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Gold-catalyzed tandem reaction of 2-alkynylanilines followed by 1,6-conjugate addition to *p*-quinone methides: efficient access to unsymmetrical diarylindolylmethanes†

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A simple, mild, efficient and chemoselective catalytic method for the straightforward synthesis of an interesting class of 2-aryl/alkyl-substituted-3-diaryl indolyl methanes in high yield is reported. This atom-efficient method proceeds *via* a gold-catalyzed one-pot sequential intramolecular hydroamination (C–N bond formation) of 2-alkynylanilines followed by a 1,6-conjugate addition to *p*-quinonemethides. The *p*-quinonemethides, which contain aldehyde functional groups, preferentially participate in 1,6-conjugate addition, while the aldehyde functional group remains unreactive.

Introduction

Triarylmethane scaffolds represent one of the privileged structural motifs in organic synthesis due to their significant contributions in several areas including as leuco dye precursors,[1] photochromic agents,[2] substrates for theoretical[3] and biological studies[4] and suitable building blocks for generating dendrimers.[5] They are also important in medicinal chemistry as anti-tubercular,[6] anti-proliferative,[7] and anti-cancer agents.[8] Several methods have been reported for the synthesis of symmetrical triarylmethanes *via* the Friedel–Crafts reaction of electron-rich heteroarenes with aromatic aldehydes, using Brønsted[9] or Lewis acid[10] catalysts. However, the synthesis of unsymmetrical triarylmethane derivatives exhibiting various biological properties (Fig. 1) is much less developed.

Recently, various research groups have reported a cross-coupling-based approach for the synthesis of triarylmethane derivatives. For instance, Molander *et al.*[11] and Kuwano[12] independently described the synthesis of unsymmetrical triarylmethanes through the Pd-catalyzed Suzuki–Miyura coupling of diarylmethyl carbonates with boronic acids. Later on, Walsh,[13] Oshima,[14] Zhang,[15] and Crudden[16] independently developed the Pd-catalyzed direct arylation of benzylic derivatives to access triarylmethanes. Jarvo[17] and Watson[18] demonstrated enantioenriched triarylmethanes through the Ni-catalyzed coupling of diarylmethanol derivatives with arylboronic acids and boronic esters, respectively. Subsequently, Nambo and Crudden reported a protocol for the synthesis of asymmetrical triarylacetonitriles[19a] and triarylmethanes[19b] through a Pd-catalyzed sequential arylation approach. Lately, the Zhang[20] group developed a phosphine catalysed synthesis of triarylmethanes using the Friedel–Crafts reaction of naphthols with *para*-quinone methides and asymmetric diarylmethanes using the reaction of alkyl vinyl ketones with *para*-quinone methides.

1 Aromatage inhibitor 2 Anti -TB agent 3 Anti inflamatory agent

Fig. 1 Unsymmetrical triarylmethane-based drugs.

Recently, the transition metal-catalyzed tandem cyclization of 2-alkynylanilines followed by C3-functionalization, particularly for 2,3-difunctionalized indoles,[21] has been developed with extraordinary improvements in terms of productivity and scope of application. In our on-going efforts with tandem cyclization reactions, the development of 3-substituted indoles stimulated by metal or Au is of growing interest. Previously, we reported an efficient Ag-catalyzed domino process for the synthesis of 2,3-disubstituted indoles from alkyne imino ethers.[22] Furthermore, the Cu-catalyzed one pot synthesis of 2-[(2-alkyl-1*H*-indol-3-yl) methylene]malonates from 2-alkynylanilines, triethyl orthoformate and diethyl malonate, followed by a Sc-catalyzed intramolecular Friedel–Crafts reaction to form the resultant heterocyclic compounds, was reported.[23] Very recently, we developed a Cu-catalyzed tandem reaction of 2-alkynylanilines with benzoquinones to access 3-indolylquinones (eqn (2), Scheme 1).[24] Similarly, a Pd-catalyzed domino process to access unsymmetrical diarylindolylmethanes (eqn (1), Scheme 1) was reported

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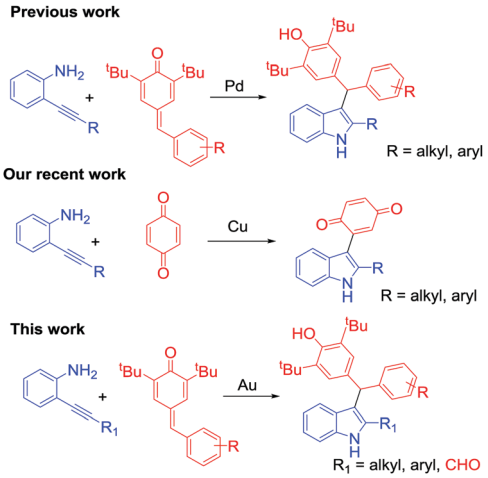


Scheme 1 Methods of synthesis of diarylindolylmethanes.

by Anand *et al.*[25] However, this reaction needs high catalyst loading and inert reaction conditions, which make it expensive. We herein describe an effective and air stable Au-catalysed tandem cyclization of 2-alkynylanilines, followed by 1,6-conjugate addition to *p*-quinone methides, as an efficient access to unsymmetrical diarylindolylmethanes.

The cyclization of 2-alkynylanilines followed by functionalization at the C3-position of free (N–H) indoles is a highly complex step as it often suffers from selective addition towards bis-electrophilic centres in the coupling partner, such as *p*-quinone methides and aldehydes,[26] under gold catalysis. Nevertheless, the present study also exploits the highly chemoselective 1,6-conjugative addition towards *p*-quinone methides in which the aldehyde group remains unreactive. This concept is reported here for the first time in the presence of two electrophilic centres.

Results and discussion

We commenced optimization studies using readily available 2-alkynylaniline **1a** and *p*-quinone methide (**2a**, 1.2 eq.) as coupling partners. Although our initial attempts with copper catalysts such as CuCN, $Cu(OAc)_2$, CuI and CuCl led to only the indole product, *p*-quinone methide (**2a**) remains unreacted (entries 1–4, Table 1). Extensive optimization experiments revealed that only gold catalysts such as $NaAuCl_4{\cdot}2H_2O$, $AuBr_3$ and AuCl (2 mol%) at room temperature afford the desired product of diarylindolylmethane with 65%, 25% and 20% yields, respectively (entries 5–7, Table 1). These results prompted us to examine various Lewis-acid catalysed tandem heterocyclization reactions in detail. In this context, a variety of catalysts such as I_2, $BiCl_3$, $InCl_3$, AgCl, $Pd(OAc)_2$ and *p*-TSA as well known alkyne bond activators were examined for this tandem cyclization process, as shown in Table 1 (entries 8–14, Table 1), using dichloromethane (DCM) as solvent. However, all the catalysts afford the tandem cyclization product of 2-alkynylaniline without further conjugative addition to *p*-quinone methide. Further extensive studies of gold catalysts such as $NaAuCl_4{\cdot}2H_2O$, $AuBr_3$ and AuCl at 50 °C predominantly result in quantitative yields of

Table 1 Optimization of the reaction conditions[a]

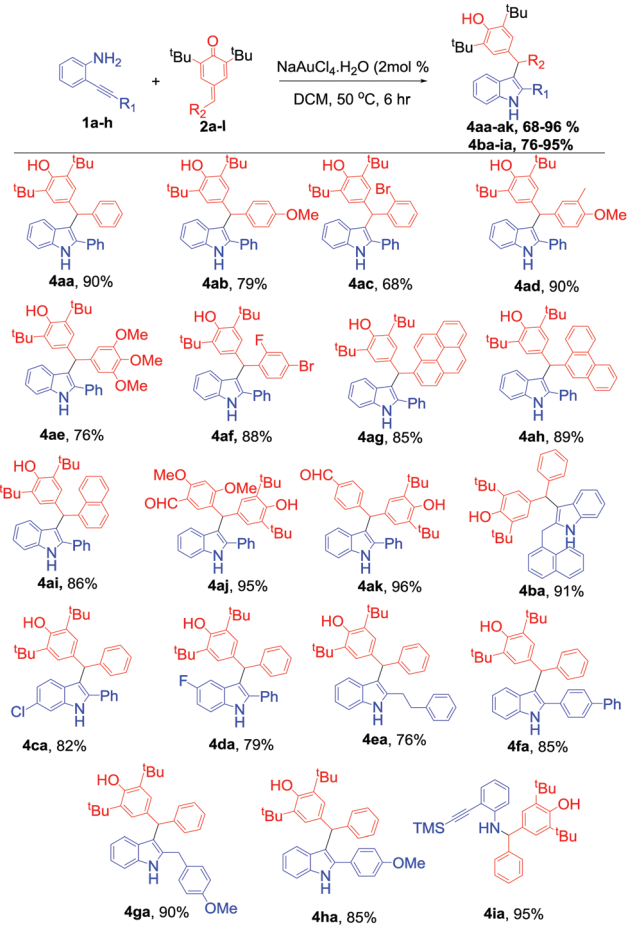
S. no.	Catalyst	Solvent	Temp (°C)	Time (h)	Yield[b] (%) 3aa	4aa
1	CuCN	DMF	100	24	90	ND
2	$Cu(OAc)_2$	DMF	100	24	72	ND
3	CuI	DMF	100	24	80	5
4	CuCl	DMF	100	24	85	ND
5	$NaAuCl_4{\cdot}3H_2O$	DCM	r.t.	24	20	65[c]
6	$AuBr_3$	DCM	r.t.	24	60	25[c]
7	Au(I)Cl	DCM	r.t.	24	65	20[c]
8	I_2	DCE	100	24	68	ND
9	AgCl	DMF	100	24	82	ND
10	$Pd(OAc)_2$	DCM	50	24	73	10
11	$InCl_3$	DCE	100	24	69	ND
12	$BiCl_3$	DCM	50	24	60	ND
13	$FeCl_3$	DCM	50	24	55	ND
14	PTSA	DCM	50	24	30	ND
15	$NaAuCl_4{\cdot}3H_2O$	DCM	50	6	Trace	90[c]
16	$AuBr_3$	DCM	50	6	20	60[c]
17	AuCl	DCM	50	6	15	52[c]
18	$NaAuCl_4{\cdot}3H_2O$	DMF	50	24	10	20
19	$NaAuCl_4{\cdot}3H_2O$	DMSO	50	24	Trace	30
20	$NaAuCl_4{\cdot}3H_2O$	Toluene	50	24	10	75
21	$NaAuCl_4{\cdot}3H_2O$	EtOH	50	24	<5	85
22	$NaAuCl_4{\cdot}3H_2O$	ACN	50	24	ND	68
23	$NaAuCl_4{\cdot}3H_2O$	THF	50	24	ND	ND

[a] All the reactions were performed with **1a** (0.2 mmol) and **2a** (0.24 mmol) in air with 20 mol% catalyst. [b] All the yields are isolated yields. [c] Reaction with 2 mol% gold catalysts. ND denotes not determined.

90%, 60% and 52%, respectively (entries 15–17, Table 1). The obtained results from screening reactions of 2-alkynylaniline (**1a**) and *p*-quinone methide (**2a**) with common organic solvents in the presence of 2 mol% $NaAuCl_4{\cdot}2H_2O$ revealed that all the solvents (except THF) promoted the tandem process in moderate to good yields (entries 18–23, Table 1). Eventually, a gold catalyst (2 mol%) was identified to be the optimal combination, resulting in 90% yield at 50 °C and a short reaction time in DCM solvent (Table 1, entry 15).

With the optimized reaction conditions, we then explored the efficiency and generality of this tandem heterocyclization process using the reaction of 2-alkynylaniline (**1a**) with various *p*-quinone methides prepared from various substituted (–OMe, –Me, –F, –Br) aromatic aldehydes (**2a–f**) using $NaAuCl_4{\cdot}2H_2O$ (2 mol%) as an efficient catalyst (Table 2). In all cases, the expected diarylindolylmethanes were obtained in good to excellent yields (**4aa–4af**). In the case of *p*-quinone methide derived from π-conjugated aromatic aldehydes such as naphthalene, pyrene and phenanthrene aldehydes, these underwent smooth conversion to their corresponding diarylindolylmethane derivatives, **4ag**, **4ah** and **4ai**, in 88%, 85% and 89% yields, respectively. Surprisingly, a highly chemoselective reaction was observed with *p*-quinone methide bearing an aldehyde functional group, where nucleophilic 1,6-conjugate addition occurs only on the quinone motif without influencing the aldehyde functional

Table 2 Tandem cyclization of 2-alkynylanilines with *p*-quinone methides

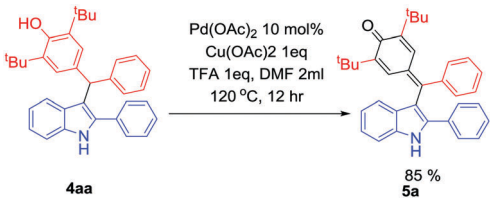


The reaction was carried out with **1** (0.2 mmol), **2** (0.24 mmol) and $NaAuCl_4{\cdot}2H_2O$ (2 mol%) in DCM (2 mL) at 50 °C for 6 h

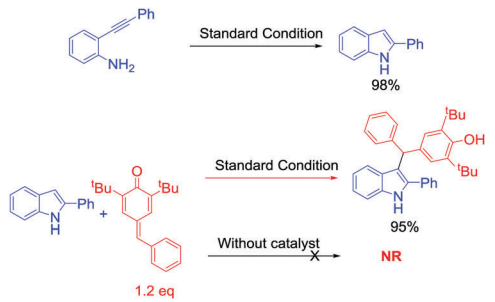
group, demonstrating the excellent chemoselectivity (entries **4aj** & **4ak**, 95% & 96%) with superb yields.

To further investigate the substrate scope, we examined various 2-alkynylanilines (**1a–j**) with **2a** under the optimized conditions, and the results are summarized in Table 2. 2-Substituted ethynylanilines (R_1 = phenyl, ethyl benzene, biphenyl, 1-methyl napthyl) (**1b–f**) were reacted efficiently with *p*-quinone methide (**2a**), leading to the desired products **4ba–4fa** in good to excellent yields (76–91%). Halogen substituted alkynyl anilines also produce moderate to good yields. Electron-rich substituted alkynyl anilines, with substituents such as methoxy groups, lead to **4ga** and **4ha** in 90% and 85% yields, respectively. Conversely, TMS substituted 2-alkynyl aniline (**2j**) does not undergo domino cyclization due to the low electrophilicity of the π-activated TMS alkyne (**1j**). However, it leads to the 1,6-conjugate addition product of amine to *p*-quinone methide (**2a**) in a quantitative yield (**4ja**, 95%). In addition, the diaryl indolylmethane (**4aa**) studied under Pd catalysis furnished the oxidation product of **4aa**, *p*-quinone indolyl methide **5a**, with 85% yield as shown in Scheme 2.

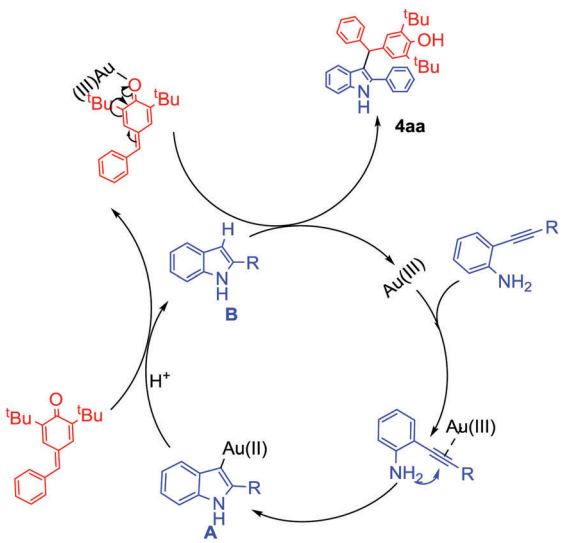
Finally, several control experiments have been performed to understand the reaction mechanism (Scheme 3). First,



Scheme 2 Application of product **4aa**.



Scheme 3 Control experiments.



Scheme 4 Proposed mechanism.

2-phenylindole (1 equiv.) was treated with *p*-quinone methide (1.2 equiv.) in the presence or absence of the Au-catalyst at 50 °C in DCM. The product **4aa** was obtained in 95% yield in 3 h in the presence of the Au-catalyst, whereas no such product was observed even after 24 h in the absence of the Au-catalyst. Based on these observations, a plausible mechanism for the formation of diarylindolylmethane was proposed, as shown in Scheme 4. This transformation pathway is initiated by the formation of the adduct between Au(III) and 2-alkynyl aniline, which undergoes further cyclization to form intermediate A. The intermediate A undergoes protonolysis in the presence of strong hydrochloric acid, which was generated during the aminoauration to afford the 2-substituted indole derivative (B). Finally, the formed 2-substituted indole reacted with *p*-quinone

methide in the presence of $NaAuCl_3 \cdot 2H_2O$ to give the resultant final product **4aa**.

Conclusions

In summary, we developed a novel Au-catalysed synthesis of diarylindolylmethane from 2-ethynylanilines and *p*-quinone methides *via* a tandem-type cyclization followed by 1,6-conjugative addition. Subsequently, chemoselective conjugative addition to C–C bond formation with *p*-quinone methide, in which the aldehyde groups in **4aj** and **4ak** remain unreactive, leads to excellent yields. We are extending this protocol to the construction of other poly aromatic compounds, the details of which will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

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