

# ChemComm

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

*Accepted Manuscripts* are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

## COMMUNICATION

Polysubstituted Cyclopenta[*b*]indoles via Relay Gold(I)/Brønsted Acid Catalysis

Cite this: DOI: 10.1039/x0xx00000x

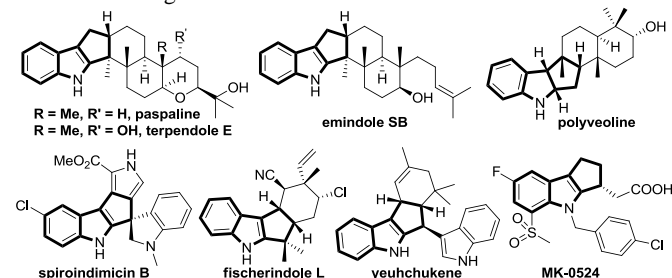
Seema Dhiman and S. S. V. Ramasastry\*<sup>a</sup>Received 00th January 2012,  
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

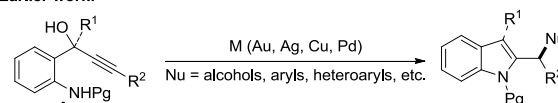
**An efficient relay catalytic process involving Au(I)/Brønsted acid to access various polysubstituted cyclopentannulated indoles from easily accessible 1-(2-aminophenyl)prop-2-ynols and readily available 1,3-dicarbonyls has been developed. In an unprecedented event, the intermediate 2-indolylmethyl cations undergo 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 wide spread occurrence in nature with intricate structural diversity often associated impressive bioactivities, and in 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, yeuhchukene, etc., in addition to medicinally important compounds such as MK-0524, Fig. 1.<sup>2</sup> Presence of complex molecular architectures coupled with impressive pharmacological properties prompted several research groups contribute significantly to the construction of cyclopentannulated indole derivatives.<sup>3</sup> However, the quest for the development of simple and efficient access to this class from readily available starting materials still remains an area of active research.

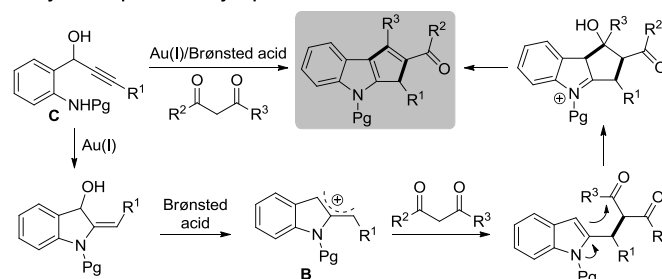
Fig. 1 Representative examples of bioactive cyclopenta[*b*]indoles.

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

(a) Earlier work:



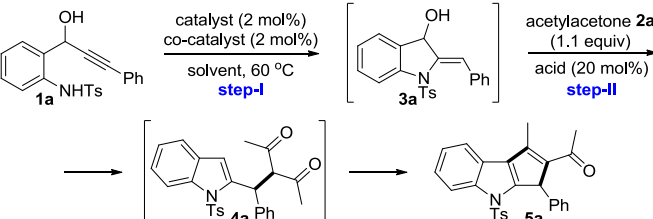
(b) Concept of this work: 1,3-dicarbonyls as nucleophiles and relay Au(I)/Brønsted acid catalyzed one-pot domino cyclopentannulation of indoles



Scheme 1 Our strategy for the synthesis of cyclopentannulated indoles.

Herein, we delineate our efforts towards the generation of indolymethyl 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 reaction for the synthesis of 1,2,3-trisubstituted cyclopenta[*b*]indoles. Accordingly, we have initiated optimization studies towards identifying effective catalytic system and other reaction parameters. Towards this, the 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.

**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>	<b>AuCl</b>	<b>K<sub>2</sub>CO<sub>3</sub></b>	<b>TfOH</b>	<b>DCE</b>	<b>18</b>	<b>90</b>
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

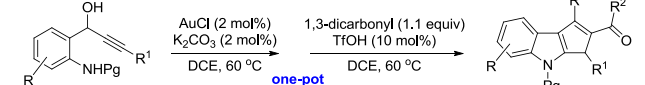
<sup>a</sup> Reaction conditions: A 5 mL glass vial was charged with **1a** (0.1 mmol), catalyst (2 mol%), co-catalyst (2 mol%) in an appropriate solvent (1 mL) and stirred at 60 °C, upon disappearance of starting compound (**1a**), acetylacetone **2a** (0.11 mmol) and an acid (20 mol%) were introduced and continued stirring 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 done at room temperature.

To begin with, cyclization of amino alcohol **1a** to indoline **3a** was explored. 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 the indoline **3a** (Table 1, entries 1-4). Interestingly, the amino alcohol **1a** generated indoline **3a** when a combination of Au(I) and base was employed,<sup>12</sup> however, subsequent transformation of the 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 indolymethyl cation formed under Lewis acidic conditions successfully underwent cation-Ene reaction with acetylacetone **2a** and furthermore the 1,3-dicarbonyl adduct **4a** via intramolecular aldol-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> Further, synthesis of cyclopentannulated indoles via 2-indolymethyl cation intermediates is underexplored.<sup>3h</sup>

**Table 2** Substrate scope with 1-(2-aminophenyl)prop-2-ynols and 1,3-dicarbonyls in the relay Au(I)/Brønsted acid catalyzed tandem process<sup>a,b</sup>



1a, R <sup>1</sup> = Ph	1c, R <sup>1</sup> = ( <i>p</i> -fluoro)Ph	1e, R <sup>1</sup> = <i>n</i> -butyl	1g, R <sup>1</sup> = cyclopropyl
1b, R <sup>1</sup> = <i>p</i> -tolyl	1d, R <sup>1</sup> = 3-thienyl	1f, R <sup>1</sup> = H	1h, R <sup>1</sup> = <i>tert</i> -OBn
1i, R = CF <sub>3</sub> , R <sup>1</sup> = <i>n</i> -butyl	1j, R = OTs, R <sup>1</sup> = 3-thienyl	1k, R = CF <sub>3</sub> , R <sup>1</sup> = ( <i>p</i> -fluoro)Ph	1l, R = MeO, R <sup>1</sup> = Ph
2a, R <sup>2</sup> = R <sup>3</sup> = Me	2d, R <sup>2</sup> = Ph, R <sup>3</sup> = Me	2e, R <sup>2</sup> = NHPg, R <sup>3</sup> = Me	2f, R <sup>2</sup> = O <sup>t</sup> Bu, R <sup>3</sup> = Me
2b, R <sup>2</sup> = Ph, R <sup>3</sup> = Me	2c, R <sup>2</sup> = R <sup>3</sup> = Ph	2d, R <sup>2</sup> = Ph, R <sup>3</sup> = CH <sub>2</sub> COPh	2e, R <sup>2</sup> = Ph, R <sup>3</sup> = CH=CHPh
2f, R <sup>2</sup> = O <sup>t</sup> Bu, R <sup>3</sup> = Me	2g, R <sup>2</sup> = OEt, R <sup>3</sup> = Ph	2h, R <sup>2</sup> = CH=CHPh, R <sup>3</sup> = Me	2i, R <sup>2</sup> = O <sup>t</sup> Bu, R <sup>3</sup> = Me
5a (1a + 2a) 18 h, 90%	5b (1a + 2b) 24 h, 86%	5c (1a + 2c) 24 h, 87%	5d (1a + 2d) 18 h, 83%
5e (1a + 2e) 24 h, 86%	5f (1b + 2d) 24 h, 67%	5g (1b + 2e) 24 h, 76%	5h (1b + 2f) 16 h, 79%
5i (1c + 2f) 17 h, 82%	5j (1c + 2g) 24 h, 83%	5k (1d + 2c) 24 h, 82%	5l (1d + 2b) 24 h, 78%
5m (1e + 2a) 16 h, 56%	5n (1e + 2e) 23 h, 51%	5o (1f + 2a) 36 h, 67%	5p (1f + 2d) 28 h, 71%
5q (1i + 2b) 19 h, 74%	5r (1i + 2c) 18 h, 69%	5s (1j + 2a) 24 h, 75%	5t (1k + 2b) 24 h, 78%
5u (1l + 2a) 11 h, 81%	5v (1a + 2h) 16 h, 63%	5w (1m) 14 h, 84%	

<sup>a</sup> Reaction conditions: A mixture of the amino alcohol **1** (0.1 mmol), AuCl (2 mol%), K<sub>2</sub>CO<sub>3</sub> (2 mol%) and DCE (1 mL) in a 5 mL glass vial were stirred at 60 °C. After complete consumption of the starting compound (**1**), 1,3-dicarbonyl **2** (0.11 mmol) and TfOH (10 mol%) were added successively and continued stirring at 60 °C until the complete disappearance of the respective 1,3-dicarbonyl adduct (**4**). <sup>b</sup> Isolated yields after silica gel column chromatography.

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 co-catalyst (base) in step-I was also studied. While no desired product was observed when sodium bicarbonate was employed as 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 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 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. Further, alkyl and aryl-bearing 1,3-diketones, 1,3,5-triketones,  $\beta$ -ketoesters and  $\beta$ -ketoamides are also well-tolerated under the reaction conditions.

Evidently from Table 2, the 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 **1e** having a pendant 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 the diketone **2a**. But reaction of **1f** with the triketone **2d**, unexpectedly formed the pyranone indole **5p**. Complex indole derivatives bearing electron-withdrawing as well as electron-donating substitutions (such as  $-\text{CF}_3$ ,  $-\text{OTs}$ ,  $-\text{OMe}$ ) on the indole moiety could also be accessed easily in high yields (Table 2, **5q-5u**). However, contrary to our expectation, the amino alcohols **1g** and **1h** failed to deliver the desired products under the reaction conditions. Presumably, the presence of acid sensitive cyclopropyl system and a 2-butyne-1,4-oxygenated system would have triggered unwanted side reactions. The molecular structure of a representative example **5v**, obtained by the reaction of **1a** and **2h**, was unambiguously confirmed by single crystal X-ray diffraction analysis (see Supporting Information for details), Fig. 2.<sup>16</sup>

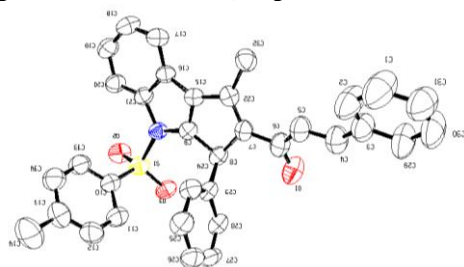
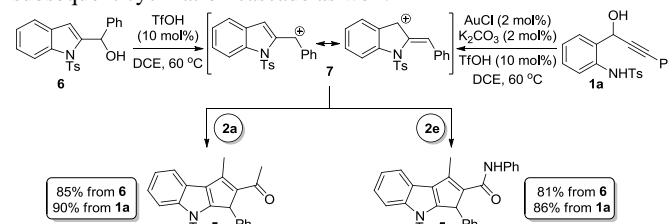


Fig. 2 ORTEP diagram of **5v**.

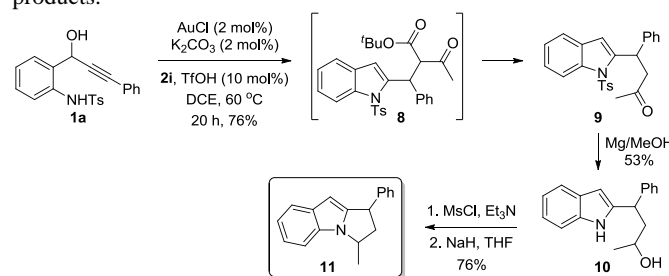
On the other hand, reaction of the amino *tert*-alcohol **1m** even in the presence of **2a** generated only the indole **5w** in 84% yield via a Nazarov electrocyclic cyclization (Table 2).<sup>6a</sup> Thus, indoles of the type **5w** could now be accessed in excellent yields with less Au(I) catalyst loading and milder reaction conditions over the existing method.<sup>6a</sup>

Since the alcohol **6** and the cationic intermediate **7** are believed to be the intermediates in the transformation of **1a** to **5a**, we planned to undertake a comparative study between the reactions of the amino alcohol **1a** and the 2-indolyl carbinol **6** under the optimized conditions, Scheme 2. It can be noted that the reaction of the amino alcohol **1a** with **2a** or **2e** is found to be efficient in generating **5a** or **5e**, respectively, when compared to the reaction of the alcohol **6** in forming **5a** and **5e**, thereby clearly demonstrating the advantage of the one-pot tandem process. It is worth mentioning that the direct Friedel-Crafts-type alkylation of unmodified 2-indolyl carbinols and 1,3-dicarbonyls as such is unprecedented<sup>17</sup> and of course the subsequent cyclization cascade as well.



**Scheme 2** Comparison between the efficiency of amino alcohol **1a** and indolyl carbinol **6** in forming the same end product. First demonstration of direct reaction between 2-indolyl carbinols and 1,3-dicarbonyls.

To further illustrate the generality and synthetic utility of this methodology, we considered an elaboration as in Scheme 3. Thus, reaction of **1a** with ketoester **2i** under the optimized conditions furnished the adduct **8**, which underwent smooth *in situ* decarboxylation to form  $\beta$ -branched 4-(2-indolyl)-2-butanone **9** in 76% yield, synthesis of which otherwise would require a multistep sequence. Indole **9** upon reaction with excess Mg in methanol generated alcohol **10** by undergoing simultaneous tosyl deprotection and ketone reduction. Selective O-mesylation and subsequent intramolecular N-alkylation<sup>18</sup> conveniently generated 1,3-disubstituted dihydropyrroloindole **11**, an important motif prevalent in a number of pharmaceutically important compounds and natural products.<sup>19</sup>



**Scheme 3** Elaboration to an advanced intermediate.

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 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 have 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. Application of this methodology for the synthesis of



biologically active natural products is currently underway in our laboratory and will be communicated shortly.

We are grateful to the DST, Govt. of India for financial support through Fast Track Scheme (SR/FT/CS-156/2011). We thank IISER Mohali for funding and for NMR, mass, and X-ray facilities. S.D. thanks IISER Mohali for a research fellowship.

## Notes and references

<sup>a</sup> Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, Sector 81, S. A. S. Nagar, Manali PO, Punjab 140306, India. E-mail: ramsastry@iisermohali.ac.in

<sup>†</sup> Electronic Supplementary Information (ESI) available: Complete experimental procedures and characterization data of all new compounds. CCDC 1029309. For ESI and crystallographic data in CIF or other electronic format, see DOI: 10.1039/c000000x

- Some selected reviews: (a) M. Somei and F. Yamada, *Nat. Prod. Rep.*, 2005, **22**, 73; (b) T. Kawasaki and K. Higuchi, *Nat. Prod. Rep.*, 2005, **22**, 761; (c) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873; (d) K. Higuchi and T. Kawasaki, *Nat. Prod. Rep.*, 2007, **24**, 843; (e) V. Sharma, P. Kumar and D. Pathak, *J. Heterocycl. Chem.*, 2010, **47**, 491; (f) A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489.
- For paspalines, terpendoles, lolines, lolitrems, see: (a) S. C. Munday-Finch, A. L. Wilkins and C. O. Miles, *J. Agric. Food Chem.*, 1998, **46**, 590; for emindoles, see: (b) H. Harms, V. Rempel, S. Kehraus, M. Kaiser, P. Hufendiek, C. E. Muller and G. M. König, *J. Nat. Prod.*, 2014, **77**, 673; for polyveolines, see: (c) I. Ngantcho, B. Nyasse, C. Denier, C. Blonski, V. Hannaert and B. Schneider, *Bioorg. & Med. Chem. Lett.*, 2010, **20**, 3495; for spiroindimicins, see: (d) W. Zhang, Z. Liu, S. Li, T. Yang, Q. Zhang, L. Ma, X. Tian, H. Zhang, C. Huang, S. Zhang, J. Ju, Y. Shen and C. Zhang, *Org. Lett.*, 2012, **14**, 3364; for fischerindoles, see: (e) J. M. Richter, Y. Ishihara, T. Masuda, B. W. Whitefield, T. Llamas, A. Pohjakallio and P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 17938; for yeuhchukene, see: (f) Y. -C. Kong, K. -F. Cheng, R. C. Cambie and P. G. Waterman, *J. Chem. Soc., Chem. Commun.*, 1986, 47.
- Some selected references for the synthesis of the cyclopenta[b]indole frameworks, see: (a) C. A. Harrison, R. Leineweber, C. J. Moody and J. M. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1127; (b) M. Ishikura, Y. Matsuzaki and I. Agata, *Chem. Commun.*, 1996, 2409; (c) E. M. Ferreira and B. M. Stoltz, *J. Am. Chem. Soc.*, 2003, **125**, 9578; (d) C. Venkatesh, P. P. Singh, H. Ila and H. Junjappa, *Eur. J. Org. Chem.*, 2006, 5378; (e) K. S. Feldman, M. R. Iyer and D. K. Hester, *Org. Lett.*, 2006, **8**, 3113; (f) M. G. Banwell, X. Ma, R. M. Taylor and A. C. Willis, *Org. Lett.*, 2006, **8**, 4959; (g) J. A. Malona, J. M. Colbourne and A. J. Frontier, *Org. Lett.*, 2006, **8**, 5661; (h) A. K. Yadav, S. Peruncheralathan, H. Ila and H. Junjappa, *J. Org. Chem.*, 2007, **72**, 1388; (i) C. Ferrer, C. H. M. Amijs and A. M. Echavarren, *Chem. Eur. J.*, 2007, **13**, 1358; (j) E. P. Balskus and C. T. Walsh, *J. Am. Chem. Soc.*, 2009, **131**, 14648; (k) N. -W. Tseng and M. Lautens, *J. Org. Chem.*, 2009, **74**, 1809; (l) F. Churrua, M. Fouteris, Y. Ishikawa, M. von Wantoch Rekowski, C. Hounsou, T. Surrey and A. Giannis, *Org. Lett.*, 2010, **12**, 2096; (m) K. Saito, H. Sogou, T. Suga, H. Kusama and N. Iwasawa, *J. Am. Chem. Soc.*, 2011, **133**, 689; (n) B. Chen, W. Fan, G. Chai and S. Ma, *Org. Lett.*, 2012, **14**, 3616; (o) B. Xu, Z. -L. Guo, W. -Y. Jin, Z. -P. Wang, Y. -G. Peng and Q. -X. Guo, *Angew. Chem. Int. Ed.*, 2012, **51**, 1059.
- For selected articles on relay gold catalysis, see: (a) G. Dyker, *Angew. Chem. Int. Ed.*, 2000, **39**, 4237; (b) G. C. Bond, *Catal. Today*, 2002, **72**, 5; (c) Haruta, M. *Nature*, 2005, **437**, 1098; (d) A. S. K. Hashmi and G. J. Hutchings, *Angew. Chem. Int. Ed.*, 2006, **45**, 7896; (e) Z. Li, C. Brouwer and C. He, *Chem. Rev.*, 2008, **108**, 3239; (f) A. Arcadi, *Chem. Rev.*, 2008, **108**, 3266; (g) D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev.*, 2008, **108**, 3351; (h) A. S. K. Hashmi and M. Rudolph, *Chem. Soc. Rev.*, 2008, **37**, 1766; (i) A. Furstner, *Chem. Soc. Rev.*, 2009, **38**, 3208; (j) M. Bandini, *Chem. Soc. Rev.*, 2011, **40**, 1358; (k) D. Qian and J. Zhang, *Chem. Eur. J.*, 2013, **19**, 6984; (l) H. Wu, Y. -P. He and L. -Z. Gong, *Org. Lett.*, 2013, **15**, 460; (m) P. -S. Wang, K. -N. Li, X. -L. Zhou, X. Wu, Z. -Y. Han, R. Guo and L. -Z. Gong, *Chem. Eur. J.*, 2013, **19**, 6234; (n) X. Wu, M. -L. Li and P. -S. Wang, *J. Org. Chem.*, 2014, **79**, 419; (o) C. Obradorsa and A. M. Echavarren, *Chem. Commun.*, 2014, **50**, 16; (p) Y. Horino, Y. Takahashi, Y. Nakashima and H. Abe, *RSC Adv.*, 2014, **4**, 6215; (q) S. Nayak, N. Ghosh and A. K. Sahoo, *Org. Lett.*, 2014, **16**, 2996.
- (a) N. T. Patil, V. S. Shinde and B. Gajula, *Org. Biomol. Chem.*, 2012, **10**, 211; (b) M. Rueping, J. Dufour and M. S. Maji, *Chem. Commun.*, 2012, **48**, 3406; (c) N. T. Patil, V. S. Shinde and B. Sridhar, *Angew. Chem. Int. Ed.*, 2013, **52**, 2251.
- (a) P. Kothandaraman, W. Rao, S. J. Foo and P. W. H. Chan, *Angew. Chem. Int. Ed.*, 2010, **49**, 4619; (b) D. Susanti, F. Koh, J. A. Kusuma, P. Kothandaraman and P. W. H. Chan, *J. Org. Chem.*, 2012, **77**, 7166; (c) S. R. Mothe, P. Kothandaraman, S. J. L. Lauw, S. M. W. Chin and P. W. H. Chan, *Chem. Eur. J.*, 2012, **18**, 6133; (d) P. Kothandaraman, B. Q. Koh, T. Limpanuparb, H. Hirao and P. W. H. Chan, *Chem. Eur. J.*, 2013, **19**, 1978.
- (a) S. Dhiman and S. S. V. Ramasastry, *Org. Biomol. Chem.*, 2013, **11**, 4299. (b) S. Dhiman and S. S. V. Ramasastry, *Org. Biomol. Chem.*, 2013, **11**, 8030. (c) S. Dhiman and S. S. V. Ramasastry, *J. Org. Chem.*, 2013, **78**, 10427. (d) B. Satpathi, S. Dhiman and S. S. V. Ramasastry, *Eur. J. Org. Chem.*, 2014, 2022. (e) S. Kasare, S. K. Bankar and S. S. V. Ramasastry, *Org. Lett.*, 2014, **16**, 4284.
- (a) C. Chowdhury, B. Das, S. Mukherjee and B. Achari, *J. Org. Chem.*, 2012, **77**, 5108; (b) N. Thirupathi, M. H. Babu, V. Dwivedi, R. Kant and M. S. Reddy, *Org. Lett.*, 2014, **16**, 2908; (c) H. Li, X. Li, H. -Y. Wang, G. N. Winston-McPherson, H. -M. J. Geng, I. A. Guzei and W. Tang, *Chem. Commun.*, 2014, **50**, 12293.
- As such, reactions of 1,3-dicarbonyls and 2-indolylmethyl cations generated by any method were never studied.
- While reactions of 2-indolylmethyl cations originating from propargylic tertiary alcohols (A) with different nucleophiles is well-established,<sup>6,8</sup> but generation of 2-indolylmethyl cations from propargylic secondary alcohols (C) and their reactions with any nucleophile is not reported thus far.
- Other NH-protecting groups (Ms, Boc, Ac) were also evaluated prior to proceeding to optimization. Only N-sulfonyl propargyl alcohols generated desired product (see Supporting Information for details).
- Step-I was found to proceed very slowly at room temperature. After several attempts, the reaction temperature was optimized to 60 °C.
- Earlier, Au(I)/Lewis acid,<sup>6a</sup> Ag(I),<sup>6b</sup> Pd,<sup>8a,8b</sup> Cu,<sup>8c</sup> conditions were reported for the conversion of **1** to **3**. For Au(I)/base mediated cyclization of 2-(1-hydroxyprop-2-ynyl)phenols to dihydrobenzofurans, see: H. Harkat, A. Blanc, J. -M. Weibel and P. Pale, *J. Org. Chem.*, 2008, **73**, 1620.
- For [3+2]-cycloadditions, see: (a) I. Kawasaki, M. Terano, A. Kurume, S. Hara, M. Yamashita and S. Ohta, *Tetrahedron Lett.*, 2005, **46**, 6549; (b) J. McNulty and D. McLeod, *Synlett* 2011, 717; (c) H. Li, R. P. Hughes and J. Wu, *J. Am. Chem. Soc.*, 2014, **136**, 6288; Also see: Ref-3a, 3d, 3k, and 3m. For Nazarov cyclizations, see: (c) J. A. Jordan, G. W. Gribble and J. C. Badenock, *Tetrahedron Lett.*, 2011, **52**, 6772; Also see: Ref-3g and 3l.
- Yield loss in general is attributed to the formation of 2-vinyl-1H-indoles in case of substrates with a pendant alkyl group on the acetylenic carbon centre.<sup>6a</sup>
- The crystal structure of **5v** has been deposited at the Cambridge Crystallographic Data Centre and the deposition number CCDC 1029309 has been assigned.
- For indirect, S<sub>N</sub>2-type reactions, see: (a) M. C. Hillier, J. F. Marcoux, D. L. Zhao, E. J. Grabowski, A. E. McKeown and R. D. Tillyer, *J. Org. Chem.*, 2005, **70**, 8385; (b) M. Bandini and A. Eichholzer, *Angew. Chem. Int. Ed.*, 2009, **48**, 9533.
- A. Kuznetsov, A. Makarov, A. E. Rubtsov, A. V. Butin and V. Gevorgyan, *J. Org. Chem.*, 2013, **78**, 12144.
- For pharmaceutically relevant compounds, see: (a) Z. Ding and N. Yoshikai, *Angew. Chem. Int. Ed.*, 2013, **52**, 8574; for bioactive natural products, see: (b) D. H. Dethe, R. D. Erande and B. D. Dherange, *Org. Lett.*, 2014, **16**, 2764.