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# Gold-catalyzed post-MCR transformations towards complex (poly)heterocycles

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**Post multicomponent reaction (MCR) transformations are one of the most successful methods leading to high structural diversity and molecular complexity. A well-known MCR, the Ugi reaction typically affords a linear peptide backbone, enabling post-Ugi transformations as an elegant solution to rigidify the Ugi adduct into more drug-like species. Not surprisingly, the development of such transformations leading to new structural frameworks has expanded rapidly over the last few years. These reactions have reached an impressive level of performance and versatility, particularly in amalgamation with gold catalysis. This review outlines the developments achieved in the past decade, highlighting the modifications that are performed in a sequential or domino fashion with emphasis on major concepts, synthetic applications of the derived products as well as mechanistic aspects.**

## Introduction

The sequencing of multicomponent reactions (MCRs) and subsequent cyclizations is a powerful strategy for the rapid

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construction of diverse (poly)heterocyclic scaffolds [1,2]. The central goal of diversity-oriented synthesis (DOS) is to generate structurally and stereochemically diverse molecules for biological evaluations. The idea is that broader diversity in the chemical library will lead to the generation of additional information from biological screenings. Therefore, the synthesis of complex polycyclic molecular scaffolds bearing resemblance to pharmaceutically relevant natural products has always remained an attractive proposition for synthetic chemists. The combination of multicomponent reactions (MCRs) and transition metal-catalyzed post-transformations provides an enormous capability to generate molecular complexity and diversity in a minimum number of steps [3,4].

With the introduction of transition metal-catalyzed reactions as a contemporary tool in synthetic organic chemistry, a significant impact has been exerted on the syntheses of well-established classes of heterocycles [5,6]. Among the various metals explored, it is no surprise that gold complexes adopt a central role in post-MCR transformations [7]. Gold has always

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been perceived as the most precious metal for thousands of years. In addition, past decades have already seen a “gold rush” with a myriad of chemical transformations in both homogenous [8,9] and heterogeneous catalysis [10]. Various new reaction modes and novel reactivities have already been discovered, due to the exceptional ability of gold complexes to activate alkynes, alkenes, and allenes towards nucleophilic attack, which is quite evident from the seminal work of Hashmi, Toste, Echavarren, and others [8,11,12]. Scheme 1 outlines a general approach for the cyclization using various gold complexes.

This concise review will focus on post-MCR transformations performed as a separate step or in a domino/cascade fashion that have been reported in the past few years employing gold catalysis.

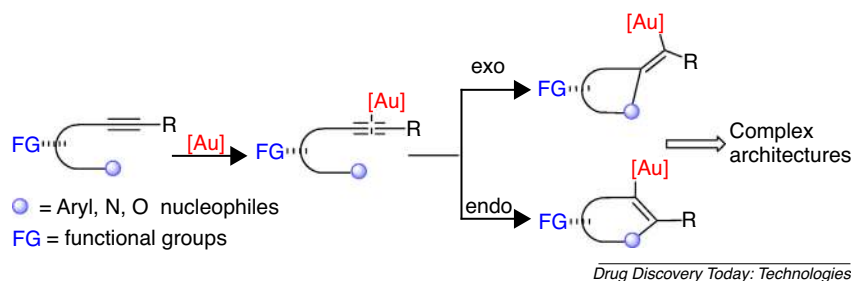
### C–C bond forming reactions

Gold-catalyzed cyclizations of (hetero)aromatic compounds with alkyne side chains have attracted considerable attention in the last decade. In particular, intramolecular gold-catalyzed hydroarylations, cycloisomerizations and cycloadditions have offered new ways for the efficient construction of biologically relevant hetero(poly)cycles [7–12]. Indole and pyrrole containing heterocyclic motifs can be seen in various natural products and pharmaceutically relevant compounds [13,14]. In addition, 7-membered *N*-containing rings fused with benzene or indole represent a common pattern in a plethora of alkaloids isolated from various natural sources, as well as in a significant series of pharmaceuticals. A large subclass of these compounds incorporates either the phenylethylamine or the tryptamine motif, both of them occur widely in nature. Dorel and Echavarren were the first to apply gold catalysis for the construction of the azepino[4,5-*b*]indole and azocino[4,5-*b*]indole core [12] followed by our group [15], where *in situ* generated cationic gold(I)-species were found to be effective for similar transformations. Notably, this AuPPh<sub>3</sub>Cl/AgOTf catalytic system was found to be an efficient replacement for our earlier reported Hg(OTf)<sub>2</sub>-catalyzed intramolecular alkyne hydroarylation reactions [16] for the synthesis of variously substituted azocino[4,5-*b*]indoles. However, one of the main problems associated with these

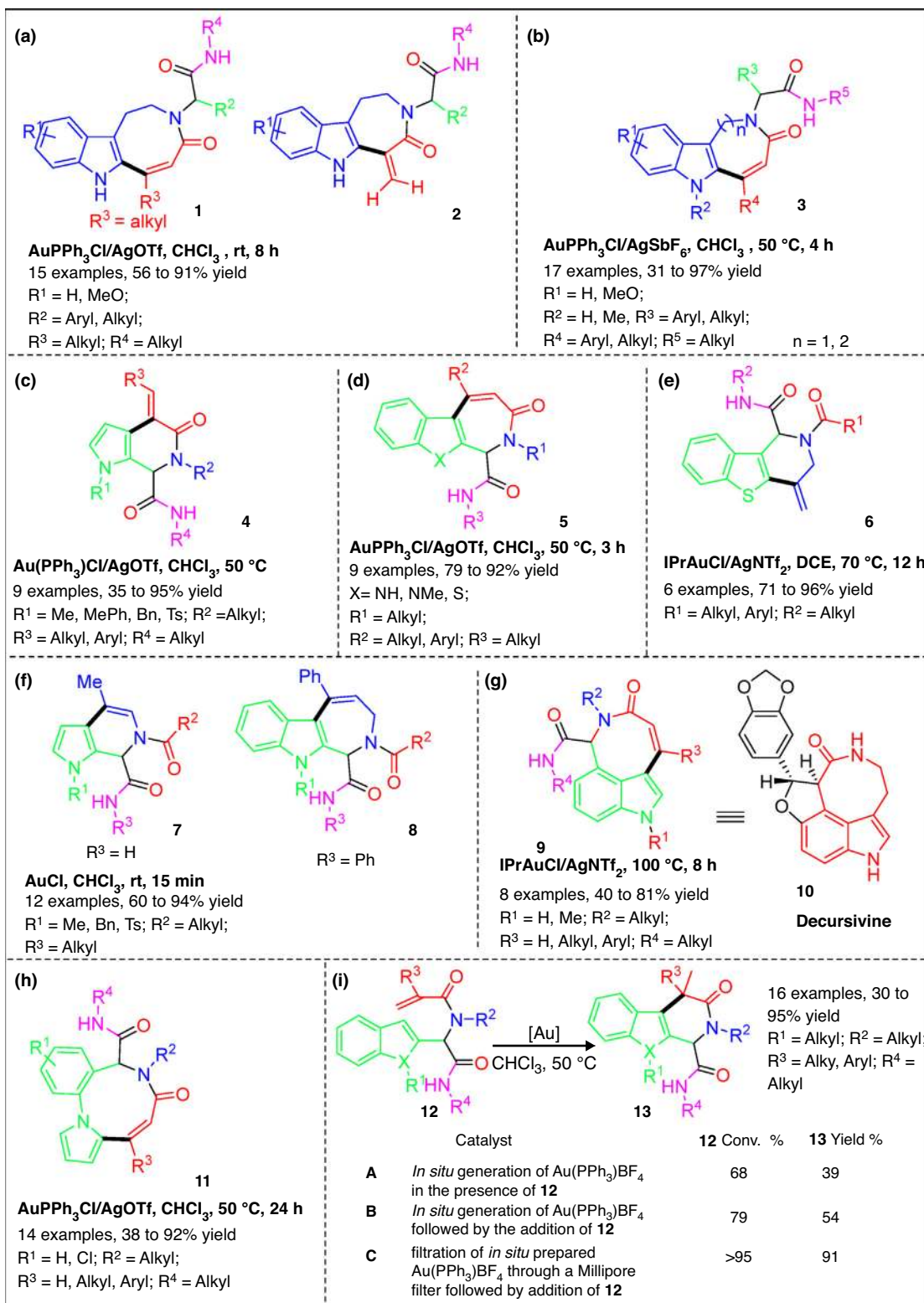
reactions was the synthesis of the starting materials, which required tedious multistep procedures along with the generation of ample waste. Moreover, from a diversity-oriented synthesis point of view, these chemical methods were also not sustainable.

In this context, isocyanide-based multicomponent reactions [4] (IMCRs) have been widely explored because of their unmatched capability to generate molecular complexity and diversity to expand the chemical space. From the past twenty years, the Ugi four-component reaction (Ugi-4CR) [17] has remained as one of the highly investigated reactions for generating multifunctional adducts, owing to the mildness of the reaction conditions, the wide application scope and the high variability (four diversity points) associated with it. Moreover, it provides an opportunity for a myriad of post-modifications depending on the functional groups introduced during the MCR, thus leading to the synthesis of several pharmacologically important heterocyclic scaffolds, mostly in two operational steps.

Our initial attempts were focused on post-Ugi modifications towards the synthesis of azepino- **1** and azacino-indoles **2**, being important members of the indole containing alkaloid family, as well as for representing as challenging synthetic targets (Scheme 2a) [18]. Moreover, these scaffolds are scarcely investigated, and reports generally deal with multi-step processes, which limits the scope and diversity. A cationic gold complex Au(PPh<sub>3</sub>)OTf, formed *in situ* by mixing of Au(PPh<sub>3</sub>)Cl and AgOTf, turned out to be the best catalyst giving maximum yields of *endo-dig* cyclized azapinoindoles **1**. Surprisingly, Ugi substrates containing a terminal alkyne, gave the *7-exo-dig* product **2**, possibly due to a metal carbene intermediate as described by Echavarren and co-workers [12]. Later on, a better cationic gold system, compared to the previous report, was optimized and utilized (Scheme 2b) [19]. The new protocol allows the synthesis of indoloazocinones **3** bearing sterically hindered substituents on the alkyne, which was not possible to achieve using the previously reported protocol. In addition, a comparative study of the new reaction conditions with the previously reported Au(PPh<sub>3</sub>)Cl/AgOTf-catalyzed hydroarylation [18] was also performed. In most cases, the current protocol proved to be



**Scheme 1.** A general scheme for gold catalyzed cyclizations.



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**Scheme 2.** Post-Ugi construction of different heterocycles via gold catalysis. Color represent different Ugi starting material viz. aldehyde (green), amine (blue), acid (red) and isocyanide (pink).

superior, delivering the desired indoloazocinones **3** with improved yields.

Fused heterocyclics with small to medium-sized rings have always remained a widely studied class of biologically interesting molecules. Intermolecular gold-catalyzed reactions of pyrroles usually lack selectivity and a less pronounced selectivity switch has been observed in the related furan cyclizations with gold- and platinum-catalysis [8]. Towards this end, Modha et al. [20] developed a regioselective approach for the synthesis of pyrrolopyridinones employing an Ugi reaction followed by a gold(I)- or platinum(II)-catalyzed intramolecular hydroarylation. Use of cationic gold  $\text{Au}(\text{PPh}_3)\text{Cl}/\text{AgOTf}$  gave 100% conversion to *exo-dig* cyclized product **4** (Scheme 2c). Thereafter, a detailed study of the scope of these protocols employing different heterocycles such as benzothio- phene and indole, was reported (Scheme 2d) [21,22]. Interestingly, when the Ugi adduct generated from the reaction of 3-formyl benzothiophene with 2-propynylamine, 2-phenylacetic acid, and *tert*-butyl isonitrile was employed,  $\text{IPrAuCl}/\text{AgNTf}_2$  scores over  $\text{Au}(\text{PPh}_3)\text{Cl}/\text{AgOTf}$  for a selective *exo-dig* cyclization to give benzothienopyridines **6** (Scheme 2e) [22].

Further, aiming to develop milder conditions for such transformations, Kumar et al. [23] described gold(I)-catalyzed post-Ugi hydroarylation towards the synthesis of biologically important heterocycles such as pyrrolopyridines **7**, pyridoin- doles, and azepinoindoles **8** at rt within 15 min (Scheme 2f). The Ugi adduct was subjected to intramolecular hydroaryla- tion with different gold catalysts ( $\text{AuCl}$ ,  $\text{AuCl}_3$ ,  $\text{AuPPh}_3\text{Cl}/\text{AgOTf}$ ,  $\text{AuPPh}_3\text{Cl}/\text{AgSbF}_6$ ), where  $\text{AuCl}$  stands out with maximum conversion. In case of phenyl-substituted alkynes or the presence of a tosyl group on the pyrrole nitrogen, no product formation was observed. When indole Ugi adducts bearing a phenyl-substituted alkyne were treated under the optimized conditions, *endo* cyclized azepinoindoles **8** were exclusively formed. 3,4-Fused tricyclic indole based natural products that contain a tricyclic azepino- or azocino-[*c,d*] indolone core **9** have emerged as interesting targets due to their intriguing biological activities and molecular archite- ctures. They are exemplified by the indole alkaloid decursivine **10**. Kumar et al. [24] envisaged that a gold-catalyzed post-Ugi regioselective intramolecular hydroarylation reaction could provide an expedient access to the azocino-[*c,d*]indolone system **9** employing cationic  $\text{IPrAuCl}/\text{AgNTf}_2$  (Scheme 2g). The application of  $\text{AuCl}_3$ ,  $\text{AuCl}$  and  $\text{AgNTf}_2$  gave almost no conversion.

Most of the literature described here deals with the post-MCR construction of six to eight-membered rings *via* gold catalysis. However, in one typical example, our group [25] has disclosed a highly efficient approach for the regioselective construction of fused nine-membered rings (diazoninone framework) **11** employing  $\text{Au}(\text{PPh}_3)\text{Cl}/\text{AgOTf}$  (Scheme 2h). Other gold-catalyst *viz.*  $\text{Au}(\text{PPh}_3)\text{Cl}/\text{AgSbF}_6$ ,  $\text{Au}(\text{PPh}_3)\text{Cl}/$

$\text{AgNTf}_2$ , or  $\text{Au}(\text{X-Phos})\text{Cl}/\text{AgOTf}$  did not improve the yield, while almost no conversion occurred with  $\text{AuCl}_3$ ,  $\text{Au}(\text{PPh}_3)\text{Cl}$ ,  $\text{AgBF}_4$ , and  $\text{AgOTf}$ .

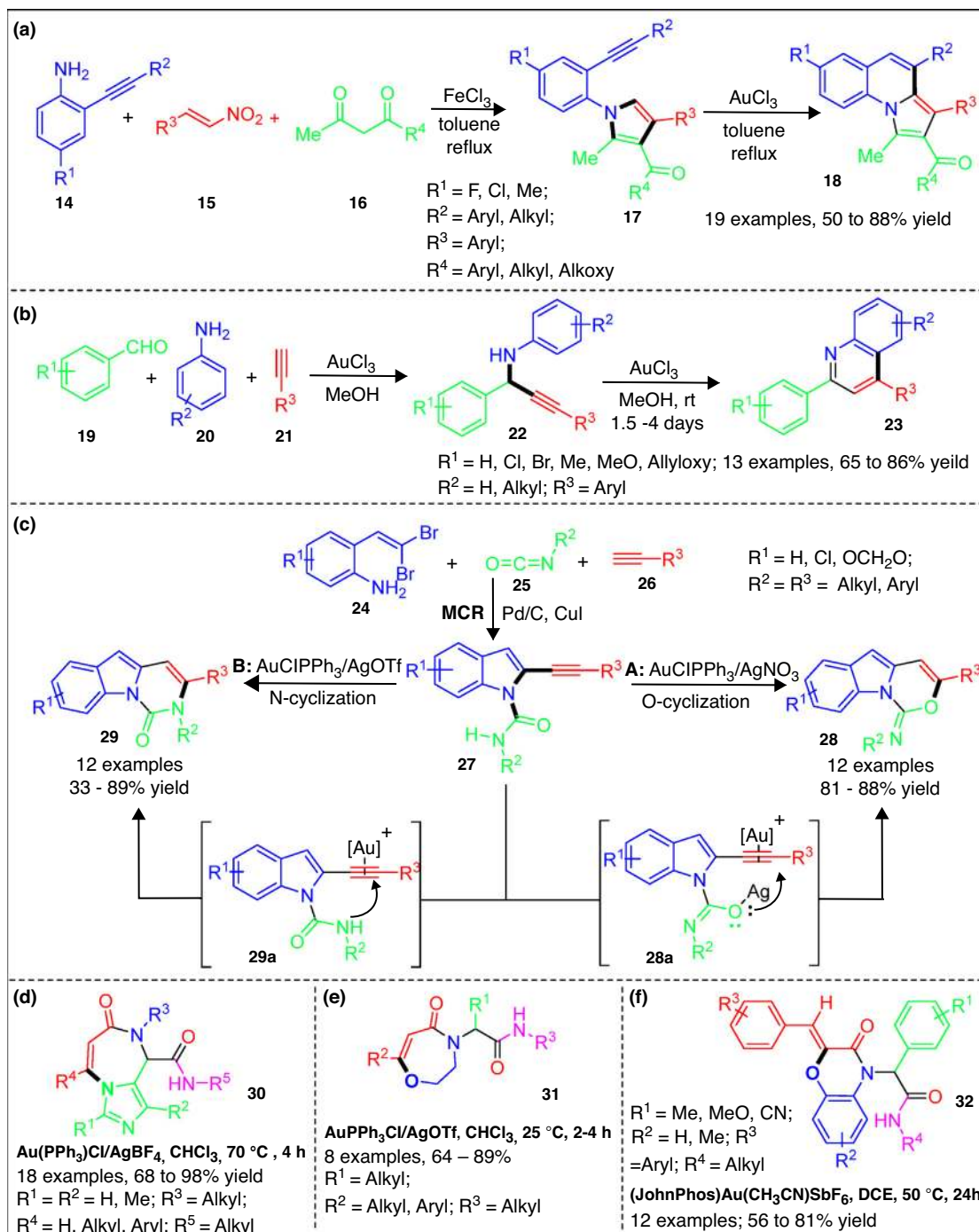
Recently, an amide remote-controlled stereoselective syn- thesis of pyrido[3,4-*b*]indoles **13** through post-Ugi gold-cata- lyzed hydro-heteroarylation has been realized employing Ugi 4-component reaction (Ugi-4CR) and further modification by freshly prepared  $\text{Au}(\text{PPh}_3)\text{Cl}/\text{AgSbF}_6$  (Scheme 2i) [26]. Repla- cing the  $\text{SbF}_6^-$  counter ion with  $\text{BF}_4^-$  enhanced the reaction performance. The stereochemistry of the product was con- firmed by a NOESY experiment. To determine the effect of silver on this gold-catalyzed hydro-heteroarylation, the reac- tion was examined under different catalytic conditions, re- vealing that filtration of *in situ* prepared  $\text{Au}(\text{PPh}_3)\text{Cl}/\text{AgBF}_4$  is an important step, resulting in a maximum yield of the desired product.

In addition to the Ugi reaction, which has been used quite frequently for the generation of suitable substrates for gold- catalyzed post-MCR modifications, a few other multicom- ponent reactions have also been reported to generate suit- able skeletons for such transformations. In one such example, Sarkar et al. [27] reported the two-step synthesis of diversely substituted pyrrolo[1,2-*a*]quinolines **18** that involves an Iron(III)-catalyzed MCR for the synthesis of substituted *N*-(2-alkynylaryl) pyrroles **17** followed by a gold(III)-catalyzed intramolecular hydroarylation of the alkyne moiety (Scheme 3a). Similarly, Xiao et al. [28] have examined the three-component reaction of benzaldehyde **19**, aniline **20**, and phenylacetylene **21** with  $\text{AuCl}_3$  as a catalyst. During initial studies, the reaction afforded two products: propargyl amine **22** and quinoline derivatives **23**. The formation of quinoline derivatives suggested that fur- ther transformation of the propargyl amine by gold catalysis ( $\text{AuCl}$  or  $\text{AuCl}_3$ ) was indeed possible under these reaction conditions (Scheme 3b).

### C–N and C–O bond forming reactions

In addition to gold-catalyzed C–C bond formations, C–N and C–O bond forming reactions have seen considerable advancement in the last decades. These reactions have proceeded in the same manner as described before, with gold catalyst in combination with various co-catalyst or additives. In one report, Gupta et al. [29] developed a chemoselective cycloisomerization processes using an or- thogonal set of gold catalysts, leading to the generation of an array of *N*-[1,3]oxazino[3,4-*a*]indol-1-ylideneamine derivatives **28** and pyrimido[1,6-*a*]indolone derivatives **29** from a common intermediate **27** (Scheme 3c). The cyclic imidate is a useful synthetic building block and an important pharmacophore. Pyrimido[1,6-*a*]indolones **29** have importance in medicinal chemistry as 5-HT<sub>3</sub> receptor antagonists, topoisomerase II inhibitors and fluorescent materials. The first step is the annulation of 2-(2,2-dibro-





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**Scheme 3.** Different MCRs and gold-catalyzed post modifications towards C–C bond formations (a–c) towards C–N bond formations (c–f)

movinyl)aniline **24**, an isocyanate **25**, and a terminal alkyne **26** in a three-component tandem format *via* Cu/Pd-catalyzed cross-coupling, to afford *N*-1 and *C*-2 functionalized indole **27**. In the subsequent step, the enyne–urea derivative undergoes chemo- and regioselective 6-*endo* cyclization to afford *O*-cyclized product in the presence of  $\text{AuCIPPh}_3/\text{AgNO}_3$ , and *N*-cyclized product in the presence of  $\text{AuCIPPh}_3/\text{AgOTf}$ . Mechanistically, the ni-

trogen of the urea, being less electronegative than oxygen, favorably attacks as a relatively softer nucleophile onto the electron-deficient alkyne to afford *N*-cyclized product **29**, a phenomenon that could be well explained following HSAB theory. In contrast, *O*-cyclization might be promoted *via* intermediate **28a** involving activation of the alkyne by gold-catalyst along with coordination of silver with the oxygen of the urea to furnish **28**.

The imidazodiazepinone core is ubiquitous in various natural products and pharmaceuticals (bretazenil, flumazenil *etc.*). It is a vital intermediate in the synthesis of pentostanin and coformycin, both naturally occurring anticancer and antiviral nucleosides [30]. In this direction, Kumar et al. have developed an expedient post-Ugi intramolecular heteroannulation approach for the synthesis of imidazodiazepinones **30** employing gold catalysis (Scheme 3d) [31].

Similarly, procedures for the synthesis of *O*-containing medium-ring heterocycles are of particular importance owing to their widespread occurrence in natural products and biologically active compounds. Peshkov et al. [32] established a general and selective entry towards the oxazepine scaffold **31** (Scheme 3e) employing gold catalysis. The *in situ* generated cationic gold complex Au(PPh<sub>3</sub>)Cl/AgOTf led to the full conversion of hydroxypropargylamide substrates within 2 h at rt, forming the desired oxazepines **31** in good to excellent yields. Recently, Singh et al. [33] have realized a gold catalyzed 6-*exo-dig* cyclization for the synthesis of benzoxazinones **32** from Ugi adducts. The precursors were first synthesized *via* an Ugi reaction followed by a reaction with Echavarren's gold(I) catalyst [JohnPhosAu(CH<sub>3</sub>CN)]Cl/AgSbF<sub>6</sub> selectively affording benzoxazinone derivatives in moderate to good yields (Scheme 3f).

### Post-MCR cascades or domino reactions

Cascade transformations are step-economical processes resulting in augmented molecular complexity and diversity, starting from simpler molecules. They are often accompanied by a high degree of chemo-, regio-, and diastereoselectivity. Some noteworthy examples from the recent literature employing gold catalysis, have been highlighted in this section.

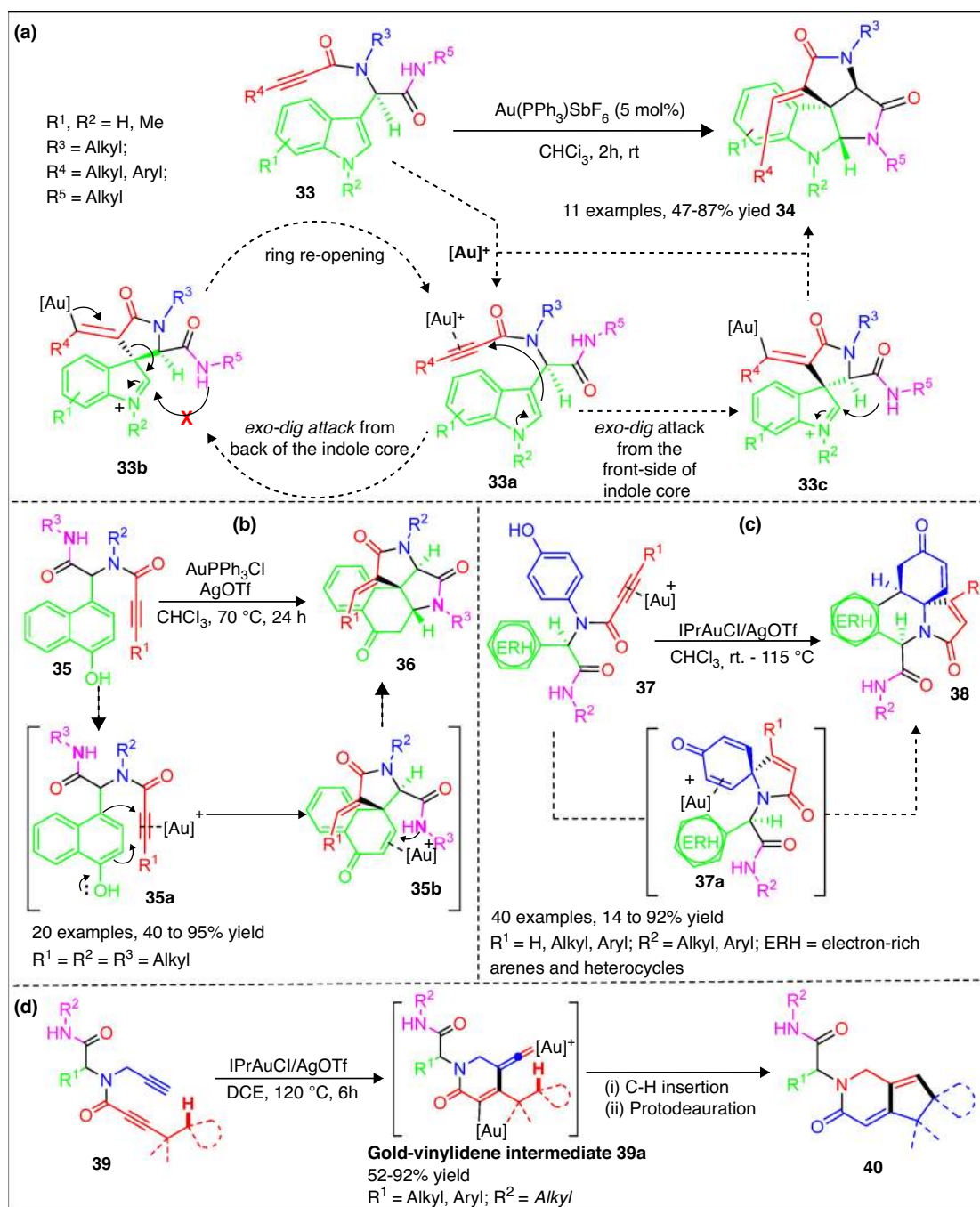
Spirocyclizations are perceived as an interesting method for generating complex heterocyclic system with built-in stereo- or regioselectivity in most cases. Accessing such alkaloids in a one-pot cascade fashion while securing diversity is highly desirable from a sustainable chemistry perspective. Modha et al. have effectively exploited the catalytic activity of  $\pi$ -acidic gold salts involving triple bond transformations by disclosing a diversity-oriented approach for the synthesis of fused polycyclic spiroindolinones **34** (Scheme 4a) [34]. The developed post-Ugi, gold(I)-catalyzed diastereoselective domino cyclization process involved a "branched-handed" pre-cyclization architecture resulting from the chiral center present in the Ugi adduct **33**. The expected outcome of the reaction was an indoloazepinone through an *endo-dig* cyclization and rearrangement sequence [18]. Instead, an *exo-dig* cyclization followed by intramolecular trapping of the spiro-intermediate occurred, resulting in the diastereoselective formation of a tetracyclic spiroindolinone **34** (Scheme 4a).

Notably, methyl substitution at the 2-position of the indole core completely inhibited the cyclization, and the starting material was quantitatively recovered. A tosyl group on

the indole nitrogen strongly diminished the nucleophilicity of this core and hence no cyclized product could be obtained. The observed diastereoselectivity of the reaction was explained by the mechanism which involves the activation of the triple bond of the Ugi adduct **33** by cationic gold, followed by a nucleophilic attack (with two possible pathways) of the C-3 position of the indole **33a**. Attack from the back side of the indole core would result in intermediate **33b**. However, trapping of the intermediate iminium ion by the secondary amide is sterically impossible and might result in ring re-opening. In contrast, when the attack occurs from the front side of the indole **33c** intermediate is formed, and trapping of the iminium ion is possible, giving rise to the desired spiroindolinone **34**. Later on, another variant of this reaction was developed giving rise to spiroindolines with propargylamines as an alkyne source [35]. The reaction was carried out with one equivalent of trifluoroacetic acid (TFA) to improve the yield. The authors suggested that, apart from being a good proton source, TFA might act as a co-ligand in this spirocyclization reaction.

Fused azaspiro tetracyclic *N*-heterocycles are prominent molecular motifs that are widely present in different alkaloids such as (+)-plicamine, (+)-tazettine and (+)-erysotramidine with a plethora of biological activities. The gold-catalyzed dearomatization/*ipso*-cyclization of phenols has attracted a lot of attention due to its unique capacity to generate highly functionalized spirocarbocycles [36]. In this direction, He et al. [37] have reported a gold(I)-catalyzed post-Ugi domino dearomatization/*ipso*-cyclization/*aza*-Michael sequence to construct diverse and complex fused azaspiro tetracyclic scaffolds **36** in only two operational steps (Scheme 4b). Different Ugi adducts **35** were synthesized from 4-hydroxy-1-naphthaldehyde as a distinctive Ugi substrate, along with amine, isocyanide, and 2-alkynoic acid, and then subjected to the domino cyclization reaction under the optimized conditions. A postulated reaction mechanism involves  $\pi$ -activation of the triple bond by *in situ* formed cationic gold(I) species (**35a**) followed by nucleophilic attack at the C-4 position of 1-naphthol in a 5-*exo-dig* fashion, resulting in the formation of the spirocarbocyclic intermediate **35b**. Subsequently, *aza*-Michael addition facilitated by  $\pi$ -activation of the cationic gold species, generates the tetracyclic scaffold **36**.

Very recently, in continuation of this idea, He et al. [38] developed an efficient gold(I)-catalyzed post-Ugi domino dearomatization/*ipso*-cyclization/Michael sequence towards a library of diverse (hetero)-arene-annulated polyheterocycles (Scheme 4c). Screening of various gold complexes, showed that Au(IPr)Cl/AgOTf gave the highest yield of the desired product at rt. The reaction proceeded well not only with aliphatic, but also with aromatic isonitriles which was unprecedented in most of the previous reports on such post-Ugi chemical transformations. Mechanistically, an *in situ* generated cationic gold(I) species activates the triple bond



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**Scheme 4.** Gold(I)-catalyzed post-MCR regioselective cascade cyclizations towards (spiro)polyheterocycles.

of the Ugi adduct **37**. Then nucleophilic attack of the phenol on the activated triple bond occurs in a 5-endo-dig fashion, resulting in the regioselective formation of the spirocyclic intermediate **37a**. Subsequently, Michael addition of the indole moiety to the newly formed cyclohexadienone is facilitated by  $\pi$ -activation by the gold species, resulting in the formation of the final product **38**.

Moving to other interesting methodologies designed by the combination of gold catalysis and post-MCR rigidifica-

tion strategies, an interesting dual  $\sigma$ - $\pi$  activation by gold catalysis towards post-Ugi transformations was reported [39]. Au(IPr)Cl/AgOTf efficiently catalyzed the regioselective cascade cyclization of *N*-propynylbutynamide **39** via  $C_{sp^3}$ -H functionalization for the synthesis of (spiro)cyclopentapyridinones **40** (Scheme 4d). Mechanistically, the first step is the formation of gold-acetylide which upon  $\pi$ -activation of the butynamide, directs the 6-endo-dig-cyclization, resulting in the formation of the gold-vinylidene intermediate **39a**. This



highly reactive species may undergo facile C–H insertion, which upon protodeauration forms the final product **40** (Scheme 4d).

### Summary and future outlook

Until recently, Pd-catalyzed (hetero)annulations mostly occupied the front seat in post-MCR transformation chemistry, with most efforts made towards post-Ugi/Heck modifications and arylation approaches as described in our previous review on the topic [3]. The development of novel transformations for generating synthetically challenging structures *via* tuning of the gold catalytic system, along with suitable substrates, has opened new doors for the synthesis of diverse heterocyclic scaffolds. Consequently, this review, highlights and discusses the rise of gold-catalyzed post-MCR transformations as an emerging field. Therefore, it would help researchers to better understand the chemistry behind this, and stimulates them to develop better synthetic methodologies.

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