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Gold-catalyzed cascade C–C and C–N bond formation: synthesis of polysubstituted indolequinones and pyrroles

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ABSTRACT

The combination of Ph_3PAuCl and AgOTf was proven to be an efficient catalyst for the cascade C–C and C–N bond formation reactions from enamines and bromoquinones or nitroolefins. This protocol affords a straightforward method for the synthesis of polysubstituted indolequinones and pyrroles in good yields.
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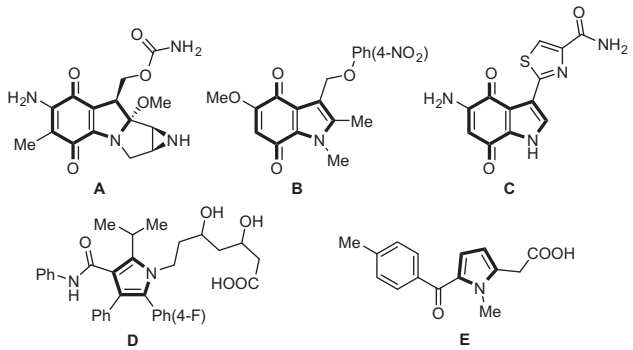
Introduction

Gold catalysis has emerged as a frontier research area in organic chemistry, owing to its excellent reactivity, compatibility with aqueous medium, and mild reaction conditions.[1] As our continued interests in gold-catalysis,[2] herein we report an efficient, convergent, and general procedure for the synthesis of polysubstituted indolequinones and pyrrole analogues through domino C–C and C–N bond forming process based on the catalysis of gold.[3]

Five-membered nitrogen containing heterocycles, such as polysubstituted indolequinones and pyrroles present privileged skeletons frequently existed in a broad range of natural products and biologically important molecules (Scheme 1),[4] also as the key intermediates for the synthesis of functional materials.[5] Consequently, developing benign, eco-friendly, and practical synthetic methods for the synthesis of these important heterocyclic scaffolds with simple substrates remains a continued strong demand.[6]

Results and discussion

In our initial study of the synthesis of polysubstituted indolequinones,[7] the cascade C–C and C–N bond formation reaction of 2-bromo-naphthalene-1,4-dione **1a** with enamine **2a** was selected as model reaction. The results are summarized in Table 1. The cascade reaction could occur under the catalysis of Au(III) complex **I** (Scheme 2) to give the corresponding **3a** in 24% yield in CH_2Cl_2 at 60 °C (Table 1, entry 1). Other Au(III) catalysts (**II**, **III**) showed similar low catalytic activity (Table 1, entries 2 and 3). The utilization of Ph_3PAuCl instead of the Au(III) catalysts resulted in an increased yield (Table 1, entry 4). To our delight, the coupling reaction provided the desired product in a satisfied yield (78%) under the catalysis of the combination of Ph_3PAuCl and AgOTf, while using AgOTf as a single catalyst offered **3a** only in 17% yield (Table 1, entries 6 and 7). The reaction did not proceed as efficiently as CH_2Cl_2 with other solvents, such as CH_3CN, MeOH, THF, hexane, and toluene (Table 1, entries 8–12). Other bases such as K_3PO_4, *t*-BuOK, and Cs_2CO_3 were also evaluated, and no improved results



Scheme 1. Some drugs containing indolequinones and pyrrole substructures.

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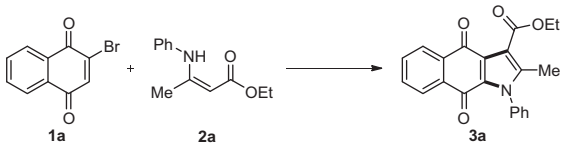
Table 1
The optimization of reaction conditions for the synthesis of indolequinone[a]

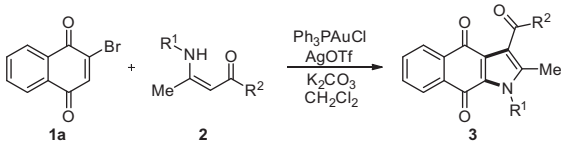


1a 2a 3a

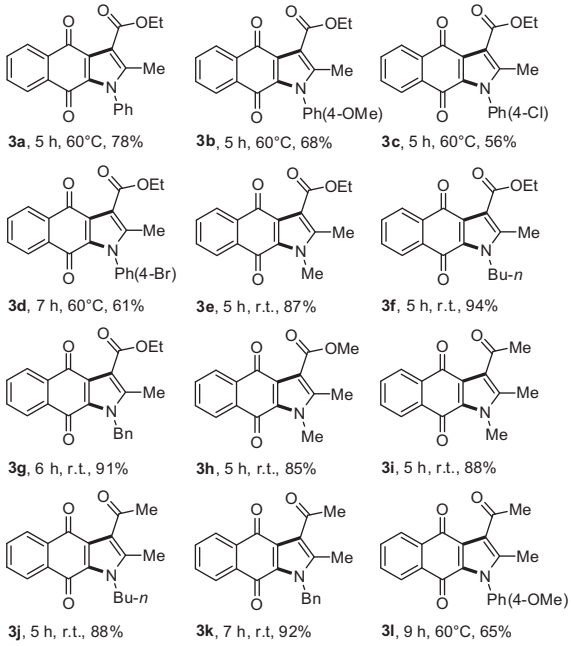
Entry	Catalyst	Solvent	Base	Yield[b]
1	**I**	CH_2Cl_2	K_2CO_3	24
2	**II**	CH_2Cl_2	K_2CO_3	16
3	**III**	CH_2Cl_2	K_2CO_3	18
4	Ph_3PAuCl	CH_2Cl_2	K_2CO_3	43
5	Bu_4NAuCl_4	CH_2Cl_2	K_2CO_3	13
6	Ph_3PAuCl + AgOTf	CH_2Cl_2	K_2CO_3	78
7	AgOTf	CH_2Cl_2	K_2CO_3	17
8	Ph_3PAuCl + AgOTf	CH_3CN	K_2CO_3	35
9	Ph_3PAuCl + AgOTf	MeOH	K_2CO_3	13
10	Ph_3PAuCl + AgOTf	THF	K_2CO_3	<10
11	Ph_3PAuCl + AgOTf	Hexane	K_2CO_3	23
12	Ph_3PAuCl + AgOTf	Toluene	K_2CO_3	28
13	Ph_3PAuCl + AgOTf	CH_2Cl_2	K_3PO_4	45
14	Ph_3PAuCl + AgOTf	CH_2Cl_2	*t*-BuOK	51
15	Ph_3PAuCl + AgOTf	CH_2Cl_2	Cs_2CO_3	63
16[c]	Ph_3PAuCl + AgOTf	CH_2Cl_2	K_2CO_3	52

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.55 mmol), solvent (2.0 mL), catalyst (5 mol %), base (1.5 mmol), 60 °C, 5 h.
[b] Isolated yield (%).
[c] 2 mol % catalyst was used.

Table 2
Scope of the reaction for the synthesis of indolequinones[a]



1a 2 3



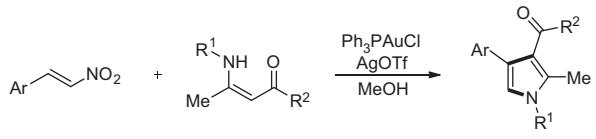
[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.55 mmol), Ph_3PAuCl (5 mol %), AgOTf (5 mol %), K_2CO_3 (1.5 mmol), CH_2Cl_2 (2.0 mL), rt or 60 °C. Yields are for the isolated products.

were obtained (Table 1, entries 13–15).[8] Further studies indicated that reducing the catalyst loading to 2% affected its catalytic efficiency (Table 1, entry 16).

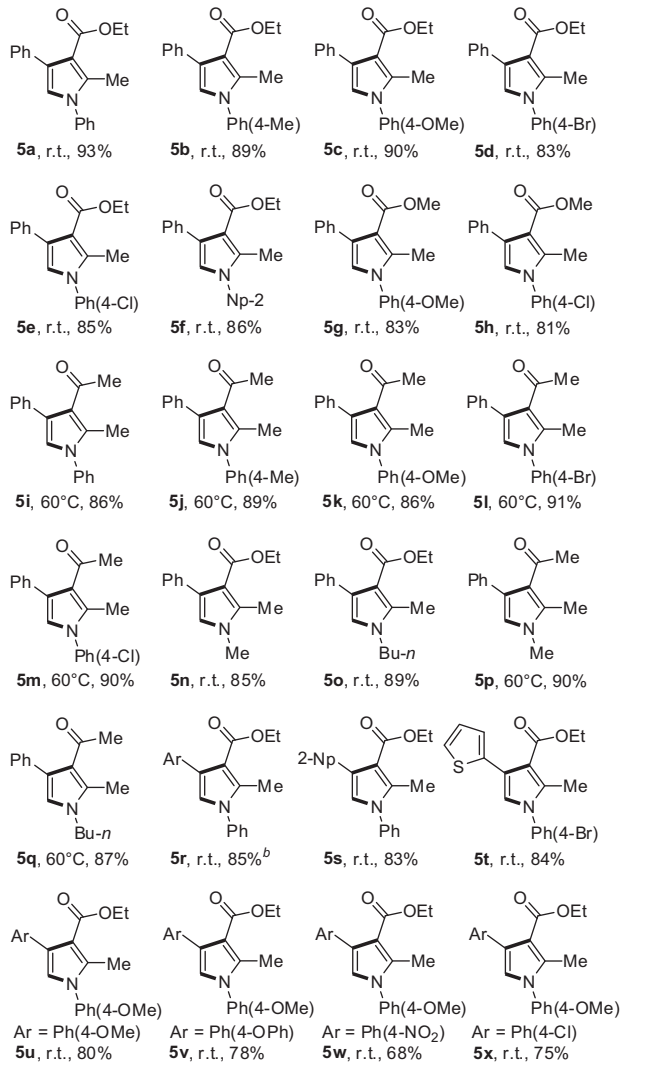
With the optimized reaction conditions in hand (Table 1, entry 6), we investigated the scope of this protocol (Table 2). It was found that electron-donating as well as electron-withdrawing groups on the aromatic rings of enamines were compatible under the reaction conditions, and offered the desired product **3a**–**d** in moderate to good yields. When alkyl-substituted β-enamino esters were tested in the reaction, better transformations were obtained even at room temperature (Table 2, **3e**–**h**). To our delight, this reaction can also tolerate a broad substituent range of β-enamino ketones (Table 2, **3i**–**l**) (Scheme 2).

To further illustrate the generality of our method using gold(I) as catalyst for the tandem C–C and C–N bond forming process, we applied this protocol to the synthesis of polysubstituted pyrroles with a series of nitroolefins.[3] Initially, treatment of **2a** with

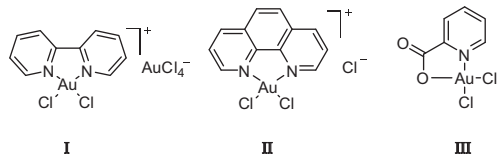
Table 3
Scope of the reaction for the synthesis of polysubstituted pyrroles[a,b]



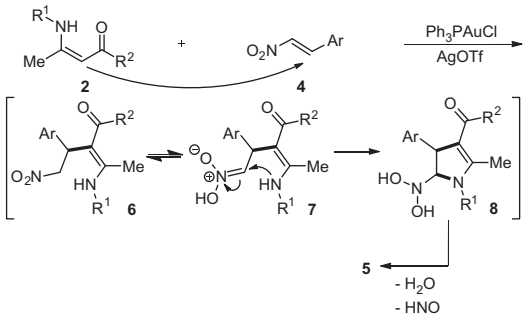
4 2 5



[a] Reaction conditions: **4** (0.50 mmol), **2** (0.55 mmol), Ph_3PAuCl (1 mol %), AgOTf (1 mol %), MeOH (2.0 mL), rt or 60 °C, 8 h. Yields are for the isolated products.
[b] Ar = 1,3,5-$(OMe)_3$Ph.



Scheme 2. Gold-complexes.



Scheme 3. Proposed reaction mechanism for the synthesis of polysubstituted pyrroles.

(*E*)-(2-nitrovinyl)benzene **4a** in the presence of the combining catalysts (Ph_3PAuCl and AgOTf) in CH_2Cl_2 gave the corresponding product **5a** in 78% yield. Control experiment using either Ph_3PAuCl or AgOTf alone furnished 48% and 41% yields, respectively. The examination of solvent effect revealed that MeOH was the best reaction media for this reaction, which proceeded in 93% yield.

To explore the generality and scope of this reaction, different enamine esters with (*E*)-(2-nitrovinyl)benzenes were examined under the optimized conditions, and the results are summarized in Table 3. To our delight, this method was found to be very general for a wide range of amines with various substituents on the aromatic rings, provided the expected products in good to excellent yields, and the electron-rich enaminoesters showed better reactivity and gave higher yields than electron-deficient ones (Table 3), **5a–h**). The reaction of nitroolefin **4a** with various enaminones also could offer the corresponding pyrrole products in good yields although it needs a higher temperature of 60 °C (Table 3), **5i–m**, **p** and **q**). When alkyl substituent enamine esters were tested in the reaction, **5n** and **5o** were obtained in 85% and 89% yields, respectively. The reaction scope was also investigated with respect to nitroolefins. Nitroolefins including methoxy-, phenoxy-, chloro-, or nitro groups on the arene proceeded smoothly to give the corresponding pyrroles in good yields (Table 3), **5u–x**). In addition, the nitrolefin possessing a thienyl group also underwent the tandem reaction to give pyrrole product **5t** in good yield.

The mechanism for the cascade reaction is not certainly clear. On the basis of literatures,[9] a plausible mechanism for the synthesis of polysubstituted pyrroles is proposed in Scheme 3. In the presence of Ph_3PAuCl and AgOTf,[10] conjugate addition of **2** to **4** gives Michael adduct **6**. Subsequently, **6** tautomerizes into the intermediate **7**, then attacked by the nitrogen atom to form **8**. Finally, the elimination of water and nitroxyl molecules affords the desired product **5**.

Conclusions

We have demonstrated a facile and mild preparation of polysubstituted indolequinone and pyrrole compounds. The combination of Ph_3PAuCl and AgOTf was proven to be an efficient catalyst for the cascade C–C and C–N bond formation reactions from enamines and bromoquinones or nitroolefins. The safe, convenient, and environmentally benign process, as well as the broad substrate scope, low catalyst loading, and good yields make this protocol very practical. Further studies for the detailed mechanism and exploration of gold-catalyzed tandem reactions for the synthesis of biologically important compounds are underway in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data (Experimental details and the characterization data.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.100.

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