HETEROCYCLES, Vol. 91, No. 5, 2015, pp. 931 - 958. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 7th January, 2015, Accepted, 16th February, 2015, Published online, 24th February, 2015
DOI: 10.3987/REV-15-818

TRANSITION METAL-CATALYZED INTRAMOLECULAR CYCLIZATION OF PROPARGYL ALCOHOLS AND THEIR DERIVATIVES FOR THE SYNTHESIS OF HIGHLY SUBSTITUTED FIVE-MEMBERED OXYGEN HETEROCYCLES

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Abstract – The transition metal-catalyzed intramolecular cyclization of propargyl alcohols and their derivatives has been widely utilized in the synthesis of five-membered oxygen heterocycles such as furans, hydrofurans, and furanones. Prerequisites for the efficient transformations into highly substituted target compounds include the regioselectivity of the cyclization step and the chemoselectivity of the transition metal-mediated activation of substrates. This review documents recent progress on the title reactions by categorizing the initial activation modes of substrates.

CONTENTS

1. INTRODUCTION

Five-membered oxygen-containing heterocycles constitute one of the most fundamental compounds in organic chemistry.[1] Among these families, the aromatic compounds, *i.e.* furans, play a central role in widespread applications. The furan skeleton is found abundantly in natural products as well as in pharmaceuticals, which demonstrates the broad spectrum of biological activities such as antibacterial, insecticidal, antidepressant, and anti-inflammatory activities.[1a,2] More recently, in the field of material science, the oligomers and polymers of furans have shown promise for application in electronic devices.[3] Furans and their derivatives have also been employed as versatile building blocks in organic synthesis due to their wide range of reactivities. The reduced forms of furans (2,3-dihydrofurans, 2,5-dihydrofurans, and tetrahydrofurans) as well as the oxidized forms, such as the keto-enol tautomers of furan-2(5*H*)-ones (α,β-unsaturated lactones or butenolides), and those of furan-3(2*H*)-ones, also have great potential in biological, medicinal, and pharmaceutical sciences, and each compound exhibits characteristic reactivities which are different from those of furans. The usefulness of these five-membered oxygen heterocycles has stimulated organic chemists to develop effective and powerful synthetic methods for their preparation.[4] In the case of furans, in addition to the traditional synthesis by either the Paal–Knorr method or the Feist–Bénary method, the transition metal-catalyzed intramolecular cyclization of acyclic precursors such as allenyl ketones, alkynyl ketones, enynes, diynes, and alkynyl cyclopropyl ketones, enable the direct synthesis of furans bearing diverse functional groups.[5] These methods have recently received an increasing amount of attention from the viewpoint of environmentally friendliness and atom efficiency. Metal catalysts, including copper, zinc, palladium, silver, and platinum, have been widely utilized for these ring closures.[5]

Propargyl alcohols and their derivatives have also attracted particular attention as versatile precursors in a range of organic syntheses.[6] This is likely to be due to the fact that they are easily prepared by the alkynylation of carbonyl compounds, or by reduction of propargyl ketones, and also because they show

various reactivities at two main reactive sites, namely the triple bond and the oxygen functional group. The triple bond is capable of coordinating to various transition metals due to its high electron density (type A interaction), and can undertake nucleophilic additions. The oxygen functional group can also coordinate to transition metals (type B interaction), which enhances the elimination of the oxygen functional group and can subsequently result in substitution with a variety of nucleophiles. In some cases, the activation of propargyl compounds is understood to be caused by the dual coordination of the triple bond and the oxygen functional group to a single transition metal (type C interaction). These three types of interactions are demonstrated in Figure 1.

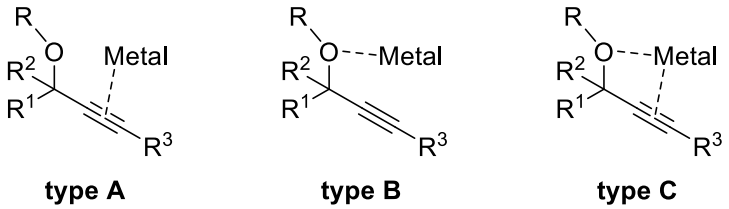
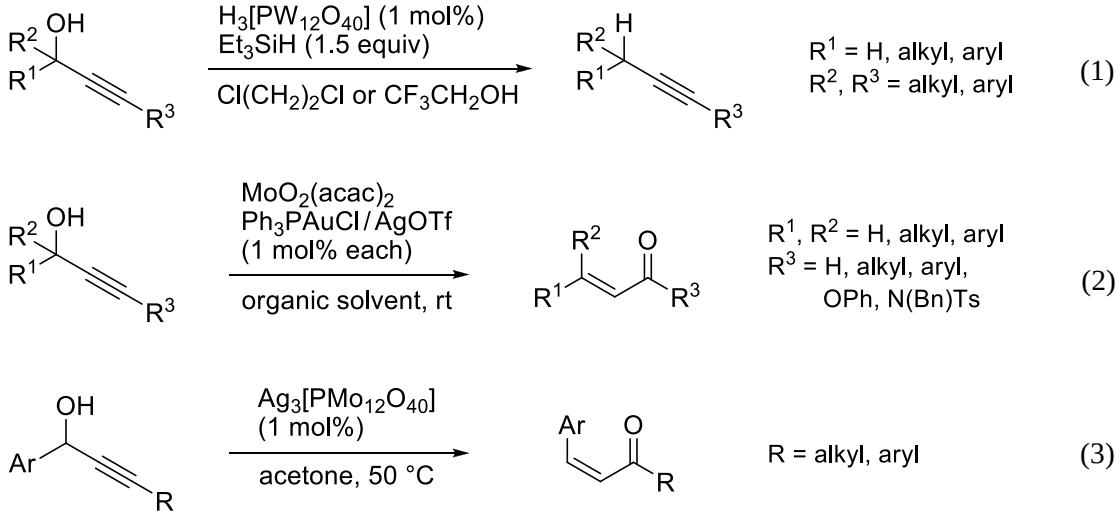


Figure 1. Interactions of propargyl alcohols and their derivatives with transition metals

Recently, we have developed a number of novel transition metal-catalyzed transformations of propargyl alcohols.[7] These transitions include the direct catalytic deoxygenation into the corresponding alkynes *via* a type B interaction (eq. 1), the rapid 1,3-rearrangement of the hydroxyl group into a variety of α,β-unsaturated carbonyl compounds *via* a type C interaction (eq. 2), and rearrangement into the synthetically challenging (*Z*)-α,β-unsaturated ketones *via* a type C interaction (eq. 3).



We then applied the use of propargyl alcohol derivatives to the synthesis of five-membered oxygen-containing heterocycles *via* a transition metal-catalyzed intramolecular cyclization.[8] In this review, we therefore document the transition metal-catalyzed intramolecular cyclizations of propargyl alcohols and their derivatives to give five-membered oxygen heterocycles, including details of our own research into the area. We have chosen to focus mainly on the discussion of the more recent literatures (since 2004), but some earlier transformations of importance are also introduced where appropriate. The contents of our review are classified into four sections based on various reaction modes (Figure 2): (a) nucleophilic cyclization triggered by acetylene activation; (b) rearrangement (or isomerization) of propargyl alcohol derivatives followed by cyclization; and (c) propargylic elimination followed by cyclization. Other types of reaction are also discussed, but are not outlined in Figure 2.

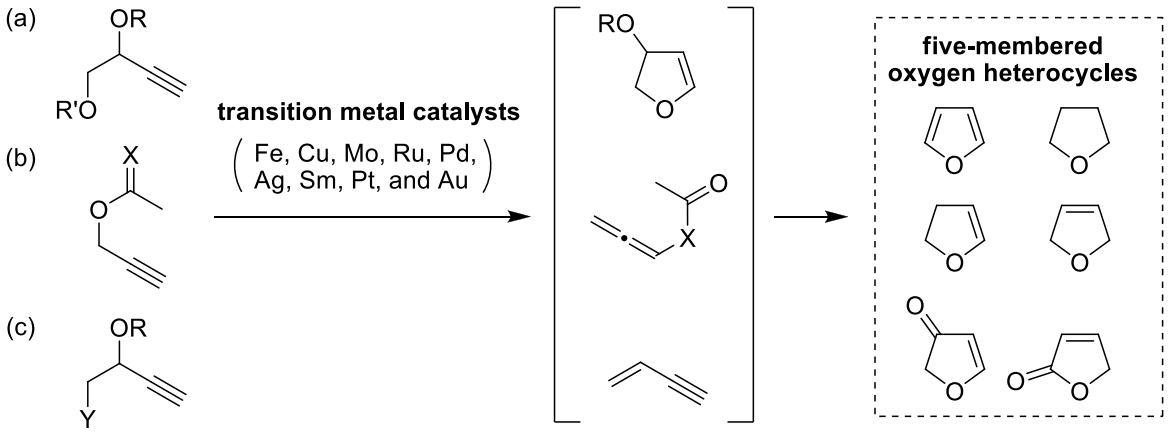
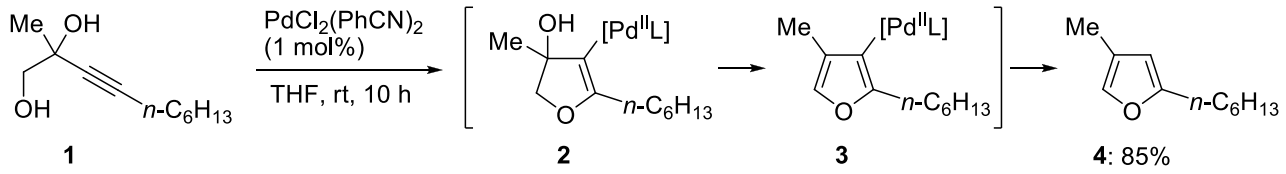


Figure 2. Various transformations of propargyl alcohols and their derivatives into five-membered oxygen heterocycles

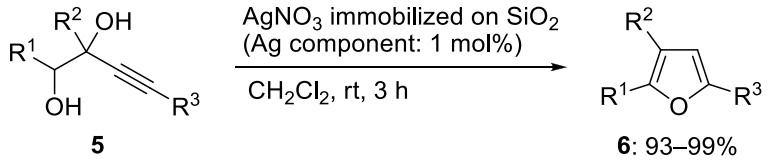
2. NUCLEOPHILIC CYCLIZATION TRIGGERED BY ACETYLENE ACTIVATION

Utimoto *et al.* reported a pioneering study into the transition metal-catalyzed intramolecular cyclization of propargyl diols to give substituted furans.[9] A typical example is shown in Scheme 1, where the hydroxyl group at the homopropargylic position of diol **1** undergoes a 5-*endo-dig* addition to the acetylene moiety, activated by coordination to the palladium catalyst, followed by dehydration to give furan **4**. In this case, the Meyer–Schuster rearrangement, one of the well-known reactions of propargyl alcohols,[6e] was not observed.



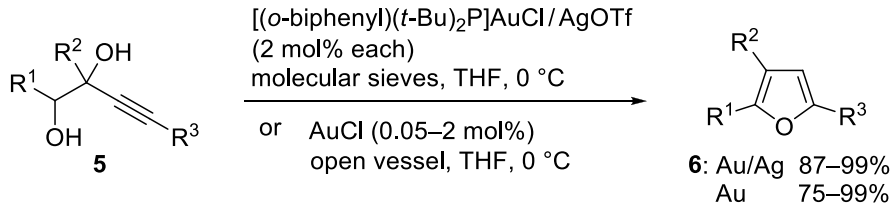
Scheme 1. Intramolecular cyclization of propargyl diol **1**

Inspired by this report, the intramolecular cyclization of propargyl diols has been extensively investigated by using a range of transition metals as follows. Miyashita *et al.* reported the $AgNO_3$-catalyzed transformation of diols **5** into furans **6** in the synthetic studies of zoanthamine alkaloids, although the process was not discussed in any great detail.[10] Later, Knight *et al.* reported a similar system where they employed a catalytic amount of $AgNO_3$ immobilized on silica gel (Scheme 2).[11] This catalytic system enabled the cyclization of **5** to take place at ambient temperature within a short reaction time.



Scheme 2. Intramolecular cyclization of diols **5** using immobilized $AgNO_3$

Aponick *et al.* disclosed that a combination of catalytic amounts of [(*o*-biphenyl)(*t*-Bu)$_2$P]AuCl and AgOTf was suitable for the cyclization of **5**, albeit with precautions taken to exclude water by the use of molecular sieves (Scheme 3).[12] In addition, they found that AuCl was active even in an open vessel.

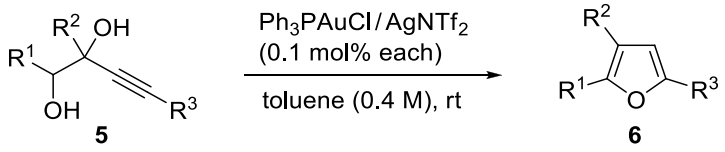


Scheme 3. Gold-catalyzed transformation of **5**

We ourselves have also been active in the area of gold-catalyzed transformations of diols. We carried out the intramolecular cyclization of **5** with a combination of Ph_3PAuCl and $AgNTf_2$, further enhancing the efficiency of the reaction by using a catalytic system, which showed high reactivity even in the presence of water.[8a] Our developed methodology was widely applicable to a range of diols and afforded furans in high yields (Table 1). In particular, we found that propargyl alcohols bearing a terminal alkyne moiety were suitable for the preparation of furans (entries 6–8), while the aforementioned methods failed to deliver any products from these substrates. Moreover, this system was successfully applied to the

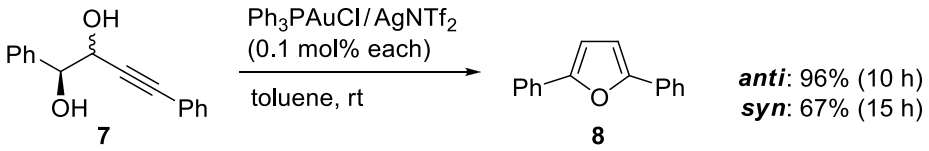
multigram-scale synthesis of furans at high concentrations (0.8 M in toluene, entry 2). We also noted that *anti*-**7** showed slightly higher reactivity than its *syn*-diastereoisomer, as outlined in Scheme 4.

Table 1. Conversion of diols **5** into furans **6** using a combination of Ph_3PAuCl and $AgNTf_2$



Entry	Substrate **5**			Time (h)	Product **6**
	R^1	R^2	R^3		Isolated yield (%)
1	H	Me	$(CH_2)_2Ph$	1	97
2[a]	H	Me	$(CH_2)_2Ph$	2	98
3	H	Me	2-thienyl	5	90
4	-$(CH_2)_4$-		Ph	3	97
5	H	H	Ph	5	90
6	H	Ph	H	8	85
7	Ph	Ph	H	10	91
8[b]	H	$Ph(CH_2)_2$	H	1.5	90

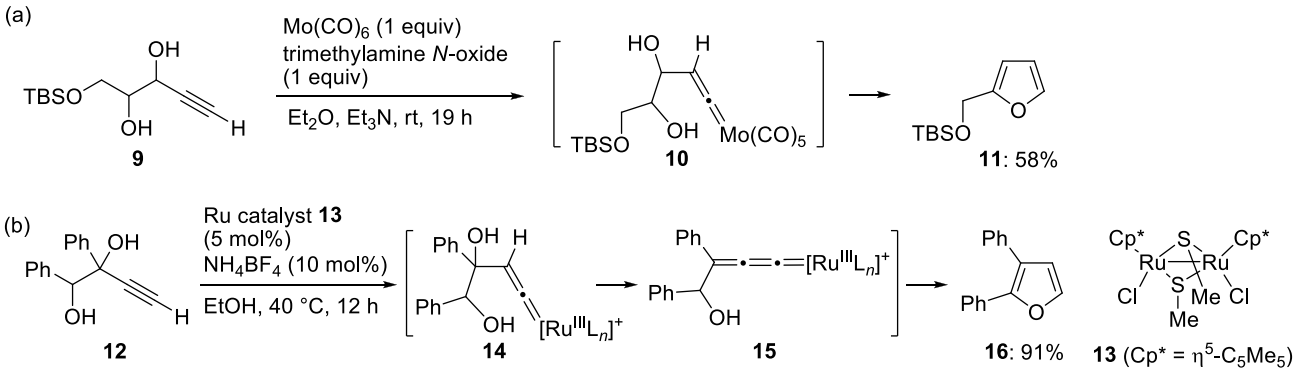
Standard conditions: Substrates **5** (2.5 mmol) were employed. a) The reaction of substrate (26 g, 127 mmol) was conducted using $Ph_3AuCl/AgNTf_2$ (0.05 mol% each) and toluene (0.8 M). b) Run at 60 °C.



Scheme 4. Influence of diastereomeric configurations on the cyclization

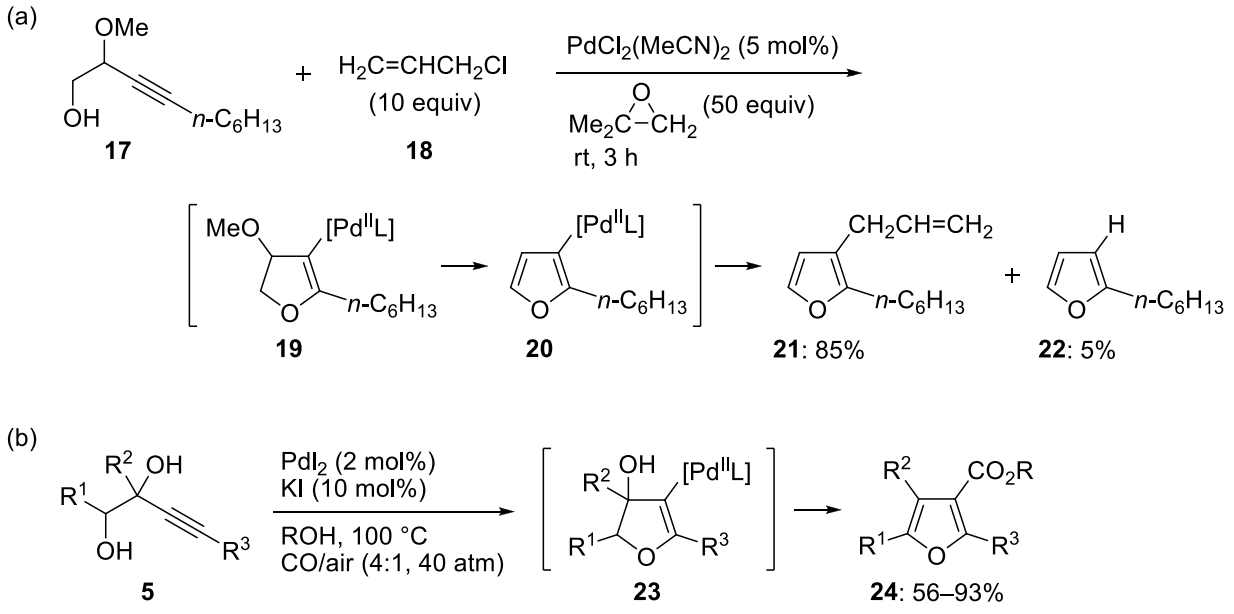
Molybdenum- and ruthenium-based catalysts were used in the preparation of furans *via* the cyclization of diols bearing a terminal alkynyl group. For example, the McDonald group disclosed the cyclization of **9**, induced by a stoichiometric amount of $Mo(CO)_6$ in the presence of trimethylamine *N*-oxide (Scheme 5a).[13] Following this, the Nishibayashi group developed a catalytic method using the methanethiolate-bridged diruthenium complex **13** (5 mol%) (Scheme 5b).[14] It was proposed that these transformations proceeded *via* the formation of metal vinylidenes **10** and **14**, which differed from the above-mentioned mechanism based on palladium, silver, and gold catalysis. The formation of ruthenium cumulenylidene **15**, considered as a key intermediate, resulted in the cyclization of the remaining

hydroxyl group to form the furan along with regeneration of the transition metal species.



Scheme 5. Reaction of diols **9** and **12**, bearing terminal alkyne moieties, with either a molybdenum or ruthenium catalyst

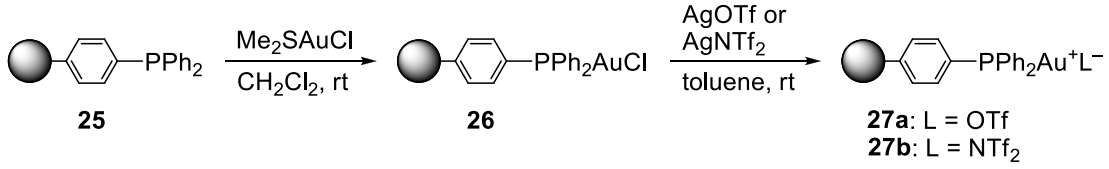
As an extension of the intramolecular cyclization of propargyl diols, the cascade cyclization/coupling reaction was investigated, promoted by complexation of a palladium catalyst to propargyl diol **17** or **5**. Utimoto *et al.* initially attempted the coupling reaction of the resultant palladium intermediate **20** with allyl halide **18** (Scheme 6a).[9] The formation of the protonated side product **22** was suppressed by using an excess amount of epoxide as a proton scavenger to give the desired 3-allylfuran **21** preferentially. More recently, Gabriele *et al.* developed the synthesis of tetrasubstituted furans **24** by the palladium-catalyzed cascade cyclization/alkoxycarbonylation (Scheme 6b).[15] They proposed that the 5-*endo-dig* cyclization occurred *via* intramolecular nucleophilic attack of the β-hydroxyl group to the palladium-activated



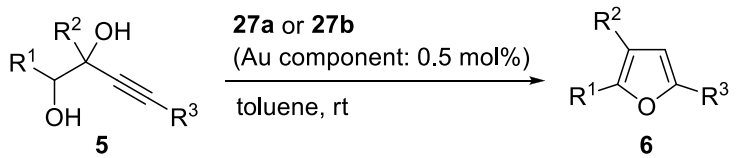
Scheme 6. Palladium-catalyzed cascade cyclization/coupling reaction of propargyl diols **17** and **5**

acetylene group (**5**→**23**), followed by alkoxycarbonylation/dehydration (**23**→**24**) in preference to protonation.

With the aim to reduce waste and to improve the applicability of these reactions, we synthesized the polystyrene-immobilized gold(I) catalysts **27a** and **27b** (Scheme 7), for the transformation of diols **5** into furans **6**.[8c] The commercially available polystyrene-bound triphenylphosphine **25** was treated with Me_2SAuCl in CH_2Cl_2, followed by the addition of either AgOTf or $AgNTf_2$ in toluene to give **27a** or **27b**, respectively. This was, to the best of our knowledge, the first example of the preparation of an immobilized cationic gold(I) catalyst. The immobilized catalysts **27a** and **27b** afforded similar results in the cyclization of **5** (Scheme 8), although a longer reaction time was required compared to our catalyst combination of Ph_3PAuCl and $AgNTf_2$. The catalyst **27a** was easily and quantitatively recovered by simple decantation, and was reused in seven further reactions without significant loss of reactivity (Table 2). We observed that during subsequent runs using the recycled catalyst, only a very small amount of gold species leached out from the polystyrene support. Moreover, **27a** was suitable for use in a flow reactor system for the rapid and continuous production of **29** (Figure 3).



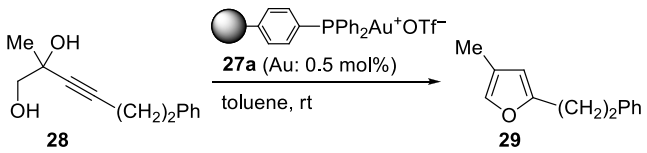
Scheme 7. Synthesis of immobilized cationic gold catalysts **27a** and **27b**



catalyst	Me, O, $(CH_2)_2Ph$	Me, O, S	O, Ph	O, Ph
27a	95% (3 h)	79% (9 h)	92% (6 h)	88% (6 h)
27b	98% (3 h)	88% (6 h)	95% (6 h)	92% (6 h)

Scheme 8. Intramolecular cyclization of **5** into **6** using either **27a** or **27b**

Table 2. Reuse of **27a** for converting **28** into **29**



Run	Time (h)	Yield (%)	Au leaching (%)
1st	2	98	0.47
2nd	2	98	0.18
3rd	2	94	0.12
4th	2	98	0.16
5th	3	97	0.15
6th	5	99	0.21
7th	7	98	0.14
8th	7	94	0.14

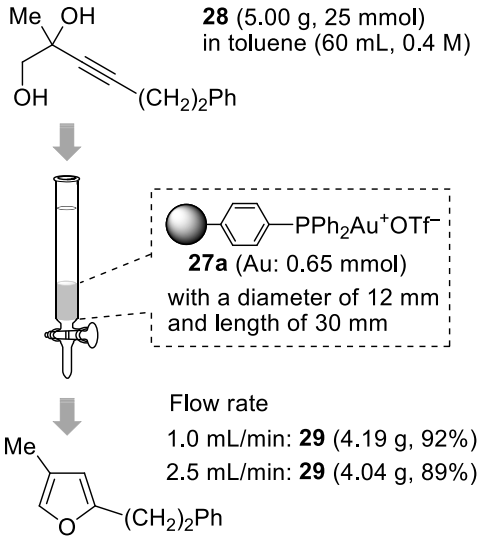
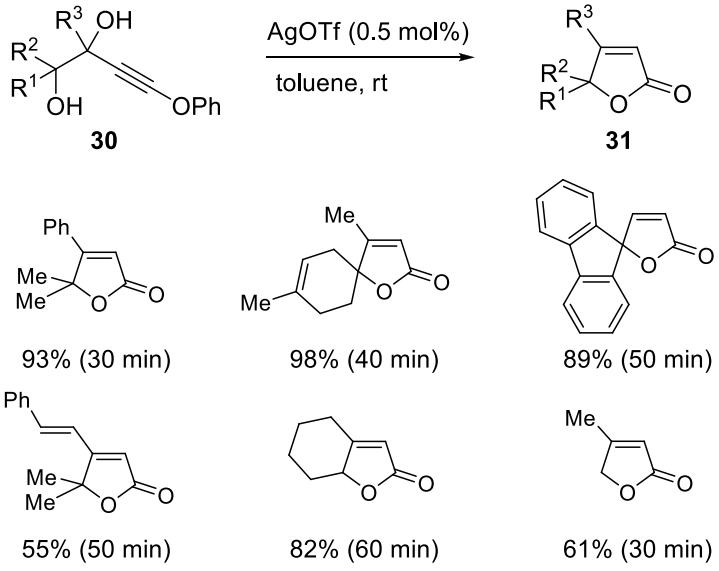


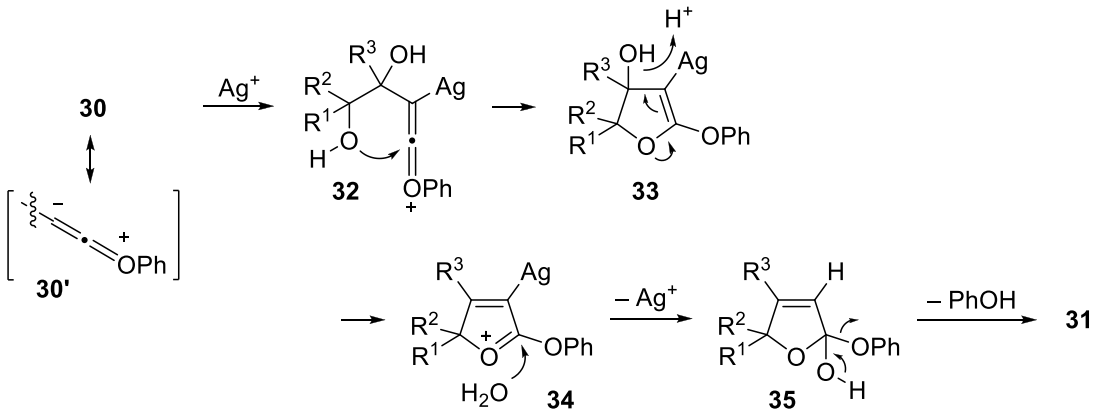
Figure 3. Continuous flow synthesis of **29**

We then applied the intramolecular cyclization reaction of propargyl diols to the synthesis of unsaturated lactones. For this purpose, propargyl diols **30** bearing a phenoxy group at the acetylene terminus were designed based on our expectations of where the phenoxy moiety would enhance the reactivity of the acetylene moiety, and also of where it would work best as a leaving group. Using AgOTf, the intramolecular cyclization of **30** proceeded smoothly at room temperature to give α,β-unsaturated lactones **31** in good to excellent yields (Scheme 9).[8d]



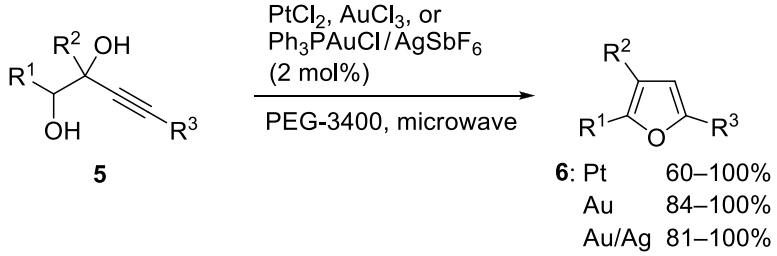
Scheme 9. AgOTf-catalyzed transformation of **30** into α,β-unsaturated lactones **31**

This method is undoubtedly beneficial for the preparation of multisubstituted α,β-unsaturated lactones (R^1, $R^2 \neq H$), whose structures are often presented as central structural elements in natural products. A plausible mechanism for this transformation is proposed in Scheme 10. The higher electron density of the phenoxyethynyl moiety of **30**, as is evident from its resonance form **30′**, accelerates coordination of the acetylene moiety to the silver cation. Oxonium intermediate **32**, generated *in situ*, is susceptible to nucleophilic attack even by sterically hindered tertiary alcohols (**32**→**33**). Subsequently, the donation of lone pair electrons from the ethereal oxygen atom results in the generation of the transient oxonium ion **34** and water. The final step involves the reaction of **34** with water to give **35**, which subsequently releases phenol to give substituted unsaturated lactones **31**.



Scheme 10. A plausible mechanism for the AgOTf-catalyzed intramolecular cyclization of **30**

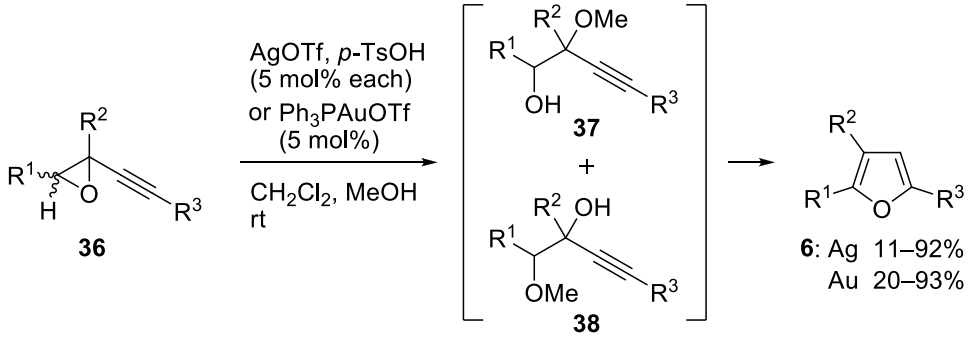
At around the same time, Lamaty *et al.* reported the use of poly(ethylene glycol) (PEG) as an alternative reaction medium to the volatile organic solvents.[16] The platinum- and gold-catalyzed reactions of **5** in PEG-3400 were conducted under microwave heating to afford a range of furans **6** in good yields (Scheme 11). PEG was thought to stabilize and encapsulate the metallic species, thus preventing aggregation and deactivation. This catalytic system allowed the reuse of these catalysts up to four times in subsequent



Scheme 11. Use of poly(ethylene glycol) as a reaction medium for conversion of **5** to **6**

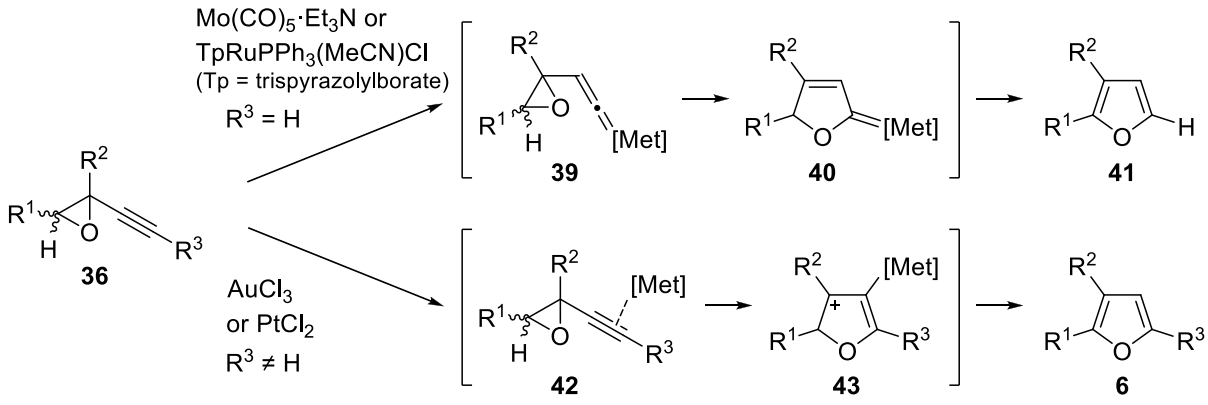
reactions, and it was found that the high reactivity of $AuCl_3$ could be maintained by the presence of a trace amount of benzoquinone during subsequent reactions.

Pale *et al.* reported the AgOTf-catalyzed reaction of propargyl epoxides **36** with methanol (Scheme 12).[17] In this reaction, the nucleophilic addition of methanol to **36** led to the opening of the epoxide ring, forming *in situ* propargyl diol intermediates **37** and **38**. Regioisomers **37** and **38** showed different reactivities to the silver catalyst, and only **37** was converted into the desired furan product **6**. The same group later disclosed that the use of $Ph_3PAuOTf$ resulted in the complete conversion of **36** to intermediates **37** and **38** at a faster rate than for the silver catalyst.[17b] In the case of gold catalysis, both **37** and **38** were consumed, albeit at different rates, leading to the formation of furans **6**.



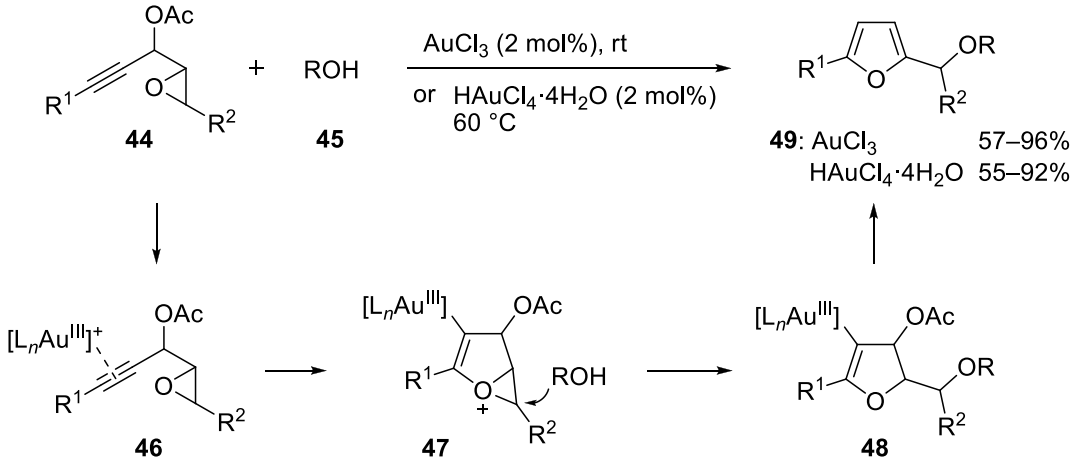
Scheme 12. Conversion of **36** into **6** *via* propargyl diol intermediates **37** and **38**

Without having to rely on the formation of propargyl diol intermediates, propargyl epoxides **36** showed high enough reactivity to form furans **41** and **6** by coordination to various transition metal catalysts, such as molybdenum, ruthenium, gold, and platinum (Scheme 13).[18] The mechanisms for these transformations include direct attack of the oxygen atom of the epoxide ring on either a metal–vinylidene species **39** or metal–alkyne π-complex **42**.



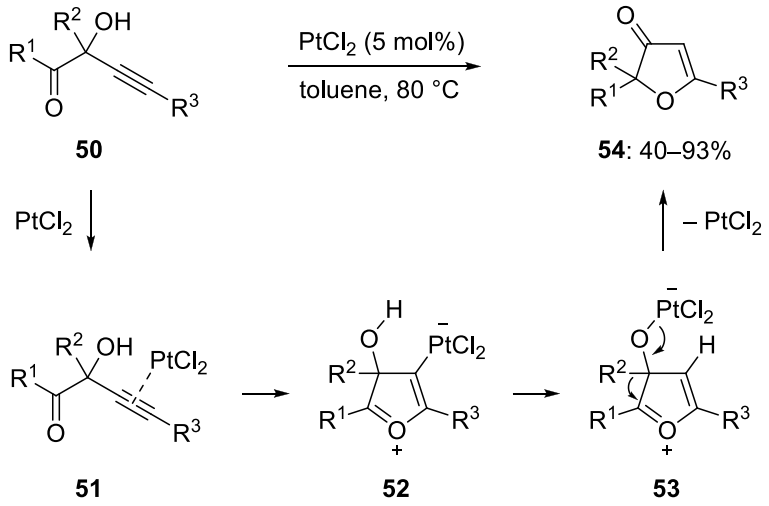
Scheme 13. Reactions of propargyl epoxides **36** with various transition metals

Moreover, Liang *et al.* reported the gold-catalyzed reaction of propargyl esters **44** bearing an epoxide moiety to give furans **49** (Scheme 14).[19] This reaction involved the alkyne activation of **44** with gold catalysts to give **46**, and the subsequent cascade *endo-dig* cyclization/nucleophilic attack to give intermediates **48**. Protonation of the gold species and elimination of acetic acid resulted in conversion of **48** to **49**. They reported that the use of $AuCl_3$ (2 mol%) at room temperature, or $HAuCl_4 \cdot 4H_2O$ (2 mol%) at 60 °C was among the most suitable condition for the transformation. Screening of a range of external nucleophiles **45** revealed that even the sterically hindered alcohols could be successfully employed in this reaction.



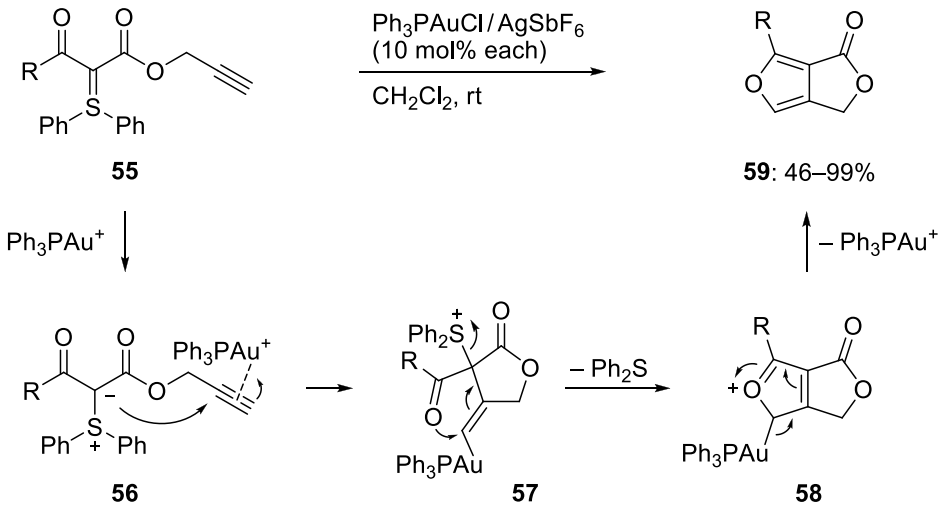
Scheme 14. Gold-catalyzed reaction of **44** with nucleophiles **45**

Aside from the hydroxyl and epoxide groups, it was also observed that the carbonyl and active methylene groups were able to react with transition metal-coordinated acetylenes, resulting in the production of five-membered oxygen-containing heterocycles. For example, the Kirsch group reported that the reaction of 2-alkynyl-2-hydroxyl carbonyl compounds **50** with transition metal catalysts afforded multisubstituted 3(2*H*)-furanones **54** *via* a cascade reaction (Scheme 15).[20] This transformation was induced by either $PtCl_2$ or $AuCl_3$, with the former giving slightly higher yields for the transformation. Activation of the alkyne moiety by either a platinum or gold catalyst allowed for heterocyclization to give the transient oxonium intermediate **52**. Finally, 1,2-shift of the substituent R^2 and elimination of the platinum species resulted in the formation of furanones **54**. In this system, the synthetically challenging spiro furanones, in which the substituents R^1 and R^2 were linked, were also successfully prepared.



Scheme 15. Platinum-catalyzed intramolecular cyclization of **50** into **54**

Another elegant example of a cationic gold-catalyzed cyclization was developed by the Maulide group. They developed the $Ph_3PAuCl/AgSbF_6$-catalyzed carbocyclization of propargyl β-keto esters **55** to give **59**, in which the furan and lactone rings were constructed simultaneously (Scheme 16).[21] Initial π-coordination of alkyne moiety of **55** to the cationic gold species enhanced its electrophilicity. The subsequent 5-*exo-dig* cyclization of the ylidic carbon with the gold-coordinated alkyne resulted in the formation of the gold–vinyl complexes **57** bearing a lactone ring. This intermediate then underwent nucleophilic attack of the acyl oxygen to release Ph_2S. Finally, the furan ring was formed along with regeneration of the cationic gold catalyst (**58**→**59**). This mechanism was confirmed by exploratory density functional theory (DFT) calculations.



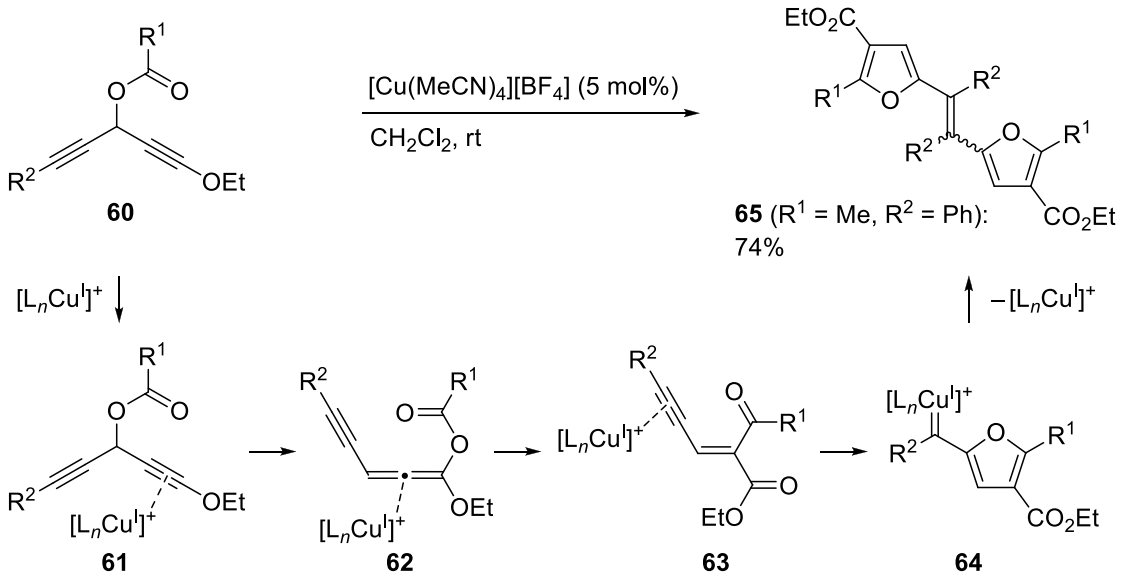
Scheme 16. Cationic gold-catalyzed cyclization of propargyl β-keto esters **55**

3. CASCADE PROCESSES INITIATED BY REARRANGEMENTS

The transition metal-promoted sigmatropic rearrangements of propargyl alcohol derivatives provided a range of different reactive intermediates, which served to construct five-membered oxygen heterocycles. In this section, the reactions are split into two categories according to the functional groups that are incorporated into the ring formation.

3.1 Participation of both the acetylene and propargylic oxygen-substituent moieties in ring formation

The reaction of diyne acylates **60** with 5 mol% of $[Cu(MeCN)_4][BF_4]$ resulted in the formation of furans **65** (Scheme 17).[22] The reaction was initiated by the [3,3]-sigmatropic rearrangement of **60** to allenyl esters **62** *via* the copper-activated electron-rich acetylene **61**. This rearrangement was followed by a copper-catalyzed multistep furan formation, consisting of the following steps: 1) 1,3-acyl shift from **62** to **63**; 2) the 5-*exo*-*dig* cyclization (**63**→**64**) *via* nucleophilic attack of the carbonyl group to the copper-coordinated acetylene; and 3) the dimerization of copper (2-furyl)carbene complexes **64** to give furans **65**, which was comprised of two furan moieties, both derived from the acetylene and the acetyloxy substituent of **60**.



Scheme 17. Cascade reaction of **60** through a rearrangement/cyclization/dimerization process

Furthermore, the reactive intermediates **64** were suitable for subjecting to further transformations, such as hydrosilylation, hydrogermanation, oxidation, or cross coupling with a diazo compound, resulting in the formation of a range of multisubstituted furans such as those shown in Figure 4.[23]

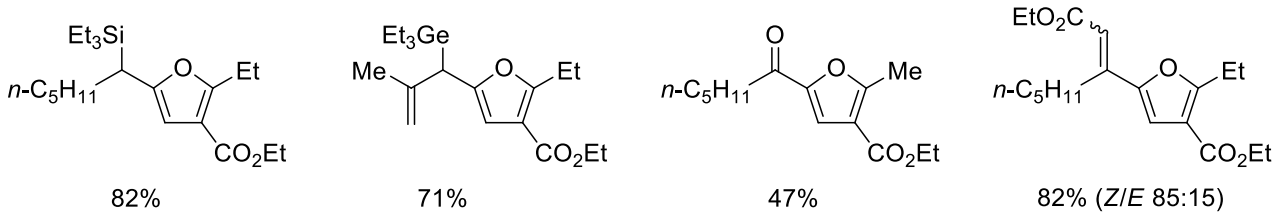
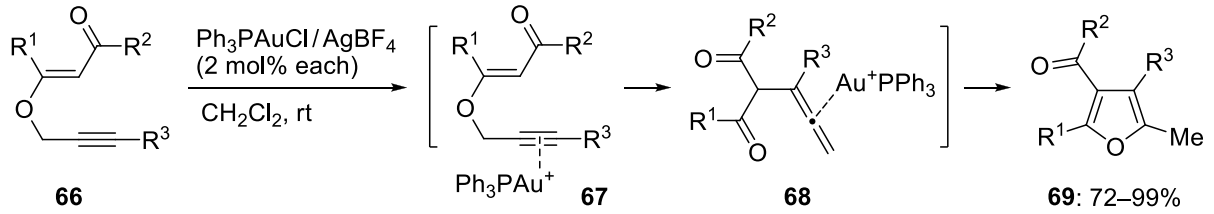


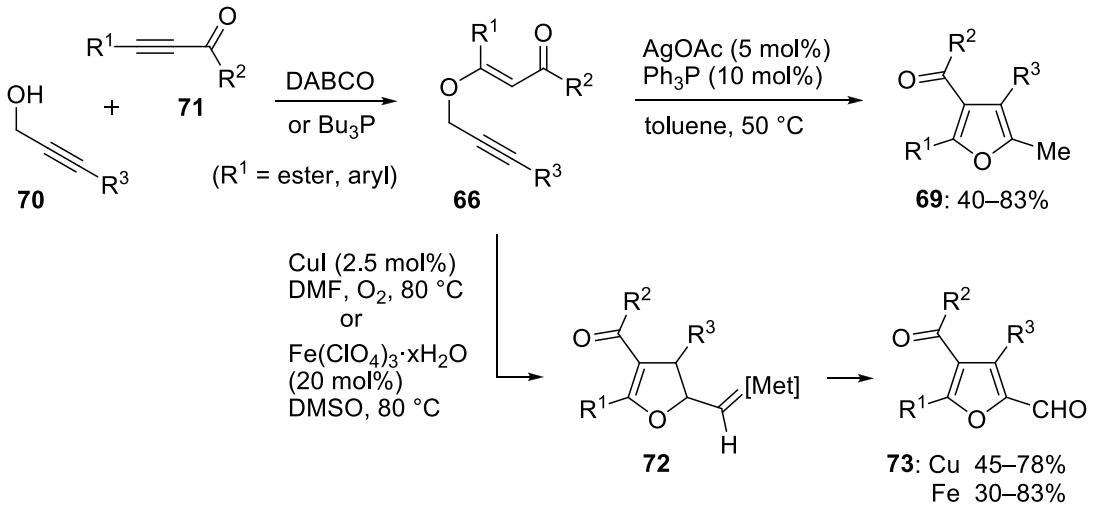
Figure 4. Regioselective synthesis of multisubstituted furans *via* (2-furyl)carbene complexes **64**

In addition to C–O bond formation (see **60**→**62** in Scheme 17), the [3,3]-sigmatropic rearrangement of propargyl alcohol derivatives can also provide an access to C–C bond formation. In 2005, Kirsch *et al.* developed the transformation of propargyl vinyl ethers **66** into furans **69** using a cationic gold catalyst, generated *in situ* from gold and silver compounds (Scheme 18).[24] The [3,3]-sigmatropic rearrangement of **66** was initiated by the π-activation of the acetylene bond with the cationic gold catalyst, followed by heterocyclization of 2,3-allenyl dione intermediates **68** to give tri- and tetrasubstituted furans **69**, derived from both the propargyl and enol moieties.



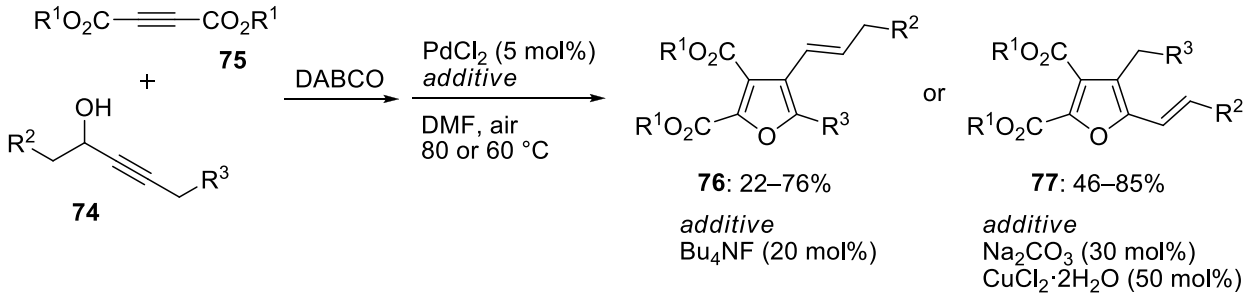
Scheme 18. Intramolecular cyclization of propargyl vinyl ethers **66**

The Jiang group later reported the transition metal-catalyzed one-pot cascade process, starting from propargyl alcohols **70** and electron deficient alkynes **71**, in the presence of a catalytic amount of DABCO or Bu_3P (Scheme 19).[25] Interestingly, variation of the transition metal catalyst resulted in the formation of a range of furans bearing different substituent groups. For example, the combined catalyst of AgOAc and Ph_3P in toluene converted **66**, generated *in situ* from **70** and **71**, into **69**.[25c] However, the use of either CuI or $Fe(ClO_4)_3{\cdot}xH_2O$ gave 2-formylfurans **73**.[25b,d] The mechanism of the silver-catalyzed reaction was considered to be similar to that of the gold-catalyzed reaction shown in Scheme 18, whereas the copper- or iron-catalyzed reaction appeared to proceed through carbene intermediates **72**, which were subsequently oxidized by oxygen to give **73**.



Scheme 19. One-pot cascade for the preparation of **69** and **73** from propargyl alcohols **70** and electron-deficient alkynes **71** *via* **66**

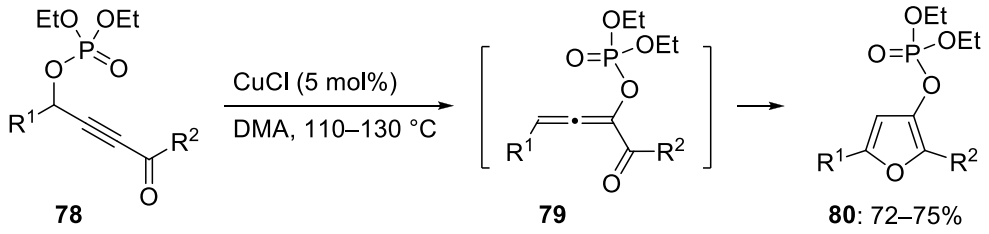
Furthermore, the palladium-catalyzed cascade reactions, initiated by the addition of **74** to **75**, provided vinyl-substituted furans **76** and **77**, in which the position of the vinyl group in the products varied depending on the additives employed in the reaction. For example, the use of Bu_4NF led to the formation of 4-vinyl furans **76**, whereas a combination of Na_2CO_3 and $CuCl_2·2H_2O$ gave 5-vinyl isomers **77** (Scheme 20).[26] These differences arose from the different reaction paths instigated by various additives.



Scheme 20. Changing the cyclization reaction pathway by variation of the additive(s)

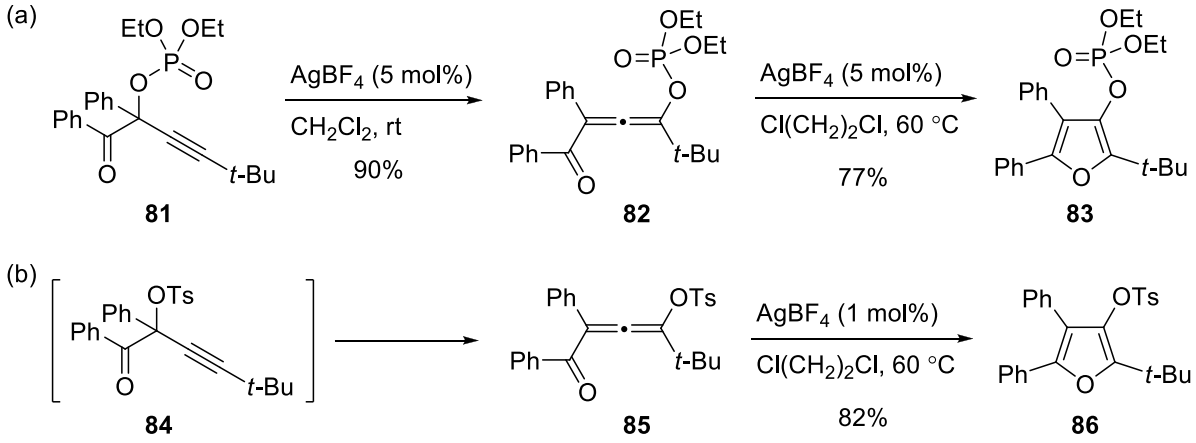
3.2 Participation of either the acetylene or the propargylic oxygen-substituent moiety in ring formation

The Gevorgyan group vigorously advanced the research relating to the use of a range of transition metal catalysts for the intramolecular cyclizations of propargyl esters bearing another carbonyl group.[27b] In the presence of 5 mol% of CuCl, 3-acylpropargyl phosphates **78** underwent a [3,3]-rearrangement of the propargyl phosphate moiety to give allenes **79**, and the subsequent intramolecular addition of the carbonyl group to the allene moiety gave trisubstituted furans **80** (Scheme 21).



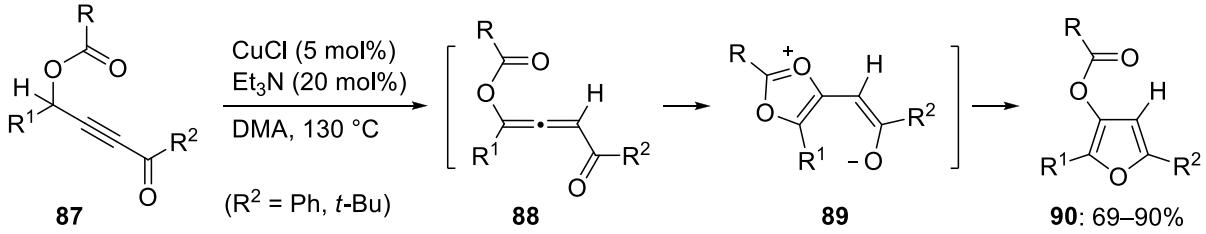
Scheme 21. Copper-catalyzed transformation of 3-acylpropargyl phosphates **78** into furans **80**

Similarly, the reaction of 1-benzoylpropargyl phosphate **81** with 5 mol% of $AgBF_4$ afforded tetrasubstituted furan **83** (Scheme 22a).[27] Tosylate **84** was found to spontaneously undergo the [3,3]-rearrangement to give allene **85**, which was subsequently cyclized to furan **86** in the presence of 1 mol% of $AgBF_4$ (Scheme 22b).



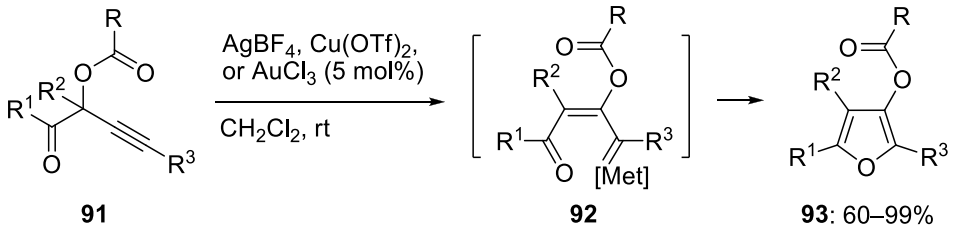
Scheme 22. Transformation of 1-acylpropargyl esters **81** and **84** into tetrasubstituted furans **83** and **86**

On a similar note, 3-acylpropargyl carboxylates **87** were converted into furans **90** upon treatment with CuCl and Et_3N (Scheme 23).[27] The first step in this reaction involves the 1,3-migration of the propargyl hydrogen on **87** to afford allene intermediates **88**, which subsequently undergoes 1,2-acyloxy shift and heterocyclization to give furans **90**.



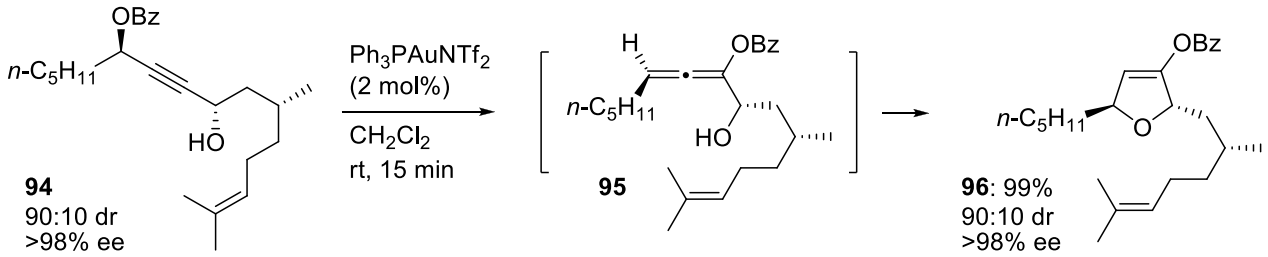
Scheme 23. Transformation of 3-acylpropargyl carboxylates **87** into furans **90** initiated by a hydrogen migration

The reaction of propargyl carboxylates **91**, bearing an acyl group at the C1-position, in the presence of a silver, copper, or gold catalyst resulted in a metal-mediated 1,2-migration of the acyloxy group to generate the transient metal–carbenoids **92**, which subsequently afforded tetrasubstituted furans **93** (Scheme 24).[27]



Scheme 24. Conversion of propargyl carboxylates **91** into furans **93** *via* metal–carbenoid intermediates **92**

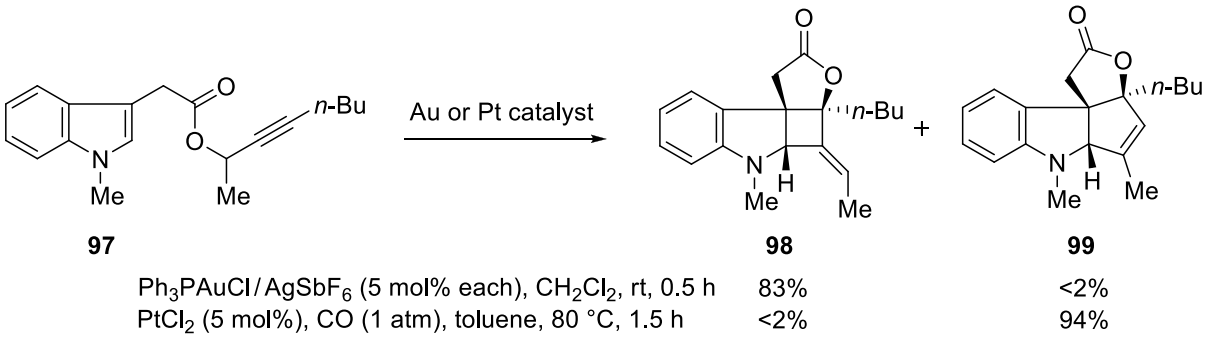
The reaction of propargyl diol monobenzoates with 2 mol% of $Ph_3PAuNTf_2$ was reported by Gagosz for the production of functionalized 2,5-dihydrofurans.[28] A typical example involves the transformation of enantio-enriched **94** into 2,5-dihydrofuran **96** with complete retention of the chiral integrity (Scheme 25). This transformation was initiated by the [3,3]-sigmatropic rearrangement of **94** to give allene intermediate **95**, which underwent heterocyclization by attack of the hydroxyl group on the gold-coordinated allene. In contrast to previously reported reactions, the hydroxyl group at the opposite propargylic position reacted ahead of the benzoyloxy group.



Scheme 25. Cationic gold-catalyzed cyclization of propargyl diol monobenzoate **94** into 2,5-dihydrofuran **96**

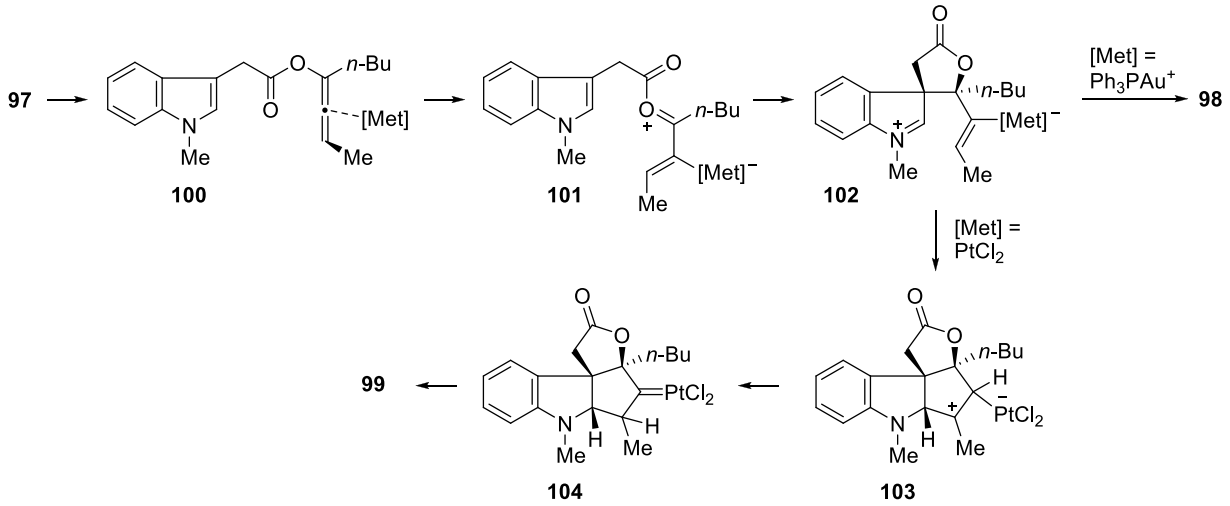
Zhang *et al.* have also studied the general reactivity of propargyl carboxylates by means of various transition metals. As a part of their ongoing research, they discovered that propargyl ester **97** bearing an indole moiety reacted with a cationic gold complex to afford the tetracyclic γ-lactone **98** bearing a 2,3-indoline-fused cyclobutane.[29a] The use of a platinum catalyst demonstrated nicely the difference in reactivity with variation in the metal catalyst. They observed that the substrate **97** yielded the fused

γ-lactone **99**, bearing a cyclopentene moiety as opposed to the cyclobutane observed using a gold catalyst (Scheme 26).[29b]



Scheme 26. Influence of transition metals on conversion of propargyl ester **97** into fused γ-lactones **98** and **99**

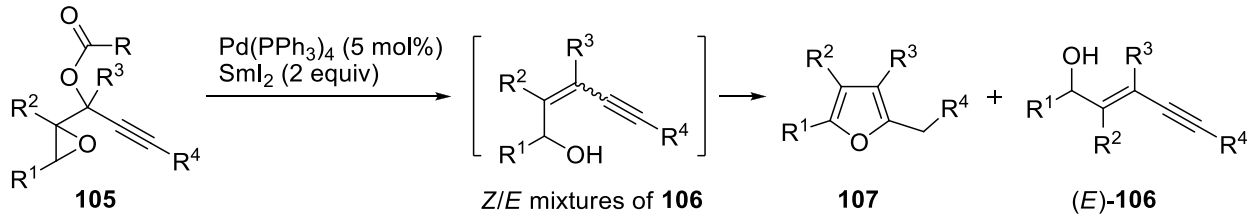
The mechanisms of both the gold- and platinum-catalyzed reactions of **97** begin with a [3,3]-sigmatropic rearrangement *via* the activation of the acetylene group by coordination to the metals. The generated allenes **100** are further activated by each catalyst to give the metal-complexed oxoniums **101**. The intramolecular electrophilic cyclization at the indole C-3 position then leads to the formation of spiro intermediates **102**, containing a vinyl–metal species. In the case of gold catalysis, the vinyl–gold moiety (Met = Ph_3PAu^+) combines with the iminium species to give **98**. Conversely, in the case of platinum catalysis (Met = $PtCl_2$), the complex undergoes a 5-*exo* cyclization followed by hydride shift (**103**→**104**). Elimination of the platinum species gives the fused γ-lactone **99** (Scheme 27).



Scheme 27. Plausible mechanisms for the gold- and platinum-catalyzed transformations of **97** into **98** and **99**

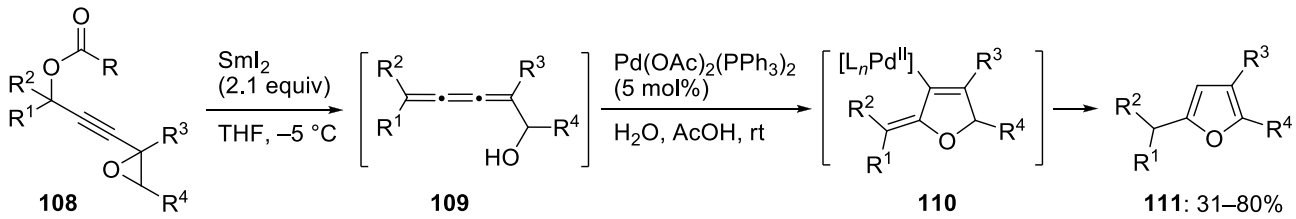
4. CASCADE PROCESSES INITIATED BY PROPARGYLIC ELIMINATION

Aurrecoechea *et al.* reported the synthesis of multisubstituted furans **107** from epoxypropargyl esters **105**, using a combination of $Pd(PPh_3)_4$ (5 mol%) and SmI_2 (2 equiv) (Scheme 28).[30] The reaction of **105** with SmI_2 caused the reductive elimination of the acyloxy group at the propargylic position to afford enynols **106**, which subsequently underwent palladium-catalyzed heterocyclization, although the yields of products **107** were by no means satisfactory. Low yields are owing to the fact that enynol intermediates **106** were generated as a mixture of *Z*- and *E*-isomers, in which only the minor *Z*-isomers were converted into furans **107**, while the major *E*-isomers remained mainly unreacted due to a sluggish cyclization rate.

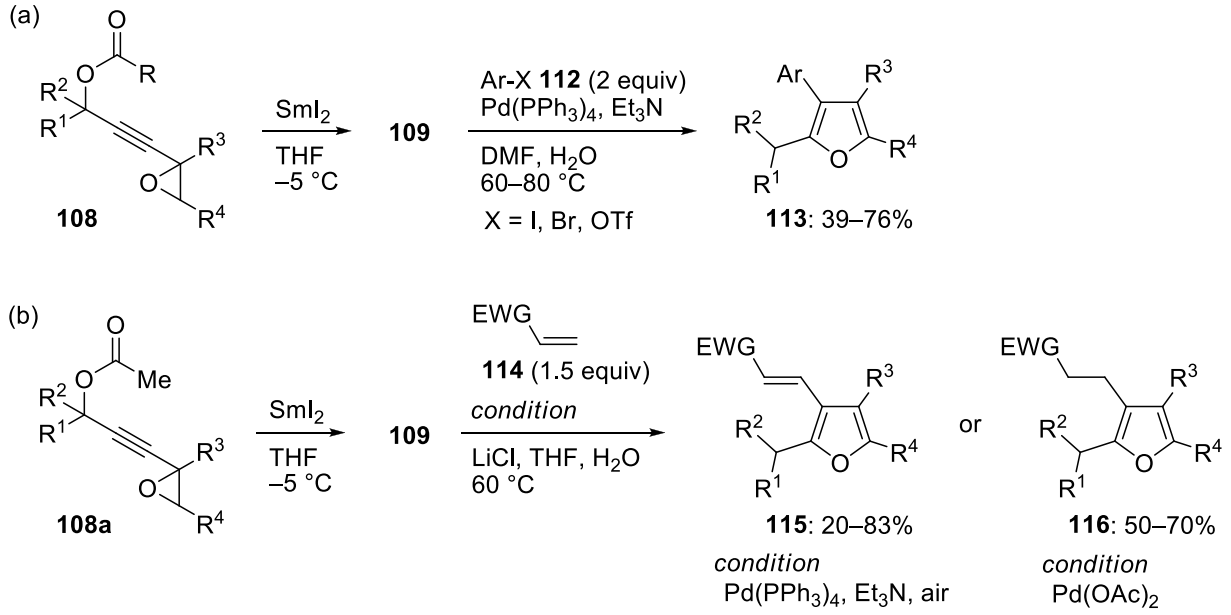


Scheme 28. Transformation of epoxypropargyl esters **105** into furans **107** using a combination of $Pd(PPh_3)_4$ and SmI_2

The Aurrecoechea group later reported that the reaction of regioisomeric epoxypropargyl esters **108** resulted in the formation of trisubstituted furans **111** (Scheme 29).[31] The first step in this one-pot process involves reduction of **108** by SmI_2 to generate hydroxymethyl-1,2,3-trienes **109**. After the complete consumption of **108**, $Pd(OAc)_2(PPh_3)_2$, H_2O, and AcOH are added directly to the reaction mixture. In the second step, the palladium catalyst promotes heterocyclization to give the transient intermediates **110**, which are protonated with AcOH to produce **111**. When aryl halides **112** or electron-withdrawing alkenes **114** are added in the second step, their coupling with intermediates **110** occurs to afford tetrasubstituted furans **113**, **115**, and **116** (Schemes 30a and 30b).[32]

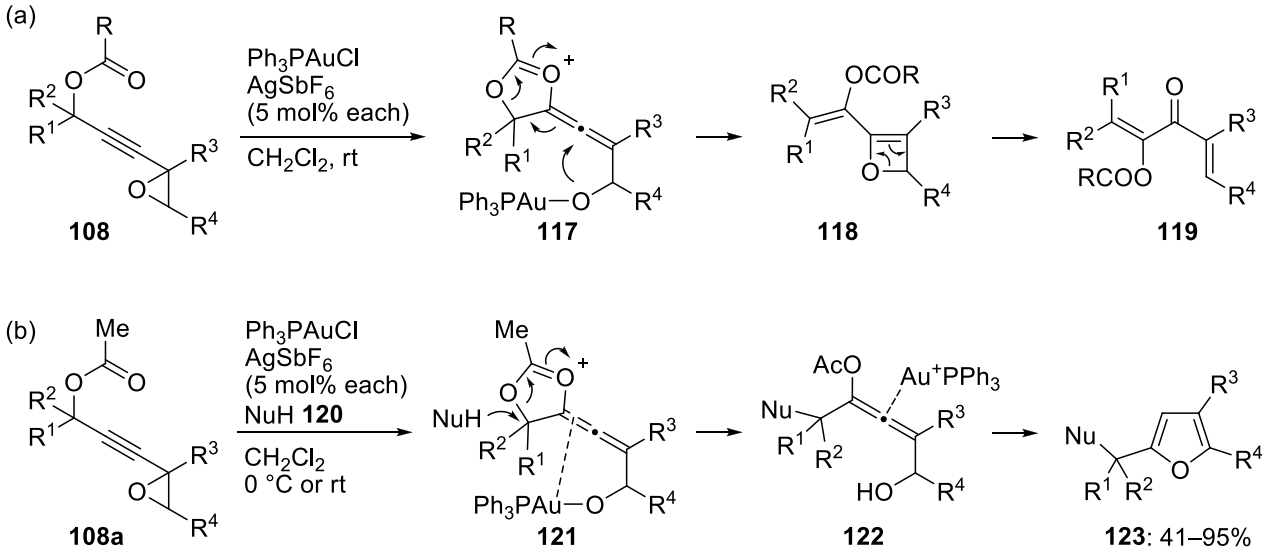


Scheme 29. Reaction of epoxypropargyl esters **108** with SmI_2 and a palladium catalyst to yield substituted furans **111**



Scheme 30. Synthesis of tetrasubstituted furans **113**, **115**, and **116** from epoxypropargyl esters **108** and **108a**

Pale *et al.* demonstrated that nucleophiles play an important role in the cationic gold-mediated formation of furans **123** from **108a**. While the reaction of **108** with Ph_3PAuCl and $AgSbF_6$ gave divinyl ketones **119** (Scheme 31a),[33a] the presence of nucleophiles **120**, such as alcohols and thiols, furnished **123** under the same conditions (Scheme 31b).[33b] Although the authors described the possibility of several mechanistic pathways for the transformation, one plausible mechanism is as follows: **108a** undergoes a gold-catalyzed



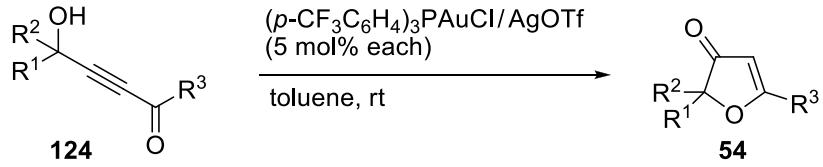
Scheme 31. Formation of **123** from **108** in the presence of nucleophiles **120**

1,2-acyloxy migration, concomitant with the epoxide opening at the propargylic position, to afford intermediates **121**, to which the addition of **120** follows. The secondary hydroxyl group present in **122** then attacks the allene moiety through assistance from coordination of the gold catalyst, and subsequent release of acetic acid gives **123**.

5. OTHER TYPES OF RING FORMATION

We disclosed that a combination of (p-$CF_3C_6H_4)_3$PAuCl and AgOTf catalyzed the intramolecular cyclization of **124** at room temperature to afford highly substituted 3(2*H*)-furanones **54** (Table 3).[8b] This method provided good isolated yields of **54** and demonstrated excellent substrate generality. Even in the presence of a sterically demanding *t*-Bu substituent, the desired product was obtained in 75% yield (entry 3). The reaction was applicable to the substrate **124**, bearing an alkenyl group as R^3, for the direct synthesis of 5-(1-alkenyl)-3(2*H*)-furanones (entry 7). Such compounds have been synthesized by the strong base-mediated aldol reaction of 5-alkyl-3(2*H*)-furanones with aldehydes followed by dehydration, although in only modest yields and with the unsatisfactory *E*/*Z*-stereoselectivity. Our method, however, resulted in the formation of the desired product in 94% yield with retention of the olefinic configuration.

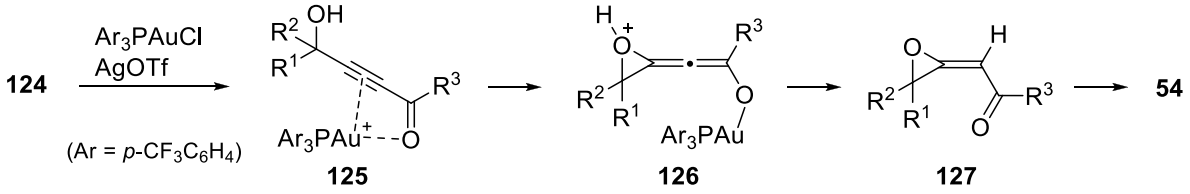
Table 3. Conversion of **124** into 3(2*H*)-furanones **54** by a combination of (p-$CF_3C_6H_4)_3$PAuCl and AgOTf



Entry	Substrate **124**			Time (h)	Product **54**
	R^1	R^2	R^3		Isolated yield (%)
1	Me	Me	$Ph(CH_2)_2$	2	91
2	Ph	Me	Me	2	94
3	Me	Me	*t*-Bu	5	75
4	$-(CH_2)_4-$		*n*-C_5H_{11}	1	83
5	Me	Me	Ph	3	92
6	Me	Me	*p*-$MeOC_6H_4$	3.5	88
7	Me	Me	(*E*)-PhCH=CH	3	94
8	Me	H	$Ph(CH_2)_2$	8	62 (90)[a]
9	H	H	$Ph(CH_2)_2$	3	55

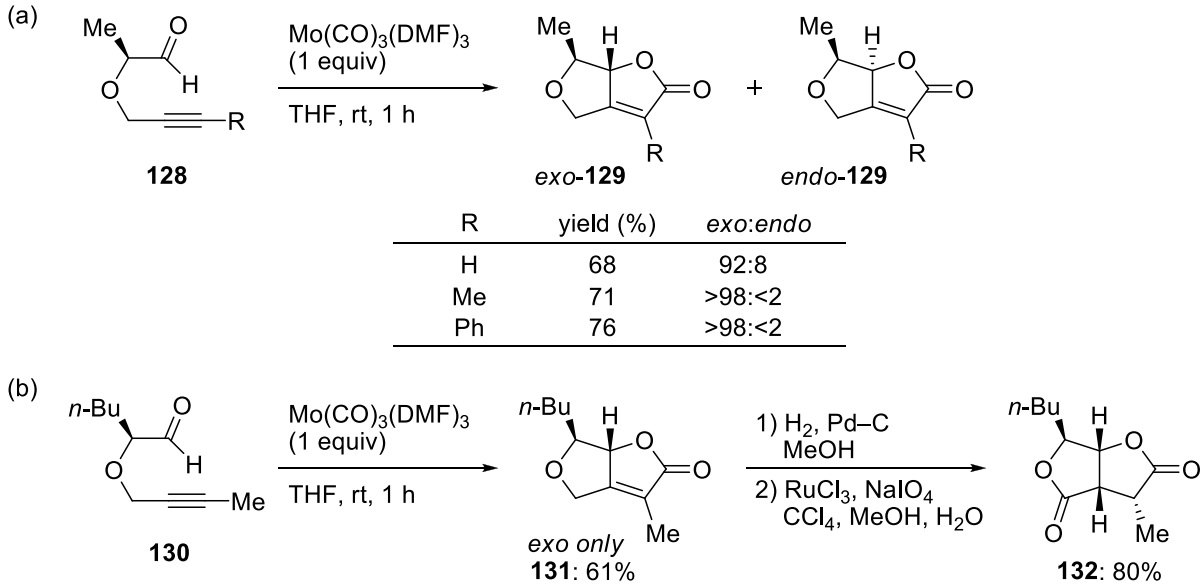
[a] NMR yield is shown in parenthesis.

Our proposed mechanism for this transformation is shown in Scheme 32. The concomitant coordination of both alkynyl and the carbonyl groups of **124** to a cationic gold species enhances the electrophilicity of the acetylene of **125**. This accelerates the subsequent Michael addition of the internal hydroxyl group, leading to the formation of the transient epoxide intermediate **127**, which then cyclized through nucleophilic attack of the carbonyl oxygen to afford **54**.



Scheme 32. A plausible mechanism for the cationic gold-catalyzed intramolecular cyclization of **124**

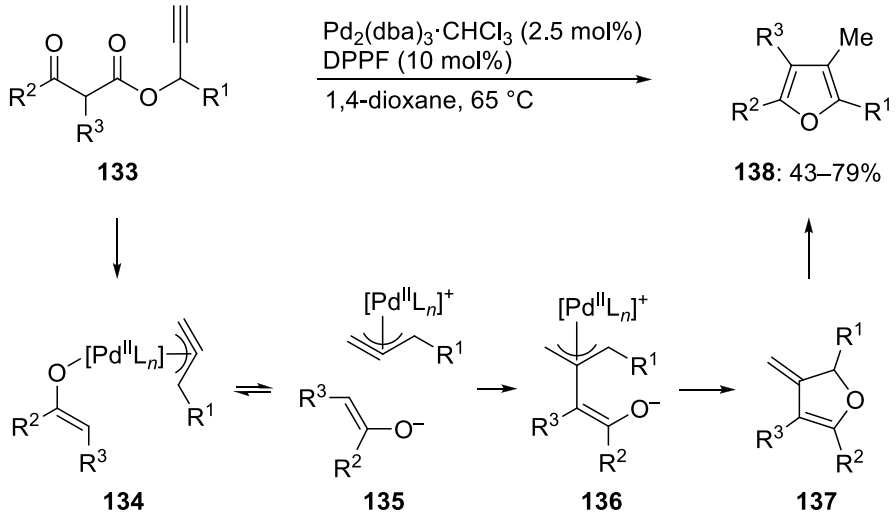
Another useful method for the formation of butenolides is the hetero-Pauson–Khand reaction, which is initiated by the activation of the acetylene moiety by transition metals. Recently, Adrio and Carretero developed a stereoselective synthesis for the preparation of fused bicyclic compounds *exo*-**129** from propargyl ethers **128** in the presence of a stoichiometric amount of $Mo(CO)_3(DMF)_3$ under mild conditions (Scheme 33a).[34] This method was also applied to the synthesis of (+)-dihydrocanadensolide **132**, an epimer of a biologically active metabolite from *Penicillium canadense* (Scheme 33b).



R	yield (%)	*exo*:*endo*
H	68	92:8
Me	71	>98:<2
Ph	76	>98:<2

Scheme 33. Hetero-Pauson–Khand reaction of propargyl ethers **128** and **130**

The final reaction which we would like to discuss is a new intramolecular cyclization reported by Yoshida *et al.*[35] The reaction involves the intramolecular cyclization of propargyl β-keto esters **133** through a $Pd_2(dba)_3{\cdot}CHCl_3$-catalyzed decarboxylative process to yield tetrasubstituted furans **138** (Scheme 34). In this system, the palladium catalyst allowed C–O bond cleavage at the propargyl position of **133** to generate the π-propargylpalladium enolate **134** with the concomitant release of CO_2. Subsequently, **134** underwent the formal [3+2]-cyclization to give **138**.



Scheme 34. Palladium-catalyzed reaction of propargyl β-keto esters **133** to afford furans **138**

6. CONCLUSION

In this review, we have summarized the recent progress on the synthesis of five-membered oxygen heterocycles, including furans, dihydrofurans, and butenolides, starting from functionalized propargyl alcohols and their derivatives, *via* a number of intramolecular cyclizations. These transformations are initiated by a wide variety of transition metal-catalyzed reactions of propargyl alcohol derivatives, such as nucleophilic cyclizations, rearrangements, and eliminations. Because these types of reactions are receiving an increasing attention in terms of their evaluation for use in regioselective synthesis of highly substituted five-membered oxygen heterocycles, further investigation is expected in this field.

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