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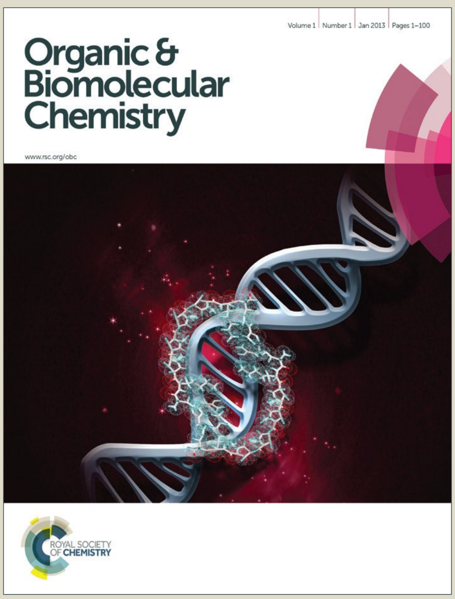

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One-pot relay catalysis: Divergent synthesis of furo[3,4-*b*]indoles and cyclopenta[*b*]indoles from 3-(2-aminophenyl)-1,4-enynols†

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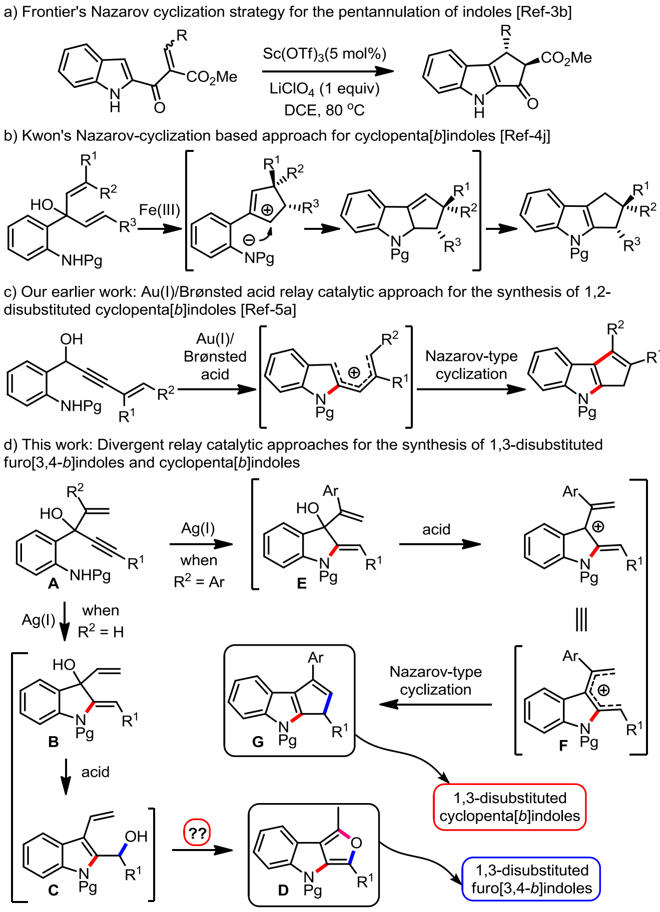
Described herein an efficient divergent strategy for the synthesis of furo[3,4-*b*]indoles via a sequential Ag(I)/Bi(III)/Pd(II) catalysis and cyclopenta[*b*]indoles via a one-pot Ag(I)/Brønsted acid relay catalysis from 3-(2-aminophenyl)-4-pentenyn-3-ols, accessible in three simple steps from 2-aminobenzaldehydes.

Indoles and indolines are considered privileged scaffolds from drug discovery standpoint.[1] Among several indole derivatives, cyclopentannulated indoles have attracted great attention from synthetic chemists owing to their occurrence in several natural products and pharmaceutically interesting compounds.[2] Consequently, several synthetic strategies were developed for cyclopenta[*b*]annulated indoles.[3] Among them, Nazarov reaction-based approaches are popular (see for example, Schemes 1a and 1b). An organized generation of a 4π-electron system is the key to accomplishing the Nazarov cyclization effectively.[4] In this context, we have recently reported a one-pot relay gold(I)/Brønsted acid relay catalytic methodology toward the synthesis of a variety of 1,2-disubstituted cyclopenta[*b*]indoles, Scheme 1c.[5a]

Relay catalysis has emerged as a powerful synthetic tool to assemble complex molecular architectures in a short and efficient manner.[6] Multi-catalyst-promoted processes can be atom-economic and thus can minimize the difficulties involved in isolation and purification of the intermediates. But the development of such processes is not always straightforward. Compatibility issues between the catalytic systems and control over the selectivity aspects complicate the advancement of such methods. Among the several existing categories, novel relay processes facilitated by two distinct metal catalysts or metal/organocatalyst binary systems have been well-explored.[7] However, to the best of our knowledge, reactions promoted by *three orthogonal metal relay* catalytic systems are not reported thus far.[8] Herein, we report our efforts towards developing a new synthetic approach for furo[3,4-*b*]indoles via Ag(I)/Bi(III)/Pd(II)-promoted relay catalytic system that integrates an intramolecular hydroamination, 1,3-allylic alcohol isomerization (1,3-AAI),[8d] and an unprecedented isofuran annulation of δ,ε-unsaturated alcohols, Scheme 1d. In addition, we also report a Ag(I)/Brønsted acid relay system that facilitates the synthesis of cyclopenta[*b*]indoles via intramolecular hydroamination and Nazarov-type cyclization cascade, Scheme 1d.



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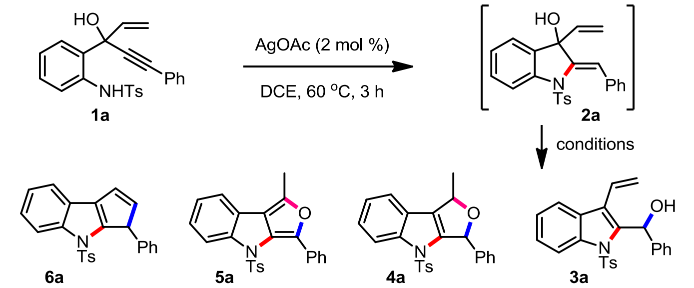
Scheme 1 Divergent approach for the synthesis of furo[3,4-*b*]indoles and cyclopenta[*b*]indoles.

Table 1 Optimization of the reaction parameters[a]



Entry	Conditions	Yield (%)[b]
1	$Bi(OTf)_3$ (10 mol%), DCE, 2 h, 0 °C-RT	**3a** (85)
2	$La(OTf)_3$ (10 mol%), DCE, 24 h, 0 °C-RT	**3a** (68)
3	$Yb(OTf)_3$ (10 mol%), DCE, 24 h, 0 °C-RT	**3a** (64)
4	PTSA (10 mol%), DCE, 12 h, 0 °C	**4a** (40)
5[c]	CSA (10 mol%), DCE, 48 h, 0 °C	**4a** (35)
6	TfOH (10 mol%), DCE, 4 h, 0 °C	**4a (–)**
7	PTSA (10 mol%), DCM, 13 h, RT	**4a** (35)
8	PTSA (10 mol%), toluene, 15 h, RT	**4a** (12)
9	PTSA (10 mol%), $MeNO_2$, 48 h, RT	**4a** (–)
10	PTSA (10 mol%), DCE, 3 h, 60 °C	**4a** (35)
11	PTSA (10 mol%), DCE, 72 h, –20 °C	**4a** (–)
12[d]	**PTSA (10 mol%), DCE, 11 h, RT**	**4a (45)**
13	i) $Bi(OTf)_3$ (5 mol%), DCE, 3 h, RT; ii) $Pd(OAc)_2$ (10 mol%), DCE, 20 h, RT	**5a** (45)
14	i) $Bi(OTf)_3$ (5 mol%), DCE, 3 h, RT; ii) $Pd(OAc)_2$ (10 mol%), DCE, 30 h, 0 °C	**5a** (43)
15[e]	**i) $Bi(OTf)_3$ (5 mol%), DCE, 3 h, RT; ii) $Pd(OAc)_2$ (10 mol%), DCE, 10 h, 60 °C**	**5a (50)**
16	i) $Bi(OTf)_3$ (5 mol%), DCE, 3 h, RT; ii) $PdCl_2$ (10 mol%), DCE, 10 h, 60 °C	**5a** (–)
17	i) $Bi(OTf)_3$ (5 mol%), DCE, 3 h, RT; ii) $Pd(dppf)Cl_2$ (10 mol%), DCE, 10 h, 60 °C	**5a** (–)
18	i) $Bi(OTf)_3$ (5 mol%), DCE, 3 h, RT; ii) CuI (10 mol%), DCE, 4 h, RT	**5a** (–)
19	i) $Bi(OTf)_3$ (5 mol%), DCE, 3 h, RT; ii) $AgNO_3$ (10 mol%), DCE, 4 h, RT	**5a** (–)

[a] Reaction conditions: See Supporting Information. [b] Isolated yields after column chromatography. [c] Reaction did not go to completion. [d] Yield based on starting material recovery. [e] Reaction performed with the isolated sample of **3a**.

It was envisioned that the designer substrates **A** could generate **B** by undergoing a Ag(I)-catalyzed 5-*exo-dig* cyclization. Subsequent acid promoted 1,3-allylic alcohol isomerization (1,3-AAI) and intramolecular etherification through a 5-*exo-trig* cyclization of **C**, especially under oxidative conditions, could afford the furo[3,4-*b*]indoles **D**, Scheme 1d.

On the other hand, the 5-*exo-dig* product **E** under acidic conditions could generate a 4π-electron system **F**, which by undergoing a Nazarov-type cyclization could provide access to cyclopenta[*b*]indoles **G**, Scheme 1d.

With this background and in continuation of our efforts towards the construction of cyclopentannulated arenes and heteroarenes,[5a,9] we started evaluating the generality of the hypothesis presented in Scheme 1d. Accordingly, we have initiated screening of various reagents and solvent combinations with **1a** as the model substrate, with the intention to obtain the pentannulated indole **6a**, Table 1.[10]

To begin with, the Au(I)-catalyzed intramolecular hydroamination conditions reported earlier by our group were tried for **2a**.[5a] However, no desired product was observed. Among few other variations attempted, to our delight, AgOAc successfully delivered the *5-exo-dig* product **2a** in excellent chemo- and regioselectivity.[11] Stage is now set for identifying suitable conditions to secure the formation of **6a**.

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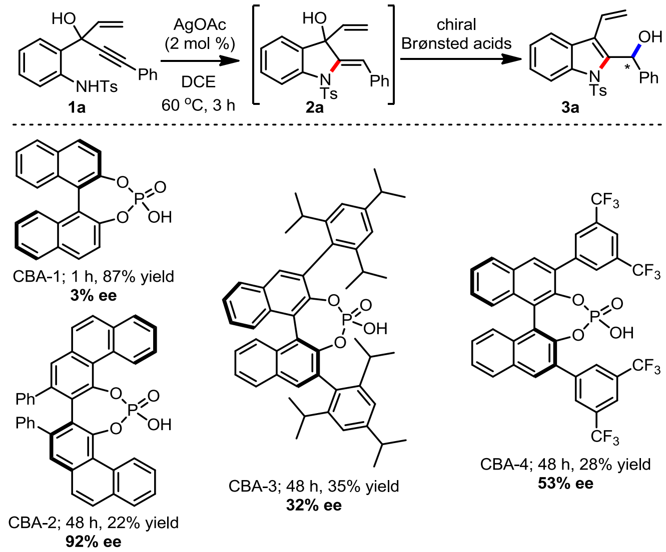
The reaction of **2a** catalysed by Lewis acids such as the triflates of Bi, La, and Yb generated only the indolyl alcohol **3a** in good yields (Table 1, entries 1-3). Subsequent evaluation of Lewis acids such as TMSOTf, BF_3OEt_2, and $FeCl_3$ gave only a complex mixture. Interestingly, under the influence of *p*-toluenesulfonic acid (PTSA) and camphorsulfonic acid (CSA), formation of the dihydrofuro[3,4-*b*]indole **4a** was observed, which presumably formed via the 5-*exo-trig* cyclization of **3a** (Table 1, entries 4 and 5). Despite realizing **4a** in moderate yields, we were pleased to establish a new one-pot approach for the synthesis of 1,3-disubstituted 3,4-dihydro-1*H*-furo[3,4-*b*]indoles.[12] Several subsequent efforts directed to improve the yield of **4a** were met with no considerable success (Table 1, entries 6-11), except that a marginal yield increment in case when the PTSA reaction was performed with the purified sample of **3a** (Table 1, entry 12).

As part of the attempts to improve the efficiency of the formation of **4a** from **2a**, we made yet another significant observation. The reaction of **3a**, obtained via $Bi(OTf)_3$ promoted reaction of **2a**, in the presence of a catalytic amount of $Pd(OAc)_2$ delivered the furo[3,4-*b*]indole **5a** in 45% yield (Table 1, entry 13). Furo[3,4-*b*]indoles serve as indole-2,3-quinodimethane synthetic analogue in diverse inter- and intramolecular Diels-Alder reactions. These intermediates have been applied for the synthesis of novel classes of heterocycles such as benzocarbazoles, pyridocarbazoles, including the antitumor alkaloid ellipticine.[13]



Scheme 2 Brief screening of chiral Brønsted acids for the enantioselective synthesis of **3a**.

Among few other variations undertaken to increase the efficiency of the reaction, only the reaction of **3a** at an elevated temperature provided **5a** with a slight increase in the yield (Table 1, entry 15). Employing a few other Pd(II), Cu(II) or

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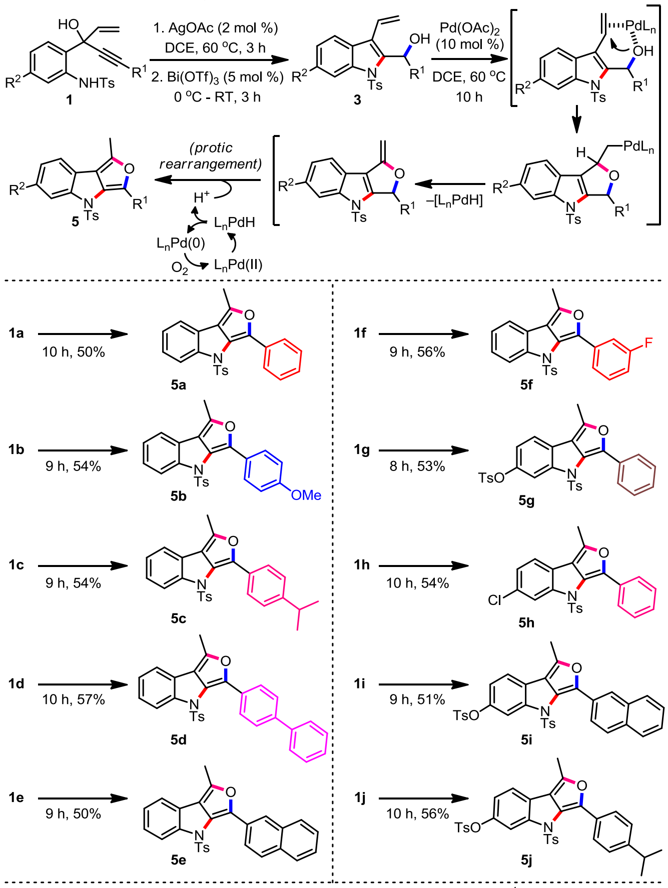
Ag(I) salts proved to be unsuccessful (Table 1, entries 16-19). Low yields of **4a** or **5a**, in general, are attributed to their inherent instability, which is well-documented in the literature.[13]

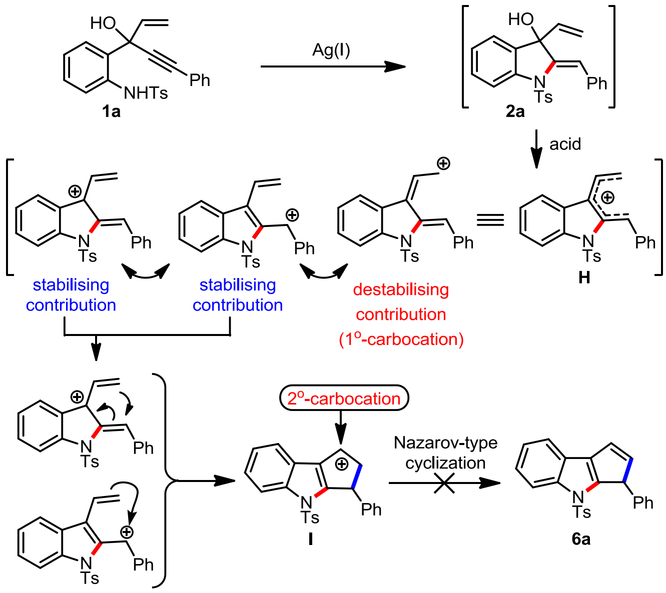
A brief screening of chiral Brønsted acids was undertaken for the one-pot enantioselective synthesis of **3a**, Scheme 2.[14] Towards this, chiral phosphoric acids CBA-1 to CBA-4 were evaluated for the transformation of **2a** to **3a**. With the (*R*)-VAPOL hydrogen phosphate CBA-2, **3a** was realized in 92% ee, however, the reaction was found to be stalling after a certain extent of conversion. On the other hand, **3a** was obtained in 87% yield with (*R*)-BINOL phosphoric acid, but almost as a racemic mixture. Several of our attempts to achieve a better result were futile. Nevertheless, a new one-pot relay Ag(I)/chiral Brønsted acid system was established for the enantioselective synthesis of **3a.**

Table 2 Substrate scope for furo[3,4-*b*]indoles[a,b]



[a] Reaction conditions: See Supporting Information. [b] Isolated yields after column chromatography.

With the optimised conditions for furo[3,4-*b*]indoles in hand, we proceeded to evaluate the substrate scope, Table 2.[15] Evidently, a wide range of structurally and electronically diverse substituents across the alkyne (R^1) and the aryl ring (R^2) were well-tolerated and generated the furoindoles **5a-5j** in moderate to good yields. A narrow yield range (50-56%) indicates the robustness of the method which in turn highlights the least dependence of the relay catalytic system on the electron-donating/withdrawing contributions of the substituents. Interestingly, the furoindoles **5** were isolated in poor yields when the reaction was carried out in a one-pot trimetallic relay mode [Ag(I)/Bi(III)/Pd(II)], better yields were observed by performing the reaction initially under a one-pot bimetallic Ag(I)/Bi(III) system followed by subjecting the purified indolyl alcohols **3** to Pd(II) catalysis. Nevertheless, this method can serve as a potential alternative to the existing approaches describing the synthesis of the interesting and short-lived furo[3,4-*b*]indoles.



Scheme 3 Plausible explanation for the non-formation of **6a** from **1a**.

After successfully establishing a new method for the synthesis of furo[3,4-*b*]indoles, we turned our attention to rationalise the non-formation of **6a** from **1a**. A mechanistic hypothesis for this observation is proposed in Scheme 3. The indoline **2a** under the influence of an acid generates the 4π-electron system **H**, which during the process of undergoing a Nazarov-type cyclization builds up the potentially destabilising 2°-carbocationic intermediate **I**. So, an additional substitution at this position creates a more stabilized 3°-carbocationic intermediate that can pave the way for the formation of the desired Nazarov cyclised product. Based on this hypothesis, we have prepared the enynol **1’k** which now possesses a phenyl group at the vinylic position.[15] The phenyl group at this position can also play a pivotal role in shifting the system from s-trans to s-cis in the pentadienyl cation intermediate **H**.

Among few Lewis and Brønsted acids evaluated for the conversion of indoline **2’k** to the Nazarov product **6k**, PTSA, CSA and TfOH were found to be optimum. So, the initial reactions were performed with all the three Brønsted acids to assess their consistency. It can be realised from Table 3 that the pentannulated indoles **6k**, **6l** and **6m** formed consistently in excellent yields under the CSA catalysis. So, CSA was chosen as the catalyst of choice for further deliberations. Subsequent evaluation of the substrate scope under the optimised conditions furnished a variety of 1,3-disubstituted cyclopenta[*b*]indoles **6n-6r** in very good yields.[16] This methodology thus can provide an efficient and robust synthetic access to several bioactive natural products and medicinally important compounds possessing cyclopenta[*b*]indole scaffold.

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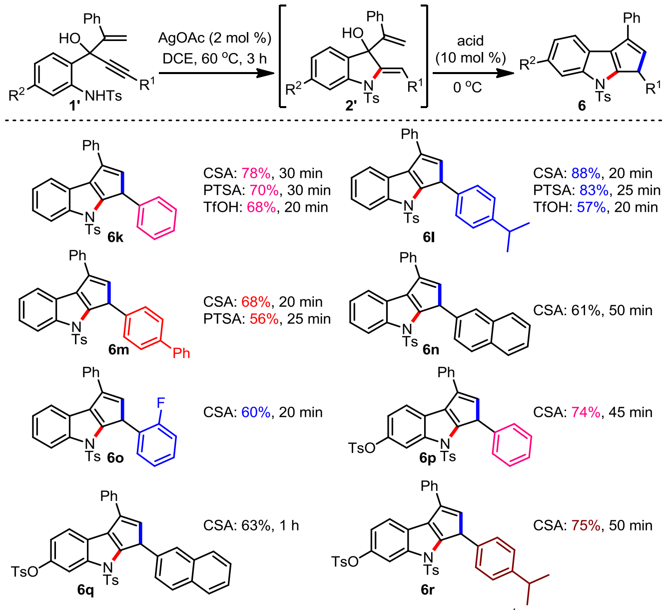
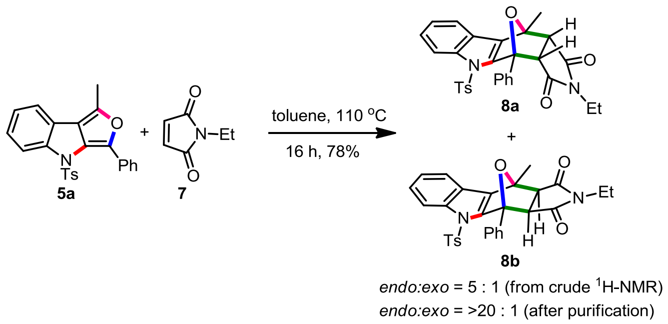
Table 3 Substrate scope for cyclopenta[*b*]indoles[a,b]



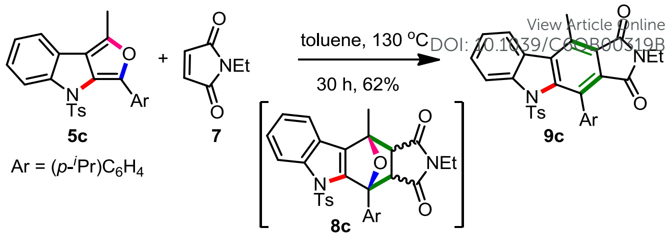
[a] Reaction conditions: See Supporting Information. [b] Isolated yields after column chromatography.

Having established new one-pot relay catalytic approaches for the furo[3,4-*b*]indoles and cyclopenta[*b*]indoles, we planned an elaboration with the former class. Earlier, Gribble and co-workers demonstrated that furo[3,4-*b*]indoles behave very well as dienes in the Diels-Alder reaction, and this strategy was widely employed in the construction of several complex molecular architectures.[13a,b,e,f] Towards this, the furoindole **5a** and N-ethylmaleimide **7** were refluxed in toluene to produce a mixture of *endo*/*exo* Diels-Alder adducts (**8a** and **8b**) in 78% yield, Scheme 4. The isomeric structures were assigned from the ^{1}H and ^{13}C-NMR data and further verified from the reported data of similar structures.[13b] This result indirectly confirms the structure of **5a** and other analogues as well.



Scheme 4 Diels-Alder reaction of the furoindole **5a** and maleimide **7**.

Interestingly, the reaction of furoindole **5c** with N-ethylmaleimide **7** under toluene reflux conditions furnished, via the [4+2] adduct **8c**, the carbazole **9c** in good yield, Scheme 5.[13] Carbazoles are considered privileged structures from medicinal chemistry standpoint. Carbazole scaffold is present in several bioactive natural products, various pharmaceuticals and functional materials.[17] This method therefore can provide an access to highly functionalized carbazoles as well.



Scheme 5 Formation of the carbazole **9c** via the Diels-Alder reaction of the furoindole **5c** and maleimide **7**.

Conclusions

In summary, we have presented for the first time, a divergent one-pot relay catalytic approach for the synthesis of 1,3-disubstituted furo[3,4-*b*]indoles and cyclopenta[*b*]indoles starting from easily accessible 3-(2-aminophenyl)-4-pentenyn-3-ols. Interesting substitution dependence on the product distribution was realised. Based on the mechanistic considerations, this phenomenon was efficiently crafted to yield the product of choice. The methodologies described herein have demonstrated great potential and will stimulate further research in the synthesis of new heterocycles. We are currently involved in extending these strategies towards the total synthesis of complex indole-based natural products and the results will be communicated in due course.

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