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Gold(I)-catalyzed one-pot reaction between 2-alkynylanilines and alkynols leading to the formation of C-3-substituted indoles: a case of formal carboamination of alkynes

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ABSTRACT

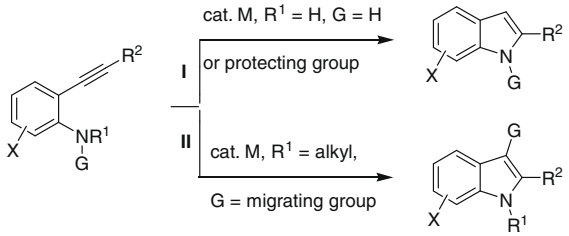
A process involving gold(I)-catalyzed formal carboamination of alkynes for the synthesis of C-3-substituted indoles has been developed. The procedure utilizes easily accessible starting materials such as 2-alkynylanilines and alkynols. A series of C-3-functionalized indoles are accessible by using this one-pot strategy. Mechanistically, the reaction involves three catalytic cycles and each of them is essentially catalyzed by a single metal catalyst, that is, $Ph_3PAuOTf$.

1. Introduction

Substituted indoles have attracted great attention due to their widespread occurrence in nature as well as their remarkable biological activities.[1] Their synthesis has been the objective of research for over a century, and a variety of well-established classical methods are now available in the literature.[2] Among a variety of methods, transition metal-catalyzed reactions are the most attractive, since those reactions can directly construct multiply-substituted indole from readily accessible starting materials under mild conditions.[3] One of the straightforward ways to access indoles is the metal-mediated intramolecular hydroamination of 2-alkynylanilines (Scheme 1, path I).[4] Another powerful method for their synthesis involves the metal-mediated intramolecular carboamination of *N*-protected 2-alkynylanilines (Scheme 1, path II).[5]

Recently, we[6] and others[7] reported a new approach for the synthesis of C-3-functionalized indoles, by metal-catalyzed reactions between alkynols and indoles. Metal-catalyzed reactions of 2-alkynylanilines **1** with electrophiles such as α,β-enones[4g] and ethyl propiolate[8] have been known to give C-3-functionalized indoles (Scheme 2, path I). Against this background, we questioned whether it might be possible to use 2-alkynylanilines, instead of indoles, for the metal-catalyzed cascade process as shown in Scheme 2 (path II). More specifically, we hypothesized that a single metal catalyst having acidic property[9] should promote three reactions such as hydroalkoxylation, hydroamination, and hydroarylation with the formation of C–O, C–N, and C–C bonds in one-pot without isolating any intermediates.[10] A successful reaction as envisioned above would provide access to C-3-substituted indoles starting from 2-ethynylanilines and alkynols. Herein, we report successful realization of the reaction by utilizing 5 mol % $Ph_3PAuOTf$, generated in situ by mixing $Au(PPh_3)Cl$ and AgOTf (5 mol % each), as a catalyst. The method shows very broad substrate scope towards alkynols and 2-alkynylanilines. Since overall formation of C–C and C–N bonds across alkynes take place, we termed this process as formal carboamination of alkynes.[11]

Initially, 4-pentyn-1-ol **1a** was treated with 2-aminophenyl alkyne **2a** in the presence of 5 mol % AgOTf in DCE at 60 °C for 12 h (Table 1, entry 1). Pleasingly, this led to the formation of C-3-



Scheme 1.

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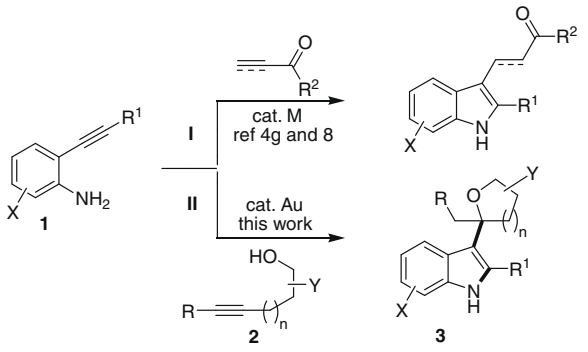
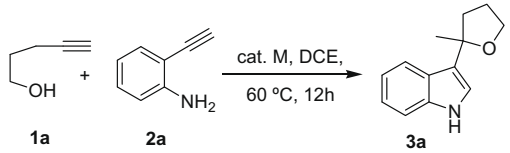


Scheme 2.

substituted indole **3a** in 52% yield. Under the same conditions, $Cu(OTf)_2$ catalyst gave **3a** in 30% yield (entry 2). The use of platinum salts such as $PtCl_2$ and $PtCl_4$ afforded **3a** in 70 and 65% yield, respectively (entries 3 and 4). When $Au(PPh_3)Cl$ and AuCl alone were employed as catalyst, the desired product was obtained in 45 and 75% yield, respectively (entries 5 and 6). The catalyst PPh_3AuOTf generated from mixing equimolar amount of $Au(PPh_3)Cl$ and AgOTf gave a slightly higher yield (entry 7). A combination of $Au(PPh_3)Cl$ with other silver salts such as $AgBF_4$ (entry 8) and $AgSbF_6$ (entry 9) was examined; however, both of them gave inferior results. The result of the study indicates that Ph_3PAuCl in combination with AgOTf is the catalyst of choice for this transformation (entry 7).

Under the optimal conditions,[12] we studied the scope of the reaction. As shown in Table 2, alkynylanilines were varied keeping 4-pentyn-1-ol **1a** as a model substrate. It is evident that a wide range of substituted 2-alkynylanilines **2b**–**k** reacted well to furnish **3b**–**k** in moderate to high yields (60–81%) regardless of the electronic nature of the aromatic ring. Particularly noteworthy is the fact that electron-withdrawing substituents on the aromatic rings were not detrimental to the reactivity as $–NO_2$, –CN–COOMe, and $–CF_3$ groups were all well tolerated (entries 1, 4, 5, 8, and 9). The reaction was also successful for halo-substituted amino-alkynes (entries 2, 6, and 7). It should be noted that this method is applicable to only terminal amino-alkynes and therefore internal alkynes cannot be employed as substrates.

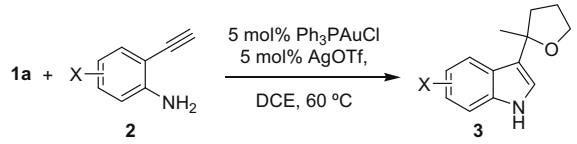
Table 1
Optimization studies[a]

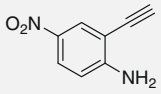
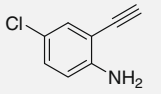
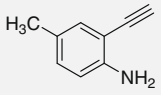
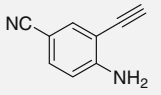
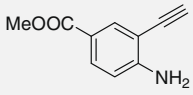
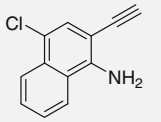
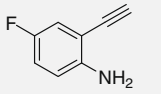
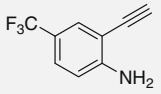
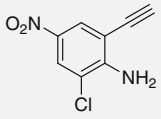
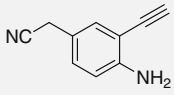


Entry	Catalyst[a]	Yield[b] (%)
1	AgOTf	52
2	$Cu(OTf)_2$	30
3	$PtCl_2$	70
4	$PtCl_4$	65
5	Ph_3PAuCl	45
6	AuCl	75
7	**Ph_3PAuCl + AgOTf**	81
8	Ph_3PAuCl + $AgBF_4$	**58**
9	Ph_3PAuCl + $AgSbF_6$	60

[a] Reaction conditions: 0.59 mmol **2a**, 1.1 equiv **1a**, 5 mol % catalyst, DCE (0.3 M), 60 °C, 12 h.
[b] Isolated yields based on **2a**.

Table 2
Scope with 2-alkynylanilines[a]



Entry	2	3	Time (h)	Yield[b] (%)
1	 **2b**	**3b**	18	60
2	 **2c**	**3c**	12	72
3	 **2d**	**3d**	12	75
4	 **2e**	**3e**	18	70
5	 **2f**	**3f**	15	68
6	 **2g**	**3g**	12	71
7	 **2h**	**3h**	12	81
8	 **2i**	**3i**	12	70
9	 **2j**	**3j**	18	69
10	 **2k**	**3k**	12	73

[a] Reaction conditions: 0.59 mmol **2**, 1.1 equiv **1a**, Ph_3PAuCl and AgOTf (5 mol % each with respect to **2**), DCE (0.3 M), 60 °C.
[b] Isolated yields based on **2**.

Next, the scope of the reaction with various alkynols was studied by using **2a** as a model substrate (Table 3). The alkynols bearing sterically demanding substituents in the tether such as **1b**, **1c**, and **1d** reacted well giving corresponding products **3l**, **3m**, and **3n** in high yields (entries 1–3). As can be judged from the entry 4, 5-hexyn-1-ol **1e** can also be used as a substrate. Even internal alkynes such as **1f**–**i** were tolerated giving the corresponding products **3p**–**s** in good yields (entries 5–8). It should be noted that in the latter case only one regioisomer **3s** was formed indicating that the **1i** cyclized in 5-*exo*-*dig* fashion (entry 8).

A plausible mechanism for the gold-catalyzed formal carboamination of alkynes is described in Figure 1. A first step would be the complexation of Au(I) catalysts to the alkyne function in **1a** which lead to intermediate **4** (Fig. 1, cycle **A**). The cyclization step may then occur directly by the attack of proximal hydroxyl group lead-