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Gold-catalyzed Cycloisomerization of 2-Aryl-2-(arylamino)-3-butyn-1-ols toward 2-(2'-Aminoaryl)-2,5-dihydrofurans

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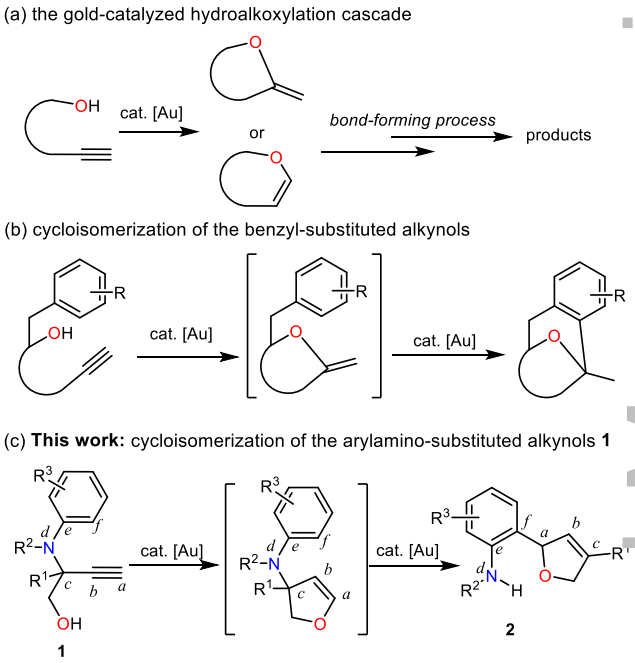
Abstract. An interesting and highly selective gold-catalyzed cycloisomerization of 2-aryl-2-(arylamino)-3-butyn-1-ols to afford 2-(2'-aminoaryl)-2,5-dihydrofurans has been reported. The reaction is atom economic and highly efficient, and tolerates many functional groups including the cyano and allyl groups. A plausible mechanism for this new cycloismerization is also proposed.

Keywords: Gold catalysis; Cycloisomerization; Alkynols; Selectivity; 2,5-Dihydrofurans

The gold-catalyzed cyclization of alkynes bearing intramolecular nucleophiles represents one of the most important methods for the synthesis of carbo- and heterocyclic structures under mild conditions.[1] In particular, the gold-catalyzed cyclization of alkynols has been extensively developed to access oxycyclic compounds.[1,2] More importantly, this cyclization could further trigger a lot of tandem processes to generate molecular complexity and diversity from some specifically designed alkynol derivatives since the initially formed enol ether moiety can usually be activated by the same gold catalyst or additional catalyst for other bond-forming reactions (Scheme 1a).[3,4] Previously Barluenga et al developed the gold-catalyzed cycloisomerization of benzyl-substituted alkynols to afford a variety of benzo-fused ethers (Scheme 1b).[5] The reaction is initiated by an intramolecular hydroalkoxylation to form the cyclic enol ethers, followed by the intramolecular hydroarylation reaction promoted by the same catalyst. Herein we disclose our discovery on a highly selective gold-catalyzed cycloisomerization of arylamino-substituted alkynols **1** to provide an efficient and unique synthesis of 2-aminoaryl-substituted 2,5-dihydrofurans **2** (Scheme 1c). Interestingly, this reaction may involve a series of consecutive transformations including intramolecular hydroalkoxylation (C–O bond formation), arylation (C–C bond formation) and a rare C–N bond cleavage process.



Scheme 1. Gold-catalyzed cycloisomerization of alkynols.

This novel transformation was occasionally found during our study on the heteronucleophilic substitution reactions of propargylic substrates.[6] We recently developed a highly regioselective aminolysis of propargylic epoxides to provide a high-yielding synthesis of 2-aryl-2-(arylamino)-3-butyn-1-ols **1**.[6e] The easy availability of these polyfunctionalized unsaturated materials led us to further explore their synthetic utility towards heterocycles. At the beginning, we performed the cyclization reaction of 2-(*N*-methylanilino)-2-phenyloct-3-yn-1-ol (**1aa**) in the presence of a catalytic amount of $(Ph_3P)AuCl$ (5 mol%) and $AgSbF_6$ (5 mol%), which gave 2-butyl-4-phenylfuran (**2aa**) in 70% yield (Scheme 2, eq. 1). The formation of **2aa** was ascribed to the ease of a deamination-aromatization process of the gold-induced cycloetherification intermediate **3aa**. The detection of the fragment byproduct *N*-methylaniline supports this assumption.

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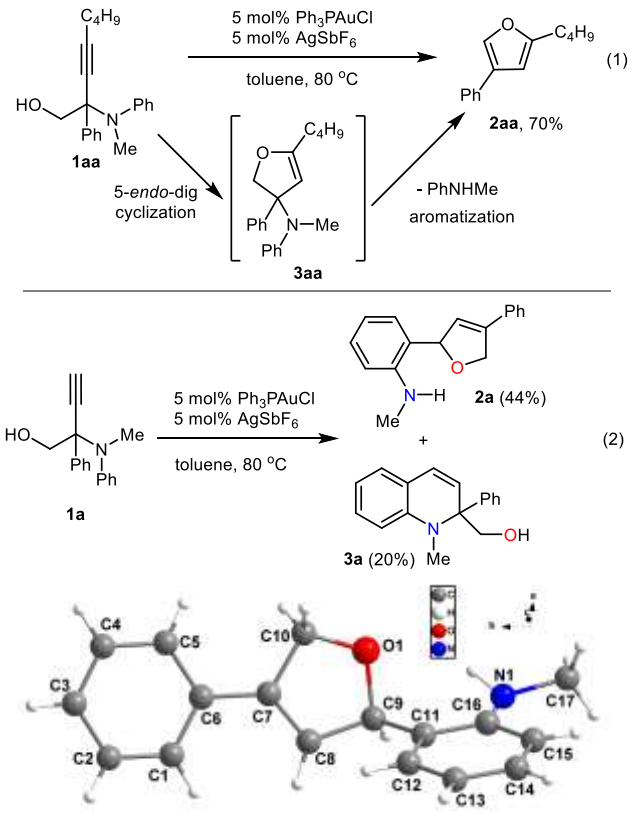


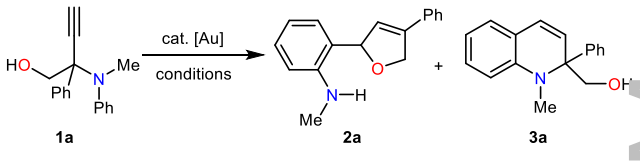
X-ray structure of **2a** (CCDC 1569495)

Scheme 2. Preliminary investigation on the gold-catalyzed cycloisomerization of 2-aryl-2-(arylamino)-3-butyn-1-ols.

Interestingly, when the terminal alkynyl amino alcohol **1a** was subjected to similar conditions, differently, two products **2a** and **3a** were obtained in 44% and 20% yield, respectively (Scheme 2, eq. 2). While the product **3a** was presumed as a result of the intramolecular hydroarylation[7] of the triple bond in **1a** and was easily identified by ^{1}H NMR spectra with the characteristic signals of the vinyl hydrogen atoms and the hydroxyl hydrogen, the structure of **2a** was not well assigned at first. Fortunately, single crystals of **2a** suitable for an X-ray diffraction study were obtained from a hexane-CH_2Cl_2 solution by slow evaporation, ultimately confirming the 2,5-dihydrofuran structure as shown in Scheme 2.[8]

It is well known that 2,5-dihydrofurans are not only important heterocycles frequently used as building blocks in organic synthesis, but also have been found in many bioactive reagents, pharmaceuticals, flavor chemicals and natural products.[9,10] Thus, new and efficient synthetic methods for functionalized 2,5-dihydrofurans is still in highly demand.[11] In this context, we attempted to improve the selectivity of the reaction for a useful synthesis of the 2,5-dihydrofuran product. Several gold catalysts generated from the bench available $(Ph_3P)AuCl$ and various silver salts were then evaluated (Table 1). No improvements were observed when the reaction was performed with a combination of $(Ph_3P)AuCl$ with AgOTf, $AgBF_4$ or $AgClO_4$ (entries 2-4). Fortunately, the selectivity could be greatly improved for a favored formation of **2a** when AgOTs was used (entry 5). Thus, when **1a** was heated with 5 mol% of $(Ph_3P)AuCl$ and 5 mol% of AgOTs at 80 °C in toluene for 0.5 h, **2a** was produced in 55% yield and only a trace amount of **3a** was detected by TLC. The use of either Ph_3PAuCl or AgOTs alone was ineffective to catalyze the reaction (entries 7 and 8). Particularly, the reaction using AgOTs alone afforded the cyclization-deamination product 3-phenylfuran in 35% yield as the major product (entry 8), suggesting that the gold catalyst plays a substantial role in the reaction. The selective formation of **2a** was also observed when $(Ph_3P)AuNTf_2$ was used, but in a slightly low yield (entry 6). Further optimizations revealed that the yield of **2a** could be improved to 65% when DCE was used as a solvent (entry 9). However, MeCN gave a yield less than 50% (entry 11). The reaction in THF also produced **2a** selectively in 60% yield (entry 11). The best result was obtained when the reaction was performed in $PhCF_3$ at 80 °C, and **2a** was obtained in 72% yield (entry 13). The reaction could also be performed at a lower temperature (e.g., 40 °C), however, a prolonged reaction time was required and the product yield dropped to 67% (entry 14).

Table 1. Optimization on reaction conditions [a]



run	catalyst	solvent	Yield (%)[b]	
			2a	**3a**
1	$Ph_3PAuCl/AgSbF_6$	toluene	44	20
2	$Ph_3PAuCl/AgOTf$	Toluene	41	20
3	$Ph_3PAuCl/AgBF_4$	Toluene	35	16
4	$Ph_3PAuCl/AgClO_4$	Toluene	28	11
5	$Ph_3PAuCl/AgOTs$	Toluene	55	trace
6	$Ph_3PAuNTf_2$	Toluene	50	trace
7	Ph_3PAuCl	Toluene	trace	trace
8[c]	AgOTs	Toluene	trace	trace
9	$Ph_3PAuCl/AgOTs$	DCE	65	trace
10[d]	$Ph_3PAuCl/AgOTs$	DCE	64	trace
11	$Ph_3PAuCl/AgOTs$	MeCN	48	trace
12	$Ph_3PAuCl/AgOTs$	THF	60	trace
13	$Ph_3PAuCl/AgOTs$	$PhCF_3$	72	trace
14[e]	$Ph_3PAuCl/AgOTs$	$PhCF_3$	67	trace

[a] Unless otherwise noted, **1a** (0.2 mmol) was treated with 5 mol% [Au] and 5 mol% [Ag] at 80 °C for 0.5 h in a solvent (2 mL).
[b] Isolated yields.
[c] 3-Phenylfuran was obtained in 35% yield.
[d] Room temperature, 3 h.
[e] 40 °C, 6 h.

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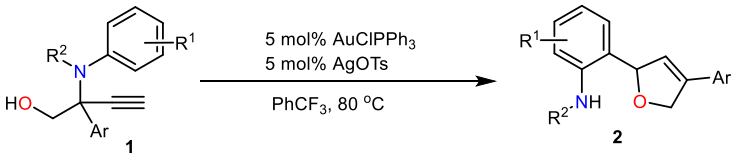
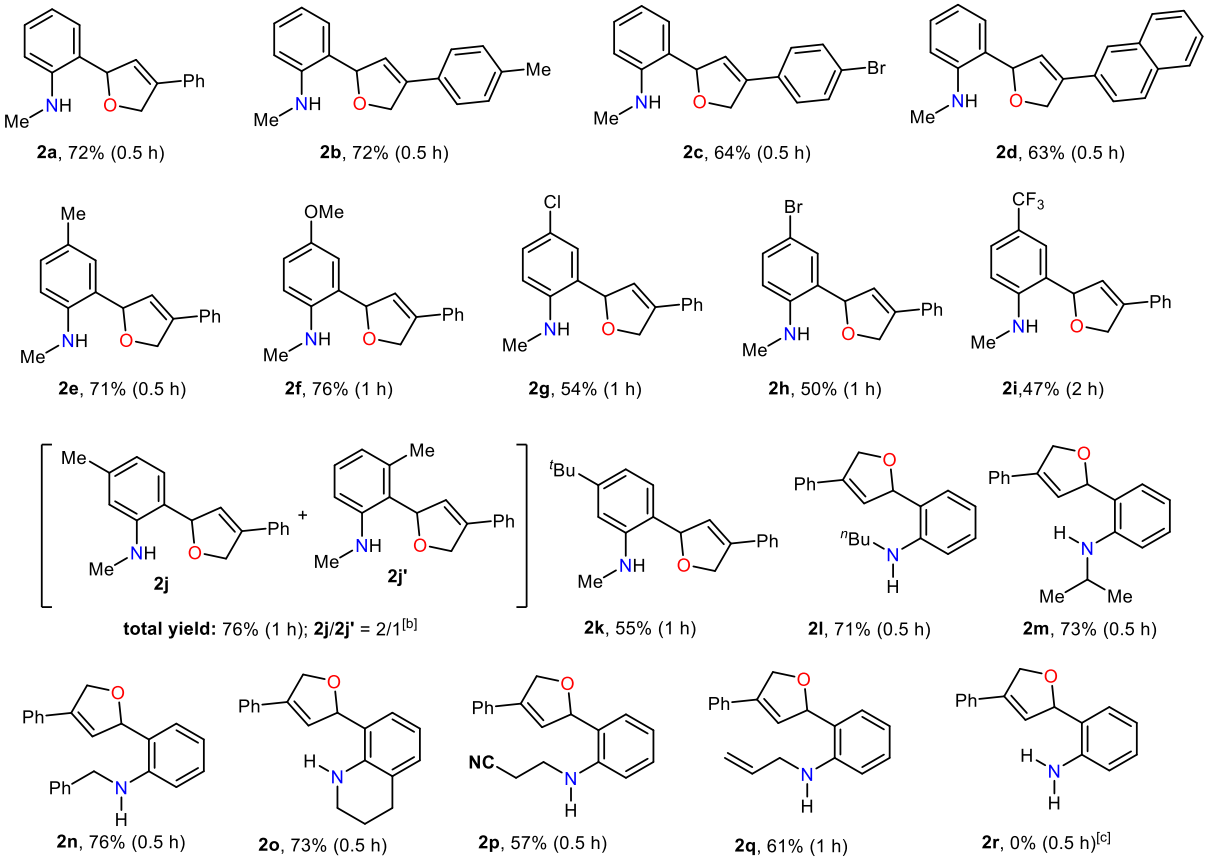
Table 2. Gold-catalyzed cycloisomerization of **1** to produce **2**[a]



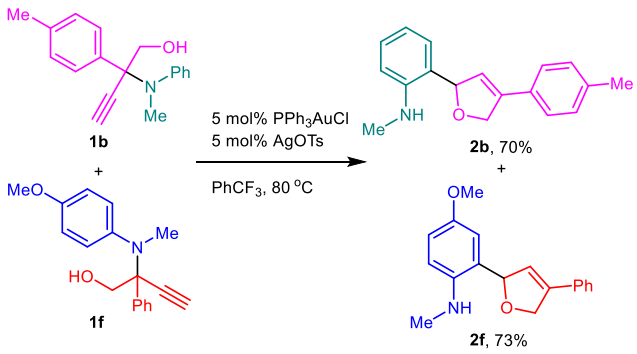


[a] Reaction conditions: **1** was treated with 5 mol% of $(Ph_3P)AuCl$ and 5 mol% of AgOTs in $PhCF_3$ at 80 °C for the specific time. Isolated yields were given.
[b] The ratio was deduced from the ^1H NMR spectra.
[c] A complex mixture was formed.

Table 2 shows the results on the preparation of various 2,5-dihydrofurans from the corresponding 2-arylamino homopropargyl alcohols by taking advantage of the gold-catalyzed protocol. The reactions proceeded smoothly with a lot of substituted 2-arylamino homopropargyl alcohols to give the desired products with high selectivity. The substituents R^1 such as methyl, chloro, methoxy, bromo and trifluoromethyl groups on the phenyl ring are tolerated. Comparatively, relatively low yields were obtained in case of R^1 as electron-withdrawing groups. When R^1 is a methyl at the *meta*-position of the phenyl ring, two regioisomers **2j** and **2j'** were obtained in a combined yield of 76% with a ratio of 2/1. Interestingly, when 2-(*N*-methyl(3-(*tert*-butyl)anilino)-2-phenyl-but-3-yn-1-ol (**2k**) was treated with the gold catalyst, the less sterically demanding product **2k** was formed exclusively in 55% yield. Moreover, we also examined the reactions of substrates bearing different substituents R^2. In addition to the methyl group, substrates bearing butyl, isopropyl, and benzyl groups are all smoothly converted into the corresponding products **2l-2n** in good yields. The reaction of a tetrahydroquinoline-derived homopropargyl alcohol also took place smoothly to give rise to the expected product **2o** in 73% yield. A cyano group is also compatible in the present reaction, as illustrated by the successful preparation of the compound **2p** in a moderate yield. Particularly interesting is that the allyl group in **1q** also survived in the reaction to afford **2q** in 61% yield. This result indicates that the present tandem transformation is prior to the Au-catalyzed skeletal reorganization of 1,6-enynes to afford 1-vinylcycloalkenes.[12] In addition, the ally group did not migrated from the N-atom to the phenyl ring in the final product, suggesting that the formation of a reactive vinyl ether is a necessity for the reaction.

However, when 2-phenyl-2-(anilino)but-3-yn-1-ol (**1r**) in which R^2 as a hydrogen atom was subjected to the gold catalytic condition, a complex mixture was generated and the desired 2,5-dihydrofuran was not detected.[13]

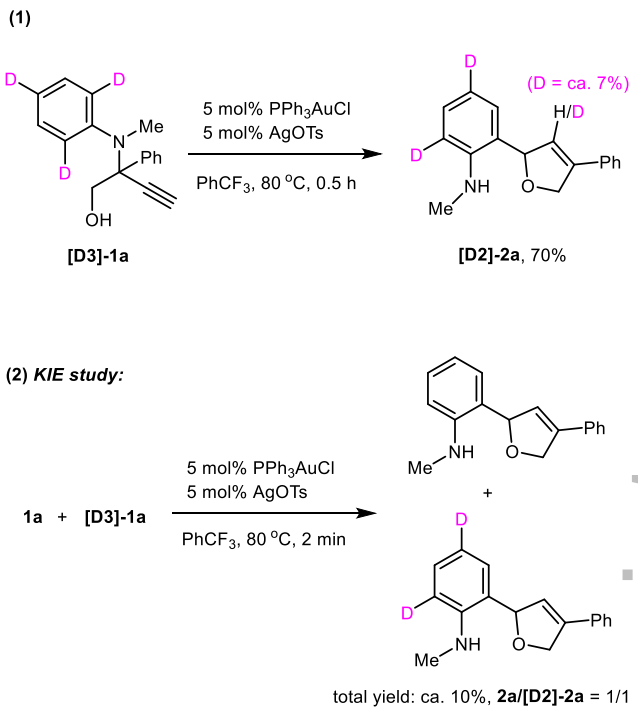
To shed light on the mechanism of the reaction, a crossover experiment using a 1/1 mixture of **1b** and **1f** was performed (Scheme 3). The reaction did not give any crossover product, indicating that a possible stepwise process, involving the formation of a cyclic allylic carbocation species directly from the C–N bond cleavage followed by the attack of the electron-rich aniline can be excluded.



Scheme 3. A crossover experiment

The labelling studies with deuterated substrates were also performed. The reaction of [**D3**]-**1a** under the optimal condition afforded **[D2]-2a** in 70% yield (Scheme 4, eq. 1). About 7% of D atom was observed in the vinyl position of **[D2]-2a**. The loss of other D atom from the product should be a result of the H/D exchange of the N-deuterated amino group (formed according to the proposed mechanism showed below) when purifying the product by column chromatography on silica. Furthermore, the treatment of a 1/1 mixture of **1a** and **[D3]-1a** under the catalytic condition for 2 min afforded **2a** and **[D2]-2a** as a 1/1 mixture in ca. 10% yield. This result indicates that the cleavage of the *ortho* C–H bond in the aniline ring is rapid and not rate-determining during the reaction, since no isotopic effect was observed.

Based on the above results and literature reports,[5] a plausible mechanism was proposed in Scheme 5. The coordination of the Au(I) species to **1** first activates the C≡C triple bond. The selective intramolecular nucleophilic attack of the hydroxyl oxygen to the activated alkyne in a 5-*endo-dig* manner then occurs to produce the intermediate **B**, protodeauration of which leads to the formation of the amino dihydrofuran **C** and regenerate the catalyst.[14] The gold catalyst should play a substantial role in the following steps to form the final product, as indicated by the results in entry 8 of Table 1 that the intermediate **C** may prudentially undergo the deamination process to give the furan product in the absence of the gold catalyst. It is reasonable to presume that further coordination of the gold catalyst



Scheme 4. The deuterium-labelled experiments

to the C=C double bond of **C** in the following step leads to the formation of the oxonium intermediate **D'**, and induces the nucleophilic attack of the electron-rich aniline scaffold to afford the iminium intermediate **E**. Accordingly, the formation of two products **2j** and **2j'** (Table 2) can be explained by the assumption that an intermediate like **D** could accept the attack of the electron-rich aniline scaffold on both sides and the steric effect led to a favored formation of the less sterically demanding product **2j**. This steric effect becomes extremely apparent when a large *t*-Bu group is incorporated on the *meta*-position of the aniline scaffold leading to the exclusive formation of the product **2k** (Table 2). Furthermore, the results of lower product yields and longer reaction time for the substrates bearing electron-withdrawing groups on the aniline scaffold (Table 2, **2g-2i**) are also consisted with such an assumption. The intermediate **E** may then evolve to the ammonium intermediate **F** via a rapid 1,3-H shift. Finally, the β-elimination reaction takes place to give the final product and liberates the gold catalyst. Alternatively, a route via the formation of the intermediate **G** from the β-elimination of **E** followed by 1,3-H shift is also possible to form the final product.

In summary, we have reported a gold-catalyzed cycloisomerization sequence of 2-aryl-2-(arylamino)-3-butyn-1-ols by using $(Ph_3P)AuCl$ and AgOTs as the optimal catalysts. The reaction is highly selective and shows a good tolerance of functional groups, providing an efficient method for the synthesis of 2-aminoaryl-substituted 2,5-dihydrofurans in moderate to good yields under mild conditions. Further study on the reaction scope and application of this method is being pursued.

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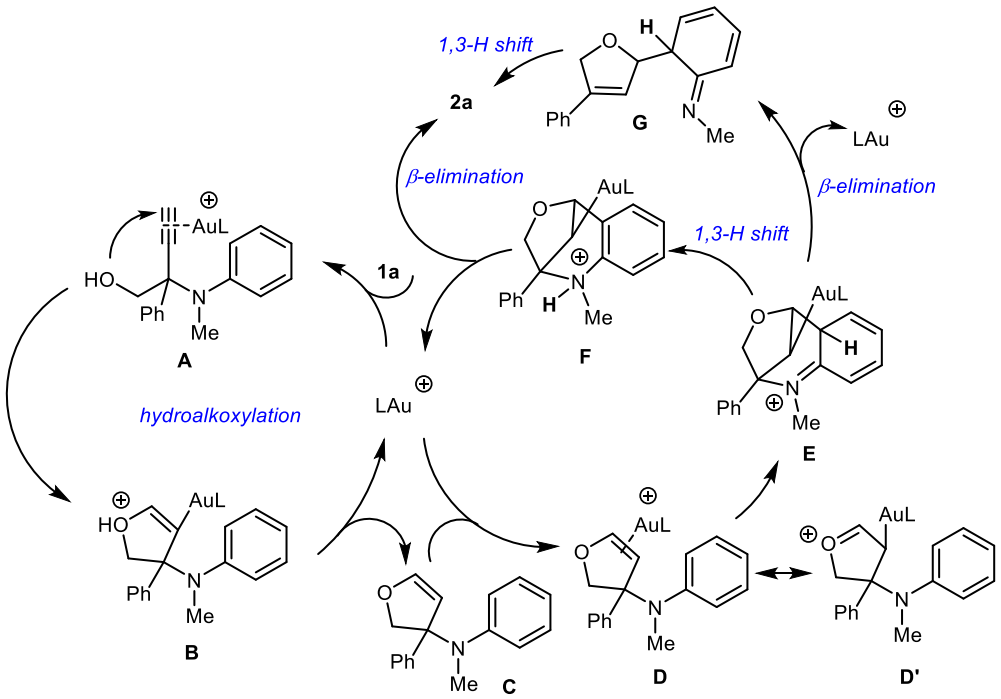

Scheme 5. The proposed mechanism

Experimental Section

Typical procedure for the gold-catalyzed cycloisomerization of 2-aryl-2-(arylamino)-3-butyn-1-ol: To a flame-dried Schlenk tube were added (PPh_3)AuCl (5.0 mg, 0.01 mmol), AgOTs (2.8 mg, 0.01 mmol) and $PhCF_3$ (1 mL) sequentially under a dry nitrogen atmosphere. The resulting mixture was stirred at room temperature for ca. 10 min, which was followed by the addition of 2-(methyl(phenyl)amino)-2-phenylbut-3-yn-1-ol **1a** (50.3 mg, 0.2 mmol) in $PhCF_3$ (1 mL) using a microsyringe. The resulting mixture was then submerged in an oil bath preheated to 80 °C. After complete consumption of the starting material (30 min), the mixture was concentrated after the addition of ca. 200 mg of silica gel under reduced pressure to afford a dry powder. The sample was purified by column chromatography on silica gel to afford **2a** (36.2 mg, 72%). White solid, Mp. 108.9−110.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42−7.32 (m, 5H), 7.27−7.23 (m, 1H), 7.14 (dd, J_1 = 8.0 Hz, J_2 = 1.4 Hz, 1H), 6.71−6.68 (m, 2H), 6.44 (dd, J_1 = 4.0 Hz, J_2 = 2.0 Hz, 1H), 6.05−6.02 (m, 1H), 5.15−5.05 (m, 2H), 4.57 (br, 1H), 2.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.0, 140.1, 132.3, 129.5, 128.8, 128.4, 127.1, 126.0, 124.9, 122.1, 116.5, 110.4, 86.4, 74.9, 30.7. HRMS (ESI-TOF): *m/z* = 252.1379, calcd for $C_{17}H_{18}NO$ [MH^+] 252.1388. The structure of this compound was further determined by an X-ray crystallographic analysis. The single crystals were obtained from a hexane-CH_2Cl_2 solution by slow evaporation. For details, see the Supporting Information.

Acknowledgements

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UPDATE

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