

Cite this: *Chem. Sci.*, 2023, 14, 13446

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Mechanistic insights into an NH₄OAc-promoted imine dance in Rh-catalysed multicomponent double C–H annulations through an N-retention/exchange dual channel†

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Developing new and understanding multicomponent reactions (MCRs) is an appealing but challenging task. Herein, Rh(III)-catalyzed multicomponent double C–H annulations of cyclic diimines (or diketones and acetone), alkynes, and ammonium acetate to assemble functionalized 1,1'-biisoquinolines and C-bridged 1,1'-bisisoquinolines with controllable ¹⁴N/¹⁵N editing in one shot has been developed. Through a combination of isotopic-labeling (²H, ¹⁸O, and ¹⁵N) experiments, crystallography, and time-dependent ESI-MS, the reaction process was studied in detail. Ammonium acetate accounts for two rounds of Hofmann elimination and iminization, thus leading to an unprecedented imine dance, cyclic imine → *N*-alkenyl imine → NH imine. The *N*-alkenyl imine can immediately guide a C–H annulation (N-retention channel), and some of it is converted into NH-imine to trigger another annulation (N-exchange channel). The channels and ¹⁵N ratios can be regulated by the reaction mode and acidity. Moreover, the resulting 1,1'-biisoquinolines are a privileged ligand scaffold which is exemplified herein by a hydrazine–iodine exchange reaction to form drug-like benzo[*c*]cinnolines.

Received 26th July 2023
Accepted 25th October 2023

DOI: 10.1039/d3sc03861k

rsc.li/chemical-science

Introduction

Catalytic multicomponent reactions (MCRs) serve as an efficient and powerful strategy for the rapid editing of molecular complexity in a single operation, thus expanding the synthetic toolbox for assembling natural products, drugs, and materials.¹ Hence, developing new highly ordered catalytic MCRs, especially from simple/commercially available raw materials, is being actively pursued. The tracking and understanding of MCRs are even more appealing yet challenging tasks. Fortunately, a combination of techniques, like crystallography and ESI-MS, has been cooperatively applied to study the processes of complex reactions.^{2,3} For example, time-dependent ESI-MS (TD

ESI-MS) by sampling at multiple time points can offer more information than simple HRMS at a single time.⁴ However, using these combined techniques in organic MCRs is rare.⁵

On the one hand, Rh-catalyzed C–H annulation has been developed as an efficient and frequently-used method to access *N*-heterocycles;⁶ but multicomponent cyclization *via* Rh catalysis is underdeveloped,⁷ especially for four or more component reactions. Recently, Li *et al.* realized a C–H activation/dual-directing group (DDG) strategy for multi-component C–H annulations to construct 1,1'-biisoquinolines (1,1'-BIQs)⁸ which cannot be obtained from the known C–H activation/1,3-diene strategy.^{9–12} These linear DDGs may form bidentate ligands to poison the metal catalyst; and other unwanted *Z/E* isomers may also be generated in their preparation. Besides, the mechanism was not studied in detail and access to C-bridged counterparts has not been documented. Consequently, we turn our attention to cyclic DDGs which can perfectly avoid these problems. Readily available 4,5-diaryl 2*H*-imidazole is an ideal cyclic DDG platform that may undergo doubly directed C–H annulations at the two aryls. Nonetheless, only two-component mono [4 + 2]¹³ and [3 + 2]¹⁴ annulations with alkynes/alkenes to obtain isoquinolines and spiroimidazole-indenes have been reported (Scheme 1a), and the mechanism of such transformations remains ambiguous. Dong assumed a direct process of **Int-B** → **Int-C'** *via* reductive elimination (RE, Scheme 1b, path A),^{13a} but the vital middle **Int-C** was not mentioned/identified. In

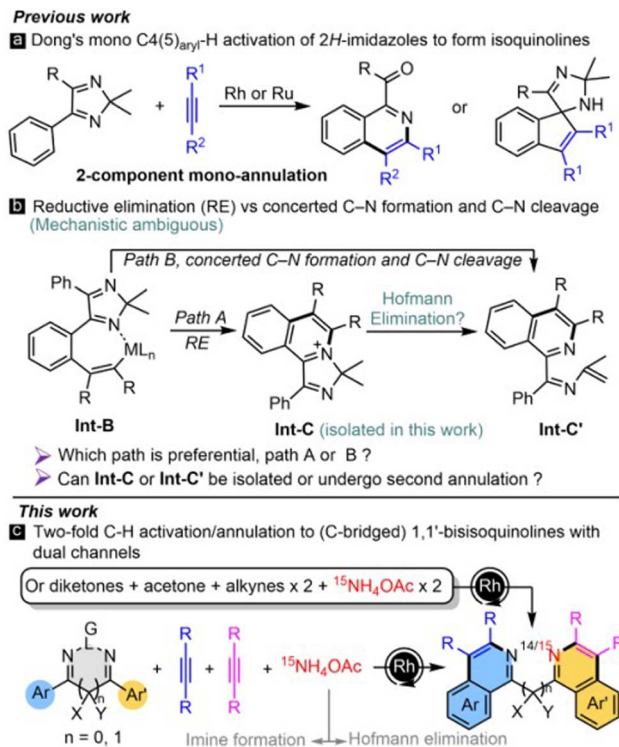
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† Electronic supplementary information (ESI) available: Experimental procedures, NMR data and crystallographic data. CCDC 2266530. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3sc03861k>

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Scheme 1 C–H activation of 2*H*-imidazoles and our design.

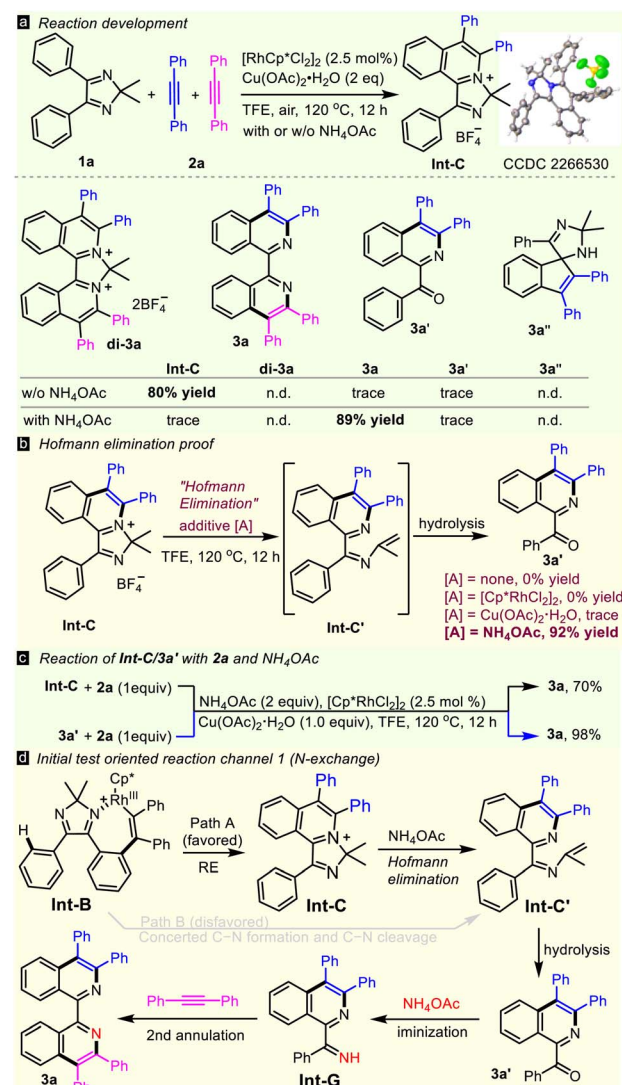
addition, the annulation of *N*-protected imines with alkynes has been mechanistically problematic for a long time, because the true paths of the two processes (path A *via* reductive elimination; path B *via* concerted C–N formation and C–N cleavage) are not yet clear (Scheme 1b).¹⁵ Obviously, isolation/determination of the cationic **Int-C** can provide direct evidence.¹⁶ Encouraged by this pioneering work, we would like to develop novel MCRs based on cyclic DDGs and to fill in the blank in the bundled mechanism.

On the other hand, NH₄OAc is a useful inorganic reagent in Rh-catalyzed three-component reactions to form isoquinolines,⁷ in which it just plays a single role of *NH*-imine formation, and ¹⁵N-labelled products are not involved. Herein, we disclose novel four/six-component reactions to assemble 1,1'-BIQs and C-bridged 1,1'-bisisoquinolines, containing dual *N*-retention and *N*-exchange channels, *via* a C–H activation/DDG strategy (Scheme 1c). The mechanism is studied in detail by a combination of isotopic labeling, crystallography, and TD ESI-MS, demonstrating NH₄OAc as a multifunctional reagent to promote two rounds of Hofmann elimination and iminization, leading to an unprecedented imine dance. ¹⁵N incorporation can be controllably edited by the two channels and is affected by reaction mode and acidity. Moreover, the current 1,1'-BIQ ligand platform shows powerful catalytic activity in Cu-catalyzed diarylation to form benzo[*c*]cinnolines.

Results and discussion

Initially, 4,5-diphenyl-2*H*-imidazole **1a** and two molecules of diphenylacetylene **2a** were subjected to a simple Rh(III)/Cu

catalytic system (Scheme 2a), but none of the complex transformations, of double annulated compound (**di-3a**), 1,1'-BIQ **3a**, acyl isoquinoline **3a'** or spiral product **3a''** occurred. In contrast, the reaction happened to stop at the first annulation, giving mono-cationic product **Int-C** in a high yield, as determined by X-ray diffraction (CCDC 2266530).¹⁷ Interestingly, 1,1'-BIQ **3a** was obtained solely in 89% yield when 2 equiv. of NH₄OAc was added. Optimization of the reaction parameters, such as *N*-sources, catalysts, oxidants, and solvents, led to give **3a** in the highest yield of 93% in the presence of NH₄OAc (2 equiv.), [Cp*RhCl₂]₂ (2.5 mol%) and Cu(OAc)₂·H₂O (1 equiv.) in TFE in air at 120 °C for 12 hours (see Table S1 in the ESI†). With treatment of **Int-C** with a single additive, such as [Cp*RhCl₂]₂, Cu(OAc)₂, or NH₄OAc, under thermodynamic conditions, only NH₄OAc successfully gave ring-opening product **3a'** in 92% yield, showing that NH₄OAc is the true promoter of Hofmann elimination (Scheme 2b). Both **Int-C** and **3a'** can transform to **3a** in the presence of alkyne **2a** and NH₄OAc (Scheme 2c), hinting that they are key intermediates in this double C–H activation.



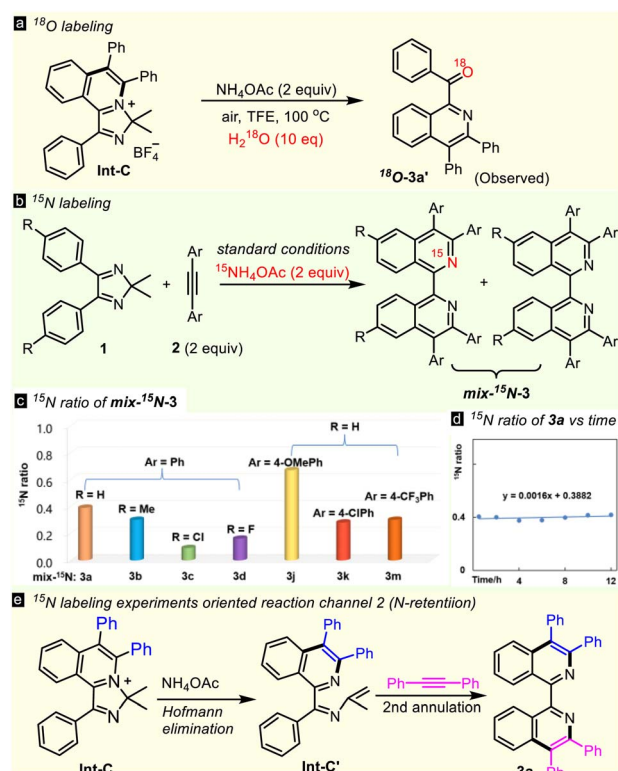
Scheme 2 Initial reaction tests and mechanistic study.

These results lead to the hypothesis of an N-exchange mechanism (channel 1, Scheme 2d): first annulation \rightarrow Hofmann elimination \rightarrow hydrolysis \rightarrow iminization \rightarrow second annulation. Undoubtedly, reductive elimination process/Hofmann elimination (path A) is favored while the concerted process (path B) is not, because intermediate **Int-C** is isolated in high yield.

To prove the above reaction mechanism, comprehensive isotopic labeling experiments (D , ^{18}O , and ^{15}N) were conducted (Scheme 3 and ESI†). The reaction of **1a** using deuterated methanol as a co-solvent furnished [**D**₄]-**1a** with 28% D-incorporation (see ESI†). While no H/D-exchange was observed from **3a'**, revealing that the first C–H activation was reversible, but the second was not. Then we performed detailed kinetic studies. For the first annulation reaction (**Int-C**), the KIE value was observed to be 2.3. A negligible KIE of 1.0 was observed in the second C–H activation. The KIE value of the diannulation reaction was found to be 3.0. These kinetic studies implied that cleavage of the first C–H bond may be involved in the rate-determining step. Furthermore, the oxygen atom in **3a'** was proved to come from water in the Hofmann elimination-hydrolysis cascade of **Int-C** by adding 10 equiv. of heavy-oxygen water (Scheme 3a), which supported the proposed hydrolytic process. Notably, some unexpected results were received when using $^{15}NH_4OAc$ as the nitrogen source (Scheme 3b). For example, the reaction of **1a** and **2a** with $^{15}NH_4OAc$ gave mix- ^{15}N -**3a** (a mixture of ^{14}N , ^{15}N - and ^{14}N , ^{14}N -**3a**) with only about 39% rather than 100% ^{15}N incorporation for one N atom of the two (Scheme 3c). Also, differentiated ^{15}N ratios were

observed for **3b** (30%), **3c** (9%), **3d** (16%), **3j** (67%), **3k** (28%), and **3m** (30%), respectively. These results revealed that another reaction route (the N-retention channel) must be included. Generally, the electron-rich substrate shows a higher ^{15}N ratio, suggesting it favors the N-exchange channel over its electron-deficient counterpart. More interestingly, the ^{15}N ratio of mix- ^{15}N -**3a** did not change ($\sim 40\%$) throughout the entire reaction time (Scheme 3d), implying that the rate-determining step may be involved in an early stage and the value of the rate constant ratio $k(N\text{-exchange})/k(N\text{-retention})$ is ~ 0.4 . Thus, an N-retention process (channel 2) in the second annulation should be included, where N-alkenyl imine **Int-C'** guides the second C–H activation directly (Scheme 3e).

To collect more process information on this dual-channel reaction, time-dependent electrospray ionization mass spectrometry (TD ESI-MS) was conducted (Fig. 1). First, at room temperature, besides substrate **1a**, fragments at 485.14, 663.22, 425.20, and 385.17 corresponding to **Int-A** [M] $^+$, **Int-B** [M] $^+$, **Int-C** [M] $^+$ /**Int-C'** [$M + H$] $^+$, and **Int-G** [$M + H$] $^+$ were detected. Then at 120 $^{\circ}C$, the signal of **Int-B** disappeared after 0.5 h because it is not very stable and it quickly takes part in the subsequent transformation. The abundances of **Int-A**, **Int-B**, and **Int-G** were low, which could be ascribed to its low concentration/stability. Initially, the abundance of **Int-C**/**Int-C'** increased, but after 2 h, they began to decrease. The abundances of **Int-F** and **3a** increased gradually during the course of the reaction. On the other hand, all the ^{15}N -labelled signals of these intermediates were observed when using $^{15}NH_4OAc$ as the N-source (see ESI†).



Scheme 3 Isotopic labeling experiments.

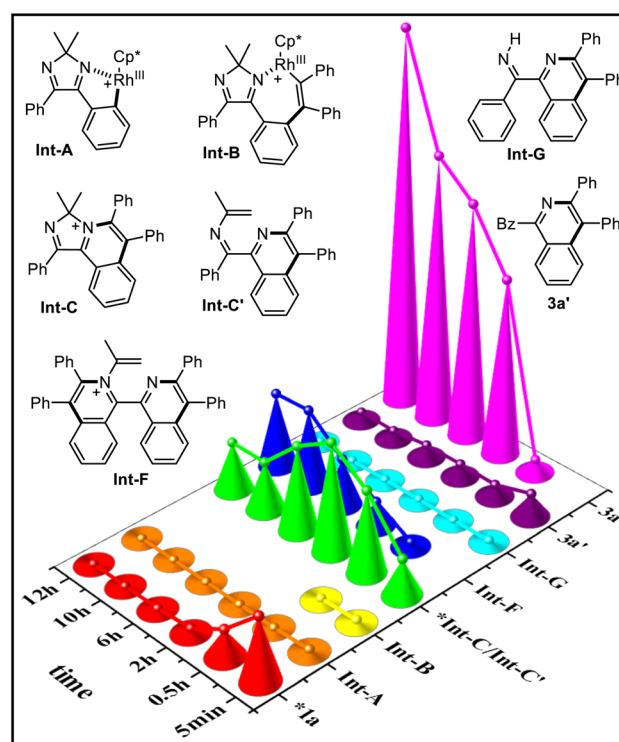


Fig. 1 Relative intensities of the reaction system at different points in time (room temperature: 5 min; 120 $^{\circ}C$: 0.5, 2, 6, 10, 12 h) under standard conditions (*intensity/100).

Based on the above experiments, especially the isotopic experiments, ESI-MS analysis, and literature precedence,^{13,14} a dual-channel mechanism is proposed (Fig. 2). The cationic $\text{Cp}^*(\text{OAc})\text{Rh}^+$ detected by ESI-MS is formed first, with the aid of $\text{Cu}(\text{OAc})_2$. Cyclic diimine **1a** induces the first C–H activation with $\text{Cp}^*(\text{OAc})\text{Rh}^+$ to form the first rhodacycle **Int-A**. Subsequent coordination and insertion with **2a** give seven-membered complex **Int-B**, which undergoes reductive elimination to produce cationic compound **Int-C**, realizing the first C–H annulation. Then, ammonium acetate-mediated Hofmann elimination occurs on **Int-C** to furnish *N*-alkenyl imine **Int-C'**, starting-up the second C–H annulation, which divides into two channels. On the one hand there is the direct C–H activation of **Int-C'** with $\text{Cp}^*\text{Rh(III)}$ species to afford the second imine-Rh species **Int-D**, which is followed by alkynyl insertion to form **Int-E**. Subsequent reductive elimination releases $\text{Cp}^*\text{Rh(I)}$ and **Int-F**, which proceeds to undergo the second Hofmann elimination to obtain final product **3a** with *N*-retention. On the other hand, hydrolysis of imine **Int-C'** yields 1-benzoyl isoquinoline **3a'**, followed by iminization with NH_4OAc to provide *NH*-imine **Int-G**. C–H activation of **Int-G** produces the third imine-Rh species **Int-H**. Subsequent insertion with alkyne and reductive elimination delivers $\text{Cp}^*\text{Rh(I)}$ species and **3a** with *N*-exchange. $\text{Cp}^*\text{Rh(III)}$ is regenerated from $\text{Cp}^*\text{Rh(I)}$ through oxidation with Cu(II) and air to guarantee the catalytic cycle.

With the optimal reaction conditions and plausible mechanism in hand, the reaction scope was then defined (Scheme 4). A number of 2*H*-imidazoles were subjected to reaction with NH_4OAc and two molecules of alkyne **2a**. 2*H*-Imidazole **1b** with methyl at the *para*-position of phenyl reacted with **2a** and NH_4OAc to afford **3b** in 64% yield. *para*-Chloro (**1c**) or -fluoro (**1d**) substituted imidazole gave **3c** and **3d** in 77% and 58% yields, respectively. Imidazole **1e** with a *meta*-methyl group gave **3e** in 80% yield with excellent regioselectivity. Thienyl-fused bipyridine **3f** was successfully obtained for the first time with acceptable yield. Unsymmetric imidazole **1g** was well tolerated to obtain unsymmetric 1,1'-BIQ **3g** in a good yield of 75%. Thus, treatment of *ortho*-OMe-substituted alkyne **2b** with **1a** afforded **3h** in a good yield of 69%. The reaction of *meta*-Br diphenylacetylene **2c** and **1a** generated **3i** in 50% yield. *para*-OMe (**2d**), -Cl (**2e**), -Br (**2f**), and -CF₃ (**2g**) substituted diphenylacetylenes smoothly underwent two-fold C–H activation and annulation and provided 1,1'-BIQs **3j–m** in good to high yields. Notably, thienyl-incorporated 1,1'-BIQs (**3f** and **3n**) were furnished with ~40% yield. Hex-3-yne underwent this reaction smoothly to give **3o** in 81% yield. Upon treatment of unsymmetric alkyl-aryl alkynes and with **1a**, two types of regioisomer were generated (**3p**). Moreover, the title products could also be obtained through a six-component reaction of benzils, acetone, alkynes ($\times 2$), and ammonium acetate ($\times 2$). For selected products (**3a**, **3c**, **3g**, **3j**, and **3m**) were formed in 46–59% yields entirely from

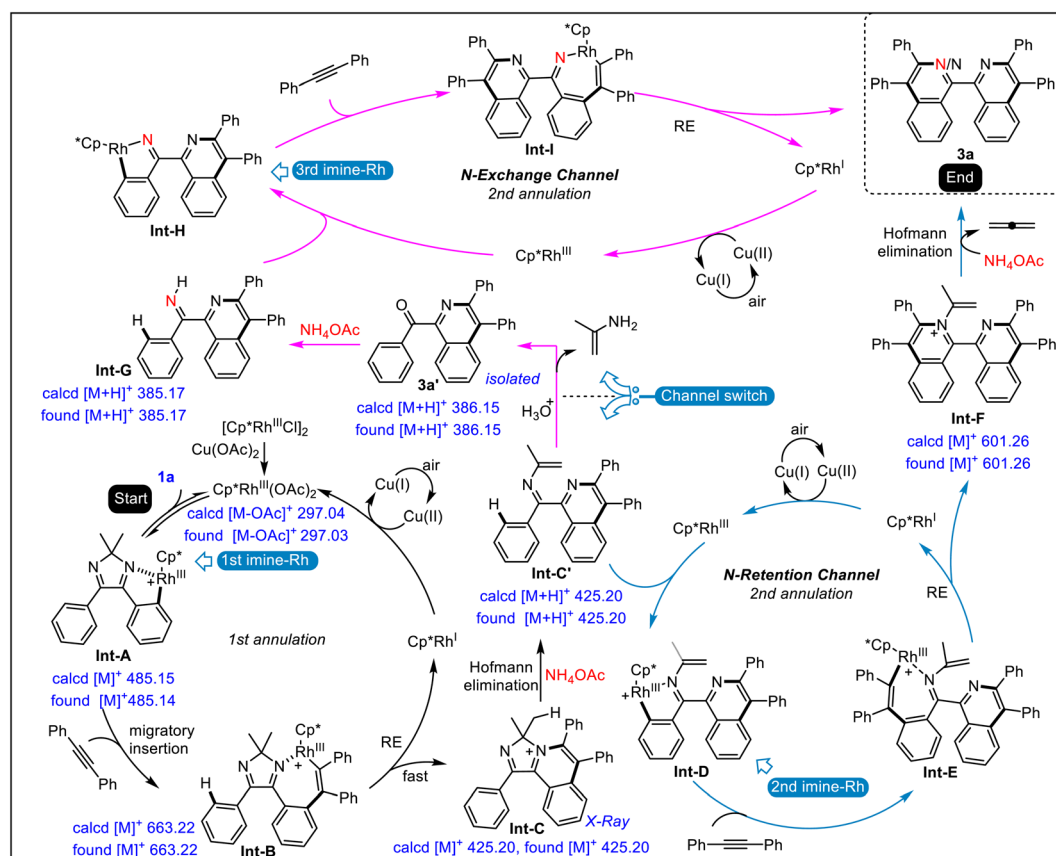
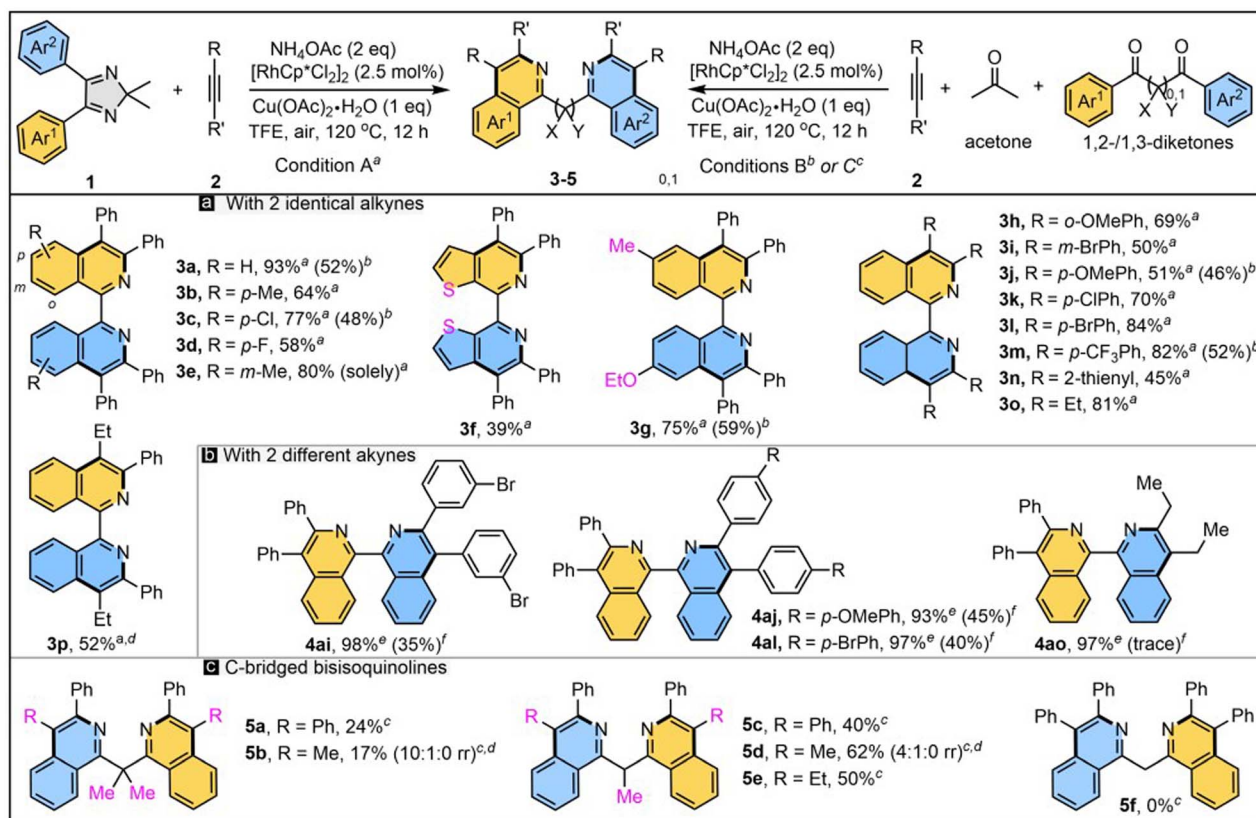


Fig. 2 A total dual-channel mechanism.



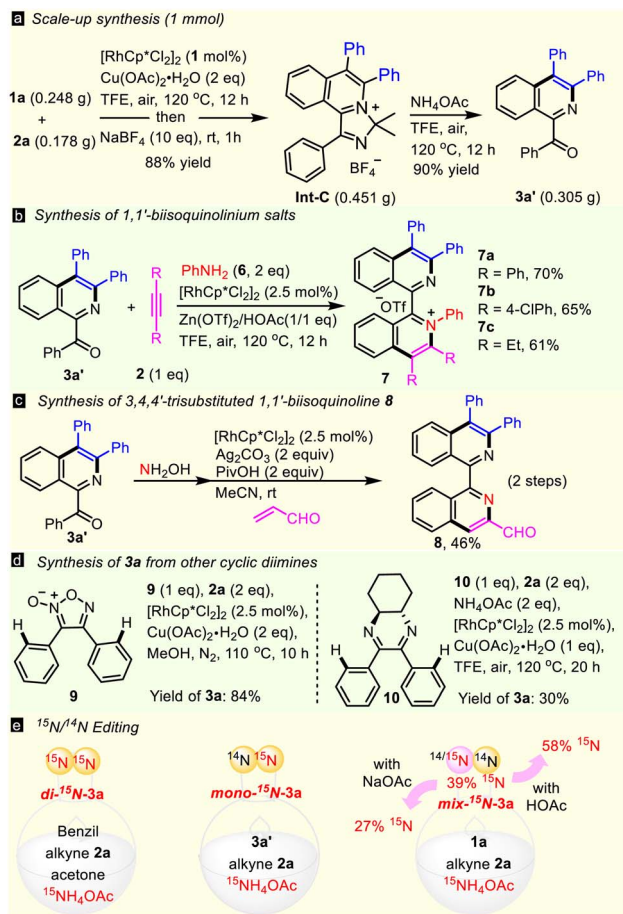


Scheme 4 Scope of Substrates. ^aReaction conditions A: **1** (0.1 mmol), **2** (0.2 mmol), $[\text{RhCp}^*\text{Cl}_2]_2$ (2.5 mol%), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1 equiv.) and NH_4OAc (2 equiv.) in TFE (2 mL) at 120 °C for 12 h under air, isolated yield. ^bReaction conditions B: benzil (0.1 mmol), acetone (0.15 mmol), **2** (0.2 mmol), $[\text{RhCp}^*\text{Cl}_2]_2$ (2.5 mol%), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1 equiv.) and NH_4OAc (2 equiv.) in TFE (2 mL) at 120 °C for 12 h under air. ^cReaction conditions C: 1,3-diketone (0.1 mmol), **2** (0.2 mmol), $[\text{RhCp}^*\text{Cl}_2]_2$ (2.5 mol%), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1 equiv.) and NH_4OAc (7 equiv.) in TFE (2 mL) at 120 °C for 12 h under air. ^dOnly the main isomer is shown. ^ePrepared from the reaction of **3a'** with alkynes. ^fPrepared in a one-pot, two-step manner.

commercially available raw materials. In addition, treatment of **3a'** with one molecule of alkynes **2** in the presence of NH_4OAc gave non-symmetric 1,1'-BIQs **4ai-4ao** in excellent yields (all over 90%), while they were obtained in low yields in a one-pot, two-step manner—albeit with high chemo-selectivity (ESI[†]).

With success in preparing non-bridged 1,1'-BIQs from 1,2-diketones, we turned our attention to 1,3-diketones, which may offer interesting C-bridged N-heterobiaryls (Scheme 4c). However, the synthesis of simple methylene-bridged 1,1'-bisquinoline **5f** was a failure, which may be due to its strong enol tautomerism. Conversely, enol tautomerism-blocked diketone was prepared and subjected to the double C–H annulation, to our delight giving *gem*-dimethyl-bridged product **5a** in 24% yield. The 1,3-diketone with only one methyl-block afforded **5c** in a higher yield of 40%. Similarly, the treatment of 1,3-diketones with non-symmetric aryl-alkyl acetylenes generated two of the three isomers. For example, symmetric **5b** and non-symmetric isomer **5b'** were obtained as a mixture in a ratio of 10 : 1. Bisquinoline **5d** was afforded in good yield (62%) with an acceptable regioselectivity ratio (r.r. = 4 : 1). The reaction of Ph–Et alkyne with diketone gave **5e** (50%) and **5e'** (16%) as two isolable isomers. To the best of our knowledge, this is the first example of constructing C-bridged 1,1'-bisquinolines through a transition-metal-catalyzed C–H activation strategy.¹⁸

Furthermore, the versatile functions of this protocol were explored (Scheme 5). First, an excellent yield (88%, 0.451 g) of product **Int-C** was obtained in a 1 mmol scale with low catalyst loading (1 mol% Rh) under air (Scheme 5a). It can smoothly convert into **3a'** with a 90% yield through Hofmann elimination and hydrolysis. When using aniline **6** as the N-source instead of NH_4OAc , some new 1,1'-biisoquinolinium salts **7a-7c** were obtained in good yields (Scheme 5b). Besides, treatment of **3a'** with hydroxylamine gave 1-oximido isoquinoline, which annulated with acrylaldehyde to form 3,4,4'-trisubstituted 1,1'-biisoquinoline **8** in 46% yield in two steps (Scheme 5c), which represents a novel type of 1,1'-BIQ. Other cyclic diimines could also undergo ring-opening double C–H annulation to form **3a**. For instance, 5-membered furoxan **9** reacted with **2a** to deliver **3a** in a high yield of 84% (Scheme 5d). Six-membered diimine **10** afforded **3a** with 30% yield through two rounds of Hofmann elimination; as expected, the di-annulation did not take place in the absence of NH_4OAc . It is noted that with both N atoms fully ¹⁵N-labelled, product di-¹⁵N-**3a** was easily obtained in 50% yield through a one-pot six-component reaction with the aid of ¹⁵NH₄OAc (Scheme 5e, left). Also, mono-¹⁵N-**3a** with only one N atom fully ¹⁵N-labelled was achieved in 95% yield from the reaction of **3a'**, **2a**, and ¹⁵NH₄OAc (Scheme 5e, middle). As hydrolysis of **Int-C'** is vital in the switch to the N-exchange



Scheme 5 Synthetic applications.

channel, ^{15}N -labeling can be handled by the pH, *i.e.*, it is enhanced from 39% to 58% when HOAc is added, but decreases to 27% in the presence of NaOAc (Scheme 5e, right). Hence, a library of controllably ^{15}N labelled 1,1'-BIQs could be facilely assembled, for the first time, by adjusting the reaction mode and acidity. Finally, the catalytic activity of this class of newly prepared bidentate ligand was surveyed in an Ullmann-type reaction to synthesize drug-like benzo[*c*]cinnolines.¹⁹ Phthalic

hydrazide (11) and cyclic diaryliodonium triflate (12) were treated in the presence of CuI (5 mol%), K_2CO_3 (2 equiv.), DMF, and a ligand (Fig. 3). Compared to well-known *N,N*-ligands, like 2,2'-bipyridine (Bipy), 1,10-phenanthroline (Phen), or *N,N'*-dimethylethylenediamine (DMEDA), 1,1'-BIQ 3a showed higher activity and gave benzo[*c*]cinnoline (13a) in the highest yield (99%). Especially for the cyano-substituted cyclic iodonium, 3a exhibited much greater efficiency with 99% yield compared to 35% for Bipy. Other 1,1'-BIQs with examples of 3e, 3j, 3m, and 3o, all gave 13b in over 75% yield.

Conclusions

In conclusion, we have developed Rh(III)-catalyzed novel multi-component reactions to assemble axial 1,1'-bisisoquinolines and C-bridged 1,1'-bisisoquinolines through a C–H activation/DDG strategy with controllable ^{15}N editing. The combinations of techniques, crystallography, TD ESI-MS, and isotopic experiments prove that the current transformations include double channels of N-retention and N-exchange. NH_4OAc plays irreplaceable multiple roles of two rounds of Hofmann elimination and iminization, leading to an unprecedented imine dance, cyclic imine \rightarrow *N*-alkenyl imine \rightarrow NH imine. The newly *in situ* formed alkenyl imine can directly guide a C–H annulation with N-retention; or it changes to NH imine *via* hydrolysis and reiminization, initiating another C–H annulation with N-exchange. The ^{15}N distribution can be predicted and further adjusted by reaction mode and acidity. In this protocol, *N*-aryl 1,1'-bisisoquinoliniums and 3,3',4'-trisubstituted 1,1'-bisisoquinoline have been synthesized for the first time. Moreover, the resultant 1,1'-BIQs are proved to be privileged *N,N*-ligands with powerful catalytic activity in Cu-catalyzed diarylation to form drug-like benzo[*c*]cinnolines. Over ten (^{15}N labelled) intermediates have been characterized by the combined techniques, confirming reductive elimination/Hofmann elimination rather than a concerted process of Rh-catalyzed C–N breaking N-annulation, and thus enriching the evidence in Rh catalysis.

Data availability

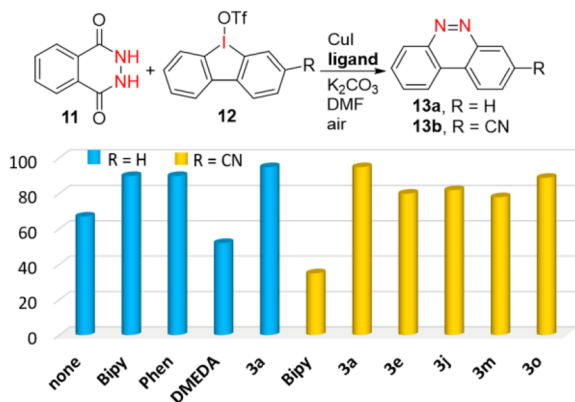
All detailed procedures, characterization data and NMR spectra are available in the ESI.†

Author contributions

S. Li conceived the concept, directed the project, performed key experiments, and wrote the paper. S. Lv and Y. Yang carried out most of the experiments. P. Zhu conducted the ESI-MS. D. Zhao conceived the concept and helped edit the manuscript. M. Zeng analysed ESI-MS data and helped edit the manuscript. S. Li, S. Lv and Y. Yang contributed equally to this work.

Conflicts of interest

The authors declare no competing financial interest.

Fig. 3 BIQ as ligand in double *N*-arylation to benzo[*c*]cinnolines.

Acknowledgements

We are grateful for the financial support from the National Natural Science Foundation of China (22001049, 22261013, 21525101 and 22171075), Guangxi Natural Science Foundation (2020GXNSFBA297003 and 2018GXNSFAA29404), the BAGUI talent program (no. 2019AC26001).

Notes and references

- (a) *Multicomponent Reactions*, ed. J. Zhu and H. Bienaymé, Wiley-VCH, Weinheim, 2005; (b) *Multicomponent Reactions*, ed. T. J. J. Müller, Science of Synthesis, Thieme, Stuttgart, 2014, vol. 1, p. 2; (c) *Multicomponent Reactions in Organic Synthesis*, ed. J. Zhu, Q. Wang and M.-X. Wang, Wiley-VCH, Weinheim, 2015.
- For selected reviews, see: (a) S. Datta, M. L. Saha and P. J. Stang, *Acc. Chem. Res.*, 2018, **51**, 2047–2063; (b) D. J. Tranchemontagne, J. L. Mendoza-Cortes, M. O'Keeffe and O. M. Yaghi, *Chem. Soc. Rev.*, 2009, **38**(5), 1257–1283.
- (a) J.-P. Zhong, B. Liu, T. Yang, Y.-J. Liu, Z.-H. Zhu, B.-F. Shi, M. Kurmoo and M.-H. Zeng, *Inorg. Chem.*, 2017, **56**, 10123–10126; (b) M.-H. Zeng, Z. Yin, Z.-H. Liu, H.-B. Xu, Y.-H. Feng, Y.-Q. Hu, L.-X. Chang, Y.-X. Zhang, J. Huang and M. Kurmoo, *Angew. Chem., Int. Ed.*, 2016, **55**, 11407–11411; (c) Y.-Q. Hu, M.-H. Zeng, K. Zhang, S. Hu, F.-F. Zhou and M. Kurmoo, *J. Am. Chem. Soc.*, 2013, **135**, 7901–7908; (d) H.-L. Zheng, X.-L. Chen, T. Li, Z. Yin, Y. Zhang, M. Kurmoo and M.-H. Zeng, *Chem.-Eur. J.*, 2018, **24**, 7906–7912.
- B. Liu, F. Yu, M. Tu, Z.-H. Zhu, Y. Zhang, Z.-W. Ouyang, Z. Wang and M.-H. Zeng, *Angew. Chem., Int. Ed.*, 2019, **58**, 3748–3753.
- (a) R. Xie, Y. Xiao, Y. Wang, Z.-W. Xu, N. Tian, S. Li and M.-H. Zeng, *Org. Lett.*, 2023, **25**, 2415–2419; (b) V. M. Williams, J. R. Kong, B. J. Ko, Y. Mantri, J. S. Brodbelt, M.-H. Baik and M. J. Krische, *J. Am. Chem. Soc.*, 2009, **131**, 16054–16062; (c) N. L. Bell, C. Xu, J. W. B. Fyfe, J. C. Vantourout, J. Brals, S. Chhabra, B. E. Bode, D. B. Cordes, A. M. Z. Slawin, T. M. McGuire and A. J. B. Watson, *Angew. Chem., Int. Ed.*, 2021, **60**, 7935–7940.
- (a) L. Zhao and R. Hua, *Chem. Rec.*, 2018, **18**, 556–569; (b) V. P. Boyarskiy, D. S. Ryabukhin, N. A. Bokach and A. V. Vasilyev, *Chem. Rev.*, 2016, **116**, 5894–5986; (c) J. C. Lewis, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2008, **41**, 1013–1025; (d) Z. Dong, Z. Ren, S. J. Thompson, Y. Xu and G. Dong, *Chem. Rev.*, 2017, **117**, 9333–9403.
- For the examples of isoquinoline syntheses, see: (a) L. Zheng, J. Ju, Y. Bin and R. Hua, *J. Org. Chem.*, 2012, **77**, 5794–5800; (b) J. Zhang, H. Qian, Z. Liu, C. Xiong and Y. Zhang, *Eur. J. Org. Chem.*, 2014, **2014**, 8110–8118; (c) H. Lee, Y.-K. Sim, J.-W. Park and C.-H. Jun, *Chem.-Eur. J.*, 2014, **20**, 323–333; (d) X. Tan, X. Hou, T. Rogge and L. Ackermann, *Angew. Chem., Int. Ed.*, 2021, **60**, 4619–4624.
- (a) S. Li, H. Lv, R. Xie, Y. Yu, X. Ye and X. Kong, *Org. Lett.*, 2020, **22**, 4207–4212; (b) S. Lv, Y.-N. Tian, Y. Yang, C. Wen and S. Li, *J. Org. Chem.*, 2022, **87**, 16019–16025; (c) C. Wen, Y. Wang, Y. Yang, Y.-N. Tian, J. Wang and S. Li, *Org. Lett.*, 2023, **25**, 2616–2621; (d) Y.-N. Tian, S. Lv, L. Huang, C. Wen, Y. Yang, X. Kong, Q. Zhu and S. Li, *Org. Chem. Front.*, 2023, **10**, 83–91.
- D.-G. Yu, F. de Azambuja, T. Gensch, C. G. Gensch and F. Glorius, *Angew. Chem., Int. Ed.*, 2014, **53**, 9650–9654.
- R. Feng, H. Ning, H. Su, Y. Gao, H. Yin, Y. Wang, Z. Yang and C. Qi, *J. Org. Chem.*, 2017, **82**, 10408–10417.
- S. Kumar, A. M. Nair and C. M. R. Volla, *Org. Lett.*, 2020, **22**, 2141–2146.
- A. Dey and C. M. R. Volla, *Org. Lett.*, 2020, **22**, 7480–7485.
- (a) X.-L. Wu and L. Dong, *Org. Lett.*, 2018, **20**, 6990–6993; (b) X.-L. Wu and L. Dong, *Asian J. Org. Chem.*, 2018, **7**, 2422–2426.
- (a) Y. Luo, H. Liu, J. Zhang, M. Liu and L. Dong, *Org. Lett.*, 2020, **22**, 7604–7608; (b) Z. Song, Z. Yang, P. Wang, Z. Shi, T. Li and X. Cui, *Org. Lett.*, 2020, **22**, 6272–6276; (c) Y. Luo, W. Pu, Y.-J. Xu and L. Dong, *Org. Chem. Front.*, 2021, **8**, 4549–4553; (d) Y. Luo, H.-Y. Zhou, Y.-C. Gang and L. Dong, *Org. Lett.*, 2022, **24**, 6940–6944.
- (a) N. Guimond, C. Gouliaras and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 6908–6909; (b) S.-C. Chuang, P. Gandeepan and C.-H. Cheng, *Org. Lett.*, 2013, **15**, 5750–5753.
- Z. Yu, Y. Zhang, J. Tang, L. Zhang, Q. Liu, Q. Li, G. Gao and J. You, *ACS Catal.*, 2020, **10**, 203–209.
- CCDC 2266530 (**Int-C**) contains the supplementary crystallographic data for this paper.
- D. E. Stephens, V. T. Nguyen, B. Chhetri, E. R. Clark, H. D. Arman and O. V. Larionov, *Org. Lett.*, 2016, **18**, 5808–5811.
- A. L. Ruchelman, S. K. Singh, A. Ray, X. Wu, J.-M. Yang, N. Zhou, A. Liu, L. F. Liu and E. J. LaVoie, *Bioorg. Med. Chem.*, 2004, **12**, 795–906.

