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Gold-catalyzed cascade C–H/C–H cross-coupling/cyclization/alkynylation: An efficient access to 3-alkynylpyrroles

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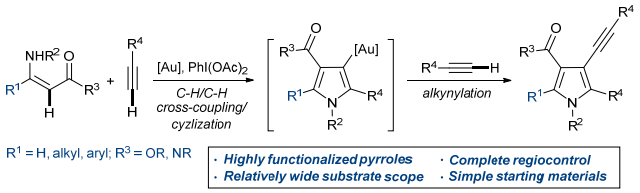
An efficient approach to 3-alkynylpyrroles has been developed through the gold-catalyzed reaction of *β*-enamino derivatives with terminal alkynes, which features complete regiocontrol, relatively wide substrate scope, and high functional group tolerance. Mechanistic studies show that the reaction proceeds through the gold-catalyzed cascade oxidative C−H/C−H cross-coupling, cyclization and alkynylation.

The construction of highly functionalized pyrroles has attracted significant attention of chemists owing to their prevalence in natural products, pharmaceuticals and organic functional materials.[1] On the other hand, acetylenes are among the most important functional groups due to their rigidity, electronic properties and easy modification.[2] Undoubtedly, the installation of alkynyl group on the pyrrole ring would offer an opportunity to discover new compounds with important functions. In contrast to the synthesis of 2-alkynylpyrroles,[3] the highly efficient and regiospecific synthesis of 3-alkynylpyrroles remains a significant challenge because of the low reactivity of the pyrrole C3 position. The limited approaches to 3-alkynylpyrroles include intra- and intermolecular cyclization, Sonogashira coupling, and the direct C–H alkynylation. The cyclization strategy employs highly functionalized alkynylamino alcohols[4] or 2*H*-azirines[5] as the starting materials that require multi-step synthesis. The Sonogashira coupling necessitates the prefunctionalization of pyrrole C3 position,[6] which is not an easy task as well. The most straightforward protocol to 3-alkynylpyrroles may be the direct C3–H alkynylation.[7,8] Unfortunately, this tactic encounters regioselectivity problems due to the inherent electronic characteristics of pyrroles. To achieve a regioselective C3–H alkynylation, the bulky triisopropylsilyl group is introduced to the nitrogen atom or both the more reactive C2 and C5 positions are blocked.[8] Thus, it is highly desirable to develop new protocols that accomplish the versatile and region-defined synthesis of 3-alkynylpyrroles from simple starting materials.

Over the past decade, significant progress has been made in the transition metal such as Pd, Rh, and Ru-catalyzed oxidative C–H/C–H cross-coupling.[9] In contrast, although gold-catalyzed C–H functionalizations have been extensively studied as a useful tool for the construction of various organic functional molecules,[10] only relatively few examples of oxidative C–H/C–H cross-coupling have been realized through gold catalysis due to the high Au(I)/Au(III) redox potential.[11] We have recently accomplished the Au-catalyzed C(sp^3)–H/C(sp)–H cross-coupling of 1,3-dicarbonyl compounds with terminal alkynes, which is followed by cyclization and oxidative alkynylation in a single operation.[12] This protocol combines the advantages of C–H functionalizations and the unique ability of gold as a mild carbophilic Lewis acid,[13] and finally offers a concise approach to 3-alkynylfurans. Inspired by this work, we rationalized that the region-defined synthesis of 3-alkynylpyrroles could be achieved through the oxidative alkynylation of the 3-pyrrolyl-gold complexes, which could be formed through the gold-catalyzed C–H/C–H cross-coupling/cyclization of readily available *β*-enamino esters and terminal alkynes (Scheme 1). Importantly, it is also possible to achieve the synthesis of C5-unsubstituted 3-alkynylpyrroles through the employment of suitable substrates.



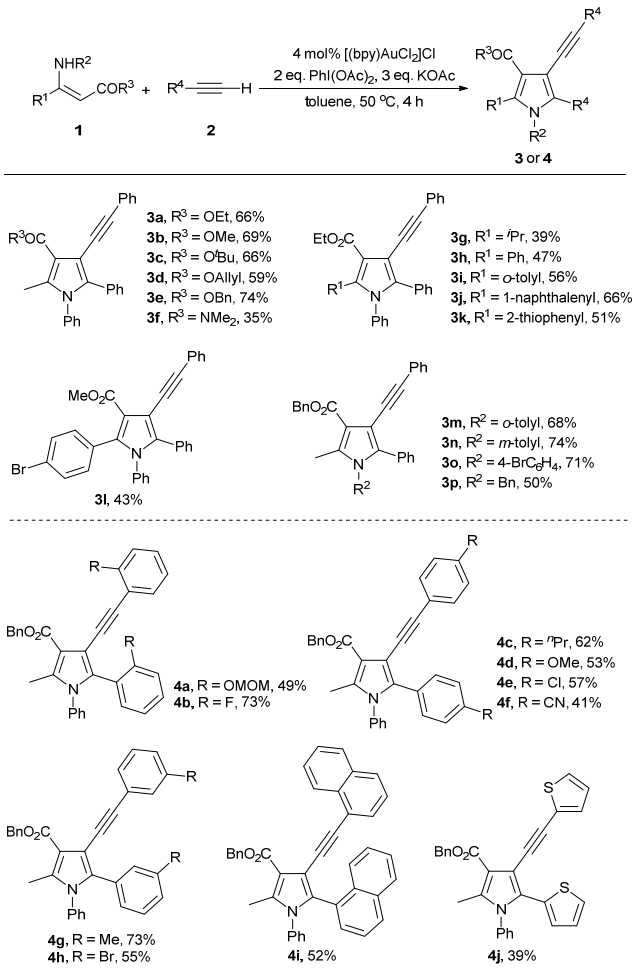
Scheme 1 Synthesis of 3-alkynylpyrroles.

To test the feasibility of our hypothesis, the reaction of (*Z*)-ethyl 3-(phenylamino)but-2-enoate (**1a**) with phenylacetylene (**2a**) was attempted. After screening various parameters including gold species, oxidants, bases, and solvents (Table S1, ESI†), the desired 3-alkynylpyrrole **3a** was obtained in good yield by using 4 mol% of $[(bpy)AuCl_2]Cl$ as the catalyst, 2.0 equiv of $PhI(OAc)_2$ as the oxidant, and 3.0 equiv of KOAc as the base in toluene at 50 ^oC for 4 h (Table S1, entry 30, ESI†). Compound **3a** was testified by X-ray crystallographic analysis (Figure S1, ESI†). Some points deserve additional remarks: (1) Besides Au(III) species, Au(I) complex such as Ph_3PAuCl also promoted the reaction (Table S1, entry 2, ESI†); (2) the reaction could proceed in the absence of a base, albeit with lower efficiency (Table S1, entry 22, ESI†); and (3) polar solvents such as CH_3CN, DMF, and MeOH completely shut down the reaction (Table S1, entries 19-21, ESI†).

With the optimized reaction conditions in hand, we then examined the scope of enamines. As illustrated in Table 1, various *β*-enamino esters were found to be suitable coupling partners, affording the corresponding pyrrole products **3** in 59%-74% yields (Table 1, **3a**-**3e**). Besides *β*-enamino esters, *β*-

enamino amide was also engaged in the reaction (Table 1, **3f**). 3-Alkynylpyrroles with an alkyl, aryl, or heteroaryl substituent at the C5 position could be synthesized by introducing different R^1 groups to the enamino esters (Table 1, **3g-3l**). In addition, the benzyl and other aryl groups were tolerated on the nitrogen atom of enamino ester **1** (Table 1, **3m-3p**).

Table 1 Synthesis of fully substituted 3-alkynylpyrroles[a]

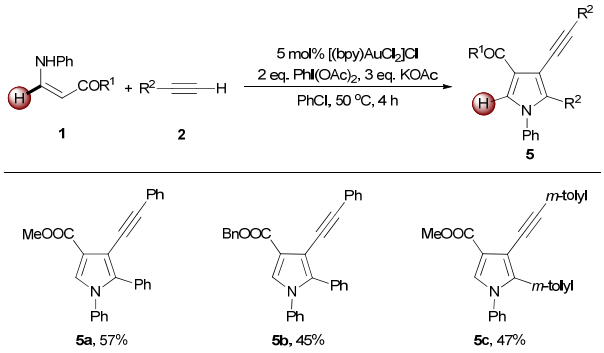


[a] Reaction conditions: enamine **1** (1.5 mmol), terminal alkyne **2** (0.6 mmol), $[(bpy)AuCl_2]Cl$ (4 mol%), $PhI(OAc)_2$ (1.2 mmol), KOAc (1.8 mmol) and toluene (3.0 mL) at 50 °C for 4 h. Isolated yields.

Subsequently, the scope of terminal alkynes was investigated (Table 1). Pleasantly, a variety of aryl and heteroaryl substituted terminal alkynes successfully participated in the reaction to afford the corresponding 3-alkynylpyrroles **4** in moderate to good yields. Both the electron-donating and electron-withdrawing substituents were well tolerated under the optimized reaction conditions (Table 1, **4a-4h**). Moreover, these groups could be introduced to the *ortho*, *meta*, and *para* positions of aryl acetylenes (Table 1, **4a-4h**). The bulky naphthalenyl group did not hinder the smooth happening of the reaction (Table 1, **4i**). It is noteworthy that this protocol could be tolerant of important functional groups such as halogen, OMOM (OMOM = methoxymethoxy) and CN. Unfortunately, aliphatic alkynes did not work in this reaction.

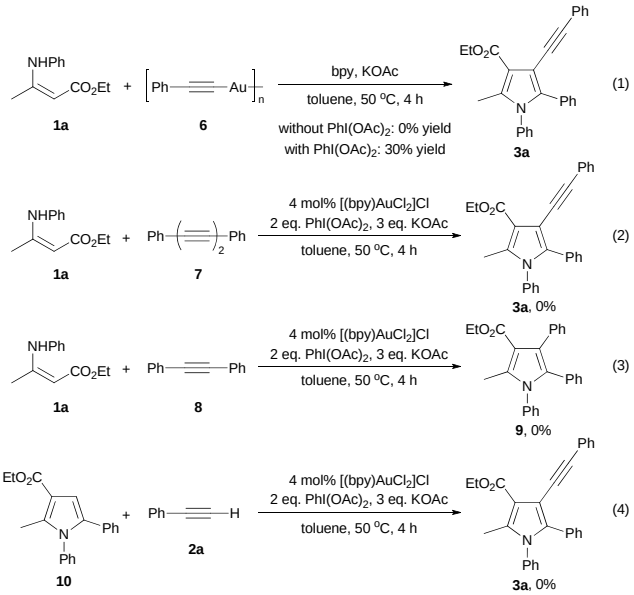
This protocol was also applicable to the reaction of 1,2-disubstituted enamines with alkynes through a proper modification of the reaction condition, which offered an efficient approach to C5-unsubstituted 3-alkynylpyrroles (Table 2, **5a-5c**), which are very useful for further synthetic transformation on the C5-positon.

Table 2 Synthesis of C5-unsubstituted 3-alkynylpyrroles[a]



[a] Reaction conditions: *β*-enamino ester **1** (1.2 mmol), terminal alkyne **2** (0.4 mmol), $[(bpy)AuCl_2]Cl$ (5 mol%), $PhI(OAc)_2$ (0.8 mmol), KOAc (1.2 mmol) and chlorobenzene (2.0 mL) at 50 °C for 4 h. Isolated yields.

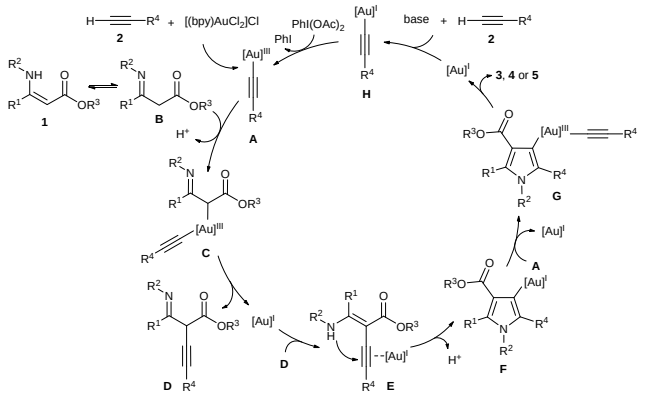
Subsequently, the mechanism of this reaction was studied. Treatment of **1a** with gold(I)-acetylide **6** failed to deliver any the desired product **3a** in the absence of an oxidant (eqn 1).[14] However, addition of 2.0 equiv of $PhI(OAc)_2$ to the reaction mixture led to the formation of **3a** in 30% yield, indicating that gold(III) rather than gold(I)-acetylide was the active species in the catalytic cycle.



Given the fact that diyne **7** resulting from the homo-coupling of **2a** was detected in the reaction system of **1a** with **2a**,[15] the reaction of **7** with **1a** was attempted (eqn 2). However, no product **3a** was observed in the reaction system, which precluded the possibility of the tandem gold-catalyzed homo-coupling of terminal alkyne and subsequent oxidative annulation of the resulting diyne with enamine. In addition, the reaction of **1a** with diphenylacetylene (**8**) did not afford any **9** (eqn 3), suggesting that the acetylenic proton is crucial for the happening of the reaction. The direct C–H alkynylation of the C3-unsubstituted

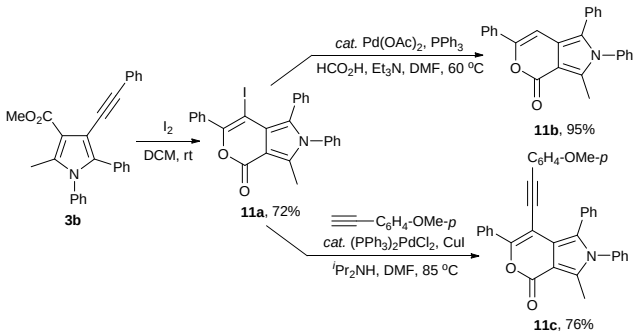
pyrrole **10** with **2a** did not work as well (eqn 4), indicating that the dehydrogenative cyclization of an enamine with an alkyne and subsequent C3−H alkynylation of the resulting pyrrole ring was not a possible pathway.

All of the above data support a mechanism that involves the gold-catalyzed tandem oxidative C−H/C−H cross-coupling of *β*-enamino ester with terminal alkyne, cyclization, and in situ oxidative alkynylation of the pyrrolyl-gold intermediate (Scheme 2).[12,16] The cascade reaction starts with the reaction of gold(III) catalyst and the terminal alkyne **2** to generate the gold(III) acetylide **A**. Meanwhile, *β*-enamino ester **1** tautomerizes to *β*-imino ester **B**.[17] The reaction of **B** with **A** forms the key gold(III) intermediate **C** and subsequent reductive elimination delivers the 2-alkynyl-*β*-imino ester **D** and a gold(I) species.[18] The tautomerization of **D** to 2-alkynyl-*β*-enamino ester **E** (or allenyl-*β*-imino ester[19]), then coordinates with gold(I) to induce the intramolecular cyclization to afford the 3-pyrrolyl-gold(I) intermediate **F**.[20] The transmetallation from **F** to **A** leads to the formation of **G**. Upon reductive elimination of **G**,[18] the corresponding product **3**, **4** or **5** is formed. The reaction of the released gold(I) complex with **2** and subsequent oxidation by $PhI(OAc)_2$ lead to the regeneration of the gold(III) acetylide **A**.



Scheme 2 Proposed mechanism.

Pyrrole-fused pyranones are important structure motifs found in many marine natural products, which have a wide range of biological activities including antitumor activity, HIV-1 integrase inhibition, and multidrug-resistance reversal.[21] Our protocol provides an efficient approach to pyrrole-fused pyranone structures. As shown in Scheme 3, 3-alkynylpyrrole **3b** readily underwent an iodocyclization reaction to afford the iodo-substituted pyrano[4,3-*c*]pyrrol-4(2*H*)-one (**11a**). The structure of **11a** was confirmed by single-crystal X-ray diffraction (Figure S2, ESI†). Compound **11a** could be further transformed to **11b** and **11c** through the hydrodehalogenation reaction and the Sonogashira coupling,[22] respectively, which may be a kind of potential skeletons for pharmaceutical molecules.



Scheme 3 Transformations of 3-alkynylpyrroles.

In summary, a concise and regio-defined approach to 3-alkynylpyrroles has been developed through the gold-catalyzed cascade oxidative C−H/C−H cross-coupling/cyclization/alkynylation of readily available enamines with terminal alkynes. The regiospecific formation of the gold 3-pyrrolyl intermediates solves the C2/C3 selectivity issue encountered in the pyrrole C−H alkynylation reactions. This protocol provides an efficient approach to pyrrole-fused pyranone structures, which enriches the chemistry of gold in catalyzing the oxidative C−H/C−H cross-couplings and further demonstrates the power of gold catalysis in constructing complex molecules.[23]

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† Electronic Supplementary Information (ESI) available: detailed experimental procedures, analytical data, and ORTEP diagrams of of **3a** (CCDC 1031864) and **11a** (CCDC 1031865). See DOI: 10.1039/b000000x/

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