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The C−H Activation/Bidirecting Group Strategy for Selective Direct Synthesis of Diverse 1,1′-Biisoquinolines

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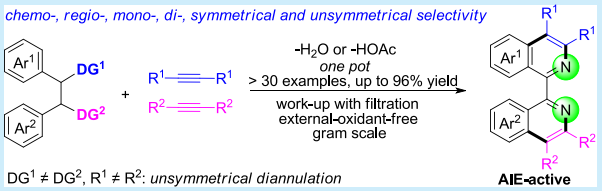
ABSTRACT: Multidentate ligands are highly important but difficult to access. Herein we disclose an atom- and step-economic synthesis of highly substituted 1,1′-biisoquinolines by a C−H activation/bididirecting group strategy. Through rational design of a bididirecting group to "N−OH + N−OAc", selective unsymmetrical diannulation with two different alkynes in a one-pot reaction has been achieved for the first time to access unsymmetrical biisoquinolines. Moreover, the resultant biisoquinolines show tunable photoluminescence and serve as aggregation-induced emission (AIE) systems.



Axially chiral biaryl compounds, such as the well-known BINAP, BINOL, and their diverse derivatives, have received considerable attention because they can be used as privileged ligands in asymmetric catalysis (Figure 1).[1] Their

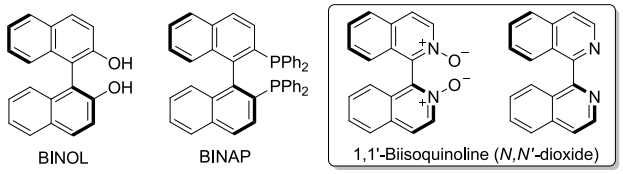


Figure 1. Axially chiral biaryl ligands.

analogues, 1,1′-biisoquinolines, showed privileged coordination with metal species, and their complexes have attractive photophysical properties.[2] Chiral 1,1′-biisoquinoline *N*,*N*′-dioxides have shown superior catalytic capacity in asymmetric propargylation reactions.[3] Unexpectedly, we found that the structural diversity of 1,1′-biisoquinoline (*N*,*N*′-dioxides) is only limited to a few symmetrical ones with −H or −Ph at the 3- and 3′-positions.[2−4] One of the possible reasons for the rare diversity of 1,1′-biisoquinoline derivatives is a tedious synthetic procedure. Another reason may be the high cost of direct functionalization of very expensive 1,1′-biisoquinoline. In addition, transition-metal-catalyzed direct C−H functionalization of multidentate ligands poses a great challenge because coordination of the substrate with the metal species may inhibit the catalysis.[5] Thus, the development of an efficient method to synthesize 1,1′-biisoquinolines is urgently needed.

In recent decades, transition-metal-catalyzed C−H bond functionalization has developed as a promising strategy for organic synthesis.[6] However, in oxidative C−H functionalization, stoichiometric oxidants such as peroxides or metal oxidants are generally required. Oximes are employed as oxidizing directing groups (DG^{ox}) without external oxidants and give H_2O as the byproduct. For example, the synthesis of isoquinolines through DG^{ox}-mediated annulation of aromatic oximes,[7] imines,[8] hydrazone,[9] azines,[10] and azides[11] with alkynes using Rh, Ru, or Co as the catalyst has been well-developed. Glorius[12a] and Qi[12b] reported the Rh^{III}-catalyzed C−H activation/1,3-diyne strategy to access 3,3′-biisoquinolines and 3,4′-biisoquinolines, respectively (Scheme 1a). More recently, Volla and co-workers reported the Ru^{II}-catalyzed C−H activation/1,3-diyne strategy to form 4,4′-biisoquinolines (Scheme 1b).[13] However, the synthesis of 1,1′-biisoquinoline derivatives through transition-metal-catalyzed C−H activation has not been reported, and to the best of our knowledge, selective unsymmetrical diannulation with two different alkynes in one pot has not been described to date.[14] In this context, we envisaged that a bidirecting group (BIDG), that is, two DGs connected with a single bond, such as a dioxime, would react with an alkyne to generate a 1-oximido isoquinoline, which would then annulate with another alkyne to afford the 1,1′-biisoquinoline (Scheme 1c).

In the frame of our interest in the synthesis and application of polyaryl N-heterocyclic compounds,[15] in this work we examined the possibility of Rh^{III}-catalyzed dual C−H activation/annulation of dioxime derivatives with alkynes to yield polyaryl 1,1′-biisoquinolines. Through rational design of the BIDGs and reaction conditions, we overcame the challenges of inhibition through coordination, the steric hindrance effect, and selectivity to assemble symmetrical and

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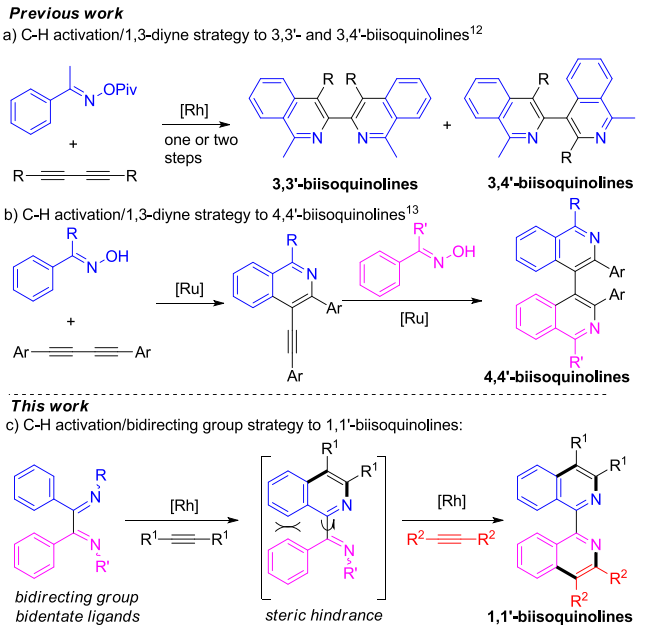
Scheme 1. Synthesis of Biisoquinolines via C−H Activation

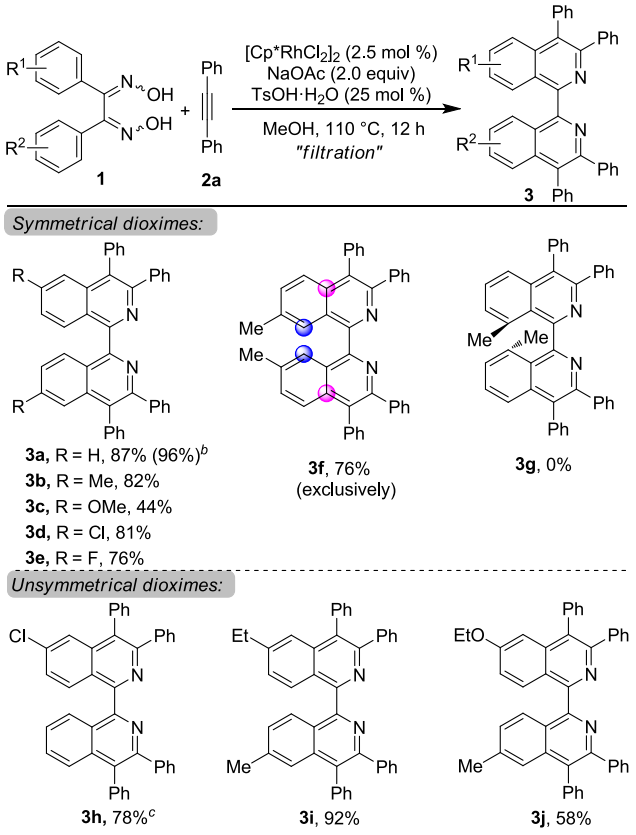


unsymmetrical 1,1′-biisoquinolines with high efficiency and good selectivity.

Initially, benzil dioxime (**1a**) (BIDG = N−OH/N−OH) and diphenylacetylene (**2a**) were selected as the model substrates, and $[RhCp^*Cl_2]_2$ (2.5 mol %) was used as a catalyst. As shown in Table S1, a catalytic amount of NaOAc proved innocent in the diannulation, and the monoannulated compound **7** was generated (Table S1, entries 1−3). The target biisoquinoline **3a** was isolated in a good yield of 80% after chromatography on silica gel when 2 equiv of NaOAc was used (entry 4). Diannulated **3a** was not formed, and only monoannulated **7** was generated in 20% yield, when the loading of $[Cp^*RhCl_2]_2$ was reduced to 1 mol % (entry 5). The reaction ceased in the absence of $[Cp^*RhCl_2]_2$ or when other catalysts (e.g., Ru and Ir) were used instead (entry 6). Pleasingly, when $TsOH\cdot H_2O$ was employed as the additive, **3a** was obtained in an excellent yield of 93% (entry 8). More interestingly, **3a** precipitated from the reaction solvent and could be gained in a high yield of 87% just by filtration (entry 9).[16] When *O*,*O*-diacetyl dioxime (**1a-diOAc**) was used instead of **1a**, **3a** was obtained in 96% yield after filtration (for details, see Table S2).

With the optimal conditions in hand, the scope of dioximes was first investigated (Scheme 2). Various symmetrical dioximes possessing either an electron-donating or electron-withdrawing functionality (**1b−e**) could diannulate with **2a** smoothly to deliver the desired 1,1′-biisoquinolines in moderate to high yields (**3b−e**). It is noted that although three regioisomers might be generated from *meta*-substituted dioxime in diannulation, here only one type of regioisomer (**3f**), annulated at sterically less hindered sites, was generated in 76% yield. *o*-Methyl dioxime was not compatible with this diannulation, which might be due to strong steric hindrance between the two methyl groups. To our delight, unsymmetrical dioximes could smoothly react with **2a** to give the target unsymmetrical biisoquinolines **3h−j** in good to excellent yields. To the best of our knowledge, this is the first example of the synthesis of unsymmetrical 1,1′-biisoquinolines. Notably,

Scheme 2. Scope of Dioximes[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $TsOH\cdot H_2O$ (25 mol %), and NaOAc (2 equiv) in MeOH (2 mL) at 110 °C for 12 h under a N_2 atmosphere. Isolated yields after filtration are shown. [b]**1a-diOAc** was used instead of **1a**. [c]At 120 °C.

all of the products could be obtained simply by filtration without further processing.

Then the scope of alkynes was tested with **1a** and **1a-diOAc** under conditions A and B, respectively (Scheme 3). Both **1a** and **1a-diOAc** could react with various alkynes smoothly to deliver the corresponding 1,1′-biisoquinolines **4b−m** in moderate to excellent yields, and the structure of **4g** was determined by single-crystal X-ray diffraction. Hex-3-yne reacted with **1a** to afford tetraalkyl-substituted molecule **4n** in 77% yield. Upon treatment of alkyl aryl alkynes with **1a**, two types of regioisomers were generated (**4o** and **4p**).

With the success of symmetrical diannulation with the same alkyne, we turned our attention to one-pot sequential diannulation with two different alkynes, which needed two separate steps in previous reports.[14] **1a** was treated with 1 equiv of alkyne **2a** under the conditions of $[RhCp^*Cl_2]_2$ (2.5 mol %) and NaOAc (1 equiv) for 5 h (step 1), and then alkyne **2f**, additional NaOAc (1 equiv), and $TsOH\cdot H_2O$ (25 mol %) were added and allowed to react for a further 10 h (step 2). However, all the three isomers, cross-annulated **5af** and homoannulated **3a** and **4f**, were generated with poor selectivity (Scheme 4, eq 1). Also, poor selectivity was observed in the one-pot, two step reaction of **1a-diOAc**, **2a**, and **2f** (Scheme 4, eq 2). Finally, we synthesized benzil *O*-acetyl dioxime (**1a-OH/OAc**), a "mixed BIDG" containing one N−OH and one N−OAc. **1a-OH/OAc** was treated with **2a** under the conditions of $[RhCp^*Cl_2]_2$ (2.5 mol %) and NaOAc (0.3

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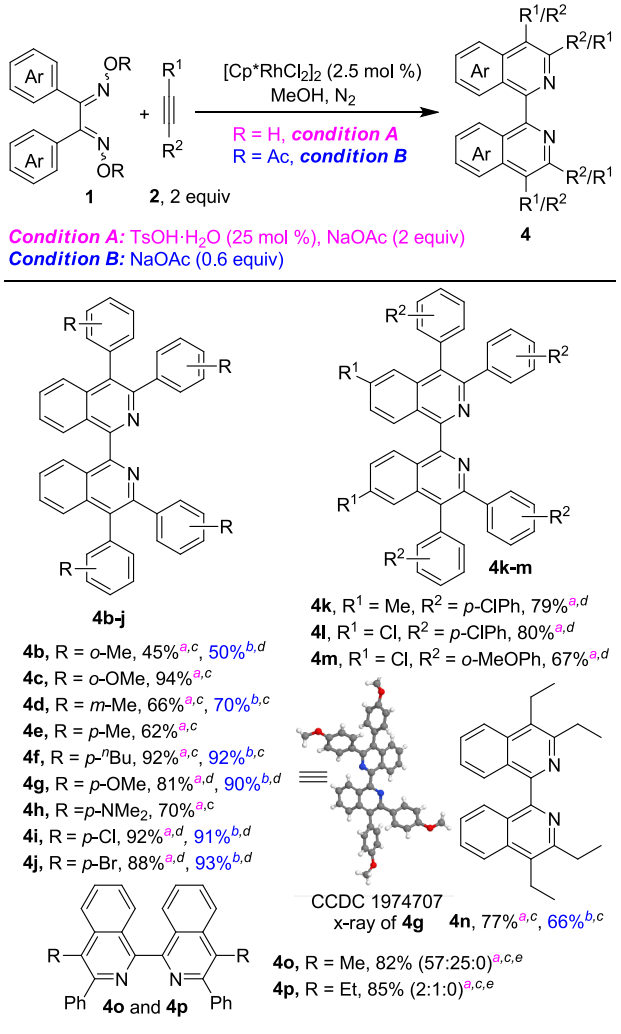
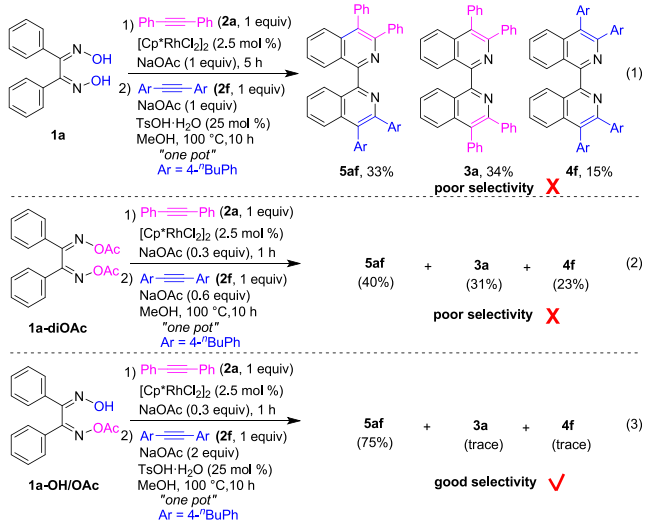
Scheme 3. Scope of Alkynes

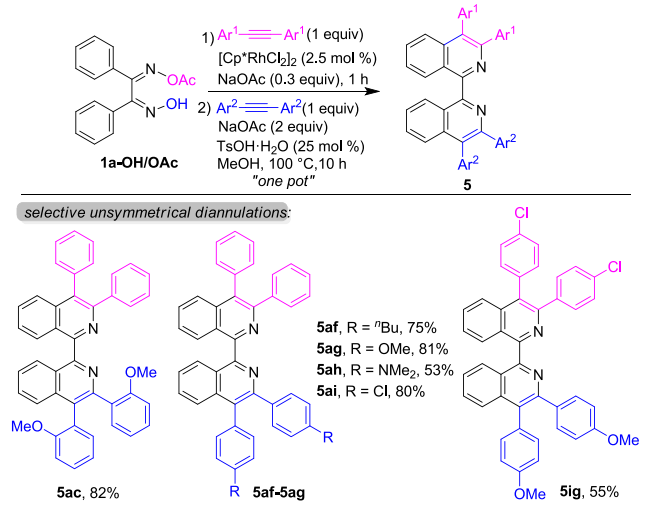


[a]Condition A: **1** (0.2 mmol), **2** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $TsOH{\cdot}H_2O$ (25 mol %), and NaOAc (2 equiv) in MeOH (2 mL) at 110 °C for 12 h. [b]Condition B: **1a-diOAc** (0.2 mmol), **2** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), and NaOAc (0.6 equiv) in MeOH (2 mL) at 100 °C for 10 h. [c]Yield after chromatography on silica gel. [d]Yield after filtration. [e]Only the main regioisomer is shown.

Scheme 4. Selectivity of Unsymmetrical Diannulation



Scheme 5. One-Pot Unsymmetrical Diannulation with Two Different Alkynes[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), and NaOAc (0.3 equiv) in MeOH (1 mL) at 100 °C for 1 h, then addition of another alkyne (0.1 mmol), NaOAc (2 equiv), and $TsOH{\cdot}H_2O$ (25 mol %) and further reaction at 100 °C for 10 h. Isolated yields after chromatography are shown.

equiv) for 1 h (step 1), followed by addition of alkyne **2f** and a further 10 h of reaction (step 2). To our delight, cross-annulated **5af** was exclusively generated in a good yield of 75% with excellent selectivity (Scheme 4, eq 3).

With the selective conditions in hand, we chose various alkynes to annulate with **1a-OH/OAc**, leading to the title unsymmetrical 1,1′-biisoquinolines **5ac**−**ig** in good yields with high selectivities (Scheme 5). For example, using **2a** for the first annulation and substituted alkynes for the second one afforded biisoquinolines **5ac**−**ai** in 53−82% yield with good selectivities. The sequential diannulation of *p*-Cl (**2i**) and *p*-OMe (**2g**) substituted alkynes with **1a-OH/OAc** afforded multifunctionalized unsymmetrical biisoquinoline **5ig** in 55% yield.

Aiming to evaluate the practicality of this catalytic process, a gram-scale experiment was conducted with **1a** (0.48 g) and **2a** (0.71 g), which gave the target product **3a** (1.06 g) in an excellent yield of 95% after filtration (Scheme 6, eq 4). Additionally, biisoquinoline *N*,*N*′-dioxide **3a-dioxide** was obtained in high yield after oxidation of **3a** (Scheme 6, eq 5), which may applied to asymmetric catalysis after chiral resolution. It is noted that both the 1,1′-biisoquinoline and its *N*,*N*′-dioxide could be synthesized in a quicker and more efficient way than before.

To gain more insight into the mechanism of this reaction, a H/D exchange experiment was first conducted in the absence of **2a**. Deuterium incorporation of 15% was observed at the *ortho* position of **1a**. Notably, **1a-diOAc** was hydrolyzed into **1a** with 46% deuterium incorporation (Scheme 7, eq 6). Moreover, an identical kinetic isotope effect (KIE) of $k_H/k_D \approx 1.0$ was observed for both the competitive and parallel deuterium experiments using substrates **1a** and/or $[D_{10}]$-**1a** with **2a** under the standard reaction conditions (Scheme 7, eq 7). These results indicated that cleavage of the C−H bond may not be involved in the rate-determining step. Furthermore, the reaction of monoannulated compound **7** with 1 equiv of **2a**

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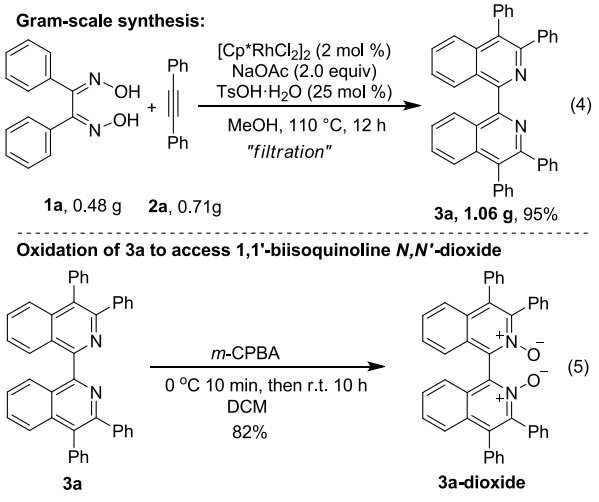
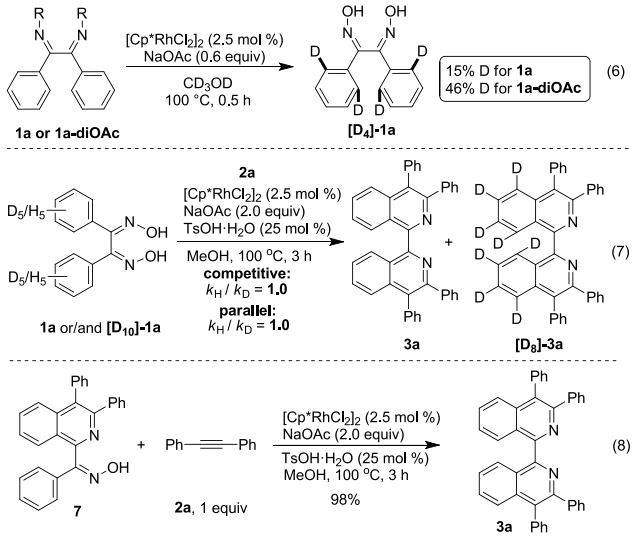
Scheme 6. Gram-scale Synthesis and Oxidation of 3a



Scheme 7. Mechanistic Studies



delivered **3a** in 98% yield, which indicated that **7** could probably be the intermediate in the diannualtion (Scheme 7, eq 8).

On the basis of the above investigation and related references,[7−14] a plausible mechanistic pathway is proposed (Scheme S1). First, cyclorhodium intermediate **A** is formed from **1a** and the rhodium catalyst through oxime-assisted reversible C−H activation. Then alkyne insertion produces cationic species **B**, which is consequently transformed to monoannulated compound **7**. A similar catalytic process (**1a** → **7**) happens to **7**, releasing the diannulated product **3a**.

Besides the synthesis and mechanistic study, we were also interested in the material properties of these novel polyaryl biisoquinolines. As we know, propeller-like organic frameworks with polyaryl substituents are promising candidates for aggregation-induced emission (AIE)-active molecules, which are widely applied in optoelectronics, bioimaging, nanoscience, etc.[17] Intrigued by the multiaryl structures of these compounds, the AIE characteristics in THF/water were tested. Typically, **3a** showed faint photoluminescence (PL) peaking at 422 nm when dissolved in THF. Increasing the water fraction (f_w) to 70% allowed a significant emission signal to be detected, and an approximately 16-fold enhancement of intensity was observed when f_w was increased to 95% (Figure 2A). Interestingly, the THF solution of **4h** (containing four

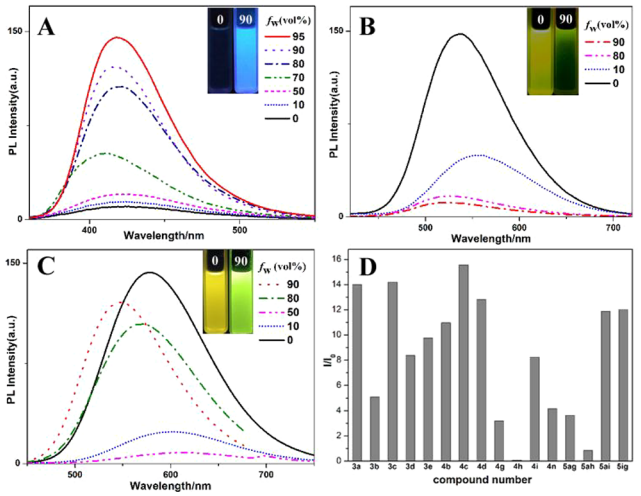


Figure 2. PL spectra of (A) **3a**, (B) **4h**, and (C) **5ah** (10 μM) in THF and THF/water mixtures with different water fractions (f_w). (D) Fluorescence responses (I/I_0) to different compounds (I_0 for f_w = 0% and I for f_w = 90%).

−NMe_2 groups) emitted strong green fluorescence under UV irradiation, and the fluorescence steeply declined when the f_w was increased (Figure 2B), demonstrating the aggregation-caused quenching (ACQ) nature. Compound **5ah** (containing two −NMe_2 groups) showed intense fluorescence emission in solution as well as in the aggregates ($I/I_0 \approx 1$) (Figure 2C). Most of the products are AIE-active, except **4h** and **5ah**, with over 5-fold enhancement of the PL intensity for f_w = 90% versus 0% (Figure 2D; for details, see the Supporting Information).

In conclusion, we have successfully developed an atom- and step-economical method for the synthesis of highly substituted 1,1′-biisoquinoline compounds from dioxime derivatives and internal alkynes, overcoming the challenges of inhibition through coordination, the steric hindrance effect, and selectivity (chemo-, regio-, mono-, di-, symmetrical, and unsymmetrical selectivity). This protocol features the following properties: (a) easily available/prepared and cheap substrates; (b) broad scope and high yields of up to 96% as well as in gram-scale synthesis; (c) workup with filtration; (d) greatly streamlined steps; (e) high atom economy of up to 96% and environmental friendliness; (f) selective *one-pot* unsymmetrical diannulation with two different alkynes; (g) tunable fluorescence between AIE and ACQ, making the compounds potentially useful as fluorophores in OLEDs and bioimaging tools. Further applications of these compounds for organocatalysis and luminescence are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01260.

Experimental procedures and characterization of related compounds (PDF)

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Accession Codes

CCDC 1974706−1974707 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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