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Fused-Ring Systems

Diversity Oriented Synthesis of Indoloazepinobenzimidazole and Benzimidazotriazolobenzodiazepine from N^1-Alkyne-1,2-diamines

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In memory of Richard Heck

Abstract: A one-pot protocol for the diversity oriented synthesis of two *N*-polyheterocycles indoloazepinobenzimidazole and benzimidazotriazolobenzodiazepine from a common N^1-alkyne-1,2-diamine building block is described. The approach involves sequential formation of benzimidazole through cyclocondensation and oxidation, which is followed by the formation of either an azepine ring (through alkyne activation and 6-*endo-dig* cyclization, 1,2-migration with ring expansion, and re-aromatization), or diazepine and triazole rings through 1,3-dipolar cycloaddition.

Introduction

The design of one-pot strategies involving domino reactions[1] for rapid access to *N*-polyheterocycles with architectural and molecular complexity remains a challenging task. The ubiquitous presence of *N*-polyheterocycles in the vast majority of drugs and natural products has led to their application as chemical probes for drug discovery.[2] Among the range of one-pot strategies reported for their synthesis, the use of alkyne-based reactants as versatile building blocks that combine both a nucleophile and an electrophile has been reported.[3] In general, these alkyne-based building blocks are condensed with another readily available mono/bifunctional reactant, thereby initiating the formation of multiple bonds through a series of intramolecular ring closures to afford a diverse range of annulated structures. Examples of alkyne-based reactants used extensively by us and others include: 2-alkynyl benzaldehyde,[4] 2-alkynyl indole,[5] and alkynones/propargyl alcohols.[6] All of these compounds contain both nucleophilic and electrophilic centers, thereby facilitating the formation of multiple bonds without isolation of intermediates in an atom-economic mode.

In a continuation of this work, we then studied the ability of N^1-alkyne-1,2-diamine **1** to act as a new alkyne-based substrate with multiple-bond-forming sites by allowing its condensation with appropriate mono- or bifunctional reactants in a one-pot format. We envisaged that condensing **1** with either 3-formyl indole derivatives **2** or with *o*-azidobenzaldehyde derivatives **8** may facilitate annulations through sequential generation of rings (five-, six-, and seven-membered) to afford structurally diverse annulated *N*-polyheterocycles. The diamine would react with the aldehyde to form a tethered benzimidazole[7] with a pendant internal alkyne that can then undergo either intramolecular carbocyclization at the C-2/C-3 of the indole or 1,3-dipolar cycloaddition with the *ortho* azide to afford annulated *N*-polyheterocylic derivatives. Herein, we report catalyst-driven diversity oriented synthesis of two annulated *N*-polyheterocycles from N^1-alkyne-1,2-diamine as a common building block in a one-pot format.

Results and Discussion

Our studies commenced with the synthesis of N^1-alkyne-1,2-phenyl diamine **1a**, which was carried out by treating *o*-phenylenediamine with (3-bromo-1-propynyl)benzene in K_2CO_3/acetone for 24 h and resulted in the formation of N^1-(3-phenylprop-2-yn-1-yl)benzene-1,2-diamine (**1a**) in satisfactory yield (not optimized). We then treated **1a** with 3-formyl indole (**2a**) in toluene at 110 °C in the presence of $AuPPh_3Cl$ and AgOTf (10 mol%, each), which led to the formation of acyclic intermediate **3aa** in 82% isolated yield (Table 1, entry 1) without formation of the annulated product.

This prompted us to employ different gold catalysts that would facilitate the cyclization of the internal alkyne and the indole through intramolecular hydroarylation of **3aa**. Gold complexes along with silver salts and iodine have been well documented to interact with the π-system of double/triple bonds, thereby leading to their activation towards nucleophilic attack.[8] Accordingly, we carried out the reaction employing $AuPPh_3Cl$ and $AgSbF_6$ (10 mol%, each) in toluene at 110 °C for 36 h, which resulted in the formation of annulated product **4aa** in 48% isolated yield along with **3aa** in 22% isolated yield (Table 1, entry 2). Interestingly, formation of only a seven-

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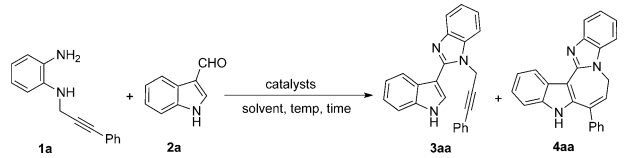
Table 1. Optimization of the synthesis of dihydroindoloazepinobenzimidazole **4aa**.[a]



Entry	Catalyst (mol%)	Solvent	T [°C]/t [h]	Yield [%][b] 3aa	4aa
1	$AgOTf/AuPPh_3Cl$ (10)	toluene	110/12	82	–
2	$AgSbF_6/AuPPh_3Cl$ (10)	toluene	110/36	22	48
3	$AgSbF_6/AuPPh_3Cl$ (10)	DMF	110/36	66	15
4	$AgSbF_6/AuPPh_3Cl$ (10)	THF	110/36	22	trace
5	$AgSbF_6/AuPPh_3Cl$ (10)	xylene	110/36	15	62
6	$AgSbF_6/AuPPh_3Cl$ (10)	xylene	130/36	13	59
7	$AgSbF_6/AuPPh_3Cl$ (15)	xylene	130/24	–	78
8	$AgSbF_6/AuPPh_3Cl$ (15)	DCE	130/36	43	8
9	$AgSbF_6/AuPPh_3Cl$ (15)	1,4 dioxane	130/24	ca. 10	trace
10	$AgSbF_6/AuPPh_3Cl$ (15)	DMA	130/24	n.r.	
11	$AgNO_3/AuPPh_3Cl$ (15)	xylene	130/24	n.r.	
12	$Ag_2CO_3/AuPPh_3Cl$ (15)	xylene	130/24	n.r.	
13	$AgNTf_2$/ $AuPPh_3Cl$ (15)	xylene	130/24	trace	–
14[c]	$AgSbF_6$ (15)	xylene	130/24	35	–
15[d]	$AuPPh_3Cl$ (15)	xylene	130/24	58	trace
16	$AuCl_3$ (15)	xylene	130/24	n.r.	
17	$AuPPh_3NTf_2$ (15)	xylene	130/24	n.r.	
18[e]	I_2 (100)	xylene	130/24	n.r.	

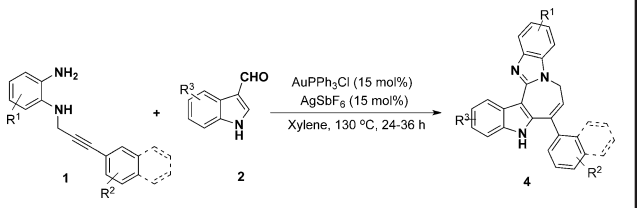
[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), solvent (5 mL) under N_2. [b] Isolated yield. n.r. = no reaction. [c] Without $AuPPh_3Cl$. [d] Without $AgSbF_6$. [e] Molecular iodine used as a catalyst.

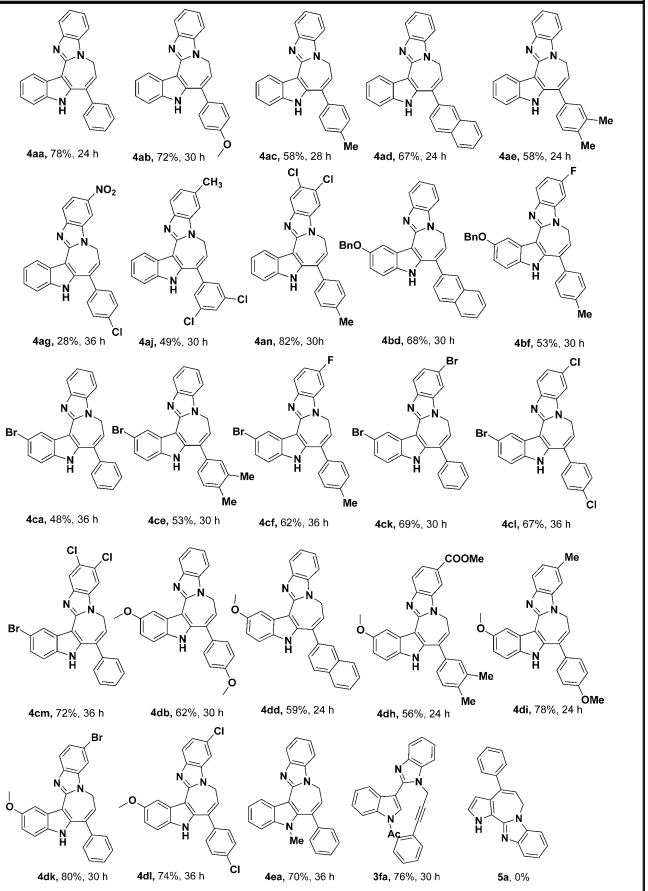
membered ring annulated to the indole and benzamidazole was observed; the formation of other regioisomers through 6-*exo-dig* cyclization was not observed.

In an attempt to improve the yield of **4aa** through complete conversion of **3aa**, we screened several solvents; however, no significant gain in the yield was achieved (Table 1, entries 3–5). Raising the temperature in xylene to 130 °C also had minimal effect on the yield of **4aa** (entry 6). Finally, an increase in the catalyst loading from 10 to 15 mol% led to complete conversion and afforded **4aa** in 78% isolated yield as the only product (entry 7). Replacing xylene with other solvents such as 1,2-dichloroethane (DCE), dioxane, or dimethylacetamide (DMA) with 15 mol% catalyst loading had little effect (entries 8–10), whereas employing other silver salts such as $AgNO_3$, Ag_2CO_3, or $AgNTf_2$ either failed to promote the reaction or produced **3aa** in trace amounts (entries 11–13). Carrying out reaction in the presence of only silver or gold salts afforded **3aa** as the major product with either no or trace amounts of **4aa** (entries 14–17). In an attempt to replace the Au/Ag complex, introduction of iodine failed to promote the reaction (entry 18). Thus, use of 15 mol% each of $AuPPh_3Cl$ and $AgSbF_6$ in xylene at 130 °C was found to be the optimal conditions for the one-pot synthesis of indoloazepinobenzimidazole **4aa**. Although gold complexes may decompose at higher temperature, a precedence exists for the employment of gold complexes at elevated temperatures.[9]

With the optimized reaction conditions in hand, we then examined the scope and limitations of the methodology. We synthesized 22 compounds based on **4** by introducing diversity in both reactants, and the products were obtained in moderate to good yields (Table 2). Substituting R^1 with electron-withdrawing groups such as nitro and fluoro, produced **4ag** and **4bf**, respectively, in reduced yields. In contrast, the presence of an electron-donating methyl substituent as R^1 led to an improvement in the isolated yield of **4di**. Notably, 4-substituted (R^1) diamines **1** produced the corresponding compound **4** as single regioisomers (**4ag**, **4aj**, **4bf**, **4cf**–**cl**, and **4dh**–**dl**). Bulkier R^1 substituents such as Br (**1k**) and Cl (**1l**) enhanced the yield and afforded **4ck**, **4cl**, **4dk**, and **4dl** in 69, 67, 80, and 74% isolated yields, respectively. Replacing R^2 in the aromatic ring of the alkyne component with either electron-donating or electron-withdrawing groups did not have a significant effect on the yield of the corresponding product **4**.

Table 2. Substrate scope of the reaction for the synthesis of indolobanzamidazoazapine derivatives **4**.[a]





[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $AuPPh_3Cl$ (15 mol%), $AgSbF_6$ (15 mol%), xylene (5 mL), 130 °C, 24–36 h, under N_2.

Replacing the aromatic ring on the alkyne with a napthalene resulted in the formation of **4ad**, **4bd**, and **4dd**, albeit in diminished yields. However, the use of indole with no substituent ($R^3 = H$) led to a smooth transformation without compromising the yield of **4**. Substituting R^3 with benzyloxy and Br afforded **4** in marginally reduced yield. However, replacing R^3 with a methoxy group in the aromatic ring of **2** led to an enhanced isolated yield of **4**. Replacement of *N*-H indole in substrate **2** with N-substituted indoles such as *N*-Me led to the corresponding annulated product **4ea** in 70% yield; however, the use of *N*-Ac or *N*-Ts indoles either led to acyclic product **3fa** or failed to initiate the reaction (Table 2).

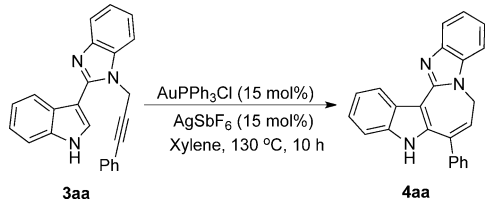
To understand the reaction mechanism, we carried out a control experiment in which intermediate **3aa** was allowed to cyclize under the standard conditions. As expected, the cyclized product **4aa** was obtained in 80% isolated yield (Scheme 1).

Based on the above experimental observation and on previous reports,[10] we propose a plausible mechanism shown in Figure 1. Initially, oxidative cyclocondensation between diamine **1a** and 3-formyl indole **2a** affords indolobenzimidazole (**3aa**) containing a pendent internal alkyne. The alkyne in **3aa** then undergoes activation following π-complexation with the aid of a cationic gold species that is formed in situ from $AuPPh_3Cl/AgSbF_6$ to afford intermediate **I**. The latter undergoes intramolecular nucleophilic attack at C-3 of the indole to afford the spirocyclic[10a–f] intermediate **II** through 6-*endo-dig* cyclization. This is then followed by 1,2-migration along with ring expansion to give intermediate **III**, which, after deprotonation, produces intermediate **IV**. In the last step, intermediate **IV** undergoes protodeauration and releases the final product **4aa** along with regeneration of the active gold catalyst.

Attempts to replace 3-formyl indole with pyrrole-2-carboxaldehyde failed to furnish the corresponding annulated product **5a** (Table 2); instead, the intermediate corresponding to **3** was isolated as the only product.

To further expand the utility of substrate **1**, we then treated it with *o*-azidobenzaldehyde (**8a**) in a one-pot format. Our investigation commenced by treating N^1-alkyne-1,2-diamine **1a** with **8a** in the presence of 10 mol% $AuPPh_3Cl$ and $AgSbF_6$, which failed to give the desired product (Table 3, entry 1). We then turned our attention towards the use of iodine as a catalyst. Gratifyingly the use of 10 mol% I_2 in MeOH at 50 °C afforded the desired product **9aa** in 86% isolated yield in 2.0 h (entry 2). Various solvents and loading of iodine were screened (entries 3–20) and best conditions were found to involve 10 mol% iodine in MeOH at 50 °C for 2 h. With the optimized conditions in hand, we next turned our attention to the scope and limitations of the reaction.

Accordingly, five compounds (**9aa**–**pc**) based on **9** were synthesized with high isolated yields (Table 4). Next, with a view to establishing the generality of our methodology, N^1-(prop-2-yn-1-yl)benzene-1,2-diamine derivatives **10** were synthesized



Scheme 1. Transformation of **3aa** into **4aa** under standard conditions.

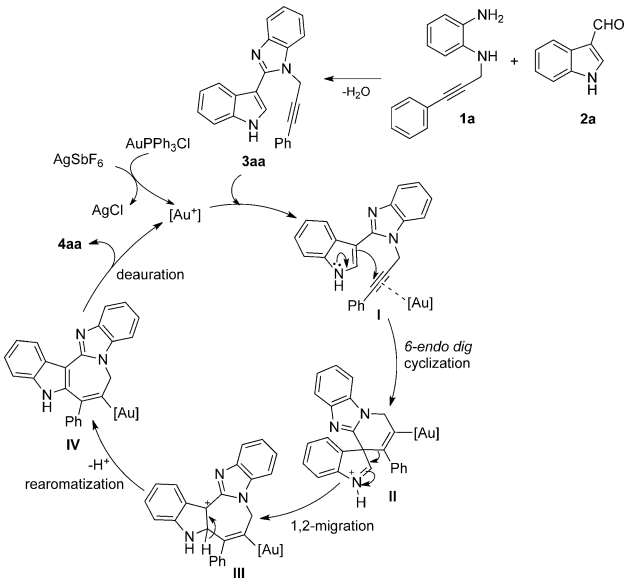
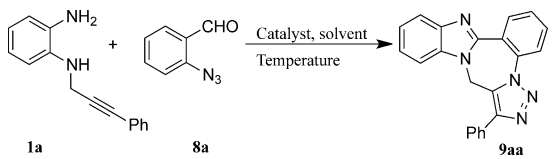


Figure 1. Plausible mechanism for the formation of **4aa**.

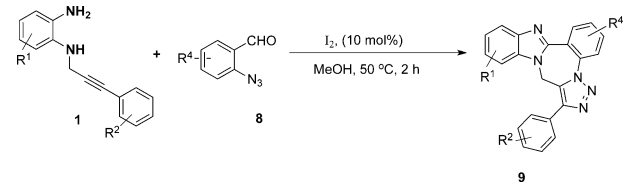
Table 3. Optimization for the synthesis of benzimidazolotriazolobenzodiazepine **9aa**.[a]

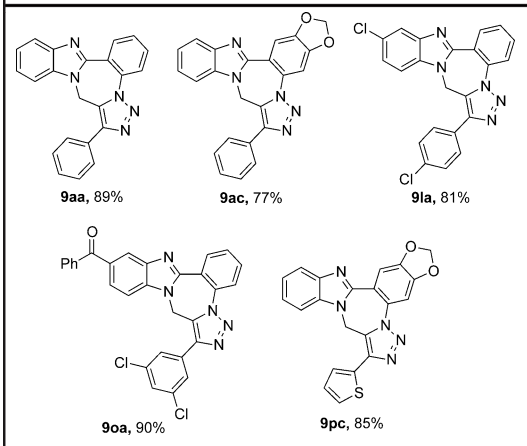


Entry	Catalyst (10 mol%)	Solvent	T [°C]/t [h]	Yield [%][b]
1[c]	$Au(PPh)_3Cl/AgSbF_6$	CH_2Cl_2	50/2.0	n.r.
2	**I_2**	**MeOH**	**50/2.0**	**86**
3	I_2	MeOH	50/1.5	68
4[d]	I_2	MeOH	50/2.0	79
5[e]	I_2	MeOH	40/2.0	47
6	I_2	EtOH	50/2.0	82
7	I_2	*t*BuOH	50/2.0	58
8	I_2	H_2O	50/2.0	trace
9	I_2	acetone	50/2.0	38
10	I_2	EtOAc	50/2.0	70
11	I_2	DMF	50/2.0	69
12	I_2	DMA	50/2.0	72
13	I_2	$CHCl_3$	50/2.0	47
14	I_2	CH_2Cl_2	50/2.0	29
15	I_2	THF	50/2.0	trace
16	I_2	DCE	50/2.0	55
17	I_2	MeCN	50/2.0	62
18	I_2	toluene	50/2.0	n.r.
19	I_2	dioxane	50/2.0	n.r.
20	I_2	DMSO	50/2.0	n.r.

[a] Reaction conditions: **1a** (0.5 mmol), **8a** (0.5 mmol), I_2 (10 mol%), solvent (5 mL). [b] Isolated yield. n.r. = no reaction. [c] 10 mol% of each Au/Ag salts was used. [d] 50 mol% of I_2 was used. [e] Reaction performed at 40 °C.

Table 4. Substrate scope of the reaction with internal alkyne **1** for the synthesis of benzimidazolotriazolobenzodiazepine derivatives **9**.[a]





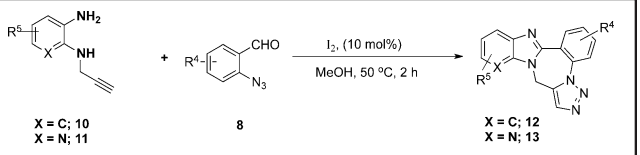
[a] Reaction conditions: **1** (0.5 mmol), **8** (0.5 mmol), I_2 (10 mol%), MeOH (5 mL), 50 °C, 2 h.

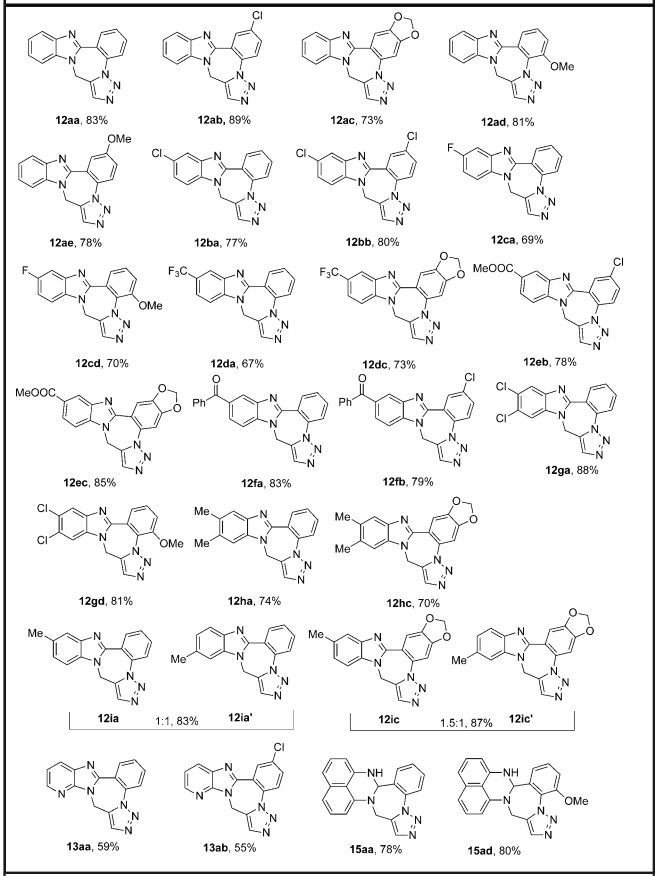
as a variant of substrate **1** containing a terminal alkyne group, and these were reacted with *o*-azidobenzaldehyde derivatives **8** under the optimized conditions. Gratifyingly, the desired benzimidazolotriazolobenzodiazepine derivatives **12** were isolated in moderate to good yields (Table 5).

Various functional groups were tolerated and substituents with either an electron-donating or an electron-withdrawing group afforded the corresponding product **12** with minimal variation in yields. Substrates with an electron-donating substituent gave better yields than those with electron-withdrawing substituents (Table 5). Monomethyl and dimethyl groups on **10** were subjected to the reaction conditions and afforded **12ha–ic** in 70–87% isolated yield. However, use of a substrate with a 4-methyl substituent gave regioisomers **12ia**/**12ia′** in 1:1 ratio and **12ic**/**12ic′** in 1.5:1 ratio (based on HPLC analysis). An electron-withdrawing group on **10** such as a 4-chloro, 4-fluoro, or a 4-trifluoromethyl group led to the corresponding product **12** in satisfactory isolated yields ranging from 67 to 80%. Replacing the arene ring in **10** with a pyridine ring (**11**) resulted in the formation of **13aa** and **13ab**, with reduced yield. The use of azido benzaldehyde **8** containing either electron-donating or electron-withdrawing groups gave similar yields of **12** and **13**.

After successfully demonstrating the efficacy of **1**, attempts were made to diversify the reaction further by replacing the internal alkyne with *N*[1]-(prop-2-yn-1-yl)naphthalene-1,8-diamine (**14a**). Its treatment with substituted **8** furnished **15aa** and **15ad** with good isolated yields (Table 5). Notably, in this case, aerial oxidation did not occur and the dihydro compounds were obtained.

Table 5. Substrate scope of the reaction with terminal alkyne **10**/**11** for the synthesis of benzimidazolotriazolobenzodiazepine derivatives **12**/**13**.[a]





[a] Reaction conditions: **10**/**11** (0.5 mmol), **8** (0.5 mmol), I_2 (10 mol%), MeOH (5 mL), 50 °C, 2 h.

A possible reaction mechanism is shown in Figure 2. Initially, activation of the carbonyl group with the aid of molecular iodine results in the formation of intermediate **A**, which, upon cyclocondensation with amine groups of **1** or **10**, forms **C**. The latter undergoes formal [3+2] cycloaddition to give the final product **9** or **12** after aerial oxidation.

Conclusions

We have demonstrated a one-pot cascade protocol for the synthesis of highly substituted dihydroindoloazepinobenzimidazole and benzimidazotriazolobenzodiazepine from a common building block under different catalytic systems. The strategy is expected to find applications in the synthesis of biologically important motifs and further studies to synthesize new molecules by utilizing this novel substrate are in progress.

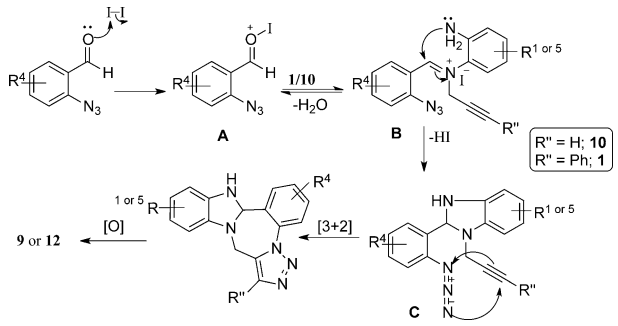


Figure 2. Plausible mechanism for the formation of **9** or **12**/**13**.

Experimental Section

General information and methods

All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with Bruker/Ascend 400 spectrometers, at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. HRMS were obtained with an Agilent 6520/QTOF-MS/MS by using the electrospray ionization (ESI) technique and a time-of-flight (TOF) analyzer. Column chromatography was performed by using silica gel (100–200 mesh) as the stationary phase. All reactions were monitored by thin-layer chromatography (TLC). The purity and characterization of these compounds were further established base on HRMS (ESI) analysis with an Agilent 6520/QTOF-MS/MS mass spectrometer. Melting points were measured with a BESTO capillary melting-point apparatus and are uncorrected. For further details, see the Supporting Information.

Synthesis

General procedure for the preparation of *N*^{1}-(3-phenylprop-2-ynyl)benzene-1,2-diamine (1) and *N*^{1}-(prop-2-ynyl)benzene-1,2-diamine (10): Starting materials **1a–p** and **10a–i**/**11a** and **14a** were prepared by treating the appropriate diamine (1.0 g, 1.0 equiv), K_2CO_3 (1.1 equiv), and substituted 3-bromo-1-phenylpropyne (1.0 equiv) or propargyl bromide (1.0 equiv) in case of **10**/**11** and **14** and stirring for 24 h at 50 °C. After completion of reaction, which was monitored by TLC, the solvent was evaporated in vacuo and the resulting mixture was diluted with water and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuo and the remaining residue was purified by column chromatography on silica gel (*n*-hexanes/EtOAc, 5:1) to give the product. Yields were not optimized.

General procedure for the synthesis of 3-formyl indole derivatives (2): All the starting materials (**2a–d**) were prepared according to reported procedures and their spectroscopic data match those of the previously reported compounds.[11a]

General procedure for the synthesis of 2-azido benzaldehydes derivatives (8): Synthesis of **8a–e** were carried out according to a reported procedure by treating substituted 2-nitrobenzaldehyde (1.0 equiv) with NaN_3 (1.5 equiv) in HMPA to give the desired products in satisfactory yields. Their spectroscopic data match those of the previously reported compounds.[11b]

General procedure for the synthesis of dihydroindolo[3′,2′:3,4]azepino[1,2-*a*]benzimidazole derivatives 4: The appropriate 3-formyl indole **2** (0.5 mmol) was added to xylene (5.0 mL) in an oven-dried round-bottomed flask equipped with a stir bar. Substituted *N*^{1}-(3-phenylprop-2-yn-1-yl)benzene-1,2-diamine 1 (1.0 equiv) was added and the flask was placed in an oil bath that was preheated at 130 °C. $AuPPh_3Cl$ (15 mol%) and $AgSbF_6$ (15 mol%) were then added and the reaction was stirred for the given time under a nitrogen environment. Upon completion of reaction (which was monitored by TLC), the resulting mixture was cooled to RT, diluted with water, and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuo and the remaining residue was purified by column chromatography on silica gel (*n*-hexanes/EtOAc, 5:1) to give the product.

General procedure for the synthesis of benzimidazotriazolobenzodiazepine derivatives 9: The appropriate *N*^{1}-(3-phenylprop-2-yn-1-yl)benzene-1,2-diamine (1.0 equiv) and 2-azidobenzaldehyde **8** (1.0 mmol) were added to MeOH (5.0 mL) in an oven-dried round-bottomed flask equipped with a stir bar. Molecular iodine (10 mol%) was added and the flask was transferred to an oil bath that was preheated at 50 °C. Upon completion of reaction (which was monitored by TLC), the resulting mixture was cooled to RT, diluted with water, and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuo and the remaining residue was purified by column chromatography on silica gel (*n*-hexanes/EtOAc) to give the product.

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