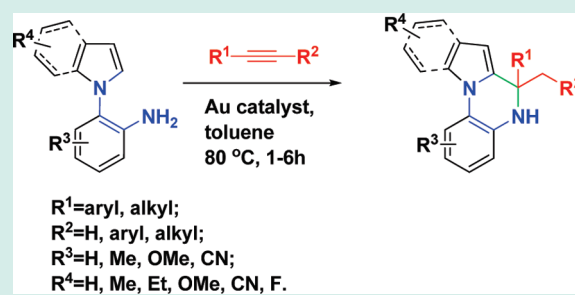


Synthesis of Pyrrolo[1,2-*a*]quinoxalines via Gold(I)-Mediated Cascade ReactionsGuannan Liu,^{†,‡} Yu Zhou,[†] Daizong Lin,[†] Jinfang Wang,[†] Lei Zhang,[†] Hualiang Jiang,[†] and Hong Liu^{†,*}[†]The Center for Drug Discovery and Design, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, P. R. China[‡]Department of Pharmacy, College of Life Sciences, China Jiliang University, Hangzhou 310018, P. R. China.

Supporting Information

ABSTRACT: In this study, we developed an efficient tandem process of hydroamination and hydroarylation using a gold catalyst to enable and study the reactions between pyrrole-substituted anilines and alkynes. The gold(I)-catalyzed reactions were achieved in toluene at 80 °C over a reaction time of 1–6 h. These reactions are applicable to a variety of aromatic amino compounds and both the terminal and internal alkynes. Substituted pyrrolo[1,2-*a*]quinoxalines were obtained in moderate to excellent yields. A presumed mechanism involving intermolecular C–N bond formation and intramolecular nucleophilic reaction via a cationic gold complex has been proposed on the basis of the deuterium labeling studies.

KEYWORDS: gold-catalyst, cascade reaction, hydroamination, hydroarylation



Efficiency is an important characteristic for the design and development of innovative strategies in chemical synthesis. One of the most effective methods of achieving synthetic efficiency is to implement a cascade reaction to enable multiple bond-forming and bond-cleaving events to occur in a single synthetic operation.¹ Among these are transition metal-catalyzed domino reactions for the synthesis of various fused polycyclic heterocyclic compounds.² Gold-catalyzed reaction cascades have attracted much interest as a result of the ability of gold ions to activate alkyne, alkene, and allene functionality under mild conditions and at low catalyst loadings.³

Although pyrrolo[1,2-*a*]quinoxalines and their 4,5-dihydro derivatives play important roles in drug discovery as biologically active compounds and valuable synthetic intermediates,⁴ the available strategies for the synthesis of these compounds are limited. So far, only a few methods have been described for the assembly of 4,5-dihydropyrrolo[1,2-*a*]quinoxalines, which normally require additional additives, long reaction times, limited reaction tolerance, and low reaction selectivity.⁵ Recently, Patil et al developed the PtBr₂- and Au(I)-catalyzed hydroamination-hydroarylation cascade reactions of 2-(1*H*-pyrrol-1-yl)anilines with alkynes to form 4,5-dihydropyrrolo[1,2-*a*]quinoxalines.⁶ Although these transformations are encouraging, they are limited to the terminal alkynes and require long reaction times.

On the basis of our previous experience with gold catalysts in the preparation of heterocycles,⁷ we describe here the scope and mechanism of an improved version of the gold-catalyzed intermolecular C–N bond formation and intramolecular nucleophilic reaction. Both terminal and internal alkynes can be used,

increasing the range of structural diversity accessible in the products. Furthermore, only a small quantity of gold catalyst (1 mol %) is needed, without other additives, and short reaction times (1–6 h) are required.

Preliminary experiments directed toward optimizing the reaction conditions of the transformation were carried out using commercially available 2-(1*H*-pyrrol-1-yl)aniline (**1A**) and phenylacetylene (**2a**) in the presence of gold catalysts in toluene. The results are shown in Table 1.

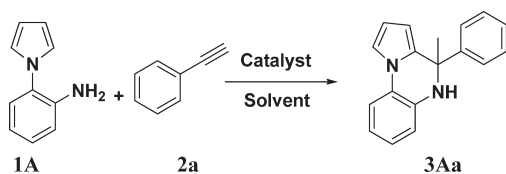
No reaction occurred in the absence of catalysts (Table 1, entry 1), and AuCl₃ provided the target product in only 25% yield (Table 1, entry 2). However, certain cationic gold(I) complexes were found to exhibit significantly better activity in this reaction (Table 1, entries 3 to 7). Among these species, catalyst 4 ([Au{P(*t*-Bu)₂(*o*-biphenyl)}]{CH₃CN}]SbF₆) was found to be superior, with the target product being obtained in 95% yield (Table 1, entry 7). Doubling the amount of Au catalyst (to 2 mol %) provided no faster or higher yielding reaction (Table 1, entry 8), and Ag(I) salts were found to be ineffective as cocatalysts (Table 1, entries 9 and 10).

The nature of the solvent plays an important role in this transformation. Toluene, acetonitrile, and ethanol provided significantly better yields than dichloromethane, THF, acetone, *N,N*-dimethylformamide, and water (Table 1, entries 7, 11–17). Changing the reaction temperature to 25 °C, 60 °C, or 100 °C adjusted the reaction times as one would expect but did not improve yields (Table 1, entries 18–20). Thus, optimal results

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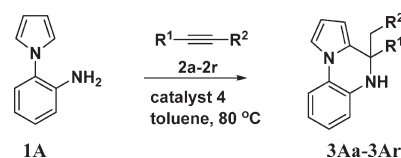
Table 1. Optimization of the Reaction Conditions^a

entry	catalyst ^b	solvent	temp (°C)	time (h)	yield (%) ^c
1		toluene	80	1	0
2	AuCl ₃	toluene	80	1	25
3	Au(PPh ₃)Cl	toluene	80	1	42
4	catalyst 1	toluene	80	1	85
5	catalyst 2	toluene	80	1	82
6	catalyst 3	toluene	80	1	76
7	catalyst 4	toluene	80	1	95
8 ^d	catalyst 4	toluene	80	1	93
9 ^e	catalyst 4	toluene	80	1	88
10 ^f	catalyst 4	toluene	80	1	86
11	catalyst 4	CH ₃ CN	80	1	84
12	catalyst 4	CH ₂ Cl ₂	80	1	63
13	catalyst 4	EtOH	80	1	90
14	catalyst 4	H ₂ O	80	1	trace
15	catalyst 4	THF	80	1	trace
16	catalyst 4	DMF	80	1	0
17	catalyst 4	acetone	80	1	trace
18	catalyst 4	toluene	r.t.	36	91
19	catalyst 4	toluene	60	3	89
20	catalyst 4	toluene	100	1	92

^a **1A** (0.40 mmol), **2a** (0.44 mmol), catalyst (1 mol %), Ar protection. ^b Catalyst 1 = [Au{P(*t*-Bu)₂(*o*-biphenyl)}]Cl; catalyst 2 = [Au{1,3-bis(2,6-di-*iso*-propylphenyl)imidazol-2-ylidene}]Cl; catalyst 3 = [Au{P-(2,4-di-*tert*-butylphenoxy)₃}]Cl; catalyst 4 = [Au{P(*t*-Bu)₂(*o*-biphenyl)}]-{CH₃CN}]SbF₆. ^c Isolated yields based on **1A**. ^d 2 mol % catalyst 4 used. ^e AgSbF₆ (5 mol %) used as cocatalyst. ^f AgOTf (5 mol %) used as cocatalyst.

were obtained when 2-(1H-pyrrol-1-yl)aniline (0.40 mmol, **1A**) and phenylacetylene (0.44 mmol, **2a**) in toluene were treated with 1 mol % of catalyst 4 in a sealed tube under Ar at 80 °C for 1 h.

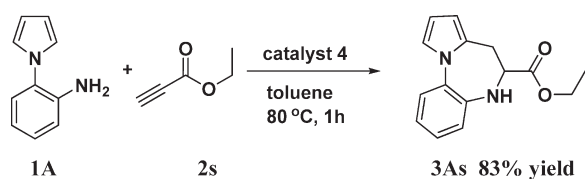
To evaluate the scope of the catalytic method, we investigated the reaction of 2-(1H-pyrrol-1-yl)aniline (**1A**) and a variety of alkynes (**2**) under the above optimized conditions. As shown in Table 2, a series of aromatic and aliphatic terminal alkynes gave the desired products **3Aa–3Ak** in moderate to good yields (53–98%) (Table 2, entries 1–11). Yields with *ortho*-substituted phenylacetylene derivatives were significantly lower than for substrates with *meta*- and *para*-substituents (**2b–2d**), presumably because of steric effects (Table 2, entries 2–4). Substrate **2e**, which possesses a 4-*tert*-butylphenyl group, was incorporated with no difficulty (Table 2, entry 5). Electronic effects were also indicated by the slight reduction in yield of substrate **2f** having an electron-donating *p*-methoxyphenyl group (Table 2, entry 6). Excellent yields were obtained irrespective of the presence of electron-withdrawing or halide groups at the R¹ position (Table 2, entries 7–9). However, the 2-pyridyl group of 2-ethynylpyridine (**2l**) was not tolerated; the desired product **3Al** was not formed and the starting materials were completely recovered (Table 2, entry 12).

Table 2. Gold(I)-Catalyzed Reaction of 2-(1H-pyrrol-1-yl)aniline **1A** and Alkynes **2**^a

entry	product	yield (%) ^b	entry	product	yield (%) ^b
1	3Aa	95	10	3Aj	80 ^c
2	3Ab	53	11	3Ak	77 ^c
3	3Ac	94	12	3Al	0 ^c
4	3Ad	98	13	3Am	98
5	3Ae	95	14	3An	96
6	3Af	82	15	3Ao	94 ^d
7	3Ag	90	16	3Ap	63 ^d
8	3Ah	93	17	3Aq	26 ^d
9	3Ai	87	18	3Ar	20 ^d

^a Reaction conditions: **1A** (0.40 mmol), **2** (0.44 mmol), catalyst 4 (1 mol %), Ar protection. ^b Isolated yield based on **1A**. ^c The reaction was carried out for 2 h. ^d The reaction was carried out for 6 h.

We were also pleased to find that the reaction was not limited to substrates with aryl groups at the R¹ position. Compounds possessing alkyl groups were transformed smoothly into the products **3Aj** and **3Ak** in good yield (Table 2, entries 10 and 11). Furthermore, certain internal alkynes were also found to be compatible (Table 2, entries 13–18). The methoxycarbonyl substituents of compounds **2m–2o** facilitated efficient transformation, and the desired products were obtained in excellent

Scheme 1. Gold(I)-Catalyzed Reaction of 2-(1*H*-pyrrol-1-yl)aniline **1A** and Ethyl Propiolate **2s**

yields, up to 98% (Table 2, entries 13–15). In contrast, internal alkyne substrates bearing more electron-rich (or noncoordinating) R^2 groups, such as ethyl and phenyl, reacted more slowly. For example, **3Ap** was obtained in 63% yield after 6 h (Table 2, entry 16), and phenyl-containing alkynes gave lower yields of the desired products **3Aq** and **3Ar** (26% and 20% yield, respectively; Table 2, entries 17 and 18). Unexpectedly, the 7-member ring-closure product ethyl 6,7-dihydro-5*H*-benzo[*b*]pyrrolo[1,2-*d*][1,4]diazepine-6-carboxylate (**3As**) was formed in excellent yield from the reaction of the starting material (**1A**) with ethyl propiolate (**2s**).⁸

To further expand the scope of this transformation, gold-catalyzed cyclizations of phenylacetylene **2a** with various pyrrole- and indole-substituted anilines **1** were investigated (Table 3). These results demonstrated that the proposed reaction could be extended to generate substituted-4-methyl-4-phenyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalines (**3Ba–3Fa**). However, the reaction was significantly effected by the nature of the R^3 substituent on the aniline ring. Thus, while 3-, 4-, and 5-methyl-substituted substrates gave similar results (Table 3, entries 1–3), a much lower yield was obtained for the electron-rich 4-methoxy analogue (Table 3, entry 4). In contrast, the electron-withdrawing 4-cyano group led to smooth conversion to the desired product (Table 3, entry 5). Good yields were also obtained for a pyrrole-substituted heterocyclic amine (Table 3, entry 6) and for the *N*-methylated aniline **1H** (Table 3, entry 7). Use of a benzylic amine (**II**) instead of aniline did not give the desired product (Table 3, entry 8).

Substitution on the pyrrole ring of 2-(substituted-1*H*-pyrrol-1-yl)anilines was also found to be important. Ethyl and methyl groups provided good yields (Table 3, entries 9, 10), but a 2-cyano-pyrrol-1-yl group and a 1*H*-pyrazol-1-yl group each gave no conversion (Table 3, entries 11, 12). The latter result presumably derives from the significantly decreased nucleophilicity of the C5 atoms of the 2-cyanopyrrole and pyrazole, respectively. Gratifyingly, indole-substituted aniline bearing a variety of substituents gave cyclized products **3Na–3Qa** in good to excellent yields (71–92%, Table 3, entries 13–16).

All the pyrrolo[1,2-*a*]quinoxalines synthesized were characterized by spectral and analytical data. As shown in Figure 1, the absolute configuration of the product was determined by X-ray analysis of **3Ai**.⁹

To gain insights into the mechanism of the reaction, we performed labeling studies with deuterated starting materials.¹⁰ The reaction of 2-(1*H*-pyrrol-1-yl)aniline **1A** with $\text{DC}\equiv\text{CPh}$ **d-2a** under our gold catalysis conditions yielded the product **d-3Aa-1**, with deuterium incorporation on the 4-methyl group (26%) as confirmed by ¹H NMR (Scheme 2, eq 1). Conversely, 28% of the 4-methyl hydrogen of **d-3Aa-2** was found to contain deuterium when *N*-deuterated 2-(1*H*-pyrrol-1-yl)aniline **d-1A** was reacted with $\text{HC}\equiv\text{CPh}$ **2a** (Scheme 2, eq 2). A similar result was obtained when the internal alkyne was used in the reaction. The treatment of **d-1A** with methyl 3-phenylpropiolate **2n** resulted in synthesis of the product **d-3An**, with deuterium incorporation at

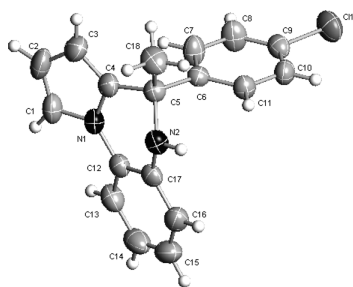
Table 3. Gold(I)-Catalyzed Reaction of Pyrrole- and Indole-Substituted Anilines **1** and Phenylacetylene **2a**^a

entry	product	yield (%) ^b	entry	product	yield (%) ^b
1	3Ba	89	9	3Ja	76
2	3Ca	85	10	3Ka	93
3	3Da	78	11	3La	0 ^d
4	3Ea	28 ^d	12	3Ma	0 ^d
5	3Fa	86 ^c	13	3Na	91 ^c
6	3Ga	79 ^c	14	3Oa	90 ^c
7	3Ha	76 ^c	15	3Pa	92 ^c
8	3Ia	0 ^d	16	3Qa	71 ^c

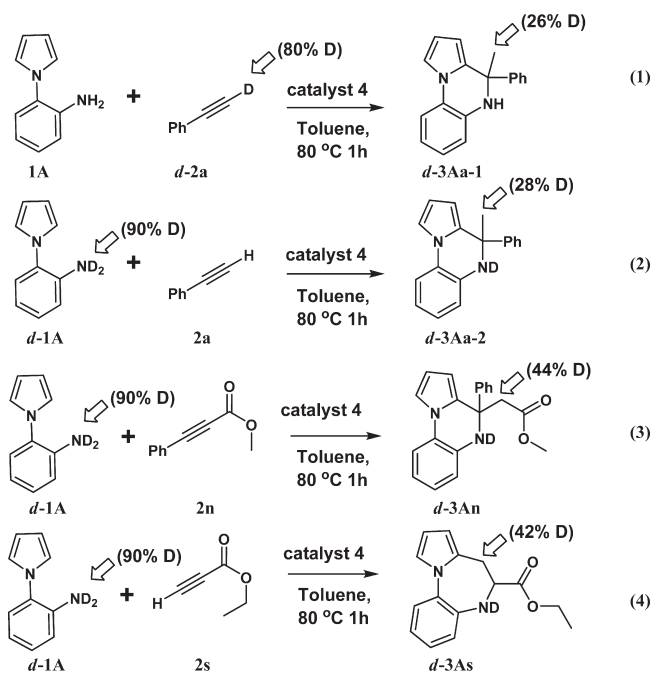
^a Reaction conditions: **1** (0.40 mmol), **2a** (0.44 mmol), catalyst **4** (1 mol %), Ar protection. ^b Isolated yield based on **1**. ^c The reaction was carried out for 3 h. ^d The reaction was carried out for 6 h.

the α -position of the carbonyl group (44%) without significant exchange to other positions (Scheme 2, eq 3). In addition, a deuterium-incorporation pattern was also observed for the reaction of *N*-deuterated 2-(1*H*-pyrrol-1-yl)aniline **d-1A** with methyl propiolate **2s** (Scheme 2, eq 4); in this case, the deuterium was selectively incorporated into the methylene group (42%) of **d-3As**.

The reaction mechanism shown in Figure 2 is proposed to account for these observations, consistent with previous investigations of gold-catalyzed reactions.^{3,11} First, the carbon–carbon triple bond of **2** is activated by coordination with the gold catalyst to form the gold-alkyne π -complex **I**. Intermolecular hydroamination of 2-(1*H*-pyrrol-1-yl)aniline **1A** gives the enamine intermediate **II**, which is followed by proton transfer to produce the cationic

Figure 1. X-ray Crystal Structure of 3Ai.⁹

Scheme 2. Deuterium-Labeling Study



intermediate **III**. The intramolecular nucleophilic reaction can then proceed *via* either path 1 or path 2 to form the imine intermediates **IV** and **IV'**, respectively. Most of the reactions proceed through path 1 to give the 6-membered intermediate **IV**. However, presumably owing to the electron-withdrawing nature of the carbonyl group, the use of ethyl propiolate **3s** as a starting material affords the 7-member ring-closure intermediate **IV'** via path 2. Finally, protonation of the resulting organogold complexes **IV** and **IV'** provides the final products **3** and **3As**, respectively, with regeneration of the gold catalyst.

In summary, we have described a versatile and efficient synthetic method in which a gold catalyst is used under mild reaction conditions to produce a broad range of functionalized 4,5-dihydropyrrolo[1,2-*a*]quinoxalines and 5,6-dihydroindolo[1,2-*a*]quinoxalines, which are useful as versatile synthetic intermediates and potentially as biologically active compounds. Deuterium labeling studies support a mechanism featuring a sequence of intermolecular hydroamination and nucleophilic pyrrole cyclization steps. We expect that the resulting biologically intriguing structures will have broad applications in our related medicinal chemistry program.

EXPERIMENTAL PROCEDURES

General Procedure for the Preparation of 4-Methyl-4-phenyl-4,5-dihydropyrrolo[1,2-*a*]quinoxaline 3Aa. To a 10 mL reac-

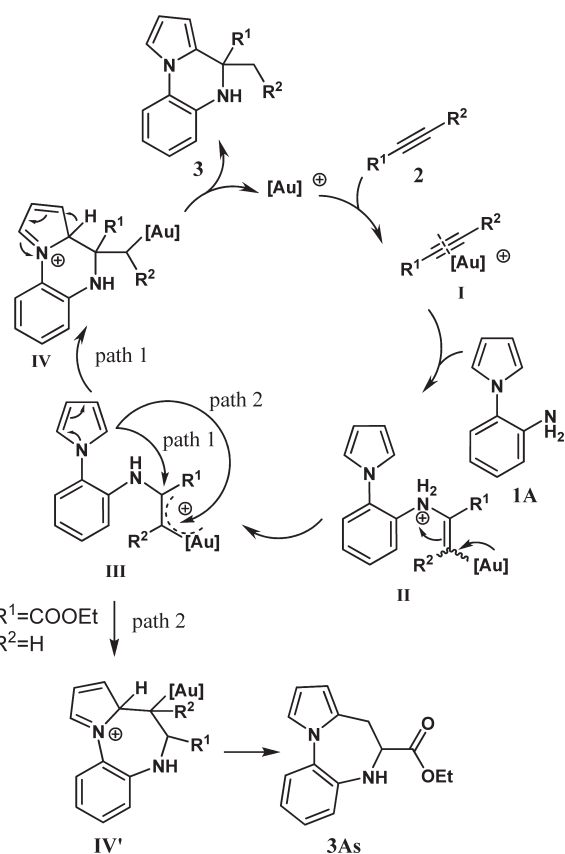


Figure 2. Possible mechanism for Au(I)-catalyzed reaction.

tion flask containing toluene (5 mL) under argon was added 2-(1*H*-pyrrol-1-yl)aniline (63.2 mg, 0.40 mmol), phenylacetylene (48 μ L, 0.44 mmol), and $[\text{Au}\{\text{P}(t\text{-Bu})_2(o\text{-biphenyl})\}\{\text{CH}_3\text{CN}\}] \text{SbF}_6$ (3 mg, 1 mol %). The resulting mixture was heated at 80 °C for 1 h, and then diluted with 20 mL of EtOAc, washed with water and brine, and dried by anhydrous Na_2SO_4 . The solvent was evaporated under reduced pressure, and the product was isolated by column chromatography with Petro Ether (PE)/EtOAc (25/1, v/v) as eluent to yield the desired product: (78 mg, 95%) as white solid; ^1H NMR (300 MHz, CDCl_3) δ = 7.32–7.22 (m, 5H), 7.19–7.16 (m, 2H), 6.97–6.91 (m, 1H), 6.81–6.76 (m, 2H), 6.36–6.34 (t, J = 3.3 Hz, 1H), 6.07–6.06 (m, 1H), 1.90 ppm (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ = 146.3, 135.1, 132.9, 128.2, 126.9, 125.7, 124.7, 119.3, 115.8, 114.6, 114.3, 109.9, 104.5, 56.9, 29.3 ppm; MS (ESI, 70 eV) m/z (%) 261 (100) $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2$ $[\text{M} + \text{H}]^+$ 261.1392, found 261.1407.

ASSOCIATED CONTENT

S Supporting Information. Additional experimental details, general information, and ^1H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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