

Metal-mediated synthesis of furans and pyrroles

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Dedicated to Professor Alan Krief on the Occasion of his 65th Birthday

Abstract

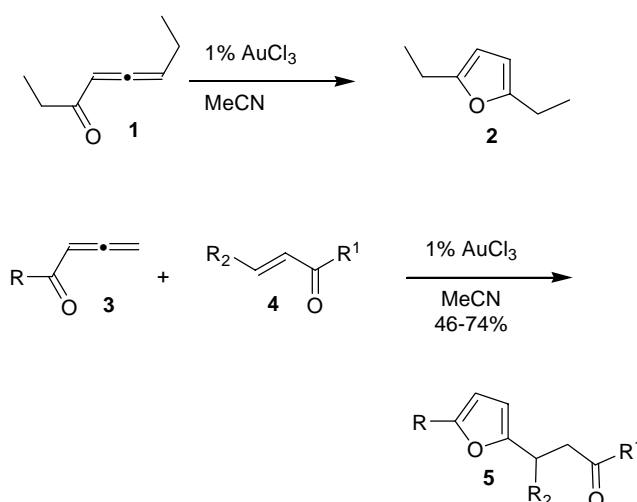
The transition metal catalyzed synthesis of furans and pyrroles is becoming an important and highly rewarding protocol in organic synthesis. This review focuses on the use of transition metal as a catalyst for the synthesis of furans and pyrroles along with their interesting mechanistic aspects. The synthetic efforts in this area will clearly culminate in tackling the major issues pertaining to atom economy and environmentally acceptable technologies for future.

Keywords: Metal catalysis, furans, pyrroles, cascade cyclization

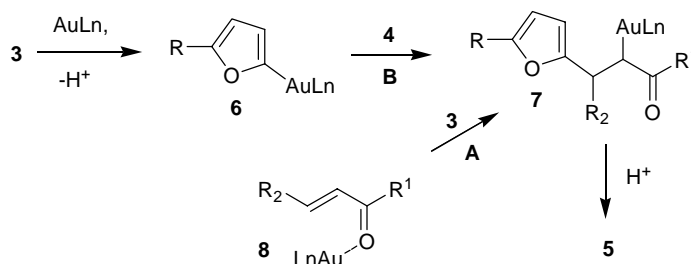
Introduction

Highly substituted furans¹ and pyrroles² are a structural component of a vast number of biologically active natural and unnatural compounds. Synthesis of them has been the objective of research for over a century, and a variety of well-established classical methods are now available in the literature.³ Development of newer approaches for heterocycle syntheses employing efficient and atom economical routes is popular research area nowadays. Among a variety of new synthetic transformations, transition metal catalyzed reactions are the most attractive methodologies, since those reactions can directly construct multiply substituted molecules from readily accessible starting materials under mild conditions.⁴ The formation of furans and pyrroles by using various transition metals has been investigated in the literature. Since the synthesis of these heterocycles is thoroughly reviewed up to 1999 and 2001, respectively, this review will discuss recent advances for the synthesis of furans and pyrroles focusing on the use of transition metals.⁵ It should be noted that the reactions in which a heterocyclic ring is essentially generated are only described. Other reactions in which a heterocyclic ring already exists in the molecule and a transition metal catalyzes the further structural manipulations are not described here.

It is reported that cyclization of allenyl ketone **1** provided furan **2** in the presence of catalytic amounts of AuCl_3 . The reaction was extended also to one pot selective cross cycloisomerization/dimerization of **3** with α,β -unsaturated ketones **4** to give C-2 substituted furans **5** (Scheme 1).⁶ The mechanism of the reaction is shown in Scheme 2. The authors believed the intermediacy of **7** and proposed two possibilities for the formation of it. Either the AuCl_3 activates the enones **4** to form **8**, which then create the new C-C bonds by an electrophilic aromatic substitution at the 5-position of the furan to provide **7** (path A), or a cyclization of **3** under gold catalysis forms a furyl-gold species **6**, which subsequently undergoes a 1,4-addition to the Michael acceptor (path B). The intermediate **7** then undergoes proto-demetalation to form **5** along with regeneration of the gold catalyst. Recently, gold(III) porphyrin complexes have been utilized for the cyclization of allenones.⁷



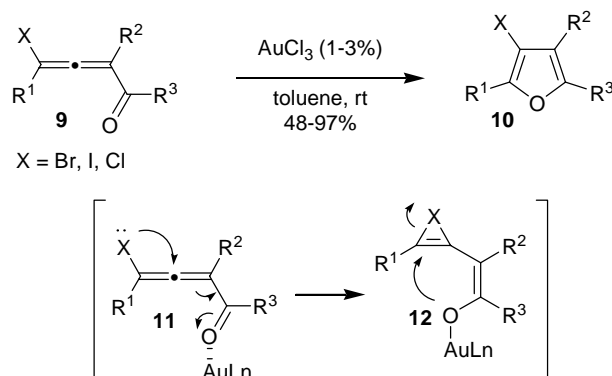
Scheme 1



Scheme 2

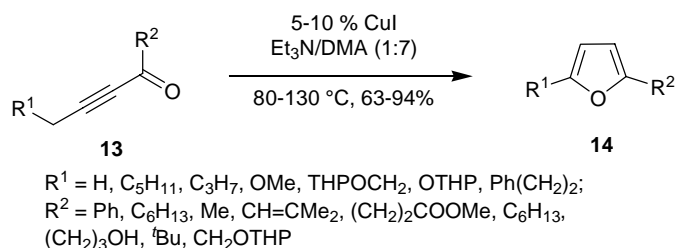
Gevorgyan *et al.* have shown that 1,2-iodine, -bromine, and -chlorine migration in haloallenyl ketones **9** takes place in the presence of AuCl_3 .⁸ For this reaction iodo and bromo allenyl ketones gave best results, compared to their chloro analogue. This chemistry is interesting not only as a novel cascade transformation but also serves as a mild, selective, and efficient approach to different types of 3-halofurans **10**. It was reported that the reaction proceeded through halirenium intermediate **12**, formed by the intramolecular Michael addition of X to the

enone moiety as shown in **11**, which *via* subsequent addition-elimination furnishes 3-halofurans **10** (Scheme 3). It is interesting to note that just by switching solvent from toluene to THF caused a dramatic change in selectivity affording 2-bromofurans as the major product.

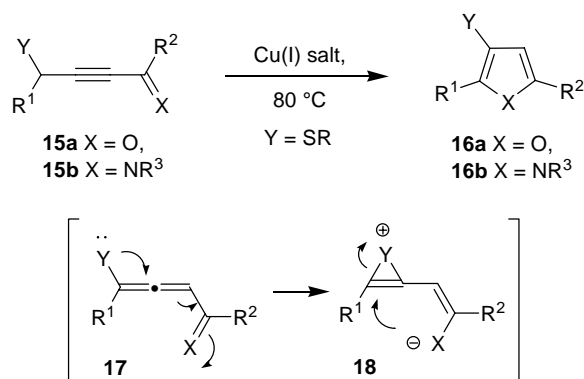


Scheme 3

Gevorgyan and coworkers have shown that alkynes can also be used, instead of allenes, for such transformations. They developed an efficient method for the synthesis of 2-monosubstituted and 2,5-disubstituted furans **14** *via* the CuI catalyzed cycloisomerisation of alkynyl ketones **13** (Scheme 4).⁹ It was demonstrated that furans containing both acid and base labile groups could be easily synthesized using this methodology. Pioneering work from the same group revealed that 3-thio substituted furans **16a** and pyrroles **16b** could be easily obtained from propargyl ketones **15a** and propargyl imines **15b**, respectively, by heating in *N,N*-dimethylacetamide in the presence of CuI (Scheme 5).¹⁰ The key in the mechanism was the 1,2 migration of the Y group from sp^2 carbon atom in allenyl species as shown in intermediate **17** and **18**.

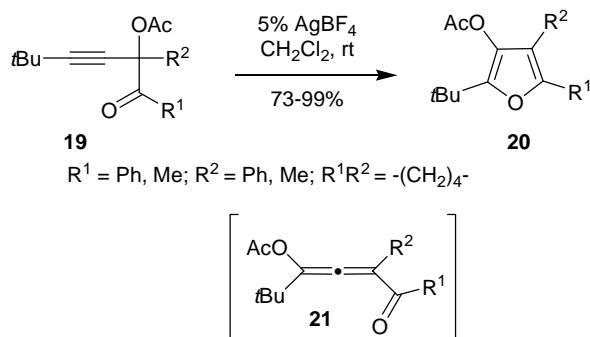


Scheme 4



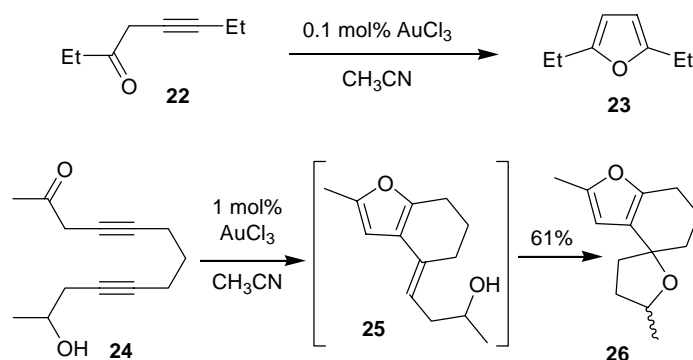
Scheme 5

The same group reported a new method for the synthesis of furans **20** from alkynyl ketones **19** *via* 1,2 migration of acetate groups (Scheme 6).¹¹ The reactions were conducted in the presence of 5 mol% AgBF₄ and at room temperature. Not only acetate group but also -OP(O)(OEt)₂ and -OTs group were migrated, however, somewhat high temperature (60 °C) was needed in order to complete the reaction. The reaction involves the intermediacy of allene **21**. This is the first example of 1,2-migration of acyloxy, phosphatyloxy and sulfonyloxy groups from sp² carbon.



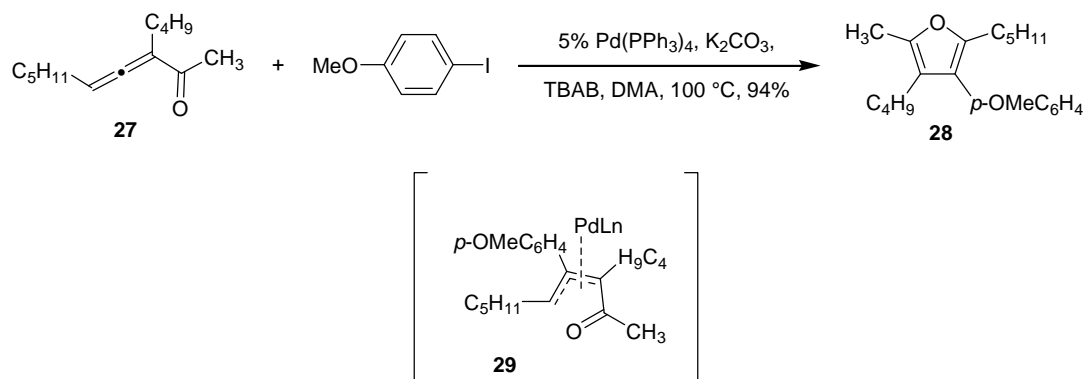
Scheme 6

The reaction of propargyl ketone such as **22** in the presence of 0.1 mol% AuCl₃ at 20 °C gave the furan **23** in essentially quantitative yield (Scheme 7). **Error! Bookmark not defined.** On the other hand, with palladium as a catalysts, heating at 100 °C was needed in order to proceed the reaction. A novel cascade cyclization of the propargyl ketone **24** for the formation of **26** in the presence of AuCl₃ was also reported in the same paper. The authors proposed the intermediacy of **25** for this cascade cyclization.



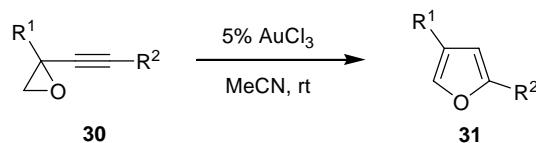
Scheme 7

The introduction of substituents at the C-4 position of the corresponding furans using a transition metal catalyzed cycloisomerization approach is generally considered as difficult task. Recently, Ma and co-workers reported palladium catalyzed cross coupling cyclization sequence to produce tetrasubstituted furan **28** from allenyl ketones **27** and *p*-iodoanisole (Scheme 9).¹² The species **29** was proposed as an intermediate.

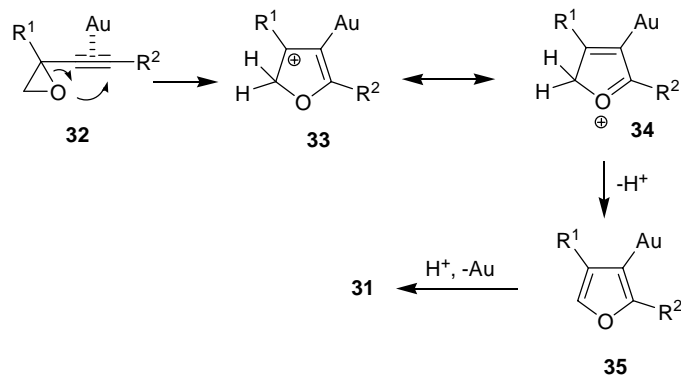


Scheme 8

An isomerization of alkynyl epoxides **30** into furans **31** in the presence of gold(III) chloride took place at room temperature (Scheme 9).¹³ The coordination of the triple bond of **30** to AuCl₃ enhances the electrophilicity of alkyne (cf **32**), and the subsequent nucleophilic attack of the epoxide oxygen at the distal position of alkyne forms the species **33**, which on isomerization-deprotonation-protodemetalation (cf **34** and **35**) gives furans **31** (Scheme 10).

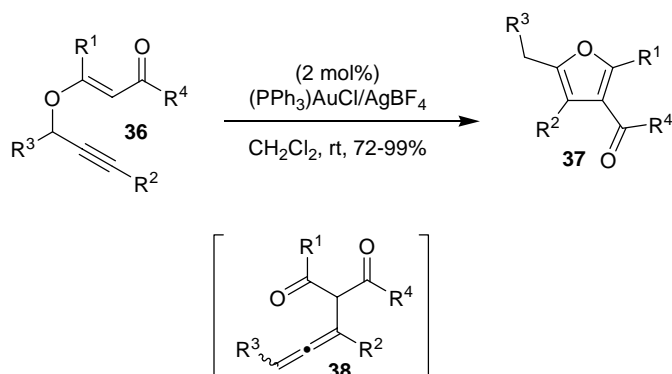


Scheme 9



Scheme 10

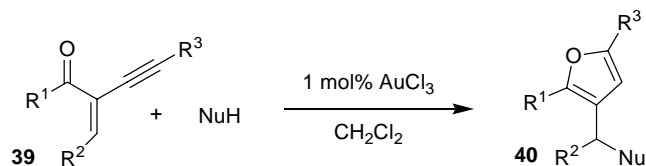
Kirsch and coworkers recently described the synthesis of highly substituted furans **37** from **36** mediated by gold(I) species.¹⁴ The reaction is accomplished at room temperature just by using 2 mol% catalyst loading. A mechanism for the cascade cyclization involves the formation of β -allenic ketone **38** which then undergoes gold(I) catalyzed 5-*exo-dig* cyclization affording furans **37** (Scheme 11).



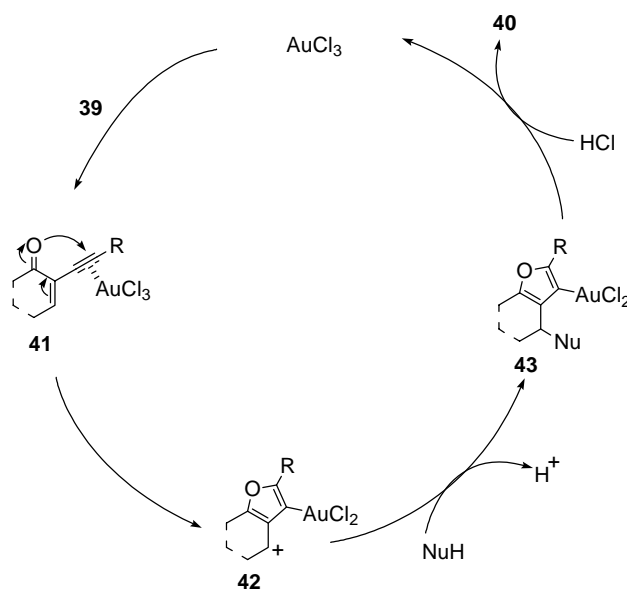
Scheme 11

Recently, Larock reported an entirely new approach for the novel cyclization of 2-(1-alkynyl)-2-alken-1-ones **39** with nucleophiles in the presence of catalytic amounts of AuCl_3 which led to the formation of highly substituted furans **40** (Scheme 12).¹⁵ Examples of nucleophiles include alcohols, activated methylenes and electron rich arenes such as *N,N*-dimethylaniline and *N*-methyl indole. The mechanism of the reaction is depicted in Scheme 13. The coordination of the triple bond of **39** to AuCl_3 enhances the electrophilicity of the triple bond (cf **41**), and subsequent nucleophilic attack of the carbonyl oxygen on the electron-deficient triple bond generates carbocation **42**. Intermolecular nucleophilic attack of nucleophiles on the carbocation gives furyl gold species **43**, which after protonation of the carbon-gold bond affords furans **40** and regenerates the catalyst AuCl_3 . The authors ruled out the possibility of an

alternative mechanism wherein AuCl_3 first acts as a Lewis acid, forming a complex with the carbonyl oxygen thereby facilitating Michael addition. We later showed that inexpensive and air stable Cu(I) in DMF could also be used as a catalyst for this reaction.¹⁶

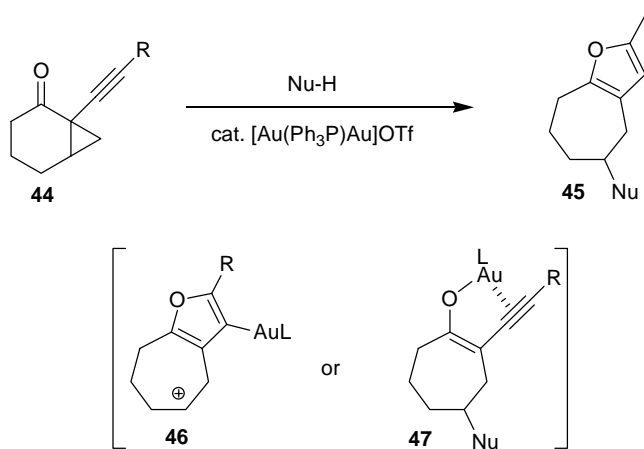


Scheme 12



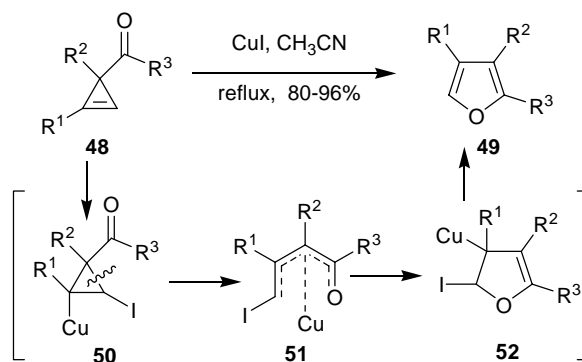
Scheme 13

Recently, Schmalz and Zhang reported the gold catalyzed atom economical cascade cyclization of the substrates of type **44** (Scheme 14).¹⁷ The process provided efficient access to highly substituted furans **45** under mild conditions. A variety of nucleophiles, such as alcohols (including *tert*-butanol), phenols, or acetic acid can be used for the reaction. The preparation of the substrate is also easy and they can be prepared by the cyclopropanation of corresponding enones. Two different intermediates **46** and **47** were proposed for this reaction.

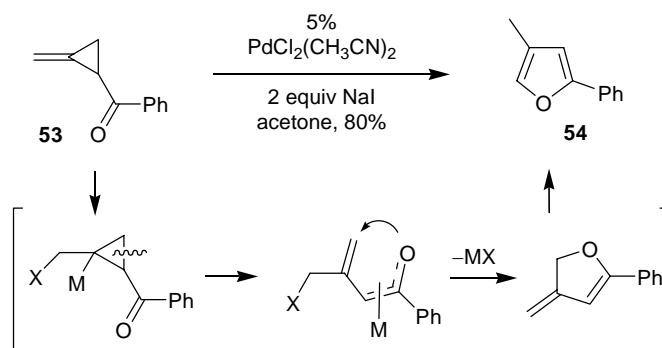


Scheme 14

Ma and Zhang developed copper (I) catalyzed regioselective cycloisomerization of cyclopropenyl ketones **48** into 2,3,4-trisubstituted furans **49** (Scheme 15).¹⁸ The regioselective iodocupration of the C=C bond of **48** produces **50** which on subsequent β -decarbocupration gives delocalized intermediate **51**. The intramolecular endo-mode insertion of the C=C bond into the oxygen-copper bond of intermediate **51** and subsequent β -halide elimination of intermediate **52** affords **49** with the regeneration of CuI. They also reported the isomerization of **53** into furan **54** in refluxing acetone in the presence of $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ and 2 equiv of sodium iodide (Scheme 16).¹⁹

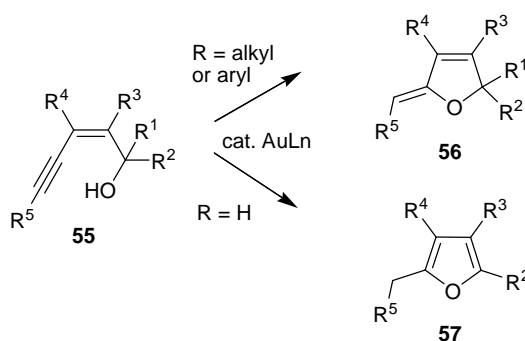


Scheme 15



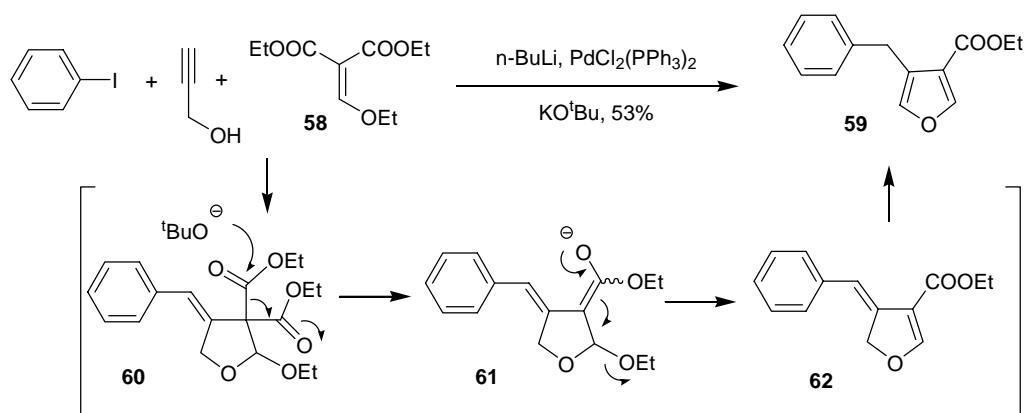
Scheme 16

The gold-catalyzed cyclization of (*Z*)-enynols **55** afforded (*Z*)-5-ylidene-2,5-dihydrofurans **56** and fully substituted furans **57** depending on the nature of R^1 group (Scheme 17).²⁰ For instance, when $\text{R} = \text{alkyl}$ or aryl , **56** was formed. On the other hand when $\text{R} = \text{H}$, **57** was obtained. Two reaction conditions were employed; i) AuCl_3 in CH_2Cl_2 ii) $(\text{PPh}_3)_3\text{AuCl}/\text{AgOTf}$. Both of them generally gave products in high yields.



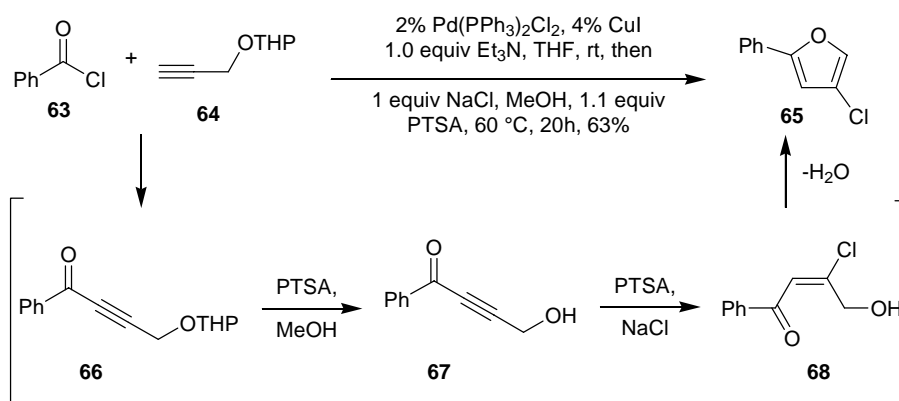
Scheme 17

A novel one pot procedure for the synthesis of functionalized furan derivatives **59**, from **58**, propargyl alcohol and iodobenzene, has been reported by Balme *et al.* (Scheme 18).²¹ It involves a conjugate addition between **58** and propargyl alcohol, a palladium-catalyzed coupling-cyclization (cf **60**), an alkoxide-induced decarboxylative elimination (cf **61**), and finally, a double bond isomerization (cf **62**).



Scheme 18

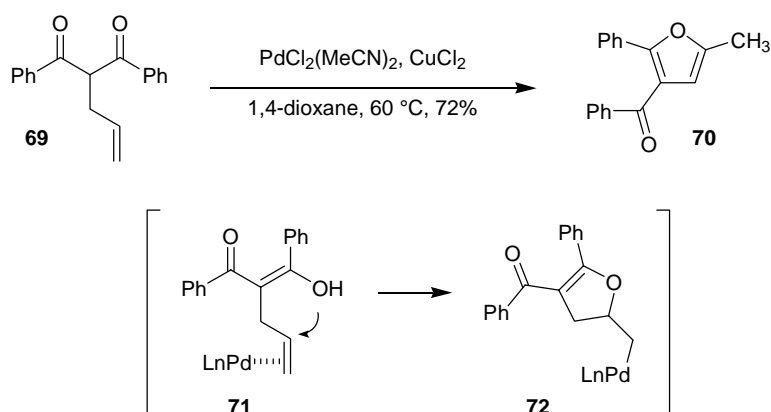
A novel sequence of Sonogashira coupling and electrophilic addition to an ynone, with concomitant deprotection and cyclocondensation, opens a new one-pot synthesis of 3-halofurans; the method can be readily elaborated to a new sequential Sonogashira–addition–cyclocondensation–Suzuki reaction to furnish 2,3,5-trisubstituted furans in a one-pot fashion. For example, reaction of **63** with **64** in the presence of Pd–Cu bimetallic system formed **66** which on treatment with PTSA gives **65** via intermediates **67** and **68** (Scheme 19).²²



Scheme 19

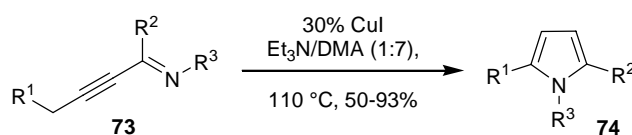
Widenhoefer and Han developed an efficient, one-pot procedure for the conversion of α -alkenyl β -diketones to 2,3,5-trisubstituted furans (Scheme 20).²³ Treatment of 4-allyl-2,6-dimethyl-3,5-heptanedione **69** with a catalytic amount of $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (5 mol %) and a stoichiometric amount of CuCl_2 (2.2 equiv) in dioxane at 60 °C for 12 h formed 3-isobutyryl-2-isopropyl-5-methylfuran **70** in 77% isolated yield. A number of α -alkenyl β -diketones underwent oxidative alkoxylation under these conditions to form 2,3,5-trisubstituted furans in moderate to good yield. Mechanistically, nucleophilic attack of enolic oxygen atom on the palladium-

complexed olefin (cf 71) would form the palladium dihydrofurylmethyl intermediate **72** which undergo β -hydride elimination and proton migration to afford furan **70**.

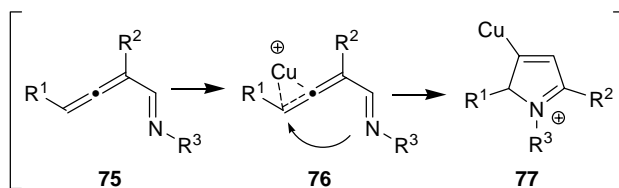


Scheme 20

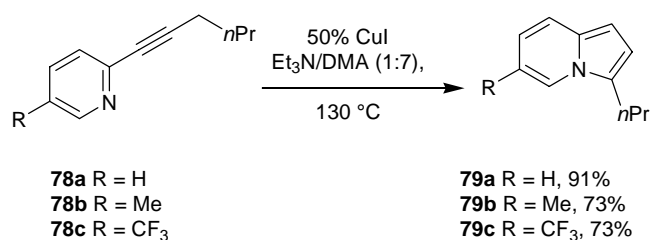
Gevorgyan *et al.* reported a new route for the synthesis of pyrroles **74** via copper(I) catalyzed cyclization of alkynyl imines **73** (Scheme 21).²⁴ Mechanistic studies revealed that this reaction proceeded *via* the propargyl-allenyl isomerization of **73** to the allenyl imines **75** and through the nucleophilic attack of the nitrogen atom of imine on the electron deficient carbon as shown in intermediate **76** which forms the copper containing pyrrole ring skeleton **77**. Isomerization in **77**, protonation and regeneration of the catalyst afford pyrroles **74**. They also applied this methodology for the synthesis of indolizidines. The copper assisted reaction of the 2-alkynylpyridines **78** provided the indolizidine derivatives **79** in good yields (Scheme 22).²⁵ The copper assisted double cyclization of bis-alkynylpyrimidine **80** afforded the 5-6-5 tricyclic heteroaromatic skeleton **81** (Scheme 23). This transformation was used as a key step in the highly diastereoselective total synthesis of (\pm)-tetraonerine T6.



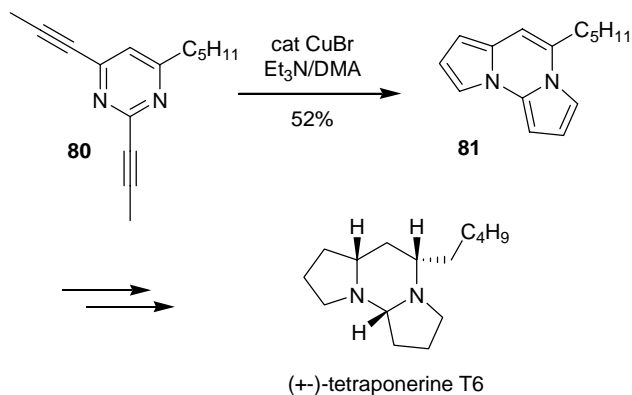
$\text{R}^1 = n\text{Bu}$, $\text{CH}_3(\text{CH}_2)_3\text{CH}=\text{CH}_2$, $\text{CN}(\text{CH}_2)_2\text{CH}_2$, $\text{OTBSCH}_2\text{CH}_3$, OTBS , H , $n\text{Pr}$; $\text{R}^2 = \text{H}$, $n\text{Pr}$, Ph , Me ; $\text{R}^3 = n\text{Bu}$, $t\text{Bu}$, Tr , 3-(ethylbutyryl), Ph



Scheme 21

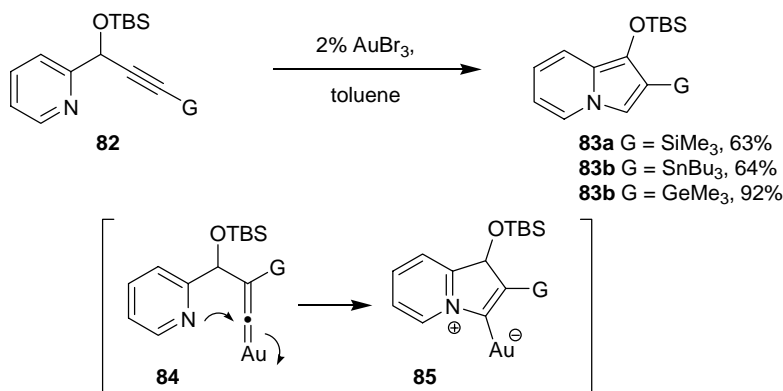


Scheme 22



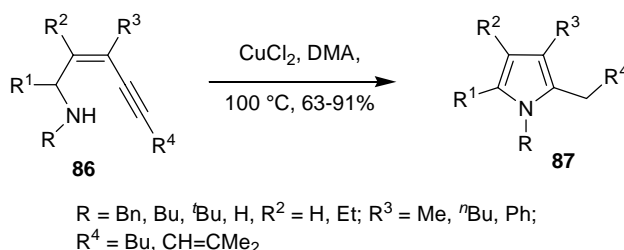
Scheme 23

A new gold catalyzed cascade cycloisomerization of propargylic derivatives **82** into pyrrole containing heterocycles **83** is known (Scheme 24).²⁶ This cascade transformation involves 1,2-migration of silyl, stannyl and germyl group and allows an efficient synthesis of various C-2 substituted fused pyrrole containing heterocycles. Mechanistically, first isomerization of alkyne **82** results in the formation of vinylidene species **84** followed by nucleophilic attack of the nitrogen lone pair at the vinylidene carbon resulting in formation of zwitterions **85** which undergo a series of 1,2-hydride shifts to furnish **83**.



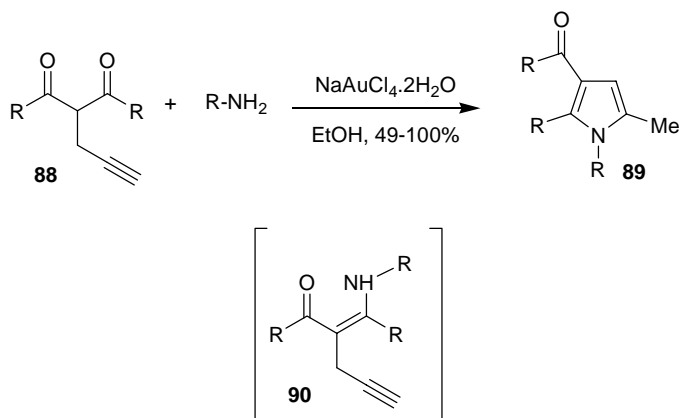
Scheme 24

The cyclization of (*Z*)-(2-en-4-ynyl)amines **86** into pyrroles **87** was reported by Gabriele and coworkers (Scheme 25).²⁷ CuCl₂ was found to be an excellent catalyst for the cyclization of the substrates substituted at C-3, while PdX₂ in conjunction with KX (X= Cl, I) turned out to be a superior catalyst for the reaction of enynamines unsubstituted at C-3.



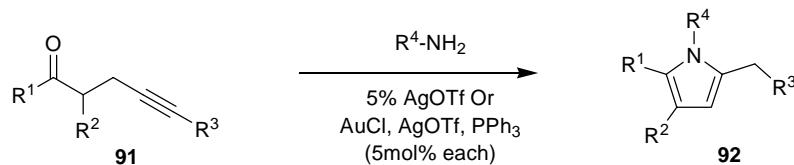
Scheme 25

The gold(III)-catalyzed sequential amination/annulation reaction of 2-propynyl-1,3-dicarbonyl compounds **88** with primary amines produces 1,2,3,5-substituted pyrroles **89** in moderate to high yields (Scheme 26).²⁸ The reaction of **88** with primary amines under the reaction conditions generates enaminone intermediate **90**. The cyclization of **90** through 5-*exo-dig* pathway followed by protonolysis of the resulting C-Au bond and subsequent isomerization reaction afford the pyrroles **89**.

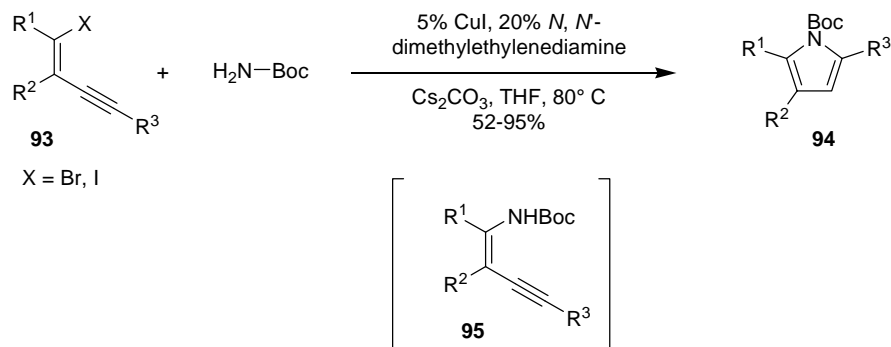


Scheme 26

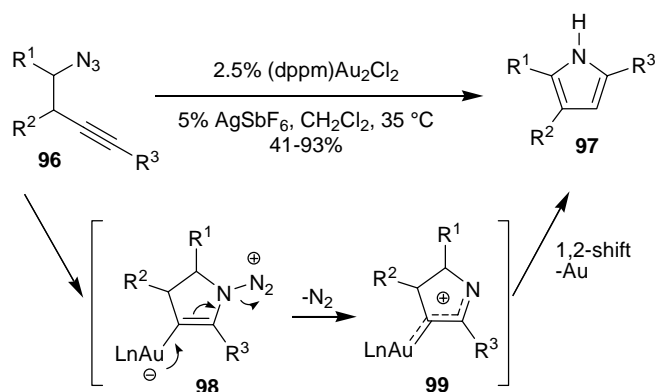
Dake and coworkers reported a domino process for the synthesis of pyrroles **92** starting from ketoalkyne **91**, and amines. Either silver trifluoromethanesulfonate or a mixture of gold(I) chloride, silver trifluoromethanesulfonate, and triphenylphosphine catalyze the formation of pyrroles from substituted β -alkynyl ketones and amines (Scheme 27).²⁹ The reactions proceed by using 5 mol % of catalyst with yields of isolated pyrroles ranging from 13% to 92%.

**Scheme 27**

A domino process involving copper catalyzed C-N coupling and intramolecular hydroamidation for the synthesis of pyrroles **94** from haloenynes **93** (via intermediate **95**) was described by Buchwald and coworkers (Scheme 28).³⁰ The reaction of a substrate bearing a terminal alkyne did not give the product, however, this transformation can be accomplished by the use of a -TMS group which masks the terminal acetylene and is deprotected in situ.

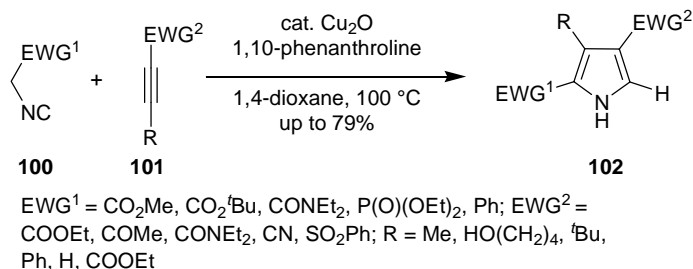
**Scheme 28**

Toste and coworkers developed gold(I) catalyzed intramolecular acetylenic Schmidt reactions of homopropargyl azides **96** for the synthesis of multiply substituted pyrroles **97** (Scheme 29).³¹ The reactions were performed under extremely mild conditions and preparation of the catalyst was also very easy. A new aspect of gold chemistry has been proposed; gold (I) serves as both to activate the alkyne to form **98** and also to donate electron density back into an electron deficient π -system as shown in **99**. Recently, Hiroya *et al.* showed that PtCl₄ in ethanol is also capable of catalyzing this reaction in the presence of suitable base.³²

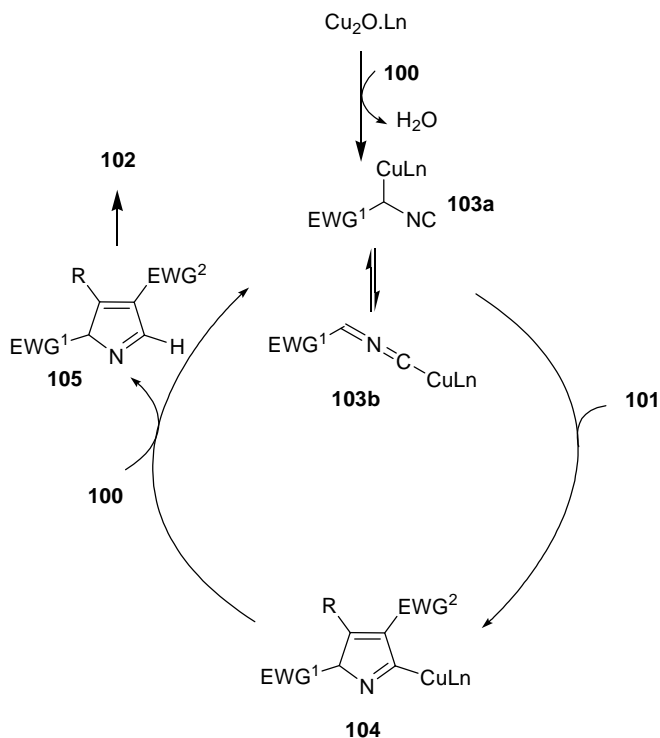


Scheme 29

The copper catalyzed reaction of isocyanides **100** with electron deficient alkynes **101** gave substituted pyrroles **102** (Scheme 30).³³ Among the catalysts tested, the combination of Cu₂O and 1,10-phenanthroline showed the highest catalytic activity. A proposed mechanism is illustrated in Scheme 31. The 1,4-addition of the nucleophilic intermediate **103a** or **103b**, generated from **100** with the extrusion of H₂O, to the alkynes **101** takes place first. The newly generated copper enolate would intramolecularly attack the isonitrile carbon to generate the cyclized intermediate **104**. This process can be termed as a formal [3 + 2] cycloaddition process. The C-Cu bond in the intermediate **104** is protonated by isocyanides, and the intermediate **105** is produced with regeneration of the copper-intermediate **103**. 1,5-Hydrogen shift in the intermediate **105** forms the pyrroles **102**.

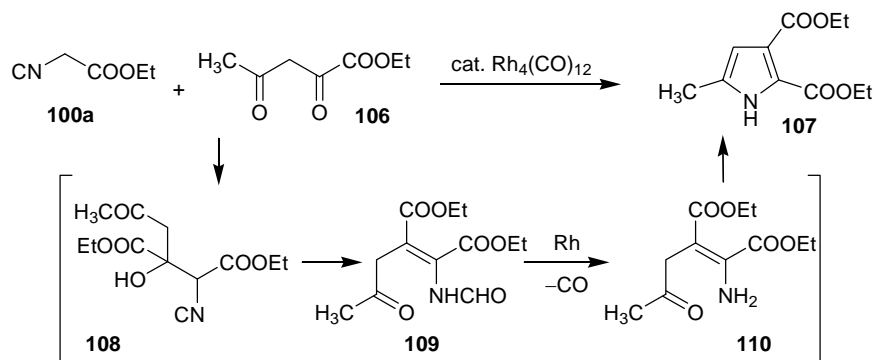


Scheme 30



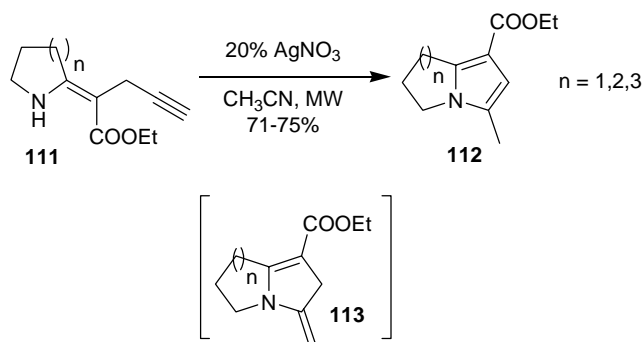
Scheme 31

Murahashi et al. reported rhodium catalyzed route for the synthesis of pyrroles **107** from isonitriles **100a** and 1,3-dicarbonyl compounds **106** (Scheme 32).³⁴ The route is based on the activation of α C-H bond of isonitriles followed by addition of it to carbonyl compounds (cf **108**) proceeds under mild and neutral conditions to give the corresponding α,β -unsaturated formamides **109**. Rhodium catalyzed decarbonylation of **109** followed by cyclocondensation of enamino intermediate **110** would give pyrrole **107**.



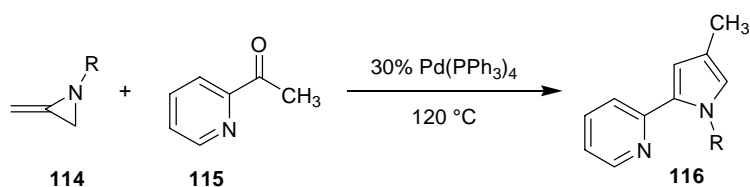
Scheme 32

The concept of silver catalyzed intramolecular hydroamination to pyrrole synthesis was reported by Dovey and coworkers for the synthesis of *N*-bridgehead pyrroles **112** from amino alkynes **111** using microwave irradiation. The reaction was believed to proceed *via* intermediate **113** which on proton migration afford products (Scheme 33).³⁵

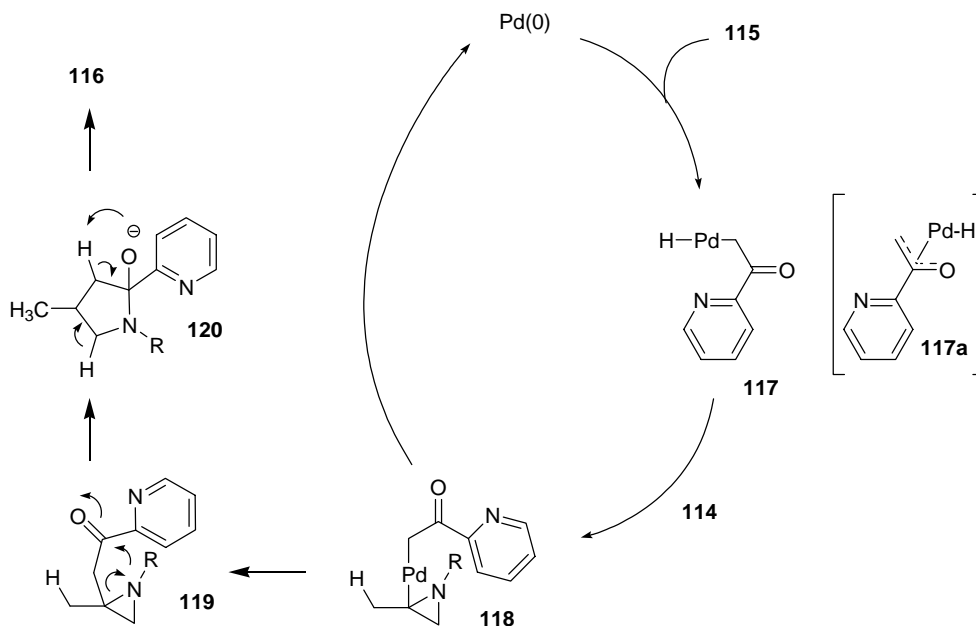


Scheme 33

The palladium-catalyzed reaction of the methyleneaziridines **114** with *o*-acetylpyridine **115** gave the *o*-pyridinylpyrroles **116** in good to high yields (Scheme 34).³⁶ Not only *o*- but also *m*- and *p*-acetylpyridines and related substrates can be used as the starting acetyl derivatives. A plausible mechanism is shown in Scheme 35. The oxidative insertion of Pd(0) into an α C-H bond of *o*-acetylpyridine **115** produces the hydridopalladium species **117** (or its oxa- π -allyl structure **117a**), and then the hydropalladation of **114** with **117** takes place as shown in **118**. Reductive elimination of palladium may then occur to afford the intermediate **119** and Pd(0) species. Subsequent cyclization affords the intermediate **120**, which after elimination of H₂O produces **116**.

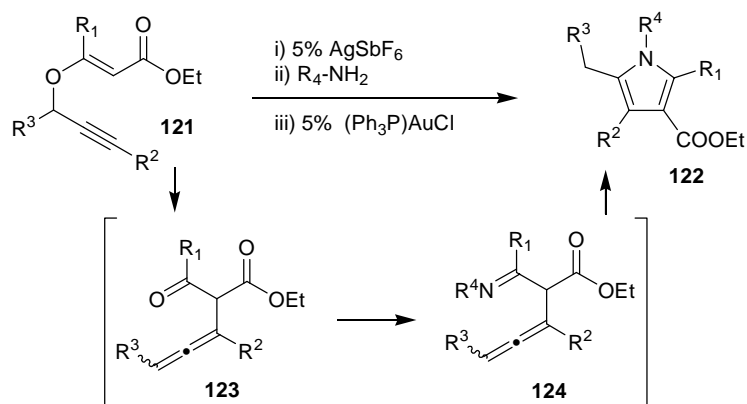


Scheme 34



Scheme 35

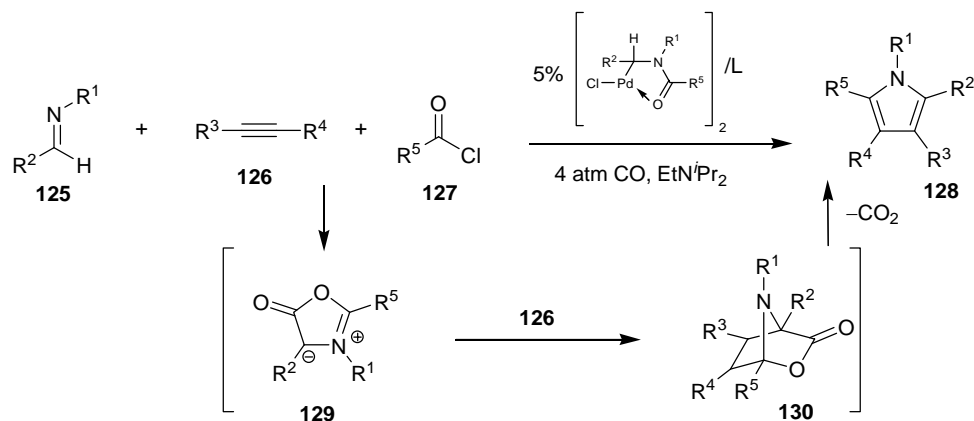
Kirsch *et al.* reported one-pot process for the synthesis of pyrroles **122** from easily accessed propargyl vinyl ethers **121** and aromatic amines (Scheme 36).³⁷ The cascade reaction proceeds through a silver(I)-catalyzed propargyl Claisen rearrangement (cf. **123**), an amine condensation (cf. **124**), and a gold(I)-catalyzed 5-exo-dig heterocyclization.



Scheme 36

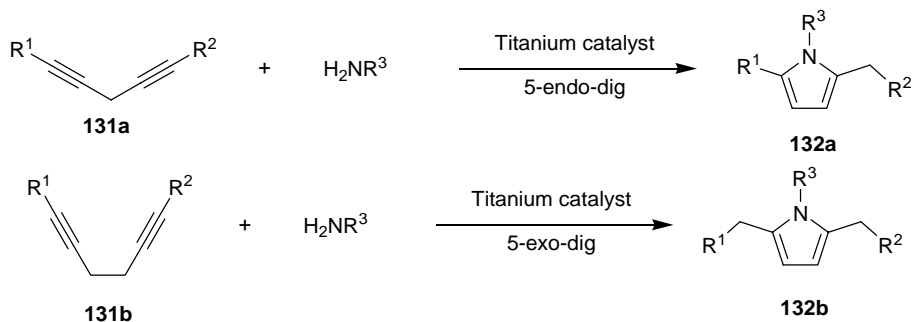
Palladium catalyzed multicomponent coupling of alkynes, imines and acid chlorides for the synthesis of multiply substituted pyrroles is reported (Scheme 27).³⁸ The approach is based upon the ability of alkynes to undergo 1,3-dipolar addition to 1,3-oxazolium-5-oxides (Munchnones) to form pyrroles. Munchnones **129** are generated from palladium-catalyzed coupling of imines

125, acid chlorides **126**, and carbon monoxide which undergo insitu [3+2] dipolar cycloaddition with **126** to give pyrroles.



Scheme 37

The intermolecular hydroamination protocol has been successfully executed for the pyrrole synthesis (Scheme 39).³⁹ Titanium-catalyzed hydroamination of 1,4-diyne **131a** and 1,5-diyne **131b** by primary amines leads to imino-alkynes that undergo in situ 5-*endo dig* and 5-*exo dig* cyclization reactions, to afford pyrroles **132a** and **132b**, respectively. It should be noted that the products 1,2,5-trisubstituted pyrroles are accessed directly from readily available diyne starting materials.



Scheme 38

In summary, we have described some recent advances in the transition metal mediated synthesis of furans and pyrroles. The most important aspect of the metal mediated synthesis lies in its efficiency, since the reaction can be performed often at lower catalyst loading and at ambient temperature. Moreover, the reaction proceeds under relatively mild conditions and tolerate a wide variety of functional groups. We think that many newer approaches for the synthesis of multiply substituted furans and pyrroles will be appeared in the future.

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