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Ag^{I}-Catalyzed Cascade Strategy: Regioselective Access to Diversely Substituted Fused Benzimidazo[2,1-*a*]isoquinolines, Naphthyridines, Thienopyridines, and Quinoxalines in Water

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An environmentally benign and operationally simple one-pot approach to the regioselective tandem synthesis of diversely substituted fused benzimidazo[2,1-*a*]isoquinolines, naphthyridines, thienopyridines, and quinoxalines from *o*-alkynylaldehydes and arylamines with tethered nucleophiles using Ag^{I} as catalyst in water is described. The reaction showed selective N–C bond formation on the more electrophilic alkynyl carbon, resulting in the regioselective *6-endo-dig* cyclized products in good to excellent yields. The proposed mechanistic pathway for the synthesis of fused heterocycles proceeding through formation of ring A prior to ring B, which formed through a second intramolecular attack of the nitrogen onto the alkynyl carbon, was supported by mechanistic experiments and X-ray crystallographic studies of isolated intermediate **U** and cyclized product **5a**. Comparative experiments showed the viability of intramolecular nucleophilic attack over intermolecular attack of an external nucleophile. This catalytic, green protocol has been efficiently applied for the bis-tandem cyclization in water.

Introduction

Immense and rapid advances in medicinal chemistry continue to underscore the need for practical and environmentally benign routes for the synthesis of small heterocyclic molecules because the majority of drugs and drug-like compounds contain heterocycles at their core.[1] Recently, transition-metal-catalyzed tandem processes have furnished a promising algorithm to address this requirement to swiftly assemble complex molecules from simple starting materials in an iterative manner.[2a–2c] This strategy is ideally suited to access diverse skeletal complexity.[2d,2e] Among the various transition metals, silver-catalyzed tandem sequences have gained substantial attention because of their ability to activate various π-systems under mild conditions at low-catalyst loading.[3]

As a privileged fragment, isoquinolines are present in a variety of natural products and in numerous pharmaceutically important compounds such as the antitumor agent carcristine A[4b] (Figure 1).[4] Isoquinoline-fused benzimidazoles have attracted considerable attention due to their immense and outstanding biological activities, such as anti-HIV-1, anticancer, antimicrobial, and antifungal properties.[5a–5d] For instance, Hoechst 33258 (Figure 1) possesses anti-PCP activity, the most common and leading cause of unhealthiness and fatality rates in AIDS patients.[5e] They also act as anti-inflammatory, antitumor, antiparasitic, and antiprotozoal agents.[5f–5h] These fused heterocycles are also used for grafting carbon nanotubes.[6] Similarly, quinoxalines are an important class of benzoheterocycles[7a] that constitute the building blocks of some organic semiconductors,[7b] are used as sensitizers in dye-sensitized solar cells,[7c] and from part of a wide range of pharmacologically active compounds including anticancer drugs such as the

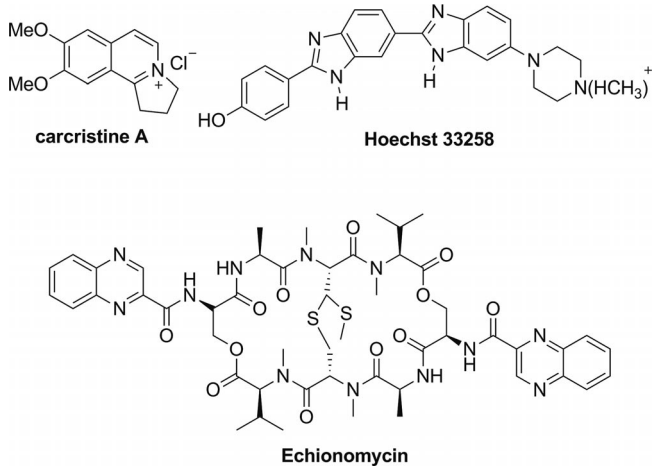

Figure 1. Examples of biologically active isoquinolines, benzimidazoles, and quinoxalines.

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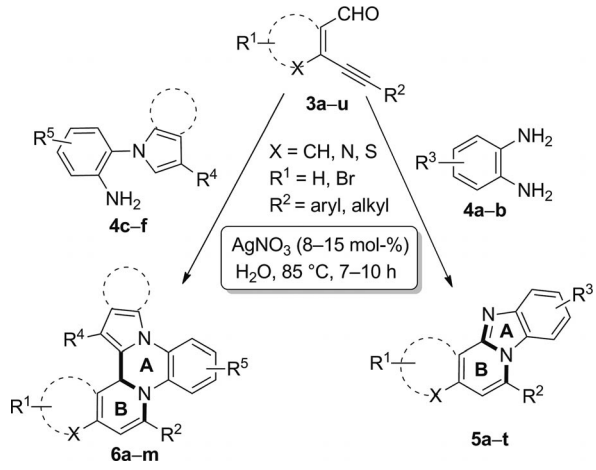
antibiotic echinomycin[7d] (Figure 1) and antimicrobial agents.[7e–7g] Furthermore, nitrogen-containing molecules exert specific binding to various targets.[7h] Thus, molecular skeletons that integrate both isoquinoline and quinoxaline moieties might possess properties of both and lead to enhanced activity. For this reason, the development of simultaneously benign and atom economical synthetic processes for rapid access to such functionalized and fused isoquinolines under mild conditions is of high demand.

In this regard, progress has been made by using tandem nucleophilic addition[8a] and electrophilic cyclization[8b–8l] with *o*-alkynylbenzaldehyde, amines, and various carbon pronucleophiles either in the absence[9,27] or in the presence of various alkynophilic Lewis acidic catalysts such as AgOTf,[10] $[In(OTf)_3]$ or $[AuClPPh_3]/[AgNTf_2]$,[11] Cu^I or Pd^{II} salts,[12a–12d] CuI/I_2,[12e] $[Mg(ClO_4)_2]/[Cu(OTf)_2]$,[13] and AuCl,[14] leading to the synthesis of 1,2-dihydroisoquinoline derivatives. Additionally, various multicomponent reactions of aldehydes, alkynes, and amines have also been carried out by using transition-metal-catalysts[15,16] such as Au^I, Ag^I, Cu^I, and $CuSO_4/C_{12}H_{25}SO_3Na$,[17] in the presence of water as a solvent, to yield aldimines.

Many organic syntheses have been carried out in environmentally benign modern solvents.[18–20] Most notably, reactions of water-insoluble organic compounds taking place in aqueous suspension, i.e., "on water", are gaining considerable attention due to their high efficiency and straightforward synthetic protocol.[21] Water, in contrast to common organic reaction solvents, is an environmentally friendly, inexpensive, nonhazardous reaction medium that often has an unparalleled effect on the rate and selectivity of organic reactions through hydrophobic interactions and enrichment of organic substrates in local hydrophobic environments.[22] It is believed that in many circumstances, the hydrophobic effect of water generates internal pressure and promotes the association of reactants in solvent cavities during reaction processes and thus accelerates reaction.[23] Various authors have reasoned that the rate accelerating effects of water can be attributed to its high heat capacity, hydrogen bonding, charge stabilization, dipolar effects, and/or high cohesive energy.[24]

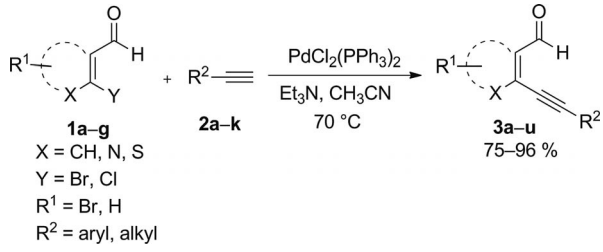
Prompted by above results and as a part of our ongoing efforts to synthesize N-heterocycles,[25] and on the basis of our recent preliminary report[26] on the synthesis of fused polyheterocycles, we herein report full details of our work on Ag^I-catalyzed regioselective tandem syntheses of benzimidazo[2,1-*a*]isoquinolines **5a**–**h**, **5t**, naphthyridines **5i**–**q**, thienopyridines **5r**–**s**, and quinoxalines **6a**–**m** (Scheme 1). The developed methodology has been extended to carry out double tandem cyclizations to access polyheterocycles **9** and **10**, which may be useful for the rapid assembly of systems with extended conjugation. This greener strategy involves the formation of three new C–N bonds (in the case of benzimidazole) and two new C–N with one C–C bond (in the case of quinoxaline), thereby leading to the formation of two heterocyclic rings in one-pot, giving fused polycyclic heterocycles. To the best of our knowledge, this environmentally friendly and atom economical tandem synthesis of diversely functionalized fused heterocycles from *ortho*-alkynylaldehydes in water has not previously been explored.



Scheme 1. Synthesis of fused benzimidazo[2,1-*a*]isoquinolines, naphthyridines, thienopyridines, and quinoxalines by Ag^I catalysis in water.

Results and Discussion

To probe the viability of the designed cascade strategy (Scheme 1), *ortho*-alkynylaldehydes **3a**–**u** were readily prepared by standard Sonogashira cross-coupling reaction of commercially available and readily accessible *ortho*-haloaldehydes **1a**–**g** with terminal alkynes **2a**–**k** (Scheme 2).[25d] This coupling procedure readily accommodated a large variety of functional groups and provided the coupling products **3a**–**u** in good to excellent yields.

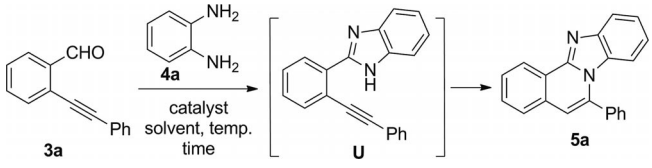


Scheme 2. Preparation of *ortho*-alkynylaldehydes.

To establish the optimal reaction conditions, we selected 2-phenylethynyl benzaldehyde (**3a**) and benzene-1,2-diamine (**4a**) as model substrates (Table 1). Interesting observations emerged from the data; reaction of **3a** (0.5 mmol) with **4a** (0.5 mmol) using 8.0 mol-% $AgNO_3$ in dichloromethane (2.0 mL) at 25 °C for 12 hours, afforded the desired product **5a** in 68% yield through exclusive *6-endo-dig* cyclization along with the formation of intermediate **U** in

25% yield (Table 1, entry 1). When different solvents such as toluene, dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), 1,2-dichloroethane (EDC), and ethanol were examined at elevated temperatures, it was observed that the respective reaction did not attain the desired levels of reactivity and led to the formation of product **5a** in 35–72% yield and intermediate **U** in 20–45% yield (Table 1, entries 2–6). Interestingly, when water was employed as a solvent, the reaction proceeded to completion and provided the desired product **5a** in 89% yield in 10 hours at 85 °C (Table 1, entry 7). When the reaction was further monitored after 5 and 7 h, and it was found that reaction was complete in 7 h, resulting in the formation of the desired product **5a** in 88% yield (Table 1, entry 9) but was incomplete after 5 h (Table 1, entry 8). It is notable that vigorous stirring was required to promote the reaction, most likely by increasing the area of contact between the organic and aqueous phase.[21a,23d] The yield of compound **5a** remained almost the same after prolonged heating (Table 1, entry 10). It was observed that decreasing catalyst loading from 8 to 5 mol-% adversely affected the yield of the product; under these conditions, compound **5a** was obtained in only 65% yield along with starting material **3a** and **4a** in 20 and 18% yield, respectively (Table 1, entry 11). Moreover, the solvent isotope effect had no noticeable impact on the yield of the product when D_2O was used in place of water (Table 1, entry 12). As expected, in the absence of catalyst, reactants remained almost unchanged during the reaction (Table 1, entry 13).

Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst (mol-%)	Solvent	*t* [°C]	Time [h]	Yield [%][b] U	5a
1	$AgNO_3$ (8)	CH_2Cl_2	25	12	25	68
2	$AgNO_3$ (8)	toluene	100	10	40	35
3	$AgNO_3$ (8)	EDC	70	10	20	72
4	$AgNO_3$ (8)	DMSO	120	10	28	58
5	$AgNO_3$ (8)	DMF	110	10	45	52
6	$AgNO_3$ (8)	EtOH	70	10	42	60
7	$AgNO_3$ (8)	H_2O	85	10	0	89
8	$AgNO_3$ (8)	H_2O	85	5	35	55
9	$AgNO_3$ (8)	H_2O	85	7	0	88
10	$AgNO_3$ (8)	H_2O	85	12	0	89
11	$AgNO_3$ (5)	H_2O	85	7	40	65
12	$AgNO_3$ (8)	D_2O	85	7	0	88
13	–	H_2O	85	7	5	trace
14	AgOAc (8)	H_2O	85	7	40	45
15	AgI (8)	H_2O	85	7	5	10
16	AgOTf (8)	H_2O	85	7	25	62
17	$PdCl_2$ (8)	H_2O	85	7	55	5
18	$Pd(OAc)_2$ (8)	H_2O	85	7	38	35
19	CuI (8)	H_2O	85	7	35	30

[a] Reagents and conditions: *o*-alkynylaldehyde **3a** (0.50 mmol), amine **4a** (0.50 mmol), solvent (2.0 mL). [b] Isolated yield.

The use of other silver catalysts with different counter anions such as AgOAc, AgI, and AgOTf resulted in inferior yields of the desired product **5a** (Table 1, entries 14–16). Transition-metal catalysts other than silver such as $PdCl_2$, $Pd(OAc)_2$, and CuI afforded the desired product **5a** in lower yields (Table 1, entries 17–19). The regioselective *6-endo-dig* cyclized product was fully characterized by ^1H, ^{13}C NMR and mass spectroscopic analysis. Disappearance of the two characteristic peaks of the alkynyl carbon of intermediate **U** in the ^{13}C NMR spectrum of the product suggested the formation of the desired cyclized product **5a**. X-ray crystallographic analysis of **5a** (Figure 2) and the intermediate **U** confirmed the formation of the *6-endo-dig* cyclized product through formation of intermediate **U** (see also the Supporting Information).

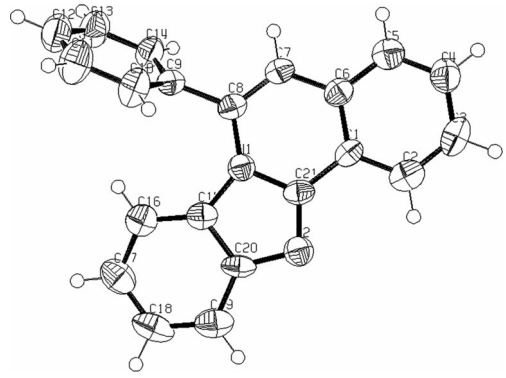


Figure 2. ORTEP drawing of compound **5a**.

Having demonstrated the viability of this cascade strategy, we next investigated the generality and scope of the transformation under the optimized condition (Table 2). As shown in Table 2, the reaction is tolerant towards a variety of *o*-alkynylaldehydes **3** bearing a range of alkynyl substituents R^2. When electron-donating groups such as phenyl or *p*-methoxyphenyl, were attached to the triple bond, the respective reaction was very well implemented to form intriguing cyclized products **5a** and **5b** in 88–93% yield; these groups increase the electron density at the distal end of the triple bond, thereby promoting the regioselective *6-endo-dig* ring closure in an efficient manner (Table 2, entries 1 and 2). On the other hand, when 4-phenoxybenzene was used as an alkynyl substituent, the reaction resulted in the formation of product **5c** in 78% yield, which may be due to operation of a (+M)-effect of ethereal oxygen in both of the phenyl rings (Table 2, entry 3). Also noteworthy is the fact that this chemistry tolerated the thiophene group, and the product **5d** was obtained in excellent yield (Table 2, entry 4). However, when the 3-methoxyphenyl group was employed, the reaction afforded compound **5e** in comparatively low yield (Table 2, entry 5). Reaction of *o*-alkynylaldehyde **3e** with 4-methylbenzene-1,2-diamine **4b** resulted in the formation of two inseparable regioisomers **5f** in 83% yield (Table 2, entry 6). A 65% isolated yield of compound **5g** was obtained when a 4-(trifluoromethyl)phenyl group was employed as R^2 (Table 2, entry 7). Interestingly, when the

Table 2. Tandem synthesis of fused benzimidazoles.[a]

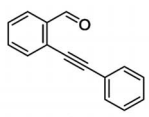
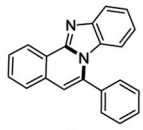
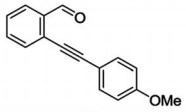
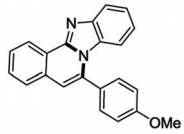
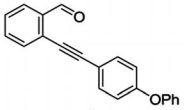
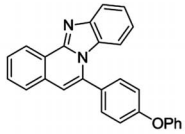
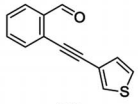
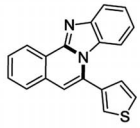
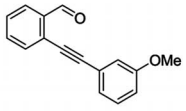
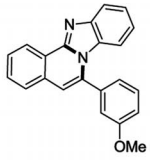
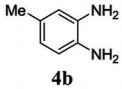
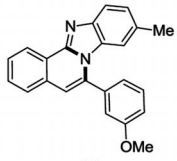
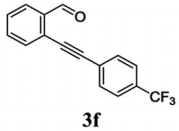
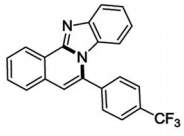
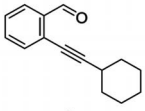
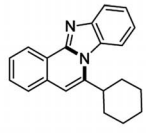
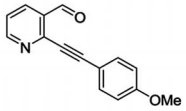
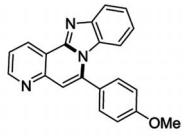
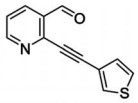
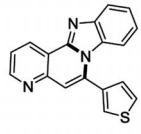
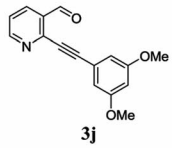
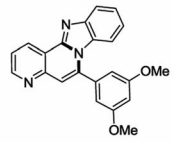
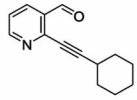
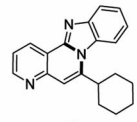
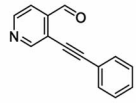
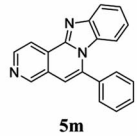
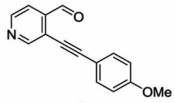
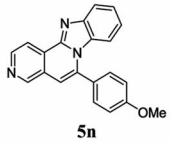
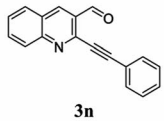
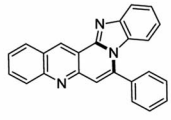
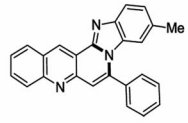
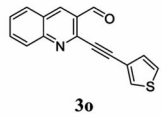
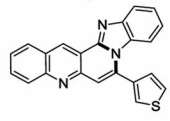
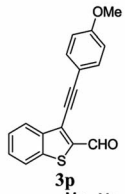
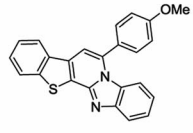
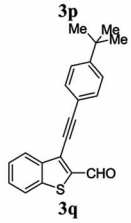
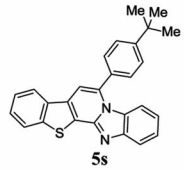
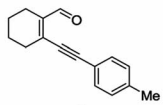
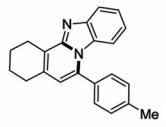
Entry	o-Alkynylaldehyde	Amine	Product	Yield [%][b]
1	 **3a**	 **4a**	 **5a**	88
2	 **3b**	**4a**	 **5b**	93
3	 **3c**	**4a**	 **5c**	78
4	 **3d**	**4a**	 **5d**	92
5	 **3e**	**4a**	 **5e**	80
6	**3e**	 **4b**	 **5f**	83
7	 **3f**	**4a**	 **5g**	65
8	 **3g**	**4a**	 **5h**	75
9	 **3h**	**4a**	 **5i**	92
10	 **3i**	**4a**	 **5j**	91

Table 2. *(continued)*

Entry	o-Alkynylaldehyde	Amine	Product	Yield [%][b]
11	 **3j**	**4a**	 **5k**	77
12	 **3k**	**4a**	 **5l**	77
13	 **3l**	**4a**	 **5m**	85
14	 **3m**	**4a**	 **5n**	90
15	 **3n**	**4a**	 **5o**	86
16	**3n**	**4b**	 **5p**	88
17	 **3o**	**4a**	 **5q**	88
18	 **3p**	**4a**	 **5r**	80
19	 **3q**	**4a**	 **5s**	78
20	 **3r**	**4a**	 **5t**	72[c]

[a] Reagents and conditions (unless otherwise noted): *o*-alkynylaldehyde **3** (0.50 mmol), amine **4a/b** (0.50 mmol), $AgNO_3$ (8.0 mol-%), H_2O (2.0 mL), 85 °C, 7 h. [b] Yield of isolated product. [c] $AgNO_3$ (15.0 mol-%) was used.

Table 3. Tandem synthesis of fused quinoxalines.[a]

Entry	*o*-Alkynylaldehyde	Amine	Product	Yield [%][b]
1	**3e**	**4c**	**6a**	78
2	**3s**	**4c**	**6b**	85
3	**3t**	**4c**	**6c**	75
4	**3f**	**4c**	**6d**	58
5	**3j**	**4c**	**6e**	80
6	**3l**	**4c**	**6f**	85
7	**3n**	**4c**	**6g**	80
8	**3o**	**4c**	**6h**	83
9	**3u**	**4d**	**6i**	89
10	**3b**	**4d**	**6j**	91
11	**3c**	**4d**	**6k**	80
12	**3a**	**4e**	**6l**	90
13	**3b**	**4f**	**6m**	45[c]

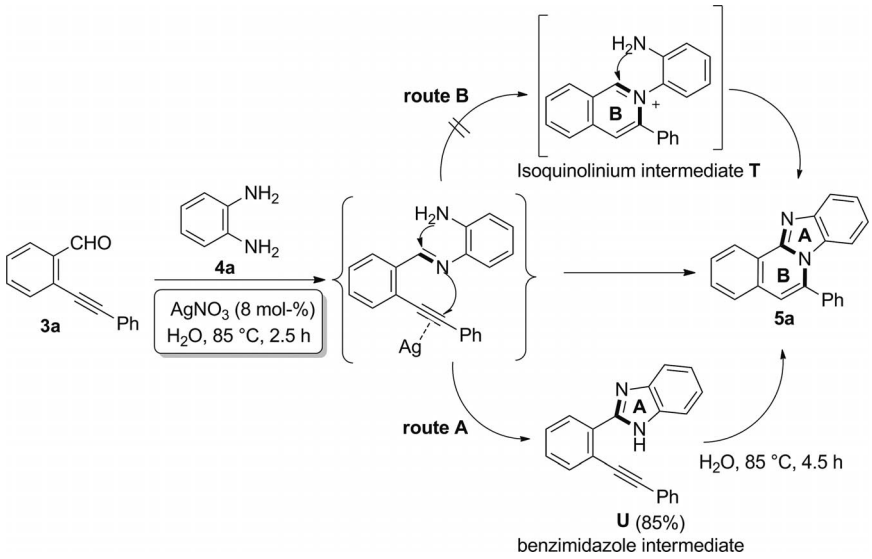
[a] Reagents and conditions (unless otherwise noted): *o*-alkynylaldehyde **3** (0.50 mmol), amine **4c**–**f** (0.50 mmol), $AgNO_3$ (8.0 mol-%), H_2O (2.0 mL), 85 °C, 7 h. [b] Yield of isolated product. [c] $AgNO_3$ (12.0 mol-%) was used and the reaction was stirred for 10 h.

cyclohexyl group was introduced, the reaction afforded the desired product **5h** in 75% yield (Table 2, entry 8).

The scope of the reaction was extended to the synthesis of medicinally important naphthyridines **5i**–**q**. Thus, 2-(arylethynyl)nicotinaldehyde **3h**–**k** and 3-(arylethynyl)isonicotinaldehyde **3l**–**m** with a variety of alkynyl substituents afforded the desired 6/7-substituted benzo[4,5]imidazo[2,1-*f*][1,6]naphthyridines **5i**–**n** in 77–92% yield (Table 2, entries 9–14). Moving onwards to two ring systems, when 2-(substituted ethynyl)quinoline-3-carbaldehydes **3n**–**o** were subjected to the reaction conditions with amines **4a**–**b**, the reaction proceeded well and afforded the fused polycyclic compounds **5o**–**q** in 86–88% yield (Table 2, entries 15–17).

To incorporate more diversity in the products, reaction of 3-[(substituted)ethynyl]benzo[*b*]thiophene-2-carbaldehyde **3p**–**q** with **4a** afforded the corresponding 6-substituted benzo[4,5]imidazo [1,2-*a*]benzo[4,5]thieno[2,3-*c*]pyridine **5r**–**s** in 78–80% yield (Table 2, entries 18 and 19). Furthermore, when aliphatic systems such as 2-(*p*-tolylethynyl)-cyclohex-1-enecarbaldehyde was employed, the reaction afforded the desired compound **5t** in good yield (72%; Table 2, entry 20).

The developed cascade strategy was successfully extended to the synthesis of functionalized polycyclic quinoxalines by the reaction of *o*-alkynylaldehydes **3** with heteroaromatic amines **4c**–**f** having tethered nucleophiles (Table 3). Reaction of *o*-alkynylaldehydes **3e**–**f**, **3j**, **3l**, **3n**–**o**, and **3s**–**t** with 2-(1*H*-pyrrol-1-yl)aniline **4c** afforded the substituted quinoxalines **6a**–**h** in good to excellent yields



Scheme 3. Mechanistic studies.

with high regioselectivity (Table 3, entries 1–8). With 3-methoxyphenyl as an alkynyl substituent, compound **6a** was obtained in 78% yield (Table 3, entry 1). 5-Bromo-2-(phenylethynyl)benzaldehyde (**3s**) afforded the bromo-substituted quinoxaline **6b** in 85% yield, which can be used for further synthetic elaboration by palladium-catalyzed coupling reactions (Table 3, entry 2). It is noteworthy that the trimethylsilyl-substituent of *o*-alkynylaldehyde **3t** remained intact during the reaction and afforded the desired cyclization product **6c** in 75% yield (Table 3, entry 3). The presence of an electron-withdrawing trifluoromethyl group in the 4-position of the phenyl of alkyne **3f** (Table 3, entry 4) led to a lower yield of the desired product **6d**, which may be due to the reduced electrophilicity at the proximal end of the alkyne moiety thereby reducing the efficiency of the desired transformation. The reaction proceeded appreciably well with heteroaromatic *ortho*-alkynylaldehydes **3j**, **3l**, and **3n**–**o**, which afforded the polyheterocyclic quinoxalines **6e**–**h** in 80–85% yield, respectively (Table 3, entries 5–8). Encouraged by the above results, we further extended the same protocol to examine its scope for the reaction of 2-(3-methyl-1*H*-indol-1-yl)aniline (**4d**) with functionally varied *o*-alkynylaldehydes **3** (Table 3). The reaction proceeded well and provided the fused indolo-quinoxalines **6i**–**m** in 45–91% yield (Table 3, entries 9–13). Of particular medicinal relevance, the fluoro-substituted quinoxaline **6l** was synthesized in 90% yield by using fluoro-substituted amine **4e** (Table 3, entry 12). It was observed that amine **4f** (without a 3-methyl group) provided the desired product **6m** in only 45% yield (Table 3, entry 13). This observation shows that the presence of a methyl group at the 3-position of the in-

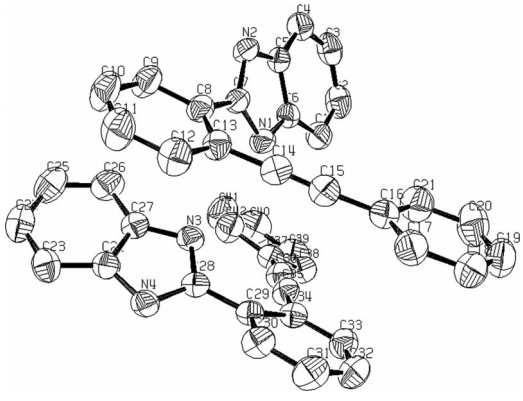
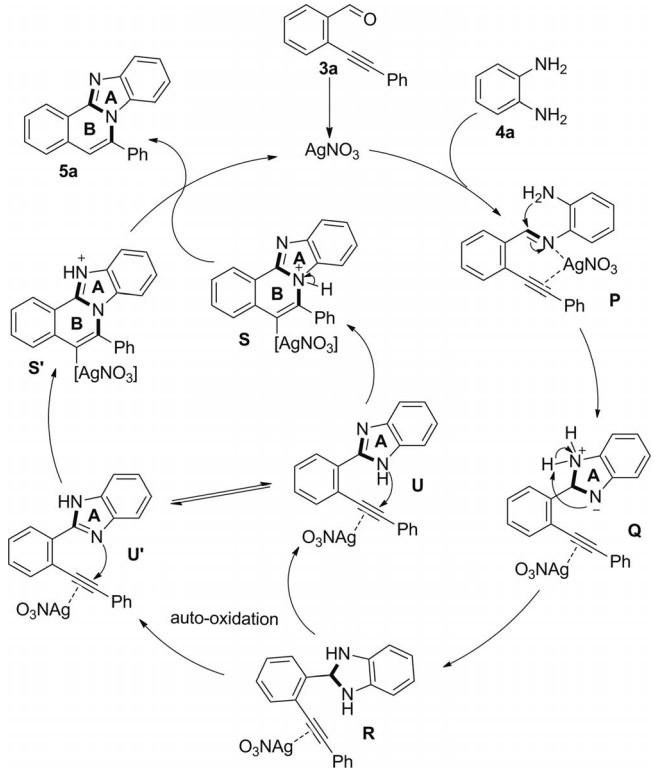


Figure 3. ORTEP diagram of intermediate **U**.



Scheme 4. Plausible mechanism.

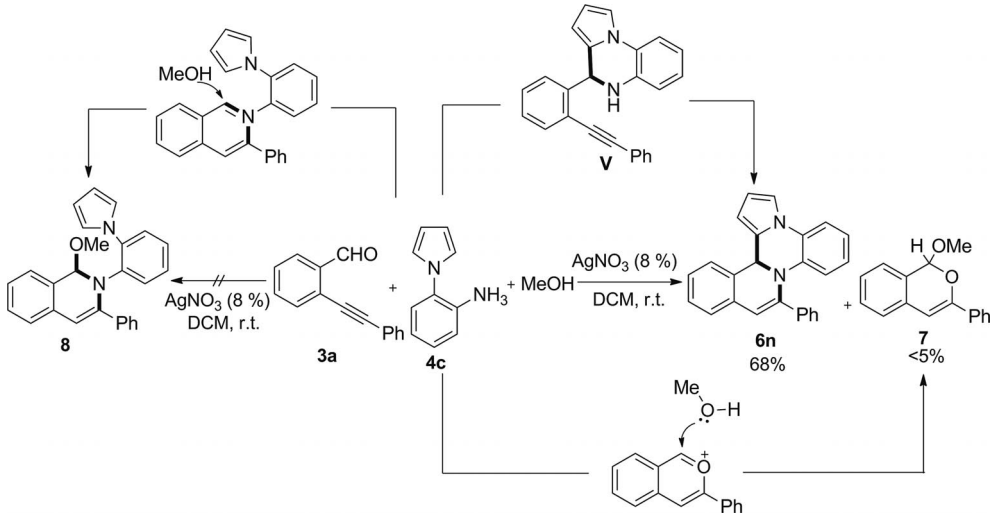
dole ring is a prerequisite for efficient intramolecular ring closure.[25a,25d]

To understand the mechanism of the designed cascade strategy, the reaction between **3a** and **4a** was examined by using 8.0 mol-% $AgNO_3$ in water (Scheme 3). After careful monitoring of the reaction, the formation of intermediate alkyne **U** as a major product was observed on TLC after 2 h. This intermediate was isolated and characterized by NMR analysis. In the ^1H NMR spectrum, the presence of a peak at δ = 10.96 ppm and its disappearance upon shaking in D_2O confirmed the presence of a proton attached to nitrogen. The presence of characteristic peaks at δ = 94.7 and 89.1 ppm in the ^{13}C NMR spectrum illustrated that both alkynylic carbon atoms remained intact. Formation of intermediate **U** was finally confirmed by X-ray crystallographic studies (Figure 3; see also the Supporting Information).

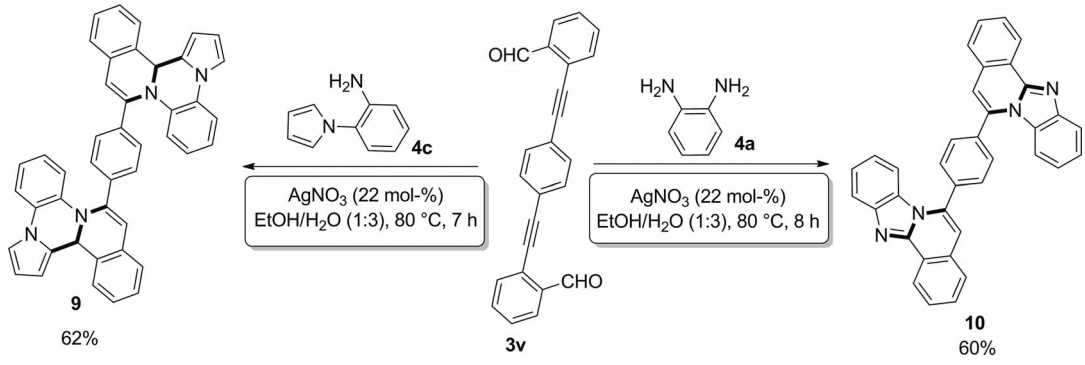
Isolation and characterization of intermediate **U** clearly confirms that the reaction proceeds through route A, leading to the formation of heterocyclic ring A first (Scheme 3), by nucleophilic attack of the NH_2 group of *o*-phenylenediamine onto imine carbon, leaving both alkynyl carbon atoms intact to generate **U**, which further undergoes a second intramolecular ring closure to give **5a**. The reaction does not proceed through route B, which would occur through the formation of isoquinolinium intermediate **T**,[12d] forming ring B first.

With these observations in hand, a plausible mechanism is proposed (Scheme 4). Reaction of alkyne **3a** and amine **4a** generates imine **P**, which, upon activation by $AgNO_3$, results in nucleophilic attack by the NH_2 group of amine **4a** onto the imine carbon to form transient intermediate **Q**, which undergoes subsequent electronic rearrangements to give unstable **R**.[27] The latter species undergoes auto-oxidation and generates isolable intermediate **U**, which might be in equilibrium with **U′**. Subsequent π complexation between alkyne and Ag^I leads to regioselective intramolecular addition of nucleophilic NH on to the alkyne to form **S** (nonaromatic), along with the possibility of forming the aromatic species **S′**, in which pyridine, like the nitrogen of the benzimidazole moiety, can attack the triple bond, both of which, after concomitant deprotonation, leads to the formation of cyclized product **5a**.

To compare the feasibility of an intramolecular and an intermolecular reaction, a competitive study was performed by carrying out the reaction between 2-(phenylethynyl)-benzaldehyde (**3a**), amine **4c**, and MeOH (1.2 equiv.) in dichloromethane using $AgNO_3$ (8.0 mol-%) as catalyst



Scheme 5. Comparative study.



Scheme 6. Bis-tandem cyclization.

(Scheme 5). The results demonstrated that fused quinoxaline **6n**[26] was formed as a major product in 68% yield along with intermediate **V**[26] in 25% yield, whereas 1-methoxy-1*H*-isochromene **7**[28] was formed in trace amounts. Formation of 2-[2-(1*H*-pyrrol-1-yl)phenyl]-1-methoxy-3-phenyl-1,2-dihydroisoquinoline (**8**) was not observed. This clearly reveals that intramolecular reaction is preferred over intermolecular reaction because amine **4c**, with a tethered nucleophile, is in proximity to attack the imine carbon, which is entropically more feasible than attack by distal methanol molecules.

We have also investigated the possibility of carrying out double tandem cyclizations, which might be useful for the rapid assembly of systems with extended conjugation. Alkyne **3v** underwent tandem reaction with amine **4a** and **4c** to afford double cyclization products **9** and **10** in 62 and 60% yield, respectively (Scheme 6). Recently, such polycyclic aromatic compounds have also been disclosed as potential candidates for photoelectronic devices and π-conjugated material such as organic semiconductor and luminescent materials.[29]

Conclusions

We have developed an environmentally benign Ag^I-catalyzed tandem protocol in water that provides facile access to an impressive variety of fused benzimidazo[2,1-*a*]isoquinolines, naphthyridines, thienopyridines, and quinoxalines in good to excellent yields with high regioselectivity and structural diversity. The activation of the alkyne is advantageously employed in the tandem cyclization by intramolecular nucleophilic attack leading to concomitant heterocyclizations in one-pot. These atom-economical transformations in water proceed with high functional-group tolerance. The proposed mechanistic pathway (mode of concomitant bond formations) was confirmed by control experiments and X-ray crystallographic studies of an intermediate and the cyclized product. This synthetic methodology provides a powerful tool for divergent preparation of polyheteroaromatics through double cyclizations, which are of high importance in material chemistry. Owing to the great skeletal diversity of the substitution pattern, this developed chemistry is attractive for the generation of libraries of various heterocyclic systems that may modulate the activity of many targets that have been beyond the horizon of traditional compound collections.

Experimental Section

General Information: ^{1}H NMR (300 MHz or 400 MHz) and ^{13}C NMR (75 MHz or 100 MHz) spectra were recorded in $CDCl_3$ or in DMSO as specified, with Jeol JNM ECX400P (400 MHz) and Bruker AV300 (300 MHz) spectrometers. Chemical shifts for ^{1}H NMR spectra are reported in ppm from tetramethylsilane with the residual $CHCl_3$ resonance as internal reference. Chemical shifts for ^{13}C NMR spectra are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet), coupling constants (*J*) in Hertz, and integration. High-resolution mass spectra were recorded with an Applied Biosystems QSTAR Elite Hybrid (QqTOF) LC/MS/MS System with electrospray mass spectrometer using positive electrospray ionization mode (ESI+). Crystal structure analysis was accomplished with an Oxford diffraction (Xcaliber S) single-crystal X-ray diffractometer. TLC analysis was performed on commercially prepared 60 F_{254} silica gel plates and visualized by either UV irradiation or by staining with I_2. Chemical yields refer to the pure isolated substances. Anhydrous forms of all reagents such as diethyl ether, THF, toluene, DMSO, DMF, ethanol, hexanes, ethyl acetate, and CH_2Cl_2 were purchased from Merck Chemical Co. and 2-Bromobenzaldehyde, terminal alkynes, silver nitrate, AgI, AgOAc, $PdCl_2$, $Pd(OAc)_2$, AgOTf, 2-(1*H*-pyrrol-1-yl)aniline, benzene-1,2-diamine, Et_3N and the palladium salts were purchased from Aldrich and were used as such without further purification unless otherwise noted. Compounds **3a**, **3b**, **3d**, **3g**, **3h**, **3m**, **3s**, and **3t** have been previously reported,[26] as have compounds **3k**, **3n** and **3o**,[25f] and also compounds **3r**[30] and **3u**.[28]

General Procedure for the Synthesis of Benzimidazo[2,1-*a*]isoquinolines 5a–h, 5t, Naphthyridines 5i–q, Thienopyridines 5r–s and 10: To a solution of *ortho*-alkynylaldehyde (**3**; 0.5 mmol), amine [**4a**–**b**; 0.5 mmol, 1.0 equiv. (2.0 equiv. for **10**)] in H_2O (2.0 mL) was added $AgNO_3$ [8.0 mol-% (22 mol-% for **10**)] and the mixture was stirred at 85 °C. After completion of reaction (indicated by TLC), H_2O (10 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (2 × 10 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (100–200 mesh; petroleum ether/ethyl acetate) to afford the desired pure products. Compounds **5a** and **5n** have been previously reported.[26]

6-(4-Methoxyphenyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (5b): Colorless crystals (150 mg, 93%); m.p. 210–214 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.89–8.86 (m, 1 H), 7.98 (d, *J* = 8.1 Hz, 1 H), 7.70–7.64 (m, 3 H), 7.52–7.49 (m, 2 H), 7.39 (td, *J* = 1.2, 8.4 Hz, 1 H), 7.11–7.08 (m, 2 H), 7.05–7.00 (m, 1 H), 6.87 (s, 1 H), 6.60 (d, *J* = 8.4 Hz, 1 H), 3.95 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 148.4, 144.3, 137.4, 131.7, 130.8, 130.7, 130.0, 127.7, 127.0, 126.6, 125.1, 124.1, 122.9, 121.2, 119.7, 114.3, 114.2, 112.6, 55.5 ppm. HRMS (ESI+): calcd. for $C_{22}H_{16}N_2O$ 324.1263; found 324.1275.

6-(4-Phenoxyphenyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (5c): Light-yellow solid (150 mg, 78%); m.p. 236–238 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.89–8.87 (m, 1 H), 7.99 (d, *J* = 8.1 Hz, 1 H), 7.73–7.67 (m, 3 H), 7.56 (d, *J* = 8.8 Hz, 2 H), 7.46–7.39 (m, 3 H), 7.23–7.17 (m, 5 H), 7.07 (td, *J* = 1.5, 8.8 Hz, 1 H), 6.92 (s, 1 H), 6.65 (d, *J* = 8.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 156.2, 148.3, 144.2, 136.9, 131.6, 130.9, 130.7, 130.1, 130.0, 129.1, 127.9, 126.6, 125.1, 124.2, 122.9, 121.3, 119.71, 119.68, 118.5, 114.1, 112.8 ppm. HRMS (ESI+): calcd. for $C_{27}H_{18}N_2O$ 386.1419; found 386.1419.

6-(Thiophen-3-yl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (5d): Yellow crystals (138 mg, 92%); m.p. 194–196 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.89 (t, *J* = 3.6 Hz, 1 H), 8.00 (d, *J* = 8.1 Hz, 1 H), 7.72–61 (m, 4 H), 7.59–7.56 (m, 1 H), 7.44–7.39 (m, 1 H), 7.29 (dd, *J* = 1.2, 5.1 Hz, 1 H), 7.11–7.05 (m, 1 H), 6.97 (s, 1 H), 6.63 (d, *J* = 8.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.2, 144.2, 134.9, 132.5, 131.4, 130.6, 130.1, 128.6, 127.9, 127.1, 126.8, 126.6, 125.1, 124.3, 123.0, 121.4,

119.7, 113.7, 113.1 ppm. HRMS (ESI+): calcd. for $C_{19}H_{12}N_2S$ 300.0721; found 300.0718.

6-(3-Methoxyphenyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (5e): Colorless crystals (129 mg, 80%); m.p. 182–184 °C (petroleum ether/CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.89 (t, J = 3.6 Hz, 1 H), 7.99 (d, J = 8.1 Hz, 1 H), 7.74–7.66 (m, 3 H), 7.51 (t, J = 7.8 Hz, 1 H), 7.40 (t, J = 7.5 Hz, 1 H), 7.19–7.12 (m, 3 H), 7.03 (t, J = 7.8 Hz, 1 H), 6.92 (s, 1 H), 6.58 (d, J = 8.4 Hz, 1 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.9, 148.3, 144.2, 137.3, 135.8, 131.6, 130.6,130.1, 127.9, 126.7, 125.1, 124.2, 122.9, 121.7, 121.3, 119.7, 115.8, 114.6, 114.2, 112.4, 55.5 ppm. HRMS (ESI+): calcd. for $C_{22}H_{16}N_2O$ 324.1273; found 324.1263.

6-(3-Methoxyphenyl)-10-methylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (5f): White solid (140 mg, 83%); major/minor ratio 1.0:0.33; m.p. 176–178 °C (petroleum ether/CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.88–8.85 [m, 2 H, including 1 H (major) + 1 H (minor)], 7.87 (d, J = 9.0 Hz, 1 H, minor), 7.76–7.65 [m, 5 H, including 3 H (major) + 2 H (minor)], 7.50 [td, J = 1.5, 8.0 Hz, 2 H, including 1 H (major) + 1 H (minor)], 7.25–7.12 [m, 6 H, including 4 H (major) + 2 H (minor)], 6.90–6.84 [m, 3 H, including 2 H (major) + 1 H (minor)], 6.44 (d, J = 7.8 Hz, 1 H, major), 6.33 (s, 1 H, minor), 3.86 (s, 3 H, major), 3.85 (s, 3 H, minor), 2.49 (s, 3 H, major), 2.28 (s, 3 H, minor) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ (major regioisomer) = 159.9, 148.2, 144.6, 137.2, 135.8, 131.5, 130.1, 129.97, 129.93, 129.8, 128.7, 127.8, 126.6, 125.0, 123.1, 121.7, 119.3, 115.7, 114.5, 113.6, 112.1, 55.5, 21.6 ppm; δ (minor regioisomer) = 147.9, 142.3, 137.3, 134.1, 131.4, 131.1, 130.7, 127.8, 125.8, 124.9, 122.9, 121.8, 119.1, 114.6, 114.1, 112.2, 55.5, 22.0 ppm. HRMS (ESI+): calcd. for $C_{23}H_{18}N_2O$ 338.1419; found 338.1418.

6-[4-(Trifluoromethyl)phenyl]benzo[4,5]imidazo[2,1-*a*]isoquinoline (5g): Colorless crystals (117 mg, 65%); m.p. 226–228 °C (petroleum ether/CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.90–8.88 (m, 1 H), 8.00 (d, J = 8.0 Hz, 1 H), 7.88 (d, J = 8.1 Hz, 2 H), 7.77–7.70 (m, 5 H), 7.42 (t, J = 7.3 Hz, 1 H), 7.05 (t, J = 7.3 Hz, 1 H), 6.91 (s, 1 H), 6.52 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.2, 144.2, 138.1, 135.8, 131.2, 130.4, 130.3, 129.8, 128.4, 126.8, 126.0, 125.9, 125.1, 124.4, 123.1, 121.5, 119.9, 113.6, 113.3 ppm. HRMS (ESI+): calcd. for $C_{22}H_{13}F_3N_2$ 362.1031; found 362.1025.

6-Cyclohexylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (5h): Yellow solid (112 mg, 75%); m.p. 150–152 °C (petroleum ether/CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.83 (dd, J = 1.2, 7.4 Hz, 1 H), 8.04 (d, J = 8.1 Hz, 1 H), 7.94 (d, J = 8.1 Hz, 1 H), 7.68–7.58 (m, 3 H), 7.54–7.48 (m, 1 H), 7.44–7.35 (m, 1 H), 6.84 (s, 1 H), 3.56–3.51 (m, 1 H), 2.34–2.31 (m, 2 H), 2.03–1.92 (m, 4 H), 1.70–1.54 (m, 3 H), 1.47–1.40 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 144.4, 144.3, 131.7, 130.4, 129.9, 127.1, 126.1, 125.0, 124.0, 122.3, 122.0, 120.0, 114.4, 107.0, 39.5, 32.1, 26.4, 26.2 ppm. HRMS (ESI+): calcd. for $C_{21}H_{20}N_2$ 300.1626; found 300.1627.

6-(4-Methoxyphenyl)benzo[4,5]imidazo[2,1-*f*][1,6]naphthyridine (5i): Yellow crystals (149 mg, 92%); m.p. 244–248 °C (petroleum ether/CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.12 (dd, J = 1.4, 8.0 Hz, 1 H), 8.97 (dd, J = 1.4, 4.4 Hz, 1 H), 7.98 (d, J = 8.1 Hz, 1 H), 7.59–7.54 (m, 3 H), 7.43 (td, J = 1.4, 8.1 Hz, 1 H), 7.15–7.14 (m, 2 H), 7.13–7.12 (m, 1 H), 7.07 (td, J = 1.4, 7.2 Hz, 1 H), 6.64 (d, J = 8.8 Hz, 1 H), 3.97 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 152.4, 148.6, 147.5, 144.4, 141.2, 132.7, 130.5, 130.4, 126.3, 124.5, 122.3, 121.8, 119.7, 118.8, 114.4, 114.3, 113.9, 55.5 ppm. HRMS (ESI+): calcd. for $C_{21}H_{15}N_3O$ 325.1215; found 325.1216.

6-(Thiophen-3-yl)benzo[4,5]imidazo[2,1-*f*][1,6]naphthyridine (5j): Yellow solid (137 mg, 91%): m.p. 222–224 °C (petroleum ether/CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.12 (dd, J = 1.5, 8.1 Hz, 1 H), 8.97 (dd, J = 2.2, 4.4 Hz, 1 H), 7.99 (d, J = 8.1 Hz, 1 H), 7.70 (dd, J = 1.5, 2.9 Hz, 1 H), 7.63–7.57 (m, 2 H), 7.45 (t, J = 7.3 Hz, 1 H), 7.33 (dd, J = 1.4, 5.1 Hz, 1 H), 7.23 (s, 1 H), 7.15–7.11 (m, 1 H), 6.67 (d, J = 8.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 148.4, 147.3, 144.3, 136.4, 134.2, 132.7, 130.4, 128.3, 127.1, 126.6, 124.6, 122.5, 122.1, 119.8, 119.0, 114.4, 113.9 ppm. HRMS (ESI+): calcd. for $C_{18}H_{11}N_3S$ 301.0674; found 301.0674.

6-(3,5-Dimethoxyphenyl)benzo[4,5]imidazo[2,1-*f*][1,6]naphthyridine (5k): Yellow crystals (136 mg, 77%): m.p. 200–202 °C (petroleum ether/CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.11 (d, J = 8.0 Hz, 1 H), 8.95 (d, J = 5.1 Hz, 1 H), 7.96 (d, J = 8.0 Hz, 1 H), 7.58–7.56 (m, 1 H), 7.41 (t, J = 8.1 Hz, 1 H), 7.17 (s, 1 H), 7.09 (t, J = 8.8 Hz, 1 H), 6.72–6.67 (m, 4 H), 3.81 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 152.4, 148.5, 147.3, 144.2, 141.0, 135.5, 132.8, 130.3, 124.7, 122.5, 122.1, 119.7, 118.9, 114.5, 113.5, 107.0, 102.4, 55.6 ppm. HRMS (ESI+): calcd. for $C_{22}H_{17}N_3O_2$ 355.1321; found 355.1320.

6-Cyclohexylbenzo[4,5]imidazo[2,1-*f*][1,6]naphthyridine (5l): Off-white solid (116 mg, 77%): m.p. 162–164 °C (petroleum ether/CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.04–9.03 (m, 1 H), 8.21 (d, J = 8.2 Hz, 1 H), 8.04 (d, J = 8.7 Hz, 1 H), 7.70–7.63 (m, 2 H), 7.56 (t, J = 7.8 Hz, 1 H), 7.49–7.45 (m, 1 H), 7.25 (s, 1 H), 3.63–3.60 (m, 1 H), 2.36–2.34 (m, 2 H), 2.07–2.05 (m, 3 H), 1.74–1.60 (m, 4 H), 1.52–1.41 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3, 148.7, 148.3, 147.8, 144.6, 132.7, 130.1, 124.4, 122.5, 122.0, 120.1, 118.1, 114.5, 108.4, 39.8, 31.9, 26.3, 26.0 ppm. HRMS (ESI+): calcd. for $C_{20}H_{19}N_3$ 301.1579; found 301.1551.

6-Phenylbenzo[4,5]imidazo[2,1-*a*][2,6]naphthyridine (5m): Yellow solid (125 mg, 85%): m.p. 208–210 °C (petroleum ether/CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.14 (s, 1 H), 8.64 (d, J = 5.2 Hz, 1 H), 8.49 (d, J = 5.8 Hz, 1 H), 8.03 (d, J = 8.7 Hz, 1 H), 7.68–7.60 (m, 5 H), 7.45 (t, J = 7.4 Hz, 1 H), 7.08 (td, J = 1.5, 7.3 Hz, 1 H), 6.99 (s, 1 H), 6.52 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.4, 147.1, 145.9, 144.1, 139.4, 134.0, 130.6, 130.2, 129.2, 129.1, 127.8, 126.2, 124.8, 122.5, 120.3, 117.5, 114.3, 109.7 ppm. HRMS (ESI+): calcd. for $C_{20}H_{13}N_3$ 295.1109; found 295.1107.

7-Phenylbenzo[*b*]benzo[4,5]imidazo[2,1-*f*][1,6]naphthyridine (5o): Yellow solid (148 mg, 86%): m.p. 260–264 °C (petroleum ether/EtOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1 H), 8.22 (d, J = 8.8 Hz, 1 H), 8.12 (d, J = 8.0 Hz, 1 H), 8.00 (d, J = 8.7 Hz, 1 H), 7.87 (td, J = 1.4, 6.6 Hz, 1 H), 7.69–7.63 (m, 6 H), 7.41 (t, J = 7.4 Hz, 1 H), 7.23 (s, 1 H), 7.07 (td, J = 1.5, 8.4 Hz, 1 H), 6.48 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 149.8, 148.6, 147.8, 144.2, 142.0, 134.0, 133.4, 131.4, 131.0, 129.1, 128.7, 127.1, 126.8, 124.3, 122.4, 119.9, 117.6, 115.8, 114.1, 108.2 ppm. HRMS (ESI+): calcd. for $C_{24}H_{15}N_3$ 345.1266; found 345.1258.

11-Methyl-7-phenylbenzo[*b*]benzo[4,5]imidazo[2,1-*f*][1,6]naphthyridine (5p): Yellow solid (158 mg, 88%); major/minor ratio 1.0:0.40; m.p. 256–258 °C (petroleum ether/EtOH). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.65 (s, 1 H, major), 9.63 (s, 1 H, minor), 8.21 [d, J = 8.7 Hz, 2 H, including 1 H (major) + 1 H (minor)], 8.11 [d, J = 8.1 Hz, 2 H, including 1 H (major) + 1 H (minor)], 7.87–7.83 (m, 2 H, major), 7.76 (s, 1 H, major), 7.65–7.61 [m, 11 H, including 6 H (major) + 5 H (minor)], 7.20 (s, 1 H, major), 6.89 (d, J = 8.1 Hz, 1 H, minor), 6.33 (d, J = 8.1 Hz, 1 H, major), 6.21 (s, 1 H, minor), 2.49 (s, 3 H, major), 2.26 (s, 3 H, minor) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ (major regioisomer) = 149.7, 148.6, 147.7, 144.6, 141.9, 134.2, 133.2, 131.3, 130.2, 129.07, 129.04, 128.7, 127.0, 126.7, 125.9, 123.9, 119.5, 117.6, 113.7, 113.5, 21.6 ppm; δ (minor regioisomer) = 149.6, 142.3, 142.1, 134.1, 133.1, 132.3, 131.2, 129.1, 128.9, 119.3, 117.7, 113.9, 113.8, 22.0 ppm. HRMS (ESI+): calcd. for $C_{25}H_{17}N_3$ 359.1422; found 359.1414.

7-(Thiophen-3-yl)benzo[*b*]benzo[4,5]imidazo[2,1-*f*][1,6]naphthyridine (5q): Yellow solid (154 mg, 88%); m.p. 258–260 °C (petroleum ether/EtOH). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.75 (s, 1 H), 8.37 (d, J = 8.8 Hz, 1 H), 8.19 (d, J = 8.8 Hz, 1 H), 8.15–8.14 (m, 1 H), 7.95–7.92 (m, 3 H), 7.79–7.70 (m, 2 H), 7.51 (dd, J = 1.4, 5.1 Hz, 1 H), 7.44 (t, J = 8.1 Hz, 1 H), 7.21–7.16 (m, 1 H), 6.52 (d, J = 8.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO + CD_3OD): δ = 149.3, 148.2, 147.3, 143.9, 137.5, 133.9, 133.2, 131.8, 130.7, 129.2, 128.8, 128.7, 128.1, 127.9, 127.0, 126.8, 124.4, 122.5, 119.7, 117.3, 113.7, 113.5 ppm. HRMS (ESI+): calcd. for $C_{22}H_{13}N_3S$ 351.0830; found 351.0834.

6-(4-Methoxyphenyl)benzo[4,5]imidazo[1,2-*a*]benzo[4,5]thieno[2,3-*c*]pyridine (5r): Yellow crystals (152 mg, 80%); m.p. 208–210 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.04 (m, 1 H), 7.98–7.96 (m, 1 H), 7.92 (d, J = 8.8 Hz, 1 H), 7.50–7.46 (m, 4 H), 7.36 (t, J = 8.1 Hz, 1 H), 7.18 (s, 1 H), 7.08 (d, J = 8.1 Hz, 2 H), 6.96 (t, J = 8.1 Hz, 1 H), 6.61 (d, J = 8.8 Hz, 1 H), 3.91 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 145.7, 144.9, 141.1, 138.1, 135.2, 134.2, 130.7, 130.4, 127.2, 126.9, 125.0, 124.9, 123.4, 122.1, 120.9, 119.7, 114.6, 114.4, 106.7, 55.5 ppm. HRMS (ESI+): calcd. for $C_{24}H_{16}N_2OS$ 380.0983; found 380.0985.

6-[4-(*tert*-Butyl)phenyl]benzo[4,5]imidazo[1,2-*a*]benzo[4,5]thieno-[2,3-*c*]pyridine (5s): Yellow crystals (158 mg, 78%); m.p. 202–204 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (dd, J = 3.0, 6.6 Hz, 1 H), 8.03 (dd, J = 2.2, 6.6 Hz, 1 H), 7.98 (d, J = 8.0 Hz, 1 H), 7.65–7.63 (m, 2 H), 7.57–7.56 (m, 2 H), 7.53–7.51 (m, 2 H), 7.41 (t, J = 8.0 Hz, 1 H), 7.35 (s, 1 H), 7.01 (td, J = 2.2, 7.3 Hz, 1 H), 6.62 (d, J = 8.7 Hz, 1 H), 1.47 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4, 145.7, 144.9, 141.1, 138.4, 135.3, 134.2, 131.6, 130.4, 129.1, 127.2, 125.9, 125.0, 124.9, 123.4, 122.1, 120.9, 119.7, 114.6, 106.7, 35.0, 31.4 ppm. HRMS (ESI+): calcd. for $C_{27}H_{22}N_2S$ 406.1504; found 406.1502.

6-(*p*-Tolyl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[2,1-*a*]isoquinoline (5t): Yellow solid (112 mg, 72%); m.p. 150–152 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 8.0 Hz, 1 H), 7.41–7.33 (m, 5 H), 6.94–6.90 (m, 1 H), 6.61 (d, J = 8.0 Hz, 1 H), 6.39 (s, 1 H), 3.16 (t, J = 5.7 Hz, 2 H), 2.79 (t, J = 6.5 Hz, 2 H), 2.52 (s, 3 H), 1.98–1.91 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 144.9, 139.7, 137.7, 137.6, 131.7, 129.8, 129.5, 129.0, 124.5, 123.5, 119.7, 119.3, 114.7, 114.4, 29.0, 24.3, 22.4, 22.2, 21.5 ppm. HRMS (ESI+): calcd. for $C_{22}H_{20}N_2$ 312.1626; found 312.1625.

X-ray Crystal Data for 5a: Crystallized in the orthorhombic crystal system with space group P 21 21 21 (petroleum ether/CH_2Cl_2). The single crystal X-ray data were collected using graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). The structures were solved using SHELXL-97 direct method and refined by the full-matrix least-squares technique on F^2 using the SHELXL-97 program within the WinGX v 1.80.05 software package. All hydrogen atoms were fixed at the calculated positions with isotropic thermal parameters, and all non-hydrogen atoms were refined anisotropically. Crystal data for **5a**: $C_{21}H_{14}N_2$; M_r = 294.34; orthorhombic group $P2_12_12_1$; a = 5.0768(6) Å, b = 14.411(2) Å, c = 20.257(3) Å, α = 90°, β = 90°, γ = 90°; V = 1482.1(3) Å^3; Z = 4; T = 293 K; $d_{calcd.}$ = 1.319 Mg/m^3; R_{int} = 0.0368, R_1 = 0.0420, wR_2 = 0.0639 [$I > 2\sigma(I)$], R_1 = 0.1306, wR_2 = 0.0796 (all data), GOF = 0.675. For further details on the crystal structure of compound **5a**, see the Supporting Information.

General Procedure for the Synthesis of Pyrrolo/Indolo-Quinoxalines 6a–m and 9: To a solution of *ortho*-alkynylaldehyde (**3**; 0.50 mmol), and amine [**4c–f**; 0.50 mmol, 1.0 equiv. (2.0 equiv. for **9**)] in H_2O (2.0 mL) was added $AgNO_3$ [8.0 mol-% (22 mol-% for **9**)] and the mixture was stirred at 85 °C for 7 h. After completion of reaction (indicated by TLC), H_2O (10 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (2 × 10 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under vacuum. The crude material was then purified by column chromatography on silica gel (100–200 mesh; petroleum ether/ethyl acetate) to afford the desired pure products (**6a–m**). Compounds **6b–c** have been previously reported.[26]

6-(3-Methoxyphenyl)-11b*H*-isoquinolino[2,1-*a*]pyrrolo[2,1-*c*]quinoxaline (6a): Colorless crystals (146 mg, 78%); m.p. 194–196 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (d, J = 7.8 Hz, 1 H), 7.28–7.14 (m, 6 H), 7.12–7.05 (m, 2 H), 6.88–6.71 (m, 2 H), 6.68–6.55 (m, 2 H), 6.44 (t, J = 3.3 Hz, 1 H), 6.28–6.26 (m, 2 H), 5.56 (s, 1 H), 3.74 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2, 143.3, 137.4, 133.6, 132.6, 132.4, 129.9, 127.9, 127.5, 126.1, 124.8, 124.6, 124.3, 123.4, 121.7, 119.9, 118.8, 117.0, 114.5, 114.4, 111.7, 110.4, 109.3, 107.9, 56.9, 55.4 ppm. HRMS (ESI+): calcd. for $C_{26}H_{20}N_2O$ 376.1576; found 376.1572.

6-[4-(Trifluoromethyl)phenyl]-11b*H*-isoquinolino[2,1-*a*]pyrrolo-[2,1-*c*]quinoxaline (6d): Colorless crystals (120 mg, 58%); m.p. 216–218 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 8.0 Hz, 2 H), 7.62 (d, J = 8.7 Hz, 2 H), 7.37–7.36 (m, 1 H), 7.31–7.28 (m, 2 H), 7.25–7.22 (m, 2 H), 7.18 (td, J = 1.5, 7.3 Hz, 1 H), 6.96 (d, J = 7.3 Hz, 1 H), 6.76 (t, J = 7.4 Hz, 1 H), 6.66 (td, J = 1.5, 8.0 Hz, 1 H), 6.52 (t, J = 2.9 Hz, 1 H), 6.36–6.35 (m, 1 H), 6.24 (d, J = 8.1 Hz, 1 H), 5.64 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.8, 139.1, 133.7, 132.1, 131.9, 128.5, 127.7, 126.3, 126.2, 126.0, 125.9, 125.2, 124.7, 124.3, 123.1, 120.4, 118.7, 118.6, 114.7, 114.6, 110.5, 108.1, 56.9 ppm. HRMS (ESI+): calcd. for $C_{26}H_{17}F_3N_2$ 414.1344; found 414.1344.

6-(3,5-Dimethoxyphenyl)-11b*H*-[1,6]naphthyridino[6,5-*a*]pyrrolo-[2,1-*c*]quinoxaline (6e): Yellow solid (162 mg, 80%); m.p. 232–234 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, J = 5.1 Hz, 1 H), 7.35–7.34 (m, 1 H), 7.27–7.24 (m, 2 H), 7.18 (d, J = 8.0 Hz, 1 H), 7.06–7.03 (m, 1 H), 6.98–6.97 (m, 2 H), 6.75 (t, J = 7.3 Hz, 1 H), 6.67 (t, J = 7.3 Hz, 1 H), 6.51–6.47 (m, 2 H), 6.37 (d, J = 8.0 Hz, 1 H), 6.33–6.32 (m, 1 H), 5.67 (s, 1 H), 3.77 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 151.9, 148.5, 147.8, 137.5, 132.3, 131.8, 128.7, 125.9, 124.5, 122.5, 122.2, 120.6, 119.2, 117.9, 114.9, 114.5, 110.6, 107.9, 104.6, 102.0, 56.6, 55.5 ppm. HRMS (ESI+): calcd. for $C_{26}H_{21}N_3O_2$ 407.1634; found 407.1645.

6-Phenyl-11b*H*-[2,6]naphthyridino[2,1-*a*]pyrrolo[2,1-*c*]quinoxaline (6f): Yellow solid (147 mg, 85%); m.p. 180–190 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (s, 1 H), 8.32 (d, J = 5.1 Hz, 1 H), 7.73 (d, J = 6.6 Hz, 2 H), 7.36–7.30 (m, 3 H), 7.22 (dd, J = 1.5, 6.6 Hz, 1 H), 7.18 (s, 1 H), 7.124–7.122 (m, 1 H), 6.85 (d, J = 5.1 Hz, 1 H), 6.70 (t, J = 7.3 Hz, 1 H), 6.59 (td, J = 1.5, 7.3 Hz, 1 H), 6.46 (t, J = 3.0 Hz, 1 H), 6.30–6.29 (m, 1 H), 6.25 (d, J = 8.0 Hz, 1 H), 5.49 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.8, 145.5, 144.9, 141.4, 135.1, 131.6, 129.4, 129.1, 128.7, 126.4, 125.9, 124.4, 121.6, 120.6, 119.5, 119.0, 114.9, 114.6, 113.0, 110.1, 108.2, 56.1 ppm. HRMS (ESI+): calcd. for $C_{24}H_{17}N_3$ 347.1422; found 347.1454.

6-Phenyl-13b*H*-benzo[2,3][1,6]naphthyridino[6,5-*a*]pyrrolo[2,1-*c*]-quinoxaline (6g): Yellow solid (158 mg, 80%); m.p. 214–216 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, J = 6.6 Hz, 1 H), 7.91 (s, 2 H), 7.67–7.62 (m, 3 H), 7.48–7.38 (m, 6 H), 7.32 (d, J = 7.8 Hz, 1 H), 6.76 (t, J = 7.2 Hz, 1 H), 6.67–6.58 (m, 2 H), 6.43–6.34 (m, 2 H), 5.89 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.6, 150.1, 147.8, 135.2, 132.2, 131.6, 129.9, 129.5, 129.2, 128.8, 127.9, 127.8, 126.7, 125.9, 124.6, 122.5, 120.7, 119.3, 117.9, 115.0, 114.7, 110.7, 108.1, 57.2 ppm. HRMS (ESI+): calcd. for $C_{28}H_{19}N_3$ 397.1579; found 397.1578.

7-(Thiophen-3-yl)benzo[*b*]benzo[4,5]imidazo[2,1-*f*][1,6]naphthyridine (6h): Yellow solid (167 mg, 83%); m.p. 210–214 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.6 Hz, 1 H), 7.68–7.60 (m, 3 H), 7.57–7.53 (m, 2 H), 7.40–7.38 (m, 4 H), 7.30 (d, J = 7.3 Hz, 1 H), 6.78 (t, J = 7.8 Hz, 1 H), 6.69 (t, J = 7.8 Hz, 1 H), 6.57 (t, J = 3.6 Hz, 1 H), 6.43 (d, J = 7.8 Hz, 2 H), 5.84 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5, 147.7, 145.6, 137.7, 132.4, 131.7, 129.5, 128.6, 128.3, 127.7, 127.1, 125.9, 125.2, 124.5, 122.6, 120.8, 118.9, 117.2, 114.9, 114.7, 110.6, 108.1, 56.9 ppm. HRMS (ESI+): calcd. for $C_{26}H_{17}N_3S$ 403.1143; found 403.1144.

17-Methyl-6-(*p*-tolyl)-17b*H*-indolo[1,2-*a*]isoquinolino[1,2-*c*]quinoxaline (6i): Colorless crystals (188 mg, 89%); m.p. 208–212 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (d, J = 8.1 Hz, 1 H), 7.83 (d, J = 8.1 Hz, 1 H), 7.72 (d, J = 7.8 Hz, 3 H), 7.38–7.29 (m, 3 H), 7.24–7.17 (m, 4 H), 7.14–7.09 (m, 1 H), 6.88–6.81 (m, 2 H), 6.67 (t, J = 7.8 Hz, 1 H), 6.43 (d, J = 7.8 Hz, 1 H), 5.71 (s, 1 H), 2.36 (s, 3 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.9, 138.9, 133.7, 133.3, 133.1, 132.8, 131.9, 130.5, 129.7, 128.7, 127.8, 127.7, 127.6, 126.1, 125.1, 124.6, 123.4, 122.7, 120.6, 120.4, 119.3, 118.9, 116.0, 115.8, 112.1, 109.4, 56.4, 21.3, 8.4 ppm. HRMS (ESI+): calcd. for $C_{31}H_{24}N_2$ 424.1939; found 424.1938.

6-(4-Methoxyphenyl)-17-methyl-17b*H*-indolo[1,2-*a*]isoquinolino-[1,2-*c*]quinoxaline (6j): Colorless crystals (200 mg, 91%); m.p. 238–240 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (d, J = 8.1 Hz, 1 H), 7.84–7.71 (m, 4 H), 7.73–7.19 (m, 4 H), 7.14–7.07 (m, 2 H), 6.93–6.81 (m, 4 H), 6.68 (td, J = 1.5, 8.1 Hz, 1 H), 6.42 (dd, J = 1.2, 7.8 Hz, 1 H), 5.70 (s, 1 H), 3.81 (s, 3 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.3, 143.6, 133.7, 133.3, 133.2, 131.8, 130.5, 128.8, 128.2, 127.9, 127.8, 127.6, 127.5, 124.9, 124.5, 123.4, 122.7, 120.6, 120.4, 119.3, 118.9, 116.0, 114.8, 114.4, 112.1, 109.4, 56.4, 55.3, 8.41 ppm. HRMS (ESI+): calcd. for $C_{31}H_{24}N_2O$ 440.1889; found 440.1887.

17-Methyl-6-(4-phenoxyphenyl)-17b*H*-indolo[1,2-*a*]isoquinolino-[1,2-*c*]quinoxaline (6k): Light-yellow solid (201 mg, 80%); m.p. 164–168 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, J = 8.1 Hz, 1 H), 7.84–7.78 (m, 3 H), 7.72 (d, J = 7.3 Hz, 1 H), 7.36–7.29 (m, 5 H), 7.27–7.21 (m, 2 H), 7.18 (s, 1 H), 7.14–7.10 (m, 2 H), 7.05–6.99 (m, 3 H), 6.88–6.84 (m, 2 H), 6.71 (td, J = 1.5, 8.4 Hz, 1 H), 6.45 (d, J = 8.0 Hz, 1 H), 5.71 (s, 1 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 156.6, 143.3, 133.7, 133.2, 133.0, 131.8, 130.5, 130.4, 129.8, 128.6, 127.9, 127.8, 127.7, 125.1, 124.6, 123.7, 123.4, 122.7, 120.6, 120.5, 119.3, 119.2, 118.9, 118.8, 116.1, 115.8, 112.0, 109.5, 56.4, 8.4 ppm. HRMS (ESI+): calcd. for $C_{36}H_{26}N_2O$ 502.2045; found 502.2046.

10-Fluoro-17-methyl-6-phenyl-17b*H*-indolo[1,2-*a*]isoquinolino-[1,2-*c*]quinoxaline (6l): Off-white solid (192 mg, 90%); m.p. 202–204 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.1 Hz, 1 H), 7.83–7.81 (m, 2 H), 7.72 (d, J = 7.2 Hz, 1 H), 7.55 (dd, J = 2.4, 9.9 Hz, 1 H), 7.41–7.31 (m, 6 H), 7.29–7.23 (m, 2 H), 7.15 (t, J = 7.5 Hz, 1 H), 6.86 (d, J = 7.5 Hz, 1 H), 6.41–6.30 (m, 2 H), 5.70 (s, 1 H), 2.32 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 155.7, 143.8, 135.4, 133.7, 132.8, 131.6, 130.7, 129.2, 129.0, 128.6, 128.4, 128.1, 127.8, 126.1, 125.3, 124.5, 123.1, 121.1, 119.6, 119.2, 116.7, 111.8, 110.1, 109.4, 103.8, 56.4, 8.4 ppm. HRMS (ESI+): calcd. for $C_{30}H_{21}FN_2$ 428.1689; found 428.1668.

6-(4-Methoxyphenyl)-17b*H*-indolo[1,2-*a*]isoquinolino[1,2-*c*]quinoxaline (6m): Off-white solid (95 mg, 45%); m.p. 162–164 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 8.0 Hz, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.69 (d, J = 8.8 Hz, 3 H), 7.28 (td, J = 1.5, 8.5 Hz, 1 H), 7.22–7.12 (m, 3 H), 7.06–7.02 (m, 2 H), 6.93 (d, J = 8.1 Hz, 1 H), 6.85–6.77 (m, 3 H), 6.64 (t, J = 5.8 Hz, 2 H), 6.37 (dd, J = 1.5, 8.1 Hz, 1 H), 5.65 (s, 1 H), 3.75 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 143.3, 134.0, 133.5, 132.9, 132.2, 132.1, 129.8, 128.0, 127.6, 127.5, 127.4, 124.7, 124.6, 123.8, 122.6, 122.0, 121.1, 120.4, 119.2, 116.3, 114.9, 114.3, 114.1, 112.2, 102.2, 57.8, 55.3 ppm. HRMS (ESI+): calcd. for $C_{30}H_{22}N_2O$ 426.1732; found 426.1732.

6-[4-(11b*H*-Isoquinolino[2,1-*a*]pyrrolo[2,1-*c*]quinoxalin-6-yl)phenyl]-11b*H*-isoquinolino[2,1-*a*]pyrrolo[1,2-*c*]quinazoline (9): Yellow solid (190 mg, 62%); m.p. 194–196 °C (petroleum ether/EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, J = 5.1 Hz, 4 H), 7.29–7.28 (m, 2 H), 7.22–7.06 (m, 10 H), 6.87 (d, J = 7.3 Hz, 2 H), 6.67 (t, J = 7.3 Hz, 2 H), 6.58 (td, J = 1.6, 7.3 Hz, 2 H), 6.46–6.44 (m, 2 H), 6.29–6.25 (m, 4 H), 5.56 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.8, 142.6, 136.0, 135.9, 133.6, 132.6, 132.4, 127.9, 127.6, 126.8, 126.7, 126.2, 124.9, 124.6, 124.3, 124.2, 123.4, 123.3, 120.1, 118.8, 118.8, 117.11, 117.06, 114.6, 114.5, 110.4, 107.9, 56.9 ppm. HRMS (ESI+): calcd. for $C_{44}H_{30}N_4$ 614.2470; found 614. 2471.

1,4-Bis(benzo[4,5]imidazo[2,1-*a*]isoquinolin-6-yl)benzene (10): Yellow solid (153 mg, 60%); m.p. 206–208 °C (petroleum ether/EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.94 (dd, J = 3.5, 6.5 Hz, 2 H), 8.09–8.03 (m, 2 H), 7.90 (d, J = 5.8 Hz, 4 H), 7.76–7.73 (m, 4 H), 7.23 (d, J = 7.3 Hz, 1 H), 7.16–7.11 (m, 3 H), 7.04 (s, 1 H), 6.75–6.71 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 144.4, 136.5, 134.7, 131.4, 130.3, 129.9, 128.3, 126.8, 125.2, 124.5, 123.1, 121.3, 120.2, 116.7, 113.9, 113.4 ppm. HRMS (ESI+): calcd. for $C_{36}H_{22}N_4$ 510.1844; found 510.1844.

2-[2-(Phenylethynyl)phenyl]-1*H*-benzo[*d*]imidazole (U): Colorless crystals (124 mg, 85%); m.p. 120–122 °C (petroleum ether/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.96 (s, 1 H, NH), 8.58 (d, J = 8.0 Hz, 1 H), 7.87–7.85 (m, 1 H), 7.69 (dd, J = 1.4, 6.0 Hz, 1 H), 7.62–7.58 (m, 2 H), 7.52 (td, J = 1.4, 6.0 Hz, 1 H), 7.48–7.43 (m, 5 H), 7.31–7.28 (m, 2 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O): δ = 8.56 (d, J = 8.0 Hz, 1 H), 7.87–7.84 (m, 1 H), 7.68 (dd, J = 1.4, 7.3 Hz, 1 H), 7.61–7.58 (m, 2 H), 7.51 (td, J = 1.4, 7.3 Hz, 1 H), 7.49–7.42 (m, 5 H), 7.32–7.28 (m, 2 H), 4.75 (s, 1 H, DOH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.5, 133.7, 131.4, 130.6, 129.6, 129.5, 129.4, 129.3, 128.9, 123.4, 122.7, 122.0, 119.8, 119.2, 110.8, 94.7, 89.1 ppm. HRMS (ESI+): calcd. for $C_{21}H_{14}N_2$ 294.1157; found 294.1155.

X-ray Data for Compound U: Crystallized in the monoclinic crystal system with space group P 1 21/n 1. The single-crystal X-ray data were collected using graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). The structures were solved using SIR-92 and refined by the full-matrix least-squares technique on F^2 using the SHELXL-97 program within the WinGX v 1.80.05 software package. All non-hydrogen atoms were refined anisotropically. Crystal data for **U**: $C_{21}H_{14}N_2$; M_r = 294.34; monoclinic group; $P12_1/n1$; a = 11.0361(9) Å, b = 18.5228(12) Å, c = 15.9836(13) Å, α = 90°, β = 104.253(8)°, γ = 90°; V = 3166.8(4) Å^3; Z = 8; T = 298(2) K; $d_{calcd.}$ = 1.235 Mg/m^3; R_{int} = 0.0368, R_1 = 0.0624, wR_2 = 0.1280

[$I > 2\sigma(I)$], $R_1 = 0.0943$, $wR_2 = 0.1425$ (all data), GOF = 1.051. For further details on the crystal structure of compound **U**, see the Supporting Information.

Supporting Information (see footnote on the first page of this article): NMR spectroscopic data of the starting compounds; copies of the ^{1}H NMR, ^{13}C NMR, and HRMS spectra of all compounds.

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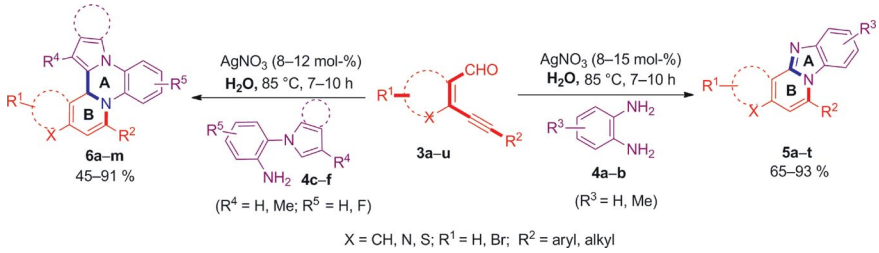

An eco-friendly, one-pot cascade approach to benzimidazoles and quinoxalines in water using $AgNO_3$ as catalyst from *o*-alkynyl aldehydes and amines with tethered nucleophiles, has been developed. Selective *6-endo-dig* regioselectivity and structural diversity are accomplished in good yields with a range of substrates. X-ray crystallographic studies and mechanistic experiments are also presented.

Keywords: Electrophilic substitution / Domino reactions / Cyclization / Polycycles / Silver

