Chinese Chemical Letters 35 (2024) 109533

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Rh(III)-Catalyzed sequential ring-retentive/-opening [4 + 2] annulations of 2*H*-imidazoles towards full-color emissive imidazo[5,1-*a*]isoquinolinium salts and AIE-active non-symmetric 1,1′-biisoquinolines

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ARTICLE INFO

Article history:
Received 12 October 2023
Revised 8 January 2024
Accepted 15 January 2024
Available online 22 January 2024

Keywords:
C–H activation/annulation
2*H*-Imidazole
Imidazo[5,1-*a*]isoquinolinium
1,1′-Biisoquinolines
Full-color emission
Ring-retentive/-opening

ABSTRACT

Rhodium-catalyzed $C4_{aryl}-H$ activation and ring-retentive annulation of 2*H*-imidazoles with internal alkynes to build imidazo[5,1-*a*]isoquinolinium salts with high yields and broad scope has been disclosed. These novel salts serve as new full-color emissive fluorophores (433–633 nm), just by simply modifying the substituents on C3 and C4 positions of isoquinoline ring. Furthermore, these salts can undergo ring-opening $C5_{aryl}-H$ activation/annulation with a different alkyne to form non-symmetric and AIE-active 1,1′-biisoquinolines, where NH_4OAc plays an indispensable role that accounts for Hofmann elimination and imine formation, leading to an unprecedented imine dance: cyclic imine → N-alkenyl imine → NH imine. The ^{15}N labelling experiments indicate that the 2nd annulation includes two pathways: N-exchange (major) and N-retention (minor).

Heteroarene-directed transition-metal-catalyzed C–H bond activation/annulation reactions have been emerging as one of the versatile toolboxes to construct extended π-conjugated polycyclic heteroaromatic molecules (PHAs) [1]. These processes are considered atom- and step-economic compared to external directing group (EDG)-mediated C–H activation and traditional cross-coupling because the heteroarene can act as intrinsic directing group (DG) that do not require preinstalling/removing an DG or any prefunctionalization [2–5]. Notably, they offer an ample opportunity to construct cationic *N*-heterocyclic salts [6–9], which otherwise are always challenging *via* traditional methods. In this regard, Cheng [10–12], Choudhury [13–15], Wang [16–18], Huang [19], Davies & Macgregor [20], Saa [21], Li [22] and You [23] have independently made considerable efforts on the synthesis of fused isoquinolinium salts through the assist with aryl heterocycles like imidazole, pyrrole, pyridine, pyrazine, quinazolinone, and so on.

Among the above *N*-heterocycles, imidazole attracts our interest more, because it is an innate DG core with all the five atoms prone to act as directing site. For instance, the C–H annulations of N1/3-aryl [13-15,24-26] and C2-aryl [27–29] in 1*H*-imidazoles have been well documented. In 2023, our group realized the first example of C–H activation/annulation of C4(5)-aryl in 1*H*-imidazoles [30]. In addition, Dong [31–35] and Cui [36] reported the seminal work on $C4_{aryl}-H$ activation of C4(5)-aryl-2*H*-imidazoles to form neutral products, 1-acyl isoquinolines (Scheme 1a) and spiroimidazole-indenes (Scheme 1b), in which only one of the two (C4 and C5) aryls could be activated. Despite this growing interest in C–H annulation of 2*H*-imidazoles, the construction of cationic molecules, 2*H*-imidazolium salts, and their photophysical properties have not been researched. Moreover, among the massive cationic fluorophores [9], full-color emissive skeleton is rare [37]. Considering the cationic nitrogen-embedded polycyclic aromatic hydrocarbons (cNe-PAHs) have many potential applications, for example, in fuel cells, semiconductors, and liquid crystals [38–41], the synthesis of 2*H*-imidazole-based cNe-PAHs should be appealing.

Encouraging by these seminal works along with our interesting in *N*-heterocycles construction [42–44], we propose that the [4 + 2] annulation of 4,5-diaryl-2*H*-imidazoles with alkynes could stop just after the reductive elimination, forming imidazo[5,1-*a*]isoquinolinium (IMIQ) salts (Scheme 1c). These new cNe-PAHs have been demonstrated to exhibit continuously tunable full-color emissions (433–633 nm). Interestingly, the cNe-PAHs can further transform into neutral, non-symmetric, axial,

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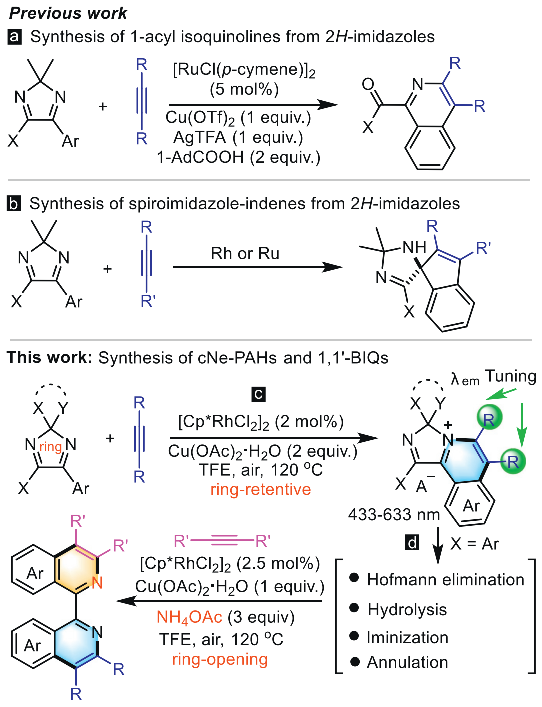
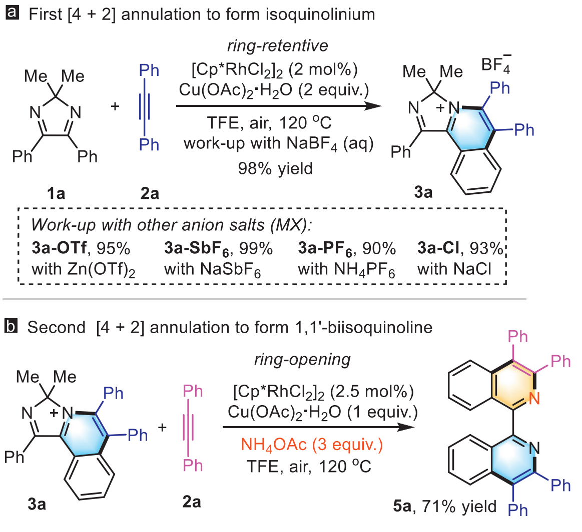
https://doi.org/10.1016/j.cclet.2024.109533



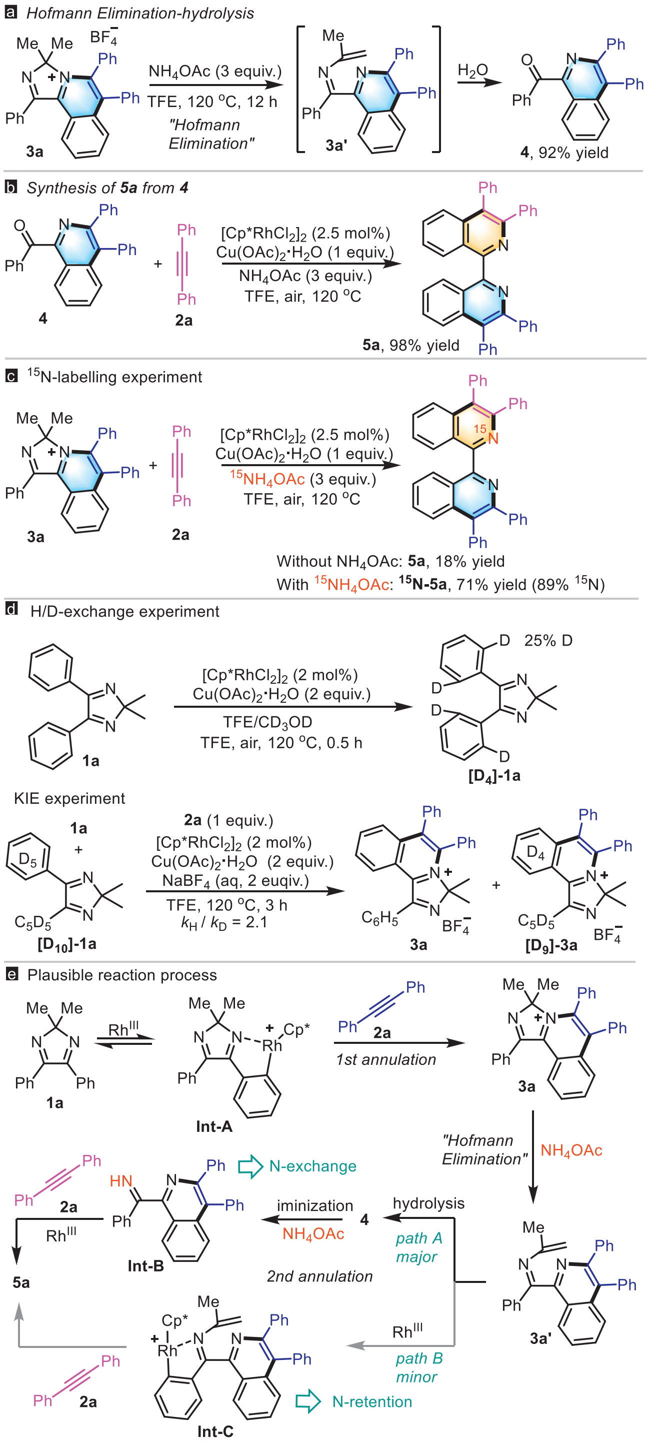
Scheme 1. C-H activation/annulation of 2*H*-imidazoles.

and aggregation-induced emission (AIE) active *N,N*-bidentate ligands, 1,1′-biisoquinolines (1,1′-BIQs, Scheme 1d), which are always challenging *via* previous C–H activation/1,3-diyne strategy that giving 3,3′-, 3,4′-, and 4,4′-BIQs [45–48]. After the mechanistic insights with ESI-MS and ^{15}N-labelling studies, we found that the ring-opening [4+2] annulation proceeds through two simultaneous routes: (a) NH_4OAc-promoted Hofmann elimination → hydrolysis → iminization → annulation; (b) NH_4OAc-promoted Hofmann elimination → annulation.

Initially, 4,5-diphenyl-2*H*-imidazole **1a** and diphenylacetylene **2a** were selected as the model substrates to react under our previous conditions of Rh/Cu(OTf)$_2$, but only trace amount of annulative product **3a** was observed (see Supporting information). To our delight, the C4$_{aryl}$–H activation/*N*-annulation occurred smoothly when presenting Rh/Cu(OAc)$_2$, giving imidazo[5,1-*a*]isoquinolinium tetrafluoroborate **3a** in a high yield of 98% after working-up with $NaBF_4$ for anion-exchange (Scheme 2a). Notably, working up with other different simple non-silver salts accessed the IMIQs with various anions such as OTf, SbF_6, PF_6, and Cl conveniently (all > 90% yield). More interestingly, **3a** could further react with one molecule of **2a** to afford ring-opening product, 1,1′-BIQ **5a** (71% yield), in the presence of Rh/Cu(OAc)$_2$/NH_4OAc (Scheme 2b).

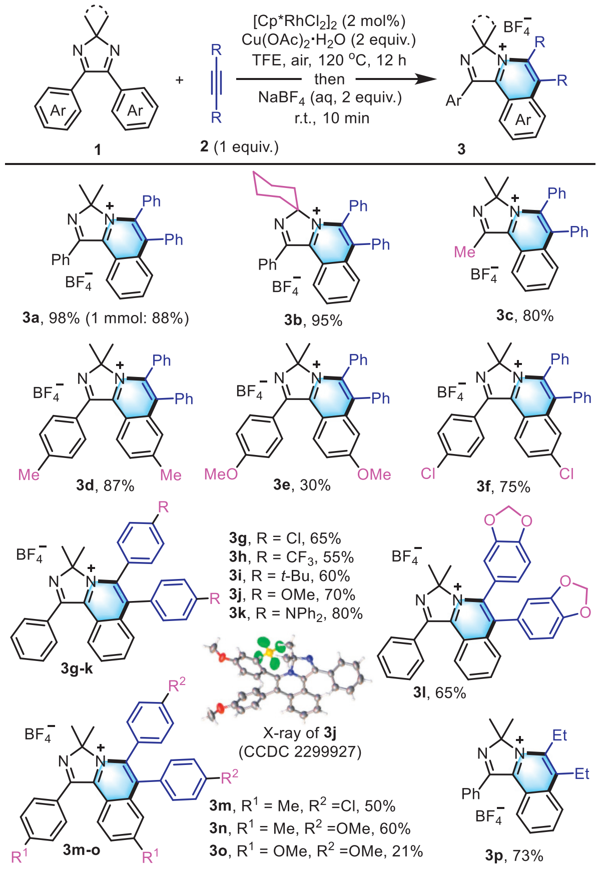


Scheme 2. Reaction evolution.



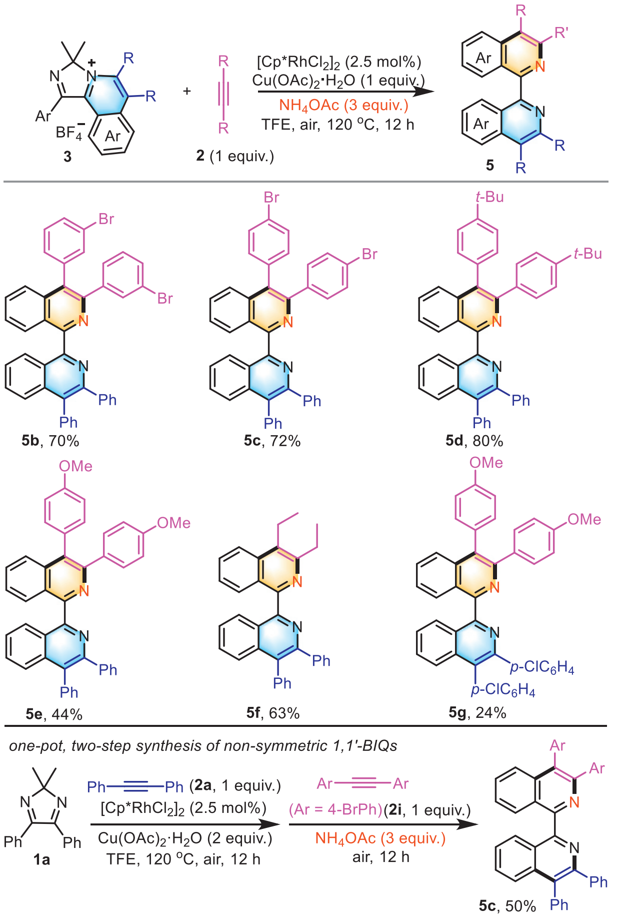
Scheme 3. Mechanistic studies.

It is noted that **3a** could transform into 1-benzoyl isoquinoline **4** just by dealing with NH_4OAc, proceeding through Hofmann elimination (giving *N*-alkenyl imine **3a′**) and hydrolysis (Scheme 3a). Thus, both **3a** and **3a′** are vital intermediates in the generation of **4** from **1a** and **2a**, while **3a** was not mentioned in Dong's report [32]. Furthermore, compound **4** reacted with **2a** smoothly to form 1,1′-BIQ **5a** in quantitative yield (Scheme 3b). **5a** was still ob-



Scheme 4. Synthesis of isoquinolinium salts. Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol), $[Cp^*RhCl_2]_2$ (2 mol%) and $Cu(OAc)_2\cdot H_2O$ (2 euqiv.) were stirred in TFE (2 mL) at 120 °C for 12 h under air, then $NaBF_4$ (2 equiv.) in H_2O (1 mL) was added to stir at room temperature for 10 min, isolated yields.

tained in 18% yield without addition of NH_4OAc, showing that the other N atom in 2*H*-imidazole can also act as a directing group to happen a second annulation (Scheme 3c). Then some isotope labeling experiments were conducted to gain more insights into the mechanism. Interestingly, a high but not full ^{15}N-labelling ratio (89%) was received, identifying that the N atom of the second isoquinoline ring mainly came from NH_4OAc and minor came from initial 2*H*-imidazole (Scheme 3c). Deuterium incorporation of 25% was observed at the ortho position of **1a** in a H/D exchange experiment, indicating the first C—H activation is reversible. Moreover, kinetic isotope effect (KIE) of $k_H/k_D \approx 2.1$ was obtained from the first annulation, showing that cleavage of the C—H bond may be involved in the rate-determining step (Scheme 3d). In this regard, the mechanism of current reaction is proposed (Scheme 3e). As in the first [4+2] annulation, the metalation and reversible C—H activation forms five-membered rhodacycle **Int-A**, which undergoes alkyne insertion and reductive elimination to give cationic salt **3a**. Distinctively, the second [4+2] annulation for the generation of 1,1′-BIQ **5a** from **3a** may include two pathways. First, *N*-alkenyl imine **3a′** is afforded through Hofmann elimination, which then drives two pathways (A and B). As in path A, **3a** hydrolyze into ketone **4**, followed by ketone-amine condensation to generate NH imine **Int-B**, which directs the second annulation with **2a** to give final product **5a** with a N-exchange manner (major). As in path B, *N*-alkenyl imine **3a′** can directly guide a C—H activation to form rhodacycle **Int-C**, which undergoes alkyne insertion and reductive elimination to deliver **5a** with a N-retention manner (minor).



Scheme 5. Synthesis of unsymmetric 1,1′-BIQs. Reaction conditions: **3** (0.1 mmol), **2** (0.1 mmol), NH_4OAc (3 equiv.), $[Cp^*RhCl_2]_2$ (2.5 mol%) and $Cu(OAc)_2\cdot H_2O$ (2 equiv.) in TFE (2 mL) at 120 °C for 12 h under air.

On the basis of the optimal reaction conditions and mechanistic studies, a series of IMIQ salts were prepared first (Scheme 4). **3a** could be also isolated in a high yield of 88% on 1 mmol scale. Spiro 2*H*-imidazole **1b** was tolerated well to yield **3b** in high yield of 95%. Non-symmetric 2,2,4-trimethyl-5-phenyl-2*H*-imidazole **1c** reacted with **2a** furnished **3c** in 80% yield. The 2*H*-imidazoles bearing Me, OMe, and Cl substituents reacted with **2a** gave **3d-f** in 87%, 30%, and 75% yield, respectively. Both electron-deficient and electron-rich alkynes were compatible well and afforded the title products (**3g-k**) in good yields. Multiple functionalized salts **3m-o** were smoothly received in 21%-60% yields. Alkyl-alkyl alkyne was intact, giving **3p** in 73% yield.

Next, the resultant IMIQ salts (**3**) were selected to react with another different alkynes with the aid of NH_4OAc, accessing non-symmetric 1,1′-BIQs (Scheme 5). Through the catalytic system of $[Cp^*RhCl_2]_2/Cu(OAc)_2/NH_4OAc$, non-symmetric 1,1′-BIQs **5b-f** were obtained in 44%-80% yields (Scheme 5). Like Br, *t*-Bu, and OMe were all intact in this novel ring-opening C—H activation and annulation. Aryl-alkyl product 3,4-diethyl-3′,4′-diphenyl-1,1′-biisoquinoline **5f** was gained in 63% yield. Multiple substituted 1,1′-BIQ **5g** was isolated in relatively low yield. Notably, such non-symmetric 1,1′-BIQs can also be obtained from 2*H*-imidazole **1** and two molecules of **2** through one-pot, two-step double C—H annulation (*e.g.*, **5c** with 50% yield). These non-symmetric 1,1′-BIQs may serve as a class of privileged bidentate ligands in organic synthesis [49].

With a series of novel IMIQ salts and non-symmetric 1,1′-BIQs in hand, the photophysical properties of these interesting scaffolds were studied. To clarify the fluorescence-structure relationship of IMIQ salts, the representative data are listed

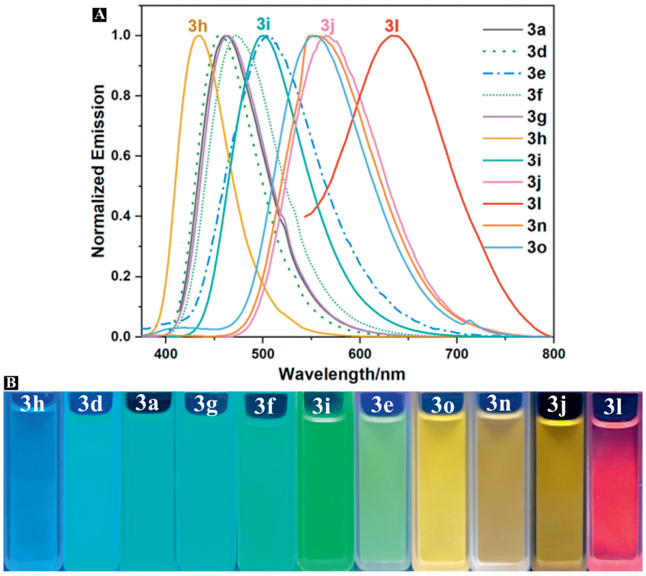
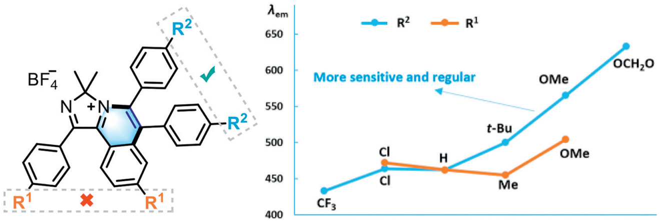


Fig. 1. (A) PL spectra of compounds **3a-o** in CH_2Cl_2 (10 μmol/L). (B) The photos of **3a-o** in CH_2Cl_2 (10 μmol/L) under 365 nm UV light.

Table 1
Fluorescence emission maxima of selected IMIQ salts.[a]



Entry	R^1	R^2	IMIQ (**3**)	λ_{em} (nm)
1	H	H	**3a**	462
2	Me	H	**3d**	455
3	OMe	H	**3e**	504
4	Cl	H	**3f**	472
5	H	Cl	**3g**	464
6	H	CF_3	**3h**	433
7	H	*t*-Bu	**3i**	500
8	H	OMe	**3j**	565
9	H	OCH_2O	**3l**	633
10	Me	OMe	**3n**	555
11	OMe	OMe	**3o**	551

[a] Measurements were performed in CH_2Cl_2 (10 μmol/L).

in Table 1 and Fig. 1. The impact of the R^1 substituent on C4 and C5 aryl of imidazole moiety is unordered. For instance, methyl (**3d**) shows a weak blue-shift while methoxy (**3e**) and chloro (**3f**) have red-shifts. In contrast, impact of the R^2 substituent is ordered and significant. For instance, an increase in the electron-withdrawing ability [50] from Cl (**3g**) to CF_3 (**3b**) enables a hypsochromic shift of emission wavelengths from 464 nm to 433 nm. Taking H as the reference R^1 substituent, the alteration of the R^2 substituent from H (**3a**) to electron-donating *t*-Bu (**3i**) and methoxy (**3j**) induce an obvious bathochromic shift of emission wavelengths from 462 nm to 500 and 565 nm, respectively. If locking R^2 as OMe and changing R^1 from H (**3j**) to Me (**3n**) and OMe (**3o**), the emission wavelengths only slightly change but do not enhance. The result indicates that the fluorescence of IMIQ is more sensitive on the group in C3 and C4 positions of isoquinoline moiety than that in other sites. Accordingly, a more electron-donating group ($-OCH_2O-$) was introduced, and the emission maximum of **4l** red-shifts to 633 nm. While **3k** with strong electron-donating *N,N*-diphenylamino (DPA) was non-emissive in the visible light region. In general, the current imidazo[5,1-*a*]isoquinolinium salts serve as new fluorophores with tunable full-color emissions (blue to red, 433–633 nm).

Moreover, the photophysical properties of non-symmetric 1,1′-BIQs were tested. We previously found that this kind of compounds were AIE active [42]. As **5e** and **5g** were determined before, AIE properties of new compounds **5b-d** and **5f** were tested. As shown in Fig. 2A, the solution of **5d** in THF showed faint photoluminescence (PL). Increasing the water fraction (f_W) to 95% allowed a significant emission signal peaking at 433 nm to be detected. The fluorescence intensity had an approximately 20-fold enhancement when f_W increased to 97% (Fig. 2B). Although the solution at this stage ($f_W = 97\%$) is still clear under ambient light, the Tyndall phenomenon shows the formation of the nano-sized aggregates. **5b**, **5c** and **5f** were also proved to be AIE-active with 7.8-, 12.2-, and 1.8-folds enhancement of intensities, respectively (Supporting information).

In summary, the rhodium-catalyzed $C4(5)_{aryl}-H$ activation and ring-retentive annulation of 2*H*-imidazoles with internal alkynes to build imidazo[5,1-*a*]isoquinolinium (IMIQ) salts with high yields and broad scope has been disclosed. These novel IMIQ salts serve as new full-color emissive fluorophores with emission wavelengths raging of 433–633 nm, just by simply modifying the substituents on C3 and C4 positions of isoquinoline ring. Furthermore, the cationic IMIQ salts can react with another different alkynes and NH_4OAc, through ring-opening annulation, to give non-symmetric and AIE-active 1,1′-biisoquinolines (1,1′-BIQs), in which NH_4OAc accounts for Hofmann elimination and imine formation, thus leading to an unprecedented imine dance: cyclic imine → *N*-alkenyl imine → NH imine. This transformation includes two pathways of N-exchange (major) and N-retention (minor), offering a convenient route to ^{15}N labelled 1,1′-BIQs. Further applications of the process developed in this effort are currently under study.

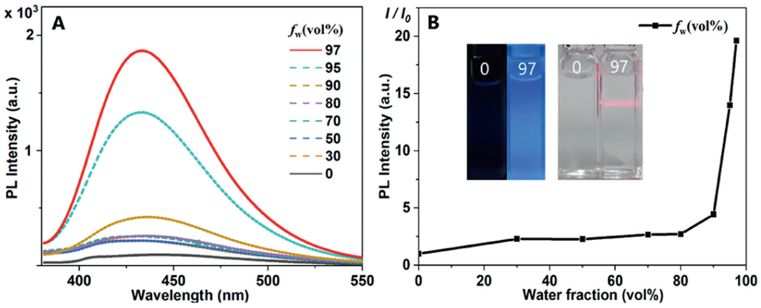


Fig. 2. (A) PL spectrum of **5d** in THF and THF/water mixtures (10 μmol/L) with different water fractions (f_w). (B) Plots of relative maximum emission intensity (I/I_0) of **5d** *versus* the solvent composition of THF/water mixture. Inset: (left) photos of **5d** at $f_w = 0$ and 97% under 365 nm UV light; (right) the Tyndall phenomenon.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We are grateful for the financial support from the National Natural Science Foundation of China (Nos. 22261013 and 22001049), Guangxi Natural Science Foundation (No. 2020GXNSFBA297003), and Magneto-Chemical Functional Materials (No. EMFM20221102). The authors also thank Prof. Ming-Hua Zeng (GXNU) for helpful ESI-MS analysis.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.109533.

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