl **72** or terphenyl **73** in 90 and 58% yield, respectively. Then the reaction of **72** and **73** with KSAc in the presence of D*i*PrPF and [Pd(P(*o*Tol)₃)₂] at 120 °C afforded heteroacene **74** and **75** in 56 and 45% yield, respectively, (Scheme 27).

Indene derivatives

Khan and Wirth [39] described the preparation of 3-Iodo-1*H*-indene derivative **77** in good yield by iodine-mediated 5-*endo-dig* carbocyclization of 2-substituted
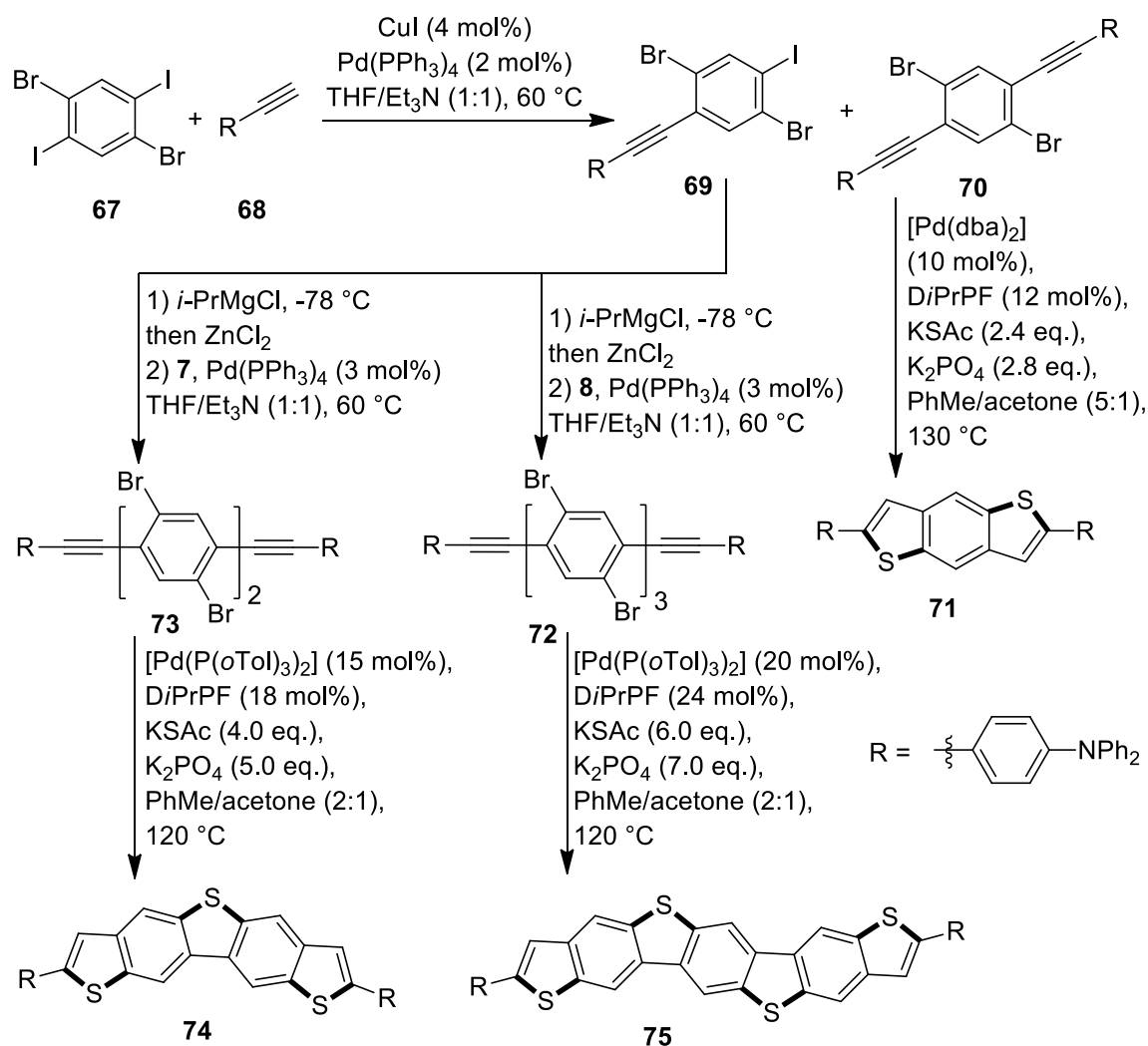
Scheme 27 Synthesis of heteroacenes **71**, **74** and **75**

ethynylmalonates **76** in the presence of I_2 and NaH as base in THF. Mechanistically, the base deprotonated the malonate **76** to furnish **B1**. Then deprotonated malonate **76** undergoes 5-*endo-dig* cyclization to give 3-Iodo-1*H*-indene derivatives **77** via intermediate **C1** (Scheme 28).

Ma et al. [40] reported the preparation of indene derivatives **80** with 75–87% yield via gold(I)-catalyzed domino C–H functionalization/5-*endo-dig* cyclization reaction of o-alkynylaryl α-diazoesters **78** and arene **79** in dichloromethane at room temperature (Scheme 29).

Indolizine derivatives

Smith et al. [41] described the Pt(II)-catalyzed cyclization of pyridine propargylic alcohols **81** using Cs_2CO_3 as base to afford indolizinone **82** with 85–95% yield (Scheme 30).

Pandya et al. described the silver-promoted preparation of indolizines **85** through tandem oxidative C–H functionalization/5-*endo-dig* cyclization. The reaction of 2-pyridylacetate **83** with phenylacetylene **84** in the presence of 2 equivalents of Ag_2CO_3 and KOAc in DMF at room temperature gives indolizines **85** with 84–89% yield.

Mechanistically, one equivalent of Ag_2CO_3 activates ethyl 2-pyridylacetate **83** via chelation to furnish **D1**,

Scheme 28 Synthesis of 3-Iodo-1*H*-indene derivatives **77**
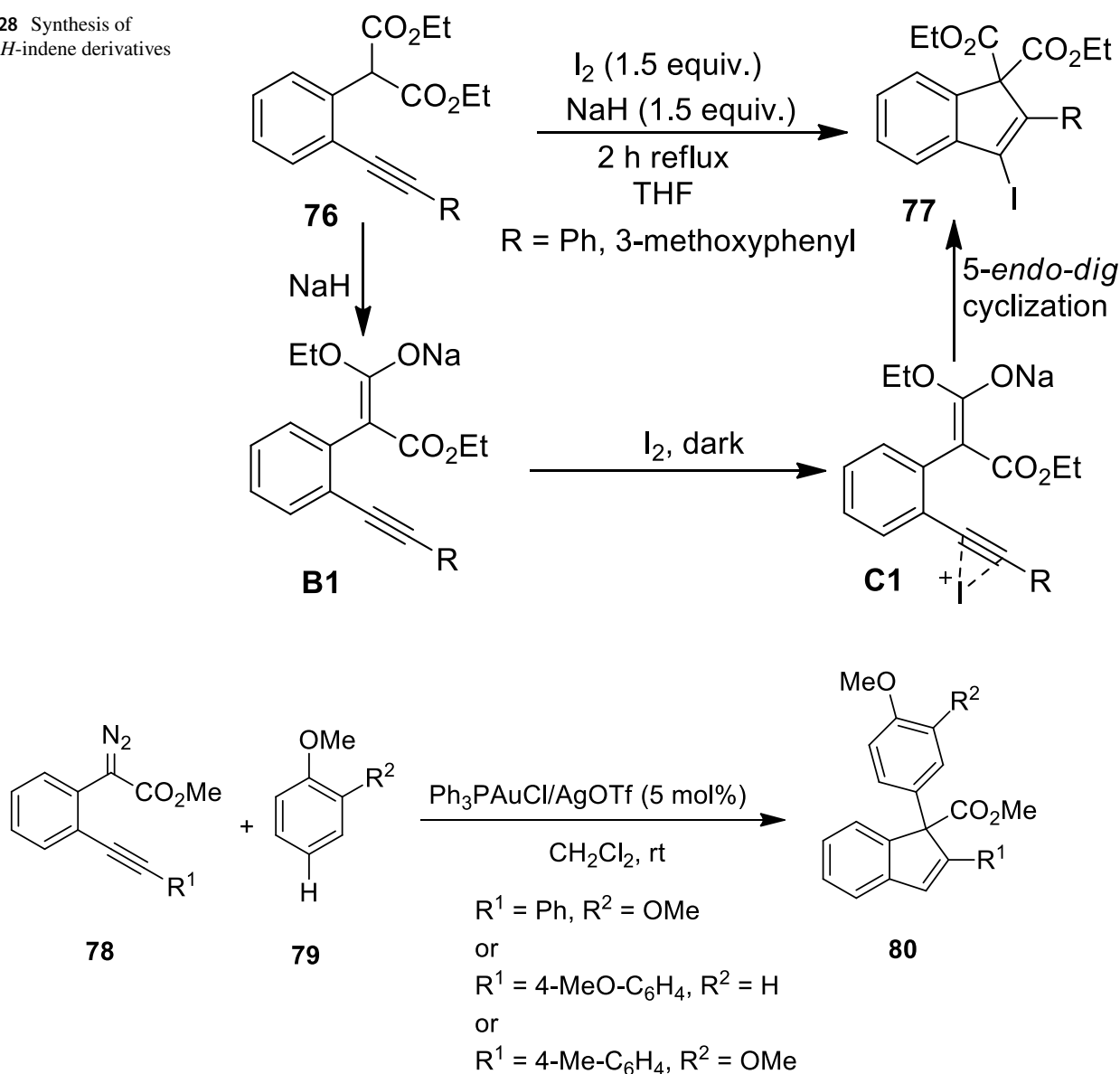
Scheme 29 Synthesis of indene derivatives **80**

while second equivalent of Ag_2CO_3 reacts with phenylacetylene **84** by chelation to give **E1**. The coupling of two intermediates (**D1** and **E1**) furnishes intermediate **F1**, which undergoes 5-*endo-dig* cyclization to give the required product **85** (Scheme 31) [42].

Kim et al. reported the synthesis of highly substituted indolizines **88** through iodine-promoted 5-*endo-dig* cyclization of propargylic acetate **87**. The propargylic acetate **87** was first synthesized from the reaction of 2-pyridinecarboxaldehyde **86** and 1-alkynyllithium via earlier reported method [43]. Exposure of acetate **87** to iodine in

dichloromethane at room temperature undergoes 5-*endo-dig* cyclization to afford indolizines **88** (Scheme 32) [44].

Isoxazole derivatives

Sugita et al. [45] reported a gold-catalyzed reaction of *O*-allyl hydroxamates **89** having an alkyne functionality for the synthesis of 3-hydroxyisoxazoles **90** and isoxazole-3-ones **91**. The cyclization of *O*-allyl hydroxamates **89** in the presence of $PicAuCl_2$ (Pic = 2-picolinate) in $(CH_2Cl)_2$

Scheme 30 Synthesis of indolizinone **82**
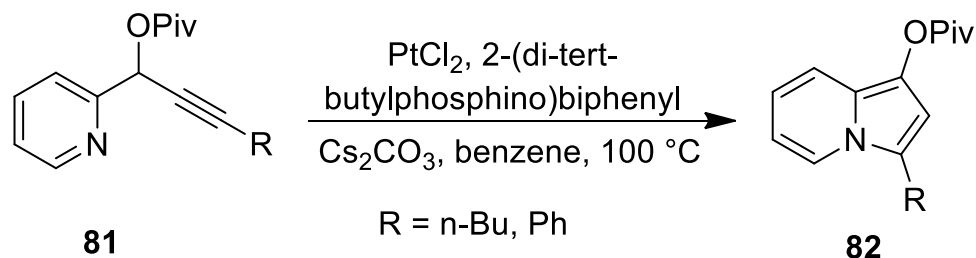
Scheme 31 Silver-mediated synthesis of indolizines **85**
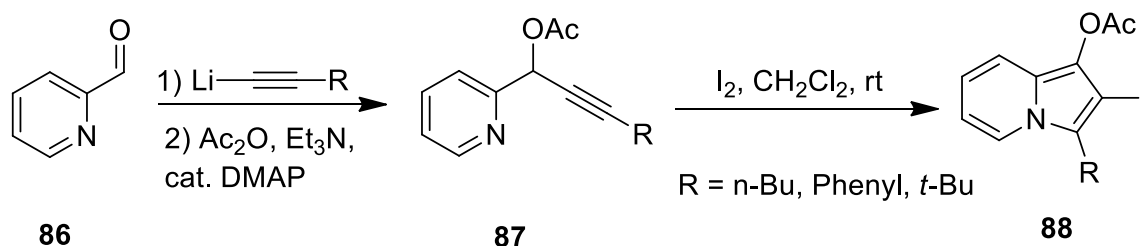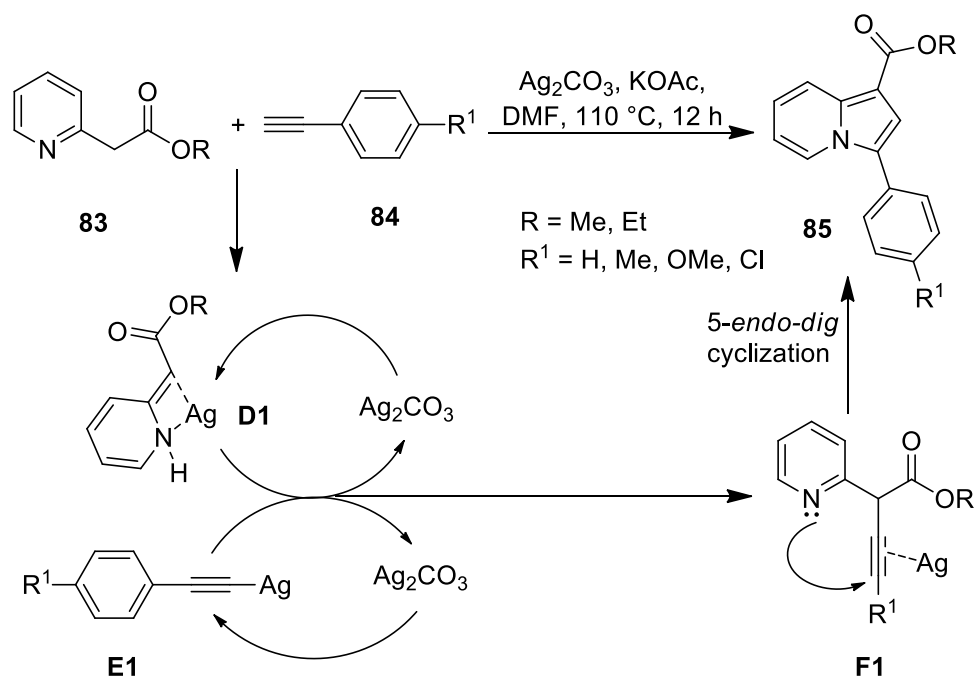
Scheme 32 Iodine mediated synthesis of indolizines **88**

gives 3-hydroxyisoxazoles **90** with 78–86% yield and small amount of isoxazole-3-ones **91**.

Mechanistically, the addition of oxygen atom of hydroxamate to Au(III)-activated alkyne moiety through 5-*endo-dig* pathway gives oxonium intermediate **H1**. The consequent [3,3] sigmatropic rearrangement of allyl group to C-4 carbon proceeded through conformation **I1** to afford intermediate **J1**, which undergoes an aromatization reaction to furnish the 3-hydroxyisoxazole **90**. The rearrangement through conformation **K1** gives the intermediate **L1**, which undergoes an aromatization reaction to afford isoxazole-3-ones **91** (Scheme 33).

Isoxazolines derivatives

Wang and Tsui [46] described the Cu(OTf)$_2$-promoted preparation of trifluoromethylated 4-isoxazolines **93** with 50–65% yield by domino 5-*endo-dig* cyclization/trifluoromethylation of propargylic *N*-hydroxylamines **92**, using Cu(OTf)$_2$, TMSCF$_3$, KF and AgOAc in DMF at room temperature.

In a mechanistic explanation, the alkyne functionality of **92** was activated using Cu(OTf)$_2$ as a Lewis acid. The 5-*endo-dig* cyclization was carried out by nucleophilic attack of the oxygen atom onto the triple bond furnishing the 4-cuprated isoxazoline **N1**. The 4-cuprated isoxazoline **N1** reacted with CF$_3$-(generated in situ from TMSCF$_3$ and KF),

in the presence of AgOAc to give the extremely reactive trifluoromethylated Cu(III) species **O1**. Finally reductive elimination forms the C-CF$_3$ bond to give required compound **93** (Scheme 34).

N-Fused heterocyclic derivatives

Xiao et al. synthesized *N*-fused heterocycles **96** through C$_{sp}$–S coupling/5-*endo-dig* cyclization. The reaction of 2-mercaptobenzoimidazole **94** and arylethyne **95** in the presence of CuCl, *N,N'*-dicyclohexylimidazolium chloride (ICy·HCl) and Et$_3$N in toluene at 80 °C afforded *N*-fused heterocycles **96** with 42–74% yield (Scheme 35).

Mechanistically, precursor **P1** formed easily and subsequent oxidative coupling with **94** gives the intermediate **Q1**, which is then converted into the alkynyl structure **R1** through transmetalation. Consequently, the *N*-fused heterocyclic compound **S1** is formed via 5-*endo-dig* cyclization, followed by Cu$^+$–H$^+$ exchange to furnish the *N*-fused heterocycle **96** (Scheme 35) [47].

Organogold complexes

Chen et al. [48] reported the ionic organogold complexes **98** with 88–90% yield synthesized through triazole-alkyne 5-*endo-dig* cyclization by the reaction of substituted triazole **97** with one equivalent of Ph$_3$PAu-SbF$_6$ in dichloromethane
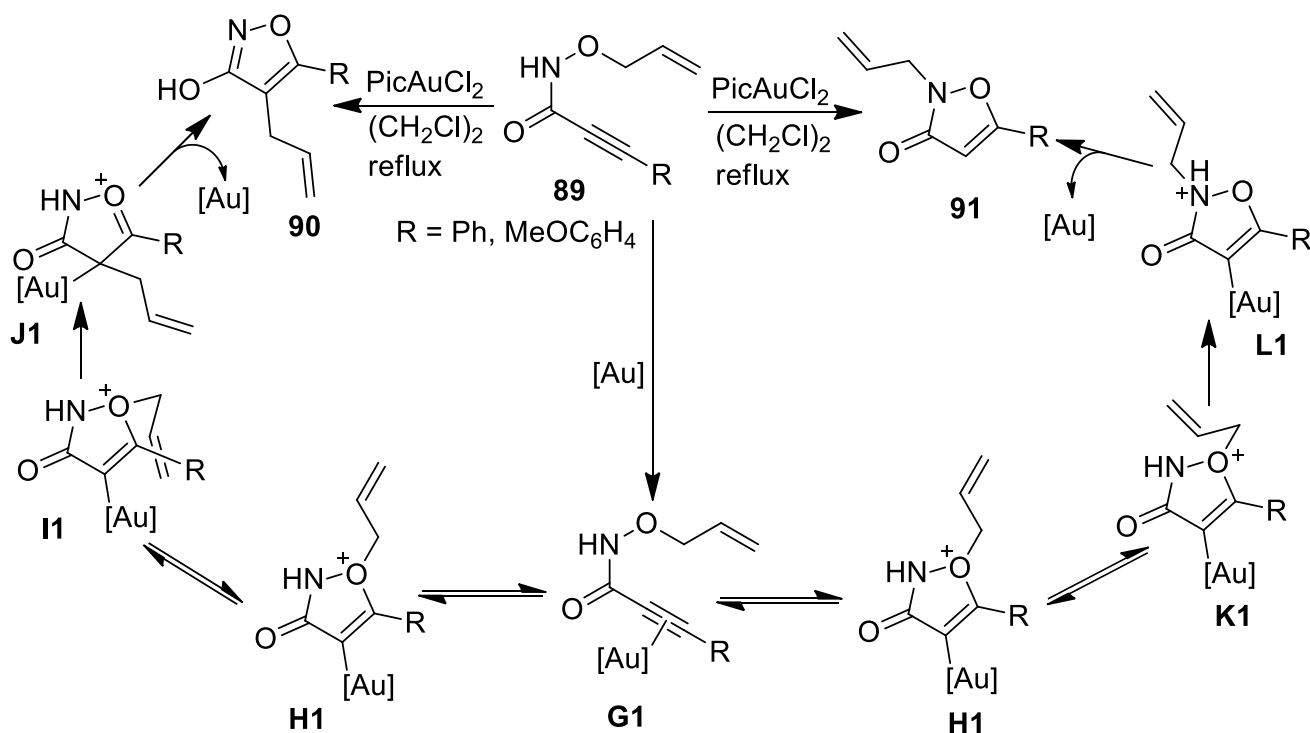
Scheme 33 Gold-catalyzed synthesis of 3-hydroxyisoxazoles **90** and isoxazole-3-ones **91**
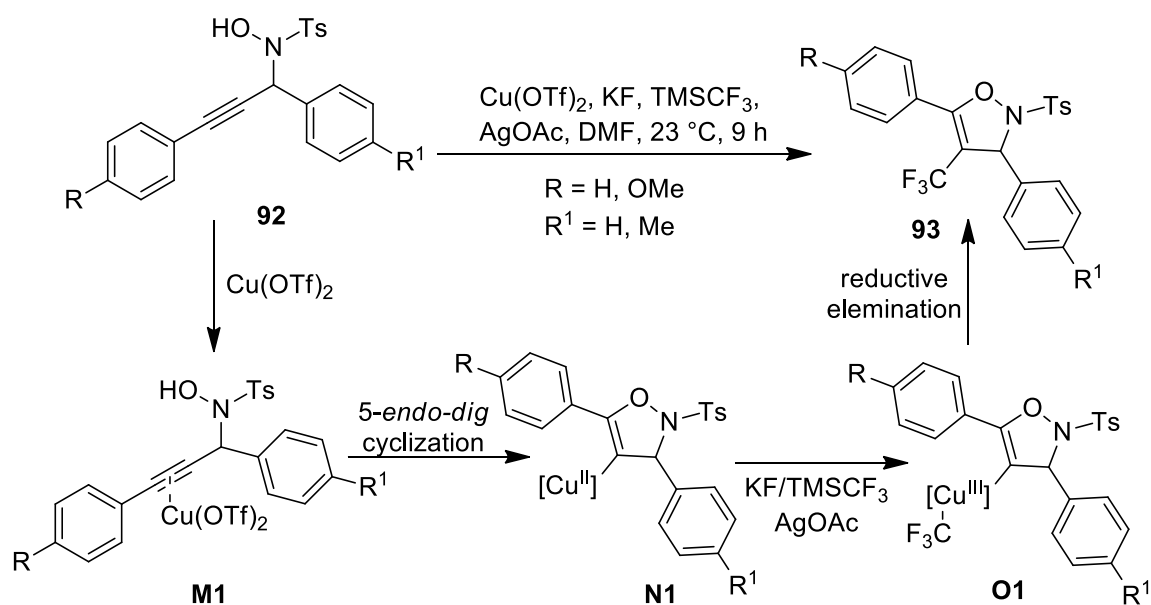
Scheme 34 Synthesis of trifluoromethylated 4-isoxazolines **93**

Scheme 35 Synthesis of *N*-fused heterocycles **96**

at room temperature. Mechanistically, 5-*endo-dig* cycliza-tion of propargyl triazole **97** gives 5-5-bicyclic intermediate **T1**, which further rearranges to give organogold complexes **98** through either 1,5-*H* shift or proton transfer (Scheme 36).
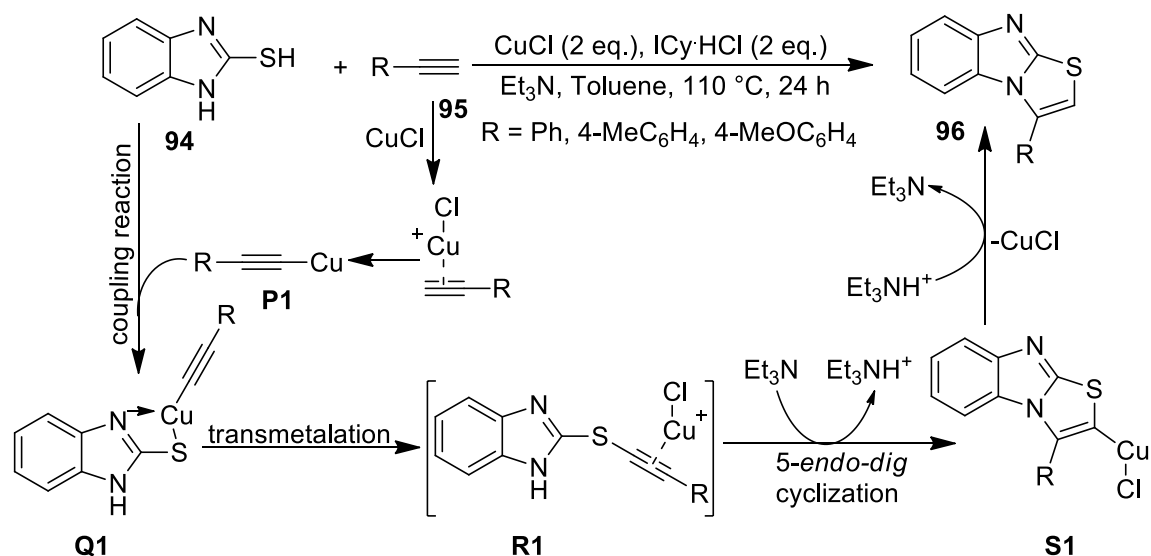
Pyrrole derivatives

Ueda et al. [49] reported the gold(I)-catalyzed preparation of substituted pyrroles **101**. The precursor **99** reacted with substituted acetylene **100** in the presence of AgOTf, gold(I) catalyst and KHSO$_4$ in xylene at 140 °C gives substituted

pyrrole **101** with 52–85% yield. In mechanistic explanation, gold acetylide is added to oxonium ion **U1** to furnish the alkyne adduct **V1**. The electrophilicity of alkyne moiety of **V1** was activated by π-coordination of the gold catalyst to give **W1**, which undergoes 5-*endo-dig* cyclization to afford **X1**. At the end, protonolysis of the carbon–gold bond in **X1** and subsequent aromatization furnishes pyrrole **101** (Scheme 37).

Bharathiraja et al. [50] described the preparation of pen-tasubstituted pyrroles **104** through a cascade reaction involv-ing aza-Michael addition, iodocyclization, and oxidative

Scheme 36 Synthesis of ionic organogold complexes **98**
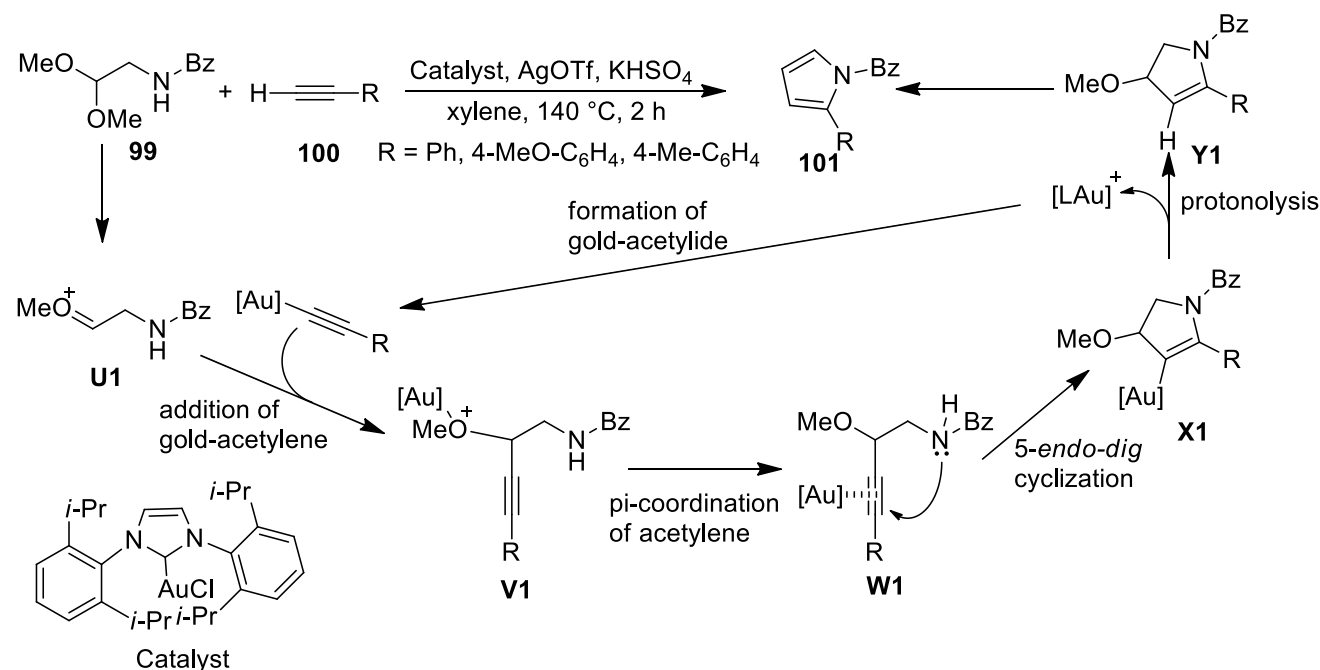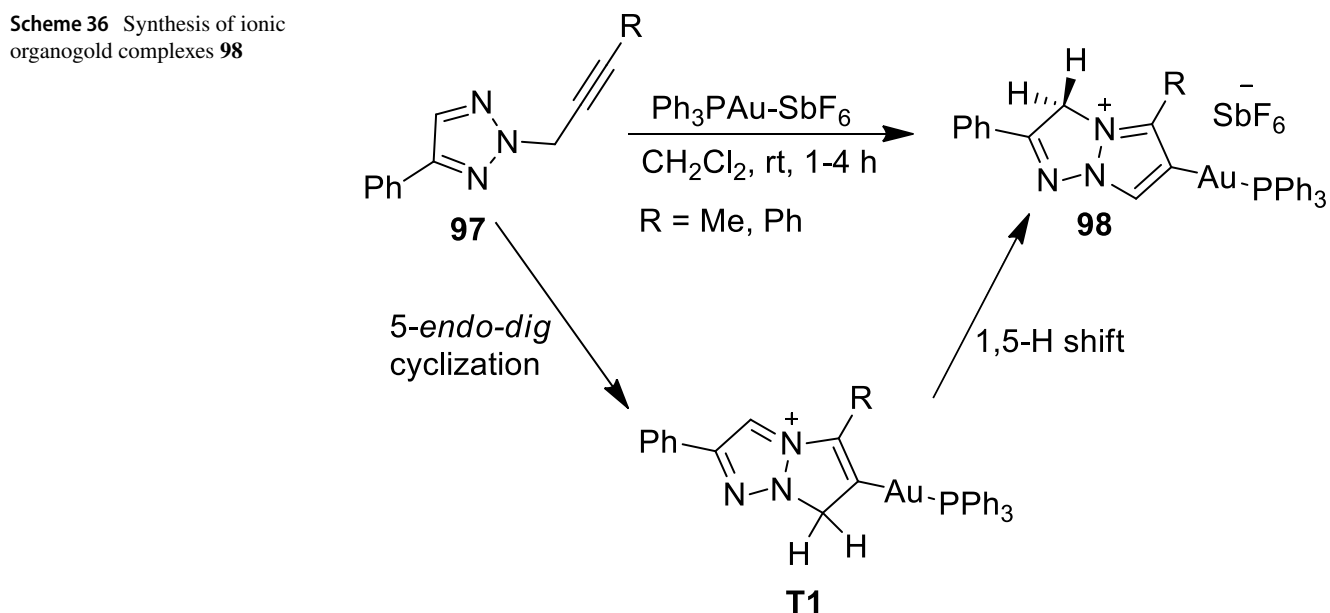
Scheme 37 Synthesis of substituted pyrroles **101**

aromatization. The reaction of 1,3-enynes **102** and amines **103** in the presence of molecular iodine and K_2CO_3 in dichloromethane at room temperature gives pentasubstituted pyrroles **104** with 72–82% yield.

Mechanistically, the intermolecular aza-Michael addition of the amine **103** to the electron-deficient conjugated 1,3-enyne **102** in the presence of iodine furnishes the intermediate **Z1**, which in the presence of base gives the iodonium intermediate **C2**. The intermediate **C2** undergoes

intramolecular cyclization to afford the dihydropyrrole derivative **D2**. The iodine-promoted oxidative aromatization of **D2** gives the required product **104** (Scheme 38).

Queiroz et al. [51] described the 'Pd'/CuI catalyzed preparation of substituted pyrroles **107** in 33–70% yield by reaction of *N*-Boc-β-iododehydroamino acid methyl ester **105** and different terminal alkynes **106** using Pd(II) catalyst, Cs_2CO_3 and CuI in dry DMF at 70 °C. It is one-pot, two-step reaction, in first step Sonogashira coupling gives
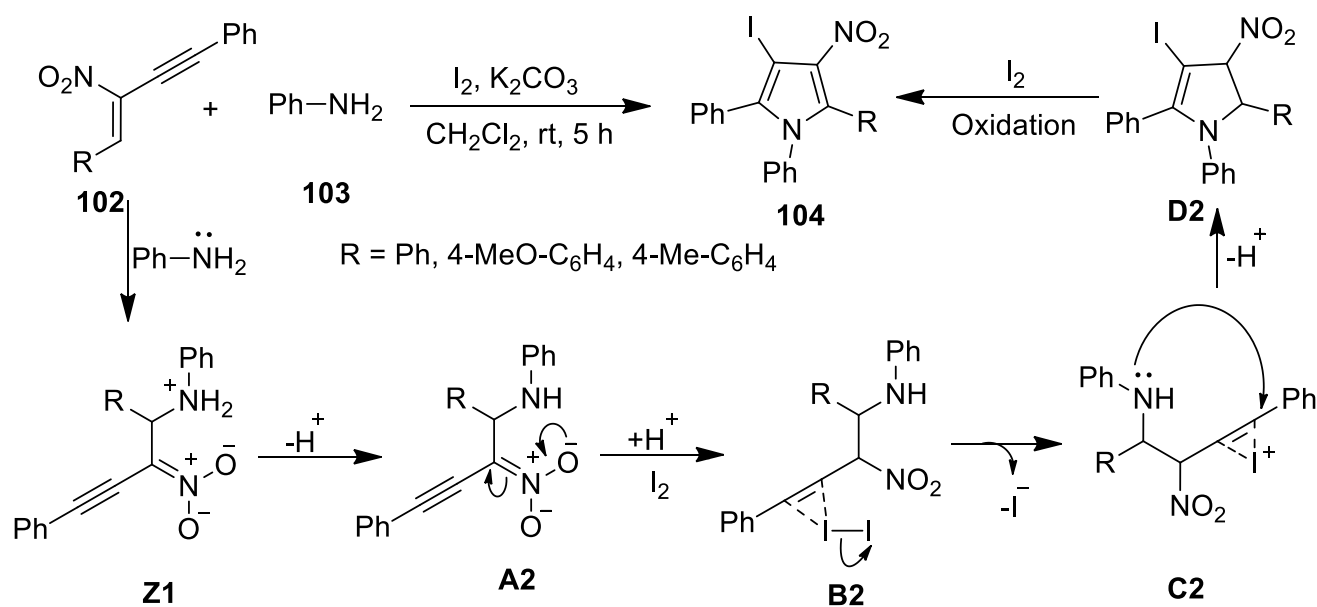
Scheme 38 Synthesis of pentasubstituted pyrroles **104**

intermediate **E2** and tandem 5-*endo-dig* cyclization gives target compound **107** (Scheme 39).

Yan et al. [52] reported the preparation of 2,3-dihydro-1*H*-pyrrolizines **109** with 84–96% yield having electron-withdrawing groups at 5-position via gold-catalyzed 5-*endo-dig* cyclization reaction of azidoenynes **108** in toluene at 80 °C (Scheme 40).

Gorin et al. [53] reported the preparation of substituted pyrroles **111** with 76–88% yield via gold(I)-catalyzed reaction of homopropargyl azides **110** in dichloromethane at 35 °C (Scheme 41). Herein gold(I) catalyst plays dual role, to activate the alkyne for nucleophilic addition and to shift the electron density into electron-deficient π-system.
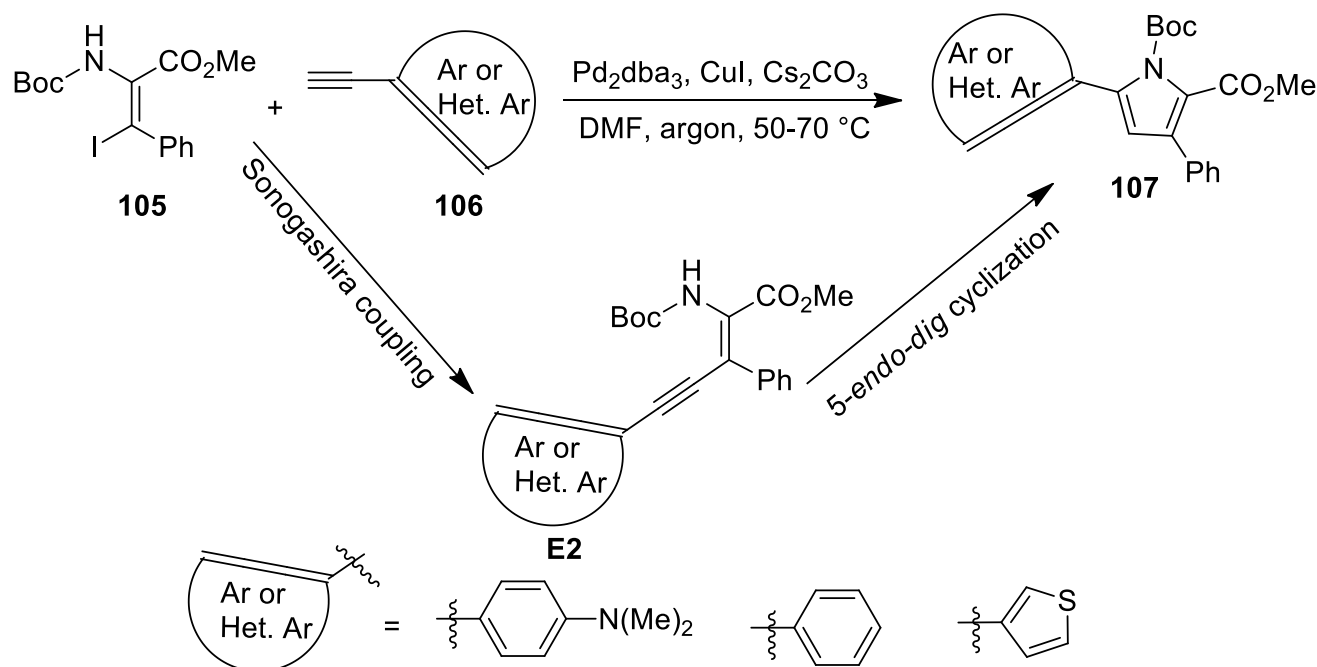
Scheme 39 Synthesis of pyrrole derivatives **107**

Scheme 40 Synthesis of 2,3-dihydro-1*H*-pyrrolizines **109**
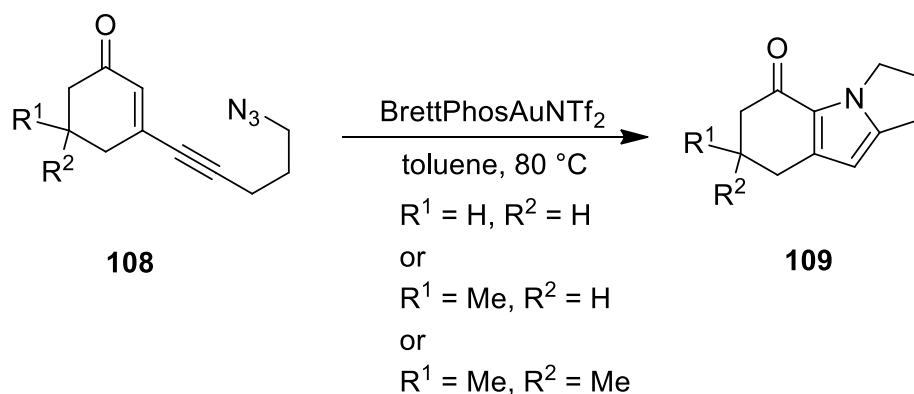
Scheme 41 Synthesis of 2,5-disubstituted pyrroles **111**
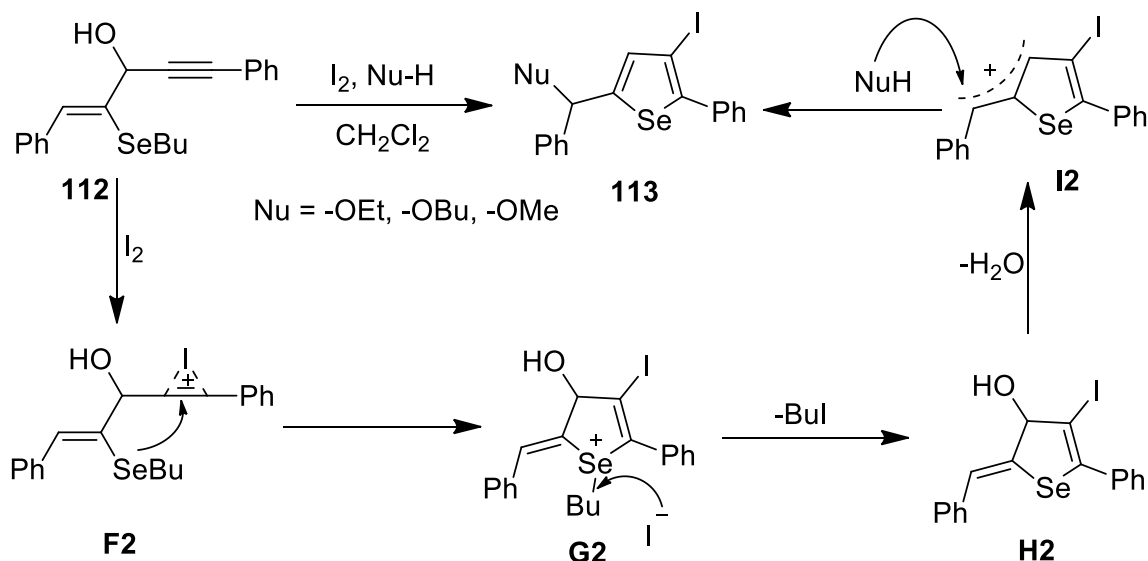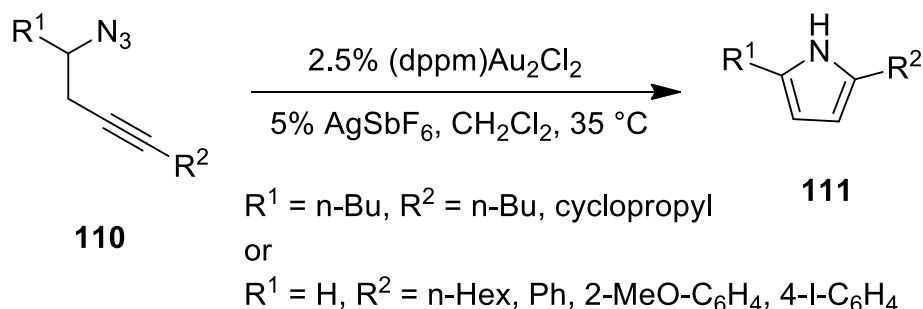
Scheme 42 Synthesis of 3-iodo-selenophenes **113**

Selenophene derivatives

Pistoia et al. [54] reported the iodine-mediated synthesis of 3-iodo-selenophenes **113** through nucleophilic cyclization of selenoenynes **112** in the presence of iodine and nucleophile in dichloromethane. Initial iodine activates carbon–carbon

triple bond of selenoenynes **112** and subsequent nucleophilic attack of the selenium atom onto activated iodonium intermediate **F2** affords the salt **G2**. The elimination of the alkyl group through S_N2 displacement by iodide anion, present in the reaction mixture, gives the dihydroselenophene **H2**. The aromatization of selenophene provides allylic cation **I2**,

which trapped by a nucleophile to give selenophene **113** (Scheme 42).

Spiro-compounds

Adler et al. described cerium(IV) ammonium nitrate (CAN) promoted 5-*endo-dig* cyclization of α-amino allenylphosphonates **114** using CAN at room temperature to give

spirodienones **115** with 80–84% yield. Mechanistically, the *para*-methoxybenzyl ring oxidized to cyclohexadienone carbocation **J2** and subsequent 5-*endo-dig* cyclization to give iminium ion **K2**. The nucleophilic addition of water to **K2** and subsequent prototropy transforms the phosphonate moiety into a leaving group to give the lactam **115** (Scheme 43) [55].

Wu et al. [56] described the gold-catalyzed intramolecular dearomatization reaction of naphthols **116** using
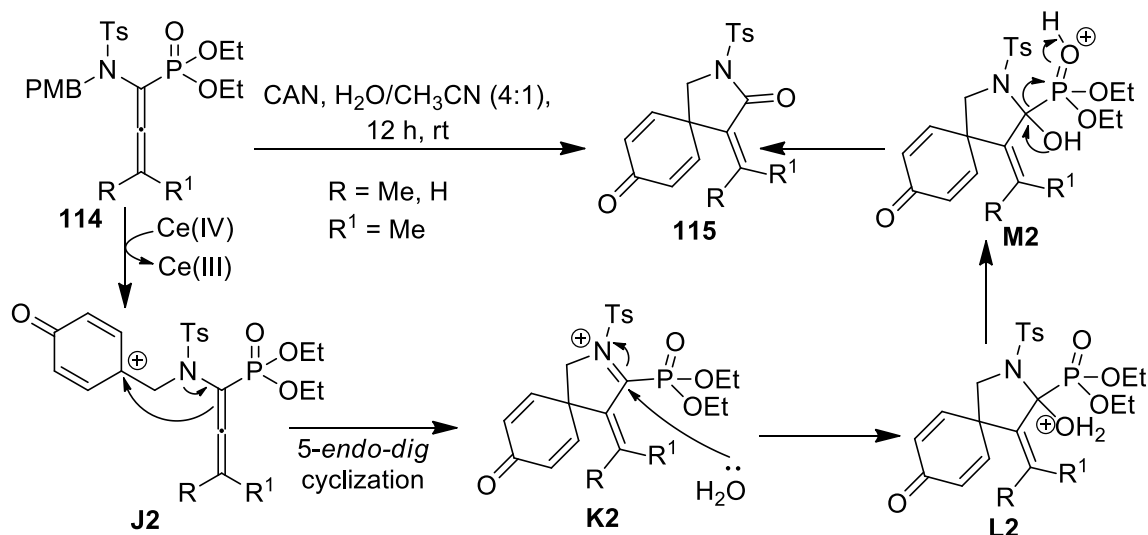
Scheme 43 Synthesis of spirodienones **115**

Scheme 44 Synthesis of spiro-carbocycles **117**
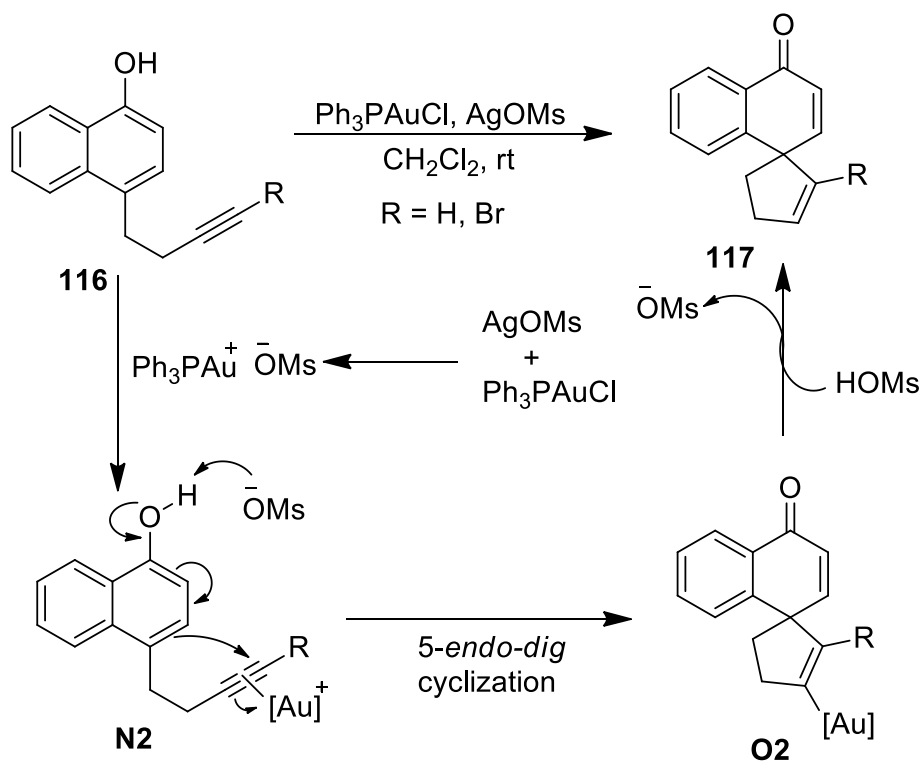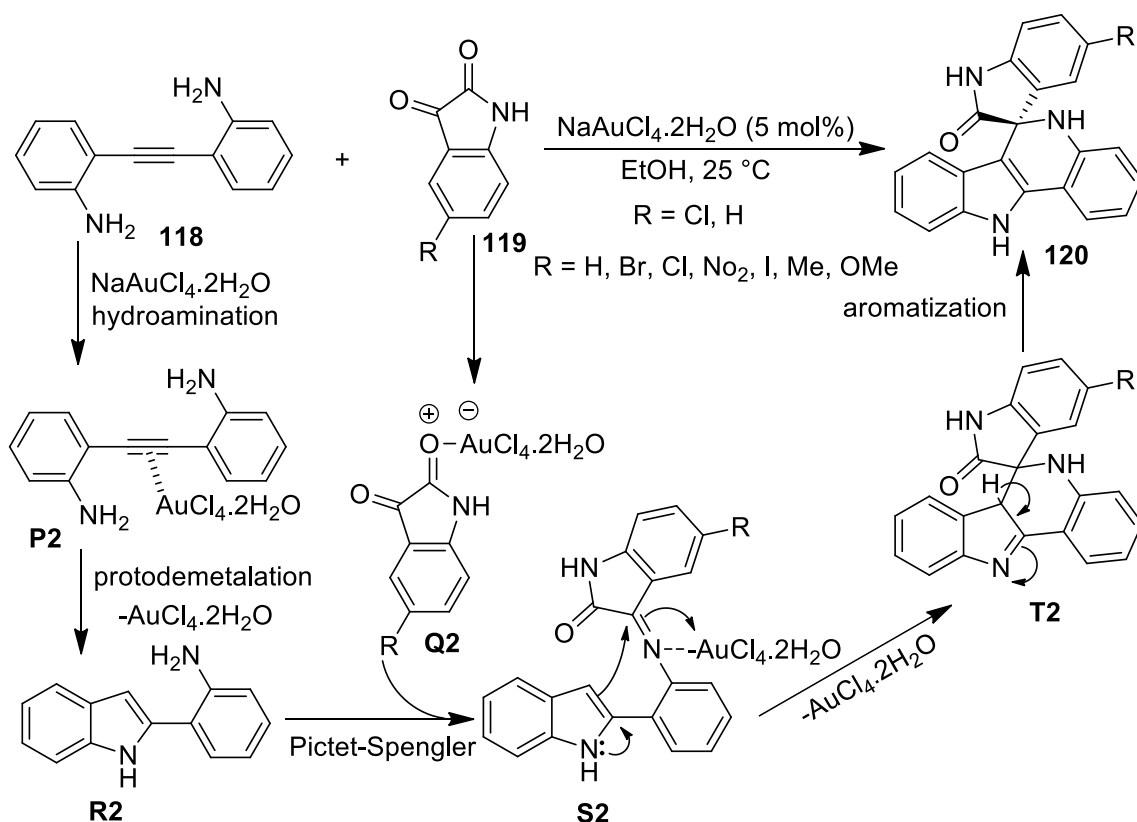
Scheme 45 Synthesis of spiroindolone derivatives **120**

Ph₃PAuCl and AgOMs in dichloromethane at room temperature to afford spirocarbocycles **117** via 5-*endo-dig* cyclization with excellent yield. In mechanistic explanation, the in situ-generated cationic gold(I) complex activated the C–C triple bond in **116**, resulting in 5-*endo-dig* cyclization with the help of parallel deprotonation by the counter anion MsO⁻, yielding the spirocyclic gold intermediate **O2**. Protodemetallation of **O2** via in situ-generated MsOH gives the desired spirocarbocyclic product **117** (Scheme 44).

Reddy et al. [57] reported the gold-catalyzed 5-*endo-dig/* spirocyclization of 2-[(2-aminophenyl)ethynyl]phenylamine **118** with isatins **119** by using NaAuCl₄·2H₂O in EtOH at 25 °C to afford corresponding spiroindolone derivatives **120** with 70–88% yield. Mechanistically, the gold(III) species coordinates to the alkyne part of **118** and subsequent nucleophilic attack of the tethered amino group, followed by protodemetalation to give *N*-(2-aminophenyl)indole **R2**. Thus imine **S2** obtained by the condensation of activated isatin and **R2**. Subsequently, gold activated the imine leading to the nucleophilic attack of the indole onto imine **S2** to give **120** (Scheme 45).

Conclusion

This review illustrates the recent applications of 5-*endo-dig* cyclizations in organic synthesis for last two decades and clearly depicted by the class of formed heterocyclic and carbocyclic compounds such as indoles, cuomarins, cyclopentenes, benzofurans, furans, pyrroles. These heterocycles and carbocycles are often observed in many pharmaceutical substances, functional materials and biologically active compounds. Also this review expresses the synthesis of organogold complexes as well as spiro-compounds.

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