ACCOUNTS
of chemical research

Gold-Catalyzed Cyclization Reactions of Allenol and Alkynol Derivatives

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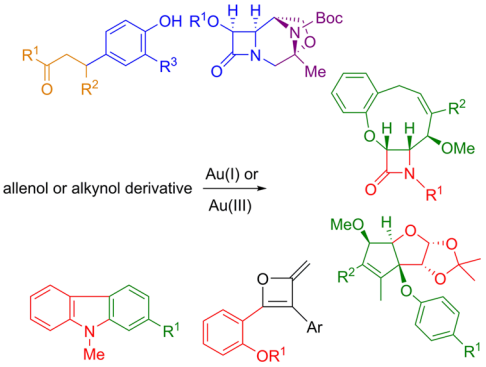
RECEIVED ON JULY 18, 2013

CONSPECTUS

Although gold is chemically inert as a bulk metal, the landmark discovery that gold nanoparticles can be effective catalysts has opened up new and exciting research opportunities in the field. In recent years, there has been growth in the number of reactions catalyzed by gold complexes [gold(I) and gold(III)], usually as homogeneous catalysts, because they are soft Lewis acids. In addition, alkynes and allenes have interesting reactivities and selectivities, notably their ability to produce complex structures in very few steps. In this Account, we describe our work in gold catalysis with a focus on the formation of C–C and C–O bonds using allenes and alkynes as starting materials. Of these, oxa- and carbo-cyclizations are perhaps the best known and most frequently studied. We have divided those contributions into sections arranged according to the nature of the starting material (allene versus alkyne).



Gold-catalyzed carbocyclizations in allenyl C2-linked indoles, allenyl-β-lactams, and allenyl sugars follow different mechanistic pathways. The cyclization of indole-tethered allenols results in the efficient synthesis of carbazole derivatives, for example. However, the compound produced from gold-catalyzed 9-*endo* carbocyclization of (aryloxy)allenyl-tethered 2-azetidinones is in noticeable contrast to the 5-*exo* hydroalkylation product that results from allenyl sugars.

We have illustrated the unusual preference for the 4-*exo*-dig cyclization in allene chemistry, as well as the rare β-hydride elimination reaction, in gold catalysis from readily available α-allenols. We have also observed in γ-allenols that a (methoxymethyl)oxy protecting group not only masks a hydroxyl functionality but also exerts directing effects as a controlling unit in a gold-catalyzed regioselectivity reversal. Our recent work has also led to a combined experimental and computational study on regioselective gold-catalyzed synthetic routes to 1,3-oxazinan-2-ones (kinetically controlled products) and 1,3-oxazin-2-one derivatives (thermodynamically favored) from easily accessible allenic carbamates.

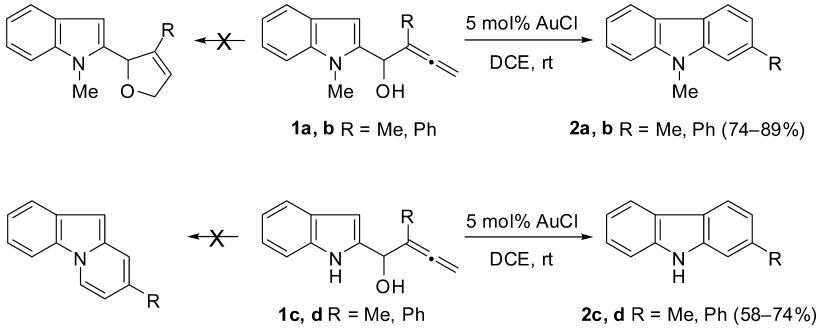
In addition, we discuss the direct gold-catalyzed cycloketalization of alkynyldioxolanes, as well as aminoketalization of alkynyloxazolidines. We performed labeling studies and density functional calculations to gain insight into the mechanisms of the bis-heterocyclization reactions. We also describe the controlled gold-catalyzed reactions of primary and secondary propargylic hydroperoxides with a variety of nucleophiles including alcohols and phenols, allowing the direct synthesis of β-functionalized ketones. Through computations and ^{18}O-labeling experiments, we discovered various aspects of the controlled reactivity of propargylic hydroperoxides with external nucleophiles under gold catalysis. The mechanism resembles a Meyer–Schuster rearrangement, but notably, the presence and geometry characteristics of the OOH functional group allow a new pathway to happen, which cannot apply to propargylic alcohols.

Introduction

Because of its chemical inertness as a bulk metal, chemists working in catalysis were not fascinated by gold until recently. However, the landmark discovery that nanosized gold [gold(0) nanoparticles] can be an effective catalyst[1] opened up new and exciting transformations. The recent

Published on the Web 01/15/2014 www.pubs.acs.org/accounts
10.1021/ar4002558

SCHEME 1. Gold-Catalyzed Controlled Carbocyclization Reaction of Allenol C2-Linked Indoles **1a**–**d** to Carbazole Derivatives **2a**–**d**



observation that subnanosized gold clusters can be exceptionally active as heterogeneous catalysts at room temperature (reaction turnover numbers of 10^7)[2] will also inspire a great number of discoveries. Little was known about the application of gold complexes [gold(I) and gold(III)] in homogeneous catalysis until Hayashi and then Teles elegantly and independently merged into this field.[3,4] The past decade has witnessed dramatic growth in the number of reactions catalyzed by gold complexes [gold(I) and gold(III)], notably in its homogeneous catalysis manifestation,[5] because of their powerful soft Lewis acidic nature. The excellent works from the laboratories of Toste, Hashmi, Corma, Echavarren, Zhang, Fürstner, Malacria, Krause, Gagosz, and many other relevant scientists have well illustrated this point. On the other hand, alkynes and allenes have shown interesting reactivities and selectivities affording complex structures in a limited number of steps.[6] Herein we account our own experience in gold catalysis with a focus on the formation of C–C and C–O bonds using allenes and alkynes as starting materials.

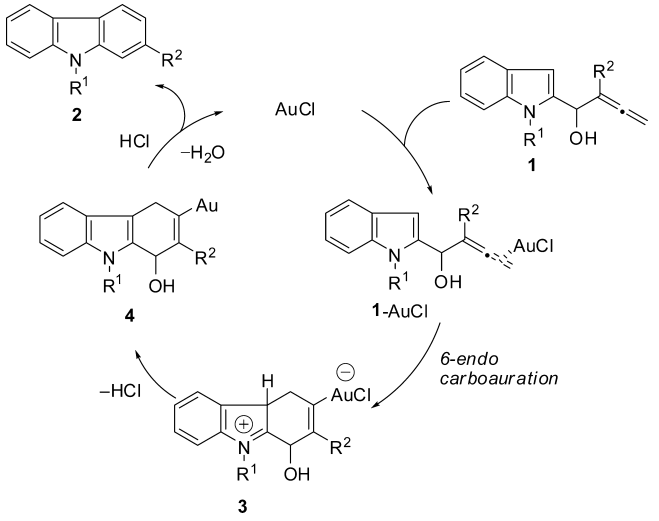
Allenes

Gold-Catalyzed Carbocyclizations in Allenyl C2-Linked Indoles, Allenyl β-Lactams, and Allenyl Sugars. The carbazole nucleus represents a key molecular motif with widespread occurrence in nature and featuring peculiar biological activities. The indole framework has been very successful in gold catalysis on reacting with alkynes.[7] The Au(I)-catalyzed cyclization of allenol C2- and C3-linked indoles afforded carbazoles.[8] A mixture of at least two different products arising from competitive C-cyclization versus O-cyclization is possible starting from indole-tethered allenols **1a** and **1b**. Nicely, substrates **1a** and **1b** gave full conversion to carbazoles **2a** and **2b** in a totally selective fashion (Scheme 1). Worthy of note, despite that gold-based catalysts are well-known for their ability to promote the O-cyclization of α-allenols,[9] no traces of dihydrofurans were detected. It was also found that this activation mode was also quite successful in the direct cyclization reaction of *NH*-indolyl allenols (Scheme 1). Thus, it is obvious from the experiments that in our functionalized system competitive heterocyclization processes are not operating. Probably, in our case, the carbazole formation must be driven by the higher stability associated with the aromatic six-membered carbocycle. It could be inferred that the 6-*endo* carbocyclization reaction of allenols **1** is thermodynamically favored.

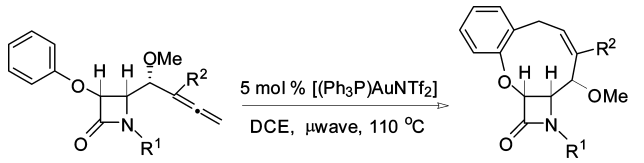
A possible pathway for the gold-catalyzed formation of carbazoles **2** from allenol C2-linked indoles **1** may initially involve the formation of a complex **1**–AuCl through coordination of the gold chloride to the distal allenic double bond. Next, chemo- and regioselective 6-*endo* carboauration forms zwitterionic species **3**. Attack at the 3-position of the indole occurs as a result of the stability of the intermediate iminium cation type **3**. Loss of HCl generates neutral species **4**, which followed by protonolysis of the carbon–gold bond and dehydration afforded carbazoles **2** with concurrent regeneration of the gold catalyst (Scheme 2).

(Aryl)allenol-tethered 2-azetidinones **5** or (aryl)allenol-tethered sugars **6**, readily prepared from 4-oxoazetidine-2-carbaldehydes or 3-*O*-(aryl) glucofuranosides, were used as starting materials for the regio- and stereoselective catalytic carbocyclization reaction in the presence of a gold(I) precatalyst.[10] Interestingly, in contrast to the gold-catalyzed reactions of (aryl)allenol-tethered sugars, which lead to the corresponding cyclopenta[*b*]furan core derivatives **8** (hydroalkylation adducts), the reactions of (aryl)allenol-tethered 2-azetidinones under identical conditions gave the nine-membered annulated β-lactam derivatives **7** (hydroarylation adducts) as the sole products (Scheme 3), through exclusive 9-*endo* carbocyclization by initial attack of the arene moiety to the distal allene carbon. Thus, it is shown that the outcome of the reaction was 9-*endo* hydroarylation versus formal 5-*exo* hydroalkylation. Moreover, the mildness of the method allowed the preparation of unusual

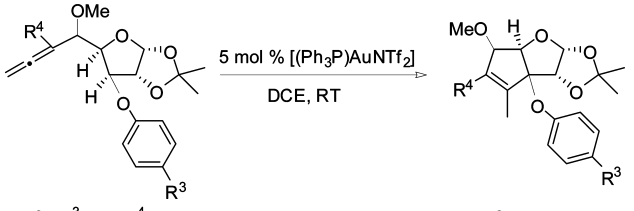
SCHEME 2. Mechanistic Explanation for the Gold-Catalyzed Carbocyclization Reaction of Allenol C2-Linked Indoles **1**



SCHEME 3. Gold-Catalyzed Carbocyclization Reaction of Allenyl-Tethered Arenes **5** and **6**



5a R^1 = isobutyl, R^2 = Me — **7a** (72%)
5b R^1 = isobutyl, R^2 = Ph — **7b** (60%)
5c R^1 = Bn, R^2 = Me — **7c** (58%)
5d R^1 = Bn, R^2 = Ph — **7d** (69%)
5e R^1 = isopropyl, R^2 = Me — **7e** (65%)
5f R^1 = isopropyl, R^2 = Ph — **7f** (59%)
5g R^1 = 2-methylallyl, R^2 = Ph — **7g** (63%)



6a R^3 = H, R^4 = Me — **8a** (46%)
6b R^3 = H, R^4 = Et — **8b** (34%)
6c R^3 = H, R^4 = $BnOCH_2$ — **8c** (48%)
6d R^3 = Br, R^4 = Me — **8d** (35%)
6e R^3 = Br, R^4 = $BnOCH_2$ — **8e** (41%)

fused 2-azetidinones without harming the sensitive four-membered ring. In order to confirm the mechanistic proposal, density functional calculations were performed to gain insight into the mechanism of the previously unknown allenic 9-*endo* hydroarylation reaction (Figure 1). Our calculations suggest that the reaction starts with the exergonic coordination of the $AuPMe_3^+$ catalyst to the distal double bond of the allenic moiety of **1M** ($\Delta G_{298} = -9.4$ kcal/mol). Then, the 9-*endo* carbocyclation reaction to produce the nine-membered ring tricyclic intermediate **2M** occurs through the transition state **TS1**. It can be concluded that the initial 9-*endo* carbocyclization reaction constitutes the bottleneck of the process in view of the corresponding endergonicity and relatively high activation barrier. Finally, the reaction ends up with the release of the $AuPMe_3^+$ catalyst, which is coordinated to the endocyclic C=C double bond of **6M**, to produce the final tricyclic species **7M**.

The pathway proposed in Scheme 4 looks valid for the formation of tricycles of type **8**. It could be presumed that the initially formed gold complex **6**-Au(L), through coordination of the gold salt to the distal allenic double bond, undergoes a 1,6-hydride shift (rare transfer of hydride versus normal nucleophilic group attack), giving rise to oxonium species. Intramolecular trapping of the oxonium group by the alkenylgold moiety generates cationic species, through formal 5-*exo* hydroalkylation. Finally, demetalation yields fused cyclopentenes **8** and regenerates the gold catalyst (Scheme 4).

Gold-Catalyzed Oxycyclization Reactions in α-Allenols and γ-Allenols. Traditionally, metal-catalyzed cyclizations on α-allenols favor a 5-endo-trig pathway. We were attracted to the possibility that a heterocycle different to a five-membered ring could be accessed by variation of the allene substitution. Starting from salicylaldehyde-derived phenyl-substituted allenols **9**, the gold-catalyzed synthesis of oxetenes **10** was achieved (Scheme 5).[11]

A mechanistic rationale for the gold-catalyzed conversion of aryl-substituted allenols **9** into oxetenes **10** is intricate. It is worth noting that the cyclization affords cycloadducts **10** from a 4-*exo*-dig cyclization/dehydrogenation process instead of that from the usually preferred 5-*endo*-trig cycloisomerization reaction. The pathway proposed in Scheme 6 looks valid for the formation of products type **10**. It could be presumed that the initially formed gold complex **11**, through coordination of the $AuCl_3$ to the distal allenic double bond, undergoes an intramolecular attack (rare 4-*exo*-dig versus normal 5-*endo*-trig oxyauration) by the hydroxy group, giving rise to the oxetene intermediate **12**. Loss of HCl in intermediate **12** generates neutral species **13**, which after 1,3-gold migration[12] leads to the formation of oxetane species **14**. Uncommon β-hydride elimination[13] rather than protonolysis of the carbon−gold bond, linked to a reaction of HCl with the gold hydride would then liberate the oxacycle type **10** with concomitant regeneration of the catalytic Au(III) salt.

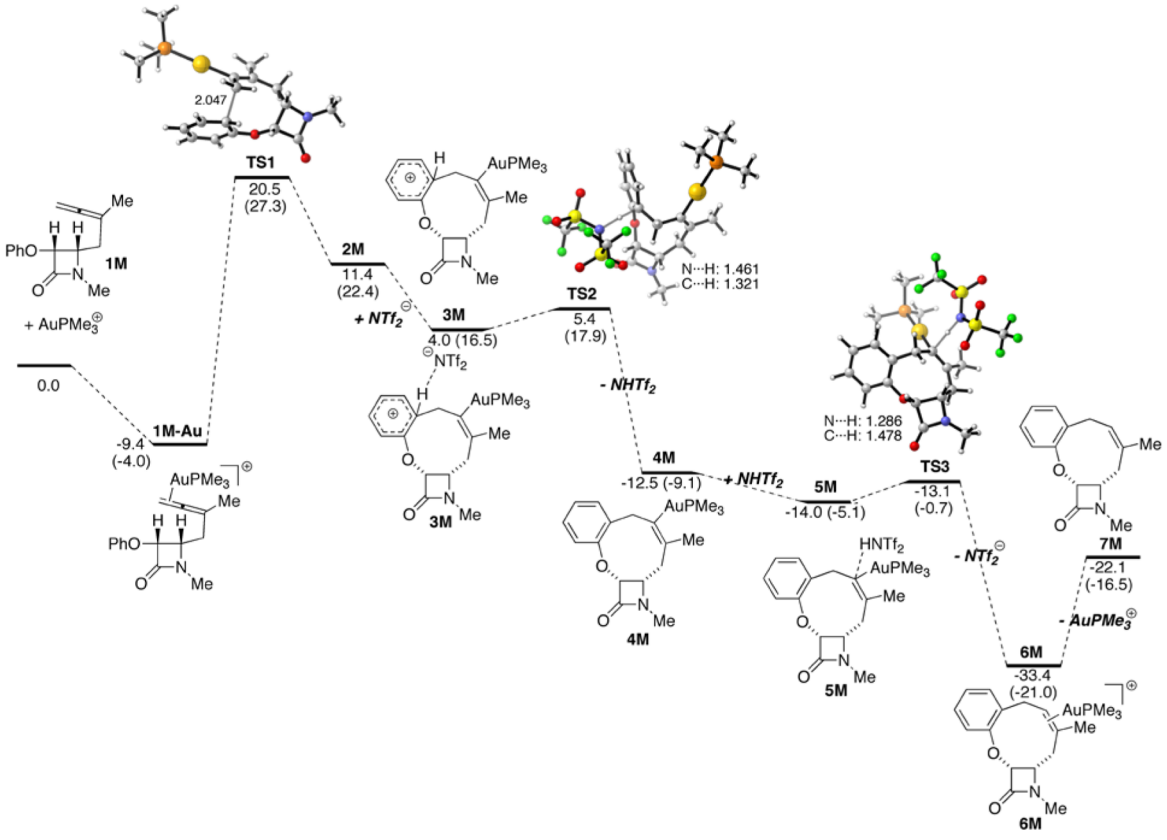
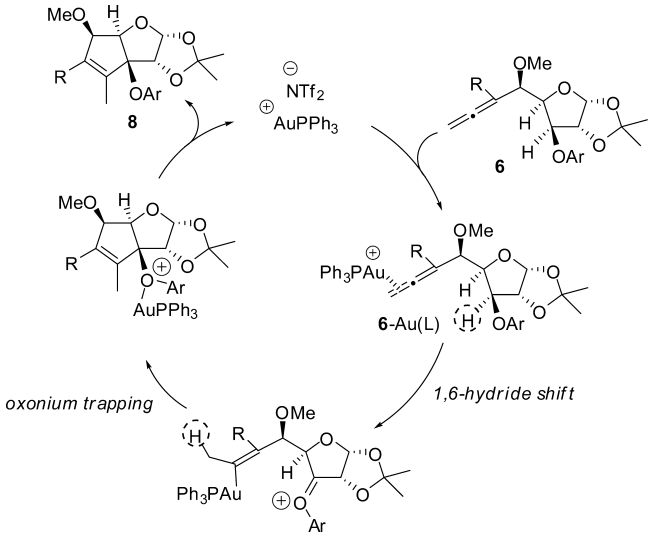


FIGURE 1. Computed reaction profile for the reaction of allenyl-β-lactam **1M** and [(PMe_3)$AuNTf_2$] catalyst.

SCHEME 4. Mechanistic Explanation for the Gold-Catalyzed Formal 5-*exo* Hydroalkylation of Allenyl-Tethered Oxyarenes **6**

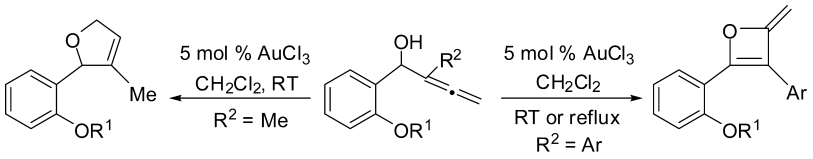


We have accomplished a regiodivergent gold-catalyzed O–C functionalization of 2-azetidinone-tethered γ-allenol derivatives.[14] The reactivity of 2-azetidinone-tethered γ-allenols toward the regioselective hydroalkoxylation reaction was tested with substrate **15a** (R^1 = Bn, R^2 = TBS) by the use of AuCl and $AuCl_3$ as catalysts. Gratifyingly, it was found that Au salts were effective as 5-*exo* selective hydroalkoxylation catalysts, affording bicycle **16a**. $AuCl_3$ was selected as catalyst of choice because of its superior performance, affording tetrahydrofuran-2-azetidinones **16** in moderate yields (Scheme 7). No regioisomeric products were detected, giving exclusively the fused five-membered oxacycle.

A possible pathway for the achievement of bicyclic tetrahydrofurans **16** from γ-allenols **15** may initially involve the formation of a complex **15**–$AuCl_3$ through coordination of the gold trichloride to the proximal allenic double bond. Next, regioselective 5-*exo* oxyauration forms zwitterionic species **17**. Loss of HCl followed by protonolysis of the carbon–gold bond of **18** affords products **16** and regenerates the gold catalyst (Scheme 8).

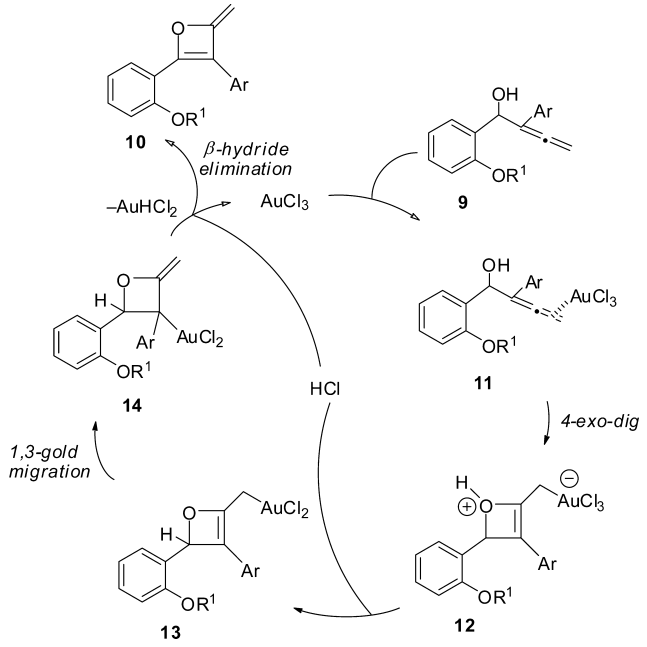
A computational study for the above heterocyclization has been carried out.[15] Density functional theory (DFT) calculations have been carried out at the PCM-M06/def2-SVP//B3LYP/def2-SVP level. The Au(III)-catalyzed cyclization of the model system γ-allenol **I** (Figure 2) takes place regio- and stereoselectively through a 5-*exo* hydroalkoxylation because of a kinetic preference governed by electronic and steric factors. The results in Figure 2 clearly point to

SCHEME 5. Synthesis of Oxetenes **10** through Oxycyclization Reaction of α-Allenols **9** under Gold Catalysis

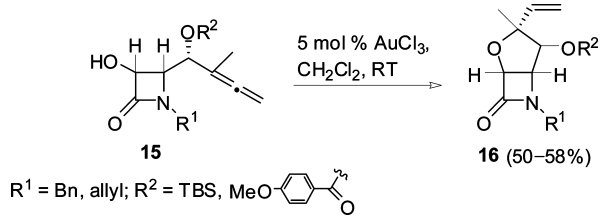


9a R^1 = prop-2-enyl, R^2 = Ph — **10a** (55%)
9b R^1 = 2-methylallyl, R^2 = Ph — **10b** (62%)
9c R^1 = 2-bromoallyl, R^2 = Ph — **10c** (85%)
9d R^1 = methyl, R^2 = Ph — **10d** (38%)
9e R^1 = prop-2-ynyl, R^2 = Ph — **10e** (35%)
9f R^1 = (*E*)-(4-chlorobut-2-enyl), R^2 = Ph — **10f** (43%)
9g R^1 = 2-methylallyl, R^2 = 4-$MeOC_6H_4$ — **10g** (48%)
9h R^1 = 2-methylallyl, R^2 = 4-BrC_6H_4 — **10h** (34%)

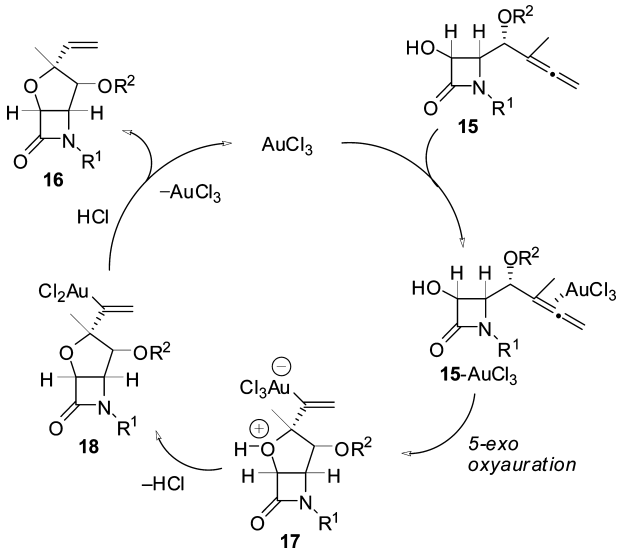
SCHEME 6. Mechanistic Explanation for the Gold-Catalyzed Oxycyclization of Aryl Substituted α-Allenols **9**



SCHEME 7. Gold-Catalyzed Cyclization of γ-Allenols for the Preparation of Five-Membered Oxacyclic β-Lactams



SCHEME 8. Possible Catalytic Cycle for the Gold-Catalyzed Cyclization of γ-Hydroxyallenes **15**



the stepwise mechanism as the most likely route. Therefore, the stepwise path is predicted to be considerably favored over the concerted path, which hence can be ruled out as operative. Overall, the 1,3-H shift is a strongly exothermic process, pointing to a somewhat irreversible character.

Having found a solution for the 5-*exo* selective hydroalkoxylation, the possibility of tuning the regioselectivity in the heterocyclization of γ-allenol derivatives was examined. Taking into account the sensitivity of the MOM group to acidic conditions, it was decided to see whether (methoxymethyl)oxy substitution may had beneficial impact on the above cyclization reactions. Thus, whether the metal-catalyzed preparation of bicycles **16** can be directly accomplished from MOM protected γ-allenol derivatives **19** was tested. It is worth noting that when allenic MOM ethers **19** were treated with $AuCl_3$, the 5-*exo* mode was completely reverted to a 7-*endo* cyclization to afford bicycles **20** in fair yields (Scheme 9).[14] It seems that the reactivity in this type of Au(III)-catalyzed reactions is determined by the presence or absence of a methoxymethyl

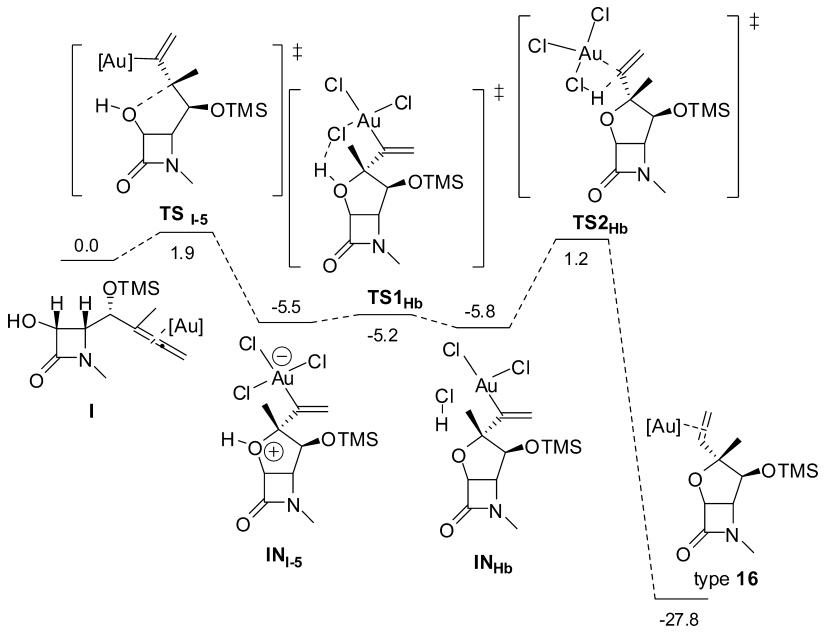
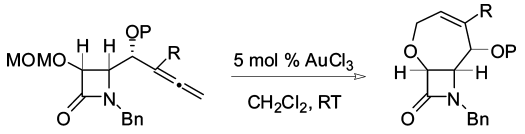


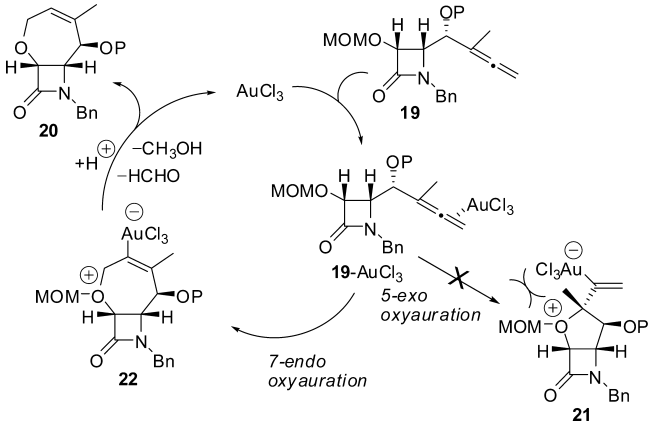
FIGURE 2. Free energy profile [kcal mol^{-1}] for the transformation of γ-allenol I into the tetrahydrofuran type **16**.

SCHEME 9. Gold-Catalyzed Cyclization of MOM-Protected γ-Hydroxyallenes for the Preparation of Seven-Membered Oxacyclic β-Lactams



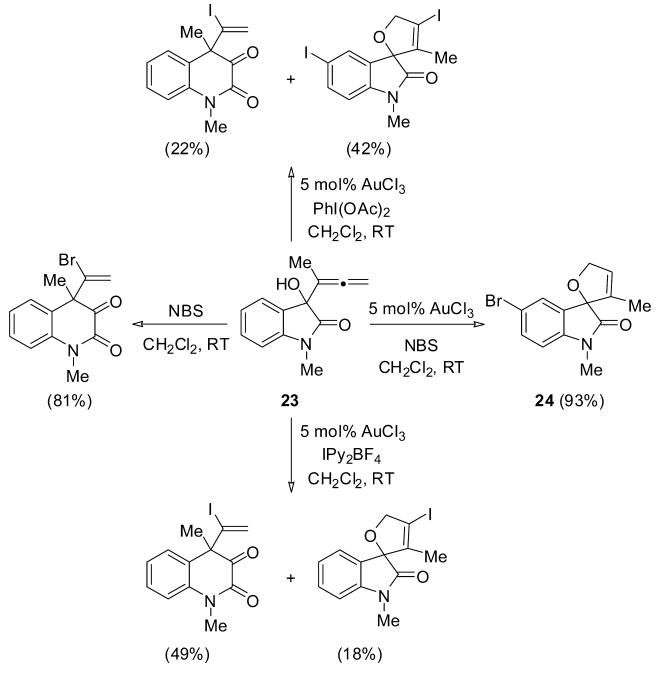
19a P = 4-MeOC$_6$H$_4$CO, R = Me — **20a** (45%)
19b P = 4-BrC$_6$H$_4$CO, R = Me — **20b** (58%)
19c P = 4-MeOC$_6$H$_4$CO, R = Ph — **20c** (62%)
19d P = MeCO, R = Ph — **20d** (75%)

SCHEME 10. Possible Catalytic Cycle for the Gold-Catalyzed Cyclization of MOM Protected γ-Allenol Derivatives **19**



protecting group at the γ-allenol oxygen atom, as the free γ-allenols **15** gave 5-*exo* hydroalkoxylation, while MOM protected γ-allenol derivatives **19** exclusively underwent a

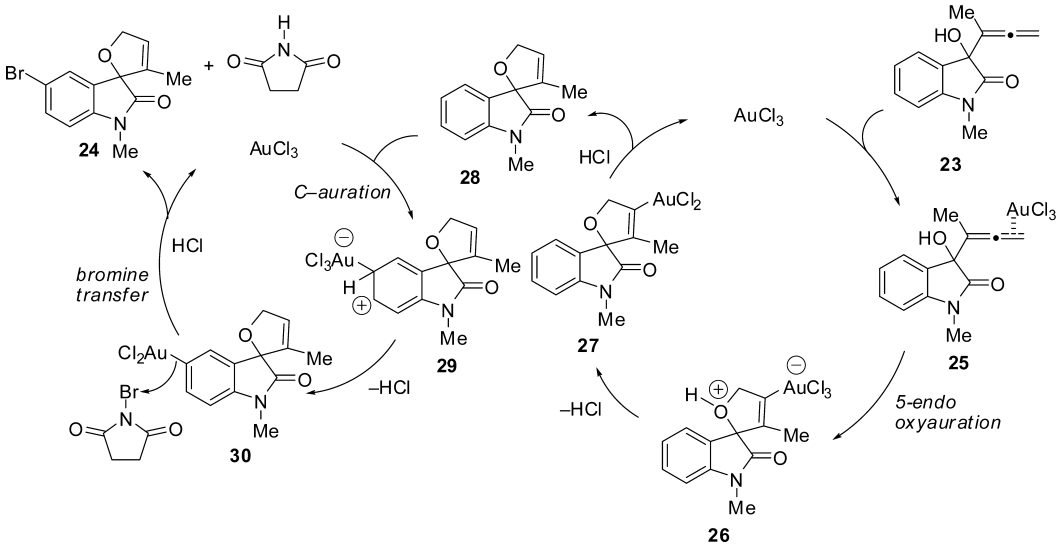
SCHEME 11. Gold-Catalyzed Simultaneous Oxycyclization/Bromination Reactions of Allenic Oxindole **23**



7-*endo* oxycyclization. Thus, it has been demonstrated that regioselectivity control in the metal-catalyzed O–C functionalization of γ-allenols can be achieved through the nature of the γ-allenol (free versus protected).

The pathway proposed in Scheme 10 looks valid for the formation of products **20** from MOM protected γ-allenol derivatives **19**. It could be presumed that the initially formed

SCHEME 12. Mechanistic Explanation for the Au(III)-Catalyzed Arene Bromination/Spirocyclization Reaction Sequence of 3-Allenyl 3-Hydroxyindolin-2-one **23**



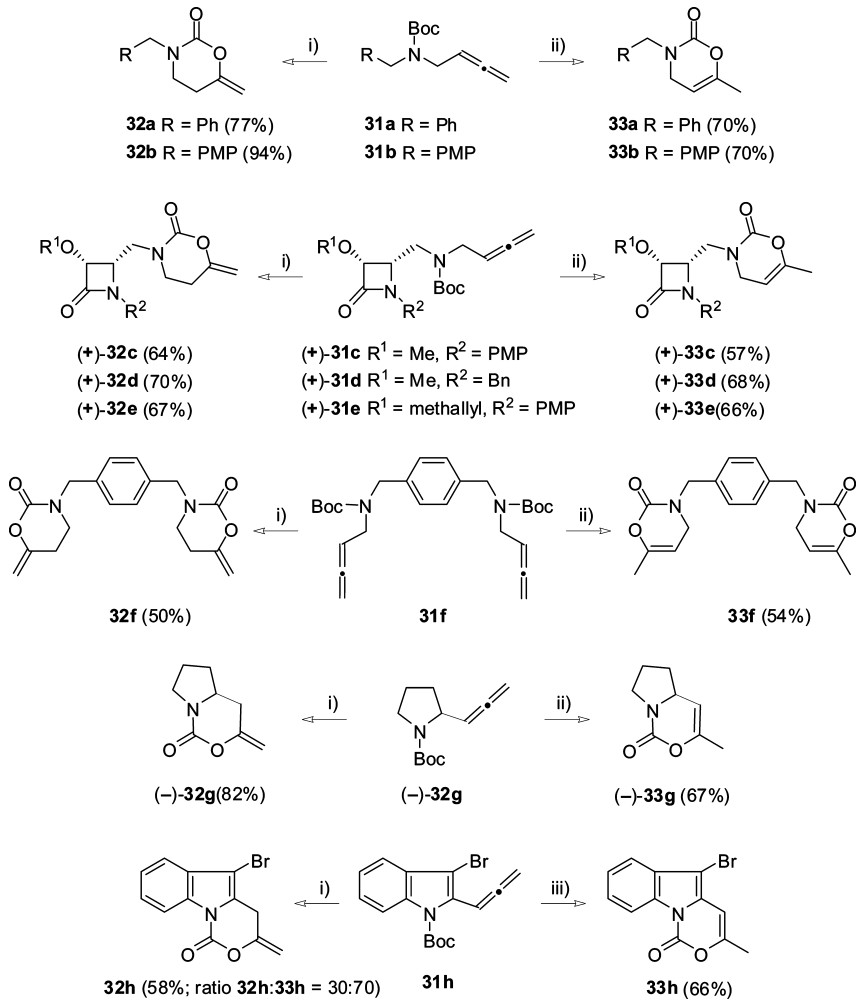
allenegold complex **19**–$AuCl_3$ undergoes an intramolecular attack (7-*endo* versus 5-*exo* oxyauration) by the (methoxymethyl)oxy group, giving rise not to species **21** but to the tetrahydrooxepine intermediate **22**. Protonolysis of the carbon–gold bond linked to an elimination of methanol and formaldehyde would then liberate the bicycle type **20** with concomitant regeneration of the Au(III) species. Probably, the proton in the last step of the catalytic cycle comes from the trace amount of water present in the solvent or the catalyst. In the presence of MOM group, 5-*exo* cyclization falters. As calculations reveals, 5-*exo* oxyauration via **21** is restricted by the steric hindrance between the (methoxymethyl)oxy group and the substituents at the quaternary stereocenter.[15]

The reactions of 3-allenyl 3-hydroxyoxindoles with a variety of halogenated reagents in the presence of catalytic amounts of precious metal salts have been explored.[16] The kind of functionalization is substrate and reaction conditions dependent: $AuCl_3$ in the presence of NBS afforded as major adducts quinoline-2,3-diones, $AuCl_3$ in the presence of I_2/PhI(OAc)$_2$ favors the formation of spirocyclic iododihydrofurans, whereas $AuCl_3$ in the presence of IPy_2BF_4 gives as major product a ring expansion adduct. An interesting case was the reaction of the allene-derived oxindole **23** because the addition of a catalytic amount of $AuCl_3$ completely suppressed the rearrangement reaction, giving instead the corresponding spirocyclic 5-bromooxindole **24** as the sole product (Scheme 11). Thus, it was shown for the first time that it is possible to use a single gold salt for performing two very different and independent transformations, namely, C–O and C–halogen bond formations,[17] in a single reaction sequence.

Mechanistically, this gold-catalyzed access to spirocyclic bromooxindole **24** might proceed in a tandem sequence involving as the first step the formation of complex **25** through coordination of gold trichloride to the distal allenic double bond of α-allenol **23**. Next, regioselective 5-*endo* oxyauration forms zwitterionic intermediate **26**, which after loss of HCl generate neutral species **27**. Protonolysis of the carbon–gold bond of **27** liberates adduct **28**, releasing the gold catalyst into the first catalytic cycle (Scheme 12). Next, spirocyclic oxindole **28** enter the second catalytic cycle, which is also gold-catalyzed, generating zwitterionic species **29** by formation of a C–Au bond in an electrophilic substitution fashion. Subsequent loss of HCl would regenerate the aromatic ring and would form the neutral arylgold(III) species **30**. Nucleophilic attack of the arylgold species **30** to *N*-bromosuccinimide liberates bromoadduct **24** and succinimide with concomitant regeneration of the gold catalyst, closing the second catalytic cycle (Scheme 12).

Gold-Catalyzed Oxycyclization Reactions of Allenic Carbamates. 1,3-Oxazin-2-ones are both biologically relevant compounds as well as valuable intermediates in organic synthesis.[18] While the synthesis of oxazinones from N-Boc-(3-butyn)-1-amines has been established,[19] the gold-catalyzed cyclization of N-Boc-allenes with the aim of establishing a protocol for the synthesis of 1,3-oxazin-2-one derivatives in which the carbamate group should serve as the source of CO_2 has only been examined recently.[20] We employed three different gold salts in our initial screening of

SCHEME 13. Controlled Oxycyclization Reactions of Allenic Carbamates **31** to 1,3-Oxazinan-2-ones **32** and 1,3-Oxazin-2-ones **33** under Selective Gold-Catalyzed Conditions[a]

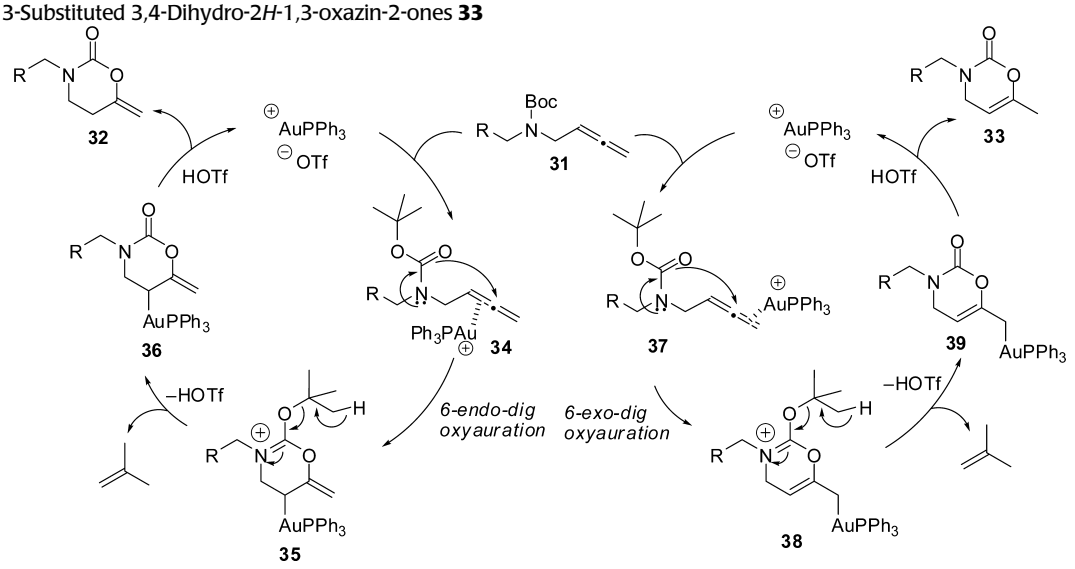


[a]Conditions: (i) 2.5 mol % [AuClPPh$_3$], 2.5 mol % AgOTf, 10 mol % PTSA, CH_2Cl_2, rt; (ii) 2.5 mol % [AuClPPh$_3$], 2.5 mol % AgOTf, 10 mol % PTSA, CH_2Cl_2, sealed tube, 130 °C.

catalysts for a model system allenic carbamate. Initially, the use of $AuCl_3$ and AuCl were tested, but both failed to catalyze the reaction. Fortunately, we found that [AuClPPh$_3$]/AgOTf was an excellent catalyst for our purpose. The reaction of allenic carbamates **31** at room temperature afforded 3-benzyl-6-methylene-1,3-oxazinan-2-ones **32** bearing an exocyclic double bond as the sole product (Scheme 13). Adding a catalytic amount of Brønsted acid (PTSA) into the reaction system did slightly improve the yield of **32**. Solvent screening demonstrated that dichloromethane was the best selection in the reaction. Interestingly, starting from allenic carbamates **31** and performing the reaction in dichloromethane at 130 °C exclusively produced a series of 6-methyl-3-substituted-3,4-dihydro-2*H*-1,3-oxazin-2-ones **33** (Scheme 13). The observed regioselectivity is worthy of note, because under our reaction conditions only 1,3-oxazinan-2-ones **32** (arising from 6-*endo-dig* cyclization) or 3,4-dihydro-2*H*-1,3-oxazin-2-ones **33** (arising from 6-*exo-dig* cyclization) were achieved, with the nucleophilic oxygen attacking the central allene carbon atom in each case. This is an interesting result, because the available examples on related metal-catalyzed allene heterocyclizations usually lead to 5-*exo*-trig cyclization; only Hashmi et al. have recently reported an attack at the central position of the allene in allenylamides.[17b] Thus, it is possible to suppress the formation of the 1,3-oxazinan-2-one ring by performing the reaction at higher temperature, yielding the 1,3-oxazin-2-one as the exclusive product. A general trend can be deduced on the basis of these results: heterocycle **33** is the thermodynamically controlled product while heterocycle **32** is the kinetically controlled product.

A possible pathway for the gold-catalyzed achievement of heterocycles **32** from allenyl-tethered carbamates **31**

SCHEME 14. Mechanistic Explanation for the Gold-Catalyzed Oxycyclization Reactions of Allenic Carbamates **31** into 6-Methylene-1,3-oxazinan-2-ones **32** or into 3-Substituted 3,4-Dihydro-2*H*-1,3-oxazin-2-ones **33**

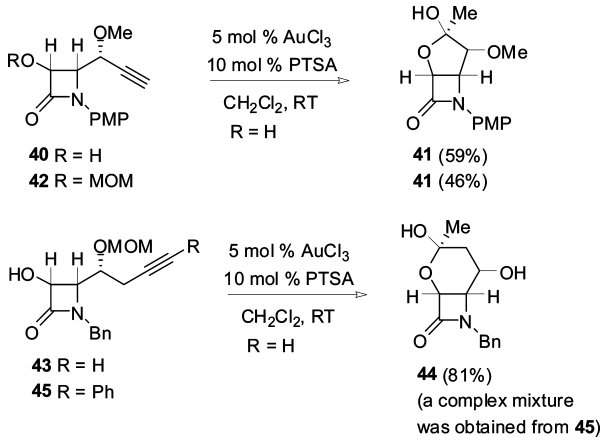


may initially involve the formation of a complex **34** through coordination of the gold salt to the proximal allenic double bond. Next, chemo- and regioselective 6-*endo*-dig oxyauration of the carbamate carbonyl moiety forms species **35**. Attack of the carbamate carbonyl group occurs as a result of the stability of the intermediate ammonium cation type **35**. Loss of proton linked to 2-methylprop-1-ene release generates neutral species **36**, which followed by protonolysis of the carbon–gold bond affords 6-methylene-1,3-oxazinan-2-ones **32** with concurrent regeneration of the gold catalyst (Scheme 14, left catalytic cycle). In line with the above mechanistic proposal, the easy breakage of the *tert*-butyl group at species **35** is essential for the formation of 1,3-oxazinan-2-ones **32**. Besides, the replacement of the *tert*-butyl group in allenic carbamates **31** by other alkyl functions, such as methyl, did not allow the preparation of heterocycles **32**. A mechanistic scenario involving the initial coordination of the gold to the distal allenic double bond leading to complex **37**, followed by a 6-*exo*-dig oxyauration, is likely for the achievement of 1,3-oxazin-2-ones **33** from allenic carbamates **31** (Scheme 14, right catalytic cycle).

Alkynes

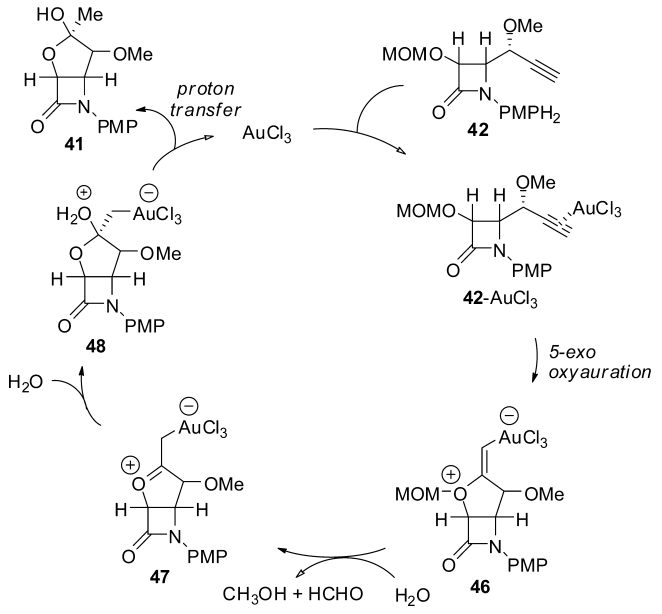
Gold-Catalyzed Oxycyclizations of Alkynol Derivatives. Activation of alkynes toward attacks by oxygen nucleophiles such as carbonyls, carboxylic acids, and alcohols is an important C–O bond-forming reaction.[21] In this context, the preparation of fused oxabicyclic β-lactams using gold catalysis through a tandem oxycyclization/hydroxylation of 2-azetidinone-linked alkynols has been accomplished.[22]

SCHEME 15. Synthesis of Fused β-Lactam Hemiacetals from 2-Azetidinone-Tethered Homopropargylic Alcohols under Gold-Catalyzed Conditions



The reaction of 2-azetidinone-tethered bishomopropargylic alcohol **40** in the presence of catalytic amounts of $AuCl_3$ provided bicycle **41** in good yield, which may result from a cycloetherification/hydroxylation sequence (Scheme 15). Interestingly, the gold-catalyzed reaction of **42**, possessing a (methoxymethyl)oxy moiety instead the free hydroxyl group, also proceeded smoothly to give the cyclization adduct **41** albeit in lower yield (Scheme 15). Notably, the observed regioselectivity (5-*exo* cyclization) was not affected by the presence of a protective group at the hydroxyl moiety. These gold-catalyzed oxycyclizations were successfully extended to trishomopropargylic alcohol **43**, yielding the oxycyclization/hydroxylation product **44** with concomitant MOM cleavage (Scheme 15). By contrast, the presence

SCHEME 16. Mechanistic Explanation for the Gold-Catalyzed Oxycyclization Reactions of Alkynol Derivative **42** into Fused β-Lactam Hemiacetal **41**

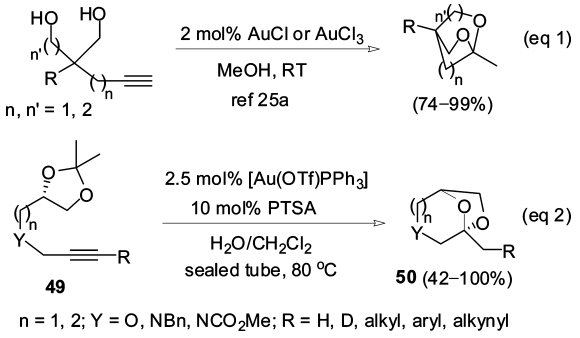


of a phenyl substituent at the terminal alkyne carbon showed a substantial effect on the reactivity, as illustrated by the fact that phenyl alkynol **45** did afford a complex mixture.

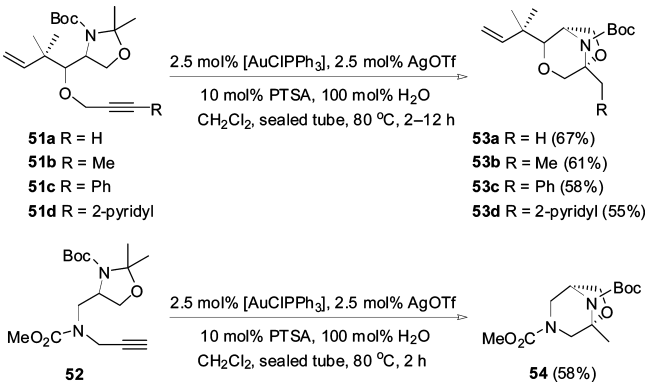
A plausible pathway for the achievement of bicyclic tetrahydrofuran **41** from the methoxymethyl ether **42** may initially involve the formation of a π-complex **42**$-AuCl_3$ through coordination of the gold trichloride to the alkyne moiety. Next, it could be presumed that the initially formed alkynegold complex **42**$-AuCl_3$ undergoes a regioselective intramolecular attack (5-*exo* versus 6-*endo* oxyauration) by the (methoxymethyl)oxy group giving rise to the vinylgold intermediate **46**, which linked to an elimination of methanol and formaldehyde would then isomerize to the metalaoxocarbenium species **47**. Probably, the water molecule in the third step of the catalytic cycle comes from the trace amount of water present in the solvent or the catalyst. Subsequent nucleophilic attack of water from the less hindered face of intermediate **47** would form the ate complex **48**. Deauration linked to proton transfer liberates adduct **41** with concomitant regeneration of the Au(III) species (Scheme 16).

The recently developed gold activation of alkynes toward simultaneous attack by two contiguous oxygen nucleophiles is an important C–O bond-forming reaction.[23] Previous work involves the use of free hydroxy groups (Scheme 17, eq 1). However, the direct bis(oxycyclization) sequence of acetonide-tethered alkynes was missed until

SCHEME 17. Selective Direct Bis(oxcyclization) Reaction of Acetonide-Tethered Alkynes **1** under Gold-Catalyzed Conditions

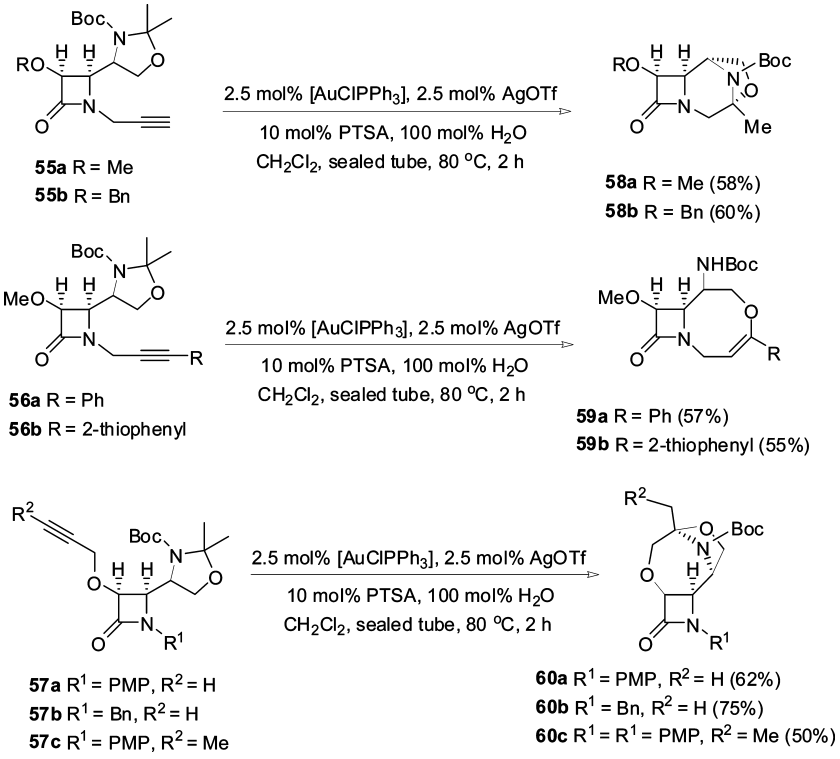


SCHEME 18. Controlled *N,O*-Cycloaminalization Reaction of Alkynyloxazolidines **51** and **52** under Gold-Catalyzed Conditions



we merged into this field.[24] Using a dioxolane ring directly instead of the deprotected 1,2-diol moiety as the starting material would be a significant breakthrough for metal-catalyzed alkyne-cycloketalization in terms of cost-effectiveness. Initial experiments were carried out using (*S*)-2,2-dimethyl-4-[(prop-2-ynyloxy)methyl]-1,3-dioxolane as a model substrate. To optimize the reaction method, different parameters involved in the metal-catalyzed reactions that could affect the formation of the desired product were tested. Nicely, it was found that [AuClPPh$_3$]/AgOTf along with a Brønsted acid (PTSA) in CH_2Cl_2 was a competent catalytic system for this purpose. In particular, the transformation was strongly influenced by the presence of water. Having established the optimal reaction conditions, the scope of the methodology was explored by subjecting a range of (prop-2-ynyloxy)methyl-tethered dioxolanes **49** to direct alkyne-cycloketalization and the results are shown in Scheme 17 (eq 2). In both cases (addition of one equivalent of water as well as the presence of large amount of water), the crude reaction mixtures are extremely clean and the acetals are the only products detected. Tolerance toward a variety of substituents (aliphatic, aromatic,

SCHEME 19. Gold-Catalyzed Preparation of Bridged Azaoxa-β-lactams **58** and **60**



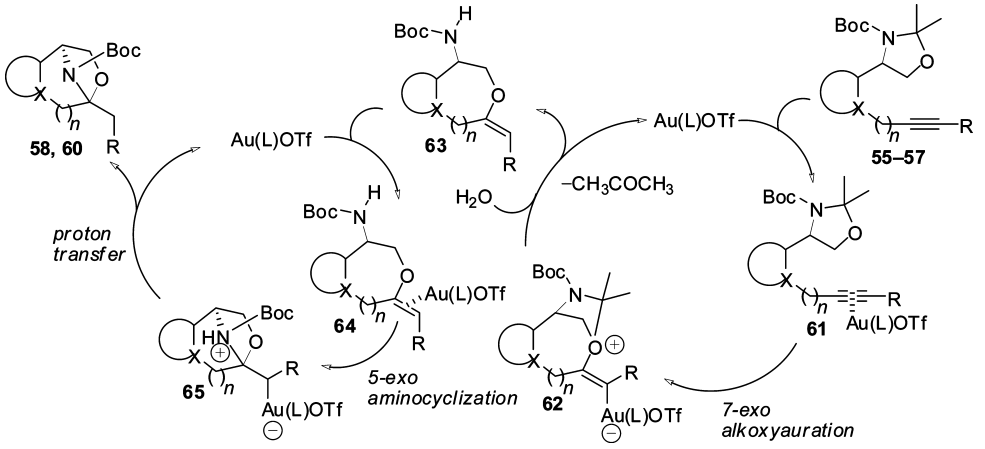
and alkynyl groups) on the acetylenic end was demonstrated by obtaining the corresponding enantiopure bridged acetals **50** in good yields.

Despite the fact that the intermolecular formation of *N,O*-aminals using external *N*-nucleophiles like anilines had been achieved,[25] the related direct intramolecular conversion of alkynes into cyclic *N,O*-aminals was not described. Therefore, the direct synthesis of *N,O*-aminals from oxazolidine-derived alkynes emerged as an attractive transformation to develop. Under the optimized reaction conditions used for the preparation of bridged acetals **50**, the catalytic protocol in gold for oxazolidine-tethered alkynes **51** and **52** was investigated. By examination of the influence of the R substituents on the alkyne side chain, it was found that substrates **51** and **52** bearing hydrogen, aryl, heteroaryl, or alkyl groups were smoothly transformed into bridged bicyclic aminals **53** and **54** in reasonable yields (Scheme 18).[26]

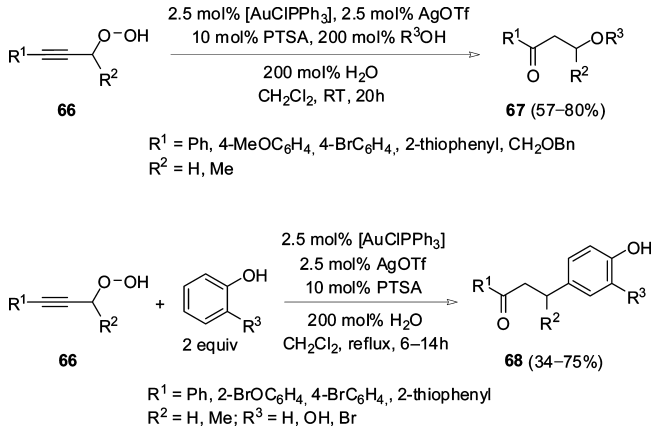
The challenging enantiopure alkynyloxazolidine-tethered 2-azetidinones **55**–**57** were tested as cyclization precursors. Remarkably, Scheme 19 shows how the mild conditions of gold catalysis allow the chemoselective formation of anellated β-lactams without harming the sensitive four-membered ring. With the terminal alkynes **55**, the system Au(OTf)PPh_3 gave the desired tricyclic bridged *N,O*-aminals **58** as the sole isomers in reasonable yields. Next, the reactivity of nonterminal alkynes **56** was investigated. Worthy of note, substituted and unsubtituted 2-azetidinone-tethered alkynes at the terminal position followed different reactivity patterns. These results show that the oxygen atom participates in the first cyclization to form a fused eight-membered ring, which is not followed by the second cyclization of the NBoc group. Significantly, in contrast to the gold-catalyzed reaction of terminal alkynyloxazolidines **55**, which lead to the 6-oxa-3,8-diazabicyclo[3.2.1]octane derivatives **58** via a 7-*exo*/5-*exo* bis-heterocyclization of the oxazolidine group toward the internal alkyne carbon (proximal adducts), the reaction of alkynyloxazolidines **56** substituted at the terminal end under identical conditions gave the 1,5-oxazocine derivatives **59** (distal adducts) as the sole products (Scheme 19), through an exclusive 8-*endo* oxycyclization by attack of the oxygen atom to the external alkyne carbon. Notably, when alkyne substituent was moved from position N1 to C3, as in 3,4-tethered alkynyloxazolidines **57**, it furnished the corresponding bridged adducts **60** in fair yields and as only one isomer in its reaction with the gold catalytic system (Scheme 18). The precious metal-catalyzed 8-*exo*/5-*exo* bis-heterocyclization of alkynyloxazolidines **57** gave tricyclic bridged *N,O*-aminals **60** bearing a seven-membered ring (Scheme 19).

A possible pathway for the gold-catalyzed alkynyloxazolidine cyclization may initially involve the formation of a

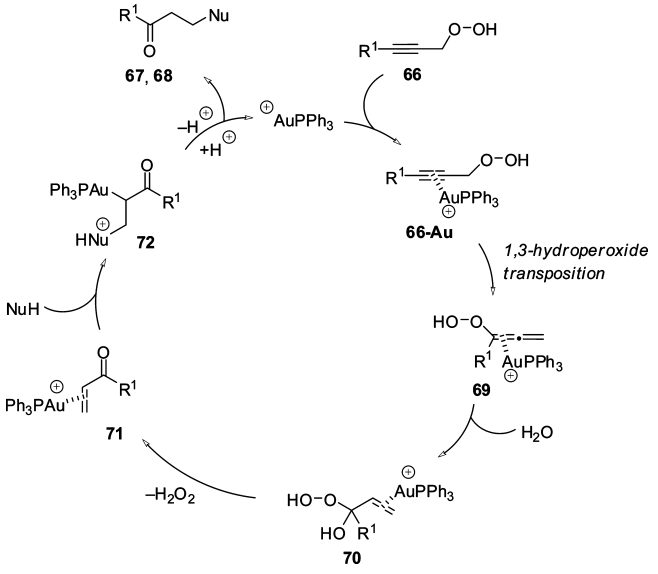
SCHEME 20. Mechanistic Explanation for the Gold-Catalyzed Bis(heterocyclization) of Alkynyloxazolidines



SCHEME 21. Controlled Gold-Catalyzed Reaction of Propargylic Hydroperoxides with Alcohols and Phenols



SCHEME 22. Mechanistic Explanation for the Gold-Catalyzed Controlled Preparation of β-Functionalized Ketones



π-complex **61** through coordination of the gold salt to the triple bond of alkynyloxazolidines **55**–**57**. Next, 7-*exo* oxymetalation forms zwitterionic enol vinylmetal species **62**. Intermediates **62** did evolve through demetalation and oxazolidine hydrolysis forming methylenic oxacycles **63** and releasing the metal catalyst into the first catalytic cycle. Methylenic oxacycles **63** enter the second catalytic cycle generating species **64** by coordination of the alkene group with the metal, thus enhancing the electrophilicity of the resulting enol ether. Subsequent intramolecular nucleophilic attack of the nitrogen to the more substituted alkene position would form the ate complex **65**. Demetalation linked to proton transfer liberates adducts **58** and **60** with concomitant regeneration of the gold catalyst, closing the second catalytic cycle (Scheme 20).[26]

Gold-Catalyzed Rearrangement of Propargylic Hydroperoxides. After the contribution by Hashmi on the formation of hydroperoxides by a one-pot sequence of gold-catalyzed isomerization/autoxidation,[27] we described the first report on the gold-catalyzed reactivity of alkynes bearing a hydroperoxide moiety.[28] As shown in Scheme 21, the above process in a one-pot operation from readily available alkynyl hydroperoxides **66** and alcohols (methanol, ethanol, ethylene glycol) serves as a general approach to β-alkoxy ketones **67**. When we investigated the reactivity of propargylic hydroperoxides **66** with phenols at room temperature, the starting materials were recovered. Only after heating at reflux temperature, the gold-catalyzed reactions evolved. Notably, the use of substituted phenols including catechol did not result in the formation of the corresponding phenoxy ketones; arylketones **68** were obtained instead as the result of a hydroarylation reaction (Scheme 21). Interestingly, compounds **68** were exclusively

isolated as the para-substituted phenol regioisomers. Worthy of note, secondary alkynyl hydroperoxides also undergo these interesting transformations.

The reaction of propargylhydroperoxides to yield β-funtionalized ketones may be catalyzed by the Au(I) salt. The catalytic reaction is likely divided into five parts. First, coordination of the carbon−carbon triple bond of propargylic hydroperoxides **66** to the Au(I) salt gives gold−π-alkynyl complex **66**−**Au**. Species **66**−**Au** evolves through a 1,3-hydroperoxide transposition to intermediate **69**. Regioselective nucleophilic addition of water to the disubstituted allene double bond in gold−allenyl complex **69** giving intermediate **70**, followed by loss of hydrogen peroxide, provides the α,β-unsaturated ketonic gold complex **71**. Next, 1,4-addition of the corresponding external nucleophile to the species **71** would form the gold intermediate **72**. Demetalation linked to proton transfer provides final products **67** and **68** and regenerates the gold catalyst, closing the catalytic cycle (Scheme 22).

Conclusions

The past few years have witnessed dramatic growth in the number of reactions catalyzed by gold complexes because of their powerful soft Lewis acidic nature. This Account has reviewed selected examples from our group to illustrate certain advances in homogeneous gold catalysis for various types of organic transformations, focusing on the formation of C−C and C−O bonds using allenes and alkynes as starting materials.

Support for this work by the MINECO (Projects CTQ2012-33664-C02-01 and CTQ2012-33664-C02-02) and Comunidad Autónoma de Madrid (Project S2009/PPQ-1752) are gratefully acknowledged.

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FOOTNOTES

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The authors declare no competing financial interest.

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