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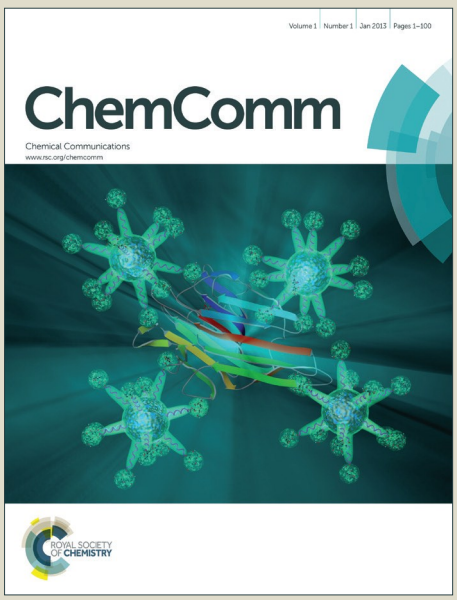

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Gold(I)-Catalyzed Highly Stereoselective Synthesis of Polycyclic Indolines: Construction of Four Contiguous Stereocenters

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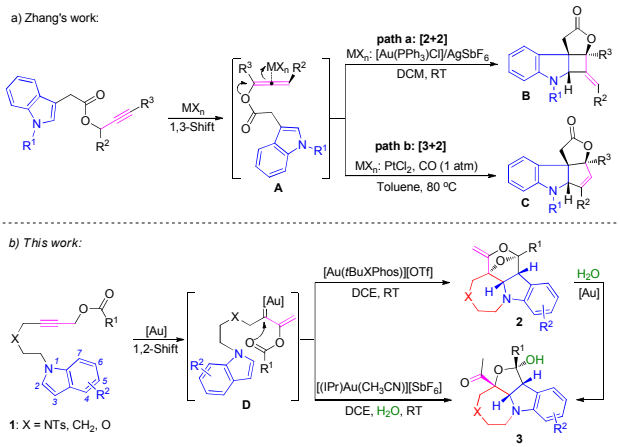
A convenient and efficient synthetic method has been developed to construct highly functionalized polycyclic indoline skeletons with four contiguous stereocenters, which are of great importance in biological and pharmaceutical chemistry. Selective formation of either the oxabridged-ring or ring-opening polycyclic indoline derivatives can be controlled by using different gold catalytic systems. A variety of polycyclic indoline derivatives were obtained in moderate to good yields under mild conditions along with moderate to excellent enantioselectivities.

The indoline moiety is a privileged heterocyclic substructure in many biologically active natural products and pharmaceutically valuable compounds.[1] Among these polyheterocycles, the structurally diverse and biologically interesting azepino[*a*]indoline skeletons, which feature a fused seven-membered ring through the N1–C2 connection, are of great importance because of their well-represented and wide distribution in pharmaceutical chemistry. For instance, azepino[*a*]indoline-based agonists were found to be a potential drug candidate for the treatment of anxiety[2a] as well as promising inhibitors against human protein kinases.[2b] To date, most documents have been concentrated on the synthesis of 2,3-fused indolines.[3] To the best of our knowledge, however, 1,2-fused indolines, especially azepino[*a*]indolines, have been prepared in a few cases.[4] Thus, the development of an efficient synthetic method to build such polyheterocyclic skeletons is in need.

Gold catalysis, which is currently a hot topic in homogeneous catalysis, can be well understood with the concept of carbophilic π-acids, which are widely employed in the activation of C–C multiple bonds.[5] In particular, gold-catalyzed cyclization of indole derivatives have attracted much attention owing to the efficient synthesis of polyheterocyclic skeletons.[6-9] Thus far, the research groups of Bandini,[6] Zhang,[7] Echavarren[8] and others[9] have intensively investigated the diverse transformations of these substrates. In 2005, the pioneering work on the intramolecular cyclization of indolyl propargylic esters catalyzed by Au^{I} species to afford polycyclic indolines **B** through [2+2] cycloaddition was reported by Zhang[7a] and co-workers. Afterwards, by varying the metal catalyst into Pt^{II}, they developed a rapid access to tetracyclic 2,3-indoline-fused cyclopentenes **C** from the same substrates[7b] (Scheme 1a). Very recently, Toste[9b] et al. reported a highly enantioselective dearomative Rautenstrauch rearrangement catalyzed by cationic gold(I), providing a straightforward method to prepare enantioenriched cyclopenta[*b*]indolines. As a part of our ongoing interest in indole derivatives and propargylic esters,[10] we have already reported several interesting transformations from indole substrates as well as propargylic esters.[11] Based on these findings, we envisaged that indoles bearing propargylic esters might undergo very interesting transformations. To our great delight, upon treatment of substrates **1** with a gold catalyst, polycyclic indolines **2** and **3** could be obtained selectively through a gold vinyl carbene intermediate **D**. Notably, the oxabridged-ring products **2** would be transformed into ring-

Scheme 1. Previous and our work on the synthesis of polycyclic indolines.



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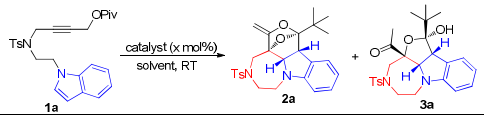
opening products **3** in the presence of water and the gold catalyst (Scheme 1b).

Initially, we started our investigation by using model substrate **1a**, 5 mol% of [Au(*t*BuXPhos)][OTf] in anhydrous DCE (1,2-dichloroethane) at room temperature (RT), giving the polycyclic oxabridged-ring product **2a** in 95% yield after 2 h (Table 1, entry 1). However, when **1a** was treated with [Au(Me$_4$*t*BuXPhos)(CH$_3$CN)][SbF$_6$], no reaction occurred, presumably due to the steric effect of the phosphine ligand (Table 1, entry 2) (for their structures, see Figure S1 in the Supporting Information). Using [(IPr)Au(CH$_3$CN)][SbF$_6$] (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) as the catalyst, we obtained a different polycyclic ring-opening product **3a** in 70% yield instead of the desired product **2a** perhaps due to the ambient water (Table 1, entry 2). The structure of **3a** has been unequivocally confirmed by X-ray diffraction.[12] The use of cationic gold(I) complex [Au(*n*BuPAd$_2$)(CH$_3$CN)][SbF$_6$] led to an increase of the yield of **3a** to 89% (Table 1, entry 4). With an electron-deficient phosphite P(OAr)$_3$ as the ligand, an inferior result was obtained (Table 1, entry 5). The reaction efficiency was significantly improved by the addition of 1.0 equivalent of water (Table 1, entries 3 and 6). 5 mol% of [Ph$_3$PAuCl]/AgNTf$_2$ did not give a better result (Table 1, entry 7). Furthermore, decreasing the employed amount of catalyst did not have significant impact on the reaction outcome (Table 1, entry 8). Thus, finally, we established the optimal reaction conditions: 5 mol% of [Au(*t*BuXPhos)][OTf] in anhydrous DCE at room temperature for the synthesis of compound **2a** or 2.5 mol% of [(IPr)Au(CH$_3$CN)][SbF$_6$] in wet DCE (anhydrous DCE with the addition of 1.0 equiv of H$_2$O) at room temperature for the synthesis of compound **3a**.

Table 1. Optimization of the Reaction Conditions.

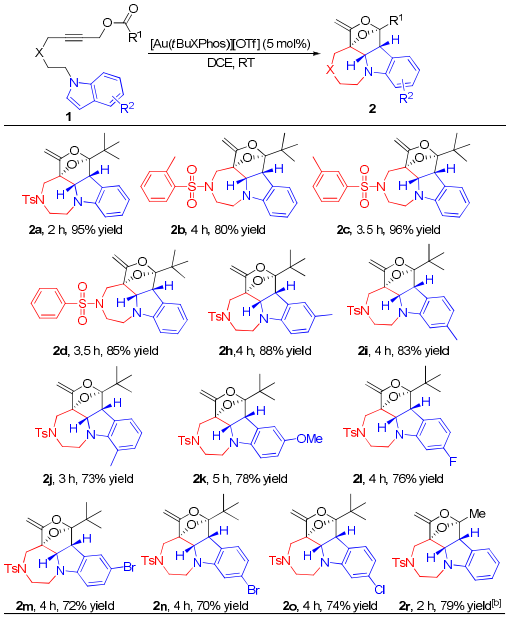


entry[a]	catalyst (x mol%)	solvent	H_2O (y eq.)	time	yield (%)[b] 2a	3a
1	[Au(*t*BuXPhos)][OTf] (5)	DCE	-	2 h	95	0
2	[Au(Me$_4$*t*BuXPhos)(CH$_3$CN)][SbF$_6$] (5)	DCE	-	6 h	0	0
3	[(IPr)Au(CH$_3$CN)][SbF$_6$] (5)	DCE	-	2 h	0	70
4	[Au(*n*BuPAd$_2$)(CH$_3$CN)][SbF$_6$] (5)	DCE	-	4 h	0	89
5	[(ArO)$_3$PAu][NTf$_2$] (5)	DCE	-	4 h	0	70
6	[(IPr)Au(CH$_3$CN)][SbF$_6$] (5)	DCE	1.0	2 h	0	85
7	[Ph$_3$PAuCl] (5)/AgNTf$_2$ (5)	DCE	1.0	1 h	0	74
8	[(IPr)Au(CH$_3$CN)][SbF$_6$] (2.5)	DCE	1.0	5 h	0	86

[a] All reactions were carried out using **1a** (0.1 mmol) in the presence of catalyst (x mol%) in DCE (1.0 mL) unless otherwise specified. [b] Isolated yields. Ar = 2,4-di-tert-butylphenyl. DCE = 1,2-dichloroethane.

With the optimized conditions in hand, we turned our attention to determine the scope and limitations of the reaction in the presence of [Au(*t*BuXPhos)][OTf]. As summarized in Table 2, all of the reactions proceeded smoothly to afford the corresponding products **2a**-**d** in good to excellent yields upon isolation (80-96%) when R^1 sulfonyl group was *p*-, *o*-, *m*-methylbenzenesulfonyl or benzenesulfonyl. Next, the scope of this transformation with respect to the indole moiety was examined. Substrates bearing either electron-donating (5-Me, 6-Me, 7-Me, 5-OMe) or electron-withdrawing (6-F, 5-Br, 6-Br, 6-Cl) groups on the indole core all afforded the corresponding products **2h**-**o** in moderate to good yields. Furthermore, the substrate **1r** bearing an acetyl (MeC(O)-) moiety instead of pivaloyl (Piv, **1a**) as the migrating group was also suitable for this cyclization. The structure of **2r** has been unequivocally confirmed by X-ray diffraction.[12]

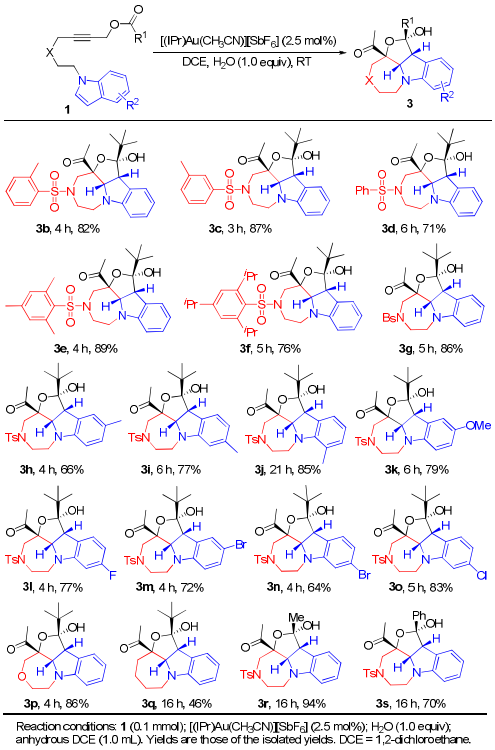
Table 2. Substrate scope of the reaction in the presence of [Au(*t*BuXPhos)][OTf].



[a] Reaction conditions: **1** (0.1 mmol); [Au(*t*BuXPhos)][OTf] (5 mol%); anhydrous DCE (1.0 mL). Yields are those of the isolated yields. [b] 2.5 mol% of [(IPr)Au(CH$_3$CN)][SbF$_6$] was used as the catalyst.

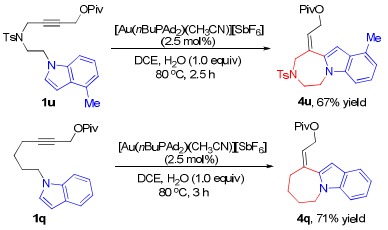
Next, further examinations were performed to extend the scope of this cyclization in the presence of [(IPr)Au(CH$_3$CN)][SbF$_6$] (Table 3). As can be seen from Table 3, substrates **1a**-**g** bearing *o*-, *m*-methylbenzenesulfonyl, benzenesulfonyl mesitylenesulfonyl (Mes), 2,4,6-triisopropylbenzenesulfonyl and *p*-bromobenzenesulfonyl (Bs) groups all gave the desired products **3a**-**g** in 71-89% yields, indicating that the electronic properties and steric effects of the sulfonyl group did not have significant impact on the reaction outcome. Meanwhile, a variety of substrates bearing either electron-donating (**1h**-**k**) or electron-withdrawing (**1l**-**o**) substituents on the indole core worked smoothly, furnishing the corresponding polycyclic adducts **3h**-**o** in 64-85% yields. Moreover, the oxygen- or carbon-tethered substrates **1p** and **1q** were also suitable for this cyclization, providing the desired products in reasonable yields. Furthermore, reactions of starting materials with an acetyl (MeC(O)-, **1r**) or a pendant benzoyl (Bz, **1s**) group were found to be well-tolerated under the standard conditions, furnishing the corresponding products **3r**-**s** in 94% and 70% yields, respectively. Moreover, we also tested a substrate bearing 4-Me on the indole core (**1u**), however the reaction became very complex under the optimized conditions. This might be due to the steric hindrance of the methyl group with the *tert*-butyl group, and therefore, the formal [3+2] cycloaddition was blocked out. Using [Au(*n*BuPAd$_2$)(CH$_3$CN)][SbF$_6$] instead of [(IPr)Au(CH$_3$CN)][SbF$_6$] as the catalyst afforded a new product **4u** through a 7-*exo*-dig cyclization process (Scheme 2).[8] Substrate **1q** also gave **4q** in 71% yield with this gold catalyst through the same reaction pathway (Scheme 2). When the migrating group was carbobenzyloxy (Cbz, X = NTs, **1t**), no reaction occurred under the standard conditions.

Table 3. Substrate scope of the reaction in the presence of [(IPr)Au(CH$_3$CN)][SbF$_6$].



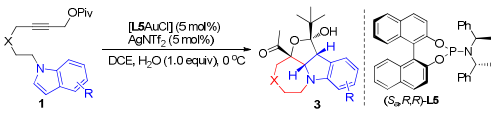
Reaction conditions: **1** (0.1 mmol); [(IPr)Au(CH$_3$CN)][SbF$_6$] (2.5 mol%); H$_2$O (1.0 equiv); anhydrous DCE (1.0 mL). Yields are those of the isolated yields. DCE = 1,2-dichloroethane.

Scheme 2. Different reaction pathway.



Driven by the demand to construct highly enantioenriched polycyclic indolines through asymmetric gold catalysis,[11a,13] which still remains a challenging topic because of the linear geometry of the gold(I) complexes, we thus attempted asymmetric synthesis of these polycyclic indolines. The results of our examination of the enantioselective cyclization of **1a** are shown in Table S1 (see Supporting Information for the details). Among the commonly used chiral phosphine ligands, the use of Feringa phosphoramidite **L5**[14] resulted in the best enantioselectivity. Optimization of the reaction conditions revealed that carrying out the reaction in DCE at 0 °C with AgNTf$_2$ as the co-catalyst was the best condition for this asymmetric reaction. Next, we performed the reaction under the optimized conditions to synthesize enantioenriched polycyclic indolines **3** and the results are summarized in Table 4. Substrates **1c**-**f** bearing *m*-methylbenzenesulfonyl, benzenesulfonyl, mesitylenesulfonyl (Mes) and 2,4,6-triisopropylbenzenesulfonyl groups gave the desired products **3c**-**f** in moderate yields along with good to excellent *ee* values (Table 4, entries 1-4). Meanwhile, a range of substituents at 5-, 6-, and 7-positions of the indole moieties were well tolerated, affording the desired products in 46-88% yields with 62-82% *ee* values, regardless of whether they were electron-donating or electron-withdrawing groups (Table 4, entries 5-11) (for more information, see Table S2 in the Supporting Information).

Table 4. Substrate scope of enantioselective Au(I)-catalyzed cyclization of **1**.

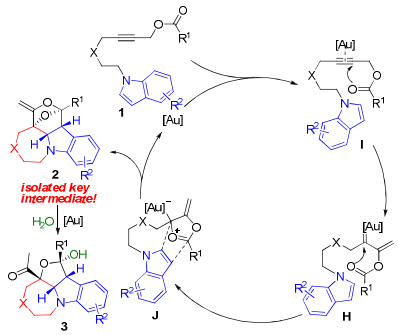


entry[a]	1	X	R	time [days]	3	yield [%][b]	ee [%][c]
1	**1c**	3-MeC$_6$H$_4$SO$_2$N	H	2	**3c**	60	80
2	**1d**	PhSO$_2$N	H	2	**3d**	43	90
3	**1e**	MesSO$_2$N	H	2	**3e**	51	83
4	**1f**	2,4,6-*i*Pr$_3$C$_6$H$_2$SO$_2$N	H	2	**3f**	40	91
5	**1h**	TsN	5-Me	2	**3h**	50	74
6	**1i**	TsN	6-Me	0.5	**3i**	46	71
7	**1j**	TsN	7-Me	2	**3j**	88	81
8	**1k**	TsN	5-OMe	2	**3k**	62	82
9	**1l**	TsN	6-F	0.5	**3l**	72	82
10[d]	**1m**	TsN	5-Br	2	**3m**	66	62
11	**1n**	TsN	6-Br	1	**3n**	85	82

[a] Reaction conditions: **1** (0.1 mmol), [**L5**AuCl] (5 mol%), AgNTf$_2$ (5 mol%), H$_2$O (1.0 equiv), anhydrous DCE (1.0 mL). [b] Yields are those of the isolated yields. [c] Determined by HPLC on a chiral stationary phase. [d] Reaction was performed at room temperature. DCE = 1,2-dichloroethane.

A plausible mechanism for this reaction is outlined in Scheme 3 on the basis of previous literature.[10g,l] Gold(I) activation of the triple bond in **1** promotes the formation of gold carbene intermediate **H** through a 1,2-acyloxy migration. A nucleophilic attack of the carbonyl group to the gold carbene results in the formation of the 1,3-dipolar intermediate **J**, which undergoes a [3+2] cycloaddition with C2−C3 of the indole moiety to afford the vinyl ketal product **2** and regenerate the gold catalyst. Finally, hydrolysis of **2** by water provides the ring-opening product **3**. Notably, **2a** was found to be stable overnight upon exposure to 3.0 equivalent of water in DCE, but was easily converted into **3a** in 86% yield when treated again with 2.5 mol% of [(IPr)Au(CH$_3$CN)][SbF$_6$] (see Scheme S6 in the Supporting Information), thus suggesting the critical role of the gold catalyst during the ring-opening event.

Scheme 3. A plausible reaction mechanism.



In conclusion, we have developed a highly efficient and accessible gold(I)-catalyzed intramolecular cyclization of indolyl propargylic esters. A variety of polycyclic indolines bearing four contiguous stereocenters are obtained in moderate to excellent yields under mild conditions in high stereoselectivities with wide azepine ring flexibility (N, C, O). The reaction mechanism is proposed on the basis of control experiments and isolated key intermediates.

Further applications of this chemistry and more detailed mechanistic investigations are underway in our laboratory.

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12 The molecular structures of products **2r** and **3a** have been determined by means of X-ray crystallographic studies. Their ORTEP drawings and the corresponding CIF data have been presented in the Supporting Information.

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Journal Name

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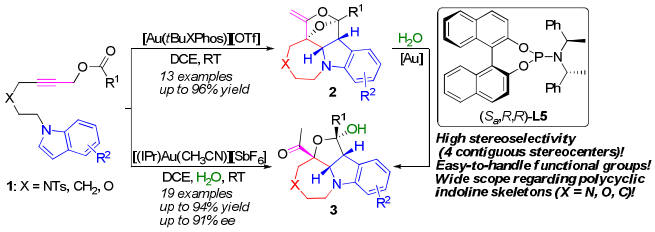
Gold(I)-Catalyzed Highly Stereoselective Synthesis of Polycyclic Indolines: Construction of Four Contiguous Stereocenters

A convenient and efficient synthetic method has been developed to construct highly functionalized polycyclic indoline skeletons with four contiguous stereocenters



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