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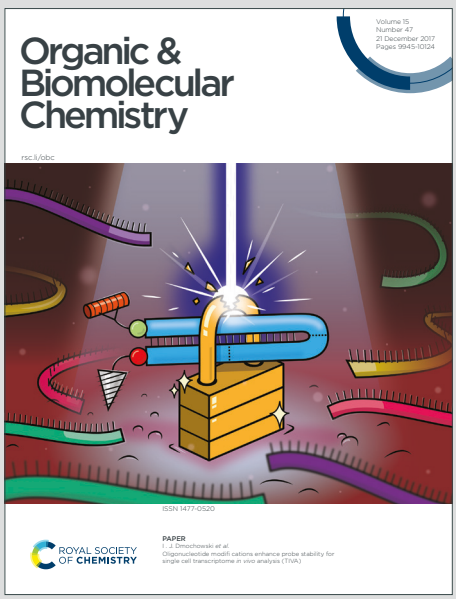

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ARTICLE

Gold-Catalysed *N*-Allenamide Cyclisation as a Platform for the Construction of Indole-Fused Quinoxaline and Quinoline Scaffolds

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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 (Figure 1).[2,3]

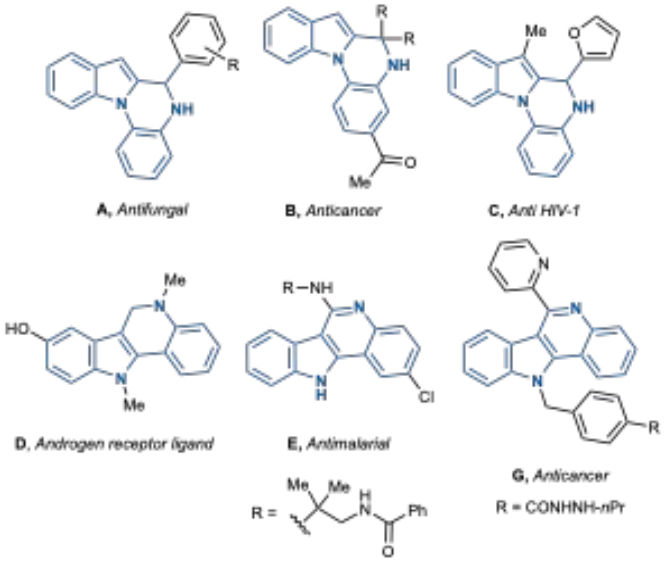

Figure 1. Biologically relevant indoloquinoxalines/quinolines.

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,2b,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 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

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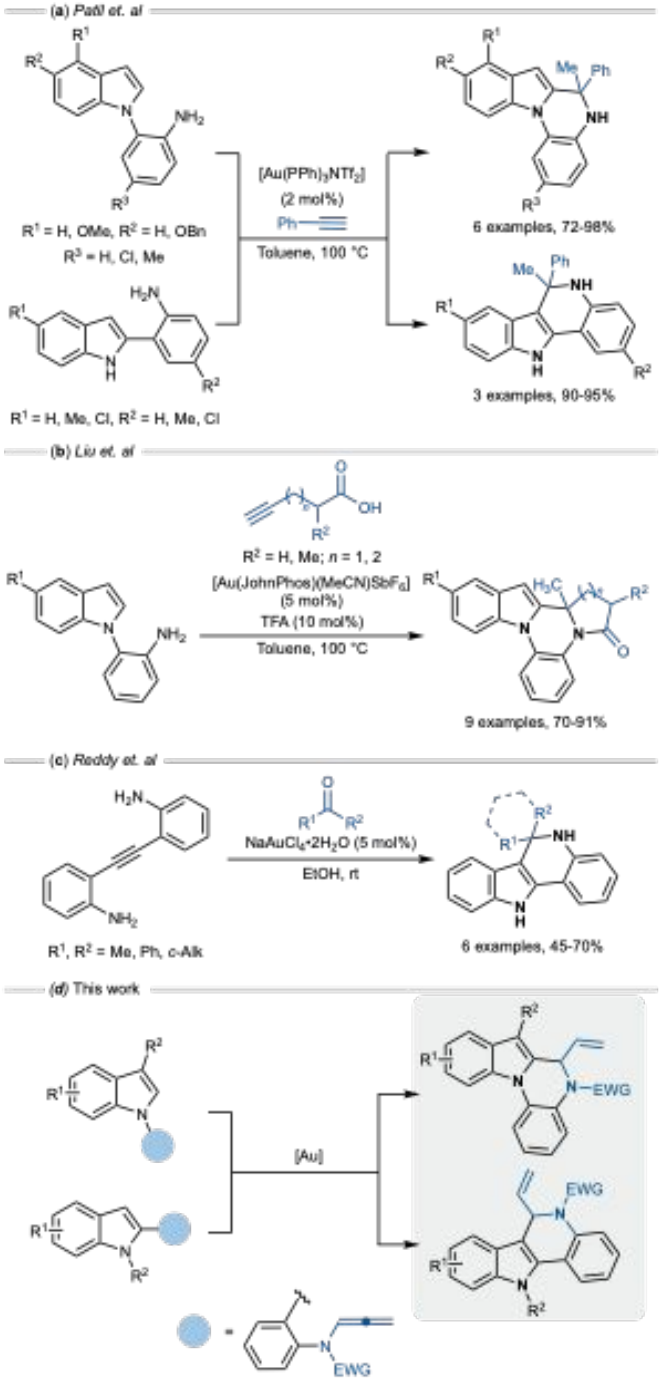
of complex indole architectures under gold catalysis,[16] we report herein a mild and efficient gold(I)-catalysed cyclization of *N*-allenamides derived from 1- and 2-(2-aminoaryl)indoles. This unified strategy provides streamlined access to both indolo[1,2-*a*]quinoxaline and indolo[3,2-*c*]quinoline derivatives (Scheme 1d).

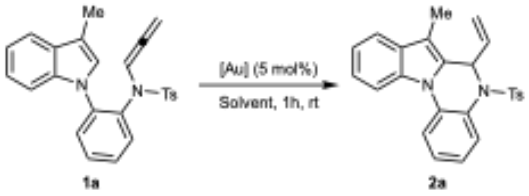


Scheme 1: Gold-catalysed syntheses of 5,6-dihydroindolo[1,2-*a*]quinoxalines and 6,11-dihydro-5*H*-indolo[3,2-*c*]quinolines and our work.

Results and discussion

For the catalyst screening, a series of gold complexes bearing different ligands and counterions were evaluated. 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.

Table 1: Optimisation of reaction conditions



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.

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 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

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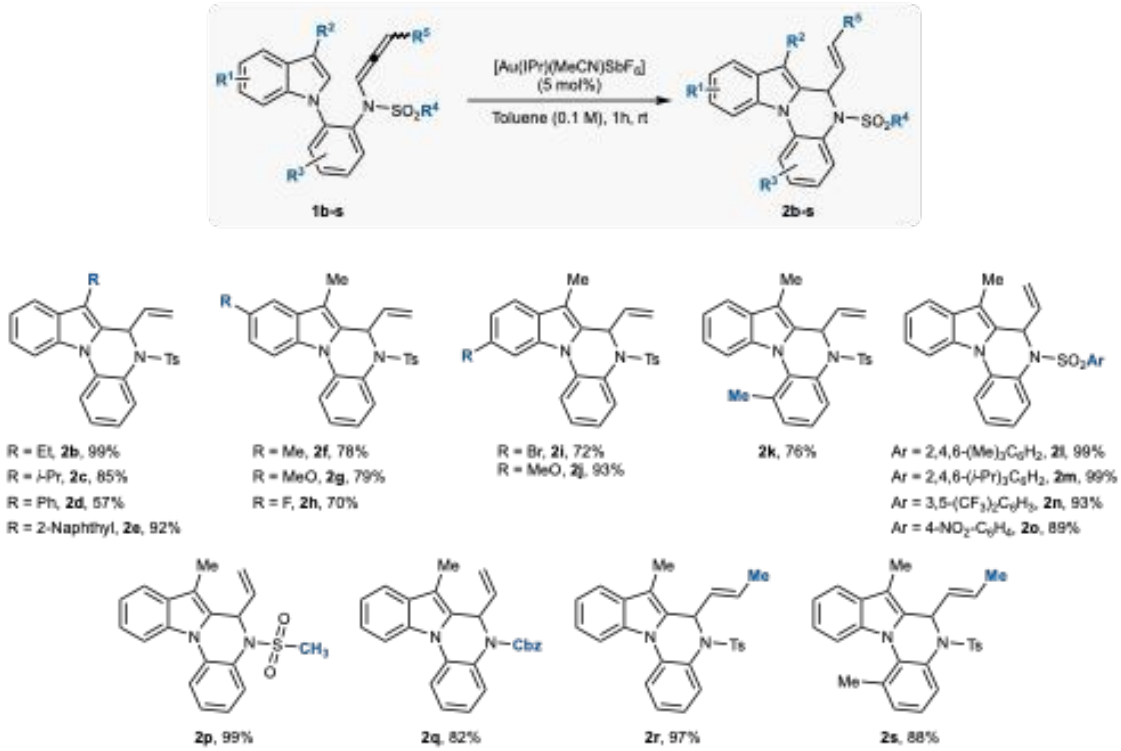
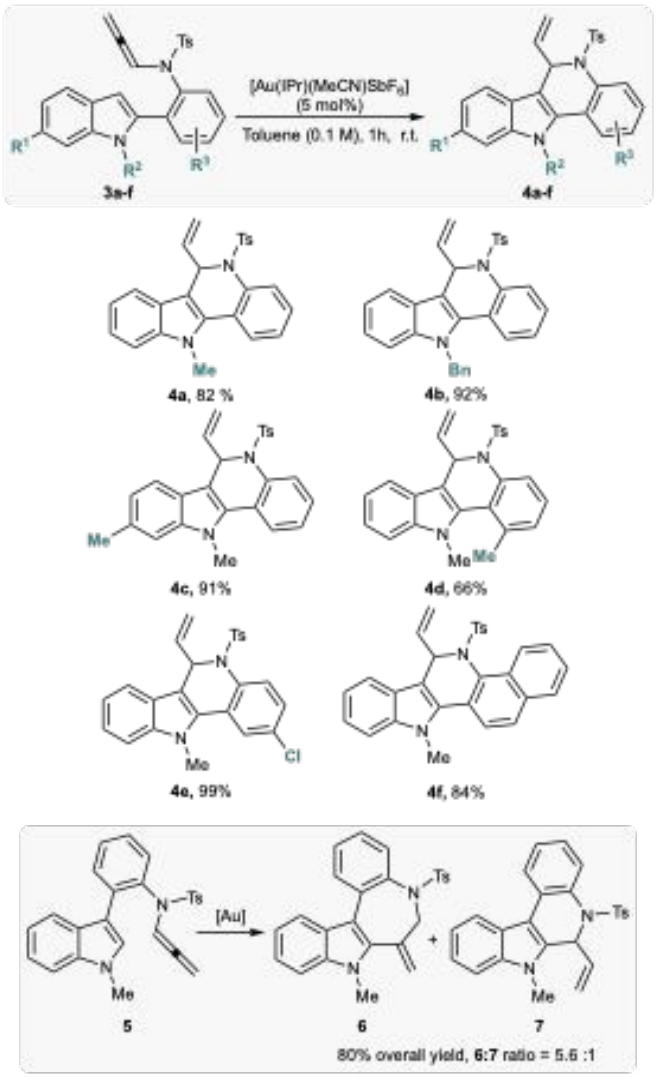
completely under the optimised conditions, without affording any detectable cyclic product. We then investigated electronic effects at the C^5- and C^6- positions of the indole ring. Allenamides **1f–j**, bearing either electron-donating or electron-withdrawing groups, were synthesised and tested. Methyl- 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.



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.

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. 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

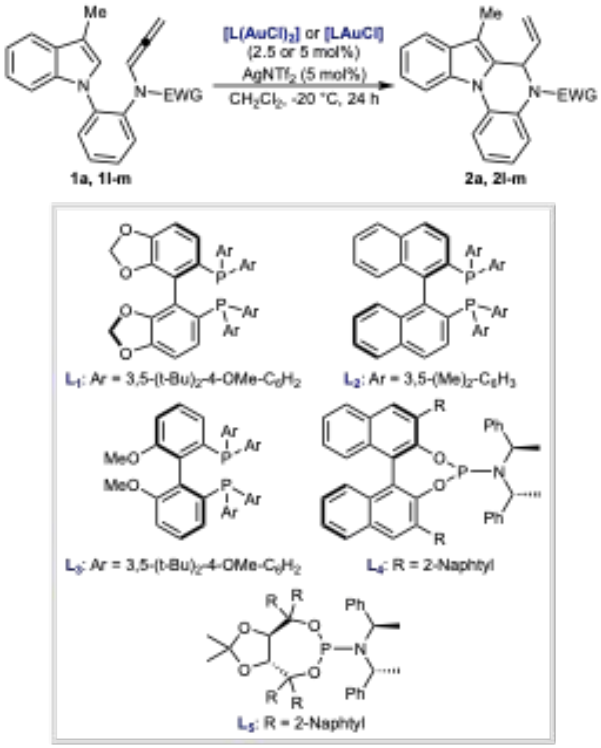
the sensitivity of the cyclization outcome to the substitution pattern of the indole framework.



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.

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 ESI 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 *e.r.*, entries 1–2). Improved results were achieved with **L_3**, a member of the BIPHEP family, which delivered **2a** in 72% yield and 79:21 *e.r.* (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 *e.r.* (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 *e.r.* was improved up to 86:14 (entries 6 and 7).

Table 2: Enantioselective version of the reaction[a]



Entry	**1**	[Au]	**2**(%)[b]	*e.r.*[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 hs. [b]Isolated yield. [c]Enantiomeric ratios (*e.r.*) determined by chiral HPLC. See Supporting Information for full experimental details.

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 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

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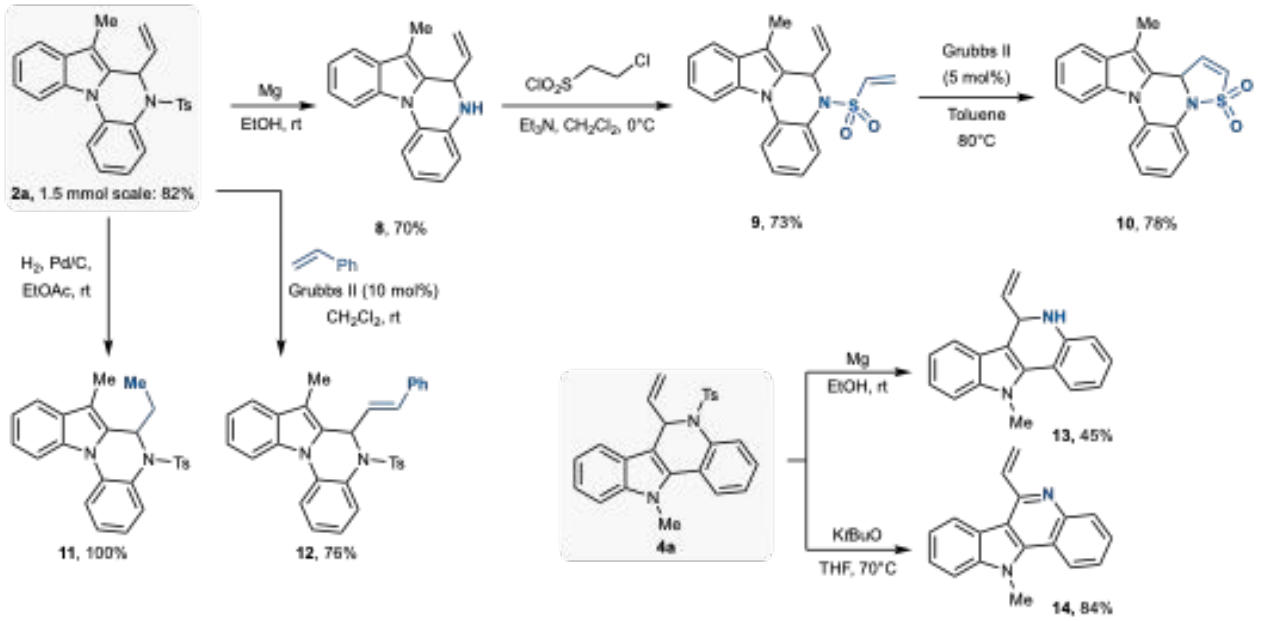
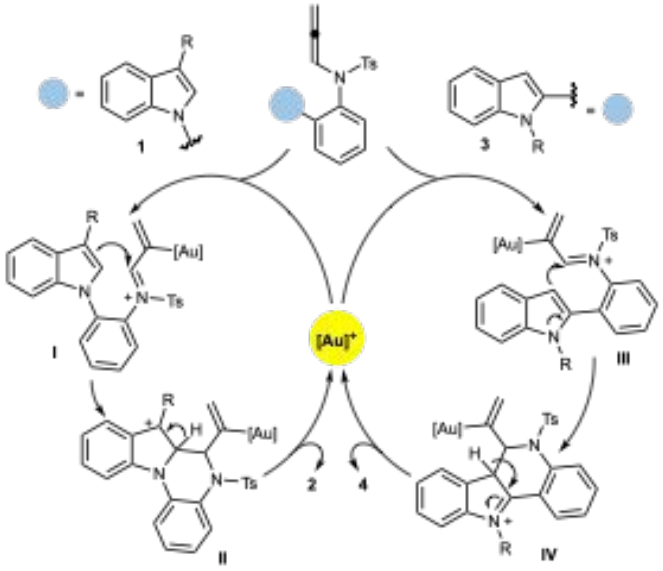
presence of a cyclic sulfone group. Then, the exocyclic double bond of **2a** could be smoothly hydrogenated to give **11** quantitatively, while an intermolecular ruthenium-catalysed metathesis with styrene afforded **12** in 76% yield. Similarly, also tosyl group of **4a**, could be easily removed to give NH-free derivative **13**, while treatment with potassium *t*-butoxide led to indolo[3,2-*c*]quinoline **14** in 84% yield.



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

On the basis of established reactivity patterns of N-allenamides under gold catalysis, [15b,15d] 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. Supplementary Information includes synthesis and characterisation of products, NMR spectra and full screening of enantioselective reaction.

Acknowledgements

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Data availability

The data supporting this article have been included as part of the Supplementary Information. Supplementary Information includes synthesis and characterisation of products, NMR spectra and full screening of enantioselective reaction.