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# Synthesis of polysubstituted cyclopenta[b]indoles via relay gold(I)/Brønsted acid catalysis†

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An efficient relay catalytic process involving Au(I)/Brønsted acid to access various polysubstituted cyclopentannulated indoles from easily accessible 1-(2-aminophenyl)prop-2-ynols and readily available 1,3-dicarbonyls has been developed. In an unprecedented event, the intermediate 2-indolylmethyl cations undergo the cation-Ene reaction with various 1,3-dicarbonyls followed by an intramolecular Friedel-Crafts-type reaction generating functionalized cyclopenta[b]indoles.

Indoles and indolines are considered to be privileged structures due to their widespread occurrence in Nature with intricate structural diversity often associated with impressive bioactivities, and in a pharmaceutical sense due to their drug-like properties.<sup>1</sup> Among indole derivatives, cyclopenta[b]indoles are especially attractive due to their presence in numerous biologically active natural products, for example, paspalines, terpendoles, emindoles, polyveolines, spiroindimicins, fischerindoles, yuehchukene, *etc.*, in addition to medicinally important compounds such as MK-0524, Fig. 1.<sup>2</sup> The presence of complex molecular architectures coupled with impressive pharmacological properties prompted several research groups to contribute

significantly to the construction of cyclopentannulated indole derivatives.<sup>3</sup> However, the quest for the development of a simple and efficient method to access this class of compounds from readily available starting materials still remains an area of active research.

On the other hand, activation of  $\pi$ -systems of alkynes and alkenes *via* gold catalysis for the synthesis of a wide range of natural products and complex molecules in an efficient and predictable manner has received significant attention during the past decade.<sup>4</sup> Especially, relay catalytic processes involving gold were demonstrated to have great potential to rapidly assemble complex chemical structures often associated with pot, step and atom economy.<sup>5</sup> Motivated by the pioneering studies by Chan<sup>6</sup> for the synthesis of indole derivatives starting from propargylic *tert*-alcohols of the type **A**, and with our experience in the chemistry of heteroaryl carbinols,<sup>7</sup> we initiated a program to develop an efficient and general methodology towards the synthesis of a novel series of cyclopentannulated indoles and to evaluate their biological efficacy, Scheme 1. Prior to commencing our investigation, a detailed literature survey revealed that the prevailing 2-indolylmethyl cation intermediate **B** was routinely trapped by nucleophiles such as alcohols, aryls, heteroaryls, *etc.*<sup>8</sup> However, to



Fig. 1 Representative examples of bioactive cyclopenta[b]indoles.

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Scheme 1 Our strategy for the synthesis of cyclopentannulated indoles.



our surprise, no attempt was ever made to employ readily available 1,3-dicarbonyl compounds as nucleophiles.<sup>9</sup>

Herein, we delineate our efforts towards the generation of indolylmethyl cations from 2-aminophenyl propargylic secondary alcohols **1**,<sup>10</sup> their reactions with a variety of 1,3-dicarbonyl compounds and subsequent intramolecular aldol-type reactions for the synthesis of 1,2,3-trisubstituted cyclopenta[*b*]indoles. Accordingly, we initiated optimization studies towards identifying an effective catalytic system and other reaction parameters. For this, amino alcohol **1a**<sup>6b,11</sup> and acetylacetone **2a** were chosen as substrates for the model reaction. The screening results are compiled in Table 1.

To begin with, cyclization of amino alcohol **1a** to indoline **3a** was explored. The reaction of **1a** in the presence of Au(I) or Ag(I) salts alone or a combination of Au(I) and silver based Lewis acids failed to deliver indoline **3a** (Table 1, entries 1–4). Interestingly, amino alcohol **1a** generated indoline **3a** when a combination of Au(I) and base was employed;<sup>12</sup> however, subsequent transformation of indoline **3a** to the desired indole **5a** was not observed upon treatment with a variety of Lewis acids, only the acetylacetone adduct **4a** was isolated

(Table 1, entries 5–7). Nevertheless, an approach for indoline **3a** via a catalytic sequence involving Au(I) and a base could be established for the first time.<sup>13</sup>

Upon further screening, Lewis acids such as Bi(OTf)<sub>3</sub> and TMSOTf gratifyingly generated the cyclopentannulated indole **5a** in very good yields (Table 1, entries 8 and 9). We were delighted especially because, as per our hypothesis, the intervening indolylmethyl cation formed under Lewis acidic conditions successfully underwent the cation-Ene reaction with acetylacetone **2a**, and furthermore the 1,3-dicarbonyl adduct **4a** via an intramolecular Friedel–Crafts-type reaction furnished 1,2,3-trisubstituted cyclopenta[*b*]indole **5a**. It is worth mentioning that the current method also constitutes a potential alternative to the traditionally employed methods for indole cyclopentannulations such as [3+2]-cycloadditions, Nazarov cyclizations, *etc.*<sup>14</sup> Furthermore, synthesis of cyclopentannulated indoles via 2-indolylmethyl cation intermediates is underexplored.<sup>3h</sup>

In order to further improve the efficiency of the reaction, we opted to investigate the influence of Brønsted acids in place of Lewis acids in step-II. Among several Brønsted acids explored, triflic acid mediated reaction in DCE delivered the cyclopentannulated indole **5a** in very good yield (Table 1, entries 10–16). Subsequently, influence of the co-catalyst (base) in step-I was also studied. While no desired product was observed when sodium bicarbonate was employed as the co-catalyst, sodium carbonate and an organic base such as triethylamine furnished **5a** only in moderate yields (Table 1, entries 17–19). Gratifyingly, further enhancement in the yield was observed when TfOH loading was reduced from 20 mol% to 10 mol% (Table 1, entry 20). Striking temperature dependence was realized when the TfOH reaction at room temperature failed to generate the desired product **5a** and only the acetylacetone adduct **4a** was isolated (Table 1, entry 21). Further attempts to enhance the yield were not encouraging (Table 1, entries 22–24).

In order to validate the generality of the unprecedented method for the synthesis of polysubstituted cyclopenta[*b*]indoles, a variety of 1-(2-aminophenyl)prop-2-ynols **1a–1m** were synthesized according to literature methods<sup>6,8</sup> and subjected to the optimized conditions, Table 2. It is noteworthy that the relay Au(I)/Brønsted acid catalyzed tandem transformation is quite general, and a diverse library of annulated indoles can be rapidly accessed in good to excellent yields (Table 2, **5a–5w**). The reaction displays significant tolerance towards various alkynols bearing electron-donating as well as electron-withdrawing aryl groups (for example, *p*-tolyl and *p*-fluorophenyl), heteroaryls such as 2-thienyl, and the alkyl groups. Furthermore, alkyl and aryl-bearing 1,3-diketones, 1,3,5-triketones, β-ketoesters and β-ketoamides are also well-tolerated under the reaction conditions.

As can be seen from Table 2, amino alcohol **1a** upon reaction with di- and triketones **2a–2d**, and ketoamide **2e** generated the respective 1,2,3-trisubstituted cyclopentannulated indoles **5a–5e** in excellent yields. Similarly, the analogous aryl and heteroaryl amino alcohols **1b–1d** upon reaction with a variety of diketones, ketoesters and ketoamides generated functionalized cyclopenta[*b*]indoles (Table 2, **5f–5l**). Significantly, reaction of

Table 1 Optimization of reaction parameters<sup>a</sup>



| Entry             | Catalyst              | Co-catalyst                     | Acid                           | Solvent           | Time (h) | Yield <sup>b</sup> (%) |
|-------------------|-----------------------|---------------------------------|--------------------------------|-------------------|----------|------------------------|
| 1                 | AuCl                  | —                               | —                              | DCE               | 48       | —                      |
| 2                 | PPh <sub>3</sub> AuCl | —                               | —                              | DCE               | 48       | —                      |
| 3                 | AuCl                  | AgOTf                           | —                              | DCE               | 48       | —                      |
| 4                 | PPh <sub>3</sub> AuCl | AgOTf                           | —                              | DCE               | 48       | —                      |
| 5 <sup>c</sup>    | AuCl                  | K <sub>2</sub> CO <sub>3</sub>  | Sc(OTf) <sub>3</sub>           | MeNO <sub>2</sub> | 48       | —                      |
| 6 <sup>c</sup>    | AuCl                  | K <sub>2</sub> CO <sub>3</sub>  | In(OTf) <sub>3</sub>           | MeNO <sub>2</sub> | 48       | —                      |
| 7 <sup>c</sup>    | AuCl                  | K <sub>2</sub> CO <sub>3</sub>  | AgOTf                          | MeNO <sub>2</sub> | 48       | —                      |
| 8                 | AuCl                  | K <sub>2</sub> CO <sub>3</sub>  | Bi(OTf) <sub>3</sub>           | MeNO <sub>2</sub> | 26       | 74                     |
| 9                 | AuCl                  | K <sub>2</sub> CO <sub>3</sub>  | TMSOTf                         | DCE               | 20       | 82                     |
| 10                | AuCl                  | K <sub>2</sub> CO <sub>3</sub>  | TFA                            | DCE               | 13       | —                      |
| 11                | AuCl                  | K <sub>2</sub> CO <sub>3</sub>  | H <sub>3</sub> PO <sub>4</sub> | DCE               | 16       | 51                     |
| 12                | AuCl                  | K <sub>2</sub> CO <sub>3</sub>  | HClO <sub>4</sub>              | DCE               | 15       | 72                     |
| 13                | AuCl                  | K <sub>2</sub> CO <sub>3</sub>  | H <sub>2</sub> SO <sub>4</sub> | DCE               | 18       | 70                     |
| 14                | AuCl                  | K <sub>2</sub> CO <sub>3</sub>  | TfOH                           | DCE               | 13       | 83                     |
| 15                | AuCl                  | K <sub>2</sub> CO <sub>3</sub>  | TfOH                           | MeNO <sub>2</sub> | 24       | 74                     |
| 16                | AuCl                  | K <sub>2</sub> CO <sub>3</sub>  | TfOH                           | Toluene           | 13       | 80                     |
| 17                | AuCl                  | NaHCO <sub>3</sub>              | —                              | DCE               | 40       | —                      |
| 18                | AuCl                  | Na <sub>2</sub> CO <sub>3</sub> | TfOH                           | DCE               | 35       | 53                     |
| 19                | AuCl                  | Et <sub>3</sub> N               | TfOH                           | DEC               | 27       | 72                     |
| 20 <sup>d</sup>   | AuCl                  | K <sub>2</sub> CO <sub>3</sub>  | TfOH                           | DCE               | 18       | 90                     |
| 21 <sup>c,e</sup> | AuCl                  | K <sub>2</sub> CO <sub>3</sub>  | TfOH                           | DCE               | 48       | —                      |
| 22 <sup>d</sup>   | PPh <sub>3</sub> AuCl | K <sub>2</sub> CO <sub>3</sub>  | TfOH                           | DCE               | 42       | 76                     |
| 23 <sup>d</sup>   | AuCl                  | K <sub>2</sub> CO <sub>3</sub>  | TMSOTf                         | DCE               | 36       | 85                     |
| 24 <sup>d</sup>   | AgOTf                 | —                               | TfOH                           | MeNO <sub>2</sub> | 34       | 63                     |

<sup>a</sup> Reaction conditions: a 5 mL glass vial was filled with **1a** (0.1 mmol), catalyst (2 mol%), co-catalyst (2 mol%) in an appropriate solvent (1 mL) and stirred at 60 °C, upon disappearance of the starting compound (**1a**), acetylacetone **2a** (0.11 mmol) and an acid (20 mol%) were introduced and stirring was continued at 60 °C until indoline **3a** and acetylacetone adduct **4a** disappeared.

<sup>b</sup> Isolated yields after silica gel column chromatography. <sup>c</sup> Intermediate **3a** formed and only the acetylacetone adduct **4a** was isolated. <sup>d</sup> 10 mol% TfOH was employed. <sup>e</sup> Step-II was carried out at room temperature.



Reaction scheme for the synthesis of indole derivatives **1a-h** and **1i-m** via the **one-pot** method:

Starting materials: **1a-h** (R<sup>1</sup> = Ph, (p-fluoro)Ph, n-butyl, cyclopropyl, p-tolyl, 3-thienyl, H, and a chiral auxiliary) and **1i-m** (R = CF<sub>3</sub>, OTs, CF<sub>3</sub>, and a chiral auxiliary).

Reaction conditions:

- Step 1: AuCl (2 mol%), K<sub>2</sub>CO<sub>3</sub> (2 mol%), DCE, 60 °C.
- Step 2: 1,3-dicarbonyl (1.1 equiv), TIOH (10 mol%), DCE, 60 °C.

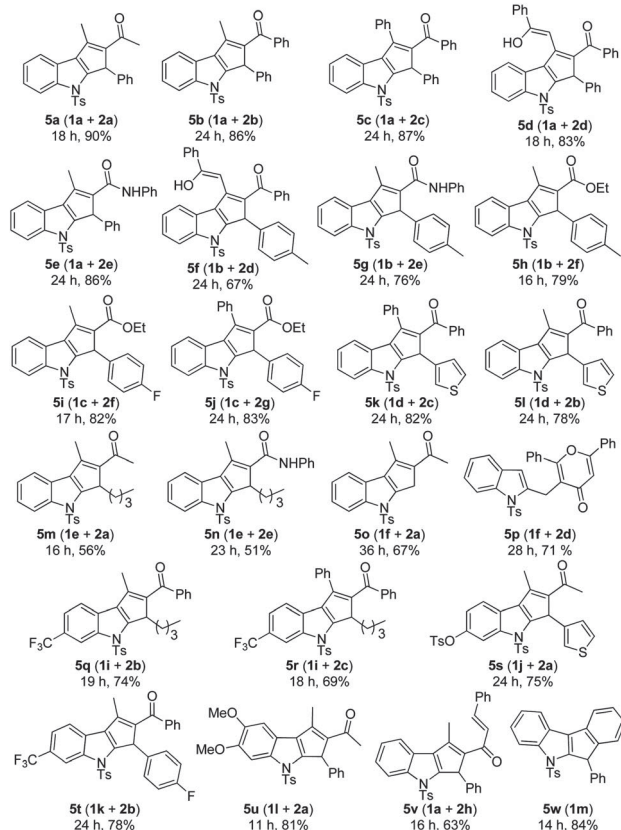
The reaction proceeds via a **one-pot** process to yield the indole derivatives **1a-h** and **1i-m**.

Structure of the starting materials:

Structure of the products:

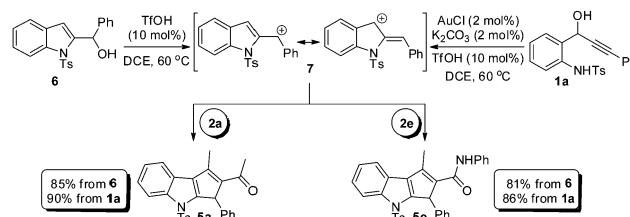
Structure of the starting materials **1i-m**:

Structure of the products **1i-m**:

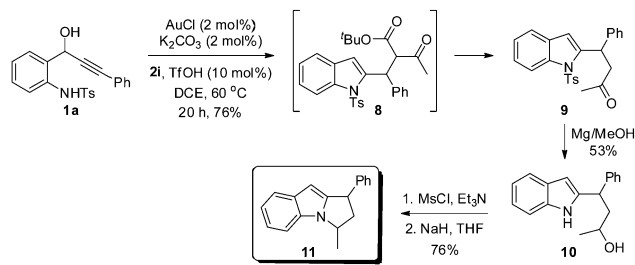


**1e**, having a pendent alkyl group on the acetylenic carbon centre, with diketones **2a** and **2e** also furnished the respective annulated indoles **5m** and **5n** though in moderate yields,<sup>15</sup> but enhanced the scope of this method. Even 1,2-disubstituted cyclopentannulated indoles (such as **5o**) could be efficiently generated by the reaction of unsubstituted alkynol **1f** with diketone **2a**. But reaction of **1f** with triketone **2d**, unexpectedly formed the pyranone indole **5p**. Complex indole derivatives

In conclusion, we have developed a general and efficient relay Au(I)/Brønsted acid catalyzed one-pot tandem process for the synthesis of medicinally significant 1,2-di- and 1,2,3-trisubstituted cyclopentannulated indoles from 1-(2-aminophenyl)prop-2-ynols

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Scheme 3 Elaboration to an advanced intermediate.

and 1,3-dicarbonyls. Key features of this method are its readily accessible starting compounds and atom, step and pot economy. During the course of our investigation, we also developed novel Au(I)/base mediated conditions for the synthesis of indolines starting from 1-(2-aminophenyl)prop-2-ynols. In addition, we have demonstrated for the first time, Friedel-Crafts-type alkylation of unmodified 2-indolyl carbinols and 1,3-dicarbonyls. A study regarding the application of this methodology for the synthesis of biologically active natural products is currently underway in our laboratory and will be communicated shortly.

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- Other NH-protecting groups (Ms, Boc, and Ac) were also evaluated prior to proceeding to optimization. Only *N*-sulfonyl propargyl alcohols generated the desired product (see the ESI† for details).
- Step-I was found to proceed very slowly at room temperature. After several attempts, the reaction temperature was optimized to 60 °C.
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