Modular Access to Diverse Bridged Indole Alkaloid Mimics via a Gold-Triggered Cascade Dearomative Spirocarbocyclization/[4 + 2] Cycloaddition Sequence

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S Supporting Information

ABSTRACT: A modular and streamlined synthetic strategy for the generation of bridged indole alkaloid-like heterocycles from easily available building blocks is elaborated. This approach utilizes an Ugi four-component reaction, establishing diversity, followed by an efficient cationic gold-triggered intramolecular cascade non-oxidative dearomative spirocarbocyclization/concerted [4 + 2] cyclization cascade, furnishing these architecturally complex and distinct bridged heterocyclic scaffolds with good diastereoselectivity.

Natural indole alkaloids featuring bridged cores often possess diverse biological and pharmacological attributes (Figure 1).¹ As a result, organic chemists have developed

Figure 1. Representative bridged natural indole alkaloids.

numerous effective strategies for the target-oriented synthesis of individual natural products appertaining to these families.² However, the rapid and streamlined construction of these natural products and their mimics with highly architectural complexity and diversity from easily available feedstocks is still highly desired,³ as it should allow fast access to large libraries of molecular architectures, serving as potential candidates for biological activity screenings in drug discovery. In this regard, the application of a multicomponent reaction and subsequent intramolecular transition-metal-catalyzed cyclization has obtained many achievements in constructing diverse complex heterocycles.⁴

Meanwhile, oxidative *ortho*-dearomatization of phenols and its derivatives⁵ has extensively been applied as a key step in putative synthetic approaches for caged and fused polycyclic frameworks like diterpenoid alkaloids through the inter- or intramolecular [4 + 2] cycloaddition of in situ generated reactive masked *ortho*-benzoquinones⁶ with various dienophiles.⁷ However, to date, integration of an intramolecular oxidative dearomatization followed by a [4 + 2] reaction with an indole core acting as a dienophile⁸ for the synthesis of bridged indole alkaloid mimics has been surprisingly scarce, probably because of the chemoselectivity issues due to the simultaneous presence of indole and phenol moieties under oxidative conditions.⁹ Notably, there are several reports on the application of gold catalysis in non-oxidative dearomatization reactions of phenol and its derivatives, which efficiently furnish highly functionalized spirocarbocycles containing 2,5-cyclohexadienones or 2,4-cyclohexadienones (Scheme 1A).¹⁰ To the best of our knowledge, the rational combination of gold-catalyzed intramolecular dearomatization and further transformations of spirocarbocycles for the construction of complex 3D scaffolds is rarely explored.¹¹ However, this strategy would be promising

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Scheme 1. Gold-Catalyzed Dearomatization of Phenols and Further Transformations

especially considering the high efficiency and broad functional group tolerance of gold catalysts.¹² Herein, we describe a modular approach for the rapid construction of bridged indole alkaloid-like heterocycles with good building-block diversity in two operational steps including the facile assembly of skeletally diverse precursors through well-developed Ugi four-component reaction (Ugi-4CR)¹³ and efficient gold-catalyzed cascade dearomative spirocarbocyclization/[4 + 2] cyclization sequence (Scheme 1B).

Our investigation commenced by examining the envisaged cascade dearomative spirocarbocyclization/[4 + 2] cycloaddition process with model substrate **1a**, which is easily prepared via Ugi-4CR of indole-3-carboxaldehyde, 2-aminophenol, *tert*-butyl isocyanide, and 2-butyneic acid. Upon treatment with 10 mol % of in situ generated cationic gold catalyst [IPrAuOTf] in CDCl₃ at rt for 12 h, the desired bridged indole alkaloid-like heterocycle **2a** was obtained in 40% yield (Table 1, entry 1). Further increasing the reaction temperature to 70 °C gave the desired product **2a** in 69% yield within 2 h (Table 1, entry 2). The subsequent screening of other gold complexes (Table 1, entries 3–6) revealed that the employment of [(IMes)AuOTf] afforded **2a** in the best isolated yield of 73% (Table 1, entry 6). No amelioration was observed when AgOAc, AgBF₄, AgSbF₆, and AgNTf₂ served as chloride scavengers for in situ formation of the cationic gold catalysts with IMesAuCl (Table 1, entries 7–10). Among the evaluation of solvents, toluene and DCE resulted in slightly decreased yields (Table 1, entries 11 and 12), whereas only a trace of **2a** was detected in acetonitrile and methanol (Table 1, entries 13 and 14). A lower catalyst loading of 5 mol % delivered **2a** in 41% yield (Table 1, entry 15). The separate employment of IMesAuCl or AgOTf led to almost no formation of the desired product **2a** (Table 1, entries 16 and 17).

Having optimized the reaction conditions, we sought to evaluate the generality of this gold-catalyzed cascade transformation. Thus, a variety of Ugi adducts **1** were readily synthesized from indole-3-carboxaldehydes and subjected to the optimal reaction conditions on a larger synthetic scale (Scheme 2). First, the examination of the influence of the *N*-indole substituent revealed that this procedure worked well with a methyl (**2a**), a hydrogen (**2b**), a benzyl (**2c**), and a phenyl (**2d**)

Table 1. Optimization of the Cascade Dearomative Spirocarbocyclization/[4 + 2] Cycloaddition Process^a

entry	catalyst	solvent	<i>t</i> (h)	<i>T</i> (°C)	yield (%) ^b
1	IPrAuCl/AgOTf	CDCl ₃	12	rt	40 ^c
2	IPrAuCl/AgOTf	CDCl ₃	2	70	69 ^c
3	XPhosAuCl/AgOTf	CDCl ₃	2	70	65
4	CyJohnPhosAuCl/AgOTf	CDCl ₃	2	70	50
5	(Ph ₃ P)AuCl/AgOTf	CDCl ₃	2	70	68
6	(IMes)AuCl/AgOTf	CDCl ₃	2	70	73 ^c
7	(IMes)AuCl/AgOAc	CDCl ₃	2	70	20
8	(IMes)AuCl/AgBF ₄	CDCl ₃	2	70	49
9	(IMes)AuCl/AgSbF ₆	CDCl ₃	2	70	42
10	(IMes)AuCl/AgNTf ₂	CDCl ₃	2	70	55
11	(IMes)AuCl/AgOTf	toluene	2	70	62 ^c
12	(IMes)AuCl/AgOTf	DCE	2	70	66
13	(IMes)AuCl/AgOTf	MeCN	2	70	trace
14	(IMes)AuCl/AgOTf	MeOH	2	70	trace
15 ^d	(IMes)AuCl/AgOTf	CDCl ₃	2	70	41
16	(IMes)AuCl	CDCl ₃	2	70	trace
17	AgOTf	CDCl ₃	2	70	trace

^aUnless otherwise stated, all reactions were performed with **1a** (0.05 mmol) and a catalyst loading of 10 mol % in a screw-cap vial with solvent (1 mL). ^bYields based on ¹H NMR analysis using 2,4,6-trimethoxybenzaldehyde as internal standard, and the diastereomeric ratio of **2a** is over 20:1 in all reactions. ^cIsolated yields. ^dCatalyst loading of 5 mol %.

group. However, an electron-withdrawing substituent such as a benzenesulfonyl group gave the bridged heterocycle **2e** in a diminished yield of 35%, and even no product **2f** was obtained in the case of an acetyl group, suggesting that not unexpectedly the C3 nucleophilicity of the indole nucleus plays a crucial role in the current process. Next, the high tolerance for the R² substituent of the secondary amide, derived from various aliphatic (**2g–k**) and aromatic (**2l–m**) isonitriles, was observed. Similarly, the effect of the R³ substituent of the tertiary propiolamide was investigated. A substituent-free propiolamide moiety (**2n**) is incompatible with this process. The propiolamide moieties bearing alkyl groups such as ethyl (**2o**), *n*-propyl (**2p**), and *n*-butyl (**2q**) were all well-converted into the desired product in 55–62% yield. However, a bulky phenyl-substituted propiolamide moiety offered the target compound **2r** in a lower yield of 35%. Subsequently, the electron-donating (Me, OMe) or electron-withdrawing (F, Br, I) substituents (**2s–x**), installed on the phenyl ring of the indole moiety, were evaluated and also appeared to be well-tolerated. Notably, the Ugi adduct bearing a pyrrolo[2,3-*b*]pyridine ring system is also applicable in this cascade cyclization, delivering the desired product **2y** in 30% yield. Unfortunately, the steric effect of a methyl substituent on the C2 of the indole moiety led to the failure of the formation of product **2z**. The bridged heterocycles **2aa–ae** with various substituents (Me, Ph, F, Cl) on both sides of the newly formed double bond could be produced in moderate to good yields of 50–75%. Additionally, the structures of compounds **2b**, **2aa**,

Scheme 2. Substrate Scope of the Cascade Dearomative Spirocarboxyclization/[4 + 2] Cycloaddition Process^a

^aAll reactions were run with **1a–ae** (0.20 mmol) and 10 mol % of (IMes)AuCl/AgOTf in a screw-cap vial with CHCl₃ (2 mL) for 2 h at 70 °C; all yields are isolated yields. Diastereomeric ratios were determined by ¹H NMR spectral analysis. ^bDecomposition of the precursor was observed. Bs = benzenesulfonyl; TMB = 1,1,3,3-tetramethylbutyl; Ad = 1-adamantyl; Np = naphthyl.

and **2ad** were unambiguously confirmed by X-ray crystallographic analysis (Figure 2).

Our efforts next sought to isolate the spirocarboxylic intermediate for further evaluation of the gold catalysts' role in the [4 + 2] cyclization. Treating the Ugi adduct **1af**, derived from benzo[*b*]thiophene-3-carbaldehyde under standard conditions, afforded the spirocarboxylic C3-linked benzothiophene **2af'** and the bridged heterocycle **2af** in yields of 65 and 25%, respectively (Scheme 3). Subsequently, the reactivity of the spirocarboxylic intermediate **2af'** under different conditions was investigated. In the absence of any catalyst or employing (IMes)AuCl/AgOTf (10 mol %), AlCl₃ (20 mol %), or AgOTf (10 mol %), the desired caged product **2af** was obtained in a similar low yield of 15–20% at 70 °C in 2 h. On the contrary, conducting the catalyst-free reaction at 115 °C for 2 h

Figure 2. Crystal structure of compounds **2b**, **2aa**, and **2ad** with thermal ellipsoids set at the 50% probability level.

Scheme 3. Capture of Spirocarboxylic C3-Linked Benzothiophene and Its Further Reaction

gave the bridged scaffold in 86% yield. These observations suggest that the cationic gold species [(IMes)Au]⁺OTf[−] is not involved in this cyclization.

A plausible mechanism for these gold-triggered cascade cyclizations is depicted in Scheme 4 on the basis of these

Scheme 4. Proposed Mechanism

observations and previous investigations.^{9–11} First, a 5-*endo*-dig nucleophilic attack of the C2 of the phenol fragment occurs on the cationic gold(I)-activated triple bond, resulting in the formation of the spirocarboxylic C3-linked indole **B**. This is followed by an intramolecular [4 + 2] cyclization of the reactive *ortho*-benzoquinone, with the indole core most probably without involvement of the gold catalyst,¹⁴ generating the bridged indole alkaloid-like heterocycle **2**. DFT calculations suggest that this intramolecular [4 + 2] cycloaddition proceeds via a concerted pericyclic process.¹⁵

Finally, a large-scale preparation of bridged heterocycle **2a** was performed with 6 mol % of gold catalyst, and its further selective hydrogenation was performed as illustrated in Scheme 5. The double bonds in both the cyclohexenone and the α,β -

Scheme 5. Hydrogenation of Bridged Heterocycle **2a^a**

^aReaction condition: (a) Pd/C, H₂ (20 atm), MeOH, rt, 16 h; (b) NaBH₄, MeOH, rt, 0.5 h.

unsaturated γ -lactam moiety of **2a** were hydrogenated with a Pd/C catalyst at 20 atm, producing polyheterocycle **4** in 99% yield. On the other hand, NaBH₄ chemoselectively reduced the carbonyl group of the cyclohexenone, and the obtained product was subsequently treated with Pd/C catalyst at 20 atm of H₂ for further hydrogenation of the double bonds, affording product **5** in 90% yield.

In summary, we have elaborated a modular and streamlined approach to construct architecturally complex bridged indole alkaloid-like heterocyclic scaffolds featuring high substituent diversity from easily available modular units. This two-step strategy employs the Ugi-4CR to introduce five diversity points and an efficient gold-triggered intramolecular dearomative cascade cyclization involving a concerted [4 + 2] cyclization to assemble the bridged nucleus. The rapid generation of 28 bridged indole alkaloid mimics with multiple new stereogenic centers embracing quaternary ones serves as a proof of concept for our approach.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01296.

Experimental procedures, characterization data, and copies of NMR spectra for all compounds (PDF)

Accession Codes

CCDC 1858538–1858540 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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