Gold-Catalyzed Cyclization Processes:
Pivotal Avenues for Organic SynthesisAmit Kumar,^{*,[a,b]} Sukhdev Singh,^[a] Sunil K. Sharma,^[b] Virinder S. Parmar,^[a,b] and Erik V. Van der Eycken^{*,[a]}*Dedicated to Professor Antonio M. Echavarren on the occasion of his 60th birthday*

ABSTRACT: Over the years, gold catalysis has materialized as an incredible synthetic approach among the scientific community. Due to the trivial reaction conditions and great functional compatibility, these progressions are synthetically expedient, because practitioners can implement them to build intricate architectures from readily amassed building blocks with high bond forming indices. The incendiary growth of gold catalysts in organic synthesis has been demonstrated as one of the most prevailing soft Lewis acids for electrophilic activation of carbon-carbon multiple bonds towards a great assortment of nucleophiles. Nowadays, organic chemists consistently employ gold catalysts to carry out a diverse array of organic transformations to build unprecedented molecular architectures. Despite all these achievements and a plethora of reports, many vital challenges remain. In this account, we describe the reactivity of various gold catalysts towards cyclization processes developed over the years. These protocols give access to a wide scope of polyheterocyclic structures, containing different medium-sized ring skeletons. This is interesting, as the quest for highly selective reactions to assemble diversely functionalized products has attracted much attention. We envisage that these newly developed chemo-, regio-, and diastereoselective protocols could provide an expedient route to architecturally cumbersome heterocycles of importance for the pharmaceutical industry.

Keywords: catalysis, cyclization, domino, gold, heterocycles

1. Introduction

The rediscovering of coinage metals for homogeneous catalysis has allowed selective manipulations of nonactivated unsaturated hydrocarbons.^[1] Gold-catalyzed cyclizations of aromatic

and heteroaromatic compounds with alkynes offer new pathways for the synthesis of natural products and structurally cumbersome heterocyclic scaffolds.^[2] Homogeneous gold-catalyzed carbocyclizations and heteroannulations have experienced an outburst, leading to the discovery of a phenomenal amount of new synthetically useful transformations, due to the exceptional ability of gold complexes to activate alkynes, alkenes, and allenes towards nucleophilic attack.^[3] Further, the soft Lewis acidity of cationic gold(I) species towards alkynes leads to diverse transformations; thereafter, this marks the characteristic features of gold catalysis.^[4]

Teles,^[5] Tanaka,^[6] and Hashmi^[7] have demonstrated the potent and versatile reactivity of gold catalysis in synthetic organic chemistry. The prominence of this synthetic revolution has been reported by a large number of groups elucidating the intimate mechanisms of gold catalysis leading to cyclization.^[8] Scheme 1 outlines a general approach for the cyclization using various gold complexes. Nucleophilic attack at the C-C triple bond is promoted upon

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Scheme 1. Reaction pathways for C-C and C-Y cyclization of alkynes.

coordination of a gold complex to the π bond, resulting in the formation of an alkenyl gold intermediate via *exo*- and *endo*-dig cyclization, followed by protodeauration.^[9] In this account, a brief overview on recent developments of various types of novel gold-catalyzed cyclization reactions carried out in our laboratory will be discussed.

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2. Intramolecular Hydroarylation (C–C bond) Reaction

Recent advances in transition metal catalysis have increased the mechanistic understanding of many transformations in heterocyclic chemistry.^[10] Furthermore, the development of new complexes has increased the fine tunability of the metal properties. Metal-catalyzed cyclizations of aromatic and heteroaromatic compounds with alkynes have attracted much attention in the last decade. In particular, intramolecular gold-catalyzed hydroarylations,^[11] cycloisomerizations,^[4,12] and cycloadditions^[13] offer new ways for the efficient construction of biologically interesting carbo- and heterocycles.^[12f] Recent elegant examples also include the use of *N*-heterocycles; for example, the research groups of Echavarren and Padwa reported cyclizations of indole derivatives in the presence of gold catalysts.^[14]

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Scheme 2. Synthesis of azocino[4,5-*b*]indoles and azepino[4,5-*b*]indoles via an intramolecular hydroarylation of the triple bond.

Scheme 3. Synthesis of azocino[5,4-*b*]indolones via intramolecular hydroarylation.

Taking a lead from the above-mentioned pioneering work, we explored the versatility of gold, which catalyzes a highly regioselective intramolecular hydroarylation reaction exclusively on the C2/C3-position of the pyrrole/indole ring.

Indole and pyrrole-annulated medium-sized rings are vital heterocyclic motifs occurring in both natural and synthetic products. Echavarren and coworkers were the first to apply gold catalysis for the construction of the azepino[4,5-*b*]indole and azocino[4,5-*b*]indole core (Scheme 2).^[14,15] The reaction outcome was shown to be strongly dependent on the nature of the employed gold catalyst. While the strong cationic Au(I) complex (JohnPhosAu-MeCN)SbF₆ gave rise to azepino[4,5-*b*]indoles **2** bearing an exocyclic double bond, AuCl₃ generally provided the azocino[4,5-*b*]indoles **3** as the major product, along with azepino[4,5-*b*]indoles **4** bearing a migrated endocyclic double bond (Scheme 2).

Inspired by Echavarren's work, we initially established a microwave-assisted Hg(OTf)₂-catalyzed intramolecular alkyne hydroarylation reaction for the synthesis of variously substituted azocino[4,5-*b*]indoles of type **6** (Scheme 3).^[16] Since most of the inorganic and organic mercury compounds are highly toxic, we were searching for an alternative catalytic system to replace Hg(OTf)₂ in our process. However, as earlier attempts to employ other Lewis acid catalysts, such as AuCl, AuCl₃, AgOTf, AgO₂CCF₃, PdCl₂, and PtCl₂ met with failure,^[16] we switched our attention to strong cationic Au(I) complexes.^[16,17] A combination of monophosphine Au(I)-

Scheme 4. Synthesis of medium-sized ring indoles via regioselective carbocyclization.

chlorides with various Ag(I)-salts is known to produce *in situ* cationic Au(I)-species. The application of 5 mol% Au(PPh₃)Cl/AgOTf with the alkynamide substrate **5** at room temperature resulted in its conversion to the 100% *endo*-cyclized indoloazocines **6** (Scheme 3). This developed protocol was not only efficient, but also overcame the use of the toxic mercury, and was compatible with the wide range of functional groups. The AuPPh₃Cl/AgOTf catalytic system was found to be an efficient replacement for the Hg(OTf)₂-catalyst, delivering target indoloazocines in improved yields.^[18]

As a result of our above endeavors regarding the chemistry of the indole core, a concise diversity-oriented approach towards the synthesis of azepino- and azocino-indoles was further developed.^[19] Different gold complexes were employed to the prefunctionalized alkynamide substrate **7** to perform an intramolecular hydroarylation reaction (Scheme 4). When alkynamide **7** (*n* = 1) was treated with 5 mol% Au(PPh₃)Cl/AgSbF₆, azepinoindole **8** was formed in good yields,^[20] whereas the use of 5 mol% Au(PPh₃)Cl/AgOTf on substrate **7** (*n* = 2) yielded the *endo-dig* cyclized azocinoindole **8**.^[20] A comparative study of both reaction conditions was performed, and showed that in most cases, the Au(PPh₃)Cl/AgSbF₆ protocol proved to be superior, delivering the desired indoloazepinones and indoloazocinones with improved yields.^[20] Surprisingly, a terminal alkyne substrate **7** (*R*⁴ = H) cyclized in an *exo-dig* fashion, leading to product **10** (Scheme 4).

The methodology exhibits excellent functional group compatibility, including bulky substituents on the alkyne, and allows the direct access to indoloazepinones and indoloazocinones in good to excellent yields. A mechanistic proposal of this transformation is depicted in Scheme 5.

Coordination of cationic gold with the alkyne **7** generates intermediate **11**. In the case of an internal alkyne, nucleophilic attack of the 3-position of the indole on the activated alkyne **11** occurs in an *endo-dig* fashion, generating intermediate **14**. This is followed by a 1,2-shift to furnish intermediate **15**, which upon deprotonation and protodeauration, results in the formation of indoloazepinones **8** or indoloazocinones **9**. In the case of a terminal alkyne, the nucleophilic attack of the

Scheme 5. Suggested reaction pathways for the regioselective carbocyclization.

3-position of the indole occurs in an *exo-dig* fashion, generating intermediate **12**, which is followed by a 1,2-shift, deprotonation, and protodeauration to furnish indolopyridinones **10** (Scheme 5).

Indole-based natural products that contain a tricyclic azepino- or azocino-[c,d]indolone core have emerged as interesting targets due to their intriguing biological activities and molecular architectures. Working on the C3 functionalization of the indole to construct a fused medium-sized ring, we developed another expedient post-Ugi, gold-catalyzed regioselective intramolecular hydroarylation process.^[21] The application of (IPr)AuCl/AgNTf₂ (10 mol%) at 100°C in DCE provides a series of tricyclic azocinoindolones **17** in good to excellent yields (Scheme 6).

To further demonstrate the synthetic utility of this methodology, propargyl amine was used as the alkyne source for the synthesis of alkyne substrate **18** (Scheme 7). When substrate **18** was subjected to intramolecular hydroarylation employing IPr(Au)NTf₂, exclusive formation of the *exo-dig* cycloisomerized product azepinoindole **19** was observed.

Azepines/pyridines fused with an aryl or heteroaryl subunit represent a widely studied class of biologically interesting medium-sized ring systems. A post-Ugi gold-catalyzed intramolecular hydroarylation approach opens a new gateway for the synthesis of diversely substituted pyrrolopyridines and azepinoindoles. Recently, to compare the reactivity of pyrrole and indole, we synthesized various alkyne substrates of type **20** (Scheme 8). Upon treatment with Au(PPh₃)Cl/AgOTf in

Scheme 6. Regioselective intramolecular hydroarylation to the azocino[5,4,3-*cd*]indolone core.

Scheme 7. Synthesis of azepino[5,4,3-*cd*]indole via intramolecular hydroarylation reaction.

Scheme 8. Synthesis of pyrrolopyridinones and azepinoindoles/azepinobenzothiophenes via intramolecular hydroarylation reaction.

chloroform, selective 6- and 7-membered ring formation was observed with pyrrole and indole alkyne substrates **20**, respectively,^[22] and this was in good to excellent yields. In the case of a pyrrole alkynamide substrate, 5-*exo-dig* attack of the aromatic ring on the activated alkyne takes place, resulting in the formation of pyrrolopyridinones **21**.^[22a] On the contrary, in the case of an indole alkynamide substrate, 7-*endo-dig* attack occurred, yielding azepinoindoles **22** and azepinobenzothiophenes **23**.^[22a]

To understand the course of the reaction, a plausible mechanism for the selective cyclization is depicted in the Scheme 9. Treatment of alkynamide **20** with the electrophilic gold(I)-catalyst results in the activation of the triple bond. In the case of pyrrole, nucleophilic attack at the activated alkyne **24** occurs in an *exo-dig* fashion to generate spiro intermediate **25**. This is followed by a 1,2-shift to furnish intermediate **26**, which upon deprotonation and protodeauration, gives the pyrrolopyridinone **21**. In the case of indole, direct attack of the nucleophilic C3-position of the heterocyclic ring on the

Scheme 9. Proposed mechanism for the formation of pyrrolopyridinones and azepinoindoles/azepinobenzothio-phenes.

activated alkyne **27** occurs in an *endo-dig* fashion, resulting in the formation of intermediate **28**. Subsequent deprotonation and protodeauration results in the formation of the corresponding azepinones **22/23** (Scheme 9). Although we have no hard proof regarding the mechanism to explain the different outcomes of the reactions, the results might be interpreted as follows. According to the literature,^[23] pyrrole performs nucleophilic attack, preferably via the C2-position, and thus 5-membered spiro intermediates **25** are obvious in our case. On the contrary, indole and benzothiophene prefer attack via their C3-position and will not form a spiro intermediate, thus allowing the Au(PPh₃)OTf to produce the *endo-dig* product.

In another similar report, propargyl amine was used as an alkyne source. The propargyl amine substrate **29** was treated with 2 mol% AuCl, resulting in the formation pyrrolopyridines **30** and azepinoindoles **31** (Scheme 10). A wide range of substituents related to the isocyanide (R²) and the carboxylic acid (R¹) were tolerated. Furthermore, when indole alkynamide-bearing phenyl-substituted alkynes (R³ = Ph) were treated under the optimized conditions, *endo*-cyclized azepinoindoles **31** were exclusively formed.^[24]

Scheme 10. Synthesis of pyrrolopyridines and azepinoindoles via intramolecular reaction.

Scheme 11. Synthesis of substituted diazoninones via an intramolecular hydroarylation process.

In the framework of our research of medium-sized ring systems, we recently elaborated a facile strategy to generate the benzo[*b*]pyrrolo[2,1-*i*][1,5]diazonin-7(6*H*)-one skeleton **33** containing a nine-membered ring (Scheme 11).^[25] The alkynamide substrate **32** was added to Au(PPh₃)Cl/AgOTf in chloroform at 50°C, resulting in the formation of a fused 9-membered ring. Pleasingly, various substituents related to the starting aldehyde (R¹), amine (R²), alkyne (R³), and isocyanide (R⁴) were tolerated, and the corresponding diazoninones **33** were isolated in good yields (Scheme 11). When a bulky phenyl-substituted alkyne (R³ = Ph) and terminal alkyne (R³ = H) were used as the starting alkynamide substrate, a drop in the yields was observed. This efficient approach allows a rapid access to the diazoninone scaffold for library generation.^[25]

Further, Liu *et al.* reported a new gold(I)-catalyzed deacylative cycloisomerization of 3-acylindole/ynes **34** into diversely substituted carbazole derivatives **35**, which are important building blocks for natural product synthesis^[26] and material science.^[27] The 6-*endo-dig* cyclization reactions occurred efficiently at room temperature in the presence of 5 mol% (*p*-CF₃C₆H₄)₃PAuOTf and 5 eq. H₂O, yielding the 2-hydroxycarbazole **35** as the exclusive product in up to 80% yield within 2 h. It is remarkable that the deployment of water is essential to carry out this cycloisomerization reaction. Moreover, in the absence of water, product **35** was formed in a meagre yield, even after prolonged reaction time. The increased

Scheme 12. Gold-catalyzed deacylative cycloisomerization of 3-acylindole/ynes.

reaction rate in the presence of water was accredited to the facilitated demetalation by water. These reactions tolerated a wide range of alkyne substituents with both aryl and alkyl groups, producing the cyclized products **35**, generally in high yields at rt (Scheme 12).

The suggested mechanistic pathway (Scheme 12) for this transformation is running via the heterolytic fragmentation of the carbonyl group. It was envisioned that the transformation of indolyl alkyne **34** into the 2-hydroxycarbazole **35** starts with the activation of the triple bond by forming the gold- π -complex **36**, which facilitates a nucleophilic attack by the indole ring. The subsequent 6-*endo-dig* ring closure affords the intermediate **37**. Further, electron donation by the carbonyl oxygen lone pair triggers the heterolytic fragmentation to give the gold species **38**, along with the loss of an acylium ion, which upon tautomerization facilitated by a proton or metal ion, followed by deauration, delivers the carbazole **35**.^[28]

3. Intramolecular Heteroannulation (C–N and C–O Bond) Reaction

In recent years, considerable advancements have been achieved in C–N and C–O bond formation reaction using various gold salts. These reactions utilize a catalytic amount of gold salt in combination with various cocatalysts. In this section, we have chosen some of the latest findings, where various gold salts were used for C–N and C–O bond formation, giving diversely substituted heterocyclic ring systems. Recently, an efficient microwave-assisted methodology for the synthesis of various 3-indolyl-2(1*H*)-pyrazinones **40** has been reported by our group, applying a gold(I)-catalyzed 5-*endo-dig* intramolecular hydroamination reaction (Scheme 13).^[29] The optimal reaction conditions comprise 30 minutes of microwave irradiation in the presence of AuCl as catalyst and TFA as cocatalyst in DCM as the solvent, at mild reaction temperature, to give the corresponding products in good yields.

Scheme 13. Microwave-assisted synthesis of 3-indolyl-2(1*H*)-pyrazinones.

Scheme 14. Synthesis of imidazo[1,2-*a*]pyrazinones via gold-catalyzed regioselective intramolecular heteroannulation of propynylaminopyrazinones.

In another report dealing with the pyrazinone scaffold, we established a facile approach for the synthesis of biologically important (dihydro)imidazo[1,2-*a*]pyrazin-8(7*H*)-one **43**, employing a cationic gold-catalyzed regioselective 5-*exo-dig* heteroannulation strategy (Scheme 14).^[30] Nucleophilic attack of the pyrazinone nitrogen on the activated alkyne **42** (when R^3 = aryl, indolyl, or pyridinyl) takes place, followed by deprotonation and protodeauration, resulting in the *exo-dig* cyclized product **43**. However, in the case of a terminal alkyne (R^3 = H), a 1,3-proton shift led to cyclized product **44**. The developed approach proved beneficial, as it allowed us to install diversity on both the 5- and 6-position of the imidazo[1,2-*a*]pyrazin-8(7*H*)-one skeleton, which is rather difficult to achieve otherwise.^[30]

The imidazodiazepinone core is abundantly present in various natural and synthetic pharmaceuticals.^[31] Recently, we have elaborated a diversity-oriented approach for the synthesis of interesting imidazo-[1,4]diazepin-7-ones **66** starting from readily available building blocks (Scheme 15).^[32] This sequence involves an Ugi-4CR, to introduce diversity, followed by an efficient gold(I)-catalyzed heteroannulation, resulting in the formation of the imidazodiazepinone **46** scaffold in excellent yields. Various substituents are well tolerated, giving good

Scheme 15. Synthesis of imidazo[1,4]diazepin-7-ones via intramolecular heteroannulation.

Scheme 16. Synthesis of *N*-substituted-3-benzazepinones.

to excellent yields. A bulky alkyne substituent, like a phenyl group, consistently reduced the progress of the reaction.

In their ongoing efforts to develop new convenient and efficient approaches, Liu and coworkers also reported an intramolecular heteroannulation of 2-alkynyl benzeneacetamides **47** in the presence of the $\text{Au(PPh}_3\text{)SbF}_6$ complex, for the synthesis of 3-benzazepinones **48**, as well as the cyclization to unexpected 5-bromo-3-benzazepinones **49**, in which AuBr_3 not only plays an activation role, but also acts as a reactant (Scheme 16). It is presumed that the reaction is initiated with the activation of the alkyne group of **47** by the $\text{Au(PPh}_3\text{)SbF}_6$ complex. This is followed by an intramolecular nucleophilic attack of the amide nitrogen to the triple bond in an *endo-dig* fashion, to give a seven-membered intermediate, which upon protodeauration, leads to the 3-benzodiazepinone **48**. However, in the case of AuBr_3 , the 2-alkynyl benzeneacetamides are supposed to undergo nucleophilic cyclization, producing intermediate **50**, which is followed by reductive elimination, leading to 5-bromo-3-benzazepinone^[33] **49** (Scheme 16). 2-Alkynyl benzeneacetamides **47**, bearing various alkyl and aryl alkynyl substituents, smoothly undergo the reaction to afford the desired 3-benzodiazepinones in moderate to high yields.^[34]

Further extending this strategy, Liu *et al.* reported a green and atom-economical protocol for the synthesis of indole-1-carboxamides **52** via an Au(I)-catalyzed intramolecular hydroamination of *N*-(2-ethynylphenyl)ureas **51** in water under microwave irradiation (Scheme 17). The reaction occurs in the

Scheme 17. Regioselective gold(I)-catalyzed intramolecular hydroamination of terminal alkynes.

presence of 10 mol% $\text{Au(PPh}_3\text{)Cl}$ and 10 mol% Ag_2CO_3 in water at 120 °C under microwave irradiation for 30 min, delivering the indole-1-carboxamides **52** in high yields. The microwave-assisted method was found to be more effective than the conventional process in terms of yield and reaction time. Substrates are readily available and functional group tolerance is high. The reaction initiates with alkyne activation by gold(I), followed by rearrangement, leading to vinylidene intermediate **53**.^[35] This undergoes nucleophilic attack by the adjacent nitrogen atom, generating the carbene complex **54**, which upon tautomerization and reductive elimination of the gold hydride complex, forms the indole-1-carboxamide **52** with the regeneration of the catalyst (Scheme 17). This type of mechanism, involving a metal vinylidene intermediate **53**, that was proposed based on the labeling studies, distinguishes this process from other gold-catalyzed cyclization procedures.^[36]

4. Tandem/Domino Cyclization

Although cascade/tandem/domino methodologies are rising to prominence,^[37] elaborate multistep synthetic sequences are still normally required for the preparation of stereochemically well-defined indoline alkaloids.^[38] As a consequence, it is not surprising to notice a growing need for selective and sustainable procedures for the preparation of densely functionalized polycyclic indolines. Gold-catalyzed carbocyclization strategies have recently attracted much attention due to their selective and efficient activation of the triple bond towards a wide range of nucleophiles. Domino/tandem approaches^[39] involving gold-catalysis lead to complex heterocyclic compounds under exceedingly mild reaction conditions. In a report published by Bandini and coworkers,^[40] readily available unprotected (NH)-indole propargylic alcohols **55/56** were used to synthesize fused tetracyclic pyranil indolines **57** and furoindolines **58** via an enantioselective gold-catalyzed cascade

Scheme 18. Enantioselective synthesis of tetracyclic fused indolines via gold-catalyzed hydroindolination.

Scheme 19. Synthesis of polycyclic spiroindolines via diastereoselective domino cyclization.

hydroindolination/iminium trapping synthetic sequence (Scheme 18).^[41]

Prompted by all these reports, we have also discovered a diversity-oriented approach for the synthesis of complex spiroindolines from readily available starting materials. An Ugi-4CR was used to construct the functionalized branched handed alkynamide substrate **60**, which successfully underwent a gold-catalyzed domino cyclization (Scheme 19). The unexpected trapping of the spiro intermediate by the sterically hindered *tert*-butyl amide, resulted in the diastereoselective formation of a tetracyclic spiroindoline **61**.^[42] The observed diastereoselectivity of the reaction could be easily explained by the mechanism shown in Scheme 19.^[43] After activation of the triple bond of the alkynamide **60** by cationic gold, nucleophilic attack at the C3-position of the indole can occur from

Scheme 20. Synthesis of spiroindoline derivatives using the amine as alkyne source.

two sides. If the attack occurs from the back side of the indole core, intermediate **64** is formed. However, trapping of the intermediate iminium ion **64** by the secondary amide, is sterically impossible. As a result, the newly formed spiro ring reopens to intermediate **62**. In contrast, when the attack occurs from the front side of the indole core, which results in spiro intermediate **63**, trapping of the iminium ion is possible, and spiroindoline **61** is formed, which possesses two newly formed chiral centers (*SS*), as shown in Scheme 19. Thus, the chiral center already present in alkynamide **60** directs the domino cyclization diastereoselectively.

Further extending this work, we applied an analogous protocol for a similar post-Ugi gold-catalyzed domino cyclization sequence to synthesize spiroindolines **66** (Scheme 20). This time, propargyl amines were used as the alkyne source.^[44] Again the reaction occurred with complete diastereoselectivity (control of three chiral centers), thereby leading to the formation of a fused spirocycle.

Recently, Naoe *et al.* reported a gold(I)-catalyzed cascade cyclization of aniline derivatives **67** bearing a conjugated diyne moiety. The reaction is running via a 5-*endo-dig* indole formation, followed by a 7-*endo-dig* cyclization to give the fused indole **68** with a seven-membered ring in good yields (Scheme 21).^[45] This reaction provides direct access to oxepino[1,7-*a*]indole (*X* = O) derivatives with wide functional group tolerance. The observed 7-*endo*-selectivity was well rationalized by DFT calculations.^[45]

5. Dual Alkyne Activation via Gold Catalysis

In recent years, a mass of studies on gold(I)-catalyzed cyclizations based on a dual activation mechanism have been reported in the literature. The independent and parallel work of the groups of Zhang^[46] and Hashmi^[47] revealed an interesting reactivity in the field of gold chemistry. Intramolecular nucleophilic attack of the β -carbon of an alkyne **71**, activated by σ -coordination to gold, on a second alkyne moiety, which is

Scheme 21. Gold(I)-catalyzed cascade cyclization of a conjugated diyne.

Scheme 22. Gold(I)-catalyzed tandem cyclization via dual σ - π activation.

Scheme 23. Synthesis of cyclopentapyridinones via gold-catalyzed tandem cyclization.

activated by π -coordination, results in the formation of a highly reactive gold vinylidene intermediate **72** (Scheme 22). This dual σ - π activation opens a new pathway for a number of unprecedented transformations. Recently, Hashmi and coworkers reported a detailed study on substituted *ortho*-dialkynyl arenes and 1,2-dialkynyl heteroaromatic systems with mechanistic understanding.^[48]

Inspired by this, and in continuation of our work on gold catalysis, we have developed an operationally simple gold-catalyzed regioselective tandem cyclization of *N*-propynylbutynamide via C(sp³)-H functionalization to give cyclopentapyridinones **74** (Scheme 23). Ugi-4CR was used to construct functionalized diyne substrates **75** (*N*-propynylbutynamides).^[49] Various substituents on the parts derived from the

Scheme 24. Plausible mechanism for the dual gold-catalyzed tandem cyclization.

isonitrile and the aldehydes were well tolerated. Electron withdrawing groups on the aromatic ring provided better yields.

Based on X-ray crystal structure analysis and the reports from Hashmi,^[50] it is now possible to draw a tentative mechanistic cycle (Scheme 24). As in related reaction pathways,^[51] the first step is the formation of a gold acetylide **76**, either by liberation of the corresponding acid or by catalytic transfer. Subsequently, as a result of the π -activation of the butynamide **77**, 6-*endo-dig* cyclization takes place, leading to the formation of gold vinylidene intermediate **78**.^[52] This highly reactive species may undergo facile C-H insertion, followed by loss of Au⁺, resulting in intermediate **79**, which upon protodeauration, forms the desired product **75**.

6. Summary and Future Outlook

In recent years, various novel methods for the selective formation of the medium-sized ring heterocycles have been documented. In this review, we have explored the deployment of gold catalysts to produce exceedingly functionalized and complex heterocyclic motifs from readily available building blocks. These developed protocols have shown high efficiency and selectivity, and their mechanisms are rationally well explained, based on the different outcomes and literature reports from our group and others. The intramolecular methodologies worked smoothly with the prefunctionalized substrates, delivering rapid routes to key building blocks for the synthesis of biologically active heterocyclic compounds. We believe that these gold-catalyzed protocols will provide a revolutionary platform to synthesize biologically important heterocyclic cores and will further find their applications in medicinal and natural products synthesis.

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