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Gold-catalysed *N*-allenamide cyclisation as a platform for the construction of indole-fused quinoxaline and quinoline scaffolds

Silvia Meraviglia, Mehri Goudarzi, Simone Borsi, Giorgio Abbiati and Valentina Pirovano *

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We report a gold-catalysed cyclisation of *N*-allenamides derived from 1- and 2-(2-aminoaryl)indoles, providing easy access to 5,6-dihydroindolo[1,2-*a*]quinoxalines and 6,11-dihydro-5*H*-indolo[3,2-*c*]quinolines. The reaction proceeds under mild conditions, tolerates diverse functional groups, and enables the synthesis of previously unexplored indole-fused heterocycles, whose versatility was demonstrated through selected post-functionalisation reactions.

Introduction

Polycyclic indoles are ubiquitous in natural products and pharmaceuticals, where they play key roles in modulating biological activity.[1] Among them, tetracyclic 5,6-dihydroindolo[1,2-*a*]quinoxalines and indolo[3,2-*c*]quinolines stand out as privileged scaffolds with diverse medicinal applications (Fig. 1).[2,3]

For example, indolo[1,2-*a*]quinoxaline **A** has shown promising antifungal activity against phytopathogenic fungi *in vitro*,[2a] whereas derivative **B** has been identified as an inhibitor of vascular endothelial growth factor receptor 3 (VEGFR-3), a target associated with cancer cell invasion and migration.[2b] In addition, Zheng and co-workers reported the anti-HIV properties of the 7-methyl-5,6-dihydroindolo[1,2-*a*]quinoxaline **C**, further underscoring the therapeutic relevance of this structural class.[2c] On the other hand, the 6,11-dihydro-indolo[3,2-*c*]quinoline derivative **D** has been investigated as a potential androgen receptor ligand,[3a] while the related indolo[3,2-*c*]quinoline **E** has displayed notable antimalarial properties.[3b] More recently, *in vitro* and *in vivo* studies revealed that indoloquindoline **F** exhibits a broad spectrum of antitumor activities.[3c]

Given their broad biological profiles, considerable effort has been devoted to developing efficient and versatile synthetic routes to these heterocycles. The most widely used approach to access 5,6-dihydroindolo[1,2-*a*]quinoxalines and 6,11-dihydro-5*H*-indolo[3,2-*c*]quinolines, relies on the Pictet–Spengler reaction between (2-aminoaryl)indoles and a carbonyl compound.[2a,b,3c,4] Complementary methods based on transition metal-catalysis have been explored, including systems based on ruthenium,[5] platinium,[6] palladium,[7] copper,[8] molybdenum,[9] scandium[10] and rhodium.[11] Gold catalysis has likewise emerged as a powerful tool for constructing these frameworks (Scheme 1). For example, Patil and co-workers reported the cyclization of 2-(1*H*-indol-1-yl)anilines and 2-(1*H*-indol-2-yl)anilines with phenylacetylene under cationic gold(I) catalysis (Scheme 1a),[12] while Liu employed a gold(I)-catalysed domino processes with alkynoic acids to generate related polycyclic derivatives (Scheme 1b).[13] A gold(III) catalyst has also been used to prepare 6,6-disubstituted 6,11-dihydro-5*H*-indolo[3,2-*c*]quinolones from 2-[(2-aminophenyl)ethynyl]phenylamines and ketones (Scheme 1c).[14] Beyond these precedents, gold-catalysed additions of N-, O-, and C-based nucleophiles to allenes

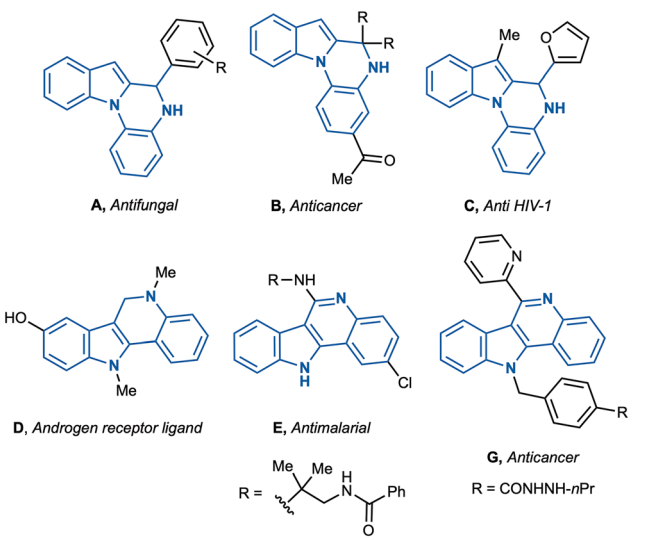
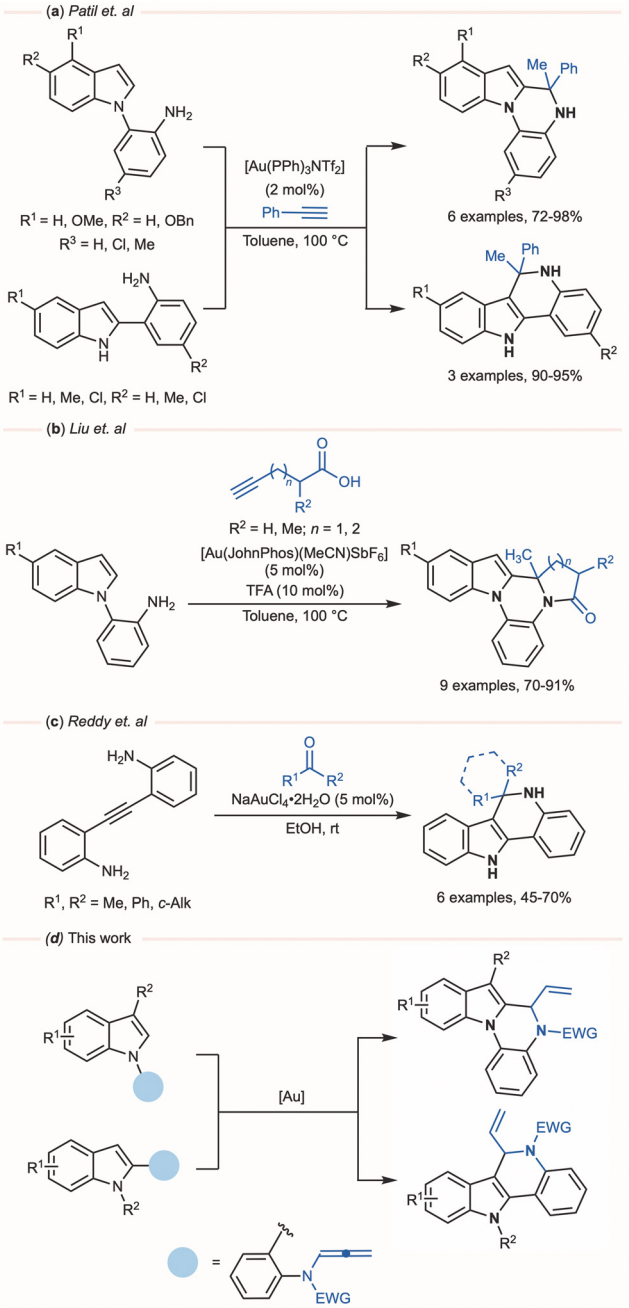


Fig. 1 Biologically relevant indoloquinoxalines/quinolines.

Dipartimento di Scienze Farmaceutiche, Sezione di Chimica Generale e Organica "A. Marchesini", Università degli Studi di Milano, Via Venezian, 21, 20133 Milano, Italy. E-mail: valentina.pirovano@unimi.it



Scheme 1 Gold-catalysed syntheses of 5,6-dihydroindolo[1,2-*a*]quinoxalines and 6,11-dihydro-5*H*-indolo[3,2-*c*]quinolines and our work.

have proven particularly attractive, owing to their high atom economy, excellent regioselectivity, and mild reaction conditions.[15] Despite the extensive study of these transformations, their application to the synthesis of indoloquinoxalines and indoloquinolines remains underexplored. Building on these premises and motivated by our group's long-standing interest in the assembly of complex indole architectures under gold catalysis,[16] we report herein a mild and efficient gold(I)-catalysed cyclization of *N*-allenamides derived from 1- and 2-(2-aminoaryl)indoles. This unified strategy provides streamlined access to both indolo[1,2-*a*]quinoxaline and indolo[3,2-*c*]quinoline derivatives (Scheme 1d).

Results and discussion

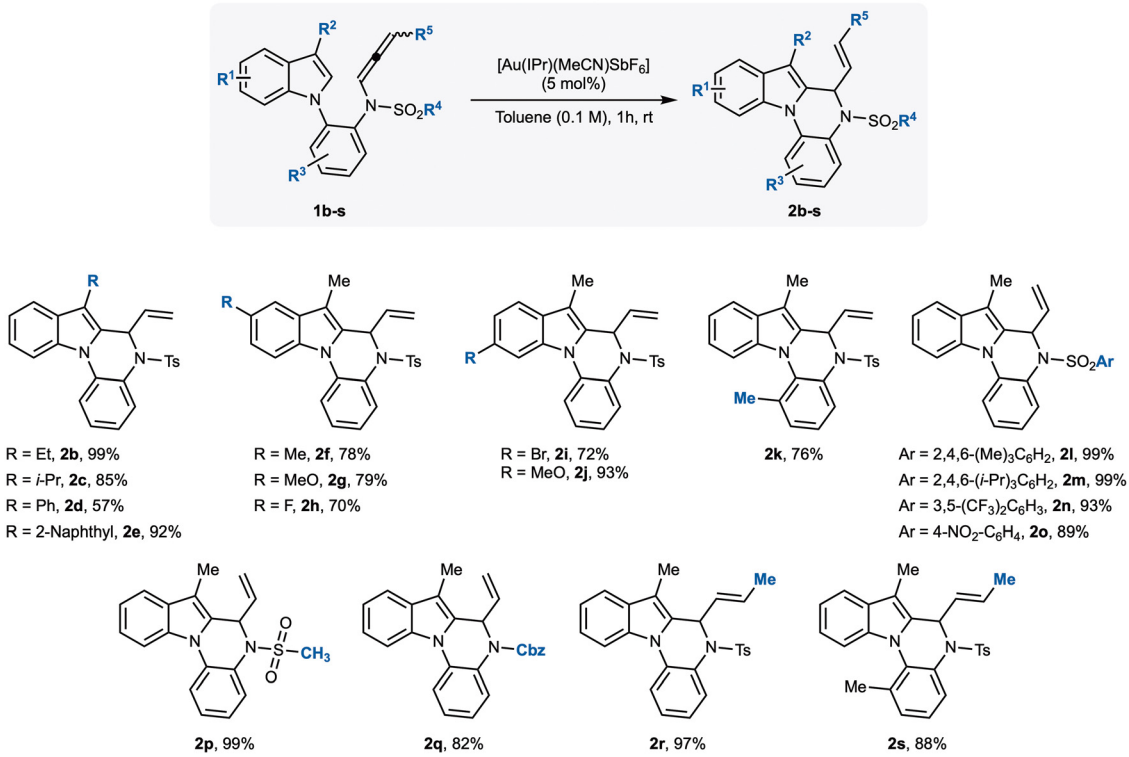
For the catalyst screening, a series of gold complexes bearing different ligands and counterions were evaluated (Table 1). In the initial experiments (entries 1–4), *N*-allenamide **1a** was reacted in dichloromethane at room temperature with cationic gold(I) complexes. In every case, the reaction proceeded to full conversion, affording product **2a** as the sole identifiable compound, although in variable yields. The phosphine complex $[Au(PPh_3)NTf_2]$ gave the lowest yield (23%, entry 4), while [Au(JohnPhos)NTf_2] and a gold(I) phosphite complex afforded 48% and 52% yield, respectively (entries 2 and 3). The highest efficiency was obtained with the cationic N-heterocyclic carbene complex $[Au(IPr)NTf_2]$, which delivered **2a**in 74% yield (entry 1). Besides **2a**, only unidentified degradation products were detected. To probe the influence of the counterion, [Au(IPr)(MeCN)SbF_6] was employed (entry 5), resulting in a slightly improved yield of 75%. Lowering the reaction temperature to −20 °C (entry 6) did not provide any advantage, instead giving a diminished yield of 62%. Changing the solvent had a more pronounced effect: in toluene, the yield increased to 84% (entry 7). Based on these results, the optimal conditions were established as those in entry 7: [Au(IPr)(MeCN)SbF_6], toluene, room temperature, 1 h. These parameters were then adopted for the subsequent scope studies.

Having established the optimal conditions, we next explored the generality of the transformation with a series of differently substituted *N*-allenamides **1b–s** (Scheme 2). We first examined modifications to the indole scaffold, focusing on substituents at the C^3-position. The methyl group of **1a** could

Table 1 Optimisation of reaction conditions[a]

Entry	[Au] (5 mol%)	Solvent (0.1 M)	**2a**[b] (%)
1	[Au(IPr)NTf_2]	CH_2Cl_2	74
2	[Au(JohnPhos)NTf_2]	CH_2Cl_2	48
3	[Au(ArO)$_3$PNTf_2]	CH_2Cl_2	52
4	[Au(PPh_3)NTf_2]	CH_2Cl_2	23
5	[Au(IPr)(MeCN)SbF_6]	CH_2Cl_2	75
6[c]	[Au(IPr)(MeCN)SbF_6]	CH_2Cl_2	62
7	[Au(IPr)(MeCN)SbF_6]	Toluene	84

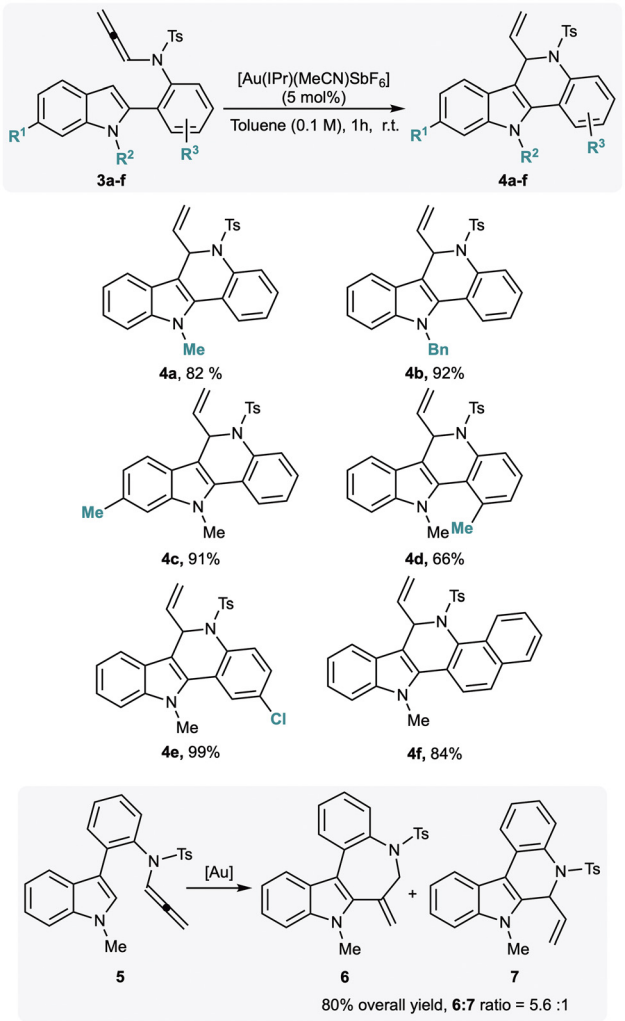
[a] Reaction conditions: **1a** (0.1 mmol), [Au] (5 mol%), in anhydrous solvent (1 ml, 0.1 M) at rt for 1 h. [b] Isolated yield. [c] Reaction performed at −20 °C. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; JohnPhos = (2-biphenyl)di-*tert*-butylphosphine; Ar = 2,4-di-*tert*-butylphenyl.



Scheme 2 Scope of the reaction. Reaction conditions: **1b–s** (0.1 mmol), [Au(IPr)(MeCN)SbF$_6$] (5 mol%), in anhydrous toluene (1 ml, 0.1 M) at rt for 1 h. Isolated yields are reported.

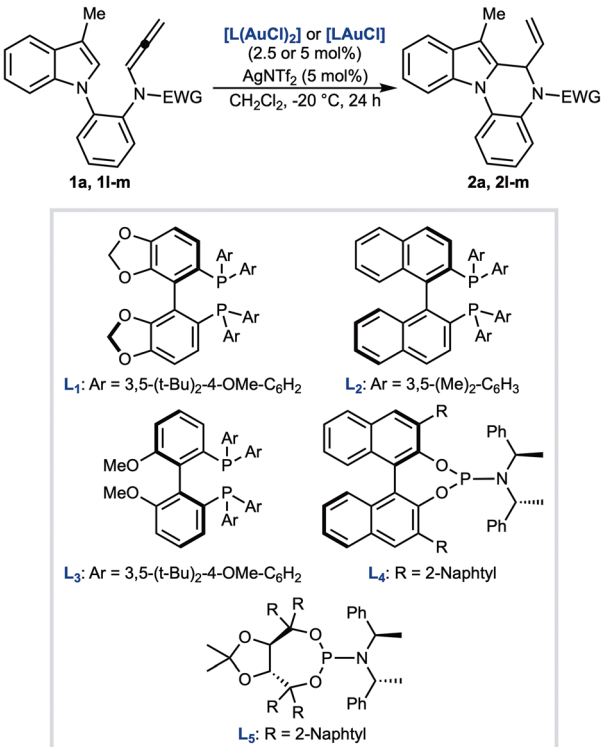
be successfully replaced with an ethyl (**1b**), iso-propyl (**1c**), phenyl (**1d**), or naphthyl group (**1e**), and in all cases the corresponding products were obtained in good to excellent yields, reaching up to 99% for the ethyl derivative. Notably, substitution at C^3 proved essential: the unsubstituted C^3–H derivative decomposed completely under the optimised conditions, without affording any detectable cyclic product. We then investigated electronic effects at the C^5- and C^6-positions of the indole ring. Allenamides **1f–j**, bearing either electron-donating or electron-withdrawing groups, were synthesised and tested. Methyl- and methoxy-substituted substrates (**1f** and **1g**) delivered the corresponding indolo[1,2-*a*]quinoxalines **2f** and **2g** in comparable yields (78% and 79%, respectively). In contrast, the introduction of a fluorine atom at C^5 resulted in a slightly diminished yield of **2h** (70%). More pronounced effects were observed with C^6-substitution: the 6-methoxy-substituted allenamide **1j** reacted efficiently to furnish **2j** in 93% yield, whereas the bromo derivative **1i** gave a lower 72% yield. We further evaluated modifications on the aniline core. An *ortho*-substituent on the aniline ring negatively impacted reactivity, as observed for **1k**, which furnished a reduced yield of the corresponding product **2k**. In contrast, the tosyl group could be successfully replaced with alternative sulfonyl protecting groups, including mesitylenesulfonyl (**2l**), 2,4,6-triisopropylbenzenesulfonyl (**2m**), 3,5-difluorobenzenesulfonyl (**2n**), and 4-nitrobenzenesulfonyl (**2o**), all affording the corresponding indolo[1,2-*a*]quinoxalines in excellent yields. The methanesulfonyl derivative **2p** was obtained in quantitative yield, further underscoring the tolerance of the transformation toward sulfonyl substituents. Finally, the aniline nitrogen could also be protected with a carbobenzyloxy (Cbz) group, with allenamide **1q** undergoing smooth cyclisation to provide **2q** in 82% yield. Extension to allenamides **1r** and **1s**, bearing non-terminal allenes, delivered the desired products **2r** and **2s** as single stereoisomers in 97% and 88% yield, respectively.

To expand the scope of our methodology and to assess its potential for constructing other indole-fused heterocyclic scaffolds, we synthesised the isomeric allenamides **3** and **5**, in which the aniline core was relocated from the indole nitrogen to the C^2- and C^3-positions, respectively. Both substrates were subjected to the optimised cyclisation conditions, and the results are summarised in Scheme 3. The C^2-functionalised allenamide **3a** (R^1 = H, R^2 = Me) underwent smooth cyclisation to afford the 6,11-dihydro-5*H*-indolo[3,2-*c*]quinoline derivative **4a** in 82% yield. Encouraged by this result, we briefly explored the reaction scope further. Substitution of the *N*-methyl group with a benzyl group furnished the corresponding product **4b** in 92% yield. Introduction of a methyl substituent at the C^5-position afforded compound **4c** in 91% yield. Modifications on the C^2-aryl ring were also tolerated: allenamides **3d–f**, bearing methyl, chloro, or naphthyl substituents, delivered the corresponding indolo[3,2-*c*]quinolines **4d–f** in yields ranging from moderate (**4d**, 66%) to excellent (**4e**, 99%). In contrast, the use of the C^3-functionalized allenamide **5** proved less successful.



Scheme 3 Expansion of the reaction scope to C^2- and C^3-allenamides **3** and **5**. Reaction conditions: **3a–f** or **5** (0.1 mmol), [Au(IPr)(MeCN)SbF$_6$)] (5 mol%), in anhydrous toluene (1 ml, 0.1 M) at rt for 1 h. Isolated yields are reported.

Table 2 Enantioselective version of the reaction[a]



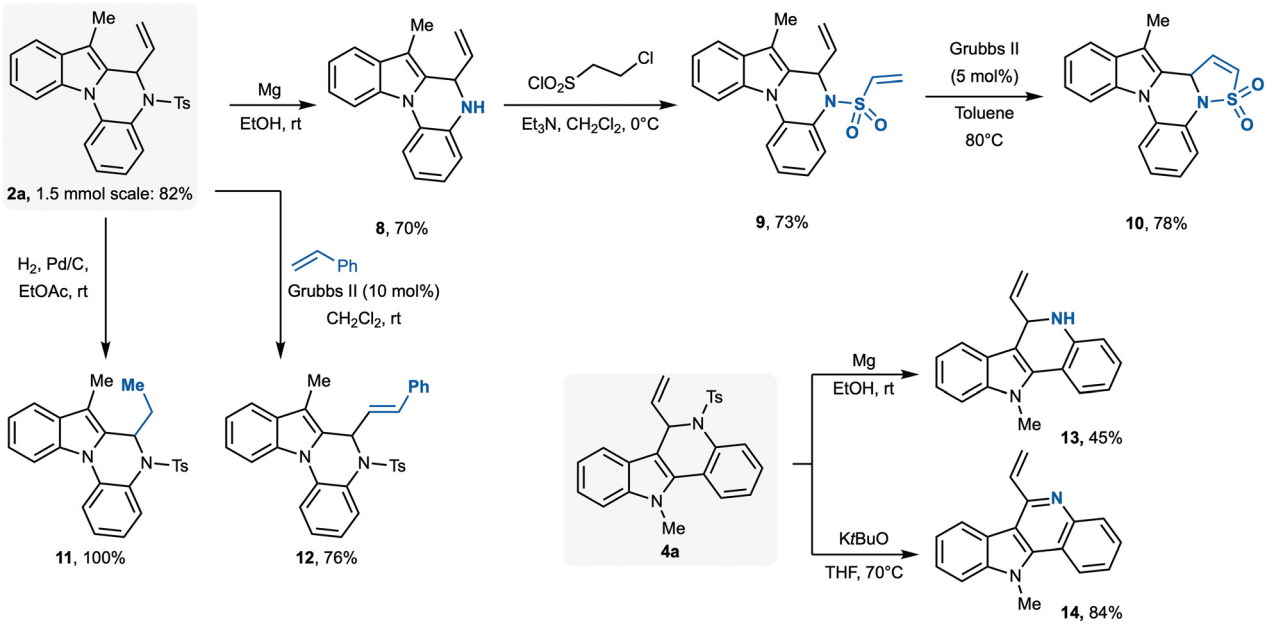
Entry	1	[Au]	2[b] (%)	er[c]
1	**1a**	[$L_1(AuCl)_2$]	40	77 : 23
2	**1a**	[$L_2(AuCl)_2$]	31	69 : 31
3	**1a**	[$L_3(AuCl)_2$]	72	79 : 21
4	**1a**	[L_4AuCl]	39	53 : 47
5	**1a**	[L_5AuCl]	72	72 : 28
6	**1l**	[$L_3(AuCl)_2$]	31	86 : 14
7	**1m**	[$L_3(AuCl)_2$]	31	53 : 47

[a] Reaction conditions: **1** (0.1 mmol), [Au] (2.5 or 5 mol%), $AgNTf_2$ (5 mol%) in anhydrous CH_2Cl_2, (0.1 M) at −20 °C for 24 h. [b] Isolated yield. [c] Enantiomeric ratios (er) determined by chiral HPLC. See SI for full experimental details.

Under the optimised gold-catalysed conditions, this substrate underwent cyclisation to give a mixture of the seven-membered and six-membered derivatives **6** and **7**, which were isolated in an overall 80% yield (**6** : **7** ratio = 5.6 : 1). These results highlight the sensitivity of the cyclization outcome to the substitution pattern of the indole framework.

The presence of a chiral center in indolo[1,2-*a*]quinoxalines **2** prompted us to develop an enantioselective version of the reaction. To this end, the cyclization of **1a** was examined in the presence of different chiral gold complexes (Table 2; see SI for the full screening). Bidentate complexes derived from (*R*)-DTBM-SEGPHOS (L_1) or (*R*)-DM-BINAP (L_2) generally afforded **2a** in low to moderate yields, while the enantioinduction was limited, with the best results obtained using L_1 (77 : 23 er, entries 1 and 2). Improved results were achieved with L_3, a member of the BIPHEP family, which delivered **2a** in 72% yield and 79 : 21 er (entry 3). Monodentate ligands such as the BINOL- and TADDOL-derived phosphoramidites L_4 and L_5 did not perform better: L_4 gave racemic **2a** in modest yield (entry 4), whereas L_5 furnished **2a** in 72% yield and 72 : 28 er (entry 5). Further variations of ligands, solvents, and counterions were explored, but none of them provided superior results compared to those obtained with L_3 (entry 3). To address this limitation, we replaced the tosyl group of the allenamide with bulkier aryl sulfonyl rings. Accordingly, allenes **1l** and **1m** were reacted in the presence of $L_3(AuCl)_2/AgNTf_2$ catalytic system at −20 °C for 24 hours. In both cases, we observed a decrease of the yield (31%), and only for **2l** the er was improved up to 86 : 14 (entries 6 and 7).

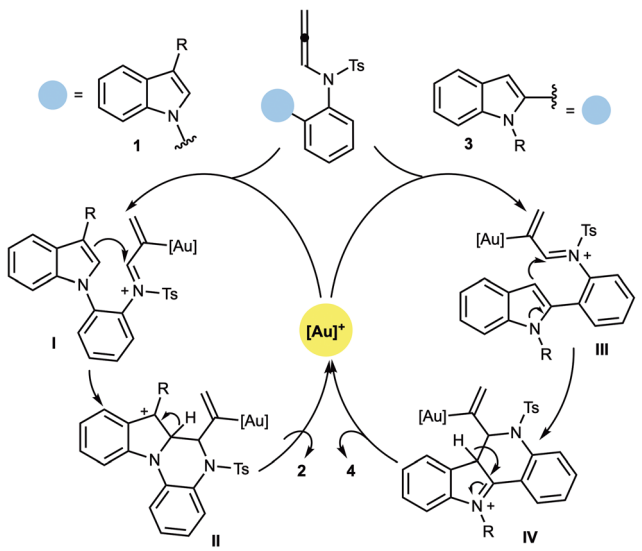
Finally, we explored the synthetic utility of the methodology by subjecting product **2a** to a series of functional group transformations (Scheme 4). To this end, its synthesis was scaled up to 1.5 mmol, affording **2a** in 82% yield. Removal of the tosyl group was achieved using magnesium in ethanol, and the



Scheme 4 Synthetic transformations of **2a** and **4a**.

corresponding NH-free derivative **8** was isolated in 70% yield. Subsequent treatment of **8** with 2-chloroethane-1-sulfonyl chloride under basic conditions provided **9** in 73% yield. An intramolecular olefin metathesis reaction, promoted by the Hoveyda–Grubbs II catalyst, furnished **10**, characterized by the presence of a cyclic sulfone group. Then, the exocyclic double bond of **2a** could be smoothly hydrogenated to give **11** quantitatively, while an intermolecular ruthenium-catalysed metathesis with styrene afforded **12** in 76% yield. Similarly, also tosyl group of **4a**, could be easily removed to give NH-free derivative **13**, while treatment with potassium *t*-butoxide led to indolo[3,2-*c*]quinoline **14** in 84% yield.

On the basis of established reactivity patterns of *N*-allenamides under gold catalysis,[15b,d] a plausible mechanistic pathway is proposed in Scheme 5 to rationalise the formation of indoloquinoxalines **2** and indoloquinolines **4**. Coordination of the allene moiety in substrates **1** or **3** to the electrophilic gold species generates the corresponding aurated iminium intermediates **I** or **III**. Intramolecular nucleophilic attack of the indole core (at C^2 for **1**, and at C^3 for **3**) onto the α-carbon of the activated allene then furnishes intermediates **II** or **IV**, respectively. Subsequent aromatisation and protodeauration deliver the corresponding cyclised products **2** and **4**



Scheme 5 Proposed reaction mechanism.

Conclusions

In summary, we have developed a gold-catalysed cyclization of *N*-allenamides derived from 1- and 2-(2-aminoaryl)indoles that provides efficient access to 5,6-dihydroindolo[1,2-*a*]quinoxalines and 6,11-dihydro-5*H*-indolo[3,2-*c*]quinolines. The methodology features mild conditions, broad substrate scope, and high functional group tolerance, while also enabling the synthesis of previously unexplored indole-fused heterocyclic scaffolds. The synthetic utility of the products was further demonstrated through a variety of post-functionalisation reactions, highlighting their potential as versatile building blocks. Given the prevalence of indole-based polycyclic structures in bioactive molecules and functional materials, we anticipate that this methodology will find broad application in the development of new heteroaromatic architectures.

Author contributions

S. M.: conceptualisation, investigation, validation, writing – original draft, data curation. M. G.: investigation, validation, writing – original draft, data curation. S. B.: investigation, data curation. G. A.: conceptualisation, writing – review & editing. V. P.: conceptualisation, funding acquisition, methodology, supervision, writing – original draft.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: synthesis and characterisation of products, NMR spectra and full screening of enantioselective reaction. See DOI: https://doi.org/10.1039/d5ob01867f.

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