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The synthesis of diverse benzazepinoindoles *via* gold-catalyzed post-Ugi alkyne hydroarylation/Michael addition sequence†

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We have developed a novel gold-catalyzed hydroarylation/Michael addition process, enabling the construction of the benzazepinoindole polycyclic scaffold in a highly efficient manner starting from readily accessible multifunctional Ugi adducts. The developed methodology is characterized by a broad substrate scope, excellent functional-group tolerance and high yields of the target benzazepinoindoles.

Introduction

Many bioactive natural products[1] and pharmaceutical agents[2] contain a polycyclic indole-fused scaffold. In particular, azepinoindole-containing derivatives (Fig. 1) constitute attractive synthetic targets due to their remarkable structural and biological properties. For example, paullone is a parent compound for a family of cyclin-dependent kinase (CDK) inhibitors possessing promising *in vitro* antitumor activity.[3] Kenpaullone, the most prominent member of this family, has been recently repurposed for amelioration of pathologic pain through the normalization of inhibitory neurotransmission.[4] Indole-fused analogues of the marine sponge alkaloid hymenialdisine[5] have been explored for inhibition of cytokine production[6] and as a general kinase inhibitory scaffold.[7] Subincanadine F, isolated from the bark of a Brazilian medicinal plant, has been shown to exhibit substantial cytotoxicity against human epidermoid carcinoma KB cells and murine lymphoma L1210 cells.[8] Arboflorine is a structurally complex pentacyclic alkaloid, isolated from *Malayan Kopsiaarborea*,[9] which complete total synthesis is yet to be achieved.[10]

The chemical and biological significance of the azepinoindole schaffold has triggered the development of a number of general synthetic methodologies for its efficient assembly.[11] In 2011, Seidel and co-workers described the construction of polycyclic benzazepinoindoles *via* diphenyl phosphate (DPP)-catalyzed redox-neutral annulation of *ortho*-aminobenzaldehydes and indoles involving a condensation/1,5-hydride shift/ring-closure sequence (Scheme 1a).[12] Apart from clear advantages such as high step and atom economy, several deficiencies such as the requirement of harsh reaction conditions and generally moderate yields of the target products should also be pointed. In an attempt to overcome these limitations, Li and co-workers developed a modification of Seidel's approach that involves a two-step sequential protocol proceeding under milder conditions. The transformation starts with

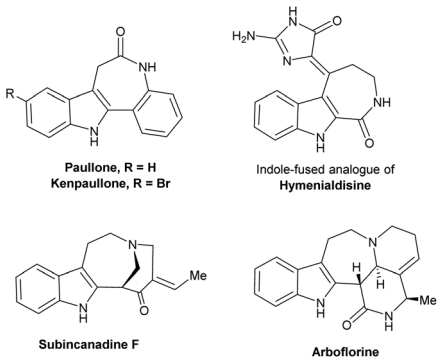

Fig. 1 Representative natural products and pharmaceuticals containing the azepinoindole core.

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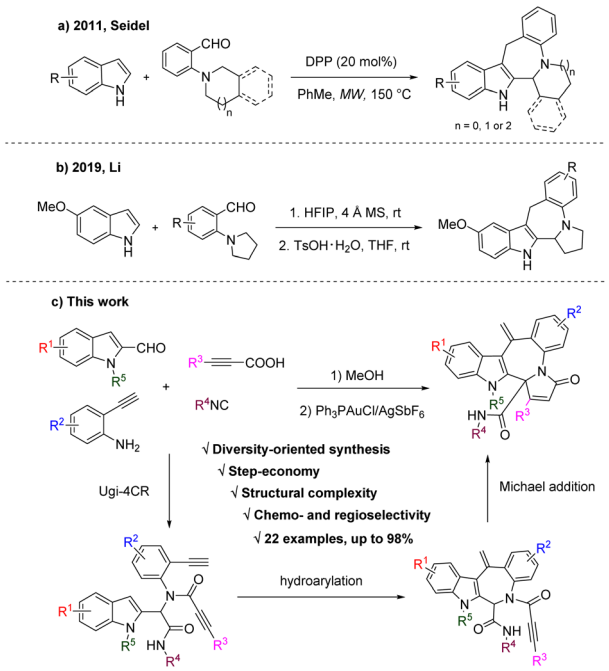


Scheme 1 Synthetic approaches towards benzazepinoindole scaffold.

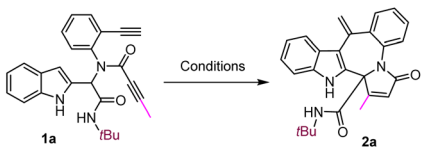
hexafluoroisopropanol (HFIP)-promoted redox-neutral cascade condensation/1,5-hydride shift/spirocyclization of *ortho*-aminobenzaldehydes and indoles furnishing spiro-fused indoline intermediates that subsequently undergo *para*-toluenesulfonic acid (PTSA)-catalyzed ring expansion to produce the final polycyclic benzazepinoindoles (Scheme 1b).[13] It should be pointed that Li's protocol was limited to specific substrates and the overall yields of target products still remain moderate. In view of significant promise of the above scaffolds in organic and medicinal chemistry, it is essential to develop novel, rapid, and efficient strategies for the preparation of diverse benzazepinoindoles.

The Ugi four component reaction (U4CR) is an attractive and robust tool for the construction of various functionalized peptidomimetics.[14] Furthermore, it offers a number of convenient venues for the synthesis of important heterocyclic scaffolds *via* transition metal-catalyzed post-Ugi transformations.[15] In this regard, our group has implemented several strategies for accessing diverse *N*-heterocyclic cores by the combination of an Ugi reaction and gold catalysis[16] that has recently emerged as an efficient catalytic tool for the construction of C–C and C–heteroatom bonds under very mild conditions.[17] In many instances the acquisition of polyheterocycles *via* post-Ugi chemistry involves alkyne functionalization.[18] In 2016, our group developed a strategy for accessing imidazole-fused polycyclic scaffolds *via* a one-pot Ugi/Michael addition process, followed by a silver-catalyzed heteroannulation.[19] In 2018, Peshkov and co-workers reported a related approach towards polycyclic indole-fused scaffolds that involved post-Ugi base-mediated Michael addition, followed by gold-catalyzed alkyne hydroarylation.[20] Both methods benefited from consecutive deployment of two alkyne functional groups in two independent steps of the synthetic sequence. Herein, we describe a new approach towards structurally diverse benzazepinoindoles *via* a gold-catalyzed post-Ugi tandem alkyne hydroarylation/Michael addition sequence (Scheme 1c). In this new catalytic method, the reactivity of two alkyne groups can be exploited in a simultaneous fashion with excellent chemo- and regioselectivity allowing to construct two C–C bonds and two rings in a single synthetic operation.

Results and discussion

We began the investigation of our new gold-catalyzed reaction cascade by using **1a** as a model substrate, which was readily obtained *via* Ugi-4CR of indole-2-carboxaldehyde, 2-butynoic acid, 2-ethynylaniline and *tert*-butyl isocyanide. The results are summarized in Table 1. When the reaction was conducted with $Ph_3PAuCl/AgOTf$ combination (10 mol%) in DCE at 100 °C for 12 h, the benzazepinoindole **2a** was obtained in 64% yield (Table 1, entry 1). Evaluating different gold catalysts as IPrAuCl, JohnPhosAuCl, XPhosAuCl or (IMes)PhosAuCl in combination with AgOTf indicated that Ph_3PAuCl is the preferred choice (Table 1, entries 2–5). Next, various silver salts including $AgNTf_2$, $AgSbF_6$, $AgBF_4$ and $AgNO_3$ were screened, allowing to boost the yield of **2a** up to 90% when using the

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	*T* (°C)	Time (h)	Yield[b] (%)
1	$Ph_3PAuCl/AgOTf$	DCE	100	12	64[c]
2	PrAuCl/AgOTf	DCE	100	12	58
3	JohnPhosAuCl/AgOTf	DCE	100	12	32
4	XPhosAuCl/AgOTf	DCE	100	12	56[c]
5	(IMes)AuCl/AgOTf	DCE	100	12	40
6	$Ph_3PAuCl/AgNTf_2$	DCE	100	12	80[c]
7	**$Ph_3PAuCl/AgSbF_6$**	**DCE**	**100**	**12**	**90**[c]
8	$Ph_3PAuCl/AgBF_4$	DCE	100	12	33
9	$Ph_3PAuCl/AgNO_3$	DCE	100	12	5
10	$Ph_3PAuCl/AgSbF_6$	MeOH	100	12	74[c]
11	$Ph_3PAuCl/AgSbF_6$	CH_3CN	100	12	60
12	$Ph_3PAuCl/AgSbF_6$	THF	100	12	78
13	$Ph_3PAuCl/AgSbF_6$	Toluene	100	12	70
14	$Ph_3PAuCl/AgSbF_6$	DCE	80	12	66[c]
15	Ph_3PAuCl	DCE	100	12	0
16	$AgSbF_6$	DCE	100	12	Trace

[a] Unless otherwise stated, all reactions were run with 0.1 mmol of Ugi adduct **1a**, 10 mol% of catalyst, and 2.0 mL of solvent in a sealed flask. [b] Yields based on ^1H NMR analysis using 2,4,6-trimethoxybenzaldehyde as internal standard. [c] Isolated yields. DCE = 1,2-dichloroethane; OTf = trifluoromethanesulfonate; IPr = 1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene; JohnPhos = (1,1′-biphenyl-2-yl)di*tert*-butylphosphine; XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene.

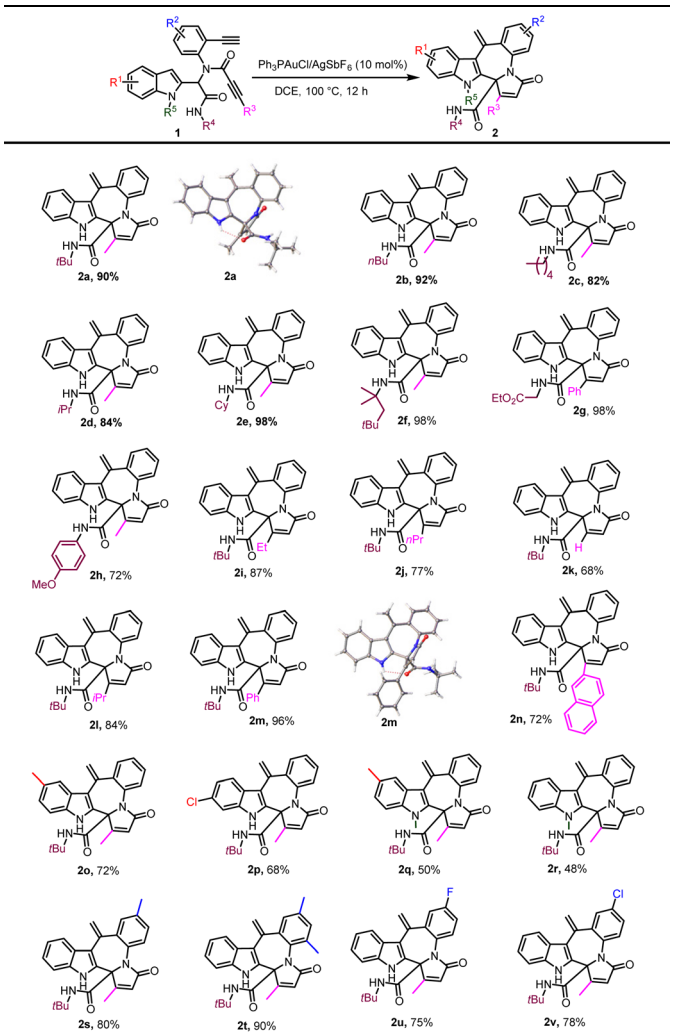
$Ph_3PAu/AgSbF_6$ combination (Table 1, entries 6–9). A detrimental effect was observed when changing the solvent to MeOH, CH_3CN, THF and toluene (Table 1, entries 10–13). When a lower temperature of 80 °C was used, **2a** was delivered in only 66% yield after 12 h (Table 1, entry 14). Applying Ph_3PAuCl or $AgSbF_6$ alone no formation of the desired **2a** was observed leaving most of **1a** unreacted.

With the optimal conditions in hand, various Ugi adducts **1** were subjected to this gold-catalyzed double cyclization process to examine its scope and limitations (Table 2). First, substrates with various isocyanide-originated secondary amide groups have been explored, delivering the corresponding benzazepinoindoles **2a–2h** in 72–98% yield. The reactions with the substrates derived from different propiolic acids also worked smoothly, furnishing the corresponding products **2i–2n** in 68–96% yield. Another set of substrates stemming from various indole-2-carboxaldehydes, including *N*-methylated ones, also performed quite well, delivering the corresponding products **2o–2r** in 48–72% yield. Finally, the introduction of alkyl and halogen groups into the 2-ethynylaniline core was well compatible with the reaction conditions, allowing to attain benzazepinoindoles **2s–2v** in 75–90% yield. Moreover, the structures of **2a** and **2m** were established by X-ray crystallographic analysis (see ESI† for more details). In addition, a scale-up experiment on 1 mmol of Ugi adduct **1m** was run to check the practicality of this strategy. Under the standard reaction conditions, the gold-catalyzed cyclization went smoothly, yielding the corresponding product **2m** in a high yield of 94% (Scheme 2).

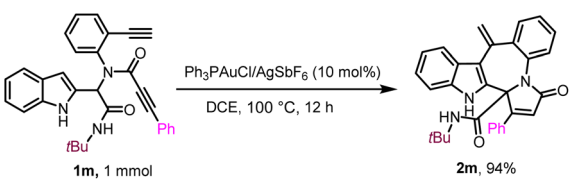
In order to extend our approach for the synthesis of polycyclic scaffolds, the Ugi adduct **1w** was prepared by Ugi-4CR of pyrrole-2-carboxaldehyde, 2-butynoic acid, 2-ethynylaniline and *tert*-butyl isocyanide. Subjecting adduct **1w** to the standard gold-catalyzed conditions, the desired benzazepinopyrrole product **2w** was obtained in 30% yield (Scheme 3).

To get some insights in the mechanistic details of our newly established tandem process, a series of control experiments featuring several model substrates have been performed. Subjecting Ugi adduct **1x**, derived from benzoic acid and thus lacking the propargylamide moiety, to the standard gold-catalysed conditions, delivered the hydroarylation product **2x** in 45% yield (Scheme 4a). It appears that a substantial part of the starting material **1x** decomposed during the reaction, resulting in an only moderate yield of the product **2x**. The application of Ugi adduct **1y**, derived from aniline lacking the terminal alkyne moiety, led to the formation of another type of hydroarylation product **2y** in 99% yield, while no formation of Michael addition product **1y′** has been observed (Scheme 4b). The outcome of these experiments, along with the outcome of our tandem process, suggest that under the cationic gold catalysis triple bond hydroarylation occurs faster than the Michael addition implying that the C3 position of the indole is more reactive towards the π-activated alkyne than the peptidyl position. It can also be concluded that the 2-ethynylaniline-derived alkyne fragment is more prone towards cationic-

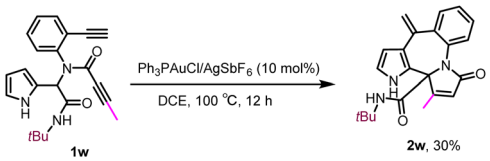
Table 2 Scope of the process[a,b]



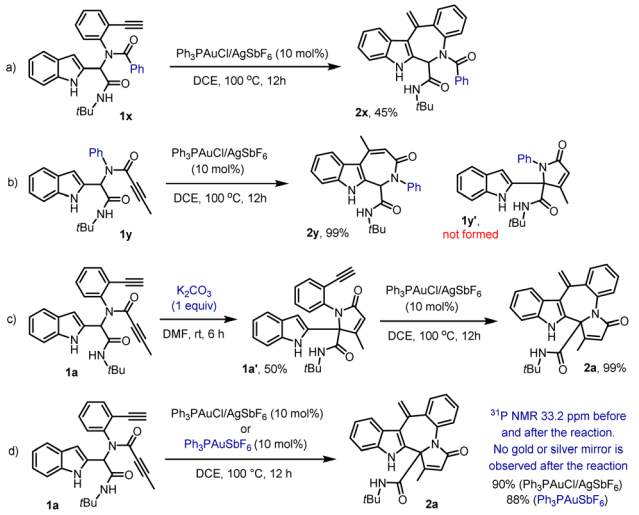
[a] All reactions were run with **1** (0.1 mmol), 10 mol% of $Ph_3PAuCl/AgSbF_6$, and 2.0 mL of DCE at 100 °C in a sealed flask for 12 h. [b] Isolated yields.



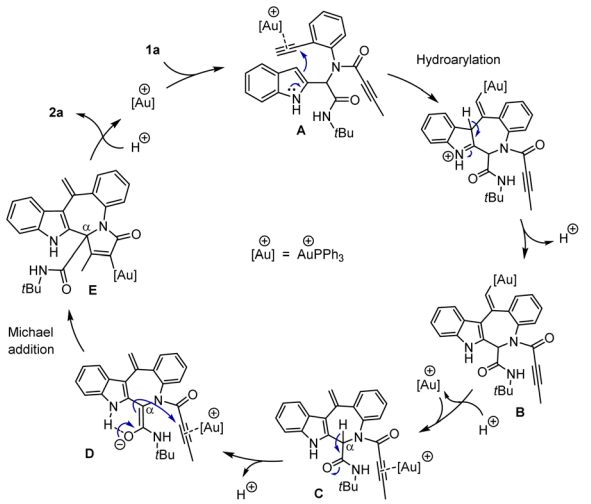
Scheme 2 Scale-up synthesis of **2m**.



Scheme 3 Synthesis of benzazepinopyrrole **2w**.



Scheme 4 Control experiments.



Scheme 5 Proposed mechanism.

gold-catalysed hydroarylation as compared to the propiolic acid derived one. However, under base-promoted conditions a reversal of reactivity has been achieved in terms of both nucleophilic and electrophilic reactive centers. Thus, in the presence of 1 equiv. of K_2CO_3, Ugi adduct **1a** has been converted into the Michael addition product **1a′** in 50% yield through the nucleophilic attack of the peptidyl enolate onto the propargyl amide fragment (Scheme 4c). Employing the resulting **1a′** as a substrate under the standard gold-catalysed conditions, benzazepinoindole **2a** could be obtained in 99% yield (Scheme 4c). Finally, we have also compared the outcome of two runs catalysed by a $Ph_3PAuCl/AgSbF_6$ combination and by a pre-made[21] silver-free cationic complex $Ph_3PAuSbF_6$ (Scheme 4d). Both reactions delivered the desired benzazepinoindole **2a** in comparable yields. Additionally, we have monitored both reactions by ^{31}P NMR (see ESI† for more details).[22] First, the spectra were measured before subjecting the reaction mixtures to heating. The major signal that probably corresponds to a cationic gold species bound to the substrate **1a**·Ph_3PAu^+ was observed at 33.2 ppm in both cases. Then, the spectra were measured upon completion of the reaction time featuring a broadened signal with decreased intensity in the same area. The latter in turn may correspond to a cationic gold species bound to the product. Other signals were also observed in ^{31}P NMR spectra under both conditions that may point at the partial decomposition of an active catalyst. However, no gold or silver mirror formation have been observed during the reaction. Overall, it can be concluded that the presence or absence of silver salt in the reaction media does not significantly affect the course of this transformation.

Based on our experimental results and available literature data,[16,17] a plausible mechanism for the gold-catalyzed cascade cyclization was proposed (Scheme 5). In the first step, the cationic gold(I) catalyst coordinates to the terminal alkyne moiety of the Ugi adduct **1a** to form gold π-complex **A**. This is followed by an intramolecular alkyne hydroarylation involving nucleophilic attack by the C3 position of the indole onto the activated triple bond to generate intermediate **B**. Upon protodeauration and subsequent coordination of gold to the remaining propiolic acid-derived triple bond, π-complex **C** is formed. Deprotonation at the peptidyl position (indicated as α) produces enolate **D** in which the negative charge is stabilized through the hydrogen bonding with the NH group of the indole.[23,24] In the absence of any apparent base the SbF_6^- counter anion may act as a proton shuttle. Subsequently, an intramolecular Michael addition of the nucleophilic α-carbon onto the π-activated propiolic acid takes place, leading to intermediate **E**. Finally, protodeauration affords the benzazepinoindole **2a** with regeneration of the cationic gold catalyst.

Conclusions

In summary, we have developed a novel method for the synthesis of diverse benzazepinoindoles through a gold-catalyzed post-Ugi intramolecular alkyne hydroarylation/Michael addition sequence. By combining an Ugi-4CR and a gold-catalyzed cascade cyclization, a structurally complex benzazepinoindole core could efficiently be assembled in a step-economical, chemo- and regioselective fashion. The overall strategy features operational simplicity as well as broad substrate scope and high functional group tolerance.

Conflicts of interest

There are no conflicts to declare.

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