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SHORT COMMUNICATION

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Gold-Catalyzed 5-*endo-dig* Cyclization of 2-[(2-Aminophenyl)-ethynyl]phenylamine with Ketones for the Synthesis of Spiroindolone and Indolo[3,2-*c*]quinolone Scaffolds

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A tandem gold-catalyzed 5-*endo-dig*/spirocyclization of 2-[(2-aminophenyl)ethynyl]phenylamines with isatins was achieved to produce the corresponding 5′,11′-dihydrospiro-[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one derivatives in good yields with high regioselectivity. This reaction proceeded well at ambient temperature under mild conditions. Ketones also participated smoothly under similar conditions to produce 6,6-disubstituted-6,11-dihydro-5*H*-indolo[3,2-*c*]-quinolones.

Introduction

The design and synthesis of pharmaceutically relevant heterocycles in a one-pot strategy is still a challenging task for synthetic chemists. In particular, the spirooxindole motif is a privileged pharmacophore and is found in numerous naturally occurring alkaloids and pharmaceutically important lead compounds (Figure 1).[1–3] A few of these compounds have been reported as cell cycle regulators (spirotyprostatin A),[4] modulators of muscarinic M1 and 5-HT2 receptors (pteropodin),[5] and also as inhibitors of tubulin polymerization (spirotryprostatin B).[6] Among them, spiroindolones represent an important class of spirocycles owing to their promising antiplasmodial activity.[7] For instance, NITD609 was found to display potent antimalarial activity in a mouse model. Consequently, a large number of reports related to the synthesis of spirooxindoles have been developed over the last decade.[8] In view of the biological importance of spirooxindoles, there is a need to develop simple and more efficient synthetic protocols for their synthesis. Many naturally occurring alkaloids and biologically active molecules possess a 2-substituted indole motif as a core structure,[9] and these derivatives have displayed a broad spectrum of biological activities such as antiestrogen,[9b,9d] 5-HT2A antagonist,[9f] anti-inflammatory,[9a,9c] and cytotoxic behavior.[9e] Of various approaches, the hydroamination of 2-alkynylaniline has received special attention,[10] because it provides direct access to C2-functionalized indoles. Among various metal complexes, gold catalysts, owing to their unique alkynophilicity, have engrossed a significant role in facilitating cycloisomerization of a wide range of alkynes tethered with different nucleophiles.[11] These gold catalysts also act as Lewis acids for the activation of electrophiles[12] to facilitate C–C and C–X bond formation.

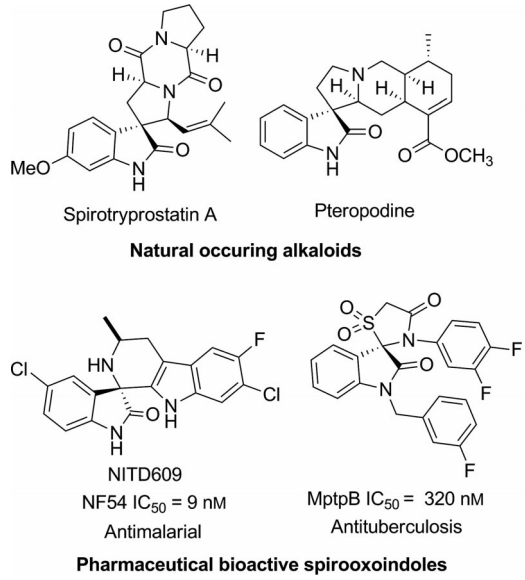

Figure 1. Spirooxindole-containing biologically active molecules.

Inspired by the unique catalytic properties of gold complexes, we also reported a domino reaction for the synthesis of tetrahydropyrido[4,3-*b*]indole scaffolds of pharmaceutical interest.[13] Following our interest in exploring novel routes for the synthesis of biologically active heterocycles

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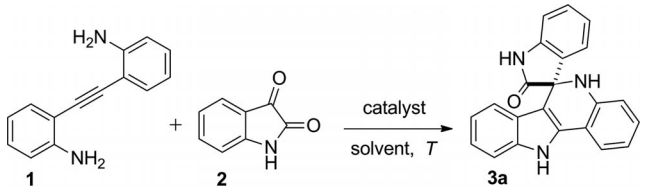
with high molecular complexity,[14] we herein report a novel strategy for the one-pot synthesis of spiroindolones from 2-[(2-aminophenyl)ethynyl]phenylamines and isatins through intramolecular hydroamination followed by Pictet–Spengler spirocyclization.

Results and Discussion

Accordingly, we first attempted the coupling of 2-[(2-aminophenyl)ethynyl]phenylamine (**1**) with isatin (**2**) in the presence of IPrAuCl [10 mol-%, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] and $AgSbF_6$ in 1,2-dichloroethane (DCE) at 25 °C. Interestingly, spiroindolone **3a** was isolated in 70% yield after 6 h (Table 1, Entry 6). Inspired by these promising results, we began a systematic screening of various Lewis acids such as $Cu(OTf)_2$, $In(OTf)_3$, and AgOTf (Tf = trifluoromethylsulfonyl) to improve the yield and reaction time. Only a trace amount of **3a** was obtained if the reaction was performed with $Cu(OTf)_2$ (10 mol-%) in DCE, although $Cu(OTf)_2$ is known to facilitate the intramolecular hydroamination of *N*-protected ethynylaniline[15] (Table 1, Entry 1).

Table 1. Screening of various catalysts in the formation of **3a**.[a]



1 2 3a

Entry	Catalyst (mol-%)	Solvent	*T* [°C]	Time [h]	Yield[b] [%]
1	$Cu(OTf)_2$	DCE	25	24	trace
2	$In(OTf)_3$ (10)	DCE	25	16	42[c]
3	$InCl_3$ (10)	DCE	25	7	60
4	AgOTf (10)	DCE	25	6	40
5	PPh_3AuCl (10)	DCE	25	12	20[c]
6	PPh_3AuCl + $AgSbF_6$ (10)	DCE	25	8	70
7	AuIPrCl + AgOTf (10)	DCE	25	6	68
8	$NaAuCl_4{\cdot}2H_2O$ (10)	EtOH	25	1.5	85
9	$NaAuCl_4{\cdot}2H_2O$ (5)	EtOH	25	1.5	85
10	$NaAuCl_4{\cdot}2H_2O$ (5)	CH_3CN	25	1.5	81
11	AuCl (10)	DCE	25	20	55
12	AuCl (10)	DCE	80	12	80

[a] Reactions were performed with **1** (0.50 mmol, 1.1 equiv.) and **2a** (0.45 mmol, 1.0 equiv.) in dry solvent (2 mL). [b] Yield of isolated product after column chromatography. [c] Both an intermediate and isatin were recovered.

Similarly, other metal triflates such as $In(OTf)_3$ and AgOTf also afforded desired adduct **3a** in low yields (42 and 40%, respectively; Table 1, Entries 2 and 4). A slight increase in the yield was observed if the reaction was performed by using $InCl_3$ (10 mol-%) in DCE at room temperature (Table 1, Entry 3). To know the catalytic efficacy of various gold complexes, we next performed the reaction by using PPh_3AuCl, PPh_3AuCl/AgOTf, $NaAuCl_4{\cdot}2H_2O$, and AuCl. To our surprise, neither Ph_3PAuCl nor its combination with an Ag^I salt was efficient or the optimal catalyst for this reaction, and product **3a** was obtained in only moderate yield (Table 1, Entries 5 and 6). Similarly, a low yield of product **3a** was obtained if the reaction was performed by using AuCl (10 mol-%) in DCE at 25 °C (Table 1, Entries 11 and 12). Indeed, an improved yield of **3a** was achieved by using $NaAuCl_4{\cdot}2H_2O$ (10 mol-%) in EtOH at 25 °C within 1.5 h (Table 1, Entry 8). To our delight, a similar yield and selectivity were observed even by reducing the catalyst loading to 5 mol-% in ethanol. However, the yield of **3a** slightly decreased to 81% if ethanol was replaced by acetonitrile (Table 1, Entry 10). The reason may be attributed to the poor solubility of isatin. After screening several gold catalysts, the best conversions were achieved by employing $NaAuCl_4{\cdot}2H_2O$ (5 mol-%) in ethanol at 25 °C, and these conditions were chosen as the optimized conditions (Table 1).

The scope of the reaction was further evaluated with respect to various isatins. As shown in Table 2, a wide range of mono- and disubstituted isatin derivatives participated well in this reaction to generate the dihydrospiro[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one derivatives, which are analogues of the Novartis antimalarial lead compound NITD609. Notably, several functional groups including halides, NO_2, and OCF_3 on the aromatic ring were well tolerated under the reaction conditions. Gratifyingly, *N*-protected isatin derivatives, including substrates with methyl, allyl, and benzyl protecting groups, also gave the desired products in fairly good yields (66–75%; Table 2, Entries 10–12). In the case of 4,7-dichloroisatin, the product was obtained in low yield after a long reaction time, which may be due to steric hindrance of the 4,7-dichloro substituents (53%, 6 h; Table 2, Entry 13). However, the electronic effects of the substituents on the aromatic ring did not show any catalytic effect on the outcome of the reaction. Thus, a series of dihydrospiroindolones were successfully synthesized in good yields by using this protocol (Table 2).

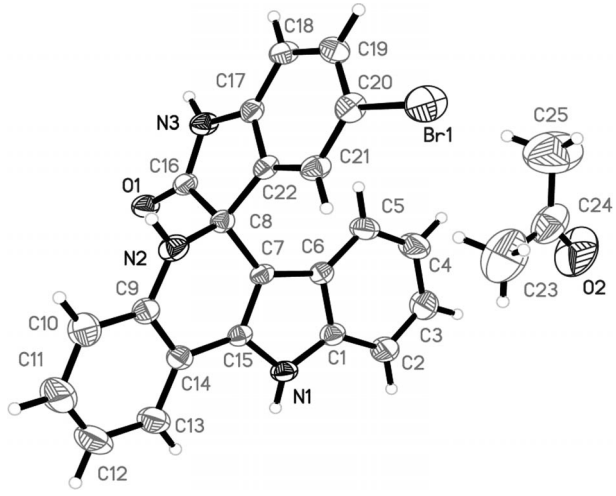
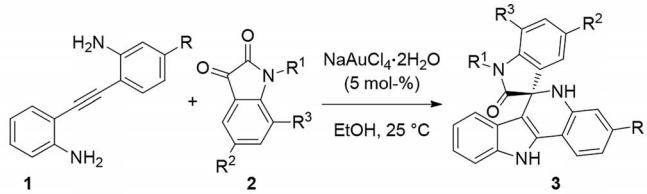
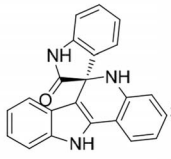
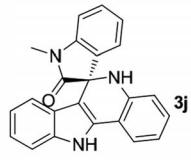
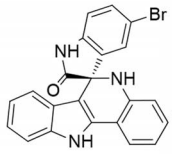
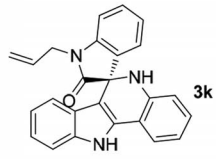
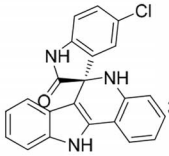
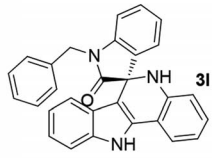
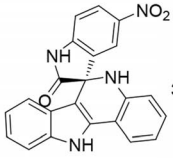
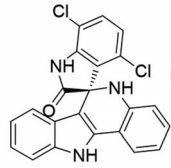
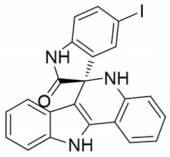
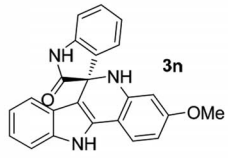
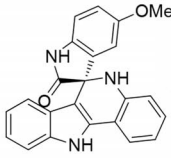
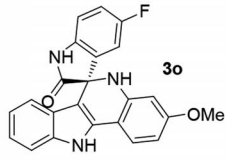
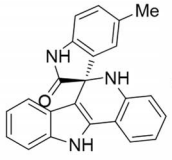
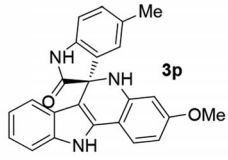
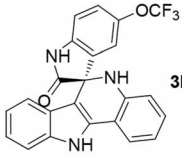
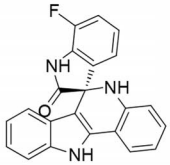


Figure 2. ORTEP diagram of **3b**.

Table 2. Au^{III}-catalyzed coupling of 2-[(2-aminophenyl)ethynyl]phenylamine[17] with isatins.[a]



1 2 3

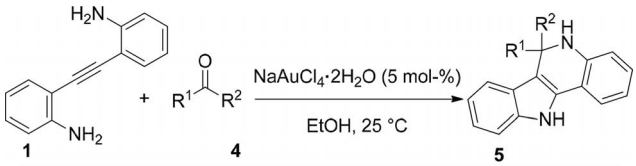
Entry	R	$R^1/R^2/R^3$	Product 3[b]	Time [h]	Yield[b] [%]	Entry	R	$R^1/R^2/R^3$	Product 3[b]	Time [h]	Yield[b] [%]
1	H	H/H/H	 3a	1.5	85	10	H	Me/H/H	 3j	2.0	75
2	H	H/Br/H	 3b	2.0	88	11	H	allyl/H/H	 3k	2.5	60
3	H	H/Cl/H	 3c	2.0	86	12	H	benzyl/H/H	 3l	1.5	66
4	H	H/NO_2/H	 3d	3.5	70	13	H	H/Cl/Cl	 3m	6.0	53
5	H	H/I/H	 3e	2.0	80	14	OMe	H/H/H	 3n	5.0	59
6	H	H/OMe/H	 3f	2.5	78	15	OMe	H/F/H	 3o	4.0	60
7	H	H/Me/H	 3g	2.5	75	16	OMe	H/Me/H	 3p	4.5	55
8	H	H/OCF_3/H	 3h	2.0	90						
9	H	H/H/F	 3i	2.5	80						

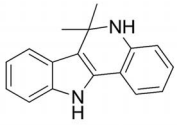
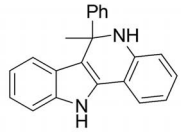
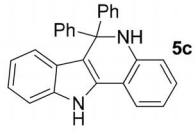
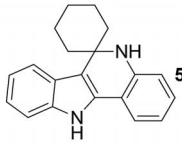
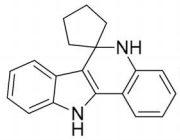
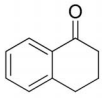
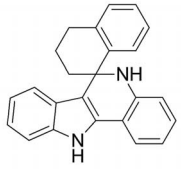
[a] Unless otherwise noted, all reactions were performed by using $NaAuCl_4 \cdot 2H_2O$ (5 mol-%), **1** (1.1 equiv.), and isatin **2** (1.0 equiv.) in dry ethanol at 25 °C. [b] Yield refers to pure products after column chromatography.

The structure of **3b** was confirmed by single-crystal X-ray diffraction analysis (Figure 2).[16]

To demonstrate the versatility of the reaction, we turned our efforts toward the cyclization of **1** with simple ketones. Interestingly, the desired 6,6-disubstituted 6,11-dihydro-5*H*-indolo[3,2-*c*]quinolones were obtained in good yields if acyclic ketones were used (45–70%; Table 3, Entries 1–3). Both acyclic and cyclic ketones successfully participated in the reaction to furnish desired products **5** in moderate to good yields (Table 3).

Table 3. Au^{III}-catalyzed coupling of 2-[(2-aminophenyl)ethynyl]-phenylamine with ketones.[a]

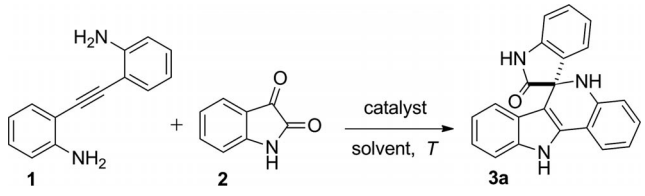


Entry	Ketone **4**	Product **5**[b]	Time [h]	Yield[c] [%]
1		 **5a**	3.0	70
2		 **5b**	4.0	66
3		 **5c**	12.0	45
4		 **5d**	6.0	52
5		 **5e**	6.0	50
6		 **5f**	4.5	69

[a] Reactions were performed with **1** (0.5 mmol) and **2** (0.75 mmol) in acetone (2 mL). [b] All the products were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy and HRMS. [c] Yield refers to pure product after column chromatography.

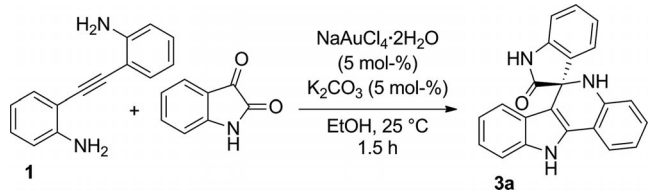
To understand the reaction pathway and whether the reaction was catalyzed by a Brønsted acid or gold(III), we performed some control experiments by using various Brønsted acids such as HCl, HOAc, *p*-toluenesulfonic acid ($PTSA·H_2O$), and TfOH under mild and harsh conditions, as depicted in Table 4. Although, these catalysts failed to promote the reaction at 25 °C (Table 4, Entries 1, 3–5), desired product **3a** was formed in low yield at high temperature after a longer reaction time with HCl (10 mol-%) (1 M in dioxane) and with TfOH (5 mol-%; Table 4, Entries 2 and 6). Further, to study the effect of the acid that was formed in situ under the reaction conditions, a control experiment was performed by using K_2CO_3 (5 mol-%) along with $NaAuCl_4·2H_2O$ (5 mol-%) in ethanol at 25 °C. To our delight, the reaction proceeded smoothly under the above conditions to afford **3a** in 85% yield in 1.5 h, as shown in Scheme 1. These results clearly ruled out Brønsted acid catalysis in the reaction.

Table 4. Screening with Brønsted acids in the formation of **3a**.[a]



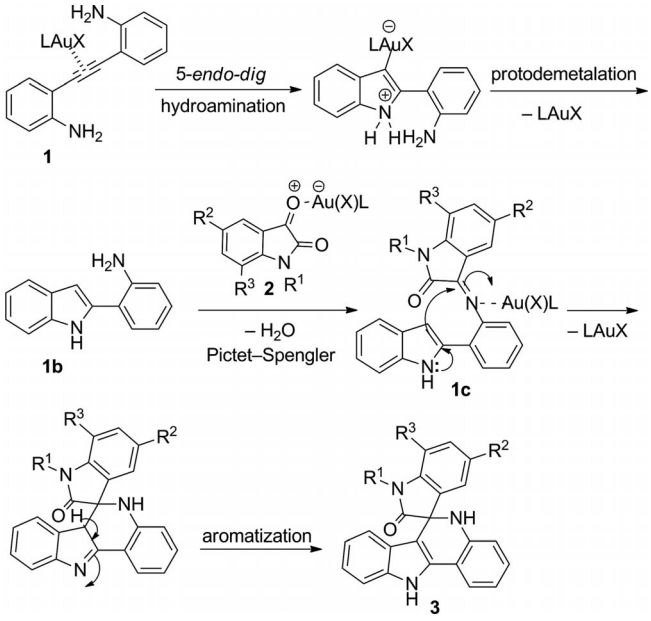
Entry	Catalyst (mol-%)	Solvent	*T* [°C]	Time [h]	Yield **3a**[b] [%]
1	HCl (10)	CH_3CN	25	24	n.r.[c]
2	HCl (10)	CH_3CN	80	24	<50[d]
3	HOAc (10)	EtOH	25	24	0
4	$PTSA·H_2O$ (10)	CH_2Cl_2	25	24	0[e]
5	TfOH (5)	CH_2Cl_2	25	48	trace
6	TfOH (5)	CH_2Cl_2	40	48	<20

[a] Reactions were performed with **1** (0.50 mmol, 1.1 equiv.) and **2a** (0.45 mmol, 1.0 equiv.) in dry solvent (2 mL). [b] Yield of isolated product. [c] n.r. = no reaction. [d] Both starting material and isatin were recovered. [e] Undesired products were obtained.



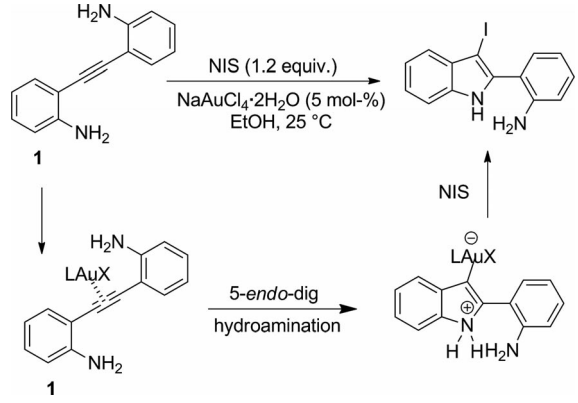
Scheme 1. Effect of base in the reaction.

A plausible mechanism is shown in Scheme 2. According to the experimental observations, the reaction is assumed to proceed by coordination of an Au^{III} species to the alkyne moiety of **1** followed by nucleophilic attack of the tethered amino group and subsequent protodemetalation to lead to *N*-(2-aminophenyl)indole **1b**. Thus-formed **1b** may undergo condensation with isatin, which is activated by Au^{III} to afford imine **1c**. Finally, activation of the imine by cationic gold species facilitates the nucleophilic attack of the indole onto imine **1c** to afford **3**. The proposed mechanism was further verified by performing the individual reaction of **1b** with isatin, which also afforded **3a**, the same as the one-pot reaction.



Scheme 2. Plausible reaction pathway.

Evidence for the formation of the vinyl–Au^{III} species was further confirmed by trapping it with *N*-iodosuccinimide (NIS), which provided the corresponding 2-(3-iodo-1*H*-indol-2-yl)aniline in 80% yield, as shown in Scheme 3.



Scheme 3. Trapping of the vinyl–Au^{III} species with NIS.

Conclusions

We successfully demonstrated a simple and efficient one-pot strategy for the synthesis of 5′,11′-dihydrospiro-[indoline-3,6′-indolo[3,2-*c*]quinolin]-2-one scaffolds through 5-*endo-dig* spirocyclization from readily accessible starting materials. This tandem process exhibits significant functional-group tolerance, broad substrate scope, and facilitates the synthesis of structurally diversified spirooxindoles under ambient conditions. This protocol also works well with simple ketones to provide indolo[3,2-*c*]quinolones of biological importance.

Experimental Section

Typical Procedure for the $NaAuCl_4·2H_2O$-Catalyzed Cyclisation: $NaAuCl_4·2H_2O$ (5 mol-%) was added to a stirred solution of 2-[(2-aminophenyl)ethynyl]phenylamine[17] (**1**)/*N*-[4-(2-amino-5-methoxyphenyl)but-3-yn-1-yl]-4-methylbenzenesulfonamide (0.5 mmol) and isatin **2**/ketone **4** (0.45/0.75 mmol) in dry ethanol (2 mL) under N_2, and the resulting mixture was stirred at room temperature. The progress of the reaction was determined by monitoring (TLC) the disappearance of the starting material (Table 1). Removal of the solvent followed by purification by silica gel column chromatography (ethyl acetate/acetone, 4:1 to 1:1) afforded pure product **3/5**.

Typical Procedure for the Formation of 2-(3-Iodo-1*H*-indol-2-yl)aniline: $NaAuCl_4·2H_2O$ (5 mol-%) was added to a stirred solution of 2-[(2-aminophenyl)ethynyl]phenylamine (**1**; 0.5 mmol) in ethanol under N_2 followed by *N*-iodosuccinimide (0.6 mmol), and the resulting mixture was stirred at room temperature for 2 h. Removal of the solvent followed by purification by silica gel column chromatography (ethyl acetate/acetone, 9:1) afforded pure 2-(3-iodo-1*H*-indol-2-yl)aniline as a brown semisolid.

Supporting Information (see footnote on the first page of this article): General experimental procedures, spectroscopic data (^1H and ^{13}C NMR), crystallographic data.

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