Accepted Article

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This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201710592
Angew. Chem. 10.1002/ange.201710592

Link to VoR: <http://dx.doi.org/10.1002/anie.201710592>
<http://dx.doi.org/10.1002/ange.201710592>

A Gold-Catalyzed Domino Cyclization Enabling Rapid Construction of Diverse Polyheterocyclic Frameworks

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Abstract: We report herein an efficient gold(I)-catalyzed post-Ugi domino dearomatization/*ipso*-cyclization/Michael sequence that enables access to libraries of diverse (hetero)arene-annulated tricyclic heterocycles. This process affords novel complex polycyclic scaffolds in moderate to good yields from readily available acyclic precursors with excellent chemo-, regio-, and diastereo-selectivity. The power of this strategy has been demonstrated by the rapid synthesis of 40 highly functionalized polyheterocycles bearing indole, pyrrole, (benzo)furan, (benzo)thiophene, pyrazole and electron-rich arenes in two-operational steps.

The great success of natural products as a source of drugs and drug leads^[1] is highly stimulating the synthetic community to develop effective strategies for the synthesis of architecturally complex natural products and natural product-like compounds as potential drug candidates for high-throughput screenings in drug discovery.^[2] However, rarely complicated heterocycles can escape a multistep synthesis due to their complexity. Simultaneously, due to the fact that compounds bearing the same privileged scaffold often exhibit similar biological activities and drug-kinetic properties, an easily diversified approach to privileged frameworks is highly anticipated for the rapid optimization of their biological properties.^[3] To this end, the combination of multicomponent reactions (MCRs)^[4] and metal-catalyzed post-transformations^[5] affords an enormous capability to yield structurally complex and diverse small molecules in a minimum number of steps.

The (hetero)arene-annulated tricyclic scaffold is widely present in several natural alkaloids such as (±)-vincadifformine,^[6] vindoline,^[7] geissoschizoline,^[8] tsitsikammamine C,^[9] fortucine^[10] and amarbellisine^[11] (Figure 1). Their good antineoplastic, antimalarial and antiviral potential has attracted considerable attention from synthetic and medicinal chemists.^[9,12] Although the target-oriented synthesis of several natural products belonging to these families have been accomplished,^[6-11] a breakthrough in synthetic methods that produces a large collection of diverse skeletons of natural products and natural product-like compounds for biological activity test is highly desired.

Figure 1. Selected natural products featuring the (hetero)arenes-annulated triheterocyclic core.

Dearomatization of phenol and its derivatives has been extensively employed as an efficient way to generate highly functionalized cyclohexadienones.^[13] It is conceivable that trapping of cyclohexadienones by extra nucleophiles like amides and amines located within the same molecule, would result in achieving higher levels of structural complexity (Scheme 1a). In this regard, several groups have developed efficient methods to prepare complex heterocycles.^[14] However, there are rare cases of electron-rich (hetero)arenes (ERH)^[15] serving as nucleophiles in conjugate additions with the newly formed unsaturated ketones. Inspired by these findings and our previous work on the development of gold-catalyzed domino sequence for biologically complex heterocycles (Scheme 1b),^[5d] we hypothesized that a gold(I)-catalyzed post-Ugi domino dearomatization/*ipso*-cyclization/Michael sequence would be quite promising to rapidly

1a. Domino sequence to generate complex polyheterocycles

1b. Tandem gold catalysis towards spiroindolines

1c. Au(I)-catalyzed post-Ugi domino sequence to diverse heterocycles

Scheme 1. Domino strategy to access complex heterocyclic scaffolds.

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Supporting information for this article is available on WWW under
<http://dx.doi.org/10.1002/anie.2017xxxx>.

construct structurally diverse and complex (hetero)arene-annulated tricyclic scaffolds (Scheme 1c).

The highly functionalized acyclic precursor (**1a**) which was readily constructed *via* Ugi four-component reaction (Ugi-4CR)^[16] of indole-2-carboxaldehyde, 4-aminophenol, *tert*-butyl isocyanide, and 2-butyric acid in 78% yield, was chosen to test the feasibility of our domino process. Upon treatment with 10 mol% of Au[PPh₃]₃OTf in CDCl₃ at 70°C for 24 h, the desired indole-annulated tricyclic heterocycle **2a** (CCDC 1572895) was obtained in 65% yield. Further screening of various gold complexes (Table 1, entries 2-5), showed that the application of IPrAuOTf gave **2a** in the highest isolated yield of 90%. To our great delight, performing the reaction at r.t. delivered **2a** in a slightly higher yield of 95%. Whereas IPrAuCl with different chloride scavengers such as AgBF₄, AgSbF₆, AgNTf₂ and AgOMs did not improve the yield (Table 1, entries 7-10), IPrAuCl or AgOTf separately led to quite low conversion (Table 1, entries 11 and 12).^[17] Among the evaluation of solvents, MeCN, MeOH and DCE led to slightly diminished yields (Table 1, entries 13-14 and 16), while almost no desired product **2a** was detected in toluene (Table 1, entry 15). The highest yield was obtained in a shortened reaction time (3 h, Table 1, entry 17). A lower catalyst loading of 5 mol% furnished **2a** in 68% yield (Table 1, entry 18).

Table 1. Optimization of the reaction conditions.^[a]

Entry	Catalyst	Solvent	Time/h	Temp./°C	Yield of 2a /%
1	AuPPh ₃ Cl/AgOTf	CDCl ₃	24	70	65
2	XPhosAuCl/AgOTf	CDCl ₃	24	70	69
3	Me ₂ SAuCl/AgOTf	CDCl ₃	24	70	28
4	[JohnPhosAu(MeCN)] SbF ₆ /AgOTf	CDCl ₃	24	70	71
5	IPrAuCl/AgOTf	CDCl ₃	24	70	93 (90 ^[c])
6	IPrAuCl/AgOTf	CDCl ₃	24	r.t.	95 ^[c]
7	IPrAuCl/AgBF ₄	CDCl ₃	24	r.t.	12
8	IPrAuCl/AgSbF ₆	CDCl ₃	24	r.t.	76
9	IPrAuCl/AgNTf ₂	CDCl ₃	24	r.t.	88
10	IPrAuCl/AgOMs	CDCl ₃	24	r.t.	83
11	IPrAuCl	CDCl ₃	24	r.t.	trace
12	AgOTf	CDCl ₃	24	r.t.	32
13	IPrAuCl/AgOTf	MeCN	24	r.t.	86
14	IPrAuCl/AgOTf	MeOH	24	r.t.	83
15	IPrAuCl/AgOTf	Toluene	24	r.t.	trace
16	IPrAuCl/AgOTf	DCE	24	r.t.	90
17	IPrAuCl/AgOTf	CDCl ₃	3	r.t.	96 ^[c]
18 ^[d]	IPrAuCl/AgOTf	CDCl ₃	24	r.t.	68

[a] Unless otherwise stated, all reactions were run with **1a** (0.05 mmol) and a catalyst loading of 10 mol% in a screw-cap vial with 1 mL of solvent. [b] Yields based on ¹H NMR analysis using 2,4,6-trimethoxybenzaldehyde as internal standard. [c] Isolated yields. [d] Catalyst loading of 5 mol%. n.d. = not detected. DCE = 1,2-dichloroethane.

With the optimal conditions in hand (Table 1, entry 17), different Ugi adducts synthesized from indole-2-carboxaldehydes were subjected to the domino process for the generation of a library of indole-annulated tricyclic heterocycles. As shown in Table 2, the high tolerance of substituents on the isonitrile, the alkyne, the indole-2-carboxaldehyde, and the amine was observed. Specifically, the reaction worked well, not only with aliphatic (**2b-g**), but also with aromatic isonitriles (**2h**).

The steric effect of the alkyne moiety did not dramatically decrease the reaction yields (**2i-l**). In case that the Ugi adducts contain a terminal alkyne, the corresponding heterocycles **2m** and **2n** were delivered in fairly low yields of 14% and 15%, respectively. The electron-donating or electron-withdrawing groups on the indole were well tolerated (**2o** and **2p**). Compared with benzyl and Boc group (**2q** and **2r**), the benzenesulfonic group on the indole nitrogen strongly reduced the C3 nucleophilicity of this core, resulting in the formation of only the spirocarbocyclic product **2s'** under standard conditions. However performing this reaction at 115°C gave the desired product **2s** in a good yield of 90%. The reactions with *ortho*-substituted 4-aminophenols also performed well and the indole-annulated tricycles **2t** and **2u** were isolated in moderate yields of 55% and 63% with full regioselectivity. However, only low yields were observed in case of *meta*-substituted 4-aminophenols, probably due to the steric effect at the β-position of the newly formed enone moiety (**2v** and **2w**).

Table 2. Synthesis of indole-annulated tricyclic heterocycles.^[a]

[a] All reactions were performed with **1** (0.20 mmol) and 10 mol% of IPrAuOTf in a screw-cap vial with 2 mL of CHCl₃ for 3-24 h; all yields are isolated yields. [b] 115°C for 24 h in DCE (2 mL). TMB = 1,1,3,3-Tetramethylbutyl; Bs = Benzenesulfonic.

For the preparation of other heteroarene-annulated tricyclic heterocycles **4**, we next planned to use the Ugi adducts **3** assembled from different heteroaromatic aldehydes, to further testify the generality of this domino process. The results are summarized in Table 3. To our delight, treatment of the pyrrole-containing Ugi adducts **3a** and **3b** under the optimal condition gave the desired pyrrole-fused polyheterocycles **4a** (CCDC 1572894) and **4b** in yield of 63% and 70%, respectively. To overcome the low nucleophilicity of other heterocycles,

modified conditions are employed to treat the Ugi adducts **3c-h** resulting in the desired fused cycles **4c-h** in moderate to good yields. Regrettably, in case of Ugi adducts from benzofuran-2-carbaldehyde, 1-phenyl-1*H*-pyrazole-5-carboxaldehyde and benzo[*b*]thiophene-3-carbaldehyde (**3d**, **3e** and **3h**), a mixture of spirocarbocyclic products **4d'**, **4e'**, **4h'** and heteroarene-annulated tricycles **4d**, **4e**, **4h** were delivered even when conducting the reaction at 115°C for a prolonged time. Moreover, treating the Ugi adducts from thiophene-2-carbaldehyde and furan-2-carbaldehyde under 115°C for 48 h only led to the formation of the spirocarbocyclic products.^[18]

Table 3. Synthesis of heteroarene-annulated tricyclic heterocycles.^[a]

[a] All reactions were conducted with **3** (0.20 mmol) and 10 mol% of IPrAuOTf in a screw-cap vial with 2 mL of solvent; all yields are isolated yields. [b] r.t. for 24 h in CHCl₃. [c] 70 °C for 24 h in CHCl₃. [d] 115 °C for 24 h in DCE. [e] 115 °C for 48 h in DCE. TMB = 1,1,3,3-Tetramethylbutyl

Next, Ugi adducts **5** prepared from electron-rich aromatic aldehydes were tested in this domino process (Table 4). Pleasingly, the reactions worked well under modified conditions in case of hydroxy and alkoxy-substituted benzaldehydes, delivering the benzene-annulated tricyclic heterocycles **6a-e** in moderate to good yields (**6c**, CCDC 1572893). The application of pyrrolidine substituted benzene gave benzene-annulated tricycle **6g** in 71% yield at r.t. Unfortunately, employing piperidine or morpholino substituted benzaldehydes singly delivered the spirocarbocyclic products **6h'** and **i'** at r.t., and only lower yields of the desired benzene-annulated tricycles **6h** and **6i** were obtained even at 115°C for 48 h. Moreover, only the spirocarbocyclic products were observed in case of simple 2-naphthaldehyde and benzaldehyde at 115°C for 48 h.^[18]

Table 4. Synthesis of arene-annulated tricyclic heterocycles.^[a]

[a] All reactions were carried out with **5** (0.20 mmol) and 10 mol% of IPrAuOTf in a screw-cap vial with 2 mL of solvent; all yields are isolated yields. [b] 70 °C for 24 h in CHCl₃. [c] 115 °C for 48 h in DCE. [d] r.t. for 24 h in CHCl₃.

The obtained spirocarbocyclic intermediates indicate that gold-catalysed dearomatization/*ipso*-cyclization proceeds firstly in a 5-*endo* fashion.^[19] To further shed light on the subsequent Michael addition, the reactions of the spirocarbocyclic intermediate **2s'** under different conditions were implemented (Scheme 2). Treating the intermediate **2s'** with 10 mol% Au[PPh₃]OTf at 115°C for 24 h delivered the desired polycyclic indole derivative **2s** in 95% yield. In contrast, no conversion was observed in the absence of cationic gold catalyst or if HOTf (10 mol%) was used. Traces of tetracycles **2s** were detected in case of AgOTf (10 mol%) or IPrAuCl (10 mol%). Thus, it was ascertained that both steps, the dearomatization/*ipso*-cyclization form **2s'**, and the subsequent Michael addition to produce polycycles **2s**, are catalyzed by cationic gold species.^[20]

Scheme 2. Reaction of the spirocarbocyclic intermediate **2s'**.

On the basis of these observations and previous reports,^[19-21] a postulated reaction mechanism for this overall transformation is illustrated in Scheme 3. Firstly, the *in situ*

generation of a cationic gold(I) species is utilized for π -activation of the triple bond of the Ugi adduct ($\pm$)-1. Then nucleophilic attack the 1-phenol to the activated triple bond occurs in a 5-*endo*-dig fashion resulting in the regioselective formation of the spirocarbocyclic intermediate **B**. Subsequently, Michael addition of the newly formed cyclohexadienones with C3 in indoles facilitated by π -activation of the cationic gold species generates indole-annulated tricyclic heterocycles ($\pm$)-2.

Scheme 3. Proposed mechanism for the gold-catalyzed diastereoselective domino cyclization.

Finally, hydrogenation of indole-annulated triheterocycle **2a** was conducted as illustrated in Scheme 4. The Pd/C catalyzed hydrogenation of the C=C bonds in both the cyclohexenone and α,β -unsaturated γ -lactam moiety of **2a** occurred at 20 atm of H₂ resulting in the formation of polyheterocycle **7** in 54% yield. On the other hand, the employment of NaBH₄ chemoselectively reduced the ketone in the cyclohexenone, and the obtained product was subsequently treated with Pd/C catalyst at 5 atm of H₂ to deliver product **8** in 60% yield through further selective hydrogenation of the C=C bond in the α,β -unsaturated γ -lactam moiety.

Scheme 4. Hydrogenation of product **2a**.

In conclusion, we have elaborated an efficient diversity-oriented post-Ugi gold-catalyzed domino dearomatization/*ipso*-cyclization/Michael addition for the synthesis of highly functionalized (hetero)arene-annulated tricyclic heterocycles from readily available starting materials in two operational stages. The first step, an Ugi-4CR, generates diversity and a first chiral centre, while the second step, a gold-catalyzed domino process, generates two rings, one quaternary carbon centre and two stereogenic centers, providing good yields as well as excellent diastereoselectivity. The cationic gold facilitates

the trapping of the newly formed unsaturated ketone with indole, pyrrole, (benzo)furan, (benzo)thiophene, pyrazole and electron-rich arenes to achieve expeditious collections of diverse polyheterocyclic scaffolds. Investigations are ongoing to expand this process to enrich the library of (hetero)arene-annulated tricyclic heterocycles and to probe their pharmaceutical potential.

Acknowledgements

Financial support was provided by the FWO [Fund for Scientific Research-Flanders (Belgium)], the Research Fund of the University of Leuven (KU Leuven) and the Ministry of Education and Science of the Russian Federation (Agreement number 02.a03.0008). YH appreciate the China Scholarship Council (CSC) for providing a doctoral scholarship. LVM thanks the Hercules Foundation for supporting the purchase of a diffractometer through project AKUL/09/0035.

Keywords: gold catalysis • heterocycles • domino cyclization • dearomatization • Ugi reaction

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Heterocycle Libraries: A facile and diversity-oriented access to diverse (hetero)arene-annulated tricyclic heterocycles from readily available precursors with full diastereoselectivity is elaborated through a post-Ugi gold(I)-catalyzed domino dearomatization/*ipso*-cyclization/Michael sequence.

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