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Mild gold-catalyzed three-component dehydrogenative coupling of terminal alkynes to amines and indole-2-carboxaldehyde†

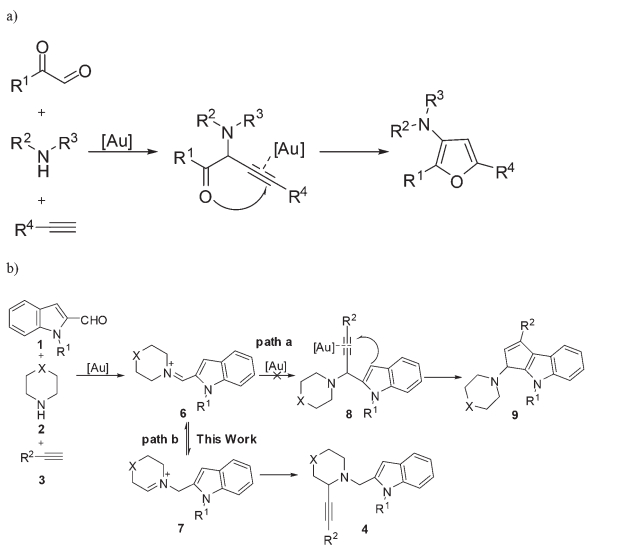
Jian Li,[a] Hongni Wang,[a] Jiangtao Sun,[a] Yang Yang[b] and Li Liu*[b]

A mild gold-catalyzed three-component dehydrogenative coupling of terminal alkynes to amines and indole-2-carboxaldehyde has been developed, which provides a practical synthetic strategy for the synthesis of indole derivatives.

Introduction

Indoles represent one important diverse family of pharmaceuticals and biologically active natural compounds.[1] Not surprisingly, numerous studies and applications have focused on the functionalization of indoles.[2] The efficiency of the synthesis can be increased significantly if the event of indole functionalization is coupled with two other or even more compounds in a cascade manner.[3] Such one-pot multicomponent coupling reactions have been developed as an attractive and powerful methodology for the formation of carbon–carbon and carbon–heteroatom bonds in a step- and atom-economical fashion.[4] Among these, a number of key building block syntheses using aldehydes, amines and alkynes as the starting materials have been reported.[5] However, an efficient synthesis with high chemo- and regioselectivity, which would enable access to complex indole derivatives *via* a cascade manner, still remains challenging. Herein, we report a mild three-component cross-dehydrogenative coupling (CDC) of terminal alkynes to amines and indole-2-carboxaldehyde *via* a gold-catalyzed condensation–alkynylation cascade as a continuation of efforts in this area.

Gold catalysts, well known for their ability to promote nucleophilic attack on acetylenes, have recently attracted interest from the synthetic chemistry community.[6] Gold catalysts have also been used in domino reactions.[7] We recently developed an efficient three-component coupling reaction of phenylglyoxal derivatives, secondary amines and terminal alkynes toward a variety of furan derivatives mediated by gold(III) (Scheme 1a).[8] With this background in mind, we have been engaged in realizing the abundance of indole derivatives *via* this one-pot multicomponent strategy. Then, indole-2-carboxaldehyde was chosen as the substrate to couple with secondary amines and terminal alkynes. We hypothesized that these three compounds would couple together under catalysis by a gold catalyst to represent the required propargylamine intermediate **8**,[9] which, upon activation of the triple bond with gold, would undergo an intramolecular cyclization[10] into disubstituted cyclopentaindole **9**. However, when the reaction was conducted under gold catalysis, product **4** was found instead of indole **9** (Scheme 1b). We proposed that the *exo*-iminium



Scheme 1 Discovery of this work and a previous report with a similar iminium isomerization process. (a) Gold(III)-catalyzed three-component coupling (TCC) reaction selective towards furans. (b) Initial discovery of the three-component dehydrogenative coupling.

[a]*School of Pharmaceutical Engineering & Life Sciences, Chang Zhou University, Changzhou, 213164, P. R. China*
[b]*School of Petrochemical Engineering, Chang Zhou University, Changzhou, 213164, P. R. China. E-mail: liliuchem@gmail.com; Fax: +86 519 86330224*

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ion **6** isomerized into *endo*-iminium ion **7**, the C(sp^3)–H bond of intermediate **7** at the C1 atom was directly activated and functionalized by terminal alkynes catalyzed by Au complexes. Such a CDC style reaction has no limitations compared with the traditional CDC alkynylation reaction, which has to use *N*-aromatic or *N*-acyl substitutions and stoichiometric exogenous oxidants.[11] This strategy might have more potential in the synthesis of complex indoles as the substrates are simple and available. Recently, Seidel developed a Cu(II)-catalyzed alkynylation of pyrrolidines during a similar iminium isomerization process,[12a,b] and Nakamura reported a similar redox cross-dehydrogenative coupling of propargylic amines and terminal alkynes catalyzed by zinc(II).[12c] Very recently, Yu and coworkers reported a similar method to access C1-alkynylated tetrahydroisoquinoline (THIQ) products (*endo*-yne-THIQs) *via* a CuI-mediated reaction,[13a] but in their system some of products were mixed with *exo*-C1-alkynylated THIQ.

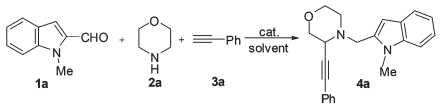
Results and discussion

Initially, we began our exploration by using the model substrate indole-2-carboxaldehyde **1a** (0.5 mmol), morpholine **2a** (0.75 mmol), and phenylacetylene **3a** (1 mmol) employing different catalysts. It was found that trace amounts of desired product **4a** was formed in the presence of copper salt CuI (Table 1, entry 1). A range of gold catalysts were subsequently evaluated, as summarized in Table 1. Ultimately, $AuBr_3$ was found to be the best catalyst for the reaction to afford the desired product **4a** in 62% yield. The other gold species gave lower efficiencies (Table 1, entries 2–5). In an attempt to improve the yield of **4a** by surveying different solvents, various solvents such as DCE, CH_3CN, DMF and toluene were tested in the reaction. They showed lower yields compared to MeOH (Table 1, entries 7–10). In addition, by lowering the temperature to 30 °C, the yield was decreased to 45%. The reaction was not improved by the presence of 10 mol% or 20 mol% $AuBr_3$. Therefore, our optimization identified that treatment of indole **1a** with 5 mol% of $AuBr_3$ as the catalyst, 1.5 equiv. of **2a** and 2 equiv. of **3a** in MeOH at 60 °C afforded **4a** in 62% isolated yield.

With the optimized reaction conditions in hand, the substrate scope of this $AuBr_3$-catalyzed cascade reaction was explored by using a wide range of different secondary amines **2** and alkynes **3** (Tables 2 and 3). We were happy to find that aryl alkynes bearing electron-donating and electron-withdrawing substituents produced the desired products in good yields (**4a**–**4g**, Table 2). Various different groups at the aromatic moiety of alkynes, such as halogen, methyl and methoxy, were well tolerated in these mild transformations. An aryl alkyne bearing long aliphatic chain such as 1-ethynyl-4-pentylbenzene could be smoothly transformed into the desired product in 72% yield (**4e**, Table 2). Furthermore, aliphatic alkyne (**4g**, Table 2) was also applicable in the target reaction in 62% yield.

Next, the scope of indole aldehydes **1** and secondary amine **2** was examined. Interestingly, by replacing morpholine with tetrahydroisoquinolines, this transformation proceeded smoothly in excellent yields. As is shown in Table 3, various aryl alkynes **3** were found to be suitable reaction partners with 1-methyl-1*H*-indole-2-carbaldehyde and THIQ providing the corresponding CDC products **5** (Table 3). Terminal alkynes **3** containing the halo, fluoro-, alkyl and methoxy groups, satisfactorily underwent reaction to afford the desired products in good yields (Table 3, **5a**–**5h**). *N*-Boc and *N*-Bn protected indoles were also tested. All of the reactions proceeded efficiently to

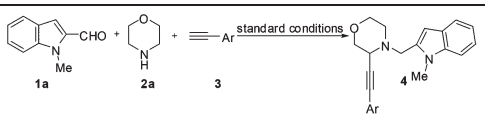
Table 1 Screening of reaction conditions for formation of **4a**[a]

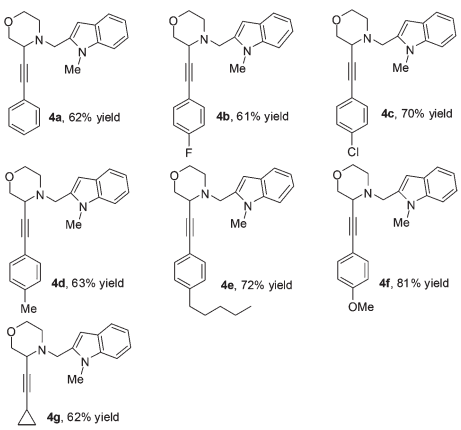


Entry	Catalyst	Solvent	Temp (°C)	Yield of **4a** (%)[b]
1	CuI	DCE	60	Trace
2	Ph_3PAuCl	MeOH	60	11
3	AuCl	MeOH	60	7
4	$HAuCl_4$	MeOH	60	51
5	$NaAuCl_4$	MeOH	60	47
6	$AuBr_3$	MeOH	60	62
7	$AuBr_3$	Toluene	60	33
8	$AuBr_3$	CH_3CN	60	21
9	$AuBr_3$	DMF	60	0
10	$AuBr_3$	DCE	60	42
11	$AuBr_3$	MeOH	30	45
12	$AuBr_3$	MeOH	80	50
13[c]	$AuBr_3$	MeOH	60	65
14[d]	$AuBr_3$	MeOH	60	67

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), **3a** (1 mmol), catalyst (5 mol%, 0.025 mmol), in solvent (2 mL) at 60 °C overnight. [b] Isolated yields. [c] 10 mol% of catalyst was employed. [d] 20 mol% of catalyst was employed.

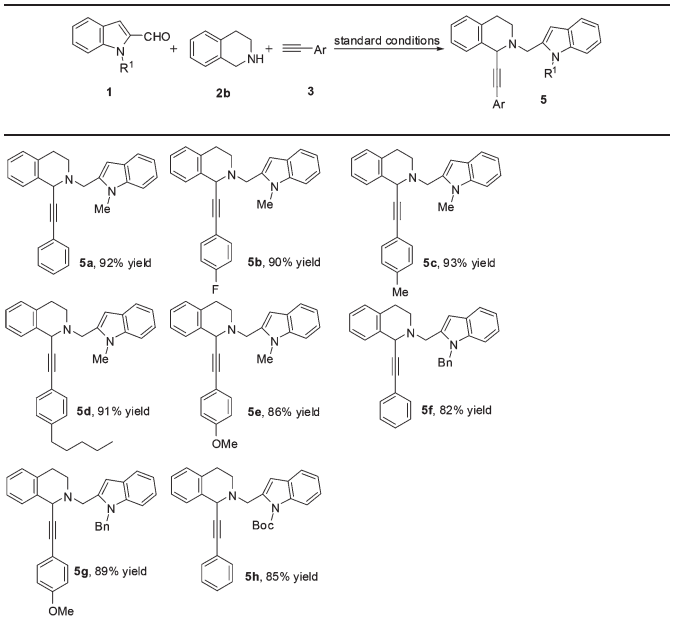
Table 2 Scope of alkynes in the morpholine C1-alkynylation[a,b]





[a] **1** (0.5 mmol), **2a** (0.75 mmol), **3** (1 mmol), $AuBr_3$ (5 mol%, 0.025 mmol), in MeOH (2 mL) at 60 °C overnight. [b] Isolated yields.

Table 3 Scope of alkynes in the THIQ C1-alkynylation[a,b]



[a] **1a** (0.5 mmol), **2b** (0.75 mmol), **3a** (1 mmol), $AuBr_3$ (5 mol%, 0.025 mmol), in MeOH (2 mL) at 60 °C overnight. [b] Isolated yields.

afford the desired products in good yields (Table 3, **5f–5h**). Subsequently, the X-ray single crystal structure of **5b** was obtained, which further unambiguously confirmed the structures of these products (Fig. 1).

However, when pyrrolidine was chosen as the secondary amine, the reaction gave a lower conversion and lower yield of 42% (Scheme 2). Other secondary amines such as piperidine and acyclic amine were also tested, however, no desired products were found.

The reaction pathway was proposed as shown in Scheme 3 (path a). Initially, intermediate **6** is generated *via* the reaction

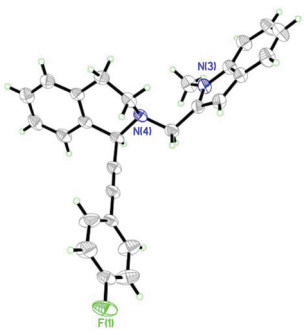
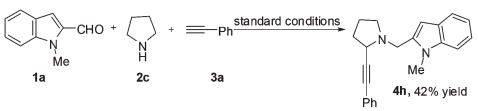
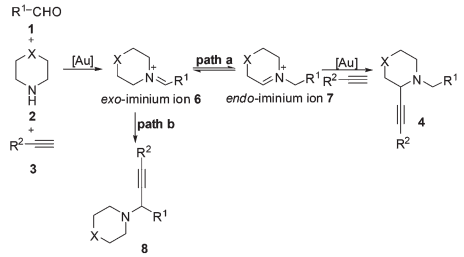


Fig. 1 X-ray diffraction structure of compound **5b**.



Scheme 2 Coupling of pyrrolidine to alkynes and indole-2-carboxaldehyde.

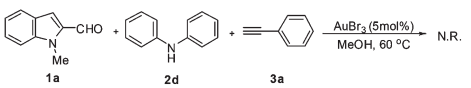


Scheme 3 The proposed mechanism to obtain *endo*-product **4**.

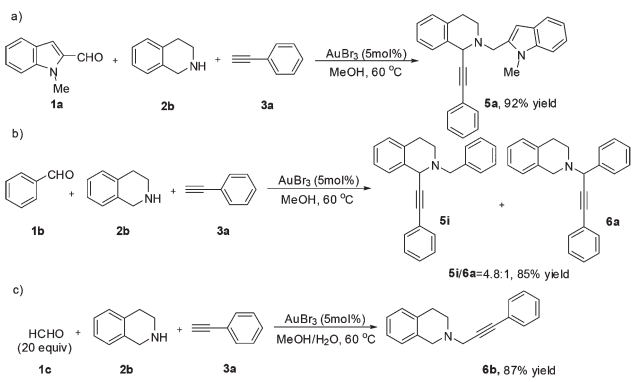
of N-protected indole-2-carboxaldehyde **1** and secondary amines **2** promoted by an Au-catalyst, which was further converted to *endo*-iminium ion **7**. The *endo*-iminium ion is more stable than the *exo*-iminium ion.[13] The terminal alkynes activated by gold[6] attack the C1 position of iminium ions **7** to afford the final *endo*-product **4**.

According to the proposed mechanism, secondary amines not bearing the α-H should not undergo this CDC process. With this idea in mind, diphenylamine was tested as the secondary amine under standard conditions. The results confirmed our speculation and the reaction did not proceed at all (Scheme 4).

Control experiments were then performed to figure out whether the steric hindrance of the aldehyde determined the *endo*/*exo* selectivity. First, we chose 1-methyl-1*H*-indole-2-carbaldehyde as the aldehyde source, which has greater steric hindrance beside the aldehyde group, the reaction was complete in 8 hours to afford the *endo*-compound **5a** in 92% yield and no *exo*-isomer was observed. When benzaldehyde was employed in this reaction, a mixture of *endo*/*exo* **5i**/**6a** was obtained and the selectivity rate was 4.8/1 determined by NMR. Finally, the smallest aldehyde was selected, which could be converted to *exo*-product **6b** in 87% yield only (Scheme 5,



Scheme 4 Three-component coupling of diphenylamine to terminal alkynes and indole-2-carboxaldehyde.



Scheme 5 Control experiments for the steric hindrance of aldehyde.

path b). The above results confirmed that the *endo*/*exo* selectivity was controlled by the steric hindrance of the aldehyde.

Conclusions

In summary, a mild gold-catalyzed three-component dehydrogenative coupling of terminal alkynes to amines and indole-2-carboxaldehyde has been developed. Only *endo*-products were obtained in good to excellent yields under standard conditions. This method provides an efficient avenue for the easy assembly of complex indole derivatives. Further studies on the scope and synthetic applications of this transformation are ongoing.

Experimental section

General experimental methods

All experiments were conducted under an air atmosphere. Flasks were flame dried and cooled under nitrogen before use. All solvents were dried appropriately. For column chromatography, 200–300 mesh silica gel was employed. ^{1}H NMR and ^{13}C NMR were recorded on a 300 MHz, 400 MHz or 500 MHz spectrometer in $CDCl_3$ solution and the chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm). For HRMS measurements, the mass analyzer is a GC-TOF-MS. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. All the indole-2-carboxaldehydes were prepared according to ref. 14.

General procedure for three-component dehydrogenative coupling

To a solution of **1** (0.5 mmol), **2** (0.75 mmol), **3** (1 mmol) in MeOH (2 mL) in a 10 mL Schlenk tube, $AuBr_3$ (5 mol%, 0.025 mmol) was added in one portion. The resulting solution was stirred at 60 °C overnight. After cooling to room temperature, the resulting mixture was filtered through a pad of celite. The volatile compounds were removed *in vacuo* and the residue was purified by column chromatography (SiO_2, petroleum ether–ethyl acetate = 10 : 1–4 : 1) to give the target compound.

Acknowledgements

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