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Copper-catalyzed tandem annulation/arylation for the synthesis of diindolylmethanes from propargylic alcohols†

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Various highly substituted 2,3′-diindolylmethane heterocycles were prepared from propargylic alcohols and indole nucleophiles *via* a transition metal-catalyzed tandem indole annulation/arylation reaction for the first time. Among the metal catalysts we examined, the most economical copper(I) catalyst provided the highest efficiency. The indole nucleophiles could also be replaced by other electron-rich arenes or alcohols.

As one of the most abundant heterocycles in natural products and pharmaceutical agents, indole continuously attracts significant attention of the synthetic community and many efficient indole annulation methods have been developed to date.[1] To increase the synthetic efficiency of indole derivatives, it is ideal to combine the indole annulation with other transformations in a cascade process. We have recently coupled indole annulation with [4+3] cycloaddition for the synthesis of cyclohepta[*b*]indoles[2] and arylation for the synthesis of 2,3′-diindolylmethanes using platinum or rhodium catalysts.[3] 2,3′-Diindolylmethanes are not only present in bioactive compounds[4] but also important precursors for other heterocycles.[5] We recently evaluated various 2,3′-diindolylmethanes as selective agonists of the arylhydrocarbon receptor,[6] which are potential therapeutics for benign prostate hyperplasia,[7] inflammation disorders,[8] and cancers.[9]

Our previously developed Pt- or Rh-catalyzed indole annulation/arylation cascade is shown in Fig. 1a. Metal carbene intermediate **4** was generated by the annulation of propargylic ether **1** *via* intermediate **3**.[10] An indole nucleophile could then react with this carbene to afford 2,3′-diindolylmethane **2**.[3] Substituent on the 2′-position can be introduced by starting with the corresponding substituted indoles. However, substituent on the 3-position of **2** cannot be introduced by this method. Being able to access these heterocycles with diverse substituents under mild conditions would help us to further study their biological activities.[6] Inspired by Chan's pioneering work on preparing indole derivatives from propargylic alcohol **5**,[11] we proposed the synthesis of 2,3′-diindolylmethane **6** from the same type of propargylic alcohol to overcome the limitation of our previous method (Fig. 1b). In addition to expensive platinum, gold, and palladium catalysts, we found that the much cheaper copper catalysts were also very effective for the synthesis of heterocycle **6** with an additional R^2-substituent from alcohol **5**. Preliminary mechanistic investigations suggest that the mechanism for the formation of **6** involves an allyl cation intermediate instead of a metal carbene intermediate in the synthesis of product **2** from ether **1**. The starting material, mechanism and products of the new method described here are thus all different from our previous approach. The current method has the advantages of being able to access more substituted indoles and use cheaper copper catalyst.

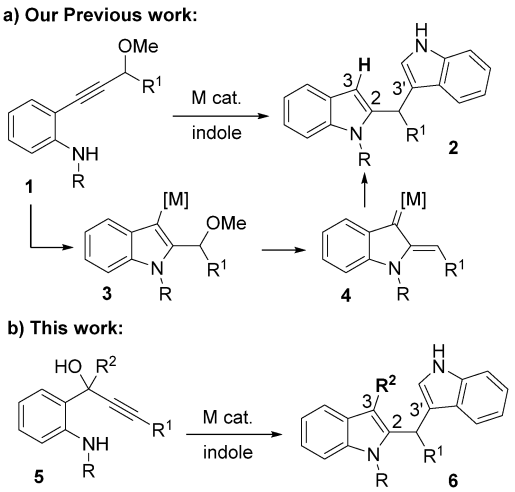

Fig. 1 Two complementary approaches for 2,3′-diindolylmethanes *via* tandem indole annulation and arylation.

Propargylic alcohol **7** was prepared according to literature procedures[12] and treated with various catalysts in the presence

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† Electronic supplementary information (ESI) available: ^{1}H NMR, ^{13}C NMR, IR, and HRMS of new compounds. CCDC 1016687 and 1016688. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc05901h

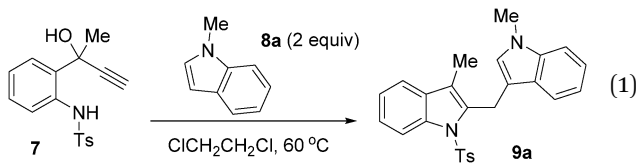
Table 1 Screening conditions[a]

Entry	Conditions	Yield (%)
1	$PtCl_2$ (10 mol%)	71
2	$Pd(OAc)_2$ (10 mol%)	55
3	$Au(PPh_3)Cl$ (10 mol%)	0
4	$Au(PPh_3)Cl$ (10 mol%), AgOTf (10 mol%)	50
5	AgO_2CCF_3 (10 mol%)	48
6	CuI	0
7	$CuCl_2$ (10 mol%)	58
8	$CuBr_2$ (10 mol%)	Trace
9	CuOTf (10 mol%)	72
10	$Cu(CH_3CN)_4PF_6$ (10 mol%)	75

[a] The yield of **9a** was determined by ^{1}H NMR of the crude product.

of *N*-methylindole **8a** (eqn (1), Table 1). A 71% yield of product **9a** was obtained when a previously used $PtCl_2$ catalyst[3] was employed (entry 1). Lower yields were observed for most other catalysts (entries 2–8). Cationic copper(I) catalysts afforded the highest yield of **9a** (entries 9 and 10). We also examined other solvents including toluene, acetonitrile, THF, dioxane, methylene chloride, methanol, and DMF. No desired product was observed in DMF. The yields ranged from 27% to 60% in other solvents. Conditions in entry 10 using an economically affordable copper catalyst were then selected for further study.

Under the conditions in entry 10 of Table 1, we also tried to replace the tosyl group in **7** by Boc or hydrogen (free aniline). No desired product was observed.



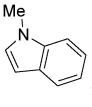
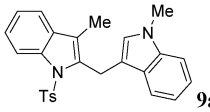
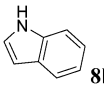
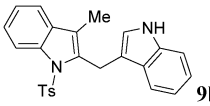
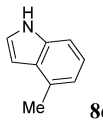
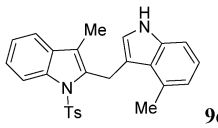
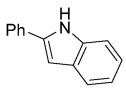
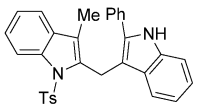
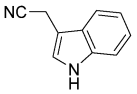
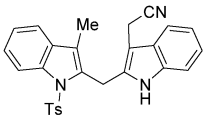
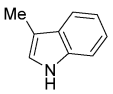
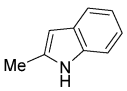
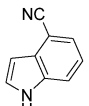
(1)

We next examined the scope of indole nucleophiles using propargylic alcohol **7** as the electrophile (eqn (2), Table 2). A similar yield was obtained for the parent indole **8b** without the *N*-methyl group. The structure of **9b** was unambiguously established by X-ray analysis (CCDC 1016687). We also tried a cationic gold catalyst (entry 4 in Table 1) for the reaction between propargylic alcohol **7** and indole **8b**. No desired product was observed in this case.

We next examined different substituents on the benzene part of indole (C4–C7 positions). Most indoles could participate in the tandem reaction. The reaction was not very sensitive to steric hindrance since 4-methyl substituted indoles **8c** worked fine. The highest yield was obtained using electron-rich indole **8d**. Other substituents such as methyl, chloro, and fluoro groups could be tolerated on 5-, 6-, and 7-positions of indoles **8e** to **8l**. A phenyl group could be tolerated on the 2-position of indole **8m**. For 3-substituted indole **8n**, the alkylation occurred on the 2-position to yield 2,2′-diindolylmethane **10**. Surprisingly, complex mixtures were observed for 2-, or 3-methyl substituted indoles **8o** and **8p**. No desired product was obtained for indole **8q**, which may be due to the combination of unfavorable steric and electronic factors.

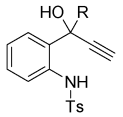
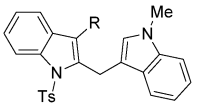
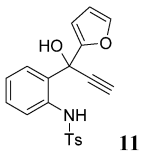
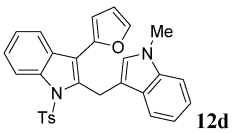
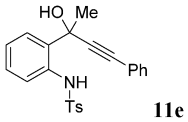
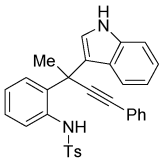
The scope of the propargylic alcohols was also examined by varying R^1 and R^2 substituents in structure **11** (eqn (3), Table 3).[11,13] The R^1 of **11** could be various alkyl groups (**11a** and **11b**) or aryl groups (**11c** and **11d**), though the yields were lower for the latter. Surprisingly, product **13** was observed when R^2 was a phenyl group in substrate **11e**. The structure of compound **13** was unambiguously

Table 2 Scope of indoles **8**[a]

Entry	Substrate	Product	Yield[b] (%)
1	 **8a**	 **9a**	73
2	 **8b**	 **9b**	75
3	 **8c**	 **9c**	77
4	**8d**, R = OMe	**9d**	95
5	**8e**, R = Me	**9e**	68
6	**8f**, R = Cl	**9f**	63
7	**8g**, R = F	**9g**	70
8	**8h**, R = Me	**9h**	70
9	**8i**, R = F	**9i**	70
10	**8j**, R = Me	**9j**	67
11	**8k**, R = Cl	**9k**	65
12	**8l**, R = F	**9l**	81
13	 **8m**	 **9m**	71
14	 **8n**	 **10**	78
15	 **8o**	A complex mixture	
16	 **8p**	A complex mixture	
17	 **8q**	No reaction	

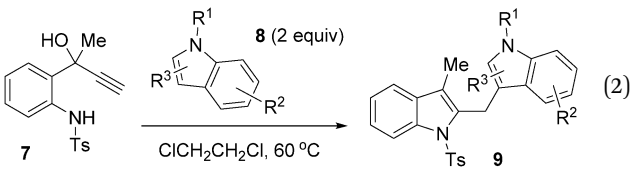
[a] Conditions: **7** (1 equiv.), indole **8** (2 equiv.), $Cu(CH_3CN)_4PF_6$ (10 mol%), 60 °C, $ClCH_2CH_2Cl$. [b] Isolated yield.

Table 3 Scope of propargylic alcohols **9**[a]

Entry	Substrate	Product	Yield[b] (%)
			
1	**11a**, R = *n*Bu	**12a**	72
2	**11b**, R = iPr	**12b**	83
3	**11c**, R = Ph	**12c**	42
4	 **11d**	 **12d**	60
5	 **11e**	 **13**	63[c]

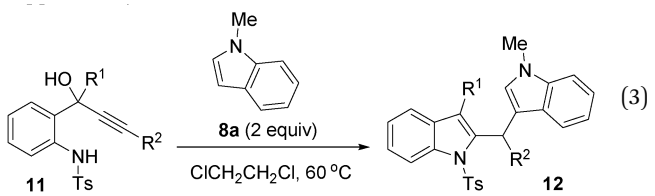
[a] Conditions: **9** (1 equiv.), indole **8a** (2 equiv.), $Cu(CH_3CN)_4PF_6$ (10 mol%), 60 °C, $ClCH_2CH_2Cl$. [b] Isolated yield. [c] Indole **8b** was employed.

determined by X-ray analysis (CCDC 1016688). No reaction occurred when both R^1 and R^2 were methyl groups. When both R^1 and R^2 were hydrogen, no desired product was observed, suggesting that the two methods outined in Fig. 1 are completely complementary to each other.



(2)

We also examined nucleophiles besides indoles. We were pleased to find that 1,3-dimethoxybenzene also participated in the tandem indole annulation/arylation cascade reaction (Fig. 2). Alcohols could also serve as nucleophiles to yield adducts **15** and **16**. Product **16** has been previously prepared from substrate **11c** using a cationic gold catalyst.[11] We demonstrated that a much more economically affordable copper catalyst was also effective for this transformation.



(3)

Chan's group reported that **7** could undergo intramolecular hydroamination to yield product **17** in the presence of a silver catalyst (Fig. 3).[14] This intermediate can undergo further cycloisomerization and addition reactions to afford various indole derivatives in the presence of a gold catalyst.[11,12,14,15] When we treated compound **17** derived from silver-catalyzed hydroamination

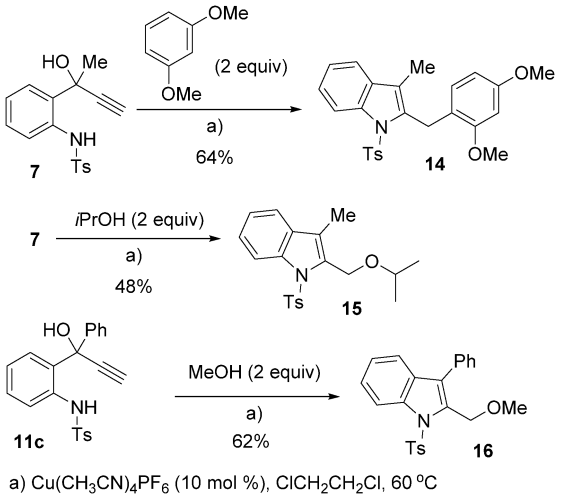


Fig. 2 Coupling with other nucleophiles.

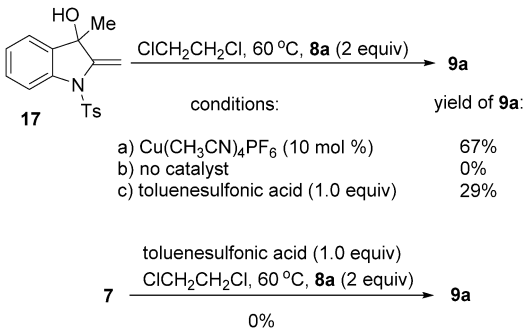


Fig. 3 Preliminary investigation of the mechanism.

with indole **8a** under our standard conditions, product **9a** was obtained. No reaction occurred between **17** and **8a** in the absence of any catalyst. Brønsted acid could promote the arylation of **17** but not the cyclization of **7**.

The mechanism for the copper-catalyzed indole annulation/arylation is proposed in Fig. 4. Copper-catalyzed intramolecular hydroamination will afford intermediate **17**, which can be trapped by indole nucleophile **8a**. The alkylation of indole **8a** occurs at the 3′-position only. In the presence of acid, an allyl cation intermediate **19** may be formed. Indole nucleophile **8a** attacks the 2α-position of the allyl cation to afford the final product **9a**.

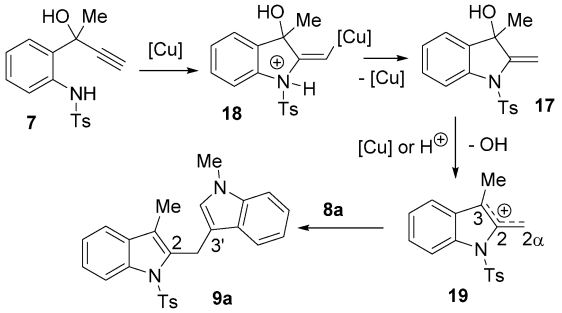


Fig. 4 Proposed mechanism.

In summary, we have developed an efficient method for the synthesis of diverse substituted 2,3′-diindolylmethanes from propargylic alcohols and indoles. The indole nucleophiles can be replaced by other carbon or oxygen nucleophiles. Being able to use economical copper catalyst to promote the hydroamination and arylation cascade reaction makes this method and the syntheses of related indole derivatives ideal for both medicinal and process chemistry.

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