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Direct access to benzofuro[2,3-*b*]quinoline and 6*H*-chromeno[3,4-*b*]quinoline cores through gold-catalyzed annulation of anthranils with arenoxyethynes and aryl propargyl ethers†

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This work reports a facile annulation of anthranils with aryloxyethynes or aryl propargyl ethers to construct useful benzofuro[2,3-*b*]quinoline and 6*H*-chromeno[3,4-*b*]quinoline frameworks, respectively; these heterocycles are not readily available from literature methods despite their biological significance. This high atom- and step-economy strategy is highlighted by a broad substrate scope. The reaction mechanism is proposed to proceed through sequential cyclizations among the oxyaryl group, gold carbene and benzaldehyde of the α-imino gold carbene intermediates.

Gold-catalyzed annulations of alkynes with isoxazoles or anthranils have received intensive attention because of their facile access to five- and six-membered azacycles in one-pot operations.[1–4] Hashmi and coworkers recently reported the gold-catalyzed [3 + 2]-annulations of anthranils with ynamides to form α-iminogold carbenes **I**, further yielding 2-amino-7-formylindole products **II**[3a] (eqn (1)). Recently, we elaborated the sequential cyclizations of these α-imino gold carbenes **I** *via* an initial attack of gold carbenes by an *N*-aryl group, followed by a Friedel–Crafts cyclization with the benzaldehyde, yielding 6*H*-indolo[2,3-*b*]quinoline derivatives efficiently (eqn (2)). To highlight the utility of such three-component annulations, this work reports the gold-catalyzed annulations of anthranils with aryloxyethynes and aryl propargyl ethers to construct benzofuro[2,3-*b*]quinoline and 6*H*-chromeno[3,4-*b*]quinoline cores, respectively (eqn (3)).

Fig. 1 depicts selected furoquinoline alkaloids[5] that occur mainly in the *Rutaceae* family. For dictamnine **I**, evolitrine **II**, γ-fagarine **III**, skimmianine **IV**, kokusaginine **V**, masculine **VI** and flindersiamine **VII**, these natural alkaloids exhibit pharmacological activities such as antiviral,[6a] antiplatelet aggregation,[6b] cytotoxic[7] and anti-acetylcholinesterase[8] activity. The alkaloids **VIII** and **IX** show antifungal[9] and anti-TB[10] activity with low toxicity. Despite their biological importance, very few synthetic procedures were reported for these furoquinoline alkaloids. The reported synthesis of furoquinolines involves multiple (3 or 4) steps, resulting in small yields of products; furthermore, the starting materials are uncommon and not readily available.[11]

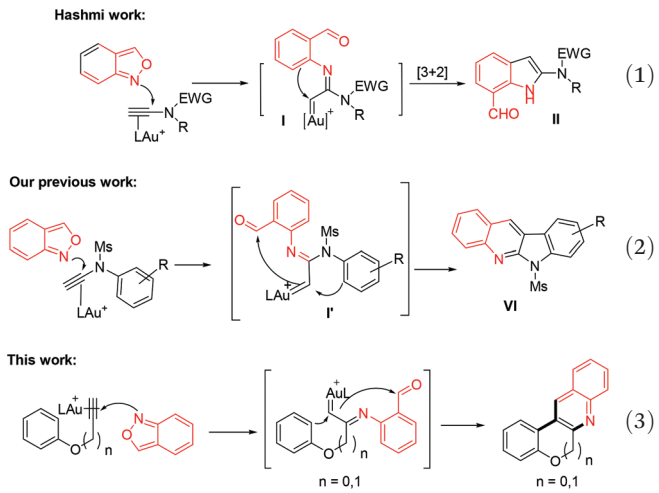

Table 1 summarizes the catalytic annulations of phenoxyethyne **1a** with anthranil **2a** over commonly used gold catalysts. We tested this reaction mixture in hot DCE (80 °C, 16 h)

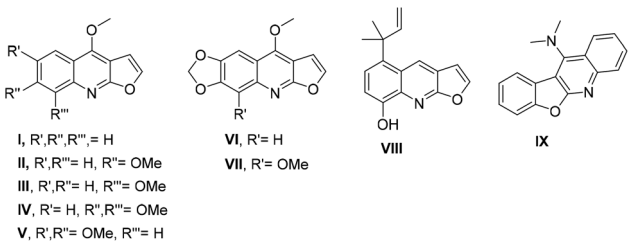

Fig. 1 Selective bioactive natural alkaloids.

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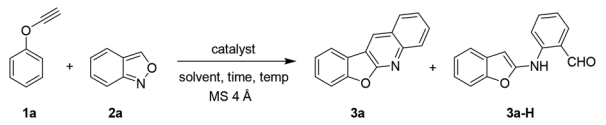
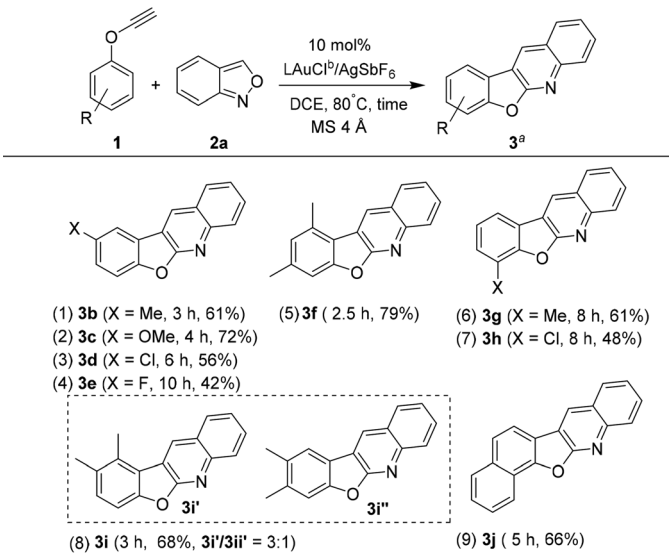
Table 1 Catalytic annulations with various gold catalysts



Entry	Catalyst (10 mol%)	Solvent	Time (h)	Temp (°C)	Yields[a] 3a	3a-H
1	LAuCl/$AgNTf_2$[b]	DCE	16	80	55	25
2	$PPh_3AuCl/AgNTf_2$	DCE	09	80	43	29
3	$(PhO_3)PAuCl/AgNTf_2$	DCE	12	80	33	40
4	IPrAuCl/$AgNTf_2$[c]	DCE	16	80	32	48
5	*t*-BuXPhosAuCl/$AgNTf_2$	DCE	10	80	50	30
6	LAuCl/$AgSbF_6$	DCE	08	80	68	—
7	LAuCl/AgOTf	DCE	12	80	54	18
8	$AgSbF_6$	DCE	20	80	—	10
9	LAuCl/$AgSbF_6$	Toluene	05	110	60	18
10	LAuCl/$AgSbF_6$	THF	15	60	61	11
11	LAuCl/$AgSbF_6$	DCM	20	40	—	25
12	LAuCl/$AgSbF_6$[d]	DCE	06	80	74	—

1a (0.2 M, 1.0 equiv.). [a] Product yields are obtained after purification from a silica column. [b] L = P(*t*-Bu)$_2$(*o*-biphenyl). [c] IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene. [d] $Zn(OTf)_2$ (20 mol%) was added with a gold catalyst in entry 12.

Table 2 Catalytic annulations with various phenoxyethynes



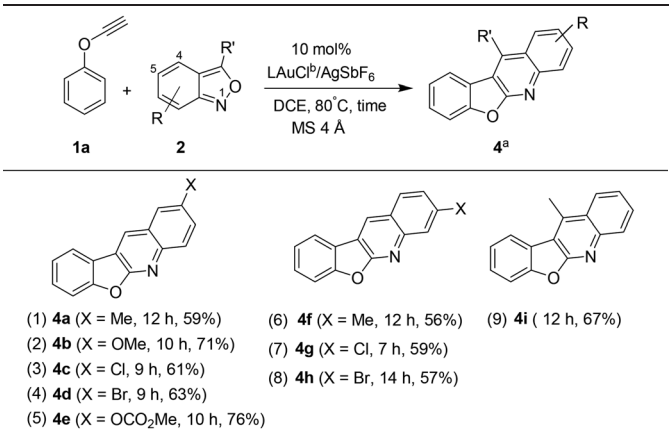
1 (0.2 M, 1.0 equiv.). [a] Product yields are obtained after purification from a silica column. [b] L = P(*t*-Bu)$_2$(*o*-biphenyl).

using 10 mol% P(*t*-Bu)$_2$(*o*-biphenyl)/$AgNTf_2$, affording the annulation product **3a** and the uncyclized benzofuran product **3a-H** in 55% and 25% yields, respectively (entry 1). We attempted to improve the yields of the desired **3a** with LAuCl/$AgNTf_2$ (L = PPh_3, $P(OPh)_3$, IPr and *t*-BuXPhos, entries 2–5), giving species **3a** in 50–43% yields, together with benzofuran **3a-H** in large amounts (29–48% yields). We thus switched to gold catalysts with different silver salts as in P(*t*-Bu)$_2$-(*o*-biphenyl)AuCl/AgX (X = SbF_6 and OTf); only $AgSbF_6$ was able to yield furoquinoline **3a** in 68% yield (entries 6–7). $AgSbF_6$ alone gave a complicated mixture of products in hot DCE (80 °C, 20 h, entry 8). For P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/$AgSbF_6$, its reactions in other solvents gave the following results (entries 9–11): toluene (**3a**, 60%), THF (**3a**, 61%), DCM (**3a-H** 25%). Compound **3a** was characterized using X-ray diffraction to confirm its benzofuro [2,3-*b*]quinoline framework.[12]

With these optimized conditions, we examined the generality of these new annulations with various aryloxyethynes **1** and benzisoxazole **2a**; the results are summarized in Table 2. For 4-substituted phenoxyalkynes **1b–1e** bearing electron-donating and -withdrawing groups X = Me, OMe, Cl and F, their resulting products **3b–3e** were obtained in 42%–72% yields (entries 1–4). Electron-rich aryl derivatives (X = Me, OMe) are expected to be more efficient because of their superior nucleophilicity toward gold carbenes. 3,5-Dimethylphenoxyalkyne **1f** yielded the desired benzofuro[2,3-*b*]quinoline **3f** in 79% yield (entry 5). The reaction was operable also with *ortho*-substituted phenoxy species **1g** and **1h**, delivering compound **3g** and **3h** with 61% and 48% yield, respectively (entries 6–7). The 3,4-disubstituted substrate **1i** produced two inseparable regioisomers **3i′** and **3i″**, in a 3 : 1 ratio; the combined yield was 68% (entry 8). Notably, the major regioisomer **3i′** arose from the electrophilic addition at the more hindered C–H aryl carbon. The reaction was extensible to 1-naphthoxyethyne **1j** to deliver compound **3j** in 67% yield (entry 9).

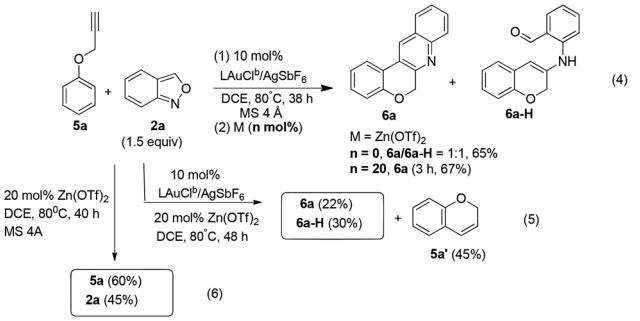
We assessed also the scope of these annulations with various anthranils (**2a–2i**), as shown in Table 3. For species **2a–2e** bearing various 5-phenyl substituents (X = Me, OMe, Cl, Br and OCO_2Me), their annulations with phenoxyethyne **1a** afforded new 6*H*-chromeno[3,4-*b*]quinoline derivatives **4a–4e** with reasonable yields (59–76%, entries 1–5). In the case of the anthranils **2f**, **2g** and **2h** bearing a C(6)-substituent, X = Me, Cl and Br, their corresponding products **4f**, **4g** and **4h** were obtained in reasonable yields (56–59%, entries 6–8). We examined the reaction on 3-substituted anthranil **2i** (R′ = Me), that afforded the desired product **4i** in 67% yield (entry 9).

Table 3 Catalytic annulations with various benzoisoxazoles



1a (0.2 M, 1.0 equiv.). [a] Product yields are obtained after purification from a silica column. [b] L = P(*t*-Bu)$_2$(*o*-biphenyl).

We sought new heterocycles using phenyl propargyl ether **5a**, anthranil **2a** (1.5 equiv.) and P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/$AgSbF_6$ in hot DCE (eqn (4)). Under standard operation, this mixture gave 6*H*-chromeno[3,4-*b*]quinoline **6a** and an uncyclized oxacycle **6a-H** in 1 : 1 molar ratio; the combined yields were 65%. When this system was added with $Zn(OTf)_2$ (20 mol%) after the gold reactions, the desired compound **6a** was produced exclusively with 67% yield; Zn(II) likely coordinates with the aldehyde to increase its electrophilicity to accelerate the final enamine/carbonyl cyclization. If the two reactants were treated with P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/$AgSbF_6$ (10 mol%) and $Zn(OTf)_2$ (20 mol%) initially in hot DCE, a by-product **5a′** was obtained in 45% yield together with compounds **6a** and **6a-H** (eqn (5)). $Zn(OTf)_2$ showed no catalytic activity toward this reactant mixture (eqn (6)). In eqn (4), we replaced $Zn(OTf)_2$ with $Sc(OTf)_3$, $GaCl_3$ and $Cu(OTf)_2$, each at 20 mol% loading, in this two-step reaction, but compound **6a-H** still remained uncyclized in 30–35% yields.



We assessed the scope of this 6*H*-chromeno[3,4-*b*]quinoline synthesis with various propargyl ethers **5** and anthranils **2** with a relay Au(I)/Zn(II) catalysis;[13] the results appear in Table 4. For ethers **5b–5e** bearing *para*-phenoxy groups (X = Me, OMe, Cl and Br), their annulations delivered the desired heterocycles **6b–6e** in 56–66% yields (entries 1–5). The regioselectivity with *meta*-substituted phenoxy compound **5f** was tested to give two isolable regioisomers **6f′** and **6f″** in 3 : 1 ratio; the major isomer **6f′** occurred from an addition at the less-hindered carbon of the phenyl group. Notably, this annulation works well on C(3)-alkyl-substituted propargyl ethers (R^2 = Me and *t*-Bu), yielding the desired products **6g** and **6h** in 51 and 59% yields, respectively. Such new heterocycles were compatible with C(5)-substituted anthranils (R^3 = Me and Br, entries 9–10), forming the desired heterocycles **6i** and **6j** in 72–81% yields. For C(6)-substituted anthranils (R^4 = OMe and Cl), their resulting compounds **6k** and **6l** were produced satisfactorily with 76–84% yields (entries 11–12). We tested the reactions on C(3)-phenyl anthranil (R^5 = Ph), yielding the desired compound **6m** in 57% yield (entry 13).

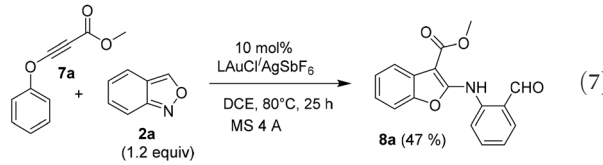
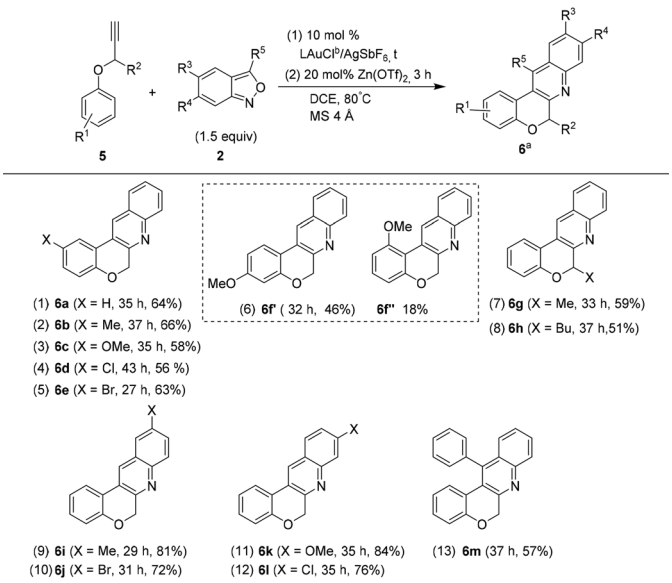
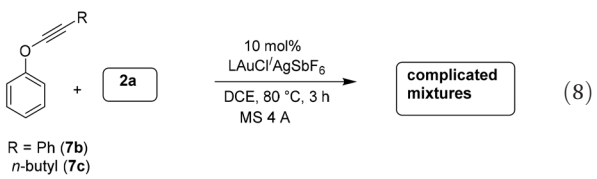


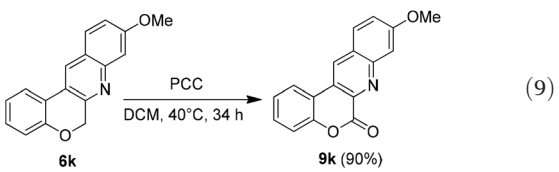
Table 4 Annulations of aryl propargyl ethers with anthranils



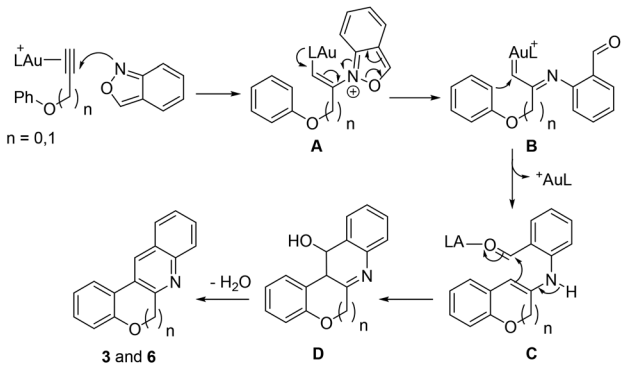
5 (0.19 M), **2** (1.5 equiv.). [a] Product yields are obtained after purification from a silica column. [b] L = P(*t*-Bu)$_2$(*o*-biphenyl).



We also prepared internal alkyne substrates **7a–c** to examine their catalytic activity. As shown in eqn (7), the gold-catalyzed annulation of an alkynoate derivative **7a** yielded compound **8a** in 47% yield (eqn (7)). For phenyl- and *n*-butyl-substituted alkynes **7b–c**, their reactions led to a complicated mixture of products (eqn (8)). For the six-membered oxacycle **6k**, its methylene group was readily oxidized with PCC to yield the lactone product **9k**, representing a distinct class of heterocycles (eqn (9)).



Scheme 1 shows a proposed mechanism of this gold-catalyzed annulation. An initial *N*-attack of anthranil **2a** at the π-alkyne complexes **1a** generated the alkenylgold species **A**, further producing the α-imino gold carbene **B** *via* cleavage of the N–O bond. This path is typical for the addition of isoxazoles or anthranils at Au-π-alkynes. A further arylation at the gold carbenes is expected to yield an oxacyclic intermediate **C** that was isolated in our catalytic system. A further carbonyl-enamine reaction generates an alcohol **D** that undergoes aromatization to give the observed products.



Scheme 1 A plausible mechanism.

Conclusions

This work reports the gold-catalyzed annulations of anthranils with aryloxyethynes or aryl propargyl ethers to yield useful benzofuro[2,3-*b*]quinoline and 6*H*-chromeno[3,4-*b*]quinoline derivatives, respectively; the former has exhibited potent biological activity but the reported synthetic procedures are long and inefficient. Our new synthesis employs readily available aryloxyethynes or aryl propargyl ethers and anthranils in a one pot operation. The mechanism of the reaction involves sequential cyclizations of an aryl group, a gold carbene and a benzaldehyde. The utility of this new synthetic strategy is highlighted by a broad substrate scope.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

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12 Crystallographic data of compound **3a** have been deposited at the Cambridge Crystallographic Data Centre: **3a** CCDC 1897138.†

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