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# Brønsted Acid Catalyzed Cascade Reactions of 2-[(2-Aminophenyl)ethynyl]phenylamine Derivatives with Aldehydes: A New Approach to the Synthesis of 2,2′-Disubstituted 1*H*,1′*H*-3,3′-Biindoles

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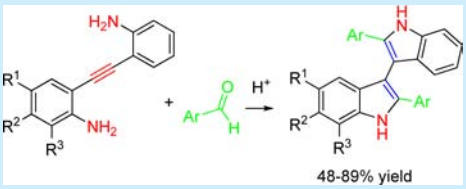
Supporting Information

**ABSTRACT:** An unusual Brønsted acid catalyzed cascade reaction of 2-[(2-aminophenyl)ethynyl]phenylamine derivatives with aryl(heteroaryl)aldehydes to afford an efficient alternative entry into 2,2′-disubstituted-1*H*,1′*H*-3,3′-biindoles under metal-free conditions is reported.




The preparation of different products from the same starting materials by variation of the reaction parameters still represents a significant challenge in organic synthesis.[1]

Recently, we reported a new one-pot approach to construct 11*H*-indolo[3,2-*c*]quinoline scaffolds **2** through a gold-catalyzed reaction of 2-[(2-aminophenyl)ethynyl]phenylamine derivatives **1** with aldehydes.[2] Due to the peculiar abilities of gold(III) and gold(I) species as $\pi$-acids for carbophilic activation, the synthesis of indole derivatives from the already available 2-alkynylanilines offered many advantages.[3] Nevertheless, we decided to explore the behavior of the same starting materials under Brønsted acid catalysis. It has been shown that some reactions can be catalyzed by gold catalysts and protons.[4] Conversely, another reaction was shown to be catalyzed by protons only.[5] A valuable tool for the selective activation of an individual functional group in the cases of bi- or polyfunctional substrates is represented by the choice of a suitable catalyst for the desired transformation.[6]

Indeed, under Brønsted acid catalysis the reaction of 2-[(2-aminophenyl)ethynyl]phenylamine derivatives **1** with aldehydes can achieve the rapid construction of 2,2′-disubstituted-1*H*,1′*H*-3,3′-biindoles **3** in an easy and efficient manner through a different sequential pathway (Scheme 1).

The synthesis of 3,3′-biindole scaffolds is of great interest due to their presence in natural products with very promising biological activities[7] as well as in pharmaceuticals[8] and functional materials.[9] A variety of syntheses of 3,3′-biindoles have been developed.[10] In particular, palladium-catalyzed Suzuki−Miyaura cross-coupling of 3-indolyl halides with 3-indolyl boronates emerged as an efficient tool to build up 3,3′-biindolys.[11] Moreover, the sequential Masuda borylation/Suzuki coupling of *N*-protected 3-iodoindoles has successfully been applied to the synthesis of 3,3′-biindoles of special interest due their antifungal, antimicrobial and cytotoxic activities.[12] However, great efforts have been directed to avoid the prefunctionalization of indoles to their halides of boronic derivatives. Then, the development of alternative approaches to the synthesis of the target 3,3′-biindoles through sequential reactions avoiding costly and time-consuming functionalization processes, including purification of the intermediates or additional steps of protection/deprotection of functional groups, is still spurring many research activities. Gold-,[13]

**Scheme 1**

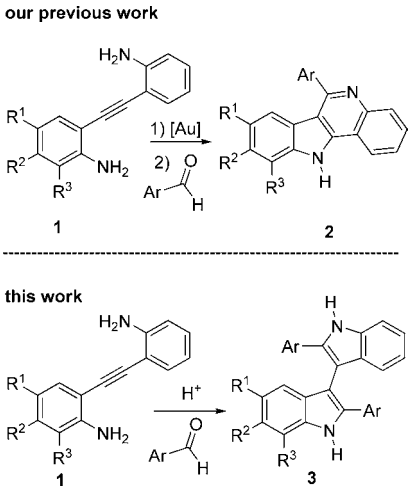



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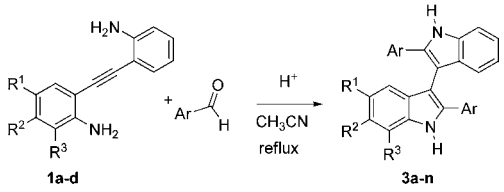
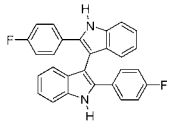
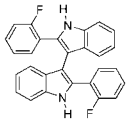
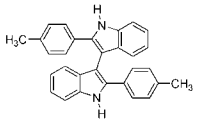
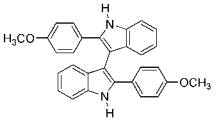
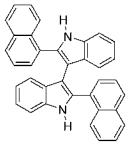
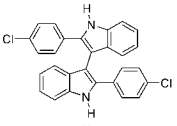
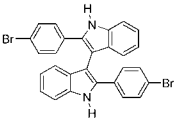
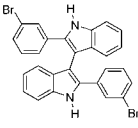
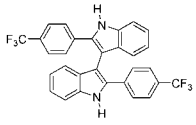
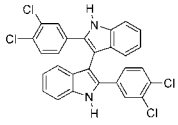
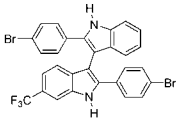
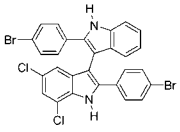
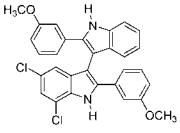
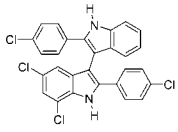
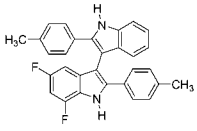
**Table 1. Substrate Scope**




**1a**: $R^1 = R^2 = R^3 = H$
**1b**: $R^1 = R^3 = H$, $R^2 = CF_3$
**1c**: $R^1 = R^3 = Cl$, $R_2 = H$
**1d**: $R^1 = R^3 = F$, $R_2 = H$

| entry | 1 | Ar | product | time (h) | yield (%)[a] |
|---|---|---|---|---|---|
| 1 | **1a** | 4-$FC_6H_4$ |  | **3a** | 1 | 80 |
| 2 | **1a** | 2-$FC_6H_4$ |  | **3b** | 2 | 48 |
| 3 | **1a** | 4-$MeC_6H_4$ |  | **3c** | 1.5 | 84 |
| 4 | **1a** | 4-$MeOC_6H_4$ |  | **3d** | 1 | 65 |
| 5 | **1a** | 1-naphthyl |  | **3e** | 2 | 51 |
| 6 | **1a** | 4-$ClC_6H_4$ |  | **3f** | 1 | 78 |
| 7 | **1a** | 4-$BrC_6H_4$ |  | **3g** | 1 | 85 |
| 8 | **1a** | 3-$BrC_6H_4$ |  | **3h** | 2 | 80 |
| 9 | **1a** | 4-$CF_3C_6H_4$ |  | **3i** | 1 | 64 |
| 10 | **1a** | 3,4-$Cl_2$ $C_6H$ |  | **3j** | 2 | 70 |
| 11 | **1b** | 4-$BrC_6H_4$ |  | **3k** | 1 | 89 |
| 12 | **1c** | 4-$BrC_6H_4$ |  | **3l** | 2 | 66 |
| 13 | **1c** | $C_6H_5$ |  | **3m** | 3 | 60 |
| 14 | **1c** | 4-$ClC_6H_4$ |  | **3n** | 3 | 50 |
| 15 | **1d** | 4-$CH_3C_6H_4$ |  | **3o** | 2 | 55 |

Reaction conditions: 1 equiv of the starting alkyne **1** was reacted in $CH_3CN$ at reflux under the presence of 3 equiv of aldehyde and a catalytic amount of HCl (a drop of HCl ACS reagent, 37%).

iron-,[14] and palladium-catalyzed[15] oxidative homocouplings of indoles via direct C−H cleavage have been reported. Furthermore, 3,3′-biindolyl products can be isolated as main or side products in transition-metal-catalyzed cyclizative homodimerization of 2-alkynylaniline derivatives.[11,16]

We wish to report herein our preliminary results on a new alternative approach to the synthesis of valuable 3,3′-biindoles **3** through a metal-free cascade process. This new protocol makes use of the already available 2-[(2-aminophenyl)ethynyl]-phenylamine derivatives **1** and inexpensive aryl(heteroaryl)-aldehydes as starting materials in the presence of a catalytic amount of HCl.

The generality of this transformation was examined, and the results are summarized in Table 1.

A variety of aryl aldehydes bearing both electron-donating and electron-withdrawing substituents were successfully used to synthesize the desired 3,3′-biindolyls in moderate to good yields. Lower yields were observed with *ortho*-substituted aryl aldehydes (Table 1, compare entries 1 and 2). It is very likely that the increase of steric hindrance is detrimental to the formation of the 3,3′-biindoles. The reaction also proceeded well when the substituents were changed on the aryl rings of the starting 2-[(2-aminophenyl)ethynyl]phenylamine **1** to give the more challenging unsymmetrically substituted 3,3′-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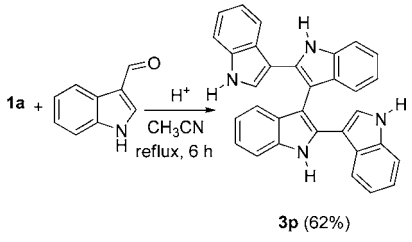
biindoles **3k**–**o** (Table 1, entries 11–15). Interestingly, the procedure was compatible with the presence of 1*H*-indole-3-carbaldehyde, which achieved the formation of the tetraindole derivative **3p** under the usual reaction conditions (Scheme 2).

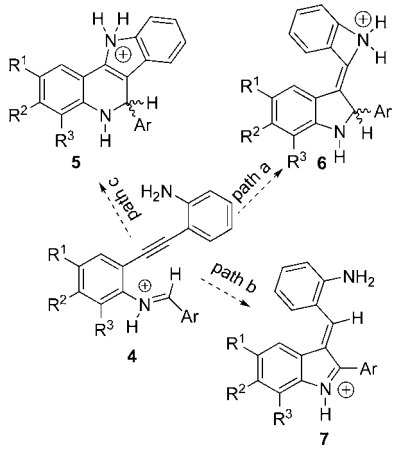
**Scheme 2**




Due to the synthetic difficulties, the synthesis of cyclic indole tetramers has been rarely reported.[17] The cyclic tetraindole skeleton is recognized as a $\pi$-extended variant of porphyrinogen and is an attractive scaffold for applications in the field of material science to afford electron-conducting and optoelectronic devices.

The detailed mechanism of this unprecedented cascade process is not completely clear at this stage. On the basis of previous studies, the intramolecular hydroamination of **1** to give the corresponding 2-substituted indole which in turn reacts with aldehydes leading sequentially to 11*H*-indolo[3,2-*c*]-quinoline scaffolds **2** results only as a consequence of the $\pi$-acid activation of the carbon–carbon triple bond. Conversely, it was envisaged that under Brønsted acid catalysis the reaction of **1** with aldehydes should lead selectively to the formation of the iminium ion **4** (Scheme 3).

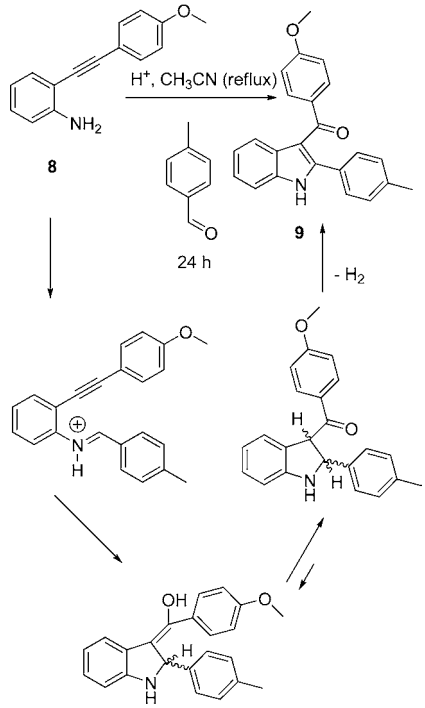
**Scheme 3**




Iminium ion–alkyne cylization-type reactions play a pivotal role for constructing nitrogen-containing cyclic compounds.[18] Both exocyclic and endocyclic nucleophile-promoted iminium ion–alkyne cyclization reactions have been reported.[19] In our cases, the formation of the 3,3′-biindoles under Brønsted acid catalysis conditions rules out the *endo*-mode cyclization of the in situ generated iminium ion to give the cation **5** (path c). The formation of this latter intermediate would lead after deprotonation/oxidative aromatization reactions to the formation of the 11*H*-indolo[3,2-*c*]quinoline scaffolds under alternative metal-free conditions. Therefore, regioselective 5-*exo*-*dig* cyclization of **4** could occur both via nucleophile-promoted iminium ion–alkyne generating the corresponding derivative **6**[20] (path a) or by means of an intramolecular ene reaction with inverse electron demand to give the intermediate **7** (path b).

Although benzazetine derivatives are poorly studied compounds,[21] their formation as unstable intermediates was postulated.[22] Intermolecular ene reactions with inverse electron demand of alkynes with iminium salts have also been reported.[23] A control experiment was conducted to gain more information on the reaction mechanism (Scheme 4).

**Scheme 4**




(4-Methoxyphenyl)-(2-*p*-tolyl-1*H*-indol-3-yl)methanone **9** was isolated in 30% yield after a prolonged time from the incomplete reaction of the 2-*p*-tolylethynylphenylamine **8** (the starting 2-alkynylaniline derivative **8** was recovered in 30% yield) with *p*-methoxybenzaldehyde.

The formation of compound **9** could result from the following sequential cascade process involving (a) condensation reaction of **8** with 4-methoxybenzaldehyde, (b) regioselective exocyclic water-promoted iminium ion–alkyne cyclization, (c) tautomerization, and (d) aromatization. Interestingly, the optimization of this unusual water-promoted iminium ion–alkyne cyclization of 2-alkynylaniline derivatives promises to accomplish a more sustainable approach to 2-aryl-3-acylindoles.[24] The difference in the reaction outcome between alkynes **8** and **1** shows the key role of the tethered amino group. Disubstituted alkynes have been reported to undergo annulation reaction with in situ generated iminium ions only with the assistance of nucleophiles which intimately participate in the transition state of these cyclization reactions.[16] Then, even if the intramolecular ene reaction with inverse electron demand cannot be excluded, the smooth formation of the 3,3′-biindole scaffolds could be supported by the free $NH_2$ action as an intramolecular nucleophilic promoter in the iminium ion–alkyne cyclization. A more in-depth investigation is needed to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fully understand the complex mechanism involving the formation of the 2,2′-disubstituted-1*H*,1′*H*-3,3′-biindoles **3**.

In summary, a new approach to the construction of a 3,3′-biindolyl backbone via Brønsted acid catalysis has been developed. In this operationally simple procedure, four chemical bonds are formed leading to the formation of two indole rings through unprecedented sequential condensation/annulation reactions of the readily available 2-[(2-aminophenyl)ethynyl]phenylamine derivatives **1** and inexpensive aryl(heteroaryl)aldehydes. Further applications of this method as well as studies to elucidate more mechanistic details are currently underway in our laboratories.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and characterization data of new products **3b,e,j−p** and **9**. Copies of $^{1}$H and $^{13}$C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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