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Ag(I)-Catalyzed Domino Cyclization–Addition Sequence with Simultaneous Carbonyl and Alkyne Activation as a Route to 2,2′-Disubstituted Bisindolylarylmethanes

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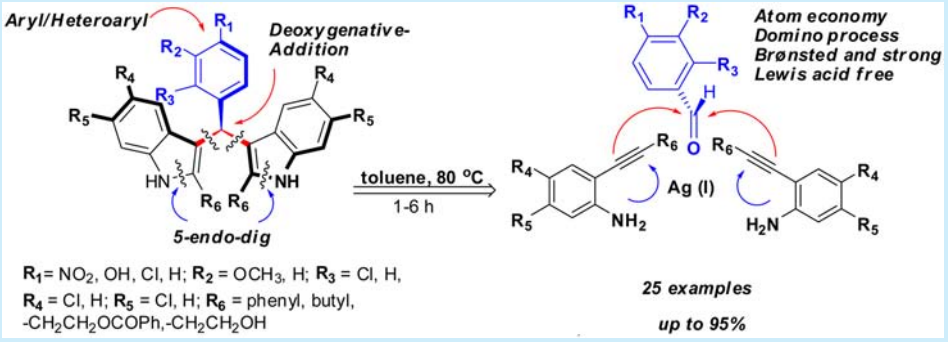
Supporting Information



ABSTRACT: An efficient synthesis of symmetrical 3, 3′-bisindolylarylmethanes with various substituents on the indole moiety has been developed by Ag(I)-catalyzed cycloisomerization and an deoxygenative addition sequence on *o*-alkynylanilines and aryl aldehydes. Ag(I) is proposed to activate alkyne unit and carbonyl moiety simultaneously leading to a *domino* first 5-*endo-dig* indole annulation, addition to C═O, second indole annulation, and its dehydroxylative addition.

Indoles are probably one of the most ubiquitous structures among heterocyclic compounds due to their presence in various natural products, pharmaceuticals, and agrochemicals[1] of proven biological record.[1,2] Novel 3,3′-bisindolylmethane alkaloids (BIMs), e.g., **1**–**5** (Figure 1), have been isolated from various terrestrial and marine natural sources,[1n,3] many of which display remarkable biological activities.[4] This, in turn, has encouraged the design and synthesis of analogues of these natural products.[3c,5]

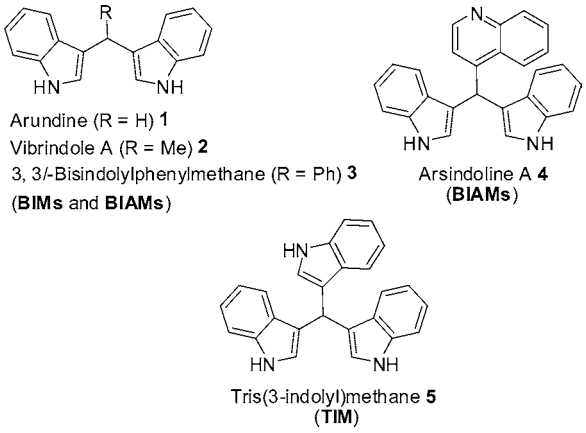


Figure 1. Privileged structures of 3,3′-bisindolylmethanealka-loids.

A majority of synthetic methods reported involve condensation of indoles with carbonyl compounds (or their synthetic equivalents) in the presence of acid or base to obtain BIMs with different structural features.[3c,5] Some metal-catalyzed processes have been developed employing similar resources,[6] such as the Re-catalyzed addition,[6d] the Pt-catalyzed bis-indolylation,[6f] and gold-catalyzed transformation,[6c] among others. Transition-metal-catalyzed cycloisomerization of *o*-alkynylanilines has become an important tool for the construction of indoles during the past two decades.[7] Recently, Campagne et al. reported the synthesis of BIMs via one-pot annulation/Friedel–Crafts alkylation employing dual catalysis of Fe(III)–Pd(II) on *o*-alkynylanilines in moderate yield.[8] However, a one-pot domino methodology for BIM formation using dual activation of *o*-alkynylanilines and aldehydes under suitable metal catalysis may offer distinct advantages. Moreover, BIMs with additional substitution in the pyrrole nucleus have been little explored to the best of our knowledge. In this paper, we report a one-pot domino process that allows quick generation of 2,2′-disubstituted 3,3′-bisindolylarylmethanes (BIAMs) from easily available starting materials using silver catalysis.

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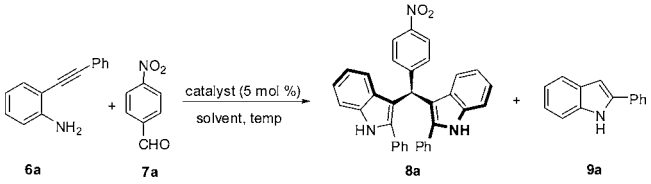
The economic attractiveness and milder nature of silver-based catalysts have made their use significant in large-scale catalytic reactions. This led us to exploration of a silver-catalyzed process for the synthesis of substituted BIAMs in view of previous success on silver-catalyzed indole formation.[9,10] We wondered whether Ag(I) might be able to make aldehydes susceptible to nucleophilic addition with simultaneous cycloisomerization of appropriately substituted alkynylanilines, which could possibly lead to BIAM derivative **3** (Figure 1). Thus, our trial commenced with unprotected *o*-alkynylanilines and aldehydes as the starting materials using Ag(I) as a catalyst as a possible domino process. Initially, the reaction was allowed to run with several silver catalysts ($AgNO_3$, Ag_2CO_3, AgOAc) that are soluble in polar protic solvents. However, none of these catalyzed the reaction even at elevated temperature (70−80 °C) in different reaction media (entries 1−4, Table 1), and a silver mirror was observed at the bottom of the flask, perhaps as a result of oxidation of the aldehyde with Ag(I) in such types of solvents and reaction conditions.

Table 1. Optimization of the Reaction Conditions[a]



6a 7a 8a 9a

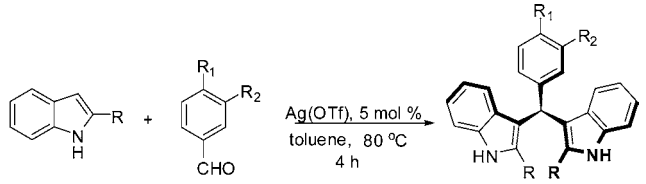
entry	catalyst (5 mol %)	solvent	temp (°C)	time (h)	yield[b,c] (%) 8a	9a
1	$AgNO_3$	AcOH + EtOH (1:1)	70	16	0	0
2	$AgNO_3$	toluene + EtOH + H_2O	80	16	0	0
3	Ag_2CO_3	toluene + EtOH + H_2O	80	16	0	0
4	AgOAc	toluene + EtOH + H_2O	80	16	0	0
5	AgOTf	DMSO	80	16	0	25
6	AgOTf	DMF	80	16	0	20
7	AgOTf	THF	60	16	30	25
8	CF_3CO_2Ag	toluene	80	16	40	10
9	AgOTf	toluene	80	2.5	88	0
10a	AgOTf + $NaHCO_3$	toluene	80	2.5	75	0
10b	AgOTf + $NaHCO_3$	toluene	80	16	75	0
11	TfOH	toluene	80	16	0	0
12		toluene + *n*-decane + $MgSO_4$ + molecular sieves (4 Å)	80	16	0	0

[a]Reaction conditions: **6a** (0.2 mmol), **7a** (0.1 mmol), catalyst (0.005 mmol), solvent (1 mL). [b]Isolated yield. [c]Under argon.

We then decided to carry out this process in polar aprotic solvents (DMSO, DMF). Considering the solubility in the reaction medium, AgOTf was employed as catalyst. Unfortunately, the only fruitful result of the reaction was the formation of the indole **9a** in low yield (entries 5 and 6). However, indicatively, AgOTf showed moderate catalytic activity in dry THF at 60 °C. BIAM **8a** indeed formed under the stated conditions (entry 7), but the yield was too low to be synthetically useful (30%). In this reaction, indole **9a** was formed as a side product (25%). After some experimentation, we found that better result could be obtained using CF_3CO_2Ag as catalyst in toluene at 80 °C (entry 8). We then decided to examine the catalytic activity of AgOTf in toluene at 80 °C for this domino process. Pleasingly, 2,2′-diaryl-3,3′-bisindolylarylmethane **8a** was produced in very good yield (88%) within 2.5 h (entry 9). Comparatively lower yield (75%) was obtained when $NaHCO_3$ was added as an additive in the above reaction (entries 10a and 10b). However, Brønsted acids (TfOH) and dehydrative conditions could not furnish BIAMs under these reaction conditions (entries 11 and 12). Consequently, AgOTf proved to be the catalyst of choice for this transformation (entry 9).

Moreover, a controlled experiment was conducted in order to investigate if 2-substituted indole could be condensed with aldehydes under the same reaction conditions (Scheme 1). BIAMs **8** were obtained in poor yield when the 2-substituted indoles **9a−c** were generated prior to the addition of aldehyde into the reaction mixture.

Scheme 1. Controlled Experimentation with 2-Substituted Indoles and Aldehydes



9a (R = Ph)
9b (R = -$(CH_2)_3CH_3$)
9c (R = -$(CH_2)_2$OCOPh)

7a (R_1 = NO_2; R_2 = H)
7b (R_1 = Cl; R_2 = H)
7d (R_1 = OH; R_2 = OMe)

8a (10%)
8f (10%)
8p (15%)

To rationalize this domino process, we could propose a plausible mechanism where Ag(I) would be supposed to initiate the coordination with alkyne unit[11] and carbonyl moiety simultaneously (pathway a, **I**, Scheme 2). This mode of activation could induce sequential 5-*endo*-*dig* indole annulation followed by addition of the C_3 of the first indole moiety to the carbonyl carbon of aryl aldehyde to furnish an Ag(I) alkoxide intermediate **II**. Ag(I) of this intermediate may then activate the alkyne unit of the second molecule of *o*-alkynylaniline leading ultimately to second indole annulation. Addition of the C-3 of second indole moiety to the benzylic carbon of bis-aryl methoxide within **II** would proceed with the substitution of Ag(I)-bound oxygen. This tandem bond-breaking−bond-forming cascade would produce our desired products 2,2′-disubstituted 3,3′-bisindolylarylmethanes (BIAMs) and water and regenerate the catalyst AgOTf as shown in Scheme 2.

An alternate possibility is the consequential domino process shown in pathway b (Scheme 2). First, the indolyl silver intermediate **IV** is formed, which next condenses with the aldehyde to form the alkoxysilver intermediate **V**. Finally, condensation between **V** and **VI** gives the desired product with simultaneous regeneration of silver triflate.[12]

To demonstrate generality, the scope of the synthesis of BIAMs was examined for this domino process using various unprotected *o*-alkynylanilines **6** and aldehydes **7** as the starting materials (Table 2). We observed that substituents on the aromatic aldehyde have an impact on the product yield. A better yield could be achieved when electron-withdrawing substituents were present in the aromatic aldehyde (entries 1, 5, 9, and 13). Moreover, ortho-substituted aryl aldehyde, e.g., 2-chlorobenzaldehyde, also underwent smooth transformation

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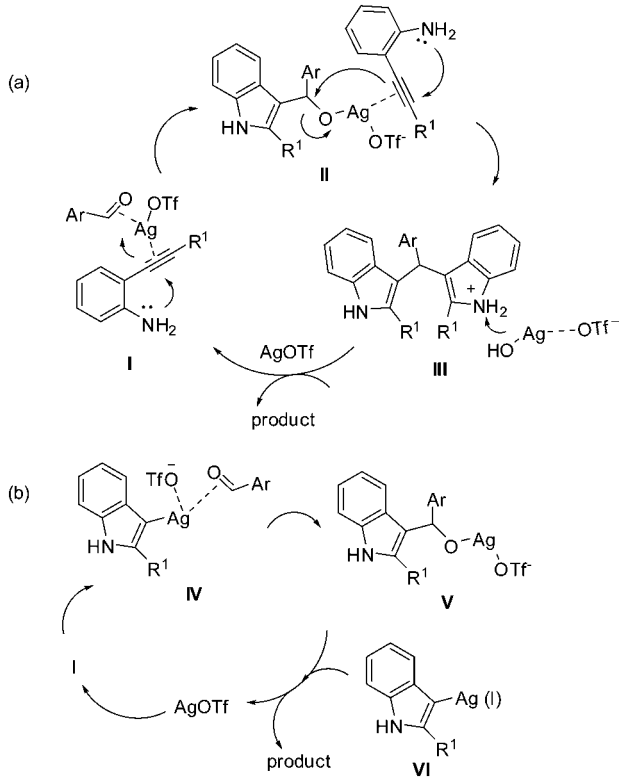
Scheme 2. Plausible Mechanism for Formation of BIAMs



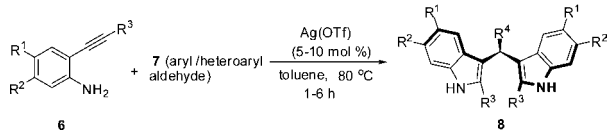
into the desired BIAMs (entries 17–19). Pleasingly, heteroaryl aldehydes like 2-thiophene-yl and 2-furanyl aldehydes responded to this domino process rapidly with similar efficiency (entries 22–25). 2-Alkynylaniline having a further substitution on the aromatic ring (entries 20 and 21) followed the course of the process in a similar fashion.

Interestingly, substituents on the alkyne unit also influenced the efficiency of this domino reaction. Substrates having a butyl or ethyl ester group on their alkyne unit responded well in this transformation. The yield of BIAMs became relatively high (entries 5, 6, 13, 14, etc.) compared to that from the substrates with a phenyl substituent. Substrates bearing an aliphatic hydroxyl group on the alkyne unit did not respond well toward this catalytic reaction. BIAM was obtained in only 55% yield when **6c** and vanillin were allowed to undergo a domino indole annulation and deoxygenative addition sequence even in the presence of 10 mol % of AgOTf at 80 °C for 6 h (entry 12). Longer reaction time and higher catalyst loading were required to obtain a moderate yield (55–70%; entries 9–13) for this type of substrates.

Although the gross structure of each of the products was secured from spectral analysis, a crystallographic confirmation was obtained on compound **8a** (ORTEP, Figure 2).

In conclusion, we have developed a facile domino process for the construction of symmetrical BIAMs having various substitutions at the 2,2′-positions of the indole from unprotected *o*-alkynylaniline and aldehyde employing Ag(I) as a metal catalyst, which involves simultaneous activation of the alkyne unit and carbonyl moiety. As BIMs are important biologically relevant scaffolds, this moiety with further substitutions at the indole ring[13] could find use in medicinal chemistry. The methodology developed is atom- as well as pot-economic and involves the use of catalytic amounts of more accessible silver salts, which may render it adaptable for large-scale synthesis.

Table 2. Scope of 2,2′-Disubstituted 3,3′-Bisindolylarylmethanes 8[a]



Entry	BIAM (% yield)[b,c]	R^1	R^2	R^3	R^4	time (h)	cat. mol %
1	**8a** (88)	H	H	Ph		2.5	5
2	**8b** (80)	H	H	Ph		1	5
3	**8c** (70)	H	H	Ph		1.5	5
4	**8d** (77)	H	H	Ph		2.5	5
5	**8e** (95)	H	H	butyl		2	5
6	**8f** (88)	H	H	butyl		1	5
7	**8g** (75)	H	H	butyl		1	5
8	**8h** (80)	H	H	butyl		3	5
9	**8i** (70)	H	H	-$(CH_2)_2$OH		6	8
10	**8j** (66)	H	H	-$(CH_2)_2$OH		6	8
11	**8k** (62)	H	H	-$(CH_2)_2$OH		6	8
12	**8l** (55)	H	H	-$(CH_2)_2$OH		6	10
13	**8m**(92)	H	H			2.5	5
14	**8n** (86)	H	H			1	5
15	**8o** (75)	H	H			2	5
16	**8p** (80)	H	H			3.5	5
17	**8q** (69)	H	H	Ph		1	5
18	**8r** (79)	H	H	butyl		1	5
19	**8s** (75)	H	H			2	5
20	**8t** (84)	Cl	H			1.5	5
21	**8u** (85)	H	Cl	Ph		2	5
22	**8v** (92)	H	H	Ph		0.75	5
23	**8w** (86)	H	H	butyl		0.75	5
24	**8x** (79)	H	H			1	5
25	**8y** (94)	H	H			0.5	5

[a]Reaction conditions: **6** (0.2 mmol), **7** (0.1 mmol), catalyst (0.01 mmol otherwise mentioned; 5 mol % with respect to alkyne), solvent (0.5 mL). [b]Isolated yield. [c]Under argon.

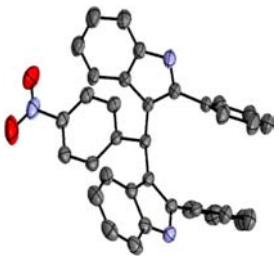


Figure 2. ORTEP diagram of **8a**.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02321.

General procedures, ^{1}H and ^{13}C NMR spectra of compounds **8a**–**y**, and X-ray structure of **8a** (PDF)

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Notes

The authors declare no competing financial interest.

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