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Gold-Catalyzed Intermolecular Reactions of (*Z*)-Enynols with Indoles for the Construction of Dihydrocyclohepta[*b*]indole Skeletons through a Cascade Friedel–Crafts/Hydroarylation Sequence

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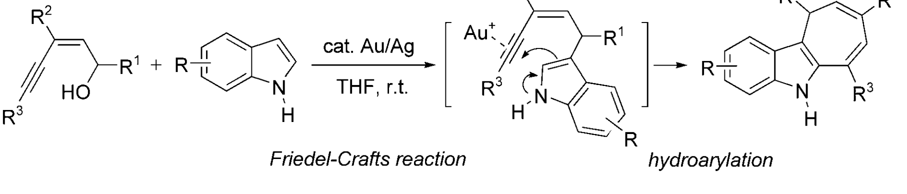
Abstract: An efficient domino approach for the synthesis of indole-fused carbocycles and their analogues from the reactions of suitably substituted (*Z*)-enynols with indoles or pyrroles under mild reaction conditions was developed. This methodology is realized by a tandem reaction using Au/Ag catalysts, which could catalyze both of the Friedel–Crafts and the hydroarylation reaction in the same vessel.

Keywords: enynols; Friedel–Crafts reaction; gold catalysis; hydroarylation; indoles

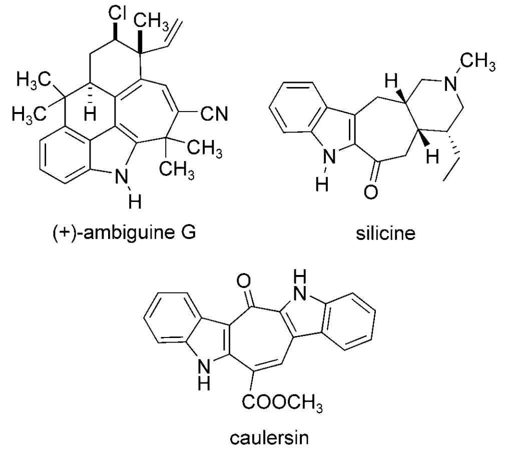
In recent years, gold(III) salts and gold(I) complexes have been shown to display considerable catalytic activity under moderate conditions, rendering them attractive reagents in organic synthesis.[1] Especially, gold catalysts have been proved to be powerful alkynophilic Lewis acids to activate the π-systems toward nucleophilic attack. The majority of studies have then concentrated on the intramolecular cyclization of alkynes bearing proximate C, O, N nucleophiles, leading to a diverse range of functionalized carbo- or heterocycles. However, there are only limited reports for the intermolecular cyclization or cycloisomerization of alkynes.[2] Recently, we have reported[3] a general synthetic approach to furans and stereodefined dihydrofurans *via* the gold-catalyzed cyclization of (*Z*)-2-en-4-yn-1-ols.[3a] We have also developed a straightforward synthesis of allylic amines from allylic alcohols through direct amination by utilization of gold as catalysts.[3b] The reactions were suggested to be initiated through the facile formation of an allylic cation intermediate.[4] On the other hand, gold complexes are also particularly active catalysts for the hydroarylation of alkynes[5] and allenes[6]. For example, the Echavarren group has reported that indoles react intramolecularly with alkynes to generate six- to eight membered-ring annulated compounds.[5b–c,7] Encouraged by these results, we envisioned that a tandem process might be achieved which could couple the Friedel–Crafts reaction *via* an allylic cation intermediate with a subsequent hydroarylation directly through the reactions of (*Z*)-enynols with indoles mediated by a single-pot catalyst (Scheme 1). This process would also enable the new C–C bond formations to occur at both the C-2 and C-



Scheme 1.

3 positions of indoles in one operation, and there is no need to isolate the intermediate arylated enynes.

The resulting products are of considerable interest as they are present as key structural subunits in indole alkaloids such as ambiguine,[8] silicine[9] and caulersin[10] (Scheme 2).

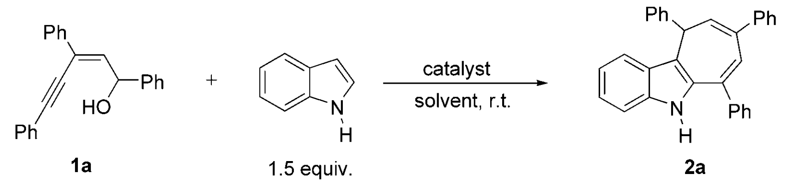


Scheme 2.

To probe the feasibility of the proposed transformations, we initially investigated the reactions of the readily available (*Z*)-1,3,5-triphenylpent-2-en-4-yn-1-ol **1a** with indole (Table 1). On the basis of our previous observations, we first examined the reactions in the presence of $AuCl_3$, however, product formation was not observed (Table 1, entry 1). After many efforts, we were pleased to find that the reaction proceed smoothly, and the desired dihydrocyclohepta[*b*]indole **2a** was obtained in 85% yield at room temperature in THF for 5 h using 5% $(PPh_3)AuCl$ and 5% $AgSbF_6$ as catalysts (entry 2). Reactions in CH_2Cl_2 only led to low conversions (entry 3). Changing the counteranion by activating $(PPh_3)AuCl$ with AgOTf afforded a lower yield of the desired product (entry 4). However, the use of cationic gold(I) complex PPh_3AuNTf_2 cleanly converted **1a** to **2a** at room temperature (entry 5). $AgSbF_6$ alone did not promote any transformation (entry 6). Interestingly, only the seven-membered ring derivative **2** was formed by a 7-*endo-dig* pathway during the cyclization, while the regioisomer derived from a 6-*exo-dig* reaction was not observed. It is noteworthy that this gold(I)-catalyzed domino reaction entails one C–O bond cleavage and two C–C bond formations in a single operation.

With this result in hand, we next examined the substrate scope with a range of trisubstituted (*Z*)-enynols (Table 2). We first examined the electronic effects of the substituents on the aromatic ring of R^1 at the C-1 position. It was found that an electron-withdrawing (Cl) substituent on the aryl group afforded the corresponding product **2b** in 92% yield (Table 2, entry 2). However, an electron-donating (OMe) substituent on the aryl group only resulted in a moderate yield (51%) of the product (entry 3). This might be due to the decreased electrophilicity of the allylic cation intermediate in the latter case. A thienyl group at C-1 was compatible under the reaction conditions with a higher catalysts loading of 10%, furnishing **2d** in 49% yield (entry 4). The structure of **2d** was confirmed by X-ray crystallography.[11] However, when the alkyl group was introduced at the C-1 position, the corresponding **2e** was formed only in 27% yield, moreover, a furan derivative was isolated as a major product. The results indicated that the reaction rate of the

Table 1. Optimization studies for the formation of dihydrocyclohepta[*b*]indole.



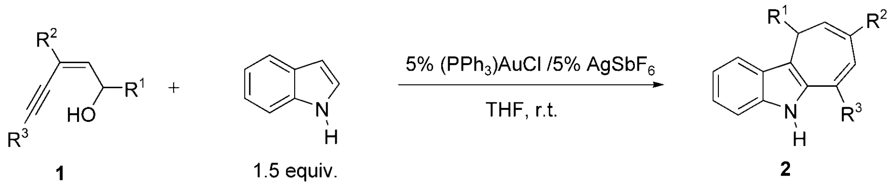
Entry	Catalyst	Solvent	Time	Yield [%] of **2a**[a]
1	5% $AuCl_3$	CH_2Cl_2	12 h	–[b]
2	5% Ph_3PAuCl, 5% $AgSbF_6$	THF	5 h	85
3	5% Ph_3PAuCl, 5% $AgSbF_6$	CH_2Cl_2	12 h	33
4	5% Ph_3PAuCl, 5% AgOTf	THF	5 h	70
5	5% $Ph_3PAuNTf_2$	THF	7 h	82
6	10% $AgSbF_6$	THF	12 h	NR[c]

[a] Isolated yields.

[b] Trace amounts of by-products were formed.

[c] NR = no reaction.

Table 2. One-pot synthesis of indole-fused carbocycles through the reactions of (*Z*)-enynols with indole.



Entry	Enynol	R^1	R^2	R^3	Time	Product	Yield [%][a]
1	**1a**	Ph	Ph	Ph	5 h	**2a**	85
2	**1b**	*p*-ClC_6H_4	Ph	Ph	4 h	**2b**	92
3	**1c**	*p*-$MeOC_6H_4$	Ph	Ph	4 h	**2c**	51
4	**1d**	2-thienyl	Ph	Ph	10 h	**2d**	49[b]
5	**1e**	*n*-C_3H_7	Ph	Ph	13 h	**2e**	66[c]
6	**1f**	Ph	Ph	*p*-$MeOC_6H_4$	5 h	**2f**	87
7	**1g**	Ph	Ph	*n*-C_4H_9	6 h	**2g**	52
8	**1h**	Ph	*n*-C_4H_9	Ph	5 h	**2h**	66
9	**1i**	Ph	-CH_2OMe	Ph	4 h	**2i**	66
10	**1j**	Ph	-CH_2OTBS	Ph	4.5 h	**2j**	54[d]
11	**1k**	Ph	*n*-C_4H_9	*n*-C_4H_9	5 h	**2k**	56

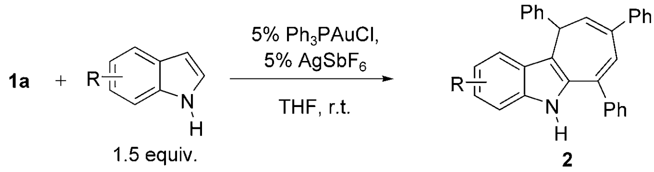
[a] Isolated yields.
[b] 10% $(PPh_3)AuCl$/10% $AgSbF_6$ was used.
[c] 1 equiv. $BF_3\cdot Et_2O$, 50 °C, 6 h, then 5% $(PPh_3)AuCl$/5% $AgSbF_6$, room temperature, 7 h.
[d] The TBS group was removed during the reaction.

Friedel–Crafts arylation in this case is much slower than that of cycloisomerization through an oxygen nucleophile. Remarkably, it was found that $BF_3\cdot Et_2O$ could effectively promote[3c] the first step of arylation reaction. Thus, by first stirring the reaction mixture in the presence of 1 equivalent of $BF_3\cdot Et_2O$ for 6 h at 50 °C, and then adding the Au/Ag catalysts at room temperature, the desired indole derivative **2e** could be obtained in 66% yield (entry 5). The above results indicated that the nature of the substituent on C-1 played an important role in this reaction. The substituent effects on C-3 and C-5 were also examined. A broad variety of (*Z*)-enynols bearing alkyl or aryl groups on C-3 and/or alkyne terminus C-5 were smoothly converted into the indole derivatives to yield **2f**–**2k** in 52–87% yields (entries 6–11). It is interesting to note that the reaction has also been accomplished starting from **1i** having a methoxy functionality, leading to **2i** in 66% yield (entry 9). A TBS-protected alcohol **1j** gave rise to a desilylated product **2j** in 54% yield, indicating that the TBS group was easily removed during the reaction (entry 10).

The cycliztions have also been successfully extended to various substituted indoles with X, OMe, or NO_2 functionalities, and moderate to good yields were realized for all cases (Table 3).

Interestingly, when terminal alkyne **1l** was used, 1-methyl-2,4-diphenyl-9*H*-carbazole **3** was obtained in 76% yield [Scheme 3, Eq. (1)]. The results indicated that a 6-*exo-dig* cyclization followed by double bond isomerization took place in the step of hydroarylation. The cyclization of enynol **1a** with pyrrole was also explored. In this case, however, a 1,8-dihydrocyclohepta[*b*]pyrrole **4** was formed in 68% yield, in which a sp^3 carbon center is located on the C-2 position of pyrrole [Scheme 3, Eq. (2)]. The structure of **4** has been verified by X-ray crystallography.[11]

Table 3. Formation of various dihydrocyclohepta[*b*]indoles.



Entry	Substrate	Time	Product	Yield [%] of 2[a]
1	5-Cl-indole	4 h	**2l**	95
2	5-Br-indole	4.5 h	**2m**	80
3	5-I-indole	5 h	**2n**	92
4	4-MeO-indole	5 h	**2o**	75
5	6-MeO-indole	5.5 h	**2p**	60
6	5-NO$_2$-indole	7 h	**2q**	51[b]

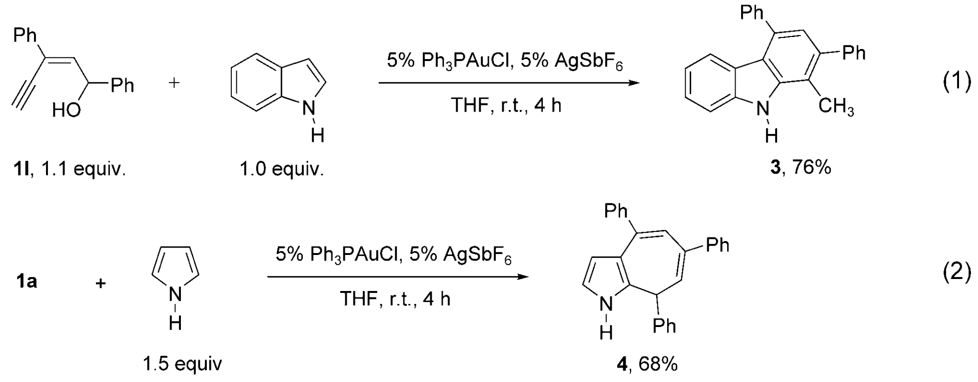
[a] Isolated yields.

[b] Reaction was carried out at room temperature for 1 h, and then at refluxing temperature for 6 h.

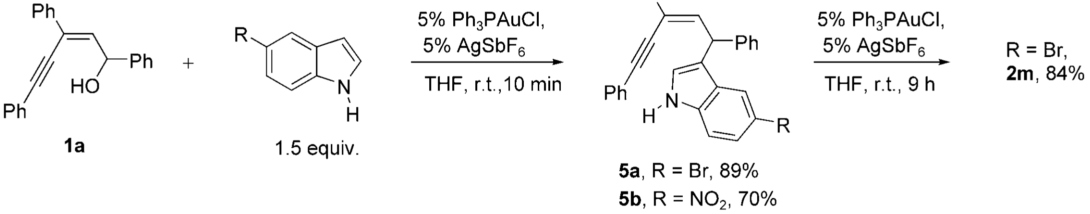
To understand the reaction mechanism, the arylated product **5** has been isolated by stopping the reaction at 10 min (Scheme 4). The structure of **5b** has also been confirmed by single-crystal analysis.[11] The results clearly showed that the Friedel–Crafts reaction selectively occurred at the C-3 position of the indole ring. The intramolecular cyclization of **5a** catalyzed by (PPh$_3$)AuCl/AgSbF$_6$ proceeded smoothly to provide the same product of **2m** as observed in the tandem process. The results strongly supported our assumption that **2** was formed through Au(I)-catalyzed hydroarylation of enyne **5** in the one-pot procedure.

We propose the following reaction mechanism for this tandem sequence (Scheme 5). The reaction is initiated by Au$^+$-assisted C–O bond cleavage of enynol **1**, resulting in the formation of an allylic cation intermediate **7**, **7** undergoes the Friedel–Crafts reaction with indole through the electrophilic attack of the indole 3-position to afford the indolyl enyne **5** and regenerate the Au$^+$ catalyst. At this point, the intermediate **5** enters into the hydroarylation sequence. Then at first, coordination of the gold complex to the triple bond of **5** to form intermediate **8** occurs, which is followed by the intramolecular nucleophilic attack of the indole ring at the triple bond, presumably *via* a spirocyclic intermediate **9**,[4d,5b,c] to give a seven-membered carbocation **10** *via* a 1,2-migration process.[12] Alternatively, intermediate **10** might be formed directly from **8**. Elimination of a proton followed by protodemetalation of the resulting organogold intermediate affords the product **2** with regeneration of the catalyst.

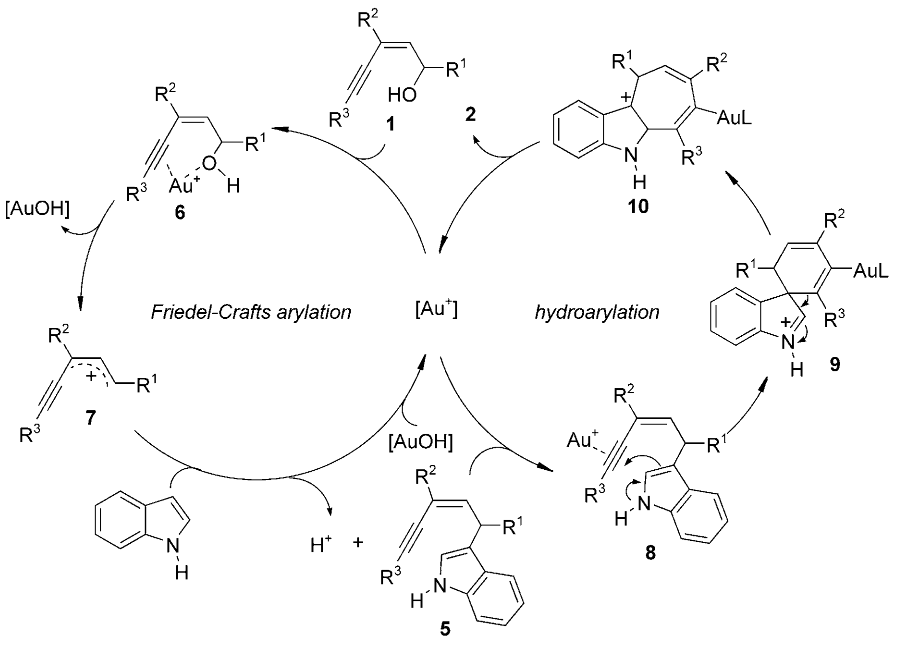
In summary, we have developed an efficient domino approach for the synthesis of indole-fused carbocycles including dihydrocyclohepta[*b*]indoles or -pyrroles and 9*H*-carbazoles *via* the cationic gold(I) complex catalyzed Friedel–Crafts/hydroarylation reactions. The Lewis acid BF$_3$·Et$_2$O was required in some cases to realize a successful domino process, depending on the substitution pattern on the enynols. Further



Scheme 3.



Scheme 4.



Scheme 5.

studies to extend the scope and synthetic utility for this Au/Ag-catalyzed cascade reaction are in progress in our laboratory.

Experimental Section

General Procedure: Au/Ag-Catalyzed One-Pot Synthesis of Dihydrocyclohepta[*b*]indole from the Reaction of a (*Z*)-2-En-4-yn-1-ol with Indole

Under argon atmosphere, to a solution of (*Z*)-enynol **1** (0.3 mmol) in 5 mL THF was added indole or its derivative (0.45 mmol). After indole was dissolved, Ph_3PAuCl (5 mol%) and $AgSbF_6$ (5 mol%, used as a 0.05 M solution in MeCN) were added successively. The resulting solution was stirred at room temperature until the reaction was complete as monitored by thin-layer chromatography. The solvent was evaporated and the residue was purified by chromatography on silica gel to afford the dihydrocyclohepta[*b*]indole derivatives.

Supporting Information

Experimental details, spectroscopic characterization of all new compounds and X-ray crystallography of compounds **2d**, **4** and **5b** are given in the Supporting Information file.

Acknowledgements

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